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Supplementary data

Isochalcogenourea-catalysed enantioselective synthesis of pyrrolidinone and chromeno-pyrrolidine heterocycles

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1. General experimental

Reactions involving moisture-sensitive reagents were carried out in flame-dried glassware under an inert atmosphere (Ar or N_2) using standard vacuum line techniques. Anhydrous solvents (Et_2O, CH_2Cl_2, THF and PhMe) were obtained after passing through an alumina column (MBraun SPS-800) or purchased in a sealed bottled under inert atmosphere. Room temperature (r.t.) refers to 18 ± 3 °C, Petrol refers to petroleum ether with the boiling range of 40–60 °C, brine refers to saturated aqueous sodium chloride solution, ether refers to diethyl ether (Et_2O). All chemicals and solvents used were purchased by pertinent brands (Sigma Aldrich, Alfa Aesar, Acros, Apollo Scientific, TCI, fluorochem) and used without further purification unless stated. Reactions involving heating were performed using DrySyn blocks or oil baths and a contact thermocouple. Under reduced pressure refers to the use of either a Büchi Rotavapor R-200 with a Büchi V491 heating Bath and Büchi V-800 vacuum controller, a Büchi Rotavapor R-210 with a Büchi V-491 heating bath and Büchi V-850 vacuum controller, a Heidolph Laborota 4001 with vacuum controller, an IKA RV10 rotary evaporator with an IKA HB10 heating bath and ILMVAC vacuum controller, or an IKA RV10 rotary evaporator with an IKA HB10 heating bath and Vacuubrand CVC3000 vacuum controller. Rotary evaporator condensers are fitted to Julabo FL601 Recirculating Coolers filled with ethylene glycol and set to −6 °C.

Analytical thin layer chromatography (TLC) [1] was performed on pre-coated aluminium plates (Kieselgel 60 F_{254} silica) plates purchased from Merck. Visualisation was achieved using ultraviolet light (254 nm) and staining with aqueous $KMnO_4$ or ethanolic vanillin solution followed by heating. Flash column chromatography was performed in glass columns fitted with porosity 3 sintered discs over Silica gel 60 (0.043–0.060 mm) using standard techniques as reported in the literature with the solvent system stated [2].

HPLC analyses were obtained on either a Shimadzu HPLC consisting of a DGU-20A5 degassing unit, LC-20AT liquid chromatography pump, SIL-20AHT autosampler, CMB-20A communications bus module, SPD-M20A diode array detector and a CTO-20A column oven or a Shimadzu HPLC consisting of a DGU-20A5R degassing unit, LC-20AD liquid chromatography pump, SIL-20AHT autosampler, SPD-20A UV/Vis detector and a CTO-20A column oven. Separation was achieved using either DAICEL CHIRALCEL OD-H and OJ-H columns or DAICEL CHIRALPAK AD-H, AS-H, IA, IB, IC and ID columns using the method stated. HPLC traces of enantiomerically enriched compounds were compared with authentic racemic spectra. Racemic compounds were synthesised under analogous reaction conditions using achiral or racemic catalysts where necessary.

Optical rotations were determined using a Perkin Elmer Precisely/Model-341 Polarimeter with a Na/Hal lamp (Na D line, 589 nm) at 20 °C.

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

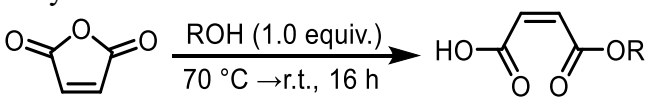
^{1}H, ^{13}C and ^{19}F nuclear magnetic resonance (NMR) spectra were recorded with Bruker AV400 with a BBFO probe, a Bruker Neo 400 with a BBF-H-D iProbe, a Bruker AVII 400 with a BBFO probe, a Bruker AVIII 500 with a CryoProbe Prodigy BBO probe, a Bruker AVIII-HD 500 with a CryoProbe Prodigy BBFO+ probe, or a Bruker AVIII-HD 700 with a CryoProbe Prodigy TCI probe in the deuterated solvent stated purchased from Sigma-Aldrich. Chemical shifts (δ) are quoted in ppm and referenced to residual solvent signals reported in literature [3–6]. $^{13}C\{^{1}H\}$ and $^{19}F\{^{1}H\}$ spectra were acquired using a proton broadband decoupling sequence. ^{13}C spectra were recorded with DEPTQ. Couplings were indicated by the use of conventional agreed abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets), td (triplet of doublets), *etc*. Coupling constants (*J*) are denoted with the number of bonds involved in the upper left and with the atoms coupling in the bottom right edge of the symbol, e.g. $^{3}J_{HH}$. The abbreviation *Ar* denotes aromatic, and app denotes apparent [7–9]. NMR peak assignments were confirmed using 2D ^{1}H correlated spectroscopy (COSY), 1D selective ^{1}H nuclear Overhauser effect spectroscopy (NOESY), 2D ^{1}H–^{13}C heteronuclear multiple-bond correlation spectroscopy (HMBC), and 2D ^{1}H–^{13}C heteronuclear single quantum coherence (HSQC) where necessary. For analysis of NMR-spectra MestReNova 11 and the tools therein were used [10,11].

Melting points were recorded on an Electrothermal 9100 melting point apparatus and are not corrected; (dec) refers to decomposition.

Mass spectrometry (m/z) data were acquired by either electrospray ionisation (ESI) or nanospray ionisation (NSI) at either the University of St Andrews Mass Spectrometry or SIRCAMS at University of Edinburgh.

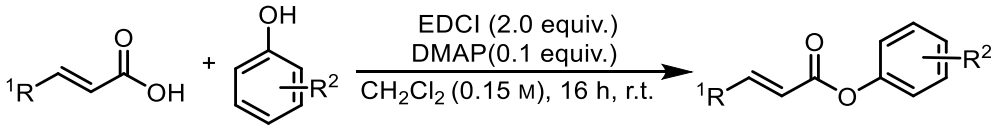
2. General procedures

General Procedure A: Synthesis of Cis-but-2-enedioic Acid Monoesters



Maleic anhydride (1.0 equiv.) and requisite alcohol (1.0 equiv.) were added at 70 °C in a sealed tube. The mixture was allowed to stir for 30 minutes at 70 °C then for 16 hours at room temperature. The reaction mixture was concentrated *in vacuo* and the resulting solid dried under vacuum to give the corresponding acid without further purification.

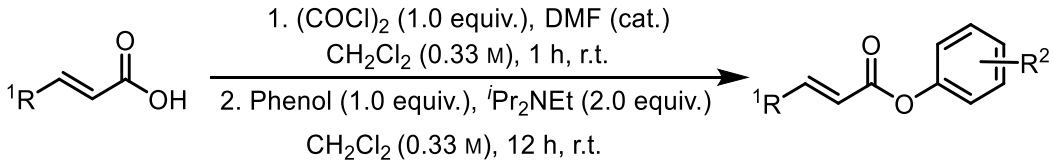
General Procedure B1: Synthesis of α,β-Unsaturated Aryl Esters



The appropriate amount of α,β-unsaturated acid (1.0 equiv.) was charged into a flame-dried flask with the appropriate amount of alcohol (1.5 equiv.), EDCI (2.0 equiv.), and DMAP (0.1 equiv.), in CH_2Cl_2 (0.15 M) at room temperature. The resulting solution was stirred for 16 hours at room temperature and then concentrated *in vacuo*. The resulting oil was dissolved in EtOAc

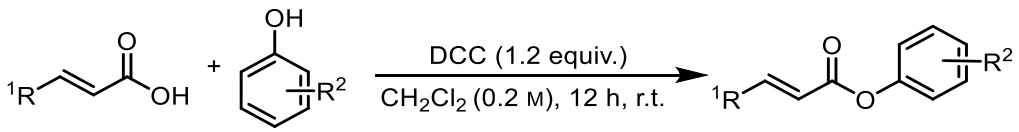
(100 mL) and washed with aqueous citric acid (10% *w/v*, 3 × 50 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was then purified by flash silica column chromatography under the conditions specified to afford the final product.

General Procedure B2: Synthesis of α,β-Unsaturated Aryl Esters



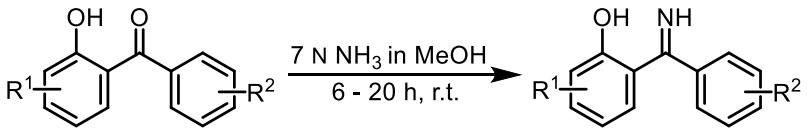
The appropriate amount of carboxylic acid (1.0 equiv.) was dissolved in CH_2Cl_2 (0.33 M) and added with oxalyl chloride (1.0 equiv.) and a few drops of DMF were added. The mixture was then stirred for 1 hour at room temperature. Diisopropylethylamine (2.0 equiv.) and the requisite aryl alcohol (1.0 equiv.) were added and stirred overnight at room temperature. The mixture was then concentrated *in vacuo,* and the residue was purified by column chromatography under the conditions specified to afford the final product.

General Procedure B3: Synthesis of α,β-Unsaturated Aryl Esters



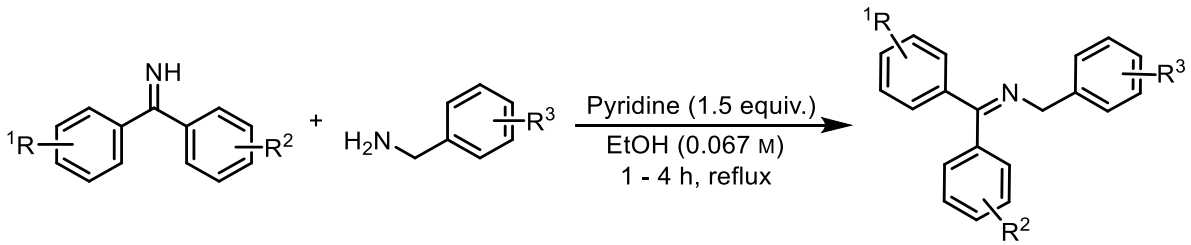
The appropriate amount of the corresponding carboxylic acid (1.0 equiv.) in CH_2Cl_2 (0.1 M) was added with the appropriate aryl alcohol (1.1 equiv.), DCC (1.1 equiv.), and DMAP (0.2 equiv.) at 0 °C. The mixture was then stirred for 12 hours at room temperature. The mixture was then filtered and concentrated *in vacuo*. The residue was purified by column chromatography under the conditions specified to afford the final product.

General Procedure C: Synthesis of 2-Hydroxybenzophenone Imine Derivatives



The appropriate amount of 2-hydroxybenzophenone derivative (1.0 equiv.) was charged with NH_3 (7 N in MeOH, 5.0 equiv.) and the reaction mixture was stirred for 6–20 hours at room temperature and was then concentrated *in vacuo*. The residue was directly used for the next step without any purification.

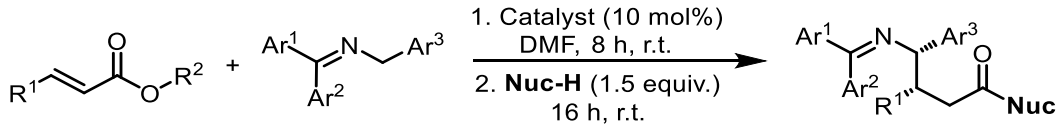
General Procedure D: Synthesis of Diarylmethanimine Schiff Bases



The appropriate amount of benzophenone imine derivative (1.0 equiv.) and benzylamine derivative (1.2 equiv.) were charged into a round-bottom flask with ethanol (0.067 M) and

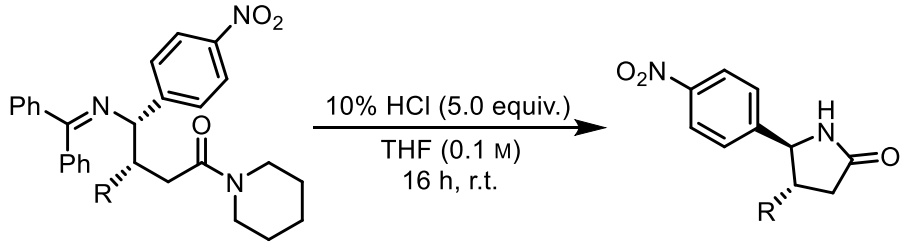
pyridine (1.5 equiv.). The reaction mixture was stirred for 1–4 hours under reflux conditions until the imine was totally consumed. If the product was precipitated, it was collected after filtering the reaction mixture otherwise, reaction mixture was concentrated *in vacuo* and the residue was purified by flash silica column chromatography under the conditions specified to afford the final product.

General Procedure E: Synthesis of γ-Imino Substituted Amides and Esters



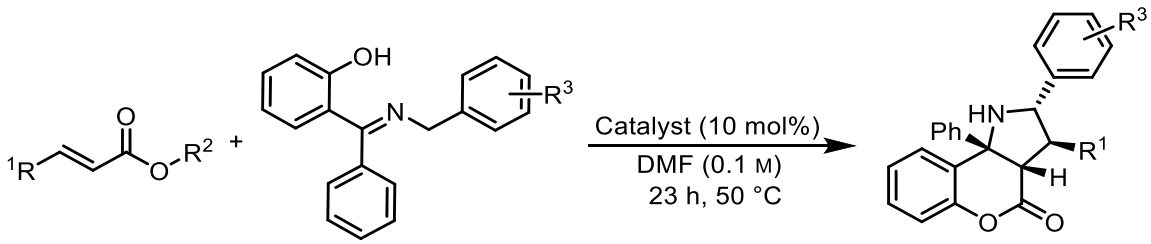
The requisite α,β-unsaturated aryl ester (1.0 equiv.), diarylmethanimine (1.5 equiv.), and isothiourea catalyst (10 mol%) were reacted in dry dimethylformamide (0.1 M) and stirred for 8 hours at room temperature. The appropriate nucleophile (1.5 equiv.) was added, and the reaction was stirred for 16 hours at room temperature. The mixture was then concentrated *in vacuo* and purified by flash column chromatography under the conditions specified to afford the final product.

General Procedure F: Synthesis of 2-Pyrrolidinone Derivatives



The requisite amount of the of γ-imino substituted amide product (1.0 equiv.) and 10% HCl (5.0 equiv.) were reacted in THF (0.1 M) and stirred for 16 hours at room temperature. The reaction mixture was then concentrated and purified by flash chromatography under the conditions specified to afford the final product.

General Procedure G: Synthesis of Chromeno-Pyrrolidine

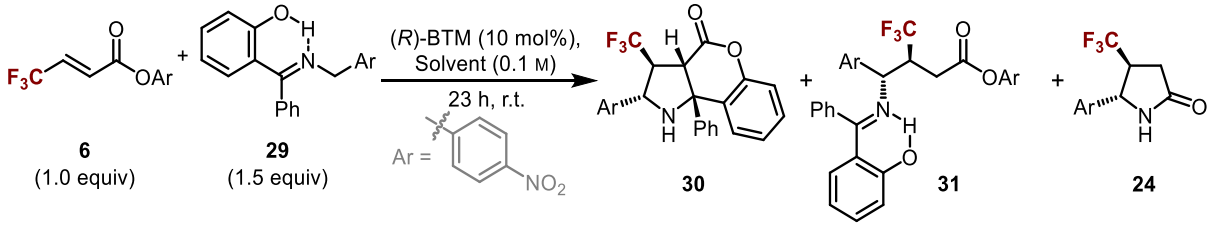


The requisite α,β-unsaturated ester (1.0 equiv.), diarylmethanimine (1.5 equiv.), isoselenourea catalyst (10 mol%) and dry dimethylformamide (0.1 M) were charged into a flame-dried round- bottom flask and stirred for 23 hours at 50 °C. The mixture was then concentrated *in vacuo* and then HCl (1.0 M) and THF (0.1 M) were added into the reaction mixture to hydrolyse the remaining starting material and side product. The mixture was concentrated *in vacuo*, diluted with CH_2Cl_2, and washed successively with saturated $NaHCO_3$ and water (× 3). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Further

purification by column chromatography was performed according to the conditions specified for the specific products.

3. Reaction solvent optimisation

Table 1. Reaction solvent optimisation.



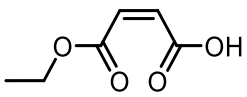
Entry	Solvent	30 Yield (%) [a]	31 Yield (%) [a]	24 Yield (%) [a]	30 er [b]	30 dr [c]
1	DMF	37	11	26	99:1	> 99:1
2	Et_2O	-	-	-	-	-
3	THF	-	-	-	-	-
4	CH_2Cl_2	-	-	-	-	-
5	Toluene	-	-	-	-	-
6	EtOAc	-	-	-	-	-
7	CH_3CN	8	N.D	N.D	N.D	> 85:15
8	DMSO	29	24	5	99:1	> 99:1
9	DMA	39	29	9	97:3	> 99:1

[a]-obtained by ^{1}H NMR analysis of the crude reaction mixture; [b]-determined by HPLC analysis on a chiral stationary phase; c-determined by ^{1}H and ^{19}F{^{1}H} NMR analysis of the crude reaction mixture. DMF = *N*,*N*-dimethylformamide, THF = tetrahydrofuran, DMSO = dimethylsulfoxide, DMA = *N*,*N*-dimethylacetamide

4. Data for the starting materials

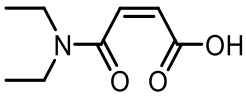
4.1 Data for α,β-unsaturated acid

(*Z*)-4-ethoxy-4-oxobutenoic acid (S1)



Following **General Procedure A**, maleic anhydride (0.98 g, 10.0 mmol) and ethanol (0.58 mL, 10.0 mmol) afforded the titled compound (1.38 g, 96%) as a white oil. **IR** ν_{max} (thin film): 2450−3650 (broad stretch, OH), 1712 (C=O), 1631 (C=C); **^{1}H NMR** (500 MHz, $CDCl_3$), δ_H: 1.35 (3H, t, $^3J_{HH}$ = 7.1, CH_2CH_3), 4.34 (2H, q, $^3J_{HH}$ = 7.1, CH_2CH_3), 6.37 (1H, d, $^3J_{HH}$ = 12.9, C*H*=CH), 6.44 (1H, d, $^3J_{HH}$ = 12.9, CH=C*H*). Spectroscopic data is in agreement with the literature [12].

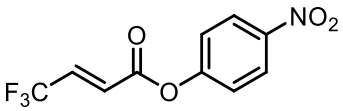
***N*,*N*-diethyl maleamic acid (S2)**



Following **General Procedure A**, maleic anhydride (0.98 g, 10.0 mmol) and diethyl amine (1.03 mL, 10.0 mmol) afforded the titled compound (1.69 g, 99%) as a yellowish-brown oil. **IR** ν_{max} (thin film): 3500 (OH), 2990 (sp^2 CH), 2937 (sp^3 CH) 1708 (C=O for acid), 1600 (C=O for amide), 1556 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$), equal ratio of rotamers were observed δ_H: 1.22 (3H, t, $^3J_{HH}$ = 7.4, rotamers 1, C*H*$_3$CH$_2$), 1.29 (3H, t, $^3J_{HH}$ = 7.2, rotamer 2, C*H*$_3$CH$_2$), 3.44–3.54 (4H, m, rotamer 1 and 2, CH$_3$C*H*$_2$), 6.41 (1H, d, $^3J_{HH}$ = 12.9, C*H*=CH), 6.61 (1H, d, $^3J_{HH}$ = 12.9, CH=C*H*). Spectroscopic data is in agreement with the literature [13].

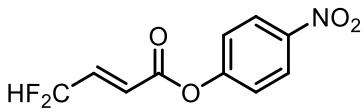
4.2 Data for α,β-unsaturated aryl esters

4-Nitrophenyl (*E*)-4,4,4-trifluorobut-2-enoate (6)



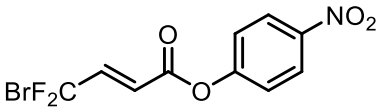
Following **General Procedure B1,** (*E*)-4,4,4-trifluorobut-2-enoic acid (759 mg, 5.40 mmol), 4-nitrophenol (1.13 g, 8.10 mmol), EDCI (2.08 g, 10.8 mmol), DMAP (66.5 mg, 0.54 mmol), and CH_2Cl_2 (40 mL) was stirred at room temperature for 16 hours, purified by flash column chromatography (4:1 Petrol:EtOAc) to give the titled compound (477 mg, 32%) as a colourless crystaline solid. **mp** 86–88 °C (Lit. **mp** 93–95 °C) [12]; **IR** ν_{max} (thin film): 3091 (Ar-H), 1739 (C=O), 1132 (C-F); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H: 6.75 (1H, dq, $^3J_{HH}$ = 15.8, $^4J_{HF}$ = 1.9, CH=C*H*COOPNP), 7.05 (1H, dq, $^3J_{HH}$ = 15.8, $^3J_{HF}$ = 6.4, CF$_3$C*H*=CH), 7.39 (2H, m, C(2, 6)Ar*H*), 8.35 (2H, m, C(3, 5)Ar*H*); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: −65.7 (3F, s, C*F*$_3$). Spectroscopic data is in agreement with the literature [12].

4-Nitrophenyl (*E*)-4,4-difluorobut-2-enoate (S3)



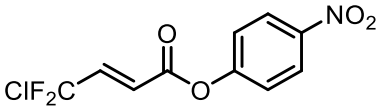
Following **General Procedure B1,** (*E*)-4,4-difluorobut-2-enoic acid (759 mg, 5.40 mmol), 4-nitrophenol (1.13 g, 8.10 mmol), EDCI (2.08 g, 10.8 mmol), DMAP (66.5 mg, 0.54 mmol), and CH_2Cl_2 (40 mL) was stirred at room temperature for 16 hours, purified by flash column chromatography (4:1 Petrol:EtOAc) to give the title compound (394 mg, 30%) as a colourless crystaline solid. **mp** 74–76 °C (Lit. **mp** 68–70 °C) [12]; **IR** ν_{max} (thin film): 3118 (Ar-H), 1735 (C=O), 1531 (N-O), 1487 (C=C), 1342 (C-F); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H: 6.36 (1H, tdd, $^2J_{HF}$ = 54.5, $^3J_{HH}$ = 3.8, $^4J_{HH}$ =1.1, CF_2H), 6.55 (1H, dtd, $^3J_{HH}$ = 15.9, $^4J_{HF}$ = 5.9, $^4J_{HH}$ = 1.1, CF_2HCH=C*H*), 7.08 (1H, dtd, $^3J_{HH}$ = 15.9, $^3J_{HF}$ = 10.3, $^3J_{HH}$ = 3.8, CF_2HC*H*=CH), 7.38 (2H, m, C(2,6)Ar*H*), 8.33 (2H, m, C(3,5)Ar*H*); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: −116.9 Spectroscopic data is in agreement with the literature [12].

4-Nitrophenyl (*E*)-4-bromo-4,4-difluorobut-2-enoate (S4)



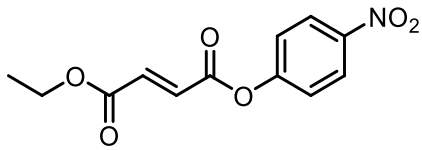
Following **General Procedure B2,** (*E*)-4-bromo-4,4-difluorobut-2-enoic acid (523 mg, 2.6 mmol), oxalyl chloride (223 µL, 2.60 mmol), and few drops of DMF in CH_2Cl_2 (8 mL) was stirred for 1 hour. Then, 4-nitrophenol (362 mg, 2.6 mmol) and $^{i}Pr_2NEt$ (905 µL, 5.20 mmol) were added, and the reaction was stirred at room temperature for 16 hours, then purified by flash column chromatography (5:1 Petrol:EtOAc) to give the title compound (432 mg, 52%) as a white crystalline solid. **mp** 78–80 °C (Lit. **mp** 79–80 °C) [14]; **IR** ν_{max} (thin film): 3118 (Ar-H), 1735 (C=O), 1531 (N-O), 1487 (C=C), 1342 (C-F); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H: 6.54 (1H, dt, $^3J_{HH}$ = 15.6, $^4J_{HF}$ = 1.8, C*H*=CHCF$_2$Br), 7.23 (1H, m, CF$_2$BrC*H*=CH), 7.39 (2H, m, C(2,6)Ar*H*), 8.35 (2H, m, C(3,5)Ar*H*). **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: −50.6. Spectroscopic data is in agreement with the literature [14].

4-Nitrophenyl (*E*)-4-chloro-4,4-difluorobut-2-enoate (S5)



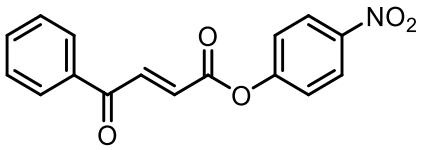
Following **General Procedure B1,** (*E*)-4-chloro-4,4-difluorobut-2-enoic acid (759 mg, 5.40 mmol), 4-nitrophenol (1.13 g, 8.10 mmol), EDCI (2.08 g, 10.8 mmol), DMAP (66.5 mg, 0.54 mmol), and CH_2Cl_2 (40 mL) were stirred at room temperature for 16 hours, purified by flash chromatography (4:1 Petrol:EtOAc) to give the title compound (394 mg, 30%) as a colorless crystal solid. **mp** 74–76 °C (Lit. **mp** 74–76 °C) [14]; **IR** ν_{max} (thin film): 3118 (Ar-H), 1735 (C=O), 1531 (N-O), 1487 (C=C), 1342 (C-F); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H: 6.63 (1H, dt, $^3J_{HH}$ = 15.5, $^4J_{HF}$ = 1.8, C*H*=CHCF$_2$Cl), 7.19 (1H, dt, $^3J_{HH}$ = 15.5, $^3J_{HF}$ = 9.0, CF$_2$ClC*H*=CH), 7.39 (2H, m, C(2,6)Ar*H*), 8.35 (2H, m, C(3,5)Ar*H*); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: −54.5. Spectroscopic data is in agreement with the literature [14].

Ethyl (4-nitrophenyl) fumarate (S6)



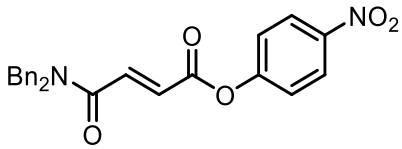
Following **General Procedure B1,** (*E*)-4-ethoxy-4-oxobut-2-enoic acid (1.44 g, 10.0 mmol), 4-nitrophenol (2.08 g, 15.0 mmol), EDCI (3.83 g, 20.0 mmol), DMAP (122 mg, 1.0 mmol), and 80 mL CH_2Cl_2 were stirred at room temperature for 16 hours and gave the titled compound (889 mg, 34%) as a white solid. **mp** 68–69 °C (Lit. **mp** 68–69 °C) [14]; **IR** ν_{max} (thin film): 3072 (Ar-H), 1716 (C=O), 1514 (N-O), 1489 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H: 1.35 (3H, t, $^3J_{HH}$ = 7.1, OCH$_2$C*H*$_3$), 4.32 (2H, q, $^3J_{HH}$ = 7.1, OC*H*$_2$CH$_3$), 7.05 (2H, m, C*H*=C*H*), 7.36 (2H, m, C(2,6)Ar*H*), 8.31 (2H, m, C(3,5)Ar*H*). Spectroscopic data is in agreement with the literature [14].

4-Nitrophenyl (*E*)-4-oxo-4-phenylbut-2-enoate (S7)



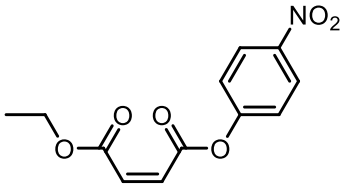
Following **General Procedure B2,** (*E*)-4-oxo-4-phenylbut-2-enoic acid (0.44 g, 2.5 mmol), oxalyl chloride (0.21 mL, 2.5 mmol), and few drops of DMF in CH_2Cl_2 (8 mL) was stirred for 1 hour. Then, 4-nitrophenol (0.34 g, 2.5 mmol) and $^{i}Pr_2NEt$ (0.87 mL, 5.0 mmol) were added and stirred at room temperature for 16 hours and gave the titled product as a yellow solid (0.15 g, 20%). **mp** 127–129 °C (Lit. **mp** 128–129 °C) [15]; **IR** ν_{max} (thin film): 3080 (Ar-H), 1747 (C=O), 1521 (N-O), 1489 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H: 7.10 (1H, d, $^3J_{HH}$ = 16.6, C*H*=CH-CO-Ph), 7.40 (2H, m, C(2,6)Ar*H*-NO_2), 7.56 (2H, m, C(3,5)Ar*H*), 7.67 (1H, m, C(4)Ar*H*), 8.05 (2H, m, C(2,6)Ar*H*), 8.13 (1H, d, $^3J_{HH}$ = 16.6 CH=C*H*-CO-Ph), 8.33 (2H, m, C(3,5)Ar*H*-NO_2). Spectroscopic data is in agreement with the literature [15].

4-Nitrophenyl (*E*)-4-(dibenzylamino)-4-oxobut-2-enoate (S8)



Following **General Procedure B3,** (*E*)-4-(dibenzylamino)-4-oxobut-2-enoic acid (2.08 g, 7.04 mmol), 4-nitrophenol (1.0 g, 7.18 mmol), DCC (1.74 g, 8.44 mmol), DMAP (172 mg, 01.41 mmol), and 7 mL CH_2Cl_2 was stirred at room temperature for 12 hours and gave the titled compound (2.20 g, 75%) as an orange solid. **mp** 62–65 °C (Lit. **mp** 62 – 64°C) [16]; **IR** ν_{max} (thin film): 3030 (Ar-H), 1741 (C=O), 1587 (N-O), 1440 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H: equal ratio of rotamers were observed 4.57 (2H, s, rotamers 1, CH_2Ph), 4.69 (2H, d, $^4J_{HH}$ = 2.4, rotamers 2, CH_2Ph), 7.10–7.21 (3H, m, rotamers 1 or 2, CH_2PhC*H* and CH_2PhNCOCH=C*H*), 7.23–7.43 (10H, m, rotamers 1 and 2, CH_2PhC*H* and C(2,6)Ar*H*-NO_2) 7.64 (1H, dd, $^3J_{HH}$ = 15.3, $^5J_{HH}$ = 2.4, CH_2PhNCOC*H*=CH), 8.28 (2H, m, C(3,5)Ar*H*-NO_2). Spectroscopic data in agreement with the literature [16].

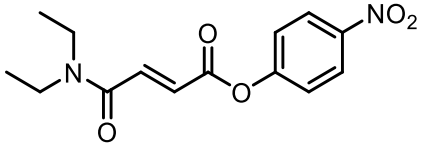
Ethyl (4-nitrophenyl) maleate (S9)



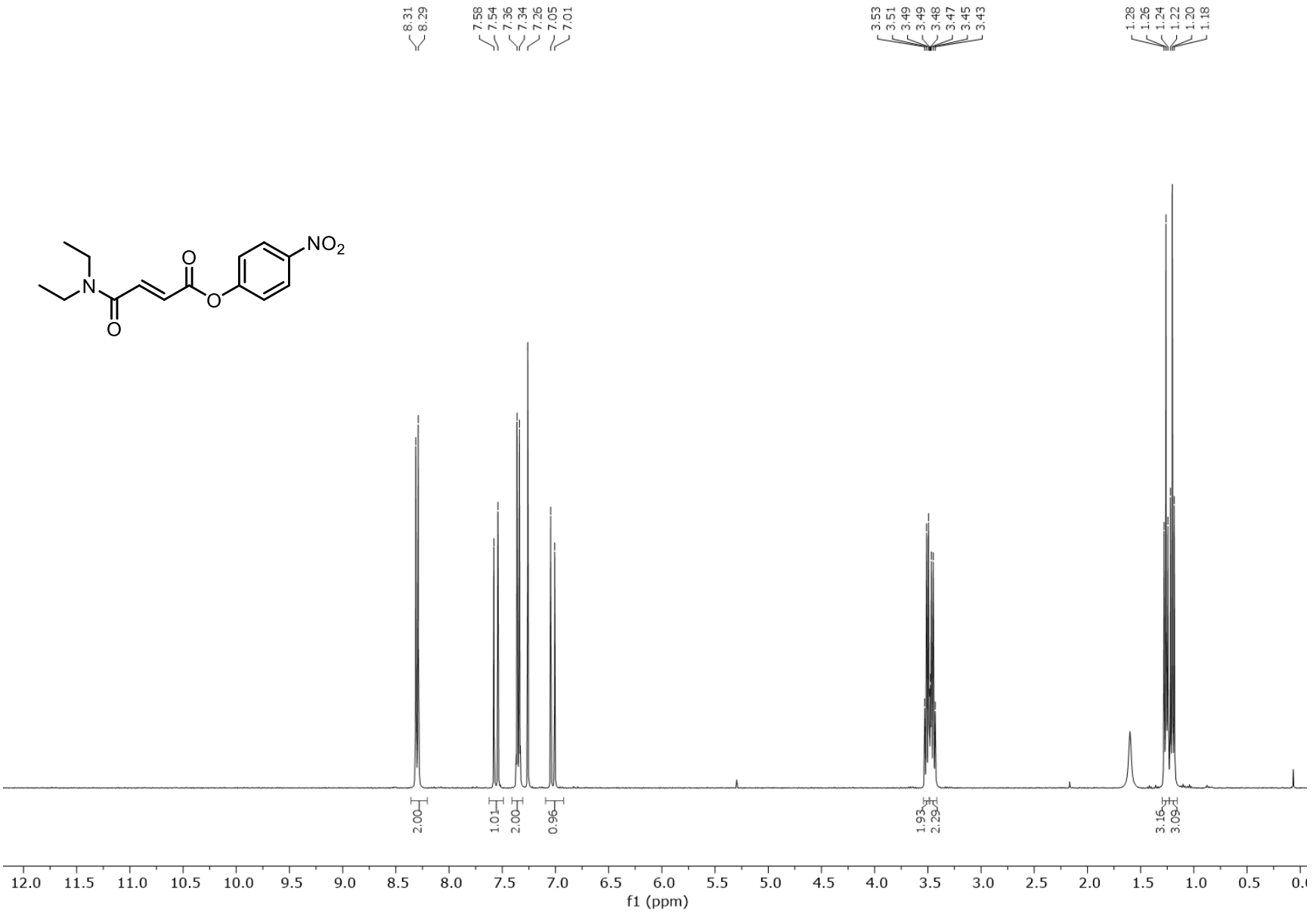
Following **General Procedure B2,** (Z)-4-ethoxy-4-oxobutenoic acid (1.4 g, 9.8 mmol), oxalyl chloride (0.88 mL, 10.3 mmol), and few drops of DMF in CH_2Cl_2 (30 mL) was stirred for 1 hour. Then, 4-nitrophenol (1.36 g, 9.8 mmol) and $^{i}Pr_2NEt$ (3.4 mL, 19.6 mmol) were added and stirred at room temperature for 16 hours and gave the titled product as off-white crystal (0.9 g, 35 %). **mp** 42–44 °C ($CHCl_3$), (Lit. **mp** 59–61°C (EtOAc)) [12]; **IR** ν_{max} (thin film): 3116 (Ar-H), 2985 (sp^3 CH), 1755 (C=O), 1720 (C=O), 1523 (asymm. N-O), 1346 (symm. N-O); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H: 1.31 (3H, t, $^3J_{HH}$ = 7.1, OCH_2CH_3), 4.28 (2H, q, $^3J_{HH}$ = 7.1, OCH_2CH_3), 6.43 (1H, d, $^3J_{HH}$ = 11.8, CH_3-CH_2-O-CO-CH=C*H*), 6.48 (1H, d, $^3J_{HH}$ = 11.8,

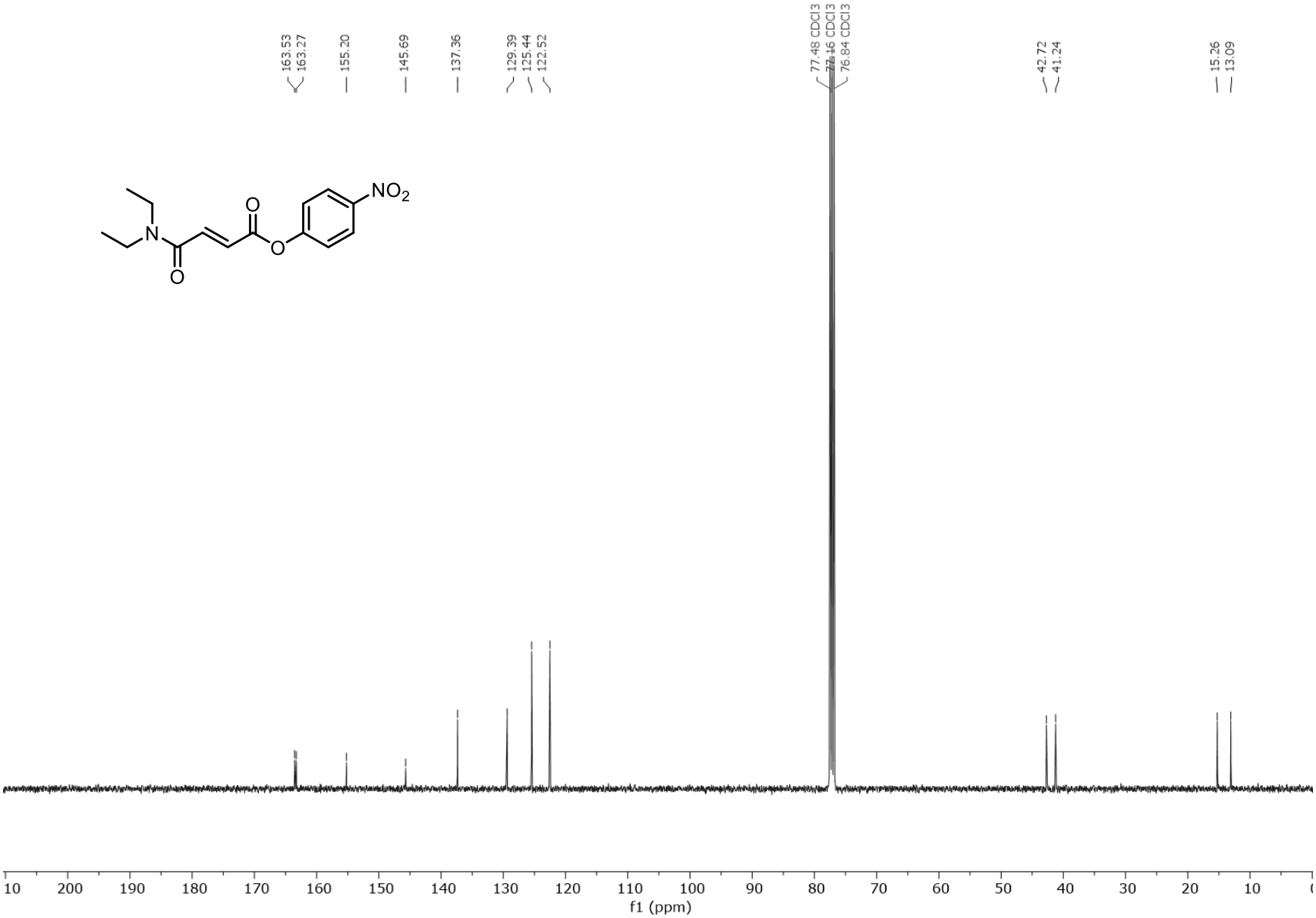
CH_3-CH_2-O-CO-C*H*=CH), 7.42 (2H, m, C(2,6)Ar*H*-NO_2), 8.30 (2H, m, C(3,5)Ar*H*-NO_2). Spectroscopic data is in agreement with the literature [12].

4-Nitrophenyl (*E*)-4-(diethylamino)-4-oxobut-2-enoate (S10)



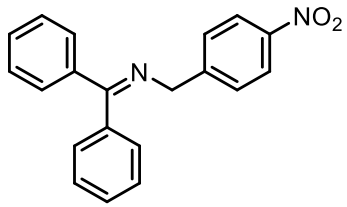
Following **General Procedure B2**, *N*,*N*-diethyl maleamic acid (764 mg, 4.47 mmol), oxalyl chloride (0.40 mL, 4.67 mmol), and few drops of DMF in CH_2Cl_2 (14 mL) were stirred for 1 hour. Then, 4-nitrophenol (622 g, 4.47 mmol), $^{i}Pr_2NEt$ (1.5 mL, 8.9 mmol) were added and stirred at room temperature for 16 hours and gave the titled product as off-white crystal (109 mg, 10%). **mp.** 72–74 °C ($CHCl_3$); **IR** ν_{max} (thin film): 3115 (Ar-H), 2978 (sp^3 CH), 1743 (C=O for ester), 1614 (C=O for amide), 1519 (asymm. N-O), 1334 (symm. N-O); **^{1}H NMR** (400 MHz, $CDCl_3$), equal ratio of rotamers were observed, δ_H: 1.20 (3H, t, $^3J_{HH}$ = 7.1, rotamers 1, C*H*$_3$CH$_2$), 1.26 (3H, t, $^3J_{HH}$ = 7.2, rotamer 2, C*H*$_3$CH$_2$), 3.42–3.54 (4H, m, rotamer 1 and 2, CH$_3$C*H*$_2$), 7.03 (1H, d, $^3J_{HH}$ = 15.2, rotamer 1 and 2, C*H*CH), 7.35 (2H, m, C(2,6)Ar*H*-NO_2), 7.56 (1H, d, $^3J_{HH}$ = 15.2, rotamer 1 and 2, CHC*H*), 8.29 (2H, m, C(3,4)Ar*H*-NO_2); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$), δ_C: 13.1 (*C*H$_3$CH$_2$), 15.3 (*C*H$_3$CH$_2$), 41.2 (CH$_3$*C*H$_2$), 42.7 (CH$_3$*C*H$_2$), 122.5 (*C*(2,6)ArH-NO_2), 125.4 (*C*(3,5)ArH-NO_2), 129.4 (*C*HCH), 137.4 (CH*C*H), 145.7 (*C*(1)Ar-NO_2), 155.2 (*C*(4)Ar-NO_2), 163.3 (*C*O), 163.5 (*C*O); **HRMS** (NSI^+) $C_{14}H_{16}N_2NaO_5^+$ ($[M+Na]^+$) requires 315.09514, found 315.0951 (−0.18 ppm).


8.31
8.29
7.58
7.54
7.36
7.34
7.26
7.05
7.01
3.53
3.51
3.49
3.49
3.48
3.47
3.45
3.43
1.28
1.26
1.24
1.22
1.20
1.18
NO2
O
N
O
O
2.00
1.01
2.00
0.96
1.93
2.29
3.16
3.09
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

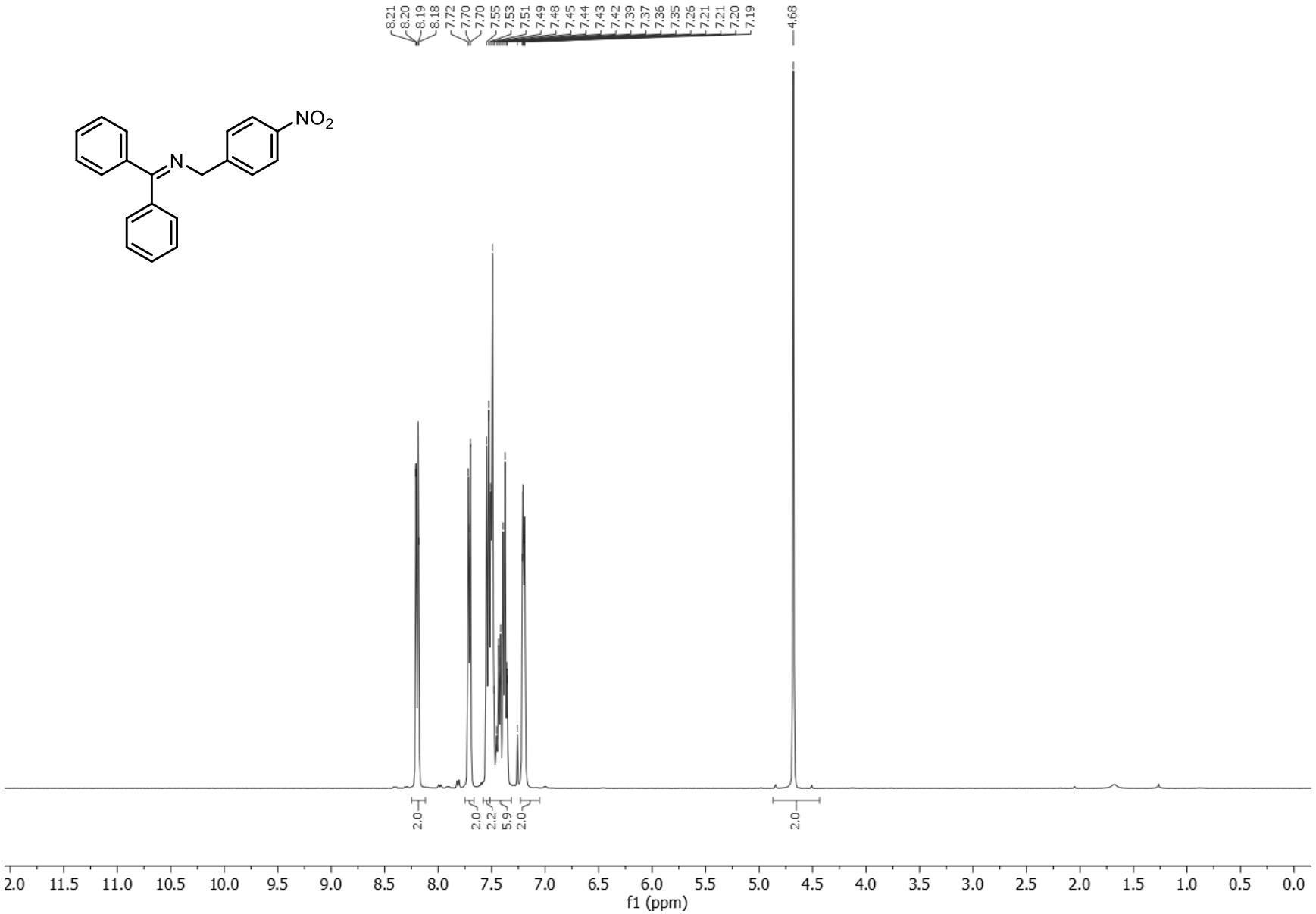

163.53
163.27
155.20
145.69
137.36
129.39
125.44
122.52
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
42.72
41.24
15.26
13.09
NO2
O
N
O
O
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

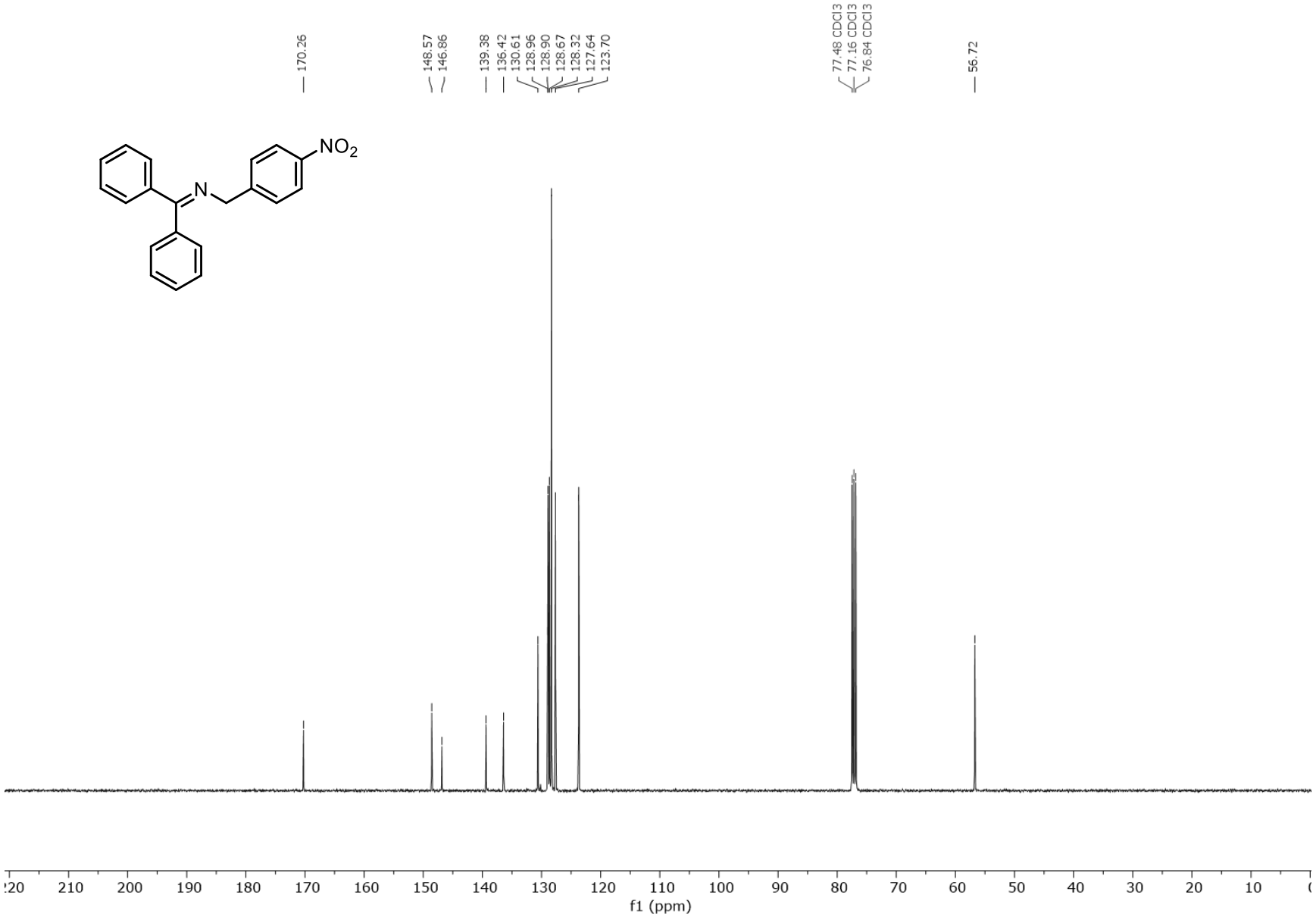
4.3 Data for diarylmethanimine schiff bases

***N*-(4-nitrophenyl)-1,1-diphenylmethanimine (7)**

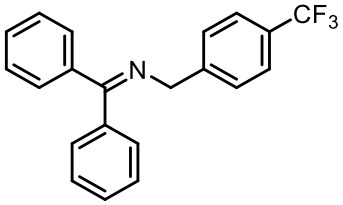


Following **General Procedure D,** diphenylmethanimine (840 µL, 5.0 mmol), 4-nitrobenzylamine hydrochloride (1.13 g, 6.0 mmol), and pyridine (604 µL, 7.5 mmol) in ethanol (75 mL) were refluxed for 1 hour and purified via flash chromatography (4:1 Petrol:EtOAc) to give the titled compound (1.5 g, 95%) as a yellow crystal. **mp** 60–62 °C; **IR** ν_{max} (thin film): 3061 (Ar-H), 1625 (C=N), 1512 (N-O), 1446 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H: 4.69 (2H, s, NC*H*$_2$Ar-NO_2), 7.22 (2H, m, N=CC(2,6)Ar$_2$*H*), 7.40–7.53 (6H, m, N=CC(3,4,5)Ar$_1$*H*, N=CC(3,4,5)Ar$_2$*H*), 7.57 (2H, m, NCH_2C(2,6)Ar*H*-NO_2), 7.72 (2H, m, N=CC(2,6)Ar$_1$*H*), 8.22 (2H, m, NCH_2C(3,5)Ar*H*-NO_2); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$), δ_C: 56.7 (C=N*C*H_2), 123.7 (O_2N-Ar*C*(3,5)H), 127.6 (Ph*C*(2,6)H), 128.3 (O_2N-ArC(2,6)H and Ph*C*(3,5)H), 128.7 (Ph*C*(2,6)H), 128.90 (Ph*C*(3,5)H), 128.96 (Ph*C*(4)H), 130.6 (Ph*C*(4)H), 136.4 (Ph*C*(1 or 4)), 139.4 (Ph*C*(1 or 4)), 146.9 (O_2N-Ar*C*(1 or 4)), 148.6 (O_2N-Ar*C*(1 or 4)), 170.3 (*C*=N); **HRMS** (ESI$^+$) $C_{20}H_{17}N_2O_2^+$ ([M+H]$^+$) requires 317.1284, found 317.1283 (−0.51 ppm).


8.21
8.20
8.19
8.18
7.72
7.70
7.70
7.55
7.53
7.51
7.49
7.48
7.45
7.44
7.43
7.42
7.39
7.37
7.36
7.35
7.26
7.21
7.21
7.20
7.19
4.68
NO2
N
2.0
2.0
2.2
5.9
2.0
2.0
2.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

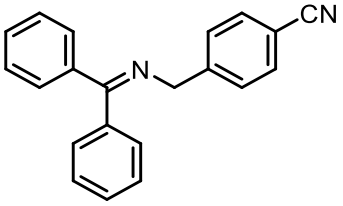

170.26
148.57
146.86
139.38
136.42
130.61
128.96
128.90
128.67
128.32
127.64
123.70
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
56.72
NO2
N
f1 (ppm)

1,1-Diphenyl-*N*-(4-(trifluoromethyl)benzyl)methanimine (S11)



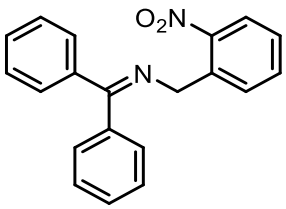
Following **General Procedure D,** diphenylmethanimine (840 µL, 5.0 mmol), (4-(trifluoromethyl)phenyl)methanamine (1.25 mL, 8.75 mmol), and pyridine (604 µL, 7.5 mmol) in ethanol (75 mL) were refluxed for 1 hour and purified via flash chromatography (4:1 Petrol:EtOAc) to give the titled compound (2.11 g, 99%) as a light yellow oil. **IR** ν_{max} (thin film): 3059 (Ar-H), 1618 (C=N), 1446 (C=C), 1119 (C-F); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H: 4.66 (2H, s, NC*H*$_2$Ar-CF_3), 7.22 (2H, m, N=CC(2,6)Ar$_2$*H*), 7.38 (2H, m, NCH_2C(2,6)Ar*H*-CF_3), 7.40–7.43 (6H, m, N=CC(3,4,5)Ar$_1$*H*, N=CC(3,4,5)Ar$_2$*H*), 7.61 (2H, m, N=CC(2,6)Ar$_1$*H*), 7.72 (2H, m, NCH_2C(3,5)Ar*H*-CF_3); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: −62.3 (3F, s, C*F*$_3$). Spectroscopic data is in agreement with the literature [17].

4-(((diphenylmethylene)amino)methyl)benzonitrile (S12)



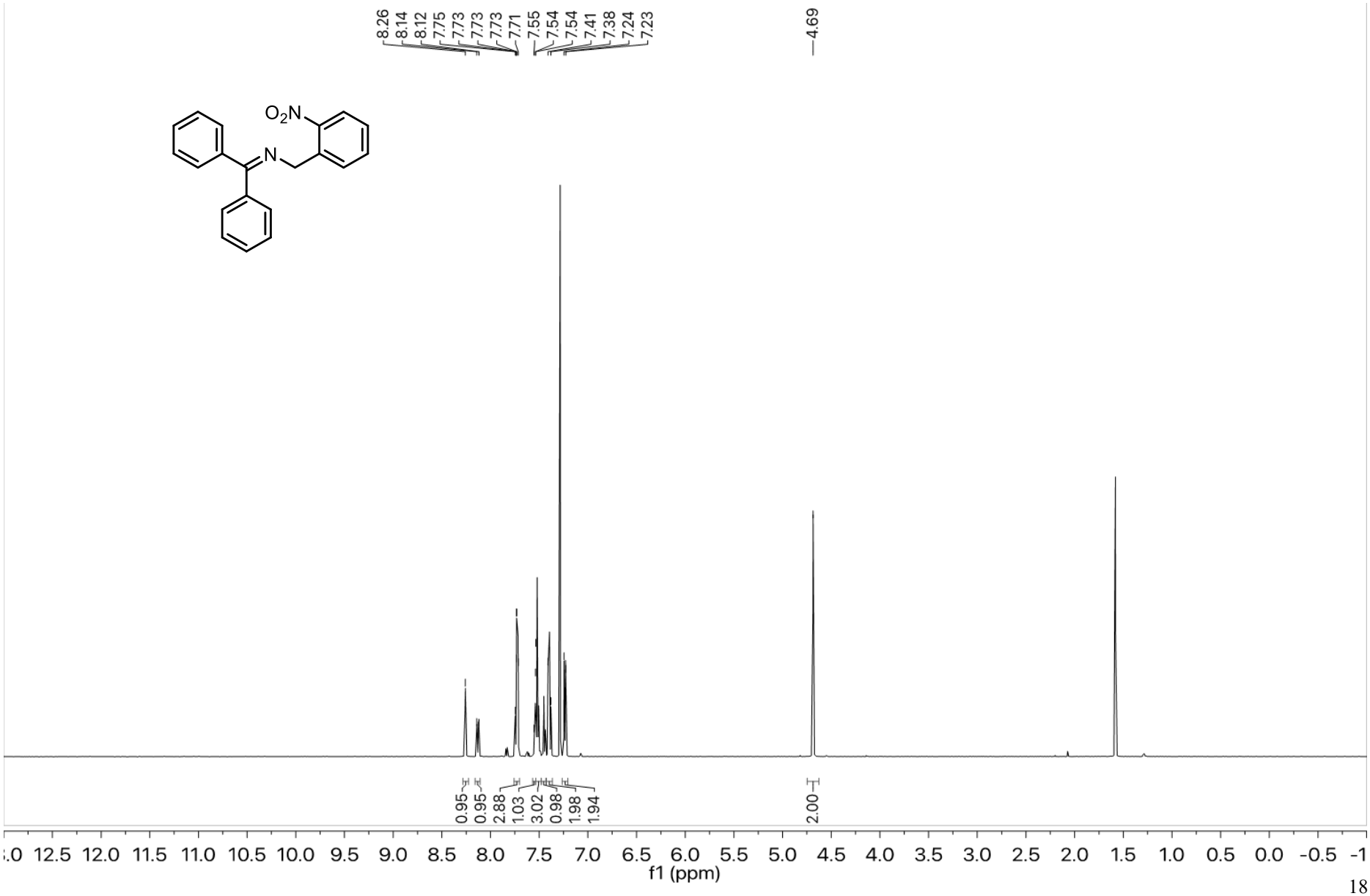
Following **General Procedure D,** diphenylmethanimine (503 µL, 3.0 mmol), 4-(aminomethyl)benzonitrile hydrochloride (607 mg, 3.6 mmol), and pyridine (362 µL, 4.5 mmol) in ethanol (45 mL) was refluxed for 1 hour and purified via flash chromatography (4:1 Petrol:EtOAc) to give the titled compound (804 mg, 90%) as a yellow solid. **mp** 66–68 ºC; **IR** ν_{max} (thin film): 3059 (Ar-H), 2250 (CN, nitrile), 1624 (C=N, imine), 1446 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H: 4.65 (2H, s, NC*H*$_2$Ar-CN), 7.21 (2H, m, N=CC(2,6)Ar$_2$*H*), 7.39–7.46 (6H, m, N=CC(3,4,5)Ar$_1$*H*, N=CC(3,4,5)Ar$_2$*H*), 7.52 (2H, m, NCH_2C(2,6)Ar*H*-CN), 7.64 (2H, m, NCH_2C(3,5)Ar*H*-CN), 7.72 (2H, m, N=CC(2,6)Ar$_1$*H*). Spectroscopic data is in agreement with the literature [18].

