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Supplementary Information for
Chirality-Matched Catalyst-Controlled Macrocyclization Reactions

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1. General Information

Room temperature is defined as 21–25 °C. The following reagents, CuBr (99.998%, STREM), CuI (99.998%, STREM), $Cu(MeCN)_4BF_4$ (>98%, TCI America), Cs_2CO_3 (99.9 %, Sigma-Aldrich) and K_3PO_4 (99.9%, Sigma-Aldrich) were purchased from the corresponding commercial suppliers and used as received. All other reagents were purchased from commercial suppliers and used without further purification, unless otherwise noted. Acetonitrile, *N*,*N*-dimethylformamide, toluene and tetrahydrofuran were obtained from a Seca Solvent System by GlassContour, in which the solvent was dried over alumina and dispensed under an atmosphere of Ar. Triethylamine (Et_3N), *N*,*N*-diisopropyl ethylamine ($^iPr_2NEt$) and pyridine were distilled over CaH_2 under a nitrogen atmosphere prior to use. All other solvents were purchased from commercial suppliers and used without further purification, unless otherwise noted.

Routine ^1H NMR spectra were recorded on Agilent 400, 500, or 600 MHz spectrometers at ambient temperature unless otherwise stated. All NMR solvents were purchased from Cambridge Isotope Laboratories and used without further purification. Chloroform-*d*, dichloromethane-d_2, acetone-d_6, acetonitrile-d_3, and deuterium oxide-d_2 were stored at ambient temperature, and methanol-d_4 and dimethylsulfoxide-d_6 ampoules were used immediately after opening. Spectra were processed using MestReNova 14.2.0 using the automatic phasing and polynomial baseline correction capabilities. Splitting was determined using the automatic multiplet analysis function with manual intervention as necessary. Spectral data are reported as follows: chemical shift (multiplicity [singlet (s), broad singlet (brs), doublet (d), triplet (t), quartet (q), pentet (p), multiplet (m), doublet of doublets (dd), doublet of doublet of doublets (ddd), doublet of triplet of doublets (dtd), doublet of doublet of doublet of doublets (dddd), doublet of triplets (dt), triplet of doublets (td), etc.], coupling constant, integration). Chemical shifts are reported in ppm (δ), and coupling constants are reported in Hz. ^1H Resonances are referenced to solvent residual peaks for $CDCl_3$ (7.26 ppm), CD_2Cl_2 (5.32 ppm), DMSO-d_6 (2.50 ppm), D_2O (4.79 ppm), CD_3CN (1.79 ppm), or CD_3OD (3.31 ppm).[1] Routine ^{13}C NMR spectra were recorded on Agilent 400, 500, or 600 MHz spectrometers with protons fully decoupled. ^{13}C Resonances are reported in ppm relative to solvent residual peaks for $CDCl_3$ (77.16 ppm), CD_2Cl_2 (53.84 ppm) or CD_3OD (49.0 ppm).[1] Note: Small deviations in chemical shifts may be observed depending on the concentration of NMR samples.

Infrared spectra were recorded on a Nicolet 6700 ATR/FT-IR spectrometer, and ν_{max} are partially reported in cm^{-1}. High-resolution mass spectrometry was performed by Chemical and Biophysical Instrumentation Center at Yale University, on a Waters Xevo Q-TOF high-resolution Mass Spectrometry using ESI. Ultra high-performance liquid chromatography-mass spectrometry (UPLC/MS) was performed on a Waters Acquity SQD2 instrument equipped with an Ultra BEH C-18 column (1.7 μm particle size, 2.1 × 50 mm), a dual atmospheric pressure chemical ionization (API)/electrospray ionization S4 (ESI) mass spectrometry detector, and a photodiode array detector. Analytical thinlayer chromatography was performed using 60 Å Silica Gel F254 pre-coated plates (0.25 mm thickness). TLC plates were visualized by irradiation with a UV lamp. R_f values are reported. Normal-phase column chromatography was performed using 60 Å Silica Gel (32–62 micron) with an appropriate mobile phase composition and gradient. Optical rotations were recorded on a Perkin-Elmer Polarimeter 341 at the sodium D-line (589 nm) using a cell of 50 mm path length. Measurements were recorded at 20 ºC. Concentration

values are reported in units of g/100 mL. Normal-phase high-performance liquid chromatography was performed using an Agilent 1100 series instrument equipped with a diode array detector and columns (chiral supports) from Daicel Chemical Industries.

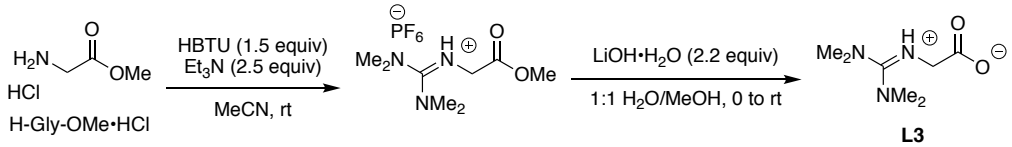
In many cases, normal-phase flash chromatography was performed using a Biotage Isolera One purification system equipped with a 10, 25, 50 or 100 g SNAP Ultra (HP Sphere, 25 μm silica) cartridge and an appropriate EtOAc/Hex linear gradient in the mobile phase. Reversed-phase column chromatography was performed using a Biotage Isolera One purification system equipped with a 15, 30, 60 or 120 g SNAP-C18 column and an appropriate MeOH/H_2O or MeCN/H_2O linear gradient in the mobile phase.

1.1 Abbreviation

Aib	2-aminoisobutyric acid
Boc	*tert*-Butoxycarbonyl
$CDCl_3$	Chloroform-*d*
CD_2Cl_2	Methylene chloride-d_2
CD_3OD	Methanol-d_4
DCM	Dichloromethane
DIPEA	*N,N*-Diisopropylethylamine
DMF	*N,N*-Dimethylformamide
DMSO	Dimethylsulfoxide
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
EtOAc	Ethyl acetate
EtOH	Ethanol
HBTU	(2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
Hex	Hexanes
HOBt	1-Hydroxybenzotriazole
HPLC	High-performance liquid chromatography
HRMS	High-resolution mass spectrometry
IPA	Isopropyl alcohol
LC-MS	Liquid chromatography mass spectrometry
MeCN	Acetonitrile
MeOH	Methanol
NBS	*N*-Bromosuccinimide
rt	Room temperature
TFA	Trifluoroacetic acid, trifluoroacetate
THF	Tetrahydrofuran
TBS	*tert*-Butyldimethylsilyl
UPLC	Ultra Performance Liquid Chromatography
TLC	Thin-layer chromatography
TMG	Tetramethylguanidine
Tol	Toluene

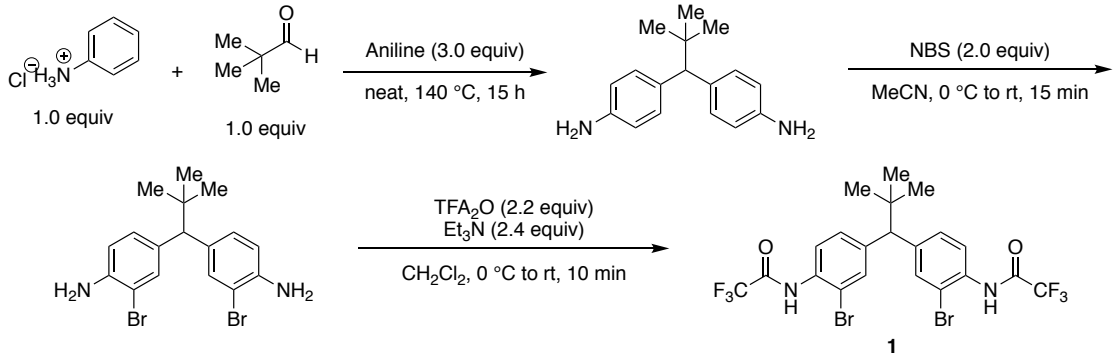
2. Synthesis of Guanidinylated Amino Acid Ligands

Guanidinylated ligands used in this study (**L1**, *ent*-**L2**, **L2**, **L3** and *ent*-**L4**) were prepared by following the previously reported procedures.[2] Example synthesis is shown below:



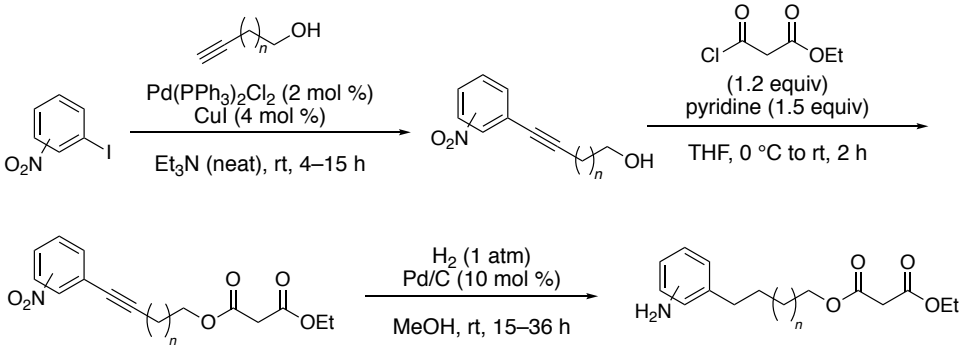
3. Synthesis of Diarylmethane

Diarylmethane **1** was prepared by following the previously reported procedures.[2a]



4. Synthesis of Bifunctional Nucleophiles

4.1 General Synthetic Routes for Bifunctional Nucleophiles:



4.2 General Procedure 1: Sonogashira Coupling

To a flamed-dried RBF equipped with a magnetic stir bar was added aryl iodide (1.00 equiv), $Pd(PPh_3)_2Cl_2$ (0.02 equiv) and CuI (0.04 equiv). Reaction vessel was evacuated and backfilled with $N_2 \times 3$. Dry Et_3N (1.0 M) (distilled over CaH_2 and stored under N_2) was added through the septa. To the stirring mixture was added alcohol (1.20 equiv). Reaction mixture was left to stir for 4–15 h until reaction was complete (monitored by TLC). The reaction mixture was diluted with EtOAc and washed with sat. NH_4Cl (aq). Aqueous layer

was extracted with EtOAc × 3. Combined organic layers were washed with sat. NaCl (aq), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude material was purified by flash chromatography to afford the desired material.

4.3 General Procedure 2: Acylation of Alcohols

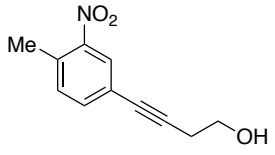
To a flame-dried RBF equipped with magnetic stir bar was added nitrobenzene **S1**–**S8** (1.00 equiv) and anhydrous THF (0.12 M). Reaction mixture was cooled to 0 °C. Dry pyridine (1.50 equiv) distilled over CaH_2 was added dropwise to the stirring mixture. Ethyl malonyl chloride (1.20 equiv) in THF (1.00 M) was subsequently added dropwise to the stirring mixture. Reaction mixture was warmed to room temperature, and left to stir for 2 hours until reaction was complete (monitored by TLC). Reaction mixture was diluted with CH_2Cl_2 and quenched with 10% (w/v) citric acid (aq). Aqueous layer was extracted with CH_2Cl_2 × 3. Combined organic layers were washed with sat. NaCl (aq), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude material was then purified by flash chromatography to afford desired material.

4.4 General Procedure 3: Hydrogenolysis & Nitro Reduction

To a flame-dried RBF equipped with magnetic stir bar was added nitrobenzene **S9–S16** and MeOH (0.5 M). Reaction mixture was sparged with N_2 for 15 minutes. Pd/C (10 wt % – 50% wet with water) was added to the reaction mixture then further sparged with N_2 for 15 minutes. Atmosphere was switched to H_2 via balloon and reaction mixture was left to stir overnight (15 h) at room temperature. The mixture was filtered through Celite ® and concentrated *in vacuo*. The crude material was purified by silica chromatography to afford the desired products.

5. Characterization and Spectra of Bifunctional Nucleophiles and Intermediates

5.1 Cross-coupled Products



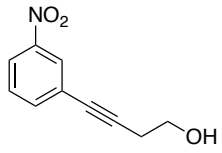
S1

4-(4-methyl-3-nitrophenyl)but-3-yn-1-ol (**S1**) was synthesized from 4-iodo-1-methyl-2-nitrobenzene following **General Procedure 1**. Crude material was purified by silica chromatography (0→40→60% EtOAc/Hex) to yield **S1** as an orange solid (1.5392 g, 99% yield).

TLC (40% EtOAc/Hex): R_f = 0.40.

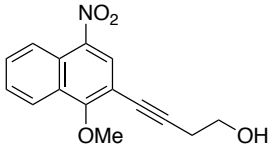
IR (FT-ATR, cm^{-1}, neat): ν_{max} 3245, 2934, 2086, 2078, 1521, 1445, 1377, 1344, 1054, 1025, 857, 667.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.51 – 7.47 (m, 1H), 7.26–25 (m, 1H), 3.83 (t, *J* = 6.2 Hz, 2H), 2.69 (t, *J* = 6.3 Hz, 2H), 2.57 (s, 3H), 1.92 (s, 1H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 149.1, 135.8, 133.3, 132.9, 127.8, 122.7, 88.9, 80.2, 61.1, 23.8, 20.5.
HRMS (ESI/Q-TOF): Exact mass calculated for $[C_{11}H_{11}NO_3 + H]^+$ requires *m/z*= 206.0817, found *m/z* = 206.0820.



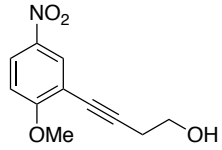
S2

4-(3-nitrophenyl)but-3-yn-1-ol (**S2**) was synthesized from 1-iodo-3-nitrobenzene following **General Procedure 1**. Crude material was purified by silica chromatography (0→40% EtOAc/Hex) to yield **S2** as a beige solid (1.6193 g, 92% yield). Characterization data is in agreement with reported values.[3]



S3

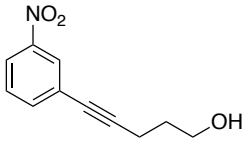
4-(1-methoxy-4-nitronaphthalen-2-yl)but-3-yn-1-ol (**S3**) was was synthesized from 2-iodo-1-methoxy-4-nitronaphthalene[4] following **General Procedure 1**. Crude material was purified by silica chromatography (0→30→60% EtOAc/Hex) to yield **S3** as a yellow solid (1.3970g, 89% yield). Characterization data is in agreement with reported values.[4]



S4

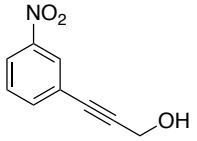
4-(2-methoxy-5-nitrophenyl)but-3-yn-1-ol (**S4**) was synthesized from 2-iodo-1-methoxy-4-nitrobenzene following **General Procedure 1**. Crude material was purified by flash chromatography (0→30→ 50% EtOAc/Hex) to yield **S4** as a beige solid (1.0670 g, 93% yield).
TLC (30% EtOAc/Hex): R_f = 0.27.
^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.25 – 8.22 (m, 1H), 8.16 (dd, *J* = 9.2, 2.7 Hz, 1H), 6.95 (d, *J* = 9.2 Hz, 1H), 3.96 (s, 3H), 3.79 (q, *J* = 6.2 Hz, 2H), 2.71 (t, *J* = 6.2 Hz, 2H), 1.93 (t, *J* = 6.3 Hz, 1H).
^{13}C NMR (101 MHz, CD_2Cl_2) δ 165.2, 144.4, 129.2, 125.6, 114.0, 110.8, 93.8, 76.8, 61.2, 57.1, 24.4.

IR (FT-ATR, cm^{-1}, neat): ν_{max} 3268, 3078, 2947, 2883, 2338, 1577, 1504, 1332, 1266, 1093, 928.
HRMS (ESI/Q-TOF): Exact mass calculated for $[C_{11}H_{11}NO_4 + H]^+$ requires *m/z*= 222.0761, found *m/z* = 222.0755.



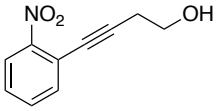
S5

5-(3-nitrophenyl)pent-4-yn-1-ol (**S5**) was synthesized from 1-iodo-3-nitrobenzene following **General Procedure 1.** Crude material was purified by silica chromatography (0→30→60% EtOAc/Hex) to yield **S5** as a pale yellow oil (1.7003g, quantitative yield). Characterization data is in agreement with reported values.[5]



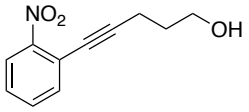
S6

3-(3-nitrophenyl)prop-2-yn-1-ol (**S6**) was synthesized from 1-iodo-3-nitrobenzene following **General Procedure 1**. Crude material was purified by silica chromatography (0→40% EtOAc/Hex) to yield **S6** as a light brown oil (0.4808 g, 92% yield). Characterization data is in agreement with reported values.[6]



S7

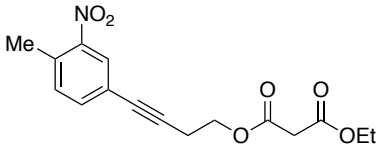
4-(2-nitrophenyl)but-3-yn-1-ol (**S7**) was synthesized from 1-iodo-2-nitrobenzene following **General Procedure 1**. Crude material was purified by silica chromatography (0 →50 →80% EtOAc/Hex) to yield **S7** as a brown oil (3.7858 g, 98% yield).
TLC (50% EtOAc/Hex): 0.46.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05–7.96 (m, 1H), 7.68–7.51 (m, 2H), 7.48–7.38 (m, 1H), 3.86 (t, *J* = 6.0 Hz, 2H), 2.75 (t, *J* = 6.0 Hz, 2H), 2.16 (s, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 150.2, 134.8, 133.0, 128.5, 124.8, 118.9, 95.8, 78.1, 61.0, 24.4.
IR (FT-ATR, cm^{-1}, neat): ν_{max} 3373, 2886, 2335, 1519, 1479, 1340, 1039, 743.
HRMS (ESI/Q-TOF): Exact mass calculated for $[C_{10}H_9NO_3 + H]^+$ requires *m/z*= 192.0655, found *m/z* = 192.0665.



S8

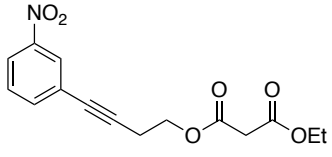
5-(2-nitrophenyl)pent-4-yn-1-ol (**S8**) was synthesized from 1-iodo-2-nitrobenzene following **General Procedure 1**. Crude material was purified by silica chromatography (0→50→80% EtOAc/Hex) to yield **S8** as a brown oil (2.8462 g, 84% yield). Characterization data is in agreement with reported values.[7]

5.2 Acylation Products



S9

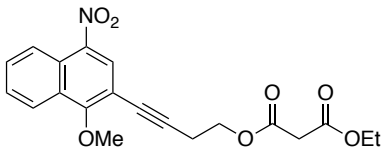
Ethyl (4-(4-methyl-3-nitrophenyl)but-3-yn-1-yl) malonate (**S9**) was synthesized from **S1** following **General Procedure 2**. Crude material was purified by silica chromatography (0→20→50% EtOAc/Hex) to yield **S9** as a pale yellow oil **(**1.2873 g, 69% yield).
TLC (30% EtOAc/Hex): R_f = 0.48.
IR (FT-ATR, cm^{-1}, neat): ν_{max} 2991, 2119, 1731, 1527, 1332, 1145, 1030, 832.
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.99 (d, *J* = 1.3 Hz, 1H), 7.50 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.27 (d, *J* = 7.4 Hz, 1H), 4.34 (t, *J* = 6.8 Hz, 2H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.42 (s, 2H), 2.79 (t, *J* = 6.8 Hz, 2H), 2.58 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 2H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 166.5, 166.5, 149.2, 135.8, 133.4, 132.9, 127.8, 122.6, 87.4, 80.0, 63.1, 61.8, 41.6, 20.5, 19.9, 14.2.
HRMS (ESI/Q-TOF): Exact mass calculated for $[C_{16}H_{17}NO_6 + H]^+$ requires *m/z*= 320.1129, found *m/z* = 320.1143.



S10

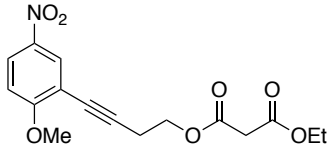
Ethyl (4-(3-nitrophenyl)but-3-yn-1-yl) malonate (**S10**) was synthesized from **S2** following **General Procedure 2**. Crude material was purified by silica chromatography (0→30→ 50% EtOAc/Hex) to yield **S10** as a pale yellow oil (1.9685 g, 76 % yield).
TLC (20% EtOAc/Hex): R_f = 0.38.
IR (FT-ATR, cm^{-1}, neat): ν_{max} 3084, 2961, 2114, 1730, 1528, 1369, 1350, 1144, 1030, 899.
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.24 (s, 1H), 8.13 (d, *J* = 8.2 Hz, 1H), 7.69 (d, *J* = 7.7 Hz, 1H), 7.47 (t, *J* = 8.0 Hz, 1H), 4.35 (t, *J* = 6.7 Hz, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.42 (s, 2H), 2.80 (t, *J* = 6.7 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.5, 166.4, 148.2, 137.5, 129.4, 126.6, 125.2, 122.9, 88.3, 80.1, 63.0, 61.8, 41.6, 19.9, 14.2.
HRMS(ESI/Q-TOF): Exact mass calculated for $[C_{15}H_{15}NO_6 + H]^+$ requires *m/z*= 306.0972, found *m/z* = 306.0970.



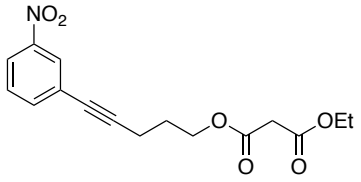
S11

Ethyl (4-(1-methoxy-4-nitronaphthalen-2-yl)but-3-yn-1-yl) malonate (**S11**) was synthesized from **S3** following **General Procedure 2**. Crude material was purified by silica chromatography (0→25% EtAOc/Hex) to yield **S11** as a yellow oil (0.8845 g, 87% yield).
TLC (30% EtOAc/Hex): R*f* = 0.35.
IR (FT-ATR, cm^{-1}, neat): ν_{max} 2965, 2906, 2084, 1751, 1720, 1620, 1511, 1321, 1269, 1143, 1037, 785.
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.62 (d, *J* = 8.7 Hz, 1H), 8.30 (dd, *J* = 9.0, 1.5 Hz, 2H), 7.73 (ddd, *J* = 8.7, 6.9, 1.4 Hz, 1H), 7.62 (ddd, *J* = 8.3, 6.9, 1.2 Hz, 1H), 4.40 (t, *J* = 6.7 Hz, 2H), 4.29 (s, 3H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.43 (s, 2H), 2.90 (t, *J* = 6.7 Hz, 2H), 1.28 (t, *J* = 7.2 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 166.5, 166.4, 162.5, 141.3, 130. 4, 130.2, 128.6, 127.7, 126.3, 123.6, 123.4, 108.5, 92.5, 77.6, 63.1, 61.9, 61.8, 41.6, 20.3, 14.2.
HRMS(ESI/Q-TOF): Exact mass calculated for $[C_{20}H_{19}NO_7 + H]^+$ requires *m/z*= 386.1234, found *m/z* = 386.1231.



S12

Ethyl (4-(2-methoxy-5-nitrophenyl)but-3-yn-1-yl) malonate (**S12**) was synthesized from **S4** following **General Procedure 2**. Crude material was purified by silica chromatography (10 →50% EtOAc/Hex) to yield the desired product **S12** as a yellow oil (1.5077 g, quantitative yield).
TLC (50% EtOAc/Hex): R_f = 0.50
IR (FT-ATR, cm^{-1}, neat): ν_{max} 3080, 2970, 1729, 1514, 1340, 1230, 1013, 749.
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.27 (d, *J* = 2.8 Hz, 1H), 8.18 (dd, *J* = 9.2, 2.8 Hz, 1H), 6.92 (d, *J* = 9.2 Hz, 1H), 4.36 (t, *J* = 6.9 Hz, 2H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.98 (s, 3H), 3.42 (s, 2H), 2.85 (t, *J* = 6.9 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$): δ 166.6, 166.5, 164.7, 141.2, 129.4, 125.5, 113.7, 110.3, 91.8, 76.4, 63.1, 61.8, 56.7, 41.6, 20.2, 14.2.
HRMS(ESI/Q-TOF): Exact mass calculated for $[C_{16}H_{17}NO_7 + Na]^+$ requires *m/z*= 358.0897, found *m/z* = 358.0926.



S13

Ethyl (5-(3-nitrophenyl)pent-4-yn-1-yl) malonate (**S13**) was synthesized from **S5** following **General Procedure 2**. Crude material was purified by silica chromatography (0→30→50% EtOAc/Hex) to provide the desired product as a yellow oil (2.1051 g, 89% yield).

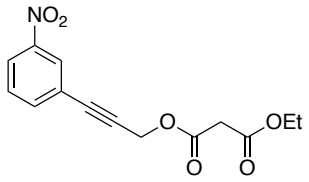
TLC (40% EtOAc/Hex): R_f = 0.50.

IR (FT-ATR, cm^{-1}, neat): ν_{max} 2961, 2324, 1729, 1528, 1368, 1349, 1146, 1031, 761, 674.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 8.17 – 8.08 (m, 1H), 7.68 (d, *J* = 7.7 Hz, 1H), 7.46 (t, *J* = 8.0 Hz, 1H), 4.32 (t, *J* = 6.2 Hz, 2H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.40 (s, 2H), 2.55 (t, *J* = 7.0 Hz, 2H), 1.98 (p, *J* = 6.7 Hz, 2H), 1.29 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7, 166.6, 148.2, 137.5, 129.4, 126.6, 125.6, 122.7, 91.6, 79.4, 64.1, 61.8, 48.4, 41.7, 27.6, 16.2, 14.2.

HRMS (ESI/Q-TOF): Exact mass calculated for $[C_{16}H_{17}NO_6 + H]^+$ requires *m/z*= 320.1129, found *m/z* = 320.1132.



S14

Ethyl (3-(3-nitrophenyl)prop-2-yn-1-yl) malonate (**S14**) was synthesized from **S6** following **General Procedure 2**. The crude material was then purified by silica chromatography (0→30→50% EtOAc/Hex) followed by reversed-phase chromatography (0→95% MeCN/H_2O) to provide the desired product as a clear oil (0.5711 g, 72% yield).

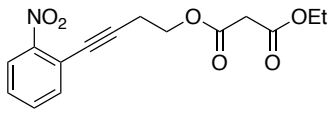
TLC (40% EtOAc/Hex): R_f = 0.64.

IR (FT-ATR, cm^{-1}, neat): ν_{max} 3084, 2964, 2324, 1754, 1731, 1529, 1370, 1350, 1140, 1029, 762, 735.

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.32 – 8.29 (m, 1H), 8.20 (ddd, *J* = 8.3, 2.2, 0.9 Hz, 1H), 7.75 (d, *J* = 7.7 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 1H), 4.99 (s, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.47 (s, 2H), 1.29 (t, *J* = 7.1 Hz, 3H).

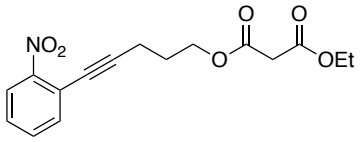
^{13}C NMR (151 MHz, $CDCl_3$): δ 166.2, 166.0, 148.2, 137.6, 129.6, 126.9, 124.0, 123.8, 85.1,84.5, 61.9, 53.4, 41.4, 14.2.

HRMS (ESI/Q-TOF): Exact mass calculated for $[C_{14}H_{13}NO_6 + H]^+$ requires *m/z*= 292.0816, found *m/z* = 292.0844.



S15

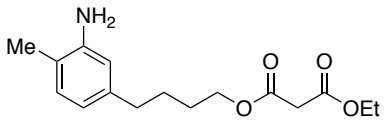
Ethyl (4-(2-nitrophenyl)but-3-yn-1-yl) malonate (**S15**) was synthesized from **S7** following **General Procedure 2**. Crude material was purified by silica chromatography (0→25→40% EtOAc/Hex) to provide the desired product as a yellow oil (453.3 g, quantitative yield).
TLC (30% EtOAc/Hex): R_f = 0.54.
IR (FT-ATR, cm^{-1}, neat): ν_{max} 2982, 2119, 1730, 1609, 1524, 1369, 1340, 1144, 1030, 745.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.2 Hz, 1H), 7.56 (dt, *J* = 15.0, 7.7 Hz, 2H), 7.43 (t, *J* = 7.7 Hz, 1H), 4.37 (t, *J* = 6.7 Hz, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.44 (s, 2H), 2.85 (t, *J* = 6.7 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6, 166.5, 150.3, 135.0, 132.8, 128.6, 124.6, 118.7, 93.9, 77.6, 62.9, 61.7, 41.6, 20.3, 14.2.
HRMS (ESI/Q-TOF): Exact mass calculated for $[C_{15}H_{17}NO_6 + H]^+$ requires *m/z* = 306.0972, found *m/z* = 306.0976.



S16

Ethyl (5-(2-nitrophenyl)pent-4-yn-1-yl) malonate (**S16**) was synthesized from **S8** following **General Procedure 2**. Crude material was purified by silica chromatography (0→30→ 60% EtOAc/Hex) to provide the desired product as a yellow oil (0.3277 g, 92% yield).
TLC (30% EtOAc/Hex): R_f = 0.48.
IR (FT-ATR, cm^{-1}, neat): ν_{max} 2981, 2230, 1728, 1524, 1368, 1341, 1186, 1145, 1030, 745.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.3 Hz, 1H), 7.54 (dt, *J* = 15.0, 7.7 Hz, 2H), 7.41 (t, *J* = 7.7 Hz, 1H), 4.34 (t, *J* = 6.2 Hz, 2H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.39 (s, 2H), 2.59 (t, *J* = 7.0 Hz, 2H), 2.00 (p, *J* = 6.6 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7, 166.7, 150.2, 134.9, 132.8, 128.3, 124.6, 119.0, 97.3, 76.9, 64.1, 61.7, 41.7, 27.5, 16.6, 14.2.
HRMS (ESI/Q-TOF): Exact mass calculated for $[C_{16}H_{17}NO_6 + H]^+$ requires *m/z*= 342.0952, found *m/z* = 342.0948.

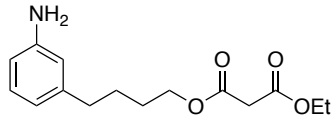
5.3 Hydrogenolysis Products: Bifunctional Nucleophiles



2a

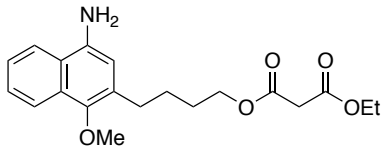
4-(3-amino-4-methylphenyl)butyl ethyl malonate (**2a**) was synthesized from **S9** following **General Procedure 3**. The crude material was purified by flash chromatography (0→40% EtOAc/Hex) to yield the desired product as a pale yellow oil (1.1674 g, 98% yield).

TLC (40% EtOAc/Hex): 0.50.
IR (FT-ATR, cm^{-1}, neat): ν_{max} 3466, 3378, 2937, 2660, 2101, 1727, 1627, 1329, 1270, 1146, 1030, 734.
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.95 (d, *J* = 7.5 Hz, 1H), 6.65 – 6.39 (m, 2H), 4.29 – 3.92 (m, 4H), 3.56 (s, 2H), 3.36 (s, 2H), 2.53 (t, *J* = 7.0 Hz, 2H), 2.13 (s, 3H), 1.81 – 1.56 (m, 4H), 1.27 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 166.8, 166.7, 144.6, 140.9, 130.5, 120.0, 118.8, 115.1, 65.6, 61.7, 41.8, 35.1, 28.2, 27.6, 17.1, 14.2.
HRMS (ESI/Q-TOF): Exact mass calculated for $[C_{16}H_{23}NO_4+H]^+$ requires *m/z*= 294.1700, found *m/z* = 294.1697.



2b

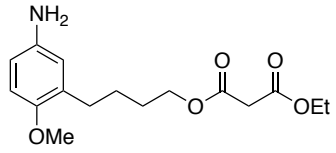
4-(3-aminophenyl)butyl ethyl malonate (**2b**) was synthesized from **S10** following **General Procedure 3**. The crude material was purified by flash chromatography (0→30→50% EtOAc/Hex) to provide the desired product as a pale yellow oil (2.2495 g, 90% yield).
TLC (40% EtOAc/Hex): R_f =0.50.
IR (FT-ATR, cm^{-1}, neat): 3467, 3376, 2941, 2860, 1725, 1622, 1331, 1268, 1148, 1030, 866. , 734.
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.06 (t, *J* = 7.6 Hz, 1H), 6.58 (d, *J* = 7.5 Hz, 1H), 6.53 (d, *J* = 7.6 Hz, 2H), 4.27 – 3.96 (m, 4H), 3.69 (s, 1H), 3.36 (s, 2H), 2.55 (t, *J* = 7.0 Hz, 2H), 1.67 (dd, *J* = 6.6, 3.1 Hz, 6H), 1.27 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$): δ 166.8, 166.7, 146.4, 143.3, 129.4, 119.0, 115.4, 113.0, 65.6, 61.7, 41.8, 35.5, 28.2, 27.5, 14.2.
HRMS (ESI/Q-TOF): Exact mass calculated for $[C_{15}H_{21}NO_4 + H]^+$ requires *m/z*= 280.1549, found *m/z* = 280.1561.



2c

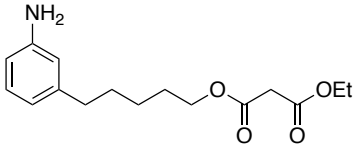
4-(4-amino-1-methoxynaphthalen-2-yl)butyl ethyl malonate (**2c**) was synthesized from **S11** following **General Procedure 3**. The crude material was purified by flash chromatography (0→50→70% EtOAc/Hex) to yield **2c** as a purple oil (1.6614 g, quantitative yield).
TLC (50% EtOAc/Hex): R_f = 0.57.
IR (FT-ATR, cm^{-1}, neat): ν_{max} 3444, 3367, 2936, 2864, 2108, 1981, 1725, 1628, 1464, 1382, 1370, 1228, 1148, 1030, 764, 708.
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.4 Hz, 1H), 7.81 (d, *J* = 8.4 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 1H), 6.66 (s, 1H), 4.24 – 4.13 (m, 4H), 3.85 (s, 3H), 3.36 (s, 2H), 2.78 – 2.73 (m, 2H), 1.74 (p, *J* = 3.5 Hz, 4H), 1.25 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 166.8, 166.7, 146.8, 137.7, 130.4, 128.7, 126.1, 124.8, 124.0, 122.7, 121.4, 112.0, 77.2, 65.5, 62.2, 61.7, 41.8, 29.2, 28.4, 27.0, 14.2.
HRMS (ESI/Q-TOF): Exact mass calculated for $[C_{20}H_{25}NO_5 + H]^+$ requires *m/z* = 360.1806, found *m/z* = 360.1810.



2d

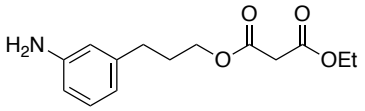
4-(5-amino-2-methoxyphenyl)butyl ethyl malonate (**2d**) was synthesized from **S12** following **General Procedure 3**. The crude material was purified by flash chromatography (0→45→70 % EtOAc/Hex) to yield **2d** as a red-brown oil (1.2556 g, 93% yield).
TLC (40% EtOAc/Hex): R_f = 0.41.
IR (FT-ATR, cm^{-1}, neat): ν_{max} 3442, 3365, 2943, 2832, 2114, 1726, 1501, 1369, 1229, 1146, 1029, 855.
^{1}H NMR (600 MHz, $CDCl_3$): δ 6.69 – 6.65 (m, 1H), 6.51 (d, *J* = 6.4 Hz, 2H), 4.19 (dt, *J* = 20.8, 6.9 Hz, 4H), 3.74 (s, 3H), 3.43 – 3.34 (m, 4H), 2.56 (t, *J* = 7.4 Hz, 2H), 1.66 (dp, *J* = 31.5, 8.4, 7.7 Hz, 4H), 1.27 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$): 166.9, 166.8, 151.0, 139.8, 131.5, 117.8, 113.6, 111.9, 65.7, 61.7, 56.1, 41.9, 29.7, 28.3, 26.2, 14.2.
HRMS (ESI/Q-TOF): Exact mass calculated for $[C_{16}H_{23}NO_5+H]^+$ requires *m/z*= 310.1649, found *m/z* = 310.1678.



2e

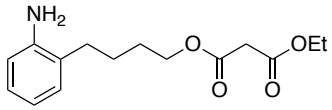
5-(3-aminophenyl)pentyl ethyl malonate (**2e**) was synthesized from **S13** following **General Procedure 3**. The crude material was purified by silica chromatography (0→40% EtOAc/Hex) to yield **2e** as an orange-yellow oil (1.6596 g, 94% yield).
TLC (40% EtOAc/Hex): R_f = 0.50.
IR (FT-ATR, cm^{-1}, neat): ν_{max} 3467, 3376, 2936, 2857, 1723, 1622, 1330, 1272, 1148, 1031, 955.
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.07 (t, *J* = 7.9 Hz, 1H), 6.59 (d, *J* = 7.5 Hz, 1H), 6.54 (d, *J* = 7.0 Hz, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 4.14 (t, *J* = 6.7 Hz, 2H), 3.72 (brs, 2H), 3.36 (s, 2H), 2.60 – 2.45 (m, 2H), 1.76 – 1.56 (m, 4H), 1.46 – 1.34 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 166.8, 166.7, 146.1, 143.8, 129.3, 119.2, 115.6, 113.0, 65.7, 61.6, 41.8, 35.9, 30.9, 28.5, 25.6, 14.2.
HRMS (ESI/Q-TOF): Exact mass calculated for $[C_{20}H_{25}NO_5 + H]^+$ requires *m/z* = 294.1700, found *m/z* = 294.1689.



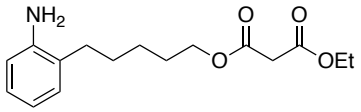
S17

3-(3-aminophenyl)propyl ethyl malonate (S17) was synthesized from **S14** following **General Procedure 3**. The crude material was purified by flash chromatography (0→20→40% EtOAc/Hex) to yield the **S17** as an orange oil (0.1053 g, 38% yield).
TLC (40% EtOAc/Hex): R_f = 0.38.
IR (FT-ATR, cm^{-1}, neat): ν_{max} 3467, 3376, 2981, 2348, 1724, 1623, 1604, 1330, 1271, 1148, 1028, 911.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (t, *J* = 7.7 Hz, 1H), 6.58 (d, *J* = 7.4 Hz, 1H), 6.53 (d, *J* = 7.6 Hz, 2H), 4.21 (q, *J* = 7.1 Hz, 2H), 4.16 (t, *J* = 6.5 Hz, 2H), 3.87 (brs, 2H), 3.38 (s, 2H), 2.66–2.38 (m, 2H), 2.05–1.86 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8, 166.7, 146.5, 142.4, 129.5, 118.9, 115.4, 113.1, 65.0, 61.7, 41.8, 32.1, 30.0, 14.2.
HRMS (ESI/Q-TOF): Exact mass calculated for $[C_{14}H_{19}NO_4 + H]^+$ requires *m/z* = 266.1388, found *m/z* = 266.1387.



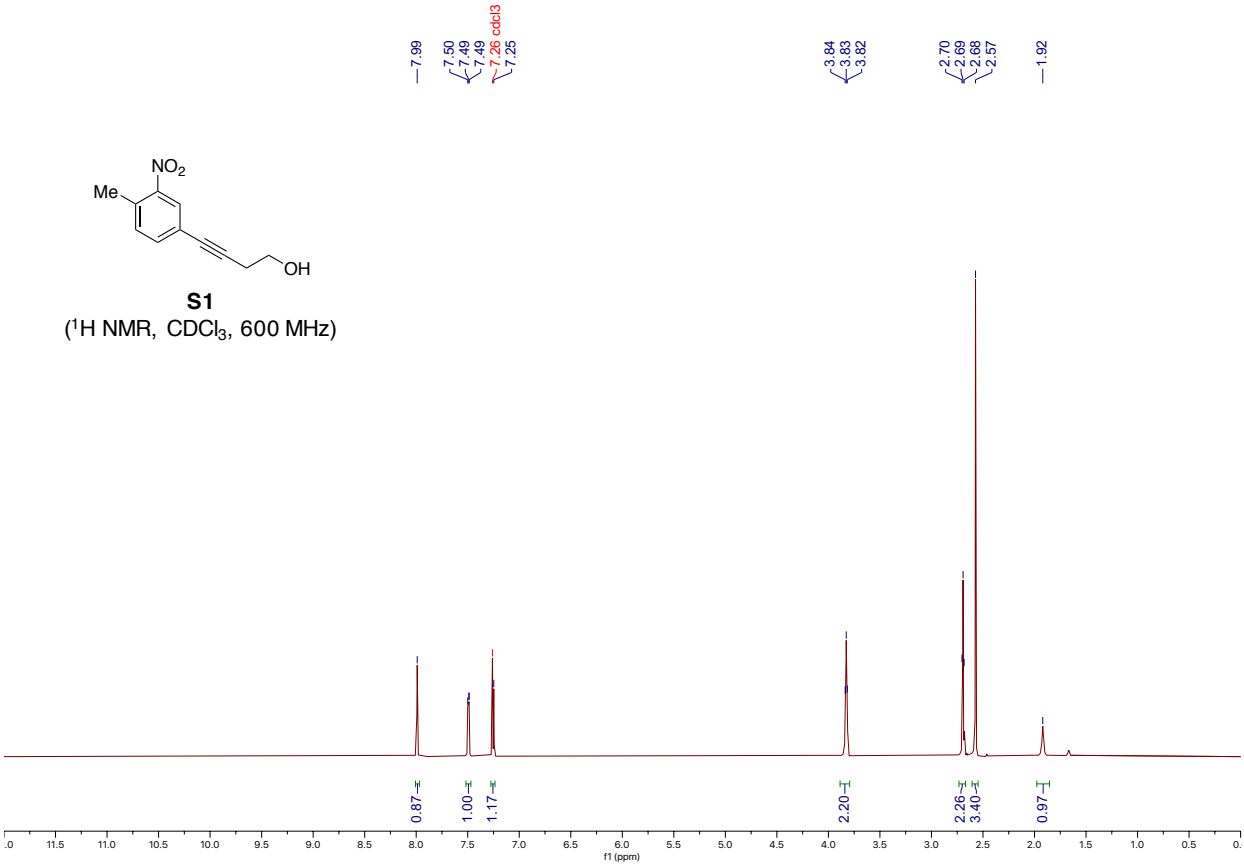
S18

4-(2-aminophenyl)butyl ethyl malonate (**S18**) was synthesized from **S15** following **General Procedure 3**. The crude material was purified by flash chromatography (0→40→75% EtOAc/Hex) to yield **S4** as a pale yellow oil (0.1119 g, 89% yield).
TLC (40% EtOAc/Hex): R_f = 0.59.
IR (FT-ATR, cm^{-1}, neat): ν_{max} 3470, 3378, 2940, 2865, 2101, 1725, 1625, 1497, 1330, 1271, 1147, 1030, 749.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 – 6.99 (m, 2H), 6.73 (t, *J* = 7.4 Hz, 1H), 6.68 (d, *J* = 7.8 Hz, 1H), 4.26 – 4.07 (m, 4H), 3.37 (s, 2H), 2.53 (t, *J* = 7.3 Hz, 2H), 1.90 – 1.62 (m, 6H), 1.27 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9, 166.7, 144.2, 129.6, 127.2, 126.1, 118.9, 115.8, 77.2, 65.4, 61.7, 41.8, 30.9, 28.5, 25.0, 14.2.
HRMS (ESI/Q-TOF): Exact mass calculated for $[C_{15}H_{21}NO_4 + H]^+$ requires *m/z* = 280.1542, found *m/z* = 280.1543.

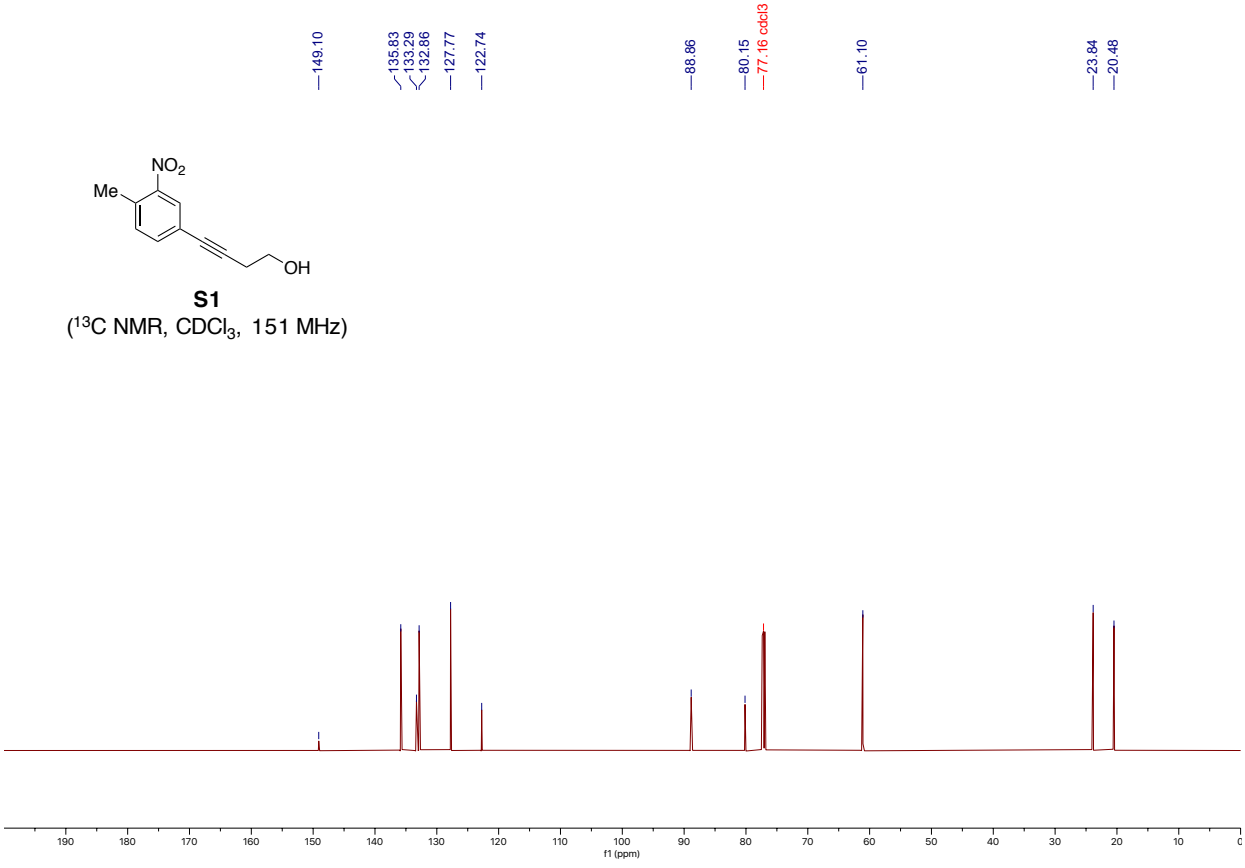


S19

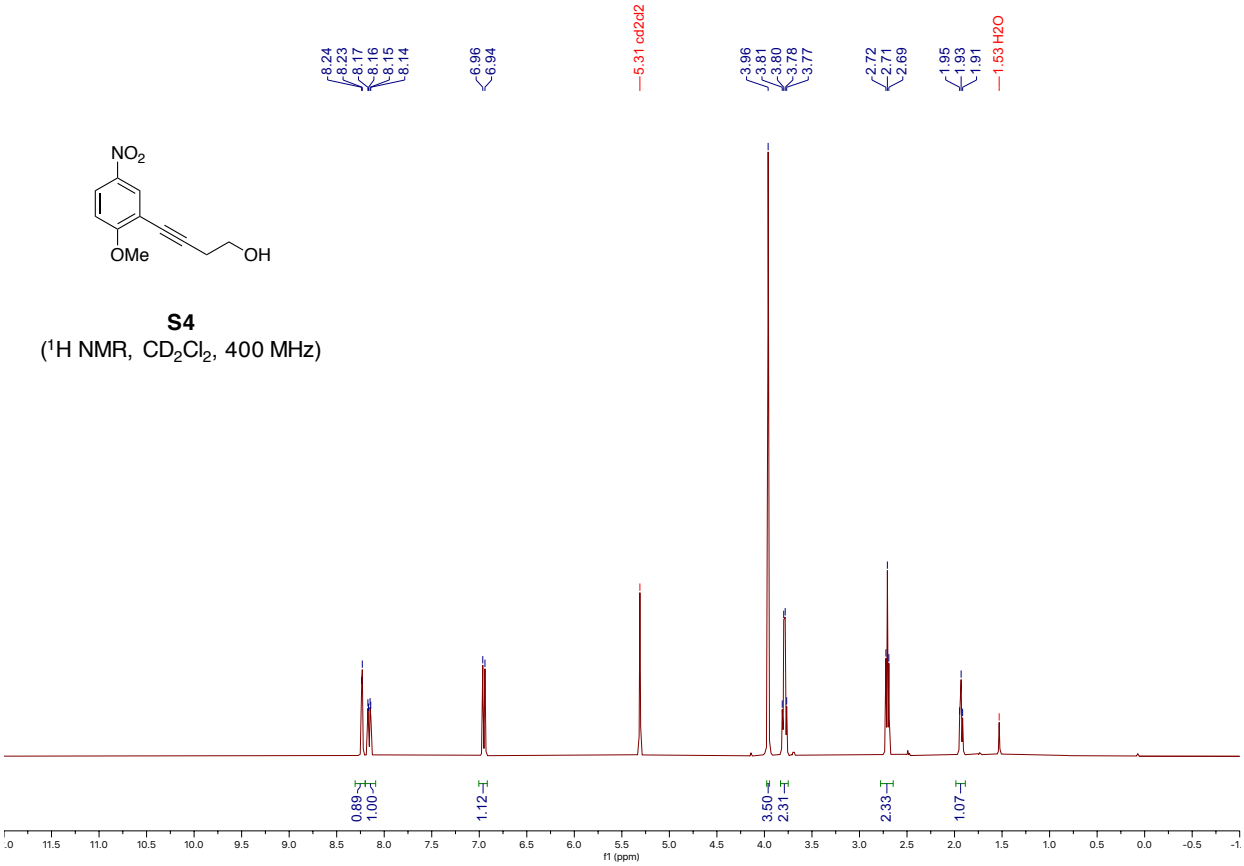
5-(2-aminophenyl)pentyl ethyl malonate (**S19**) was synthesized from **S16** following **General Procedure 3**. The crude material was purified by flash chromatography (0→35→70% EtOAc/Hex) to yield **S19** as an orange oil (0.2561 g, 82% yield).
TLC (40% EtOAc/Hex): R_f = 0.61.
IR (FT-ATR, cm^{-1}, neat): ν_{max} 3466, 3380, 2935, 2860, 2113, 1725, 1624, 1497, 1330, 1269, 1147, 1031, 749.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (d, *J* = 7.4 Hz, 2H), 6.77 – 6.61 (m, 2H), 4.31 – 4.06 (m, 4H), 3.69 (d, *J* = 10.3 Hz, 1H), 3.37 (s, 2H), 2.71 – 2.43 (m, 2H), 1.86 – 1.61 (m, 6H), 1.45 (p, *J* = 7.5 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 166.8, 166.7, 144.1, 129.6, 127.1, 126.6, 119.0, 115.8, 65.6, 61.7, 41.8, 31.3, 28.5, 28.4, 25.9, 14. 2.
HRMS (ESI/Q-TOF): Exact mass calculated for $[C_{16}H_{23}NO_4 + H]^+$ requires *m/z* = 294.1696, found *m/z* = 294.1700.



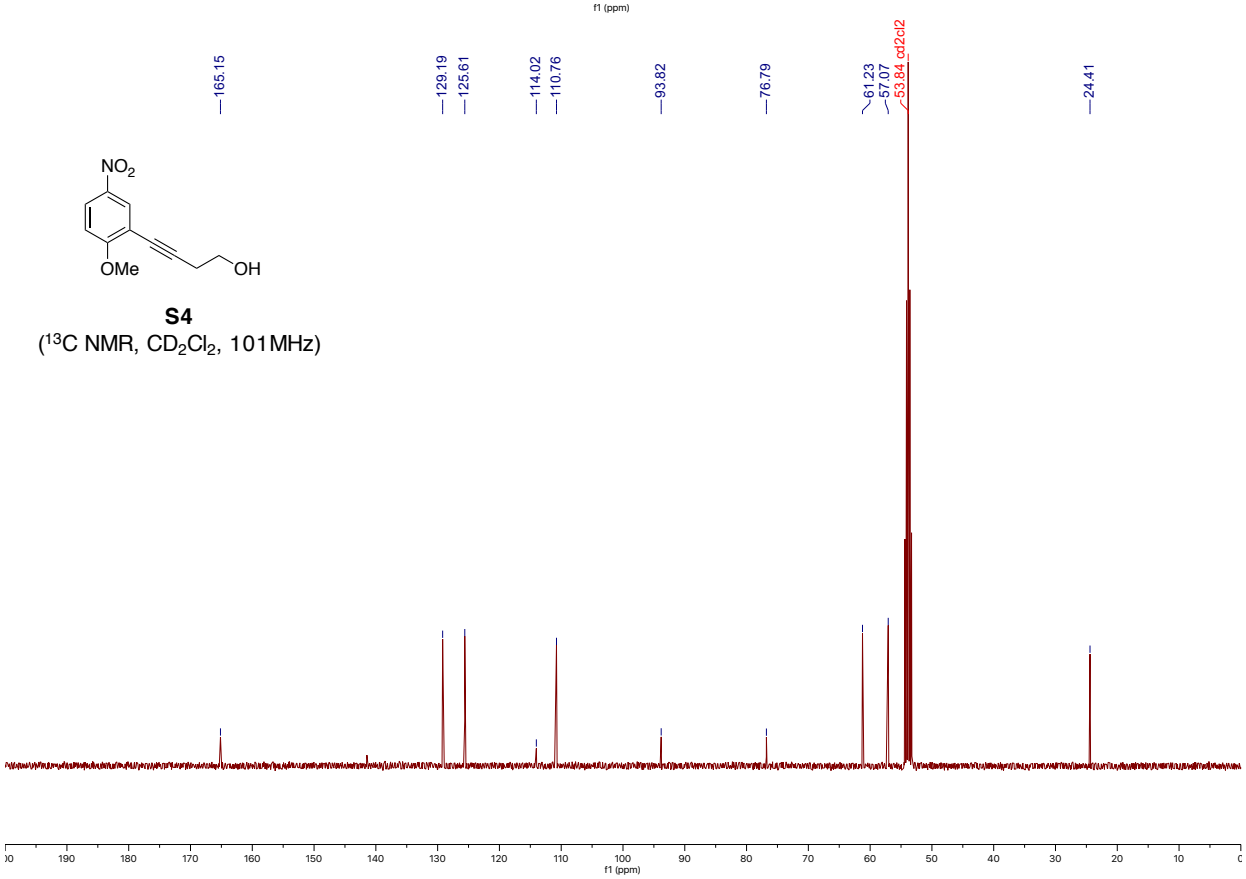
S1
(^{1}H NMR, $CDCl_3$, 600 MHz)



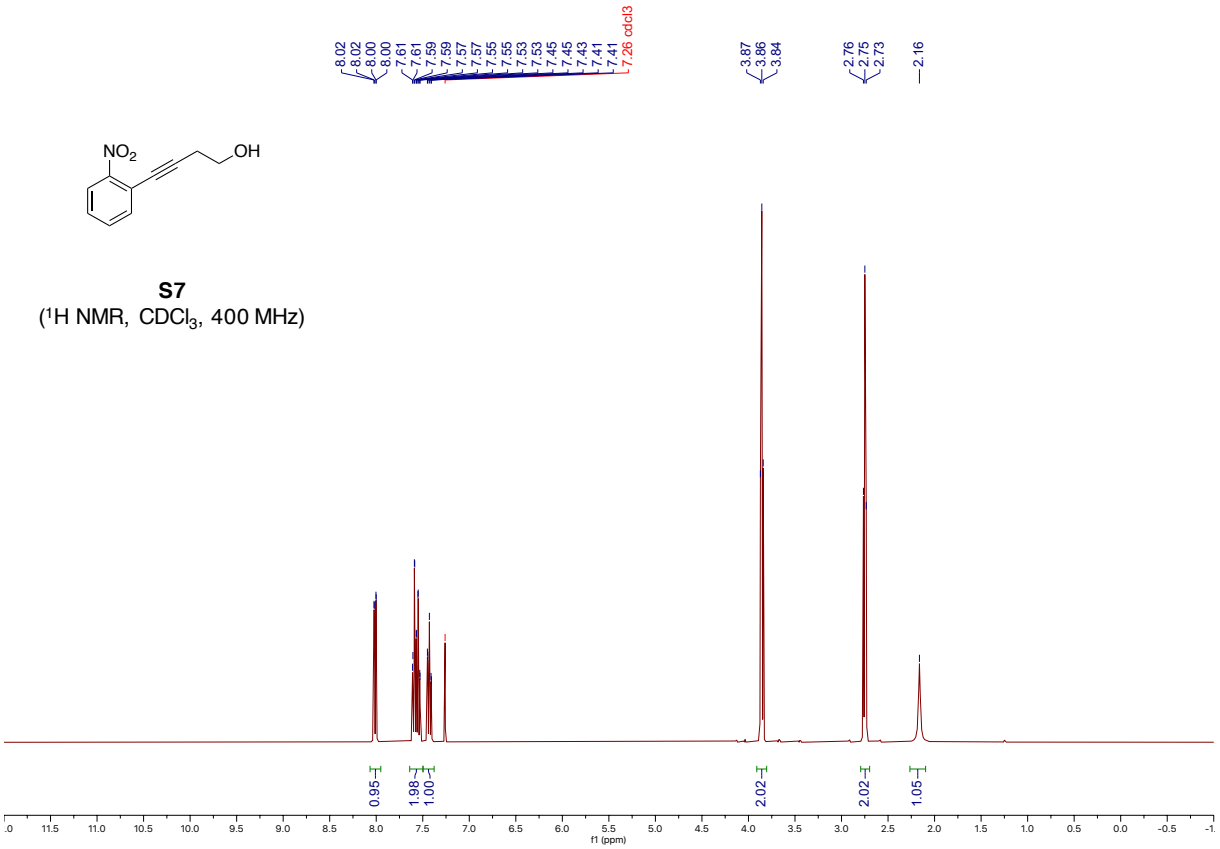
S1
(^{13}C NMR, $CDCl_3$, 151 MHz)



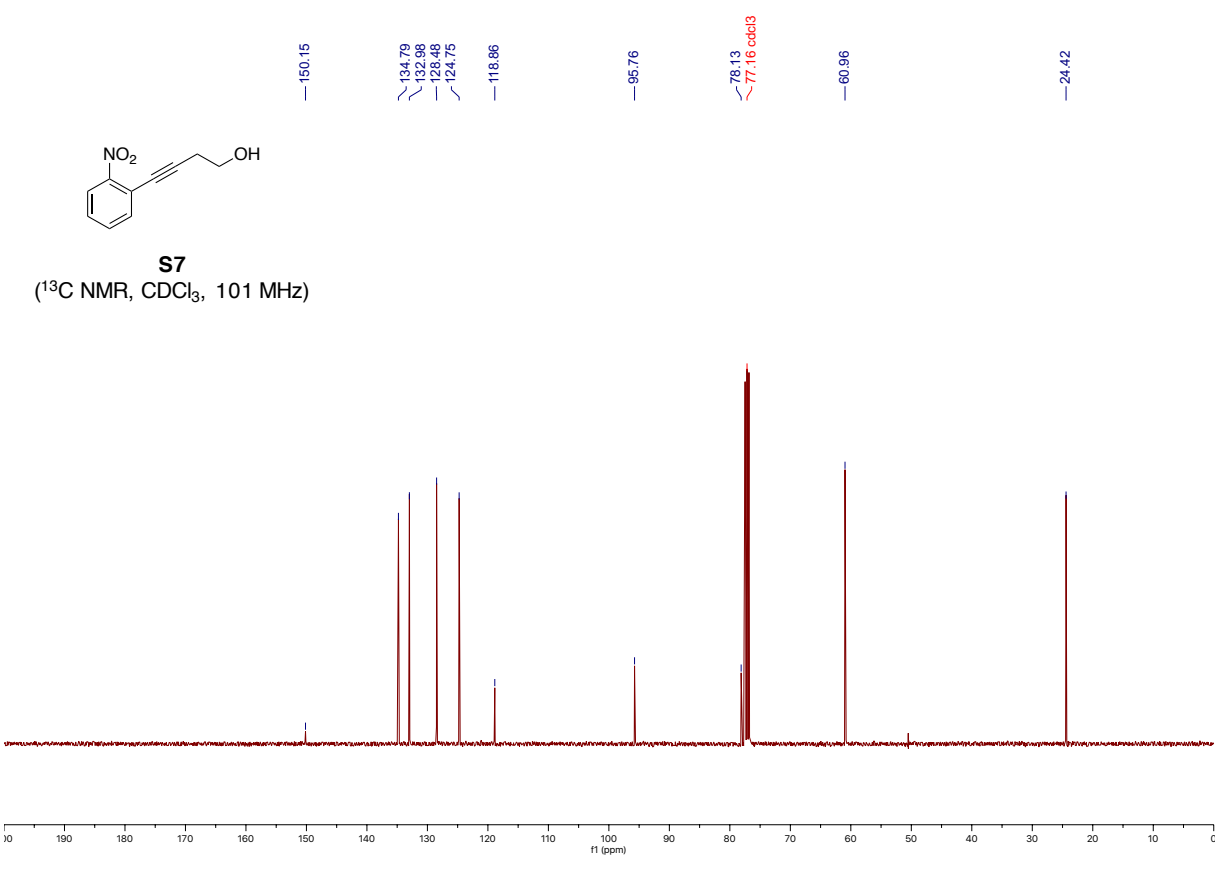
S4
(^{1}H NMR, CD_2Cl_2, 400 MHz)



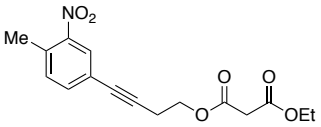
S4
(^{13}C NMR, CD_2Cl_2, 101MHz)



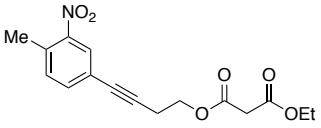
S7
(^{1}H NMR, $CDCl_3$, 400 MHz)



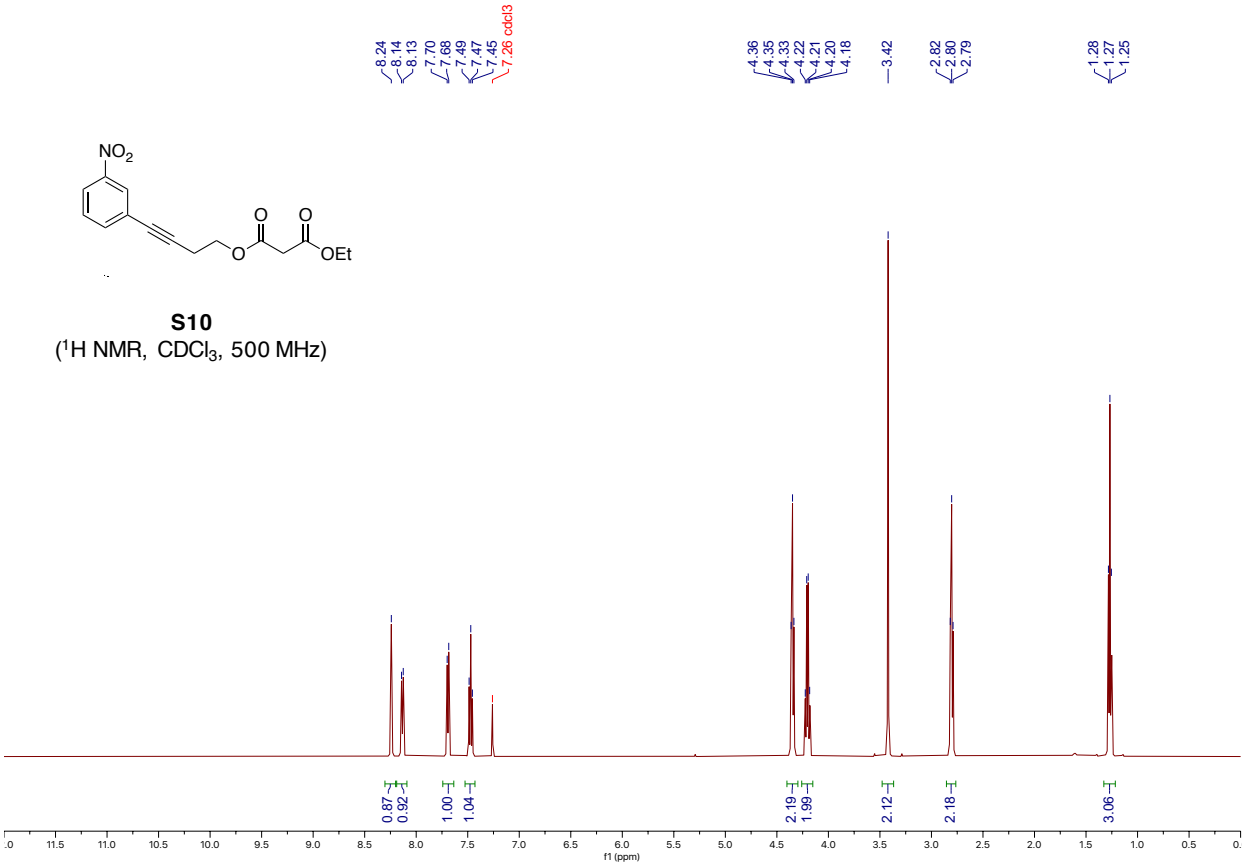
S7
(^{13}C NMR, $CDCl_3$, 101 MHz)



