Contents

1. General

Reactions involving moisture sensitive reagents were carried out in flame-dried glassware under an inert atmosphere (N_2 or Ar) using standard vacuum line techniques. Anhydrous solvents (Et_2O, CH_2Cl_2, THF, DMSO, DMF and PhMe) were obtained after passing through an alumina column (Mbraun SPS-800). Anhydrous solvents (PhCl, PhF, $PhCF_3$, PhMe, *t*-BuPh, *m*-xylene, mesitylene, anisole, benzene, $CHCl_3$, DCE, MTBE, CPME, EtOAc, *t*-BuOAc, perfluorooctane, pivalonitrile, valeronitrile) were obtained by storing in an oven-dried Schlenk flask over activated 4 Å molecular sieves under an inert atmosphere, sieves were activated at 250 °C overnight under high vacuum.[1] Solvents used for purification purposes (Hexane, PhMe, Et_2O, CH_2Cl_2, EtOAc, NEt_3, MeOH) were used as obtained from suppliers without further purification. Hexane is defined as *n*-hexane. All other solvents and commercial reagents were used as received without further purification.

n-Butyllithium (*n*-BuLi) solutions were titrated before use, using THF and diphenyl acetic acid as the indicator. 6 mL of the bought ethyl iododifluoroacetate was washed with aq. $Na_2S_2O_3$ (3 x 10 mL), dried over $MgSO_4$. Distillation of the solution gave the ethyl iododifluoroacetate as a colourless liquid by trapping with a cooling bath of dry ice/acetone, bp 36 – 37 °C (0.8 mbar). The liquid was stored in an amber vial and kept at –12 °C until used.

Room temperature (RT) refers to 20 – 25 °C. Temperatures of 0 °C and –78 °C were obtained using ice/water and CO_2(s)/acetone baths or EtOAc/liquid N_2, respectively. Reactions involving heating were performed using DrySyn blocks and a contact thermocouple.

Under reduced pressure refers to the use of either a Büchi Rotavapor R-200 with a Büchi V-491 heating bath and Büchi V-800 vacuum controller, a Büchi Rotavapor R-210 with a Büchi V-491 heating bath and Büchi V-850 vacuum controller, a Heidolph Laborota 4001 with vacuum controller, an IKA RV10 rotary evaporator with a IKA HB10 heating bath and ILMVAC vacuum controller, or an IKA RV10 rotary evaporator with a IKA HB10 heating bath and Vacuubrand CVC3000 vacuum controller. Rotary evaporator condensers are fitted to Julabo FL601 Recirculating Coolers filled with ethylene glycol and set to 0 °C.

Analytical thin layer chromatography (TLC) was performed using pre-coated aluminium backed plates (Merck Kieselgel 60 F254 silica). Visualisation was achieved under UV light

(short–wave λ = 254, long–wave λ = 340 nm) and/or with staining with aqueous potassium permanganate solution, ethanolic vanillin solution, ethanolic phosphomolybdic acid (PMA) solution or Seebach's 'Magic' stain (ceric ammonium molybdate solution), followed by gentle heating. Flash chromatography was performed using compressed air on glass columns containing porosity 2/3 sintered disks over Kieselgel 60 silica, using the solvent system and gradient stated. Distillation was performed using a short pathway distillation using a DrySyn heating block with a contact thermocouple and pressure stated from Schlenk line and high vacuum pump (Edwards RV8). Otherwise from a Büchi Glass Oven B-585 Kugelrohr with a Vacuubrand MD1C vacuum controller using the temperature and pressure stated.

Compound names have been generated using ChemDraw® Professional (PerkinElmer) software.

Melting points were recorded on a Buchi melting point M–565 apparatus and are uncorrected. Solvents are reported in brackets when the solid was recrystallized and *dec* refers to decomposition.

Optical rotations were measured on a Perkin Elmer Precisely/Model-341 polarimeter operating at the sodium D line with a 100 mm path cell at 20 °C. Values are given: $[\alpha]_D^{20}$ (*c* in grams per 100 mL, solvent).

Chiral high performance liquid chromatography (HPLC) was performed on an Agilent 1260 Infinity II HPLC consisting of a 1260 Infinity II Quaternary Pump with integrated 4-channel degassing unit, 1260 Infinity II Vialsampler, 1290 Infinity II Multicolumn Thermostat, 1260 Infinity II Diode Array Detector WR. Separation was achieved using either Daicel CHIRALPAK® AD-H, AS-H columns or Daicel CHIRALCEL® OJ-H or OD-H columns using the method stated. All columns (4.6 mm ø x 250 mm, 5 μm particle size) were used with a corresponding guard column (4 mm ø x 10 mm, 5 μm particle size). HPLC traces of enantiomerically enriched compounds were compared with authentic racemic samples. Solvents are given as a ratio, solvent flow rates are reported in mL/min. Wavelengths (λ) are reported in nm, temperatures are reported in °C and retention times (t_R) are reported in minutes.

Infrared spectra were recorded on a Shimadzu IRAffinity-1 Fourier transform IR spectrophotometer fitted with a Specac Quest ATR accessory (diamond puck). Spectra were recorded neat with characteristic absorption wavenumbers (ν_{max}) reported in cm^{-1}.

NMR spectra (^{1}H, $^{13}C\{^{1}H\}$, ^{19}F and $^{19}F\{^{1}H\}$) on either a Bruker AV300 with a BBFO probe (^{1}H 300 MHz; $^{13}C\{^{1}H\}$ 75 MHz; $^{19}F\{^{1}H\}$ 282 MHz), a Bruker AV400 with a BBFO probe (^{1}H 400 MHz; $^{13}C\{^{1}H\}$ 101 MHz; $^{19}F\{^{1}H\}$ 377 MHz), a Bruker AVII 400 with a BBFO probe (^{1}H 400 MHz; $^{13}C\{^{1}H\}$ 101 MHz; $^{19}F\{^{1}H\}$ 376 MHz), a Bruker AVIII-HD 500 with a Smart Probe BBFO+ probe (^{1}H 500 MHz, $^{13}C\{^{1}H\}$ 126 MHz, $^{19}F\{^{1}H\}$ 470 MHz), a Bruker AVIII 500 with a CryoProbe Prodigy BBO probe (^{1}H 500 MHz, $^{13}C\{^{1}H\}$ 126 MHz, ^{19}F 471 MHz) or a Bruker AVIII-HD 700 with a CryoProbe Prodigy BBO probe TCI (^{1}H 700 MHz, $^{13}C\{^{1}H\}$ 176 MHz, ^{19}F 659 MHz) in the deuterated solvent stated. Throughout the document $^{13}C\{^{1}H\}$ will be written as ^{13}C. All NMR spectra were recorded at 20 °C unless otherwise stated. ^{1}H and ^{13}C chemical shifts are quoted in parts per million (ppm) relative to the residual solvent peak. ^{1}H and ^{13}C NMR are internally referenced to $CDCl_3$ (7.26 and 77.16 ppm, respectively), acetone-d_6 (2.05 and 29.84 ppm, respectively), DMSO-d_6 (2.50 and 39.52 ppm, respectively), C_6D_6 (7.16 and 128.06 ppm, respectively), MeOH-d_4 (3.31 and 49.00 ppm, respectively), PhMe-d_8 (2.31 and 20.43 ppm). All coupling constants, *J*, are quoted in Hz. Multiplicities are indicated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and multiples thereof.

High resolution mass spectrometry were acquired by electrospray ionisation (ESI) at the University of St Andrews Mass Spectrometry Facility or at the University of Edinburgh Mass Spectrometry Facility.

Ultraviolet/Visible–Light Spectrometry (UV/Vis) absorption spectra were recorded on an Agilent Technologies Cary 3500 Series UV/Vis spectrometer, samples were run in quartz cuvettes (10 mm path length), data interval (1 nm) Scan rate (3000 nm min^{-1}), detector module (multicell Peltier UV/Vis). Solvents and concentrations are stated with the respective spectrum.

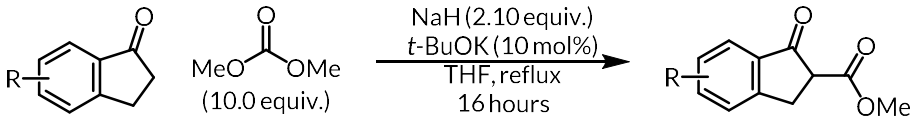
Photochemical reactions were carried out in VWR Screw Vial 4 mL 45 × 14.75 mm (Cat. No. 548-0051), sealed with VWR Screw Cap PP 3 mm Hole 8.5 mm (Cat No. 548-0096) fitted with VWR Septum 12 mm Si/PTFE 55° Shorea 1.5 mm (Cat No. 548-0475) unless stated otherwise,

under an atmosphere of nitrogen. The vials were irradiated within commercially available, EvoluChem PhotoRedOx Box™. Reaction temperatures were maintained at ~28 °C, with fans incorporated within the EvoluChem PhotoRedOx Box™.

Photochemical reactions were irradiated with the commercially available sources of light as stated. The sources of light are characterised as follows: λ of light source in nm, (part number, colour of light type of LED, electric power (W), relative irradiance (mW/cm^2).
Unless otherwise stated, light sources are EvoluChem type LEDs. **6200 K** (HCK1012-03-005, CREE XTE LED, 18 W, 24 mW/cm^2). **525 nm** (HCK1012-03-004, CREE XPE LED, 18 W, 18 mW/cm^2). **380 nm** (HCK1012-03-013, LG LED, 18 W, 8 mW/cm^2). In instances that a household 23 W CFL (Phillips Tornado T2, 2700 K, 23 W) was used, reaction temperatures were maintained with the use of a commercially available household fan (Elpine Electricals 6" clip and desk fan, model: 31371c).

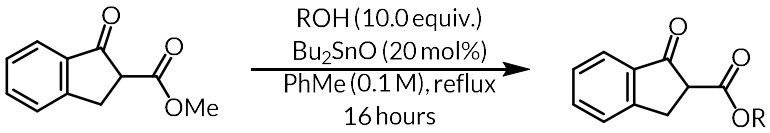
2. General Procedures

2.1 General Procedure A: Acylation of 1-Indanones



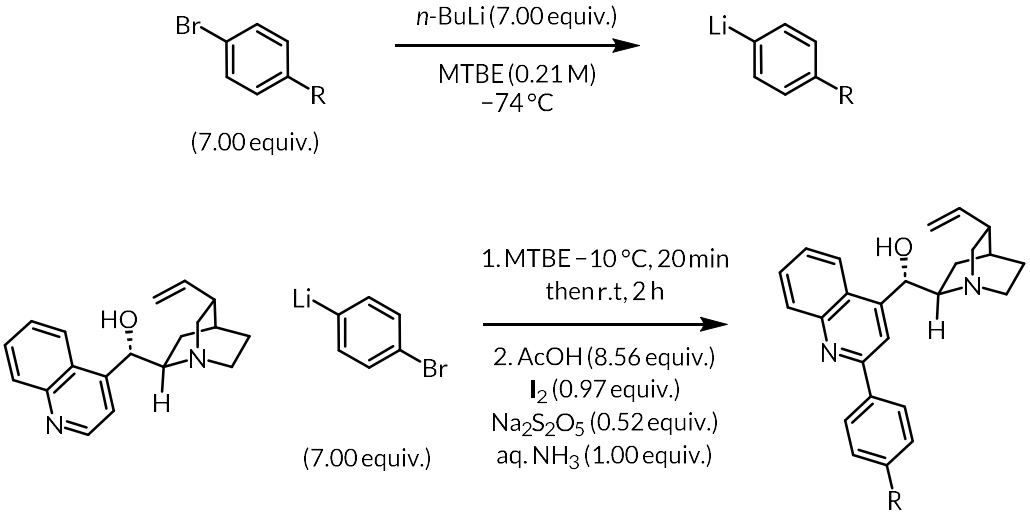
To a flame-dried 3-neck round-bottom flask equipped with a reflux condenser, under a flow of N_2, NaH (60% in mineral oil, 2.10 equiv.) was added to anhydrous THF (0.26 M). To this solution was added dimethyl carbonate (10.0 equiv.) and a catalytic amount of *t*-BuOK (10 mol%) sequentially at RT. The mixture was stirred for 5 min and then a solution of the specified 1-indanone (1.0 equiv.) in anhydrous THF (0.44 M) was added dropwise. The reaction was stirred for 16 hours at reflux. The resulting mixture was put in an ice bath and 1 M HCl (3.8 mL per mmol of 1-indanone) was added. The mixture was then extracted with EtOAc (9 mL × 3 per mmol of 1-indanone), washed with water (3.8 mL per mmol of 1-indanone) and brine (6.5 mL per mmol of 1-indanone), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was subjected to purification by column chromatography.

2.2 General Procedure B: Transesterification of β-ketoesters



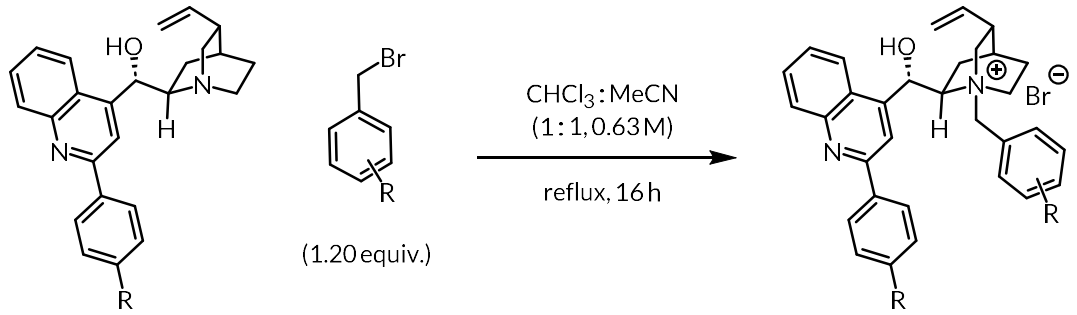
To a flame dried 2-necked round-bottom flask equipped with a reflux condenser, under a flow of N_2 and at RT, Bu_2SnO (20 mol%) was added to anhydrous PhMe (0.1 M). Methyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (1.0 equiv.) was added to the solution, followed by the appropriate alcohol (10.0 equiv.). The reaction mixture was refluxed for 3 hours, cooled to RT, and concentrated *in vacuo*. The crude product was purified by column chromatography.

2.3 General Procedure C: Arylation of (+)-Cinchonine



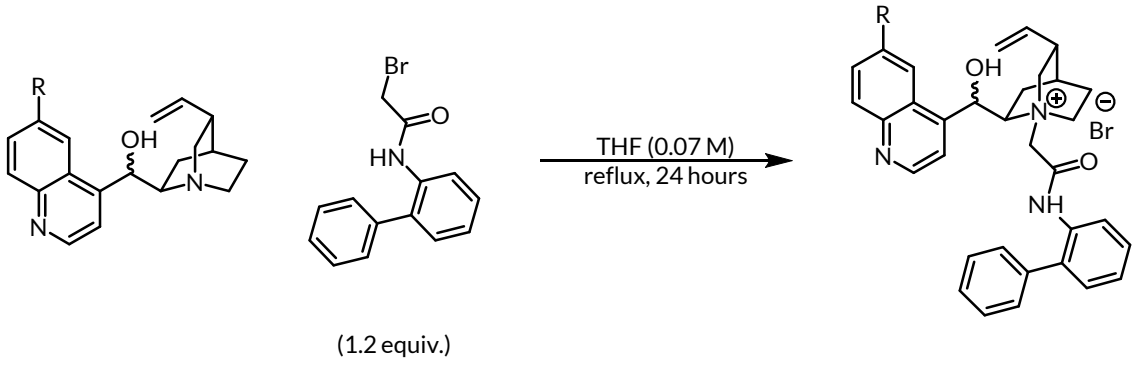
Synthesised according to a modified literature procedure,[2] *n*-BuLi (7.00 equiv.) was added to a solution of 4-substituted aryl bromide (7.00 equiv.) in anhydrous MTBE (0.21 M) at –74 °C. The organolithium was immediately transferred via cannula to a separate flask of (+)-cinchonine (1.00 equiv.) in anhydrous MTBE (0.21 M) and stirred at –10 °C for 20 min, the mixture was warmed to room temperature and stirred for a further 2 h. The reaction was quenched by dropwise addition of AcOH (8.56 equiv.), water (30 mL per 2.13 mmol of (+)-cinchonine) and EtOAc (30 mL per 2.13 mmol of (+)-cinchonine). Solid iodine (0.97 equiv. per 2.13 mmol of (+)-cinchonine) was added portionwise. A solution of sodium metabisulfite (0.52 equiv. per 2.13 mmol of (+)-cinchonine) in water (10.0 mL per 2.13 mmol of (+)-cinchonine) was added. Aqueous ammonia (28% approx. 1.00 equiv. per 2.13 mmol of (+)-cinchonine) was added until pH 10 is reached. The aqueous phase was extracted with EtOAc (3 × 30 mL per 2.13 mmol of (+)-cinchonine), the organic layers were combined, washed with brine (30 mL per 2.13 mmol of (+)-cinchonine), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography.

2.4 General Procedure D: Benzylation of (+)-Cinchonine Aryl Derivatives



Synthesised according to a modified literature procedure,[2] substituted benzyl bromide (1.20 equiv.) was added to a solution of the (+)-cinchonine derivative (1.00 equiv.) in MeCN : $CHCl_3$ (1 : 1, 0.63 M). The reaction mixture was stirred for 16 h at reflux under an inert atmosphere. The crude reaction mixture was concentrated *in vacuo*. The crude product was dissolved in CH_2Cl_2 (3 mL per 1.00 mmol of (+)-cinchonine derivative) and MeOH (0.3 mL per 1.00 mmol of (+)-cinchonine derivative), followed by dropwise addition of Et_2O (1 mL per 1.00 mmol of (+)-cinchonine derivative). The mixture was concentrated *in vacuo* until a solid began to form, further addition of Et_2O (2 × 1 mL per 1.00 mmol of (+)-cinchonine derivative) and concentrated *in vacuo* and the Et_2O mixture was placed in a –20 °C freezer overnight, the resulting solid was collected by filtration and washed with ice cold Et_2O to give the title compound.

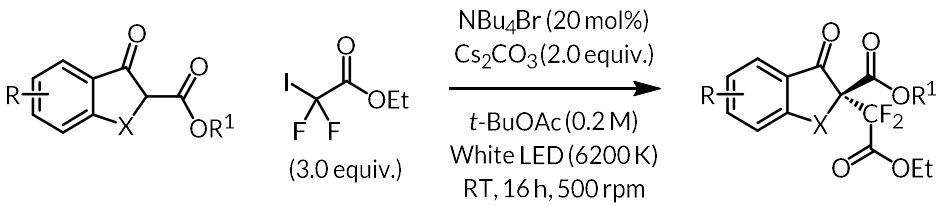
2.5 General Procedure E: Acetamidylation of Cinchona Alkaloids



Following a modified procedure, *N*-([1,1'-biphenyl]-2-yl)-2-bromoacetamide (4.08 mmol, 1.20 equiv.) was added to a solution of the appropriate cinchona alkaloid (3.40 mmol, 1.00 equiv.) in anhydrous THF (0.07 M). The mixture was refluxed for 24 hours, cooled to RT, and concentrated *in vacuo*. The crude product was dissolved in hot CH_2Cl_2 (~6 mL per 3.40 mmol

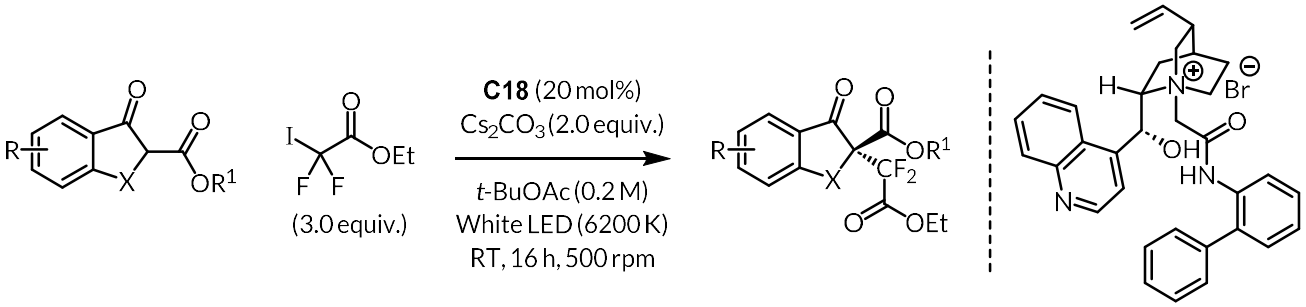
of cinchona alkaloid) and Et_2O (~1 mL per 3.40 mmol of cinchona alkaloid) was added dropwise. After cooling to RT, the solution was placed in a –20 °C freezer overnight, the resulting solid was collected by filtration and washed with ice cold Et_2O.

2.6 General Procedure F: Light-Initiated Phase-Transfer Catalysed Racemic α-Difluoroalkylation of β-Ketoesters



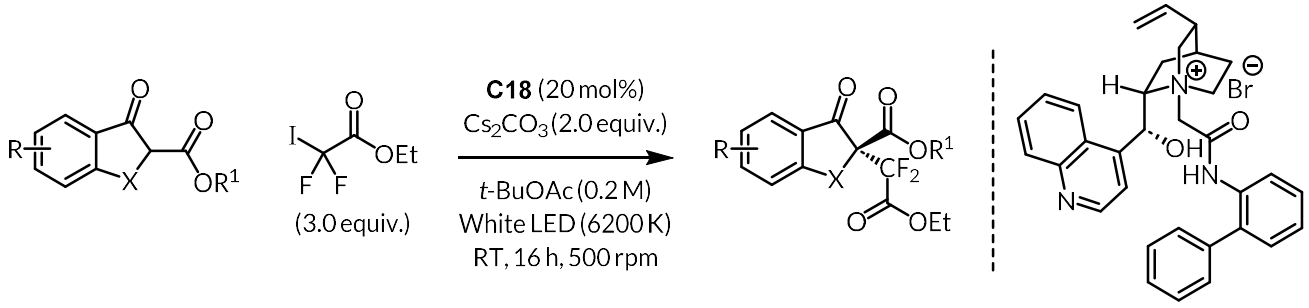
To a flame dried vial equipped with a Teflon-coated cross stirrer bar, the appropriate β-ketoester (0.1 mmol, 1.0 equiv.) and NBu_4Br (0.02 mmol, 0.2 equiv.) were added, the vial was sealed with a lid equipped with a septum and backfilled with nitrogen over three cycles. *t*-BuOAc (0.2 M), ethyl difluoroiodoacetate (0.3 mmol, 3 equiv.) and Cs_2CO_3 (0.2 mmol, 2.0 equiv.) were sequentially added. The reaction mixture was degassed via sparging at –10 °C (ice/NaCl bath) for 10 minutes, refilled with nitrogen and sealed with parafilm. The vial was suspended within a photobox equipped with a white LED (6200 K) placed on a stirrer plate. After being irradiated and stirred (500 rpm) for 16 hours, the solution was diluted with CH_2Cl_2 (3 mL) and filtered through a plug of silica. The silica plug was washed with CH_2Cl_2 (2 × 3 mL). The crude product was concentrated *in vacuo*, diluted with PhMe (~ 5 mL) to remove remaining *t*-BuOAc, and concentrated *in vacuo* again. The crude product was purified by column chromatography.

2.7 General Procedure G: Light-Initiated Phase-Transfer Catalysed Asymmetric α-Difluoroalkylation of β-Ketoesters



To a flame dried vial equipped with a Teflon-coated cross stirrer bar, the appropriate β-ketoester (0.1 mmol, 1.0 equiv.) and phase–transfer catalyst (**C18**) (0.02 mmol, 0.2 equiv.) were added, the vial was sealed with a lid equipped with a septum and backfilled with nitrogen over three cycles. *t*-BuOAc (0.2 M), ethyl difluoroiodoacetate (0.3 mmol, 3 equiv.) and Cs_2CO_3 (0.2 mmol, 2.0 equiv.) were sequentially added. The reaction mixture was degassed via sparging at –10 °C (ice/NaCl bath) for 10 minutes, refilled with nitrogen and sealed with parafilm. The vial was suspended within a photobox equipped with a white LED (6200 K) placed on a stirrer plate. After being irradiated and stirred (500 rpm) for 16 hours, the solution was diluted with CH_2Cl_2 (3 mL) and filtered through a plug of silica. The silica plug was washed with CH_2Cl_2 (2 × 3 mL). The crude product was concentrated *in vacuo*, diluted with PhMe (~ 5 mL) to remove remaining *t*-BuOAc, and concentrated *in vacuo* again. The crude product was purified by column chromatography.

2.8 General Procedure H: Light-Initiated Phase-Transfer Catalysed Asymmetric α-Difluoroalkylation of β-Ketoesters (0.5 mmol scale)

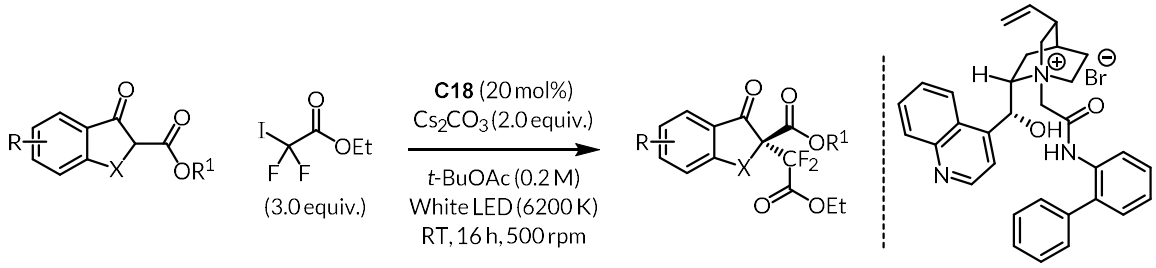


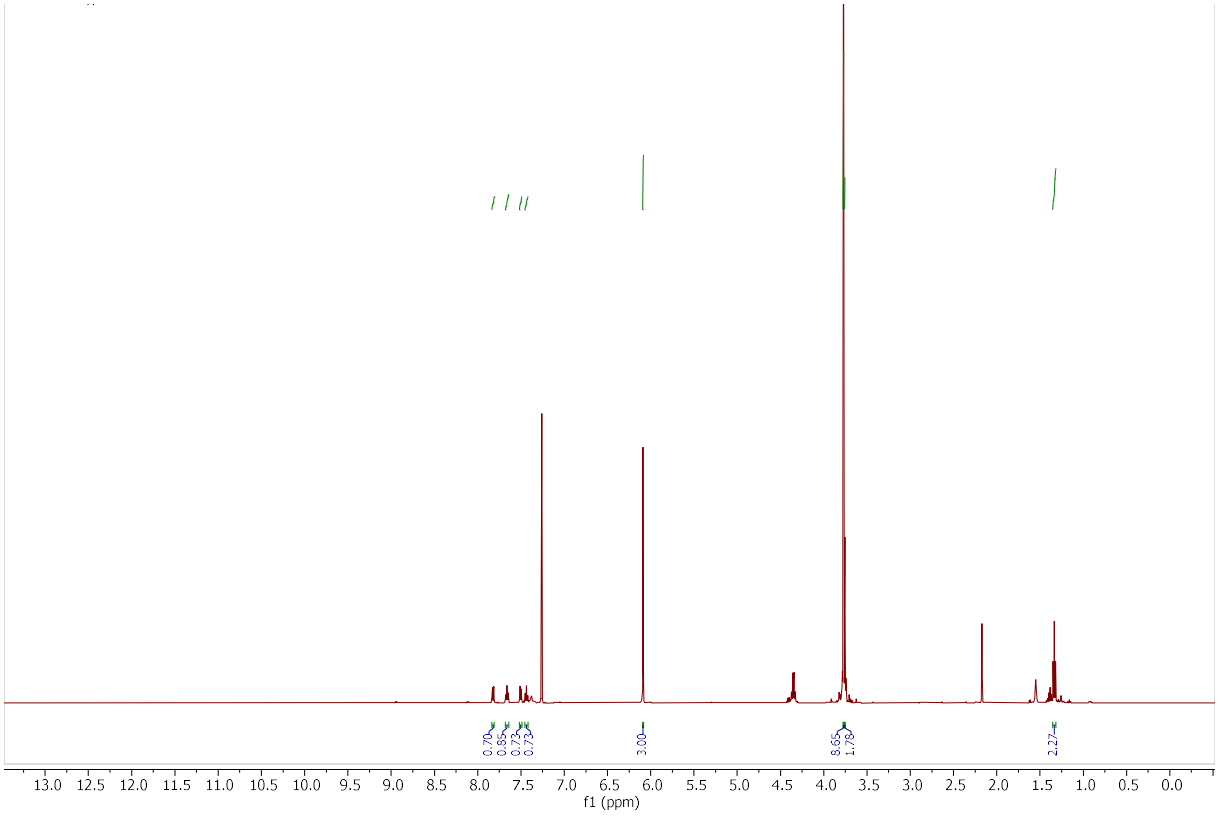
To a flame dried 8 mL vial equipped with a Teflon-coated cross stirrer bar, the appropriate β-ketoester (0.5 mmol, 1.0 equiv.) and phase–transfer catalyst (**C18**) (0.1 mmol, 0.2 equiv.) were added, the vial was sealed with a lid equipped with a septum and backfilled with nitrogen over three cycles. *t*-BuOAc (0.2 M), ethyl difluoroiodoacetate (1.5 mmol, 3 equiv.) and Cs_2CO_3 (1 mmol, 2.0 equiv.) were sequentially added. The reaction mixture was degassed via sparging at –10 °C (ice/NaCl bath) for 20 minutes, refilled with nitrogen and sealed with parafilm. The vial was suspended within a photobox equipped with a white LED (6200 K) placed on a stirrer plate. After being irradiated and stirred (500 rpm) for 16 hours, the solution was diluted with CH_2Cl_2 (5 mL) and filtered through a plug of silica. The silica plug was washed with CH_2Cl_2 (2 × 10 mL). The crude product was concentrated *in vacuo*, diluted with

$CHCl_3$ (~ 5 mL) to remove remaining *t*-BuOAc, and concentrated *in vacuo* again. The crude product was purified by column chromatography.

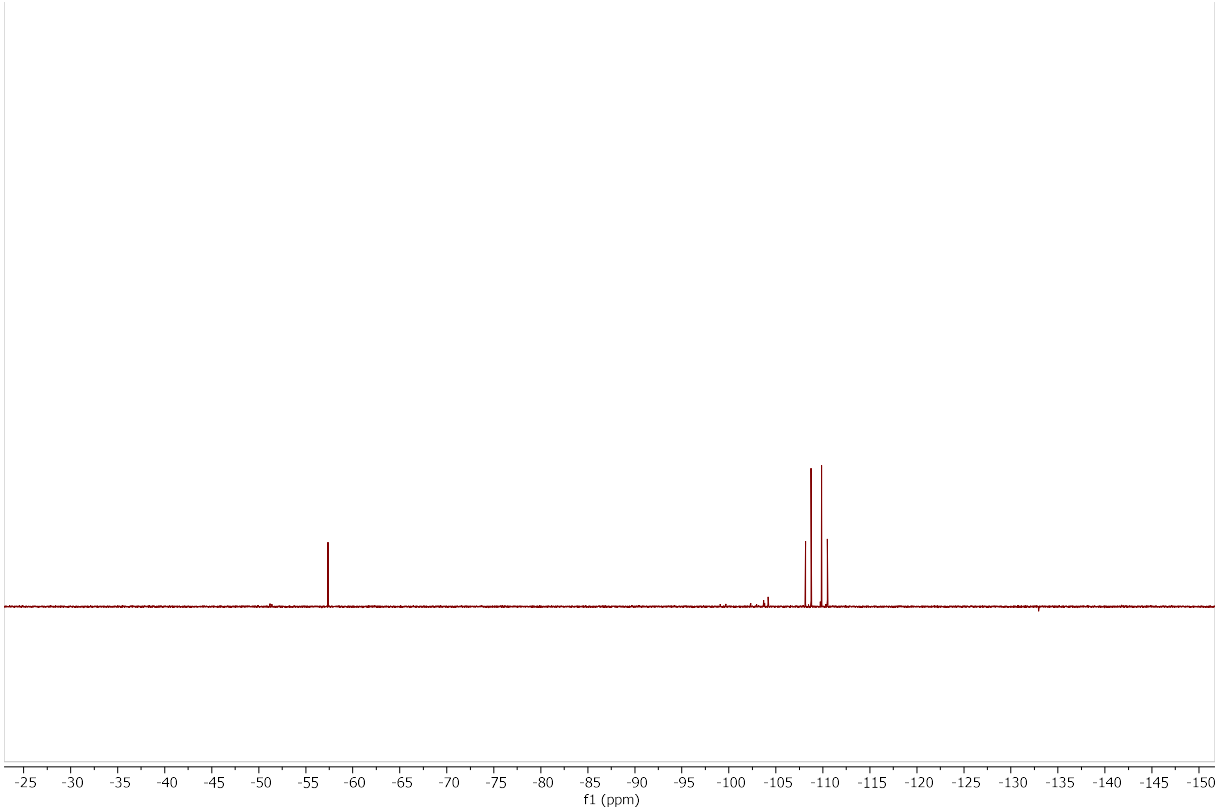
3. Optimisation and Screening

3.1 Representative ^{1}H and ^{19}F NMR Spectra





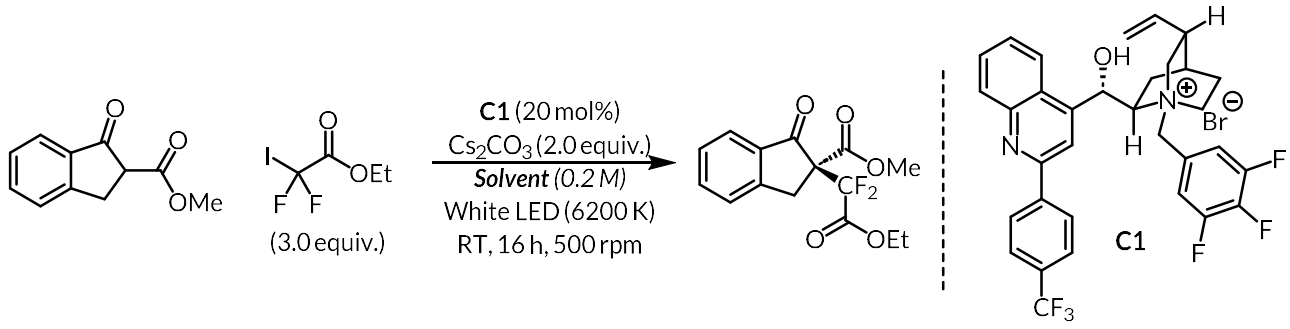
^{1}H NMR spectrum of crude reaction mixture with 1,3,5-trimethoxybenzene (0.33 equiv.) as an internal standard



^{19}F NMR spectrum of crude reaction mixture

Unless otherwise stated, all optimisation reaction were performed on a 0.1 mmol scale of **1a** following General Procedure G. Yields given refer to ^{1}H NMR yields using 1,3,5-trimethoxybenzene (0.33 equiv.) as an internal standard.

3.2 Solvent Screening

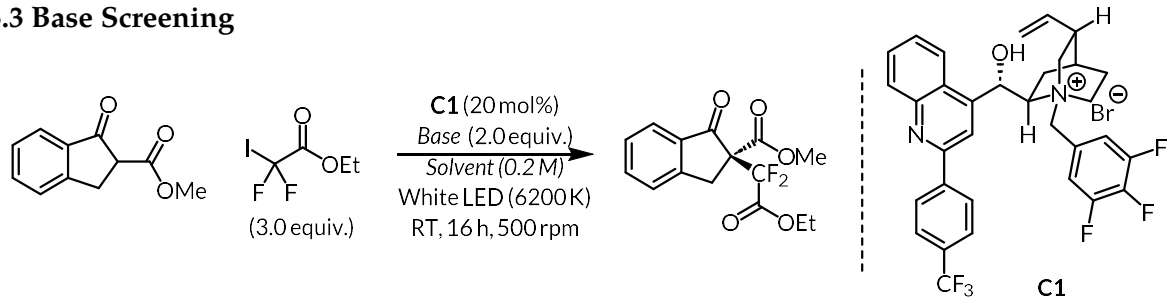


Initial optimisation was carried out using catalyst **C1.**

Solvent	**^{1}H NMR Yield/%**	**er [(*R*) : (*S*)]**
PhCl : Perfluorooctane 2:1 (64 h)	10	43 : 57
CH_2Cl_2	16	36 : 64
$CHCl_3$	95	32 : 68
DCE	65	41 : 59
EtOAc	96	41 : 59
Perfluorooctane	0	N/A
PhCl	44	42 : 58
PhF	65	34 : 66
$PhCF_3$	30	45 : 55
Mesitylene	59	39 : 61
Toluene	61	44 : 56
Benzene	70	36 : 64
m-xylene	30	47 : 53
Anisole	54	39 : 61
MTBE	90	41 : 59
CPME	25	44 : 56
n-Hexane	63	50 : 50
t-BuOAc	88	35 : 65
t-BuPh	64	31 : 69

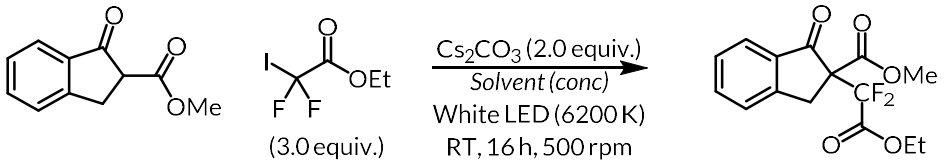
CH_2Cl_2, $CHCl_3$, *t*-BuPh, *t*-BuOAc were taken on for further base screening.

3.3 Base Screening



Base (2.0 equiv.)	^{1}H NMR Yield/%	er [(*R*) : (*S*)]
CH_2Cl_2		
Na_2CO_3	0	N/A
K_2CO_3	50	41 : 59
Cs_2CO_3	64	36 : 64
K_2HPO_4	0	N/A
K_3PO_4	72	46 : 54
KOH	16	48 : 52
$CsOH·H_2O$	30	44 : 56
$CHCl_3$		
Cs_2CO_3	95	32 : 68
K_2CO_3	40	43 : 57
K_3PO_4	57	41 : 59
***t*-BuPh**		
Cs_2CO_3	64	31 : 69
K_2CO_3	20	48 : 52
$CsOH·H_2O$	0	N/A
K_3PO_4	57	49 : 51
***t*-BuOAc**		
Cs_2CO_3	88	35 : 65
K_2CO_3	81	48 : 52
K_3PO_4	85	48 : 52
CsF	77	31 : 69
CsOAc	70	48 : 62

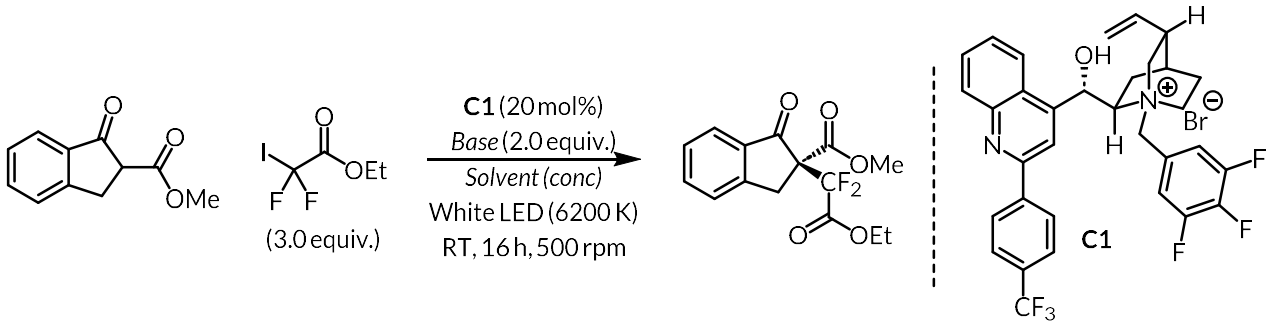
3.4 Dual Solvent System and Concentration



Conditions	^{1}H NMR Yield/%
t-BuPh : *n*-hexane (9 : 1) [0.2 M]	85
t-BuPh : *n*-hexane (1 : 1) [0.2 M]	78
t-BuPh [0.1 M]	64
t-BuPh [0.4 M]	69

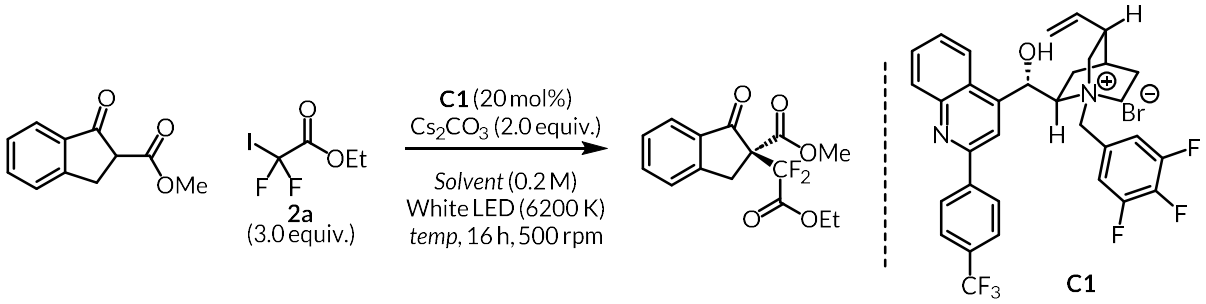
Owing to the highly facile background reactivity in the absence of the PTC a non-polar solvent was added, and the concentration varied in an attempt to minimise the uncatalysed pathway.

3.5 Presence of Water



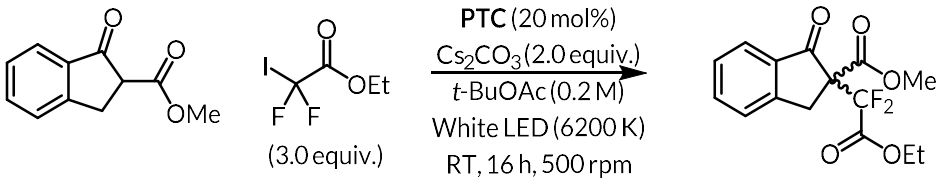
Conditions	^{1}H NMR Yield/%	er [(*R*) : (*S*)]
Cs_2CO_3, dry *t*-BuPh (0.2 M)	63	42 : 58
Cs_2CO_3, dry *t*-BuOAc (0.2 M)	100	30 : 70
sat. aq. Cs_2CO_3 (4 : 1) + *t*-BuPh (0.2 M)	trace	37 : 63
sat. aq. Cs_2CO_3 (4 : 1) + *t*-BuOAc (0.2 M)	63	43 : 57

3.6 Miscellaneous Screening

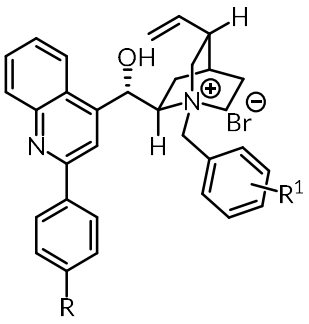


Solvent	Temperature	Conditions	**^{1}H NMR Yield/%**	**er [(*R*) : (*S*)]**
t-BuOAc	RT	dropwise addition of **2a** (over 6 h)	19	46 : 54
t-BuOAc	RT	distilled **2a**	64	40 : 60
t-BuOAc	5 °C	**2a** straight from bottle	78	39 : 61
t-BuPh	5 °C	**2a** straight from bottle	59	40 : 60

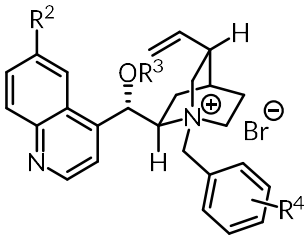
3.7 Catalyst Screening



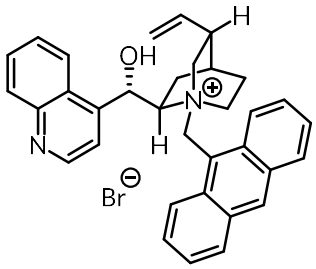
List of cinchona alkaloid derived phase-transfer catalysts:



C1: R = CF_3, R^1 = 3,4,5-F_3
C2: R = CF_3, R^1 = 3,5-Br_2
C3: R = CF_3, R^1 = H
C4: R = H, R^1 = H

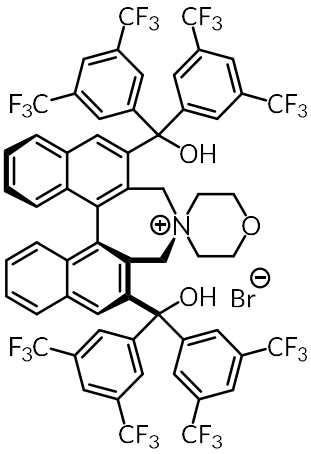


C5: R^2 = H, R^3 = H, R^4 = H
C6: R^2 = H, R^3 = H, R^4 = 3,4,5-F_3
C7: R^2 = H, R^3 = H, R^4 = 4-F
C8: R^2 = H, R^3 = H, R^4 = 3,5-Br_2
C9: R^2 = OMe, R^3 = H, R^4 = H
C10: R^2 = OMe, R^3 = allyl, R^4 = H
C11: R^2 = OMe, R^3 = Bn, R^4 = H

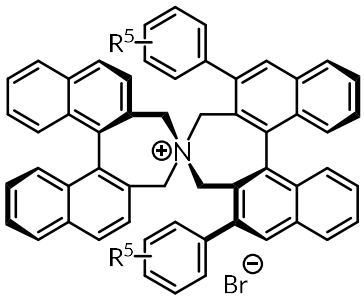


C12

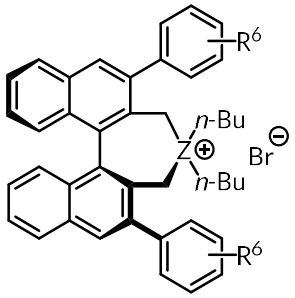
List of Maruoka-type derived phase-transfer catalysts:



C13

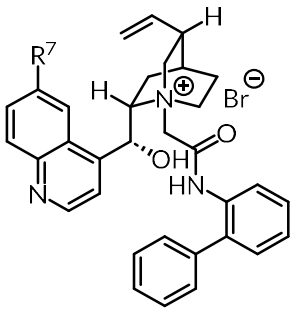


C14: R^5 = 3,5-$(CF_3)_2$
C15: R^5 = 3,4,5-F_3

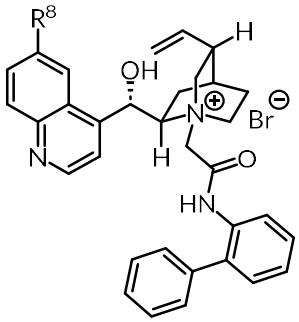


C16: Z = P, R^6 = 3,5-$(CF_3)_2$
C17: Z = N, R^6 = 3,4,5-F_3

List of acetamide-branched cinchona phase-transfer catalysts:



C18: R^7 = H
C19: R^7 = OMe

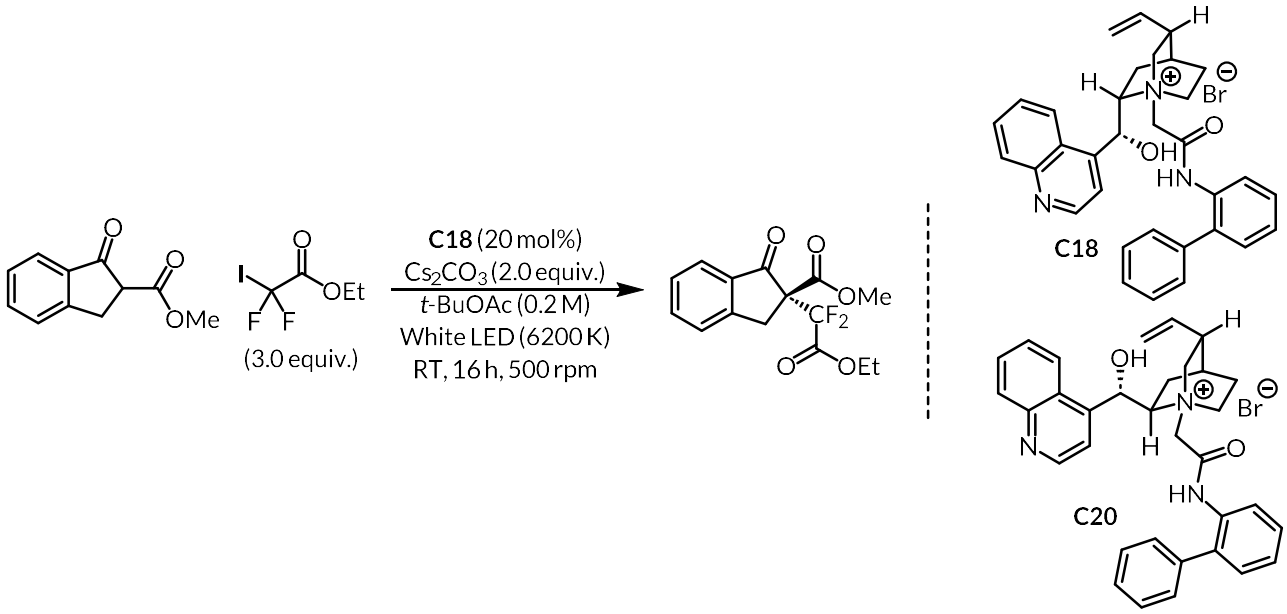


C20: R^8 = H
C21: R^8 = OMe

Catalyst (20 mol%)	^{1}H NMR Yield/%	er [(*R*) : (*S*)]
C1	88	35 : 65
C2	82	46 : 54
C3	69	37 : 63
C4	66	50 : 50
C5	75	50 : 50
C6	83	49 : 51
C7	79	49 : 51
C8	71	50 : 50
C9	67	49 : 51
C10	37	50 : 50
C11	55	50 : 50
C12	22	50 : 50
C13	73	50 : 50
C14	43	50 : 50
C15	72	50 : 50
C16	55	50 : 50
C17	73	50 : 50
C18	100	74 : 26
C19	92	73 : 27

C20	78	32 : 68
C21	81	28 : 72

2.7 Re-Optimisation with Catalysts C18 and C20



Deviation	**^{1}H NMR Yield/%**	**er [(*R*) : (*S*)]**
As above	99	74 : 26
380 nm	59	54 : 46
525 nm	55	70 : 30
23 W CFL	20	71 : 29
CH_2Cl_2	99	69 : 31
t-BuOAc (0.4 M)	59	54 : 46
C20, *t*-BuOAc	78	32 : 68
C20, PhMe	27	39 : 61
C20, Et_2O	73	41 : 59
C20, CH_2Cl_2	75	28 : 72
C20, PhCl	83	38 : 62

4. Mechanistic Investigations

4.1 UV/Vis

Individual UV-Vis spectra of the starting materials were collected (Fig. A), the mixture of the materials (Fig. B), the inclusion of Cs_2CO_3 to the individual materials (Fig. C), the mixture of materials with the inclusion of Cs_2CO_3 (Fig. D) and the standard reaction mixture under racemic phase-transfer conditions (Fig. E).

In each of the spectra, equivalents from General Procedure F were used at a concentration of 0.0024 M relative to the limiting reagent of the β-ketoester.

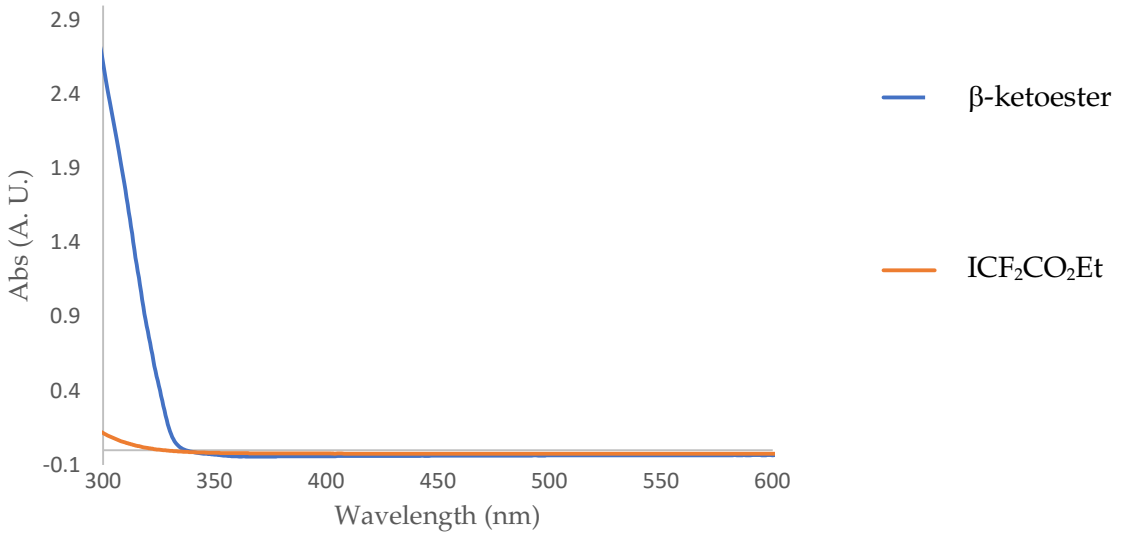


Figure. A: Individual absorption spectra of β-ketoester and ethyl difluoroiodoacetate (c = 0.0024 M in *t*-BuOAc)

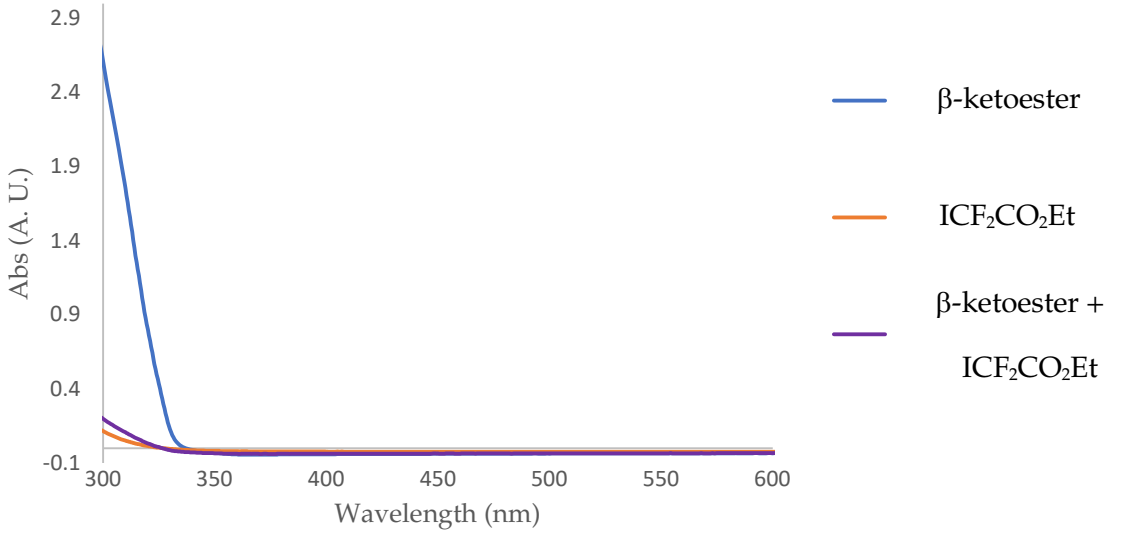


Figure. B: Individual absorption spectra of β-ketoester, ethyl difluoroiodoacetate and the combination of the starting materials (c = 0.0024 M in *t*-BuOAc).

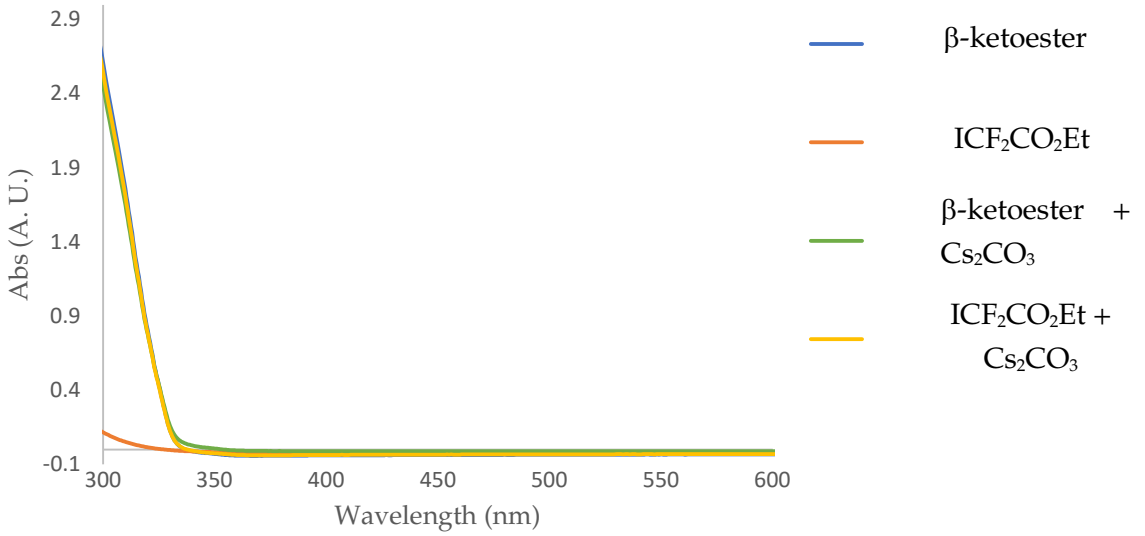


Figure. C: Individual absorption spectra of β-ketoester, ethyl difluoroiodoacetate and these starting materials in the presence of Cs_2CO_3 (c = 0.0024 M in *t*-BuOAc)

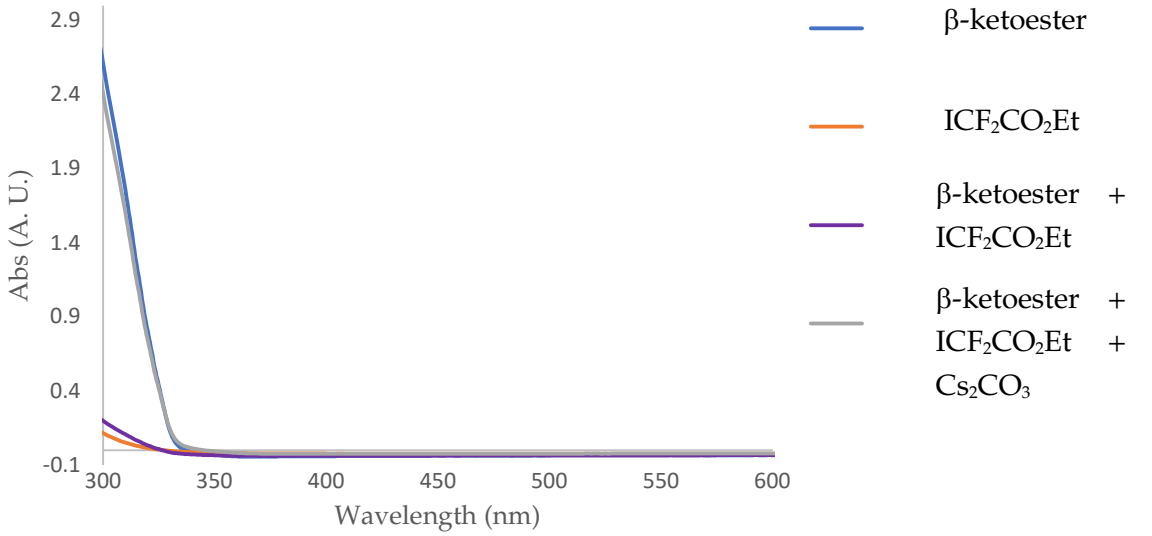


Figure D: Individual absorption spectra of β-ketoester, ethyl difluoroiodoacetate, combination of the two starting materials and the combination of the starting materials in the presence of Cs_2CO_3 (c = 0.0024 M in *t*-BuOAc)

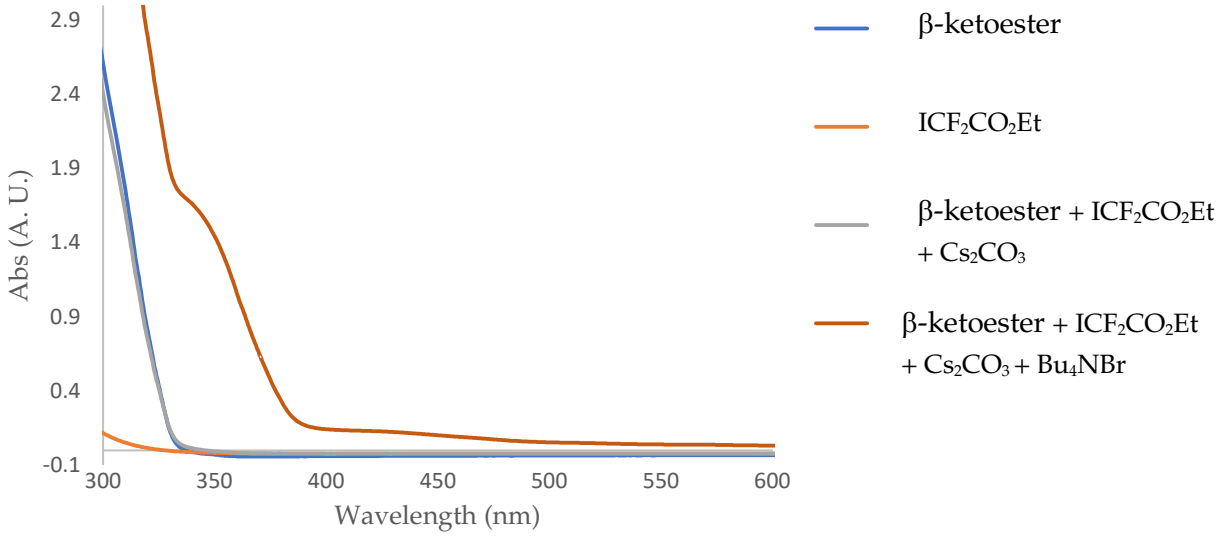


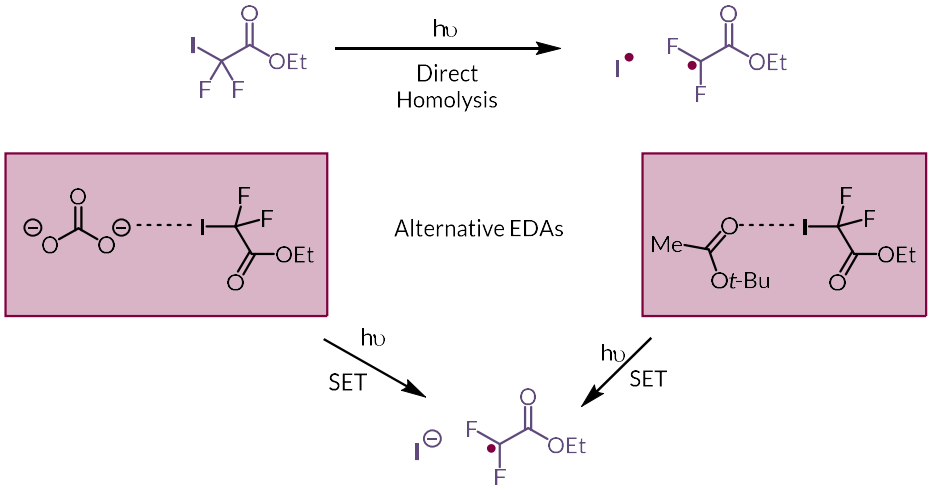
Figure E: Individual absorption spectra of β-ketoester, ethyl difluoroiodoacetate, the combination of the starting materials in the presence of Cs_2CO_3 and combination of the starting materials in the presence of Cs_2CO_3 and Bu_4NBr (c = 0.0024 M in *t*-BuOAc)

From the obtained spectra, a clear bathochromic shift can be observed with the inclusion of a racemic phase-transfer catalyst.

4.2 Alternative Routes for Radical Generation

Direct Irradiation and Alternative EDAs

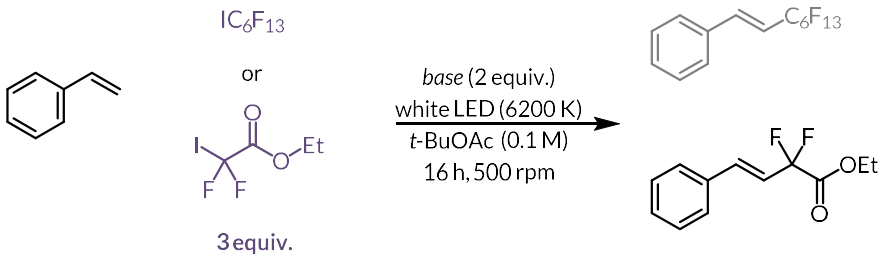
Others have postulated that direct excitation and subsequent homolytic cleavage will afford the desired ethyl difluoroacetate radical.[3] Alternatively, other EDA complexes could be forming between the radical precursor and either the base or solvent. For the latter, there is no spectroscopic evidence to suggest that an EDA forms between *t*-BuOAc and ICF_2CO_2Et. This has been proposed for other solvents such as acetone.[4]



To probe this further, modification of a known ATRA procedure across a styrene was used.[3] The reaction conditions from General Procedure F were adapted. When both our chosen base (Cs_2CO_3) and solvent (*t*-BuOAc) were employed, a small amount of product was formed. Inclusion of the organic base that Melchiorre utilised,[2] DBU, for racemic reactivity, results in 21% of the desired ATRA product. Finally, removal of any base, affords the product in 81% yield. These results suggest that direct homolysis of the C–I bond can occur in *t*-BuOAc.

To understand if this facile C–I homolysis was occurring more rapidly with ICF_2CO_2Et than perfluorohexyl iodide, which was used by Melchiorre.[2] It was decided to employ perfluorohexyl iodide under the same conditions in replacement of ethyl difluoroiodoacetate. In the presence and absence of Cs_2CO_3 none of the desired ATRA product was observed by ^{19}F NMR with near quantitative return of the fluorinated starting material. Thus demonstrating radical formation is more facile with ICF_2CO_2Et over perfluorohexyl iodide

and the latter does not undergo appreciable C–I homolysis with the white LED used in this study.

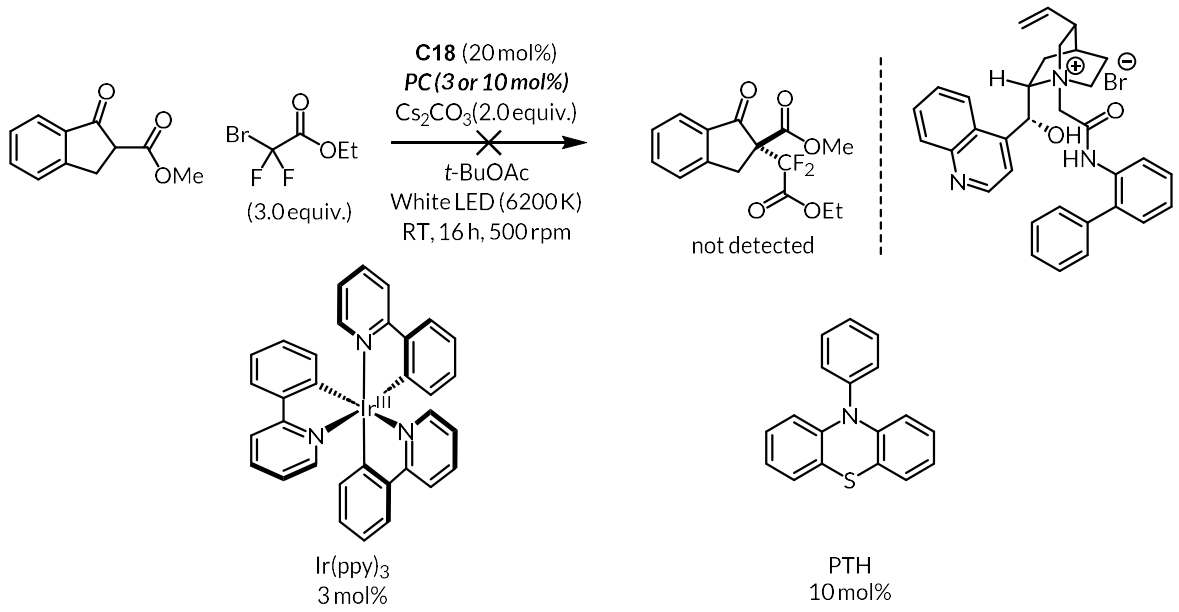


Radical Precursor	Base	^{19}F NMR Yield/%
ICF_2CO_2Et	Cs_2CO_3	10
ICF_2CO_2Et	DBU	21
ICF_2CO_2Et	none	81
IC_6F_{13}	Cs_2CO_3	0
IC_6F_{13}	none	0

All reactions were carried out under standard inert conditions in vials equipped with stirrer and septa, Cs_2CO_3 (0.2 mmol, 2.0 equiv.), styrene (0.1 mmol, 1 equiv.), ethyl difluoroiodoacetate or perfluorohexyl iodide (0.3 mmol, 3 equiv.) and t-BuOAc (0.1 M) were sequentially added. All reactions were monitored by ^{19}F NMR, using fluorobenzene (0.2 mmol, 2.0 equiv.) as an internal standard.

4.3 Addition of Photocatalyst

The inclusion of photocatalysts to generate the desired radical from ethyl difluorobromoacetate was attempted. General Procedure G was followed with the addition of either $Ir(ppy)_3$ (3 mol%) or PTH (10 mol%).

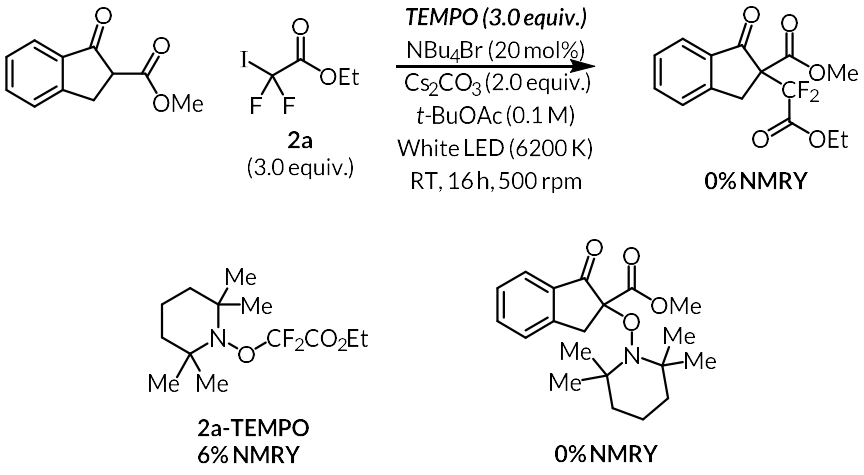


All reactions were carried out under those outlined in General Procedure G, photocatalysts were added with ***C18****.*

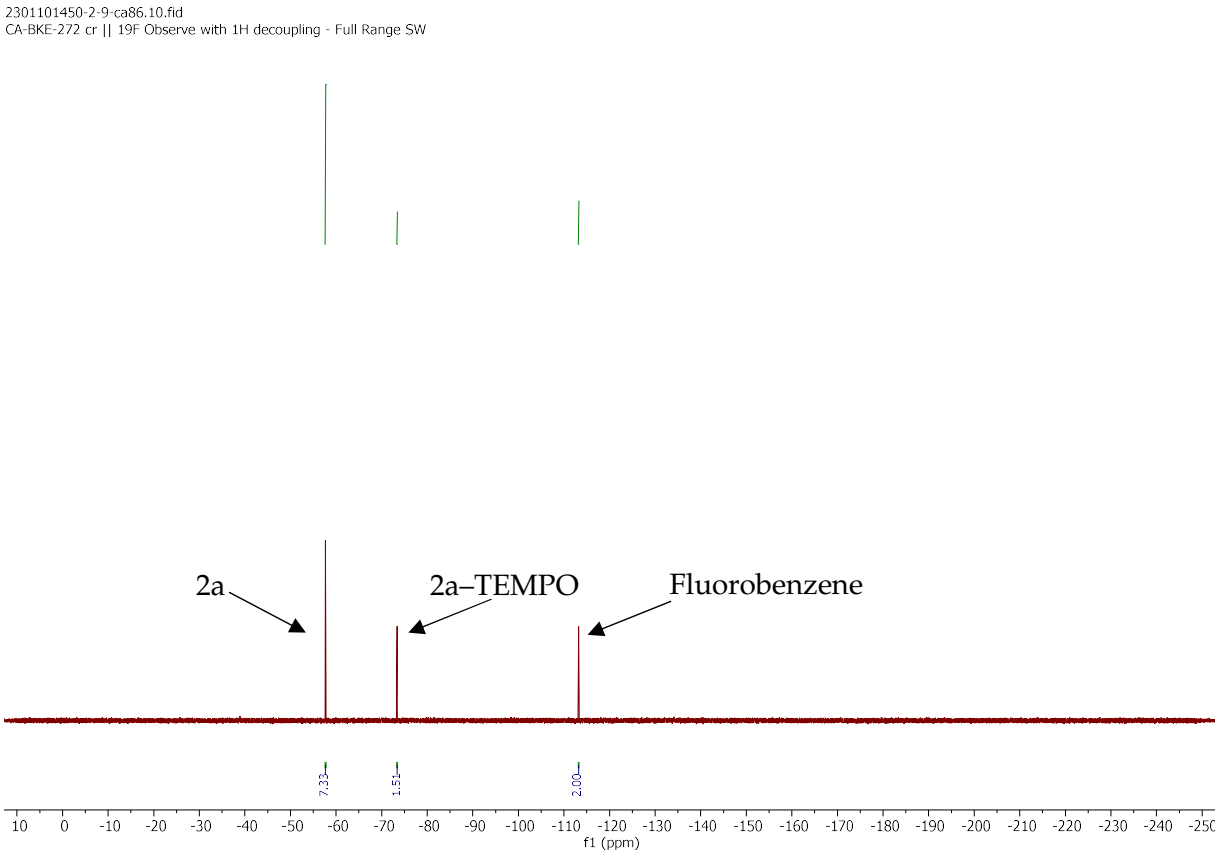
When either catalyst was used, complete consumption of the β-ketoester and ethyl difluorobromoacetate was observed but no product was detected.

4.4 TEMPO Additive

Further evidence of a radical mechanism was obtained with the addition of TEMPO. Only the difluoroethylacetate–TEMPO adduct was formed in a low yield. Indicating that the difluoroalkyl radical is formed during the reaction, and that the presence of TEMPO disrupts product formation.



The reaction was carried out as outlined in General Procedure F; TEMPO (3.0 equiv.) was added with NBu_4Br. The reaction was monitored by ^{19}F NMR, using fluorobenzene (0.2 mmol, 2.0 equiv.) as an internal standard.



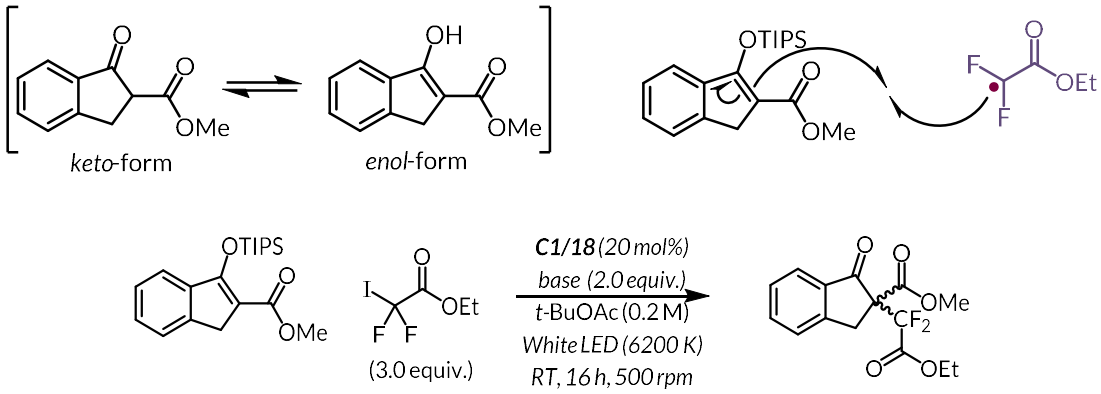
The ^{19}F chemical shift for **2a-TEMPO** data is in accordance with the literature.[5]

4.5 Background Reactivity

Silyl Enol Ether

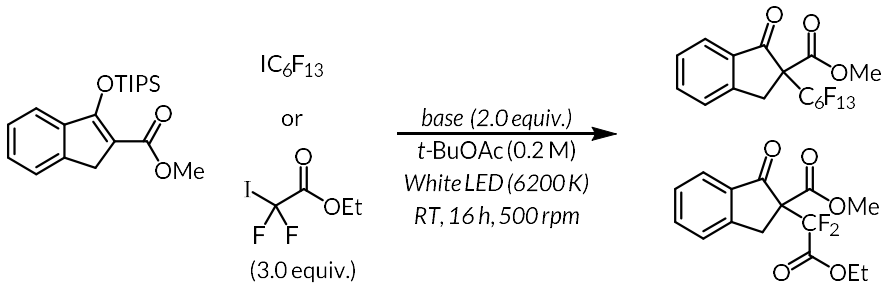
We hypothesised the mildly nucleophilic tautomeric enol form of the β-ketoester, **1a**, could potentially be intercepting the radical, resulting in no stereocontrol in the crucial bond forming step. Many of the β-ketoester starting materials had varying amounts of the enol present when isolated as observed by ^1H NMR, and even spectroscopically pure samples could still tautomerise under the reaction conditions. To test this theory, the OTIPS silyl enol

ether was made and tested as model for the enol under various conditions based on General Procedure G.



Cat	Base	^{19}F NMR Yield/%	er [(*R*) : (*S*)]
C1	None	0	N/A
C1	Cs_2CO_3	8	36 : 64
C18	CsF	74	74 : 26

All reactions were carried out using a modified version of General Procedure G, with variations noted in the table.

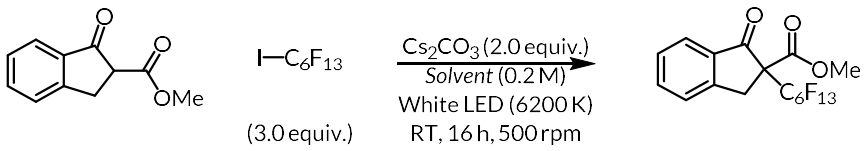


Radical Precursor	Base	^{19}F NMR Yield/%
ICF_2CO_2Et	None	Trace
ICF_2CO_2Et	Cs_2CO_3	13
IC_6F_{13}	None	0
IC_6F_{13}	Cs_2CO_3	Trace

All reactions were carried out using a modified version of General Procedure G, with variations noted in the table.

Racemic Reactivity Without a Phase-Transfer Catalyst

To ascertain why such a facile background reactivity was occurring, we employed perfluorohexyl iodide that has been shown to successfully undergo a similar mechanism as which we have proposed. Under our reaction conditions, there was a marked decrease in a non-PTC background reactivity. Taking previously used conditions a background reaction could still be observed albeit it a much lower yield.[2]



Radical Precursor	Solvent	^{1}H NMR Yield/%
ICF_2CO_2Et	*t*-BuOAc	52
ICF_2CO_2Et	*t*-BuPh	76
IC_6F_{13}	*t*-BuOAc	18
IC_6F_{13}	PhCl : C_8F_{18} (2 : 1)	9
IC_6F_{13}	PhCl	8
IC_6F_{13}	C_8F_{18}	0

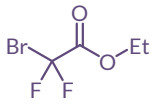
Unless otherwise stated, all reactions were carried out under those outlined in General Procedure F, perfluorohexyl iodide (3.0 equiv) was used in place of ethyl difluoroiodoacetate, no NBu_4Br was added. The reaction was monitored by ^{1}H NMR, using 1,3,5-trimethoxybenzene (0.033 mmol, 0.33 equiv.) as an internal standard.

N.B. In all cases there was no return of the β-ketoester starting material with the exception of using C_8F_{18} as the solvent (16% NMR yield of β-ketoester starting material).

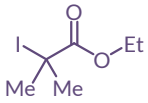
Product data was in accordance with literature data.[2]

5 Unsuccessful Substrates

5.1 Radical Precursors

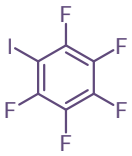


0% Yield

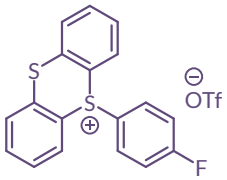


0% Yield

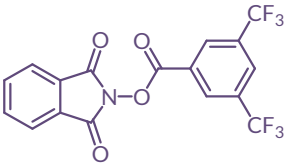
0% Yield



0% Yield

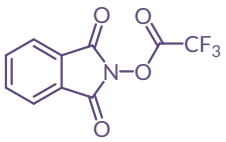


0% Yield



0% Yield

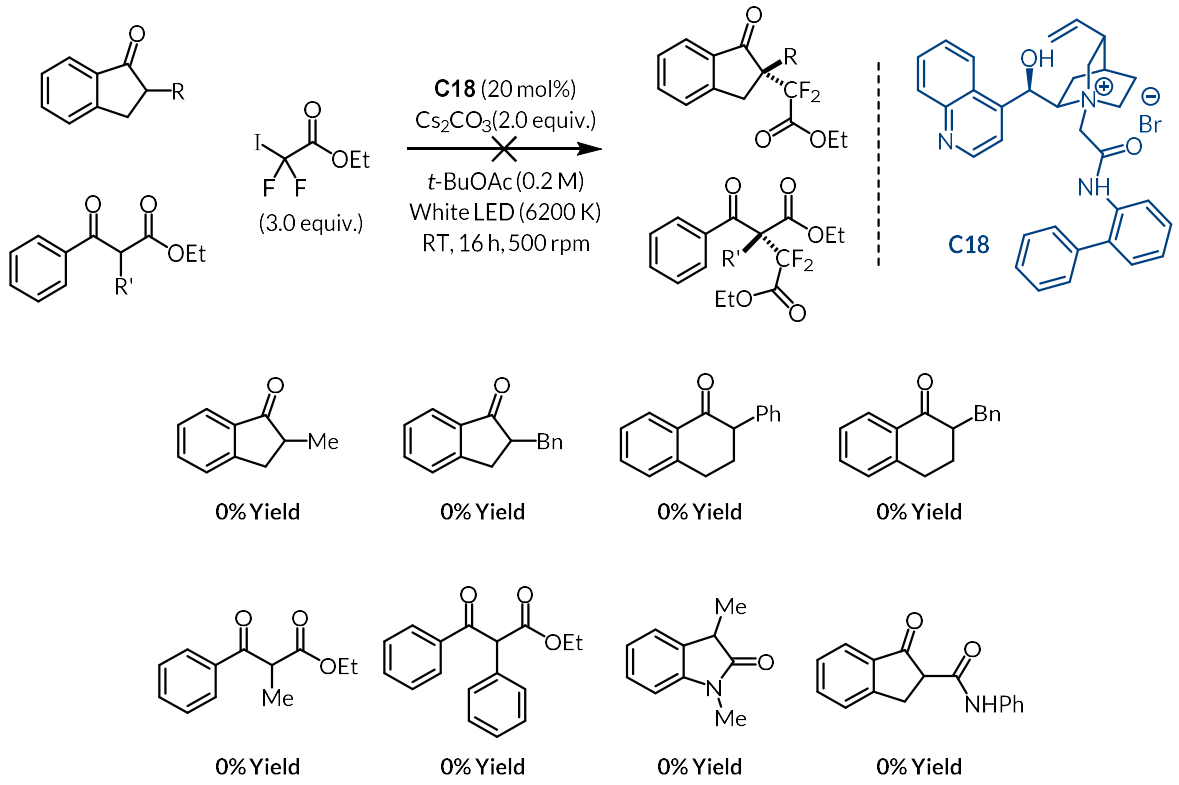
0% Yield



0% Yield

When subjected to General Procedure F/G in replacement of ethyl difluoroiodoacetate, the above radical precursors resulted in full return of the β-ketoester (**1a**) in each case, *in situ* ^{19}F NMR analysis identified near full return of the fluorinated radical precursors. When *N*-phthalimide esters were employed, no return of the radical precursors was observed.

5.2 Alternative α-Substituted Carbonyls



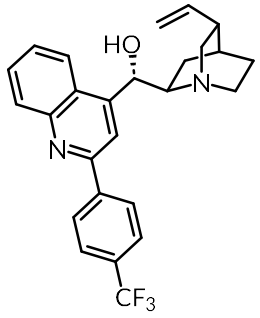
When the above α-substituted carbonyl precursors were submitted to General Procedure F/G in replacement of β-ketoester (**1a**), full return of each precursor was observed, with the exception of the β-ketoamide (20% return by ^{1}H NMR). *In situ* ^{19}F NMR analysis identified near full return of the fluorinated radical precursor.

6. Characterisation

6.1 Catalyst and Ligand Synthesis

The following catalysts were purchased from chemical suppliers: **C13** from TCI, **C14** and **C15** from FUJIFILM Wako Pure Chemical Corporation**, C16** from STREM, **C12** and **C17** from Sigma-Aldrich. Catalysts **C2**,[6] **C5**,[7] **C7**,[8] **C8**,[8] **C9**,[9] **C10**,[10] and **C11**[11] were synthesised according to literature procedures.