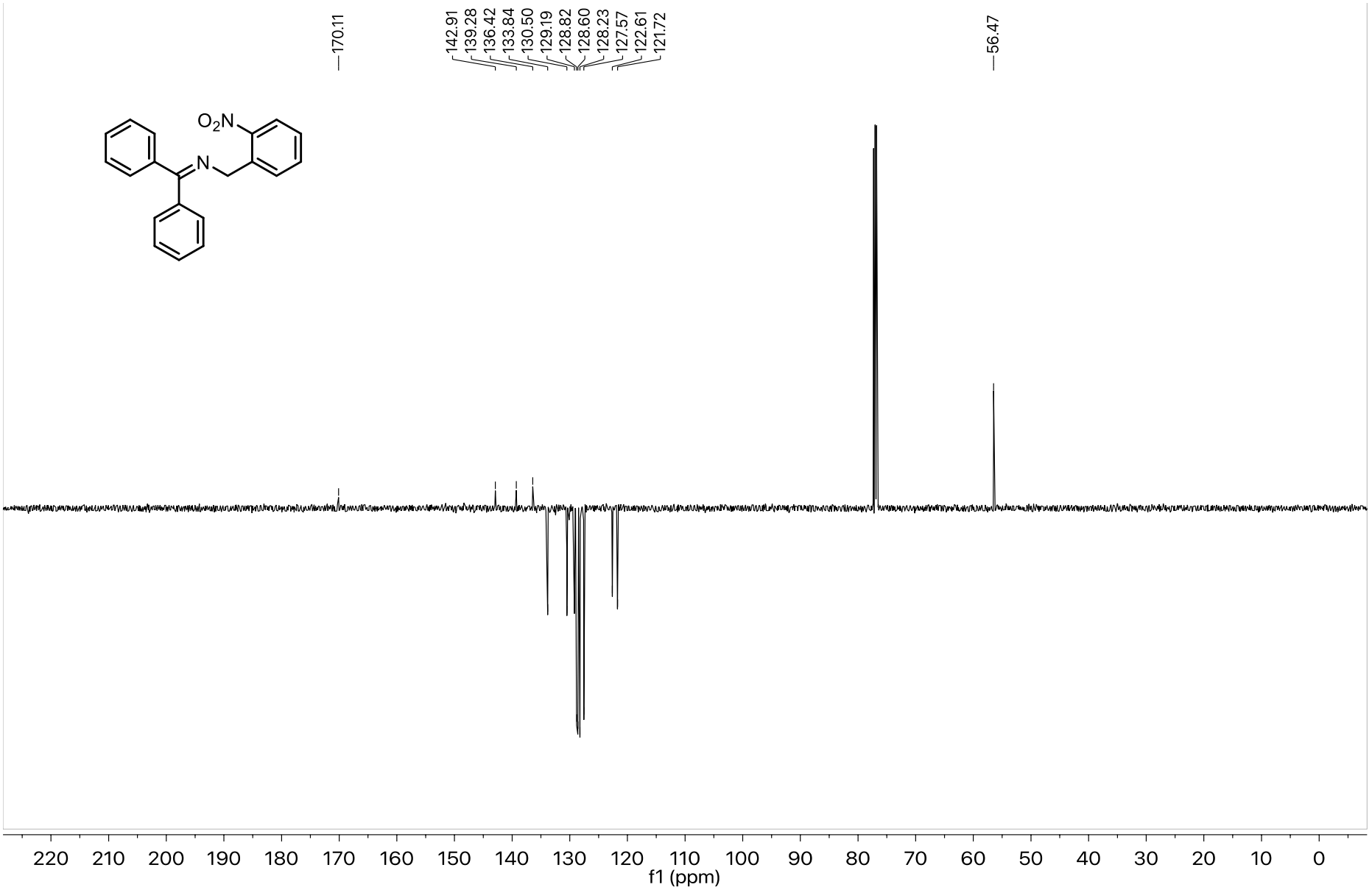
***N*-(2-nitrobenzyl)-1,1-diphenylmethanimine (S13)**



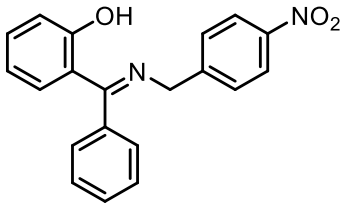
Following **General Procedure D,** diphenylmethanimine (503 µL, 3.0 mmol), (2-nitrophenyl)methanamine (679 mg, 3.6 mmol), and pyridine (362 µL, 4.5 mmol) in ethanol (45 mL) were refluxed for 1 hour to give the titled compound (927 mg, 98%) as a yellow solid. **mp** 66 – 68 ºC; **IR** ν_{max} (thin film): 3062 (Ar-H), 1618 (C=N), 1519 (N-O), 1443 (C=C); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H: 4.69 (2H, s, NC*H*$_2$Ar-NO_2), 7.23–7.24 (2H, m,

$NCH_2C(2,6)Ar_1H$), 7.38–7.54 (6H, m, $N{=}CC(3,4,5)Ar_1H$, $N{=}CC(3,4,5)Ar_2H$), 7.54–7.55 (1H, m, $NCH_2C(5)ArH\text{-}NO_2$), 7.71–7.73 (2H, m, $NCH_2C(2,6)Ar_2H$), 7.73–7.75 (1H, m, $NCH_2C(6)ArH\text{-}NO_2$), 8.12–8.14 (1H, m, $NCH_2C(4)ArH\text{-}NO_2$), 8.26 (1H, m, $NCH_2C(3)ArH\text{-}NO_2$); **$^{13}C\{^1H\}$ NMR** (101 MHz, $CDCl_3$) δ_C: 56.5 ($NCH_2Ar\text{-}NO_2$), 121.7 ($NCH_2C(4)Ar\text{-}NO_2$), 122.6 ($NCH_2C(3)Ar\text{-}NO_2$), 127.6 ($N{=}CC(2,6)Ar_1$), 128.2 ($N{=}CC(3,5)Ar_1$), 128.6 ($N{=}CC(2,6)Ar_2$), 128.8 ($N{=}CC(3,5)Ar_2$), 129.2 ($NCH_2C(5)Ar\text{-}NO_2$), 130.5 ($N{=}CC(4)Ar_1$, $N{=}CC(4)Ar_2$), 133.8 ($NCH_2C(6)Ar\text{-}NO_2$), 136.4 ($NCH_2C(1)Ar\text{-}NO_2$), 139.3 ($N{=}CC(1)Ar_1$, $N{=}CC(1)Ar_2$),), 142.9 ($NCH_2C(2)Ar\text{-}NO_2$), 170.1 ($C{=}N$); **HRMS** (NSI^+) $C_{20}H_{17}N_2O_2^+$ ($[M+H]^+$) requires 317.1283, found 317,1285 (−0.5 ppm).


8.26
8.14
8.12
7.75
7.73
7.73
7.73
7.71
7.55
7.54
7.54
7.41
7.38
7.24
7.23
4.69
O2N
N
0.95
0.95
2.88
1.03
3.02
0.98
1.98
1.94
2.00
f1 (ppm)

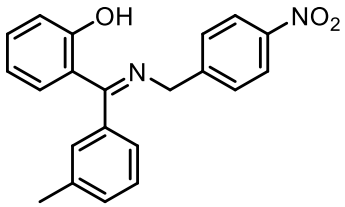

170.11
142.91
139.28
136.42
133.84
130.50
129.19
128.82
128.60
128.23
127.57
122.61
121.72
56.47
O2N
N
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

(*E*)-*N*-4-Nitrobenzyl-2-hydroxybenzophenoneimine (29)

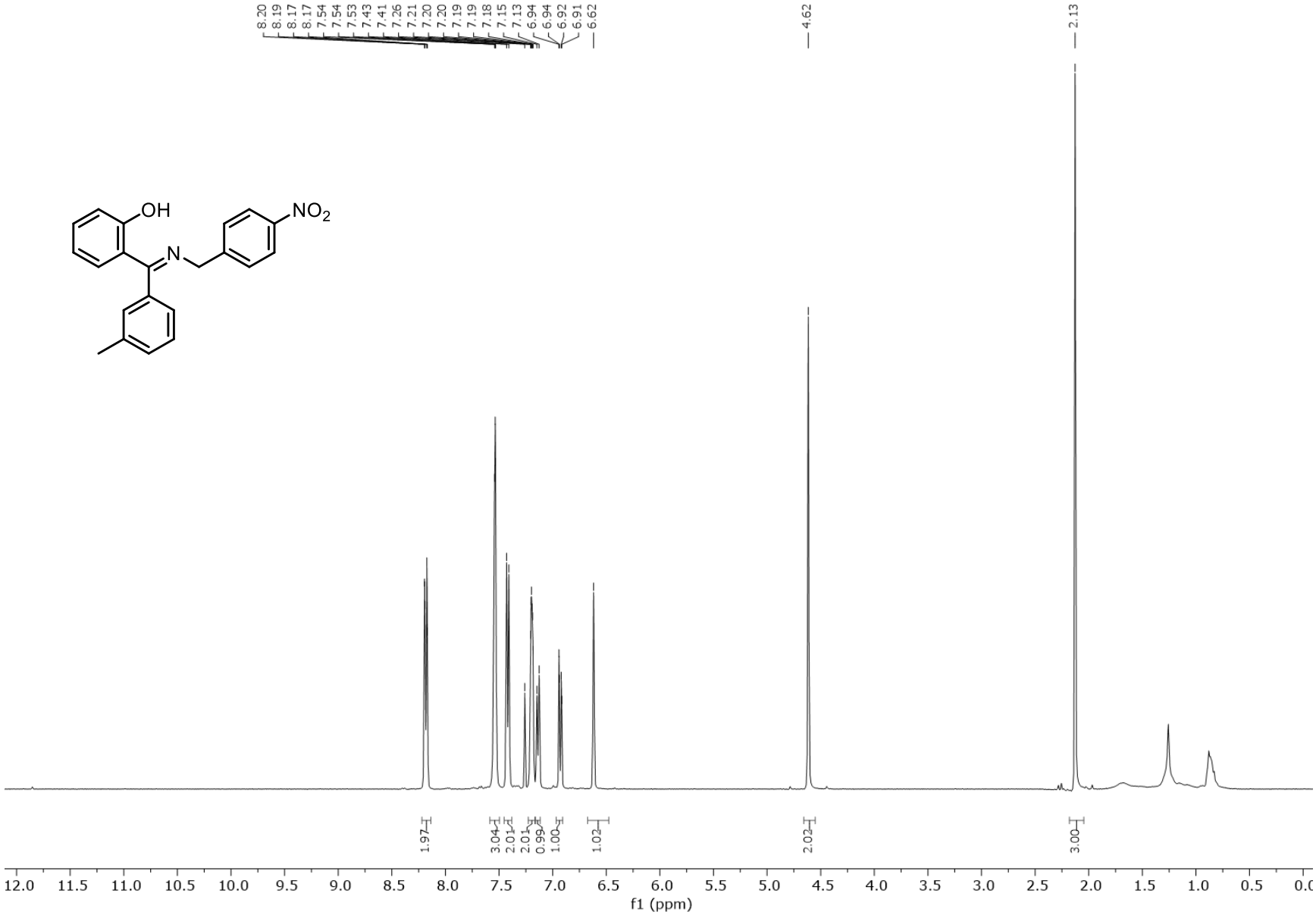


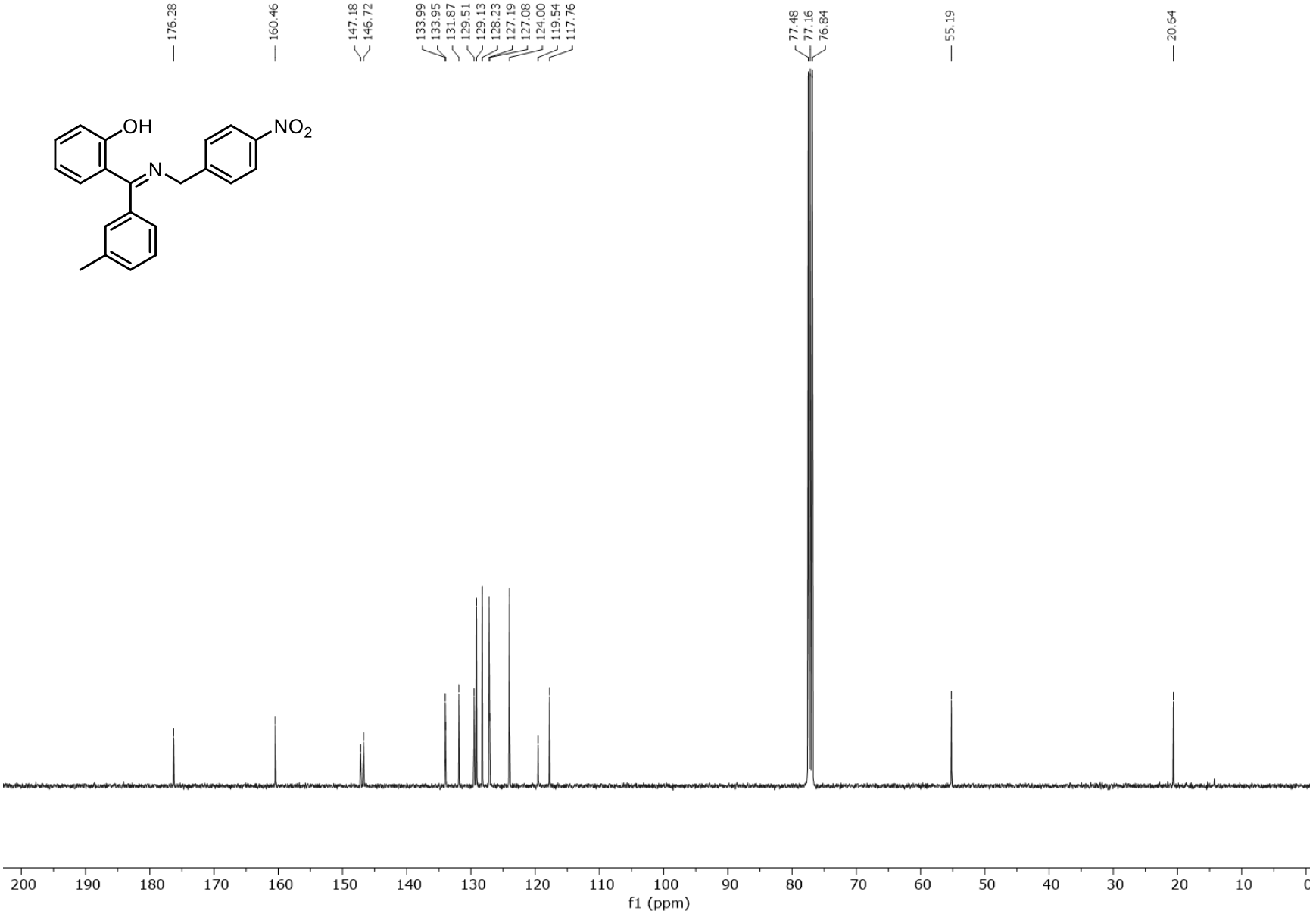
Following **General Procedure D,** 2-hydroxybenzophenoneimine (2.54 g, 12.9 mmol), 4-nitrobenzylamine (2.36 g, 15.5 mmol), pyridine (1.58 mL, 19.4 mmol), and ethanol (139 mL) were refluxed for 3 hours. The reaction mixture was cooled to ambient temperature and the precipitate was filtered through a funnel, and washed with ethanol to give the titled compound (3.32 g, 77.5%) as yellow powder. **mp** 128–129 °C (Lit. **mp** 152–153 °C) [17]; **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H: 4.64 (2H, s, H_2CN=C), 6.70 (1H, ddd, $^3J_{HH}$ = 7.9, 7.3, $^4J_{HH}$ = 1.7, HO-ArC(5)*H*), 6.85 (1H, dd, $^3J_{HH}$ = 7.9, $^4J_{HH}$ = 1.7, HO-ArC(6)*H*), 7.02 (1H, dd, $^3J_{HH}$ = 8.4, $^4J_{HH}$ = 1.2, HO-ArC(3)*H*), 7.18–7.23 (2H, m, PhC(2, 6)*H*), 7.32 (1H, ddd, $^3J_{HH}$ = 8.4, 7.3, $^4J_{HH}$ = 1.7, HO-ArC(4)*H*), 7.39–7.45 (2H, m, O_2N-ArC(2,6)*H*), 7.50–7.57 (3H, m, PhC(3,4,5)*H*), 8.17–8.21 (2H, m, O_2N-ArC(3,5)*H*). Spectroscopic data is in agreement with the literature [19].

(*E*)-*N*-4-Nitrobenzyl-4-methyl-2-hydroxybenzophenoneimine (S14)



Following **General Procedure D,** 4-methyl2-hydroxybenzophenoneimine (1.9 g, 9.4 mmol), 4-nitrobenzylamine (2.12 g, 11.3 mmol), pyridine (1.13 mL, 14.1 mmol), and ethanol (140 mL) were refluxed for 6 hours. Purification by column chromatography (19:1 hexane:EtOAc) gave the title compound (1.6 g, 80.6%) as a yellow solid. **mp** 62–63 °C; **IR** ν_{max} (thin film): 3011 (Ar-H), 2854 (CH_3), 1606 (C=N), 1597 and 1440 (C=C), 1517 (asymm. NO_2), 1342 (symm. NO_2), 1238 (C-O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 2.13 (3H, s, CH_3), 4.62 (2H, s, C=NCH_2), 6.62 (1H, s, H_3C-ArC(3)*H*), 6.93 (1H, d, $^3J_{HH}$ = 8.4, H_3C-ArC(6)*H*), 7.14 (1H, d, $^3J_{HH}$ = 8.4, H_3C-ArC(5)*H*) 7.16–7.23 (2H, m, PhC(2,6)*H*), 7.38–7.46 (2H, m, O_2N-ArC(2,6)*H*), 7.48–7.59 (3H, m, PhC(3,4,5)*H*), 8.15–8.23 (2H, m, O_2N-CAr(3,5)*H*); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$), δ_C: 20.6 (*C*H_3), 55.2 (C=N*C*H_2), 117.8 (H_3C-Ar*C*(6)H), 119.5 (H_3C-Ar*C*(2)), 124.0 (O_2N-Ar*C*(3,5)H), 127.1 (H_3C-Ar*C*(4)), 127.2 (Ar*C*(2,6)H), 128.3 (O_2N-ArC(2,6)H), 129.1 (Ar*C*(3,5)H), 129.5 (Ar*C*(4)H), 131.9 (H_3C-Ar*C*(3)H), 133.9 (Ar*C*(1)), 134.0 (H_3C-Ar*C*(5)H) 146.7 (O_2N-Ar*C*(1)), 147.2 (O_2N-Ar*C*(4)), 160.5 (H_3C-Ar*C*(1)), 176.3 (*C*=N); **HRMS** (ESI$^+$) $C_{21}H_{17}N_2NaO_3^+$ ([M+Na]$^+$) requires 369.1215, found 369.1209 (−1.7 ppm).

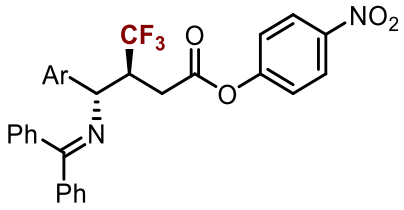

8.20
8.19
8.17
8.17
7.54
7.54
7.53
7.43
7.41
7.26
7.21
7.20
7.20
7.19
7.19
7.18
7.15
7.13
6.94
6.94
6.92
6.91
6.62
4.62
2.13
OH
N
NO2
1.97
3.04
2.01
2.01
0.99
1.00
1.02
2.02
3.00
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


176.28
160.46
147.18
146.72
133.99
133.95
131.87
129.51
129.13
128.23
127.19
127.08
124.00
119.54
117.76
77.48
77.16
76.84
55.19
20.64
OH
N
NO2
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

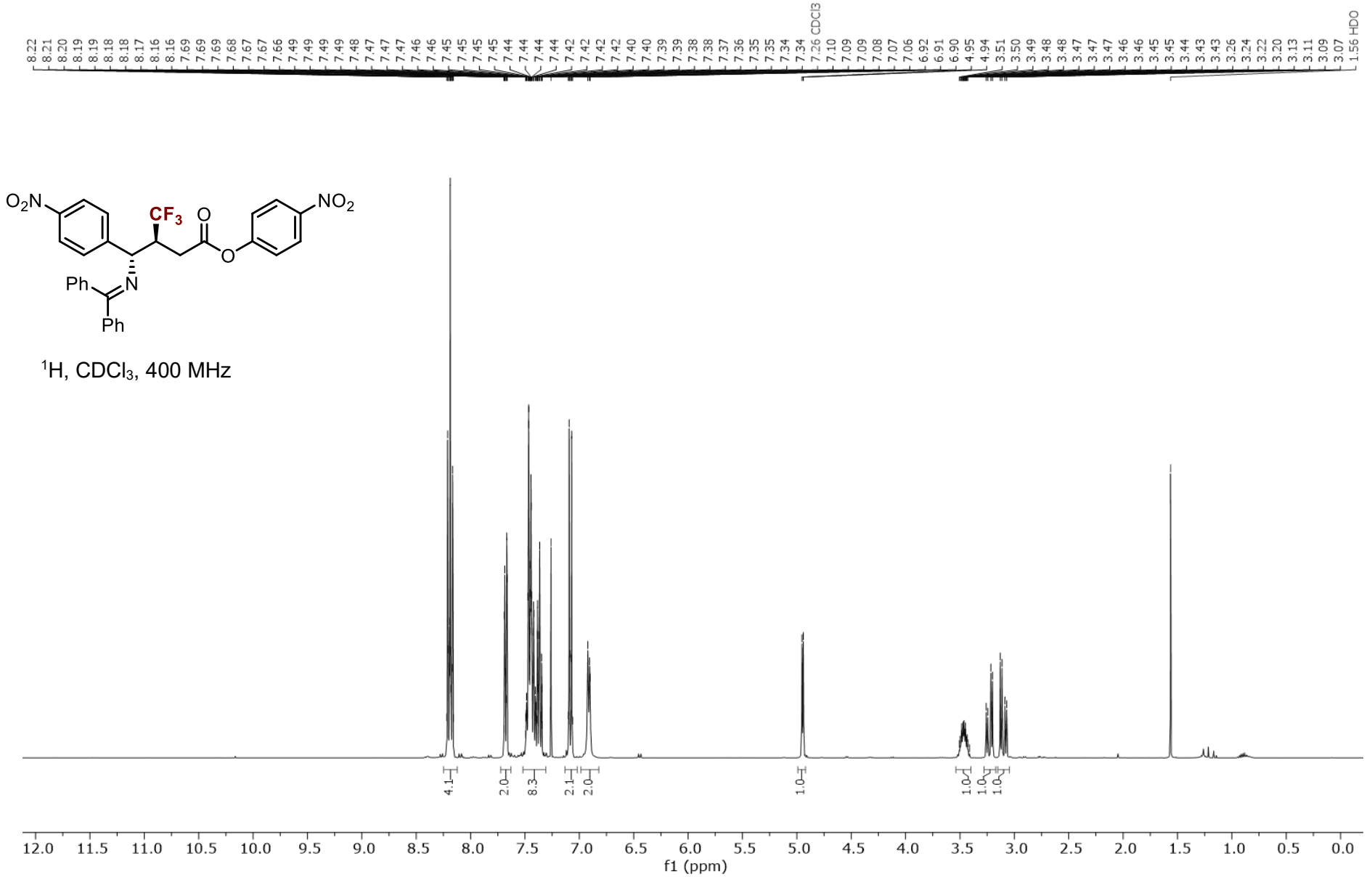
5. Data for the products

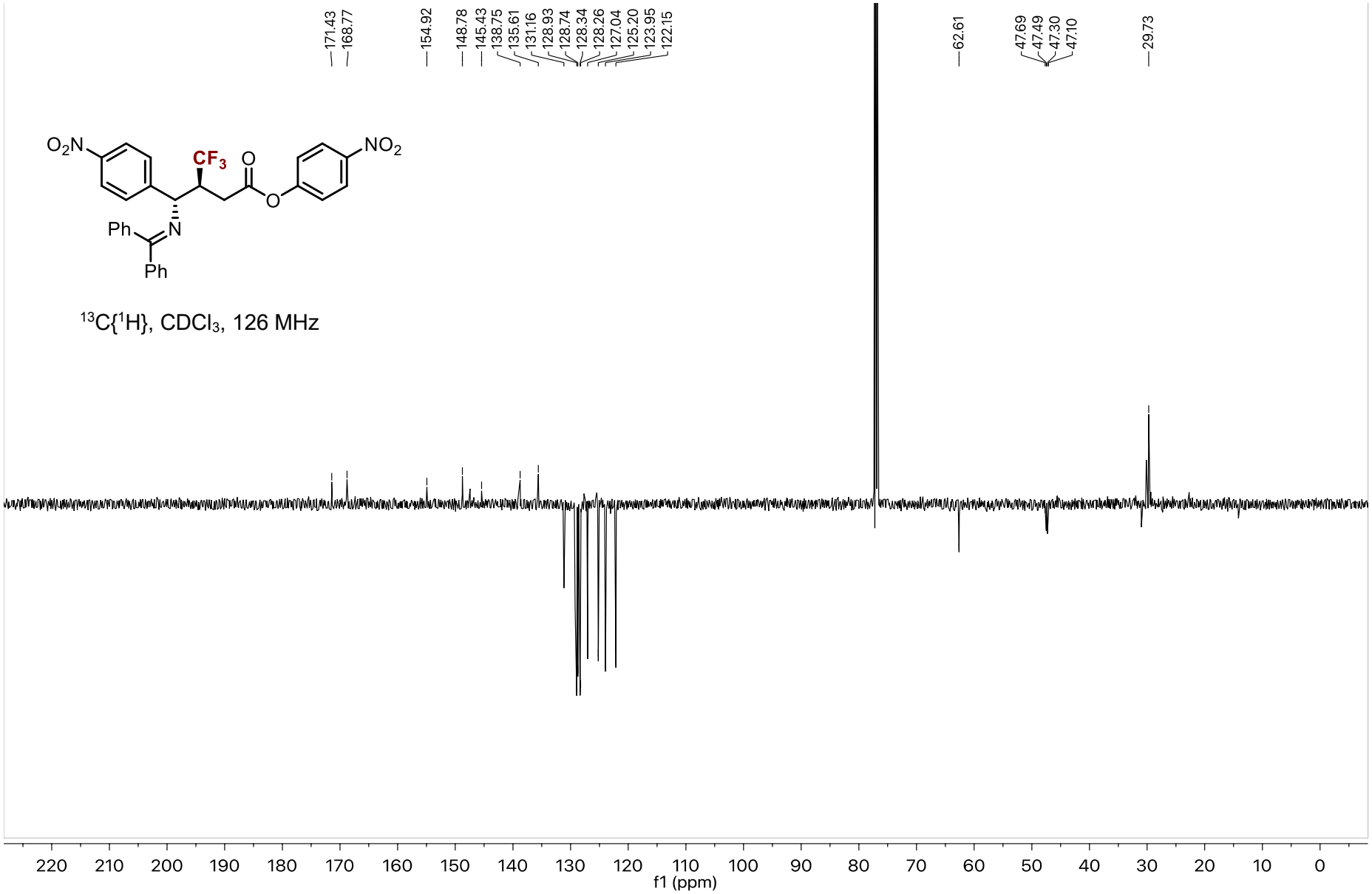
5.1 Data for Michael addition product

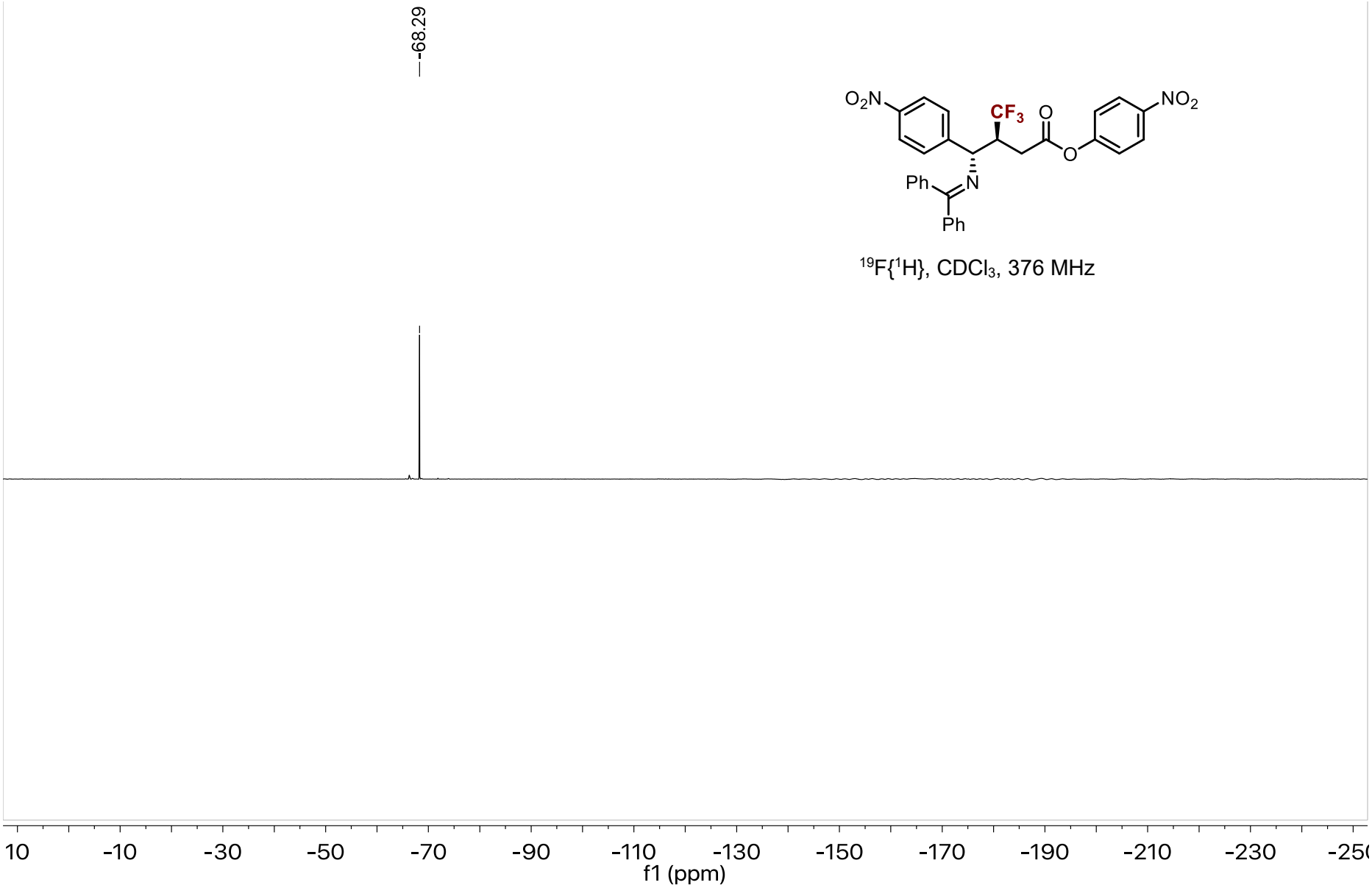
4-nitrophenyl (*S*)-3-((*S*)-((diphenylmethylene)amino)(4-nitrophenyl)methyl)-4,4,4-trifluorobutanoate (8)



The 4-nitrophenyl (*E*)-4,4,4-trifluorobut-2-enoate (26.2 mg, 0.1 mmol), *N*-(4-nitrobenzyl)-1,1-diphenylmethanimine (47.6 mg, 0.15 mmol), (*R*)-(+)-BTM (2.5 mg, 0.01 mmol), and anhydrous DMF (1 mL) were stirred at room temperature for 8 hrs, purified by flash chromatography (10:1 Petrol:EtOAc) to give the titled compound as an inseparable mixture of diastereomers (95:5 dr) as an colorless oil (41 mg, 56%). $[\alpha]_D^{20}$ −1.13 (*c* 3.9, $CHCl_3$); **Chiral HPLC analysis** Chiralpak IB (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 211 nm, 30 °C) t_R(*S,R*): 30.4 min, t_R(*S,S*): 55.1 min, 5:95 er; **IR** ν_{max} (thin film): 2922 (Ar-H), 1766 (C=O), 1766 (C=O ester), 1523 (asymm. NO_2), 1346 (symm. NO_2), 1113 (C-F); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H: 3.12 (1H, dd, $^3J_{HH}$ = 17.3, $^4J_{HF}$ = 6.4, C*H*$_A$H$_B$CO$_2$Ar), 3.24 (1H, dd, $^3J_{HH}$ = 17.3, $^4J_{HF}$ = 5.8, CH$_A$*H*$_B$CO$_2$Ar), 3.48 (1H, m, C*H*CH$_A$H$_B$CO$_2$Ar), 4.96 (1H, d, $^3J_{HH}$ =4.48, C*H*CHCH$_A$H$_B$CO$_2$Ar), 6.93 (2H, d, $^3J_{HH}$ = 6.87, N=CC(2,6)Ar$_1$*H*), 7.10 (2H, m, CO$_2$C(2,6)Ar*H*-NO$_2$), 7.39 (2H, m, N=CC(4)Ar$_1$*H* and N=CC(4)Ar$_2$*H*), 7.47 (6H, m, N=CC(3,5)Ar$_1$*H*, N=CC(3,5)Ar$_2$*H*, C=NCHC(2,6)Ar$_3$*H*-NO$_2$), 7.69 (2H, m, N=CC(2,6)Ar$_2$*H*), 8.22 (4H, m, CO$_2$C(3,5)Ar$_4$*H*-NO$_2$, C=NCHC(3,5)Ar$_3$*H*-NO$_2$); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$), δ_C: 29.7 (*C*H$_A$H$_B$CO$_2$Ar), 47.4 (q, $^2J_{CF}$ = 24.9, *C*HCH$_A$H$_B$CO$_2$Ar), 62.6 (C=N*C*HPh-NO$_2$), 122.1 (CO$_2$*C*(2,6)Ar-NO$_2$), 123.9 (C=NCH*C*(3,5)Ar$_3$-NO$_2$), 125.2 (CO$_2$*C*(3,5)Ar-NO$_2$), 127.0 (N=C*C*(2,6)Ar$_1$), 128.3 (-*C*F$_3$), 128.4 (N=C*C*(3,5)Ar$_1$, N=C*C*(3,5)Ar$_2$,), 128.7 (N=C*C*(4)Ar$_1$, N=C*C*(4)Ar$_2$), 128.9 (N=C*C*(2,6)Ar$_2$), 131.2 (C=NCH*C*(2,6)Ar$_3$-NO$_2$), 135.6 (N=C*C*(1)Ar$_1$), 138.8 (N=C*C*(1)Ar$_2$), 145.4 (CO$_2$*C*(4)Ar-NO$_2$), 147.8 (C=NCH*C*(4)Ar$_3$-NO$_2$), 148.8 (C=NCH*C*(1)Ar$_3$-NO$_2$), 154.9 (CO$_2$*C*(1)Ar-NO$_2$),168.8 (*C*O$_2$Ar-NO$_2$), 171.4 (*C*=N); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: −68.29 (3F, s, C*F*$_3$); **HRMS** (NSI$^+$) $C_{21}H_{21}F_3N_2O_2^+$ ([M+Na]$^+$) requires 600.1353, found 600.1343 (−1.7 ppm).


8.22 8.21 8.20 8.19 8.18 8.18 8.17 8.16 8.16 7.69 7.69 7.69 7.68 7.67 7.67 7.66 7.49 7.49 7.49 7.49 7.48 7.47 7.47 7.47 7.46 7.46 7.45 7.45 7.45 7.44 7.44 7.44 7.42 7.42 7.42 7.40 7.40 7.39 7.39 7.38 7.38 7.37 7.36 7.35 7.35 7.34 7.34 7.26 CDCl3 7.10 7.09 7.09 7.08 7.07 7.06 6.92 6.91 6.90 4.95 4.94 3.51 3.50 3.49 3.48 3.48 3.47 3.47 3.47 3.46 3.46 3.45 3.45 3.44 3.43 3.43 3.26 3.24 3.22 3.20 3.13 3.11 3.09 3.07 1.56 HDO
O2N
CF3
O
NO2
Ph
N
Ph
Ph
1H, CDCl3, 400 MHz
4.1
2.0
8.3
2.1
2.0
1.0
1.0
1.0
1.0
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

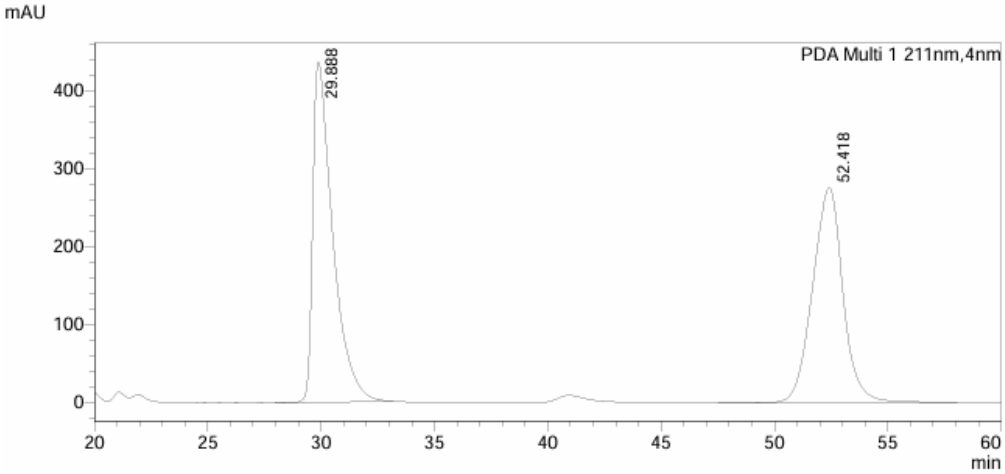

171.43
168.77
154.92
148.78
145.43
138.75
135.61
131.16
128.93
128.74
128.34
128.26
127.04
125.20
123.95
122.15
62.61
47.69
47.49
47.30
47.10
29.73
O2N
CF3
O
NO2
O
Ph
N
Ph
13C{1H}, CDCl3, 126 MHz
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


-68.29
O2N
CF3
O
NO2
Ph
N
Ph
19F{1H}, CDCl3, 376 MHz
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
-210
-230
f1 (ppm)

HPLC Data for **4-nitrophenyl (*S*)-3-((*S*)-((diphenylmethylene)amino)(4-nitrophenyl)methyl)-4,4,4-trifluorobutanoate**: Chiralpak IB (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 211 nm, 30 °C) t_R(*S,R*): 30.4 min, t_R(*S,S*): 55.1 min, 5:95 er.

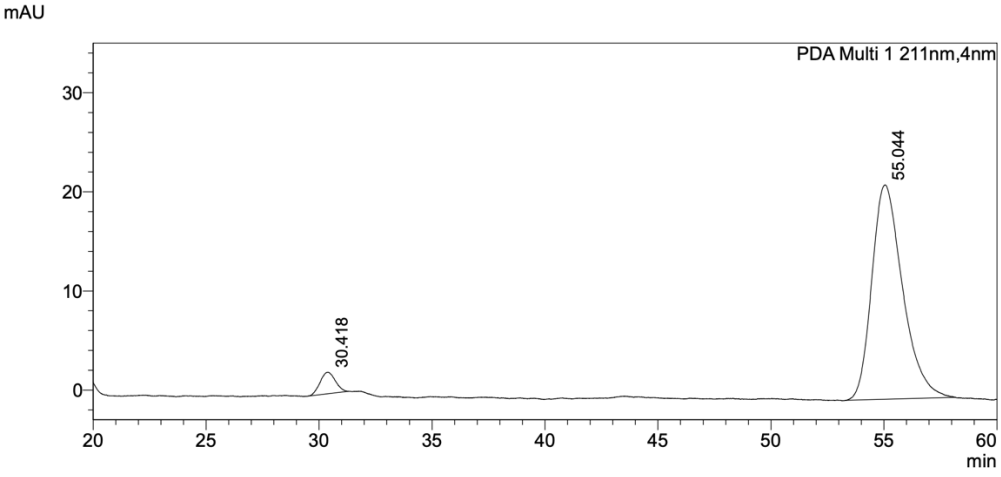
PDA Ch1 211nm

Peak#	Ret. Time	Area%
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2	52.418	48.878
Total		100.000

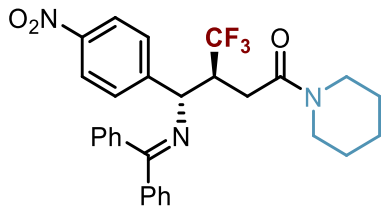


PDA Ch1 211nm

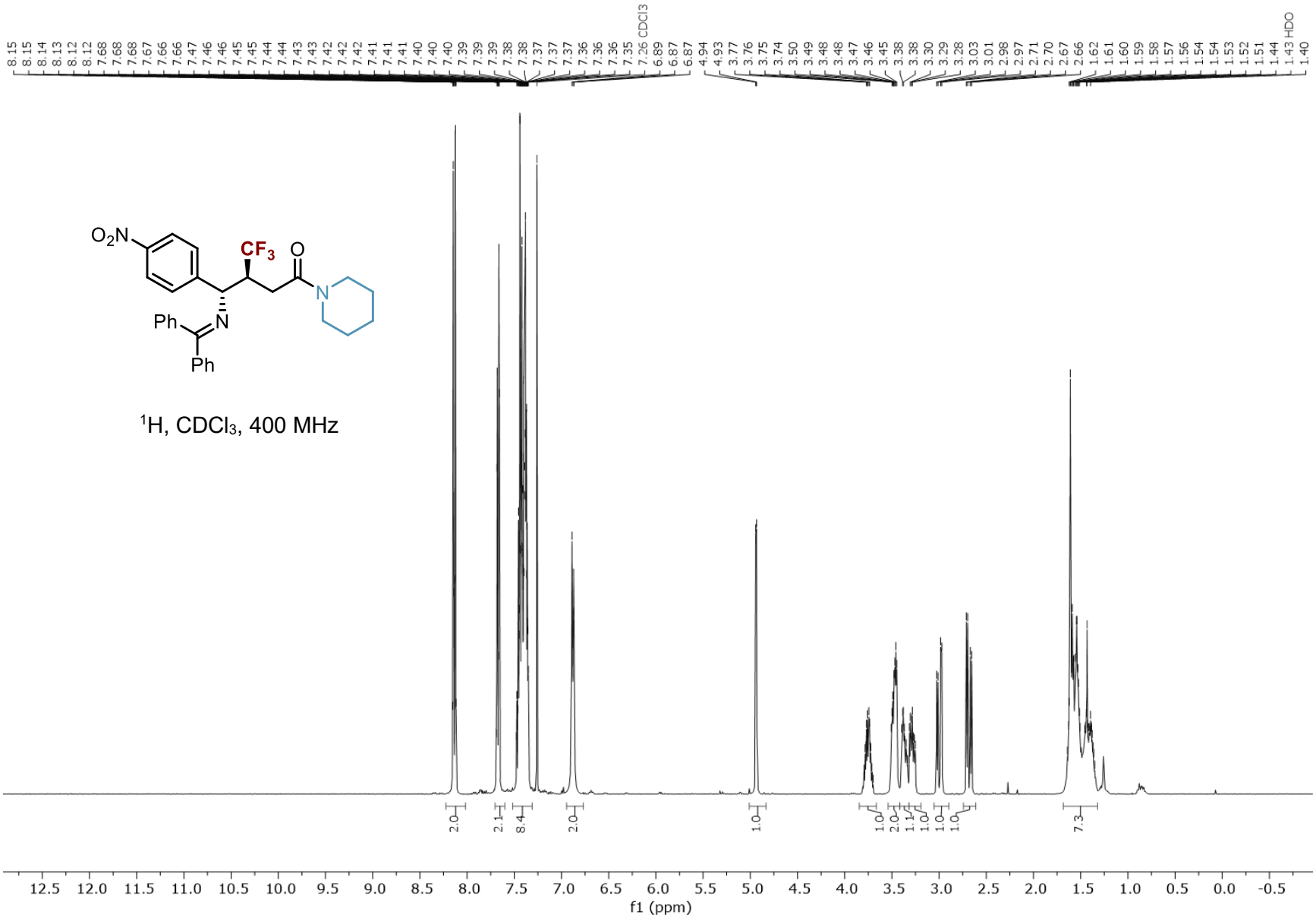
Peak#	Ret. Time	Area%
1	30.418	4.760
2	55.044	95.240
Total		100.000

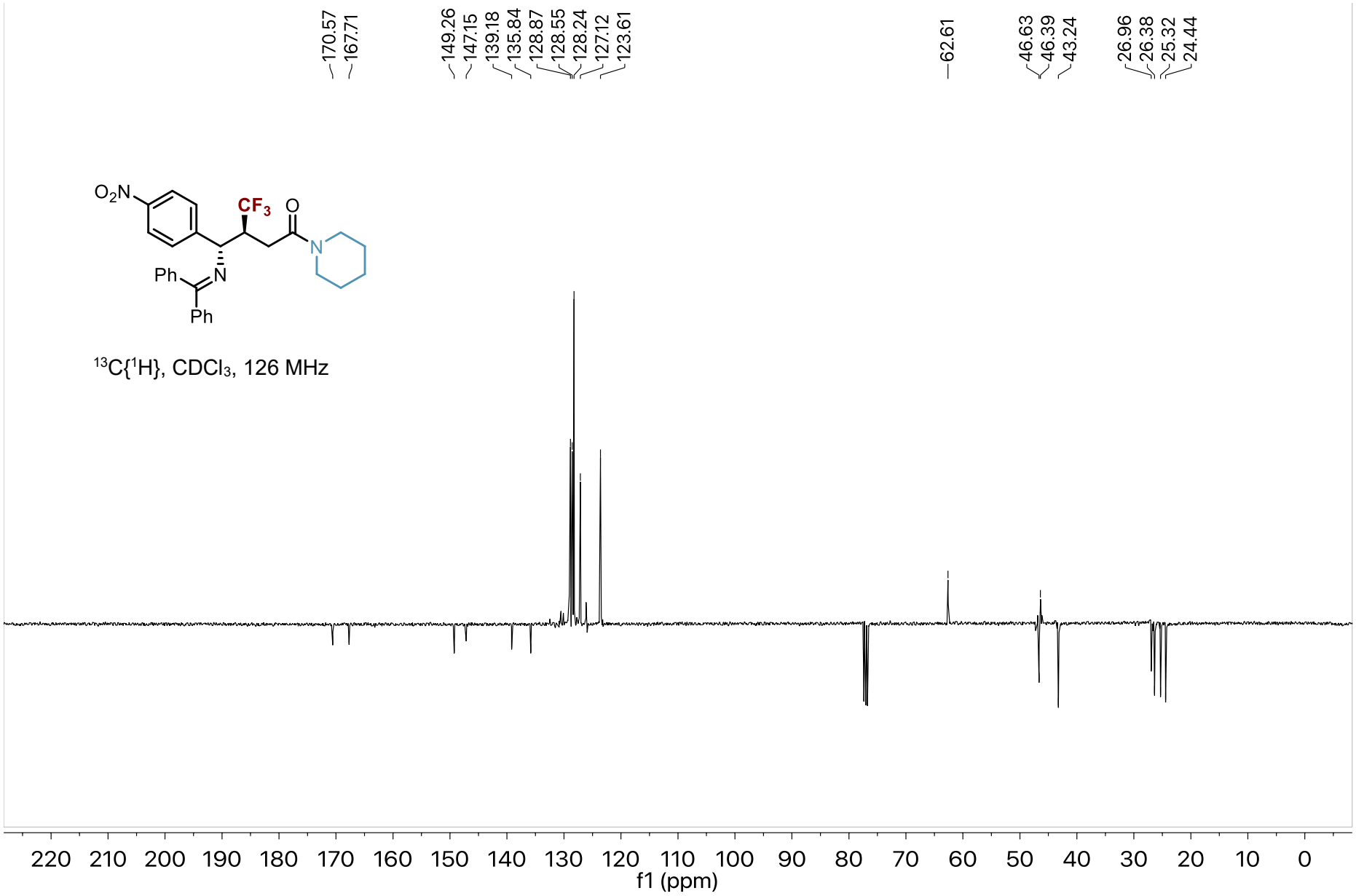


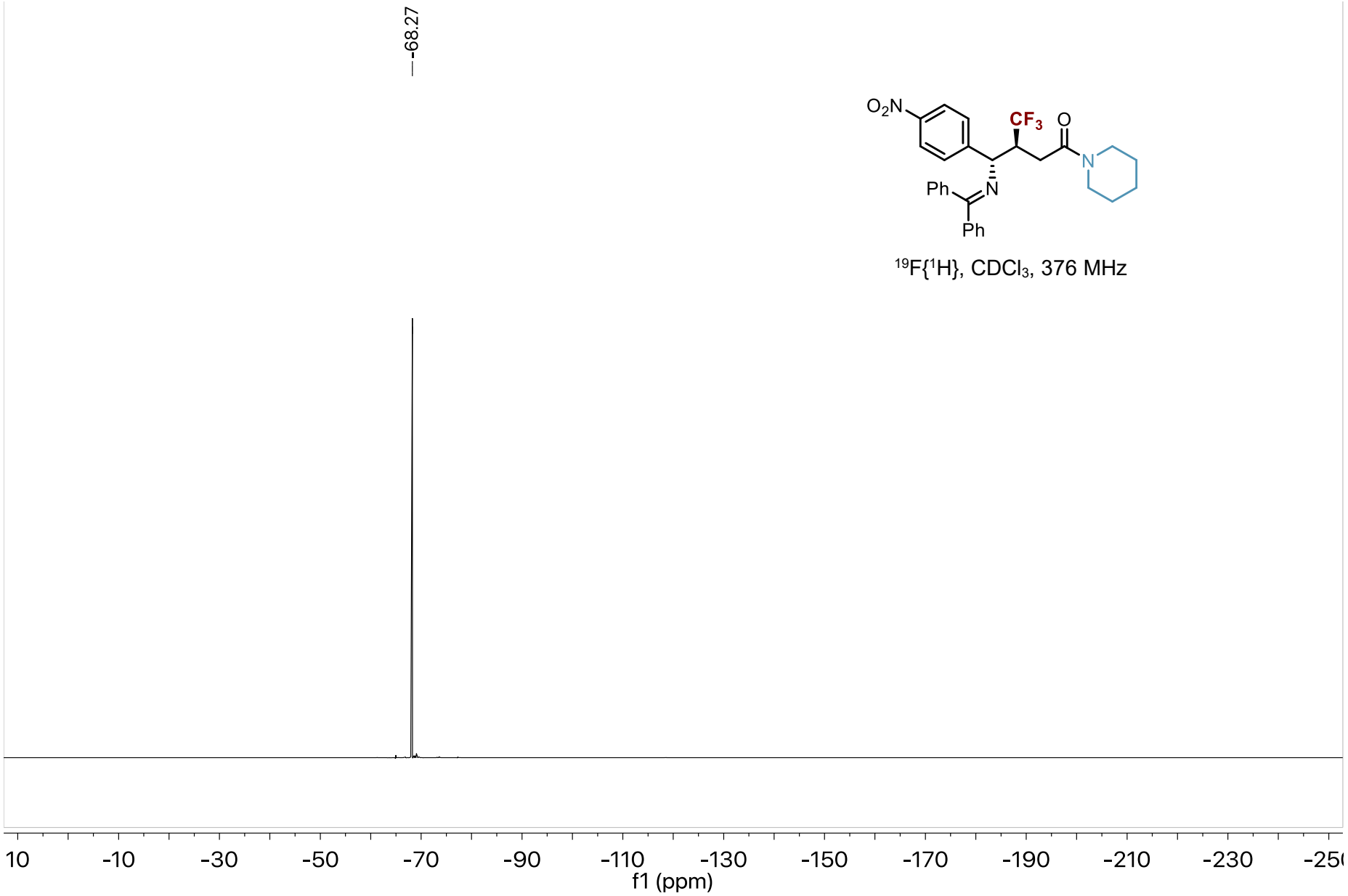
(*S*)-3-((*S*)-((diphenylmethylene)amino)(4-nitrophenyl)methyl)-4,4,4-trifluoro-1-(piperidin-1-yl)butan-1-one (11)



Following **General Procedure E,** 4-nitrophenyl (*E*)-4,4,4-trifluorobut-2-enoate (26.2 mg, 0.1 mmol), *N*-(4-nitrobenzyl)-1,1-diphenylmethanimine (47.5 mg, 0.15 mmol), (*R*)-(+)-BTM (2.5 mg, 0.01 mmol), and anhydrous DMF (1 mL) were stirred at room temperature for 8 hours. The reaction mixture was then added with piperidine (14.8 µL, 0.15 mmol) and was stirred for another 16 hours, then purified by flash chromatography (4:1 Hexane:EtOAc) to give the titled compound as an inseparable mixture of diastereomers (96:4 dr) as a garnet red solid (42.4 mg, 81%). **mp** 136 – 138 °C, $[\alpha]_D^{20}$ −6.1 (*c* 4.3, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak IA (97.5:2.5 Hexane:IPA, flow rate 1 mLmin^{-1}, 254 nm, 30 °C) t_R(*S,S*): 17.9 min, t_R(*R,R*): 27.4 min, 95:5 er; **IR** ν_{max} (thin film): 2939 (Ar-H), 1629 (C=O amide), 1519 (asymm. NO_2), 1445 (C=C), 1342 (symm. NO_2), 1107 (C-F); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H: 1.45–1.59 (6H, m, CONC(2)H_2C(3)H_2C(4)H_2C(5)H_2C(6)H_2), 2.71 (1H, dd, $^3J_{HH}$ = 16.7, $^4J_{HF}$ = 5.8, F_3CCHC$H_A$$H_B$), 3.04 (1H, dd, $^3J_{HH}$ = 16.7, $^4J_{HF}$ = 5.2, F_3CCHCH$_A$$H_B$), 3.32–3.51 (4H, m, CONC(2)H_2C(3)H_2C(4)H_2C(5)H_2C(6)H_2), 3.75 (1H, m, F_3CC*H*CH$_A$$H_B$), 4.96 (1H, d, $^3J_{HH}$ = 3.5, C=NC*H*Ar$_3$-NO_2), 6.91 (2H, m, N=CC(4)Ar$_1$*H*, N=CC(4)Ar$_2$*H*), 7.46 (8H, m, N=CC(2,3,5,6)Ar$_1$*H*, N=CC(2,3,5,6)Ar$_2$*H*), 7.71 (2H, m, C=NCHC(2,6)Ar$_3$*H*-NO_2), 8.17 (2H, m, C=NCHC(3,5)Ar$_3$*H*-NO_2); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 24.4, 25.3 and 26.4, (CONC(2)H_2*C*(3)H_2*C*(4)H_2*C*(5)H_2C(6)H_2), 26.9 (F_3CCH*C*H$_A$$H_B$), 43.2 and 46.6 (CON*C*(2)H_2C(3)H_2C(4)H_2C(5)H_2*C*(6)H_2), 46.5 (q, $^2J_{CF}$ = 46.5, F_3C*C*HCH$_A$$H_B$), 62.6 (C=N*C*HAr$_3$-$NO_2$), 123.6 (C=NCH*C*(3,5)Ar$_3$-NO_2), 127.1 (N=C*C*(4)Ar$_1$, N=C*C*(4)Ar$_2$), 128.2 (N=C*C*(2,3,5,6)Ar$_1$, N=C*C*(2,3,5,6)Ar$_2$), 127.3 (q, $^1J_{CF}$ = 279.7, *C*F_3), 128.9 (C=NCH*C*(2,6)Ar$_3$-NO_2), 135.8 and 139.2 (N=C*C*(1)Ar$_1$, N=C*C*(1)Ar$_2$), 147.1 (C=NCH*C*(4)Ar$_3$-NO_2), 149.3 (C=NCH*C*(1)Ar$_3$-NO_2), 167.7 (F_3CCHCH$_A$$H_B$*C*O), 170.6 (*C*=N); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: −68.3 (3F, s, C*F*$_3$); **HRMS** (NSI$^+$) $C_{29}H_{29}F_3N_3O_3^+$ ([M+H]$^+$) requires 524.2163, found 524.2143 (−2.5 ppm).


8.15 8.15 8.14 8.13 8.12 8.12 7.68 7.68 7.68 7.67 7.66 7.66 7.47 7.46 7.46 7.45 7.45 7.44 7.44 7.43 7.43 7.42 7.42 7.42 7.41 7.41 7.41 7.40 7.40 7.40 7.39 7.39 7.39 7.38 7.38 7.37 7.37 7.37 7.36 7.36 7.35 7.26 CDCl3 6.89 6.87 6.87 4.94 4.93 3.77 3.76 3.75 3.74 3.50 3.49 3.48 3.48 3.47 3.46 3.45 3.38 3.38 3.30 3.29 3.28 3.03 3.01 2.98 2.97 2.71 2.70 2.67 2.66 1.62 1.61 1.60 1.59 1.58 1.57 1.56 1.54 1.54 1.53 1.52 1.51 1.44 1.43 HDO 1.40
O2N
CF3
O
N
Ph
N
Ph
1H, CDCl3, 400 MHz
2.0 2.1 8.4 2.0 1.0 1.0 2.0 1.1 1.0 1.0 1.0 7.3
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

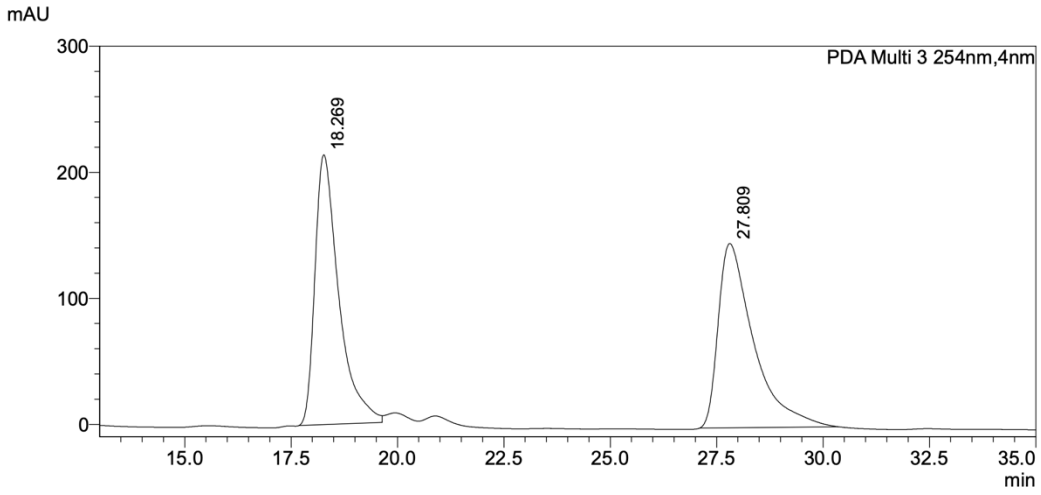

170.57
167.71
149.26
147.15
139.18
135.84
128.87
128.55
128.24
127.12
123.61
62.61
46.63
46.39
43.24
26.96
26.38
25.32
24.44
O2N
CF3
O
N
Ph
N
Ph
13C{1H}, CDCl3, 126 MHz
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


-68.27
O2N
CF3
O
N
Ph
N
Ph
19F{1H}, CDCl3, 376 MHz
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
-210
-230
f1 (ppm)

HPLC Data for **(*S*)-3-((*S*)-((diphenylmethylene)amino)(4-nitrophenyl)methyl)-4,4,4-trifluoro-1-(piperidin-1-yl)butan-1-one**: Chiralpak IA (97.5:2.5 Hexane:IPA, flow rate 1 mLmin^{-1}, 254 nm, 30 °C) t_R(*S,S*): 17.9 min, t_R(*R,R*): 27.4 min, 95:5 er.