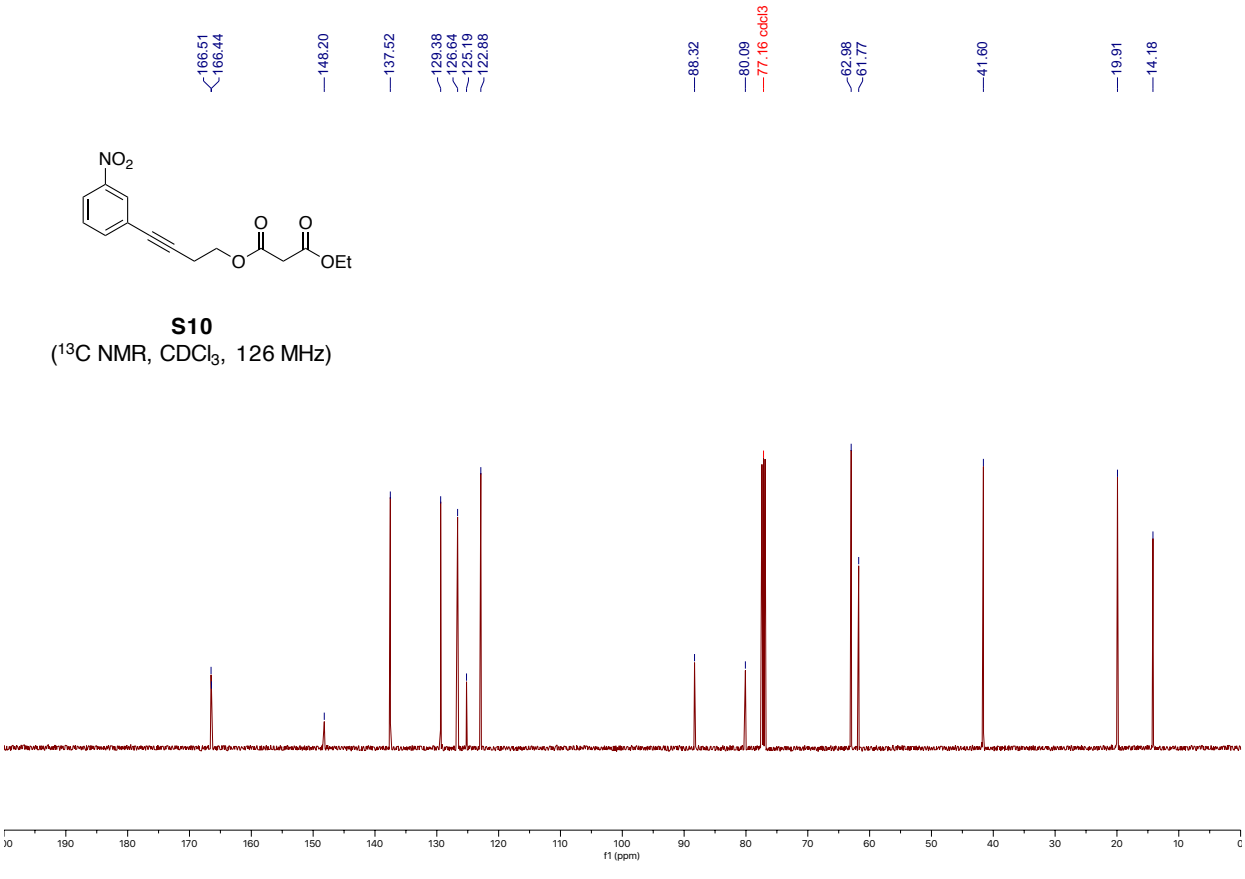
S9
(^{1}H NMR, $CDCl_3$, 600 MHz)



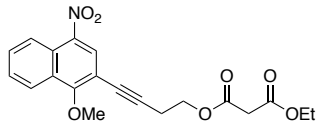
S9
(^{13}C NMR, $CDCl_3$, 151 MHz)



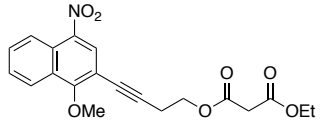
S10
(^{1}H NMR, $CDCl_3$, 500 MHz)



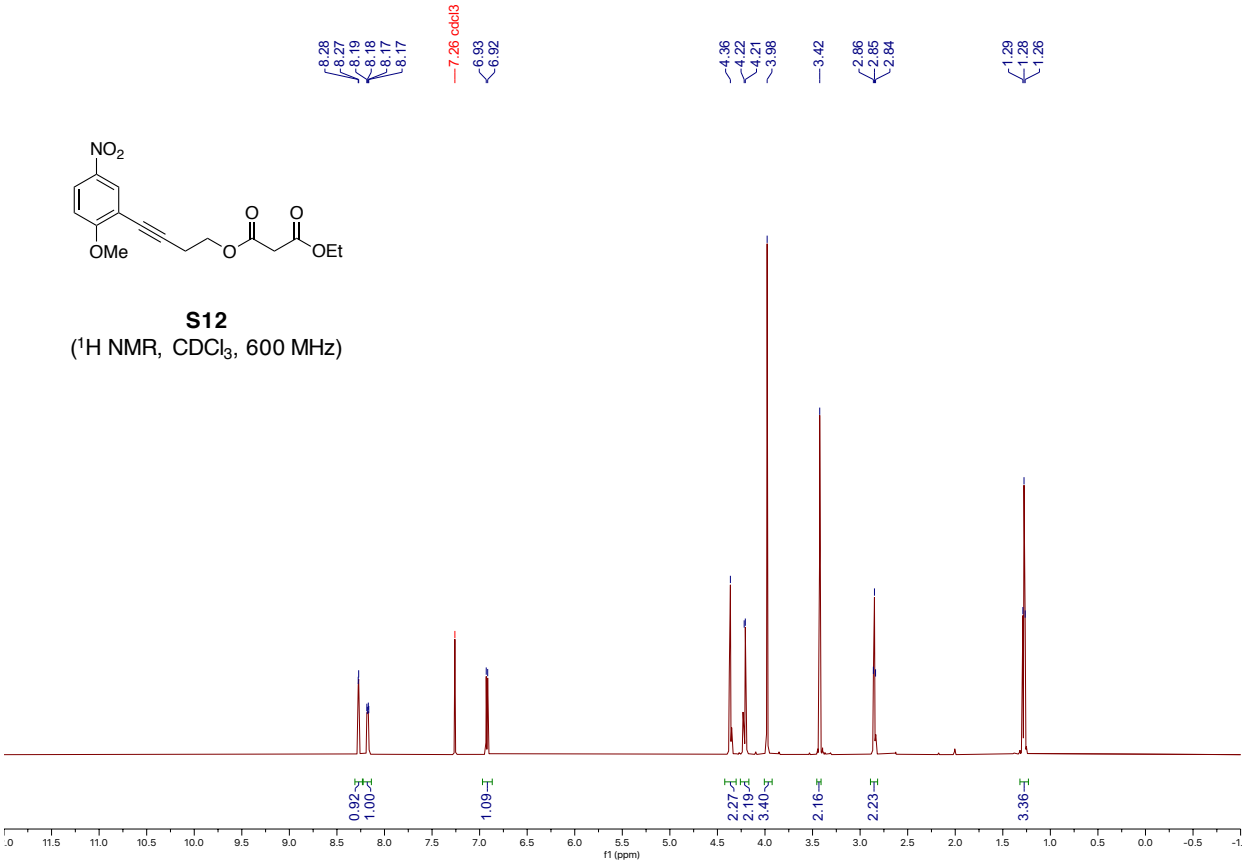
S10
(^{13}C NMR, $CDCl_3$, 126 MHz)



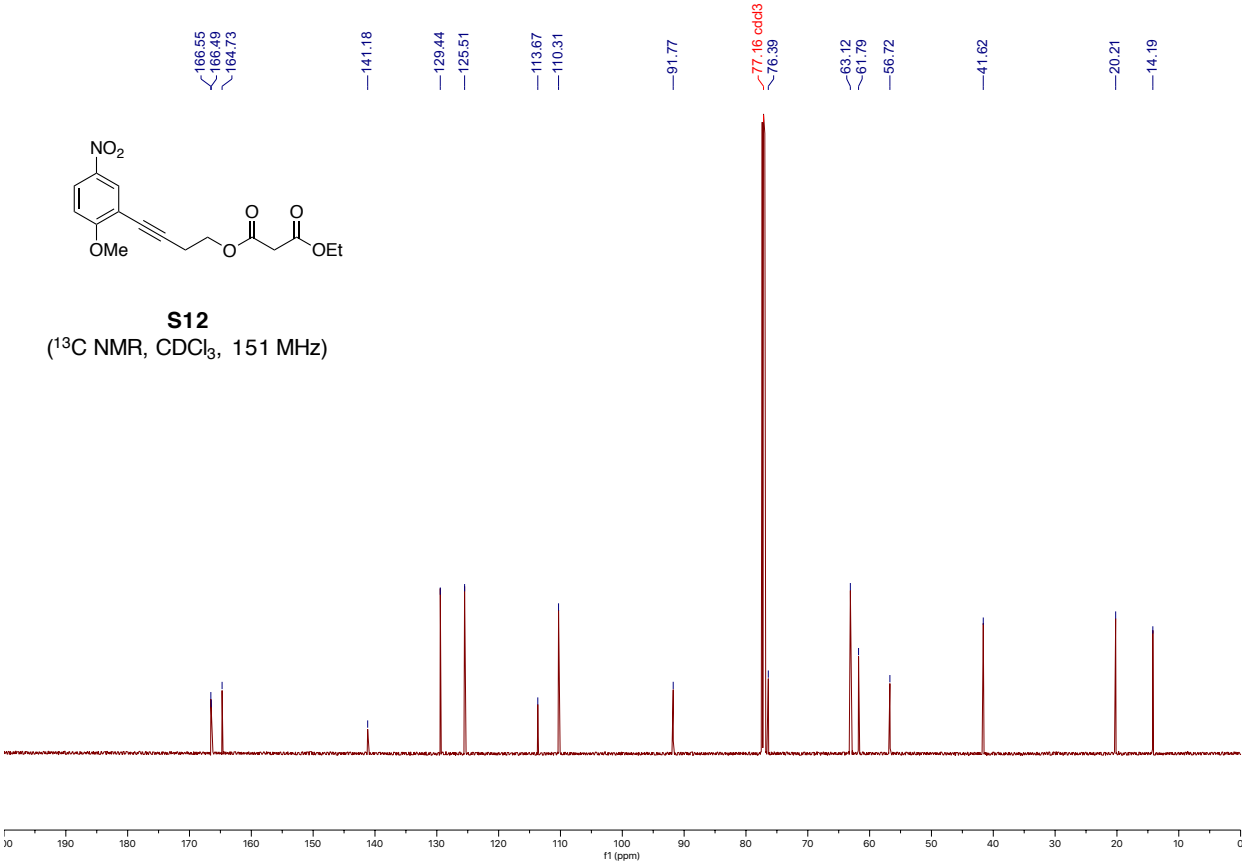
S11
(^{1}H NMR, $CDCl_3$, 400 MHz)



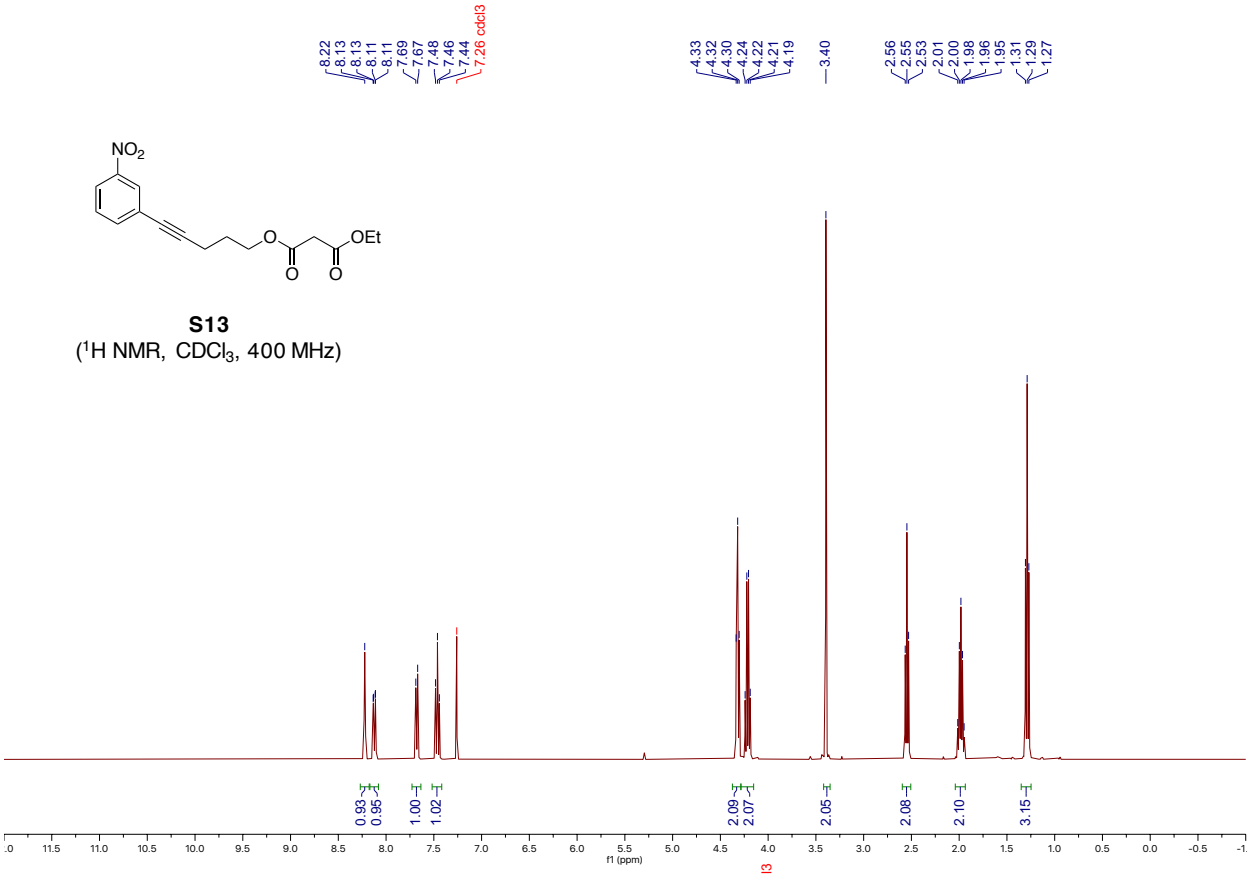
S11
(^{13}C NMR, $CDCl_3$, 151 MHz)



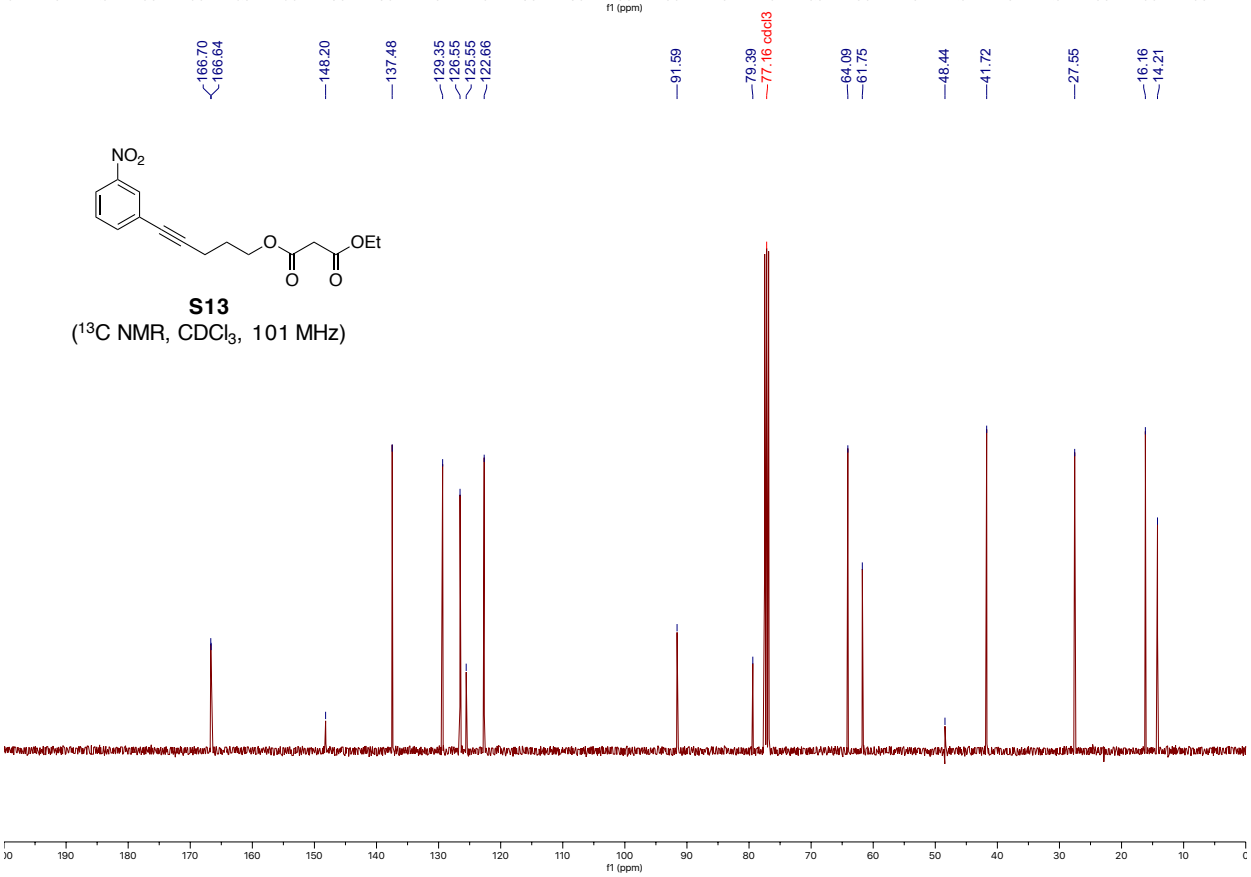
S12
(^{1}H NMR, $CDCl_3$, 600 MHz)



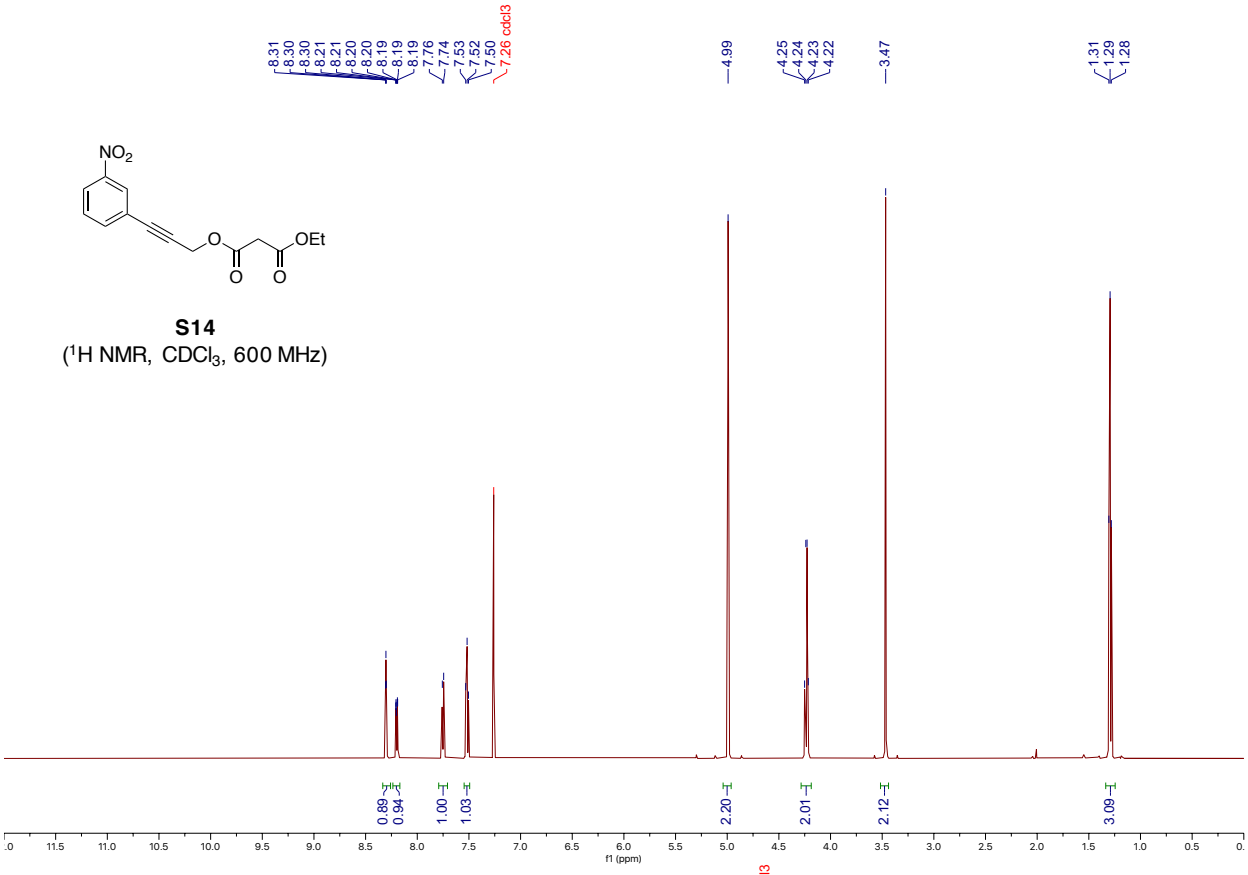
S12
(^{13}C NMR, $CDCl_3$, 151 MHz)



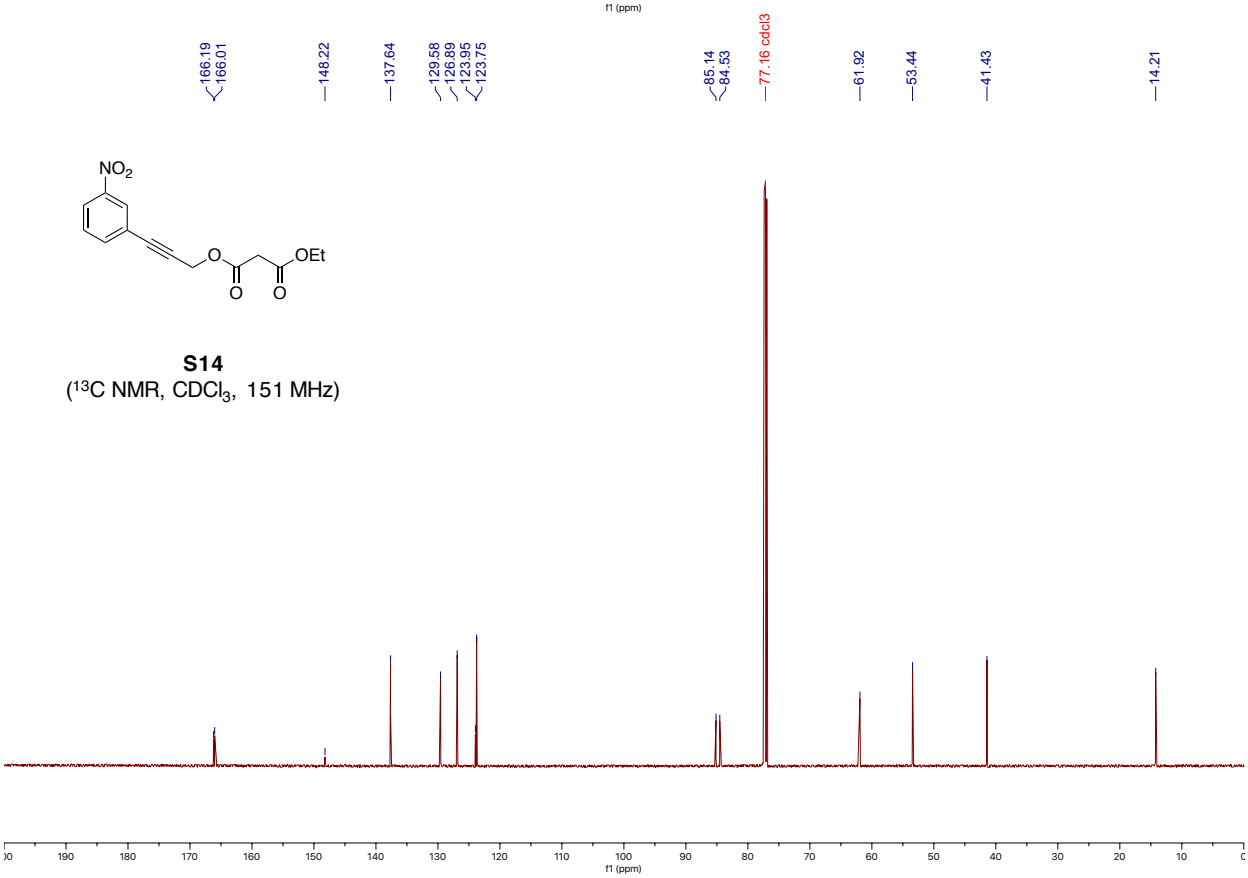
S13
(^{1}H NMR, $CDCl_3$, 400 MHz)



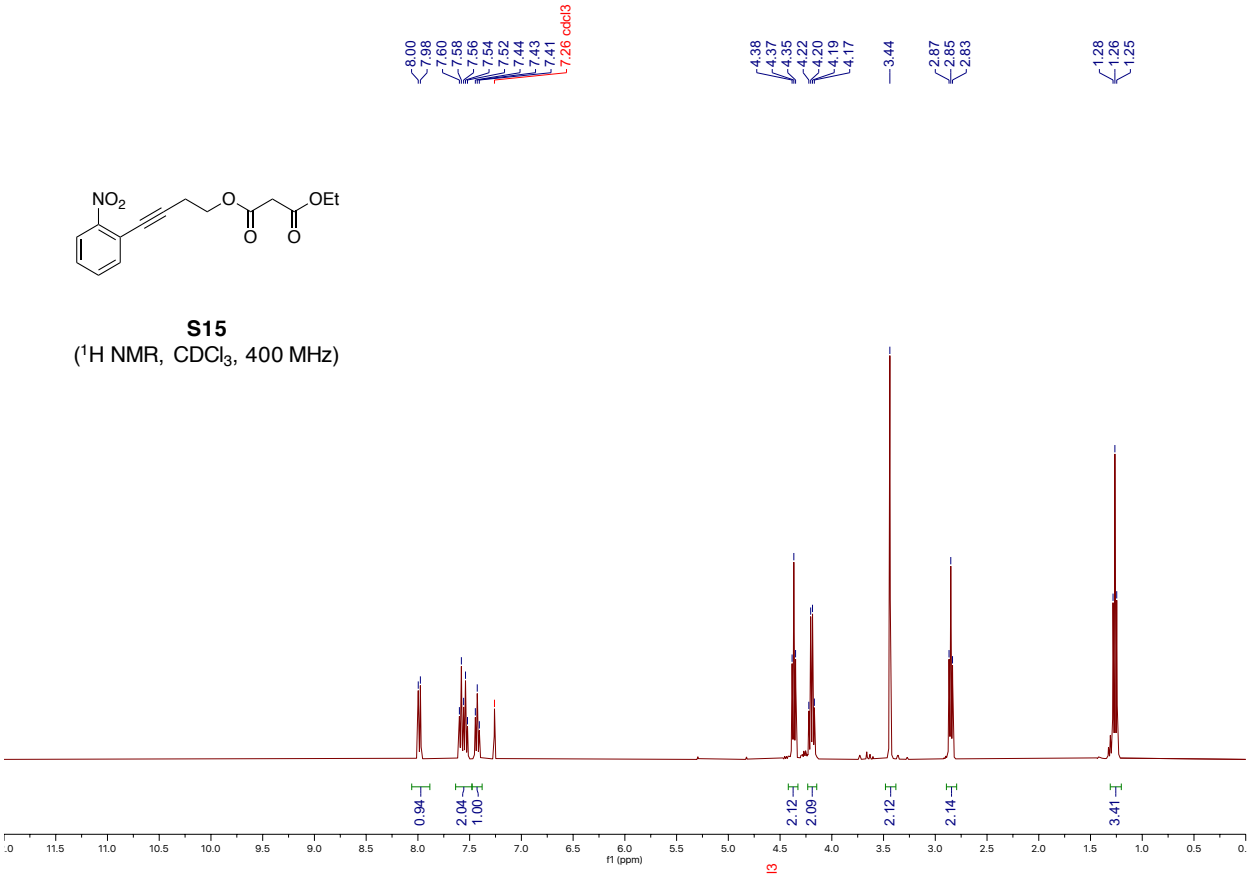
S13
(^{13}C NMR, $CDCl_3$, 101 MHz)



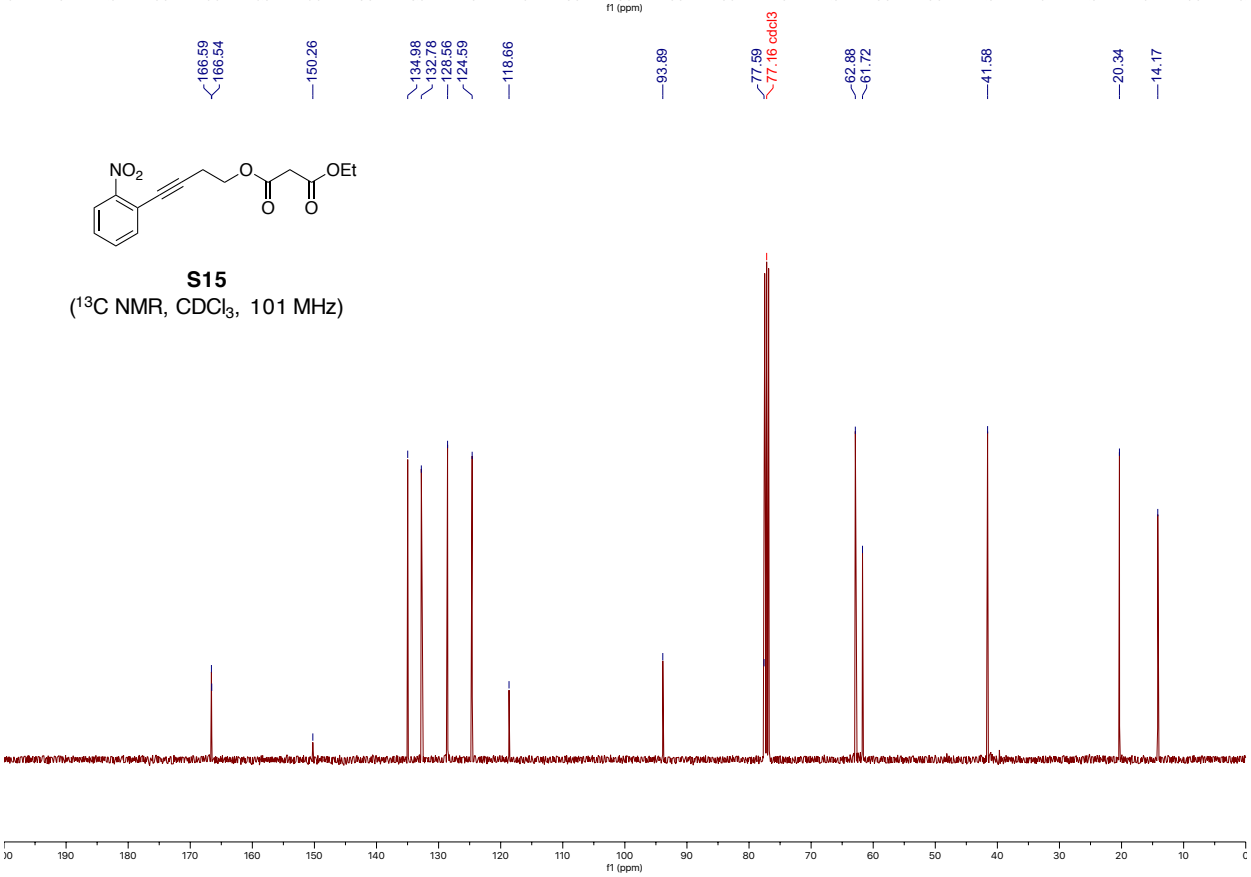
S14
(^{1}H NMR, $CDCl_3$, 600 MHz)



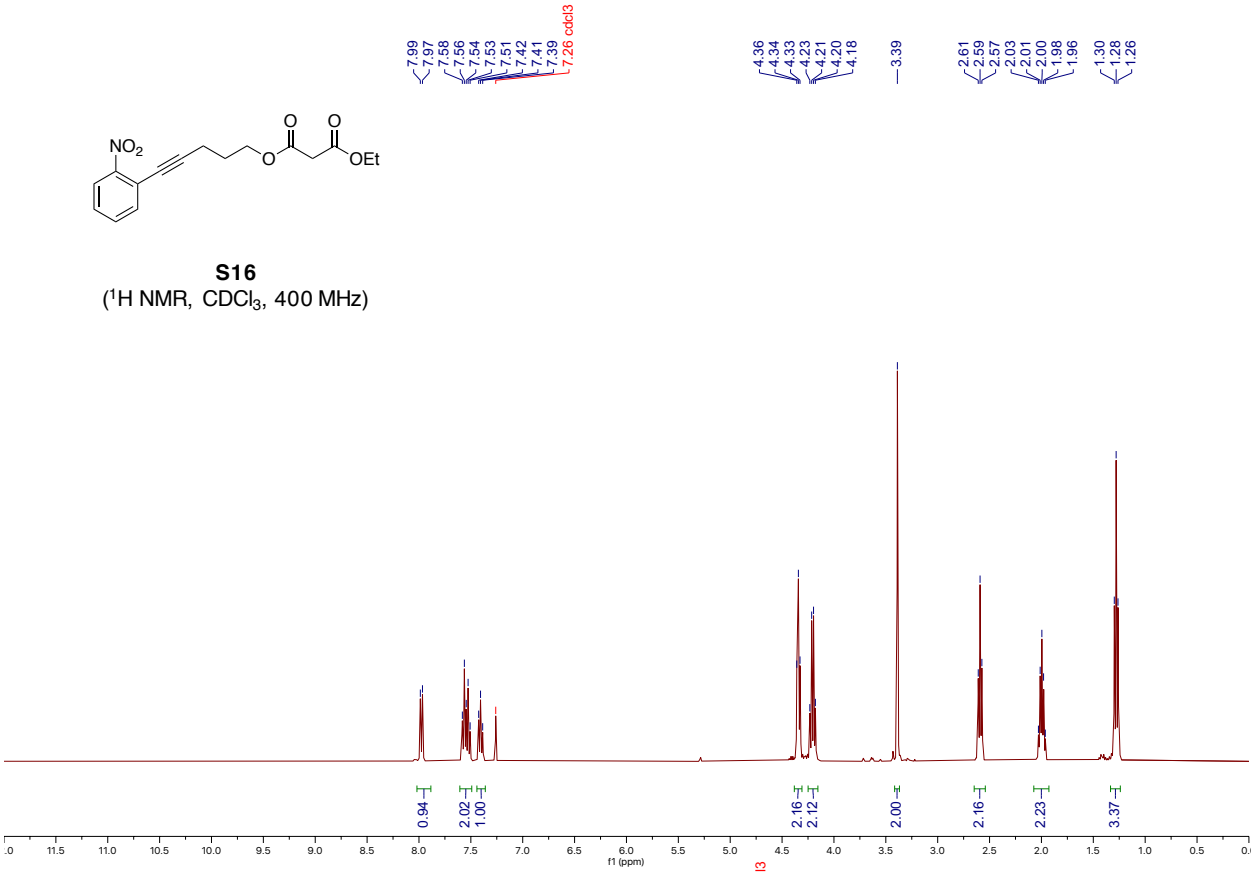
S14
(^{13}C NMR, $CDCl_3$, 151 MHz)



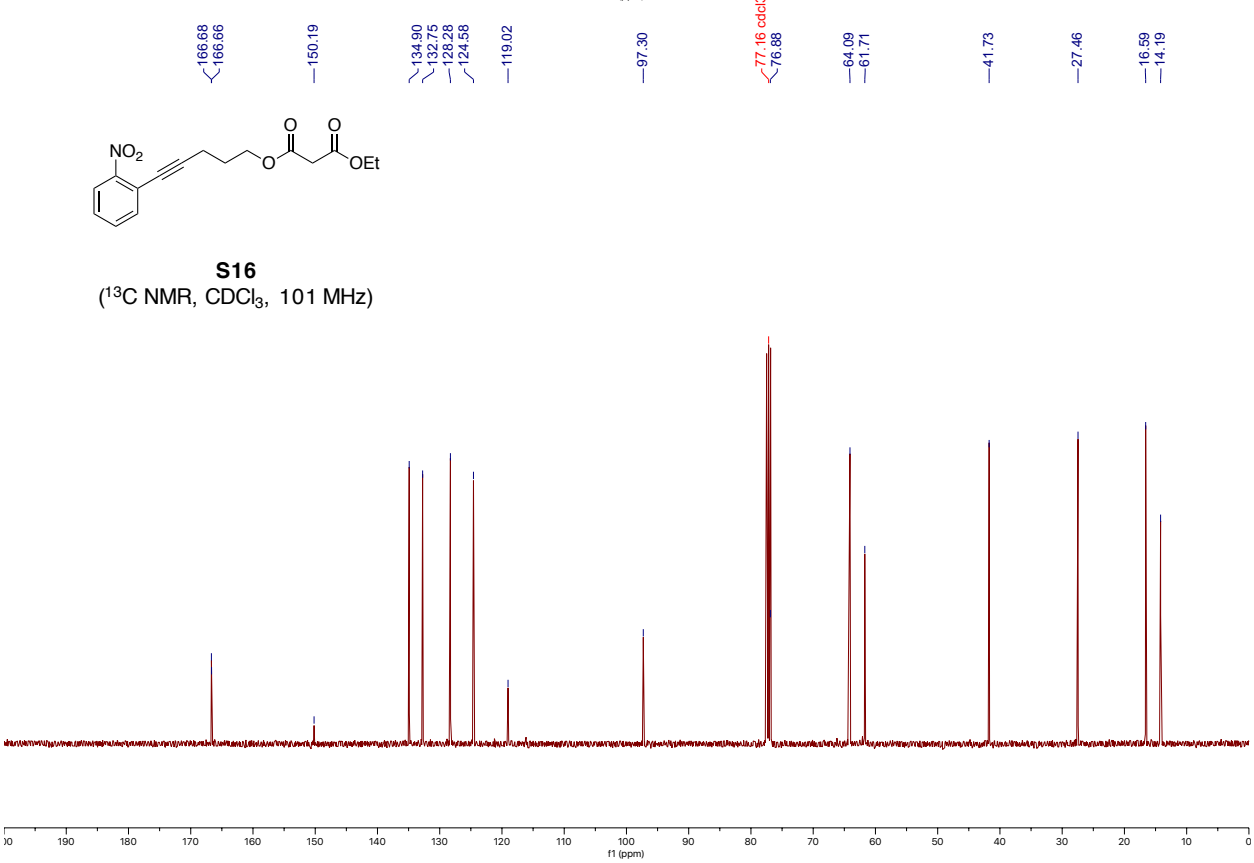
S15
(^{1}H NMR, $CDCl_3$, 400 MHz)



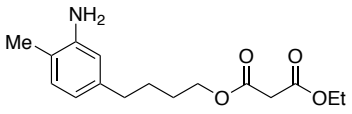
S15
(^{13}C NMR, $CDCl_3$, 101 MHz)



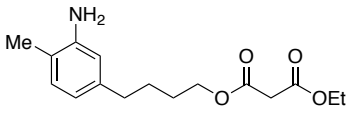
S16
(^{1}H NMR, $CDCl_3$, 400 MHz)



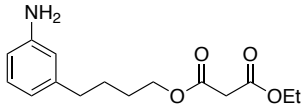
S16
(^{13}C NMR, $CDCl_3$, 101 MHz)



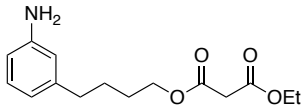
2a
(^{1}H NMR, $CDCl_3$, 500 MHz)



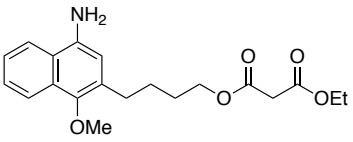
2a
(^{13}C NMR, $CDCl_3$, 126 MHz)



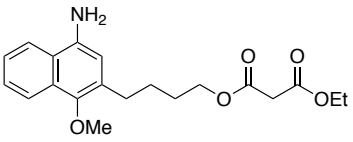
2b
(^{1}H NMR, $CDCl_3$, 600 MHz)



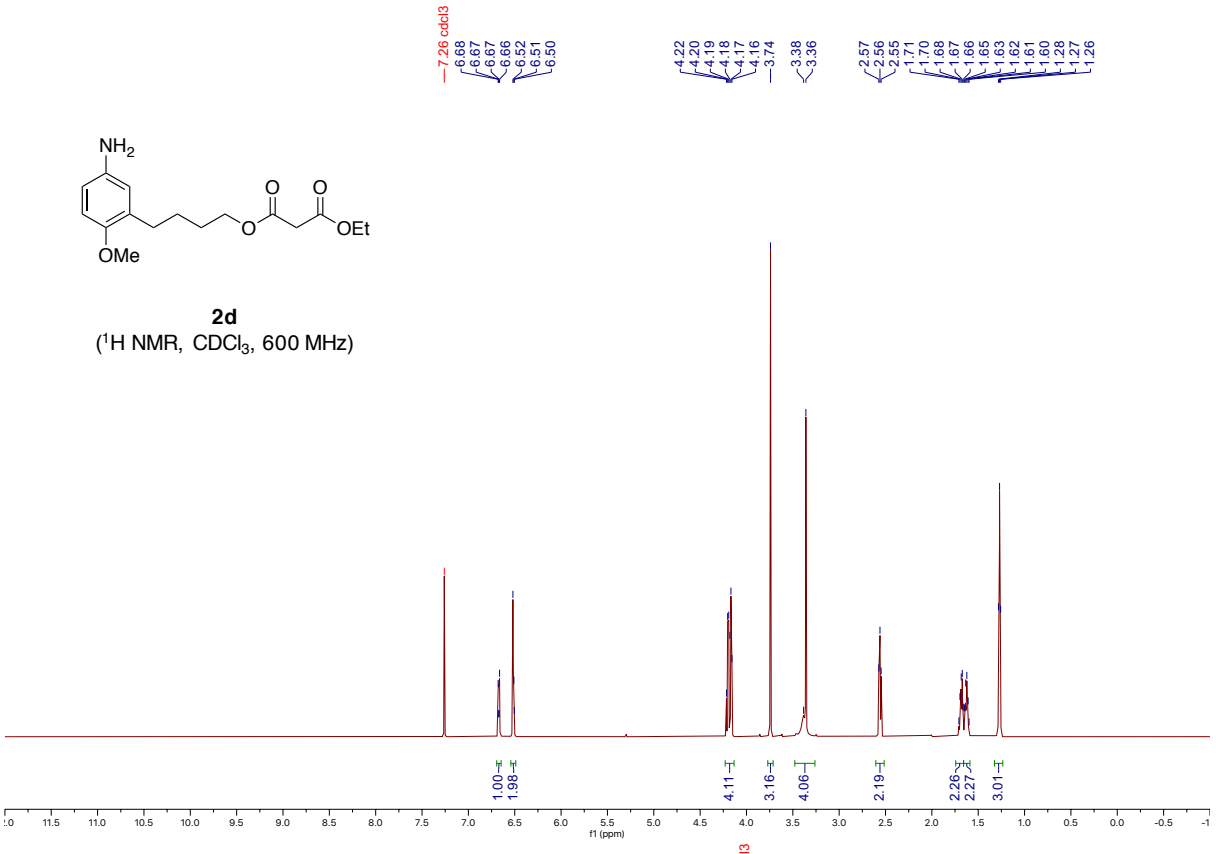
2b
(^{13}C NMR, $CDCl_3$, 151 MHz)

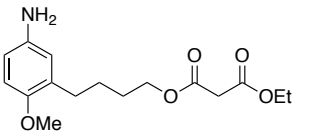


2c
(^{1}H NMR, $CDCl_3$, 600 MHz)



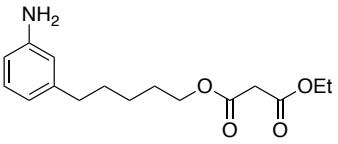
2c
(^{13}C NMR, $CDCl_3$, 151 MHz)



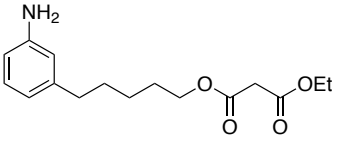


2d
(^{1}H NMR, $CDCl_3$, 600 MHz)

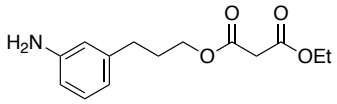
2d
(^{13}C NMR, $CDCl_3$, 126 MHz)



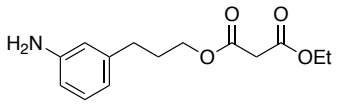
2e
(^{1}H NMR, $CDCl_3$, 600 MHz)



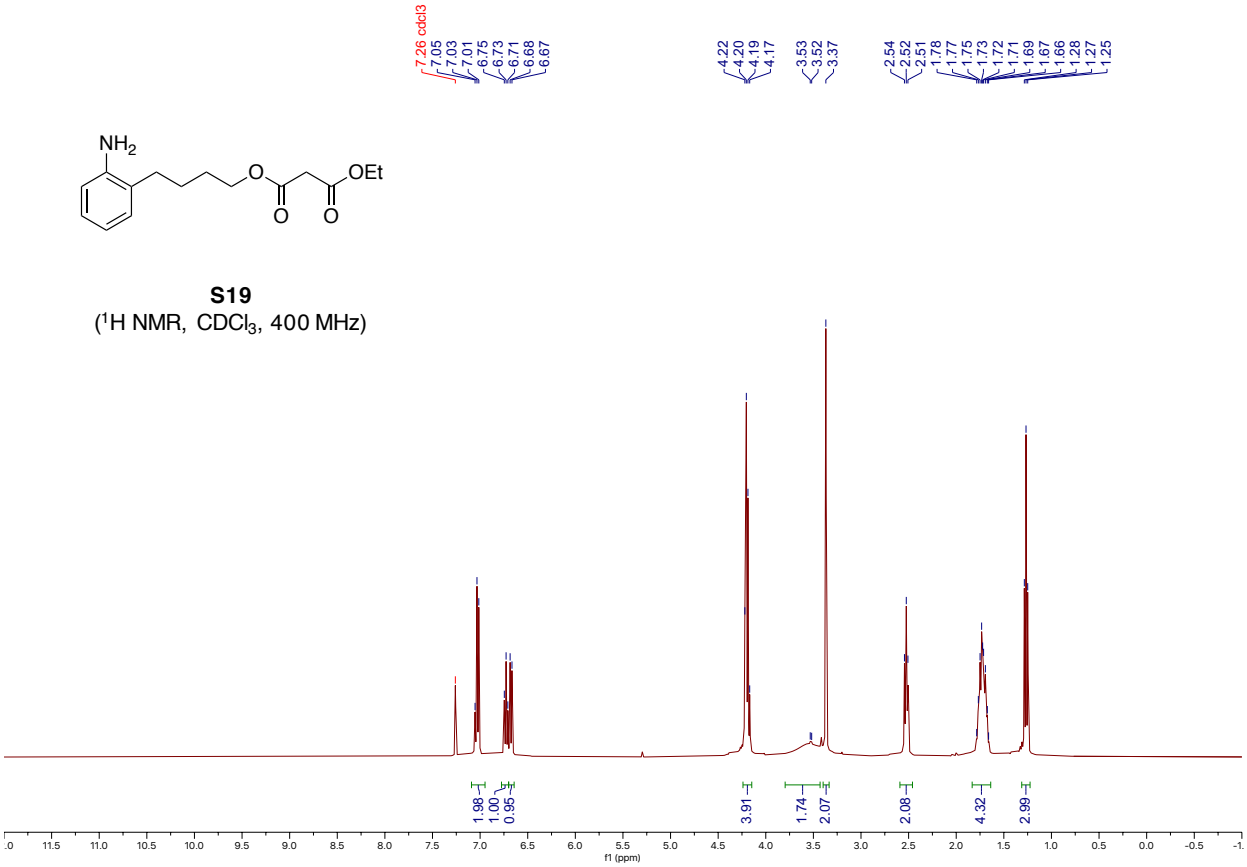
2e
(^{13}C NMR, $CDCl_3$, 151 MHz)



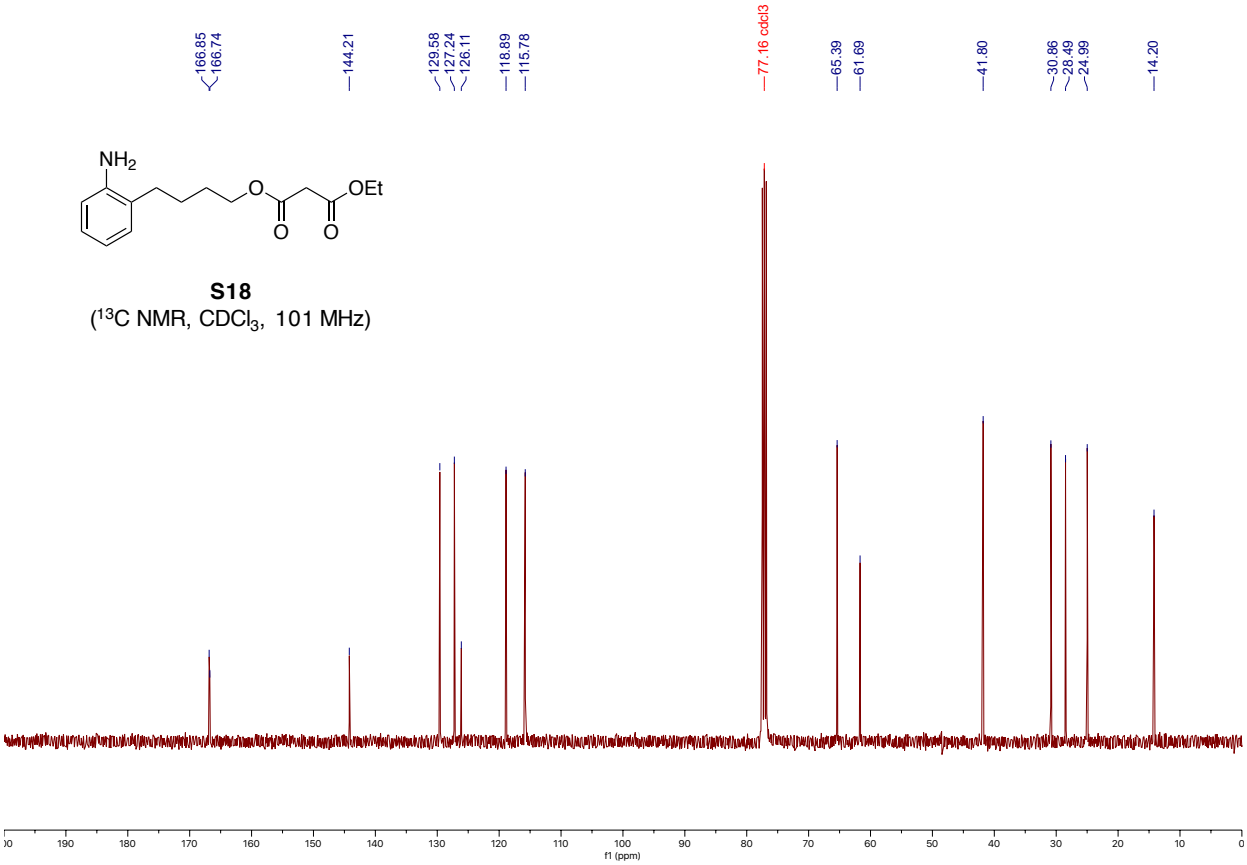
S17
(^{1}H NMR, $CDCl_3$, 400 MHz)



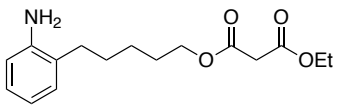
S17
(^{13}C NMR, $CDCl_3$, 101 MHz)



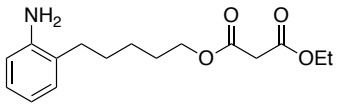
S19
(^{1}H NMR, $CDCl_3$, 400 MHz)



S18
(^{13}C NMR, $CDCl_3$, 101 MHz)



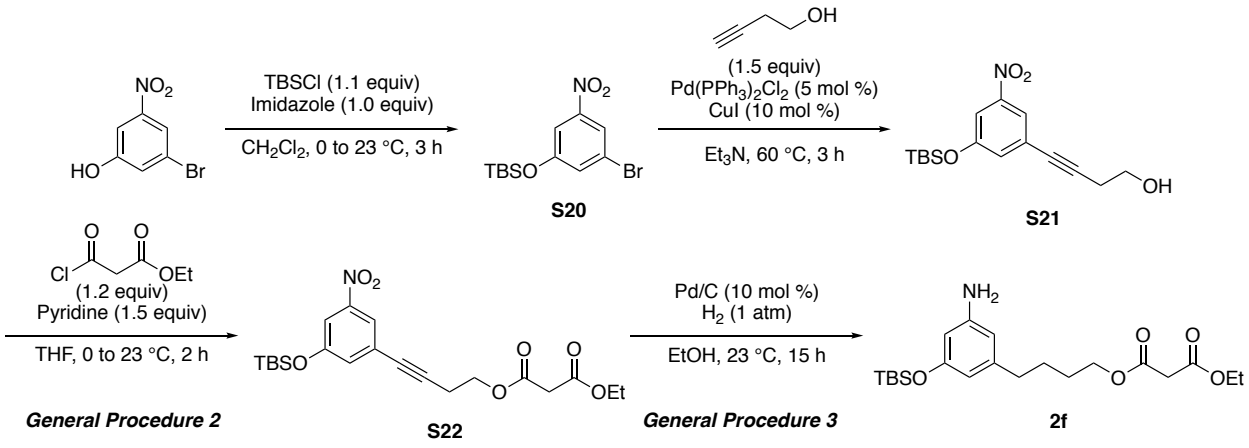
S19
(^{1}H NMR, $CDCl_3$, 400 MHz)



S19
(^{13}C NMR, $CDCl_3$, 126 MHz)

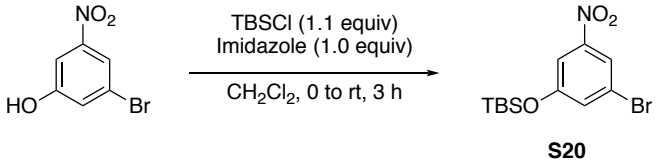
6. Synthesis of Aminophenol 2f

6.1 General Synthetic Route to 2f



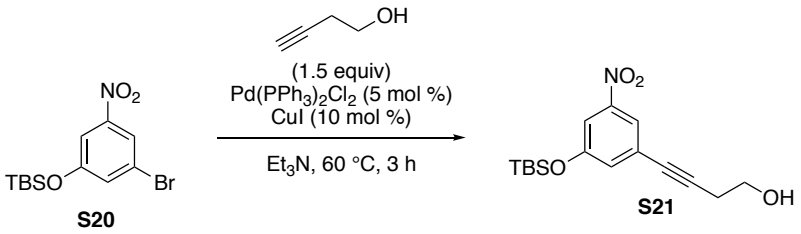
6.2 Characterization of Aminophenol 2f and Intermediates

(3-bromo-5-nitrophenoxy)(*tert*-butyl)dimethylsilane (S20)



To a RBF equipped with a magnetic stir bar was added 3-bromo-5-nitrophenol (2.000 g, 9.17 mmol, 1.00 equiv), TBSCl (1.5210 g, 10.09 mmol, 1.10 equiv) and CH_2Cl_2 (9.17 mL, 1.0 M). Reaction mixture was cooled to 0 °C. Imidazole (0.6243 g, 9.17 mmol, 1.00 equiv) was added in one portion to the stirring mixture. Reaction mixture was allowed to warm to room temperature and was left to stir for 3 hours (until consumption of the starting material was observed by TLC). Reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with 10% citric acid (w/v) (20 mL). Aqueous layer was extracted with CH_2Cl_2 (10 mL × 3). Combined organic layers were washed with saturated NaCl (aq) (40 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to yield an orange-brown solid. Crude material was used without in the subsequent step without further purification (2.8996 g, 95% yield).
TLC (1% EtOAc/Hex): R_f = 0.35.
IR (FT-ATR, cm^{-1}, neat): ν_{max} 3090, 2954, 2930, 2859, 1980, 1532, 1450, 1343, 1274, 1096, 999, 839, 664.
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (t, *J* = 1.8 Hz, 1H), 7.59 (t, *J* = 2.1 Hz, 1H), 7.30 (t, *J* = 1.9 Hz, 1H), 1.00 (s, 9H), 0.26 (s, 6H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 157.2, 149.5, 129.6, 122.9, 119.8, 114.1, 25.6, 18.3, –4.4.
HRMS (ESI/Q-TOF): Exact mass calculated for $[C_{12}H_{18}BrNO_3Si + H]^+$ requires *m/z* = 332.0312, found *m/z* = 332.0314.

4-(3-((*tert*-butyldimethylsilyl)oxy)-5-nitrophenyl)but-3-yn-1-ol (**S21**)



To a flame-dried RBF equipped with a magnetic stir bar was added **S20** (2.1667 g, 6.52 mmol, 1.00 equiv), $Pd(PPh_3)_2Cl_2$ (0.2288 g, 0.33 mmol, 0.05 equiv) and CuI (0.1242 g, 0.65 mmol, 0.10 equiv). RBF was sparged with N_2 for 15 minutes. Dry Et_3N (6.5 mL, 1.0 M) (stored under CaH_2) was added. 3-butyn-1-ol (0.74 mL, 9.78 mmol, 1.50 equiv) (stored under N_2 in a one-dram vial with a septa cap) was added dropwise through the septum. Reaction mixture was left to stir for 3 hours at 60 °C. (Note: Prolonged reaction time leads to decreased yield due to cleavage of the TBS group) Reaction mixture was cooled to room temperature, then diluted with EtOAc (15 mL). Reaction mixture was washed with sat. NH_4Cl (aq) (15 mL). Aqueous layer was extracted with EtOAc (10 mL × 3). Combined organic layers were washed with sat. NaCl(aq) (40 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to yield a viscous brown oil. Crude material was purified by flash chromatography (0→30→60% EtOAc/Hex) to yield **S21** as an orange-brown solid (1.7362 g, 83% yield).

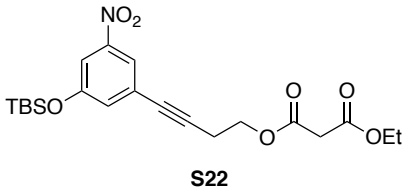
TLC (40% EtOAc/Hex): $R_f = 0.54$.

IR (FT-ATR, cm^{-1}, neat): ν_{max} 3301, 2935, 2862, 2114, 1530, 1426, 1343, 1256, 1185, 1034, 781.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.82 (m, 1H), 7.58 (t, J = 2.2 Hz, 1H), 7.16 (dd, J = 2.2, 1.4 Hz, 1H), 3.85 (t, J = 6.3 Hz, 2H), 2.71 (t, J = 6.3 Hz, 2H), 1.76 (brs, 1H), 0.99 (s, 9H), 0.24 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.3, 149.1, 129.2, 125.8, 119.8, 114.9, 89.4, 80.3, 61.1, 25.6, 23.9, 18.3, –4.33.

HRMS (ESI/Q-TOF): Exact mass calculated for $[C_{16}H_{23}NO_4Si + H]^+$ requires m/z = 322.1469, found m/z = 322.1479.

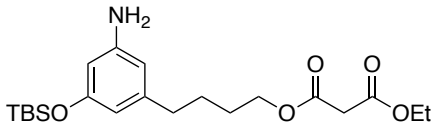


4-(3-((*tert*-butyldimethylsilyl)oxy)-5-nitrophenyl)but-3-yn-1-yl ethyl malonate (**S22**) was synthesized following from **S21** following **General Procedure 2**. Crude material was purified by flash chromatography (0→20→40% EtOAc/Hex) to yield **S22** as a pale yellow oil (2.2784 g, 97% yield).

TLC (20% EtOAc/Hex): $R_f = 0.38$.

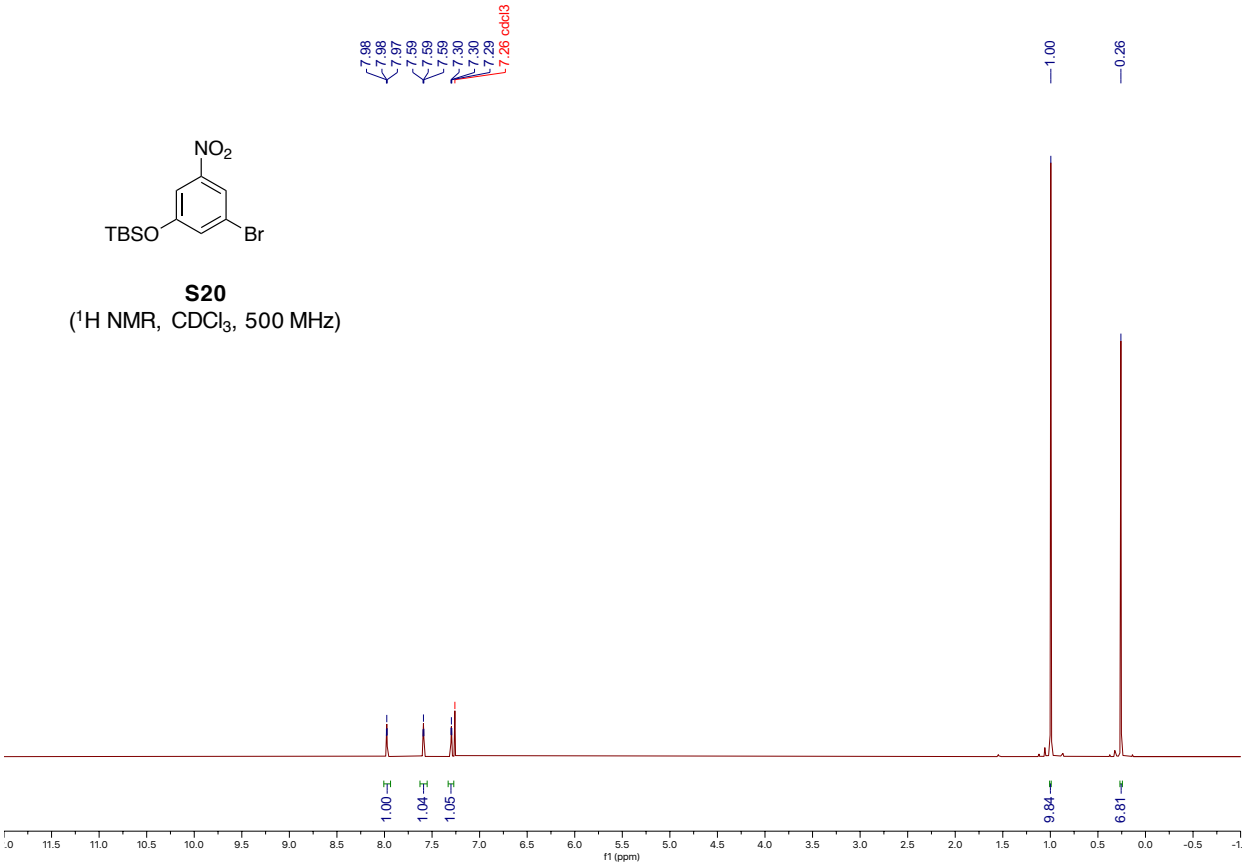
IR (FT-ATR, cm^{-1}, neat): ν_{max} 2955, 2931, 2859, 2113, 1734, 1614, 1535, 1348, 1256, 1184, 1146, 1032, 840.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.87 – 7.83 (m, 1H), 7.58 (t, *J* = 2.2 Hz, 1H), 7.15 (dd, *J* = 2.2, 1.4 Hz, 1H), 4.34 (t, *J* = 6.8 Hz, 2H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.42 (s, 2H), 2.79 (t, *J* = 6.8 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.99 (s, 9H), 0.25 (s, 6H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 166.6, 166.5, 156.4, 149.1, 129.2, 125.6, 119.8, 115.0, 87.9, 80.2, 63.0, 61.8, 41.6, 25.7, 19.9, 18.3, 14.2, –4.3.
HRMS (ESI/Q-TOF): Exact mass calculated for $[C_{21}H_{29}NO_7Si+H]^+$ requires *m/z*= 436.1786, found *m/z* = 436.1786.