(*S*)-(2-(4-(trifluoromethyl)phenyl)quinolin-4-yl)((1*S*,2*R*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methanol (C1a)



Following General Procedure C, *n*-BuLi (5.1 mL, 12.8 mmol, 2.5 M) was added to a solution of 4-bromobenzotrifluoride (1.79 mL, 12.8 mmol) in anhydrous MTBE (5 mL). The organolithium was immediately transferred via cannula to a separate flask of (+)-cinchonine (1.5 g, 5.1 mmol) in anhydrous MTBE (25 mL) and stirred for 20 min at –10 °C, the mixture was warmed to RT and stirred for a further 2 h. The reaction was quenched by dropwise addition of AcOH (2.5 mL), water (30 mL) and EtOAc (30 mL). Solid iodine (1.25 g) was added portionwise. A solution of sodium metabisulfite (0.50 g) in water (10.0 mL) was added. Aqueous ammonia (28% approx. 4 mL) was added until pH 10 is reached. The aqueous phase was extracted with EtOAc (3 × 30 mL), the organic layers were combined, washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. After purification by column chromatography (*n*-hexane : EtOAc : MeOH : Et_3N, 63 : 30 : 5 : 2 – 53 : 40 : 5 : 2 increase by 5% EtOAc per 250 mL) to give the title product **C1a** (1.31 g, 59%) as a pale yellow solid. Data was in accordance with the literature.[2]

Mp: 264 – 267 °C (*dec*)

Specific Rotation: $[\alpha]_D^{20}$ +63.5 (*c* 0.3, DMSO) {Lit.[2] $[\alpha]_D^{25}$ = +70.0 (*c* 0.6, DMSO)}

ν_{max} (film): 2936, 2878, 1599 (C–N), 1323, 1165 (C–O), 1111, 1072, 849, 758, 682, 409

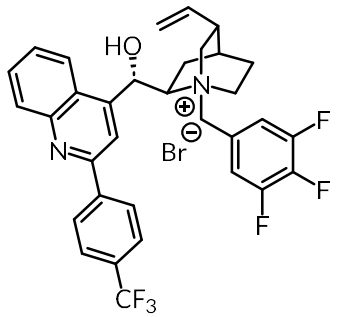
^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 8.30 (2H, d, *J* 8.1), 8.21 (1H, d, *J* 8.6), 8.10 (1H, s), 8.05 (1H, d, *J* 8.5), 7.76 (3H, dd, *J* 20.7, 8.0), 7.58 (1H, app. t, *J* 7.7), 5.98 (1H, app. ddd, *J* 17.4, 10.4, 7.4), 5.73 (1H, d, *J* 5.0), 5.05 – 4.98 (2H, m), 3.19 (2H, dd, *J* 12.2, 7.2), 2.93 (2H, dd, *J* 14.1, 9.6), 2.79 (1H, dt, *J* 13.3, 8.7), 2.24 (1H, q, *J* 8.3), 2.04 – 1.96 (1H, m), 1.79 (1H, s), 1.36 – 1.29 (1H, m)

^{13}C NMR (176 MHz, $CDCl_3$) δ_C: 155.5, 149.8, 148.4, 143.1, 140.1, 131.2 (app. d, *J* 32.9, unable to assign as quartet due to overlapping peaks), 130.8, 129.6, 128.0, 125.9, 125.8, 125.1, 124.9, 123.6, 122.8, 116.1, 115.3, 71.4, 60.3, 50.2, 49.6, 39.8, 28.3, 26.1, 20.9

^{19}F{^{1}H} NMR (471 MHz, $CDCl_3$) δ_F: −62.6 (CF_3)

HRMS: (ESI^+): $C_{26}H_{26}F_3N_2O$ $[M+H]^+$ found 439.1981, requires 439.1997 (−3.6 ppm)

(1*S*,2*R*,4*S*,5*R*)-2-((*S*)-hydroxy(2-(4-(trifluoromethyl)phenyl)quinolin-4-yl)methyl)-1-(3,4,5-trifluorobenzyl)-5-vinylquinuclidin-1-ium bromide (C1)



Following General Procedure D, 5-(bromomethyl)-1,2,3-trifluorobenzene (0.48 mL, 3.59 mmol) was added to a solution of the (+)-cinchonine derivative **C1a** (1.31 g, 2.99 mmol) in MeCN : $CHCl_3$ (1 : 1, 64 mL). The reaction mixture was stirred for 24 h at 50 °C under an inert atmosphere. The crude reaction mixture was concentrated *in vacuo*. The crude product was dissolved in CH_2Cl_2 (8 mL) and MeOH (1 mL), followed by dropwise addition of Et_2O (3 mL). The mixture was concentrated *in vacuo* until a solid began to form, further addition of Et_2O (2 × 3 mL) and concentration *in vacuo* and the Et_2O mixture was placed in a –20 °C freezer overnight, the resulting solid was collected by filtration and washed with ice-cold Et_2O to give

the title compound **C1** (1.19 g, 68%) as a yellow powder. Data was in accordance with the literature.[2]

Mp: 255 – 257 °C (*dec*) (Et_2O)

Specific Rotation: $[\alpha]_D^{20}$ +132.0 (*c* 0.3, DMSO) {Lit.[2] $[\alpha]_D^{20}$ +132.0 (*c* 0.3, DMSO)}

ν_{max} (film): 3021, 1597, 1535, 1350, 1325, 1215 (C–O), 767, 669

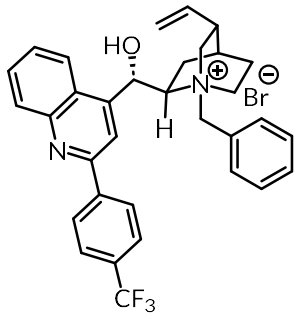
^{1}H NMR (500 MHz, DMSO–d_6) δ_H: 8.51 (2H, d, *J* 8.1), 8.42 – 8.38 (2H, m), 8.22 (1 H, dd, *J* 8.5, 1.3), 7.98 (2H, d, *J* 8.2), 7.95 – 7.89 (3H, m), 7.81 – 7.76 (1H, m), 6.88 (1H, d, *J* 3.6), 6.54 (1H, s), 6.10 (1H, ddd, *J* 17.5, 9.9, 7.3), 5.27 – 5.14 (3H, m), 4.92 (1H, d, *J* 12.5), 4.25 – 4.17 (1H, m), 3.99 – 3.86 (2H, m), 3.58 (1H, t, *J* 11.4), 3.05 (1H, q, *J* 9.9), 2.61 (1H, q, *J* 8.5), 2.41 (1H, t, *J* 11.7), 1.86 (1H, s), 1.81 – 1.70 (2H, m), 1.19 – 1.11 (1H, m).

^{13}C NMR (126 MHz, DMSO–d_6) δ_C: 154.2, 150.1 (app. d, *J* 253.4), 147.7, 146.7, 142.4, 137.2, 130.3, 130.2, 129.8 (app. d, *J* 31.5), 128.1, 127.8, 126.0 (d, *J* 3.8), 125.4, 125.0, 123.9 (d, *J* 6.1), 123.2, 118.9 (d, *J* 19.1), 117.3 (d, *J* 11.5), 67.8, 65.2, 60.7, 56.0, 54.2, 37.2, 26.3, 23.1, 20.5.

^{19}F{^{1}H} NMR (471 MHz, DMSO–d_6) δ_F: −61.0 (3F), −134.5 (2F, dd, *J* 21.9, 8.8), −159.5 (1F, tt, *J* 22.0, 6.7).

HRMS: (ESI^+): $C_{33}H_{29}F_6N_2O$ $[M-Br]^+$ found 583.2163, requires 583.2184 (−3.6 ppm)

(1*S*,2*R*,4*S*,5*R*)-1-benzyl-2-((*S*)-hydroxy(2-(4-(trifluoromethyl)phenyl)quinolin-4-yl)methyl)-5-vinylquinuclidin-1-ium bromide (C3)



Following General Procedure D, to a solution of (+)-cinchonine derivative **C1a** (228 mg, 0.52 mmol) in THF (6 mL), benzyl bromide (74 µL, 0.62 mmol) was added. The reaction mixture

was stirred overnight at 50 °C under an inert atmosphere. The crude reaction mixture was concentrated *in vacuo*. The crude product was dissolved in CH_2Cl_2 (7 mL) and MeOH (3 mL), followed by dropwise addition of Et_2O (3 mL). The mixture was concentrated *in vacuo* until a solid began to form, further addition of Et_2O (2 × 3 mL) and concentration *in vacuo* and the Et_2O mixture was placed in a –20 °C freezer overnight, the resulting solid was collected by filtration and washed with ice-cold Et_2O to give the title compound **C3** (263 mg, 83%) as an off-white powder.

Mp: 214 – 216 °C

Specific Rotation: $[\alpha]_D^{20}$ +131.1 (*c* 0.5, DMSO)

ν_{max} (film): 3145 (O–H), 2947, 1595, 1589, 1550, 1510, 1421, 1323 (C–N), 1109, 1063, 847.

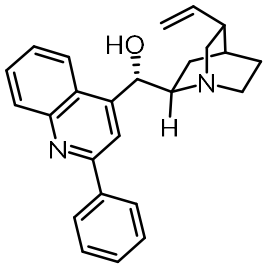
^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 8.52 (2H, d, *J* 8.0), 8.45 – 8.37 (2H, m), 8.22 (1H, app. dd, *J* 8.4, 2.4), 8.00 – 7.96 (2H, m), 7.94 – 7.89 (1H, m,), 7.82 – 7.74 (4H, m), 7.63 – 7.56 (3H, m), 6.95 (1H, app. dt, *J* 9.2, 4.0), 6.60 (1H, app. br. s,), 6.11 (1H, ddd, *J* 17.5, 10.4, 7.3), 5.25 – 5.19 (2H, m) 5.17 – 5.07 (1H, m), 5.00 – 4.89 (1H, m), 4.23 – 4.17 (1H, m), 4.01 – 3.91 (2H, m), 3.50 (1H, t, *J* 11.6), 2.96 (1H, app. q, *J* 10.1), 2.65 (1H, app. q, *J* 8.9), 2.42 (1H, app. t, *J* 11.9), 1.86 (1H, s), 1.77 (2H, app. d, *J* 10.7), 1.19 – 1.12 (1H, m).

^{13}C NMR (176 MHz, DMSO-d_6) δ_C: 154.2, 147.7, 146.8, 142.4, 137.2, 133.8, 130.3, 130.2, 129.9, 129.7, 129.0, 128.1, 127.9, 127.7, 125.9, 125.1, 123.9, 123.8, 123.5, 117.3, 117.1, 67.3, 65.2, 64.9, 62.5, 56.0, 53.9, 37.0. 26.4, 23.0, 20.5.

^{19}F NMR (471 MHz, DMSO-d_6) δ_F: –61.0 (CF_3).

HRMS: (ESI^+): $C_{33}H_{32}F_3N_2O$ $[M–Br]^+$ found 529.2468, requires 529.2461 (+1.3 ppm).

(*S*)-(2-phenylquinolin-4-yl)((1*S*,2*R*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methanol (C4a)



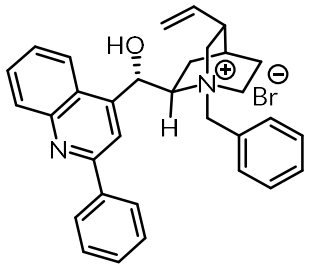
Following General Procedure C, *n*-BuLi (2.5 M, 6 mL, 14.9 mmol) was added to a solution of bromobenzene (1.6 mL, 14.9 mmol) in anhydrous MTBE (10 mL) at –74 °C. The organolithium was transferred to (+)-cinchonine (628 mg, 2.13 mmol) in anhydrous MTBE (10 mL).The reaction was quenched with sequential addition of AcOH (1.05 mL), water (30 mL), EtOAc (30 mL), solid iodine (523 mg, 2.06 mmol), sodium metabisulfite (1.10 mmol in 10 mL of water), and aqueous ammonia (28%, approx. 83 µL) until pH 10 is reached. The crude product was purified by column chromatography (PhMe : MeOH : NEt_3 95 : 4 : 1 – 85 : 14 : 1), to afford the title compound **C4a** (229 mg, 29%) as a white solid. All data was in agreement with the literature.[6]

Mp: 246 – 248 °C {Lit.[6] (255 – 257 ºC)}

Specific Rotation: $[\alpha]_D^{20}$ +157.1 (*c* 0.1, $CHCl_3$) {Lit.[6] $[\alpha]_D^{20}$ + 175.0 (*c* 0.1, $CHCl_3$)}

^{1}H NMR (700 MHz, DMSO-d_6) δ_H: 8.26 (3H, ddd, *J* 15.7, 8.3, 1.2), 8.12 (1H, app. s), 8.08 (1H, dd, *J* 8.4, 1.3), 7.74 (1H, ddd, *J* 8.3, 6.8, 1.3), 7.61 – 7.55 (3H, m), 7.53 – 7.49 (1H, m), 6.11 (1H, ddd, *J* 17.6, 10.3, 7.6), 5.75 (1H, d, *J* 5.0), 5.34 (1H, dd, *J* 7.8, 5.0), 5.13 – 5.05 (2H, m), 3.12 (1H, q, *J* 8.4), 3.04 – 2.96 (1H, m), 2.65 (1H, dd, *J* 13.5, 9.7), 2.18 (1H, q, *J* 8.4), 1.91 – 1.86 (1H, m), 1.72 – 1.68 (1H, m), 1.57 – 1.39 (3H, m). Unable to resolve peak at 2.50 due residual deuterated solvent.

(1*S*,2*R*,4*S*,5*R*)-1-benzyl-2-((*S*)-hydroxy(2-phenylquinolin-4-yl)methyl)-5-vinylquinuclidin-1-ium bromide (C4)



Following General Procedure D, to a solution of (+)-cinchonine derivative **C4a** (228 mg, 0.52 mmol) in THF (6 mL), benzyl bromide (74 µL, 0.62 mmol) was added. The reaction mixture was stirred overnight at 50 °C under an inert temperature atmosphere. After purification by recrystallisation (MeOH : Et_2O – 2 mL : 0.5 mL) the title compound **C4** (76 mg, 74%) was isolated as a white powder.

Mp: 223 – 224 °C (Et_2O)

Specific Rotation: $[\alpha]_D^{20}$ +190.7 (*c* 0.3, DMSO)

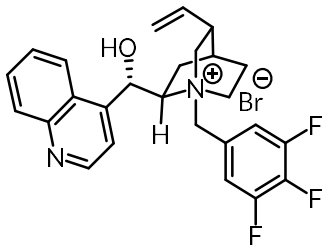
ν_{max} (film): 3121 (O–H), 2012, 1993, 1595, 1458, 1341 (C–N), 1125, 920, 893.

^{1}H NMR (700 MHz, DMSO-d_6) δ_H: 8.39 (1H, d, *J* 8.5), 8.34 (1H, s), 8.29 (2H, d, *J* 7.7), 8.19 (1H, d, *J* 8.4), 7.89 (1H, t, *J* 7.6), 7.77 (3H, app. d, *J* 6.7), 7.67 – 7.53 (6H, m), 6.93 (1H, br. s), 6.59 (1H, s), 6.10 (1H, ddd, *J* 17.5, 10.4, 7.3), 5.27 – 5.19 (2H, m), 5.13 (1H, d, *J* 12.5), 4.95 (1H, d, *J* 12.5), 4.21 (1H, t, *J* 10.5), 3.97 (2H, q, *J* 10.6), 3.50 (1H, t, *J* 11.7), 2.96 (1H, q, *J* 10.2), 2.65 (1H, q, *J* 8.9), 2.41 (1H, t, *J* 11.9), 1.87 (1H, br. s), 1.76 (2H, t, *J* 10.5), 1.19 – 1.11 (1H, m).

^{13}C NMR (176 MHz, DMSO-d_6) δ_C: 155.6, 147.3, 138.3, 137.3, 133.8, 130.2, 130.0, 129.7, 129.1, 129.0, 127.9, 127.4, 127.3, 123.9, 123.6, 117.3, 117.1, 67.3, 65.2, 62.4, 56.0, 53.8, 36.9, 26.4, 23.0, 20.6. Not all carbon environments observed.

HRMS: (ESI^+): $C_{32}H_{33}N_2O$ $[M–Br]^+$ found 461.2586, requires 461.2587 (+1.3 ppm)

(1*S*,2*R*,4*S*,5*R*)-2-((*S*)-hydroxy(quinolin-4-yl)methyl)-1-(3,4,5-trifluorobenzyl)-5-vinylquinuclidin-1-ium bromide (C6)



To a solution of (+)-cinchonine (589 mg, 2.00 mmol) in THF (50 mL), 5-(bromomethyl)-1,2,3-trifluorobenzene (266 µL, 2.00 mmol) was added. The solution was refluxed overnight, once cooled to room temperature the reaction mixture was poured onto cold MTBE (50 mL). The precipitate was collected under vacuum filtration. After purification recrystallisation, MeOH : MTBE (10 : 3, 13 mL) to give the title compound **C6** (738 mg, 71%) as a coral solid.

Mp: 241 °C (*dec*) (MeOH: MTBE).

Specific Rotation: $[\alpha]_D^{20}$ + 140.7 (*c* 0.4, MeOH).

ν_{max} (film): 3009 (O–H), 1587, 1533, 1510, 1352 (C–N), 1234, 1038, 923.

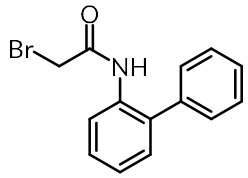
^{1}H NMR (700 MHz, $CDCl_3$) δ_H: 8.82 (1H, d, *J* 4.3), 8.22 (1H, d, *J* 8.2), 7.81 (1H, d, *J* 4.4), 7.49 (2H, app. d, *J* 8.6), 6.92 (2H, dt, *J* 41.1, 7.3), 6.47 – 6.28 (3H, m), 5.83 (1H, app. dt, *J* 17.0, 8.6), 5.52 (1H, dd, *J* 42.1, 12.5), 5.24 (2H, dd, *J* 43.1, 13.9), 4.50 (1H, t, *J* 11.0), 4.21 – 4.08 (2H, m), 3.21 (1H, t, *J* 11.6), 2.83 – 2.75 (1H, m), 2.34 (1H, app. d, *J* 10.8), 2.08 (1H, t, *J* 12.6), 1.85 – 1.65 (3H, m), 0.80 – 0.70 (1H, m).

^{13}C NMR (176 MHz, $CDCl_3$) δ_C: 149.4, 146.9, 143.7, 134.6, 127.01 (app. dd, *J* 263.4, 205.1) 122.8, 119.5, 118.6, 118.5, 67.1, 65.5, 59.5, 56.5, 54.0, 38.0, 26.9, 23.7, 21.8. Not all carbon peaks observed.

^{19}F NMR (659 MHz, $CDCl_3$) δ_F: –130.9 – –131.1 (2F, m), –156.0 – –156.4 (1F, m).

HRMS: (ESI^+): $C_{39}H_{38}N_3O_2$ $[M–Br]^+$ found 439.2004, requires 439.1992 (+2.7 ppm)

***N*-([1,1'-biphenyl]-2-yl)-2-bromoacetamide (C18a)**



Synthesised according to literature procedure,[12] to a solution of 2-aminobiphenyl (1.12 g, 6.61 mmol, 1.00 equiv.) in CH_2Cl_2 (8 mL) a solution of aqueous K_2CO_3 (1.08 g, 7.79 mmol, 1.18 equiv.) in H_2O (8.8 mL) was added and cooled to 0 °C. To the mixture a solution of bromoacetyl bromide (2.00 g, 9.91 mmol, 1.50 equiv.) in CH_2Cl_2 (8 mL) was added dropwise. The mixture was stirred for a further hour at 0 ^{0}C, warmed to RT and stirred overnight. The aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL), the combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. After purification by column chromatography (*n*-hexane : EtOAc : Et_3N, 99 : 0 : 1 – 75 : 24 : 1)* to give the title product **C18a** (1.00 g, 71%) as a grey solid. Data was in accordance with the literature.[12]

*Neutralised silica used in purification; neutralisation achieved with 1% Et_3N when packing the column.

Mp: 96 – 98 °C {Lit.[12] (128 – 129 °C)}

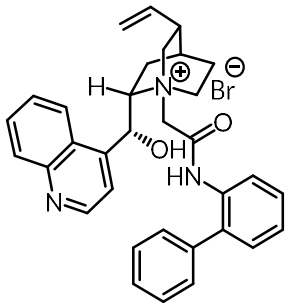
ν_{max} (film): 3019, 2953, 1688 (C=O), 1508, 1215 (C–N), 743, 702, 667.

^{1}H NMR (400 MHz, DMSO-d_6) δ_H: 9.69 (1H, s), 7.52 (1H, d, *J* 7.8), 7.48 – 7.42 (2H, m), 7.41 – 7.30 (6H, m), 3.95 (2H, s).

^{13}C NMR (101 MHz, DMSO-d_6) δ_C: 165.3, 138.4, 136.4, 134.0, 130.4, 128.9, 128.5, 127.8, 127.4, 126.6, 126.4, 29.7.

HRMS: (ESI$^+$) $C_{14}H_{12}BrNNaO$ $[M+Na]^+$ found 311.9991, requires 311.9995 (+1.3 ppm)

(1*S*,2*S*,4*S*,5*R*)-1-(2-([1,1'-Biphenyl]-2-ylamino)-2-oxoethyl)-2-((*R*)-hydroxy(quinolin-4-yl)methyl)-5-vinylquinuclidin-1-ium bromide (C18)



Following General Procedure E, *N*-([1,1'-biphenyl]-2-yl)-2-bromoacetamide (1.18 g, 4.08 mmol), (–)-cinchonidine (1.00 g, 3.40 mmol), in anhydrous THF (49 mL). The mixture was refluxed for 24 hours. After purification by recrystallisation, CH_2Cl_2 : Et_2O (6 : 1, 7 mL) to give the title compound **C18** (1.21 g, 73%) as beige crystals. Data was in accordance with the literature.[12]

mp: 141 – 143 °C (CH_2Cl_2 : Et_2O) {Lit.[12] (149 – 150 °C)}.

Specific Rotation: $[\alpha]_D^{20}$ −36.8 (*c* 0.5, DMSO) {Lit.[12] $[\alpha]_D^{20}$ −44.6 (*c* 1.1, MeOH)}.

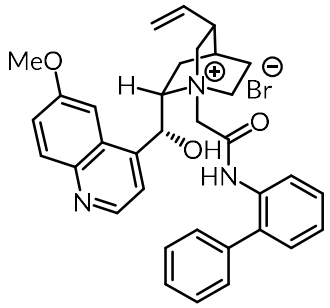
ν_{max} (film): 3011 (O–H), 2955, 1686 (C=O), 1589, 1530, 1510, 1234, 1215 (C–N), 743, 700, 664.

^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ_H: 10.42 (1H, t, *J* 10.2), 8.96 (1H, d, *J* 4.5), 8.06 (2H, t, *J* 8.8), 7.79 (1H, t, *J* 7.6), 7.73 (1H, d, *J* 4.5), 7.61 – 7.53 (2H, m), 7.51 – 7.42 (5H, m), 7.35 (2H, t, *J* 7.6), 7.22 (1H, t, *J* 7.4), 6.72 (1H, d, *J* 3.7), 5.90 (1H, s), 5.62 (1H, ddd, *J* 16.9, 10.6, 5.8), 5.10 (1H, d, *J* 17.3), 4.93 (1H, d, *J* 10.6), 4.66 (1H, d, *J* 15.8), 4.43 (1H, d, *J* 15.7), 4.36 – 4.29 (1H, m), 4.24 (1H, t, *J* 9.7), 3.91 (1H, d, *J* 12.6), 3.69 – 3.55 (2H, m), 2.78 (1H, s), 2.11 – 2.01 (2H, m), 1.96 – 1.86 (2H, m).

^{13}C NMR (500 MHz, DMSO-*d*$_6$) δ_C: 163.2, 150.2, 147.6, 144.9, 138.7, 137.9, 137.7, 133.0, 130.7, 129.9, 129.5, 128.7, 128.6, 128.2, 127.5, 127.3, 127.2, 127.0, 124.2, 123.2, 119.9, 115.9, 65.4, 64.5, 60.1, 59.0, 55.6, 36.9, 25.3, 24.7, 20.9.

HRMS: (ESI^+): $C_{33}H_{34}N_3O_2$ $[M–Br]^+$ found 504.2652, requires 504.2646 (+1.3 ppm).

(1*S*,2*S*,4*S*,5*R*)-1-(2-([1,1'-Biphenyl]-2-ylamino)-2-oxoethyl)-2-((*R*)-hydroxy(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidin-1-ium bromide (C19)



Following General Procedure E, *N*-([1,1'-biphenyl]-2-yl)-2-bromoacetamide (118 mg, 0.41 mmol), quinine (100 mg, 0.34 mmol), in anhydrous THF (4.9 mL). The mixture was refluxed for 24 hours. After purification by recrystallisation, CH_2Cl_2 : Et_2O (6 : 1, 0.7 mL) to give the title compound **C19** (68 mg, 34%) as brown crystals.

mp: 75 – 78 °C (CH_2Cl_2 : Et_2O).

Specific Rotation: $[\alpha]_D^{20}$ −81.9 (*c* 0.5, DMSO).

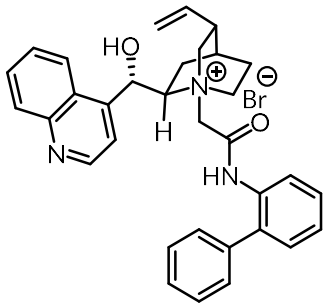
ν_{max} (film): 3019, 2953, 1688 (C=O), 1620, 1508, 1240 (C–N), 1215, (C–O), 743, 702, 667.

^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 10.66 (1H, s), 8.77 (1H, d, *J* 4.6), 7.92 (1H, d, *J* 9.2), 7.70 (1H, d, *J* 4.6), 7.44 (6H, q, *J* 6.3), 7.34 (3H, t, *J* 6.8), 7.19 (2H, dd, *J* 8.1, 5.2), 6.79 (1H, s), 5.77 (1H, s), 5.58 (1H, ddd, *J* 16.6, 10.8, 5.1), 4.96 (2H, dd, *J* 38.5, 14.0), 4.70 (1H, d, *J* 16.4), 4.40 (3H, t, *J* 13.1), 3.79 – 3.73 (1H, m), 3.55 (3H, s), 2.75 (1H, s), 2.06 (2H, s), 1.83 (1H, t, *J* 11.9), 0.96 – 0.88 (1H, m).

^{13}C NMR (126 MHz, DMSO-d_6) δ_C: 163.5, 157.8, 147.2, 143.7, 143.4, 138.9, 138.0, 132.9, 131.3, 130.4, 128.5, 128.3, 128.0, 127.6, 127.2, 127.2, 125.4, 120.2, 115.4, 100.9, 65.7, 62.8, 59.5, 58.6, 56.7, 55.7, 36.5, 25.3, 24.8, 21.3.

HRMS: (ESI^+): $C_{34}H_{36}N_3O_3$ $[M-Br]^+$ found 534.2755, requires 534.2751 (+0.7 ppm).

(1*S*,2*R*,4*S*,5*R*)-1-(2-([1,1'-Biphenyl]-2-ylamino)-2-oxoethyl)-2-((*S*)-hydroxy(quinolin-4-yl)methyl)-5-vinylquinuclidin-1-ium bromide (C20)



Following General Procedure E, *N*-([1,1'-biphenyl]-2-yl)-2-bromoacetamide (118 mg, 0.41 mmol), (+)-cinchonine (100 mg, 0.34 mmol), in anhydrous THF (4.9 mL). The mixture was refluxed for 24 hours. After purification by recrystallisation, CH_2Cl_2 : Et_2O (6 : 1, 0.7 mL) to give the title compound **C20** (143 mg, 68%) as white crystals.

mp:164 – 168 °C (CH_2Cl_2 : Et_2O).

Specific Rotation: $[\alpha]_D^{20}$ +70.1 (*c* 0.2, DMSO).

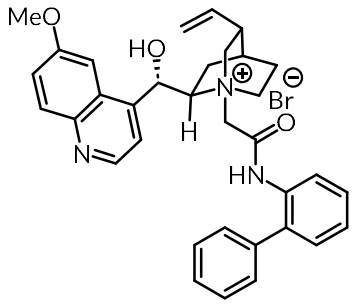
ν_{max} (film): 3017(O–H), 2957, 1686 (C=O), 1589, 1572, 1215 (C–N), 926, 743, 702, 665.

^{1}H NMR (700 MHz, DMSO-d_6) δ_H: 10.52 (1H, s), 8.97 (1H, d, *J* 4.4), 8.19 (1H, d, *J* 8.4), 8.08 (1H, d, *J* 8.4), 7.79 (1H, t, *J* 7.6), 7.76 (1H, d, *J* 4.5), 7.59 (1H, dd, *J* 14.2, 7.4), 7.50 – 7.41 (6H, m), 7.39 (2H, t, *J* 7.5), 7.27 (1H, t, *J* 7.4), 6.76 (1H, d, *J* 3.4), 6.00 – 5.93 (2H, m), 5.27 – 5.23 (2H, m), 4.73 (1H, d, *J* 15.7), 4.40 (1H, d, *J* 15.6), 4.30 (1H, ddd, *J* 12.0, 8.9, 2.6), 4.15 (1H, t, *J* 10.0), 3.86 (1H, t, *J* 11.1), 3.78 (1H, t, *J* 11.3), 3.45 (1H, app. dq, *J* 16.6, 7.9), 2.77 (1 H, q, *J* 8.8), 2.11 (1H, t, *J* 11.8), 1.92 – 1.76 (3H, m), 0.93 (1H, app. dd, *J* 13.9, 6.8).

^{13}C NMR (176 MHz, DMSO-d_6) δ_C: 163.1, 150.1, 147.6, 144.8, 138.7, 137.9, 136.6, 133.1, 130.6, 129.8, 129.4, 128.7, 128.5, 128.2, 127.5, 127.4, 127.3, 127.1, 124.4, 123.5, 120.0, 117.2, 65.6, 65.0, 58.9, 56.7, 37.1, 26.1, 22.9, 20.3, 11.3.

HRMS: (ESI^+): $C_{33}H_{34}N_3O_2$ $[M–Br]^+$ found 504.2637, requires 504.2646 (+1.7 ppm).

(1*S*,2*R*,4*S*,5*R*)-1-(2-([1,1'-Biphenyl]-2-ylamino)-2-oxoethyl)-2-((*S*)-hydroxy(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidin-1-ium bromide (C21)



Following General Procedure E, *N*-([1,1'-biphenyl]-2-yl)-2-bromoacetamide (118 mg, 0.41 mmol), quinidine (111 mg, 0.34 mmol), in anhydrous THF (4.9 mL). The mixture was refluxed for 24 hours. After purification by recrystallisation, CH_2Cl_2 : Et_2O (6 : 1, 0.7 mL) to give the title compound **C21** (88 mg, 42%) as grey crystals.

mp: 76 – 79 °C (CH_2Cl_2 : Et_2O).

Specific Rotation: $[\alpha]_D^{20}$ +85.5 (*c* 0.3, DMSO).

ν_{max} (film): 2951, 1688 (C=O), 1508, 1240 (C–O), 1229 (C–N), 1026, 743, 719, 702, 664.

^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 10.56 (1H, s), 8.78 (1H, d, *J* 4.6), 7.93 (1H, d, *J* 9.8), 7.72 (1H, d, *J* 4.6), 7.53 – 7.48 (1H, m), 7.48 – 7.33 (8H, m), 7.30 – 7.25 (1H, m), 6.76 (1H, s), 5.97 (1H, ddd, *J* 17.2, 10.6, 6.7), 5.89 (1H, s), 5.28 – 5.22 (1H, m), 4.66 (1H, d, *J* 16.5), 4.41 – 4.24 (3H, m), 3.79 – 3.70 (1H, m), 3.63 (1H, t, *J* 11.2), 3.55 (3H, s, *J* 1.9), 2.77 (1H, q, *J* 8.9), 2.04 (1H, t, *J* 12.1), 1.92 – 1.80 (3H, m), 0.91 – 0.83 (1H, m). Unable to resolve peak at 3.32 ppm due to residual water.

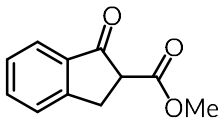
^{13}C NMR (126 MHz, DMSO-d_6) δ_C: 163.5, 157.8, 147.2, 143.7, 143.3, 138.7, 137.8, 136.5, 133.0, 131.3, 130.4, 128.5, 128.0, 127.5, 127.3, 127.2, 125.6, 122.2, 120.3, 117.1, 101.5, 66.1, 63.6, 60.2, 58.8, 56.6, 55.7, 37.2, 26.3, 22.7, 20.4.

HRMS: (ESI^+): $C_{34}H_{36}O_3N_3$ $[M-Br]^+$ found 534.2738, requires 534.2757 (−3.6 ppm).

6.2 Starting Materials

The following substrates were purchased from chemical suppliers: **1s, 2a** and **2d** from Fluorochem, **2b** from Apollo Scientific, and **2c** from TCI. Substrates **1t**,[13] **1u**,[14] **1v**,[13] **1w**,[15] **1x**[15] were synthesised according to literature procedures.

Methyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (1a)



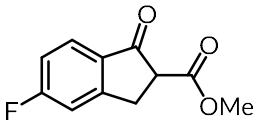
Following General Procedure A, NaH (60% in mineral oil, 3.30 g, 82.5 mmol) in anhydrous THF (146 mL), dimethyl carbonate (31.9 mL, 378 mmol), *t*-BuOK (424 mg, 3.78 mmol), 2,3-dihydro-1*H*-inden-1-one (5.00 g, 37.8 mmol) in anhydrous THF (51.6 mL) for 16 hours. After purification by column chromatography (*n*-hexane : EtOAc, 100 : 0 – 80 : 20, gradient run 5% increase per 250 mL), to give the title compound (5.40 g, 75%) as a dark yellow solid. The product was present as a mixture of keto/enol tautomers by ^{1}H NMR. To obtain the pure keto tautomer a subsequent recrystallisation can be carried out. The keto/enol mixed product (5.40 g) was refluxed in Et_2O (~10 mL) until all material had dissolved. After cooling to RT the solution was placed in a –20 °C freezer overnight, the resulting crystals were collected by filtration and washed with ice cold Et_2O to give the title compound (5.25 g, 73%) as colourless crystals. Data was in accordance with the literature.[16]

Mp: 59 – 60 °C {Lit.[16] (51 – 55 °C)}.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 7.77 (1H, d, *J* 7.7), 7.62 (1H, td, *J* 7.5, 1.2), 7.50 (1H, dt, *J* 7.8, 1.0), 7.42 – 7.37 (1H, m), 3.79 (3H, s), 3.74 (1H, dd, *J* 8.3, 4.0), 3.57 (1H, dd, *J* 17.2, 4.1), 3.38 (1H, dd, *J* 17.2, 8.3).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 199.6, 169.7, 153.7, 135.6, 135.3, 128.0, 126.7, 124.8, 53.3, 52.9, 30.4.

Methyl 5-fluoro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (1b)



Following General Procedure A, NaH (60% in mineral oil, 239 mg, 9.95 mmol) in anhydrous THF (18.2 mL), dimethyl carbonate (4.0 mL, 47.4 mmol), *t*-BuOK (53 mg, 0.47 mmol), 5-fluoro-2,3-dihydro-1*H*-inden-1-one (711 mg, 4.74 mmol) in anhydrous THF (10.8 mL) for 16 hours. After purification by column chromatography (*n*-hexane : EtOAc, 100 : 0 – 80 : 20, gradient run 5% increase per 75 mL), to give the title compound (789 mg, 80%) as a brown solid.

Mp: 57 – 58°C.

ν_{max} (film): 2955, 2361, 1742 (C=O), 1711 (C=O), 1593, 1248, 1086, 750.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H: keto : enol (9.1 : 1). 7.81 (1H, dd, *J* 8.5, 5.3 **keto Ar–H**), 7.62 (0.11H, dd, *J* 8.4, 5.1, **enol Ar–H**), 7.22 – 7.17 (1.16H, m, **keto/enol Ar–H**), 7.15 – 7.09 (1.14H, m, **keto/enol Ar–H**), 3.88 (0.35H, s, **enol OMe**), 3.82 (3H, s, **keto OMe**), 3.79 (1H, app. dd, *J* 8.3, 4.0, **keto C–H**), 3.59 (1H, dd, *J* 17.5, 4.0, **keto C–H**), 3.54 (0.23H, s, **enol C–H**), 3.39 (1H, dd, *J* 17.5, 8.3, **keto C–H**).

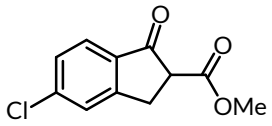
^{13}C NMR (126 MHz, $CDCl_3$) δ_C: Keto: 197.6, 169.4, 167.7 (d, *J* 257.9), 156.7 (d, *J* 10.4), 127.2 (d, *J* 10.8), 116.5 (d, *J* 24.0), 113.40 (d, *J* 22.6), 53.5, 53.1, 30.2.

Enol: 166.7, 163.3, 145.8, 131.7, 122.2 (d, *J* 9.4), 114.58 (d, *J* 23.6), 112.5 (d, *J* 23.3), 102.1, 51.4, 32.7.

^{19}F NMR (471 MHz, $CDCl_3$) δ_F: −101.2 (1F, app. td, *J* 8.6, 5.1, **keto**), −110.9 (1F, app. td, *J* 9.0, 5.1, **enol**).

HRMS: (ESI^+) $C_{11}H_9FO_3$ $[M+H]^+$ found 209.0612, requires 209.0609 (+1.8 ppm).

Methyl 5-chloro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (1c)



Following General Procedure A, NaH (60% in mineral oil, 126 mg, 3.15 mmol) in anhydrous THF (5.8 mL), dimethyl carbonate (1.3 mL, 15.0 mmol), *t*-BuOK (17 mg, 0.15 mmol), 5-chloro-2,3-dihydro-1*H*-inden-1-one (250 mg, 1.50 mmol) in anhydrous THF (3.4 mL) for 16 hours. After purification by column chromatography (*n*-hexane : EtOAc, 100 : 0 – 85 : 15, gradient run 5% increase per 50 mL), to give the title compound (212 mg, 63%) as a grey solid.

Mp: 79 – 81°C.

ν_{max} (film): 3022, 2955, 1744 (C=O), 1715 (C=O), 1215, 1204, 752.

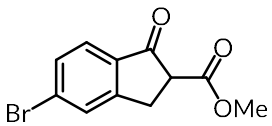
^{1}H NMR (500 MHz, $CDCl_3$) δ_H: keto : enol (4 : 1). 7.70 (1H, dd, *J* 8.2, 0.6, **keto Ar–H**), 7.56 (0.26 H, dd, *J* 8.1, 0.5, **enol Ar–H**), 7.51 (1H, d, *J* 1.0, **keto Ar–H**), 7.46 (0.25H, dd, *J* 1.8, 0.8, **enol Ar–H**), 7.40 – 7.35 (1.27H, m, **keto/enol Ar–H**), 3.86 (0.75H, s, **enol OMe**), 3.80 (3H, s, **keto OMe**), 3.76 (1H, dd, *J* 8.3, 4.0, **keto C–H**), 3.56 (1H, dd, *J* 17.4 3.9, **keto C–H**), 3.51 (0.5H, s, **enol C–H**), 3.35 (1H, ddd, *J* 17.4, 8.3, 0.7, **keto C–H**).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C: Keto: 198.0, 169.3, 155.1, 142.3, 133.8, 128.9, 126.9, 125.9, 53.3, 53.1, 30.1.

Enol: 144.8, 135.8, 135.5, 127.5, 125.4, 121.8, 102.6, 51.5, 32.5.

HRMS: (ESI^+) $C_{11}H_9{}^{35}ClO_3$ $[M+H]^+$ found 225.0313, requires 225.0313 (+2.4 ppm)

Methyl 5-bromo-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (1d)



Following General Procedure A, NaH (60% in mineral oil, 99.5 mg, 2.49 mmol) in anhydrous THF (4.6 mL), dimethyl carbonate (1.0 mL, 11.8 mmol), *t*-BuOK (13 mg, 0.12 mmol), 5-bromo-

2,3-dihydro-1*H*-inden-1-one (250 mg, 1.18 mmol) in anhydrous THF (2.7 mL) for 16 hours. After purification by column chromatography (*n*-hexane : EtOAc, 100 : 0 – 90 : 10, gradient run 5% increase per 50 mL), to give the title compound (170 mg, 53%) as a yellow powder.

Mp: 87 – 88 °C.

ν_{max} (film): 3024, 2953, 1742 (C=O), 1713 (C=O), 1215, 1204, 748.

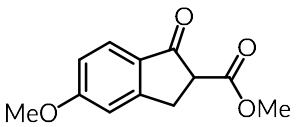
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: keto : enol (3.4 : 1). 7.69 (1H, d, *J* 0.9, **keto Ar–H**), 7.64 (0.34H, d, *J* 0.5, **enol Ar–H**), 7.62 (1H, s, **keto Ar–H**), 7.56 – 7.48 (1.56H, m, **keto/enol Ar–H**), 3.86 (0.88H, s, **enol OMe**), 3.80 (3H, s, **keto OMe**), 3.74 (1H, dd, *J* 8.3, 4.0, **keto C–H**), 3.56 (1H, dd, *J* 17.4, 4.0, **keto C–H**), 3.50 (0.57H, s, **enol CH_2**), 3.40 – 3.32 (1H, m, **keto C–H**).

^{13}CNMR (101 MHz, $CDCl_3$) δ_C: Keto: 198.3, 169.2, 155.2, 134.2, 131.7, 131.1, 130.0, 126.0, 53.2, 53.1, 30.0.

Enol: 130.3, 128.3, 124.1, 122.1, 51.5, 32.5. Remaining quaternary carbons not observed.

HRMS: (ESI^+) $C_{11}H_9{}^{79}BrO_3$ $[M+H]^+$ found 268.9812, requires 268.9808 (+1.6 ppm).

Methyl 5-methoxy-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (1e)



Following General Procedure A, NaH (60% in mineral oil, 129 mg, 3.24 mmol) in anhydrous THF (5.9 mL), dimethyl carbonate (1.3 mL, 15.4 mmol), *t*-BuOK (17 mg, 0.15 mmol), 5-methoxy-2,3-dihydro-1*H*-inden-1-one (250 mg, 1.54 mmol) in anhydrous THF (3.50 mL) for 16 hours. After purification by column chromatography (*n*-hexane : EtOAc, 100 : 0 – 75 : 25, gradient run 5% increase per 50 mL), to give the title compound (248 mg, 73%) as a white solid.

Mp: 75 – 77 °C.

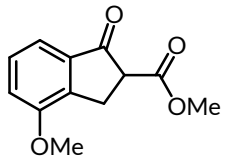
ν_{max} (film): 3019, 2953, 1740 (C=O), 1705 (C=O), 1260 (C–O), 1090, 754.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: Only keto tautomer present. 7.72 – 7.68 (1H, m), 6.95 – 6.90 (2H, m), 3.89 (3H, s), 3.79 (3H, s), 3.72 (1H, dd, *J* 8.2, 4.0), 3.51 (1H, dd, *J* 17.3, 3.9), 3.31 (1H, dd, *J* 17.3, 8.2).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 197.6, 170.0, 166.0, 156.9, 128.5, 126.5, 116.1, 109.7, 55.9, 53.5, 52.9, 30.4.

HRMS: (ESI^+) $C_{12}H_{13}O_4$ $[M+H]^+$ found 221.0808, requires 221.0808 (–0.1 ppm)

Methyl 4-methoxy-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (1f)



Following General Procedure A, NaH (60% in mineral oil, 129 mg, 3.24 mmol) in anhydrous THF (5.9 mL), dimethyl carbonate (1.3 mL, 15.4 mmol), *t*-BuOK (17 mg, 0.15 mmol), 4-methoxy-2,3-dihydro-1*H*-inden-1-one (250 mg, 1.54 mmol) in anhydrous THF (3.50 mL) for 16 hours. After purification by column chromatography (*n*-hexane : EtOAc, 100 : 0 – 75 : 25, gradient run 5% increase per 50 mL), to give the title compound (251 mg, 74%) as a pink solid.

Mp: 72 – 73 °C.

ν_{max} (film): 3023, 2957, 1752 (C=O), 1724 (C=O), 1327, 1215 (Ar C–O), 1165, 1130, 748, 667.

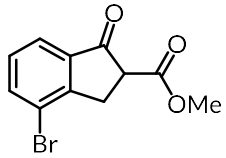
^{1}H NMR (500 MHz, $CDCl_3$) δ_H: keto : enol (8.1 : 1). 7.39 – 7.34 (2H, m, **keto/enol Ar–H**), 7.28 (0.14H, dd, *J* 7.6, 0.8, **enol Ar–H)**, 7.08 – 7.04 (1H, m, **keto Ar–H**), 6.94 (0.13H, dd, *J* 8.1, 0.9, **enol Ar–H**), 3.91 (3H, s, **keto Ar–OMe**), 3.90 (0.39H, s, **enol Ar–OMe**), 3.86 (0.37H, s, **enol OMe**), 3.79 (3H, s, **keto OMe**), 3.72 (1H, dd, *J* 8.1, 3.8, **keto C–H**), 3.47 – 3.41 (1H, m, **keto/enol C–H**), 3.29 (1H, dd, *J* 17.7, 8.1, **keto C–H**).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C: Keto: 199.8, 169.7, 157.0, 142.7, 136.8, 129.5, 116.2, 115.7, 55.7, 53.2, 52.9, 27.3.

Enol: 169.9, 155.7, 138.5, 130.8, 128.8, 115.9, 113.5, 111.3, 102.4, 55.5, 51.4, 30.0.

HRMS: (ESI^+) $C_{12}H_{13}O_4$ $[M+H]^+$ found 205.0859, requires 205.0859 (–0.2 ppm).

Methyl 4-bromo-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (1g)



Following General Procedure A, NaH (60% in mineral oil, 303 mg, 12.6 mmol) in anhydrous THF (23 mL), dimethyl carbonate (5.1 mL, 60.2 mmol), *t*-BuOK (68 mg, 0.60 mmol), 4-bromo-2,3-dihydro-1*H*-inden-1-one (1.27 g, 6.02 mmol) in anhydrous THF (14 mL) for 16 hours. After purification by column chromatography (*n*-hexane : EtOAc, 100 : 0 – 90 : 10, gradient run 5% increase per 125 mL), to give the title compound (574 mg, 36%) as beige crystals.

Mp: 80 – 83 °C.

ν_{max} (film): 2361, 2342, 1658 (C=O), 1234, 1186, 767.

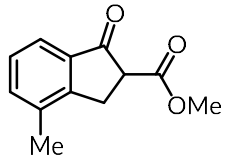
^{1}H NMR (500 MHz, $CDCl_3$) δ_H: keto : enol (2.2 : 1). 7.77 (2H, app. ddd, *J* 33.9, 7.7, 1.0, **keto Ar–H**), 7.58 (0.91H, app. ddd, *J* 20.3, 7.7, 0.9, **enol Ar–H**), 7.34 – 7.27 (1.52H, m, **keto/enol Ar–H**), 3.88 (1.37H, s, **enol OMe**), 3.81 (3H, s, **keto OMe**), 3.78 (1H, dd, *J* 8.3, 4.0, **keto C–H**), 3.53 – 3.47 (1.53H, m, **keto/enol C–H**), 3.33 (1H, dd, *J* 17.8, 8.3, **keto C–H**).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C: Keto: 198.8, 169.1, 153.4, 138.4, 137.3, 129.8, 123.7, 122.1, 53.2, 53.1, 34.2.

Enol: 143.2, 138.6, 138.4, 132.5, 128.9, 120.0, 119.8, 103.1, 51.6, 31.5. C–OH not observed.

HRMS: (ESI^+) $C_{11}H_9{}^{79}BrO_3$ $[M+H]^+$ found 268.9809, requires 268.9808 (+0.6 ppm).

Methyl 4-methyl-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (1h)



Following General Procedure A, NaH (60% in mineral oil, 86 mg, 3.59 mmol) in anhydrous THF (6.6 mL), dimethyl carbonate (1.4 mL, 17.1 mmol), *t*-BuOK (19 mg, 0.17 mmol), 4-methyl-2,3-dihydro-1*H*-inden-1-one (250 mg, 1.71 mmol) in anhydrous THF (3.9 mL) for 16 hours.

After purification by column chromatography (*n*-hexane : EtOAc, 100 : 0 – 95 : 5, gradient run 5% increase per 100 mL), to give the title compound (284 mg, 81%) as pale pink powder.

Mp: 73 – 74 °C.

ν_{max} (film): 3020, 1742 (C=O), 1713 (C=O), 1215, 745, 667.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H: keto : enol (5.5: 1). 7.62 (1H, d, *J* 7.6, **keto Ar–H**), 7.50 (0.16H, d, *J* 7.5, **enol Ar–H**), 7.44 (1H, d, *J* 7.3, **keto Ar–H**), 7.32 (1.20H, app. t, *J* 7.6, **keto/enol Ar–H**), 7.24 (0.18H, app. d, **enol Ar–H**), 3.87 (0.51H, s, **enol OMe**), 3.80 (3H, s, **keto OMe**), 3.75 (1H, dd, *J* 8.2, 3.9, **keto C–H**), 3.48 – 3.40 (1.41H, m **keto/enol Ar–Me**), 3.27 (1H, dd, *J* 17.3, 8.2 **keto C–H**), 2.37* (3.62H, d, *J* 4.9, **keto/enol Ar–Me**).

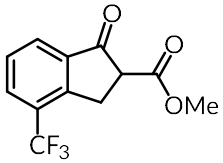
*Overlapping singlets.

^{13}C NMR (126 MHz, $CDCl_3$) δ_C: Keto: 199.9, 169.8, 152.7, 136.1, 134.1, 128.2, 122.2, 53.2, 52.9, 29.3, 17.9.

Enol: 142.1, 136.6, 136.0, 135.2, 130.7,127.4, 118.6, 102.1, 51.4, 31.7, 18.1. C–OH not observed.

HRMS: (ESI$^+$) $C_{12}H_{13}O_4$ $[M+H]^+$ found 221.0808, requires 221.0808 (–0.4 ppm)

Methyl 1-oxo-4-(trifluoromethyl)-2,3-dihydro-1*H*-indene-2-carboxylate (1i)



Following General Procedure A, NaH (60% in mineral oil, 50.4 mg, 2.10 mmol) in anhydrous THF (3.8 mL), dimethyl carbonate (0.8 mL, 99.9 mmol), *t*-BuOK (11.2 mg, 1.00 mmol), 4-(trifluoromethyl)-2,3-dihydro-1*H*-inden-1-one (200 mg, 1.71 mmol) in anhydrous THF (2.3 mL) for 16 hours. After purification by column chromatography (*n*-hexane : EtOAc, 100 : 0 – 90 : 10, gradient run 5% increase per 100 mL), to give the title compound (139 mg, 54%) as white solid.

Mp: 65 – 67 °C.

ν_{max} (film): 3026, 2959, 1748 (C=O), 1724 (C=O), 1325, 1121, 1105, 754.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H: keto : enol (1 : 1). 10.26 (1H, s, **enol OH**), 7.94 (1H, d, *J* 7.7, **keto Ar–H**), 7.88 (1H, d, *J* 7.2, **keto Ar–H**), 7.78 (1H, dd, *J* 7.7, 2.2, **enol Ar–H**), 7.66 – 7.62 (1H, m, **enol Ar–H**), 7.56 – 7.46 (2H, m, **keto/enol Ar–H**), 3.86 (3H, s, **enol OMe**), 3.81 – 3.77 (4H, m, **keto OMe/C–H**),* 3.72 (1H, dd, *J* 18.0, 4.3 **keto C–H**), 3.67 (2H, s, **enol C–H**), 3.56 (1H, dd, *J* 18.0, 8.3, **keto C–H**). *Unable to resolve due to overlapping environments.

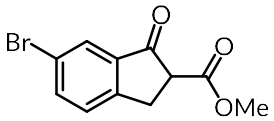
^{13}C NMR (126 MHz, $CDCl_3$) δ_C: Keto: 198.2, 168.9, 150.8, 136.8, 132.2 (q, *J* 4.6), 128.8, 128.5, 125.0 (d, *J* 57.1), 122.9 (d, *J* 57.4), 120.7 (d, *J* 57.7), 53.1, 52.8, 29.3.

Enol: 169.7, 140.4, 138.6, 128.3, 127.6, 127.0 (d, *J* 32.6), 126.8 (d, *J* 45.0), 126.0 (q, *J* 4.5), 124.2, 103.2, 51.5, 32.0.

^{19}F NMR (471 MHz, $CDCl_3$) δ_F: −62.1 (CF_3, s, **enol**), −62.3 (CF_3, s, **keto**).

HRMS: (ESI^+) $C_{12}H_9F_3NaO_3$ $[M+Na]^+$ found 281.0397, requires 281.0396 (+0.4 ppm).

Methyl 6-bromo-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (1j)



Following General Procedure A, NaH (60% in mineral oil, 303 mg, 12.6 mmol) in anhydrous THF (23 mL), dimethyl carbonate (5.1 mL, 60.2 mmol), *t*-BuOK (68 mg, 0.60 mmol), 6-bromo-2,3-dihydro-1*H*-inden-1-one (1.27 g, 6.02 mmol) in anhydrous THF (14 mL) for 16 hours. After purification by column chromatography (*n*-hexane : PhMe, 100 : 0 – 50 : 50, gradient run 10% increase per 75 mL), to give the title compound (334 mg, 21%) as an orange powder.

Mp: 126 – 127 °C.

ν_{max} (film): 3019, 1721 (C=O), 1657 (C=O), 1213, 746, 667.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: keto : enol (2.4 : 1). 7.90 (1H, dd, *J* 2.0, 0.6, **keto Ar–H**), 7.77 (0.41H, dd, *J* 1.9, 0.6, **enol Ar–H**), 7.73 (1H, dd, *J* 8.1, 2.0, **keto Ar–H**), 7.53 (0.43H, dd, *J* 8.0, 1.9, **enol Ar–H**), 7.40 (1H, dd, *J* 8.2, 0.8, **keto Ar–H**), 7.33 (0.42H, dd, *J* 8.0, 0.7, **enol Ar–H**), 3.86

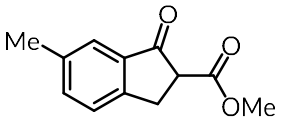
(1.29H, s, **enol OMe**), 3.80 (3H, s, **keto OMe**), 3.77 (1H, dd, *J* 8.3, 4.0, **keto C–H**), 3.52 (1H, dd, *J* 17.4, 3.9, **keto C–H**), 3.47 (0.85H, d, *J* 0.7, **enol C–H**), 3.33 (1H, dd, *J* 17.4, 8.2, **keto C–H**).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C: Keto: 198.1, 169.2, 152.2, 138.4, 137.1, 128.2, 127.7, 122.2, 53.5, 53.1, 39.0, 30.0.

Enol: 168.3, 141.8, 139.0, 132.3, 126.3, 124.0, 121.0, 51.5, 32.4, 29.8. C–OH not observed.

HRMS: (ESI$^+$) $C_{11}H_9{}^{79}BrO_3$ $[M+H]^+$ found 268.9811, requires 268.9807 (+1.4 ppm)

Methyl 6-methyl-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (1k)



Following General Procedure A, NaH (60% in mineral oil, 86 mg, 3.59 mmol) in anhydrous THF (6.6 mL), dimethyl carbonate (1.4 mL, 17.1 mmol), *t*-BuOK (19 mg, 0.17 mmol), 6-methyl-2,3-dihydro-1*H*-inden-1-one (250 mg, 1.71 mmol) in anhydrous THF (3.9 mL) for 16 hours. After purification by column chromatography (*n*-hexane : EtOAc, 100 : 0 – 75 : 25, gradient run 5% increase per 100 mL), to give the title compound (314 mg, 90%) as a brown powder.

Mp: 73 – 74 °C.

ν_{max} (film): 3022, 2953, 1738 (C=O), 1705 (C=O), 1211 1150, 750, 492.

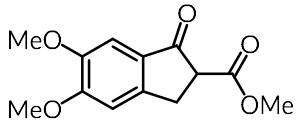
^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 7.67 (1H, s, **keto Ar–H**), 7.56 – 7.53 (1.17H, m, **keto/enol Ar–H**), 7.49 (1H, d, *J* 7.8, **keto Ar–H**), 7.45 (0.13H, d, *J* 7.7, **enol Ar–H**), 7.34 (0.15H, d, *J* 7.7, **enol Ar–H**), 3.95 (0.38H, s, **enol OMe**), 3.89 (3H, s, **keto OMe**), 3.83 (1H, dd, *J* 8.2, 4.0, **keto C–H**), 3.61 (1H, dd, *J* 17.1, 4.0, **keto C–H**), 3.57 (0.27H, s, **enol C–H**), 3.43 (1H, dd, *J* 17.1, 8.2, **keto C–H**), 2.52 (0.46H, s, **keto CH_3**), 2.50 (3H, s, **enol CH_3**).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C: Keto: 199.7, 169.8, 151.2, 138.0, 136.8, 126.3, 124.7, 121.3, 53.6, 52.9, 30.1, 21.2.

Enol: 140.5, 137.1, 136.9, 135.5, 130.6, 124.6, 102.5, 51.3, 32.2, 21.5. Remaining quaternary peaks not observed.

HRMS: (ESI$^+$) $C_{12}H_{13}O_4$ [M+H]$^+$ found 205.0858, requires 205.0859 (–0.5 ppm)

Methyl 5,6-dimethoxy-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (1l)



Following General Procedure A, NaH (60% in mineral oil, 328 mg, 8.19 mmol) in anhydrous THF (15 mL), dimethyl carbonate (3.3 mL, 39.0 mmol), *t*-BuOK (44 mg, 0.39 mmol), 5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one (750 mg, 3.90 mmol) in anhydrous THF (9 mL) for 16 hours. After purification by column chromatography (*n*-hexane : EtOAc 100 : 0 – 50 : 50, gradient run 10% increase per 200 mL), to give the title compound (887 mg, 91%) as a beige solid.

Mp: 156 – 159 °C.

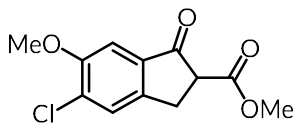
ν_{max} **(film):** 2957, 2839, 1721 (C=O), 1690 (C=O), 1310, 1252 (C–O), 1194 (C–O), 1022, 876, 525.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H: Only keto tautomer present. 7.17 (1H, s), 6.91 (1H, s), 3.98 (3H, s), 3.90 (3H, s), 3.79 (3H, s), 3.73 (1H, dd, *J* 7.9, 3.5), 3.46 (1H, dd, *J* 17.1, 3.4), 3.28 (1H dd, *J* 17.1, 7.9).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 198.0, 170.0, 156.2, 149.9, 149.4, 128.0, 107.4, 104.9, 56.5, 56.3, 53.5, 52.9, 30.1.

HRMS: (ESI$^+$) $C_{13}H_{14}O_5$ [M+H]$^+$ found 251.0913, requires 251.0914 (–0.4 ppm)

Methyl 5-chloro-6-methoxy-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (1m)



Following General Procedure A, NaH (60% in mineral oil, 126 mg, 3.15 mmol) in anhydrous THF (5.8 mL), dimethyl carbonate (1.3 mL, 15.0 mmol), *t*-BuOK (17 mg, 0.15 mmol), 5-chloro,

6-methoxy-2,3-dihydro-1*H*-inden-1-one (295 mg, 1.50 mmol) in anhydrous THF (3.4 mL) for 16 hours. After purification by column chromatography (*n*-hexane : Et_2O, 100 : 0 – 80 : 20, gradient run 5% increase per 100 mL), to give the title compound (246 mg, 64%) as a grey solid.

Mp: 116 – 119 °C.

ν_{max} (film): 3019, 2955, 1742 (C=O), 1709 (C=O), 1439, 1204 (C–O), 1194 (C–O), 1051, 750, 721.

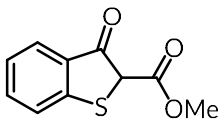
^{1}H NMR (500 MHz, $CDCl_3$) δ_H: keto : enol (6.7 : 1). 7.52 (1H, s, **keto Ar–H**), 7.46 (0.15H, s, **enol Ar–H**), 7.23 (1H, s, **keto Ar–H**), 7.17 (0.15H, s, **enol Ar–H**), 3.95 (0.45H, s, **enol Ar–OMe**), 3.92 (3H, s, **keto Ar–OMe**), 3.85 (0.45H, s, **enol OMe**), 3.79 (3H, s, **keto OMe**), 3.75 (1H, dd, *J* 8.1, 3.8, **keto C–H**), 3.52 – 3.42 (1.34H, m, **keto/enol C–H**), 3.29 (1H, dd, *J* 17.2, 8.3, **keto C–H**).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C: Keto: 198.5, 169.4, 155.4, 146.5, 134.7, 131.9, 126.6, 105.8, 56.5, 53.7, 53.0, 29.5.

Enol: 154.6, 136.5, 135.8, 128.1, 124.6, 103.8, 103.4, 56.6, 51.5, 31.9. Remaining quaternary carbons not observed.

HRMS: (ESI^+) $C_{12}H_{11}{}^{35}ClO_3$ $[M+H]^+$ found 277.0243, requires 277.0238 (+1.9 ppm)

Methyl 3-oxo-2,3-dihydrobenzo[*b*]thiophene-2-carboxylate (1n)



Following General Procedure A, NaH (60% in mineral oil, 112 mg, 2.80 mmol) in anhydrous THF (5.2 mL), dimethyl carbonate (1.1 mL, 13.3 mmol), *t*-BuOK (15 mg, 0.13 mmol), benzo[*b*]thiophen-3(2*H*)-one (200 mg, 1.33 mmol) in anhydrous THF (3.3 mL) for 16 hours. After purification by column chromatography (*n*-hexane), to give the title compound (123 mg, 44%) as pink crystals. Data was in accordance with the literature.[17]

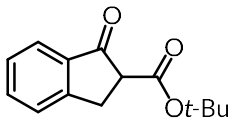
ν_{max} (film): 3019, 2953, 1660 (C=O), 1445, 1308, 1216 (C–O), 1148, 748, 733, 667.

Mp: 106 – 108 °C {Lit.[17] (103 – 106 °C)}.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H: Only enol tautomer is present. 10.14 (1H, s, **enol OH**), 7.94 (1H, d, *J* 8.6), 7.74 (1H, d, *J* 8.4), 7.50 (1H, t, *J* 7.4), 7.40 (1H, t, *J* 7.2), 3.96 (3H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 167.8, 159.7, 139.0, 130.5, 129.0, 124.6, 123.3, 123.1, 101.8, 52.3.

***tert*-Butyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (1o)**



Following General Procedure B, Bu_2SnO (164 mg, 0.66 mmol), PhMe (33.0 mL), methyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (**1a**) (628 mg, 3.30 mmol), *t*-BuOH (3.2 mL, 33.0 mmol) were refluxed for 16 hours. After purification by column chromatography (*n*-hexane : EtOAc, 100 : 0 – 80 : 20, gradient run 5% increase per 100 mL), to give the title compound (445 mg, 58%) as a purple oil.

ν_{max} (film): 2976, 2931, 1709 (C=O), 1256, 1146 (C–O), 843, 760, 467.

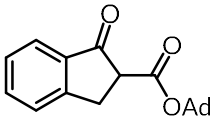
^{1}H NMR (500 MHz, $CDCl_3$) δ_H: keto : enol (7.69 : 1). 7.75 (1.04H, d, *J* 7.7, **keto/enol Ar–H**), 7.60 (1.16H, t, *J* 7.5, **keto/enol Ar–H**), 7.49 (1.03H, d, *J* 7.7, **keto/enol Ar–H**), 7.38 (1.52H, t, *J* 7.5, **keto/enol Ar–H**), 3.62 (1H, dd, *J* 8.3, 4.0, **keto C–H**), 3.53 – 3.46 (1.30H, m, **keto/enol C–H**), 3.33 (1H, dd, *J* 17.2, 8.2, **keto C–H**), 1.57 (1.17H, s, **enol O*t*-Bu**), 1.49 (9H, s, **keto O*t*-Bu**).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C: Keto: 200.2, 168.5, 153.8, 137.3, 135.4, 127.8, 126.7, 124.7, 82.2, 54.5, 30.5, 28.1.

Enol: 143.1, 135.6, 134.7, 129.1, 127.4, 126.8, 124.7, 123.9, 120.6, 104.1, 81.1, 28.6.

HRMS: (ESI$^+$) $C_{14}H_{16}O_3$ $[M+H]^+$ found 255.0991, requires 255.0992 (–0.2 ppm).

Adamantan-1-yl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (1p)



Following General Procedure B, Bu_2SnO (100 mg, 0.40 mmol), PhMe (20 mL), methyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (**1a**) (380 mg, 3.30 mmol), 1-adamantol (913 mg, 6.00 mmol) were refluxed for 16 hours. After purification by column chromatography (*n*-hexane : EtOAc, 100 : 0 – 90 : 10, gradient run 10% increase per 200 mL), to give the title compound (203 mg, 33%) as a pink solid. Data was in accordance with the literature.[18]

Mp: 99 – 103 °C {Lit.[18] (103 °C)}.

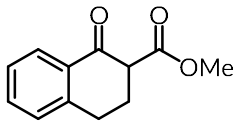
ν_{max} (film): 3021, 2913, 2855, 1707 (C=O), 1256, 1207 (C–O), 1053, 746, 667.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H: keto : enol (6.25 : 1). 7.76 (1H, d, *J* 7.7, **keto Ar–H**), 7.61 (1.19H, app. td, *J* 7.5, 1.3, **keto/enol Ar–H**), 7.49 (1H, d, *J* 7.7, **keto/enol Ar–H**), 7.45 (0.16H H, d, *J* 7.2 **enol Ar–H**), 7.42 – 7.34 (1.37H, m, **keto/enol Ar–H**), 3.62 (1H, dd, *J* 8.2, 3.9, **keto C–H**), 3.52 – 3.46 (1.34H, m, **keto/enol C–H**), 3.33 (1H, dd, *J* 17.2, 8.2, **keto C–H**), 2.23 (1.31H, s, **enol C–H**), 2.14 (9H, s, **keto C–H**), 1.76 – 1.56 (7.70H, m, **keto/enol C–H**).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C: Keto: 200.2, 168.1, 153.8, 135.3, 127.8, 126.6, 125.2, 124.7, 82.3, 54.7, 41.3, 36.3, 36.2, 31.0, 30.9, 30.8, 30.5.
Enol: 143.2, 137.4, 135.6, 129.1, 126.8, 126.4, 124.7, 120.6, 104.2, 81.3, 45.5, 41.9, 41.5, 41.0, 36.0, 33.0, 31.0, 29.8.

HRMS: (ESI^+) $C_{20}H_{22}O_3$ $[M+H]^+$ found 311.1641, requires 311.1642 (–0.1 ppm)

Methyl 1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (1q)



To a flame-dried 3-neck round–bottom flask equipped with a reflux condenser, under a flow of N_2, NaH (60% in mineral oil, 2.92 equiv.) was added to anhydrous MeOH (0.1 mL, 171 M). To this solution was added, dimethyl carbonate (17 mL, 205 mmol, 12.0 equiv.) and a catalytic amount of *t*-BuOK (192 mg, 1.71 mmol, 0.1 equiv.) sequentially at RT. The mixture was stirred for 5 min and then 3,4-dihydronaphthalen-1(2*H*)-one (2.3 mL, 17.1 mmol, 1.0 equiv.) was added dropwise. The reaction was stirred for 3 hours at reflux. The resulting mixture was put

in an ice bath and 3 M HCl (40 mL) was added. The mixture was then extracted with EtOAc (3 × 30 mL), washed with water (10 mL) and brine (15 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. After purification by column chromatography (hexane : EtOAc, 100 : 0 – 90 : 10, gradient run 5% increase per 150 mL), to give the title compound (2.67 g, 76%) as a pink powder. Data was in accordance with the literature.[19]

Mp: 60 – 63 °C {Lit.[19] (83 – 86 °C)}.

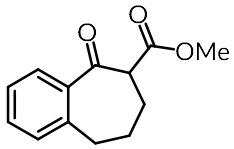
ν_{max} (film): 3024, 2951, 2846, 1742 (C=O), 1684 (C=O), 1645, 1439, 1265, 1213 (C–O), 1084, 745, 727.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H: keto : enol (2 : 1). 12.41 (0.49H, s, **enol OH**), 8.05 (1H, dd, *J* 7.9, 1.5, **keto Ar–H**), 7.80 (0.51H, dd, *J* 7.6, 1.6, **enol Ar–H**), 7.50 (1H, app. td, *J* 7.5, 1.5, **keto Ar–H**), 7.36 – 7.23 (unable to resolve due to $CDCl_3$, m, **keto/enol Ar–H**), 7.17 (0.54H, app. dd, *J* 7.2, 1.0, **keto/enol Ar–H**), 3.82 (1H, s, **enol OMe**), 3.78 (3H, s, **keto OMe**), 3.63 (1H, dd, *J* 10.4, 4.7 **keto C–H**), 3.10 – 2.95 (2H, m, **keto/enol C–H**), 2.81 (1H, app. dd, *J* 8.8, 6.7, **keto C–H**), 2.59 – 2.46 (2H, m, **keto/enol C–H**), 2.36 (1H, m, **keto C–H**).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C: Keto: 193.3, 170.8, 143.8, 134.1, 131.8, 128.9, 127.5, 126.7, 54.6, 51.8, 27.9, 26.5.

Enol: 173.2, 165.2, 139.5, 130.7, 130.1, 127.9, 127.0, 124.5, 97.0, 52.5, 27.7, 20.6.

Methyl 5-oxo-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-6-carboxylate (1r)



A solution of 5-phenylpentanoic acid (500 mg, 2.81 mmol, 1.00 equiv.) in triflic acid (2.8 mL, 31.7 mmol, 11.3 equiv.) was stirred at 5 °C to RT over 2 hrs. Ice was slowly added, and the mixture was extracted with Et_2O (3 × 25 mL), the organic layer was washed with sat. aq. $NaHCO_3$ (25 mL), water (25 mL) and brine (25 mL). Dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The intermediate (165 mg, 37%) was taken directly to the next step

without purification. Following General Procedure A, NaH (60% in mineral oil, 87 mg, 2.16 mmol) in anhydrous THF (4 mL), dimethyl carbonate (0.9 mL, 10.3 mmol), *t*-BuOK (12 mg, 0.10 mmol), 6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-one (165 mg, 1.03 mmol) in anhydrous THF (2.3 mL) for 16 hours. After purification by column chromatography (*n*-hexane : Et_2O, 100 : 0 – 95 : 0, gradient run 5% increase per 75 mL), to give the title compound (123 mg, 44%) as a yellow wax.

ν_{max} (film): 3021 (C–OH), 2859, 2361, 1684 (C=O), 1640, 1614, 1439, 1271, 1252, 1204 (C–O), 1094, 999, 750.

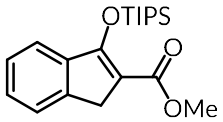
^{1}H NMR (500 MHz, $CDCl_3$) δ_H: keto : enol (1 : 42.9). 12.62 (1H, s, **enol OH**), 7.63 (1H, dd, *J* 7.2, 1.9 **Ar–H enol**), 7.38 – 7.30 (2H, m, **keto/enol Ar–H**), 7.22 (1H, dd, *J* 7.1, 1.9, **keto/enol Ar–H**), 3.83 (3H, s, **enol OMe**), 3.76 (0.07H, s, **keto OMe**), 2.95 (0.05H, app. q, *J* 4.5, **keto C–H**), 2.64 (2H, t, *J* 6.8, **enol C–H**), 2.17 – 2.05 (4H, m, **keto/enol C–H**).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C: Keto: 170.9, 141.4, 138.1, 132.6, 130.0, 129.3, 126.9, 56.6, 52.4, 33.0, 29.8, 25.4, 24.4.

Enol: 173.5, 170.6, 141.2, 135.8, 130.2, 129.1, 127.3, 126.5, 100.3, 51.9, 33.6, 31.9, 21.9.

HRMS: (ESI^+) $C_{13}H_{14}O_3$ $[M+H]^+$ found 219.1016, requires 219.1016 (+0.3 ppm).

Methyl 3-((triisopropylsilyl)oxy)-1*H*-indene-2-carboxylate (TIPS *enol* 1a)



To a solution of methyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (250 mg, 1.31 mmol, 1.00 equiv.) in anhydrous CH_2Cl_2 (10 mL) was added Et_3N (0.33 mL, 2.37 mmol, 1.8 equiv) at RT under argon. Subsequently, TIPSOTf (0.42 mL, 1.58 mmol, 1.2 equiv) was slowly added at 0 °C, and the resulting solution was stirred at RT for 1 hour. A solution of $NaHCO_3$ (5%, 15 mL) was added, and the mixture was extracted with CH_2Cl_2 (2 × 15 mL). The organic phases were combined, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. After

purification by column chromatography (*n*-hexane : Et_2O : Et_3N, 99 : 0 : 1 – 94 : 4 : 1 , gradient run 1% increase per 100 mL), to give the title compound (198 mg, 42%) as a white semi-solid.

Neutralised silica used in purification; neutralisation achieved with 1% Et_3N when packing the column.

ν_{max} (film): 2941, 2864, 1744 (C=O), 1462, 1240, 1227, 1152, 924, 883, 754.

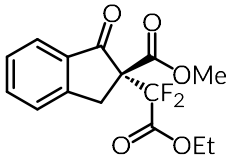
^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 7.54 – 7.50 (1H, m), 7.46 – 7.42 (1H, m), 7.39 – 7.32 (2H, m), 3.79 (3H, s), 3.61 (2H, s), 1.42 (3H, q, *J* 7.5), 1.15 (18H, d, *J* 7.6).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 165.5, 161.5, 142.6, 141.2, 128.4, 126.7, 124.5, 120.7, 110.8, 50.9, 35.0, 18.1, 14.3.

HRMS: (ESI^+) $C_{20}H_{30}NaO_4Si$ $[M+Na]^+$ found 385.1808, requires 385.1806 (+0.8 ppm).

6.3 Products

Methyl (*R*)-2-(2-ethoxy-1,1-difluoro-2-oxoethyl)-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (*R*)-3a)



Following General Procedure G, methyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (**1a**) (19 mg, 0.10 mmol), PTC (**C18**) (12 mg, 0.02 mmol), *t*-BuOAc (0.50 mL), ethyl difluoroiodoacetate (38 μL, 0.3 mmol) and Cs_2CO_3 (65 mg, 0.20 mmol) for 16 hours. After purification by column chromatography (PhMe), to give the title compound (31 mg, 99%) as a colourless oil.

Specific Rotation $[\alpha]_D^{20}$ −7.7 (*c* 2.06, $CHCl_3$).

Chiral HPLC: DAICEL CHIRALPAK AD-H (*n*-hexane : IPA, 95 : 5, flow rate = 1 mL min^{-1}, λ = 254 nm, 30 °C) t_{minor}: 12.1 min, t_{major}: 13.2 min, 26 : 74 er

ν_{max} (film): 2959, 1748 (C=O), 1722 (C=O), 1607, 1275, 1215, 1130, 1038, 756, 419.

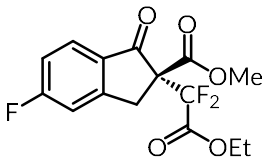
^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 7.82 (1H, app. dt, *J* 7.7, 1.0), 7.66 (1H, app. td, *J* 7.5, 1.2), 7.50 (1H, app. dt, *J* 7.7, 0.9), 7.43 (1H, app. ddt, *J* 8.0, 7.2, 0.8), 4.35 (2H, q, *J* 7.2), 3.83 – 3.69 (5H, m, unable to resolve quartet and singlet), 1.33 (3H, t, *J* 7.1).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 194.8, 167.5 (dd, *J* 6.8, 2.5), 162.5 (t, *J* 31.8), 152.1, 136.1, 135.2, 128.4, 126.3, 125.3, 113.9 (dd, *J* 265.0, 255.6), 63.9 – 63.4 (m), 53.5, 35.03 (t, *J* 3.5), 13.9.

^{19}F{^{1}H} NMR (471 MHz, $CDCl_3$) δ_F: −108.5 (1F, d, *J* 277.8), −110.2 (1F, d, *J* 278.1).

HRMS: (ESI^+): $C_{15}H_{14}F_2O_5$ $[M+Na]^+$ found 335.0692, requires 335.0707 (−4.5 ppm).

Methyl (*R*)-2-(2-ethoxy-1,1-difluoro-2-oxoethyl)-5-fluoro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (*R*)-3b



Following General Procedure G, methyl 5-fluoro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (**1b**) (21 mg, 0.10 mmol), PTC (**C18**) (12 mg, 0.02 mmol), *t*-BuOAc (0.50 mL), ethyl difluoroiodoacetate (38 μL, 0.3 mmol) and Cs_2CO_3 (65 mg, 0.20 mmol) for 16 hours. After purification by column chromatography (PhMe), to give the title compound (30.4 mg, 92%) as a colourless oil.

Specific Rotation: $[\alpha]_D^{20}$ −13.8 (*c* 2.03, $CHCl_3$).

Chiral HPLC: DAICEL CHIRALPAK AD-H (*n*-hexane : IPA, 98 : 2, flow rate = 0.5 mL min^{-1}, λ = 220 nm, 30 °C) t_{minor}: 24.9 min, t_{major}: 26.7 min, 28 : 72 er

ν_{max} (film): 2926, 2853, 1749 (C=O), 1722 (C=O), 1616, 1595, 1260, 1132, 1066, 752, 433.

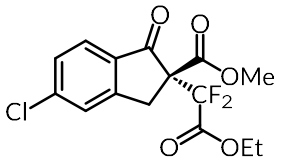
^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 7.83 (1H, dd, *J* 8.5, 5.2), 7.18 – 7.11 (2H, m), 4.36 (2H, q, *J* 7.1), 3.81 – 3.69 (5H, m), 1.35 (3H, t, *J* 7.2).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 192.9, 167.9 (d, *J* 259.0), 167.3 – 167.2 (m), 162.5 (t, *J* 31.6), 155.1 (d, *J* 10.5), 127.8 (d, *J* 10.8), 116.9 (d, *J* 24.0), 113.8 (dd, *J* 265.9, 255.4), 113.2 (d, *J* 23.0), 63.9 (dd, *J* 23.8, 20.8), 63.7, 53.6, 34.9, 34.9, 13.9.

^{19}F{^{1}H} NMR (471 MHz, $CDCl_3$) δ_F: −99.9 – −100.0 (1F, m), −108.6 (1F, d, *J* 278.9), −110.4 (1F, d, *J* 278.6).

HRMS: (ESI^+) $C_{15}H_{13}F_3O_5$ $[M+Na]^+$ found 353.0596, requires 353.0613 (−4.8 ppm).

Methyl (*R*)-5-chloro-2-(2-ethoxy-1,1-difluoro-2-oxoethyl)-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (*R*)-3c



Following General Procedure G, methyl 5-chloro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (**1c**) (23 mg, 0.10 mmol), PTC (**C18**) (12 mg, 0.02 mmol), *t*-BuOAc (0.50 mL), ethyl difluoroiodoacetate (38 μL, 0.3 mmol) and Cs_2CO_3 (65 mg, 0.20 mmol) for 16 hours. After purification by column chromatography (PhMe), to give the title compound (35 mg, 84%) as a yellow oil.

Specific Rotation: $[\alpha]_D^{20}$ −24.6 (*c* 2.03, $CHCl_3$).

Chiral HPLC: DAICEL CHIRALPAK AD-H (*n*-hexane : IPA, 95 : 5, flow rate = 1 mL min^{-1}, λ = 254 nm, 30 °C) t_{minor}: 12.8 min, t_{major}: 15.3 min, 26 : 74 er

ν_{max} (film): 2959, 2926, 1749 (C=O), 1724 (C=O), 1599, 1584, 1263, 1130, 1067, 899, 750, 424.

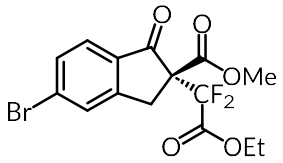
^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 7.52 – 7.49 (1H, m), 7.43 – 7.40 (1H, m), 4.39 – 4.33 (2H, m), 3.81 – 3.67 (5H, m, unable to resolve singlet and quartet), 1.35 (3H, t, *J* 7.2).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 193.4, 167.1 (d, *J* 6.3), 162.4 (t, *J* 31.4), 153.5, 142.8, 133.6, 129.3, 126.6, 126.4, 113.8 (dd, *J* 265.4, 255.3), 64.1 – 63.7 (m), 53.7, 34.8 (t, *J* 3.6), 13.9.

^{19}F{^{1}H} NMR (471 MHz, $CDCl_3$) δ_F: −108.5 (1F, d, *J* 279.2), −110.3 (1F, d, *J* 279.1).

HRMS: (ESI$^+$) $C_{15}H_{13}{}^{35}ClF_2O_5$ $[M+H]^+$ found 347.0491, requires 347.0492 (+0.4 ppm).

Methyl (*R*)-5-bromo-2-(2-ethoxy-1,1-difluoro-2-oxoethyl)-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (*R*)-3d



Following General Procedure G, methyl 5-bromo-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (**1d**) (27 mg, 0.10 mmol), PTC (**C18**) (12 mg, 0.02 mmol), *t*-BuOAc (0.50 mL), ethyl difluoroiodoacetate (38 μL, 0.3 mmol) and Cs_2CO_3 (65 mg, 0.20 mmol) for 16 hours. After purification by column chromatography (PhMe), to give the title compound (24 mg, 60%) as a yellow solid.

Mp: 56 – 57 °C.

Specific Rotation: $[\alpha]_D^{20}$ −27.7 (*c* 1.57, $CHCl_3$).

Chiral HPLC: DAICEL CHIRALCEL OD-H (*n*-hexane : IPA, 95 : 5, flow rate = 1 mL min^{-1}, λ = 254 nm, 30 °C) t_{minor}: 10.4 min, t_{major}: 11.7 min, 35 : 65 er

ν_{max} (film): 2959, 2851, 1749 (C=O), 1724 (C=O), 1597, 1581, 1317, 1265, 1132, 1057, 1036, 419.

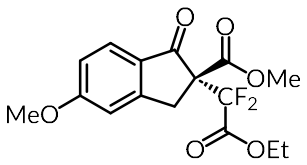
^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 7.70 – 7.66 (2H, m), 7.59 – 7.56 (1H, m), 4.36 (2H, qd, *J* 7.2, 0.9), 3.81 – 3.68 (5H, m, unable to resolve singlet and quartet), 1.35 (3H, t, *J* 7.1).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 193.6, 167.1 (d, J 6.6), 162.4 (t, J 31.6), 153.6, 134.0, 132.1, 131.7, 129.7, 126.4, 113.8 (dd, J 266.0, 255.6), 63.9 – 63.5 (m), 53.6, 34.7 (t, J 3.6), 13.9.

^{19}F{^{1}H} NMR (471 MHz, $CDCl_3$) δ_F: −108.4 (1F, d, *J* 279.1), −110.3 (1F, d, *J* 279.2).

HRMS: (ESI^+) $C_{15}H_{13}{}^{79}BrF_2O_5$ $[M+H]^+$ found 390.9975, requires 390.9987 (+3.1 ppm).

Methyl (*R*)-2-(2-ethoxy-1,1-difluoro-2-oxoethyl)-5-methoxy-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (*R*)-3e



Following General Procedure G, methyl 5-methoxy-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (**1e**) (22 mg, 0.10 mmol), PTC (**C18**) (12 mg, 0.02 mmol), *t*-BuOAc (0.50 mL), ethyl difluoroiodoacetate (38 μL, 0.3 mmol) and Cs_2CO_3 (65 mg, 0.20 mmol) for 16 hours. After purification by column chromatography (PhMe : CH_2Cl_2 100 : 0 – 80 : 20, gradient run 10% increase per 100 mL), to give the title compound (17 mg, 49%) as a yellow oil.

Specific Rotation: $[\alpha]_D^{20}$ −18.4 (*c* 1.13, $CHCl_3$).

Chiral HPLC: DAICEL CHIRALPAK AD-H (*n*-hexane : IPA, 90 : 10, flow rate = 1 mL min^{-1}, λ = 254 nm, 30 °C) t_{minor}: 15.7 min, t_{major}: 17.6 min, 30 : 70 er

ν_{max} (film): 2924, 2851, 1746 (C=O), 1713 (C=O), 1599, 1310, 1265, 1126, 754, 419, 409.

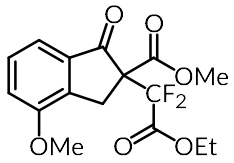
^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 7.74 (1H, d, *J* 8.6), 6.97 – 6.93 (1H, m), 6.91 – 6.90 (1H, m), 4.35 (2H, q, *J* 7.1), 3.90 (3H, s), 3.78 – 3.63 (5H, m, unable to resolve singlet and quartet), 1.34 (3H, t, *J* 7.2).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 192.7, 167.8 (d, *J* 6.3), 166.4, 162.7 (t, *J* 31.8), 155.3, 128.3, 127.1, 116.6, 114.0 (dd, *J* 265.3, 255.0), 109.4, 64.0 (dd, *J* 23.7, 20.8), 63.5, 56.0, 53.5, 35.0 (t, *J* 3.6), 13.9.

^{19}F NMR (471 MHz, $CDCl_3$) δ_F: −108.8 (d, *J* 277.3), −110.6 (d, *J* 277.2).

HRMS: (ESI^+) $C_{16}H_{16}F_2O_6$ $[M+H]^+$ found 343.0999, requires 343.0988 (+3.3 ppm).

Methyl 2-(2-ethoxy-1,1-difluoro-2-oxoethyl)-4-methoxy-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate 3f



Following General Procedure G, methyl 4-methoxy-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (**1f**) (22 mg, 0.10 mmol), PTC (**C18**) (12 mg, 0.02 mmol), *t*-BuOAc (0.50 mL), ethyl difluoroiodoacetate (38 μL, 0.3 mmol) and Cs_2CO_3 (65 mg, 0.20 mmol) for 16 hours. After purification by column chromatography (PhMe : CH_2Cl_2 100 : 0 – 90 : 10, gradient run 10% increase per 100 mL), to give the title compound (26 mg, 75%) as a yellow oil.

Chiral HPLC: DAICEL CHIRALCEL OD-H (*n*-hexane : IPA, 95 : 5, flow rate = 1 mL min^{-1}, λ = 254 nm, 30 °C) t_{major}: 9.2 min, t_{minor}: 9.9 min, 55 : 45 er

ν_{max} (film): 3023, 2845, 1749 (C=O), 1726 (C=O), 1605, 1491, 1265, 754, 667, 419.

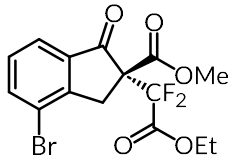
^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 7.41 – 7.39 (1H, m), 7.09 (1H, app. p, *J* 4.2), 4.35 (1H, q, *J* 7.1), 3.92 (3H, s), 3.75 (3H, s), 3.71 – 3.58 (1H, m), 1.33 (2H, t, *J* 7.1).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 195.0, 167.5 (dd, *J* 6.5, 2.6), 162.4 (t, *J* 31.8), 156.7, 141.1, 136.6, 130.0, 116.3 (d, *J* 63.1), 113.9 (dd, *J* 264.7, 255.6), 63.7 – 63.1 (m), 55.7, 53.4, 32.1 (t, *J* 3.6), 13.9.

^{19}F{^{1}H} NMR (471 MHz, $CDCl_3$) δ_F: −108.6 (1F, d, *J* 278.4), −110.3 (1F, d, *J* 278.4).

HRMS: (ESI$^+$) $C_{16}H_{16}F_2O_6$ $[M+H]^+$ found 343.0999, requires 343.0988 (+3.3 ppm).

Methyl (*R*)-4-bromo-2-(2-ethoxy-1,1-difluoro-2-oxoethyl)-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (*R*)-3g



Following General Procedure G, methyl 4-bromo-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (**1g**) (27 mg, 0.10 mmol), PTC (**C18**) (12 mg, 0.02 mmol), *t*-BuOAc (0.50 mL), ethyl difluoroiodoacetate (38 μL, 0.3 mmol) and Cs_2CO_3 (65 mg, 0.20 mmol) for 16 hours. After purification by column chromatography (PhMe), to give the title compound (29 mg, 74%) as a yellow oil.

Specific Rotation: $[\alpha]_D^{20}$ −22.9 (*c* 1.93, $CHCl_3$).