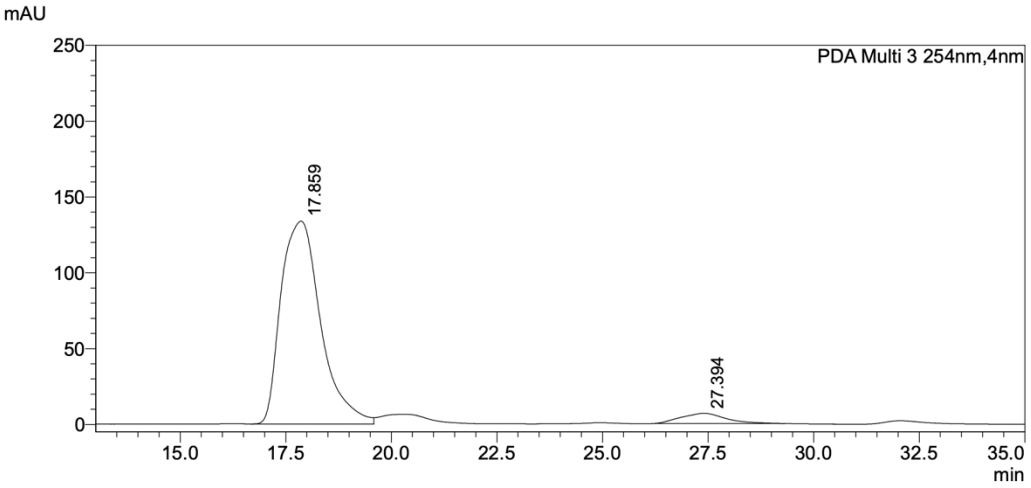
PDA Ch3 254nm

Peak#	Ret. Time	Area%
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2	27.809	50.278
Total		100.000

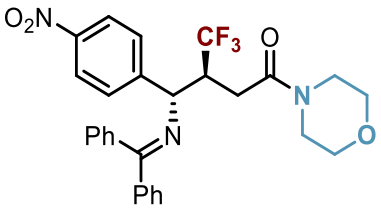


PDA Ch3 254nm

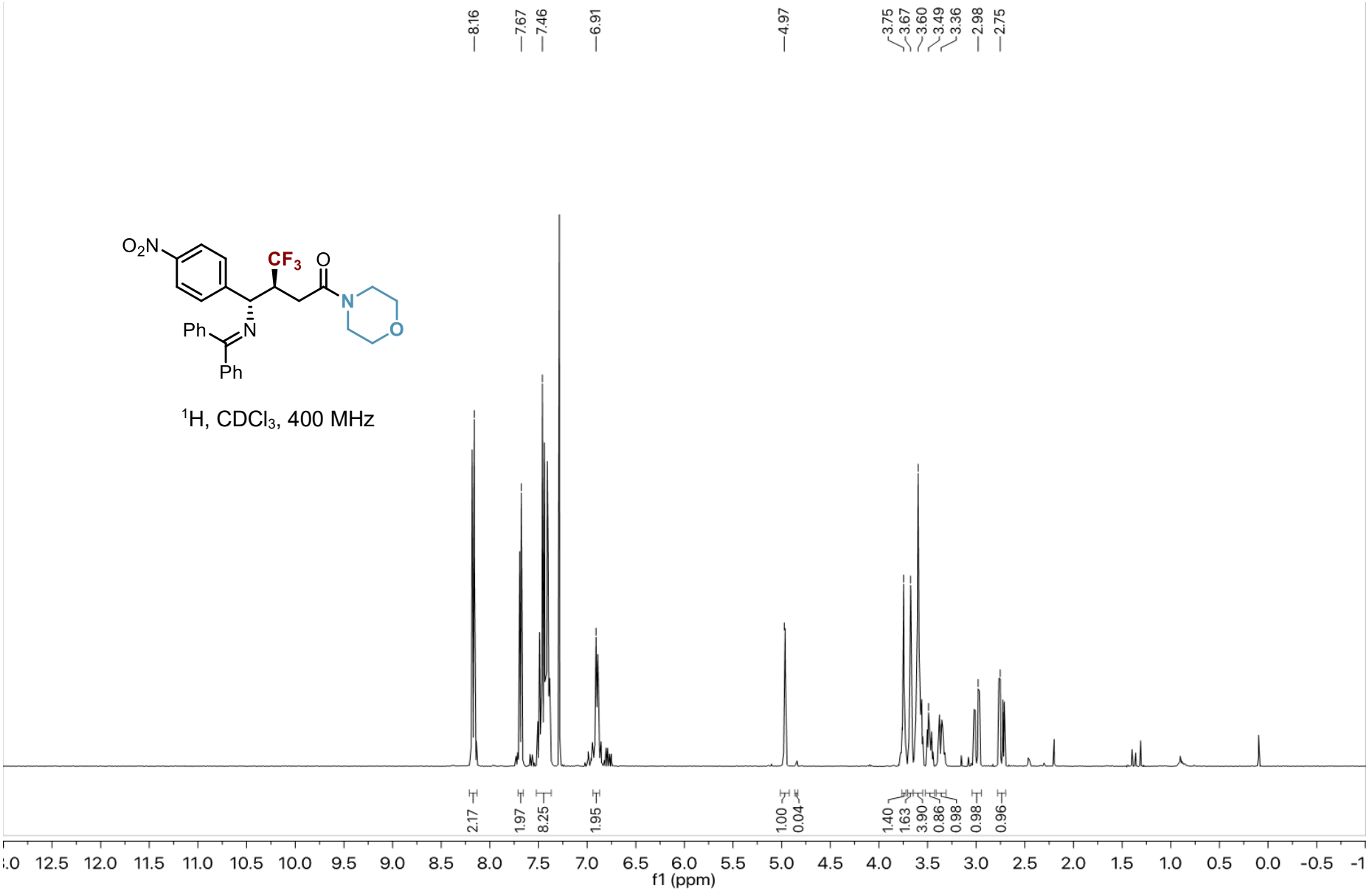
Peak#	Ret. Time	Area%
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2	27.394	5.308
Total		100.000

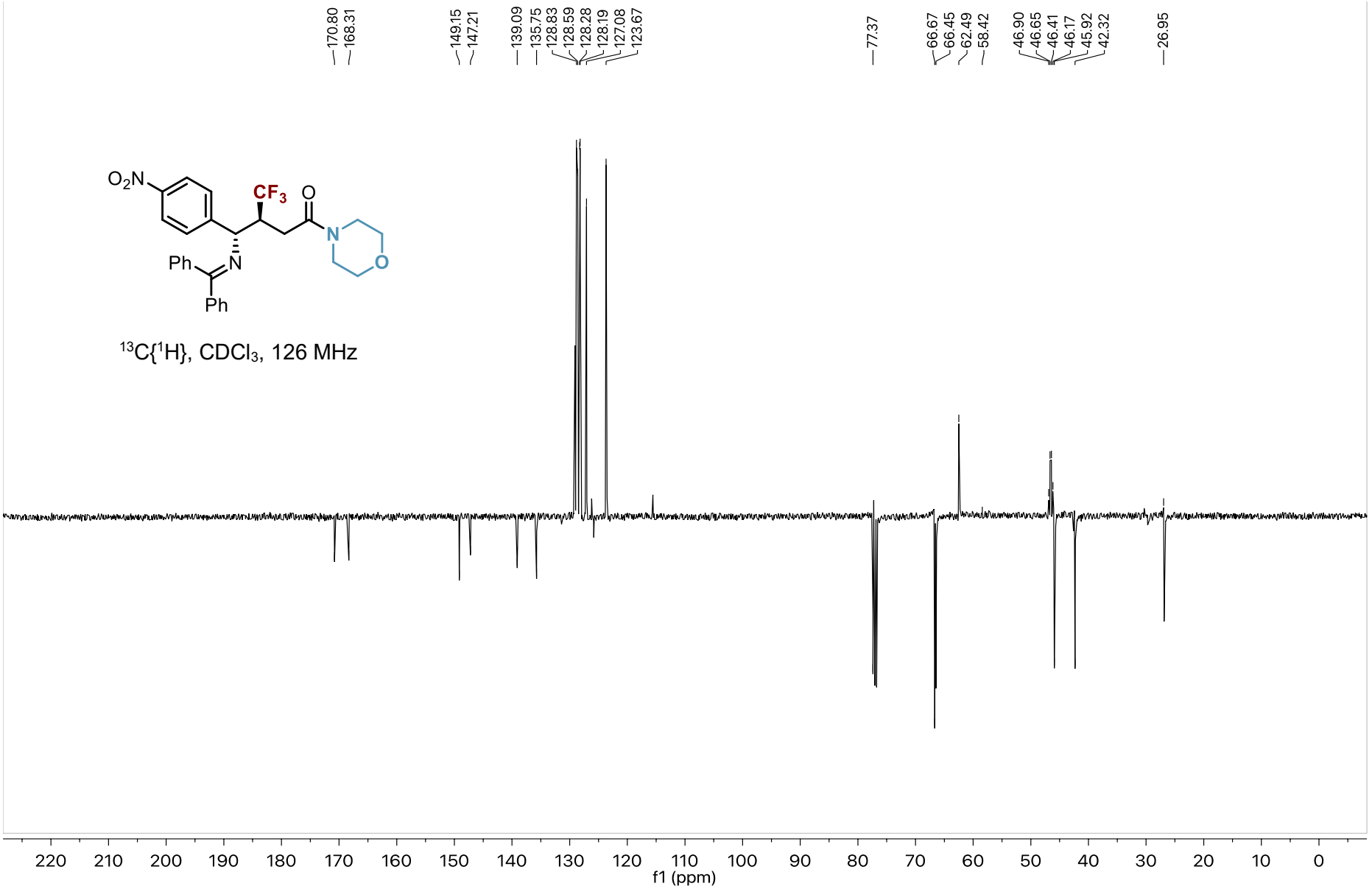


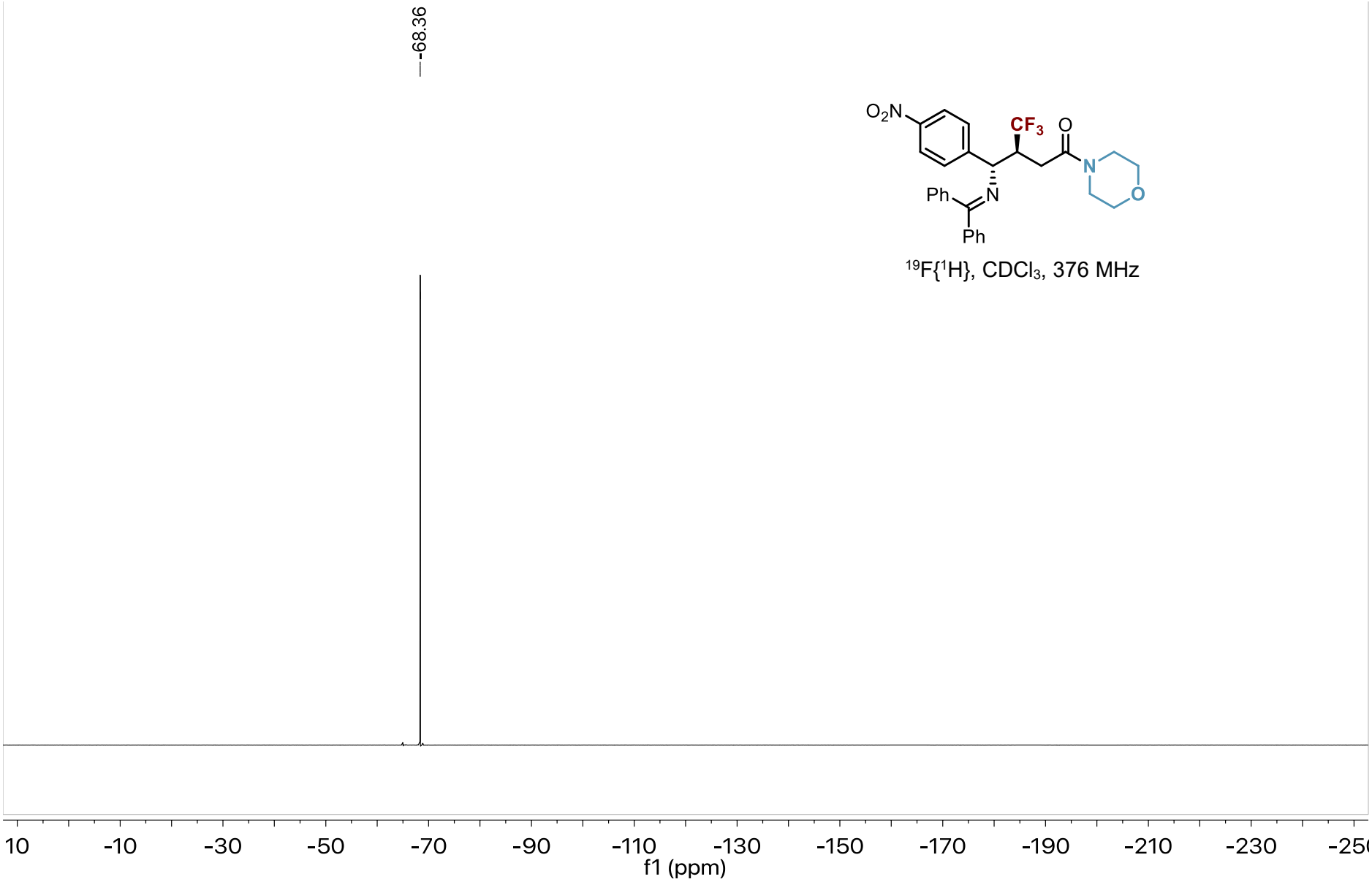
(*S*)-3-((*S*)-((diphenylmethylene)amino)(4-nitrophenyl)methyl)-4,4,4-trifluoro-1-morpholinobutan-1-one (12)



Following **General Procedure E,** 4-nitrophenyl (*E*)-4,4,4-trifluorobut-2-enoate (26.2 mg, 0.1 mmol), *N*-(4-nitrobenzyl)-1,1-diphenylmethanimine (47.5 mg, 0.15 mmol), (*R*)-(+)-BTM (2.5 mg, 0.01 mmol), and anhydrous DMF (1 mL) was stirred at room temperature for 8 hours. The reaction mixture was then added with morpholine (12.9 µL, 0.15 mmol) and was stirred for another 16 hours, then purified by flash chromatography (4:1 Petrol:EtOAc) to give the titled compound as an inseparable mixture of diastereomers (96:4 dr) as a colorless oil (39 mg, 75%). $[\alpha]_D^{20}$ –1.13 (*c* 3.9, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak IB (95:5 Hexane:IPA, flow rate 1 $mLmin^{-1}$, 220 nm, 30 °C) t_R(*S,R*): 19.1 min, t_R(*S,S*): 23.6 min, 6:94 er; **IR** ν_{max} (thin film): 2922 (Ar-H), 1643 (C=O amide), 1519 (asymm. NO_2), 1444 (C=C), 1344 (symm. NO_2), 1111 (C-F); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H: 2.75 (1H, dd, $^3J_{HH}$ = 16.6, $^4J_{HH}$ = 5.7, $CF_3CHCH_AH_B$), 2.98 (1H, dd, $^3J_{HH}$ = 16.7, $^4J_{HH}$ = 5.2, $F_3CCHCH_AH_BCO$), 3.36–3.49 (2H, m, $CONC(2)H_2C(3)H_2OC(5)H_2C(6)H_2$), 3.59 (4H, m, $CONC(2)H_2C(3)H_2OC(5)H_2C(6)H_2$), 3.67(2H, m, $CONC(2)H_2C(3)H_2OC(5)H_2C(6)H_2$) 3.75 (1H, m, $F_3CCHCH_AH_B$), 4.97 (1H, d, $^3J_{HH}$ = 3.5, $C{=}NCHAr_3\text{-}NO_2$), 6.91 (2H, m, $N{=}CC(4)Ar_1H$, $N{=}CC(4)Ar_2H$), 7.46 (8H, m, $N{=}CC(2,3,5,6)Ar_1H$, $N{=}CC(2,3,5,6)Ar_1H$), 7.67 (2H, m, $C{=}NCHC(2,6)Ar_3H\text{-}NO_2$), 8.16 (2H, m, $C{=}NCHC(3,5)Ar_3H\text{-}NO_2$); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$), δ_C: 26.9 ($F_3CCHCH_AH_B$), 42.3 and 45.9 ($CONC(2)H_2C(3)H_2OC(5)H_2C(6)H_2$), 46.65 (q, $^2J_{CF}$ = 24.4, $F_3CCHCH_AH_B$), 66.5 and 66.7 ($CONC(2)H_2C(3)H_2OC(5)H_2C(6)H_2$), 123.7 ($C{=}NCHC(3,5)Ar_3\text{-}NO_2$), 127.1 ($N{=}CC(4)Ar_1$, $N{=}CC(4)Ar_2$), 128.2 ($N{=}CC(3,5)Ar_1$, $N{=}CC(3,5)Ar_2$), 128.3 (q, $^1J_{CF}$ = 279.4, CF_3), 128.6 ($N{=}CC(2,5)Ar_1$, $N{=}CC(2,6)Ar_2$), 128.8 ($C{=}NCHC(2,6)Ar_3\text{-}NO_2$), 135.6 and 139.1 ($N{=}CC(1)Ar_1$, $N{=}CC(1)Ar_2$), 147.2 ($C{=}NCHC(4)Ar_3\text{-}NO_2$), 149.2 ($C{=}NCHC(1)Ar_3\text{-}NO_2$), 168.3 ($F_3CHCH_AH_BCON$), 170.8 (*C*=N); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: −68.4 (3F, s, CF_3); **HRMS** (NSI^+) $C_{28}H_{27}F_3N_3O_4^+$ ($[M+H]^+$) requires 526.1955, found 526.1944 (−0.85 ppm).


8.16
7.67
7.46
6.91
4.97
3.75
3.67
3.60
3.49
3.36
2.98
2.75
O2N
CF3
O
N
Ph
N
O
Ph
1H, CDCl3, 400 MHz
2.17
1.97
8.25
1.95
1.00
0.04
1.40
1.63
3.90
0.86
0.98
0.98
0.96
f1 (ppm)

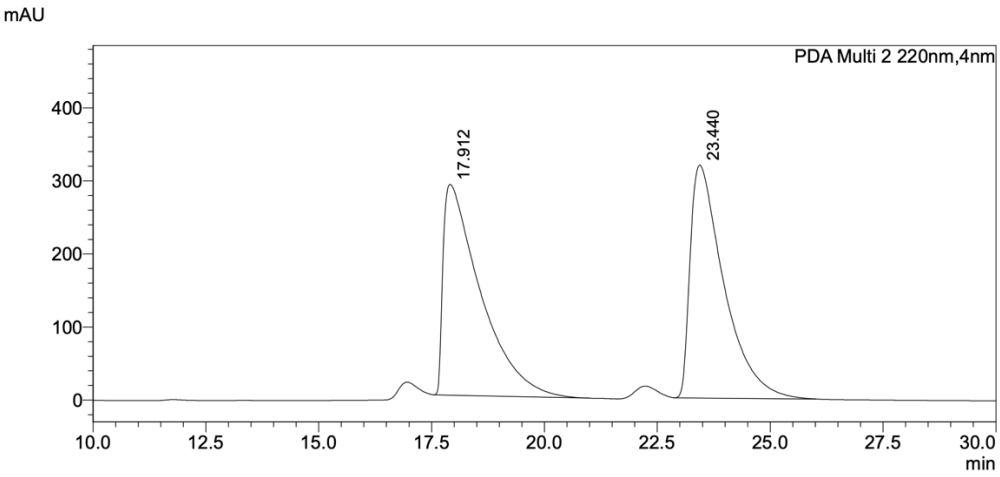

170.80
168.31
149.15
147.21
139.09
135.75
128.83
128.59
128.28
128.19
127.08
123.67
77.37
66.67
66.45
62.49
58.42
46.90
46.65
46.41
46.17
45.92
42.32
26.95
O2N
CF3
O
N
O
Ph
N
Ph
13C{1H}, CDCl3, 126 MHz
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


-68.36
O2N
CF3
O
N
O
Ph
N
Ph
19F{1H}, CDCl3, 376 MHz
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
-210
-230
f1 (ppm)

HPLC Data for **(*S*)-3-((*S*)-((diphenylmethylene)amino)(4-nitrophenyl)methyl)-4,4,4-trifluoro-1-morpholinobutan-1-one**: Chiralpak IB (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 220 nm, 30 °C) t_R(*S,R*): 19.1 min, t_R(*S,S*): 23.6 min, 6:94 er.

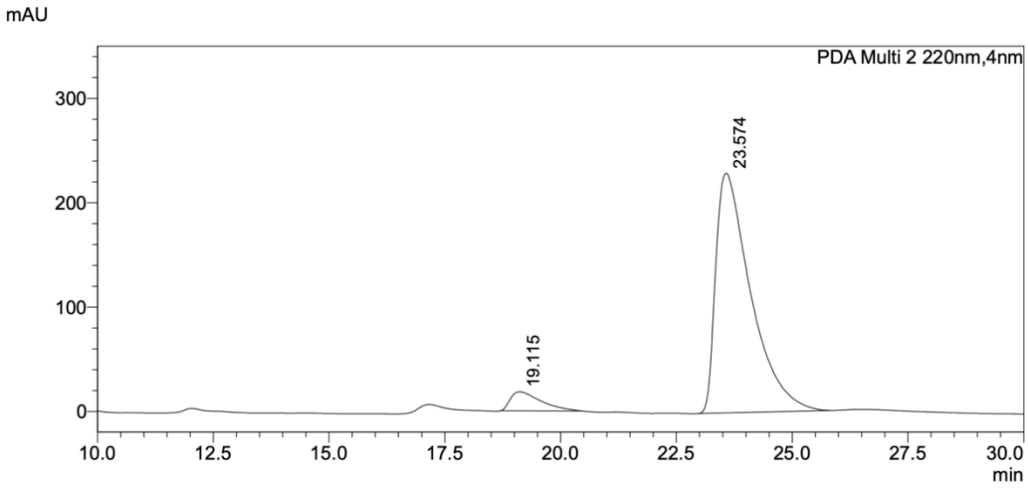
PDA Ch2 220nm

Peak#	Ret. Time	Area%
1	17.912	50.087
2	23.440	49.913
Total		100.000

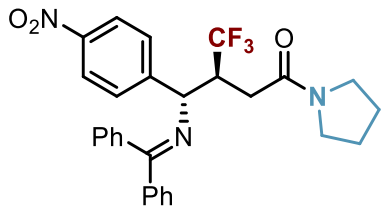


PDA Ch2 220nm

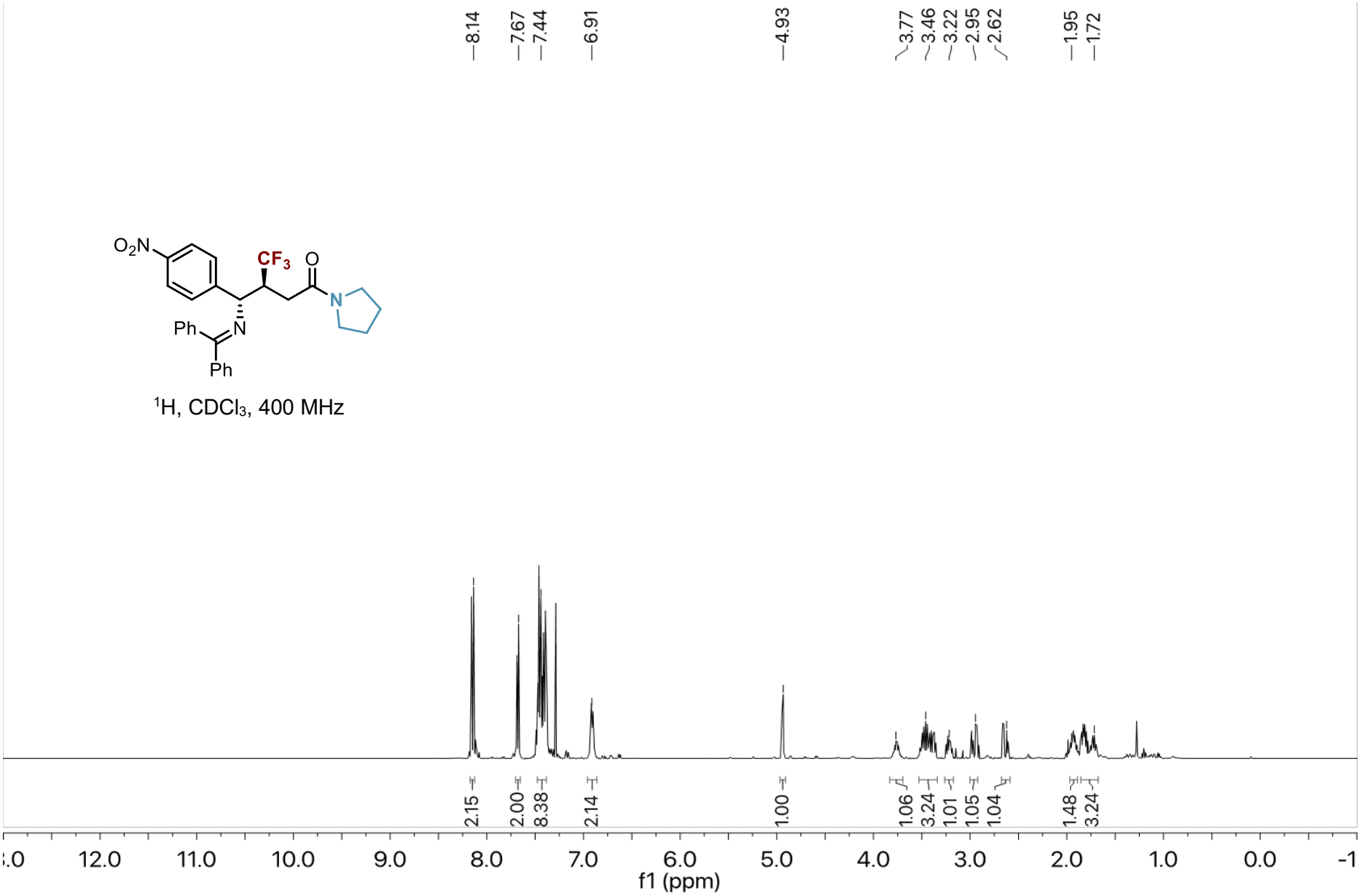
Peak#	Ret. Time	Area%
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2	23.574	93.546
Total		100.000



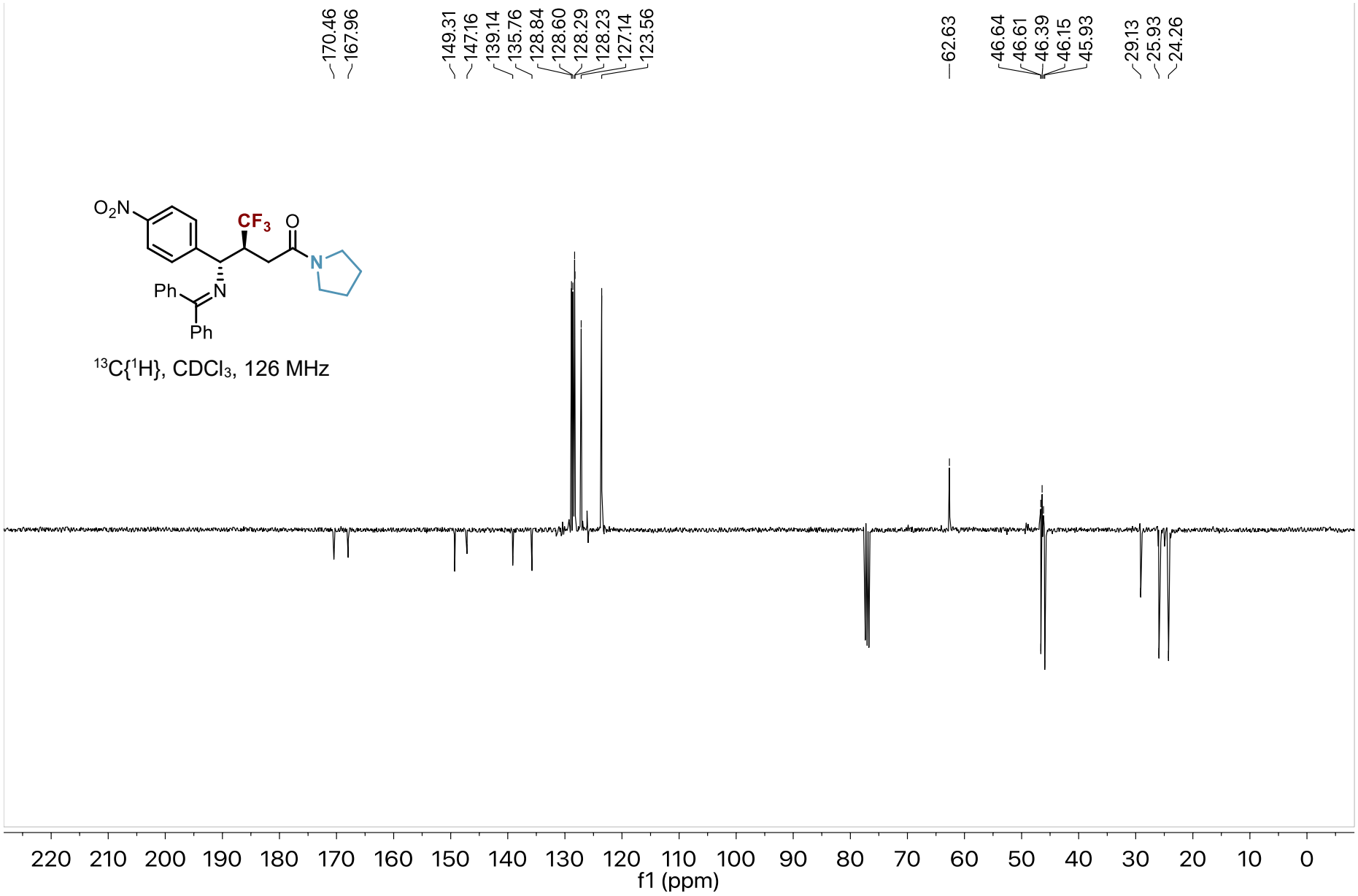
(*S*)-3-((*S*)-((diphenylmethylene)amino)(4-nitrophenyl)methyl)-4,4,4-trifluoro-1-(pyrrolidin-1-yl)butan-1-one (13)

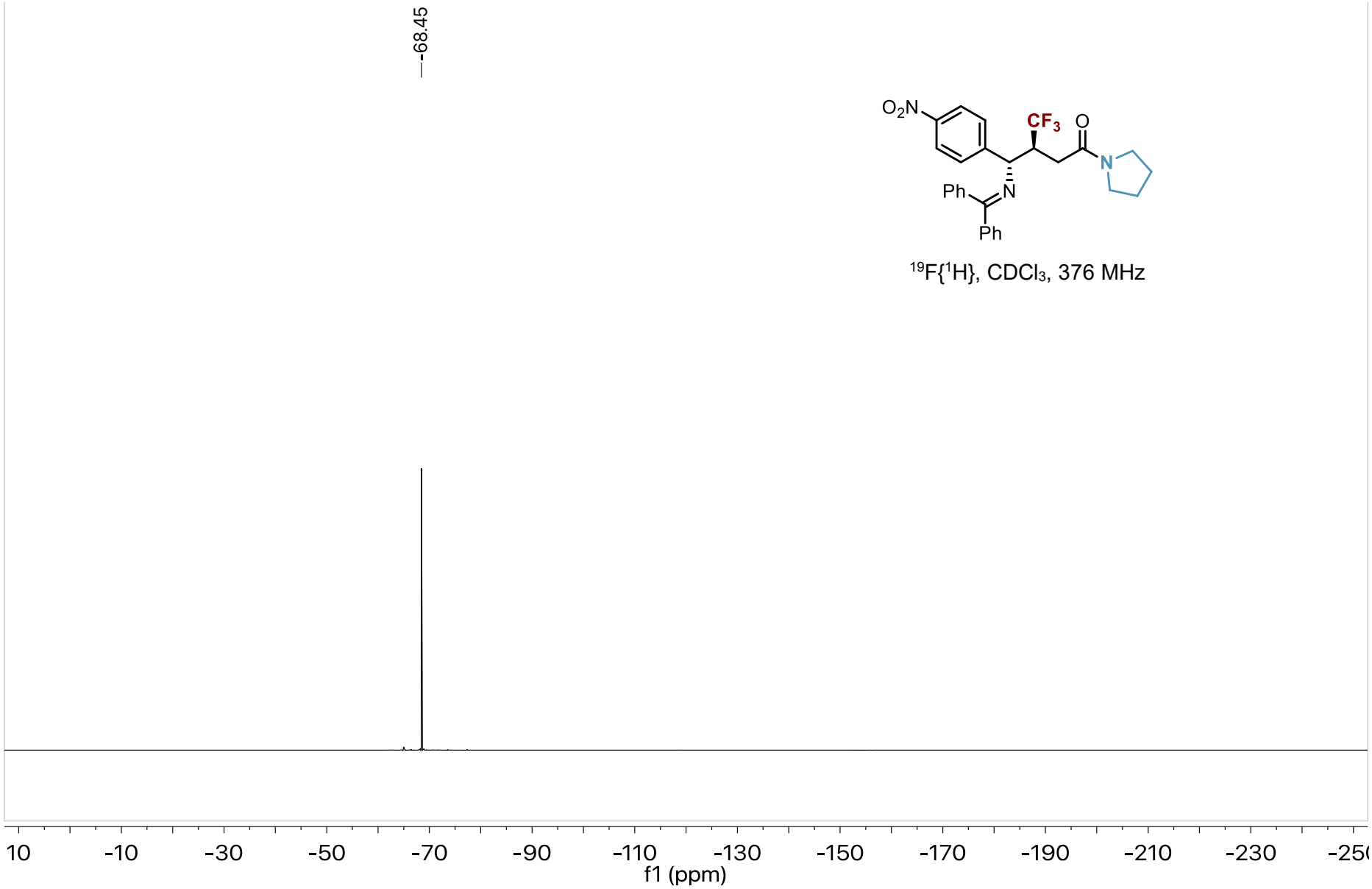


Following **General Procedure E,** 4-nitrophenyl (*E*)-4,4,4-trifluorobut-2-enoate (26.2 mg, 0.1 mmol), *N*-(4-nitrobenzyl)-1,1-diphenylmethanimine (47.5 mg, 0.15 mmol), (*R*)-(+)-BTM (2.5 mg, 0.01 mmol), and anhydrous DMF (1 mL) was stirred at rt for 8 hrs. The reaction mixture was then added with pyrrolidine (12.3 µL, 0.15 mmol) and was stirred for another 16 hrs, then purified by flash chromatography 3:1 Hexane:EtOAc (R_f = 0.20) to give the titled compound as an inseparable mixture of diastereomers (96:4 dr) as a garnet red oil (36 mg, 71%). $[\alpha]_D^{20}$ –8.7 (*c* 3.6, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak IB (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 254 nm, 30 °C) t_R(*S,R*): 13.6 min, t_R(*S,S*): 17.7 min, 7:93 er; **IR** ν_{max} (thin film): 2951 (Ar-H), 1639 (C=O amide), 1519 (asymm. NO_2), 1444 (C=C), 1344 (symm. NO_2), 1109 (C-F); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H: 1.72–1.95 (4H, m, CONC(1)H_2C(2)*H_2*C(3)*H_2*C(4)H_2), 2.62 (1H, dd, $^3J_{HH}$ = 16.4, $^4J_{HF}$ = 6.0, F_3CCHC*H_A*H_B), 2.95 (1H, dd, $^3J_{HH}$ = 16.4, $^4J_{HF}$ = 6.25, F_3CCHCH_A*H_B*), 3.22–3.46 (CONC(1)*H_2*C(2)H_2C(3)H_2C(4)*H_2*), 3.77 (F_3CC*H*C$H_A$$H_B$), 4.93 (1H, d, $^3J_{HH}$ = 3.97, C=NC*H*Ar$_3$-NO_2), 6.91 (2H, m, N=CC(4)Ar$_1$*H*, N=CC(4)Ar$_2$*H*), 7.44 (8H, m, N=CC(2,3,5,6)Ar$_1$*H*, N=CC(2,3,5,6)Ar$_2$*H*), 7.67 (2H, m, C=NCHC(2,6)Ar$_3$*H*-NO_2), 8.14 (2H, m, C=NCHC(3,5)Ar$_3$*H*-NO_2); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$), δ_C: 24.3 and 25.9 (CONC(1)H_2*C*(2)H_2*C*(3)H_2C(4)H_2), 29.1 (F_3CCH*C*$H_A$$H_B$), 45.9 and 46.6 (CON*C*(1)H_2C(2)H_2C(3)H_2*C*(4)H_2), 46.4 (q, $^2J_{CF}$ = 24.7, F_3C*C*HC$H_A$$H_B$), 62.6 (C=N*C*HAr$_3$-$NO_2$), 123.6 (C=NCH*C*(3,5)Ar$_3$-NO_2), 127.1 (N=C*C*(4)Ar$_1$, N=C*C*(4)Ar$_2$), 128.2 and 128.3 (N=C*C*(2,3,5,6)Ar$_1$, N=C*C*(2,3,5,6)Ar$_2$), 128.6 (q, $^1J_{CF}$ = 280.9, *C*F_3), 128.9 (C=NCH*C*(2,6)Ar$_3$-NO_2), 135.8 and 139.1 (N=C*C*(1)Ar$_1$, N=C*C*(1)Ar$_2$), 147.2 (C=NCH*C*(4)Ar$_3$-NO_2), 149.3 (C=NCH*C*(1)Ar$_3$-NO_2), 167.9 (F_3CCHC$H_A$$H_B$*C*O), 170.5 (*C*=N); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: −68.5 (3F, s, C*F_3*); **HRMS** (NSI$^+$) $C_{28}H_{27}F_3N_3O_3^+$ ([M+H]$^+$) requires 510.1999, found 510.1988 (−2.2 ppm).



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

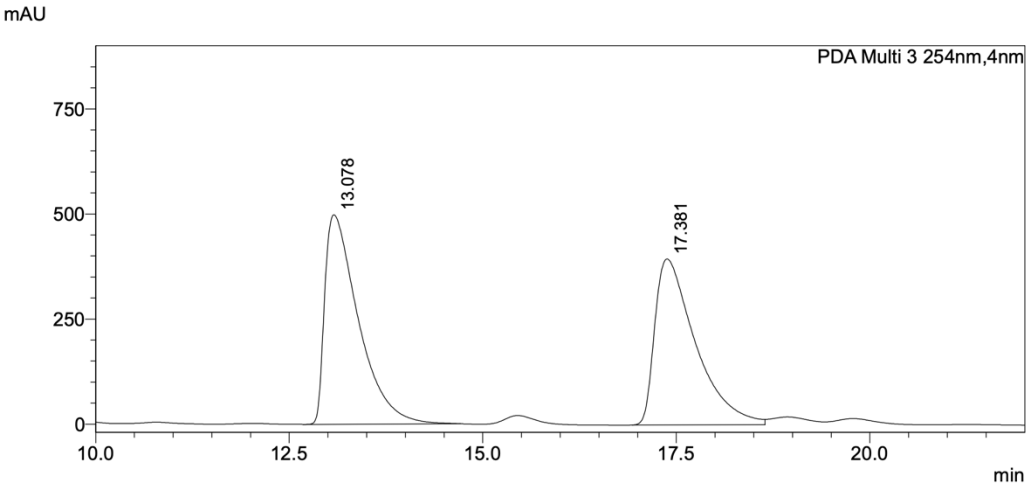

170.46
167.96
149.31
147.16
139.14
135.76
128.84
128.60
128.29
128.23
127.14
123.56
62.63
46.64
46.61
46.39
46.15
45.93
29.13
25.93
24.26
O2N
CF3
O
N
Ph
N
Ph
13C{1H}, CDCl3, 126 MHz
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


-68.45
O2N
CF3
O
N
Ph
N
Ph
19F{1H}, CDCl3, 376 MHz
10
-10
-30
-50
-70
-90
-110
-130
-150
-170
-190
-210
-230
f1 (ppm)

HPLC Data for **(*S*)-3-((*S*)-((diphenylmethylene)amino)(4-nitrophenyl)methyl)-4,4,4-trifluoro-1-(pyrrolidin-1-yl)butan-1-one**: Chiralpak IB (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 254 nm, 30 °C) t_R(*S,R*): 13.6 min, t_R(*S,S*): 17.7 min, 7:93 er

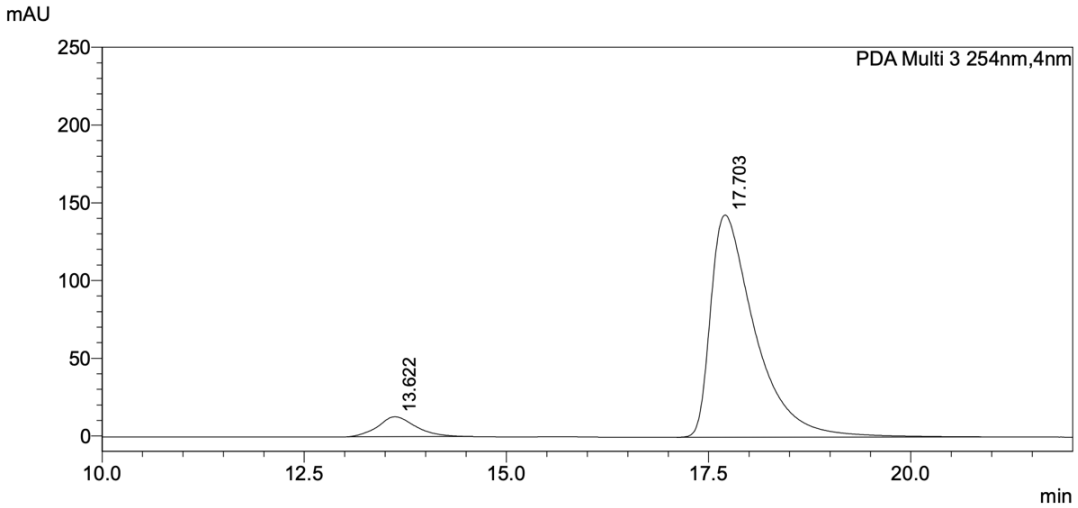
PDA Ch3 254nm

Peak#	Ret. Time	Area%
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2	17.381	49.027
Total		100.000

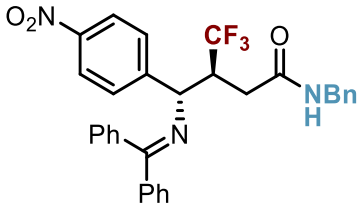


PDA Ch3 254nm

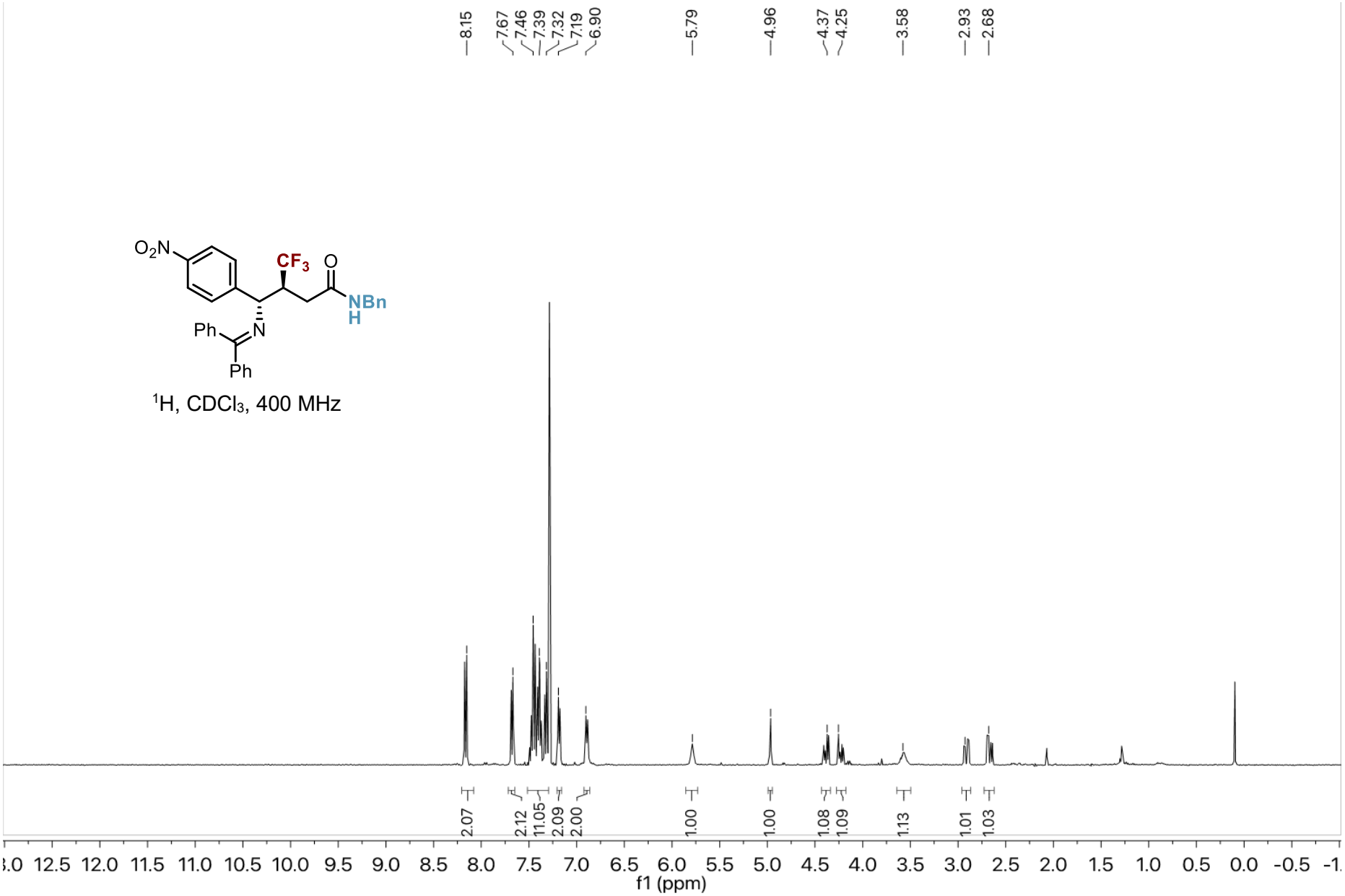
Peak#	Ret. Time	Area%
1	13.622	7.106
2	17.703	92.894
Total		100.000

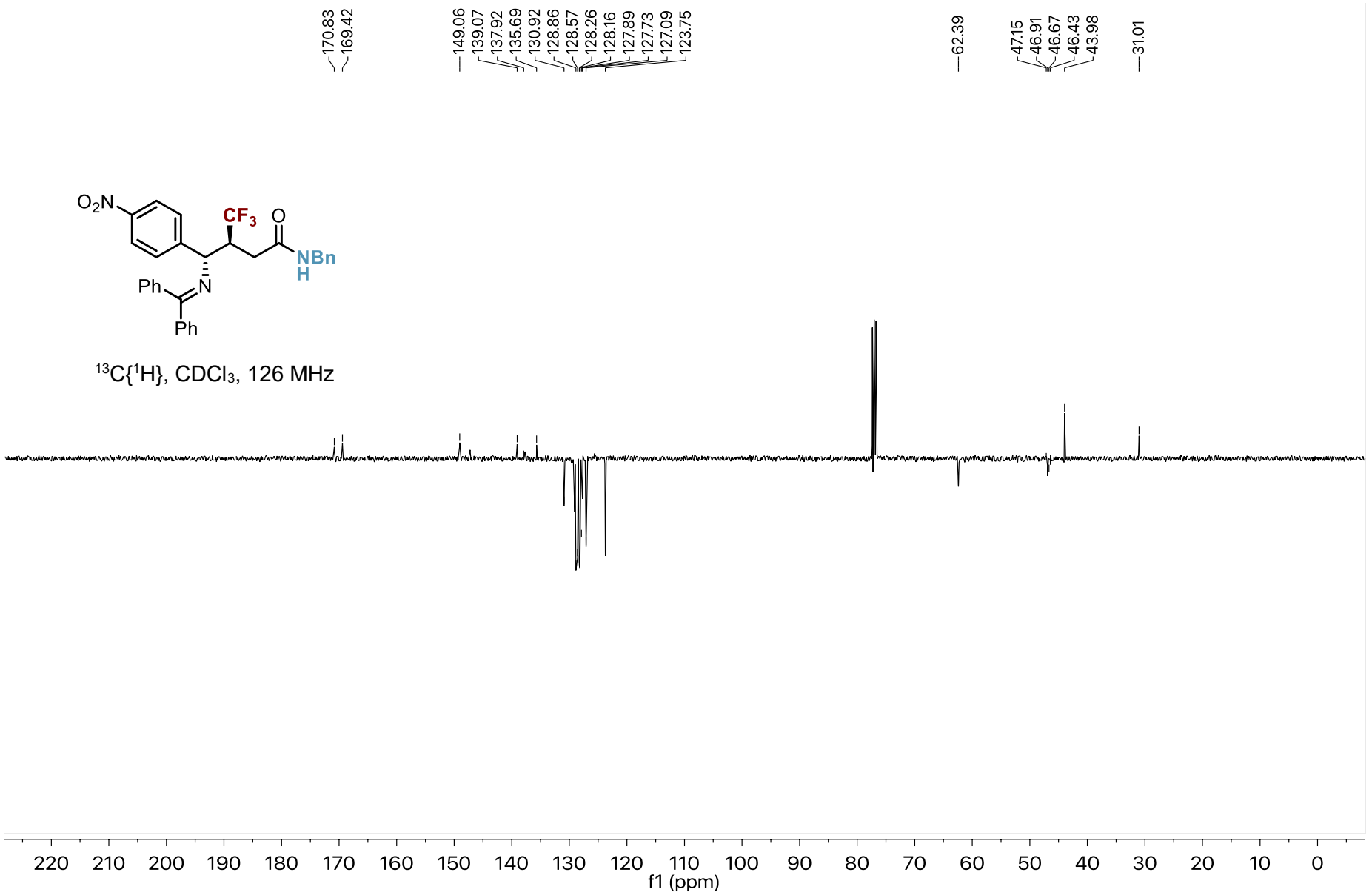


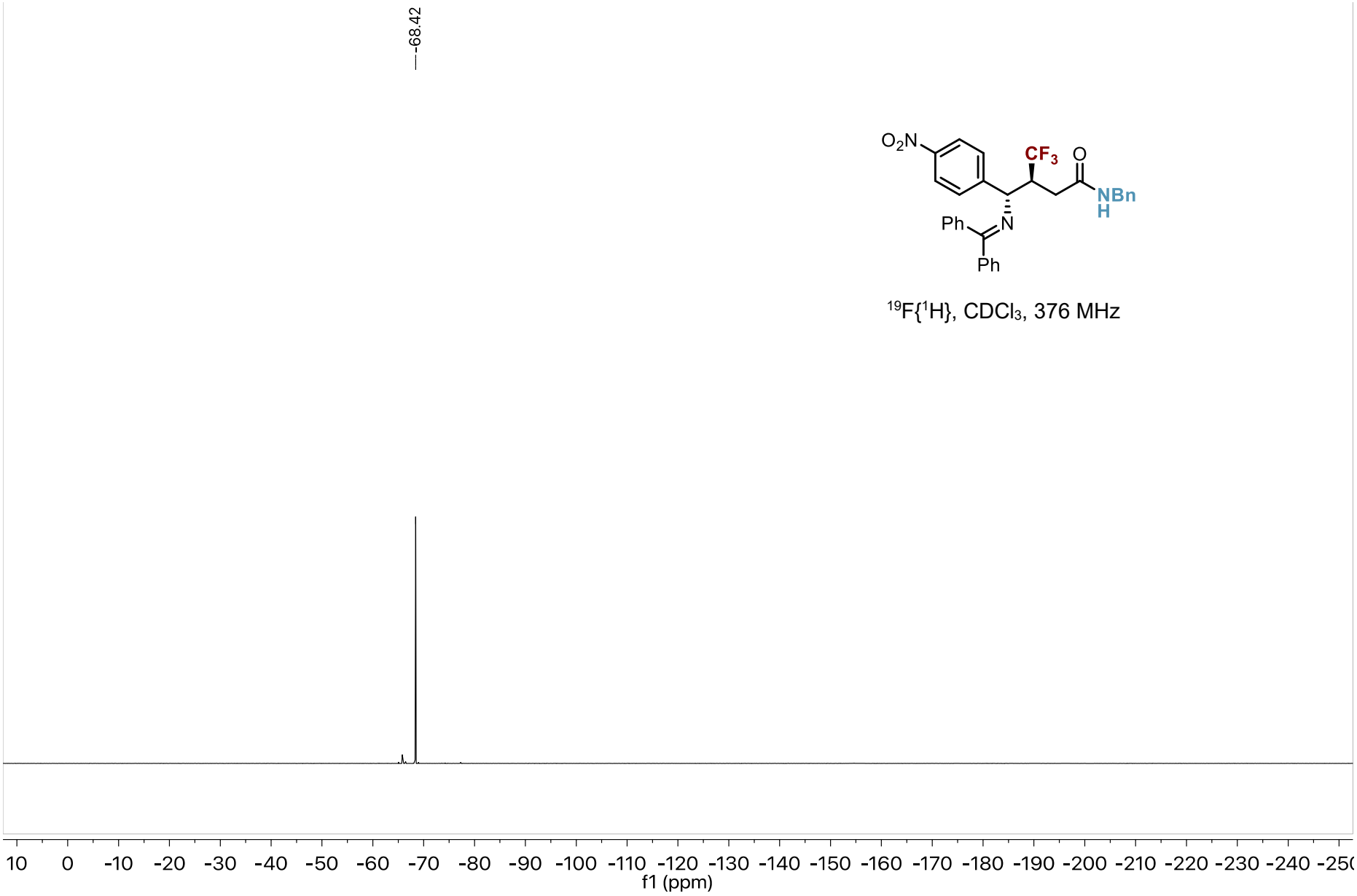
(*S*)-*N*-benzyl-3-((*S*)-((diphenylmethylene)amino)(4-nitrophenyl)methyl)-4,4,4-trifluorobutanamide (14)



Following **General Procedure E,** 4-nitrophenyl (*E*)-4,4,4-trifluorobut-2-enoate (26.2 mg, 0.1 mmol), *N*-(4-nitrobenzyl)-1,1-diphenylmethanimine (47.5 mg, 0.15 mmol), (*R*)-(+)-BTM (2.5 mg, 0.01 mmol), and anhydrous DMF (1 mL) was stirred at rt for 8 hrs. The reaction mixture was then added with benzylamine (16.4 μL, 0.15 mmol) and was stirred for another 16 hrs, then purified by flash chromatography 3:1 Hexane:EtOAc (R_f = 0.50) to give the titled compound as an inseparable mixture of diastereomers (94:6 dr) as a garnet red oil (35 mg, 64%). $[\alpha]_D^{20}$ –5.1 (*c* 3.5, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak ADH (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 254 nm, 30 °C) t_R(*S,S*): 25.9 min, t_R(*S,R*): 49.6 min, 94:6 er; **IR** ν_{max} (thin film): 2929 (Ar-H), 1658 (C=O amide), 1519 (asymm. NO_2), 1447 (C=C), 1344 (symm. NO_2), 1111 (C-F); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H: 2.68 (1H, dd, $^3J_{HH}$ = 16.0, $^4J_{HF}$ = 6.6, $F_3CHCH_AH_BCO$), 2.93 (1H, dd, $^3J_{HH}$ = 16.0, $^4J_{HF}$ = 5.0, $F_3CCHCH_AH_BCO$), 3.58 (1H, m, $F_3CCHCH_AH_BCO$), 4.25 (1H, dd, $^2J_{HH}$ = 14.6, $^3J_{HH}$ = 5.8, $CONHCH_AH_BPh$), 4.37 (1H, dd, $^2J_{HH}$ = 14.6, $^3J_{HH}$ = 5.4, $CONHCH_AH_BPh$), 4.96 (1H, d, $^3J_{HH}$ = 3.3, C=NC*H*Ar$_3$-NO_2), 5.79 (1H, t, $^3J_{HH}$ = 5.7, $CONHCH_AH_BPh$), 6.90 (2H, d, $^3J_{HH}$ = 7.21, N=CC(4)Ar$_1$*H*, N=CC(4)Ar$_2$*H*), 7.19 (2H, m, $CONHCH_AH_BC(2,6)ArH$), 7.32 (3H, m, $CONHCH_AH_BC(3,4,5)ArH$), 7.39–7.46 (8H, m, N=CC(2,3,5,6)Ar$_1$*H*, N=CC(2,3,5,6)Ar$_2$*H*), 7.67 (2H, m, C=NCHC(2,6)Ar$_3$*H*-NO_2), 8.17 (2H, m, C=NCHC(3,5)Ar$_3$*H*-NO_2); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$), δ_C: 31.0 ($F_3CCHCH_AH_BCO$), 43.9 ($CONHCH_AH_BPh$), 46.8 (q, $^2J_{CF}$ = 24.4, $F_3CCHCH_AH_BCO$), 62.4 (C=N*C*HAr$_3$-NO_2), 123.8 (C=NCH*C*(3,5)Ar$_3$-NO_2), 127.1 (N=C*C*(4)Ar$_1$, N=C*C*(4)Ar$_2$), 127.7 (*C*F3), 127.9 ($CONHCH_AH_BC(2,6)Ph$), 128.2 and 128.3 (N=C*C*(2,3,5,6)Ar$_1$, N=C*C*(2,3,5,6)Ar$_2$), 128.6 ($CONHCH_AH_BC(3,4,5)Ph$), 128.9 (C=NCH*C*(2,6)Ar$_3$-NO_2), 130.9 (C=NCH*C*(4)Ar$_3$-NO_2), 135.7 and 139.1 (N=C*C*(1)Ar$_1$, N=C*C*(1)Ar$_2$) 137.7 ($CONHCH_AH_BC(1)Ph$), 149.1 (C=NCH*C*(1)Ar$_3$-NO_2), 169.4 (*C*=O), 170.8 (*C*=N); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: −68.4 (3F, s, C*F*$_3$); **HRMS** (NSI^+) $C_{31}H_{27}F_3N_3O_3^+$ ($[M+H]^+$) requires 546.2004, found 546.1987 (−2.3 ppm).