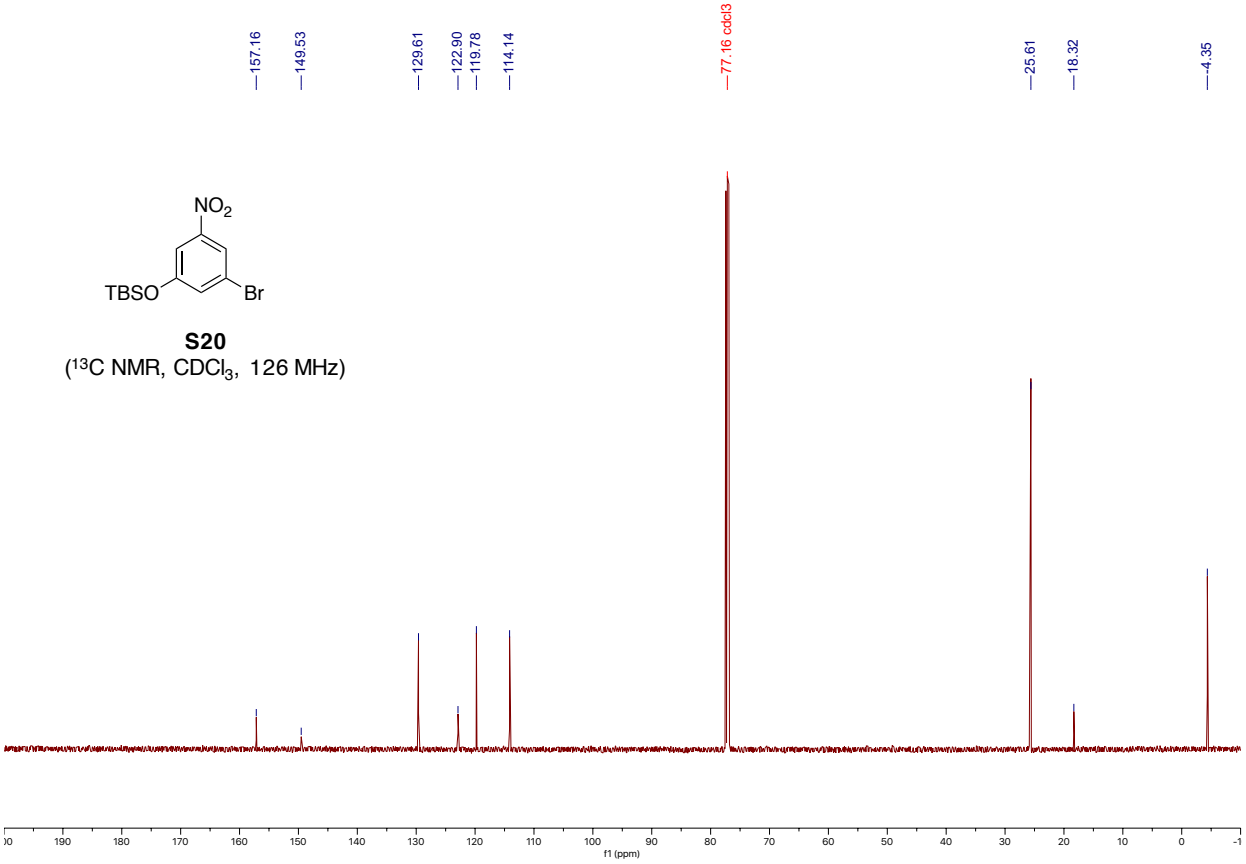


2f

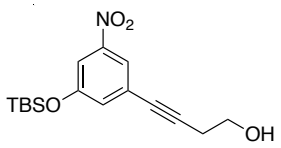
4-(3-amino-5-((*tert*-butyldimethylsilyl)oxy)phenyl)butyl ethyl malonate (**2f**) was synthesized from **S22** following **General Procedure 3**. Crude material was purified by silica chromatography (0→25→35% EtOAc/Hex) to yield **2f** as an orange oil (2.0160 g, 94% yield).
TLC (30% EtOAc/Hex): R_f = 0.50.
IR (FT-ATR, cm^{-1}, neat): ν_{max} 3468, 3380, 2930, 2957, 1730, 1591, 1330, 1176, 1150, 835.
^{1}H NMR (600 MHz, $CDCl_3$) δ 6.13 (s, 1H), 6.08 (s, 1H), 6.03 (t, *J* = 2.0 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 4.15 (t, *J* = 6.2 Hz, 2H), 3.58 (s, 2H), 3.36 (s, 2H), 2.47 (t, *J* = 7.1 Hz, 2H), 1.65 (tdt, *J* = 10.7, 7.8, 3.2 Hz, 6H), 1.27 (t, *J* = 7.1 Hz, 2H), 0.97 (s, 9H), 0.18 (s, 6H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 166.8, 166.7, 156.75, 147.5, 144.3, 110.9, 108.8, 104.9, 65.6, 61.7, 60.5, 41.8, 35.4, 28.1, 27.4, 25.8, 21.2, 18.3, 14.2, –4.2.
HRMS (ESI/Q-TOF): Exact mass calculated for $[C_{21}H_{35}NO_5Si+H]+$ requires *m/z*= 410.2357, found *m/z* = 410.2357.



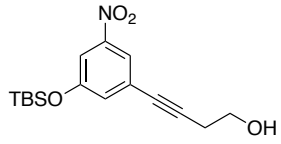
S20
(^{1}H NMR, $CDCl_3$, 500 MHz)



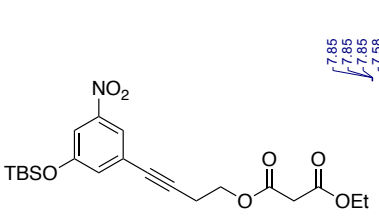
S20
(^{13}C NMR, $CDCl_3$, 126 MHz)



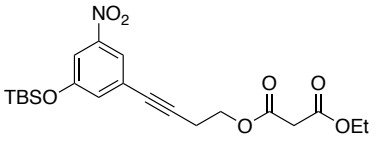
S21
(^{1}H NMR, $CDCl_3$, 400 MHz)



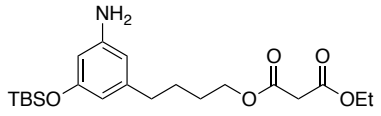
S21
(^{13}C NMR, $CDCl_3$, 101 MHz)



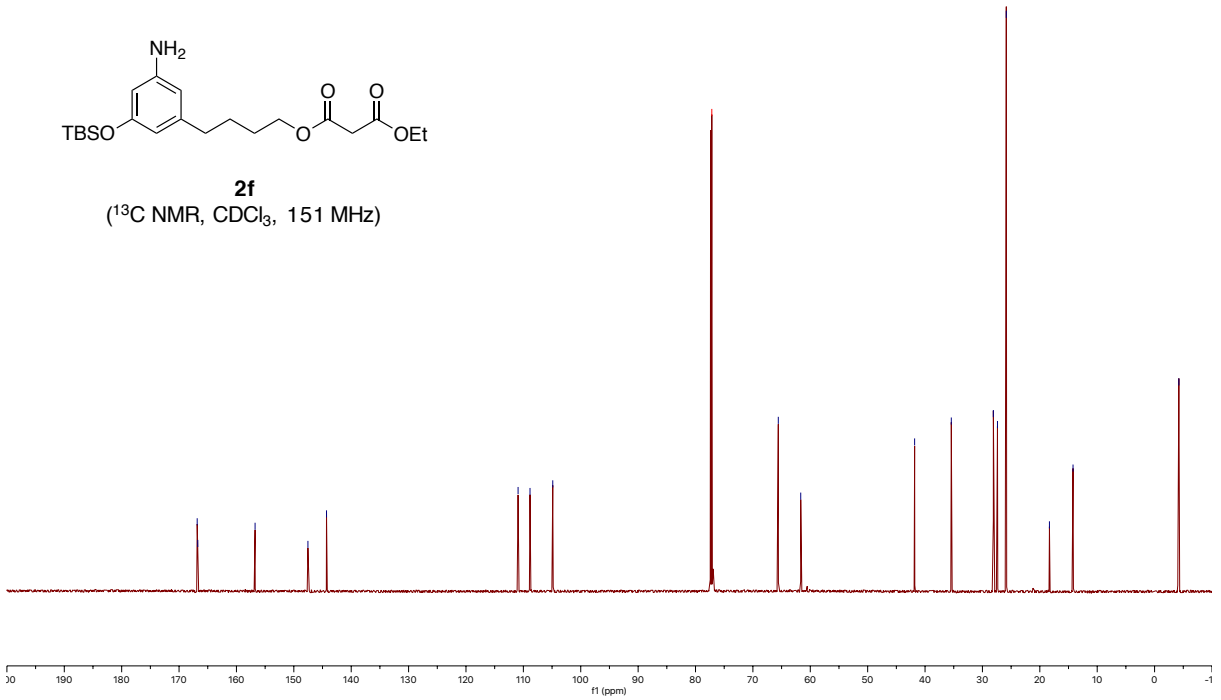
S22
(^{1}H NMR, $CDCl_3$, 600 MHz)



S22
(^{13}C NMR, $CDCl_3$, 151 MHz)

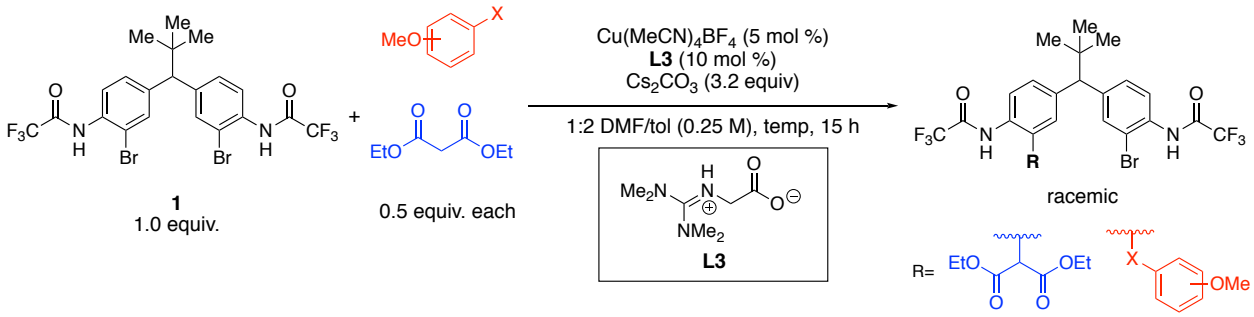


2f
(^{1}H NMR, $CDCl_3$, 600 MHz)



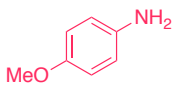
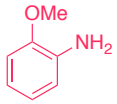
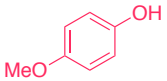
2f
(^{13}C NMR, $CDCl_3$, 151 MHz)

7. Bimolecular Competition Experiments: Determination of Chemoselectivity



To an oven-dried 5-mL Schlenk flask was added Cs_2CO_3 (0.2085g, 0.64 mmol, 3.20 equiv). The flask was sealed with a rubber septum and flamed-dried under vacuum. Upon cooling to room temperature, **1** (0.1208 g, 0.2 mmol, 1.00 equiv), $Cu(MeCN)_4BF_4$ (0.0031 g, 0.01 mmol, 0.05 equiv), **L3** (0.0035g, 0.02 mmol, 0.10 equiv) and a magnetic stir bar were added to the flask. The flask was sealed with a new rubber septum and further secured with Parafilm®. The flask was connected to vacuum for 5 min and backfilled with N_2. This process was repeated two additional times. 1:2 DMF/Tol mixture (0.6 mL) was added through the septum, and the mixture was allowed to stir for 15 min at room temperature, after which nucleophiles were added (0.2 mL of a 1.0 M stock solution w.r.t each nucleophile). The solution was left to stir for 15 h at room temperature. The mixture was diluted with EtOAc and transferred to a separatory funnel. The organic layer washed with a solution of saturated NH_4Cl (aq). The organic layer was separated and the aqueous layer was extracted with EtOAc (5 mL × 3). The organic layer was washed with sat. NaCl (aq) (20 mL). The combined organic layer was then dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Yield was determined using ^1H NMR by comparing the relative integration of each substrate's methine peak to an internal standard of 1,4-bis(trimethylsilyl)benzene. (Note: In competition experiments between diethyl malonate and aniline, glacial acetic acid was added to convert all C–N coupled products to cyclodehydrated products following previously reported methods.[2c])

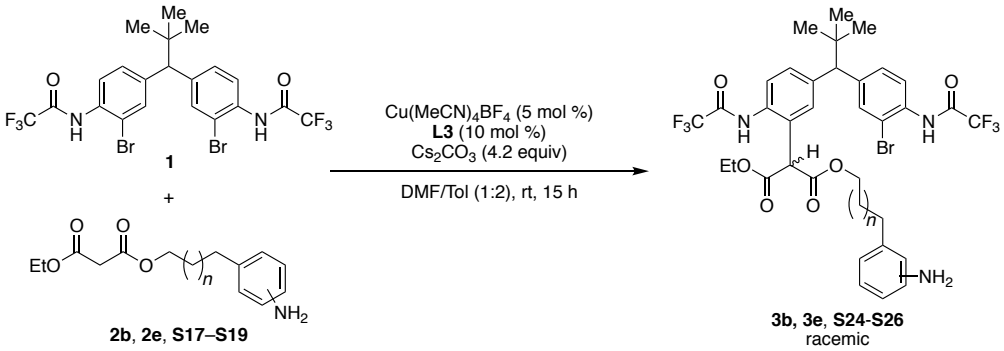
7.1 Table S1. Bimolecular competition experiments[a]

Entry	Nuc	Temp (°C)	SM (%)	Mono C–C (%)	Mono C–N (%)	C–C:C–X ratio
1		23	47	35	5	***7.0:1***
2		45	37	34	5	***7.0:1***
3		23	64	31	-	***1.:0***
4		45	63	34	-	***1:0***
5		23	43	28	17	***1.6:1***
6		45	43	18	30	***1:1.7***

[a] Conversion determined using ^{1}H NMR by comparing the relative integration of each substrate's methine peak to an internal standard of 1,4-bis(trimethylsilyl)benzene.

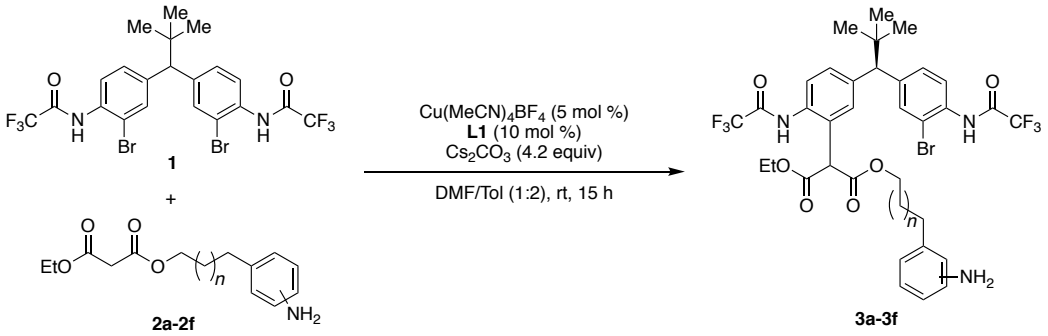
8. Procedures for Cu-catalyzed Intermolecular C–C Coupling

8.1 Procedure 4: Cu-catalyzed Intramolecular C–C Coupling with an Achiral Ligand



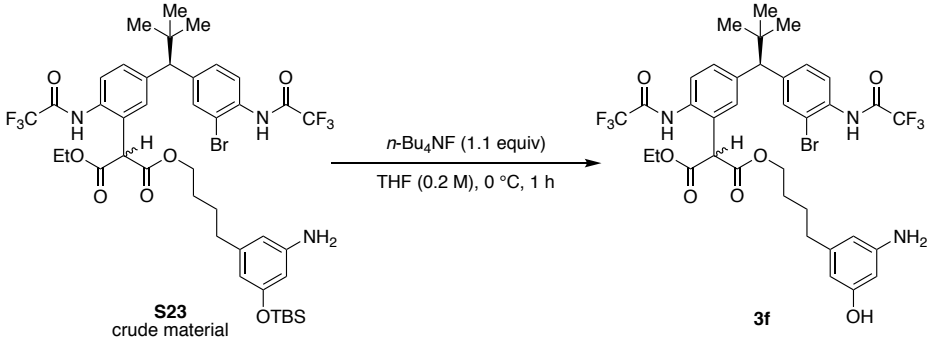
Cs_2CO_3 (4.20 equiv) was flamed-dried under vacuum in a 5-mL Schlenk flask. Upon cooling to room temperature, **1** (0.1208 g, 0.2 mmol, 1.00 equiv), $Cu(MeCN)_4BF_4$ (0.0031 g, 0.01 mmol, 0.05 equiv), **L3** (0.0035g, 0.02 mmol, 0.10 equiv) and a magnetic stir bar were added to the flask. The flask was sealed with a new rubber septum and further secured with Parafilm M®. The flask was put under vacuum for 5 min and backfilled with N_2. This process was repeated two additional times. 1:2 DMF/Tol mixture (0.6 mL) was added through the septum, and the mixture was allowed to stir for 15 min at room temperature, after which the bis-nucleophile (1.0 equiv) in 1:2 DMF/Tol mixture (0.2 mL) was added. The solution was left to stir for 15 h at room temperature. The mixture was diluted with EtOAc and transferred to a separatory funnel. The organic layer washed with saturated NH_4Cl (aq). The organic layer was separated and the aqueous layer was extracted with EtOAc (5 mL × 3). Combined organic layers were washed with sat. NaCl (aq), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography with EtOAc/Hex gradient.

8.2 Procedure 5: Preparation of Enantioenriched Diarylmethanes by C–C Coupling



Cs_2CO_3 (2.4632 g, 7.56 mmol, 4.20 equiv) was flamed-dried under vacuum in a 10-mL Schlenk flask. Upon cooling to room temperature, **1** (1.0875 g, 1.8 mmol, 1.00 equiv), $Cu(MeCN)_4BF_4$ (0.0283 g, 0.09 mmol, 0.05 equiv), **L1** (0.0755 g, 0.18 mmol, 0.10 equiv) and a magnetic stir bar were added to the flask. The flask was sealed with a new rubber septum and further secured with Parafilm M®. The flask was put under vacuum for 5 min and backfilled with N_2. This process was repeated two additional times. 1:2 DMF/Tol mixture (6.0 mL) was added through the septum, and the mixture was allowed to stir for 15 min at room temperature, after which the bis-nucleophile **2a-2f** (1.98 mmol, 1.10 equiv) in Tol (0.8 mL) was added. The vial was rinsed with DMF (0.4 mL) and added to the stirring mixture. The reaction mixture was left to stir for 15 h at room temperature. The mixture was diluted with EtOAc (20 mL) and transferred to a separatory funnel. The organic layer washed with saturated NH_4Cl (aq) (20 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (10 mL × 3). Combined rganic layers were washed with sat. NaCl (aq) (50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography with EtOAc/Hex gradient.

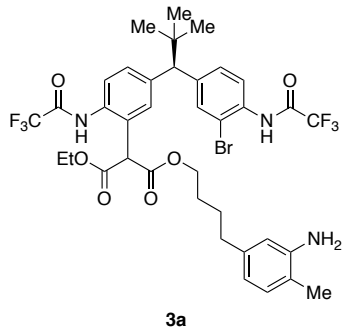
8.3 Procedure 6: TBS Deprotection en route to Aminophenol 3f



Crude material containing **S23** (~1.8 mmol, 1.00 equiv) was dissolved in THF (9.0 mL, 0.2 M). The solution was cooled to 0 °C. *n*-Bu_4NF (1.0 M solution in THF, 1.98 mmol, 1.10 equiv, 1.98 mL) was added dropwise to the stirring mixture. Reaction mixture was left to stir at 0 °C for 1 h, until the consumption of starting material was observed by TLC. Reaction mixture was diluted with EtOAc and transferred to a separatory funnel. The

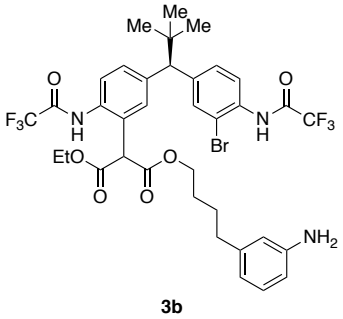
oranic layer was washed with 10% citric acid (aq). The aqueous layer was extracted with EtOAc × 3. Combined organic layers were washed with sat. NaCl (aq), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude material was purified by flash chromatography with EtOAc/Hex gradient.

8.4 Characterization and Spectra of Linear Precursors



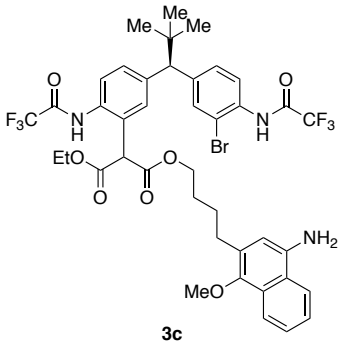
3a

1-(4-(3-amino-4-methylphenyl)butyl) 3-ethyl 2-(5-((*R*)-1-(3-bromo-4-(2,2,2-trifluoroacetami do)phenyl)-2,2-dimethylpropyl-)-2-(2,2,2 trifluoroacetamido)phenyl)malonate (3a) was synthesized from **2a** following **Procedure 5**. Crude material was purified by silica chromatography (0→30→60% EtOAc/Hex) to yield the desired product as a white solid (0.9775 g, 66% yield, 94:6 er). The product is isolated as a 1.0:1 mixture of diastereomers.
TLC (30% EtOAc/Hex): R_f = 0.42.
IR (FT-ATR, cm^{-1}, neat): ν_{max} 3382, 2952, 2866, 2287, 2124, 1721, 1531, 1281, 1152, 1028, 759.
^{1}H NMR (500 MHz, $CDCl_3$) δ 10.22 (s, 1H), 8.41 (s, 1H), 8.20 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.60 (d, *J* = 1.7 Hz, 1H), 7.48 (dt, *J* = 8.4, 2.0 Hz, 2H), 7.43 (d, *J* = 8.6 Hz, 1H), 7.22 (d, *J* = 1.6 Hz, 1H), 6.93 (d, *J* = 7.4 Hz, 1H), 6.46 (d, *J* = 7.9 Hz, 2H), 4.62 (s, 1H), 4.32 – 4.03 (m, 4H), 3.68&3.68 (s*, 1H), 3.56 (brs, 2H), 2.46 (td, *J* = 7.5, 2.8 Hz, 2H), 2.13 (s, 3H), 1.71 – 1.50 (m, 4H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.01&1.01 (s*, 9H). (Note: *indicates overlap of two diastereomeric singlets that may appear as an apparent doublet)
^{13}C NMR (151 MHz, $CDCl_3$) δ 168.9, 168.8, 168.8, 168.7, 155.6 (q, *J* = 37.3 Hz), 154.7 (q, *J* = 37.7 Hz), 144.6, 142.1&142.1, 141.0 &141.0, 140.7, 133.8, 133.7&133.7, 132.6, 131.6, 130.5, 130.4, 129.9&129.8, 125.9, 125.6, 121.7&121.7, 120.0&120.0, 118.8, 116.1 (q, *J* = 288.4 Hz), 115.7 (q, *J* = 288.4 Hz), 115.1, 114.0, 66.9&66.9, 63.0&63.0, 62.9&62.9, 57.5, 35.4, 34.9, 29.2, 27.9&27.8, 27.4&27.4, 17.0, 13.9.
^{19}F NMR (471 MHz, $CDCl_3$) δ –75.83, –76.03.
HRMS (ESI/Q-TOF): Exact mass calculated for $[C_{37}H_{40}BrF_6N_3O_6+H]^+$ requires *m/z* = 818.2065, found *m/z* = 818.2075.
Optical Rotation: α_D^{20}= + 15.6 ° (*c* = 0.5, MeOH, 94:6 er)
HPLC (Chiralpak® AD-H column, 10% IPA/Hexanes eluent, 1.00 mL min^{-1} flow rate, 25 °C, 250 nm, 1.0:1 dr): major diastereomers t_R= 21.3 min, 29.9 min; minor diastereomers t_R= 23.5 min, 34.1 min.



3b

1-(4-(3-aminophenyl)butyl) 3-ethyl 2-(5-((*R*)-1-(3-bromo-4-(2,2,2-trifluoroacetamido)phenyl -2,2-dimethylpropyl)-2-(2,2,2-trifluoroacetamido)phenyl)malonate (**3b**) was synthesized from **2b** following **Procedure 5**. Crude material was purified by silica chromatography (0→30→60% EtOAc/Hex) to yield the desired product as a white solid (0.9392 g, 65% yield, 94:6 er). The product is isolated as a 1.0:1 mixture of diastereomers.
TLC (30% EtOAc/Hex): R_f = 0.39.
IR (FT-ATR, cm^{-1}, neat): ν_{max} 3378, 2951, 2288, 2110, 1721, 1531, 1281, 1151, 1027, 903, 606.
^{1}H NMR (600 MHz, $CDCl_3$): δ 10.21 (s, 1H), 8.40 (s, 1H), 8.20 (d, *J* = 8.6 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.59 (s, 1H), 7.47 (d, *J* = 8.3 Hz, 1H), 7.43 (d, *J* = 8.5 Hz, 1H), 7.20 (s, 1H), 7.04 (t, *J* = 7.7 Hz, 1H), 6.52 (d, *J* = 7.7 Hz, 2H), 6.47 (s, 1H), 4.61 (s, 1H), 4.34 – 4.04 (m, 4H), 3.67 (s, 1H), 2.47 (t, *J* = 7.3 Hz, 2H), 1.70 – 1.46 (m, 4H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.00 (s, 9H).
^{13}C NMR (151 MHz, $CDCl_3$): δ 168.9, 168.8, 168.8, 168.7, 155.7 (q, *J* = 37.2 Hz), 154.8 (q, *J* = 37.7 Hz), 146.2, 143.2, 142.1&142.1, 141.0&141.0, 133.8, 133.7, 132.7, 131.6, 130.5&130.4, 129.9&129.9, 129.4, 125.9, 125.7, 121.7, 119.1, 116.1 (q, *J* = 289.9 Hz), 115.7 (q, *J* = 288.4 Hz), 115.5, 114.0, 113.1, 66.9&66.8, 63.1&63.1, 63.0&63.0, 57.6, 35.5, 35.3, 29.2, 27.9&27.9, 27.3&27.3, 14.0.
^{19}F NMR (471 MHz, $CDCl_3$) δ –75.82, –76.03.
HRMS (ESI/Q-TOF): Exact mass calculated for $[C_{36}H_{38}BrF_6N_3O_6 + H]^+$ requires *m/z* = 804.1908, found *m/z* = 804.1922.
Optical Rotation: α_D^{20} = + 15.0 ° (*c* = 0.5, MeOH, 94:6 er)
HPLC: (Chiralpak® AD-H column, 10% IPA/Hexanes eluent, 1.00 mL min^{-1} flow rate, 25 °C, 250 nm, 1.0:1 dr): major diastereomers t_R= 22.6 min, 30.3 min; minor diastereomers t_R= 25.3 min, 38.1 min.



3c

1-(4-(4-amino-1-methoxynaphthalen-2-yl)butyl) 3-ethyl 2-(5-((*R*)-1-(3-bromo-4-(2,2,2-trifluoroacetamido)phenyl)-2,2-dimethylpropyl)-2-(2,2,2-trifluoroacetamido)phenyl)malonate (**3c**) was synthesized from **2c** following **Procedure 5**. Crude material was purified by silica chromatography (0→35→75% EtOAc/Hex) to yield the desired product as a beige solid (1.1229g, 71% yield, 94:6 er). The product is isolated as a 1.0:1 mixture of diastereomers.

TLC (30% EtOAc/Hex): R_f = 0.43.

IR (FT-ATR, cm^{-1}, neat): ν_{max} 3309, 2952, 2110, 1722, 1531, 1281, 1152, 1030, 764, 606.

^{1}H NMR (600 MHz, $CDCl_3$) δ 10.23 (s, 1H), 8.38 (s, 1H), 8.16 (dd, *J* = 8.5, 5.6 Hz, 1H), 8.03 (d, *J* = 8.2 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.57 (s, 1H), 7.52 – 7.36 (m, 4H), 7.20 (s, 1H), 6.54 (s, 1H), 4.62&4.62 (s*, 1H), 4.32 – 4.12 (m, 4H), 3.98 (brs, 2H), 3.82 (s, 3H), 3.65&3.64 (s*, 1H), 2.68 (t, *J* = 7.4 Hz, 2H), 1.79 – 1.53 (m, 4H), 1.22 (t, *J* = 6.8 Hz, 3H), 0.98&0.95 (s*, 9H). (Note: *indicates overlap of two diastereomeric singlets that may appear as an apparent doublet)

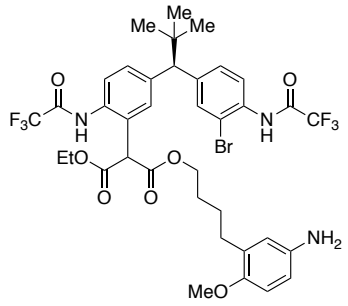
^{13}C NMR (151 MHz, $CDCl_3$) δ 168.9, 168.8, 168.8, 168.7, 155.7 (q, *J* = 37.8 Hz), 154.8 (q, *J* = 37.8 Hz), 146.4, 142.1&142.1, 141.1&141.0, 138.5&138.5, 133.8, 133.7&133.7, 132.7, 131.6, 130.5&130.4, 130.3, 129.9&129.8, 128.6, 126.1&126.1, 125.9, 125.7, 124.7&124.7, 123.9, 122.7, 121.8, 121.4, 116.1 (q, *J* = 288.4 Hz), 115.7 (q, *J* = 289.9 Hz), 114.0, 111.5&111.5, 66.9&66.8, 63.1&63.0, 63.0, 62.2, 57.6, 35.4, 29.2&29.1, 29.1&29.1, 28.1&28.1, 26.8&26.8, 14.0.

^{19}F NMR (376 MHz, $CDCl_3$) δ –75.83, –75.84, –76.04.

HRMS (ESI/Q-TOF): Exact mass calculated for $[C_{41}H_{42}BrF_6N_3O_7 + H]^+$ requires *m/z* = 884.2172, found *m/z* = 884.2190.

Optical Rotation: α_D^{20}= +12.9° (*c* = 0.5, MeOH, 94:6 er)

HPLC (Chiralpak® IB column, 6% EtOH/Hexanes eluent, 1.10 mL min^{-1} flow rate, 250 nm, 25 °C, 1.0:1 dr): major diastereomers t_R= 42.7 min, 51.0 min; minor diastereomers t_R = 29.9 min, 32.2 min.



3d

1-(4-(5-amino-2-methoxyphenyl)butyl) 3-ethyl 2-(5-((*R*)-1-(3-bromo-4-(2,2,2 trilfluoroacet-amido)phenyl)-2,2-dimethylpropyl)-2-(2,2,2-trifluoroacetamido)phenyl)malonate (**3d**) was synthesized from **2d** following **Procedure 5**. Crude material was purified by silica chromatography (0→40→85% EtOAc/Hex) to yield the desired product as a pale pink solid (1.0358 g, 69% yield, 92:8 er). The product is isolated as a 1.0:1 mixture of diastereomers.

TLC (40% EtOAc/Hex): R_f = 0.53.

IR (FT-ATR, cm^{-1}, neat): ν_{max} 3373, 2952, 2872, 2117, 1720, 1530, 1281, 1152, 1030, 733.

^{1}H NMR (600 MHz, $CDCl_3$) δ 10.22 (s, 1H), 8.42 (d, *J* = 11.5 Hz, 1H), 8.19 (dd, *J* = 8.4, 4.8 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.59 (s, 1H), 7.47 (d, *J* = 8.2 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.21 (s, 1H), 6.65 (d, *J* = 8.5 Hz, 1H), 6.51 (d, *J* = 8.4 Hz, 1H), 6.46 (s, 1H), 4.62 (s, 1H), 4.29 – 4.10 (m, 4H), 3.71 (s, 3H), 3.67 (s, 1H), 3.28 (brs, 2H), 2.50 (t, *J* = 7.4 Hz, 2H), 1.63 (q, *J* = 6.6 Hz, 2H), 1.57 – 1.49 (m, 2H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.01&1.00 (s*, 9H). (Note: *indicates overlap of two diastereomeric singlets that may appear as an apparent doublet)

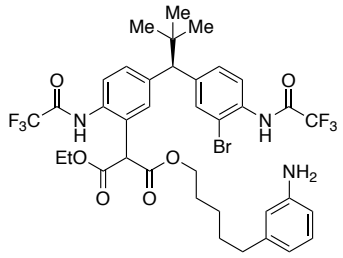
^{13}C NMR (151 MHz, $CDCl_3$) δ168.9, 168.8, 168.8, 168.7, 155.6 (q, *J* = 37.3 Hz), 154.8 (q, *J* = 37.8 Hz), 150.9, 142.1&142.1, 141.0, 139.7&139.7, 133.8, 132.7, 131.6, 131.3, 130.4, 129.9&129.9, 125.9, 125.6, 121.8&121.8, 117.8, 116.1 (q, *J* = 288.4 Hz), 115.7 (q, *J* = 289.9 Hz), 114.1, 114.0, 113.6, 111.9&111.9, 67.0&67.0, 63.0, 57.6, 56.1, 35.5, 29.6&29.6, 29.2, 28.0&28.0, 26.0&26.0, 14.0.

^{19}F NMR (376 MHz, $CDCl_3$) δ –75.79, –75.81, –76.00.

HRMS (ESI/Q-TOF): Exact mass calculated for $[C_{37}H_{40}BrF_6N_3O_7 + H]^+$ requires *m/z* = 834.2014, found *m/z* = 834.2022.

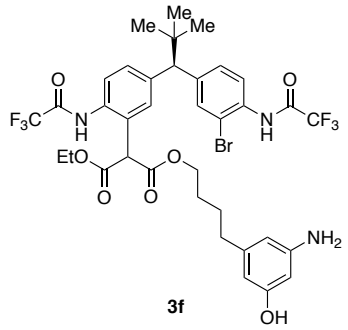
Optical Rotation: α_D^{20}= +14.5° (*c* = 0.5, MeOH, 92:8 er)

HPLC (Chiralpak® AD-H column, 7% IPA/Hexanes eluent, 1.25 mL min^{-1} flow rate, 250 nm, 25 °C, 1.0:1 dr): major diastereomers t_R= 47.1 min, 62.3 min, minor diastereomers t_R= 53.4 min, 93.5 min.



3e

1-(5-(3-aminophenyl)pentyl) 3-ethyl 2-(5-((*R*)-1-(3-bromo-4-(2,2,2-trifluoroacetamido)phen yl)-2,2-dimethylpropyl)-2-(2,2,2-trifluoroacetamido)phenyl)malonate (**3e**) was synthesized
from **2e** following **Procedure 5**. Crude material was purified by silica chromatography (0→30→60% EtOAc/Hex) to yield the desired product as a beige solid (0.7228 g, 59% yield, 90:10 er). The product is isolated as a 1.0:1 mixture of diastereomers.
TLC (30% EtOAc/Hex): R_f = 0.38.
IR (FT-ATR, cm^{-1}, neat): ν_{max} 3374, 3310, 2952, 2864, 2104, 1722, 1530, 1281, 1152, 1028, 749.
^{1}H NMR (600 MHz, $CDCl_3$) δ 10.20 (s, 1H), 8.38 (s, 1H), 8.21 (t, *J* = 8.1 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.60 (s, 1H), 7.48 (d, *J* = 8.4 Hz, 1H), 7.45 (d, *J* = 8.6 Hz, 1H), 7.21 (s, 1H), 7.05 (td, *J* = 7.6, 2.4 Hz, 1H), 6.55 – 6.50 (m, 2H), 6.47 (d, *J* = 10.2 Hz, 1H), 4.62 (s, 1H), 4.27 – 4.07 (m, 4H), 3.68 (s, 1H), 3.61 (brs, 2H), 2.44 (dt, *J* = 11.1, 7.7 Hz, 2H), 1.68 – 1.50 (m, 4H), 1.35 – 1.21 (m, 5H), 1.02 (s, 9H).
^{13}C NMR (126 MHz, $CDCl_3$): δ 168.8, 168.7, 155.6 (q, *J* = 37.3 Hz), 154.8 (q, *J* = 37.8 Hz), 146.5&146.5, 143.6, 142.1&142.1, 141.0, 133.8, 133.8, 132.7, 131.7, 130.5, 130.4, 129.9&129.9, 129.3, 125.9, 125.7, 121.8&121.7, 118.9, 116.1 (q, *J* = 241.9 Hz), 115.7 (q, *J* = 240.7 Hz), 115.4, 114.0&114.0, 112.8, 66.9&66.9, 63.0&63.0, 57.6&57.6, 35.8, 35.5, 30.8, 29.2, 28.2&28.2, 25.4, 14.0.
^{19}F NMR (376 MHz, $CDCl_3$) δ –75.84, –76.05.
HRMS (ESI/Q-TOF): Exact mass calculated for $[C_{37}H_{40}BrF_6N_3O_6+H]^+$ requires *m/z* = 818.2065, found *m/z* = 818.2079.
Optical Rotation: α_D^{20}= +14.6° (*c* = 0.5, MeOH, 90:10 er)
HPLC: (Chiralpak® AD-H column, 4% EtOH/Hexanes eluent, 1.25 mL min^{-1} flow rate, 254 nm, 20 °C, 1.0:1 dr): major diastereomers t_R= 41.8 min, 49.9 min; minor diastereomers t_R = 37.9 min, 75.2 min.



3f

1-(4-(3-amino-5-hydroxyphenyl)butyl) 3-ethyl 2-(5-((*R*)-1-(3-bromo-4-(2,2,2-trifluoroaceta mido)phenyl)-2,2-dimethylpropyl)-2-(2,2,2-trifluoroacetamido)phenyl)malonate (**3f**) was synthesized from **2f** following **Procedure 5** followed by **Procedure 6**. Crude material was purified by silica chromatography (0→40→80% EtOAc/Hex) to yield the desired product as a pink solid (0.4895 g, 60% yield, 93:7 er). The product is isolated as a 1.0:1 mixture of diastereomers.

TLC (50% EtOAc/Hex): R_f = 0.46.

IR (FT-ATR, cm^{-1}, neat): ν_{max} 3382, 2922, 2855, 2293, 1736, 1458, 1283, 1158, 1028, 908, 734.

^{1}H NMR (600 MHz, $CDCl_3$) δ 10.26 (s, 1H), 8.55 – 8.42 (m, 1H), 8.16 (dd, 1H), 7.77 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.50 – 7.43 (m, 1H), 7.41 (ddd, *J* = 13.6, 8.6, 1.7 Hz, 1H), 7.21 (dd, *J* = 12.4, 1.7 Hz, 1H), 6.02 – 6.00 (m, 2H), 5.94 (d, *J* = 17.1 Hz, 1H), 4.63&4.62 (s*, 1H), 4.33 – 4.07 (m, 4H), 3.66 (s, 1H), 2.36 (dt, *J* = 12.6, 7.4 Hz, 2H), 1.58 (dq, *J* = 13.8, 6.7 Hz, 2H), 1.52 – 1.44 (m, 2H), 1.25 (td, *J* = 7.1, 3.3 Hz, 3H), 1.00&0.99 (s*, 9H). (Note: *indicates overlap of two diastereomeric singlets that may appear as an apparent doublet)

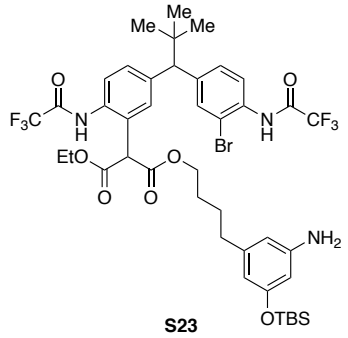
^{13}C NMR (151 MHz, $CDCl_3$) δ 169.0, 169.0, 168.7, 168.7, 156.9&156.8, 155.8 (q, *J* = 37.5 Hz), 154.8 (q, *J* = 37.8 Hz), 147.8&147.7, 144.5&144.5, 142.2&142.1, 141.2, 133.9&133.8, 133.7, 132.5&132.5, 131.6&131.6, 130.6&130.5, 129.8&129.8, 125.9, 125.7, 122.0&121.8, 114.2&114.1, 108.2&108.1, 106.1&106.1, 100.1&100.1, 66.9&66.8, 63.1, 63.0, 57.6&57.6, 35.4&35.4, 35.0&35.0, 29.2&29.2, 27.7&27.6, 27.0&26.9, 13.96.

^{19}F NMR (471 MHz, $CDCl_3$): –75.81, –75.82, –76.01.

HRMS (ESI/Q-TOF): Exact mass calculated for $[C_{36}H_{38}BrF_6N_3O_7 + H]^+$ requires *m/z* = 820.1857, found *m/z* = 820.1890.

Optical Rotation: α_D^{20}= +13.1° (*c* = 0.5, MeOH, 93:7 er)

HPLC (Chiralpak® AD-H column, 16% IPA/Hexanes eluent, 1.25 mL min^{-1} flow rate, 250 nm, 25 °C, 1.0:1 dr): major diastereomers t_R= 12.2 min, 19.4 min; minor diastereomers t_R = 13.9 min, 28.0 min.



S23

1-(4-(3-amino-5-((*tert*-butyldimethylsilyl)oxy)phenyl)butyl) 3-ethyl 2-(5-(1-(3-bromo-4-(2,2,2-trifluoroacetamido)phenyl)-2,2-dimethylpropyl)-2-(2,2,2-trifluoroacetamido)phenyl) malonate (**S23**) was prepared from **3f** using **Procedure 4**. Crude material was purified by silica chromatography (0→25→60% EtOAc/Hex) to yield **S23** as a white solid (0.1007 g, 54% yield). **S23** was synthesized to prepare the authentic standard of **4f**.

TLC (30% EtOAc/Hex): R_f = 0.44.

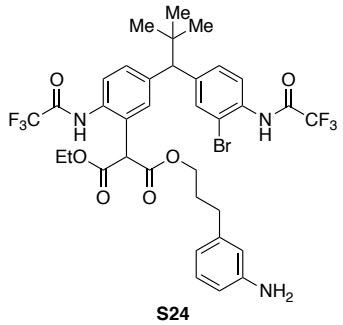
IR (FT-ATR, cm^{-1}, neat): ν_{max} 3436, 3233, 2931, 2860, 2115, 1728, 1660, 1387, 1255, 1153, 1094, 838, 660.

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.22 (s, 1H), 8.42 (s, 1H), 8.19 (d, *J* = 8.5 Hz, 1H), 7.78 (d, *J* = 8.3 Hz, 1H), 7.60 (s, 1H), 7.52 – 7.46 (m, 1H), 7.44 (d, *J* = 8.5 Hz, 1H), 7.22 (s, 1H), 6.08 (s, 1H), 6.05 (s, 1H), 6.03 (s, 1H), 4.63 (s, 1H), 4.27 – 4.08 (m, 4H), 3.68 (s, 1H), 3.57 (brs, 2H), 2.41 (t, *J* = 7.1 Hz, 2H), 1.66 – 1.59 (m, 2H), 1.57 – 1.49 (m, 2H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.01 (s, 9H), 0.97 (s, 9H), 0.18 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.9, 168.8, 168.8, 168.7, 156.7, 155.6 (q, *J* = 37.3 Hz), 154.7 (q, *J* = 37.7 Hz), 147.5, 144.1, 142.1&142.1, 141.0, 133.8, 133.7, 132.6, 131.6, 130.5&130.4, 129.9&129.8, 125.9, 125.6, 121.8, 116.1 (q, *J* = 288.5 Hz), 115.7 (q, *J* = 288.5 Hz), 114.0&114.0, 110.9, 108.8, 104.9, 66.9&66.8, 63.0&63.0, 62.9&62.9, 57.5, 35.4, 35.3, 29.1, 27.8&27.8, 27.2& 27.2, 25.8, 18.3, 13.9, –4.3.

^{19}F NMR (471 MHz, $CDCl_3$) δ –75.82, –75.83, –76.02.

HRMS (ESI/Q-TOF): Exact mass calculated for $[C_{42}H_{52}BrF_6N_3O_7Si + H]^+$ requires *m/z* = 932.2740, found *m/z* = 932.2746.



S24

1-(3-(3-aminophenyl)propyl) 3-ethyl 2-(5-(1-(3-bromo-4-(2,2,2-trifluoroacetamido)phenyl)-2,2-dimethylpropyl)-2-(2,2,2-trifluoroacetamido)phenyl)malonate (**S24**) was synthesized from **S17** following **Procedure 4**. Crude material was purified by silica chromatography (0→40→80% EtOAc/Hex) to yield the desired product as a white solid (0.3641 g, 67% yield).

TLC (30% EtOAc/Hex): R_f = 0.42.

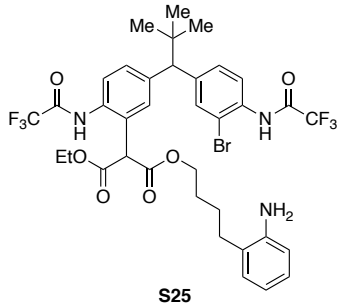
IR (FT-ATR, cm-1, neat): ν_{max} 3383, 2962, 2204, 2103, 1720, 1604, 1531, 1281, 1153, 1027, 734.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.24 (s, 1H), 8.40 (s, 1H), 8.17 (t, *J* = 8.1 Hz, 1H), 7.85 – 7.77 (m, 1H), 7.60 (dd, *J* = 5.5, 1.9 Hz, 1H), 7.53 – 7.48 (m, 1H), 7.47 – 7.41 (m, 1H), 7.25 (dd, *J* = 4.9, 2.6 Hz, 2H), 7.02 (td, *J* = 7.7, 3.7 Hz, 1H), 6.53 – 6.49 (m, 1H), 6.48 – 6.43 (m, 1H), 6.36 (d, *J* = 8.3 Hz, 1H), 4.65&4.65 (s*, 1H), 4.32 – 4.06 (m, 4H), 3.73 (brs, 2H), 3.70 (s, 1H), 2.44 (q, *J* = 7.5 Hz, 2H), 1.93–1.79 (m, 2H), 1.25 (t, *J* = 7.1, 3H), 1.03&1.02 (s*, 9H). (Note: *indicates overlap of two diastereomeric singlets that may appear as an apparent doublet)

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.8, 168.8, 168.7, 155.7 (q, *J* = 37.4 Hz), 154.7 (q, *J* = 38.0 Hz), 146.4&146.3, 142.1, 141.9, 141.1&141.1, 133.8&133.7, 133.7, 132.6&132.6, 131.6&131.6, 130.5&130.4, 129.8&129.8, 129.5&129.4, 125.9, 125.7&125.7, 121.8, 118.9, 116.1 (q, *J* = 289.9 Hz), 115.7 (q, *J* = 289.9 Hz), 115.4, 114.1, 113.2, 66.0, 63.1, 63.0, 57.5, 35.4&35.4, 31.7&31.7, 29.7, 29.2, 14.0.

^{19}F NMR (376 MHz, $CDCl_3$) δ –75.84, –76.04.

HRMS (ESI/Q-TOF): Exact mass calculated for $[C_{35}H_{36}BrF_6N_3O_6 + H]^+$ requires m/z = 790.1751, found *m/z* = 790.1746.



S25

1-(4-(2-aminophenyl)butyl) 3-ethyl 2-(5-(1-(3-bromo-4-(2,2,2-trifluoroacetamido)phenyl)-2,2-dimethylpropyl)-2-(2,2,2-trifluoroacetamido)phenyl)malonate (**S25**) was synthesized from **S18** following **Procedure 4**. Crude material was purified by silica chromatography (0→30→60% EtOAc/Hex) to yield the desired product as a white solid.

Yield: 84% (0.1347 g)

TLC (30% EtOAc/Hex): R_f =0.39.

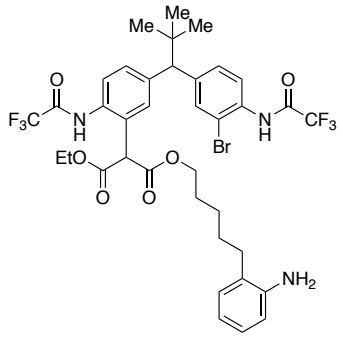
IR (FT-ATR, cm^{-1}, neat): ν_{max} 3386, 3021, 2966, 1968, 1737, 1531, 1283, 1215, 1158, 1030, 903, 667.

^{1}H NMR (600 MHz, $CDCl_3$) δ 10.21 (s, 1H), 8.40 (s, 1H), 8.19 (d, *J* = 8.5 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.59 (s, 1H), 7.48 (d, *J* = 8.4 Hz, 1H), 7.43 (d, *J* = 8.5 Hz, 1H), 7.22 (brs, 1H), 7.02 (t, *J* = 7.6 Hz, 1H), 6.98 – 6.93 (m, 1H), 6.70 (td, *J* = 7.4, 3.9 Hz, 1H), 6.65 (d, *J* = 7.9 Hz, 1H), 4.64&4.63 (s*, 1H), 4.31 – 4.10 (m, 4H), 3.68&3.67 (s*, 1H), 3.43 (brs, 2H), 2.43 (t, *J* = 7.7 Hz, 2H), 1.68 (p, *J* = 6.6 Hz, 2H), 1.57 (p, *J* = 7.4 Hz, 2H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.01&1.00 (s*, 9H). (Note: *indicates overlap of two diastereomeric singlets that may appear as an apparent doublet)

^{13}C NMR (151 MHz, $CDCl_3$): δ 168.9, 168.9, 168.8, 168.7, 155.7 (q, *J* = 37.8 Hz), 154.8 (q, *J* = 37.8 Hz), 144.1, 142.1&142.0, 141.1&141.1, 133.7, 133.7, 132.6, 131.6, 130.5&130.4, 129.9& 129.8, 129.5&129.5, 127.2&127.2, 126.0&126.0, 125.8&125.7, 121.7, 118.9&118.9, 116.1 (q, *J* = 288.4 Hz), 115.8*, 115.8*, 115.7 (q, *J* = 288.4 Hz), 114.0*, 114.0*, 66.7*, 66.7*, 63.1*, 63.1*, 63.0&62.9, 57.5&57.5, 35.4, 30.7, 29.2&29.1, 28.2&28.2, 24.8, 13.9.

^{19}F NMR (471 MHz, $CDCl_3$): δ –75.83, –76.03.

HRMS (ESI/Q-TOF): Exact mass calculated for $[C_{36}H_{38}BrF_6N_2O_6 + H]^+$ requires *m/z*= 804.1908, found *m/z* = 804.1905.



S26

1-(5-(2-aminophenyl)pentyl) 3-ethyl 2-(5-(1-(3-bromo-4-(2,2,2-trifluoroacetamido)phenyl)-2,2-dimethylpropyl)-2-(2,2,2-trifluoroacetamido)phenyl)malonate (**S26)** was synthesized from **S19** following **Procedure 4**. Crude material was purified by silica chromatography (0→30→60% EtOAc/Hex) to yield the desired product as a white solid (0.4192 g, 60% yield).

TLC (40% EtOAc/Hex): $R_f = 0.59$.

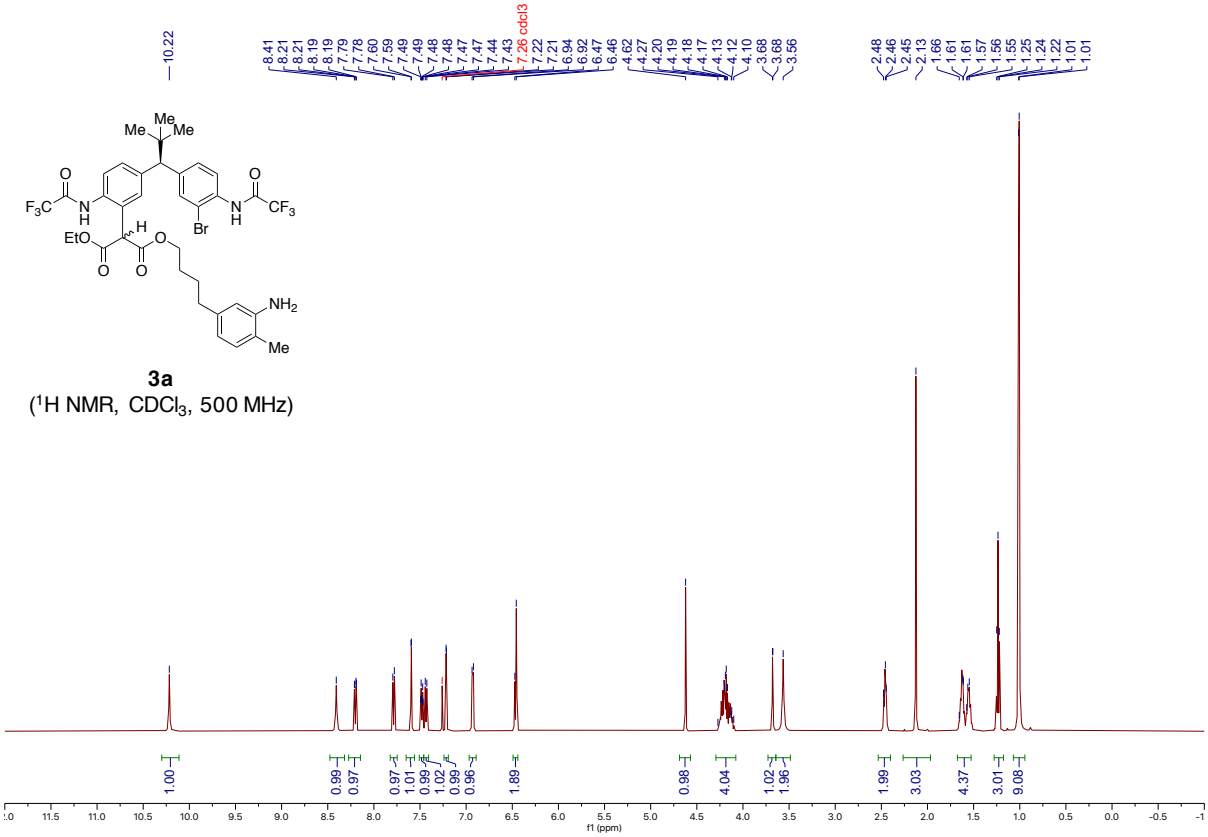
IR (FT-ATR, cm^{-1}, neat): ν_{max} 3384, 2952, 2864, 2381, 2201, 1982, 1720, 1531, 1281, 1151, 1028, 750.

^{1}H NMR (600 MHz, $CDCl_3$) δ 10.23 (s, 1H), 8.39 (d, *J* = 9.5 Hz, 1H), 8.20 (t, *J* = 7.6 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.60 (s, 1H), 7.48 (d, *J* = 8.3 Hz, 1H), 7.44 (d, *J* = 8.5 Hz, 1H), 7.22 (s, 1H), 7.05 – 7.00 (m, 1H), 6.98 (t, *J* = 6.6 Hz, 1H), 6.72 (t, *J* = 6.8 Hz, 1H), 6.68 – 6.63 (m, 1H), 4.63 (s, 1H), 4.28 – 4.07 (m, 4H), 3.68 (s, 1H), 3.06 (brs, 2H), 2.47 – 2.36 (m, 2H), 1.66 – 1.51 (m, 4H), 1.35 – 1.28 (m, 2H), 1.27 – 1.22 (m, 3H), 1.02 (s, 9H).

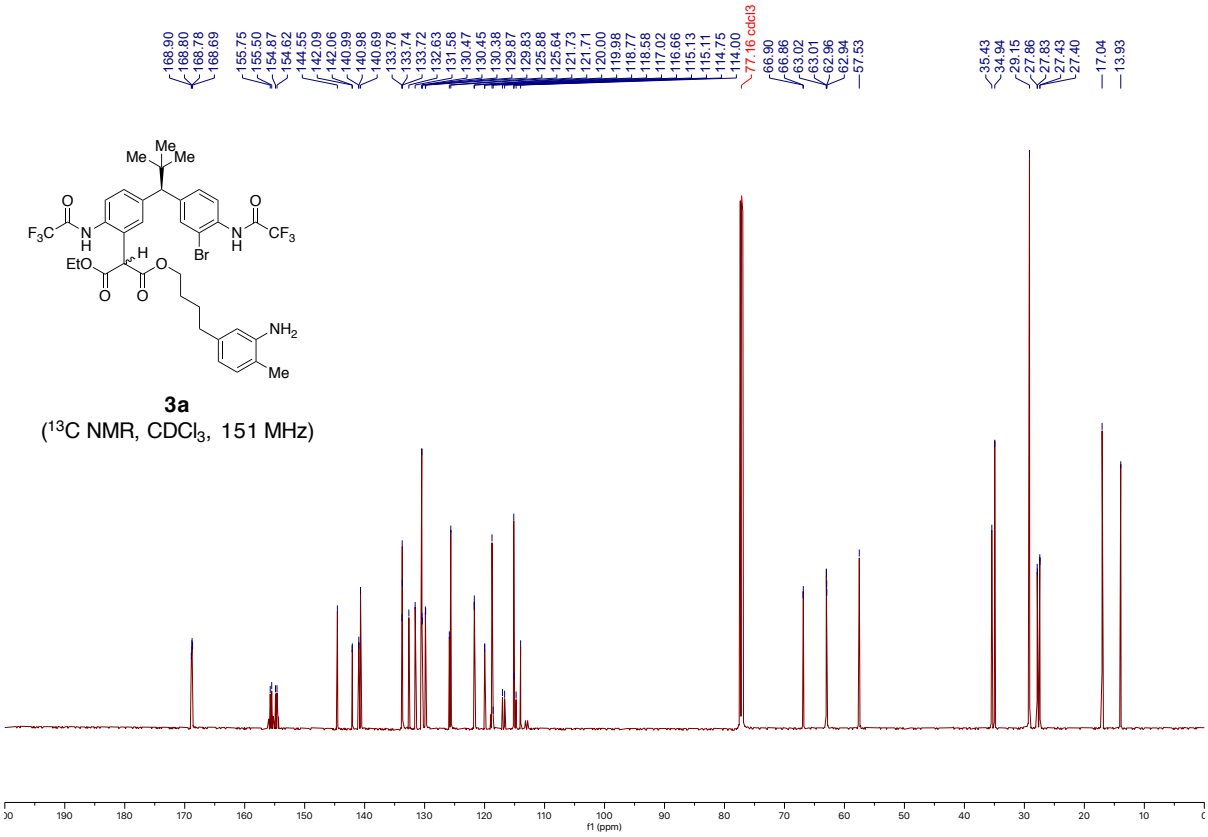
^{13}C NMR (151 MHz, $CDCl_3$): δ 168.9, 168.8, 168.8, 168.7, 155.6 (q, *J* = 37.4 Hz), 154.8 (q, *J* = 37.7 Hz), 144.1, 142.1&142.1, 141.0, 133.8&133.8, 133.8, 132.6, 131.6, 130.5&130.4, 129.9& 129.8, 129.5, 127.1, 126.5, 125.9, 125.7, 121.8&121.7, 118.9, 116.1 (q, *J* = 288.4 Hz), 115.7 (q, *J* = 288.4 Hz), 115.8, 114.1&114.0, 66.8, 63.1, 63.0, 57.6, 35.5, 31.2, 29.2, 28.2, 25.7, 14.0.

^{19}F NMR (471 MHz, $CDCl_3$) δ –75.82, –76.03.

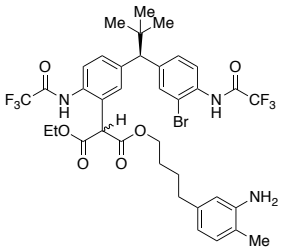
HRMS (ESI/Q-TOF): Exact mass calculated for $[C_{37}H_{40}BrF_6N_2O_6 + H]^+$ requires *m/z*= 815.2065, found *m/z* = 815.2059.