Chiral HPLC: DAICEL CHIRALPAK -H (*n*-hexane : IPA, 95 : 5, flow rate = 1 mL min^{-1}, λ = 254 nm, 30 °C) t_{minor}: 12.8 min, t_{major}: 14.8 min, 29 : 71 er

ν_{max} (film): 2920, 2851, 1751 (C=O), 1730 (C=O), 1599, 1458, 1319, 1262, 1171, 1134, 808.

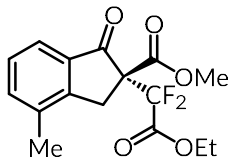
^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 7.83 (1H, dd, *J* 7.8, 1.0), 7.78 (1H, dd, *J* 7.6, 1.0), 7.38 – 7.32 (1H, m), 4.37 (2H, q, *J* 7.2), 3.77 (3H, s), 3.74 – 3.62 (3H, m), 1.35 (3H, t, *J* 7.2).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 194.1, 167.0 (app. s), 162.3 (t *J* 31.8), 151.8, 138.8, 137.0, 130.1, 124.1, 121.7, 113.7 (app. s), 53.7, 64.0 – 63.6 (m), 36.13 (t, *J* 3.4), 13.9.

^{19}F{^{1}H} NMR (471 MHz, $CDCl_3$) δ_F: −108.4 (1F, dd, *J* 280.2, 148.3), −110.1 (1F, dd, *J* 279.9, 115.6).

HRMS: (ESI^+) $C_{15}H_{13}{}^{79}BrF_2O_5$ $[M+H]^+$ found 390.9981, requires 390.9987 (+1.6 ppm).

Methyl (*R*)-2-(2-ethoxy-1,1-difluoro-2-oxoethyl)-4-methyl-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (*R*)-3h



Following General Procedure G, methyl 4-methyl-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (**1h**) (20 mg, 0.10 mmol), PTC (**C18**) (12 mg, 0.02 mmol), *t*-BuOAc (0.50 mL), ethyl difluoroiodoacetate (38 μL, 0.3 mmol) and Cs_2CO_3 (65 mg, 0.20 mmol) for 16 hours. After purification by column chromatography (PhMe) to give the title compound (31 mg, 94%) as a colourless oil.

Specific Rotation: $[\alpha]_D^{20}$ −15.0 (*c* 2.05, $CHCl_3$).

Chiral HPLC: DAICEL CHIRALPAK AD-H (*n*-hexane : IPA, 95 : 5, flow rate = 1 mL min^{-1}, λ = 254 nm, 30 °C) t_{minor}: 8.9 min, t_{major}: 9.9 min, 29 : 71 er

ν_{max} (film): 1748 (C=O), 1724 (C=O), 1593, 1437, 1317, 1271, 1171, 1128, 1171, 789, 754, 421.

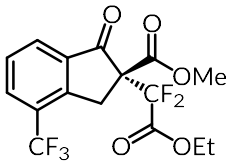
^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 7.65 (1H, d, *J* 7.6), 7.46 (1H, d, *J* 7.3), 7.35 (1H, t, *J* 7.5), 4.36 (2H, q, *J* 7.1), 3.76 (3H, s), 3.63 (2H, q, *J* 17.9), 2.38 (3H, s), 1.34 (3H, t, *J* 7.2).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 195.1, 167.6 (app. s), 162.6 (t, *J* 31.8), 151.0, 136.6, 135.8, 135.0, 128.6, 122.7, 114.0 (dd, *J* 265.2, 255.6), 64.0 – 63.0 (m), 53.5, 34.0 (t, *J* 3.6), 17.9, 13.9.

^{19}F{^{1}H} NMR (471 MHz, $CDCl_3$) δ_F: −108.5 (1F, d, *J* 277.5), −110.3 (1F, d, *J* 277.6).

HRMS: (ESI^+) $C_{16}H_{16}F_2O_5$ $[M+H]^+$ found 327.1040, requires 327.1039 (+0.3 ppm).

Methyl (*R*)-2-(2-ethoxy-1,1-difluoro-2-oxoethyl)-1-oxo-4-(trifluoromethyl)-2,3-dihydro-1*H*-indene-2-carboxylate (*R*)-3i



Following General Procedure G, methyl 4-(trifluoromethyl)-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (**1i**) (26 mg, 0.10 mmol), PTC (**C18**) (11.7 mg, 0.02 mmol), *t*-BuOAc (0.50 mL, ethyl difluoroiodoacetate (38 μL, 0.3 mmol) and Cs_2CO_3 (65 mg, 0.20 mmol) for 16 hours. After purification by column chromatography (PhMe), to give the title compound (20 mg, 53%) as a colourless oil.

Specific Rotation: $[\alpha]_D^{20}$ −10.1 (*c* 1.33, $CHCl_3$).

Chiral HPLC: DAICEL CHIRALPAK AD-H (*n*-hexane : IPA, 99.5 : 0.5, flow rate = 0.5 mL min^{-1}, λ = 254 nm, 30 °C) t_{minor}: 31.4 min, t_{major}: 33.1 min, 34 : 66 er

ν_{max} (film): 1753 (C=O), 1732 (C=O), 1597, 1434, 1329, 1179, 1126, 754, 417.

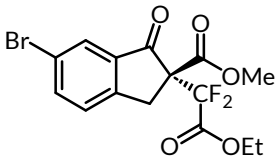
^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 8.01 (1H, d, *J* 7.7), 7.93 (1H, d, *J* 7.6), 7.59 (1H, t, *J* 7.6), 4.37 (2H, q, *J* 7.1), 3.98 – 3.85 (2H, app. m), 3.78 (3H, s), 1.35 (3H, t, *J* 7.1).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 193.6, 166.8 (d, *J* 7.2), 162.2 (t, *J* 31.6), 149.2, 136.7, 132.7 (q, *J* 4.7), 128.9, 128.7, 128.6, 128.4, 128.1, 123.6 (q, *J* 273.5), 113.7 (dd, *J* 265.8, 256.3), 63.8, 63.8 – 63.3 (m), 53.7, 34.0, 13.9.

^{19}F{^{1}H} NMR (471 MHz, $CDCl_3$) δ_F: −62.2 (CF_3), −108.2 (1F, d, *J* 280.3), −109.9 (1F, d, *J* 280.0).

HRMS: (ESI^+) $C_{16}H_{13}F_5O_5$ $[M+H]^+$ found 381.0758, requires 381.0756 (+0.6 ppm).

Methyl (*R*)-6-bromo-2-(2-ethoxy-1,1-difluoro-2-oxoethyl)-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (*R*)-3j



Following General Procedure G, methyl 6-bromo-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (**1j**) (27 mg, 0.10 mmol), PTC (**C18**) (12 mg, 0.02 mmol), *t*-BuOAc (0.50 mL), ethyl difluoroiodoacetate (38 μL, 0.3 mmol) and Cs_2CO_3 (65 mg, 0.20 mmol) for 16 hours. After purification by column chromatography (PhMe) to give the title compound (27 mg, 69%) as a waxy yellow solid.

Specific Rotation: $[\alpha]_D^{20}$ −8.2 (*c* 1.80, $CHCl_3$).

Chiral HPLC: DAICEL CHIRALCEL OD-H (*n*-hexane : IPA, 95 : 5, flow rate = 1 mL min^{-1}, λ = 254 nm, 30 °C) t_{minor}: 9.5 min, t_{major}: 10.3 min, 32 : 68 er

ν_{max} (film): 2956, 2359, 1749 (C=O), 1728 (C=O), 1599, 1435, 1317, 1282, 1254, 1186, 1132, 1067, 692, 496.

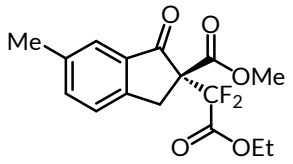
^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 7.95 – 7.93 (1H, m), 7.76 (1H, dd, *J* 8.1, 1.9), 7.39 (1H, dd, *J* 8.2, 0.7), 4.39 – 4.32 (2H, m), 3.78 – 3.64 (5H, m, unable to resolve singlet and quartet), 1.35 (3H, t, *J* 7.2).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 193.4, 167.1, 162.4 (t, *J* 31.5), 150.6, 138.8, 137.0, 128.1, 127.9, 122.6, 113.8 (dd, *J* 266.3, 255.9), 64.3 – 63.9 (app. m), 63.7, 53.7, 34.8, 13.9.

^{19}F{^{1}H} NMR (471 MHz, $CDCl_3$) δ_F: −108.3 (1F, d, *J* 279.4), −110.1 (1F, d, *J* 279.3).

HRMS: (ESI$^+$) $C_{15}H_{13}{}^{79}BrF_2O_5$ $[M+H]^+$ found 390.9973, requires 390.9987 (+3.6 ppm)

Methyl (*R*)-2-(2-ethoxy-1,1-difluoro-2-oxoethyl)-6-methyl-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (*R*)-3k



Following General Procedure G, methyl 6-methyl-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (**1k**) (20 mg, 0.10 mmol), PTC (**C18**) (12 mg, 0.02 mmol), *t*-BuOAc (0.50 mL), ethyl difluoroiodoacetate (38 μL, 0.3 mmol) and Cs_2CO_3 (65 mg, 0.20 mmol) for 16 hours. After purification by column chromatography (PhMe : CH_2Cl_2 100 : 0 – 90 : 10, gradient run 10% increase per 100 mL), to give the title compound (17 mg, 53%) as a colourless oil.

Specific Rotation: $[\alpha]_D^{20}$ −16.5 (*c* 1.16, $CHCl_3$).

Chiral HPLC: DAICEL CHIRALPAK AD-H (*n*-hexane : IPA, 95 : 5, flow rate = 0.5 mL min^{-1}, λ = 280 nm, 30 °C) t_{minor}: 24.2 min, t_{major}: 26.0 min, 33 : 67 er

ν_{max} (film): 3030, 2957, 2928, 1748 (C=O), 1721 (C=O), 1281, 1219, 1155, 1128, 752, 407.

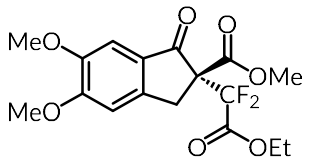
^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 7.61 (1H, s), 7.49 – 7.46 (1H, m), 7.40 – 7.37 (1H, m), 4.35 (2H, q, *J* 7.2), 3.77 – 3.63 (5H, m, unable to resolve singlet and quartet), 2.42 (3H, s), 1.33 (3H, t, *J* 7.1)

^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 194.8, 167.6, 162.6 (t, *J* 31.8), 149.5, 138.5, 137.4, 135.4, 126.0, 125.2, 114.0 (dd, *J* 265.0, 255.4), 64.3 – 63.8 (app. m), 63.6, 53.5, 34.7, 21.2, 13.9.

^{19}F{^{1}H} NMR (471 MHz, $CDCl_3$) δ_F: −108.6 (1F, d, *J* 278.0), −110.3 (1F, d, *J* 277.8).

HRMS: (ESI$^+$) $C_{16}H_{16}F_2O_5$ $[M+H]^+$ found 327.1046, requires 327.1039 (+2.3 ppm).

Methyl (*R*)-2-(2-ethoxy-1,1-difluoro-2-oxoethyl)-5,6-dimethoxy-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (*R*)-3l



Following General Procedure G, methyl 5,6-dimethoxy-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (**1l**) (25 mg, 0.10 mmol), PTC (**C18**) (12 mg, 0.02 mmol), *t*-BuOAc (0.50 mL), ethyl difluoroiodoacetate (38 μL, 0.3 mmol) and Cs_2CO_3 (65 mg, 0.20 mmol) for 16 hours. After purification by column chromatography (PhMe : CH_2Cl_2 100 : 0 – 50 : 50, gradient run 10% increase per 50 mL), to give the title compound (33.0 mg, 89%) as a yellow solid.

Mp: 136 – 138 °C.

Specific Rotation: $[\alpha]_D^{20}$ −15.8 (*c* 2.2, $CHCl_3$).

Chiral HPLC: DAICEL CHIRALPAK AD-H (*n*-hexane : IPA, 95 : 5, flow rate = 1 mL min^{-1}, λ = 254 nm, 30 °C) t_{minor}: 39.3 min, t_{major}: 46.2 min, 32 : 68 er

ν_{max} (film): 3022, 2926, 2853, 1744 (C=O), 1707 (C=O), 1591, 1503, 1314, 1271, 1250, 1221, 1128, 1008, 752, 665.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 7.20 (1H, s), 6.89 (1H, s), 4.36 (2H, q, *J* 7.1), 3.99 (3H, s), 3.92 (3H, s), 3.76 (3H, s), 3.73 – 3.59 (2H, m), 1.35 (3H, t, *J* 7.2).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 193.1, 167.8 (d, *J* 4.5), 162.7 (t, *J* 31.8), 156.7, 150.2, 147.9, 128.0, 114.0 (dd, *J* 265.4, 255.0), 107.0, 105.3, 64.4 – 63.8 (m), 63.5, 56.6, 56.3, 53.4, 34.8, 34.7, 34.7, 13.9.

^{19}F{^{1}H} NMR (471 MHz, $CDCl_3$) δ_F: −108.9 (1F, d, *J* 276.7), −110.7 (1F, d, *J* 276.7).

HRMS: (ESI$^+$) $C_{17}H_{18}F_2O_7$ $[M+H]^+$ found 327.1046, requires 327.1039 (+2.3 ppm).

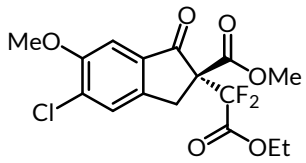
This product was also synthesised on a 0.5 mmol scale.

Following General Procedure H, methyl 5,6-dimethoxy-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (**1l**) (125 mg, 0.50 mmol), PTC (**C18**) (60 mg, 0.1 mmol), *t*-BuOAc (2.50 mL), ethyl difluoroiodoacetate (190 μL, 1.5 mmol) and Cs_2CO_3 (325 mg, 1.0 mmol) for 16 hours. After

purification by column chromatography (PhMe : CH_2Cl_2 100 : 0 – 50 : 50, gradient run 10% increase per 50 mL), to give the title compound (162 mg, 87%) as a yellow oil in 34 : 66 er.

Attempts to run this reaction on a 1 mmol scale in a 25 mL Schlenk tube being irradiated with two white LEDs (6200 K) were not successful with only trace amounts of product formed.

Methyl (*R*)-5-chloro-2-(2-ethoxy-1,1-difluoro-2-oxoethyl)-6-methoxy-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (*R*)-3m



Following General Procedure G, methyl 5-chloro-6-methoxy-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (**1m**) (26 mg, 0.10 mmol), PTC (**C18**) (12 mg, 0.02 mmol), *t*-BuOAc (0.50 mL), ethyl difluoroiodoacetate (38 μL, 0.3 mmol) and Cs_2CO_3 (65 mg, 0.20 mmol) for 16 hours. After purification by column chromatography (PhMe : CH_2Cl_2 100 : 0 – 85 : 15, gradient run 5% increase per 50 mL), to give the title compound (30 mg, 78%) as a yellow oil.

Specific Rotation: $[\alpha]_D^{20}$ −15.0 (*c* 1.97, $CHCl_3$).

Chiral HPLC: DAICEL CHIRALPAK AD-H (*n*-hexane : IPA, 90 : 10, flow rate = 1 mL min^{-1}, λ = 254 nm, 30 °C) t_{minor}: 12.5 min, t_{major}: 15.4 min, 33 : 67 er

ν_{max} (film): 3022, 2160, 1748 (C=O), 1721 (C=O), 1601, 1582, 1483, 1410, 1305, 1260, 1217, 1126, 1039, 748, 667.

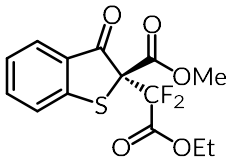
^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 7.53 (1H, s), 7.27 (1H, s), 4.36 (2H, q, *J* 7.2), 3.95 (3H, s), 3.76 (3H, s), 3.73 – 3.60 (2H, m), 1.35 (3H, t, *J* 7.1).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 193.8, 167.3 (d, *J* 8.7), 162.4 (t, *J* 31.7), 155.7, 145.0, 134.6, 132.5, 127.8, 113.8 (dd, *J* 265.7, 255.7), 64.2 (dd, *J* 23.7, 20.7), 63.7, 56.6, 53.6, 34.2 (t, *J* 3.6), 13.9.

^{19}F{^{1}H} NMR (471 MHz, $CDCl_3$) δ_F: −108.6 (1F, d, *J* 279.1), −110.3 (1F, d, *J* 278.9).

HRMS: (ESI$^+$) $C_{16}H_{15}{}^{35}ClF_2O_6$ $[M+H]^+$ found 377.0593, requires 377.0598 (+1.3 ppm).

Methyl (*S*)-2-(2-ethoxy-1,1-difluoro-2-oxoethyl)-3-oxo-2,3-dihydrobenzo[*b*]thiophene-2-carboxylate (*R*)-3n



Following General Procedure G, methyl 3-oxo-2,3-dihydrobenzo[*b*]thiophene-2-carboxylate (**1n**) (21 mg, 0.10 mmol), PTC (**C18**) (12 mg, 0.02 mmol), *t*-BuOAc (0.50 mL), ethyl difluoroiodoacetate (38 μL, 0.3 mmol) and Cs_2CO_3 (65 mg, 0.20 mmol) for 16 hours. After purification by column chromatography (PhMe) to give the title compound (21 mg, 63%) as a yellow oil.

Specific Rotation: $[\alpha]_D^{20}$ +12.2 (*c* 1.39, $CHCl_3$).

Chiral HPLC: DAICEL CHIRALPAK AS-H (*n*-hexane : IPA, 95 : 5, flow rate = 0.8 mL min^{-1}, λ = 254 nm, 30 °C) t_{minor}: 18.0 min, t_{major}: 19.5 min, 35 : 65 er

ν_{max} (film): 2957, 2926, 2855, 1749 (C=O), 1718 (C=O), 1587, 1451, 1281, 1248, 1221, 1120, 1015, 758, 415.

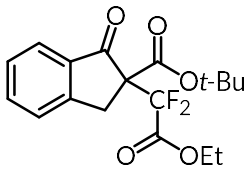
^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 7.84 (1H, dd, *J* 7.8, 1.3), 7.62 (1H, app. td, *J* 7.7, 1.3), 7.42 (1H, d, *J* 8.0), 7.31 (1H, app. t, *J* 7.5), 4.39 – 4.31 (2H, m), 3.80 (3H, s), 1.30 (3H, t, *J* 7.2).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 191.1, 165.2, 161.6 (t, *J* 31.6), 150.3, 136.7, 129.5, 128.1, 126.2, 124.0, 113.1 (dd, *J* 260.8, 260.1), 64.0, 54.1, 29.9, 13.8.

^{19}F{^{1}H} NMR (471 MHz, $CDCl_3$) δ_F: −105.0 (1F, d, *J* 278.9), −108.2 (1F d, *J* 278.9).

HRMS: (ESI^+) $C_{14}H_{12}F_2O_5S$ $[M+H]^+$ found 331.0446, requires 331.0446 (+0.1 ppm).

***tert*-Butyl 2-(2-ethoxy-1,1-difluoro-2-oxoethyl)-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (3o)**



Following General Procedure G, *tert*-butyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (**1o**) (23 mg, 0.10 mmol), PTC (**C18**) (12 mg, 0.02 mmol), *t*-BuOAc (0.50 mL), ethyl difluoroiodoacetate (38 μL, 0.3 mmol) and Cs_2CO_3 (65 mg, 0.20 mmol) for 16 hours. After purification by column chromatography (PhMe) to give the title compound (22 mg, 61%) as a colourless oil.

Chiral HPLC: DAICEL CHIRALPAK AD-H (*n*-hexane : IPA, 98 : 2, flow rate = 0.5 mL min^{-1}, λ = 254 nm, 30 °C) t_{minor}: 18.1 min, t_{major}: 19.7 min, 45 : 55 er

ν_{max} (film): 2984, 2936, 1738 (C=O), 1719 (C=O), 1607, 1466, 1371, 1271, 1215, 1150, 1022, 839, 752, 405.

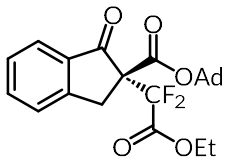
^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 7.80 (1H, d, *J* 7.7), 7.64 (1H, app. td, *J* 7.5, 1.2), 7.49 (1H, app. dt, *J* 7.8, 1.0), 7.44 – 7.40 (1H, m), 4.34 (2H, q, *J* 7.1), 3.81 – 3.65 (2H, m), 1.41 (9H, s), 1.34 (3H, t, *J* 7.1).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 195.2, 165.9 (d, *J* 7.2), 162.7 (t, *J* 32.1), 152.3, 135.8, 135.4, 128.2, 126.2, 125.1, 84.1, 114.0 (dd, *J* 265.1, 253.8), 64.6 (dd, *J* 23.3, 20.1), 63.4, 35.3, 27.8, 25.0, 24.6, 13.9.

^{19}F{^{1}H} NMR (471 MHz, $CDCl_3$) δ_F: −108.1 (1F, d, *J* 278.0), −109.9 (1F, d, *J* 278.0).

HRMS: (ESI$^+$) $C_{18}H_{20}F_2O_5$ $[M+H]^+$ found 377.1171, requires 377.1177 (−1.6 ppm).

Adamantan-1-yl (*R*)-2-(2-ethoxy-1,1-difluoro-2-oxoethyl)-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (*R*)-3p



Following General Procedure G, adamantan-1-yl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (**1p**) (31 mg, 0.10 mmol), PTC (**C18**) (12 mg, 0.02 mmol), *t*-BuOAc (0.50 mL), ethyl difluoroiodoacetate (38 μL, 0.3 mmol) and Cs_2CO_3 (65 mg, 0.20 mmol) for 16 hours. After purification by column chromatography (PhMe) to give the title compound (18 mg, 42%) as a yellow oil. The data was in accordance with the literature and the absolute stereochemistry was assigned by comparison of the specific rotation.[20]

Specific Rotation: $[\alpha]_D^{20}$ −9.6 (*c* 1.21, $CHCl_3$).

Chiral HPLC: DAICEL CHIRALPAK AD-H (*n*-hexane : IPA, 95 : 5, flow rate = 0.5 mL min^{-1}, λ = 280 nm, 30 °C) t_{minor}: 18.9 min, t_{major}: 22.5 min, 35 : 65 er

ν_{max} (film): 2914, 2855, 1776, 1738 (C=O), 1722 (C=O), 1607, 1462, 1317, 1263, 1215, 1134, 1051 1024, 839, 797, 766, 421.

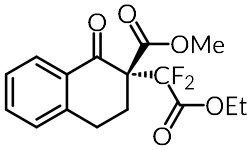
^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 7.80 (1H, d, *J* 7.7), 7.64 (1H, app. td, *J* 7.4, 1.2), 7.49 (1H, d, *J* 7.7), 7.41 (1H, app. t, *J* 7.5), 4.35 (2H, app. qd, *J* 7.1, 1.2), 3.78 (1H, d, *J* 17.8), 3.68 (1H, d, *J* 17.8), 2.13 (3H, s), 2.04 (6H, d, *J* 3.0), 1.61 (6H, d, *J* 3.1), 1.35 (3H, t, *J* 7.1).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 195.3, 165.6 (d, *J* 7.2), 162.8 (t, *J* 32.1), 152.3, 135.7, 135.4, 128.1, 126.2, 125.1, 114.0 (dd, *J* 265.0, 253.5), 84.1, 64.7 (dd, *J* 23.2, 20.1), 63.4, 41.0, 36.1, 35.5 (t, *J* 3.9), 31.0, 14.0.

^{19}F{^{1}H} NMR (471 MHz, $CDCl_3$) δ_F: −108.2 (1F, d, *J* 278.3), −110.1 (1F, d, *J* 277.9).

HRMS: (ESI^+) $C_{22}H_{26}F_2O_5$ $[M+H]^+$ found 433.1814, requires 433.1821 (+1.6 ppm).

Methyl (*R*)-2-(2-ethoxy-1,1-difluoro-2-oxoethyl)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (*R*)-3q



Following General Procedure G, methyl 1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (**1q**) (20 mg, 0.10 mmol), PTC (**C18**) (12 mg, 0.02 mmol), *t*-BuOAc (0.50 mL), ethyl difluoroiodoacetate (38 μL, 0.3 mmol) and Cs_2CO_3 (65 mg, 0.20 mmol) for 16 hours. After purification by column chromatography (PhMe) to give the title compound (19 mg, 57%) as a grey oil.

Specific Rotation: $[\alpha]_D^{20}$ +3.2 (*c* 1.24, $CHCl_3$).

Chiral HPLC: DAICEL CHIRALPAK AD-H (*n*-hexane : IPA, 95 : 5, flow rate = 1 mL min^{-1}, λ = 254 nm, 30 °C) t_{minor}: 14.8 min, t_{major}: 16.9 min, 28 : 72 er

ν_{max} (film): 3021, 1753 (C=O), 1690 (C=O), 1602, 1456, 1312, 1246, 1215, 1086, 806, 754, 667, 417.

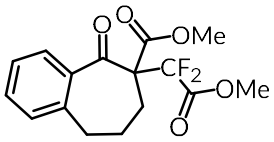
^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 8.08 (1H, dd, *J* 8.0, 1.5), 7.52 (1H, app. td, *J* 7.5, 1.4), 7.37 – 7.31 (1H, m), 7.26 – 7.23 (1H, m), 4.41 (2H, app. qd, *J* 7.2, 1.7), 3.75 (3H, s), 3.03 (1H, ddd, *J* 17.3, 4.7, 2.7), 2.92 (1H, ddd, *J* 17.3, 13.1, 4.3), 2.82 (1H, ddd, *J* 13.3, 4.3, 2.7), 2.61 (1H, td, *J* 13.2, 4.8), 1.39 (3H, t, *J* 7.2).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 199.7, 167.1 (d, *J* 8.2), 162.8 (t, *J* 31.5), 138.9, 137.9, 133.3, 130.3, 129.5, 127.2, 114.5 (app. t, *J* 262.0). 66.5 (app. d, *J* 23.7), 63.4, 53.2, 31.8, 24.9 (t, *J* 4.3), 22.0, 14.0.

^{19}F{^{1}H} NMR (471 MHz, $CDCl_3$) δ_F: −111.6 (1F, d, *J* 5.6).

HRMS: (ESI$^+$) $C_{22}H_{26}F_2O_5$ $[M+H]^+$ found 327.1050, requires 327.1039 (+3.5 ppm).

Methyl 6-(1,1-difluoro-2-methoxy-2-oxoethyl)-5-oxo-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-6-carboxylate (3r)



Following General Procedure G, methyl 5-oxo-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-6-carboxylate (**1r**) (22 mg, 0.10 mmol), PTC (**C18**) (12 mg, 0.02 mmol), *t*-BuOAc (0.50 mL), ethyl difluoroiodoacetate (38 μL, 0.3 mmol) and Cs_2CO_3 (65 mg, 0.20 mmol) for 16 hours. After purification by column chromatography (PhMe) to give the title compound (27 mg, 78%) as a colourless oil.

Chiral HPLC: DAICEL CHIRALPAK AD-H (*n*-hexane : IPA, 95 : 5, flow rate = 1 mL min^{-1}, λ = 254 nm, 30 °C) t_{major}: 9.5 min, t_{minor}: 11.1 min, 52 : 48 er

ν_{max} (film): 2926, 1776 (C=O), 1744 (C=O), 1680, 1597, 1312, 1258, 1240 1213, 909, 752, 731, 648.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 7.66 (1H, dd, *J* 7.7, 1.5), 7.46 (1H, app. td, *J* 7.5, 1.5), 7.32 (1H, app. td, *J* 7.6, 1.2), 7.15 (1H, d, *J* 7.5), 4.49 – 4.36 (2H, m), 3.81 (3H, s), 2.92 (1H, ddd, *J* 15.0, 11.1, 6.7), 2.79 (1H, ddd, *J* 15.0, 6.0, 4.0), 2.61 (1H, ddd, *J* 14.5, 5.5, 3.8), 2.18 (1H, ddd, *J* 14.5, 10.4, 6.6), 2.07 – 1.93 (2H, m), 1.41 (3H, t, *J* 7.2).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 199.7 (d, *J* 3.1), 167.1 (d, *J* 8.0), 162.8 (t, *J* 31.6), 138.9, 137.9, 133.3, 130.3, 129.5, 127.2, 114.5 (t, *J* 261.9), 66.6 (dd, *J* 23.7, 19.2), 63.4, 53.2, 31.7, 24.9 (t, *J* 4.2), 22.0, 14.0.

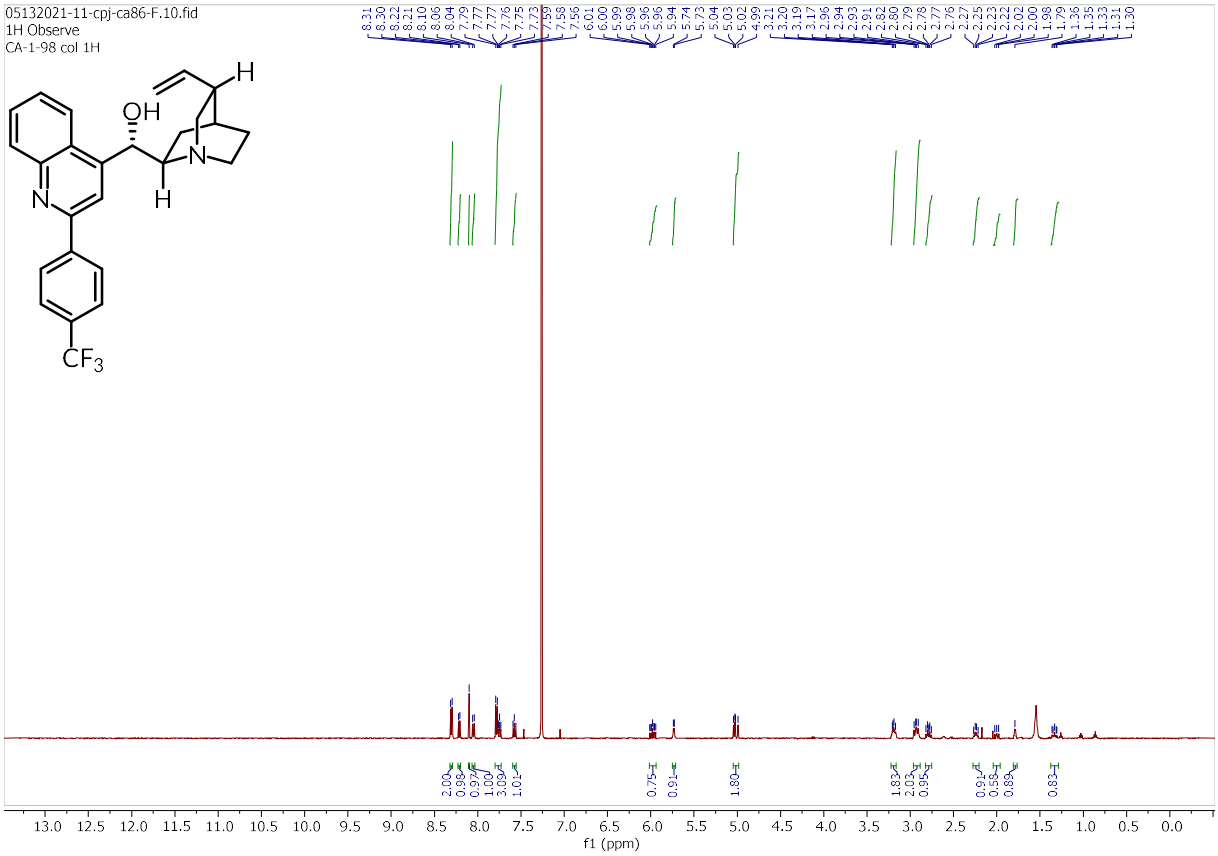
^{19}F{^{1}H} NMR (471 MHz, $CDCl_3$) δ_F: −107.1 (1F, d, *J* 268.2), −111.3 (1F, d, *J* 268.2).

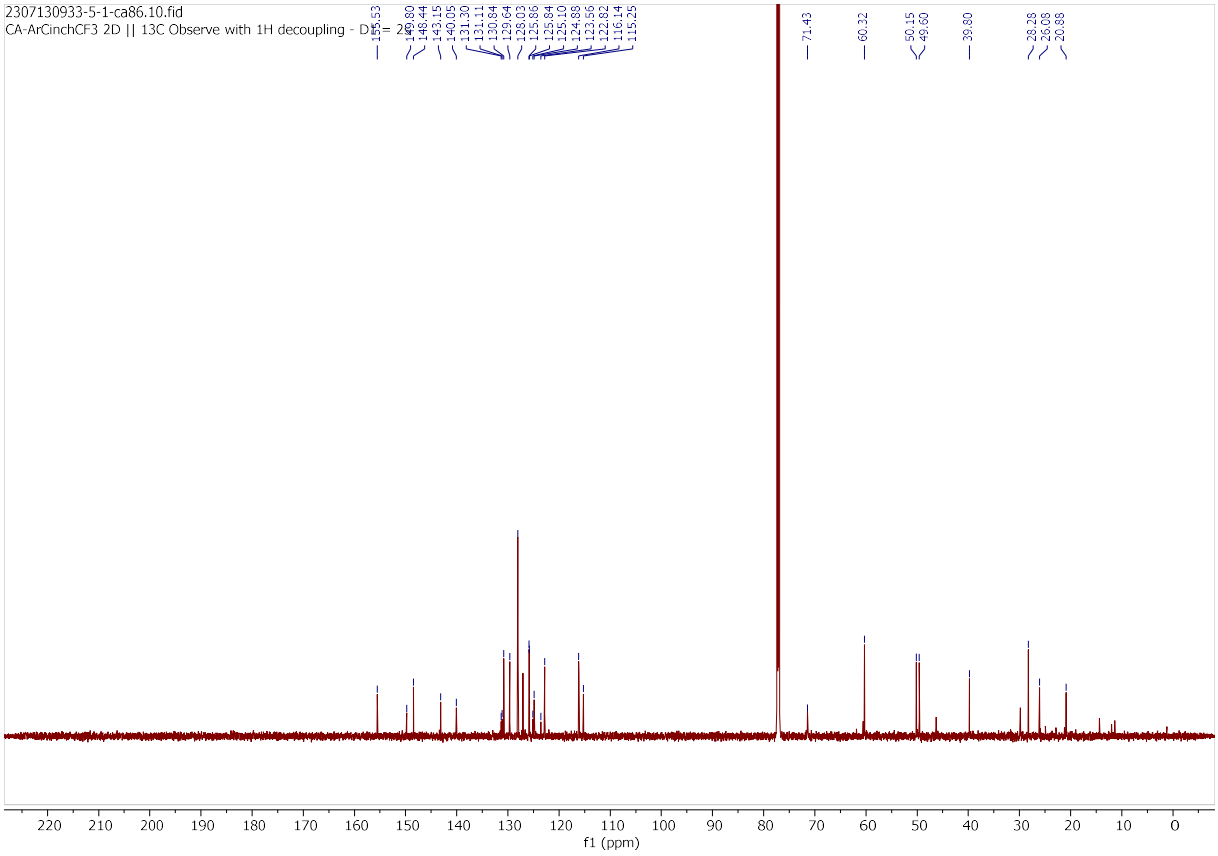
HRMS: (ESI^+) $C_{22}H_{26}F_2O_5$ $[M+H]^+$ found 341.1172, requires 341.1170 (+0.8 ppm)

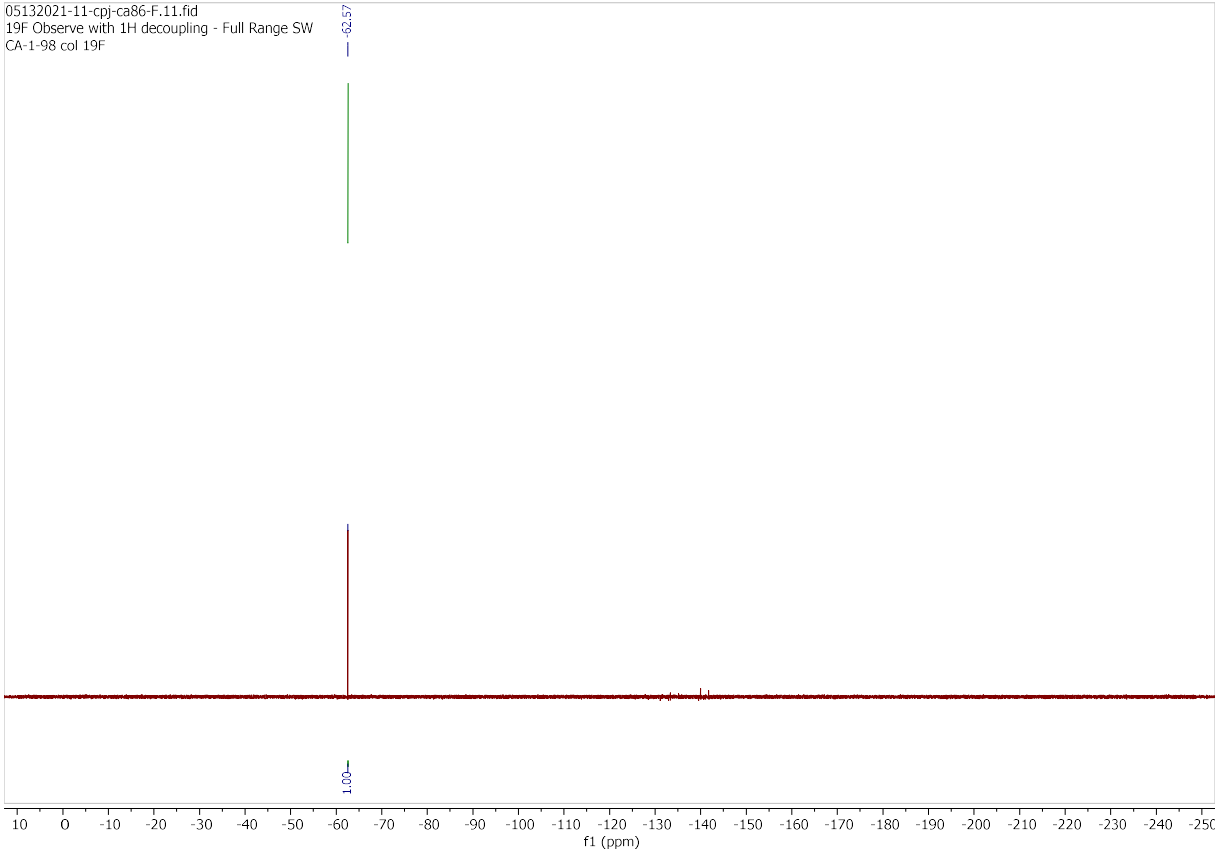
7. Spectra

7.1 Catalysts

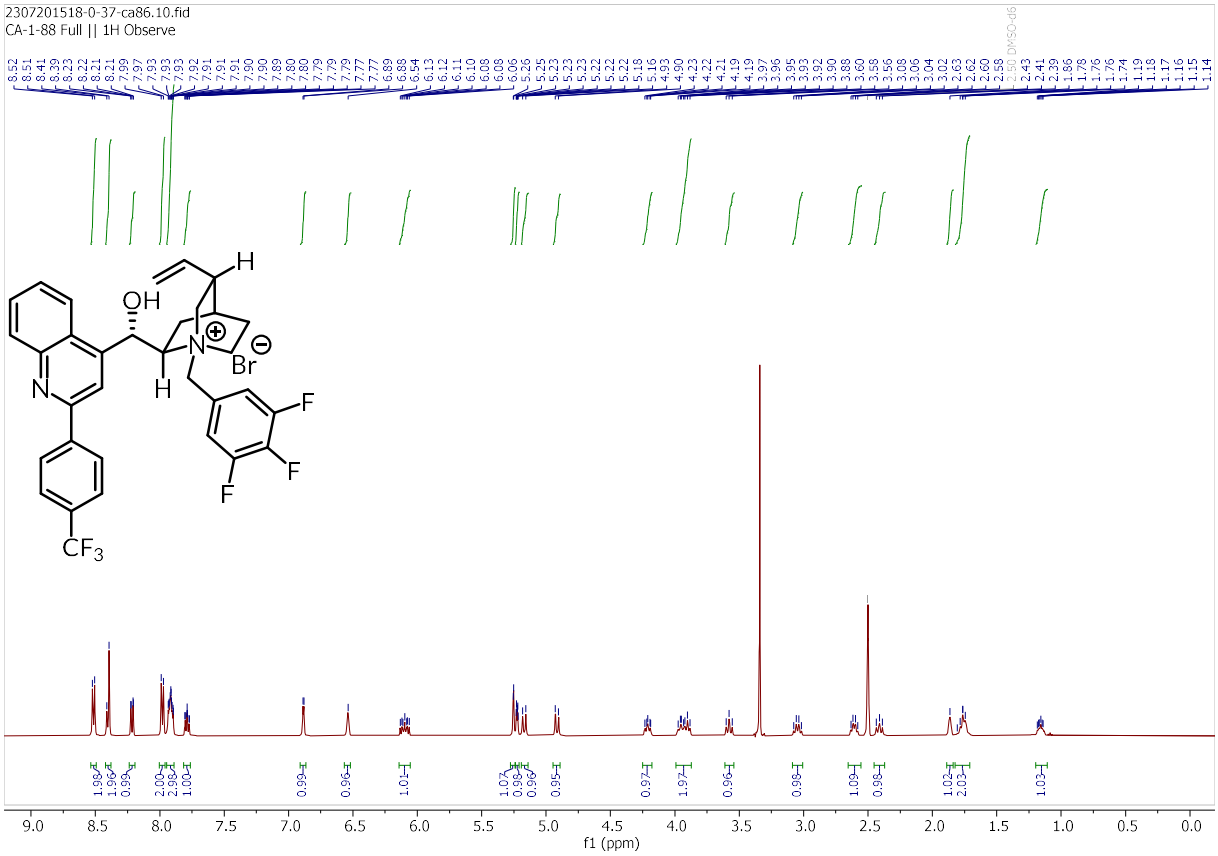
(C1a)

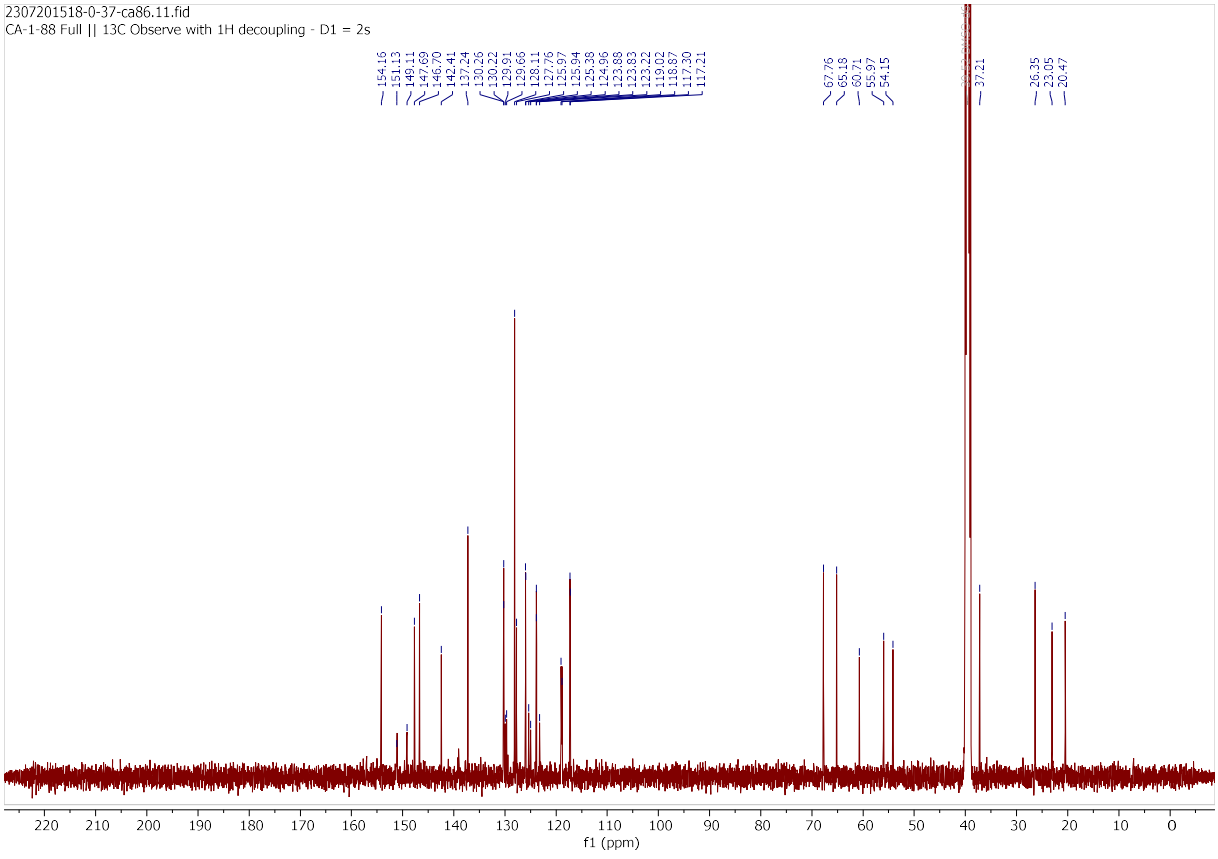


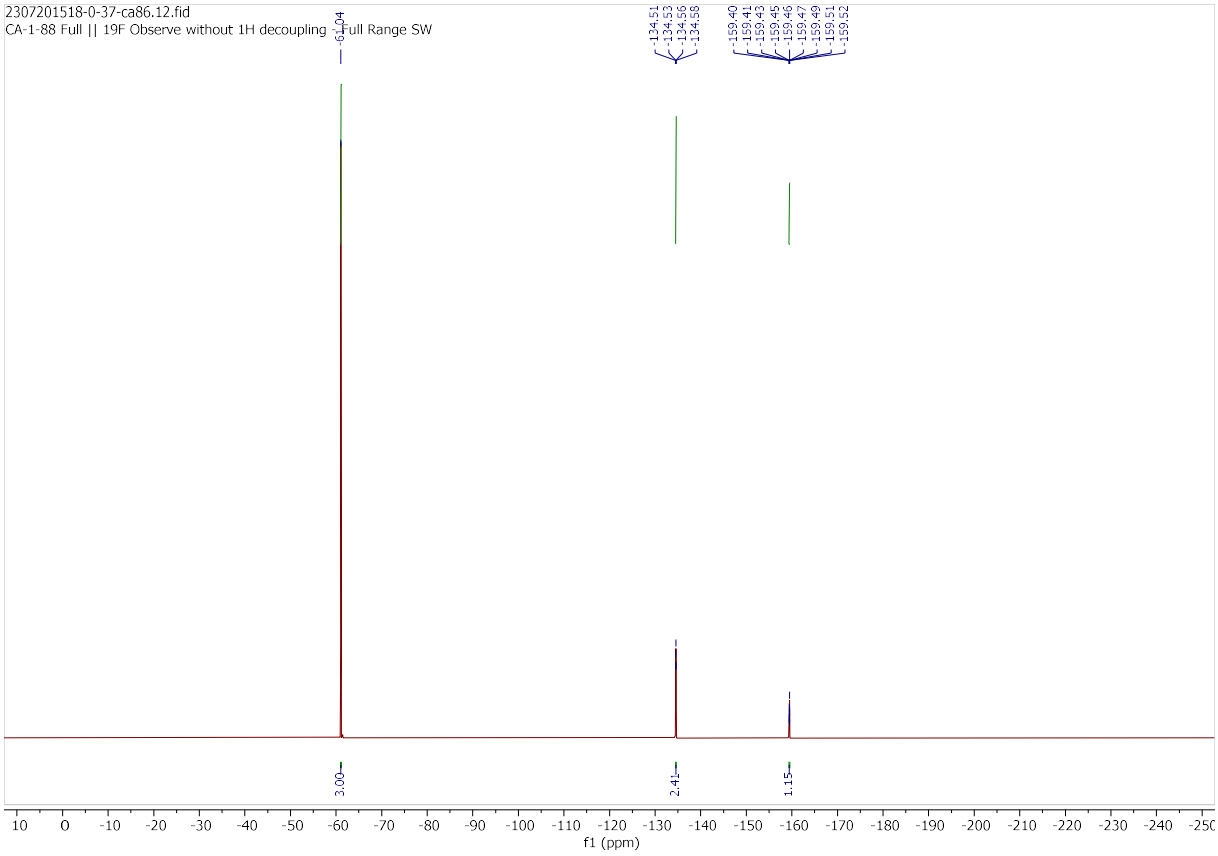

2307130933-5-1-ca86.10.fid
CA-ArCinchCF3 2D || 13C Observe with 1H decoupling - D
155.53
149.80
148.44
143.15
140.05
131.30
131.11
130.84
129.64
128.03
125.86
125.84
125.10
124.88
123.56
122.82
116.14
115.25
71.43
60.32
50.15
49.60
39.80
28.28
26.08
20.88
f1 (ppm)


05132021-11-cpj-ca86-F.11.fid
19F Observe with 1H decoupling - Full Range SW
CA-1-98 col 19F
-62.57
1.00
f1 (ppm)

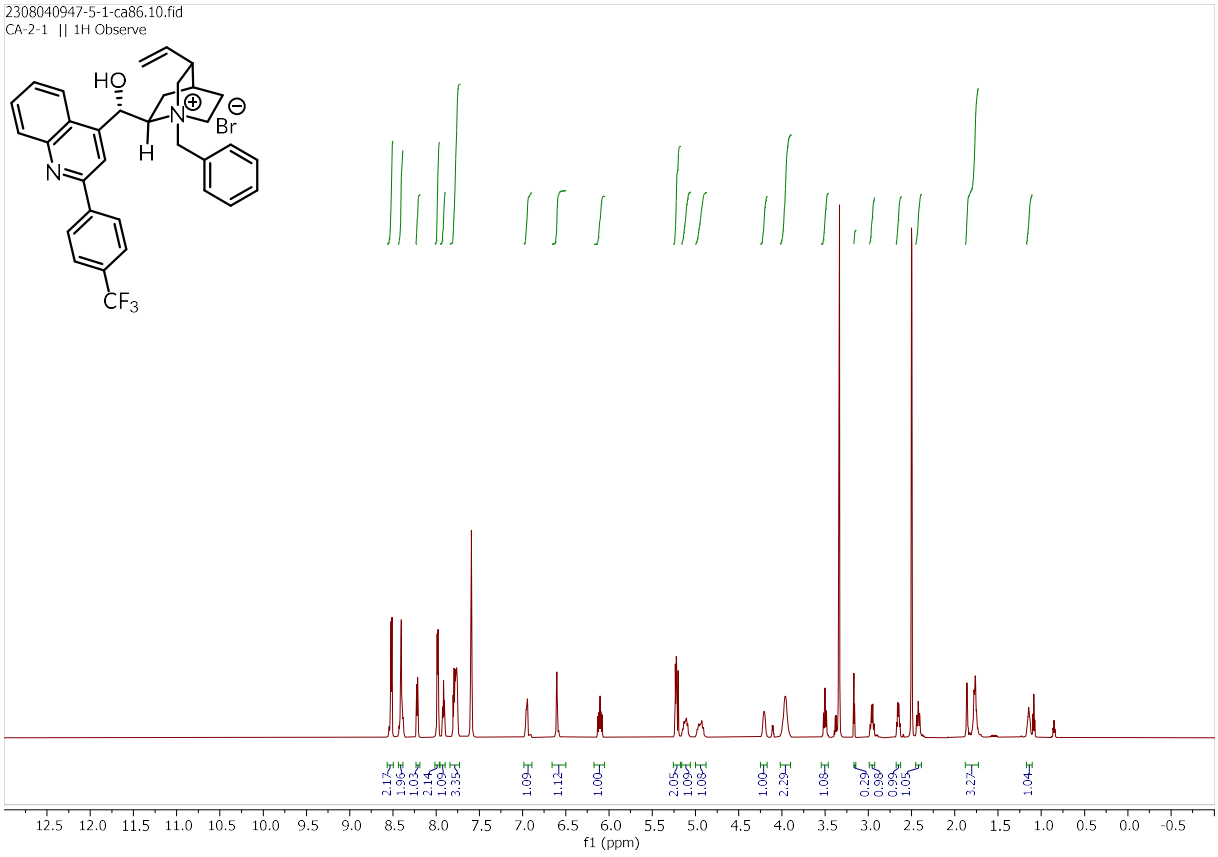
(C1)

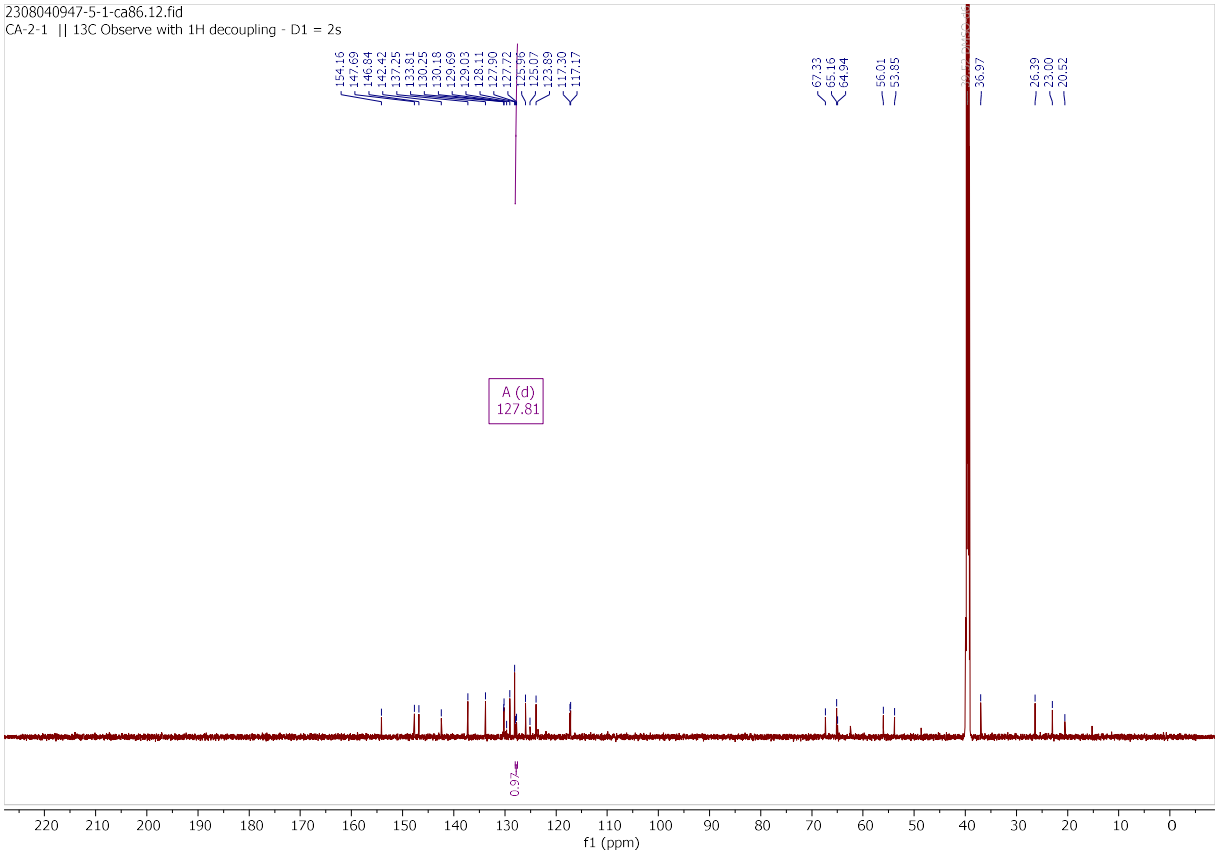

2307201518-0-37-ca86.10.fid
CA-1-88 Full || 1H Observe
f1 (ppm)

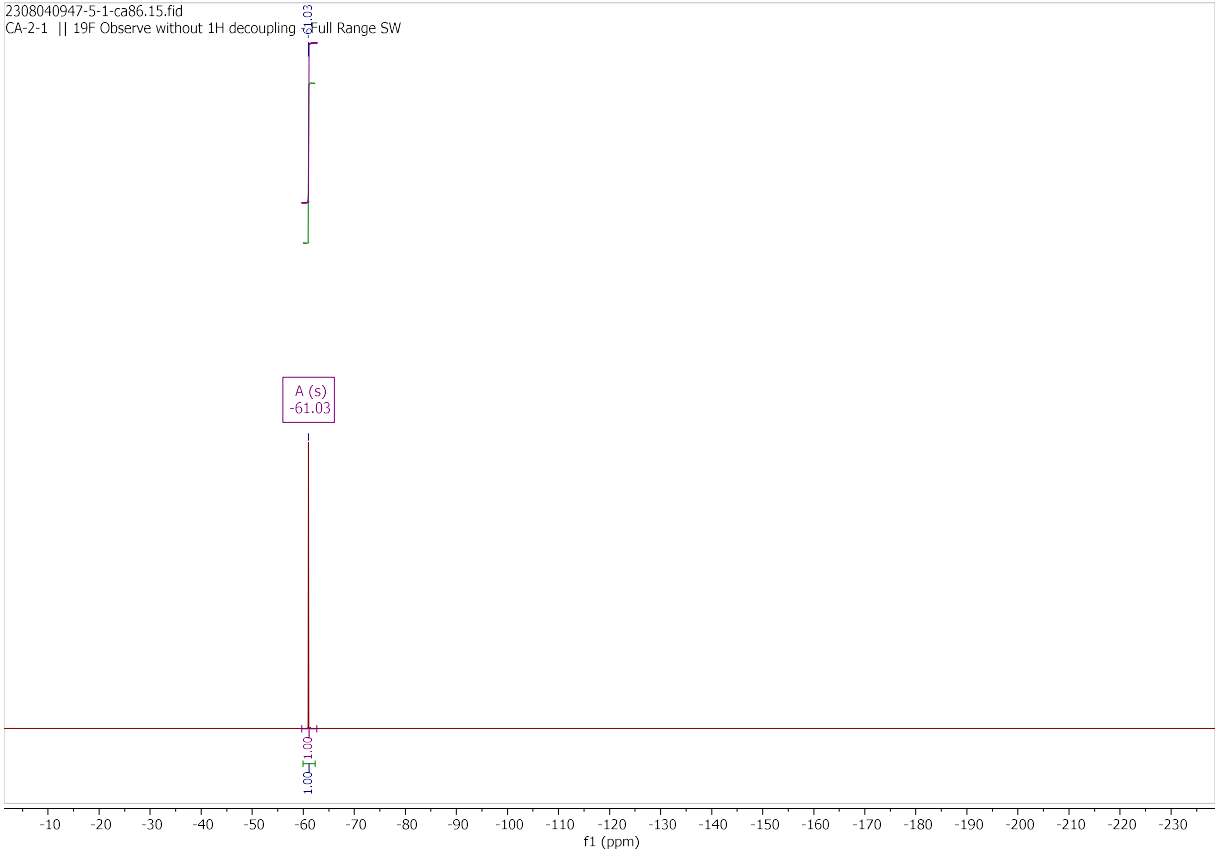

2307201518-0-37-ca86.11.fid
CA-1-88 Full || 13C Observe with 1H decoupling - D1 = 2s
f1 (ppm)


2307201518-0-37-ca86.12.fid
CA-1-88 Full || 19F Observe without 1H decoupling Full Range SW
-61.04
-134.51
-134.53
-134.56
-134.58
-159.40
-159.41
-159.43
-159.45
-159.46
-159.47
-159.49
-159.51
-159.52
3.00
2.41
1.15
f1 (ppm)

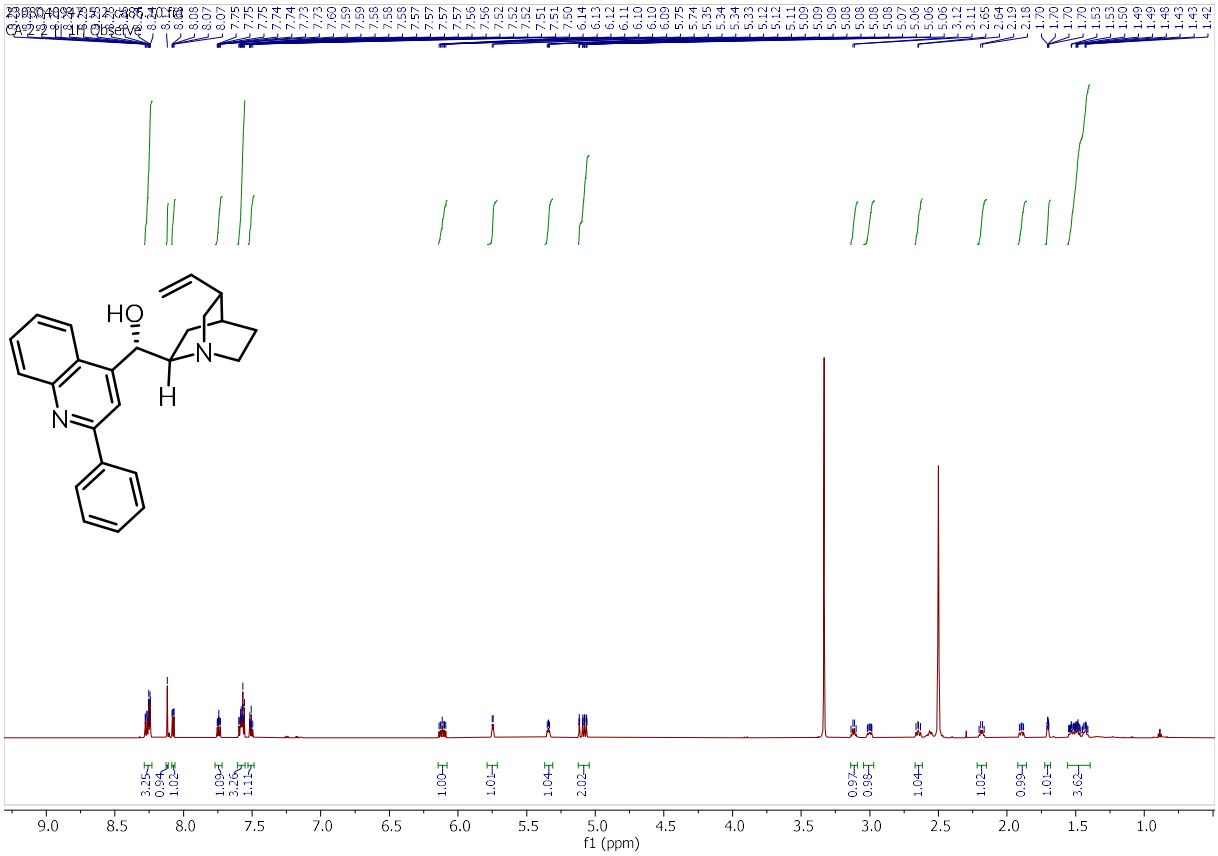
(C3)


2308040947-5-1-ca86.10.fid
CA-2-1 || 1H Observe
HO
N
H
N
Br
CF3
2.12
1.96
1.02
2.14
1.09
3.35
1.09
1.12
1.00
2.05
1.09
1.08
1.00
2.29
1.08
0.29
0.99
0.99
1.05
3.27
1.04
f1 (ppm)

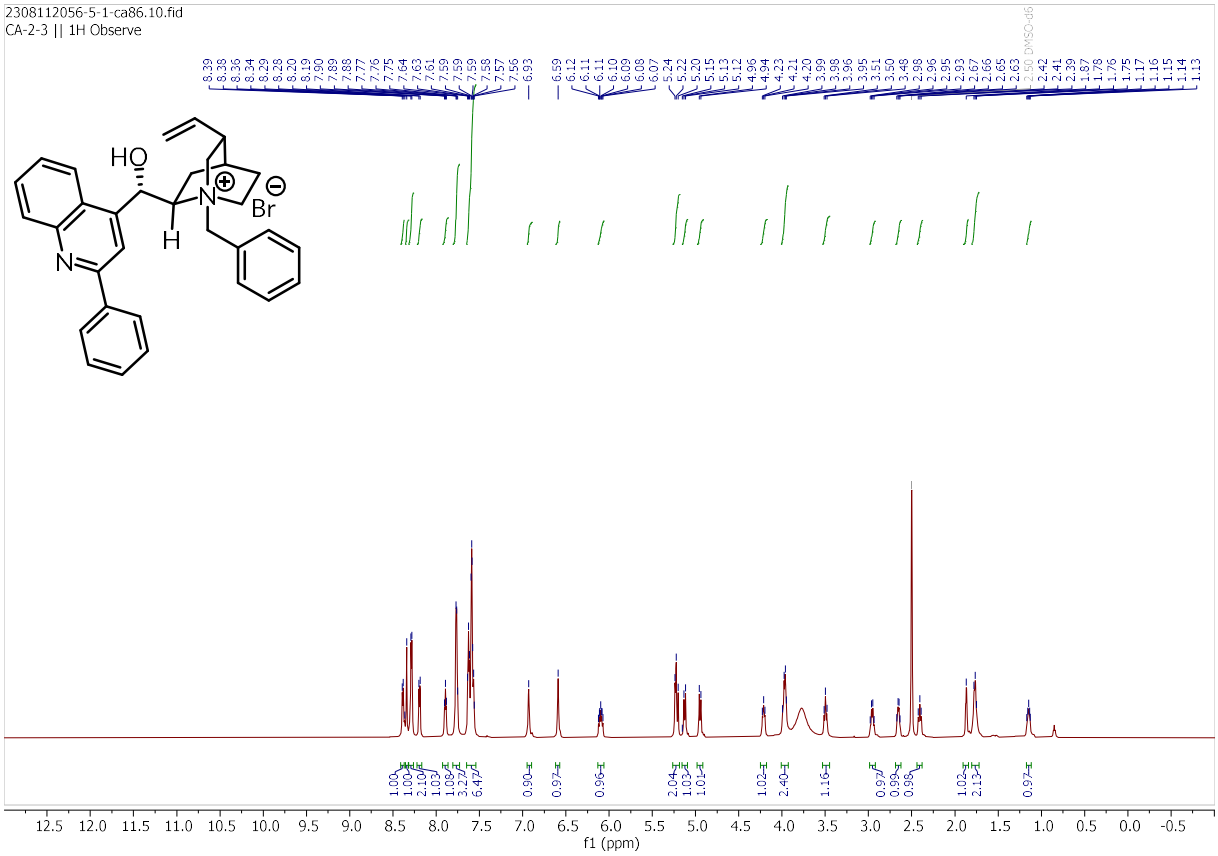

2308040947-5-1-ca86.12.fid
CA-2-1 || 13C Observe with 1H decoupling - D1 = 2s
154.16
147.69
146.84
142.42
137.25
133.81
130.25
130.18
129.69
129.03
128.11
127.90
127.72
125.96
125.07
123.89
117.30
117.17
67.33
65.16
64.94
56.01
53.85
36.97
26.39
23.00
20.52
A (d)
127.81
0.97
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

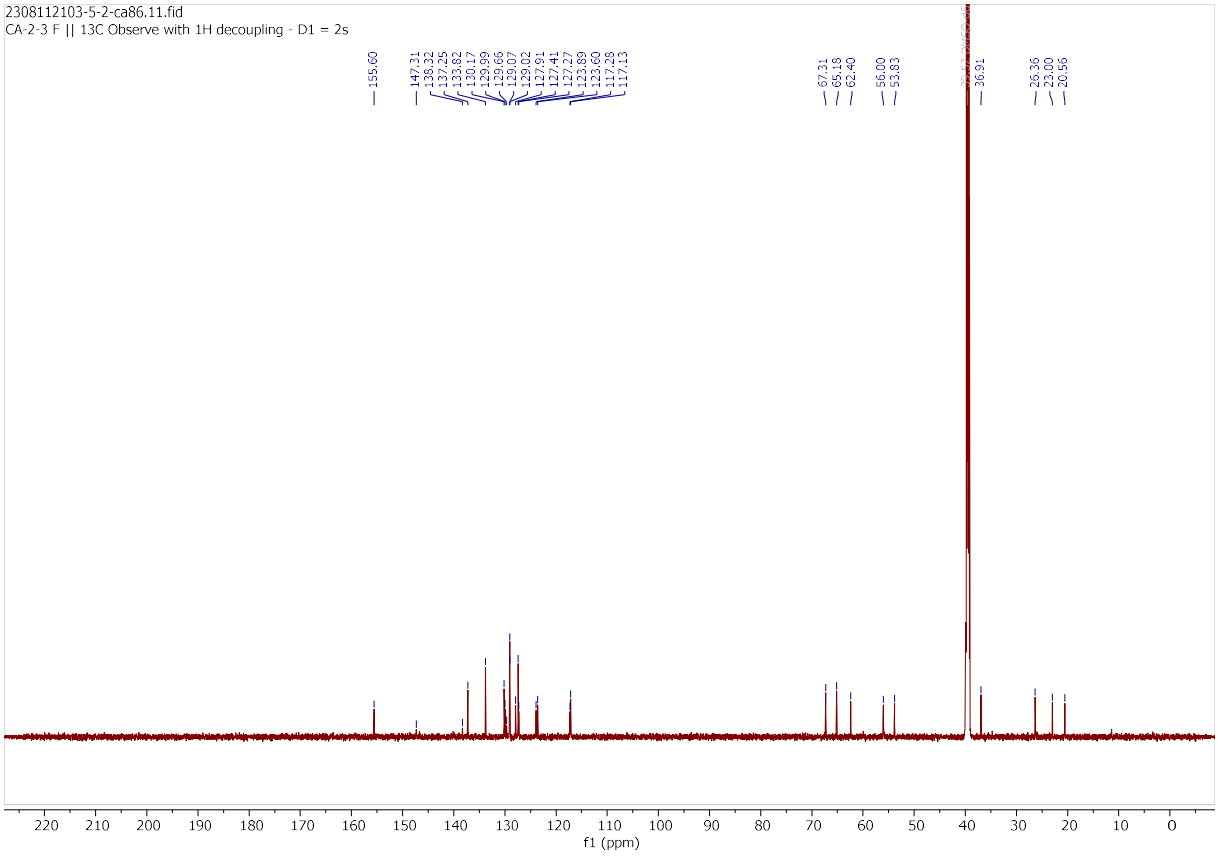

2308040947-5-1-ca86.15.fid
CA-2-1 || 19F Observe without 1H decoupling - Full Range SW
-61.03
A (s)
-61.03
1.00
1.00
-10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230
f1 (ppm)

(C4a)

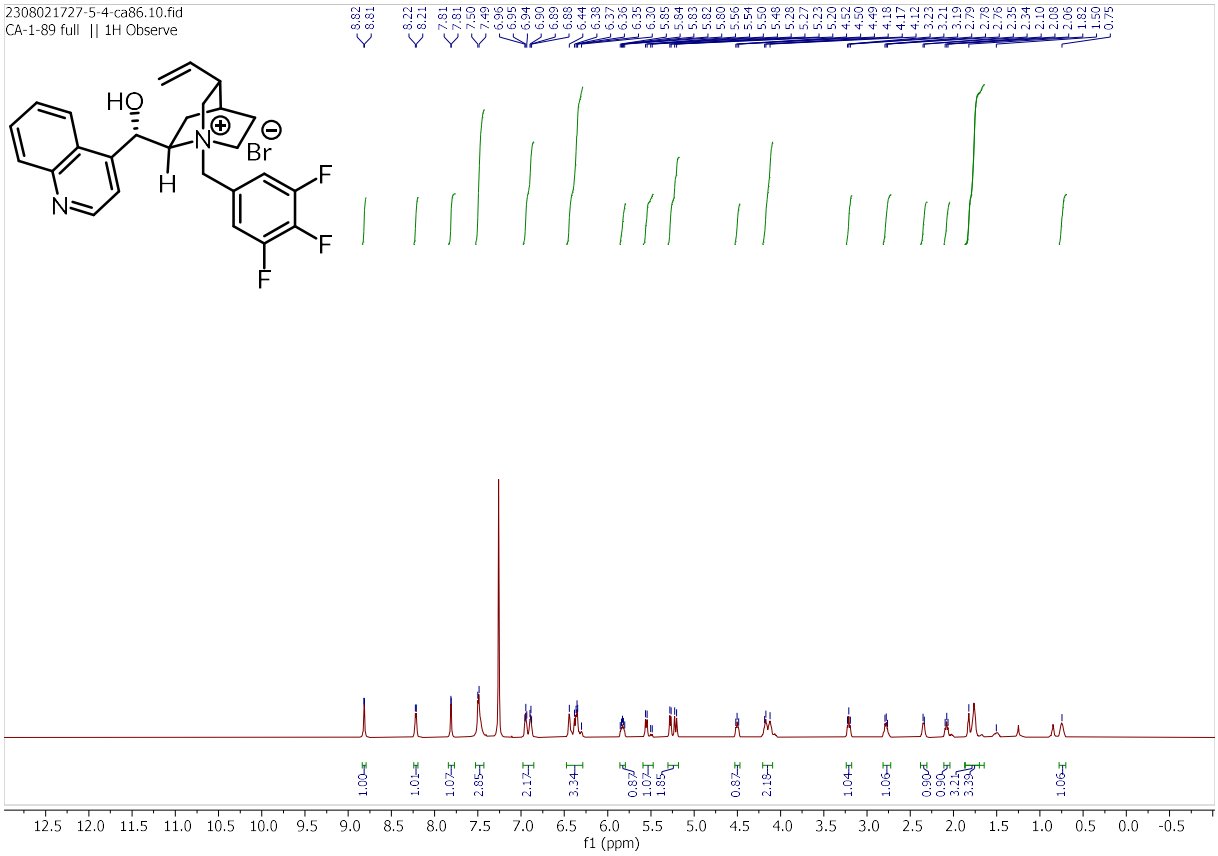


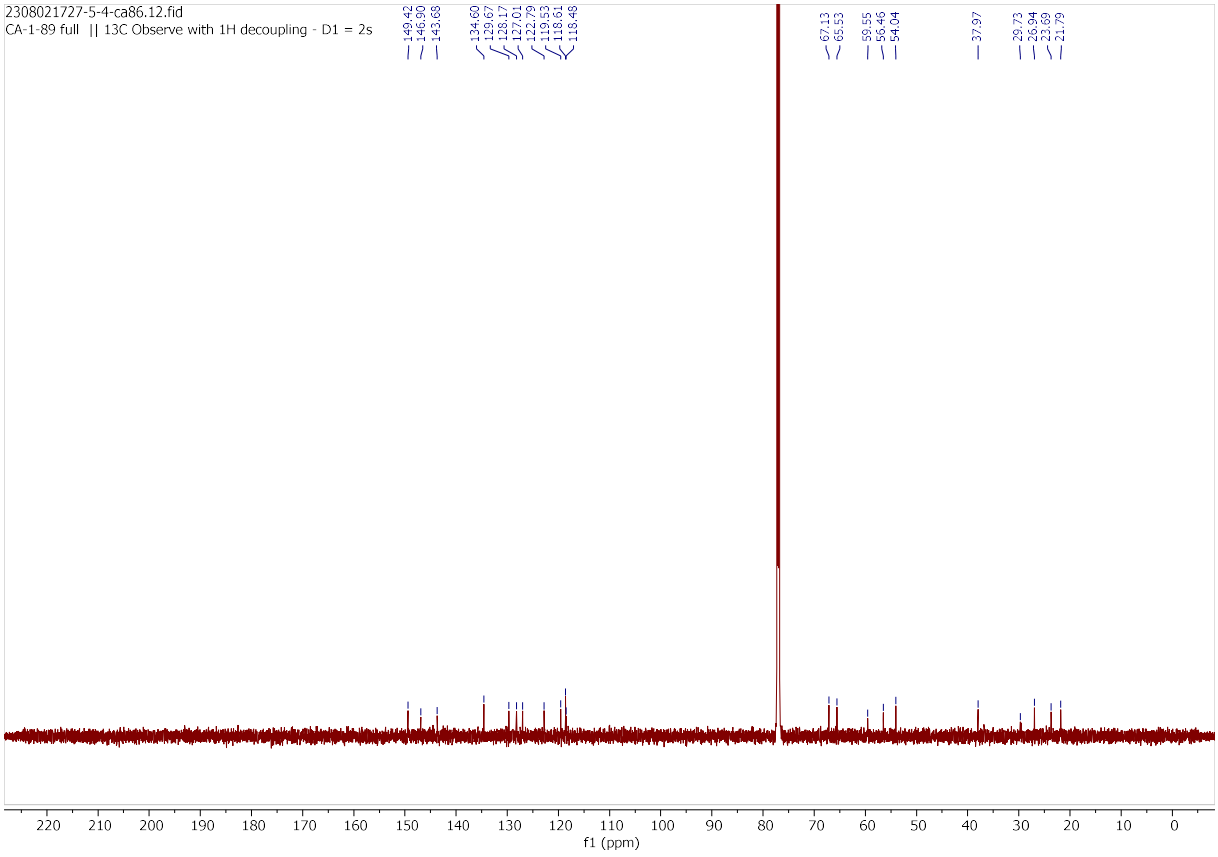
(C4)

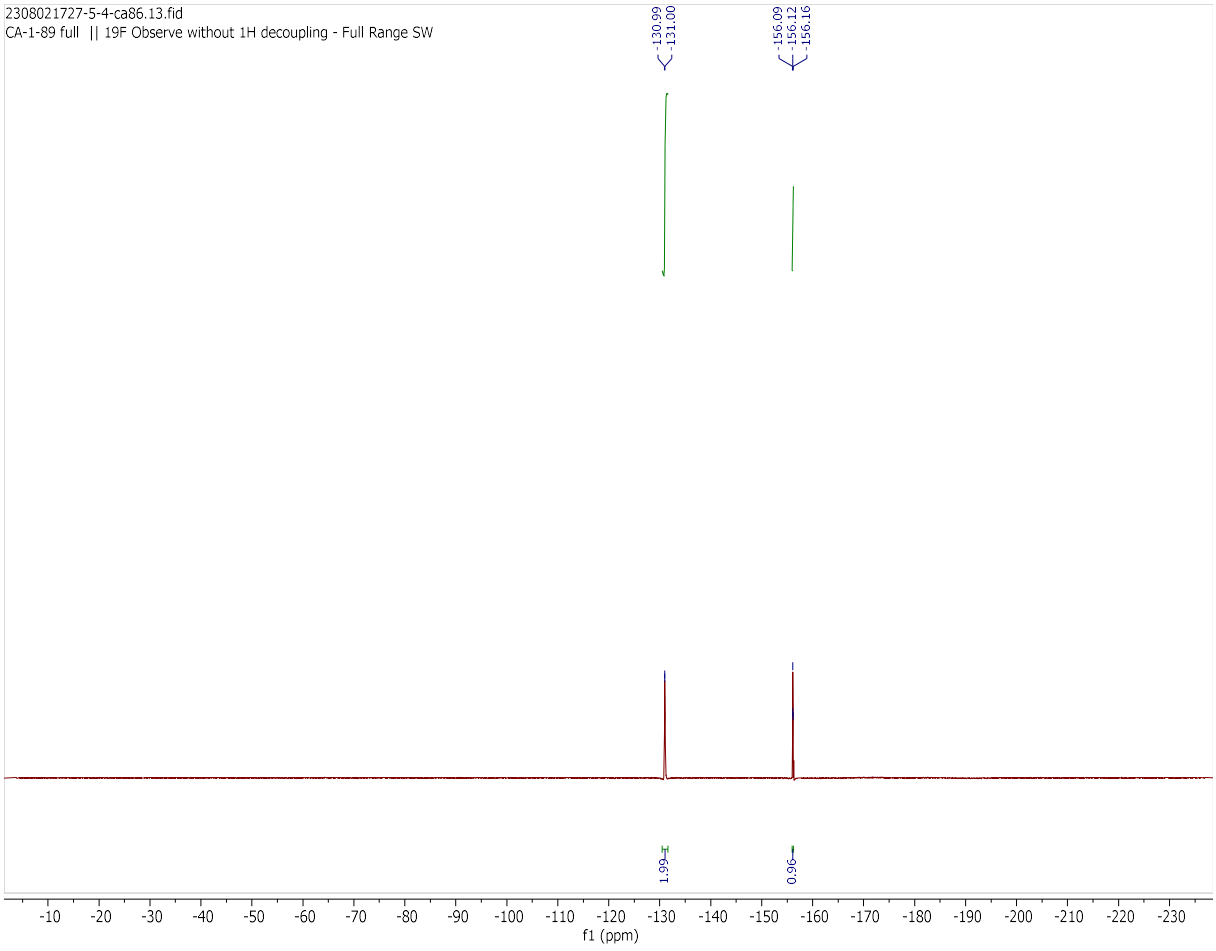

2308112056-5-1-ca86.10.fid
CA-2-3 || 1H Observe
HO
N
H
N
Br
f1 (ppm)


2308112103-5-2-ca86.11.fid
CA-2-3 F || 13C Observe with 1H decoupling - D1 = 2s
f1 (ppm)

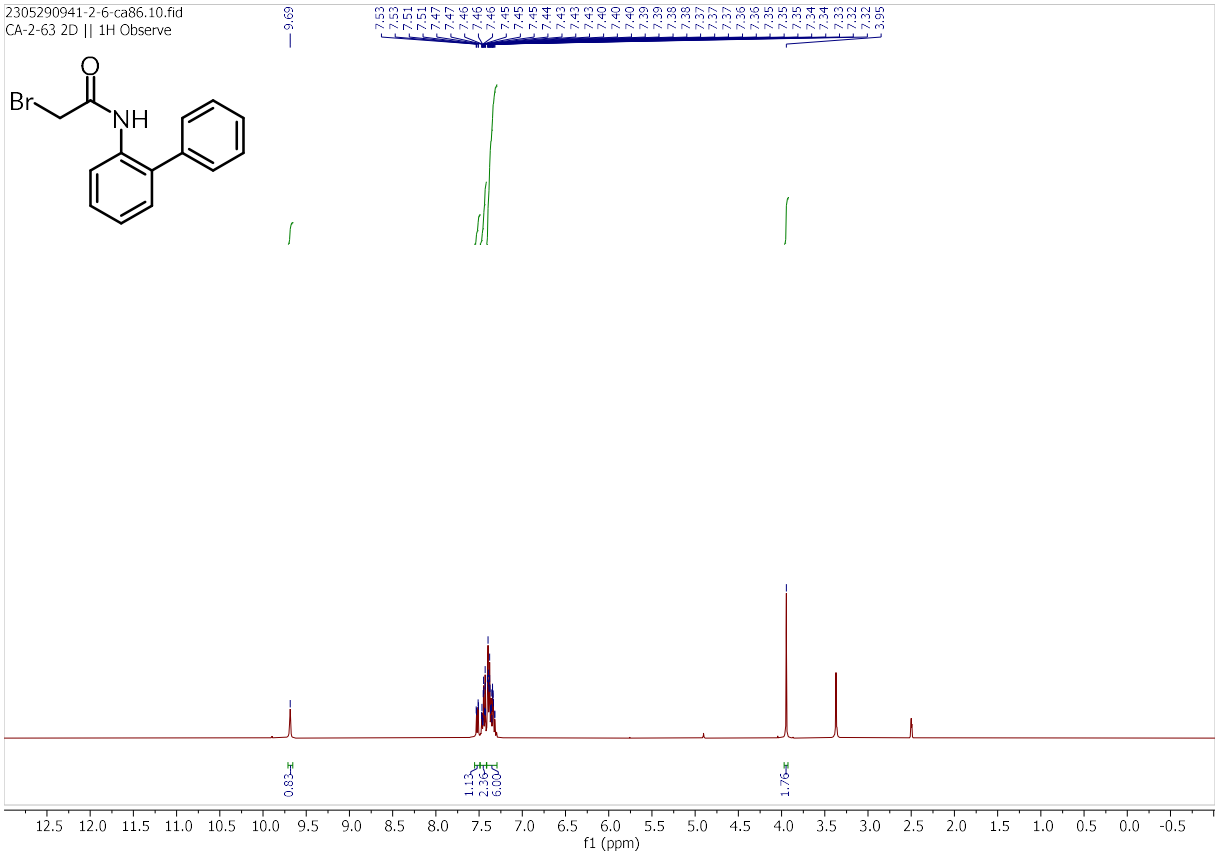
(C6)

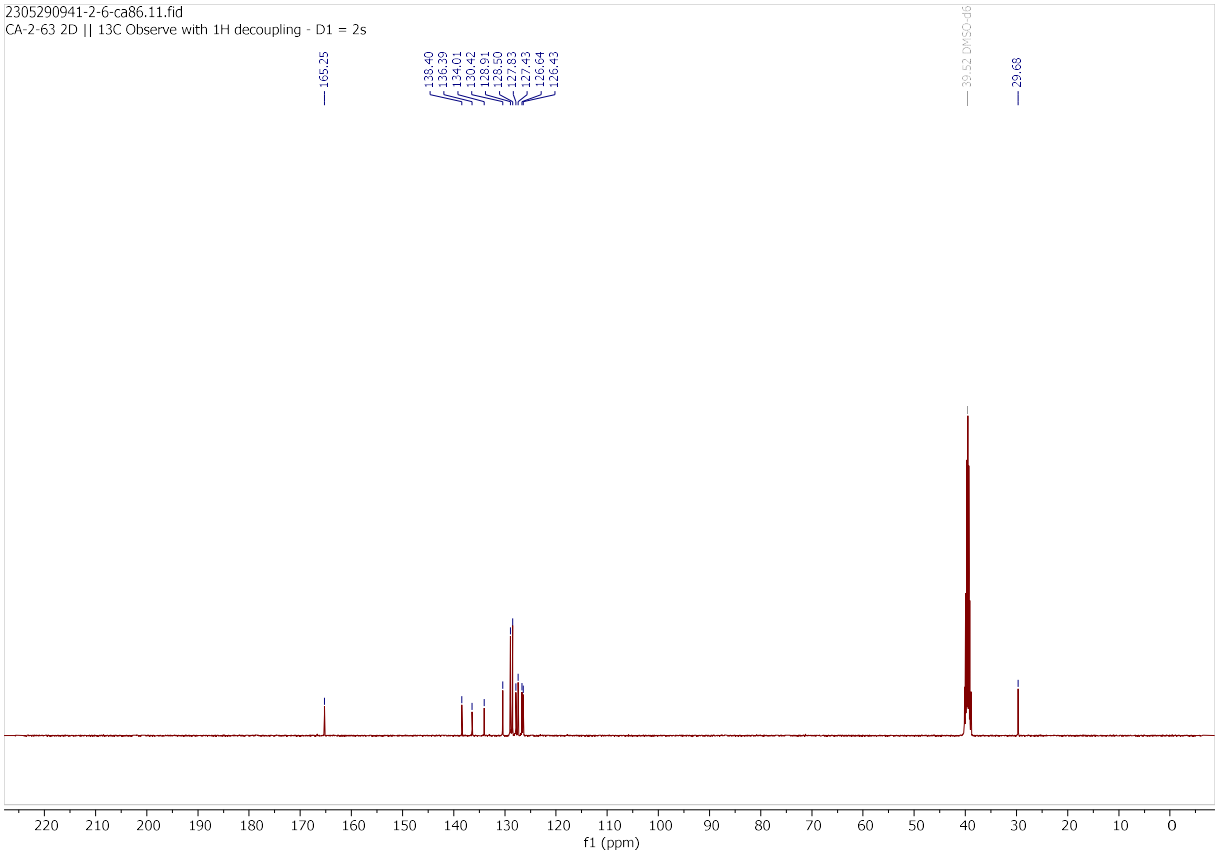

2308021727-5-4-ca86.10.fid
CA-1-89 full || 1H Observe
HO
N
Br
H
F
F
F
f1 (ppm)


