Supporting Information

Cobalt-catalysed (4+3)-annulation of oxiranes with 4-vinyl indoles: stereospecific access to fused oxepinoindoles

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General Information. 1*H*-Indole-4-carbaldehyde, styrene, 1,2-epoxybutane, AD-mix-*α*, $Sc(OTf)_3$ (99%), $Ni(OTf)_2$ (96%), $Zn(OTf)_2$ (98%), $Cu(OTf)_2$ (98%), $FeCl_3$ (97%), $CoCl_2$ (97%), $CoCl_2•6H_2O$ (98%), $Co(OAc)_2•4H_2O$ (>98%), $Pd(PPh_3)_4$ (99%) and oxone were purchased from Aldrich and used as received. (*R*)-Styrene oxide (>96%) was purchased from TCI and used as such. *m*-CPBA was purchased from SRL and used as such. KO^{t}Bu (98%) and DABCO (>98%) were purchased from Spectrochem and used as received. K_2CO_3, Na_2CO_3, Cs_2CO_3, NaOAc and DBU were purchased from Merck and used as received. The solvents were dried prior to use according to the standard procedure. SRL silica gel G/GF 254 plates were used for analytical TLC and SRL silica gel (100-200 mesh) was used for column chromatography. NMR (^{1}H, ^{13}C and ^{19}F) spectra were recorded with Bruker Avance III 600, 500 and 400 MHz spectrometers using $CDCl_3$ as solvent and Me_4Si as an internal standard. Chemical shifts (δ) and spin-spin coupling constant (*J*) are reported in ppm and in Hz, respectively, and other data are reported as follows: s = singlet, d = doublet, t = triplet, m = multiplet, q = quartet, dd = doublet of doublets. Melting points were determined using a Büchi B-540 apparatus and are uncorrected. FT-IR spectra were collected on Perkin Elmer IR spectrometer. Q-ToF ESI-MS instrument was used for recording mass spectra. Single crystal X-ray data of (±)**-7** was collected on a Bruker SMART APEX equipped with a CCD area detector using Mo/Kα radiation and the structure was solved by direct method using *SHELXL-2018/3* (Göttingen, Germany).

Sample Preparation for Crystal Growth. The compound (±)**-7** was dissolved in minimum volume of acetonitrile and kept at room temperature for slow evaporation (3 days). Needle shaped crystal was formed that was subjected to X-ray diffraction analysis.

Crystal Structure and Data of (±)**-7**

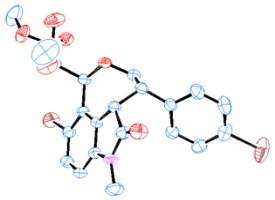
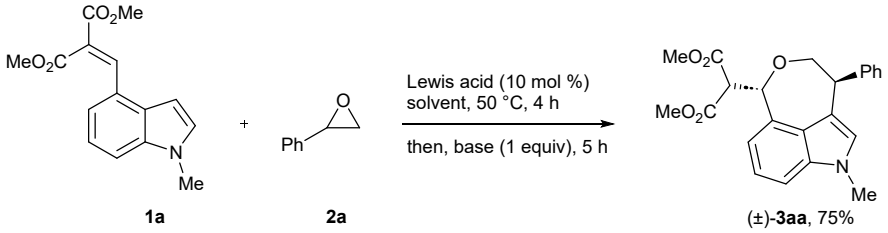


Figure S1. ORTEP diagram of Dimethyl 2-(9-bromo-4-(4-bromophenyl)-6-methyl-5-oxo-1,3,4,4a,5,6-hexahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)**-7** with 50% ellipsoid (CCDC 2481146). H-Omitted for clarity.

Identification code	(±)-**7**
Empirical formula	'C23H21Br2NO6'
Formula weight	567.23
Crystal habit, colour	needle/Colorless
Temperature, *T*/K	296 K
Wavelength, λ/Å	0.71073
Crystal system	'monoclinic'
Space group	'P 21/c'
Unit cell dimensions	a = 10.123(5) Å b = 26.415(11) Å c = 8.733(4) Å α = 90 β = 103.709(1) γ = 90
Volume, *V*/Å^3	2268.8(18)
Z	4
Calculated density, Mg·m^{-3}	1.661
Absorption coefficient, μ/mm^{-1}	3.613
F(000)	1136
θ range for data collection	2.21 to 25.37°
Limiting indices	-12 ≤ h ≤ 12, –32 ≤ k ≤ 32, –10 ≤ l ≤ 10
Reflection collected / unique	4297/3524
Completeness to θ	99.7%
Absorption correction	None
Max. and min. transmission	0.865 and 0.714
Refinement method	'SHELXL-2018/3 (Sheldrick, 2015)'
Data / restraints / parameters	4297/0/292
Goodness–of–fit on F^2	1.093
Final *R* indices [*I*>2sigma(*I*)]	R1 = 0.0373, wR2 = 0.1105
R indices (all data)	R1 = 0.0496, wR2 = 0.1242

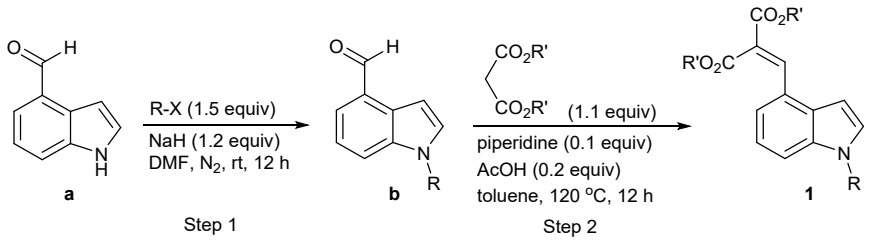
Table S1. Optimization of the reaction conditions[a,b,c]



Entry	Lewis acid	Base	Solvent	Yield (%)[b]
1	$Sc(OTf)_3$	KO^{t}Bu	CH_2Cl_2	n.d.
2	$Ni(OTf)_2$	KO^{t}Bu	CH_2Cl_2	trace
3	$Zn(OTf)_2$	KO^{t}Bu	CH_2Cl_2	16
4	$Cu(OTf)_2$	KO^{t}Bu	CH_2Cl_2	trace
5	$FeCl_3$	KO^{t}Bu	CH_2Cl_2	trace
6	$CoCl_2$	KO^{t}Bu	CH_2Cl_2	23
7	$CoCl_2$•$6H_2O$	KO^{t}Bu	CH_2Cl_2	35
8	$Ni(ClO_4)_2$•$6H_2O$	KO^{t}Bu	CH_2Cl_2	15
9	$Co(OAc)_2$•$4H_2O$	KO^{t}Bu	CH_2Cl_2	57
[c]10	$Co(OAc)_2$•$4H_2O$	KO^{t}Bu	CH_2Cl_2	75
[c]11	$Co(OAc)_2$•$4H_2O$	K_2CO_3	CH_2Cl_2	61
[c]12	$Co(OAc)_2$•$4H_2O$	Na_2CO_3	CH_2Cl_2	55
[c]13	$Co(OAc)_2$•$4H_2O$	Cs_2CO_3	CH_2Cl_2	41
[c]14	$Co(OAc)_2$•$4H_2O$	NaOAc	CH_2Cl_2	trace
[c]15	$Co(OAc)_2$•$4H_2O$	DBU	CH_2Cl_2	n.d.
[c]16	$Co(OAc)_2$•$4H_2O$	DABCO	CH_2Cl_2	n.r.
[c]17	$Co(OAc)_2$•$4H_2O$	KO^{t}Bu	$(CH_2Cl)_2$	60
[c]18	$Co(OAc)_2$•$4H_2O$	KO^{t}Bu	toluene	n.d.
[c]19	$Co(OAc)_2$•$4H_2O$	KO^{t}Bu	THF	trace
[c]20	$Co(OAc)_2$•$4H_2O$	KO^{t}Bu	CH_3CN	45

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), Lewis acid (10 mol %), solvent (3 mL), 50 °C, 4 h, then, base (0.2 mmol), 5 h. [b]Isolated yield. [c]4 Å MS used. n.r.= no reaction. n.d.= not detected.

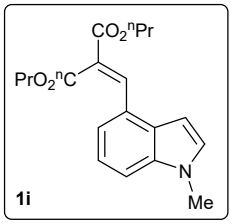
Scheme S1. General Procedure for the Synthesis of Alkylidene Indole Malonates 1a-k.[1]



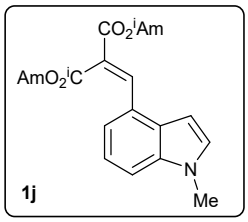
Step-1: 1*H*-Indole-4-carbaldehyde **a** (3 mmol, 1 equiv, 435 mg) was added to a suspension of NaH (3.6 mmol, 60% dispersion in mineral oil, 1.2 equiv, 144 mg) in DMF (10 mL) at 0 °C under nitrogen atmosphere. The reaction mixture was allowed to stir at the same temperature for 30 minutes and then alkyl halide (4.5 mmol, 1.5 equiv) was added dropwise. The resultant mixture was then stirred at room temperature for 12 h. After completion, as monitored by TLC, the reaction mixture was diluted with ethyl acetate (30 mL), washed with brine (2 x 10 mL) and ice-water (1 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by silica gel column chromatography using hexane and ethyl acetate as eluent to give **b**.

Step-2: To a solution of **b** (2 mmol, 1 equiv) in toluene (10 mL), was added dialkyl malonate (2.2 mmol, 1.1 equiv), piperidine (0.2 mmol, 0.1 equiv, 17 mg) and AcOH (0.4 mmol, 0.2 equiv, 24 mg) and the resultant mixture was stirred at 120 °C for 12 h in a pre-heated oil bath under calcium chloride tube. After completion, as monitored by TLC, the solvent was evaporated and the reaction mixture was diluted with ethyl acetate (30 mL) and washed with saturated $NaHCO_3$ solution (1 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by silica gel column chromatography using hexane and ethyl acetate as eluent to give **1**.

Substrates **1i**, **1j**, **1m**, **1n**, **1o** and **1q** are new and their complete characterization data are given. Compound **1l** and **1p** are prepared according to the reported procedure.[1b]

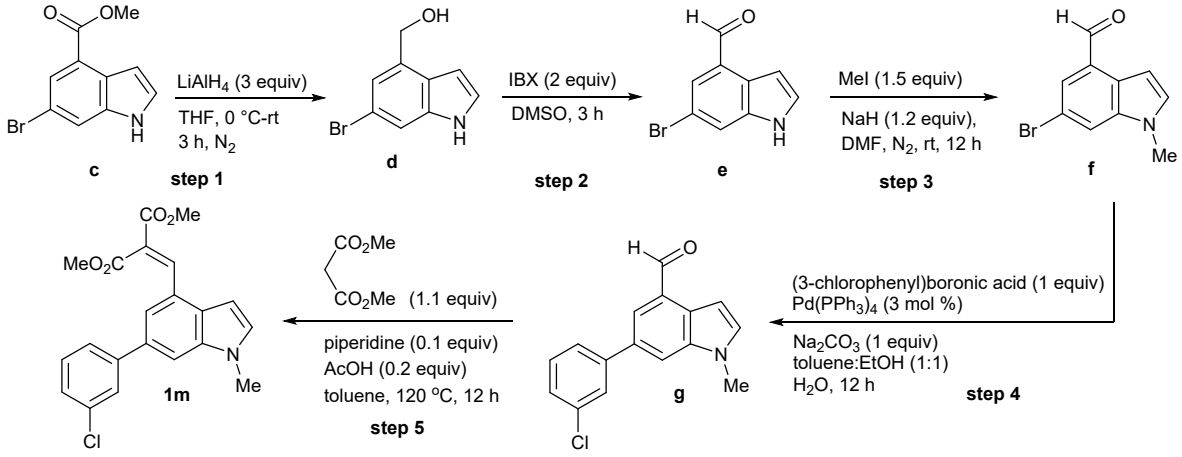


Dipropyl 2-((1-methyl-1H-indol-4-yl)methylene)malonate 1i. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.50; orange sticky liquid; yield 75% (740 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.37-7.35 (m, 1H), 7.31-7.30 (m, 1H), 7.20-7.16 (m, 1H), 7.14-7.13 (m, 1H), 6.65-6.64 (m, 1H), 4.25-4.18 (m, 4H), 3.80 (s, 3H), 1.79-1.70 (m, 2H), 1.68-1.61 (m, 2H), 0.99 (t, *J* = 7.6 Hz, 3H), 0.84 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4, 164.7, 140.4, 136.9, 130.1, 129.0, 125.9, 125.1, 121.6, 119.4, 111.7, 99.3, 67.3, 67.1, 33.1, 22.1, 21.8, 10.5, 10.4; FT-IR (KBr) 2976, 1727, 1619, 1433, 1260, 1222, 1124, 750 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{24}NO_4$: 330.1700, found: 330.1702.



Diisoamyl 2-((1-methyl-1H-indol-4-yl)methylene)malonate 1j. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.55; yellow sticky liquid; yield 68% (785 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.37-7.35 (m, 1H), 7.30-7.29 (m, 1H), 7.20-7.16 (m, 1H), 7.139-7.131 (m, 1H), 6.64-6.63 (m, 1H), 4.32-4.24 (m, 4H), 3.80 (s, 3H), 1.81-1.68 (m, 1H), 1.64-1.59 (m, 2H), 1.57-1.54 (m, 1H), 1.51-1.46 (m, 2H), 0.97 (d, *J* = 6.8 Hz, 6H), 0.86 (d, *J* = 6.4 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4, 164.7, 164.6, 140.4, 136.9, 130.1, 125.9, 125.1, 121.5, 119.4, 111.7, 99.3, 64.2, 37.3, 37.1, 33.1, 25.2, 24.8, 22.6, 22.4; FT-IR (KBr) 2958, 1725, 1679, 1267, 1228, 1079, 752 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{32}NO_4$: 386.2326, found: 386.2325.

Scheme S2. Procedure for the Synthesis of 1m.



Step-1: To a solution of **c** (5 mmol, 1 equiv, 1265 mg) in THF (20 mL) at 0 °C under nitrogen atmosphere, $LiAlH_4$ (15 mmol, 3 equiv, 570 mg) was added portion wise. The reaction mixture was gradually allowed to warm up to room temperature and stirred for 3 h. After completion, the reaction mixture was quenched with saturated NH_4Cl (30 mL) and extracted with ethyl acetate (3 x 20 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by silica gel column chromatography using ethyl acetate and hexane as an eluent to afford **d**.

Step-2: To a suspension of IBX (8 mmol, 2 equiv, 2240 mg) in DMSO (15 mL), was added (6-bromo-1*H*-indol-4-yl)methanol **d** (4 mmol, 1 equiv, 900 mg) and the resultant mixture was stirred at room temperature for 3 h under air. The reaction mixture was then diluted with ethyl acetate (30 mL), washed with brine (1 x 10 mL) and ice-water (1 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by silica gel column chromatography using hexane and ethyl acetate as eluent to give **e**.

Step-3: To a suspension of NaH (3.6 mmol, 60% dispersion in mineral oil, 1.2 equiv, 144 mg) in DMF (10 mL) at 0 °C, was added 6-bromo-1*H*-indole-4-carbaldehyde **e** (3 mmol, 1 equiv, 669 mg), under nitrogen atmosphere. The reaction mixture was stirred at the same temperature for 30 minutes and then methyl iodide (4.5 mmol, 1.5 equiv, 639 mg) was added dropwise. The mixture was then allowed to stir at room temperature for 12 h. After completion, as monitored by TLC, the reaction mixture was diluted with ethyl acetate (30 mL), washed with brine (1 x 10 mL) and ice-

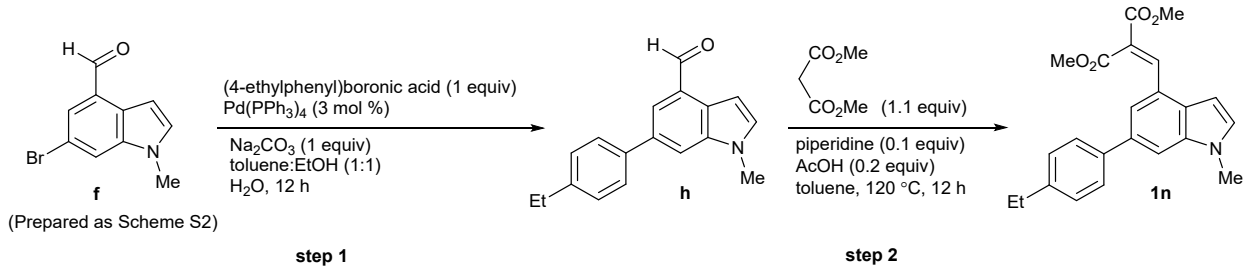
water (1 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by silica gel column chromatography using hexane and ethyl acetate as eluent to give **f**.

Step-4: To a solution of **f** (2 mmol, 1 equiv, 474 mg) in toluene/EtOH (1:1, 6 mL), was added (3-chlorophenyl)boronic acid (2 mmol, 1 equiv, 312 mg), $Pd(PPh_3)_4$ (3 mol %, 0.03 equiv, 34 mg), Na_2CO_3 (2 mmol, 1 equiv, 212 mg) and H_2O (100 µL). The mixture was stirred at 100 °C for 12 h in a pre-heated oil bath under nitrogen atmosphere. After 12 h, the reaction mixture was cooled to room temperature and diluted with ethyl acetate (15 mL) and washed with brine (1 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by silica gel column chromatography using hexane and ethyl acetate as eluent to give **g**.

Step-5: To a solution of **g** (1 mmol, 1 equiv, 269 mg) in toluene (5 mL), was added dimethyl malonate (1.1 mmol, 1.1 equiv, 145 mg), piperidine (0.1 mmol, 0.1 equiv, 8.5 mg) and AcOH (0.2 mmol, 0.2 equiv, 12 mg) and the resulting mixture was allowed to stir at 120 °C for 12 h in a pre-heated oil bath under calcium chloride tube. After completion, as monitored by TLC, the solvent was evaporated and the reaction mixture was diluted with ethyl acetate (15 mL) and washed with saturated $NaHCO_3$ (1 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by silica gel column chromatography using hexane and ethyl acetate as eluent to give **1m**.

Dimethyl 2-((6-(3-chlorophenyl)-1-methyl-1H-indol-4-yl)methylene)malonate 1m. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.48; yellow sticky liquid; yield 61% (233 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.59 (s, 1H), 7.53 (s, 1H), 7.49-7.48 (m, 2H), 7.39-7.36 (m, 1H), 7.32-7.30 (m, 1H), 7.19 (s, 1H), 6.65 (s, 1H), 3.88 (d, J = 10.5 Hz, 6H), 3.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 164.9, 143.6, 140.9, 137.5, 134.8, 133.8, 131.3, 130.2, 128.7, 127.5, 127.0, 125.7, 125.5, 125.3, 119.0, 110.4, 99.4, 52.8, 33.2; FT-IR (KBr) 2950, 2923, 2853, 1724, 1594, 1434, 1220, 1075, 751 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{19}ClNO_4$: 384.0997, found: 384.0976.

Scheme S3. Procedure for the Synthesis of 1n.



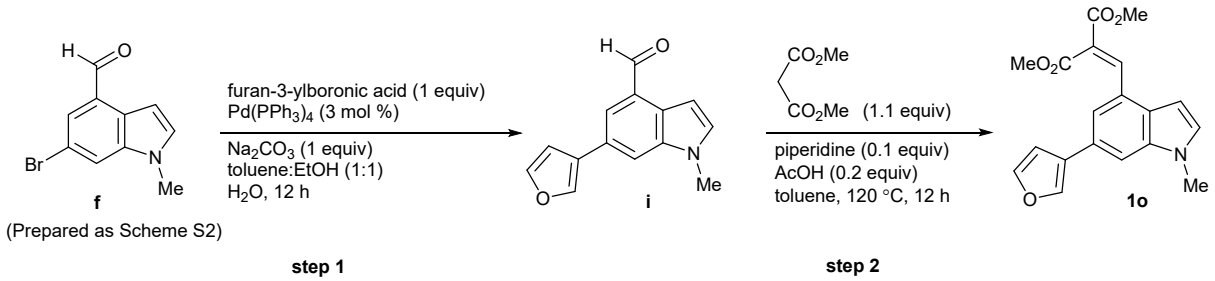
Step-1: To a solution of **f** (2 mmol, 1 equiv, 474 mg, prepared as described in Scheme S2) in toluene/EtOH (1:1, 6 mL), was added (4-ethylphenyl)boronic acid (2 mmol, 1 equiv, 300 mg), $Pd(PPh_3)_4$ (3 mol %, 0.03 equiv, 34 mg), Na_2CO_3 (2 mmol, 1 equiv, 212 mg) and H_2O (100 µL). The mixture was stirred at 100 °C for 12 h in a pre-heated oil bath under nitrogen atmosphere. After 12 h, the reaction mixture was cooled to room temperature and diluted with ethyl acetate (10 mL) and washed with brine (1 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by silica gel column chromatography using hexane and ethyl acetate as eluent to give **h**.

Step-2: To a solution of **h** (1 mmol, 1 equiv, 263 mg) in toluene (5 mL), was added dimethyl malonate (1.1 mmol, 1.1 equiv, 145 mg), piperidine (0.1 mmol, 0.1 equiv, 8.5 mg) and AcOH (0.2 mmol, 0.2 equiv, 12 mg) and the resulting mixture was allowed to stir at 120 °C for 12 h in a pre-heated oil bath under calcium chloride tube. After completion, as monitored by TLC, the solvent was evaporated and the reaction mixture was diluted with ethyl acetate (15 mL) and washed with saturated $NaHCO_3$ solution (1 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by silica gel column chromatography using hexane and ethyl acetate as eluent to give **1n**.

Dimethyl 2-((6-(4-ethylphenyl)-1-methyl-1H-indol-4-yl)methylene)malonate 1n. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.51; orange sticky liquid; yield 63% (237 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.57-7.54 (m, 4H), 7.31-7.29 (m, 2H), 7.15-7.14 (m, 1H), 6.65-6.64 (m, 1H), 3.89 (s, 3H), 3.82 (s, 6H), 2.75 (q, *J* = 7.6 Hz, 2H), 1.30 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.6, 164.9, 143.2, 141.2, 139.0, 137.5, 135.2, 130.8, 128.4, 128.1, 127.2, 125.2, 125.0, 119.1, 110.3, 99.2, 52.7, 52.6, 33.1, 28.5, 15.6; FT-IR (KBr) 2950,

2924, 2855, 1728, 1506, 1435, 1301, 1258, 1075 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{24}NO_4$: 378.1700, found: 378.1688.

Scheme S4. Procedure for the Synthesis of 1o.



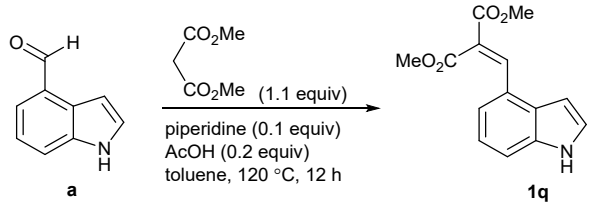
Step-1: To a solution of **f** (2 mmol, 1 equiv, 474 mg, prepared as described in Scheme S2) in toluene/EtOH (1:1, 6 mL), was added furan-3-ylboronic acid (2 mmol, 1 equiv, 222 mg), $Pd(PPh_3)_4$ (3 mol %, 0.03 equiv, 34 mg), Na_2CO_3 (2 mmol, 1 equiv, 212 mg) and H_2O (100 μL). The mixture was stirred at 100 °C for 12 h in a pre-heated oil bath under nitrogen atmosphere. After 12 h, the reaction mixture was cooled to room temperature and diluted with ethyl acetate (10 mL) and washed with brine (1 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by silica gel column chromatography using hexane and ethyl acetate as eluent to give **i**.

Step-2: To a solution of **i** (1 mmol, 1 equiv, 225 mg) in toluene (5 mL), was added dimethyl malonate (1.1 mmol, 1.1 equiv, 145 mg), piperidine (0.1 mmol, 0.1 equiv, 8.5 mg) and AcOH (0.2 mmol, 0.2 equiv, 12 mg) and the resulting mixture was allowed to stir at 120 °C for 12 h in a pre-heated oil bath under calcium chloride guard tube. After completion, as monitored by TLC, the solvent was evaporated and the residue was diluted with ethyl acetate (15 mL) and washed with saturated $NaHCO_3$ solution (1 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by silica gel column chromatography using hexane and ethyl acetate as eluent to give **1o**.

Dimethyl 2-((6-(furan-3-yl)-1-methyl-1H-indol-4-yl)methylene)malonate 1o. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.40; yellow sticky liquid; yield 53% (180 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.748-7.743 (m, 1H), 7.49 (t, *J* = 1.6 Hz, 1H), 7.44-7.43 (m, 2H), 7.13 (d, *J* = 3.2 Hz, 1H), 6.739-6.732 (m, 1H), 6.617-6.610 (m, 1H), 3.88 (s, 3H), 3.81

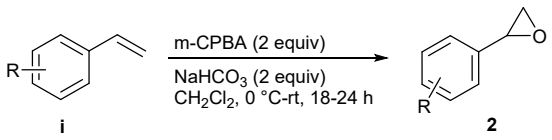
(s, 3H), 3.79 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.6, 164.8, 143.8, 141.0, 138.2, 137.4, 130.7, 128.1, 127.0, 126.2, 125.5, 125.2, 117.9, 109.1, 108.9, 99.4, 52.8, 52.7, 33.1; FT-IR (KBr) 2951, 2924, 2852, 1724, 1614, 1508, 1435, 1299, 1072, 1059, 1025, 869 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{18}NO_5$: 340.1179, found: 340.1175.

Scheme S5. Synthesis of Dimethyl 2-((1H-indol-4-yl)methylene)malonate 1q.



To a solution of 1*H*-indole-4-carbaldehyde **a** (1 mmol, 1 equiv, 145 mg) in toluene (5 mL), was added dimethyl malonate (1.1 mmol, 1.1 equiv, 145 mg), piperidine (0.1 mmol, 0.1 equiv, 8.5 mg) and AcOH (0.2 mmol, 0.2 equiv, 12 mg) and the resulting mixture was allowed to stir at 120 °C for 12 h in a pre-heated oil bath under calcium chloride tube. After completion, as monitored by TLC, the solvent was evaporated and the reaction mixture was diluted with ethyl acetate (15 mL) and washed with saturated $NaHCO_3$ solution (1 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by silica gel column chromatography using hexane and ethyl acetate as eluent to give **1q**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.30; green sticky liquid; yield 85% (220 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 8.29 (s, 1H), 7.46 (d, *J* = 8 Hz, 1H), 7.31-7.27 (m, 2H), 7.19-7.15 (m, 1H), 6.72-6.71 (m, 1H), 3.89 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 165.0, 141.4, 136.0, 125.7, 124.9, 124.8, 122.1, 119.7, 113.8, 100.9, 52.78, 52.75; FT-IR (KBr) 2950, 2924, 2855, 1728, 1506, 1435, 1301, 1075 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{14}H_{14}NO_4$: 260.0917, found: 260.0918.

Scheme S6. General Procedure for the Synthesis of Oxiranes.[2]

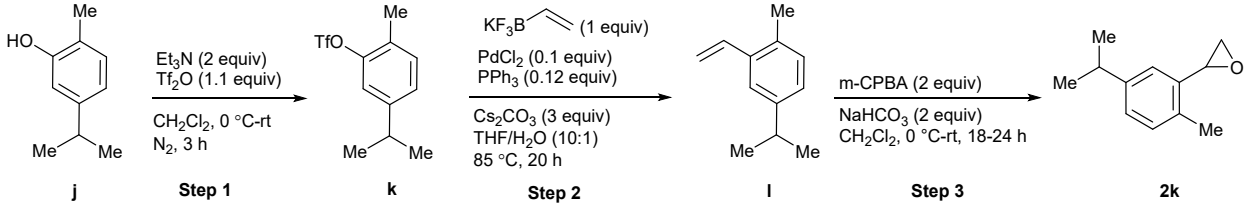


Styrene **i** (2 mmol, 1 equiv) was dissolved in CH_2Cl_2 (5 mL) in a 25 mL double neck round-bottom flask under nitrogen atmosphere. $NaHCO_3$ (4 mmol, 2 equiv, 336 mg) was added to the flask in

one portion and the reaction was cooled to 0 °C in an ice bath. The flask was fitted with an addition funnel containing *m*-CPBA (4 mmol, 2 equiv, 688 mg) dissolved in CH_2Cl_2 (10 mL), adding dropwise over 15 minutes. The resultant mixture was stirred at 0 °C for an additional 15 minutes and then allowed to warm up to room temperature and stirred overnight. The resulting mixture was washed twice each with saturated aqueous Na_2CO_3 (5 mL) and $Na_2S_2O_3$ (5 mL) and extracted using CH_2Cl_2 (3 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by silica gel column chromatography using hexane and ethyl acetate as an eluent to afford the oxiranes **2b**-**e**, **2g**-**h**, **2j**-**m** and **2o**.

Oxiranes **2f′**[2], **2i′**[2] and **2n**[2b] are known and were prepared according to the reported procedure. Oxirane **2k** is new and its complete characterization data is given.

Scheme S7. Procedure for the Synthesis of Oxirane 2k.



Step-1: To a solution of carvacrol **j** (3 mmol, 1 equiv, 450 mg) in CH_2Cl_2 (10 mL) at room temperature, was added Et_3N (6 mmol, 2 equiv, 606 mg) under nitrogen atmosphere and the resulting mixture was allowed to cool to 0 °C. Then, Tf_2O (3.3 mmol, 1.1 equiv, 930 mg) was added dropwise over a period of 5 minutes. The mixture was allowed to warm up to room temperature and stirred for an additional 3 hours under nitrogen atmosphere. After complete consumption of starting materials, as monitored by TLC, the reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with saturated NH_4Cl (1 x 20 mL) and the aqueous layer was extracted using CH_2Cl_2 (2 x 20 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using hexane and ethyl acetate as eluent to give **k**.[2f]

Step-2: An oven dried pressure tube was charged with **k** (2 mmol, 1 equiv, 564 mg), potassium vinyltrifluoroborate (2 mmol, 1 equiv, 268 mg), $PdCl_2$ (0.2 mmol, 0.1 equiv, 35 mg), PPh_3 (0.24 mmol, 0.12 equiv, 62 mg), Cs_2CO_3 (6 mmol, 3 equiv, 1956 mg) and THF (6 mL). Then, 0.6 mL

H_2O was added and the reaction mixture was flushed with nitrogen and allowed to stir at 85 °C for 20 h in a pre-heated oil bath under nitrogen atmosphere. After completion, the resulting mixture was cooled to room temperature, diluted with CH_2Cl_2 (10 mL) and washed with H_2O (5 mL). The aqueous layer was extracted using CH_2Cl_2 (2 x 20 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using hexane and ethyl acetate as eluent to give **l**.[2f]

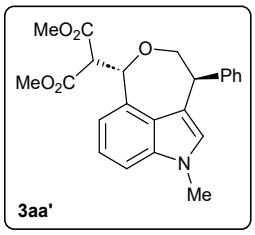
Step-3: Styrene **l** (1 mmol, 1 equiv, 160 mg) was dissolved in CH_2Cl_2 (5 mL) in a 25 mL double neck round-bottom flask under nitrogen atmosphere. $NaHCO_3$ (2 mmol, 2 equiv, 168 mg) was added to the flask in one portion and the reaction was cooled to 0 °C in an ice bath. The flask was then fitted with an addition funnel containing *m*-CPBA (2 mmol, 2 equiv, 344 mg) dissolved in CH_2Cl_2 (5 mL), adding dropwise over 10 minutes. The reaction mixture was stirred at 0 °C for an additional 15 minutes and then allowed to warm up to room temperature and stirred overnight. The resulting mixture was successively washed with saturated aqueous Na_2CO_3 (2 x 5 mL) and $Na_2S_2O_3$ (2 x 5 mL) and extracted with CH_2Cl_2 (2 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by silica gel column chromatography using hexane and ethyl acetate as an eluent to afford the oxirane **2k**.

2-(5-Isopropyl-2-methylphenyl)oxirane 2k. Analytical TLC on silica gel, 1:49 ethyl acetate/hexane R_f = 0.55; colorless liquid; yield 91% (160 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.075-7.070 (m, 3H), 3.99-3.97 (m, 1H), 3.15-3.13 (m, 1H), 2.89-2.82 (m, 1H), 2.70 (dd, *J* = 6, 2.8 Hz, 1H), 2.37 (s, 3H), 1.22-1.20 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.0, 135.7, 133.5, 129.9, 125.7, 122.2, 50.7, 50.2, 33.9, 24.17, 24.11, 18.4; FT-IR (KBr) 2960, 1729, 1500, 1460, 1382, 1177, 882, 822 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{12}H_{17}O$: 177.1274, found: 177.1260.

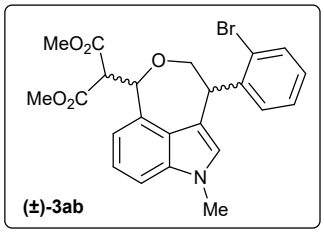
General Procedure for the Synthesis of (±)**-3aa-oa**. Indolyl malonate **1** (0.2 mmol, 1 equiv), oxirane **2** (0.24 mmol, 1.2 equiv), $Co(OAc)_2$•$4H_2O$ (0.01 mmol, 0.1 equiv, 2.49 mg) and 4 Å molecular sieves (100 mg) were stirred in CH_2Cl_2 (3 mL) at 50 °C for 4 h in a pre-heated oil bath under calcium chloride tube. Then, KO^{t}Bu (0.2 mmol, 1 equiv, 22 mg) was added and the resulting mixture was stirred at the same temperature for an additional 5 h. After completion, as monitored by TLC, the reaction mixture was allowed to cool to room temperature and diluted with CH_2Cl_2

(5 mL) and passed through a short pad of celite using CH_2Cl_2 (10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using ethyl acetate and hexane as an eluent to afford (±)-**3**.

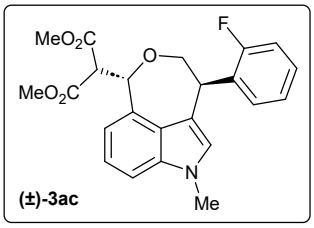
General Procedure for the Enantiospecific Synthesis of 3aa′, **3af′**, **3ai′**, **3ba′** and **3ha′**. Indole **1** (0.2 mmol, 1 equiv), enantioenriched oxirane **2′** (0.24 mmol, 1.2 equiv), $Co(OAc)_2$•$4H_2O$ (0.01 mmol, 0.1 equiv, 2.49 mg) and 4 Å molecular sieves (100 mg) were stirred in CH_2Cl_2 (3 mL) at 50 °C for 4 h in a pre-heated oil bath under calcium chloride tube. Then, KO^{t}Bu (0.2 mmol, 1 equiv, 22 mg) was added and the resulting mixture was stirred at the same temperature for an additional 5 h. The purification was performed as above presented general procedure. The enantiomeric excess was determined using chiral HPLC.



Dimethyl 2-((1*S*,4*S*)-6-methyl-4-phenyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate 3aa′. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.60; yellow sticky liquid; yield 71% (55 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.26 (m, 5H), 7.25-7.22 (m, 1H), 7.17 (t, *J* = 7.6 Hz, 1H), 6.77 (d, *J* = 7.6 Hz, 1H), 6.479-6.475 (m, 1H), 5.62 (d, *J* = 6 Hz, 1H), 4.53-4.48 (m, 1H), 4.41-4.36 (m, 2H), 3.90-3.86 (m, 1H), 3.83 (s, 3H), 3.68 (s, 3H), 3.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 167.5, 142.1, 137.5, 134.8, 128.8, 128.7, 128.5, 127.0, 125.1, 121.3, 118.4, 114.4, 108.7, 82.9, 79.1, 57.6, 53.0, 52.5, 47.6, 32.9; FT-IR (KBr) 2950, 1736, 1454, 1300, 1246, 1155, 744, 702 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{24}NO_5$: 394.1649, found: 394.1651; $[\alpha]_D^{25}$ = +30 (c = 0.01, $CHCl_3$); HPLC: *ee* for major diastereomer = 98% *ee* [CHIRALPAK AD-H, hexane/^{i}PrOH = 80:20, flow rate: 1 mL/min, λ= 254 nm, t_R = 8.40 min (major), 10.73 min (minor)].

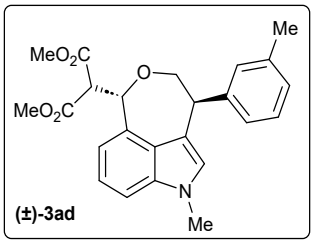


Dimethyl 2-(4-(2-bromophenyl)-6-methyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)**-3ab**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.54; brown sticky liquid;; yield 61% (57 mg);mixture of diastereomers (dr = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61-7.59 (m, 1H), 7.54-7.52 (m, 0.26H), 7.25-7.19 (m, 2.16H), 7.18-7.15 (m, 3H), 7.12-7.07 (m, 1.25H), 7.03-6.99 (m, 0.28H), 6.81-6.79 (m, 0.28H), 6.78 (s, 0.25H), 6.77 (d, *J* = 7.2 Hz, 1H), 6.50-6.49 (m, 1H), 5.72 (d, *J* = 6 Hz, 0.25H), 5.64 (d, *J* = 6 Hz, 1H), 5.07-5.03 (m, 1H), 5.00-4.98 (m, 0.27H), 4.51-4.47 (m, 0.28H), 4.45-4.41 (m, 1H), 4.39 (d, *J* = 6 Hz, 1H), 4.35 (d, *J* = 5.6 Hz, 1H), 4.16-4.13 (m, 0.28H), 3.91-3.83 (m, 4H), 3.77 (s, 0.75H), 3.72 (s, 0.74H), 3.69 (s, 3H), 3.67 (s, 3H), 3.61 (s, 0.73H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.56, 168.50, 167.56, 167.50, 143.8, 137.5, 137.4, 134.8, 134.7, 132.3, 132.2, 128.4, 128.1, 127.87, 127.84, 127.6, 127.1, 125.9, 125.1, 124.7, 123.6, 121.4, 121.3, 117.2, 116.4, 114.9, 114.5, 108.8, 108.7, 83.1, 82.2, 74.9, 57.7, 57.6, 53.0, 52.8, 52.6, 52.5, 45.0, 32.9; FT-IR (KBr) 2924, 2853, 1736, 1435, 1244, 1155, 745 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{23}H_{22}BrNNaO_5$: 494.0574, found: 494.0564.

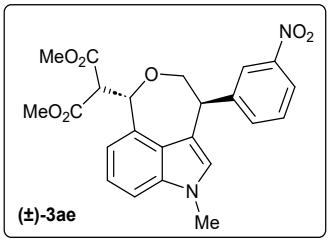


Dimethyl 2-(4-(2-fluorophenyl)-6-methyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)**-3ac**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.51; yellow sticky liquid; yield 65% (53 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.20 (m, 3H), 7.16 (t, *J* = 7.6 Hz, 1H), 7.09-7.04 (m, 2H), 6.77 (d, *J* = 7.2 Hz, 1H), 6.497-6.494 (m, 1H), 5.63 (d, *J* = 6 Hz, 1H), 4.85 (dd, *J* = 10.8, 4.4 Hz, 1H), 4.43-4.39 (m, 2H), 3.99-3.93 (m, 1H), 3.83 (s, 3H), 3.68 (s, 3H), 3.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 167.5, 162.3 (d, $J_{C\text{-}F}$ = 245 Hz), 137.6, 134.7, 130.8 (d, $J_{C\text{-}F}$ = 4.7 Hz), 128.8 (d, $J_{C\text{-}F}$ = 14.3 Hz), 128.6 (d, $J_{C\text{-}F}$ = 8.1 Hz), 127.8, 124.9, 124.2 (d,

$J_{C\text{-}F}$ = 3.5 Hz), 121.3, 117.2, 115.8 (d, $J_{C\text{-}F}$ = 22.3 Hz), 114.5, 108.7, 82.9, 57.6, 53.0, 52.6, 40.6, 32.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -119.5; FT-IR (KBr) 2924, 1736, 1454, 1247, 1155, 748 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{23}H_{22}FNNaO_5$: 434.1374, found: 434.1363.

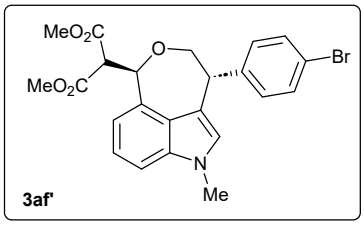


Dimethyl 2-(6-methyl-4-(m-tolyl)-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)**-3ad**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.61; yellow sticky liquid; yield 62% (50 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.20 (m, 2H), 7.18-7.14 (m, 1H), 7.08-7.06 (m, 3H), 6.76 (d, *J* = 7.2 Hz, 1H), 6.487-6.483 (m, 1H), 5.61 (d, *J* = 5.6 Hz, 1H), 4.48-4.44 (m, 1H), 4.41-4.35 (m, 2H), 3.89-3.86 (m, 1H), 3.83 (s, 3H), 3.68 (s, 3H), 3.64 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 167.5, 142.1, 138.1, 137.5, 134.9, 129.6, 128.6, 128.4, 127.7, 126.0, 125.1, 121.2, 118.6, 114.4, 108.7, 82.9, 79.2, 57.7, 53.0, 52.5, 47.5, 32.9, 21.5; FT-IR (KBr) 2924, 2855, 1737, 1455, 1123, 747 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{24}H_{25}NNaO_5$: 430.1625, found: 430.1624.