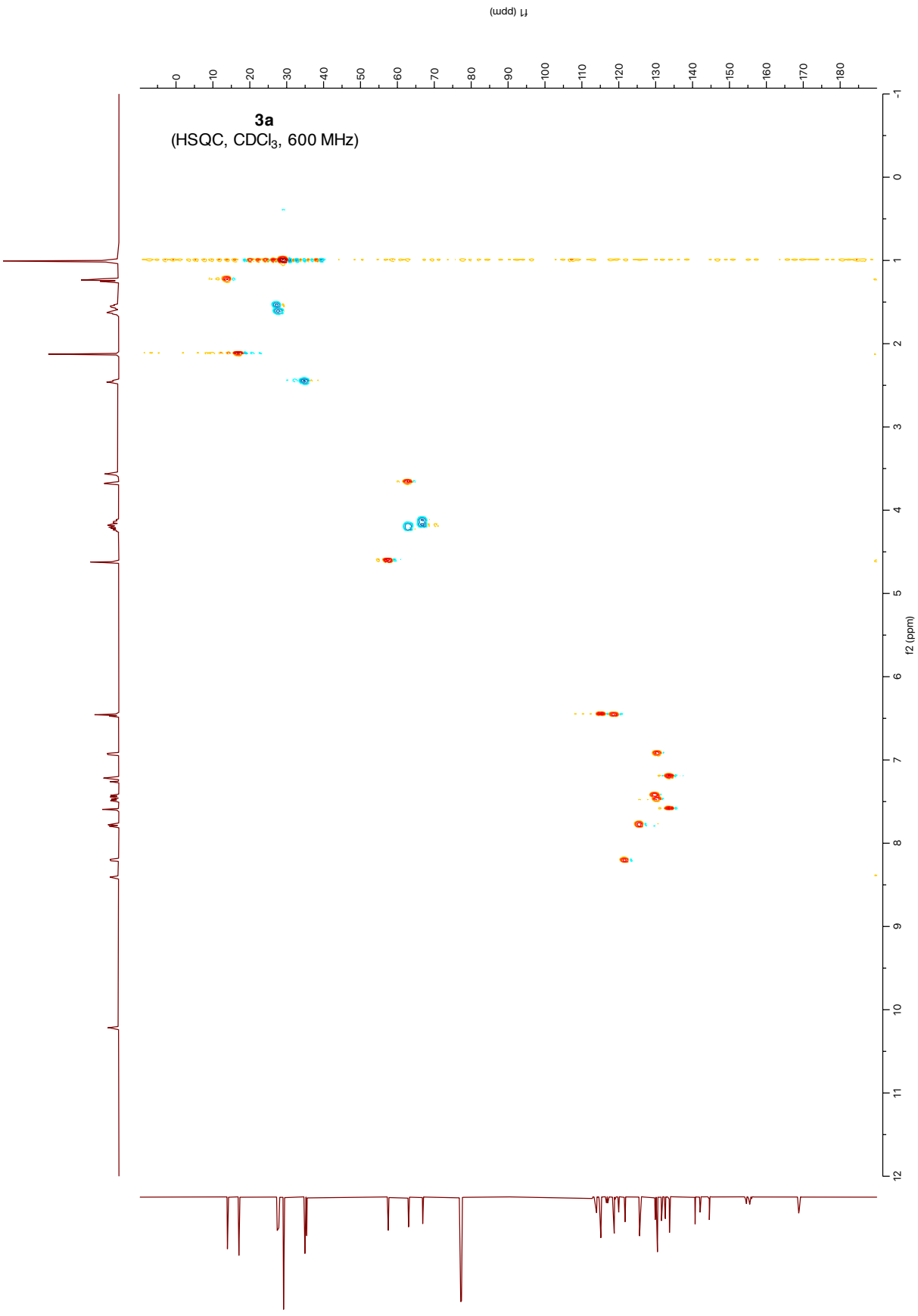
3a
(^{1}H NMR, $CDCl_3$, 500 MHz)

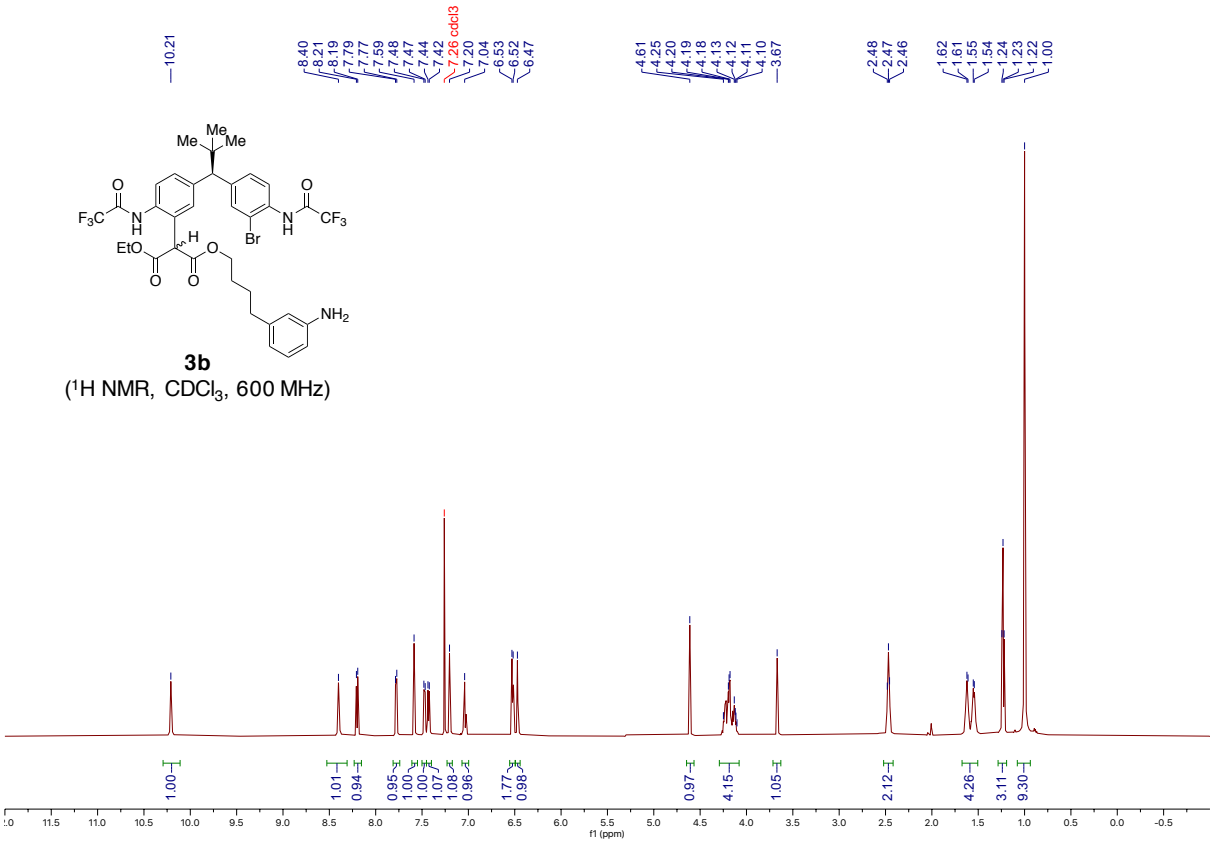


3a
(^{13}C NMR, $CDCl_3$, 151 MHz)



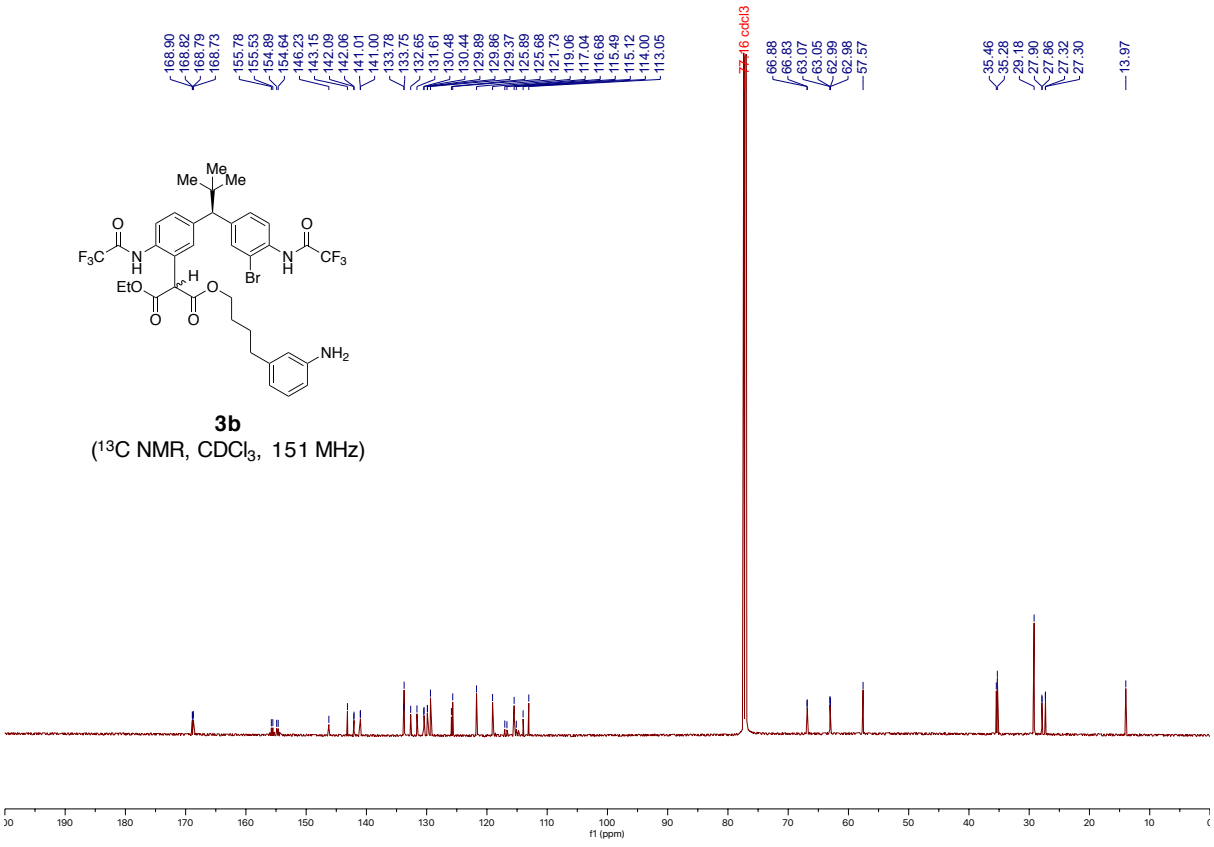
3a
(^{19}F NMR, $CDCl_3$, 471 MHz)


3a
(HSQC, CDCl3, 600 MHz)
f1 (ppm)
f2 (ppm)



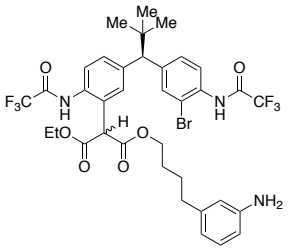
3b

(^{1}H NMR, $CDCl_3$, 600 MHz)



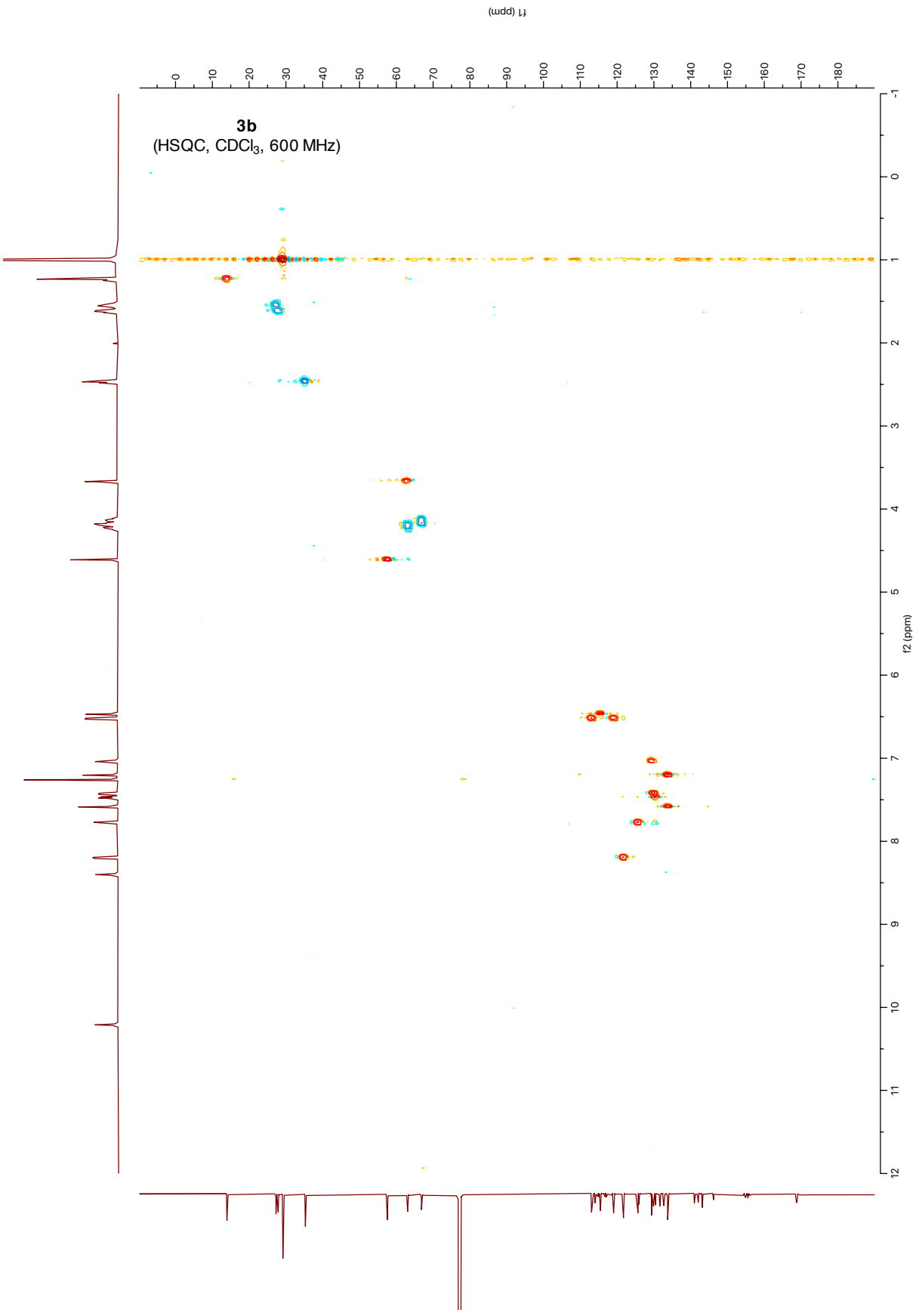
3b

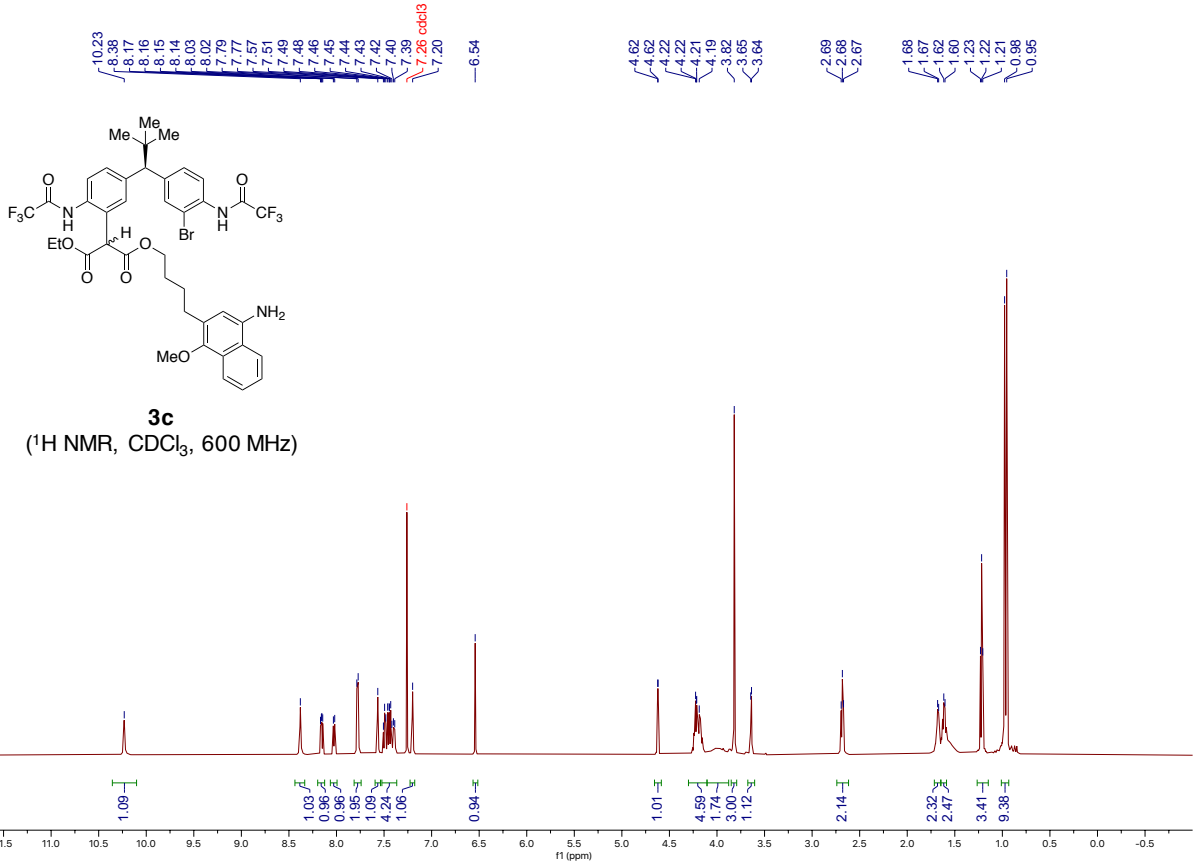
(^{13}C NMR, $CDCl_3$, 151 MHz)



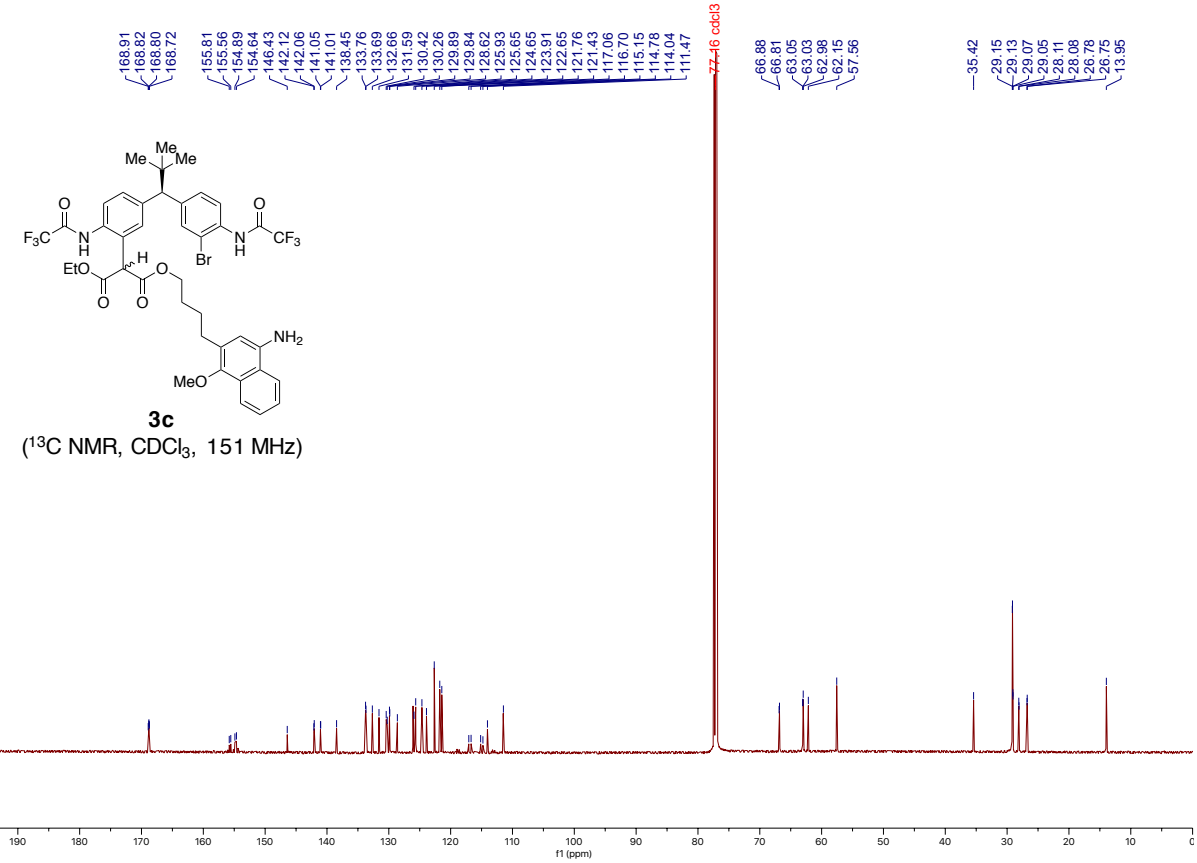
3b

(^{19}F NMR, $CDCl_3$, 471 MHz)

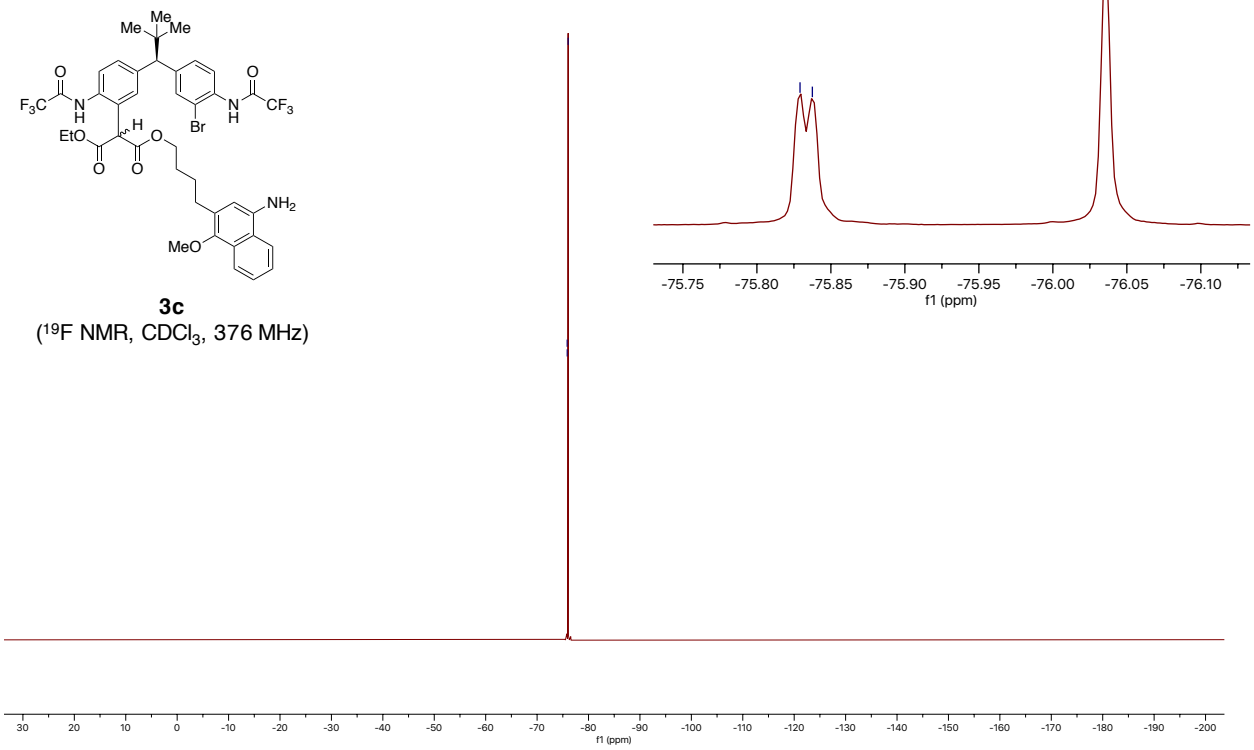

f1 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
3b
(HSQC, CDCl3, 600 MHz)
-1
0
1
2
3
4
5
6
7
8
9
10
11
12
f2 (ppm)



3c
(^{1}H NMR, $CDCl_3$, 600 MHz)

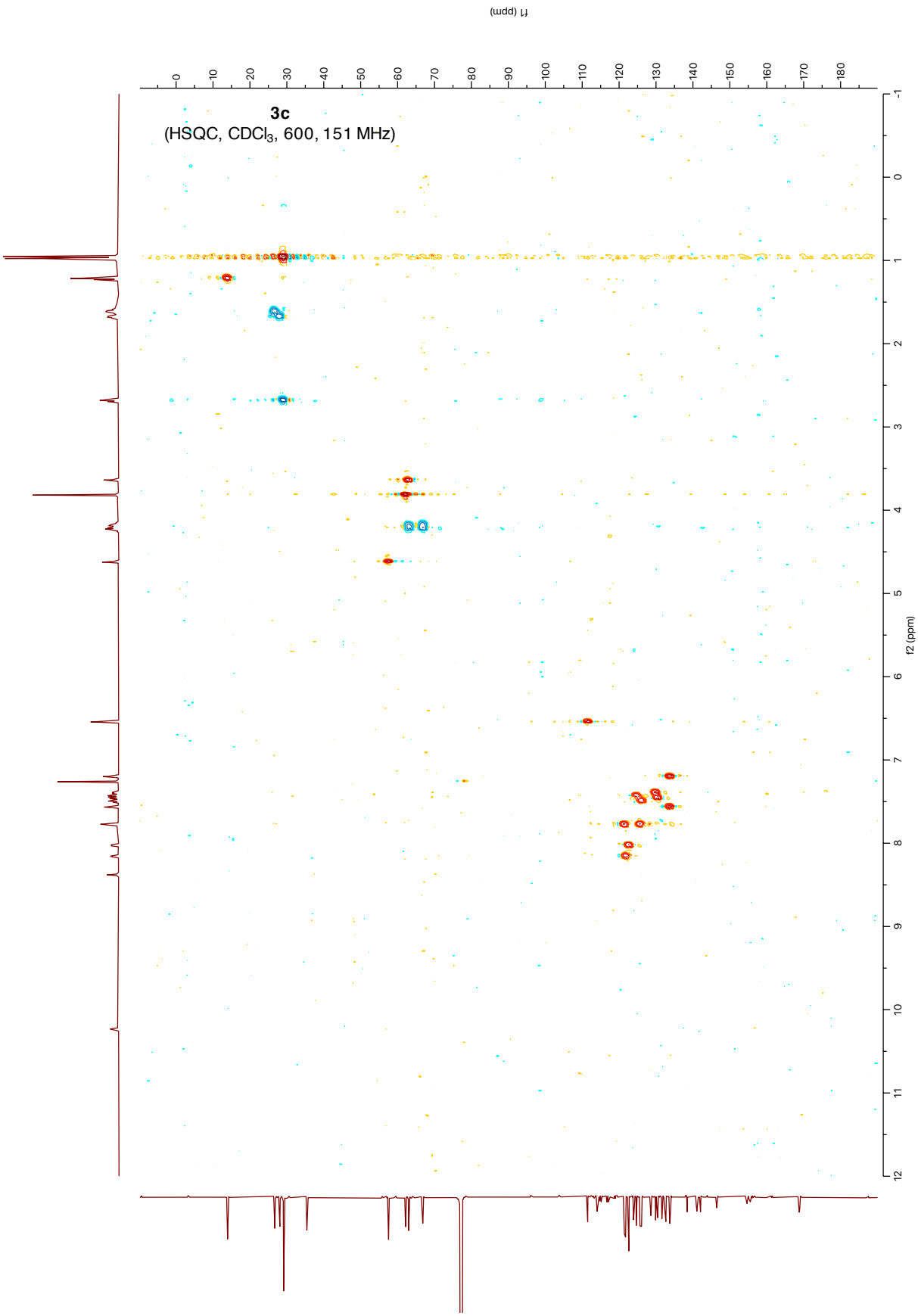


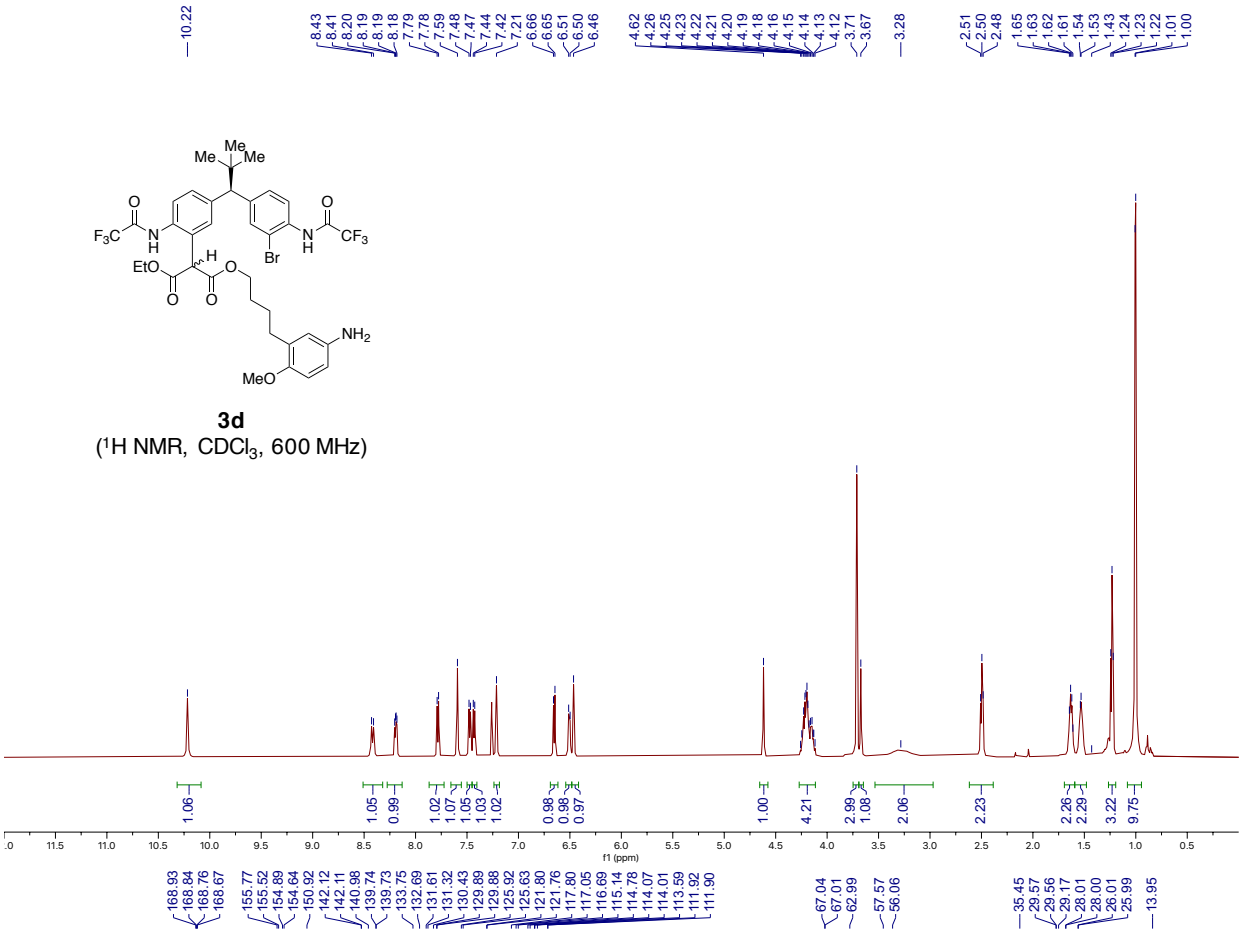
3c
(^{13}C NMR, $CDCl_3$, 151 MHz)



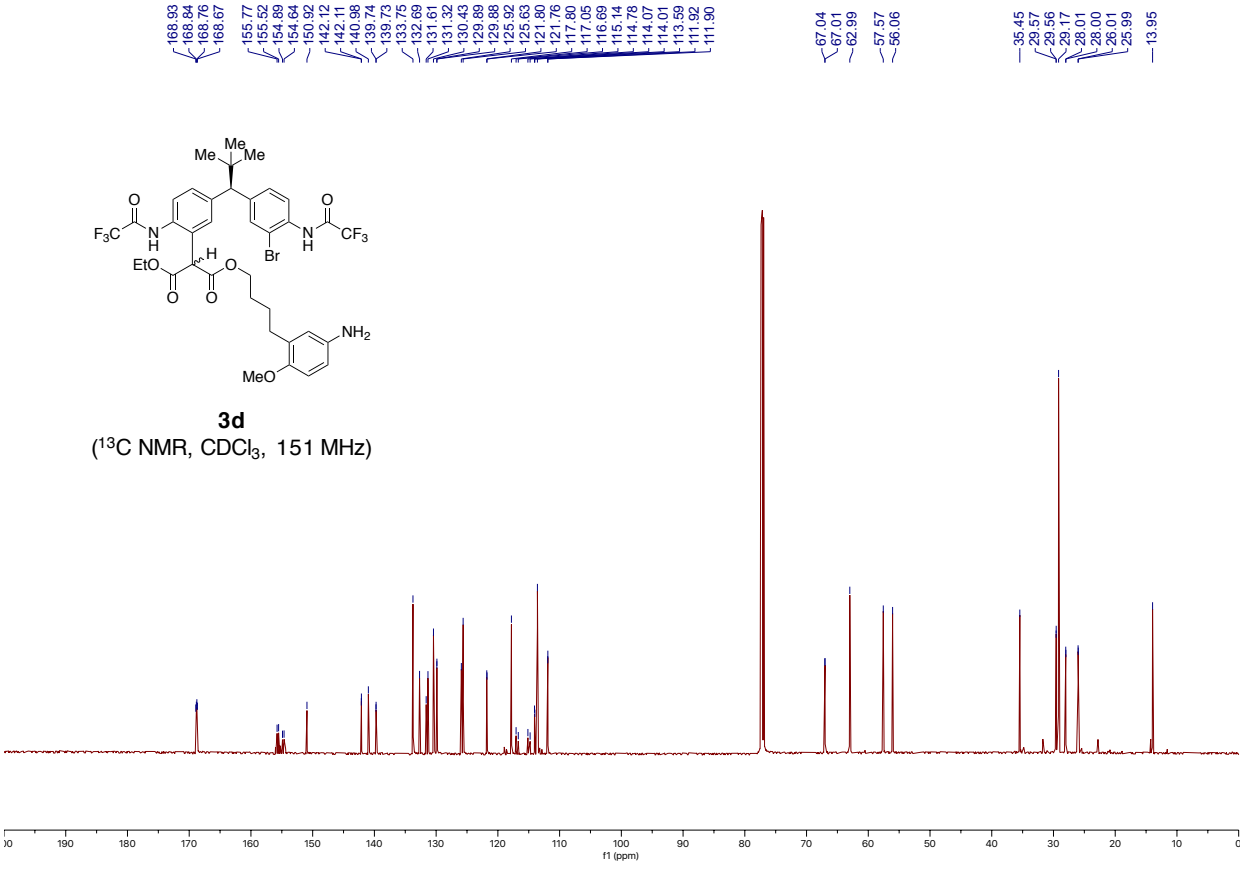
3c

(^{19}F NMR, $CDCl_3$, 376 MHz)

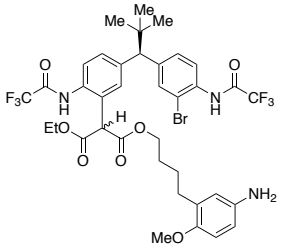

3c
(HSQC, CDCl3, 600, 151 MHz)
f1 (ppm)
f2 (ppm)



3d
(^{1}H NMR, $CDCl_3$, 600 MHz)

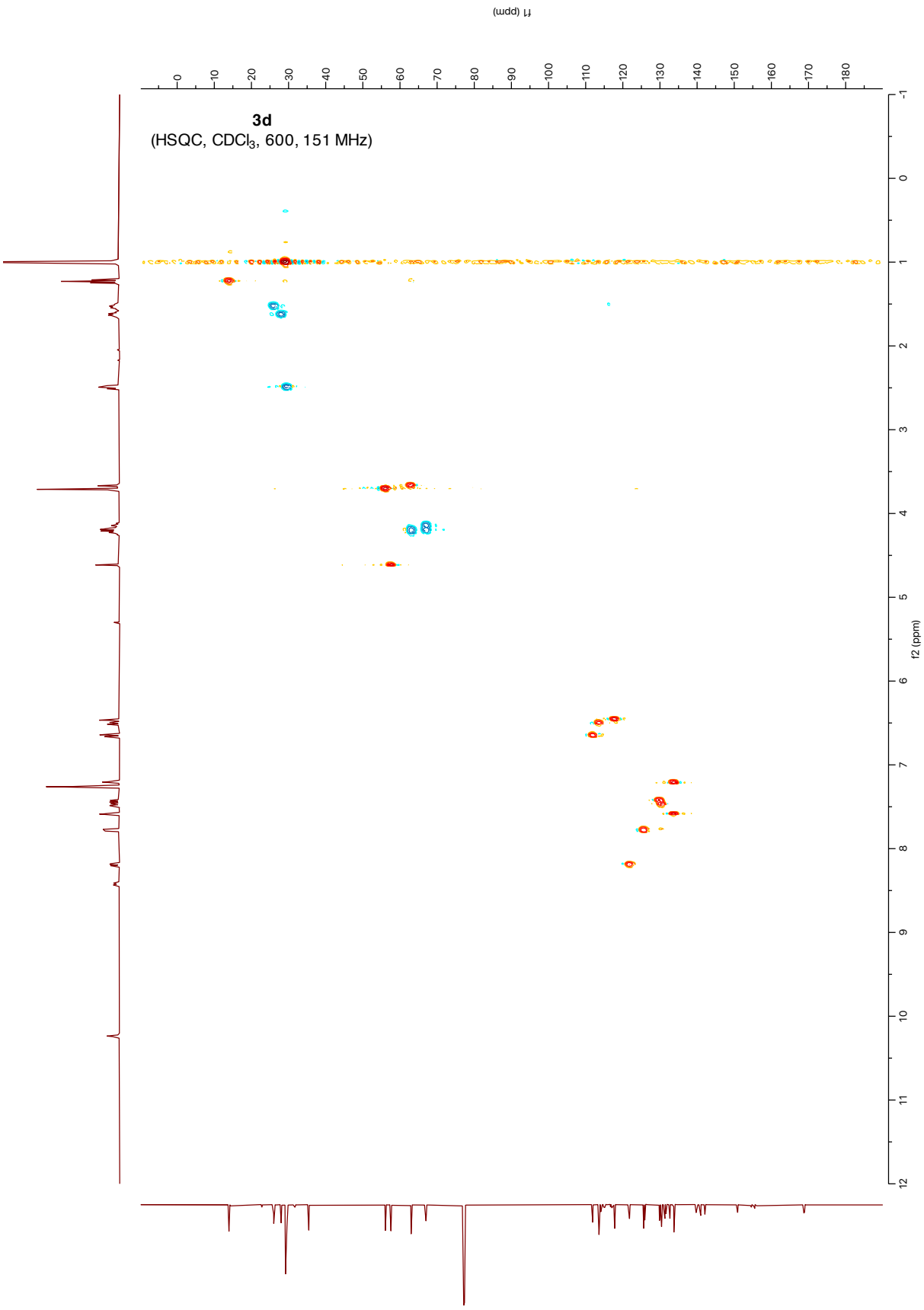


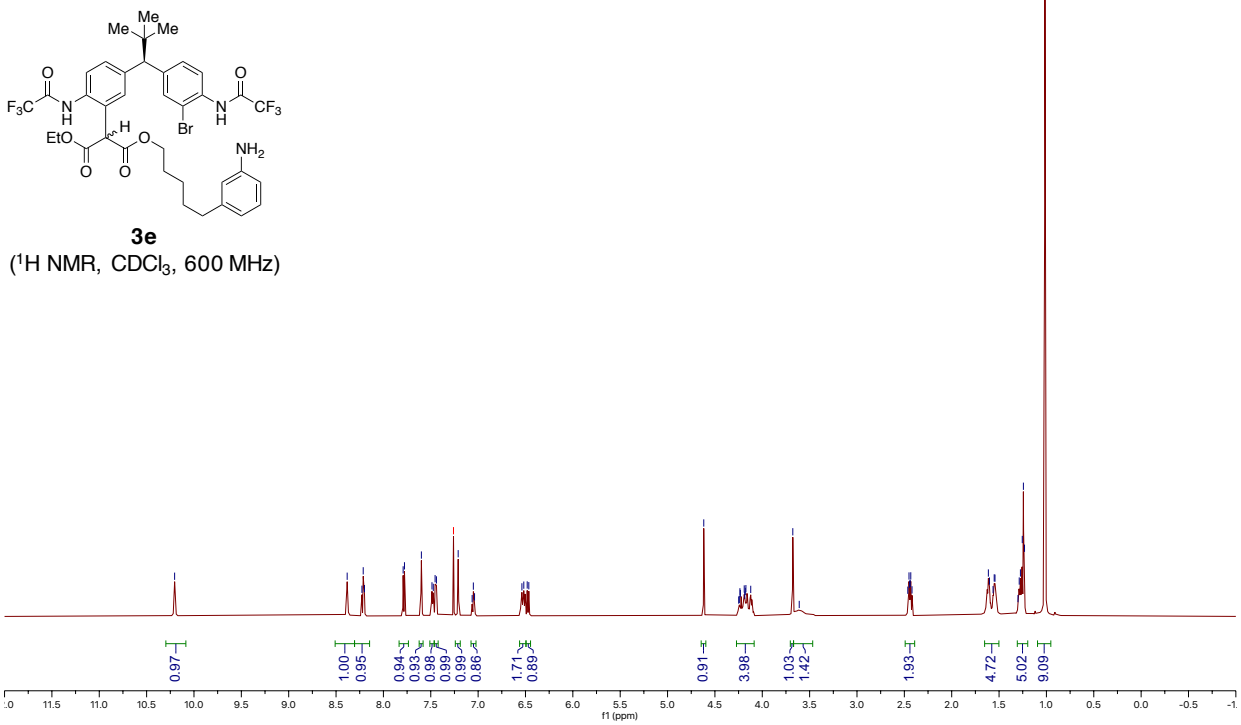
3d
(^{13}C NMR, $CDCl_3$, 151 MHz)



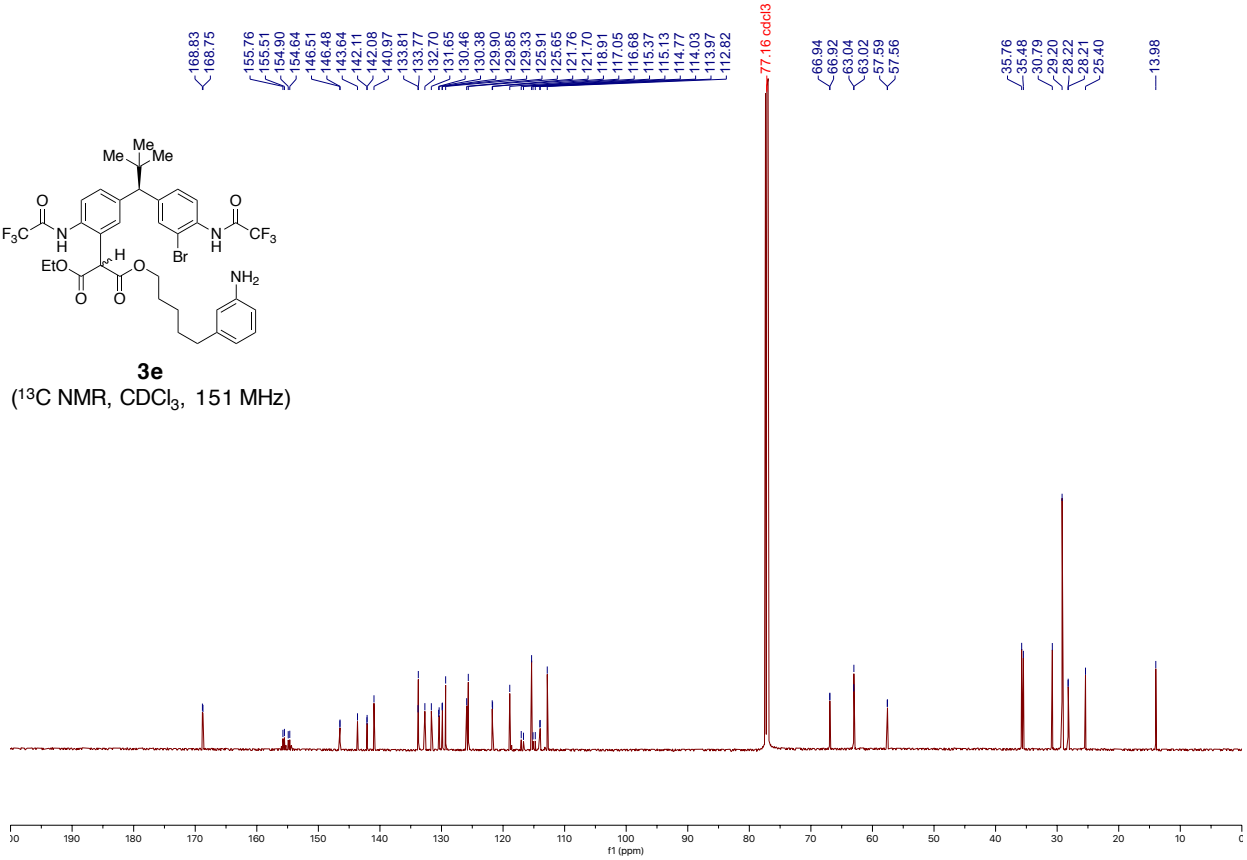
3d

(^{19}F NMR, $CDCl_3$, 376 MHz)

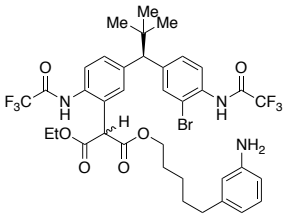

3d
(HSQC, CDCl3, 600, 151 MHz)
f1 (ppm)
f2 (ppm)



3e
(^{1}H NMR, $CDCl_3$, 600 MHz)

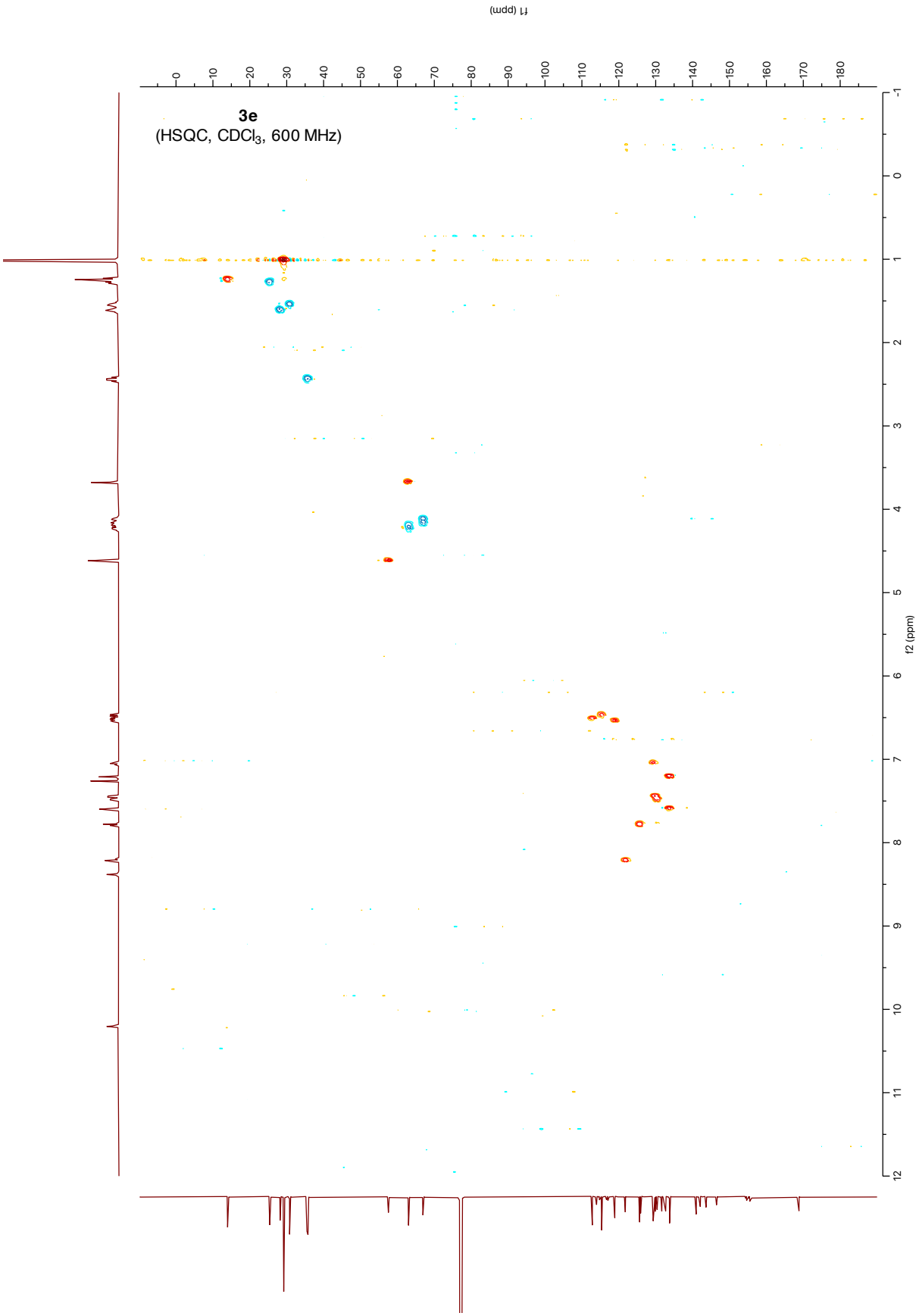


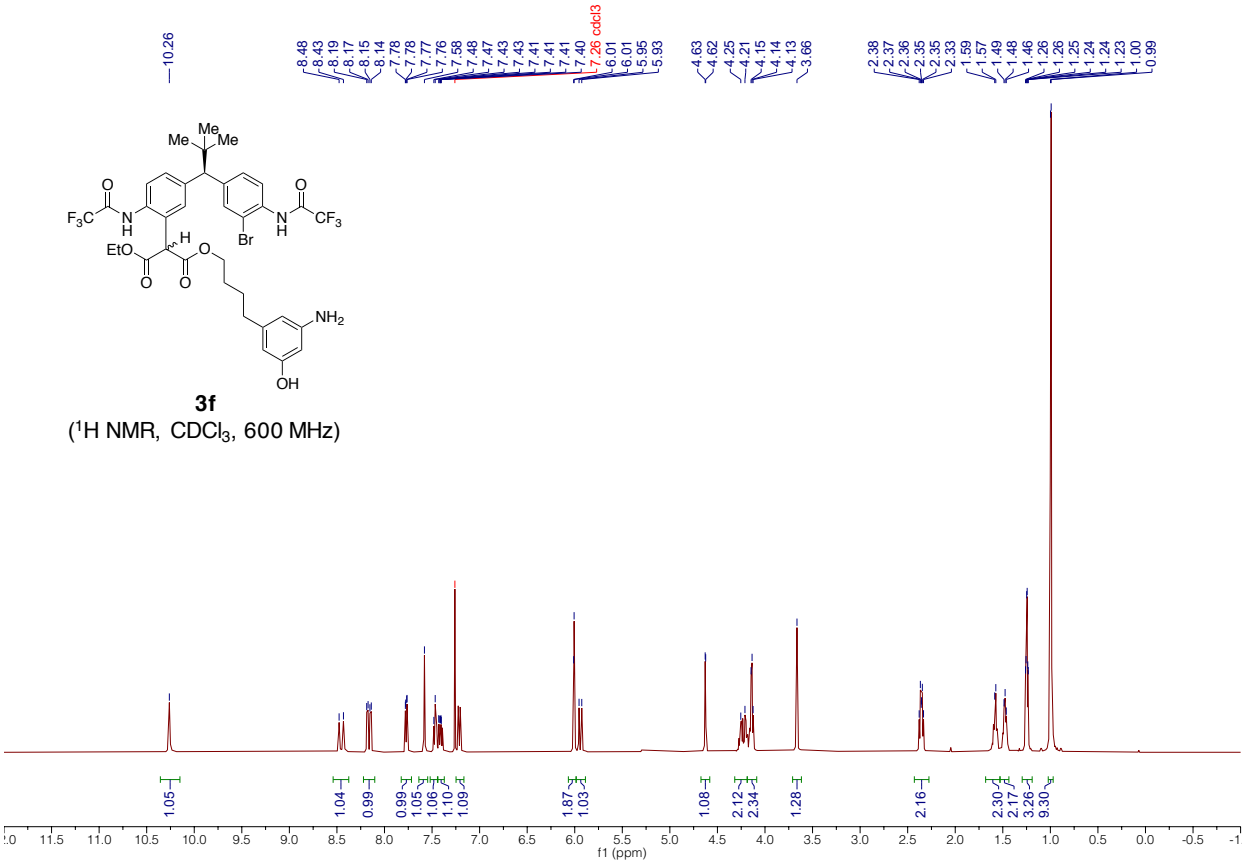
3e
(^{13}C NMR, $CDCl_3$, 151 MHz)



3e

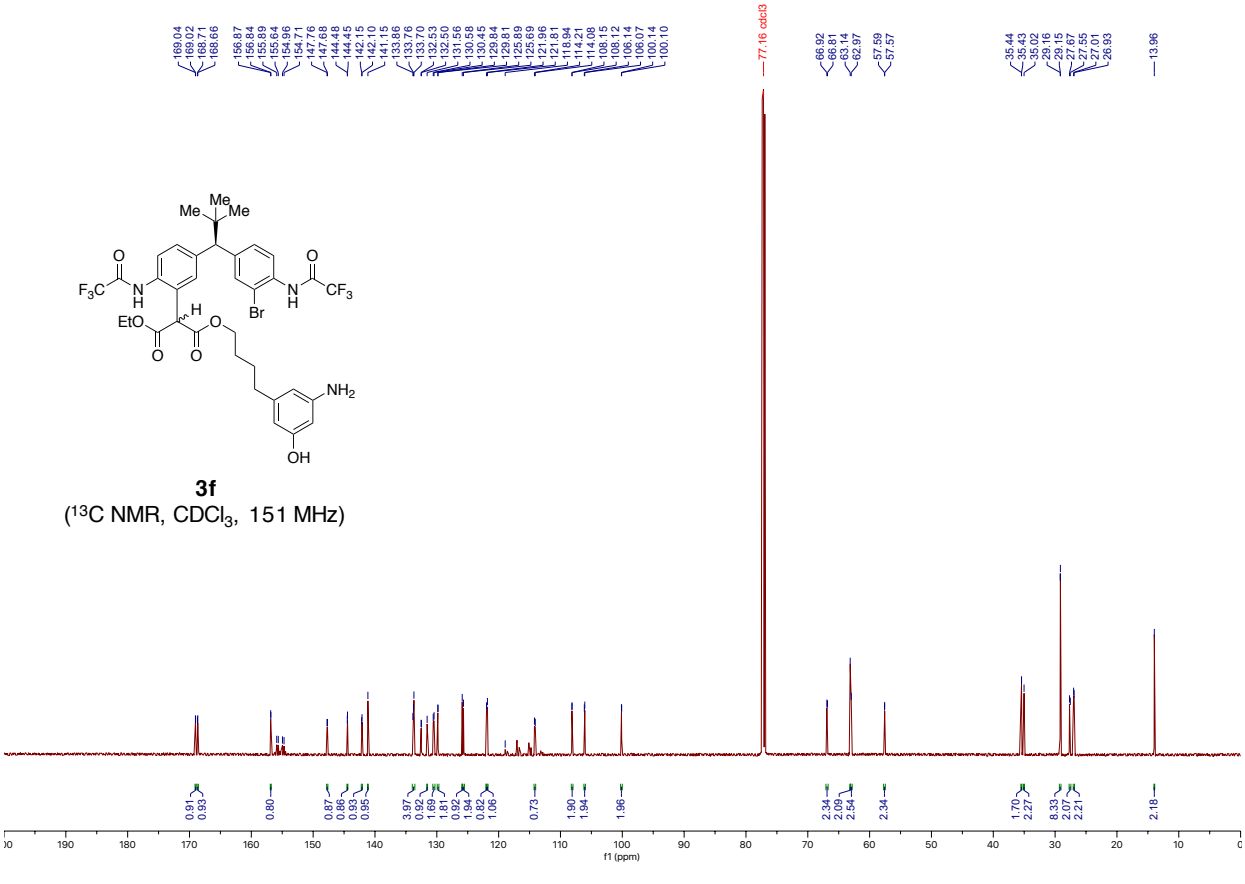
(^{19}F NMR, $CDCl_3$, 376 MHz)


3e
(HSQC, CDCl3, 600 MHz)
f1 (ppm)
f2 (ppm)



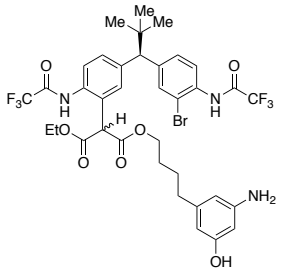
3f

(^{1}H NMR, $CDCl_3$, 600 MHz)



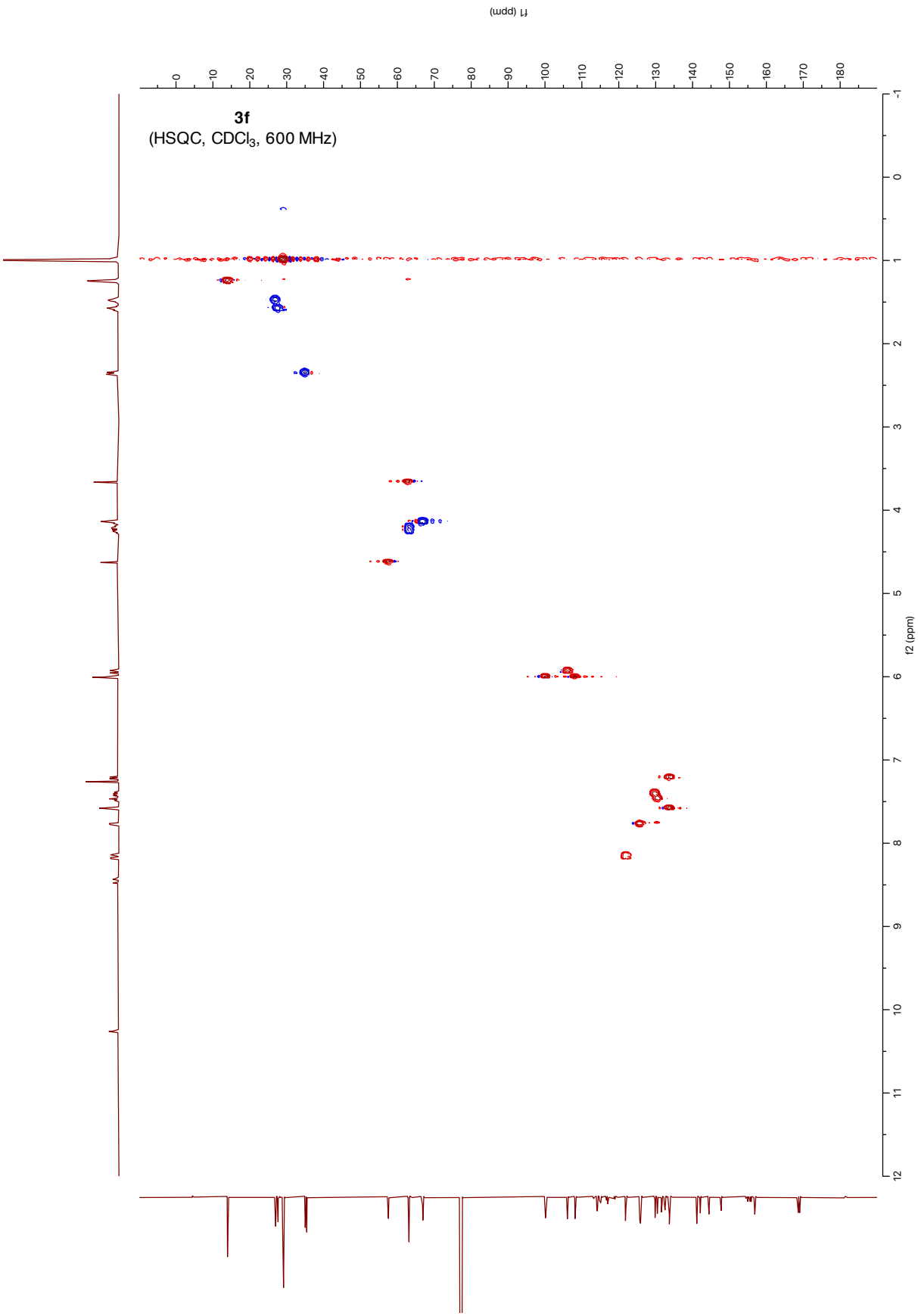
3f

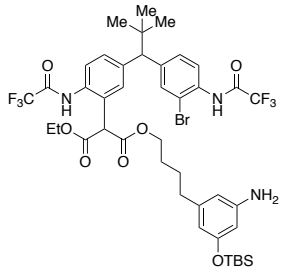
(^{13}C NMR, $CDCl_3$, 151 MHz)



3f

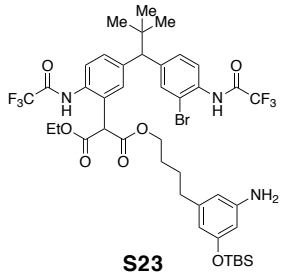
(^{19}F NMR, $CDCl_3$, 500 MHz)


f1 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
3f
(HSQC, CDCl3, 600 MHz)
-1
0
1
2
3
4
5
6
7
8
9
10
11
12
f2 (ppm)



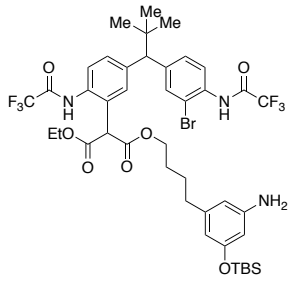
S23

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

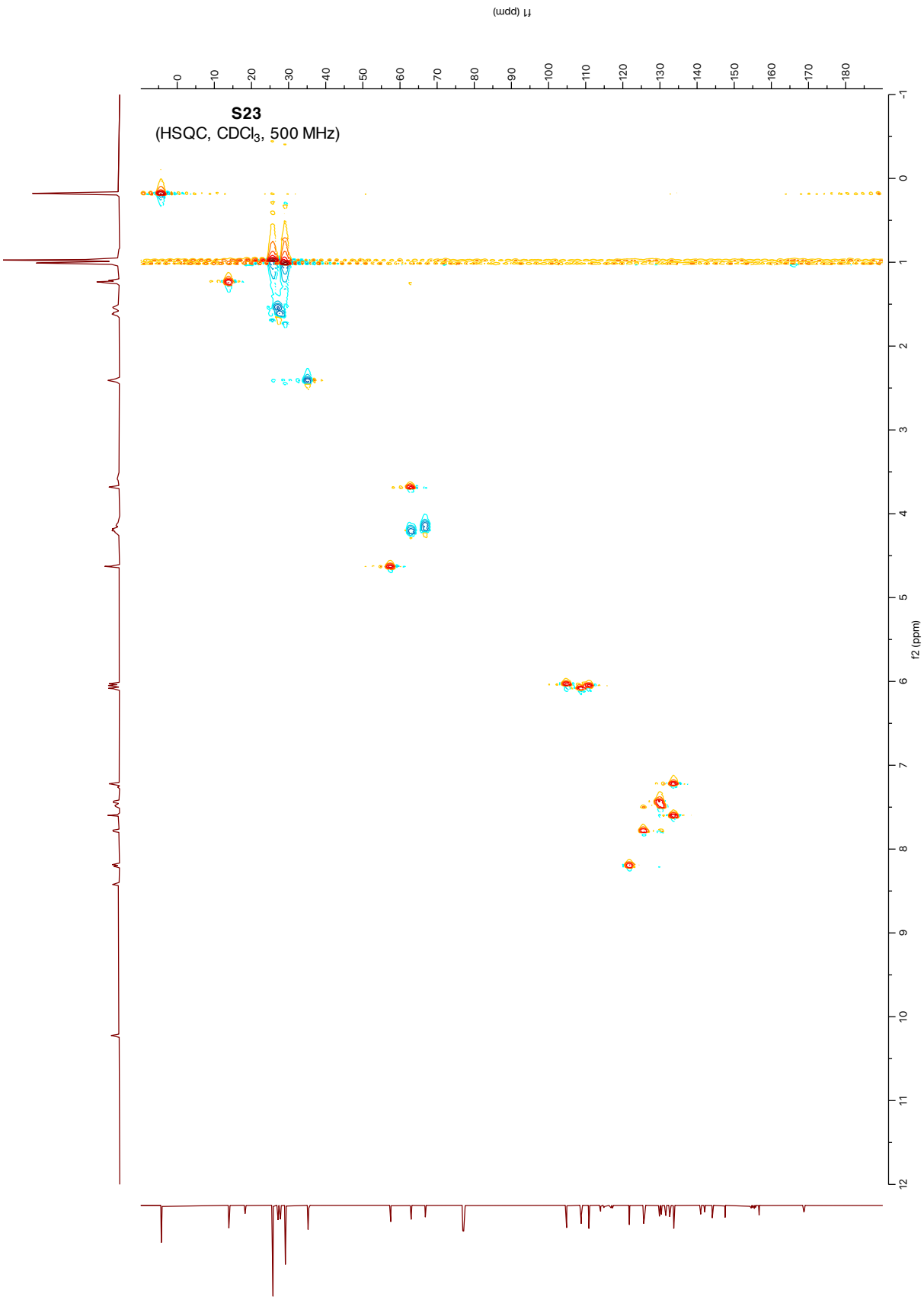


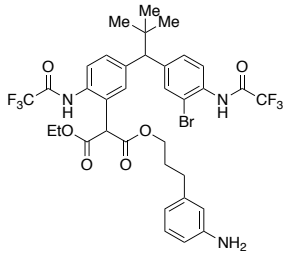
S23

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

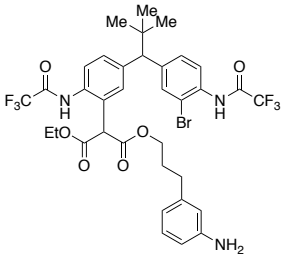


S23
(^{19}F NMR, $CDCl_3$, 471 MHz)

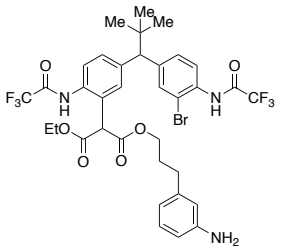

S23
(HSQC, CDCl3, 500 MHz)
f1 (ppm)
f2 (ppm)