2308021727-5-4-ca86.12.fid
CA-1-89 full || 13C Observe with 1H decoupling - D1 = 2s
f1 (ppm)

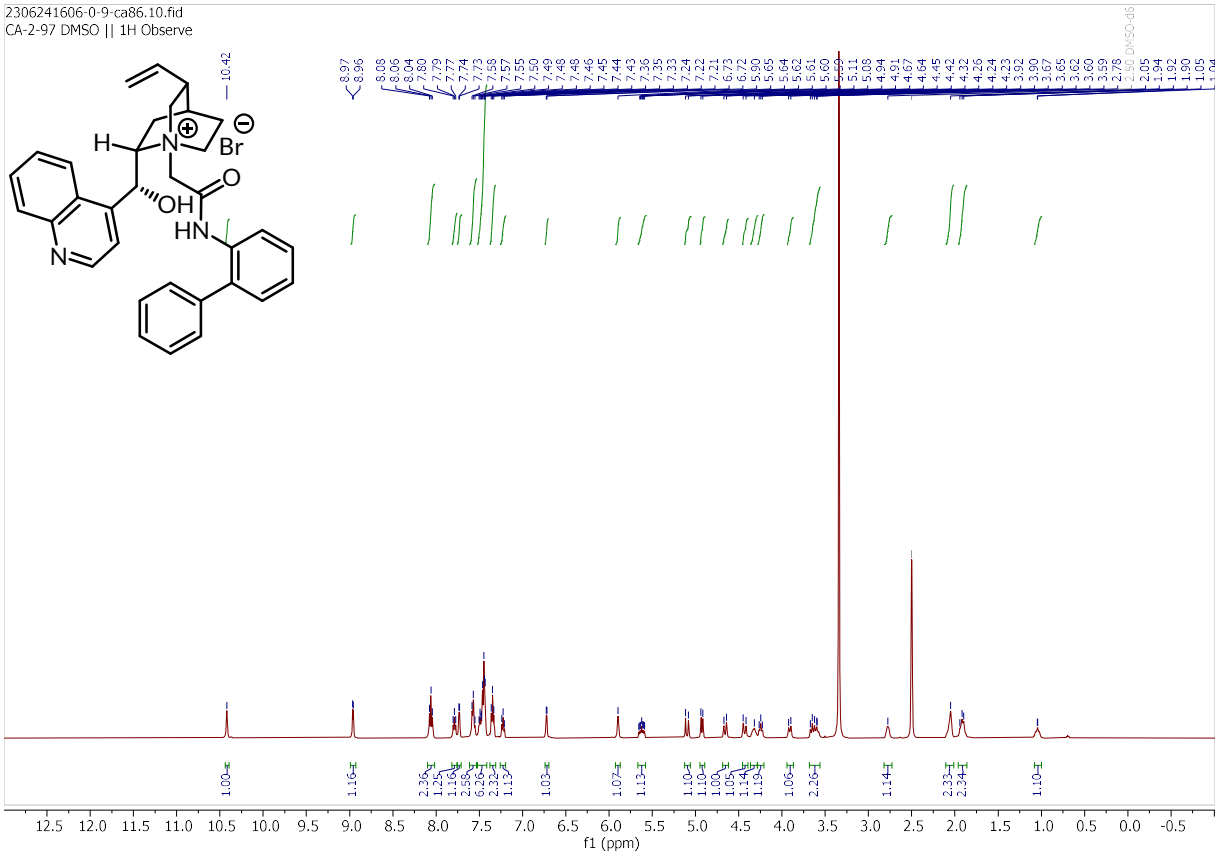

2308021727-5-4-ca86.13.fid
CA-1-89 full || 19F Observe without 1H decoupling - Full Range SW
-130.99
-131.00
-156.09
-156.12
-156.16
1.99
0.96
-10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230
f1 (ppm)

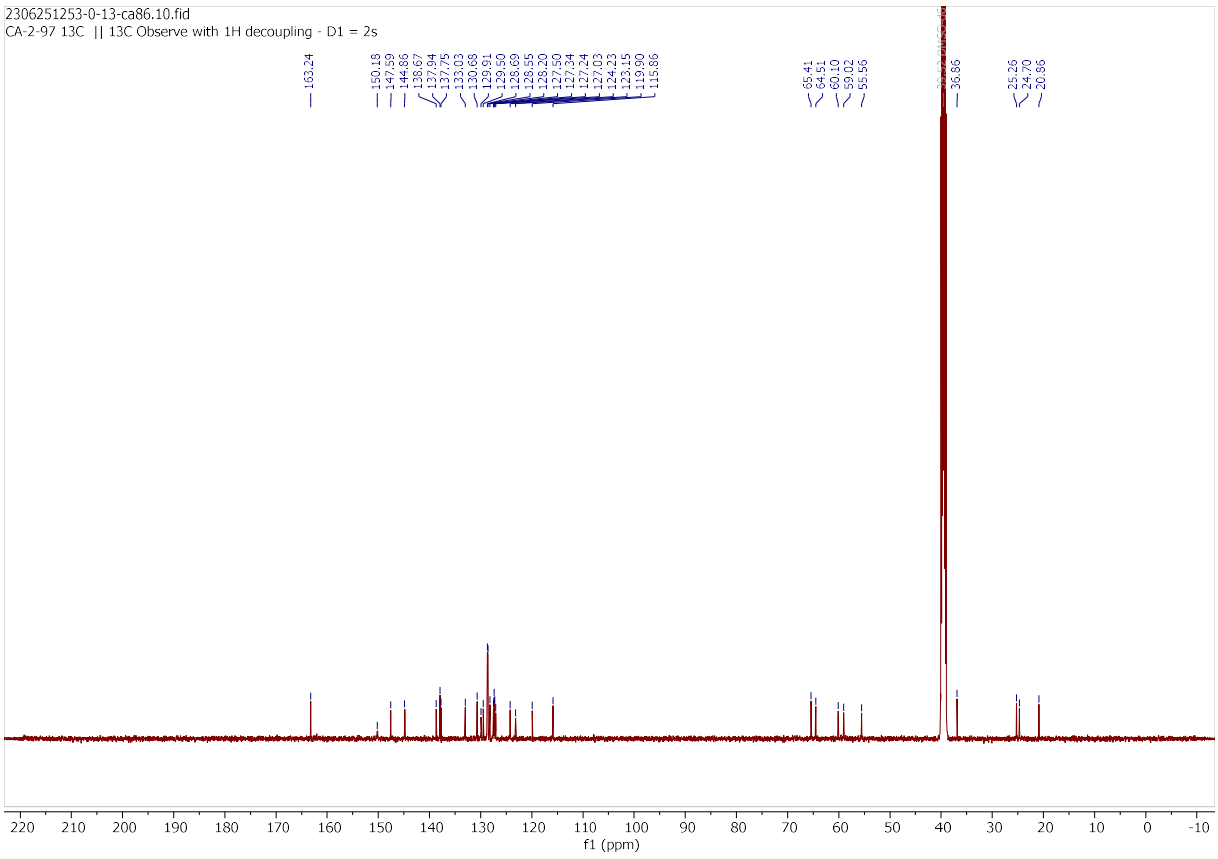
(C18a)


2305290941-2-6-ca86.10.fid
CA-2-63 2D || 1H Observe
Br
O
NH
f1 (ppm)

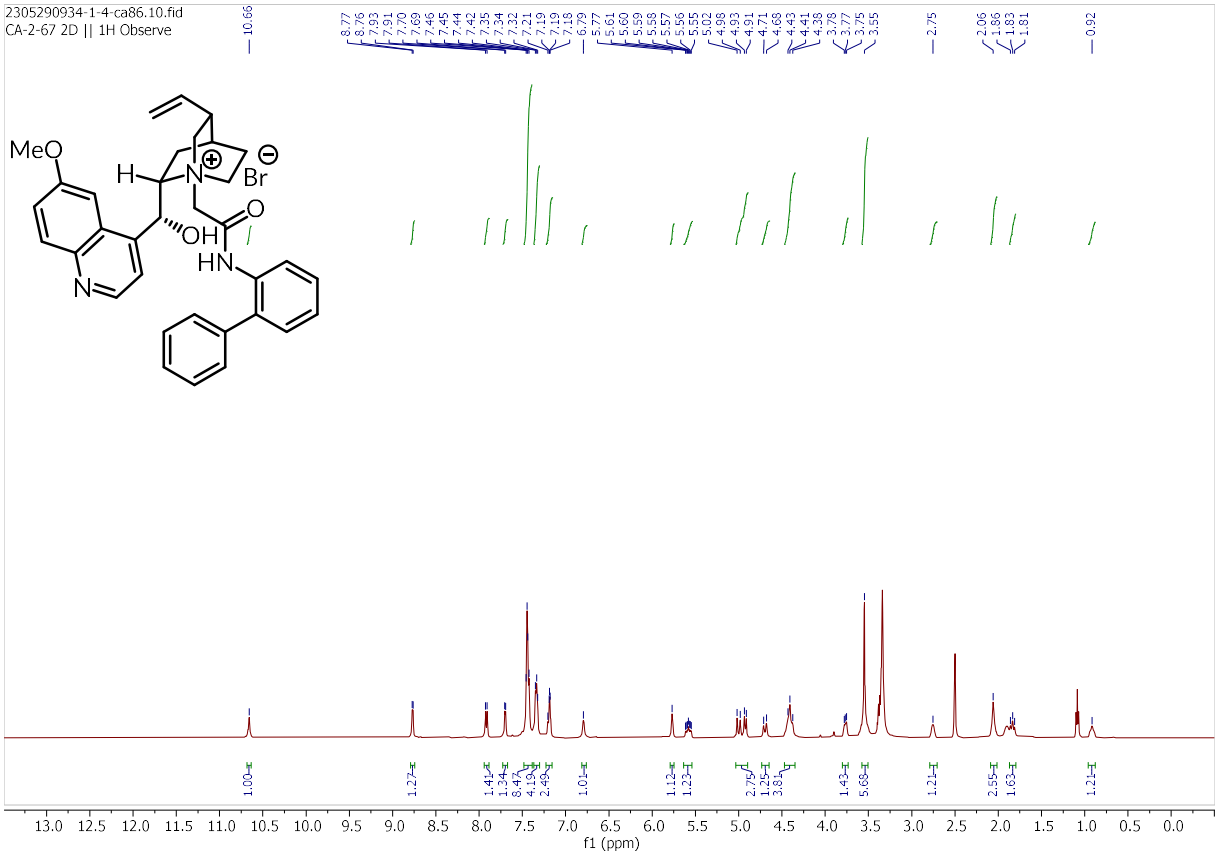

2305290941-2-6-ca86.11.fid
CA-2-63 2D || 13C Observe with 1H decoupling - D1 = 2s
f1 (ppm)

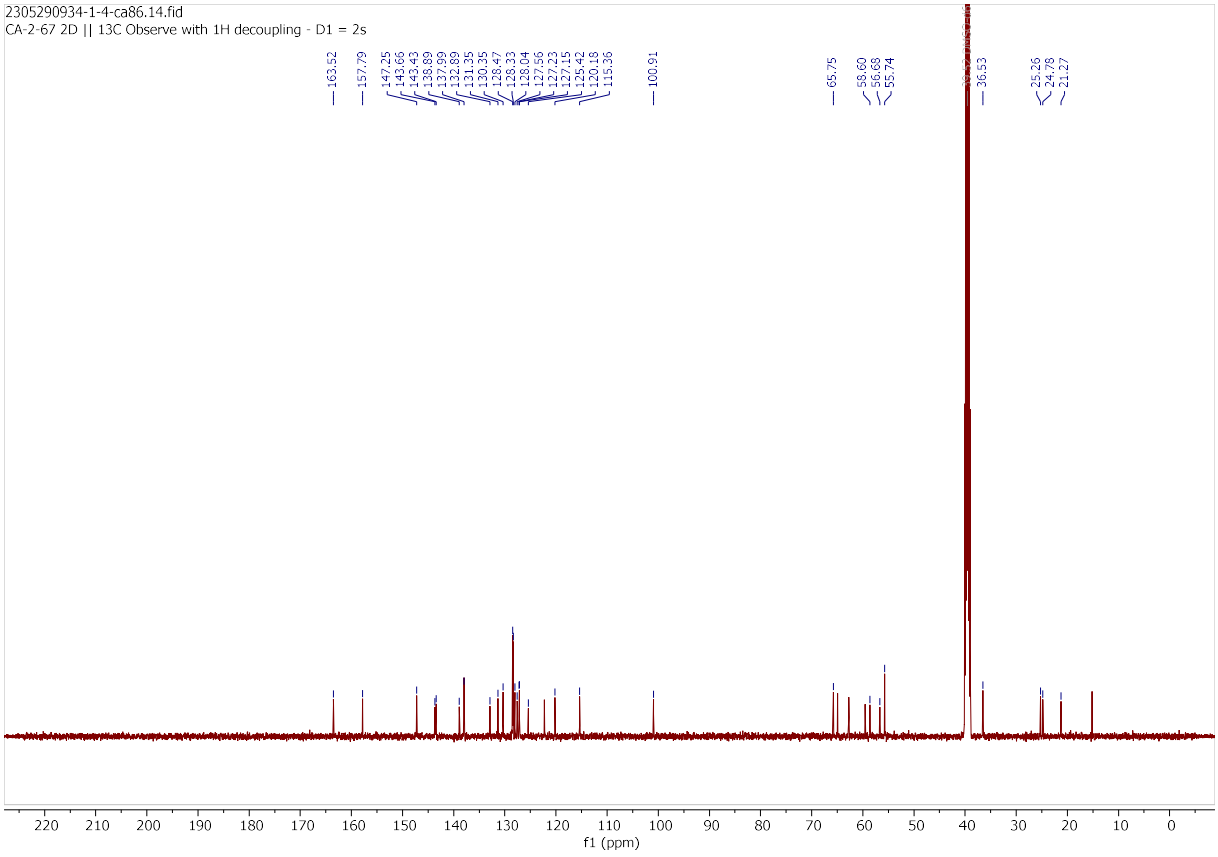
(C18)


2306241606-0-9-ca86.10.fid
CA-2-97 DMSO || 1H Observe
f1 (ppm)

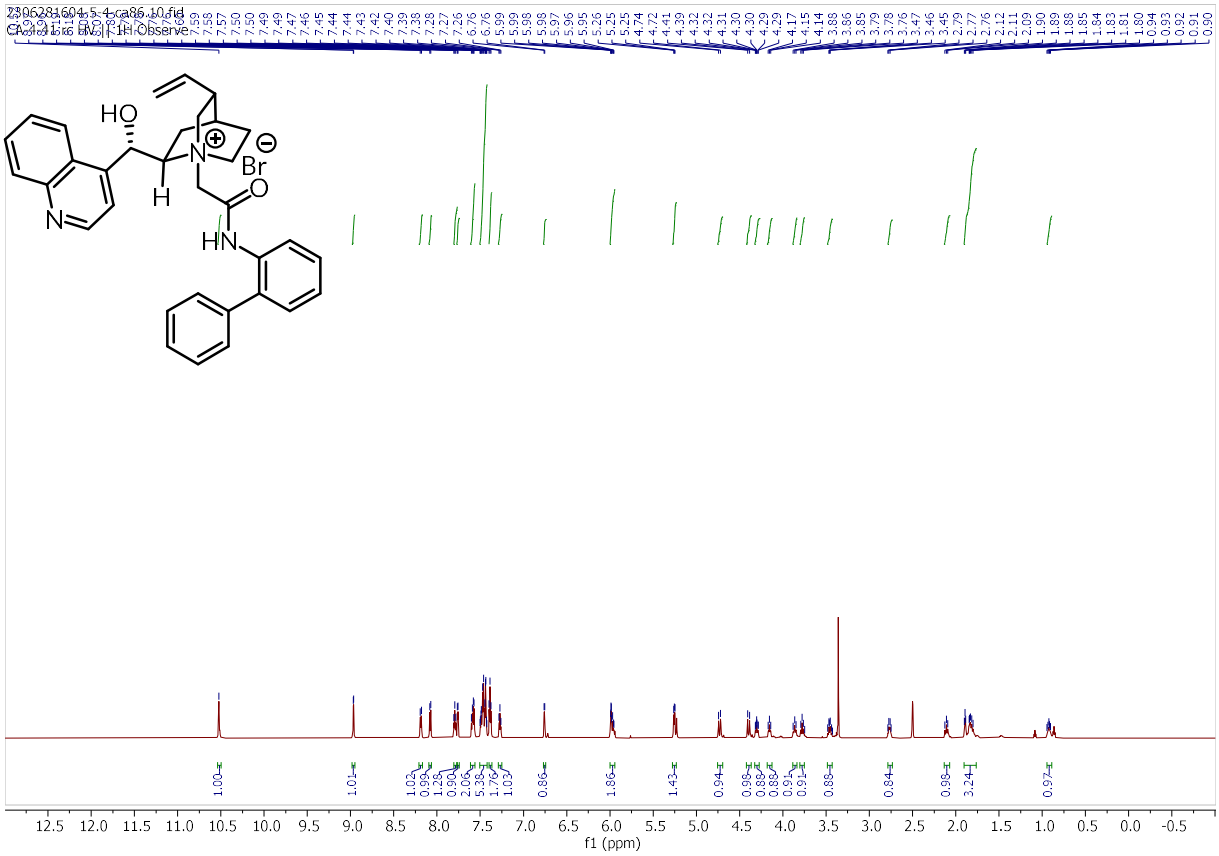

2306251253-0-13-ca86.10.fid
CA-2-97 13C || 13C Observe with 1H decoupling - D1 = 2s
f1 (ppm)

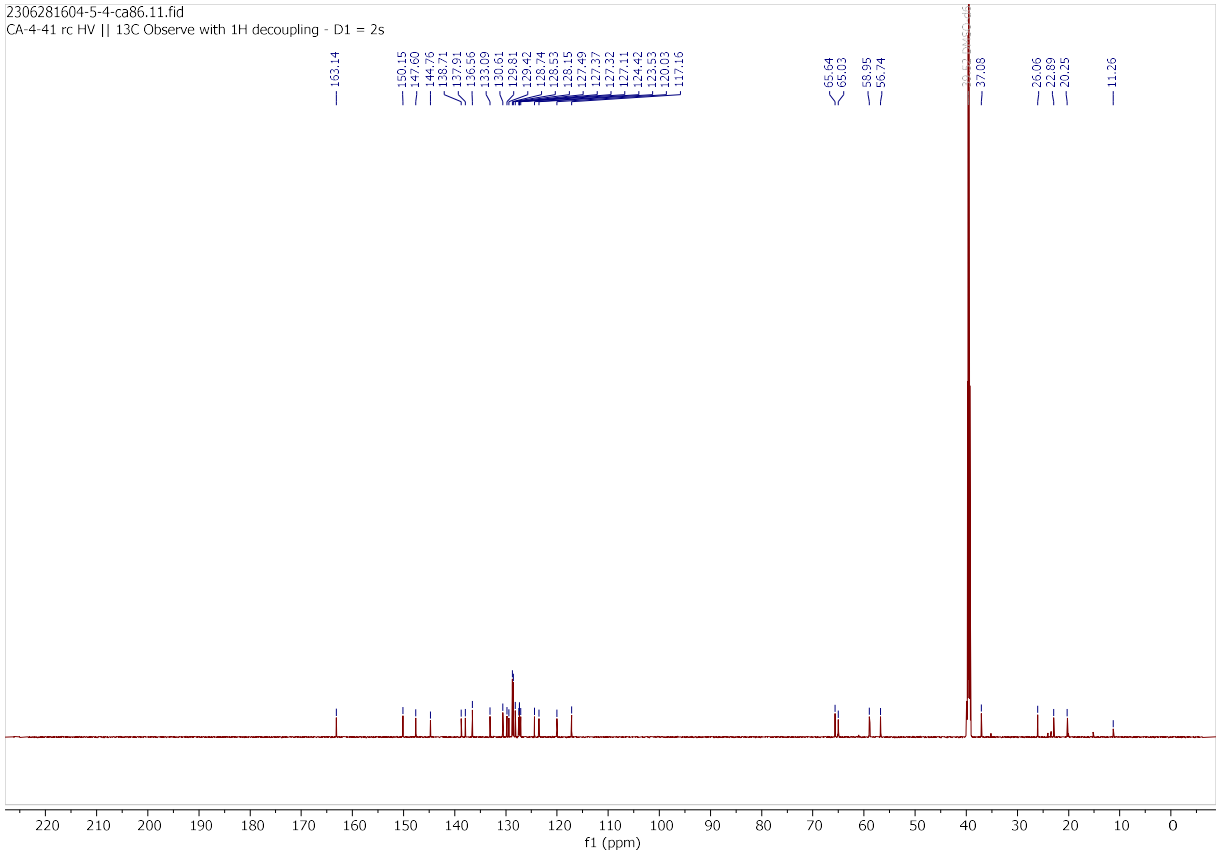
(C19)


2305290934-1-4-ca86.10.fid
CA-2-67 2D || 1H Observe
MeO
H
N
Br
O
OH
HN
N
f1 (ppm)

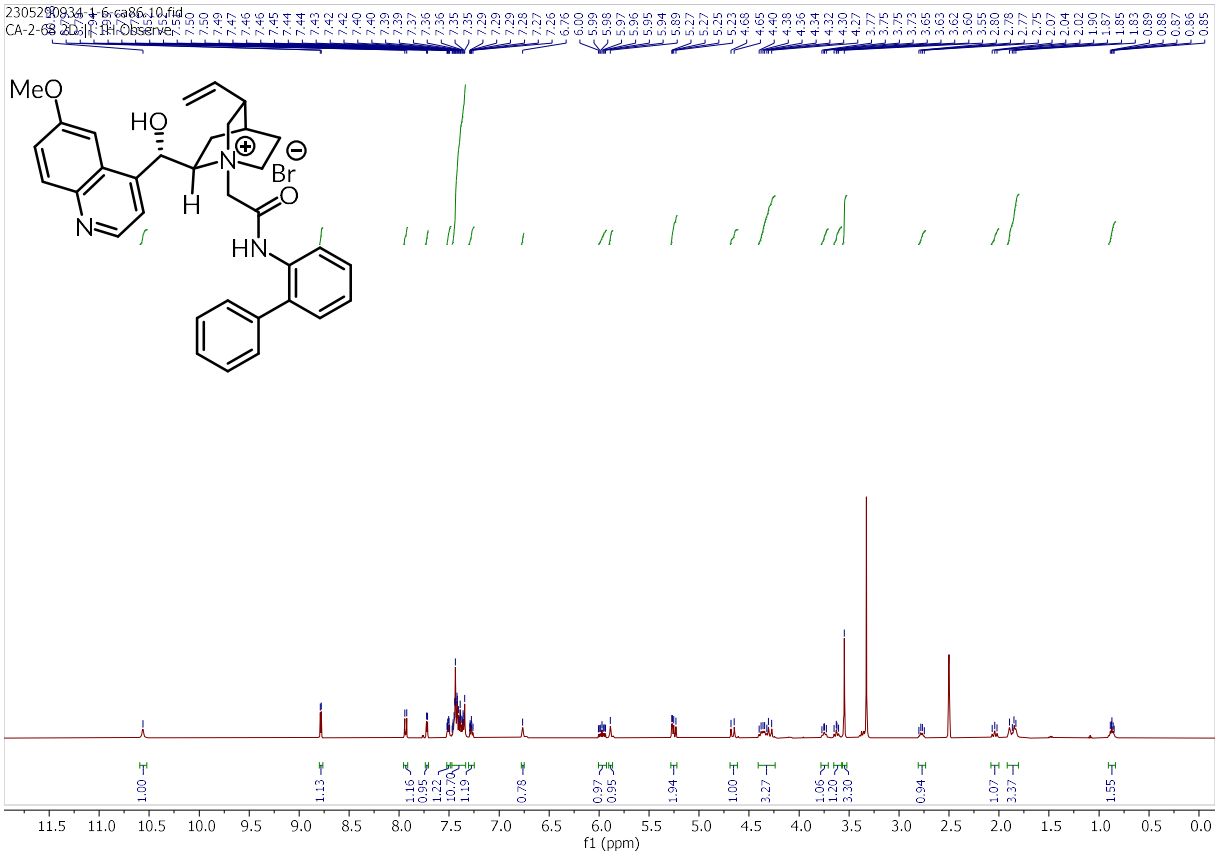

2305290934-1-4-ca86.14.fid
CA-2-67 2D || 13C Observe with 1H decoupling - D1 = 2s
f1 (ppm)

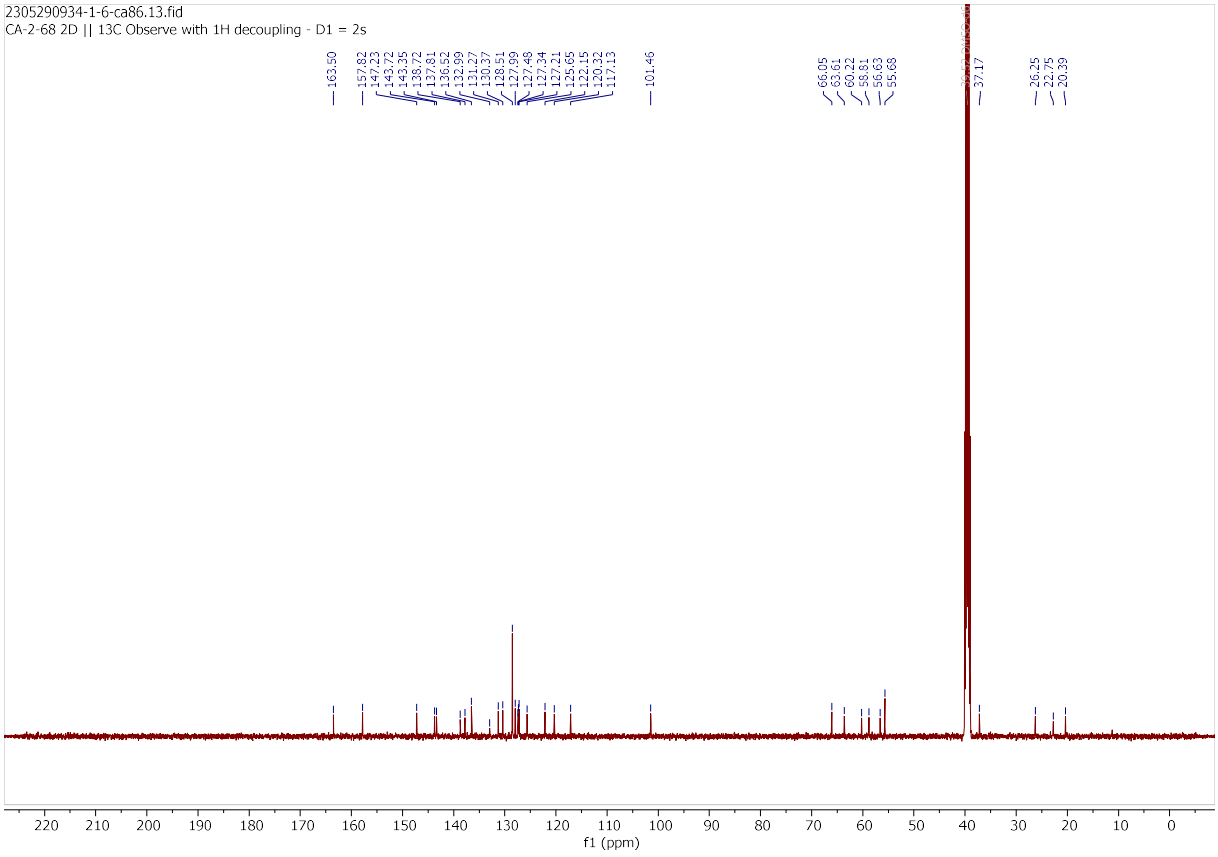
(C20)


2306281604-5-4-ca86.10.fid
CA-4-41 rc HV || 1H Observe
HO
N
Br
O
H
N
HN
1.00
1.01
1.02
0.99
1.28
0.90
2.06
5.38
1.76
1.03
0.86
1.86
1.43
0.94
0.98
0.88
0.88
0.91
0.91
0.88
0.84
0.98
3.24
0.97
f1 (ppm)


2306281604-5-4-ca86.11.fid
CA-4-41 rc HV || 13C Observe with 1H decoupling - D1 = 2s
163.14
150.15
147.60
146.76
139.71
137.91
135.66
133.89
130.81
129.81
129.42
128.74
128.53
128.15
127.49
127.37
127.32
127.11
124.42
123.53
120.03
117.16
65.64
65.03
58.95
56.74
37.08
26.06
22.89
20.25
11.26
f1 (ppm)

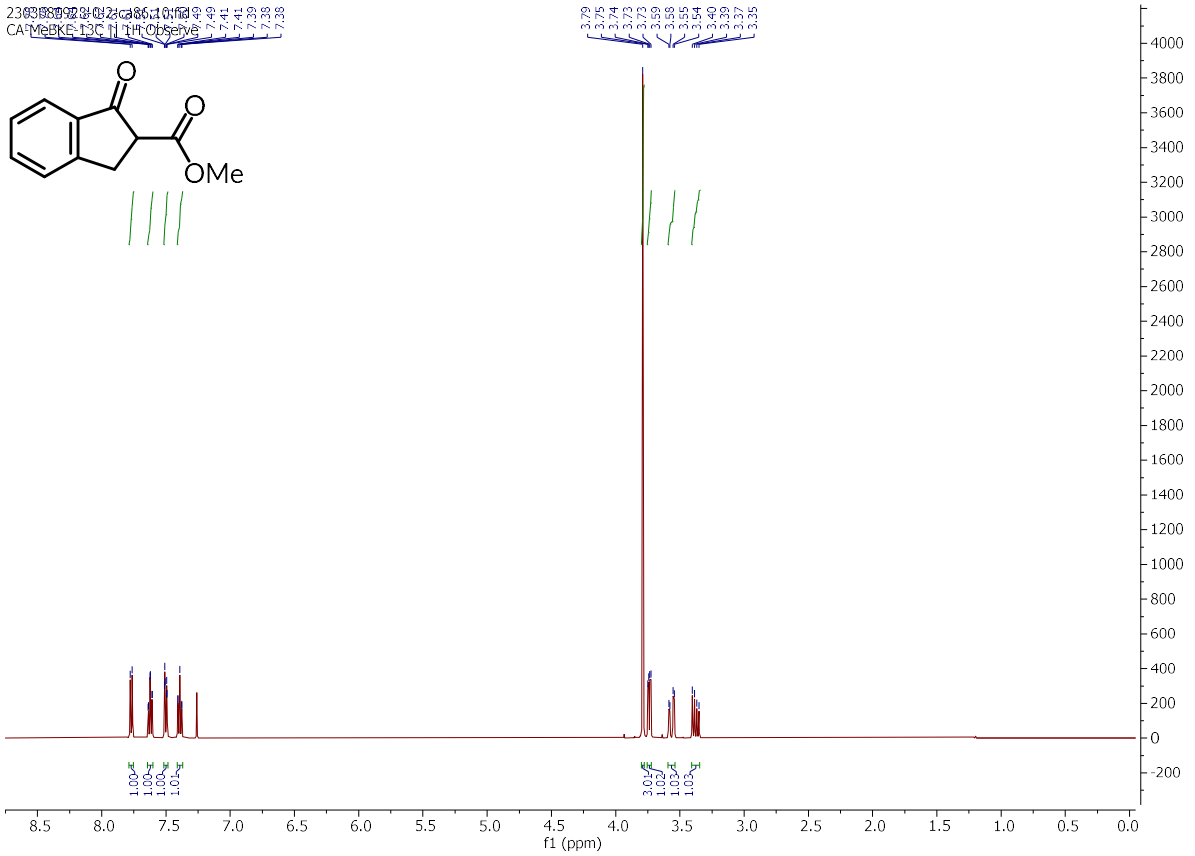
(C21)

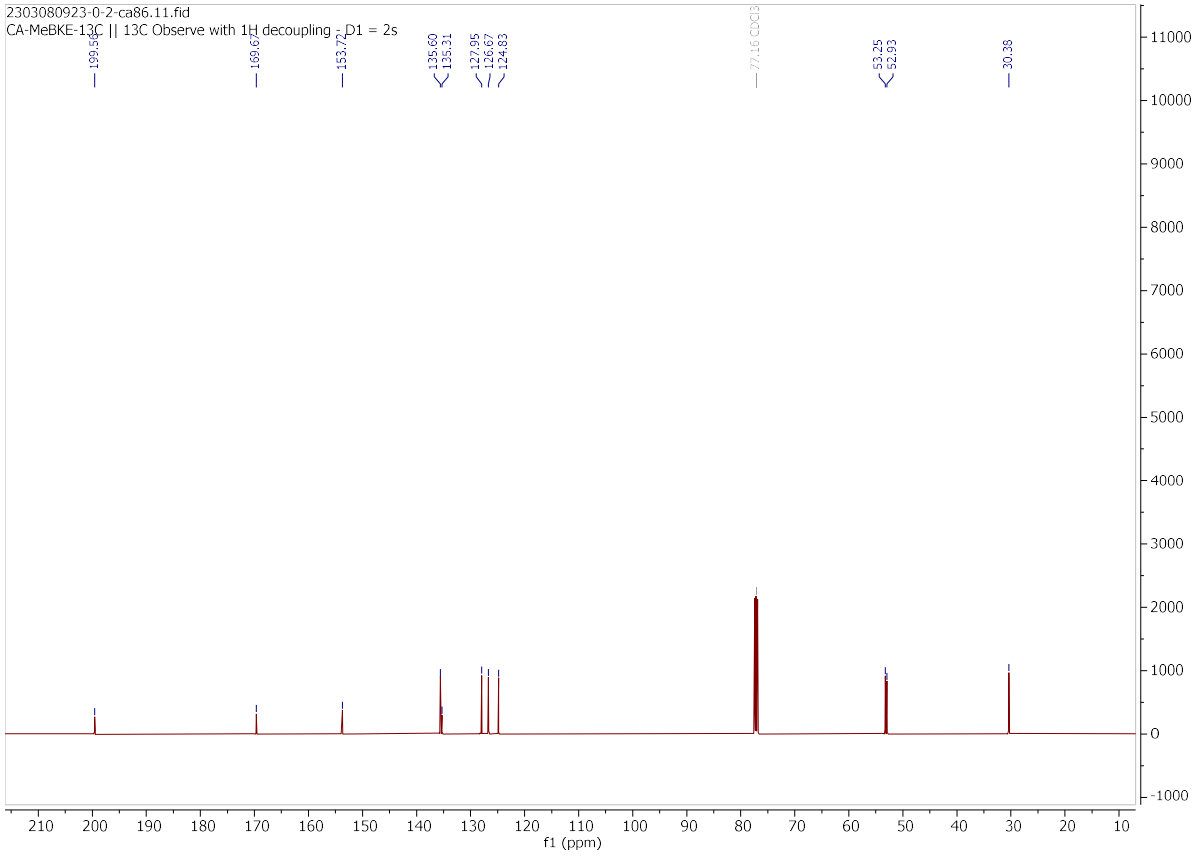

2305290934-1-6-ca86.10.fid
CA-2-68 2D || 1H Observe
MeO
HO
N
Br
H
O
HN
f1 (ppm)


2305290934-1-6-ca86.13.fid
CA-2-68 2D || 13C Observe with 1H decoupling - D1 = 2s
f1 (ppm)

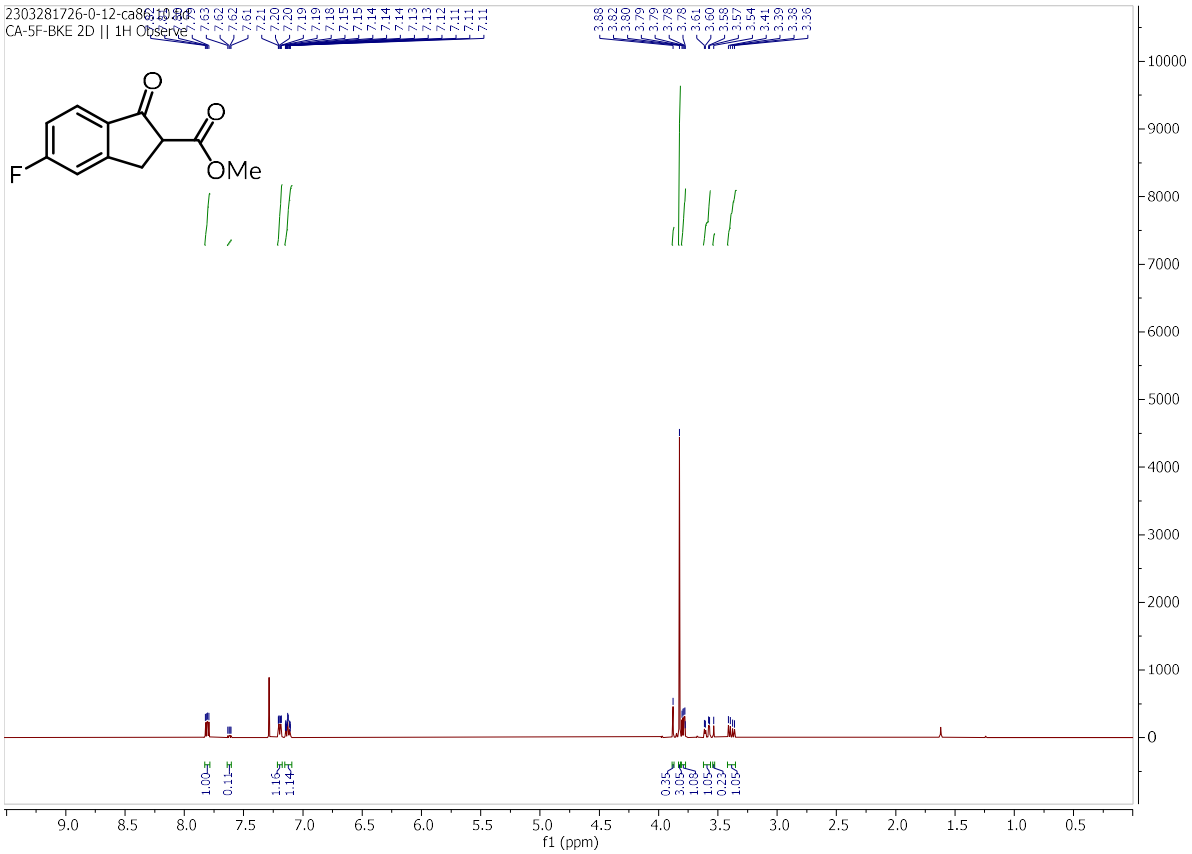
7.2 Starting Materials

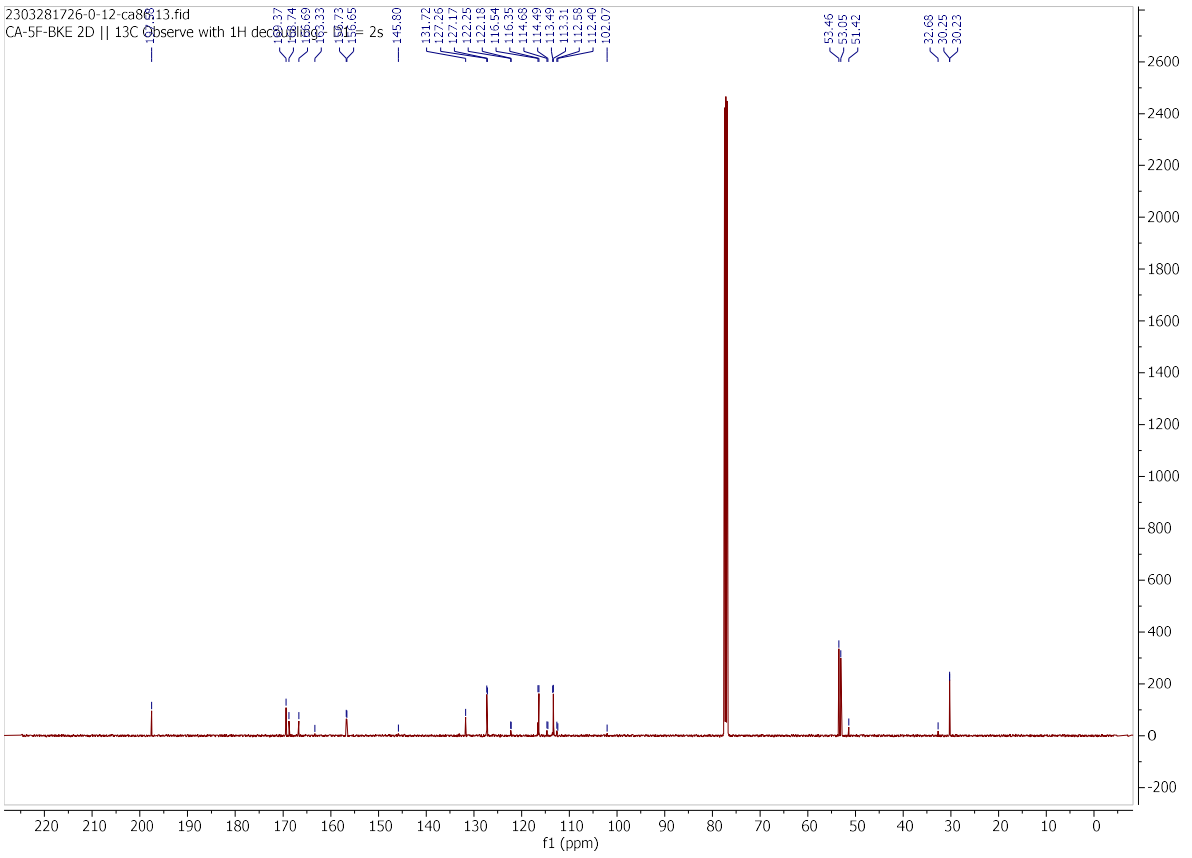
(1a)

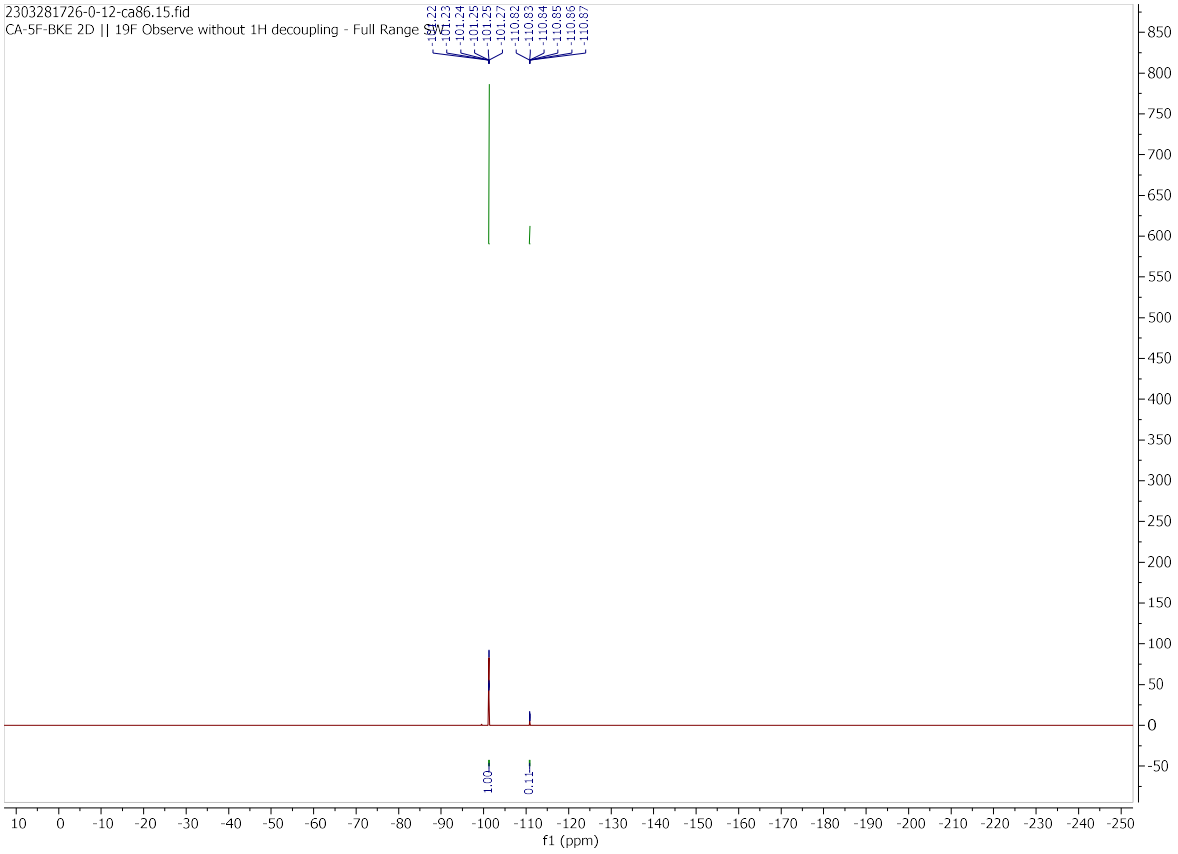




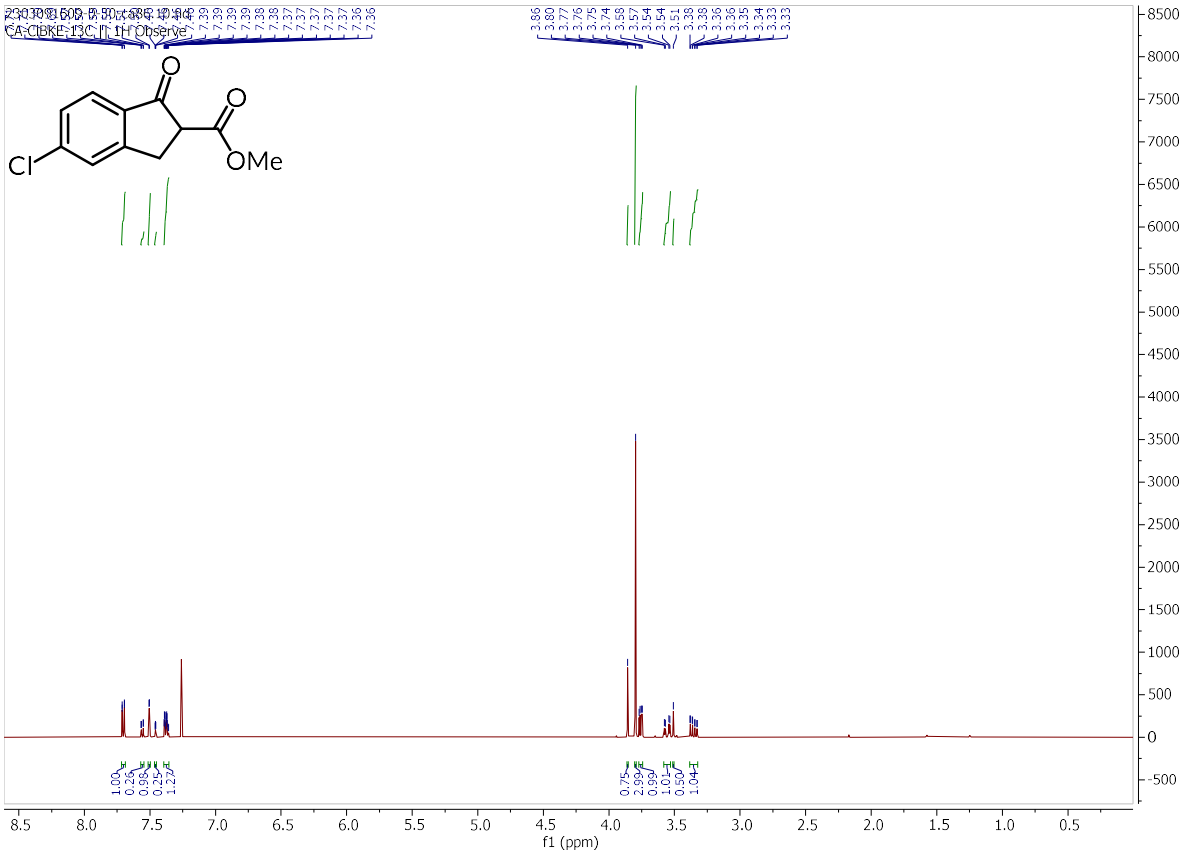
(1b)

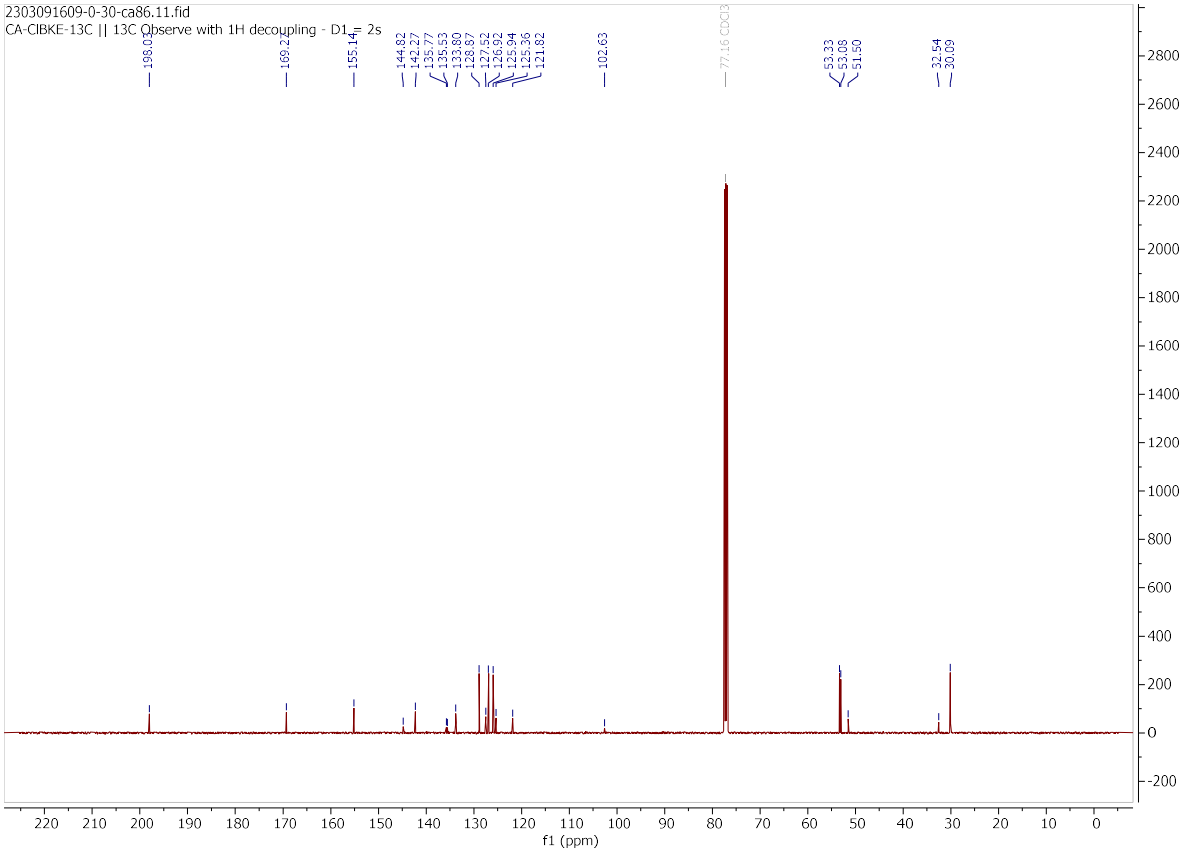

2303281726-0-12-ca86.10.84
CA-5F-BKE 2D || 1H Observe
F
O
O
OMe
f1 (ppm)


2303281726-0-12-ca86.13.fid
CA-5F-BKE 2D || 13C Observe with 1H decoupling
f1 (ppm)

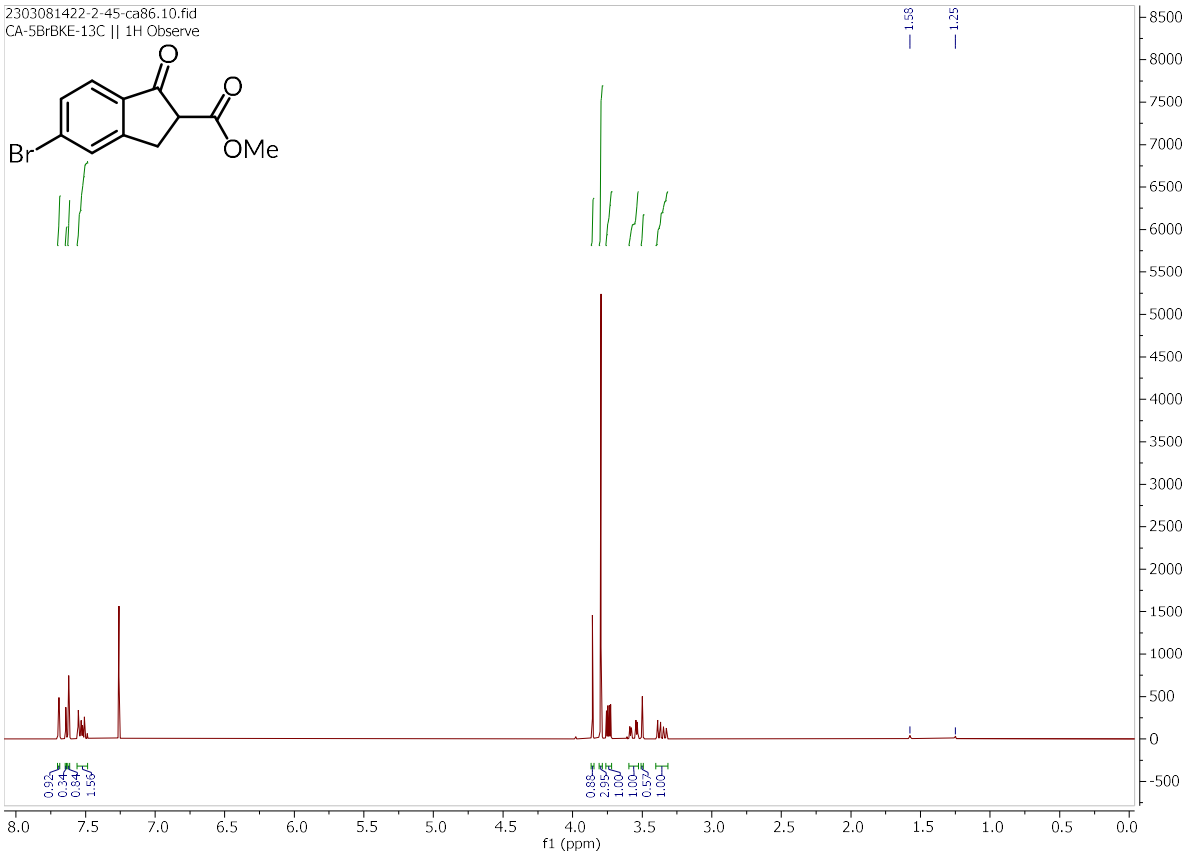

2303281726-0-12-ca86.15.fid
CA-5F-BKE 2D || 19F Observe without 1H decoupling - Full Range SW
-101.22
-101.23
-101.24
-101.25
-101.25
-101.27
-110.82
-110.83
-110.84
-110.85
-110.86
-110.87
1.00
0.11
f1 (ppm)

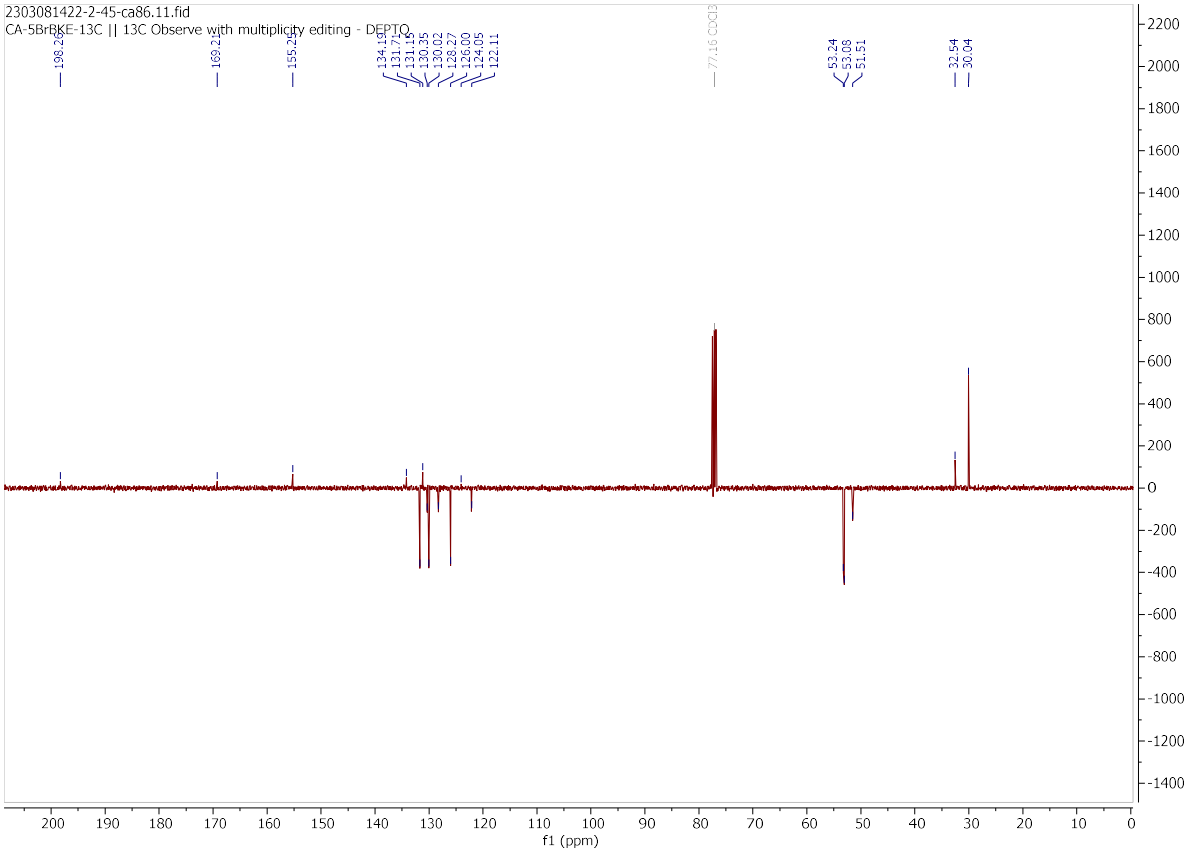
(1c)


CA-CLBKE-13C || 1H Observe
3.86
3.80
3.77
3.76
3.75
3.74
3.58
3.57
3.54
3.54
3.51
3.38
3.38
3.36
3.36
3.35
3.34
3.33
3.33
Cl
O
O
OMe
1.00
0.25
0.96
0.25
1.27
0.75
2.99
0.89
1.01
0.50
1.04
f1 (ppm)

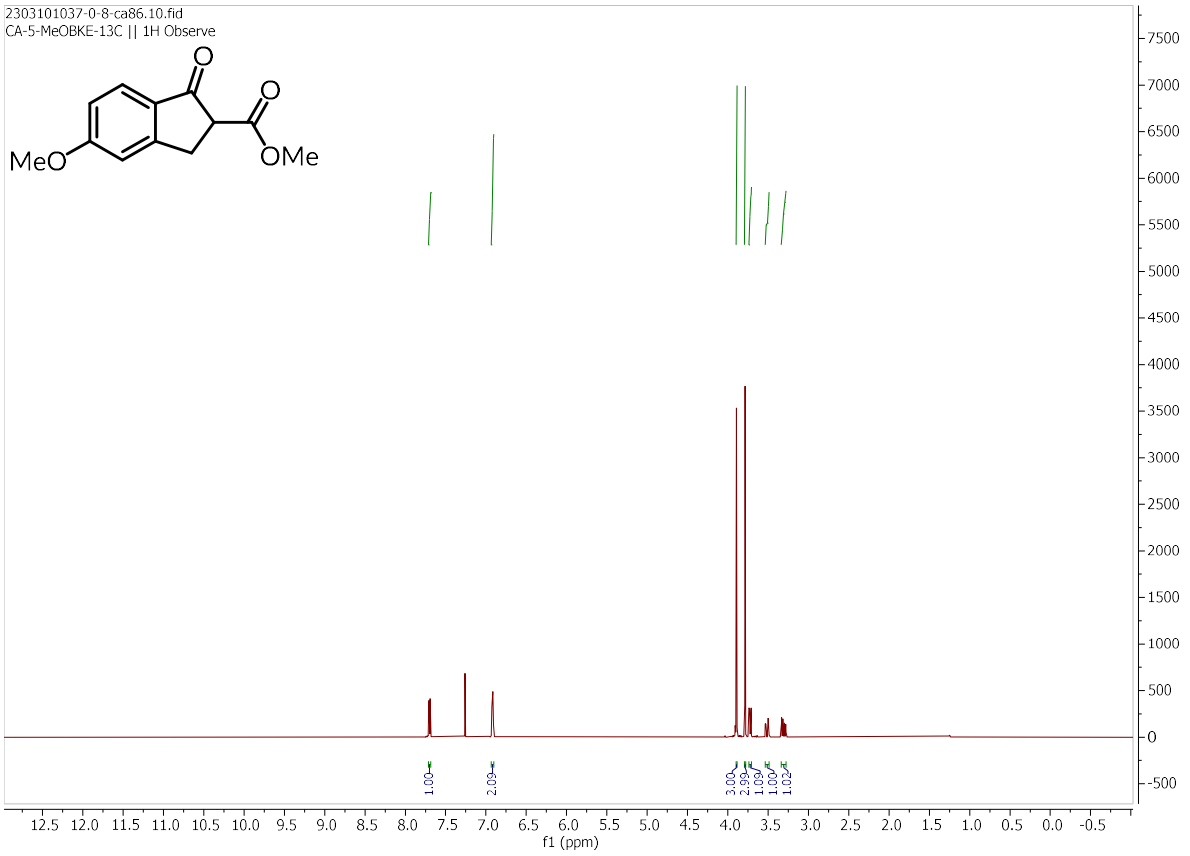

2303091609-0-30-ca86.11.fid
CA-ClBKE-13C || 13C Observe with 1H decoupling - D1 = 2s
198.03
169.27
155.14
144.82
142.27
135.77
135.53
133.80
128.87
127.52
126.92
126.34
125.35
121.82
102.63
77.16 CDCl3
53.33
53.08
51.50
32.54
30.09
f1 (ppm)

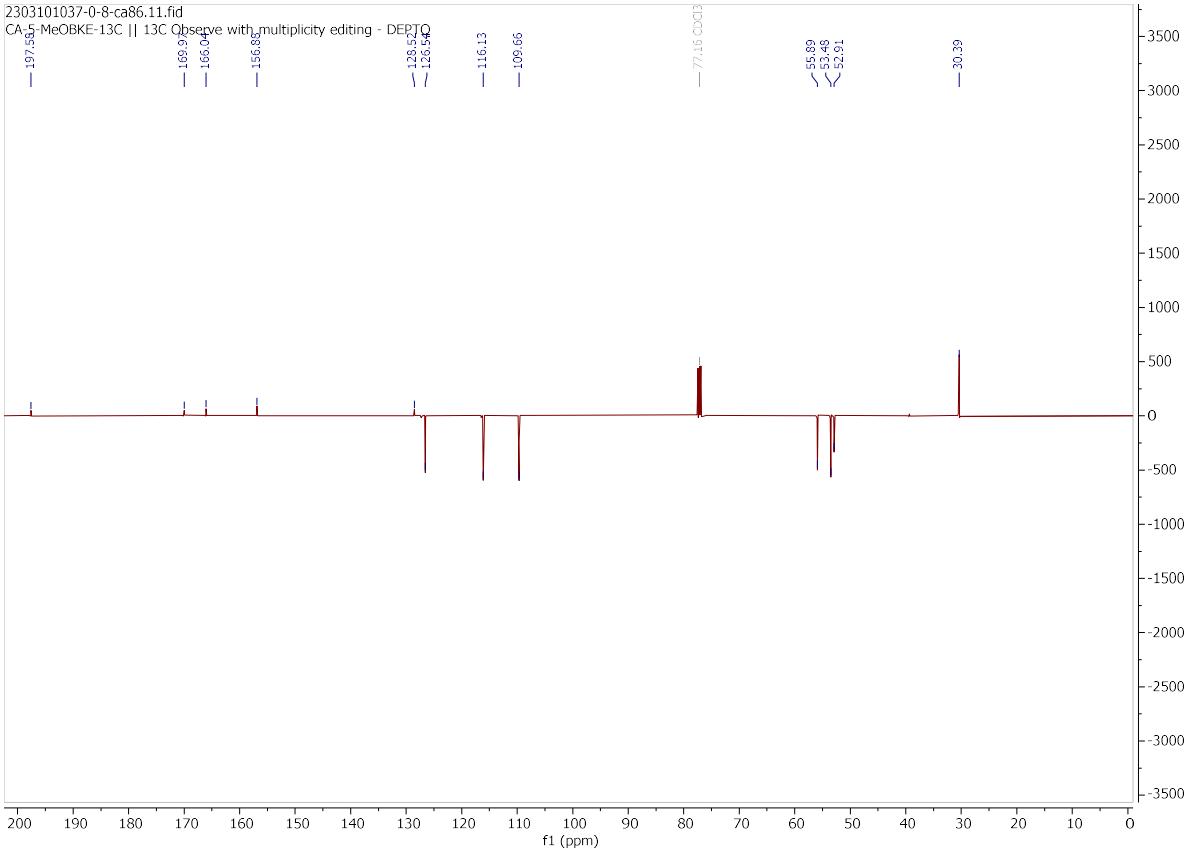
(1d)


2303081422-2-45-ca86.10.fid
CA-5BrBKE-13C || 1H Observe
Br
O
O
OMe
1.58
1.25
f1 (ppm)

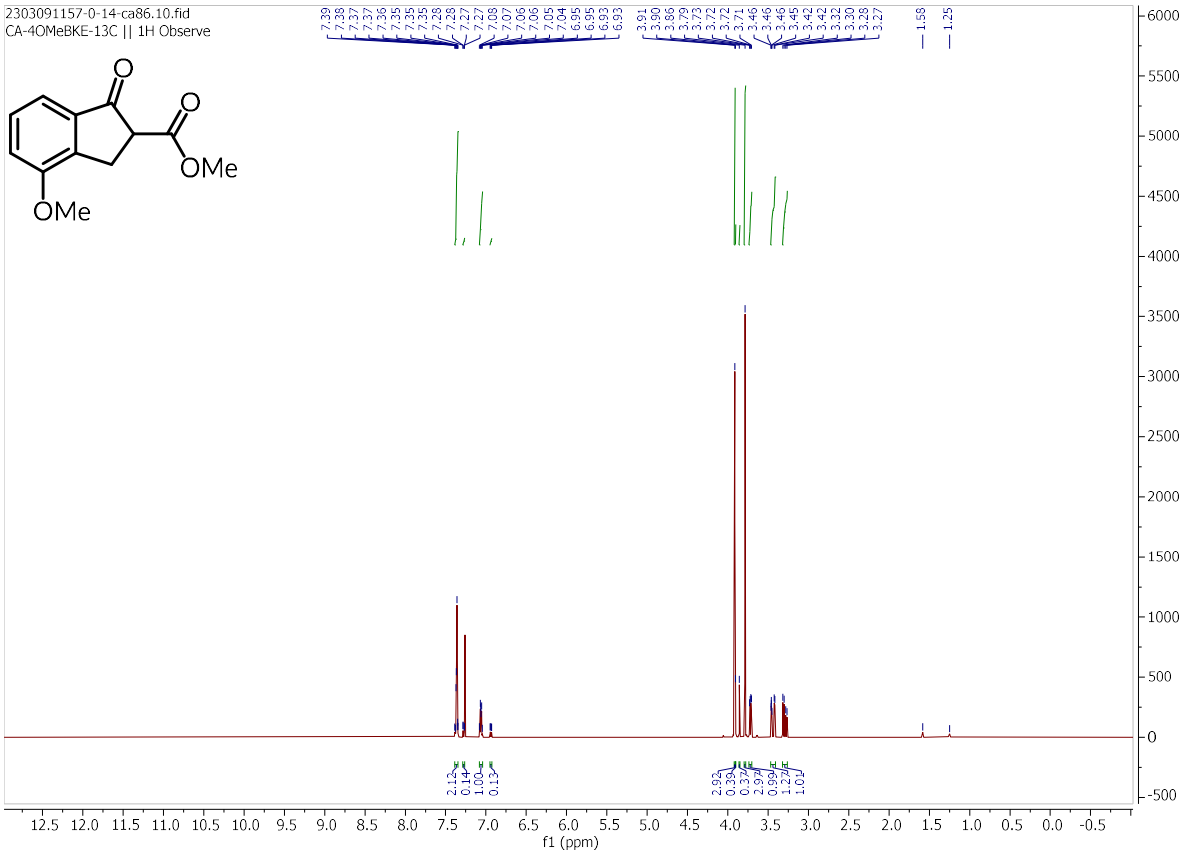

2303081422-2-45-ca86.11.fid
CA-5BrBKE-13C || 13C Observe with multiplicity editing - DEPTQ
198.26
169.21
155.25
134.19
131.74
131.15
130.35
130.02
128.27
126.00
124.05
122.11
77.16 CDCl3
53.24
53.09
51.51
32.54
30.04
f1 (ppm)

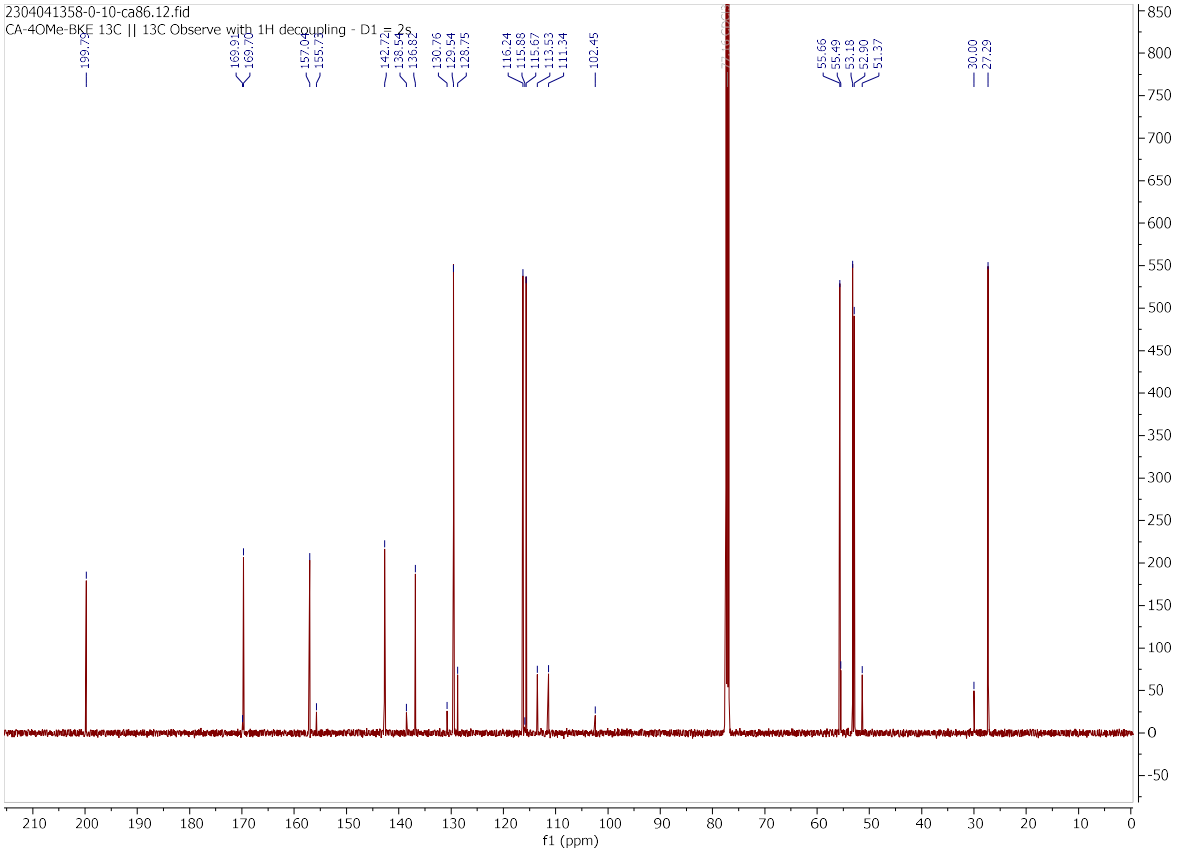
(1e)


2303101037-0-8-ca86.10.fid
CA-5-MeOBKE-13C || 1H Observe
O
O
MeO
OMe
1.00
2.09
3.00
2.99
1.09
1.00
1.02
f1 (ppm)

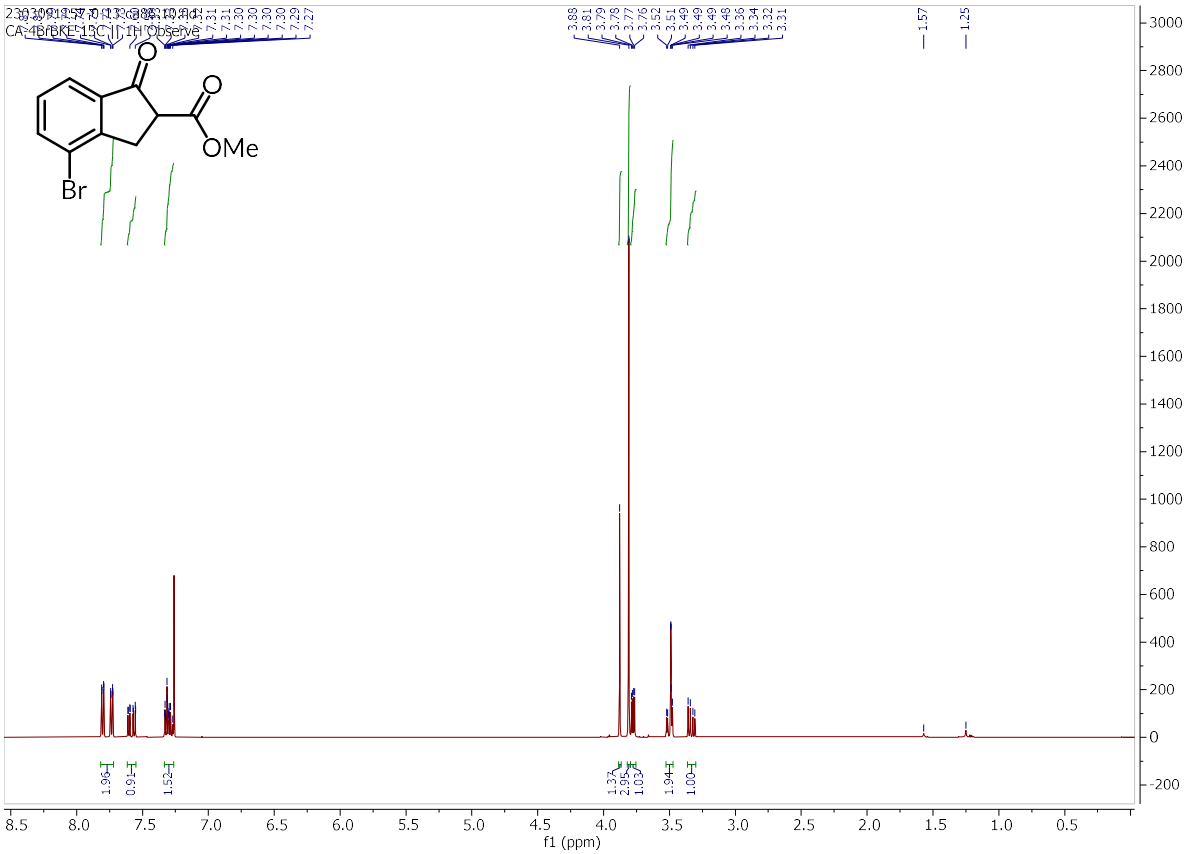

2303101037-0-8-ca86.11.fid
CA-5-MeOBKE-13C || 13C Observe with multiplicity editing - DEPTQ
197.58
169.97
166.04
156.85
128.52
126.54
116.13
109.66
77.16 CDCl3
55.89
53.48
52.91
30.39
f1 (ppm)

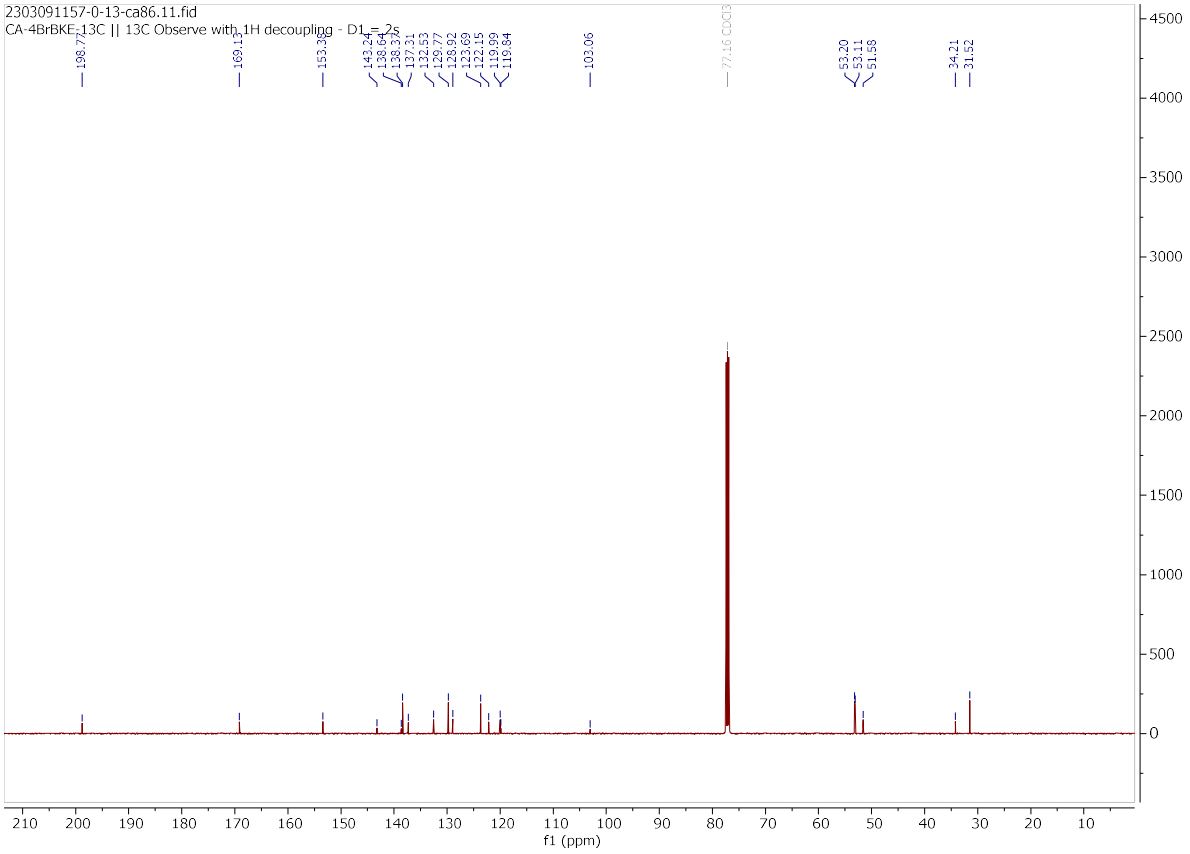
(1f)


2303091157-0-14-ca86.10.fid
CA-4OMeBKE-13C || 1H Observe
O
O
OMe
OMe
7.39
7.38
7.37
7.37
7.36
7.35
7.35
7.35
7.28
7.28
7.27
7.27
7.08
7.07
7.06
7.06
7.05
7.04
6.95
6.95
6.93
6.93
3.91
3.90
3.86
3.79
3.73
3.72
3.72
3.71
3.46
3.46
3.45
3.42
3.32
3.30
3.28
3.27
1.58
1.25
2.12
0.14
1.00
0.13
2.92
0.39
0.37
2.97
0.99
1.29
1.01
f1 (ppm)

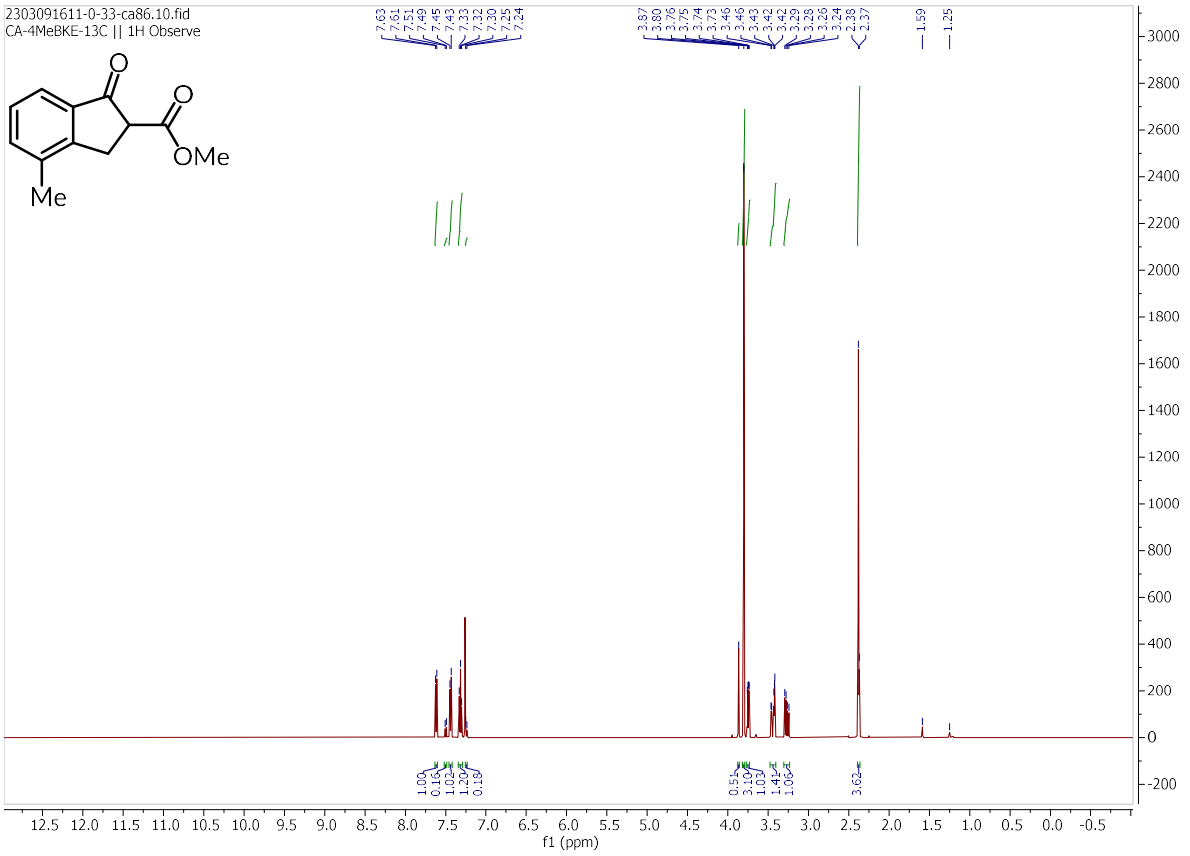

2304041358-0-10-ca86.12.fid
CA-4OMe-BKF 13C || 13C Observe with 1H decoupling - D1 2s
199.79
169.91
169.70
157.04
155.72
142.74
138.54
136.82
130.76
129.54
128.75
116.24
115.88
115.67
113.53
111.34
102.45
77.16
55.66
55.49
53.18
52.90
51.37
30.00
27.29
f1 (ppm)

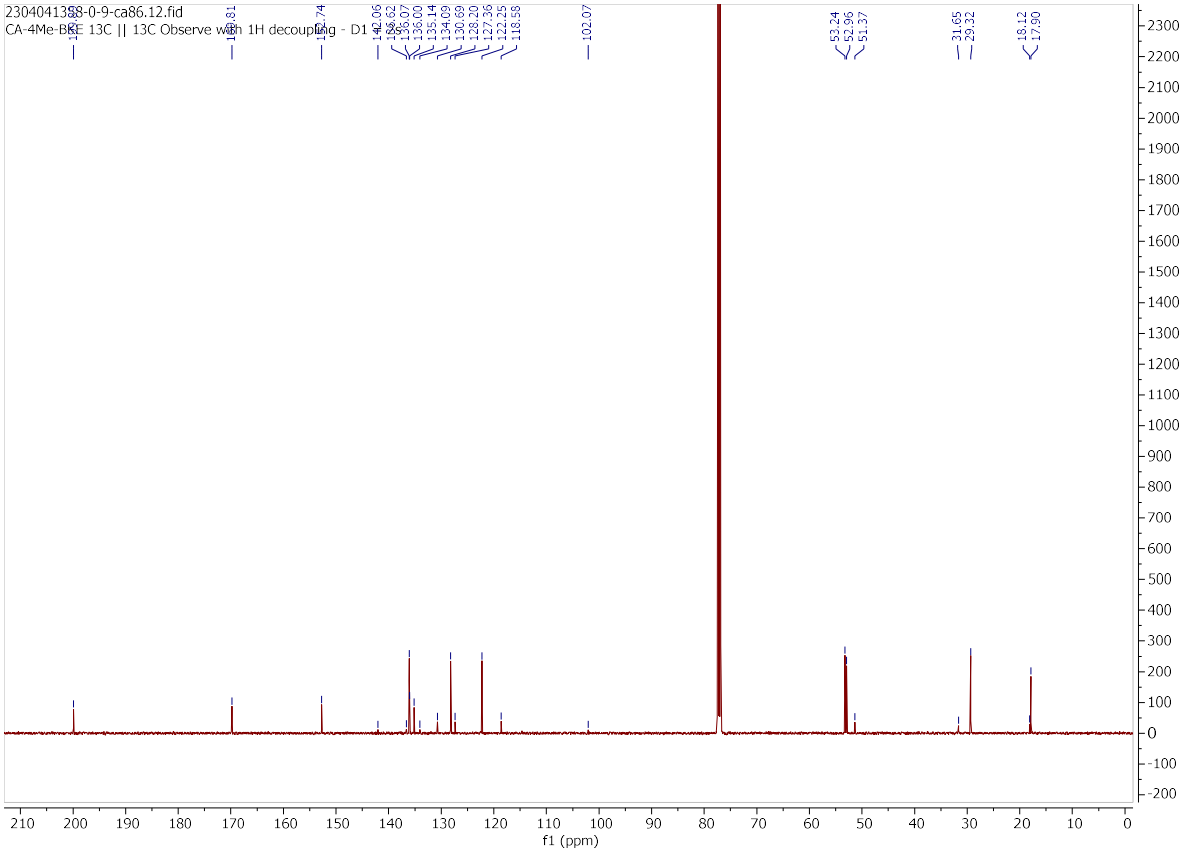
(1g)