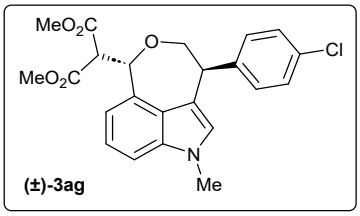


Dimethyl 2-(6-methyl-4-(3-nitrophenyl)-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)**-3ae**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.48; yellow sticky liquid; yield 77% (67 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14-8.11 (m, 2H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.51-7.47 (m, 1H), 7.27-7.25 (m, 1H), 7.20 (t, *J* = 7.2 Hz, 1H), 6.80 (d, *J* = 7.2 Hz, 1H), 6.444-6.441 (m, 1H), 5.65 (d, *J* = 5.6 Hz, 1H), 4.67-4.62 (m, 1H), 4.41-4.37 (m, 2H), 3.90 (t, *J* = 11.6 Hz, 1H), 3.83 (s, 3H), 3.70 (s, 3H), 3.64 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 167.4, 148.6, 144.4, 137.6, 135.2, 134.5, 129.6, 128.3, 124.9, 123.7, 122.2, 121.7, 117.1, 114.8,

108.9, 82.9, 78.2, 57.5, 53.0, 52.5, 47.3, 33.0; FT-IR (KBr) 2924, 2853, 1734, 1525, 1455, 1346, 1245, 1081, 738 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{23}H_{22}N_2NaO_7$: 461.1319, found: 461.1317.

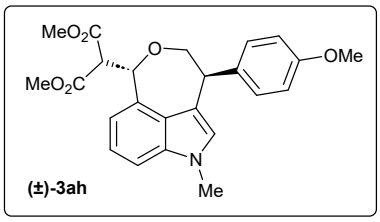


Dimethyl 2-((1*R*,4*R*)-4-(4-bromophenyl)-6-methyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate 3af′. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.65; brown sticky liquid; yield 70% (65 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.4 Hz, 2H), 7.24-7.22 (m, 1H), 7.19-7.14 (m, 3H), 6.77 (d, *J* = 7.6 Hz, 1H), 6.459-6.455 (m, 1H), 5.61 (d, *J* = 5.6 Hz, 1H), 4.49-4.45 (m, 1H), 4.40-4.32 (m, 2H), 3.86-3.82 (m, 4H), 3.68 (s, 3H), 3.64 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 167.4, 141.2, 137.6, 134.7, 131.7, 130.6, 128.4, 125.0, 121.4, 120.8, 118.0, 114.6, 108.8, 82.9, 78.7, 57.6, 53.0, 52.5, 47.1, 32.9; FT-IR (KBr) 2925, 2855, 1736, 1455, 1299, 1155, 1010, 747 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{23}H_{22}BrNNaO_5$: 494.0574, found: 494.0546; $[\alpha]_D^{25}$ = -25 (c = 0.04, $CHCl_3$); HPLC: *ee* for major diastereomer = 95% *ee* [CHIRALPAK AD-H, hexane/^{i}PrOH = 90:10, flow rate: 1 mL/min, λ= 254 nm, t_R = 25.52 min (minor), 28.50 min (major)].

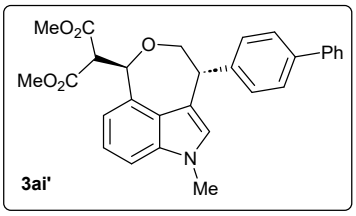


Dimethyl 2-(4-(4-chlorophenyl)-6-methyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)**-3ag**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.62; brown sticky liquid; yield 71% (60 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.4 Hz, 2H), 7.25-7.15 (m, 4H), 6.77 (d, *J* = 7.2 Hz, 1H), 6.46-6.45 (m, 1H), 5.61 (d, *J* = 5.6 Hz, 1H), 4.51-4.47 (m, 1H), 4.40 (d, *J* = 5.6 Hz, 1H), 4.36 (dd, *J* = 11.6, 4.8 Hz, 1H), 3.86-3.80 (m, 4H), 3.68 (s, 3H), 3.64 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.5, 167.4, 140.7, 137.6, 134.7, 132.7, 130.2, 128.8,

128.4, 125.0, 121.4, 118.1, 114.5, 108.7, 82.9, 78.7, 57.6, 53.0, 52.5, 47.0, 32.9; FT-IR (KBr) 2951, 2863, 1734, 1488, 1298, 1155, 749 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{23}H_{22}ClNNaO_5$: 450.1079, found: 450.1074.

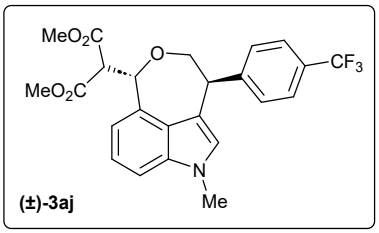


Dimethyl 2-(4-(4-methoxyphenyl)-6-methyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)**-3ah**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.60; yellow sticky liquid; yield 67% (56 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.14 (m, 4H), 6.87 (d, *J* = 8.4 Hz, 2H), 6.76 (d, *J* = 7.6 Hz, 1H), 6.487-6.483 (m, 1H), 5.60 (d, *J* = 5.6 Hz, 1H), 4.48-4.43 (m, 1H), 4.41 (d, *J* = 5.6 Hz, 1H), 4.35 (dd, *J* = 11.6, 4.8 Hz, 1H), 3.86-3.82 (m, 4H), 3.81 (s, 3H), 3.68 (s, 3H), 3.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 167.5, 158.5, 137.5, 134.8, 134.2, 129.8, 128.5, 125.0, 121.2, 118.8, 114.3, 113.9, 108.7, 82.8, 79.3, 57.6, 55.3, 53.0, 52.5, 46.8, 32.9; FT-IR (KBr) 2924, 2853, 1736, 1609, 1509, 1455, 1301, 1248, 748 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{24}H_{25}NNaO_6$: 446.1574, found: 446.1584.

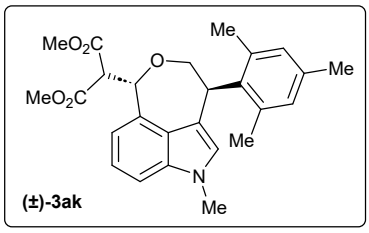


Dimethyl 2-((1*R*,4*R*)-4-([1,1'-biphenyl]-4-yl)-6-methyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate 3ai′. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.63; colorless sticky liquid; yield 69% (64 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.5 Hz, 2H), 7.56 (d, *J* = 8 Hz, 2H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.35 (d, *J* = 7.5 Hz, 3H), 7.24 (s, 1H), 7.18 (t, *J* = 7.5 Hz, 1H), 6.78 (d, *J* = 7 Hz, 1H), 6.54 (s, 1H), 5.64 (d, *J* = 5.5 Hz, 1H), 4.57-4.54 (m, 1H), 4.44-4.40 (m, 2H), 3.91 (t, *J* = 11.5 Hz, 1H), 3.84 (s, 3H), 3.70 (s, 3H), 3.65 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 167.5, 141.2, 141.0, 139.9, 137.6, 134.9, 129.3, 128.9, 128.6, 127.3, 127.1, 125.1, 121.3, 118.4, 114.5, 108.7, 82.9, 79.0, 57.7, 53.0, 52.5, 47.3, 32.9; FT-IR (KBr) 2923, 2852,

1737, 1301, 1340, 1156, 746 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{29}H_{27}NNaO_5$: 492.1781, found: 492.1777; $[\alpha]_D^{25}$ = -53.33 (c = 0.03, $CHCl_3$); HPLC: *ee* for major diastereomer = 96% *ee* [CHIRALPAK AD-H, hexane/^{i}PrOH = 90:10, flow rate: 1 mL/min, λ= 254 nm, t_R = 19.13 min (minor), 24.99 min (major)].

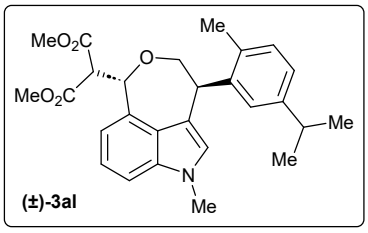


Dimethyl 2-(6-methyl-4-(4-(trifluoromethyl)phenyl)-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)**-3aj**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.50; yellow sticky liquid; yield 72% (66 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8 Hz, 2H), 7.40 (d, *J* = 8 Hz, 2H), 7.24-7.13 (m, 2H), 6.79 (d, *J* = 7.6 Hz, 1H), 6.446-6.443 (m, 1H), 5.63 (d, *J* = 5.2 Hz, 1H), 4.60-4.56 (m, 1H), 4.40-4.35 (m, 2H), 3.87 (t, *J* = 11.6 Hz, 1H), 3.83 (s, 3H), 3.69 (s, 3H), 3.64 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 167.4, 146.3, 137.6, 134.7, 129.3, 128.4, 127.6 (q, J_{C-F} = 270 Hz), 125.6 (q, J_{C-F} = 3.6 Hz), 125.0, 121.5, 117.6, 114.6, 108.8, 82.9, 78.5, 57.6, 53.0, 52.5, 47.5, 33.0; ^{19}F NMR (470 MHz, $CDCl_3$) δ -62.3; FT-IR (KBr) 2927, 1735, 1485, 1325, 1241, 1046, 735 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{24}H_{22}F_3NNaO_5$: 484.1342, found: 484.1330.

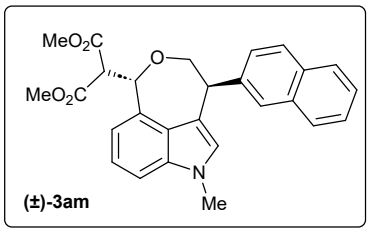


Dimethyl 2-(4-mesityl-6-methyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)**-3ak**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.64; yellow sticky liquid; yield 60% (52 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.22 (m, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 6.91 (s, 1H), 6.78 (s, 1H), 6.74 (d, *J* = 7.2 Hz, 1H), 6.408-6.404 (m, 1H), 5.57 (d, *J* = 6 Hz, 1H), 4.97-4.93 (m, 1H), 4.42 (d, *J* = 6 Hz, 1H), 4.32 (dd, *J* = 12, 5.6 Hz, 1H), 4.12 (t, *J* = 11.6 Hz, 1H), 3.85 (s,

3H), 3.68 (s, 3H), 3.66 (s, 3H), 2.46 (s, 3H), 2.27 (s, 3H), 1.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 167.7, 137.8, 137.5, 137.4, 136.1, 135.0, 134.5, 131.0, 129.0, 126.8, 124.6, 121.2, 117.6, 114.1, 108.7, 83.4, 76.3, 57.6, 53.1, 52.6, 42.0, 32.8, 22.0, 21.5, 20.9; FT-IR (KBr) 2922, 1739, 1454, 1302, 1156, 744 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{26}H_{29}NNaO_5$: 458.1938, found: 458.1935.

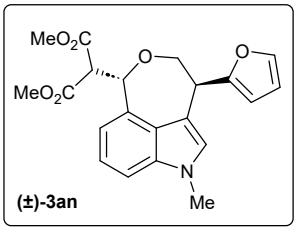


Dimethyl 2-(4-(5-isopropyl-2-methylphenyl)-6-methyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)**-3al**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.62; orange sticky liquid; yield 59% (53 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23-7.13 (m, 3H), 7.05-7.02 (m, 1H), 6.98 (s, 1H), 6.77 (d, *J* = 7.2 Hz, 1H), 6.427-6.423 (m, 1H), 5.61 (d, *J* = 5.6 Hz, 1H), 4.73-4.70 (m, 1H), 4.44 (d, *J* = 6 Hz, 1H), 4.38 (dd, *J* = 11.6, 4.8 Hz, 1H), 3.92 (t, *J* = 11.6 Hz, 1H), 3.85 (s, 3H), 3.67 (s, 3H), 3.66 (s, 3H), 2.39 (s, 3H), 2.80-2.73 (m, 1H), 1.17-1.14 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 167.6, 146.8, 140.0, 137.6, 134.9, 133.8, 130.4, 128.1, 125.1, 124.5, 121.2, 118.4, 114.2, 108.7, 83.1, 57.5, 53.0, 52.6, 33.8, 32.9, 24.2, 24.1; FT-IR (KBr) 2953, 2922, 2853, 1738, 1455, 1155, 747 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{27}H_{31}NNaO_5$: 472.2094, found: 472.2096.

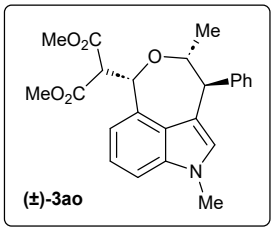


Dimethyl 2-(6-methyl-4-(naphthalen-2-yl)-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)**-3am**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.55; yellow sticky liquid; yield 66% (58 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84-7.78 (m, 4H), 7.50-7.45 (m, 2H), 7.37-7.34 (m, 1H), 7.26-7.24 (m, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 6.80 (d, *J* = 7.6 Hz, 1H), 6.47-

6.46 (m, 1H), 5.66 (d, J = 5.6 Hz, 1H), 4.71-4.66 (m, 1H), 4.48-4.44 (m, 1H), 4.44-4.42 (m, 1H), 4.00 (t, J = 11.6 Hz, 1H), 3.84 (s, 3H), 3.664-3.662 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.6, 167.5, 139.5, 137.6, 134.9, 133.6, 132.7, 128.7, 128.2, 127.8, 127.7, 127.5, 127.1, 126.1, 125.7, 125.1, 121.3, 118.5, 114.5, 108.7, 83.0, 79.0, 57.7, 53.0, 52.5, 47.7, 32.9; FT-IR (KBr) 2922, 2851, 1737, 1454, 1247, 1129, 747 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{27}H_{25}NNaO_5$: 466.1625, found: 466.1608.

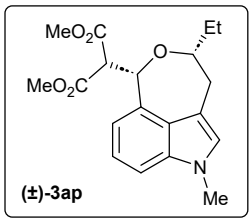


Dimethyl 2-(4-(furan-2-yl)-6-methyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)**-3an**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.41; yellow sticky liquid; yield 60% (46 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.35 (m, 1H), 7.23-7.21 (m, 1H), 7.17-7.13 (m, 1H), 6.765-6.761 (m, 1H), 6.75-6.73 (m, 1H), 6.34-6.33 (m, 1H), 6.17 (d, J = 3.2 Hz, 1H), 5.60 (d, J = 5.6 Hz, 1H), 4.70-4.66 (m, 1H), 4.52-4.48 (m, 1H), 4.38 (d, J = 5.6 Hz, 1H), 3.96 (t, J = 11.6 Hz, 1H), 3.83 (s, 3H), 3.72 (s, 3H), 3.64 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 167.5, 154.9, 141.7, 137.7, 134.5, 127.8, 124.5, 121.4, 115.0, 114.5, 110.1, 108.8, 106.4, 82.8, 76.4, 57.7, 53.0, 52.5, 40.7, 33.0; FT-IR (KBr) 2922, 2851, 1736, 1456, 1155, 745 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{21}H_{21}NNaO_6$: 406.1261, found: 406.1269.

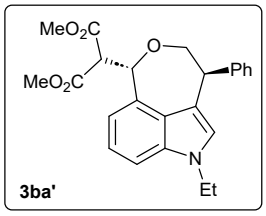


Dimethyl 2-(3,6-dimethyl-4-phenyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)**-3ao**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.57; yellow sticky liquid; yield 68% (55 mg); mixture of diastereomers (dr = 3.8:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.29 (m, 2.89H), 7.21-7.19 (m, 3.81H), 7.17-7.13 (m, 3.15H), 6.78 (s, 1H), 6.75 (d, J = 7.2 Hz, 1H),

6.70 (d, *J* = 7.2 Hz, 0.27H), 6.31 (s, 0.26H), 5.67 (d, *J* = 5.2 Hz, 1H), 4.44-4.40 (m, 1H), 4.38 (d, *J* = 5.2 Hz, 1H), 4.35 (d, *J* = 6.8 Hz, 0.32H), 4.21-4.20 (m, 1H), 4.069-4.062 (m, 0.35H), 3.87 (s, 0.79H), 3.81 (s, 3H), 3.68 (s, 0.80H), 3.67 (s, 3H), 3.64 (s, 0.80H), 3.62 (s, 3H), 1.07-1.06 (m, 3.84H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.9, 168.7, 167.7, 167.6, 144.0, 143.7, 137.4, 137.3, 135.4, 135.3, 130.0, 129.2, 129.1, 128.5, 128.0, 127.6, 126.7, 126.0, 125.6, 125.1, 121.3, 121.1, 119.5, 118.6, 114.3, 114.0, 108.5, 108.4, 84.9, 82.1, 81.3, 58.3, 58.2, 54.0, 52.9, 52.7, 52.4, 52.3, 51.1, 32.8, 20.4, 20.2; FT-IR (KBr) 2951, 1732, 1453, 1434, 1320, 1245, 1155, 741, 703 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{24}H_{25}NNaO_5$: 430.1625, found: 430.1610.

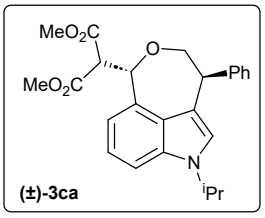


Dimethyl 2-(3-ethyl-6-methyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)-**3ap**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.66; brown sticky liquid; yield 51% (35 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.4 Hz, 1H), 7.10 (t, *J* = 7.2 Hz, 1H), 6.85 (s, 1H), 6.65 (d, *J* = 7.2 Hz, 1H), 5.61 (d, *J* = 6.8 Hz, 1H), 4.29 (d, *J* = 6.8 Hz, 1H), 3.84 (s, 3H), 3.82-3.75 (m, 1H), 3.73 (s, 3H), 3.64 (s, 3H), 3.13-3.08 (m, 1H), 2.98-2.91 (m, 1H), 1.77-1.66 (m, 1H), 1.65-1.58 (m, 1H), 0.97 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7, 167.6, 137.6, 135.6, 126.2, 125.8, 121.3, 113.9, 113.0, 108.4, 84.7, 80.7, 58.3, 52.9, 52.4, 33.5, 32.8, 29.6, 10.3; FT-IR (KBr) 2950, 2922, 1738, 1455, 1434, 1321, 1155, 1065, 744 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{19}H_{23}NNaO_5$: 368.1468, found: 368.1459.

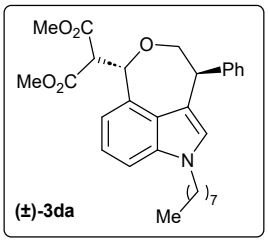


Dimethyl 2-((1*S*,4*S*)-6-ethyl-4-phenyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate 3ba′. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.46; yellow sticky liquid; yield 74% (60 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.26 (m, 6H), 7.15 (t, *J* = 7.6 Hz,

1H), 6.75 (d, J = 7.2 Hz, 1H), 6.54-6.53 (m, 1H), 5.61 (d, J = 6 Hz, 1H), 4.52-4.48 (m, 1H), 4.41-4.36 (m, 2H), 4.09-4.03 (m, 2H), 3.89-3.83 (m, 4H), 3.65 (s, 3H), 1.36 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 167.5, 142.2, 136.6, 134.9, 129.0, 128.6, 126.9, 126.8, 125.3, 121.1, 118.5, 114.3, 108.8, 83.0, 79.2, 57.6, 53.0, 52.5, 47.8, 41.0, 15.5; FT-IR (KBr) 2951, 2873, 1736, 1435, 1155, 747, 702 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{24}H_{25}NNaO_5$: 430.1625, found: 430.1631; $[\alpha]_D^{25}$ = +20 (c = 0.02, $CHCl_3$); HPLC: *ee* for major diastereomer = 98% *ee* [CHIRALPAK AD-H, hexane/^{i}PrOH = 80:20, flow rate: 1 mL/min, λ= 254 nm, t_R = 6.53 min (major), 7.68 min (minor)].

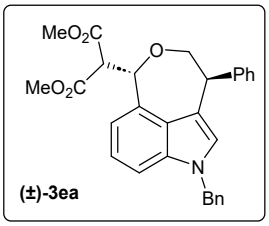


Dimethyl 2-(6-isopropyl-4-phenyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)**-3ca**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.48; yellow sticky liquid; yield 78% (65 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.26 (m, 6H), 7.14 (t, J = 7.6 Hz, 1H), 6.75 (d, J = 7.6 Hz, 1H), 6.64-6.63 (m, 1H), 5.60 (d, J = 5.6 Hz, 1H), 4.65-4.58 (m, 1H), 4.53-4.48 (m, 1H), 4.40-4.34 (m, 2H), 3.87-3.81 (m, 4H), 3.66 (s, 3H), 1.44 (d, J = 6.8 Hz, 3H), 1.39 (d, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 167.6, 142.2, 136.5, 134.9, 129.0, 128.6, 126.9, 125.3, 123.4, 120.9, 118.4, 114.4, 108.9, 83.0, 79.4, 57.6, 53.0, 52.5, 47.9, 47.0, 22.86, 22.82; FT-IR (KBr) 2925, 2853, 1737, 1434, 1192, 1129, 746, 701 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{25}H_{27}NNaO_5$: 444.1781, found: 444.1782.

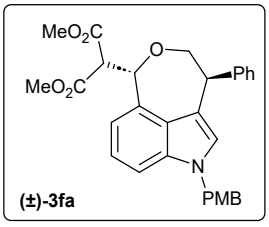


Dimethyl 2-(6-octyl-4-phenyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)**-3da**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.52; yellow sticky liquid; yield

81% (79 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.26 (m, 5H), 7.24 (s, 1H), 7.14 (t, *J* = 7.6 Hz, 1H), 6.74 (d, *J* = 7.6 Hz, 1H), 6.517-6.513 (m, 1H), 5.60 (d, *J* = 5.6 Hz, 1H), 4.53-4.48 (m, 1H), 4.40-4.35 (m, 2H), 3.98 (t, *J* = 7.2 Hz, 2H), 3.88-3.83 (m, 4H), 3.65 (s, 3H), 1.25-1.22 (m, 12H), 0.86 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 167.5, 142.2, 136.8, 134.8, 129.0, 128.5, 127.6, 126.9, 125.2, 121.0, 118.2, 114.3, 108.9, 83.0, 79.3, 57.7, 53.0, 52.5, 47.7, 46.5, 31.8, 30.2, 29.29, 29.27, 27.1, 22.7, 14.2; FT-IR (KBr) 2927, 2855, 1738, 1435, 1258, 1125, 747, 701 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{30}H_{37}NNaO_5$: 514.2564, found: 514.2548.

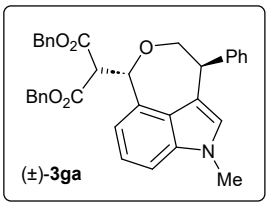


Dimethyl 2-(6-benzyl-4-phenyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)-**3ea**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.49; brown sticky liquid; yield 68% (63 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.26 (m, 6H), 7.24-7.22 (m, 2H), 7.19-7.17 (m, 1H), 7.09 (t, *J* = 7.6 Hz, 1H), 7.04-7.02 (m, 2H), 6.75 (d, *J* = 7.2 Hz, 1H), 6.599-6.595 (m, 1H), 5.62 (d, *J* = 5.6 Hz, 1H), 5.26-5.16 (m, 2H), 4.55-4.51 (m, 1H), 4.41-4.37 (m, 2H), 3.88 (t, *J* = 12 Hz, 1H), 3.83 (s, 3H), 3.66 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 167.5, 142.1, 137.5, 137.2, 134.9, 128.9, 128.8, 128.6, 128.1, 127.6, 127.0, 126.6, 125.5, 121.5, 119.1, 114.7, 109.3, 82.9, 79.2, 57.7, 53.0, 52.5, 50.2, 47.7; FT-IR (KBr) 2923, 2852, 1737, 1434, 1160, 735, 700 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{29}H_{28}NO_5$: 470.1962, found: 470.1948.

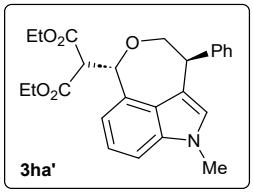


Dimethyl 2-(6-(4-methoxybenzyl)-4-phenyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)**-3fa**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.46; yellow sticky liquid; yield 58% (57 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.26 (m, 5H), 7.20 (d, *J* =

8.4 Hz, 1H), 7.09 (t, *J* = 7.6 Hz, 1H), 7.00 (d, *J* = 8.8 Hz, 2H), 6.80 (d, *J* = 8.8 Hz, 2H), 6.74 (d, *J* = 7.6 Hz, 1H), 6.58-6.57 (m, 1H), 5.61 (d, *J* = 6 Hz, 1H), 5.19-5.09 (m, 2H), 4.54-4.50 (m, 1H), 4.40-4.36 (m, 2H), 3.90-3.86 (m, 1H), 3.83 (s, 3H), 3.75 (s, 3H), 3.66 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 167.5, 159.1, 142.1, 137.1, 134.9, 129.5, 128.9, 128.6, 128.09, 128.04, 127.0, 125.5, 121.4, 118.9, 114.6, 114.2, 109.3, 82.9, 79.2, 57.7, 55.4, 53.0, 52.5, 49.7, 47.7; FT-IR (KBr) 2926, 1736, 1513, 1434, 1248, 1175, 1031, 702 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{30}H_{29}NNaO_6$: 522.1887, found: 522.1889.

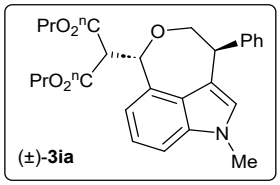


Dibenzyl 2-(6-methyl-4-phenyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)-3ga. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.61; yellow sticky liquid; yield 68% (74 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.32 (m, 7H), 7.30-7.29 (m, 1H), 7.27-7.26 (m, 2H), 7.25-7.19 (m, 4H), 7.13-7.12 (m, 1H), 7.10-7.08 (m, 2H), 6.77 (d, *J* = 5.2 Hz, 1H), 6.477-6.474 (m, 1H), 5.68 (d, *J* = 3.6 Hz, 1H), 5.36-5.34 (m, 1H), 5.24-5.22 (m, 1H), 5.12-5.10 (m, 1H), 5.07-5.04 (m, 1H), 4.50 (d, *J* = 3.6 Hz, 1H), 4.48-4.45 (m, 1H), 4.26 (dd, *J* = 8, 3.2 Hz, 1H), 3.84 (t, *J* = 7.6 Hz, 1H), 3.70 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.9, 166.8, 142.3, 137.6, 135.7, 135.6, 134.9, 128.9, 128.68, 128.60, 128.47, 128.44, 128.42, 128.3, 128.1, 127.9, 126.9, 125.2, 121.3, 118.6, 114.7, 108.6, 82.6, 78.6, 67.5, 66.9, 58.1, 47.7, 32.9; FT-IR (KBr) 2925, 1733, 1454, 1122, 739, 698 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{35}H_{31}NNaO_5$: 568.2094, found: 568.2107.

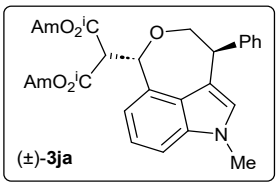


Diethyl 2-((1*S*,4*S*)-6-methyl-4-phenyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate 3ha′. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.58; yellow sticky

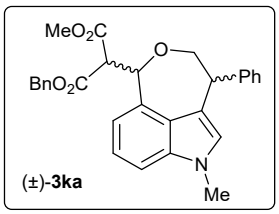
liquid; yield 63% (53 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.27 (m, 5H), 7.23 (d, *J* = 8.0 Hz, 1H), 7.16 (t, *J* = 7.5 Hz, 1H), 6.78 (d, *J* = 7.5 Hz, 1H), 6.46 (s, 1H), 5.61 (d, *J* = 5.5 Hz, 1H), 4.53-4.49 (m, 1H), 4.39-4.32 (m, 3H), 4.28-4.22 (m, 1H), 4.19-4.12 (m, 1H), 4.11-4.05 (m, 1H), 3.87 (t, *J* = 11.5 Hz, 1H), 3.67 (s, 3H), 1.30 (t, *J* = 7.0 Hz, 3H), 1.08 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.2, 167.0, 142.3, 137.6, 135.2, 129.0, 128.6, 128.5, 126.9, 125.2, 121.2, 118.6, 114.5, 108.6, 82.9, 79.0, 61.8, 61.2, 58.0, 47.7, 32.9, 14.2, 14.1; FT-IR (KBr) 2925, 1732, 1454, 1300, 1155, 1123, 1095, 743, 702 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{25}H_{27}NNaO_5$: 444.1781, found: 444.1781; $[\alpha]_D^{25}$ = -20 (c = 0.01, $CHCl_3$); HPLC: *ee* for major diastereomer = 97% *ee* [CHIRALPAK AD-H, hexane/^{i}PrOH = 80:20, flow rate: 1 mL/min, λ= 254 nm, t_R = 7.78 min (major), 8.82 min (minor)].



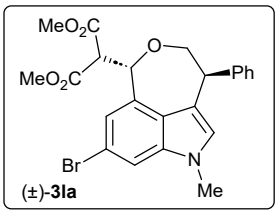
Dipropyl 2-(6-methyl-4-phenyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)-**3ia**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.60; yellow sticky liquid; yield 61% (54 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.26 (m, 5H), 7.23-7.21 (m, 1H), 7.15 (t, *J* = 7.2 Hz, 1H), 6.79 (d, *J* = 7.2 Hz, 1H), 6.46-6.45 (m, 1H), 5.62 (d, *J* = 5.6 Hz, 1H), 4.52-4.48 (m, 1H), 4.37-4.34 (m, 2H), 4.28-4.22 (m, 1H), 4.19-4.13 (m, 1H), 4.07-3.96 (m, 2H), 3.87 (t, *J* = 11.6 Hz, 1H), 3.67 (s, 3H), 1.74-1.65 (m, 2H), 1.52-1.45 (m, 2H) 0.95 (t, *J* = 7.2 Hz, 3H), 0.76 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 167.1, 142.3, 137.6, 135.2, 129.0, 128.6, 128.4, 126.9, 125.2, 121.2, 118.6, 114.5, 108.5, 82.8, 79.0, 67.4, 66.8, 58.1, 47.7, 32.9, 22.0, 21.9, 10.4, 10.3; FT-IR (KBr) 2929, 2878, 1733, 1455, 1299, 1123, 744, 701 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{27}H_{31}NNaO_5$: 472.2094, found: 472.2092.



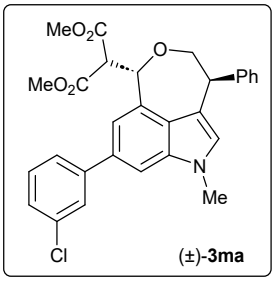
Diisopentyl 2-(6-methyl-4-phenyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)**-3ja**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.64; yellow sticky liquid; yield 49% (40 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.27 (m, 5H), 7.22 (d, *J* = 8 Hz, 1H), 7.15 (t, *J* = 7.2 Hz, 1H), 6.79-6.77 (m, 1H), 6.45 (s, 1H), 5.61-5.60 (m, 1H), 4.51-4.47 (m, 1H), 4.38-4.19 (m, 4H), 4.11-4.00 (m, 2H), 3.86 (t, *J* = 11.6 Hz, 1H), 3.67 (s, 3H), 1.77-1.65 (m, 1H), 1.42-1.28 (m, 5H), 0.92-0.90 (m, 6H), 0.76-0.74 (m, 3H), 0.70-0.68 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 167.2, 142.3, 137.6, 135.1, 128.9, 128.6, 128.4, 126.9, 125.1, 121.2, 118.6, 114.5, 108.5, 82.7, 78.8, 64.5, 63.7, 58.1, 47.7, 37.2, 37.1, 32.9, 25.0, 24.5, 22.6, 22.5, 22.4, 22.2; FT-IR (KBr) 2956, 2925, 2868, 1734, 1454, 1156, 1121, 746, 701 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{31}H_{40}NO_5$: 506.2901, found: 506.2908.



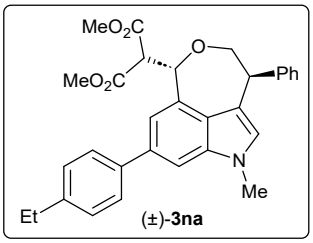
1-Benzyl 3-methyl 2-(6-methyl-4-phenyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)**-3ka**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.55; brown sticky liquid; yield 56% (52 mg); mixture of diastereomers (dr = 3:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.27 (m, 10.34H), 7.24-7.17 (m, 6.86H), 7.15-7.11 (m, 1.76H), 7.08-7.06 (m, 1.69H), 6.78 (d, *J* = 7.6 Hz, 0.72H), 6.72 (d, *J* = 7.2 Hz, 0.70H), 6.46 (s, 1.38H), 5.64 (dd, *J* = 10.8, 5.2 Hz, 1.63H), 5.35-5.32 (m, 0.72H), 5.24-5.20 (m, 0.70H), 5.12-5.03 (m, 2H), 4.51-4.41 (m, 3.39H), 4.33-4.28 (m, 1.70H), 3.88-3.82 (m, 1.71H), 3.81 (s, 3H), 3.68 (s, 2.12H), 3.67 (s, 2.13H), 3.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 167.9, 167.4, 166.9, 142.2, 142.1, 137.59, 137.54, 135.6, 135.4, 134.8, 128.97, 128.95, 128.68, 128.60, 128.5, 128.4, 128.3, 128.1, 127.9, 126.99, 126.97, 125.1, 125.0, 121.3, 121.2, 118.5, 118.4, 114.56, 114.50, 108.69, 108.65, 82.8, 82.7, 79.0, 78.8, 67.5, 66.9, 57.89, 57.83, 52.9, 52.5, 47.68, 47.64, 32.9, 29.8; FT-IR (KBr) 2923, 2853, 1734, 1454, 1300, 1153, 742, 700 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{29}H_{27}NNaO_5$: 492.1781, found: 492.1765.



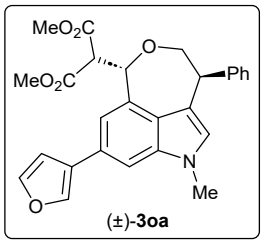
Dimethyl 2-(8-bromo-6-methyl-4-phenyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)**-3la**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.48; brown sticky liquid; yield 66% (62 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (s, 1H), 7.34-7.26 (m, 3H), 7.25-7.23 (m, 2H), 6.87-6.86 (m, 1H), 6.448-6.444 (m, 1H), 5.57 (d, *J* = 5.6 Hz, 1H), 4.50-4.45 (m, 1H), 4.38-4.32 (m, 2H), 3.87-3.84 (m, 4H), 3.67 (s, 3H), 3.64 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 167.1, 141.7, 138.3, 136.4, 129.1, 128.8, 128.6, 127.1, 124.1, 118.9, 117.8, 114.6, 111.7, 82.2, 78.8, 57.4, 53.1, 52.6, 47.4, 33.0; FT-IR (KBr) 2950, 2865, 1733, 1454, 1434, 1243, 1128, 701 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{23}H_{22}BrNNaO_5$: 494.0574, found: 494.0557.



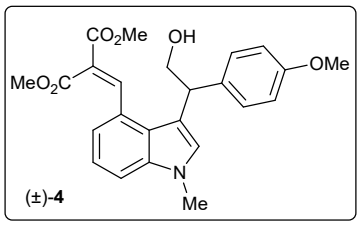
Dimethyl 2-(8-(3-chlorophenyl)-6-methyl-4-phenyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)**-3ma**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.51; yellow sticky liquid; yield 63% (63 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.49-7.48 (m, 1H), 7.39-7.29 (m, 9H), 6.98 (s, 1H), 6.52 (s, 1H), 5.67-5.65 (m, 1H), 4.53-4.51 (m, 1H), 4.47-4.46 (m, 1H), 4.42-4.40 (m, 1H), 3.89 (t, *J* = 12 Hz, 1H), 3.84 (s, 3H), 3.73 (s, 3H), 3.67 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 167.5, 144.1, 141.9, 138.0, 135.3, 134.7, 133.3, 130.1, 129.5, 128.9, 128.6, 127.4, 127.1, 126.8, 125.5, 124.9, 118.6, 114.2, 107.3, 82.9, 79.1, 57.6, 53.0, 52.6, 47.5, 33.0; FT-IR (KBr) 2950, 1733, 1593, 1456, 1245, 1128, 786, 700 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{29}H_{26}ClNNaO_5$: 526.1392, found: 526.1368.



Dimethyl 2-(8-(4-ethylphenyl)-6-methyl-4-phenyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)**-3na**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.53; yellow sticky liquid; yield 71% (70 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.4 Hz, 2H), 7.40 (s, 1H), 7.35-7.27 (m, 7H), 7.02 (s, 1H), 6.499-6.495 (m, 1H), 5.67 (d, *J* = 5.6 Hz, 1H), 4.55-4.51 (m, 1H), 4.48 (d, *J* = 5.6 Hz, 1H), 4.42 (dd, *J* = 11.6, 4.8 Hz, 1H), 3.90 (t, *J* = 11.6 Hz, 1H), 3.84 (s, 3H), 3.71 (s, 3H), 3.66 (s, 3H), 2.74 (q, *J* = 7.6 Hz, 2H), 1.30 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 167.5, 143.0, 142.1, 139.6, 138.1, 135.0, 134.9, 129.0, 128.9, 128.6, 128.4, 127.3, 127.0, 124.3, 118.5, 114.4, 107.1, 83.0, 79.1, 57.7, 53.0, 52.5, 47.6, 32.9, 28.6, 15.7; FT-IR (KBr) 2928, 2870, 1735, 1455, 1245, 1127, 828, 702 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{31}H_{31}NNaO_5$: 520.2094, found: 520.2088.

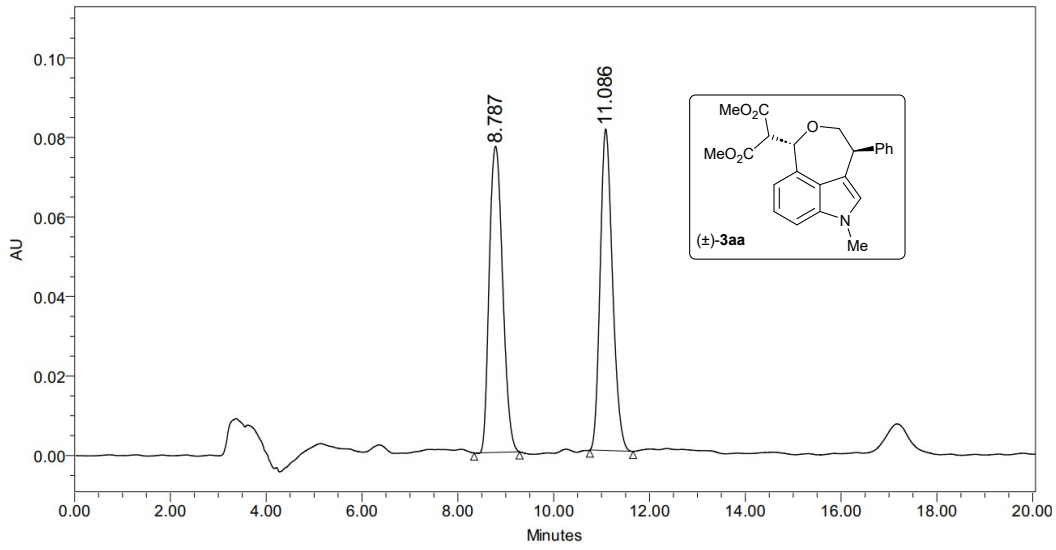


Dimethyl 2-(8-(furan-3-yl)-6-methyl-4-phenyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)**-3oa**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.43; yellow sticky liquid; yield 55% (50 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71-7.70 (m, 1H), 7.49-7.48 (m, 1H), 7.33-7.28 (m, 6H), 6.92-6.91 (m, 1H), 6.72-6.71 (m, 1H), 6.47-6.46 (m, 1H), 5.62 (d, *J* = 5.5 Hz, 1H), 4.52-4.48 (m, 1H), 4.44-4.42 (m, 1H), 4.40-4.37 (m, 1H), 3.88 (t, *J* = 11.5 Hz, 1H), 3.83 (s, 3H), 3.70 (s, 3H), 3.65 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 167.5, 143.7, 142.0, 138.1, 138.0, 135.2, 128.9, 128.6, 127.4, 127.0, 125.8, 124.4, 118.7, 113.3, 109.3, 105.9, 82.8, 79.1, 57.7, 53.0, 52.6, 47.5, 33.0; FT-IR (KBr) 2923, 2854, 1737, 1452, 1435, 1159, 1131, 1021, 872, 702 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{25}NNaO_6$: 482.1574, found: 482.1580.



