Salt-Stabilized Alkylzinc Pivalates: Versatile Reagents for Cobalt-Catalyzed Selective 1,2-Dialkylation

*Jie Lin,[‡1] Kaixin Chen,[‡1] Jixin Wang,[1] Jiawei Guo,[1] Siheng Dai,[1] Ying Hu,[1] and Jie Li[1,2]**

[1] Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry, Chemical Engineering and Materials Science, Soochow University, Suzhou 215123, China
[2] State Key Laboratory and Institute of Elemento-Organic Chemistry, Haihe Laboratory of Sustainable Chemical Transformations, College of Chemistry, Nankai University, Tianjin 300071, China

* *E-mail: jjackli@suda.edu.cn*

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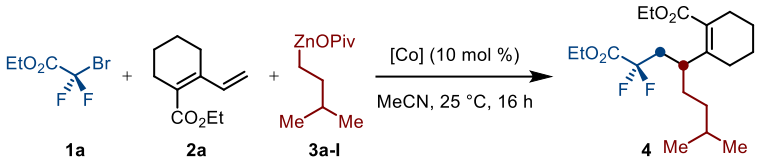
1. General Remarks

Unless otherwise indicated, all reactions were carried out with magnetic stirring and in flame-dried glassware under nitrogen. Syringes used to transfer reagents and solvents were purged with N_2 prior to use. The following starting materials were synthesized according to previously described methods: difluoroalkyl halides,[1-4] ketone esters,[5,8] enol triflates,[6] alkenyl acetates,[9] olefins.[7] Other chemicals were obtained from commercial sources and were used without further purification. Yields refer to isolated compounds, estimated to be > 95% pure as determined by ^{1}H-NMR and GC-analysis. Reactions were monitored by gas chromatography (GC and GC-MS) or thin layer chromatography (TLC). TLC were performed using aluminum plates covered with SiO_2 (Merck 60, F-254) and visualized by UV detection. Purification *via* column chromatography was performed using Merck silica gel 60 (40–63 mm 230–400 mesh ASTM from Merck). THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen. NMR spectra were recorded in $CDCl_3$ and chemical shifts (δ) are reported in parts per million (ppm). Mass spectra and high resolution mass spectra (HR-MS) were recorded using electro ionization (EI) except where otherwise noted. GCs were recorded on machines of the type Hewlett-Packard 6890 (Hewlett Packard, 5% phenylmethylpolysiloxane; length: 15 m, diameter: 0.25 mm; film thickness: 0.25 μm).

2. Optimization Studies

Table S1. Optimization for Co-catalyzed alkyldifluoroalkylation of dienoate with alkylzinc pivalate. [a]

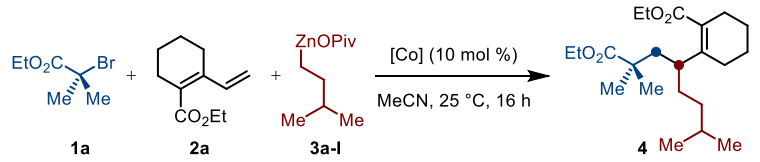


1a 2a 3a-I 4

entry	modifications	yield (%)[b]	entry	modifications	yield (%)[b]
1	$CoCl_2$	57	8	$CoCl(PPh_3)_3$	trace
2	$CoBr_2$	58	**9**	**CoI_2**	**78[c]**
3	CoI_2	62	10	TMEDA	68[c,d]
4	$Co(acac)_2$	56	11	1,10-phen	63[c,e]
5	$Co(acac)_3$	34	12	dppbz	31[c,e]
6	$CoBr_2$•DME	49	13	dcype	55[c,e]
7	$Co(OAc)_2$	46	14	without [Co]	0[c]

[a] Reaction conditions: **1a** (2.0 equiv), **2a** (0.15 mmol, 1.0 equiv), **3a-I** (2.0 equiv), [Co] (10 mol %), MeCN (1.5 mL), 25 °C, 16 h. [b] Isolated yields. [c] **1a** (0.15 mmol, 1.0 equiv), **2a** (1.5 equiv), **3a-I** (2.5 equiv). [d] TMEDA (30 mol %) as the ligand. [e] ligand (11 mol %).

Table S2. Optimization for Co-catalyzed alkyldialkylation of dienoate with alkylzinc pivalate. [a]

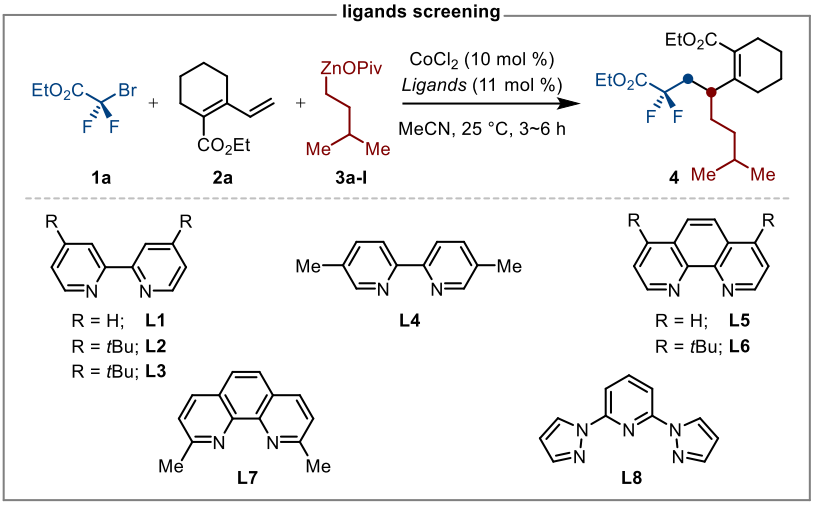


1a 2a 3a-I 4

entry	modifications	yield (%)[b]	entry	modifications	yield (%)[b]
1	$CoCl_2$	40	8	neo	44[e]
2	$CoBr_2$	36	9	dtbbpy	35[e]
3	CoI_2	44	**10**	**TMEDA**	**61[c,d]**
4	$Co(acac)_2$	38	11	1,10-phen	45[e]
5	$CoCl(PPh_3)_3$	trace	12	dppbz	36[e]
6	$CoBr_2$•DME	38	13	dcype	36[e]
7	$Co(OAc)_2$	36	14	without [Co]	0[c]

[a] Reaction conditions: **1a** (2.0 equiv), **2a** (0.15 mmol, 1.0 equiv), **3a-I** (2.5 equiv), [Co] (10 mol %), MeCN (1.5 mL), 25 °C, 16 h. [b] Isolated yields. [c] **1a** (0.15 mmol, 1.0 equiv), **2a** (1.5 equiv), **3a-I** (2.5 equiv), [Co] (10 mol %), MeCN (1.5 mL), 0 °C, 16 h. [d] TMEDA (30 mol %) as the ligand. [e] ligand (11 mol %).

Table S3. Ligands screening. [a]



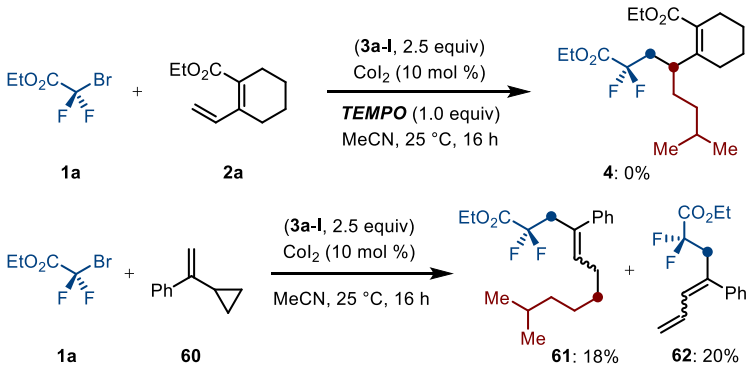
entry	ligand	yield (%)[b]	entry	ligand	yield (%)[b]
1	none	57	6	**L5**	54
2	**L1**	46	7	**L6**	61
3	**L2**	57	8	**L7**	61
4	**L3**	46	9	**L8**	57
5	**L4**	55			

[a] Reaction conditions: **1a** (2.0 equiv), **2a** (0.15 mmol, 0.15 equiv), **3a-I** (2.0 equiv), [Co] (10 mol %), MeCN (1.5 mL), 25 °C, 16 h.

3. Additional Experiments

a) Mechanistic Studies for Cobalt-Catalyzed Modular Alkyldifluoroalkylation of Dienoates :

i) Radical evidence



Scheme S1. Radical evidence.

procedures for scheme S1a:

To a suspension of dienoate **2a** (0.225 mmol, 1.5 equiv), CoI_2 (10 mol %), difluoroalkyl bromide **1a** (0.15 mmol, 1.0 equiv), ***TEMPO*** (1.0 equiv) in anhydrous MeCN (1.5 mL) was added isopentylzinc pivalate **3a-I** (0.375 mmol, 2.5 equiv), the reaction mixture was stirred at 25 °C for 16 h under an atmosphere of N_2. At ambient temperature, the reaction was detected by GC analysis.

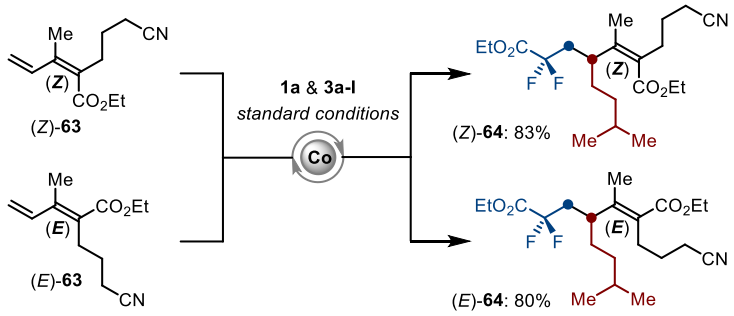
procedures for scheme S1b:

To a suspension of α-cyclopropyl styrene **60** (0.225 mmol, 1.5 equiv), CoI_2 (10 mol %), difluoroalkyl bromide **1a** (0.15 mmol, 1.0 equiv) in anhydrous MeCN (1.5 mL) was added isopentylzinc pivalate **3a-I** (0.375 mmol, 2.5 equiv), the reaction mixture was stirred at 25 °C for 16 h under an atmosphere of N_2. At ambient temperature, the solvent was evaporated in vacuo and the remaining residue was purified by column chromatography on silica gel (petroleum ether/EtOAc) to yield the products of **61** and **62**.

ii) Stereoselective control of acyclic dienoates 63

procedures for scheme S2:

To a suspension of dienoate (*Z*)-**63** *or* (*E*)-**63** (0.225 mmol, 1.5 equiv), CoI_2 (10 mol %), difluoroalkyl bromide **1a** (0.15 mmol, 1.0 equiv) in anhydrous MeCN (1.5 mL) was added isopentylzinc pivalate **3a-I** (0.375 mmol, 2.5 equiv), the reaction mixture was stirred at 25 °C for 16 h under an atmosphere of N_2. At ambient temperature, the solvent was evaporated in vacuo and the remaining residue was purified by column chromatography on silica gel (petroleum ether/EtOAc) to yield the products of (*Z*)-**64** *or* (*E*)-**64**.

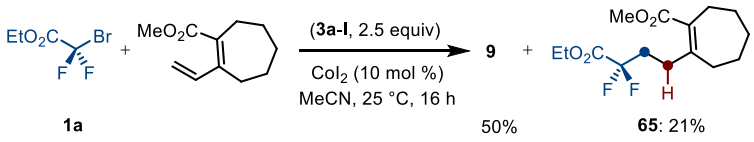


Scheme S2. Stereoselective control of acyclic dienoates (*Z*)-**64** or (*E*)-**64**.

iii) Difluoroalkyl-protonation of dienoate

procedures for scheme S3:

To a suspension of methyl 2-vinylcyclohept-1-ene-1-carboxylate (0.225 mmol, 1.5 equiv), CoI_2 (10 mol %), difluoroalkyl bromide **1a** (0.15 mmol, 1.0 equiv) in anhydrous MeCN (1.5 mL) was added isopentylzinc pivalate **3a-I** (0.375 mmol, 2.5 equiv), the reaction mixture was stirred at 25 °C for 16 h under an atmosphere of N_2. At ambient temperature, the solvent was evaporated in vacuo and the remaining residue was purified by column chromatography on silica gel (petroleum ether/EtOAc) to yield the products of **9** *and* **65**.

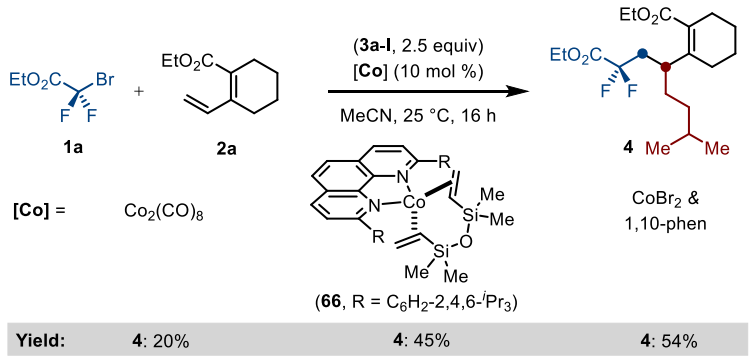


Scheme S3. Cobalt-catalyzed difluoroalkyl-protonation of dienoate.

iv) Reactivity of cobalt complexes

procedures for scheme S4:

To a suspension of dienoate **2a** (0.225 mmol, 1.5 equiv), different **[Co]**-source (10 mol %), difluoroalkyl bromide **1a** (0.15 mmol, 1.0 equiv) in anhydrous MeCN (1.5 mL) was added isopentylzinc pivalate **3a-I** (0.375 mmol, 2.5 equiv), the reaction mixture was stirred at 25 °C for 16 h under an atmosphere of N_2. At ambient temperature, the solvent was evaporated in vacuo and the remaining residue was purified by column chromatography on silica gel (petroleum ether/EtOAc) to yield the product of **4**.



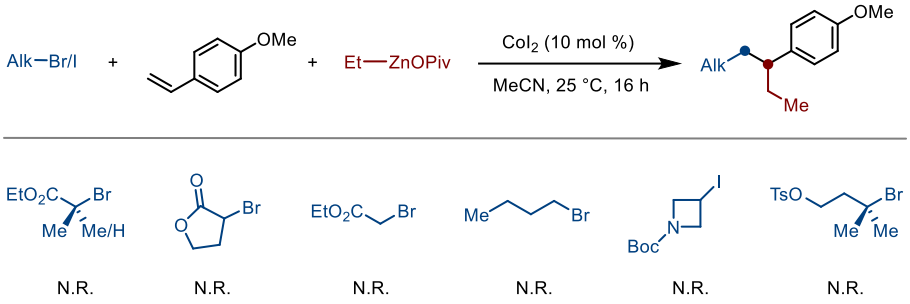
Scheme S4. Alkyldifluoroalkylation of dienoate by different cobalt catalysts.

b) Other relevant experiments:

i) Control experiments for cobalt-catalyzed dialkylation with styrenes

procedures for scheme S5:

To a suspension of styrene (0.225 mmol, 1.5 equiv), CoI_2 (10 mol %), alkyl bromide/iodide (0.15 mmol, 1.0 equiv) in anhydrous MeCN (1.5 mL) was added ethylzinc pivalate **3c** (0.375 mmol, 2.5 equiv), the reaction mixture was stirred at 25 °C for 16 h under an atmosphere of N_2.

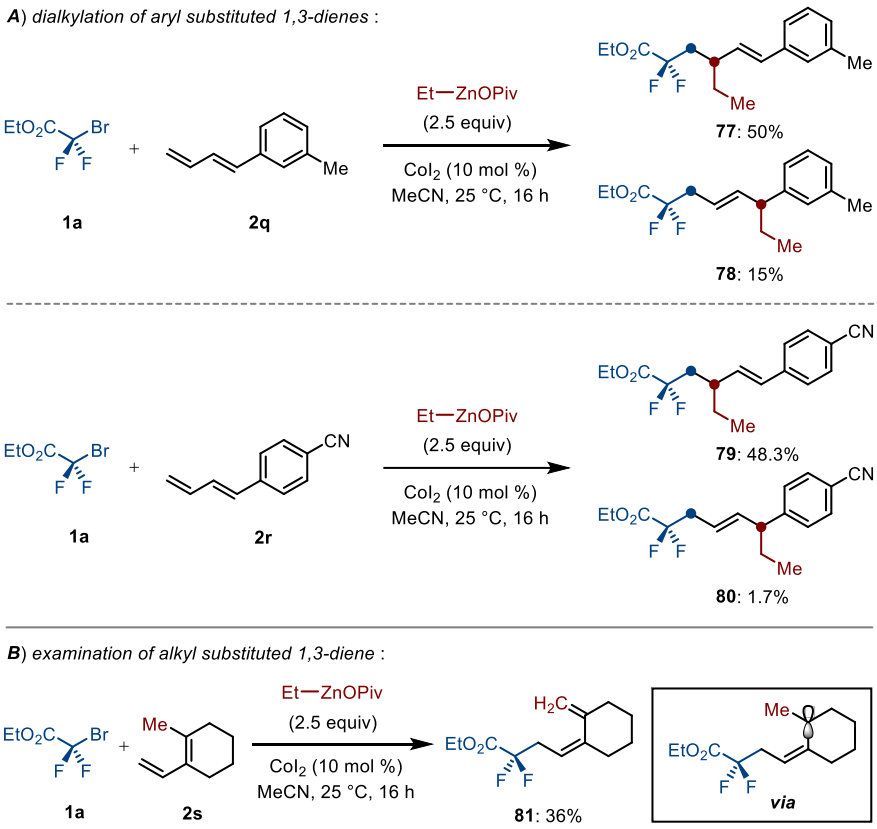


Scheme S5. Control experiments for cobalt-catalyzed dialkylation with styrenes.

ii) Control experiments with 1,3-dienes

procedures for scheme S6:

To a suspension of conjugated diene (0.225 mmol, 1.5 equiv), CoI_2 (10 mol %), difluoroalkyl bromide **1a** (0.15 mmol, 1.0 equiv) in anhydrous MeCN (1.5 mL) was added ethylzinc pivalate **3c** (0.375 mmol, 2.5 equiv), the reaction mixture was stirred at 25 °C for 16 h under an atmosphere of N_2. At ambient temperature, the solvent was evaporated in vacuo and the remaining residue was purified by column chromatography on silica gel (petroleum ether/EtOAc) to yield the product.



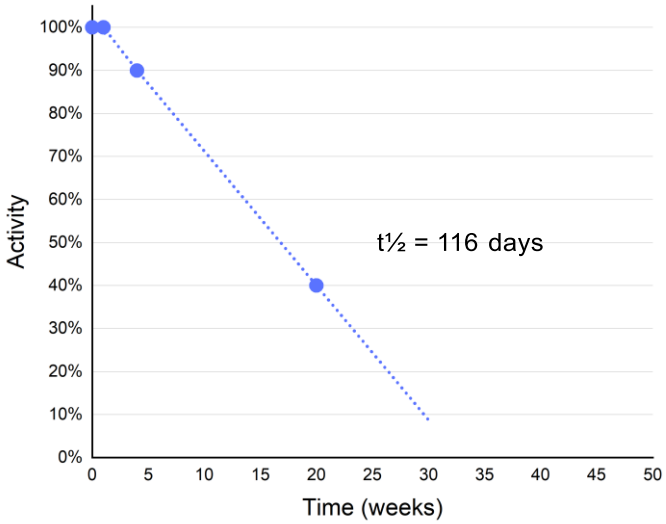
Scheme S6. Control experiments with 1,3-dienes

iii) Stability studies of alkylzinc reagents

Table S4. Stability of solid alkylzinc pivalates after storage under nitrogen (25°C).

	ZnOPiv
Time	Percentage of the remaining active alkylzinc species[a] (%)
0 week	100
1 week	100
4 weeks	90
5 months	40

[a] Determined by titration with a stock solution of iodine.

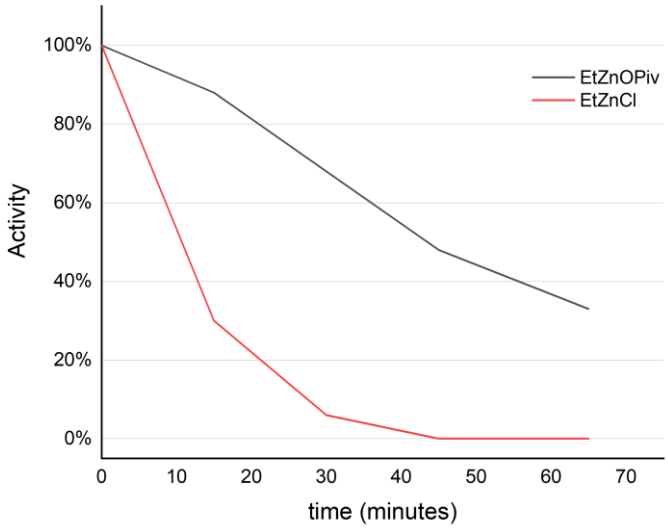


Scheme S7. Activity curve over time

Table S5. Stability comparison of liquid alkylzinc reagents in fully exposed air (25°C).[b]

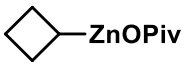
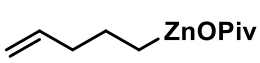
	Et—ZnOPiv	Et—ZnCl
Time	Percentage of the remaining active alkylzinc species[a] (%)	
0 min	100	100
15 mins	88	30
30 mins	68	6
45 mins	48	0
65 mins	33	0

[a] Determined by titration with a stock solution of iodine. [b] Air humidity: 68%.

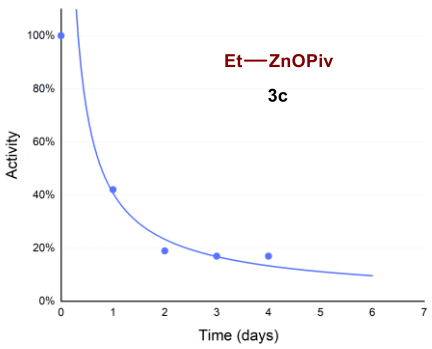


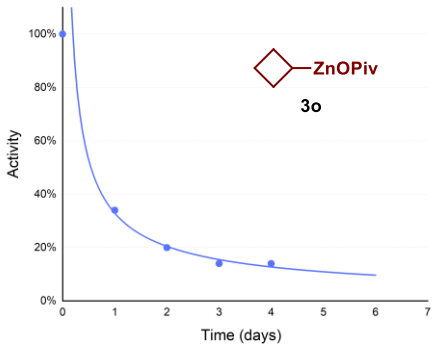
Scheme S8. Activity curve over time

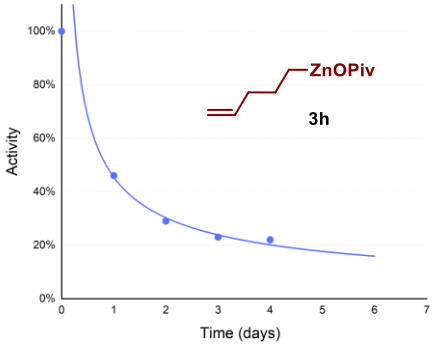
Table S6. Stability of solid alkylzinc pivalates after completely sealing under air (25°C).[b]

	Et—ZnOPiv **3c**	 **3o**	 **3h**
Time	Percentage of the remaining active alkylzinc species[a] (%)		
0 day	100	100	100
1 days	42	34	46
2 days	19	20	29
3 days	17	14	23
4 days	17	14	22

[a] Determined by titration with a stock solution of iodine. [b] Average air humidity: 72%.





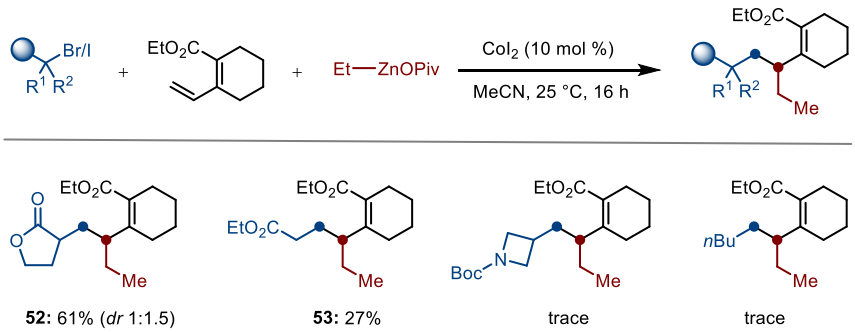


Scheme 9. Activity curve over time

***iv*) Study on reaction of primary and secondary alkyl halides**

procedures for scheme S6:

To a suspension of dienoate **2a** (0.225 mmol, 1.5 equiv), CoI_2 (10 mol %), alkyl bromide/iodide (0.15 mmol, 1.0 equiv) in anhydrous MeCN (1.5 mL) was added ethylzinc pivalate **3c** (0.375 mmol, 2.5 equiv), the reaction mixture was stirred at 25 °C for 16 h under an atmosphere of N_2. At ambient temperature, the solvent was evaporated in vacuo and the remaining residue was purified by column chromatography on silica gel (petroleum ether/EtOAc) to yield the product.



Scheme S10. Primary and secondary alkyl halides

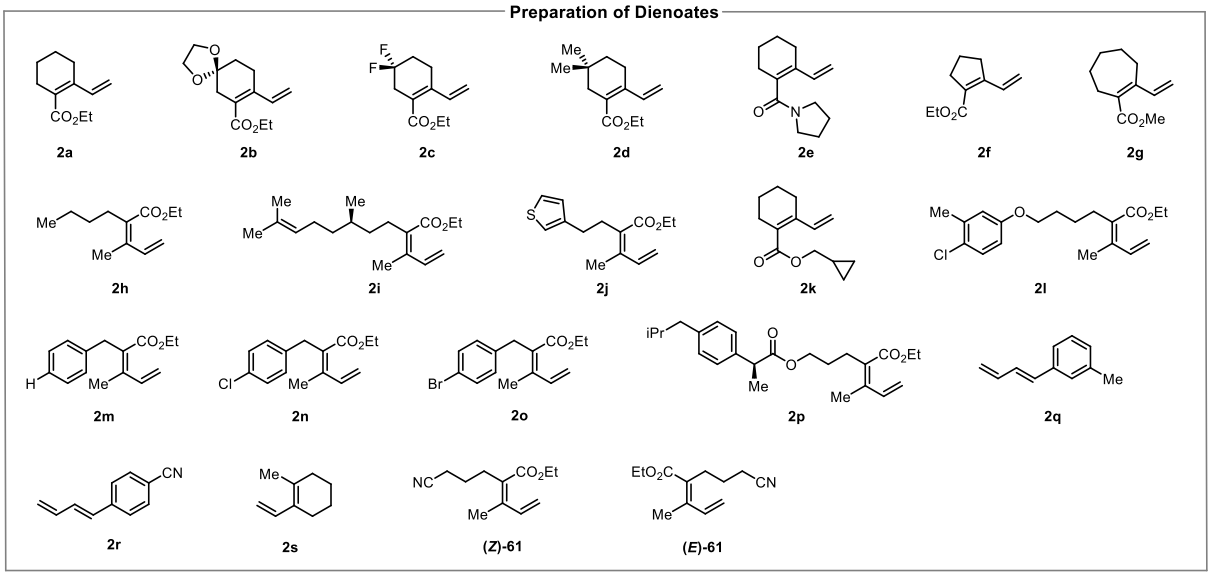
4. Representative Procedures

4.1 Preparation of $Zn(OPiv)_2$:

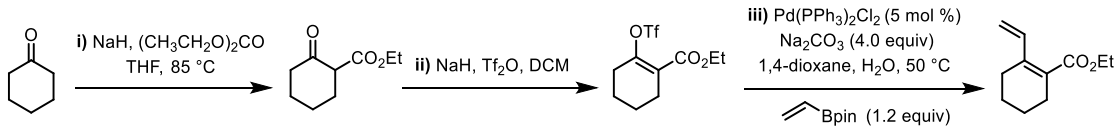
Pivalic acid (20.4 g, 22.6 mL, 200 mmol) was placed in a dry and argon-flushed 500 mL three-necked roundbottom flask, equipped with a magnetic stirring bar, a septum and a pressure equalizer, and was dissolved in dry THF (120 mL). The mixture was cooled to 0 °C, and a solution of Et_2Zn (13.0 g, 10.8 mL, 105 mmol) in dry THF (120 mL) was added over a period of 30 min under vigorous stirring. Then, the ice-bath was removed and stirring was continued at 25 °C for one additional hour at which point bubbling has ceased (a thick slurry was formed). The solvent was removed in vacuo and the solid residue was dried for at least 4 h longer. $Zn(OPiv)_2$ was obtained in quantitative yield, as a puffy amorphous white solid.

4.2 Preparation of olefins 2

Table S7. Preparation of Dienoates



General procedure A



Scheme S11. Preparation of cyclic dienotes

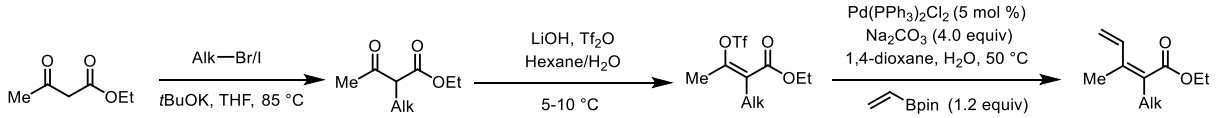
i) NaH (40 mmol, 2.0 eq, 60% in mineral oil) was added in 50 mL THF to form a suspension. And then commercial available ketone (20 mmol, 1.0 eq) was added to the mixture and stirred at rt for 10 min. Then diethyl carbonate (40 mmol, 2.0 eq) was added to the solution at rt and kept stirring at reflux conditions for 2-3 h. Upon completion as indicated by TLC, the reaction

was quenched with saturated aqueous NH_4HCO_3 and followed by the addition of acetic acid (1 M) at rt. The reaction mixture was then extracted with ethyl acetate, washed with brine, dried over Na_2SO_4, filtered and concentrated to give the crude product, which was purified by column chromatography on silica gel (petroleum ether/EtOAc) to obtain the corresponding cyclic ketoesters.[5]

***ii*)** A dry round-bottom flask equipped with a magnetic stirbar was charged with dry dichloromethane (12.0 mL) and the flask was cooled to 0 °C in an ice bath. Next, NaH 60% dispersion in mineral oil (144 mg, 3.60 mmol, 1.2 equiv) was added in one portion and the suspension was stirred for 5 minutes. Then, a solution of the ketoester (3.00 mmol, 1.0 equiv) in dry dichloromethane (3.0 mL) was added dropwise to the suspension at 0 °C. Once the addition was finished, the mixture was stirred for 30 min at 0 °C. After that time, Tf_2O 1M in CH_2Cl_2 (3.6 mL, 3.60 mmol, 1.2 equiv) was added dropwise to the content at 0 °C and the reaction mixture was warmed to room temperature and stirred overnight. Then it was quenched with the addition of H_2O (10 mL) and the resulting layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic phase was washed with brine, dried over Na_2SO_4 and filtered. The solvent was removed and the residue was purified by flash chromatography on silica gel to afford the corresponding products.[6]

***iii*)** Enol triflate (4 mmol, 1.0 equiv), vinylboronic acid pinacol ester (4.8 mmol, 1.2 equiv), $Pd(PPh_3)_2Cl_2$ (0.2 mmol, 0.05 equiv) and Na_2CO_3 (16 mmol, 4.0 equiv) were dissolved in a mixture of 1,4-dioxane/H_2O (2.5:1, 12 mL). The resulting mixture was deoxygenated with a stream of nitrogen for 10 min, then heated to 50 °C until completion of the reaction (monitored by TLC, typically < 60 min). The mixture was cooled to rt and quenched with saturated NH_4Cl (10 mL). The reaction mixture was extracted with EtOAc. The combined organic solution was washed with H_2O and brine, dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give **2a-2p**.[7]

General procedure B



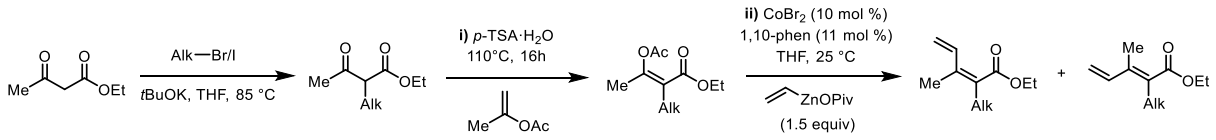
Scheme S12. Preparation of α- alkyl substituted dienotes

***i*)** To a suspension of *t*-BuOK (22 mmol, 1.1 eq) in THF (40 mL) was added ethyl acetoacetate or tert-butyl acetoacetate (20 mmol, 1.0 eq) at 0 °C. The resulting clear solution was stirred at

0 °C for 30 min, and then alkyl bromide or alkyl iodide (24 mmol, 1.2 eq) in THF (10 mL) was added to the solution. After heating under reflux conditions for 12 h, the reaction was quenched with saturated aqueous NH_4Cl. Then the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, then dried over Na_2SO_4, filtered and concentrated to give crude product, which was purified by column chromatography on silica gel (petroleum ether/EtOAc) to give α- alkyl substituted ketoesters.[8]

***ii*)** General Procedure for the synthesis of **(*Z*)-Enol Triflates**: The starting acetoacetate derivative (4 mmol) was added to a round-bottom flask and dissolved in either hexanes or toluene (20 mL, 0.2 M). The solution was cooled with an ice bath to 5-10°C (internal temperature) followed by addition of a saturated aqueous solution of LiOH (6 mL, ~30 mmol) in one portion. The resulting biphasic mixture was vigorously stirred at 5-10°C for ~5 minutes followed by the addition of triflic anhydride (10 mmol) dropwise at a rate to maintain the internal temperature between 5-15 ºC. Upon completion of the reaction (as judged by TLC, typically < 10min), the biphasic solution was diluted with H_2O (5mL) and the layers were separated. The aqueous layer was extracted with EtOAc (1 x 10mL). The combined organic layers were washed with H_2O, brine, and dried over Na_2SO_4. The organic layer was filtered and concentrated under reduced pressure to yield the corresponding crude (Z)-enol triflate, which was purified by column chromatography on silica gel (petroleum ether/EtOAc).[6] Then, follow steps ***iii*)** in **Procedure A** to obtain the corresponding alkenes.

General procedure C



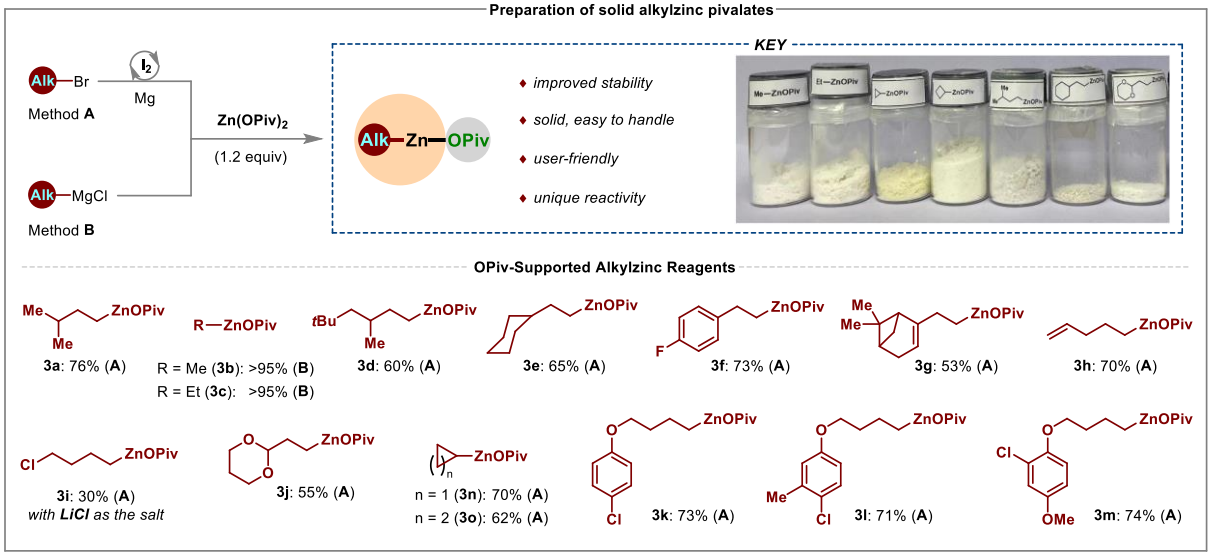
Scheme S13. Preparation of α- alkyl substituted dienotes

***i*)** Firstly, follow steps ***i*)** in **Procedure B** to obtain the corresponding substituted ketoesters. Then, a solution of ketoester (10 mmol, 1.0 equiv) in *iso*-propenyl acetate (10 mL) was added *p*-TSA H_2O (1.0 mmol, 0.1 equiv). The resulting mixture was heated under reflux conditions (110 ℃) for 18 hours. The mixture was allowed to cool to rt and the remaining *iso*-propenyl acetate was removed under reduced pressure. The brown oily residue was extracted with ethyl acetate and washed with water. Afterwards the organic phase was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The remaining residue was purified by column chromatography on silica gel (petroleum ether /EtOAc) to yield alkenyl acetates.[9]

ii) A suspension of $CoBr_2$ (10 mol %), 1,10-phen (11 mol%), alkenyl acetates (7 mmol, 1.0 equiv), alkenylzinc pivalates (10.5 mmol, 1.5 equiv) in degas THF (15.0 mL) was stirred at room temperature for 6 h. At ambient temperature, the solvent was evaporated in vacuo and the remaining residue was purified by column chromatography on silica gel (petroleum ether /EtOAc) to yield products **(*Z*)-61** and **(*E*)-61**.

4.3 Preparation of Alkylzinc Pivalates 3

Table S8. Solid alkylzinc pivalates



General procedure D

Two 25mL Schlenck flasks were oven-dried and allowed to cool to room temperature under vacuum. Both flasks were then backfilled with argon 3 times. One flask was charged with Mg turnings (7.5 mmol, 1.5 equiv), I_2 (0.05 mmol, 0.01 equiv) and anhydrous THF (2.0 mL). To the other flask were added alkyl bromide (1.0 equiv, 5 mmol) and anhydrous THF (3 mL). A small portion of the alkyl bromide solution (approx. 1 mL) was added to the Mg and I_2, and the mixture was vigorously stirred. The flask was heated gently with a heat gun until the dark brown color disappeared. The rest of the alkyl bromide solution was added dropwisely to keep the solution boiling gently. After completion of the addition, the flask was heated at 60 ºC for 1 h in an oil bath. Atfer cooling to room temperature, the resulting solution of Grignard reagent was titrated with I_2 according to Knochel's method to afford Grignard reagents with concentration typically ranging 0.4-0.8 M in THF. $Zn(OPiv)_2$ (1.2 equiv) is then added to afford a solution of the corresponding zinc reagent **3a–3h, 3j–3o**.

General procedure E

LiCl (1.25 equiv) was dried under high vacuum and allowed to cool to room temperature, then $Zn(OPiv)_2$ (1.1equiv), Mg turnings (2.4 equiv) and THF (1 M solution relating to the aryl bromide) were added. The reaction mixture was cooled to 0 °C and the corresponding aryl bromide (1.0 equiv) was then added. The reaction was stirred at room temperature for 5h to afford a solution of the corresponding zinc reagent **3i**. The concentration of organozinc reagent was determined by iodometric titration.

4.4 Preparation of 4–59

General procedure F

To a suspension of dienoate **2** (0.225 mmol, 1.5 equiv), CoI_2 (10 mol %), difluoroalkyl bromide **1** (0.15 mmol, 1.0 equiv) in anhydrous MeCN (1.5 mL) was added alkylzinc pivalate **3** (0.375 mmol, 2.5 equiv), the reaction mixture was stirred at 25 °C for 16 h under an atmosphere of N_2. At ambient temperature, the solvent was evaporated in vacuo and the remaining residue was purified by column chromatography on silica gel (petroleum ether/EtOAc) to yield the products.

General procedure G

To a suspension of dienoate **2** (0.15 mmol, 1.0 equiv), CoI_2 (10 mol %), TMEDA (5.2 mg, 30 mol %), difluoroalkyl bromide **1** (0.30 mmol, 2.0 equiv) in anhydrous MeCN (1.5 mL) was added alkylzinc pivalate **3** (0.375 mmol, 2.5 equiv), the reaction mixture was stirred at 25 °C for 16 h under an atmosphere of N_2. At ambient temperature, the solvent was evaporated in vacuo and the remaining residue was purified by column chromatography on silica gel (petroleum ether/EtOAc) to yield the products.

General procedure H

To a suspension of dienoate **2** (0.225 mmol, 1.5 equiv), CoI_2 (10 mol %), TMEDA (5.2 mg, 30 mol %), alkyl bromide **1** (0.15 mmol, 1.0 equiv) in anhydrous MeCN (1.5 mL) was added alkylzinc pivalate **3** (0.375 mmol, 2.5 equiv), the reaction mixture was stirred at 0 °C for 16 h under an atmosphere of N_2. At ambient temperature, the solvent was evaporated in vacuo and the remaining residue was purified by column chromatography on silica gel (petroleum ether/EtOAc) to yield the products.

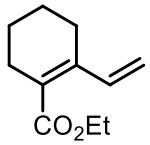
General procedure I

To a suspension of dienoate **2** (0.15 mmol, 1.0 equiv), CoI_2 (10 mol %), alkyl bromide **1** (0.30 mmol, 2.0 equiv) in anhydrous MeCN (1.5 mL) was added alkylzinc pivalate **3** (0.375 mmol, 2.5 equiv), the reaction mixture was stirred at 0 °C for 16 h under an atmosphere of N_2. At

ambient temperature, the solvent was evaporated in vacuo and the remaining residue was purified by column chromatography on silica gel (petroleum ether/EtOAc) to yield the products.

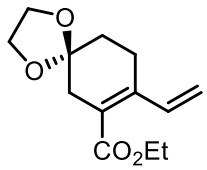
5. Characterization Data

5.1 Characterization data of olefins 2a–2p:



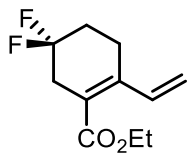
Ethyl 2-vinylcyclohex-1-ene-1-carboxylate (2a)

The general procedure **A** was followed using **triflates** (4 mmol) for 1 h. Purification by column chromatography (petroleum ether/EtOAc 50:1) yielded **2a** (688 mg, 95%) as a yellow liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.10 (dd, *J* = 17.5, 11.1, 1H), 5.36 (d, *J* = 17.5, 1H), 5.15 (d, *J* = 11.1, 1H), 4.22 (q, *J* = 7.1, 2H), 2.38 (d, *J* = 5.2, 2H), 2.31 (t, *J* = 5.0, 2H), 1.64 (dd, *J* = 6.2, 3.2, 4H), 1.30 (t, *J* = 7.1, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.5, 140.4, 135.6, 129.5, 115.3, 60.6, 27.4, 25.5, 22.2, 22.0, 14.4. HR-MS (EI) m/z calcd for $C_{11}H_{16}O_2$ [M+H$^+$] 181.1223, found 181.1226.



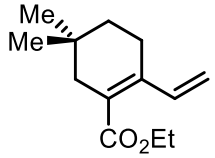
Ethyl 8-vinyl-1,4-dioxaspiro[4.5]dec-7-ene-7-carboxylate (2b)

The general procedure **A** was followed using **triflates** (4 mmol) for 1 h. Purification by column chromatography (petroleum ether/EtOAc 10:1) yielded **2b** (908 mg, 95%) as a yellow liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.30 (dd, *J* = 17.6, 11.1, 1H), 5.44 (d, *J* = 17.5, 1H), 5.24 (d, *J* = 11.1, 1H), 4.21 (q, *J* = 7.1, 2H), 4.05 – 3.96 (m, 4H), 2.65 – 2.53 (m, 4H), 1.81 (t, *J* = 6.6, 2H), 1.30 (t, *J* = 7.1, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 167.7, 141.4, 134.9, 125.8, 116.7, 107.3, 64.6, 60.7, 37.1, 30.4, 25.3, 14.3. HR-MS (EI) m/z calcd for $C_{13}H_{18}O_4$ [M+H$^+$] 239.1278, found 239.12820.



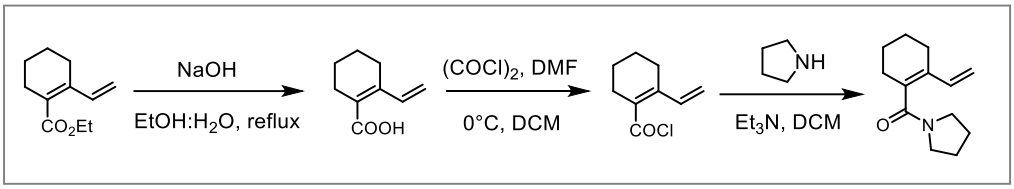
Ethyl 5,5-difluoro-2-vinylcyclohex-1-ene-1-carboxylate (2c)

The general procedure **A** was followed using **triflates** (3 mmol) for 1 h. Purification by column chromatography (petroleum ether/EtOAc 50:1) yielded **2c** (599 mg, 92%) as a yellow liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.37 (dd, *J* = 17.6, 11.1, 1H), 5.47 (dd, *J* = 17.6, 0.8, 1H), 5.31 (dd, *J* = 11.1, 0.6, 1H), 4.23 (q, *J* = 7.1, 2H), 2.88 (tt, *J* = 19.8, 9.9, 2H), 2.64 (t, *J* = 6.8, 2H), 2.07 (dq, *J* = 20.3, 6.8, 2H), 1.31 (t, *J* = 7.1, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 166.8, 141.5, 134.3, 123.3 (t, $^{3}J_{C\text{-}F}$ = 5.5), 122.2 (t, $^{1}J_{C\text{-}F}$ = 239.0), 117.9, 61.0, 36.2 (t, $^{2}J_{C\text{-}F}$ = 28.1), 29.6 (t, $^{2}J_{C\text{-}F}$ = 24.4), 24.5 (t, $^{3}J_{C\text{-}F}$ =5.5), 14.3. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -97.03 (s). HR-MS (EI) m/z calcd for $C_{11}H_{14}F_2O_2$ [M+H$^+$] 217.1035, found 217.1036.

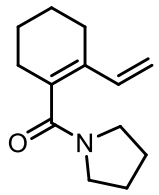


Ethyl 5,5-dimethyl-2-vinylcyclohex-1-ene-1-carboxylate (2d)

The general procedure **A** was followed using **triflates** (10 mmol) for 1 h. Purification by column chromatography (petroleum ether/EtOAc 50:1) yielded **2d** (1.88 g, 90%) as a yellow liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.06 (dd, *J* = 17.5, 11.0, 1H), 5.31 (dd, *J* = 17.5, 0.8, 1H), 5.10 (d, *J* = 11.1, 1H), 4.14 (d, *J* = 7.1, 2H), 2.27 (ddd, *J* = 8.5, 4.5, 2.1, 2H), 2.09 (s, 2H), 1.35 (t, *J* = 6.6, 2H), 1.24 (t, *J* = 7.1, 3H), 0.87 (s, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.4, 139.2, 135.3, 128.4, 115.4, 60.5, 41.0, 34.6, 28.7, 28.0, 23.4, 14.4. HR-MS (EI) m/z calcd for $C_{13}H_{20}O_2$ [M+H$^+$] 209.1536, found 209.1537.



Scheme S14. Preparation of 2e

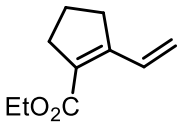


Pyrrolidin-1-yl(2-vinylcyclohex-1-en-1-yl)methanone (2e)

***i*)** Add **2a** (5.0 mmol, 1.0 equiv) to the reaction bottle, before adding NaOH (5.0 equiv), then add EtOH/H_2O = 3:1 (0.85 M), refluxing at 85°C for 4 h. The PH was adjusted to 1 with HCl and extracted with ethyl acetate or diethyl ether. The organic phase was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The residue was purified by

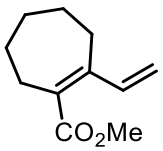
column chromatography (petroleum ether/EtOAc = 1:1) to give corresponding carboxylic acids (760 mg, 89%).

ii) A round-bottom flask or culture tube was charged with carboxylic acid (1 mmol, 1.0 equiv), DCM (4.0 mL, 0.25 M) and oxalyl chloride (1.3 equiv). A drop of DMF was added, then the mixture was stirred vigorously at room temperature for 1 h. Take another reaction bottle and added tetrahydropyrrole (1.0 equiv), DCM (0.5 M) and Et_3N (2.0 eq) in turn. The mixture of dienyl chloride was added at 0°C. The mixture was stirred at room temperature for 12 h. The reaction was then quenched with H_2O and extracted with DCM. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash silica gel chromatography (petroleum ether/EtOAc = 1:1) to give **2e** (183 mg, 90%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.35 (dd, J = 17.3, 10.9, 1H), 5.18 (d, J = 17.3, 1H), 4.99 (d, J = 10.9, 1H), 3.49 (t, J = 6.6, 2H), 3.24 (t, J = 6.5, 2H), 2.20 (d, J = 35.8, 4H), 1.91 – 1.79 (m, 4H), 1.69 – 1.58 (m, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 171.1, 135.4, 135.2, 131.2, 113.3, 47.3, 45.1, 27.0, 26.0, 24.6, 23.6, 22.2, 22.1. HR-MS (EI) m/z calcd for $C_{13}H_{19}NO_4$ [M+H$^+$] 205.1539, found 205.1540.



Ethyl 2-vinylcyclopent-1-ene-1-carboxylate (2f)

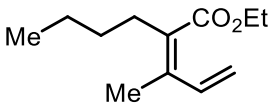
The general procedure **A** was followed using **triflates** (4 mmol) for 1 h. Purification by column chromatography (petroleum ether/EtOAc 50:1) yielded **2f** (648 mg, 97%) as a yellow liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.26 (dd, J = 5.3, 3.2, 1H), 1.64 – 1.61 (m, 2H), 1.26 (q, J = 2.1, 2H), 0.81 (ddd, J = 4.7, 3.4, 1.4, 4H), 0.57 – 0.54 (m, 2H), 0.39 (t, J = 2.1, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 166.0, 151.8, 132.0, 130.2, 120.4, 60.1, 34.5, 33.8, 21.3, 14.5. HR-MS (EI) m/z calcd for $C_{10}H_{14}O_2$ [M+H$^+$] 167.1067, found 167.1069.



Methyl 2-vinylcyclohept-1-ene-1-carboxylate (2g)

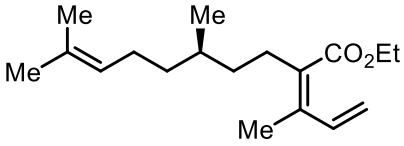
The general procedure **A** was followed using **triflates** (4 mmol) for 1 h. Purification by column chromatography (petroleum ether/EtOAc 50:1) yielded **2g** (652 mg, 90%) as a yellow liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.01 (dd, J = 17.3, 11.0, 1H), 5.39 (d, J = 17.3, 1H), 5.19 (d, J = 11.0, 1H), 3.74 (s, 3H), 2.55 – 2.41 (m, 4H), 1.77 (dt, J = 12.0, 6.0, 2H), 1.52 (qd, J = 11.3,

5.9, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.4, 147.7, 135.6, 133.9, 116.0, 51.7, 32.1, 30.7, 28.4, 26.3, 25.4. HR-MS (EI) m/z calcd for $C_{11}H_{16}O_2$ [M+H$^+$] 181.1223, found 181.1225.



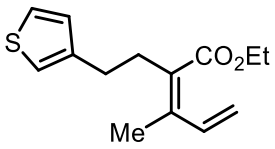
Ethyl (*Z*)-2-(but-3-en-2-ylidene)hexanoate (2h)

The general procedure **B** was followed using **(*Z*)-enol triflates** (3 mmol) for 1 h. Purification by column chromatography (petroleum ether/EtOAc 50:1) yielded **2h** (530 mg, 90%) as a yellow liquid. H-NMR (400 MHz, $CDCl_3$): δ = 6.89 (dd, *J* = 17.3, 10.9, 1H), 5.35 (dd, *J* = 17.3, 1.0, 1H), 5.16 (dd, *J* = 10.9, 0.9, 1H), 4.23 (q, *J* = 7.1, 2H), 2.41 – 2.33 (m, 2H), 1.88 (s, 3H), 1.43 – 1.28 (m, 7H), 0.90 (t, *J* = 7.1, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.3, 137.2, 136.4, 133.3, 115.9, 60.6, 31.0, 30.6, 22.7, 14.4, 14.0, 14.0. HR-MS (EI) m/z calcd for $C_{12}H_{20}O_2$ [M+H$^+$] 197.1536, found 197.1539.



Ethyl (*R*,*Z*)-2-(but-3-en-2-ylidene)-5,9-dimethyldec-8-enoate (2i)

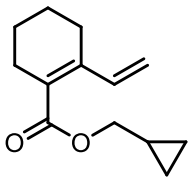
The general procedure **B** was followed using **(*Z*)-enol triflates** (1.9 mmol) for 1 h. Purification by column chromatography (petroleum ether/EtOAc 50:1) yielded **2i** (475 mg, 90%) as a yellow liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.92 (dd, *J* = 17.3, 10.9, 1H), 5.35 (dd, *J* = 17.3, 0.7, 1H), 5.17 (d, *J* = 11.0, 1H), 5.09 (ddd, *J* = 7.1, 5.9, 1.3, 1H), 4.23 (q, *J* = 7.1, 2H), 2.46 – 2.28 (m, 2H), 2.05 – 1.91 (m, 2H), 1.89 (s, 3H), 1.69 (d, *J* = 9.5, 3H), 1.59 (d, *J* = 4.2, 3H), 1.49 – 1.34 (m, 3H), 1.31 (dd, *J* = 8.9, 5.3, 3H), 1.28 – 1.11 (m, 2H), 0.91 (d, *J* = 6.4, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.1, 137.3, 136.4, 133.3, 131.3, 124.9, 116.0, 60.6, 36.9, 35.8, 32.6, 28.5, 25.9, 25.6, 19.6, 17.8, 14.4, 13.9. HR-MS (EI) m/z calcd for $C_{18}H_{30}O_2$ [M+H$^+$] 279.2319, found 279.2321.



Ethyl (*Z*)-3-methyl-2-[2-(thiophen-3-yl)ethyl]penta-2,4-dienoate (2j)

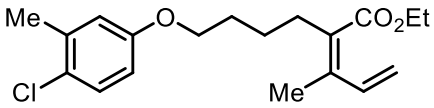
The general procedure **B** was followed using **(*Z*)-enol triflates** (2.66 mmol) for 1 h. Purification by column chromatography (petroleum ether/EtOAc 50:1) yielded **2j** (630 mg, 95%) as a yellow liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.23 (dd, *J* = 4.7, 3.1, 1H), 6.96 (ddd, *J* = 10.2, 6.4, 5.6, 3H), 5.37 (dd, *J* = 17.3, 0.9, 1H), 5.20 (dd, *J* = 11.0, 0.8, 1H), 4.23 (q, *J* = 7.1, 2H),

2.82 – 2.64 (m, 4H), 1.81 (s, 3H), 1.32 (t, J = 7.1, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.7, 141.8, 138.9, 136.2, 131.5, 128.4, 125.4, 120.7, 116.6, 60.7, 32.1, 29.4, 14.4, 14.0. HR-MS (EI) m/z calcd for $C_{14}H_{18}O_2S$ [M+H$^+$] 251.1100, found 251.1101.



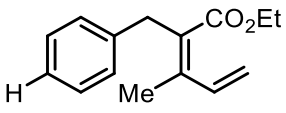
Cyclopropylmethyl 2-vinylcyclohex-1-ene-1-carboxylate (2k)

The steps are the same as **2e**. Purification by column chromatography (petroleum ether/EtOAc 50:1) yielded **2k** as a yellow liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.12 (dd, J = 17.5, 11.0, 1H), 5.36 (d, J = 17.5, 1H), 5.15 (d, J = 11.1, 1H), 4.00 (d, J = 7.2, 2H), 2.39 (s, 2H), 2.31 (d, J = 4.8, 2H), 1.68 – 1.63 (m, 4H), 1.20 – 1.12 (m, 1H), 0.61 – 0.54 (m, 2H), 0.30 (dd, J = 5.9, 4.8, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.6, 140.3, 135.7, 129.6, 115.2, 69.3, 27.5, 25.5, 22.2, 22.0, 10.0, 3.4. HR-MS (EI) m/z calcd for $C_{13}H_{18}O_2$ [M+H$^+$] 207.1380, found 207.1382.



Ethyl (*Z*)-2-(but-3-en-2-ylidene)-6-(4-chloro-3-methylphenoxy)hexanoate (2l)

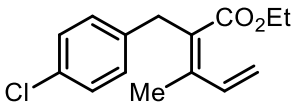
The general procedure **B** was followed using **(*Z*)-enol triflates** (1.2 mmol) for 1 h. Purification by column chromatography (petroleum ether/EtOAc 50:1) yielded **2l** (338 mg, 84%) as a yellow liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.20 (d, J = 8.7, 1H), 6.93 (dd, J = 17.3, 10.9, 1H), 6.75 (d, J = 2.9, 1H), 6.65 (dd, J = 8.7, 2.9, 1H), 5.38 (dd, J = 17.3, 1.0, 1H), 5.19 (dd, J = 11.0, 0.9, 1H), 4.24 (q, J = 7.1, 2H), 3.91 (t, J = 6.4, 2H), 2.50 – 2.42 (m, 2H), 2.33 (s, 3H), 1.90 (s, 3H), 1.80 (dt, J = 14.5, 6.5, 2H), 1.61 (tt, J = 9.9, 6.4, 2H), 1.31 (t, J = 7.1, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.0, 157.7, 137.9, 137.0, 136.3, 132.5, 129.7, 125.8, 117.2, 116.3, 113.2, 68.0, 60.7, 30.4, 29.1, 25.3, 20.4, 14.4, 14.1. HR-MS (EI) m/z calcd for $C_{19}H_{25}ClO_3$ [M+H$^+$] 337.1565, found 337.1562.



Ethyl (*Z*)-2-benzyl-3-methylpenta-2,4-dienoate (2m)

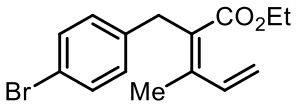
The general procedure **B** was followed using **(*Z*)-enol triflates** (3 mmol) for 1 h. Purification by column chromatography (petroleum ether/EtOAc 50:1) yielded **2m** (680 mg, 98%) as a yellow liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.28 – 7.23 (m, 2H), 7.14 (ddd, J = 28.3, 11.9, 7.4, 4H), 5.45 (dd, J = 17.3, 0.9, 1H), 5.26 (dd, J = 11.0, 0.8, 1H), 4.13 (q, J = 7.1, 2H), 3.80 (s,

2H), 1.96 (s, 3H), 1.17 (t, J = 7.1, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.3, 140.1, 139.1, 136.2, 130.8, 128.5, 128.4, 126.3, 117.1, 60.7, 36.5, 14.8, 14.2. HR-MS (EI) m/z calcd for $C_{15}H_{18}O_2$ [M+H$^+$] 231.1380, found 231.1378.



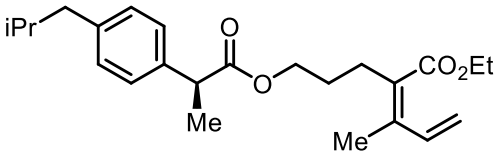
Ethyl (*Z*)-2-(4-chlorobenzyl)-3-methylpenta-2,4-dienoate (2n)

The general procedure **B** was followed using **(*Z*)-enol triflates** (4 mmol) for 1 h. Purification by column chromatography (petroleum ether/EtOAc 80:1) yielded **2n** (338 mg, 91%) as a yellow liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.25 – 7.20 (m, 2H), 7.17 – 7.06 (m, 3H), 5.46 (dd, J = 17.3, 0.8, 1H), 5.28 (dd, J = 11.0, 0.7, 1H), 4.14 (q, J = 7.1, 2H), 3.75 (s, 2H), 1.95 (s, 3H), 1.19 (t, J = 7.1, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.0, 140.7, 137.7, 136.1, 132.0, 130.2, 129.8, 128.6, 117.5, 60.8, 35.8, 14.9, 14.3. HR-MS (EI) m/z calcd for $C_{15}H_{17}ClO_2$ [M+H$^+$] 265.0990, found 265.0992.



Ethyl (*Z*)-2-(4-bromobenzyl)-3-methylpenta-2,4-dienoate (2o)

The general procedure **B** was followed using **(*Z*)-enol triflates** (3 mmol) for 1 h. Purification by column chromatography (petroleum ether/EtOAc 50:1) yielded **2o** (827 mg, 89%) as a yellow liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.40 – 7.35 (m, 2H), 7.13 (dd, J = 17.3, 11.0, 1H), 7.05 (d, J = 8.4, 2H), 5.46 (dd, J = 17.3, 0.7, 1H), 5.28 (d, J = 11.0, 1H), 4.14 (q, J = 7.1, 2H), 3.74 (s, 2H), 1.95 (s, 3H), 1.19 (t, J = 7.1, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.0, 140.8, 138.2, 136.1, 131.5, 130.1, 130.0, 120.0, 117.5, 60.8, 35.8, 14.9, 14.2. HR-MS (EI) m/z calcd for $C_{15}H_{17}BrO_2$ [M+H$^+$] 309.0485, found 309.0483.

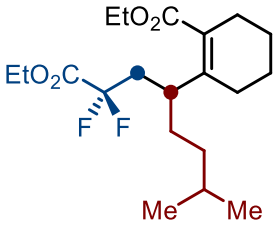


Ethyl (*S*, *Z*)-2-{3-[(2-(4-*iso*butylphenyl)propanoyl)oxy)propyl}-3-methylpenta-2,4-dienoate (2p)

The general procedure **B** was followed using **(*Z*)-enol triflates** (3 mmol) for 1 h. Purification by column chromatography (petroleum ether/EtOAc 50:1) yielded **2p** (984 mg, 85%) as a yellow liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.20 (d, J = 8.1, 2H), 7.08 (d, J = 8.1, 2H), 6.93 (dd, J = 17.3, 10.9, 1H), 5.39 – 5.31 (m, 1H), 5.19 (d, J = 11.0, 1H), 4.21 (q, J = 7.1, 2H), 4.07 (t, J = 6.2, 2H), 3.69 (q, J = 7.1, 1H), 2.44 (d, J = 7.2, 2H), 2.38 – 2.31 (m, 2H), 1.84 (dt, J =

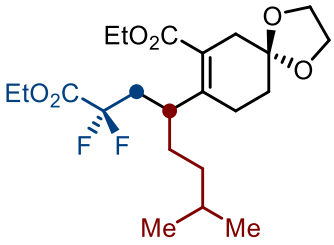
13.5, 6.8, 1H), 1.78 – 1.68 (m, 5H), 1.49 (d, *J* = 7.2, 3H), 1.29 (t, *J* = 7.1, 3H), 0.89 (d, *J* = 6.6, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 174.8, 169.6, 140.6, 138.7, 137.9, 136.2, 131.3, 129.4, 127.3, 116.6, 64.1, 60.7, 45.3, 45.2, 30.3, 27.8, 27.1, 22.5, 18.6, 14.4, 14.0. HR-MS (EI) m/z calcd for $C_{24}H_{34}O_4$ [M+H$^+$] 387.2530, found 387.2534.

5.2 Characterization data of 4–76:



Ethyl 2-(1-ethoxy-2,2-difluoro-7-methyl-1-oxooctan-4-yl)cyclohex-1-ene-1-carboxylate (4)

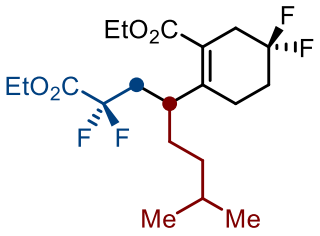
The general procedure **F** was followed using **2a** (0.225 mmol), **difluoroalkyl halide** (0.15 mmol) and **3a** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 80:1) yielded **4** (44 mg, 78%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.30 (q, *J* = 7.1, 2H), 4.17 (qd, *J* = 7.1, 2.0, 2H), 3.50 – 3.41 (m, 1H), 2.32 – 2.24 (m, 2H), 2.23 – 1.91 (m, 4H), 1.64 – 1.56 (m, 4H), 1.49 (dt, *J* = 13.1, 6.6, 1H), 1.44 – 1.37 (m, 2H), 1.35 (t, *J* = 7.2, 3H), 1.29 (t, *J* = 7.1, 3H), 1.16 (ddt, *J* = 12.4, 10.6, 6.3, 1H), 1.04 (tdd, *J* = 13.2, 8.7, 6.0, 1H), 0.86 (dd, *J* = 6.6, 2.2, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.5, 164.2 (t, $^2J_{C\text{-}F}$ = 32.7), 145.1, 127.5, 116.2 (t, $^1J_{C\text{-}F}$ = 251.0), 62.8, 60.1, 37.6 (t, $^2J_{C\text{-}F}$ = 22.1), 36.2, 35.5 (t, $^3J_{C\text{-}F}$ = 3.2), 31.1, 28.0, 27.2, 23.9, 22.7, 22.4, 22.2, 22.0, 14.2, 13.9. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -103.22 (d, *J* = 262.5), -104.09 (d, *J* = 262.4). HR-MS (EI) m/z calcd for $C_{20}H_{32}F_2O_4$ [M+H$^+$] 375.2341, found 375.2345.



Ethyl 8-(1-ethoxy-2,2-difluoro-7-methyl-1-oxooctan-4-yl)-1,4-dioxaspiro[4.5]dec-7-ene-7-carboxylate (5)

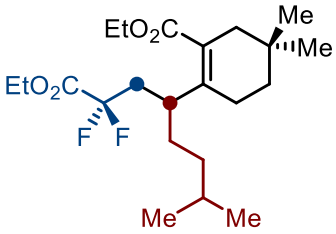
The general procedure **F** was followed using **2b** (0.225 mmol), **difluoroalkyl halide** (0.15 mmol) and **3a** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 5:1) yielded **5** (55 mg, 85%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ =

4.33 – 4.26 (m, 2H), 4.17 (tt, *J* = 7.2, 3.6, 2H), 4.02 – 3.93 (m, 4H), 3.76 – 3.68 (m, 1H), 2.52 (q, *J* = 17.7, 2H), 2.33 – 2.04 (m, 4H), 1.72 (t, *J* = 6.5, 2H), 1.57 – 1.37 (m, 3H), 1.34 (t, *J* = 7.2, 3H), 1.28 (t, *J* = 7.1, 3H), 1.21 – 1.11 (m, 1H), 1.11 – 1.00 (m, 1H), 0.86 (d, *J*=6.6, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 168.0, 164.3(t, $^2J_{C\text{-}F}$ = 32.8), 146.7, 124.9, 116.2 (t, $^1J_{C\text{-}F}$ = 251.1), 107.4, 64.6, 64.6, 62.9, 60.4, 37.8 (t, $^2J_{C\text{-}F}$ = 22.3), 37.4, 36.2, 34.9 (t, $^3J_{C\text{-}F}$ = 3.3), 31.3, 30.7, 28.1, 23.8, 22.8, 22.5, 14.3, 14.0. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -103.13 (d, *J* = 262.6), -103.97 (d, *J* = 263.0). HR-MS (EI) m/z calcd for $C_{22}H_{34}F_2O_6$ [M+H$^+$] 433.2396, found 433.2399.



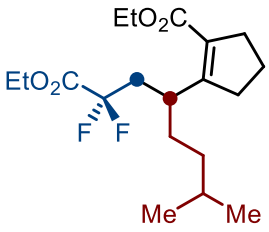
Ethyl 2-(1-ethoxy-2,2-difluoro-7-methyl-1-oxooctan-4-yl)-5,5-difluorocyclohex-1-ene-1-carboxylate (6)

The general procedure **F** was followed using **2c** (0.225 mmol), **difluoroalkyl halide** (0.15 mmol) and **3a** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 80:1) yielded **6** (49 mg, 80%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.30 (qd, *J* = 7.1, 1.6, 2H), 4.19 (q, *J* = 7.1, 2H), 3.90 – 3.80 (m, 1H), 2.89 – 2.72 (m, 2H), 2.43 – 2.12 (m, 4H), 2.10 – 1.90 (m, 2H), 1.54 – 1.37 (m, 3H), 1.34 (t, *J* = 7.2, 3H), 1.30 (t, *J* = 7.1, 3H), 1.22 – 1.12 (m, 1H), 1.06 – 0.95 (m, 1H), 0.86 (dd, *J* = 6.6, 1.6, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 167.0, 164.1 (t, $^2J_{C\text{-}F}$ = 32.7), 147.1, 123.1 (dd, $^3J_{C\text{-}F}$ = 6.3, 4.4), 122.3 (t, $^1J_{C\text{-}F}$ = 238.9), 116.0 (t, $^1J_{C\text{-}F}$ = 251.2), 63.0, 60.8, 37.6 (t, $^2J_{C\text{-}F}$ = 22.3), 36.3 (t, $^2J_{C\text{-}F}$ = 28.0), 36.1, 34.6, 31.4, 29.8 (t, $^2J_{C\text{-}F}$ = 24.3), 28.1, 22.8, 22.5, 14.2, 14.0. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -95.45 (d, *J* = 235.9), -97.01 (d, *J* = 235.9), -103.09 (d, *J* = 264.7), -104.20 (d, *J* = 264.6). HR-MS (EI) m/z calcd for $C_{20}H_{30}F_4O_4$ [M+H$^+$] 411.2153, found 411.2157.



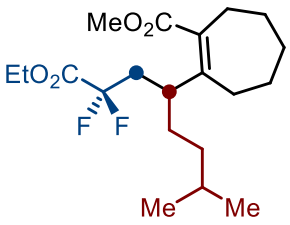
Ethyl 2-(1-ethoxy-2,2-difluoro-7-methyl-1-oxooctan-4-yl)-5,5-dimethylcyclohex-1-ene-1-carboxylate (7)

The general procedure **F** was followed using **2d** (0.225 mmol), **difluoroalkyl halide** (0.15 mmol) and **3a** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 80:1) yielded **7** (54 mg, 90%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.30 (qd, J = 7.1, 1.2, 2H), 4.16 (qd, J = 7.1, 1.9, 2H), 3.53 – 3.44 (m, 1H), 2.30 – 2.15 (m, 1H), 2.15 – 1.96 (m, 5H), 1.53 – 1.39 (m, 3H), 1.38 – 1.32 (m, 5H), 1.29 (t, J = 7.1, 3H), 1.17 (ddt, J = 12.3, 10.5, 6.2, 1H), 1.10 – 0.96 (m, 1H), 0.92 (d, J = 10.4, 6H), 0.85 (dd, J = 6.6, 2.2, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.7, 164.4 (t, $^{2}J_{C\text{-}F}$ = 32.7), 143.7, 126.9, 116.3 (t, $^{1}J_{C\text{-}F}$ = 251.1), 62.9, 60.2, 41.0, 37.9 (t, $^{2}J_{C\text{-}F}$ = 22.1), 36.46, 35.3 (t, $^{3}J_{C\text{-}F}$ = 3.0), 34.9, 31.4, 28.8, 28.6, 28.1, 27.7, 22.9, 22.5, 21.8, 14.3, 14.0. ^{19}F-NMR (376 MHz, $CDCl_3$) δ = -103.39 (d, J = 262.6), -104.21 (d, J = 262.6). HR-MS (EI) m/z calcd for $C_{22}H_{36}F_2O_4$ [M+H$^+$] 403.2654, found 403.2657.



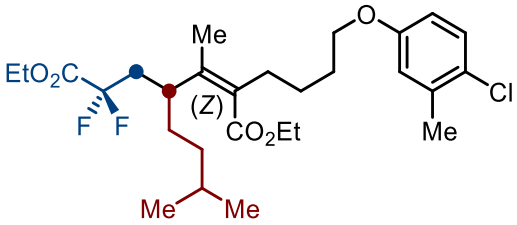
Ethyl 2-(1-ethoxy-2,2-difluoro-7-methyl-1-oxooctan-4-yl)cyclopent-1-ene-1-carboxylate (8)

The general procedure **F** was followed using **2f** (0.225 mmol), **difluoroalkyl halide** (0.15 mmol) and **3a** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 80:1) yielded **8** (37 mg, 68%) as a colorless oil.^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.27 (q, J = 7.1, 2H), 4.18 (q, J = 7.1, 2H), 3.92 – 3.83 (m, 1H), 2.60 (t, J = 7.3, 2H), 2.51 – 2.30 (m, 2H), 2.29 – 2.11 (m, 2H), 1.86 – 1.73 (m, 2H), 1.56 – 1.36 (m, 3H), 1.34 (dd, J = 9.2, 5.1, 3H), 1.29 (t, J = 7.1, 3H), 1.15 (ddd, J = 16.8, 12.4, 5.9, 1H), 1.05 – 0.95 (m, 1H), 0.85 (d, J = 6.6, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 166.0, 164.2 (t, $^{2}J_{C\text{-}F}$ = 32.7), 158.6, 129.9, 116.1 (t, $^{1}J_{C\text{-}F}$ = 251.0), 62.9, 59.9, 38.1 (t, $^{2}J_{C\text{-}F}$ = 22.4), 36.3, 33.9, 32.9, 32.4 (t, $^{3}J_{C\text{-}F}$ = 3.7), 31.9, 28.0, 22.8, 22.5, 21.7, 14.4, 14.0. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -103.35 (s), -103.38 (s). HR-MS (EI) m/z calcd for $C_{19}H_{30}F_2O_4$ [M+H$^+$] 361.2185, found 361.2188.



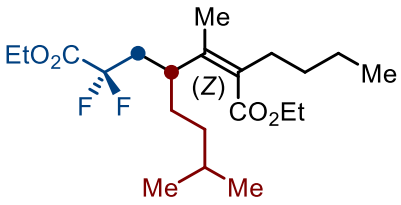
Methyl 2-(1-ethoxy-2,2-difluoro-7-methyl-1-oxooctan-4-yl)cyclohept-1-ene-1-carboxylate (9)

The general procedure **F** was followed using **2g** (0.225 mmol), **difluoroalkyl halide** (0.15 mmol) and **3a** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 80:1) yielded **9** (28 mg, 50%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.34 – 4.26 (m, 2H), 3.70 (s, 3H), 3.36 – 3.27 (m, 1H), 2.49 – 2.34 (m, 2H), 2.22 – 2.03 (m, 4H), 1.82 – 1.69 (m, 2H), 1.61 – 1.38 (m, 7H), 1.35 (t, J = 7.1, 3H), 1.21 – 1.02 (m, 2H), 0.86 (dd, J = 6.6, 2.5, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.7, 164.3 (t, $^{2}J_{C\text{-}F}$ = 32.9), 151.3, 133.2, 116.3 (t, $^{1}J_{C\text{-}F}$ = 251.2), 62.9, 51.4, 37.5 (t, $^{2}J_{C\text{-}F}$ = 22.1), 36.7 (t, $^{3}J_{C\text{-}F}$ = 3.4), 36.5, 32.6, 31.1, 28.9, 28.1, 26.4, 26.3, 22.8, 22.6, 14.0. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -102.77 (d, J = 262.6), -103.60 (d, J = 262.8). HR-MS (EI) m/z calcd for $C_{20}H_{32}F_2O_4$ [M+H$^+$] 375.2341, found 375.2339.



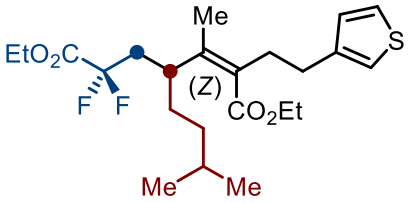
Diethyl (*Z*)-2-[4-(4-chloro-3-methylphenoxy)butyl]-6,6-difluoro-4-isopentyl-3-methylhept-2-enedioate (10)

The general procedure **F** was followed using **2l** (0.225 mmol), **difluoroalkyl halide** (0.15 mmol) and **3a** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 30:1) yielded **10** (51 mg, 64%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.20 (d, J = 8.7, 1H), 6.75 (d, J = 2.9, 1H), 6.65 (dd, J = 8.7, 3.0, 1H), 4.34 – 4.25 (m, 2H), 4.23 – 4.12 (m, 2H), 3.90 (t, J = 6.4, 2H), 3.29 (tt, J = 8.6, 5.7, 1H), 2.36 – 2.30 (m, 5H), 2.27 – 2.02 (m, 2H), 1.81 – 1.72 (m, 2H), 1.64 (s, 3H), 1.60 – 1.36 (m, 5H), 1.34 (t, J = 7.2, 3H), 1.28 (t, J = 7.1, 3H), 1.20 – 1.10 (m, 1H), 1.00 (tdd, J = 11.8, 8.5, 4.9, 1H), 0.86 (d, J = 2.0, 3H), 0.84 (d, J = 1.9, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = -169.8, 164.3 (t, $^{2}J_{C\text{-}F}$ = 32.3), 157.8, 142.4, 137.0, 130.9, 129.7, 125.7, 117.2, 116.2 (t, $^{1}J_{C\text{-}F}$ = 251.3), 113.2, 68.0, 62.9, 60.3, 37.7 (t, $^{2}J_{C\text{-}F}$ = 22.2), 36.7, 36.3, 31.2, 30.1, 29.0, 28.1, 24.9, 22.8, 22.5, 20.4, 14.3, 14.0, 13.1. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -103.59 (d, J = 6.4). HR-MS (EI) m/z calcd for $C_{28}H_{41}ClF_2O_5$ [M+H$^+$] 531.2683, found 531.2680.



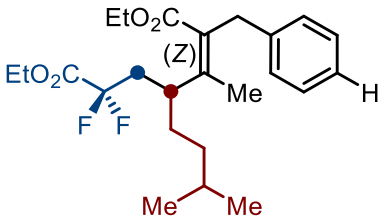
Diethyl (*Z*)-2-butyl-6,6-difluoro-4-isopentyl-3-methylhept-2-enedioate (11)

The general procedure **F** was followed using **2h** (0.225 mmol), **difluoroalkyl halide** (0.15 mmol) and **3a** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 80:1) yielded **11** (40 mg, 68%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.29 (q, J = 7.1, 2H), 4.23 – 4.12 (m, 2H), 3.25 (tt, J = 8.5, 5.7, 1H), 2.29 – 2.01 (m, 4H), 1.62 (s, 3H), 1.46 (ddd, J = 17.4, 12.1, 6.1, 2H), 1.39 – 1.31 (m, 7H), 1.29 (t, J = 7.1, 4H), 1.15 (ddd, J = 16.9, 12.5, 5.9, 1H), 1.01 (tdd, J = 11.0, 7.5, 3.4, 1H), 0.89 (t, J = 7.1, 3H), 0.85 (dd, J = 6.6, 2.4, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.0, 164.3 (t, $^{2}J_{C\text{-}F}$ = 32.7), 141.5, 131.5, 116.2 (t, $^{1}J_{C\text{-}F}$ = 251.0), 62.9, 60.2, 37.8 (t, $^{2}J_{C\text{-}F}$ = 22.2), 36.7 (t, $^{3}J_{C\text{-}F}$ = 3.3), 36.3, 31.2, 30.6, 30.2, 28.1, 22.8, 22.6, 22.5, 14.3, 14.0, 14.0, 12.9. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -103.14 (d, J = 263.5), -103.98 (d, J = 263.1). HR-MS (EI) m/z calcd for $C_{21}H_{36}F_2O_4$ [M+H$^+$] 391.2654, found 391.2650.



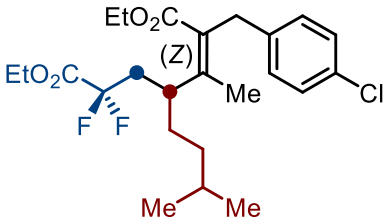
Diethyl (*Z*)-6,6-difluoro-4-isopentyl-3-methyl-2-[2-(thiophen-3-yl)ethyl]hept-2-enedioate (12)

The general procedure **F** was followed using **2j** (0.225 mmol), **difluoroalkyl halide** (0.15 mmol) and **3a** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 50:1) yielded **12** (43 mg, 65%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.22 (dd, J = 4.7, 3.1, 1H), 6.97 – 6.90 (m, 2H), 4.34 – 4.25 (m, 2H), 4.22 – 4.13 (m, 2H), 3.34 (tt, J = 8.4, 5.7, 1H), 2.76 – 2.68 (m, 2H), 2.60 – 2.53 (m, 2H), 2.24 – 2.03 (m, 2H), 1.54 (s, 3H), 1.47 (dd, J = 13.2, 6.5, 1H), 1.43 – 1.37 (m, 1H), 1.34 (dd, J = 8.7, 5.6, 4H), 1.30 (t, J = 7.1, 3H), 1.20 – 1.10 (m, 1H), 1.03 – 0.94 (m, 1H), 0.86 (dd, J = 6.6, 4.0, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.6, 164.3 (t, $^{2}J_{C\text{-}F}$ = 32.8), 143.6, 142.0, 130.1, 128.5, 125.3, 120.6, 116.2 (t, $^{1}J_{C\text{-}F}$ = 251.1), 62.9, 60.4, 37.7 (t, $^{2}J_{C\text{-}F}$ = 22.2), 36.2, 36.6 (t, $^{3}J_{C\text{-}F}$ = 3.2), 31.7, 31.2, 29.0, 28.1, 22.8, 22.5, 14.3, 14.0, 13.0. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -103.58 (s), -103.60 (s). HR-MS (EI) m/z calcd for $C_{23}H_{34}F_2O_4S$ [M+H$^+$] 445.2219, found 445.2222.



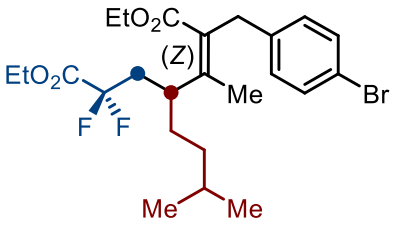
Diethyl (*Z*)-2-benzyl-6,6-difluoro-4-isopentyl-3-methylhept-2-enedioate (13)

The general procedure **F** was followed using **2m** (0.225 mmol), **difluoroalkyl halide** (0.15 mmol) and **3a** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 80:1) yielded **13** (39 mg, 61%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.27 – 7.22 (m, 2H), 7.19 – 7.13 (m, 3H), 4.34 – 4.22 (m, 2H), 4.14 – 4.04 (m, 2H), 3.74 – 3.62 (m, 2H), 3.55 (tt, *J* = 8.8, 5.6, 1H), 2.34 – 2.05 (m, 2H), 1.68 (s, 3H), 1.44 (tdd, *J* = 14.4, 11.0, 5.2, 3H), 1.34 (t, *J* = 7.2, 3H), 1.27 – 1.18 (m, 1H), 1.16 (t, *J* = 7.1, 3H), 1.05 (tdd, *J* = 12.3, 7.0, 5.2, 1H), 0.86 (dd, *J* = 6.6, 4.9, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.1, 164.3 (t, $^{2}J_{C\text{-}F}$ = 32.7), 145.7, 139.5, 129.5, 128.4, 128.3, 126.1, 116.2 (t, $^{1}J_{C\text{-}F}$ =251.2), 62.9, 60.3, 37.7 (t, $^{2}J_{C\text{-}F}$ = 22.2), 36.4, 36.1, 31.5, 28.1, 22.8, 22.5, 14.2, 14.0, 13.9. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -102.90 (d, *J* = 263.6), -103.82 (d, *J* = 263.7). HR-MS (EI) m/z calcd for $C_{24}H_{34}F_2O_4$ [M+H$^+$] 425.2498, found 425.2501.



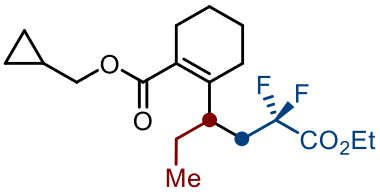
Diethyl (*Z*)-2-(4-chlorobenzyl)-6,6-difluoro-4-isopentyl-3-methylhept-2-enedioate (14)

The general procedure **F** was followed using **2n** (0.225 mmol), **difluoroalkyl halide** (0.15 mmol) and **3a** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 50:1) yielded **14** (53 mg, 78%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 8.4, 2H), 7.10 (d, *J* = 8.5, 2H), 4.33 – 4.24 (m, 2H), 4.13 – 4.05 (m, 2H), 3.66 (d, *J* = 17.0, 2H), 3.56 (tt, *J* = 8.8, 5.4, 1H), 2.31 – 2.04 (m, 2H), 1.67 (s, 3H), 1.45 (qdd, *J* = 13.4, 8.9, 5.5, 3H), 1.34 (t, *J* = 7.2, 3H), 1.23 – 1.13 (m, 4H), 1.09 – 0.97 (m, 1H), 0.86 (dd, *J* = 6.6, 4.1, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 168.9, 164.2 (t, $^{2}J_{C\text{-}F}$ = 32.7), 146.3, 138.0, 131.8, 129.7, 129.1, 128.5, 116.2 (t, $^{1}J_{C\text{-}F}$ = 251.1), 62.9, 60.4, 37.7 (t, $^{2}J_{C\text{-}F}$ = 22.2), 36.4, 35.5, 31.5, 28.1, 22.8, 22.5, 14.2, 14.0, 13.9. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -102.66 (d, *J* = 264.5), -104.17 (d, *J* = 263.7). HR-MS (EI) m/z calcd for $C_{24}H_{33}ClF_2O_4$ [M+H$^+$] 459.2108, found 459.2114.



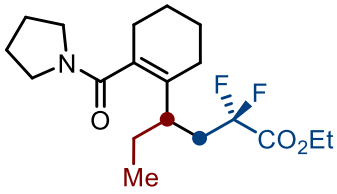
Diethyl (*Z*)-2-(4-bromobenzyl)-6,6-difluoro-4-isopentyl-3-methylhept-2-enedioate (15)

The general procedure **F** was followed using **2o** (0.225 mmol), **difluoroalkyl halide** (0.15 mmol) and **3a** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 50:1) yielded **15** (44 mg, 58%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.37 (d, J = 8.4, 2H), 7.05 (d, J = 8.4, 2H), 4.33 – 4.24 (m, 2H), 4.14 – 4.05 (m, 2H), 3.71 – 3.51 (m, 3H), 2.33 – 2.04 (m, 2H), 1.67 (d, J = 6.0, 3H), 1.54 – 1.36 (m, 3H), 1.34 (t, J = 7.2, 3H), 1.26 – 1.15 (m, 4H), 1.09 – 0.97 (m, 1H), 0.86 (dd, J = 6.6, 4.1, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 168.71, 164.08 (t, $^{2}J_{C\text{-}F}$ = 32.7), 146.34, 138.41, 131.33, 129.98, 128.83, 119.74, 116.03 (t, $^{1}J_{C\text{-}F}$ =251.1), 62.81, 60.32, 37.55 (t, $^{2}J_{C\text{-}F}$ = 22.2), 36.24, 35.46, 31.39, 27.94, 22.69, 22.41, 14.09, 13.90, 13.83. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -102.64 (d, J = 263.9), -104.17 (d, J = 264.0). HR-MS (EI) m/z calcd for $C_{24}H_{33}BrF_2O_4$ [M+H$^+$] 503.1603, found 503.1598.



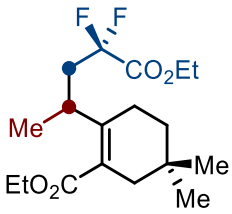
Cyclopropylmethyl 2-(6-ethoxy-5,5-difluoro-6-oxohexan-3-yl)cyclohex-1-ene-1-carboxylate (16)

The general procedure **G** was followed using **2k** (0.15 mmol), **difluoroalkyl bromide** (0.30 mmol) and **3c** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 50:1) yielded **16** (37 mg, 68%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.28 (q, J = 7.1, 2H), 3.93 (tt, J = 11.4, 5.7, 2H), 3.41 (dq, J = 8.9, 5.8, 1H), 2.34 – 1.96 (m, 6H), 1.60 (d, J = 2.6, 4H), 1.52 – 1.38 (m, 2H), 1.33 (t, J = 7.2, 3H), 1.15 (ddd, J = 7.6, 4.4, 2.9, 1H), 0.83 (t, J = 7.4, 3H), 0.58 – 0.50 (m, 2H), 0.31 – 0.22 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.8, 164.4 (t, $^{2}J_{C\text{-}F}$ = 32.8), 144.6, 128.0, 116.3 (t, $^{1}J_{C\text{-}F}$ = 251.1), 69.1, 62.9, 37.5 (t, $^{2}J_{C\text{-}F}$ = 22.3), 37.0, 27.3, 26.4, 23.9, 22.3, 22.1, 14.0, 11.8, 9.9, 3.4, 3.4. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -103.16 (d, J = 262.5), -104.34 (d, J = 262.5). HR-MS (EI) m/z calcd for $C_{19}H_{28}F_2O_4$ [M+H$^+$] 359.2028, found 359.2030.



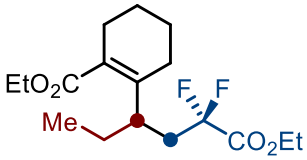
Ethyl 2,2-difluoro-4-(2-(pyrrolidine-1-carbonyl)cyclohex-1-en-1-yl)hexanoate (17)

The general procedure **G** was followed using **2e** (0.15 mmol), **difluoroalkyl bromide** (0.30 mmol) and **3n** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 1:1) yielded **17** (27 mg, 52%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.30 (q, J = 6.9, 2H), 3.43 (d, J = 28.9, 3H), 3.29 (s, 1H), 2.61 – 2.44 (m, 1H), 2.10 (ddd, J = 18.3, 12.8, 6.5, 4H), 1.93 – 1.81 (m, 6H), 1.63 (s, 4H), 1.53 – 1.38 (m, 2H), 1.34 (t, J = 7.1, 3H), 0.85 (t, J = 7.4, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.95, 164.52 (t, $^{2}J_{C\text{-}F}$ = 32.9), 135.23, 131.87, 116.42 (t, $^{1}J_{C\text{-}F}$ = 251.2), 62.99, 47.05, 45.12, 38.17, 26.47, 26.06, 24.51, 22.83, 22.52, 22.33, 14.07, 12.05. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -104.49 (d, J = 256.8). HR-MS (EI) m/z calcd for $C_{19}H_{29}F_2NO_3$ [M+H$^+$] 358.2188, found 358.2187.



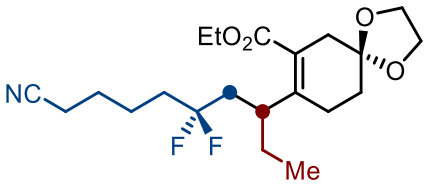
Ethyl 2-(5-ethoxy-4,4-difluoro-5-oxopentan-2-yl)-5,5-dimethylcyclohex-1-ene-1-carboxylate (18)

The general procedure **F** was followed using **2d** (0.225 mmol), **difluoroalkyl halide** (0.15 mmol) and **3b** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 50:1) yielded **18** (26 mg, 50%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.31 (q, J = 7.1, 2H), 4.22 – 4.12 (m, 2H), 3.59 (m, 1H), 2.34 – 2.18 (m, 1H), 2.16 – 1.96 (m, 5H), 1.38 – 1.32 (m, 5H), 1.32 – 1.27 (m, 3H), 1.11 (d, J = 6.9, 3H), 0.91 (d, J = 3.2, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.6, 164.4 (t, $^{2}J_{C\text{-}F}$ = 32.8), 145.6, 125.1, 116.3 (t, $^{1}J_{C\text{-}F}$ = 251.3), 62.9, 60.3, 40.7, 38.8 (t, $^{2}J_{C\text{-}F}$ = 22.2), 34.9, 30.4, 28.5, 28.1, 21.9, 19.7, 14.3, 14.0. ^{19}F-NMR (376 MHz, $CDCl_3$) δ = -104.03 (d, J = 261.7), -104.80 (d, J = 260.9). HR-MS (EI) m/z calcd for $C_{18}H_{28}F_2O_4$ [M+H$^+$] 347.2028, found 347.2023.



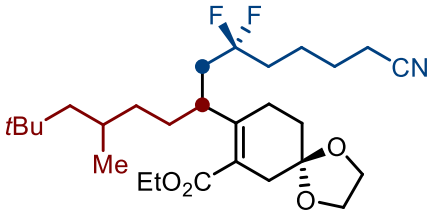
Ethyl 2-(6-ethoxy-5,5-difluoro-6-oxohexan-3-yl)cyclohex-1-ene-1-carboxylate (19)

The general procedure **F** was followed using **2a** (0.225 mmol), **difluoroalkyl halide** (0.15 mmol) and **3c** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 50:1) yielded **19** (40 mg, 80%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.33 – 4.26 (m, 2H), 4.22 – 4.13 (m, 2H), 3.40 (tt, *J* = 8.8, 5.7, 1H), 2.35 – 1.90 (m, 6H), 1.65 – 1.56 (m, 4H), 1.53 – 1.38 (m, 2H), 1.35 (t, *J* = 7.2, 3H), 1.29 (t, *J* = 7.1, 3H), 0.84 (t, *J* = 7.4, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.7, 164.4 (t, $^{2}J_{C\text{-}F}$ = 32.8), 144.7, 128.0, 116.3 (t, $^{1}J_{C\text{-}F}$ = 251.0), 62.9, 60.2, 37.5 (t, $^{2}J_{C\text{-}F}$ = 22.2), 37.0 (t, $^{3}J_{C\text{-}F}$ = 3.3), 27.3, 26.4, 23.9, 22.4, 22.2, 14.3, 14.0, 11.8. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -103.22 (d, *J* = 263.1), -104.23 (d, *J* = 262.2). HR-MS (EI) m/z calcd for $C_{17}H_{26}F_2O_4$ [M+H$^+$] 333.1872, found 333.1877.



Ethyl 8-(9-cyano-5,5-difluorononan-3-yl)-1,4-dioxaspiro[4.5]dec-7-ene-7-carboxylate (20)

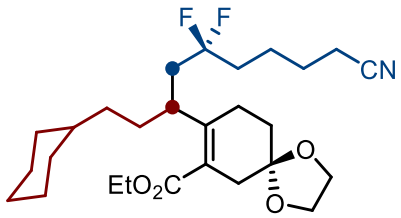
The general procedure **G** was followed using **2b** (0.15 mmol), **difluoroalkyl iodide** (0.30 mmol) and **3c** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 5:1) yielded **20** (45 mg, 67%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.22 – 4.13 (m, 2H), 4.04 – 3.94 (m, 4H), 3.60 – 3.51 (m, 1H), 2.54 (s, 2H), 2.37 (t, *J* = 7.0, 2H), 2.25 (qd, *J* = 17.7, 8.8, 2H), 2.08 – 1.80 (m, 4H), 1.72 (dd, *J* = 13.4, 6.7, 4H), 1.66 – 1.58 (m, 2H), 1.55 – 1.37 (m, 2H), 1.29 (t, *J* = 7.1, 3H), 0.83 (t, *J* = 7.4, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 168.5, 146.7, 125.0, 124.8 (t, $^{1}J_{C\text{-}F}$ = 241.5), 119.6, 107.4, 64.6, 60.5, 39.7 (t, $^{2}J_{C\text{-}F}$ = 24.6), 37.4, 37.1 (t, $^{3}J_{C\text{-}F}$ = 4.0), 35.2 (t, $^{2}J_{C\text{-}F}$ = 25.4), 30.7, 27.0, 25.3, 23.5, 21.6 (t, $^{3}J_{C\text{-}F}$ = 4.6), 17.1, 14.3, 11.8. ^{19}F-NMR (376 MHz, $CDCl_3$) δ = -94.30 (d, *J* = 242.7), -95.83 (d, *J* = 242.7). HR-MS (EI) m/z calcd for $C_{21}H_{31}F_2NO_4$ [M+H$^+$] 400.2294, found 400.2297.



Ethyl 8-(1-cyano-5,5-difluoro-10,12,12-trimethyltridecan-7-yl)-1,4-dioxaspiro[4.5]dec-7-ene-7-carboxylate (21)

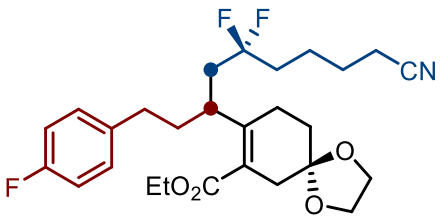
The general procedure **G** was followed using **2b** (0.15 mmol), **difluoroalkyl iodide** (0.30 mmol) and **3d** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 5:1) yielded **21** (51 mg, 69%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.21 – 4.10

(m, 2H), 4.02 – 3.91 (m, 4H), 3.66 – 3.52 (m, 1H), 2.57 – 2.45 (m, 2H), 2.35 (t, *J* = 7.1, 2H), 2.31 – 2.18 (m, 2H), 2.07 – 1.77 (m, 4H), 1.74 – 1.57 (m, 6H), 1.48 – 1.30 (m, 3H), 1.27 (t, *J* = 7.1, 3H), 1.21 – 0.95 (m, 4H), 0.86 (t, *J* = 4.4, 12H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 168.4, 168.3, 147.4, 147.1, 124.8 (t, $^1J_{C\text{-}F}$ = 241.6), 124.7, 124.6, 119.6, 107.4, 107.4, 64.6, 64.6, 60.4, 51.5, 51.2, 40.1 (t, $^2J_{C\text{-}F}$ = 24.4), 39.9 (t, $^2J_{C\text{-}F}$ = 24.6), 37.4, 36.9, 36.7, 35.7 (t, $^3J_{C\text{-}F}$ = 3.8), 35.3 (t, $^2J_{C\text{-}F}$ = 25.5), 35.2 (t, $^2J_{C\text{-}F}$ = 25.5), 31.8, 31.6, 31.2, 31.2, 30.8, 30.1, 29.5, 29.3, 25.3, 23.7, 22.8, 22.5, 21.6 (t, $^3J_{C\text{-}F}$ = 4.6), 17.1, 14.4. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -95.02 (ddd, *J* = 284.4, 242.6, 27.5). HR-MS (EI) m/z calcd for $C_{28}H_{45}F_2NO_4$ [M+H$^+$] 498.3389, found 498.3382.