CA-4BrBKF15C || 1H Observe
O
O
OMe
Br
7.31
7.31
7.30
7.30
7.30
7.29
7.27
3.88
3.81
3.79
3.78
3.77
3.76
3.52
3.51
3.49
3.49
3.49
3.48
3.36
3.34
3.32
3.31
1.57
1.25
1.96
0.91
1.52
1.37
2.95
1.03
1.94
1.00
f1 (ppm)

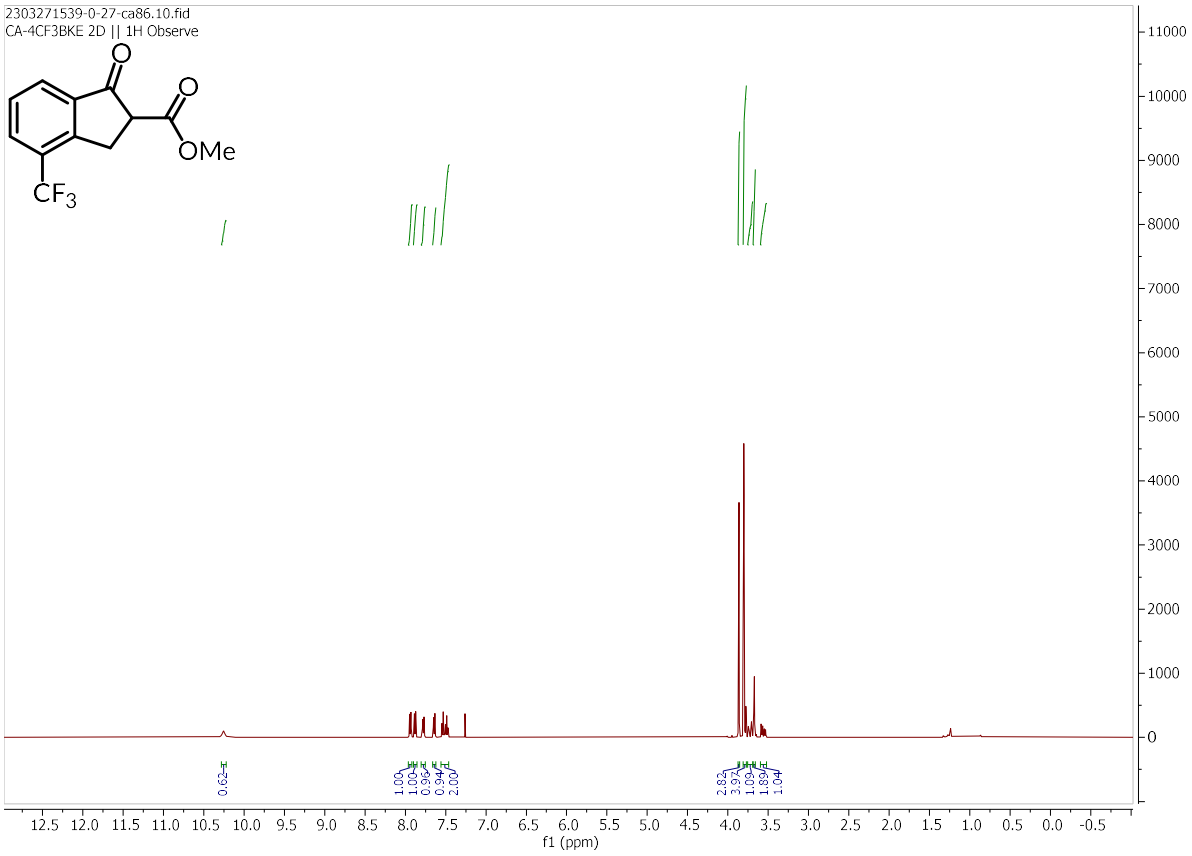

2303091157-0-13-ca86.11.fid
CA-4BrBKE-13C || 13C Observe with 1H decoupling - D1 = 2s
198.77
169.13
153.36
143.24
138.64
138.33
137.31
132.53
129.77
128.92
123.69
122.15
119.99
119.84
103.06
77.16 CDCl3
53.20
53.11
51.58
34.21
31.52
f1 (ppm)

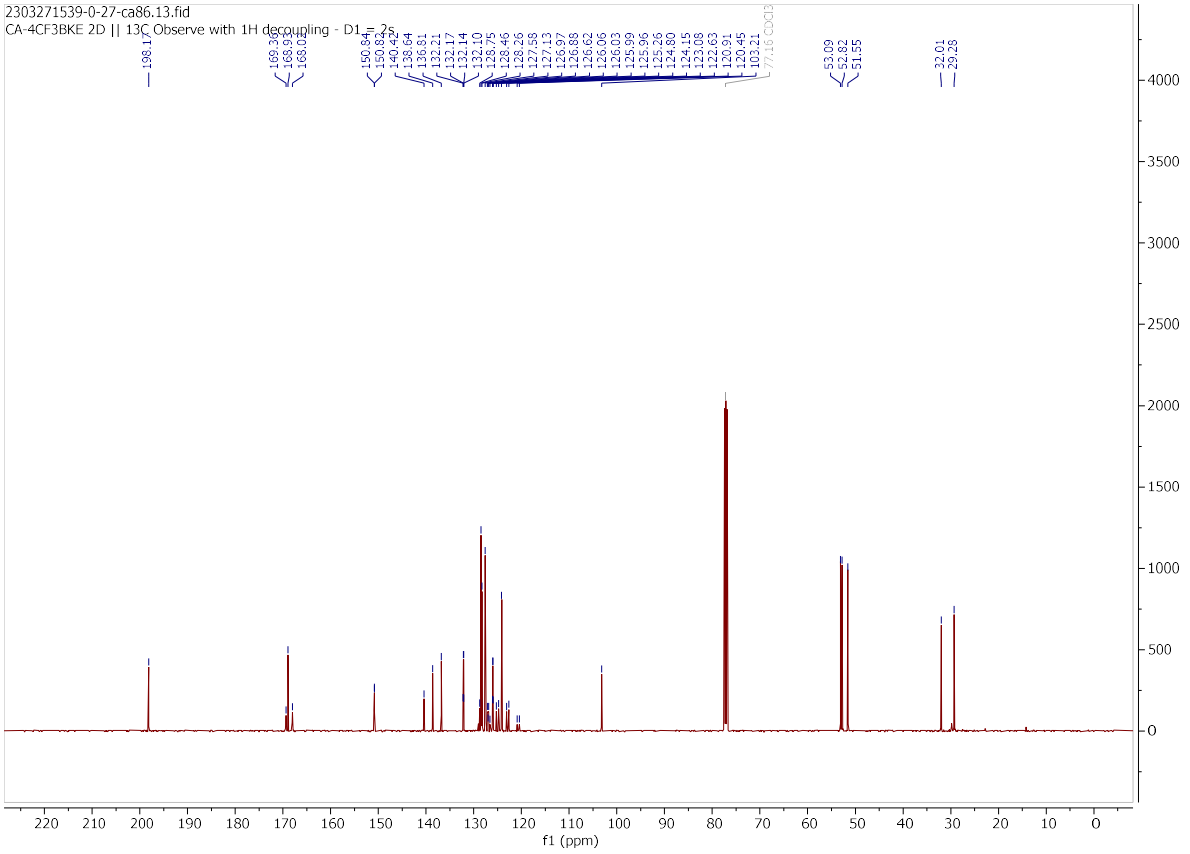
(1h)

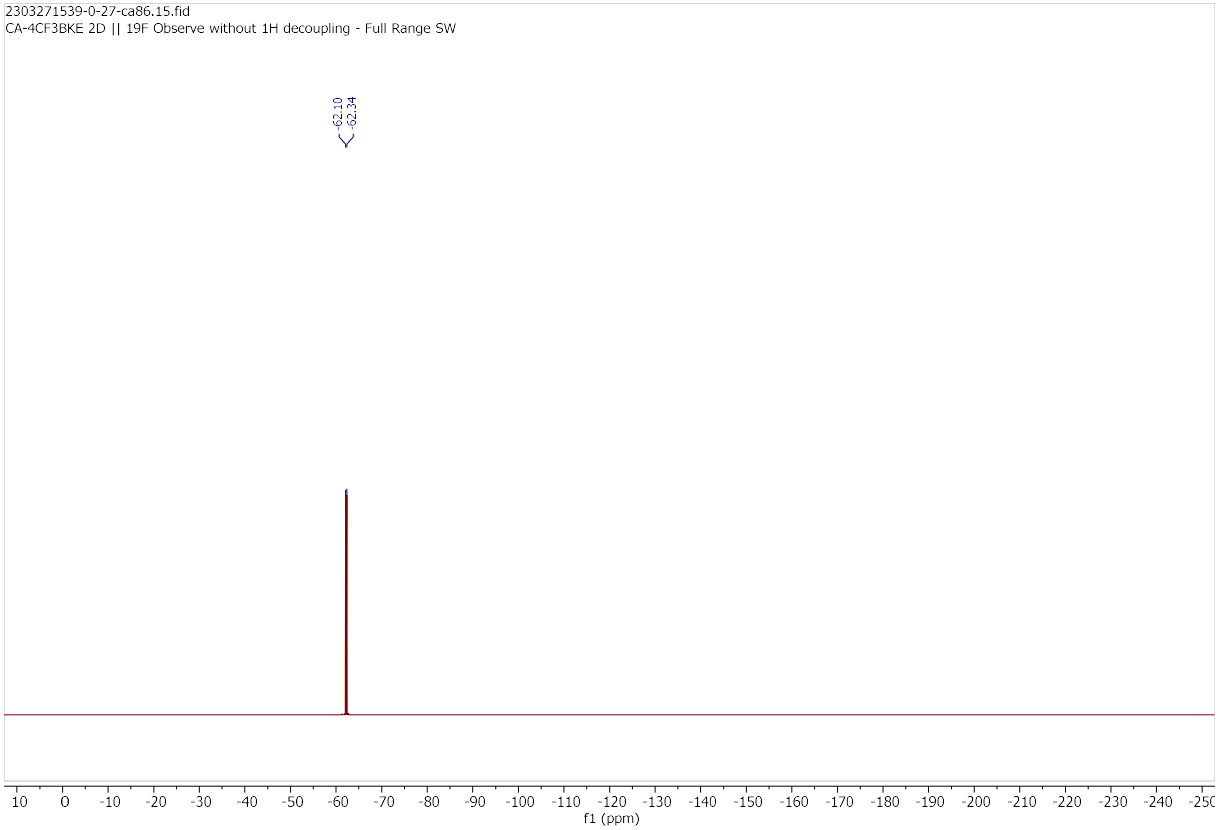

2303091611-0-33-ca86.10.fid
CA-4MeBKE-13C || 1H Observe
O
O
OMe
Me
7.63
7.61
7.51
7.49
7.45
7.43
7.33
7.32
7.30
7.25
7.24
3.87
3.80
3.76
3.75
3.74
3.73
3.46
3.43
3.42
3.42
3.29
3.28
3.26
3.24
2.38
2.37
1.59
1.25
1.00
0.16
1.02
1.20
0.18
0.51
3.10
1.03
1.41
1.05
3.62
f1 (ppm)


2304041388-0-9-ca86.12.fid
CA-4Me-BKE 13C || 13C Observe with 1H decoupling - D1
199.88
169.81
153.74
142.06
136.62
136.07
136.00
135.14
134.09
130.69
128.20
127.36
122.25
118.58
102.07
53.24
52.96
51.37
31.65
29.32
18.12
17.90
f1 (ppm)

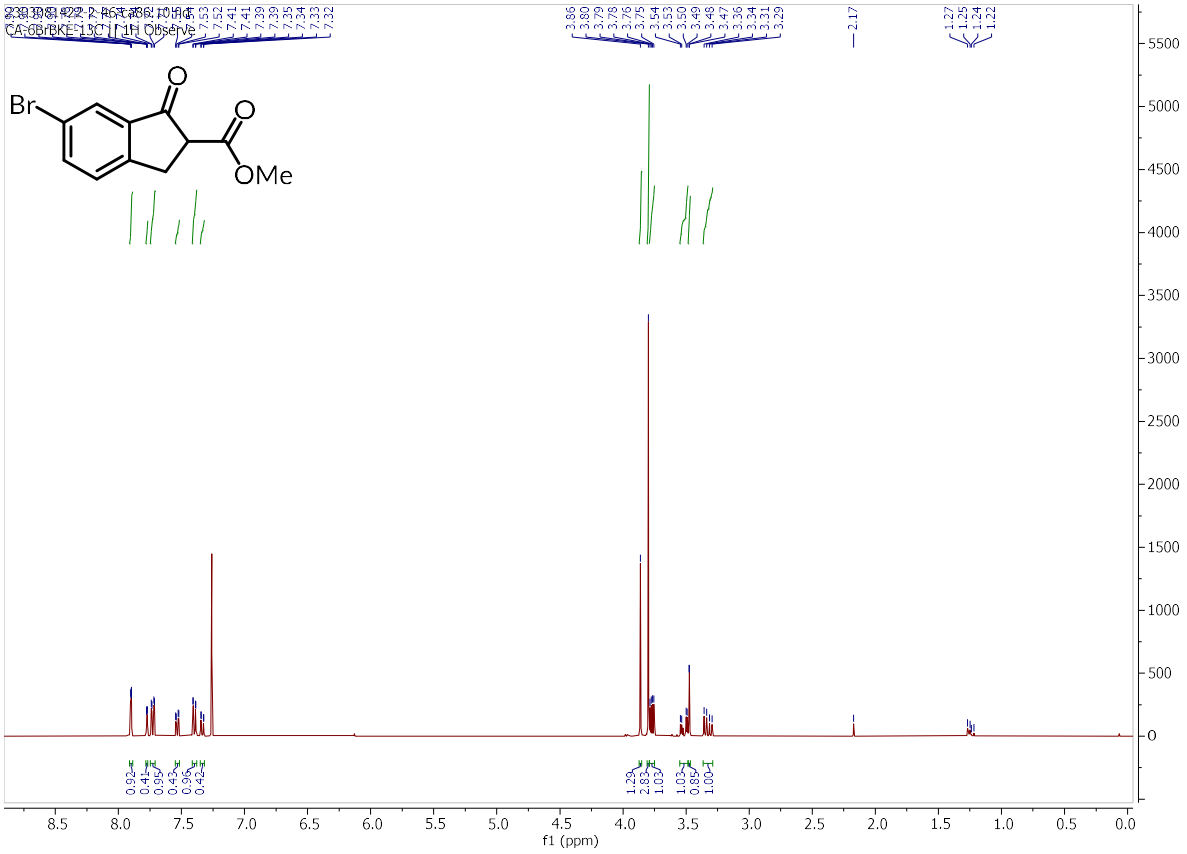
(1i)

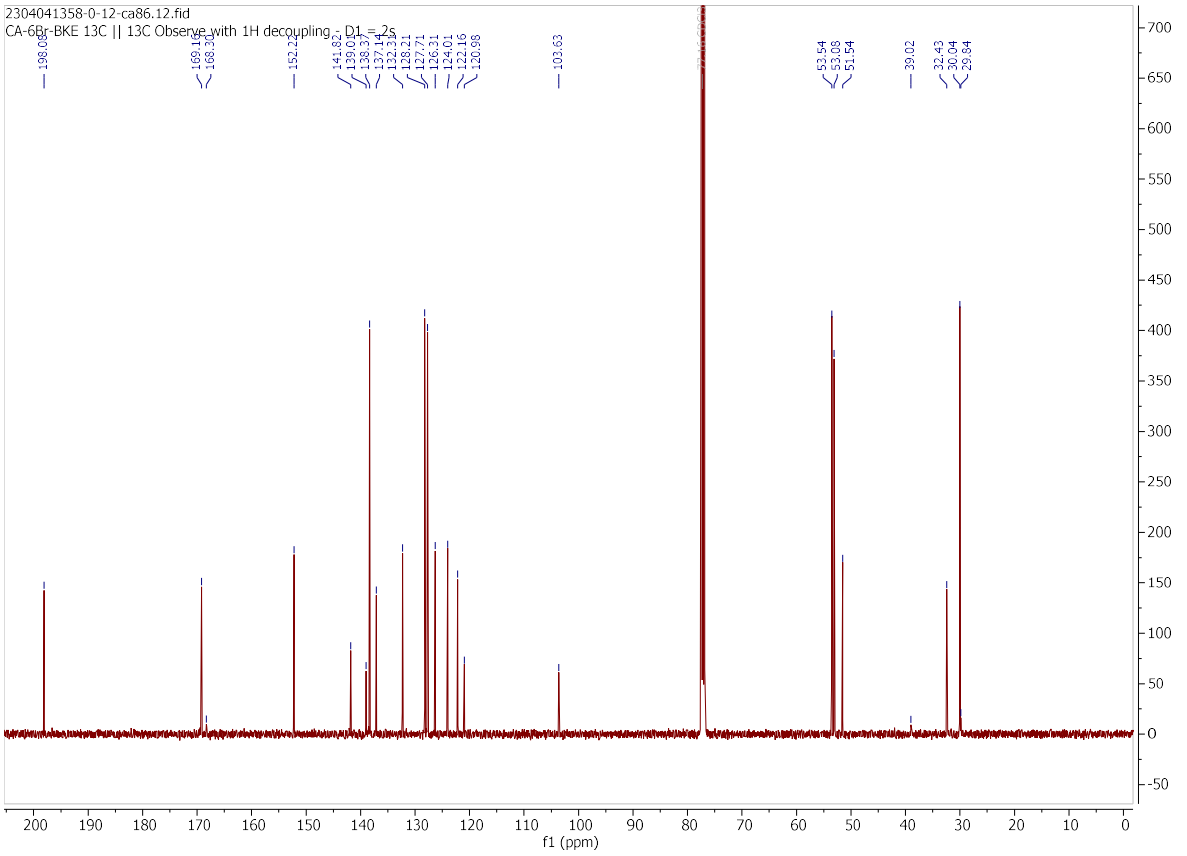

2303271539-0-27-ca86.10.fid
CA-4CF3BKE 2D || 1H Observe
O
O
OMe
CF3
0.62
1.00
1.06
0.96
0.94
2.00
2.82
2.97
1.08
1.89
1.04
f1 (ppm)


2303271539-0-27-ca86.13.fid
CA-4CF3BKE 2D || 13C Observe with 1H decoupling - D1 = 2s
198.17
169.36
168.93
168.08
150.84
150.83
140.42
138.64
136.81
132.21
132.17
132.14
132.10
128.75
128.46
128.26
127.58
127.13
126.97
126.88
126.62
126.06
126.03
125.99
125.96
125.26
124.80
124.15
123.08
122.63
120.91
120.45
103.21
77.16 CDCl3
53.09
52.82
51.55
32.01
29.28
4000
3500
3000
2500
2000
1500
1000
500
0
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

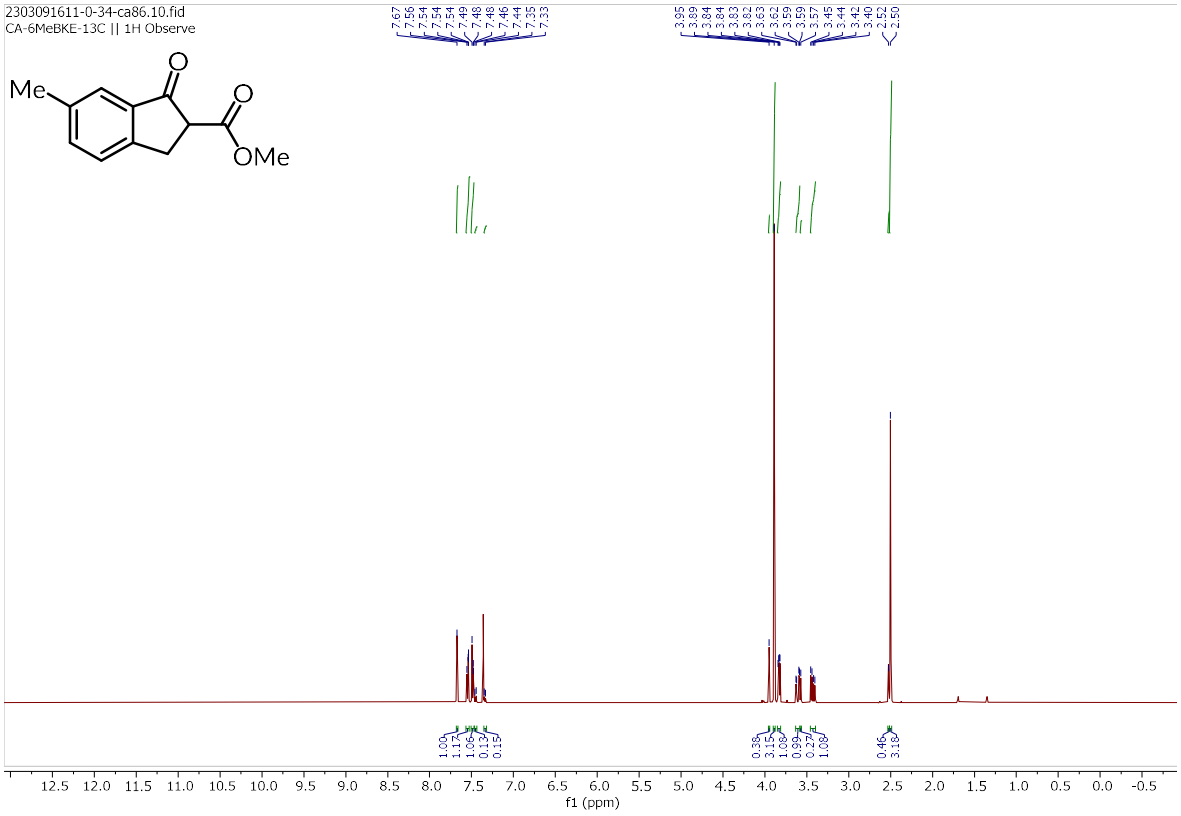

2303271539-0-27-ca86.15.fid
CA-4CF3BKE 2D || 19F Observe without 1H decoupling - Full Range SW
62.10
62.34
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 -250
f1 (ppm)

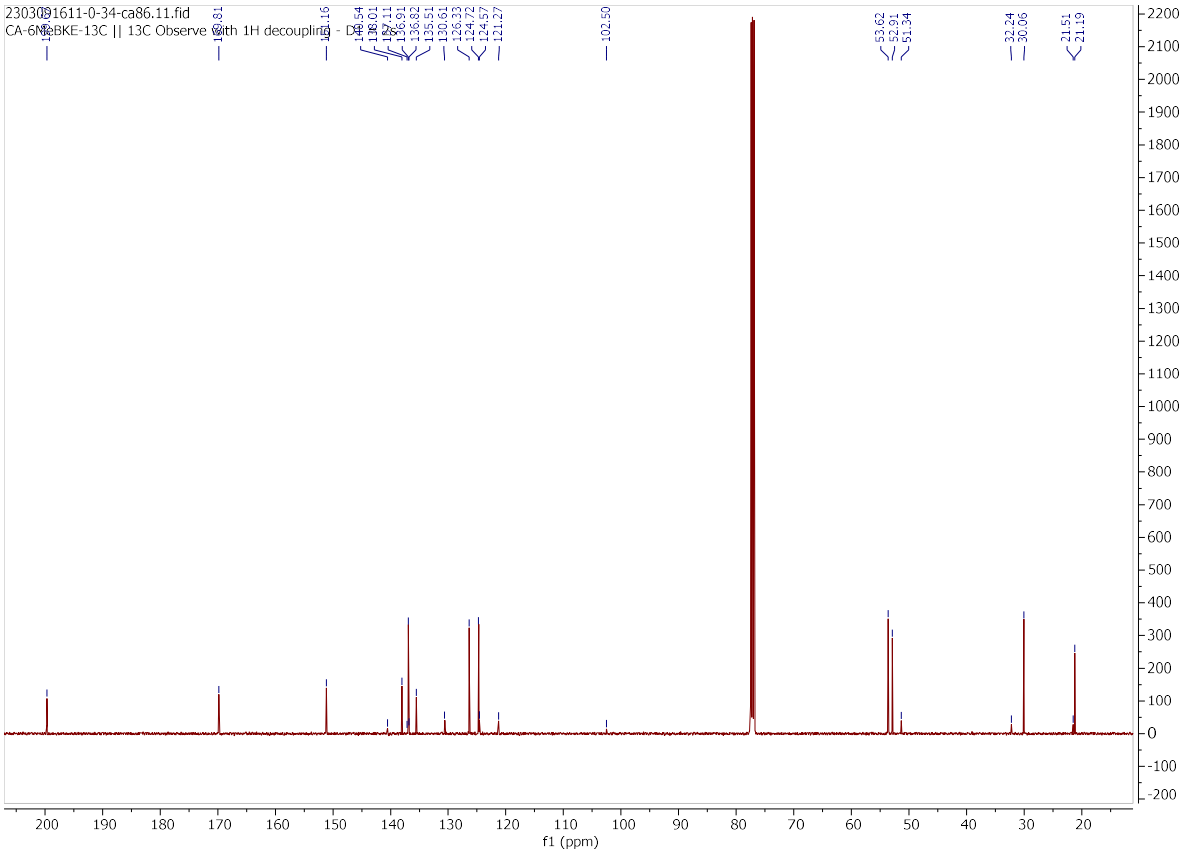
(1j)


Br
O
O
OMe
f1 (ppm)

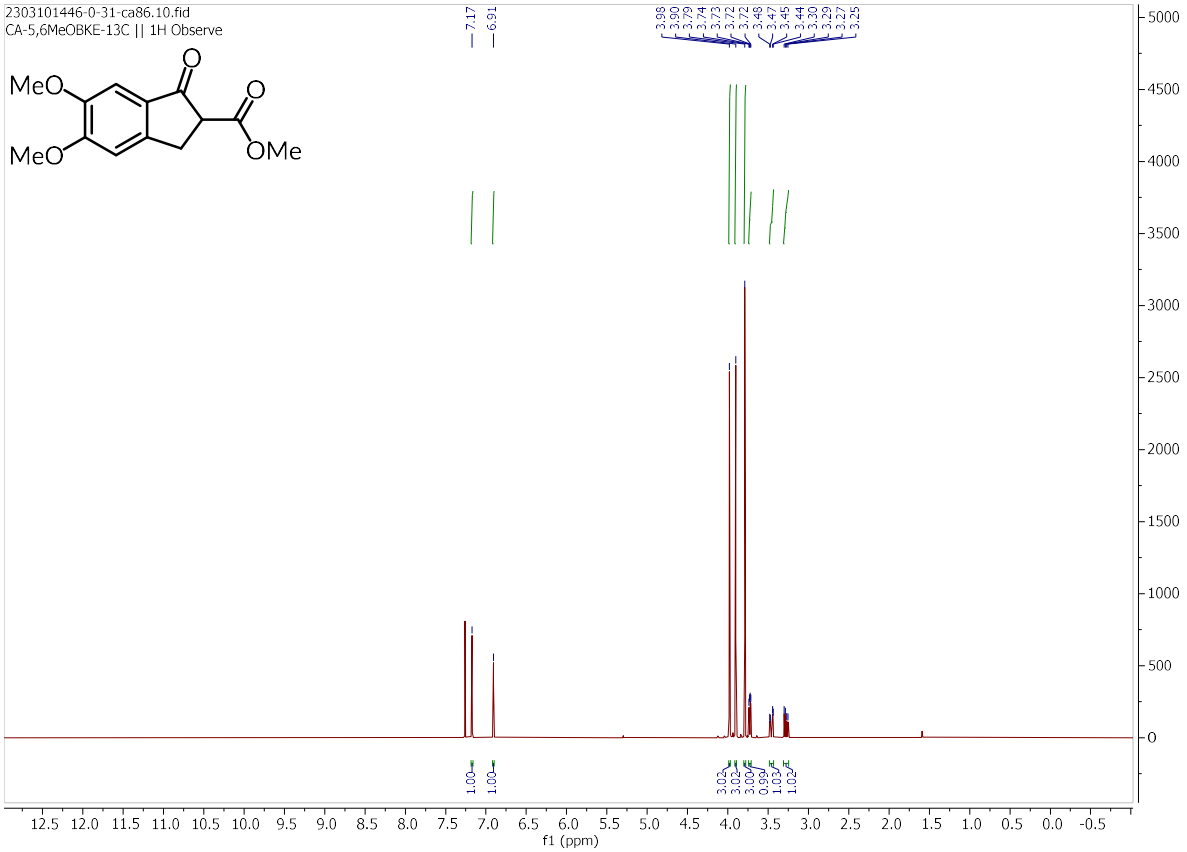

2304041358-0-12-ca86.12.fid
CA-6Br-BKE 13C || 13C Observe with 1H decoupling - D1 = 2s
f1 (ppm)

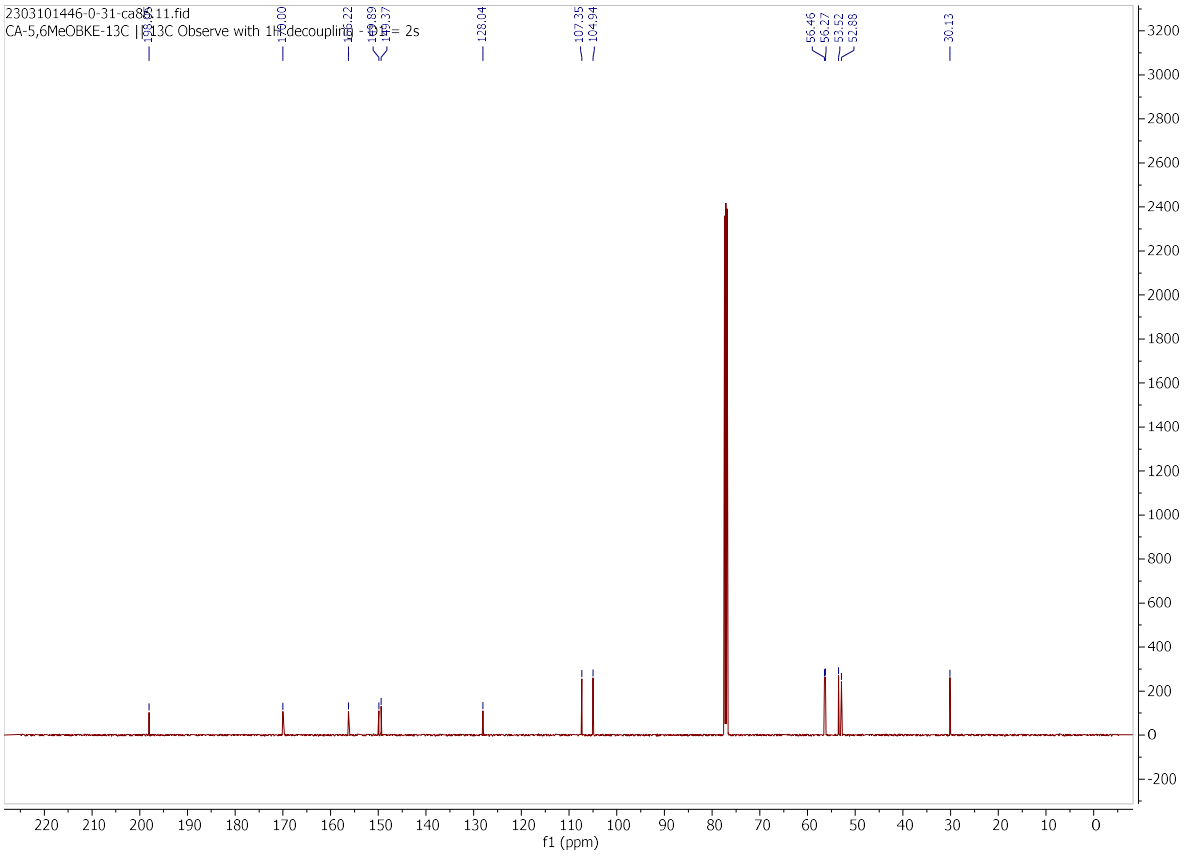
(1k)


2303091611-0-34-ca86.10.fid
CA-6MeBKE-13C || 1H Observe
Me
O
O
OMe
f1 (ppm)

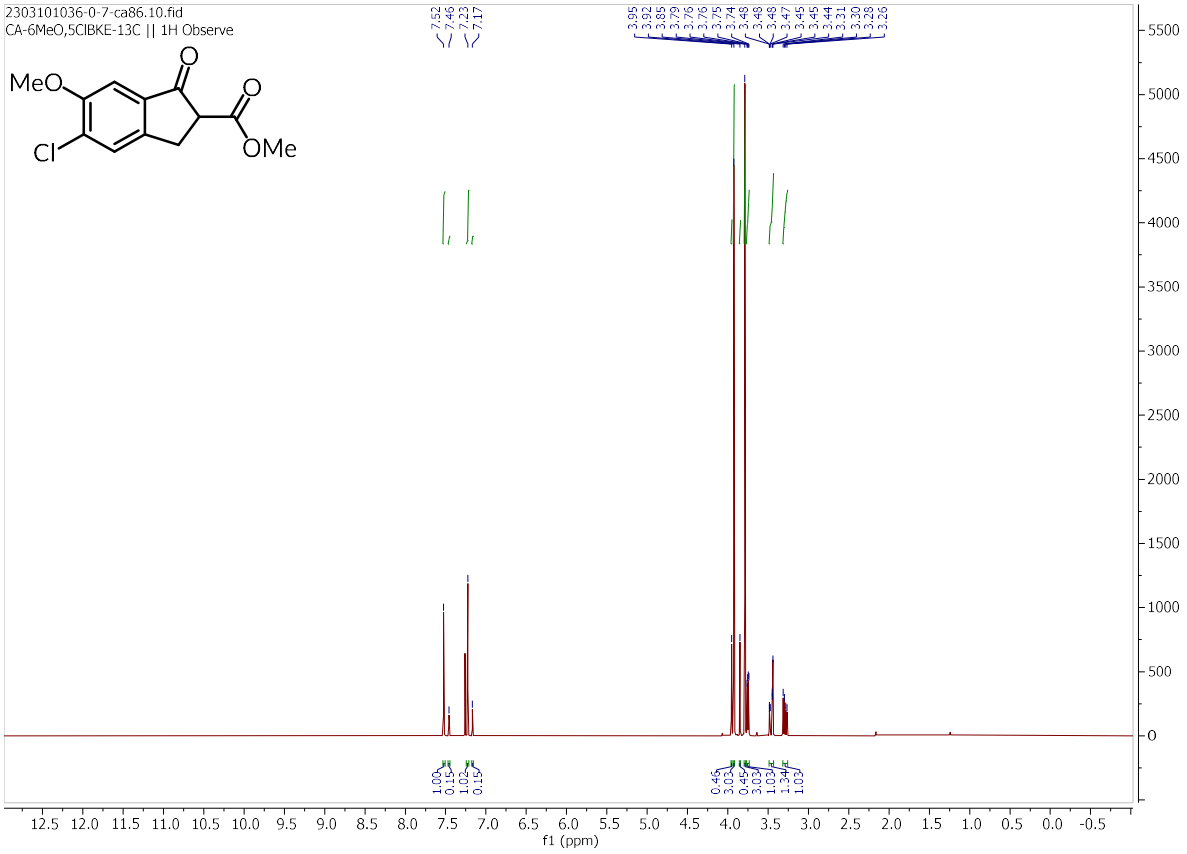

2303091611-0-34-ca86.11.fid
CA-6MeBKE-13C || 13C Observe with 1H decoupling
f1 (ppm)

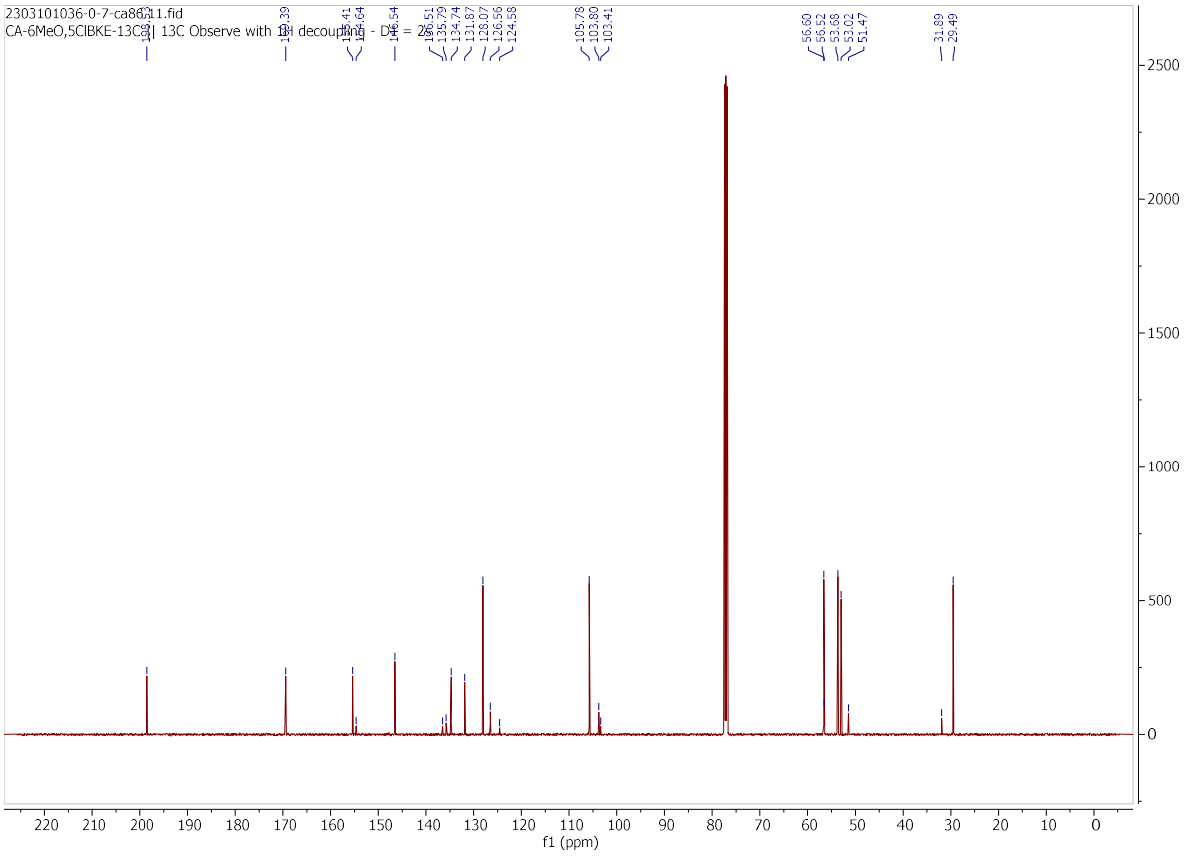
(1l)


2303101446-0-31-ca86.10.fid
CA-5,6MeOBKE-13C || 1H Observe
MeO
MeO
O
O
OMe
7.17
6.91
3.98
3.90
3.79
3.74
3.73
3.72
3.72
3.48
3.47
3.45
3.44
3.30
3.29
3.27
3.25
1.00
1.00
3.03
3.02
3.02
3.00
3.00
1.03
1.02
f1 (ppm)

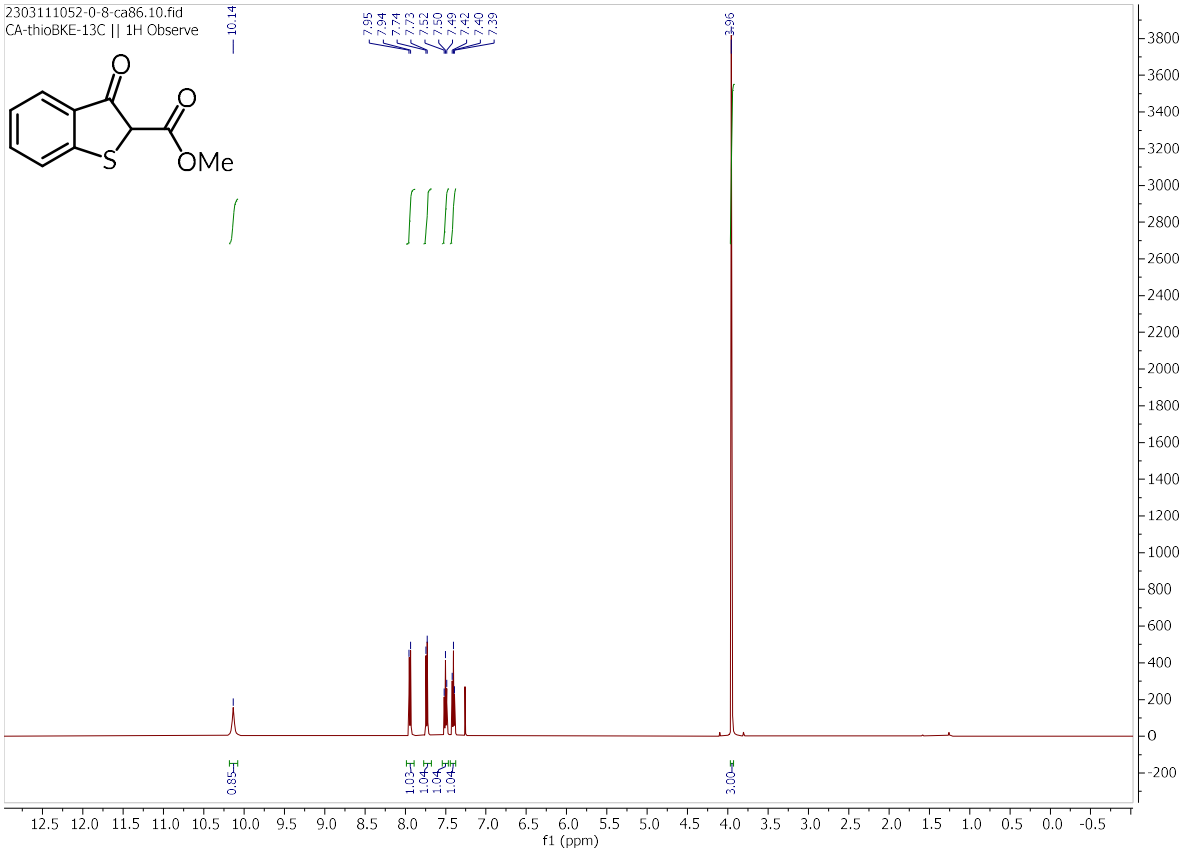

2303101446-0-31-ca86.11.fid
CA-5,6MeOBKE-13C || 13C Observe with 1H decoupling 2s
170.00
165.22
149.89
149.37
128.04
107.35
104.94
56.46
56.27
53.52
52.88
30.13
f1 (ppm)

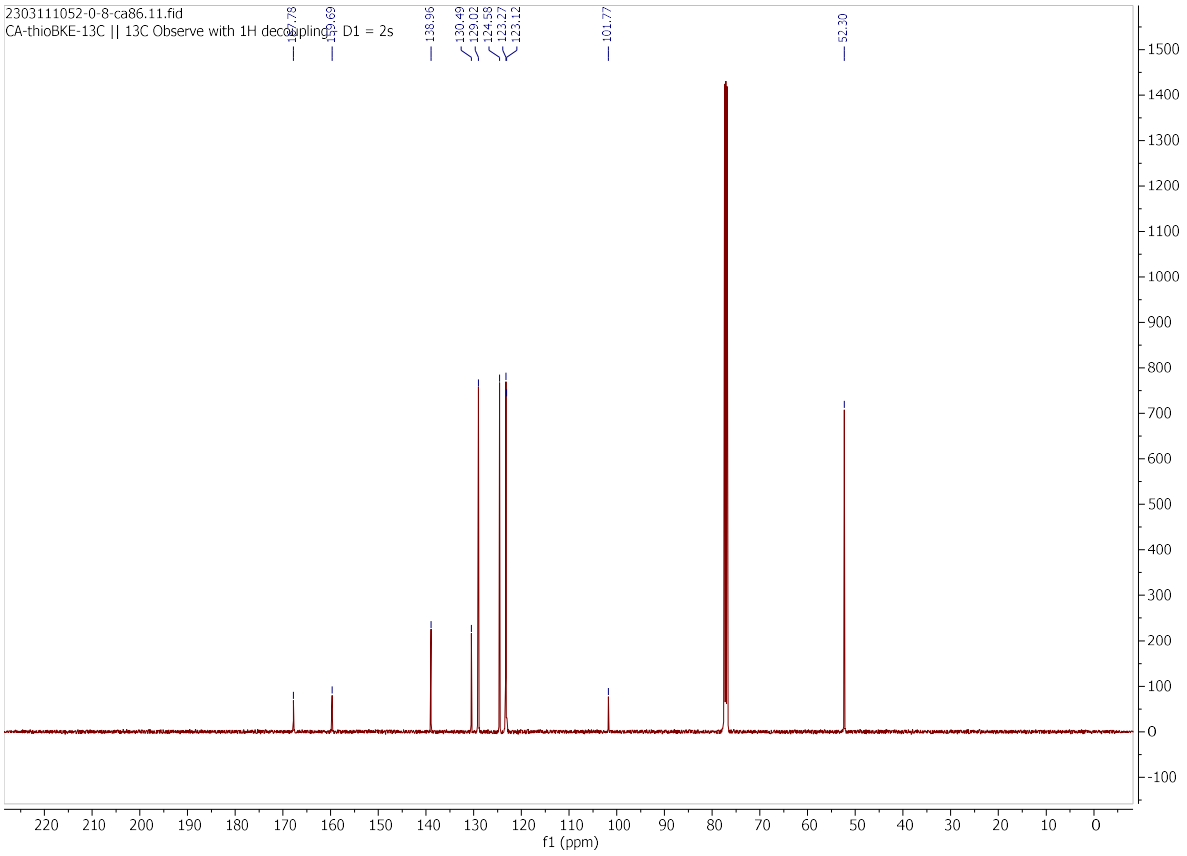
(1m)


2303101036-0-7-ca86.10.fid
CA-6MeO,5ClBKE-13C || 1H Observe
MeO
O
O
Cl
OMe
f1 (ppm)

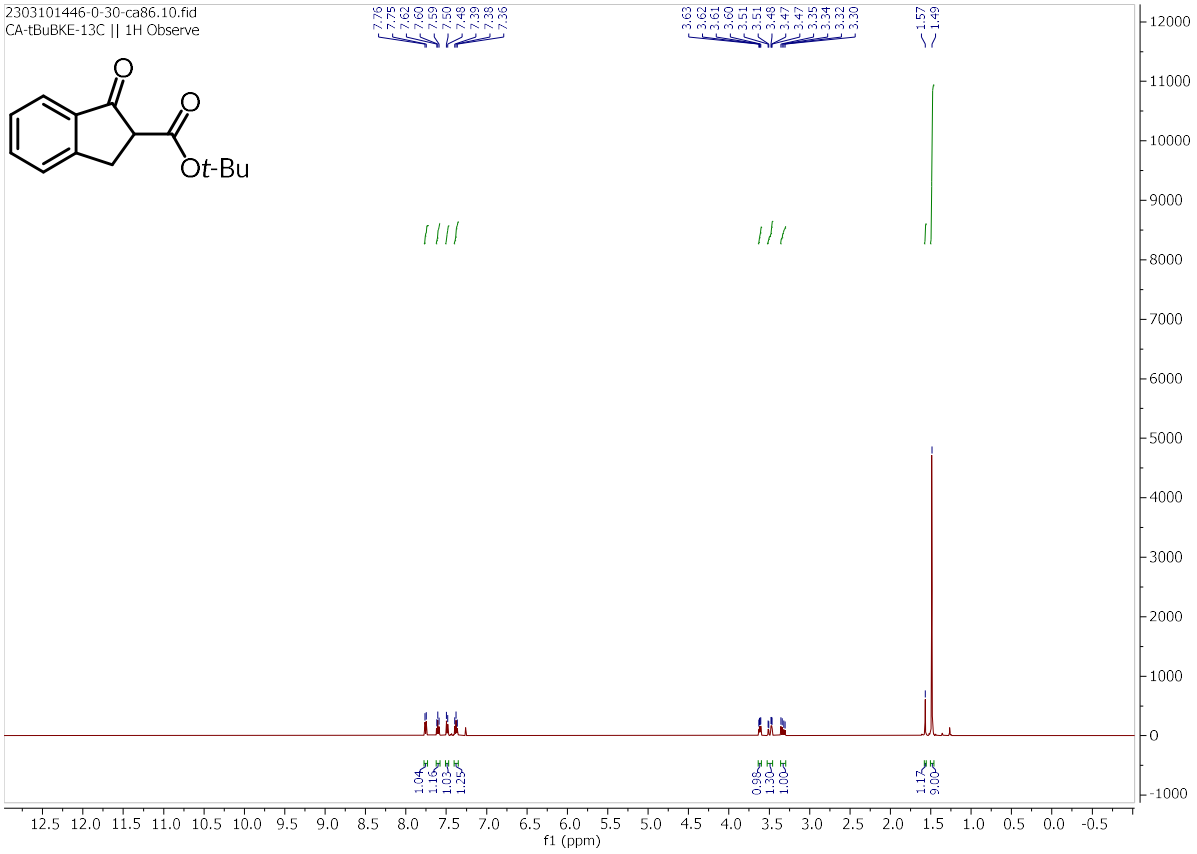

2303101036-0-7-ca86.11.fid
CA-6MeO,5ClBKE-13C || 13C Observe with 1H decoupling - DS = 2
f1 (ppm)

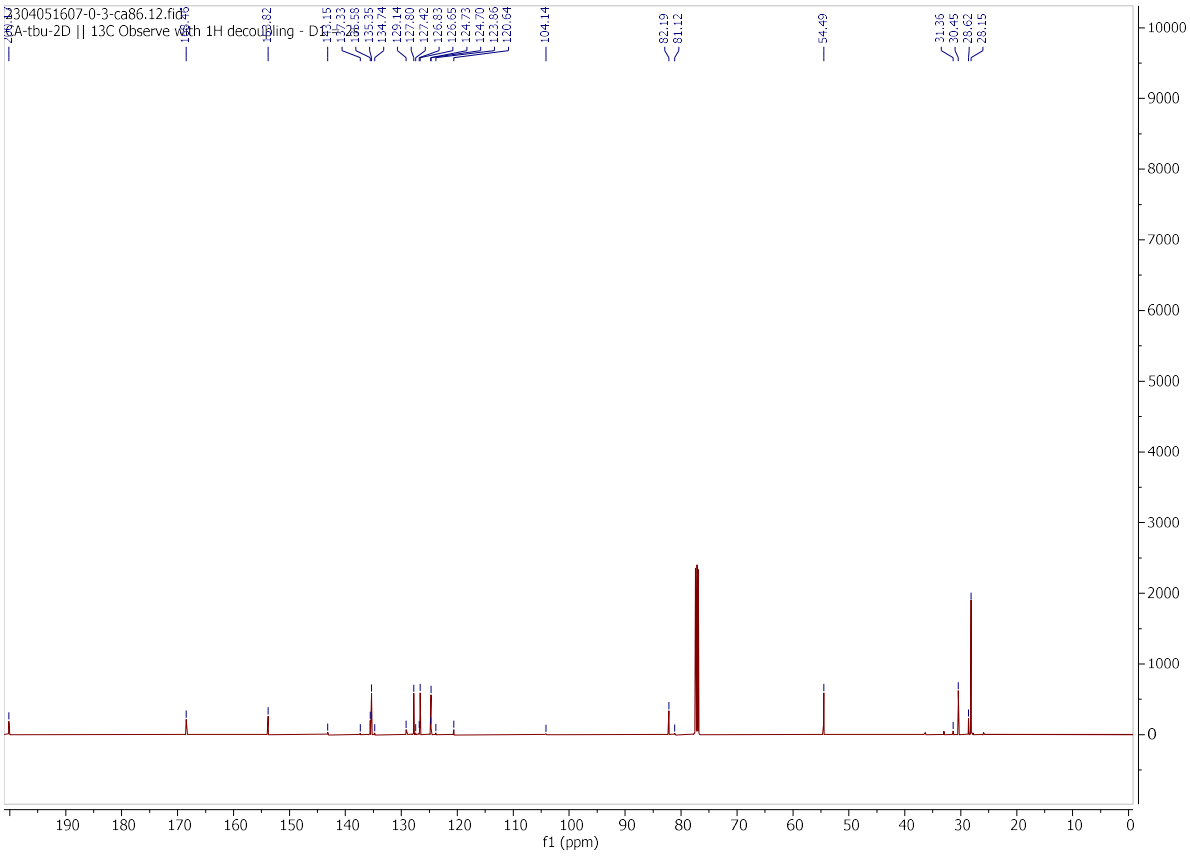
(1n)


2303111052-0-8-ca86.10.fid
CA-thioBKE-13C || 1H Observe
10.14
7.95
7.94
7.74
7.73
7.52
7.50
7.49
7.42
7.40
7.39
3.96
O
O
S
OMe
0.85
1.03
1.04
1.04
1.04
3.00
f1 (ppm)

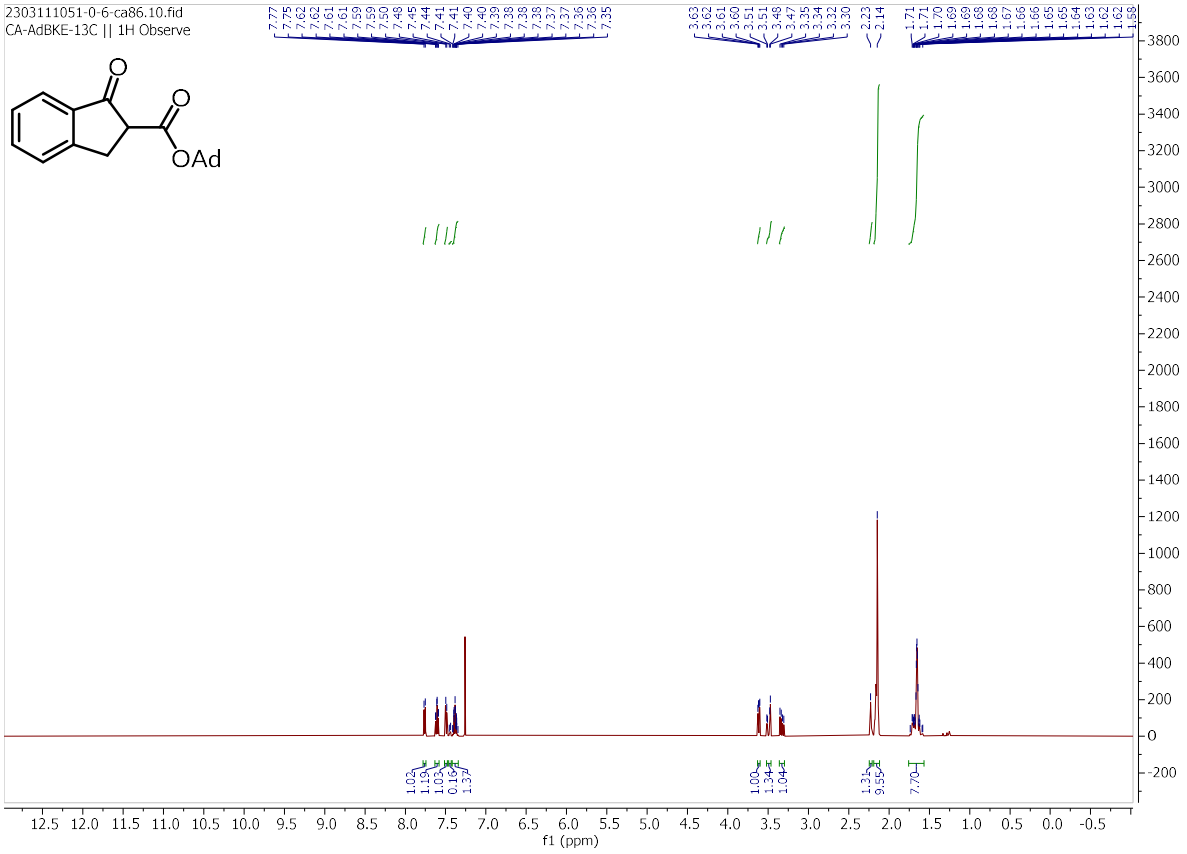

2303111052-0-8-ca86.11.fid
CA-thioBKE-13C || 13C Observe with 1H decoupling D1 = 2s
170.78
159.69
138.96
130.49
129.02
124.58
123.27
123.12
101.77
52.30
f1 (ppm)

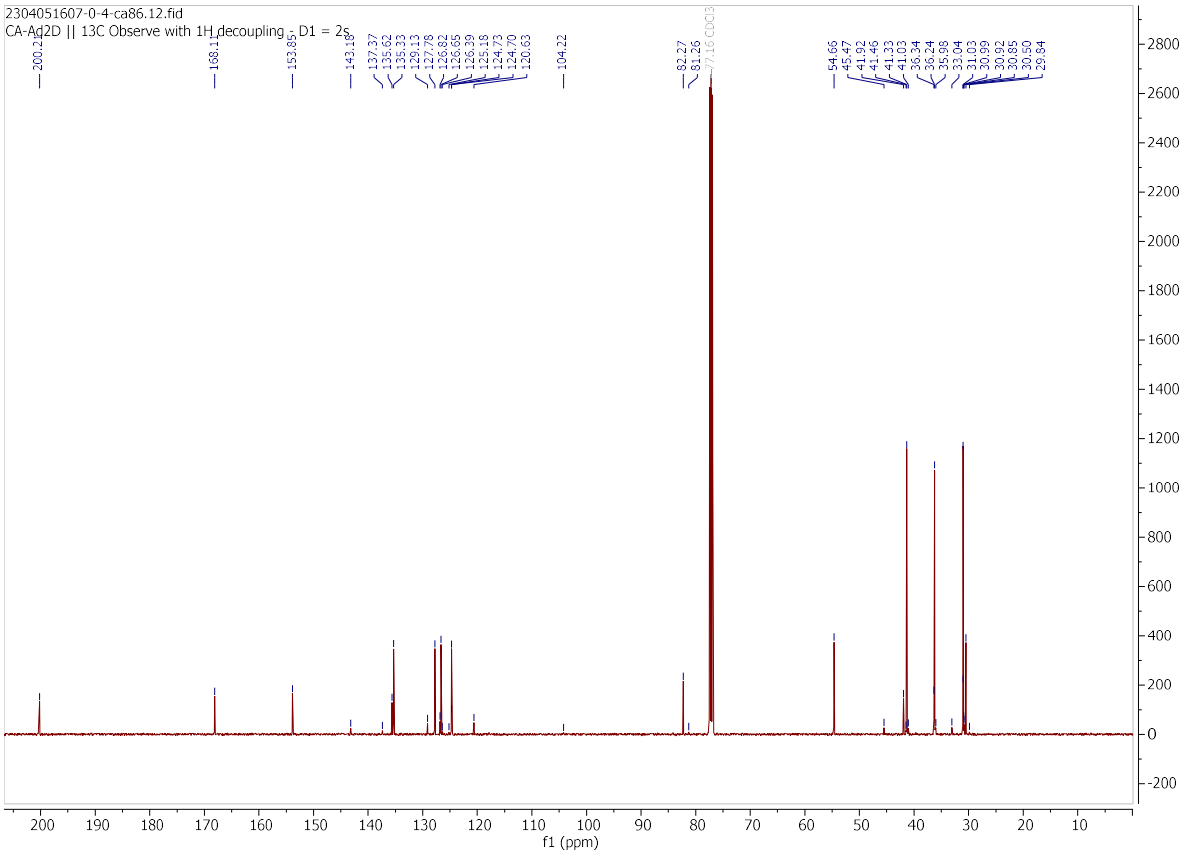
(1o)


2303101446-0-30-ca86.10.fid
CA-tBuBKE-13C || 1H Observe
Ot-Bu
f1 (ppm)

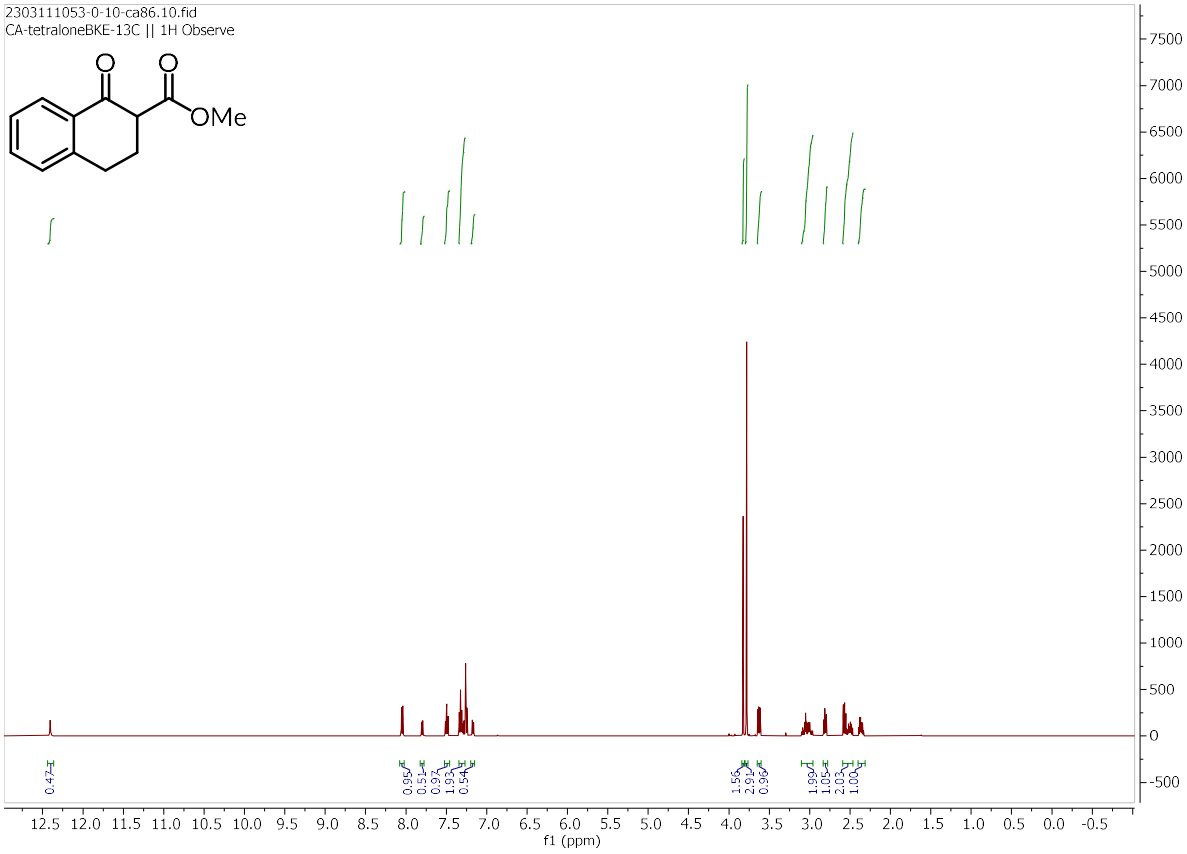

2304051607-0-3-ca86.12.fid
CA-tbu-2D || 13C Observe with 1H decoupling - DEPTO
f1 (ppm)

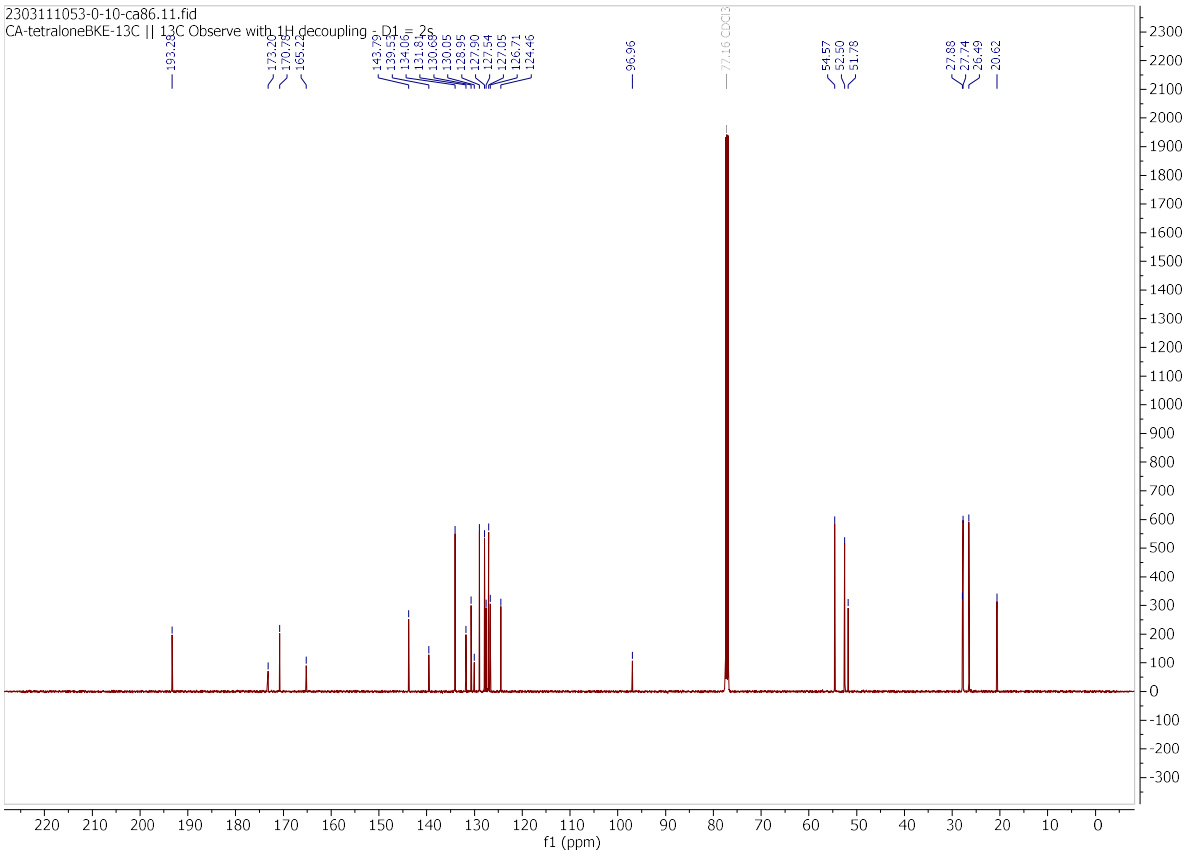
(1p)


2303111051-0-6-ca86.10.fid
CA-AdBKE-13C || 1H Observe
OAd
f1 (ppm)

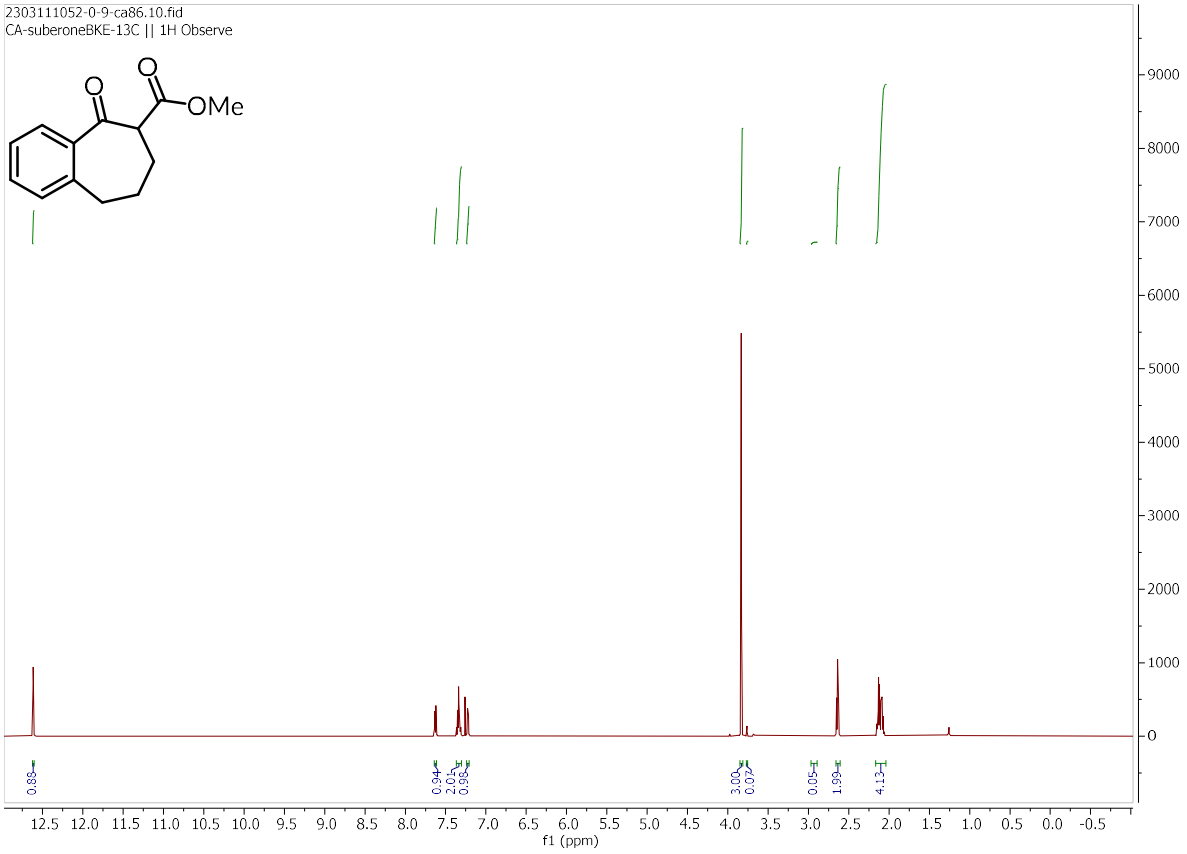

2304051607-0-4-ca86.12.fid
CA-Ad2D || 13C Observe with 1H decoupling, D1 = 2s
f1 (ppm)

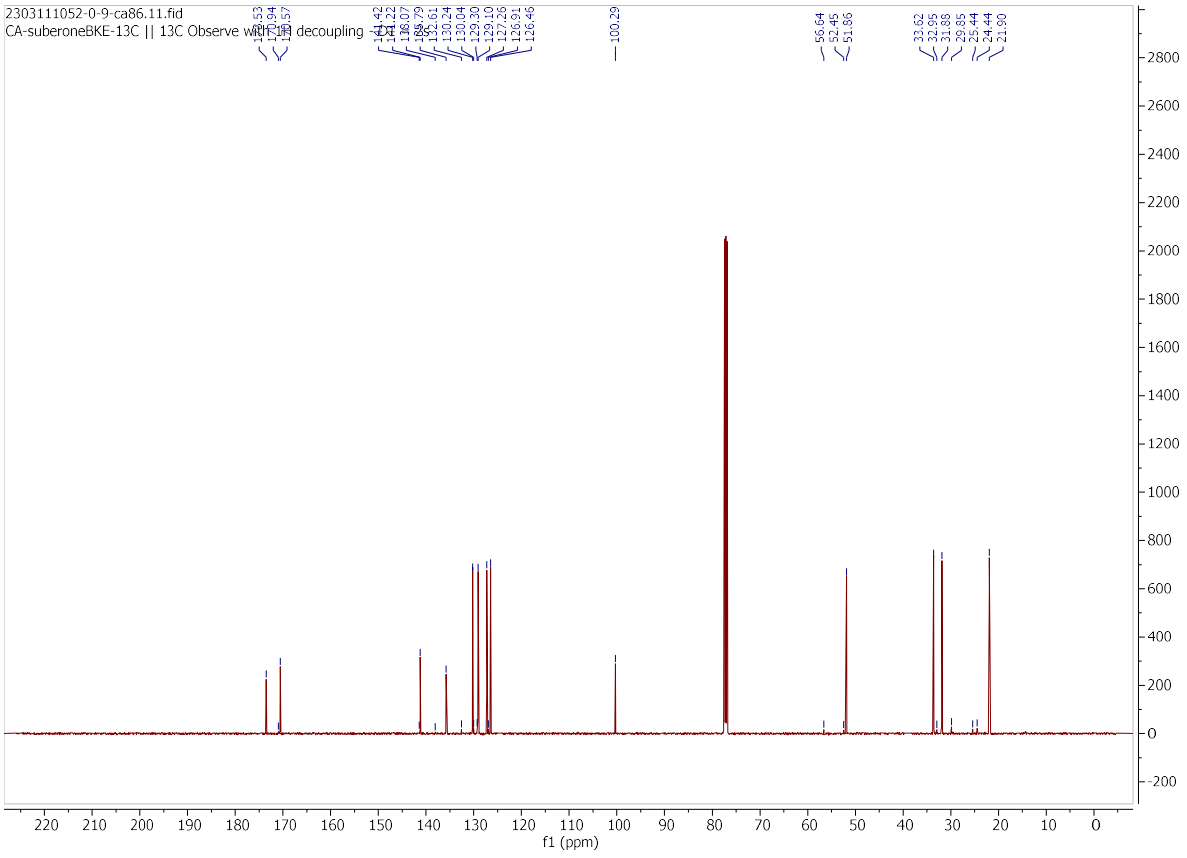
(1q)


2303111053-0-10-ca86.10.fid
CA-tetraloneBKE-13C || 1H Observe
OMe
f1 (ppm)

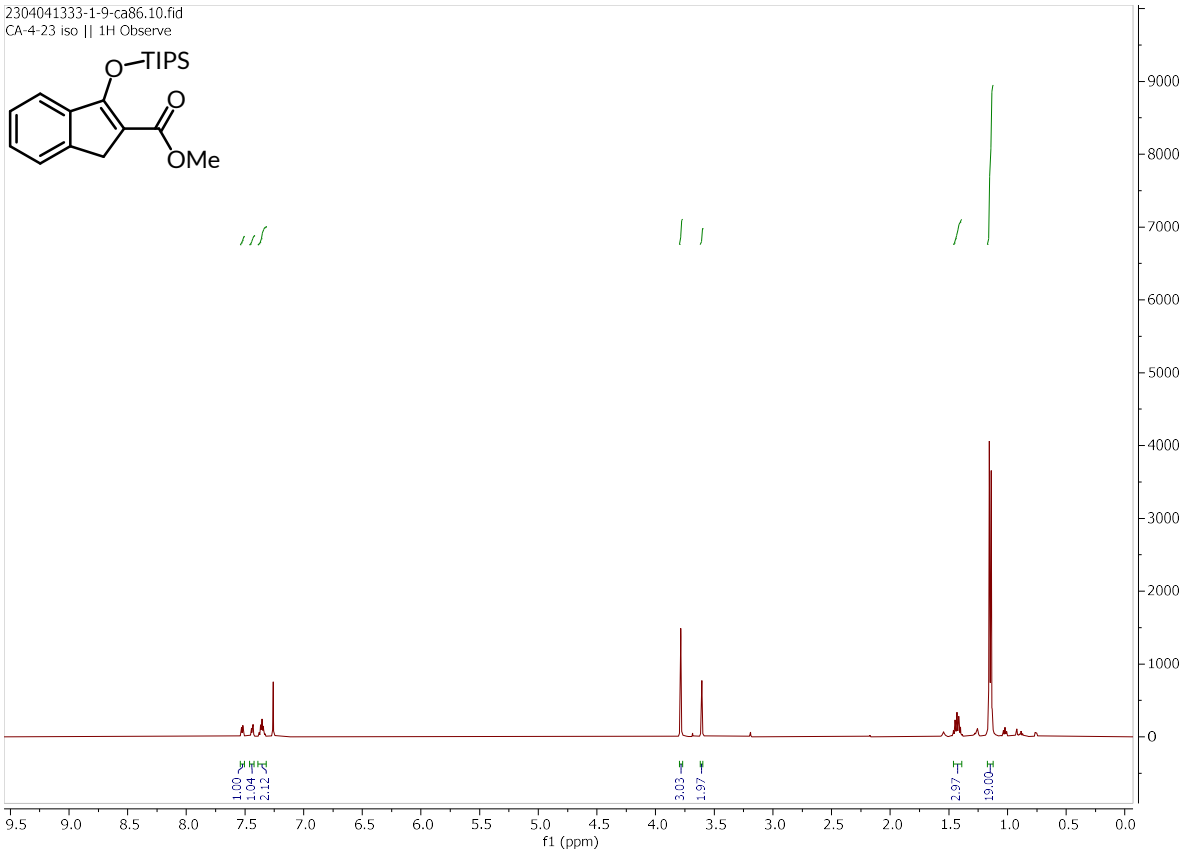

2303111053-0-10-ca86.11.fid
CA-tetraloneBKE-13C || 13C Observe with 1H decoupling - D1 2s
193.28
173.20
170.78
165.22
143.79
139.53
134.06
131.84
130.68
130.05
128.95
127.90
127.54
127.05
126.71
124.46
96.96
77.16 CDCl3
54.57
52.50
51.78
27.88
27.74
26.49
20.62
f1 (ppm)

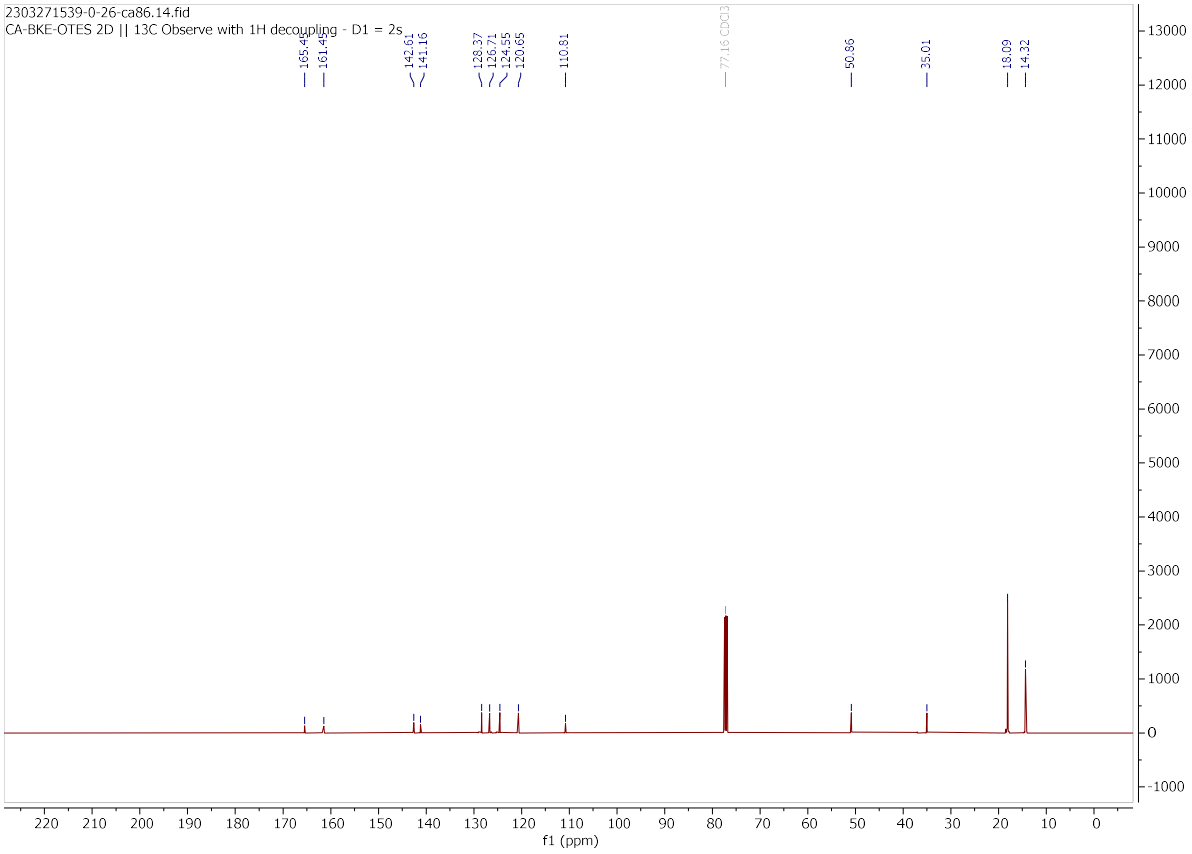
(1r)


2303111052-0-9-ca86.10.fid
CA-suberoneBKE-13C || 1H Observe
OMe
f1 (ppm)


2303111052-0-9-ca86.11.fid
CA-suberoneBKE-13C || 13C Observe with 1H decoupling
f1 (ppm)

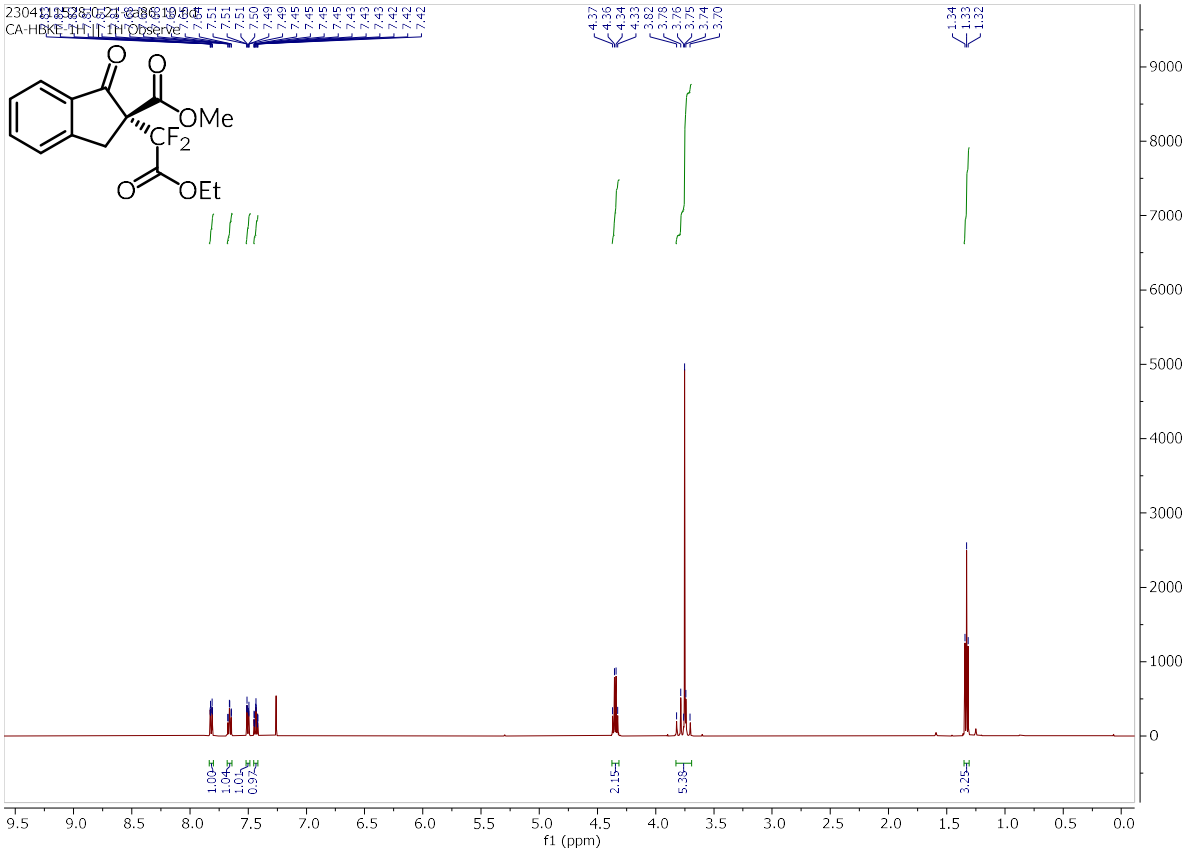
(TIPS *enol* 1a)

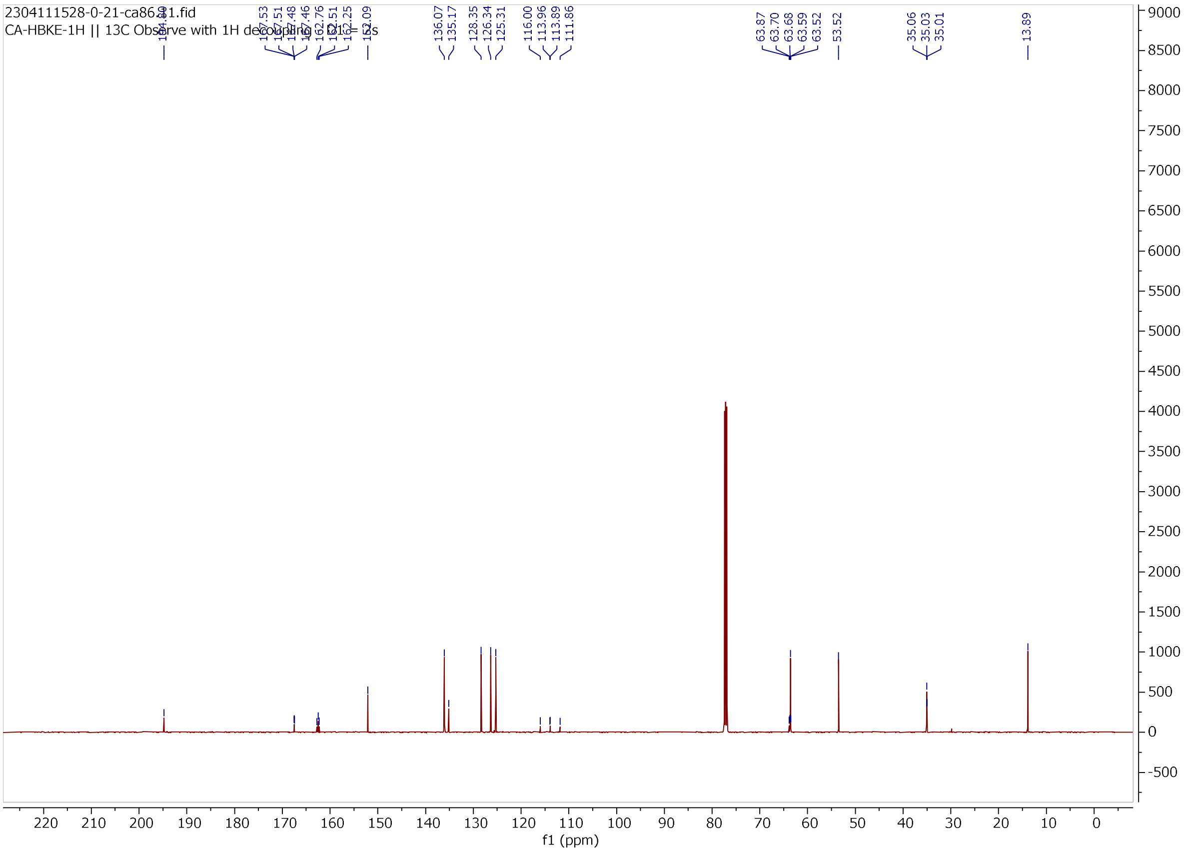

2304041333-1-9-ca86.10.fid
CA-4-23 iso || 1H Observe
TIPS
O
OMe
1.00
1.04
2.12
3.03
1.97
2.97
19.00
f1 (ppm)