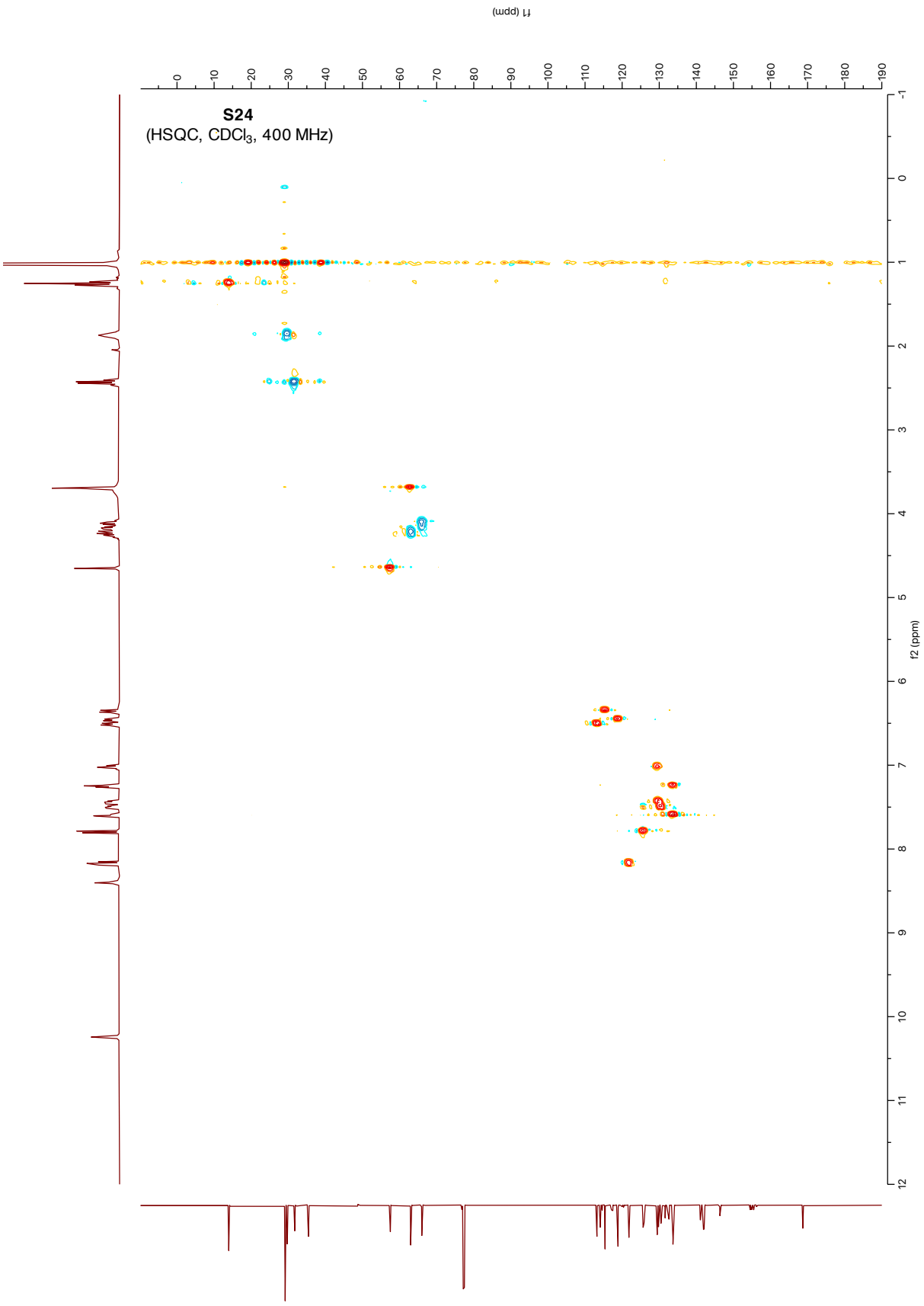
S24
(^{1}H NMR, $CDCl_3$, 400 MHz)

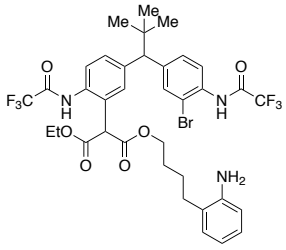


S24
(^{13}C NMR, $CDCl_3$, 101 MHz)

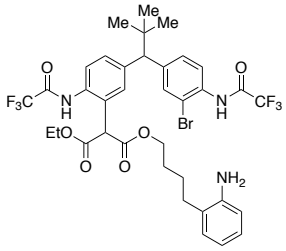


S24
(^{19}F NMR, $CDCl_3$, 376 MHz)

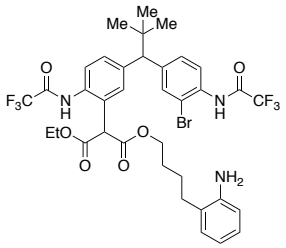

S24
(HSQC, CDCl3, 400 MHz)
f1 (ppm)
f2 (ppm)



S25
(^{1}H NMR, $CDCl_3$, 600 MHz)

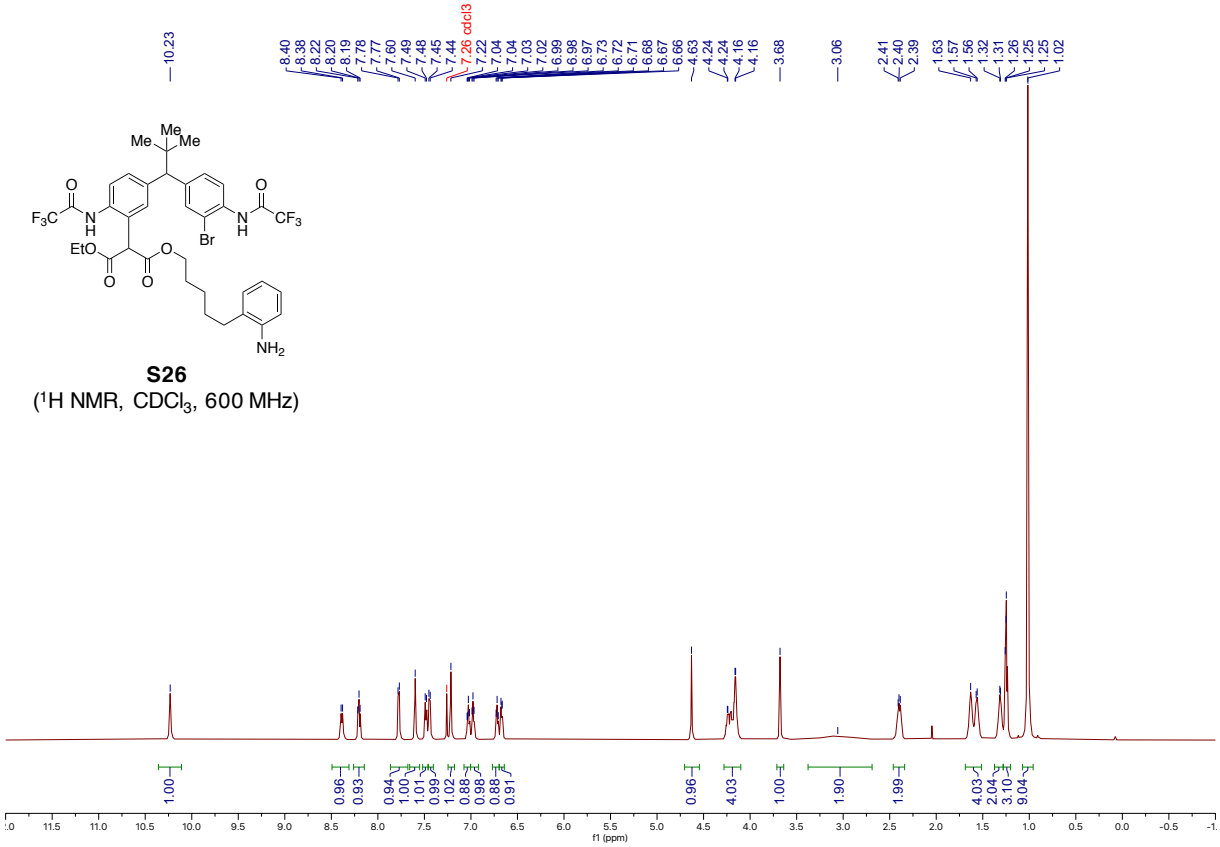


S25
(^{13}C NMR, $CDCl_3$, 151 MHz)

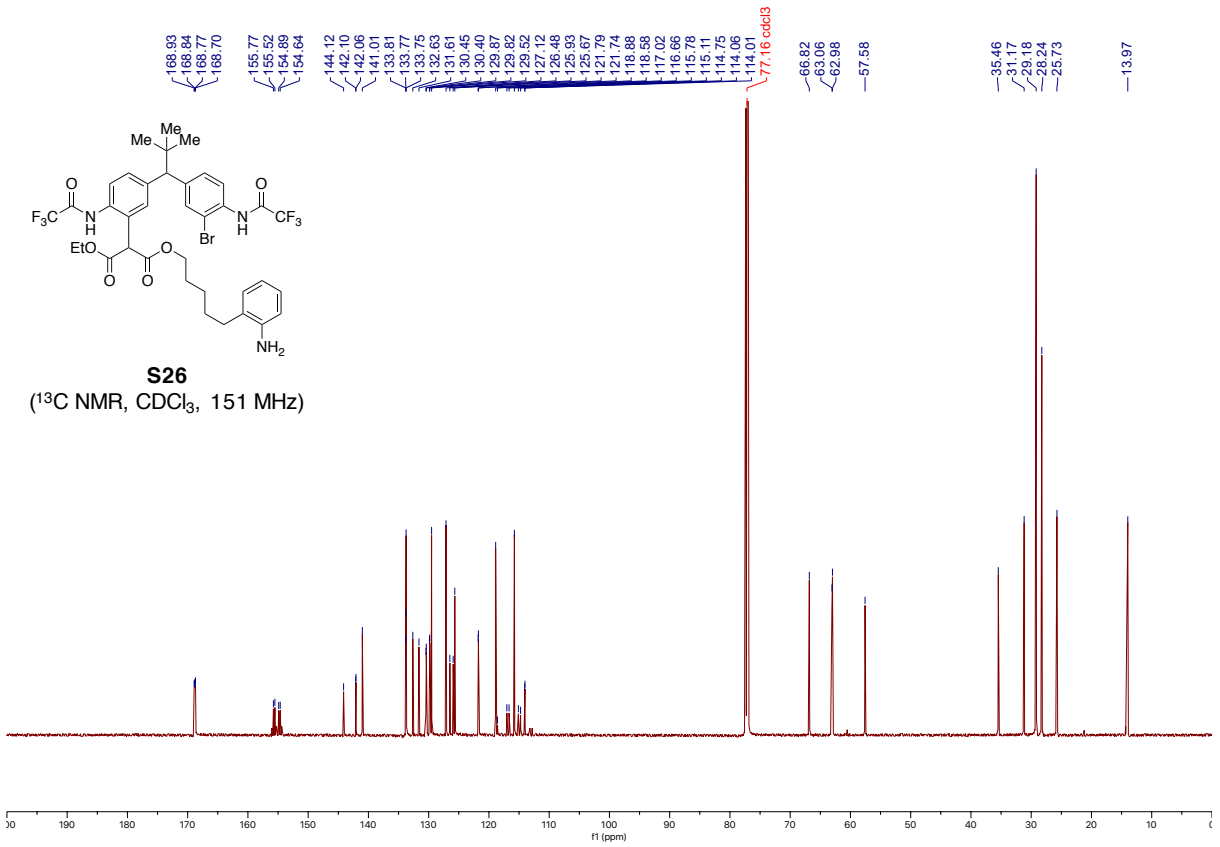


S25
(^{19}F NMR, $CDCl_3$, 471 MHz)

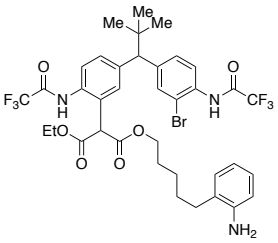

S25
(HSQC, CDCl3, 600 MHz)
f1 (ppm)
f2 (ppm)



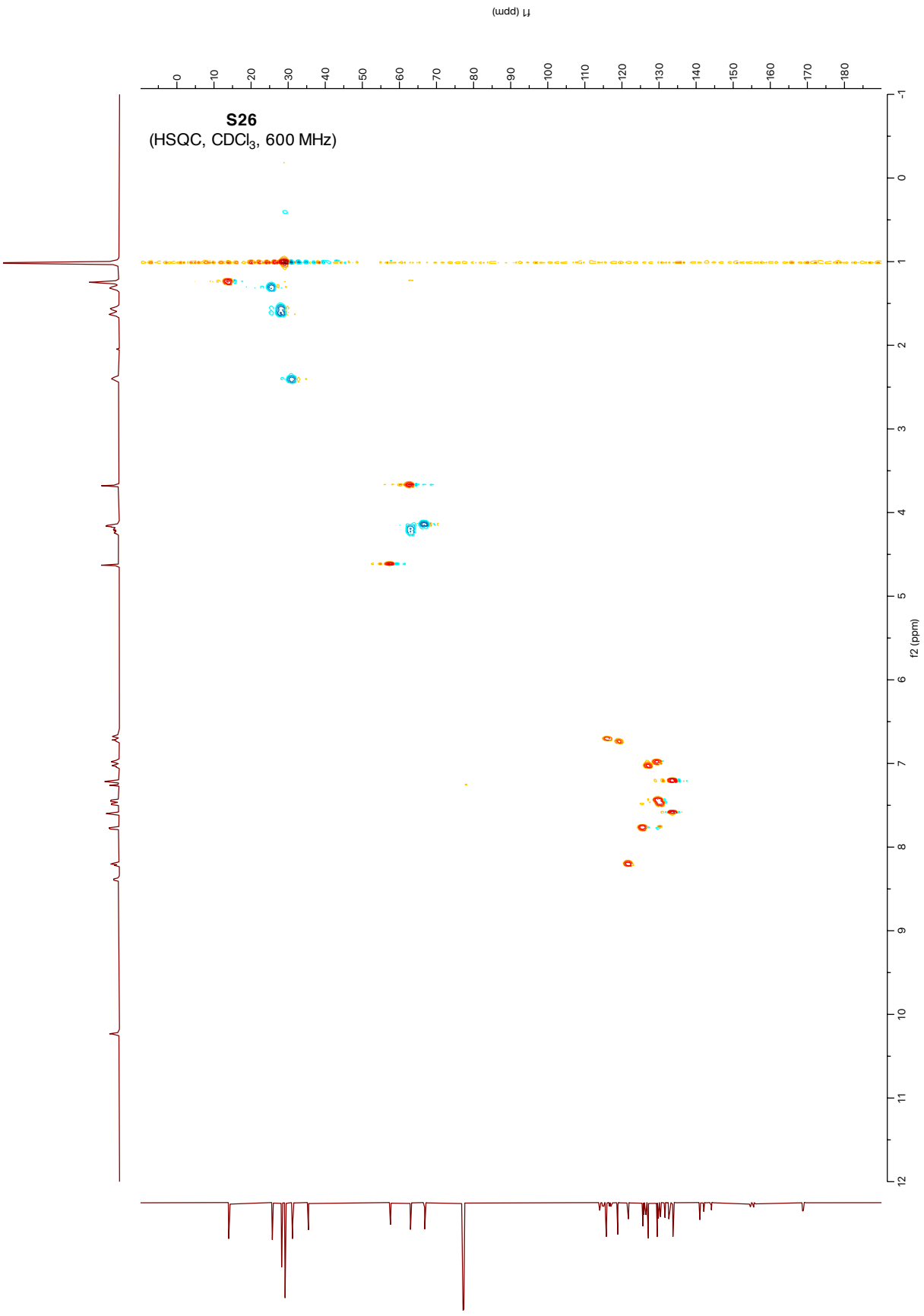
S26
(^{1}H NMR, $CDCl_3$, 600 MHz)



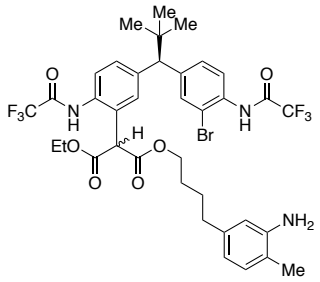
S26
(^{13}C NMR, $CDCl_3$, 151 MHz)



S26
(^{19}F NMR, $CDCl_3$, 471 MHz)

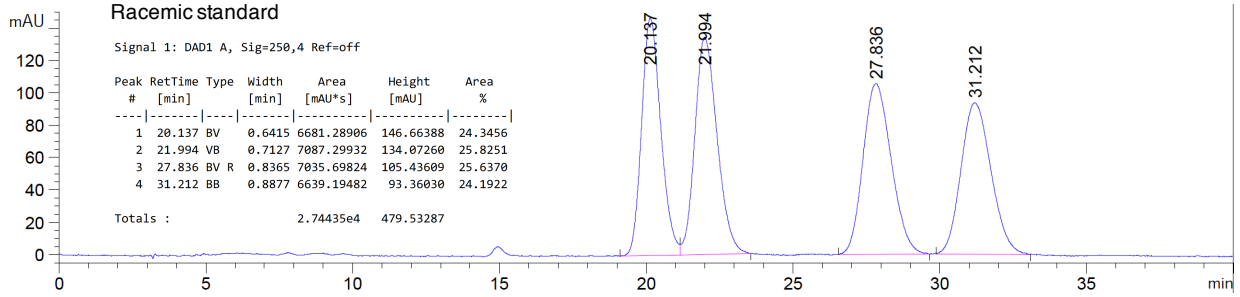

S26
(HSQC, CDCl3, 600 MHz)
f1 (ppm)
f2 (ppm)

8.5 HPLC Traces of Linear Precursors (3a-3f)



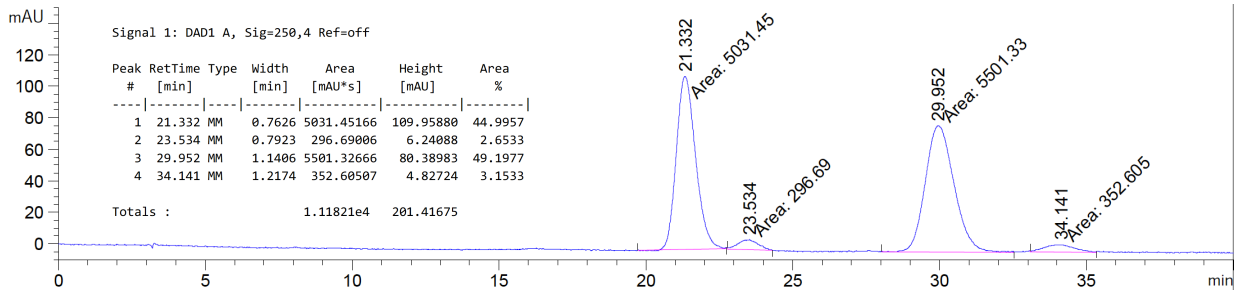
3a
Chiralpak AD-H
10% IPA/Hexanes, 1.00 mL/min, 25 °C, 250 nm

Racemic standard



Signal 1: DAD1 A, Sig=250,4 Ref=off

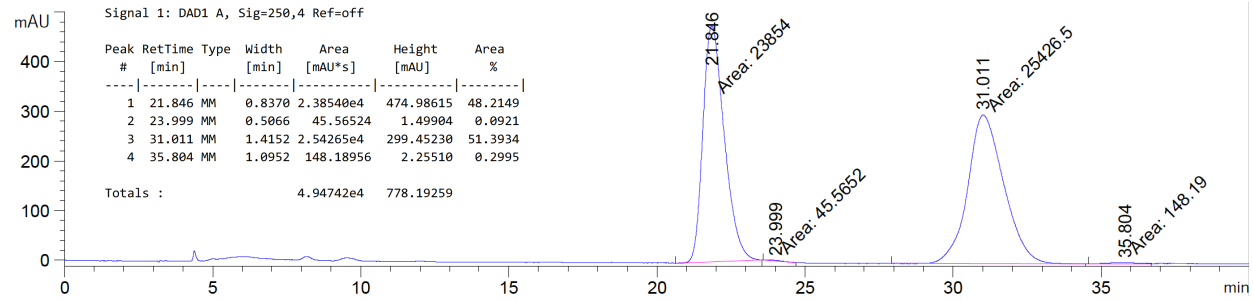
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.137	BV	0.6415	6681.28906	146.66388	24.3456
2	21.994	VB	0.7127	7087.29932	134.07260	25.8251
3	27.836	BV R	0.8365	7035.69824	105.43609	25.6370
4	31.212	BB	0.8877	6639.19482	93.36030	24.1922
Totals :				2.74435e4	479.53287	



Signal 1: DAD1 A, Sig=250,4 Ref=off

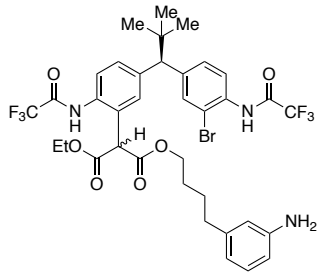
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.332	MM	0.7626	5031.45166	109.95880	44.9957
2	23.534	MM	0.7923	296.69006	6.24088	2.6533
3	29.952	MM	1.1406	5501.32666	80.38983	49.1977
4	34.141	MM	1.2174	352.60507	4.82724	3.1533
Totals :				1.11821e4	201.41675	

Recovered SM (**3a**) after macrocyclization with mismatched ligand **L2**



Signal 1: DAD1 A, Sig=250,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.846	MM	0.8370	2.38540e4	474.98615	48.2149
2	23.999	MM	0.5066	45.56524	1.49904	0.0921
3	31.011	MM	1.4152	2.54265e4	299.45230	51.3934
4	35.804	MM	1.0952	148.18956	2.25510	0.2995
Totals :				4.94742e4	778.19259	



3b

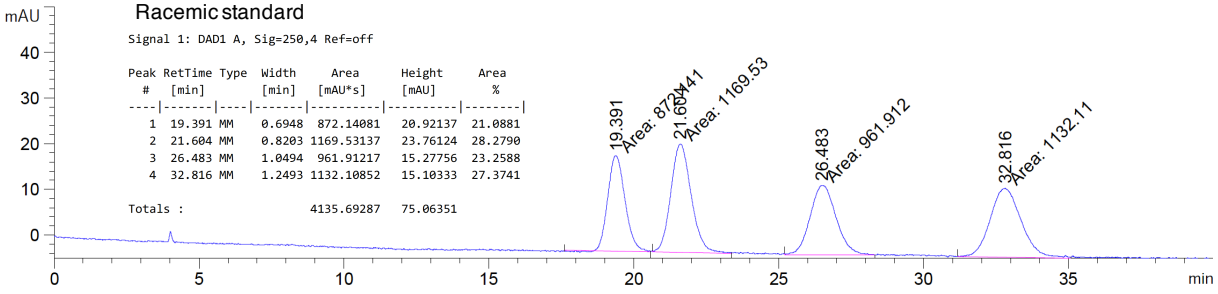
Chiralpak AD-H

10% IPA/Hexanes, 1.00 mL/min, 25 °C, 250 nm

Racemic standard

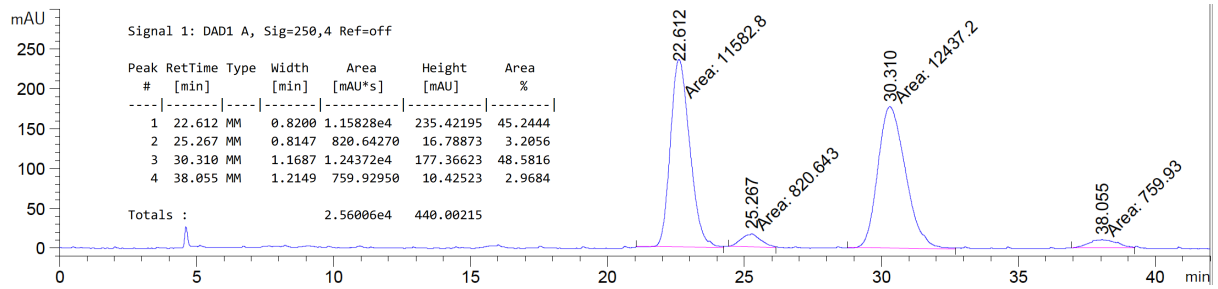
Signal 1: DAD1 A, Sig=250,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.391	MM	0.6948	872.14081	20.92137	21.0881
2	21.604	MM	0.8203	1169.53137	23.76124	28.2790
3	26.483	MM	1.0494	961.91217	15.27756	23.2588
4	32.816	MM	1.2493	1132.10852	15.10333	27.3741
Totals :				4135.69287	75.06351	



Signal 1: DAD1 A, Sig=250,4 Ref=off

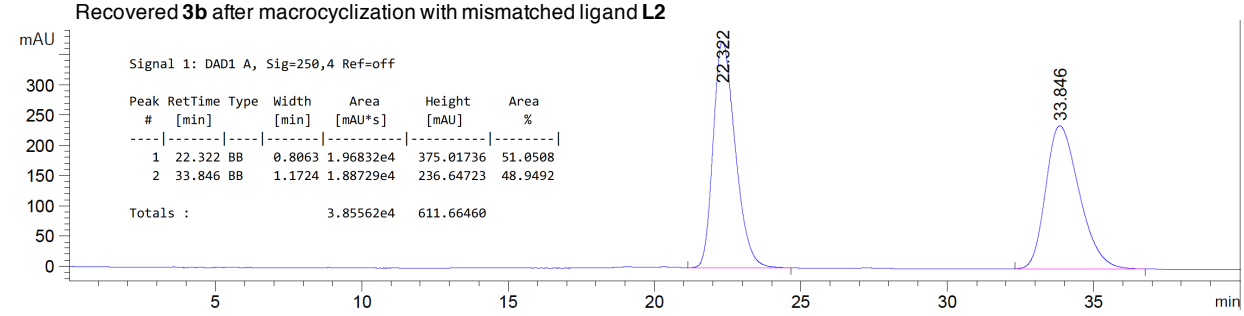
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.612	MM	0.8200	1.15828e4	235.42195	45.2444
2	25.267	MM	0.8147	820.64270	16.78873	3.2056
3	30.310	MM	1.1687	1.24372e4	177.36623	48.5816
4	38.055	MM	1.2149	759.92950	10.42523	2.9684
Totals :				2.56006e4	440.00215	

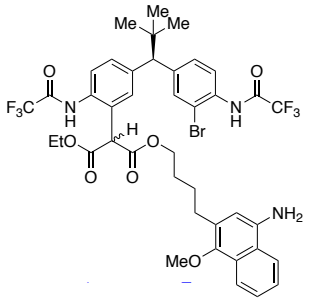


Recovered **3b** after macrocyclization with mismatched ligand **L2**

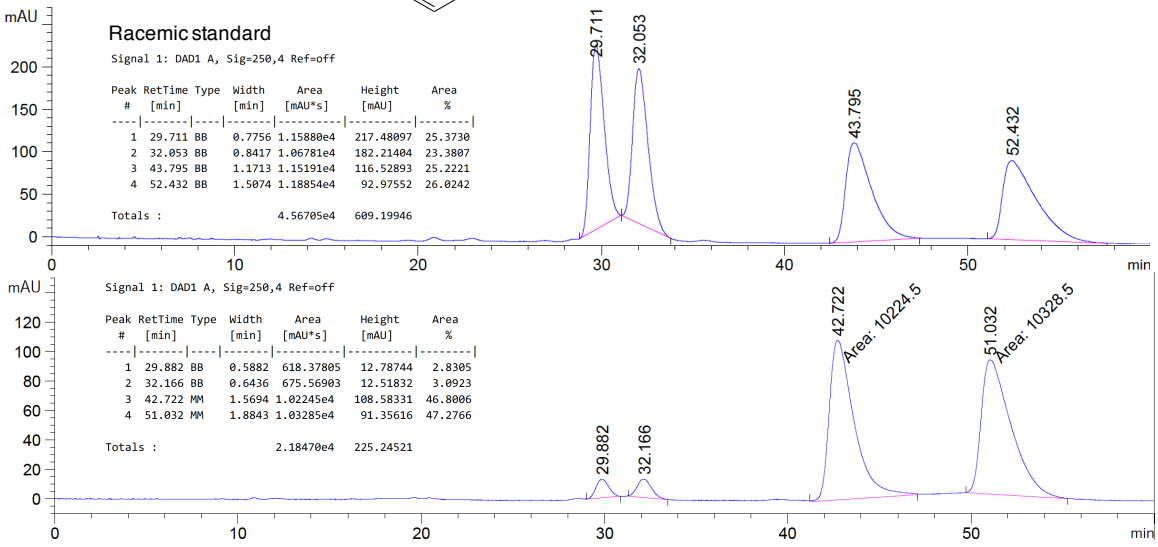
Signal 1: DAD1 A, Sig=250,4 Ref=off

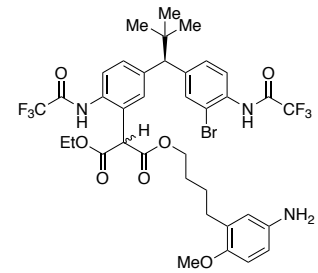
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.322	BB	0.8063	1.96832e4	375.01736	51.0508
2	33.846	BB	1.1724	1.88729e4	236.64723	48.9492
Totals :				3.85562e4	611.66460	



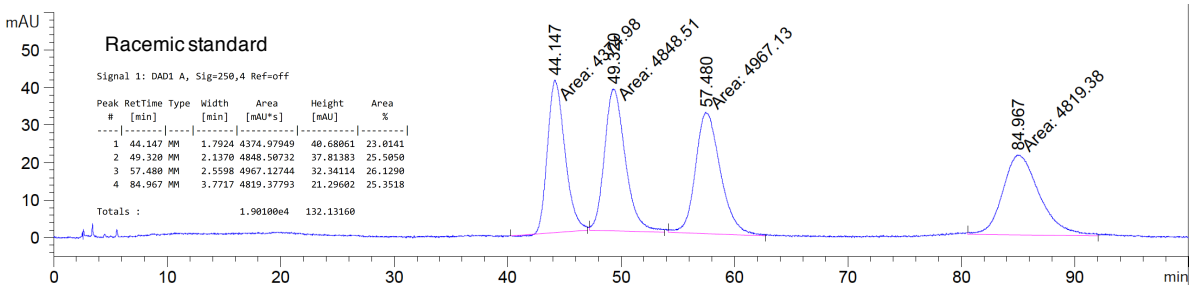


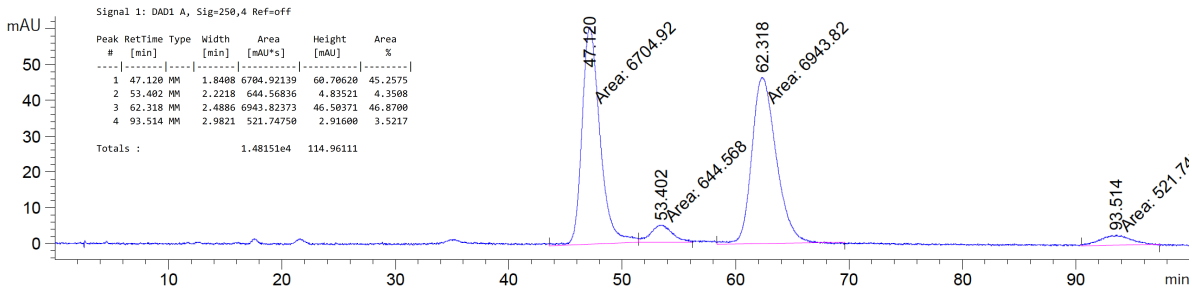
3c
Chiralpak AD-H
6% EtOH/Hexanes, 1.200 mL/min, 25 °C, 250 nm

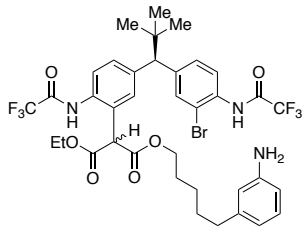




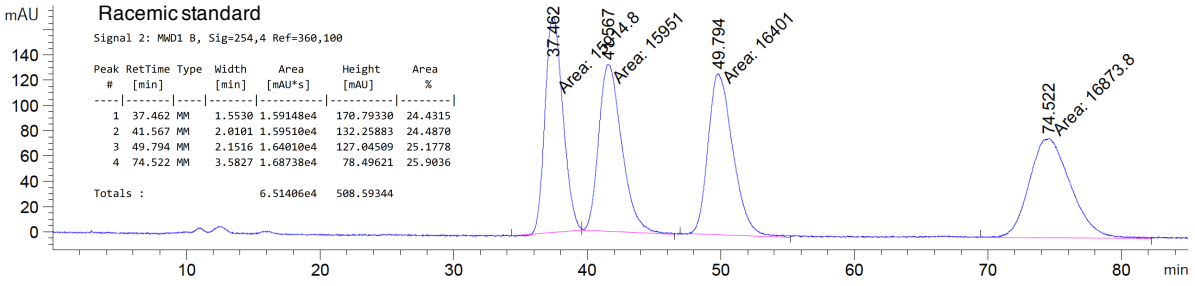
3d
Chiralpak AD-H
7% IPA/Hexanes, 1.250 mL/min, 25 °C, 250 nm

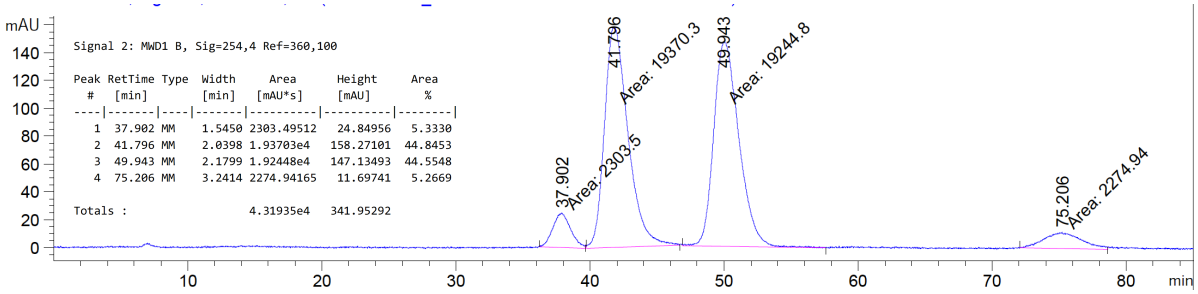


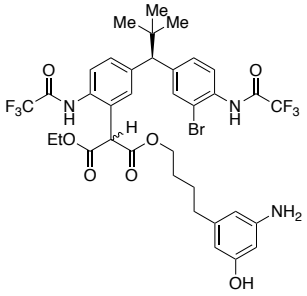




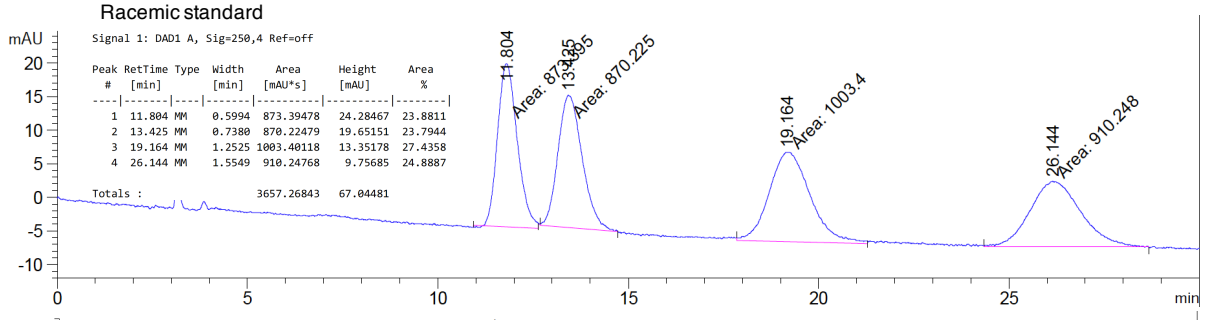
3e
Chiralpak AD-H
4% EtOH/Hexanes, 1.25 mL/min, 25 °C, 254 nm

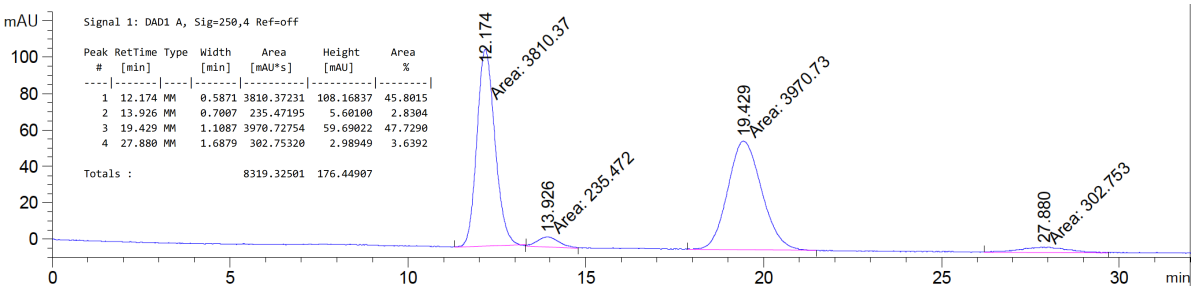






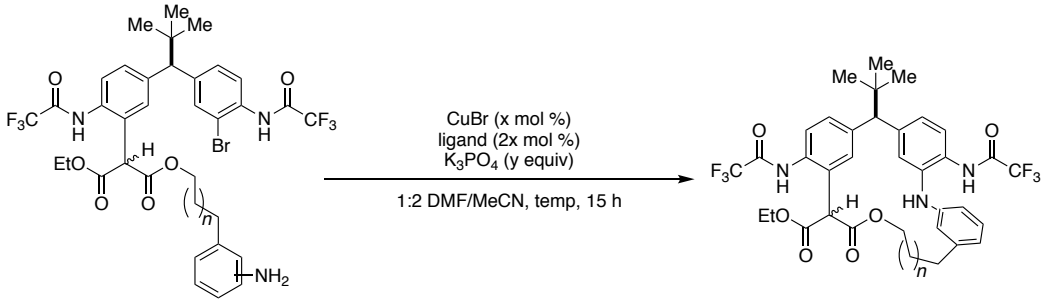
3f
Chiralpak AD-H
16% IPA/Hexanes, 1.25 mL/min, 25 °C, 250 nm





9. Reaction Optimizations and Procedures for Macrocyclization via Cu-catalyzed intramolecular C–N cross-coupling

9.1 Procedure 7: Protocols for Small-Scale Intramolecular Ullmann cross-coupling



To an oven dried two-dram vial equipped with magnetic stir bar was added Cu(I) source (0.007 mmol, 0.10 equiv), peptide ligand (0.014 mmol, 0.20 equiv) and flame-dried K_3PO_4 (0.294 mmol, 4.20 equiv). The flask was sealed with a septa cap and further secured with Teflon tape. The flask was sparged with N_2 for 10 minutes. Diarylmethane (0.07 mmol, 1.00 equiv) was added to a separate oven dried dram vial and sparged with N_2 for 5 minutes. The vials were taken into the glove box. A 1:2 DMF/MeCN solution (0.36 mL, 0.19 M) was added to the vial containing Cu(I). The resulting reaction mixture was left to stir for 10 minutes. Diarylmethane was dissolved in a 1:2 DMF/MeCN solution (0.1 mL) and added to the mixture. The vial was further rinsed with DMF/MeCN (0.1 mL) and added to the stirring mixture. The reaction mixture was capped and secured with Teflon tape, then left to stir for 15 h at the indicated temperature. After 15 h, the reaction mixture was diluted with EtOAc and transferred to a separatory funnel. The organic layer was washed with a solution of saturated NH_4Cl (aq). The organic layer was separated and the aqueous layer was extracted with EtOAc × 3. Combined organic layers were washed with sat. NaCl (aq). The combined organic layers were then dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Percent yield was determined via ^1H NMR by comparing the relative integration of malonate peak of the desired product to an internal NMR standard of 1,4-bis(trimethylsilyl)benzene (see Figure S1).

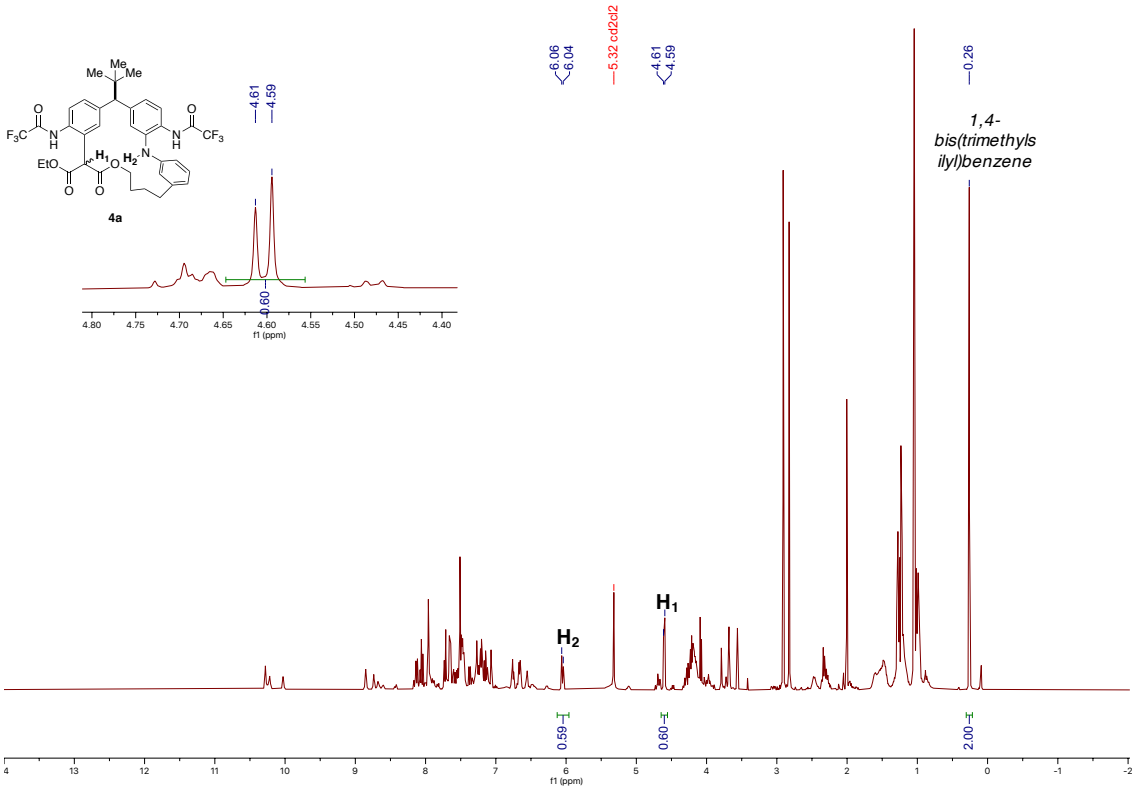
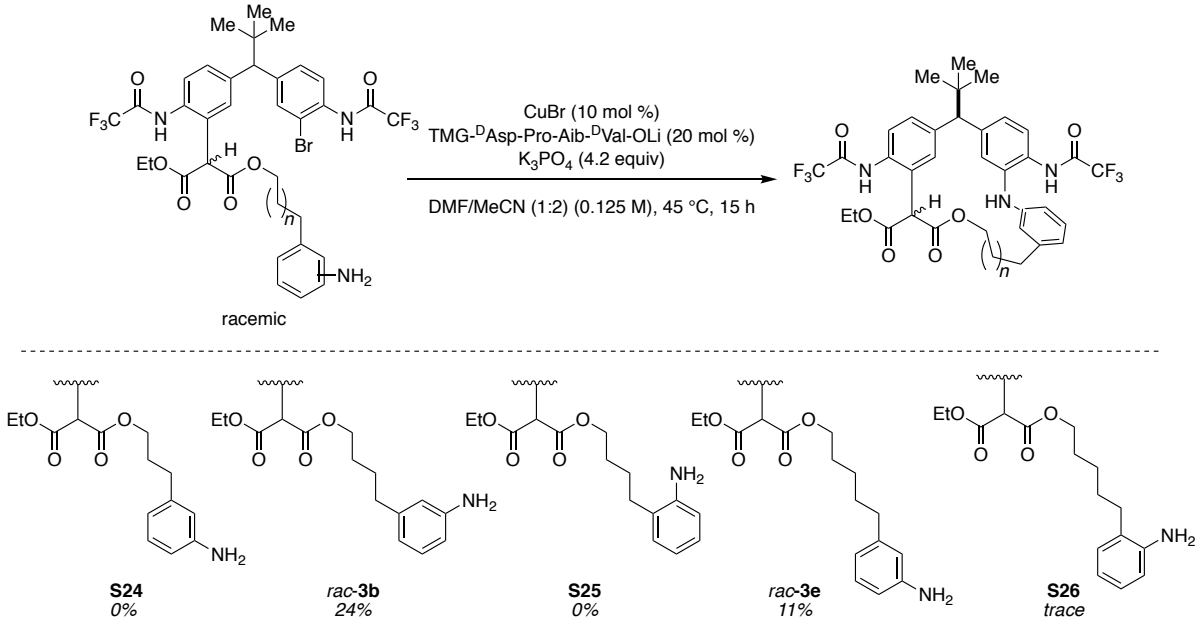


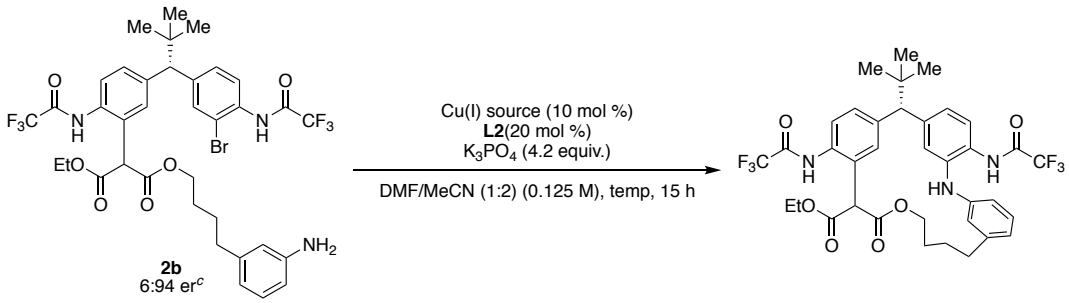
Figure S1. Sample of Determination of NMR yield.

9.2 Identification of Optimal Model Substrates [a,b c]



a) Reactions were executed according to **Procedure 7**. b) Yield was determined using ^{1}H NMR by comparing to an internal NMR standard 1,4-bis(trimethylsilyl)benzene. c) Linear precursors were prepared using **Procedure 5**.

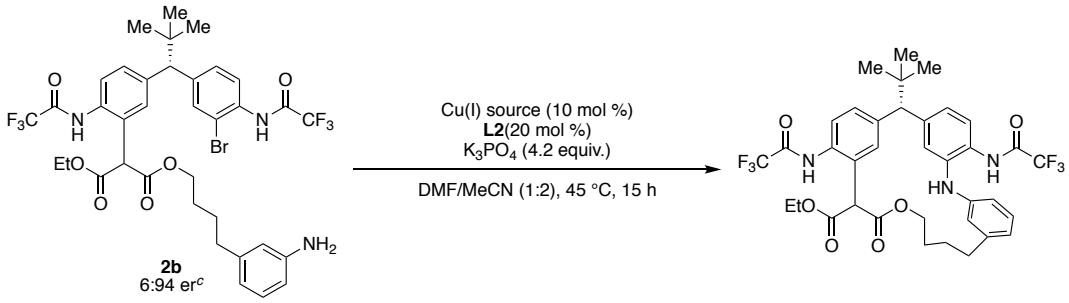
9.3 Table S2: Cu(I) Screen



Entry[a]	Cu (I)	Temp (°C)	Yield (%)[b]
1	CuBr	45	44
2	CuBr	23	47
3	CuI	45	39
4	CuI	23	48
5	$Cu(MeCN)_4BF_4$	45	36

a) Reactions were executed according to **Procedure 7**. b) Yield was determined using ^{1}H NMR by comparing to an internal standard 1,4-bis(trimethylsilyl)benzene. c) **2b** was prepared using *ent*-**L1** following **Procedure 6**. In the main text, **2b** was prepared using **L1**.

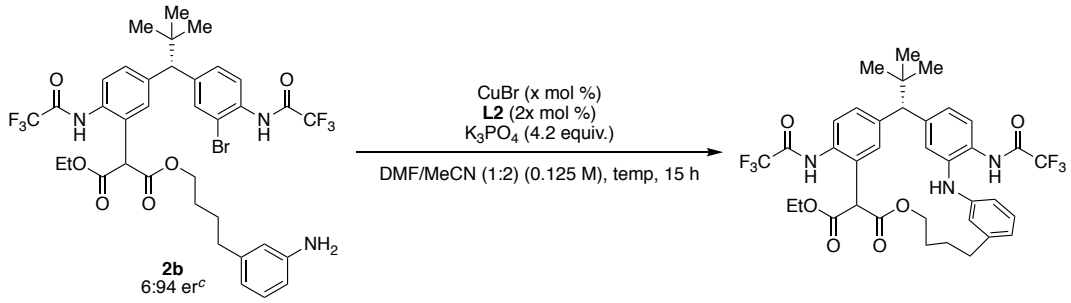
9.4 Table S3: Concentration Effects



Entry[a]	Concentration (M)	Yield (%)[b]
1	0.25	17
2	0.125	44
3	0.06	33
4	0.05	23
5	0.01	9

a) Reactions were executed according to **Proxedure 7**. b) Yields were determined using ^{1}H NMR by comparing to an internal standard 1,4-bis(trimethylsilyl)benzene. c) **2b** was prepared using *ent*-**L1** following **Procedure 6**. In the main text, **2b** was prepared using **L1**.

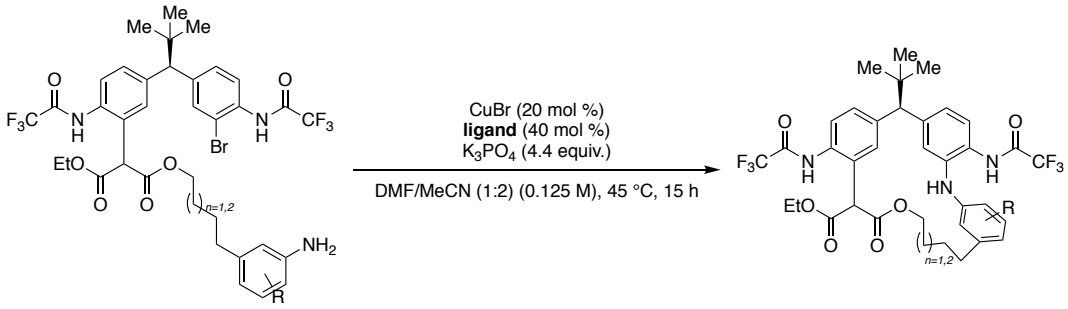
9.5 Table S4: Temperature & Copper Loading



Entry[a,c]	Cu(I) (mol %)	Temp (°C)	Yield (%)[b,d,]
1	CuBr (5 mol %)	45	34
2	CuBr (10 mol %)	45	44
3	CuBr (10 mol %)	23	47
3	CuBr (20 mol %)	45	50
4	CuBr (20 mol %)	23	61
5	CuBr (20 mol %)	30	60

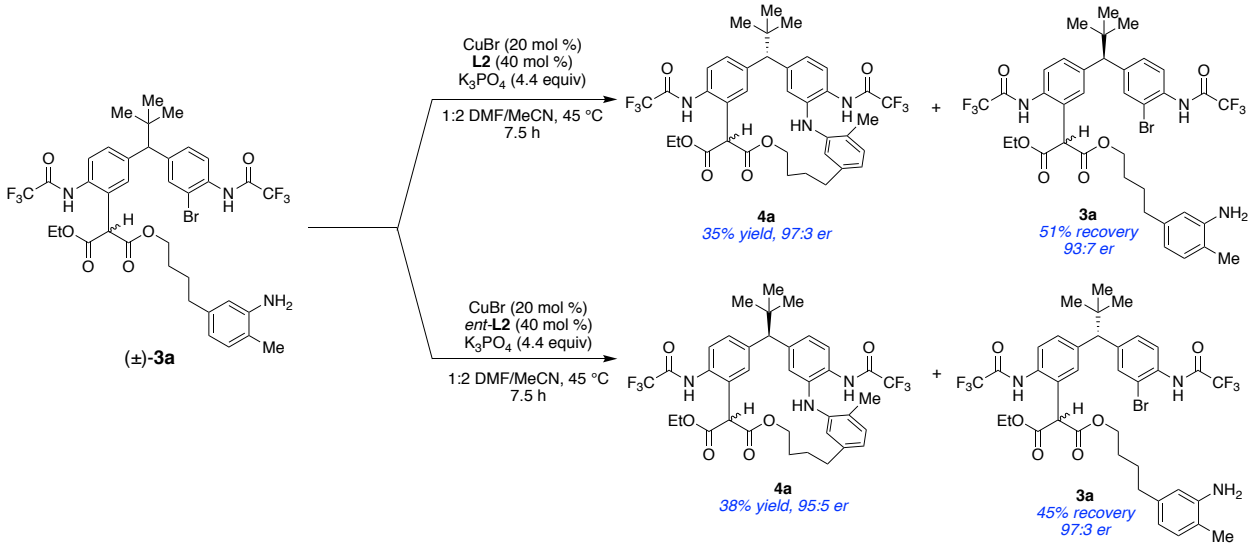
a) Reactions were executed according to **Procedure 7**. b) Yield was determined using ^{1}H NMR by comparing to an internal standard 1,4-bis(trimethylsilyl)benzene. c) All reactions carried out with 1:2 ratio of Cu(I):peptide ligand based on previous optimization.[2] d) Reaction proceeds at room temperature, but 45 °C was chosen as the optimal condition due to most consistent reproducibility outside the glovebox.

10. Procedure 8: Macrocyclization of Diarylmethanes Under Optimized Conditions



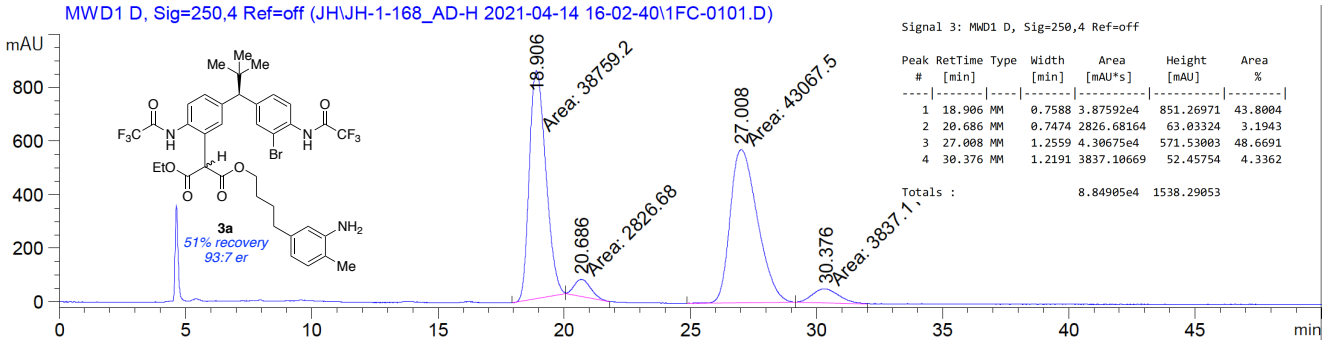
K_3PO_4 (0.1401 g, 0.66 mmol, 4.40 equiv) was flamed-dried under vacuum in a 5-mL Schlenk flask. Upon cooling to room temperature, CuBr (0.0043 g, 0.03 mmol, 0.20 equiv), peptide ligand (0.06 mmol, 0.40 equiv) and a magnetic stir bar were added to the flask. The flask was sealed with a new rubber septum and further secured with Parafilm ®. The flask was evacuated for 5 minutes and backfilled with N_2. This process was repeated two additional times. 1:2 DMF/MeCN mixture (0.8 mL) was added through the septum, and the mixture was allowed to stir for 15 min at room temperature, after which diarylmethane **3a-3f** (0.15 mmol, 1.00 equiv) in MeCN (0.2 mL) was added. The vial was rinsed with DMF (0.2 mL) which was also added to the reaction mixture. The reaction mixture was left to stir for 15 h at 45 °C. After 15 h, the reaction mixture was diluted with EtOAc (10 mL) and transferred to a separatory funnel. The organic layer washed with saturated NH_4Cl (aq) (10 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (5 mL × 3). Combined organic layers were washed with sat. NaCl (aq) (30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography with EtOAc/Hex gradient.

11. Kinetic Resolution of Diarylmethanes Under Optimized Conditions



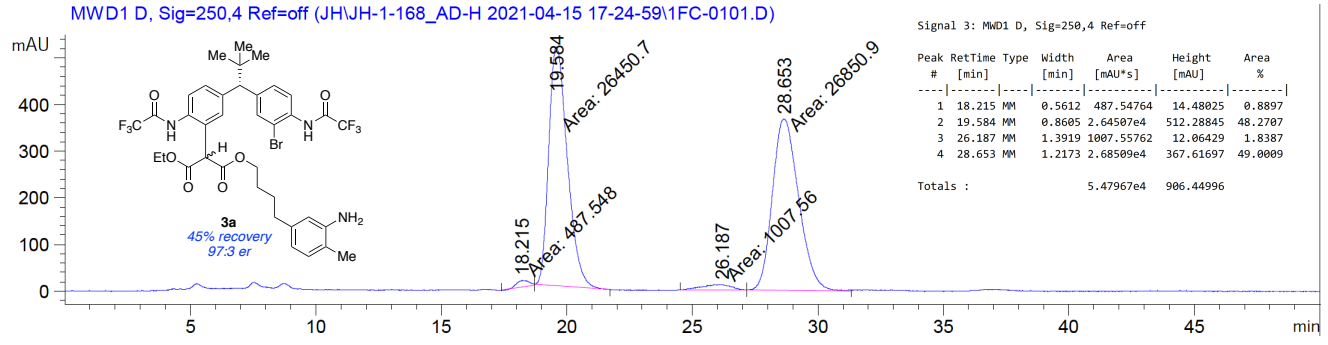
Reactions were executed according to **Procedure 8** for the indicated time.

HPLC Conditions: Chiralpak® AD-H column, 10% IPA/Hex eluent, 1.00 mL/min flow rate, 25 °C, 250 nm. See SI section 8.5 for racemic standard.



Signal 3: MWD1 D, Sig=250,4 Ref=off

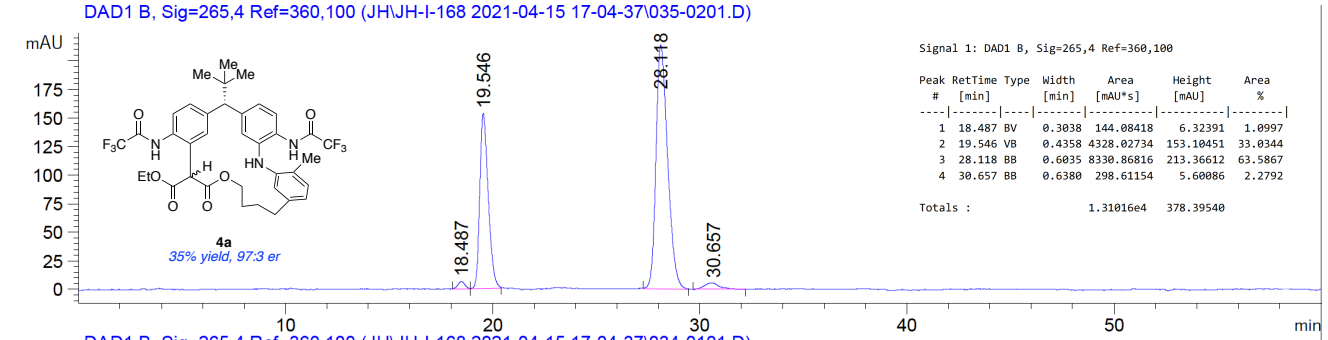
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.906	MM	0.7588	3.87592e4	851.26971	43.8004
2	20.686	MM	0.7474	2826.68164	63.03324	3.1943
3	27.008	MM	1.2559	4.30675e4	571.53003	48.6691
4	30.376	MM	1.2191	3837.10669	52.45754	4.3362
Totals :				8.84905e4	1538.29053	



Signal 3: MWD1 D, Sig=250,4 Ref=off

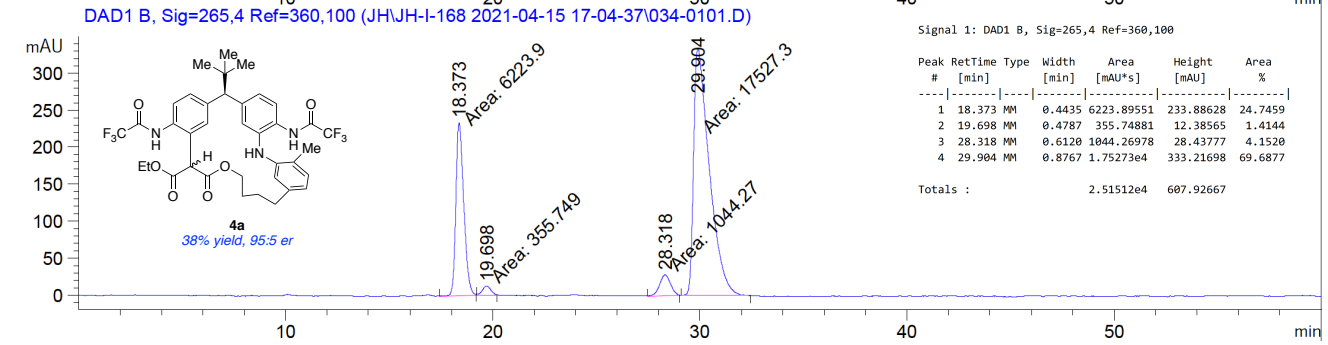
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.215	MM	0.5612	487.54764	14.48025	0.8897
2	19.584	MM	0.8605	2.64507e4	512.28845	48.2707
3	26.187	MM	1.3919	1007.55762	12.06429	1.8387
4	28.653	MM	1.2173	2.68509e4	367.61697	49.0009
Totals :				5.47967e4	906.44996	

HPLC Conditions: Chiralpak® IB column, 55% MeCN/H_2O eluent with 0.5% formic acid buffer, 1.25 mL min^{-1} flow rate, 25 °C, 265 nm. See SI section 12.1 for racemic standard.



Signal 1: DAD1 B, Sig=265,4 Ref=360,100

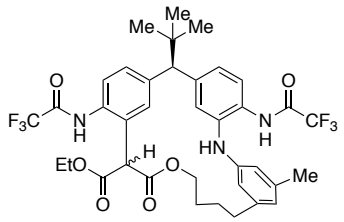
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.487	BV	0.3038	144.08418	6.32391	1.0997
2	19.546	VB	0.4358	4328.02734	153.10451	33.0344
3	28.118	BB	0.6035	8330.86816	213.36612	63.5867
4	30.657	BB	0.6380	298.61154	5.60086	2.2792
Totals :				1.31016e4	378.39540	



Signal 1: DAD1 B, Sig=265,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.373	MM	0.4435	6223.89551	233.88628	24.7459
2	19.698	MM	0.4787	355.74881	12.38565	1.4144
3	28.318	MM	0.6120	1044.26978	28.43777	4.1520
4	29.904	MM	0.8767	1.75273e4	333.21698	69.6877
Totals :				2.51512e4	607.92667	

12. Characterization and Spectra of Macrocyclic Products (4a-4f, 5f)



4a

Ethyl (4*R*)-4-(*tert*-butyl)-1^{5}-methyl-7-oxo-3^{6},5^{4}-bis(2,2,2-trifluoroacetamido)-8-oxa-2-aza-1,3,5(1,3)-tribenzenacyclododecaphane-6-carboxylate (**4a**) was synthesized from **3a** following **Procedure 8**. Crude material was purified by silica chromatography (0→20→85% EtOAc/Hex) to yield the desired product as a white solid. **4a** is observed as a 1.7:1 mixture of diastereomers CD_2Cl_2 at 25 °C by ^{1}H NMR.

Yield: 67% (0.0740 g) using *ent*-**L2**

TLC (30% EtOAc/Hex): R_f = 0.86, 0.81.

IR (FT-ATR, cm^{-1}, neat): ν_{max} 3245, 2964, 2254, 1723, 1533, 1402, 1285, 1159, 904, 723.

^{1}H NMR (500 MHz, CD_2Cl_2): **major diastereomer**: δ 10.29 (s, 1H), 8.71 (s, 1H), 8.06 (d, *J* = 8.5 Hz, 1H), 7.75 – 7.64 (m, 2H)*, 7.47 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.17 (d, *J* = 1.8 Hz, 1H), 7.07 (d, *J* = 1.6 Hz, 1H), 7.06 – 7.00 (m, 1H)*, 6.58 (dd, *J* = 7.5, 1.3 Hz, 1H)*, 5.95 (s, 1H)*, 5.09 (s, 1H), 4.59 (s, 1H), 4.32 – 4.12 (m, 3H)*, 4.01 – 3.93 (m, 1H), 3.81 (s, 1H), 3.70 (s, 1H), 2.32 – 2.18 (s + m, 5H)*, 1.59 – 1.38 (m, 2H)*, 1.28 (t, *J* = 7.1 Hz, 3H), 1.19 – 1.09 (m, 2H)*, 1.06 (s, 9H)*; **minor diastereomer**: δ 10.08 (s, 1H), 8.55 (s, 1H), 8.15 (d, *J* = 8.5 Hz, 1H), 7.75 – 7.64 (m, 1H)*, 7.52 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.38 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.26 (d, *J* = 1.7 Hz, 1H), 7.21 (d, *J* = 1.8 Hz, 1H), 7.06 – 7.00 (m, 1H)*, 6.58 (dd, *J* = 7.5, 1.3 Hz, 1H)*, 5.95 (s, 1H)*, 5.13 (s, 1H), 4.61 (s, 1H), 4.32 – 4.12 (m, 3H)*, 4.11 – 4.02 (m, 1H), 3.81 (s, 1H), 2.32 – 2.18 (s + m, 5H)*, 1.59 – 1.38 (m, 2H)*, 1.23 (t, *J* = 7.1 Hz, 3H), 1.19 – 1.09 (m, 2H)*, 1.06 (brs, 9H)*. (* Indicates overlap of peaks corresponding to the major and minor diastereomers.)