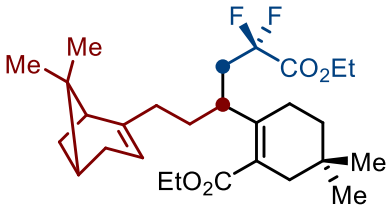
Ethyl 8-(9-cyano-1-cyclohexyl-5,5-difluorononan-3-yl)-1,4-dioxaspiro[4.5]dec-7-ene-7-carboxylate (22)

The general procedure **G** was followed using **2b** (0.15 mmol), **difluoroalkyl iodide** (0.30 mmol) and **3e** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 5:1) yielded **22** (48 mg, 66%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.21 – 4.12 (m, 2H), 4.03 – 3.93 (m, 4H), 3.63 – 3.54 (m, 1H), 2.59 – 2.45 (m, 2H), 2.41 – 2.33 (m, 2H), 2.32 – 2.17 (m, 2H), 2.06 – 1.80 (m, 4H), 1.74 – 1.58 (m, 11H), 1.49 – 1.33 (m, 2H), 1.28 (t, *J* = 7.1, 3H), 1.22 – 1.00 (m, 6H), 0.90 – 0.80 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 168.4, 147.3, 124.9 (t, $^1J_{C\text{-}F}$ = 241.6), 124.5, 119.6, 107.4, 64.6, 64.6, 60.5, 39.9 (t, $^2J_{C\text{-}F}$ = 24.6), 37.8, 37.4, 35.8 (t, $^3J_{C\text{-}F}$ = 3.9), 35.2 (t, $^2J_{C\text{-}F}$ = 25.5), 34.9, 33.6, 33.3, 31.4, 30.8, 26.8, 26.5, 26.5, 25.3, 23.7, 21.6 (t, $^3J_{C\text{-}F}$ = 4.6), 17.1, 14.4. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -94.18 (d, *J* = 242.6), -95.76 (d, *J* = 242.4). HR-MS (EI) m/z calcd for $C_{27}H_{41}F_2NO_4$ [M+H$^+$] 482.3076, found 482.3080.



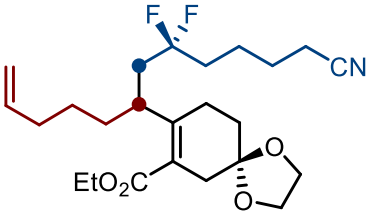
Ethyl 8-[9-cyano-5,5-difluoro-1-(4-fluorophenyl)nonan-3-yl]-1,4-dioxaspiro[4.5]dec-7-ene-7-carboxylate (23)

The general procedure **G** was followed using **2b** (0.15 mmol), **difluoroalkyl iodide** (0.30 mmol) and **3f** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 5:1) yielded **23** (51 mg, 69%) as a colorless oil. ^{1}H-NMR (400 MHz,): δ = 7.13 – 7.06 (m, 2H), 6.97 – 6.89 (m, 2H), 4.15 (q, J = 7.1, 2H), 4.04 – 3.94 (m, 4H), 3.78 – 3.68 (m, 1H), 2.60 – 2.43 (m, 4H), 2.39 – 2.27 (m, 4H), 2.11 – 1.81 (m, 4H), 1.80 – 1.61 (m, 8H), 1.28 (t, J = 7.1, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 168.3, 162.6, 160.1, 146.6, 137.8, 129.8, 129.7, 125.3, 124.7 (t, $^{1}J_{C\text{-}F}$ = 241.8), 119.6, 115.2, 115.0, 107.3, 64.7, 64.6, 60.6, 39.9 (t, $^{2}J_{C\text{-}F}$ = 24.6), 37.4, 35.8, 35.4 (t, $^{2}J_{C\text{-}F}$ = 25.4), 32.8, 30.7, 27.2, 25.3, 23.8, 21.6 (t, $^{3}J_{C\text{-}F}$ = 4.6), 17.1, 14.3. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -95.21 (dd, J = 662.5, 243.0), -117.83 (s). HR-MS (EI) m/z calcd for $C_{27}H_{34}F_3NO_4$ [M+H$^+$] 494.2513, found 494.2517.



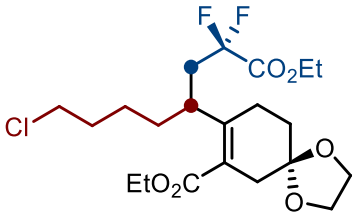
Ethyl 2-{1-[(5*R*)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl]-6-ethoxy-5,5-difluoro-6-oxohexan-3-yl}-5,5-dimethylcyclohex-1-ene-1-carboxylate (24)

The general procedure **F** was followed using **2d** (0.225 mmol), **difluoroalkyl bromide** (0.15 mmol) and **3g** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 70:1) yielded **24** (36 mg, 50%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.15 (s, 1H), 4.30 (dd, J = 14.2, 7.1, 2H), 4.22 – 4.12 (m, 2H), 3.51 (s, 1H), 2.43 – 1.66 (m, 16H), 1.56 – 1.41 (m, 2H), 1.37 – 1.27 (m, 9H), 0.92 (d, J = 8.9, 6H), 0.80 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.5, 169.4, 164.2 (t, $^{2}J_{C\text{-}F}$ = 32.7), 148.1, 148.0, 143.4, 143.2, 127.1, 127.1, 116.1 (t, $^{1}J_{C\text{-}F}$ = 251.1), 115.9, 115.8, 62.8, 60.2, 45.9, 45.8, 40.9, 37.9, 37.8 (t, $^{2}J_{C\text{-}F}$ = 22.2), 35.1, 34.7, 31.7, 31.6, 31.2, 31.1, 28.7, 28.6, 28.4, 27.7, 27.6, 26.3, 21.2, 14.2, 13.9. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -96.91 – -109.40 (m,). HR-MS (EI) m/z calcd for $C_{28}H_{42}F_2O_4$ [M+H$^+$] 481.3124, found 481.3128.



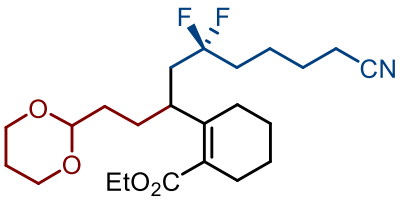
Ethyl 8-(12-cyano-8,8-difluorododec-1-en-6-yl)-1,4-dioxaspiro[4.5]dec-7-ene-7-carboxylate (25)

The general procedure **G** was followed using **2b** (0.15 mmol), **difluoroalkyl iodide** (0.30 mmol) and **3h** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 5:1) yielded **25** (45 mg, 68%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.77 (ddt, *J* = 16.9, 10.2, 6.7, 1H), 5.04 – 4.90 (m, 2H), 4.23 – 4.12 (m, 2H), 4.04 – 3.92 (m, 4H), 3.71 – 3.61 (m, 1H), 2.59 – 2.47 (m, 2H), 2.36 (t, *J* = 7.1, 2H), 2.24 (ddt, *J* = 17.7, 12.8, 6.6, 2H), 2.08 – 1.80 (m, 6H), 1.75 – 1.67 (m, 4H), 1.62 (dt, *J* = 8.8, 2.8, 2H), 1.50 – 1.31 (m, 3H), 1.31 – 1.26 (m, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 168.4, 147.0, 138.8, 124.8 (t, $^{1}J_{C\text{-}F}$ = 241.6), 124.8, 119.6, 114.8, 107.4, 64.6, 60.5, 39.9 (t, $^{2}J_{C\text{-}F}$ = 24.6), 37.4, 35.4 (t, $^{3}J_{C\text{-}F}$ = 3.9), 35.3 (t, $^{2}J_{C\text{-}F}$ = 25.4), 33.8, 33.4, 30.7, 26.5, 25.3, 23.7, 21.6 (t, $^{3}J_{C\text{-}F}$ =4.6), 17.1, 14.4. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -94.33 (d, *J* = 242.8), -95.85 (d, *J* = 242.7). HR-MS (EI) m/z calcd for $C_{24}H_{35}F_2NO_4$ [M+H$^+$] 440.2607, found 440.2611.



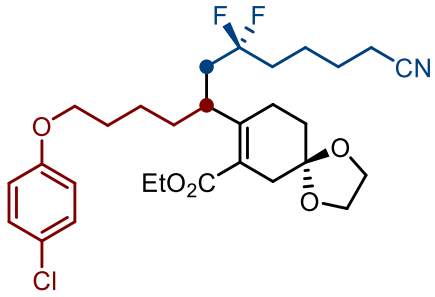
Ethyl 8-(8-chloro-1-ethoxy-2,2-difluoro-1-oxooctan-4-yl)-1,4-dioxaspiro[4.5]dec-7-ene-7-carboxylate (26)

The general procedure **F** was followed using **2b** (0.225 mmol), **difluoroalkyl bromide** (0.15 mmol) and **3i** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 10:1) yielded **26** (27 mg, 41%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.34 – 4.25 (m, 2H), 4.20 – 4.13 (m, 2H), 4.02 – 3.93 (m, 4H), 3.79 (dd, *J* = 13.3, 7.1, 1H), 3.51 (t, *J* = 6.8, 2H), 2.52 (q, *J* = 17.8, 2H), 2.33 – 2.08 (m, 4H), 1.82 – 1.69 (m, 4H), 1.52 – 1.37 (m, 3H), 1.34 (t, *J* = 7.2, 4H), 1.29 (t, *J* = 7.1, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 167.9, 164.2 (t, $^{2}J_{C\text{-}F}$ = 32.7), 146.2, 125.4, 116.1 (t, $^{1}J_{C\text{-}F}$ = 251.2), 107.3, 64.6, 64.6, 63.0, 60.5, 44.9, 37.8 (t, $^{2}J_{C\text{-}F}$ = 22.4), 37.4, 34.4 (t, $^{3}J_{C\text{-}F}$ = 3.2), 32.7, 32.5, 30.7, 24.3, 23.8, 14.3, 14.0. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -103.08 (d, *J* = 263.3), -104.15 (d, *J* = 263.0). HR-MS (EI) m/z calcd for $C_{21}H_{31}ClF_2O_6$ [M+H$^+$] 453.1850, found 453.1855.



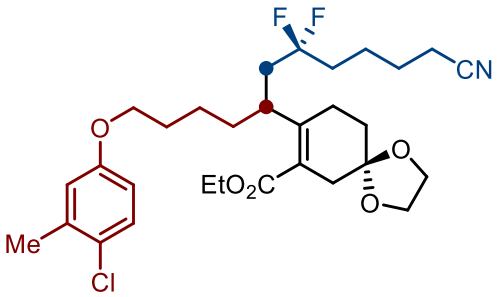
Ethyl 2-[9-cyano-1-(1,3-dioxan-2-yl)-5,5-difluorononan-3-yl]cyclohex-1-ene-1-carboxylate (27)

The general procedure **G** was followed using **2a** (0.15 mmol), **difluoroalkyl iodide** (0.30 mmol) and **3j** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 5:1) yielded **27** (33 mg, 77%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.49 (t, J = 4.6, 1H), 4.16 (qd, J = 7.1, 1.2, 2H), 4.08 (dd, J = 11.5, 4.0, 2H), 3.80 – 3.68 (m, 2H), 3.43 (dd, J = 8.1, 5.2, 1H), 2.36 (t, J = 7.0, 2H), 2.27 (s, 2H), 2.12 – 1.94 (m, 4H), 1.94 – 1.78 (m, 3H), 1.70 (dd, J = 14.6, 7.4, 2H), 1.66 – 1.56 (m, 7H), 1.56 – 1.42 (m, 4H), 1.28 (t, J = 7.1, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.8, 145.3, 127.6, 124.9 (t, $^{1}J_{C\text{-}F}$ = 241.6), 119.6, 102.2, 67.0, 60.3, 39.9 (t, $^{2}J_{C\text{-}F}$ = 24.4), 35.9 (t, $^{3}J_{C\text{-}F}$ = 3.8), 35.3 (t, $^{2}J_{C\text{-}F}$ = 25.5), 32.9, 27.8, 27.3, 25.9, 25.3, 23.8, 22.3, 22.1, 21.6 (t, $^{3}J_{C\text{-}F}$ = 4.6), 17.1, 14.4. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -94.67 (d, J = 242.7), -95.40 (d, J = 242.6). HR-MS (EI) m/z calcd for $C_{23}H_{35}F_2NO_4$ [M+H$^+$] 428.2607, found 428.2612.



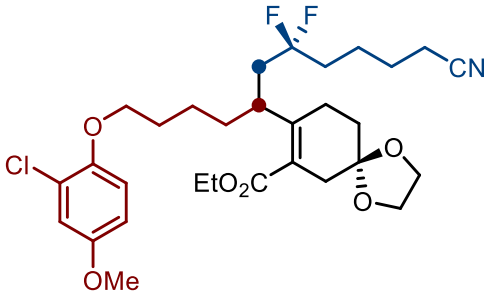
Ethyl 8-[1-(4-chlorophenoxy)-11-cyano-7,7-difluoroundecan-5-yl]-1,4-dioxaspiro[4.5]dec-7-ene-7-carboxylate (28)

The general procedure **G** was followed using **2b** (0.15 mmol), **difluoroalkyl iodide** (0.30 mmol) and **3k** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 5:1) yielded **28** (53 mg, 64%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.24 – 7.18 (m, 2H), 6.82 – 6.76 (m, 2H), 4.16 (q, J = 7.1 Hz, 2H), 4.02 – 3.93 (m, 4H), 3.90 (t, J = 6.5 Hz, 2H), 3.79 – 3.61 (m, 1H), 2.53 (s, 2H), 2.36 (t, J = 7.0 Hz, 2H), 2.33 – 2.16 (m, 2H), 2.09 – 1.81 (m, 4H), 1.78 – 1.66 (m, 6H), 1.66 – 1.59 (m, 2H), 1.49 (dt, J = 16.6, 7.4 Hz, 2H), 1.43 – 1.33 (m, 2H), 1.26 (d, J = 7.1 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 168.4, 157.8, 147.0, 129.4, 127.2, 125.4, 124.8 (t, $^{1}J_{C\text{-}F}$ = 241.6 Hz), 119.6, 115.9, 107.4, 68.1, 64.7, 64.6, 60.6, 39.9(t, $^{2}J_{C\text{-}F}$ = 24.7 Hz), 37.4, 35.4 (t, $^{2}J_{C\text{-}F}$ = 25.5 Hz), 33.7, 30.7, 29.2, 25.3, 23.7, 23.6, 21.6(t, $^{3}J_{C\text{-}F}$ = 4.6 Hz), 17.1, 14.4. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -94.47 (d, J = 242.8 Hz), -96.07 (d, J = 242.9 Hz). HR-MS (EI) m/z calcd for $C_{29}H_{38}ClF_2NO_5$, [M+H$^+$] 554.2479 found 554.2476.



Ethyl 8-[1-(4-chloro-3-methylphenoxy)-11-cyano-7,7-difluoroundecan-5-yl]-1,4-dioxaspiro[4.5]dec-7-ene-7-carboxylate (29)

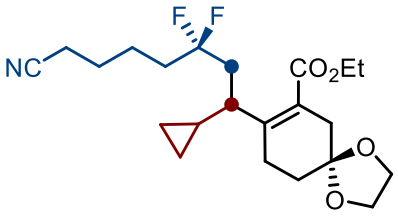
The general procedure **G** was followed using **2b** (0.15 mmol), **difluoroalkyl iodide** (0.30 mmol) and **3l** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 5:1) yielded **29** (45 mg, 53%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.20 (dd, J = 8.7, 5.0, 1H), 6.76 (dd, J = 8.1, 2.9, 1H), 6.65 (td, J = 8.3, 3.0, 1H), 4.21 – 4.11 (m, 2H), 4.04 – 3.93 (m, 4H), 3.92 – 3.84 (m, 2H), 3.76 – 3.65 (m, 1H), 2.53 (s, 2H), 2.36 (t, J = 7.0, 2H), 2.33 (s, 3H), 2.27 (dd, J = 15.0, 6.7, 2H), 2.08 – 1.31 (m, 16H), 1.28 (td, J = 7.1, 4.6, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 168.3, 157.7, 147.0, 137.0, 129.6, 125.7, 124.9, 124.8 (t, $^{2}J_{C\text{-}F}$ = 241.6), 119.6, 117.2, 113.2, 107.4, 68.0, 64.6, 64.6, 60.5, 39.9 (t, $^{2}J_{C\text{-}F}$ = 24.6), 37.4, 35.4 (t, $^{2}J_{C\text{-}F}$ = 25.5), 33.7, 30.7, 29.6, 29.3, 25.9, 25.3, 23.7, 21.6 (t, $^{3}J_{C\text{-}F}$ = 4.7), 20.4, 17.1, 14.4. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -94.45 (d, J = 242.8), -96.05 (d, J = 242.9). HR-MS (EI) m/z calcd for $C_{30}H_{40}ClF_2NO_5$ [M+H$^+$] 568.2636, found 568.2640.



Ethyl 8-[1-(2-chloro-4-methoxyphenoxy)-11-cyano-7,7-difluoroundecan-5-yl]-1,4-dioxaspiro[4.5]dec-7-ene-7-carboxylate (30)

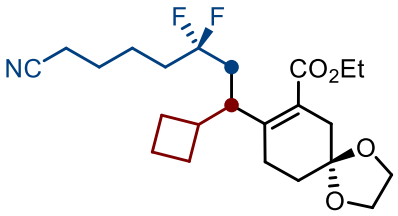
The general procedure **G** was followed using **2b** (0.15 mmol), **difluoroalkyl iodide** (0.30 mmol) and **3m** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 5:1) yielded **30** (45 mg, 51%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.93 (d, J = 3.0 Hz, 1H), 6.85 (d, J = 9.0 Hz, 1H), 6.73 (dd, J = 9.0, 3.0 Hz, 1H), 4.17 (q, J = 7.1 Hz, 2H), 4.01 – 3.92 (m, 6H), 3.75 (s, 3H), 3.71 (dd, J = 10.2, 4.3 Hz, 1H), 2.53 (s, 2H), 2.36 (t, J = 7.0 Hz, 2H), 2.31 – 2.20 (m, 2H), 2.00 – 1.89 (m, 2H), 1.86 – 1.68 (m, 8H), 1.65 – 1.60 (m, 2H), 1.56 – 1.46 (m, 2H), 1.42 (dd, J = 14.2, 6.9 Hz, 2H), 1.26 (d, J = 7.1 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 168.3, 153.8, 148.9, 146.9, 124.7, 124.7 (t, $^{1}J_{C\text{-}F}$ = 241.7 Hz), 123.7, 119.5, 115.9, 115.0, 112.9, 107.3, 69.8, 64.5, 60.4, 55.9, 39.8 (t, $^{2}J_{C\text{-}F}$ = 24.6 Hz), 37.3, 35.3 (t, $^{4}J_{C\text{-}F}$ = 3.8 Hz), 35.2 (t, $^{2}J_{C\text{-}F}$ = 25.4 Hz), 33.6, 30.6, 29.2, 27.0, 25.2, 23.6, 21.5 (t, $^{3}J_{C\text{-}F}$ = 4.6 Hz), 17.0, 14.2. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -94.62 (d, J = 243.7 Hz), -96.13 (d, J = 241.8 Hz). HR-MS (EI) m/z calcd for $C_{30}H_{40}ClF_2NO_6$ [M+H$^+$] 584.2585, found 584.2588.



Ethyl 8-(7-cyano-1-cyclopropyl-3,3-difluoroheptyl)-1,4-dioxaspiro[4.5]dec-7-ene-7-carboxylate (31)

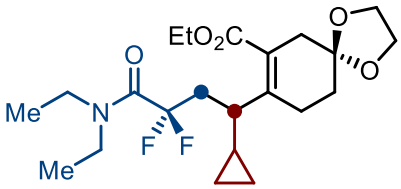
The general procedure **G** was followed using **2b** (0.15 mmol), **difluoroalkyl iodide** (0.30 mmol) and **3n** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 5:1) yielded **31** (48 mg, 78%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.18 – 4.09 (m, 2H), 3.99 (pd, J = 7.8, 4.3, 4H), 2.90 (td, J = 9.2, 5.3, 1H), 2.54 (s, 2H), 2.51 – 2.40 (m, 2H), 2.36 (t, J = 7.0, 2H), 2.23 – 2.02 (m, 2H), 1.96 – 1.80 (m, 2H), 1.76 (t, J = 6.5, 2H), 1.73 – 1.67 (m, 2H), 1.66 – 1.59 (m, 2H), 1.26 (t, J = 7.1, 3H), 0.85 – 0.74 (m, 1H), 0.65 – 0.51 (m, 1H), 0.44 – 0.34 (m, 1H), 0.32 – 0.15 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 168.2, 148.1, 124.5 (t, $^{1}J_{C\text{-}F}$ = 241.1), 123.2, 119.6, 107.4, 64.6, 64.6, 60.4, 40.8, 39.7 (t, $^{2}J_{C\text{-}F}$ = 24.9), 37.3, 35.3 (t, $^{2}J_{C\text{-}F}$ = 25.6), 30.8, 25.2, 24.7, 21.6, 17.0, 15.7, 14.3, 6.4, 3.9. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -94.67 (d, J = 242.8), -96.03 (d, J = 242.7). HR-MS (EI) m/z calcd for $C_{22}H_{31}F_2NO_4$ [M+H$^+$] 412.2294, found 412.2299.



Ethyl 8-(7-cyano-1-cyclobutyl-3,3-difluoroheptyl)-1,4-dioxaspiro[4.5]dec-7-ene-7-carboxylate (32)

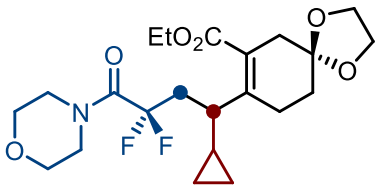
The general procedure **G** was followed using **2b** (0.15 mmol), **difluoroalkyl iodide** (0.30 mmol) and **3o** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 5:1) yielded **32** (45 mg, 70%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.26 – 4.17 (m, 2H), 4.05 – 3.91 (m, 4H), 3.63 (t, J = 9.1, 1H), 2.53 (s, 2H), 2.37 (t, J = 7.1, 2H), 2.33 – 2.02 (m, 4H), 1.94 – 1.57 (m, 15H), 1.31 (t, J = 7.1, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ =

168.6, 145.7, 125.0, 124.7 (t, $^{1}J_{C\text{-}F}$ = 241.3), 119.6, 107.4, 64.6, 64.6, 60.5, 39.1, 37.4, 36.5 (t, $^{2}J_{C\text{-}F}$ = 25.0), 34.9 (t, $^{2}J_{C\text{-}F}$ = 25.4), 30.7, 28.0, 27.1, 25.7, 25.3, 21.5 (t, $^{3n}_{C\text{-}F}$ = 4.7), 17.3, 17.0, 14.4. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -94.38 (d, J = 242.6), -95.37 (d, J = 242.6). HR-MS (EI) m/z calcd for $C_{23}H_{33}F_2NO_4$ [M+H$^+$] 426.2450, found 426.2448.



Ethyl 8-[1-cyclopropyl-4-(diethylamino)-3,3-difluoro-4-oxobutyl]-1,4-dioxaspiro[4.5]dec-7-ene-7-carboxylate (33)

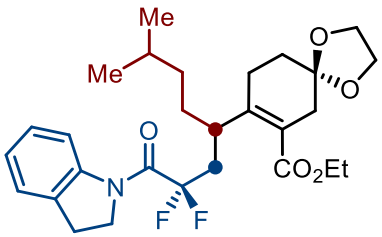
The general procedure **F** was followed using **2b** (0.225 mmol), **difluoroalkyl bromide** (0.15 mmol) and **3n** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 5:1) yielded **33** (50 mg, 78%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.11 (q, J = 7.1, 2H), 4.01 – 3.91 (m, 4H), 3.60 – 3.21 (m, 4H), 3.03 (dd, J = 15.4, 8.4, 1H), 2.56 – 2.35 (m, 6H), 1.74 (t, J = 6.9, 2H), 1.23 (t, J = 7.1, 3H), 1.14 (dt, J = 14.0, 7.0, 6H), 0.87 – 0.78 (m, 1H), 0.56 – 0.47 (m, 1H), 0.42 – 0.32 (m, 1H), 0.31 – 0.22 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 168.2, 163.0 (t, $^{2}J_{C\text{-}F}$ = 29.3), 148.4, 122.8, 119.4 (t, $^{1}J_{C\text{-}F}$ = 255.5), 107.5, 64.6, 64.5, 60.2, 41.9 (t, $^{3}J_{C\text{-}F}$ = 6.3), 41.6, 40.2, 37.7 (t, $^{2}J_{C\text{-}F}$ = 22.6), 37.3, 30.8, 24.9, 15.2, 14.3, 14.2, 12.4, 6.3, 3.8. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -98.26 (d, J = 280.2), -99.70 (d, J = 280.2). HR-MS (EI) m/z calcd for $C_{22}H_{33}F_2NO_5$ [M+H$^+$] 430.2400, found 430.2405.



Ethyl 8-(1-cyclopropyl-3,3-difluoro-4-morpholino-4-oxobutyl)-1,4-dioxaspiro[4.5]dec-7-ene-7-carboxylate (34)

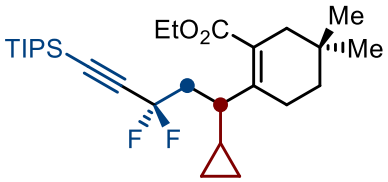
The general procedure **F** was followed using **2b** (0.225 mmol), **difluoroalkyl bromide** (0.15 mmol) and **3n** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 3:1) yielded **34** (57 mg, 85%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.17 – 4.07 (m, 2H), 4.03 – 3.94 (m, 4H), 3.76 – 3.59 (m, 8H), 3.05 (dd, J = 16.6, 7.1, 1H), 2.59 – 2.37 (m, 6H), 1.82 – 1.69 (m, 2H), 1.27 – 1.23 (t, J = 7.06, 3H), 0.92 – 0.74 (m, 1H), 0.60 – 0.36 (m, 2H), 0.32 – 0.21 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 168.1, 162.3 (t, $^{2}J_{C\text{-}F}$ = 29.5), 148.2, 122.9, 119.2 (t, $^{1}J_{C\text{-}F}$ = 255.4), 107.5, 66.9, 66.8, 64.6, 64.6, 60.3, 46.6 (t, $^{3}J_{C\text{-}F}$ = 6.4), 43.5, 40.1, 37.5 (t, $^{2}J_{C\text{-}F}$ = 22), 37.3, 30.8, 24.9, 15.3, 14.3, 6.3, 3.9. ^{19}F-NMR (376 MHz,

$CDCl_3$): δ = -97.89 (d, J = 282.0), -98.74 (d, J = 282.0). HR-MS (EI) m/z calcd for $C_{22}H_{30}F_2NO_6$ [M+H$^+$] 444.2192, found 444.2183.



Ethyl 8-[2,2-difluoro-1-(indolin-1-yl)-7-methyl-1-oxooctan-4-yl]-1,4-dioxaspiro[4.5]dec-7-ene-7-carboxylate (35)

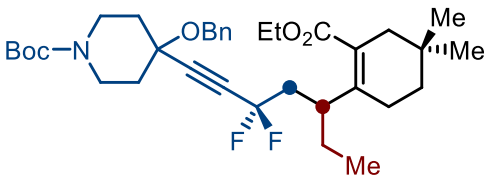
The general procedure **F** was followed using **2b** (0.225 mmol), **difluoroalkyl bromide** (0.15 mmol) and **3a** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 5:1) yielded **35** (72 mg, 95%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.19 (d, J = 8.3, 1H), 7.21 (t, J = 6.9, 2H), 7.08 (t, J = 7.1, 1H), 4.38 – 4.24 (m, 2H), 4.10 (qq, J = 10.8, 7.1, 2H), 4.00 – 3.90 (m, 4H), 3.83 – 3.74 (m, 1H), 3.17 (t, J = 8.3, 2H), 2.58 – 2.23 (m, 6H), 1.78 – 1.69 (m, 2H), 1.56 – 1.40 (m, 3H), 1.26 – 1.19 (m, 4H), 1.14 – 1.04 (m, 1H), 0.87 (d, J = 6.6, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 168.4, 161.6 (t, $^2J_{C\text{-}F}$ = 30.3), 147.2, 142.9, 131.8, 127.6, 125.1, 124.7, 124.4, 119.3 (t, $^1J_{C\text{-}F}$ = 255.4), 118.0, 107.5, 64.6, 64.6, 60.3, 48.1 (t, $^3J_{C\text{-}F}$ = 8.0), 37.4, 37.3 (t, $^2J_{C\text{-}F}$ = 22.0), 36.3, 35.0, 31.7, 30.8, 28.8, 28.2, 23.9, 22.8, 22.6, 14.3. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -101.27 (d, J = 281.1), -102.05 (d, J = 280.9). HR-MS (EI) m/z calcd for $C_{28}H_{37}F_2NO_5$ [M+H$^+$] 506.2713, found 506.2717.



Ethyl 2-(1-cyclopropyl-3,3-difluoro-5-(triisopropylsilyl)pent-4-yn-1-yl)-5,5-dimethylcyclohex-1-ene-1-carboxylate (36)

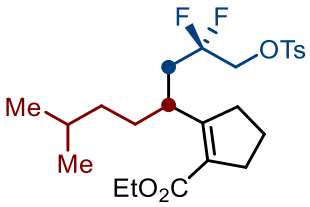
The general procedure **G** was followed using **2d** (0.15 mmol), **difluoroalkyl bromide** (0.30 mmol) and **3n** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 80:1) yielded **36** (56 mg, 78%) as an oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.12 (qd, J = 7.1, 1.0, 2H), 2.77 (dd, J = 16.6, 7.1, 1H), 2.47 – 2.25 (m, 3H), 2.17 (dt, J = 18.3, 5.9, 1H), 2.04 (dd, J = 12.7, 10.1, 2H), 1.38 (t, J = 6.6, 2H), 1.26 (d, J = 7.1, 3H), 1.08 (d, J = 2.2, 21H), 0.92 (d, J = 4.4, 6H), 0.86 – 0.81 (m, 1H), 0.61 – 0.52 (m, 1H), 0.41 – 0.21 (m, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.6, 145.0, 125.1, 113.5 (t, $^1J_{C\text{-}F}$ = 233.9), 100.1 (t, $^2J_{C\text{-}F}$ = 38.8), 89.2 (t, $^4J_{C\text{-}F}$ = 5.3), 60.1, 42.9 (t, $^3J_{C\text{-}F}$ =25.7), 41.7, 40.8, 35.0, 28.8, 28.6, 27.4, 23.3,

18.6, 15.1, 14.3, 11.1, 7.0, 3.6. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -80.20 (d, J = 272.2), -82.43 (d, J = 272.2). HR-MS (EI) m/z calcd for $C_{28}H_{46}F_2O_2Si$ [M+H$^+$] 481.3308, found 481.3310.



***tert*-Butyl 4-(benzyloxy)-4-{5-[2-(ethoxycarbonyl)-4,4-dimethylcyclohex-1-en-1-yl]-3,3-difluorohept-1-yn-1-yl}piperidine-1-carboxylate (37)**

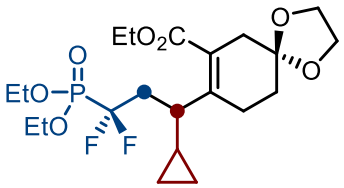
The general procedure **F** was followed using **2d** (0.225 mmol), **difluoroalkyl bromide** (0.15 mmol) and **3c** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 20:1) yielded **37** (37 mg, 41%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.37 – 7.29 (m, 5H), 4.64 (s, 2H), 4.13 (dtt, J = 10.8, 7.3, 3.7, 2H), 3.47 (dddd, J = 24.9, 12.6, 10.5, 3.5, 5H), 2.29 – 1.96 (m, 9H), 1.92 – 1.81 (m, 2H), 1.56 (dd, J = 14.0, 6.5, 1H), 1.46 (s, 9H), 1.36 (t, J = 5.6, 2H), 1.25 (t, J = 7.1, 3H), 0.92 (s, 6H), 0.83 (t, J = 7.4, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.6, 154.7, 143.8, 138.3, 128.5, 127.8, 127.8, 126.9, 114.5 (t, $^1J_{C\text{-}F}$ = 234.1), 86.9 (t, $^3J_{C\text{-}F}$ = 6.5), 80.7 (t, $^2J_{C\text{-}F}$ = 40.7), 79.9, 72.1, 66.3, 60.2, 42.5 (t, $^2J_{C\text{-}F}$ = 25.1), 40.9, 37.9, 34.9, 28.6, 28.4, 28.1, 26.3, 22.1, 14.4, 12.0. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -79.06 (d, J = 272.8), -81.94 (d, J = 272.8). HR-MS (EI) m/z calcd for $C_{35}H_{49}F_2NO_5$ [M+H$^+$] 602.3652, found 602.3657.



Ethyl 2-[2,2-difluoro-7-methyl-1-(tosyloxy)octan-4-yl]cyclopent-1-ene-1-carboxylate (38)

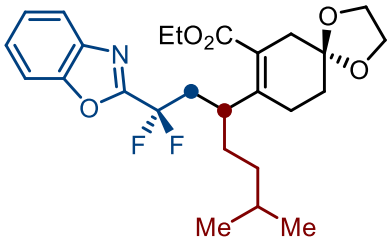
The general procedure **F** was followed using **2f** (0.225 mmol), **difluoroalkyl bromide** (0.15 mmol) and **3a** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 50:1) yielded **38** (42 mg, 59%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.79 (d, J = 8.3, 2H), 7.35 (d, J = 8.1, 2H), 4.23 – 4.09 (m, 4H), 3.85 – 3.69 (m, 1H), 2.64 – 2.53 (m, 2H), 2.45 (s, 3H), 2.43 – 2.27 (m, 2H), 2.13 – 1.92 (m, 2H), 1.82 – 1.73 (m, 2H), 1.51 – 1.31 (m, 3H), 1.27 (t, J = 7.1, 3H), 1.13 – 0.90 (m, 2H), 0.83 (dd, J = 6.6, 0.8, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 166.2, 159.1, 145.4, 132.4, 130.1, 129.7, 128.2, 120.8 (t, $^1J_{C\text{-}F}$ = 244.1), 68.1 (t, $^2J_{C\text{-}F}$ = 35.1), 59.9, 37.2 (t, $^2J_{C\text{-}F}$ = 22.5), 36.3, 33.8, 32.7, 32.5 (t, $^3J_{C\text{-}F}$ = 3.7), 32.3, 27.9,

22.8, 22.4, 21.8, 21.7, 14.4. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -101.96 (d, J = 257.8), -103.27 (d, J = 257.8). HR-MS (EI) m/z calcd for $C_{24}H_{34}F_2O_5S$ [M+H$^+$] 473.2168, found 473.2172.



Ethyl 8-[1-cyclopropyl-3-(diethoxyphosphoryl)-3,3-difluoropropyl]-1,4-dioxaspiro[4.5]dec-7-ene-7-carboxylate (39)

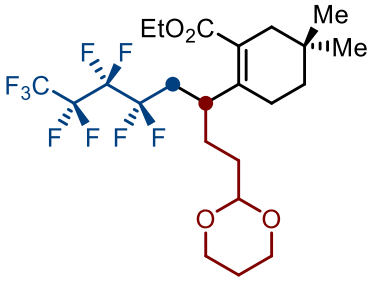
The general procedure **F** was followed using **2b** (0.225 mmol), **difluoroalkyl bromide** (0.15 mmol) and **3n** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 1:1) yielded **39** (36 mg, 51%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.30 – 4.19 (m, 4H), 4.12 (q, J = 7.1, 2H), 4.03 – 3.92 (m, 4H), 3.10 (dd, J = 16.5, 7.2, 1H), 2.62 – 2.14 (m, 6H), 1.79 – 1.68 (m, 2H), 1.36 (t, J = 7.1, 6H), 1.26 – 1.22 (m, 3H), 0.89 – 0.74 (m, 1H), 0.62 – 0.34 (m, 2H), 0.28 (pd, J = 9.2, 5.0, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 168.1, 147.9, 123.1, 119.6 (t, $^1J_{C\text{-}F}$ = 261.1), 107.5, 64.6, 64.6, 60.4, 39.5, 39.4, 37.3, 36.6 (t, $^2J_{C\text{-}F}$ = 20.0), 36.4 (t, $^2J_{C\text{-}F}$ = 20.1), 30.9, 27.2, 24.9, 16.6, 16.5, 15.2, 14.3, 6.6, 4.0. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -112.54 (qd, J = 296.5, 108.5, 2F). HR-MS (EI) m/z calcd for $C_{21}H_{33}F_2O_7P$ [M+H$^+$] 467.2005, found 467.2008.



Ethyl 8-[1-(benzo[d]oxazol-2-yl)-1,1-difluoro-6-methylheptan-3-yl]-1,4-dioxaspiro[4.5]dec-7-ene-7-carboxylate (40)

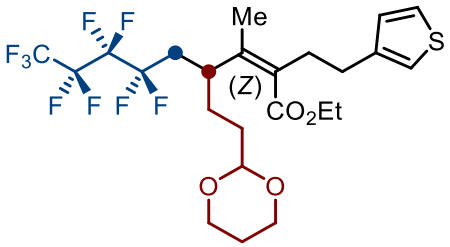
The general procedure **F** was followed using **2b** (0.225 mmol), **difluoroalkyl bromide** (0.15 mmol) and **3a** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 10:1) yielded **40** (29 mg, 40%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.79 (d, J = 7.4, 1H), 7.59 (d, J = 7.6, 1H), 7.47 – 7.37 (m, 2H), 4.03 – 3.83 (m, 7H), 2.73 – 2.43 (m, 2H), 2.42 – 2.20 (m, 4H), 1.72 – 1.63 (m, 2H), 1.55 – 1.40 (m, 3H), 1.22 – 1.15 (m, 4H), 1.07 (ddd, J = 18.2, 12.5, 6.0, 1H), 0.85 (dd, J = 6.6, 0.7, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 168.0, 158.3 (t, $^2J_{C\text{-}F}$ = 33.6), 150.7, 146.5, 140.2, 126.8, 125.3, 124.9, 121.3, 116.8 (t, $^1J_{C\text{-}F}$ = 242.7), 111.5, 107.3, 64.6, 64.5, 60.3, 39.3 (t, $^2J_{C\text{-}F}$ = 22.8), 37.3, 36.2, 35.1, 31.6, 30.7, 28.2,

23.9, 22.8, 22.6, 14.2. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -96.70 (d, J = 275.2), -98.46 (d, J = 275.2). HR-MS (EI) m/z calcd for $C_{26}H_{33}F_2NO_5$ [M+H$^+$] 478.2400, found 478.2404.



Ethyl 2-[1-(1,3-dioxan-2-yl)-5,5,6,6,7,7,8,8,8-nonafluorooctan-3-yl]-5,5-dimethylcyclohex-1-ene-1-carboxylate (41)

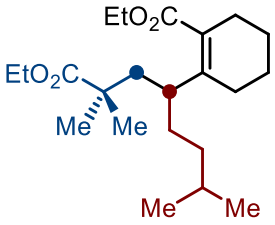
The general procedure **F** was followed using **2d** (0.225 mmol), **difluoroalkyl iodide** (0.15 mmol) and **3j** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 30:1) yielded **41** (36 mg, 44%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.51 (t, J = 3.4 Hz, 1H), 4.17 (q, J = 7.1 Hz, 2H), 4.08 (dd, J = 11.3, 3.8 Hz, 2H), 3.74 (td, J = 12.1, 2.3 Hz, 2H), 3.69 – 3.60 (m, 1H), 2.33 – 2.16 (m, 1H), 2.16 – 1.96 (m, 6H), 1.68 – 1.47 (m, 4H), 1.40 – 1.33 (m, 2H), 1.32 – 1.29 (m, 1H), 1.27 (t, J = 7.1 Hz, 3H), 0.92 (s, 3H), 0.91 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.5, 142.2, 127.8, 102.0, 67.0, 67.0, 60.4, 40.9, 34.9, 34.0, 33.6 (t, $^2J_{C\text{-}F}$ = 21.2 Hz), 32.8, 28.5, 28.4, 28.1, 27.8, 25.9, 21.6, 14.3. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -81.06 (ddd, J = 13.6, 6.8, 3.5 Hz), -111.18 – -118.07 (m), -124.59 (dd, J = 20.2, 10.0 Hz), -125.88 (ddd, J = 24.5, 15.3, 6.5 Hz). HR-MS (EI) m/z calcd for $C_{23}H_{31}F_9O_4$ [M+H$^+$] 543.2151, found 543.2148.



Ethyl (*Z*)-4-[2-(1,3-dioxan-2-yl)ethyl]-6,6,7,7,8,8,9,9,9-nonafluoro-3-methyl-2-[2-(thiophen-2-yl)ethyl]non-2-enoate (42)

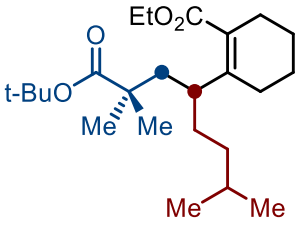
The general procedure **F** was followed using **2j** (0.225 mmol), **difluoroalkyl iodide** (0.15 mmol) and **3j** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 10:1) yielded **42** (46 mg, 53%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.25 – 7.16 (m, 1H), 6.94 (d, J = 4.1 Hz, 2H), 4.51 (t, J = 4.6 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 4.08 (dd, J = 11.2, 4.5 Hz, 2H), 3.74 (td, J = 12.2, 2.3 Hz, 2H), 3.64 – 3.44 (m, 1H), 2.78 – 2.68 (m, 2H), 2.62 – 2.53 (m, 2H), 2.24 – 1.89 (m, 3H), 1.64 – 1.57 (m, 2H), 1.55 (s, 3H), 1.53 – 1.32 (m,

3H), 1.28 (t, J = 7.1 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.5, 142.0, 141.9, 131.0, 128.5, 125.4, 120.7, 102.0, 67.0, 67.0, 60.5, 35.3, 33.7 (t, $^2J_{C\text{-}F}$ = 21.2 Hz), 32.7, 31.7, 29.0, 27.4, 25.9, 14.3, 12.7. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -81.06 (ddd, J = 9.9, 8.7, 3.0 Hz), -107.27 – -117.07 (m), -124.60 (dd, J = 20.4, 10.0 Hz), -125.88 (ddd, J = 20.9, 9.5, 5.0 Hz). HR-MS (EI) m/z calcd for $C_{24}H_{29}F_9O_4S$ [M+H$^+$] 585.1716, found 585.1708.



Ethyl 2-(1-ethoxy-2,2,7-trimethyl-1-oxooctan-4-yl)cyclohex-1-ene-1-carboxylate(43)

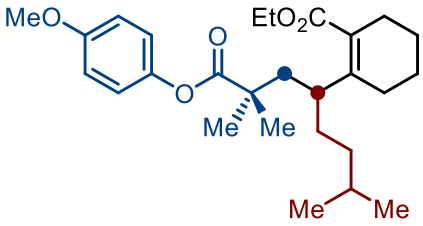
The general procedure **H** was followed using **2a** (0.225 mmol), **alkyl bromide** (0.15 mmol) and **3a** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 50:1) yielded **43** (34 mg, 61%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.22 – 4.11 (m, 2H), 4.06 (q, J = 7.1, 2H), 3.19 – 3.09 (m, 1H), 2.27 (t, J = 11.8, 2H), 2.16 – 2.03 (m, 1H), 1.99 – 1.88 (m, 1H), 1.70 (dd, J = 14.1, 7.7, 1H), 1.65 – 1.52 (m, 6H), 1.43 (td, J = 13.3, 6.7, 1H), 1.26 (dt, J = 19.3, 7.1, 8H), 1.14 (d, J = 4.0, 6H), 0.99 (ddd, J = 19.7, 11.6, 6.0, 1H), 0.83 (dd, J = 6.6, 2.5, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 178.2, 170.1, 147.9, 126.2, 60.4, 60.1, 43.6, 42.1, 38.6, 36.6, 32.2, 28.3, 27.4, 26.3, 25.1, 24.2, 22.9, 22.6, 22.5, 22.3, 14.4, 14.2. HR-MS (EI) m/z calcd for $C_{22}H_{38}O_4$ [M+H$^+$] 367.2843, found 367.2847.



Ethyl 2-(1-(tert-butoxy)-2,2,7-trimethyl-1-oxooctan-4-yl)cyclohex-1-ene-1-carboxylate (44)

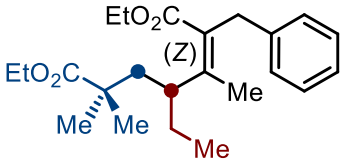
The general procedure **H** was followed using **2a** (0.225 mmol), **alkyl bromide** (0.15 mmol) and **3a** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 50:1) yielded **44** (30 mg, 51%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.16 (dddd, J = 18.0, 10.8, 7.1, 3.7, 2H), 3.10 – 3.00 (m, 1H), 2.25 (s, 2H), 2.16 – 2.06 (m, 1H), 1.93 (dd, J = 16.4, 3.6, 1H), 1.68 (dd, J = 14.1, 5.8, 1H), 1.62 – 1.52 (m, 5H), 1.42 (s, 9H), 1.26 (dt, J = 8.5, 6.7, 6H), 1.17 – 1.11 (m, 1H), 1.09 (s, 6H), 1.04 – 0.93 (m, 1H), 0.83 (dd, J = 6.6, 2.7, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 177.7, 170.3, 147.7, 126.1, 79.7, 60.1, 43.0, 42.7, 39.0, 36.8,

31.9, 28.4, 28.1, 27.4, 24.3, 23.9, 23.0, 22.6, 22.5, 22.4, 14.5. HR-MS (EI) m/z calcd for $C_{24}H_{42}O_4$ [M+H$^+$] 395.3156, found 395.3160.



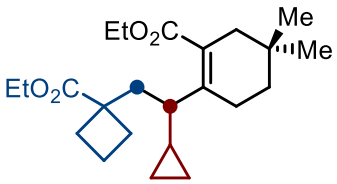
Ethyl 2-(1-(4-methoxyphenoxy)-2,2,7-trimethyl-1-oxooctan-4-yl)cyclohex-1-ene-1-carboxylate (45)

The general procedure **H** was followed using **2a** (0.225 mmol), **alkyl bromide** (0.15 mmol) and **3a** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 50:1) yielded **45** (35 mg, 53%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.00 (d, J = 9.0, 2H), 6.87 (d, J = 9.0, 2H), 4.15 (qq, J = 10.8, 7.1, 2H), 3.79 (s, 3H), 3.29 – 3.19 (m, 1H), 2.27 (s, 2H), 2.20 – 2.07 (m, 1H), 2.04 – 1.92 (m, 1H), 1.88 – 1.74 (m, 2H), 1.58 (d, J = 12.0, 4H), 1.47 (dt, J = 13.2, 6.6, 1H), 1.34 (dd, J = 8.2, 3.8, 1H), 1.30 (d, J = 5.6, 6H), 1.28 – 1.23 (m, 4H), 1.16 (ddd, J = 13.2, 10.3, 6.8, 1H), 1.08 – 0.97 (m, 1H), 0.85 (dd, J = 6.6, 2.9, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 177.0, 170.2, 157.1, 147.5, 144.8, 126.5, 122.4, 114.4, 60.1, 55.7, 43.3, 42.6, 38.8, 36.7, 32.3, 28.3, 27.4, 26.8, 24.8, 24.2, 23.0, 22.6, 22.4, 22.3, 14.4. HR-MS (EI) m/z calcd for $C_{27}H_{40}O_5$ [M+H$^+$] 445.2949, found 445.2950.



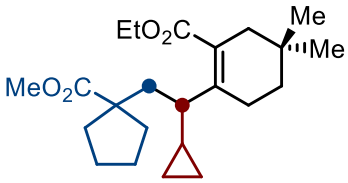
Diethyl (*Z*)-2-benzyl-4-ethyl-3,6,6-trimethylhept-2-enedioate (46)

The general procedure **H** was followed using **2m** (0.225 mmol), **alkyl bromide** (0.15 mmol) and **3c** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 50:1) yielded **46** (34 mg, 62%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.23 (d, J = 6.6, 2H), 7.16 (d, J = 7.2, 3H), 4.14 – 4.04 (m, 4H), 3.67 (s, 2H), 3.18 (tt, J = 8.0, 6.1, 1H), 1.74 (dd, J = 14.2, 7.7, 1H), 1.69 – 1.58 (m, 4H), 1.37 (ddd, J = 12.5, 10.0, 7.2, 2H), 1.29 – 1.22 (m, 5H), 1.20 (d, J = 10.7, 2H), 1.17 – 1.13 (m, 8H), 0.83 (t, J = 7.4, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 178.1, 169.5, 148.0, 139.7, 128.6, 128.4, 126.0, 60.4, 60.2, 43.5, 42.1, 40.8, 36.3, 27.6, 26.1, 25.3, 14.3, 14.3, 14.2, 12.1. HR-MS (EI) m/z calcd for $C_{23}H_{34}O_4$ [M+H$^+$] 375.2530, found 375.2528.



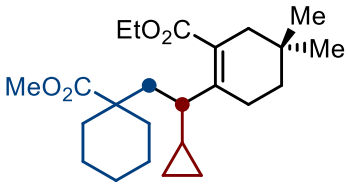
Ethyl 2-(1-cyclopropyl-2-(1-(ethoxycarbonyl)cyclobutyl)ethyl)-5,5-dimethylcyclohex-1-ene-1-carboxylate (47)

The general procedure **H** was followed using **2d** (0.225 mmol), **alkyl bromide** (0.15 mmol) and **3a** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 50:1) yielded **47** (32 mg, 56%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.18 – 4.01 (m, 4H), 2.45 – 2.15 (m, 6H), 2.06 – 1.81 (m, 7H), 1.41 – 1.29 (m, 2H), 1.27 – 1.22 (m, 6H), 0.94 (s, 3H), 0.89 (s, 3H), 0.73 – 0.63 (m, 1H), 0.45 – 0.37 (m, 1H), 0.32 – 0.21 (m, 1H), 0.16 – 0.04 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 177.1, 169.8, 147.4, 124.0, 60.4, 60.0, 47.4, 43.9, 42.0, 40.9, 35.0, 32.3, 29.6, 29.6, 28.6, 26.8, 23.1, 16.1, 14.8, 14.4, 14.3, 7.2, 3.0. HR-MS (EI) m/z calcd for $C_{23}H_{36}O_4$ [M+H$^+$] 377.2686, found 377.2688.



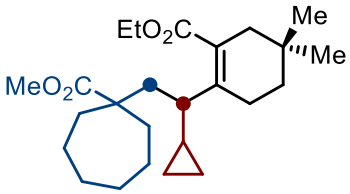
Ethyl 2-(1-cyclopropyl-2-(1-(methoxycarbonyl)cyclopentyl)ethyl)-5,5-dimethylcyclohex-1-ene-1-carboxylate (48)

The general procedure **I** was followed using **2d** (0.15 mmol), **alkyl bromide** (0.30 mmol) and **3n** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 50:1) yielded **48** (25 mg, 44%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.17 – 4.03 (m, 2H), 3.72 (dd, J = 6.9, 4.3, 1H), 3.62 (s, 3H), 2.41 (dd, J = 16.3, 6.9, 1H), 2.25 (s, 2H), 2.17 – 1.95 (m, 5H), 1.86 (dd, J = 13.8, 6.9, 1H), 1.67 – 1.59 (m, 3H), 1.47 (ddd, J = 17.7, 12.8, 7.1, 2H), 1.41 – 1.31 (m, 2H), 1.26 (t, J = 7.6, 5H), 0.92 (d, J = 19.1, 6H), 0.69 (ddd, J = 12.6, 7.9, 4.8, 1H), 0.53 – 0.40 (m, 1H), 0.35 – 0.24 (m, 1H), 0.20 – 0.10 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 178.4, 170.0, 147.6, 123.9, 60.1, 53.5, 51.7, 44.3, 43.1, 41.0, 38.3, 35.8, 35.0, 29.6, 28.7, 26.8, 25.3, 24.9, 23.0, 15.5, 14.4, 7.4, 3.2. HR-MS (EI) m/z calcd for $C_{23}H_{36}O_4$ [M+H$^+$] 377.2686, found 377.2681.



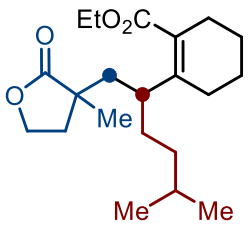
Ethyl 2-(1-cyclopropyl-2-(1-(methoxycarbonyl)cyclohexyl)ethyl)-5,5-dimethylcyclohex-1-ene-1-carboxylate (49)

The general procedure **I** was followed using **2d** (0.15 mmol), **alkyl bromide** (0.30 mmol) and **3n** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 50:1) yielded **49** (24 mg, 40%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.20 – 4.06 (m, 2H), 3.62 (s, 3H), 2.53 (d, J = 7.8, 1H), 2.23 (t, J = 6.3, 2H), 2.08 – 1.92 (m, 4H), 1.85 (dd, J = 6.5, 2.7, 2H), 1.51 (d, J = 3.8, 3H), 1.34 (dd, J = 8.3, 5.6, 3H), 1.27 (t, J = 7.1, 5H), 0.91 (d, J = 17.4, 6H), 0.72 – 0.60 (m, 1H), 0.48 (ddd, J = 13.7, 8.8, 4.8, 1H), 0.32 – 0.13 (m, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 177.4, 169.9, 147.6, 123.8, 60.1, 51.5, 46.5, 44.1, 41.8, 41.0, 35.0, 34.9, 34.3, 29.4, 28.7, 27.1, 26.0, 23.3, 23.2, 16.6, 14.4, 7.3, 3.5. HR-MS (EI) m/z calcd for $C_{24}H_{38}O_4$ [M+H$^+$] 391.2843, found 391.2848.



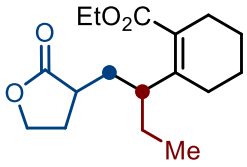
Methyl 1-(2-cyclopropyl-2-(2-(ethoxycarbonyl)-4,4-dimethylcyclohex-1-en-1-yl)ethyl)cycloheptane-1-carboxylate (50)

The general procedure **I** was followed using **2d** (0.15 mmol), **alkyl bromide** (0.30 mmol) and **3n** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 50:1) yielded **50** (27 mg, 43%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.12 (qd, J = 7.1, 3.9, 2H), 3.61 (s, 3H), 2.46 (d, J = 8.9, 1H), 2.22 (d, J = 8.9, 2H), 1.90 – 1.85 (m, 1H), 1.76 – 1.71 (m, 2H), 1.46 (s, 15H), 1.27 (s, 3H), 0.91 (d, J = 19.1, 6H), 0.74 – 0.60 (m, 1H), 0.53 – 0.42 (m, 1H), 0.34 – 0.11 (m, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 178.5, 170.0, 147.6, 123.8, 60.1, 57.3, 51.9, 51.6, 49.1, 44.5, 41.0, 37.6, 36.0, 35.1, 32.2, 30.4, 30.3, 29.9, 29.5, 28.7, 27.0, 24.3, 23.7, 23.6, 16.2, 14.4, 7.3, 3.3. HR-MS (EI) m/z calcd for $C_{25}H_{40}O_4$ [M+H$^+$] 405.2999, found 405.2998.



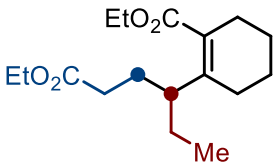
Ethyl 2-(5-methyl-1-((R)-3-methyl-2-oxotetrahydrofuran-3-yl)hexan-2-yl)cyclohex-1-ene-1-carboxylate (51)

The general procedure **H** was followed using **2a** (0.225 mmol), **alkyl bromide** (0.15 mmol) and **3a** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 10:1) yielded **51** (27 mg, 51%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.29 – 4.10 (m, 4H), 3.29 – 3.05 (m, 1H), 2.39 – 2.16 (m, 3H), 2.15 – 1.93 (m, 3H), 1.81 (ddd, *J* = 24.4, 14.5, 9.2, 1H), 1.59 (qd, *J* = 10.6, 5.7, 5H), 1.51 – 1.39 (m, 1H), 1.37 – 1.24 (m, 5H), 1.21 (s, 3H), 1.17 – 0.94 (m, 2H), 0.85 – 0.79 (m, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 182.5, 182.4, 170.3, 170.3, 147.2, 146.5, 127.5, 126.8, 65.3, 65.3, 60.2, 42.7, 42.2, 39.8, 39.6, 38.9, 37.7, 36.6, 36.5, 33.8, 33.7, 33.0, 32.6, 28.2, 28.1, 27.5, 27.4, 24.1, 23.9, 22.9, 22.9, 22.7, 22.6, 22.6, 22.5, 22.4, 22.3, 22.2, 22.1, 14.4. HR-MS (EI) m/z calcd for $C_{21}H_{34}O_4$ [M+H$^+$] 351.2530, found 351.2529.



Ethyl 2-(1-(2-oxotetrahydrofuran-3-yl)butan-2-yl)cyclohex-1-ene-1-carboxylate (52)

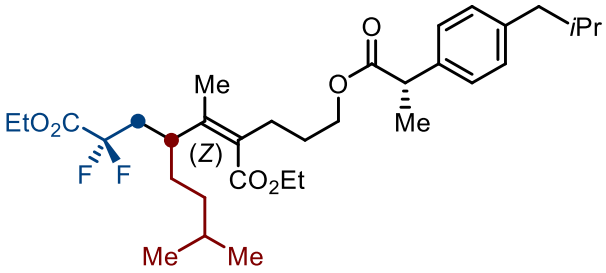
The general procedure **F** was followed using **2a** (0.225 mmol), **alkyl halide** (0.15 mmol) and **3c** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 80:1) yielded **52** (27 mg, 61%) (*dr* 1:1.5) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.32 (td, *J* = 8.8, 2.2, 1H), 4.25 – 4.10 (m, 3H), 2.92 – 2.82 (m, 1H), 2.55 (ddd, *J* = 14.9, 8.7, 2.3, 1H), 2.33 (dd, *J* = 22.2, 11.8, 3H), 2.13 – 2.02 (m, 1H), 1.99 (s, 2H), 1.90 – 1.77 (m, 1H), 1.71 – 1.51 (m, 6H), 1.46 – 1.39 (m, 1H), 1.28 (t, *J* = 7.1, 3H), 0.82 (t, *J*=7.4, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 180.3, 170.6, 143.5, 129.5, 66.8, 60.3, 41.8, 37.8, 34.2, 29.3, 27.4, 27.0, 23.0, 22.45, 22.2, 14.5. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.31 (td, *J* = 8.8, 2.0, 1H), 4.22 – 4.10 (m, 3H), 2.96 – 2.87 (m, 1H), 2.57 (ddd, *J* = 20.1, 9.9, 3.9, 1H), 2.48 – 2.39 (m, 1H), 2.33 (dd, *J* = 24.4, 8.8, 1H), 2.21 (dd, *J* = 14.8, 6.4, 1H), 2.07 – 1.85 (m, 4H), 1.58 (ddd, *J* = 9.7, 8.1, 4.2, 5H), 1.44 (dt, *J* = 13.3, 8.7, 2H), 1.28 (t, *J* = 7.1, 3H), 0.80 (t, *J* = 7.4, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 180.0, 170.5, 144.5, 128.3, 66.6, 60.4, 43.0, 38.4, 34.6, 29.6, 27.2, 25.4, 23.4, 22.4, 22.2, 14.5, 12.0. HR-MS (EI) m/z calcd for $C_{17}H_{26}O_4$ [M+H$^+$] 295.1904, found 295.1902.



Ethyl 2-(6-ethoxy-6-oxohexan-3-yl)cyclohex-1-ene-1-carboxylate (53)

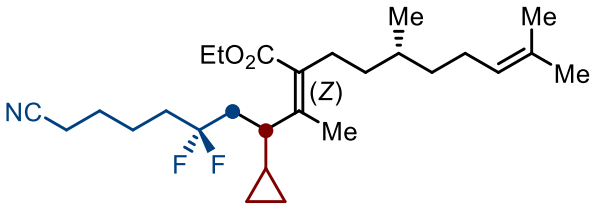
The general procedure **F** was followed using **2a** (0.225 mmol), **alkyl halide** (0.15 mmol) and **3c** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc

80:1) yielded **53** (12 mg, 27%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.21 – 4.05 (m, 4H), 2.86 – 2.76 (m, 1H), 2.31 – 2.15 (m, 4H), 1.95 (d, J = 5.5, 2H), 1.75 – 1.56 (m, 7H), 1.26 (dt, J = 15.6, 7.1, 7H), 0.80 (t, J=7.4, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 174.1, 170.4, 144.5, 128.5, 60.3, 60.2, 43.5, 32.6, 28.2, 27.2, 26.4, 23.1, 22.5, 22.2, 14.4, 14.4, 12.1. HR-MS (EI) m/z calcd for $C_{17}H_{28}O_4$ [M+H$^+$] 297.2060, found 297.2062.



Diethyl (*Z*)-6,6-difluoro-2-{3-[((*S*)-2-(4-isobutylphenyl)propanoyl)oxy)propyl}-4-isopentyl-3-methylhept-2-enedioate (54)

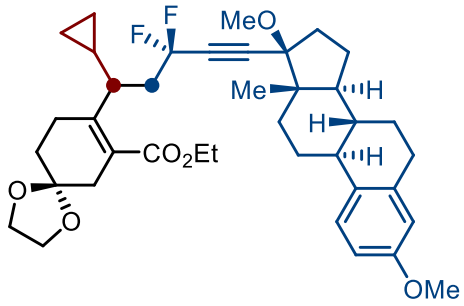
The general procedure **F** was followed using **2p** (0.225 mmol), **difluoroalkyl bromide** (0.15 mmol) and **3a** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 30:1) yielded **54** (58 mg, 67%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.19 (d, J = 7.9, 2H), 7.08 (d, J = 7.8, 2H), 4.27 (q, J = 7.0, 2H), 4.21 – 4.10 (m, 2H), 4.05 (t, J = 6.2, 2H), 3.68 (q, J = 7.1, 1H), 3.39 – 3.20 (m, 1H), 2.44 (d, J = 7.1, 2H), 2.27 – 1.97 (m, 4H), 1.83 (td, J = 13.5, 6.8, 1H), 1.75 – 1.62 (m, 2H), 1.52 – 1.36 (m, 8H), 1.33 (t, J = 7.1, 3H), 1.26 (t, J = 7.1, 3H), 1.18 – 0.92 (m, 2H), 0.89 (d, J = 6.6, 6H), 0.86 – 0.79 (m, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 174.8, 169.4, 164.2 (t, $^{2}J_{C\text{-}F}$ = 32.8), 143.5, 143.5, 140.6, 138.0, 137.9, 129.8, 129.4, 127.3, 116.1 (t, $^{1}J_{C\text{-}F}$ = 251.1), 64.1, 64.1, 62.8, 60.3, 45.3, 45.1, 37.7 (t, $^{2}J_{C\text{-}F}$ = 22.1), 36.6 (t, $^{3}J_{C\text{-}F}$ = 3.0), 36.2, 31.2, 30.3, 28.0, 27.4, 26.7, 22.8, 22.5, 18.6, 18.6, 14.3, 14.0, 12.9. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -102.80 (t, J = 16.9), -103.50 (t, J = 17.0), -103.66 (t, J = 17.1), -104.36 (t, J = 17.3). HR-MS (EI) m/z calcd for $C_{33}H_{50}F_2O_6$ [M+H$^+$] 581.3648, found 581.3652.



Ethyl (*Z*)-10-cyano-4-cyclopropyl-2-((*R*)-3,7-dimethyloct-6-en-1-yl)-6,6-difluoro-3-methyldec-2-enoate (55)

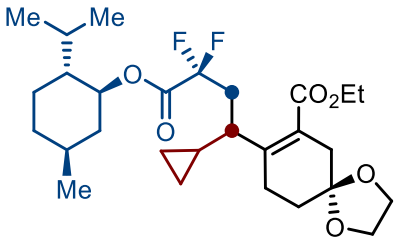
The general procedure **G** was followed using **2i** (0.15 mmol), **difluoroalkyl iodide** (0.30 mmol) and **3n** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc

15:1) yielded **55** (39 mg, 58%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.09 (ddd, J = 7.1, 5.8, 1.3, 1H), 4.19 – 4.07 (m, 2H), 2.43 (td, J = 9.2, 5.1, 1H), 2.36 (t, J = 7.0, 2H), 2.26 (ddt, J = 19.2, 10.9, 5.3, 2H), 2.19 – 1.80 (m, 7H), 1.76 (s, 3H), 1.71 – 1.66 (m, 5H), 1.59 (d, J=6.0, 4H), 1.45 – 1.31 (m, 3H), 1.26 (t, J = 7.1, 3H), 1.22 – 1.09 (m, 2H), 0.89 (d, J = 6.4, 3H), 0.81 – 0.70 (m, 1H), 0.60 – 0.32 (m, 2H), 0.31 – 0.16 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.3, 143.0, 131.2, 129.8, 125.0, 124.6 (t, $^{1}J_{C\text{-}F}$ = 242.5), 119.6, 60.2, 42.6, 39.8 (t, $^{2}J_{C\text{-}F}$ = 26.4), 37.0, 35.5, 35.2 (t, $^{2}J_{C\text{-}F}$ = 24.1), 32.5, 28.0, 25.9, 25.7, 25.3, 21.6, 19.6, 17.8, 17.1, 15.7, 14.4, 13.9, 6.3, 3.8. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -93.57 – -96.26 (m, 2F). HR-MS (EI) m/z calcd for $C_{27}H_{43}F_2NO_2$ [M+H$^+$] 452.3335, found 452.3342.



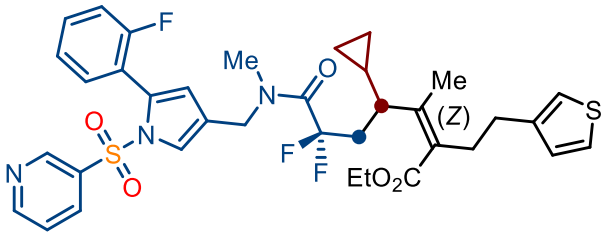
Ethyl 8-(1-cyclopropyl-5-[3,17-dimethoxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-yl]-3,3-difluoropent-4-yn-1-yl)-1,4-dioxaspiro[4.5]dec-7-ene-7-carboxylate (56)

The general procedure **F** was followed using **2b** (0.225 mmol), **difluoroalkyl bromide** (0.15 mmol) and **3n** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 15:1) yielded **56** (66 mg, 67%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.20 (d, J = 8.6 Hz, 1H), 6.71 (dd, J = 8.5, 2.4 Hz, 1H), 6.62 (d, J = 2.5 Hz, 1H), 4.21 – 4.06 (m, 2H), 4.04 – 3.93 (m, 4H), 3.77 (s, 3H), 3.40 (s, 3H), 3.28 – 3.05 (m, 1H), 2.97 – 2.74 (m, 2H), 2.63 – 2.47 (m, 3H), 2.47 – 2.17 (m, 6H), 2.08 – 1.79 (m, 5H), 1.76 (t, J = 6.6 Hz, 2H), 1.73 – 1.62 (m, 1H), 1.57 – 1.34 (m, 4H), 1.24 (td, J = 7.2, 1.9 Hz, 3H), 0.88 (s, 3H), 0.87 – 0.76 (m, 1H), 0.68 – 0.53 (m, 1H), 0.46 – 0.16 (m, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 167.8, 167.8, 157.6, 148.4, 148.2, 138.0, 132.6, 126.5, 123.2, 123.1, 114.3 (t, $^{1}J_{C\text{-}F}$ = 233.8 Hz), 113.9, 111.6, 107.5, 88.1 (t, $^{3}J_{C\text{-}F}$ = 6.3Hz),85.7, 81.8 (t, $^{2}J_{C\text{-}F}$ = 40.4 Hz), 64.6, 64.6, 60.3, 60.3, 55.3, 53.7, 49.8, 48.0, 43.5, 43.4, 42.9 (t, $^{2}J_{C\text{-}F}$ = 25.8 Hz).41.1, 39.3, 37.3, 36.3, 34.4, 31.7, 30.9, 29.9, 27.3, 26.6, 25.3, 22.9, 22.8, 15.0, 14.3, 14.25, 12.8, 6.9, 6.8, 3.8. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -78.78 (dd, J = 270.6, 5.6 Hz), -81.01 (dd, J = 270.6, 111.2 Hz). HR-MS (EI) m/z calcd for $C_{39}H_{50}F_2O_6$ [M+H$^+$] 653.3648, found 653.3645.



Ethyl 8-{1-cyclopropyl-3,3-difluoro-4-{[(*1R,2R,5S*)-2-isopropyl-5-methylcyclohexyl]oxy}-4-oxobutyl}-1,4-dioxaspiro[4.5]dec-7-ene-7-carboxylate (57)

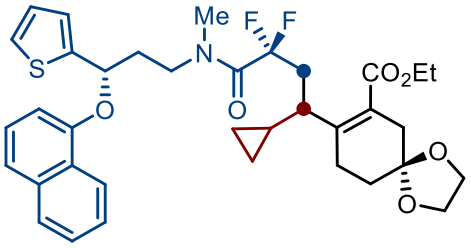
The general procedure **F** was followed using **2b** (0.225 mmol), **difluoroalkyl bromide** (0.15 mmol) and **3n** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 10:1) yielded **57** (61 mg, 80%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.78 (td, J = 10.9, 4.4 Hz, 1H), 4.21 – 4.07 (m, 2H), 4.04 – 3.94 (m, 4H), 3.00 (dq, J = 9.6, 7.0 Hz, 1H), 2.67 – 2.48 (m, 3H), 2.46 – 2.22 (m, 3H), 2.12 – 1.95 (m, 1H), 1.95 – 1.83 (m, 1H), 1.82 – 1.63 (m, 4H), 1.59 – 1.40 (m, 2H), 1.26 (td, J = 7.1, 1.2 Hz, 3H), 1.14 – 1.00 (m, 2H), 0.92 (td, J = 6.8, 3.3 Hz, 6H), 0.89 – 0.86 (m, 1H), 0.86 – 0.78 (m, 1H), 0.76 (d, J = 7.0 Hz, 3H), 0.66 – 0.48 (m, 1H), 0.46 – 0.33 (m, 1H), 0.36 – 0.17 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 168.0, 167.9, 164.0 (t, $^{2}J_{C\text{-}F}$ = 33.4 Hz), 147.9, 147.6, 123.4, 123.4, 116.0 (t, $^{1}J_{C\text{-}F}$ = 251.4 Hz), 107.5, 64.6, 64.6, 60.4, 47.0, 46.9, 40.4, 40.4, 37.5 (t, $^{2}J_{C\text{-}F}$ = 21.9 Hz), 37.3, 37.3, 26.2, 25.0, 23.5, 23.4, 22.1, 20.1, 20.9, 16.3, 16.2, 14.9, 14.8, 14.3, 6.8, 6.8, 3.8, 3.8. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -102.53 (dd, J = 322.7, 265.8 Hz), -105.34 (dd, J = 266.1, 201.2 Hz). HR-MS (EI) m/z calcd for $C_{28}H_{42}F_2O_6$ [M+H$^+$] 513.3022, found 513.3026.



Ethyl (*Z*)-4-cyclopropyl-6,6-difluoro-7-{{[5-(2-fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1H-pyrrol-3-yl]methyl}(methyl)amino}-3-methyl-7-oxo-2-[2-(thiophen-2-yl)ethyl]hept-2-enoate (58)

The general procedure **F** was followed using **2j** (0.225 mmol), **difluoroalkyl bromide** (0.15 mmol) and **3n** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 3:1) yielded **58** (100 mg, 93%) as a colorless oil. ^{1}H-NMR (400 MHz, C_2D_6SO): δ = 8.86 (t, J = 4.3 Hz, 1H), 8.56 (d, J = 1.6 Hz, 1H), 7.94 – 7.81 (m, 1H), 7.66 – 7.57 (m, 2H), 7.56 – 7.45 (m, 1H), 7.43 – 7.35 (m, 1H), 7.27 – 7.16 (m, 2H), 7.16 – 7.01 (m, 2H), 6.99 – 6.73 (m, 1H), 6.41 – 6.17 (m, 1H), 4.61 – 4.26 (m, 2H), 4.17 – 3.87 (m, 2H), 3.04 (d, J = 13.3 Hz,

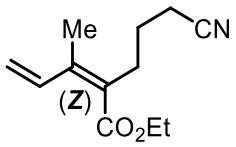
2H), 2.77 (s, 1H), 2.73 – 2.53 (m, 2H), 2.47 – 2.07 (m, 5H), 1.83 (d, J = 3.7 Hz, 1H), 1.65 (d, J = 2.4 Hz, 2H), 1.22 (t, J = 7.1 Hz, 1H), 1.13 (t, J = 7.1 Hz, 1H), 1.06 (t, J = 7.1 Hz, 1H), 0.91 – 0.77 (m, 1H).0.51 – 0.40 (m, 1H), 0.38 – 0.25 (m, 1H), 0.23 – -0.32 (m, 2H). ^{13}C-NMR (100 MHz, C_2D_6SO): δ = 169.6, 169.5, 169.4, 160. 6 (d, $^{1}J_{C\text{-}F}$ = 247.0 Hz), 155.4, 147.3, 144.4, 144.2, 144.1, 141.2, 141.9, 135.1, 135.1, 134.6, 134.6, 133.1, 133.0, 132.1, 132.0, 129.5, 129.4, 128.9 (d,$^{3}J_{C\text{-}F}$ = 5.9 Hz), 128.6, 128.5, 128.4, 128.2, 128.1, 126.3, 126.0, 125.0, 125.0, 124.7, 124.3, 124.3, 124.2, 123.5, 123.4, 121.2, 121.2, 121.1, 121.1, 119.0, 118.4 (dd, $^{1}J_{C\text{-}F}$ = 258.7, 253.8 Hz), 117.9, 115.7 (d, $^{2}J_{C\text{-}F}$ = 21.5 Hz), 60.3, 60.2, 60.1, 45.0, 44.9, 41.8, 41.0, 37.5 (t, $^{2}J_{C\text{-}F}$ = 22.1Hz), 34.9, 34.3 (t, $^{3}J_{C\text{-}F}$ = 8.1 Hz), 31.4, 30.5, 29.7, 28.9, 28.8, 15.8, 15.4, 15.3, 15.2, 15.1, 14.6, 14.4, 14.3, 14.0, 13.9, 6.3, 6.1, 4.4, 4.3, 4.1, 4.0. ^{19}F-NMR (376 MHz, C_2D_6SO): δ = -93.68 (dd, J = 275.4, 247.5 Hz), -96.33 (dd, J = 161.3, 112.4 Hz), -97.14 (dd, J = 114.8, 65.9 Hz), -98.27 (dd, J = 244.4, 226.0 Hz), -111.47 (d, J = 12.9 Hz), -111.55 (d, J = 16.4 Hz). HR-MS (EI) m/z calcd for $C_{36}H_{38}F_3N_3O_5S_2$ [M+H$^+$] 714.2278, found 714.2277.



Ethyl 8-{1-cyclopropyl-3,3-difluoro-4-{methyl[(*S*)-3-(naphthalen-1-yloxy)-3-(thiophen-2-yl)propyl]amino}-4-oxobutyl}-1,4-dioxaspiro[4.5]dec-7-ene-7-carboxylate (59)

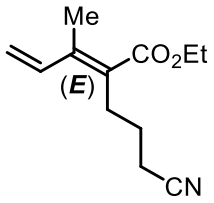
The general procedure **F** was followed using **2b** (0.225 mmol), **difluoroalkyl bromide** (0.15 mmol) and **3n** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 5:1) yielded **59** (77 mg, 78%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.37 – 8.28 (m, 1H), 7.82 – 7.72 (m, 1H), 7.55 – 7.45 (m, 2H), 7.40 (d, J = 8.3 Hz, 1H), 7.31 – 7.26 (m, 1H), 7.24 – 7.17 (m, 1H), 7.10 – 7.01 (m, 1H), 6.93 (dd, J = 8.7, 4.0 Hz, 1H), 6.82 (dd, J = 10.3, 5.4 Hz, 1H), 5.77 – 5.60 (m, 1H), 4.08 (qd, J = 7.0, 2.3 Hz, 2H), 4.01 – 3.85 (m, 4H), 3.82 – 3.52 (m, 1H), 3.14 (s, 2H), 3.09 – 3.00 (m, 1H), 2.97 (d, J = 7.6 Hz, 1H), 2.76 – 2.13 (m, 8H), 1.88 – 1.66 (m, 2H), 1.34 – 1.25 (m, 1H), 1.21 (tt, J = 8.9, 4.5 Hz, 3H), 0.88 – 0.74 (m, 1H), 0.58 – 0.47 (m, 1H), 0.43 – 0.33 (m, 1H), 0.25 (m, 2H). ^{13}C-NMR (100 MHz, CDCl3): δ = 168.2, 163.7 (t, $^{2}J_{C\text{-}F}$ = 29.3 Hz), 153.1, 148.2, 144.6, 134.7, 127.7, 126.8, 126.8, 126.5, 126.5, 126.2, 125.8, 125.7, 125.5, 125.5, 125.16, 125.1, 125.1, 124.9, 123.0, 122.9, 122.1, 122.1, 121.0, 121.0, 119.2 (dd, $^{1}J_{C\text{-}F}$ = 257.4, 253.5 Hz), 107.5, 107.1, 107.0, 74.4, 64.6, 64. 6, 64.5, 60.5, 60.3, 47.2, 40.1, 38.0 (t, $^{3}J_{C\text{-}F}$ = 11.3 Hz), 37.5, 37.3, 36.0, 36.0, 35. 5, 35.4, 30.9, 24.9, 21.2, 15.3, 15.2, 14.3, 14.3, 6.4, 3.9, 3.8. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -97.18 (dd, J = 279.5,

63.2 Hz), -98.36 (dd, J = 148.6, 31.6 Hz), -99.10 (dd, J = 150.8, 31.1 Hz), -99.96 (dd, J = 282.1, 37.7 Hz). HR-MS (EI) m/z calcd for $C_{36}H_{41}F_2NO_6S$ [M+H$^+$] 654.2695, found 654.2696.



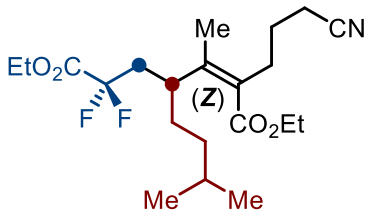
Ethyl (*Z*)-2-(3-cyanopropyl)-3-methylpenta-2,4-dienoate ((*Z*)-63)

The general procedure **C** was followed using **alkenyl acetates** (3 mmol) for 6 h. Purification by column chromatography (petroleum ether/EtOAc 20:1) yielded **(*Z*)-63** (156 mg, 50%) as a yellow liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.96 (dd, J = 17.3, 11.0, 1H), 5.43 (d, J = 17.3, 1H), 5.25 (d, J = 11.0, 1H), 4.24 (q, J = 7.1, 2H), 2.58 – 2.52 (m, 2H), 2.38 (t, J = 7.0, 2H), 1.94 (s, 3H), 1.81 (dt, J = 14.6, 7.2, 2H), 1.32 (t, J = 7.1, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.3, 140.0, 135.9, 130.0, 119.6, 117.4, 61.0, 29.5, 24.7, 16.9, 14.4, 14.4. HR-MS (EI) m/z calcd for $C_{12}H_{17}NO_2$ [M+H$^+$] 208.1332, found 208.1336.



Ethyl (*E*)-2-(3-cyanopropyl)-3-methylpenta-2,4-dienoate ((*E*)-63)

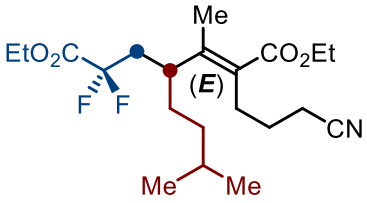
The general procedure **C** was followed using **alkenyl acetates** (3 mmol) for 6 h. Purification by column chromatography (petroleum ether/EtOAc 20:1) yielded **(*E*)-63** (150 mg, 50%) as a yellow liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.76 (dd, J = 17.1, 10.9, 1H), 5.54 (d, J = 17.2, 1H), 5.39 (d, J = 10.9, 1H), 4.24 (q, J = 7.1, 2H), 2.58 (t, J = 7.6, 2H), 2.36 (t, J = 7.1, 2H), 2.03 (s, 3H), 1.85 – 1.75 (m, 2H), 1.32 (t, J = 7.1, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.9, 139.8, 134.3, 129.5, 119.6, 119.4, 60.8, 28.1, 25.3, 16.8, 16.2, 14.4. HR-MS (EI) m/z calcd for $C_{12}H_{17}NO_2$ [M+H$^+$] 208.1332, found 208.1337.



Diethyl (*Z*)-2-(3-cyanopropyl)-6,6-difluoro-4-isopentyl-3-methylhept-2-enedioate ((*Z*)-64)

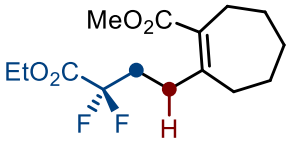
The general procedure **F** was followed using **(*Z*)-63** (0.225 mmol), **difluoroalkyl bromide** (0.15 mmol) and **3a** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum

ether/EtOAc 10:1) yielded **(*Z*)-64** (50 mg, 83%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.28 (qd, *J* = 7.1, 1.7, 2H), 4.22 – 4.12 (m, 2H), 3.34 (tt, *J* = 8.8, 5.7, 1H), 2.42 (td, *J* = 7.3, 3.3, 2H), 2.35 (t, *J* = 7.0, 2H), 2.15 (dddd, *J* = 19.4, 16.0, 9.1, 4.7, 2H), 1.76 (p, *J* = 7.2, 2H), 1.68 (s, 3H), 1.51 – 1.35 (m, 3H), 1.33 (dd, *J* = 9.0, 5.3, 3H), 1.28 (t, *J* = 7.1, 3H), 1.19 – 1.08 (m, 1H), 1.03 – 0.92 (m, 1H), 0.84 (dd, *J* = 6.6, 1.6, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.2, 164.1 (t, $^{2}J_{C\text{-}F}$ = 32.8), 144.9, 128.8, 119.8, 116.1 (t, $^{1}J_{C\text{-}F}$ = 252.2), 62.9, 60.6, 37.5 (t, $^{2}J_{C\text{-}F}$ = 22.1), 36.7 (t, $^{3}J_{C\text{-}F}$ = 3.0), 36.2, 31.3, 29.0, 28.0, 24.3, 22.8, 22.5, 16.6, 14.3, 14.0, 13.3. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -102.69 (d, *J* = 264.7), -104.68 (d, *J* = 264.6). HR-MS (EI) m/z calcd for $C_{21}H_{33}F_2NO_4$ [M+H$^+$] 402.2450, found 402.2448.



Diethyl (*E*)-2-(3-cyanopropyl)-6,6-difluoro-4-isopentyl-3-methylhept-2-enedioate ((*E*)-64)

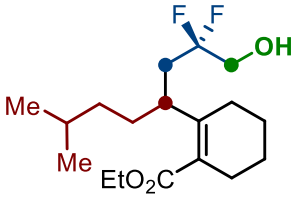
The general procedure **F** was followed using **(*E*)-63** (0.225 mmol), **difluoroalkyl bromide** (0.15 mmol) and **3a** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 10:1) yielded **(*E*)-64** (48 mg, 80%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.33 – 4.25 (m, 2H), 4.23 – 4.11 (m, 2H), 3.34 (tt, *J* = 8.8, 5.7, 1H), 2.43 (td, *J* = 7.2, 3.3, 2H), 2.35 (t, *J* = 7.0, 2H), 2.24 – 2.05 (m, 2H), 1.77 (p, *J* = 7.2, 2H), 1.68 (s, 3H), 1.52 – 1.35 (m, 3H), 1.33 (dd, *J*=9.6, 4.7, 3H), 1.28 (t, *J* = 7.1, 3H), 1.19 – 1.08 (m, 1H), 1.04 – 0.92 (m, 1H), 0.84 (dd, *J* = 6.6, 1.6, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.1, 164.0 (t, $^{2}J_{C\text{-}F}$ = 32.8), 144.8, 128.7, 119.7, 116.0 (t, $^{1}J_{C\text{-}F}$ = 251.1), 62.8, 60.5, 37.4 (t, $^{2}J_{C\text{-}F}$ = 22.2), 36.6 (t, $^{3}J_{C\text{-}F}$ = 3.0), 36.1, 31.2, 28.9, 27.9, 24.1, 22.7, 22.4, 16.5, 14.2, 13.9, 13.1. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -102.69 (d, *J* = 264.0), -104.68 (d, *J* = 264.5). HR-MS (EI) m/z calcd for $C_{21}H_{33}F_2NO_4$ [M+H$^+$] 402.2450, found 402.2454.



Methyl 2-(4-ethoxy-3,3-difluoro-4-oxobutyl) cyclohept-1-ene-1-carboxylate (65)

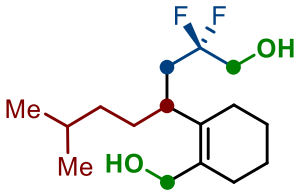
The general procedure **F** was followed using **2g** (0.225 mmol), **difluoroalkyl bromide** (0.15 mmol) and **3a** (0.375 mmol) for 16 h. Purification by column chromatography (petroleum ether/EtOAc 100:1) yielded **65** (10 mg, 21%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.34 (q, *J* = 7.1, 2H), 3.72 (s, 3H), 2.48 – 2.38 (m, 4H), 2.30 – 2.16 (m, 4H), 1.81 – 1.71 (m,

2H), 1.50 (dt, J = 11.0, 5.6, 4H), 1.36 (t, J = 7.2, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.1, 164.3 (t, $^2J_{C\text{-}F}$ = 32.7), 151.4, 132.5, 116.1 (t, $^1J_{C\text{-}F}$ = 250.7), 63.0, 51.5, 35.6, 33.1 (t, $^2J_{C\text{-}F}$ = 23.3), 32.5, 30.2, 29.4 (t, $^3J_{C\text{-}F}$ = 4.7), 26.4, 25.8, 14.1. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -106.55 (s). HR-MS (EI) m/z calcd for $C_{15}H_{22}F_2O_4$ [M+H$^+$] 305.1559, found 305.1562.



Ethyl 2-(2,2-difluoro-1-hydroxy-7-methyloctan-4-yl) cyclohex-1-ene-1-carboxylate (67)

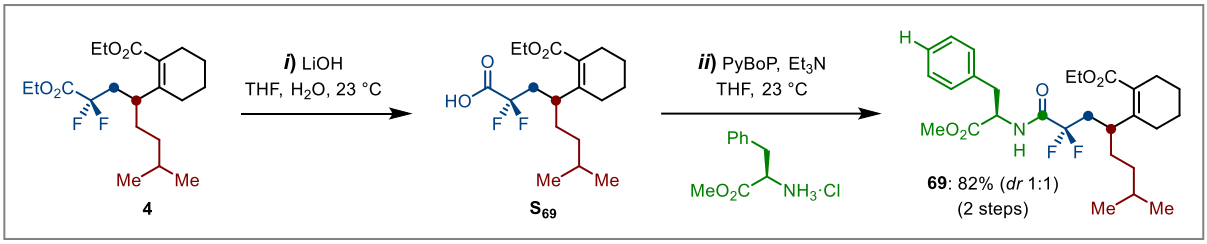
To a suspension of **4** (0.20 mmol, 1.0 equiv) in EtOH (4 mL) was added $NaBH_4$ (0.40 mmol, 2.0 equiv) at room temperature. The reaction mixture was stirred at 90 °C under an atmosphere of N_2 for 3 h. After filtration and removal of the solvents under reduced pressure, the residue was purified by column chromatography (petroleum ether/EtOAc = 10:1) to give **67** (51 mg, 77%) as an oil.[10] ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.22 – 4.14 (m, 2H), 3.79 (dddd, J = 25.7, 17.8, 8.0, 4.8, 2H), 3.29 (td, J = 11.9, 6.3, 1H), 2.91 (t, J = 7.4, 1H), 2.36 (dd, J = 13.3, 9.9, 1H), 2.25 – 1.91 (m, 5H), 1.61 (dd, J = 10.0, 5.4, 4H), 1.52 – 1.31 (m, 3H), 1.28 (t, J = 7.1, 3H), 1.11 – 0.95 (m, 2H), 0.85 (dd, J = 6.6, 2.3, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.4, 147.0, 126.8, 124.0 (t, $^1J_{C\text{-}F}$ = 243.2), 63.4 (t, $^2J_{C\text{-}F}$ = 32.5), 60.5, 36.9 (t, $^2J_{C\text{-}F}$ = 23.1),36.5, 36.3, 30.7, 27.9, 27.0, 23.9, 22.8, 22.3, 22.2, 22.0, 14.2. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -100.14 (d, J = 252.6), -104.66 (d, J = 252.5). HR-MS (EI) m/z calcd for $C_{18}H_{30}F_2O_3$ [M+H$^+$] 333.2236, found 333.2239.



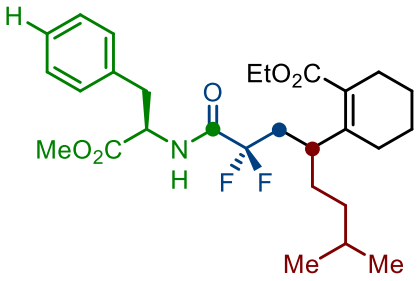
2,2-Difluoro-4-[2-(hydroxymethyl)cyclohex-1-en-1-yl]-7-methyloctan-1-ol (68)

To a suspension of **4** (0.3 mmol, 1.0 equiv) in THF (1 mL) was added $LiAlH_4$ (0.75 mmol, 2.5 equiv) in THF (1 mL) at room temperature. The reaction mixture was stirred at rt under an atmosphere of N_2 for 30 min. Then the mixture was quenched with 1M HCl solution and extracted with EtOAc. Dry the combined organic layer over Na_2SO_4. After filtration and removal of the solvents under reduced pressure, the residue was purified by column chromatography (petroleum ether/EtOAc = 3:1) to give **68** (58 mg, 66%) as a colorless oil.[11] ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.30 (d, J = 11.6, 1H), 3.88 (d, J = 11.6, 1H), 3.76 – 3.66 (m,

2H), 2.93 (s, 1H), 2.20 (dd, J = 20.2, 14.6, 1H), 2.10 (dd, J = 21.7, 7.5, 2H), 2.01 – 1.83 (m, 3H), 1.64 – 1.52 (m, 4H), 1.51 – 1.30 (m, 3H), 1.06 – 0.95 (m, 2H), 0.85 (dd, J = 6.6, 2.9, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 136.7, 131.2, 123.9 (t, $^1J_{C\text{-}F}$ = 242.8), 63.9 (t, $^2J_{C\text{-}F}$ = 32.7), 62.8, 37.1 (t, $^2J_{C\text{-}F}$ = 22.7), 36.7, 31.2, 28.7, 28.1, 22.9, 22.8, 22.8, 22.4. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -102.50 (d, J = 250.1), -106.65 (d, J = 249.9). HR-MS (EI) m/z calcd for $C_{16}H_{28}F_2O_2$ [M+H$^+$] 291.2130, found 291.2132.



Scheme S15. Preparation of 69

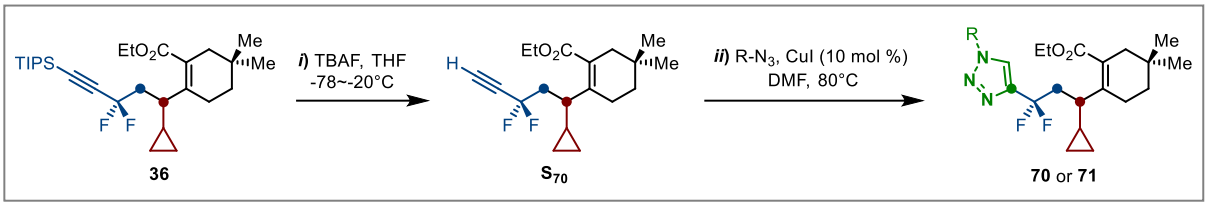


Ethyl 2-{2,2-difluoro-1-[(1-methoxy-1-oxo-3-phenylpropan-2-yl)amino]-7-methyl-1-oxooctan-4-yl}cyclohex-1-ene-1-carboxylate (69)

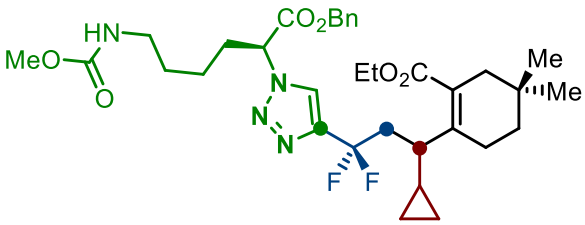
***i*)** Add **4** (0.3 mmol, 1.0 equiv) to the reaction bottle, before adding LiOH (17.0 equiv), then add THF/H_2O = 2.5:1 (0.1 M), stirring at room temperature for 4 h. The PH was adjusted to 1 with HCl and extracted with ethyl acetate. The organic phase was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The residue was purified by column chromatography (petroleum ether/EtOAc = 1:1) to give **S$_{69}$** (103 mg, 99%).[11]

***ii*)** A suspension of **S$_{69}$** (0.3 mmol, 1.0 equiv), L-phenylalanine (2.0 equiv), PyBop (1.2 equiv), Et_3N (4.0 equiv) in anhydrous THF (3.0 mL) was stirred at rt for 12 h under an atmosphere of N_2. After the reaction is complete, the solvent was evaporated in vacuo and the remaining residue was diluted with H_2O. The aqueous layer was extracted with EtOAc. Afterwards the organic phase was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The residue was purified by column chromatography (petroleum ether/EtOAc = 5:1) to give **69** (125 mg, 82%) as a colorless oil.[11] ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.32 – 7.22 (m, 3H), 7.14 – 7.06 (m, 2H), 6.93 (d, J = 7.0, 1H), 4.83 – 4.76 (m, 1H), 4.21 – 4.09 (m, 2H), 3.71 (d, J = 2.7, 3H), 3.40 (dt, J = 15.1, 7.7, 1H), 3.23 – 3.09 (m, 2H), 2.35 – 1.87 (m, 6H), 1.59

(d, J = 7.6, 4H), 1.51 – 1.33 (m, 3H), 1.27 (td, J = 7.1, 4.5, 3H), 1.18 – 0.97 (m, 2H), 0.85 (dt, J = 6.6, 1.9, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 171.0, 170.9, 170.0, 169.9, 164.0 (t, $^2J_{C\text{-}F}$ = 29.4), 163.9 (t, $^2J_{C\text{-}F}$ = 29.4), 144.9, 144.7, 135.5, 135.4, 129.4, 129.3, 128.8, 128.7, 127.8, 127.5, 127.4, 117.9 (t, $^1J_{C\text{-}F}$ = 252.1), 117.8 (t, $^1J_{C\text{-}F}$ = 253.8), 60.2, 53.6, 53.5, 52.5, 52.5, 37.9, 37.7, 37.0, 36.9, 36.8, 36.6, 36.6, 36.4, 36.3, 36.3, 35.7, 35.7, 31.5, 31.5, 28.1, 27.3, 23.9, 23.8, 22.8, 22.5, 22.3, 22.3, 22.2, 22.2. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -104.50 (ddd, J = 911.0, 692.3, 257.7). HR-MS (EI) m/z calcd for $C_{28}H_{39}F_2O_5$ [M+H$^+$] 508.2869, found 508.2876.



Scheme S16. Preparation of **70** or **71**.

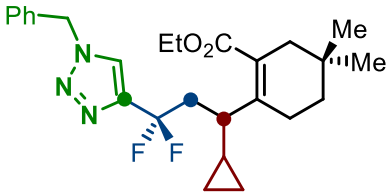


Ethyl 2-{3-[1-[1-(benzyloxy)-6-((methoxycarbonyl)amino)-1-oxohexan-2-yl]-1*H*-1,2,3-triazol-4-yl)-1-cyclopropyl-3,3-difluoropropyl}-5,5-dimethylcyclohex-1-ene-1-carboxylate (70)

***i*)** To a Schlenk flask was added **36** (1.3 mmol, 1.0 equiv) and anhydrous THF (15 mL) under argon. TBAF (1 M in THF, 1.2 equiv) was added slowly at -78 ºC. The reaction mixture was stirred at same reaction temperature for 1 h. The reaction was monitored by TLC. After compound **36** was consumed completely, the reaction was allowed to warm to -20 ºC slowly. The reaction was then quenched with saturated aqueous NH_4Cl solution. After stirring for 5 min at 0 ºC, the resulting mixture was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash silica gel chromatography (petroleum ether/EtOAc = 80:1) to give **S$_{70}$** (379 mg, 90%) as a yellow oil.[13]

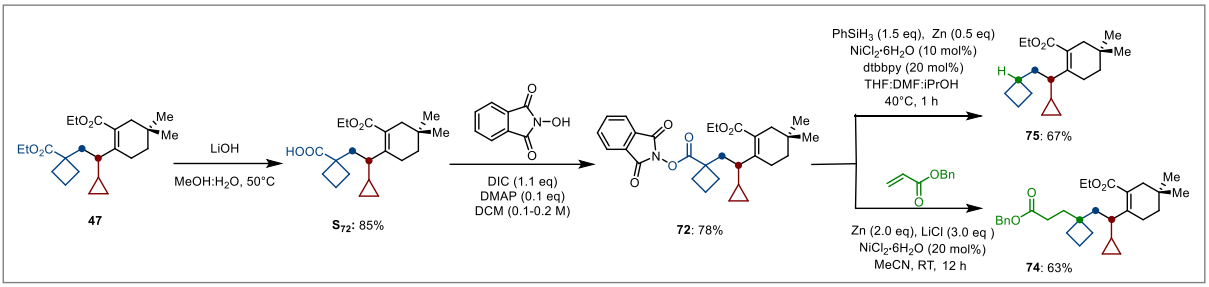
***ii*)** A suspension of **S$_{70}$** (0.1 mmol, 1.0 equiv), **R-N$_3$** (0.1 mmol, 1.0 equiv), CuI (10 mol % mol) in anhydrous DMF (1.0 mL) was stirred at 80 ℃ for 12 h under an atmosphere of N_2. After the reaction is complete, the solvent was evaporated in vacuo and the remaining residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 5:1) to yield

product **70** (59.2 mg, 92%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.93 (s, 1H), 7.38 – 7.29 (m, 5H), 5.38 – 5.28 (m, 1H), 5.14 – 5.00 (m, 2H), 4.94 – 4.83 (m, 1H), 4.07 (q, J = 7.1, 2H), 3.78 (s, 3H), 3.17 (d, J = 6.0, 2H), 2.80 – 2.63 (m, 3H), 2.31 – 2.08 (m, 4H), 1.96 (s, 2H), 1.54 (dq, J = 13.2, 6.7, 2H), 1.34 (td, J = 12.4, 6.5, 2H), 1.29 – 1.20 (m, 5H), 0.93 – 0.86 (m, 6H), 0.85 – 0.76 (m, 1H), 0.52 – 0.29 (m, 2H), 0.28 – 0.11 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.9, 168.9, 156.5, 144.8, 144.6, 136.7, 128.6, 128.2, 125.0, 124.9, 121.8, 119.2 (t, $^{1}J_{C\text{-}F}$ = 237.5), 66.8, 62.9, 60.2, 60.1, 53.3, 41.5, 41.1, 40.8, 40.8, 40.5, 39.9 (t, $^{2}J_{C\text{-}F}$ = 24.2), 39.8 (t, $^{2}J_{C\text{-}F}$ = 24.4), 34.8, 34.8, 32.46, 32.4, 29.3, 28.9, 28.8, 28.5, 28.5, 27.3, 27.2, 22.9, 22.8, 22.7, 22.7, 15.6, 15.4, 14.3, 6.6, 6.5, 3.5. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -88.93 (d, J = 264.7), -89.99 (d, J = 264.6), -88.95 (d, J = 264.6), -90.03 (d, J = 264.6). HR-MS (EI) m/z calcd for $C_{34}H_{46}F_2N_4O_6$ [M+H$^+$] 645.3458, found 645.3465.