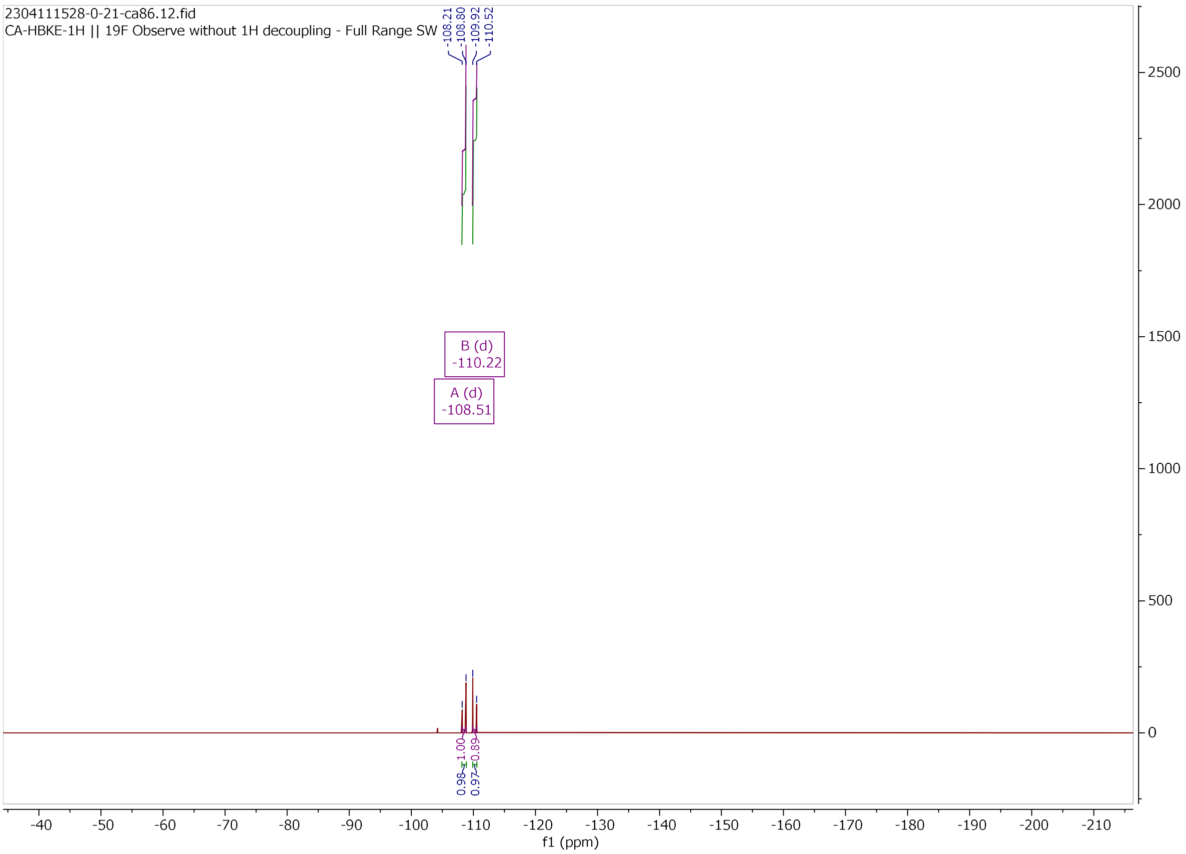

2303271539-0-26-ca86.14.fid
CA-BKE-OTES 2D || 13C Observe with 1H decoupling - D1 = 2s
165.49
161.45
142.61
141.16
128.37
126.71
124.55
120.65
110.81
77.16 CDCl3
50.86
35.01
18.09
14.32
f1 (ppm)

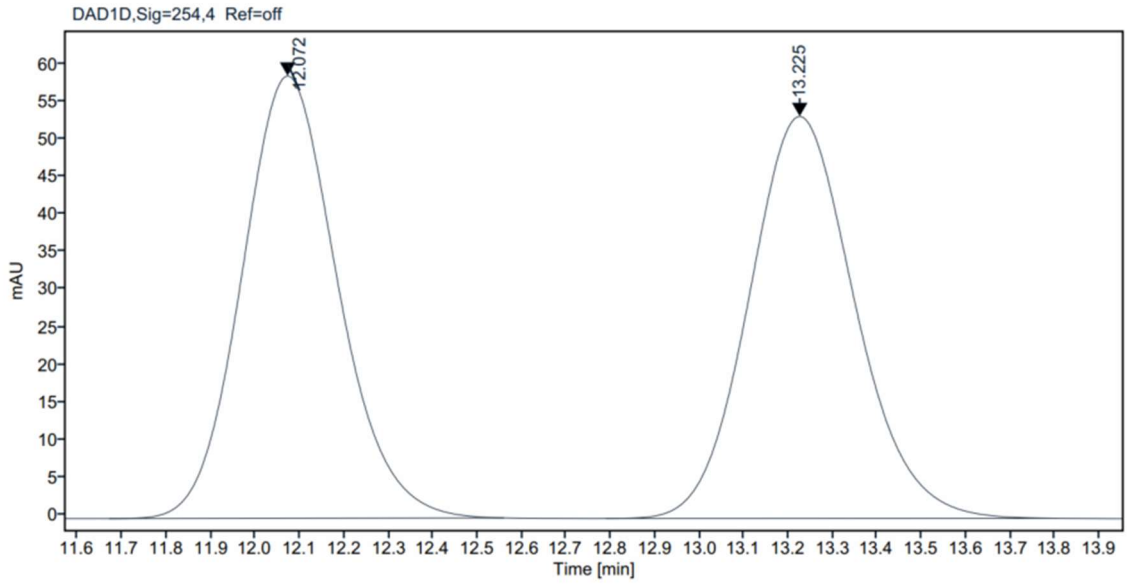
7.3 Products

(*R*)-3a



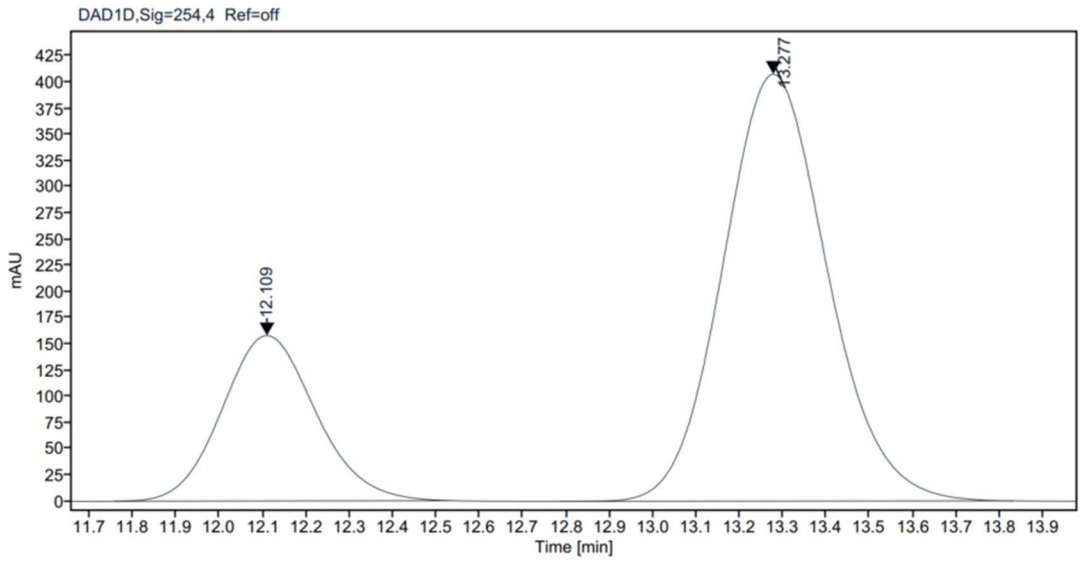

2304111528-0-21-ca86.11.fid
CA-HBKE-1H || 13C Observe with 1H decoupling
136.07
135.17
128.35
126.34
125.31
116.00
113.96
113.89
111.86
63.87
63.70
63.68
63.59
63.52
53.52
35.06
35.03
35.01
13.89
f1 (ppm)


2304111528-0-21-ca86.12.fid
CA-HBKE-1H || 19F Observe without 1H decoupling - Full Range SW
-108.21
-108.80
-109.92
-110.52
B (d)
-110.22
A (d)
-108.51
0.98
1.00
0.97
0.89
f1 (ppm)



Signal: DAD1D,Sig=254,4 Ref=off

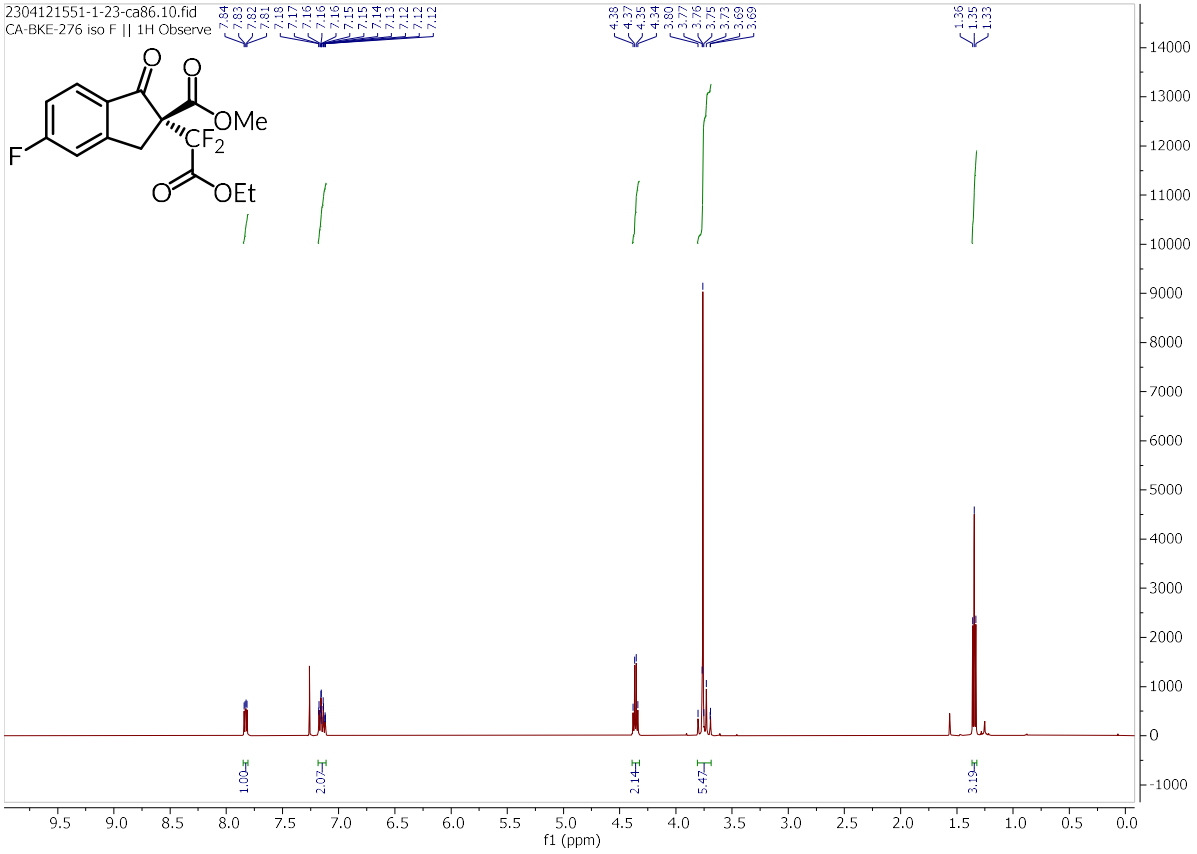
RT [min]	Type	Width [min]	Area	Height	Area%	Name
12.072	MM m	0.8886	882.4146	58.8938	49.8665	
13.225	MM m	1.0176	887.1386	53.5262	50.1335	

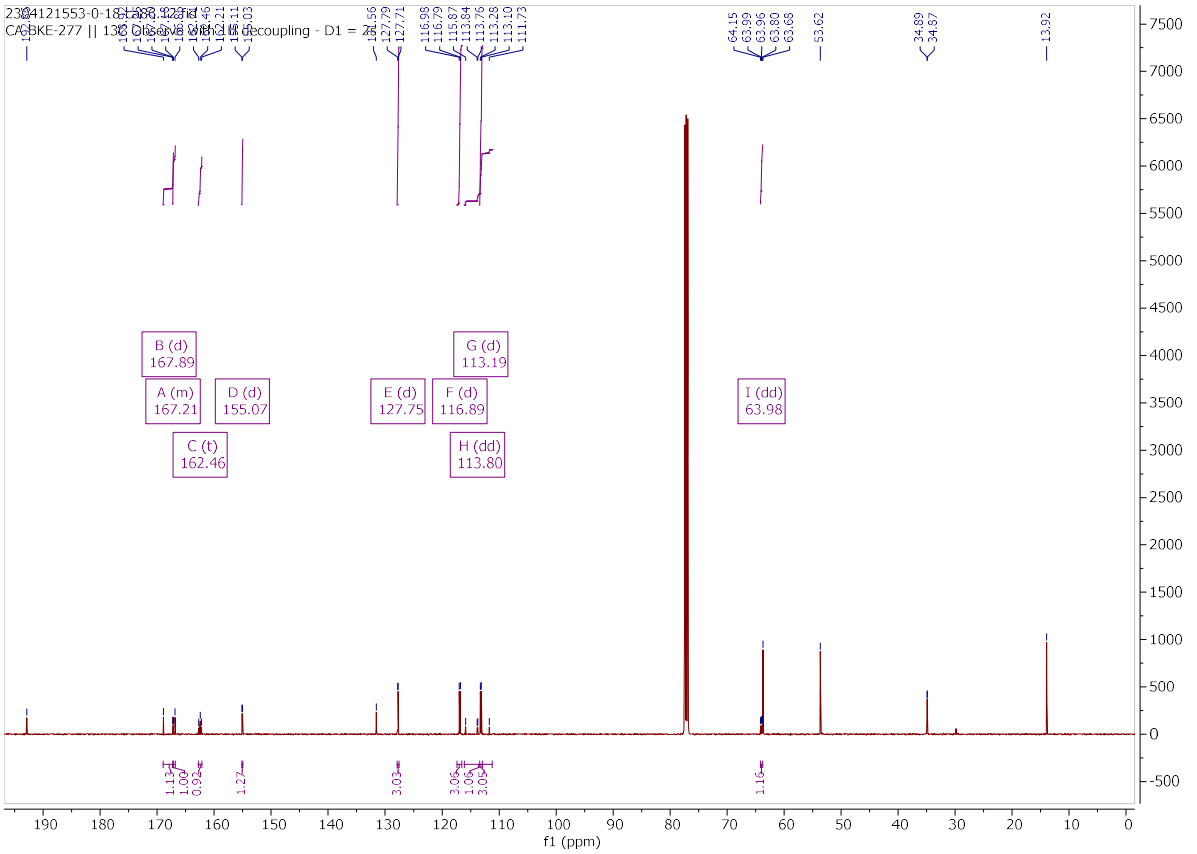


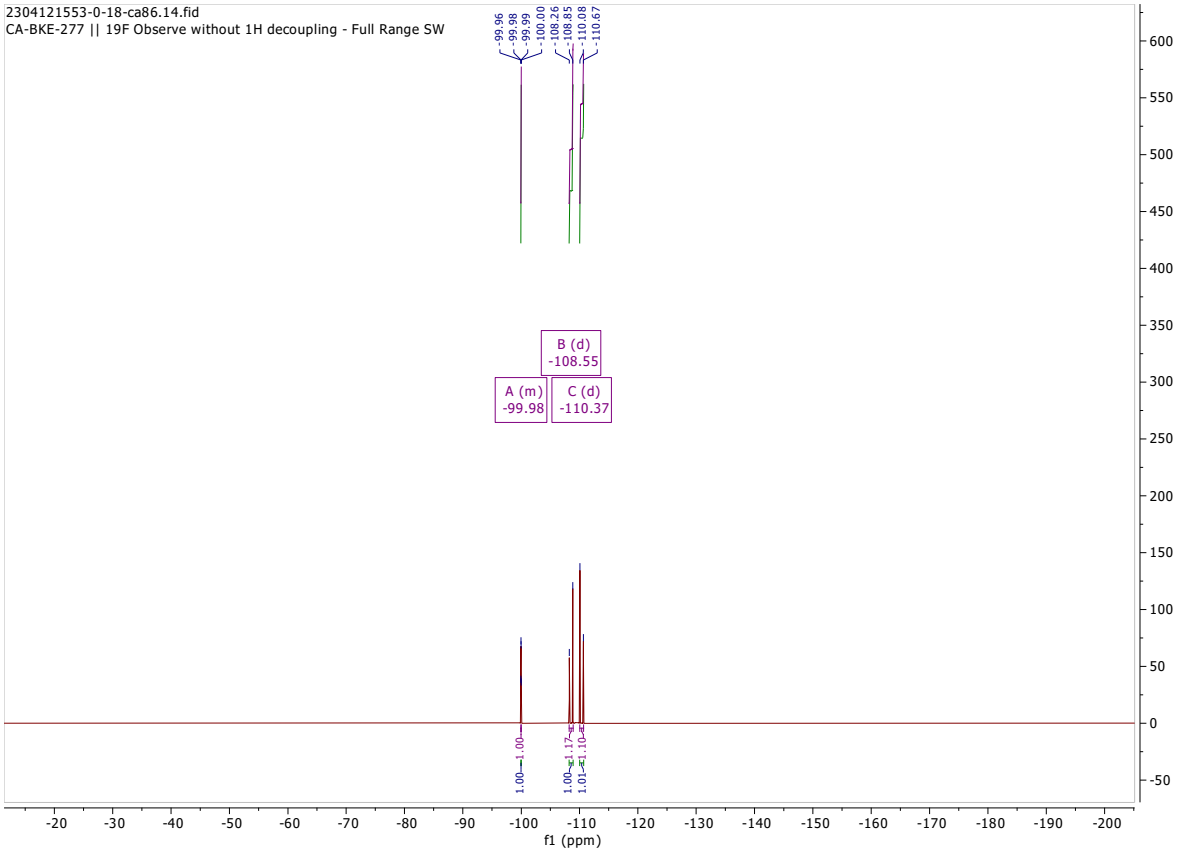
Signal: DAD1D,Sig=254,4 Ref=off

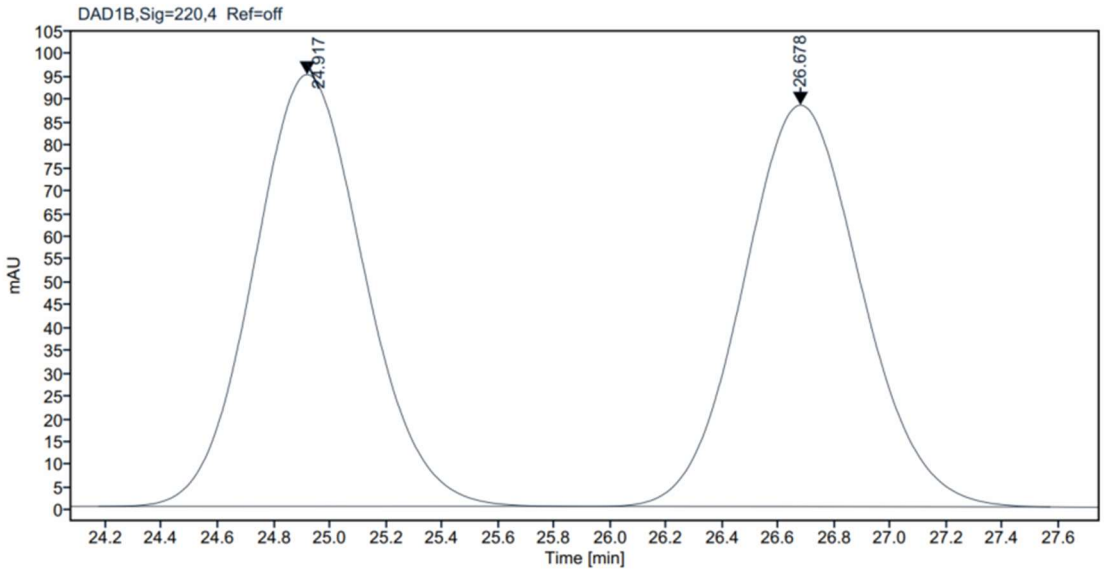
RT [min]	Type	Width [min]	Area	Height	Area%	Name
12.109	MM m	0.7835	2382.6023	158.1581	25.8005	
13.277	MM m	1.0446	6852.1023	408.0479	74.1995	

(*R*)-3b


2304121551-1-23-ca86.10.fid
CA-BKE-276 iso F || 1H Observe
f1 (ppm)

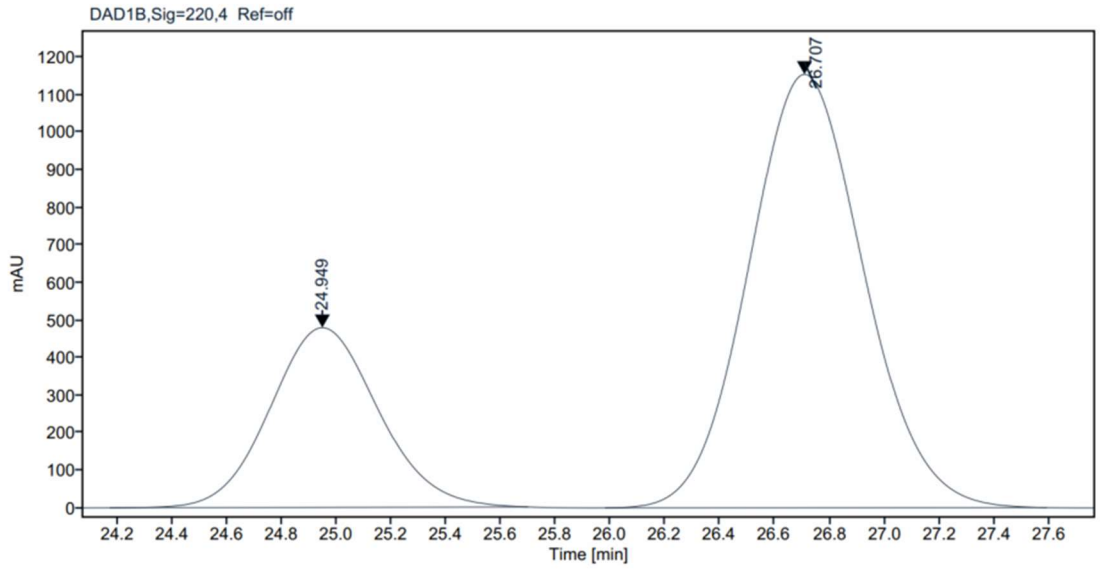

CA-BKE-277 || 13C Observe with 1H decoupling - D1 = 2s
B (d) 167.89
A (m) 167.21
D (d) 155.07
C (t) 162.46
G (d) 113.19
E (d) 127.75
F (d) 116.89
H (dd) 113.80
I (dd) 63.98
f1 (ppm)





Signal: DAD1B,Sig=220,4 Ref=off

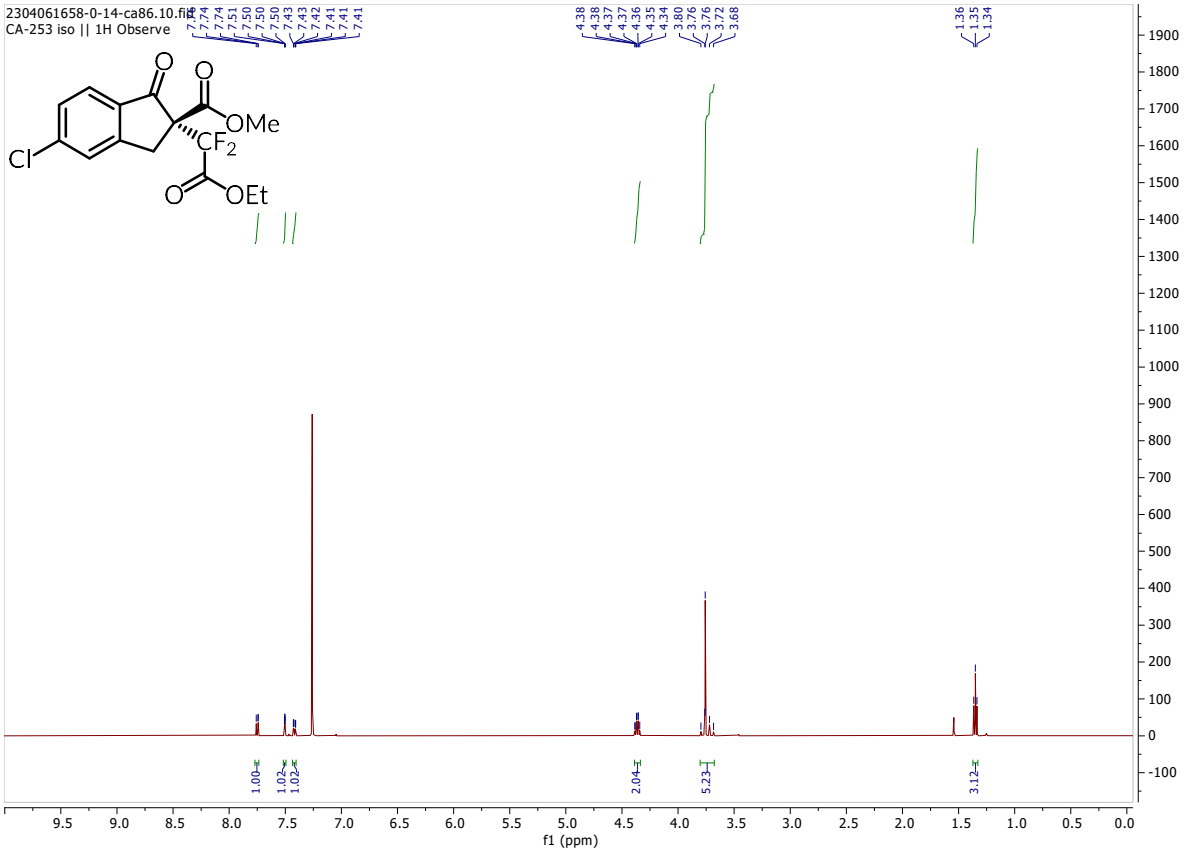
RT [min]	Type	Width [min]	Area	Height	Area%	Name
24.917	MM m	1.6125	2601.7633	94.6071	50.1784	
26.678	MM m	1.7845	2583.2630	87.9869	49.8216	

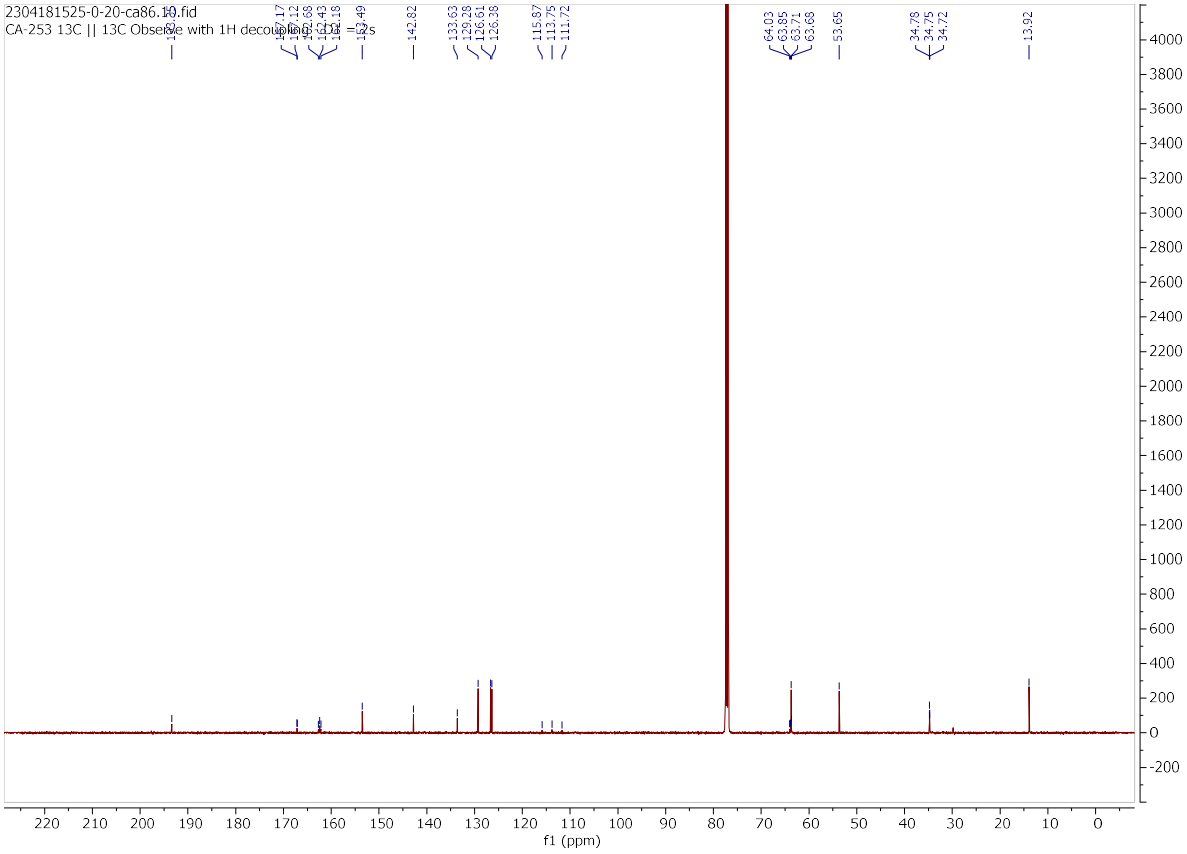


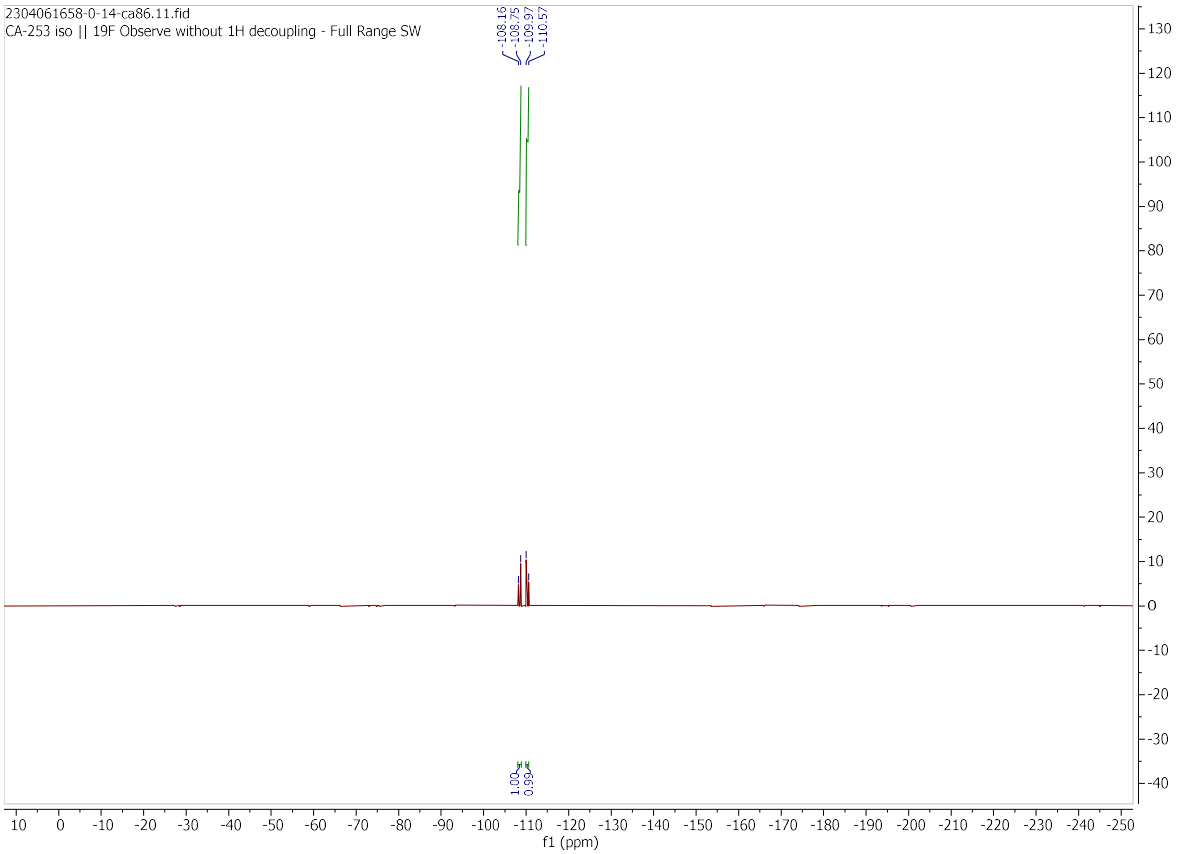
Signal: DAD1B,Sig=220,4 Ref=off

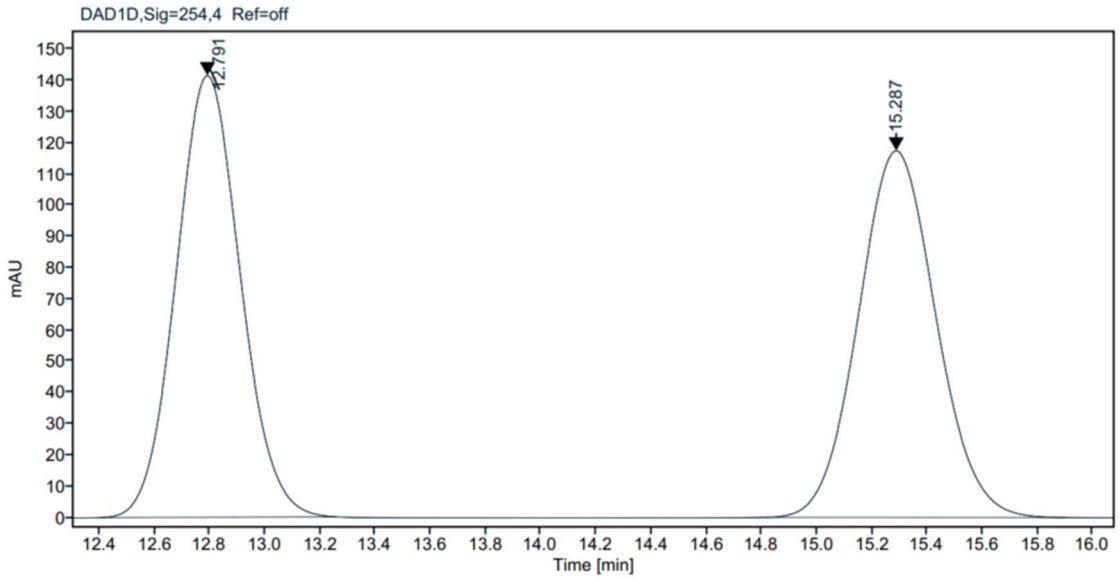
RT [min]	Type	Width [min]	Area	Height	Area%	Name
24.949	MM m	1.5265	13164.7600	478.5962	28.0286	
26.707	MM m	1.6125	33804.1821	1154.3652	71.9714	

(*R*)-3c



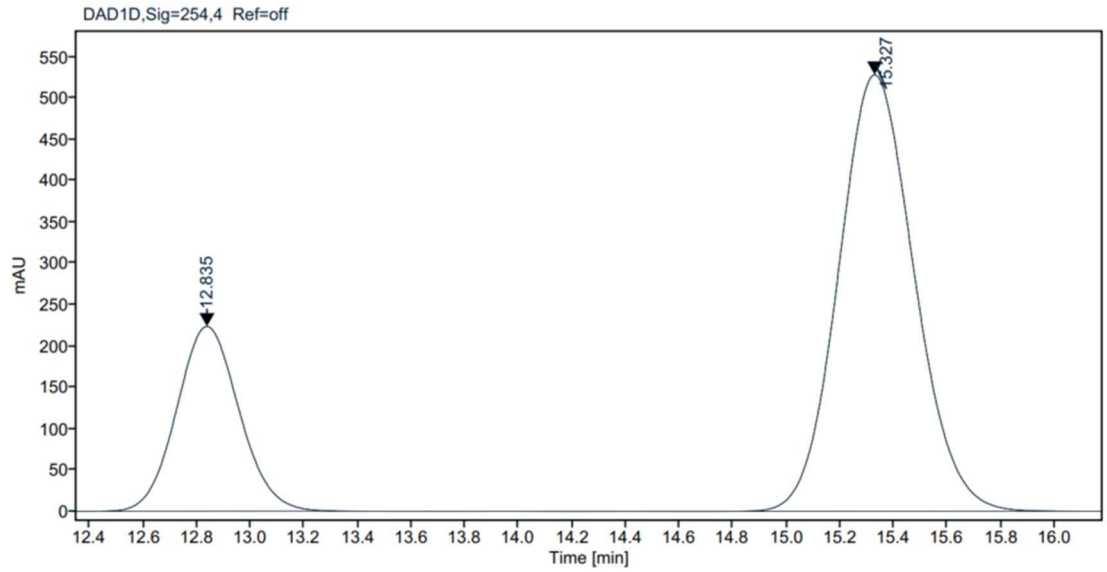

2304181525-0-20-ca86.10.fid
CA-253 13C || 13C Observe with 1H decoupling - d1 =2s
160.17
159.12
157.68
156.43
156.18
152.49
142.82
133.63
129.28
126.61
126.38
115.87
113.75
111.72
64.03
63.85
63.71
63.68
53.65
34.78
34.75
34.72
13.92
f1 (ppm)


2304061658-0-14-ca86.11.fid
CA-253 iso || 19F Observe without 1H decoupling - Full Range SW
-108.16
-108.75
-109.97
-110.57
1.00
0.99
f1 (ppm)



Signal: DAD1D,Sig=254,4 Ref=off

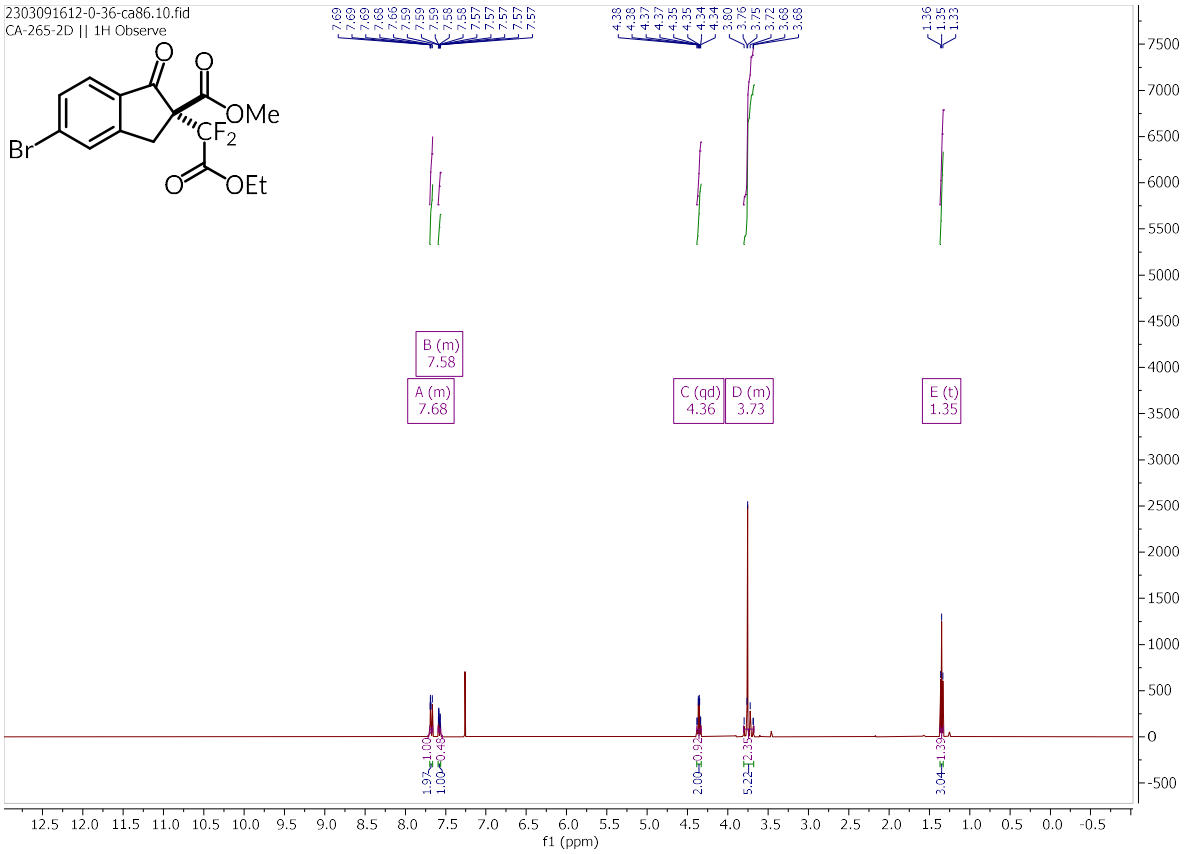
RT [min]	Type	Width [min]	Area	Height	Area%	Name
12.791	MM m	0.8599	2291.4504	141.5594	49.9210	
15.287	MM m	1.0892	2298.7053	117.5061	50.0790	

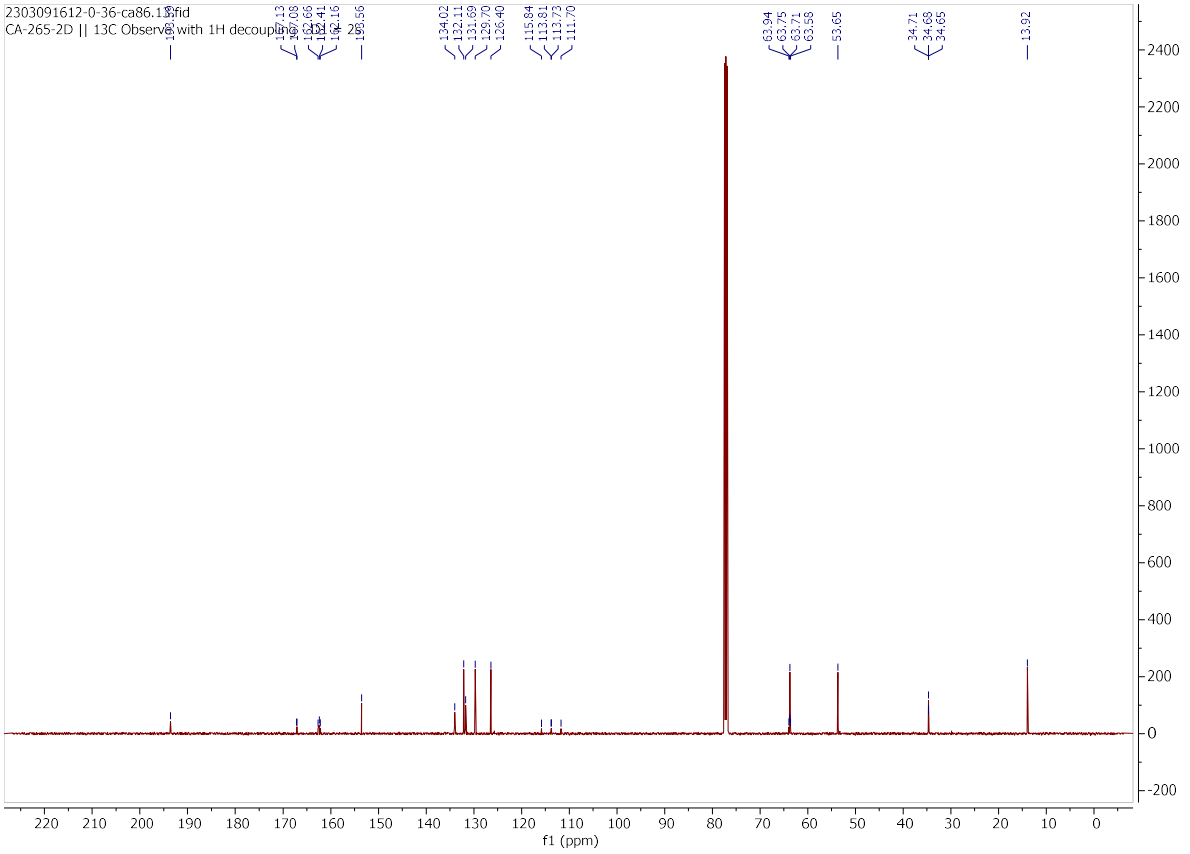


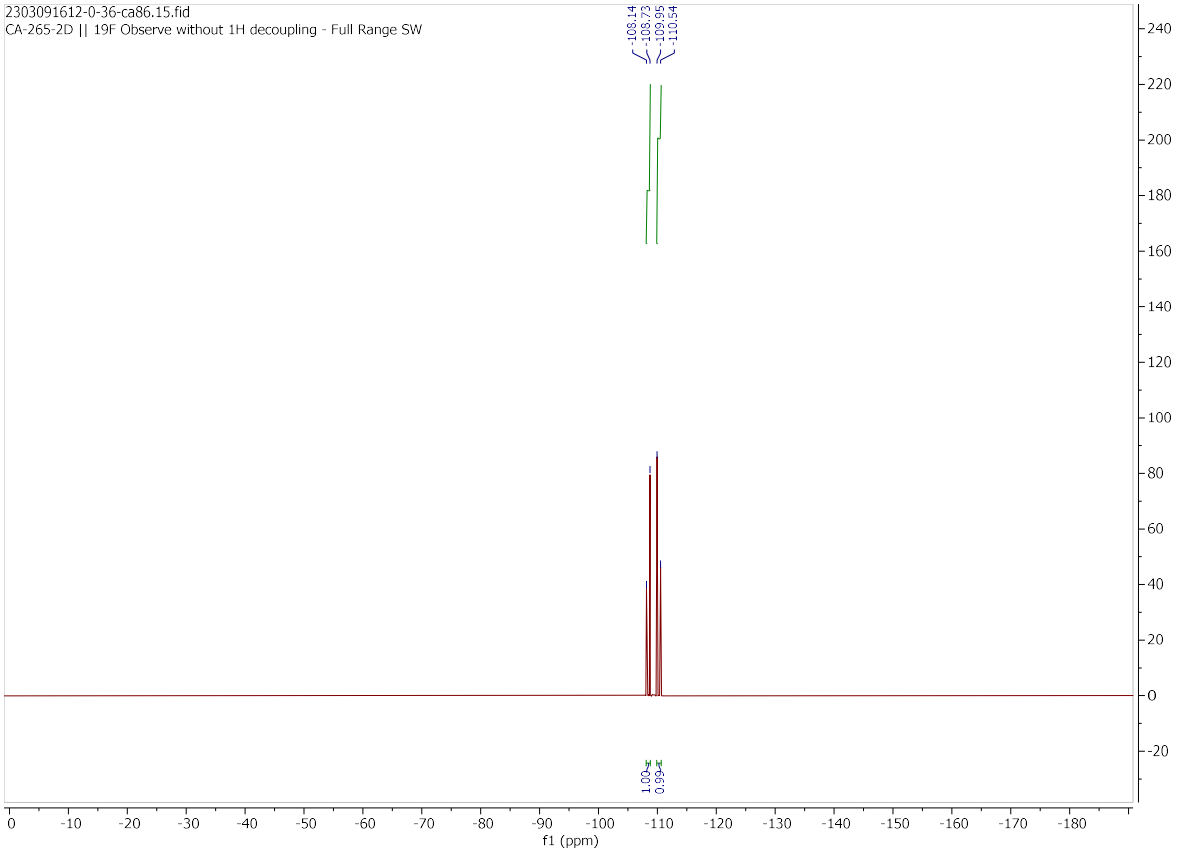
Signal: DAD1D,Sig=254,4 Ref=off

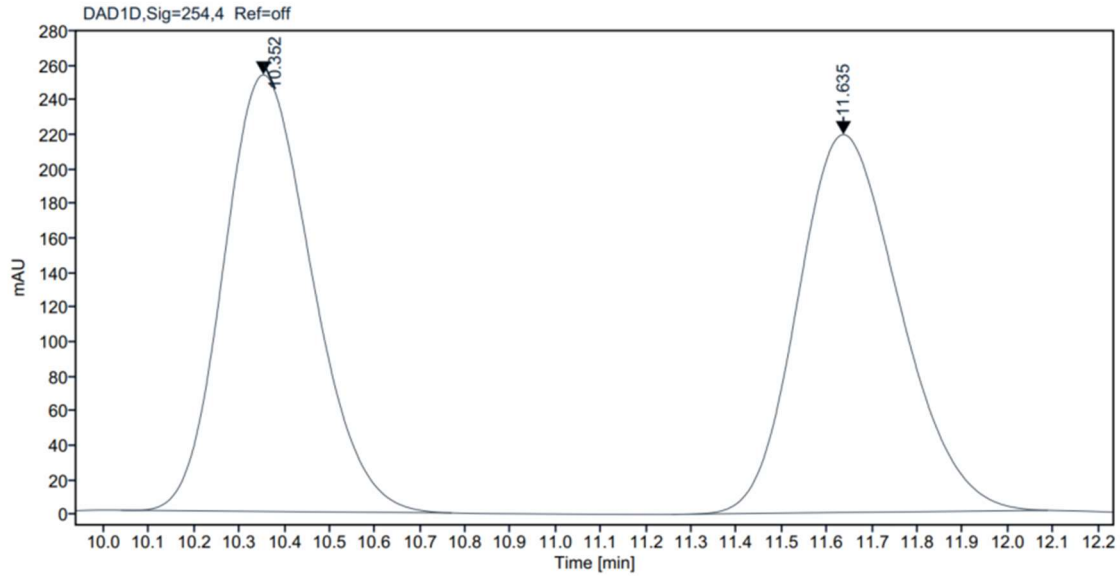
RT [min]	Type	Width [min]	Area	Height	Area%	Name
12.835	MM m	0.8743	3625.1311	223.7594	25.9087	
15.327	MM m	1.1896	10366.8141	528.5193	74.0913	

(*R*)-3d


2303091612-0-36-ca86.10.fid
CA-265-2D || 1H Observe
Br
O
O
OMe
CF2
O
OEt
B (m)
7.58
A (m)
7.68
C (qd)
4.36
D (m)
3.73
E (t)
1.35
f1 (ppm)

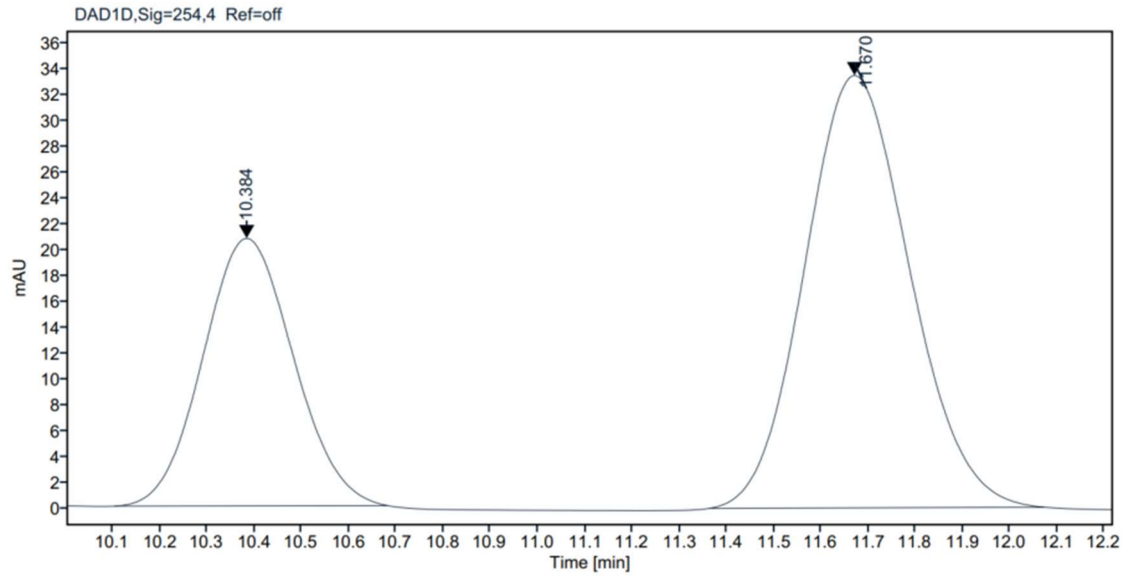

CA-265-2D || 13C Observe with 1H decoupling
f1 (ppm)


2303091612-0-36-ca86.15.fid
CA-265-2D || 19F Observe without 1H decoupling - Full Range SW
-108.14
-108.73
-109.95
-110.54
1.00
0.99
f1 (ppm)



Signal: DAD1D,Sig=254,4 Ref=off

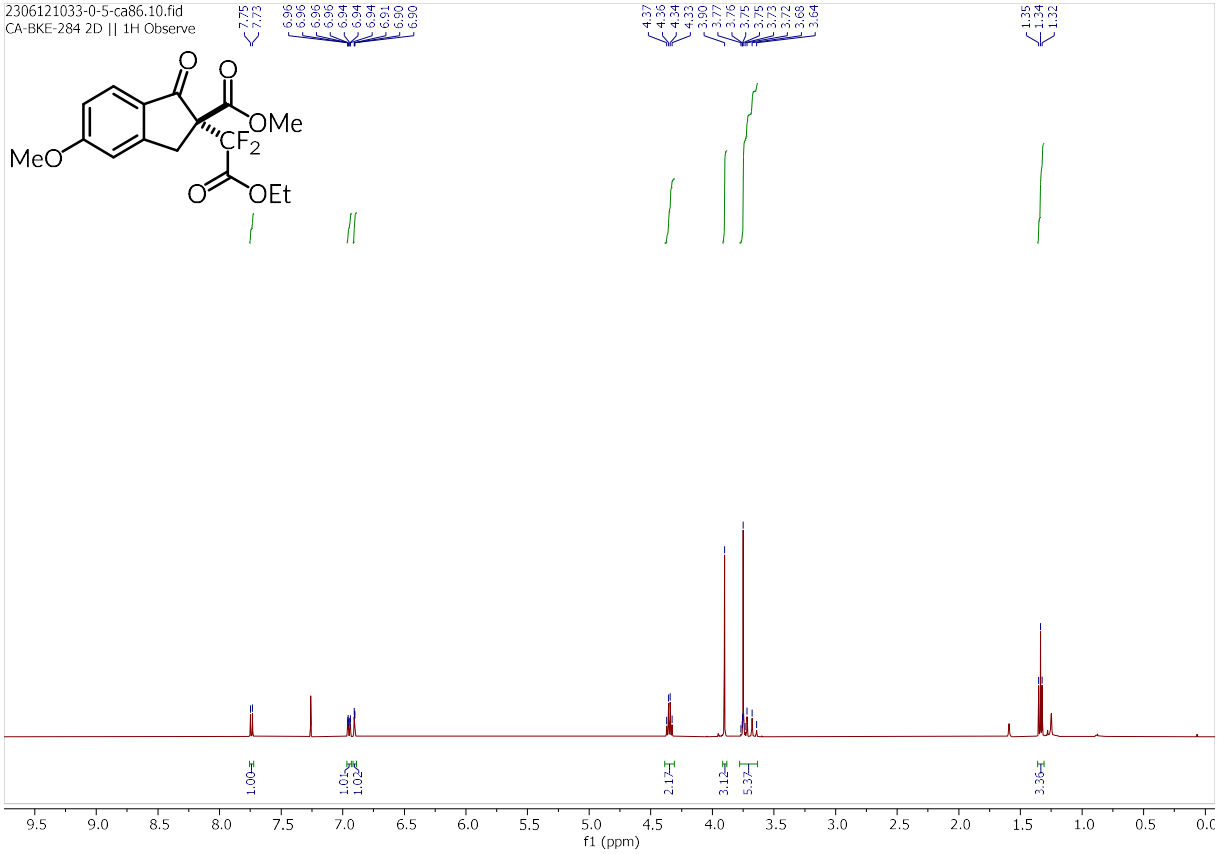
RT [min]	Type	Width [min]	Area	Height	Area%	Name
10.352	MM m	0.7322	3431.0778	252.8187	49.9681	
11.635	MM m	0.8313	3435.4555	218.8549	50.0319	

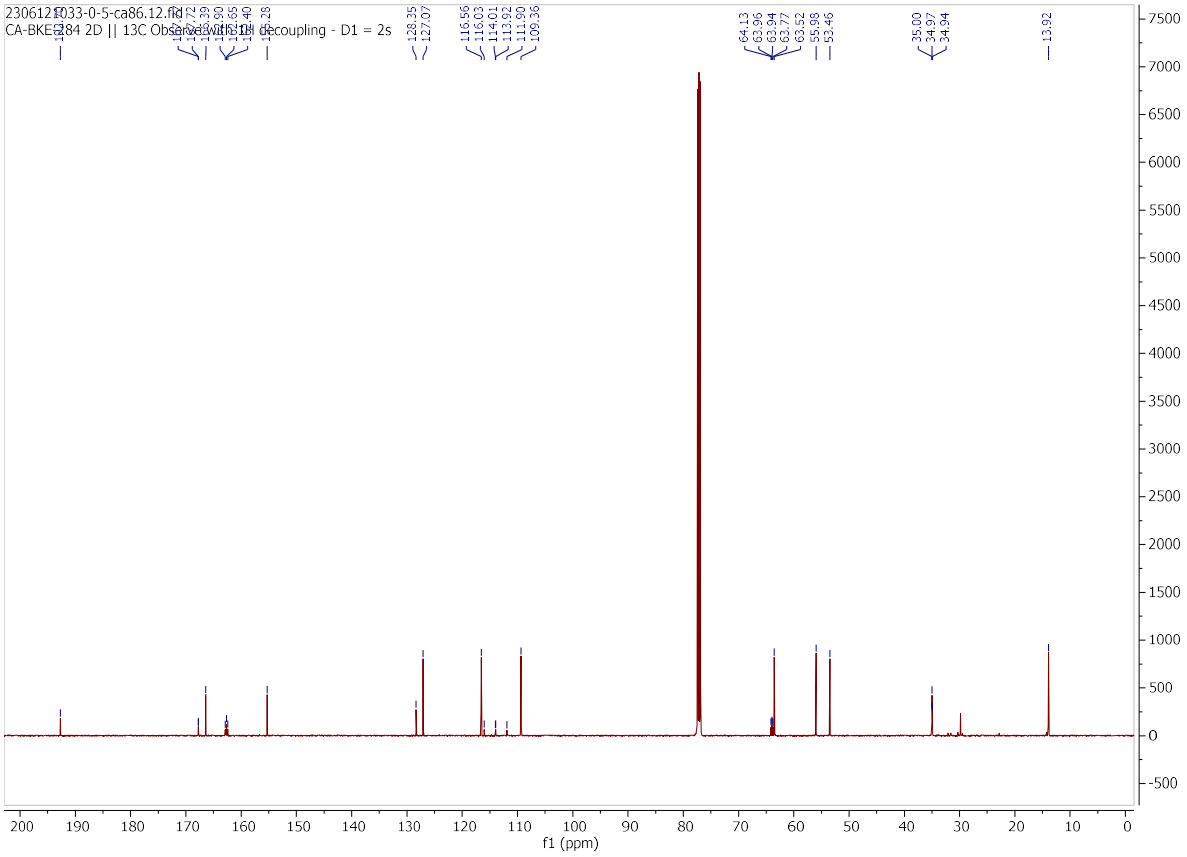


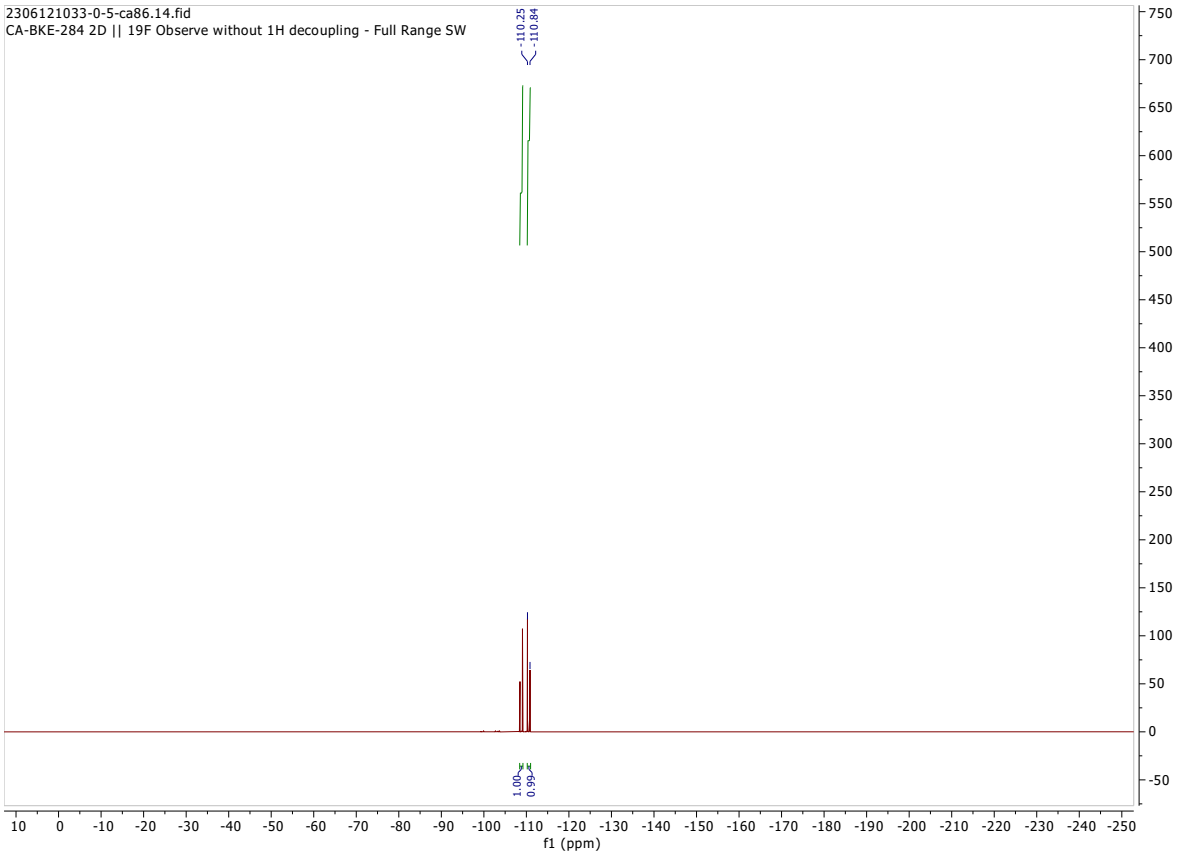
Signal: DAD1D,Sig=254,4 Ref=off

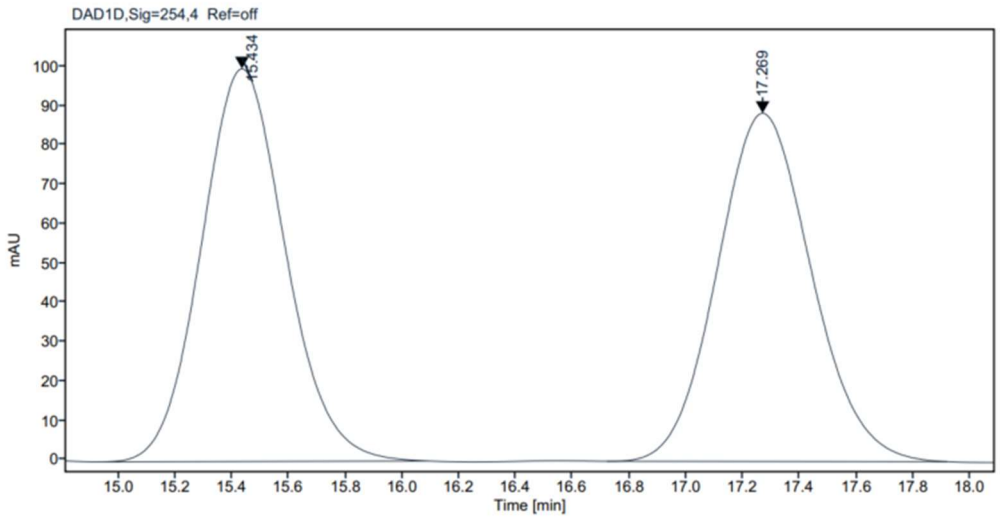
RT [min]	Type	Width [min]	Area	Height	Area%	Name
10.384	MM m	0.5791	275.8317	20.7512	34.7440	
11.670	MM m	0.7104	518.0658	33.5400	65.2560	

(*R*)-3e


2306121033-0-5-ca86.10.fid
CA-BKE-284 2D || 1H Observe
MeO
OMe
CF2
OEt
f1 (ppm)

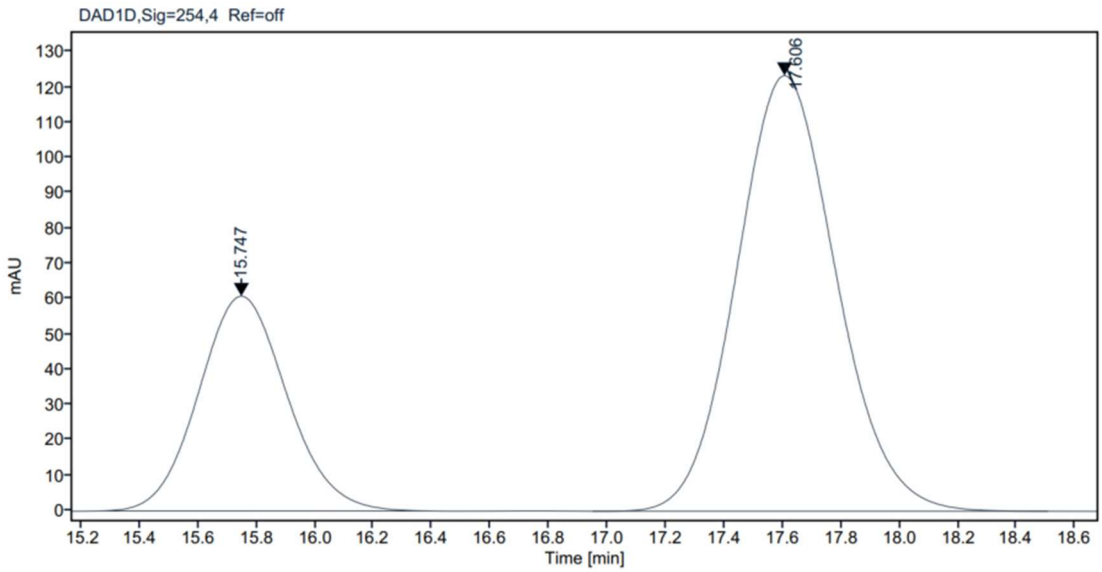

2306121033-0-5-ca86.12.fid
CA-BKE-284 2D || 13C Observe with 1H decoupling - D1 = 2s
f1 (ppm)





Signal: DAD1D,Sig=254,4 Ref=off

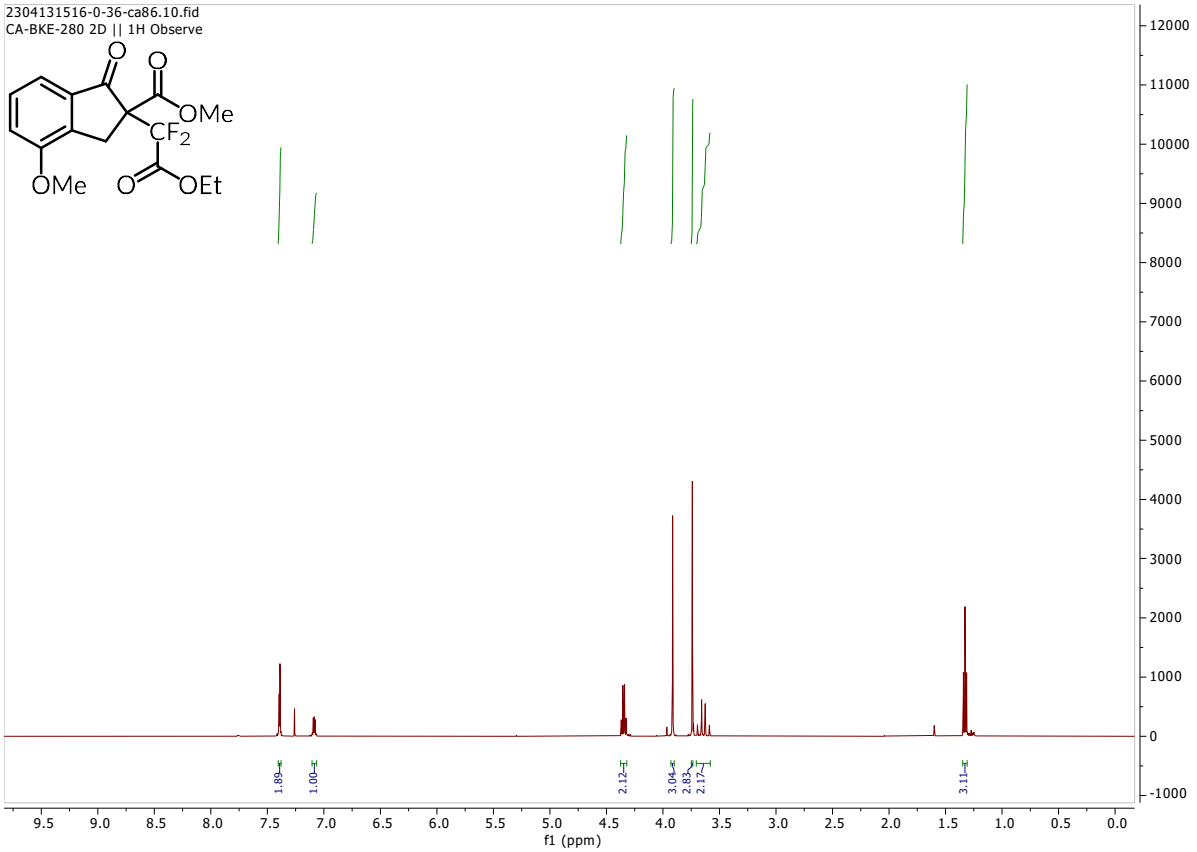
RT [min]	Type	Width [min]	Area	Height	Area%	Name
15.434	MM m	1.1825	2059.1538	99.8023	50.1538	
17.269	MM m	1.2004	2046.5272	88.4785	49.8462	

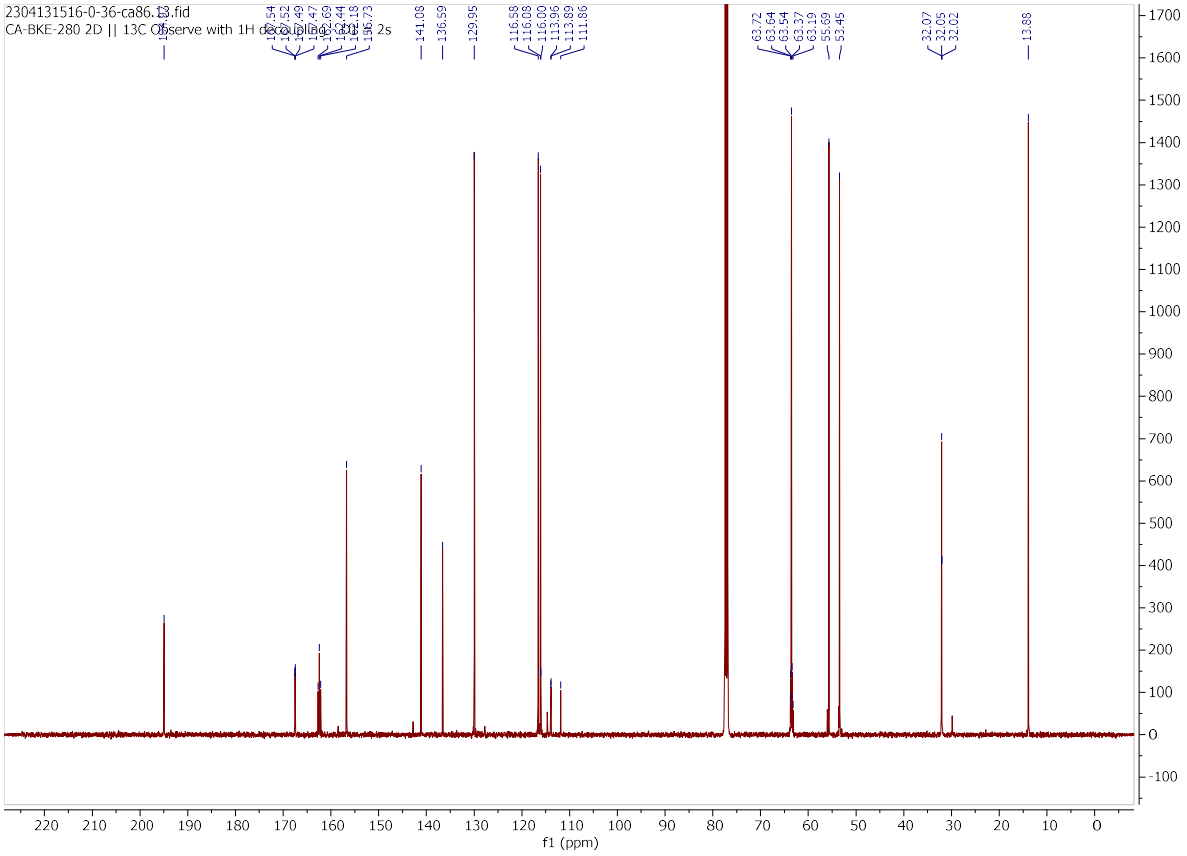


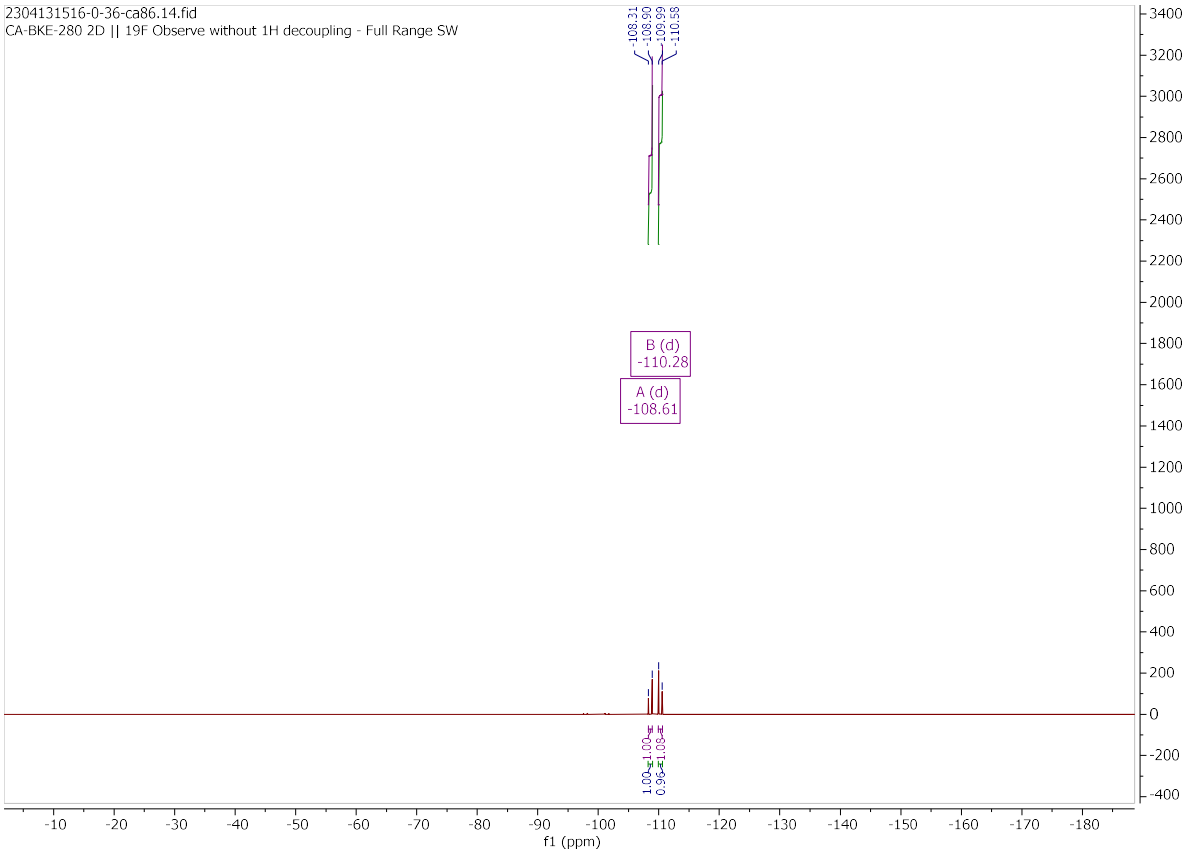
Signal: DAD1D,Sig=254,4 Ref=off

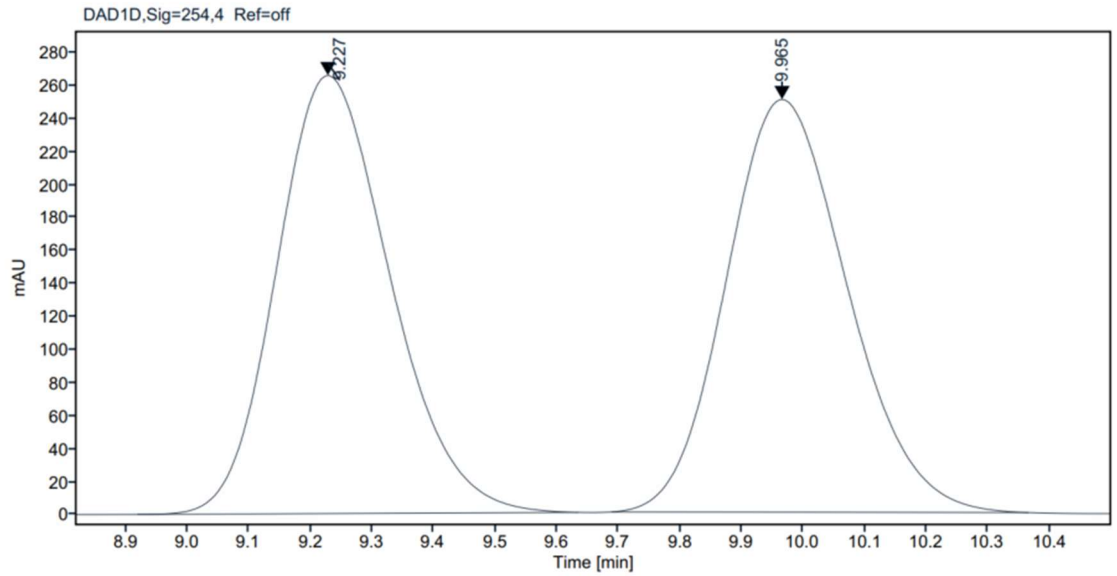
RT [min]	Type	Width [min]	Area	Height	Area%	Name
15.747	MM m	1.1287	1278.6137	60.9239	30.3976	
17.606	MM m	1.5587	2927.6896	123.5655	69.6024	

3f



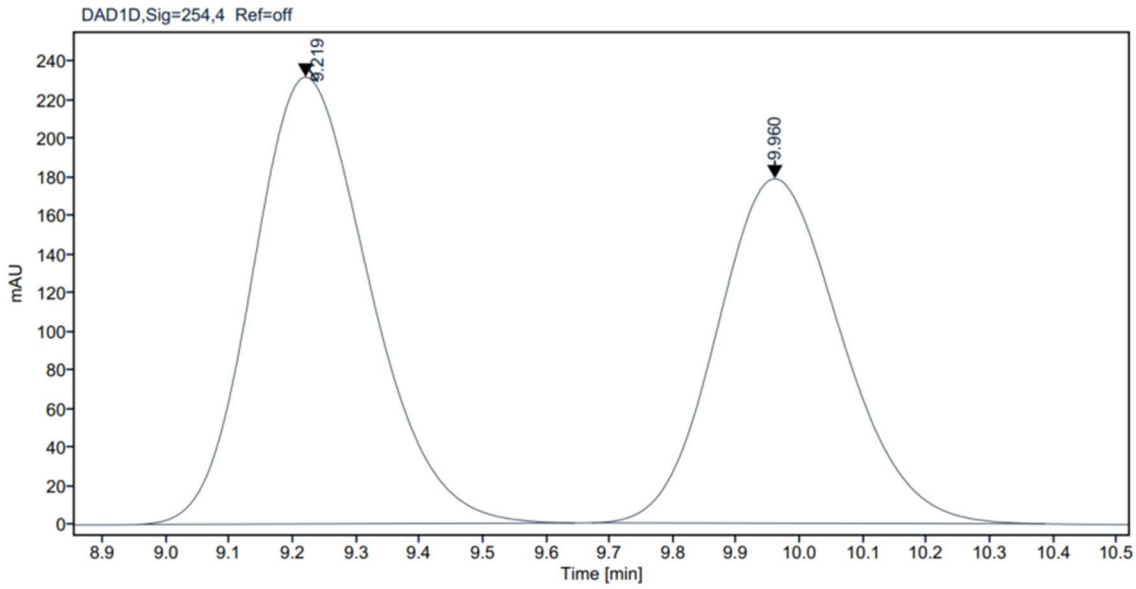

2304131516-0-36-ca86.13.fid
CA-BKE-280 2D || 13C Observe with 1H decoupling - d1 2s
141.08
136.59
129.95
116.58
116.08
116.00
113.96
113.89
111.86
63.72
63.64
63.54
63.37
63.19
55.69
53.46
32.07
32.05
32.02
13.88
f1 (ppm)


2304131516-0-36-ca86.14.fid
CA-BKE-280 2D || 19F Observe without 1H decoupling - Full Range SW
-108.31
-108.90
-109.99
-110.58
B (d)
-110.28
A (d)
-108.61
1.00
1.00
0.96
1.08
f1 (ppm)



Signal: DAD1D,Sig=254,4 Ref=off

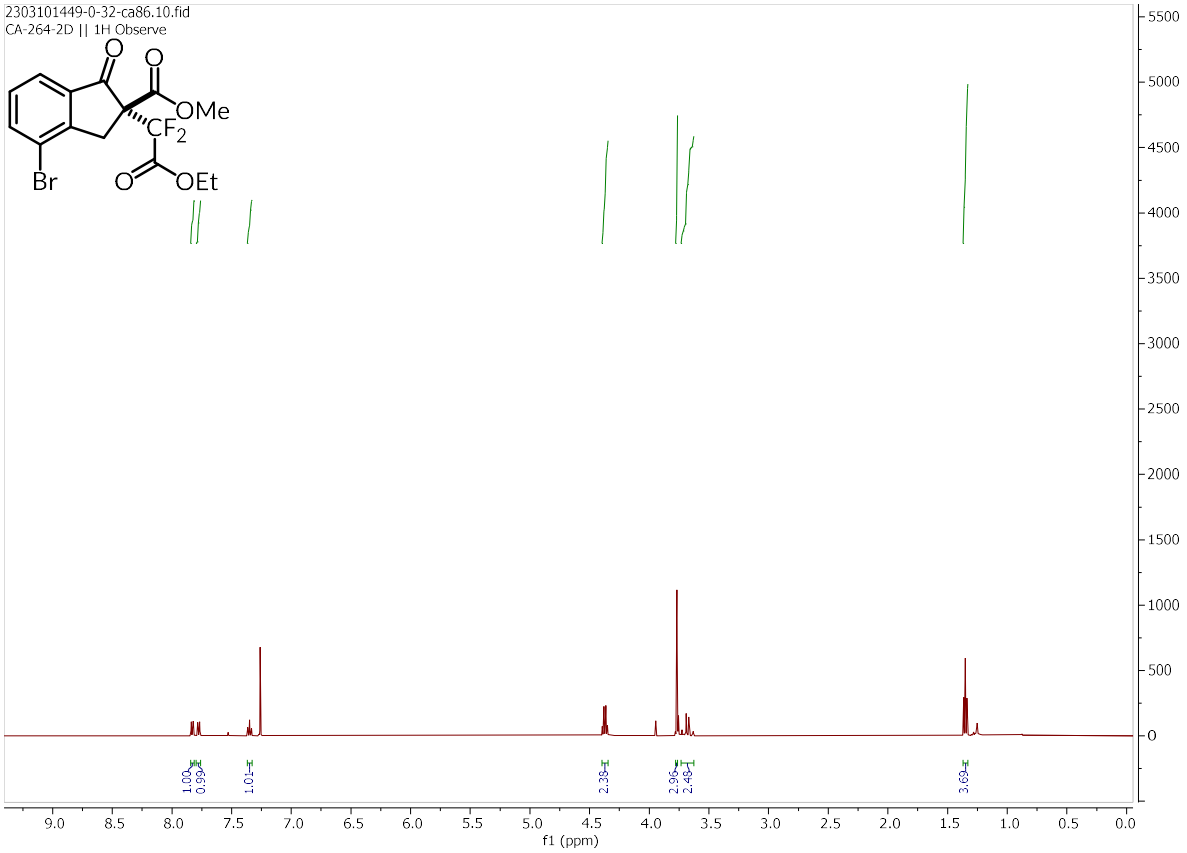
RT [min]	Type	Width [min]	Area	Height	Area%	Name
9.227	MM m	0.7167	3401.1801	265.4629	49.8066	
9.965	MM m	0.6775	3427.5918	250.1469	50.1934	