Dimethyl 2-((3-(2-hydroxy-1-(4-methoxyphenyl)ethyl)-1-methyl-1H-indol-4-yl)methylene)malonate (±)**-4**. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.30; brown sticky liquid; yield 85% (72 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.34 (d, *J* = 8.4 Hz, 1H), 7.22-7.18 (m, 3H), 7.14 (t, *J* = 7.6 Hz, 1H), 7.03 (d, *J* = 7.2 Hz, 1H), 6.85-6.83 (m, 2H), 4.53 (t, *J* = 6.4 Hz, 1H), 4.13-4.04 (m, 2H), 3.86 (s, 3H), 3.82 (s, 3H), 3.76 (s, 3H), 3.64 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.2, 164.5, 158.7, 144.0, 137.6, 133.6, 129.8, 128.3, 126.8, 126.3, 125.9, 121.7, 119.8, 115.1, 114.1, 111.5, 67.6, 55.3, 52.5, 52.4, 45.8, 33.1; FT-IR (KBr) 3395, 2930, 2851, 1736, 1609, 1509, 1455, 1301, 1248, 748 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{26}NO_6$: 424.1755, found: 424.1766.

HPLC chromatograms



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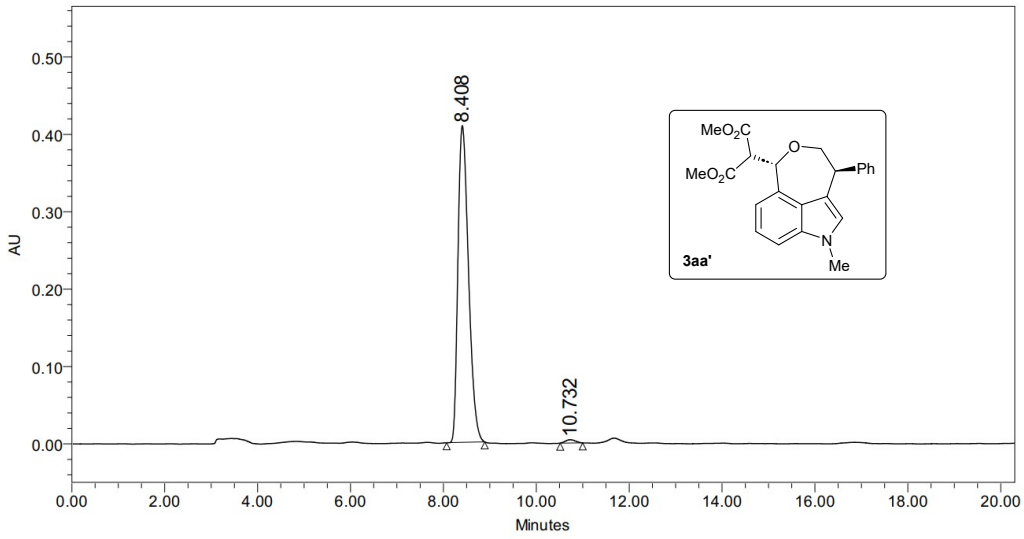

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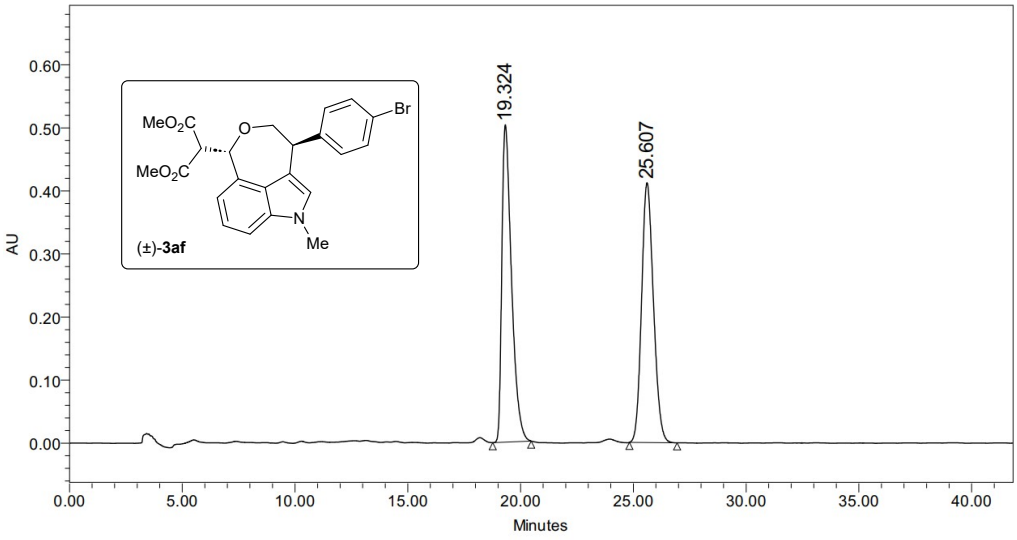

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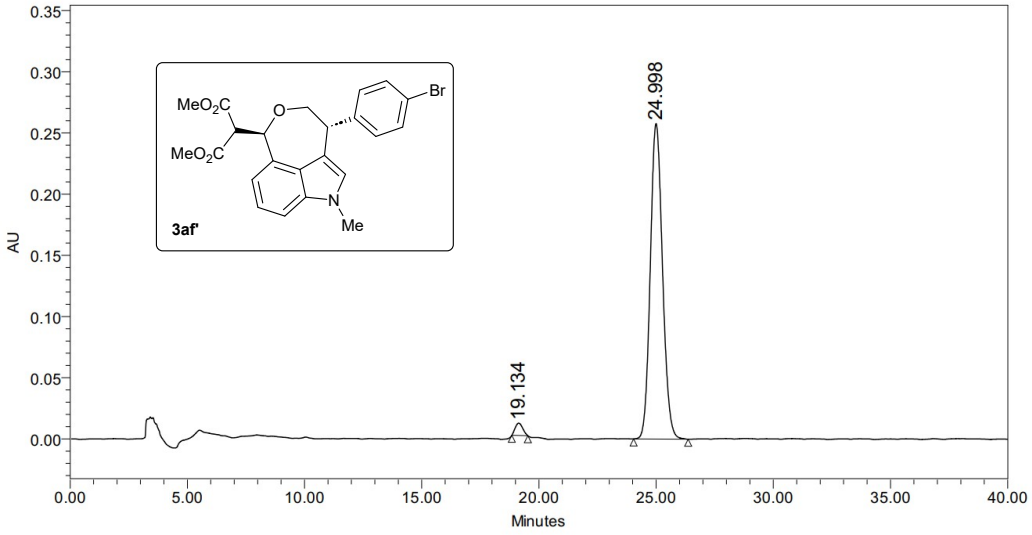

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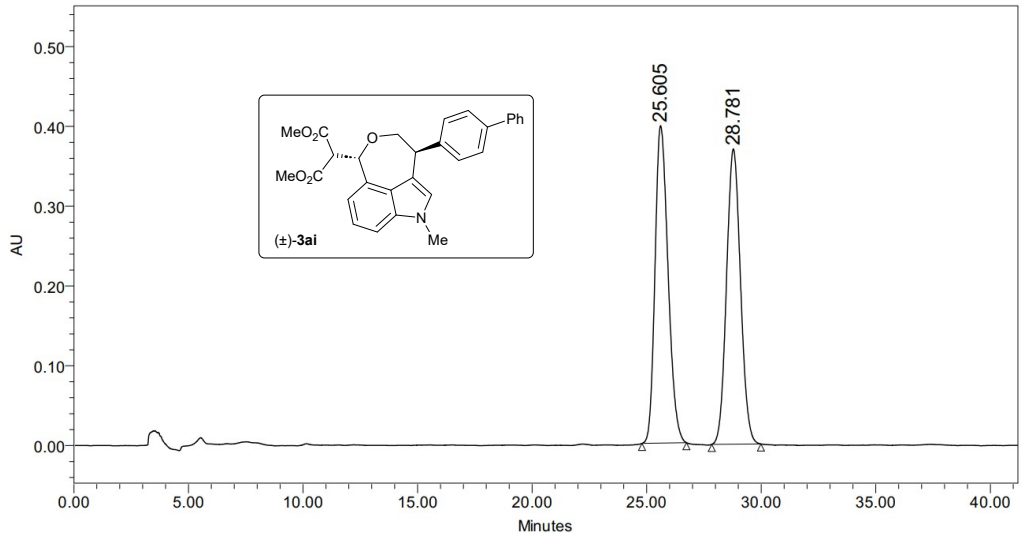

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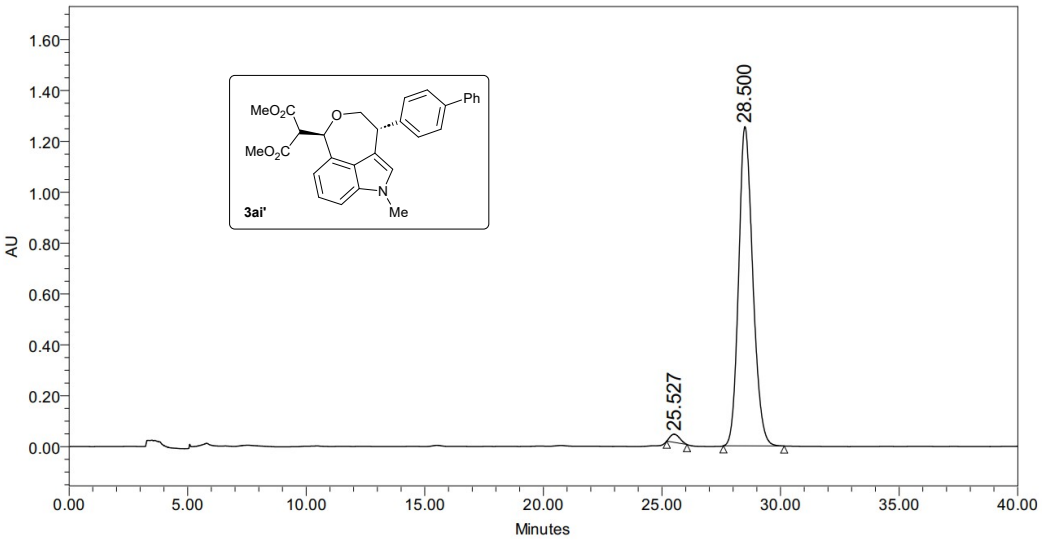

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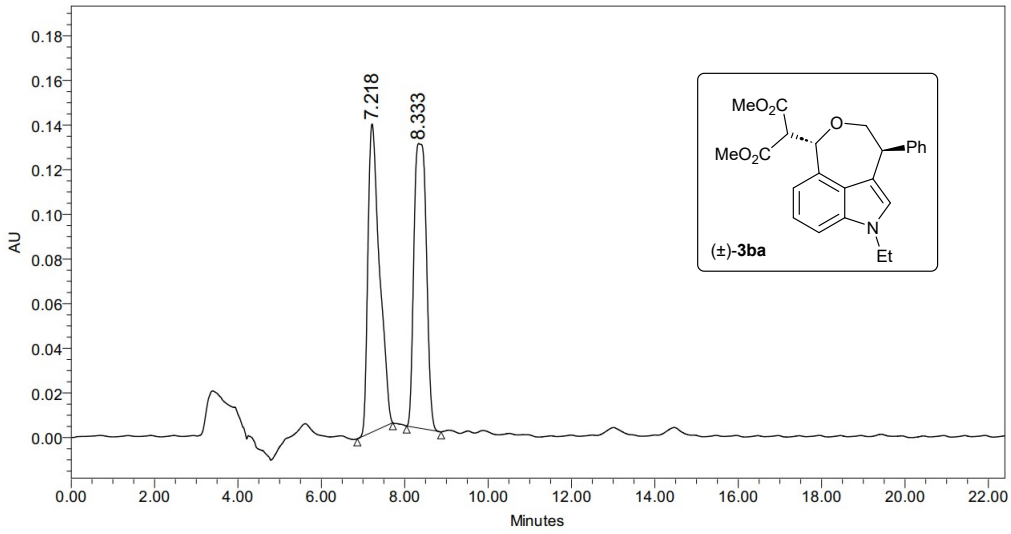
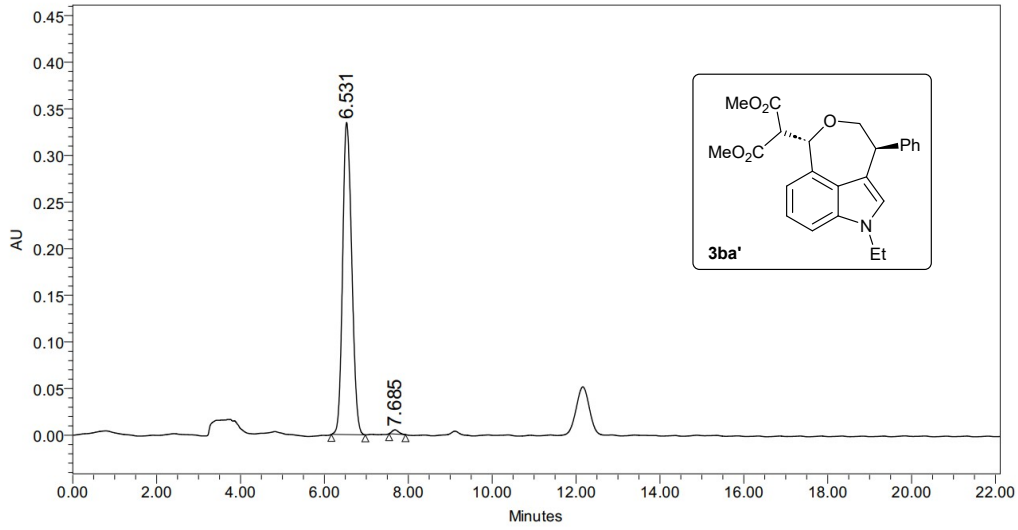
1	25.527	894491	1.68	31971
2	28.500	52196242	98.32	1255623



	RT	Area	% Area	Height
1	7.218	2663726	50.06	138058
2	8.333	2657424	49.94	127486



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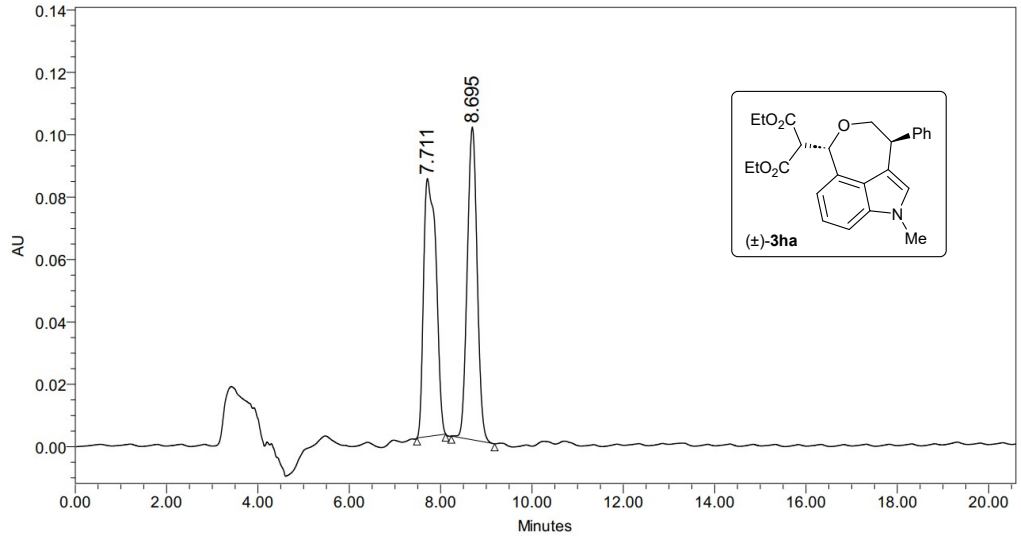
2	7.685	49120	0.96	4501



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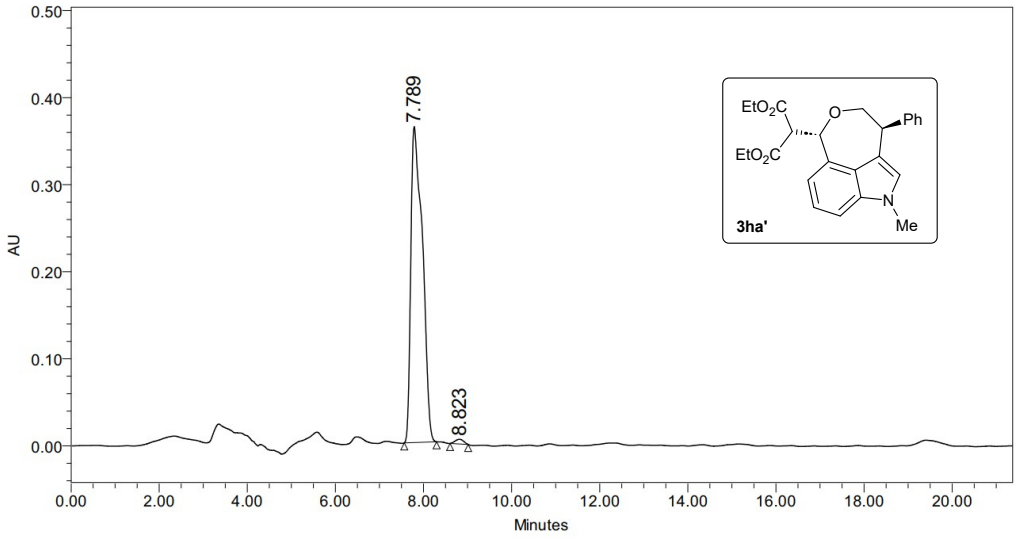
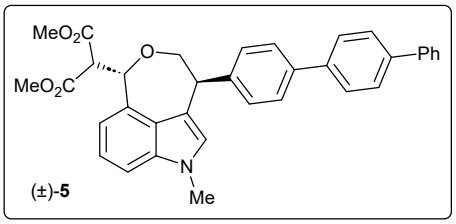
1	7.711	1562903	50.88	82705
2	8.695	1509014	49.12	100261



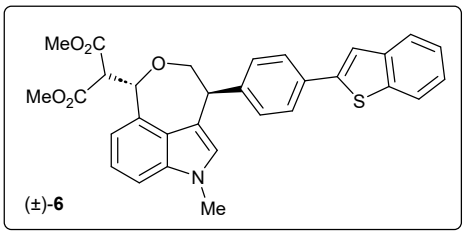
	RT	Area	% Area	Height
1	7.789	6621137	98.92	362813
2	8.823	72235	1.08	5396

Procedure for Scale-up Synthesis of (±)**-3af**. Indolyl malonate **1a** (2 mmol, 1 equiv, 546 mg), oxirane **2f** (2.4 mmol, 1.2 equiv, 475 mg), $Co(OAc)_2.4H_2O$ (0.2 mmol, 0.10 equiv, 36 mg) and and 4 Å molecular sieves (1 g) were stirred in CH_2Cl_2 (5 mL) at 50 °C for 4 h in a pre-heated oil bath under calcium chloride tube. Then, KO^{t}Bu (2 mmol, 1 equiv, 224 mg) was added and the resulting mixture was stirred at the same temperature for an additional 5 h. After completion, as monitored by TLC, the reaction mixture was allowed to cool to room temperature and diluted with CH_2Cl_2 (10 mL) and passed through a short pad of celite using CH_2Cl_2 (20 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using ethyl acetate and hexane as an eluent to afford (±)**-3af**.

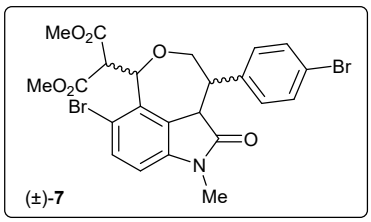


Dimethyl 2-(4-([1,1':4',1''-terphenyl]-4-yl)-6-methyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)**-5**.[3] To a solution of (±)**-3af** (0.1 mmol, 1 equiv, 47 mg) in toluene/EtOH (1:1, 3 mL), was added [1,1'-biphenyl]-4-ylboronic acid (0.1 mmol, 1 equiv, 19 mg), $Pd(PPh_3)_4$ (0.03 mmol, 0.03 equiv, 3 mg), Na_2CO_3 (0.1 mmol, 1 equiv, 11 mg) and H_2O (100 µL). The mixture was stirred at 100 °C for 12 h in a pre-heated oil bath under a nitrogen atmosphere. After 12 h, the reaction mixture was cooled to room temperature and diluted with ethyl acetate (10 mL) and washed with brine (1 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by silica gel column chromatography using hexane and ethyl acetate as eluent to give (±)**-5**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.45; brown sticky liquid; yield 85% (46 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (s, 4H), 7.66 (d, *J* = 6.8 Hz, 2H), 7.61 (d, *J* = 8 Hz, 2H), 7.46 (t, *J* = 7.2 Hz, 2H), 7.38-7.36 (m, 3H), 7.26-7.24 (m, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 6.79 (d, *J* = 7.2 Hz, 1H), 6.567-6.564 (m, 1H), 5.65 (d, *J* = 6 Hz, 1H), 4.59-4.55 (m, 1H), 4.46-4.42 (m, 2H), 3.92 (t, *J* = 11.6 Hz, 1H), 3.84 (s, 3H), 3.70 (s, 3H), 3.66 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 167.5, 141.3, 140.8, 140.1, 139.8, 139.3, 137.6, 134.8, 129.4, 128.9, 128.6, 127.6, 127.4, 127.2, 127.1, 125.1, 121.3, 118.4, 114.5, 108.7, 82.9, 79.0, 57.7, 53.0, 52.5,

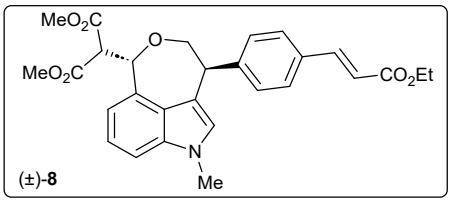
47.3, 32.9; FT-IR (KBr) 3028, 2949, 2867, 1734, 1483, 1243, 1155, 1126, 826, 765, 740 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{35}H_{31}NNaO_5$: 568.2094, found: 568.2082.



Dimethyl 2-(4-(4-(benzo[b]thiophen-2-yl)phenyl)-6-methyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)-**6**.[3] To a solution of (±)-**3af** (0.1 mmol, 1 equiv, 47 mg) in toluene/EtOH (1:1, 3 mL), was added the benzo[b]thiophen-2-ylboronic acid (0.1 mmol, 1 equiv, 17 mg), $Pd(PPh_3)_4$ (0.03 mmol, 0.03 equiv, 3 mg), Na_2CO_3 (0.1 mmol, 1 equiv, 11 mg) and H_2O (100 µL). The mixture was stirred at 100 °C for 12 h in a pre-heated oil bath under a nitrogen atmosphere. After 12 h, the reaction mixture was cooled to room temperature and diluted with ethyl acetate (10 mL) and washed with brine (1 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by silica gel column chromatography using hexane and ethyl acetate as eluent to give (±)-**6**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.38; brown sticky liquid; yield 62% (32 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84-7.82 (m, 1H), 7.78-7.76 (m, 1H), 7.68 (d, *J* = 8 Hz, 2H), 7.54 (s, 1H), 7.36-7.30 (m, 5H), 7.18 (t, *J* = 7.6 Hz, 1H), 6.79 (d, *J* = 7.2 Hz, 1H), 6.54-6.53 (m, 1H), 5.64 (d, *J* = 5.6 Hz, 1H), 4.57-4.53 (m, 1H), 4.43-4.39 (m, 2H), 3.93-3.86 (m, 1H), 3.84 (s, 3H), 3.70 (s, 3H), 3.65 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 167.5, 144.1, 142.4, 140.8, 139.5, 137.6, 134.8, 133.1, 129.5, 128.5, 126.7, 125.1, 124.6, 124.4, 123.6, 122.4, 121.4, 119.3, 118.1, 114.5, 108.8, 82.9, 78.8, 57.6, 53.0, 52.6, 47.4, 32.9; FT-IR (KBr) 2925, 2855, 1737, 1455, 1434, 1245, 1156, 746 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{31}H_{27}NNaO_5S$: 548.1502, found: 548.1476.

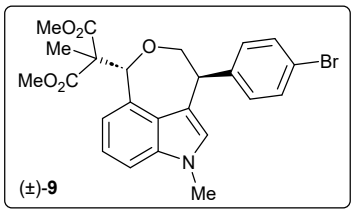


Dimethyl 2-(9-bromo-4-(4-bromophenyl)-6-methyl-5-oxo-1,3,4,4a,5,6-hexahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)**-7**.[4] To a solution of (±)**-3af** (0.1 mmol, 1 equiv, 47 mg) and KBr (0.1 mmol, 1 equiv, 12 mg) in ^{t}BuOH/H_2O (20:1) (2 mL) at room temperature, was added oxone (0.12 mmol, 1.2 equiv, 37 mg) and allowed to stir for 4 h under calcium chloride tube. After completion, as monitored by TLC, the reaction mixture was quenched with saturated aq. $Na_2S_2O_3$ (5 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with brine (5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by silica gel column chromatography using hexane and ethyl acetate as an eluent to afford (±)**-7**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.30; colorless solid; mp 154-155 ^{o}C; yield 55% (31 mg); mixture of diastereomers (dr = 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.4 Hz, 1H), 7.30 (t, *J* = 8 Hz, 0.49H), 7.24-7.20 (m, 2.63H), 6.86 (d, *J* = 8 Hz, 0.35H), 6.71 (d, *J* = 7.6 Hz, 0.34H), 6.63 (d, *J* = 8 Hz, 1H), 6.57-6.53 (m, 2.46H), 5.57-5.56 (m, 1H), 5.53-5.51 (m, 0.32H), 4.57 (d, *J* = 8.8 Hz, 1H), 4.43-4.38 (m, 1.67H), 4.34 (d, *J* = 2.4 Hz, 1H), 4.07-4.00 (m, 1.36H), 3.84 (s, 3H), 3.72-3.71 (m, 2H), 3.63 (s, 3H), 3.52-3.46 (m, 1.34H), 2.90 (s, 1H), 2.87 (s, 3H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.0, 175.7, 167.8, 167.2, 166.97, 166.91, 145.1, 144.4, 137.5, 137.0, 135.1, 134.1, 133.6, 131.6, 131.5, 129.88, 129.80, 129.1, 127.2, 124.5, 121.7, 121.5, 119.9, 113.4, 109.1, 107.6, 82.4, 82.1, 72.7, 72.4, 55.3, 55.1, 53.1, 52.9, 52.8, 52.7, 46.9, 46.6, 45.9, 45.7, 29.8, 26.0; FT-IR (KBr) 2955, 2881, 1715, 1602, 1437, 1354, 1146, 1009, 1071, 809 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{22}Br_2NO_6$: 565.9808, found: 565.9805.



Dimethyl (E)-2-(4-(4-(3-ethoxy-3-oxoprop-1-en-1-yl)phenyl)-6-methyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)malonate (±)**-8**.[5] To a solution of (±)**-3af** (0.1 mmol, 1 equiv, 47 mg) in CH_3CN (2 mL), was added ethyl acrylate (0.2 mmol, 2 equiv, 22 µL), Et_3N (0.5 mmol, 5 equiv, 70 µL), $Pd(OAc)_2$ (0.01 mmol, 0.1 equiv, 2.3 mg) and tri-*o*-tolylphosphine (0.02 mmol, 0.2 equiv, 6 mg). The resultant mixture was stirred at 90 °C for 6 h in a pre-heated oil bath

under nitrogen atmosphere. After completion, as monitored by TLC, the reaction mixture was cooled to room temperature, diluted with ethyl acetate (5 mL) and passed through a short pad of celite using ethyl acetate (5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by silica gel column chromatography using hexane and ethyl acetate as eluent to give (±)-**8**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.45; yellow sticky liquid; yield 68% (33 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 16 Hz, 1H), 7.49-7.47 (m, 2H), 7.30-7.28 (m, 2H), 7.25-7.15 (m, 2H), 6.78 (d, *J* = 7.2 Hz, 1H), 6.478-6.474 (m, 1H), 6.44 (d, *J* = 16 Hz, 1H), 5.62 (m, 1H), 4.55-4.51 (m, 1H), 4.40-4.35 (m, 2H), 4.29 (q, *J* = 7.2 Hz, 2H), 3.89-3.86 (m, 1H), 3.83 (s, 3H), 3.69 (s, 3H), 3.64 (s, 3H), 1.34 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 167.5, 167.2, 144.6, 144.4, 137.5, 134.7, 133.3, 129.5, 128.47, 128.41, 125.0, 121.4, 118.0, 117.9, 114.5, 108.8, 82.9, 78.7, 60.6, 57.6, 53.0, 52.6, 47.5, 32.9, 14.4; FT-IR (KBr) 2923, 2852, 1737, 1709, 1635, 1454, 1305, 1163, 1090, 1041, 743 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{28}H_{29}NNaO_7$: 514.1836, found: 541.1807.



Dimethyl 2-(4-(4-bromophenyl)-6-methyl-1,3,4,6-tetrahydrooxepino[5,4,3-cd]indol-1-yl)-2-methylmalonate (±)-**9**.[6] To a solution of NaH (60% dispersion in mineral oil, 0.15 mmol, 1.5 equiv, 6 mg) in THF (2 mL) at 0 °C was added a solution of (±)-**3af** (0.1 mmol, 1 equiv, 47 mg) in THF (3 mL) under nitrogen atmosphere. The resultant mixture was stirred at room temperature for 30 minutes. Then, MeI (0.2 mmol, 2 equiv, 28 mg) was added dropwise and the mixture was allowed to stir overnight at room temperature. After completion, as monitored by TLC, the reaction mixture was quenched with saturated aq. NH_4Cl (5 mL) and extracted with ethyl acetate (3 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by silica gel column chromatography using hexane and ethyl acetate as eluent to give (±)-**9**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.60; colorless sticky liquid; yield 91% (44 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.4 Hz, 2H), 7.24-7.23 (m, 1H), 7.16-7.13 (m, 3H), 6.67 (d, *J* = 7.8 Hz, 1H), 6.46 (s, 1H), 5.89 (s, 1H), 4.41-4.38 (m, 1H), 4.24 (dd, *J* = 11.4, 4.8 Hz, 1H), 3.86-3.82

(m, 4H), 3.78 (s, 3H), 3.68 (s, 3H), 1.49 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 170.4, 141.2, 137.7, 133.5, 131.7, 130.7, 128.6, 125.7, 121.2, 120.8, 118.0, 116.2, 108.5, 86.7, 78.6, 60.8, 53.1, 53.0, 47.1, 32.9, 14.6; FT-IR (KBr) 2925, 2855, 1736, 1455, 1299, 1155, 1010, 747 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{24}H_{24}BrNNaO_5$: 508.0730, found: 508.0725.

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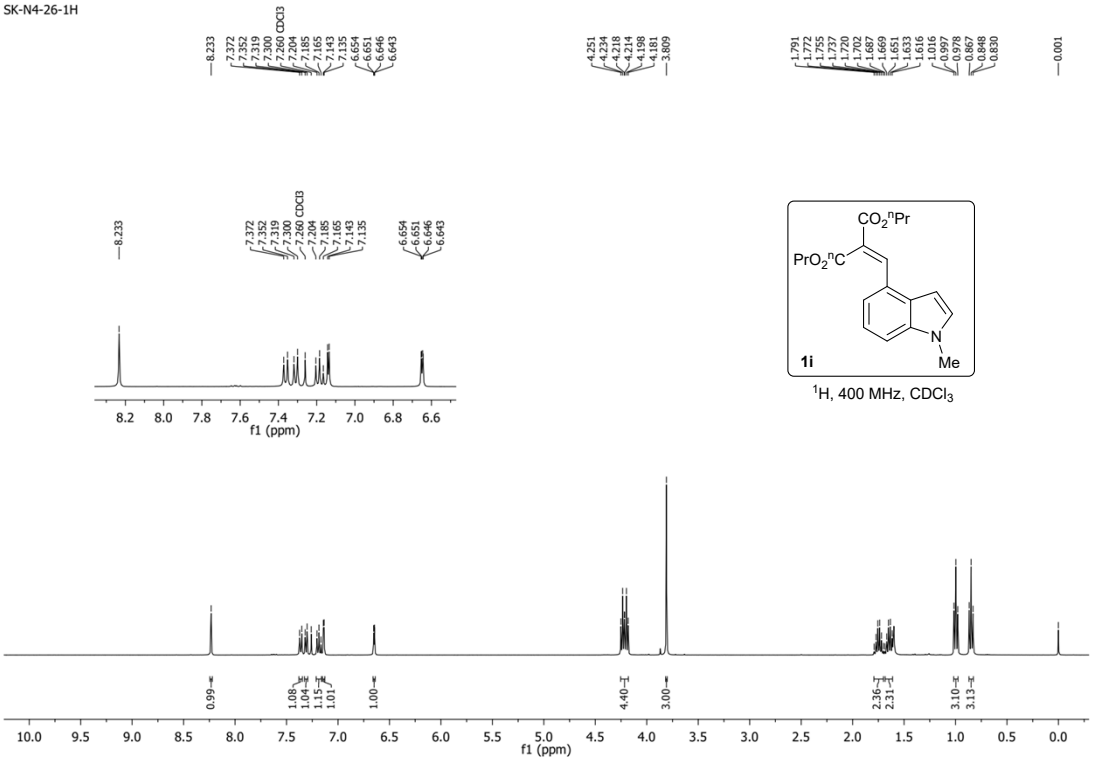
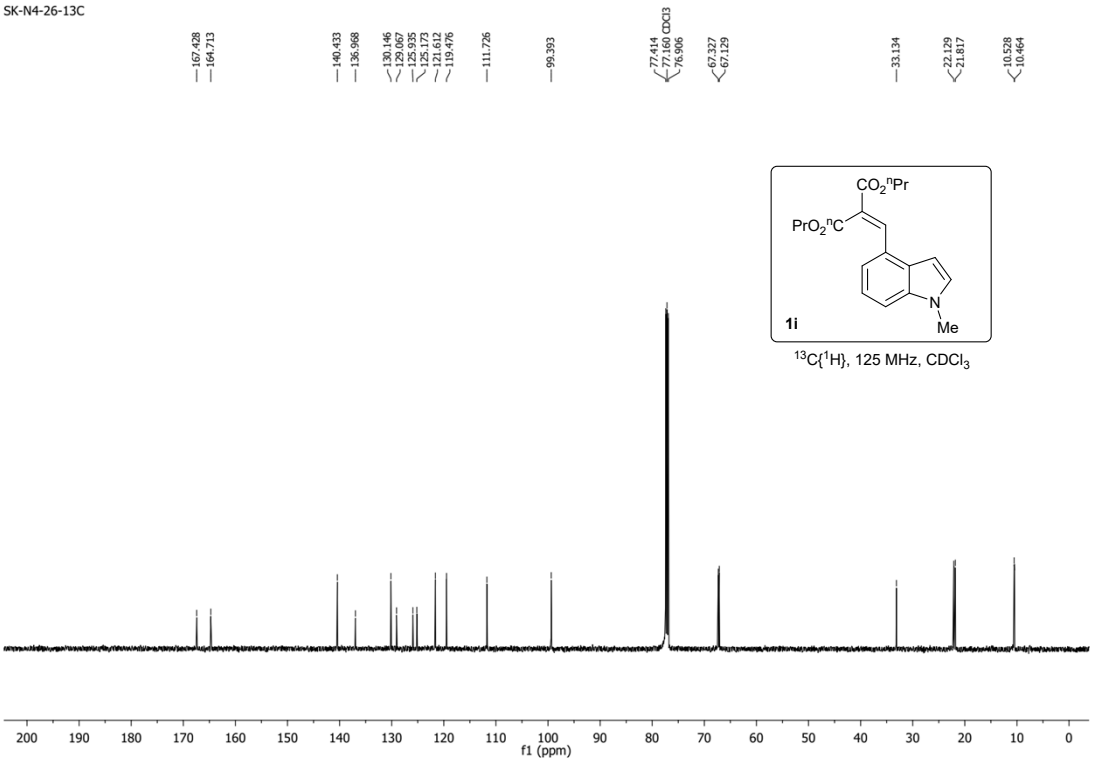
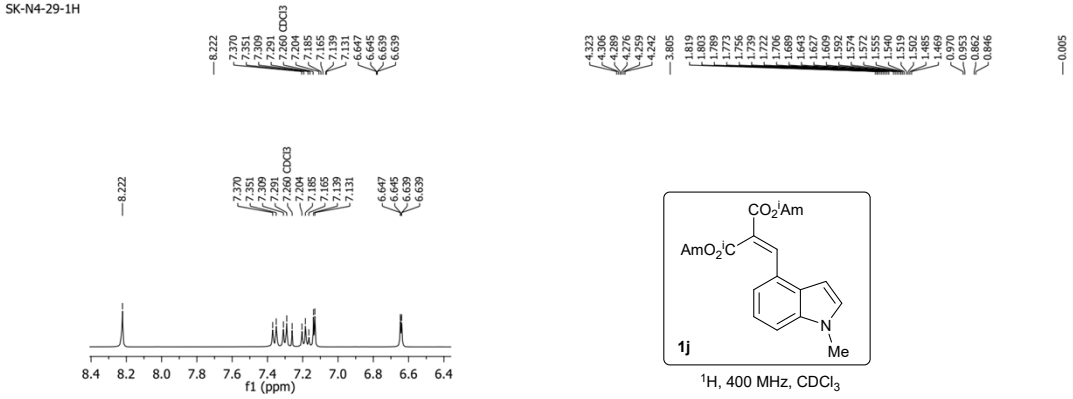
^{1}H ,^{13}C and ^{19}F NMR Spectra

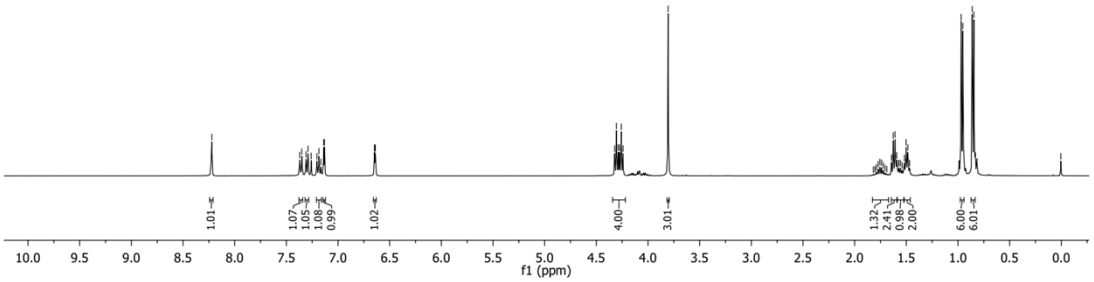




SK-N4-29-1H



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



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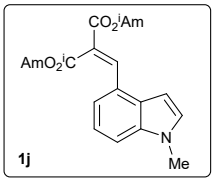
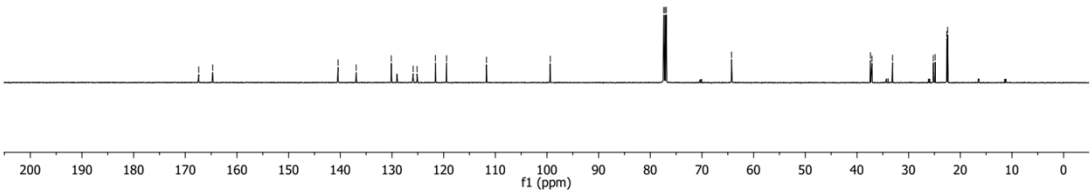


$^{13}C\{^{1}H\}$, 125 MHz, $CDCl_3$



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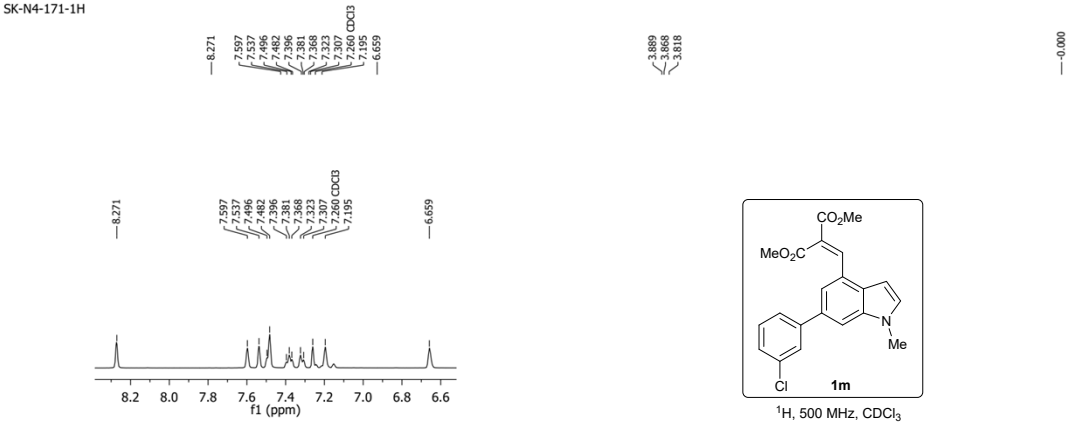
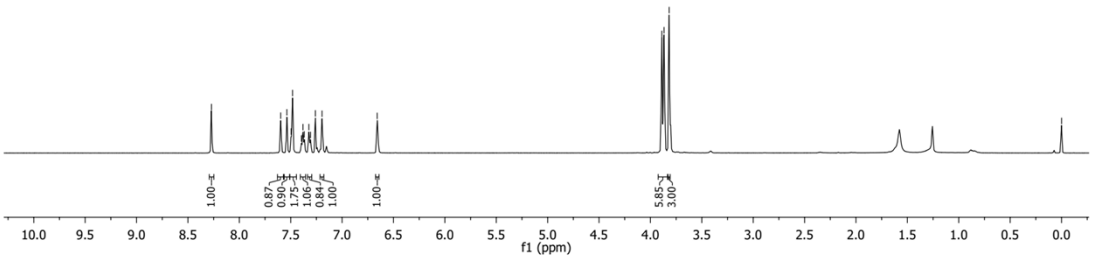