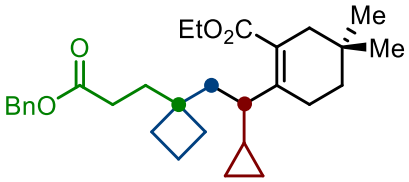


Ethyl 2-[3-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-1-cyclopropyl-3,3-difluoropropyl]-5,5-dimethylcyclohex-1-ene-1-carboxylate (71)

A suspension of **S$_{70}$** (0.1 mmol, 1.0 equiv), **R-N$_3$** (0.1 mmol, 1.0 equiv), CuI (10 mol %) in anhydrous DMF (1.0 mL) was stirred at 80 °C for 12 h under an atmosphere of N_2. After the reaction is complete, the solvent was evaporated under reduced pressure and the remaining residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 10:1) to yield product **71** (25.6 mg, 55%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.57 (s, 1H), 7.41 – 7.35 (m, 3H), 7.34 – 7.28 (m, 2H), 5.52 (s, 2H), 4.01 (q, J = 7.1, 2H), 2.80 – 2.56 (m, 3H), 2.21 (t, J = 6.0, 2H), 1.89 (s, 2H), 1.34 (dt, J = 11.9, 5.8, 1H), 1.20 (dd, J = 12.1, 5.0, 4H), 0.89 (d, J = 10.6, 6H), 0.84 – 0.77 (m, 1H), 0.50 – 0.41 (m, 1H), 0.36 – 0.22 (m, 2H), 0.16 (td, J = 9.4, 4.7, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.0, 145.4 (t, $^{2}J_{C\text{-}F}$ = 33.4), 144.4, 134.1, 129.4, 129.1, 128.5, 125.0, 122.3, 119.3 (t, $^{1}J_{C\text{-}F}$ = 237.3), 60.1, 54.4, 41.2 (t, $^{3}J_{C\text{-}F}$ = 3.4), 40.9, 39.8 (t, $^{2}J_{C\text{-}F}$ = 24.6), 34.8, 29.0, 28.5, 27.1, 22.5, 15.6, 14.3, 6.4, 3.5. ^{19}F-NMR (377 MHz, $CDCl_3$): δ = -88.59 (d, J = 264.0), -90.18 (d, J = 264.0). HR-MS (EI) m/z calcd for $C_{26}H_{33}F_2N_3O_2$ [M+H$^+$] 458.2614, found 458.2617.



Scheme S17. Preparation of 74 and 75



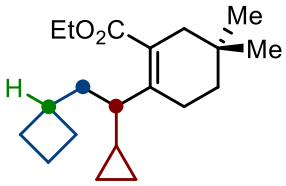
Ethyl 2-(2-(1-(3-(benzyloxy)-3-oxopropyl)cyclobutyl)-1-cyclopropylethyl)-5,5-dimethylcyclohex-1-ene-1-carboxylate (74)

***i*)** Add **47** (0.8 mmol, 1.0 equiv) to the reaction bottle, before adding LiOH (17.0 equiv), then add MeOH:H_2O = 2.5:1 (0.1 M), stirring at 50 °C for 12 h. The solvent was removed under reduced pressure. The PH was adjusted to 1 with HCl and extracted with ethyl acetate. The organic phase was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The residue was purified by column chromatography (petroleum ether/EtOAc = 10:1) to give **S72** (236 mg, 85%).

***ii*)** A round-bottom flask or culture tube was charged with **S72** (0.35 mmol, 1.0 equiv), nucleophile (N-hydroxy-phthalimide) (1.2 equiv), and DMAP (0.1 equiv). Dichloromethane was added (3 mL, 0.1 – 0.2 M), and the mixture was stirred vigorously. DIC (1.0 equiv) was then added dropwise via syringe, and the mixture was allowed to stir until the acid was consumed (determined by TLC). Typical reaction times were between 0.5 h and 12 h. The mixture was filtered (over Celite, silica gel, or through a fritted funnel) and rinsed with additional CH_2Cl_2/Et_2O. The residue was purified by flash silica gel chromatography (petroleum ether/EtOAc = 10:1) to give **72** (135 mg, 78%).

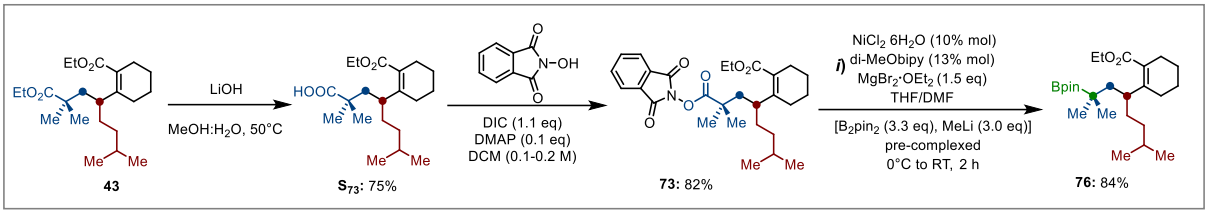
***iii*)** A culture tube was charged with LiCl (3.0 equiv). Next, **72** (0.10 mmol, 1.0 equiv), Zn powder (2.0 equiv), and $Ni(ClO_4)_2$•$6H_2O$ (0.2 equiv) were added. A stir bar was added, and the culture tube was evacuated. The tube was backfilled with N_2 from a balloon, and Michael acceptor (2.0 equiv) was added via syringe. To the reaction mixture was added MeCN (0.35 mL, 0.4 M), and the mixture was stirred overnight at ambient temperature. After at least 12 hours, H_2O (distilled) and sat. aq. NH_4Cl solution (1:1 v/v) were added. The mixture was extracted with EtOAc, and the organic layer was dried over Na_2SO_4. The residue was purified

by flash silica gel chromatography (petroleum ether/EtOAc = 20:1) to give **74** (29 mg, 63%) as a colorless oil.[14] ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.40 – 7.28 (m, 5H), 5.11 (s, 2H), 4.18 – 3.95 (m, 2H), 2.40 – 2.19 (m, 5H), 2.08 – 1.91 (m, 2H), 1.89 – 1.76 (m, 5H), 1.76 – 1.62 (m, 5H), 1.43 – 1.30 (m, 2H), 1.30 – 1.14 (m, 3H), 0.93 (t, *J*=9.5, 6H), 0.77 – 0.65 (m, 1H), 0.58 – 0.45 (m, 1H), 0.31 (ddd, *J* = 13.5, 9.0, 4.8, 1H), 0.26 – 0.10 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 174.2, 170.2, 146.9, 136.3, 128.7, 128.4, 128.3, 124.0, 66.3, 60.1, 51.3, 42.8, 42.1, 41.2, 41.0, 35.1, 32.6, 32.5, 32.0, 29.6, 29.4, 28.7, 27.0, 22.8, 16.3, 16.2, 15.6, 14.4, 7.4, 3.4. HR-MS (EI) m/z calcd for $C_{30}H_{42}O_4$ [M+H$^+$] 467.3156, found 467.3153.

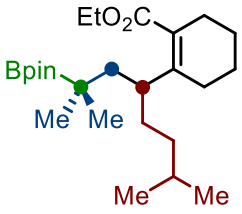


Ethyl 2-(2-cyclobutyl-1-cyclopropylethyl)-5,5-dimethylcyclohex-1-ene-1-carboxylate (75)

A culture tube was charged with **70** (0.1 mmol, 1.0 equiv), Zn metal (0.05 mmol, 0.5 equiv) and a stir bar. The tube was then evacuated and backfilled with argon from a balloon. Anhydrous THF (0.5 mL) and i-PrOH (0.05 mL) were added. A solution of $NiCl_2$•$6H_2O$/dtbbpy (1.0 M in DMF, 0.1 mL, 10 mol% $NiCl_2$•$6H_2O$, 20 mol% dtbbpy) and $PhSiH_3$ (18 µL, neat, 1.5 equiv) were added in quick succession. *NOTE: It is important to add the $PhSiH_3$ quickly after addition of the [Ni] stock solution. Diminished yields were observed when this procedure is not followed.* The culture tube was then placed in a preheated 40 °C oil bath and stirred for 1 hour. The mixture was then removed from the oil bath, allowed to cool to room temperature, and quenched with H_2O (distilled) and sat. aq. NH_4Cl solution (1:1 v/v). The mixture was extracted with EtOAc, and the organic layer was dried over Na_2SO_4. The residue was purified by flash silica gel chromatography (petroleum ether/EtOAc = 20:1) to give **75** (20 mg, 67%) as a colorless oil.[14] ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.18 – 4.02 (m, 2H), 2.32 (dddd, *J* = 49.5, 24.3, 15.9, 7.7, 2H), 2.00 (ddd, *J* = 10.7, 9.5, 5.9, 4H), 1.84 – 1.71 (m, 3H), 1.68 – 1.56 (m, 4H), 1.55 – 1.42 (m, 2H), 1.35 (dd, *J* = 12.5, 6.1, 1H), 1.27 – 1.23 (m, 3H), 0.96 (s, 3H), 0.87 (s, 3H), 0.78 – 0.61 (m, 1H), 0.50 (ddd, *J* = 17.0, 10.8, 6.8, 1H), 0.42 – 0.08 (m, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.4, 146.5, 124.3, 60.1, 45.3, 41.4, 40.9, 35.1, 34.5, 28.8, 28.7, 27.5, 22.6, 18.5, 15.0, 14.5, 6.3, 2.7. HR-MS (EI) m/z calcd for $C_{20}H_{32}O_2$ [M+H$^+$] 305.2475, found 305.2470.



Scheme S18. Preparation of 76



Ethyl 2-(2,7-dimethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)octan-4-yl)cyclohex-1-ene-1-carboxylate (76)

i) Follow the steps described above to get **73**. A screw-capped culture tube charged with **73** (0.15 mmol, 1.0 equiv.) and $MgBr_2$•OEt_2 (1.5 equiv) was evacuated and backfilled with argon for three times. Suspension A [0.6 mL, $NiCl_2$•$6H_2O$ (10 mol%)/di-MeObipy (13 mol%) in THF] was added via a syringe. The mixture was stirred vigorously at room temperature until no granular $MgBr_2$•OEt_2 was observed. This suspension was cooled to 0 °C before a suspension of [B_2pin_2Me]Li was added in one portion (*note: do not add it dropwise!*). After stirring for 1 h at 0 °C, the reaction was warmed to room temperature and stirred for another 1 h. The reaction mixture was diluted with Et_2O (10 mL), filtered through a short pad of silica gel and celite (top layer: celite, bottom layer: silica gel, v/v celite:silica gel = 1:1), and washed with Et_2O. The filtrate was concentrated, and the crude product was purified by flash column chromatography petroleum ether/EtOAc = 20:1) to give **76** (53 mg, 84%) as a colorless oil.[15] ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.22 – 4.05 (m, 2H), 2.97 (dt, J = 14.3, 7.1, 1H), 2.30 – 2.17 (m, 2H), 2.17 – 2.03 (m, 1H), 1.92 (dd, J = 12.4, 5.4, 1H), 1.63 – 1.52 (m, 5H), 1.44 (dd, J = 12.3, 5.8, 1H), 1.27 (t, J = 7.1, 5H), 1.21 (d, J = 1.6, 12H), 1.17 – 1.04 (m, 2H), 1.03 – 0.93 (m, 1H), 0.89 (d, J = 1.2, 5H), 0.83 (dd, J = 6.6, 4.2, 7H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5, 148.2, 125.7, 83.0, 60.0, 44.0, 39.8, 37.1, 31.3, 28.3, 27.3, 27.1, 25.0, 24.8, 24.3, 23.2, 22.6, 22.4, 14.5. HR-MS (EI) m/z calcd for $C_{25}H_{45}BO_4$ [M+H$^+$] 421.3484, found 421.3485.

6. References

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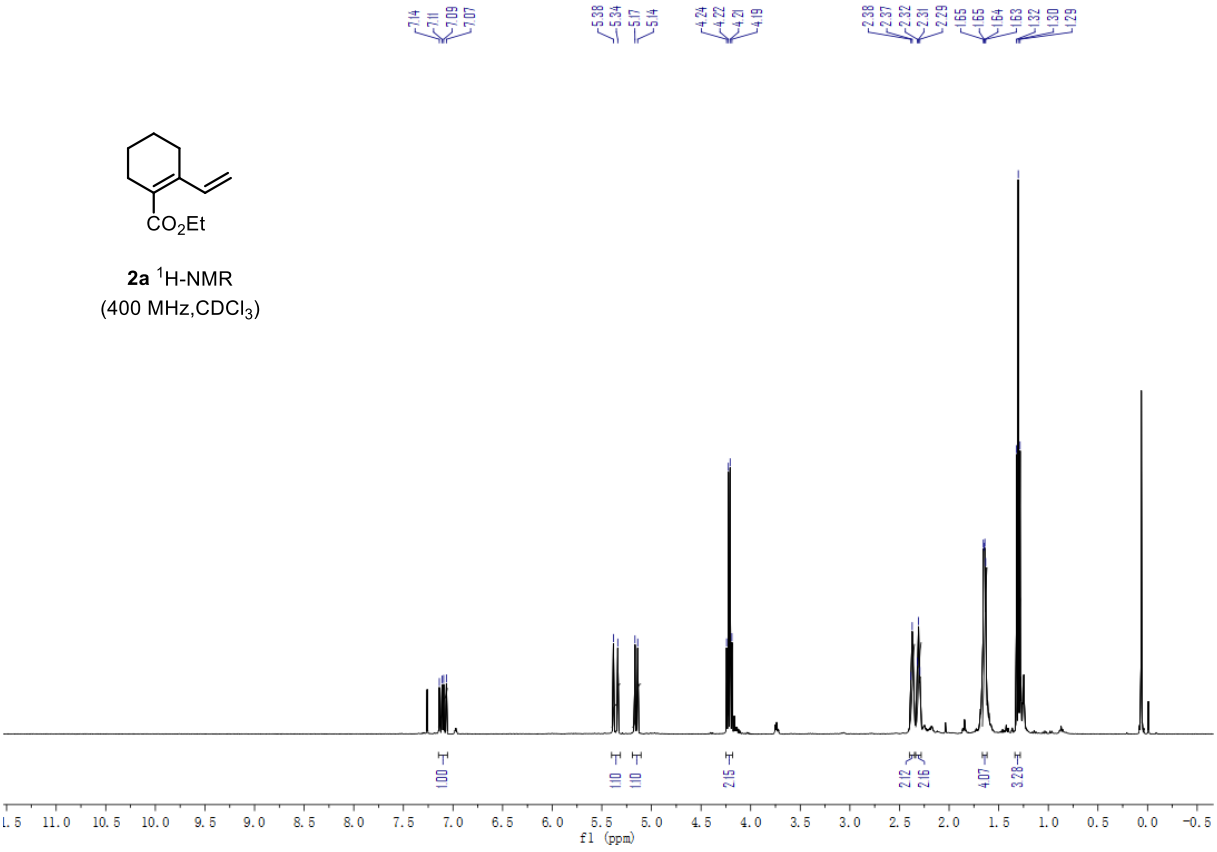
7. NMR Spectra



2a ^{1}H-NMR
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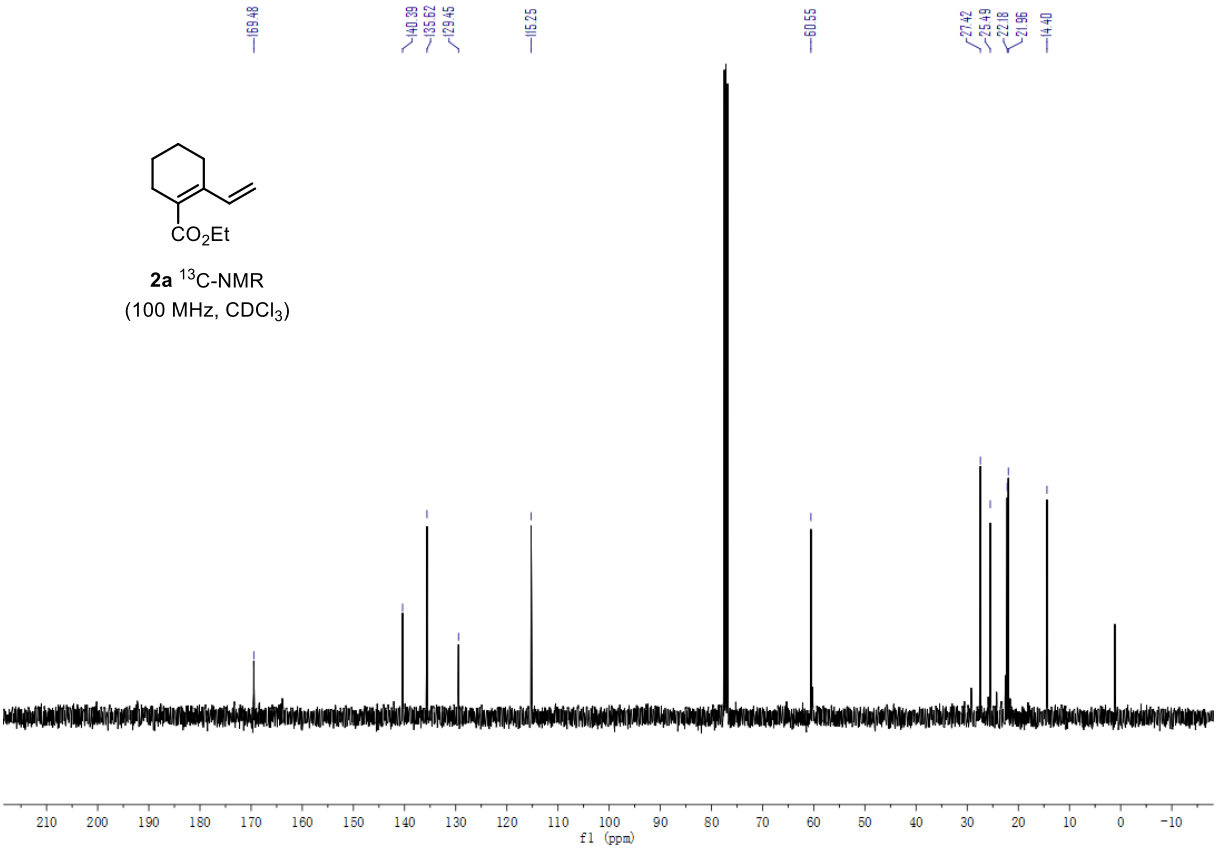

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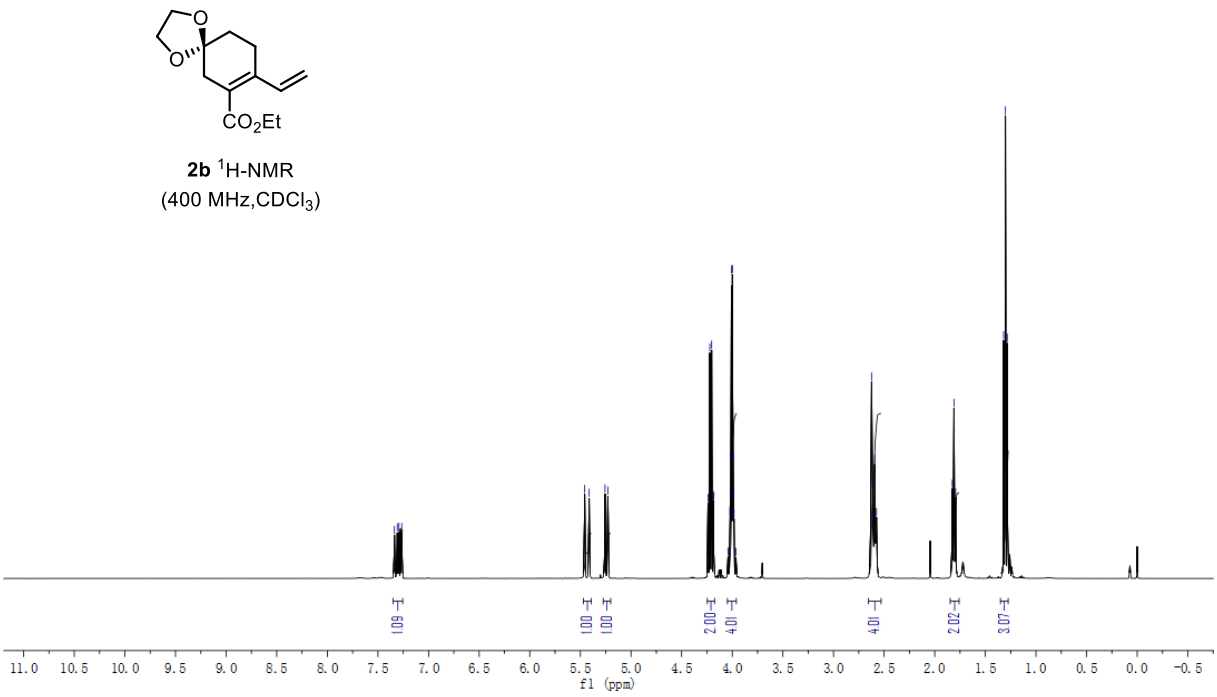

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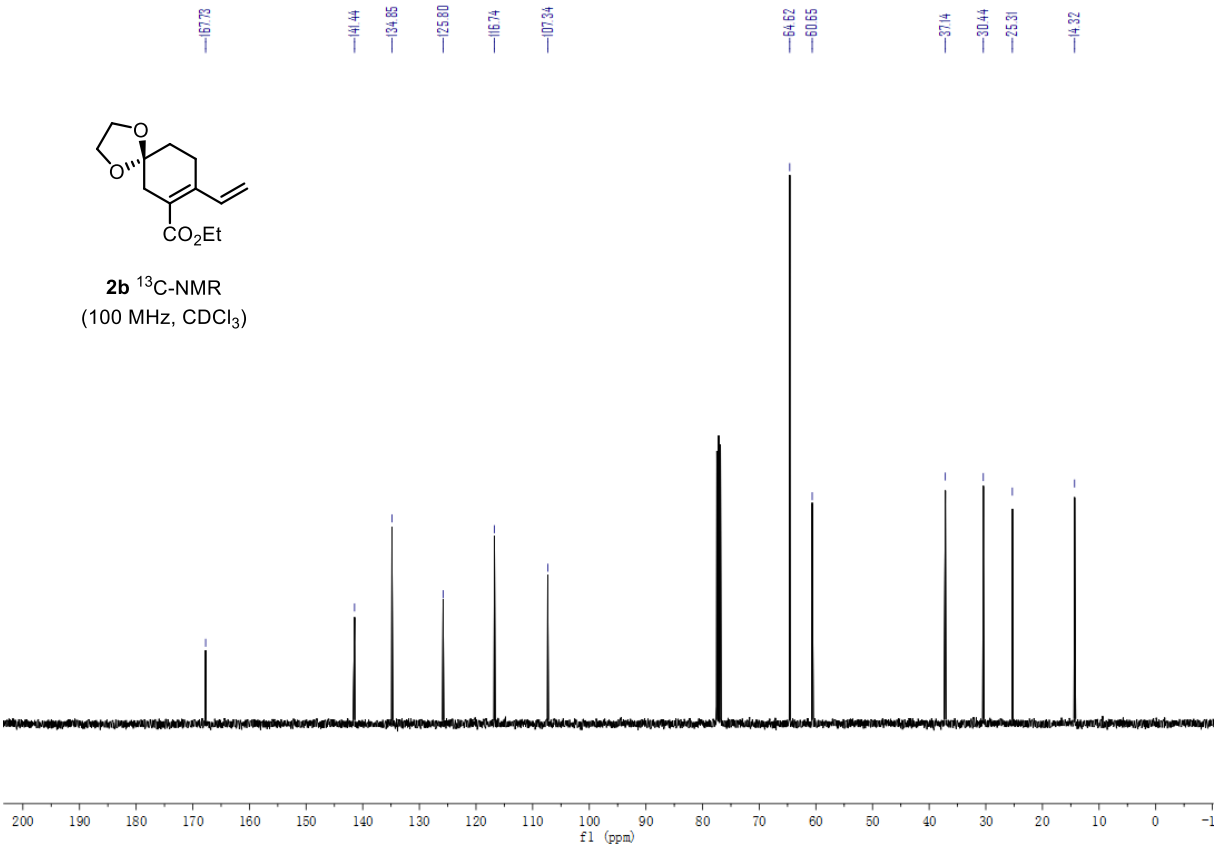

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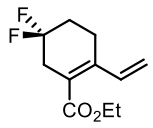

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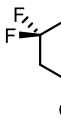

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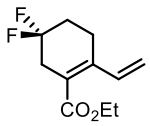

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2d ^{1}H-NMR
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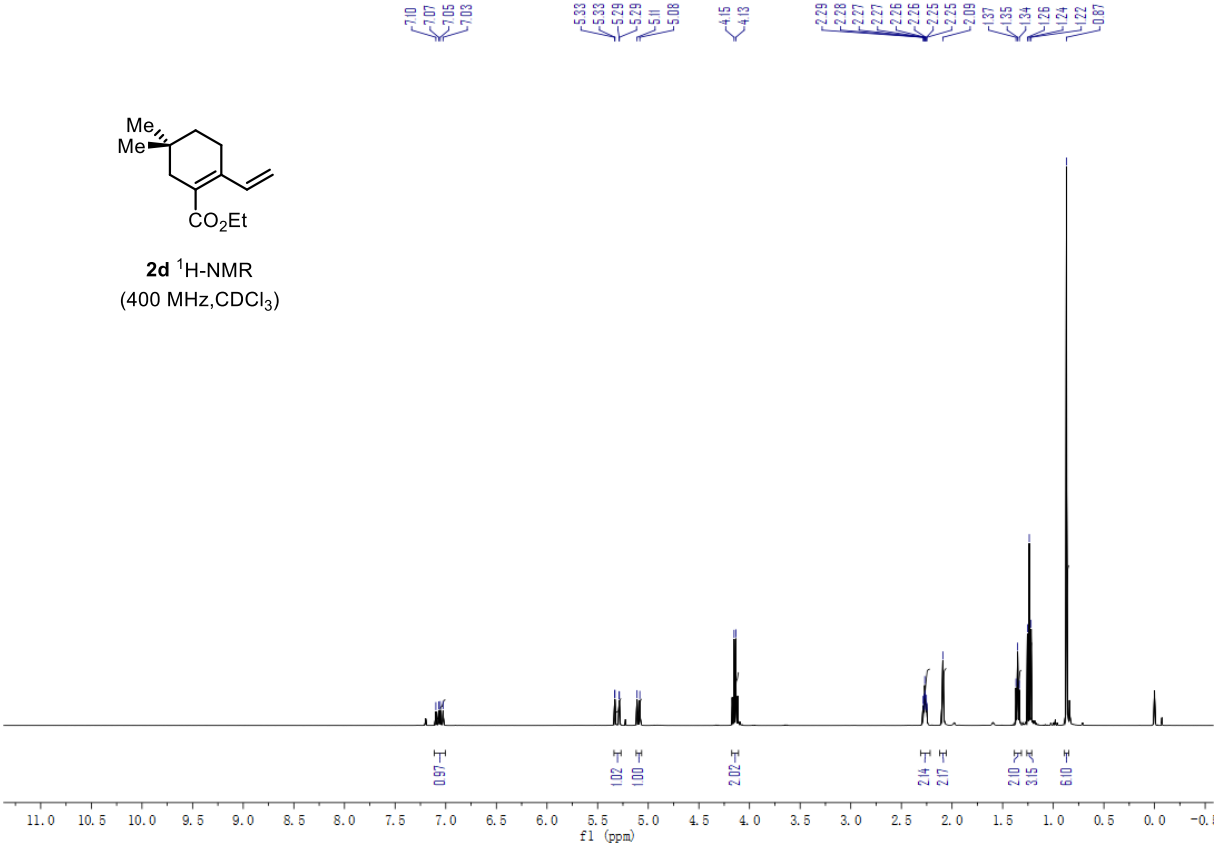

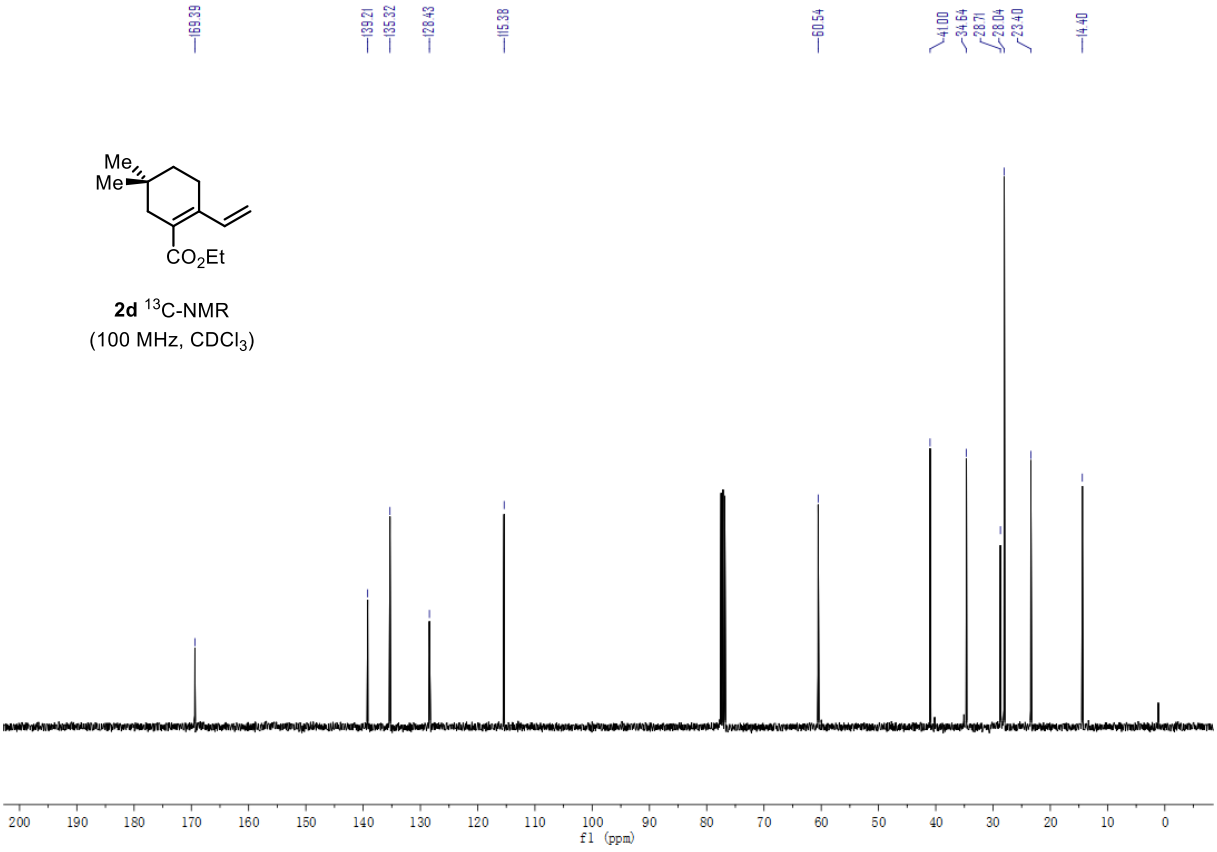

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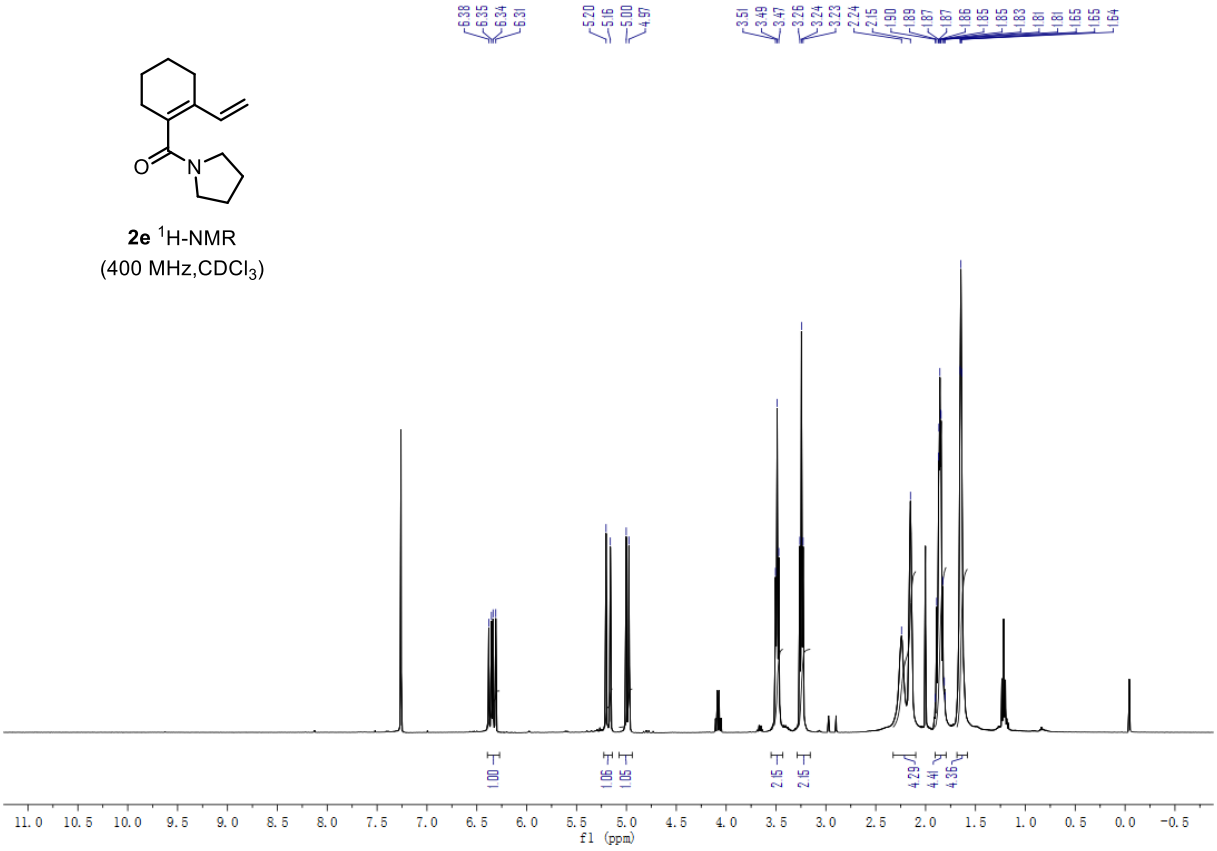

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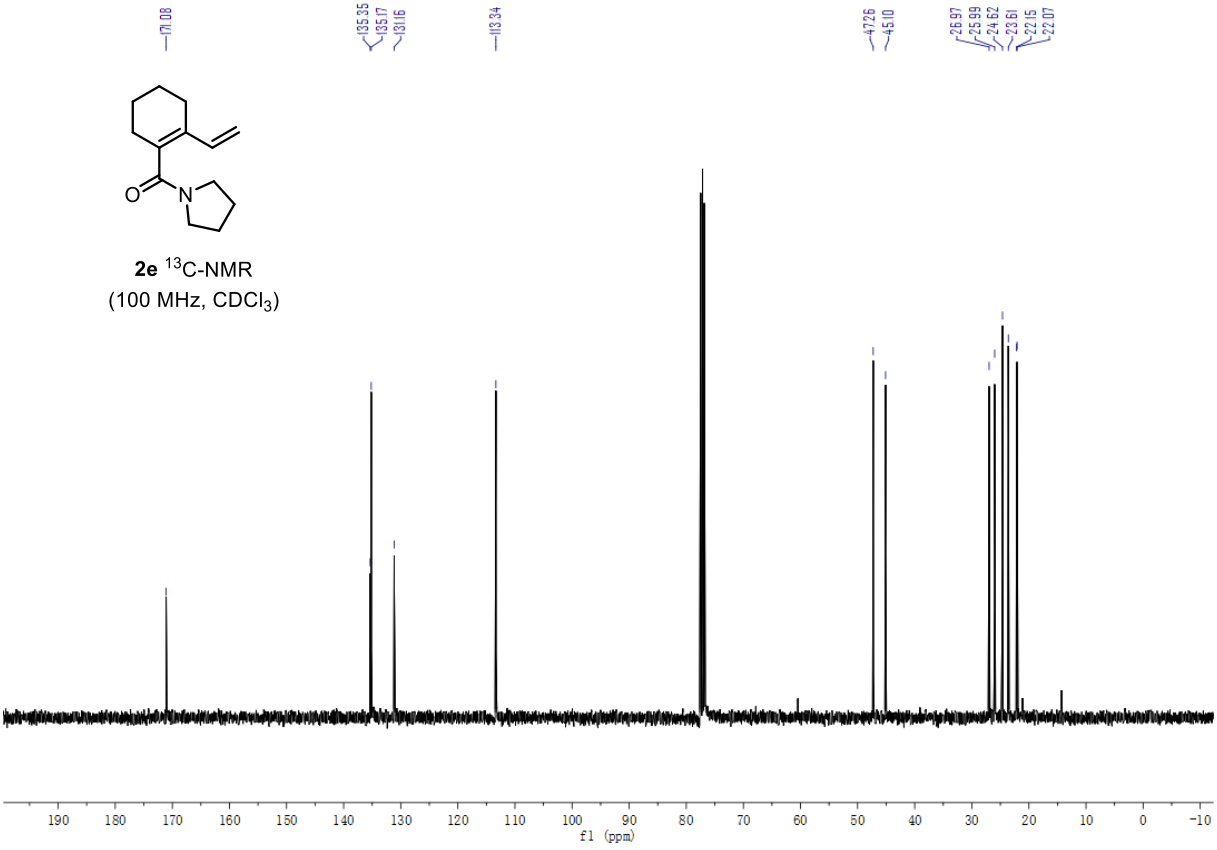

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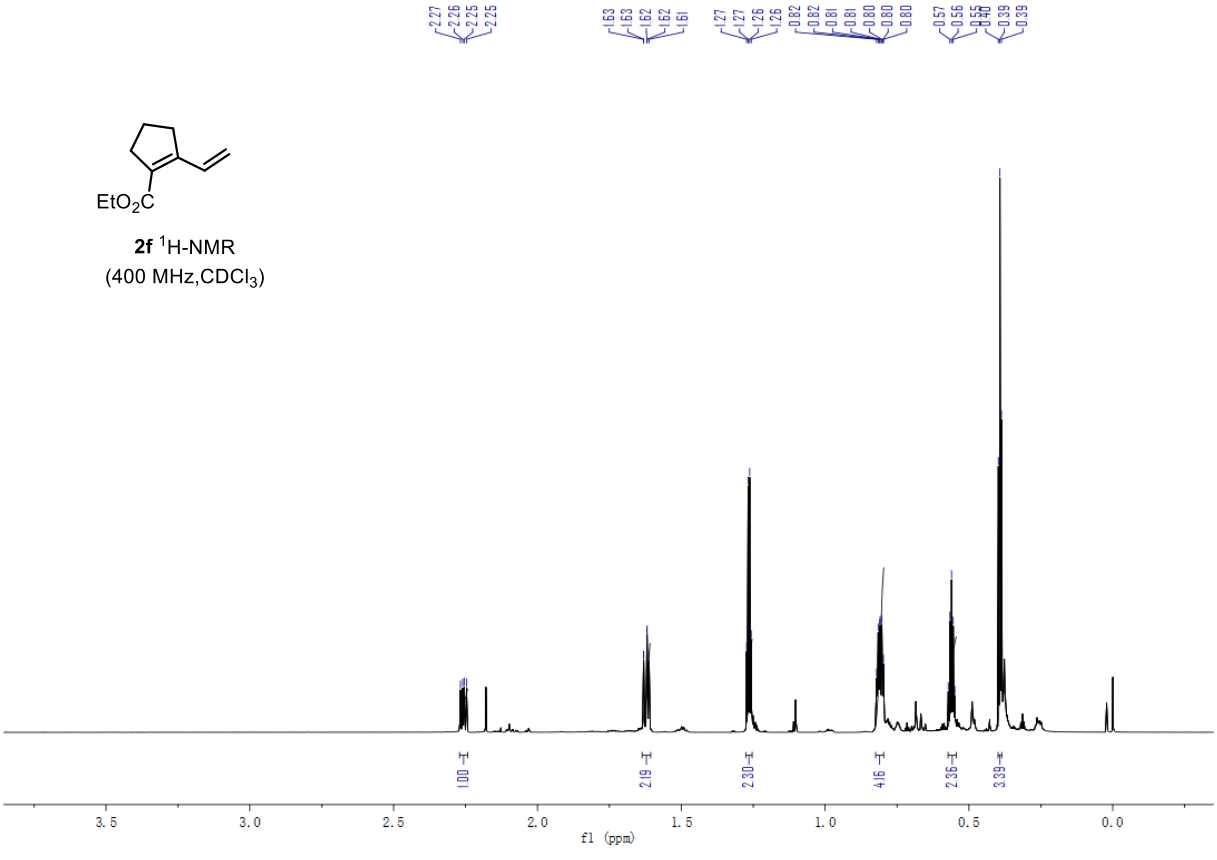

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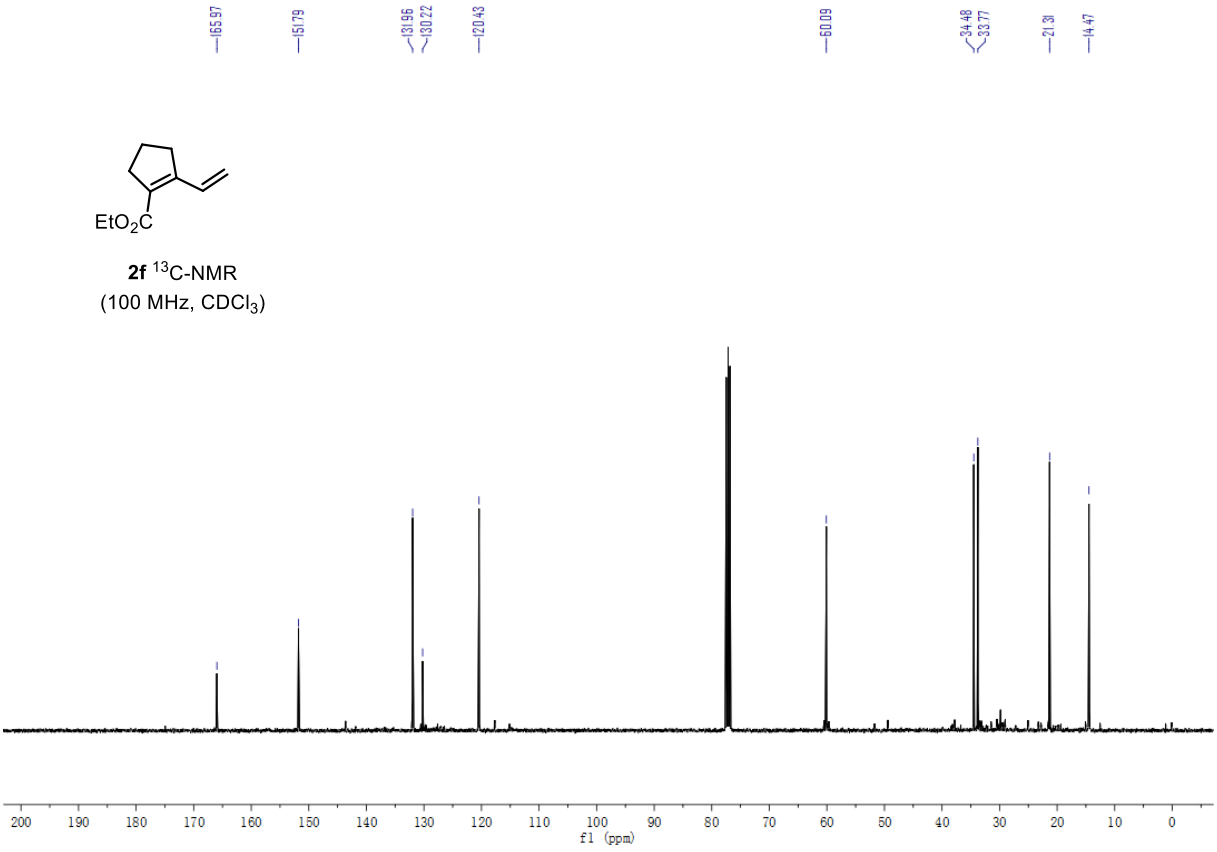

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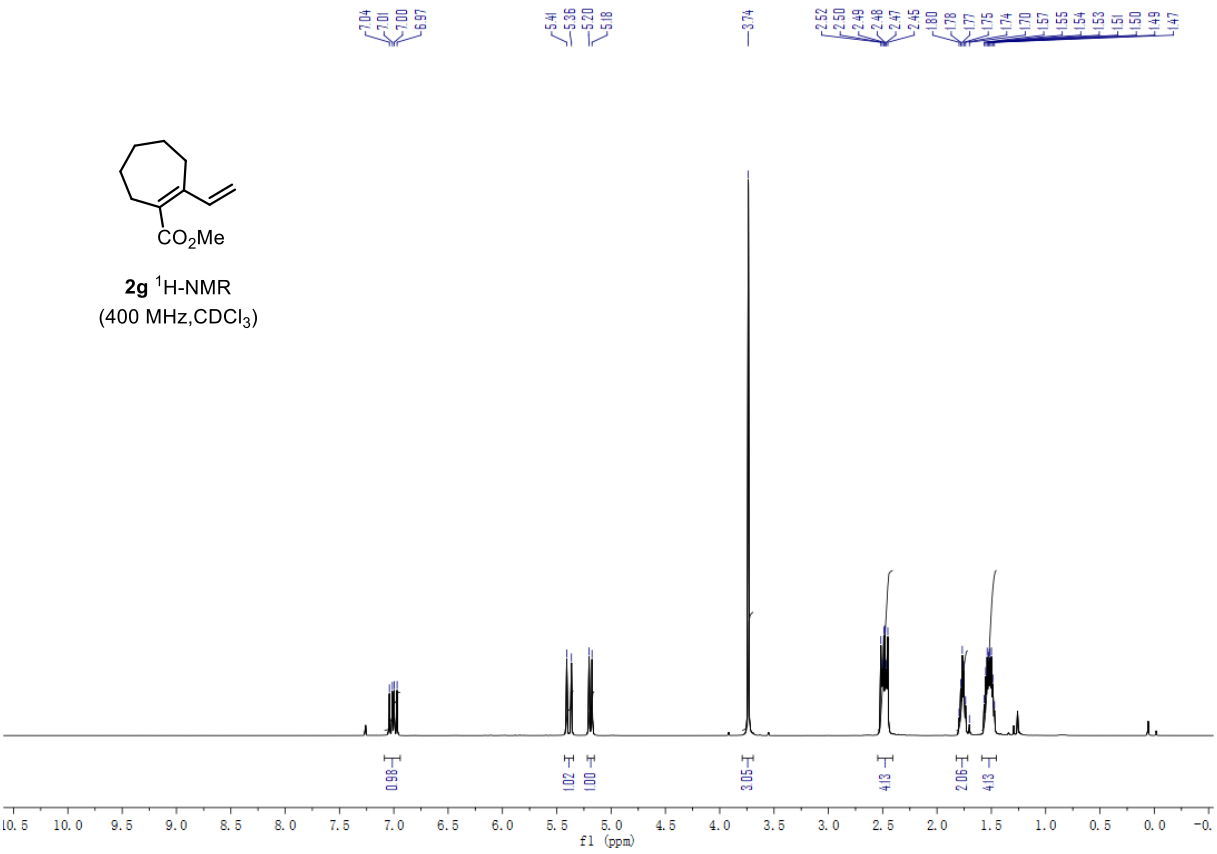

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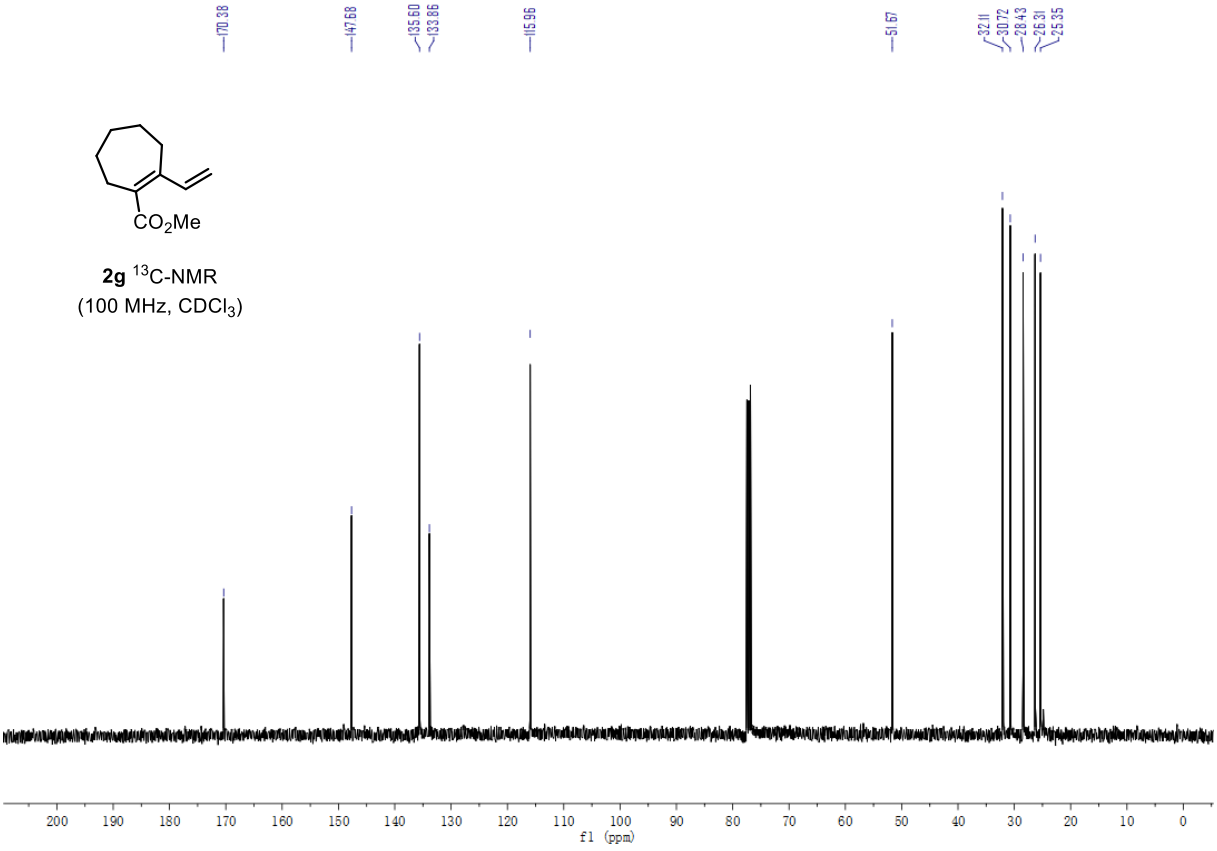

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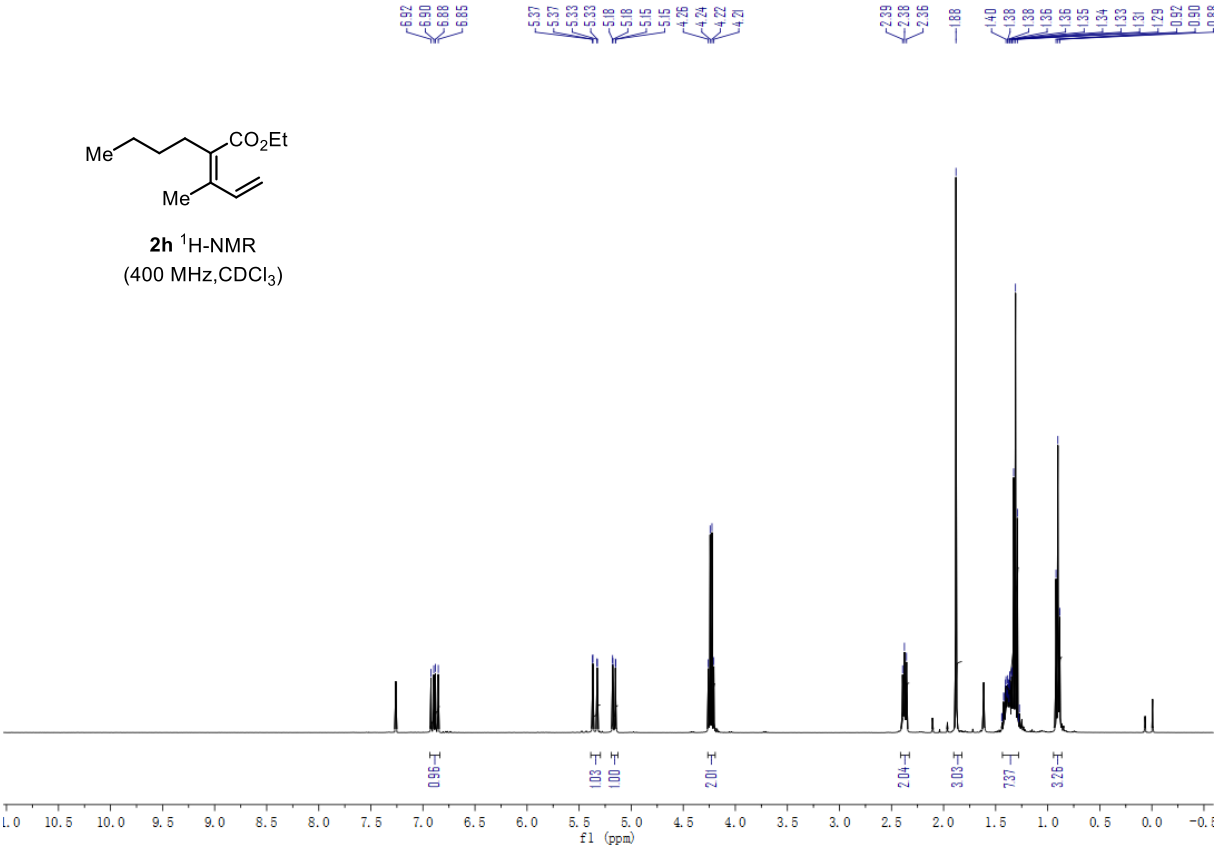

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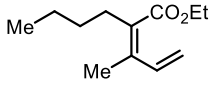

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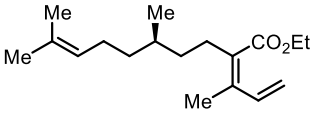

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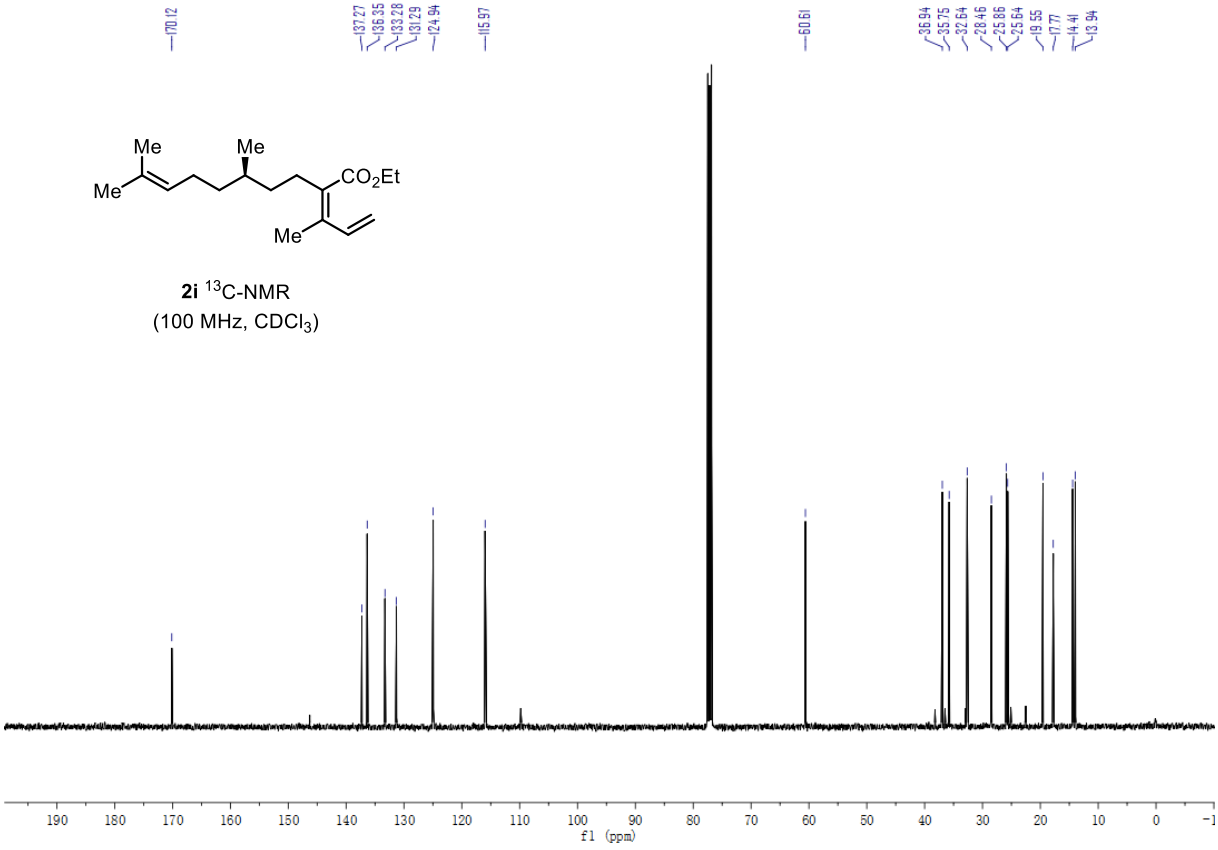

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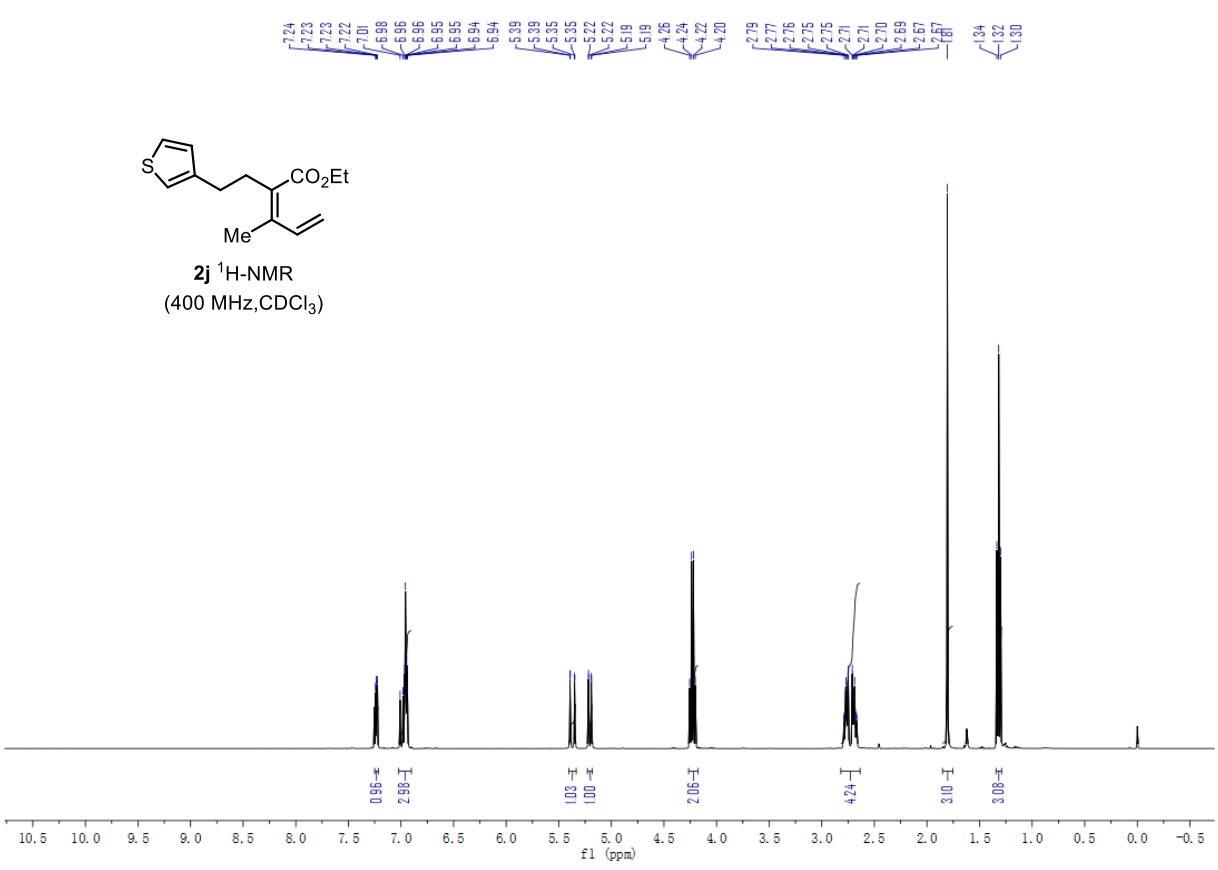

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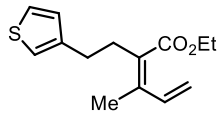

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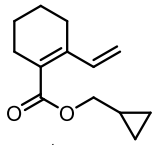

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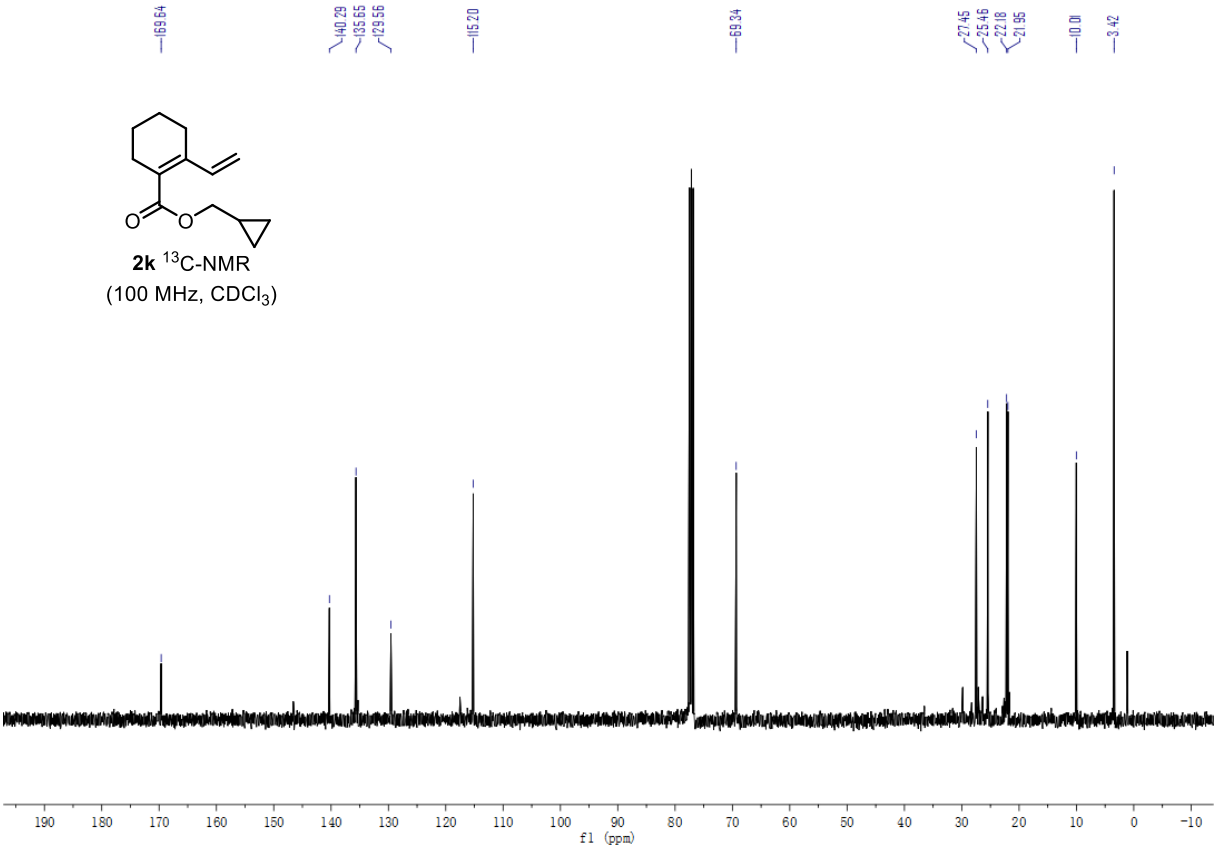

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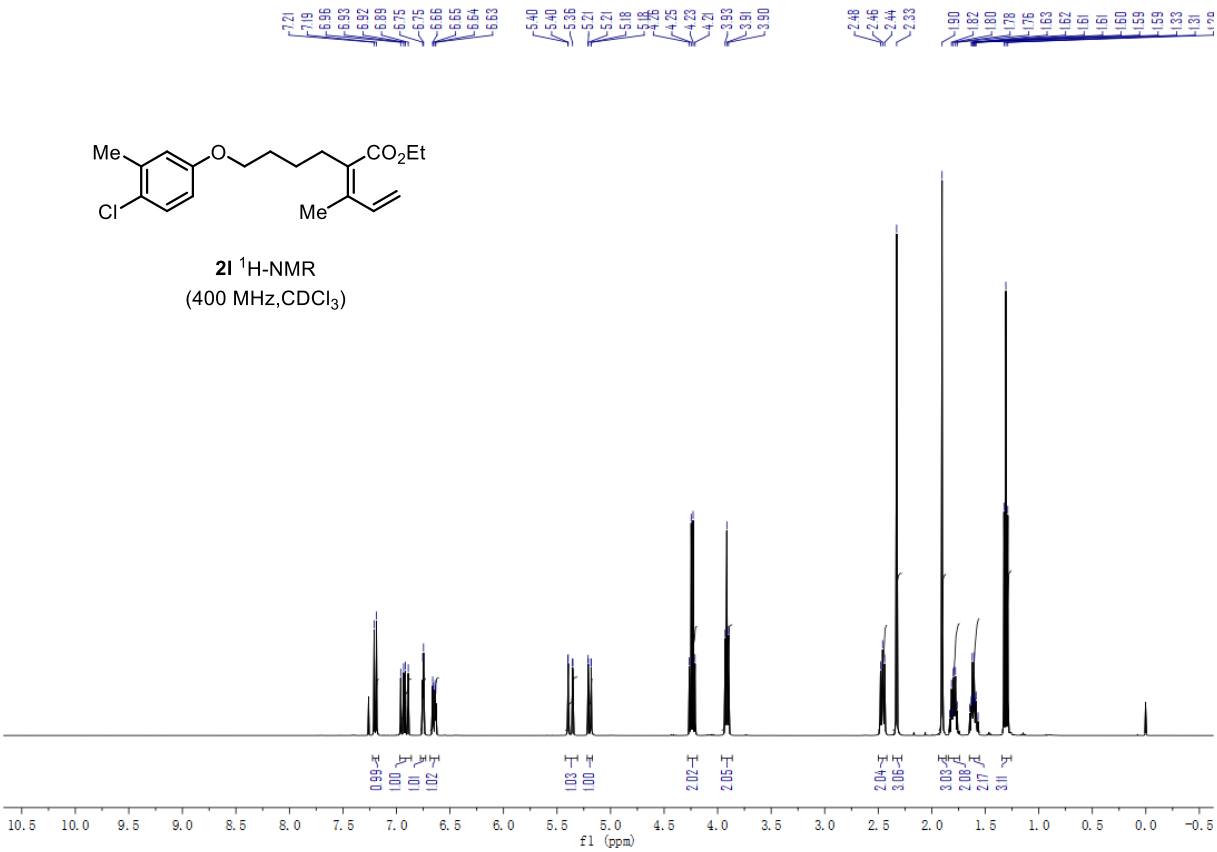

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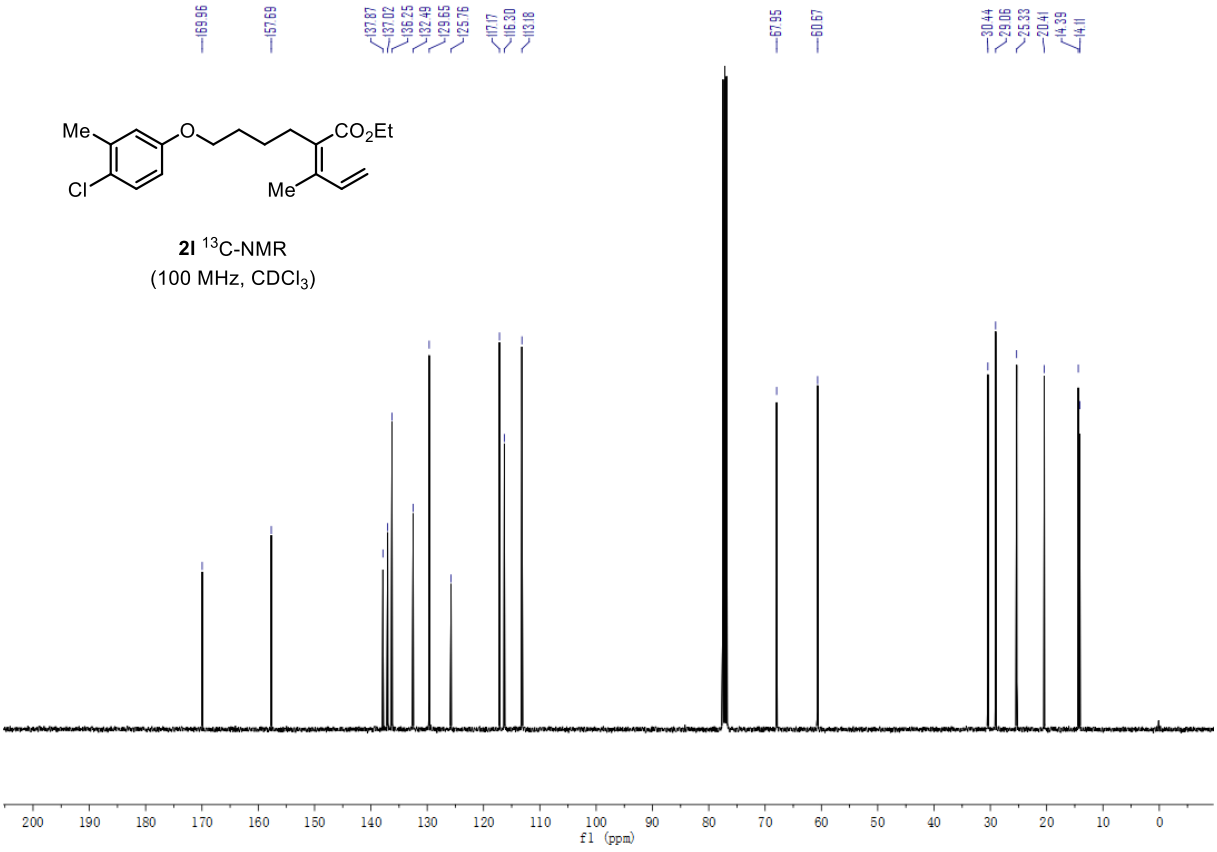

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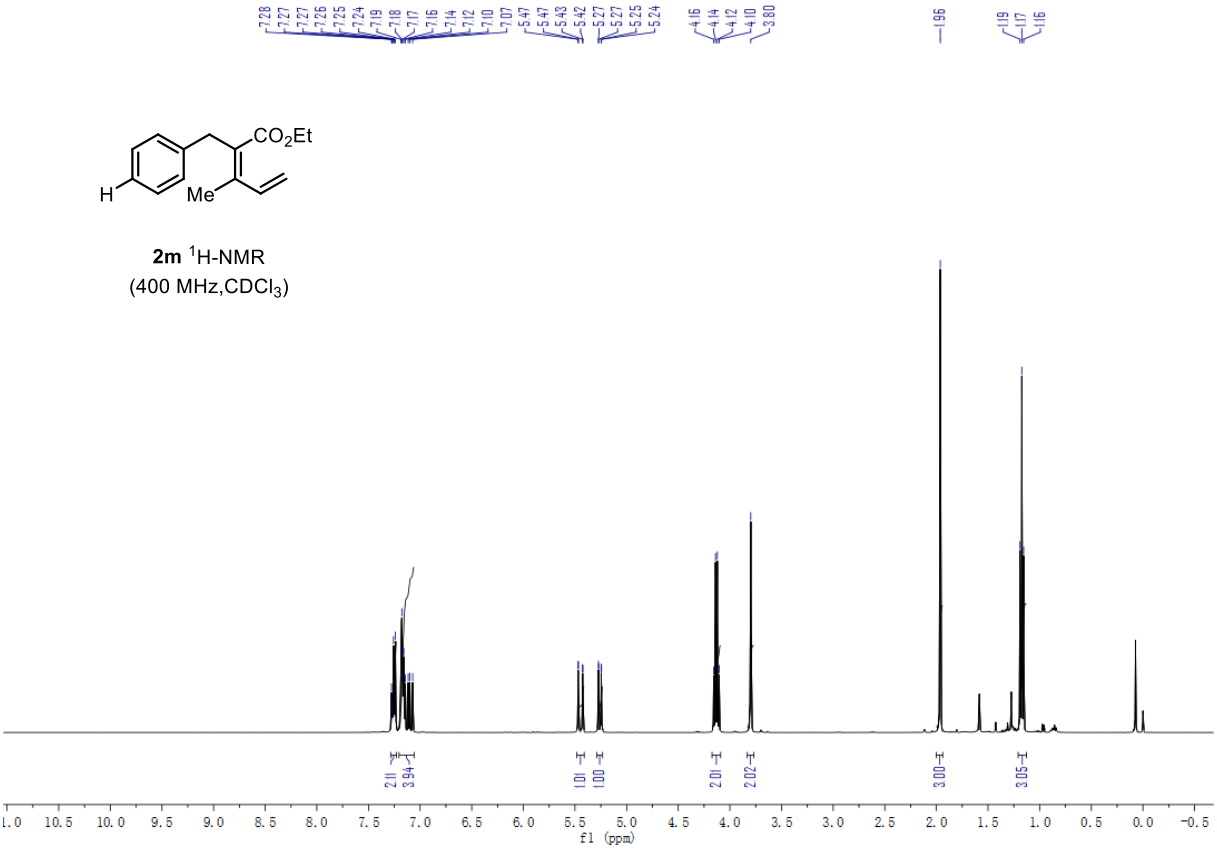

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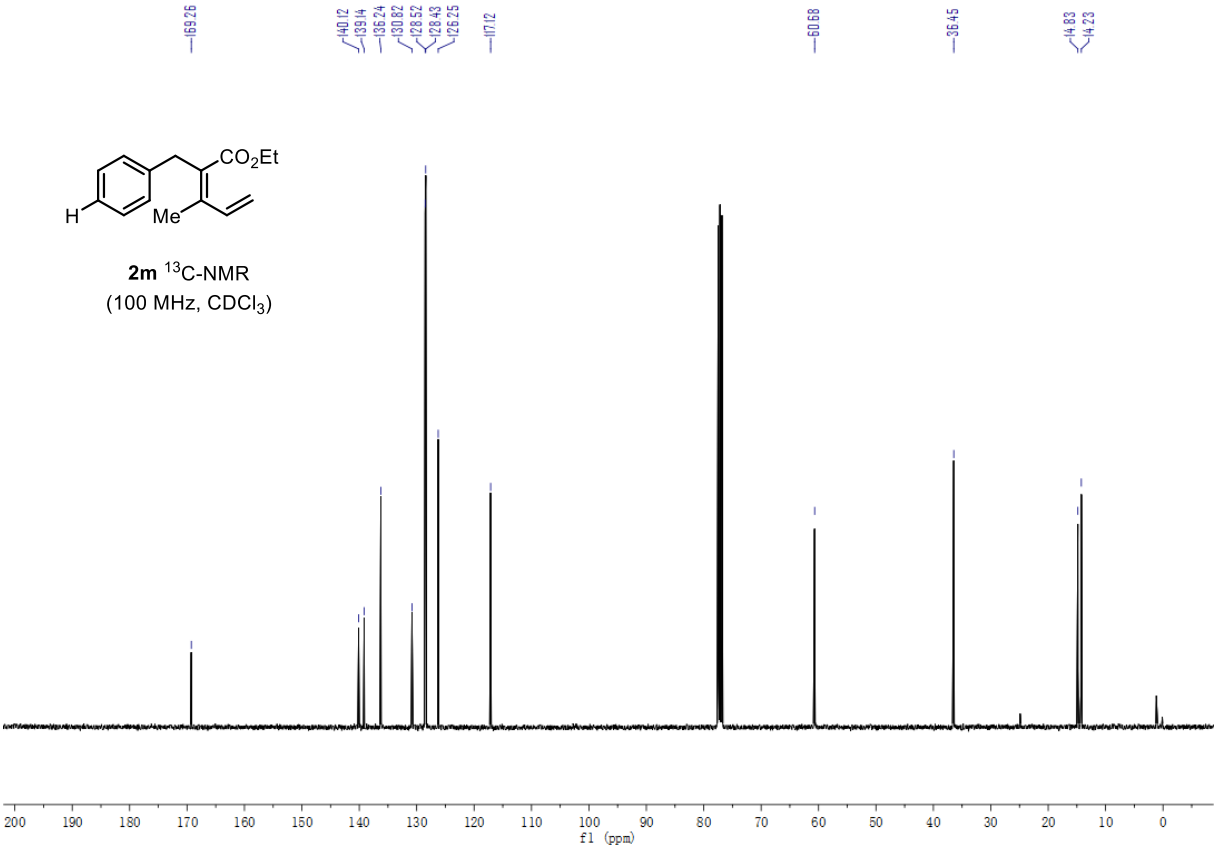

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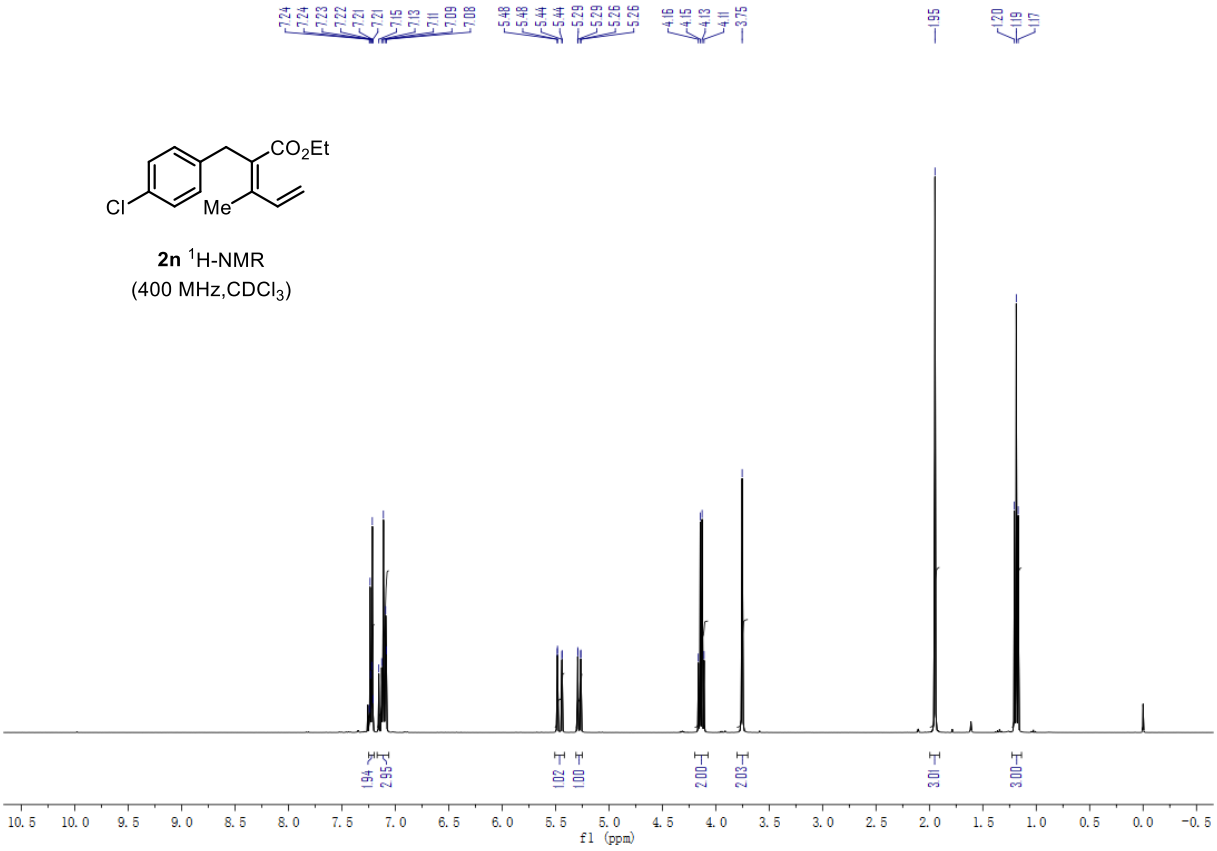

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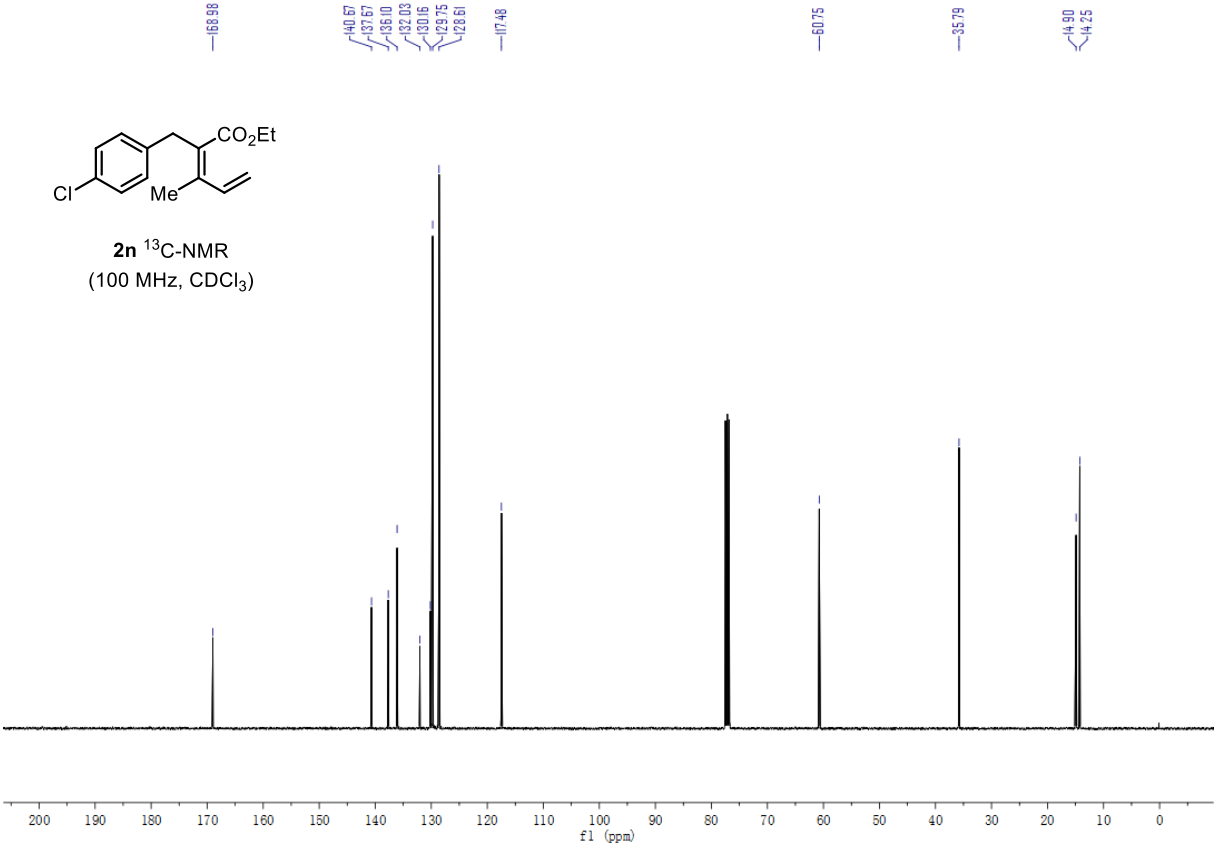

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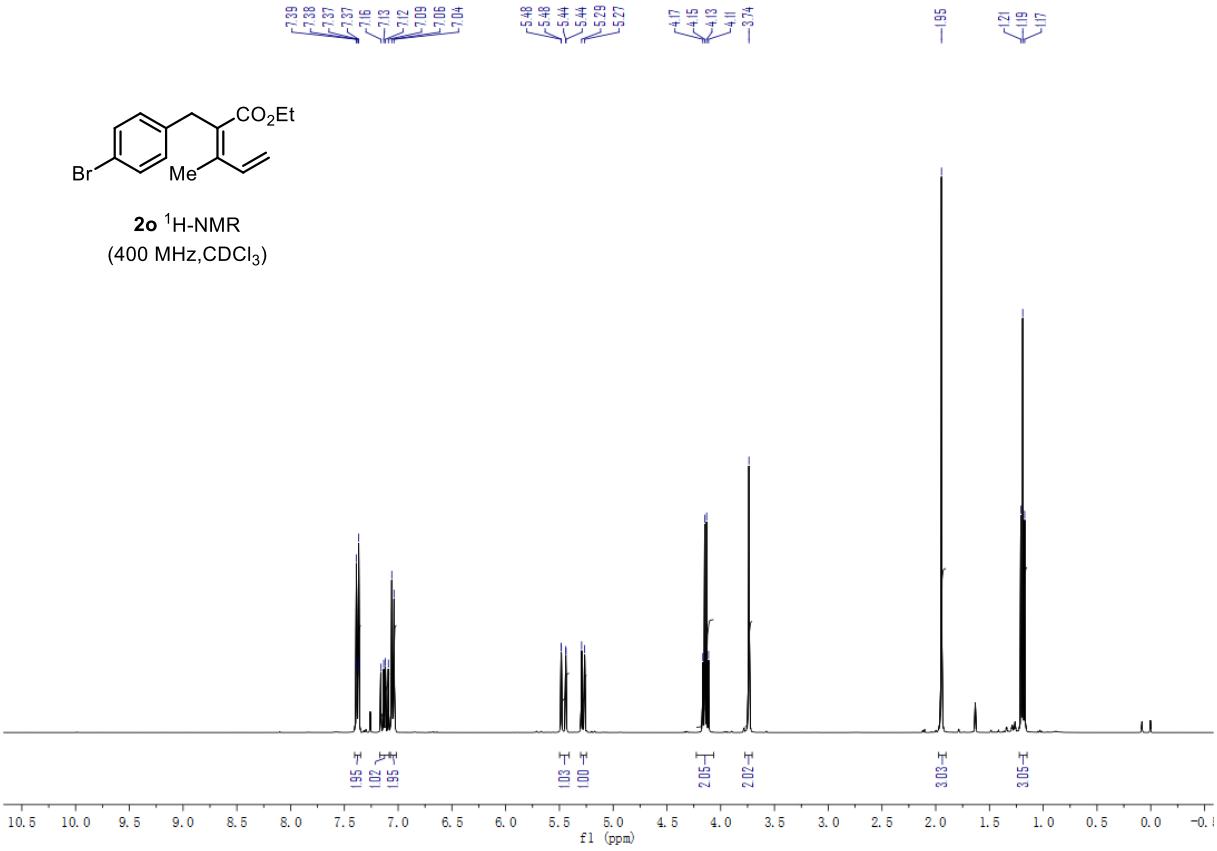

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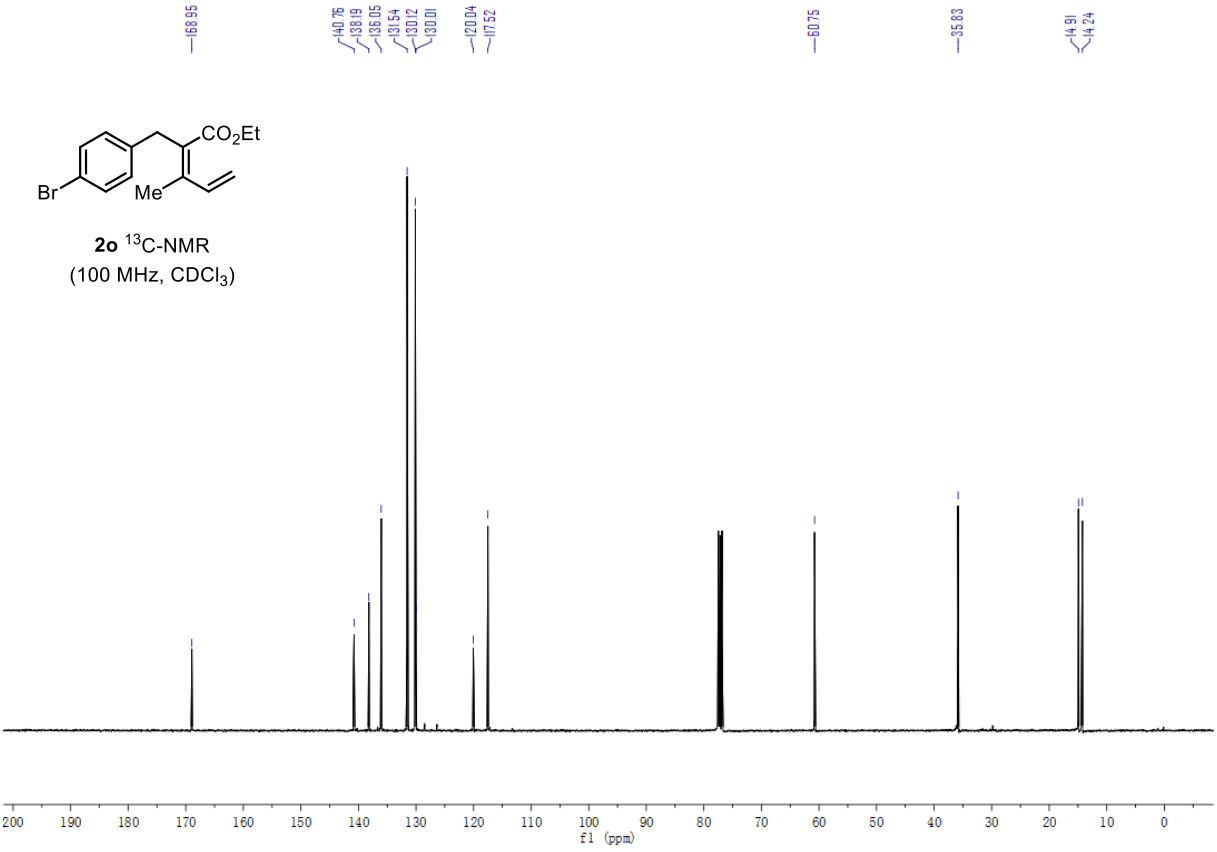

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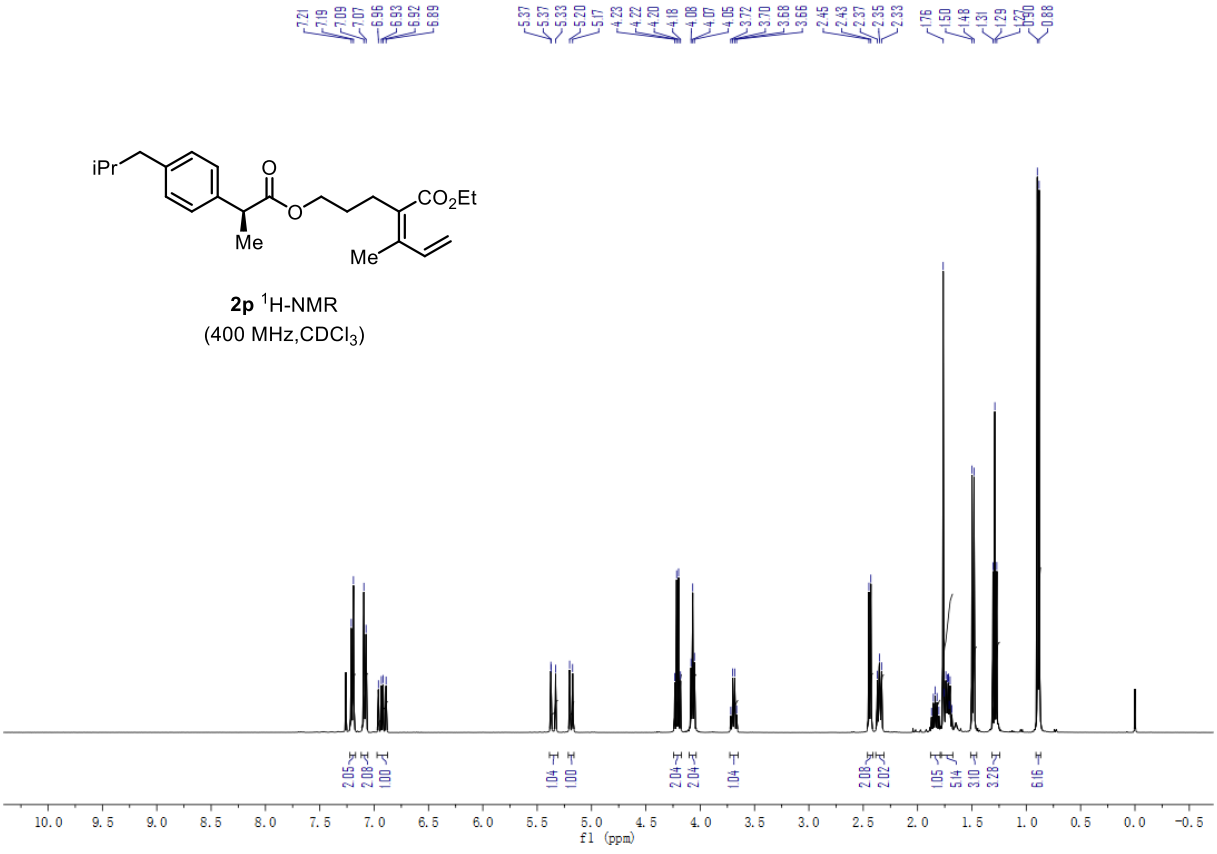

2p ^{1}H-NMR
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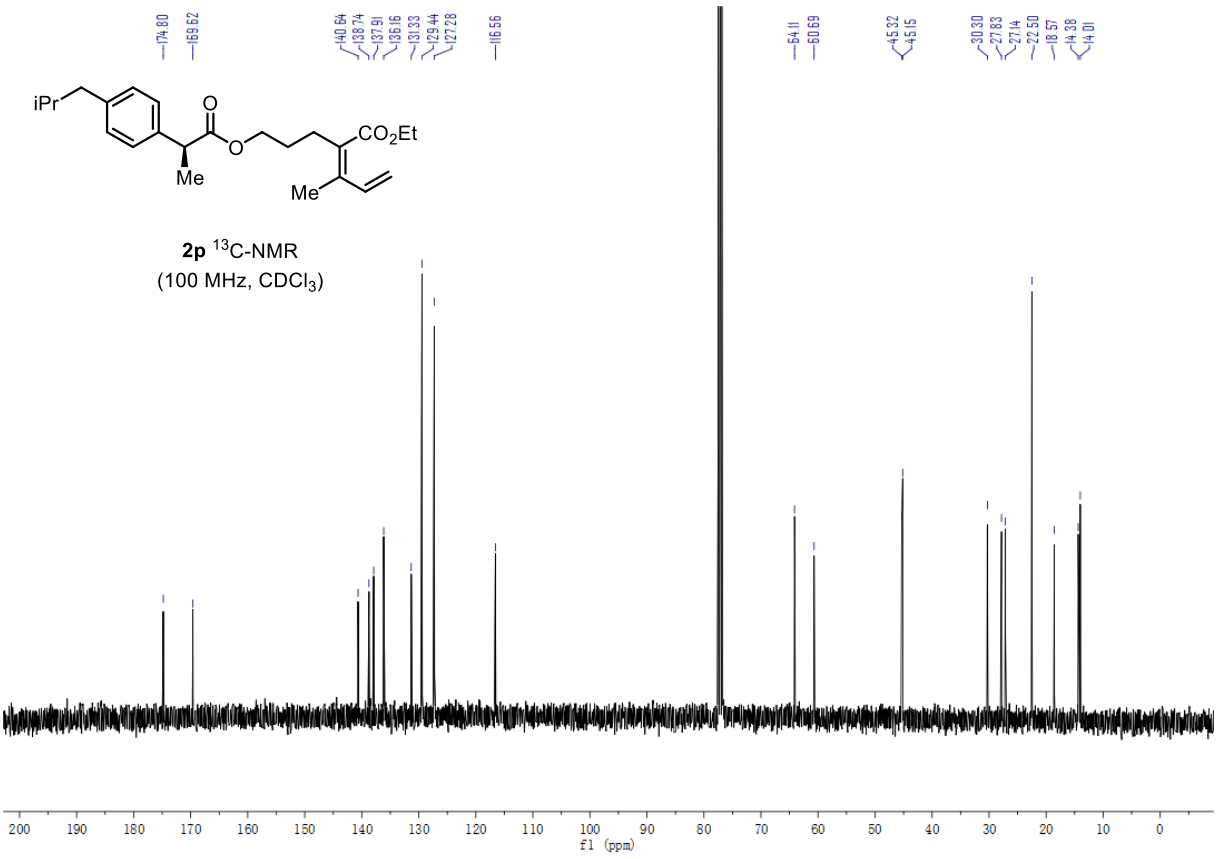