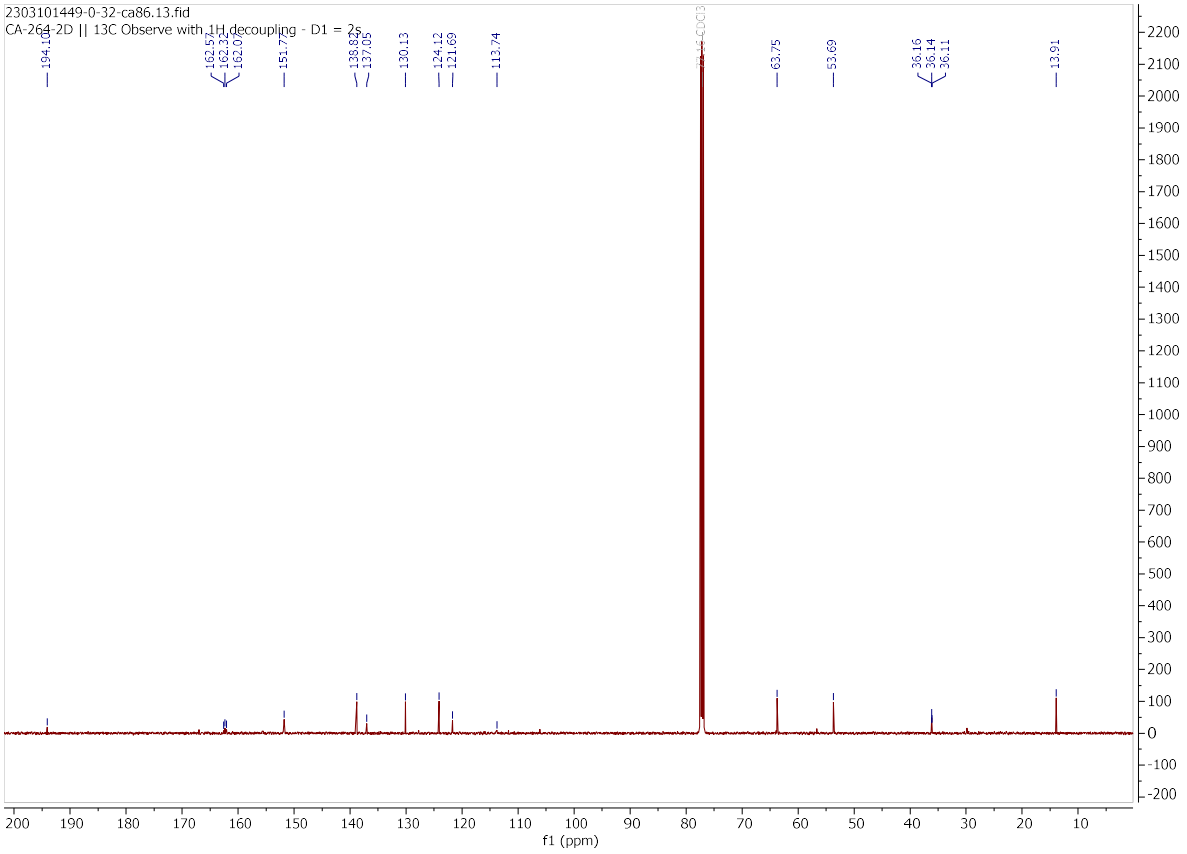


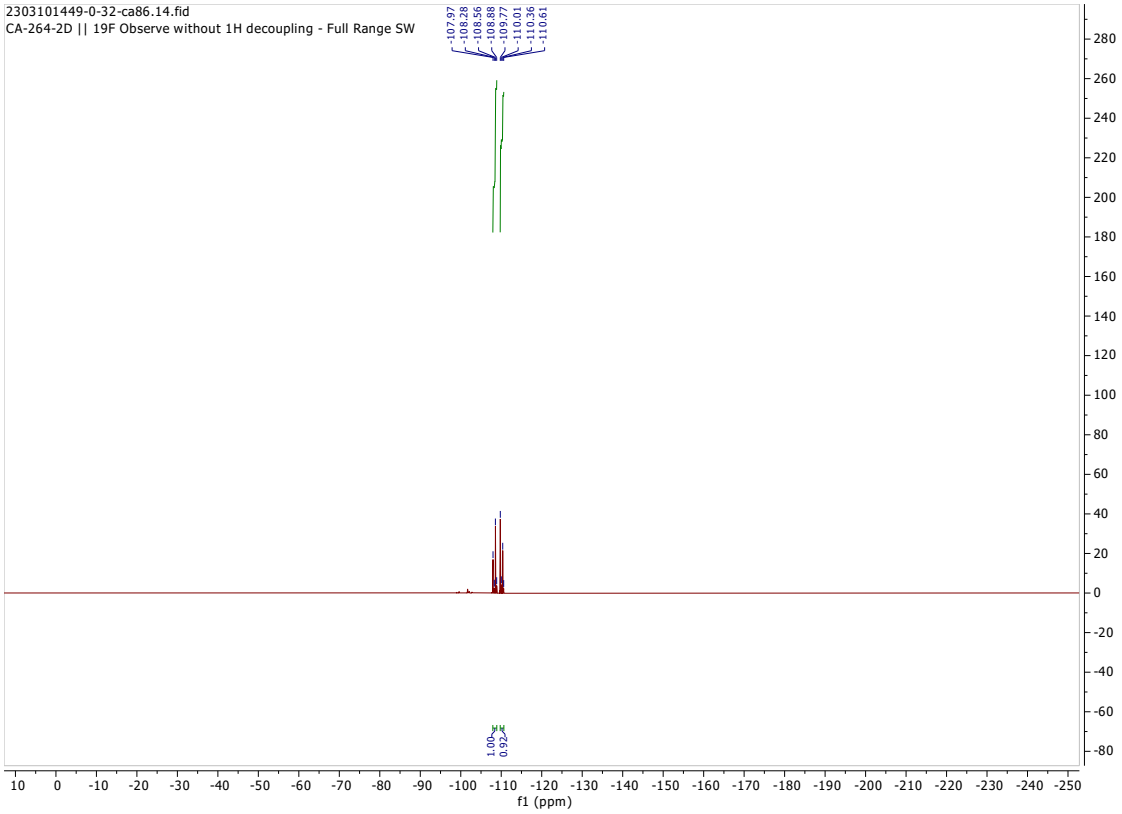
Signal: DAD1D,Sig=254,4 Ref=off

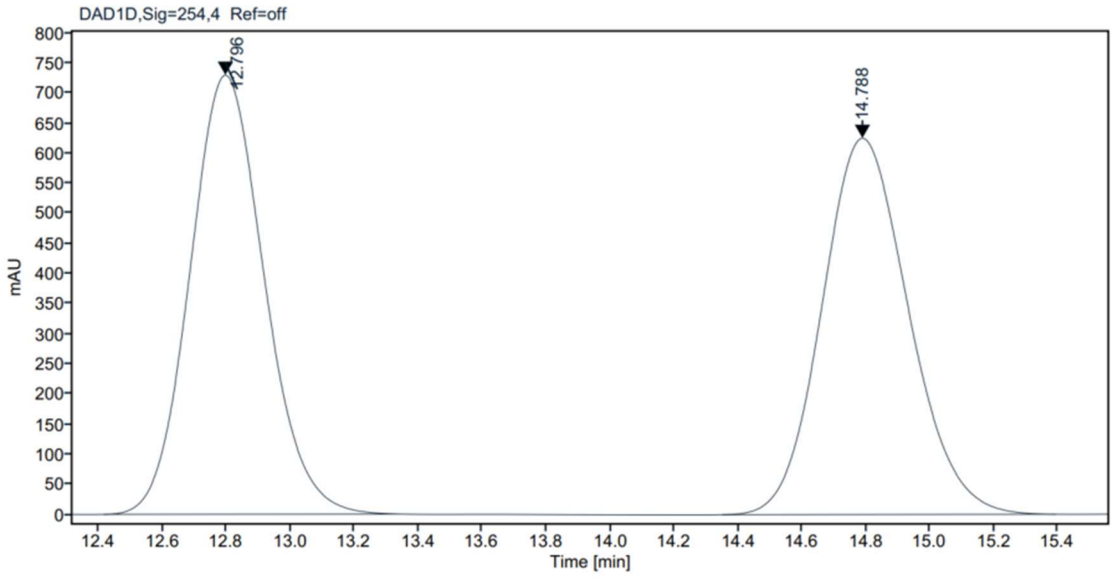
RT [min]	Type	Width [min]	Area	Height	Area%	Name
9.219	MM m	0.6910	2958.4637	231.4588	54.8020	
9.960	MM m	0.7153	2439.9928	178.4976	45.1980	

(*R*)-3g


2303101449-0-32-ca86.10.fid
CA-264-2D || 1H Observe
OMe
CF2
Br
OEt
1.00
0.99
1.01
2.38
2.96
2.48
3.69
f1 (ppm)

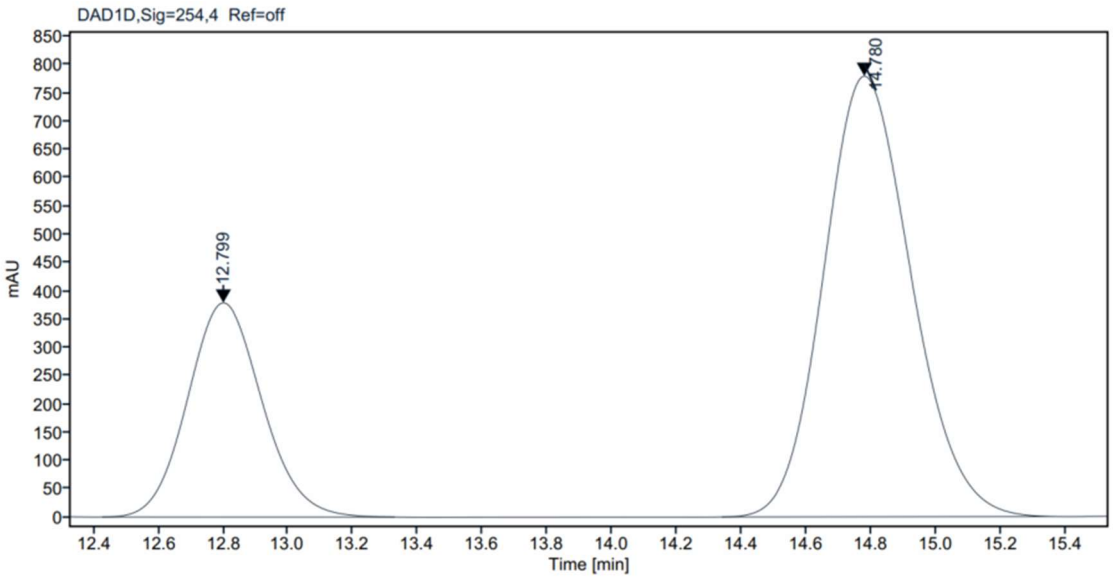

2303101449-0-32-ca86.13.fid
CA-264-2D || 13C Observe with 1H decoupling - D1 = 2s
194.10
162.57
162.32
162.07
151.72
138.82
137.05
130.13
124.12
121.69
113.74
77.48
77.16
76.84
63.75
53.69
36.16
36.14
36.11
13.91
f1 (ppm)





Signal: DAD1D,Sig=254,4 Ref=off

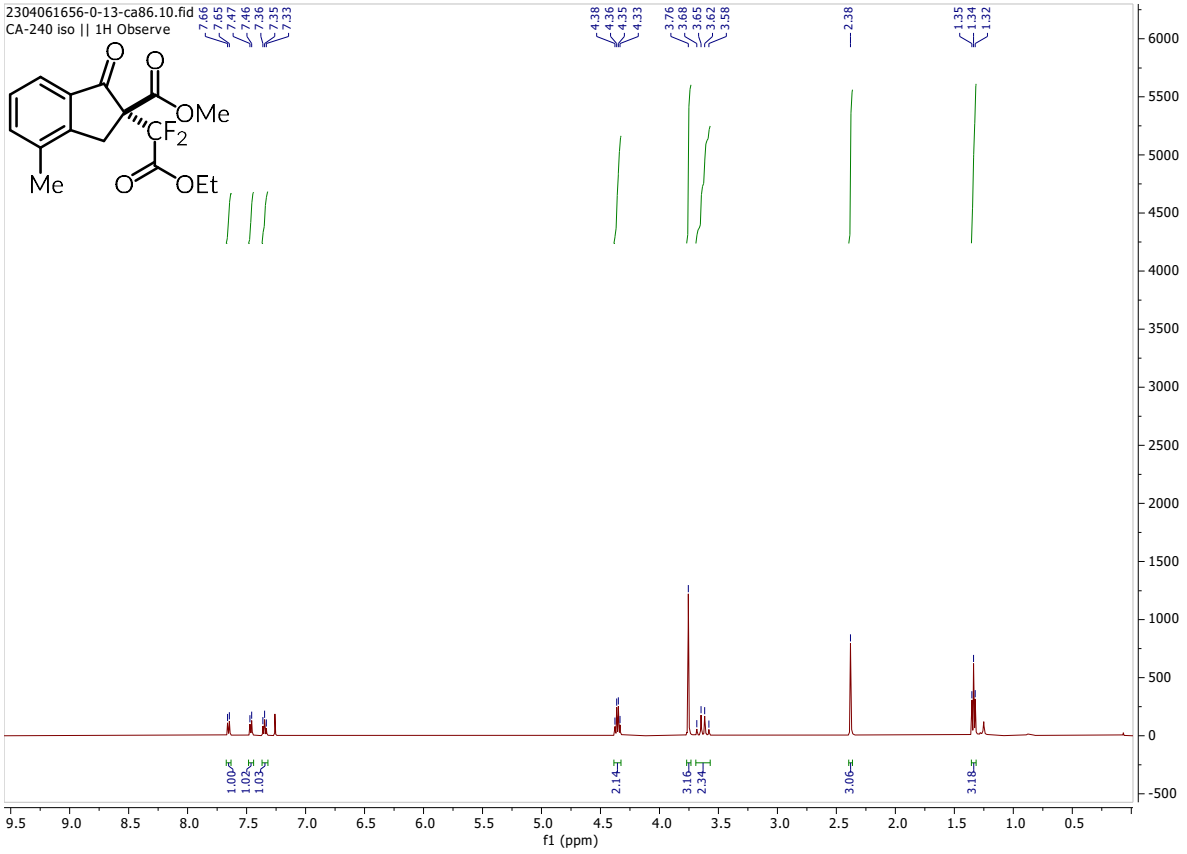
RT [min]	Type	Width [min]	Area	Height	Area%	Name
12.796	MM m	0.9316	11770.8501	729.0064	50.0514	
14.788	MM m	1.0437	11746.6829	624.7078	49.9486	

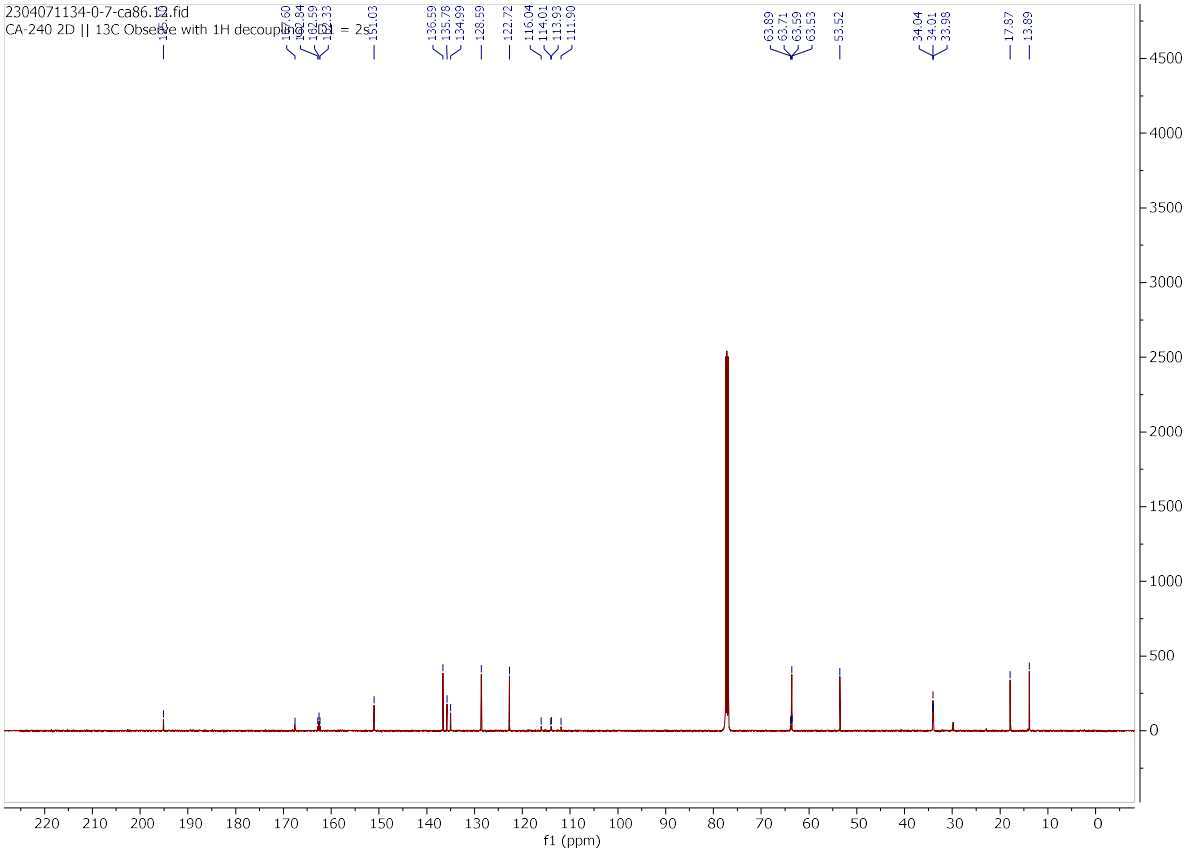


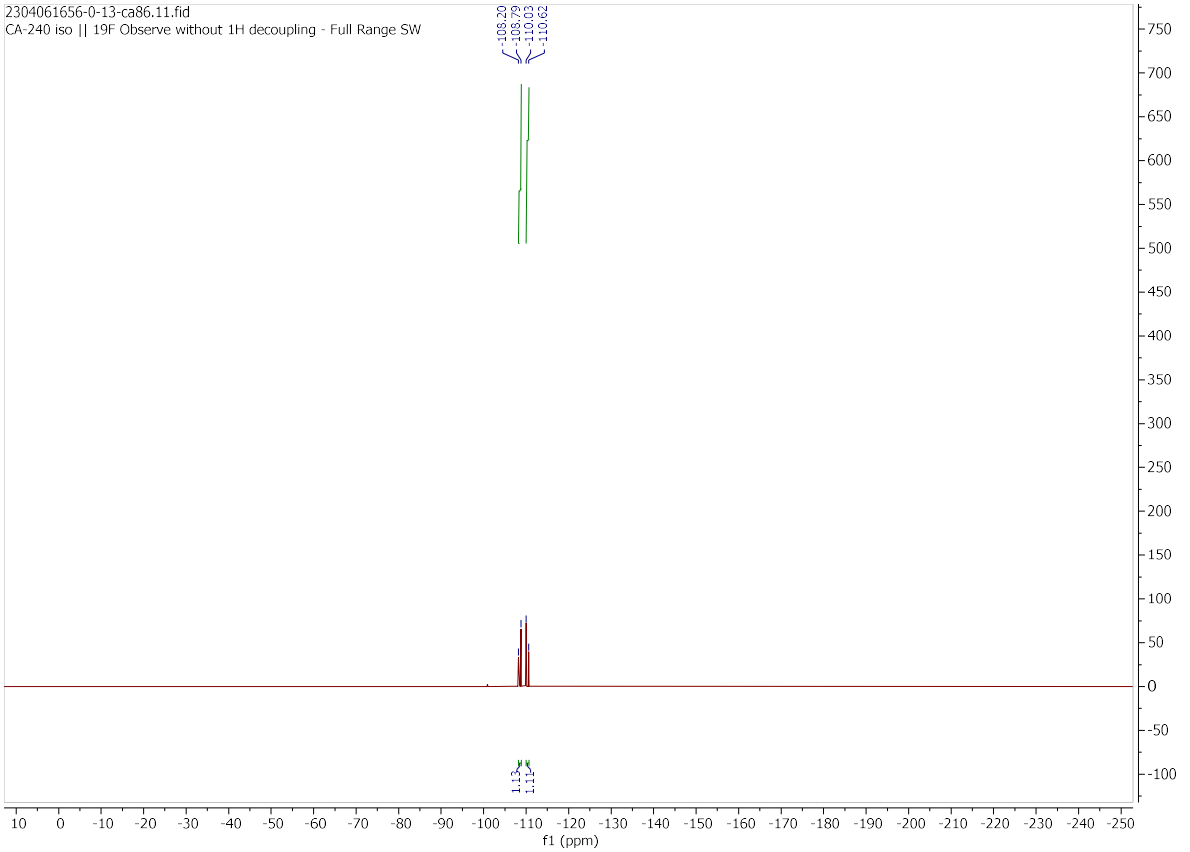
Signal: DAD1D,Sig=254,4 Ref=off

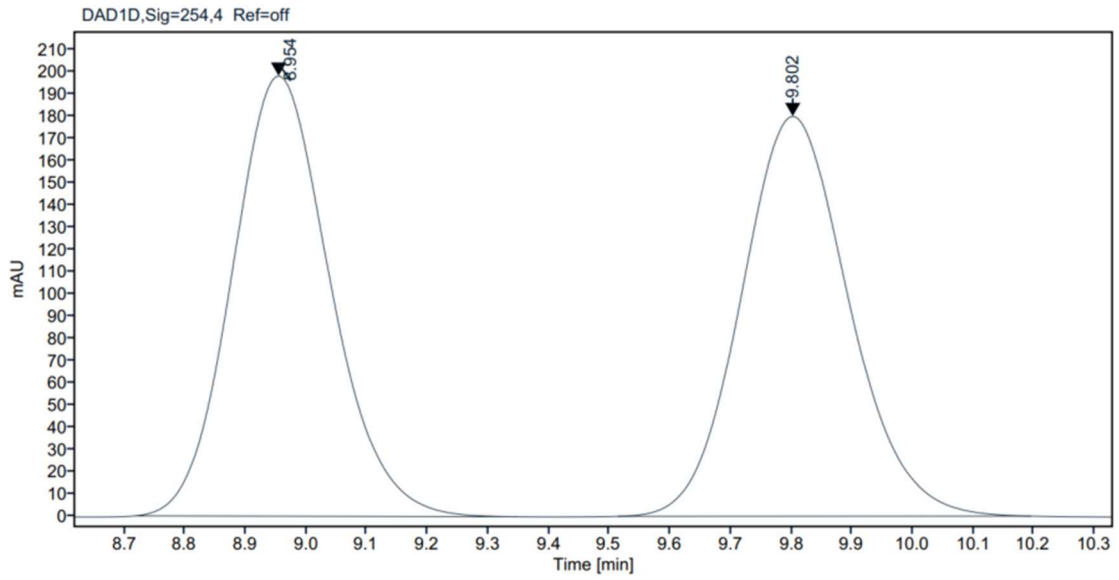
RT [min]	Type	Width [min]	Area	Height	Area%	Name
12.799	MM m	0.9049	6069.4781	378.8658	29.2542	
14.780	MM m	1.0293	14677.8785	779.2605	70.7458	

(*R*)-3h



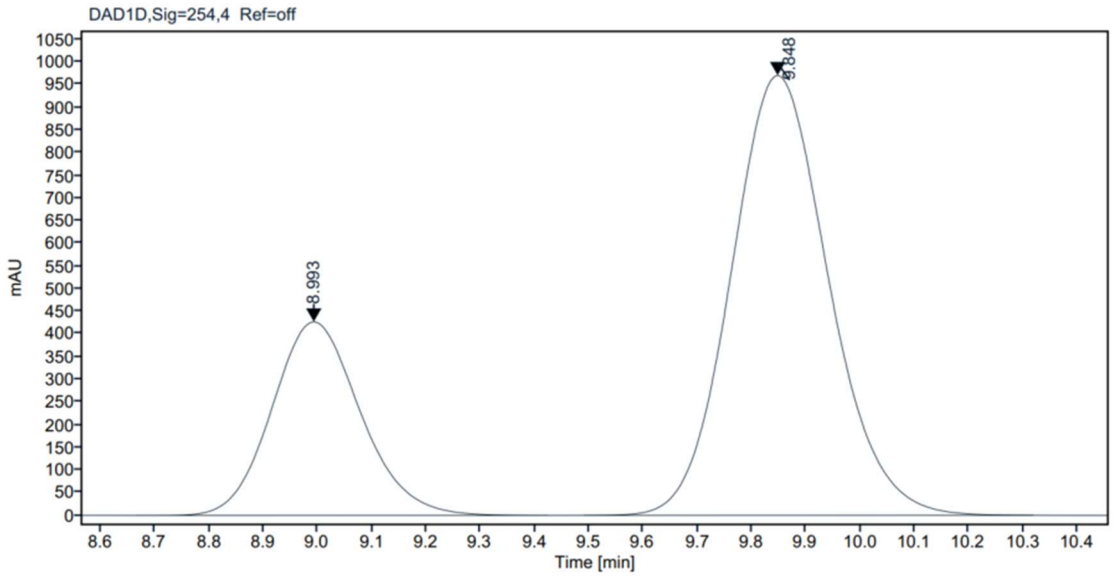

2304071134-0-7-ca86.12.fid
CA-240 2D || 13C Observe with 1H decoupling - D1 = 2s
162.60
160.94
160.59
160.33
151.03
136.59
135.78
134.99
128.59
122.72
116.04
114.01
113.93
111.90
63.89
63.71
63.59
63.53
53.52
34.04
34.01
33.98
17.87
13.89
f1 (ppm)


2304061656-0-13-ca86.11.fid
CA-240 iso || 19F Observe without 1H decoupling - Full Range SW
-108.20
-108.79
-110.03
-110.62
f1 (ppm)



Signal: DAD1D,Sig=254,4 Ref=off

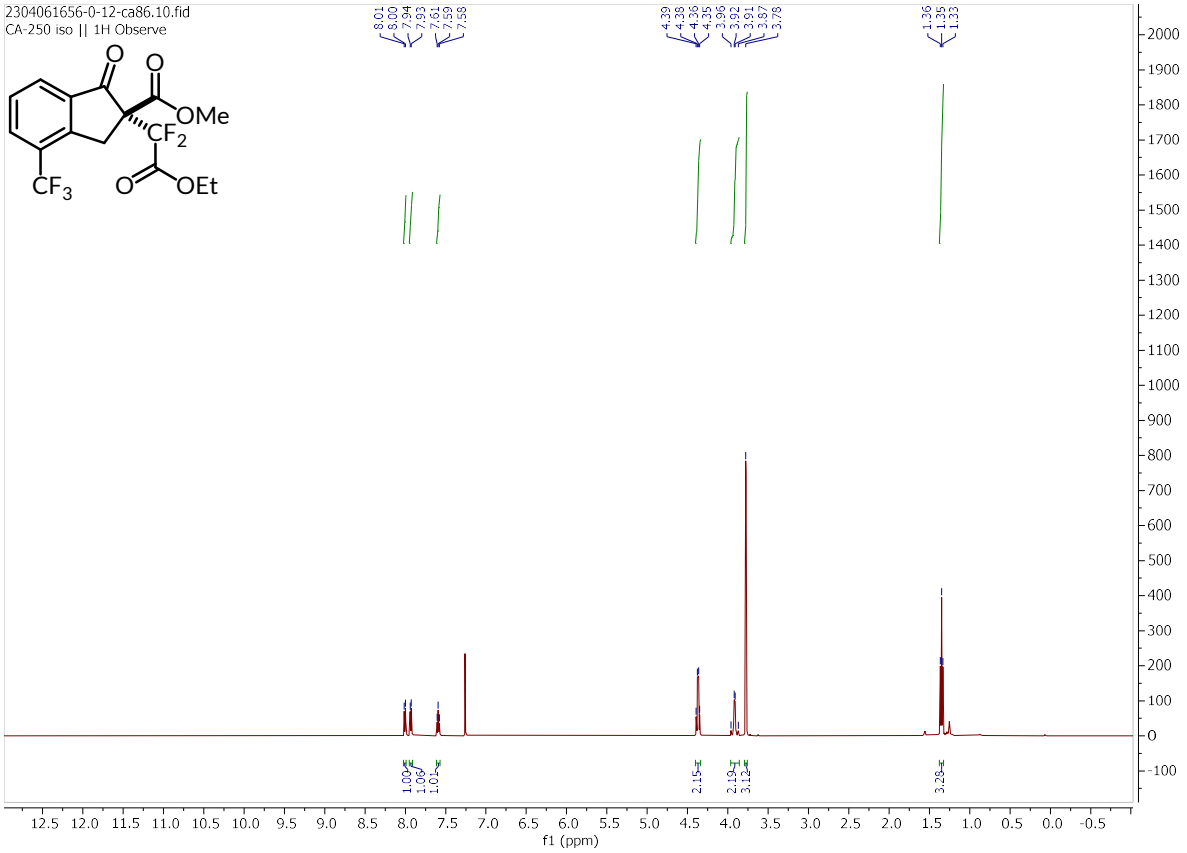
RT [min]	Type	Width [min]	Area	Height	Area%	Name
8.954	MM m	0.6306	2220.0848	198.1102	50.0015	
9.802	MM m	0.6813	2219.9529	179.9709	49.9985	

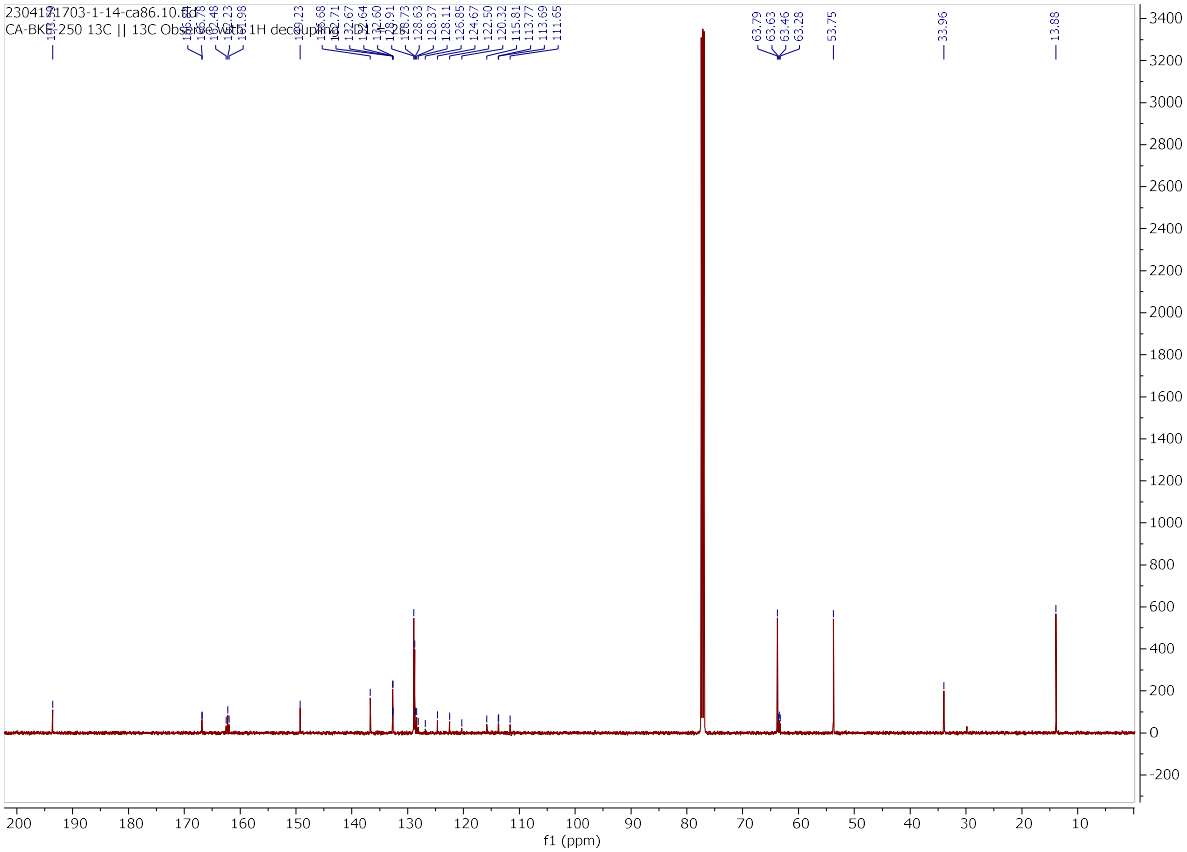


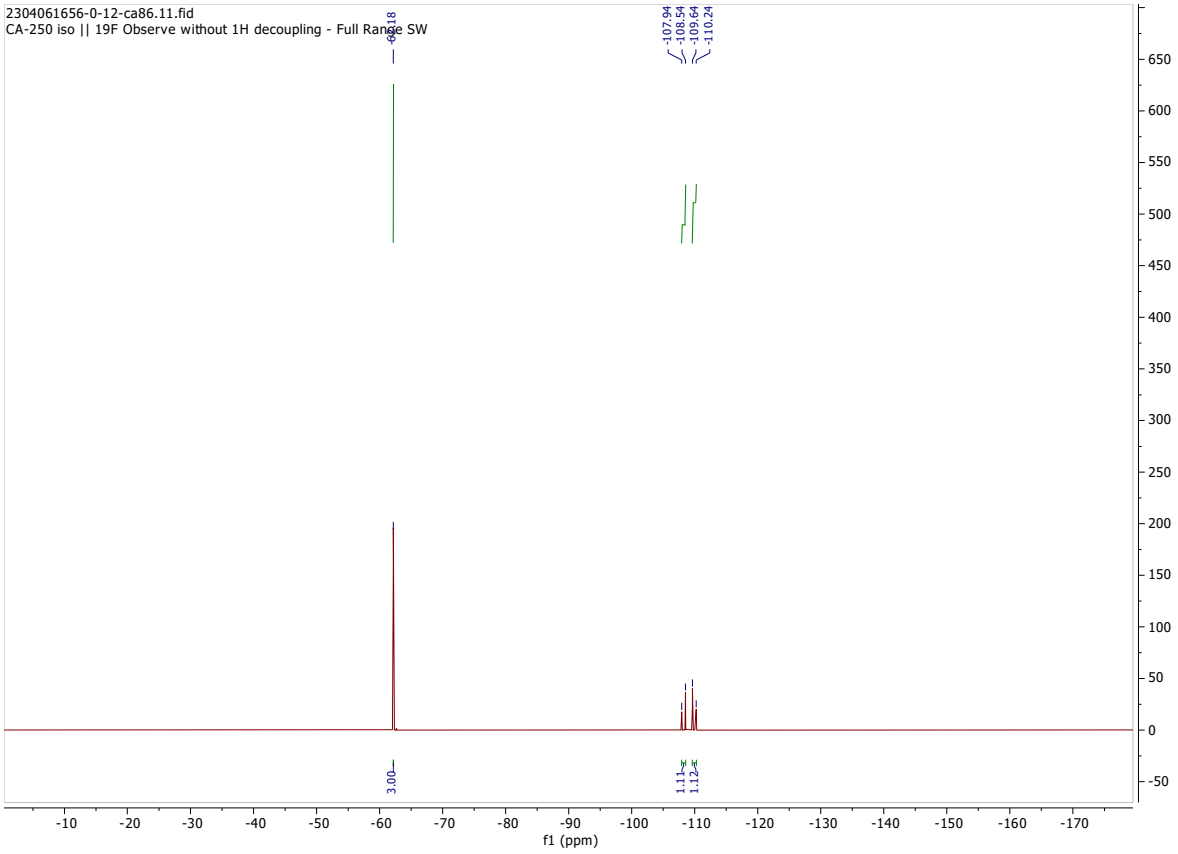
Signal: DAD1D,Sig=254,4 Ref=off

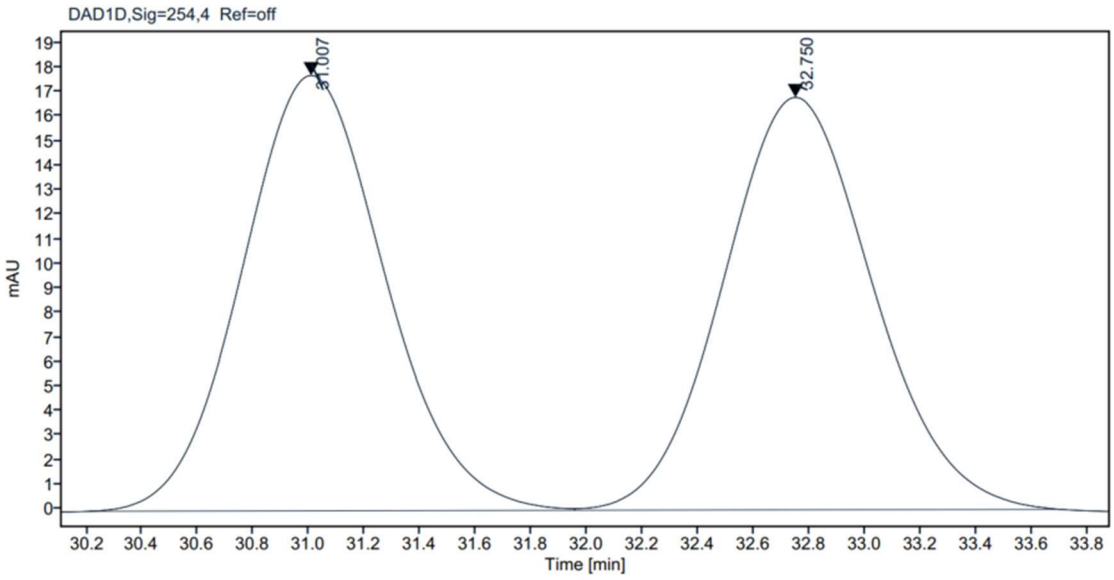
RT [min]	Type	Width [min]	Area	Height	Area%	Name
8.993	MM m	0.7593	4846.6746	427.0793	28.5839	
9.848	MM m	0.8286	12109.2969	970.2446	71.4161	

(*R*)-3i


2304061656-0-12-ca86.10.fid
CA-250 iso || 1H Observe
f1 (ppm)

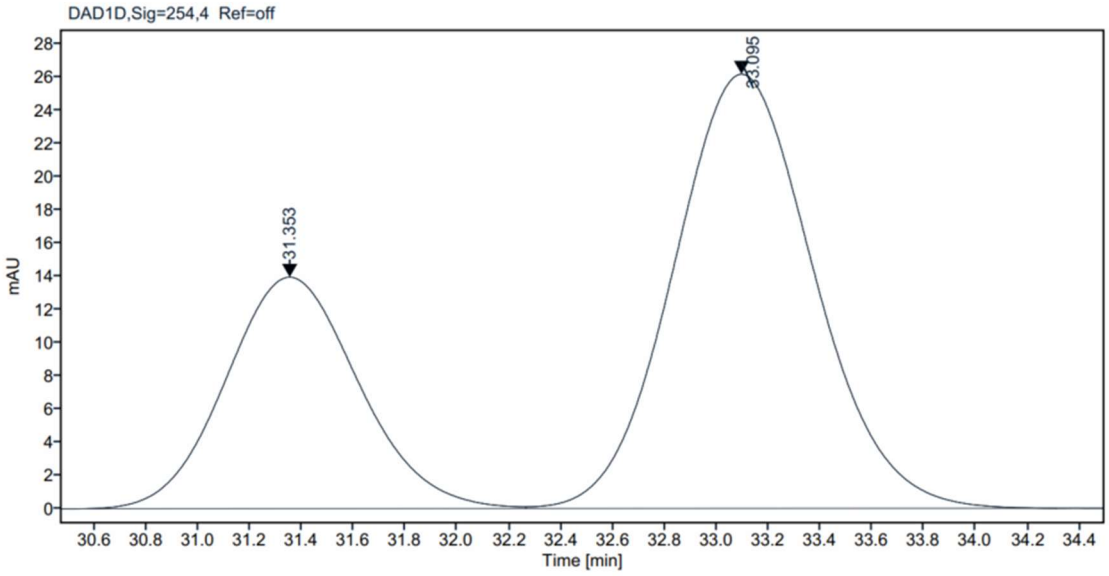

CA-BKE-250 13C || 13C Observe with 1H decoupling
f1 (ppm)





Signal: DAD1D,Sig=254,4 Ref=off

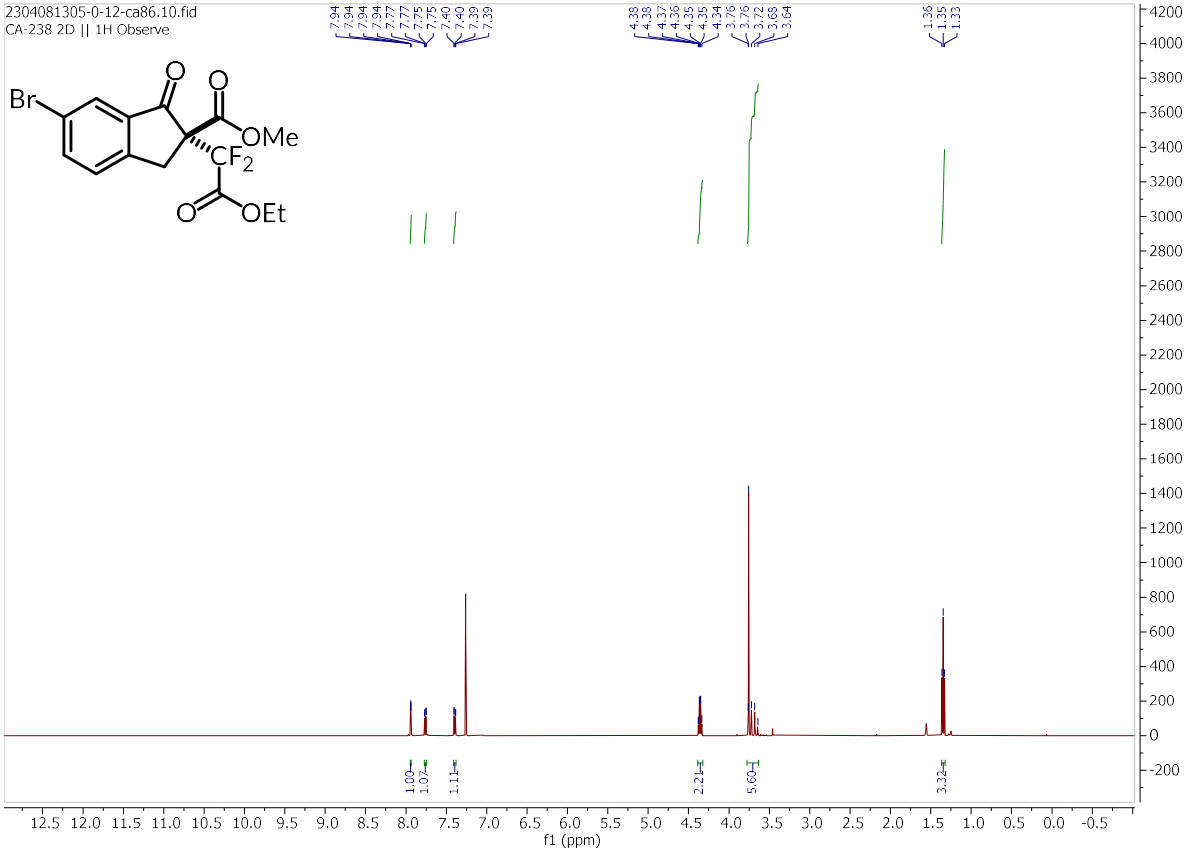
RT [min]	Type	Width [min]	Area	Height	Area%	Name
31.007	MM m	1.7493	632.5060	17.7392	50.1864	
32.750	MM m	1.7493	627.8075	16.8103	49.8136	

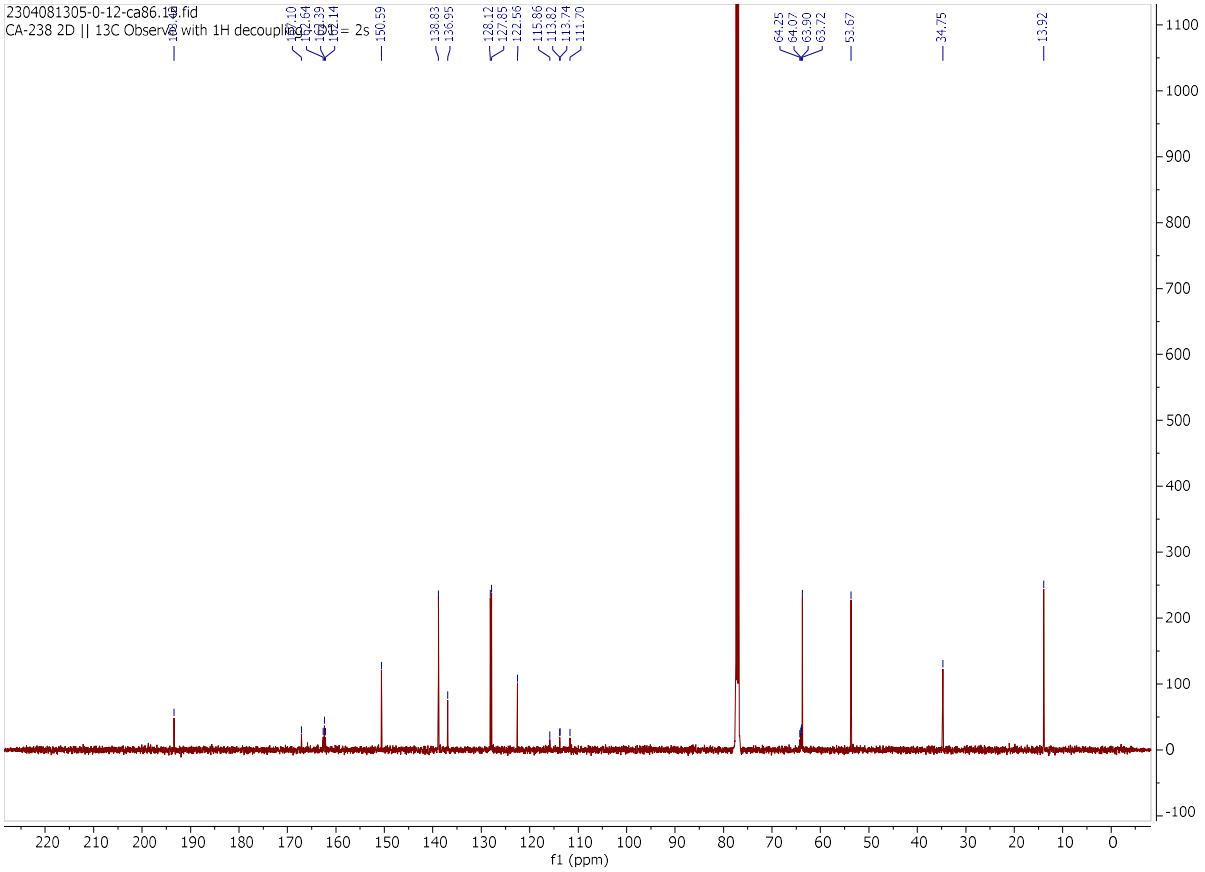


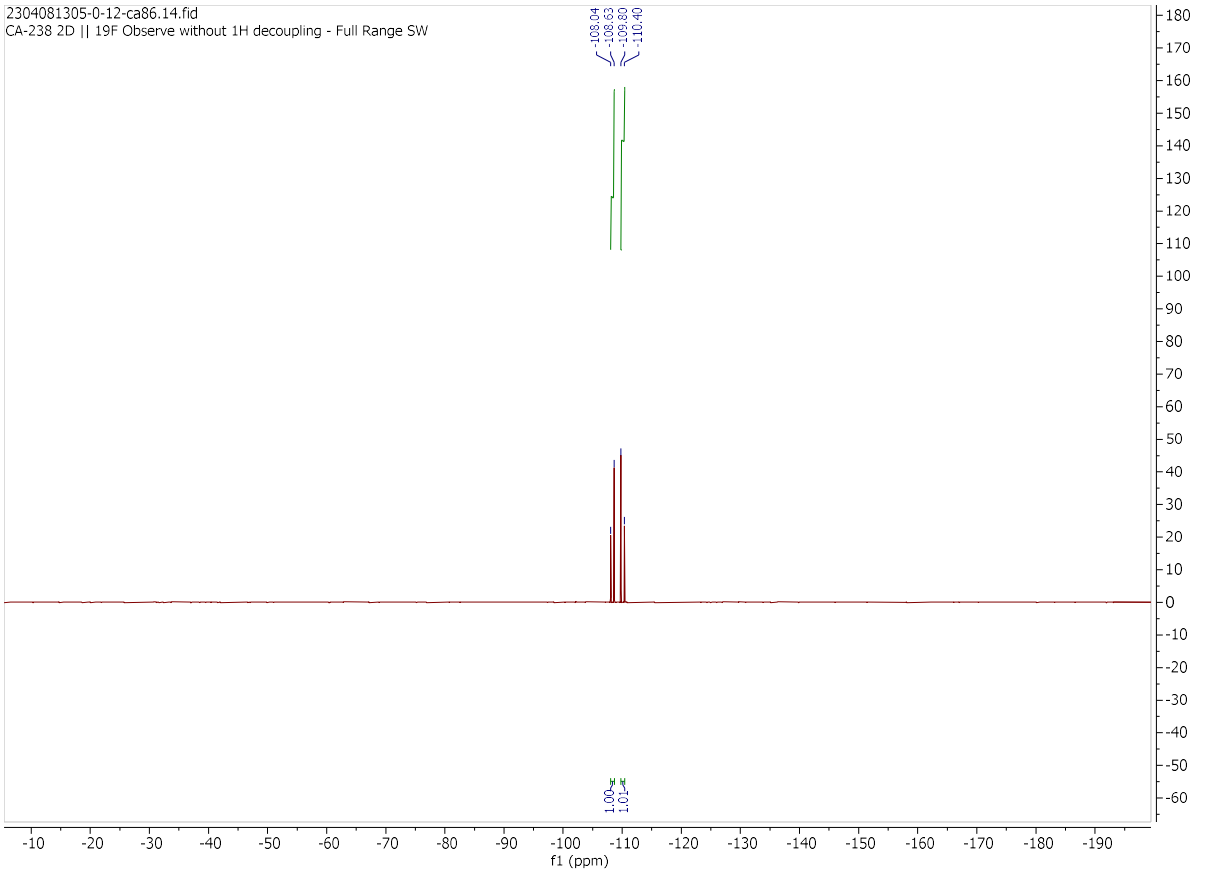
Signal: DAD1D,Sig=254,4 Ref=off

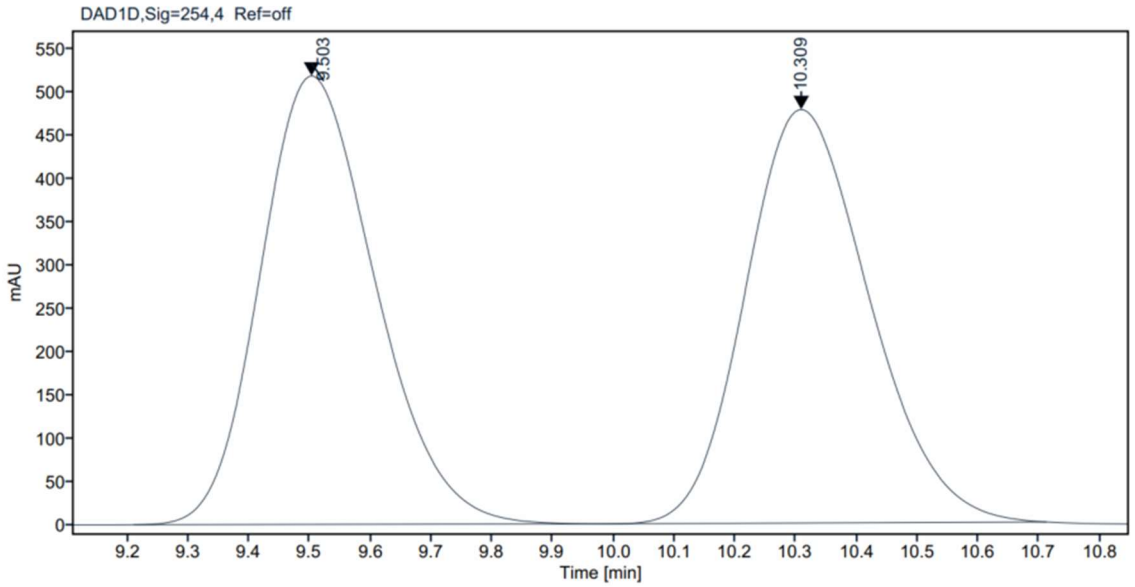
RT [min]	Type	Width [min]	Area	Height	Area%	Name
31.353	MM m	1.6941	496.9330	13.9295	33.5331	
33.095	MM m	2.0486	984.9836	26.1389	66.4669	

(*R*)-3j


2304081305-0-12-ca86.10.fid
CA-238 2D || 1H Observe
Br
O
O
OMe
CF2
O
OEt
f1 (ppm)

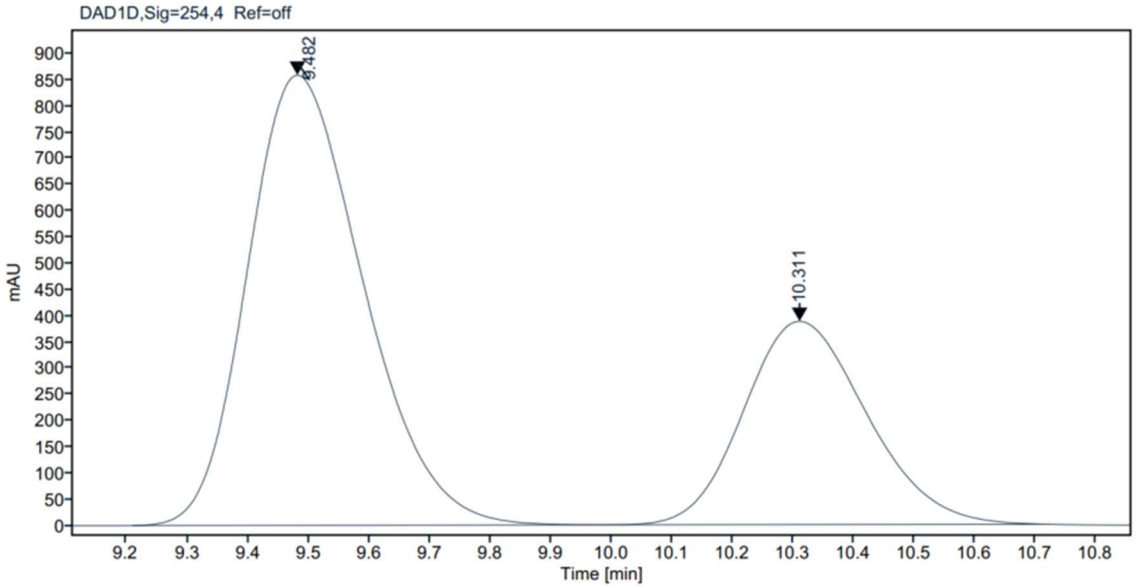

2304081305-0-12-ca86.15.fid
CA-238 2D || 13C Observe with 1H decoupling - d1 = 2s
196.10
162.64
159.39
150.59
138.83
136.95
128.12
127.85
122.56
115.86
113.82
113.74
111.70
64.25
64.07
63.90
63.72
53.67
34.75
13.92
f1 (ppm)


2304081305-0-12-ca86.14.fid
CA-238 2D || 19F Observe without 1H decoupling - Full Range SW
-108.04
-108.63
-109.80
-110.40
1.00
1.02
f1 (ppm)



Signal: DAD1D,Sig=254,4 Ref=off

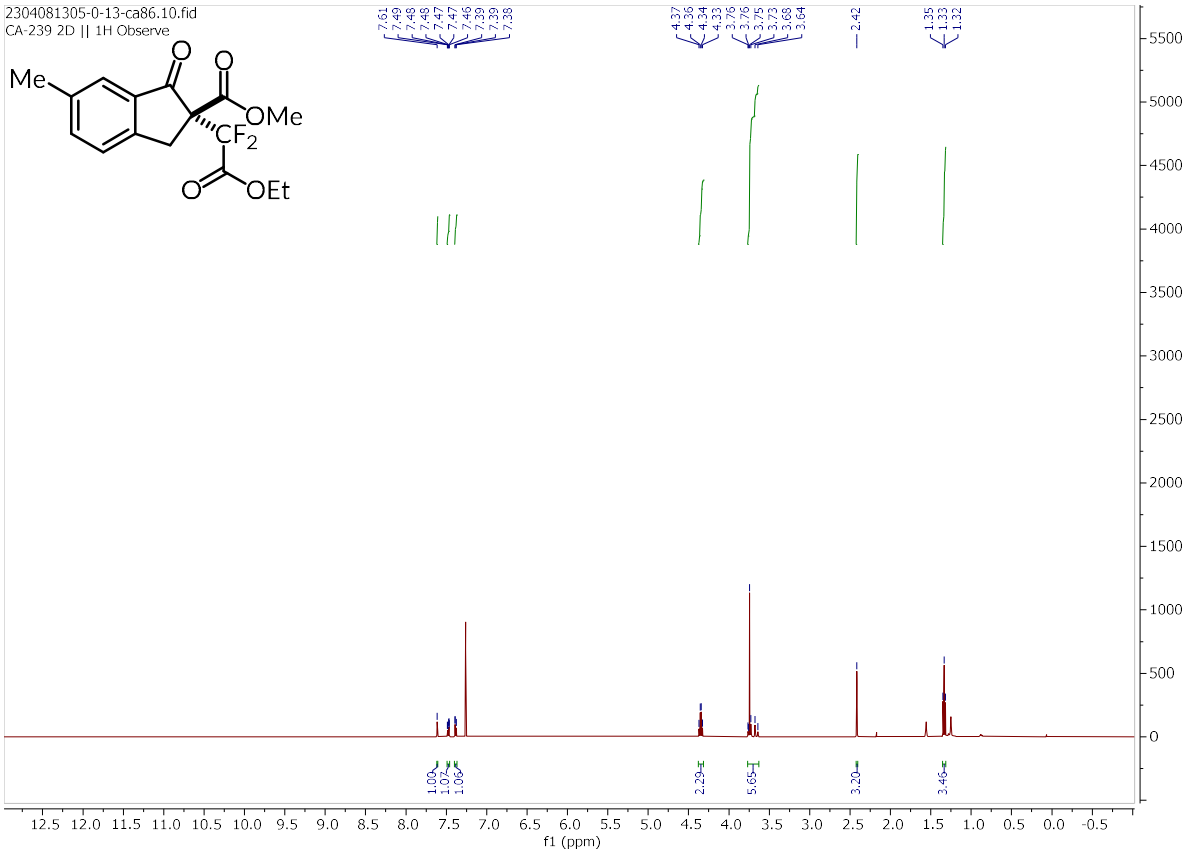
RT [min]	Type	Width [min]	Area	Height	Area%	Name
9.503	MM m	0.7514	6814.0983	518.5834	50.1634	
10.309	MM m	0.7514	6769.6983	478.1255	49.8366	

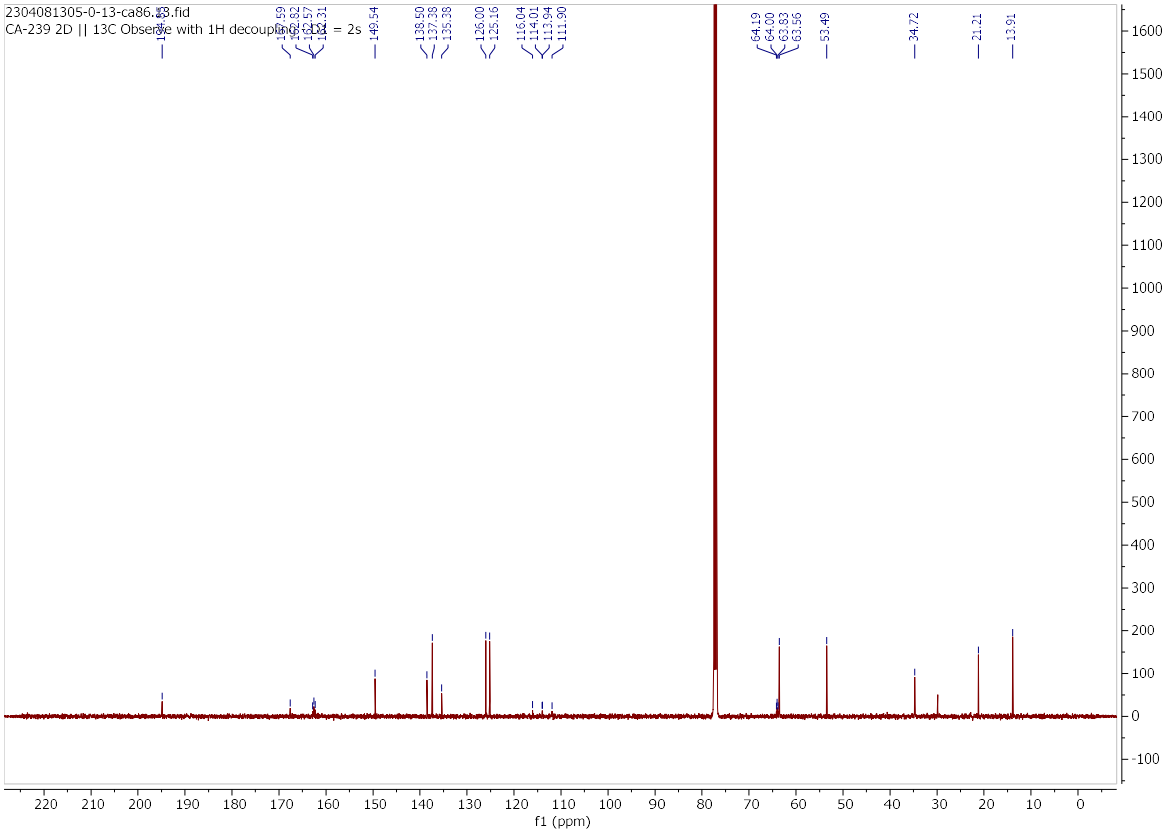


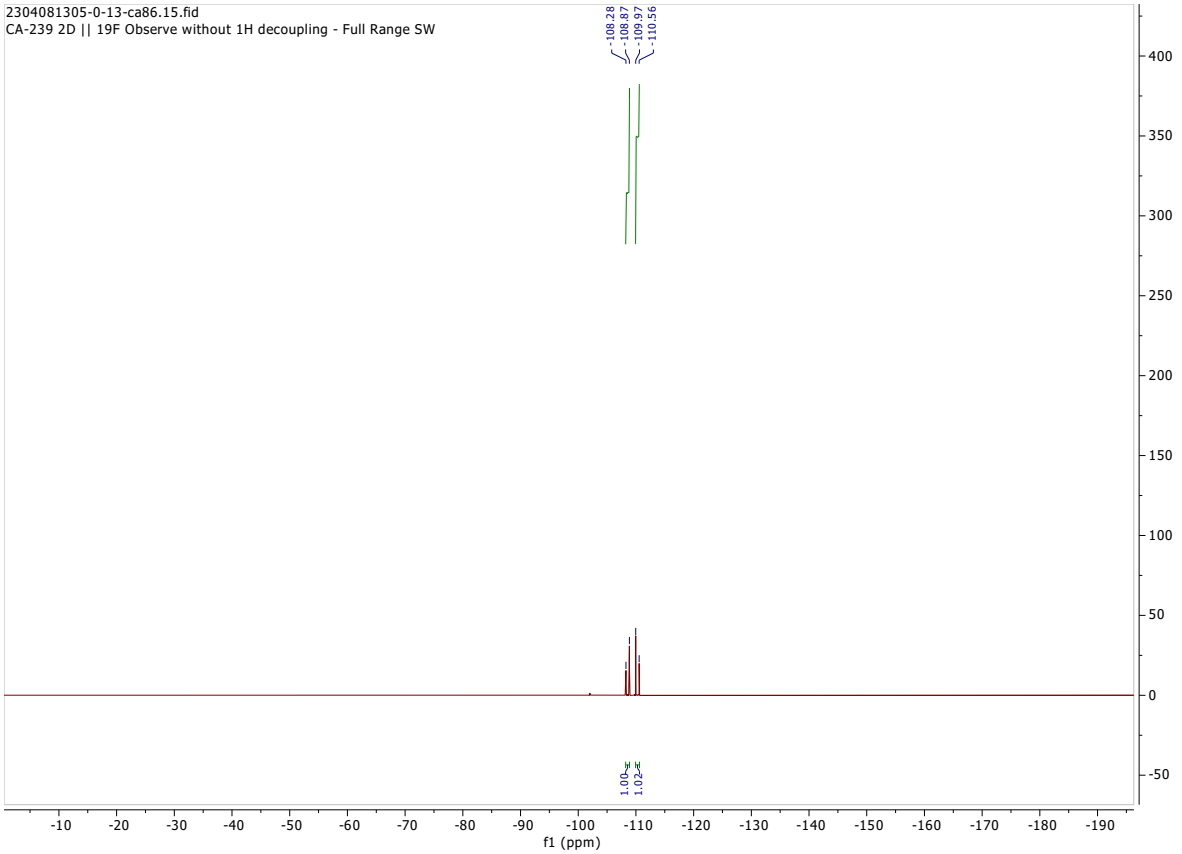
Signal: DAD1D,Sig=254,4 Ref=off

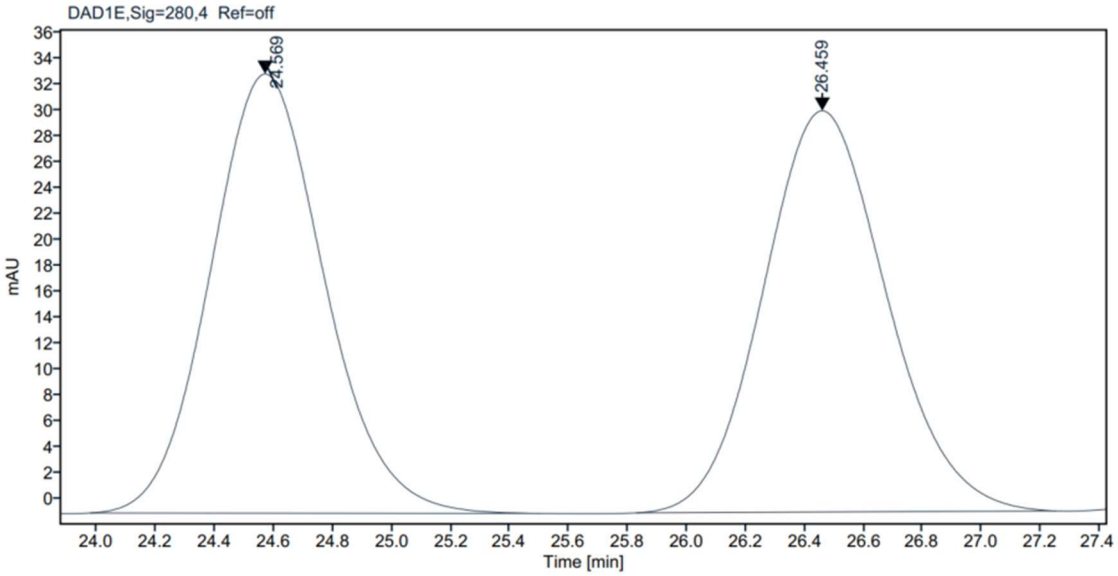
RT [min]	Type	Width [min]	Area	Height	Area%	Name
9.482	MM m	0.7994	11389.4524	858.0930	67.5403	
10.311	MM m	0.7144	5473.7542	387.5555	32.4597	

(*R*)-3k


2304081305-0-13-ca86.10.fid
CA-239 2D || 1H Observe
Me
O
O
OMe
CF2
O
OEt
f1 (ppm)

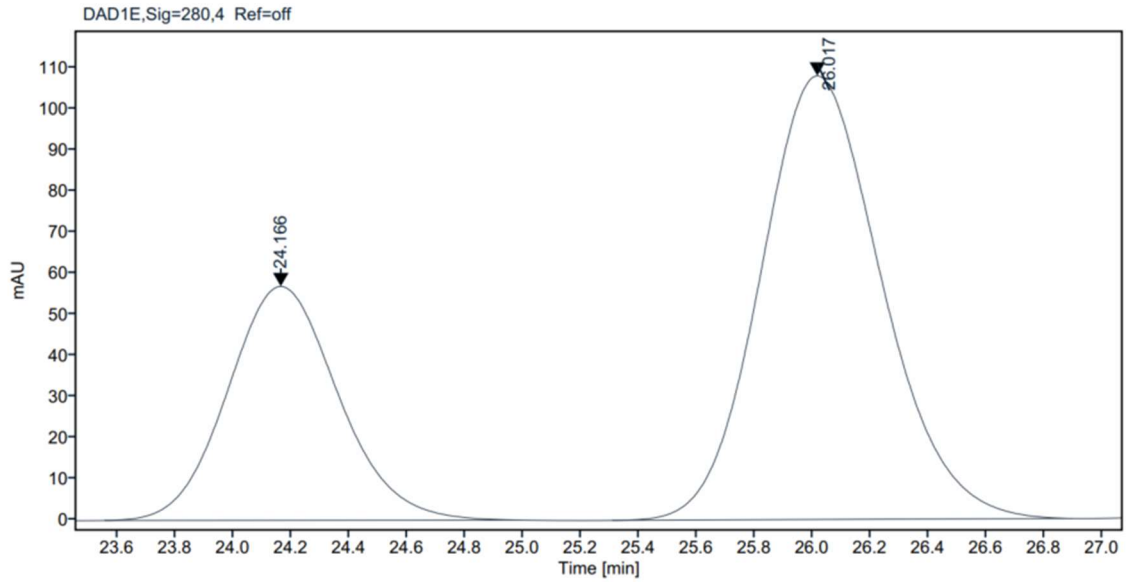

2304081305-0-13-ca86.13.fid
CA-239 2D || 13C Observe with 1H decoupling
f1 (ppm)





Signal: DAD1E,Sig=280,4 Ref=off

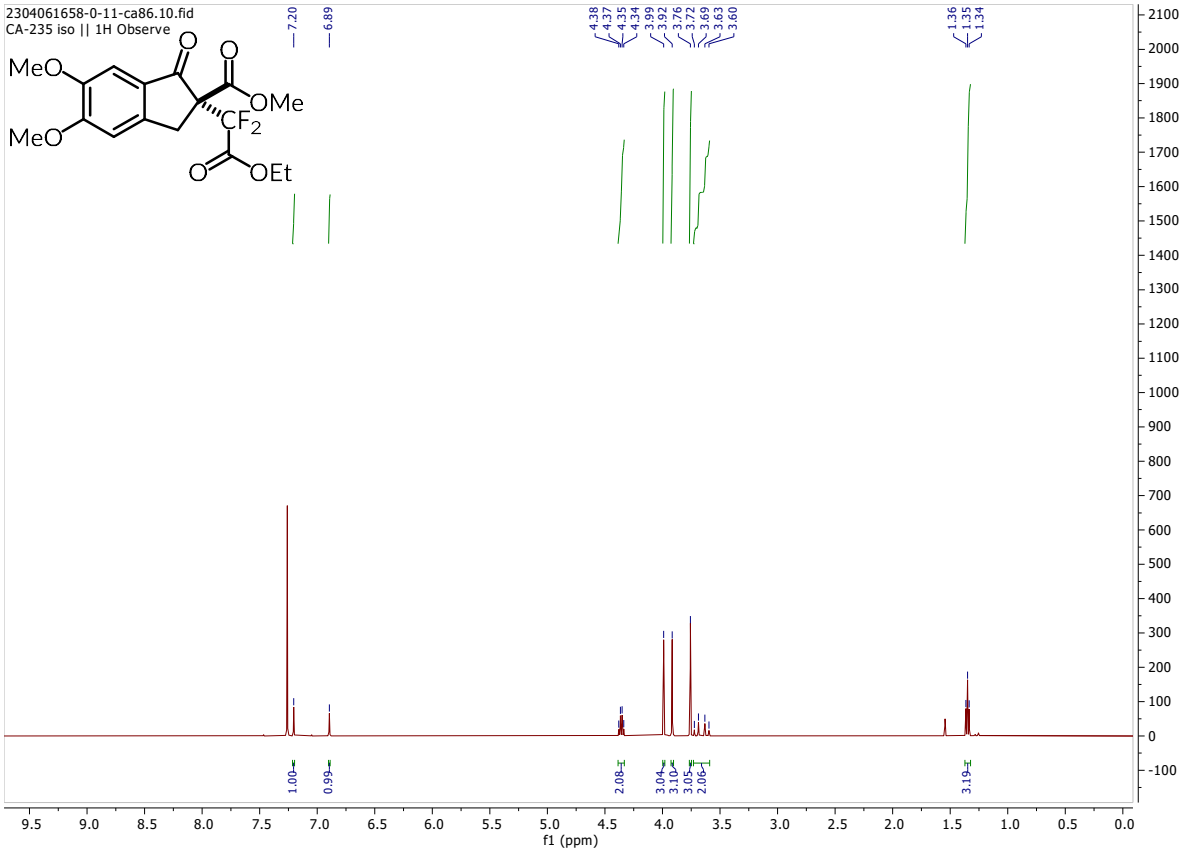
RT [min]	Type	Width [min]	Area	Height	Area%	Name
24.569	MM m	1.5268	911.5006	33.9991	50.2652	
26.459	MM m	1.4250	901.8808	31.0607	49.7348	

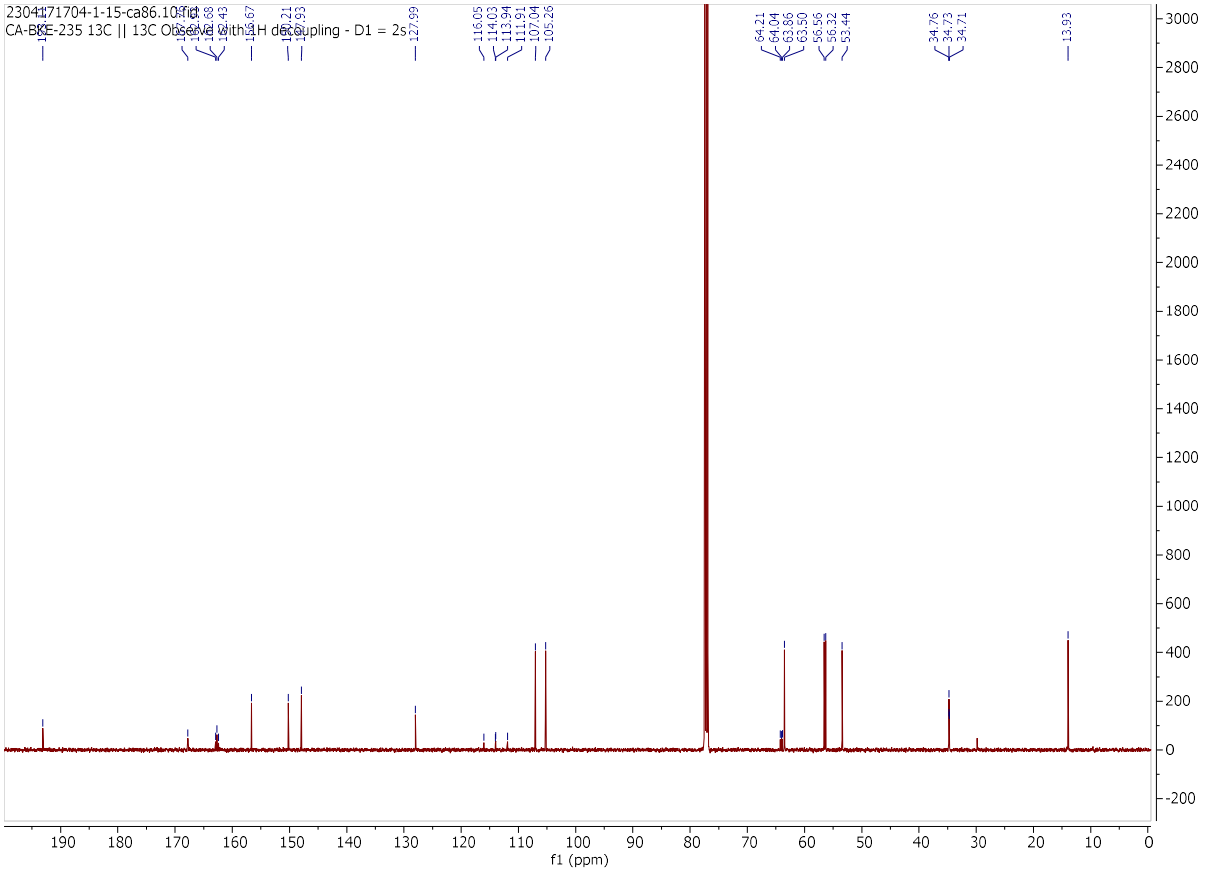


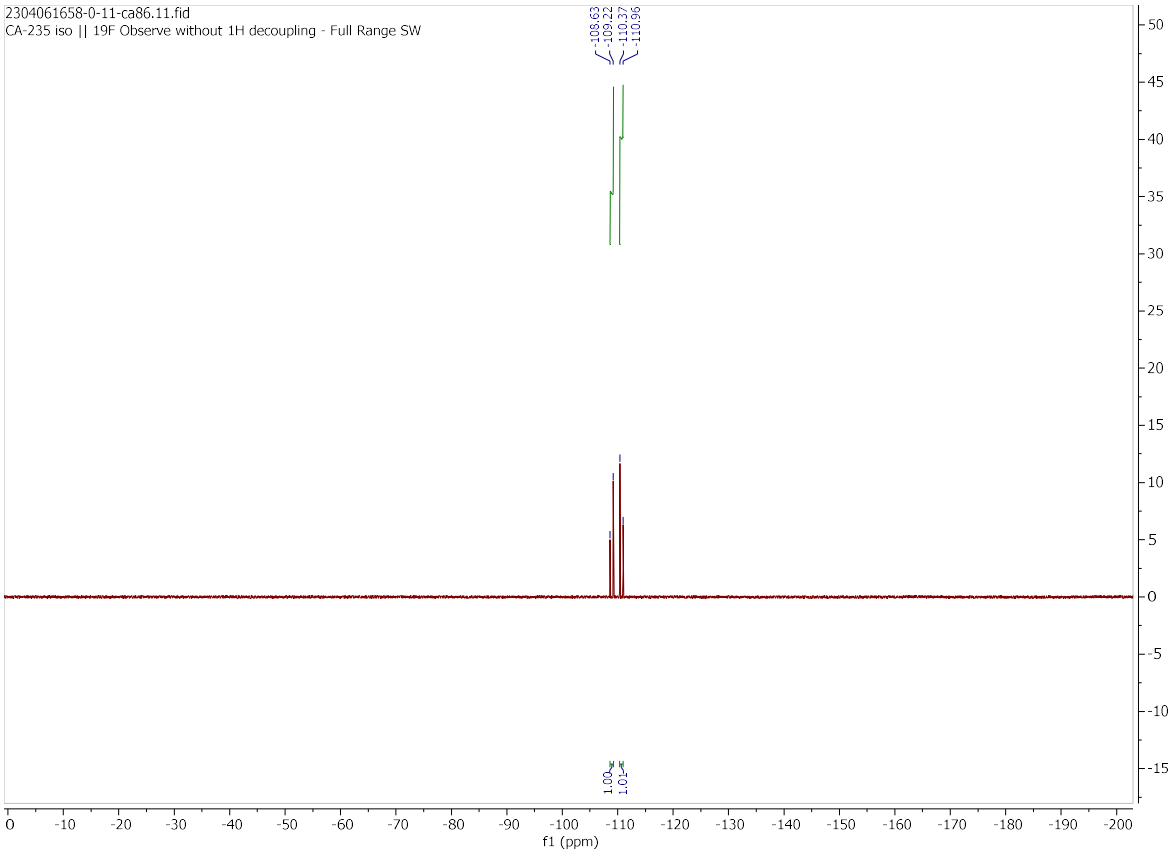
Signal: DAD1E,Sig=280,4 Ref=off

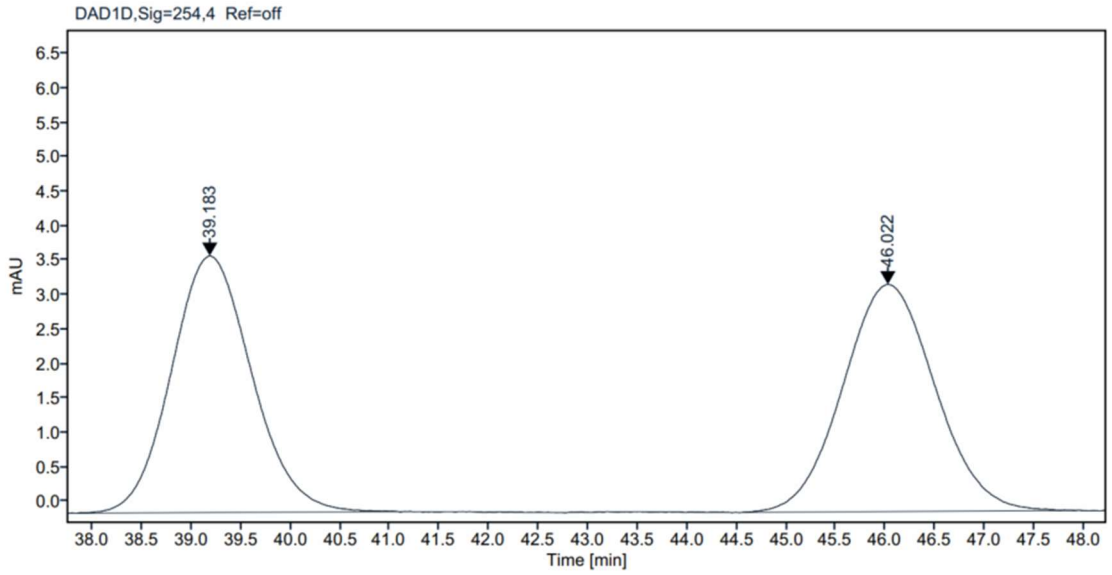
RT [min]	Type	Width [min]	Area	Height	Area%	Name
24.166	MM m	1.4426	1511.0189	56.9269	32.5505	
26.017	MM m	1.5868	3131.0520	107.9751	67.4495	

(*R*)-3l



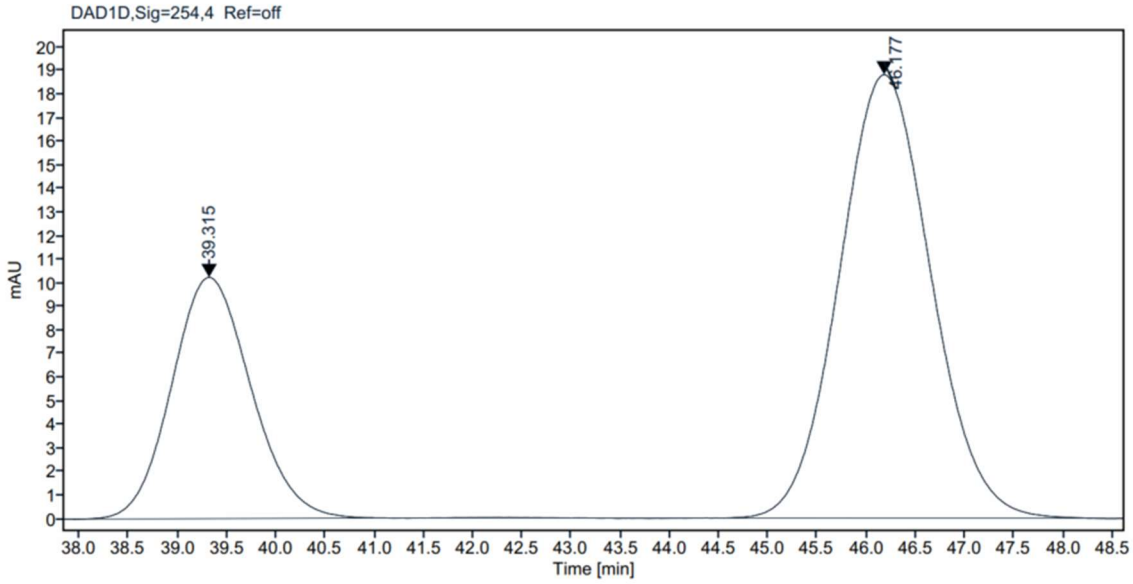

2304171704-1-15-ca86.10.fid
CA-BKE-235 13C || 13C Observe with 1H decoupling - D1 = 2s
127.99
116.05
114.03
113.94
111.91
107.04
105.26
64.21
64.04
63.86
63.50
56.56
56.32
53.44
34.76
34.73
34.71
13.93
f1 (ppm)


2304061658-0-11-ca86.11.fid
CA-235 iso || 19F Observe without 1H decoupling - Full Range SW
-108.63
-109.22
-110.37
-110.96
1.00
1.01
f1 (ppm)



Signal: DAD1D,Sig=254,4 Ref=off

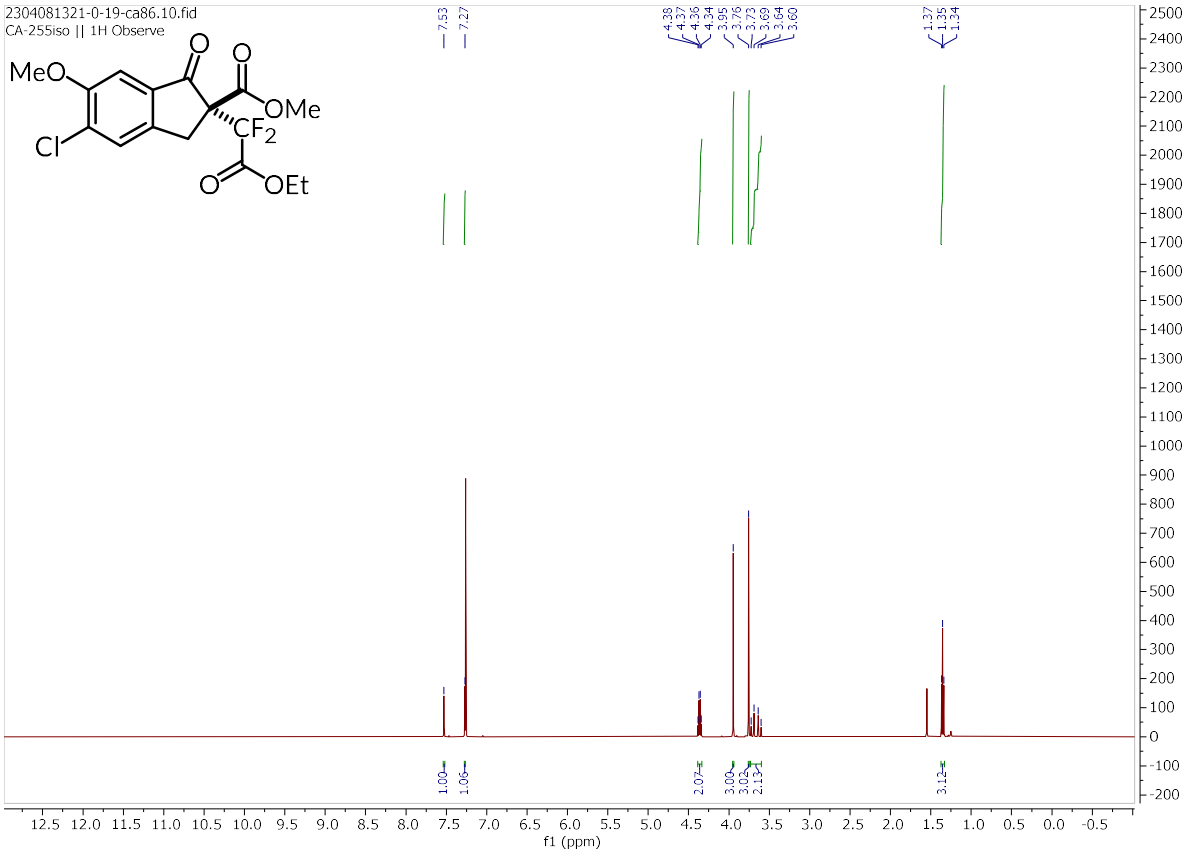
RT [min]	Type	Width [min]	Area	Height	Area%	Name
39.183	MM m	3.3115	210.0031	3.7237	49.6439	
46.022	MM m	3.3545	213.0160	3.2946	50.3561	