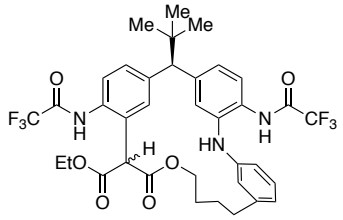
^{13}C NMR (151 MHz, CD_2Cl_2): **major diastereomer**: δ 169.8, 169.1, 155.9–154.6 (m, overlapping quartets of **C**=O(CF_3)), 144.1, 142.5, 142.3, 141.8, 135.4, 134.0, 132.6, 130.8, 130.0, 129.1*, 128.9, 127.0, 126.5, 125.7, 122.8 (q, *J* = 288.4 Hz), 116.1 (q, *J* = 288.4 Hz), 122.6, 121.6, 121.1, 114.1, 66.7, 63.4, 63.2, 57.8, 35.8, 35.4, 29.4, 28.7, 28.6, 17.3*, 14.1; **minor diastereomer****: δ 169.2, 169.2, 155.9–154.6 (m, overlapping quartets of **C**=O(CF_3)), 143.9, 142.7, 142.0, 141.7, 133.6, 132.5, 132.2, 130.8, 130.6, 129.1*, 128.5, 127.8, 126.5,125.4, 122.7, 121.6, 121.4, 113.8 , 66.2, 63.5, 63.2, 57.5, 35.2, 35.1, 29.4, 28.1, 28.0, 17.3*, 14.0. (Note: * indicates overlap of peaks corresponding multiple peaks; ** peaks corresponding to (C=O)**C**F_3 for the minor diastereomer were not observed at the signal-to-noise ratio of the measurement.)

^{19}F NMR (471 MHz, CD_2Cl_2): δ –76.17, –76.52, –76.52, –76.54.

HRMS: Exact mass calculated for $[C_{37}H_{39}F_6N_3O_6 + H]^+$ requires *m/z*= 736.2816, found *m/z* = 736.2832.

Optical Rotation: α_D^{20} = + 69.5 ° (*c* = 0.5, MeOH, >99:1 er)

HPLC (Chiralpak® IB column, 55% MeCN/H_2O eluent with 0.5% formic acid buffer, 1.25 mL min^{-1} flow rate, 25 °C, 265 nm, observed as 1.9:1 dr): major diastereomers t_R= 20.8 min, 34.4 min; minor diastereomers t_R = 22.5 min, 32.7 min.



4b

Ethyl (4*R*)-4-(*tert*-butyl)-7-oxo-3^{6},5^{4}-bis(2,2,2-trifluoroacetamido)-8-oxa-2-aza-1,3,5(1,3)-tribenzenacyclododecaphane-6-carboxylate (**4b**) was synthesized from **3b** following **Procedure 8**. Crude material was purified by silica chromatography (0→25→75% EtOAc/Hex) to yield the desired product as a white solid. **4b** is observed as a 2.5:1 mixture of diastereomers CD_2Cl_2 at 25 °C by ^{1}H NMR.

Yield: 50% (0.0536 g) using *ent*-**L2**

TLC (30% EtOAc/Hex): R_f = 0.80.

IR (FT-ATR, cm^{-1}, neat): ν_{max} 3331, 2952, 2867, 2119, 1717, 1501 1532, 1283, 1196, 1152, 906, 727.

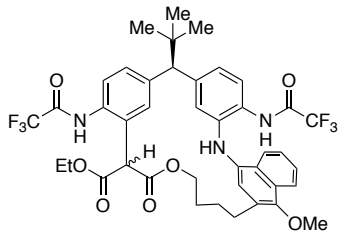
^{1}H NMR (500 MHz, CD_2Cl_2): **major diastereomer**: δ 10.29 (s, 1H), 8.75 (s, 1H), 8.09 (d, *J* = 8.5 Hz, 1H), 7.72 (d, *J* = 8.5 Hz, 1H), 7.69 – 7.62 (m, 1H)*, 7.49 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.24 – 7.19 (m, 1H)*, 7.17 – 7.12 (m, 1H)*,7.07 (d, *J* = 1.9 Hz, 1H), 6.80 – 6.75 (m, 1H)*, 6.70 – 6.64 (m, 1H)*, 6.04 (s, 1H), 5.23 (s, 1H), 4.60 (s, 1H), 4.32 – 4.13 (m, 3H)*, 3.97 (ddd, *J* = 11.0, 7.2, 4.0 Hz, 1H), 3.69 (s, 1H), 2.39 – 2.19 (m, 2H)*, 1.52 – 1.41 (m, 2H)*, 1.28 (t, *J* = 7.1 Hz, 3H), 1.20 – 1.11 (m, 2H)*, 1.05 (s, 9H)**; minor diastereomer**: δ 10.05 (s, 1H), 8.67 (s, 1H), 8.17 (d, *J* = 8.5 Hz, 1H), 7.69 – 7.62 (m, 1H)*, 7.52 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.38 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.27 (d, *J* = 1.8 Hz, 1H), 7.24 – 7.19 (m, 1H)*, 7.17 – 7.12 (m, 1H)*, 6.80 – 6.75 (m, 1H)*, 6.70 – 6.64 (m, 1H)*, 6.01 (s, 1H), 5.33 (s, 1H), 4.61 (s, 1H), 4.32 – 4.13 (m, 3H)*, .4.10 – 4.01 (m, 1H), 3.80 (s, 1H), 2.39 – 2.19 (m, 2H)*, 1.52 – 1.41 (m, 2H)*, 1.24 (t, *J* = 7.1 Hz, 3H), 1.20 – 1.11 (m, 2H)*, 1.05 (s, 9H). (Note: * indicates overlap of peaks corresponding to the major and minor diastereomers.)

^{13}C NMR (151 MHz, CD_2Cl_2) **major diastereomer**: δ 169.7, 169.1, 155.5 (q, *J* = 64.9 Hz), 155.2 (q, *J* = 64.9 Hz), 146.1, 144.3, 142.5, 135.3, 133.9, 132.6, 132.5, 130.2, 129.6,* 129.2, 128.5, 126.9, 126.4, 125.6, 121.5, 121.4, 116.4 (q, *J* = 288.4 Hz), 116.1 (q, *J* = 288.4 Hz), 115.4, 114.5, 66.7, 63.5, 63.4, 57.8, 35.9, 35.4, 29.4*, 28.6, 28.2, 14.0; **minor diastereomer****: 169.2, 169.1, 146.0, 144.3, 142.4, 142.2, 142.1, 133.5, 132.5, 132.1, 130.8, 129.6*,128.5, 127.8, 126.5, 125.4, 121.7, 121.3, 115.2, 114.2, 66.3, 63.2, 63.1, 57.4, 35.4, 35.2, 29.4*, 28.0, 28. 0, 14.0. (Note: * indicates overlap of peaks corresponding multiple peaks; ** peaks corresponding to (C=O)**C**F_3 for the minor diastereomer were not observed at the signal-to-noise ratio of the measurement.)

^{19}F NMR (471 MHz, CD_2Cl_2) δ –76.09, –76.36, –76.51, –76.53.

HRMS: Exact mass calculated for $[C_{36}H_{37}F_6N_3O_6 + H]^+$ requires *m/z*= 722.2659, found *m/z* = 736.2661.

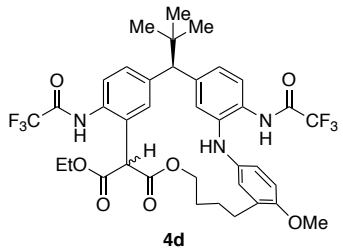
Optical: α_D^{20} = + 69.9 ° (*c* = 0.5, MeOH, >99:1 er)
HPLC (Chiralpak® IB connected to Chiralpak® IC column, 55% MeCN/H_2O eluent with 0.5% formic acid buffer, 1.25 mL min^{-1} flow rate, 25 °C, 265 nm, observed as 1.1:1 dr): major diastereomers t_R= 22.3 min, 34.9 min; minor diastereomers t_R = 23.3 min, 33.7 min.



4c

Ethyl (4*R*)-4-(*tert*-butyl)-1^4-methoxy-7-oxo-3^6,5^4-bis(2,2,2-trifluoroacetamido)-8-oxa-2-aza-1(1,3)-naphthalena-3,5(1,3)-dibenzenacyclododecaphane-6-carboxylate (4c) was synthesized from **3c** following **Procedure 8**. Crude material was purified by silica chromatography (0→25→80% EtOAc/Hex) to yield the desired product as a beige solid. **4c** is observed as a 2.1:1 mixture of diastereomers in CD_2Cl_2 at 25 °C by ^{1}H NMR.
Yield: 57% (0.0687 g) using *ent*-**L2**
TLC (30% EtOAc/Hex): R_f = 0.63, 0.66.
IR (FT-ATR, cm^{-1}, neat): ν_{max} 3277, 2953, 2870, 2089, 1717, 1597, 1532, 1387, 1282, 1151, 1032, 906, 752.
^{1}H NMR (500 MHz, CD_2Cl_2): major diastereomer: δ 10.27 (s, 1H), 8.67 (s, 1H), 8.21 – 8.05 (m, 2H)*, 8.04 (d, *J* = 8.5 Hz, 1H), 7.73 – 7.64 (m, 2H)*, 7.61 – 7.47 (m, 2H),* 7.44 (d, *J* = 8.4 Hz, 1H), 7.16 (s, 1H), 7.07 (s, 1H), 6.09 (s, 1H), 5.73 (s, 1H), 5.71 (s, 1H), 4.60 (s, 1H), 4.34 – 4.13 (m, 3H)*, 4.07 – 3.98 (m, 1H), 3.84 (s, 3H), 3.71 (s, 1H), 2.69 – 2.39 (m, 2H)*, 1.64 – 1.49 (m, 2H)*, 1.36 – 1.15 (m, 5H)*, 1.05 (s, 9H); minor diastereomer: 10.12 (s, 1H), 8.45 (s, 1H), 8.21 – 8.05 (m, 3H)*, 7.73 – 7.64 (m, 1H)*, 7.61 – 7.47 (m, 3H),* 7.38 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.31 (s, 1H), 7.25 (s, 1H), 6.11 (s, 1H), 4.62 (s, 1H), 4.34 – 4.13 (m, 3H)*, 4.09 (dt, *J* = 9.5, 4.3 Hz, 1H), 3.82 (s, 1H), 3.81 (s, 3H), 2.69 – 2.39 (m, 2H)*, 1.64 – 1.49 (m, 2H)*, 1.36 – 1.15 (m, 5H)*, 1.06 (s, 9H). (Note: * indicates overlap of peaks corresponding to the major and minor diastereomers.)
^{13}C NMR (126 MHz, CD_2Cl_2): major diastereomer: δ 169.9, 169.1, 156.0–154.9 (m, overlapping quartets for ((C=O)**C**F_3), 148.4, 142.6, 137.5, 135.4, 134.9, 132.6, 131.0, 129.1–129.0*, 127.8, 126.8–126.7*, 126.6, 125.8, 125.7, 123.1, 122.0, 121.1, 116.4 (q, *J* = 289.8 Hz), 116.1 (q, J = 288.9 Hz), 113.6, 66.8, 63.5, 63.4, 62.4, 57.8, 35.3, 29.7, 29.4, 29.1, 27. 4, 14.1; **minor diastereomer****: δ 169.3, 169.2, 156.0–154.9 (overlapping multiplets for ((C=O)CF_3), 148.7, 142.91, 142.1, 137.2, 134.3, 132.3,130.7, 129.6, 129.1–129.0*, 127.6, 127.4, 126.8–126.7*, 126.5, 125.9, 125.9, 125.4, 123.2, 121.9, 121.2, 113.2, 66.3, 63.2, 63.2, 62.4, 57.6, 35.3, 29.4, 28.5, 28.5, 27.2, 14.0. (Note: * indicates numerous peaks corresponding to major or minor diastereomers. See page S110 for the spectra.) **Peaks of (C=O)**C**F_3 for the minor diastereomer were not observed at the signal-to-noise ratio of the measurement.)
^{19}F NMR (471 MHz, CD_2Cl_2) δ –76.22, –76.52, –76.53, –76.67.
HRMS: Exact mass calculated for $[C_{41}H_{41}F_6N_3O_7 + H]^+$ requires *m/z*= 802.2921, found *m/z* = 802.2922.

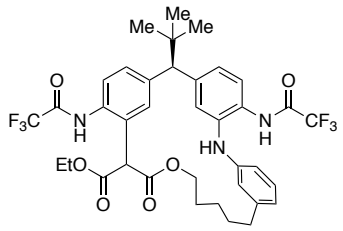
Optical Rotation: α_D^{20} = + 50.7 ° (*c* = 0.5, MeOH, 99:1 er)
HPLC (Chiralpak® IB column, 55% MeCN/H_2O eluent with 0.5% formic acid buffer, 1.25 mL min^{-1} flow rate, 25 °C, 265 nm, observed as 1.4:1 dr): major enantiomers t_R= 50.4 min, 91.3 min; minor enantiomers t_R= 52.8 min, 81.8 min. (Note: Retention times are prone to change due to prolonged run time. Order of elution of diastereomers remains consistent.)



4d

Ethyl (4*R*)-4-(*tert*-butyl)-1^4-methoxy-7-oxo-3^6,5^4-bis(2,2,2-trifluoroacetamido)-8-oxa-2-aza-1,3,5(1,3)-tribenzenacyclododecaphane-6-carboxylate (**4d**) was synthesized from **3d** following **Procedure 8**. Crude material was purified by silica chromatography (0→30→85% EtOAc/Hex) to yield the desired product as a ligh pink solid. **4d** is observed as a 2.8:1 mixture of diastereomers CD_2Cl_2 at 25 °C by ^{1}H NMR.
Yield: 49% (0.0553 g) using *ent*-**L2**.
TLC (30% EtOAc/Hex): R_f = 0.71.
IR (FT-ATR, cm^{-1}, neat): ν_{max} 3321, 2953, 2115, 1717, 1597, 1533, 1500, 1282, 1220, 1152, 1032, 906, 750, 667.
^{1}H NMR (500 MHz, CD_2Cl_2) **major diastereomer**: δ 10.29 (s, 1H), 8.60 (s, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.68 – 7.60 (m, 1H)*, 7.48 – 7.35 (m, 1H)*, 7.09 (s, 1H), 7.06 (s, 1H), 6.79 (brs, 2H)*, 6.24 (s, 1H), 5.10 (s, 1H), 4.61 (s, 1H), 4.33 – 4.18 (m, 3H)*, 4.07 – 3.95 (m, 1H)*, 3.78 (s, 3H), 3.64 (s, 1H), 2.54 – 2.43 (m, 1H), 2.32 – 2.21 (m, 1H), 1.64 – 1.46 (m, 2H),* 1.29 – 1.11 (m, 5H),* 1.04 (s, 9H)*; **minor diastereomer**: 9.87 (s, 1H), 8.62 (s, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.68 – 7.60 (m, 1H)*, 7.48 – 7.35 (m, 2H)*, 7.24 (s, 1H), 7.16 (s, 1H), 6.79 (brs, 2H)*, 6.19 (s, 1H), 5.12 (s, 1H), 4.62 (s, 1H), 4.33 – 4.18 (m, 3H)*, 4.07 – 3.95 (m, 1H)*3.76 (s, 3H), 3.75 (s, 1H), 2.39 (t, *J* = 7.6 Hz, 2H), 1.64 – 1.46 (m, 2H),* 1.29 – 1.11 (m, 5H),* 1.04 (s, 9H)*. (Note: * indicates overlap of peaks corresponding to major and minor diastereomers)
^{13}C NMR (126 MHz, CD_2Cl_2) **major diastereomer**: δ 169.5, 169.2, 156.0–154.9 (m, overlapping quartets), 153.0, 142.6*, 142.4, 138.0, 136.4, 135.3, 132.6, 132.6, 132.2, 129.3, 126.2, 126.0, 125.7, 124.8, 122.4, 118.3, 117.4, 116.4 (q, *J* = 283.5 Hz), 116.3 (q, *J* = 284.8 Hz), 111.7, 66.7, 63.7, 63.3, 57.9, 56.1, 35.4, 30.0, 29.4, 29.0, 25.9, 14.1*; **minor diastereomer****: δ 169.0, 169.9, 153.0, 142.6*, 142.3, 138.3, 135.9, 132.4, 132.0, 131.8, 128.8, 127.7, 126.6, 126.4, 126.2, 125.4, 121.8, 118.7, 117.3, 111.9, 66.4, 63.3, 63.1, 56.9, 56.1, 35.3, 29.4*, 28.8, 28.1, 26.0, 14.1* (Note: *Indicates overlapping peaks of two diastereomers; **Peaks of (C=O)CF_3, (C=O)CF_3 for the minor diastereomer were not observed at the signal-to-noise ratio of the measurement).
^{19}F NMR (471 MHz, CD_2Cl_2) δ –75.95, –76.20, –76.46, –76.54.
HRMS: Exact mass calculated for $[C_{37}H_{39}F_6N_3O_7 + H]^+$ requires *m/z*= 752.2770, found *m/z* = 752.2774.
Optical Rotation: α_D^{20} = + 64.4 ° (*c* = 0.5, MeOH, 98:2 er)

HPLC (Chiralpak® IB column, 50% MeCN/H_2O eluent with 0.5% formic acid buffer, 1.00 mL min^{-1} flow rate, 25 °C, 265 nm, observed as 3.0:1 dr): major enantiomer t_R= 17.2 min; minor enantiomer t_R= 15.4 min. Unresolved pair of major and minor enantiomers t_R = 11.7 min.



4e

Ethyl (4*R*)-4-(tert-butyl)-7-oxo-3^{6},5^{4}-bis(2,2,2-trifluoroacetamido)-8-oxa-2-aza-1,3,5(1,3)-tribenzenacyclotridecaphane-6-carboxylate (**4e**) was synthesized from **3e** following **Procedure 8**. Crude material was purified by silica chromatography (0→25→80% EtOAc/Hex) to yield **4e** as a beige solid. **4e** is observed as a 1.9:1 mixture of diastereomers in CD_2Cl_2 at 25 °C by ^{1}H NMR.

Yield: 23% (0.0254 g)

TLC (30% EtOAc/Hex): R_f =0.76.

IR (FT-ATR, cm^{-1}, neat): ν_{max} 3324, 2945, 2863, 2125, 1715, 1590, 1531, 1284, 1153, 1026, 907, 732.

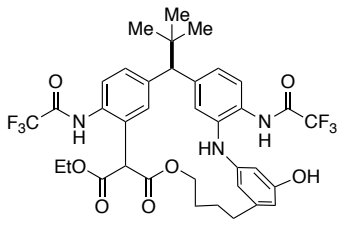
^{1}H NMR (600 MHz, CD_2Cl_2): **major diastereomer**: δ 10.37 (s, 1H), 8.45 (s, 1H), 7.97 (d, *J* = 8.3 Hz, 1H), 7.66 (d, *J* = 8.2 Hz, 1H), 7.44 (s, 1H), 7.31 – 7.28 (m, 2H), 7.24 – 7.15 (m, 2H)*, 6.81 – 6.72 (m, 2H)*, 6.37 (s, 1H), 5.42 (s, 1H), 4.52 (s, 1H), 4.27 – 4.11 (m, 4H), 3.81 (s, 1H), 2.61 (dt, *J* = 12.6, 6.1 Hz, 1H), 2.47 – 2.35 (m, 1H)*, 1.63 – 1.37 (m, 4H)*, 1.29 – 1.08 (m, 5H)*, 1.03 (s, 9H); **minor diastereomer**: 10.21 (s, 1H), 8.54 (s, 1H), 7.93 (d, *J* = 8.5 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.57 (d, *J* = 7.0 Hz, 1H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.24 – 7.15 (m, 2H)*, 7.07 (s, 1H), 6.81 – 6.72 (m, 2H)*, 6.35 (s, 1H), 5.33 (s, 1H), 4.56 (s, 1H), 4.27 – 4.11 (m, 3H)*, 4.04 (ddd, *J* = 10.7, 6.9, 3.5 Hz, 1H), 3.70 (s, 1H), 2.51 (dt, *J* = 13.9, 7.0 Hz, 1H), 2.47 – 2.35 (m, 1H)*, 1.63 – 1.37 (m, 4H)*, 1.25 (t, *J* = 7.1 Hz, 3H), 1.29 – 1.08 (m, 5H)*, 1.04 (s, 9H). (Note: * indicates overlap of peaks corresponding to major and minor diastereomers)

^{13}C NMR (151 MHz, CD_2Cl_2): **major diastereomer**: δ 170.3, 168.4, 156.1–154.8 (m, overlapping quartets of (**C**=O)CF_3), 144.6, 144.3, 142.0, 141.8, 134.0, 132.8–132.6*,132.1, 129.7, 129.6, 129.0, 128.5, 126.4–125.3*, 124.6, 122.0, 121.6, 116.5, 116.4 (q, *J* = 288.4 Hz), 116.1 (q, *J* = 288.4 Hz), 114.5, 67.6, 63.2, 63.1, 58.1, 36.0, 35.5, 30.7, 29.3, 28.5, 25.6, 14.0; **minor diastereomer****: δ 169.4, 169.3, 156.1–154.8 (m, overlapping quartets), 144.8, 144.3, 142.5, 142.3, 135.5, 134.8, 132.8–132.6*, 128.0, 126.4–125.3*, 122.3, 122.1, 117.0, 116.6, 67.4, 63.3, 63.2, 57.7, 36.1, 35.3, 30.3, 29.4, 28.3, 26.1, 14.0. (Note: *indicates numerous peaks corresponding to major or minor diastereomers. See page S116 for the spectra; **peaks of (C=O)**C**F_3 for the minor diastereomer were not observed at the signal-to-noise ratio of the measurement.)

^{19}F NMR (471 MHz, CD_2Cl_2) δ –76.08, –76.28, –76.54.

HRMS: Exact mass calculated for $[C_{37}H_{39}F_6N_3O_6 + H]^+$ requires *m/z*= 736.2821, found *m/z* = 736.2823.

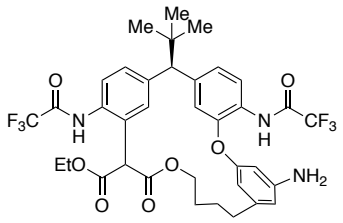
Optical Rotation: α_D^{20} = + 9.8 ° (*c* = 0.5, MeOH, 99:1 er)
HPLC: (Chiralpak® IB column, 55% MeCN/H_2O eluent, 1.00 mL min^{-1} flow rate, 25 °C, 265 nm, observed as 2.1:1 dr): major enantiomers t_R= 25.6 min, 31.9 min; minor enantiomers t_R= 33.5 min, 35.9 min.



4f

Ethyl (4*R*)-4-(*tert*-butyl)-1^5-hydroxy-7-oxo-3^6,5^4-bis(2,2,2-trifluoroacetamido)-8-oxa-2-aza-1,3,5(1,3)-tribenzenacyclododecaphane-6-carboxylate (**4f**) was synthesized from **3f** following **Procedure 8**. Crude material was purified by silica chromatography (0→25→80% EtOAc/Hex) to yield **4f** as an off-white solid. **4f** is observed as a 2.5:1 mixture of diastereomers in CD_2Cl_2 at 25 °C by ^{1}H NMR.
Yield: 43% (0.0477 g) using *ent*-**L2**
TLC (30% EtOAc/Hex): R_f = 0.33.
IR (FT-ATR, cm^{-1}, neat): ν_{max} 3344, 3021, 2953, 2868, 2118, 1715, 1597, 1533, 1282, 1215, 1153, 1028, 836, 750.
^{1}H NMR (600 MHz, CD_2Cl_2): **major diastereomer**: δ 10.29 (s, 1H), 8.69 (s, 1H), 8.08 (d, *J* = 8.5 Hz, 1H), 7.72 (d, *J* = 8.5 Hz, 1H), 7.69 – 7.63 (m, 1H)*, 7.47 (d, *J* = 8.5 Hz, 1H), 7.20 (s, 1H)*, 7.07 (s, 1H), 6.25 (s, 1H)*, 6.13 (s, 1H)*, 5.57 (s, 1H)*, 5.17 (s, 1H), 5.00 (s, 1H)*, 4.59 (s, 1H), 4.35 – 4.12 (m, 3H)*, 3.96 (ddd, *J* = 11.0, 7.3, 3.9 Hz, 2H), 3.69 (s, 1H), 2.29 – 2.17 (m, 2H)*, 1.53 – 1.36 (m, 2H)*, 1.28 (t, *J* = 7.1 Hz, 3H), 1.18 – 1.07 (m, 2H)*, 1.04 (s, 9H)**; minor diastereomer**: δ 10.06 (s, 1H), 8.62 (s, 1H), 8.16 (d, *J* = 8.5 Hz, 1H), 7.69 – 7.63 (m, 1H)*, 7.51 (d, *J* = 8.5 Hz, 1H), 7.37 (d, *J* = 8.3 Hz, 1H), 7.27 (s, 1H), 7.20 (s, 1H)*, 6.25 (s, 1H)*, 6.13 (s, 1H)*, 5.57 (s, 1H)*, 5.26 (s, 1H), 5.00 (s, 1H)*, 4.61 (s, 1H), 4.35 – 4.12 (m, 3H)*, 4.03 (dt, *J* = 10.8, 5.2 Hz, 1H), 3.80 (s, 1H), 2.29 – 2.17 (m, 2H)*, 1.53 – 1.36 (m, 2H)*, 1.23 (t, *J* = 7.2 Hz, 3H), 1.18 – 1.07 (m, 2H)*, 1.04 (s, 9H)*. (Note: *indicates overlap of major and minor diastereomers)
^{13}C NMR (151 MHz, CD_2Cl_2): **major diastereomer**: δ 169.8, 169.1, 157.2*, 156.2–154.7 (m, overlapping quartets of (**C**=O)CF_3), 147.5, 145.7, 142.5, 142.1, 135.3, 133.7, 132.5, 130.2, 129.2, 128.9, 127.1, 126.4, 125.6, 121.5, 116.4 (q, *J* = 288.41 Hz), 116.1 (q, *J* = 289.92 Hz), 108.4, 107.0, 102.2, 66.6, 63.5, 63.4, 57.8, 35.9, 35.3, 29.4*, 28.6, 27.9, 14.0; **minor diastereomer****: δ 169.3, 169.2, 157.2*, 147.4, 145.7, 142.4, 142.2, 133.3, 132.6, 132.4, 132.2, 130.9, 128.8, 128.0, 126.5, 125.4, 121.3, 108.9, 106.6, 101.7, 66.3, 63.3, 63.1, 57.4, 35.4, 35.2, 29.4*, 28.0, 27.8, 14.0. (Note: *indicates overlapping peaks of major and minor diastereomers; **peaks of (C=O)CF_3, (C=O)CF_3 for the minor diastereomer were not observed at the signal-to-noise ratio of the measurement).
^{19}F NMR (471 MHz, CD_2Cl_2) δ –76.11, –76.37, –76.51, –76.54.
HRMS: Exact mass calculated for $[C_{36}H_{37}F_6N_3O_7 + H]^+$ requires *m/z* = 738.2608, found *m/z* = 738.2599.
Optical Rotation: α_D^{20} = + 91.0 ° (*c* = 0.5, MeOH, >99:1 er)

HPLC (Chiralpak® IB column, 55% MeCN/H_2O eluent with 0.5% formic acid buffer, 1.20 mL min^{-1} flow rate, 25 °C, 265 nm, observed as 1.8:1 dr): major enantiomer t_R= 8.4 min; minor enantiomer t_R= 8.9 min. Unresolved pair of major and minor enantiomers t_R = 14.7 min.



5f

Ethyl (4*R*)-1^5-amino-4-(*tert*-butyl)-7-oxo-3^6,5^4-bis(2,2,2-trifluoroacetamido)-2,8-dioxa-1,3,5(1,3)-tribenzenacyclododecaphane-6-carboxylate (**5f**) was synthesized from **3f** following **Procedure 8**. Crude material was purified by silica chromatography (0→45→80% EtOAc/Hex eluent) to yield the desired product **5f** as a white solid. **5f** is observed as a 4.3:1 mixture of diastereomers CD_2Cl_2 at 25 °C by ^{1}H NMR.

Yield: 11% (0.0126 g) with **L3**

TLC (40% EtOAc/Hex): R_f= 0.53.

IR (FT-ATR, cm^{-1}, neat): ν_{max} 3389, 3288, 2953, 2868, 2126, 1727, 1590, 1535, 1289, 1159, 1030, 835.

^{1}H NMR (500 MHz, CD_2Cl_2): **major diastereomer**: δ 10.28 (s, 1H), 8.43 (s, 1H), 8.30 (d, *J* = 8.5 Hz, 1H), 7.72 (d, *J* = 8.5 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 1H), 7.42–7.40 (m, 1H)*, 7.30 (s, 1H), 7.06 (s, 1H)*, 6.90 (s, 1H), 6.39 (s, 1H), 6.24 (s, 1H), 4.60 (s, 1H), 4.34 – 4.17 (m, 3H)*, 3.96 (ddd, *J* = 11.1, 7.3, 3.9 Hz, 1H), 3.82 (brs, 2H), 3.66 (s, 1H), 2.29 – 2.23 (m, 2H)*, 1.52–1.45 (m, 2H)*, 1.29 (t, *J* = 7.1 Hz, 3H), 1.17–1.10 (m, 2H)*, 1.04 (s, 9H); **minor diastereomer**: 9.87 (s, 1H), 8.36 (s, 1H), 8.28 (d, *J* = 8.6 Hz, 1H), 7.65 (d, *J* = 8.3 Hz, 1H), 7.42–7.40 (m, 1H)*, 7.37 (d, *J* = 8.4 Hz, 1H), 7.06 (s, 1H)*, 6.36 (s, 1H), 6.23 (s, 1H), 4.65 (s, 1H), 4.34 – 4.17 (m, 3H)*, 4.07–4.02 (m, 1H), 3.82 (brs, 2H), 3.77 (s, 1H), 2.34–2.31 (m, 1H), 2.29 – 2.23 (m, 1H)*, 1.52–1.45 (m, 2H)*, 1.25 (t, *J* = 7.1 Hz, 3H), 1.17–1.10 (m, 2H)*, 1.03 (s, 9H). (*indicates overlap of peaks corresponding to the major and minor diastereomers.)

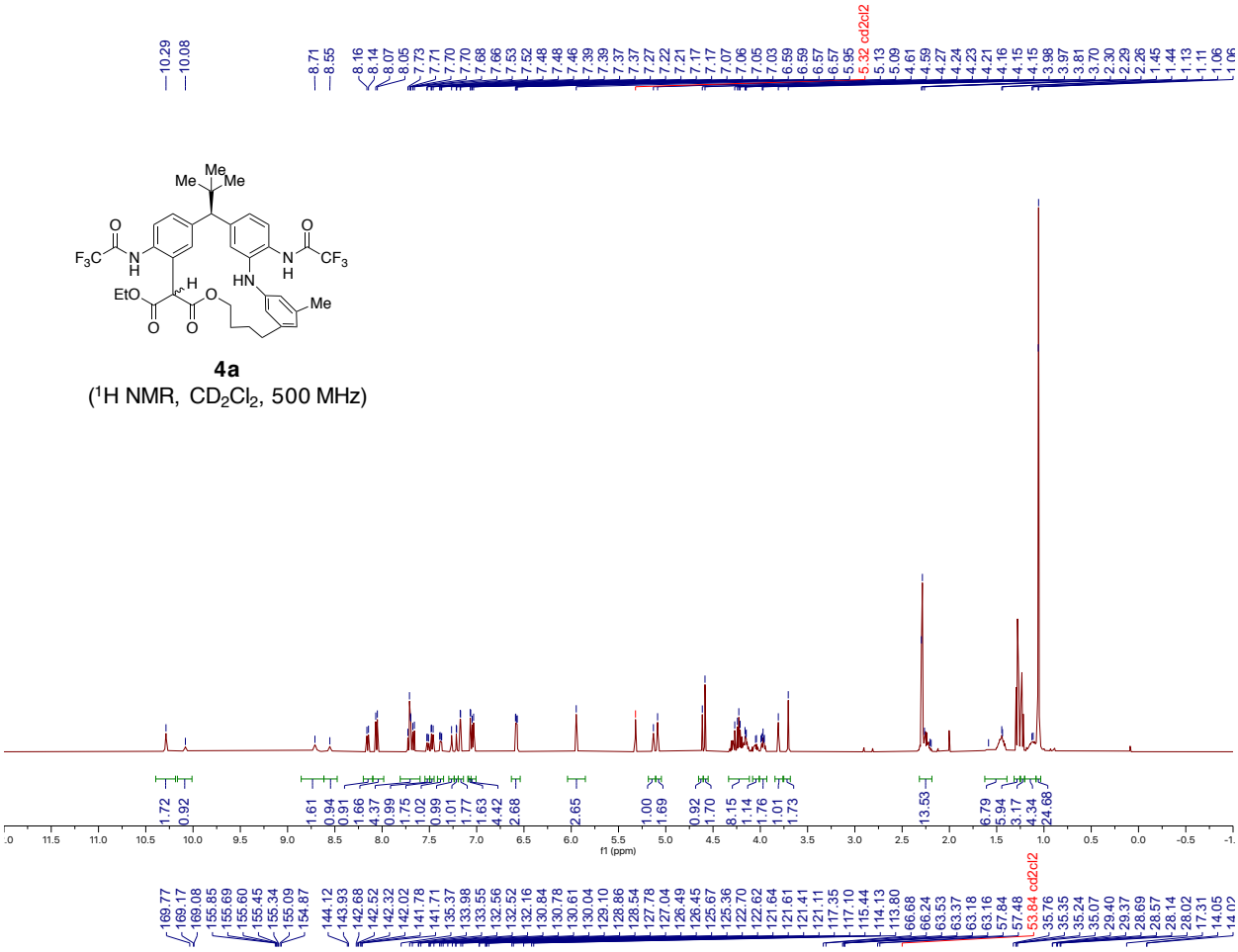
^{13}C NMR (126 MHz, CD_2Cl_2): **major diastereomer**: δ 169.8, 168.9, 158.2, 155.5 (q, *J* = 36.5 Hz), 154.7 (q, *J* = 36.5 Hz), 148.8, 146.0, 145.8, 142.3, 141.6, 135.2,* 132.6, 129.3, 126.3, 125.1, 125.6, 124.9, 121.5, 120.8, 116.4 (q, *J* = 287.9 Hz), 116.1 (q, *J* = 288.5 Hz), 111.1, 105.7, 103.2, 66.4, 63.5, 63.4, 57.8, 35.7, 35.4, 29.4, 28.6, 27.7, 14.1*; **minor diastereomer****: δ 169.3, 168.8, 158.3, 148.9, 145.7, 142.2, 142.0, 135.2*, 132.4, 132.1, 132.0,126.7, 126.5, 126.0, 125.5, 121.7, 121.1, 111.5, 105.6, 102.5, 66.1, 63.3, 63.2, 56.9, 35.3, 35.3, 29.3, 27.8, 27.4, 14.1*.

(Note: *indicates a peak corresponding to both the major and minor diastereomers; **peaks of (C=O)CF_3, (C=O)CF_3 for the minor diastereomer were not observed at the signal-to-noise ratio of the measurement)

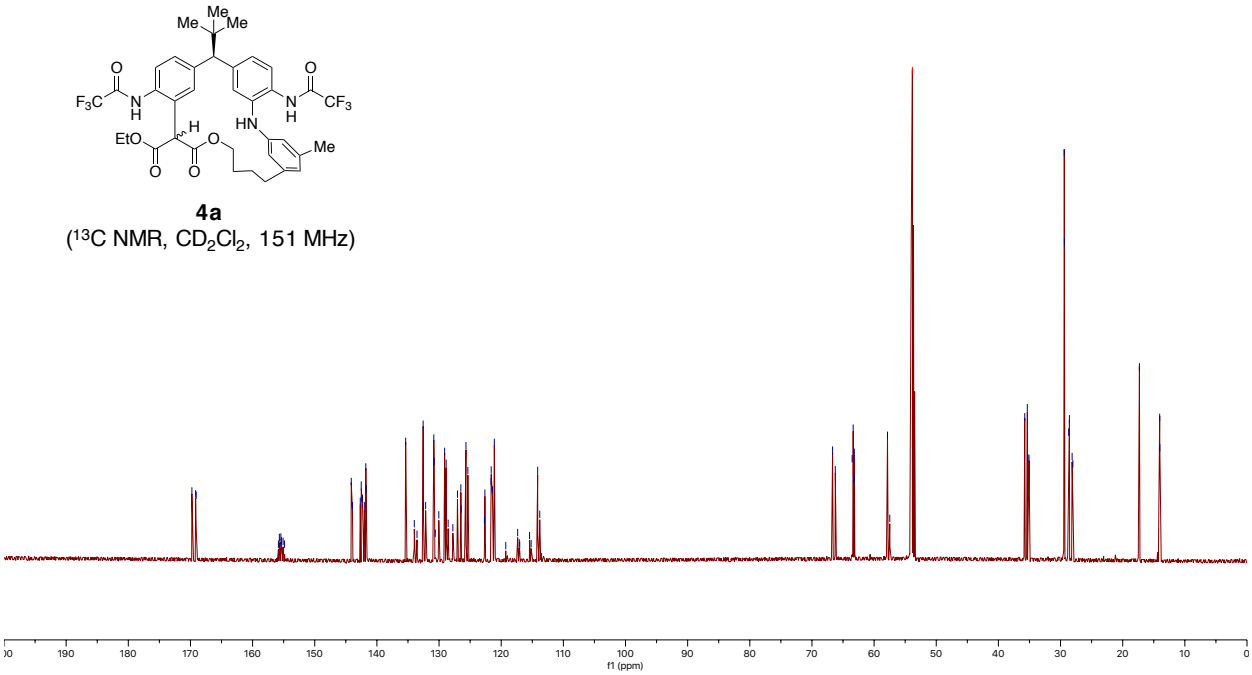
^{19}F NMR (471 MHz, CD_2Cl_2) δ –76.26, –76.36, –76.48, –76.57.

Optical Rotation: α_D^{20}= +25.9° (*c* = 0.3, MeOH, 93:7 er)

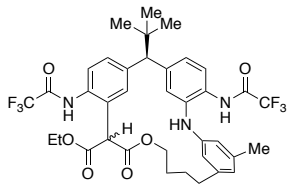
HRMS: Exact mass calculated for $[C_{36}H_{37}F_6N_3O_7 + H]^+$ requires *m/z* =738.2609, found *m/z* = 738.2593.



4a
(^{1}H NMR, CD_2Cl_2, 500 MHz)

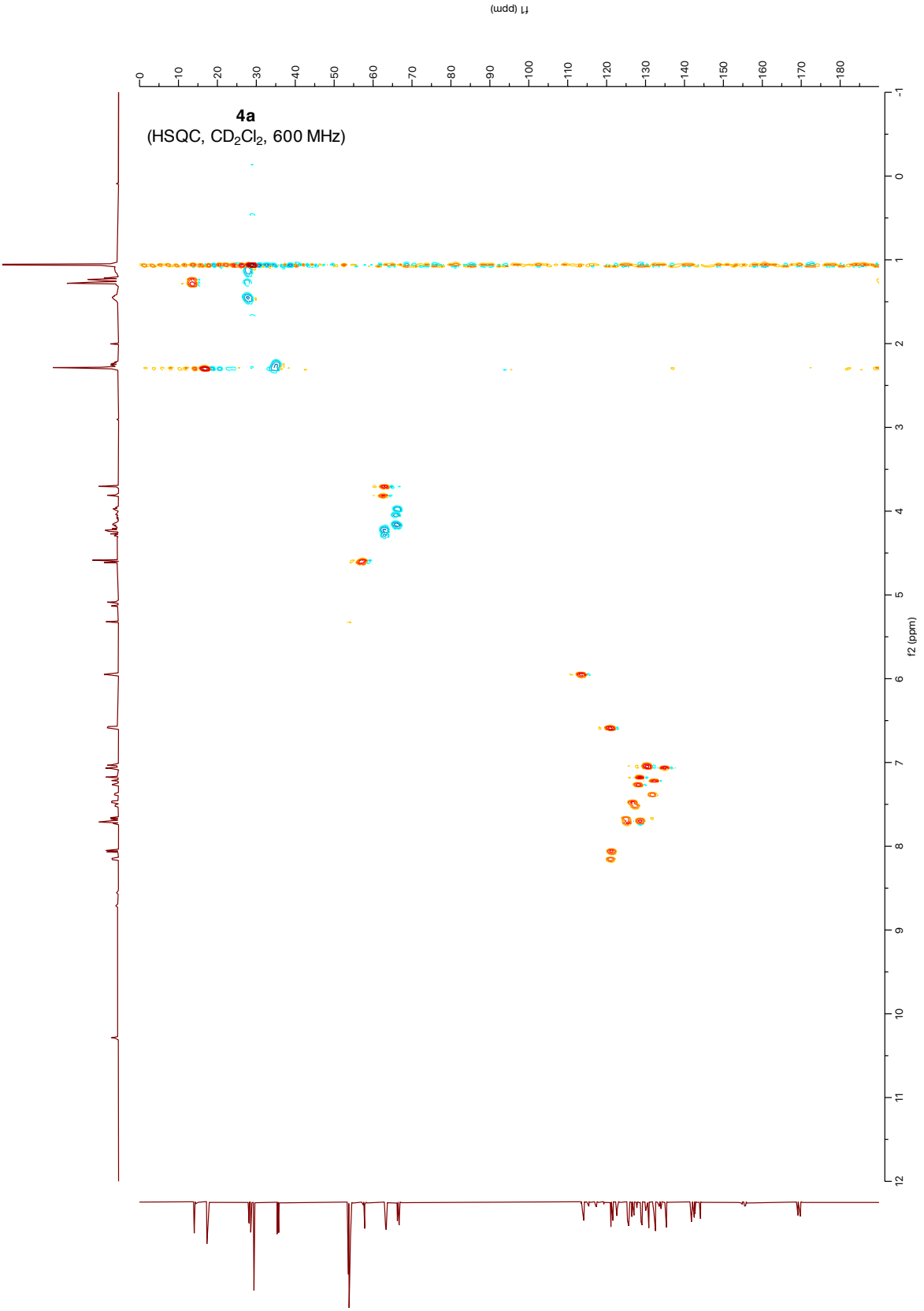


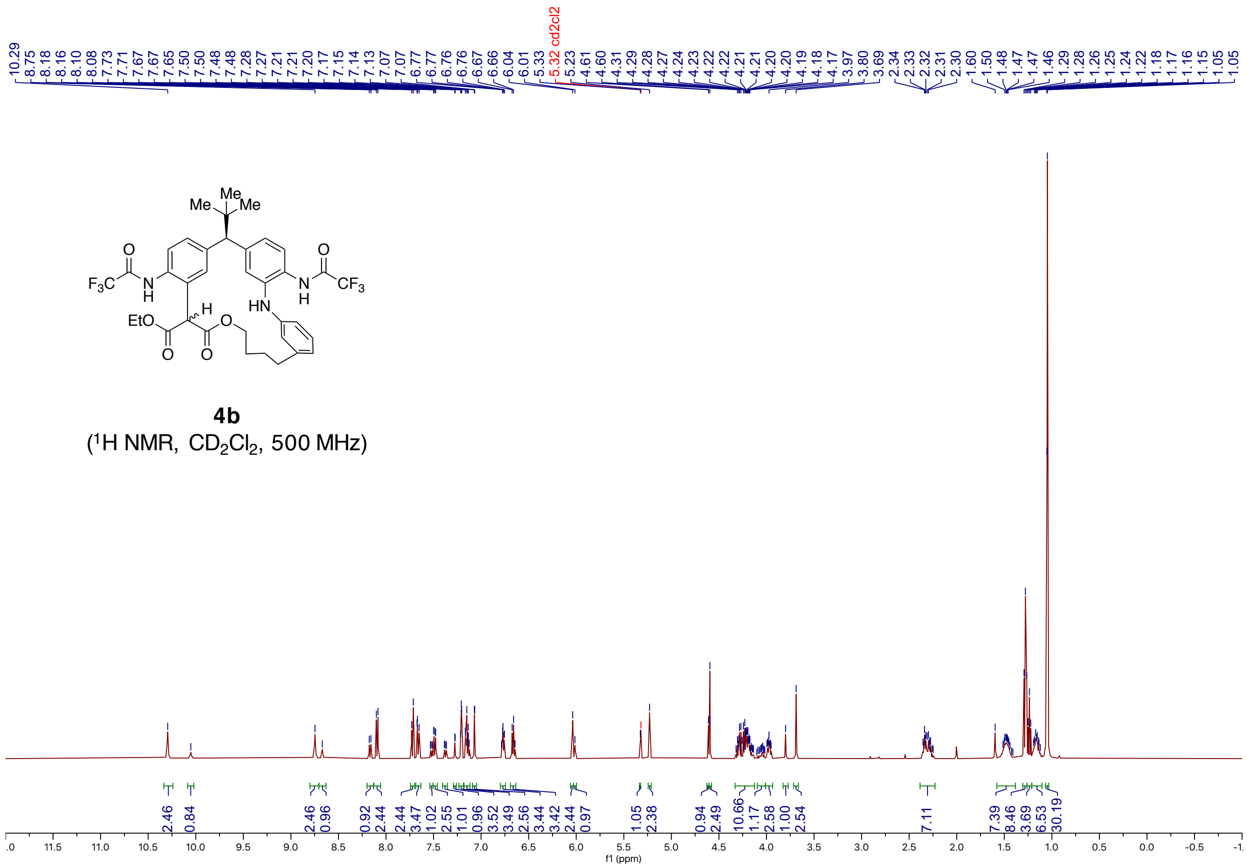
4a
(^{13}C NMR, CD_2Cl_2, 151 MHz)



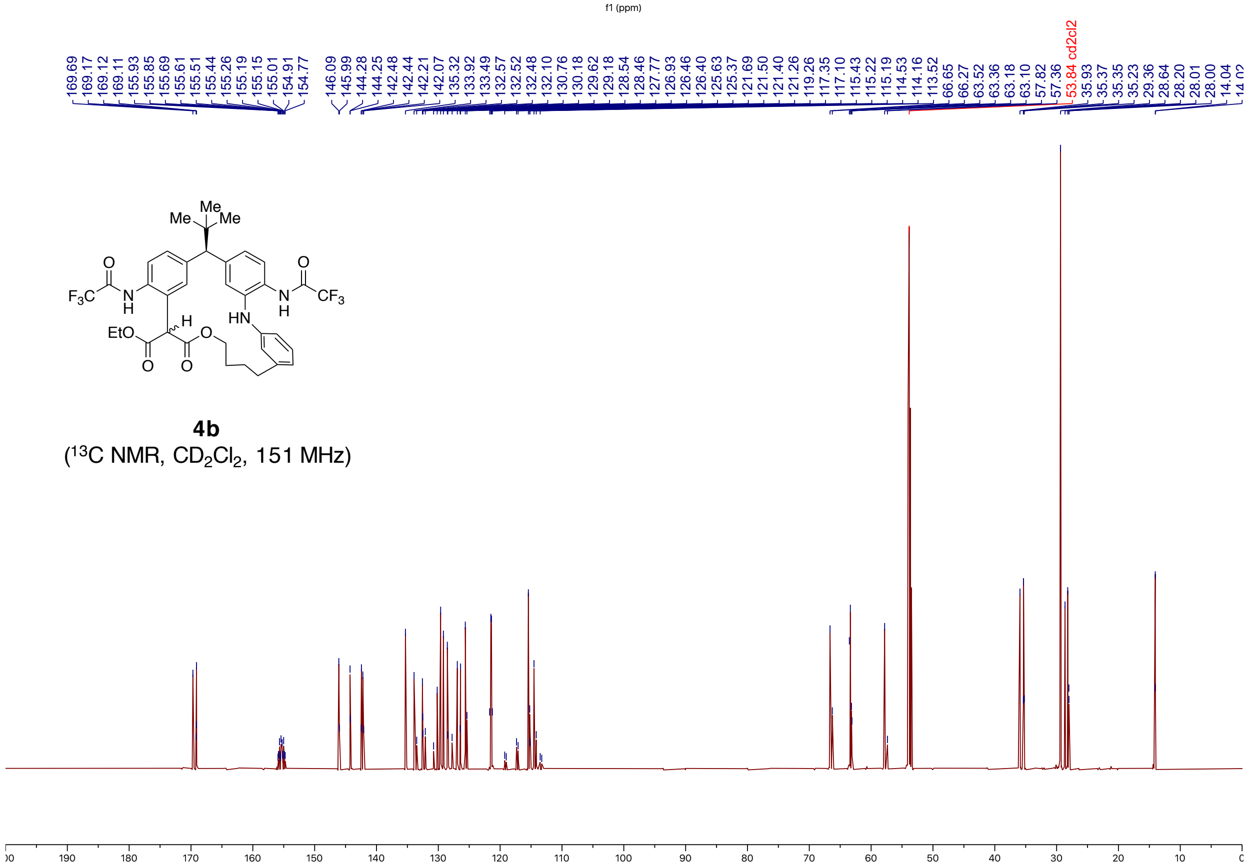
4a

(^{1}H NMR, CD_2Cl_2, 471 MHz)

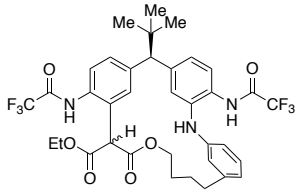

4a
(HSQC, CD_2Cl_2, 600 MHz)
f1 (ppm)
f2 (ppm)



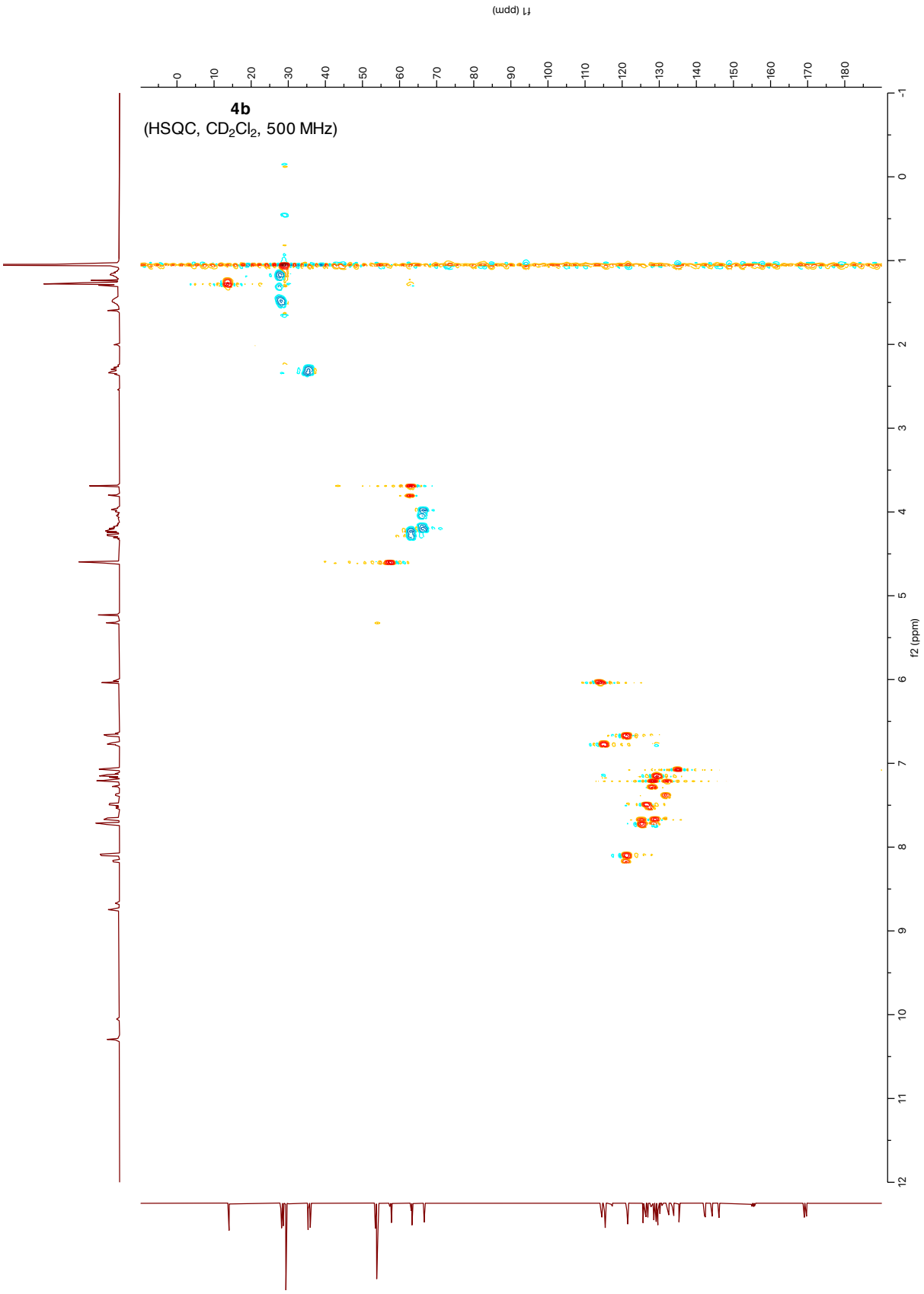
4b
(^{1}H NMR, CD_2Cl_2, 500 MHz)

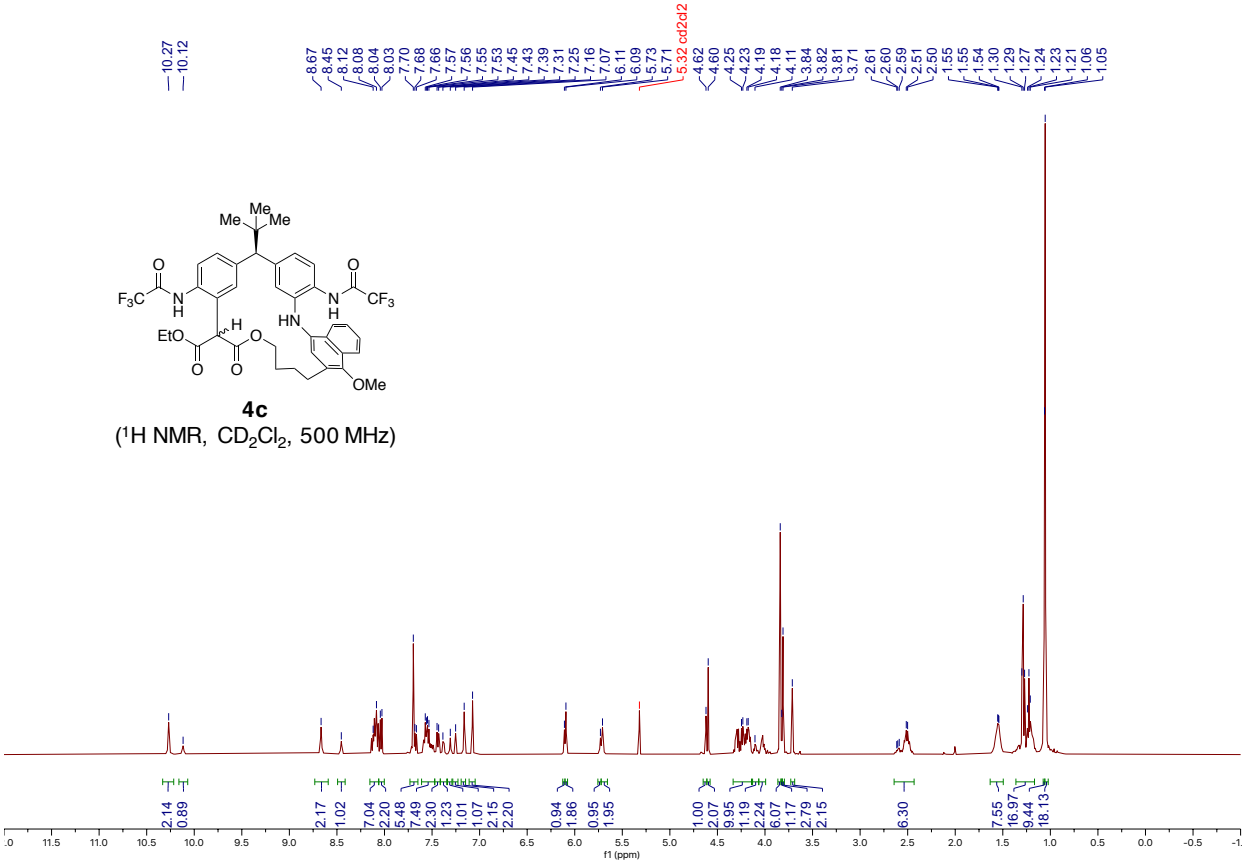


4b
(^{13}C NMR, CD_2Cl_2, 151 MHz)

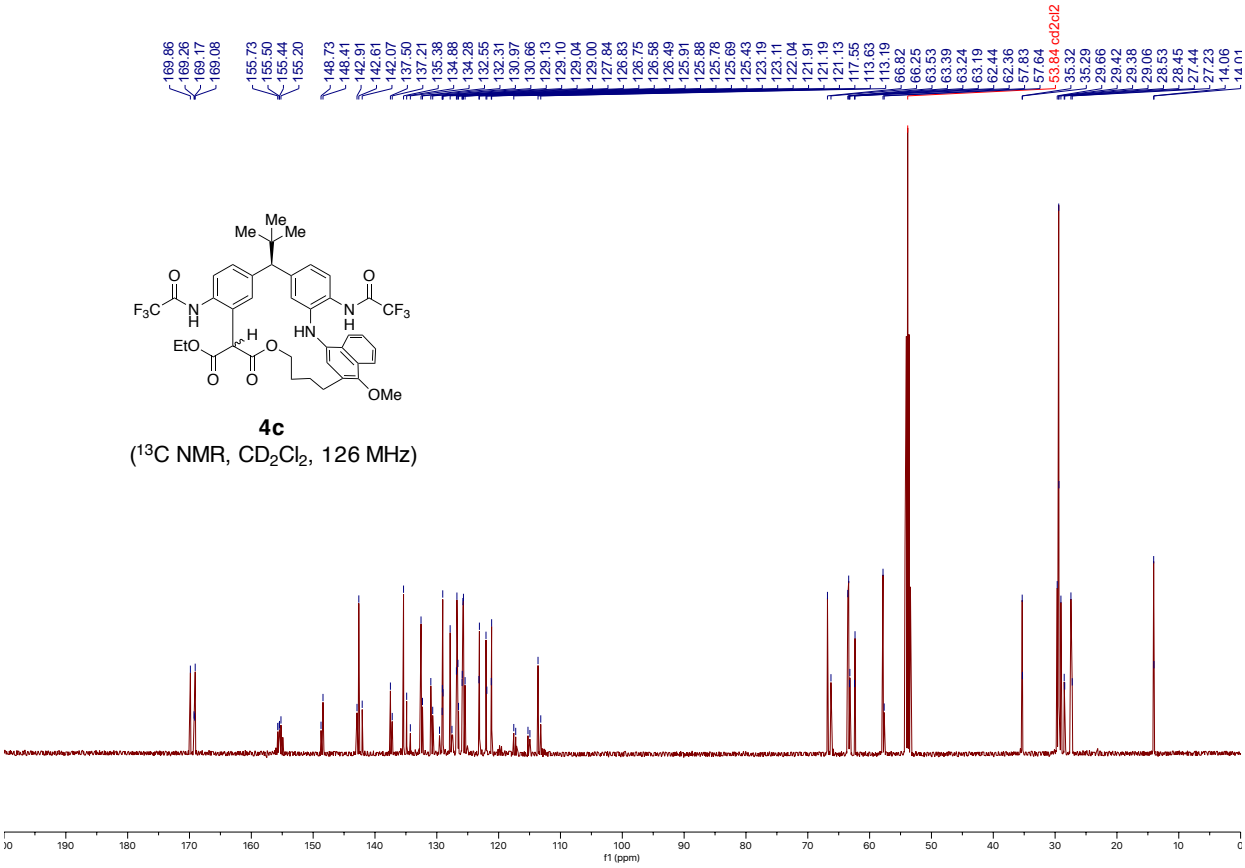


4b
(^{19}F NMR, CD_2Cl_2, 471 MHz)

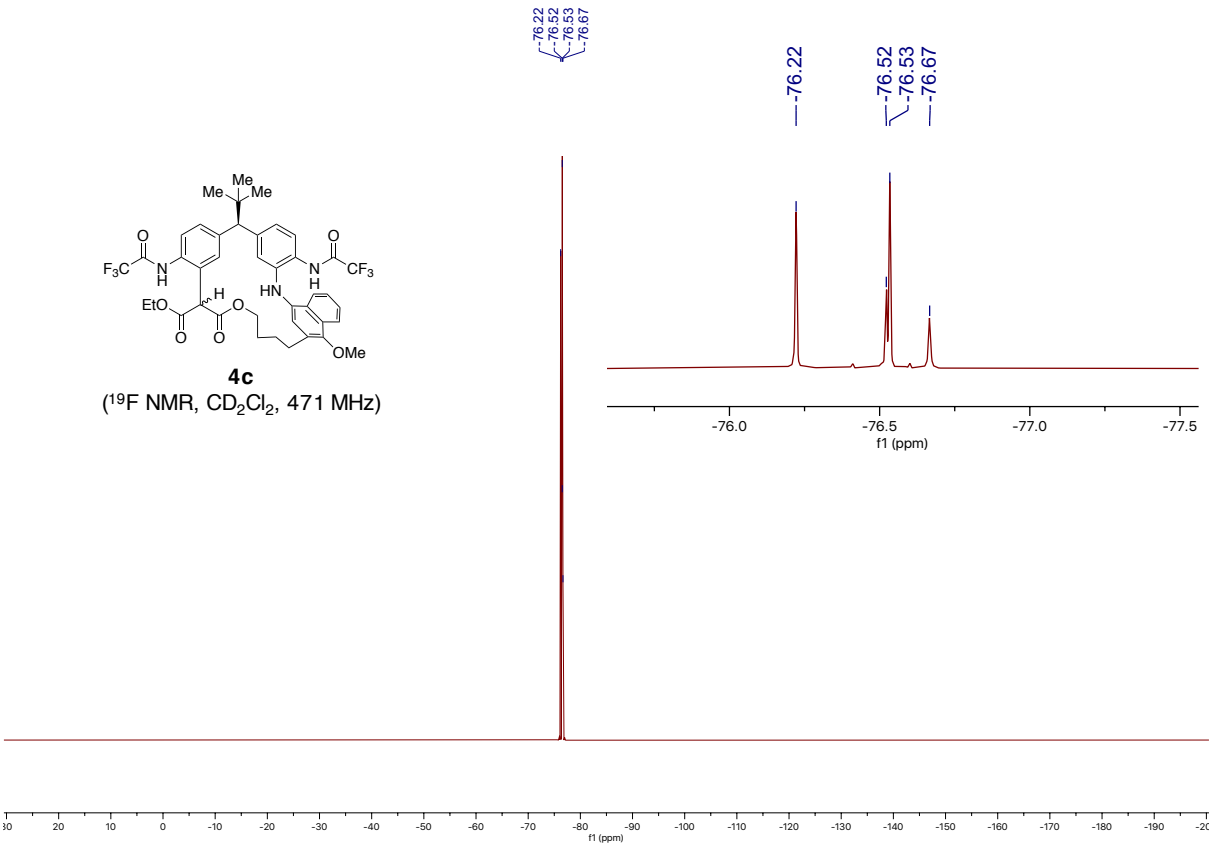

4b
(HSQC, CD_2Cl_2, 500 MHz)
f1 (ppm)
f2 (ppm)



4c
(^{1}H NMR, CD_2Cl_2, 500 MHz)