8.15
7.67
7.46
7.39
7.32
7.19
6.90
5.79
4.96
4.37
4.25
3.58
2.93
2.68
O2N
CF3
O
NBn
H
Ph
N
Ph
1H, CDCl3, 400 MHz
2.07
2.12
11.05
2.09
2.00
1.00
1.00
1.08
1.09
1.13
1.01
1.03
f1 (ppm)

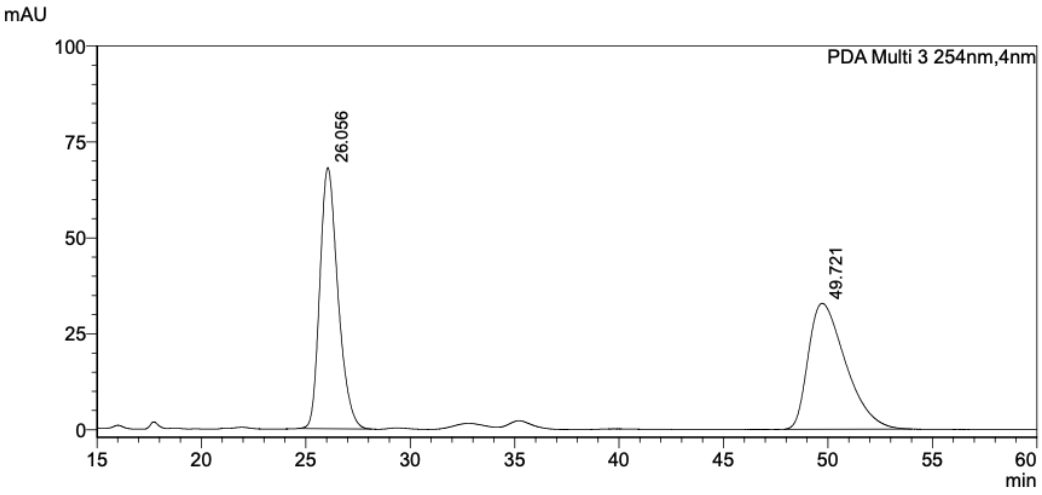

170.83
169.42
149.06
139.07
137.92
135.69
130.92
128.86
128.57
128.26
128.16
127.89
127.73
127.09
123.75
62.39
47.15
46.91
46.67
46.43
43.98
31.01
O2N
CF3
O
NBn
H
Ph
N
Ph
13C{1H}, CDCl3, 126 MHz
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


-68.42
O2N
CF3
O
NBn
H
Ph
N
Ph
19F{1H}, CDCl3, 376 MHz
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 -25(
f1 (ppm)

HPLC Data for **(*S*)-*N*-benzyl-3-((*S*)-((diphenylmethylene)amino)(4-nitrophenyl)methyl)-4,4,4-trifluorobutanamide** : Chiralpak ADH (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 254 nm, 30 °C) t_R(*S,S*): 25.9 min, t_R(*S,R*): 49.6 min, 94:6 er;

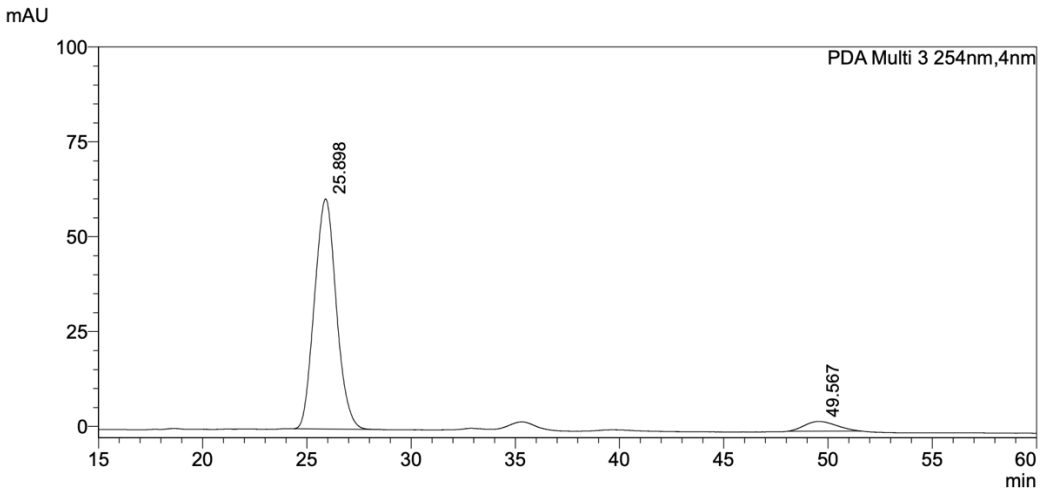
PDA Ch3 254nm

Peak#	Ret. Time	Area%
1	26.056	50.182
2	49.721	49.818
Total		100.000

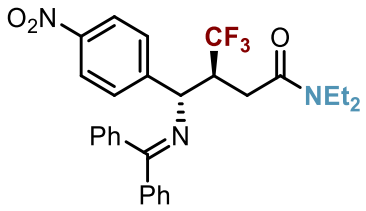


PDA Ch3 254nm

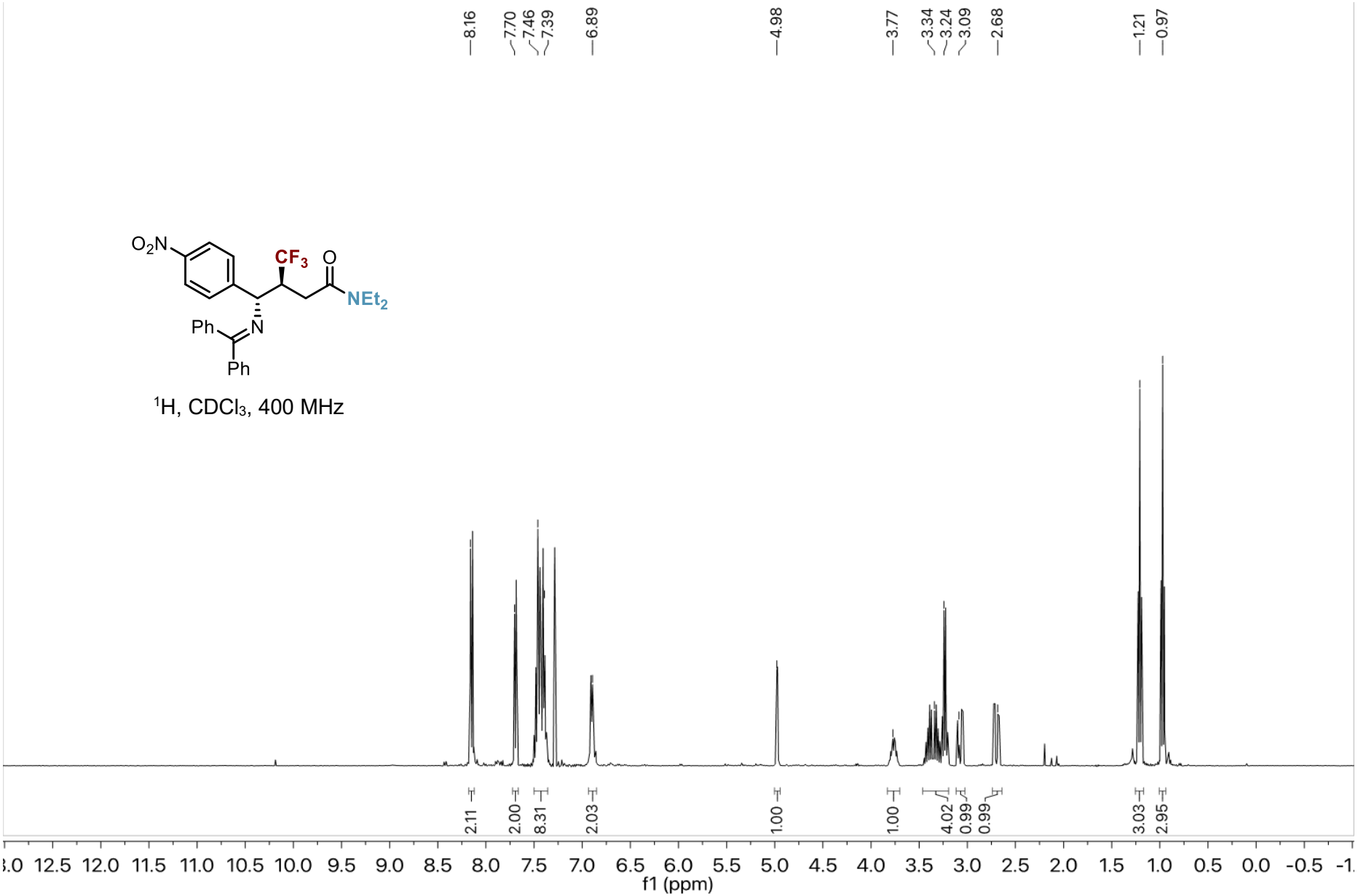
Peak#	Ret. Time	Area%
1	25.898	94.194
2	49.567	5.806
Total		100.000

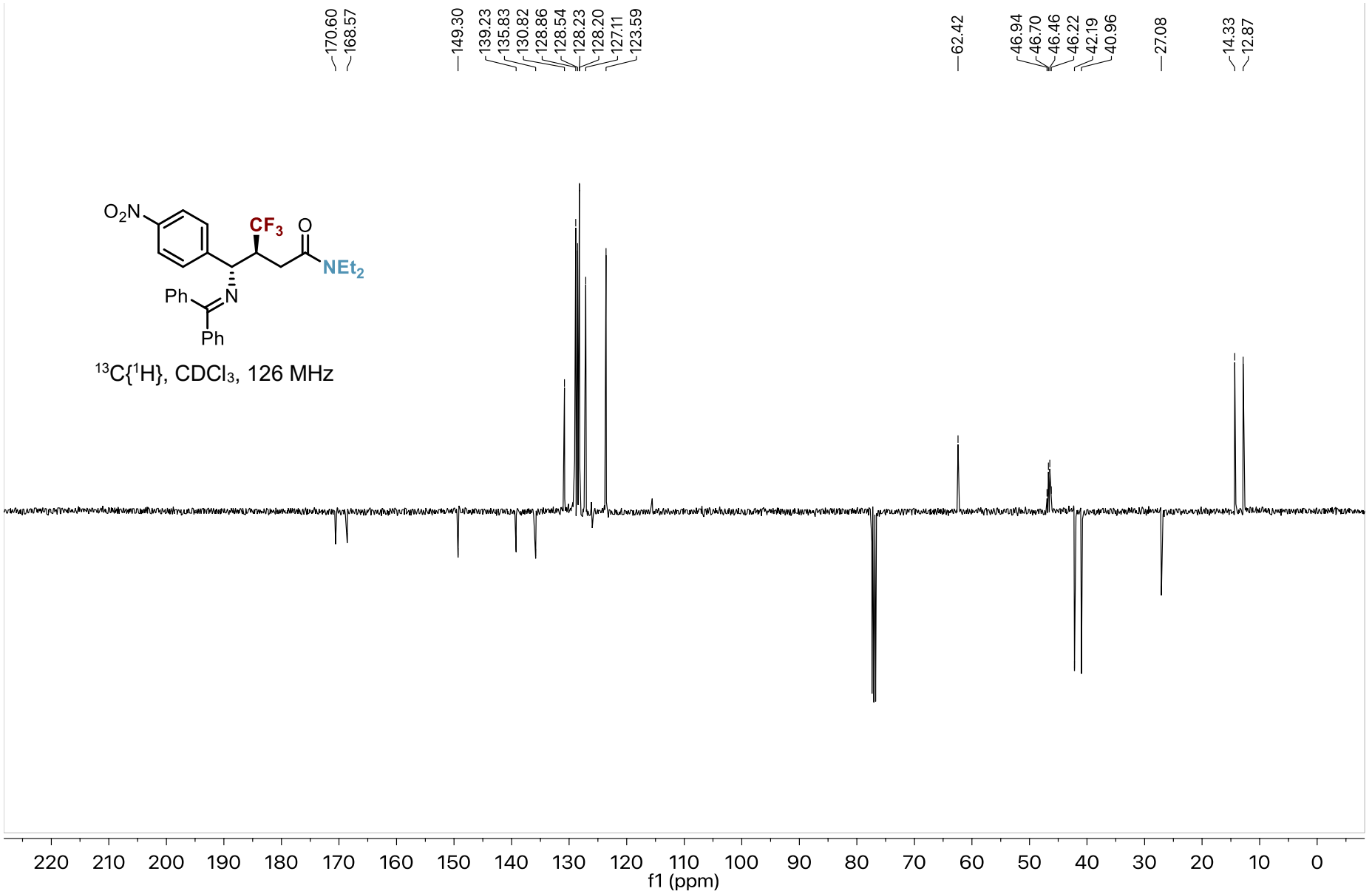


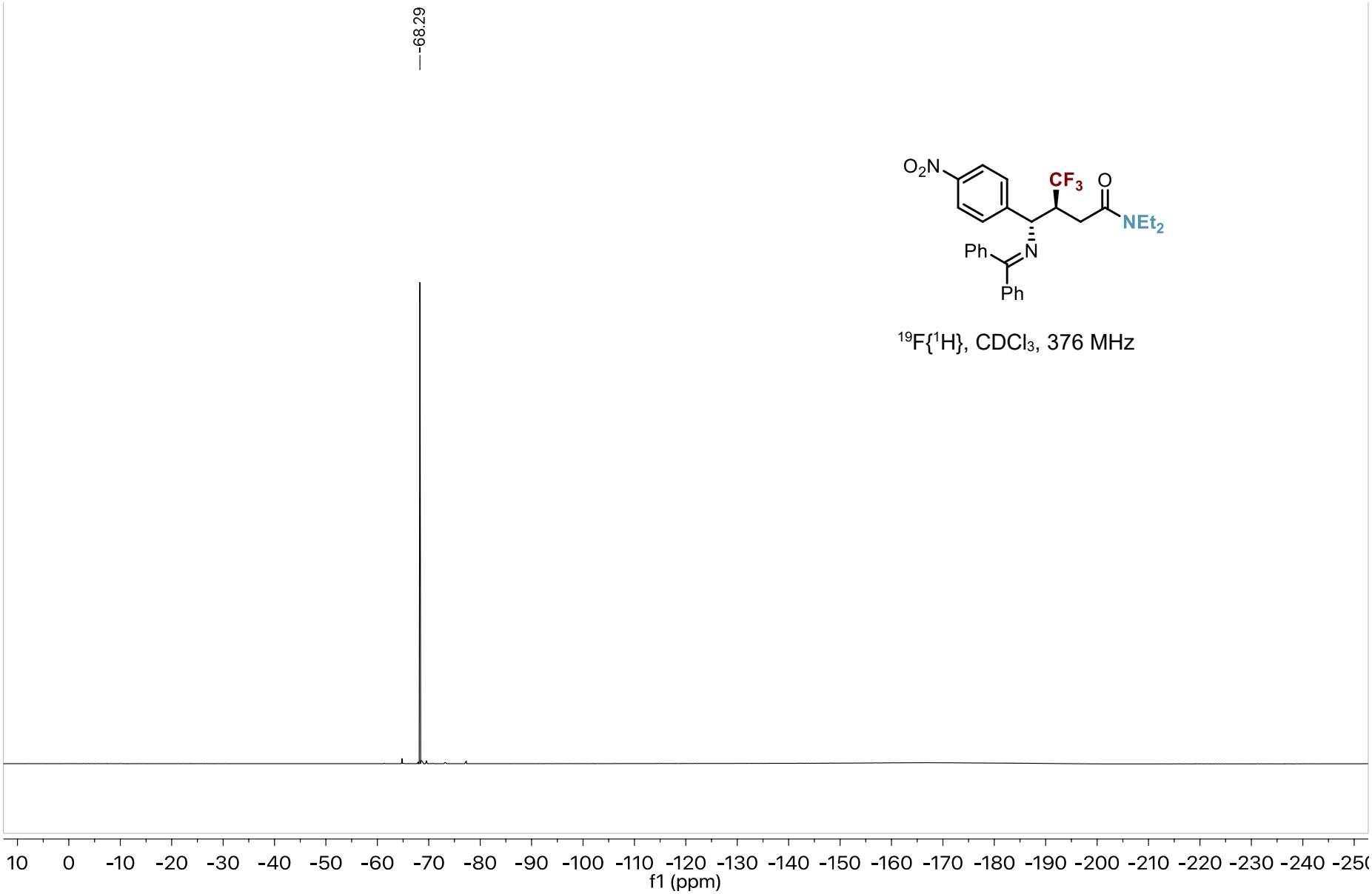
(*S*)-3-((*S*)-((diphenylmethylene)amino)(4-nitrophenyl)methyl)-*N*,*N*-diethyl-4,4,4-trifluorobutanamide (15)



Following **General Procedure E,** 4-nitrophenyl (*E*)-4,4,4-trifluorobut-2-enoate (26.2 mg, 0.1 mmol), *N*-(4-nitrobenzyl)-1,1-diphenylmethanimine (47.5 mg, 0.15 mmol), (*R*)-(+)-BTM (2.5 mg, 0.01 mmol), and anhydrous DMF (1 mL) was stirred at rt for 8 hrs. The reaction mixture was then added with diethylamine (15.5 µL, 0.15 mmol) and was stirred for another 16 hrs, then purified by flash chromatography 4:1 Hexane:EtOAc (R_f = 0.49) to give the titled compound as an inseparable mixture of diastereomers (94:6 dr) as a garnet red oil (36 mg, 70%). $[\alpha]_D^{20}$ –0.7 (*c* 3.6, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak ADH (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 270 nm, 30 °C) t_R(*S,S*): 8.1 min, t_R(*S,R*): 13.1 min, 92:8 er; **IR** ν_{max} (thin film): 2979 (Ar-H), 1639 (C=O amide), 1519 (asymm. NO_2), 1447 (C=C), 1342 (symm. NO_2), 1105 (C-F); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H: 0.97 (3H, t, $^3J_{HH}$ = 7.1, CON(CH_2CH_3)), 1.21 (3H, t, $^3J_{HH}$ = 7.1, CON(CH_2CH_3)), 2.68 (1H, dd, $^3J_{HH}$ = 16.5, $^4J_{HF}$ = 5.4, $F_3CCHCH_AH_BCO$), 3.09 (1H, dd, $^3J_{HH}$ = 16.6, $^4J_{HF}$ = 5.6, $F_3CCHCH_AH_BCO$), 3.24 – 3.34 (4H, m, CON(CH_2CH_3)$_2$), 3.77 (1H, m, $F_3CCHCH_AH_BCO$), 4.98 (1H, d, $^3J_{HH}$ = 4.2, C=N$CHAr_3$-NO_2), 6.89 (2H, m, N=CC(4)Ar_1H, N=CC(4)Ar_2H), 7.39–7.46 (8H, m, N=CC(2,3,5,6)Ar_1H, N=CC(2,3,5,6)Ar_2H), 7.70 (2H, m, C=NCHC(2,6)Ar_3H-NO_2), 8.16 (2H, m, C=NCHC(3,5)Ar_3H-NO_2); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$), δ_C: 12.9 and 14.3 (CON(CH_2CH_3)$_2$), 27.1 ($F_3CCHCH_AH_BCO$), 40.9 and 42.2 (CON(CH_2CH_3)$_2$), 46.7 (q, $^2J_{CF}$ = 24.3, $F_3CCHCH_AH_BCO$), 62.4 (C=N$CHAr_3$-NO_2), 123.6 (C=NCHC(3,5)Ar_3-NO_2), 127.1 (N=CC(4)Ar_1, N=CC(4)Ar_2), 128.2 (N=CC(2,3,5,6)Ar_1, N=CC(2,3,5,6)Ar_2), 127.4 (q, $^1J_{CF}$ = 281.6, CF_3), 128.9 (C=NCHC(2,6)Ar_3-NO_2), 130.8 (C=NCHC(4)Ar_3-NO_2), 135.8 and 139.2 (N=CC(1)Ar_1, N=CC(1)Ar_2), 149.3 (C=NCHC(1)Ar_3-NO_2), 168.6 (C=O), 170.6 (C=N); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: −68.3 (3F, s, CF_3); **HRMS** (NSI$^+$) $C_{28}H_{29}F_3N_3O_3^+$ ([M+H]$^+$) requires 512.2155, found 512.2150 (−1.1 ppm).


8.16
7.70
7.46
7.39
6.89
4.98
3.77
3.34
3.24
3.09
2.68
1.21
0.97
O2N
CF3
O
NEt2
Ph
N
Ph
1H, CDCl3, 400 MHz
2.11
2.00
8.31
2.03
1.00
1.00
4.02
0.99
0.99
3.03
2.95
f1 (ppm)

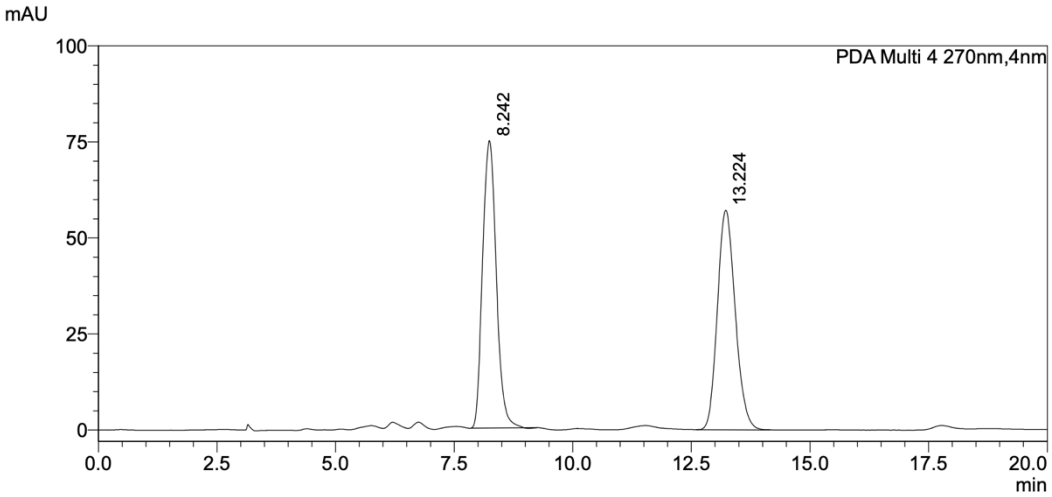

170.60
168.57
149.30
139.23
135.83
130.82
128.86
128.54
128.23
128.20
127.11
123.59
62.42
46.94
46.70
46.46
46.22
42.19
40.96
27.08
14.33
12.87
O2N
CF3
O
NEt2
Ph
N
Ph
13C{1H}, CDCl3, 126 MHz
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


-68.29
O2N
CF3
O
NEt2
Ph
N
Ph
19F{1H}, CDCl3, 376 MHz
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 -250
f1 (ppm)

HPLC Data for **(*S*)-3-((*S*)-((diphenylmethylene)amino)(4-nitrophenyl)methyl)-*N*,*N*-diethyl-4,4,4-trifluorobutanamide**: Chiralpak ADH (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 270 nm, 30 °C) t_R(*S,S*): 8.1 min, t_R(*S,R*): 13.1 min, 92:8 er;

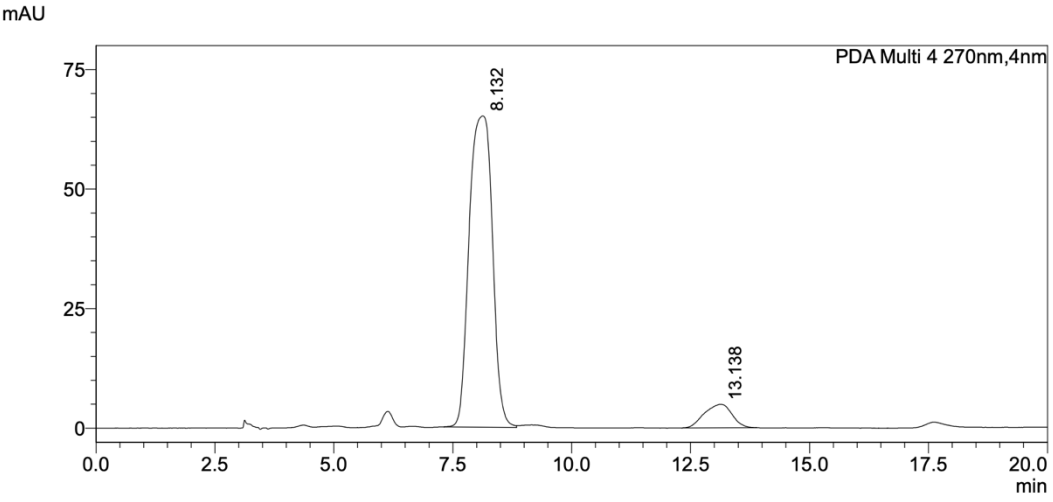
PDA Ch4 270nm

Peak#	Ret. Time	Area%
1	8.242	50.166
2	13.224	49.834
Total		100.000

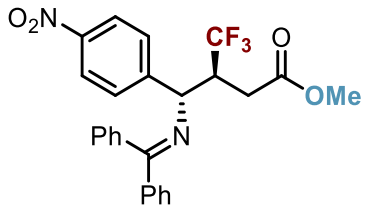


PDA Ch4 270nm

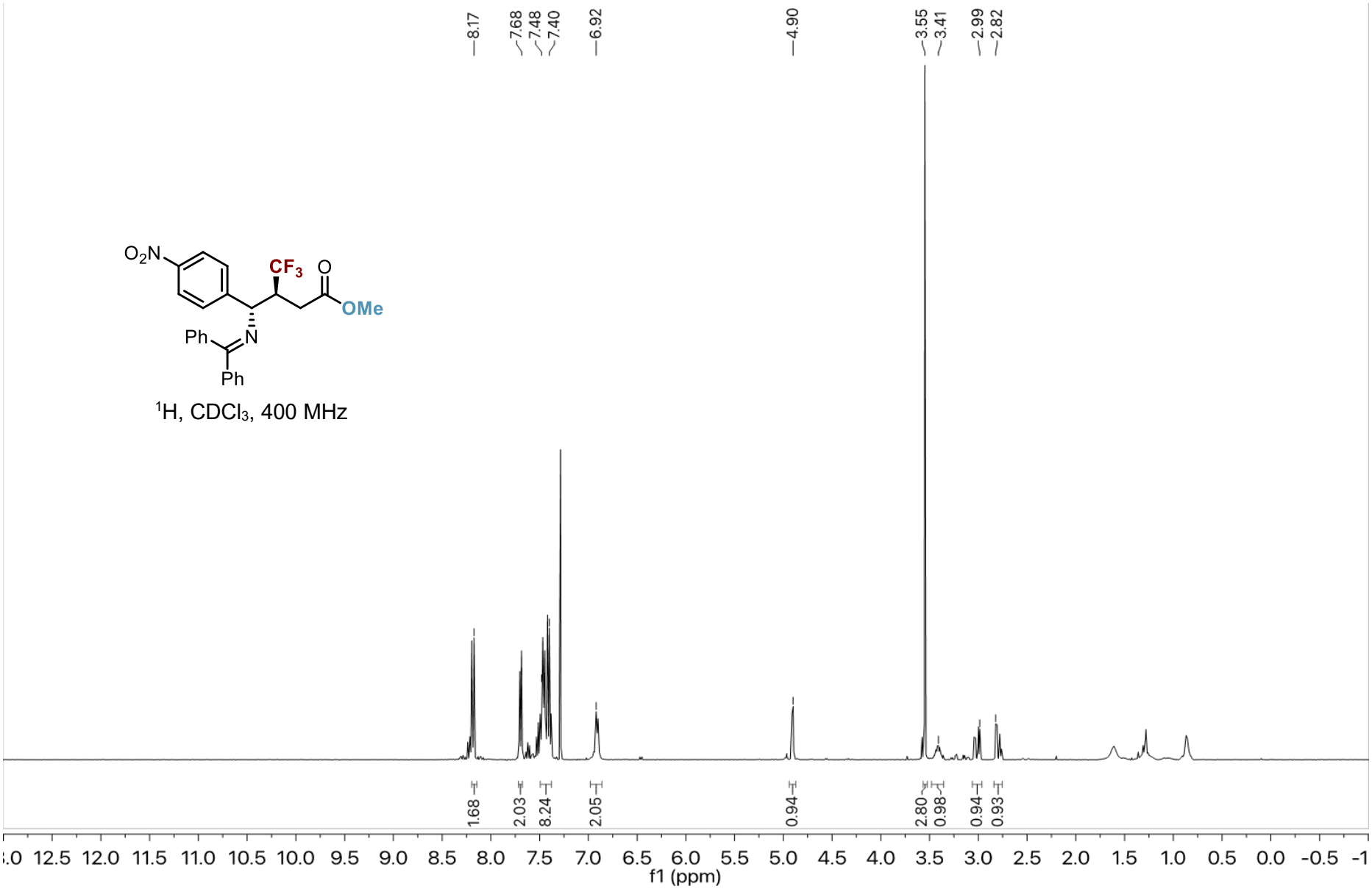
Peak#	Ret. Time	Area%
1	8.132	91.756
2	13.138	8.244
Total		100.000

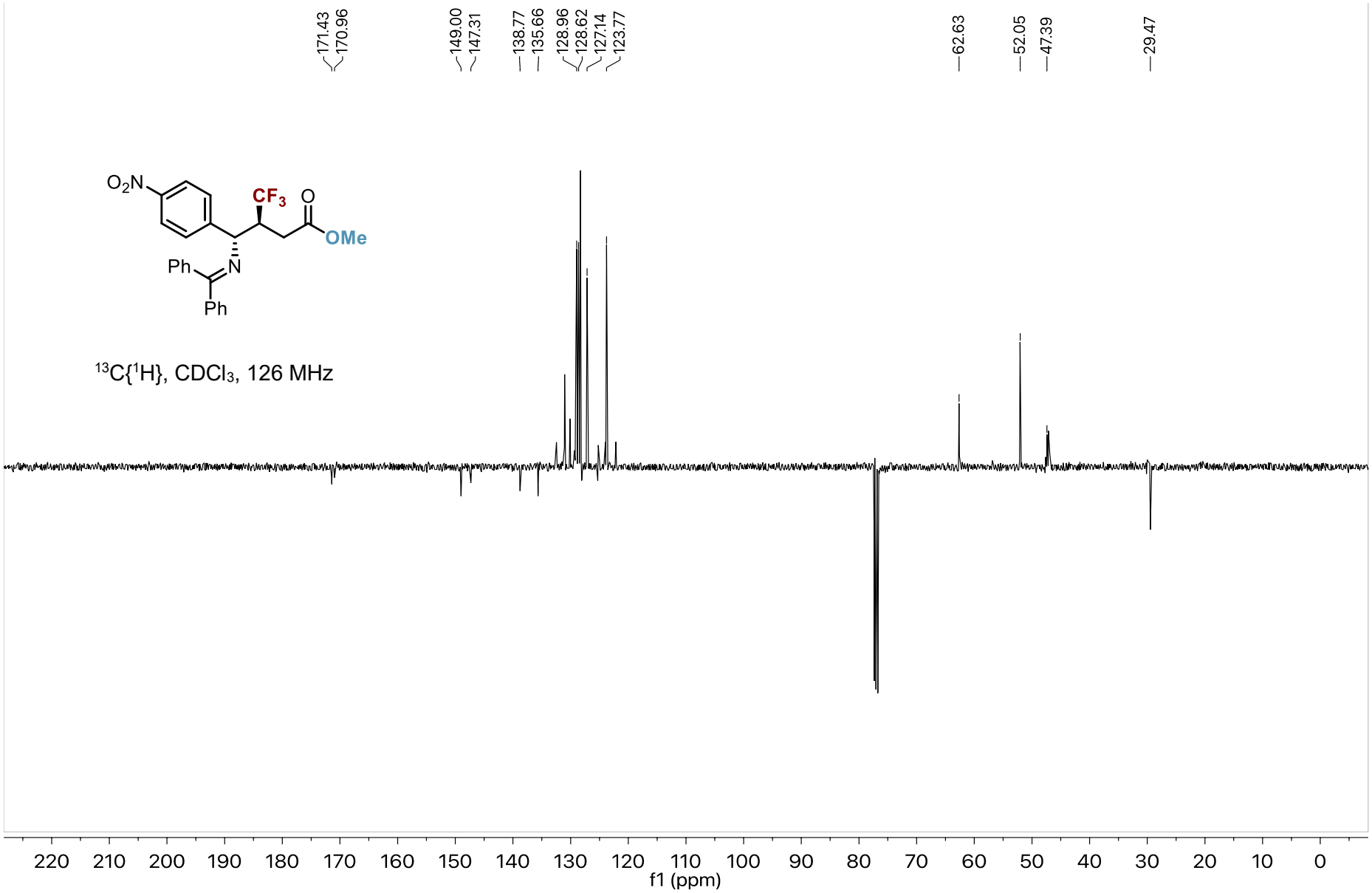


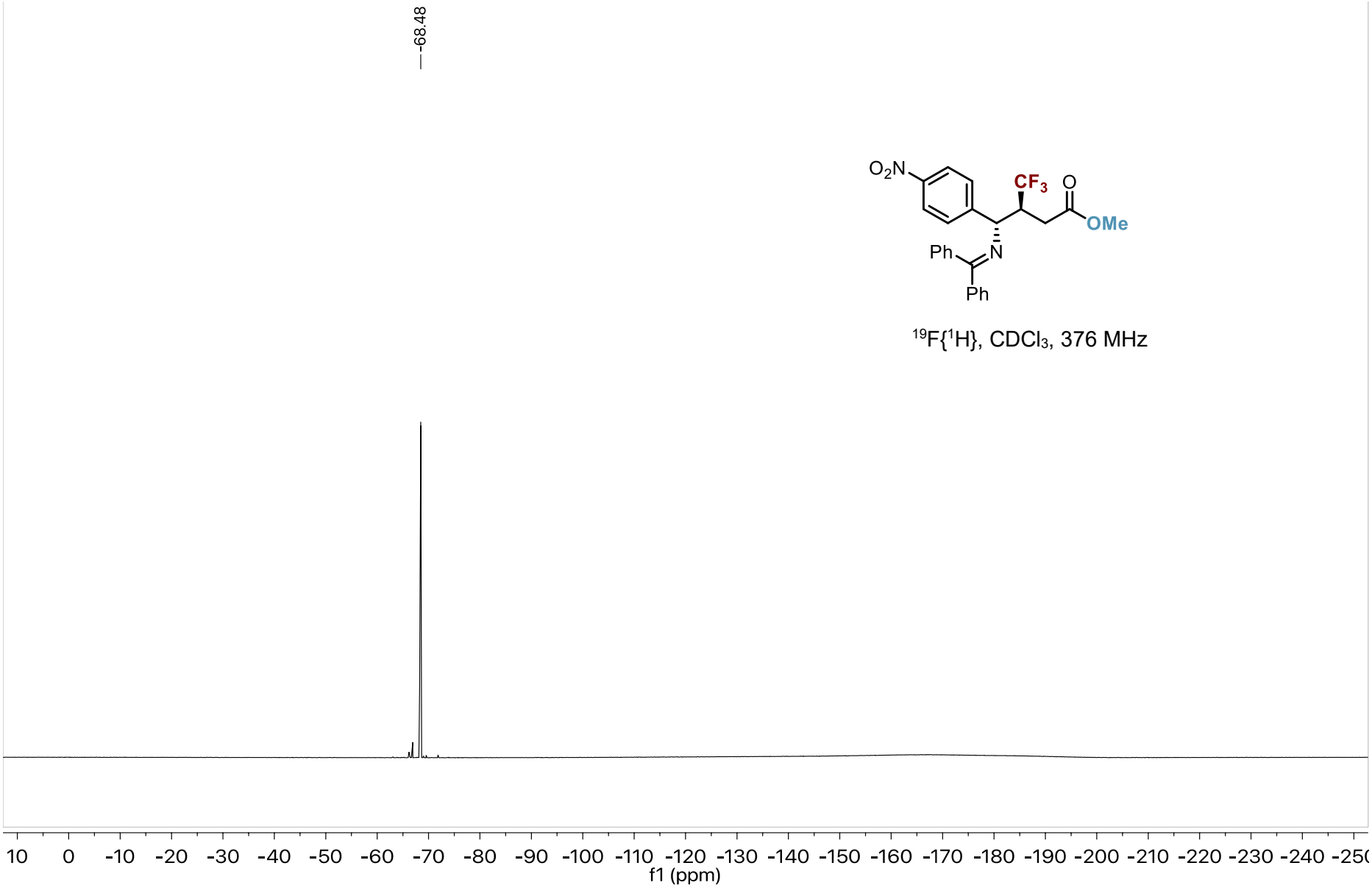
Methyl (*S*)-3-((*S*)-((diphenylmethylene)amino)(4-nitrophenyl)methyl)-4,4,4-trifluorobutanoate (16)



Following **General Procedure E,** 4-nitrophenyl (*E*)-4,4,4-trifluorobut-2-enoate (26.2 mg, 0.1 mmol), *N*-(4-nitrobenzyl)-1,1-diphenylmethanimine (47.5 mg, 0.15 mmol), (*R*)-(+)-BTM (2.5 mg, 0.01 mmol), and anhydrous DMF (1 mL) were stirred at rt for 8 hrs. The reaction mixture was then added with methanol (20.2 µL, 0.5 mmol) and was stirred for another 16 hrs, then purified by flash chromatography 2:1 Hexane:CH_2Cl_2 (R_f = 0.21) to give the titled compound as an inseparable mixture of diastereomers (97:3 dr) as a colorless oil (29 mg, 61%). $[\alpha]_D^{20}$ +5.1 (*c* 0.85, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak IB (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 220 nm, 30 °C) t_R(*S,R*): 32.1 min, t_R(*R,S*): 55.3 min, 98:2 er; **IR** ν_{max} (thin film): 2953 (Ar-H), 1739 (C=O, ester), 1521 (asymm. NO_2), 1447 (C=C), 1346 (symm. NO_2), 1113 (C-F); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H: 2.82 (1H, dd, $^3J_{HH}$ = 17.0, $^4J_{HF}$ = 5.9, $F_3CCHCH_AH_BCO$), 2.99 (1H, dd, $^3J_{HH}$ = 17.0, $^4J_{HF}$ = 5.9, $F_3CCHCH_AH_BCO$), 3.41 (1H, m, $F_3CCHCH_AH_BCO$), 3.55 (3H, s, CO_2CH_3), 4.90 (1H, d, $^3J_{HH}$ = 4.2, C=NCHAr$_3$-NO_2), 6.92 (2H, m, N=CC(4)Ar$_1$*H*, N=CC(4)Ar$_2$*H*), 7.40–7.48 (8H, m, N=CC(2,3,5,6)Ar$_1$*H*, N=CC(2,3,5,6)Ar$_2$*H*), 7.68 (2H, m, C=NCHC(2,6)Ar$_3$*H*-NO_2), 8.17 (2H, m, C=NCHC(3,5)Ar$_3$*H*-NO_2); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$), δ_C: 29.5 ($F_3CCHCH_AH_BCO$), 47.4 (q, $^2J_{CF}$ = 24.9, $F_3CCHCH_AH_BCO$), 52.1 (CO_2CH_3), 62.6 (C=NCHAr$_3$-NO_2), 123.8 (C=NCHC(3,5)Ar$_3$-NO_2), 127.1 (N=CC(4)Ar$_1$, N=CC(4)Ar$_2$), 128.2 and 128.3 (N=CC(2,3,5,6)Ar$_1$, N=CC(2,3,5,6)Ar$_2$), 128.6 (q, $^1J_{CF}$ = 292.1, CF_3), 128.9 (C=NCHC(2,6)Ar$_3$-NO_2), 135.7 and 138.8 (N=CC(1)Ar$_1$, N=CC(1)Ar$_2$), 147.3 (C=NCHC(1)Ar$_3$-NO_2), 149.0 (C=NCHC(4)Ar$_3$-NO_2), 170.9 (*C*=N), 171.4 (*C*=O); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: −68.5 (3F, s, CF_3); **HRMS** (NSI$^+$) $C_{25}H_{22}F_3N_2O_4^+$ ([M+H]$^+$) requires 471.1519, found 471.1523 (−0.8 ppm).


8.17
7.68
7.48
7.40
6.92
4.90
3.55
3.41
2.99
2.82
O2N
CF3
O
OMe
Ph
N
Ph
1H, CDCl3, 400 MHz
1.68
2.03
8.24
2.05
0.94
2.80
0.98
0.94
0.93
f1 (ppm)

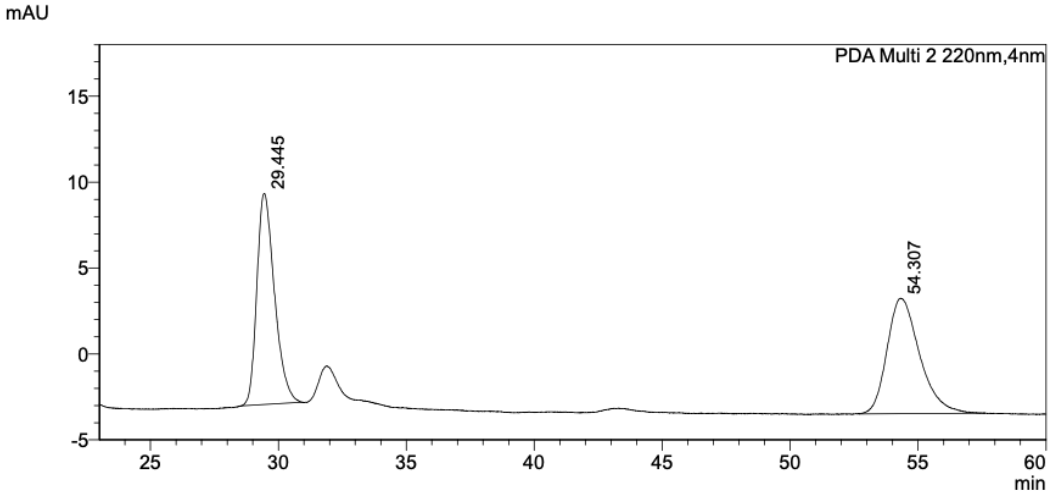

171.43
170.96
149.00
147.31
138.77
135.66
128.96
128.62
127.14
123.77
62.63
52.05
47.39
29.47
O2N
CF3
O
OMe
Ph
N
Ph
13C{1H}, CDCl3, 126 MHz
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


-68.48
O2N
CF3
O
OMe
Ph
N
Ph
19F{1H}, CDCl3, 376 MHz
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 -250
f1 (ppm)

HPLC Data for **Methyl (*S*)-3-((*S*)-((diphenylmethylene)amino)(4-nitrophenyl)methyl)-4,4,4-trifluorobutanoate**: Chiralpak IB (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 220 nm, 30 °C) t_R(*S,R*): 32.1 min, t_R(*R,S*): 55.3 min, 98:2 er;

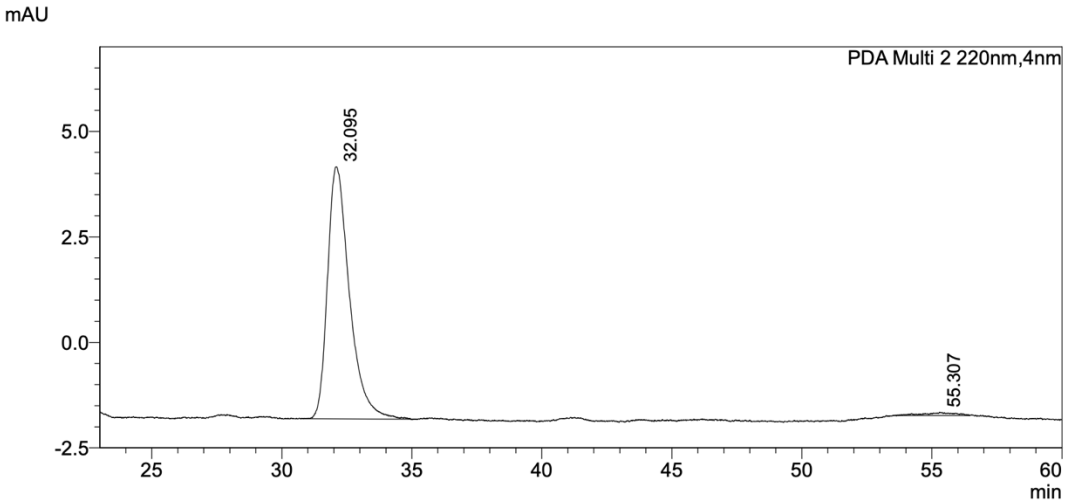
PDA Ch2 220nm

Peak#	Ret. Time	Area%
1	29.445	49.753
2	54.307	50.247
Total		100.000

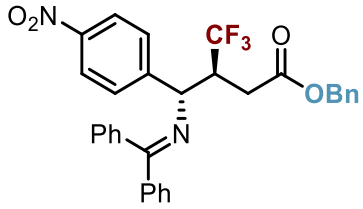


PDA Ch2 220nm

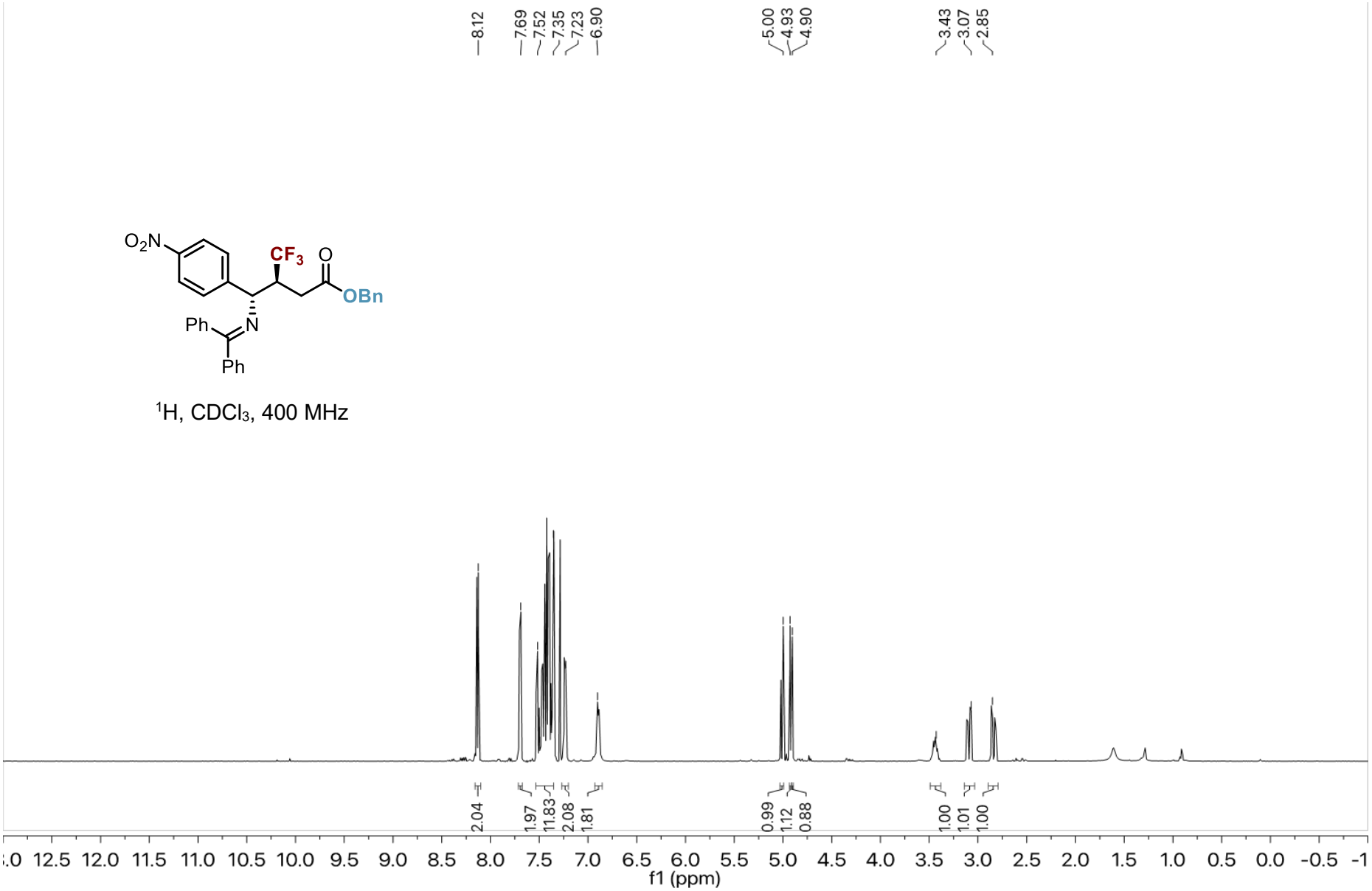
Peak#	Ret. Time	Area%
1	32.095	98.240
2	55.307	1.760
Total		100.000

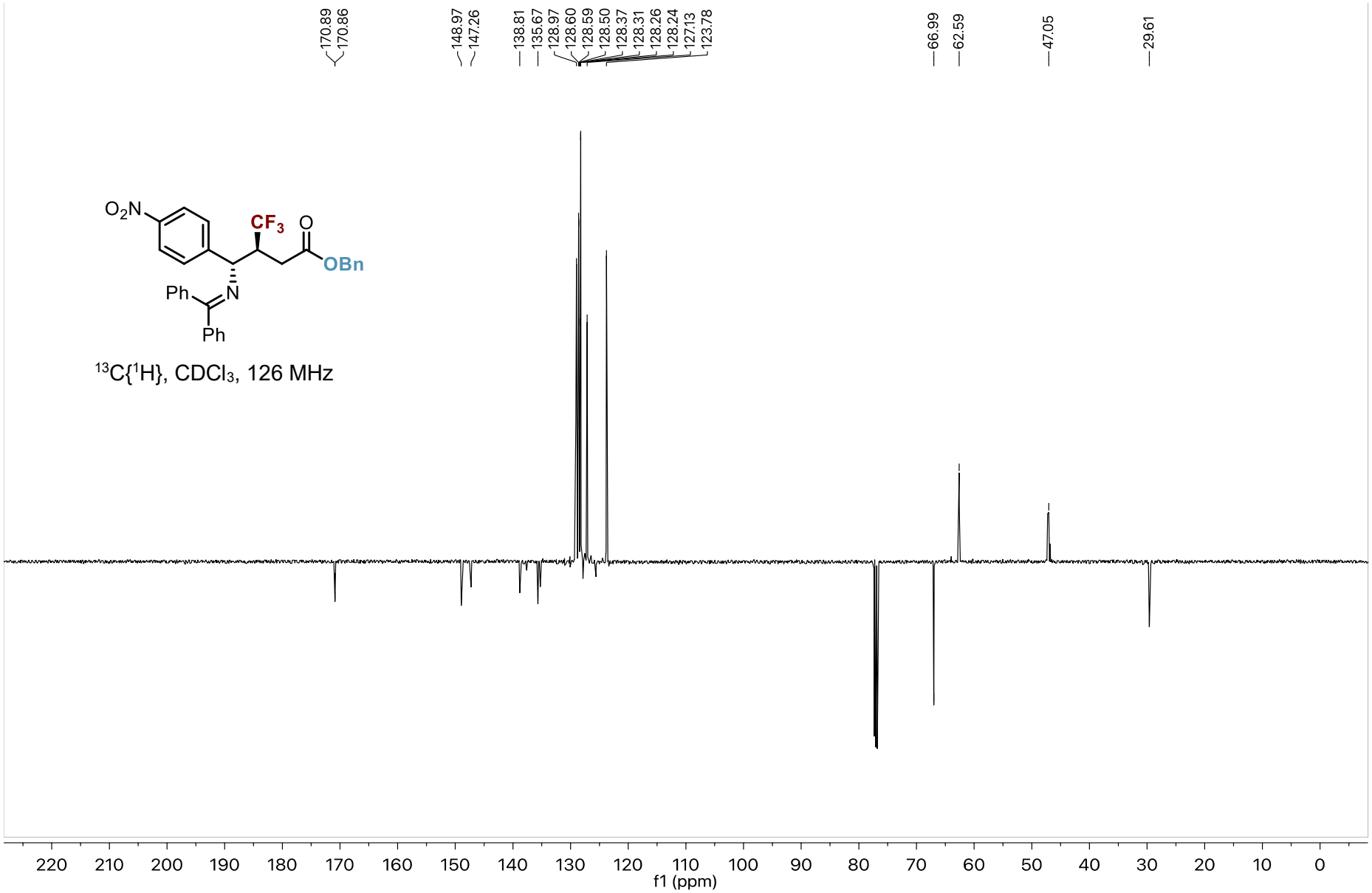


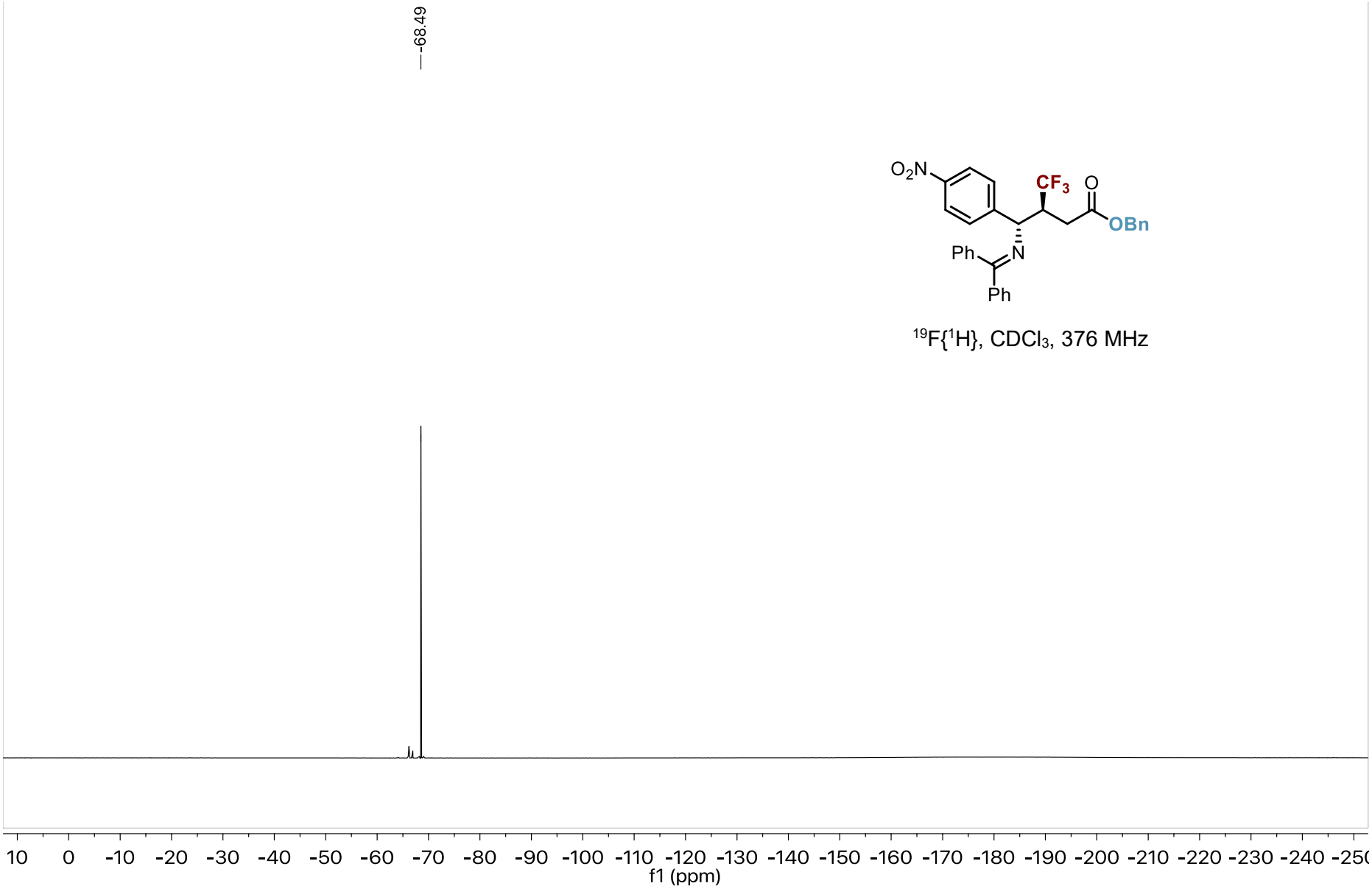
Benzyl (*S*)-3-((*S*)-((diphenylmethylene)amino)(4-nitrophenyl)methyl)-4,4,4-trifluorobutanoate (17)



Following **General Procedure E,** 4-nitrophenyl (*E*)-4,4,4-trifluorobut-2-enoate (26.2 mg, 0.1 mmol), *N*-(4-nitrobenzyl)-1,1-diphenylmethanimine (47.5 mg, 0.15 mmol), (*R*)-(+)-BTM (2.5 mg, 0.01 mmol), and anhydrous DMF (1 mL) was stirred at rt for 8 hrs. The reaction mixture was then added with benzyl alcohol (54 µL, 0.5 mmol) and was stirred for another 16 hrs, then purified by flash chromatography 2:1 Hexane:CH_2Cl_2 (R_f = 0.21) to give the titled compound as an inseparable mixture of diastereomers (96:4 dr) as a colorless oil (27 mg, 49%). $[\alpha]_D^{20}$ –27.4 (*c* 0.7, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak IC (99:1 Hexane:IPA, flow rate 1 mLmin^{-1}, 254 nm, 30 °C) t_R(*S,R*): 15.4 min, t_R(*S,S*): 17.2 min, 8:92 er; **IR** ν_{max} (thin film): 3062 (Ar-H), 1737 (C=O, ester), 1521 (asymm. NO_2), 1447 (C=C), 1346 (symm. NO_2), 1113 (C-F); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H: 2.85 (1H, dd, $^3J_{HH}$ = 17.2, $^4J_{HF}$ = 5.7, $F_3CCHCH_AH_BCO$), 3.07 (1H, dd, $^3J_{HH}$ = 17.2, $^4J_{HF}$ = 5.9, $F_3CCHCH_AH_BCO$), 3.43 (1H, m, $F_3CCHCH_AH_BCO$), 4.90 (1H,m ,C=NCHAr$_3$-NO_2), 4.93–5.00 (2H, m, CO_2CH_2Ph), 6.90 (2H, m, N=CC(4)Ar$_1H$, N=CC(4)Ar$_2H$), 7.23 (2H, m, CO_2CH_2C(2,6)ArH), 7.35–7.52 (11H, m, N=CC(2,3,5,6)Ar$_1H$, N=CC(2,3,5,6)Ar$_2H$, CO_2CH_2C(3,4,5)ArH), 7.69 (2H, m, C=NCHC(2,6)Ar$_3H$-NO_2), 8.12 (2H, m, C=NCHC(3,5)Ar$_3H$-NO_2); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$), δ_C: 29.6 ($F_3CCHCH_AH_BCO$), 47.1 (q, $^2J_{CF}$ = 24.9, $F_3CCHCH_AH_BCO$), 62.6 (C=NCHAr$_3$-NO_2), 66.9 (CO_2CH_2Ph), 123.8 (C=NCHC(3,5)Ar$_3$-NO_2), 127.1 (N=CC(4)Ar$_1$, N=CC(4)Ar$_2$), 128.2 (N=CC(2,3,5,6)Ar$_1$, N=CC(2,3,5,6)Ar$_2$), 127.0 (q, $^1J_{CF}$ = 291.0, CF_3), 128.4 (CO_2CH_2C(4)Ar), 128.5 (CO_2CH_2C(1)Ar), 128.6 (CO_2CH_2C(3,5)Ar), 128.6 (CO_2CH_2C(1,2)Ar), 128.9 (C=NCHC(2,6)Ar$_3$-NO_2), 135.7 and 138.8 (N=CC(1)Ar$_1$, N=CC(1)Ar$_2$), 147.3 (C=NCHC(4)Ar$_3$-NO_2), 148.9 (C=NCHC(1)Ar$_3$-NO_2), 170.8 (C=O), 170.9 (C=N); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: −68.5 (3F, s, CF_3); **HRMS** (NSI$^+$) $C_{31}H_{25}F_3N_2O_4Na^+$ ([M+Na]$^+$) requires 569.1659, found 569.1656 (−0.54 ppm).