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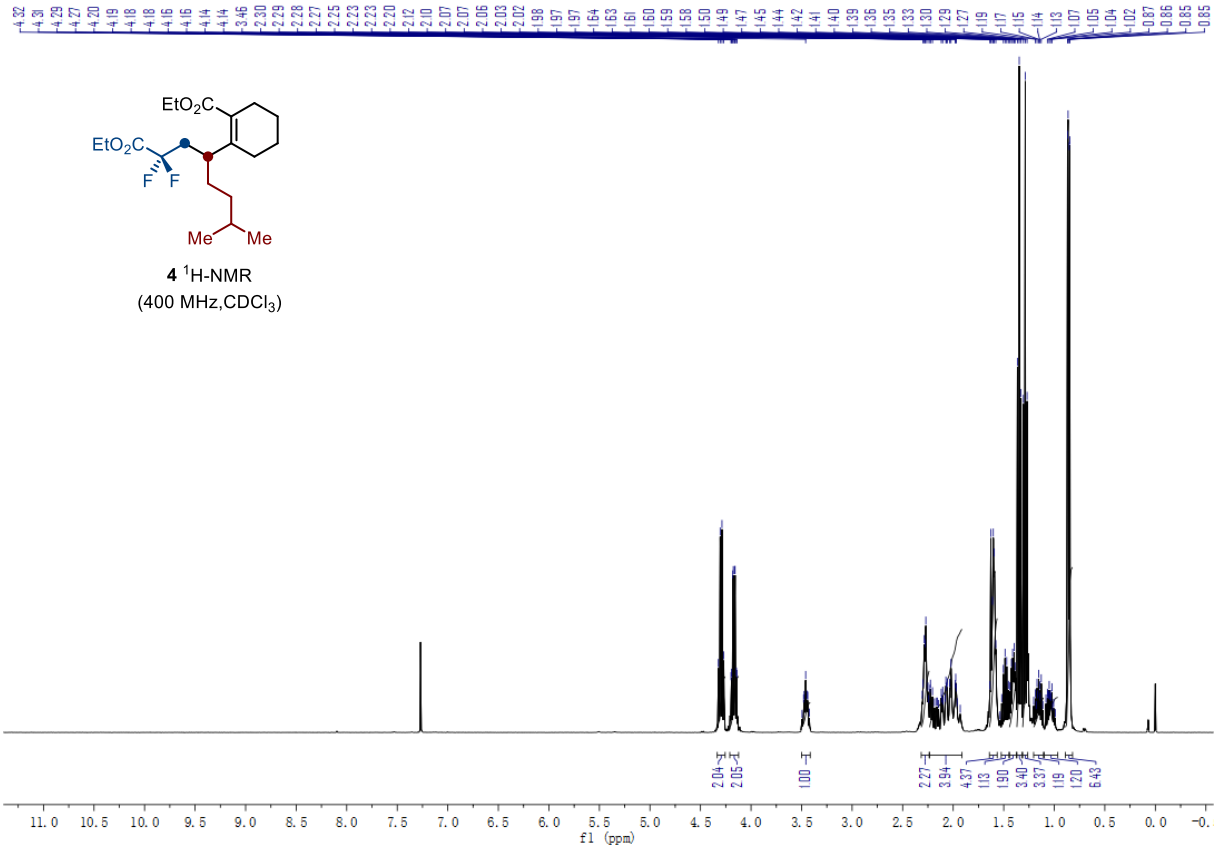

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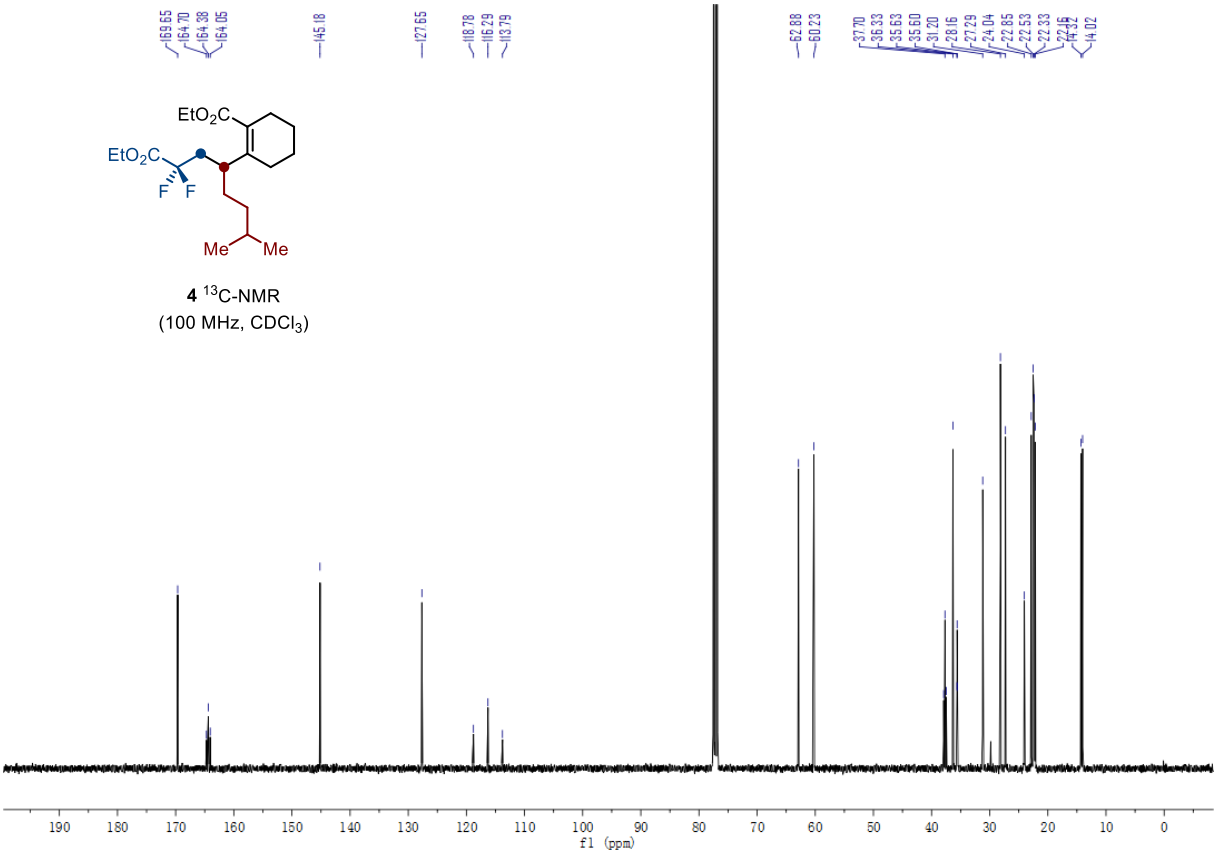

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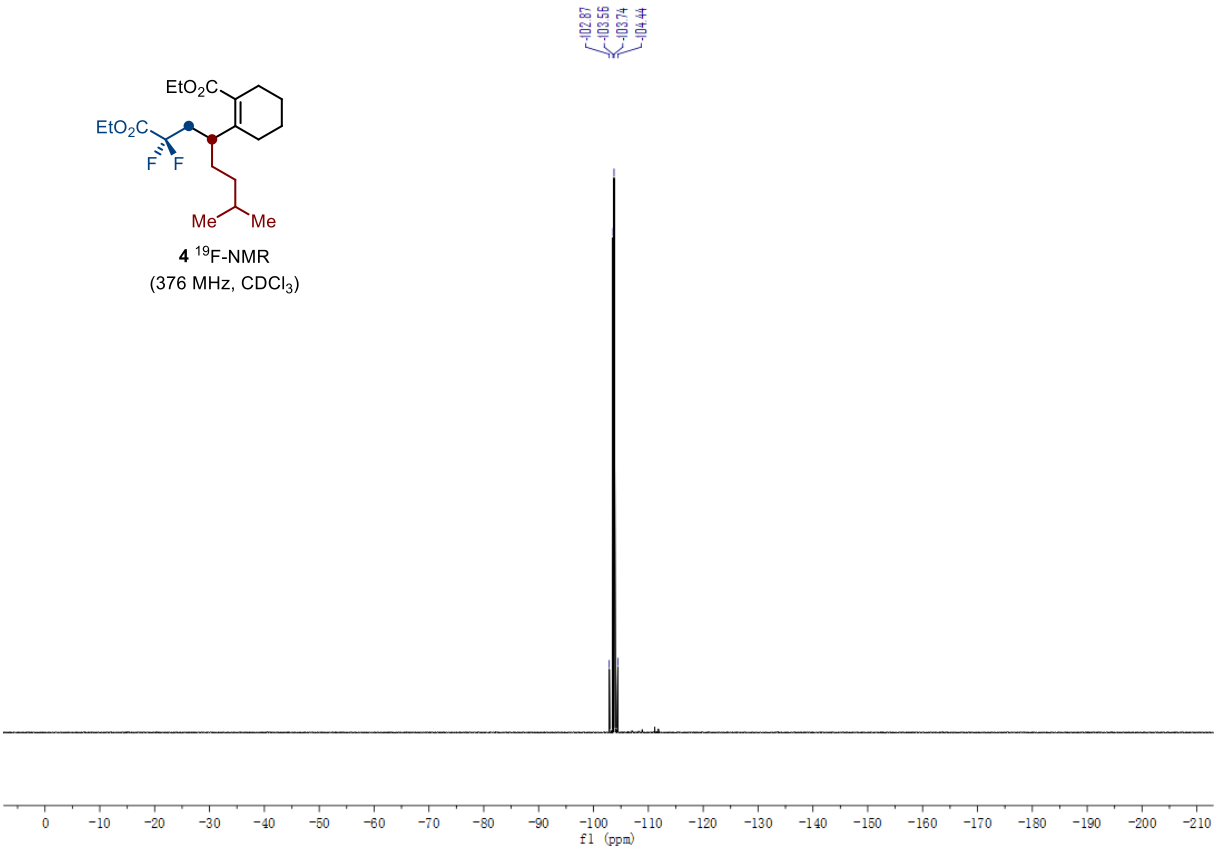
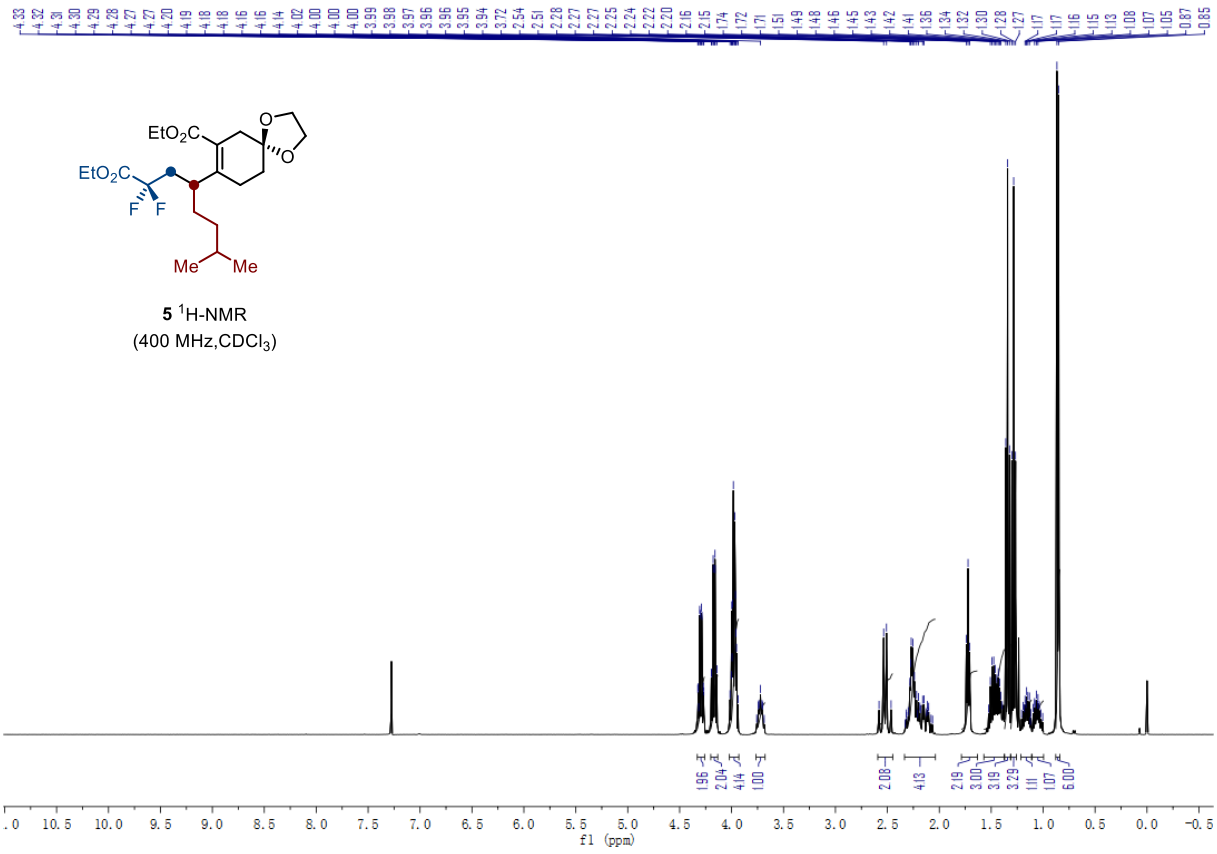
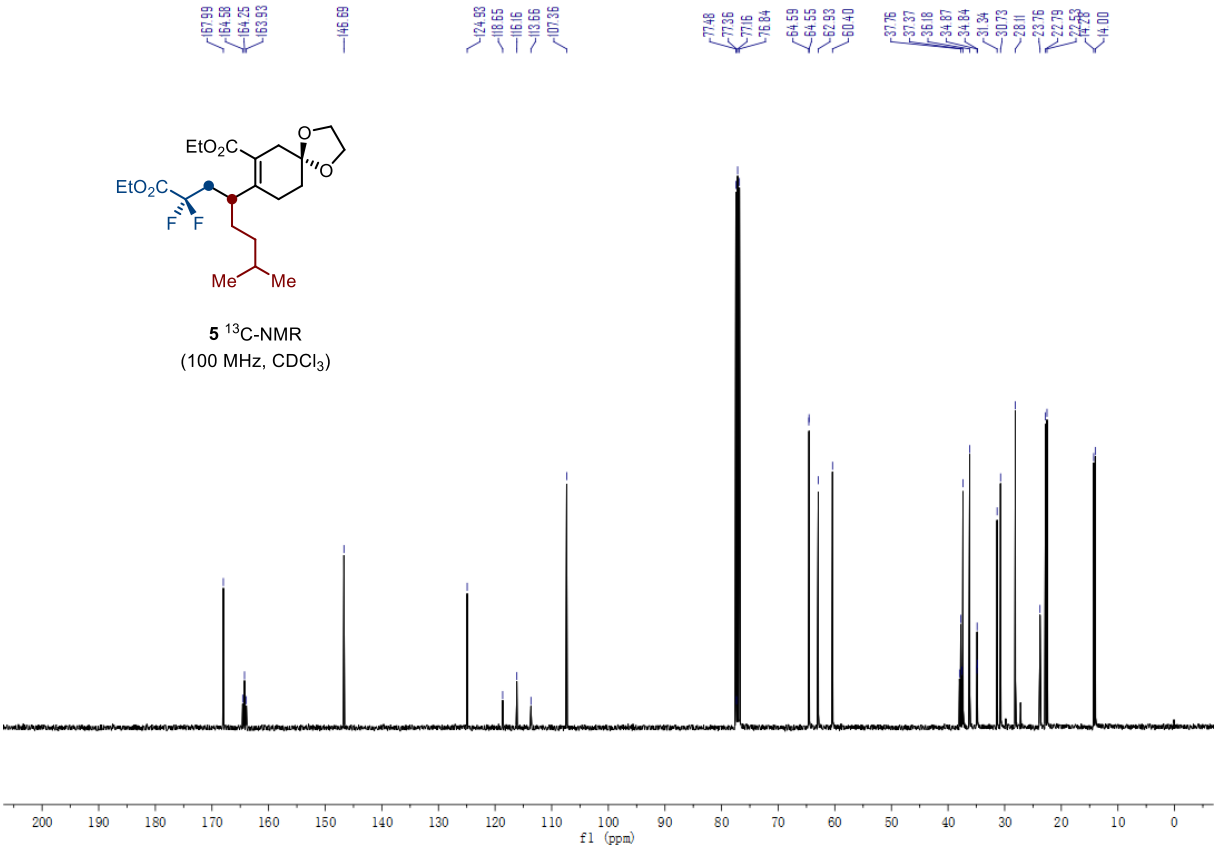


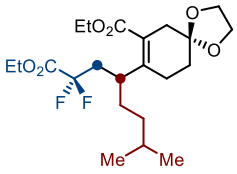
4 ^{19}F-NMR
(376 MHz, $CDCl_3$)



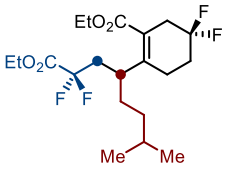
5 ^{1}H-NMR
(400 MHz,$CDCl_3$)



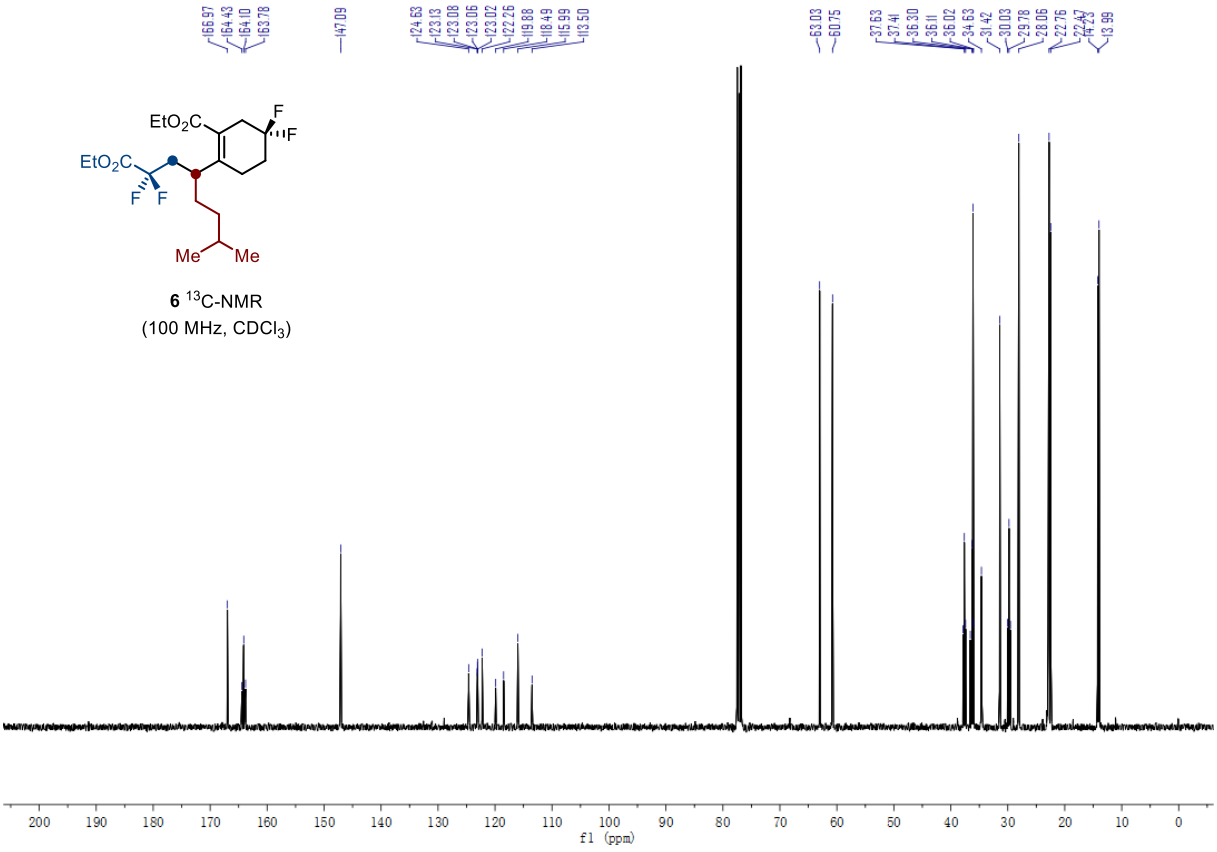
5 ^{13}C-NMR
(100 MHz, $CDCl_3$)



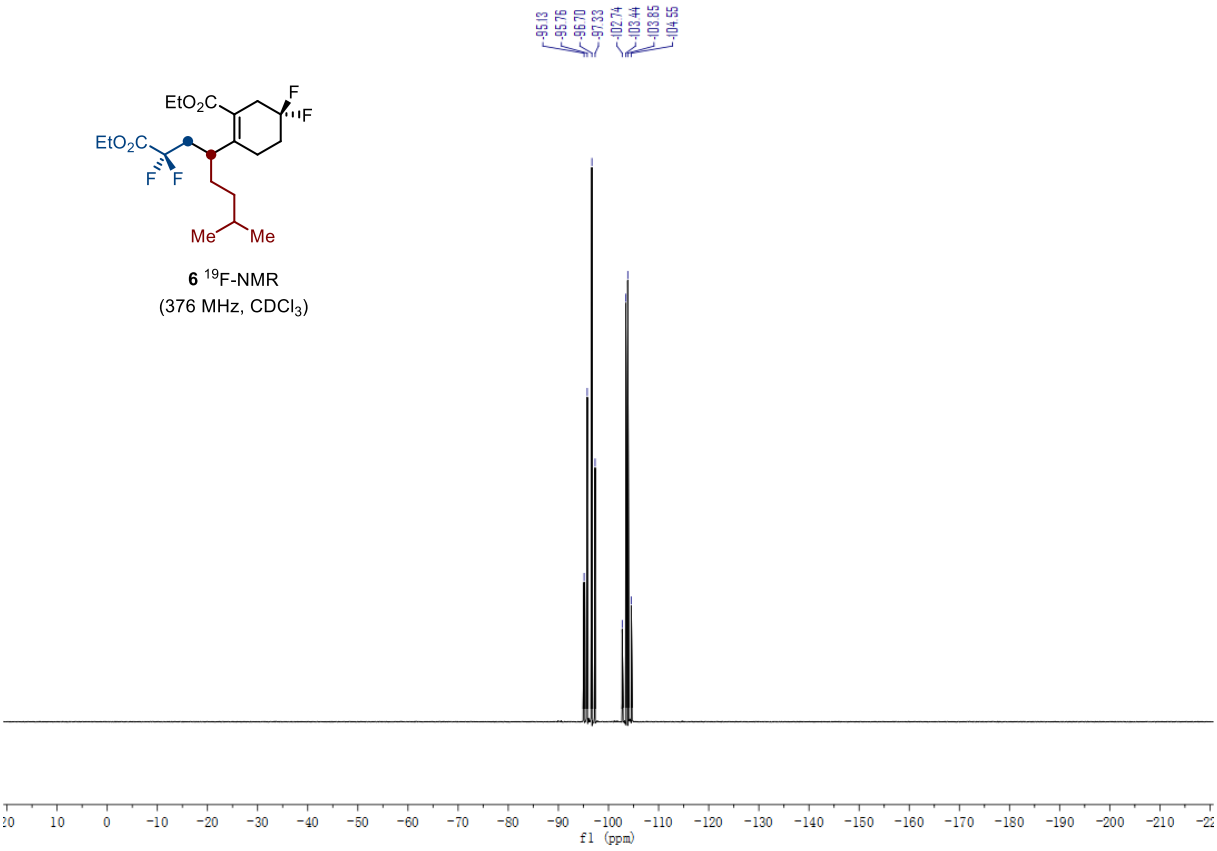
5 ^{19}F-NMR
(376 MHz, $CDCl_3$)



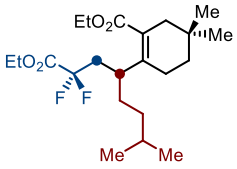
6 ^{1}H-NMR
(400 MHz,$CDCl_3$)



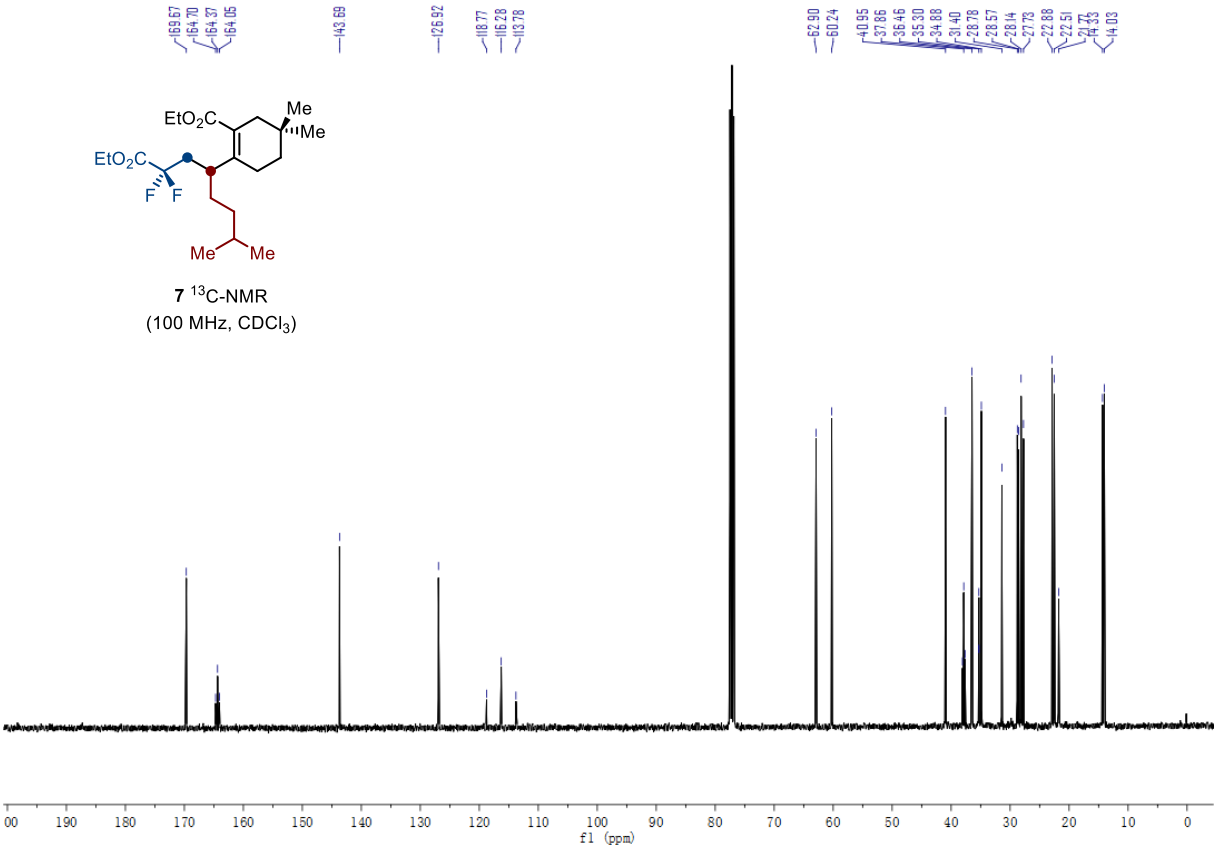
6 ^{13}C-NMR
(100 MHz, $CDCl_3$)



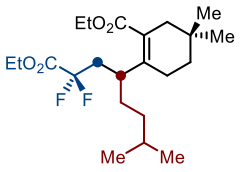
6 ^{19}F-NMR
(376 MHz, $CDCl_3$)



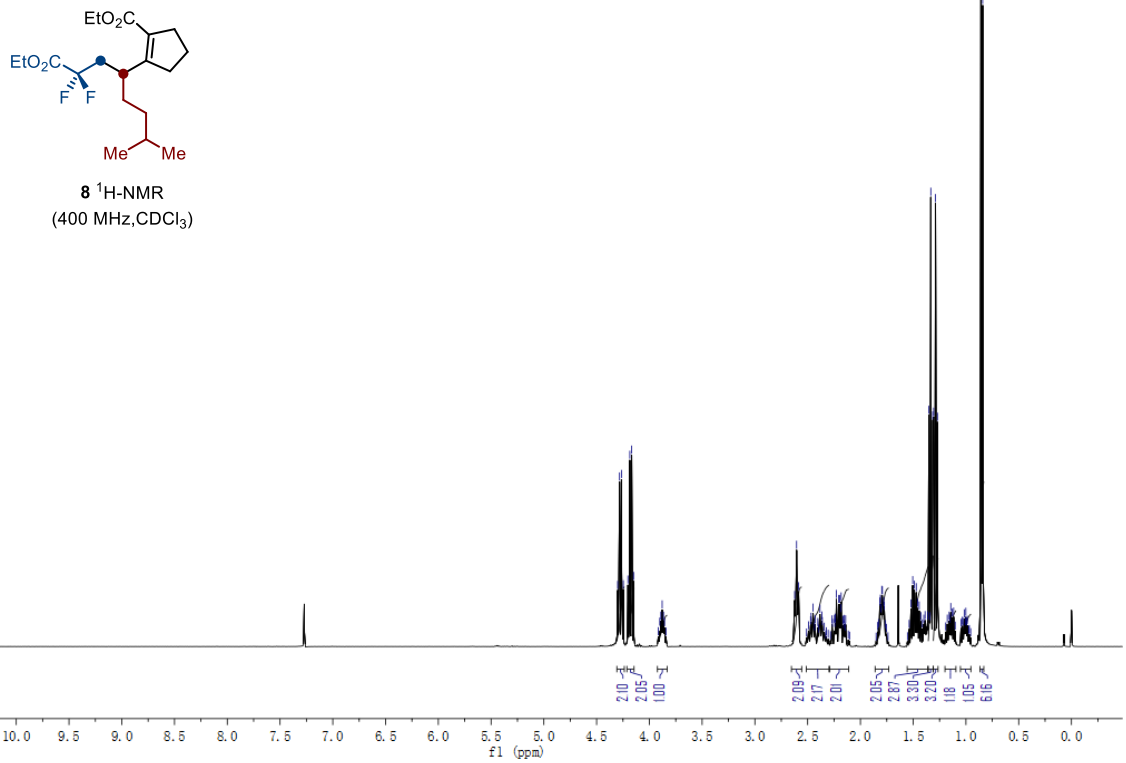
7 ^{1}H-NMR
(400 MHz,$CDCl_3$)



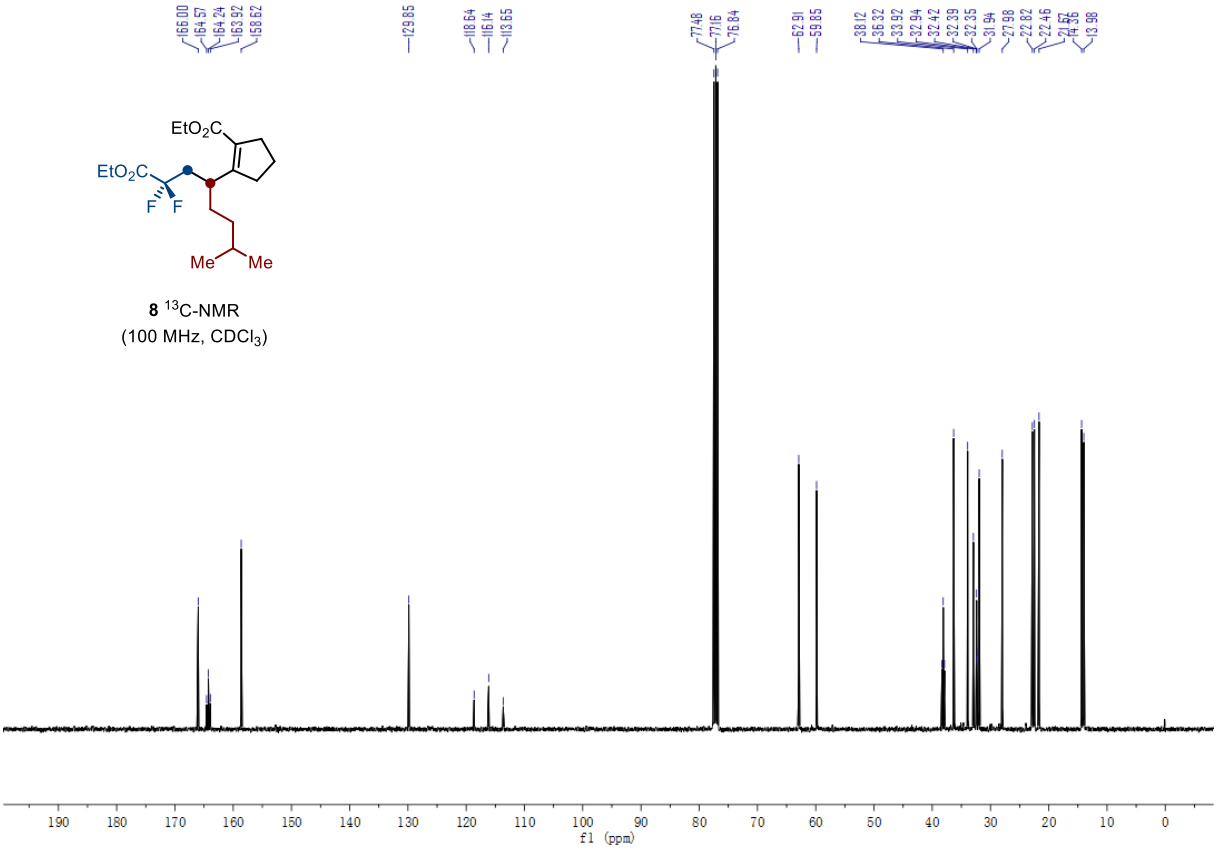
7 ^{13}C-NMR
(100 MHz, $CDCl_3$)



7 ^{19}F-NMR
(376 MHz, $CDCl_3$)

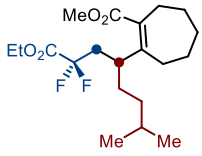


8 ^{1}H-NMR
(400 MHz,$CDCl_3$)

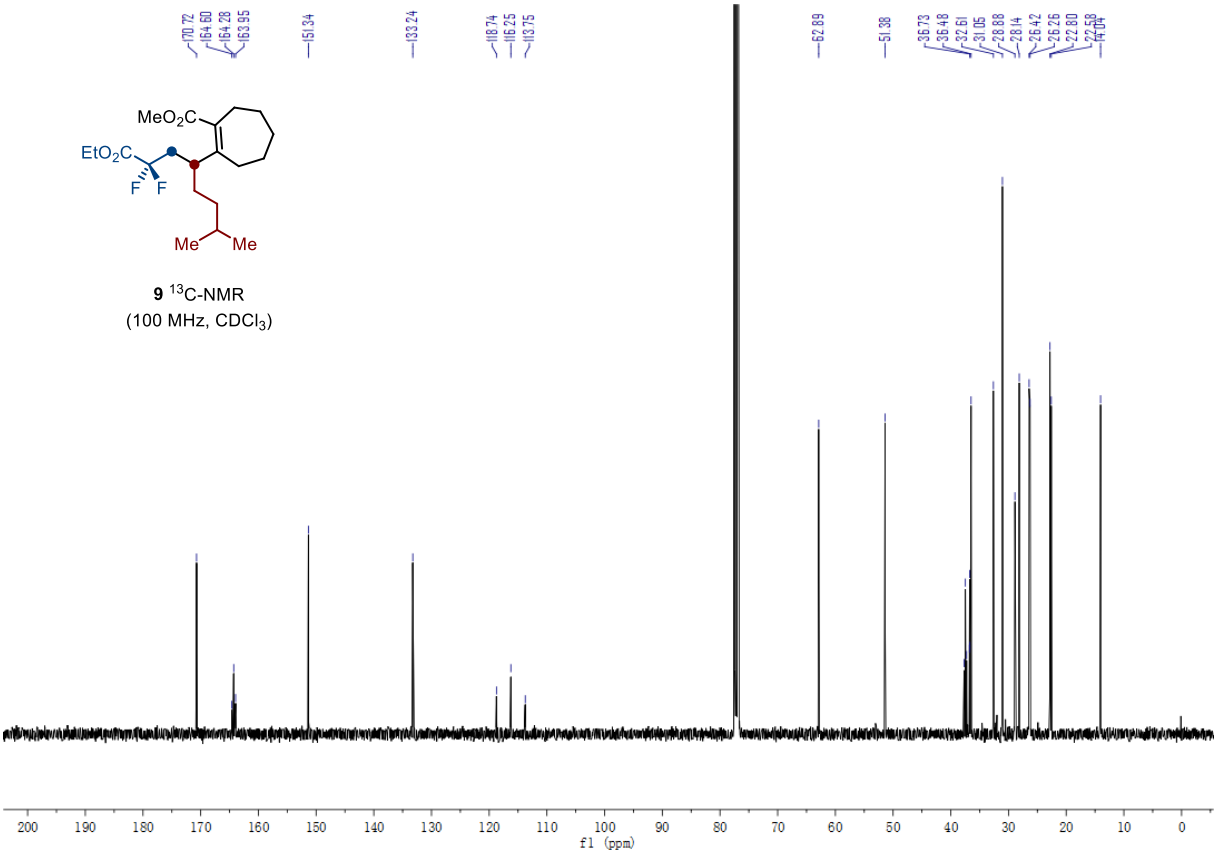


8 ^{13}C-NMR
(100 MHz, $CDCl_3$)

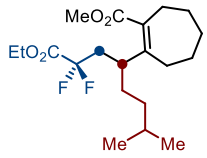
8 ^{19}F-NMR
(376 MHz, $CDCl_3$)



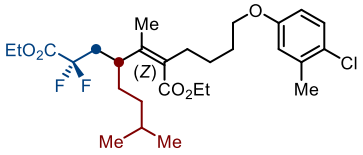
9 ^{1}H-NMR
(400 MHz,$CDCl_3$)



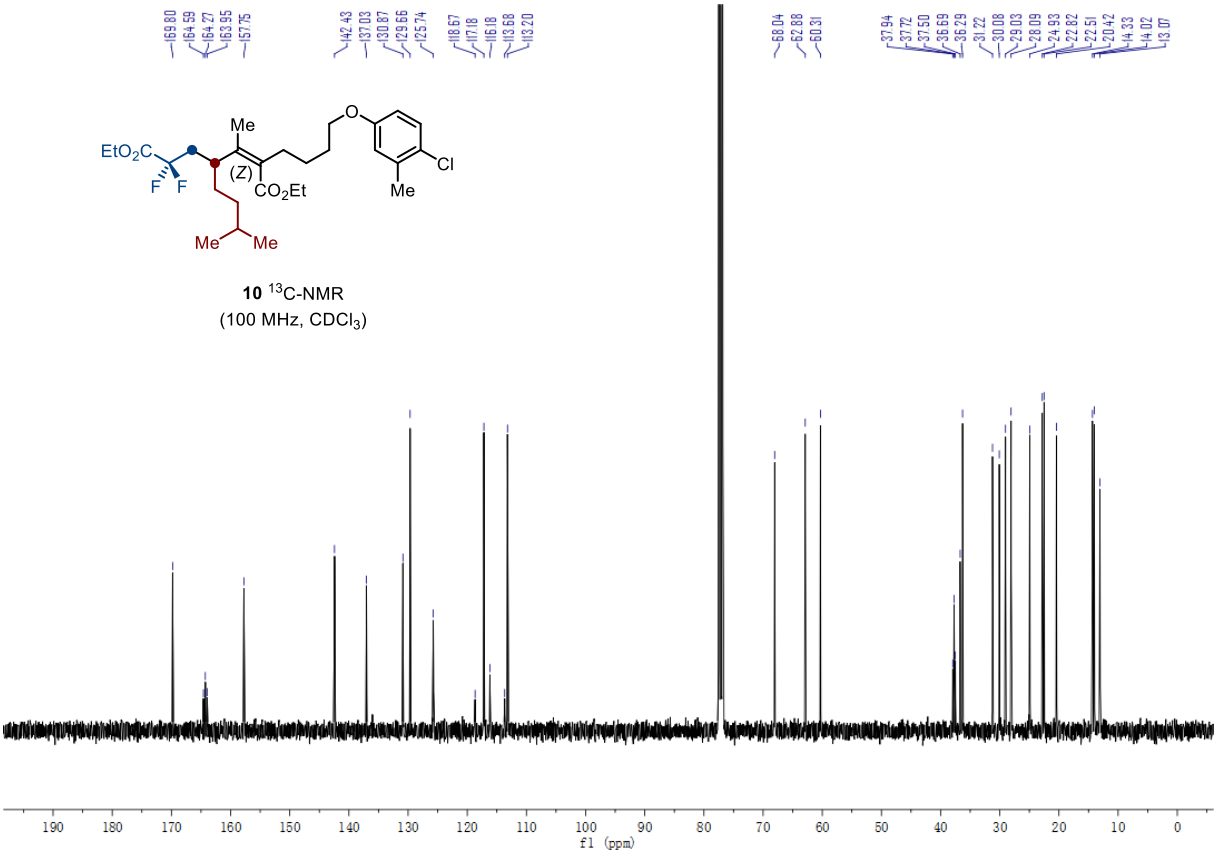
9 ^{13}C-NMR
(100 MHz, $CDCl_3$)



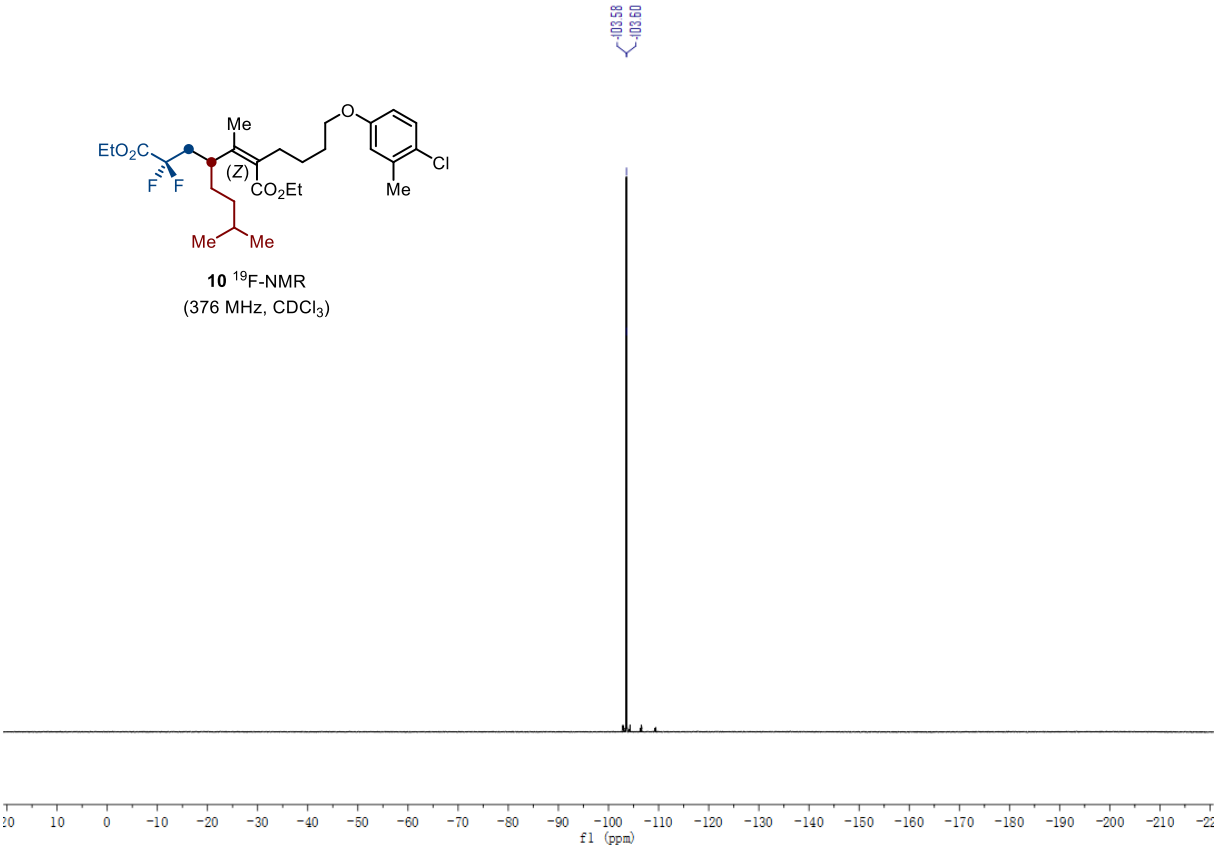
9 ^{19}F-NMR
(376 MHz, $CDCl_3$)



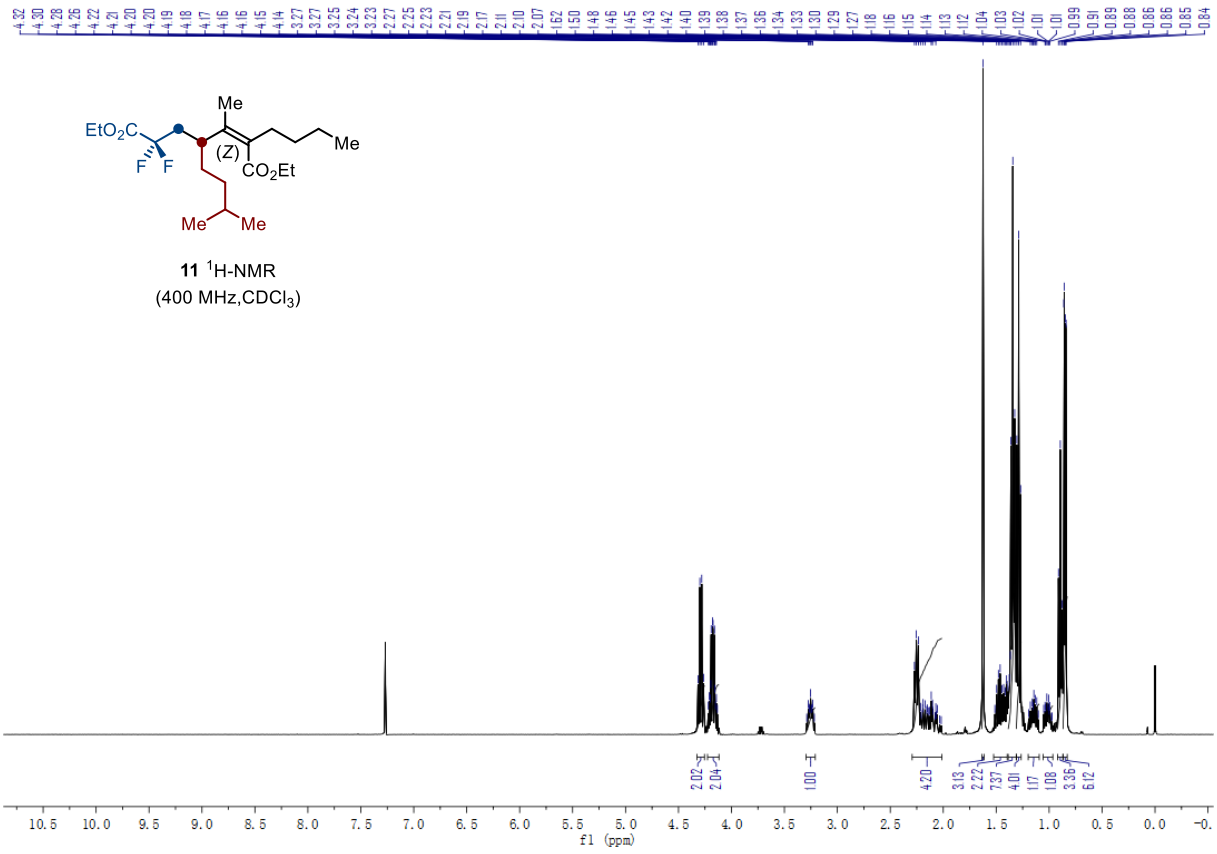
10 ^{1}H-NMR
(400 MHz,$CDCl_3$)



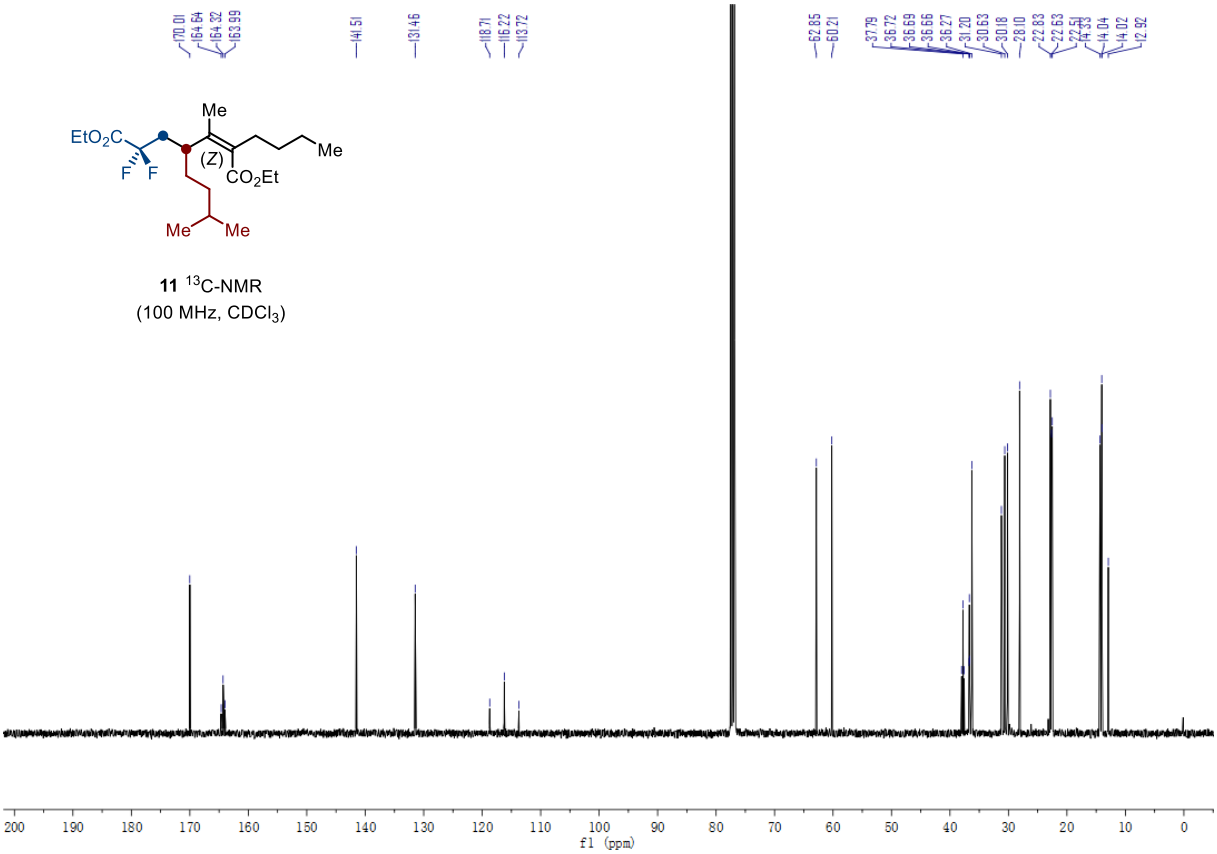
10 ^{13}C-NMR
(100 MHz, $CDCl_3$)



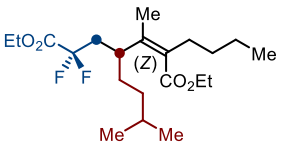
10 ^{19}F-NMR
(376 MHz, $CDCl_3$)



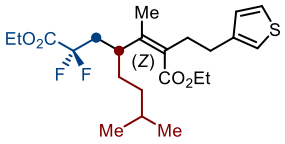
11 ^{1}H-NMR
(400 MHz,$CDCl_3$)



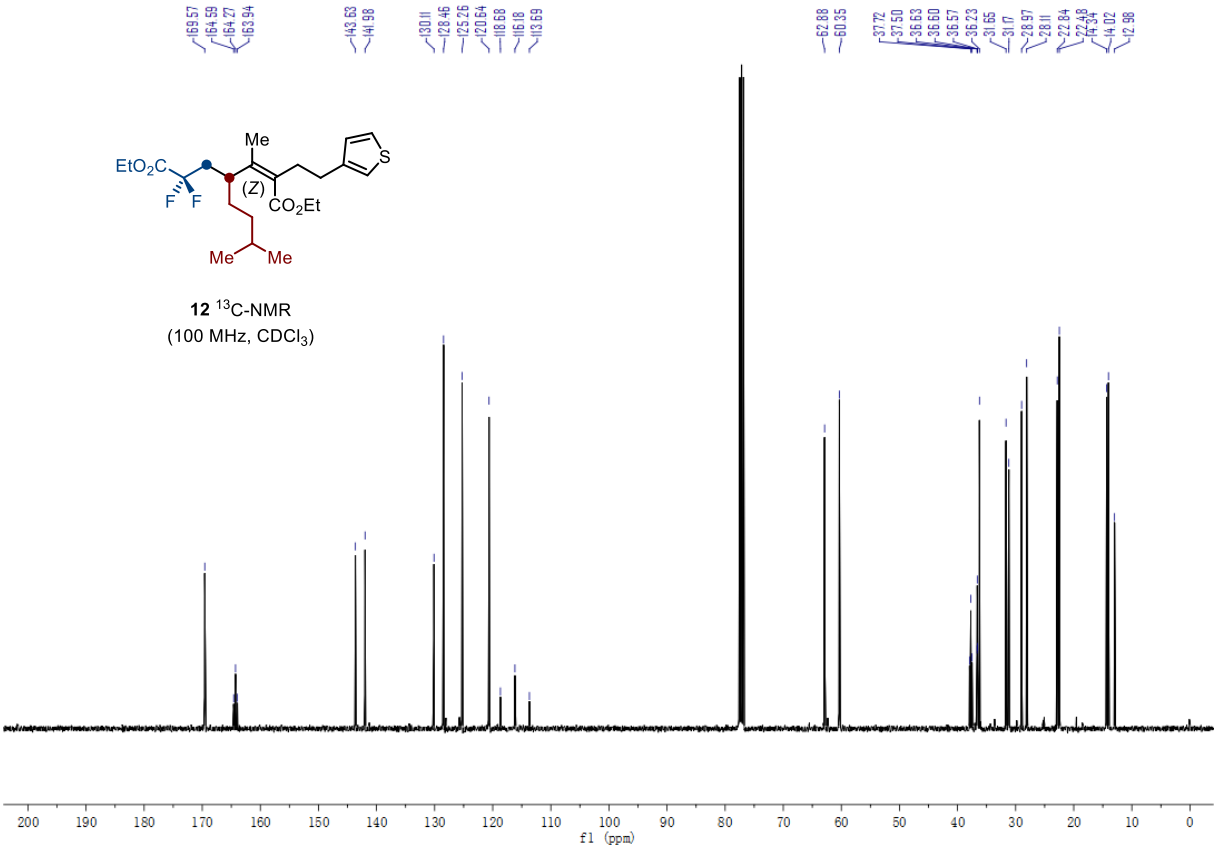
11 ^{13}C-NMR
(100 MHz, $CDCl_3$)



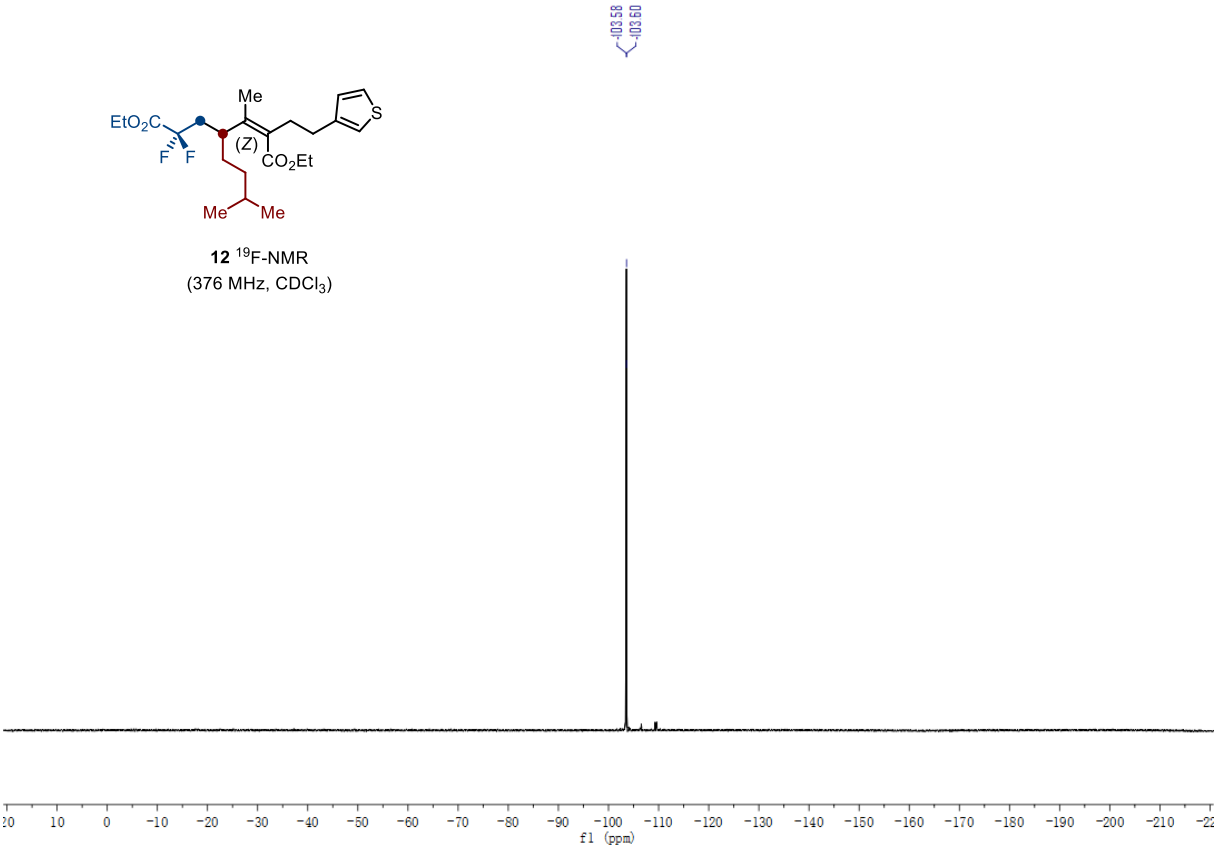
11 ^{19}F-NMR
(376 MHz, $CDCl_3$)



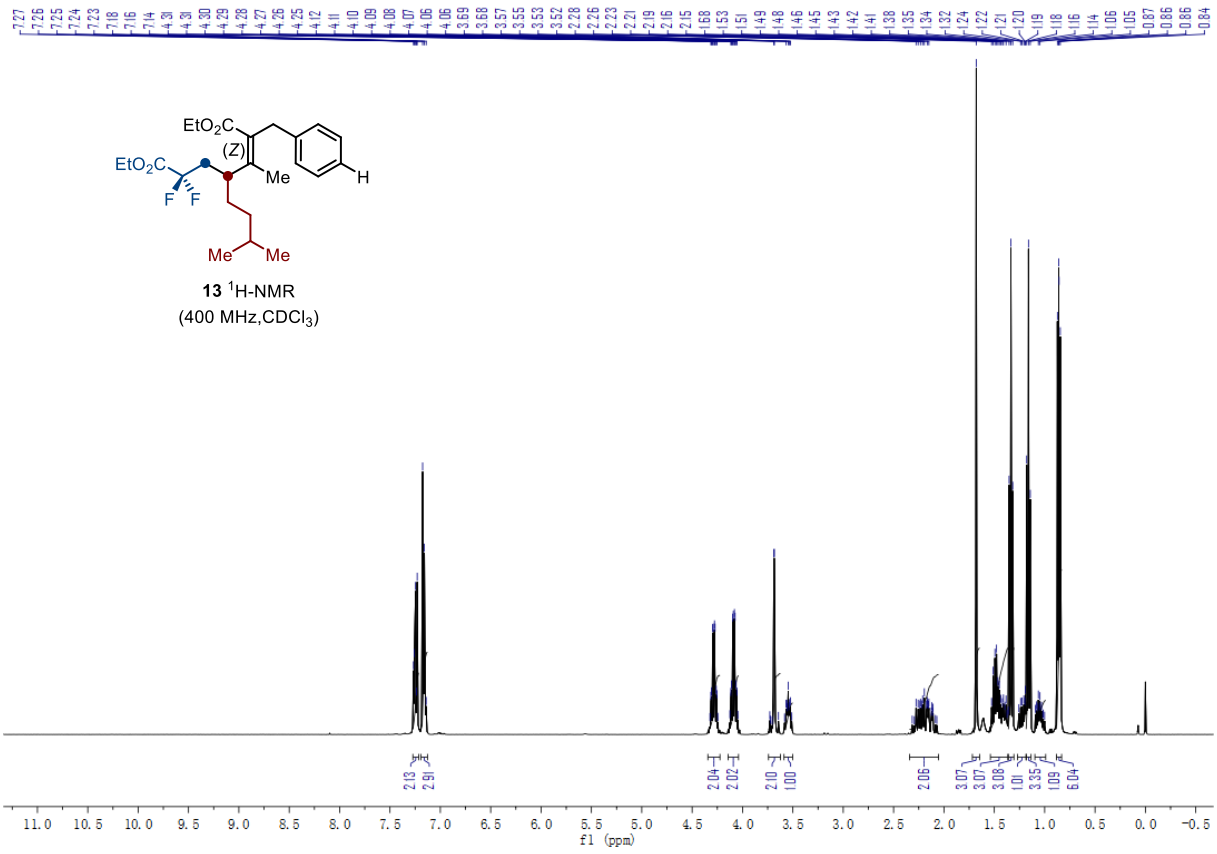
12 ^{1}H-NMR
(400 MHz,$CDCl_3$)



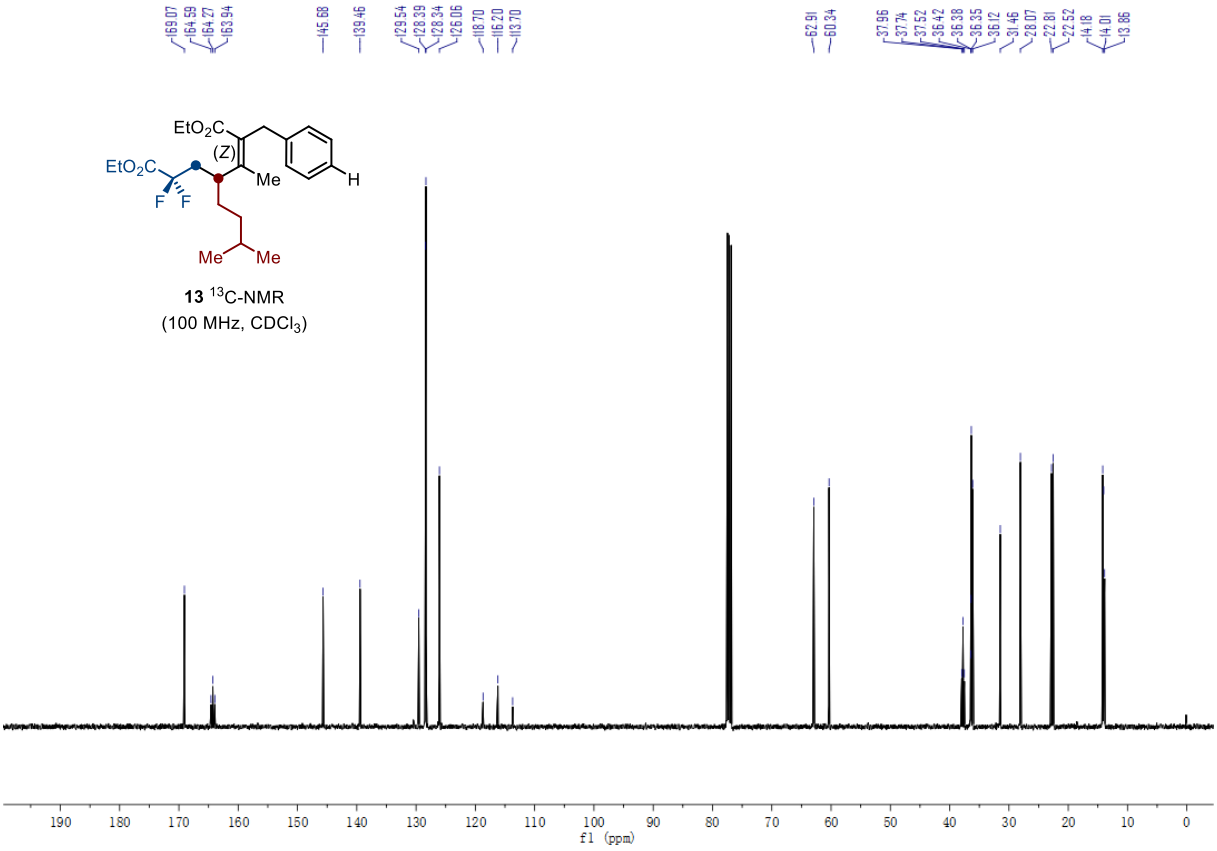
12 ^{13}C-NMR
(100 MHz, $CDCl_3$)



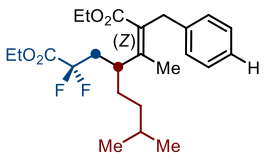
12 ^{19}F-NMR
(376 MHz, $CDCl_3$)



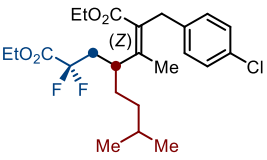
13 ^{1}H-NMR
(400 MHz,$CDCl_3$)



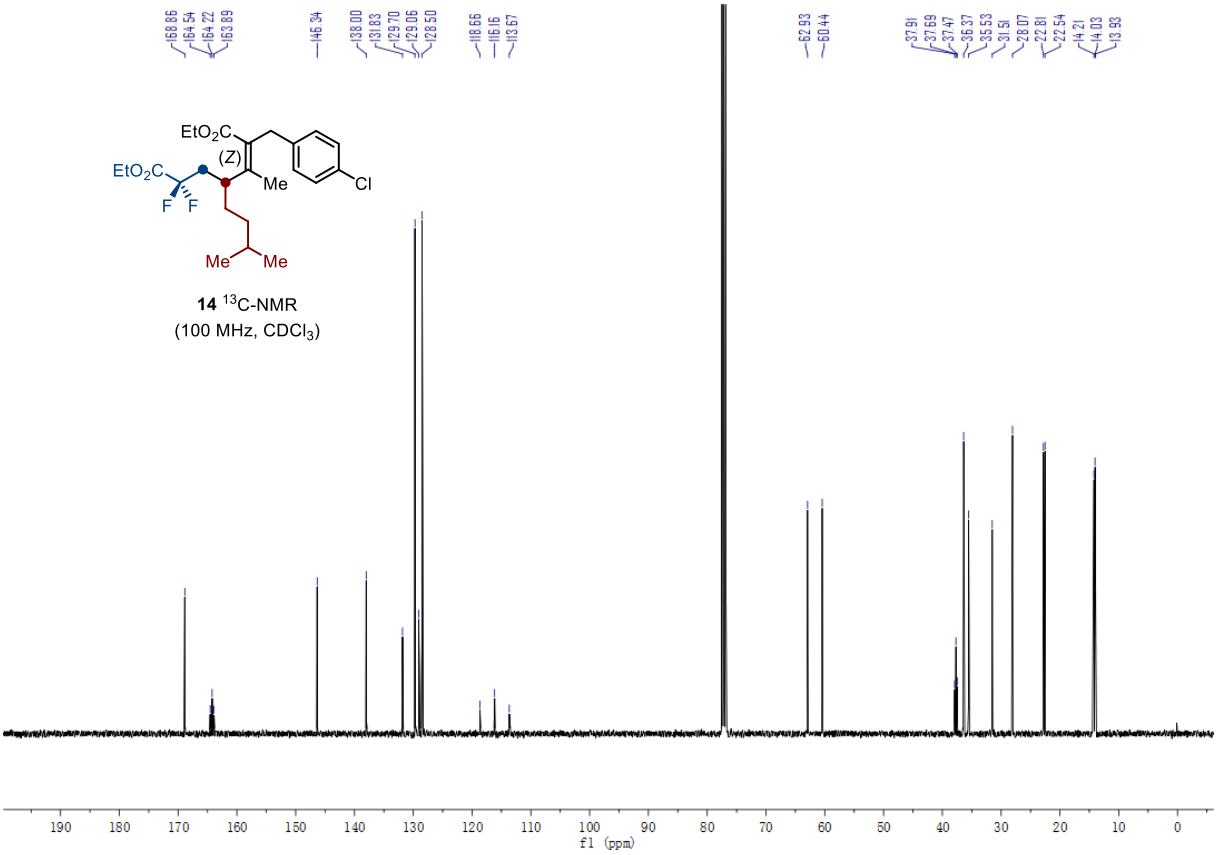
13 ^{13}C-NMR
(100 MHz, $CDCl_3$)



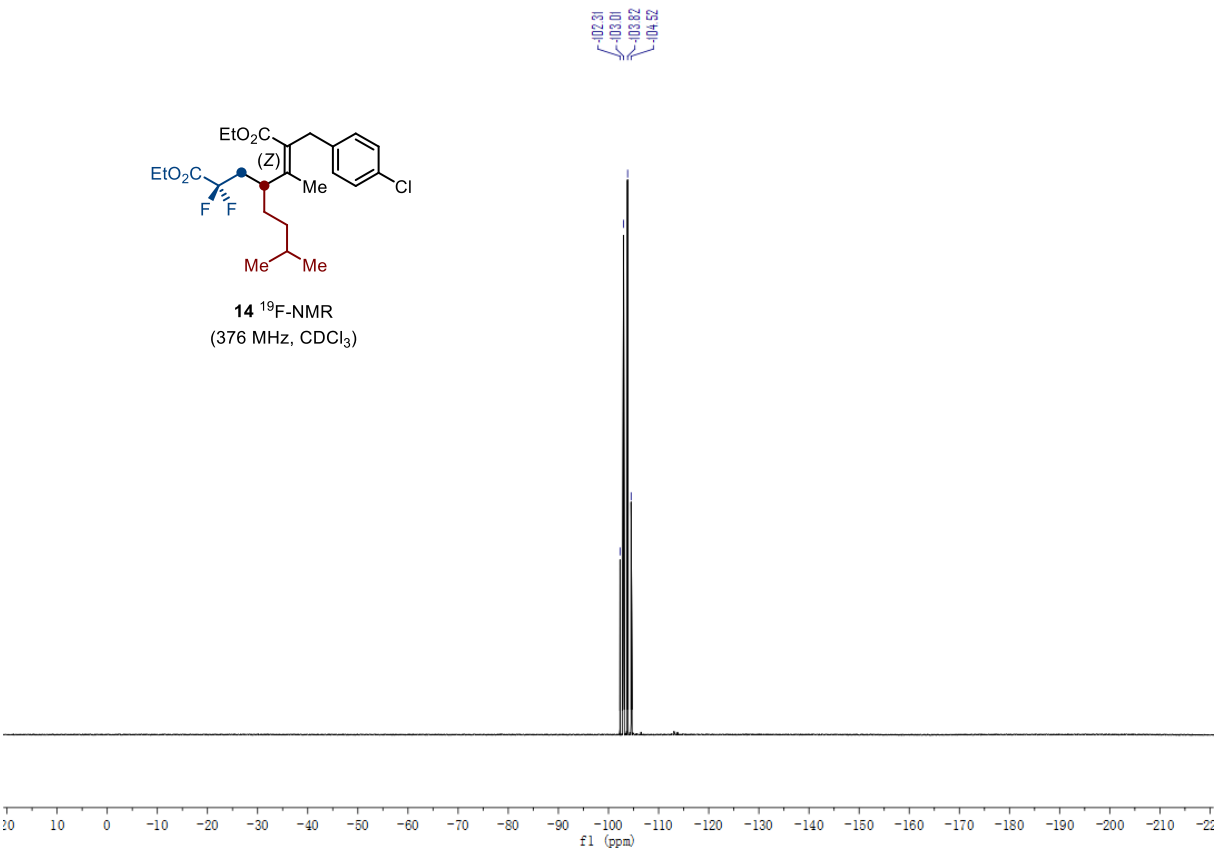
13 ^{19}F-NMR
(376 MHz, $CDCl_3$)



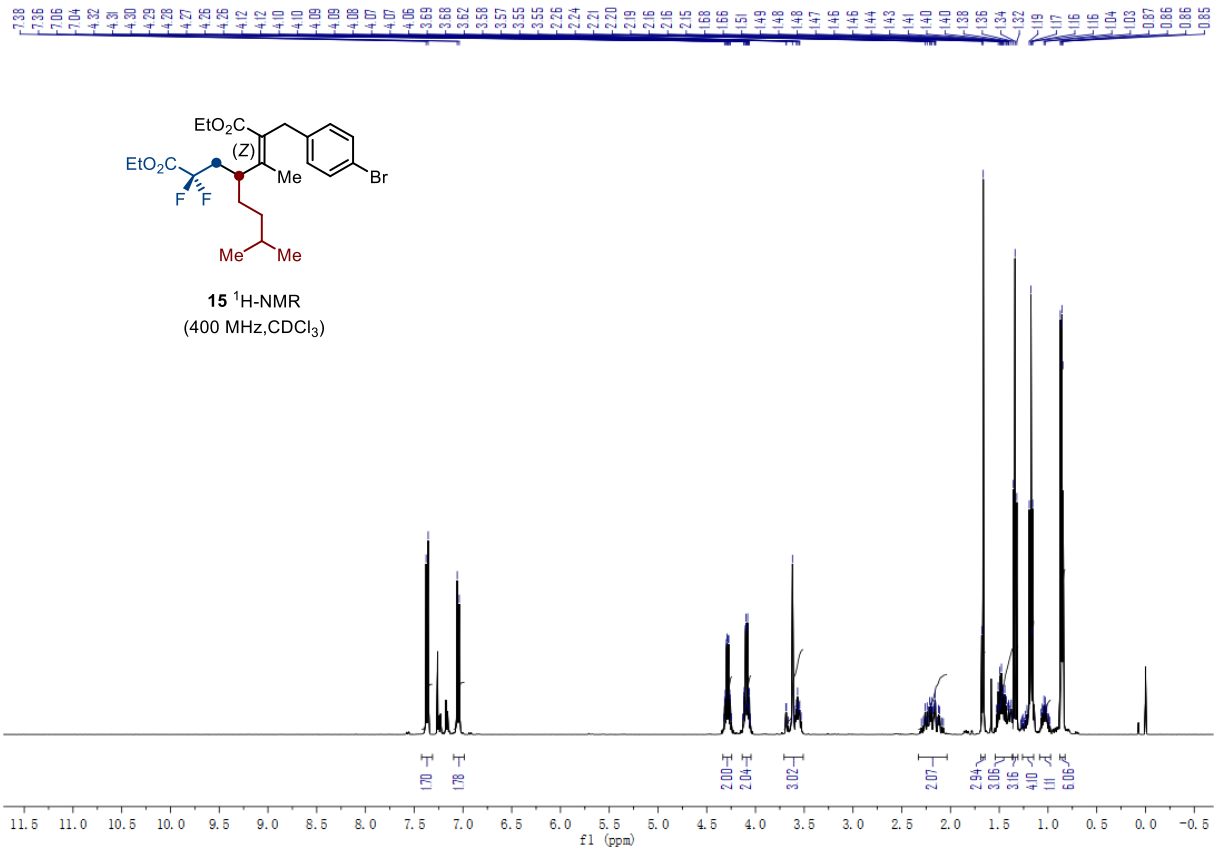
14 ^{1}H-NMR
(400 MHz,$CDCl_3$)



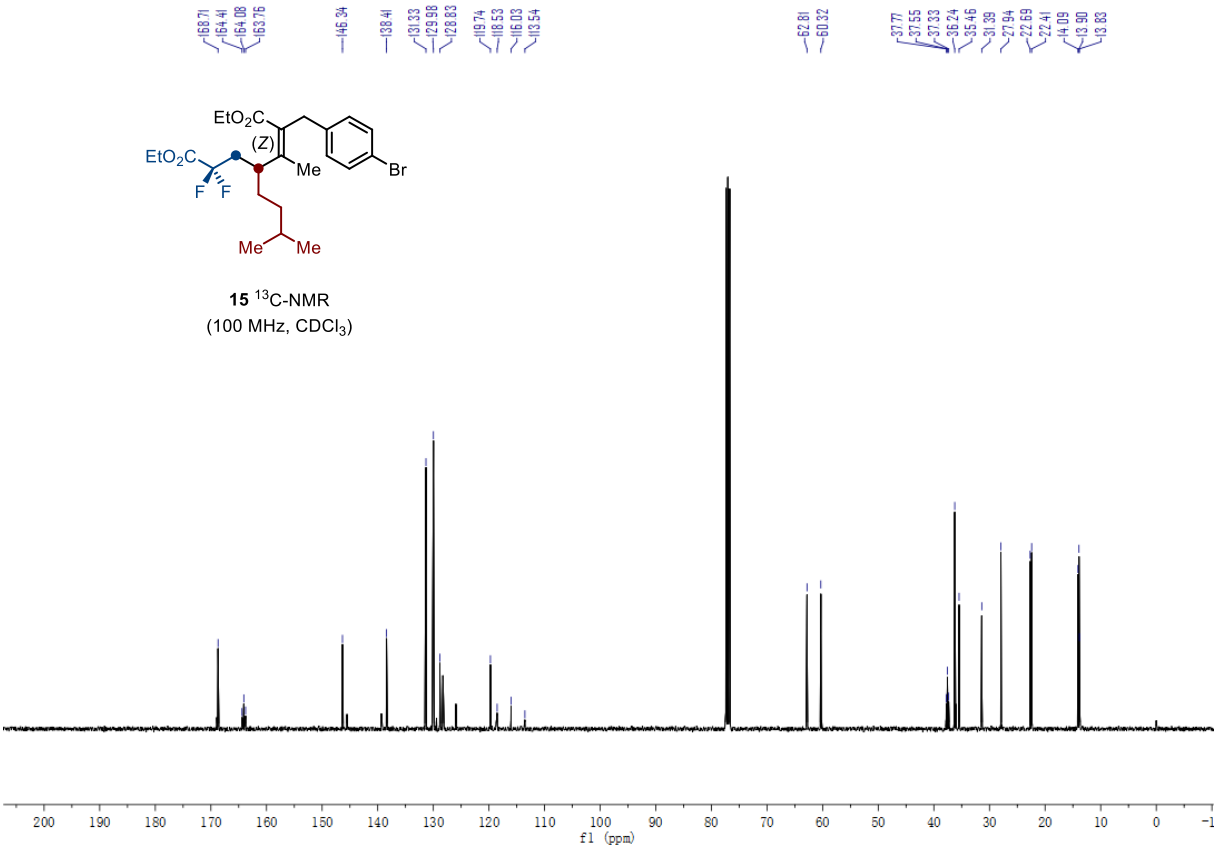
14 ^{13}C-NMR
(100 MHz, $CDCl_3$)



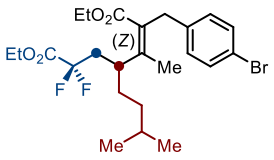
14 ^{19}F-NMR
(376 MHz, $CDCl_3$)



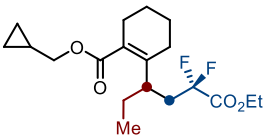
15 ^{1}H-NMR
(400 MHz,$CDCl_3$)



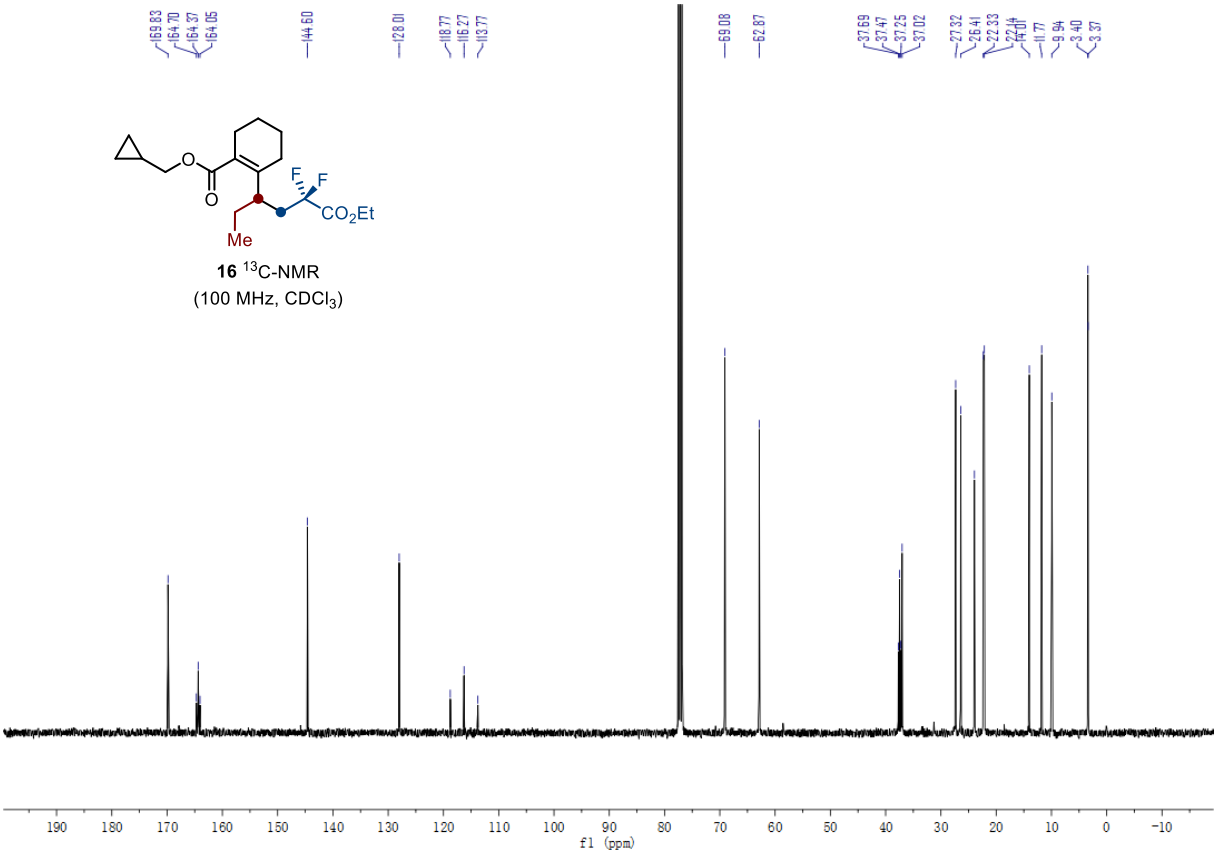
15 ^{13}C-NMR
(100 MHz, $CDCl_3$)



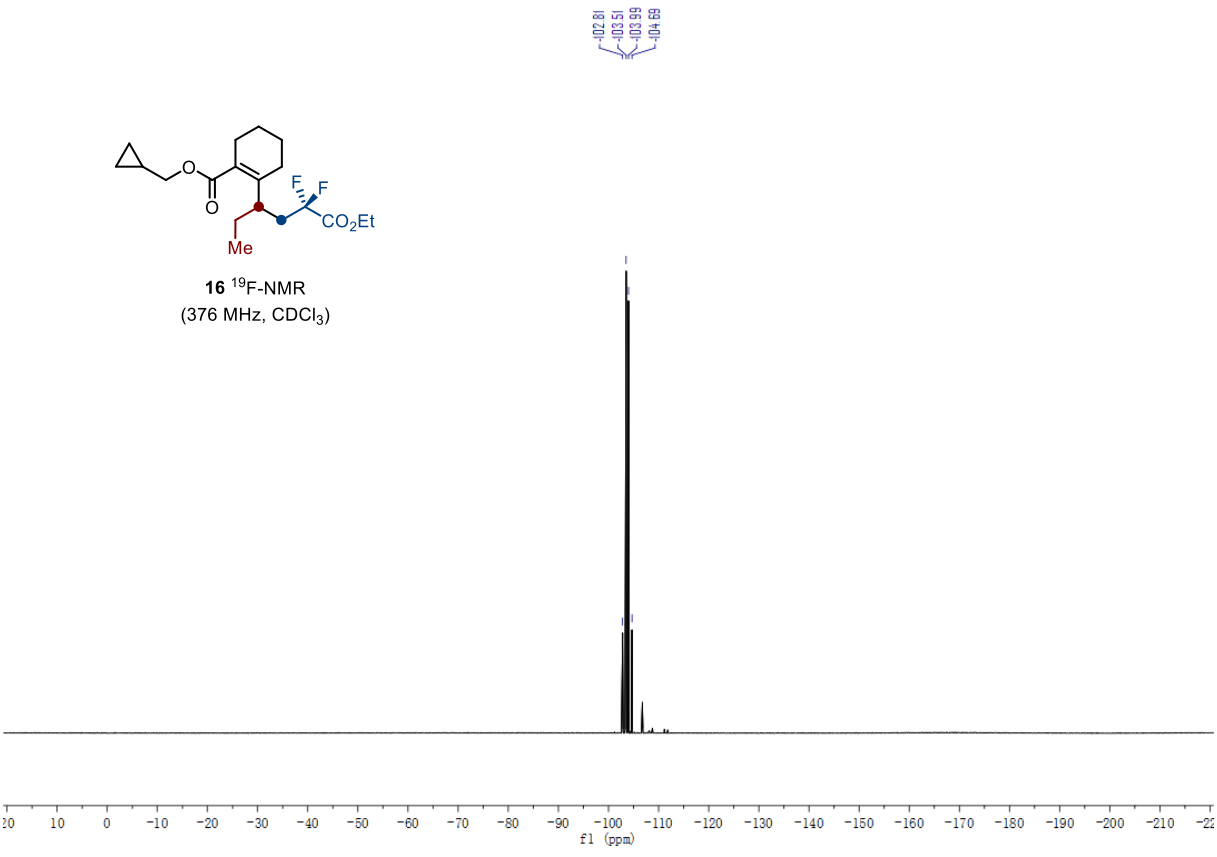
15 ^{19}F-NMR
(376 MHz, $CDCl_3$)



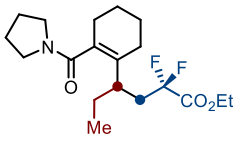
16 ^{1}H-NMR
(400 MHz,$CDCl_3$)



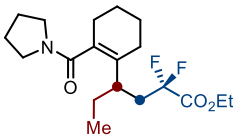
16 ^{13}C-NMR
(100 MHz, $CDCl_3$)



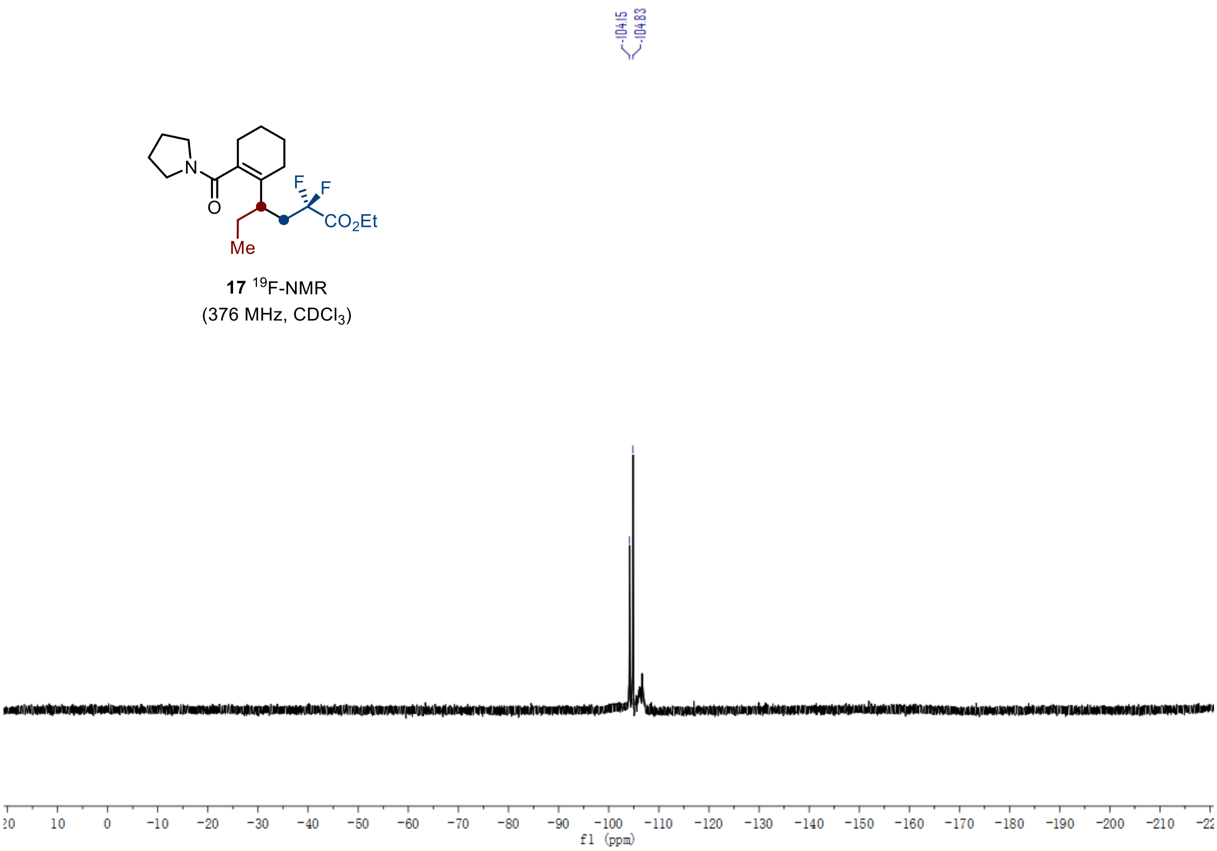
16 ^{19}F-NMR
(376 MHz, $CDCl_3$)

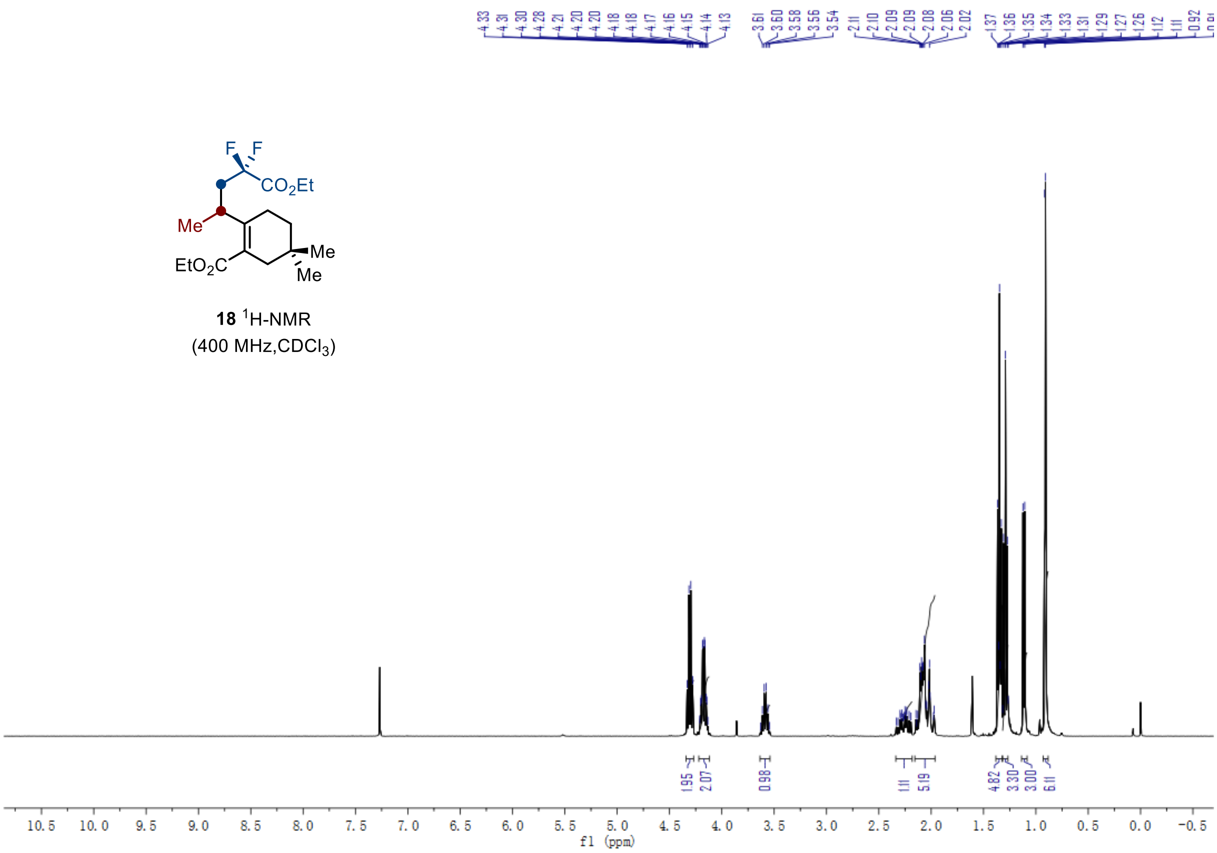


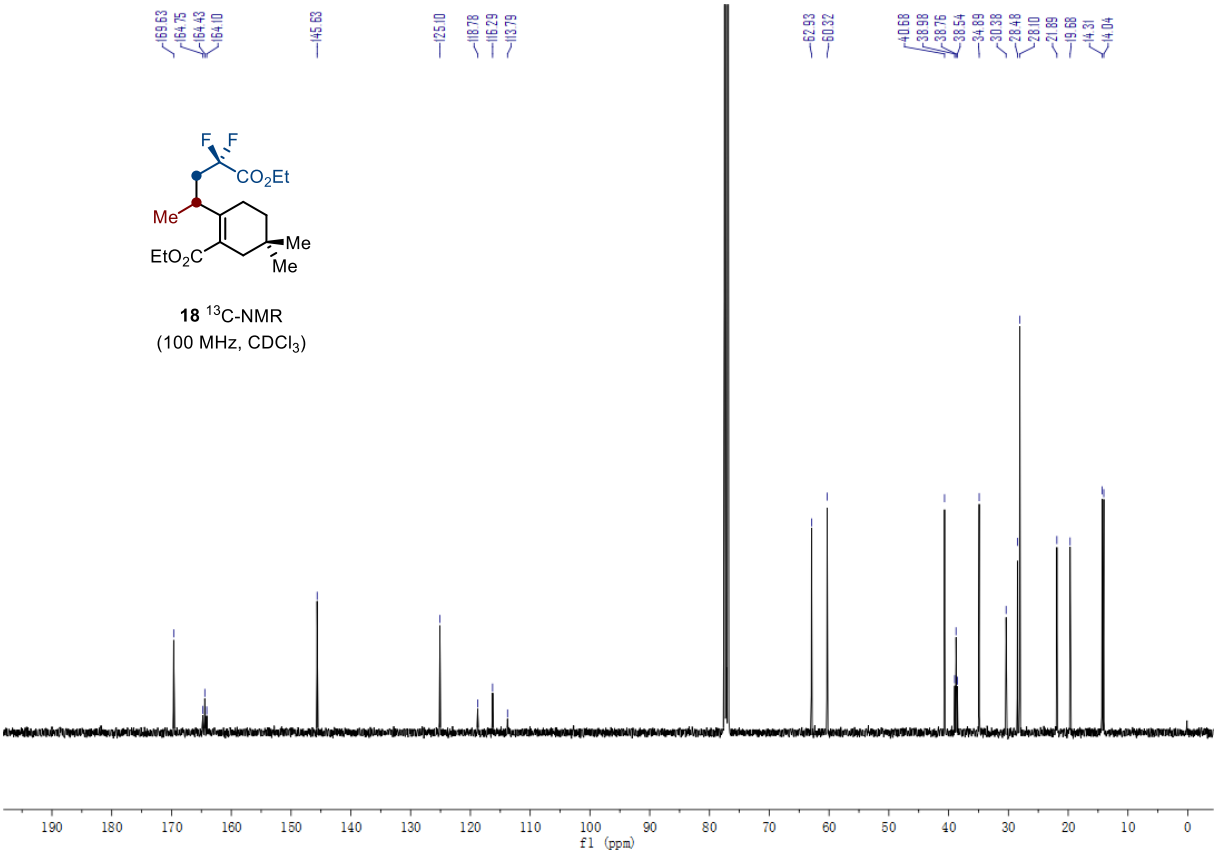
17 ^{1}H-NMR
(400 MHz,$CDCl_3$)



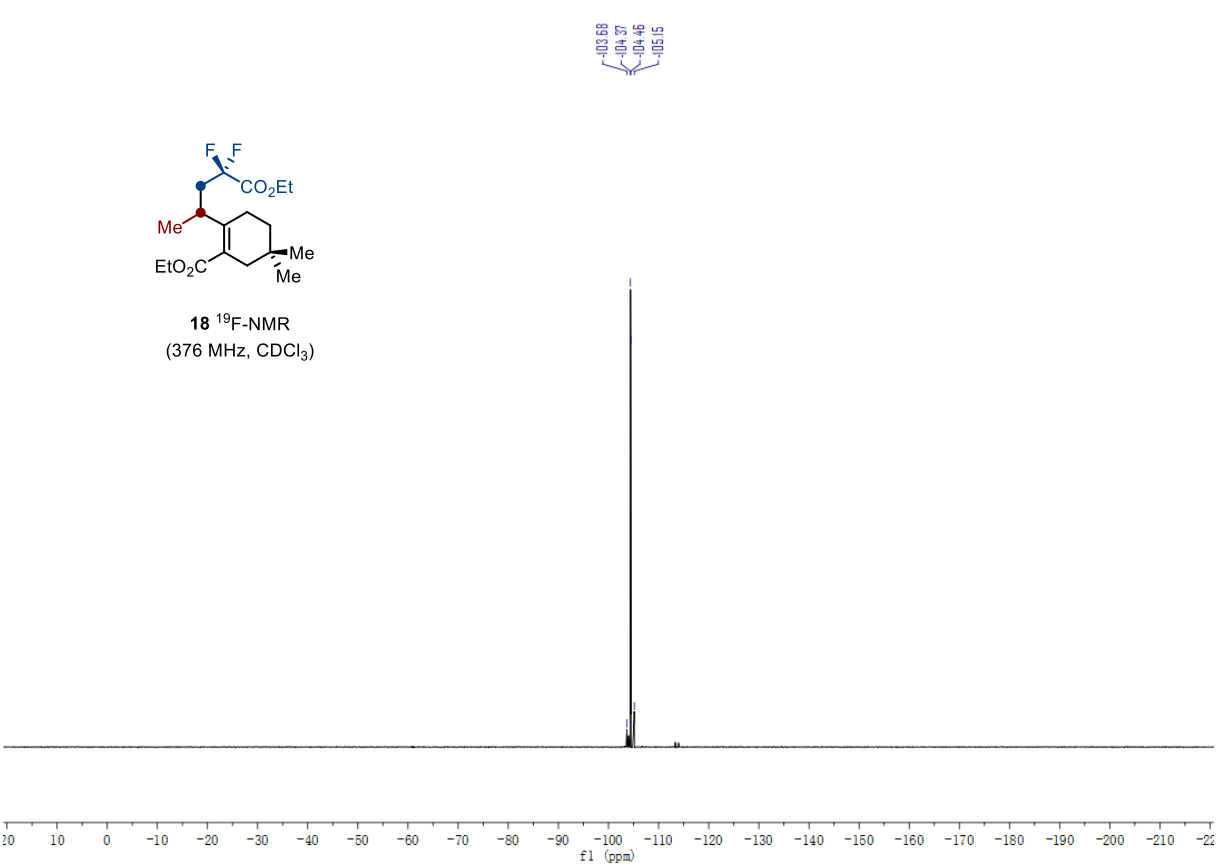
17 ^{13}C-NMR
(100 MHz, $CDCl_3$)