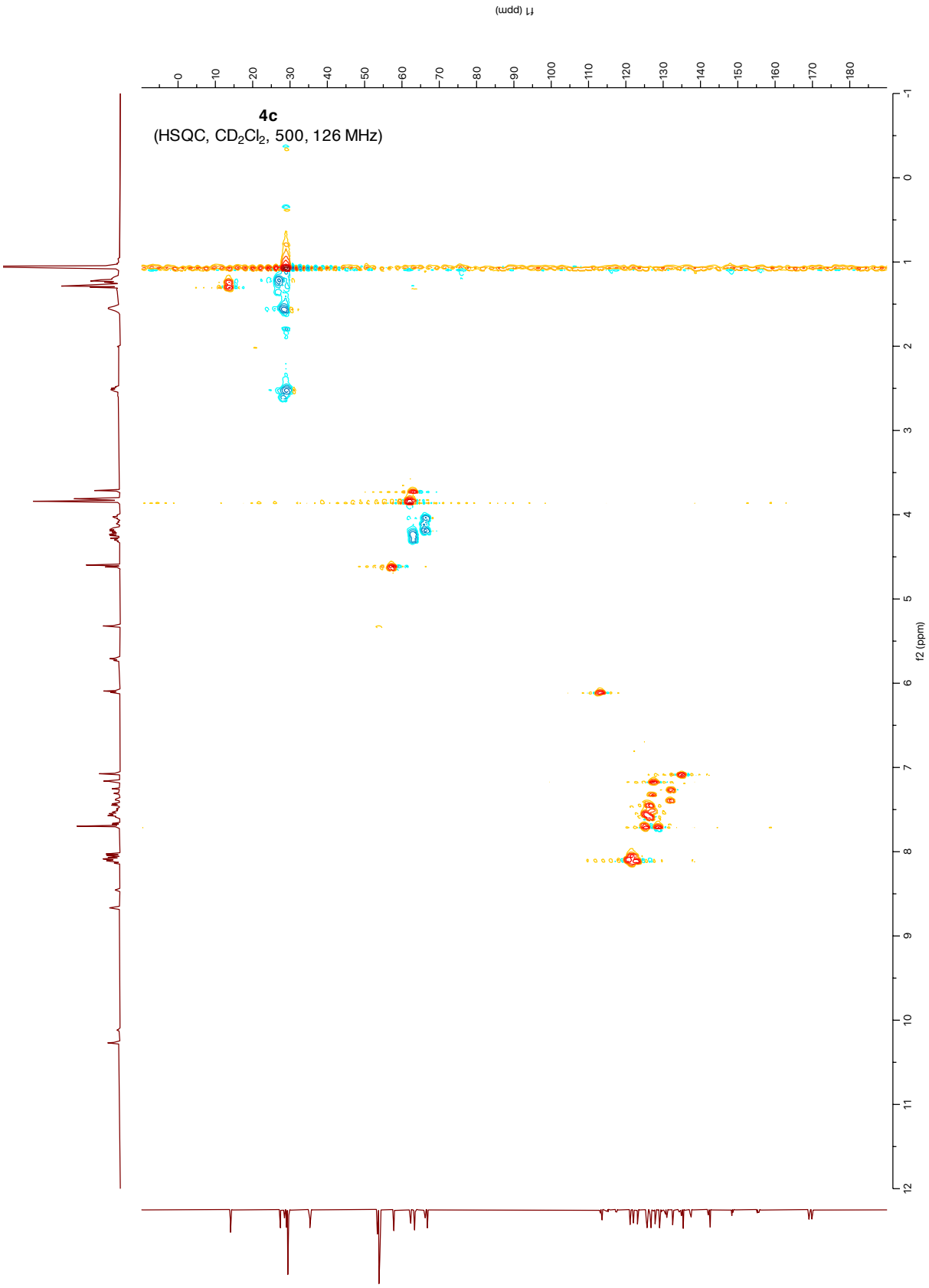


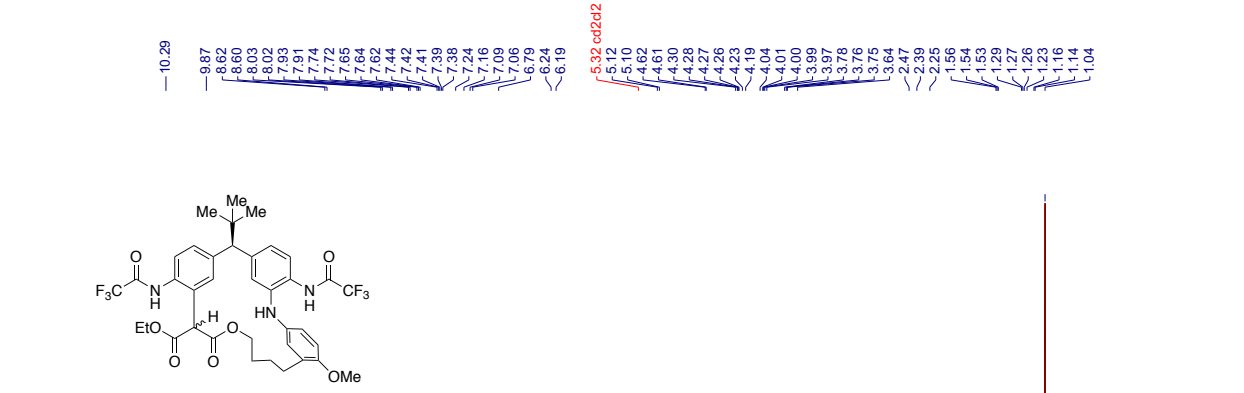
4c
(^{13}C NMR, CD_2Cl_2, 126 MHz)



4c

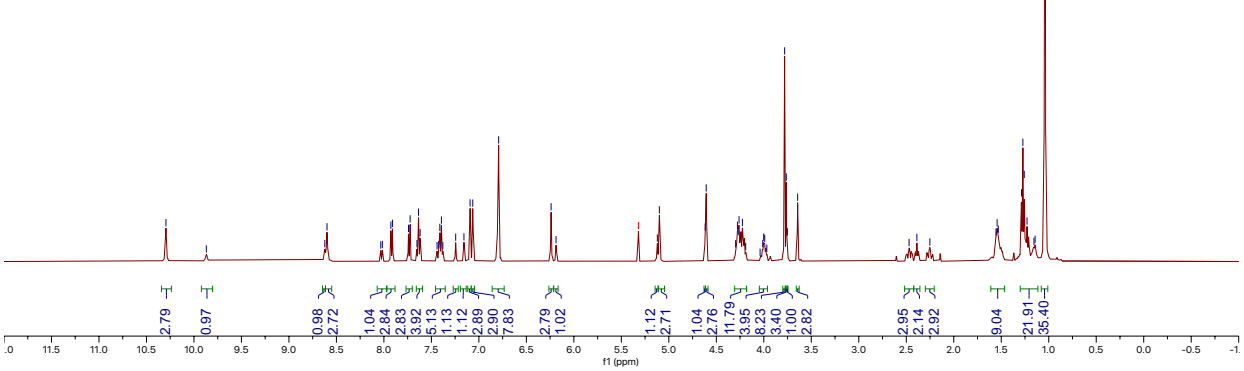
(^{19}F NMR, CD_2Cl_2, 471 MHz)

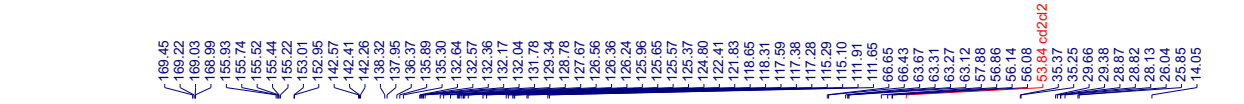

f1 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
4c
(HSQC, CD2Cl2, 500, 126 MHz)
-1
0
1
2
3
4
5
6
7
8
9
10
11
12
f2 (ppm)

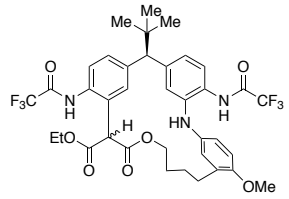


4d

(^{1}H NMR, CD_2Cl_2, 500 MHz)

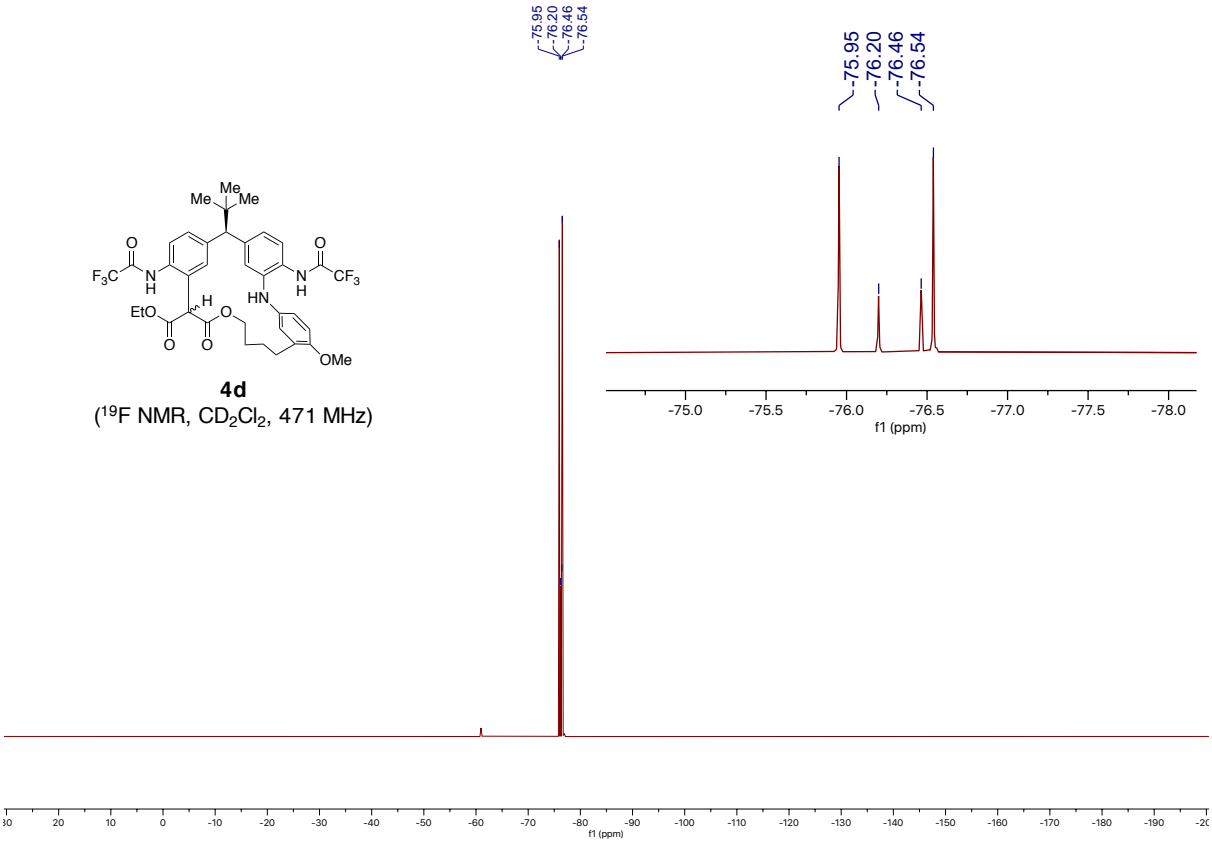






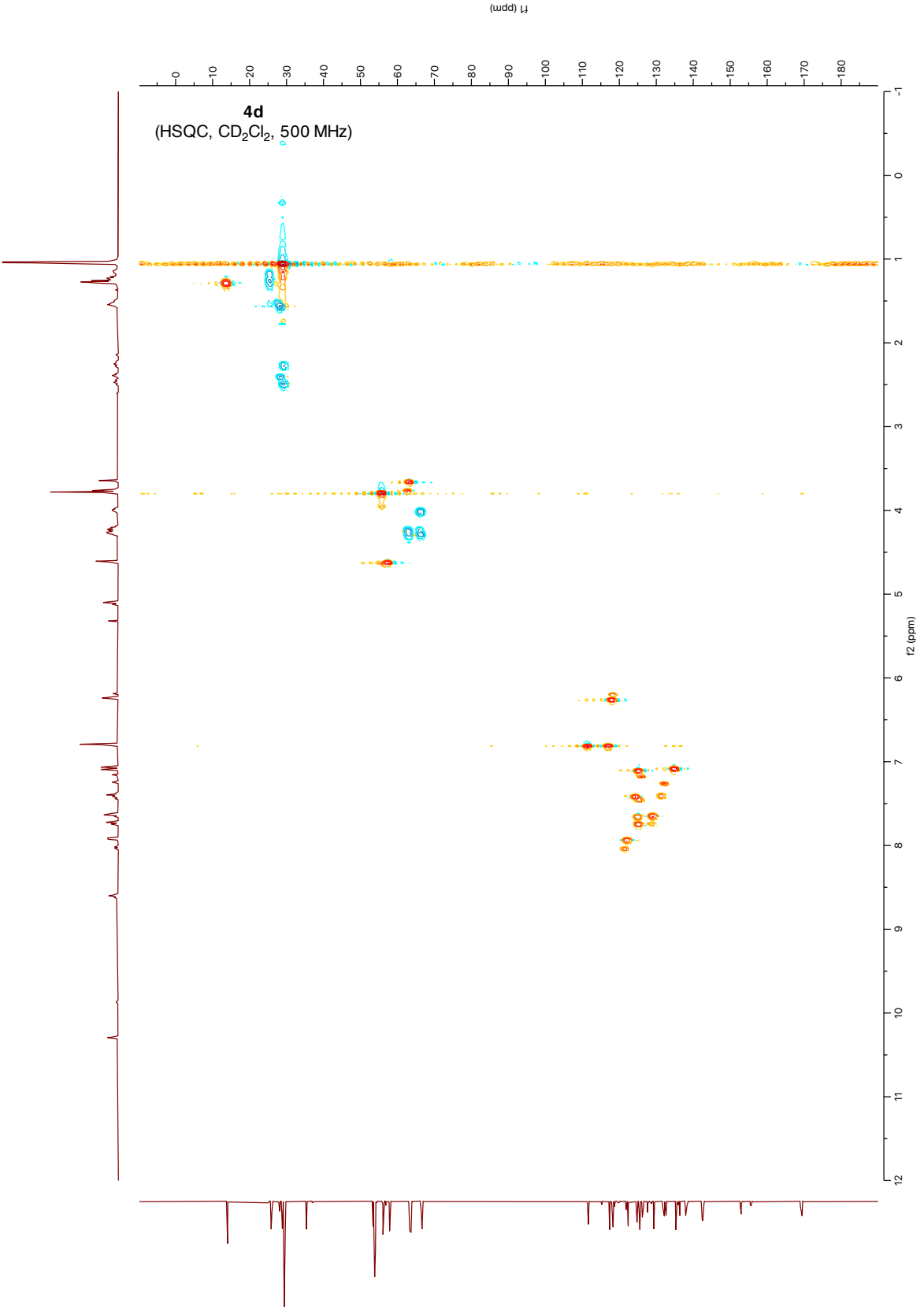
4d

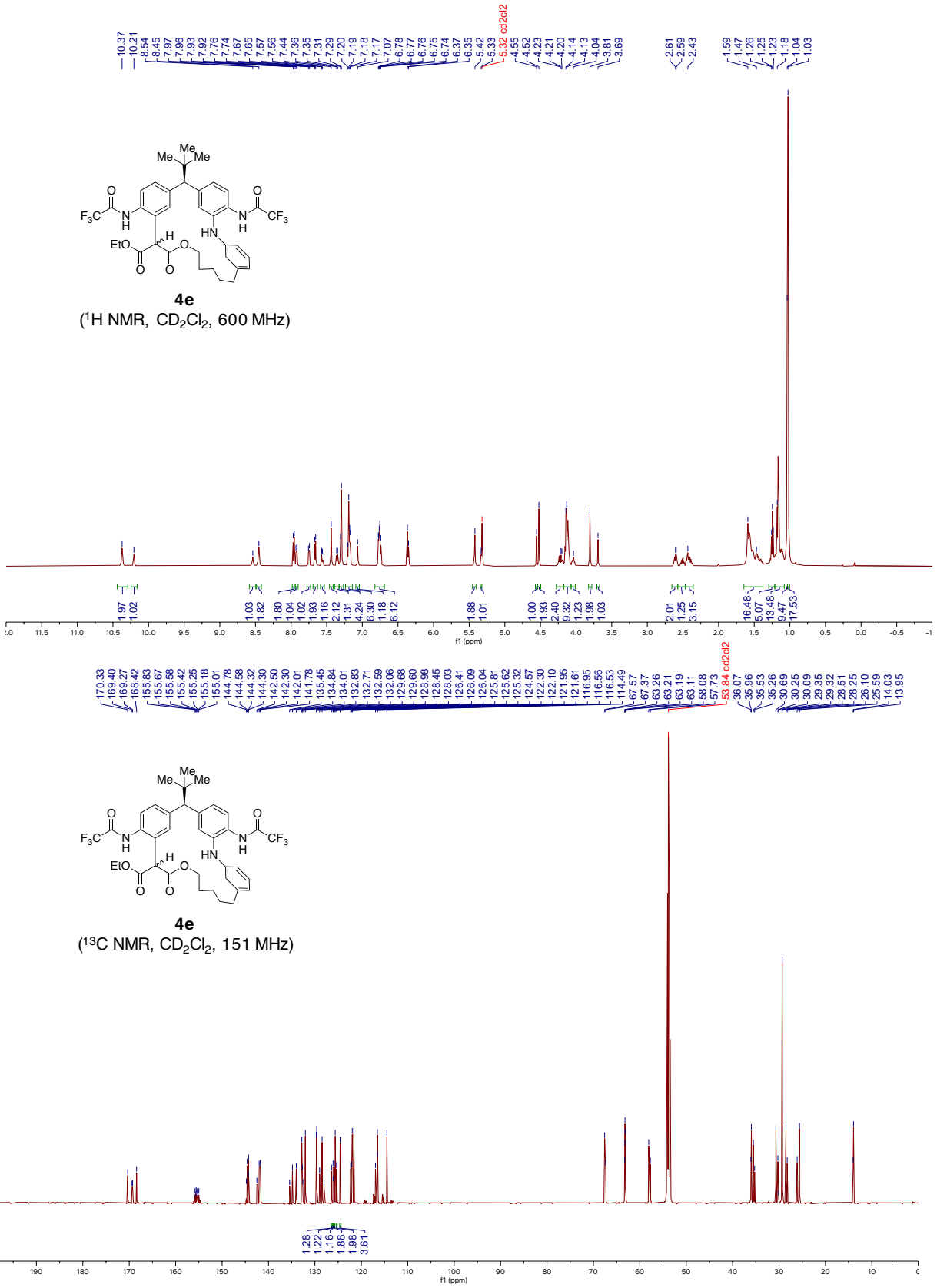
(^{13}C NMR, CD_2Cl_2, 126 MHz)

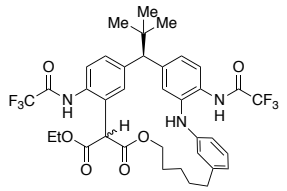


4d

(^{19}F NMR, CD_2Cl_2, 471 MHz)

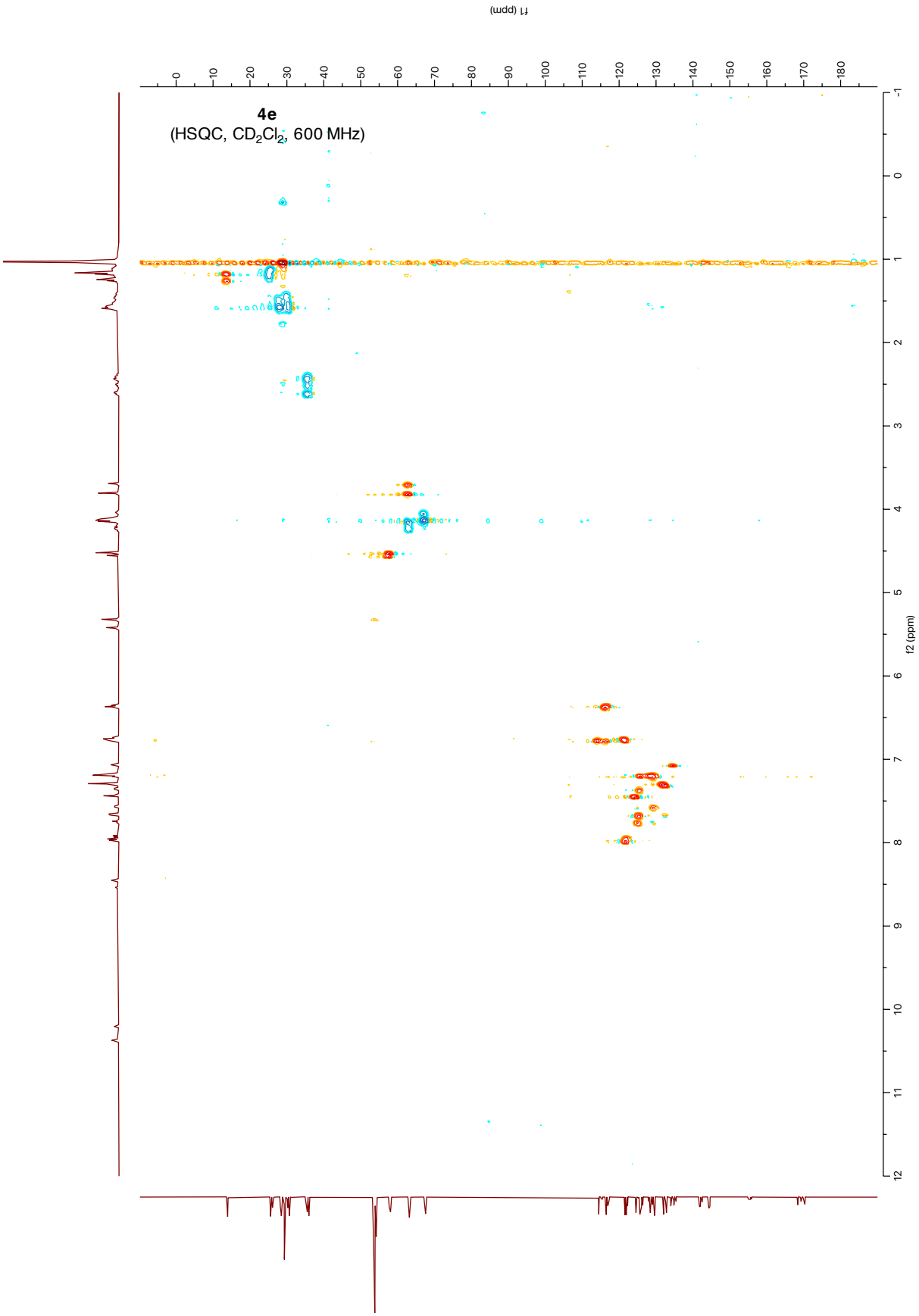

f1 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
4d
(HSQC, CD2Cl2, 500 MHz)
f2 (ppm)
-1
0
1
2
3
4
5
6
7
8
9
10
11
12

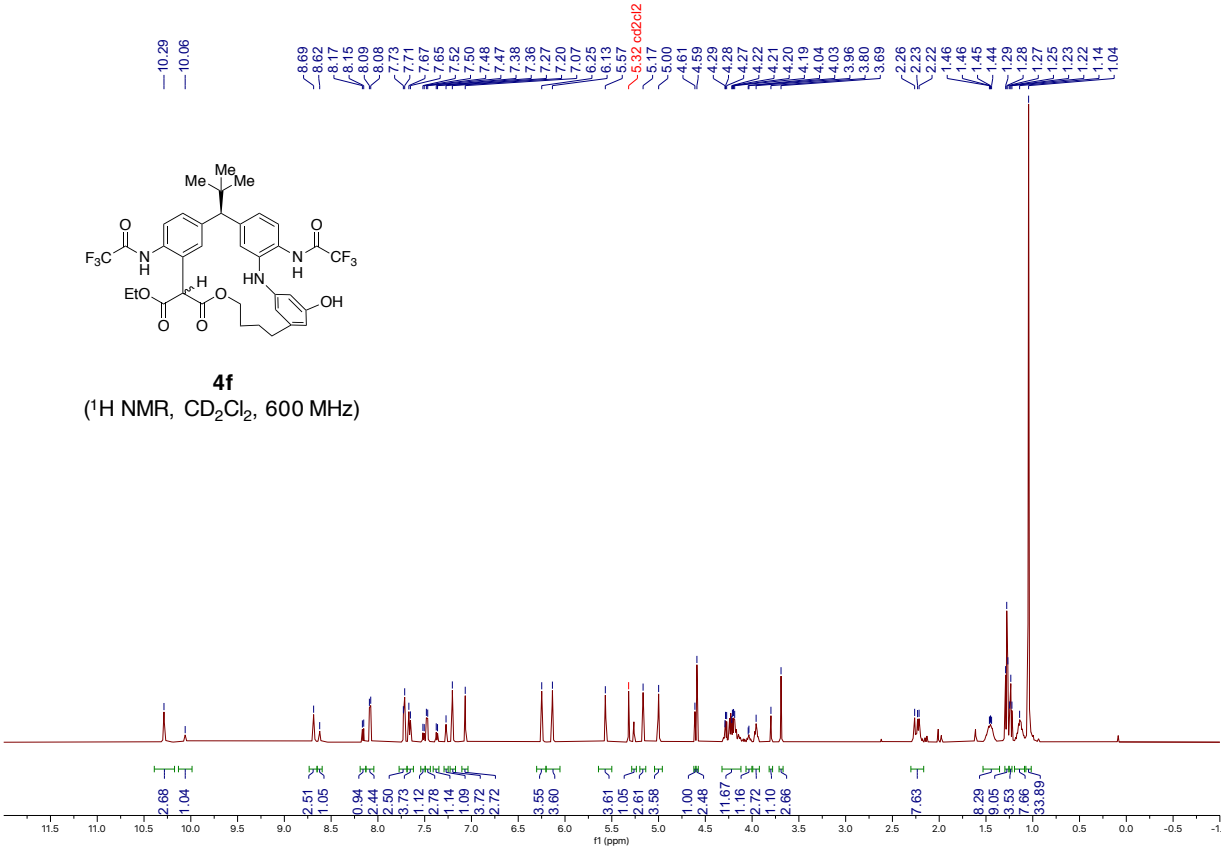

Me
Me
Me
O
F3C
N
H
O
N
H
CF3
HN
H
EtO
O
O
O
4e
(1H NMR, CD2Cl2, 600 MHz)
cd2cl2
f1 (ppm)
4e
(13C NMR, CD2Cl2, 151 MHz)
cd2cl2
f1 (ppm)



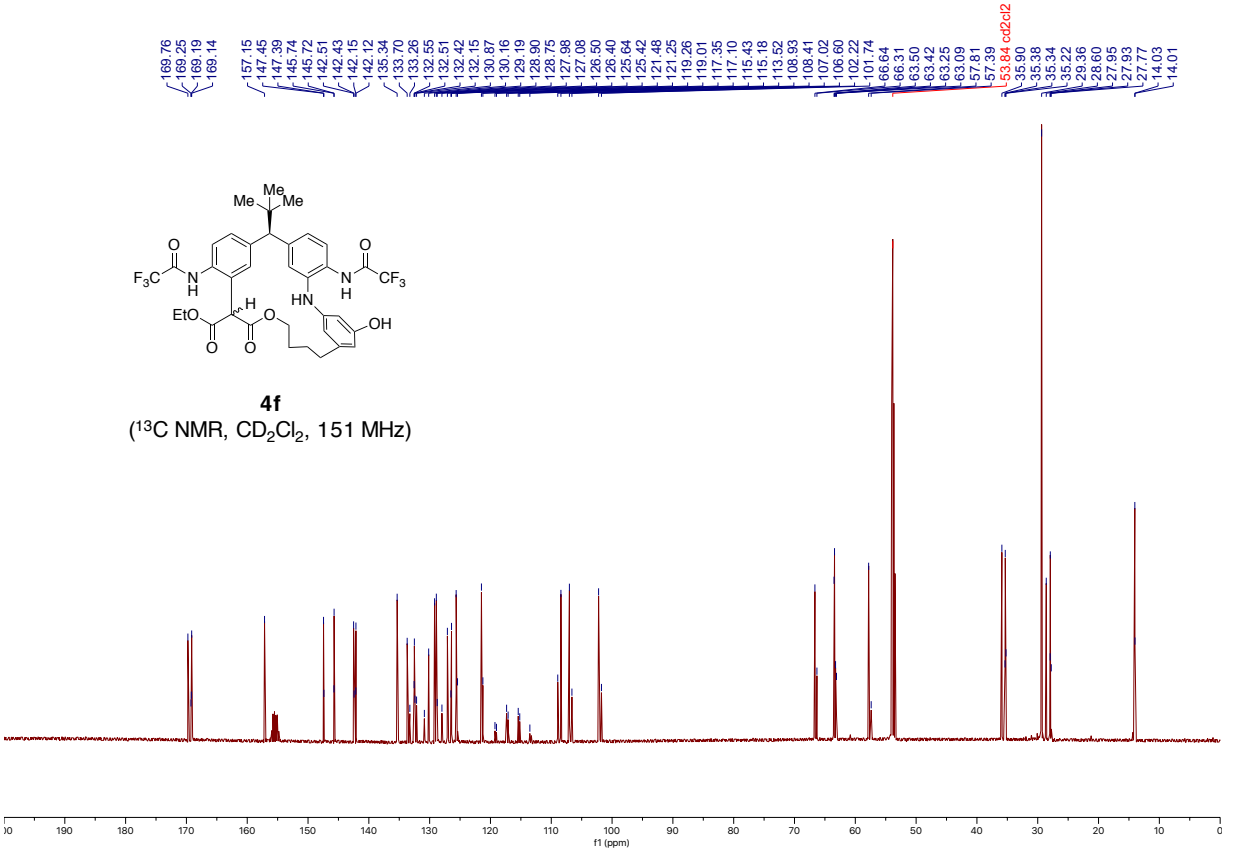
4e

(^{19}F NMR, CD_2Cl_2, 471 MHz)

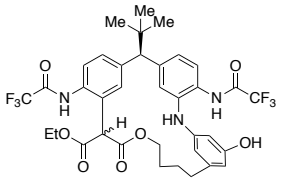

4e
(HSQC, CD2Cl2, 600 MHz)
f1 (ppm)
f2 (ppm)



4f
(^{1}H NMR, CD_2Cl_2, 600 MHz)

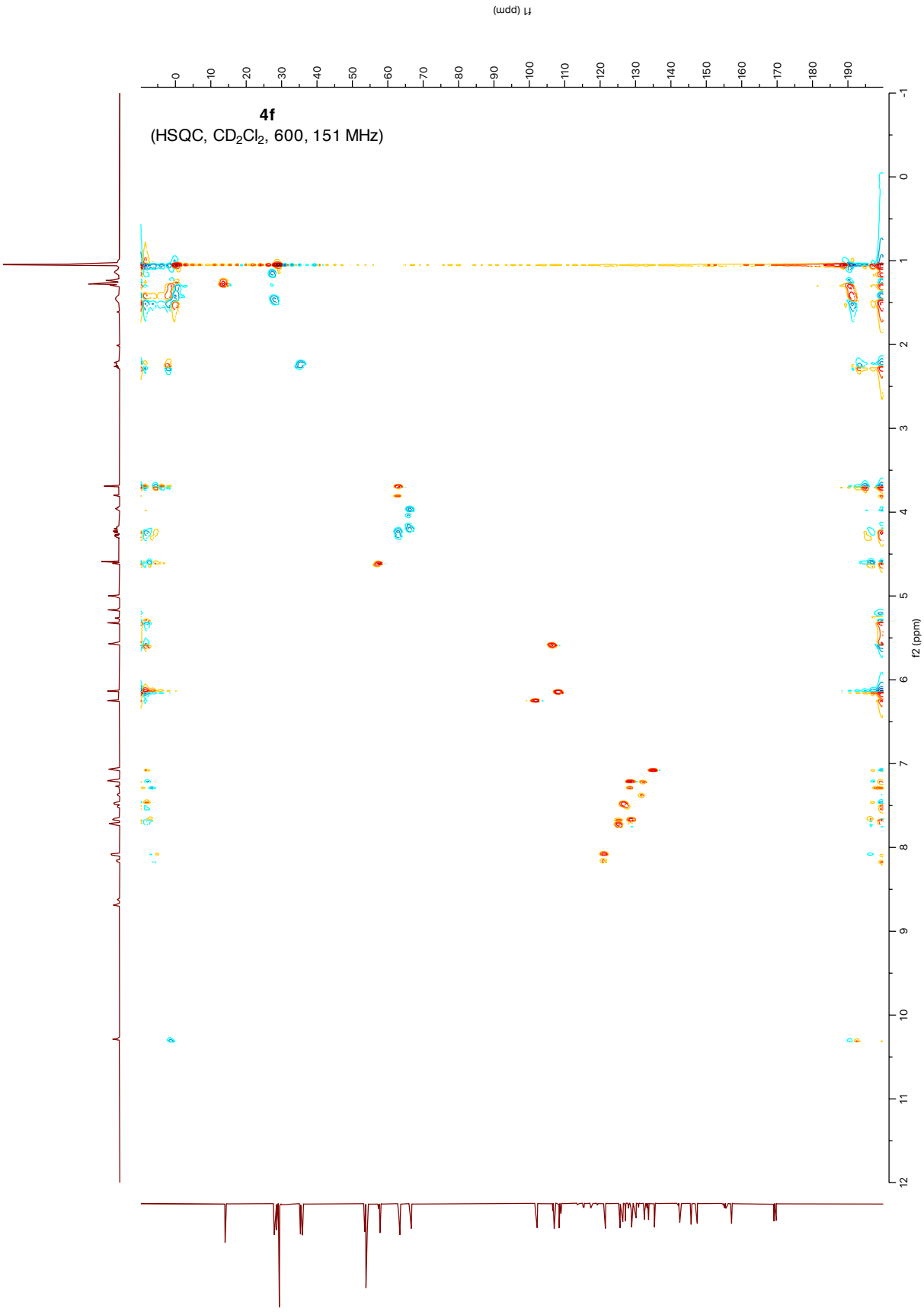


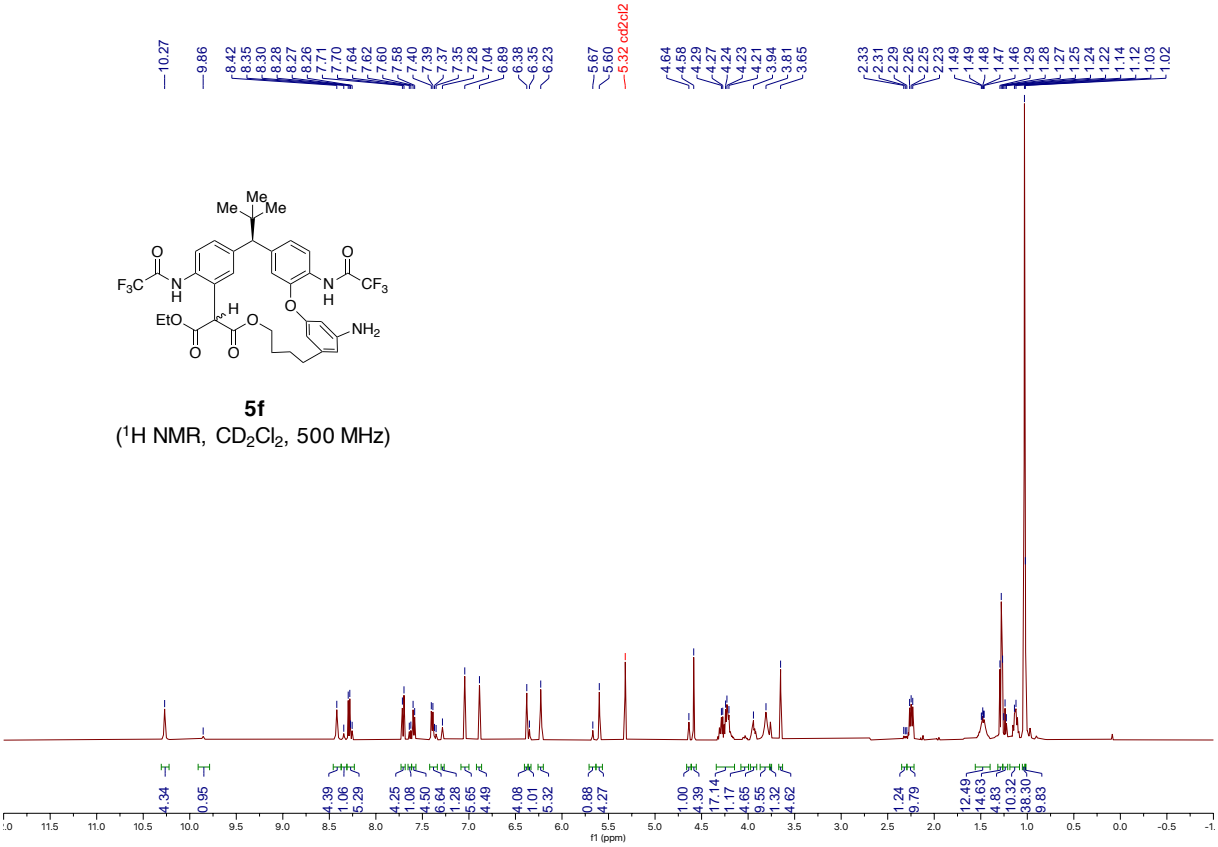
4f
(^{13}C NMR, CD_2Cl_2, 151 MHz)



4f

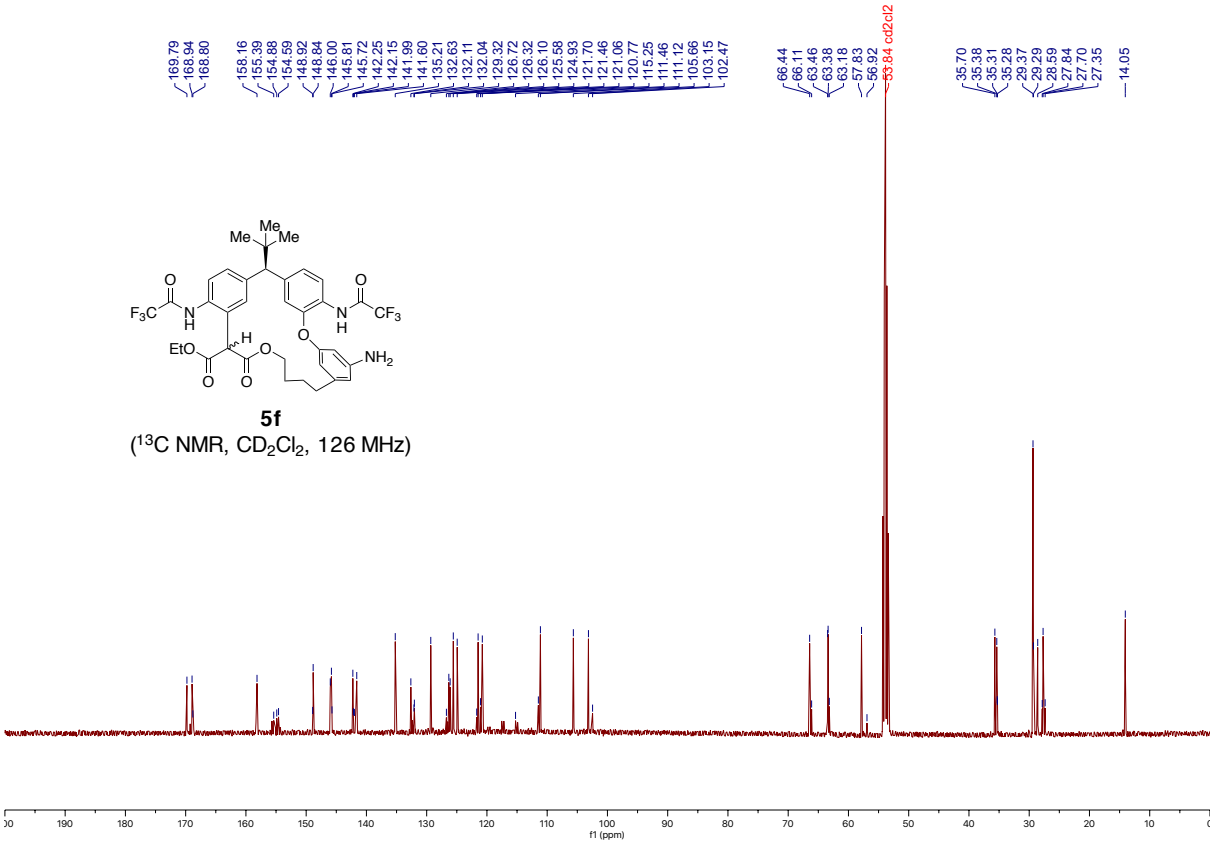
(^{19}F NMR, CD_2Cl_2, 471 MHz)


f1 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
4f
(HSQC, CD2Cl2, 600, 151 MHz)
-1
0
1
2
3
4
5
6
7
8
9
10
11
12
f2 (ppm)



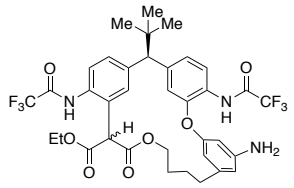
5f

(^{1}H NMR, CD_2Cl_2, 500 MHz)



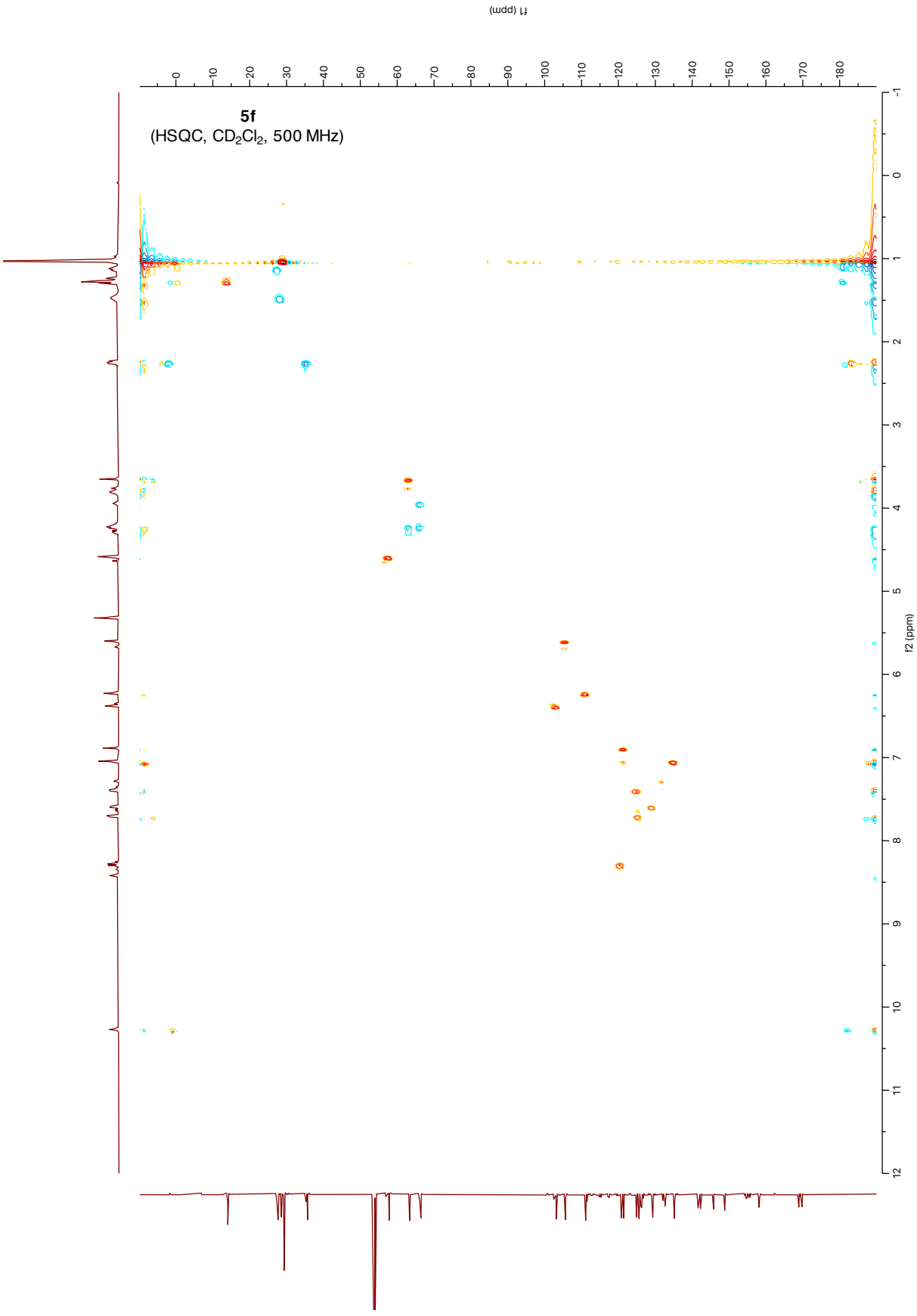
5f

(^{13}C NMR, CD_2Cl_2, 126 MHz)

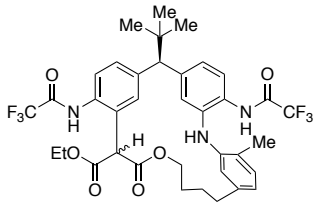


5f

(^{19}F NMR, CD_2Cl_2, 471 MHz)


5f
(HSQC, CD2Cl2, 500 MHz)
f1 (ppm)
f2 (ppm)

12.1 HPLC Traces of Macrocyclic Compounds (4a-f)

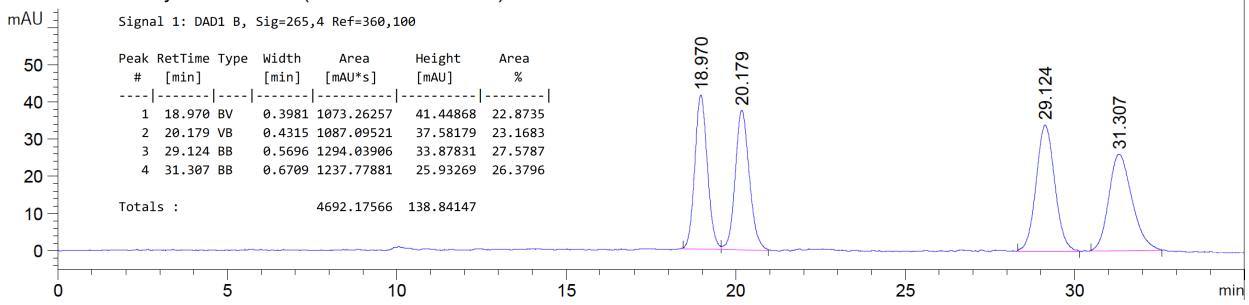


4a
Chiralpak IB
55% MeCN/H_2O with 0.5% formic acid, 1.250 mL/min, 25 °C, 265 nm

Analytical standard (observed as 1.2:1 dr)

Signal 1: DAD1 B, Sig=265,4 Ref=360,100

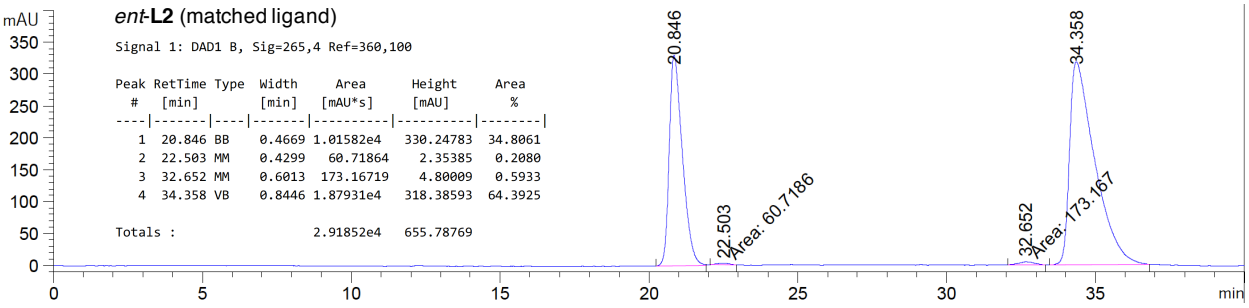
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.970	BV	0.3981	1073.26257	41.44868	22.8735
2	20.179	VB	0.4315	1087.09521	37.58179	23.1683
3	29.124	BB	0.5696	1294.03906	33.87831	27.5787
4	31.307	BB	0.6709	1237.77881	25.93269	26.3796
Totals :				4692.17566	138.84147	



ent-**L2** (matched ligand)

Signal 1: DAD1 B, Sig=265,4 Ref=360,100

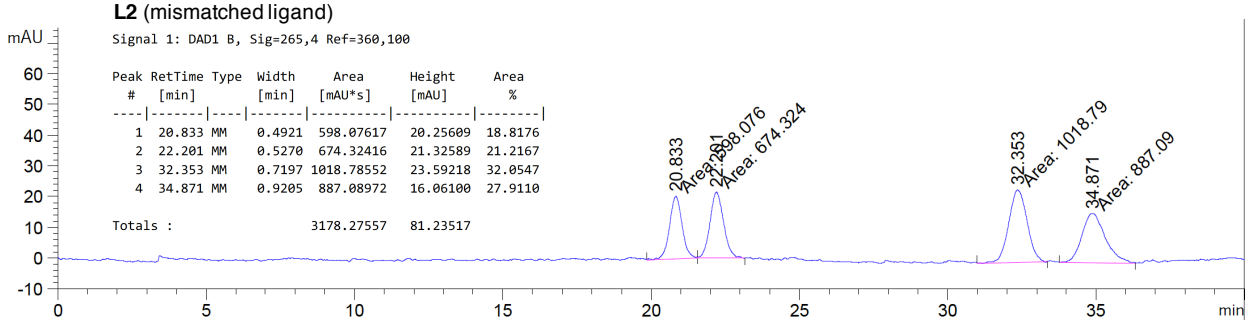
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.846	BB	0.4669	1.01582e4	330.24783	34.8061
2	22.503	MM	0.4299	60.71864	2.35385	0.2080
3	32.652	MM	0.6013	173.16719	4.80009	0.5933
4	34.358	VB	0.8446	1.87931e4	318.38593	64.3925
Totals :				2.91852e4	655.78769	



L2 (mismatched ligand)

Signal 1: DAD1 B, Sig=265,4 Ref=360,100

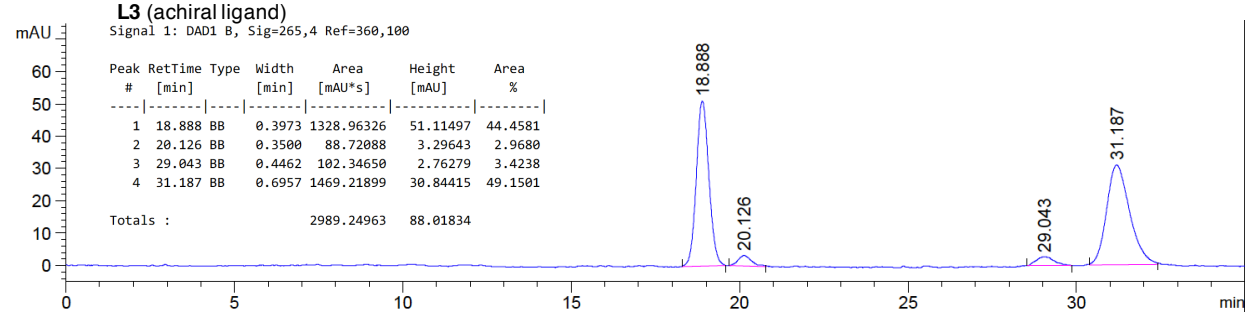
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.833	MM	0.4921	598.07617	20.25609	18.8176
2	22.201	MM	0.5270	674.32416	21.32589	21.2167
3	32.353	MM	0.7197	1018.78552	23.59218	32.0547
4	34.871	MM	0.9205	887.08972	16.06100	27.9110
Totals :				3178.27557	81.23517	

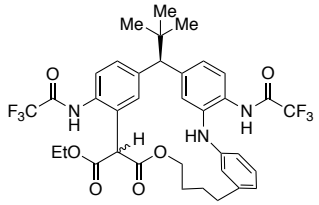


L3 (achiral ligand)

Signal 1: DAD1 B, Sig=265,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.888	BB	0.3973	1328.96326	51.11497	44.4581
2	20.126	BB	0.3500	88.72088	3.29643	2.9680
3	29.043	BB	0.4462	102.34650	2.76279	3.4238
4	31.187	BB	0.6957	1469.21899	30.84415	49.1501
Totals :				2989.24963	88.01834	

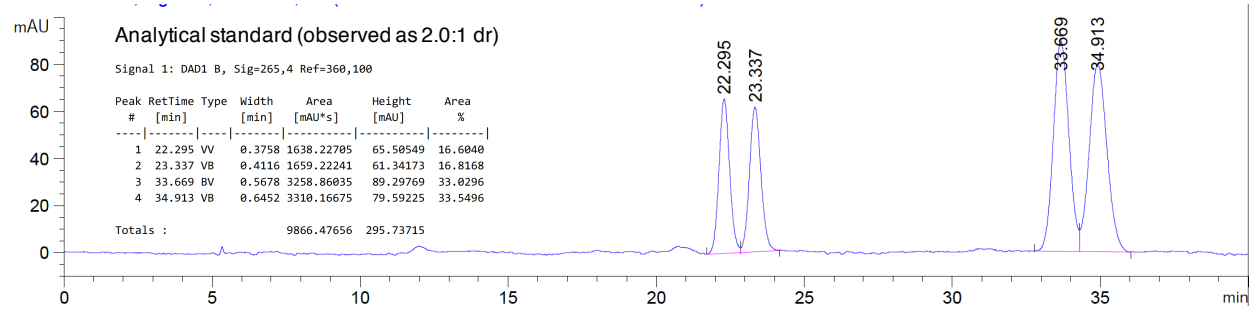


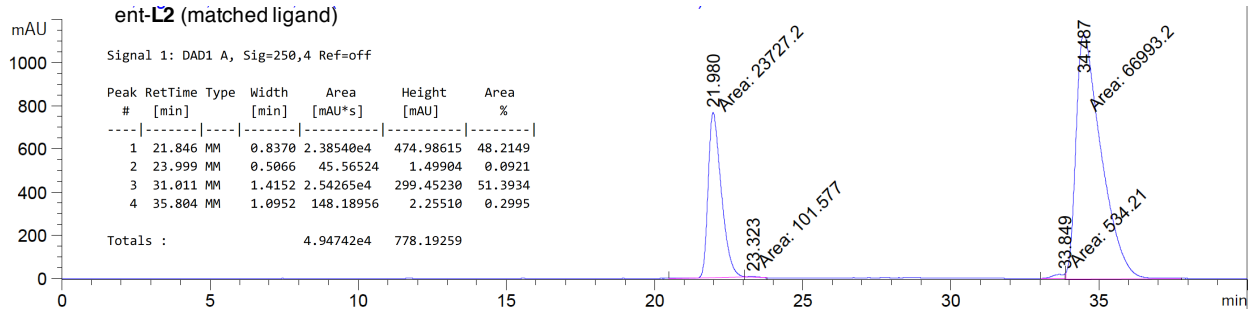


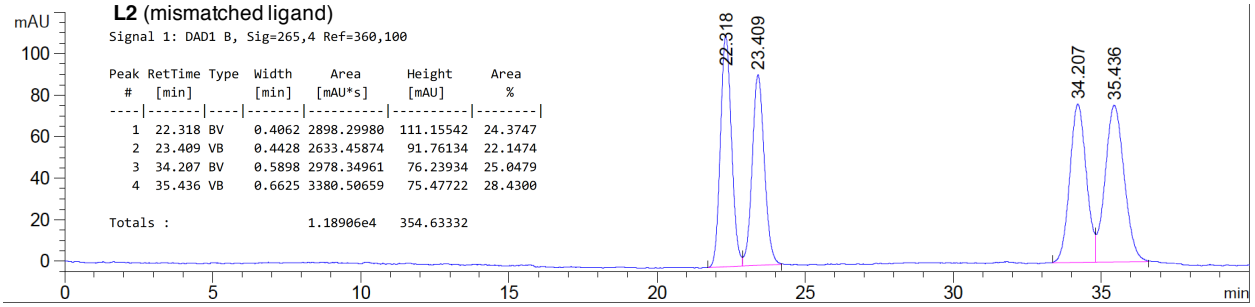
4b

Chiralpak IB connected to Chiralpak IC

55% MeCN/H_2O with 0.5% formic acid, 1.250 mL/min, 25 °C, 265 nm

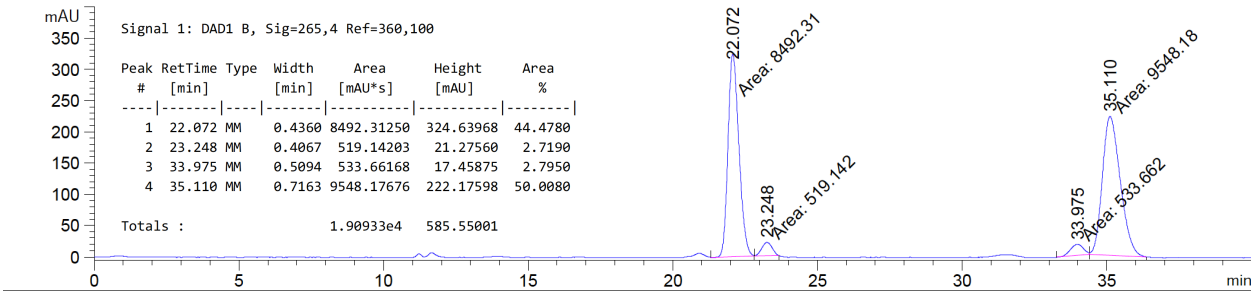


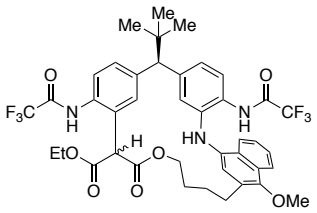




L3 (achiral ligand)

DAD1 B, Sig=265,4 Ref=360,100 (JH\JH-I-168 2020-10-07 13-23-48\015-0101.D)

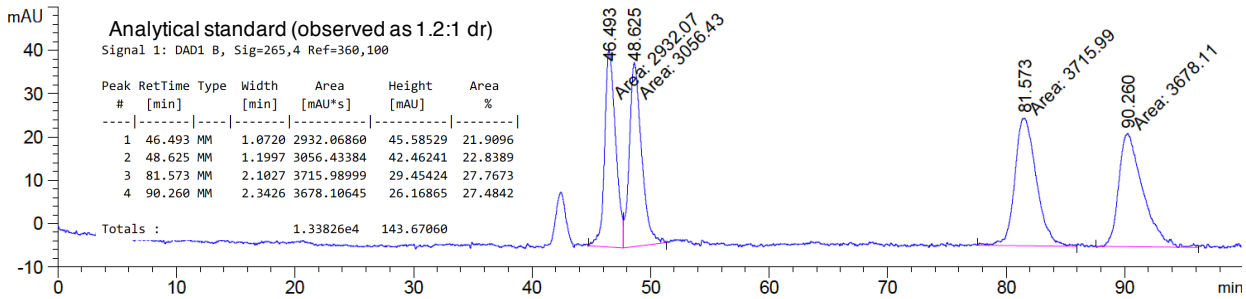


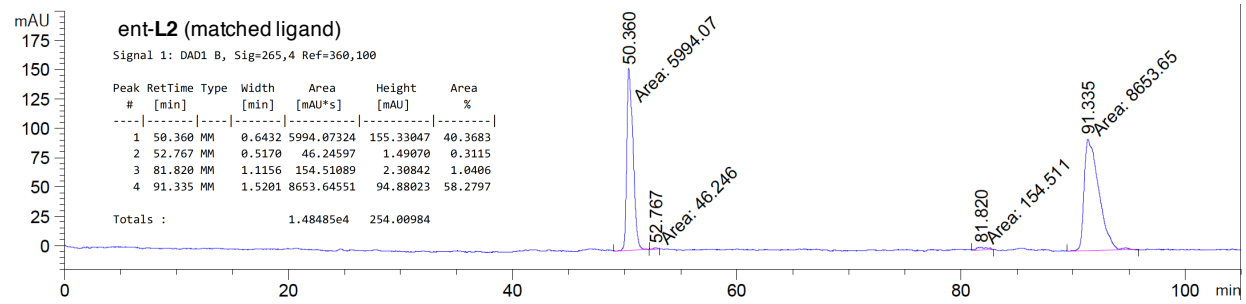


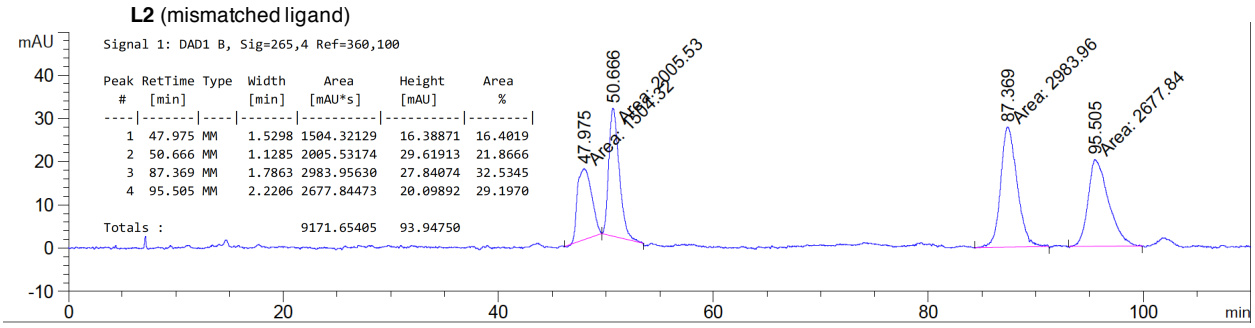
4c

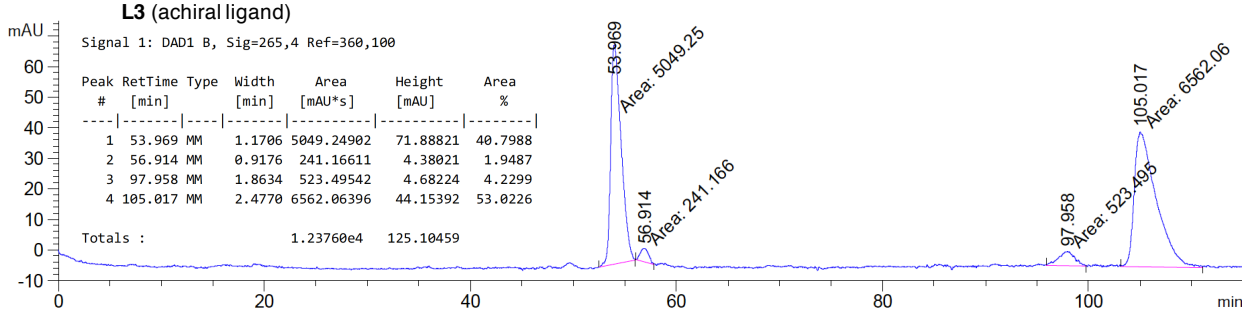
Chiralpak IB

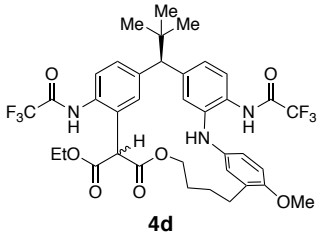
55% MeCN/H_2O with 0.5% formic acid, 1.250 mL/min, 25 °C, 265 nm







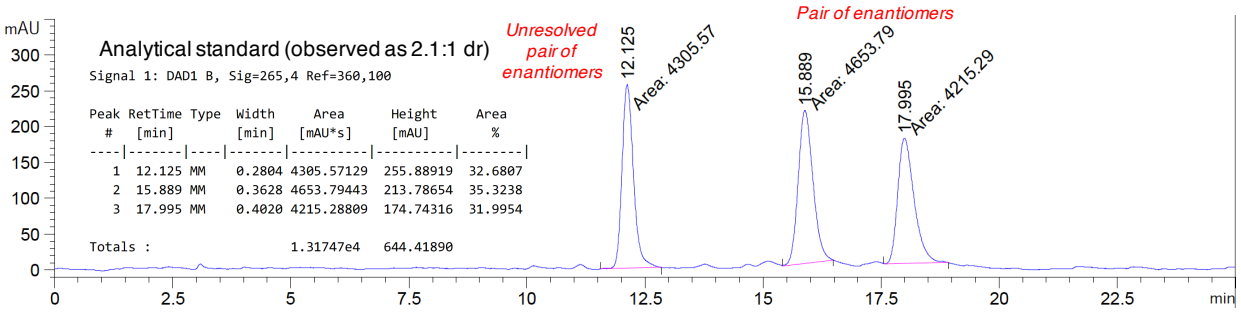


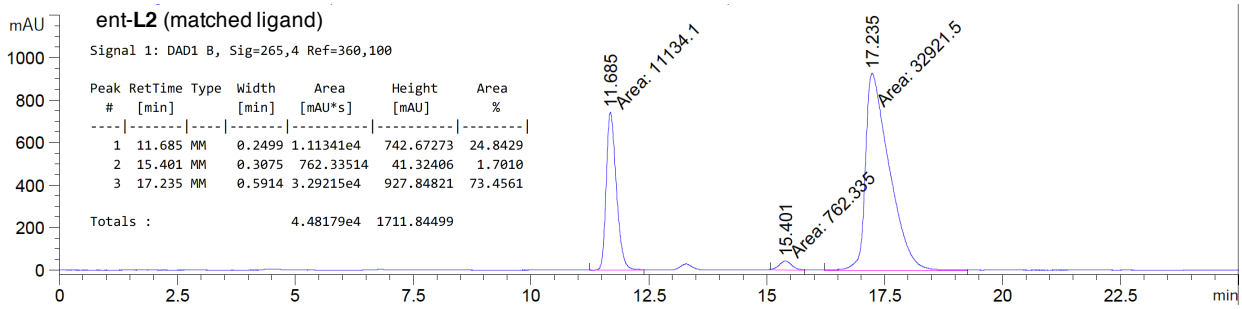


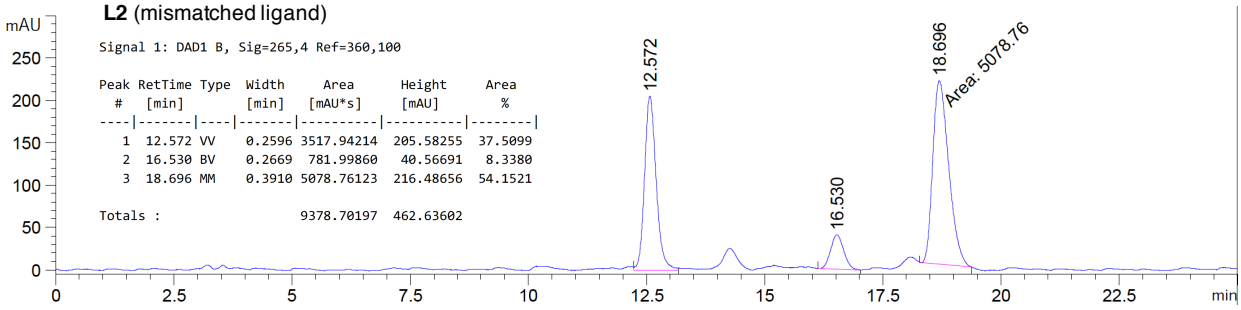
4d

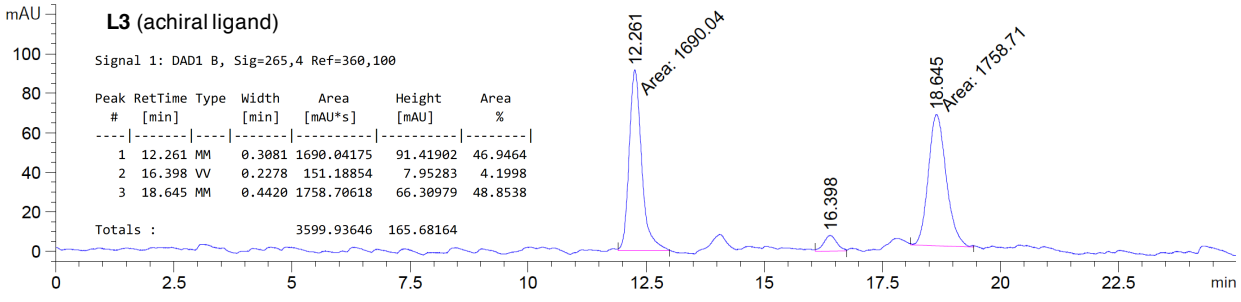
Chiralpak IB

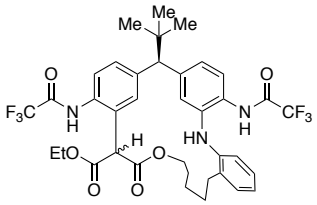
50% MeCN/H_2O with 0.5% formic acid, 1.000 mL/min, 25 °C, 265 nm.