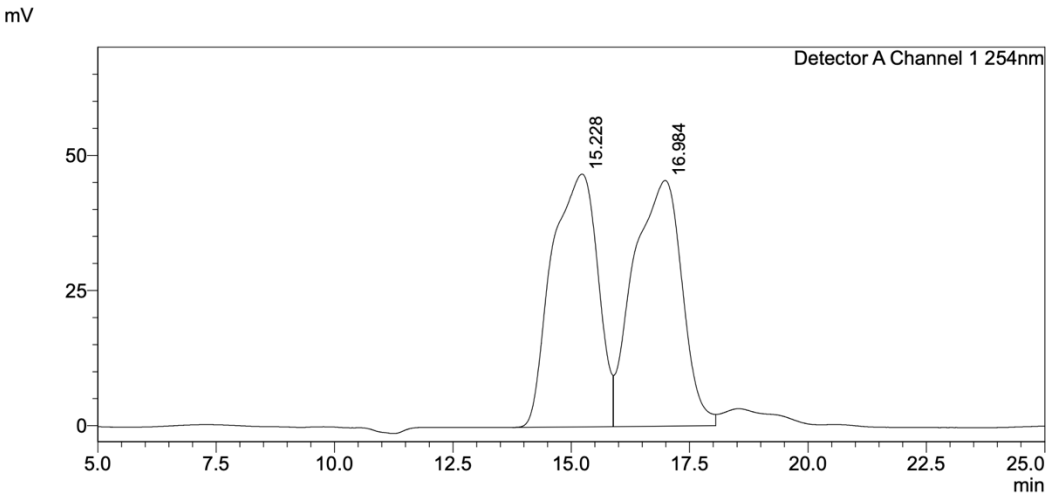

8.12
7.69
7.52
7.35
7.23
6.90
5.00
4.93
4.90
3.43
3.07
2.85
O2N
CF3
O
OBn
Ph
N
Ph
1H, CDCl3, 400 MHz
2.04
1.97
11.83
2.08
1.81
0.99
1.12
0.88
1.00
1.01
1.00
f1 (ppm)


170.89
170.86
148.97
147.26
138.81
135.67
128.97
128.60
128.59
128.50
128.37
128.31
128.26
128.24
127.13
123.78
66.99
62.59
47.05
29.61
O2N
CF3
O
OBn
Ph
N
Ph
13C{1H}, CDCl3, 126 MHz
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

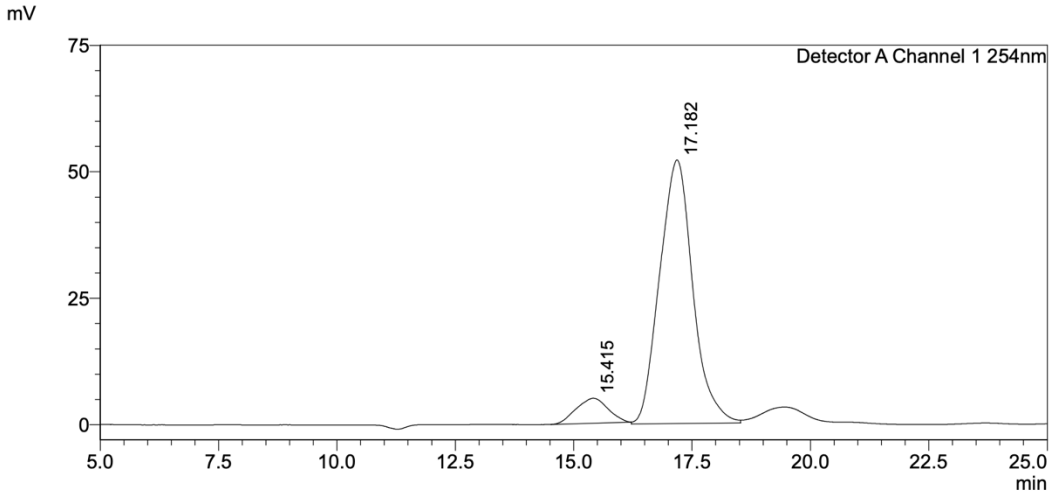

-68.49
O2N
CF3
O
OBn
Ph
N
Ph
19F{1H}, CDCl3, 376 MHz
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 -250
f1 (ppm)

HPLC Data for **Benzyl (*S*)-3-((*S*)-((diphenylmethylene)amino)(4-nitrophenyl)methyl)-4,4,4-trifluorobutanoate**: Chiralpak IC (99:1 Hexane:IPA, flow rate 1 mLmin^{-1}, 254 nm, 30 °C) t_R(*S,R*): 15.4 min, t_R(*S,S*): 17.2 min, 8:92 er;

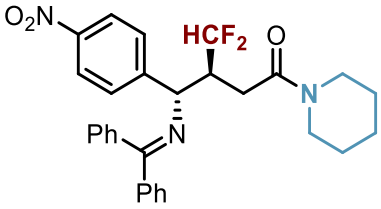
Peak#	Ret. Time	Area%
1	15.228	49.394
2	16.984	50.606
Total		100.000



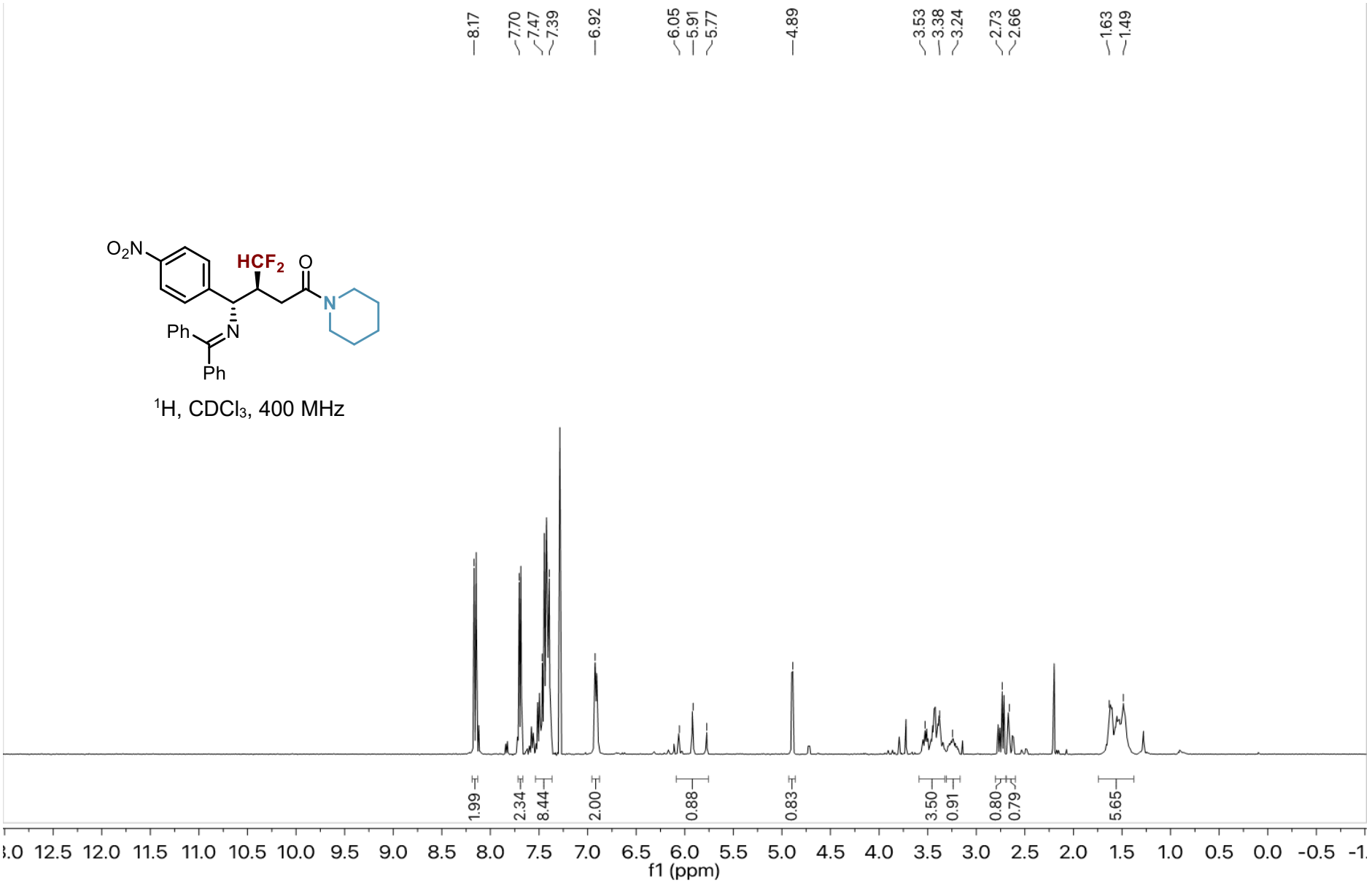
Peak#	Ret. Time	Area%
1	15.415	8.284
2	17.182	91.716
Total		100.000

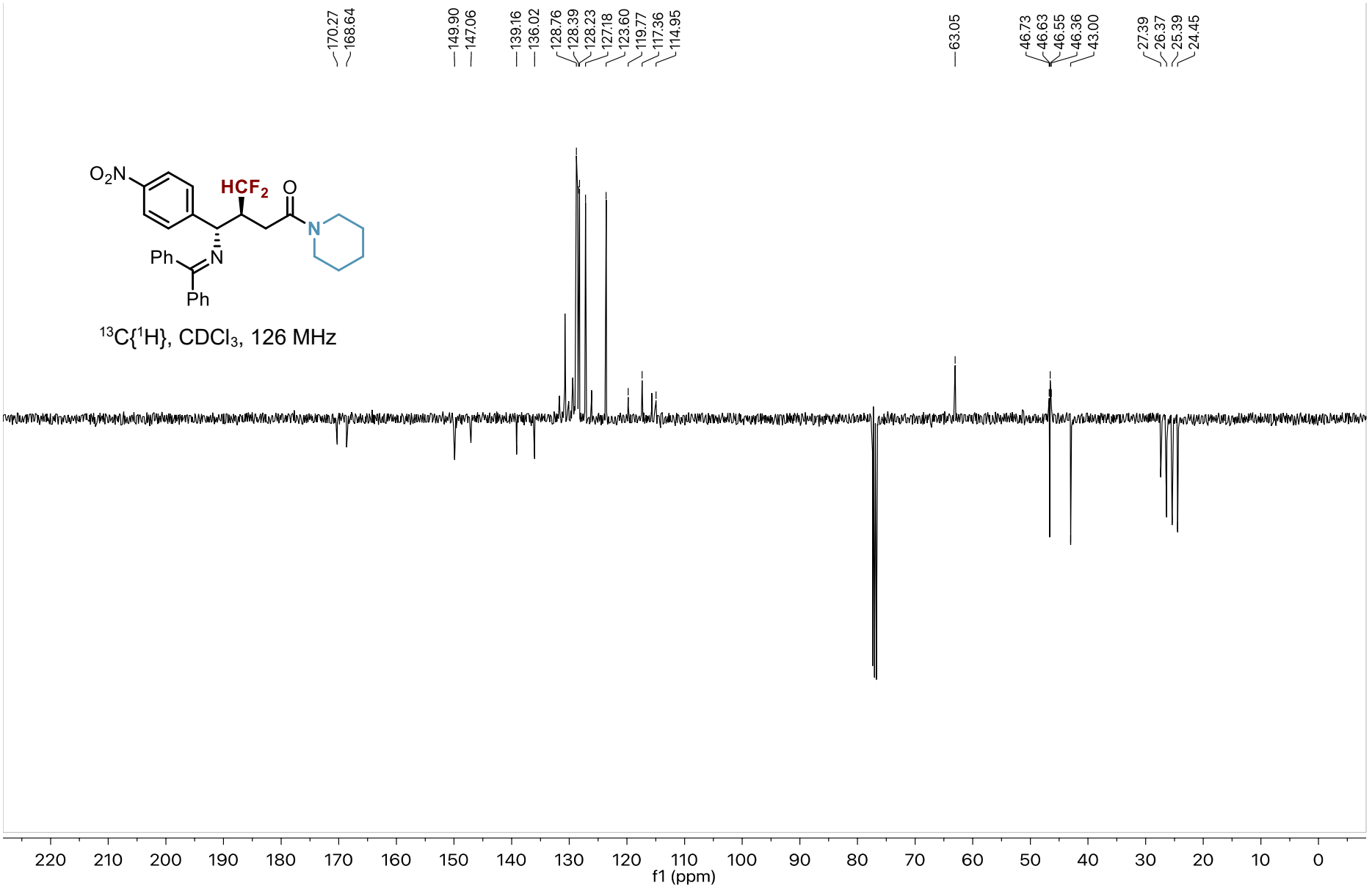


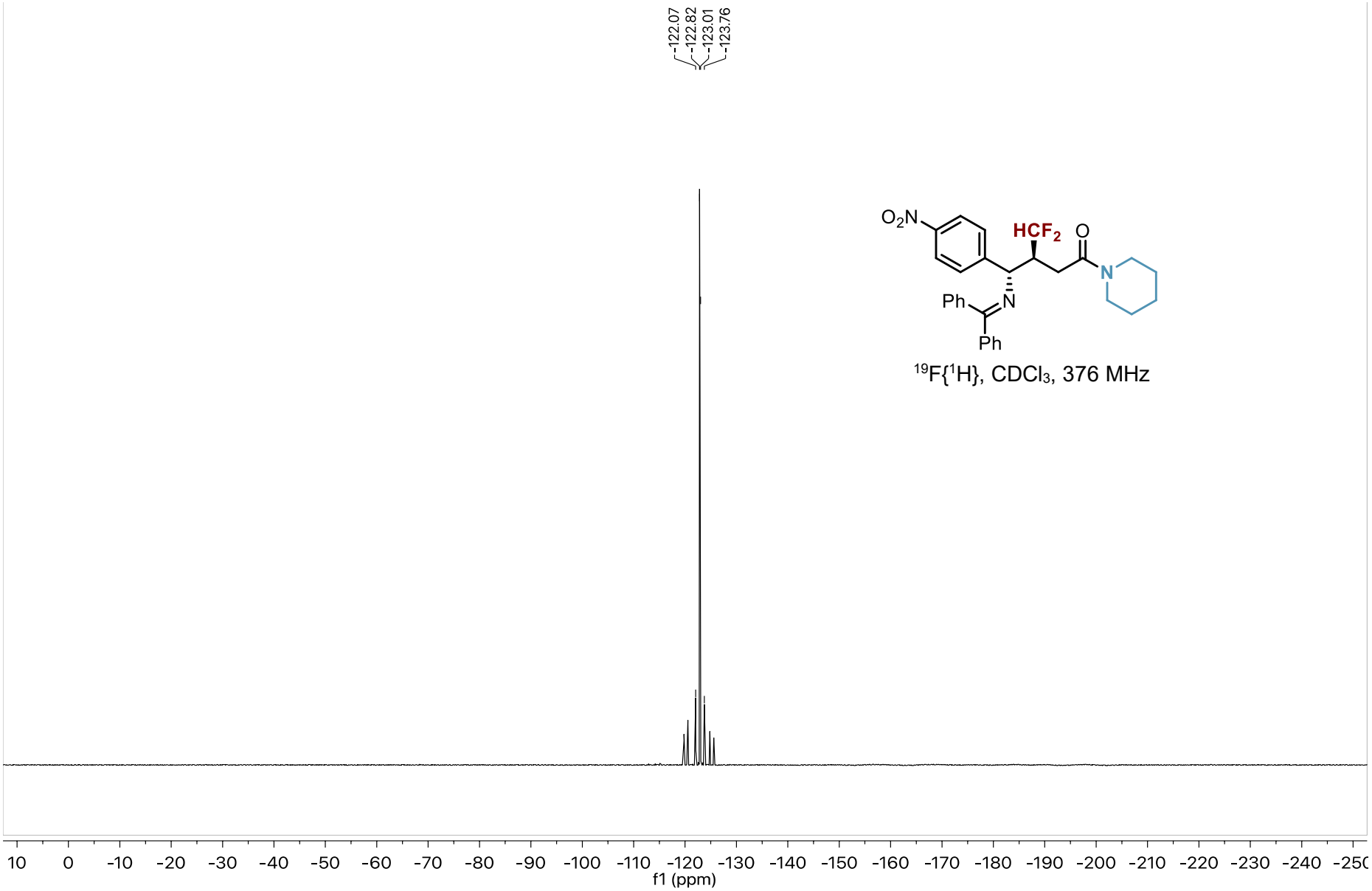
(3*S*,4*S*)-3-(difluoromethyl)-4-((diphenylmethylene)amino)-4-(4-nitrophenyl)-1-(piperidin-1-yl)butan-1-one (18)



Following **General Procedure E,** 4-nitrophenyl (*E*)-4,4-difluorobut-2-enoate (24.3 mg, 0.1 mmol), *N*-(4-nitrobenzyl)-1,1-diphenylmethanimine (47.5 mg, 0.15 mmol), (*R*)-(+)-BTM (2.5 mg, 0.01 mmol), and anhydrous DMF (1 mL) were stirred at room temperature for 8 hours. The reaction mixture was then added with piperidine (14.8 µL, 0.15 mmol) and was stirred for another 16 hours, then purified by flash chromatography (2:1 Hexane:EtOAc) to give the titled compound as an inseparable mixture of diastereomers (89:11 dr) as a colorless oil (14.2 mg, 28%). $[\alpha]_D^{20}$ −19.3 (*c* 1.4, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak IB (95:5 Hexane:IPA, flow rate 1 $mLmin^{-1}$, 254 nm, 30 °C) t_R(*R,R*): 12.5 min, t_R(*S,S*): 15.2 min, 8:92 er; **IR** ν_{max} (thin film): 2937 (Ar-H), 1622 (C=O, amide), 1520 (asymm. NO_2), 1445 (C=C), 1344 (symm. NO_2); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H: 1.49–1.63 (6H, m, CONC(2)H_2C(3)H_2C(4)H_2C(5)H_2C(6)H_2), 2.66 (1H, dd, $^3J_{HH}$ = 16.5, $^4J_{HF}$ = 4.9, $HF_2CCHCH_AH_B$), 2.73 (1H, dd, $^3J_{HH}$ = 16.5, $^4J_{HF}$ = 7.3, $HF_2CCHCH_AH_B$), 3.24 (1H, m, $HF_2CCHCH_AH_B$), 3.38–3.53 (4H, m, CONC(2)H_2C(3)H_2C(4)H_2C(5)H_2C(6)H_2), 4.89 (1H, d, $^3J_{HH}$ = 4.9, C=NC*H*Ar$_3$-NO_2), 5.77–6.05 (1H, td, $^2J_{HF}$ = 66.3, $^3J_{HH}$ = 3.4, CF_2H), 6.92 (2H, m, N=CC(4)Ar$_1$*H*, N=CC(4)Ar$_2$*H*), 7.39–7.47 (8H, m, N=CC(2,3,5,6)Ar$_1$*H*, N=CC(2,3,5,6)Ar$_2$*H*), 7.70 (2H, m, C=NCHC(2,6)Ar$_3$*H*-NO_2), 8.17 (2H, m, C=NCHC(3,5)Ar$_3$*H*-NO_2); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 24.4, 25.4 and 26.4 (CONC(2)H_2*C*(3)H_2*C*(4)H_2*C*(5)H_2C(6)H_2), 27.4 ($HF_2CCHCH_AH_B$), 43.0, 46.55 (t, $^2J_{CF}$ = 18.7, $HF_2CCHCH_AH_B$), 46.63, 63.1 (C=N*C*HAr$_3$-NO_2), 117.4 (t, $^1J_{CF}$ = 242.3, CF_2H), 123.6 (C=NCH*C*(3,5)Ar$_3$-NO_2), 127.2 (N=C*C*(4)Ar$_1$, N=C*C*(4)Ar$_2$), 128.2 and 128.4 (N=C*C*(2,3,5,6)Ar$_1$, N=C*C*(2,3,5,6)Ar$_2$), 128.8 (C=NCH*C*(2,6)Ar$_3$-NO_2), 136.0 and 139.2 (N=C*C*(1)Ar$_1$, N=C*C*(1)Ar$_2$), 147.1 (C=NCH*C*(4)Ar$_3$-NO_2), 149.9 (C=NCH*C*(1)Ar$_3$-NO_2), 168.6 (*C*=O), 170.3 (*C*=N); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: −125.7–−119.8 (2F, d, $^2J_{FH}$ = 282.3, C*F*$_2$H); **HRMS** (NSI$^+$) $C_{29}H_{30}F_2N_3O_3^+$ ([M+H]$^+$) requires 506.2242, found 506.2246 (−0.75 ppm).


8.17
7.70
7.47
7.39
6.92
6.05
5.91
5.77
4.89
3.53
3.38
3.24
2.73
2.66
1.63
1.49
O2N
HCF2
O
N
Ph
N
Ph
1H, CDCl3, 400 MHz
1.99
2.34
8.44
2.00
0.88
0.83
3.50
0.91
0.80
0.79
5.65
f1 (ppm)

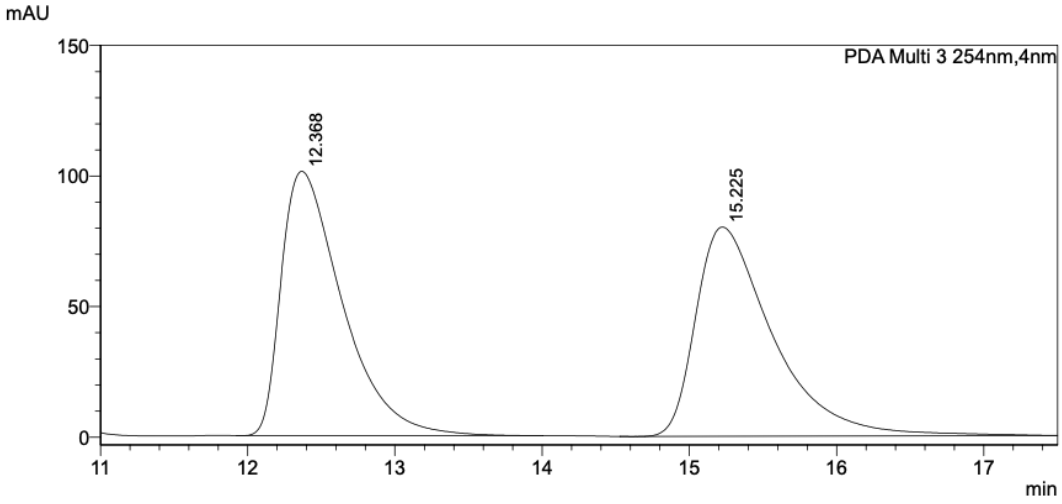

170.27
168.64
149.90
147.06
139.16
136.02
128.76
128.39
128.23
127.18
123.60
119.77
117.36
114.95
63.05
46.73
46.63
46.55
46.36
43.00
27.39
26.37
25.39
24.45
O2N
HCF2
O
N
Ph
N
Ph
13C{1H}, CDCl3, 126 MHz
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


-122.07
-122.82
-123.01
-123.76
O2N
HCF2
O
N
Ph
N
Ph
19F{1H}, CDCl3, 376 MHz
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 -250
f1 (ppm)

HPLC Data for **(3*S*,4*S*)-3-(difluoromethyl)-4-((diphenylmethylene)amino)-4-(4-nitrophenyl)-1-(pipe-ridin-1-yl)butan-1-one**: Chiralpak IB (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 254 nm, 30 °C) t_R(*R,R*): 12.5 min, t_R(*S,S*): 15.2 min, 8:92 er;

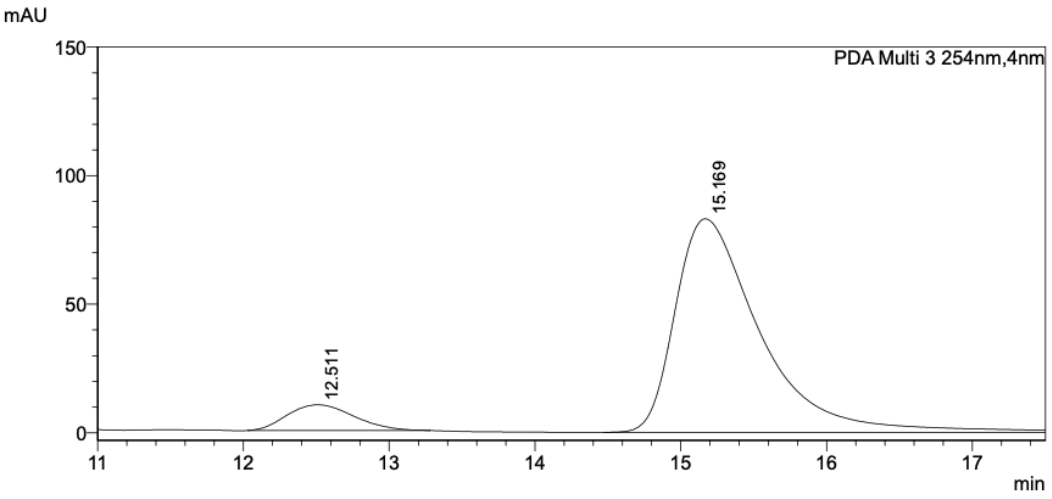
PDA Ch3 254nm

Peak#	Ret. Time	Area%
1	12.368	50.015
2	15.225	49.985
Total		100.000

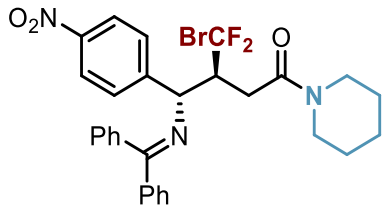


PDA Ch3 254nm

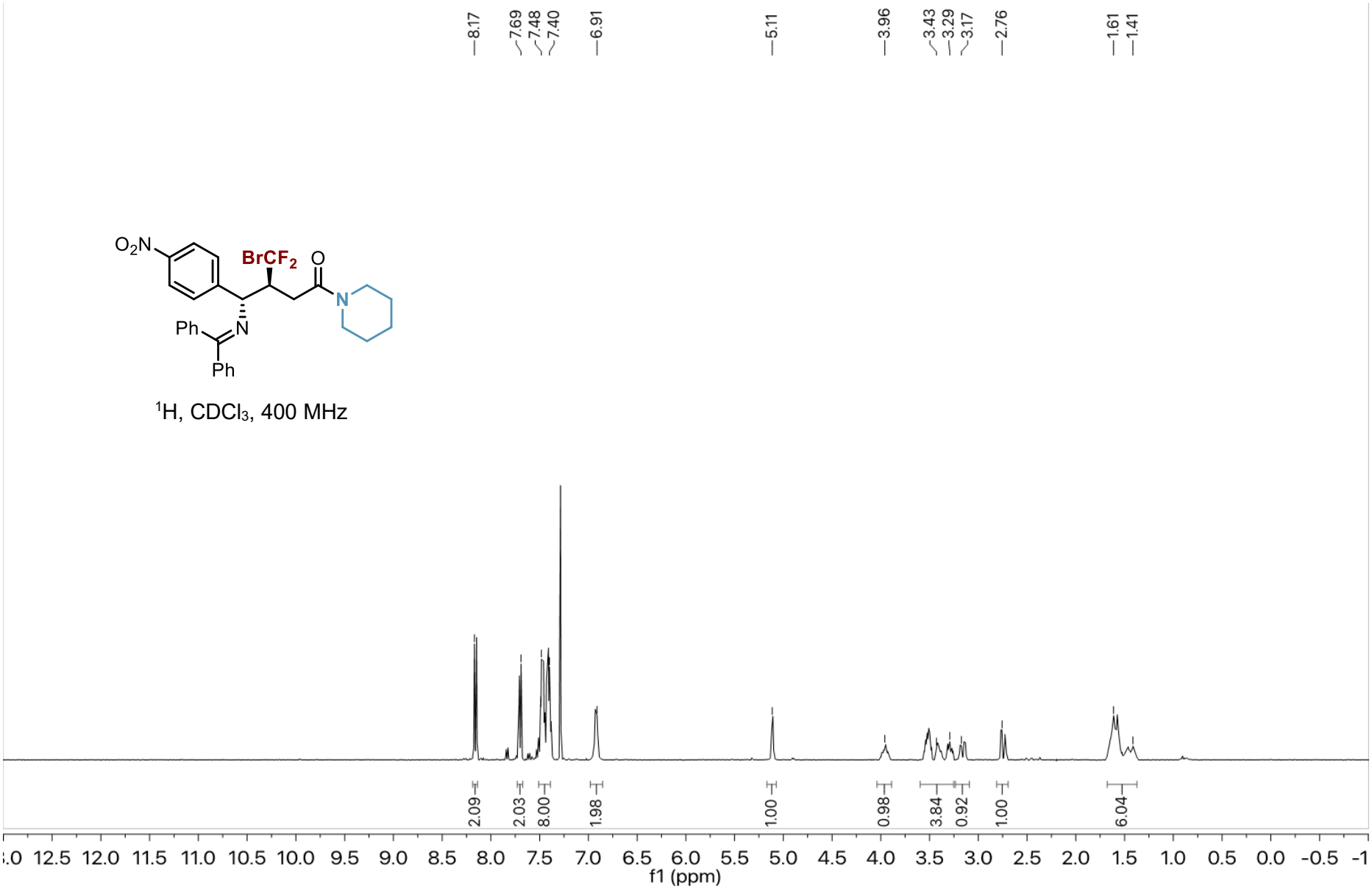
Peak#	Ret. Time	Area%
1	12.511	8.493
2	15.169	91.507
Total		100.000

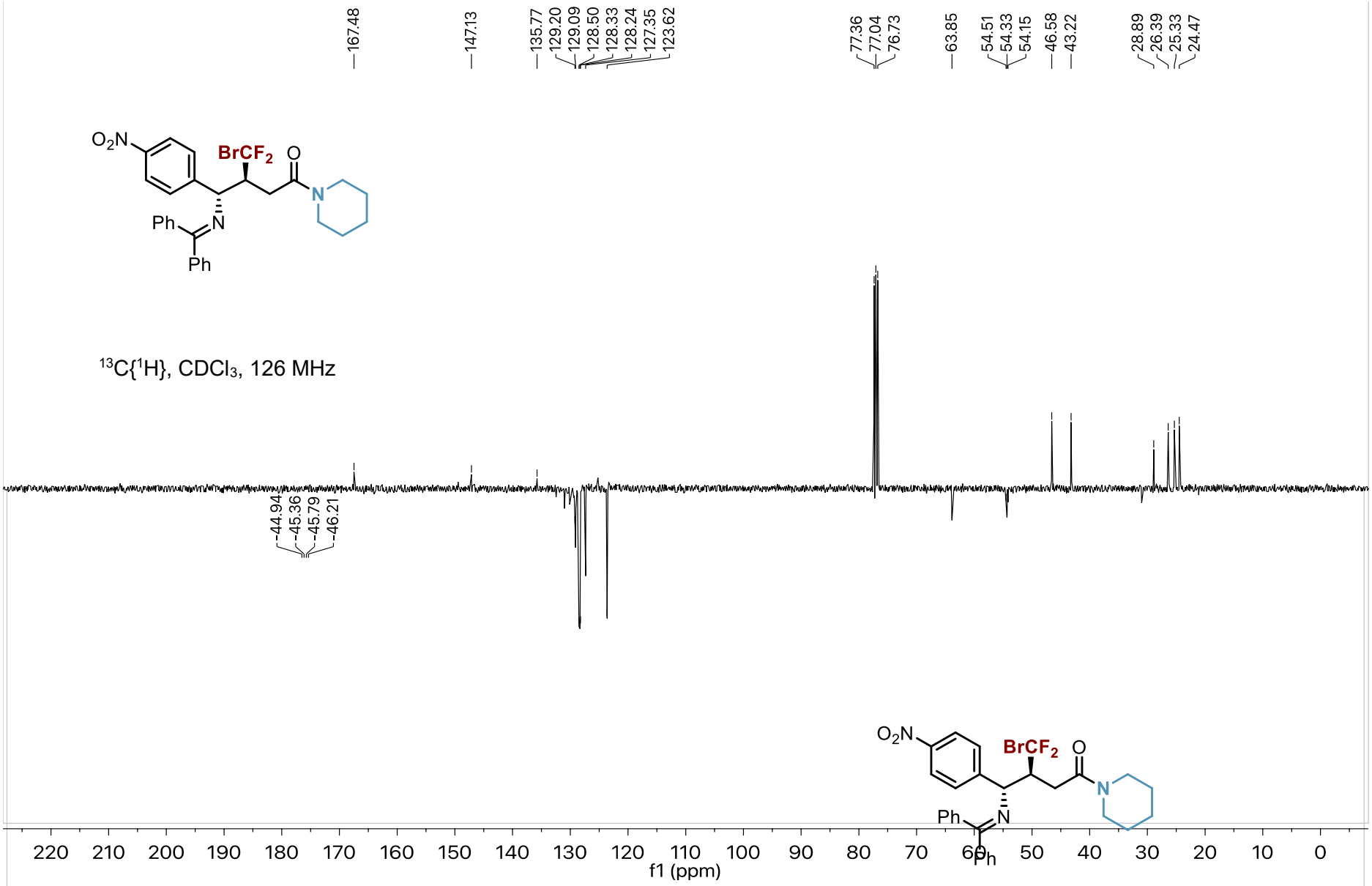


(*S*)-4-bromo-3-((*S*)-((diphenylmethylene)amino)(4-nitrophenyl)methyl)-4,4-difluoro-1-(piperidin-1-yl)butan-1-one (20)



Following **General Procedure E,** 4-nitrophenyl (*E*)-4-bromo-4,4-difluorobut-2-enoate (32.2 mg, 0.1 mmol), *N*-(4-nitrobenzyl)-1,1-diphenylmethanimine (47.5 mg, 0.15 mmol), (*R*)-(+)-BTM (2.5 mg, 0.01 mmol), and anhydrous DMF (1 mL) were stirred at room temperature for 8 hrs. The reaction mixture was then added with piperidine (14.8 µL, 0.15 mmol) and was stirred for another 16 hrs, then purified by flash chromatography 2:1 Hexane:EtOAc (R_f = 0.41) to give the titled compound as an inseparable mixture of diastereomers (96:4 dr) as a colorless oil (28.4 mg, 40%). $[\alpha]_D^{20}$ +6.0 (*c* 1.6, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak IB (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 211 nm, 30 °C) t_R(*R,R*): 9.7 min, t_R(*S,S*): 12.2 min, 11:89 er; **IR** ν_{max} (thin film): 2938 (Ar-H), 1633 (C=O, amide), 1519 (asymm. NO_2), 1445 (C=C), 1344 (symm. NO_2); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H: 1.41–1.61 (6H, m, CONC(2)H_2C(3)*H_2*C(4)*H_2*C(5)*H_2*C(6)H_2), 2.76 (1H, dd, $^3J_{HH}$ = 16.6, $^4J_{HF}$ = 4.9, $BrF_2CCHCH_AH_B$), 3.17 (1H, dd, $^3J_{HH}$ = 16.9, $^4J_{HF}$ = 6.3, $BrF_2CCHCH_AH_B$), 3.29–3.43 (4H, m, CONC(2)*H_2*C(3)H_2C(4)H_2C(5)H_2C(6)*H_2*), 3.96 (1H, m, $BrF_2CCHCH_AH_B$), 5.11 (1H, d, $^3J_{HH}$ = 3.0, C=NC*H*Ar_3-NO_2), 6.91 (2H, m, N=CC(4)Ar_1*H*, N=CC(4)Ar_2*H*), 7.40–7.48 (8H, m, N=CC(2,3,5,6)Ar_1*H*, N=CC(2,3,5,6)Ar_2*H*), 7.69 (2H, m, C=NCHC(2,6)Ar_3*H*-NO_2), 8.17 (2H, m, C=NCHC(3,5)Ar_3*H*-NO_2); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$), δ_C: 24.5, 25.3 and 26.4 (CONC(2)H_2*C*(3)H_2*C*(4)H_2*C*(5)H_2C(6)H_2), 28.9 ($BrF_2CCHCH_AH_B$), 43.2 and 46.6 (CON*C*(2)H_2C(3)H_2C(4)H_2C(5)H_2*C*(6)H_2), 54.3 (t, $^2J_{CF}$ = 17.9, $BrF_2CCHCH_AH_B$), 63.9 (C=N*C*HAr_3-NO_2), 123.6 (C=NCH*C*(3,5)Ar_3-NO_2), 127.4 (N=C*C*(4)Ar_1, N=C*C*(4)Ar_2), 128.2 and 128.3 (N=C*C*(2,3,5,6)Ar_1, N=C*C*(2,3,5,6)Ar_2), 128.5 (-*C*F_2Br), 129.1 (C=NCH*C*(2,6)Ar_3-NO_2), 135.8 (N=C*C*(1)Ar_1, N=C*C*(1)Ar_2), 147.1 (C=NCH*C*(4)Ar_3-NO_2), 149.5 (C=NCH*C*(1)Ar_3-NO_2), 167.5 (*C*=O), 170.9 (*C*=N); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: −46.2–−44.9 (2F, d, $^3J_{FH}$ = 158.5, C*F_2*Br); **HRMS** (NSI$^+$) $C_{29}H_{29}BrF_2N_3O_3^+$ ([M+H]$^+$) requires 584.1355, found 584.1357 (+0.36 ppm).

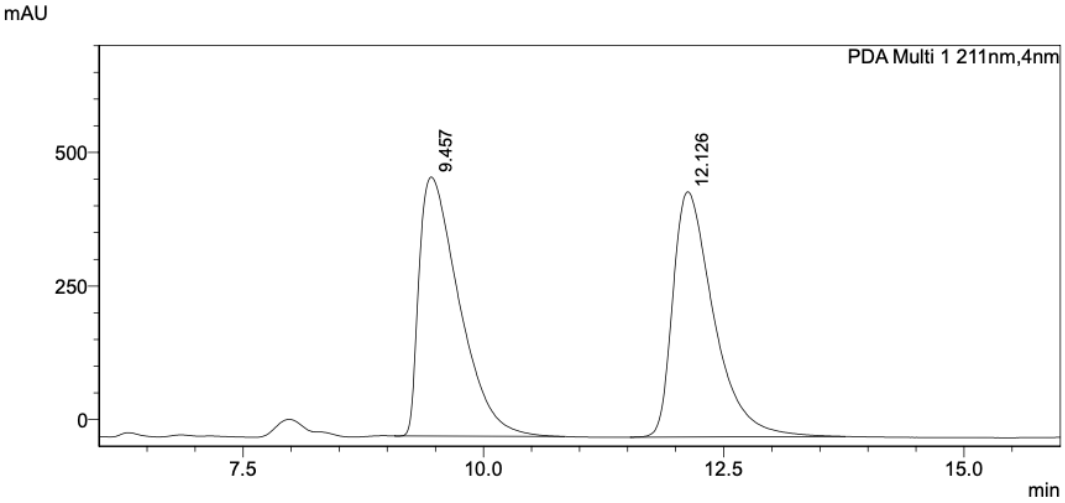

8.17
7.69
7.48
7.40
6.91
5.11
3.96
3.43
3.29
3.17
2.76
1.61
1.41
O2N
BrCF2
O
N
Ph
N
Ph
1H, CDCl3, 400 MHz
2.09
2.03
8.00
1.98
1.00
0.98
3.84
0.92
1.00
6.04
f1 (ppm)


167.48
147.13
135.77
129.20
129.09
128.50
128.33
128.24
127.35
123.62
77.36
77.04
76.73
63.85
54.51
54.33
54.15
46.58
43.22
28.89
26.39
25.33
24.47
O2N
BrCF2
O
N
Ph
N
Ph
13C{1H}, CDCl3, 126 MHz
44.94
45.36
45.79
46.21
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)
19F{1H}, CDCl3, 376 MHz

HPLC Data for **(*S*)-4-bromo-3-((*S*)-((diphenylmethylene)amino)(4-nitrophenyl)methyl)-4,4-difluoro-1-(piperidin-1-yl)butan-1-one**: Chiralpak IB (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 211 nm, 30 °C) t_R(*R,R*): 9.7 min, t_R(*S,S*): 12.2 min, 11:89 er;

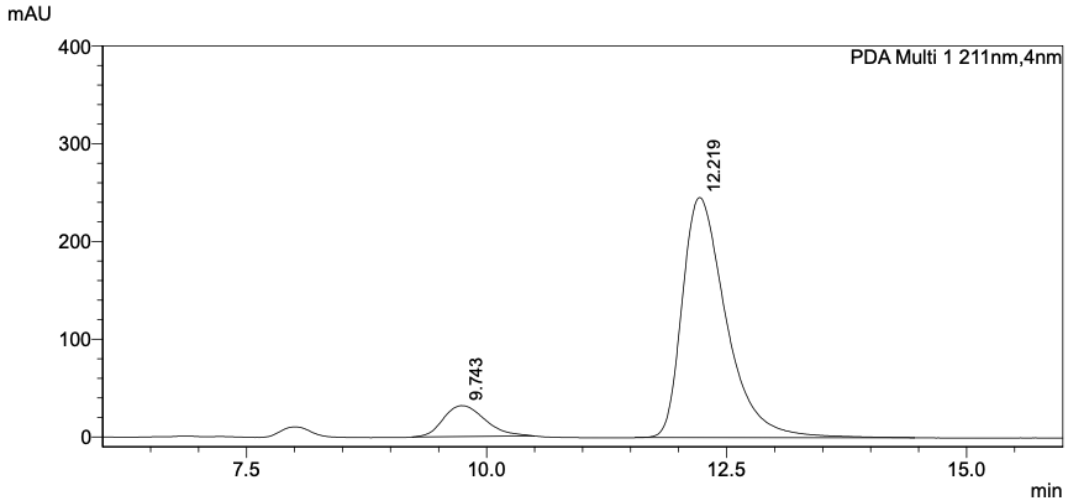
PDA Ch1 211nm

Peak#	Ret. Time	Area%
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2	12.126	49.089
Total		100.000

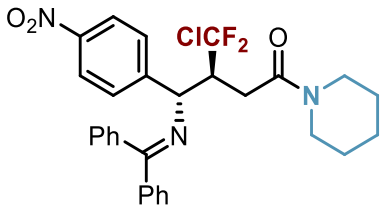


PDA Ch1 211nm

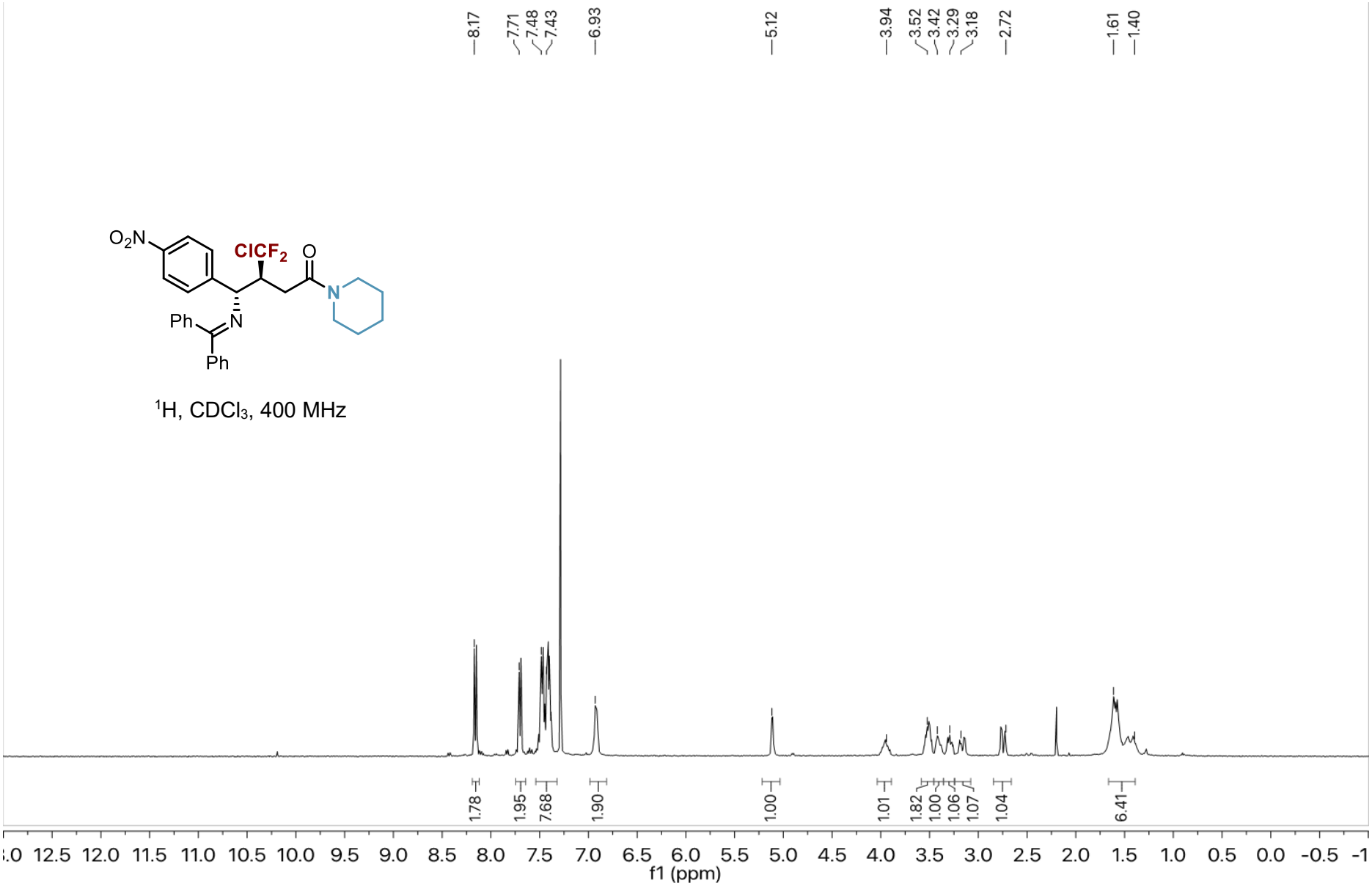
Peak#	Ret. Time	Area%
1	9.743	10.921
2	12.219	89.079
Total		100.000

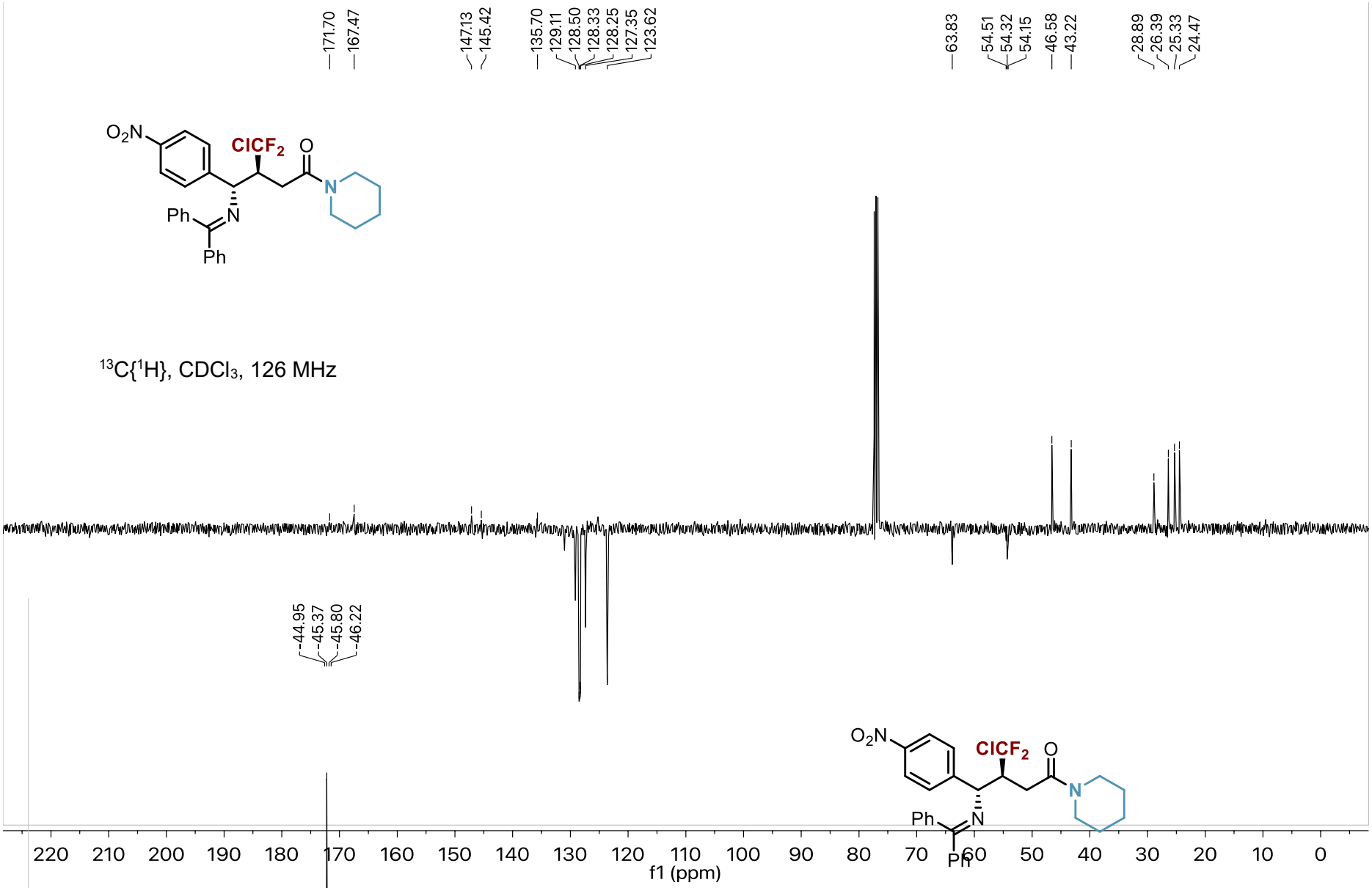


(*S*)-4-chloro-3-((*S*)-((diphenylmethylene)amino)(4-nitrophenyl)methyl)-4,4-difluoro-1-(piperidin-1-yl)butan-1-one (19)



Following **General Procedure E,** 4-nitrophenyl (*E*)-4-chloro-4,4-difluorobut-2-enoate (27.8 mg, 0.1 mmol), *N*-(4-nitrobenzyl)-1,1-diphenylmethanimine (47.5 mg, 0.15 mmol), (*R*)-(+)-BTM (2.5 mg, 0.01 mmol), and anhydrous DMF (1 mL) were stirred at rt for 8 hrs. The reaction mixture was then added with piperidine (14.8 µL, 0.15 mmol) and was stirred for another 16 hrs, then purified by flash chromatography 2:1 Hexane:EtOAc (R_f = 0.53) to give the titled compound as an inseparable mixture of diastereomers (94:6 dr) as a colorless oil (21.1 mg, 39%). $[\alpha]_D^{20}$ –4.3 (*c* 2.1, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak IB (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 270 nm, 30 °C) t_R(*R,R*): 9.6 min, t_R(*S,S*): 12.2 min, 15:85 er; **IR** ν_{max} (thin film): 2938 (Ar-H), 1639 (C=O, amide), 1520 (asymm. NO_2), 1445 (C=C), 1342 (symm. NO_2); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H: 1.40–1.61 (6H, m, CONC(2)H_2C(3)H_2C(4)H_2C(5)H_2C(6)H_2), 2.72 (1H, dd, $^3J_{HH}$ = 16.6, $^4J_{HF}$ = 4.6, $ClF_2CCHCH_AH_B$), 3.18 (1H, dd, $^3J_{HH}$ = 16.6, $^4J_{HF}$ = 5.2, $ClF_2CCHCH_AH_B$), 3.29–3.52 (4H, m, CONC(2)H_2C(3)H_2C(4)H_2C(5)H_2C(6)H_2), 3.94 (1H, m, $ClF_2CCHCH_AH_B$), 5.12 (1H, d, $^3J_{HH}$ = 3.0, C=NC*H*Ar$_3$-NO_2), 6.93 (2H, m, N=CC(4)Ar$_1$*H*, N=CC(4)Ar$_2$*H*), 7.43–7.48 (8H, m, N=CC(2,3,5,6)Ar$_1$*H*, N=CC(2,3,5,6)Ar$_2$*H*), 7.71 (2H, m, C=NCHC(2,6)Ar$_3$*H*-NO_2), 8.17 (2H, m, C=NCHC(3,5)Ar$_3$*H*-NO_2); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 24.5, 25.3 and 26.4 (CONC(2)H_2*C*(3)H_2*C*(4)H_2*C*(5)H_2C(6)H_2), 28.9 ($ClF_2CCHCH_AH_B$), 43.2 and 46.6 (CON*C*(2)H_2C(3)H_2C(4)H_2C(5)H_2*C*(6)H_2), 54.3 (t, $^2J_{CF}$ = 18.1, $ClF_2CCHCH_AH_B$), 63.9 (C=N*C*HAr$_3$-NO_2), 123.6 (C=NCH*C*(3,5)Ar$_3$-NO_2), 127.4 (N=C*C*(4)Ar$_1$, N=C*C*(4)Ar$_2$), 128.2 and 128.3 (N=C*C*(2,3,5,6)Ar$_1$, N=C*C*(2,3,5,6)Ar$_2$), 128.5 (-*C*F_2Cl), 129.1 (C=NCH*C*(2,6)Ar$_3$-NO_2), 135.7 (N=C*C*(1)Ar$_1$, N=C*C*(1)Ar$_2$), 145.4 (C=NCH*C*(1)Ar$_3$-NO_2), 147.1 (C=NCH*C*(4)Ar$_3$-NO_2), 167.5 (*C*=O), 171.7 (*C*=N); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: −46.2–−44.9 (2F, d, $^3J_{FH}$ = 158.4, C*F*$_2$Cl); **HRMS** (NSI$^+$) $C_{29}H_{29}ClF_2N_3O_3^+$ ([M+H]$^+$) requires 540.1860, found 540.1858 (–0.37 ppm).