F
F
N
O
CO2Et
Me
17 19F-NMR
(376 MHz, CDCl3)
-104.15
-104.83
f1 (ppm)

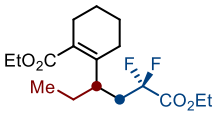

F
F
CO2Et
Me
EtO2C
Me
Me
18 1H-NMR
(400 MHz,CDCl3)
1.95
2.07
0.98
1.11
5.19
4.82
3.30
3.00
6.11
f1 (ppm)



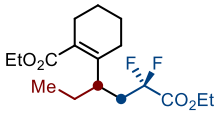
18 ^{13}C-NMR
(100 MHz, $CDCl_3$)



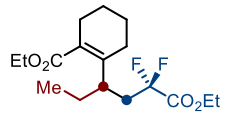
18 ^{19}F-NMR
(376 MHz, $CDCl_3$)



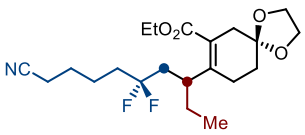
19 ^{1}H-NMR
(400 MHz,$CDCl_3$)



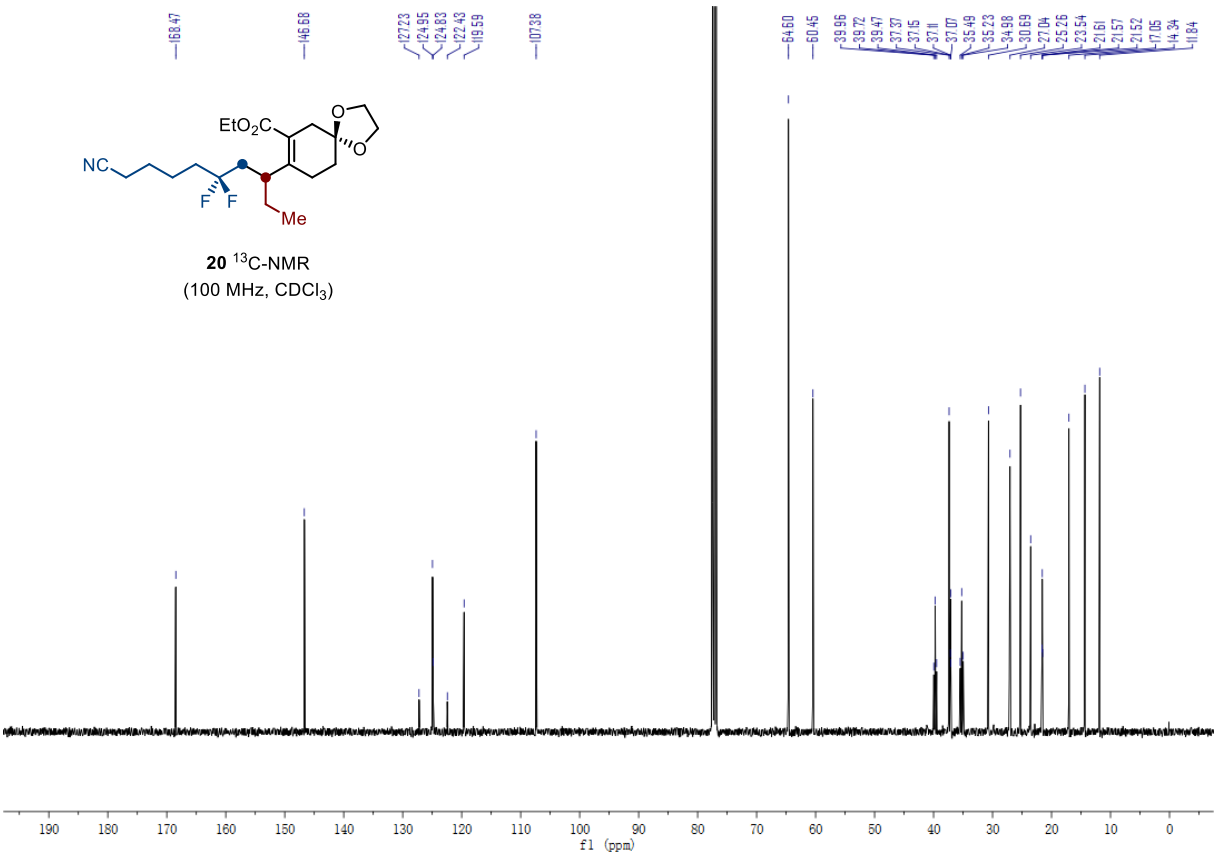
19 ^{13}C-NMR
(100 MHz, $CDCl_3$)



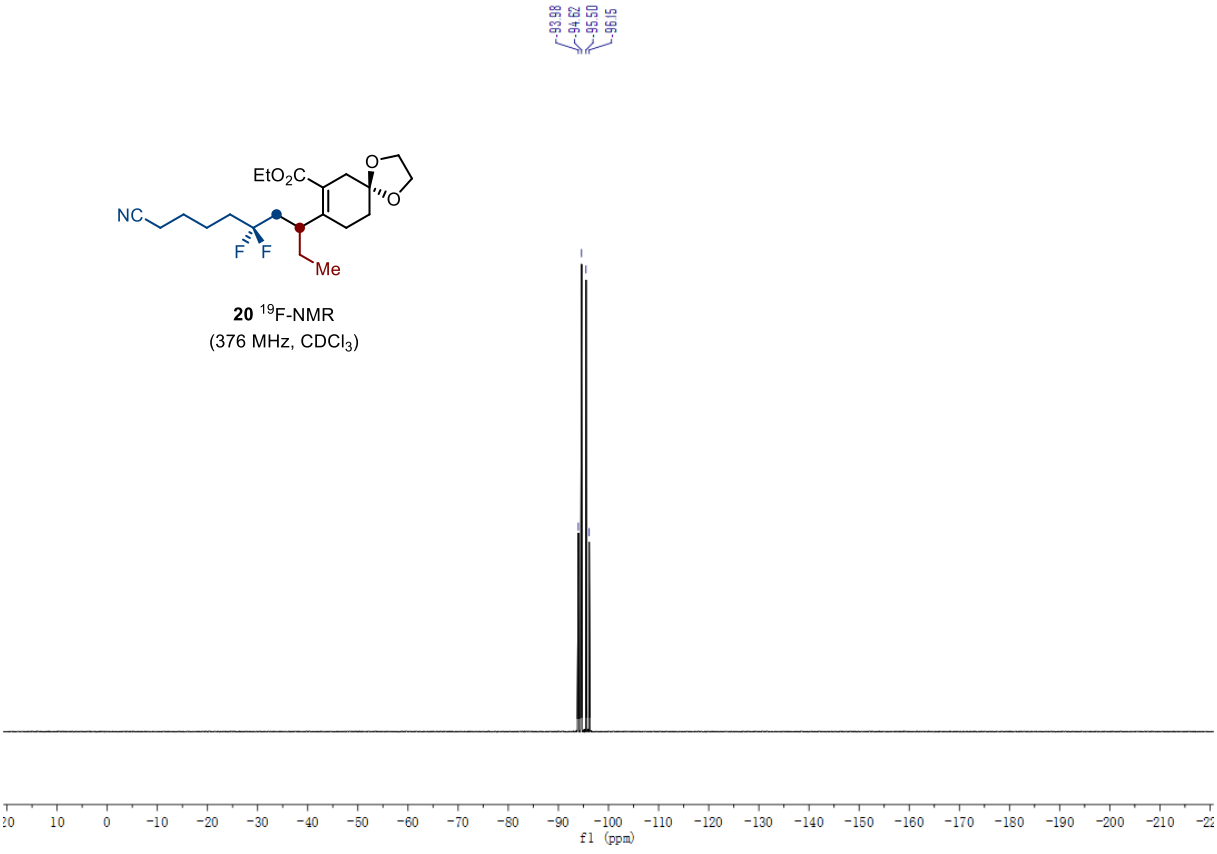
19 ^{19}F-NMR
(376 MHz, $CDCl_3$)



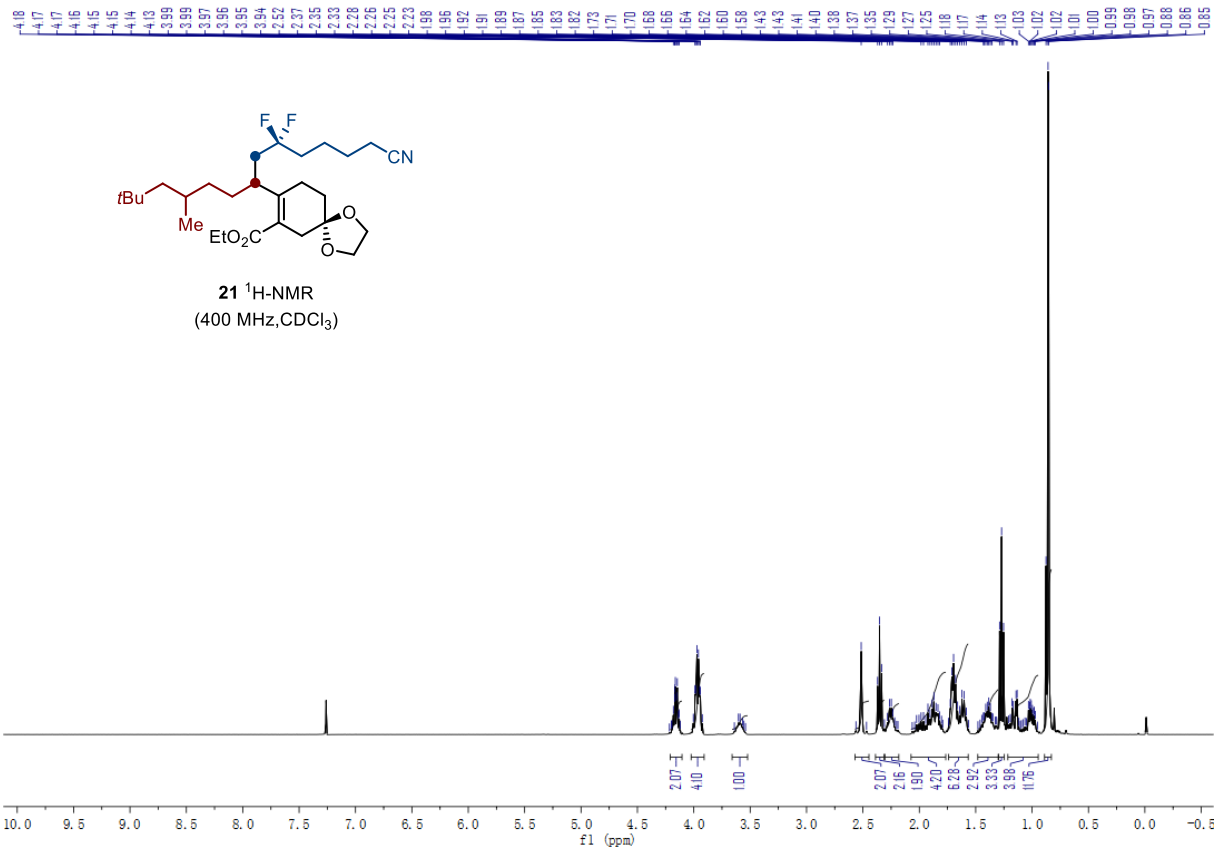
20 ^{1}H-NMR
(400 MHz,$CDCl_3$)



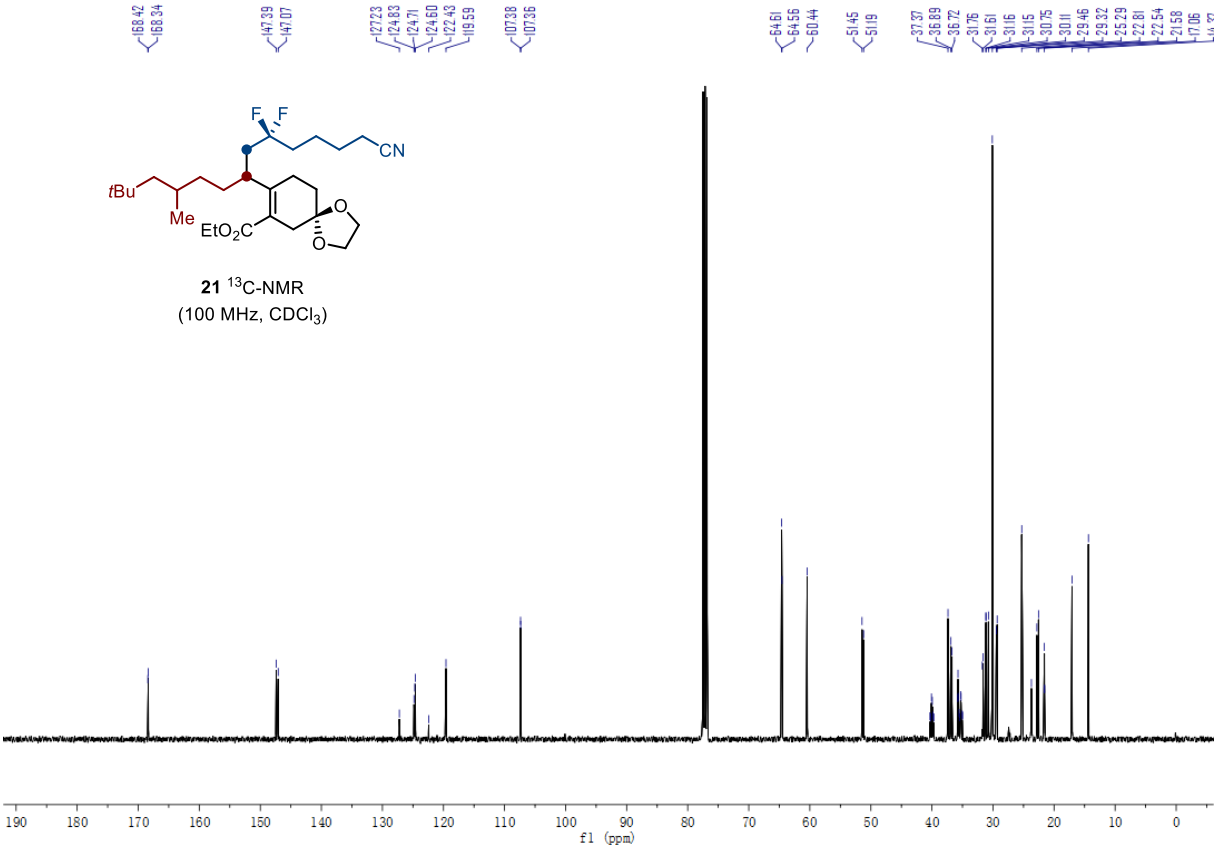
20 ^{13}C-NMR
(100 MHz, $CDCl_3$)



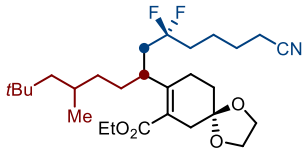
20 ^{19}F-NMR
(376 MHz, $CDCl_3$)



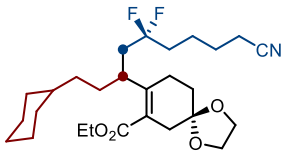
21 ^{1}H-NMR
(400 MHz,$CDCl_3$)



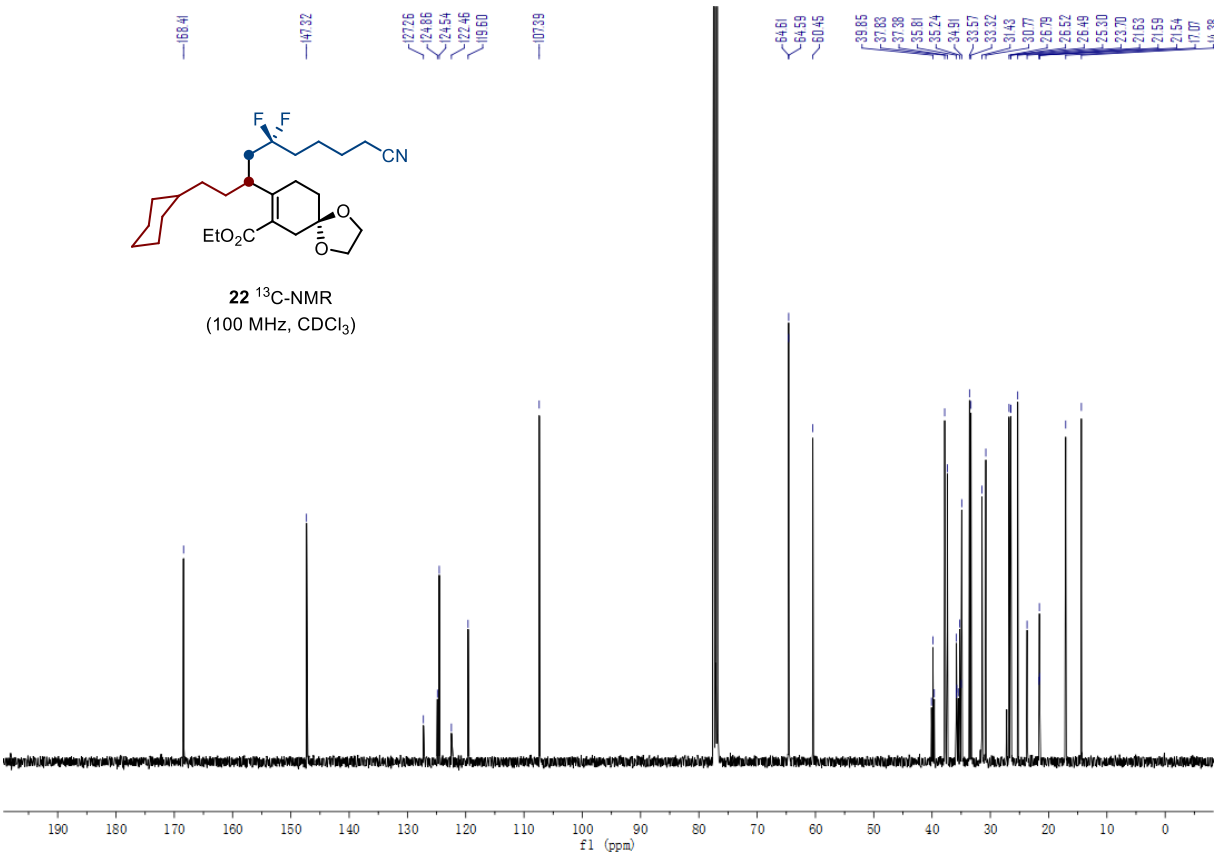
21 ^{13}C-NMR
(100 MHz, $CDCl_3$)



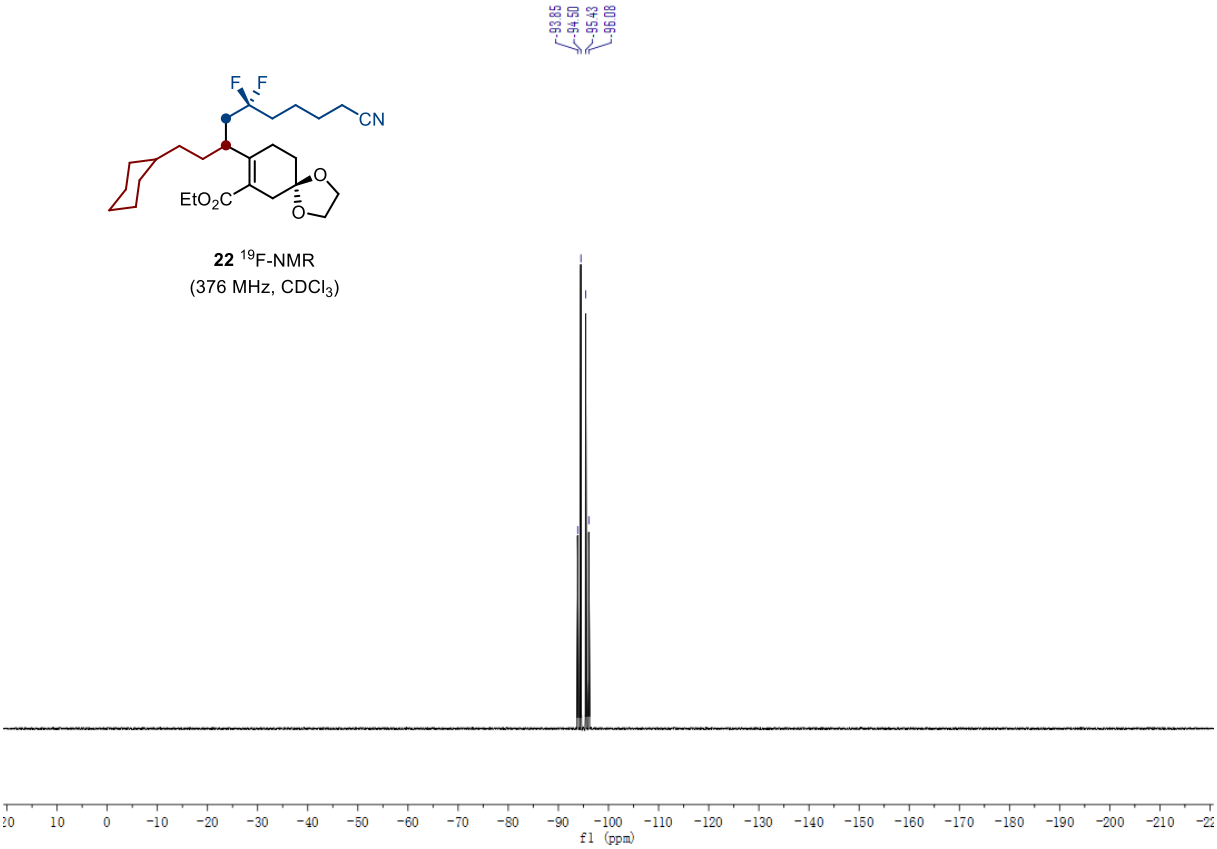
21 ^{19}F-NMR
(376 MHz, $CDCl_3$)



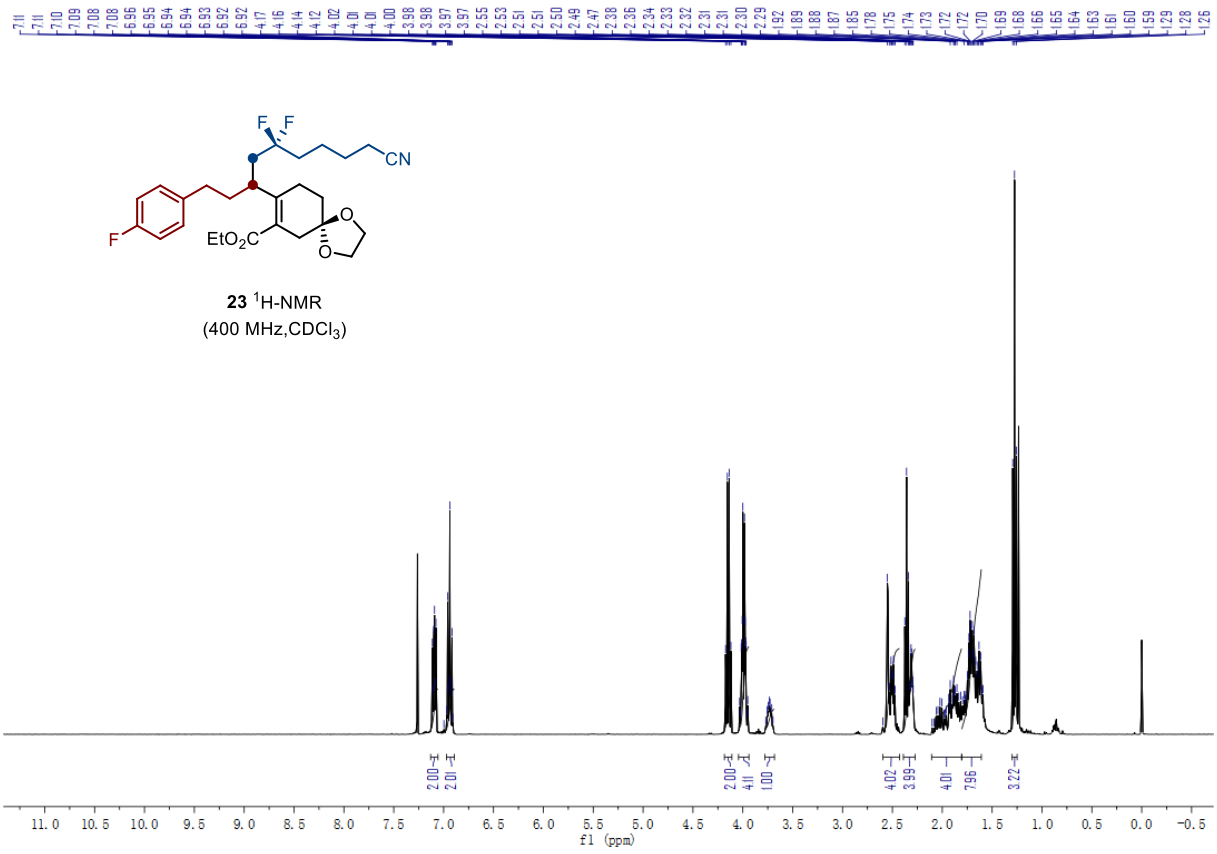
22 ^{1}H-NMR
(400 MHz,$CDCl_3$)



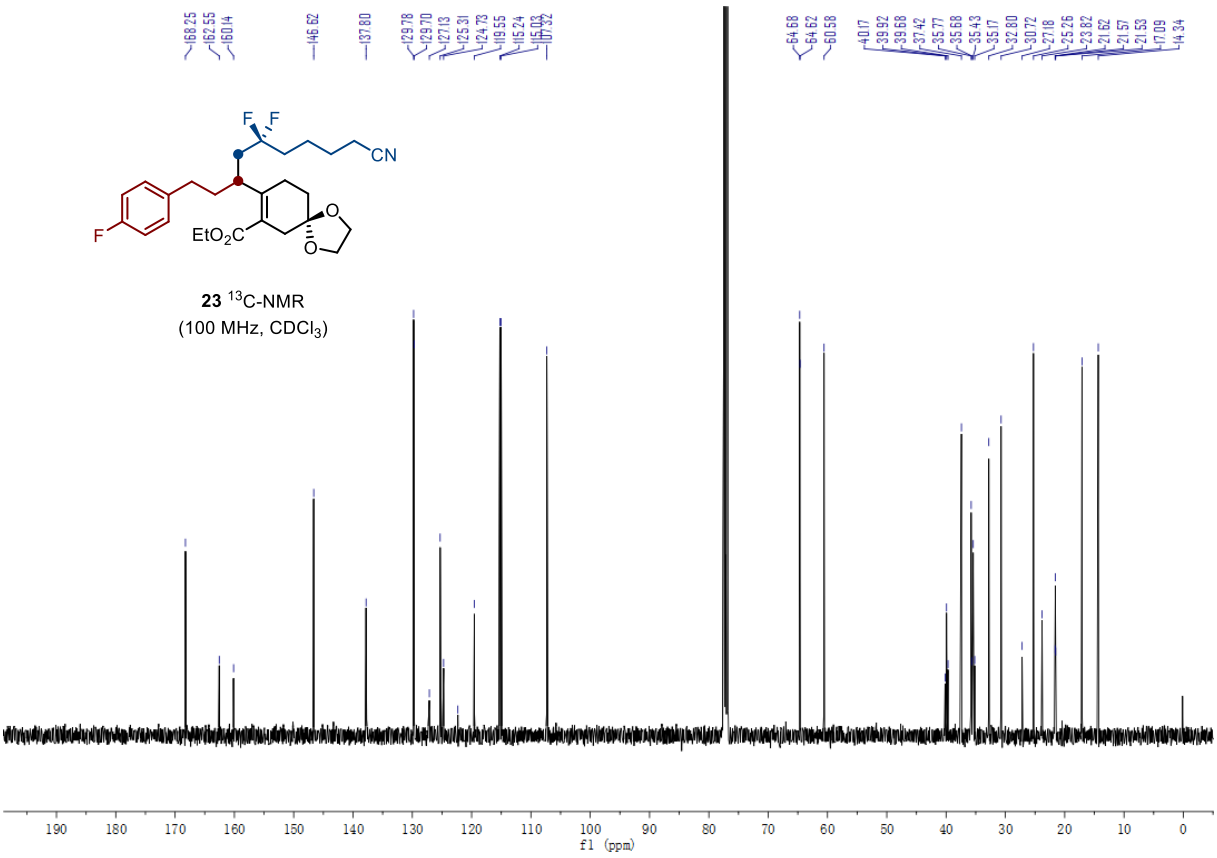
22 ^{13}C-NMR
(100 MHz, $CDCl_3$)



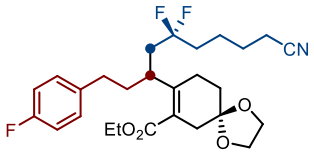
22 ^{19}F-NMR
(376 MHz, $CDCl_3$)



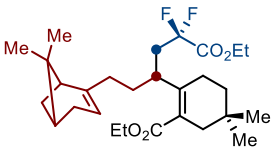
23 ^{1}H-NMR
(400 MHz,$CDCl_3$)



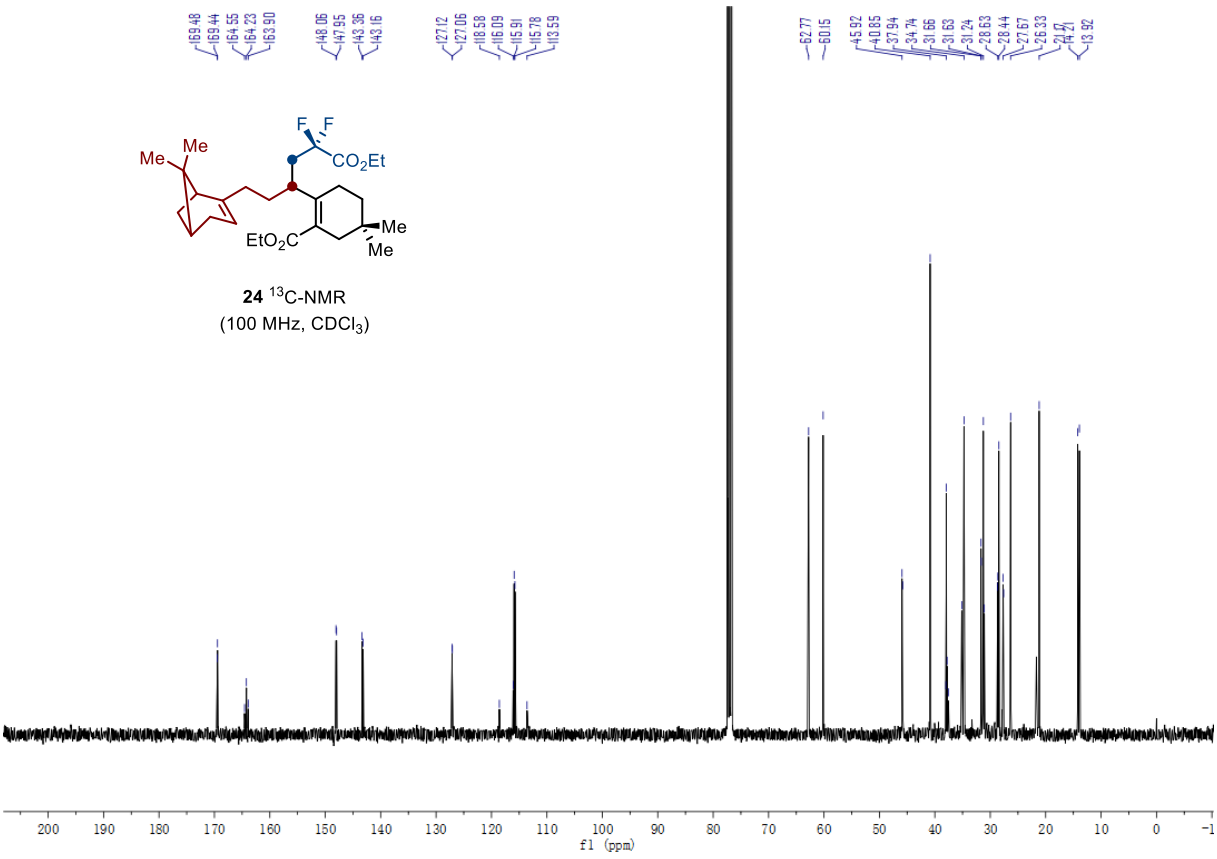
23 ^{13}C-NMR
(100 MHz, $CDCl_3$)



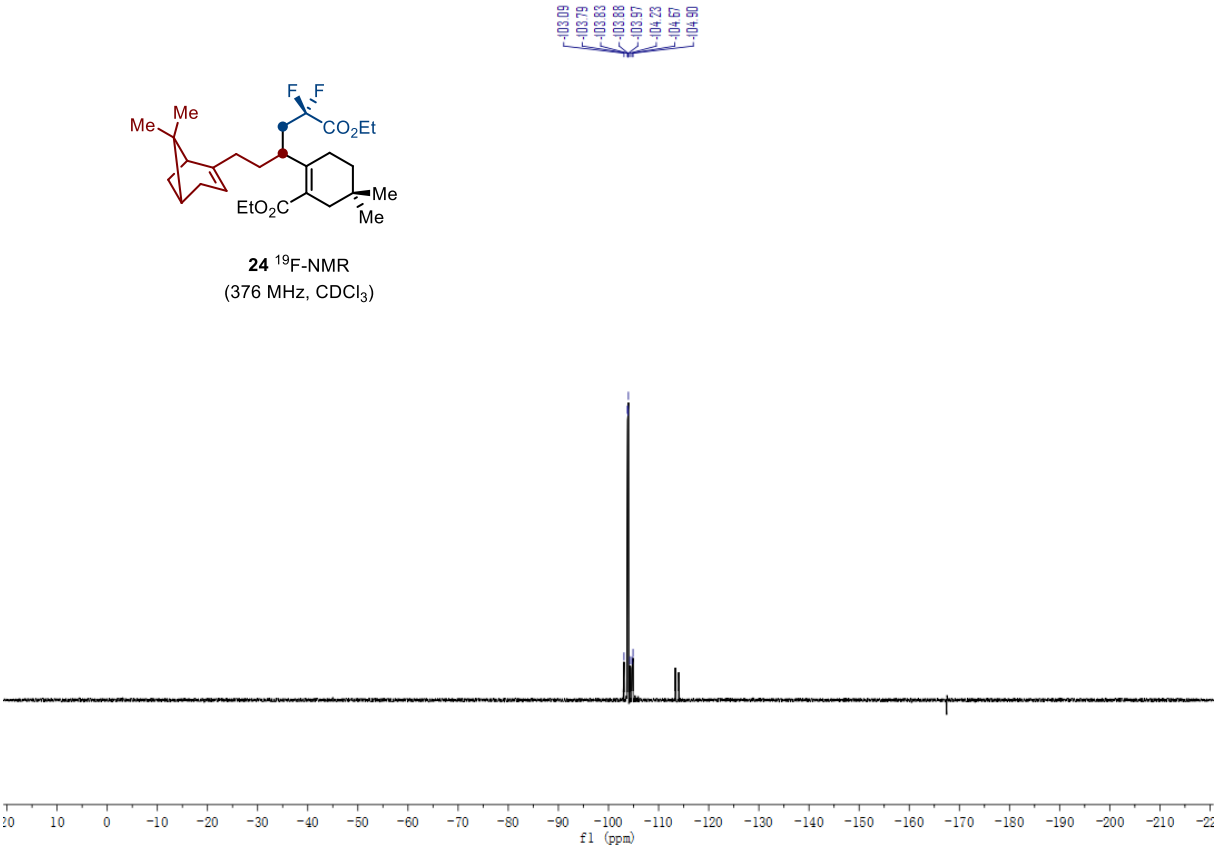
23 ^{19}F-NMR
(376 MHz, $CDCl_3$)



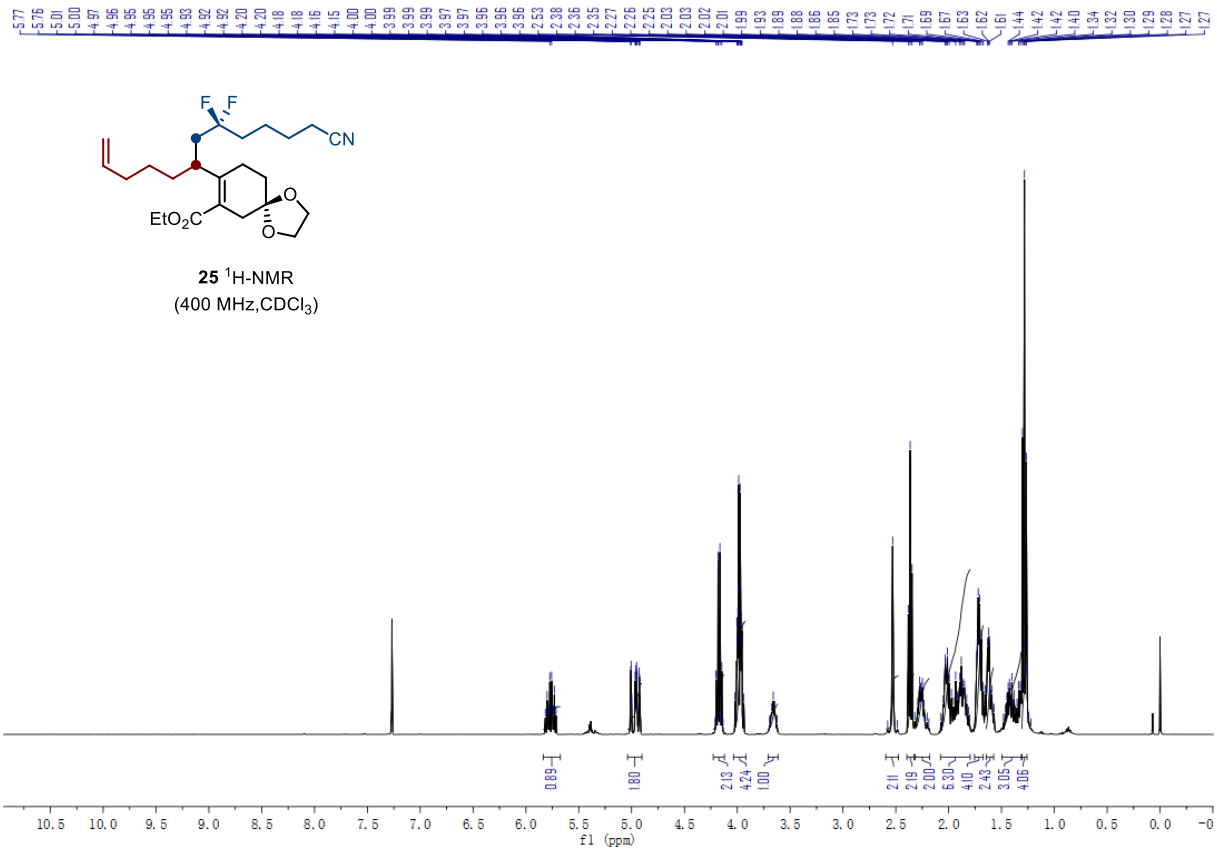
24 ^{1}H-NMR
(400 MHz,$CDCl_3$)



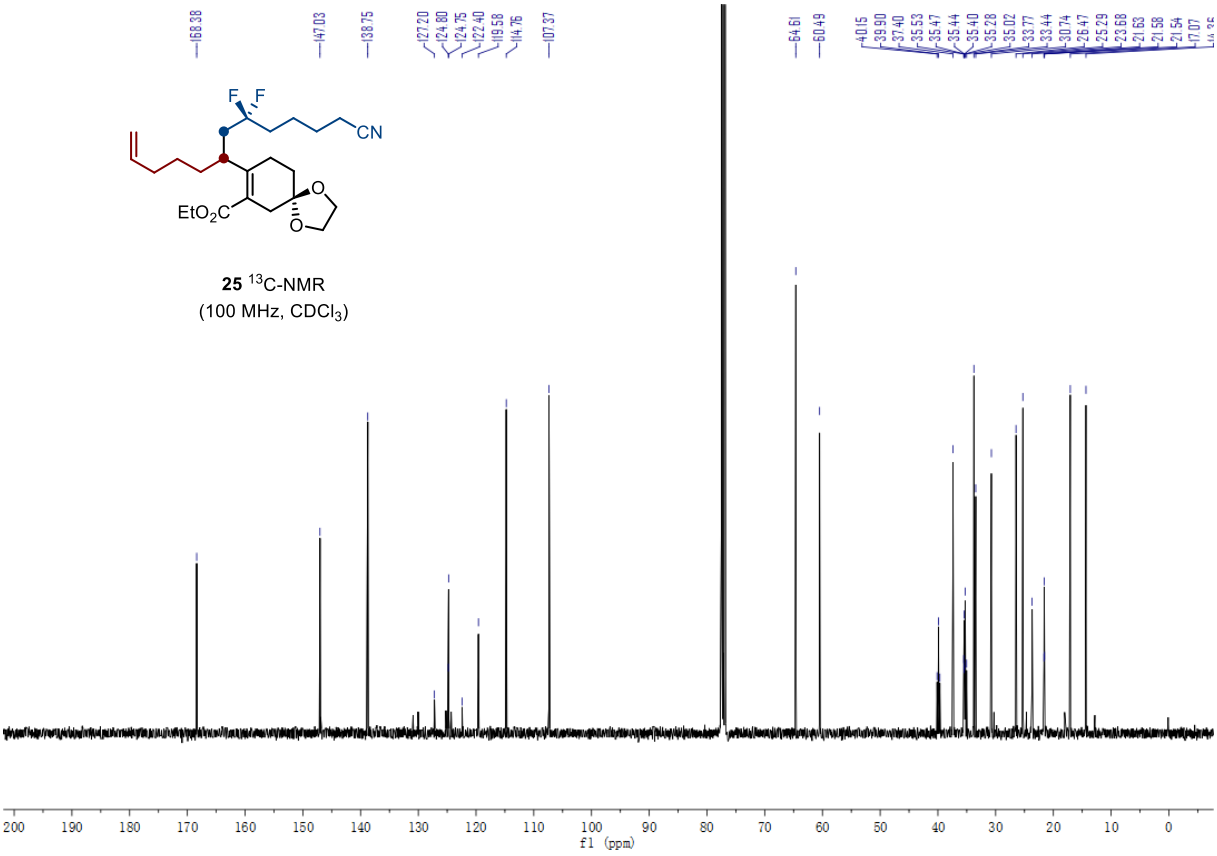
24 ^{13}C-NMR
(100 MHz, $CDCl_3$)



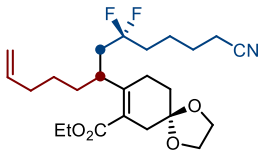
24 ^{19}F-NMR
(376 MHz, $CDCl_3$)



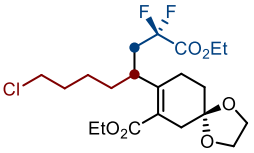
25 ^{1}H-NMR
(400 MHz,$CDCl_3$)



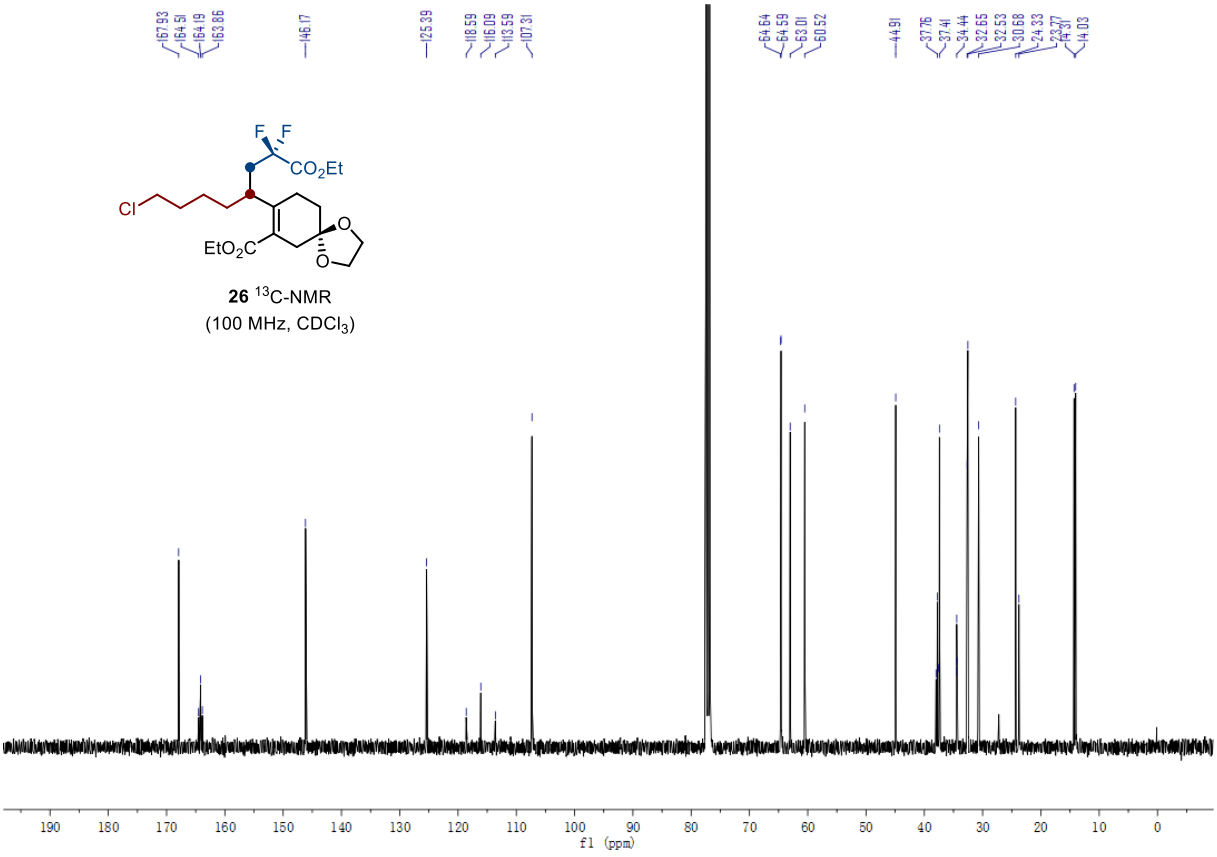
25 ^{13}C-NMR
(100 MHz, $CDCl_3$)



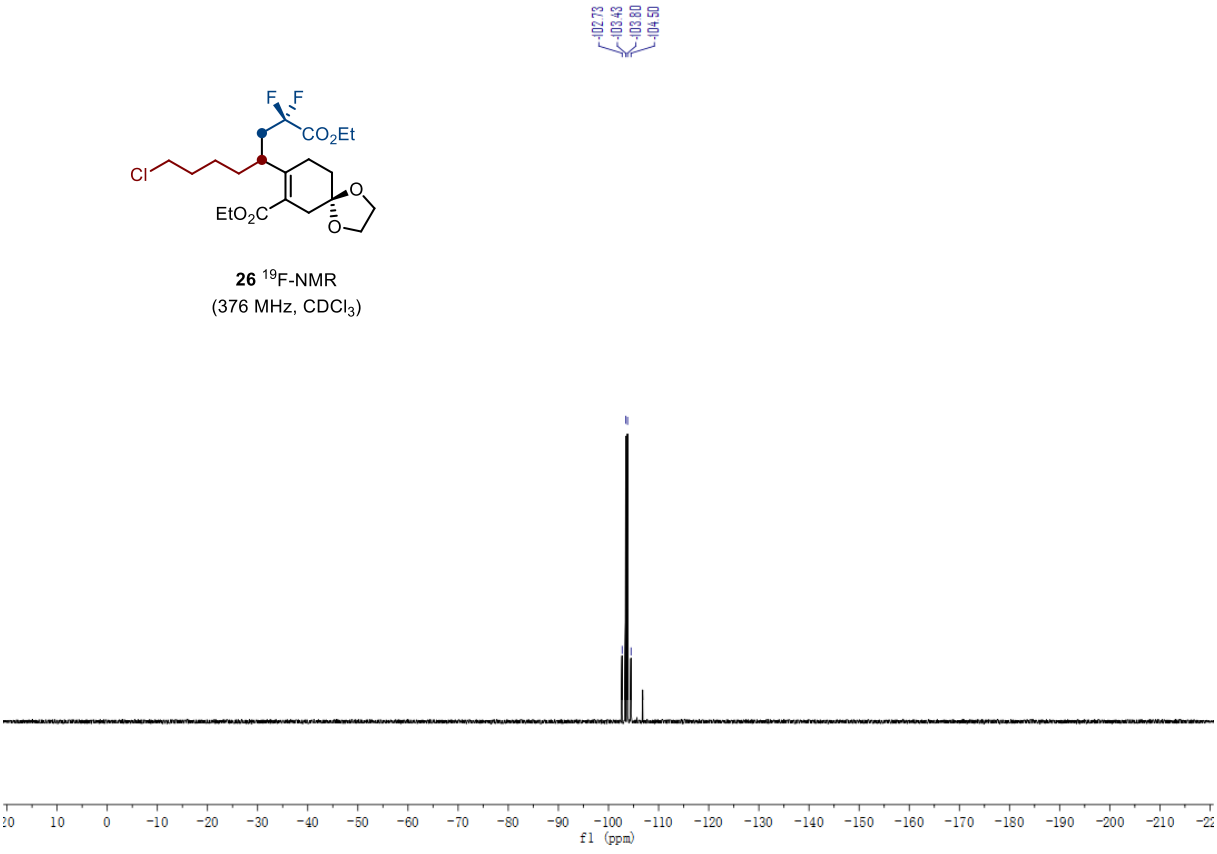
25 ^{19}F-NMR
(376 MHz, $CDCl_3$)



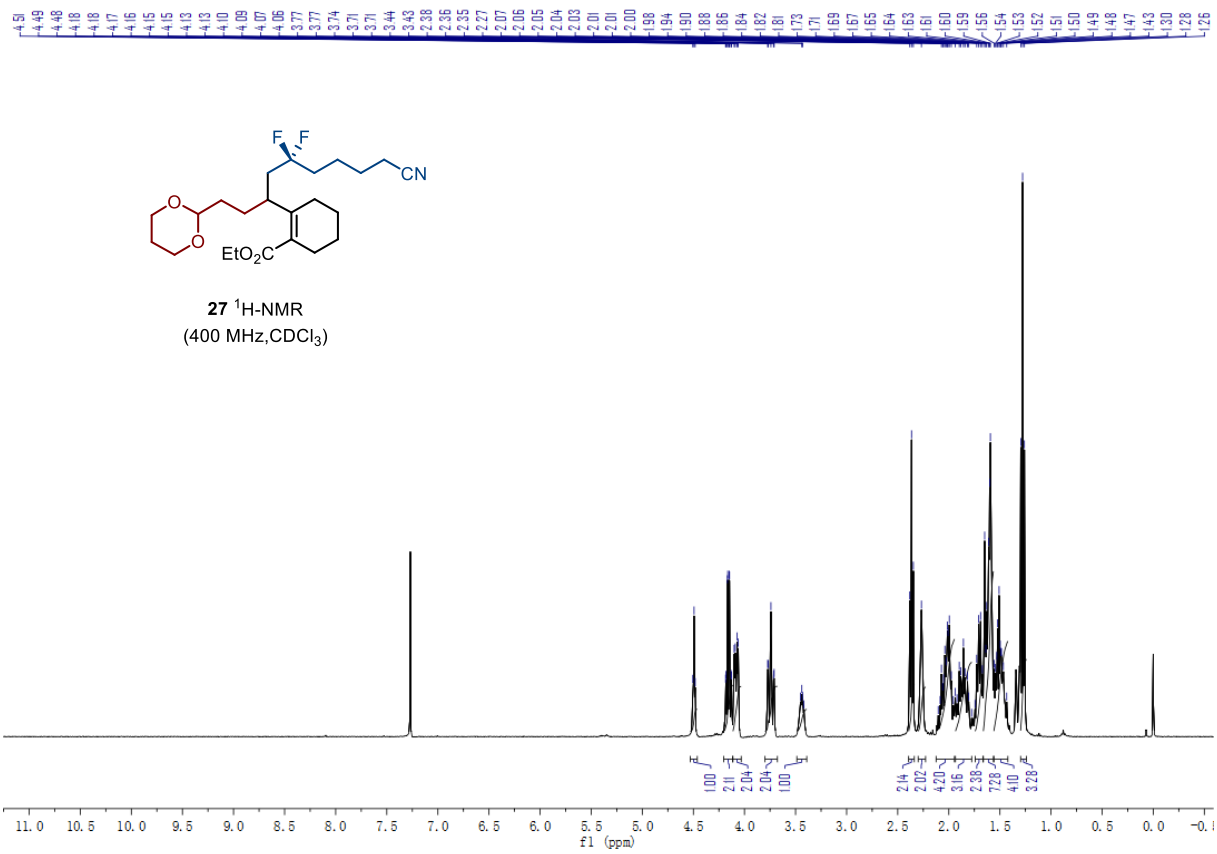
26 ^{1}H-NMR
(400 MHz,$CDCl_3$)



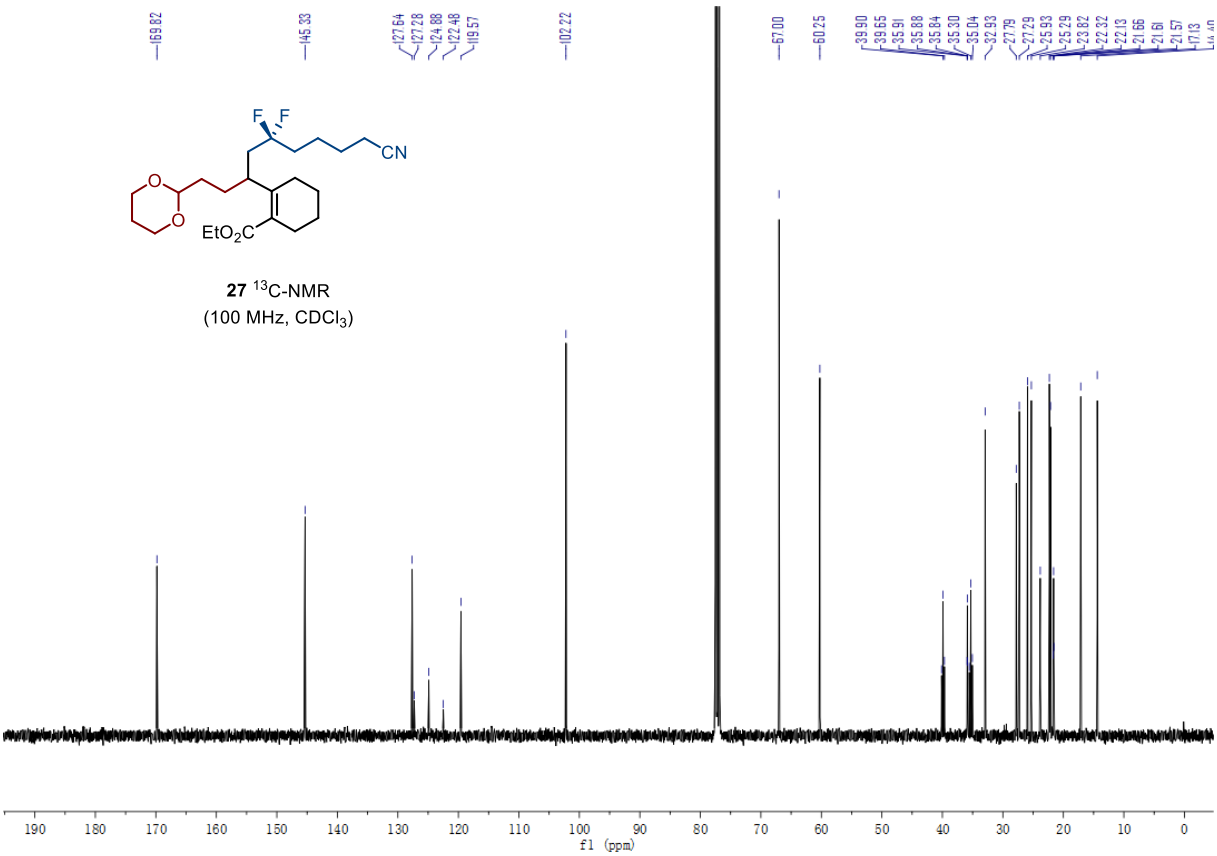
26 ^{13}C-NMR
(100 MHz, $CDCl_3$)



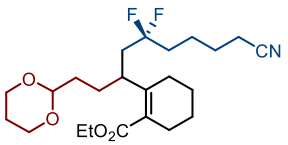
26 ^{19}F-NMR
(376 MHz, $CDCl_3$)



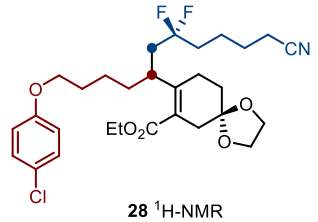
27 ^{1}H-NMR
(400 MHz,$CDCl_3$)



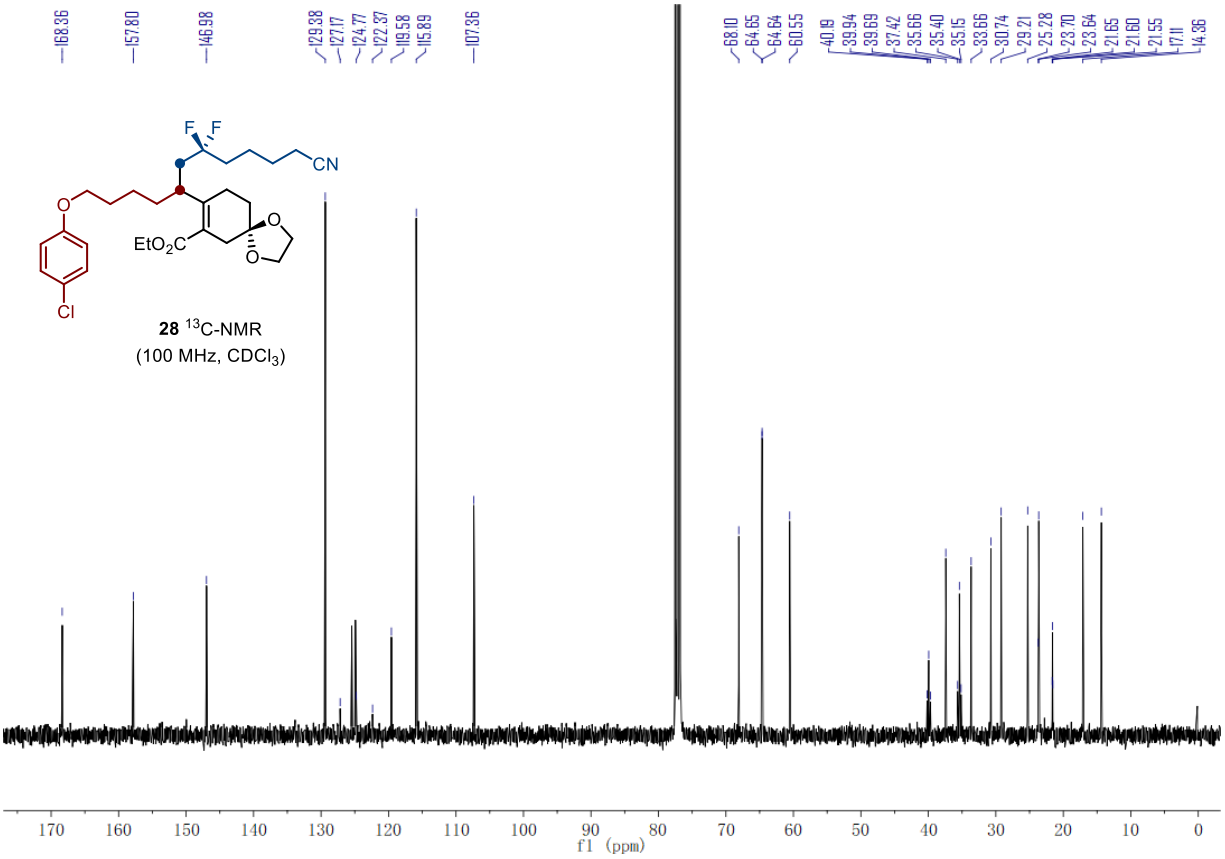
27 ^{13}C-NMR
(100 MHz, $CDCl_3$)



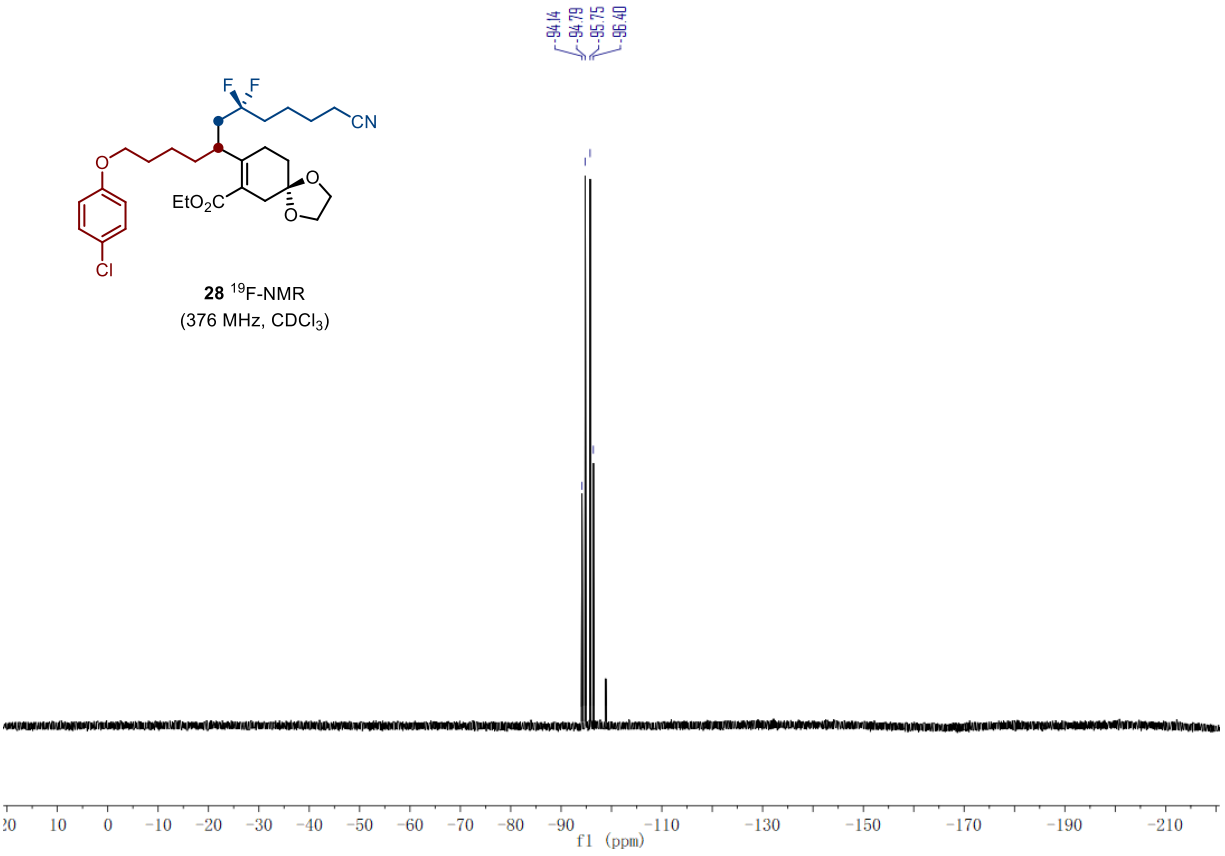
27 ^{19}F-NMR
(376 MHz, $CDCl_3$)



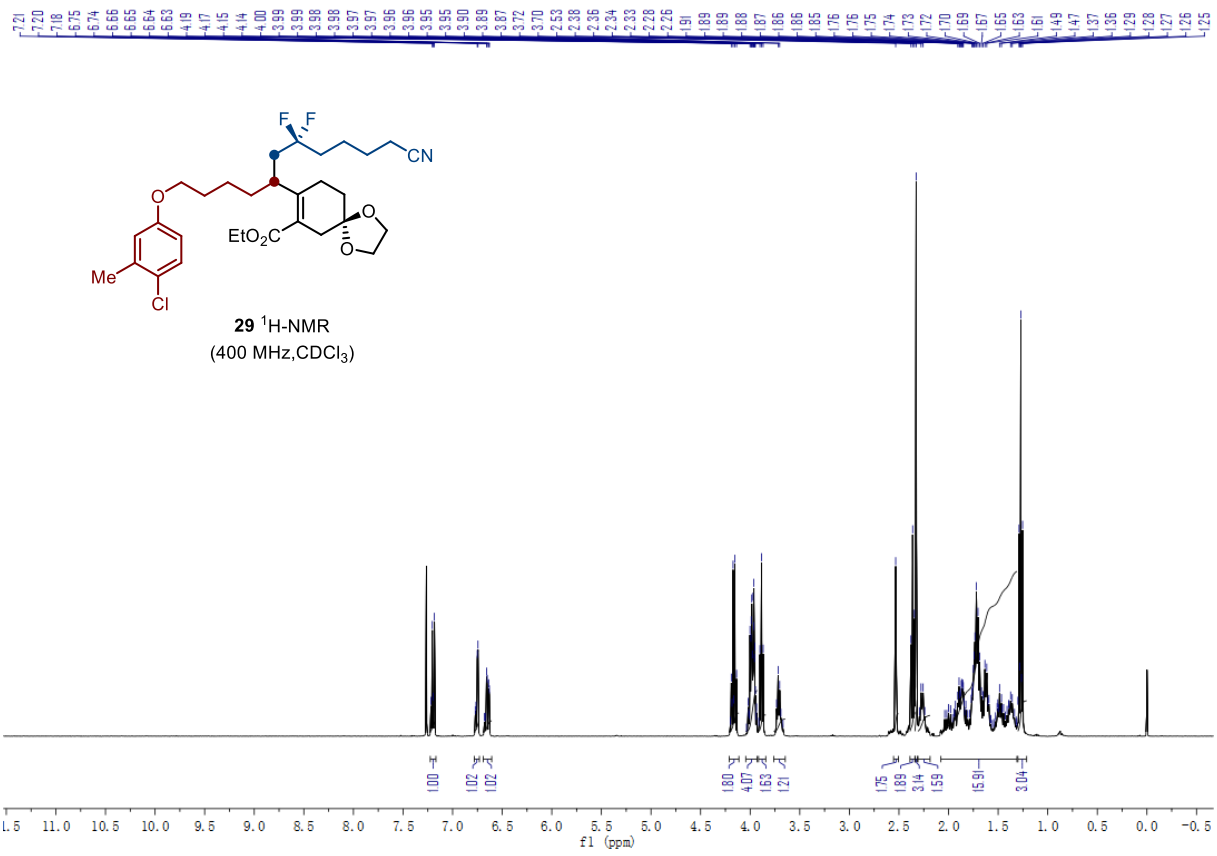
28 ^{1}H-NMR
(400 MHz,$CDCl_3$)



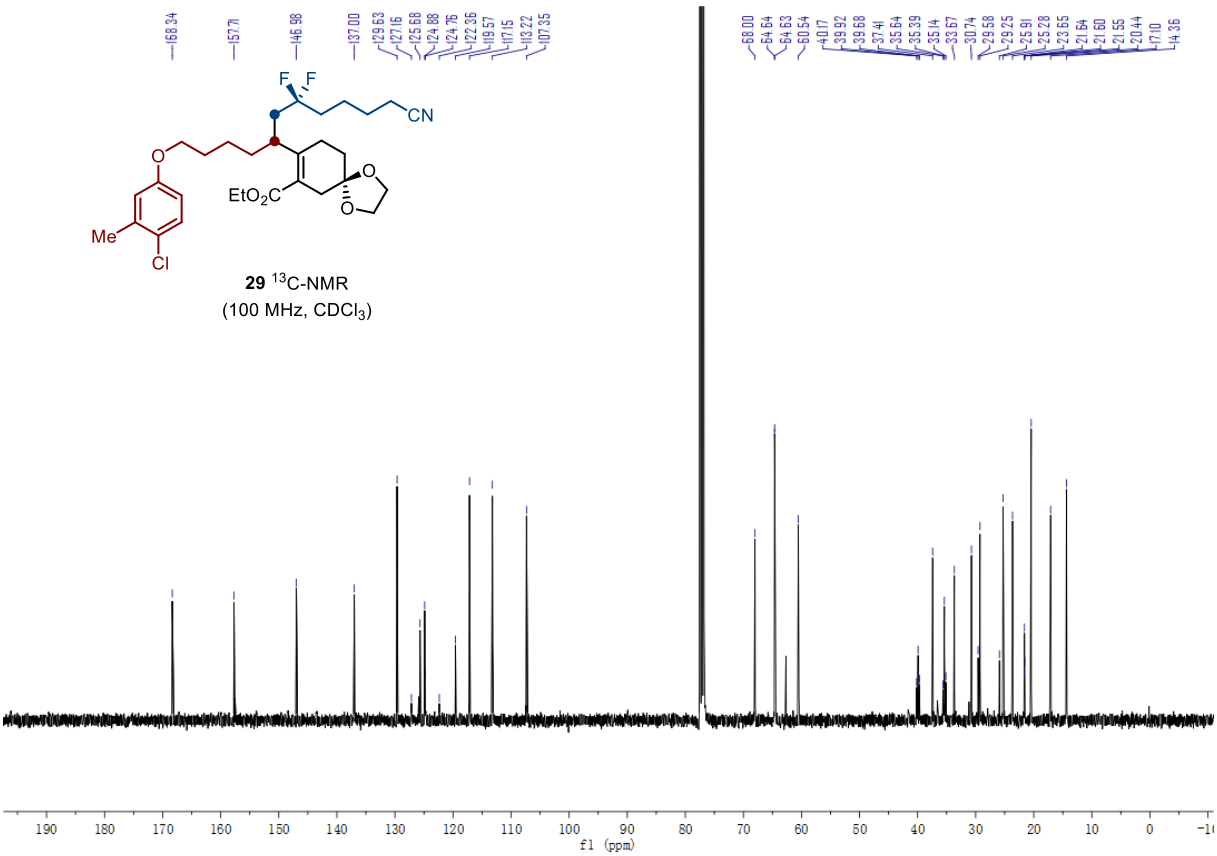
28 ^{13}C-NMR
(100 MHz, $CDCl_3$)



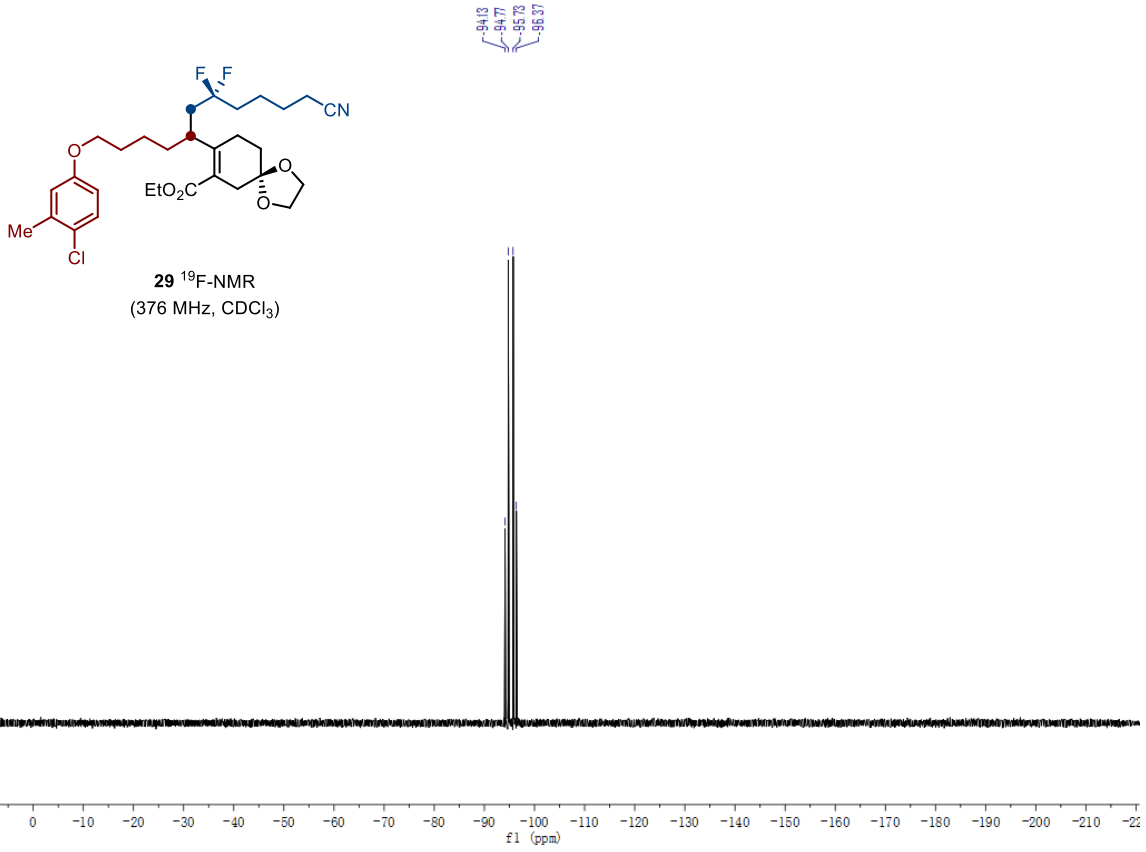
28 ^{19}F-NMR
(376 MHz, $CDCl_3$)



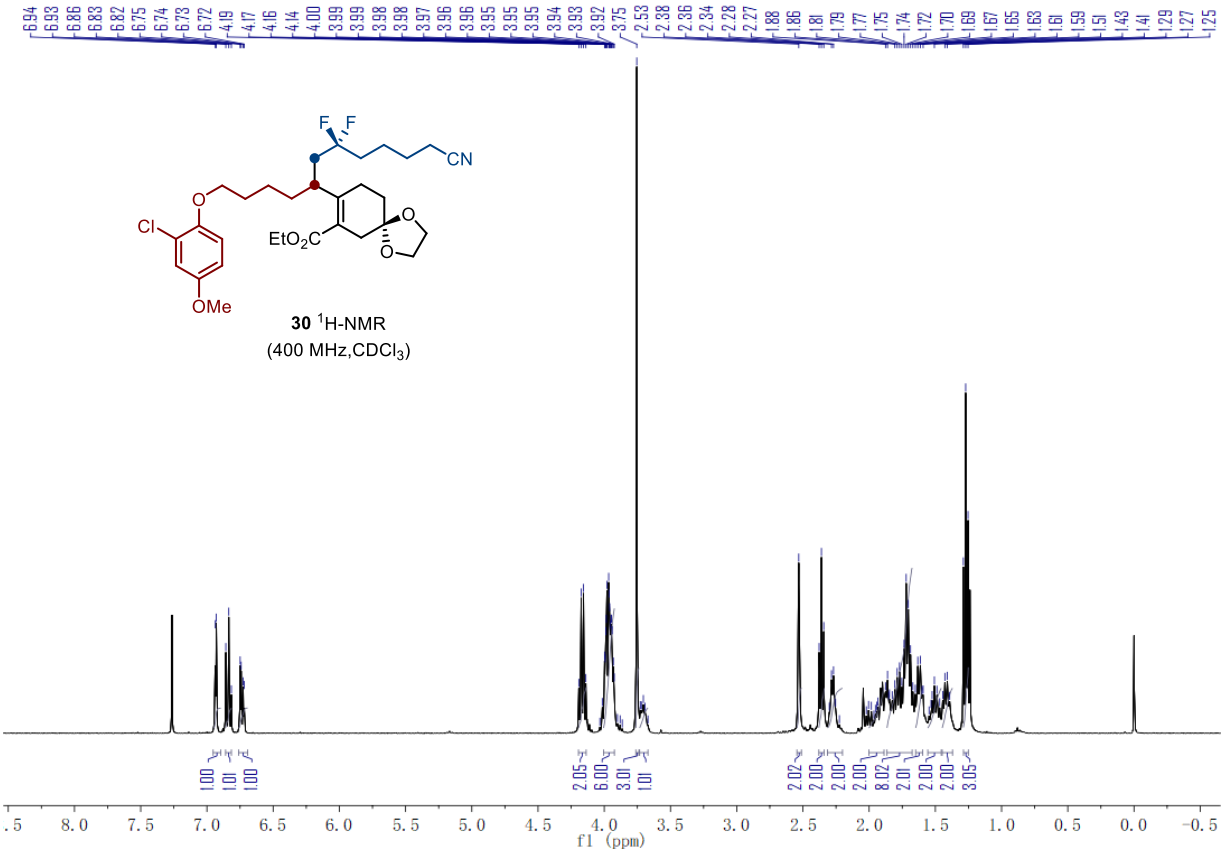
29 ^{1}H-NMR
(400 MHz,$CDCl_3$)



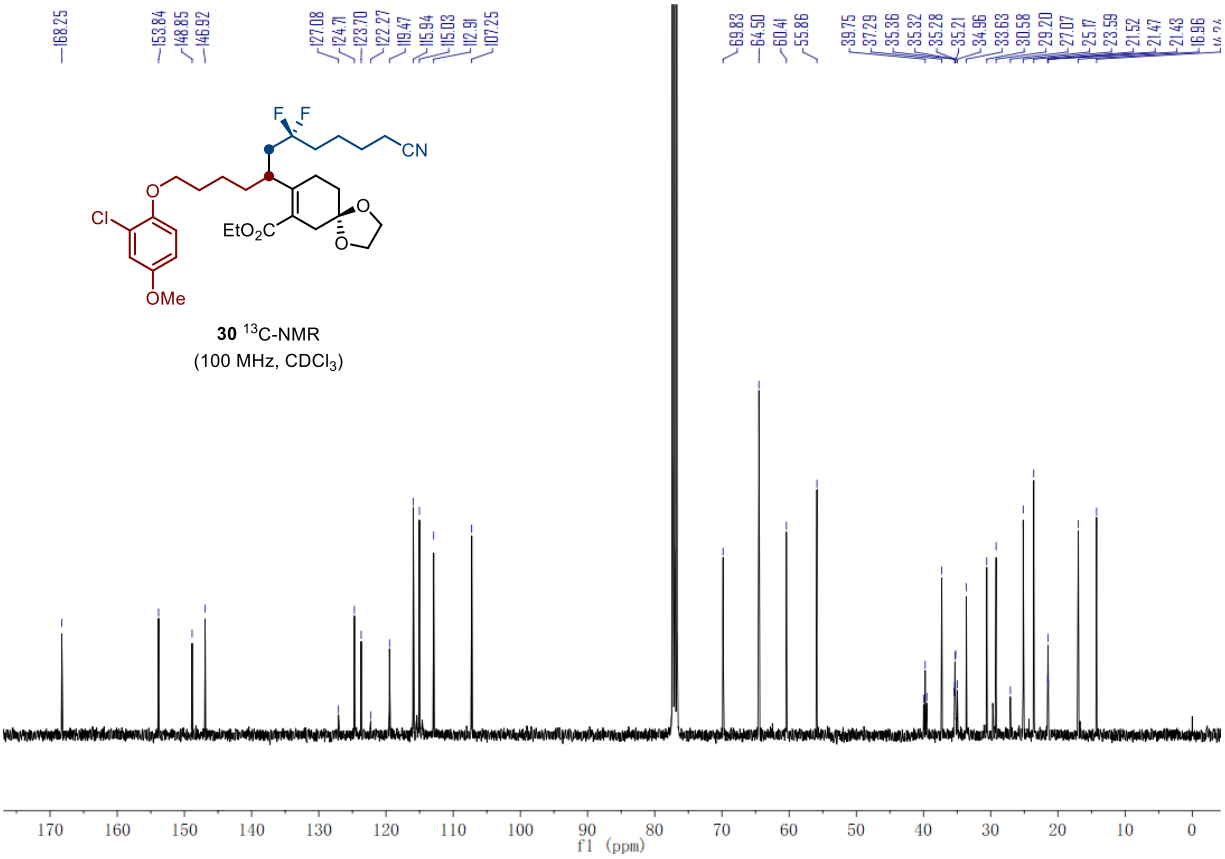
29 ^{13}C-NMR
(100 MHz, $CDCl_3$)



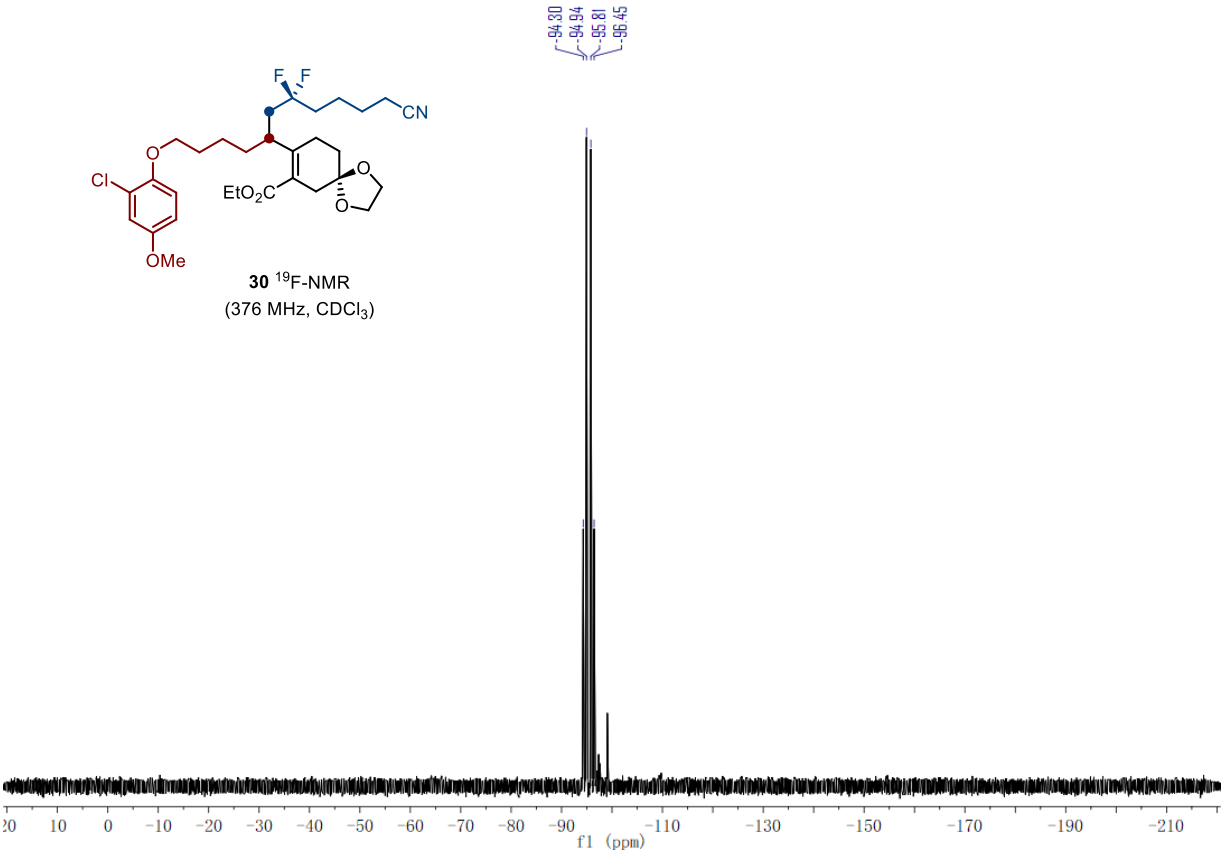
29 ^{19}F-NMR
(376 MHz, $CDCl_3$)



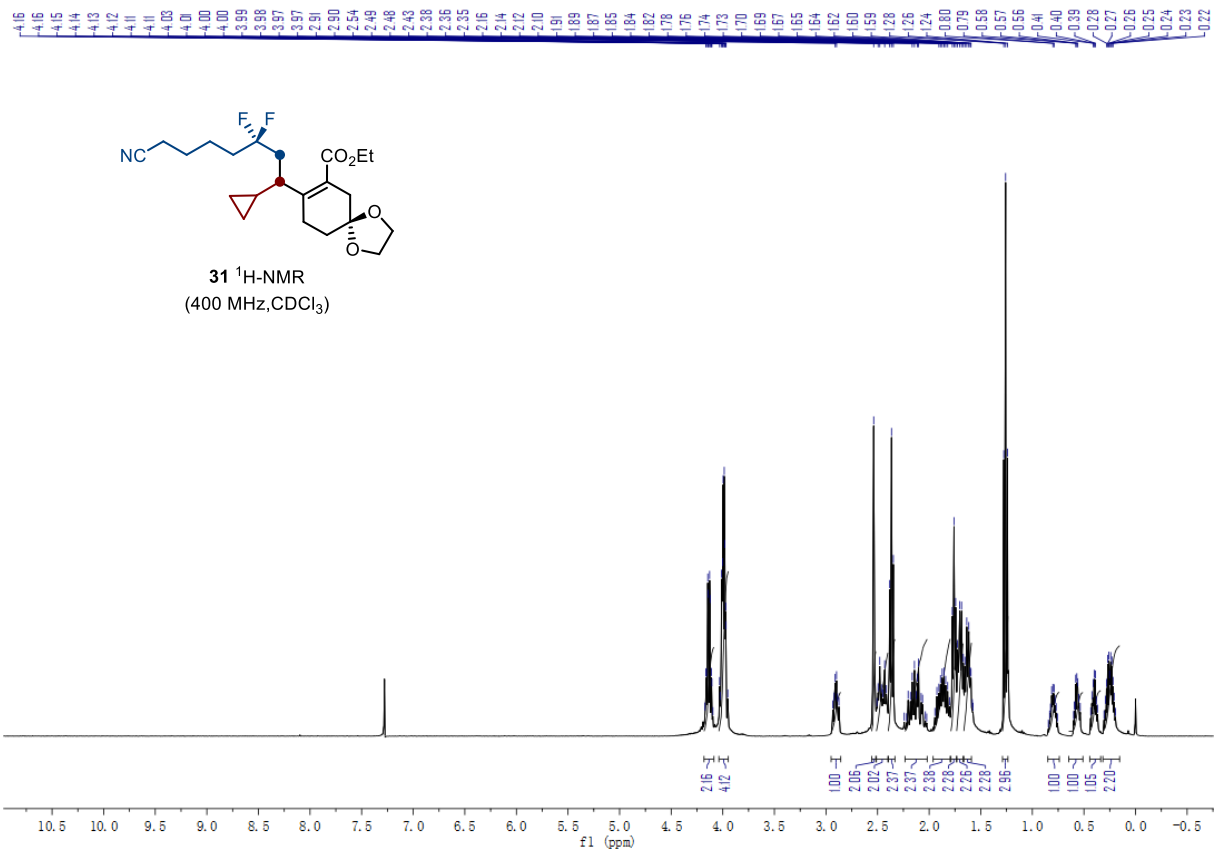
30 ^{1}H-NMR
(400 MHz,$CDCl_3$)



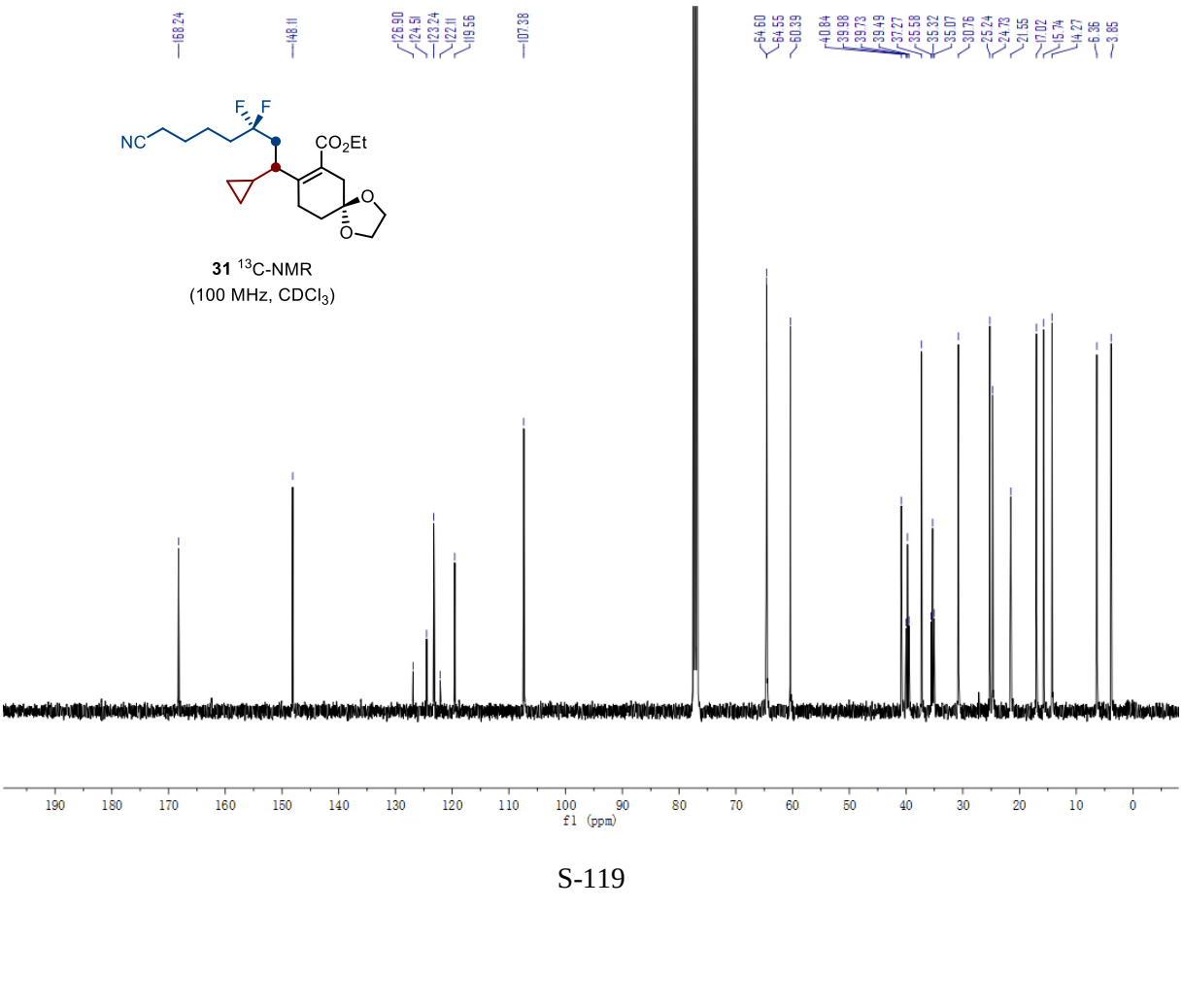
30 ^{13}C-NMR
(100 MHz, $CDCl_3$)



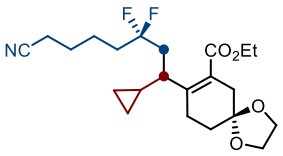
30 ^{19}F-NMR
(376 MHz, $CDCl_3$)



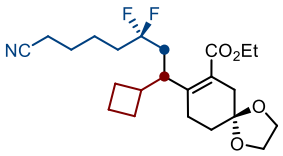
31 ^{1}H-NMR
(400 MHz,$CDCl_3$)



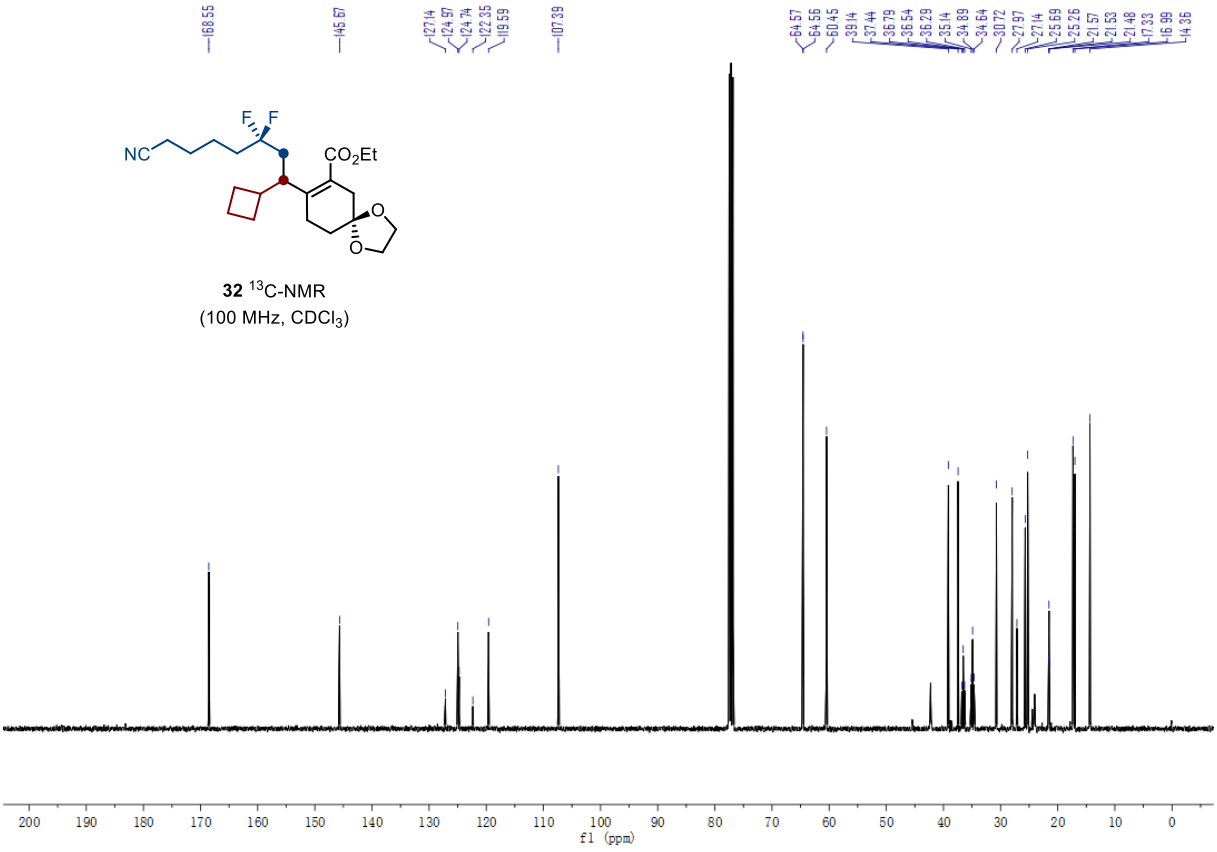
31 ^{13}C-NMR
(100 MHz, $CDCl_3$)



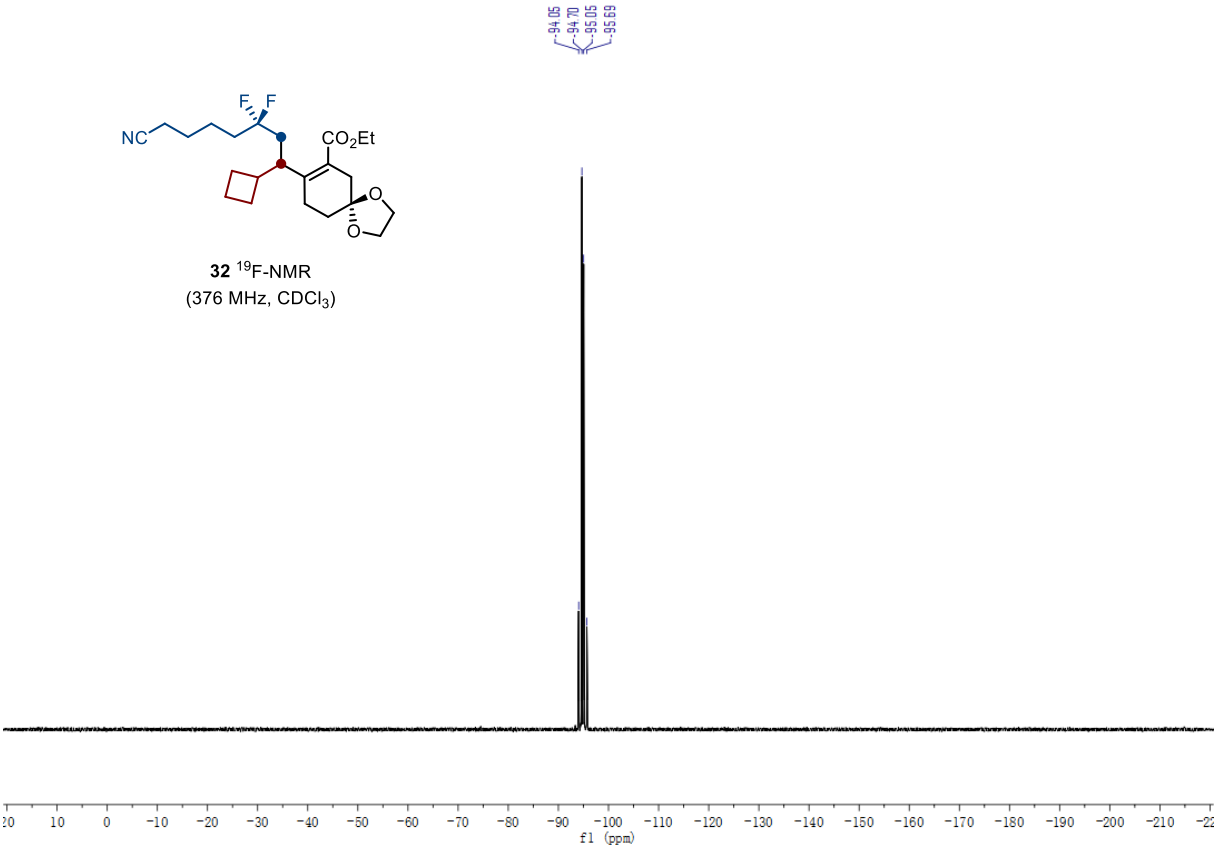
31 ^{19}F-NMR
(376 MHz, $CDCl_3$)