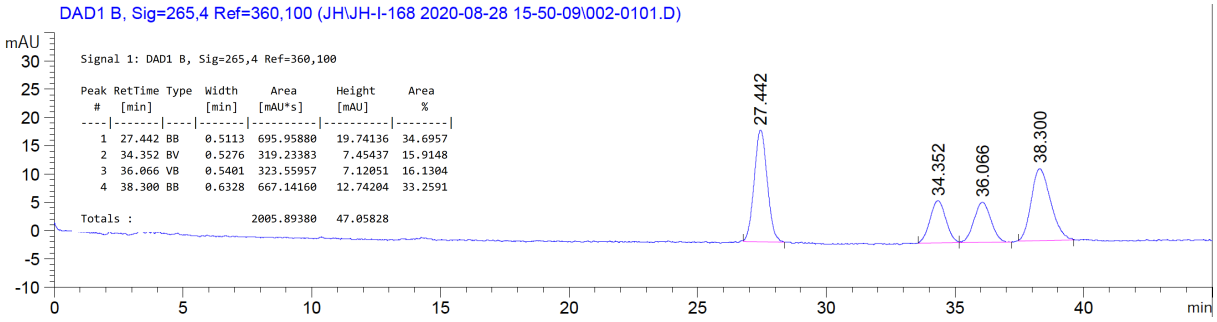
4e

Chiralpak IB

55% MeCN/H_2O with 0.5% formic acid, 1.000 mL/min, 25 °C, 265 nm

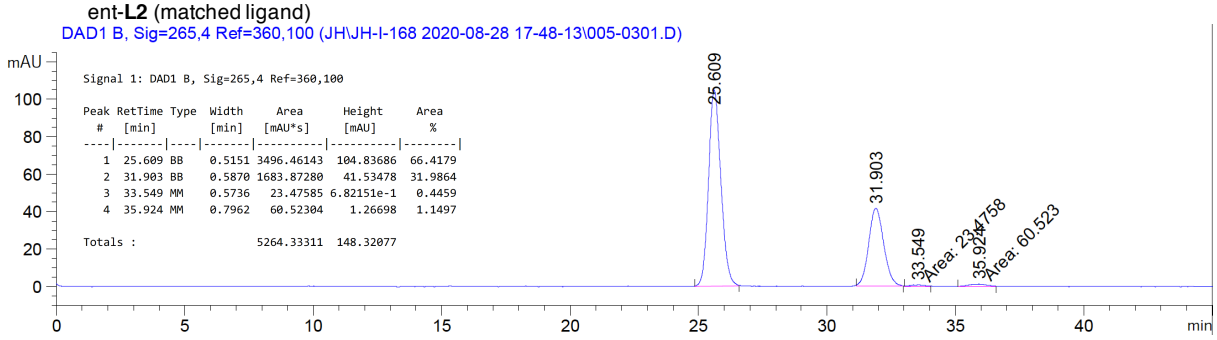
Analytical standard (observed as 2.1:1 dr)

DAD1 B, Sig=265,4 Ref=360,100 (JH\JH-I-168 2020-08-28 15-50-09\002-0101.D)



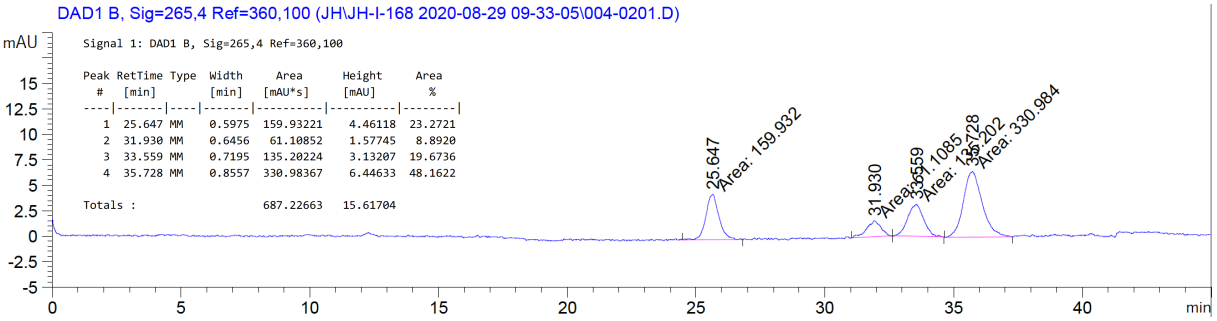
ent-**L2** (matched ligand)

DAD1 B, Sig=265,4 Ref=360,100 (JH\JH-I-168 2020-08-28 17-48-13\005-0301.D)



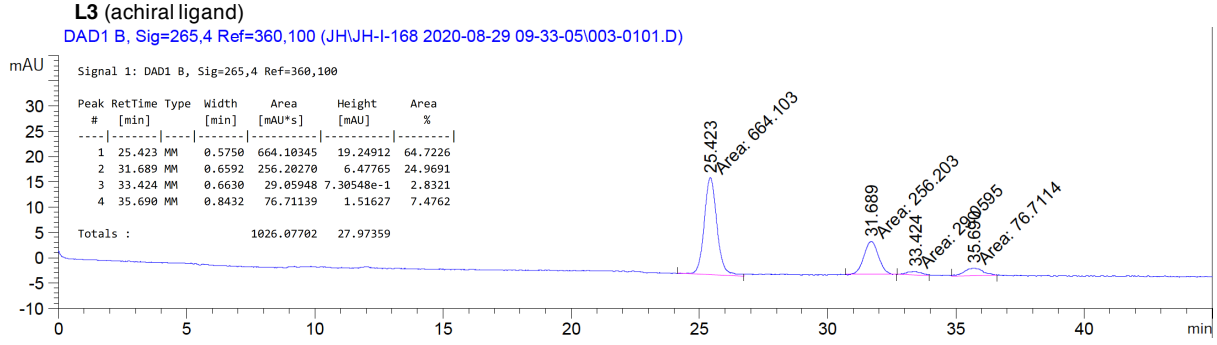
L2 (mismatched ligand)

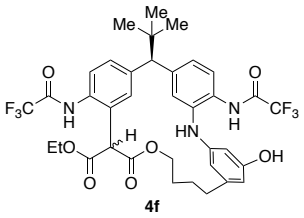
DAD1 B, Sig=265,4 Ref=360,100 (JH\JH-I-168 2020-08-29 09-33-05\004-0201.D)



L3 (achiral ligand)

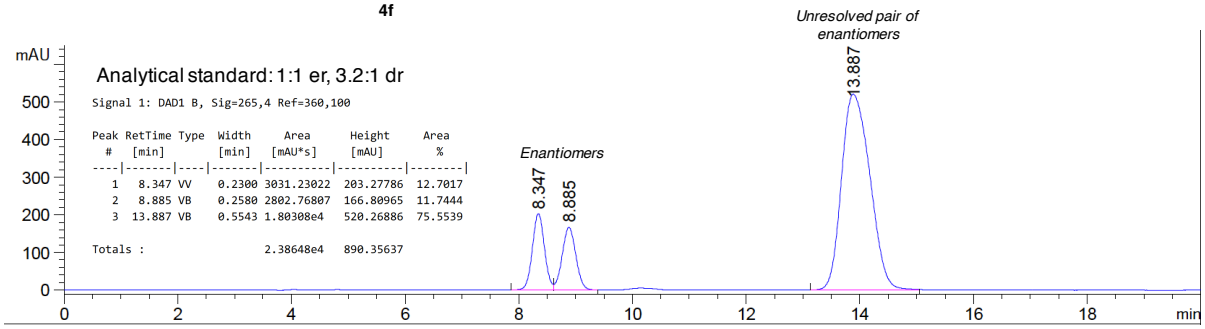
DAD1 B, Sig=265,4 Ref=360,100 (JH\JH-I-168 2020-08-29 09-33-05\003-0101.D)

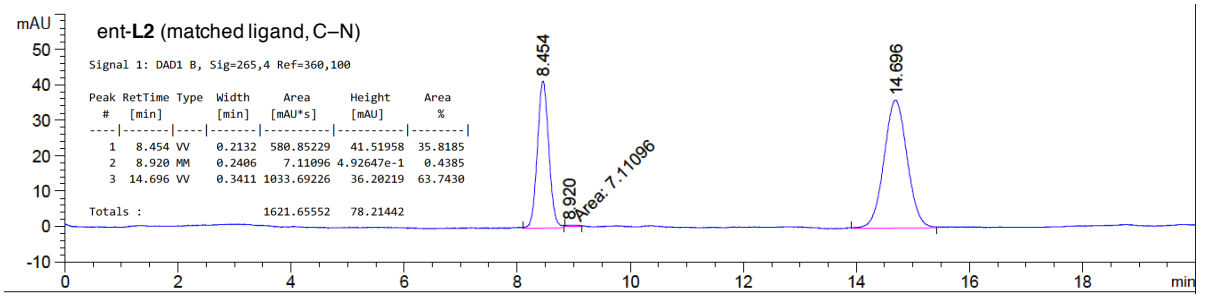


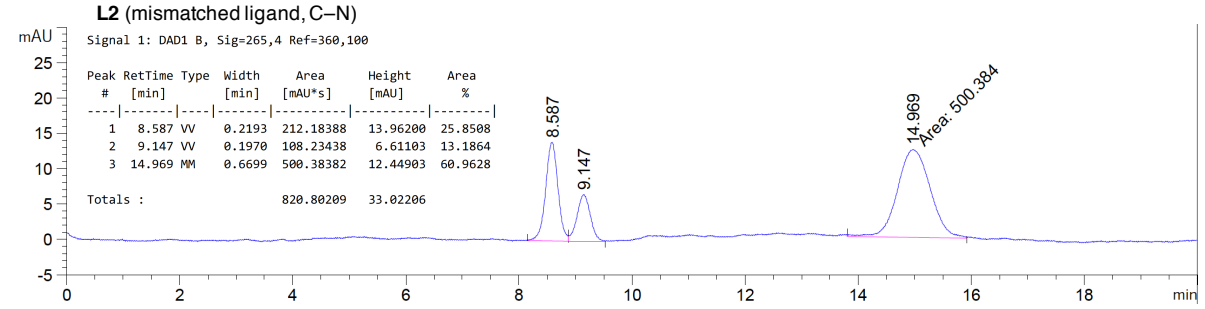


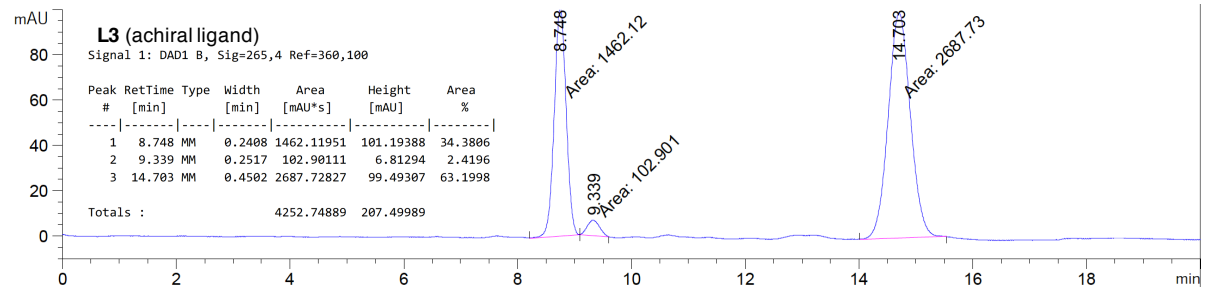
4f

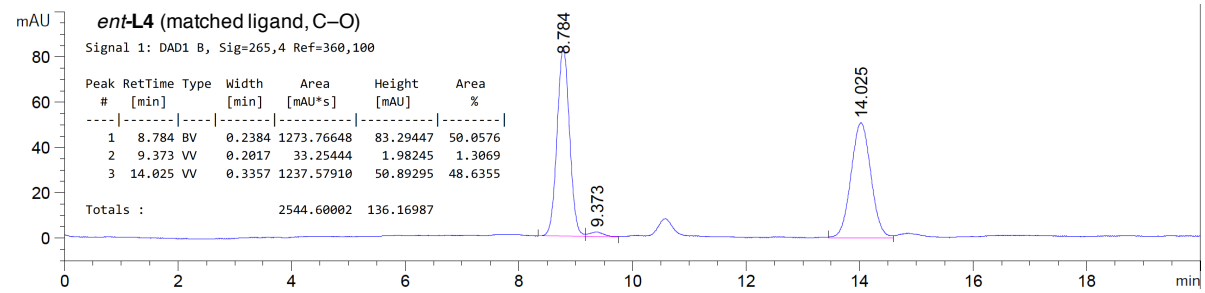
Chiralpak IB
55% MeCN/H2O with 0.5% formic acid
1.200 mL/min, 25 °C, 265 nm



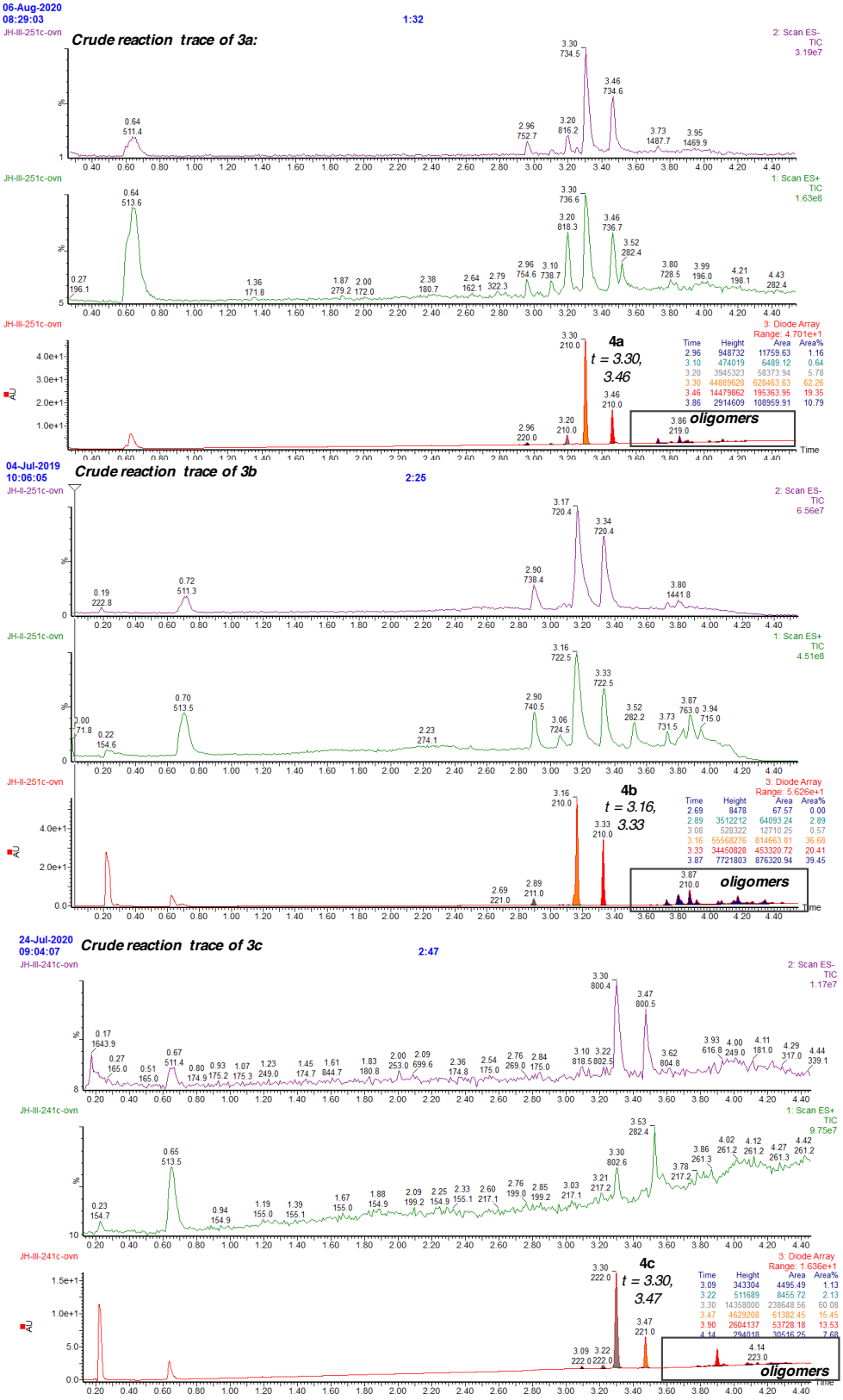




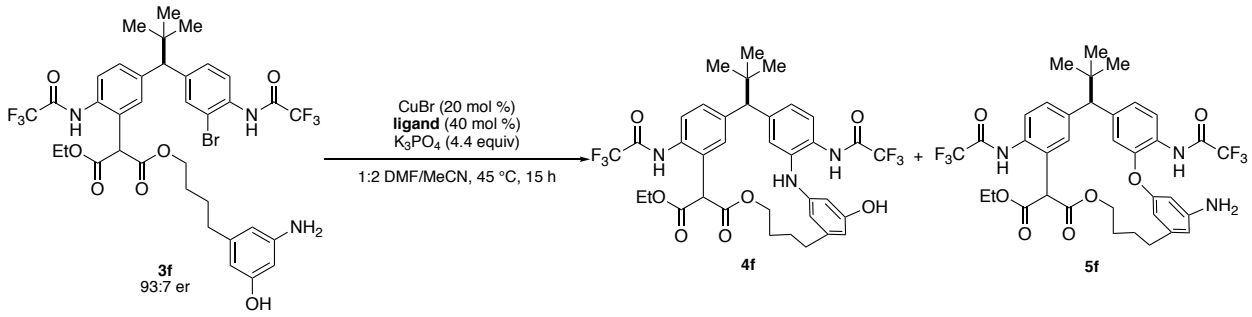




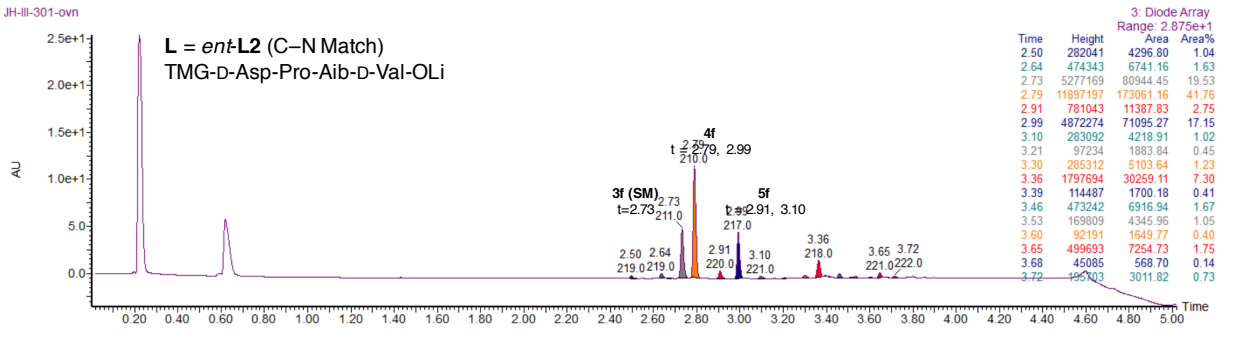
13. Product Distribution: Macrocyclization of 3a, 3b and 3c (UPLC-MS Traces)

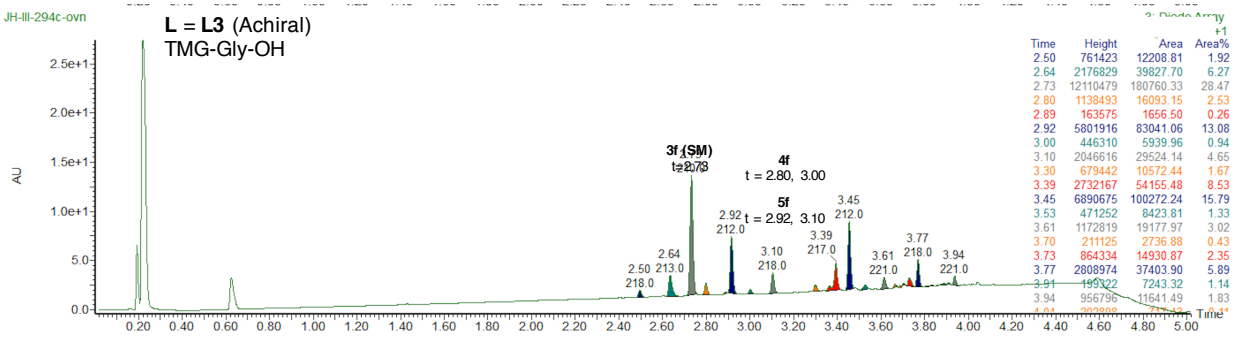


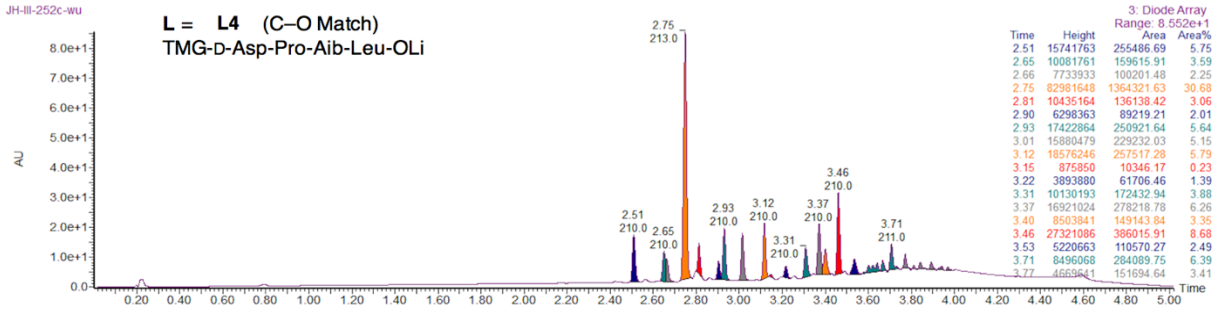
14. Product Distribution: Macrocyclization of Aminophenol 3f (UPLC-MS Traces)

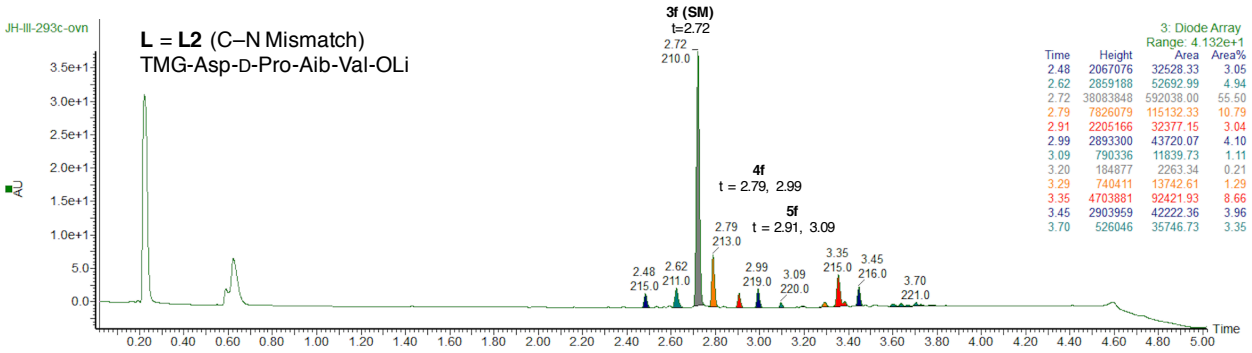


Reaction executed following **Procedure 8**.








JH-III-293c-ovn
L = L2 (C–N Mismatch)
TMG-Asp-D-Pro-Aib-Val-OLi
3f (SM)
t=2.72
2.72
210.0
4f
t = 2.79, 2.99
5f
t = 2.91, 3.09
2.79
213.0
2.48
215.0
2.62
211.0
2.99
219.0
3.09
220.0
3.35
215.0
3.45
216.0
3.70
221.0
AU
Time
3: Diode Array
Range: 4.132e+1
Time Height Area Area%
2.48 2067076 32528.33 3.05
2.62 2859188 52692.99 4.94
2.72 38083848 592038.00 55.50
2.79 7826079 115132.33 10.79
2.91 2205166 32377.15 3.04
2.99 2893300 43720.07 4.10
3.09 790336 11839.73 1.11
3.20 184877 2263.34 0.21
3.29 740411 13742.61 1.29
3.35 4703881 92421.93 8.66
3.45 2903959 42222.36 3.96
3.70 526046 35746.73 3.35

15. NMR Studies

15.1 VT-NMR Experiments[a,b,c]

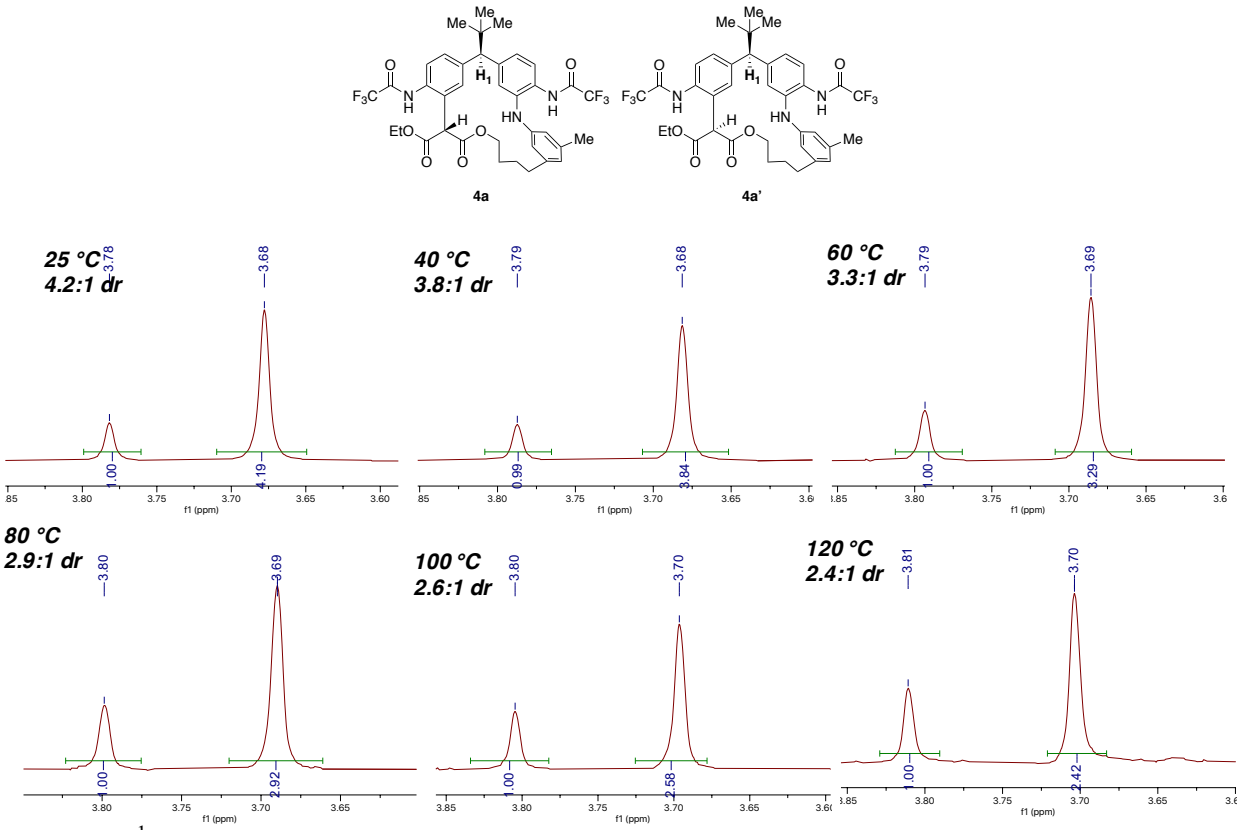


Figure S2. ^{1}H NMR spectra of **4a** and **4a'**(H_1) in DMSO-d_6 from 25–120 °C. a) VT-NMR experiments were performed on a Agilent 500 MHz spectrometer in DMSO-d_6. b) No convergence is observed between two sets of peaks corresponding to H_1. Change in ratio between two diastereomers is observed.

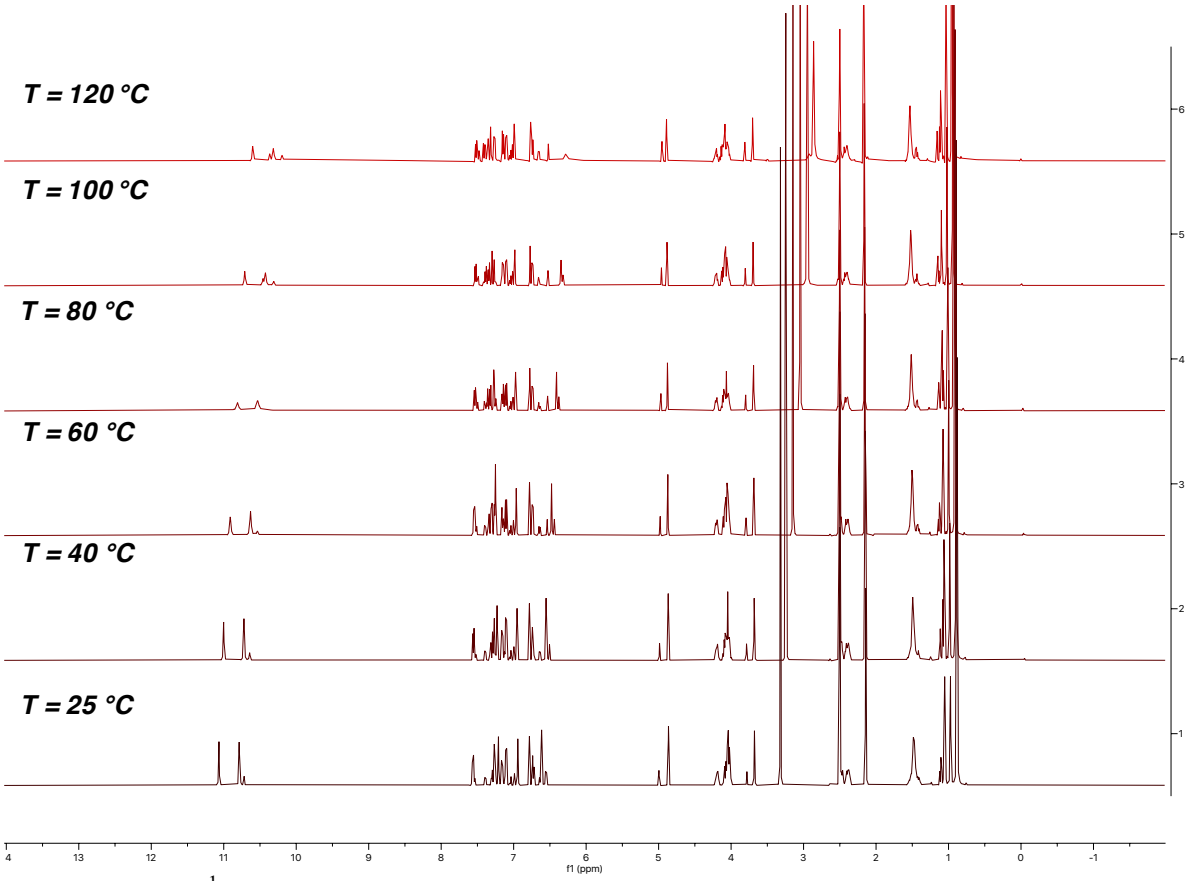


Figure S3. Full ^{1}H NMR spectra of **4a** and **4a'** in DMSO-d_6 from 25–120 °C. a) VT-NMR experiments were performed on Agilent 500 MHz spectrometer in DMSO-d_6. c) No significant decomposition is observed.

15.2 Deuterium Incorporation in Methanol-d_4:

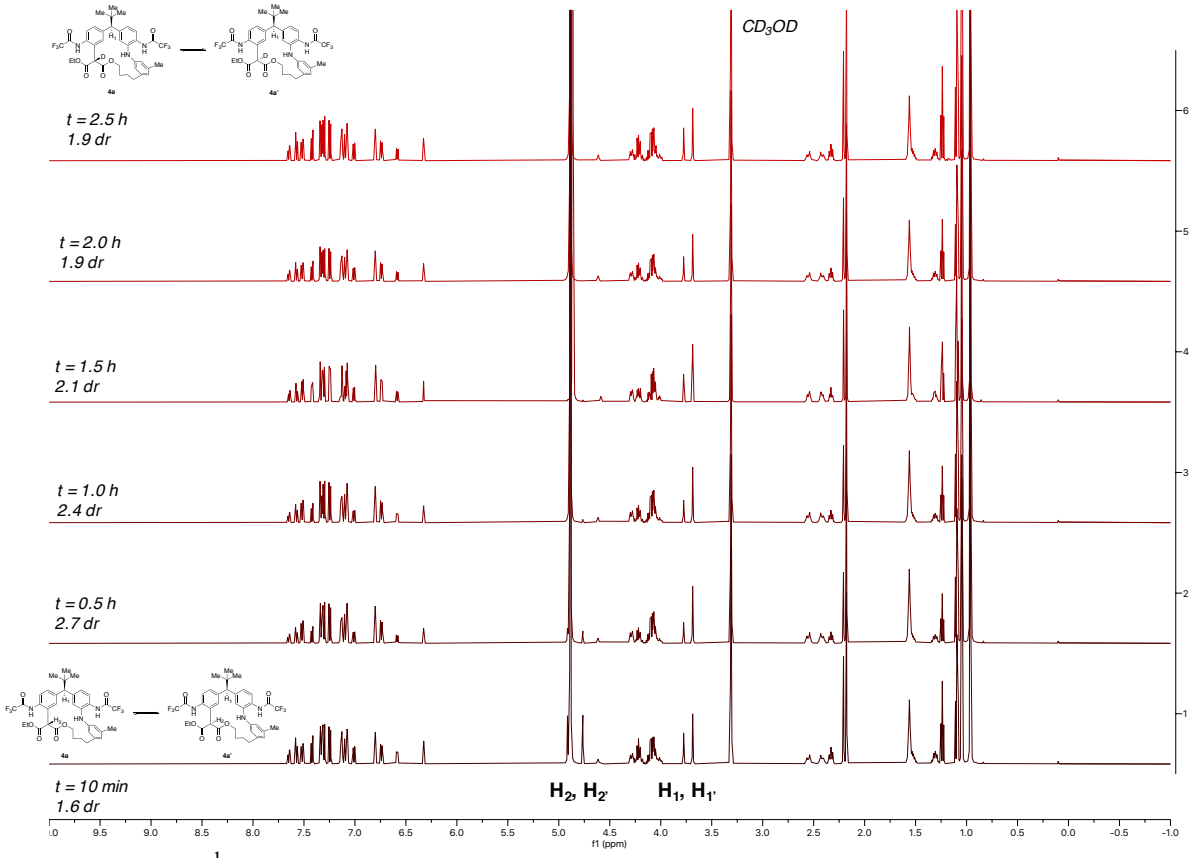
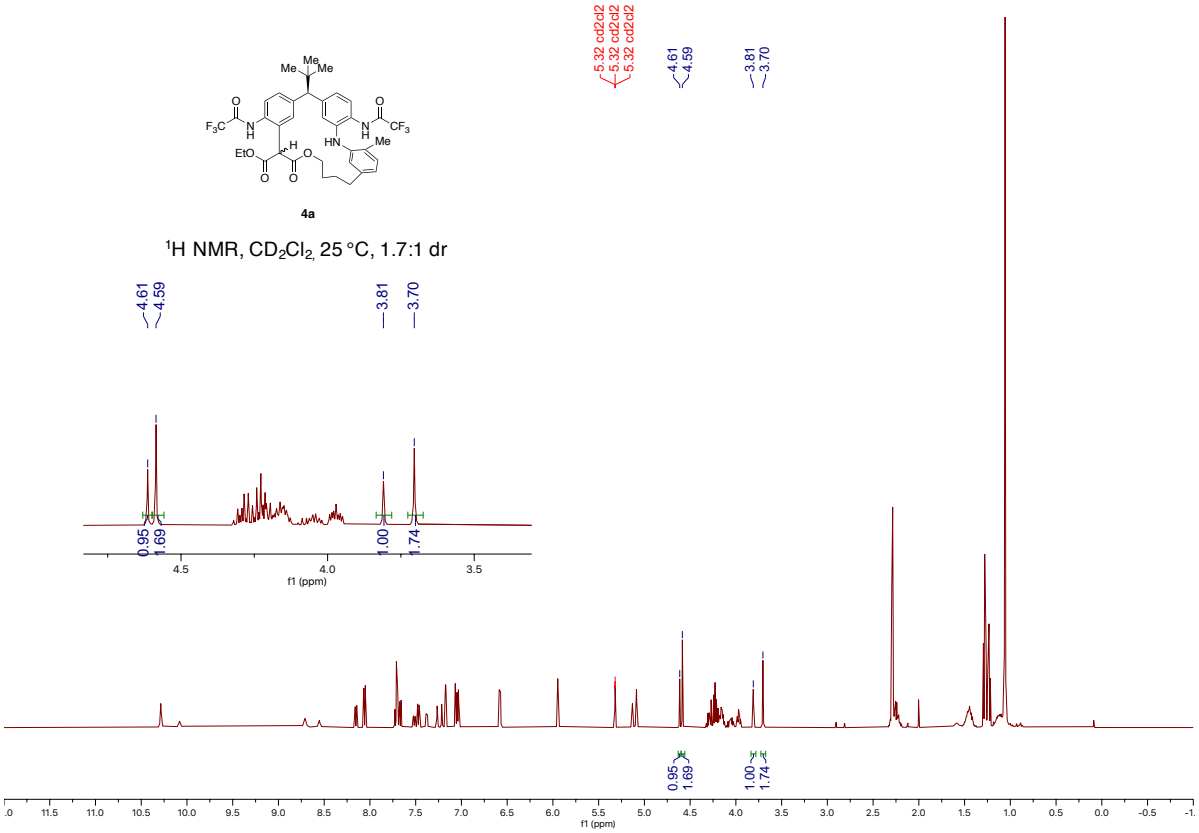
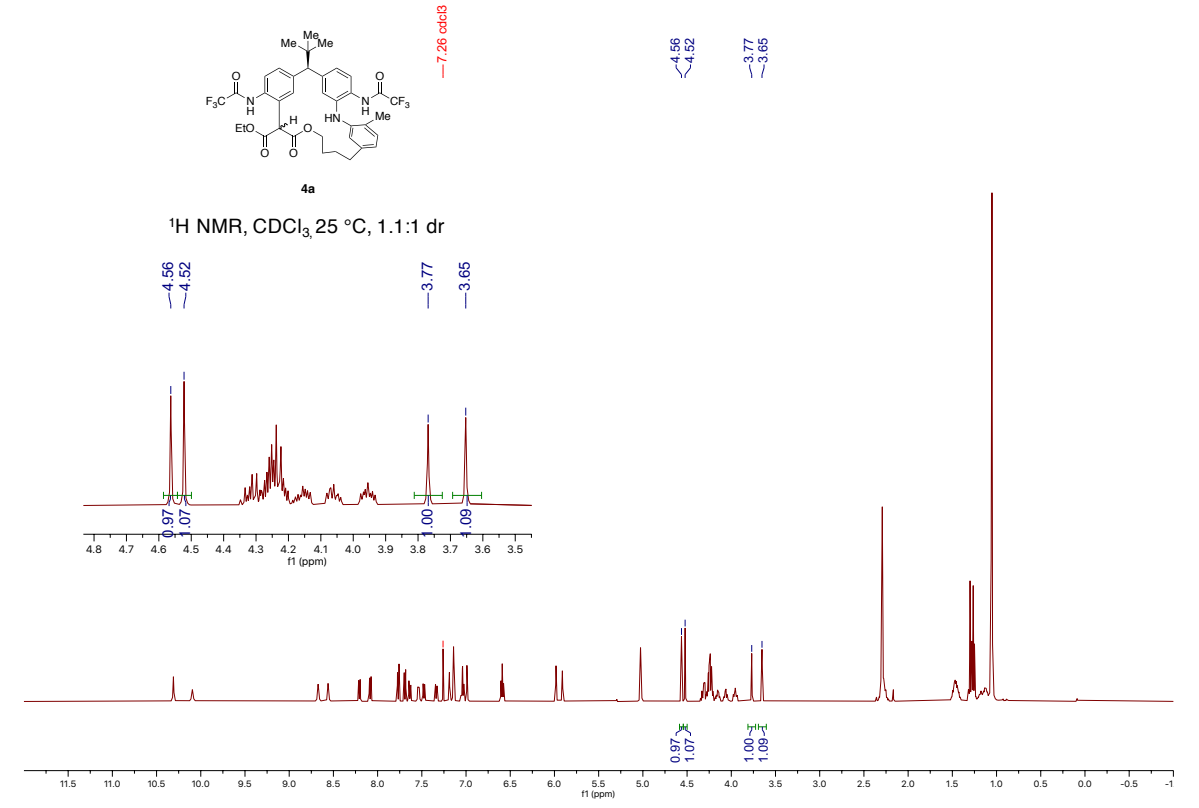
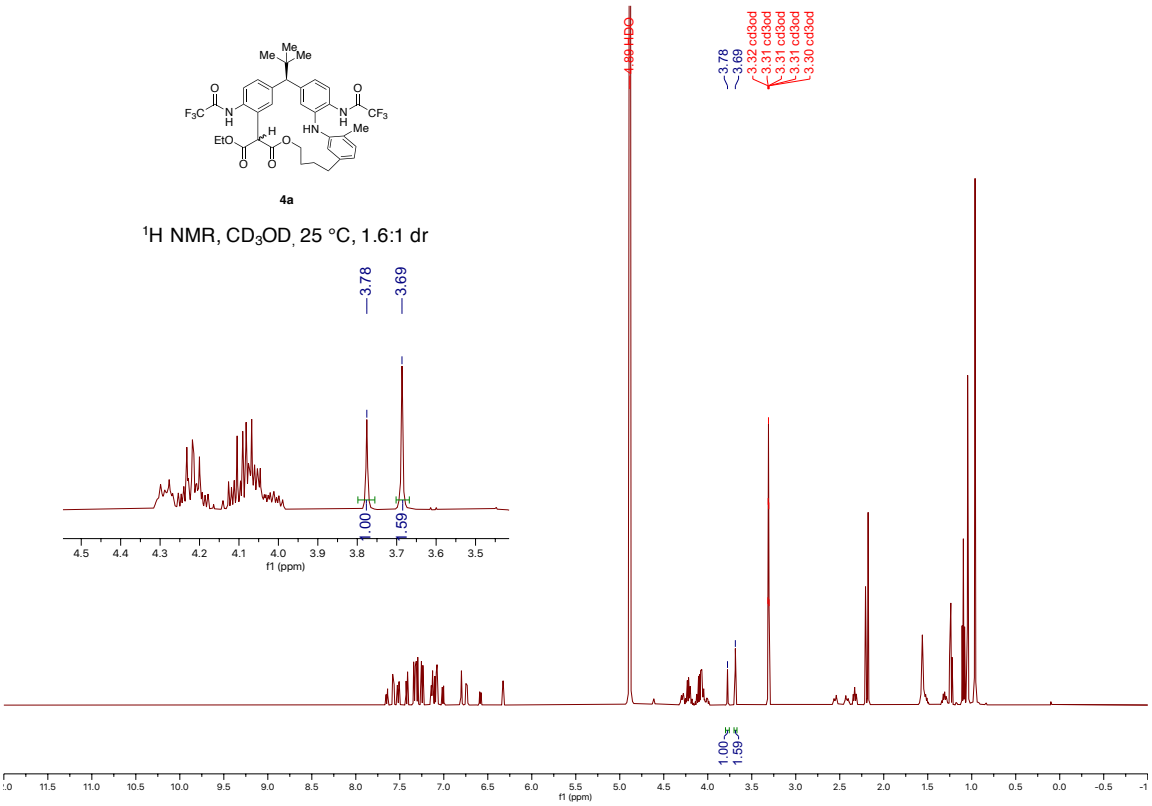


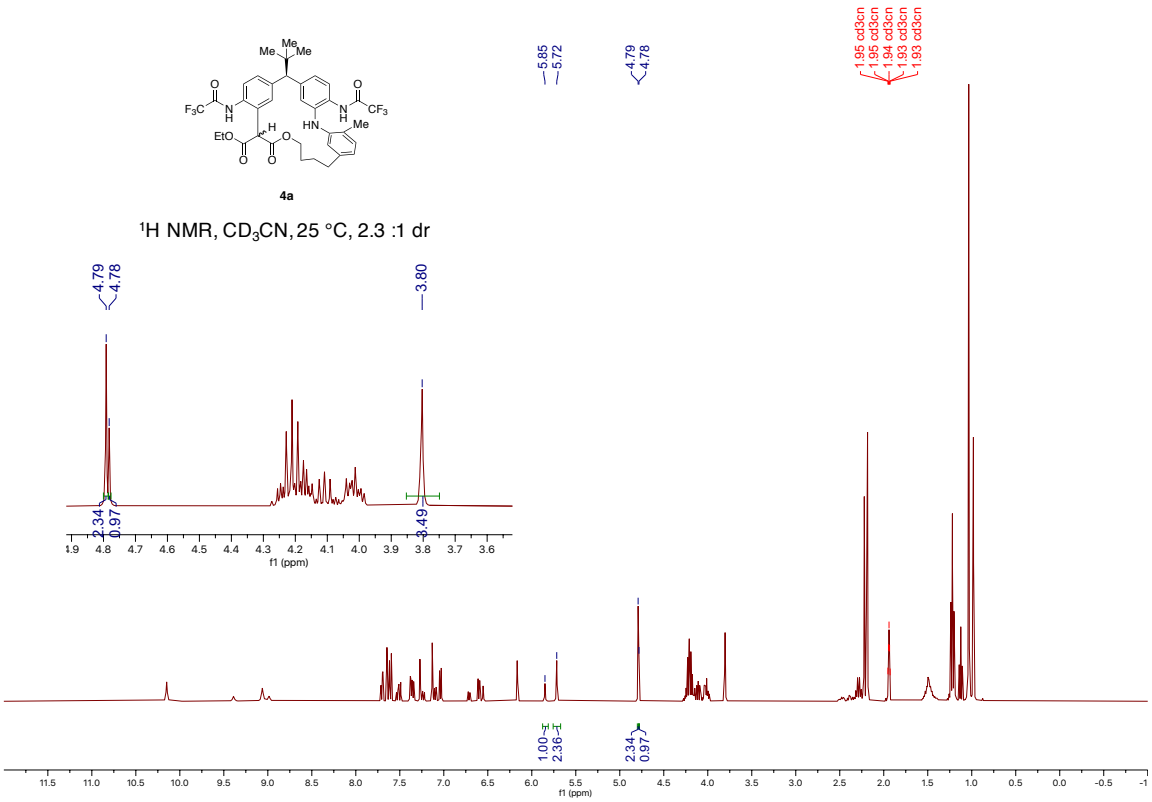
Figure S4. Full ^{1}H NMR spectrum of **4a** and **4a'** in methanol-d_4.

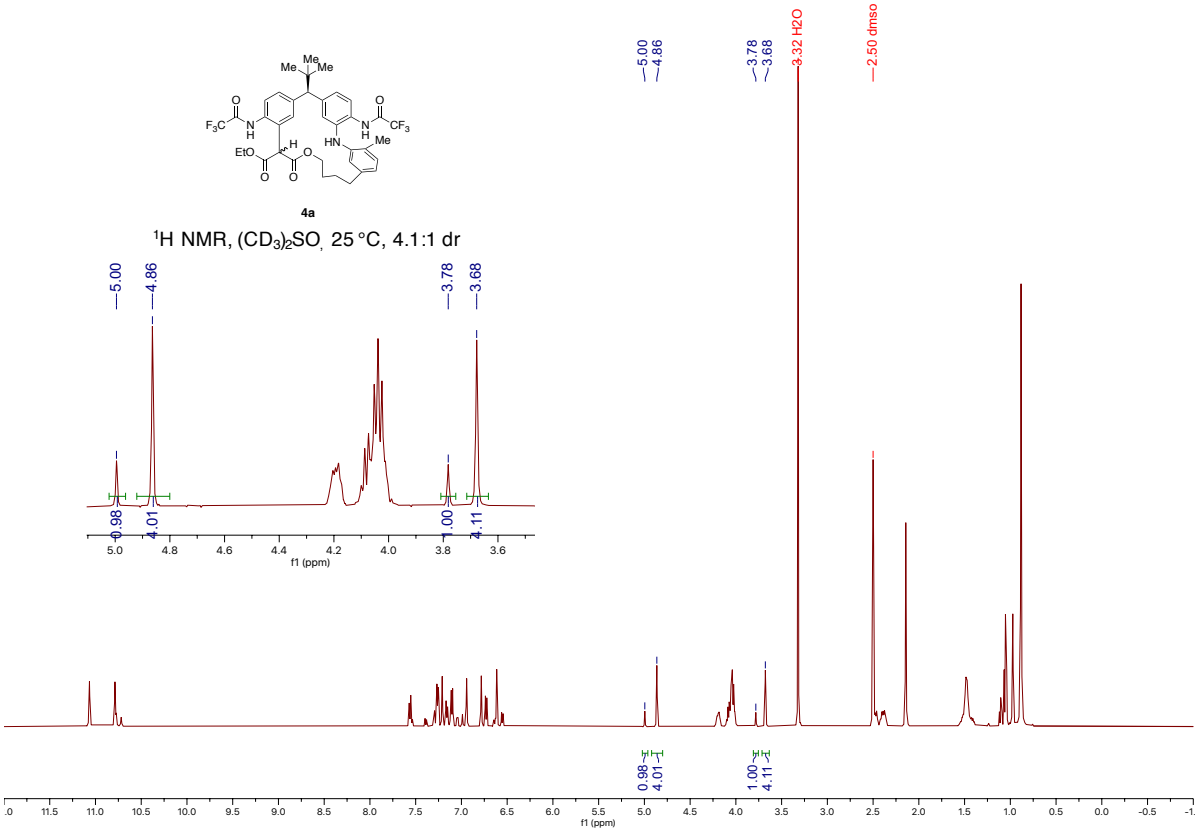
15.3 ^{1}H NMR Spectra of 4a in Different NMR Solvents






4a
^{1}H NMR, CD_3OD, 25 °C, 1.6:1 dr
3.78
3.69
4.88 HDO
3.32 cd3od
3.31 cd3od
3.31 cd3od
3.31 cd3od
3.30 cd3od
1.00
1.59
f1 (ppm)


4a
^{1}H NMR, CD_3CN, 25 °C, 2.3 :1 dr
4.79
4.78
3.80
5.85
5.72
4.79
4.78
1.95 cd3cn
1.95 cd3cn
1.94 cd3cn
1.93 cd3cn
1.93 cd3cn
2.34
0.97
3.49
1.00
2.36
2.34
0.97
f1 (ppm)


4a
^{1}H NMR, $(CD_3)_2SO$, 25 °C, 4.1:1 dr
5.00
4.86
3.78
3.68
3.32 H2O
2.50 dmso
0.98
4.01
1.00
4.11
f1 (ppm)

16. Crystallographic Data

Experimental

Low-temperature diffraction data (ω-scans) were collected on a Rigaku MicroMax-007HF diffractometer coupled to a Saturn994+ CCD detector with Cu Kα (λ = 1.54178 Å) for the structure of 4a. The diffraction images were processed and scaled using Rigaku Oxford Diffraction software (CrysAlisPro; Rigaku OD: The Woodlands, TX, 2015). The structure was solved with SHELXT and was refined against F^2 on all data by full-matrix least squares with SHELXL (Sheldrick, G. M. Acta Cryst. 2008, A64, 112–122). All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the U value of the atoms to which they are linked (1.5 times for methyl groups). There are several sites for disorder in this structure. The CF_3 groups are disordered over two positions. All chemically equivalent 1,2 and 1,3 distances in the disordered models were restrained to be similar. Their atomic displacement parameters were also restrained to be similar. Two of the esters were also disordered over two positions. The disordered C-O and C-C distances were restrained to be similar. The full numbering scheme of compound 4a can be found in the full details of the X-ray structure determination (CIF), which is included as Supporting Information. CCDC number 2081828 (**4a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

A Bayesian statistical analysis of the Bijvoet pairs suggest the model reported here is the true model, with an exceedingly small probability of a model with the opposite chirality or a racemic twin. This analysis was calculated with the PLATON software package (A.L.Spek, Acta Cryst. 2009, D65, 148-155.).

Model as presented in the CIF

Space Group	$P2_1$
Wavelength	1.54184
Flack x	-0.05(8)
Parsons z ..	-0.03(7)

Bayesian Statistics

Student_T υ	12
Select Pairs	6773
θ_Min	3.11°
θ _Max	66.59 °
P2(true)	1.000
P3(true)	1.000
P3(rac-twin)	0.7E-13
P3(false)	0.2E-49
G	1.0501

G (su)	0.1347
Hooft y	-0.03(7)
Inverted model	
Space Group	P21
Wavelength	1.54184
Flack x	1.05(8)
Parsons z ..	1.03(7)
Bayesian Statistics	
Student_T υ	12
Select Pairs	6773
θ_Min	3.11
θ _Max	66.59
P2(true)	0.3E-49
P3(true)	0.3E-49
P3(rac-twin)	0.8E-13
P3(false)	1.000
G	-1.0481
G (su)	0.1347
Hooft y	1.02(7)

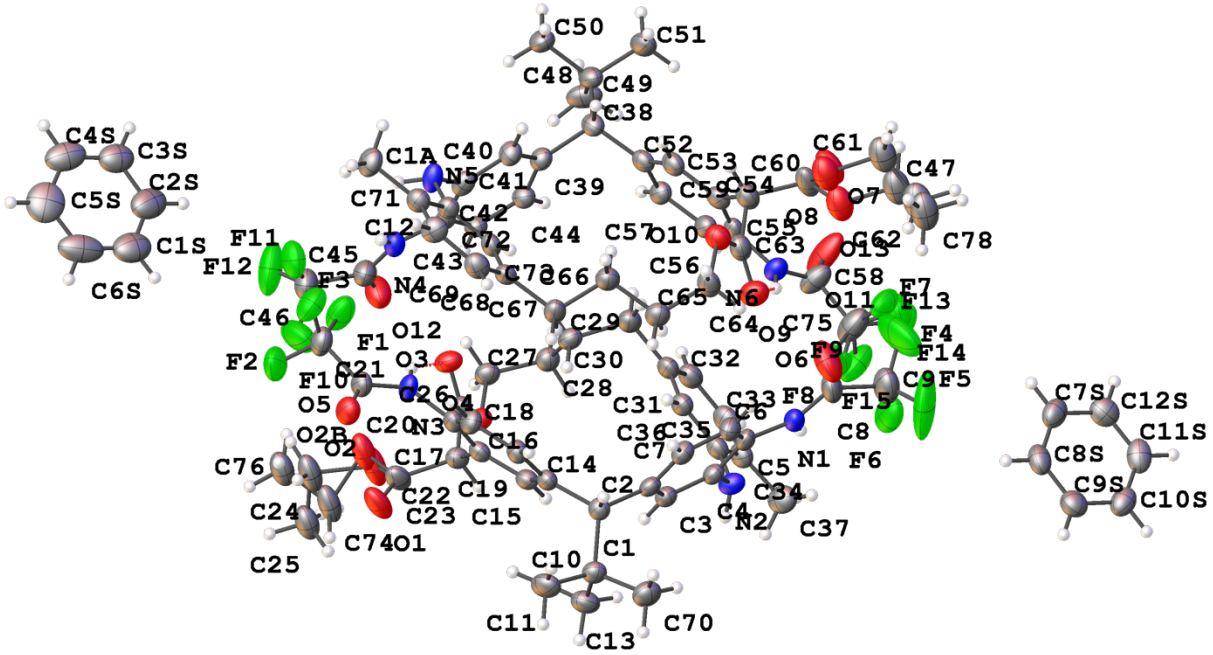


Figure 1. The complete numbering scheme of 4a with 50% thermal ellipsoid probability levels. The hydrogen atoms are shown as circles for clarity.

Table 1. Crystal data and structure refinement for 4a.

Identification code	007b-21047
Empirical formula	C43 H45 F6 N3 O6
Formula weight	813.82
Temperature	93(2) K
Wavelength	1.54184 Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 9.83610(10) Å α = 90°.
	b = 22.6576(3) Å β = 102.3820(10)°.
	c = 18.7122(2) Å γ = 90°.
Volume	4073.24(8) $Å^3$
Z	4
Density (calculated)	1.327 Mg/m^3
Absorption coefficient	0.906 mm^{-1}
F(000)	1704
Crystal size	0.200 x 0.200 x 0.020 mm^3
Crystal color and habit	colorless plate
Diffractometer	Rigaku Saturn 944+ CCD
Theta range for data collection	2.417 to 66.593°.
Index ranges	-11<=h<=11, -26<=k<=26, -22<=l<=22
Reflections collected	123574
Independent reflections	14178 [R(int) = 0.0925]
Observed reflections (I > 2sigma(I))	11671
Completeness to theta = 66.593°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.90494
Solution method	SHELXT-2014/5 (Sheldrick, 2014)
Refinement method	SHELXL-2014/7 (Sheldrick, 2014)
Data / restraints / parameters	14178 / 199 / 1129
Goodness-of-fit on F^2	1.015
Final R indices [I>2sigma(I)]	R1 = 0.0559, wR2 = 0.1356
R indices (all data)	R1 = 0.0723, wR2 = 0.1474
Absolute structure parameter	-0.05(8)
Largest diff. peak and hole	0.554 and -0.463 e.$Å^{-3}$

References

1. G. R. Fulmer *et al.*, NMR Chemical Shifts of Trace Impurities: Common Laboratory Solvents, Organics, and Gases in Deuterated Solvents Relevant to the Organometallic Chemist. *Organometallics* **29**, 2176–2179 (2010).

2. a) B. Kim, A. J. Chinn, D. R. Fandrick, C. H. Senanayake, R. A. Singer, S. J. Miller, Distal Stereocontrol Using Guanidinylated Peptides as Multifunctional Ligands: Desymmetrization of Diarylmethanes via Ullman Cross-Coupling. *J. Am. Chem. Soc.* **138**, 7939–7945 (2016). b) A. J. Chinn, B. Kim, Y. Kwon, S. J. Miller, Enantioselective Intermolecular C–O Bond Formation in the Desymmetrization of Diarylmethines Employing a Guanidinylated Peptide-Based Catalyst. *J. Am. Chem. Soc.* **139**, 18107–18114 (2017). c) Y. Kwon, A. J. Chinn, B. Kim,S. J. Miller, Divergent Control of Point and Axial Stereogenicity: Catalytic Enantioselective C–N Bond-Forming Cross-Coupling and Catalyst-Controlled Atroposelective Cyclodehydration. *Angew. Chem. Int. Ed.* **57**, 6251–6255 (2018).

3. E. Moreau *et al.*, Optimized *N*-Phenyl-*N'*-(2-chloroethyl)ureas as Potential Antineoplastic Agents: Synthesis and Growth Inhibition Activity. *Bioorg. Med. Chem.* **13**, 6703–6712 (2005).

4. F. A. Abulwerdi *et al.*, 3-Substituted-*N*-(4-Hydroxynaphthalen-1-yl)arylsulfonamides as a Novel Class of Selective Mcl-1 Inhibitors: Structure-Based Design, Synthesis, SAR, and Biological Evaluation. *J. Med. Chem.* **57**, 4111–4133 (2014).

5. C. Holt, G. Alachouzos, A. J. Frontier, Leveraging the Halo-Nazarov Cyclization for the Chemodivergent Assembly of Functionalized Haloindenes and Indanones. *J. Am. Chem. Soc.* **141**, 5461–5469 (2019).

6. B. R. Ambler, S. Peddi, R. A. Altman, Ligand-Controlled Regioselective Copper-Catalyzed Trifluoromethylation To Generate (Trifluoromethyl)allenes. *Org. Lett.* **17**, 2506–2509 (2015).

7. P. Patel, C. V. Ramana, Divergent Pd(II) and Au(III) mediated nitroalkynol cycloisomerizations. *Org. Biomol. Chem.* **9**, 7327–7334 (2011).