^{1}H, 500 MHz, $CDCl_3$



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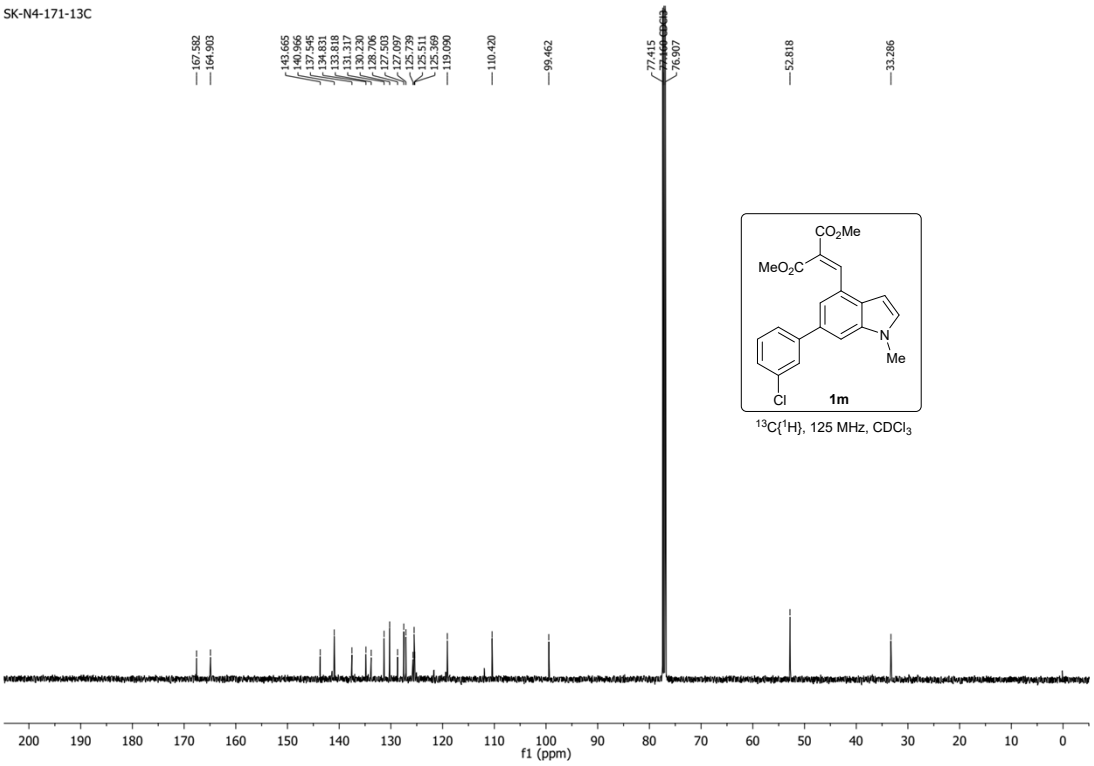
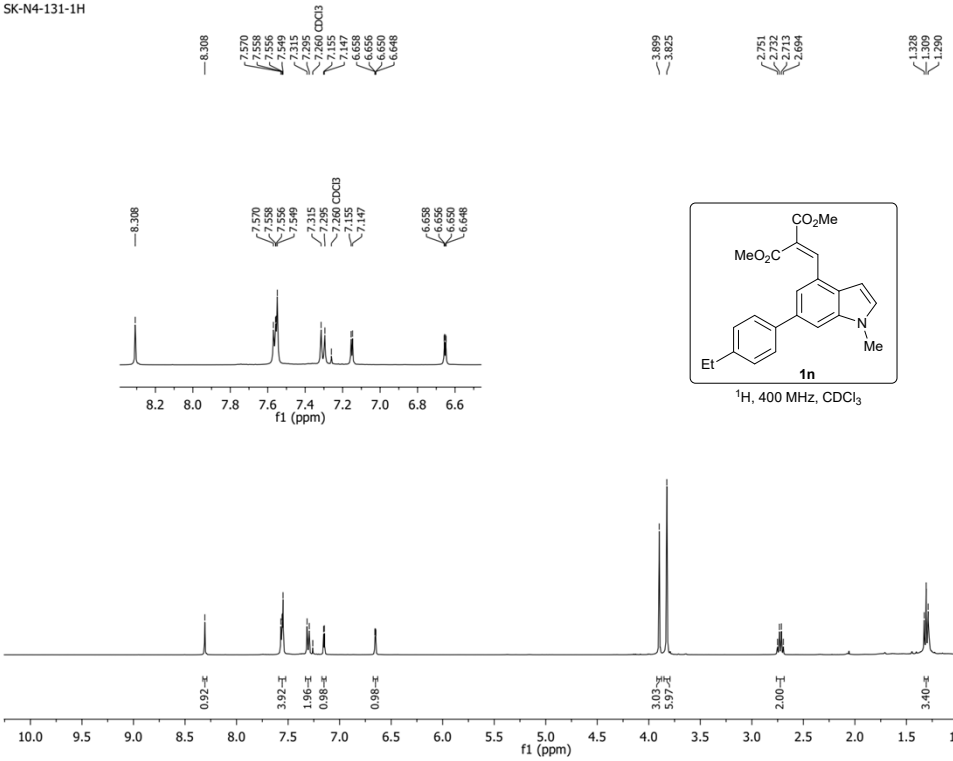


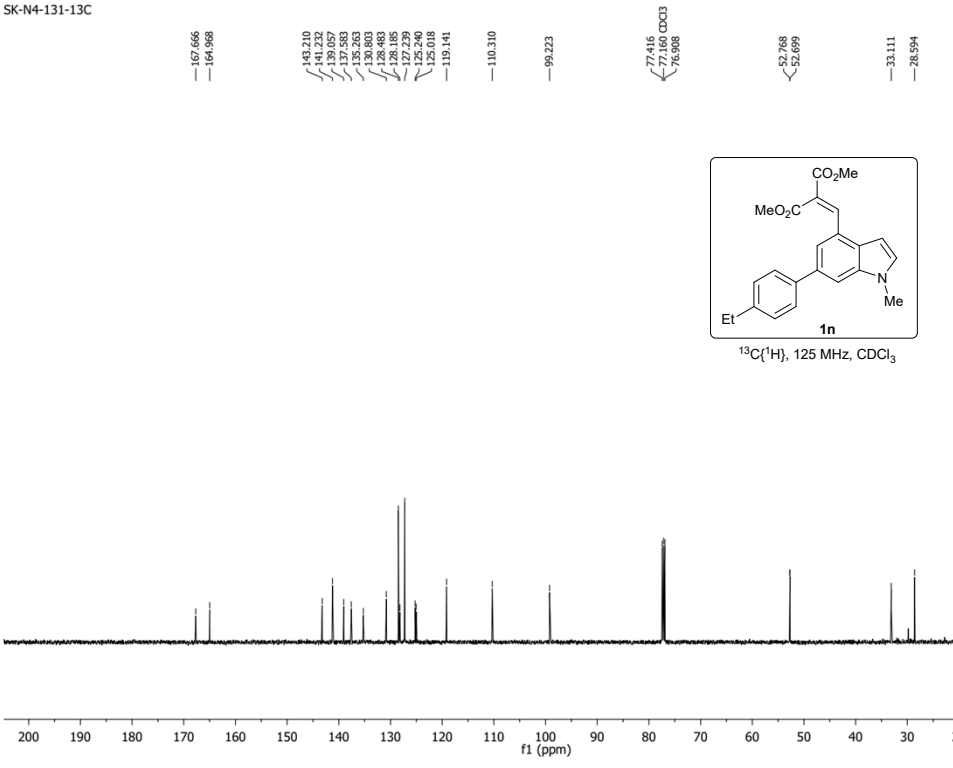
$^{13}C\{^{1}H\}$, 125 MHz, $CDCl_3$

SK-N4-131-1H



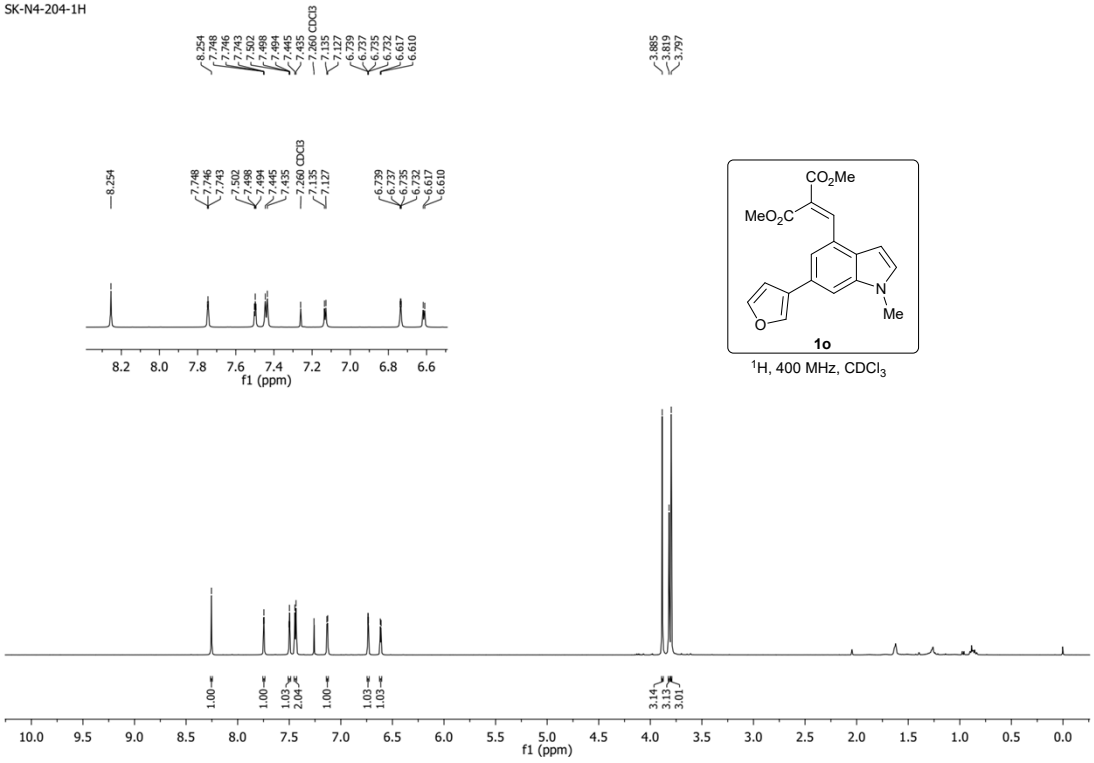
^{1}H, 400 MHz, $CDCl_3$

SK-N4-131-13C

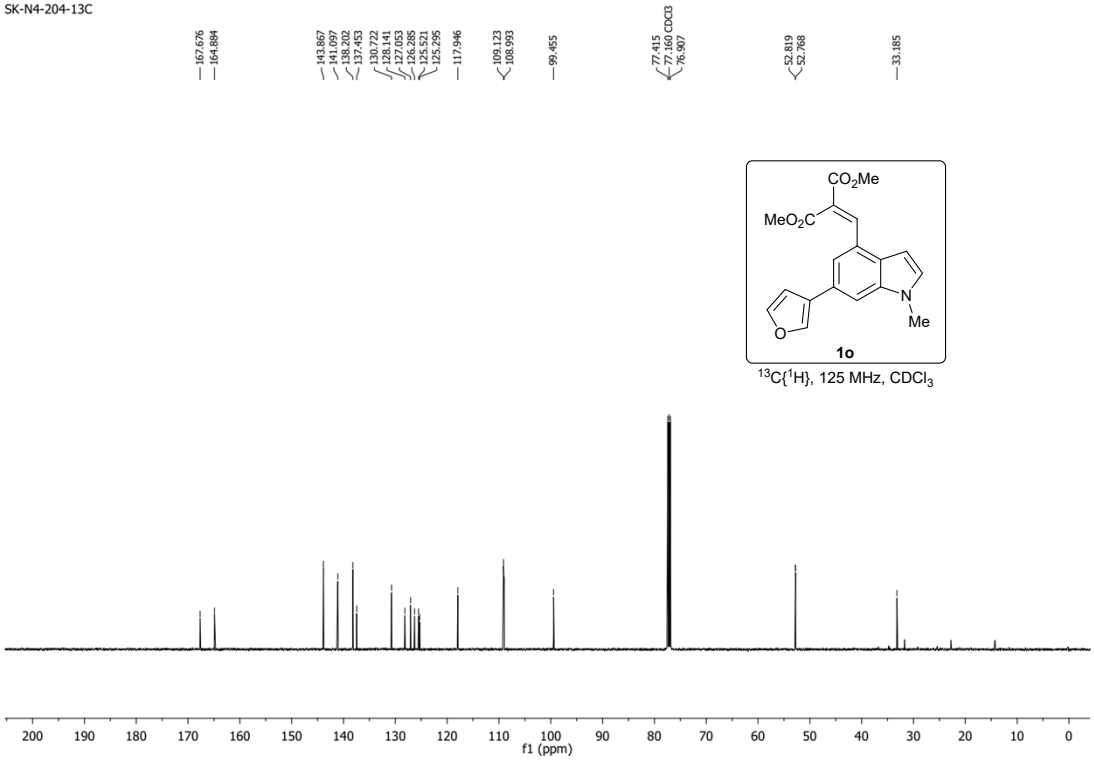


$^{13}C\{^{1}H\}$, 125 MHz, $CDCl_3$

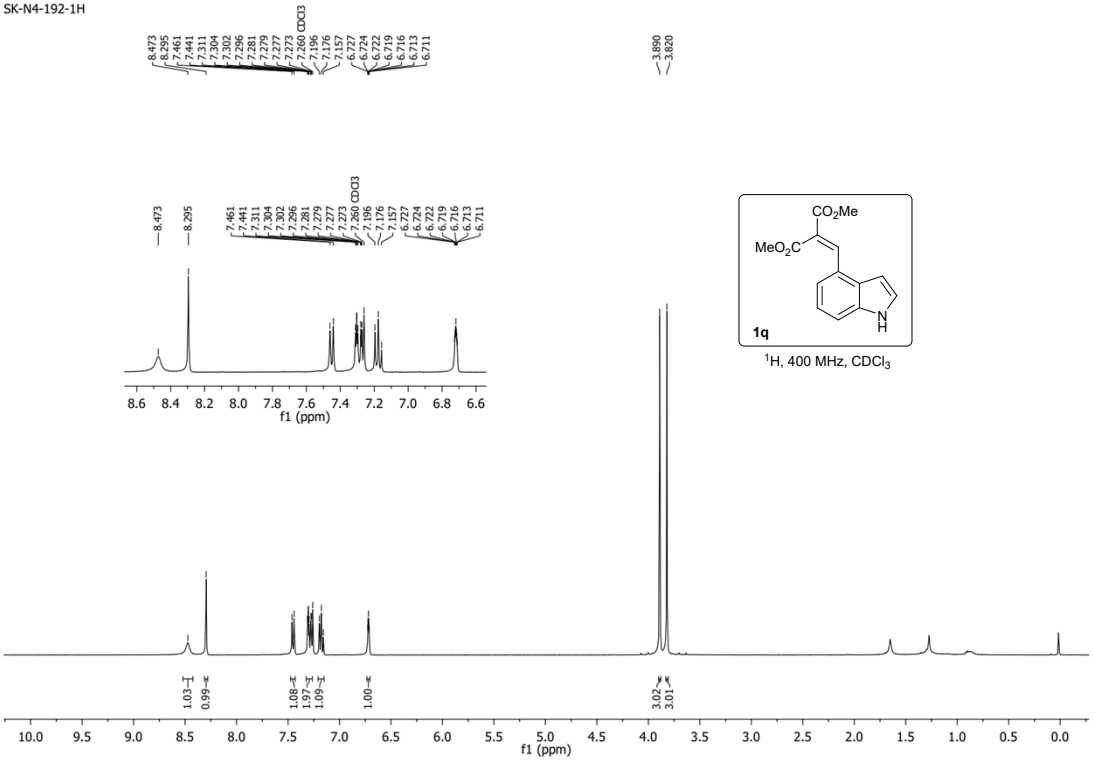
SK-N4-204-1H



SK-N4-204-13C

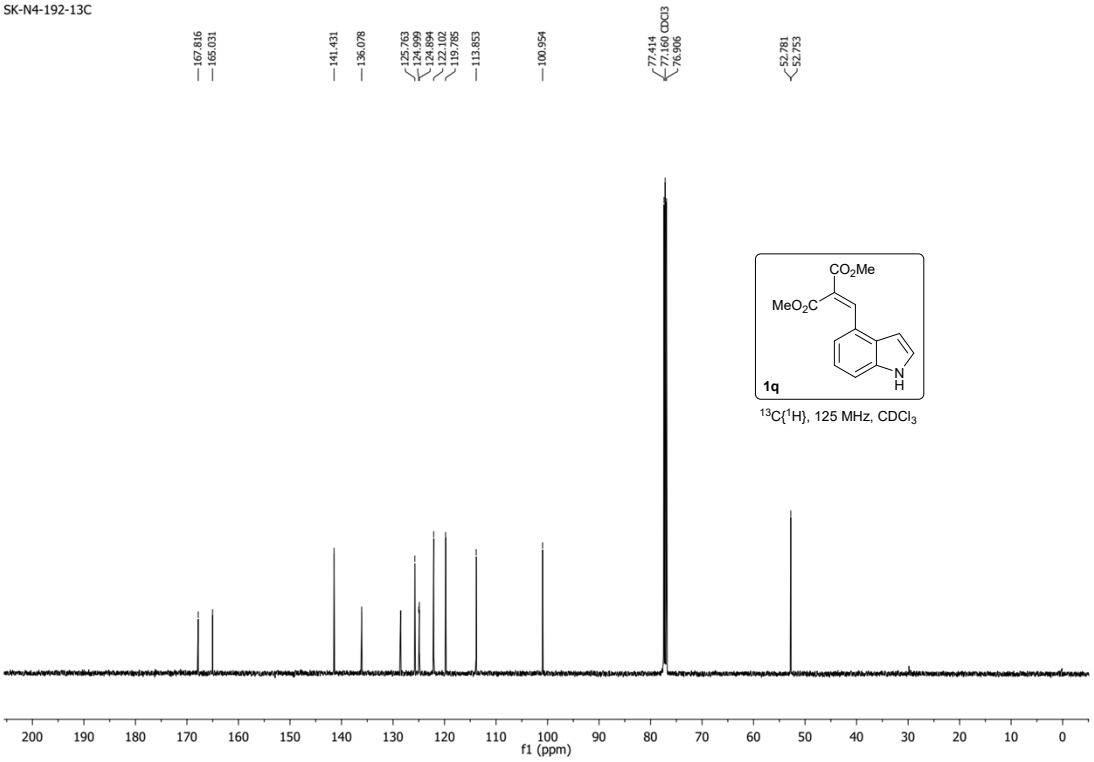


SK-N4-192-1H



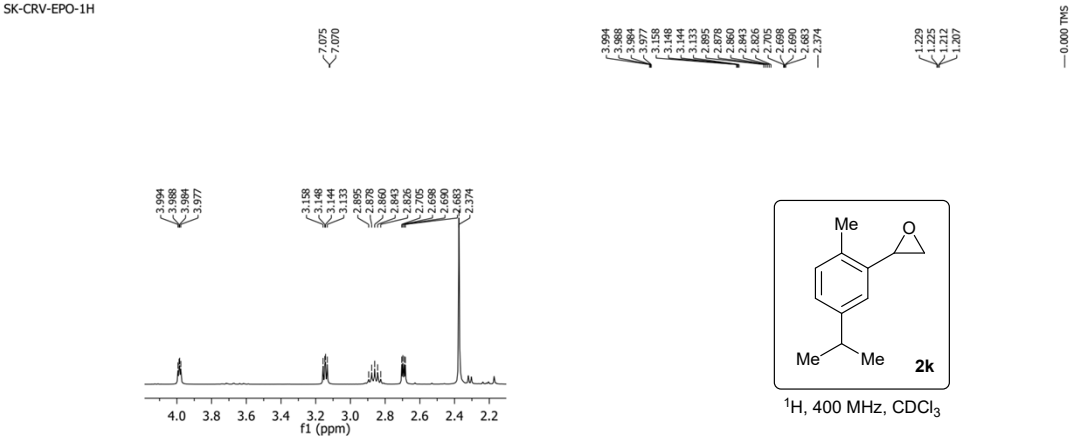
^{1}H, 400 MHz, $CDCl_3$

SK-N4-192-13C

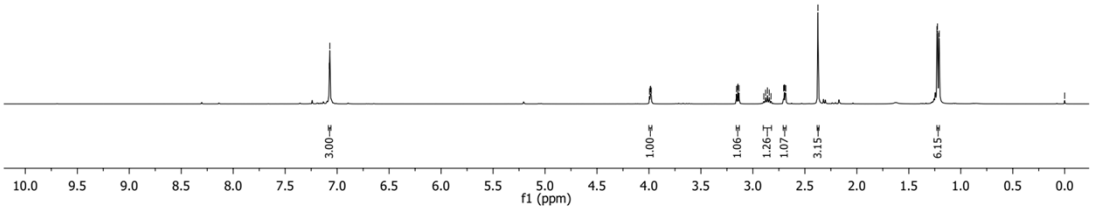


$^{13}C\{^{1}H\}$, 125 MHz, $CDCl_3$

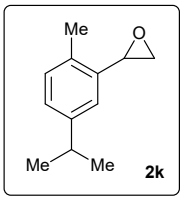
SK-CRV-EPO-1H



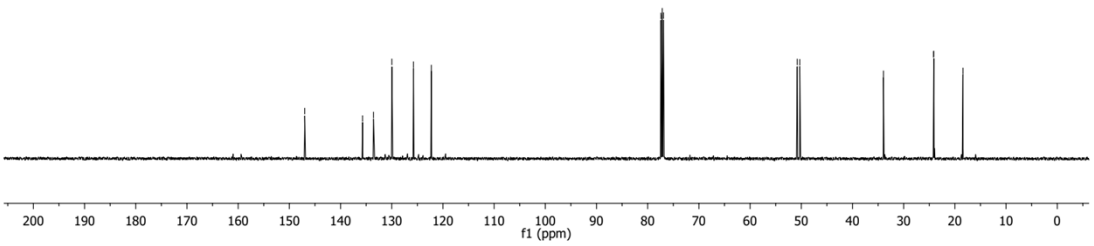
^{1}H, 400 MHz, $CDCl_3$



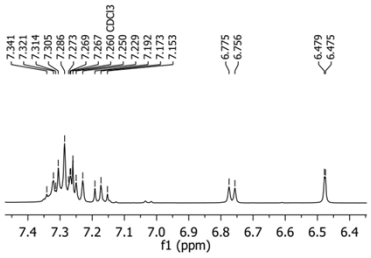
SK-CRV-EPO-13C

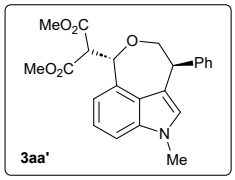


$^{13}C\{^{1}H\}$, 125 MHz, $CDCl_3$

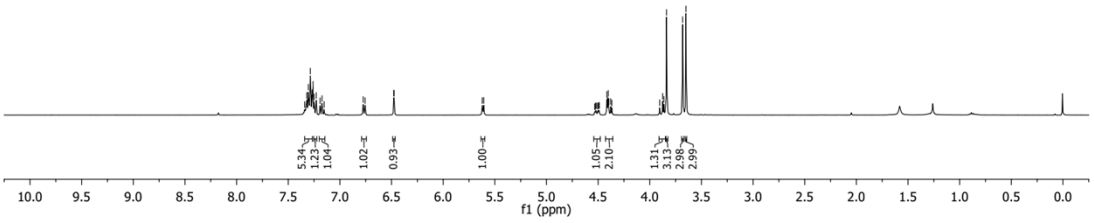


SK-N4-NOR

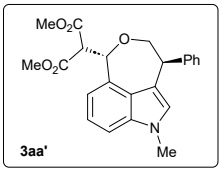




^{1}H, 400 MHz, $CDCl_3$

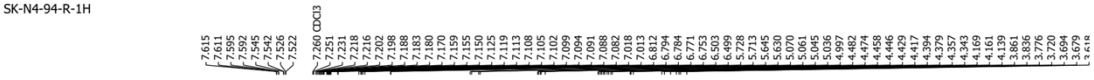


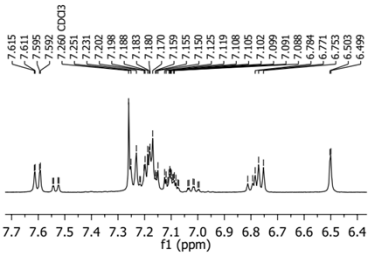
SK-N4-NOR-13C

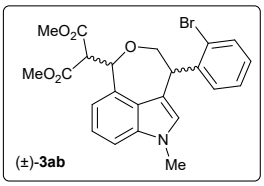


$^{13}C\{^{1}H\}$, 100 MHz, $CDCl_3$

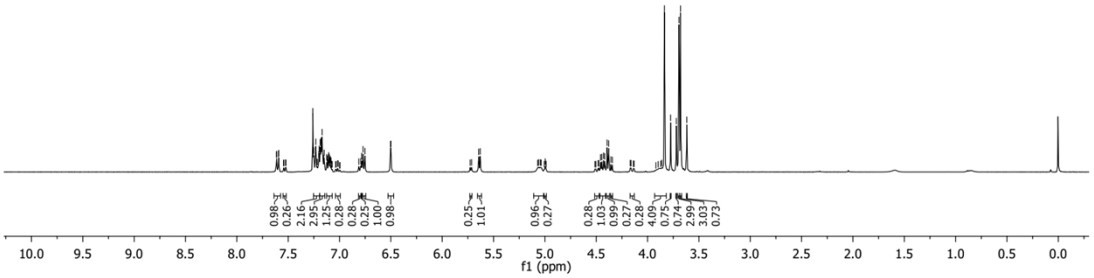
SK-N4-94-R-1H



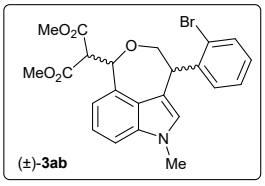




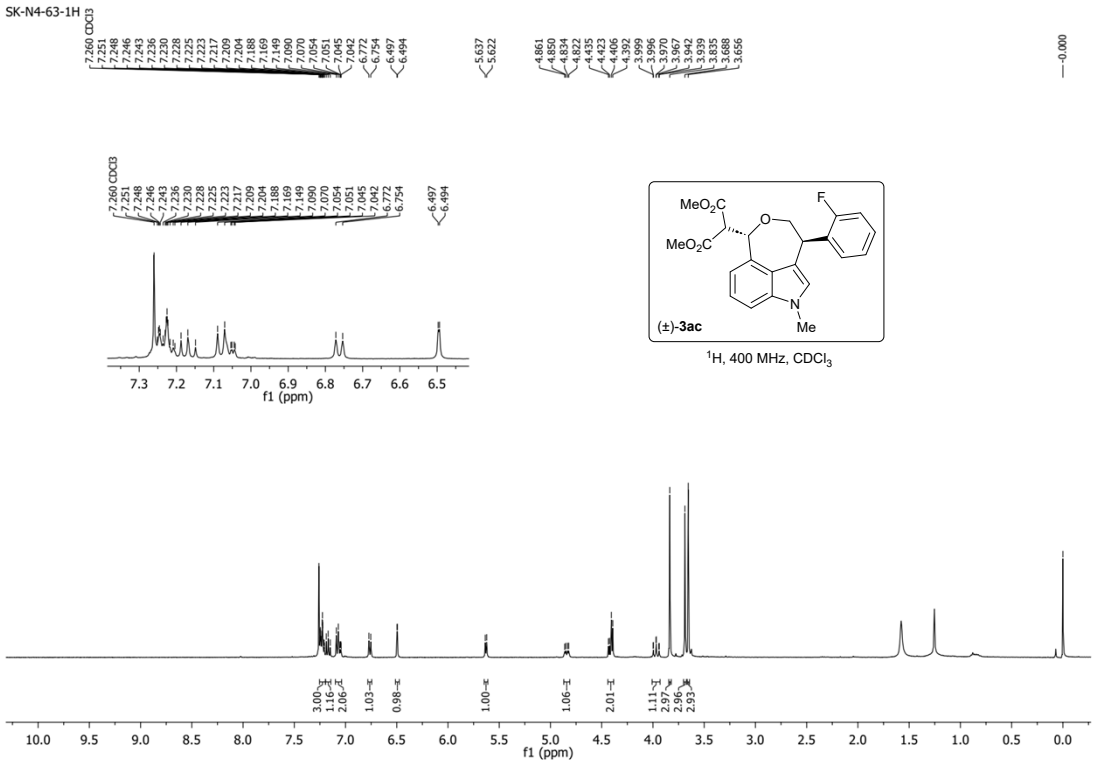
^{1}H, 400 MHz, $CDCl_3$

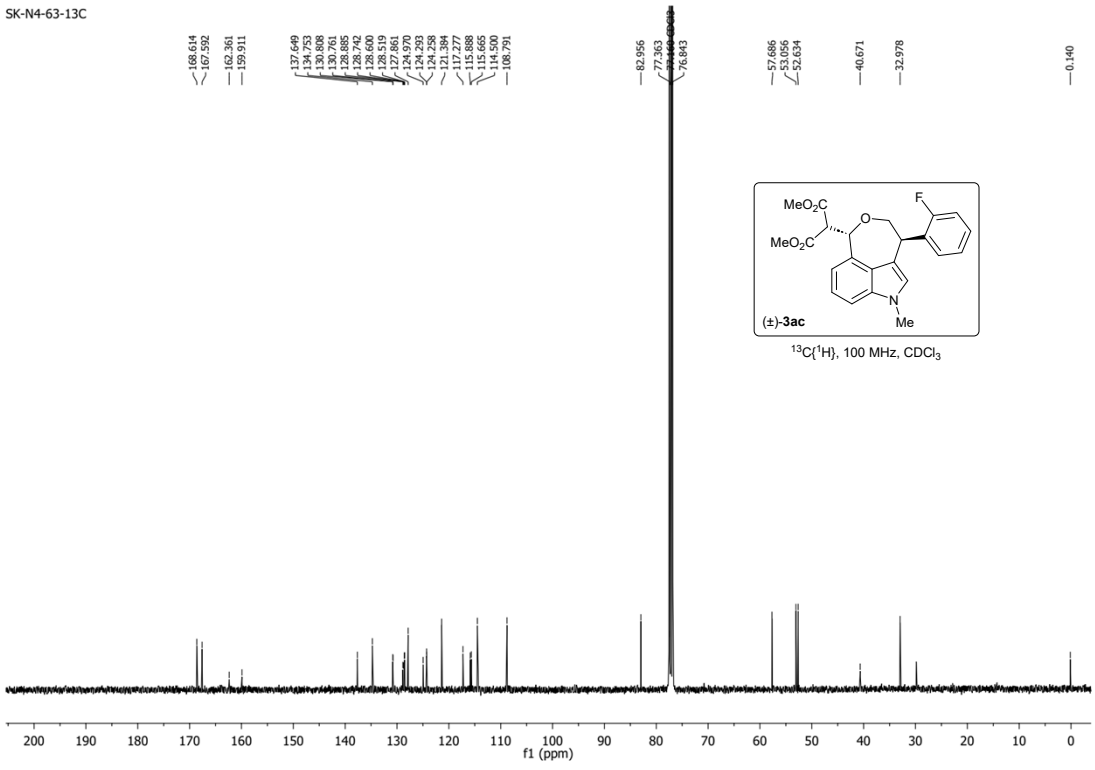


SK-N4-94-13C

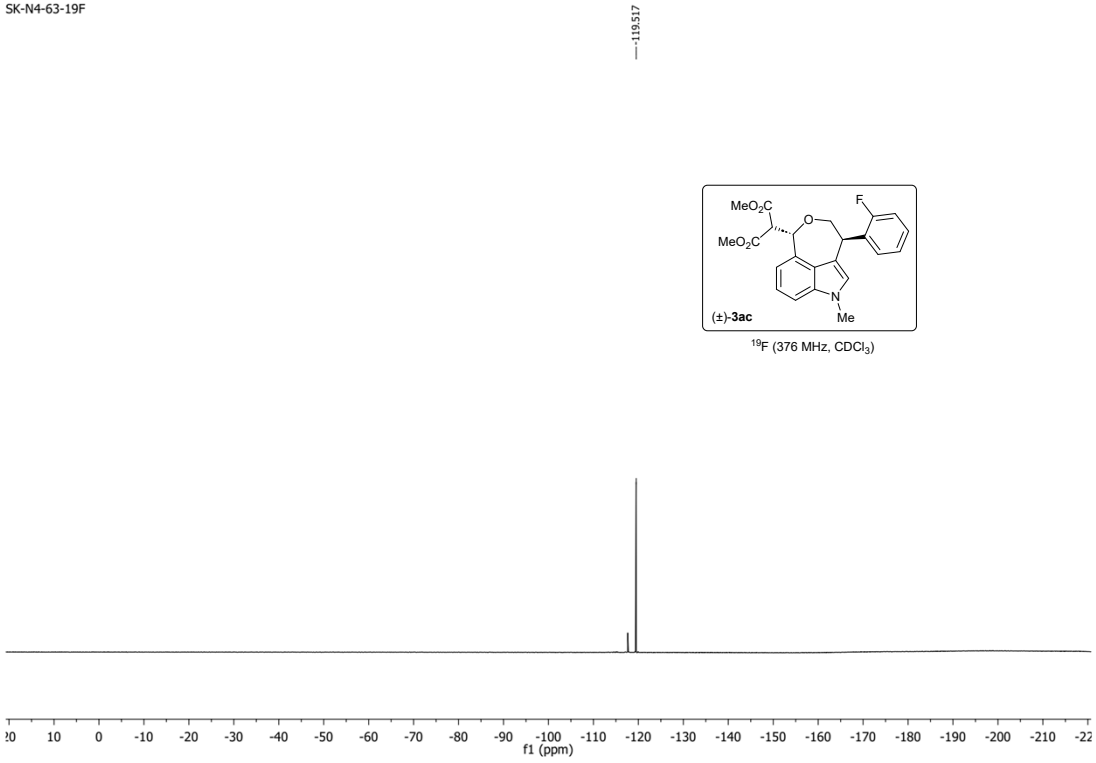


$^{13}C\{^{1}H\}$, 100 MHz, $CDCl_3$


SK-N4-63-1H
(±)-3ac
^{1}H, 400 MHz, $CDCl_3$

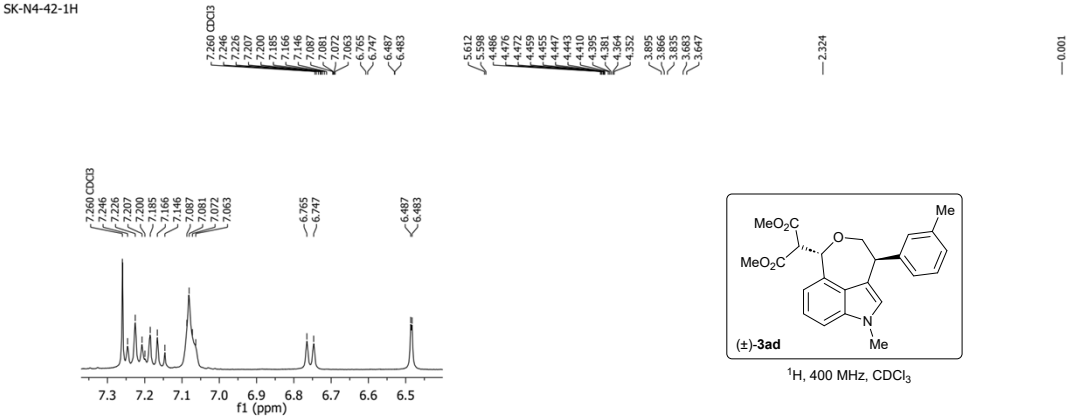

SK-N4-63-13C
(±)-3ac
$^{13}C\{^1H\}$, 100 MHz, $CDCl_3$

SK-N4-63-19F



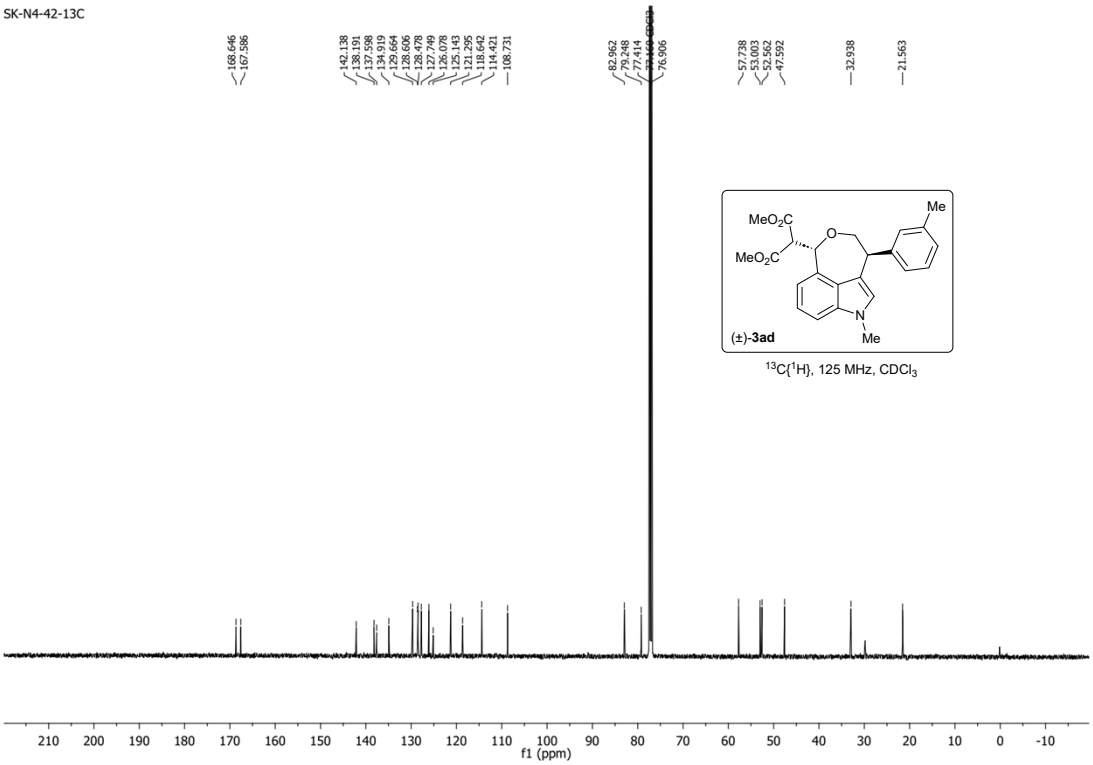
^{19}F (376 MHz, $CDCl_3$)