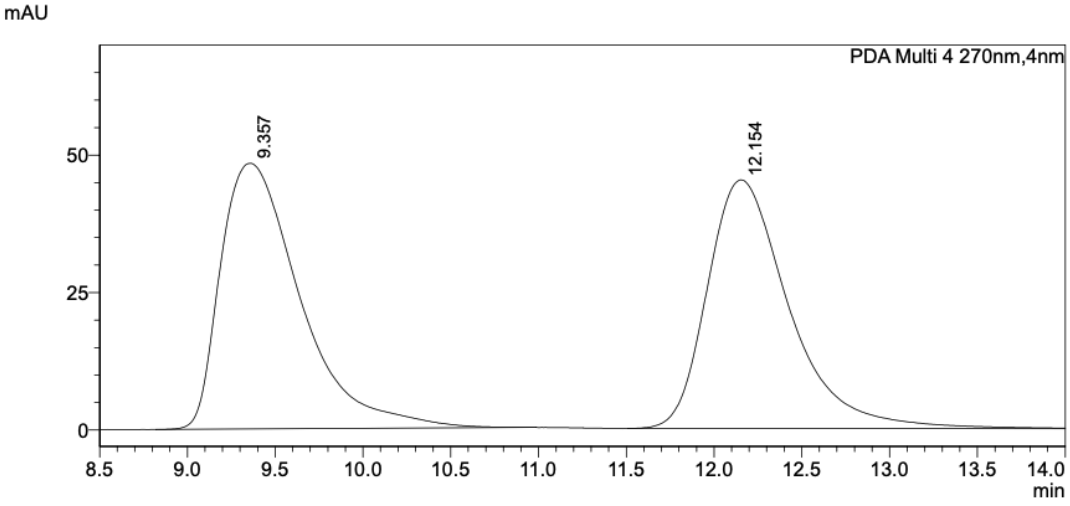

8.17
7.71
7.48
7.43
6.93
5.12
3.94
3.52
3.42
3.29
3.18
2.72
1.61
1.40
O2N
ClCF2
O
N
Ph
N
Ph
1H, CDCl3, 400 MHz
1.78
1.95
7.68
1.90
1.00
1.01
1.82
1.00
1.06
1.07
1.04
6.41
f1 (ppm)


171.70
167.47
147.13
145.42
135.70
129.11
128.50
128.33
128.25
127.35
123.62
63.83
54.51
54.32
54.15
46.58
43.22
28.89
26.39
25.33
24.47
O2N
ClCF2
O
N
Ph
N
Ph
13C{1H}, CDCl3, 126 MHz
-44.95
-45.37
-45.80
-46.22
O2N
ClCF2
O
N
Ph
N
Ph
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)
19F {1H}, CDCl3, 376 MHz

HPLC Data for **(*S*)-4-chloro-3-((*S*)-((diphenylmethylene)amino)(4-nitrophenyl)methyl)-4,4-difluoro-1-(piperidin-1-yl)butan-1-one**: Chiralpak IB (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 270 nm, 30 °C) t_R(*R,R*): 9.6 min, t_R(*S,S*): 12.2 min, 15:85 er;

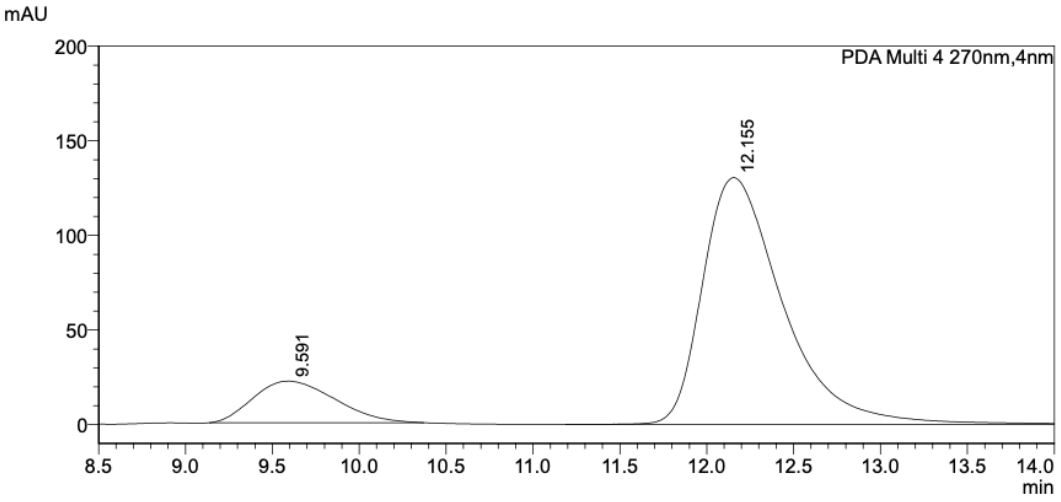
PDA Ch4 270nm

Peak#	Ret. Time	Area%
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2	12.154	49.037
Total		100.000

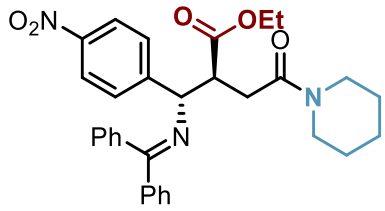


PDA Ch4 270nm

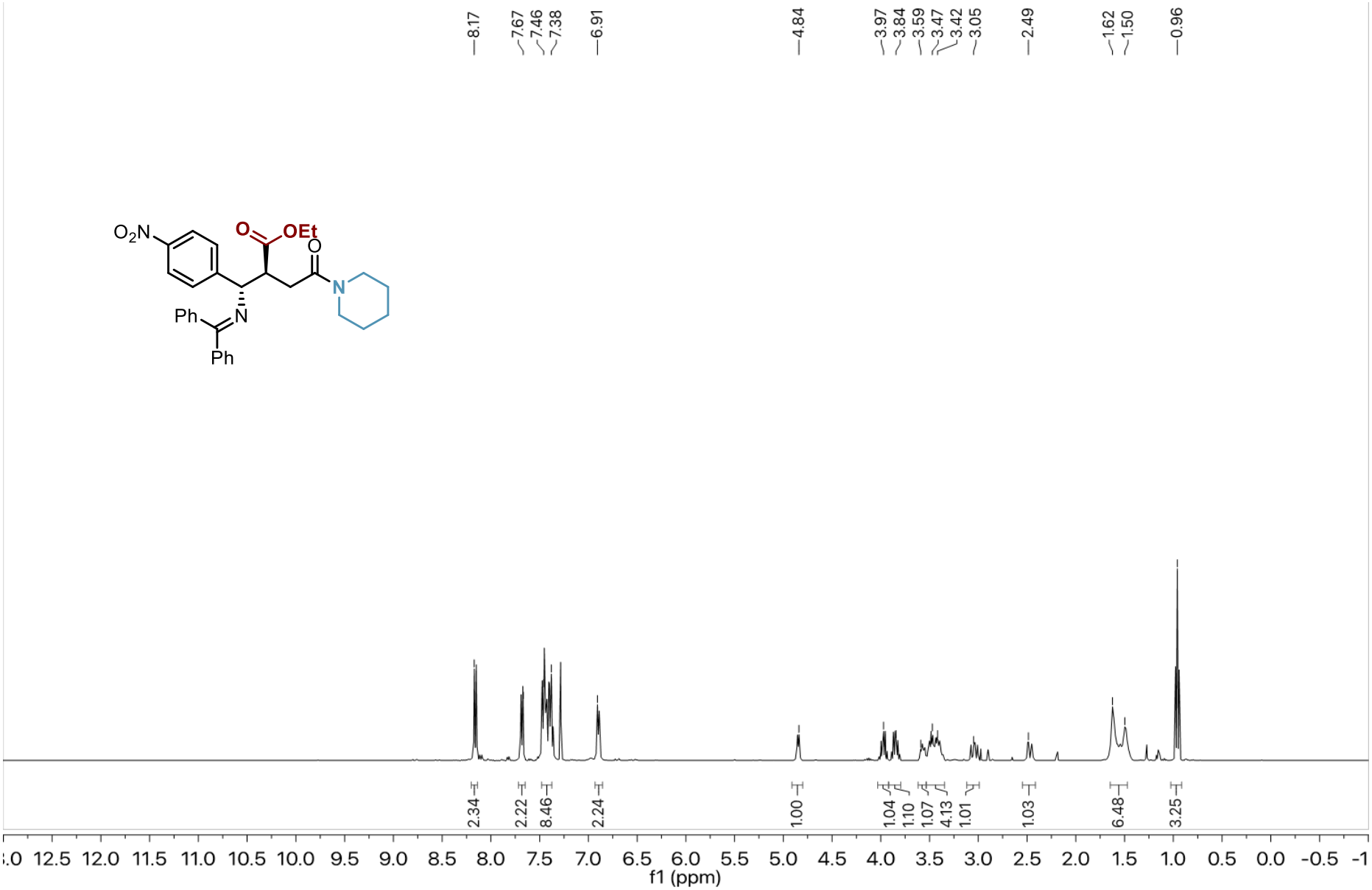
Peak#	Ret. Time	Area%
1	9.591	14.579
2	12.155	85.421
Total		100.000

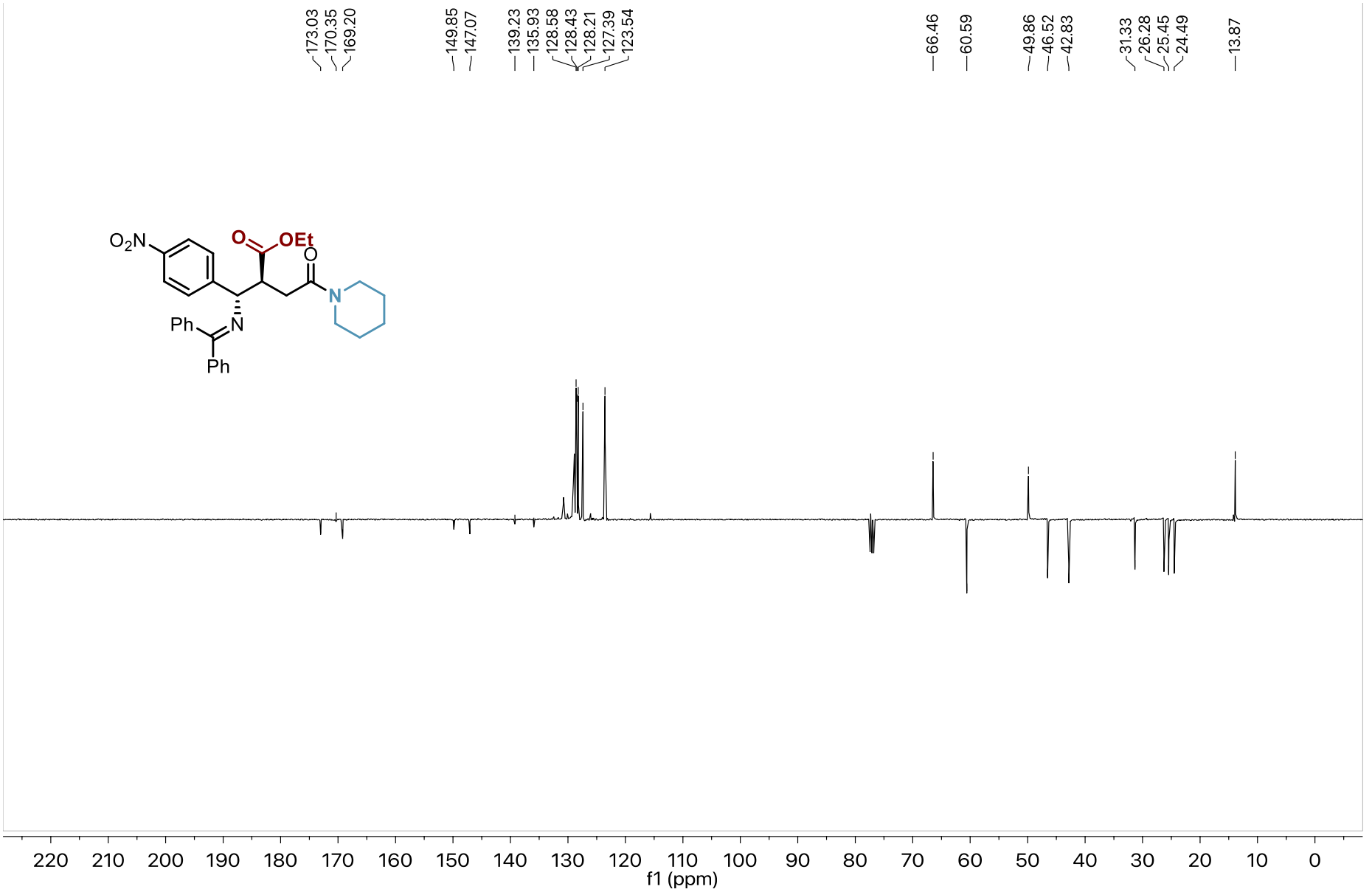


Ethyl (*S*)-2-((*S*)-((diphenylmethylene)amino)(4-nitrophenyl)methyl)-4-oxo-4-(piperidin-1-yl)butanoate (21)



Following **General Procedure E,** Ethyl (4-nitrophenyl) fumarate (26.5 mg, 0.1 mmol), *N*-(4-nitrobenzyl)-1,1-diphenylmethanimine (47.5 mg, 0.15 mmol), (*R*)-(+)-BTM (2.5 mg, 0.01 mmol), and anhydrous DMF (1 mL) was stirred at 0 ºC for 8 hrs. The reaction mixture was then added with piperidine (14.8 µL, 0.15 mmol) and was stirred for another 16 hrs, then purified by flash chromatography 4:1 Hexane:EtOAc (R_f = 0.09) to give the titled compound as an inseparable mixture of diastereomers (89:11 dr) as a colorless oil (39.6 mg, 75%). $[\alpha]_D^{20}$ –5.0 (*c* 4.0, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak IB (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 254 nm, 30 °C) t_R(*S,S*): 16.8 min, t_R(*S,R*): 25.6 min, 91:9 er; **IR** ν_{max} (thin film): 2938 (Ar-H), 1730 (C=O, ester),1638 (C=O, amide), 1519 (asymm. NO_2), 1344 (symm. NO_2); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H: 0.96 (3H, t, $^3J_{HH}$ = 7.1, $CO_2CH_2CH_3$), 1.50–1.65 (6H, m, CONC(2)H_2C(3)H_2C(4)H_2C(5)H_2C(6)H_2), 2.49 (1H, dd, $^2J_{HH}$ = 16.3, $^3J_{HH}$ = 3.1, $EtO_2CCHCH_AH_B$), 3.05 (1H, dd, $^2J_{HH}$ = 16.2, $^3J_{HH}$ = 10.7, $EtO_2CCHCH_AH_B$), 3.42–3.47 (4H, m, CONC(2)H_2C(3)H_2C(4)H_2C(5)H_2C(6)H_2), 3.59 (1H, m, $EtO_2CCHCH_AH_B$), 3.84 (1H, dq, $^2J_{HH}$ = 10.7, $^3J_{HH}$ = 7.1, $CO_2CH_AH_BCH_3$), 3.97 (1H, dq, $^2J_{HH}$ = 10.8, $^3J_{HH}$ = 7.2, $CO_2CH_AH_BCH_3$), 4.84 (1H, d, $^3J_{HH}$ = 6.4, C=NC*H*Ar$_3$-NO_2), 6.91 (2H, m, N=CC(4)Ar$_1$*H*, N=CC(4)Ar$_2$*H*), 7.38 – 7.46 (8H, m, N=CC(2,3,5,6)Ar$_1$*H*, N=CC(2,3,5,6)Ar$_2$*H*), 7.67 (2H, m, C=NCHC(2,6)Ar$_3$*H*-NO_2), 8.17 (2H, m, C=NCHC(3,5)Ar$_3$*H*-NO_2); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$), δ_C: 13.9 ($CO_2CH_2CH_3$), 24.5, 25.4 and 26.3 (CONC(2)H_2C(3)H_2C(4)H_2C(5)H_2C(6)H_2), 31.3 ($EtO_2CCHCH_AH_B$), 42.8 and 46.5 (CONC(2)H_2C(3)H_2C(4)H_2C(5)H_2C(6)H_2), 49.9 ($EtO_2CCHCH_AH_B$), 60.6 ($CO_2CH_2CH_3$), 66.5 (C=NCHAr$_3$-NO_2), 123.5 (C=NCHC(3,5)Ar$_3$-NO_2), 127.4 (N=CC(4)Ar$_1$, N=CC(4)Ar$_2$), 128.2 and 128.4 (N=CC(2,3,5,6)Ar$_1$, N=CC(2,3,5,6)Ar$_2$), 128.6 (C=NCHC(2,6)Ar$_3$-NO_2), 135.9 and 139.2 (N=CC(1)Ar$_1$, N=CC(1)Ar$_2$), 147.1 (C=NCHC(4)Ar$_3$-NO_2), 149.9 (C=NCHC(1)Ar$_3$-NO_2), 169.2 ($EtO_2CCHCH_AH_BC$=O), 170.4 (C=N), 173.0 ($EtO_2CCHCH_AH_BC$=O); **HRMS** (NSI$^+$) $C_{31}H_{34}N_3O_5^+$ ([M+H]$^+$) requires 528.2493, found 528.2475 (+3.4 ppm).

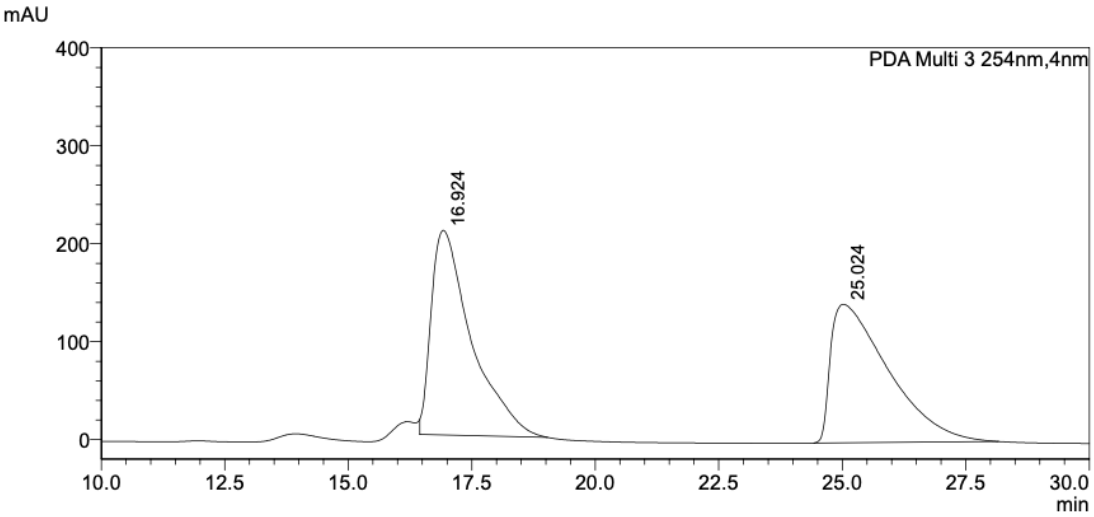

8.17
7.67
7.46
7.38
6.91
4.84
3.97
3.84
3.59
3.47
3.42
3.05
2.49
1.62
1.50
0.96
O2N
O
OEt
O
N
Ph
N
Ph
2.34
2.22
8.46
2.24
1.00
1.04
1.10
1.07
4.13
1.01
1.03
6.48
3.25
f1 (ppm)


173.03
170.35
169.20
149.85
147.07
139.23
135.93
128.58
128.43
128.21
127.39
123.54
66.46
60.59
49.86
46.52
42.83
31.33
26.28
25.45
24.49
13.87
O2N
O
OEt
O
N
Ph
N
Ph
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

HPLC Data for **Ethyl (*S*)-2-((*S*)-((diphenylmethylene)amino)(4-nitrophenyl)methyl)-4-oxo-4-(piperidin-1-yl)butanoate:** Chiralpak IB (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 254 nm, 30 °C) t_R(*S,S*): 16.8 min, t_R(*R,R*): 25.6 min, 91:9 er;

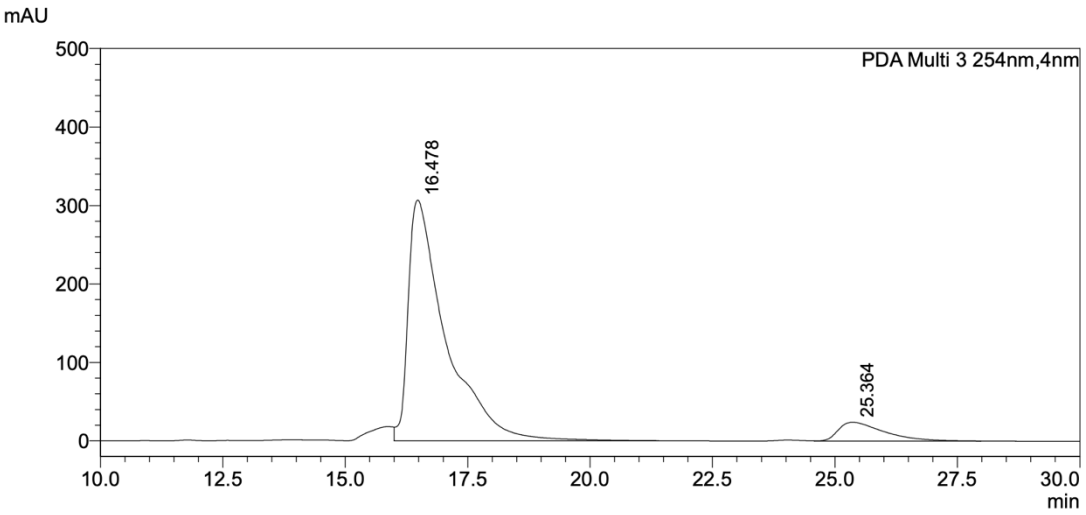
PDA Ch3 254nm

Peak#	Ret. Time	Area%
1	16.924	50.805
2	25.024	49.195
Total		100.000

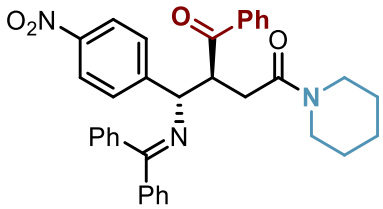


PDA Ch3 254nm

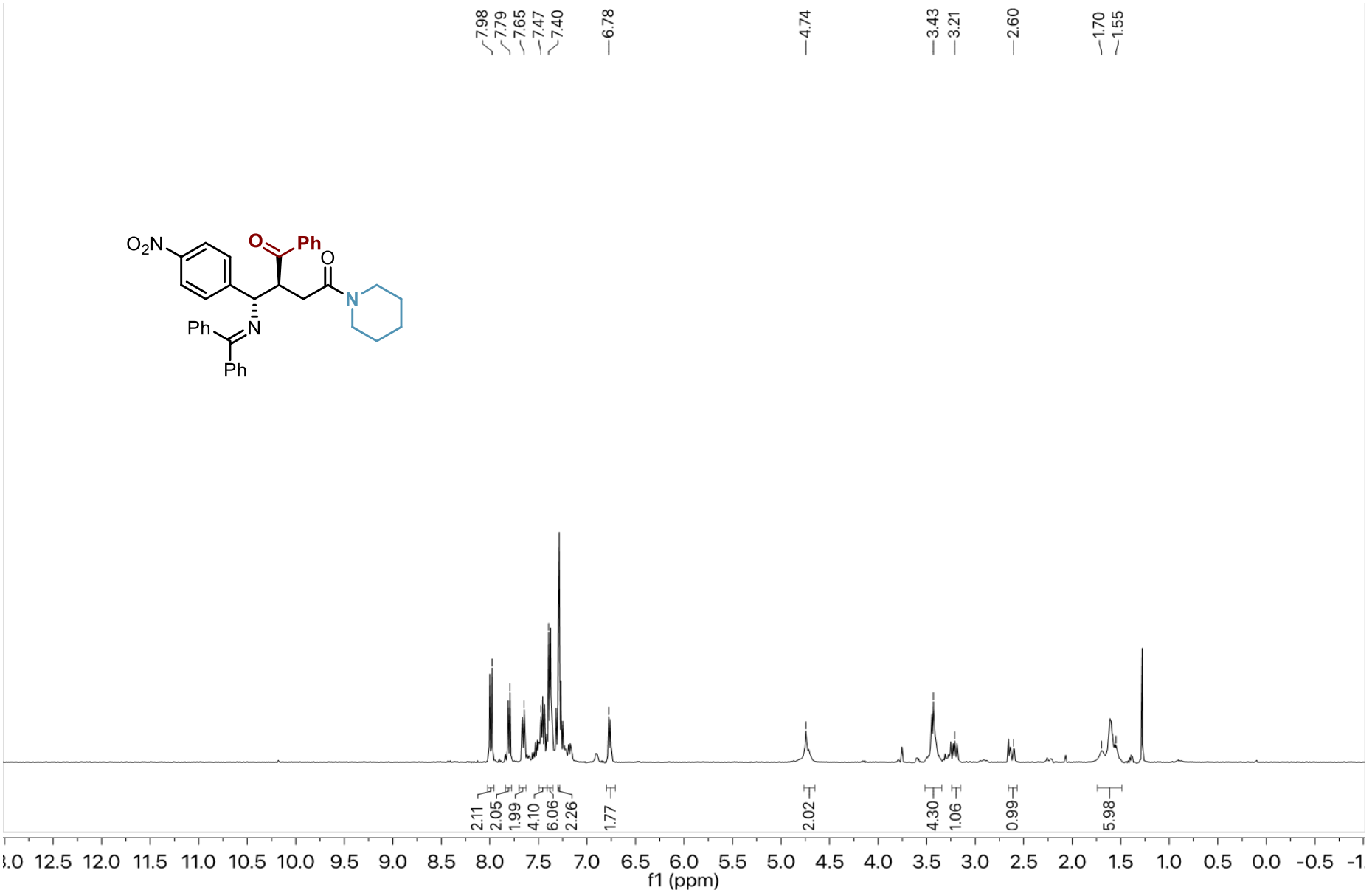
Peak#	Ret. Time	Area%
1	16.478	91.373
2	25.364	8.627
Total		100.000

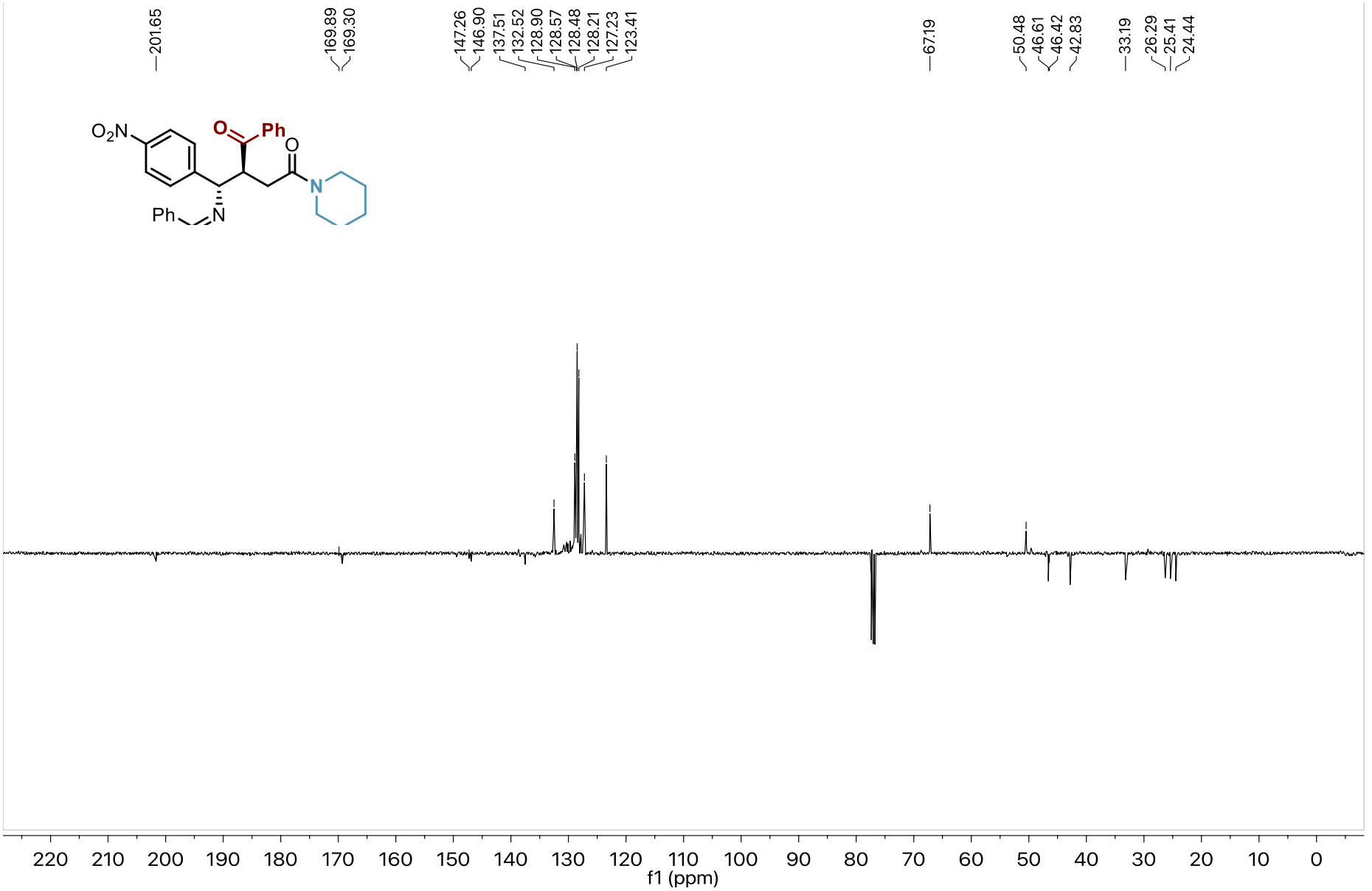


(*S*)-2-((*S*)-((diphenylmethylene)amino)(4-nitrophenyl)methyl)-1-phenyl-4-(piperidin-1-yl)butane-1,4-dione (23)



Following **General Procedure E,** (*E*)-4-oxo-4-phenylbut-2-enoate (29.7 mg, 0.1 mmol), *N*-(4-nitrobenzyl)-1,1-diphenylmethanimine (47.5 mg, 0.15 mmol), (*R*)-(+)-BTM (2.5 mg, 0.01 mmol), and anhydrous DMF (1 mL) was stirred at rt for 8 hrs. The reaction mixture was then added with piperidine (14.8 µL, 0.15 mmol) and was stirred for another 16 hrs, then purified by flash chromatography 4:1 Hexane:EtOAc (R_f = 0.09) to give the titled compound as an inseparable mixture of diastereomers (85:15 dr) as a colorless oil (19.6 mg, 35%). $[\alpha]_D^{20}$ +47.9 (*c* 2.0, $CHCl_3$); **Chiral HPLC analysis:** Chiralpak IA (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 254 nm, 30 °C) **major diastereomer** t_R(*S,R*): 25.8 min, t_R(*S,S*): 48.7 min, 15:85 er; **IR** ν_{max} (thin film): 2932 (Ar-H), 1633 (C=O, amide), 1519 (asymm. NO_2), 1344 (symm. NO_2); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H: 1.55–1.70 (6H, m, CONC(2)H_2C(3)*H_2*C(4)*H_2*C(5)*H_2*C(6)H_2), 2.60 (1H, dd, $^2J_{HH}$ = 16.3, $^3J_{HH}$ = 2.9, PhOCCHC*H_A*H_B), 3.21 (1H, dd, $^2J_{HH}$ = 16.1, $^3J_{HH}$ = 9.8, PhOCCHCH_A*H_B*), 3.43 (4H, m, CONC(2)*H_2*C(3)H_2C(4)H_2C(5)H_2C(6)*H_2*), 4.74 (2H, m, C=NC*H*Ar$_3$-NO_2, PhOCC*H*C$H_A$$H_B$), 6.78 (2H, d, $^3J_{HH}$ = 7.2, CON(CH_2C(4)Ar*H*)$_2$), 7.27–7.40 (8H, m, N=CC(2,3,5,6)Ar$_1$*H*, N=CC(2,3,5,6)Ar$_2$*H*), 7.47 (3H, m, COC(3,4,5)Ar*H*), 7.65 (2H, m, C=NCHC(2,6)Ar$_3$*H*-NO_2), 7.79 (COC(2,6)Ar*H*), 7.98 (2H, m, C=NCHC(3,5)Ar$_3$*H*-NO_2); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$), δ_C: 24.4, 25.4 and 26.3 (CONC(2)H_2*C*(3)H_2*C*(4)H_2*C*(5)H_2C(6)H_2), 33.2 (PhOCCH*C*$H_A$$H_B$), 42.8 and 46.6 (CON*C*(2)H_2C(3)H_2C(4)H_2C(5)H_2*C*(6)H_2), 50.5 (PhOC*C*HC$H_A$$H_B$), 67.2 (C=N*C*HAr$_3$-$NO_2$), 123.4 (C=NCH*C*(3,5)Ar$_3$-NO_2), 127.2 ((N=C*C*(4)Ar$_1$, N=C*C*(4)Ar$_2$), 128.2 and 128.5 (N=C*C*(2,3,5,6)Ar$_1$, N=C*C*(2,3,5,6)Ar$_2$, CO*C*(3,4,5)Ar), 128.6 (CO*C*(2,6)Ar), 128.9 (C=NCH*C*(2,6)Ar$_3$-NO_2), 132.5 (CO*C*(1)Ar), 137.5 (N=C*C*(1)Ar$_1$, N=C*C*(1)Ar$_2$), 146.9 (C=NCH*C*(1)Ar$_3$-NO_2), 147.3 (C=NCH*C*(4)Ar$_3$-NO_2), 169.3 (*C*ONC$_6$H$_{10}$), 169.9 (*C*=N), 201.7(*C*OPh); **HRMS** (NSI$^+$) $C_{35}H_{33}N_3O_4^+$ ([M+H]$^+$) requires 560.2549, found 560.2528 (−2.8 ppm).


7.98
7.79
7.65
7.47
7.40
6.78
4.74
3.43
3.21
2.60
1.70
1.55
O2N
O
Ph
O
N
Ph
N
Ph
2.11
2.05
1.99
4.10
6.06
2.26
1.77
2.02
4.30
1.06
0.99
5.98
f1 (ppm)

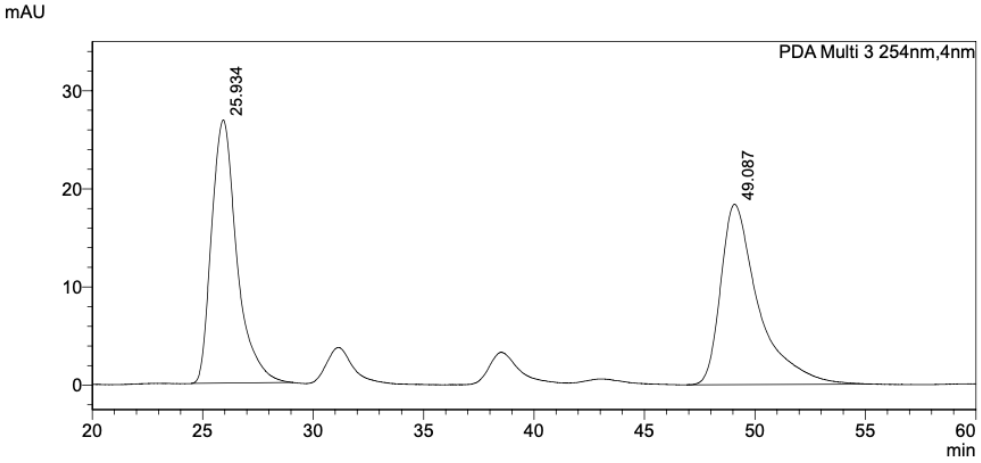

201.65
169.89
169.30
147.26
146.90
137.51
132.52
128.90
128.57
128.48
128.21
127.23
123.41
67.19
50.48
46.61
46.42
42.83
33.19
26.29
25.41
24.44
O2N
O
Ph
O
N
Ph
N
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

HPLC Data for **(*S*)-2-((*S*)-((diphenylmethylene)amino)(4-nitrophenyl)methyl)-1-phenyl-4-(piperidin-1-yl)butane-1,4-dione:** Chiralpak IA (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 254 nm, 30 °C) **major diastereomer** t_R(*S,R*): 25.8 min ,t_R(*S,S*): 48.7 min, 15:85 er;

Major Diastereomer

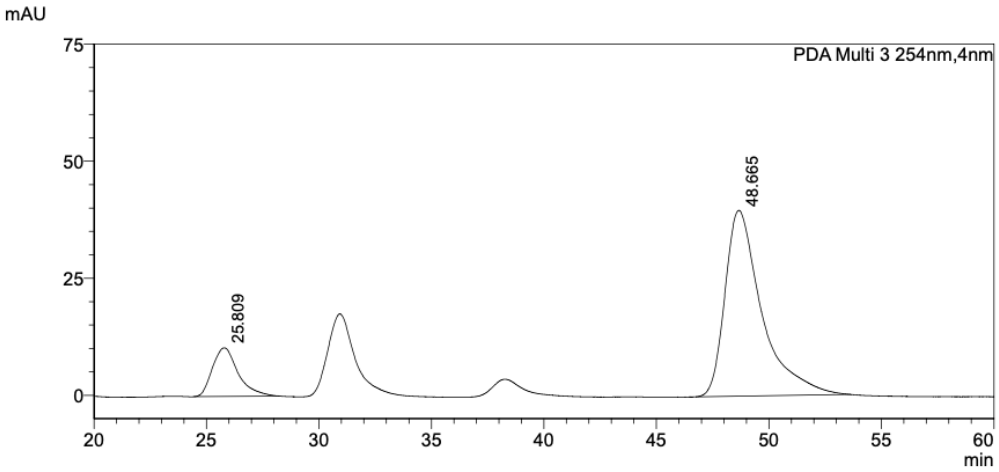
PDA Ch3 254nm

Peak#	Ret. Time	Area%
1	25.934	49.451
2	49.087	50.549
Total		100.000

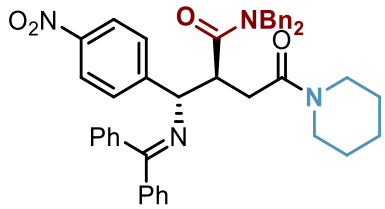


PDA Ch3 254nm

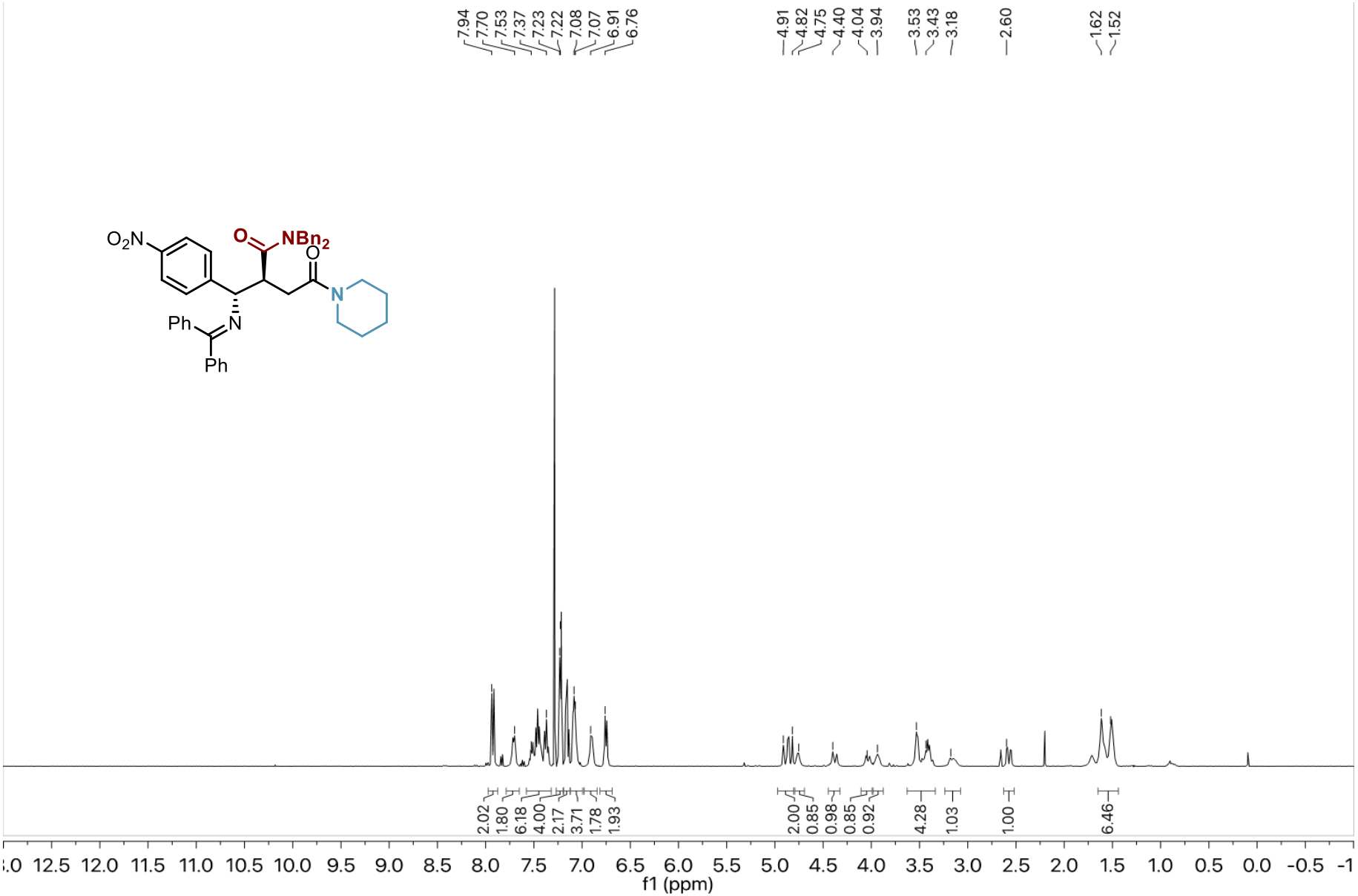
Peak#	Ret. Time	Area%
1	25.809	15.420
2	48.665	84.580
Total		100.000

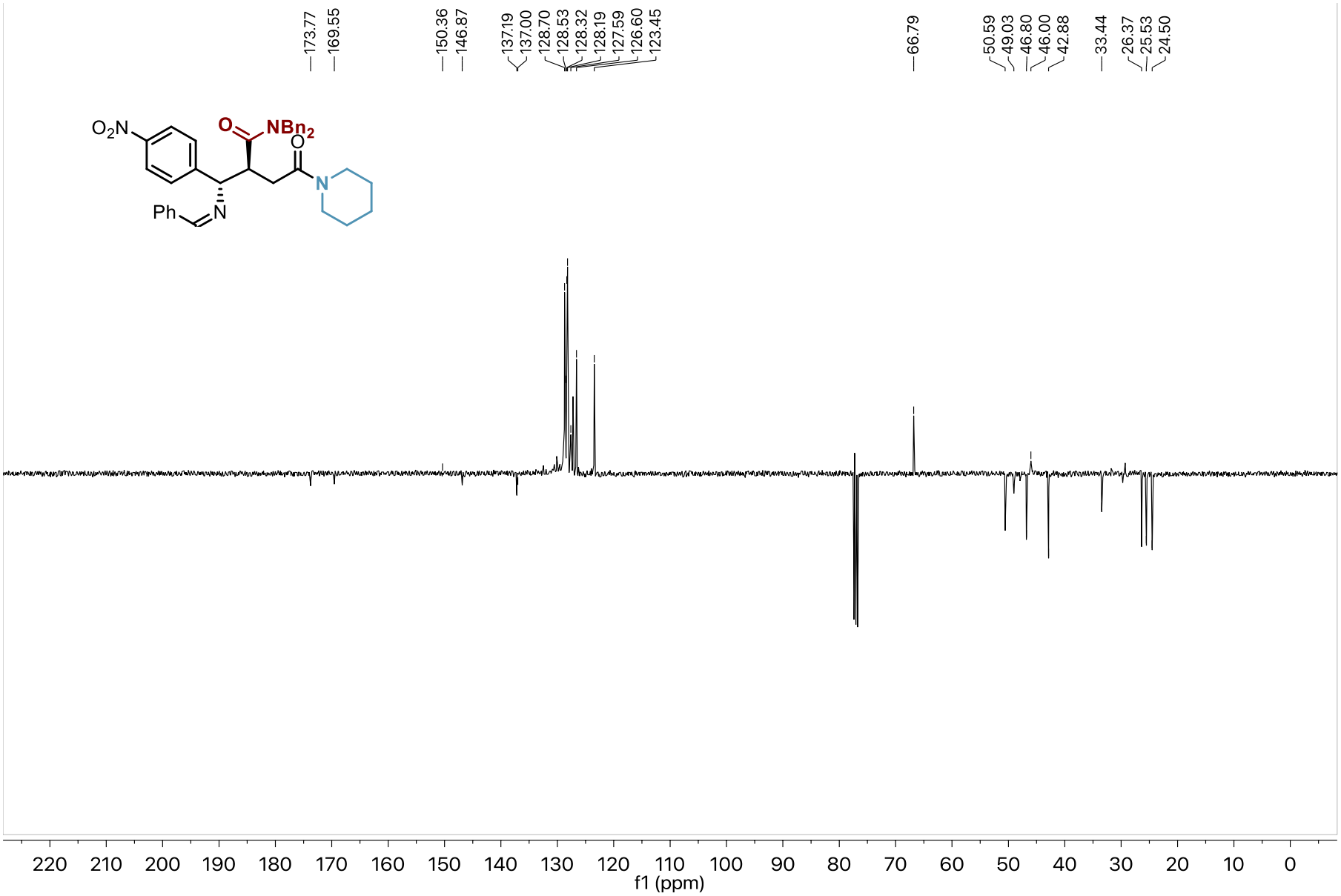


(*S*)-*N*,*N*-dibenzyl-2-((*S*)-((diphenylmethylene)amino)(4-nitrophenyl)methyl)-4-oxo-4-(piperidin-1-yl)butanamide (22)



Following **General Procedure E,** (*E*)-4-(dibenzylamino)-4-oxobut-2-enoate (41.6 mg, 0.1 mmol), *N*-(4-nitrobenzyl)-1,1-diphenylmethanimine (47.5 mg, 0.15 mmol), (*R*)-(+)-BTM (2.5 mg, 0.01 mmol), and anhydrous DMF (1 mL) were stirred at rt for 8 hrs. The reaction mixture was then added with piperidine (14.8 µL, 0.15 mmol) and was stirred for another 16 hrs, then purified by flash chromatography 4:1 Hexane:EtOAc (R_f = 0.09) to give the titled compound as an inseparable mixture of diastereomers (97:3 dr) as a colorless oil (26.4 mg, 20%). $[\alpha]_D^{20}$ +6.3 (*c* 1.2, $CHCl_3$); **Chiral HPLC analysis:** Chiralpak IA (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 254 nm, 30 °C) t_R(*S,R*): 15.5 min, t_R(*S,S*): 32.3 min, 3:97 er; **IR** ν_{max} (thin film): 2936 (Ar-H), 1638 (C=O, amide), 1519 (asymm. NO_2), 1344 (symm. NO_2); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H: 1.52–1.62 (6H, m, CONC(2)H_2C(3)H_2C(4)H_2C(5)H_2C(6)H_2), 2.60 (1H, dd, $^2J_{HH}$ = 15.8, $^3J_{HH}$ = 3.6, Bn_2NOCCHC$H_A$$H_B$), 3.18 (1H, m, , Bn_2NOCCHC$H_A$$H_B$), 3.43–3.53 (4H, m, CONC(2)H_2C(3)H_2C(4)H_2C(5)H_2C(6)H_2), 3.94 (1H, m, Bn_2NOCC*H*C$H_A$$H_B$), 4.04–4.40 (2H, d, $^2J_{HH}$ = 15.8, CON(C$H_A$$H_B$Ph)$_2$), 4.75 (1H, s, C=NC*H*Ar$_3$-NO_2), 4.82–4.91 (CON(C$H_A$$H_B$Ph)$_2$), 6.76 (2H, d, $^3J_{HH}$ = 7.4, CON(CH_2C(4)Ar*H*)$_2$), 6.91 (2H, m, N=CC(4)Ar$_1$*H*, N=CC(4)Ar$_2$*H*), 7.07–7.08 (4H, m, CON(CH_2C(3,5)Ar*H*)$_2$), 7.22–7.23 (4H, m, CON(CH_2C(2,6)Ar*H*)$_2$), 7.37–7.53 (8H, m, N=CC(2,3,5,6)Ar$_1$*H*, N=CC(2,3,5,6)Ar$_2$*H*), 7.70 (2H, m, C=NCHC(2,6)Ar$_3$*H*-NO_2), 7.94 (2H, m, C=NCHC(3,5)Ar$_3$*H*-NO_2); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$), δ_C: 24.5, 25.5 and 26.4 (CONC(2)H_2*C*(3)H_2*C*(4)H_2*C*(5)H_2C(6)H_2), 33.4 (Bn_2NOCCH*C*$H_A$$H_B$), 42.9 and 46.8 (CON*C*(2)H_2C(3)H_2C(4)H_2C(5)H_2*C*(6)H_2), 46.0 (Bn_2NOC*C*HC$H_A$$H_B$), 49.1 and 50.6 (CON(*C*H_2Ph)$_2$), 66.8 (C=N*C*HAr$_3$-NO_2), 123.5 (C=NCH*C*(3,5)Ar$_3$-NO_2), 126.6 (CON(CH_2*C*(4)Ar)$_2$), 127.6 (N=C*C*(4)Ar$_1$, N=C*C*(4)Ar$_2$), 128.2 (CON(CH_2*C*(2,3,5,6)Ar)$_2$), 128.3 and 128.5 (N=C*C*(2,3,5,6)Ar$_1$, N=C*C*(2,3,5,6)Ar$_2$), 128.7 (C=NCH*C*(2,6)Ar$_3$-NO_2), 137.0 (CON(CH_2*C*(1)Ar)$_2$), 137.2 (N=C*C*(1)Ar$_1$, N=C*C*(1)Ar$_2$), 146.9 (C=NCH*C*(1)Ar$_3$-NO_2), 150.4 (C=NCH*C*(4)Ar$_3$-NO_2), 169.6 (*C*ONC$_6$H$_{10}$), 173.8 (*C*=N, *C*ON(CH_2Ph)$_2$); **HRMS** (NSI$^+$) $C_{43}H_{43}N_4O_4^+$ ([M+H]$^+$) requires 679.3278, found 679.3279 (−0.03 ppm).

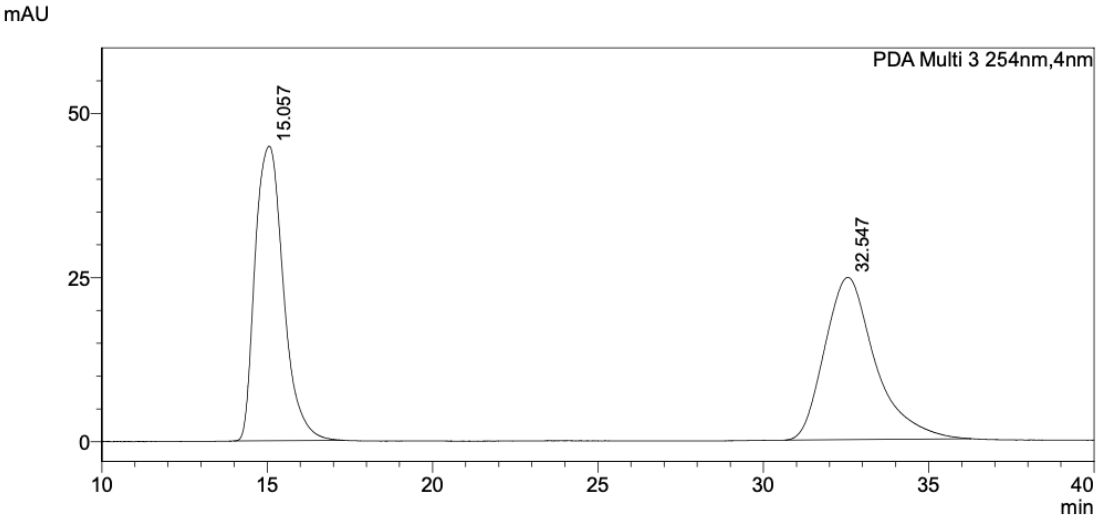

7.94
7.70
7.53
7.37
7.23
7.22
7.08
7.07
6.91
6.76
4.91
4.82
4.75
4.40
4.04
3.94
3.53
3.43
3.18
2.60
1.62
1.52
O2N
O
NBn2
O
N
Ph
N
Ph
2.02
1.80
6.18
4.00
2.17
3.71
1.78
1.93
2.00
0.85
0.98
0.85
0.92
4.28
1.03
1.00
6.46
f1 (ppm)


173.77
169.55
150.36
146.87
137.19
137.00
128.70
128.53
128.32
128.19
127.59
126.60
123.45
66.79
50.59
49.03
46.80
46.00
42.88
33.44
26.37
25.53
24.50
O2N
O
NBn2
O
N
Ph
N
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

HPLC Data for **(*S*)-*N*,*N*-dibenzyl-2-((*S*)-((diphenylmethylene)amino)(4-nitrophenyl)methyl)-4-oxo-4-(piperidin-1-yl)butanamide:** Chiralpak IA (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 254 nm, 30 °C) t_R(*S,R*): 15.5 min , t_R(*S,S*): 32.3 min, 3:97 er;

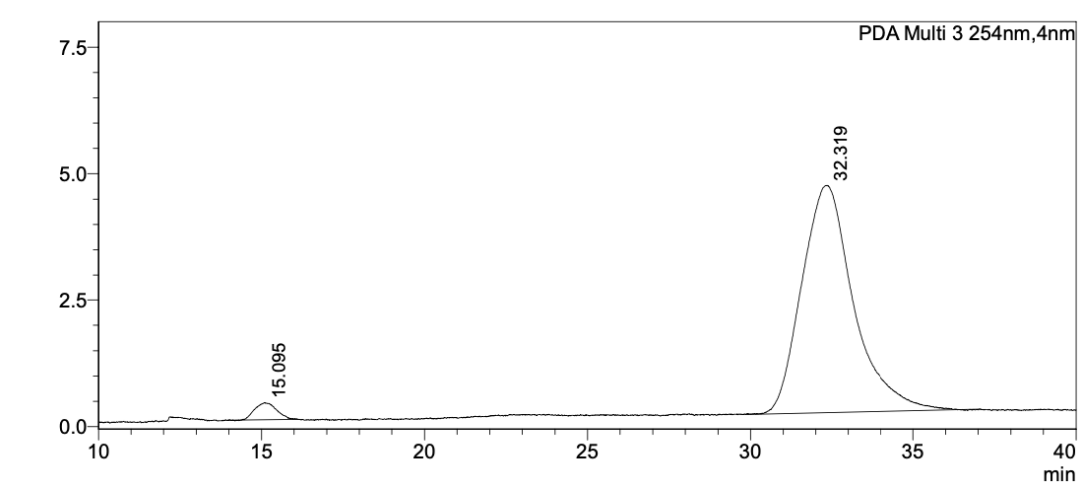
PDA Ch3 254nm

Peak#	Ret. Time	Area%
1	15.057	50.488
2	32.547	49.512
Total		100.000



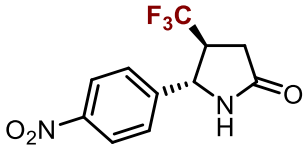
PDA Ch3 254nm

Peak#	Ret. Time	Area%
1	15.095	3.114
2	32.319	96.886
Total		100.000

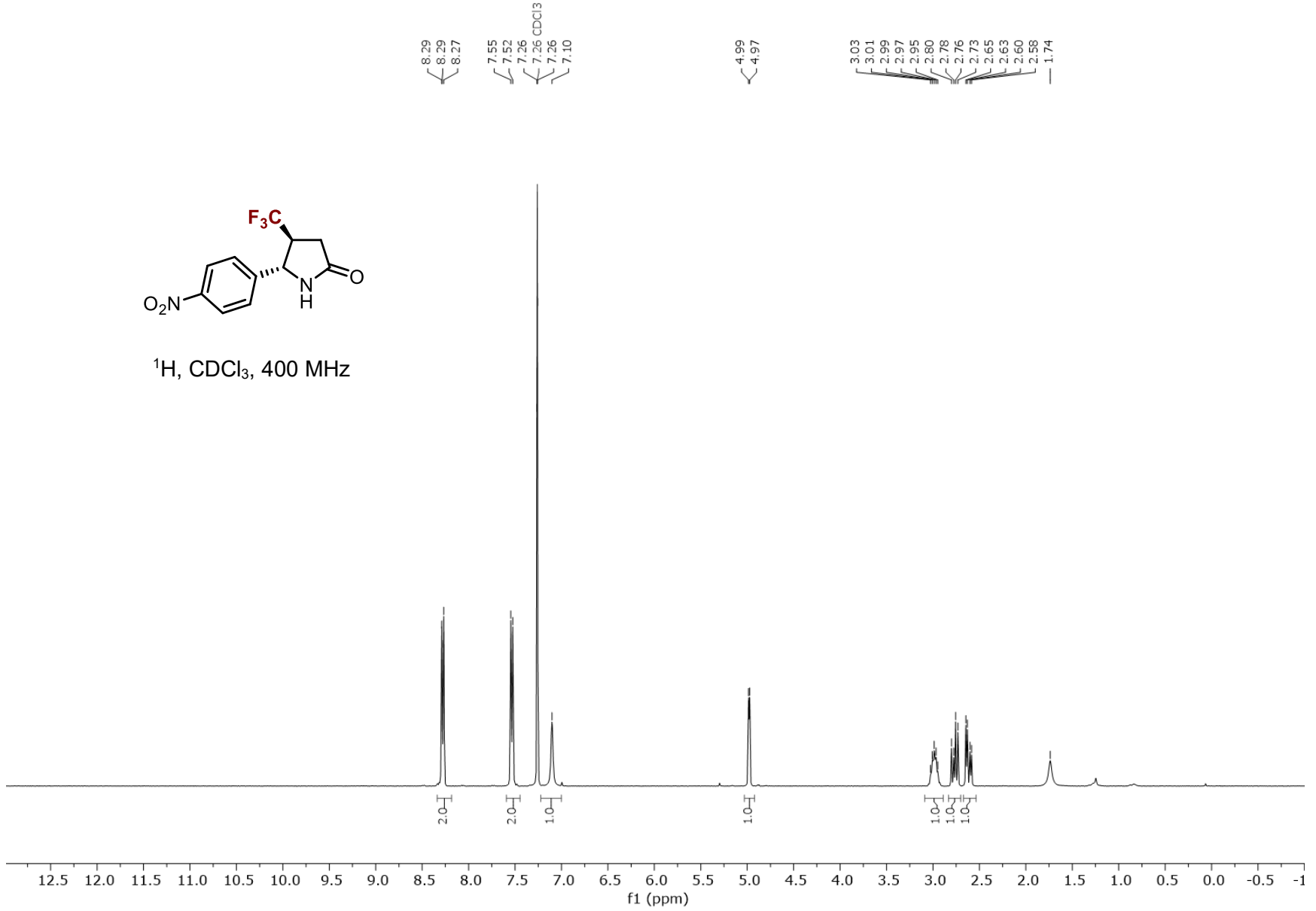


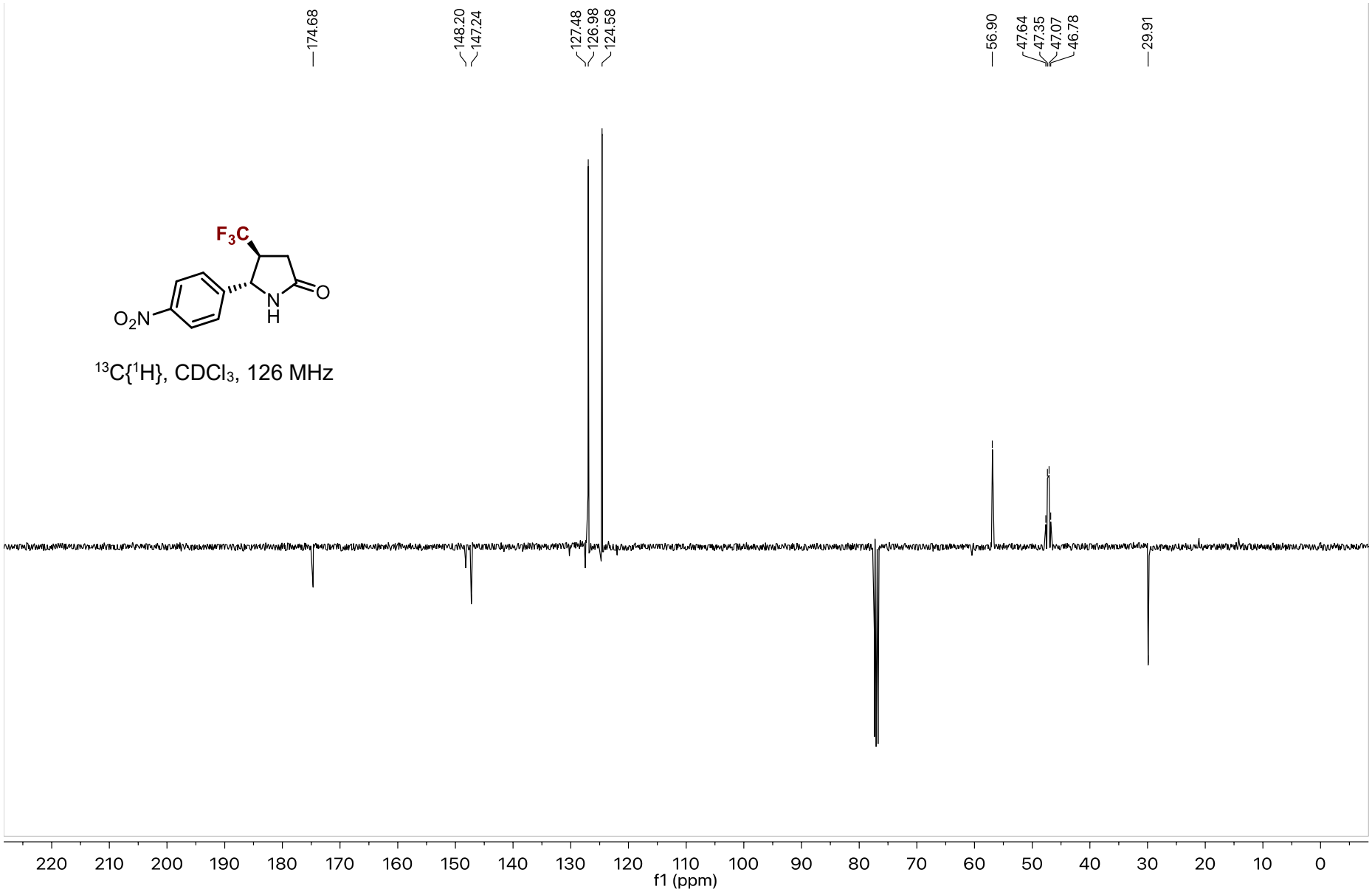
5.2 Data for pyrrolidinone products

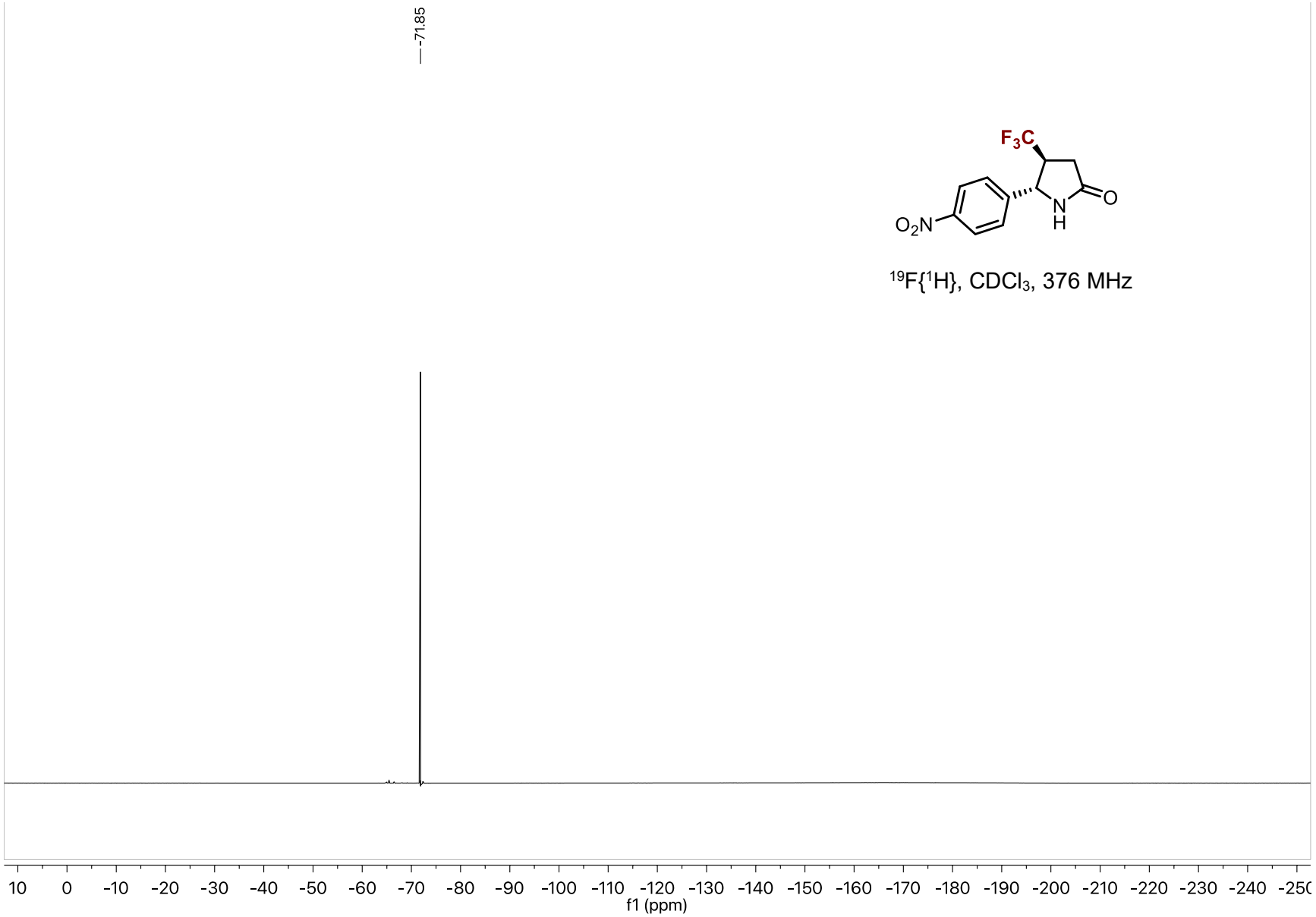
(4*S*,5*S*)-5-(4-nitrophenyl)-4-(trifluoromethyl)pyrrolidin-2-one (24)



Following **General Procedure F,** (*S*)-3-((*S*)-((diphenylmethylene)amino)(4-nitrophenyl)methyl)-4,4,4-trifluoro-1-(piperidin-1-yl)butan-1-one **11** (78.7 mg, 0.15 mmol) was stirred with 10% HCl (230 µL, 0.75 mmol) at rt for 1 hr. The reaction mixture was then concentrated and purified by flash chromatography 1:4 Hexane:EtOAc (R_f = 0.53) to give the titled compound as an inseparable mixture of diastereomers (96:4 dr) as a beige solid (73.9 mg, 90%). **mp** 98−100 °C; $[\alpha]_D^{20}$ +11.2 (*c* 1.2, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak IA (85:15 Hexane:IPA, flow rate 1 mLmin^{-1}, 254 nm, 30 °C) t_R(*S,R*): 11.5 min, t_R(*S,S*): 13.6 min, 94:6 er; **IR** ν_{max} (thin film): 3219 (N-H), 1639 (C=O amide), 1519 (asymm. NO_2), 1384 (symm. NO_2), 1111 (C-F); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H: 2.61–2.67 (1H, dd, $^3J_{HH}$ = 17.8, $^4J_{HH}$ = 6.7, NHCH(Ar)CH(CF_3)CH_AH$_B$C=O), 2.76–2.83 (1H, dd, $^3J_{HH}$ = 17.8, $^4J_{HH}$ = 10.2, NHCH(Ar)CH(CF_3)CH$_A$*H*$_B$C=O), 3.01 (1H, m, NHCH(Ar)C*H*(CF_3)CH$_A$H$_B$C=O), 4.99 (1H, d, $^3J_{HH}$ = 5.2, NHC*H*(Ar)CH(CF_3)CH$_A$H$_B$C=O), 7.19 (1H, bs, N-*H*), 7.55–7.57 (2H, m, C(2,6)Ar*H*-NO_2), 8.29 – 8.31 (2H, m, C(3,5)Ar*H*-NO_2); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$), δ_C: 29.9 (NHCH(Ar)CH(CF_3)*C*H$_A$H$_B$C=O), 47.2 (q, $^2J_{CF}$ = 28.8, NHCH(Ar)*C*H(CF_3)CH$_A$H$_B$C=O), 56.9 (NH*C*H(Ar)CH(CF_3)CH$_A$H$_B$C=O), 124.6 (*C*(3,5)Ar-NO_2), 126.9 (*C*(2,6)Ar-NO_2), 125.8 (q, $^1J_{CF}$ = 280.6, *C*F_3), 147.2 (*C*(1)Ar-NO_2), 148.2 (*C*(6)Ar-NO_2), 174.7 (*C*=O); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: −71.9 (3F, s, C*F*$_3$); **HRMS** (NSI$^+$) $C_{11}H_{10}F_3N_2O_3^+$ ([M+H]$^+$) requires 275.0633, found 275.0638 (−1.8 ppm).