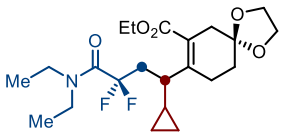
32 ^{1}H-NMR
(400 MHz,$CDCl_3$)



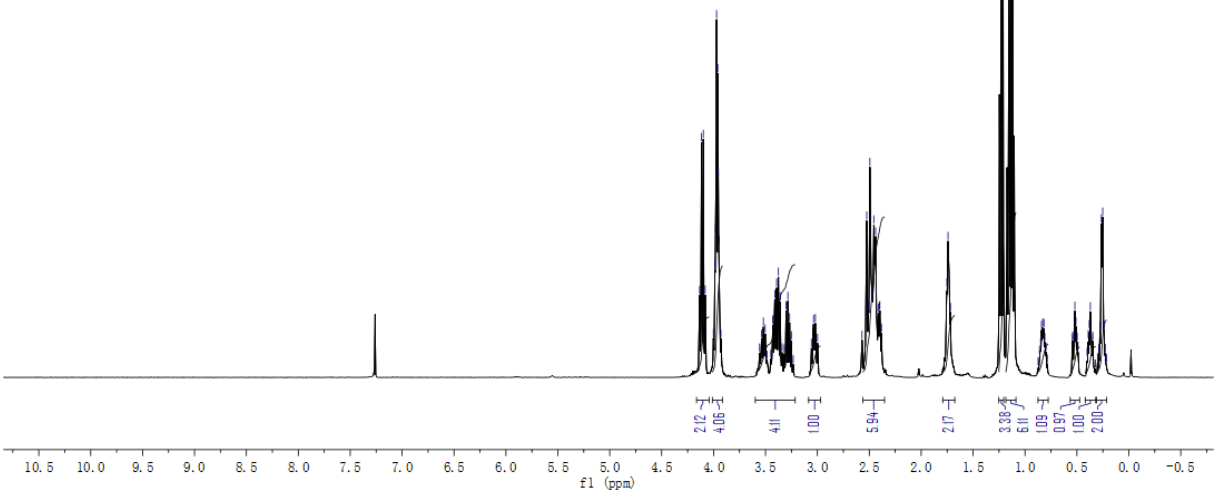
32 ^{13}C-NMR
(100 MHz, $CDCl_3$)

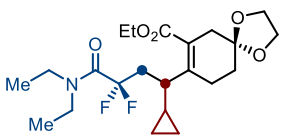


32 ^{19}F-NMR
(376 MHz, $CDCl_3$)

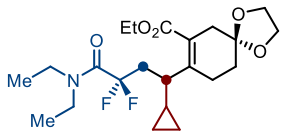


33 ^{1}H-NMR
(400 MHz,$CDCl_3$)

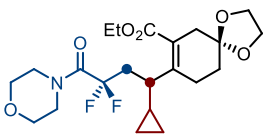




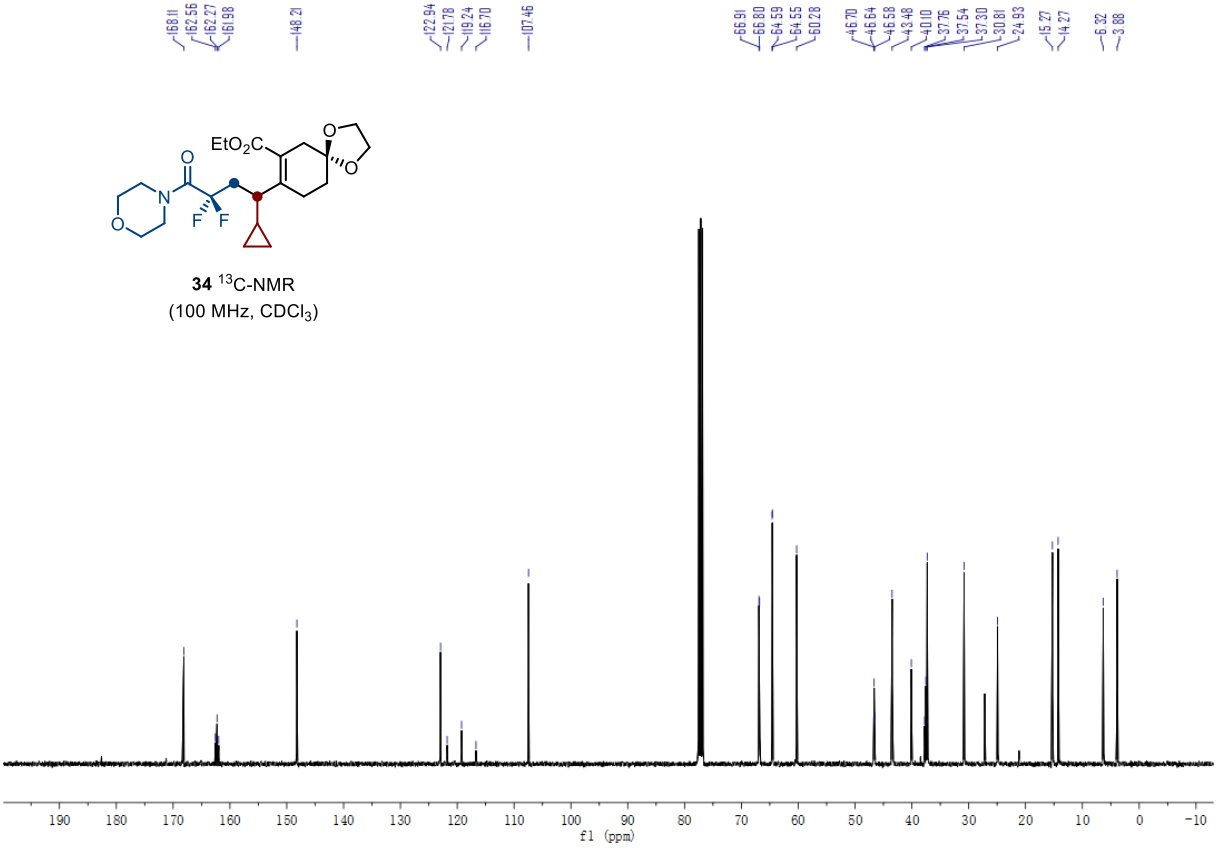
33 ^{13}C-NMR
(100 MHz, $CDCl_3$)



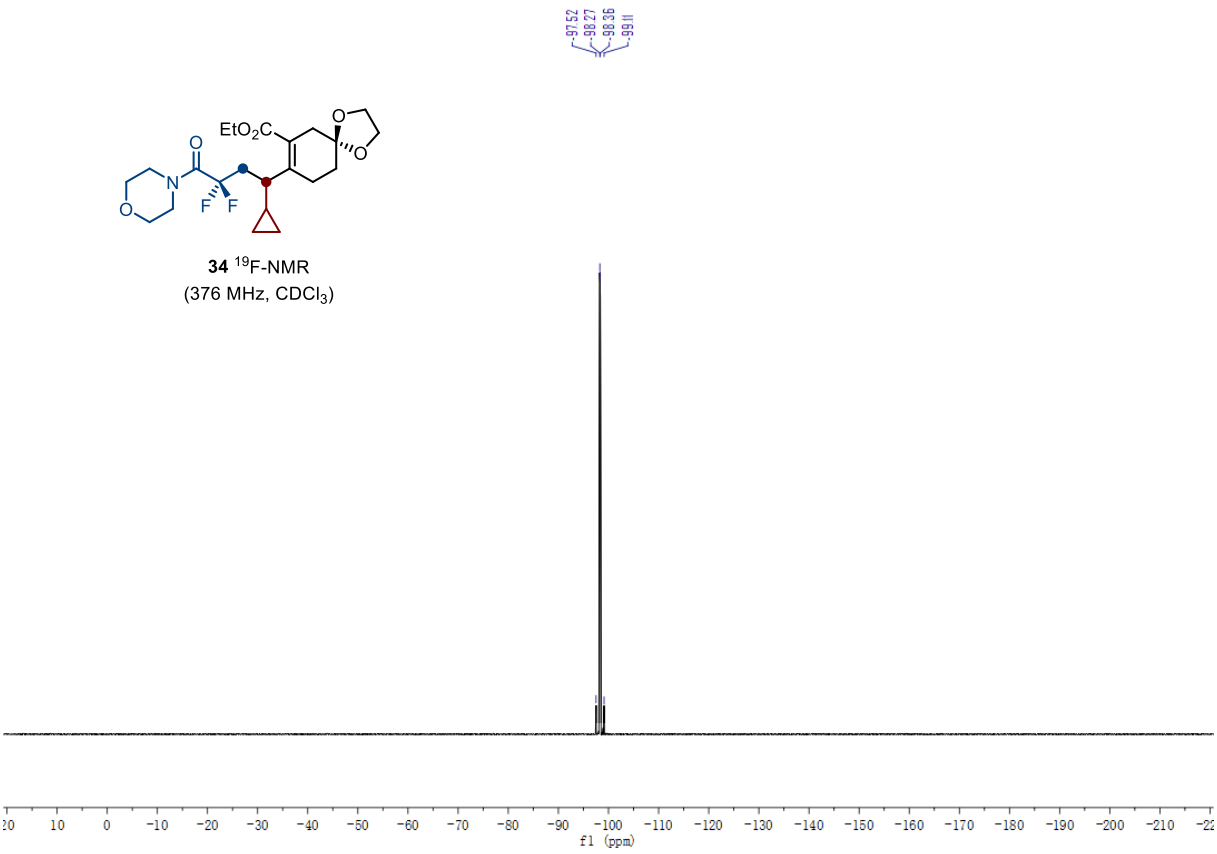
33 ^{19}F-NMR
(376 MHz, $CDCl_3$)



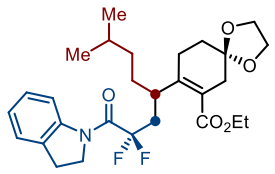
34 ^{1}H-NMR
(400 MHz,$CDCl_3$)



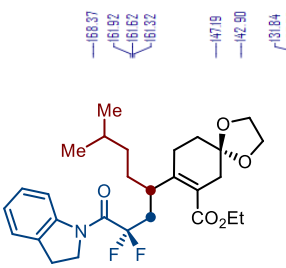
34 ^{13}C-NMR
(100 MHz, $CDCl_3$)



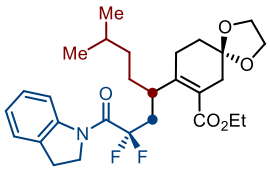
34 ^{19}F-NMR
(376 MHz, $CDCl_3$)



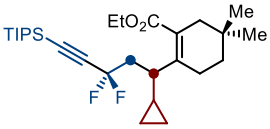
35 ^{1}H-NMR
(400 MHz,$CDCl_3$)



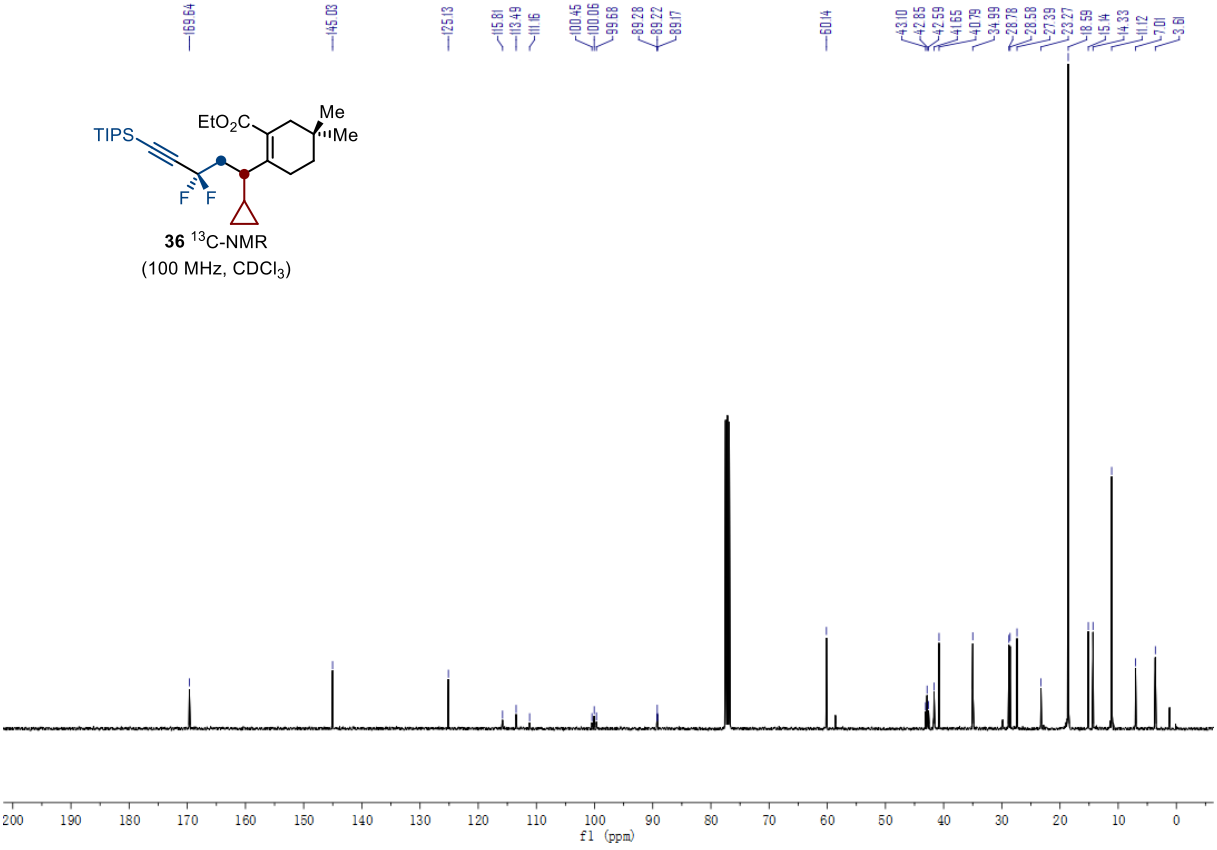
35 ^{13}C-NMR
(100 MHz, $CDCl_3$)



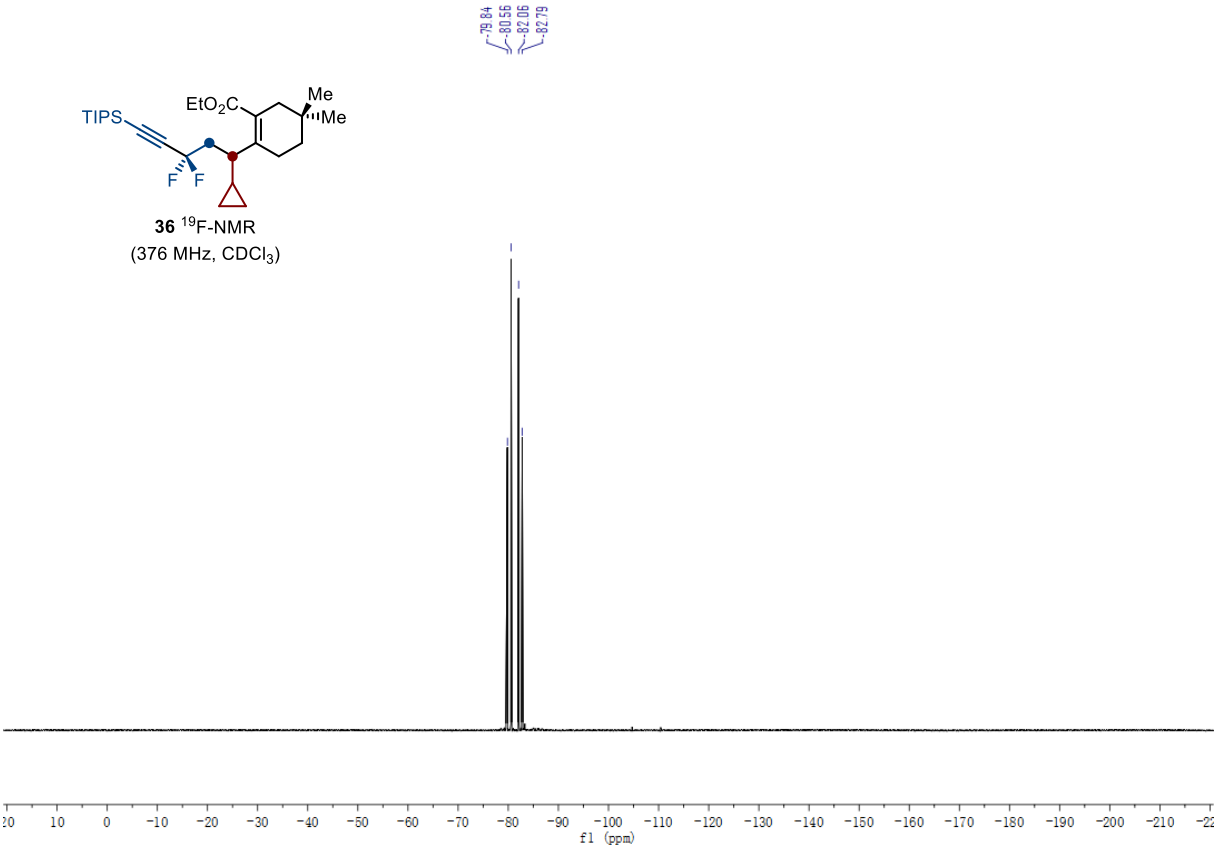
35 ^{19}F-NMR
(376 MHz, $CDCl_3$)



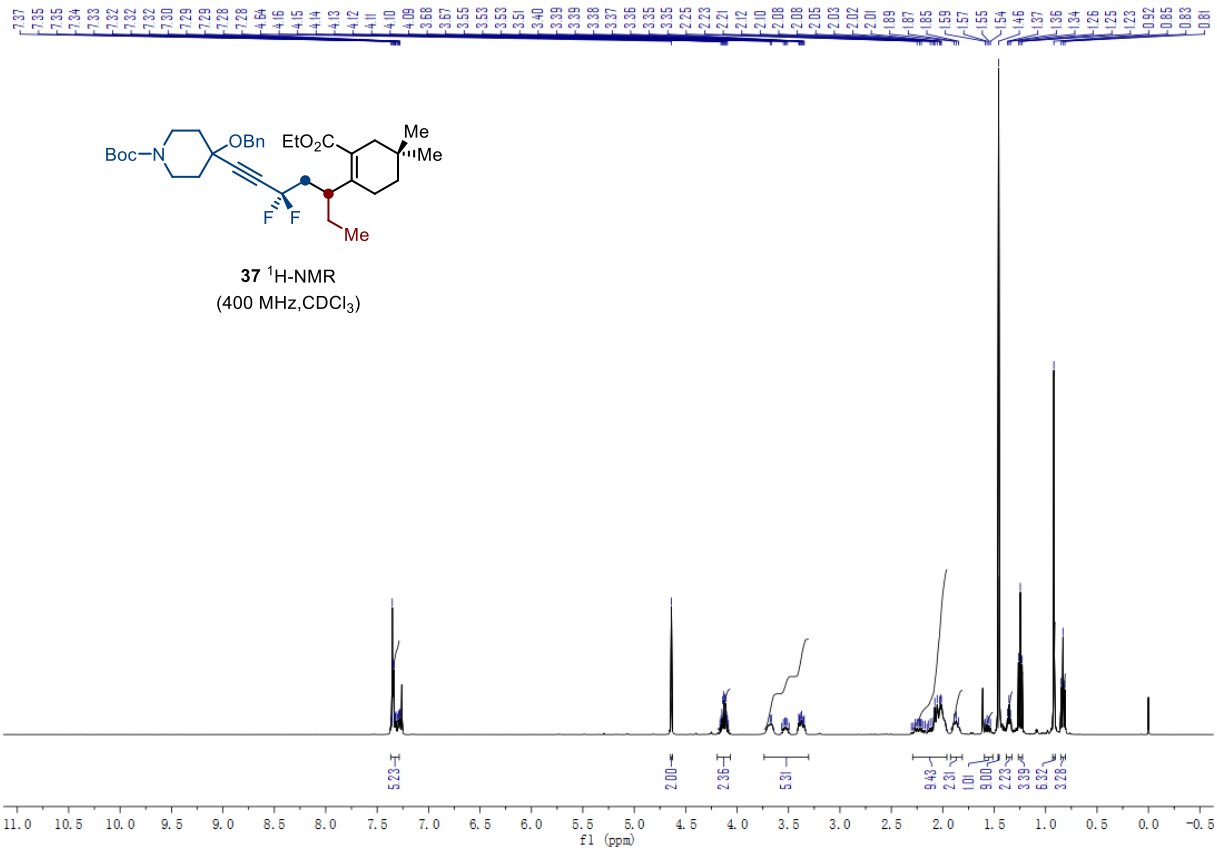
36 ^{1}H-NMR
(400 MHz,$CDCl_3$)



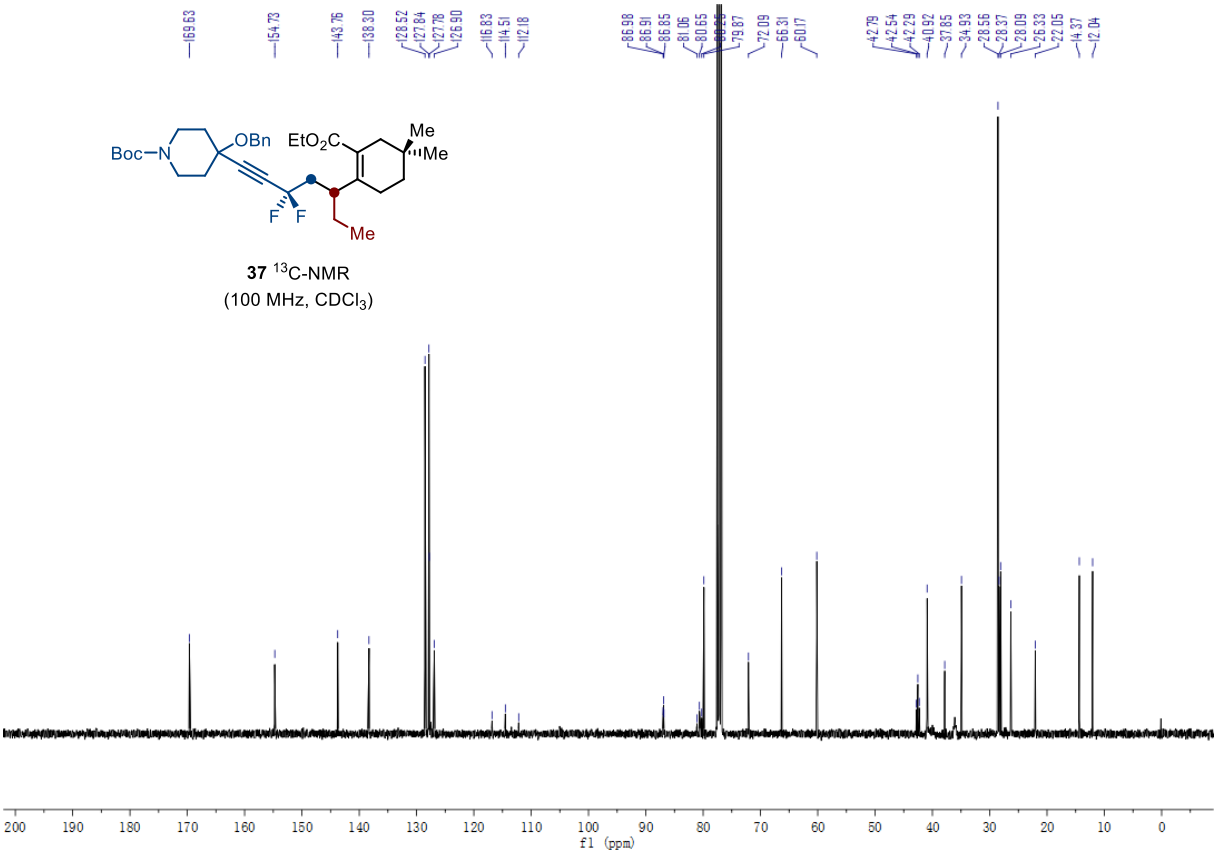
36 ^{13}C-NMR
(100 MHz, $CDCl_3$)



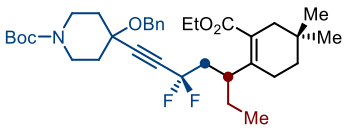
36 ^{19}F-NMR
(376 MHz, $CDCl_3$)



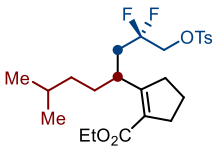
37 ^{1}H-NMR
(400 MHz,$CDCl_3$)



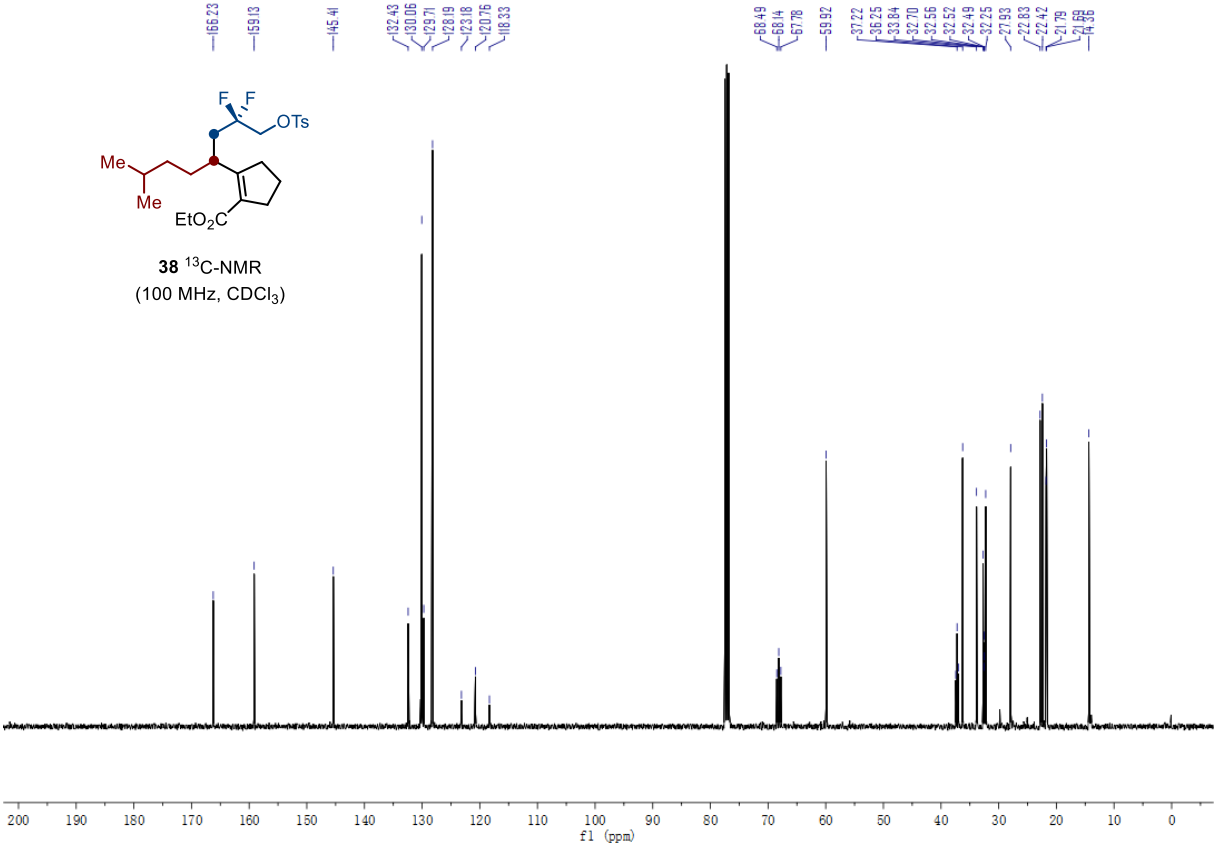
37 ^{13}C-NMR
(100 MHz, $CDCl_3$)



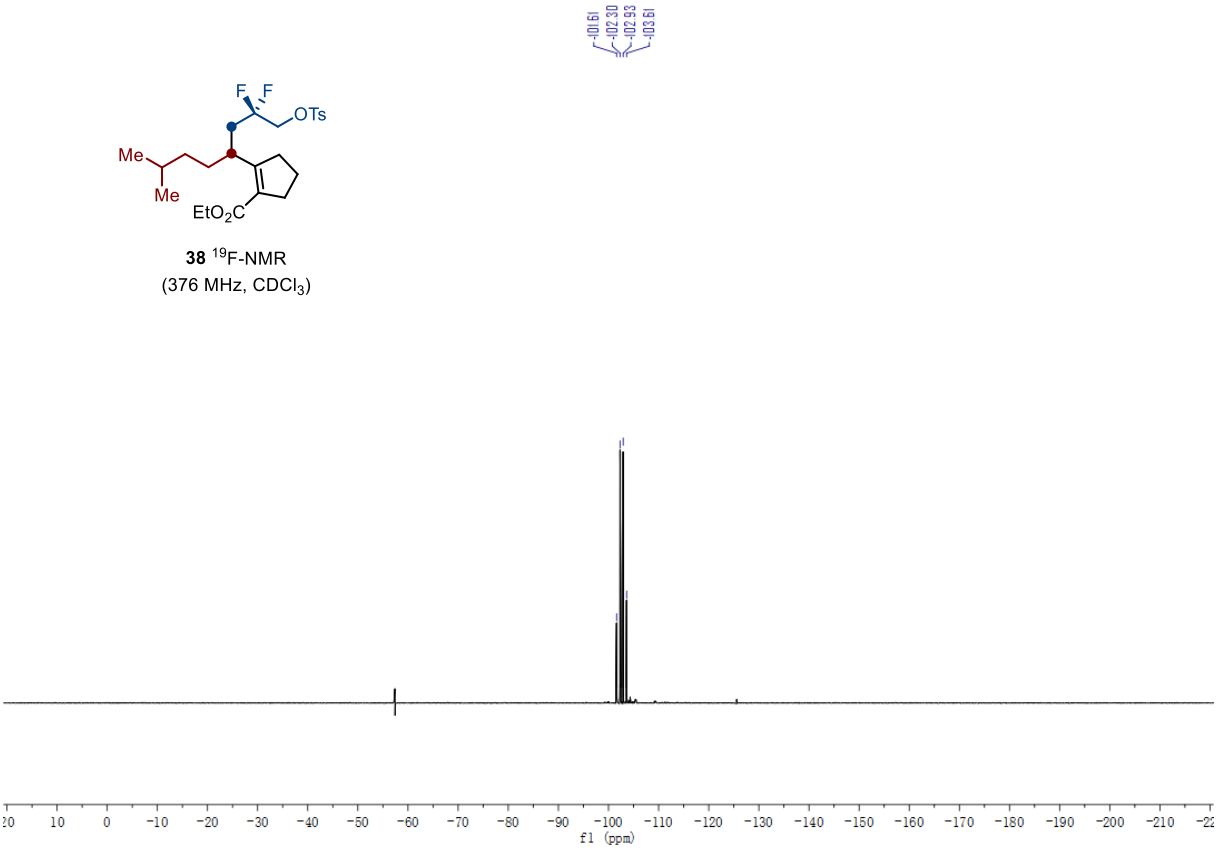
37 ^{19}F-NMR
(376 MHz, $CDCl_3$)



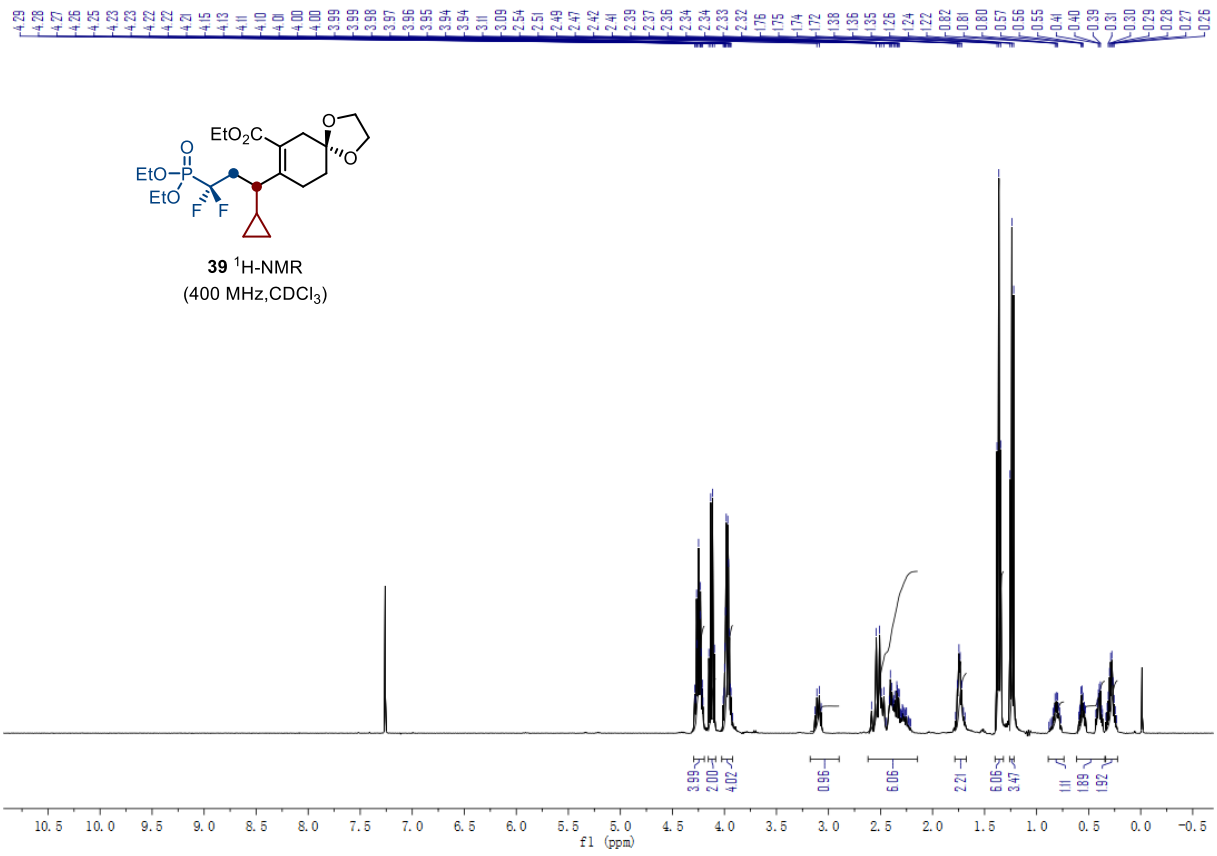
38 ^{1}H-NMR
(400 MHz,$CDCl_3$)



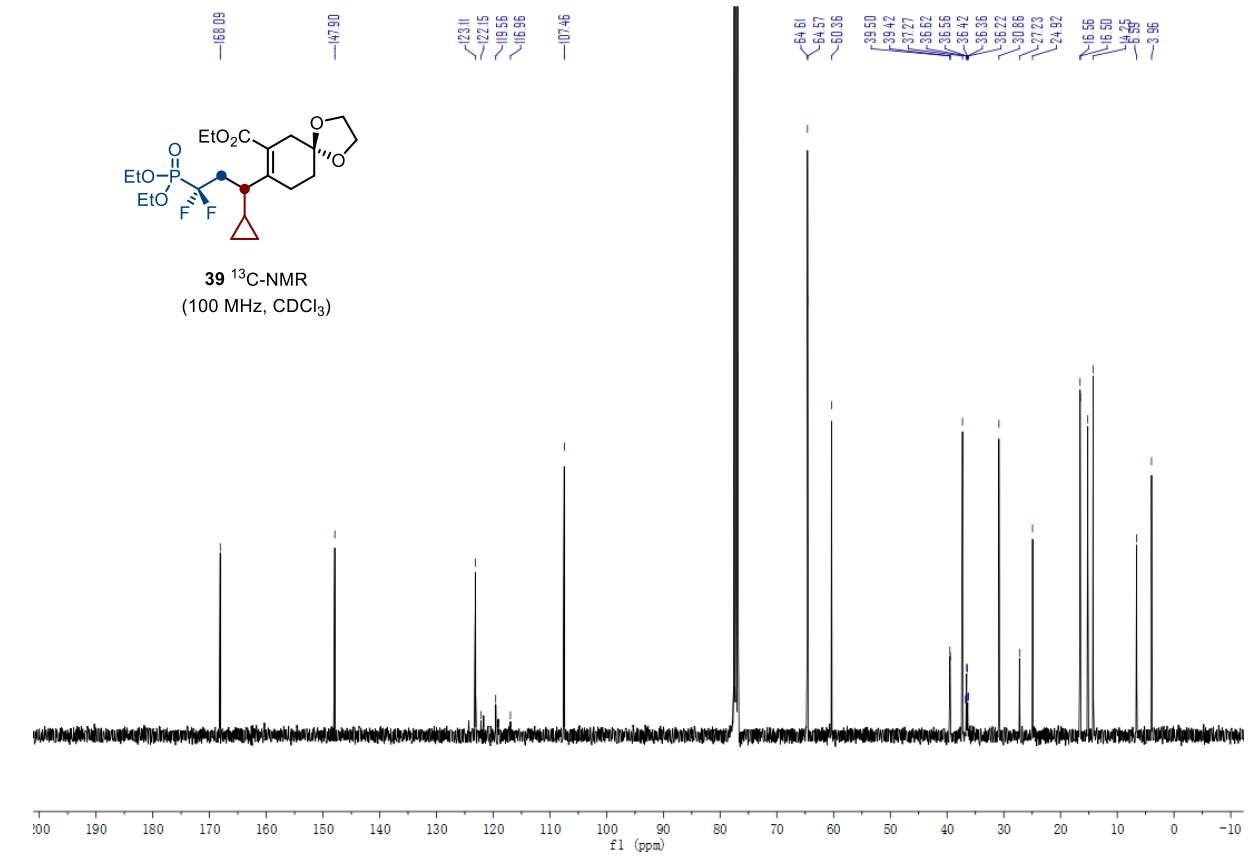
38 ^{13}C-NMR
(100 MHz, $CDCl_3$)



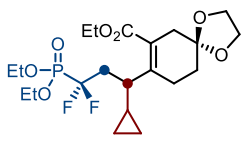
38 ^{19}F-NMR
(376 MHz, $CDCl_3$)



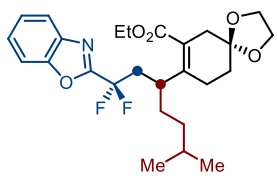
39 ^{1}H-NMR
(400 MHz,$CDCl_3$)



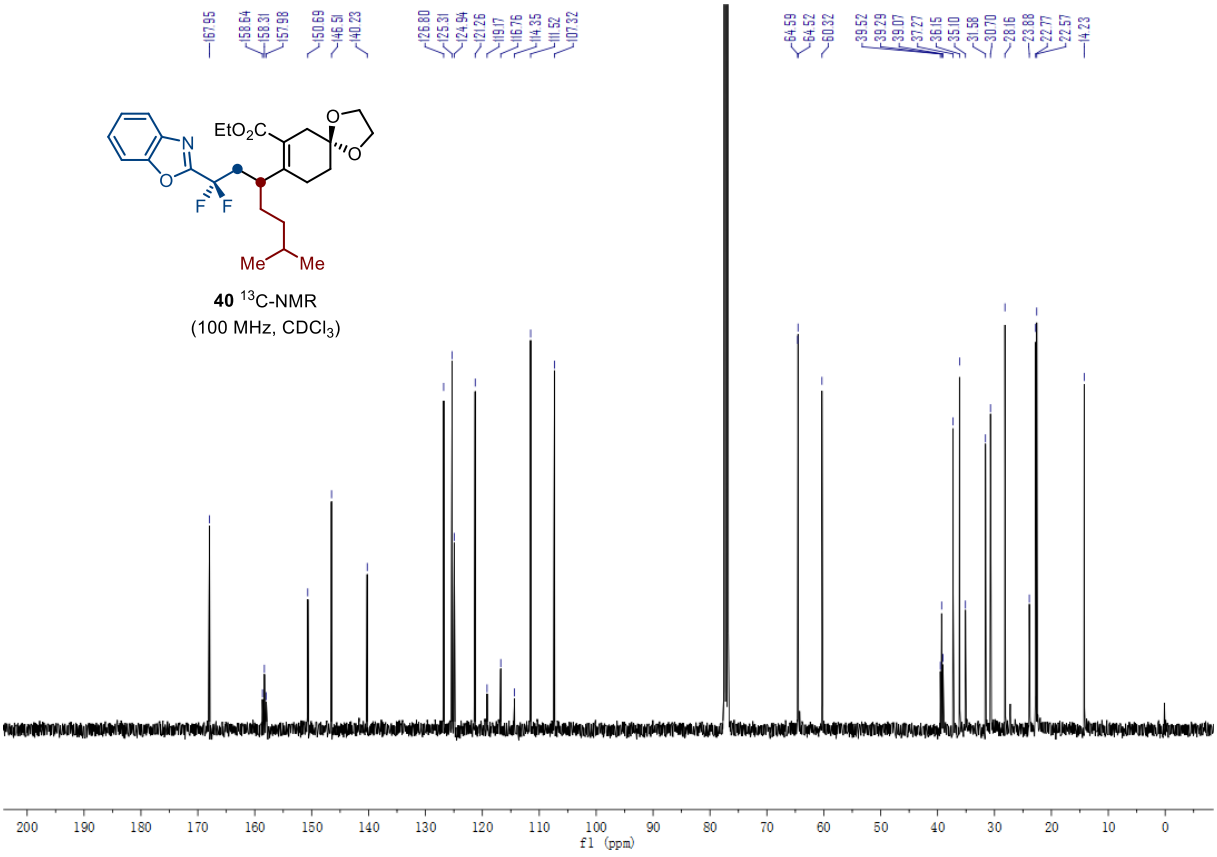
39 ^{13}C-NMR
(100 MHz, $CDCl_3$)



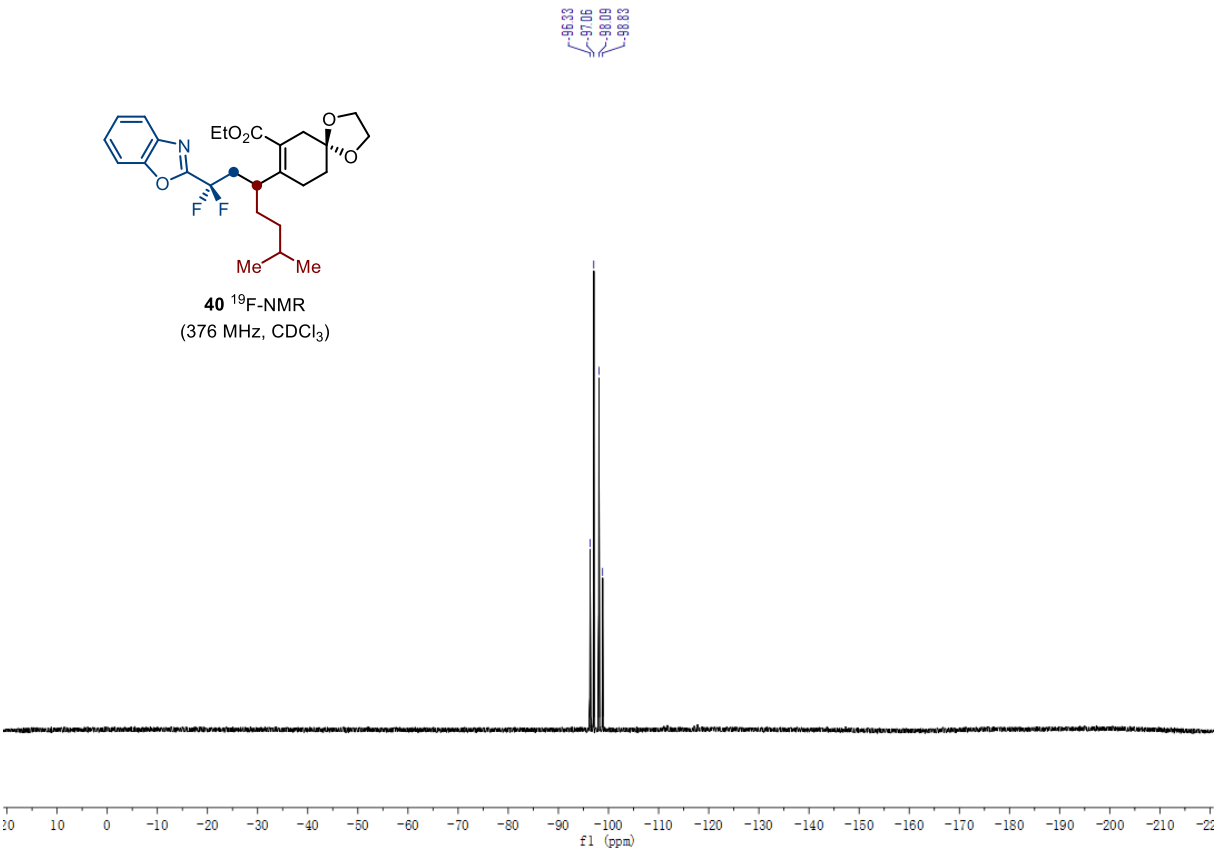
39 ^{19}F-NMR
(376 MHz, $CDCl_3$)



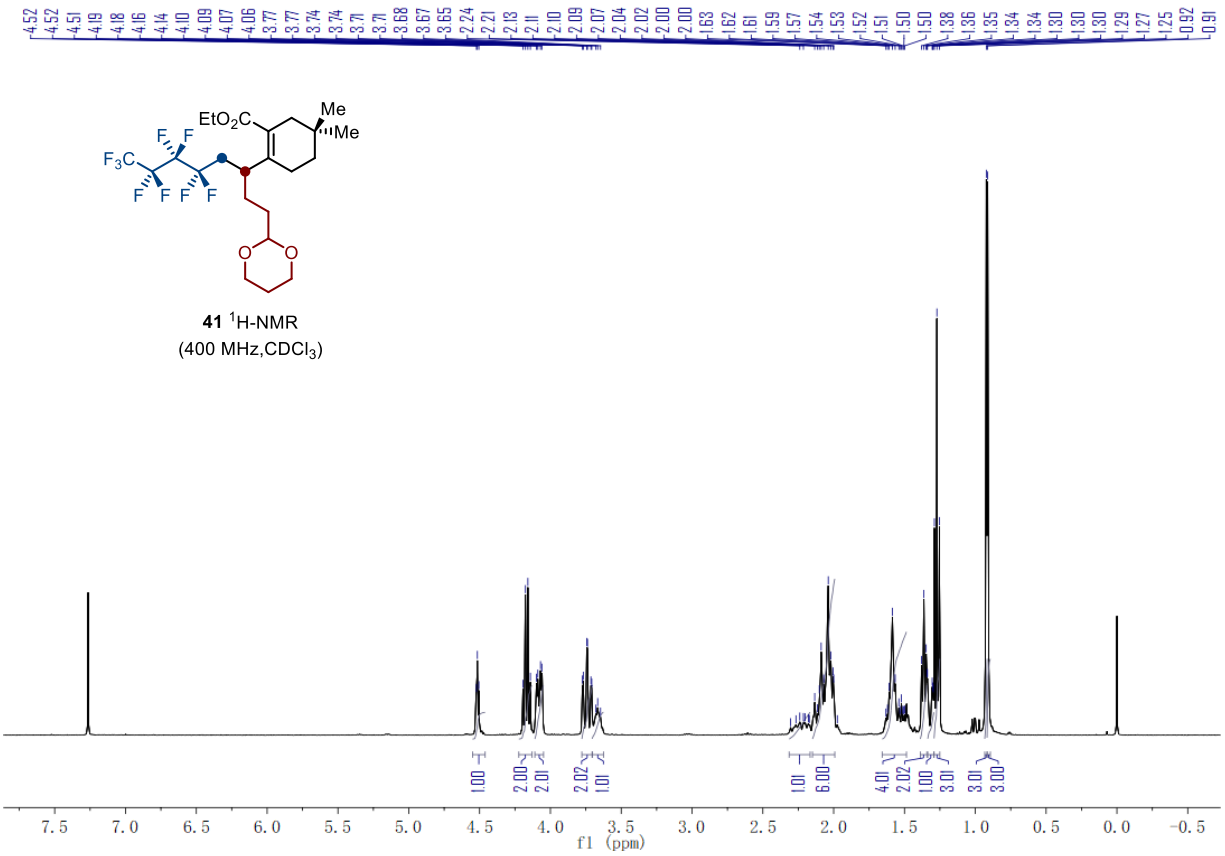
40 ^{1}H-NMR
(400 MHz,$CDCl_3$)

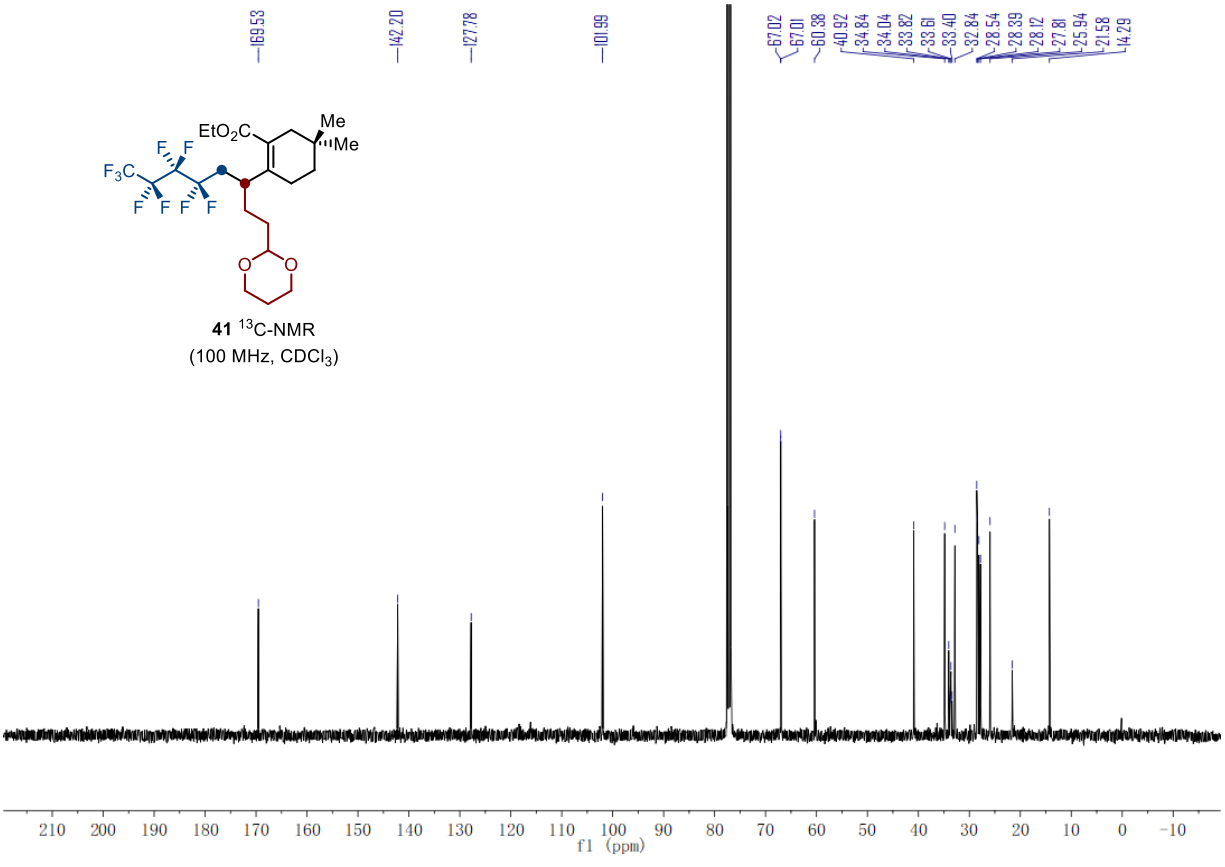


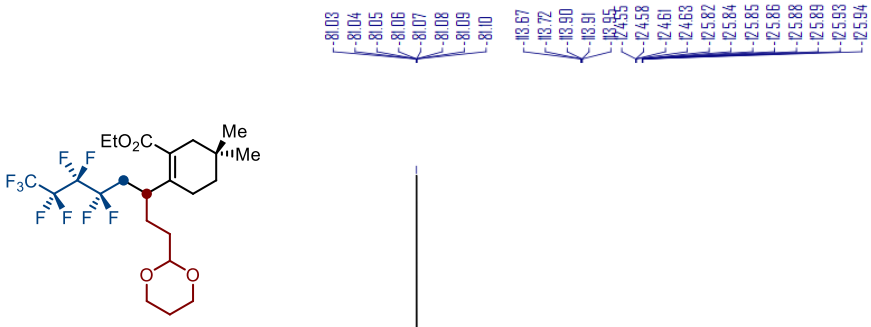
40 ^{13}C-NMR
(100 MHz, $CDCl_3$)



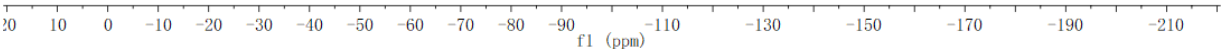
40 ^{19}F-NMR
(376 MHz, $CDCl_3$)

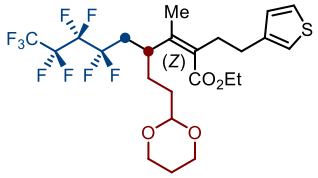

EtO2C
Me
Me
F3C
F
F
F
F
F
F
O
O
41 1H-NMR
(400 MHz,CDCl3)
f1 (ppm)


EtO2C
Me
Me
F3C
F
F
F
F
F
F
O
O
41 13C-NMR
(100 MHz, CDCl3)
f1 (ppm)

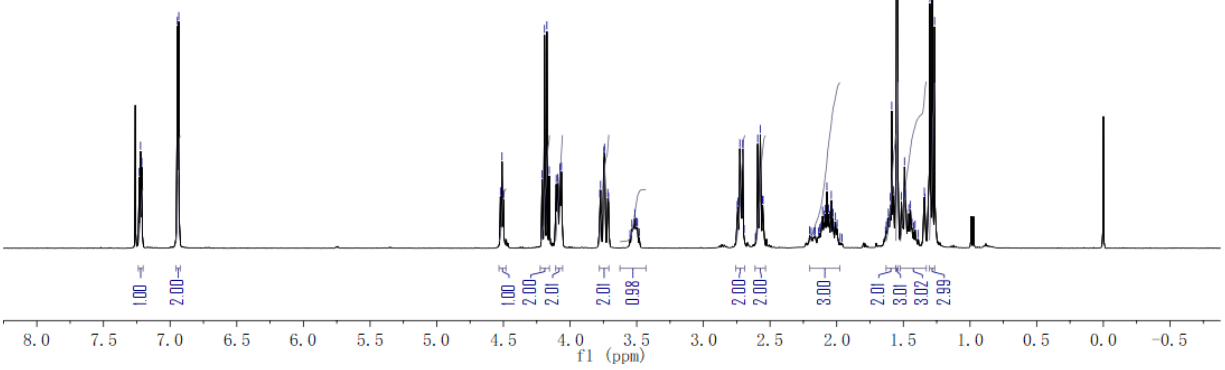


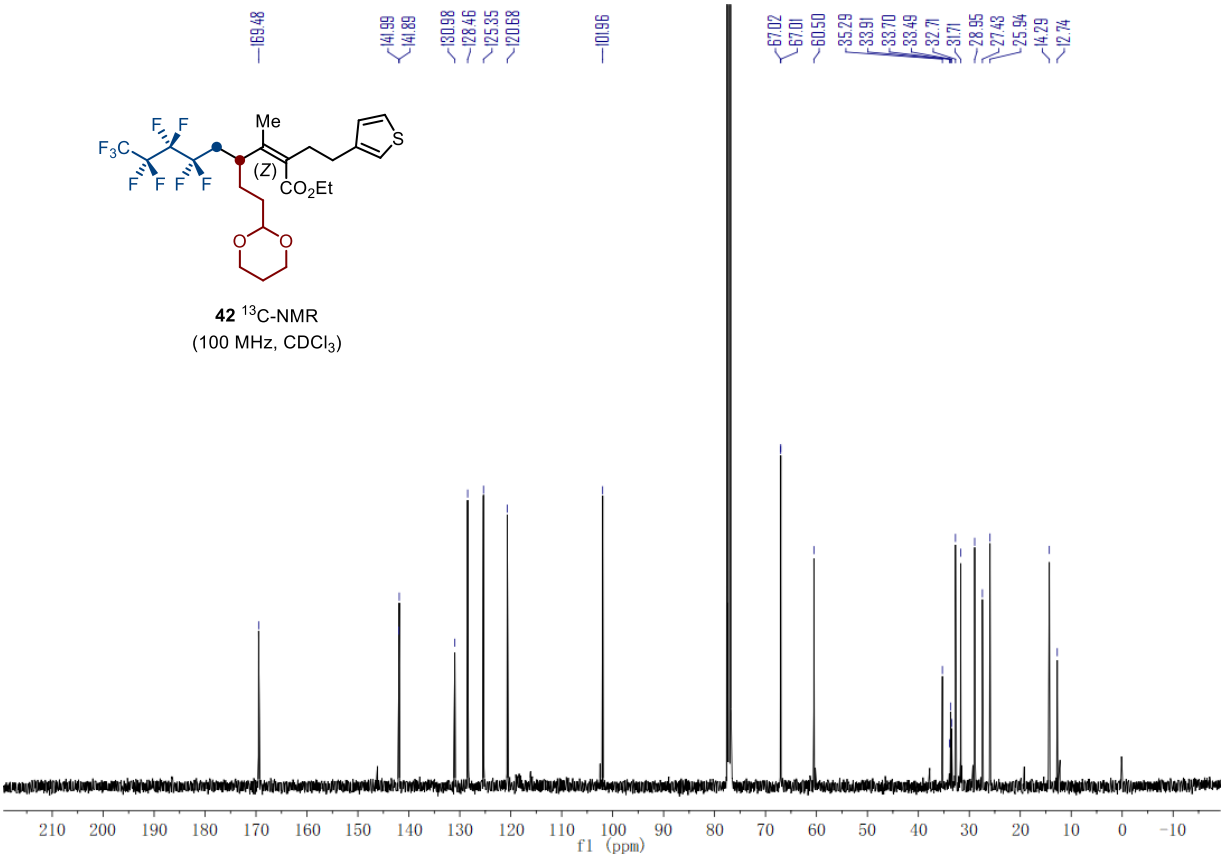
41 ^{19}F-NMR
(376 MHz, $CDCl_3$)



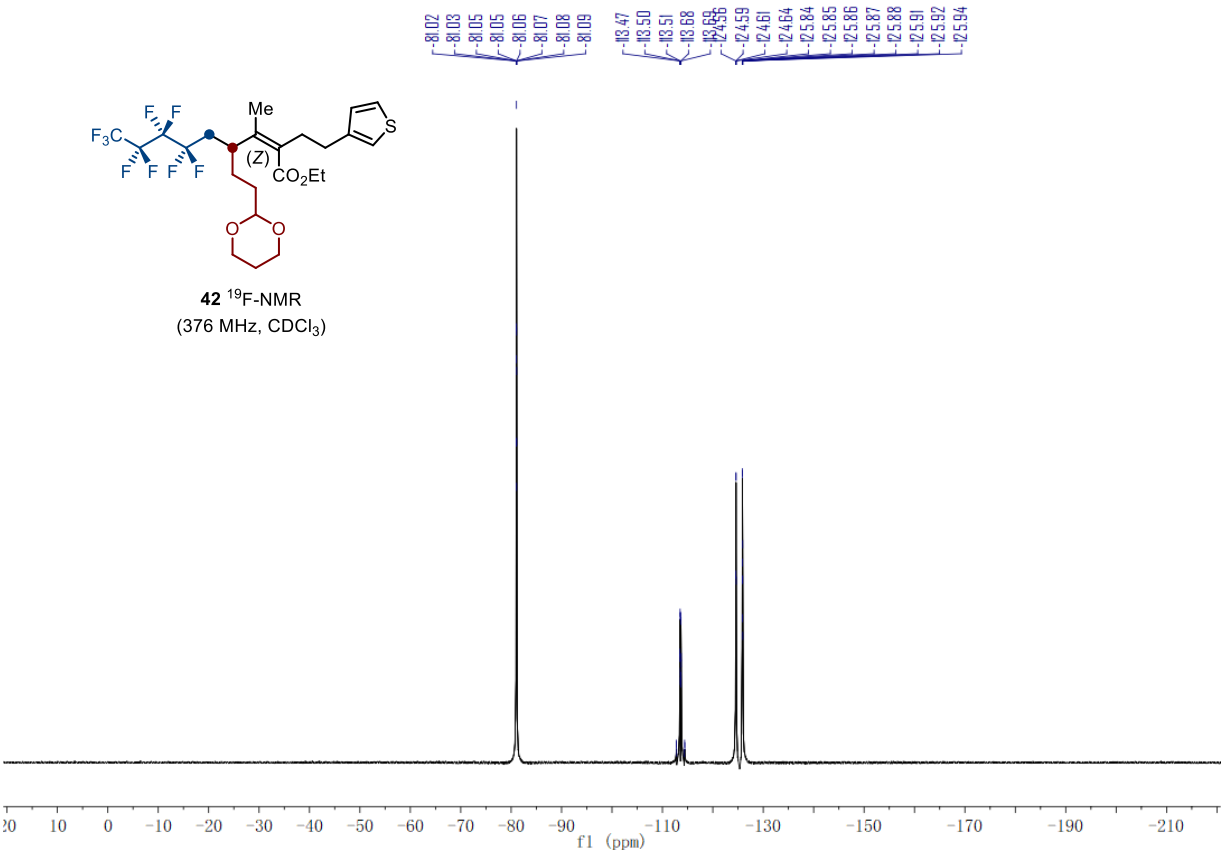


42 ^{1}H-NMR
(400 MHz,$CDCl_3$)

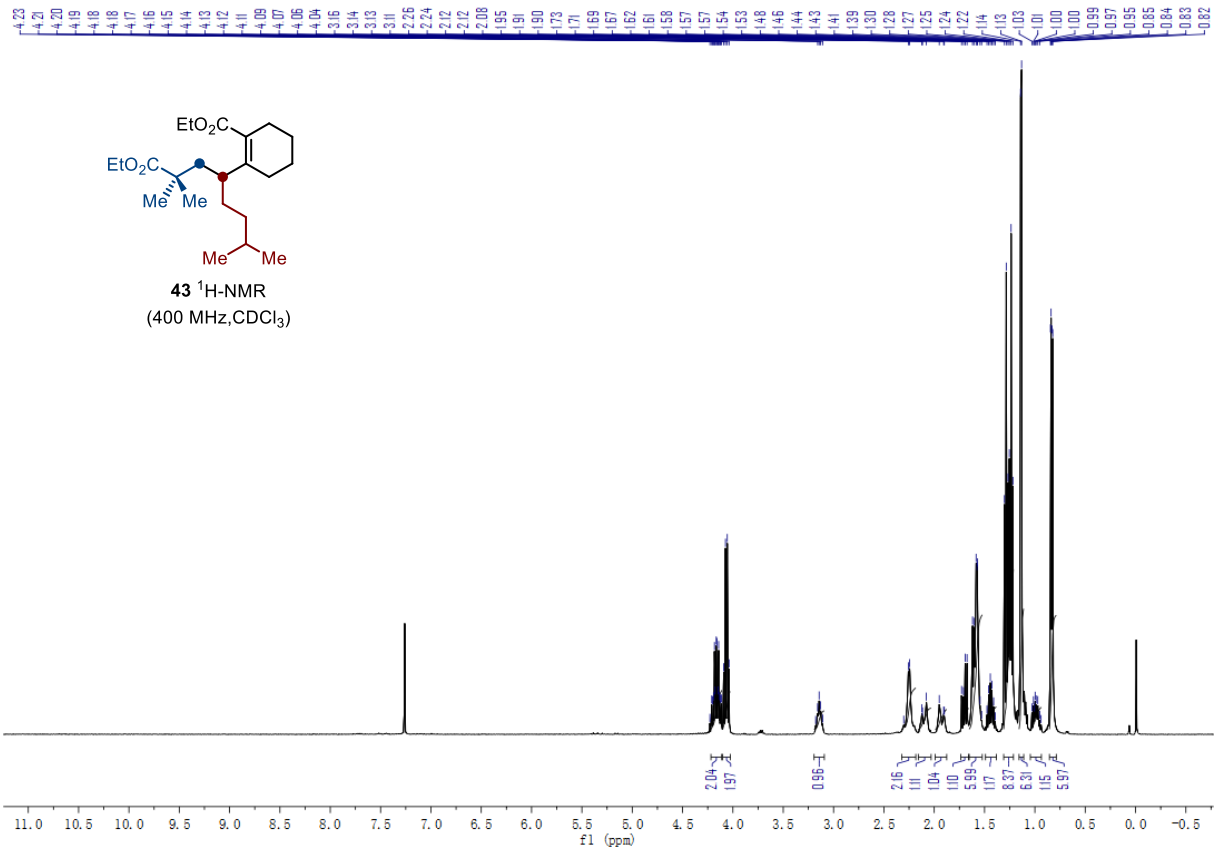




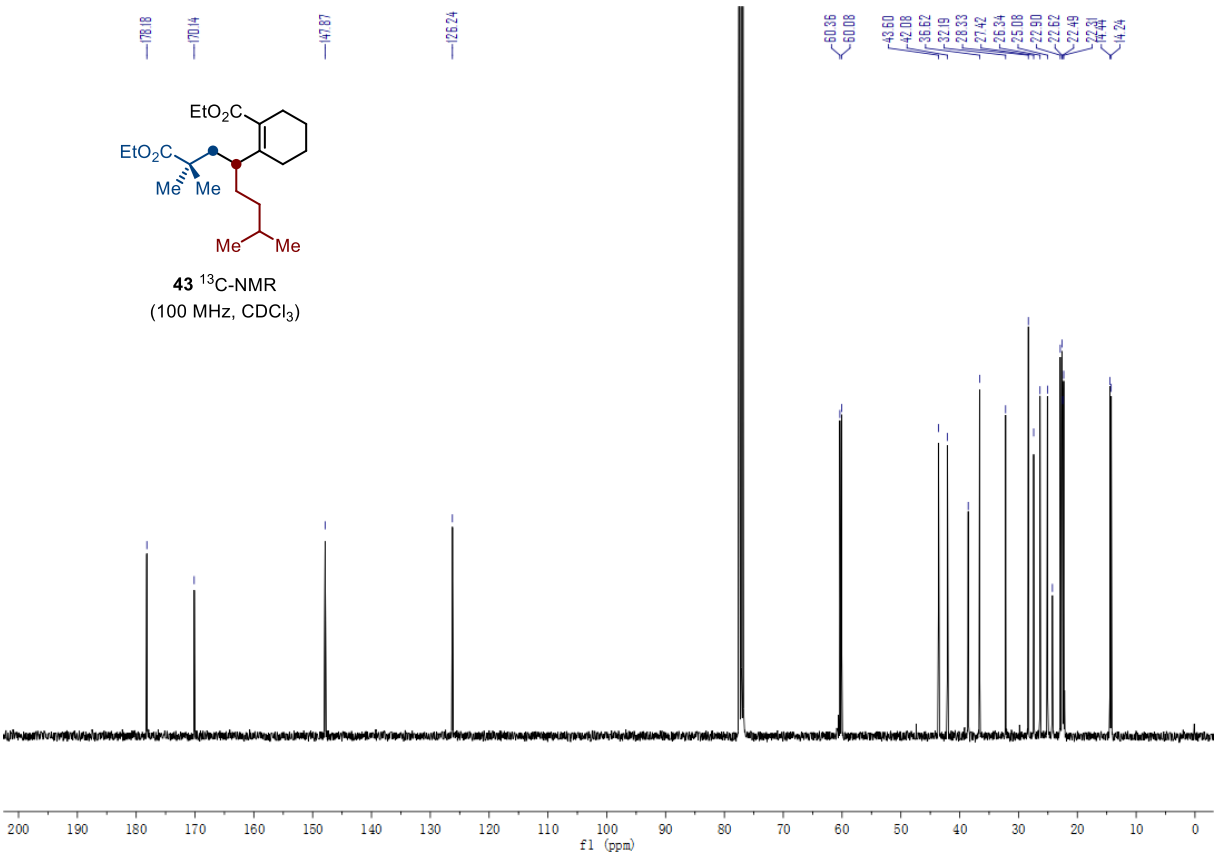
42 ^{13}C-NMR
(100 MHz, $CDCl_3$)



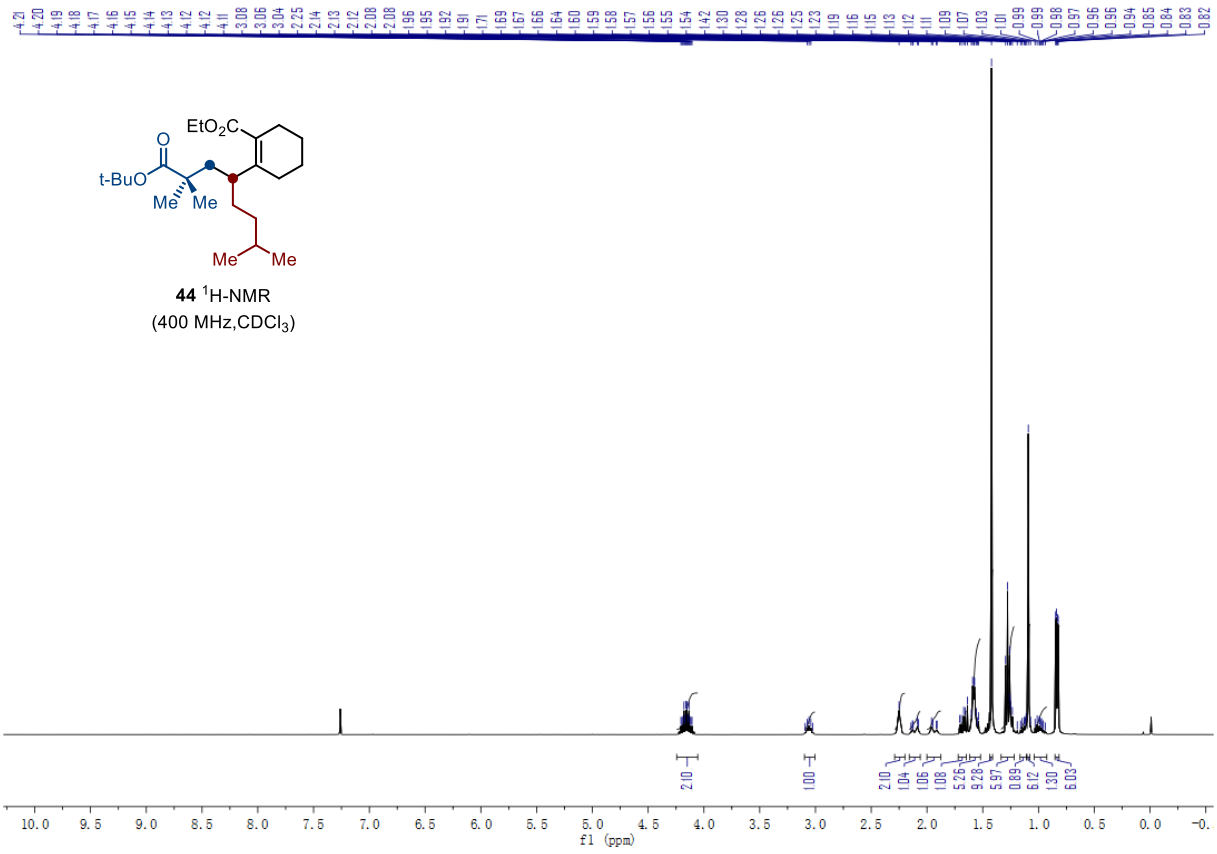
42 ^{19}F-NMR
(376 MHz, $CDCl_3$)



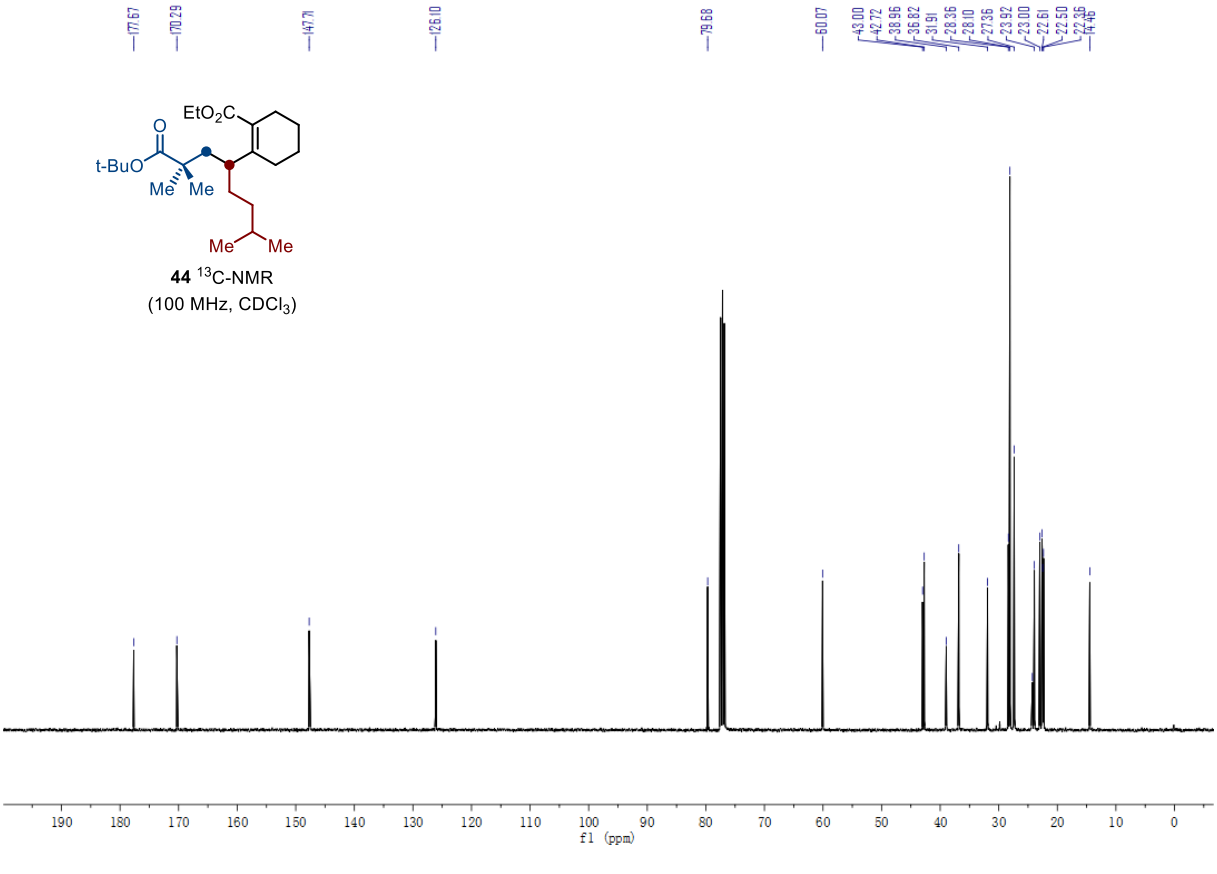
43 ^{1}H-NMR
(400 MHz,$CDCl_3$)



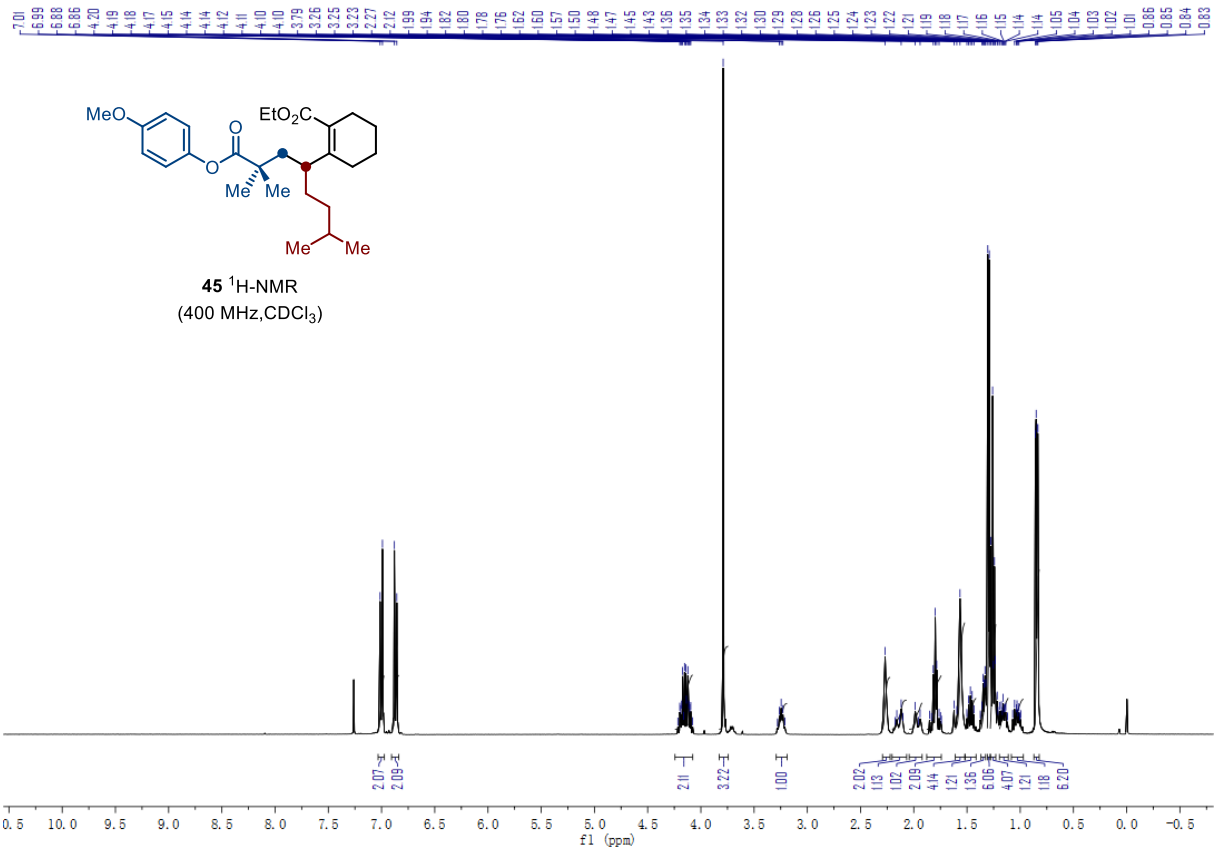
43 ^{13}C-NMR
(100 MHz, $CDCl_3$)



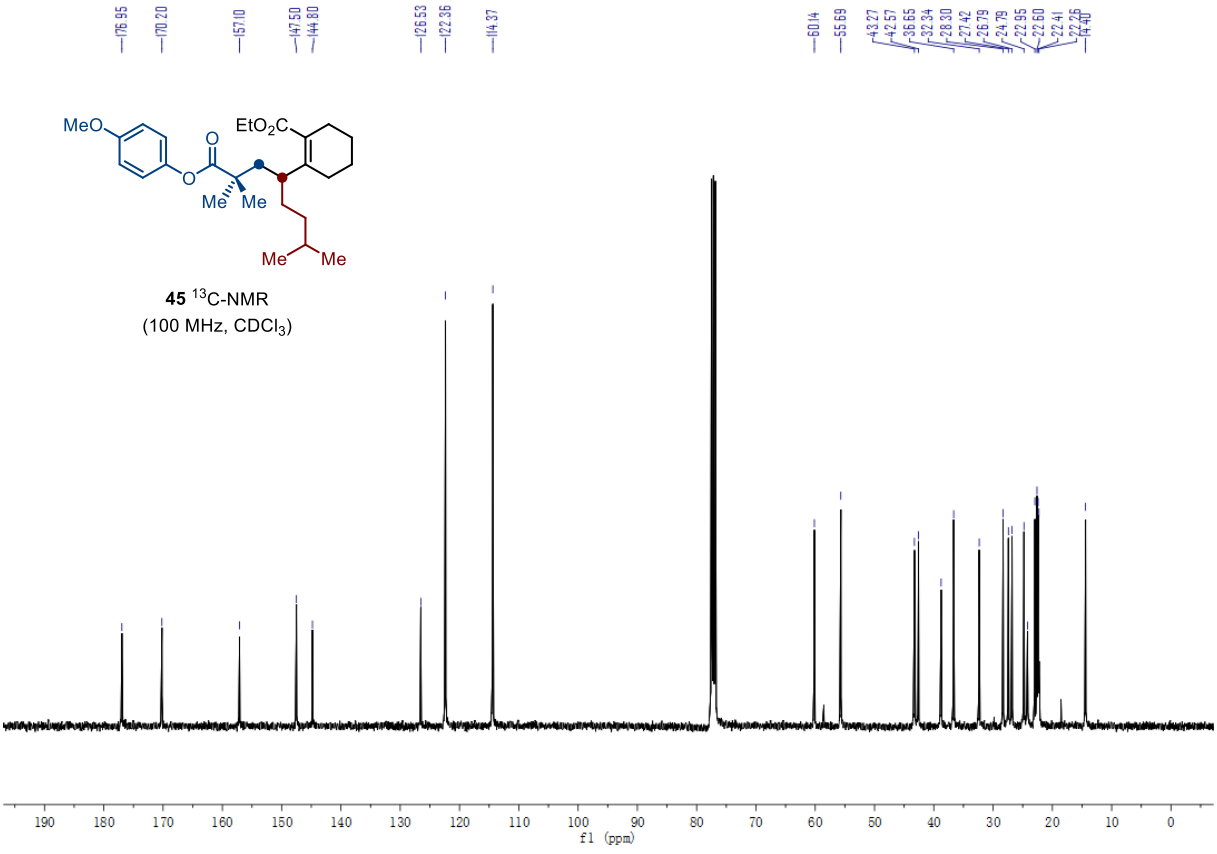
44 ^{1}H-NMR
(400 MHz,$CDCl_3$)



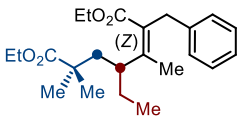
44 ^{13}C-NMR
(100 MHz, $CDCl_3$)



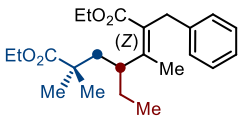
45 ^{1}H-NMR
(400 MHz,$CDCl_3$)



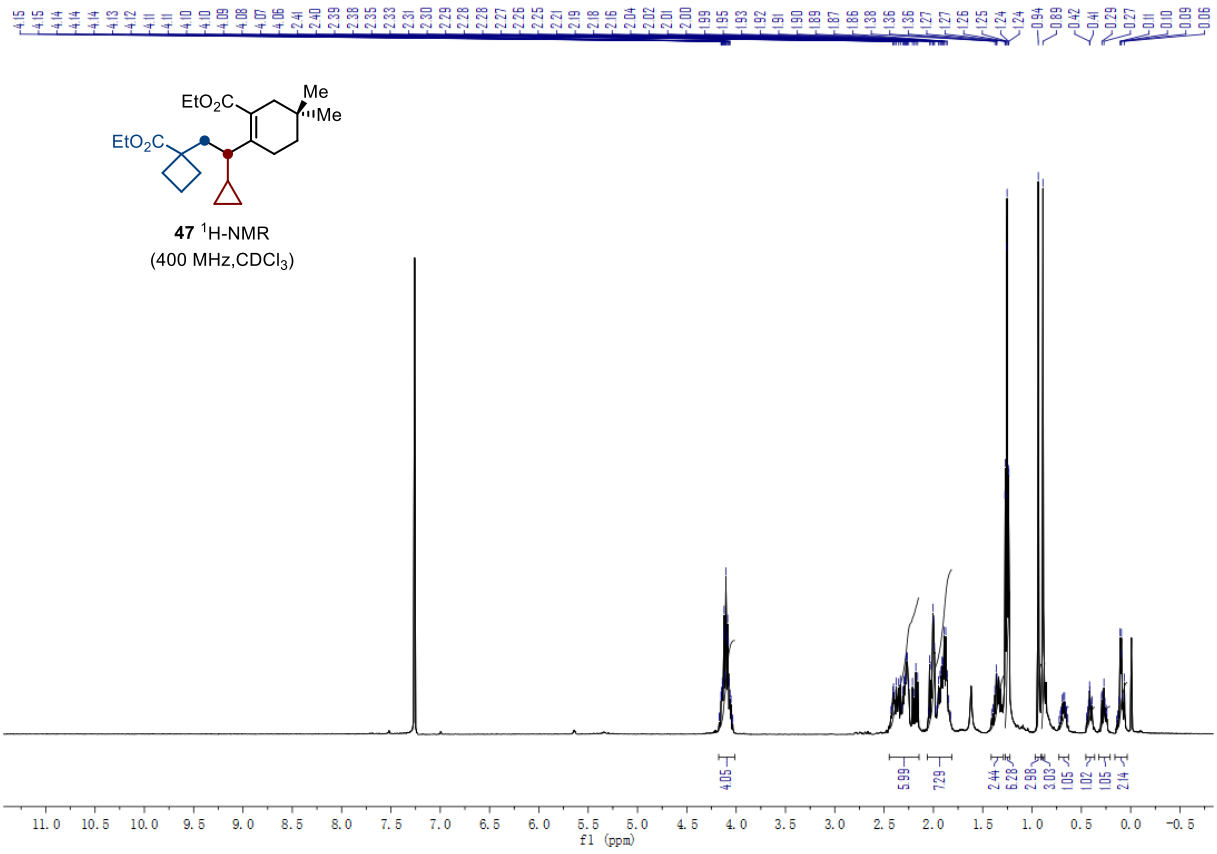
45 ^{13}C-NMR
(100 MHz, $CDCl_3$)

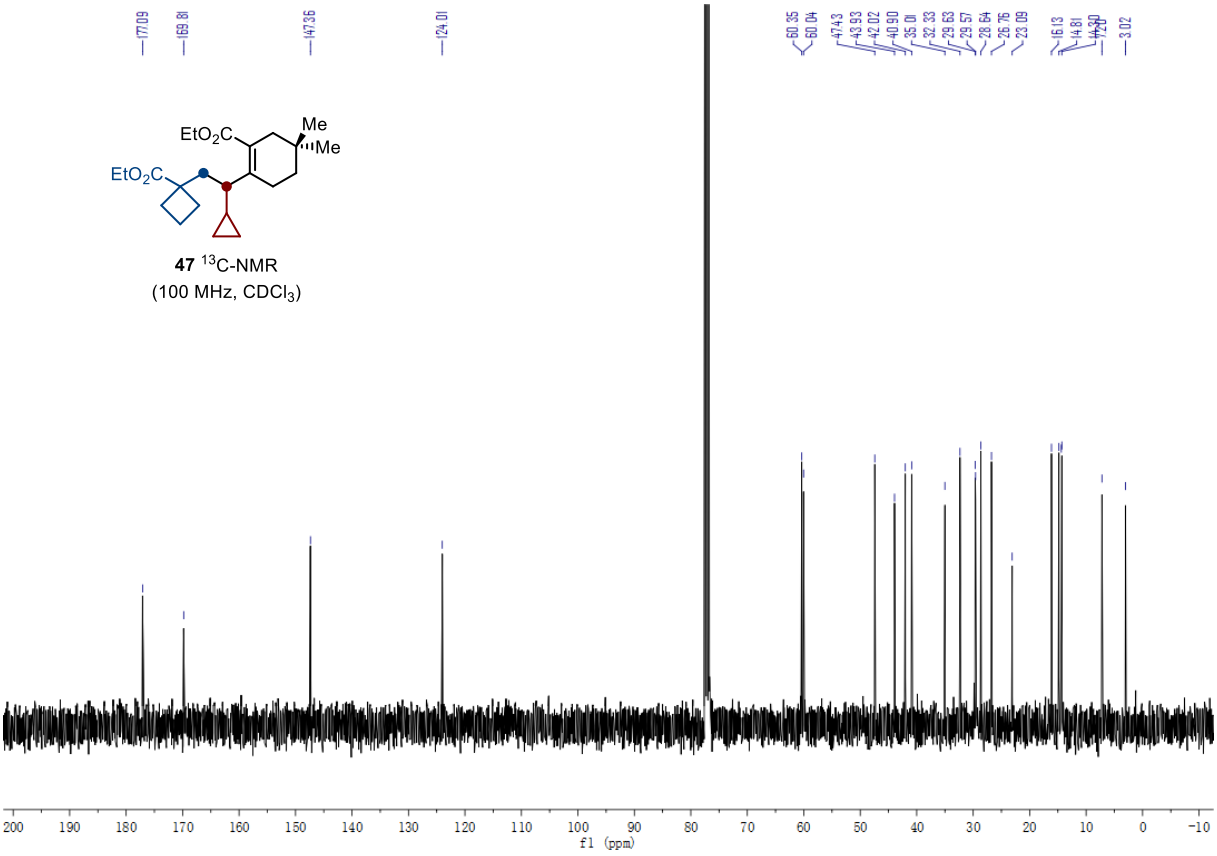


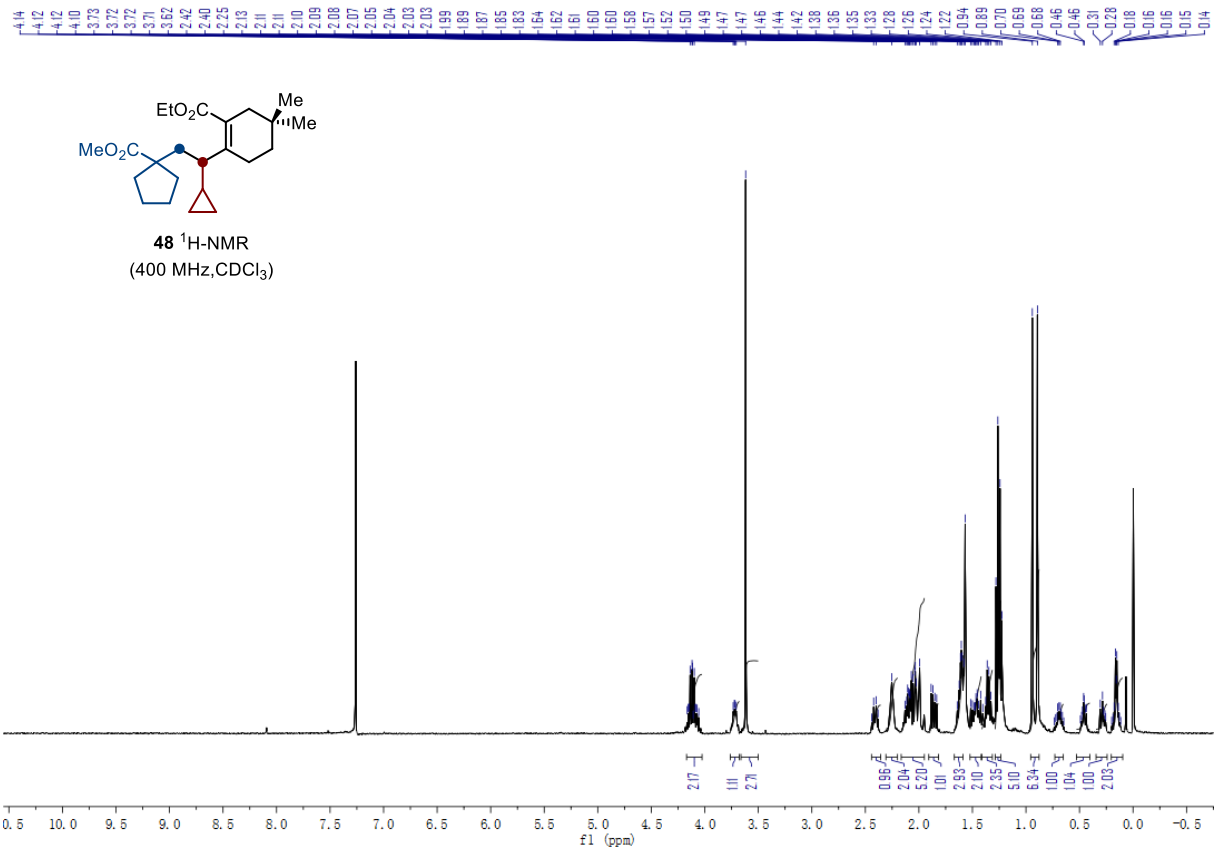
46 ^{1}H-NMR
(400 MHz,$CDCl_3$)

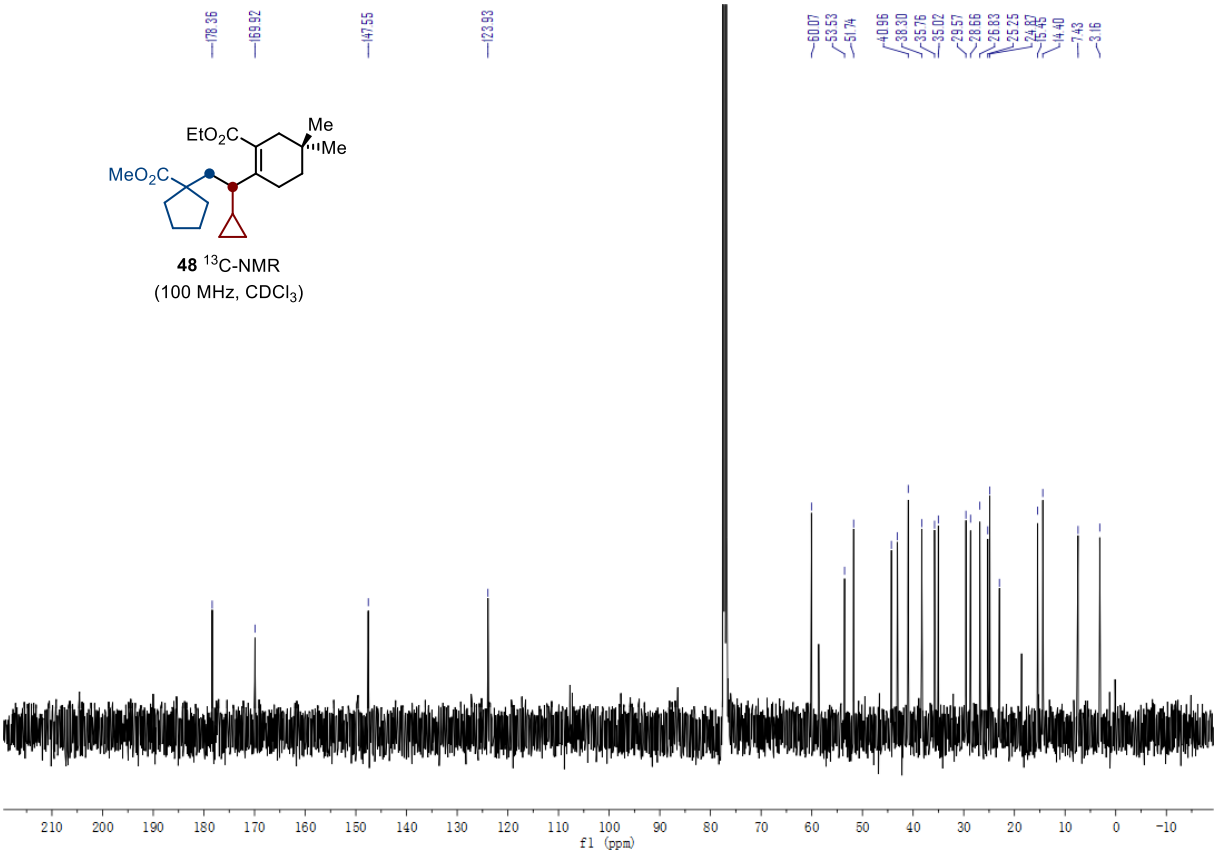


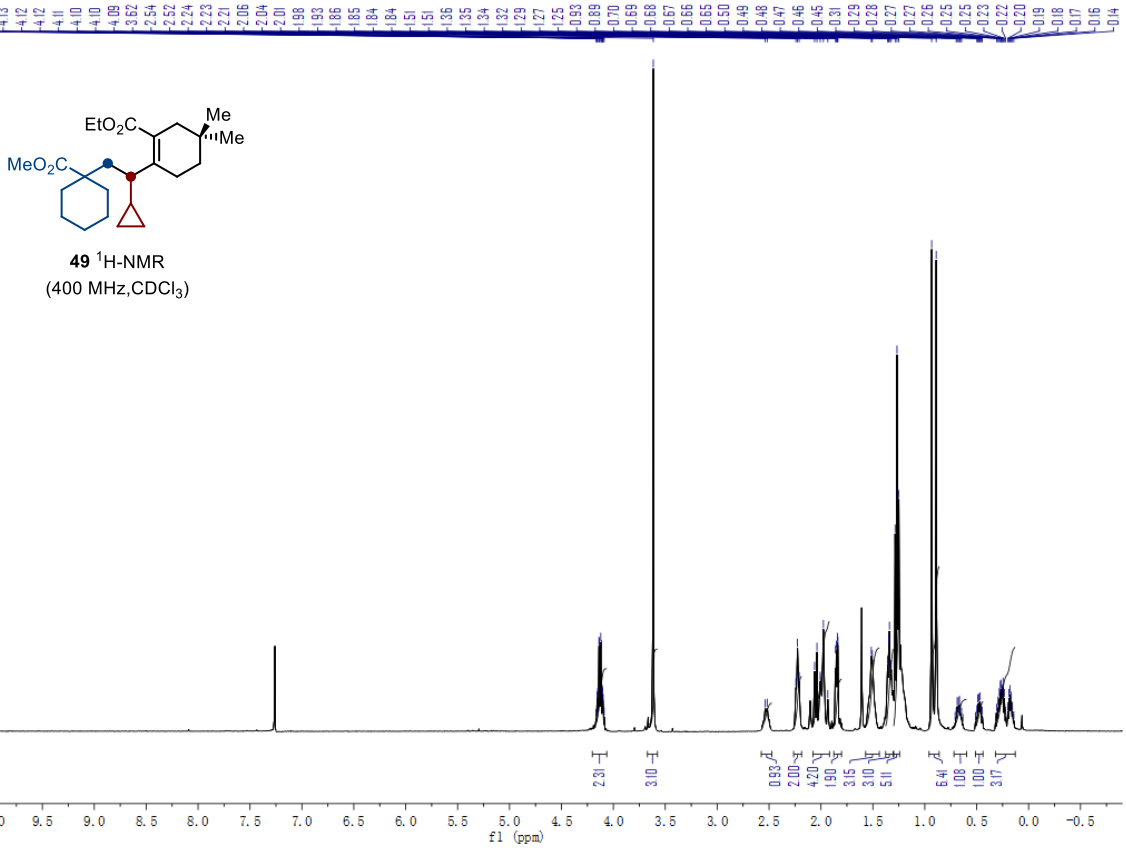
46 ^{13}C-NMR
(100 MHz, $CDCl_3$)