SK-N4-1H



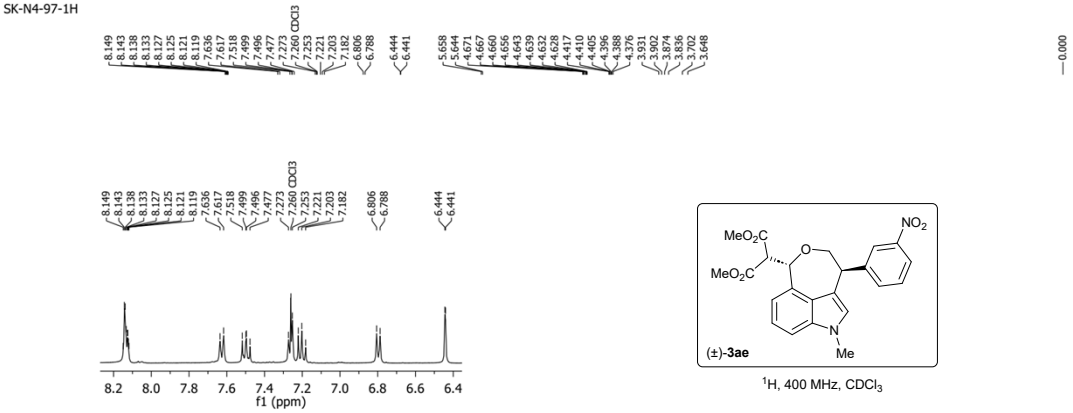
^{1}H, 400 MHz, $CDCl_3$

SK-N4-13C

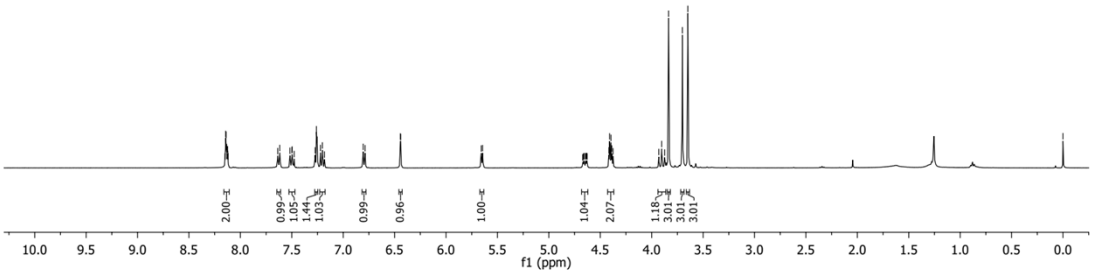


$^{13}C\{^1H\}$, 125 MHz, $CDCl_3$

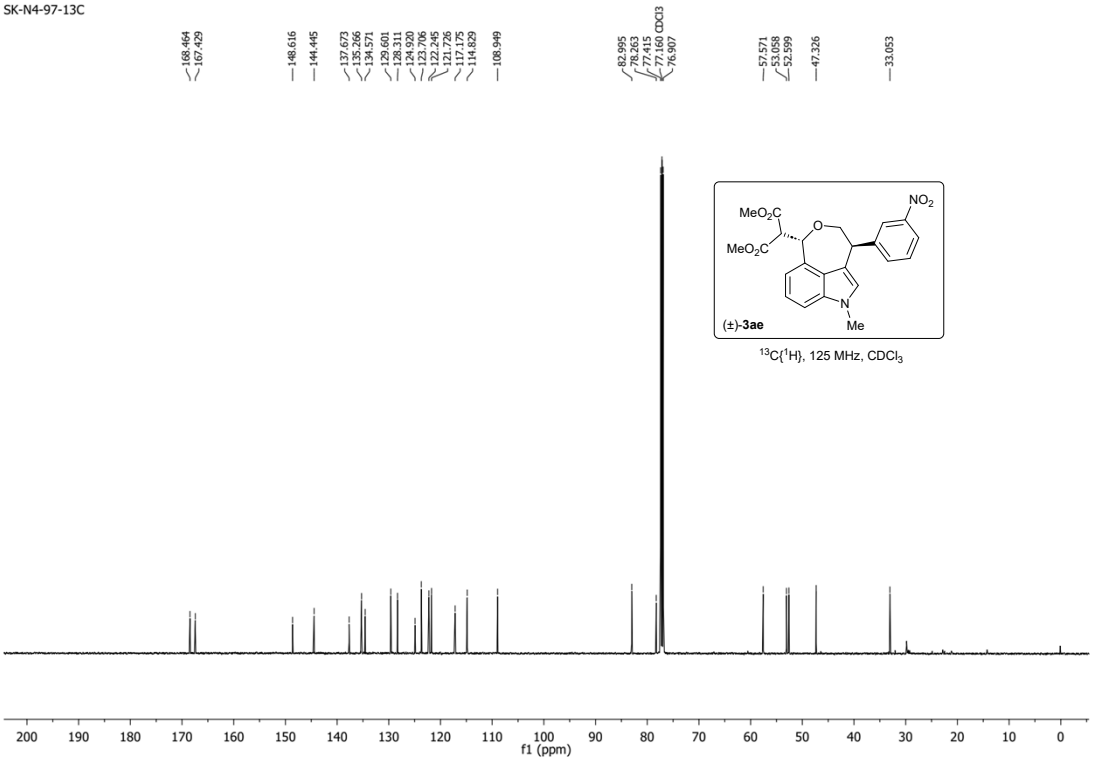
SK-N4-97-1H



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

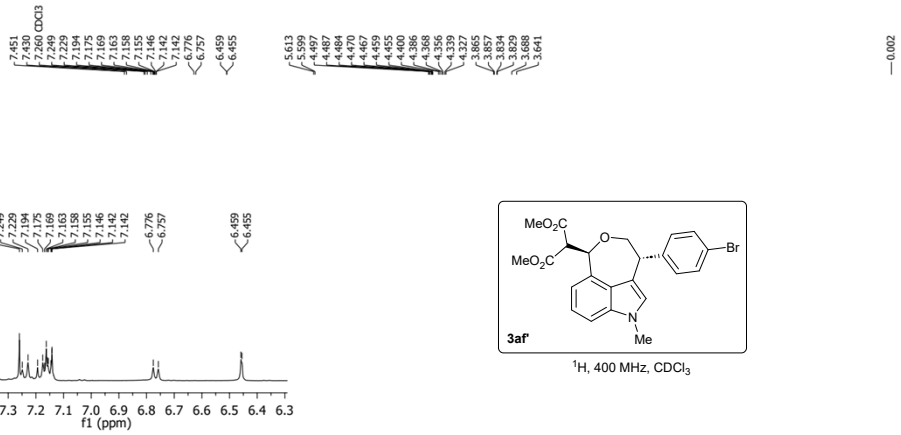


SK-N4-97-13C

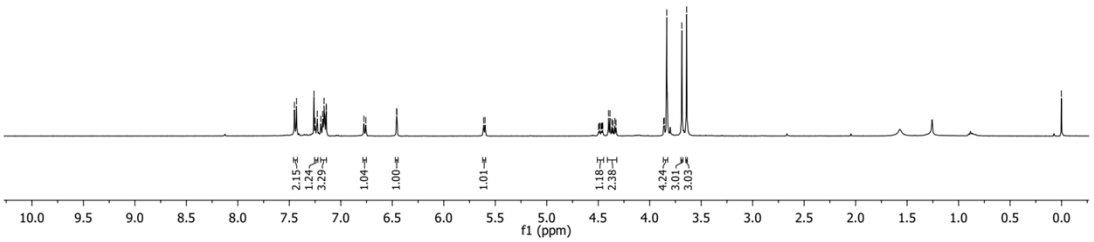


$^{13}C\{^1H\}$, 125 MHz, $CDCl_3$

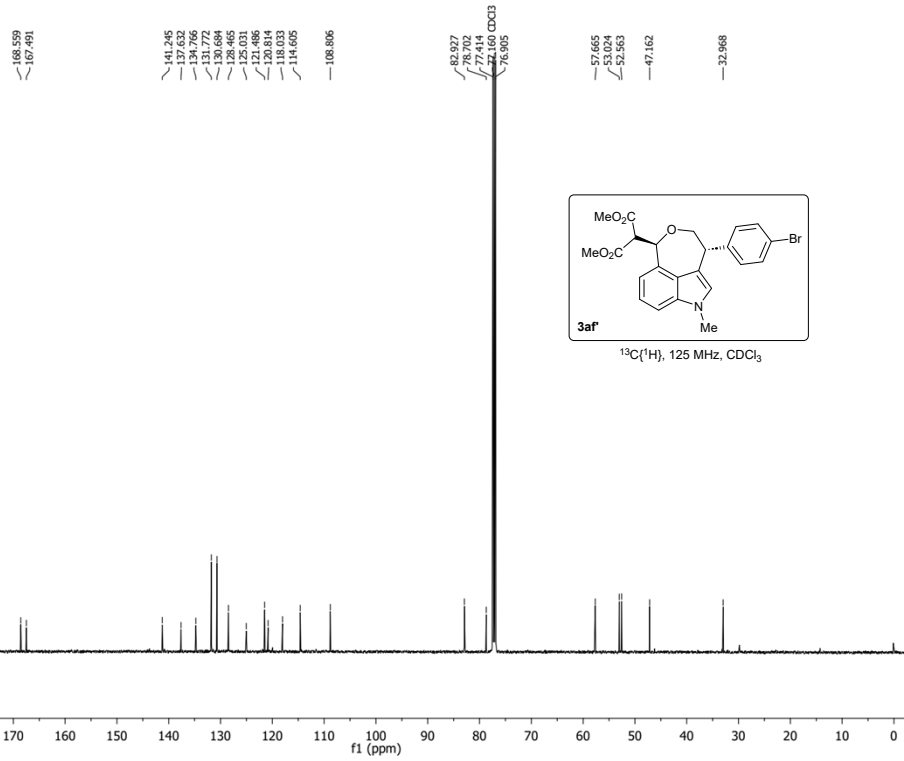
SK-N4-40-1H



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

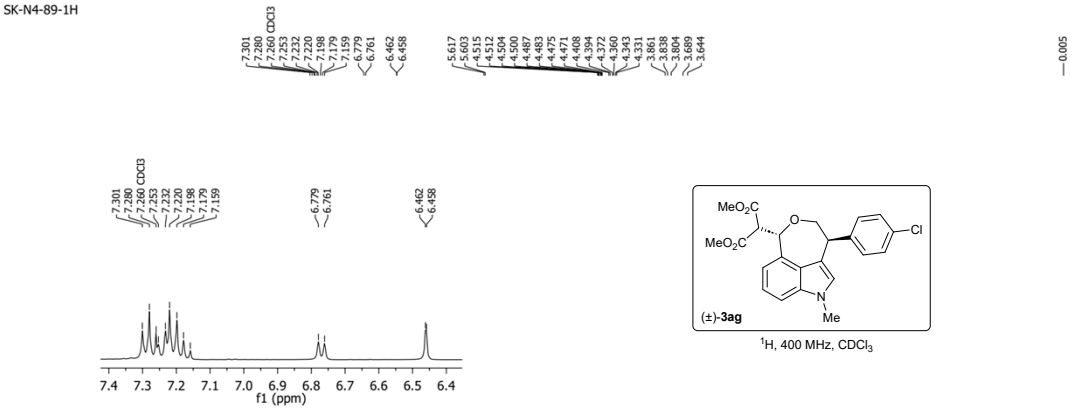


SK-N4-40-13C



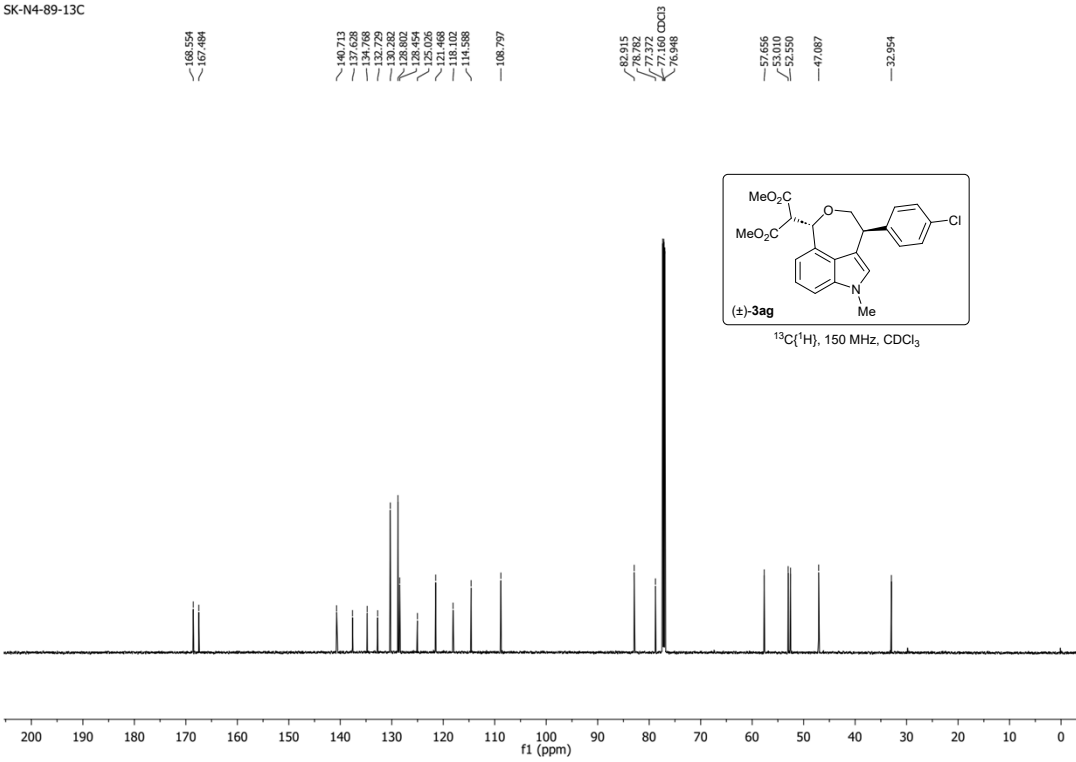
^{13}C{^{1}H}, 125 MHz, $CDCl_3$

SK-N4-89-1H



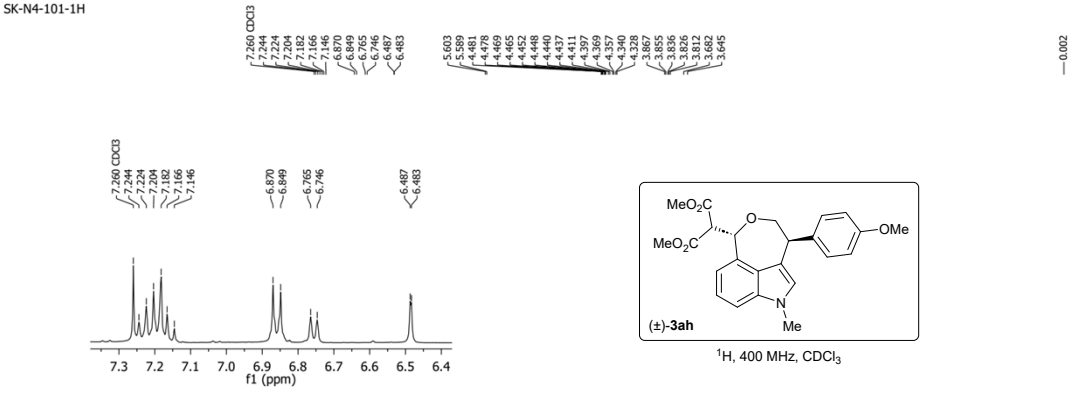
^{1}H, 400 MHz, $CDCl_3$

SK-N4-89-13C

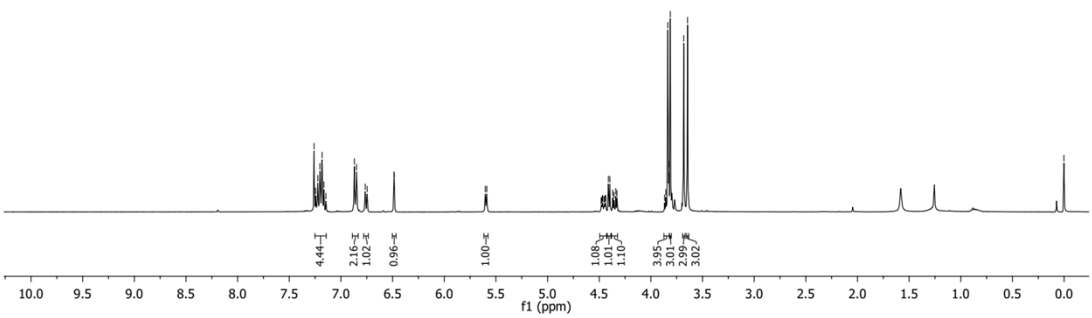


$^{13}C\{^{1}H\}$, 150 MHz, $CDCl_3$

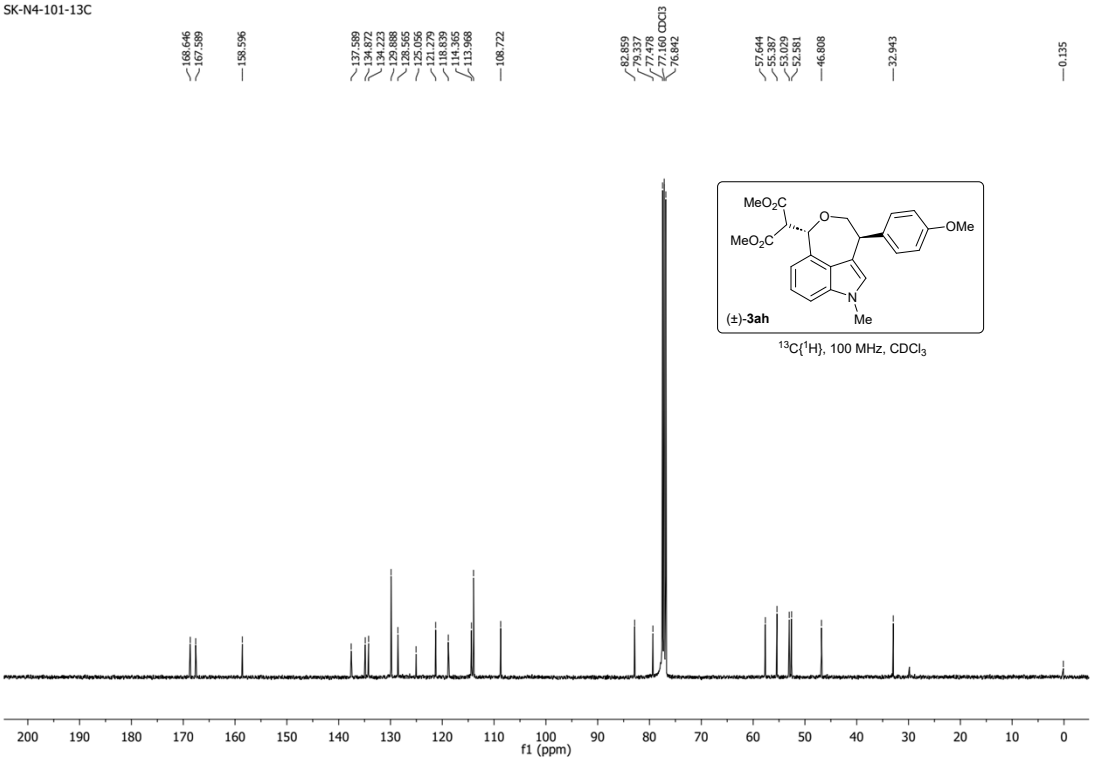
SK-N4-101-1H



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

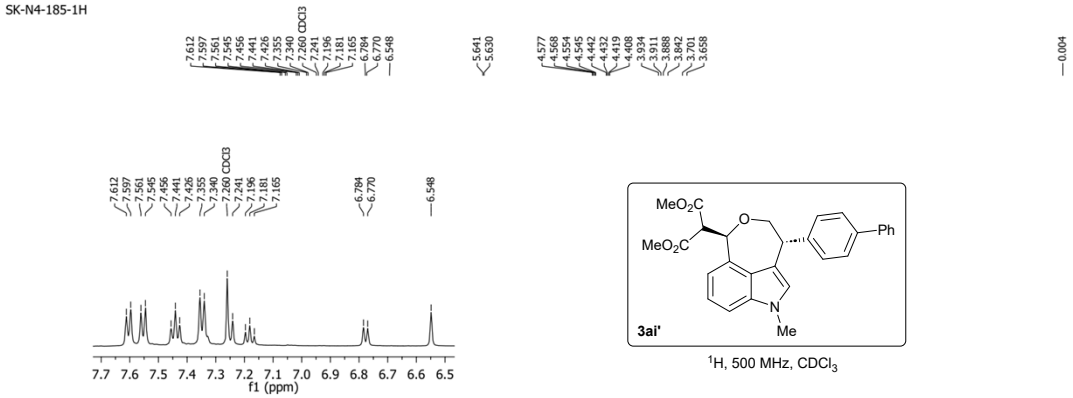


SK-N4-101-13C

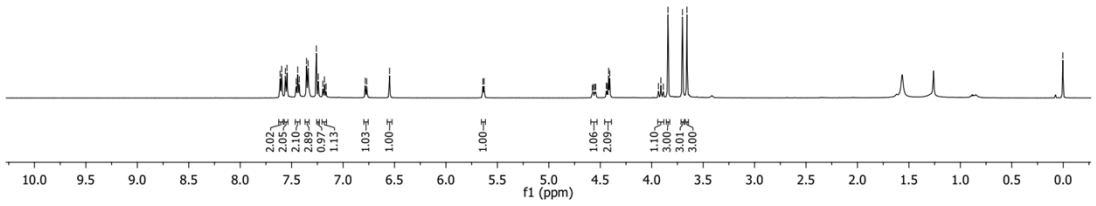


$^{13}C\{^1H\}$, 100 MHz, $CDCl_3$

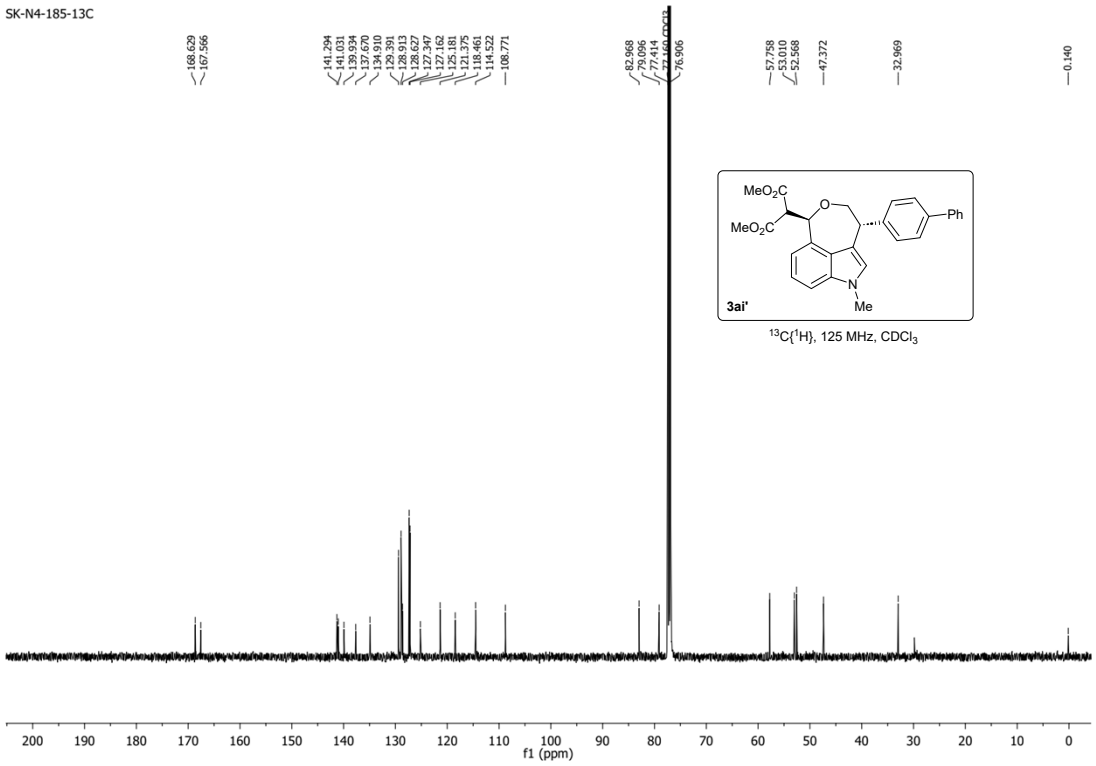
SK-N4-185-1H



^{1}H, 500 MHz, $CDCl_3$

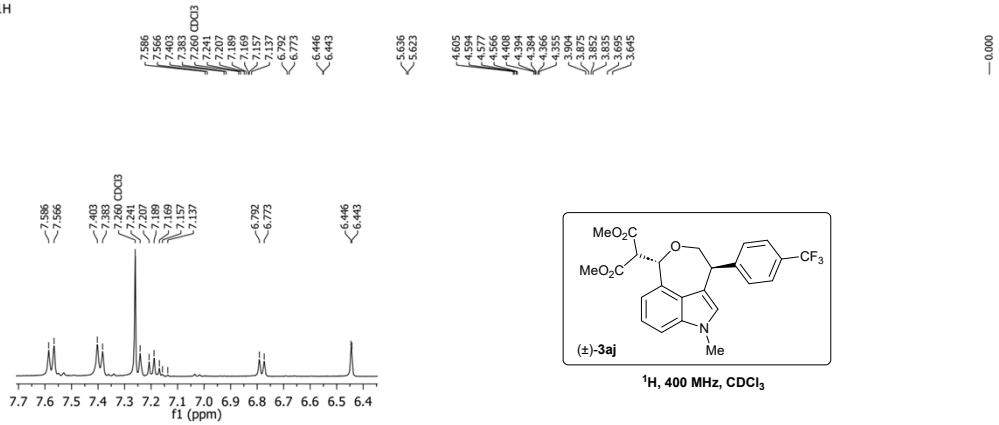


SK-N4-185-13C



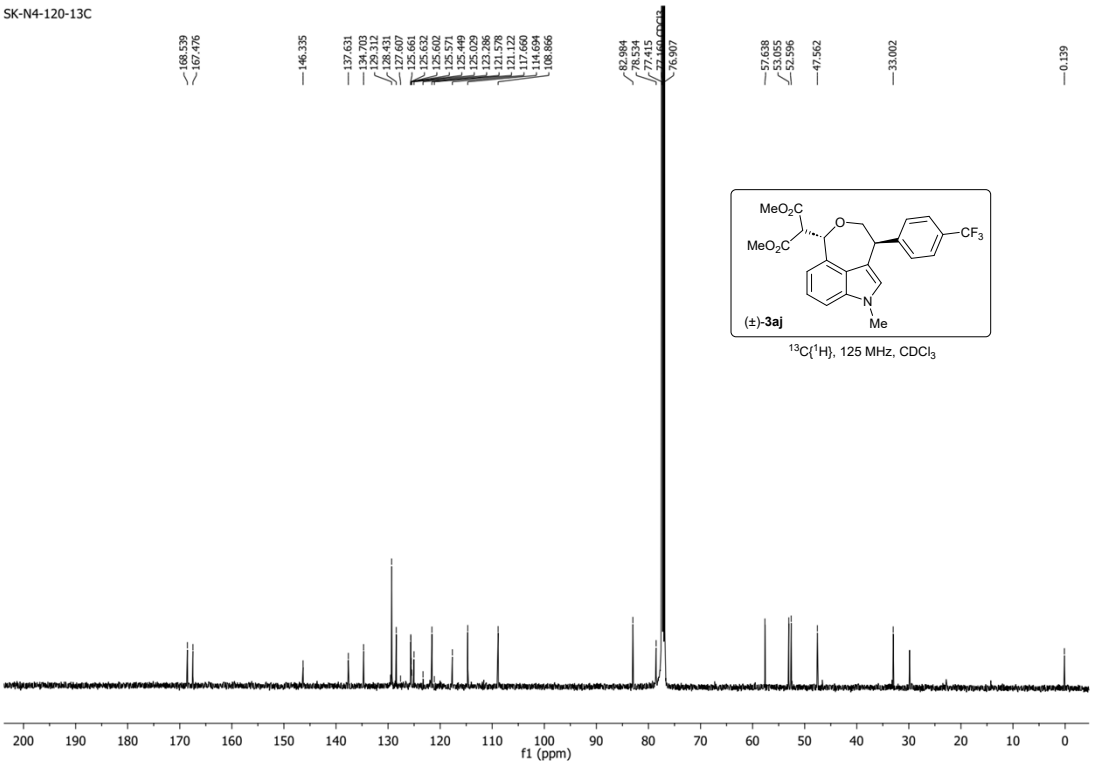
$^{13}C\{^1H\}$, 125 MHz, $CDCl_3$

SK-N4-120-1H



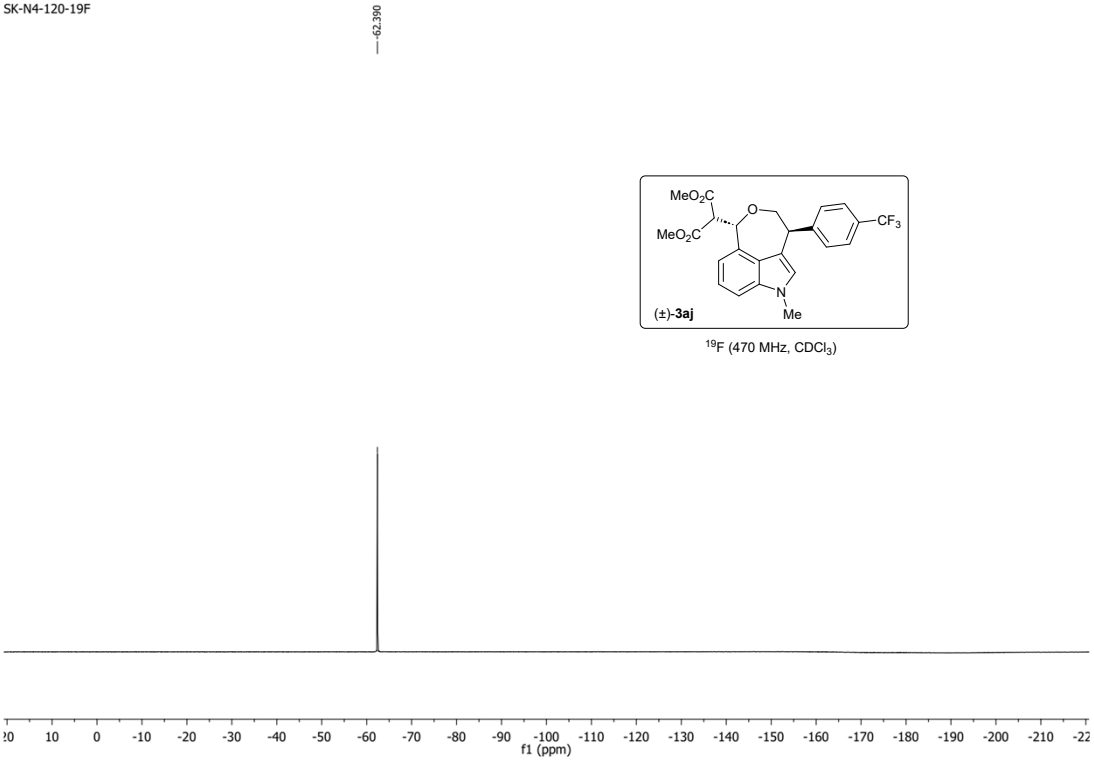
^{1}H, 400 MHz, $CDCl_3$

SK-N4-120-13C



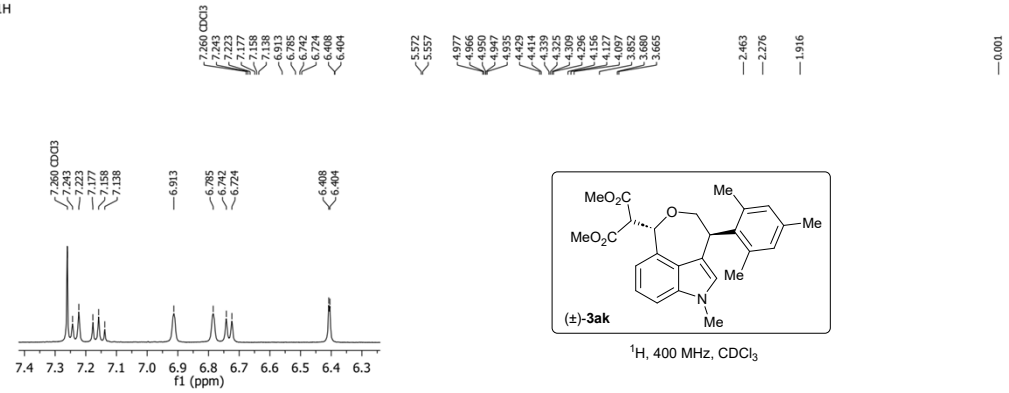
$^{13}C\{^1H\}$, 125 MHz, $CDCl_3$

SK-N4-120-19F

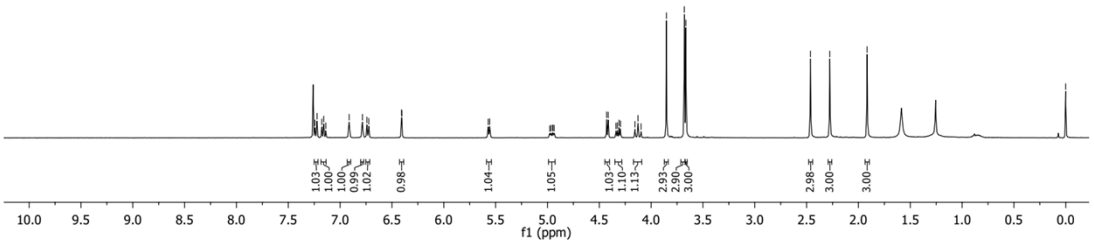


^{19}F (470 MHz, $CDCl_3$)