8.29
8.29
8.27
7.55
7.52
7.26
7.26 CDCl3
7.26
7.10
4.99
4.97
3.03
3.01
2.99
2.97
2.95
2.80
2.78
2.76
2.73
2.65
2.63
2.60
2.58
1.74
F3C
O2N
N
H
O
1H, CDCl3, 400 MHz
2.0
2.0
1.0
1.0
1.0
1.0
1.0
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

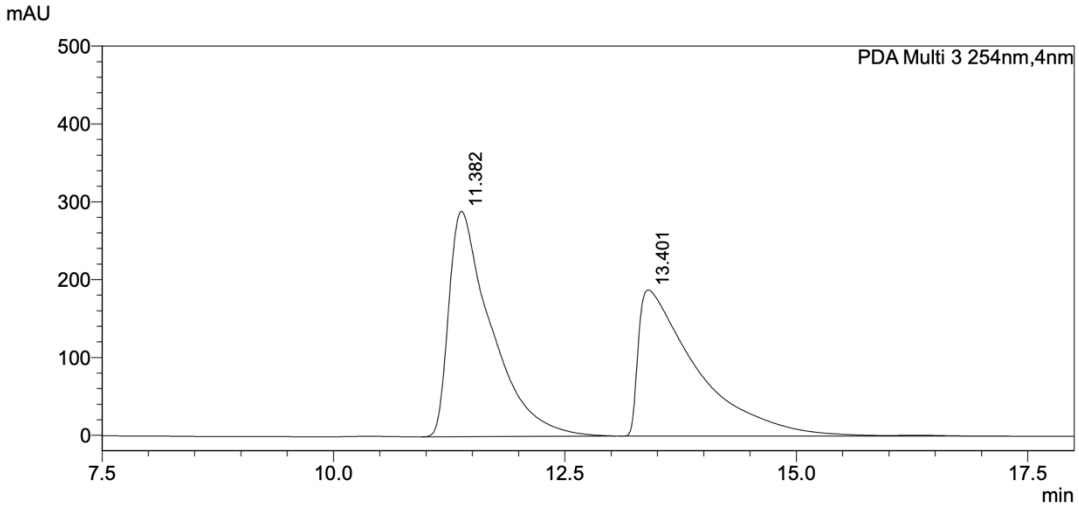

174.68
148.20
147.24
127.48
126.98
124.58
56.90
47.64
47.35
47.07
46.78
29.91
F3C
O2N
N
H
O
13C{1H}, CDCl3, 126 MHz
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


-71.85
F3C
O2N
N
H
O
19F{1H}, CDCl3, 376 MHz
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 -250
f1 (ppm)

HPLC Data for **(4*S*,5*S*)-5-(4-nitrophenyl)-4-(trifluoromethyl)pyrrolidin-2-one Chiral HPLC analysis.** Chiralpak IA (85:15 Hexane:IPA, flow rate 1 mLmin^{-1}, 254 nm, 30 °C) t_R(*S,R*): 11.5 min, t_R(*S,S*): 13.6 min, 94:6 er

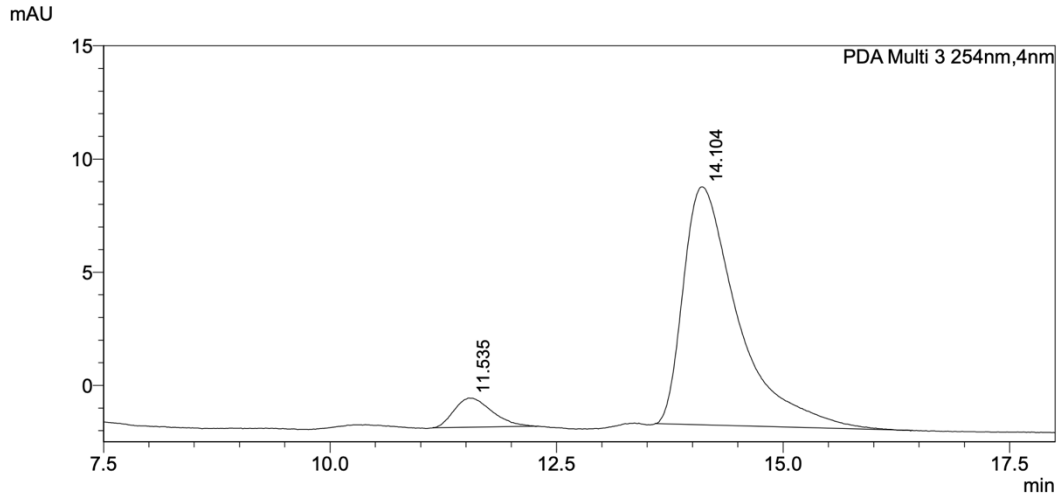
PDA Ch3 254nm

Peak#	Ret. Time	Area%
1	11.382	50.918
2	13.401	49.082
Total		100.000

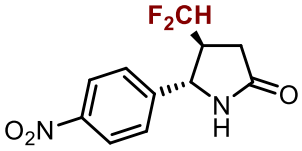


PDA Ch3 254nm

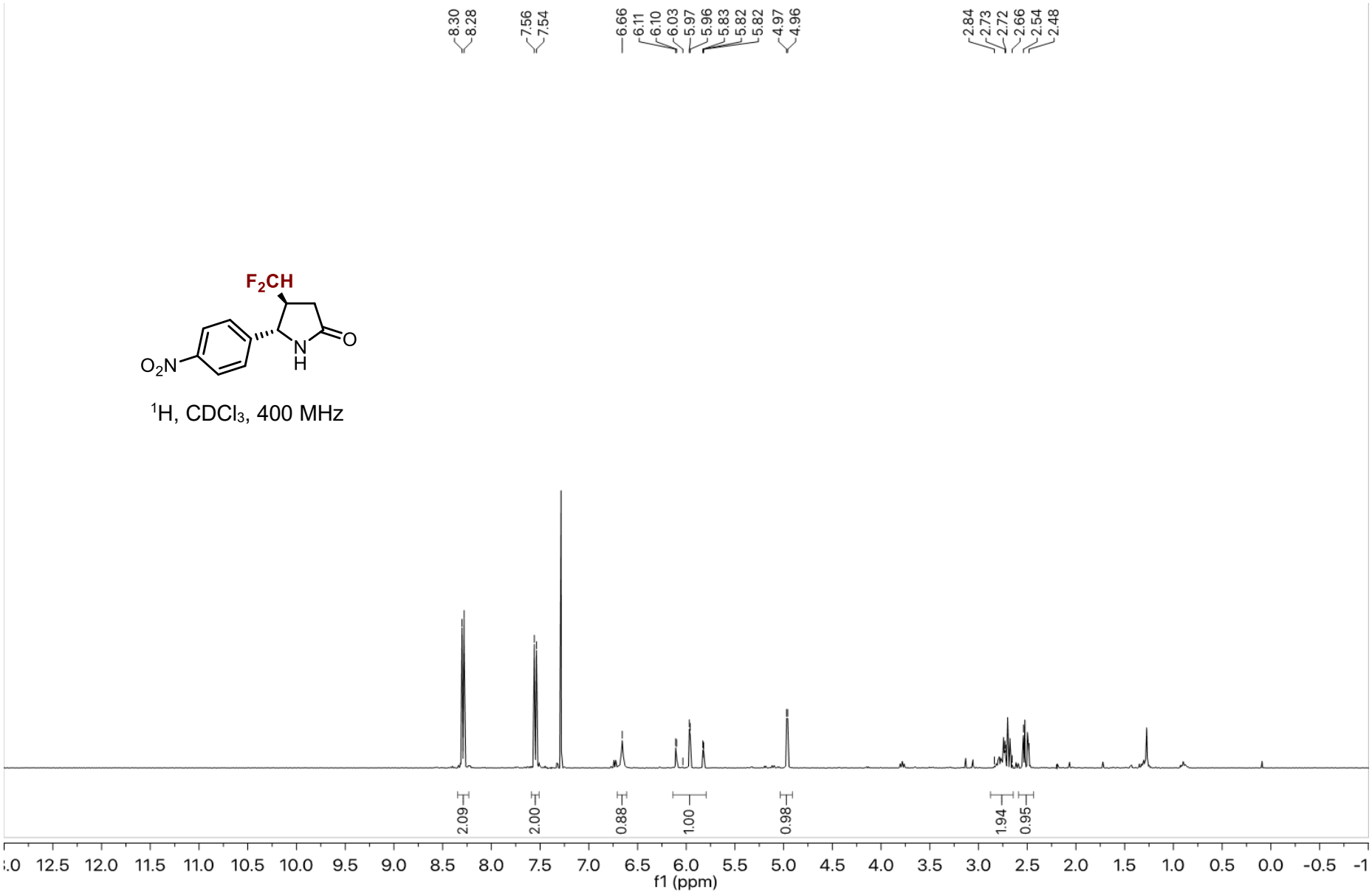
Peak#	Ret. Time	Area%
1	11.534	6.270
2	13.601	93.730
Total		100.000

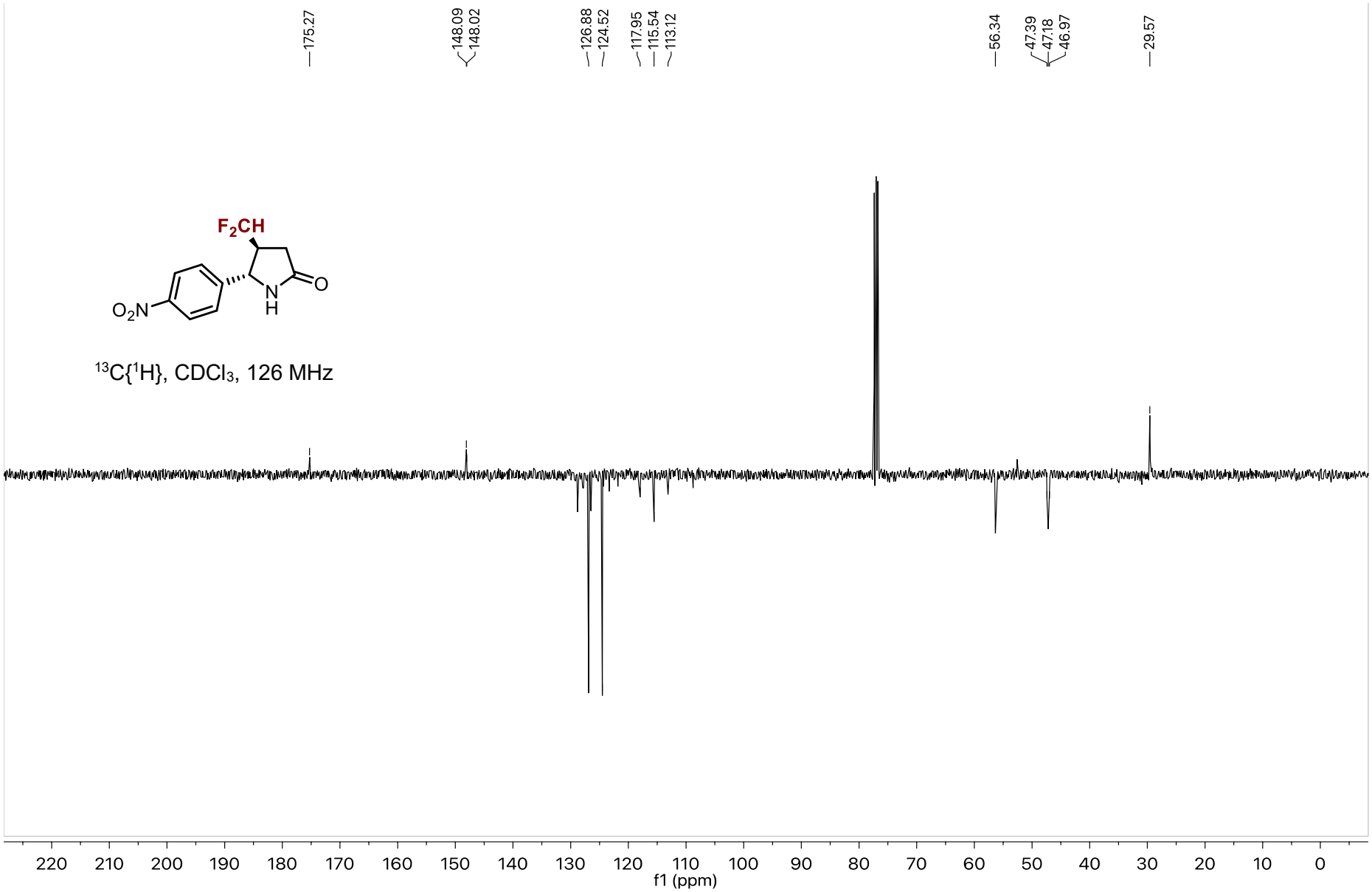


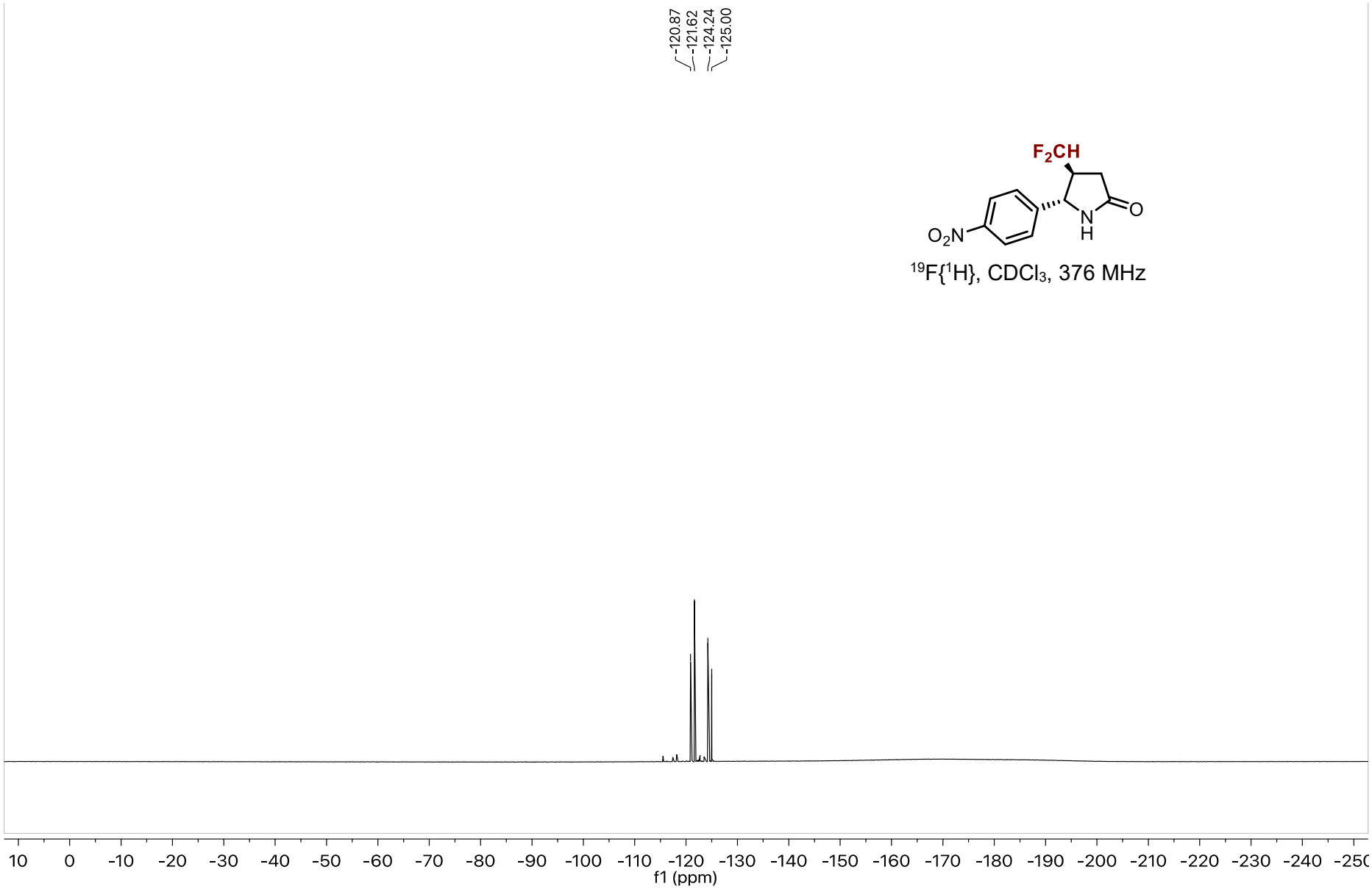
(4*S*,5*S*)-4-(difluoromethyl)-5-(4-nitrophenyl)pyrrolidin-2-one (25)



Following **General Procedure F,** ((3*S*,4*S*)-3-(difluoromethyl)-4-((diphenylmethylene)amino)-4-(4-nitrophenyl)-1-(pipe-ridin-1-yl)butan-1-one **18** (57.2 mg ,0.1 mmol) was stirred with 10% HCl (100 µL, 0.5 mmol) at rt for 1 hr. The reaction mixture was then concentrated and purified by flash chromatography 1:4 Hexane:EtOAc (R_f = 0.50) to give the titled compound as an inseparable mixture of diastereomers (90:10 dr) as a colorless oil (24.3 mg, 95%). $[\alpha]_D^{20}$ +10.1 (*c* 1.0, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak IA (97.5:2.5 Hexane:IPA, flow rate 1 mLmin^{-1}, 254 nm, 30 °C) t_R(*S,S*): 17.9 min, t_R(*S,R*): 27.4 min, 8:92 er; **IR** ν_{max} (thin film): 2926 (Ar-H), 1701 (C=O, amide), 1519 (asymm. NO_2), 1348 (symm. NO_2), 1039 (C-F); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H: 2.48–2.54 (1H, m, NHCH(Ar)CH(CF_2H)CH_AH_BC=O), 2.66–2.72 (1H, m, NHCH(Ar)CH(CF_2H)CH_AH_BC=O), 2.73–2.84 (1H, m, NHCH(Ar)C*H*(CF_2H)CH_AH_BC=O), 4.96–4.97 (1H, d, $^3J_{HH}$ = 4.7, NHCH(Ar)C*H*(CF_2H)CH_AH_BC=O), 5.82–6.11 (1H, td, $^2J_{HF}$ = 55.7, $^3J_{HH}$ = 3.7, NHCH(Ar)CH(CF_2H)CH_AH_BC=O), 6.66 (N-*H*), 7.54–7.56 (2H, m, C(2,6)Ar*H*-NO_2), 8.28–8.30 (2H, m, C(3,5)Ar*H*-NO_2); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$), δ_C: 29.6 (NHCH(Ar)CH(CF_2H)*C*H_AH_BC=O), 47.2 (t, $^2J_{CF}$ = 21.2, NHCH(Ar)*C*H(CF_2H)CH_AH_BC=O), 56.3 (NH*C*H(Ar)CH(CF_2H)CH_AH_BC=O), 115.5 (t, $^1J_{CF}$ = 243.0, *C*F_2H), 124.5 (*C*(3,5)Ar-NO_2), 126.9 (*C*(2,6)Ar-NO_2), 148.0 (*C*(1)Ar-NO_2), 148.1(*C*(4)Ar-NO_2), 175.3 (*C*=O); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: −124.6 (d, $^2J_{FF}$ = 284.8, C*F*$_a$F$_b$H), −121.2 (d, $^2J_{FF}$ = 284.8, CF$_a$*F*$_b$H); **HRMS** (NSI$^+$) $C_{11}H_9F_2N_2O_3^-$ ([M-H]$^-$) requires 255.0587, found 255.0586 (−0.39 ppm).


8.30
8.28
7.56
7.54
6.66
6.11
6.10
6.03
5.97
5.96
5.83
5.82
5.82
4.97
4.96
2.84
2.73
2.72
2.66
2.54
2.48
F2CH
O2N
N
H
O
1H, CDCl3, 400 MHz
2.09
2.00
0.88
1.00
0.98
1.94
0.95
f1 (ppm)

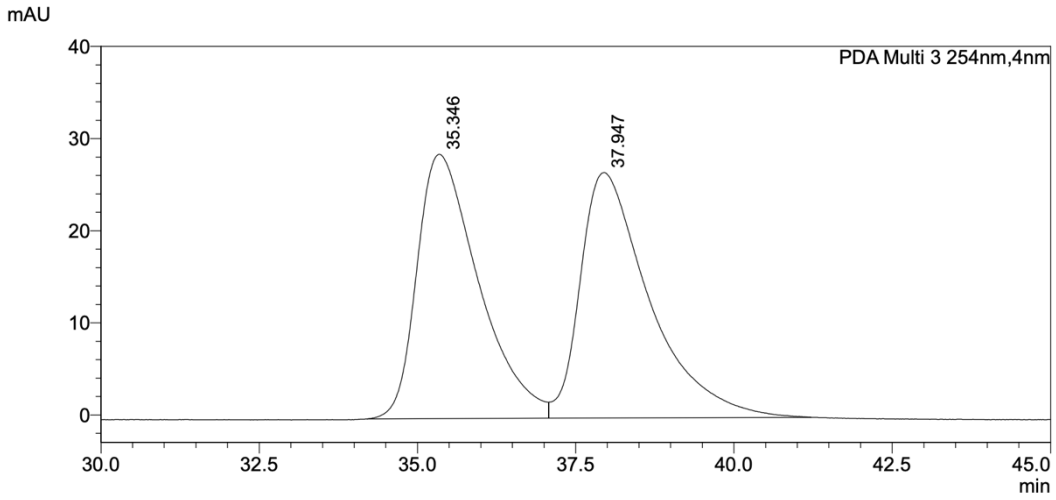

175.27
148.09
148.02
126.88
124.52
117.95
115.54
113.12
56.34
47.39
47.18
46.97
29.57
F2CH
O2N
N
H
O
13C{1H}, CDCl3, 126 MHz
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


-120.87
-121.62
-124.24
-125.00
F2CH
O2N
N
H
O
19F{1H}, CDCl3, 376 MHz
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 -250
f1 (ppm)

HPLC Data for **(4*S*,5*S*)-4-(difluoromethyl)-5-(4-nitrophenyl)pyrrolidin-2-one**: Chiralpak IA (97.5:2.5 Hexane:IPA, flow rate 1 mLmin^{-1}, 254 nm, 30 °C) t_R(*S,S*): 17.9 min, t_R(*S,R*): 27.4 min, 8:92 er.

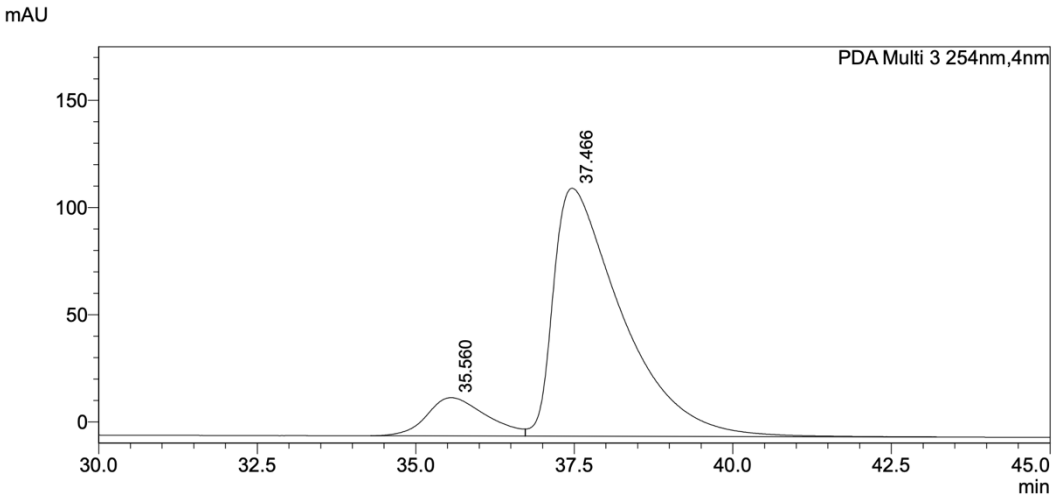
PDA Ch3 254nm

Peak#	Ret. Time	Area%
1	35.346	49.033
2	37.947	50.967
Total		100.000

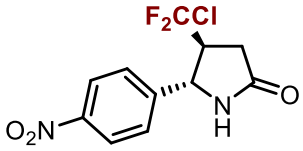


PDA Ch3 254nm

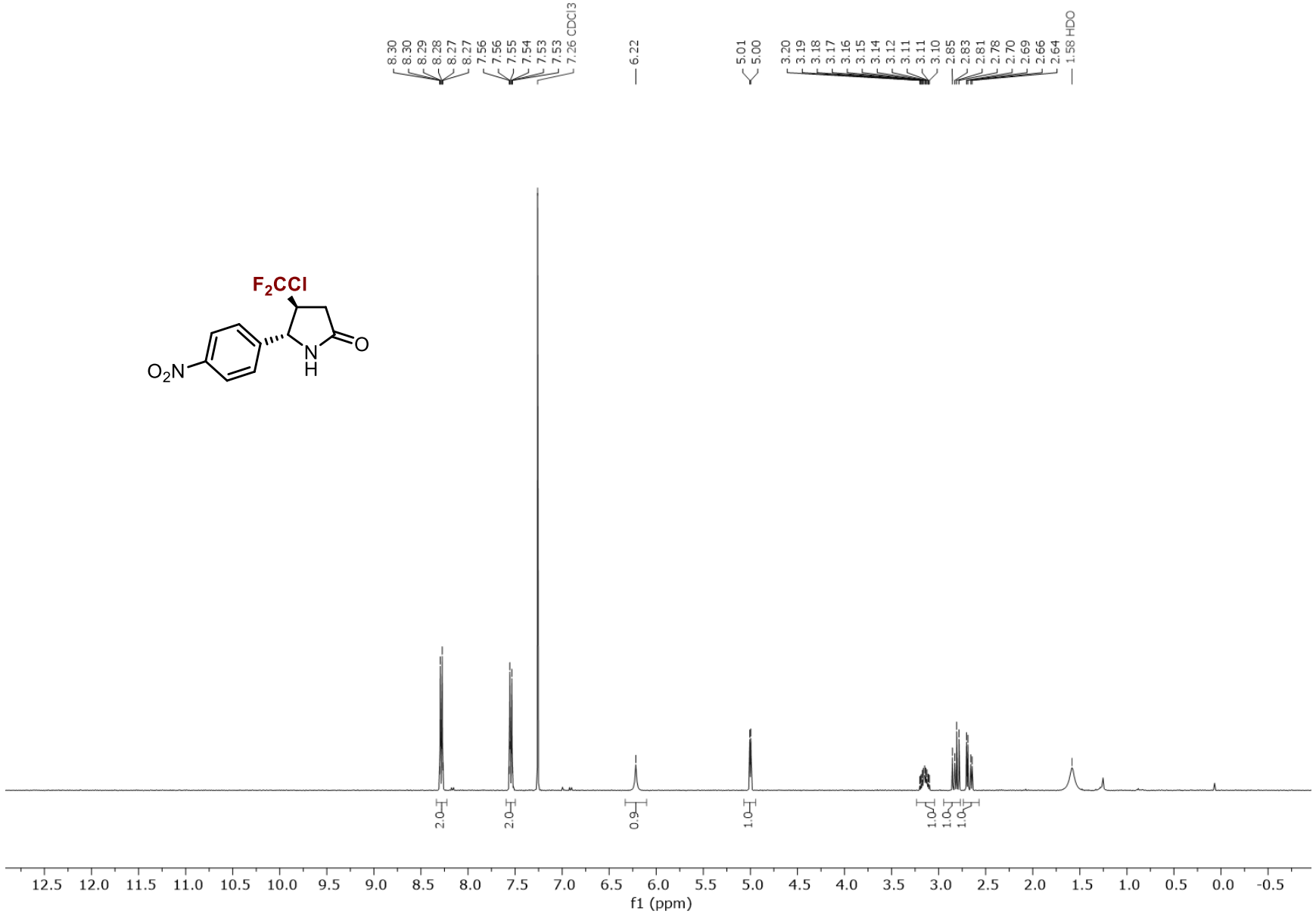
Peak#	Ret. Time	Area%
1	35.560	7.888
2	37.466	92.112
Total		100.000

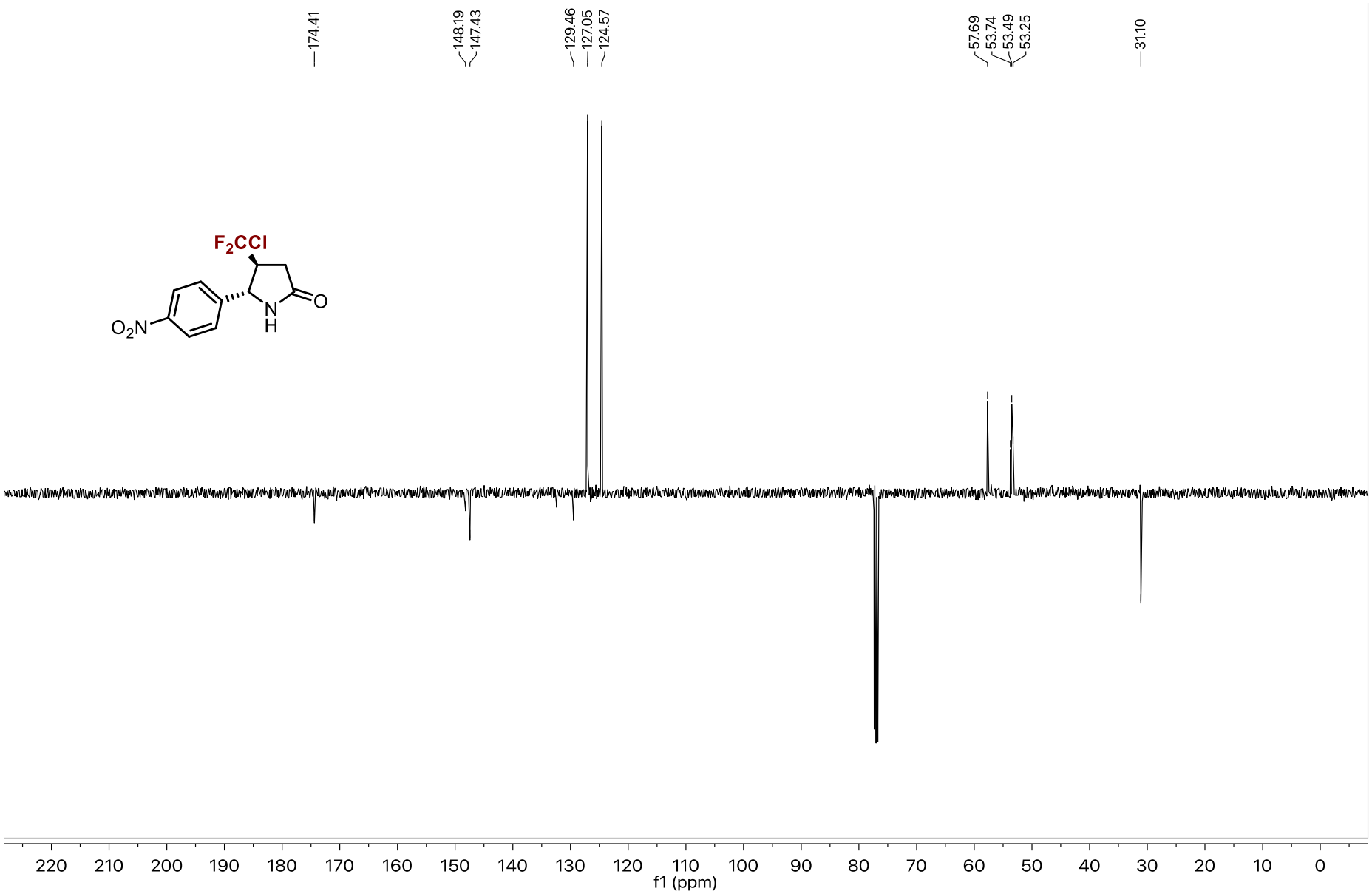


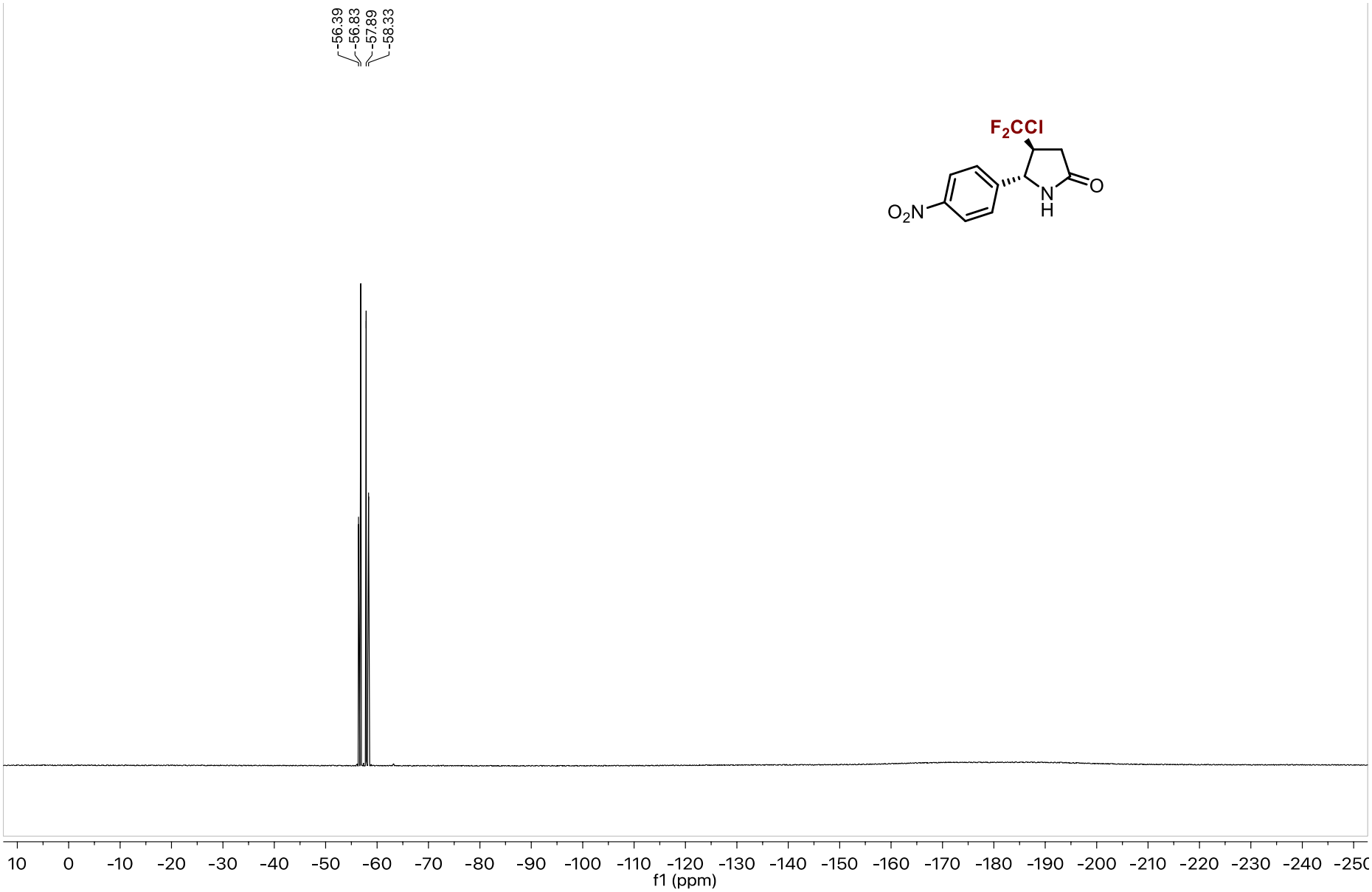
(4*S*,5*S*)-4-(chlorodifluoromethyl)-5-(4-nitrophenyl)pyrrolidin-2-one (26)



Following **General Procedure F,** (*S*)-4-chloro-3-((*S*)-((diphenylmethylene)amino)(4-nitrophenyl)methyl)-4,4-difluoro-1-(piperidin-1-yl)butan-1-one **19** (108 mg, 0.20 mmol) was stirred with 10% HCl (200 µL, 1.0 mmol) at rt for 1 hr. The reaction mixture was then concentrated and purified by flash chromatography 1:4 Hexane:EtOAc (R_f = 0.55) to give the titled compound as an inseparable mixture of diastereomers (94:6 dr) as a colorless oil (52 mg, 90%). $[\alpha]_D^{20}$ +18.1 (*c* 1.8, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak ADH (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 254 nm, 30 °C) t_R(*S,R*): 31.8 min, t_R(*S,S*): 33.5 min, 9:91 er; **IR** ν_{max} (thin film): 3113 (Ar-H), 1705 (C=O, amide), 1521 (asymm. NO_2), 1350 (symm. NO_2); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H: 2.65–2.71 (1H, dd, $^3J_{HH}$ = 18.0, $^4J_{HF}$ = 6.0, NHCH(Ar)CH(CF_2Cl)CH_AH$_B$C=O), 2.80–2.87 (1H, dd, $^3J_{HH}$ = 18.0, $^4J_{HF}$ = 9.9, NHCH(Ar)CH(CF_2Cl)CH$_A$H$_B$C=O), 3.12–3.22 (1H, m, NHCH(Ar)C*H*(CF_2Cl)CH$_A$H$_B$C=O), 5.03–5.04 (1H, dd, $^3J_{HH}$ = 4.5, NHC*H*(Ar)CH(CF_2Cl)CH$_A$H$_B$C=O), 6.91 (N-*H*), 7.56–7.58 (2H, m, 2H, m, C(2,6)Ar*H*-NO_2), 8.29–8.31 (2H, m, 2H, m, C(3,5)Ar*H*-NO_2); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$), δ_C: 31.1 (NHCH(Ar)CH(CF_2Cl)*C*H$_A$H$_B$C=O), 53.5 (t, $^2J_{CF}$ = 24.6, NHCH(Ar)*C*H(CF_2Cl)CH$_A$H$_B$C=O), 57.7 (NH*C*H(Ar)CH(CF_2Br)CH$_A$H$_B$C=O), 124.6 (*C*(3,5)Ar-NO_2), 127.1 (*C*(2,6)Ar-NO_2), 129.5 (t, $^1J_{CF}$ = 293.1, *C*F_2Cl), 147.4 (*C*(4)Ar-NO_2), 148.2 (*C*(1)Ar-NO_2), 174.4 (*C*=O); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: −58.1 (d, $^2J_{FF}$ = 166.9, C*F*$_a$F$_b$Cl), −56.6 (d, $^2J_{FF}$ = 166.9, CF$_a$*F*$_b$Cl); **HRMS** (NSI$^+$) $C_{11}H_{10}ClF_2N_2O_3^+$ ([M+H]$^+$) requires 291.0343, found 291.0338(−1.56 ppm).


8.30
8.30
8.29
8.28
8.27
8.27
7.56
7.56
7.55
7.54
7.53
7.53
7.26 CDCl3
6.22
5.01
5.00
3.20
3.19
3.18
3.17
3.16
3.15
3.14
3.12
3.11
3.11
3.10
2.85
2.83
2.81
2.78
2.70
2.69
2.66
2.64
1.58 HDO
F2CCl
O2N
N
H
O
2.0
2.0
0.9
1.0
1.0
1.0
1.0
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

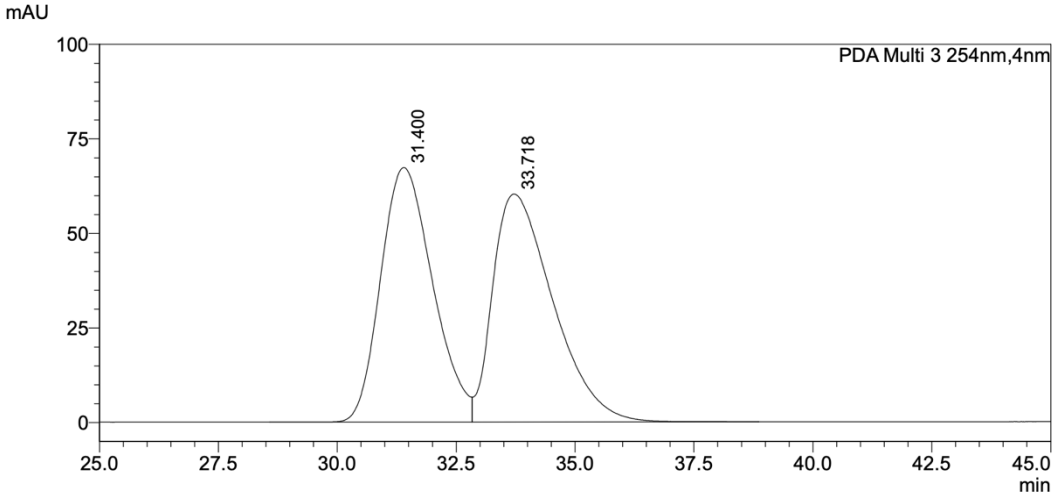

174.41
148.19
147.43
129.46
127.05
124.57
57.69
53.74
53.49
53.25
31.10
F2CCl
O2N
N
H
O
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


-56.39
-56.83
-57.89
-58.33
F2CCl
O2N
N
H
O
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 -250
f1 (ppm)

HPLC Data for **((4*S*,5*R*)-4-(chlorodifluoromethyl)-5-(4-nitrophenyl)pyrrolidin-2-one**: Chiralpak ADH (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 254 nm, 30 °C) t_R(*S,R*): 31.8 min, t_R(*S,S*): 33.5 min, 9:91 er.

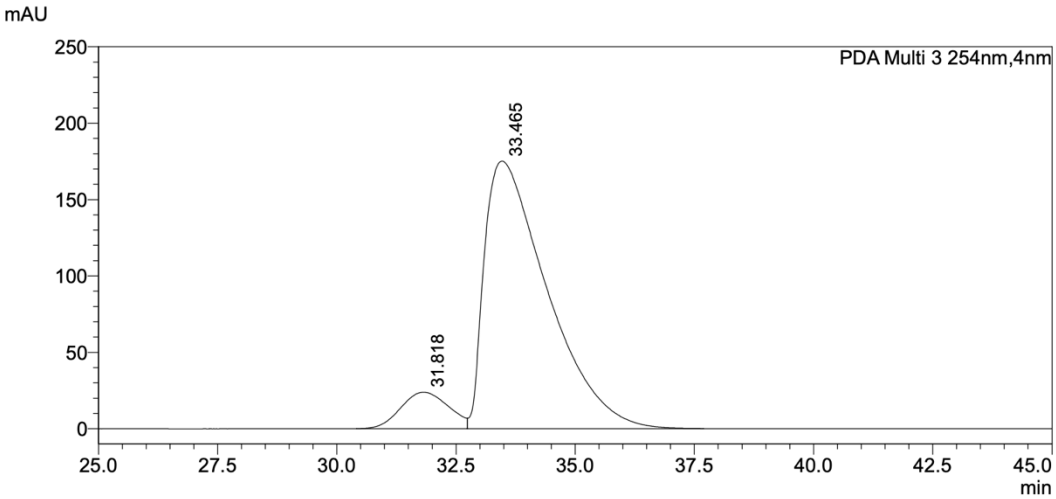
PDA Ch3 254nm

Peak#	Ret. Time	Area%
1	31.400	49.077
2	33.718	50.923
Total		100.000

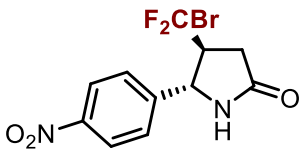


PDA Ch3 254nm

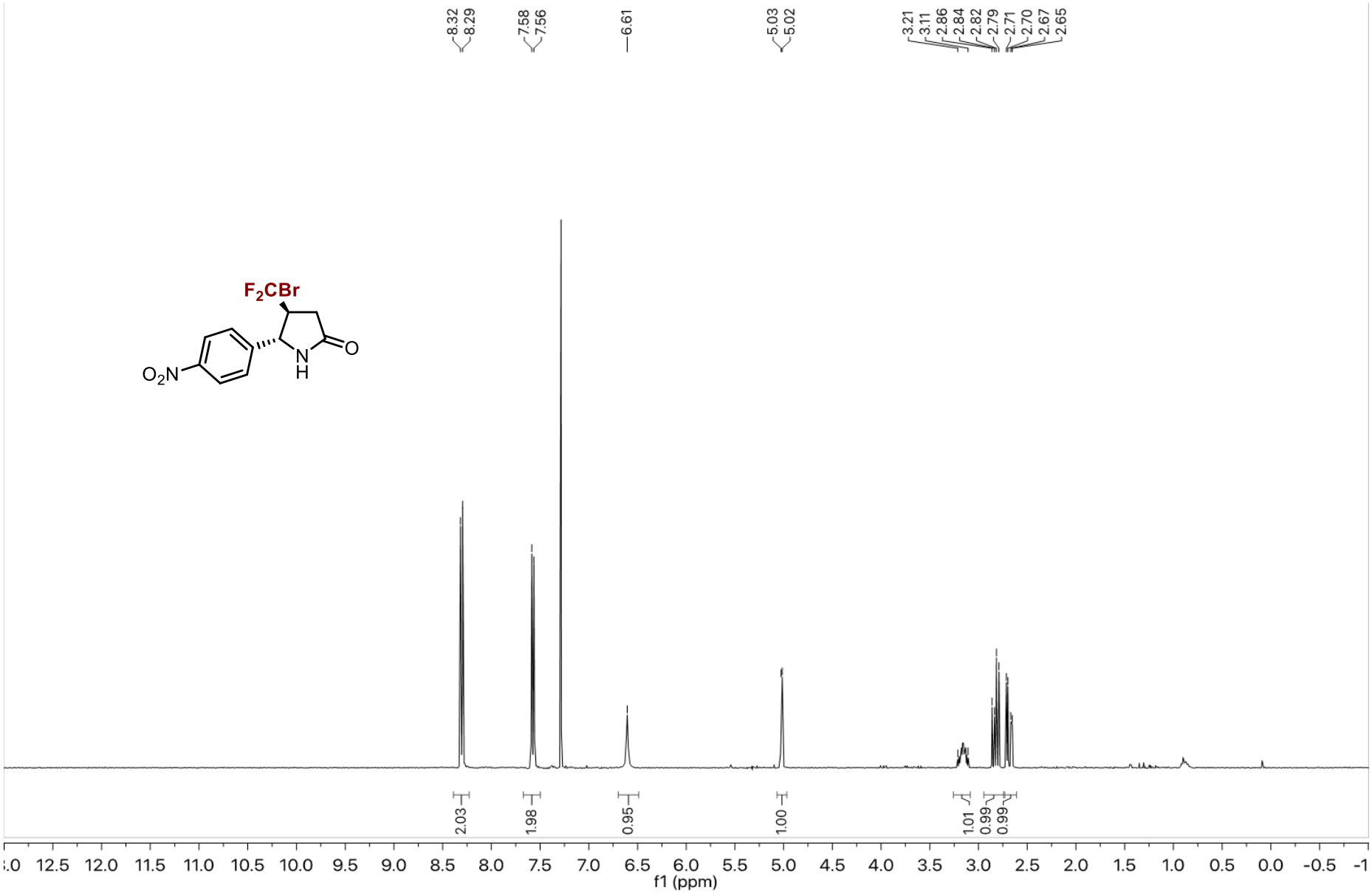
Peak#	Ret. Time	Area%
1	31.818	9.361
2	33.465	90.639
Total		100.000

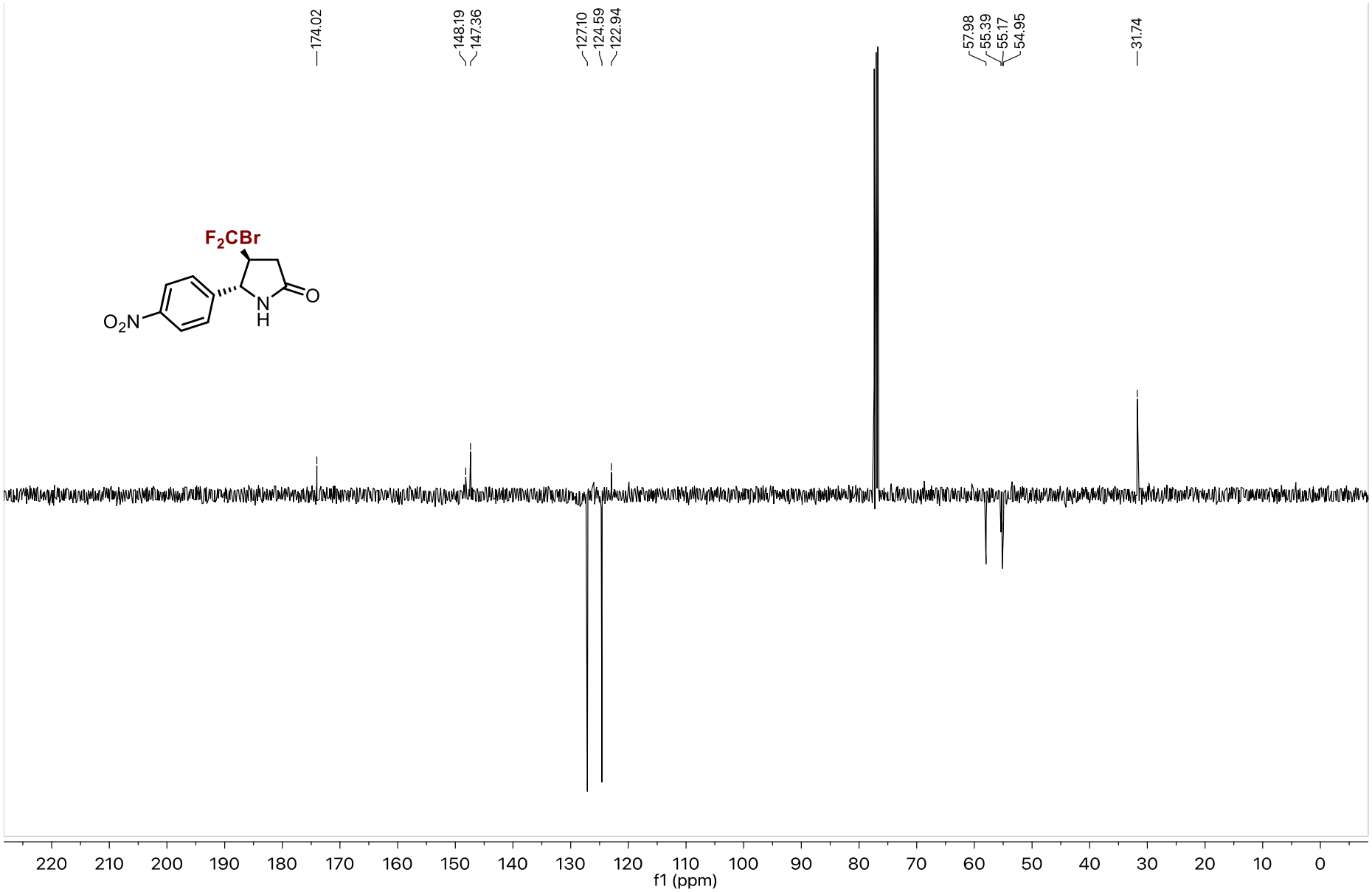


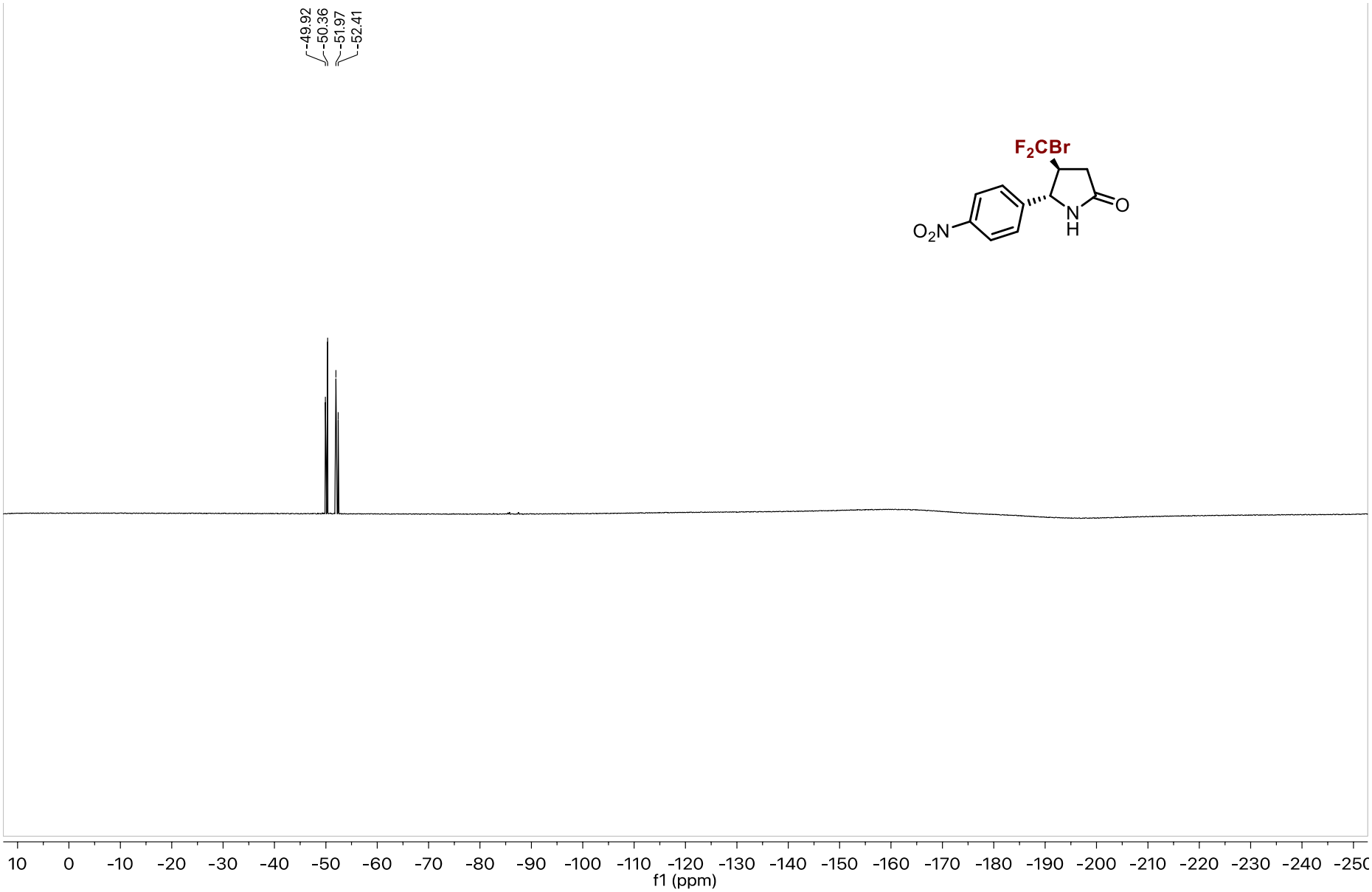
(4*S*,5*S*)-4-(bromodifluoromethyl)-5-(4-nitrophenyl)pyrrolidin-2-one (27)



Following **General Procedure F,** (*S*)-4-bromo-3-((*S*)-((diphenylmethylene)amino)(4-nitrophenyl)methyl)-4,4-difluoro-1-(piperidin-1-yl)butan-1-one **20** (116.6 mg ,0.2 mmol) was stirred with 10% HCl (200 µL, 1.0 mmol) at rt for 1 hr. The reaction mixture was then concentrated and purified by flash chromatography 1:4 Hexane:EtOAc (R_f = 0.52) to give the titled compound as an inseparable mixture of diastereomers (94:6 dr) as a colorless oil (61.6 mg, 92%). $[\alpha]_D^{20}$ +15.3 (*c* 1.5, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak ADH (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 254 nm, 30 °C) t_R(*S,R*): 35.7 min, t_R(*S,S*): 38.1 min, 91:9 er; **IR** ν_{max} (thin film): 3111 (Ar-H), 1705 (C=O, amide), 1519 (asymm. NO_2), 1350 (symm. NO_2), 1101 (C-F); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H: 2.65–2.71 (1H, dd, $^3J_{HH}$ = 18.0, $^4J_{HF}$ = 5.9, NHCH(Ar)CH(CF_2Br)C$H_A$$H_B$C=O), 2.79–2.86 (1H, dd, $^3J_{HH}$ = 18.0, $^4J_{HF}$ = 9.9, NHCH(Ar)CH(CF_2Br)C$H_A$$H_B$C=O), 3.11–3.21 (1H, m, NHCH(Ar)C*H*(CF_2Br)C$H_A$$H_B$C=O), 5.02–5.03 (1H, dd, $^3J_{HH}$ = 4.4, NHC*H*(Ar)CH(CF_2Br)C$H_A$$H_B$C=O), 6.61 (N-*H*), 7.56–7.58 (2H, m, 2H, m, C(2,6)Ar*H*-NO_2), 8.29–8.32 (2H, m, 2H, m, C(3,5)Ar*H*-NO_2); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$), δ_C: 31.7 (NHCH(Ar)CH(CF_2Br)*C*$H_A$$H_B$C=O), 55.2 (t, $^2J_{CF}$ = 22.2, NHCH(Ar)*C*H(CF_2Br)C$H_A$$H_B$C=O), 57.9 (NH*C*H(Ar)CH(CF_2Br)C$H_A$$H_B$C=O), 122.9 (t, $^1J_{CF}$ = 306.6, *C*F_2Br), 124.6 (*C*(3,5)Ar-NO_2), 127.1 (*C*(2,6)Ar-NO_2), 147.4 (*C*(4)Ar-NO_2), 148.2 (*C*(1)Ar-NO_2), 174.0 (*C*=O); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: −52.2 (d, $^2J_{FF}$ = 164.5, C*F*$_a$F$_b$Br), −50.1 (d, $^2J_{FF}$ = 164.5, CF$_a$*F*$_b$Br); **HRMS** (NSI$^+$) $C_{11}H_9BrF_2N_2O_3^+$ ([M+Na]$^+$) requires 356.9663, found 356.9653 (-2.80 ppm).