EtO2C
Me
Me
EtO2C
47 1H-NMR
(400 MHz,CDCl3)
f1 (ppm)

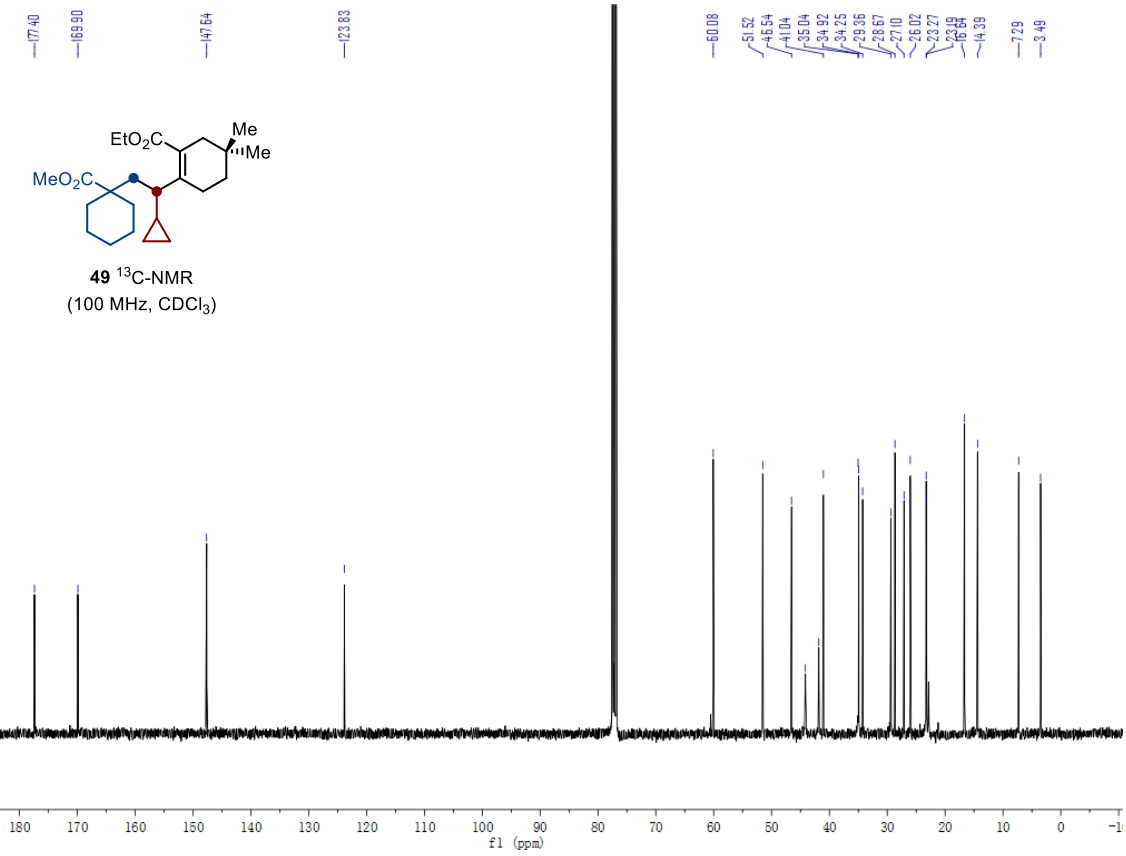

EtO2C
Me
Me
EtO2C
47 13C-NMR
(100 MHz, CDCl3)
f1 (ppm)


EtO2C
Me
Me
MeO2C
48 1H-NMR
(400 MHz,CDCl3)
f1 (ppm)

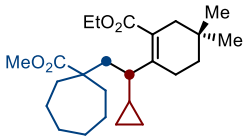

EtO2C
Me
Me
MeO2C
48 13C-NMR
(100 MHz, CDCl3)
f1 (ppm)



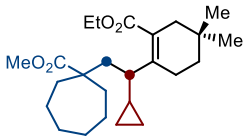
49 ^{1}H-NMR
(400 MHz,$CDCl_3$)



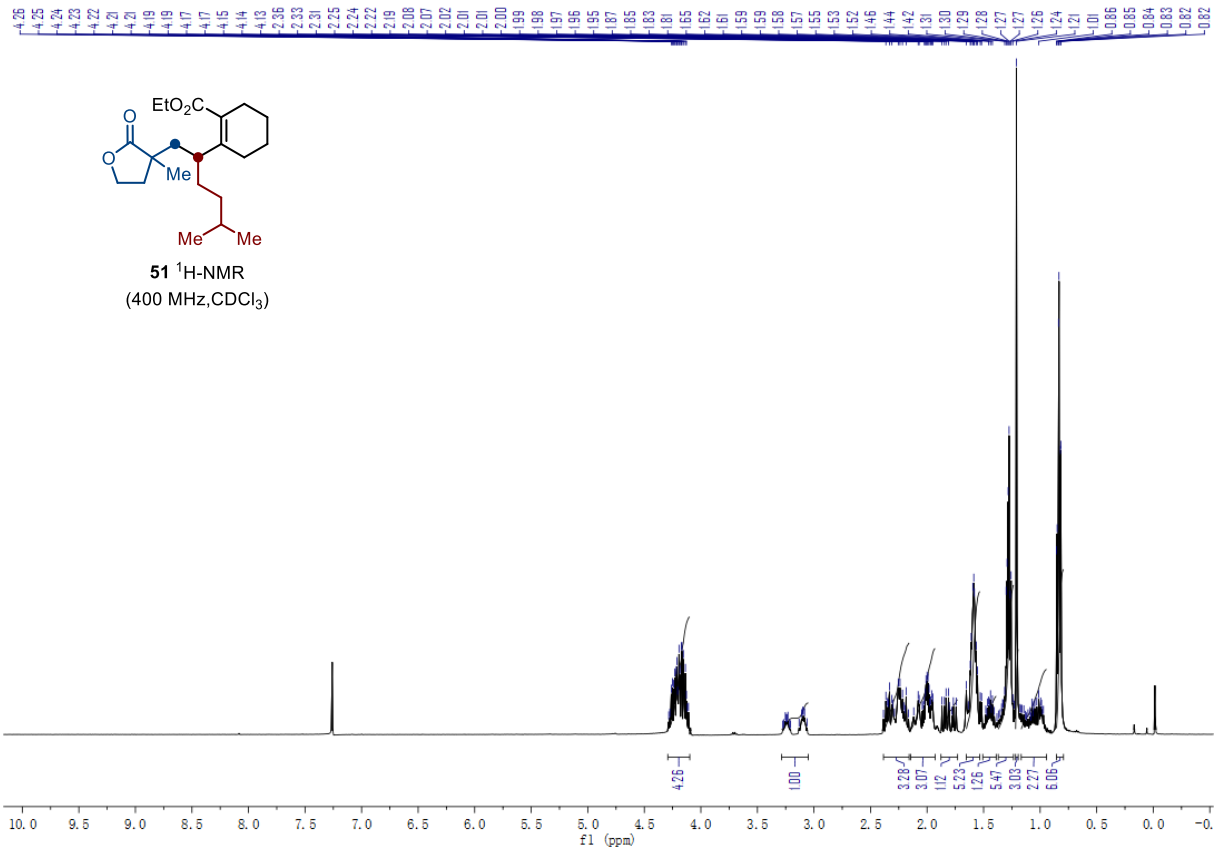
49 ^{13}C-NMR
(100 MHz, $CDCl_3$)



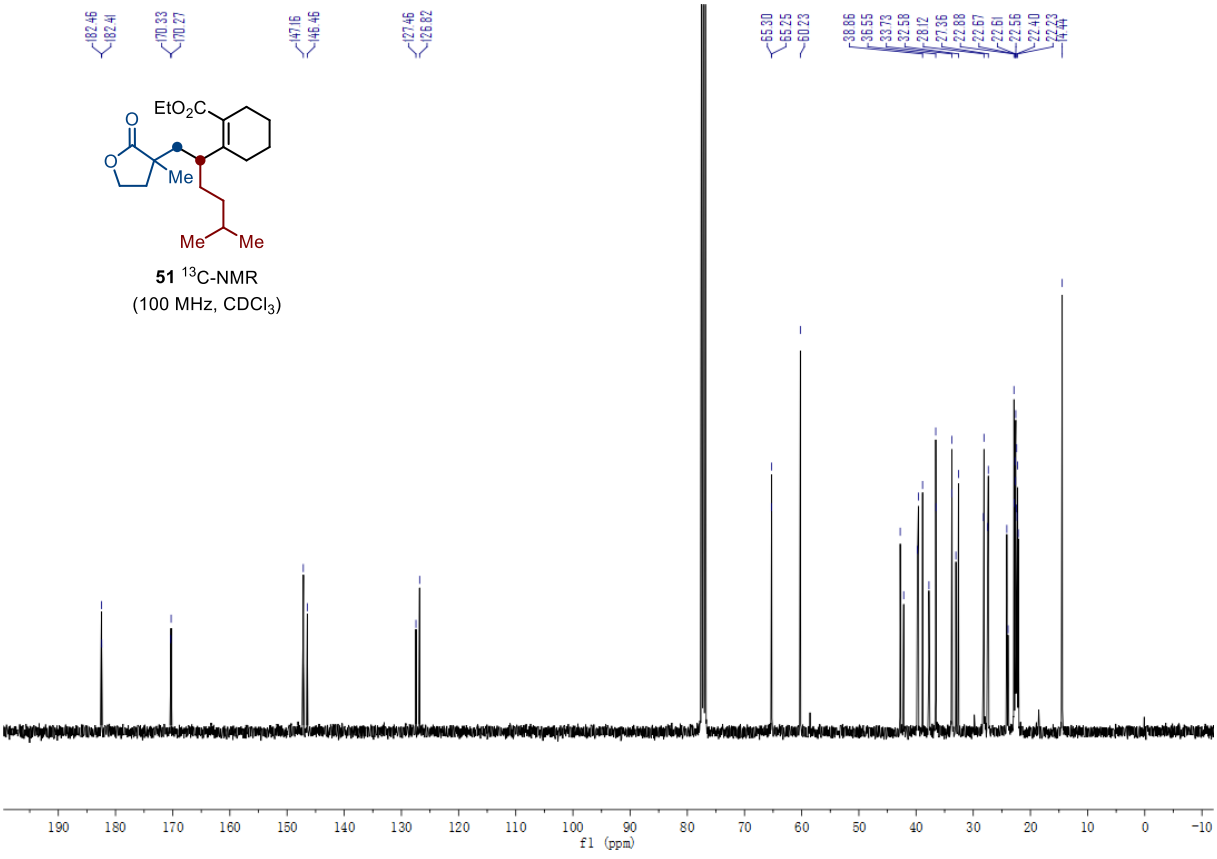
50 ^{1}H-NMR
(400 MHz,$CDCl_3$)



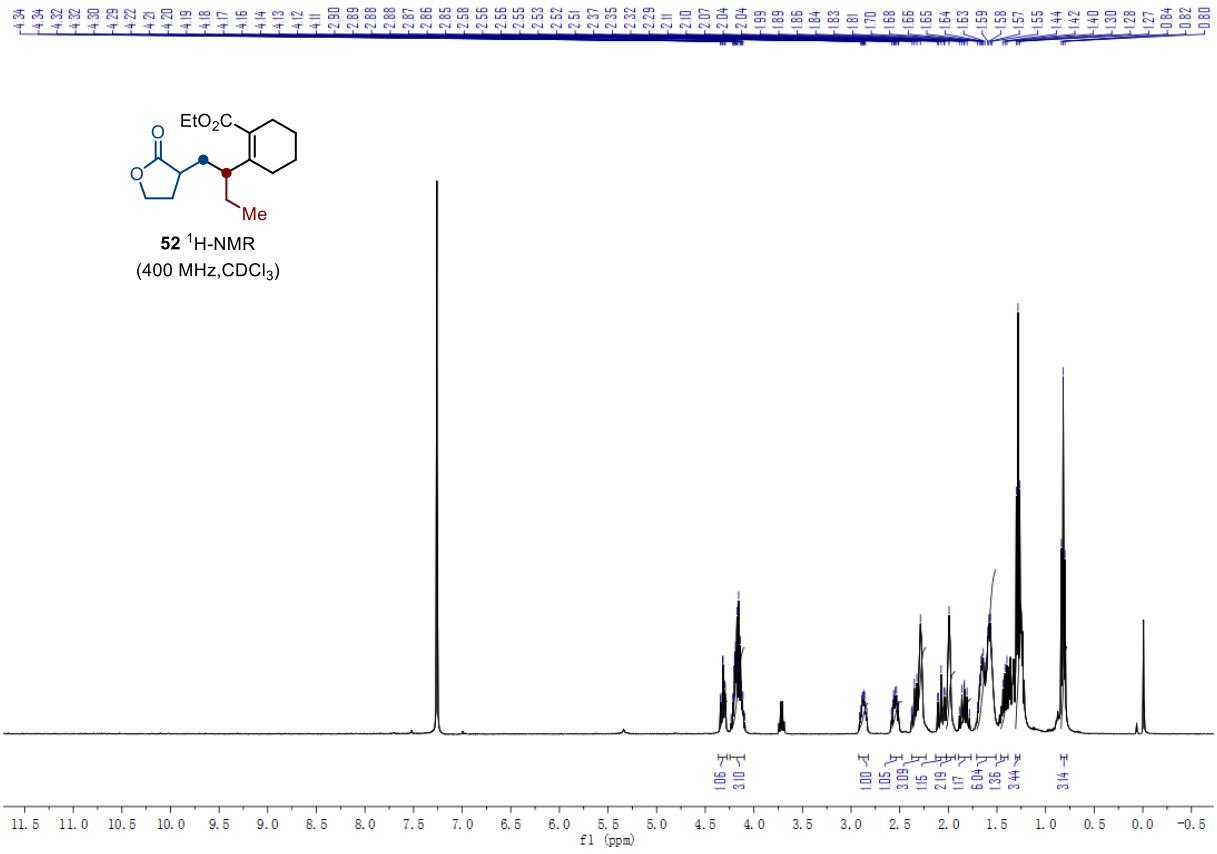
50 ^{13}C-NMR
(100 MHz, $CDCl_3$)

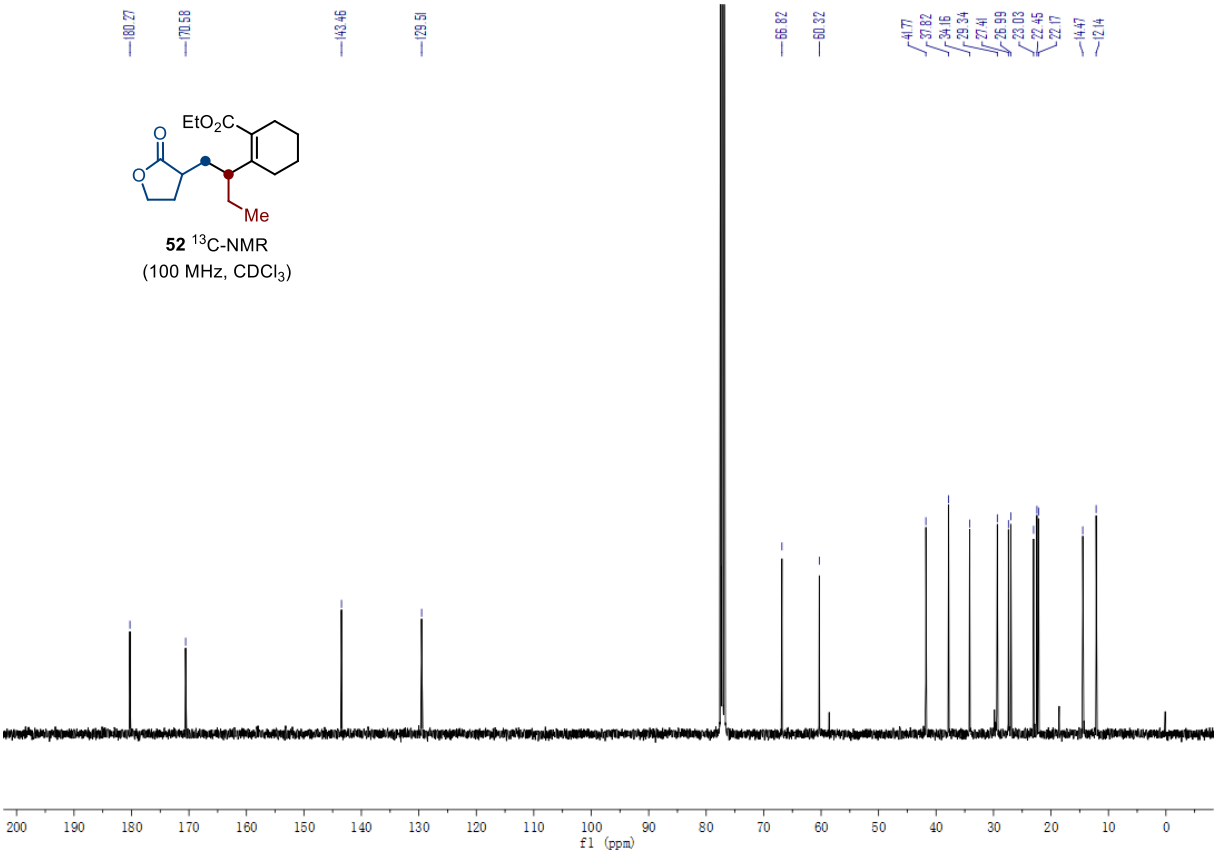


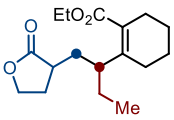
51 ^{1}H-NMR
(400 MHz,$CDCl_3$)



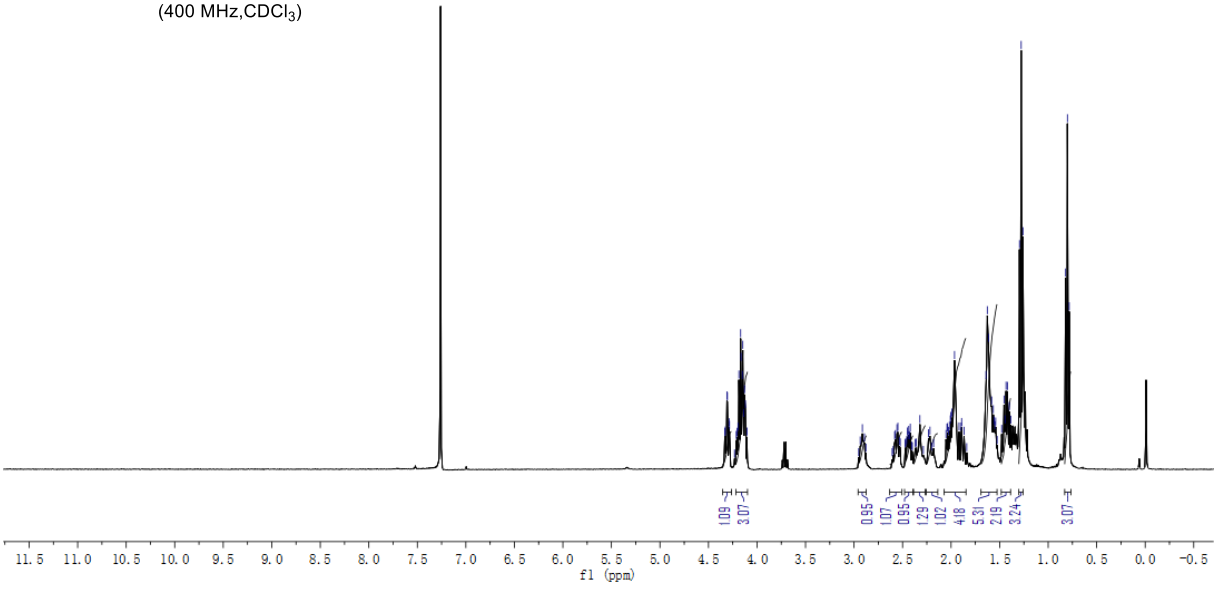
51 ^{13}C-NMR
(100 MHz, $CDCl_3$)

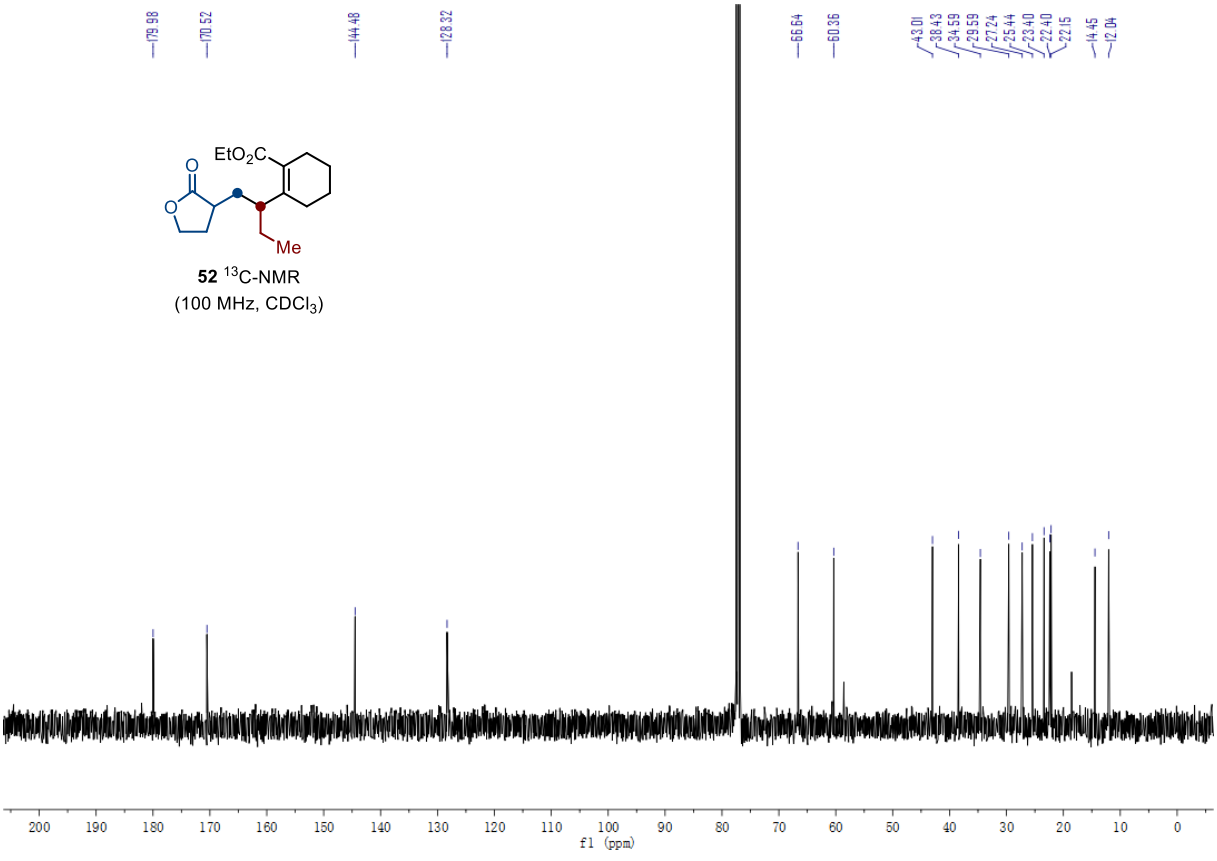

EtO2C
O
O
Me
52 1H-NMR
(400 MHz,CDCl3)
f1 (ppm)


EtO2C
O
O
Me
52 13C-NMR
(100 MHz, CDCl3)
f1 (ppm)

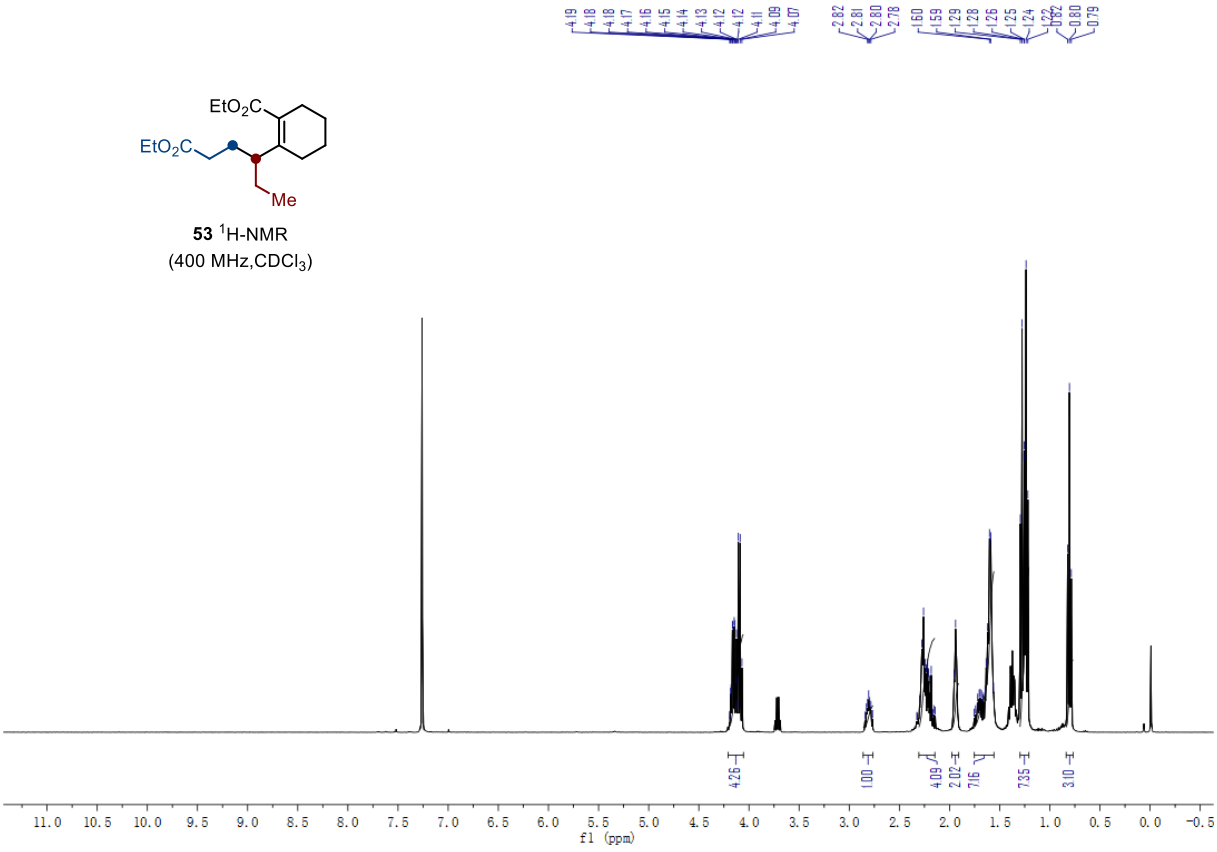


52 ^{1}H-NMR
(400 MHz,$CDCl_3$)

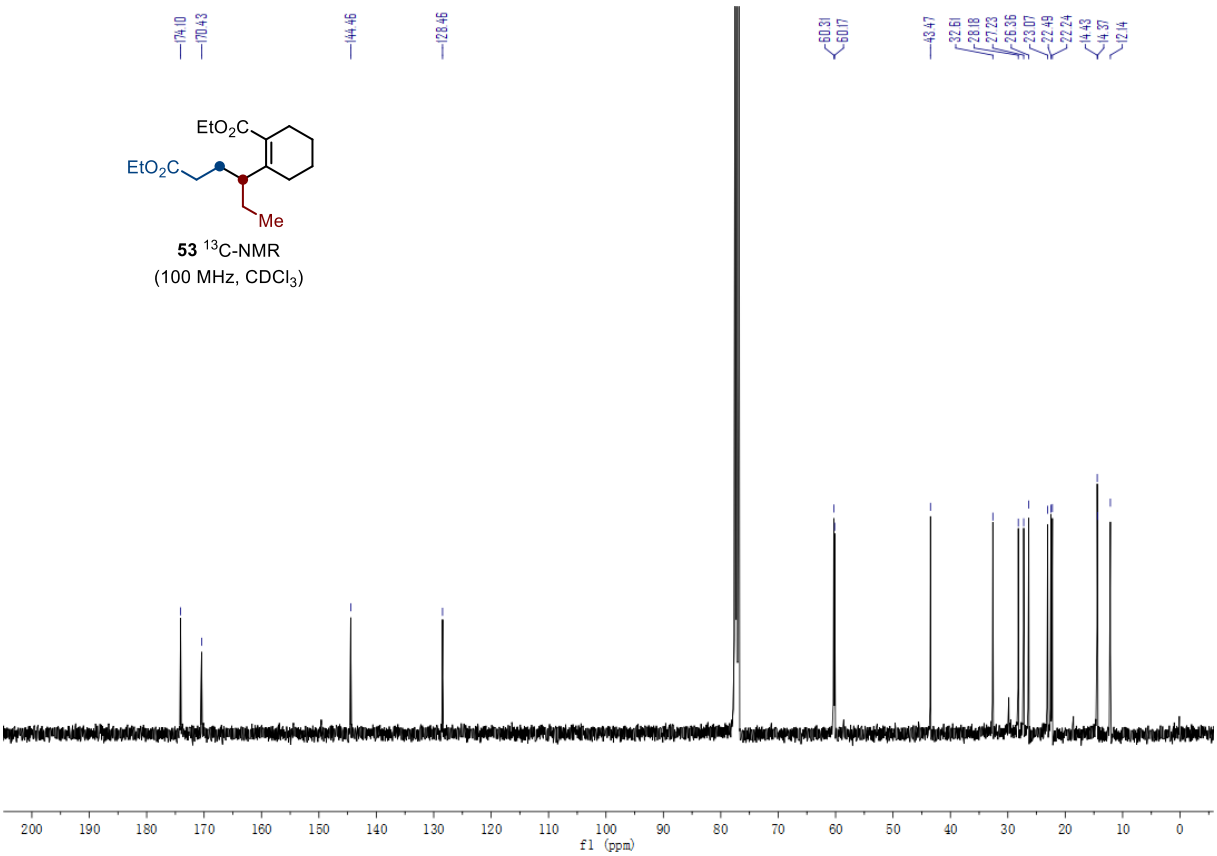




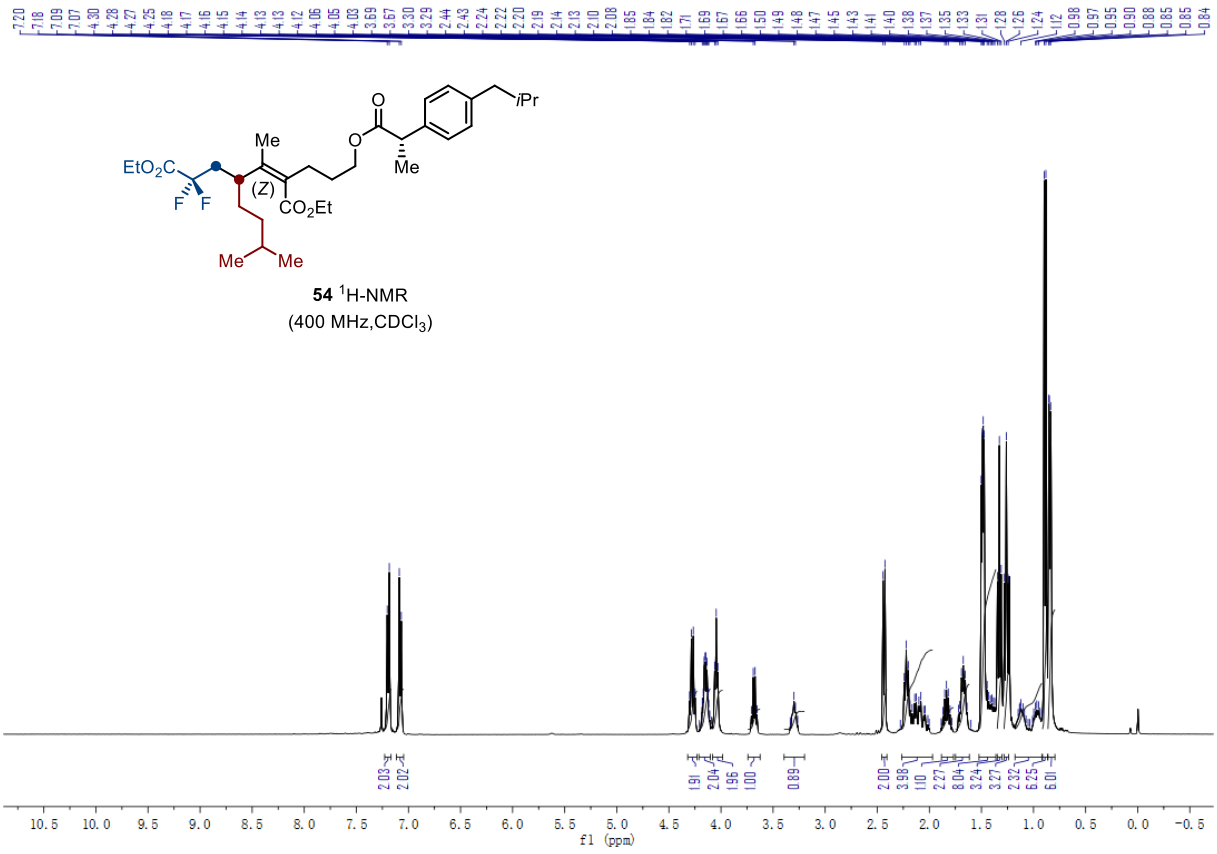
52 ^{13}C-NMR
(100 MHz, $CDCl_3$)



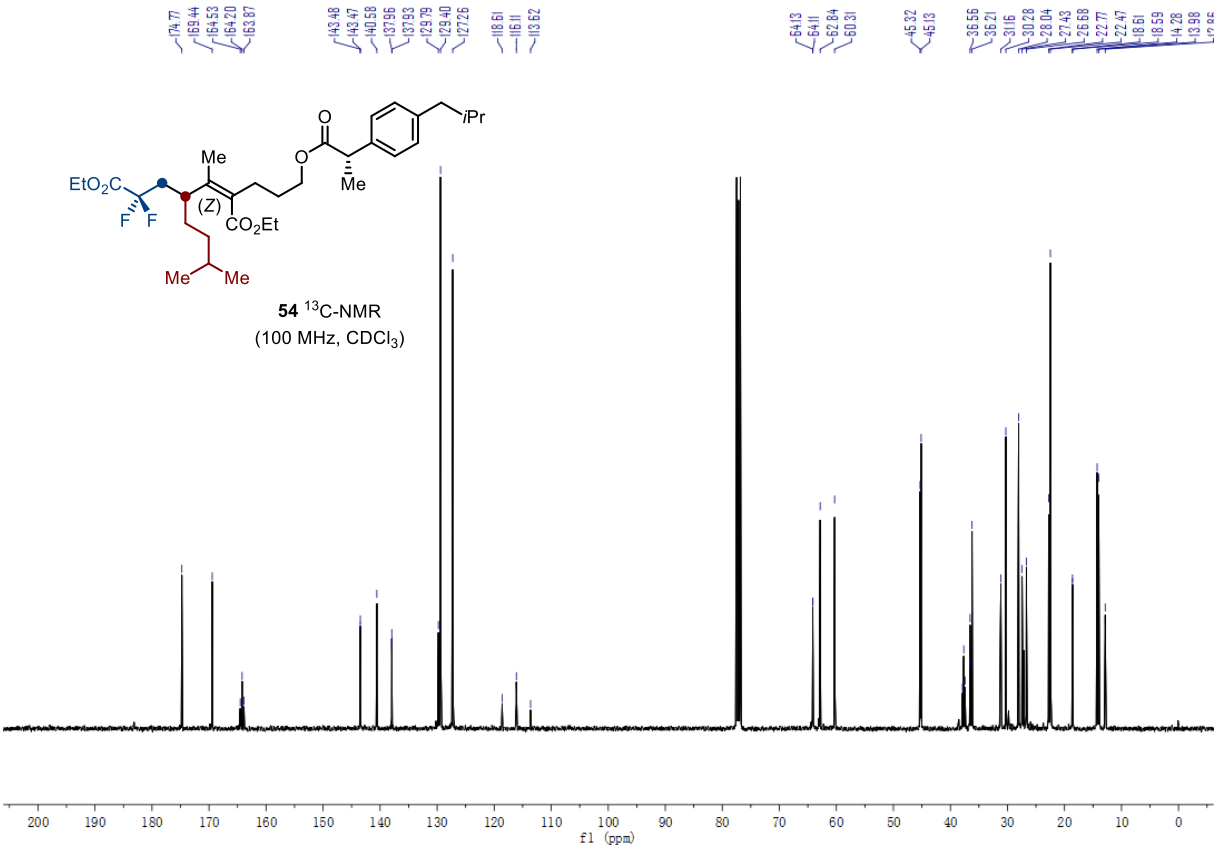
53 ^{1}H-NMR
(400 MHz,$CDCl_3$)



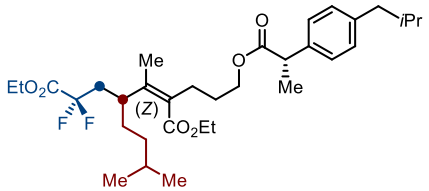
53 ^{13}C-NMR
(100 MHz, $CDCl_3$)



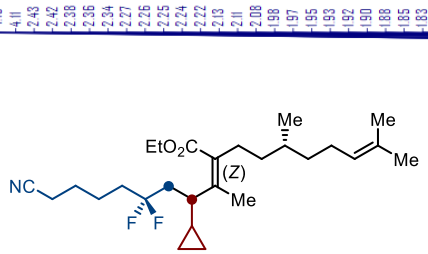
54 ^{1}H-NMR
(400 MHz,$CDCl_3$)



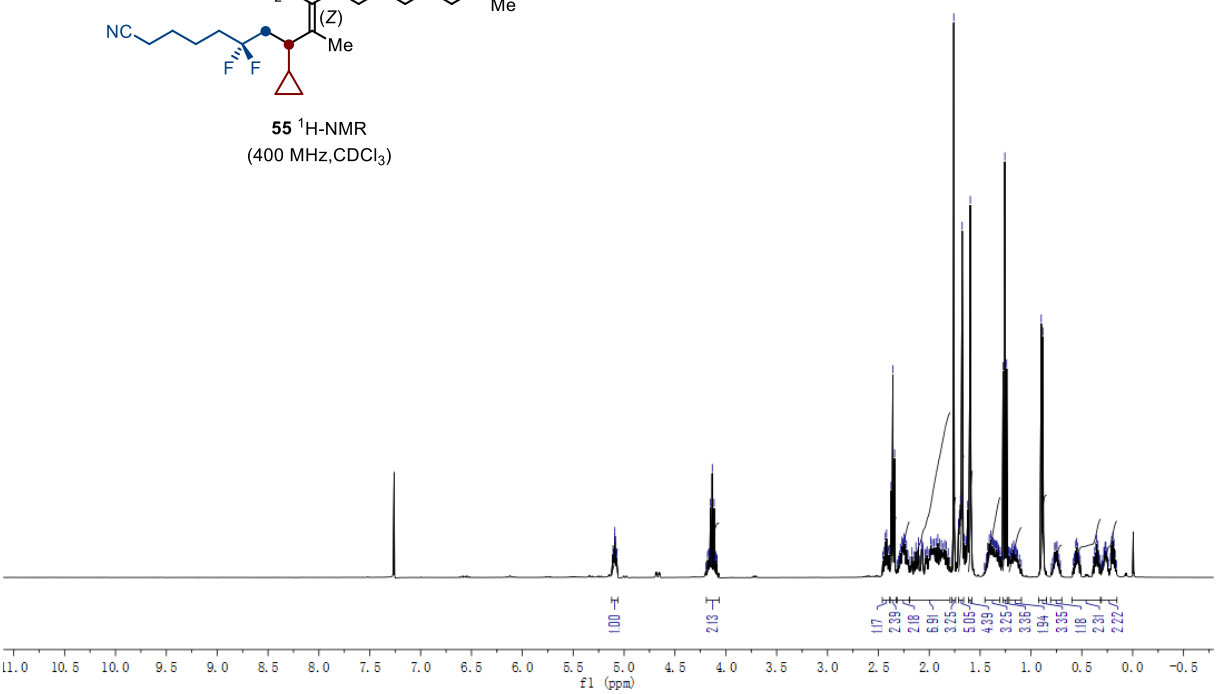
54 ^{13}C-NMR
(100 MHz, $CDCl_3$)

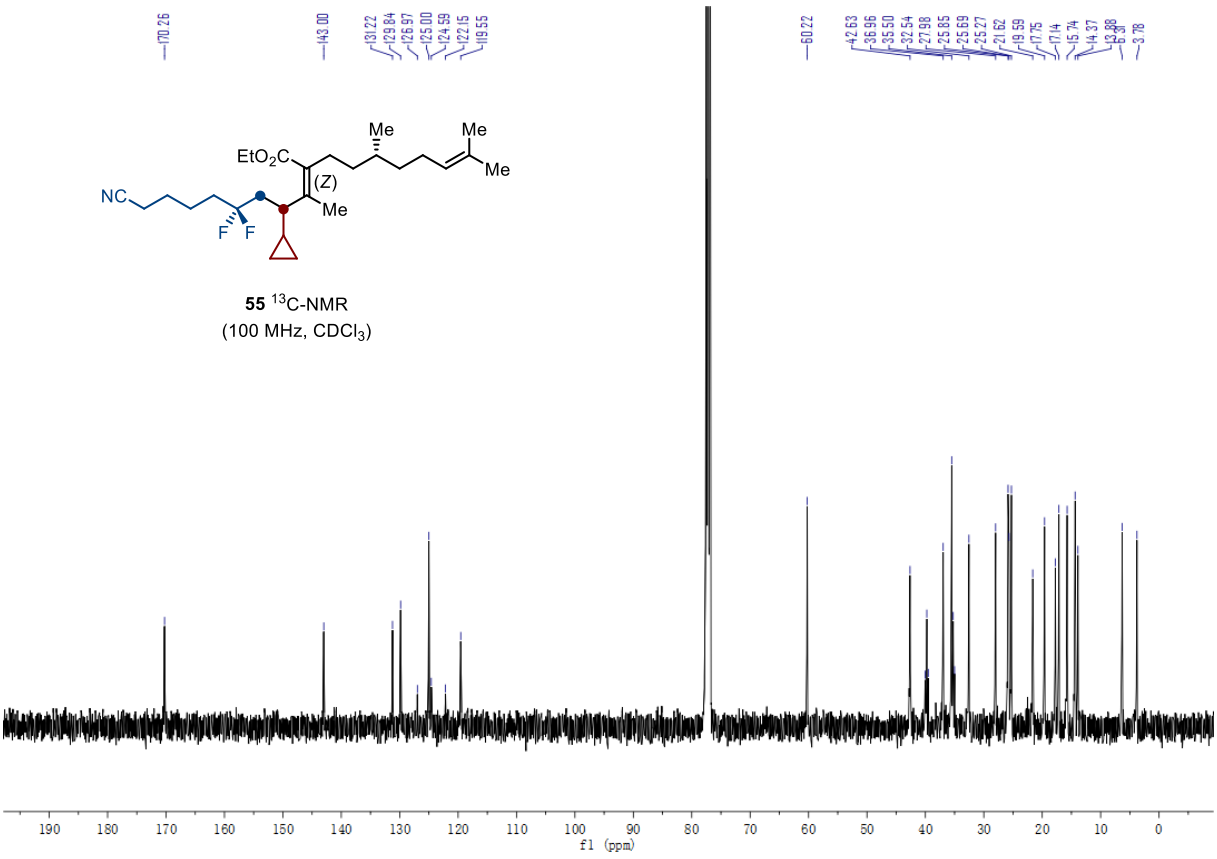


54 ^{19}F-NMR
(376 MHz, $CDCl_3$)

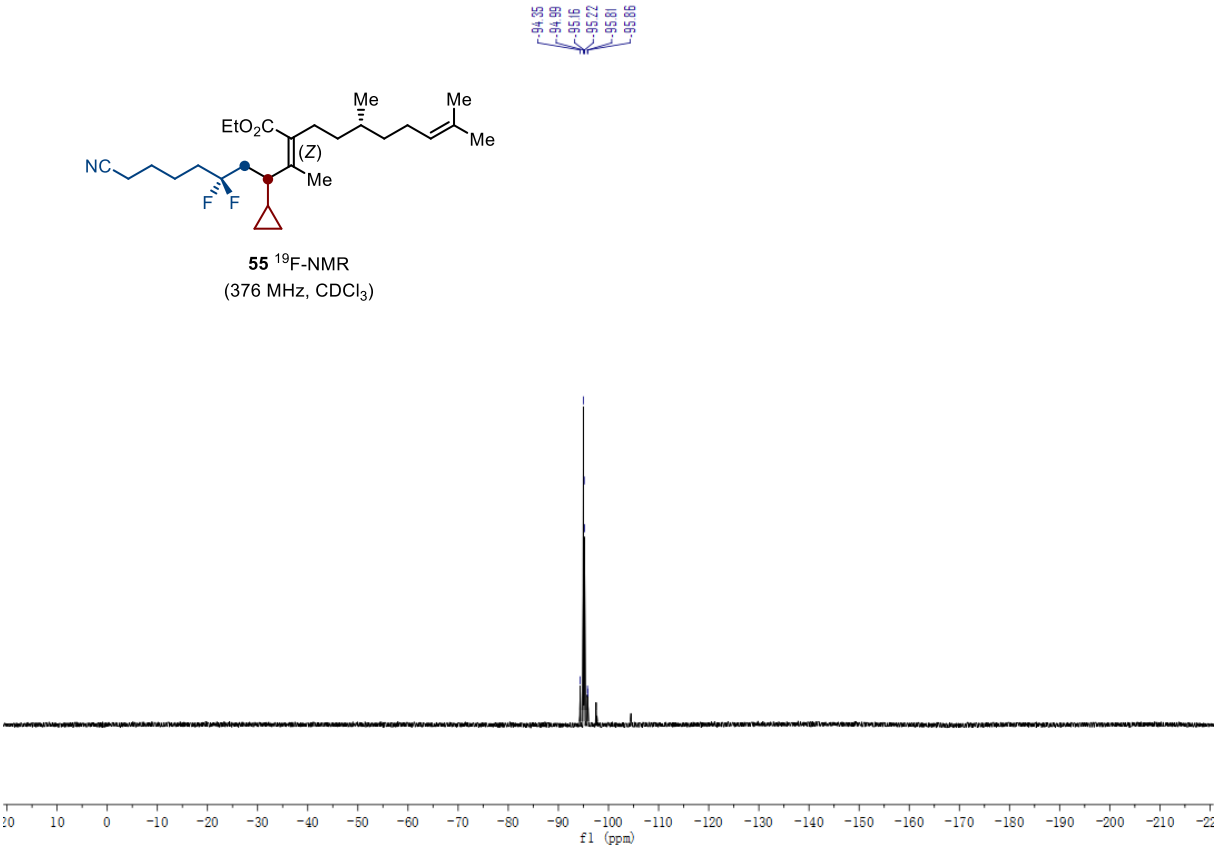


55 ^{1}H-NMR
(400 MHz,$CDCl_3$)

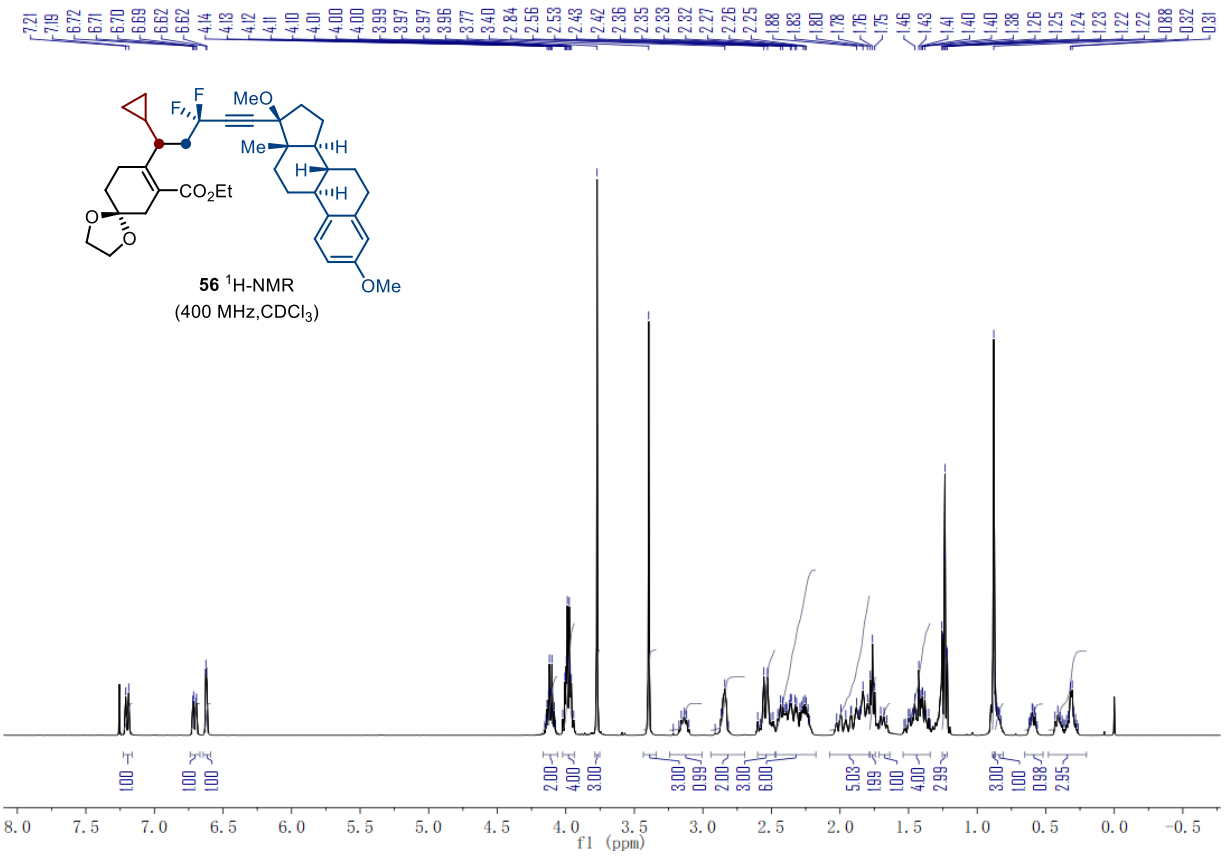




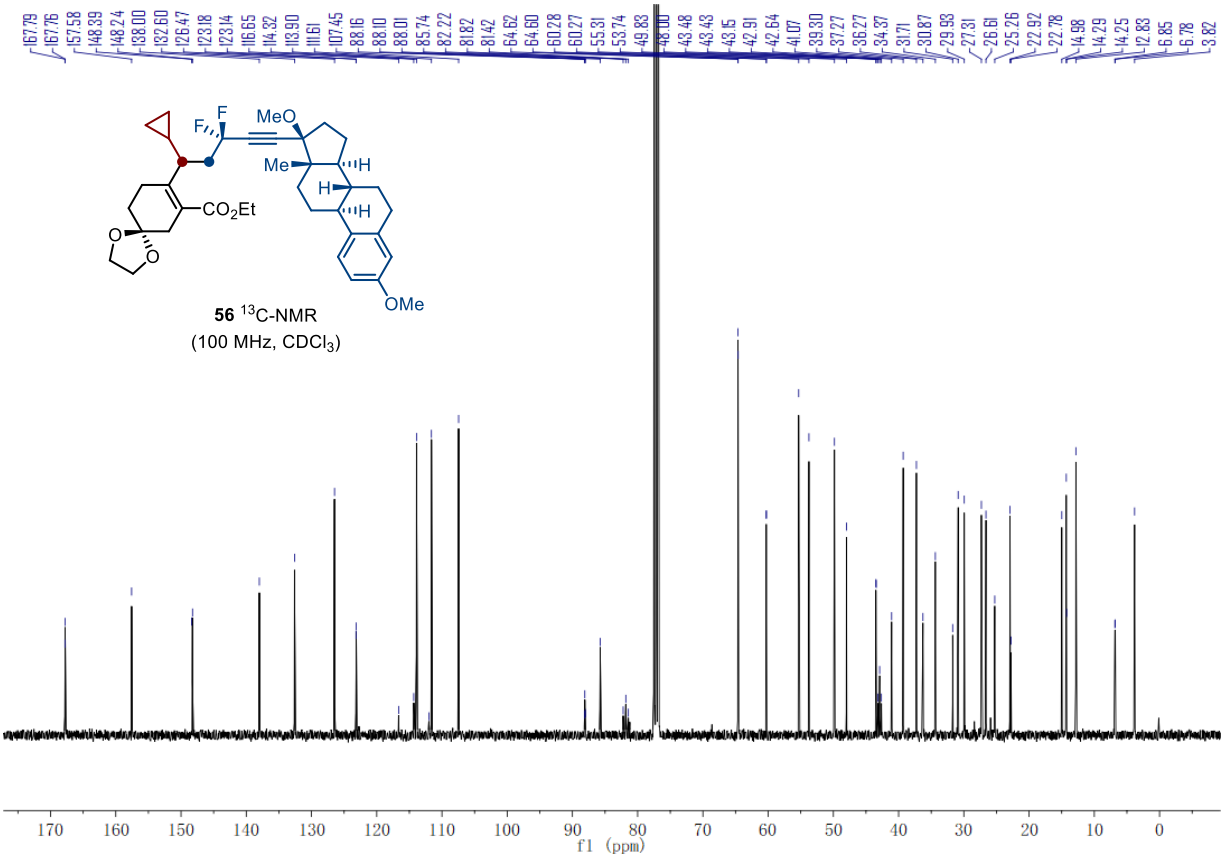
55 ^{13}C-NMR
(100 MHz, $CDCl_3$)



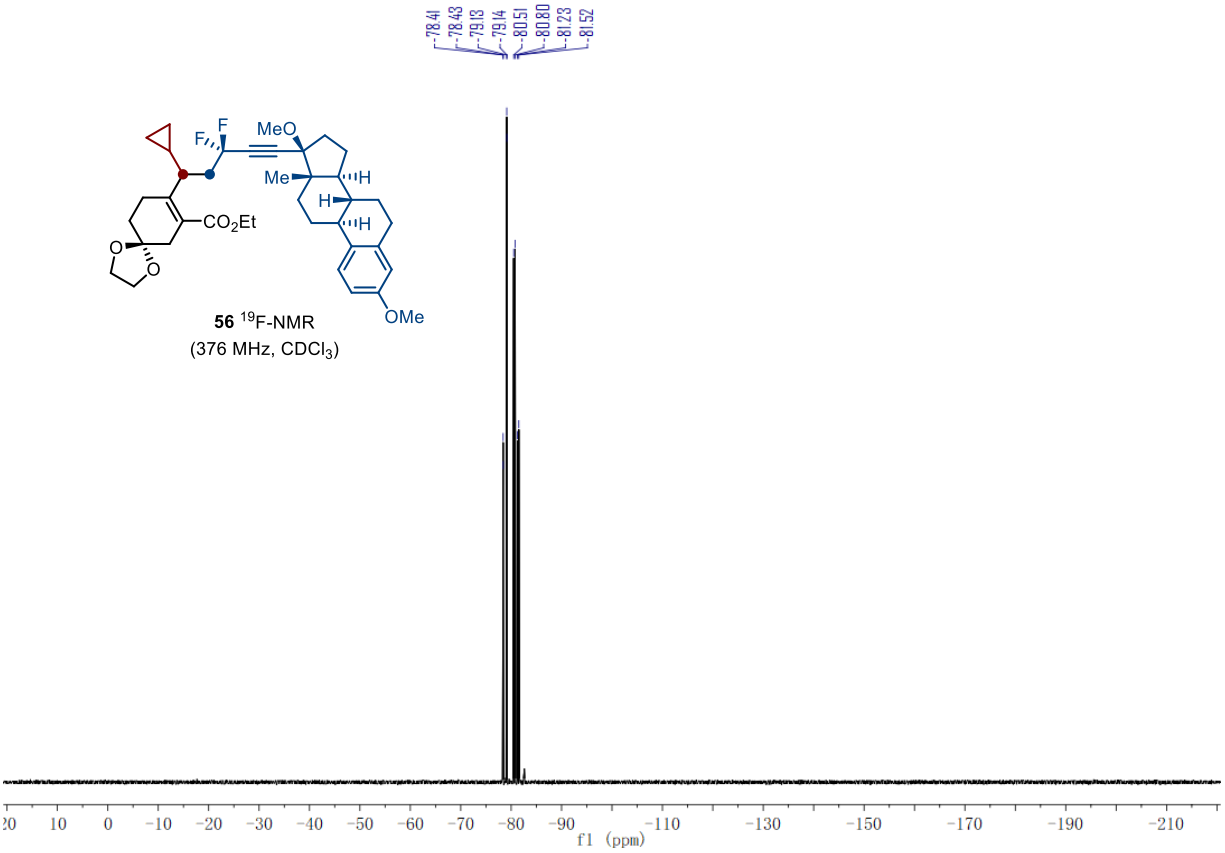
55 ^{19}F-NMR
(376 MHz, $CDCl_3$)



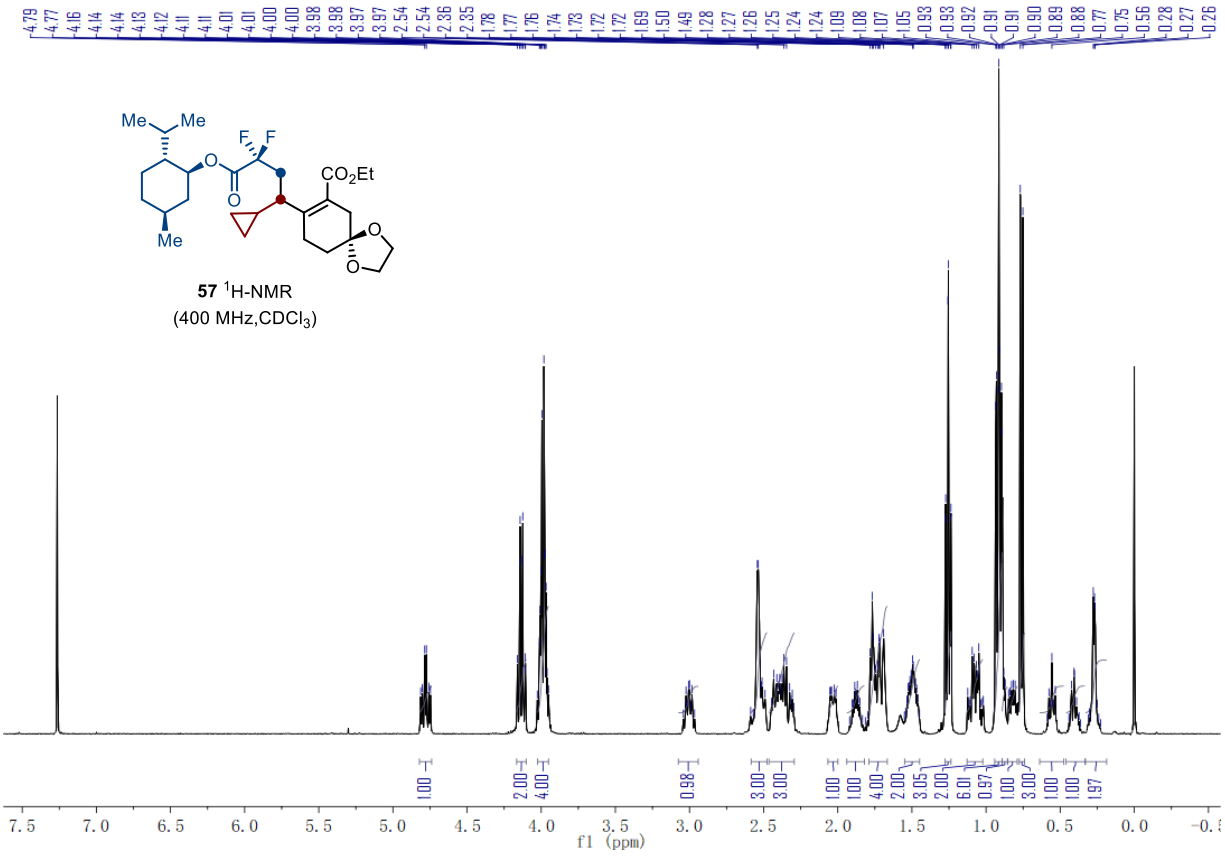
56 ^{1}H-NMR
(400 MHz,$CDCl_3$)



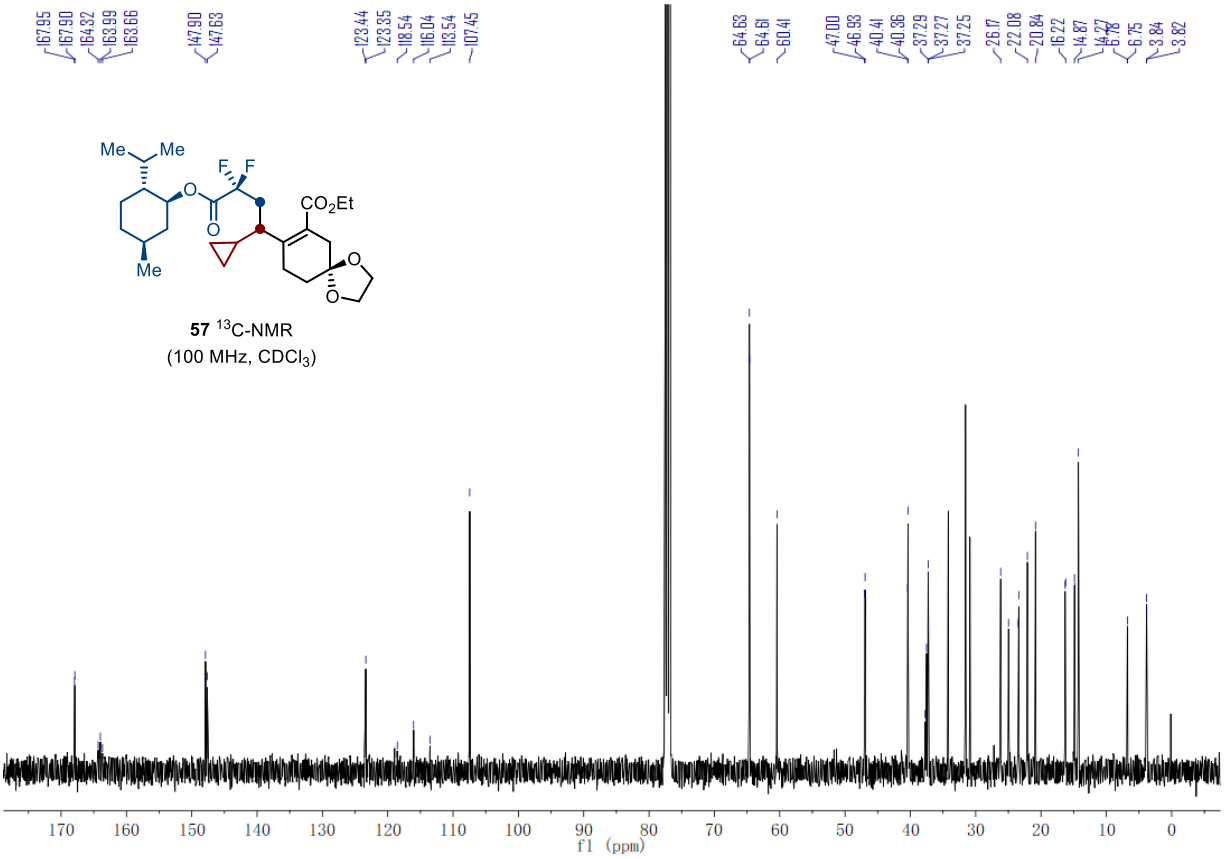
56 ^{13}C-NMR
(100 MHz, $CDCl_3$)



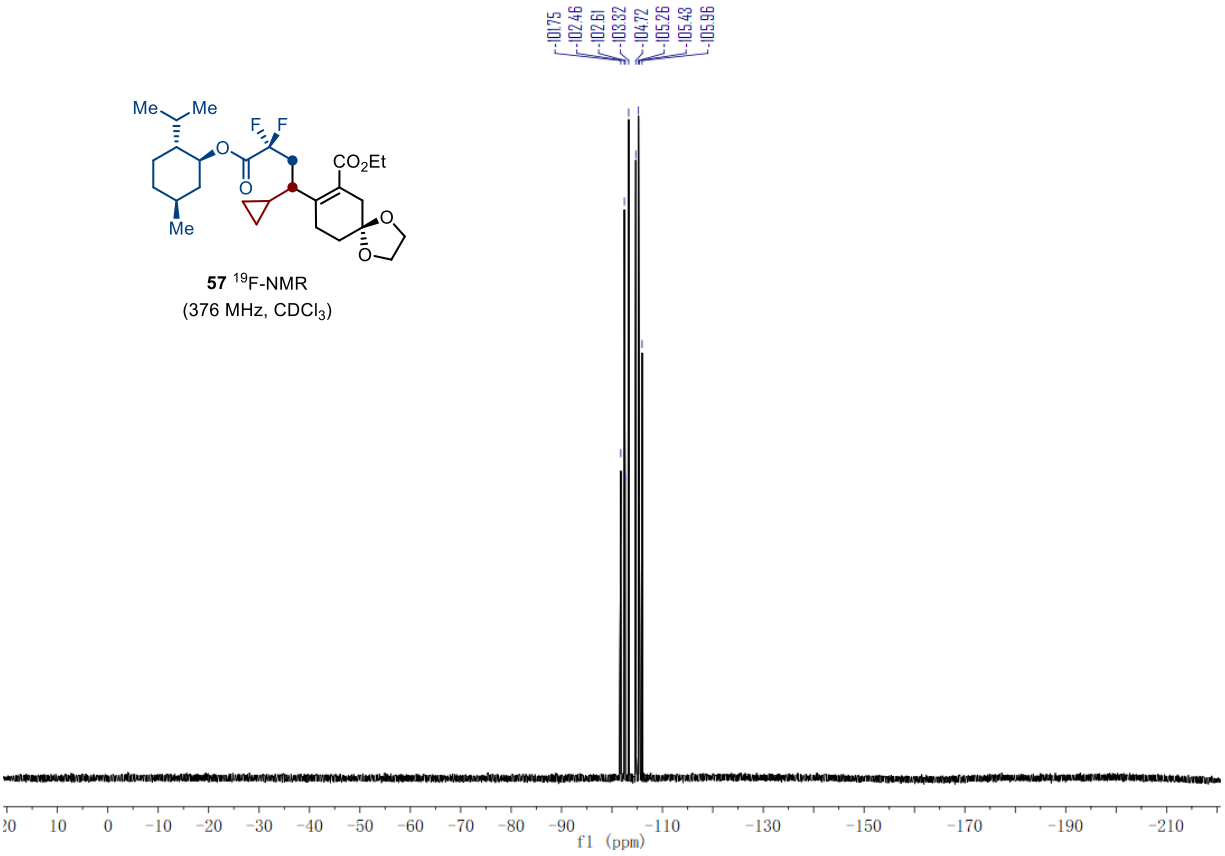
56 ^{19}F-NMR
(376 MHz, $CDCl_3$)



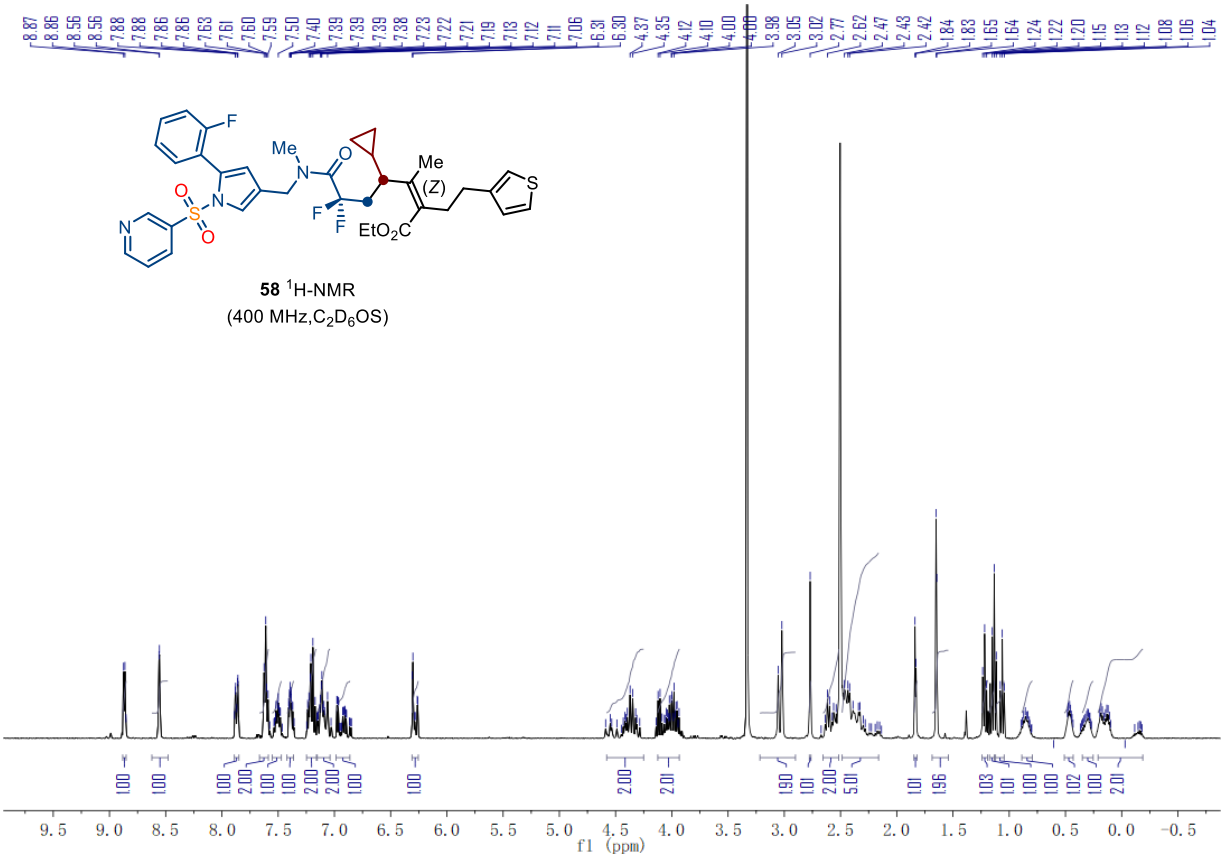
57 ^{1}H-NMR
(400 MHz,$CDCl_3$)



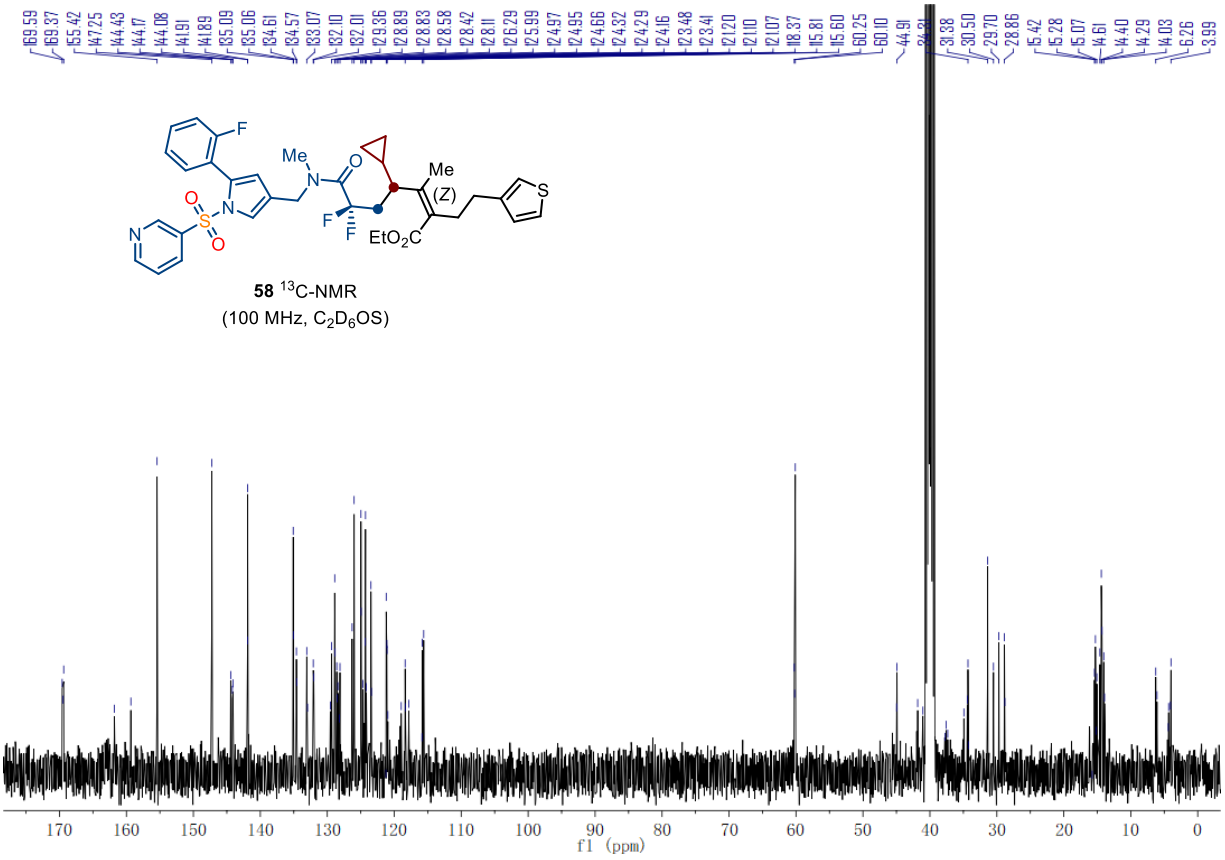
57 ^{13}C-NMR
(100 MHz, $CDCl_3$)



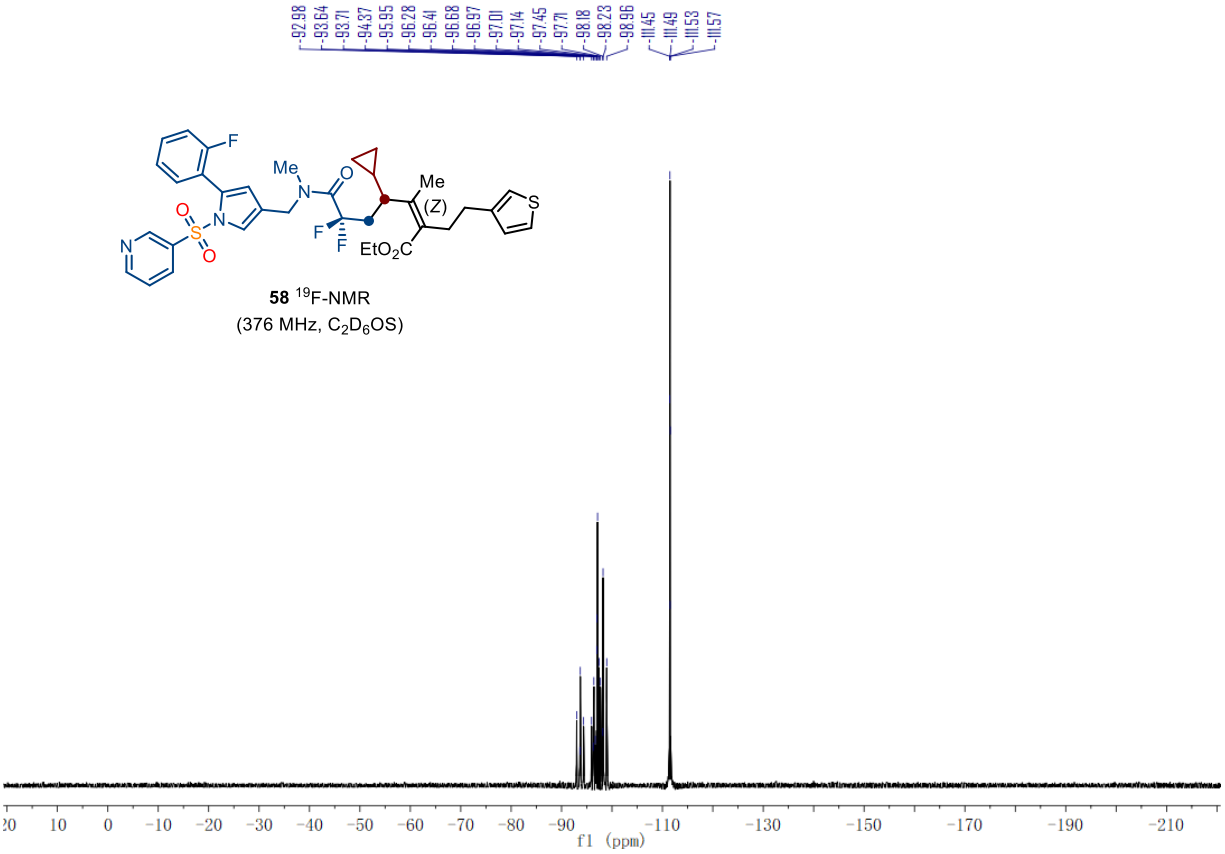
57 ^{19}F-NMR
(376 MHz, $CDCl_3$)



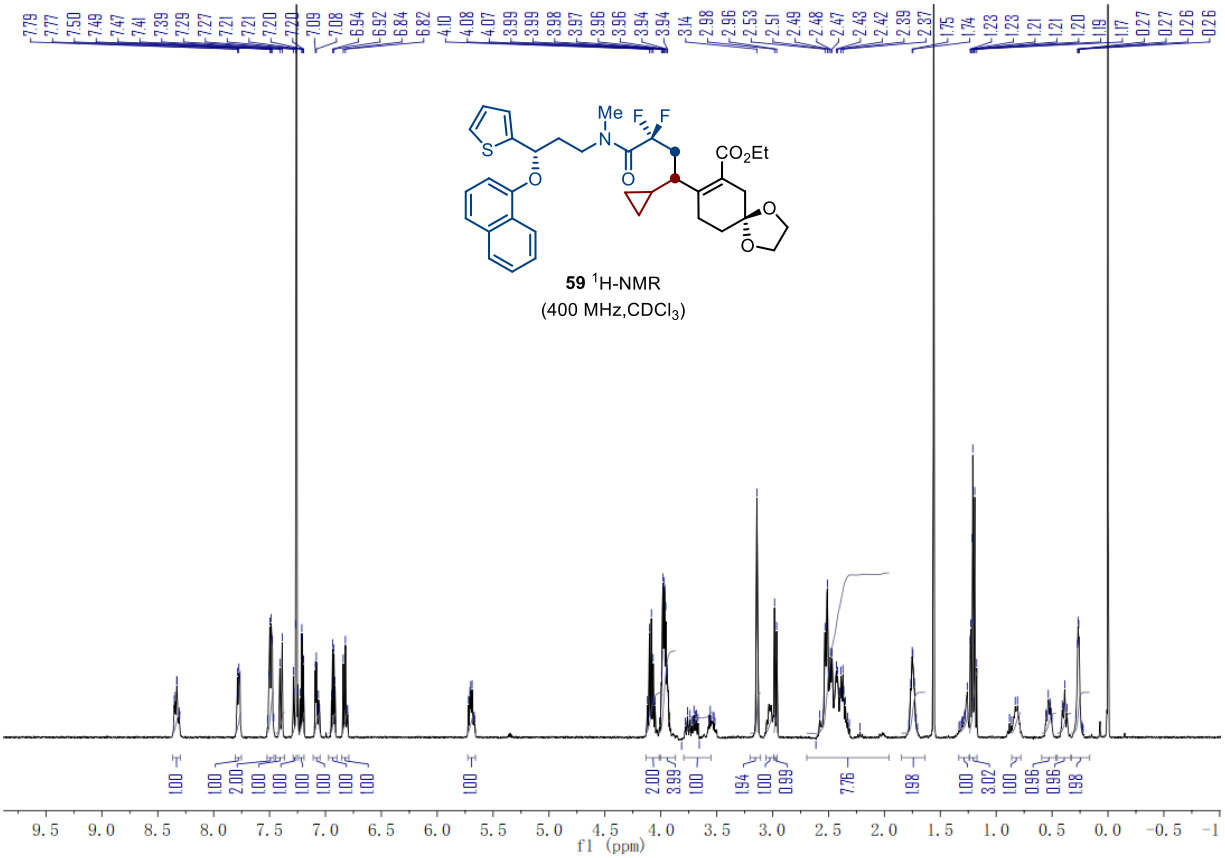
58 ^{1}H-NMR
(400 MHz,C_2D_6OS)



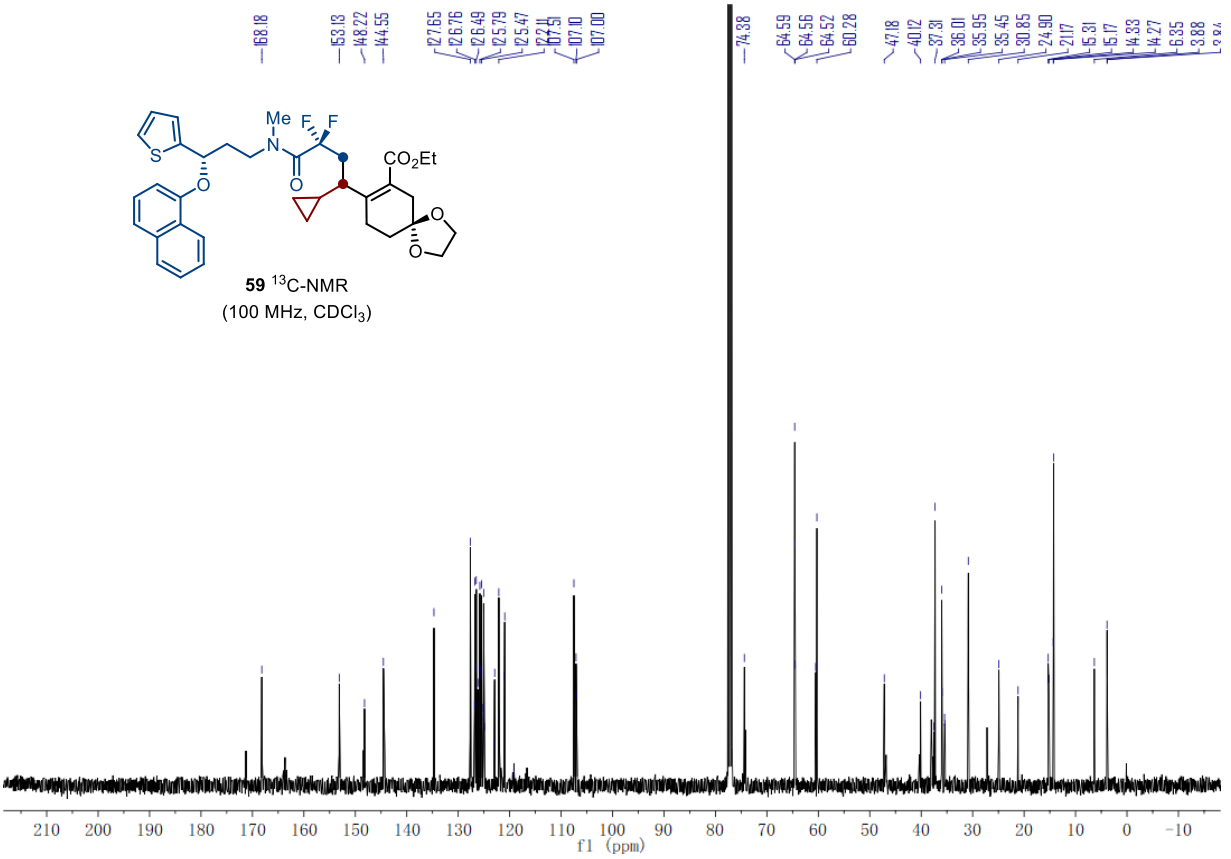
58 ^{13}C-NMR
(100 MHz, C_2D_6OS)



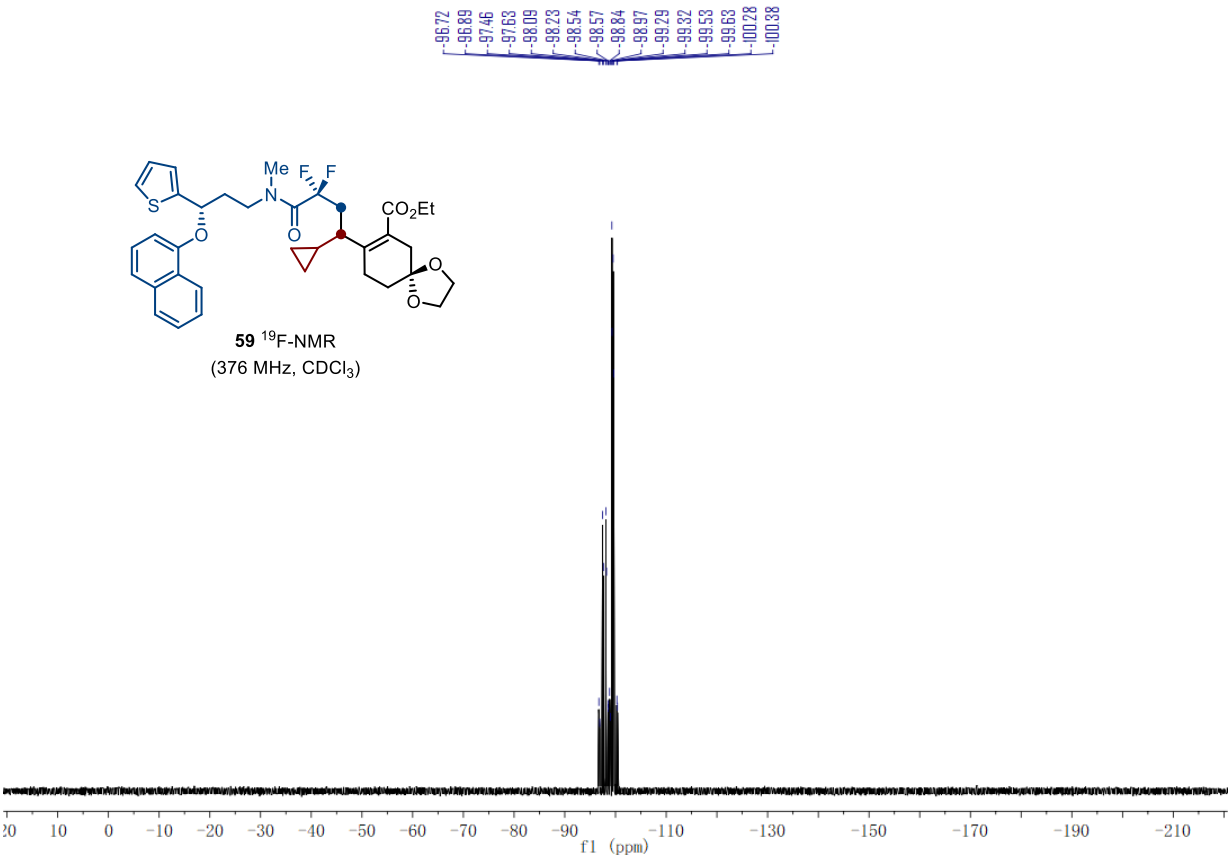
58 ^{19}F-NMR
(376 MHz, C_2D_6OS)



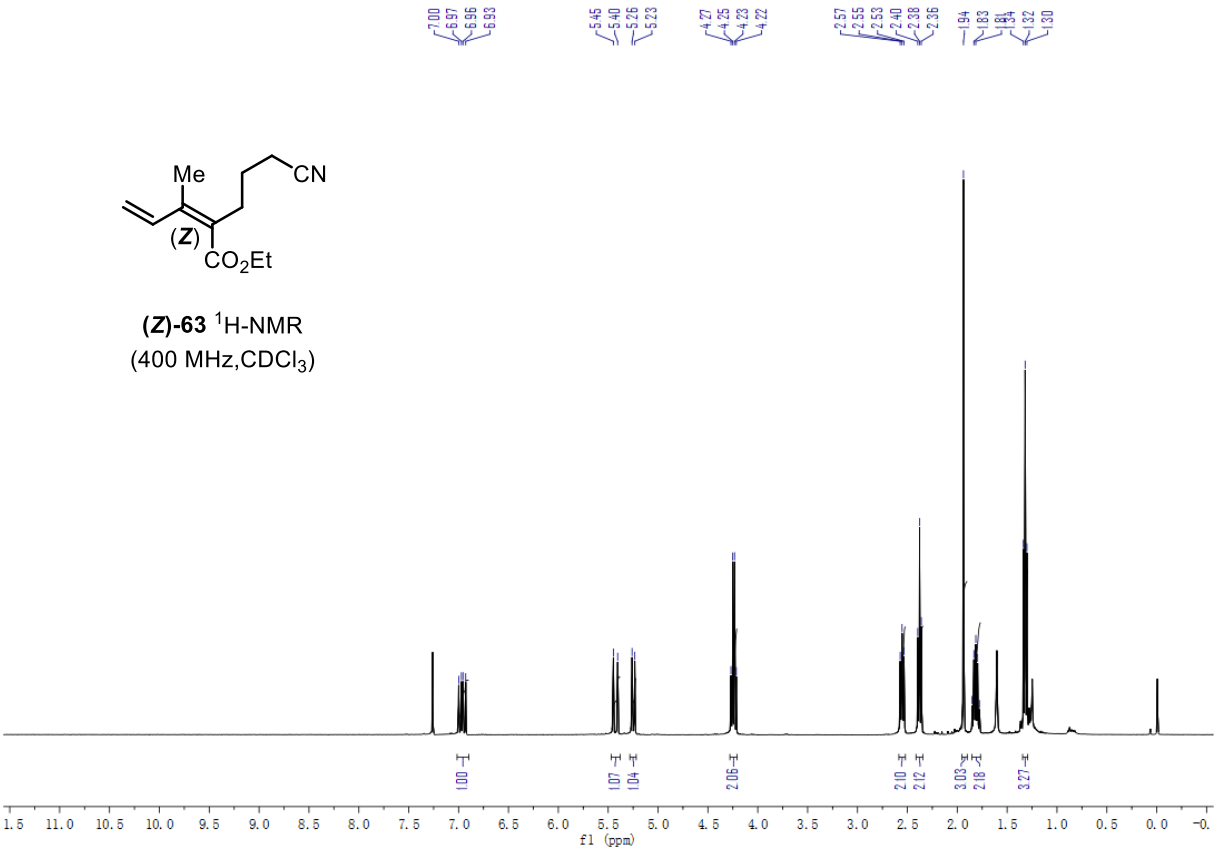
59 ^{1}H-NMR
(400 MHz,$CDCl_3$)

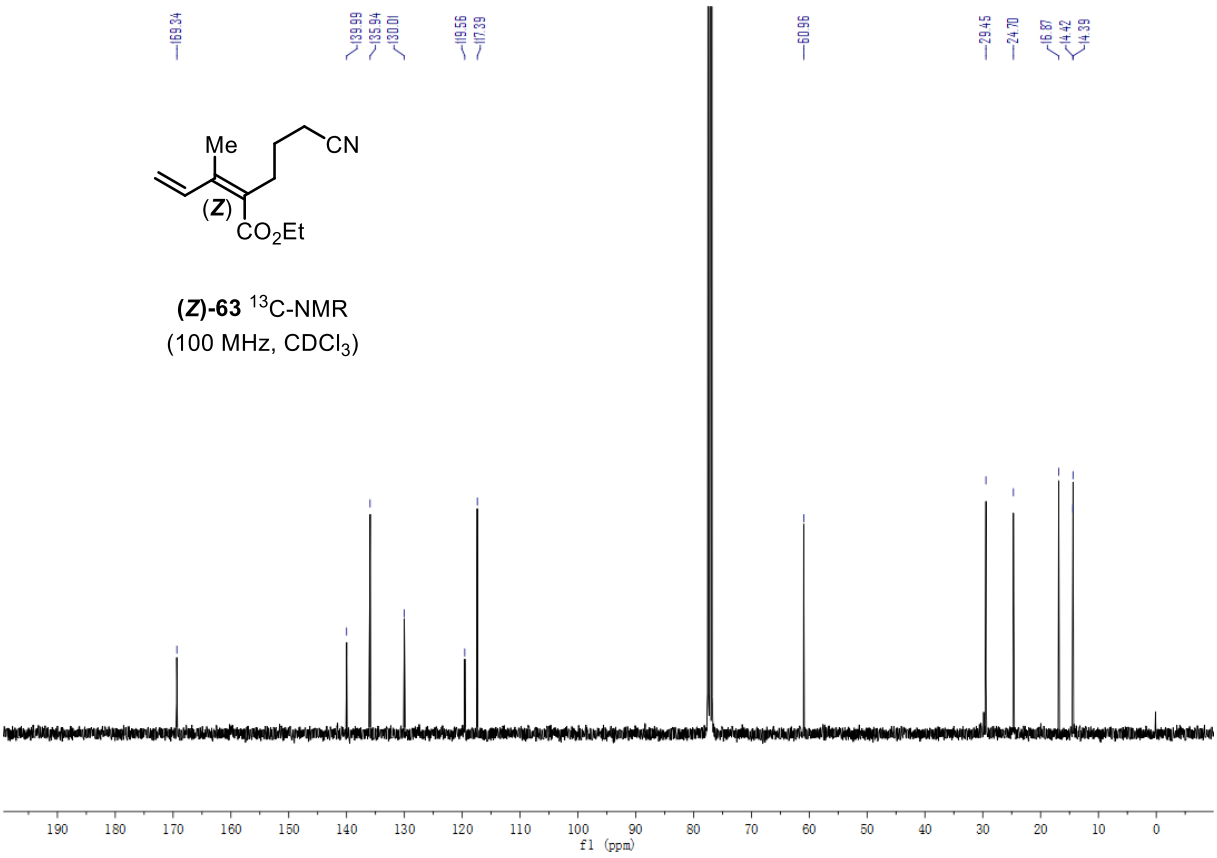


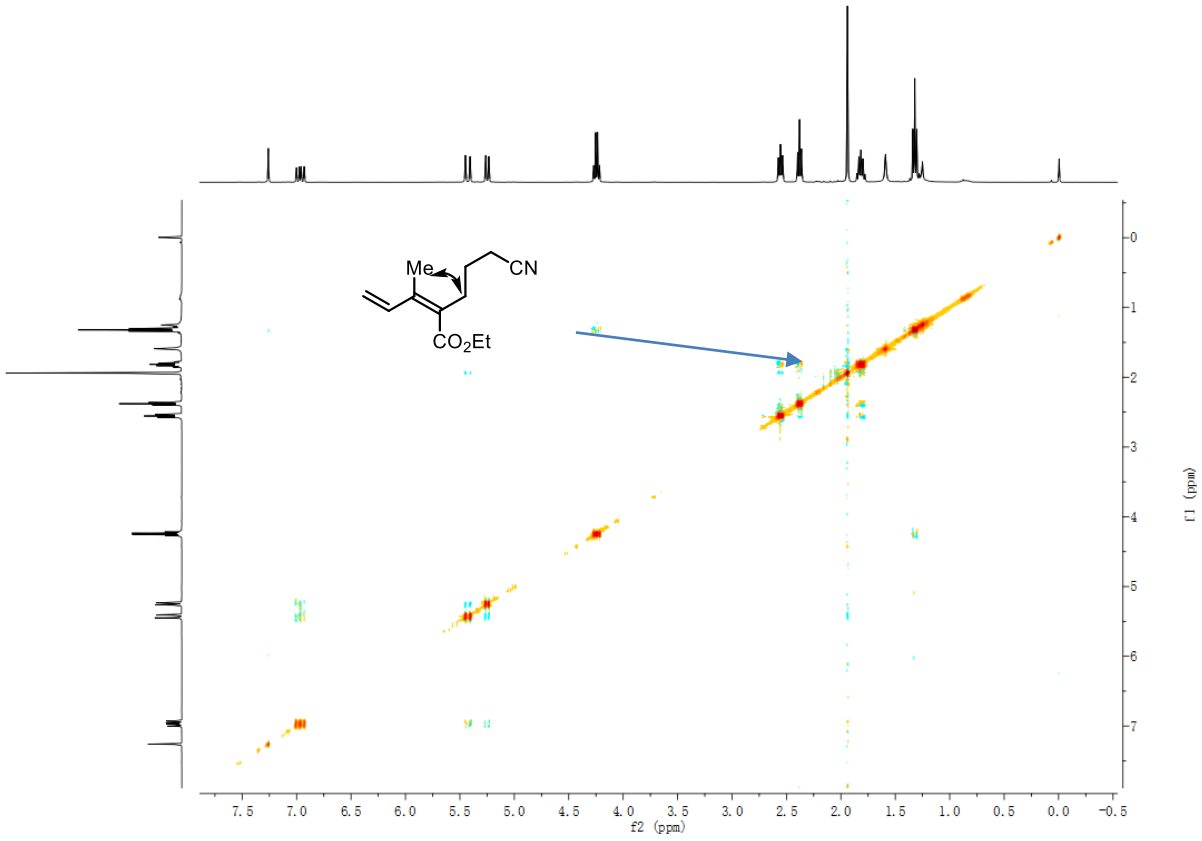
59 ^{13}C-NMR
(100 MHz, $CDCl_3$)

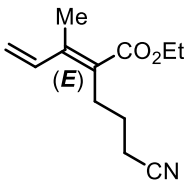


59 ^{19}F-NMR
(376 MHz, $CDCl_3$)