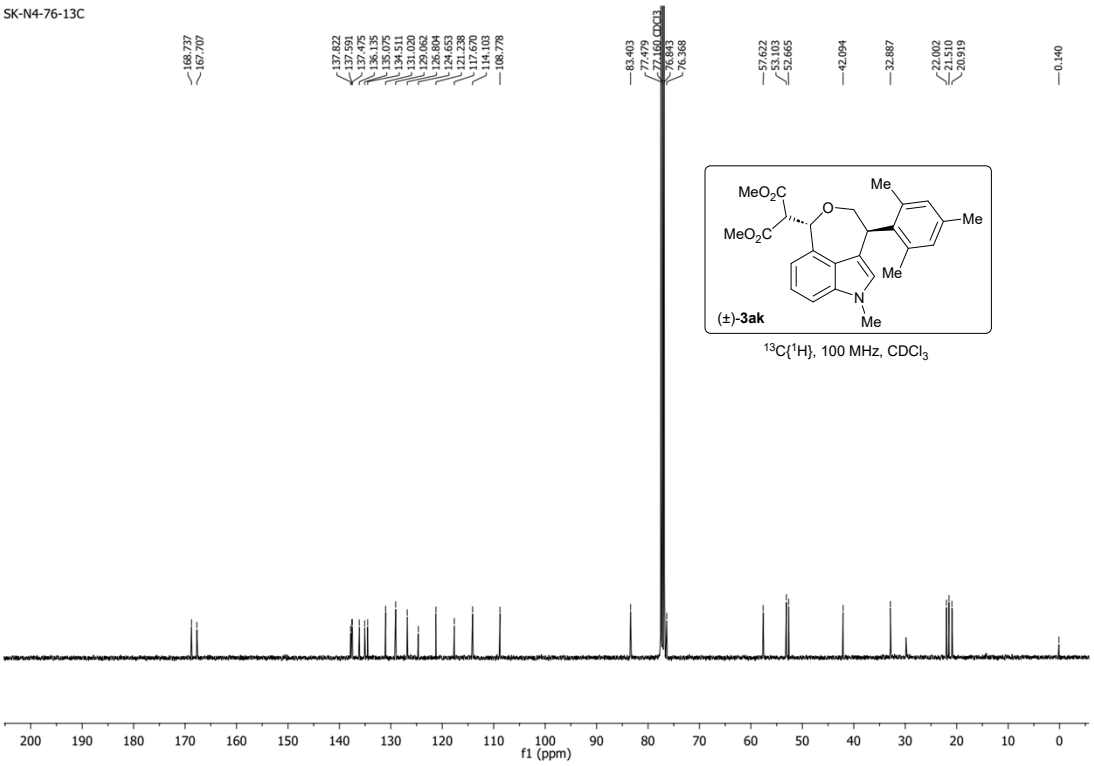
SK-N4-76-1H



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

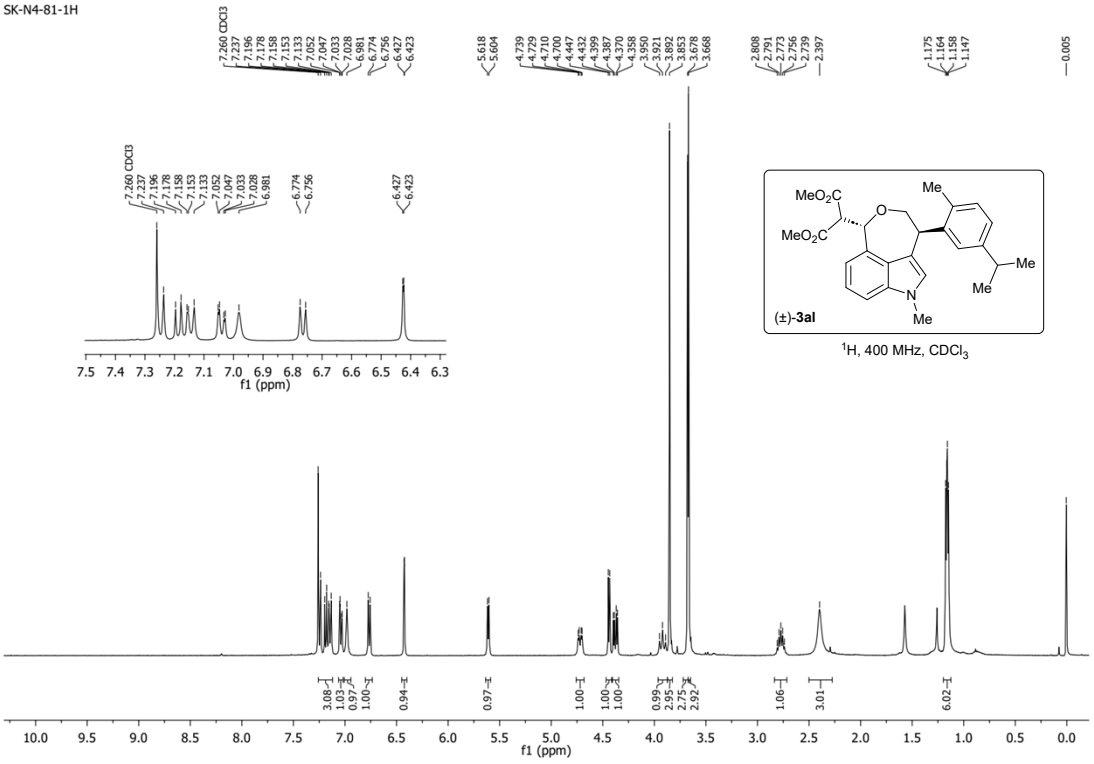


SK-N4-76-13C



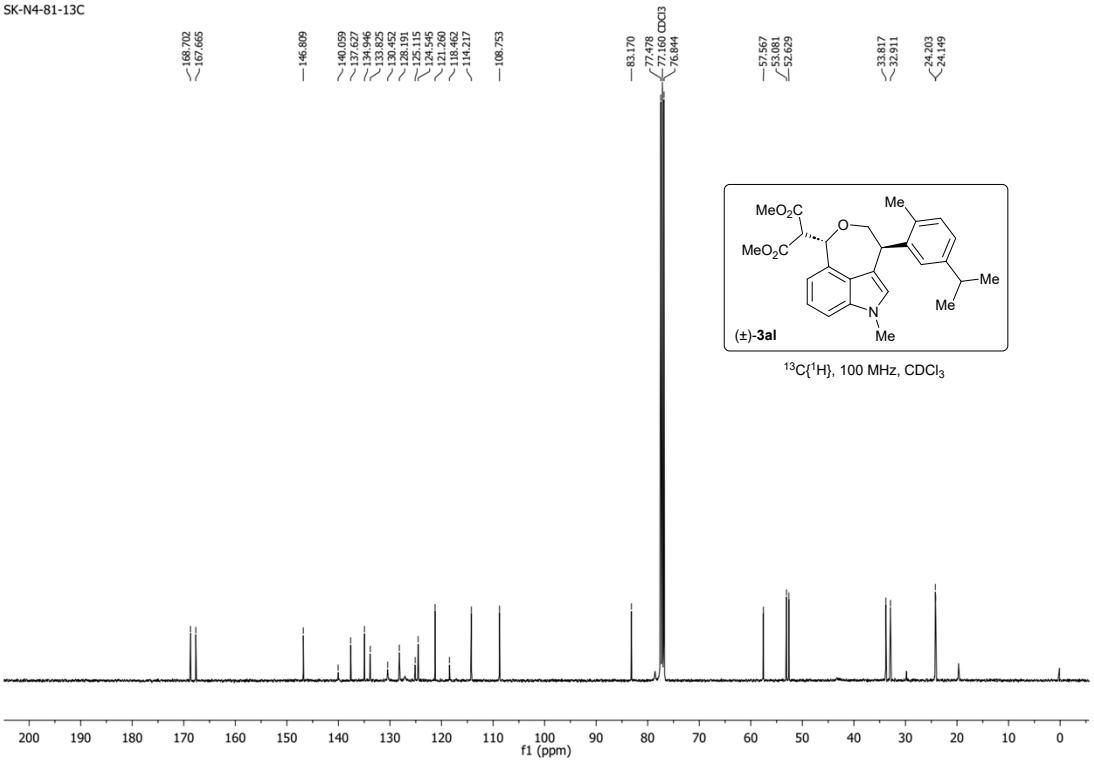
$^{13}C\{^1H\}$, 100 MHz, $CDCl_3$

SK-N4-81-1H



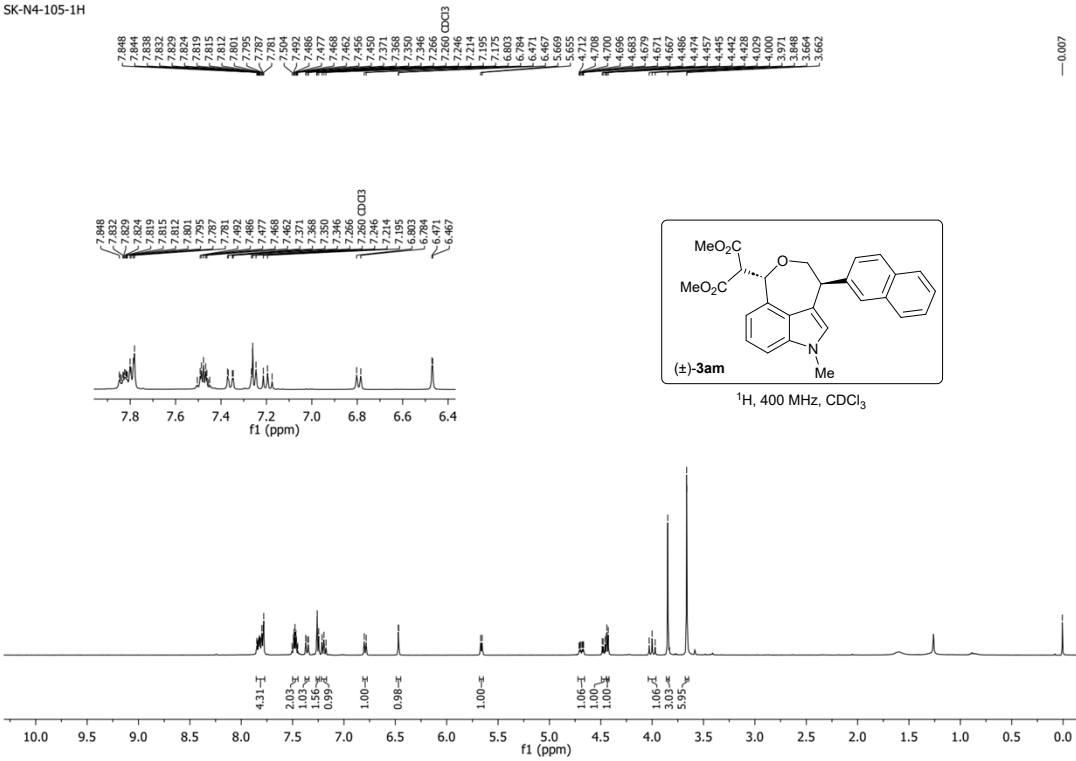
^{1}H, 400 MHz, $CDCl_3$

SK-N4-81-13C



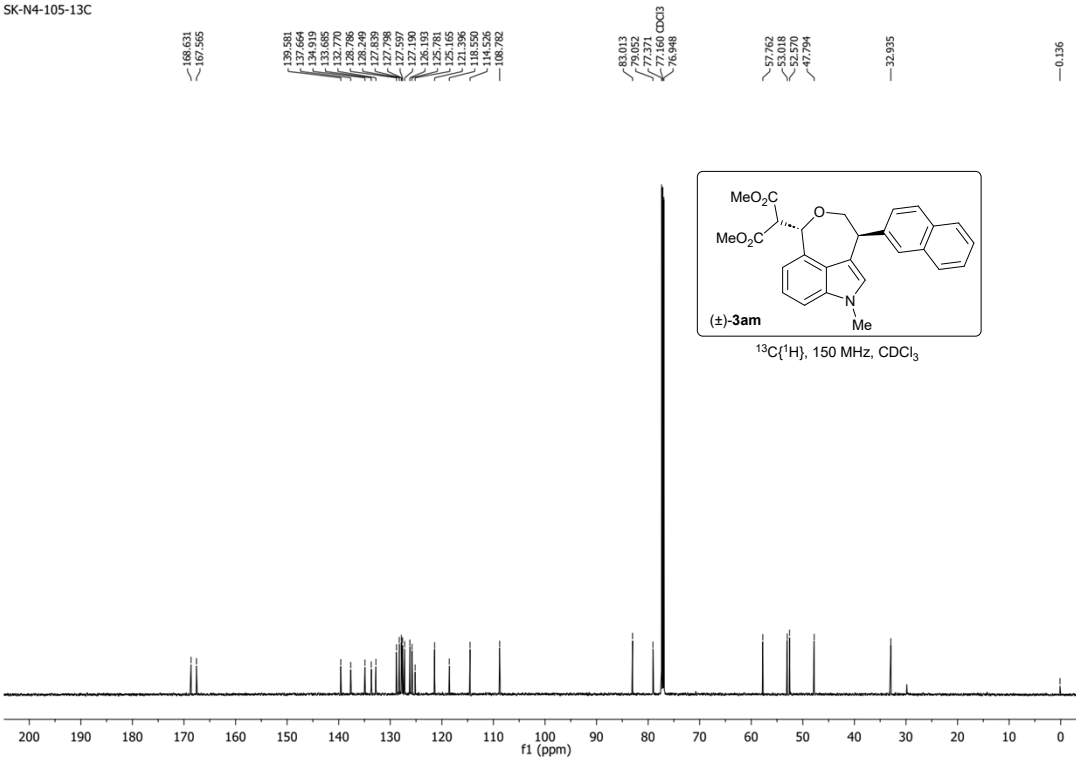
^{13}C{^{1}H}, 100 MHz, $CDCl_3$

SK-N4-105-1H

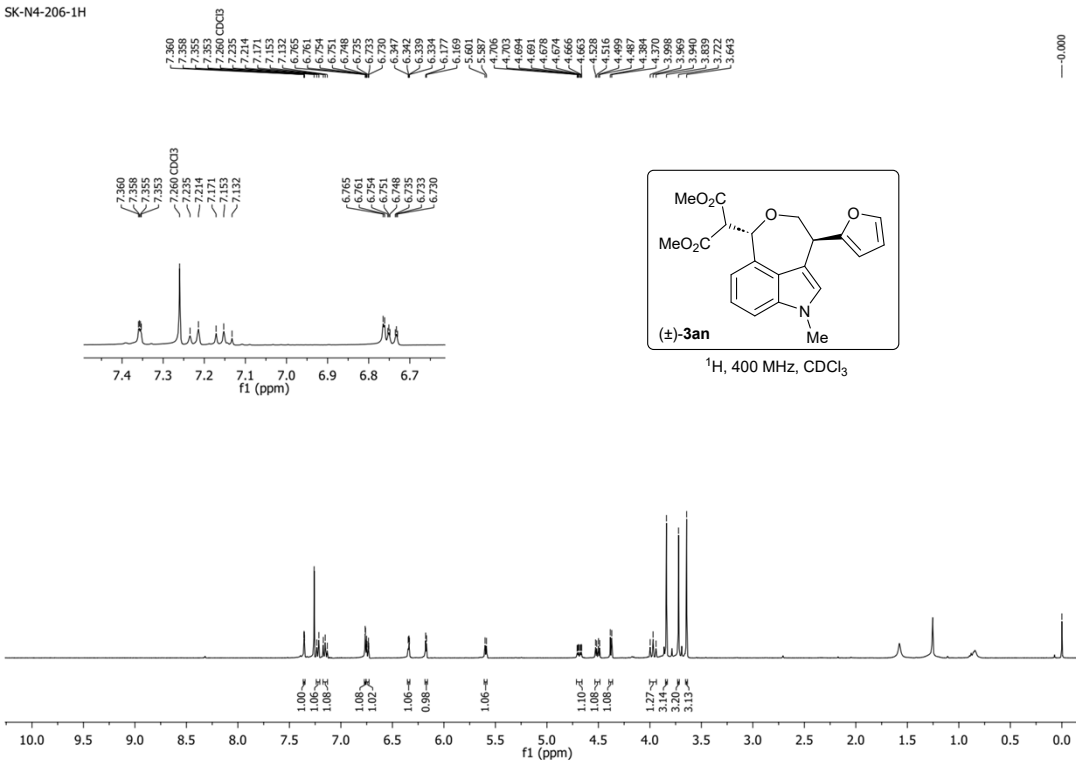


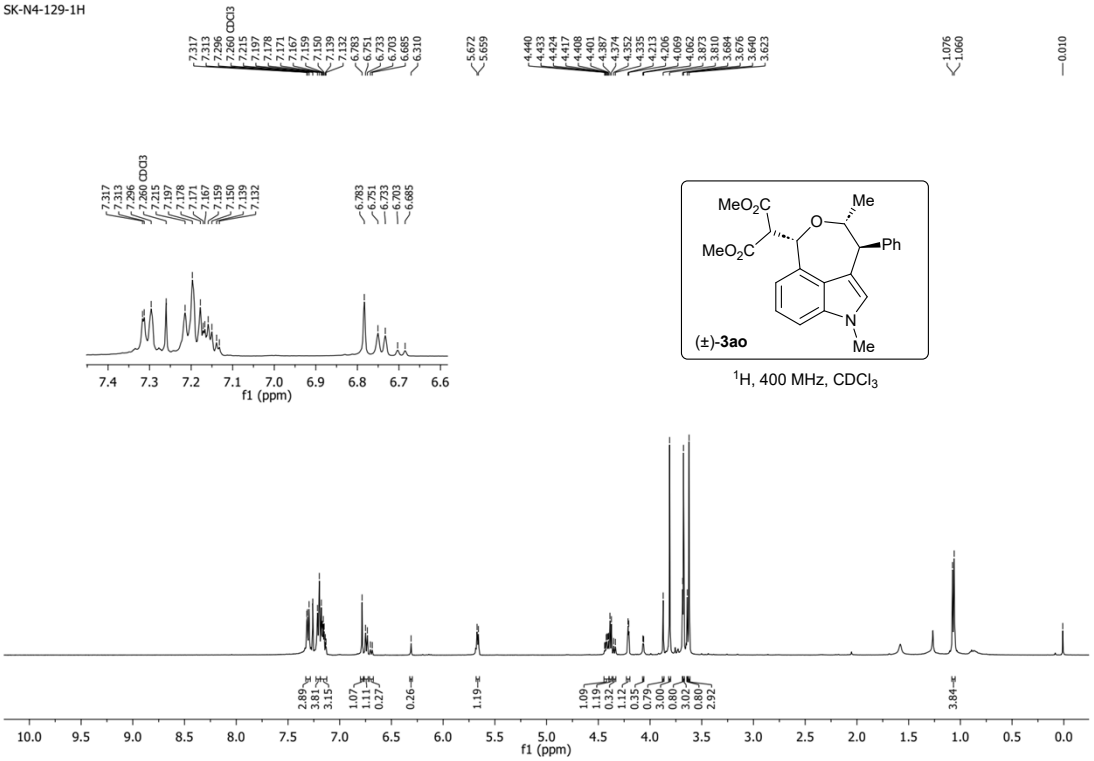
^{1}H, 400 MHz, $CDCl_3$

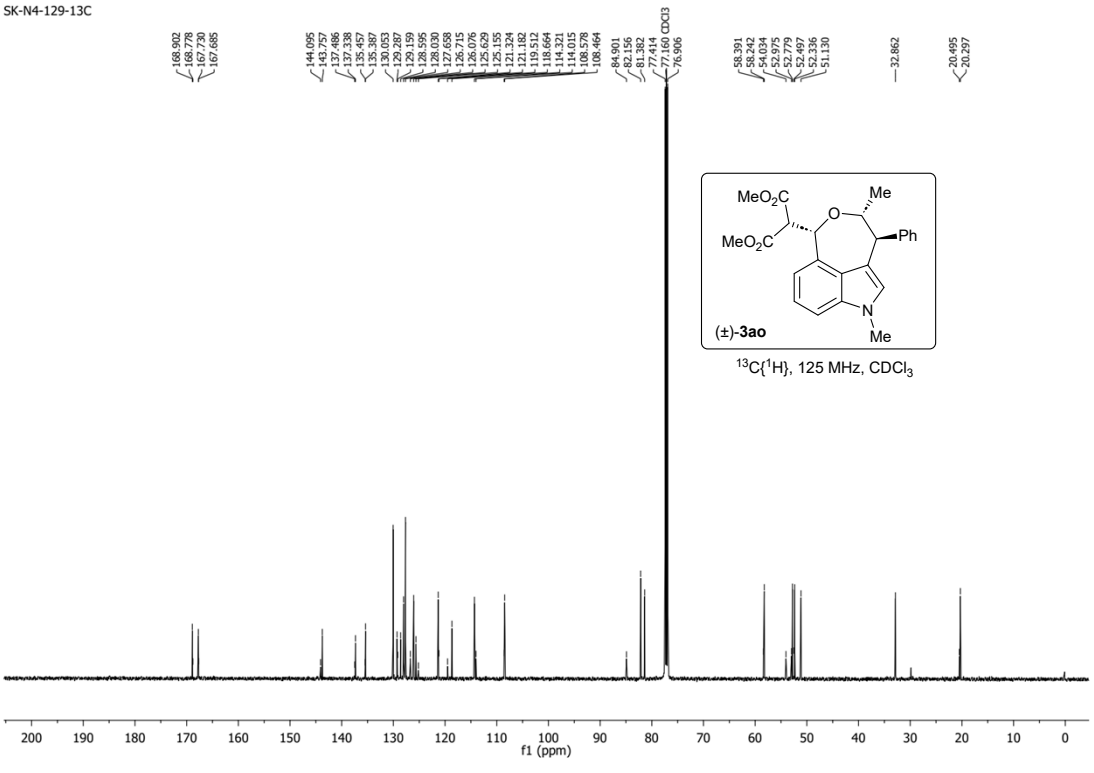
SK-N4-105-13C

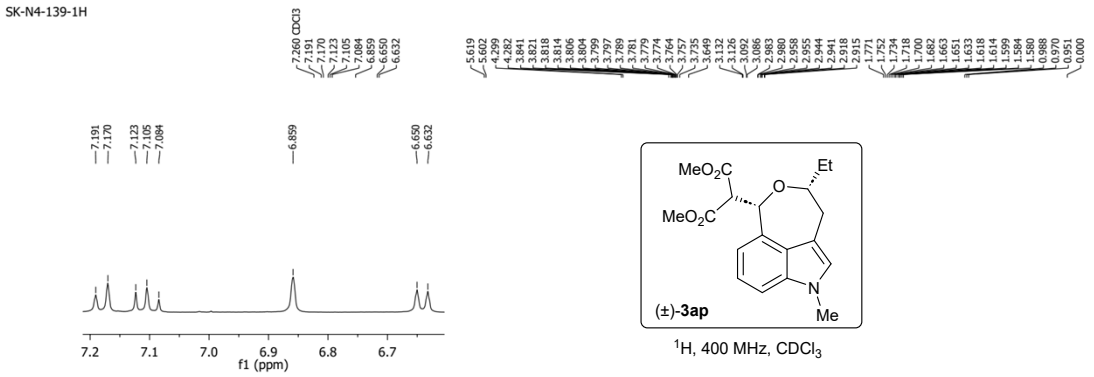


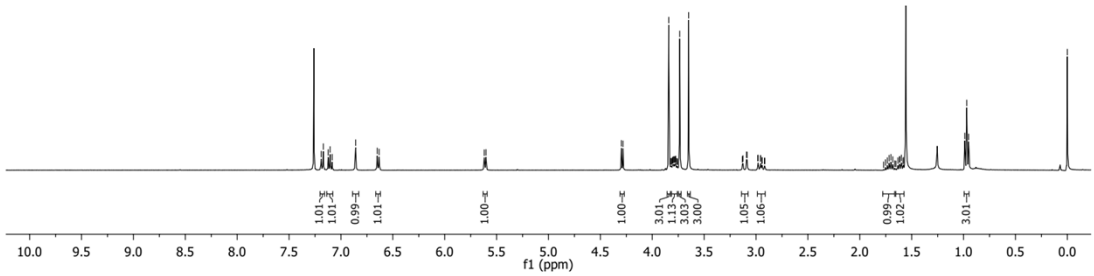
^{13}C{^{1}H}, 150 MHz, $CDCl_3$

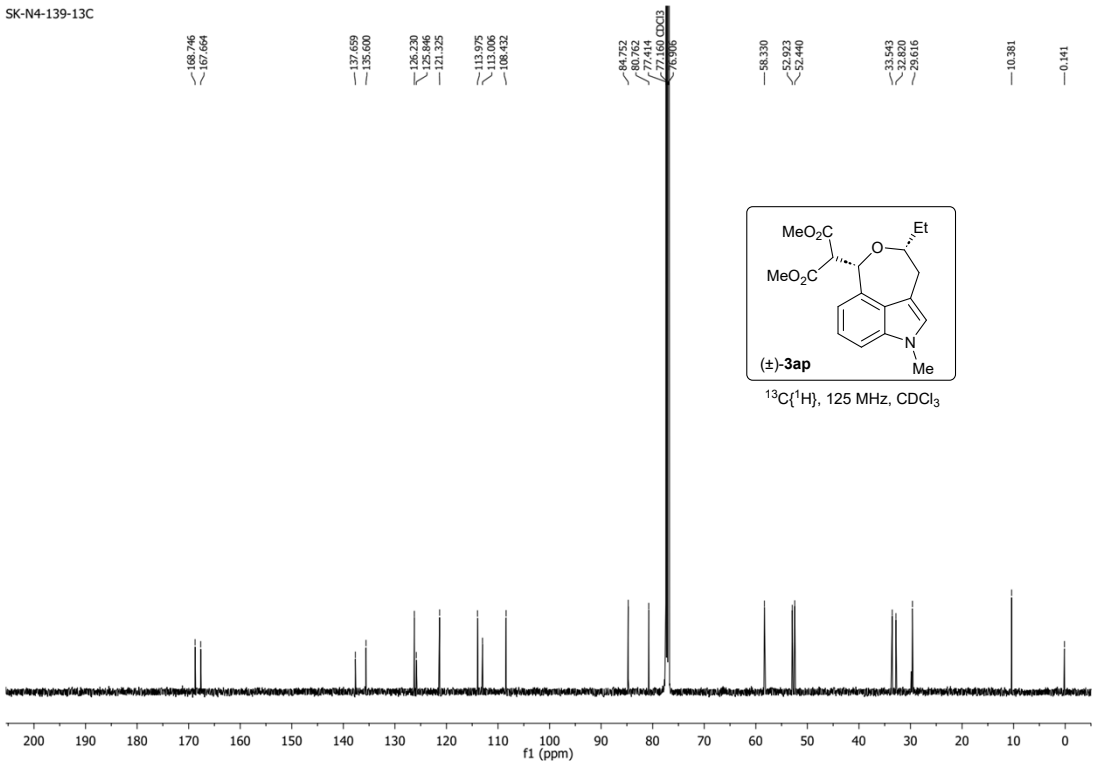

SK-N4-206-1H
7.360
7.358
7.355
7.353
7.260 CDCl3
7.235
7.214
7.171
7.153
7.132
6.765
6.761
6.754
6.751
6.748
6.735
6.733
6.730
6.347
6.342
6.339
6.334
6.177
6.169
5.601
5.587
4.706
4.703
4.694
4.691
4.678
4.674
4.666
4.663
4.528
4.516
4.499
4.487
4.384
4.370
3.998
3.969
3.940
3.839
3.722
3.643
0.000
MeO2C
MeO2C
O
O
N
Me
(±)-3an
1H, 400 MHz, CDCl3
1.00
1.06
1.08
1.08
1.02
1.06
0.98
1.06
1.10
1.08
1.08
1.27
3.14
3.20
3.13
f1 (ppm)
SK-N4-206-13C
168.575
167.529
154.969
141.726
137.720
134.595
127.823
124.561
121.421
115.098
114.574
110.188
108.821
106.403
82.844
77.415
77.161
77.160 CDCl3
76.907
76.476
57.705
53.033
52.577
40.736
33.018
13C{1H}, 125 MHz, CDCl3
f1 (ppm)

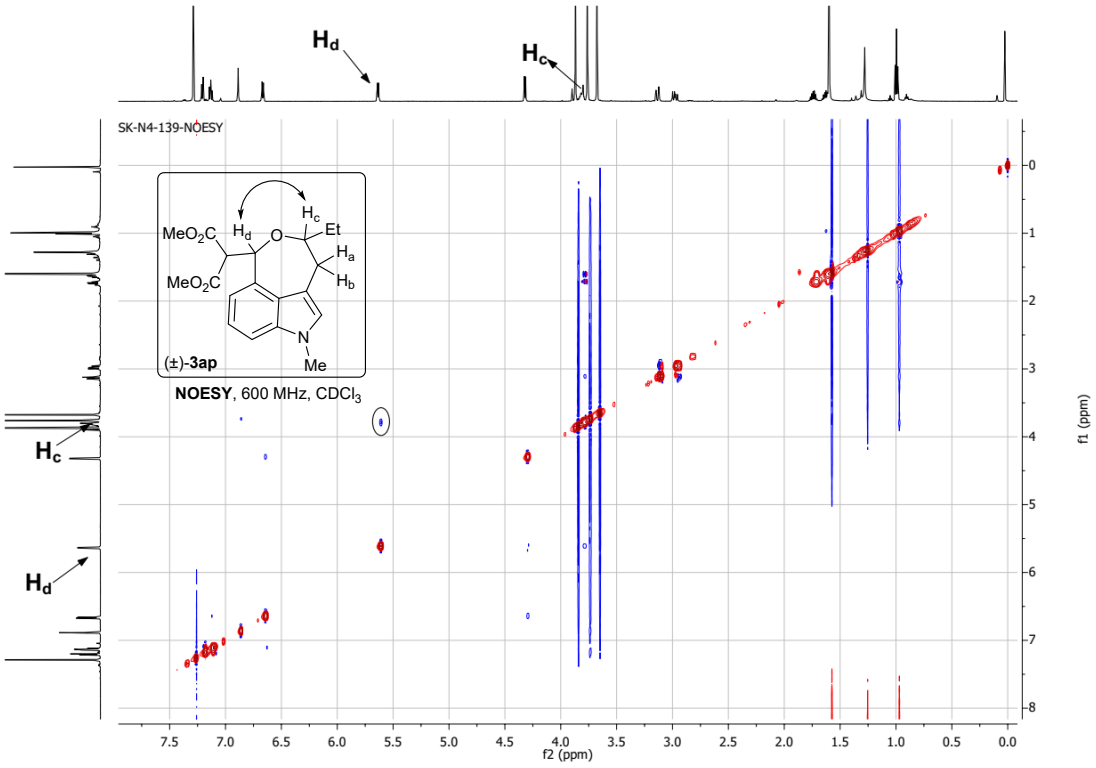

SK-N4-129-1H
MeO2C
MeO2C
Me
O
Ph
N
Me
(±)-3ao
1H, 400 MHz, CDCl3
f1 (ppm)


SK-N4-129-13C
MeO2C
MeO2C
Me
O
Ph
N
Me
(±)-3ao
13C{1H}, 125 MHz, CDCl3
f1 (ppm)

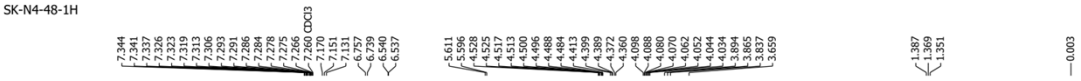

SK-N4-139-1H
7.260 CDCl3
7.191
7.170
7.123
7.105
7.084
6.859
6.650
6.632
7.191
7.170
7.123
7.105
7.084
6.859
6.650
6.632
7.2
7.1
7.0
6.9
6.8
6.7
f1 (ppm)
MeO2C
Et
O
MeO2C
N
Me
(±)-3ap
1H, 400 MHz, CDCl3

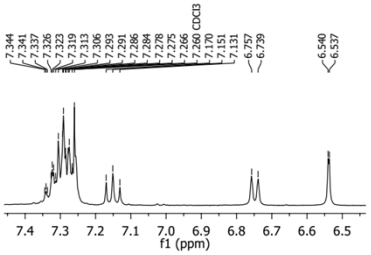

1.01
1.01
0.99
1.01
1.00
1.00
3.01
1.13
2.07
3.00
1.05
1.06
0.99
1.02
3.01
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

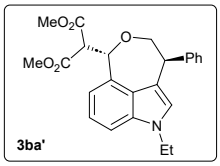

SK-N4-139-13C
168.746
167.664
137.659
135.600
126.230
125.846
121.325
113.975
113.006
108.432
84.752
80.762
77.414
77.160 CDCl3
76.906
58.330
52.923
52.440
33.543
32.820
29.616
10.381
-0.141
MeO2C
Et
O
MeO2C
N
Me
(±)-3ap
13C{1H}, 125 MHz, CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Hd
Hc
SK-N4-139-NOESY
MeO2C
Hd
O
Hc
Et
Ha
Hb
MeO2C
N
Me
(±)-3ap
NOESY, 600 MHz, CDCl3
Hc
Hd
f2 (ppm)
f1 (ppm)