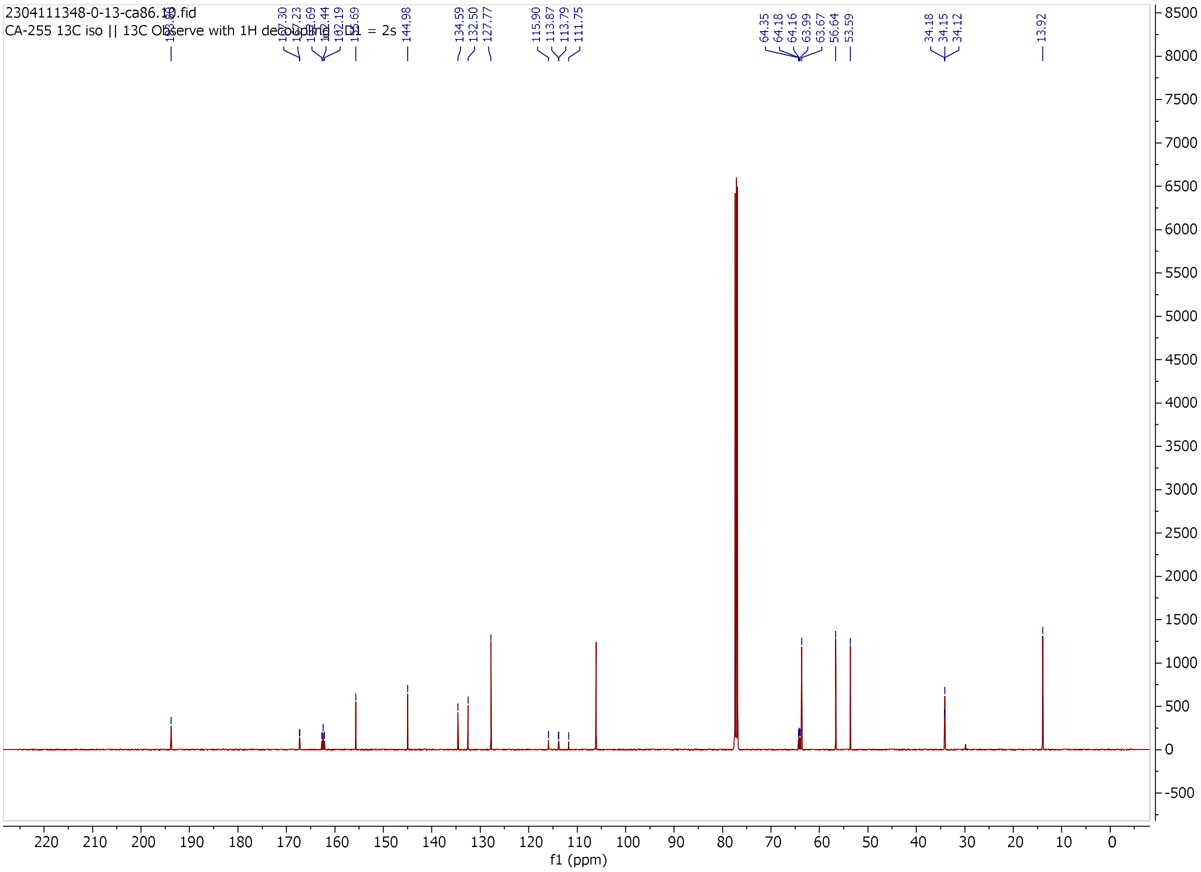


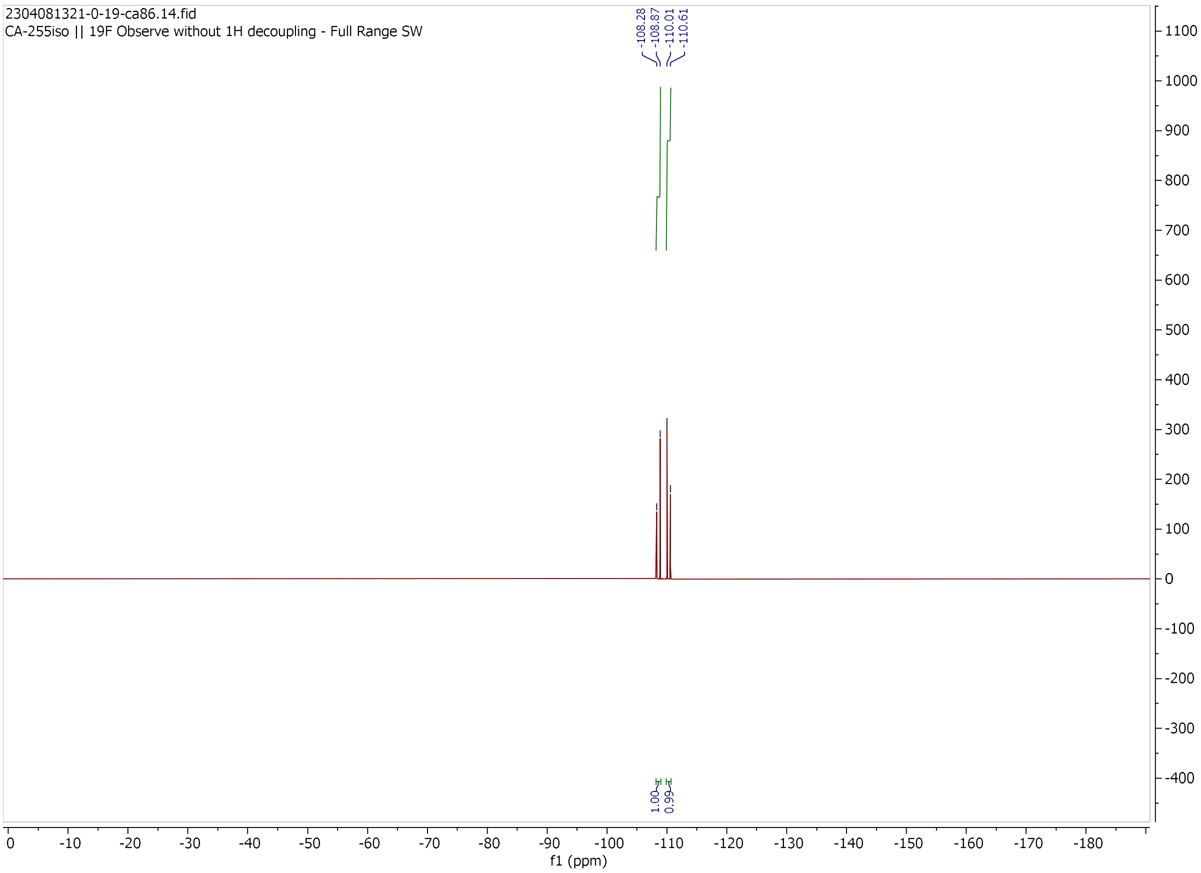
Signal: DAD1D,Sig=254,4 Ref=off

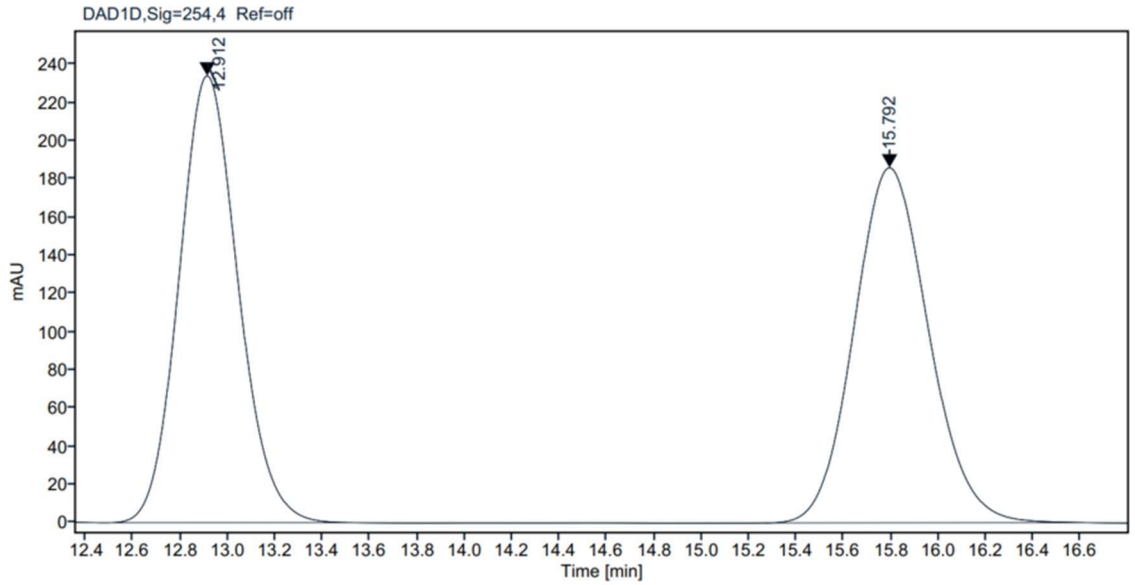
RT [min]	Type	Width [min]	Area	Height	Area%	Name
39.315	MM m	3.0964	572.9052	10.2244	31.9663	
46.177	MM m	3.8705	1219.3112	18.7938	68.0337	

(*R*)-3m


2304081321-0-19-ca86.10.fid
CA-255iso || 1H Observe
MeO
Cl
O
O
OMe
CF2
O
OEt
7.53
7.27
4.38
4.37
4.36
4.34
3.95
3.76
3.73
3.69
3.64
3.60
1.37
1.35
1.34
1.00
1.06
2.07
3.00
3.02
2.13
3.12
f1 (ppm)

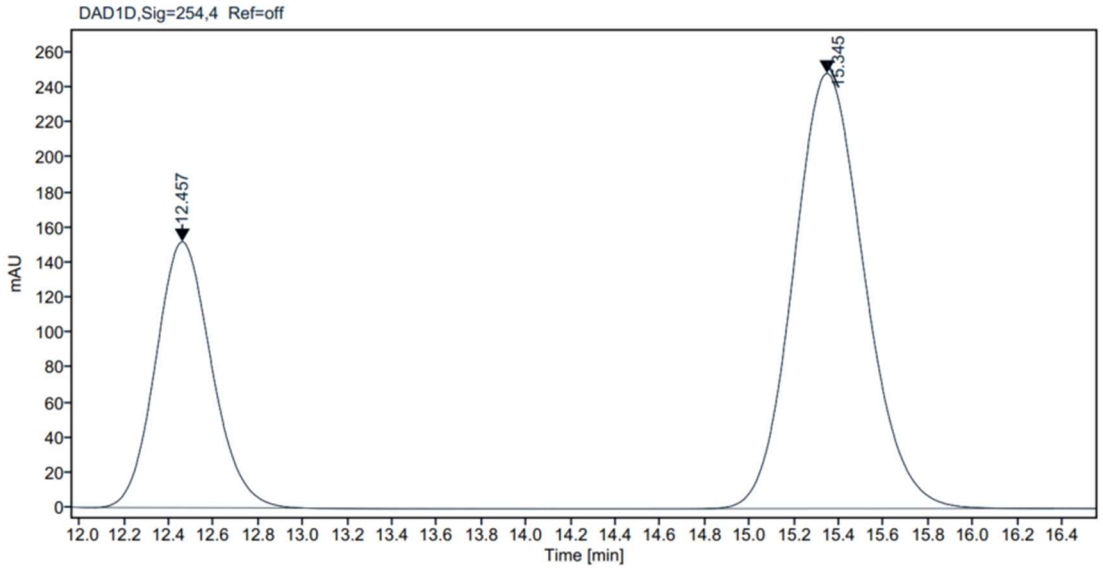

CA-255 13C iso || 13C Observe with 1H decoupling
144.98
134.59
132.50
127.77
115.90
113.87
113.79
111.75
64.35
64.18
64.16
63.99
63.67
56.64
53.59
34.18
34.15
34.12
13.92
f1 (ppm)


2304081321-0-19-ca86.14.fid
CA-255iso || 19F Observe without 1H decoupling - Full Range SW
-108.28
-108.87
-110.01
-110.61
1.00
0.99
f1 (ppm)



Signal: DAD1D,Sig=254,4 Ref=off

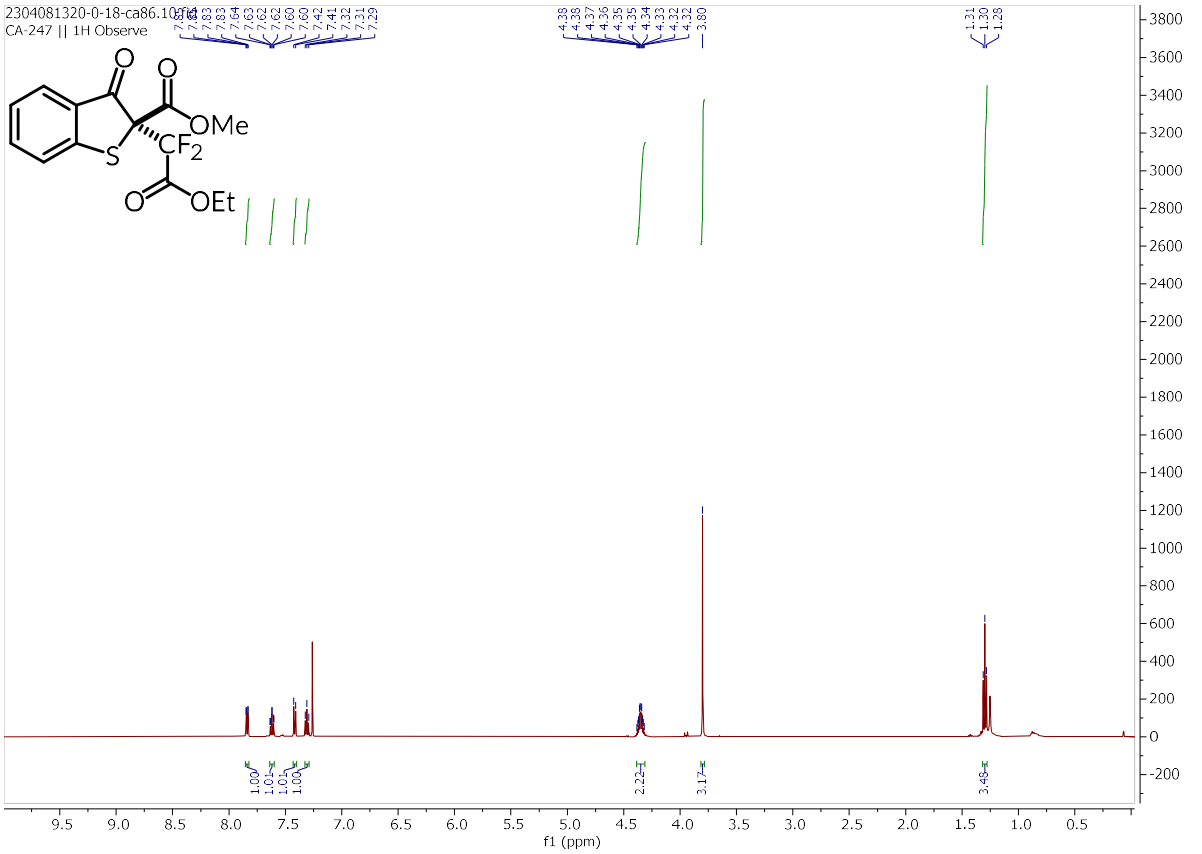
RT [min]	Type	Width [min]	Area	Height	Area%	Name
12.912	MM m	1.0750	4055.4954	234.0865	49.9001	
15.792	MM m	1.3437	4071.7353	186.0361	50.0999	

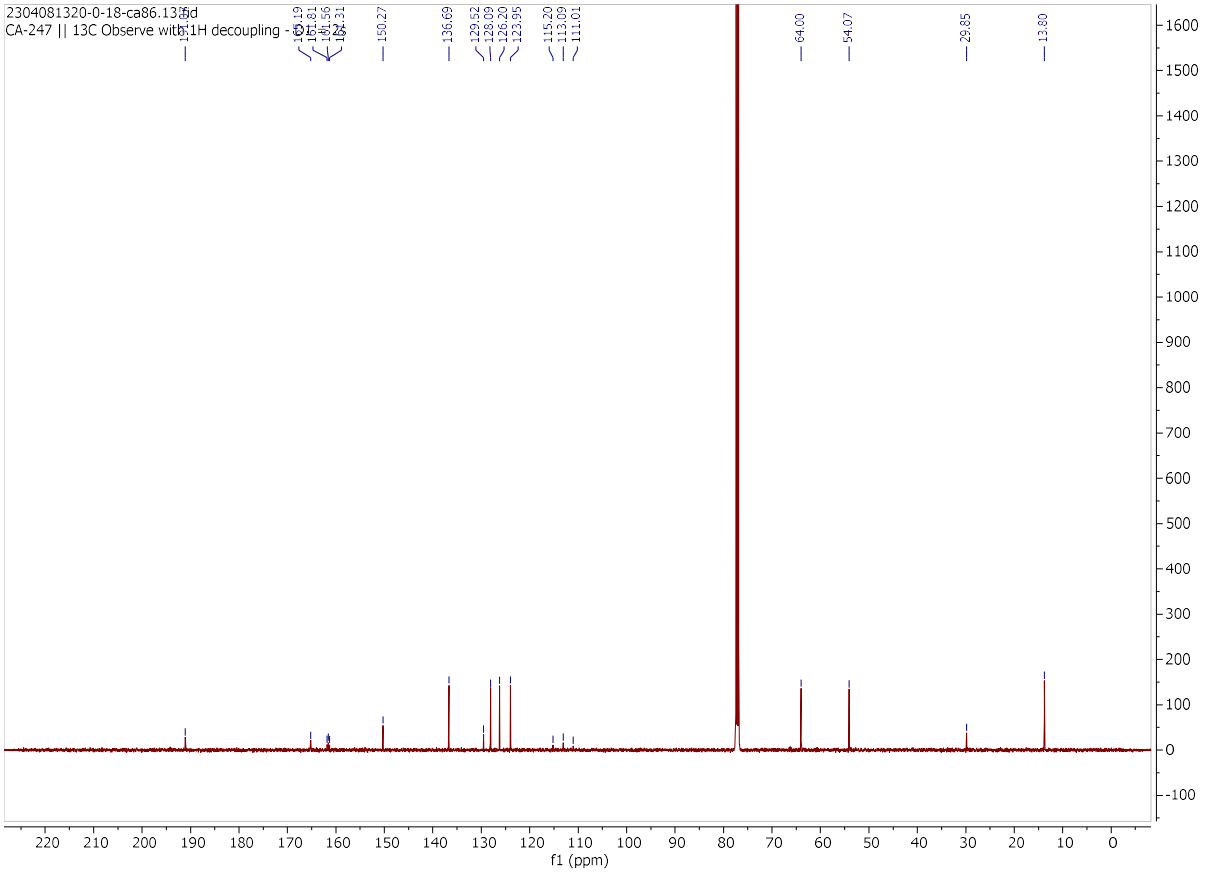


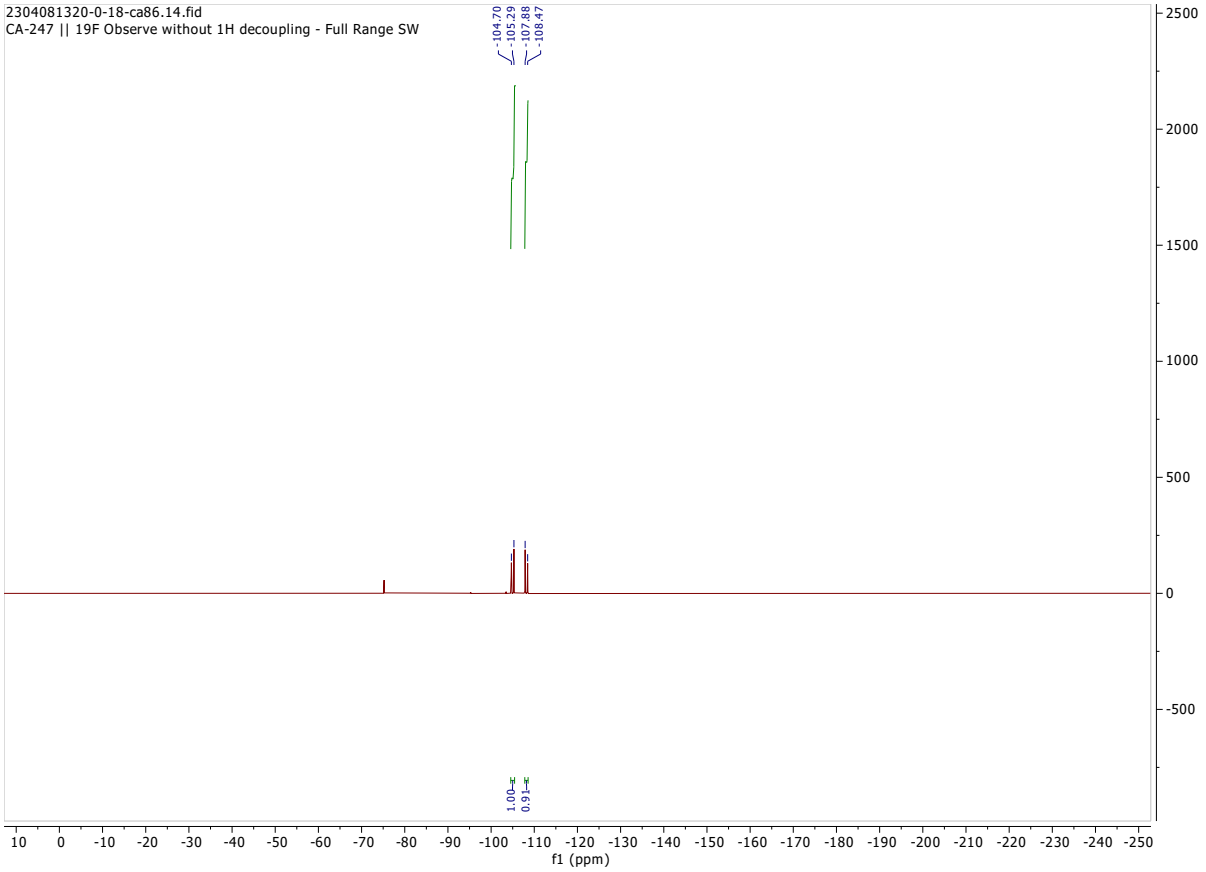
Signal: DAD1D,Sig=254,4 Ref=off

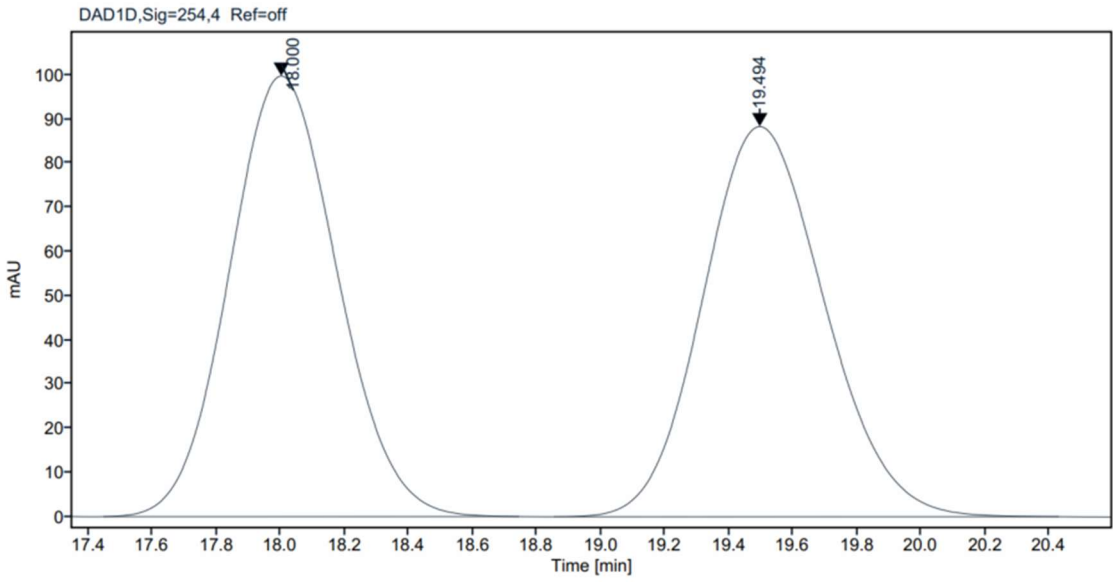
RT [min]	Type	Width [min]	Area	Height	Area%	Name
12.457	MM m	0.9317	2636.8444	151.7684	32.5269	
15.345	MM m	1.5587	5469.8030	248.2845	67.4731	

(*R*)-3n


2304081320-0-18-ca86.10.fid
CA-247 || 1H Observe
7.84
7.83
7.64
7.63
7.62
7.60
7.42
7.41
7.32
7.31
7.29
4.38
4.37
4.36
4.35
4.34
4.33
4.32
3.80
1.31
1.30
1.28
OMe
CF2
OEt
1.00
1.01
1.01
1.00
2.22
3.17
3.48
f1 (ppm)

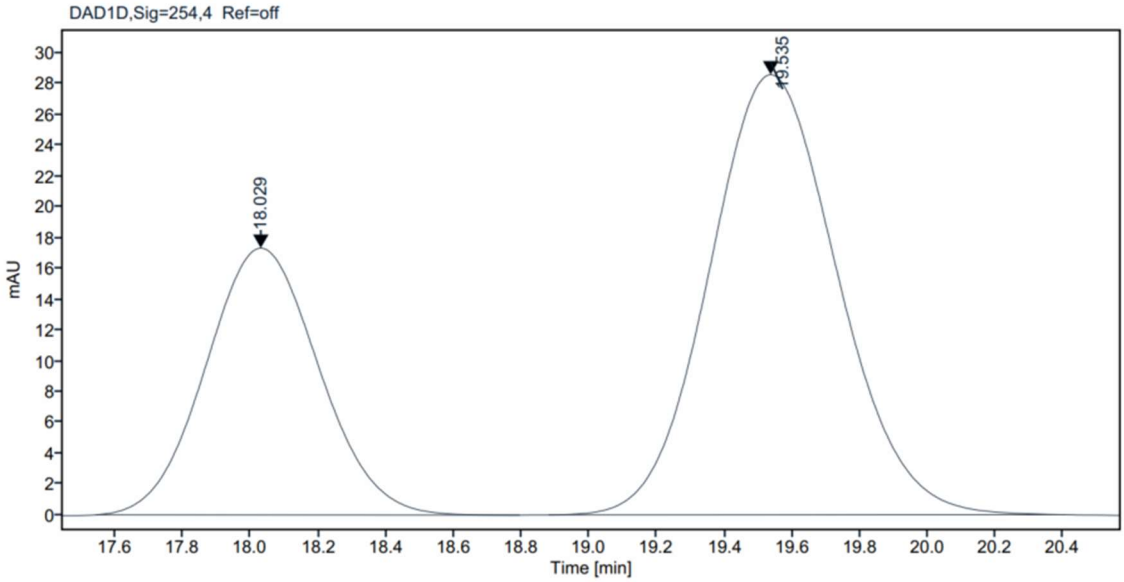

2304081320-0-18-ca86.13.fid
CA-247 || 13C Observe with 1H decoupling
165.19
161.81
156.56
154.31
150.27
136.69
129.52
128.09
126.20
123.95
115.20
113.09
111.01
64.00
54.07
29.85
13.80
f1 (ppm)





Signal: DAD1D,Sig=254,4 Ref=off

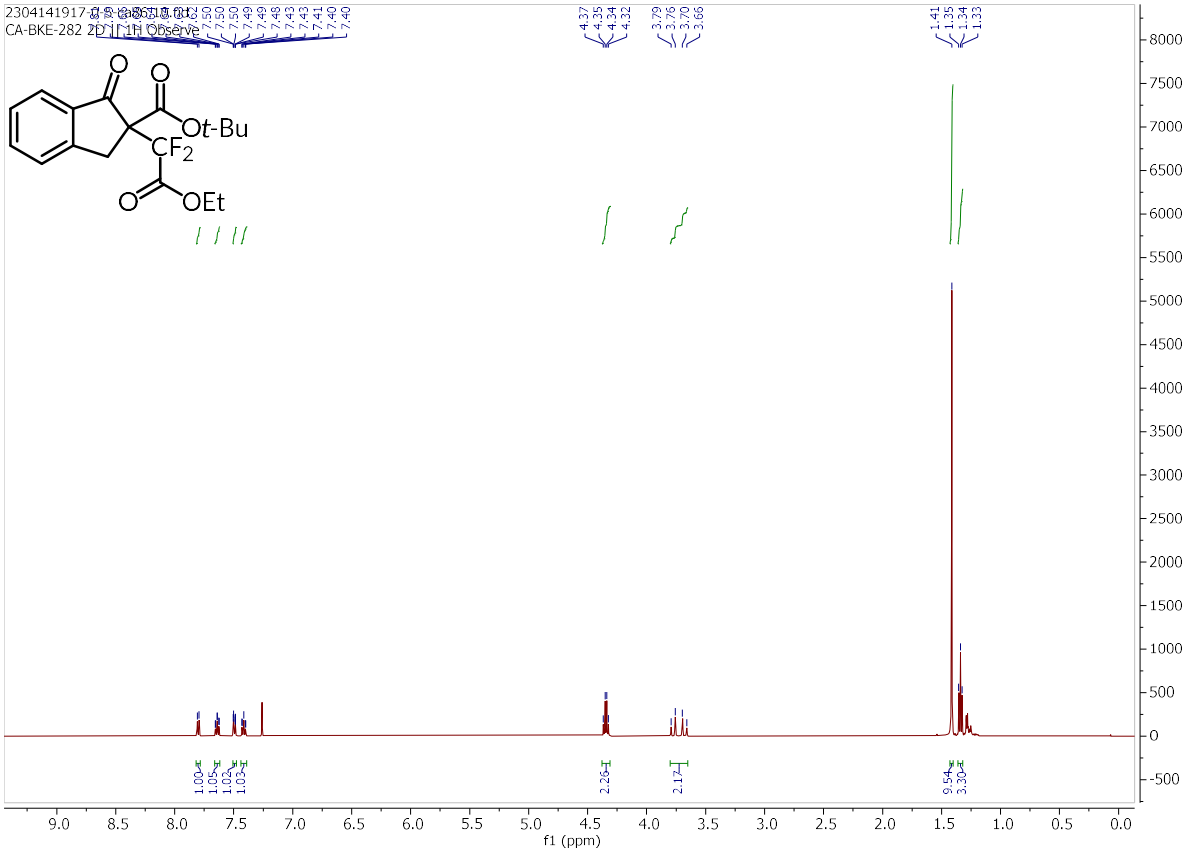
RT [min]	Type	Width [min]	Area	Height	Area%	Name
18.000	MM m	1.2979	2338.1527	99.6243	50.0429	
19.494	MM m	1.5769	2334.1416	88.2312	49.9571	

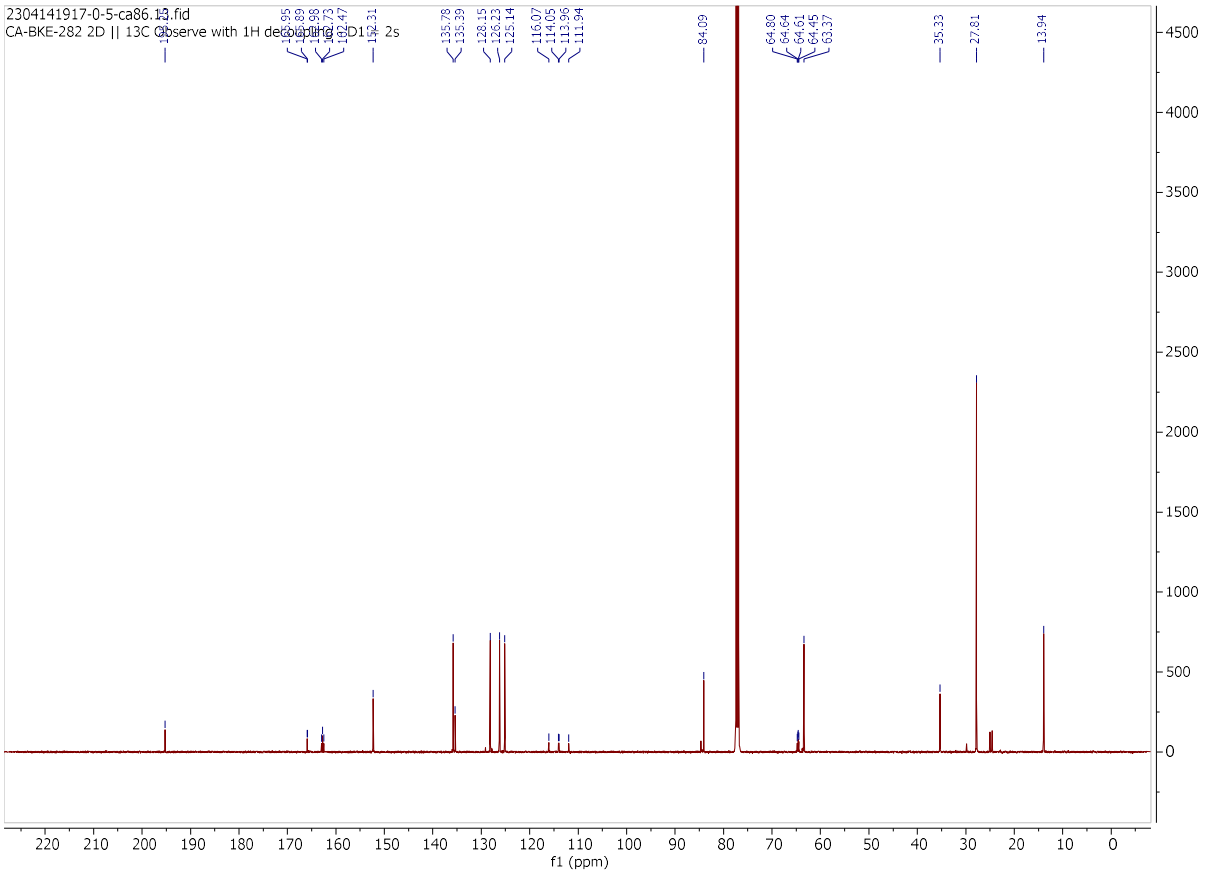


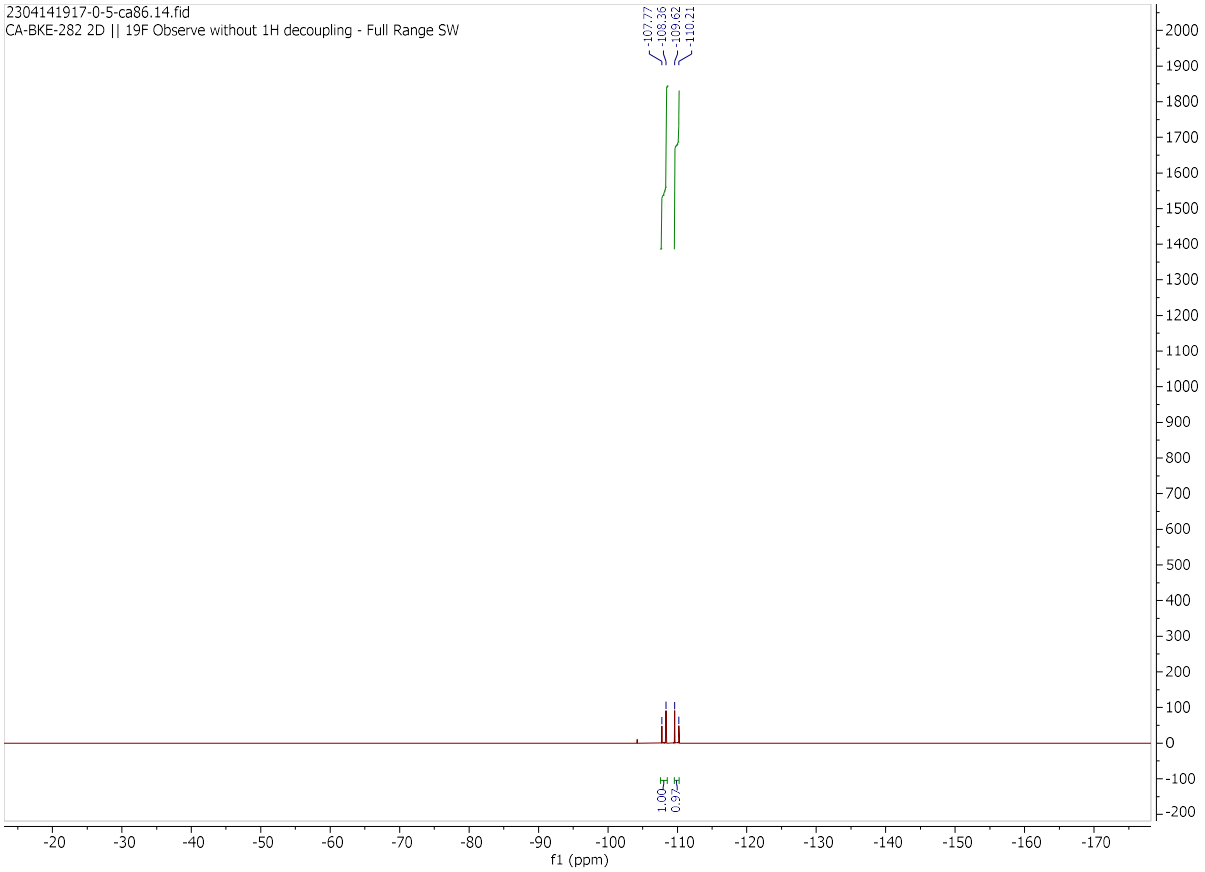
Signal: DAD1D,Sig=254,4 Ref=off

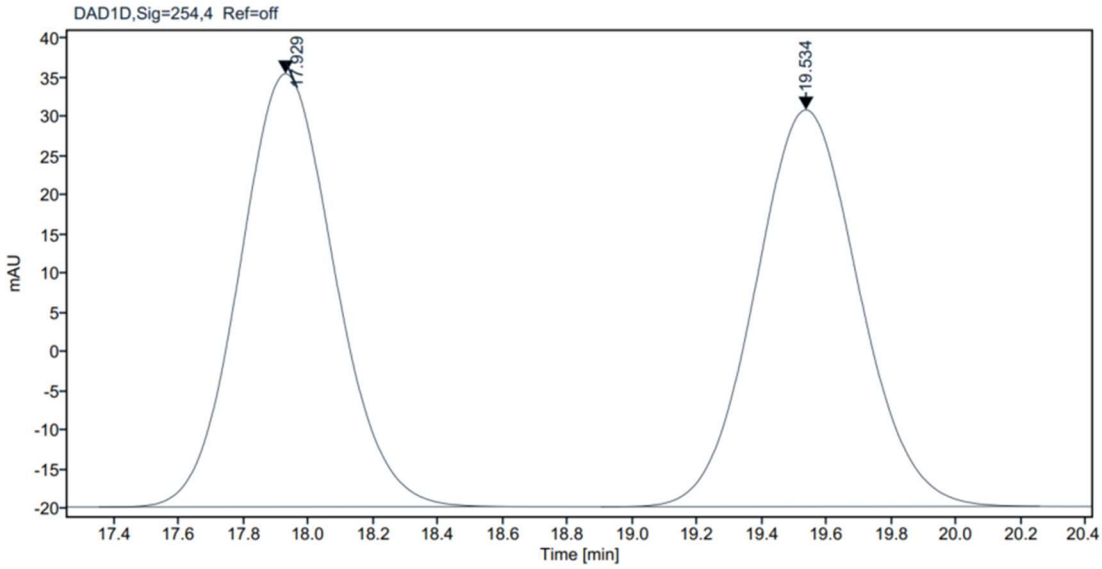
RT [min]	Type	Width [min]	Area	Height	Area%	Name
18.029	MM m	1.2524	402.3971	17.3267	34.8415	
19.535	MM m	1.5256	752.5383	28.5806	65.1585	

3o


CA-BKE-282 2D || 1H Observe
Ot-Bu
CF2
OEt
f1 (ppm)

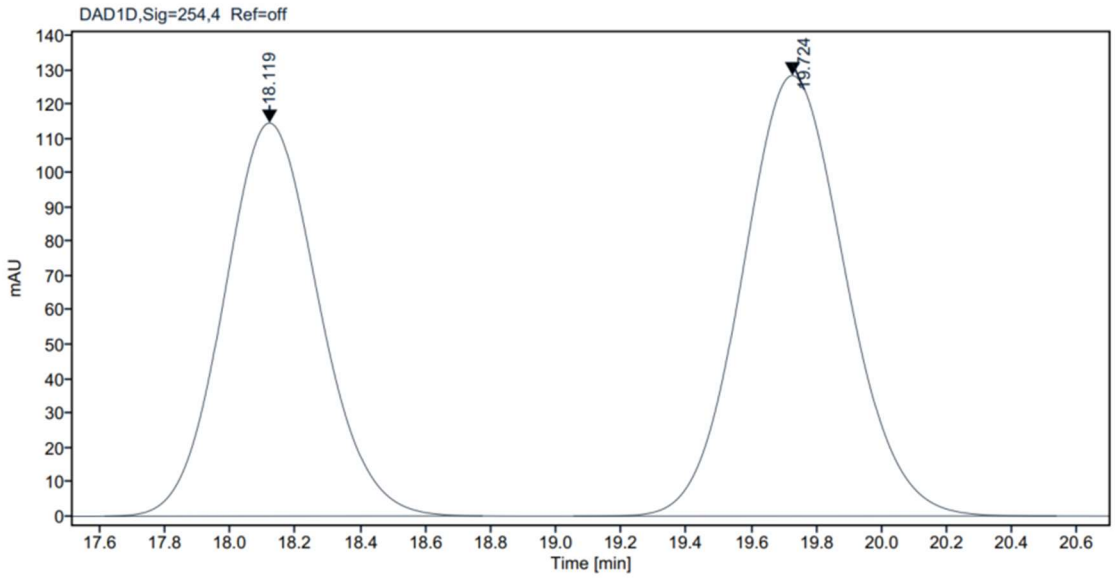

CA-BKE-282 2D || 13C Observe with 1H decoupling
f1 (ppm)


2304141917-0-5-ca86.14.fid
CA-BKE-282 2D || 19F Observe without 1H decoupling - Full Range SW
-107.77
-108.36
-109.62
-110.21
1.00
0.97
f1 (ppm)



Signal: DAD1D,Sig=254,4 Ref=off

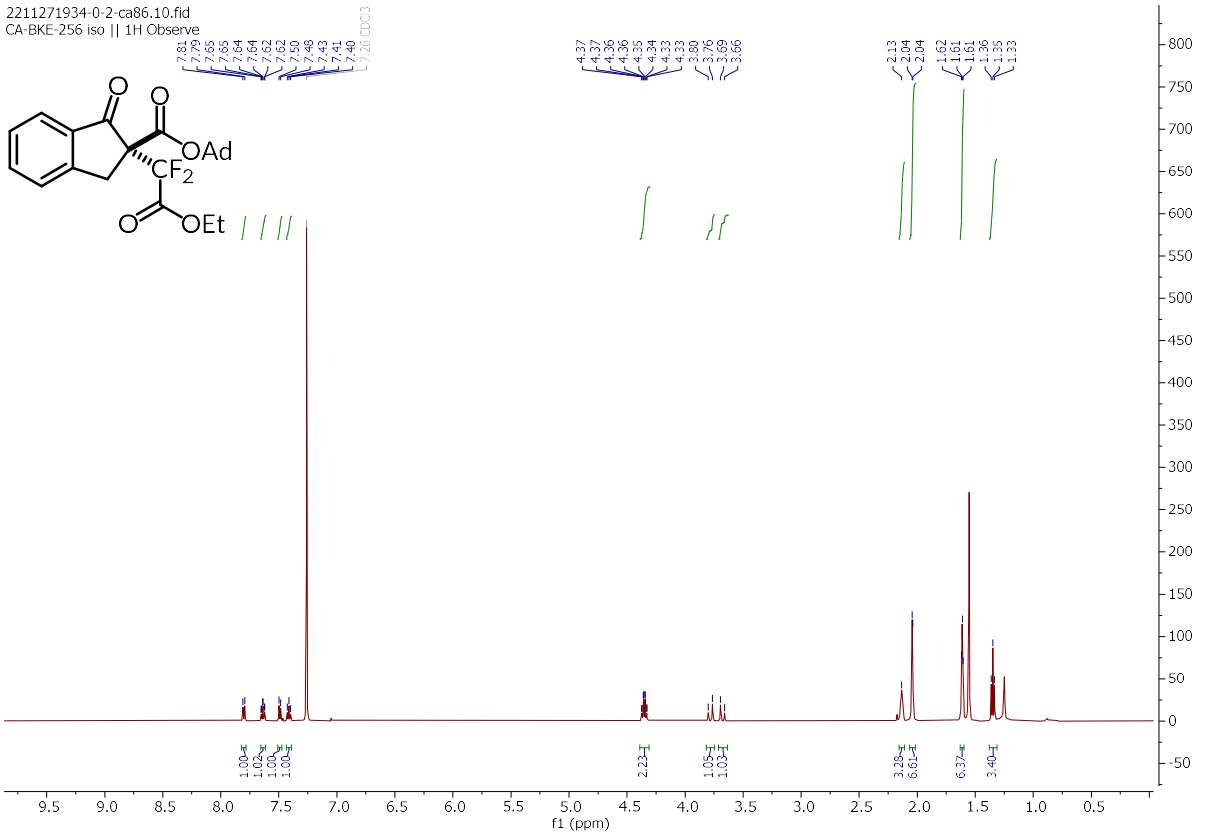
RT [min]	Type	Width [min]	Area	Height	Area%	Name
17.929	MM m	1.2470	1123.3794	55.1842	49.9436	
19.534	MM m	1.3545	1125.9175	50.5393	50.0564	

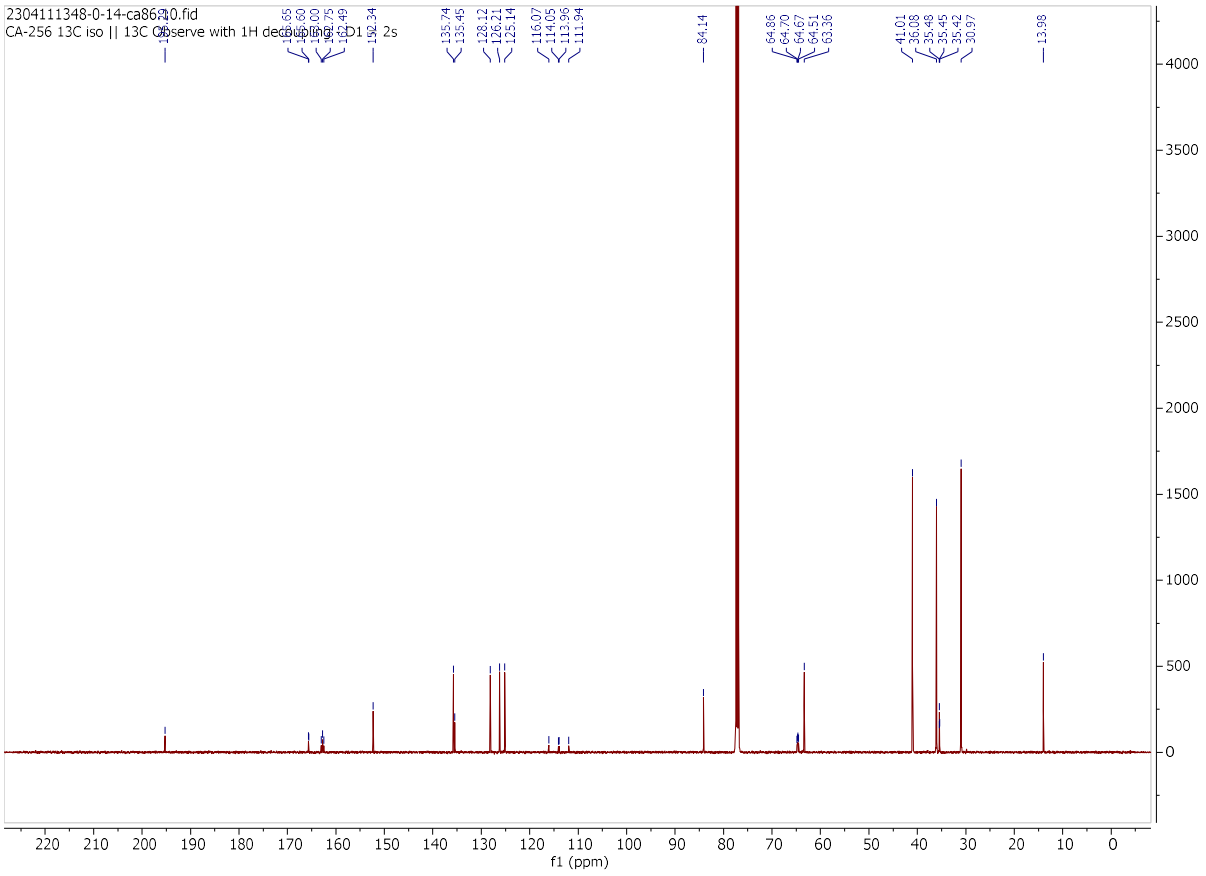


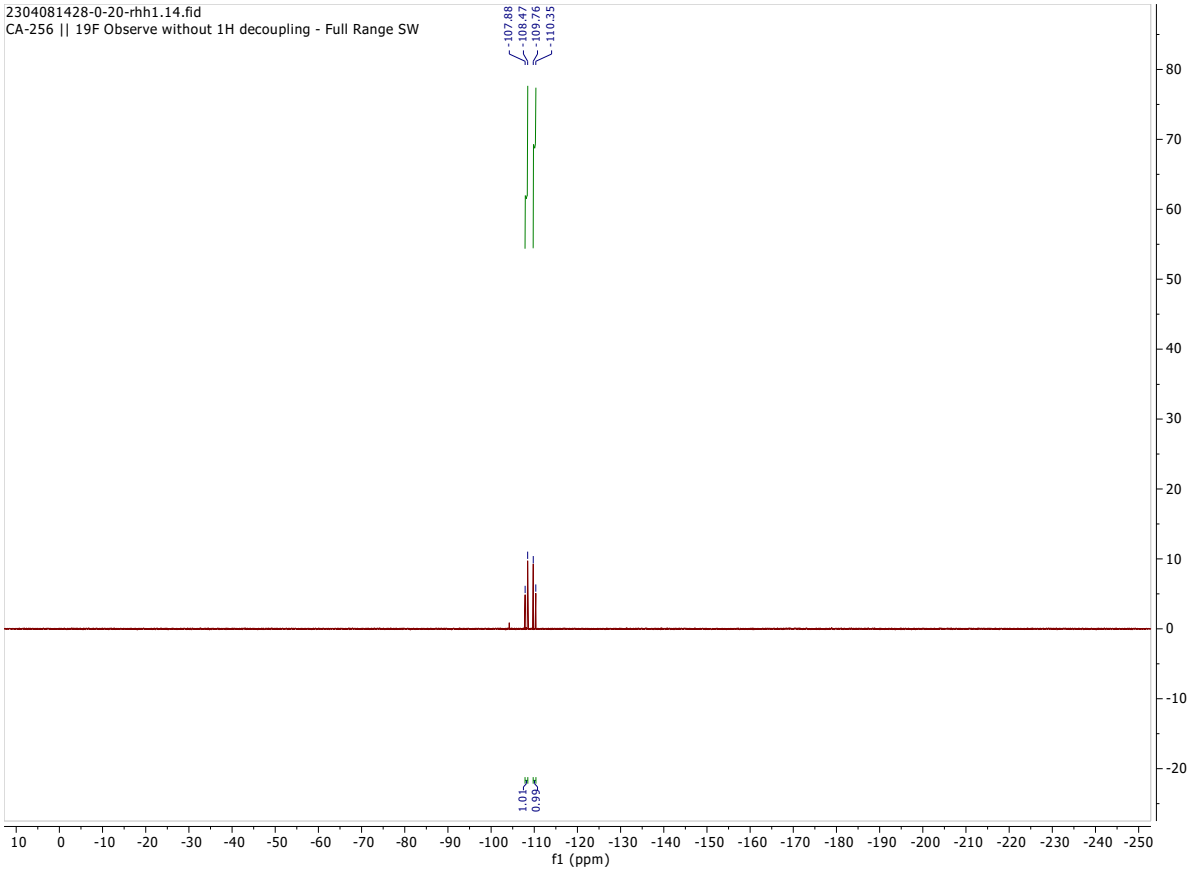
Signal: DAD1D,Sig=254,4 Ref=off

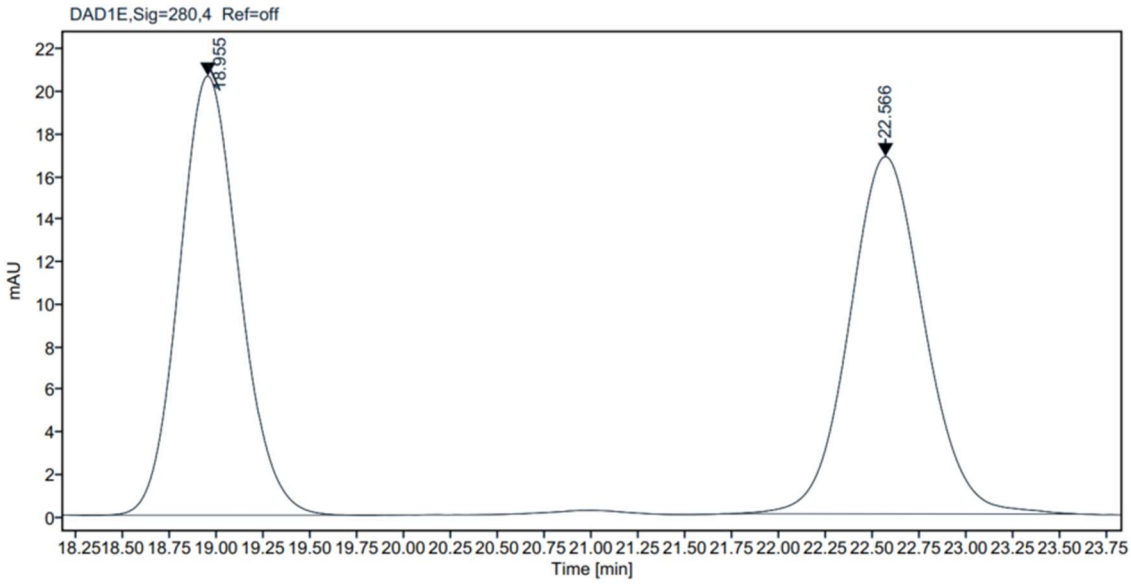
RT [min]	Type	Width [min]	Area	Height	Area%	Name
18.119	MM m	1.1610	2326.4952	114.6375	45.0832	
19.724	MM m	1.4835	2833.9537	128.4660	54.9168	
		Sum	**5160.4489**			

(*R*)-3p


2211271934-0-2-ca86.10.fid
CA-BKE-256 iso || 1H Observe
OAd
CF2
OEt
f1 (ppm)

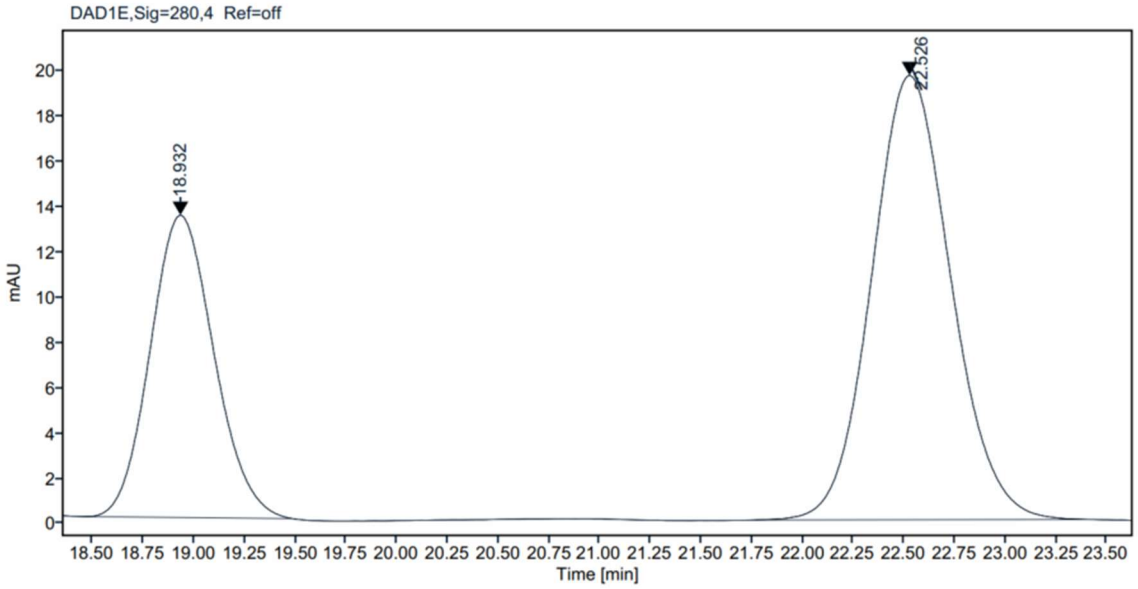

2304111348-0-14-ca86.10.fid
CA-256 13C iso || 13C Observe with 1H decoupling, D1 2s
f1 (ppm)





Signal: DAD1E,Sig=280,4 Ref=off

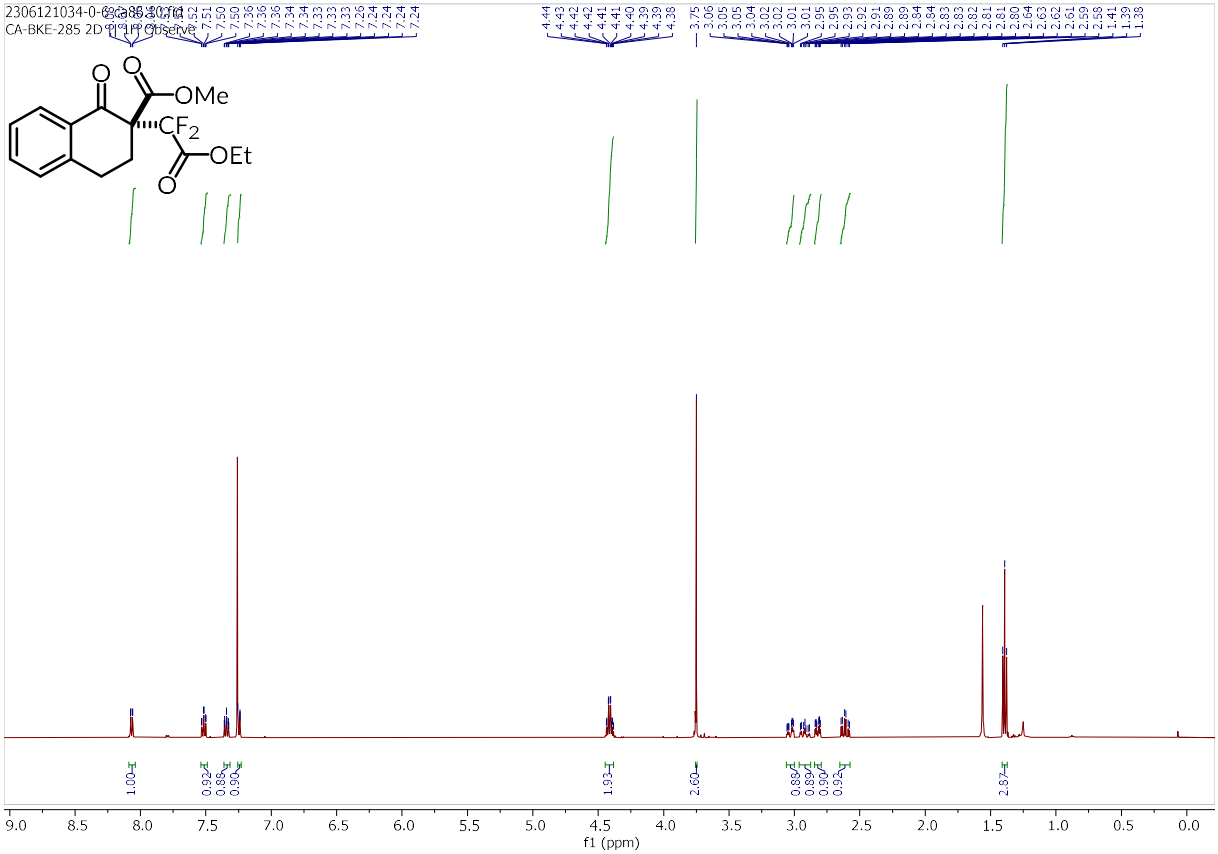
RT [min]	Type	Width [min]	Area	Height	Area%	Name
18.955	MM m	1.5695	460.3169	20.6745	49.5796	
22.566	MM m	1.8706	468.1224	16.8193	50.4204	

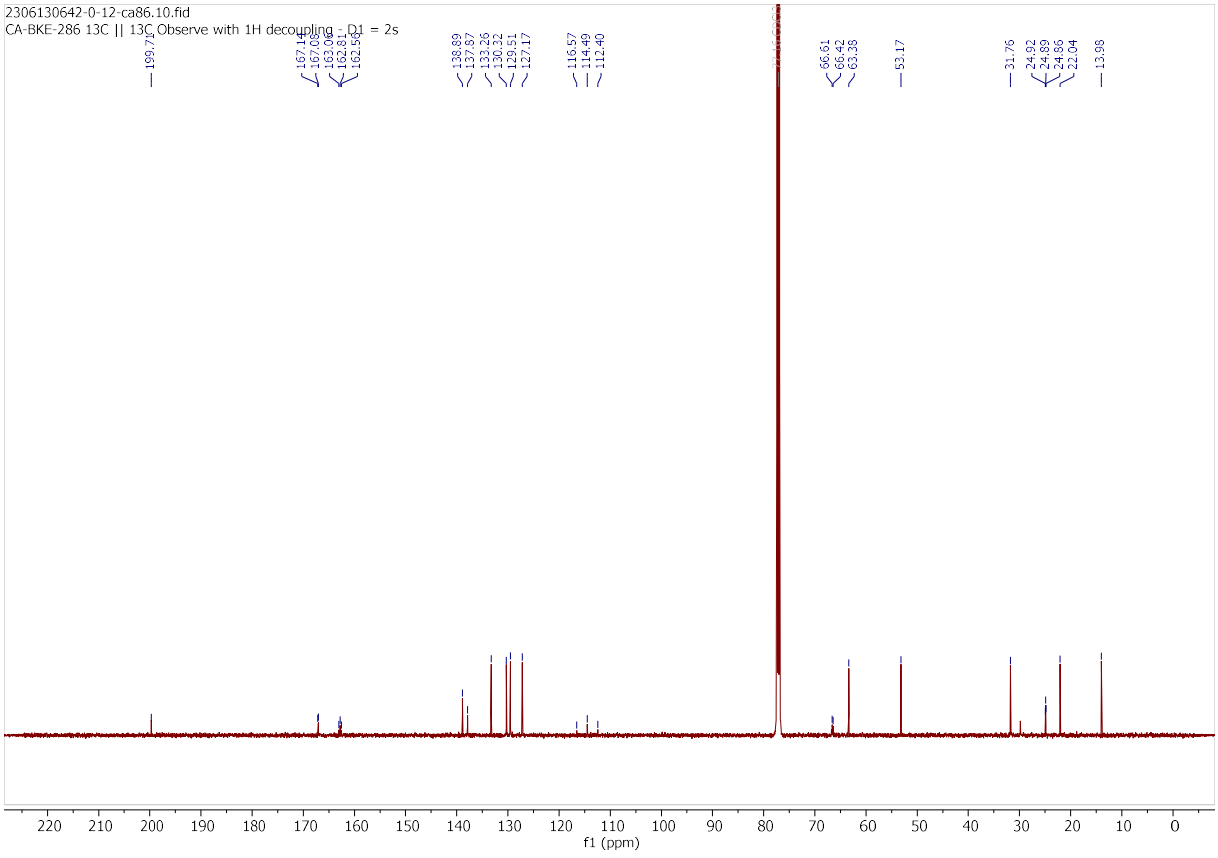


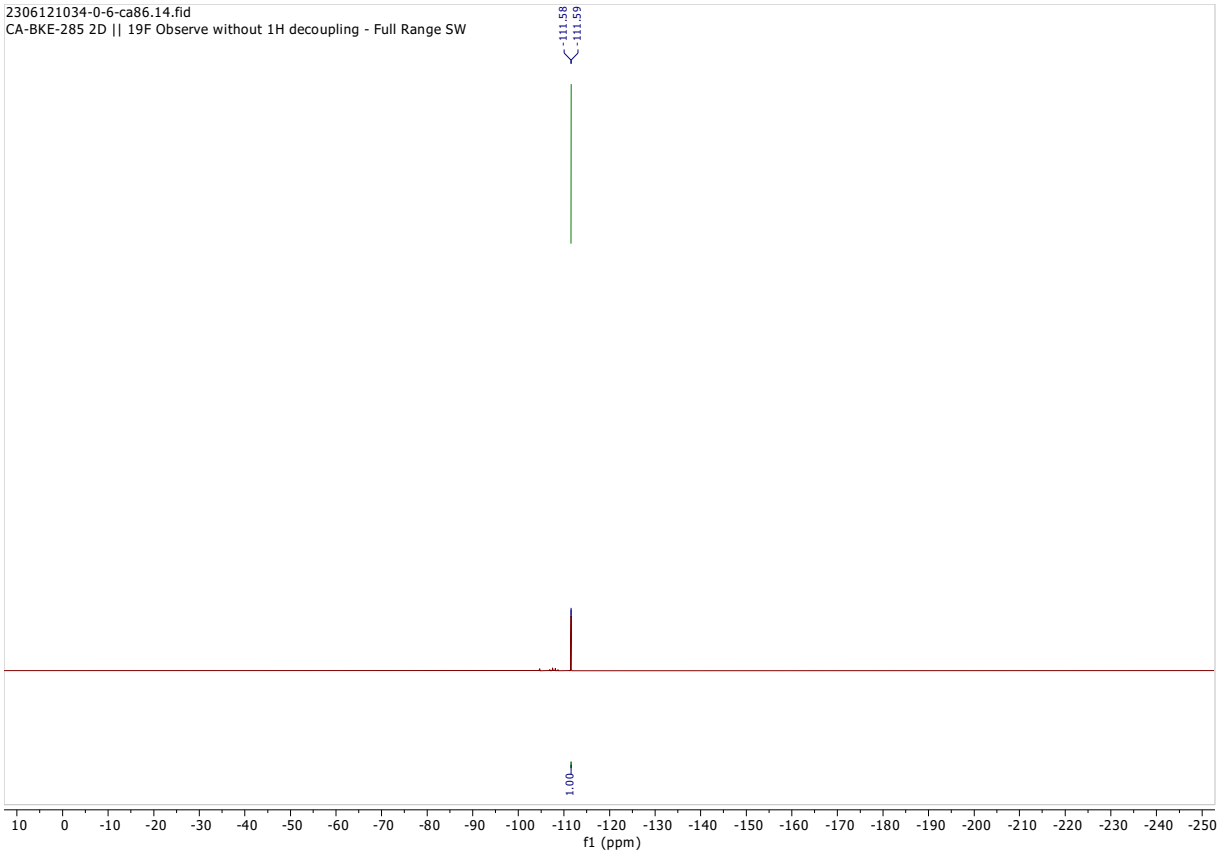
Signal: DAD1E,Sig=280,4 Ref=off

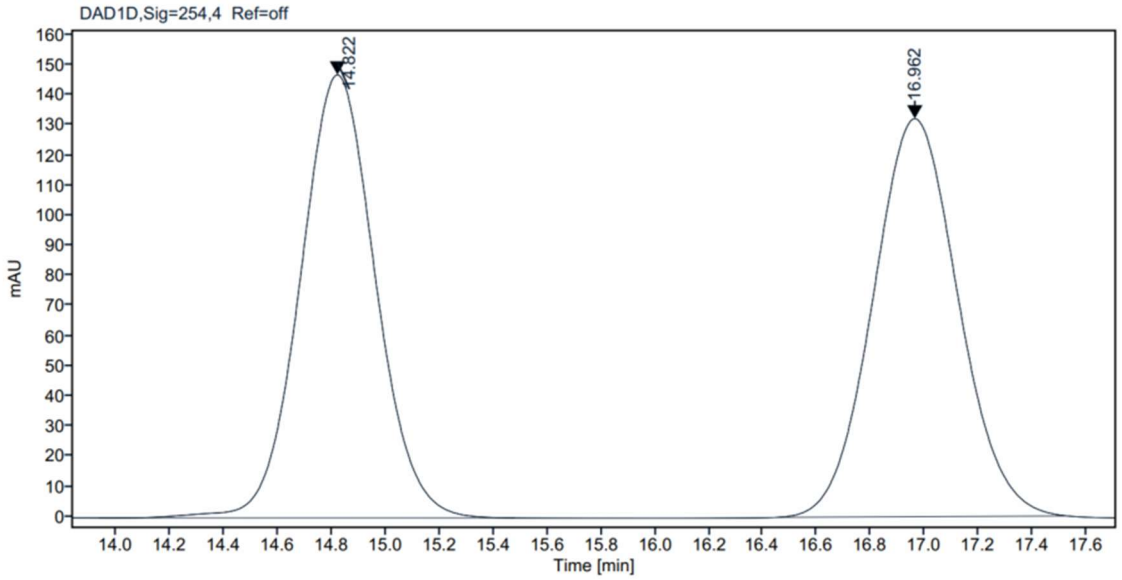
RT [min]	Type	Width [min]	Area	Height	Area%	Name
18.932	MM m	1.0320	291.4146	13.3414	35.3427	
22.526	MM m	1.6555	533.1254	19.6121	64.6573	

(*R*)-3q


2306121034-0-ca86.10.fid
CA-BKE-285 2D
OMe
CF2
OEt
f1 (ppm)

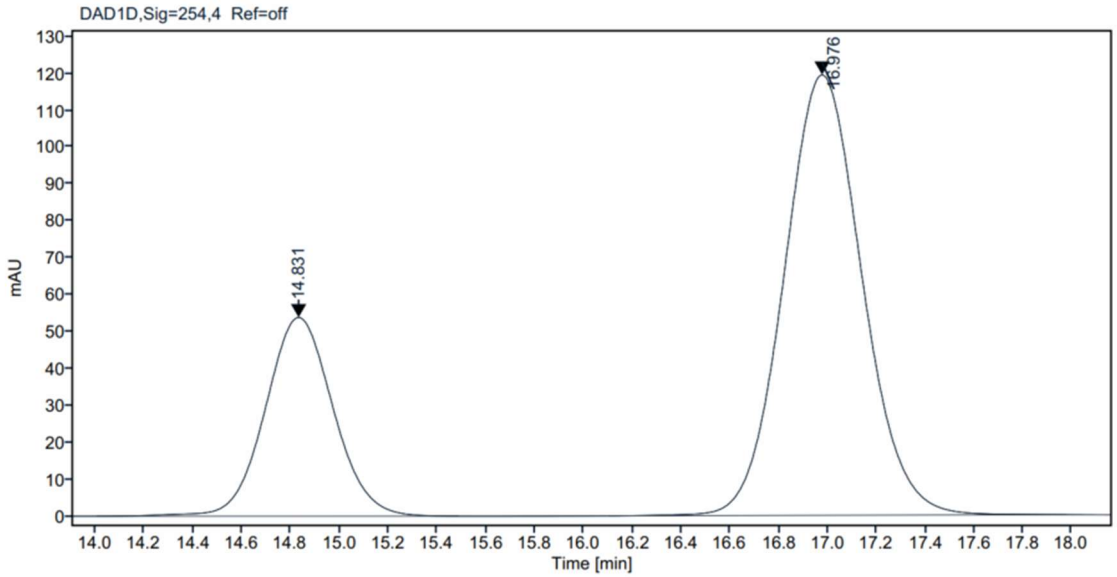

2306130642-0-12-ca86.10.fid
CA-BKE-286 13C || 13C Observe with 1H decoupling - D1 = 2s
f1 (ppm)





Signal: DAD1D,Sig=254,4 Ref=off

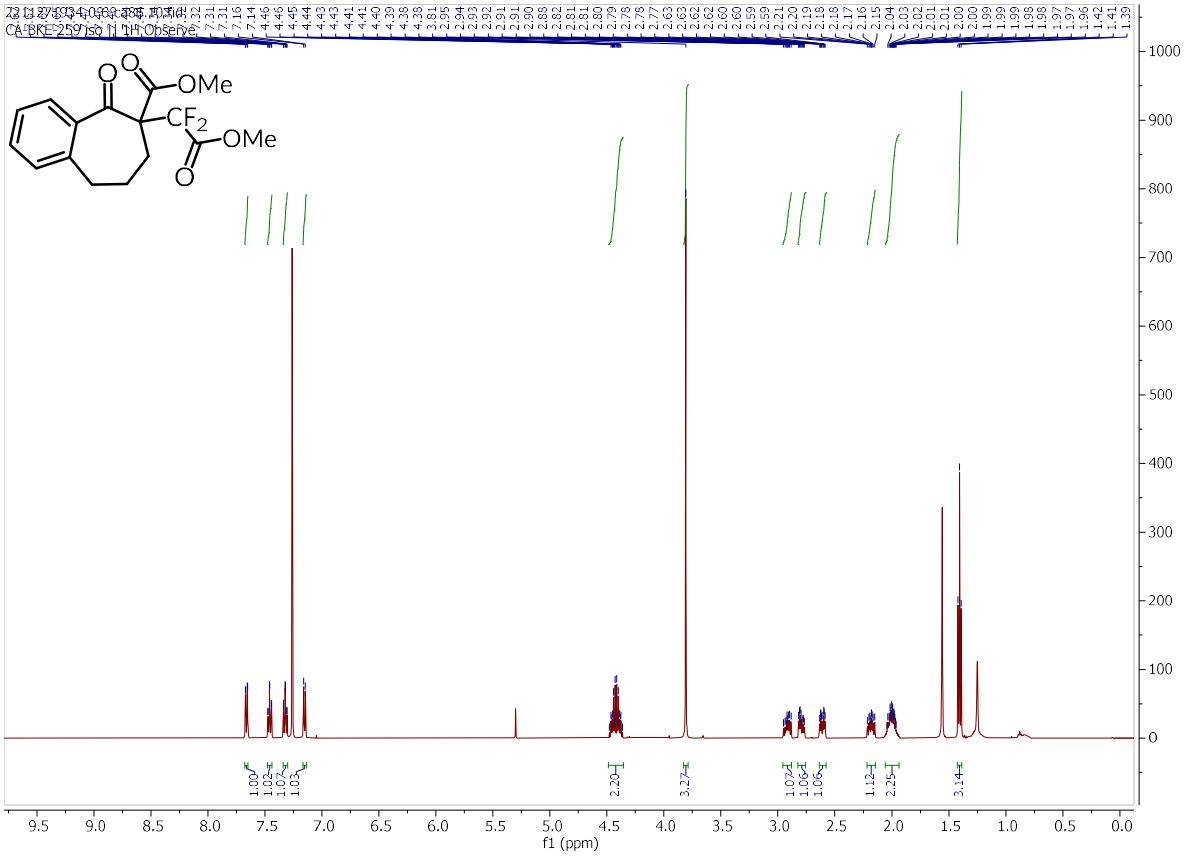
RT [min]	Type	Width [min]	Area	Height	Area%	Name
14.822	MM m	1.5408	2846.7754	147.1193	49.5577	
16.962	MM m	1.0742	2897.5937	132.1453	50.4423	

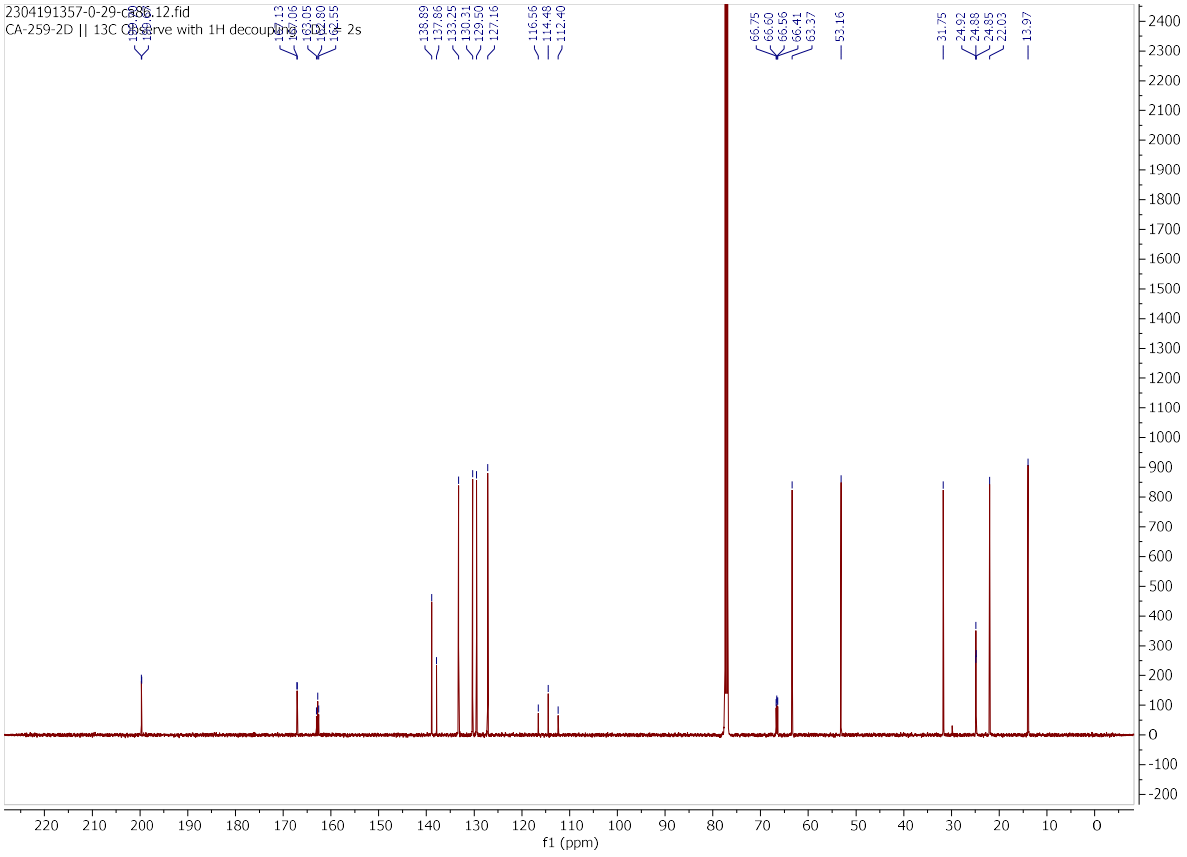


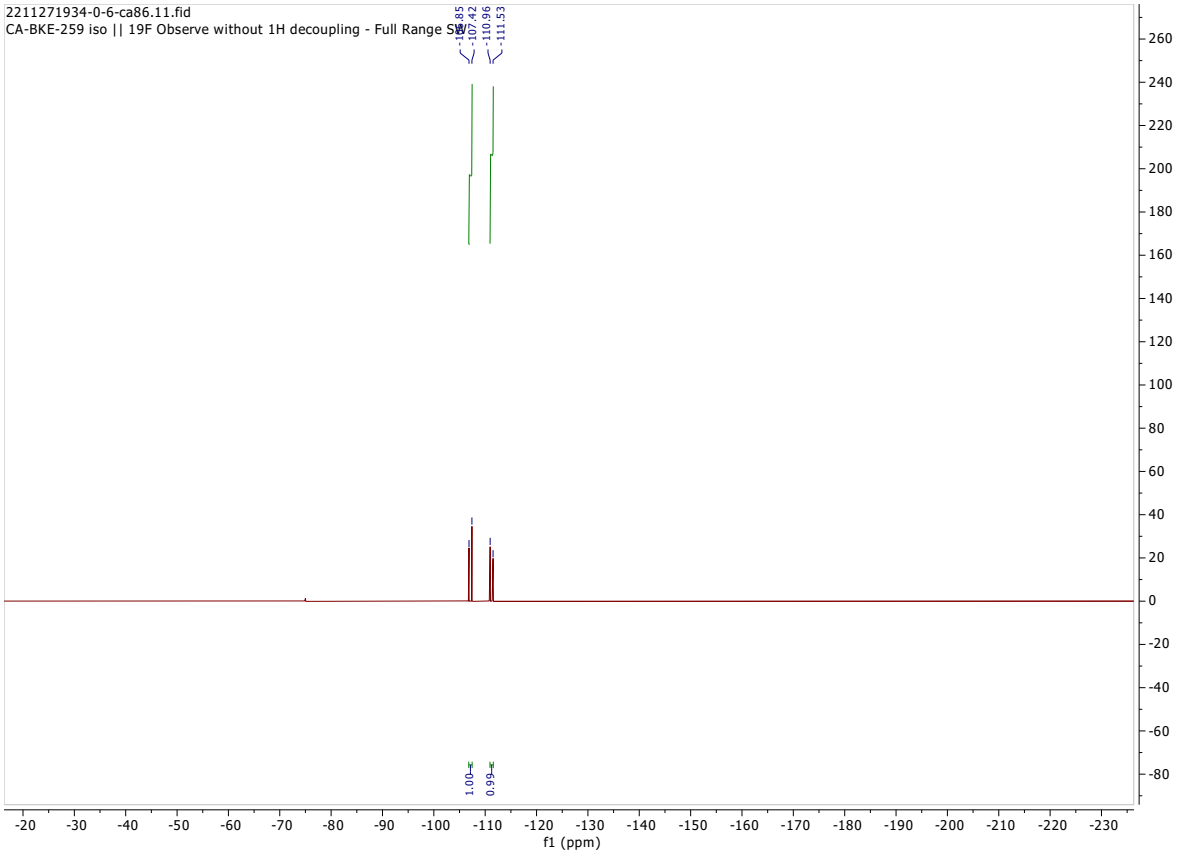
Signal: DAD1D,Sig=254,4 Ref=off

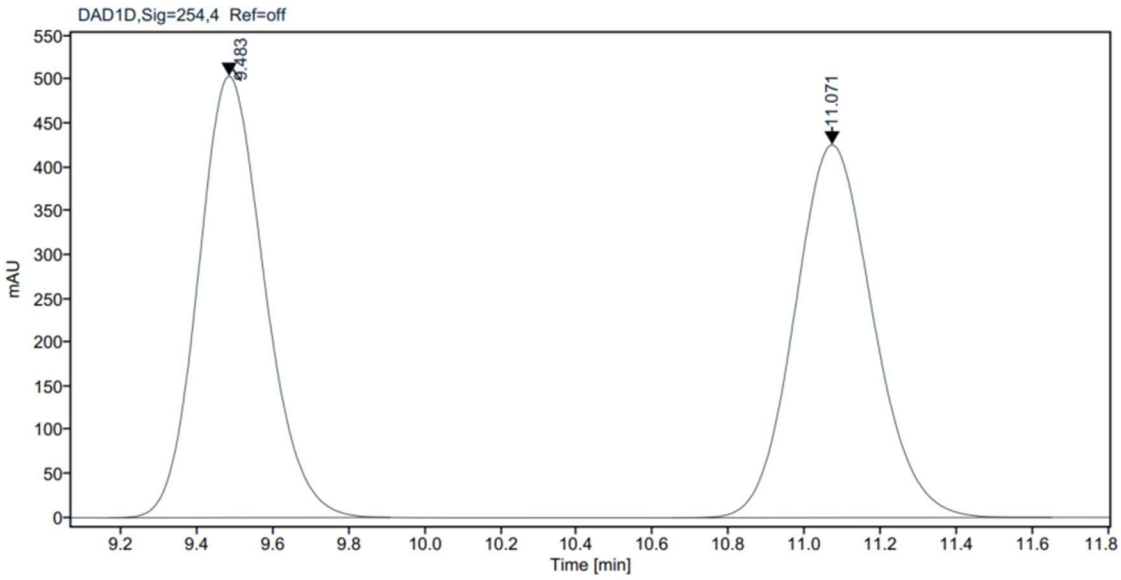
RT [min]	Type	Width [min]	Area	Height	Area%	Name
14.831	MM m	1.4837	1040.9873	53.8320	28.2032	
16.976	MM m	1.8763	2650.0393	119.3431	71.7968	

3r


OMe
CF2
OMe
f1 (ppm)

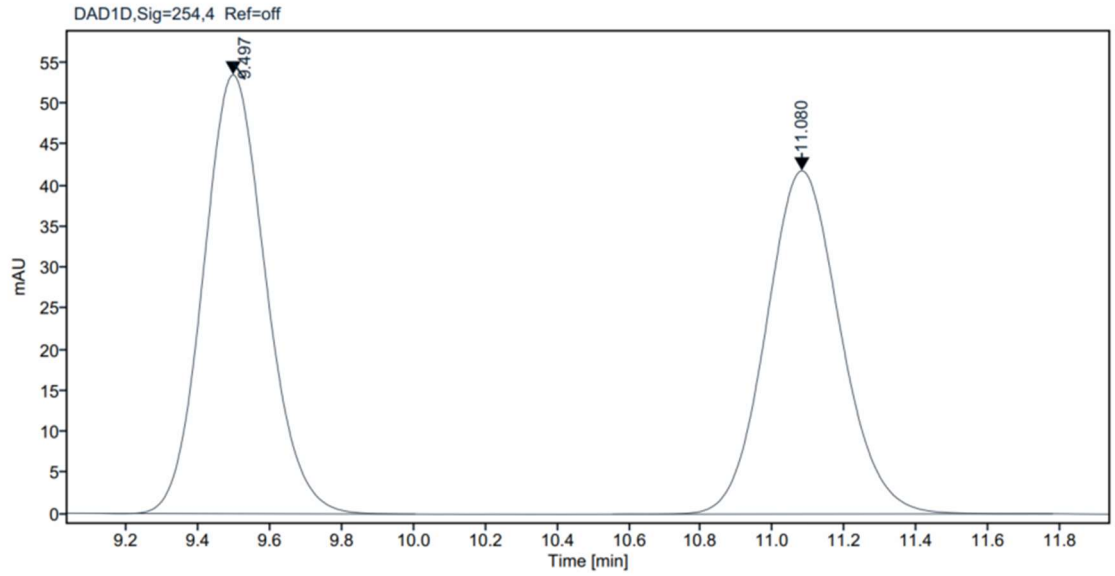

2304191357-0-29-cas6.12.fid
CA-259-2D || 13C Observe with 1H decoupling 2s
f1 (ppm)





Signal: DAD1D,Sig=254,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
9.483	MM m	0.7418	6096.4262	504.2255	49.9655	
11.071	MM m	0.9999	6104.8490	425.8716	50.0345	



Signal: DAD1D,Sig=254,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
9.497	MM m	0.8708	644.2239	53.4609	51.8302	
11.080	MM m	1.2256	598.7277	41.8102	48.1698	

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