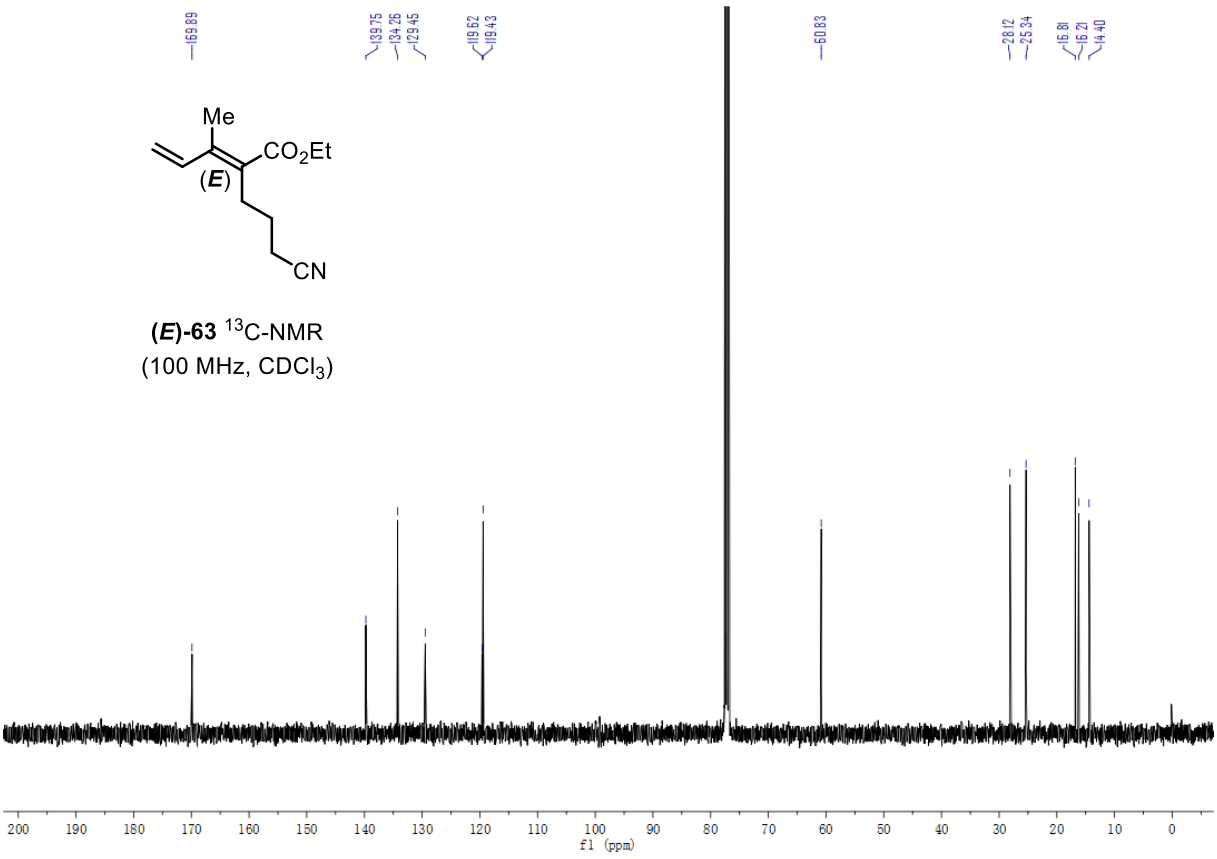

Me
CN
(Z)
CO2Et
(Z)-63 1H-NMR
(400 MHz,CDCl3)
f1 (ppm)


Me
CN
(Z)
CO2Et
(Z)-63 13C-NMR
(100 MHz, CDCl3)
f1 (ppm)

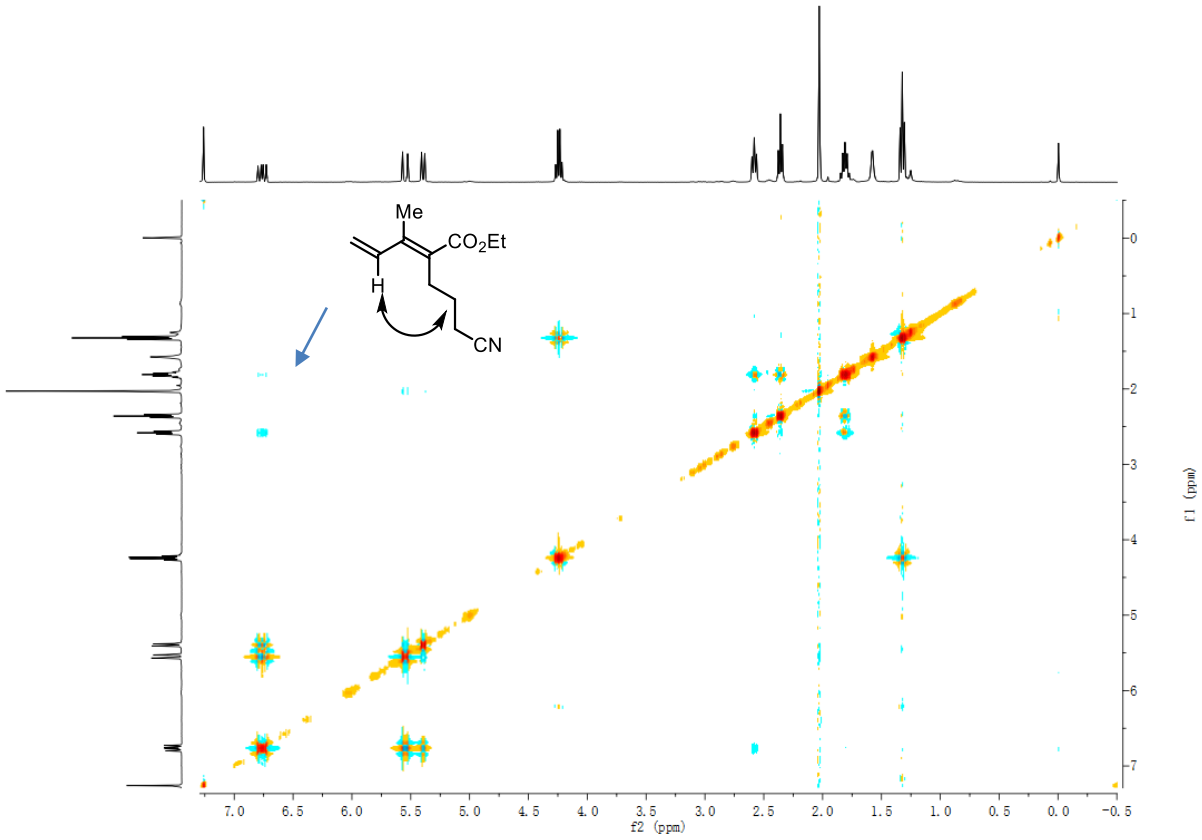


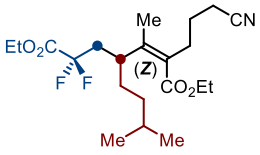


(*E*)-63 ^{1}H-NMR
(400 MHz,$CDCl_3$)

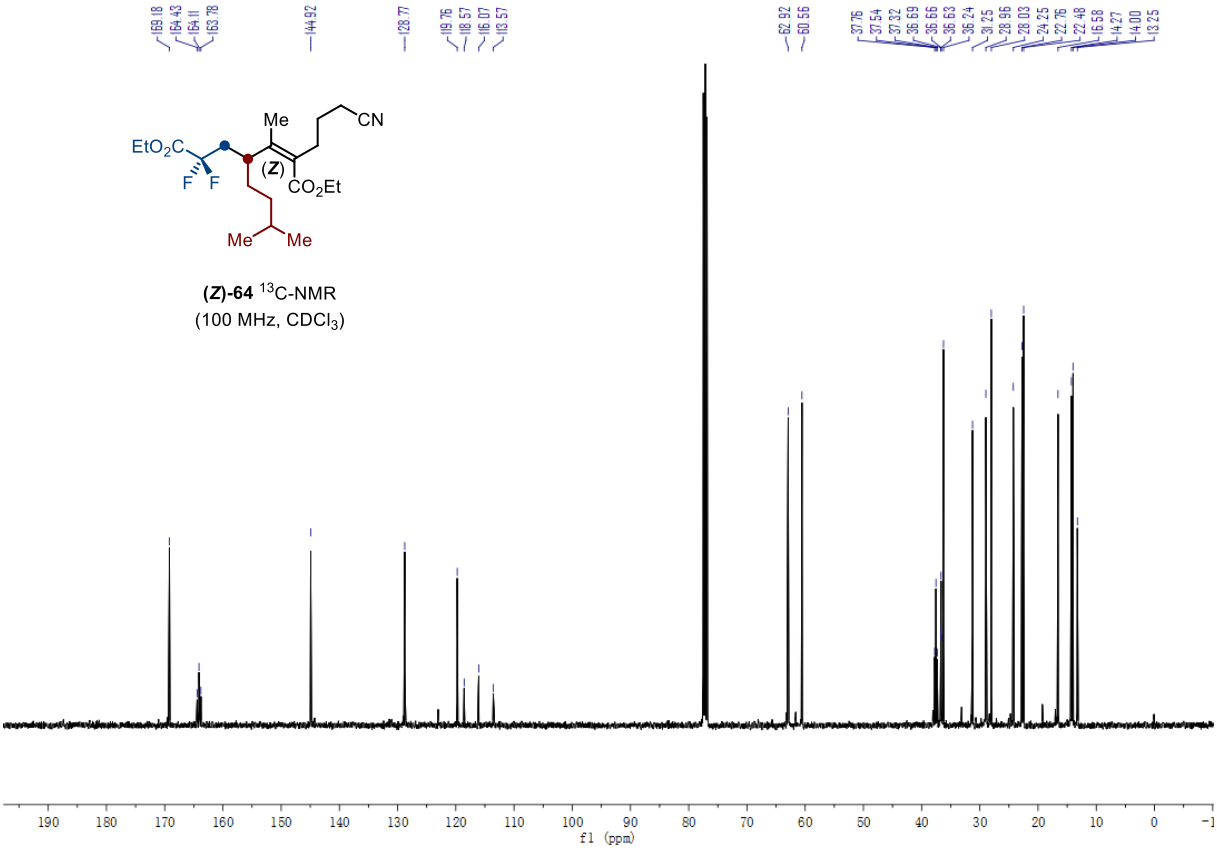


(*E*)-63 ^{13}C-NMR
(100 MHz, $CDCl_3$)

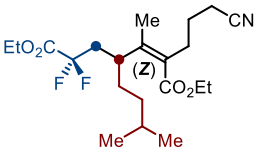




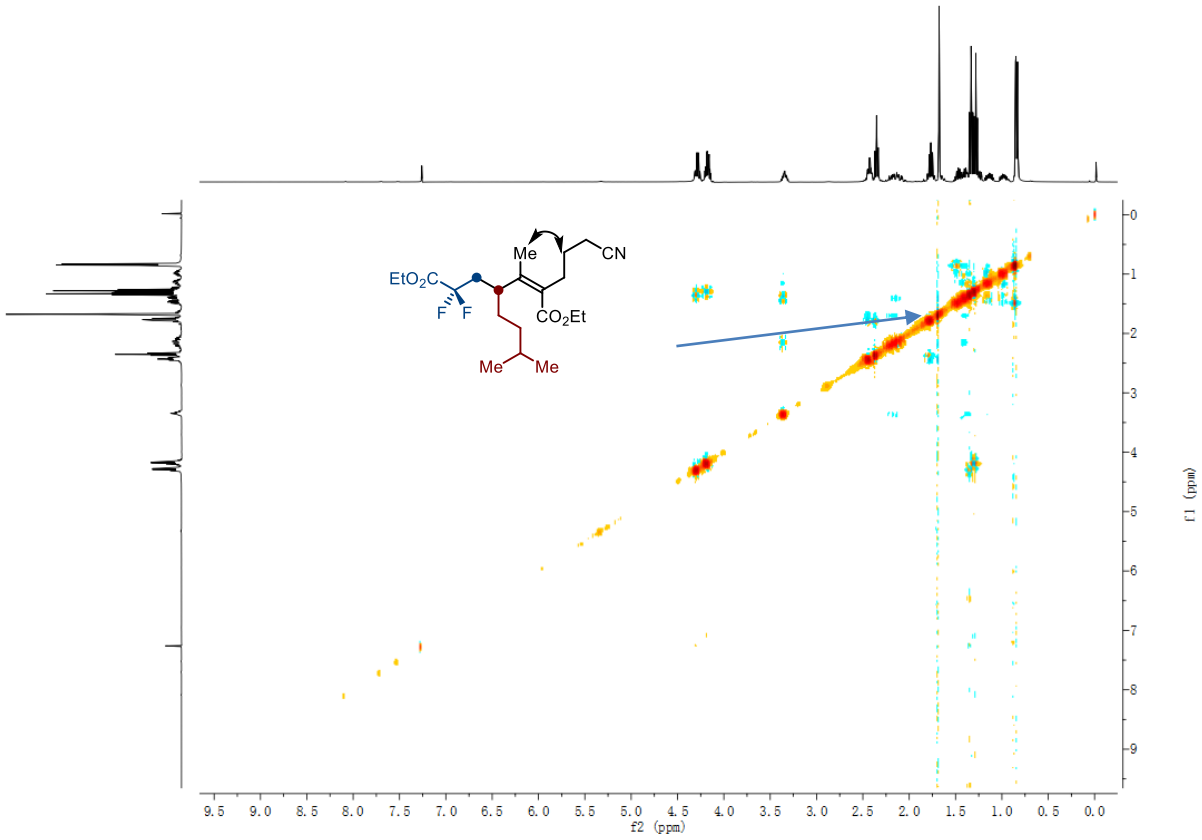
(*Z*)-64 ^{1}H-NMR
(400 MHz,$CDCl_3$)

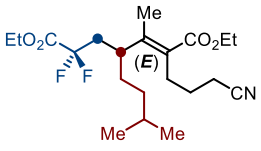


(*Z*)-64 ^{13}C-NMR
(100 MHz, $CDCl_3$)

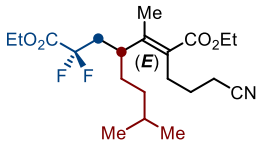


(*Z*)-64 ^{19}F-NMR
(376 MHz, $CDCl_3$)

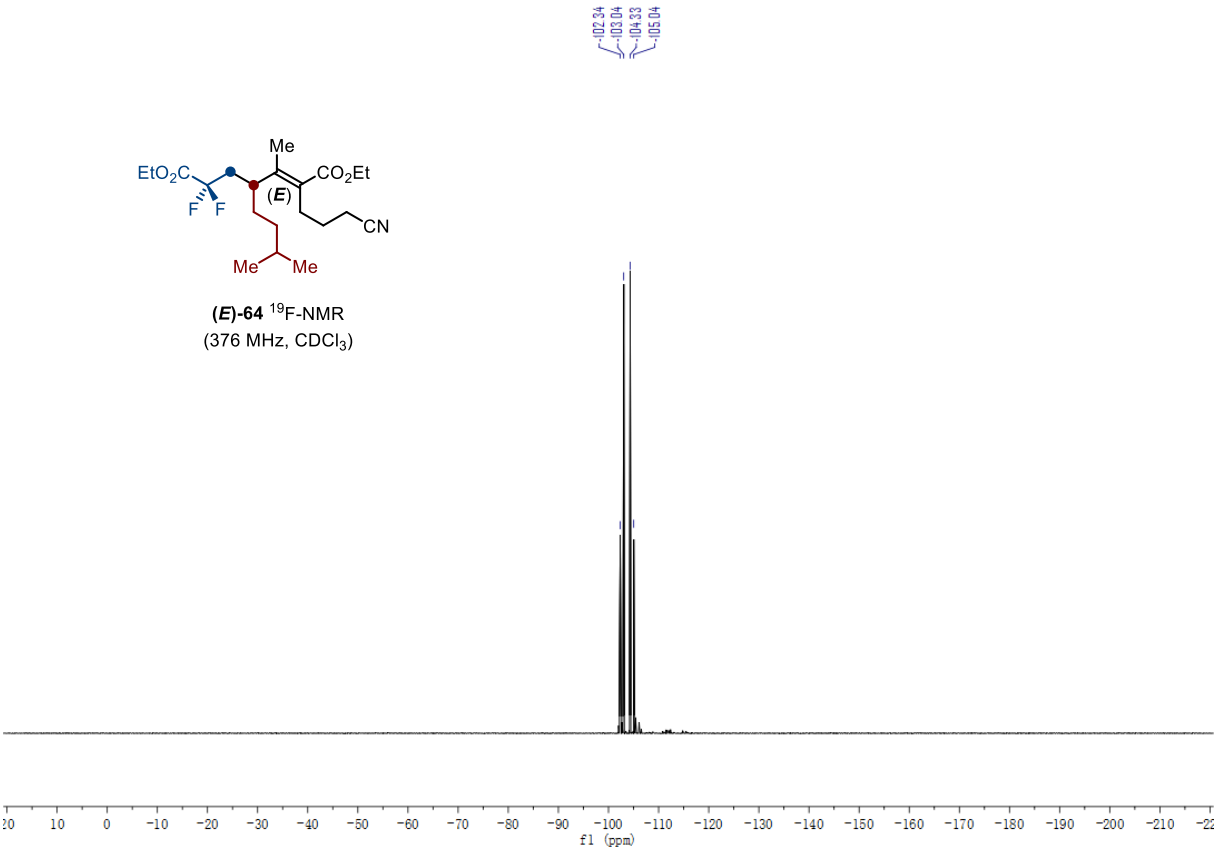




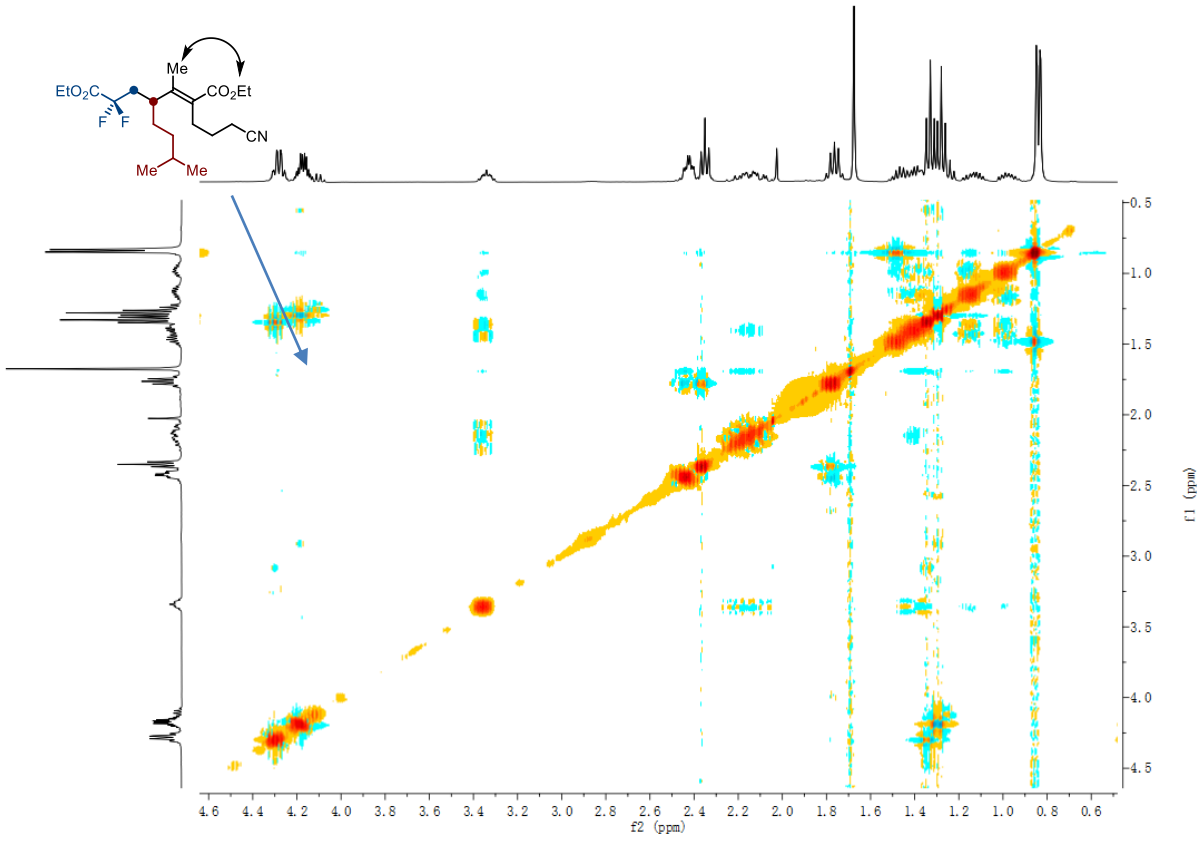
(*E*)-64 ^{1}H-NMR
(400 MHz,$CDCl_3$)

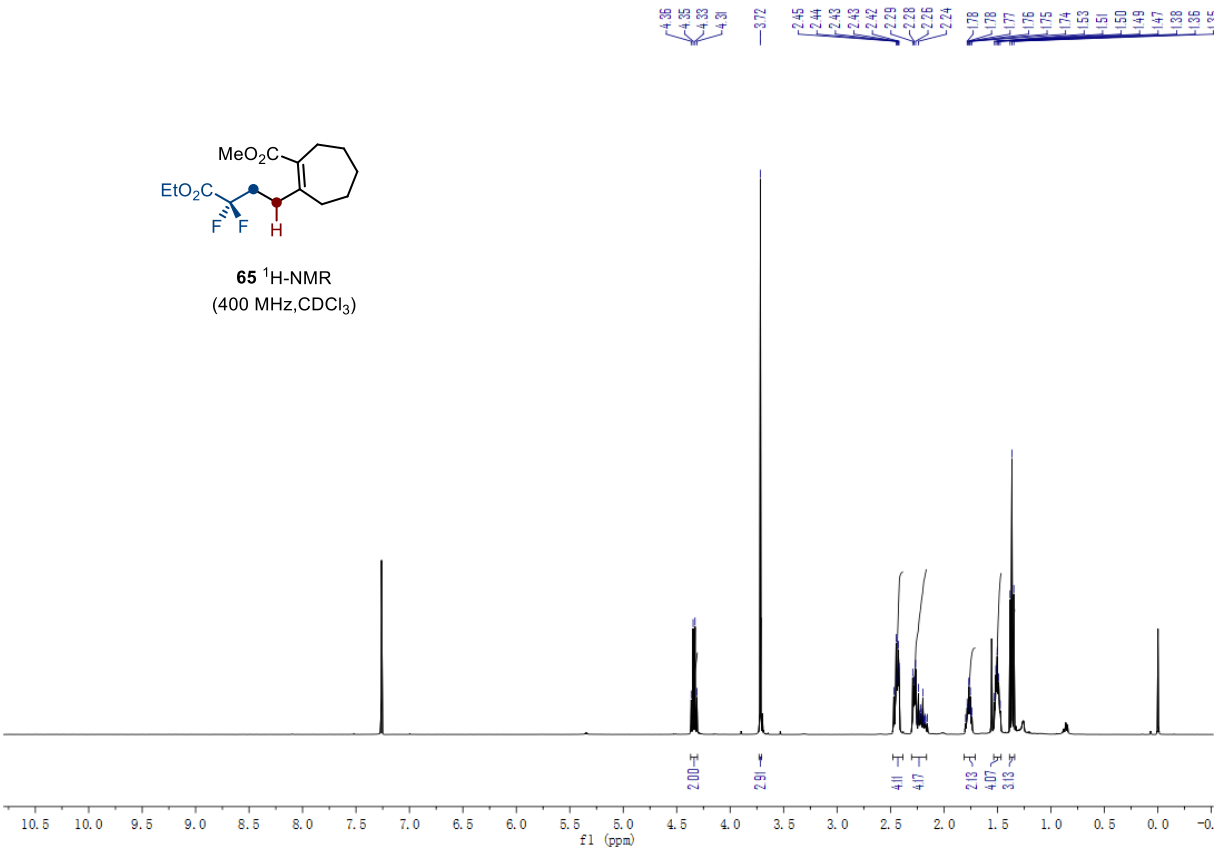


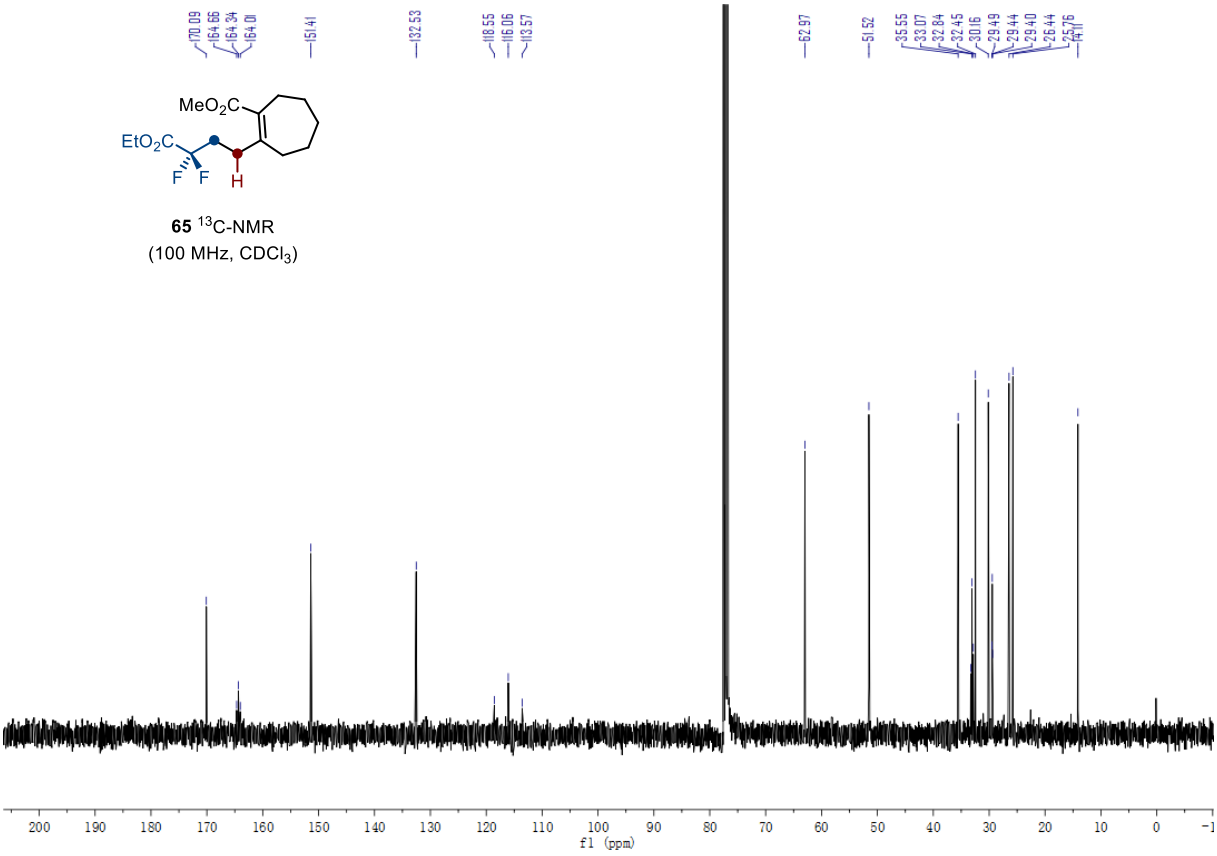
(*E*)-64 ^{13}C-NMR
(100 MHz, $CDCl_3$)

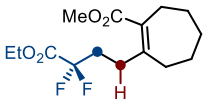


(*E*)-64 ^{19}F-NMR
(376 MHz, $CDCl_3$)

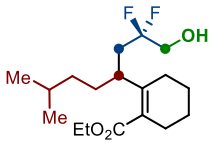



MeO2C
EtO2C
F F
H
65 1H-NMR
(400 MHz,CDCl3)
f1 (ppm)

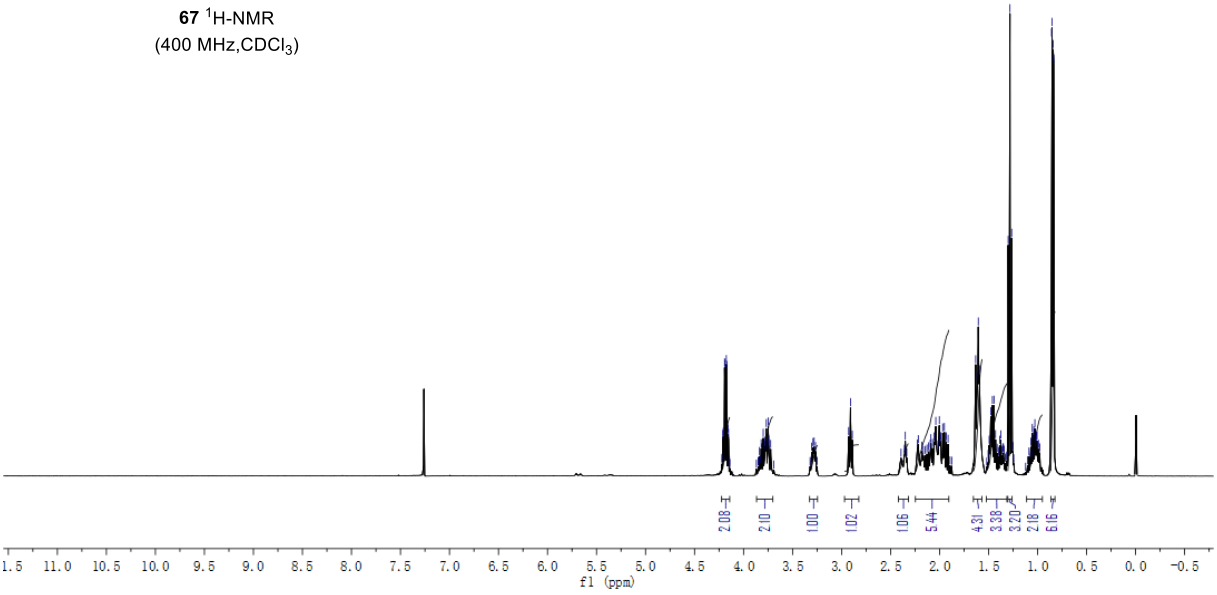

MeO2C
EtO2C
F F
H
65 13C-NMR
(100 MHz, CDCl3)
f1 (ppm)

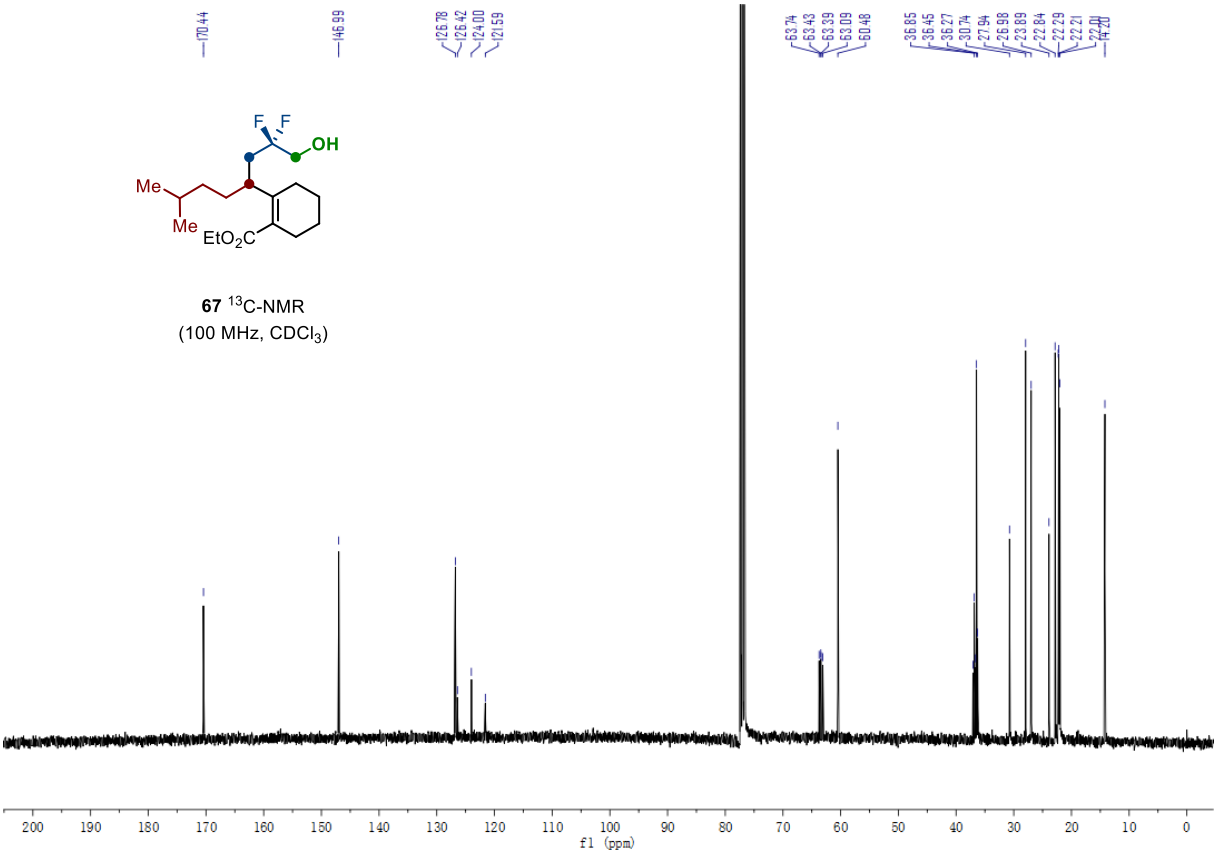


65 ^{19}F-NMR
(376 MHz, $CDCl_3$)

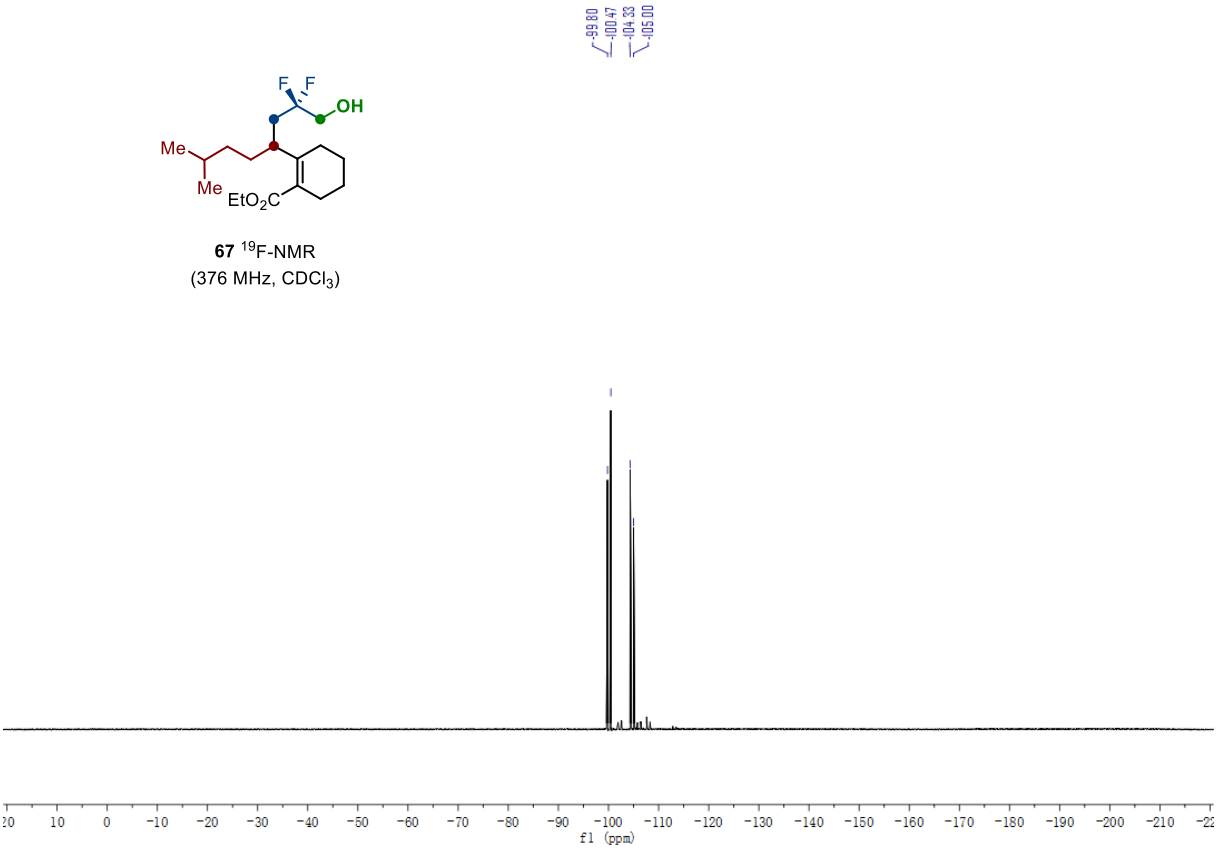


67 ^{1}H-NMR
(400 MHz,$CDCl_3$)

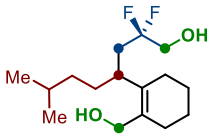




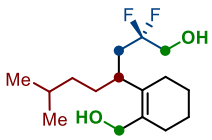
67 ^{13}C-NMR
(100 MHz, $CDCl_3$)



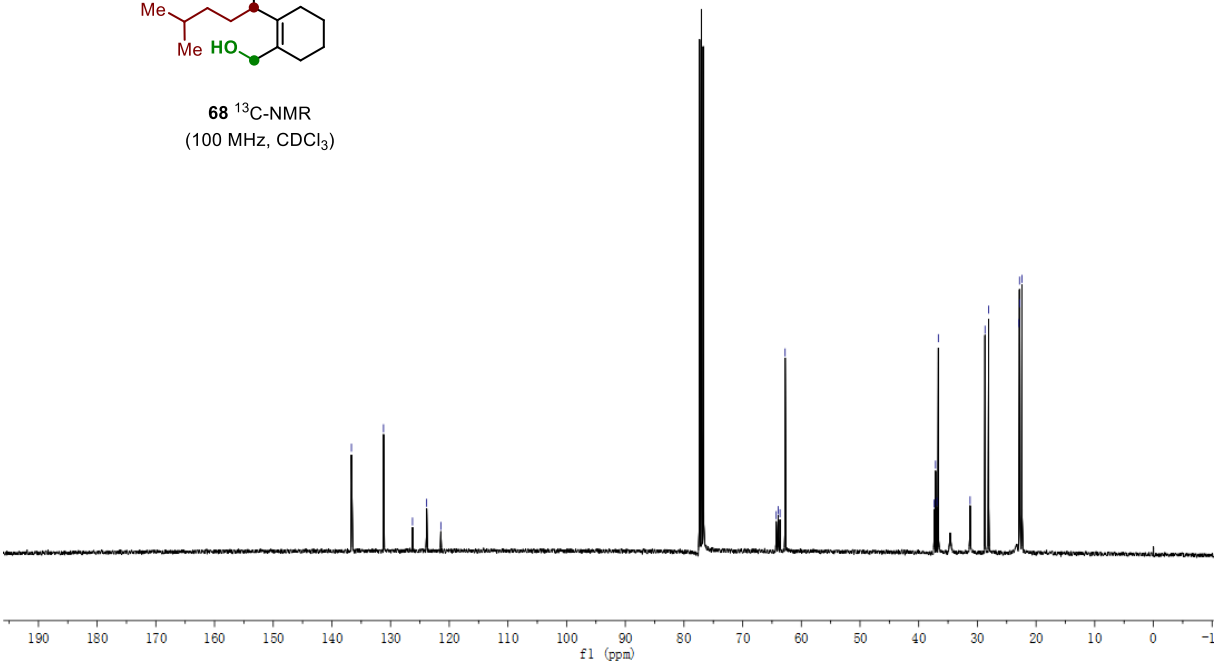
67 ^{19}F-NMR
(376 MHz, $CDCl_3$)

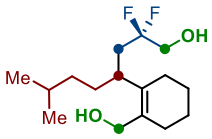


68 ^{1}H-NMR
(400 MHz,$CDCl_3$)

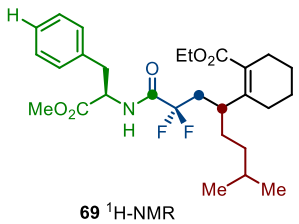


68 ^{13}C-NMR
(100 MHz, $CDCl_3$)

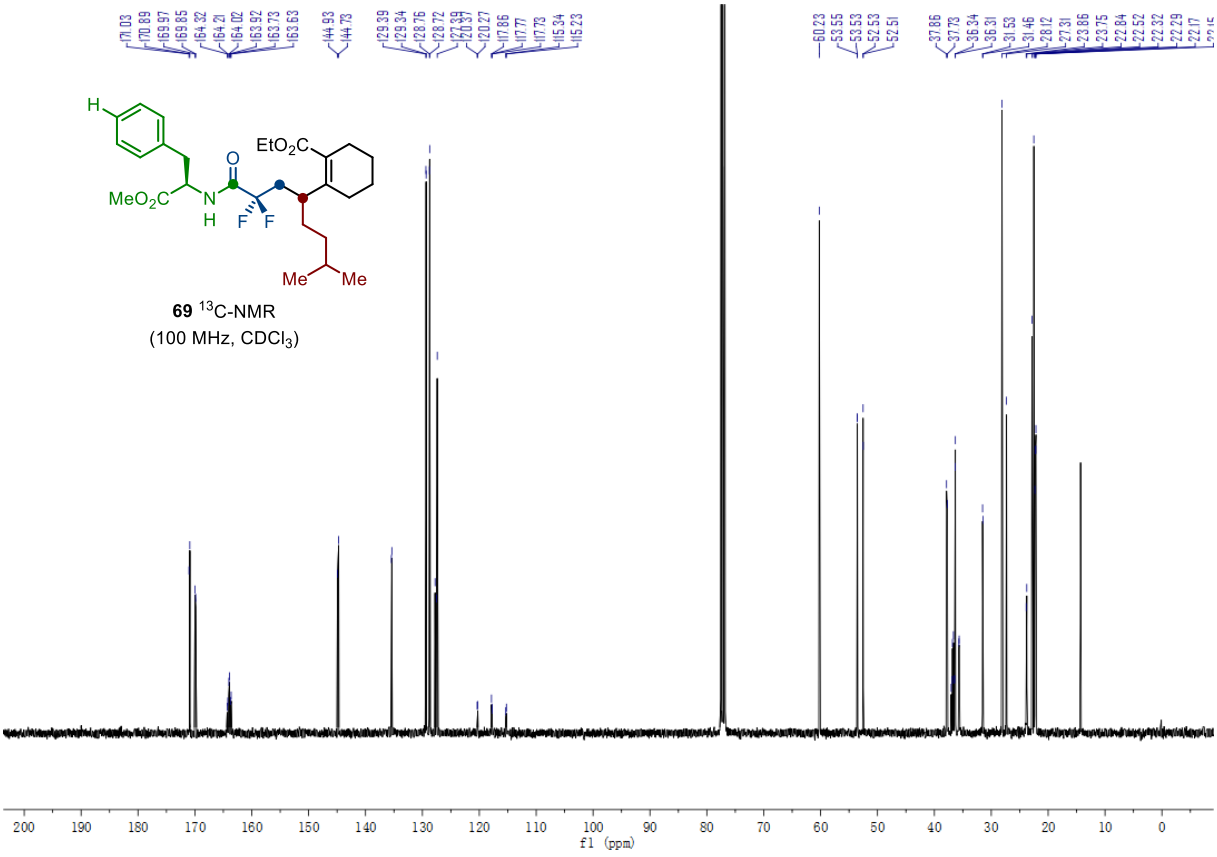




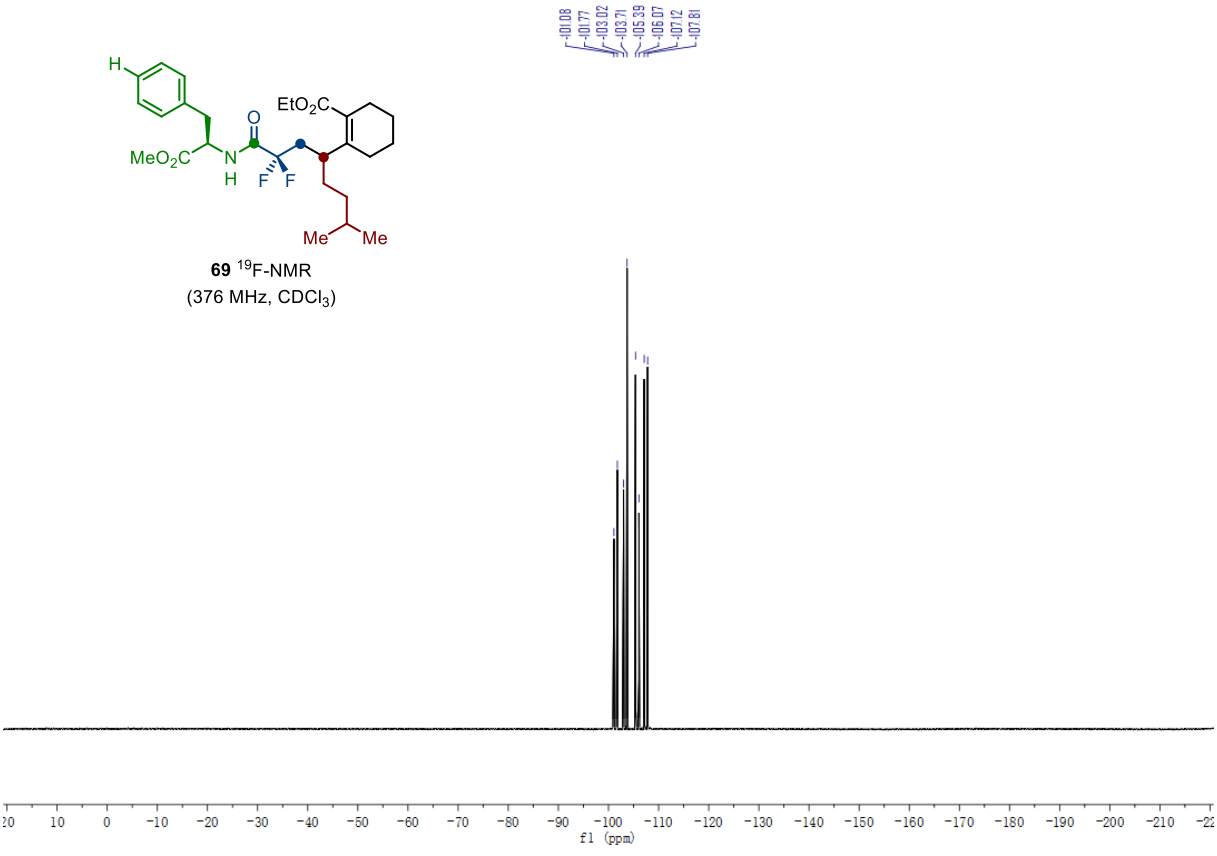
68 ^{19}F-NMR
(376 MHz, $CDCl_3$)



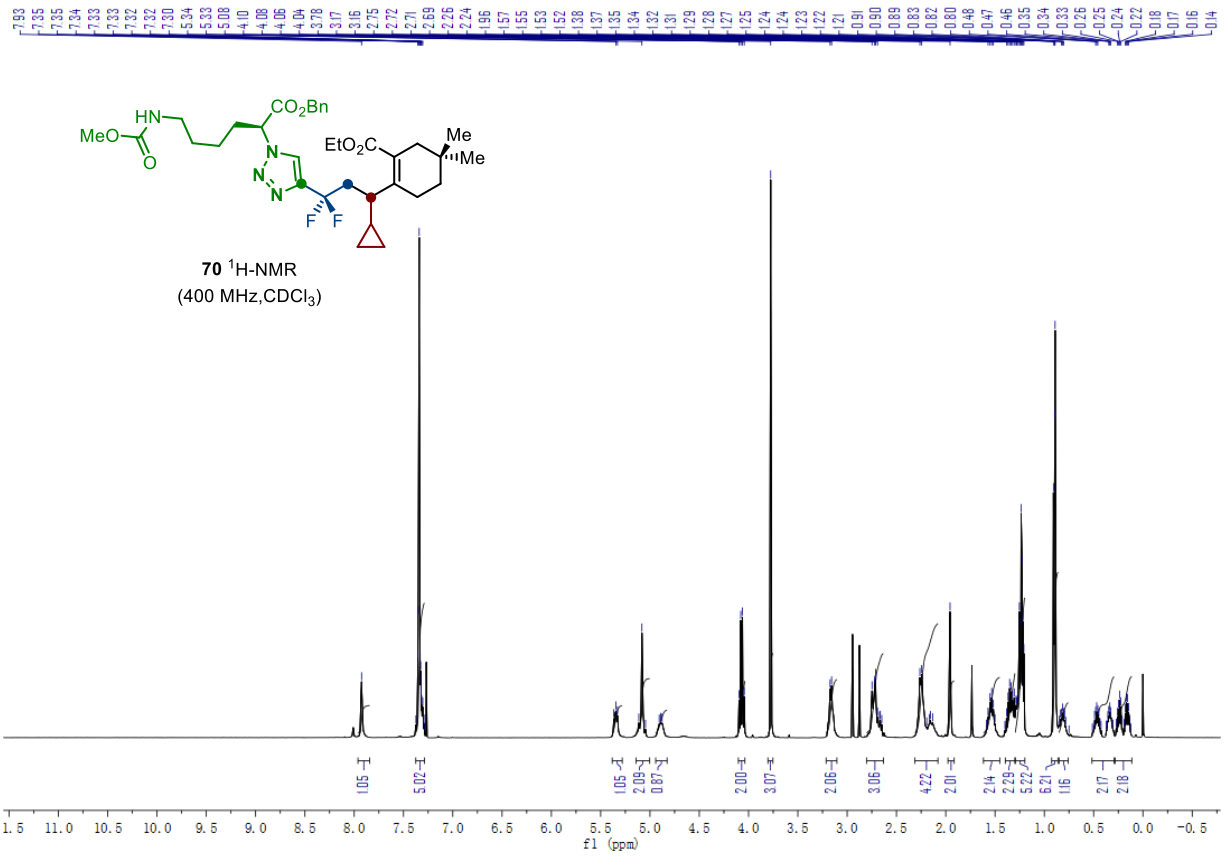
69 ^{1}H-NMR
(400 MHz,$CDCl_3$)

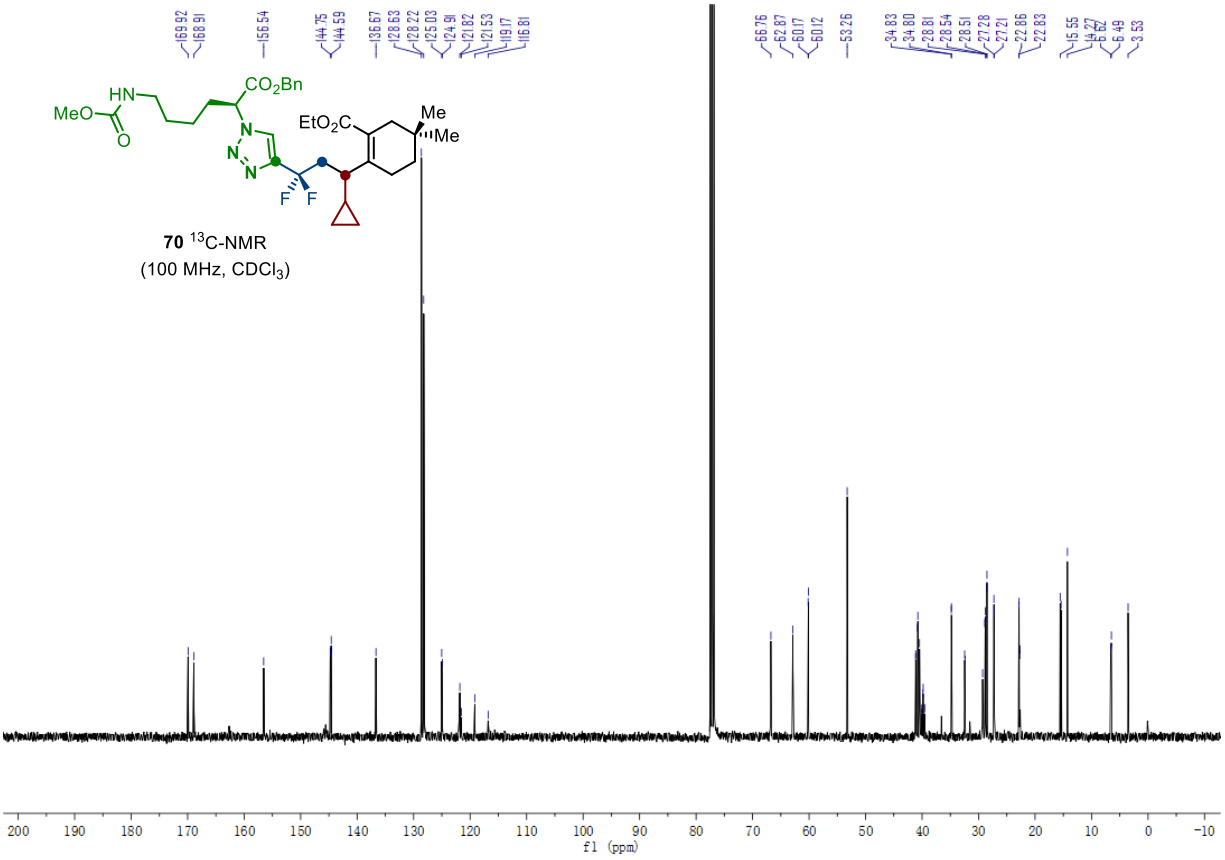


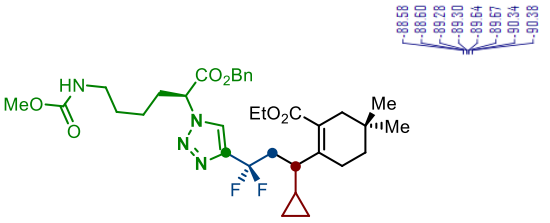
69 ^{13}C-NMR
(100 MHz, $CDCl_3$)



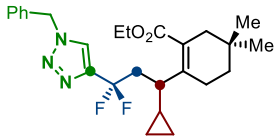
69 ^{19}F-NMR
(376 MHz, $CDCl_3$)


70 ^{1}H-NMR
(400 MHz,$CDCl_3$)
f1 (ppm)

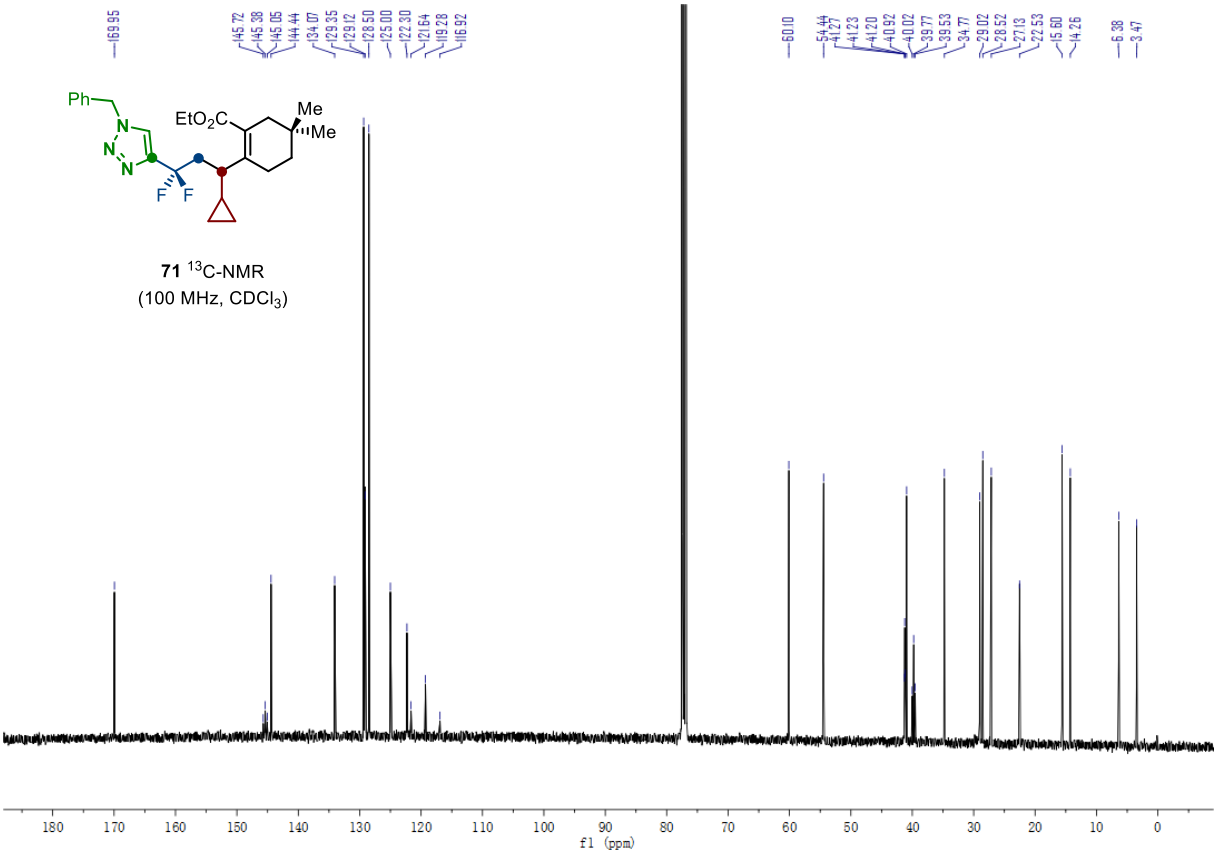

70 ^{13}C-NMR
(100 MHz, $CDCl_3$)
f1 (ppm)



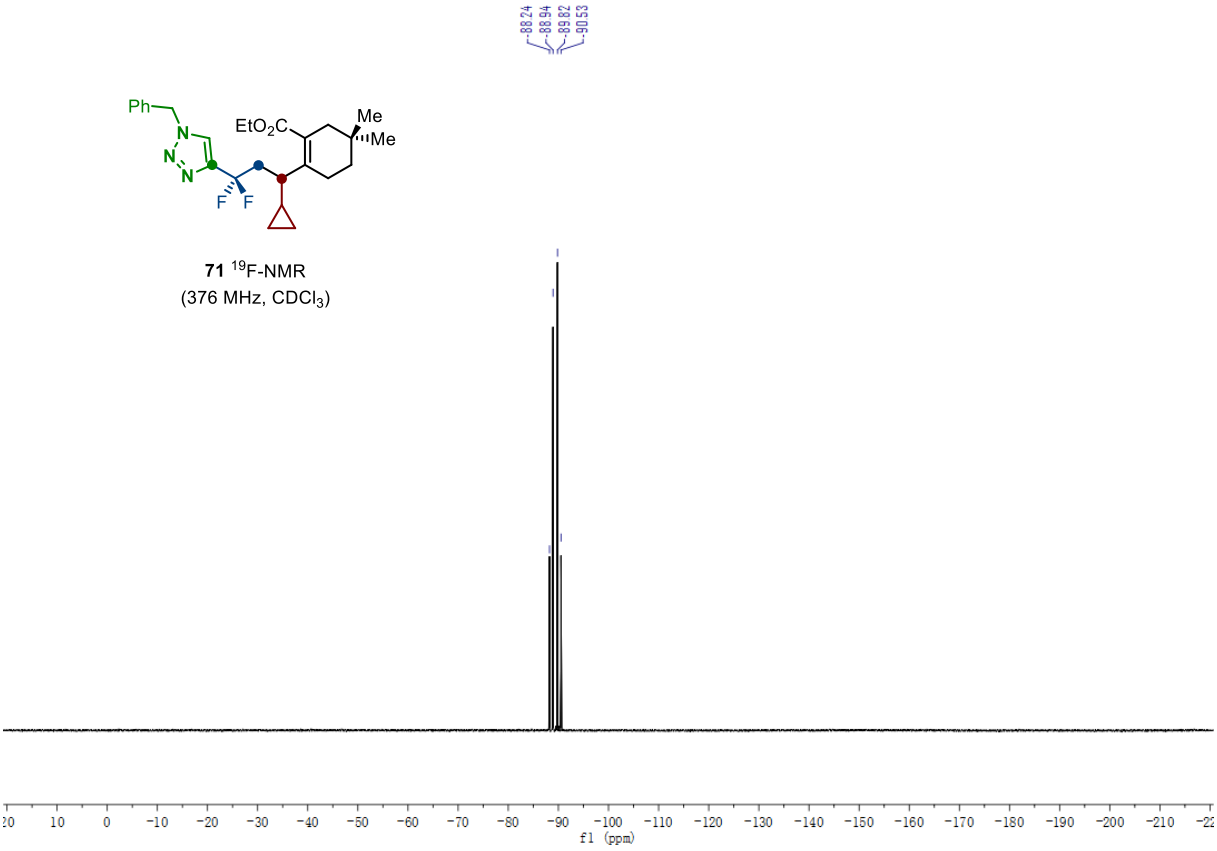
70 ^{19}F-NMR
(376 MHz, $CDCl_3$)



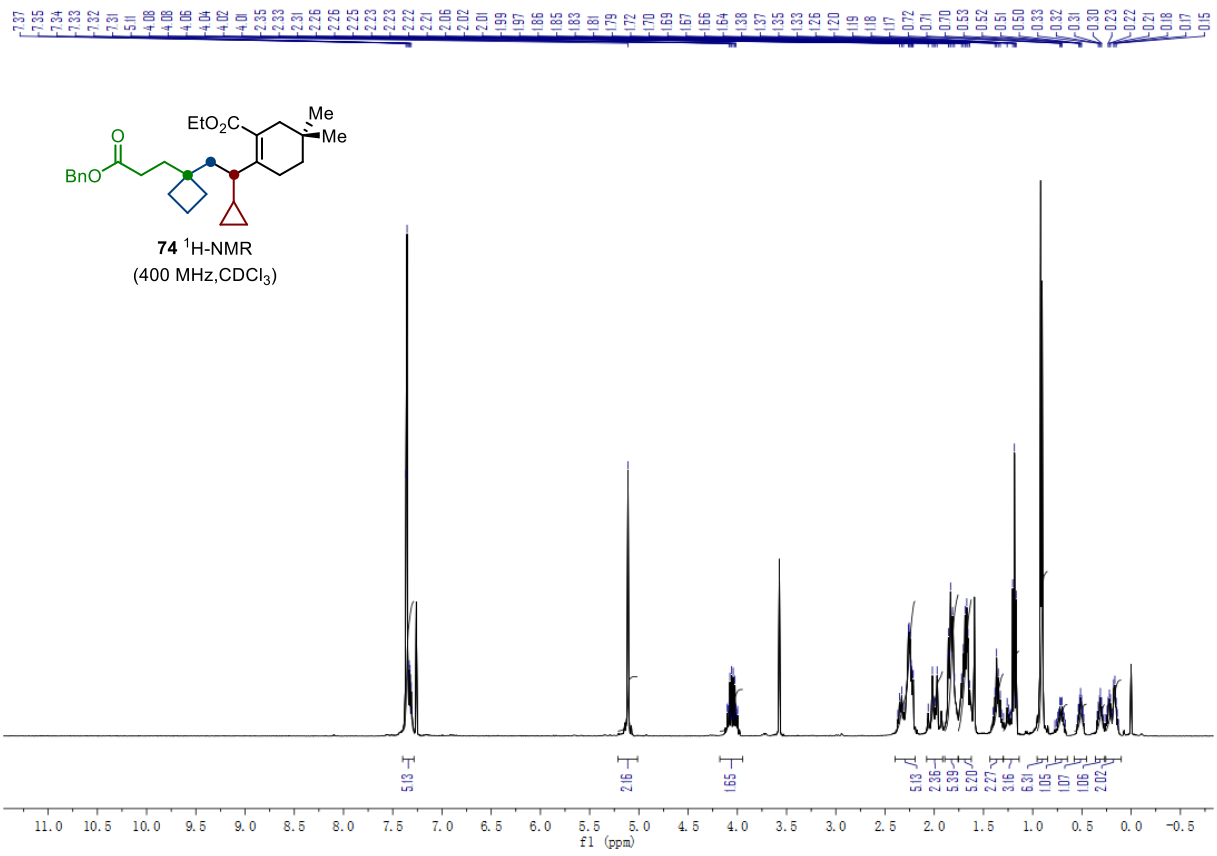
71 ^{1}H-NMR
(400 MHz,$CDCl_3$)

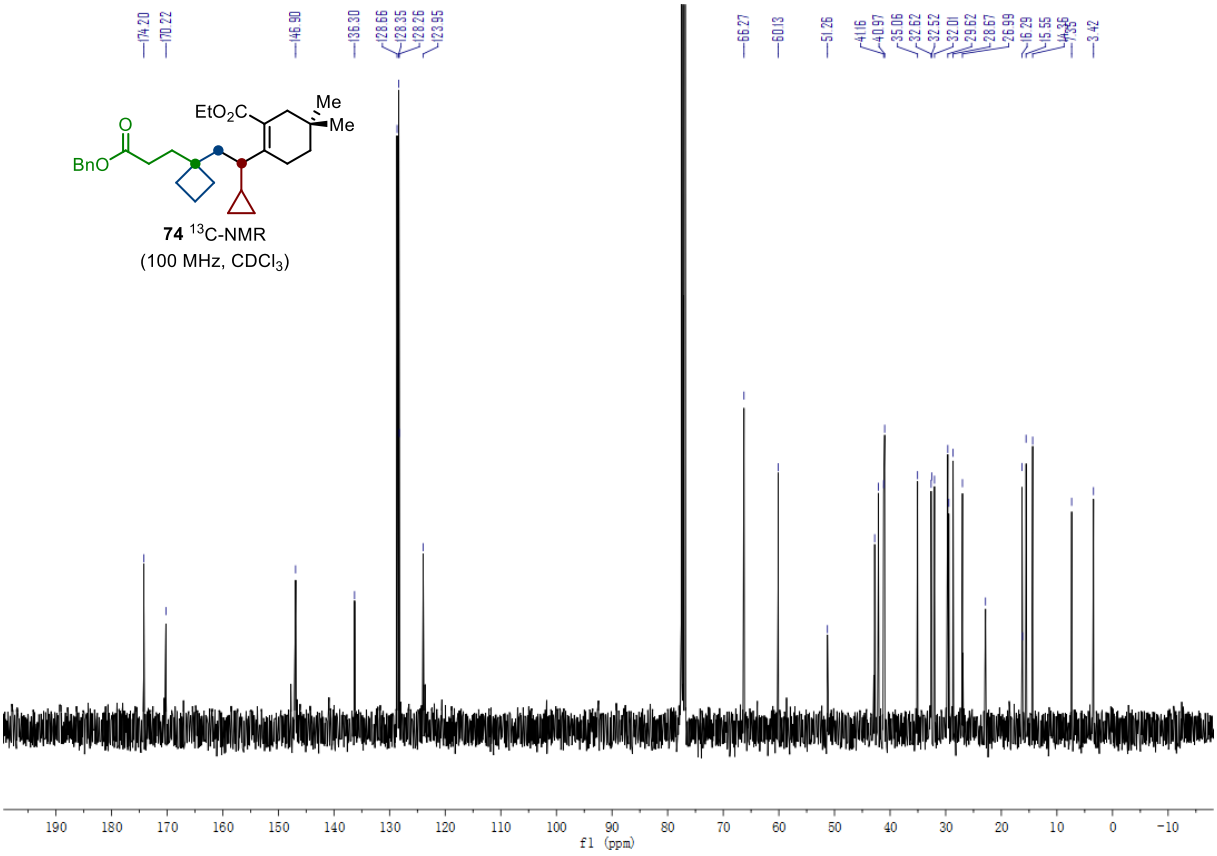


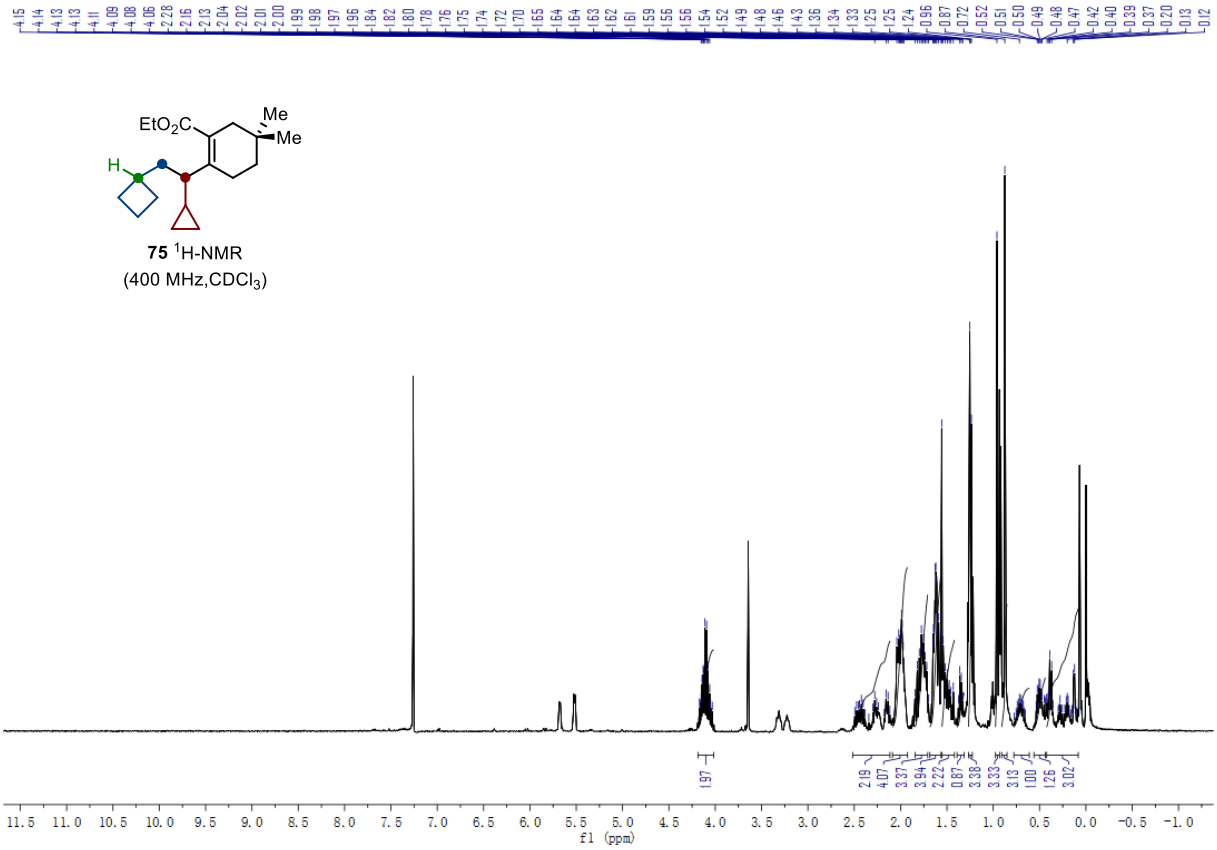
71 ^{13}C-NMR
(100 MHz, $CDCl_3$)

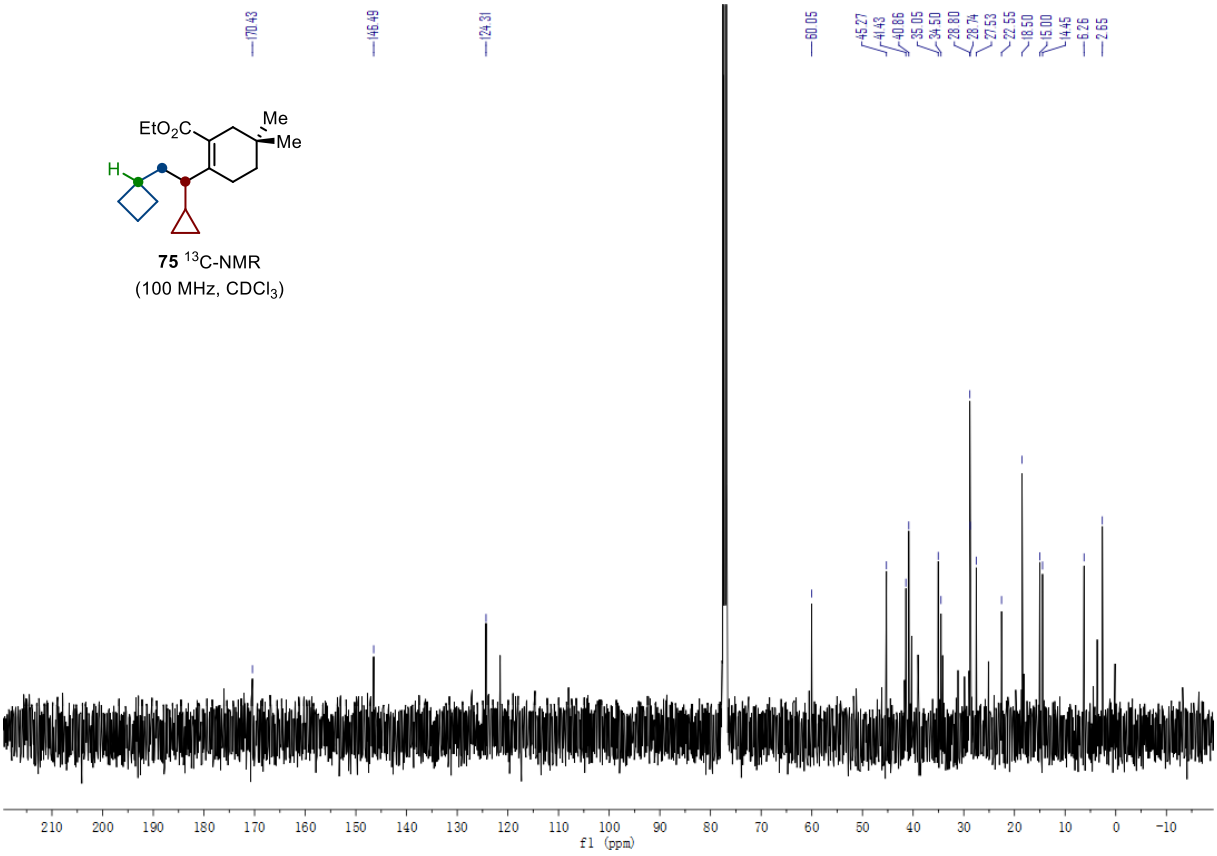


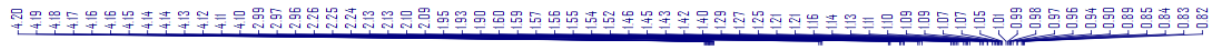
71 ^{19}F-NMR
(376 MHz, $CDCl_3$)

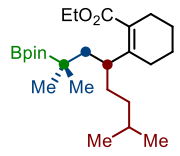

EtO2C
Me
Me
O
BnO
74 1H-NMR
(400 MHz,CDCl3)
f1 (ppm)


EtO2C
Me
Me
O
BnO
74 13C-NMR
(100 MHz, CDCl3)
f1 (ppm)

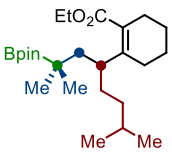

EtO2C
Me
Me
H
75 1H-NMR
(400 MHz,CDCl3)
f1 (ppm)


EtO2C
Me
Me
H
75 13C-NMR
(100 MHz, CDCl3)
f1 (ppm)

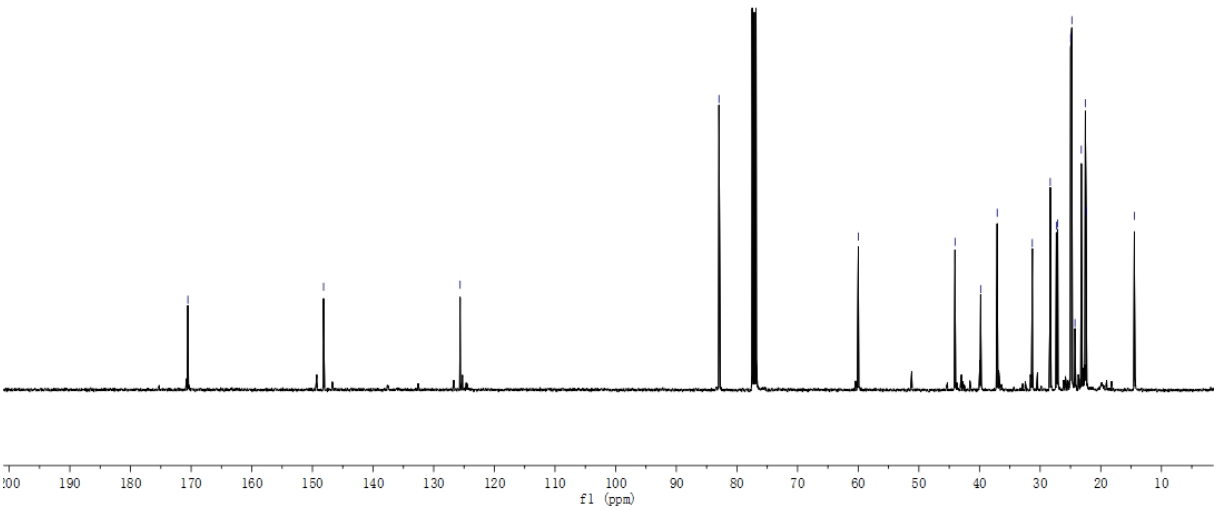


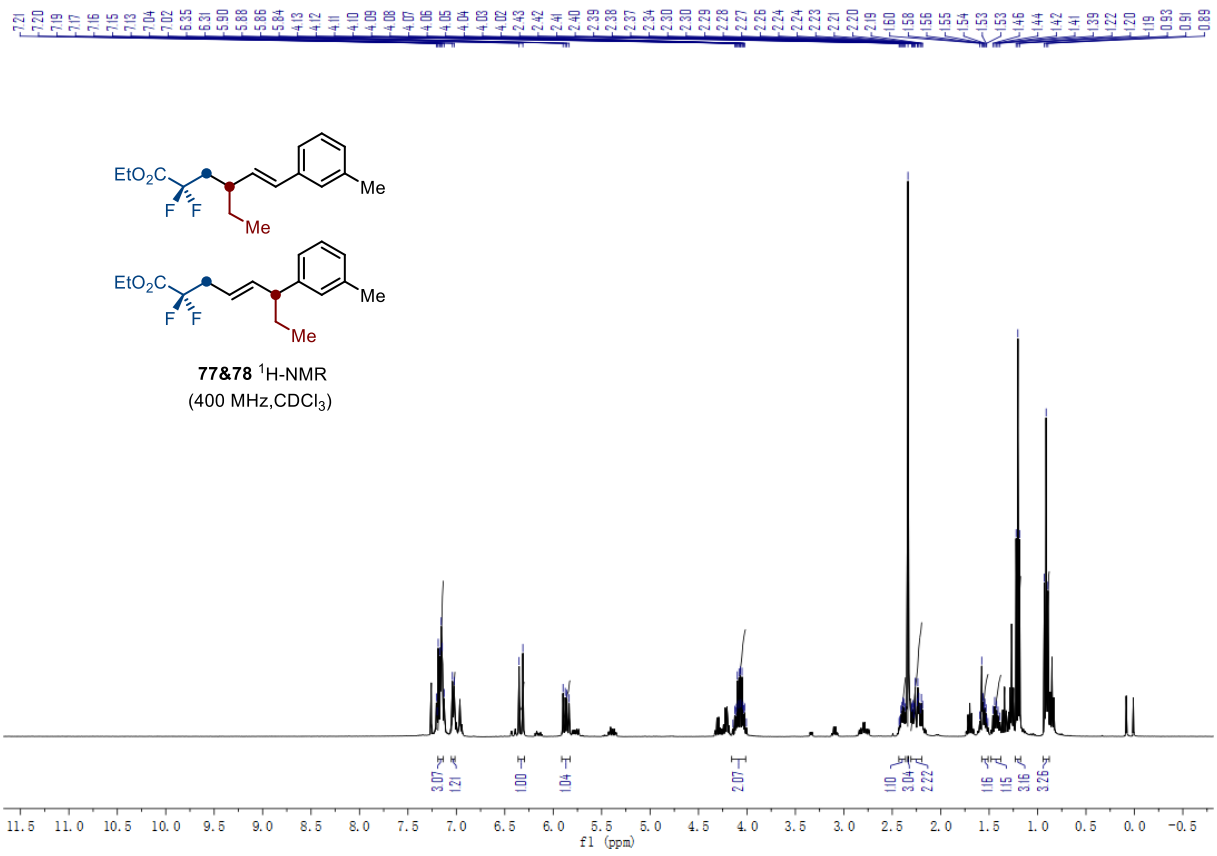


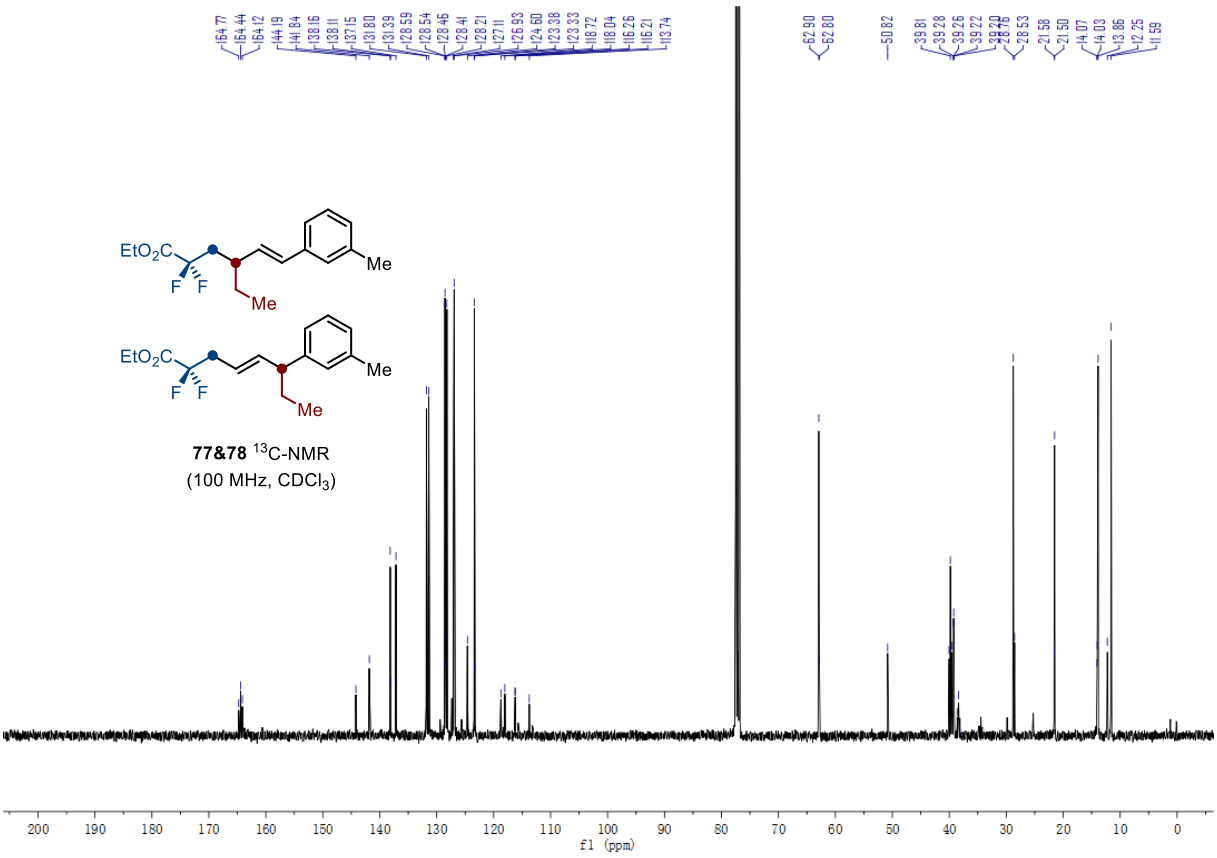
76 ^{1}H-NMR
(400 MHz,$CDCl_3$)

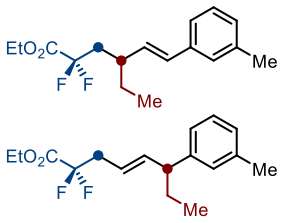


76 ^{13}C-NMR
(100 MHz, $CDCl_3$)

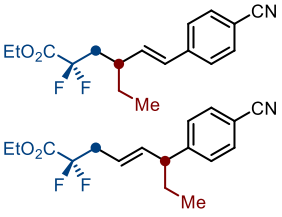



EtO2C
F F
Me
Me
EtO2C
F F
Me
Me
77&78 1H-NMR
(400 MHz,CDCl3)
f1 (ppm)

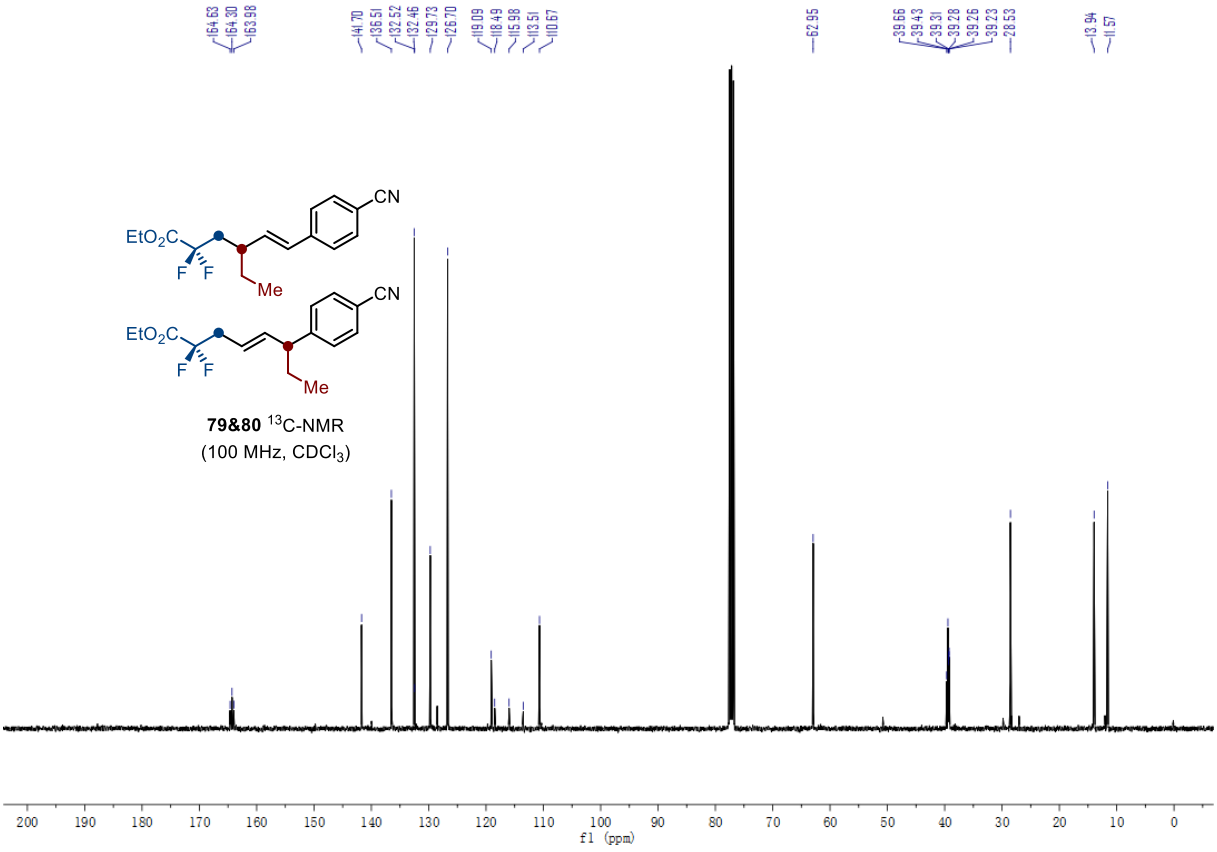

EtO2C
F F
Me
Me
EtO2C
F F
Me
Me
77&78 13C-NMR
(100 MHz, CDCl3)
f1 (ppm)



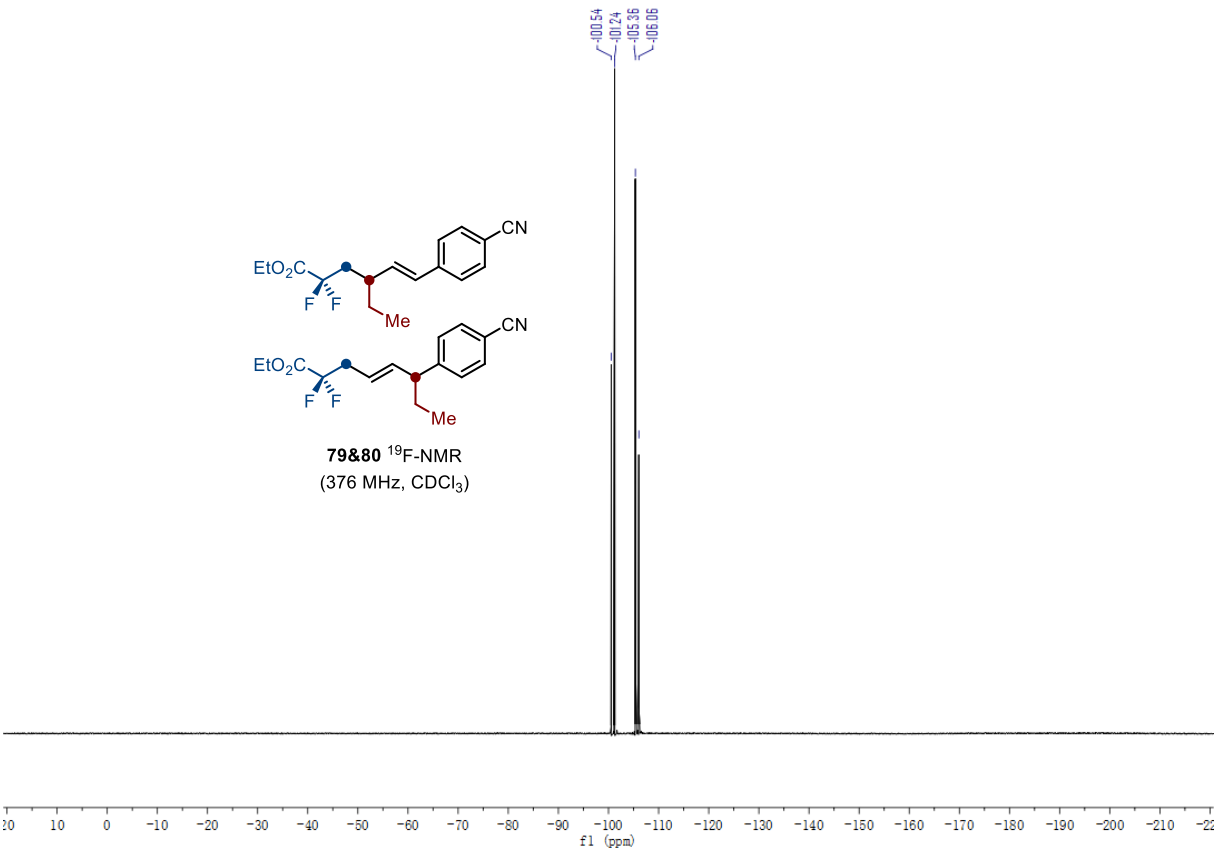
77&78 ^{19}F-NMR
(376 MHz, $CDCl_3$)



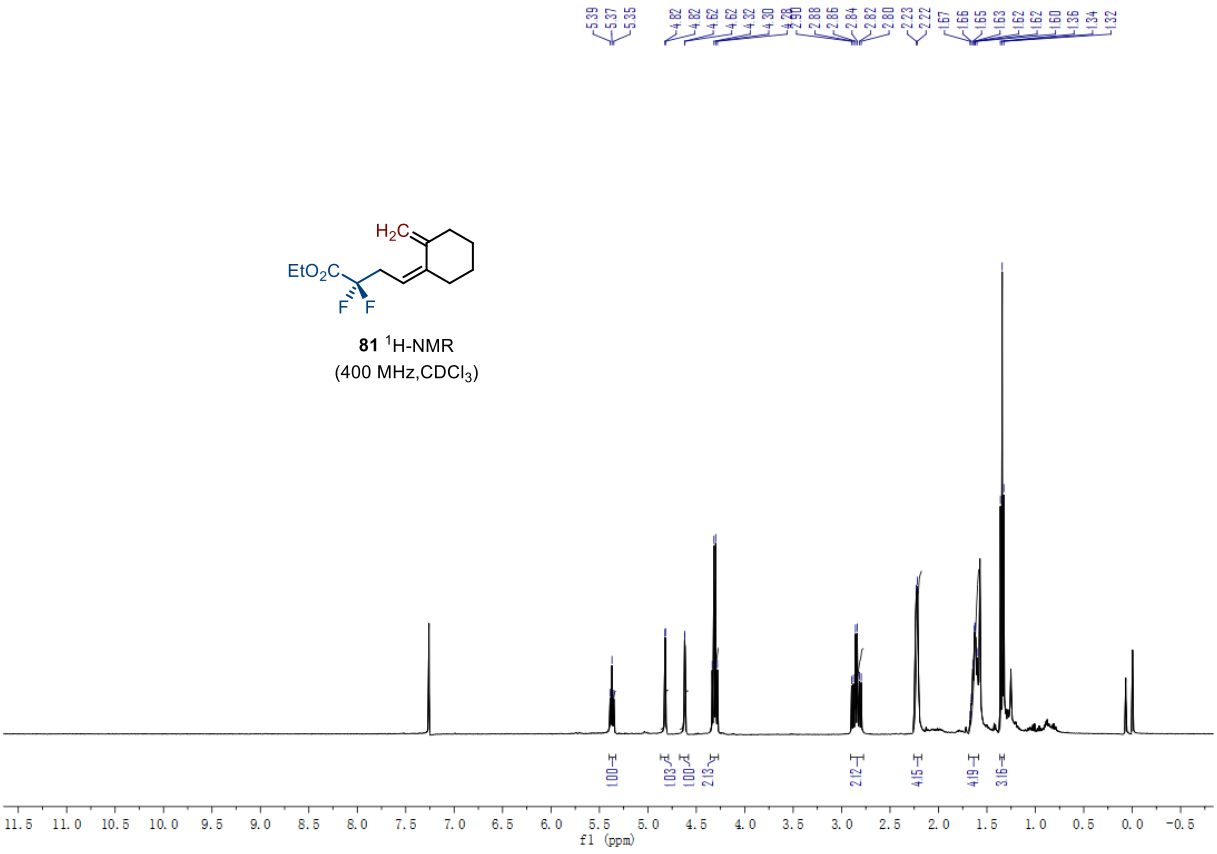
79&80 ^{1}H-NMR
(400 MHz,$CDCl_3$)



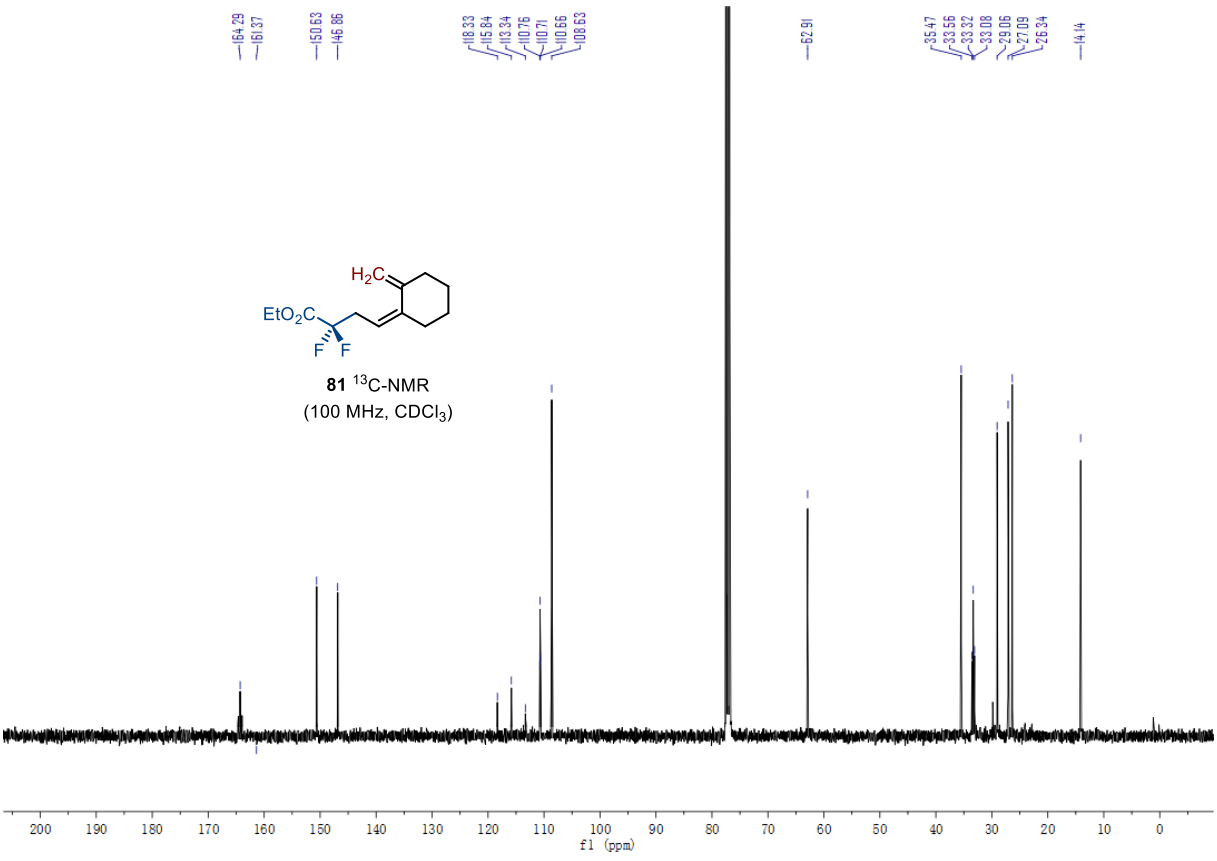
79&80 ^{13}C-NMR
(100 MHz, $CDCl_3$)



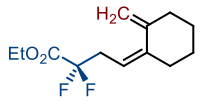
79&80 ^{19}F-NMR
(376 MHz, $CDCl_3$)



81 ^{1}H-NMR
(400 MHz,$CDCl_3$)



81 ^{13}C-NMR
(100 MHz, $CDCl_3$)



81 ^{19}F-NMR
(376 MHz, $CDCl_3$)