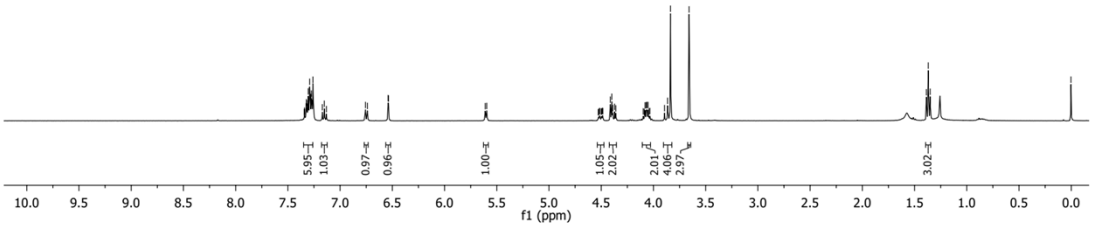
SK-N4-48-1H



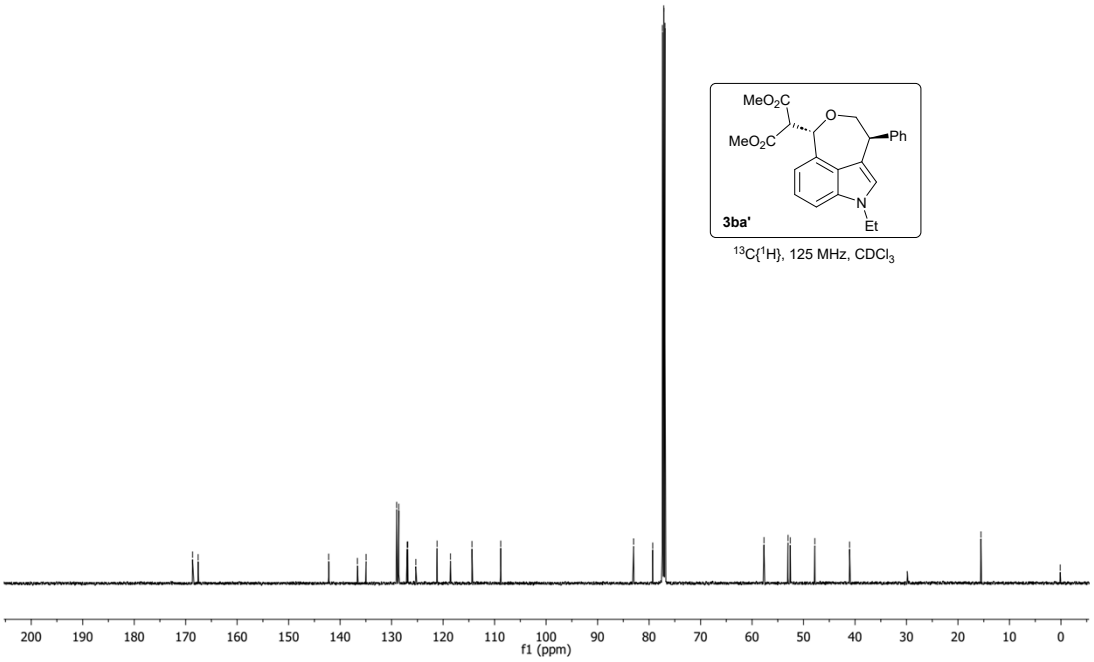




^{1}H, 400 MHz, $CDCl_3$

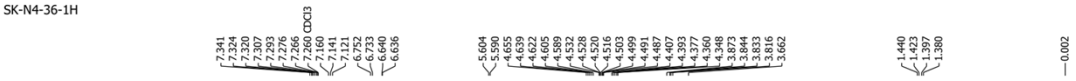


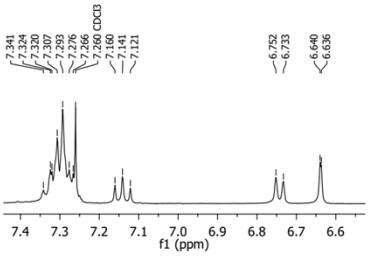
SK-N4-48-13C

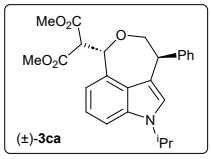


$^{13}C\{^{1}H\}$, 125 MHz, $CDCl_3$

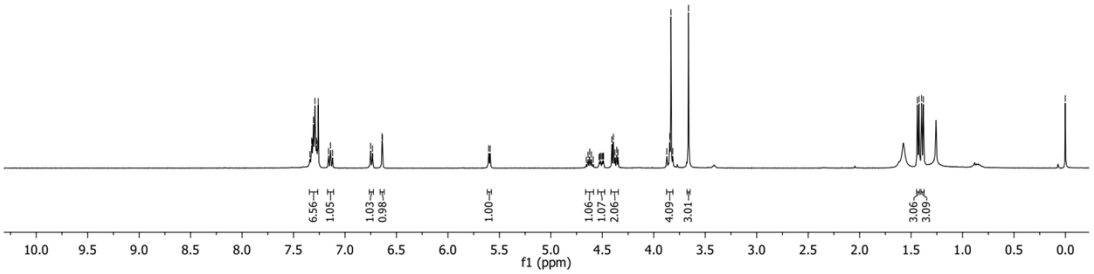
SK-N4-36-1H



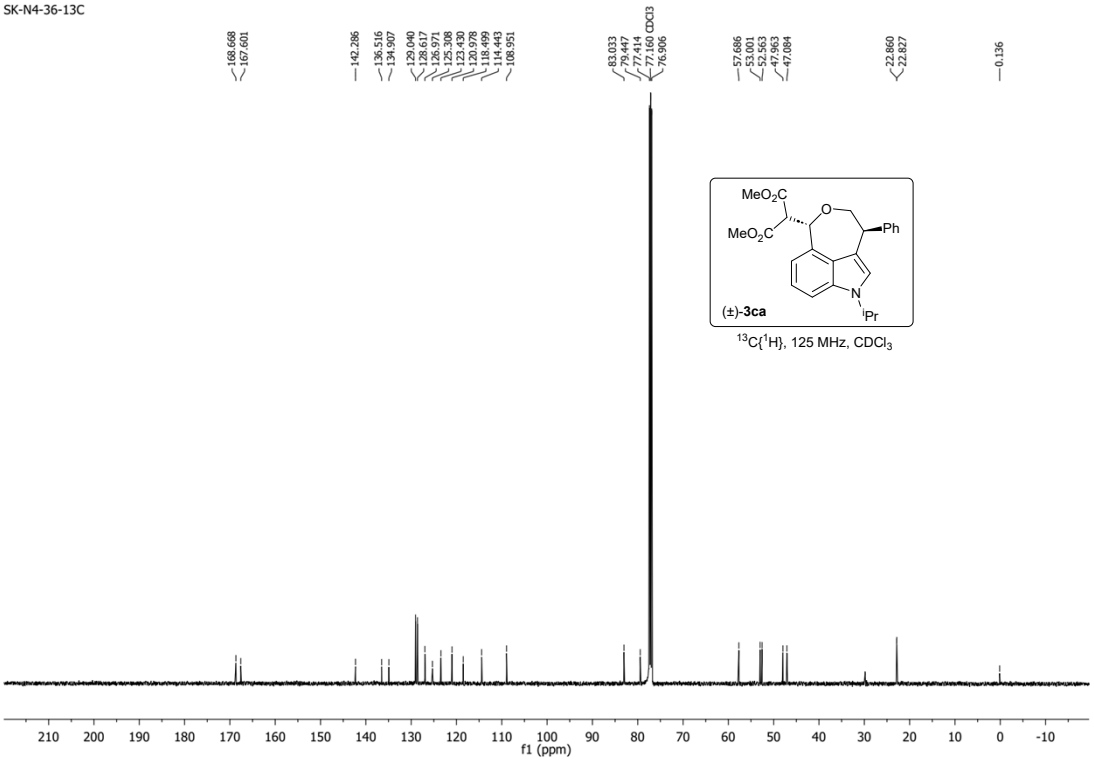




^{1}H, 400 MHz, $CDCl_3$

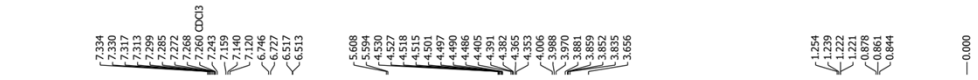


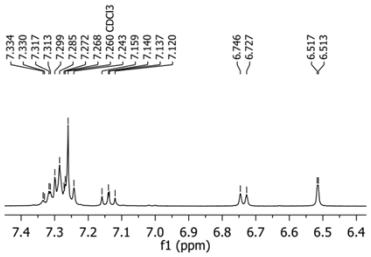
SK-N4-36-13C

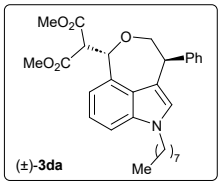


$^{13}C\{^{1}H\}$, 125 MHz, $CDCl_3$

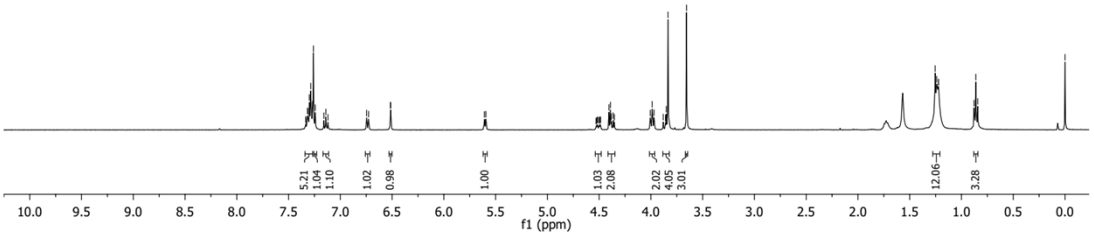
SK-N4-1H



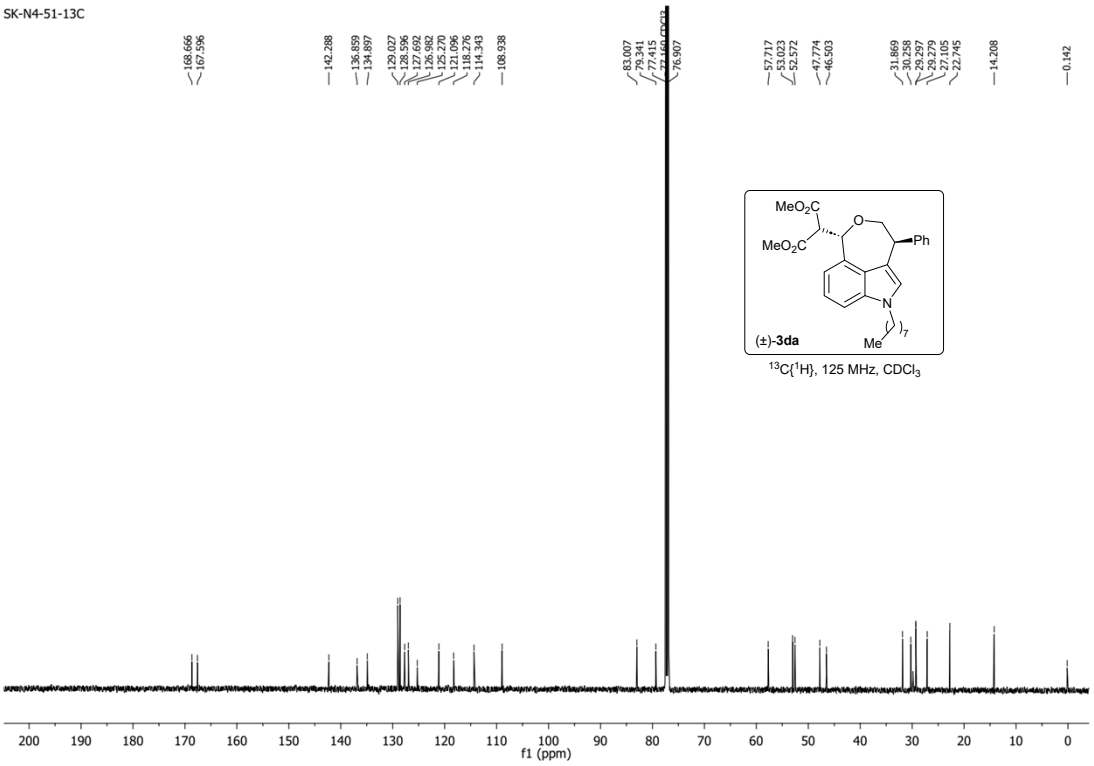




^{1}H, 400 MHz, $CDCl_3$

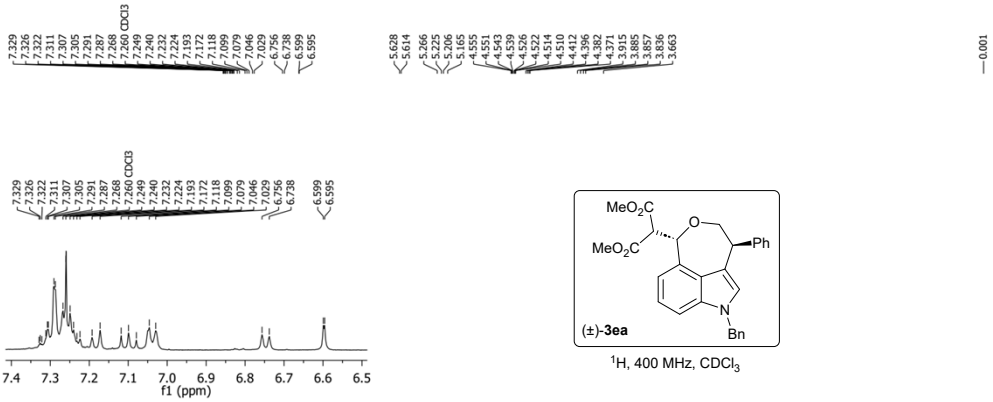


SK-N4-13C

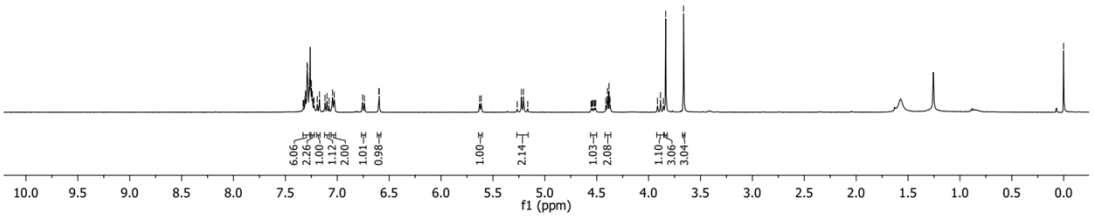


$^{13}C\{^{1}H\}$, 125 MHz, $CDCl_3$

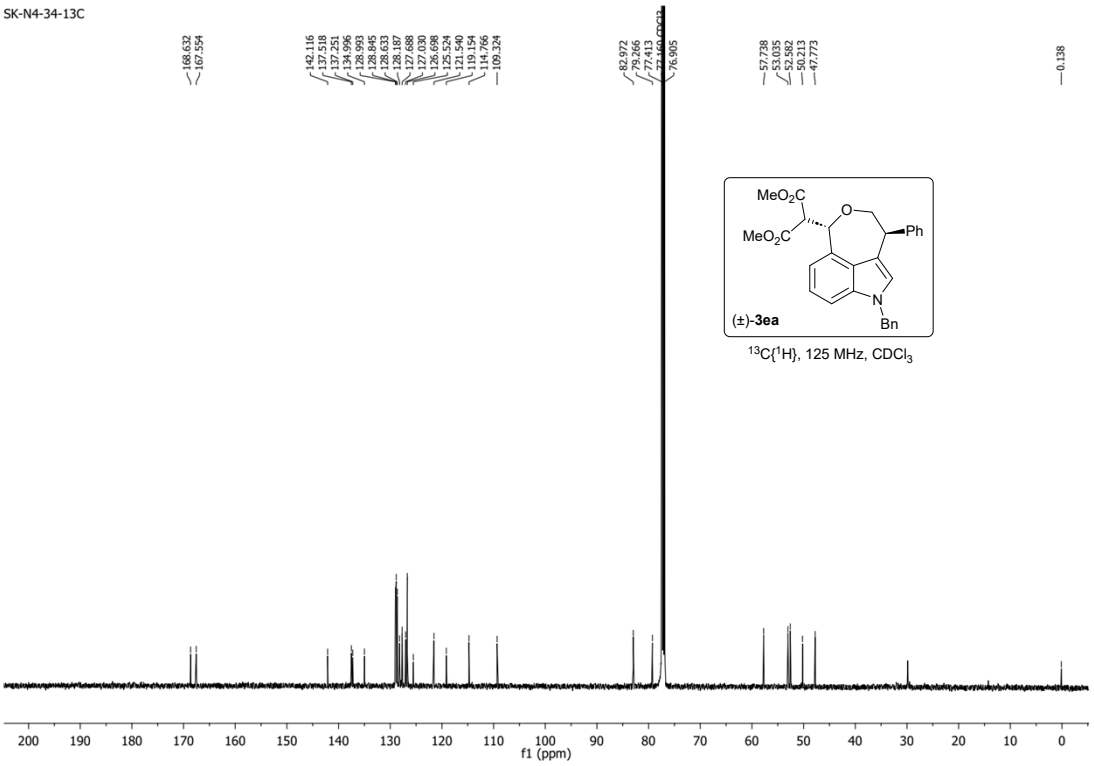
SK-N4-34-1H



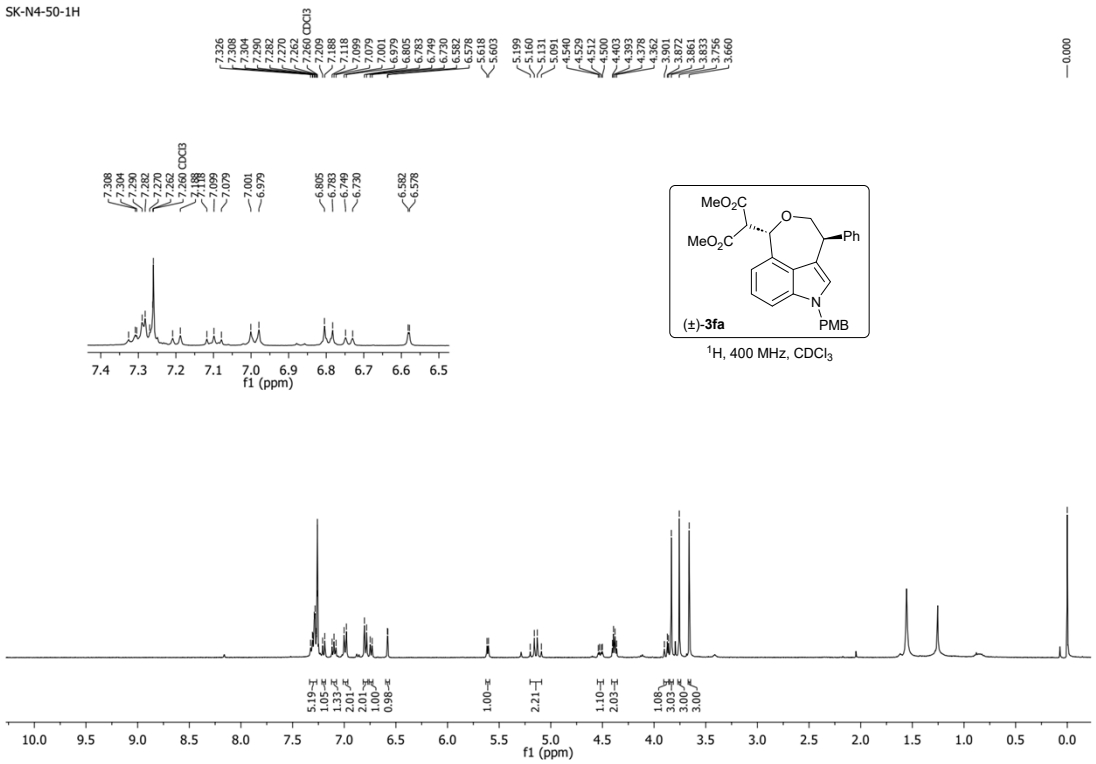
^{1}H, 400 MHz, $CDCl_3$

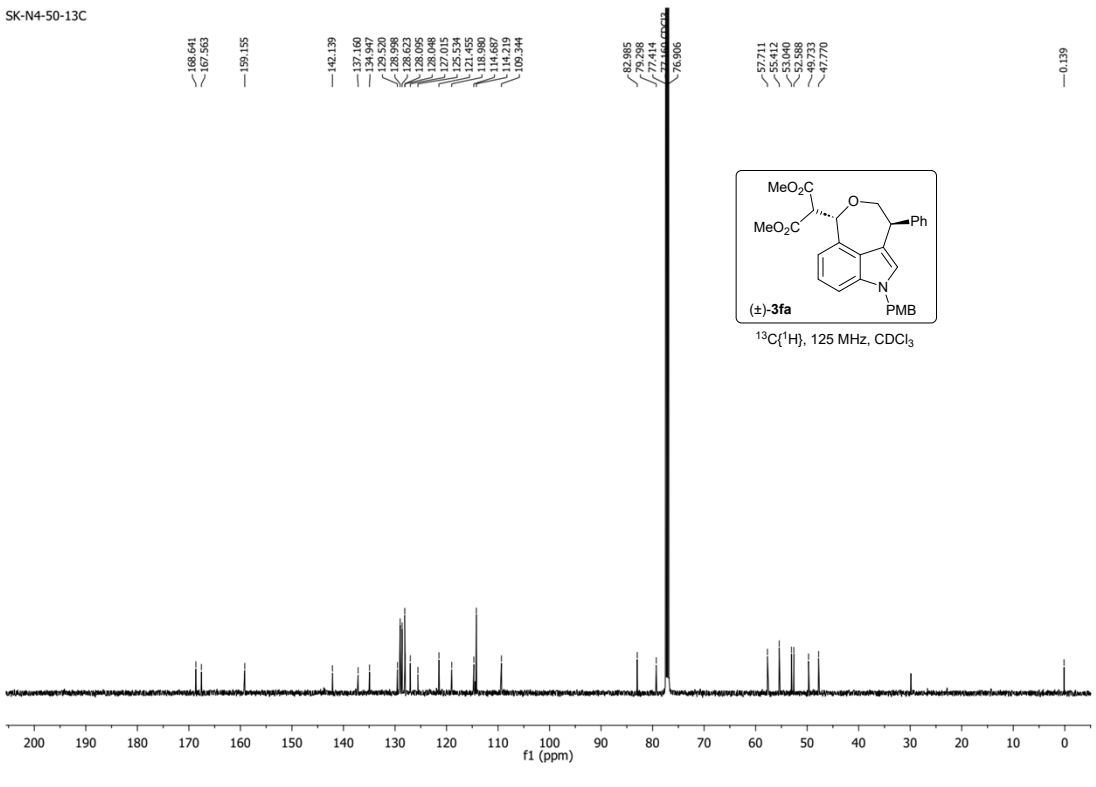


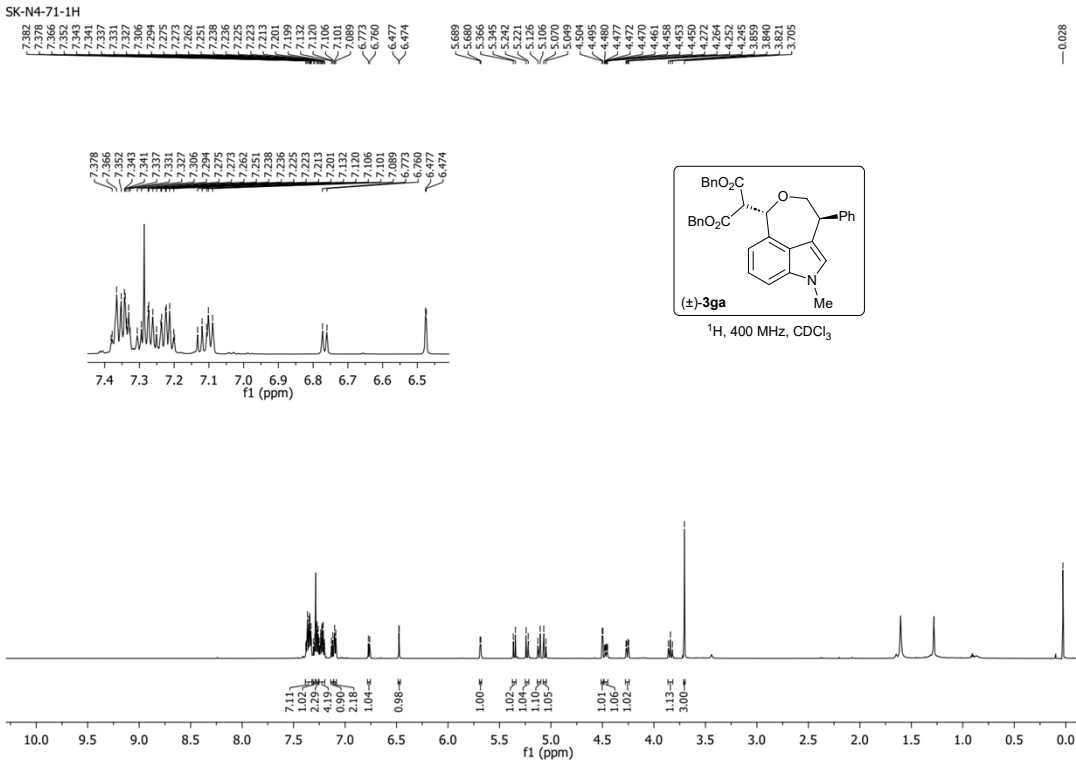
SK-N4-34-13C

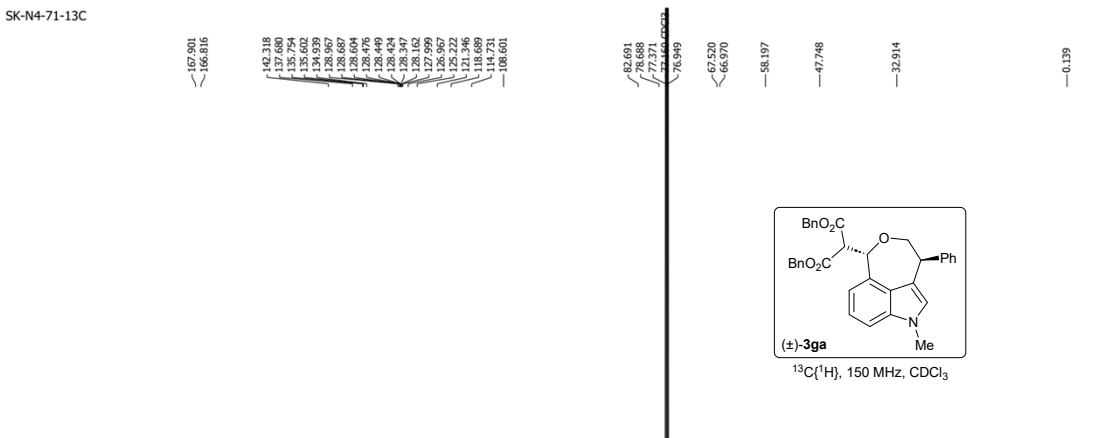


$^{13}C\{^{1}H\}$, 125 MHz, $CDCl_3$


SK-N4-50-1H
MeO2C
MeO2C
O
Ph
N
PMB
(±)-3fa
1H, 400 MHz, CDCl3
f1 (ppm)

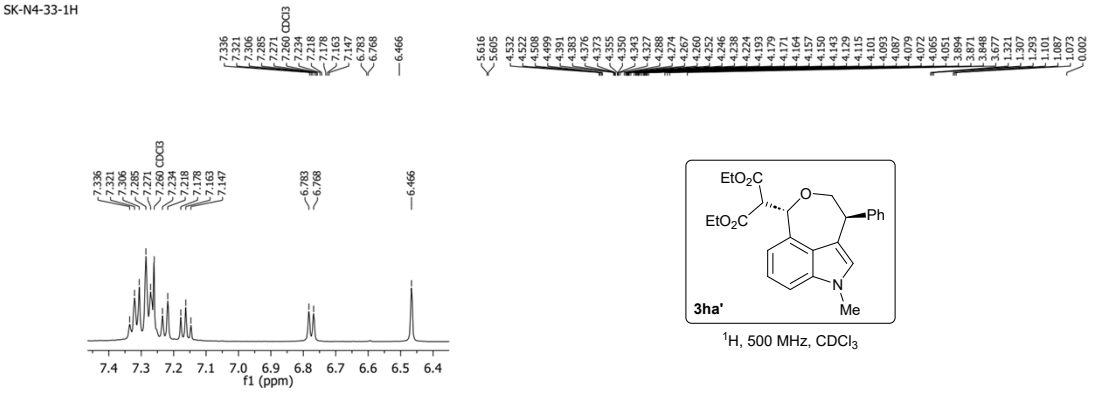

SK-N4-50-13C
MeO2C
MeO2C
O
Ph
N
PMB
(±)-3fa
13C{1H}, 125 MHz, CDCl3
f1 (ppm)


SK-N4-71-1H
BnO2C
BnO2C
O
Ph
N
Me
(±)-3ga
1H, 400 MHz, CDCl3
f1 (ppm)

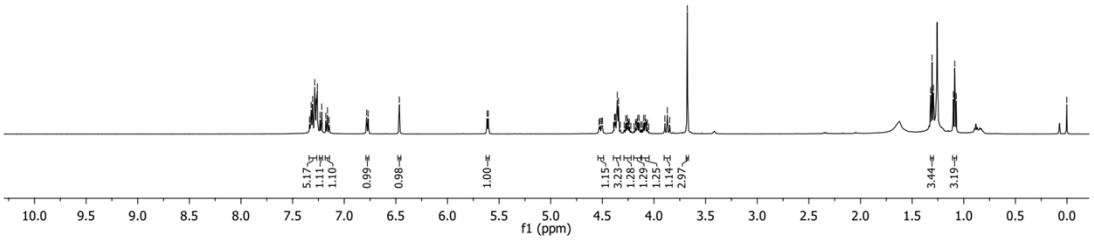

f1 (ppm)

SK-N4-71-13C
BnO2C
BnO2C
O
Ph
N
Me
(±)-3ga
13C{1H}, 150 MHz, CDCl3
f1 (ppm)

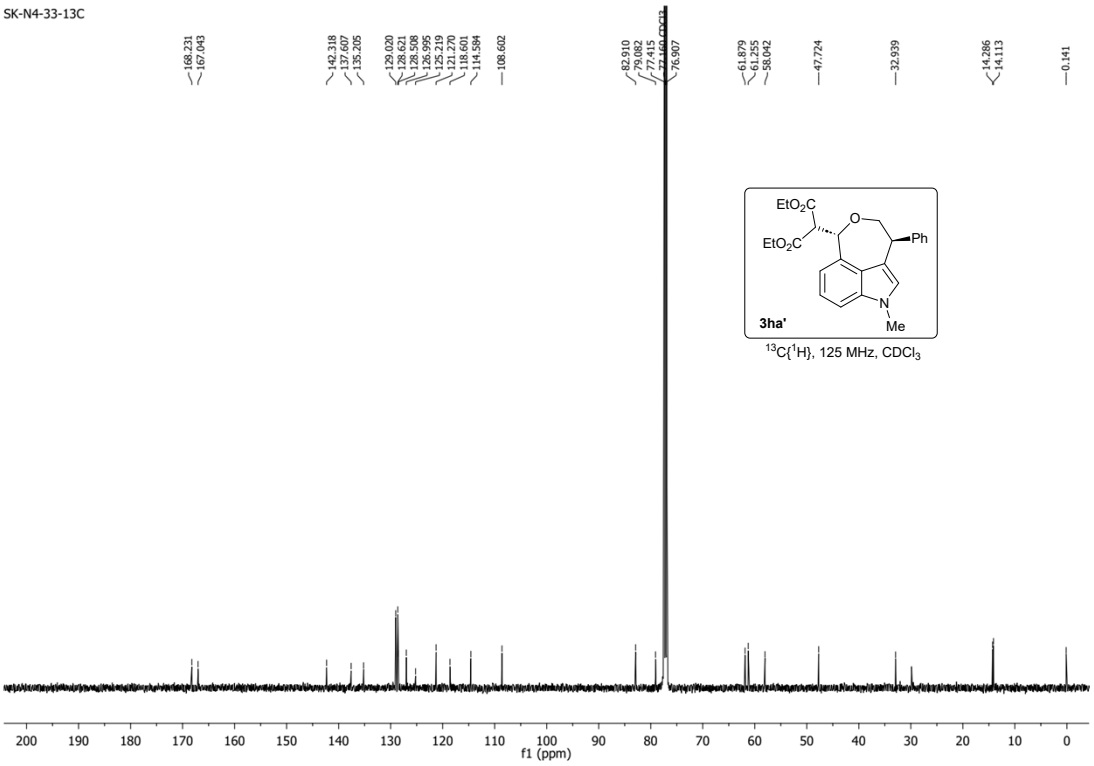
SK-N4-33-1H



^{1}H, 500 MHz, $CDCl_3$

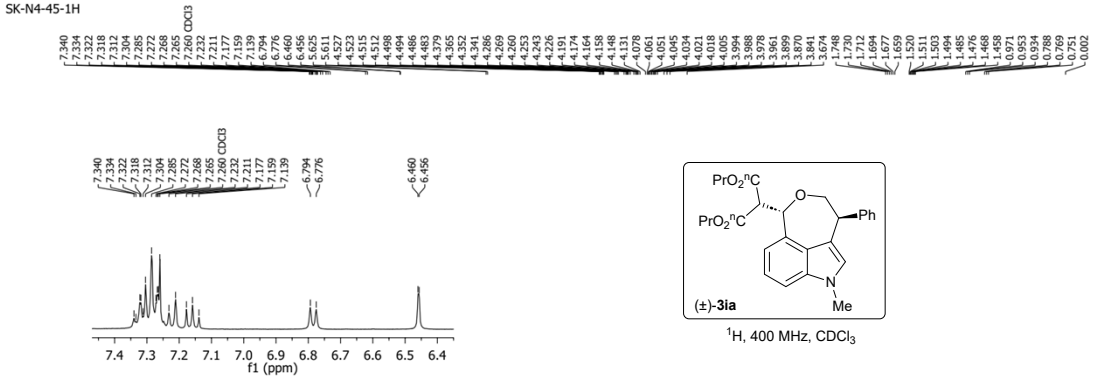


SK-N4-33-13C

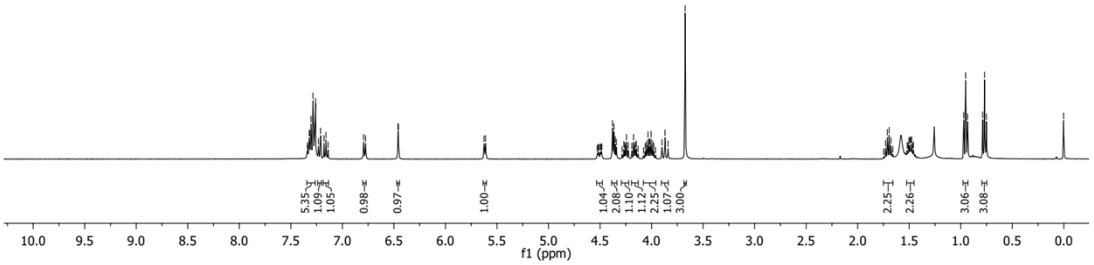


$^{13}C\{^1H\}$, 125 MHz, $CDCl_3$

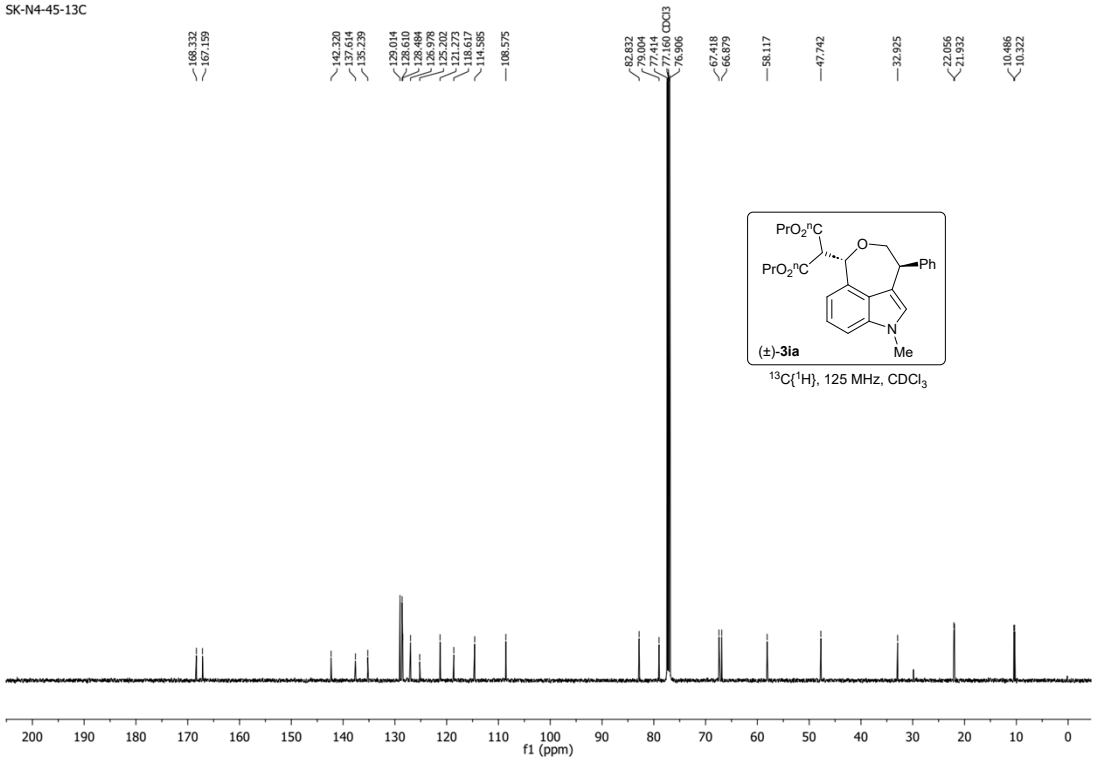
SK-N4-45-1H



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

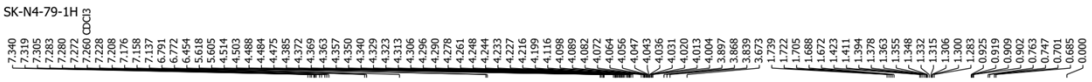


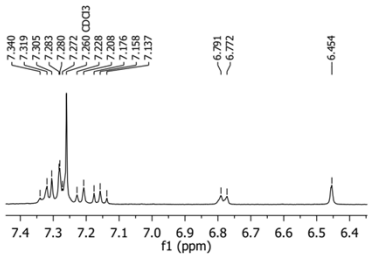
SK-N4-45-13C

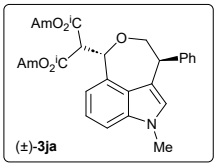


$^{13}C\{^1H\}$, 125 MHz, $CDCl_3$

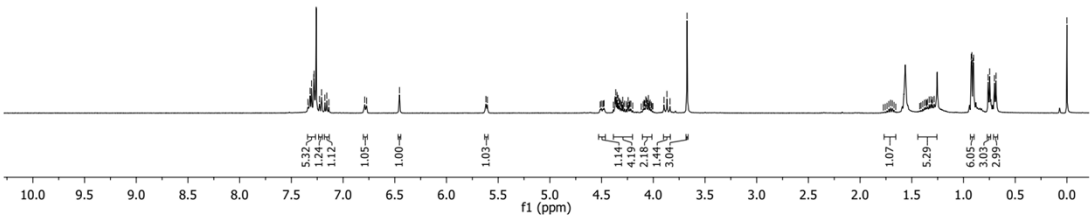
SK-N4-79-1H



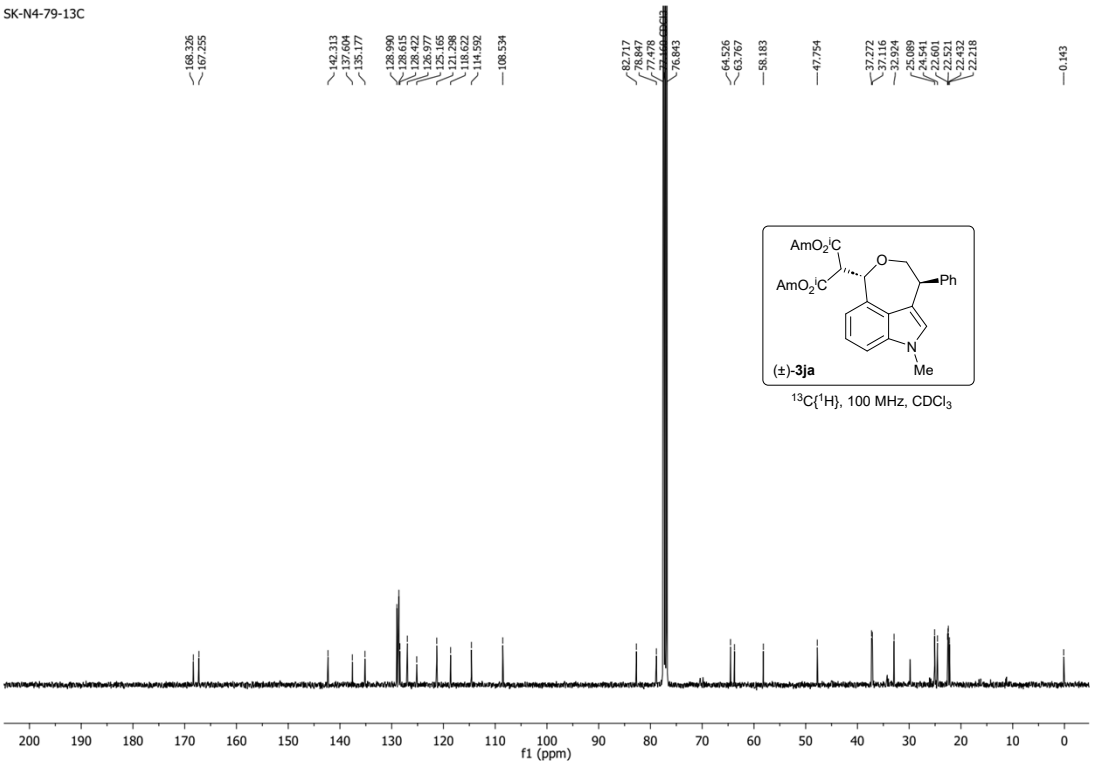




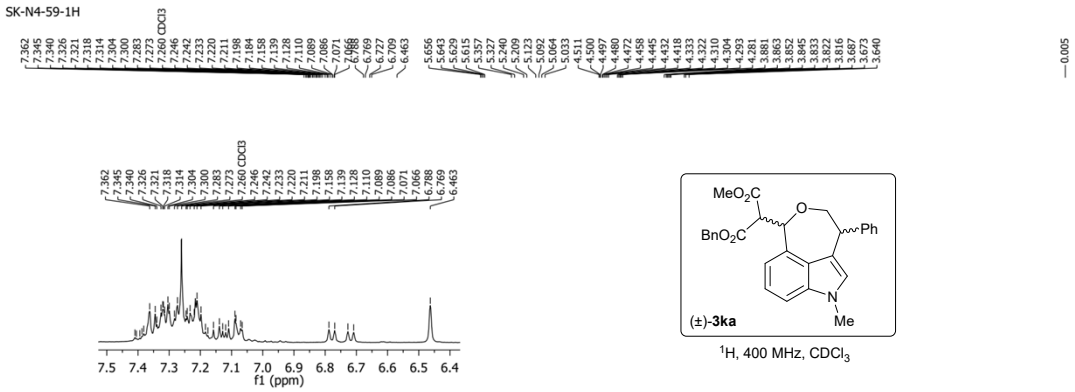
^{1}H, 400 MHz, $CDCl_3$



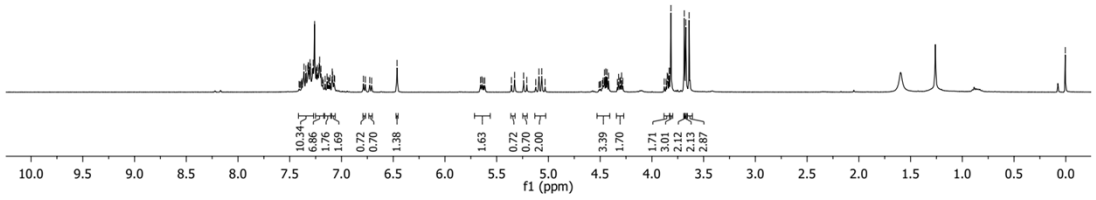
SK-N4-79-13C

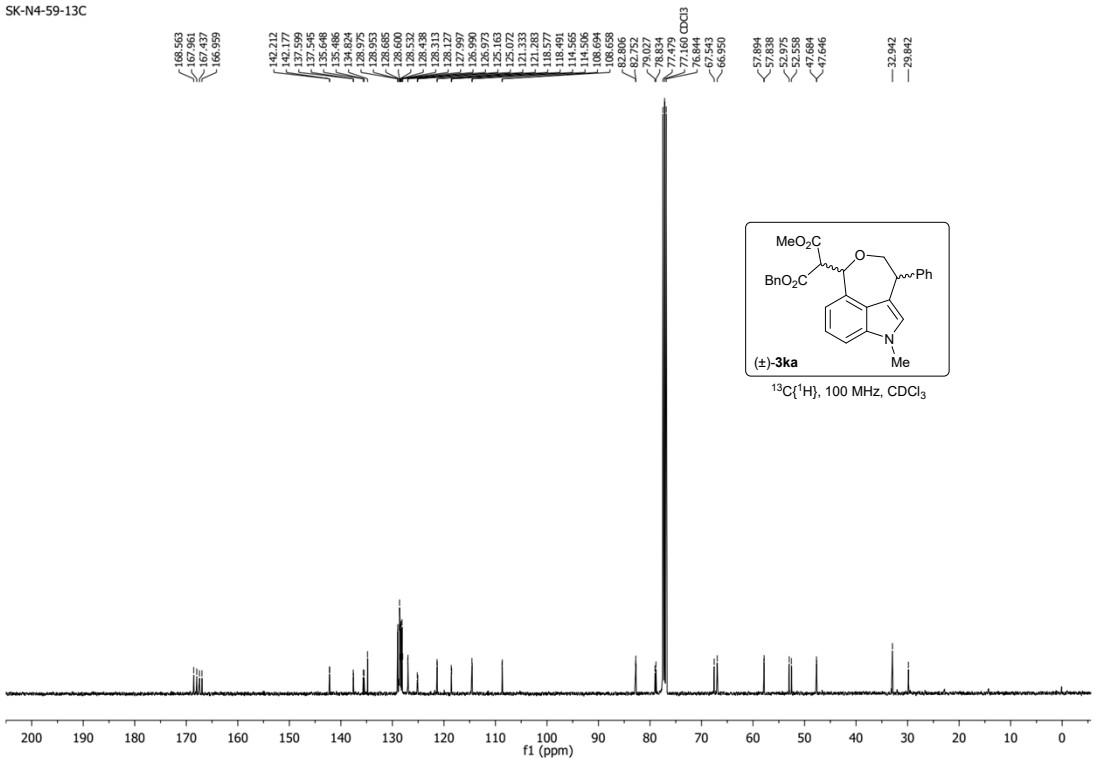


^{13}C{^{1}H}, 100 MHz, $CDCl_3$



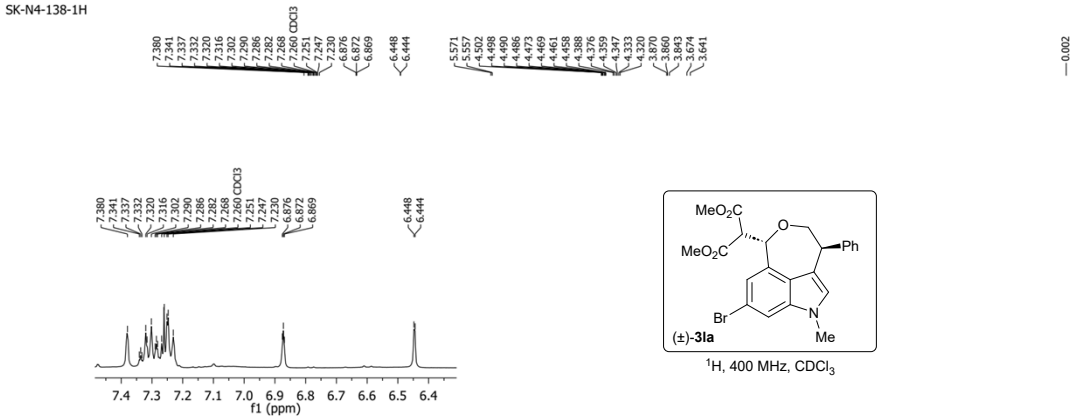
^{1}H, 400 MHz, $CDCl_3$





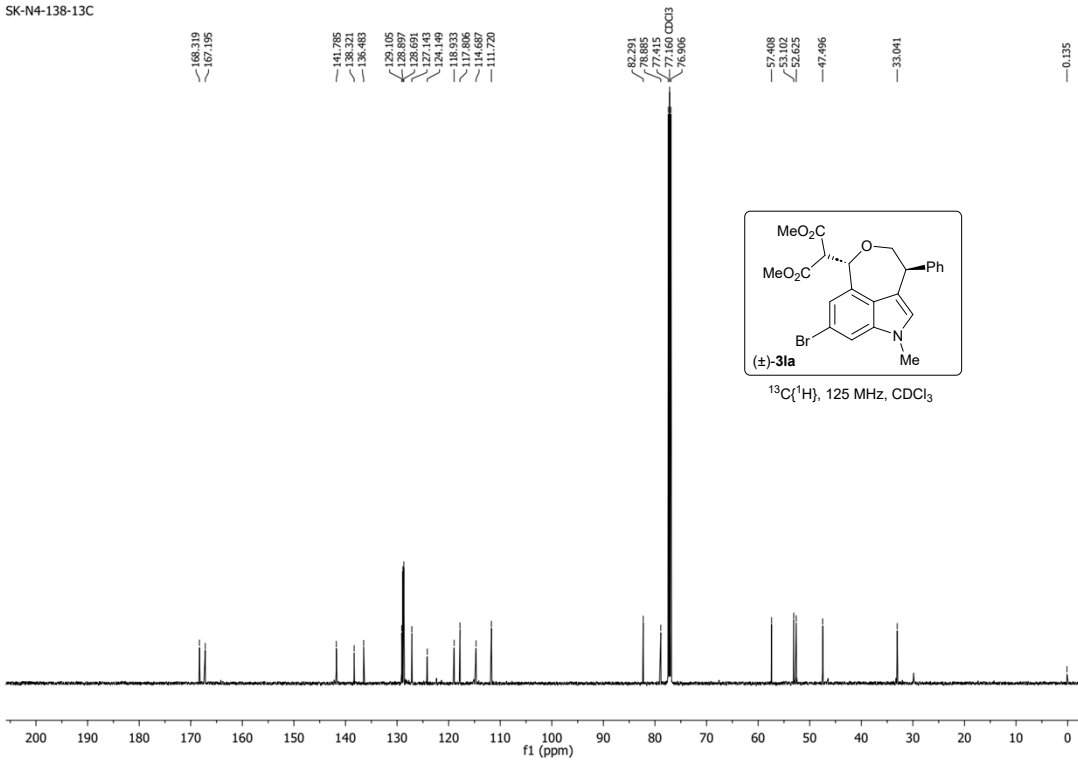
$^{13}C\{^1H\}$, 100 MHz, $CDCl_3$

SK-N4-138-1H



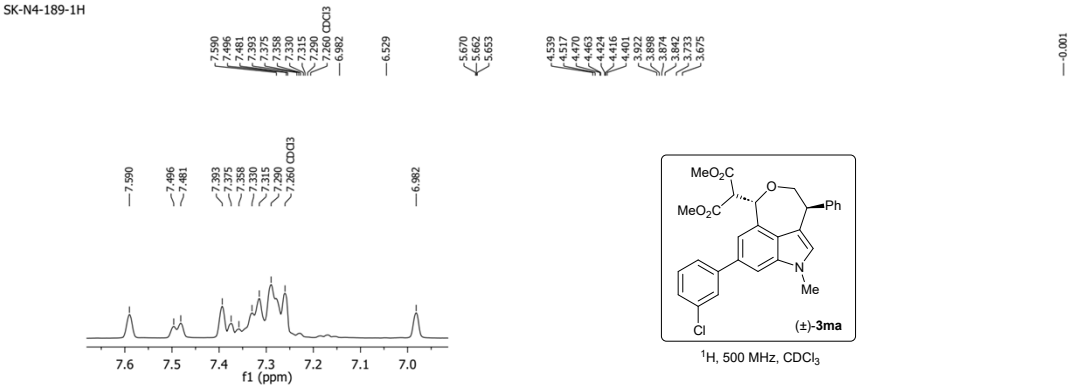
^{1}H, 400 MHz, $CDCl_3$

SK-N4-138-13C

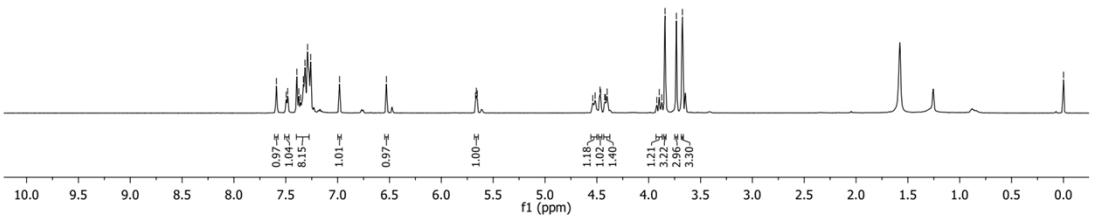


^{13}C{^{1}H}, 125 MHz, $CDCl_3$

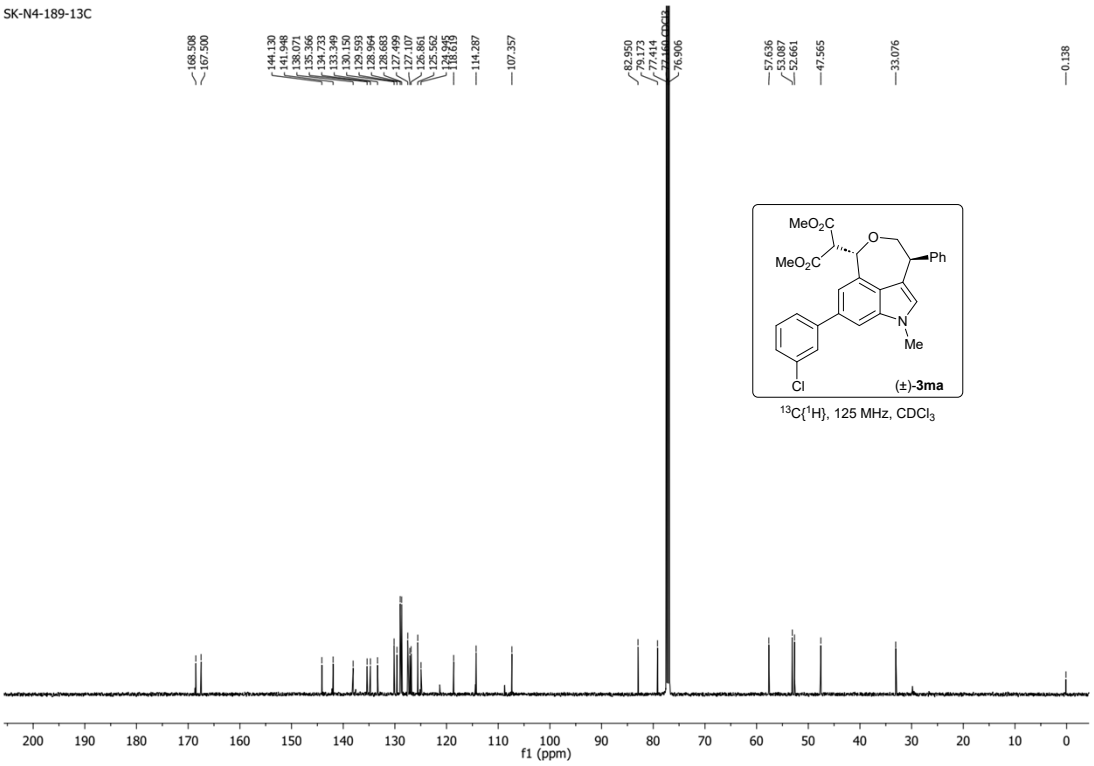
SK-N4-189-1H



^{1}H, 500 MHz, $CDCl_3$

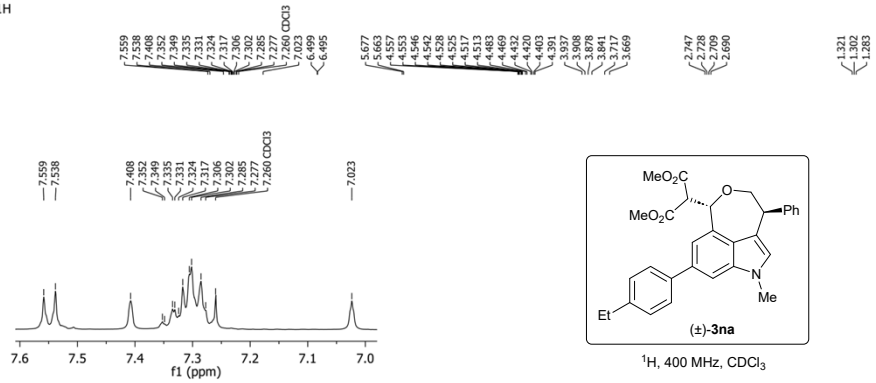


SK-N4-189-13C

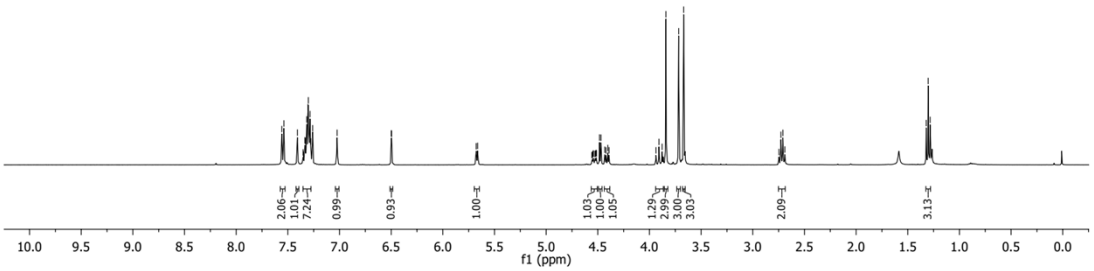


$^{13}C\{^1H\}$, 125 MHz, $CDCl_3$

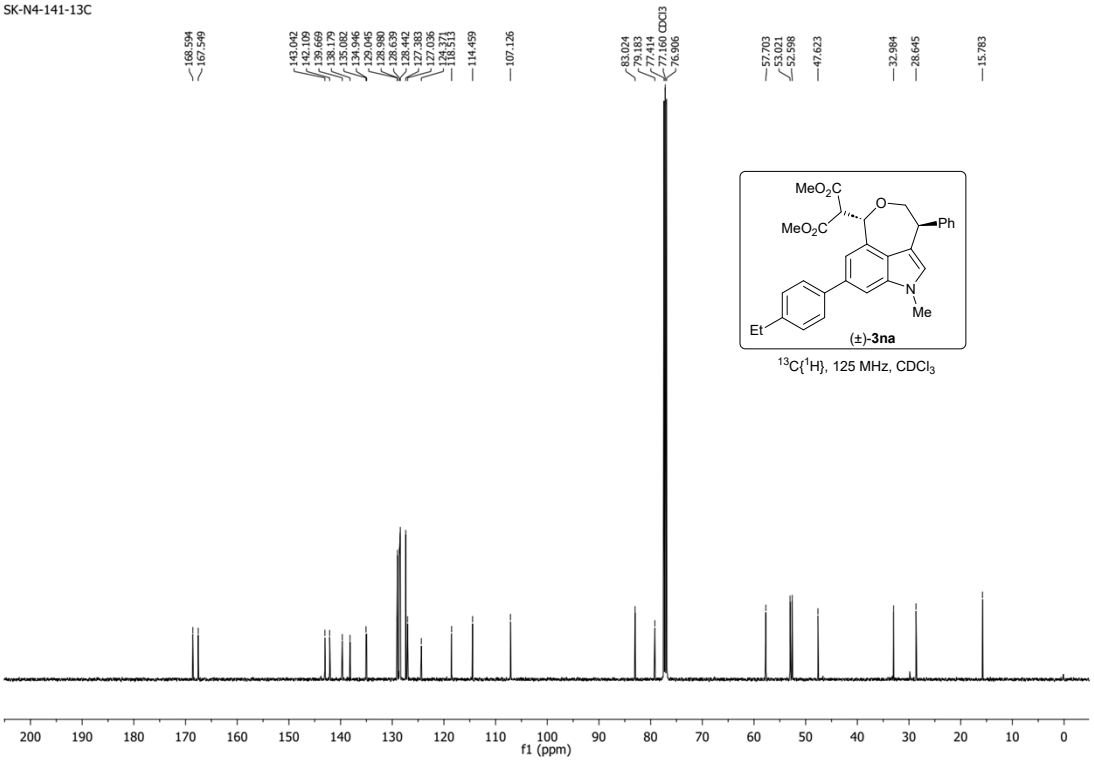
SK-N4-141-1H



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

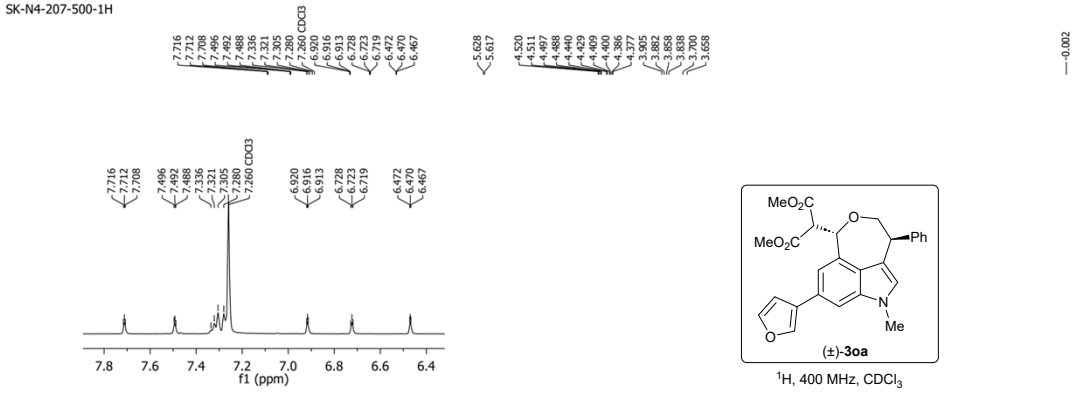


SK-N4-141-13C



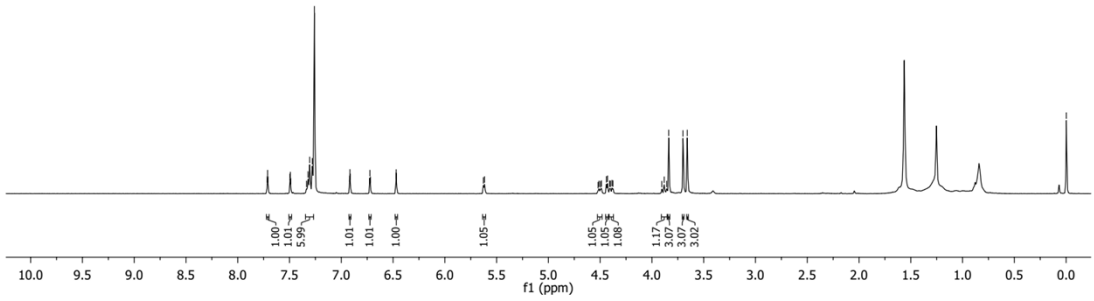
^{13}C{^{1}H}, 125 MHz, $CDCl_3$

SK-N4-207-500-1H

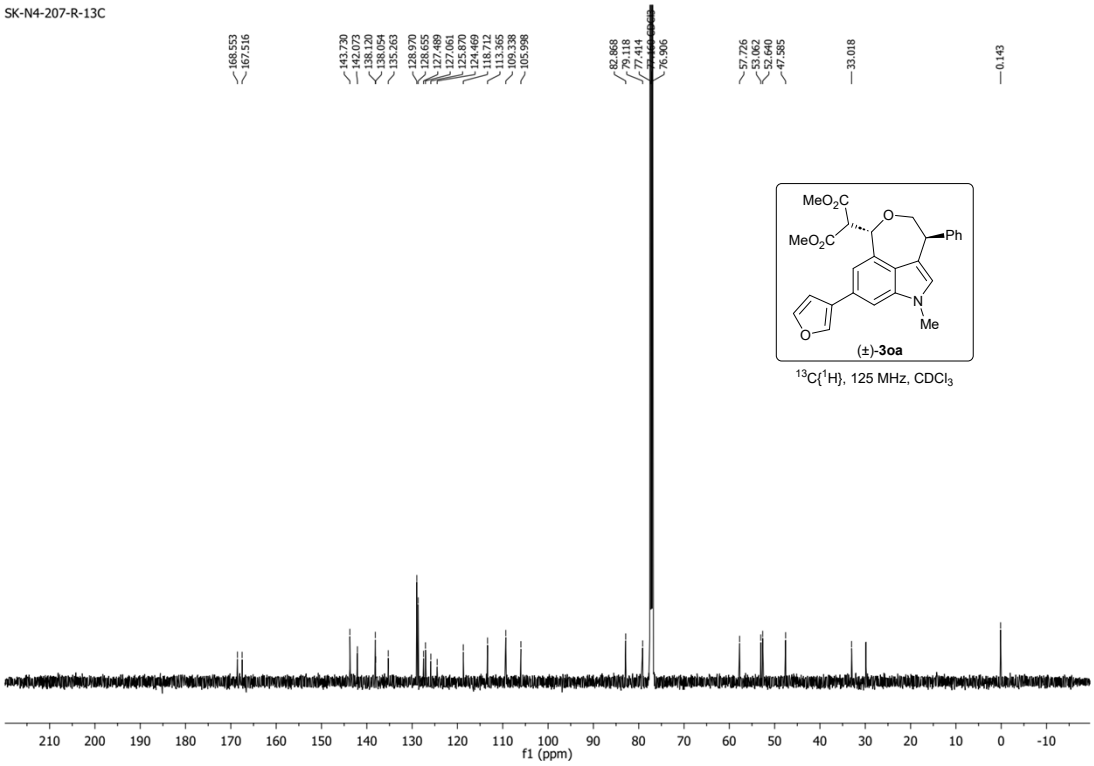


(±)-**3oa**

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



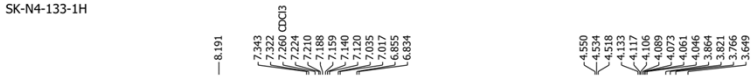
SK-N4-207-R-13C

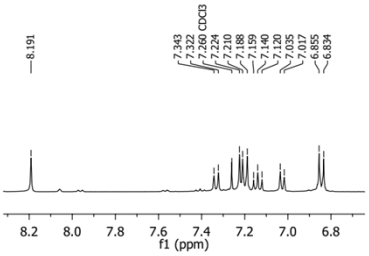


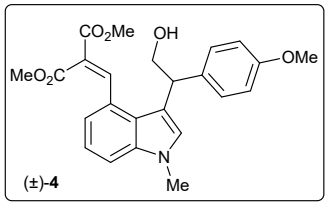
(±)-**3oa**

$^{13}C\{^{1}H\}$, 125 MHz, $CDCl_3$

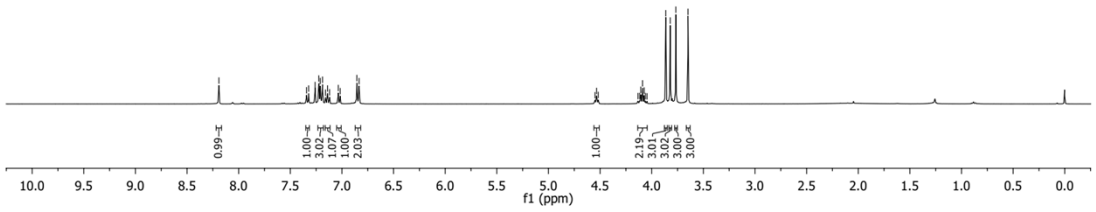
SK-N4-133-1H



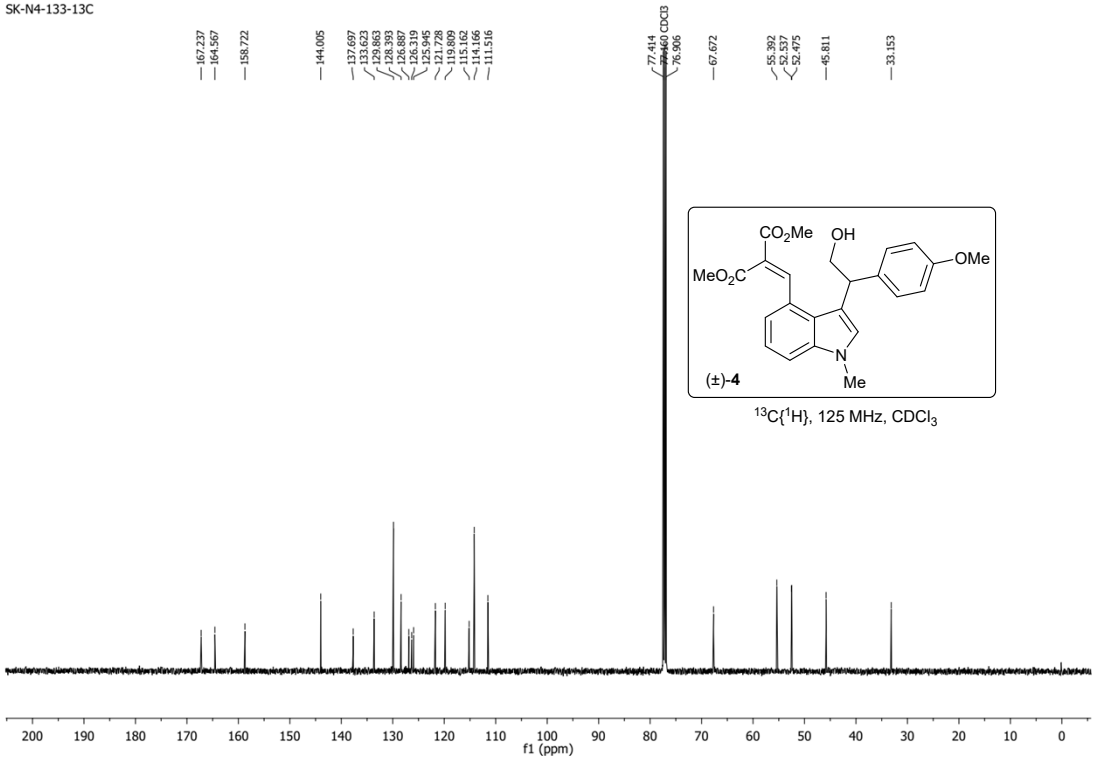




^{1}H, 400 MHz, $CDCl_3$

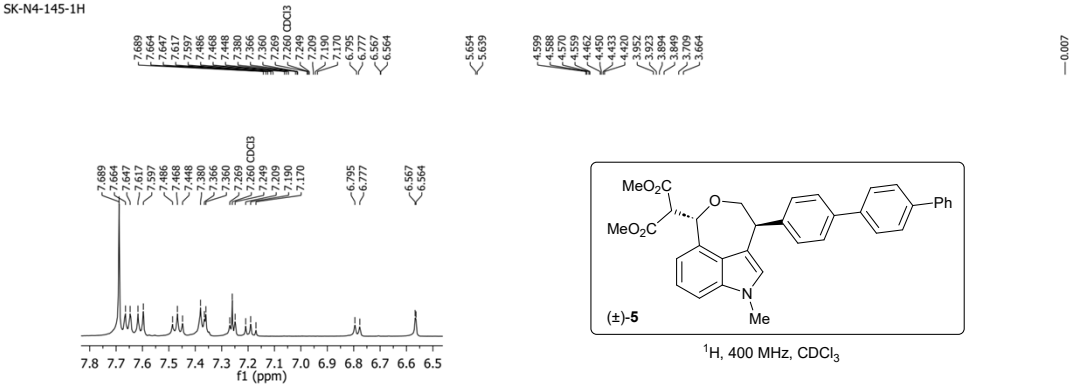


SK-N4-133-13C

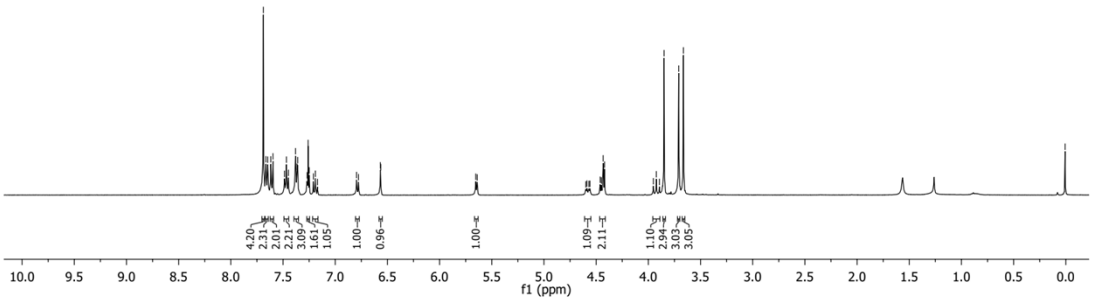


^{13}C{^{1}H}, 125 MHz, $CDCl_3$

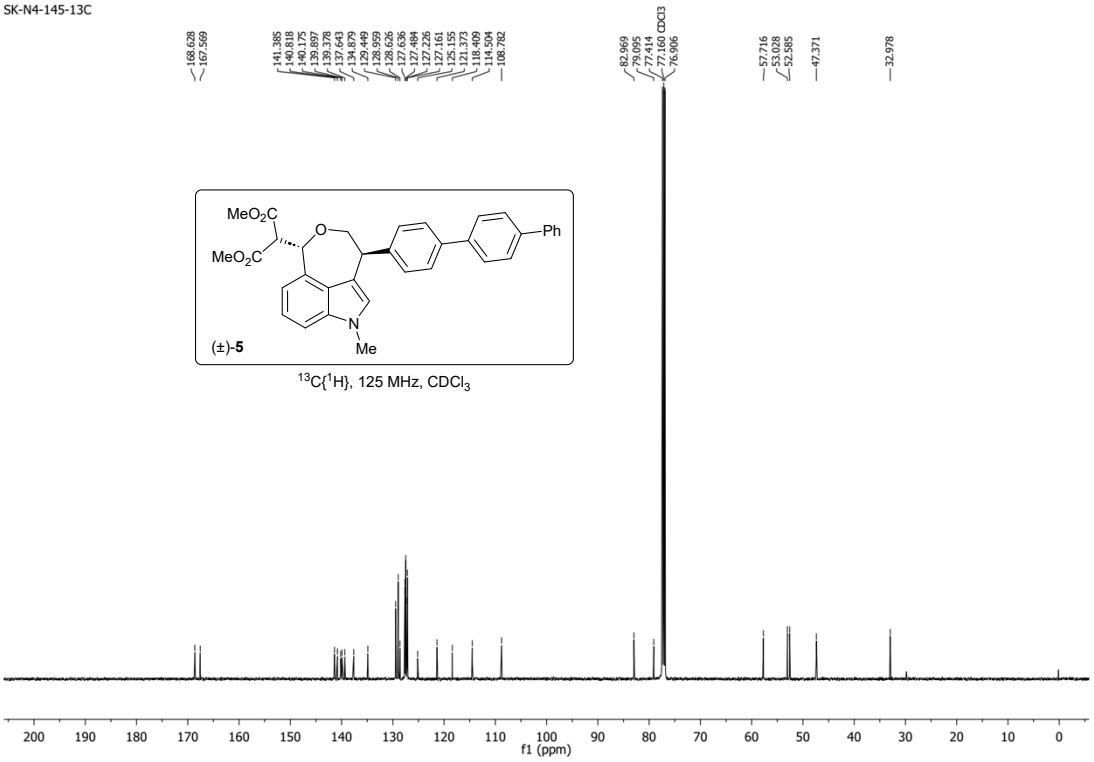
SK-N4-145-1H



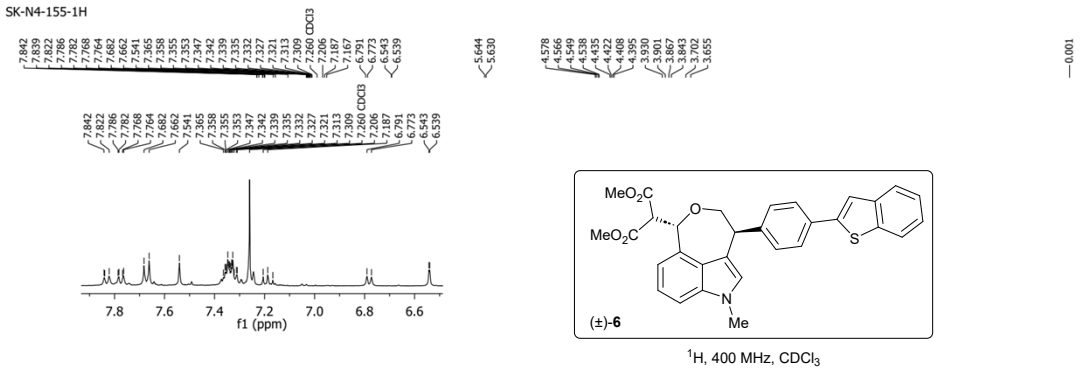
^{1}H, 400 MHz, $CDCl_3$



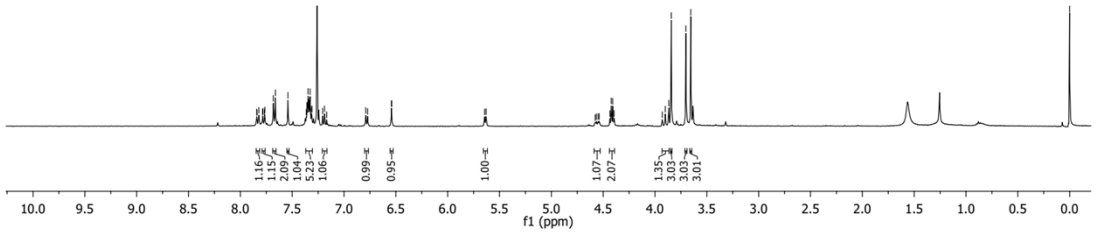
SK-N4-145-13C

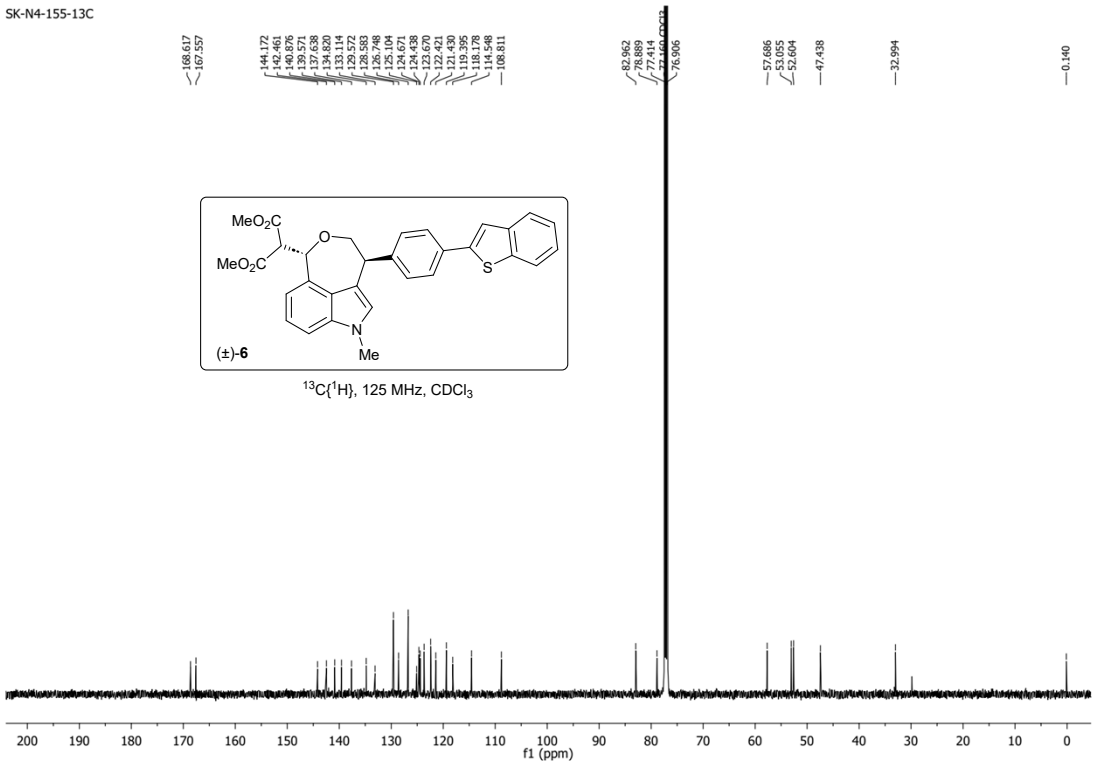


$^{13}C\{^{1}H\}$, 125 MHz, $CDCl_3$



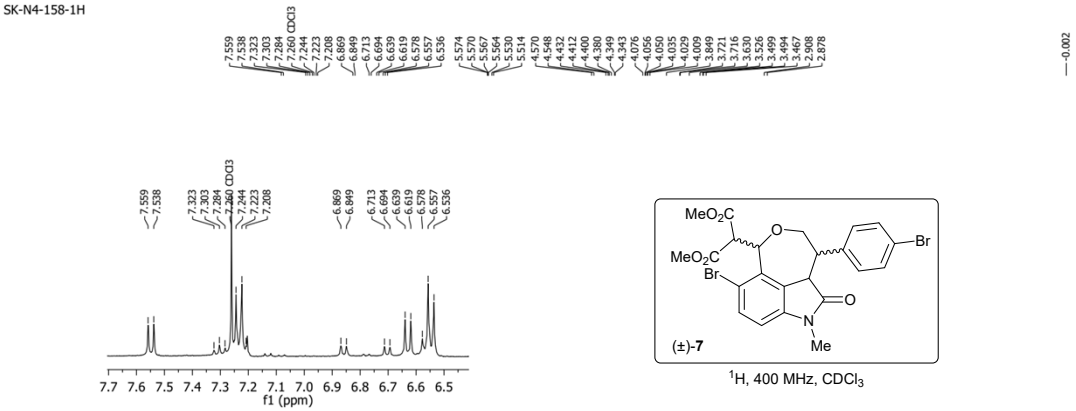
^{1}H, 400 MHz, $CDCl_3$



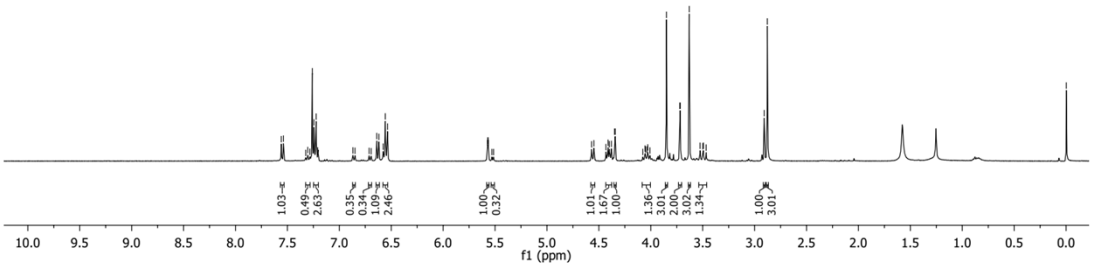


^{13}C{^{1}H}, 125 MHz, $CDCl_3$

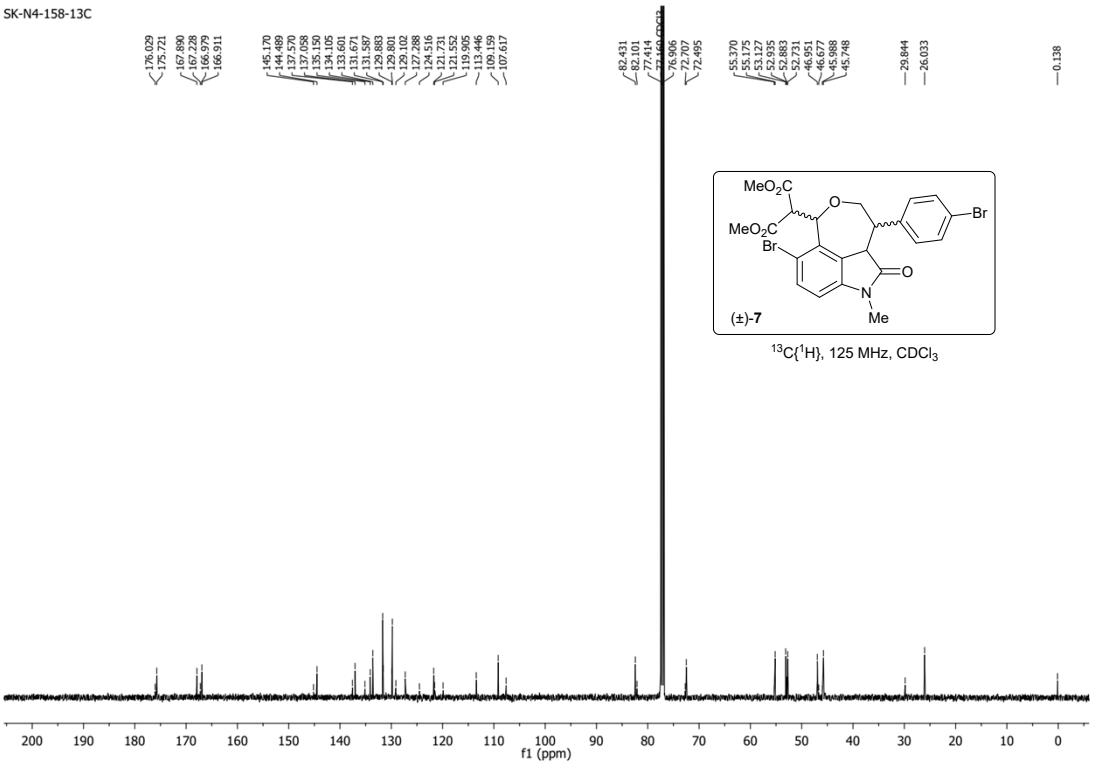
SK-N4-158-1H



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

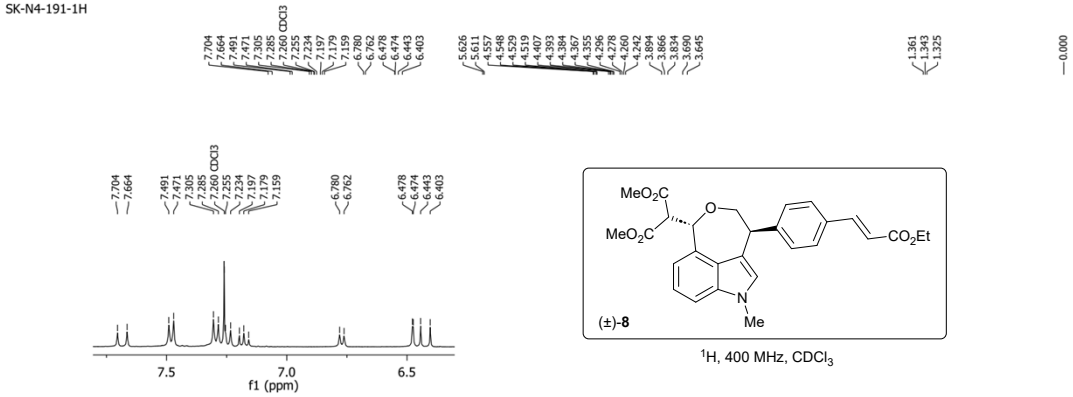


SK-N4-158-13C

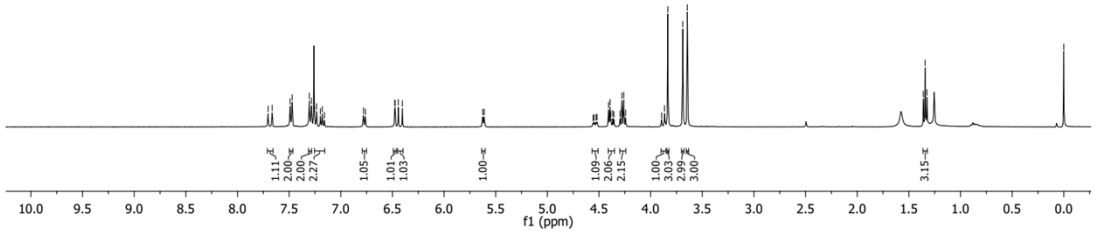


$^{13}C\{^{1}H\}$, 125 MHz, $CDCl_3$

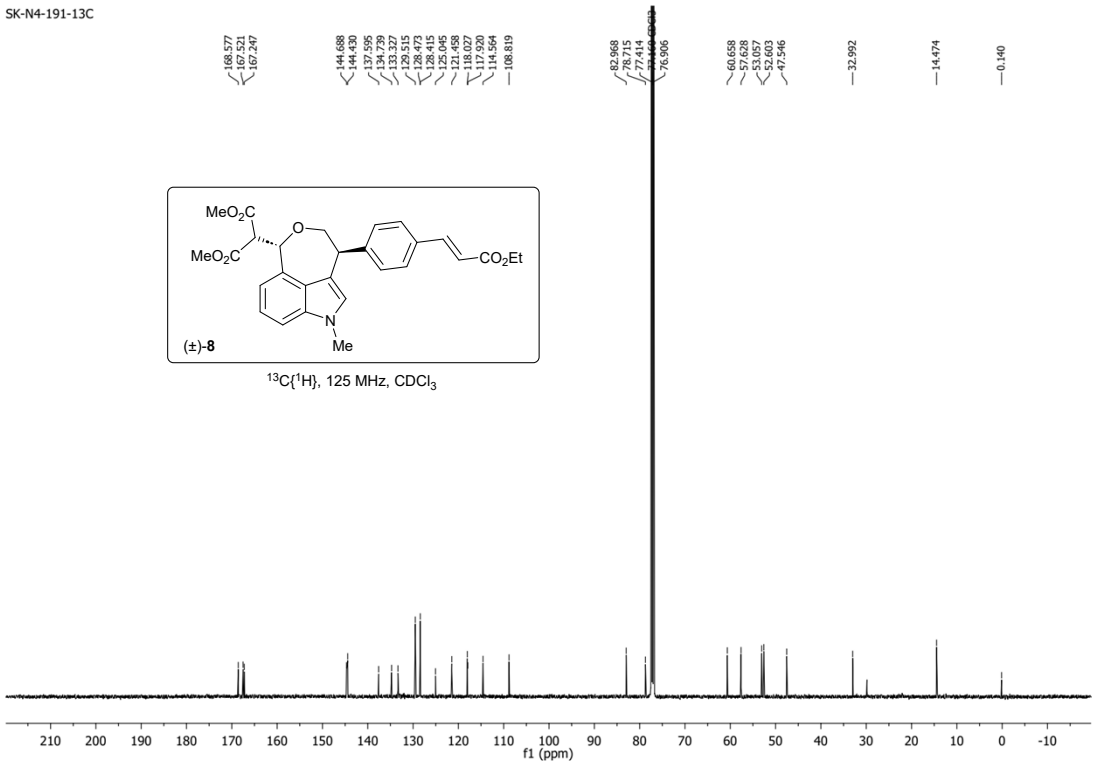
SK-N4-191-1H



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

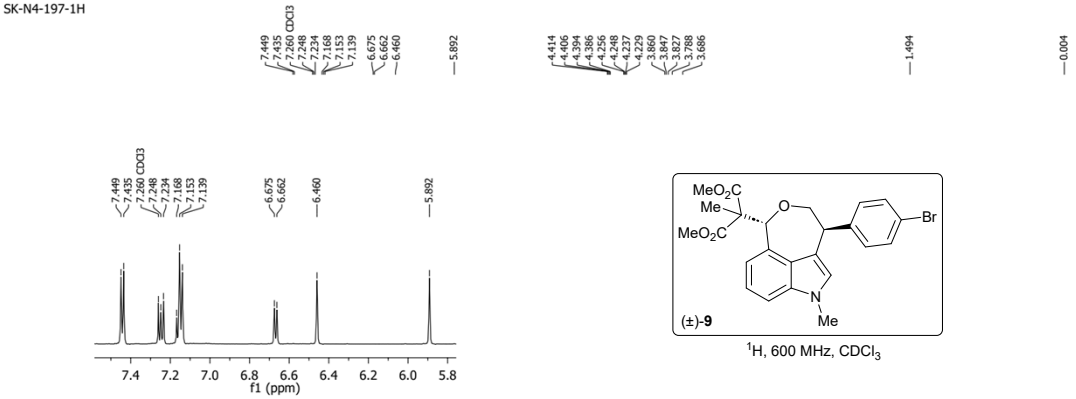


SK-N4-191-13C

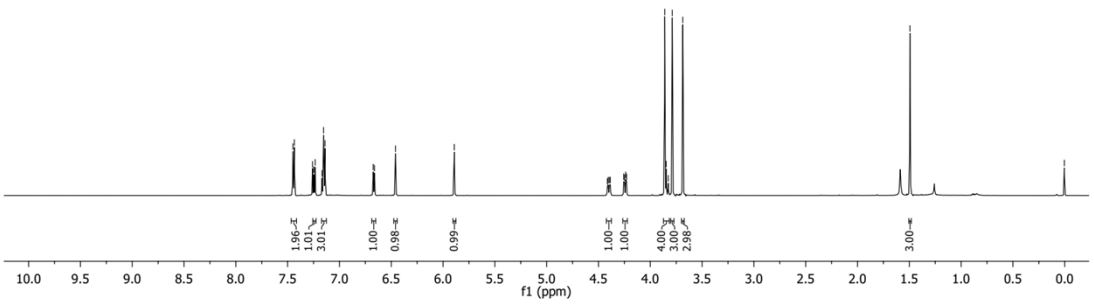


$^{13}C\{^{1}H\}$, 125 MHz, $CDCl_3$

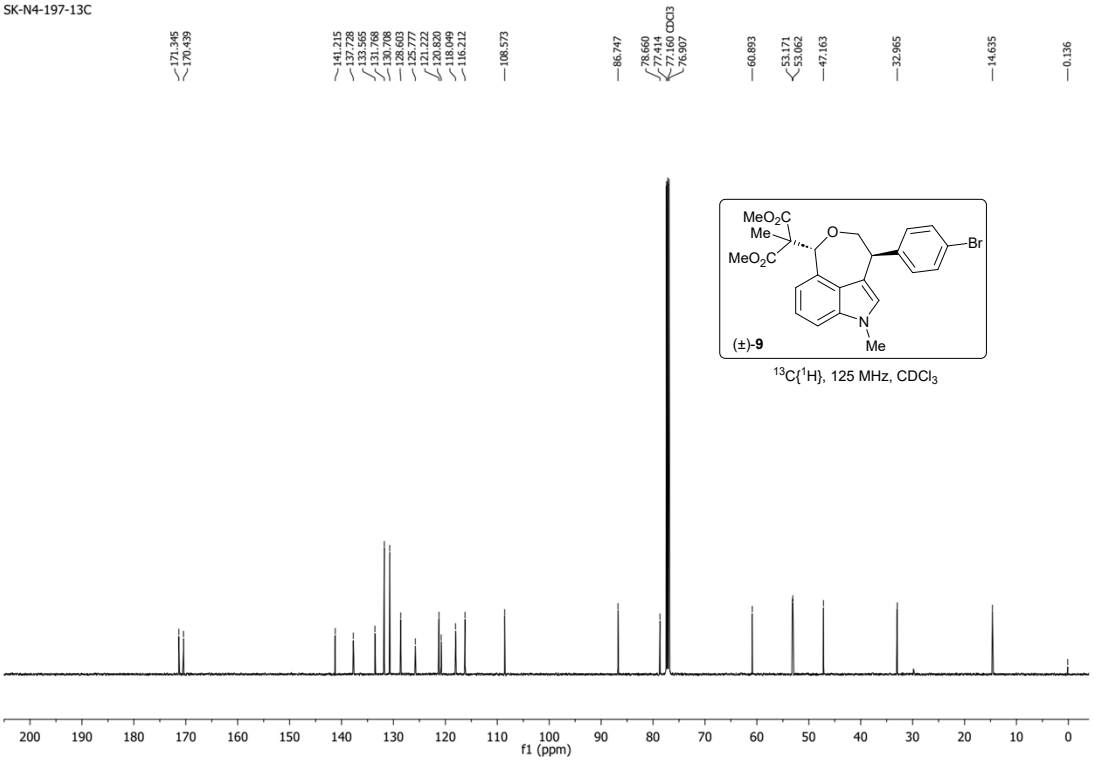
SK-N4-197-1H



^{1}H, 600 MHz, $CDCl_3$



SK-N4-197-13C



^{13}C{^{1}H}, 125 MHz, $CDCl_3$