8.32
8.29
7.58
7.56
6.61
5.03
5.02
3.21
3.11
2.86
2.84
2.82
2.79
2.71
2.70
2.67
2.65
F2CBr
O2N
N
H
O
2.03
1.98
0.95
1.00
1.01
0.99
0.99
f1 (ppm)

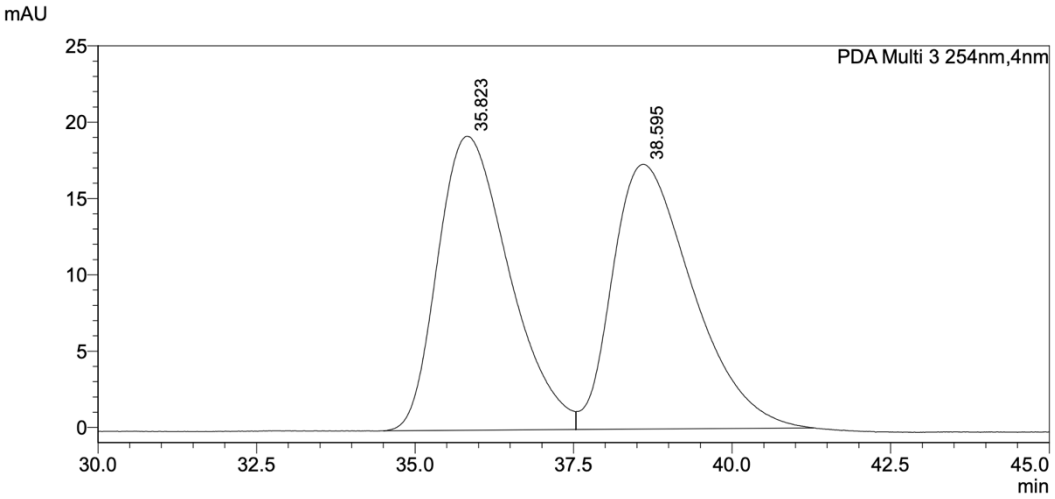

174.02
148.19
147.36
127.10
124.59
122.94
57.98
55.39
55.17
54.95
31.74
F2CBr
O2N
N
H
O
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


-49.92
-50.36
-51.97
-52.41
F2CBr
O2N
N
H
O
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 -250
f1 (ppm)

HPLC Data for **(4*S*,5*S*)-4-(bromodifluoromethyl)-5-(4-nitrophenyl)pyrrolidin-2-one**: Chiralpak ADH (95:5 Hexane:IPA, flow rate 1 mLmin^{-1}, 254 nm, 30 °C) t_R(*S,R*): 35.7 min, t_R(*S,S*): 38.1 min, 91:9 er.

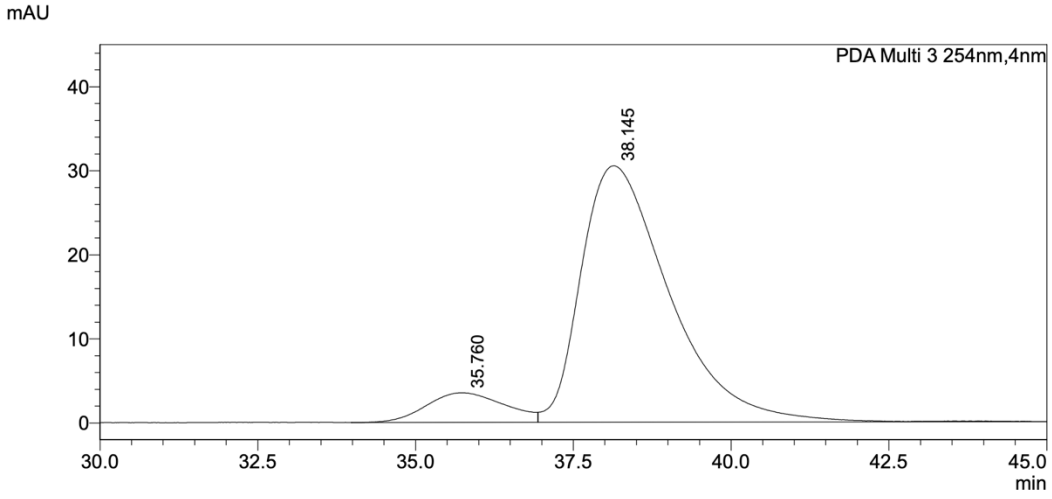
PDA Ch3 254nm

Peak#	Ret. Time	Area%
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2	38.595	50.208
Total		100.000

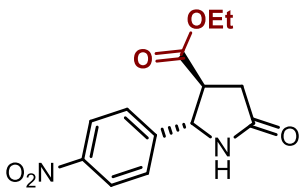


PDA Ch3 254nm

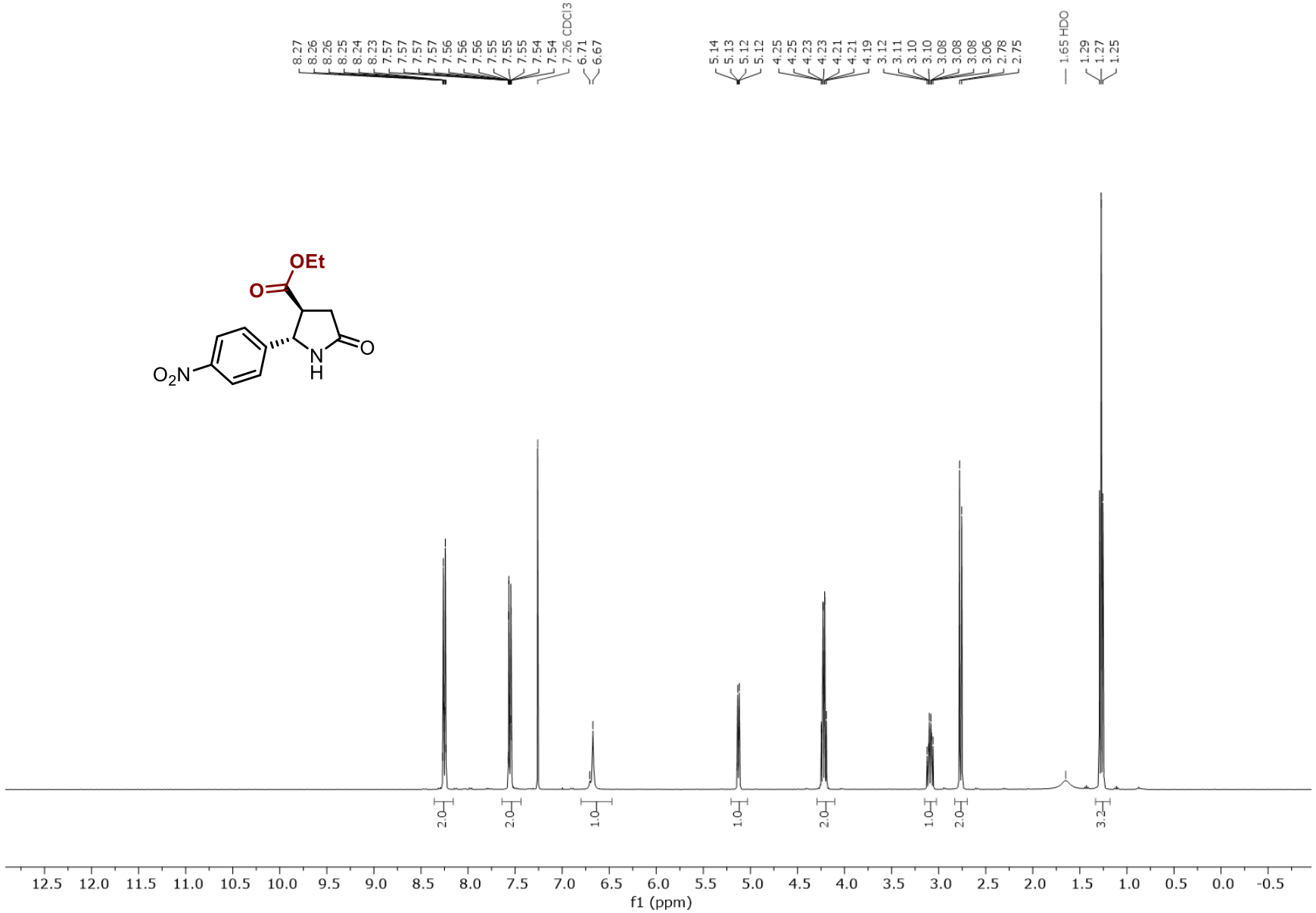
Peak#	Ret. Time	Area%
1	35.760	9.316
2	38.145	90.684
Total		100.000

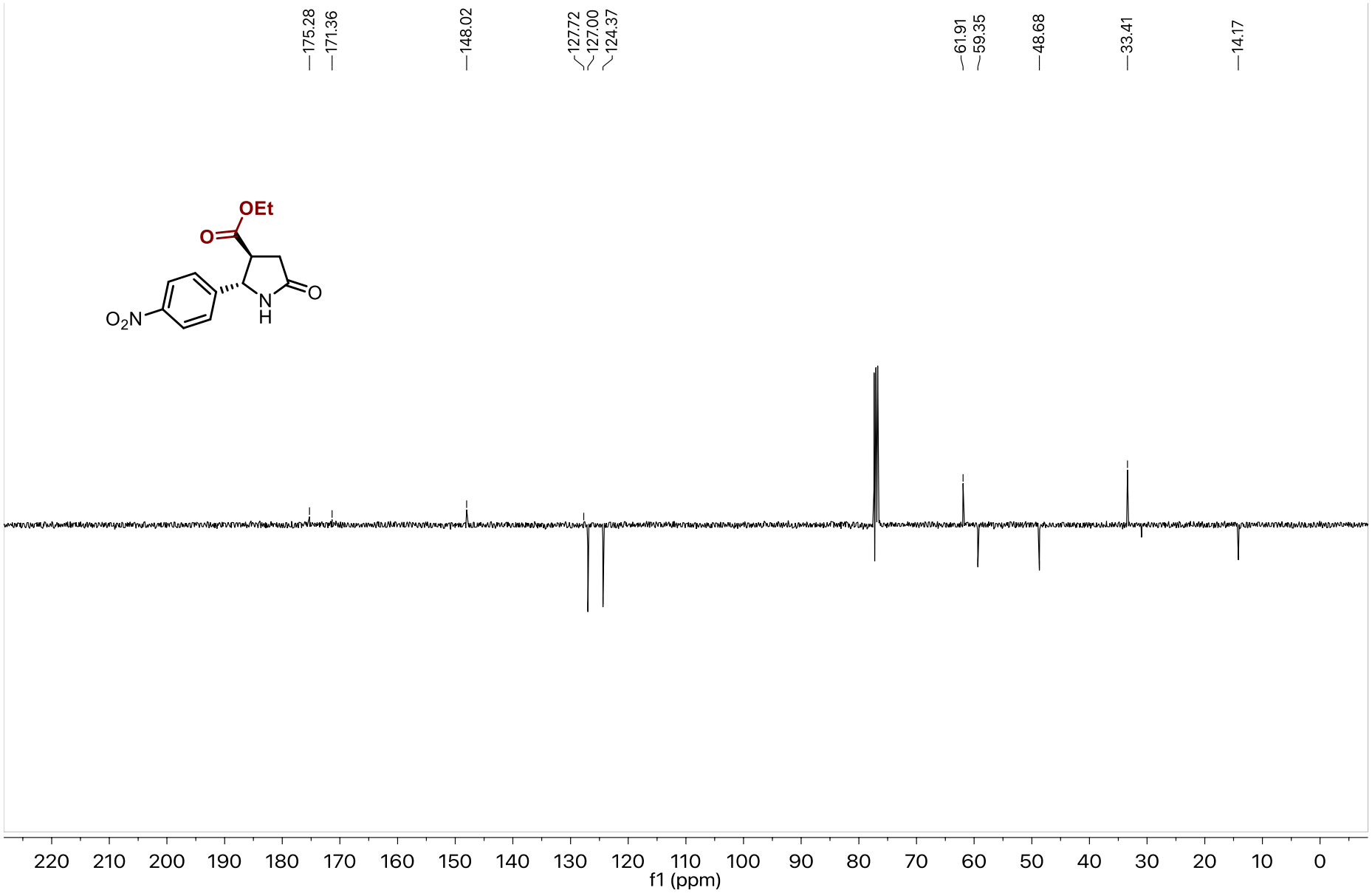


Ethyl (2*S*,3*S*)-2-(4-nitrophenyl)-5-oxopyrrolidine-3-carboxylate (28)



Following **General Procedure F,** Ethyl (*S*)-2-((*S*)-((diphenylmethylene)amino)(4-nitrophenyl)methyl)-4-oxo-4-(piperidin-1-yl)butanoate **21** (106 mg, 0.2 mmol) was stirred with 10% HCl (200 µL, 1.0 mmol) at rt for 1 hr. The reaction mixture was then concentrated and purified by flash chromatography 1:4 Hexane:EtOAc (R_f = 0.40) to give the titled compound as an inseparable mixture of diastereomers (86:14 dr) as a colorless oil (50 mg, 90%). $[\alpha]_D^{20}$ +148.8 (*c* 0.4, $CHCl_3$); **Chiral HPLC analysis.** Chiralpak IB (85:15 Hexane:IPA, flow rate 1 mLmin^{-1}, 254 nm, 30 °C) t_R(*S,S*): 33.8 min, t_R(*R,S*): 37.5 min, 92:8 er; **IR** ν_{max} (thin film): 2983 (Ar-H), 1730 (C=O, ketone), 1701 (C=O, amide), 1519 (asymm. NO_2), 1348 (symm. NO_2); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H: 1.27 (3H, t, $^3J_{HH}$ = 7.2, OCH_2CH_3), 2.77 (2H, d, $^3J_{HH}$ = 9.2, NHCH(Ar)CH(CO_2Et)CH_2C=O), 3.09 (1H, td, $^3J_{HH}$ = 9.2, $^3J_{HH}$ = 6.8, NHCH(Ar)C*H*(CO_2Et)CH_2C=O), 4.21–4.28 (2H, m, OCH_2CH_3), 5.13 (1H, d, $^3J_{HH}$ = 6.8, NHC*H*(Ar)CH(CO_2Et)CH_2C=O), 6.84 (1H, s, N-*H*), 7.57–7.60 (2H, m, C(2,6)Ar*H*-NO_2), 8.27–8.30 (2H, m, C(3,5)Ar*H*-NO_2); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$), δ_C: 14.2 (OCH_2CH_3), 33.4 (NHCH(Ar)CH(CO_2Et)CH_AH_BC=O), 48.7 (NHCH(Ar)*C*H(CO_2Et)CH_AH_BC=O), 59.4 (NH*C*H(Ar)CH(CO_2Et)CH_AH_BC=O), 61.9 (O*C*H_2CH_3), 124.4 (*C*(3,5)Ar-NO_2), 127.0 (*C*(2,6)Ar-NO_2), 127.7 (*C*(1)Ar-NO_2), 148.0 (*C*(4)Ar-NO_2), 171.4 (*C*O_2Et), 175.3 (*C*=O); **HRMS** (NSI$^+$) $C_{13}H_{14}N_2O_5Na^+$ ([M+Na]$^+$) requires 301.0795, found 301.0788 (−2.3 ppm).

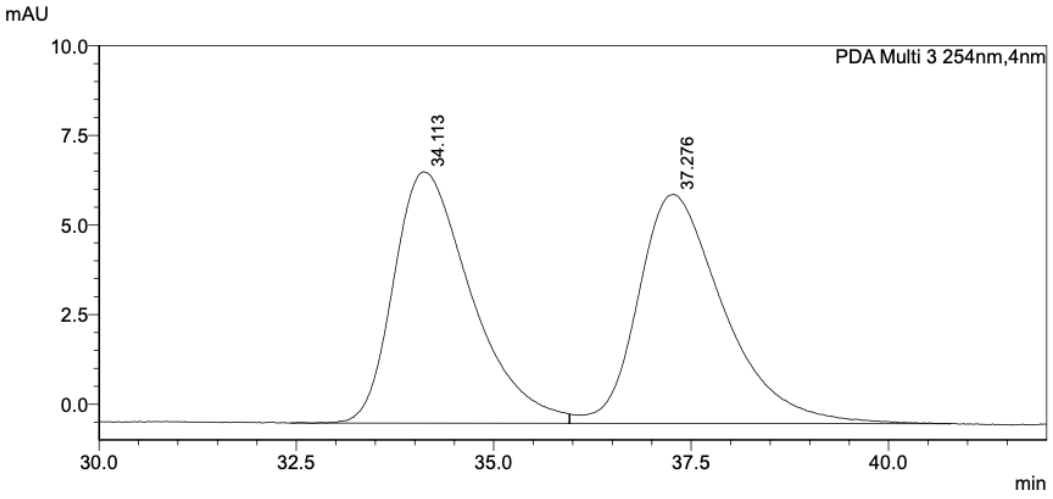

8.27
8.26
8.26
8.25
8.24
8.23
7.57
7.57
7.57
7.57
7.56
7.56
7.56
7.55
7.55
7.55
7.54
7.54
7.26 CDCl3
6.71
6.67
5.14
5.13
5.12
5.12
4.25
4.25
4.23
4.23
4.21
4.21
4.19
3.12
3.11
3.10
3.10
3.08
3.08
3.08
3.06
2.78
2.75
1.65 HDO
1.29
1.27
1.25
OEt
O
O
N
H
O2N
2.0
2.0
1.0
1.0
2.0
1.0
2.0
3.2
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


175.28
171.36
148.02
127.72
127.00
124.37
61.91
59.35
48.68
33.41
14.17
OEt
O
O
N
H
O2N
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

HPLC Data for **Ethyl (2*R*,3*S*)-2-(4-nitrophenyl)-5-oxopyrrolidine-3-carboxylate**: Chiralpak IB (85:15 Hexane:IPA, flow rate 1 mLmin^{-1}, 254 nm, 30 °C) t_R(*S,S*): 33.8 min, t_R(*R,S*): 37.5 min, 92:8 er.

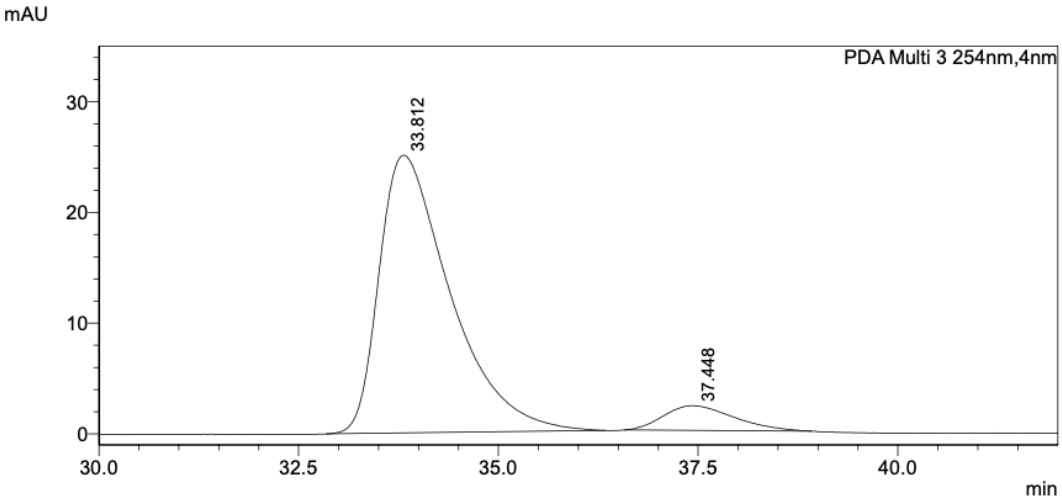
PDA Ch3 254nm

Peak#	Ret. Time	Area%
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2	37.276	50.245
Total		100.000



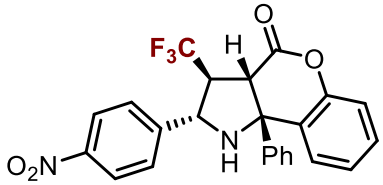
PDA Ch3 254nm

Peak#	Ret. Time	Area%
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2	37.448	8.138
Total		100.000

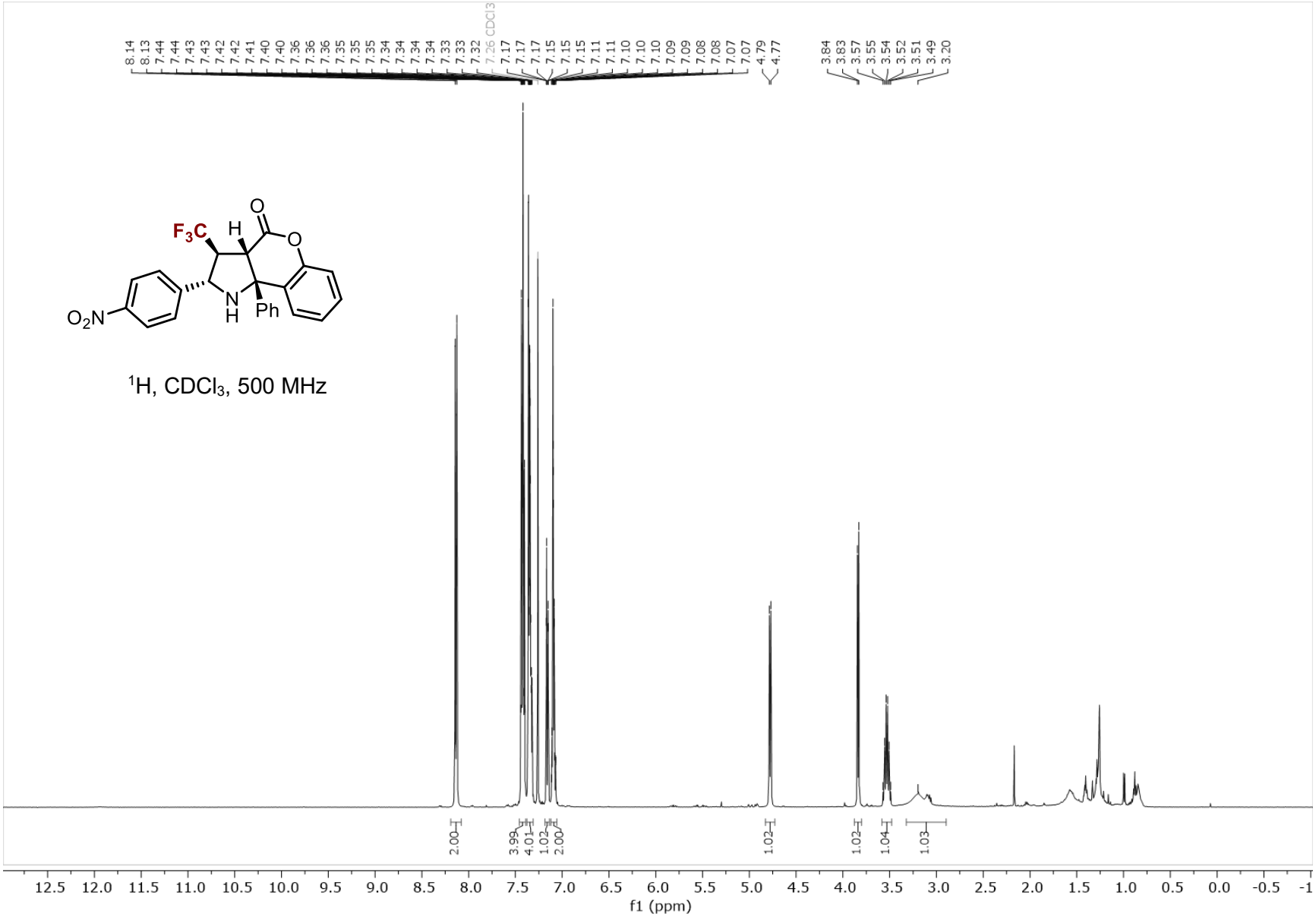


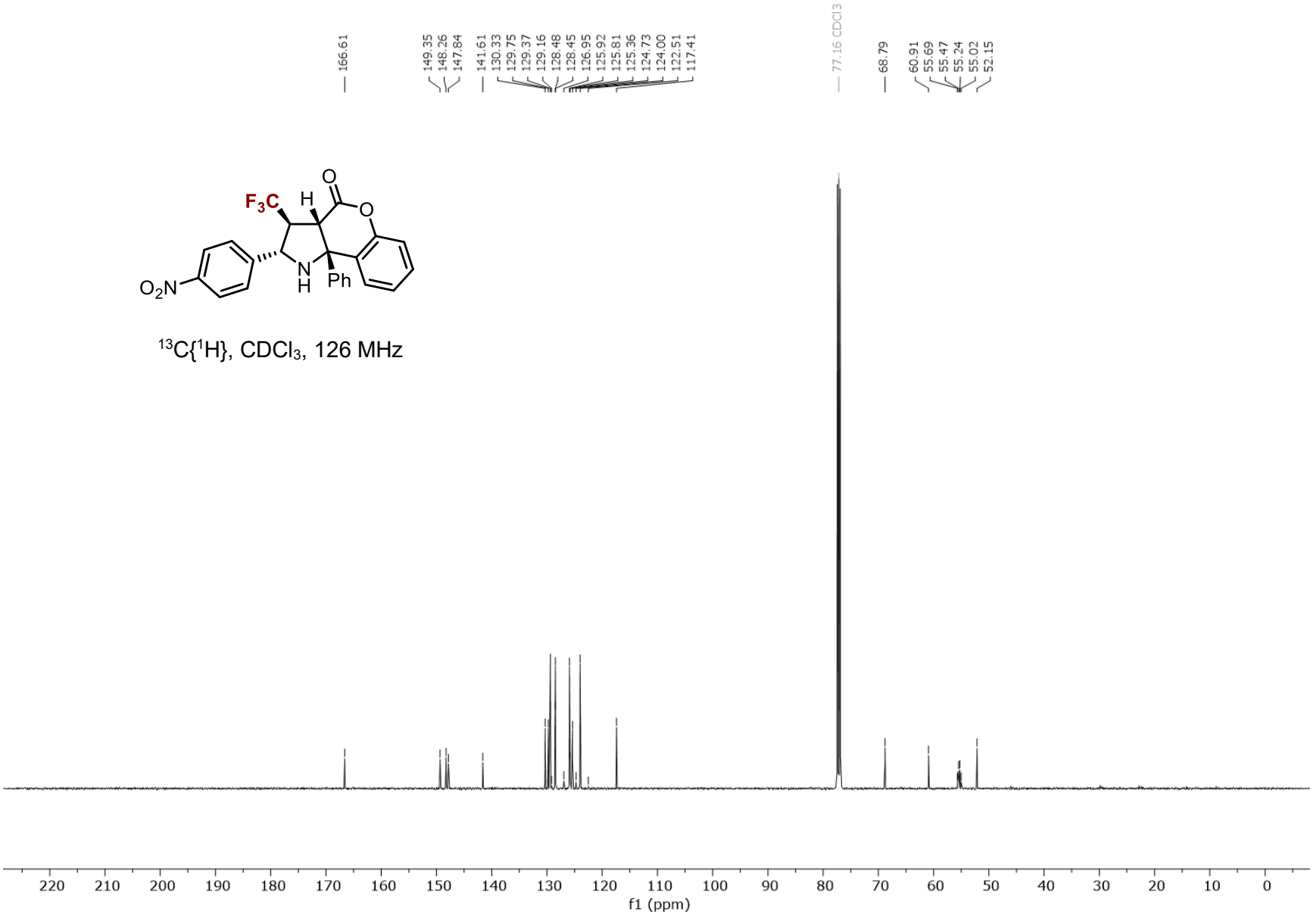
5.3 Data for chromeno-pyrrolidine products

(2*S*,3*S*,3a*S*,9b*S*)-2-(4-Nitrophenyl)-9b-phenyl-3-(trifluoromethyl)-2,3,3a,9b-tetrahydrochromeno[4,3-*b*]pyrrol-4(1*H*)-one (30)

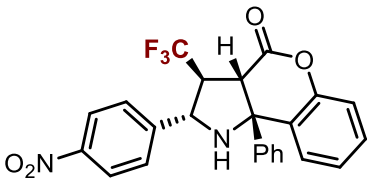


Following **General Procedure G**, 4-nitrophenyl (*E*)-4,4,4-trifluorobut-2-enoate (52.2 mg, 0.20 mmol), (*E*)-*N*-4-nitrobenzyl-2-hydroxybenzophenoneimine (99.6 mg, 0.30 mmol), and (2*S*,3*R*)-8-MeO-HyperSe (8.0 mg, 0.02 mmol), and dimethylformamide (2 mL) were stirred for 23 h at 50 °C. The mixture was then concentrated *in vacuo* and stirred in 1 M HCl (1 mL) and THF (2 mL) for one hour. The mixture was concentrated *in vacuo*, diluted with CH_2Cl_2, and washed successively with saturated $NaHCO_3$ and water (× 3). Further purification by flash column chromatography (2:3 CH_2Cl_2:Hexane) gave the title compound as an inseparable mixture of diastereomers (99:1 dr) as a colourless oil (45.4 mg, 50%). $[\alpha]_D^{20}$ +100.0 (*c* 0.7, $CHCl_3$); **Chiral HPLC analysis** Chiralpak IB (95:5 Hexane:^{i}PrOH, flow rate 1 mL·min^{-1}, 211 nm, 30 °C) t_R(2*R*,3*R*,3a*R*,9b*R*): 33.6 min, t_R(2*S*,3*S*,3a*S*,9b*S*): 44.3 min, 1:99 er; **IR** ν_{max} (thin film): 3062 (Ar-H), 1770 (C=O), 1519 (asymm. NO_2), 1346 (symm. NO_2), 1113 (C-F); **^{1}H NMR** (500 MHz, $CDCl_3$), δ_H: 3.20 (1H, broad s, N*H*), 3.53 (1H, qdd, $^3J_{HF}$ = 8.7, 7.9, 7.2, F_3CCH), 3.84 (1H, d, $^3J_{HH}$ = 7.2, F_3CCHC(3a)*H*), 4.78 (1H, d, $^3J_{HH}$ = 7.9, HNC(2)*H*), 7.06–7.12 (2H, m, ArC(8,9)*H*), 7.13–7.17 (1H, m, ArC(6)*H*), 7.31–7.37 (4H, m, ArC(7)*H*, PhC(2,4,6)*H*), 7.39–7.45 (4H, m, O_2N-ArC(2,6)*H*, PhC(3,5)*H*) 8.10–8.15 (2H, m, O_2N-ArC(3,5)*H*); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$) δ_C: 52.2 (*C*(3a)COO), 55.4 (q, $^2J_{CF}$ = 28.3, F_3CC(3)H), 60.9 (*C*(2)H), 68.8 (*C*(9b)), 117.4 (Ar*C*(6)H), 124.0 (O_2N-Ar*C*(3,5)H), 125.4 (Ar*C*(8)H), 125.8 (Ar*C*(9a)), 125.8 (q, $^1J_{CF}$ = 279.2, *C*F_3), 125.9 (Ph*C*(2,6)H), 128.5 (Ph*C*(4)H), 128.5 (O_2N-Ar*C*(2,6)H), 129.4 (Ph*C*(3,5)H), 129.6 (Ar*C*(9)H), 130.3 (Ar*C*(7)H), 141.6 (Ph*C*(1)), 147.8 (O_2N-Ar*C*(4)), 148.3 (O_2N-Ar*C*(1)), 149.4 (Ar*C*(5a)), 166.6 (O*C*(4)-O); **^{19}F NMR** (470, $CDCl_3$) δ_F: −67.58 (3F, d, $^3J_{HF}$ = 8.7, C*F*$_3$); **HRMS** (ESI$^+$) $C_{24}H_{16}F_3N_2O_4^+$ ([M−H]$^+$) requires 453.1057, found 453.1052 (−1.0 ppm).


8.14
8.13
7.44
7.44
7.43
7.43
7.42
7.42
7.41
7.40
7.40
7.36
7.36
7.35
7.35
7.35
7.34
7.34
7.34
7.34
7.33
7.33
7.32
7.26 CDCl3
7.17
7.17
7.17
7.15
7.15
7.15
7.11
7.11
7.10
7.10
7.10
7.09
7.09
7.08
7.08
7.07
7.07
4.79
4.77
3.84
3.83
3.57
3.55
3.54
3.52
3.51
3.49
3.20
F3C
H
O
O
N
H
Ph
O2N
1H, CDCl3, 500 MHz
2.00
3.99
4.01
1.02
2.00
1.02
1.02
1.04
1.03
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)



$^{13}C\{^{1}H\}$, $CDCl_3$, 126 MHz

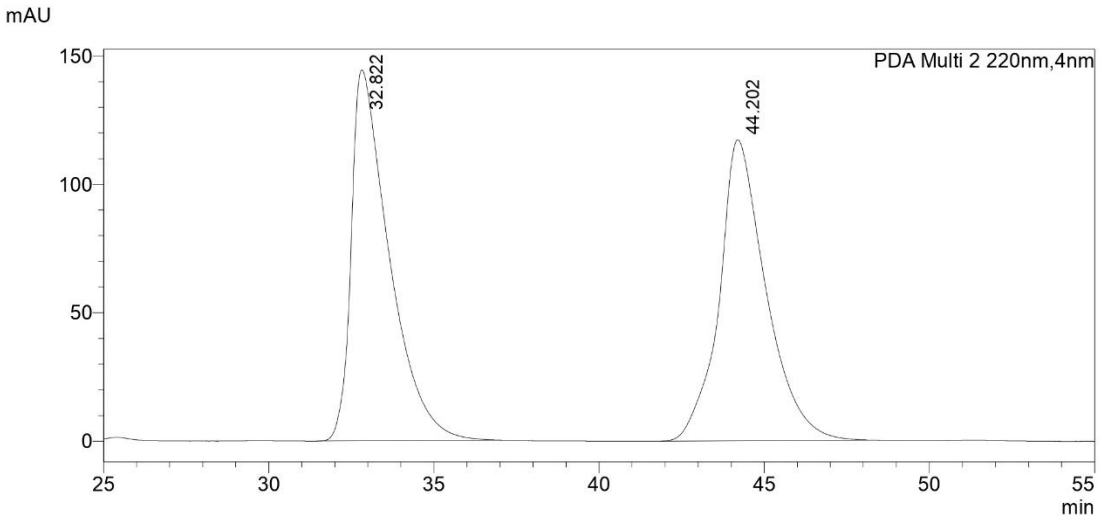


^{19}F, $CDCl_3$, 470 MHz

<Peak Table>

PDA Ch2 220nm

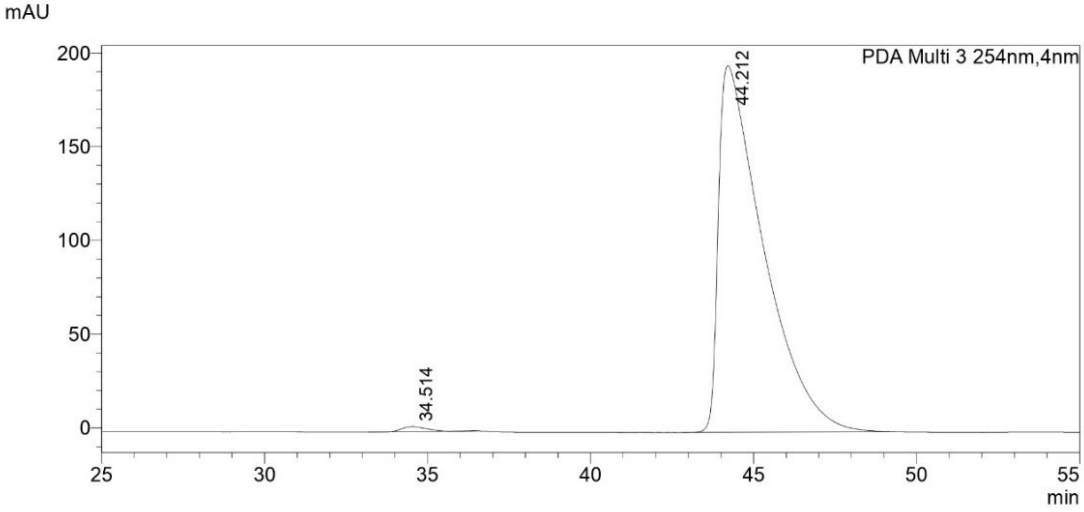
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Total		100.000



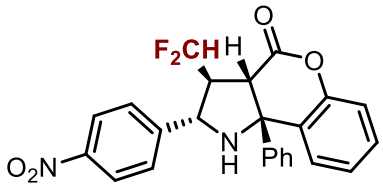
<Peak Table>

PDA Ch3 254nm

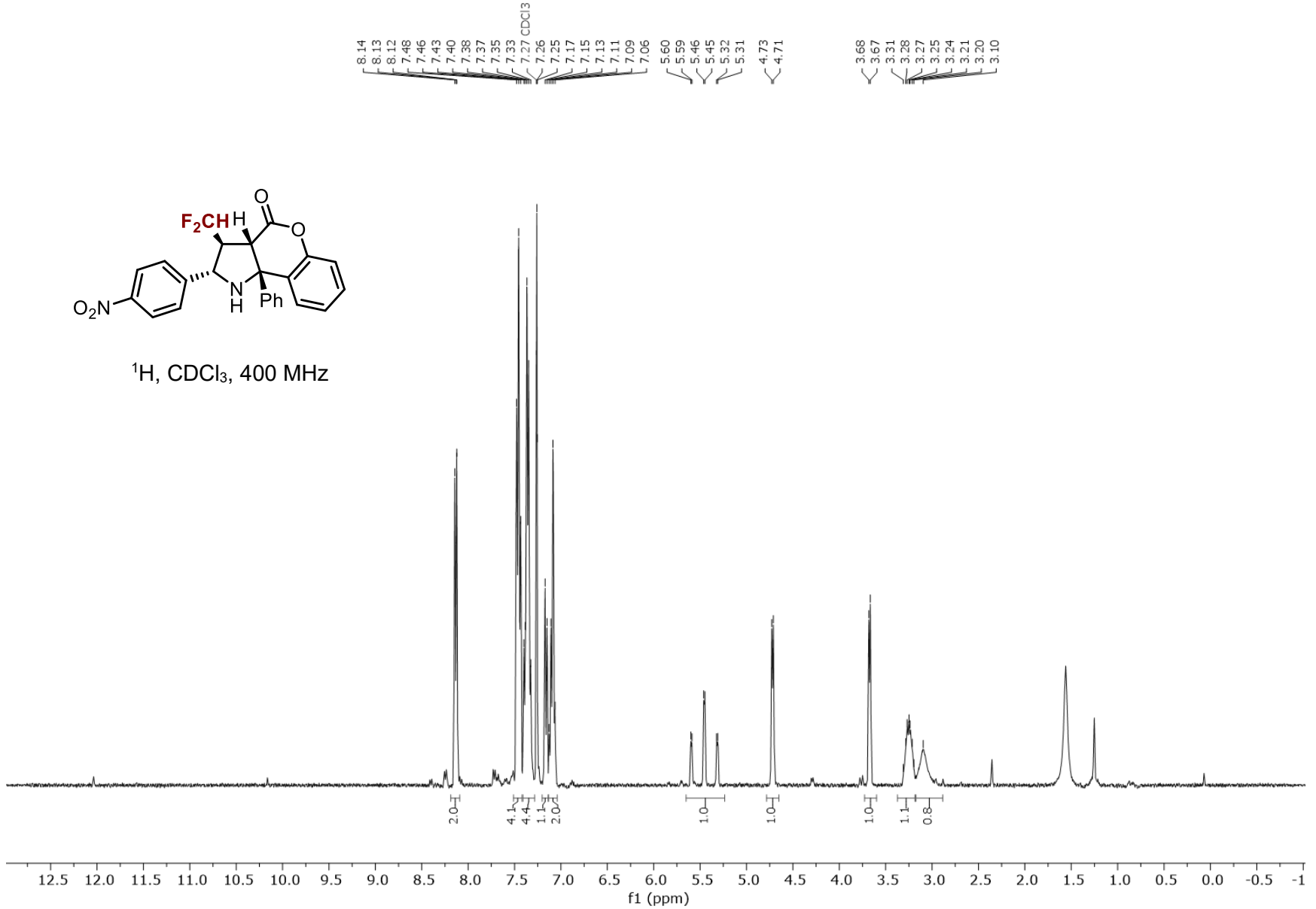
Peak#	Ret. Time	Area%
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2	44.212	99.326
Total		100.000

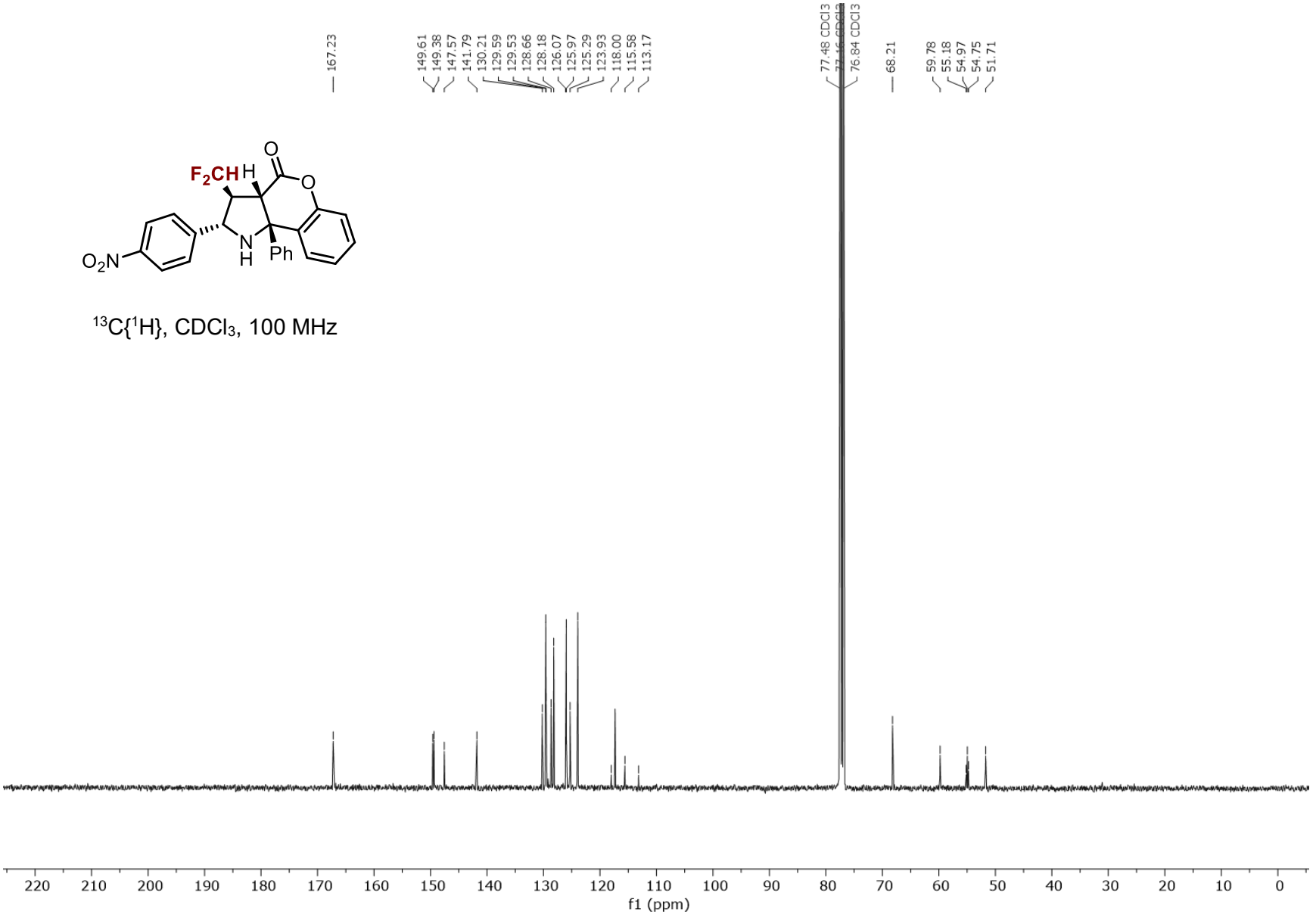


(2S,3S,3aS,9bS)-3-(difluoromethyl)-2-(4-nitrophenyl)-9b-phenyl-2,3,3a,9b-tetrahydrochromeno[4,3-b]pyrrol-4(1H)-one (33)

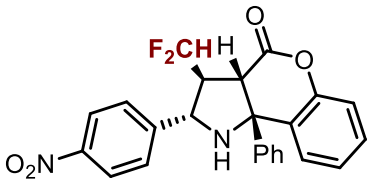


Following **General Procedure G**, 4-nitrophenyl (*E*)-4,4-difluorobut-2-enoate (97.2 mg, 0.40 mmol), (*E*)-*N*-4-nitrobenzyl-2-hydroxybenzophenoneimine (199.2 mg, 0.60 mmol), and (2*S*,3*R*)-8-MeO-HyperSe (16.0 mg, 0.04 mmol), and dimethylformamide (4 mL) were stirred for 23 h at 50 °C. The mixture was then concentrated *in vacuo* and stirred in 1 M HCl (2 mL) and THF (4 mL) for one hour. The mixture was concentrated *in vacuo*, diluted with CH_2Cl_2, and washed successively with saturated $NaHCO_3$ and water (× 3). Further purification by flash column chromatography (First set:- 2:3 CH_2Cl_2:Hexane and second set:- pure toluene) gave the title compound as an inseparable mixture of diastereomers (95:5 dr) as a colourless oil (36.5 mg, 21%). $[\alpha]_D^{20}$ −172.5 (*c* 0.4, $CDCl_3$); **Chiral HPLC analysis** Chiralpak OD-H (95:5 Hexane:^{i}PrOH, flow rate 1 mL·min^{-1}, 211 nm, 30 °C) t_R(2*R*,3*R*,3a*R*,9b*R*): 53.1 min, t_R(2*S*,3*S*,3a*S*,9b*S*): 59.3 min, 3:97 er; **IR** ν_{max} (thin film): 3352 (Ar-H), 3064 (sp^{3}C-H), 1753 (C=O), 1517 (asymm. NO_2), 1348 (symm. NO_2); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H: 3.10 (1H, broad s, N*H*), 3.18–3.32 (1H, m, HF_aF_bCCH), 3.67 (1H, d, $^3J_{HH}$ = 6.5, C(3a)*H*), 4.72 (1H, d, $^3J_{HH}$ = 6.8, HNC(2)*H*), 5.45 (1H, app.td $^2J_{HF}$ = 55.3, $^3J_{HH}$ = 5.0, HF_aF_bC), 7.04–7.13 (2H, m, ArC(8,9)*H*), 7.13–7.19 (1H, m, ArC(6)*H*), 7.30–7.41 (4H, m, ArC(7)*H*, PhC(2,4,6)*H*), 7.42–7.50 (4H, m, O_2N-ArC(2,6)*H*, PhC(3,5)*H*), 8.10–8.17 (2H, m, O_2N-ArC(3,5)*H*); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ_C: 51.7 (app.t, $^3J_{CF}$ = 4.1, *C*(3a)COO), 55.0 (t, $^2J_{CF}$ = 21.7, HF_aF_bCC(3)H), 59.8 (*C*(2)H), 68.2 (*C*(9b)), 115.6 (t, $^1J_{CF}$ = 243.0, HF_aF_bC), 117.3 (Ar*C*(6)H), 124.0 (O_2N-Ar*C*(3,5)H), 125.3 (Ar*C*(8)H or Ar*C*(9)H), 126.0 (Ph*C*(2,6)H), 126.1 (Ar*C*(9a)), 128.2 (O_2N-Ar*C*(2,6)H), 128.7 (Ph*C*(4)H), 129.5 (Ar*C*(8)H or Ar*C*(9)H), 129.6 (Ph*C*(3,5)H), 130.2 (Ar*C*(7)H), 141.8 (Ph*C*(1)), 147.6 (O_2N-Ar*C*(4)), 149.4 (O_2N-Ar*C*(1)), 149.6 (Ar*C*(5a)), 167.2 (O*C*(4)-O); **^{19}F{^{1}H} NMR** (376, $CDCl_3$) δ_F: −122.13 (1F, $^2J_{FF}$ = 286.9, HF_aF_bC), −117.90 (1F, $^2J_{FF}$ = 286.9, HF_aF_bC); **HRMS** (ESI$^+$) $C_{24}H_{18}F_2N_2NaO_4^+$ ([M+Na]$^+$) requires 459.11268, found 459.1126 (−0.28 ppm).


8.14
8.13
8.12
7.48
7.46
7.43
7.40
7.38
7.37
7.35
7.33
7.27 CDCl3
7.26
7.25
7.17
7.15
7.13
7.11
7.09
7.06
5.60
5.59
5.46
5.45
5.32
5.31
4.73
4.71
3.68
3.67
3.31
3.28
3.27
3.25
3.24
3.21
3.20
3.10
F2CH
H
O
O
N
H
Ph
O2N
1H, CDCl3, 400 MHz
2.0
4.1
4.4
1.1
2.0
1.0
1.0
1.0
1.1
0.8
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)



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



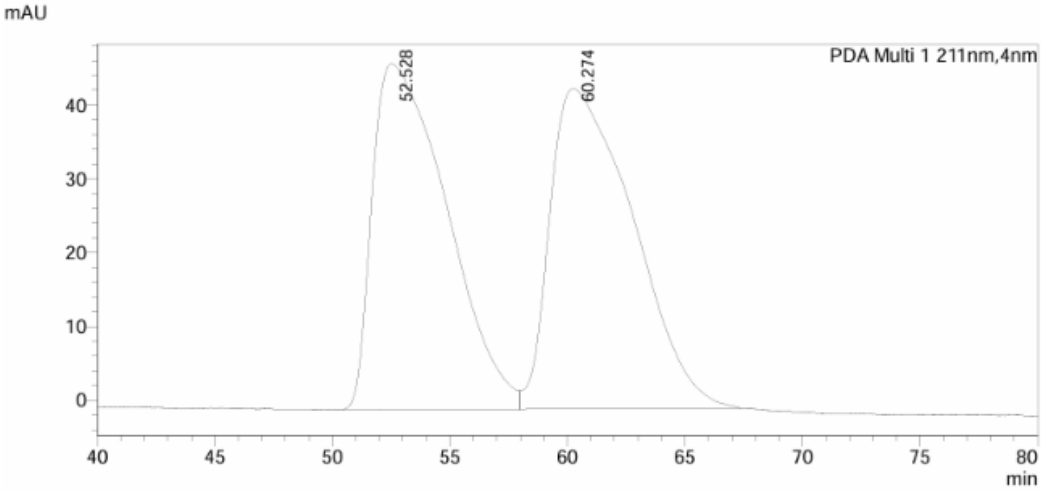
$^{19}F\{^{1}H\}$, $CDCl_3$, 376 MHz

<Peak Table>

PDA Ch1 211nm

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Total		100.000

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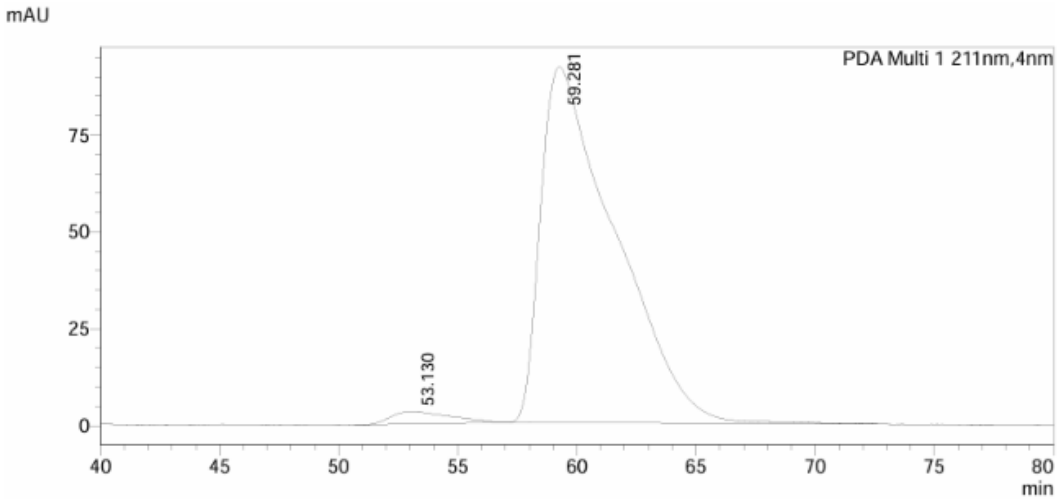


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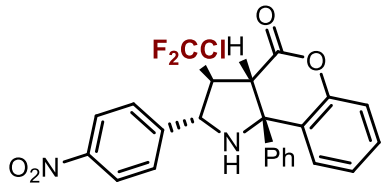
PDA Ch1 211nm

Peak#	Ret. Time	Area%
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2	59.281	97.334
Total		100.000

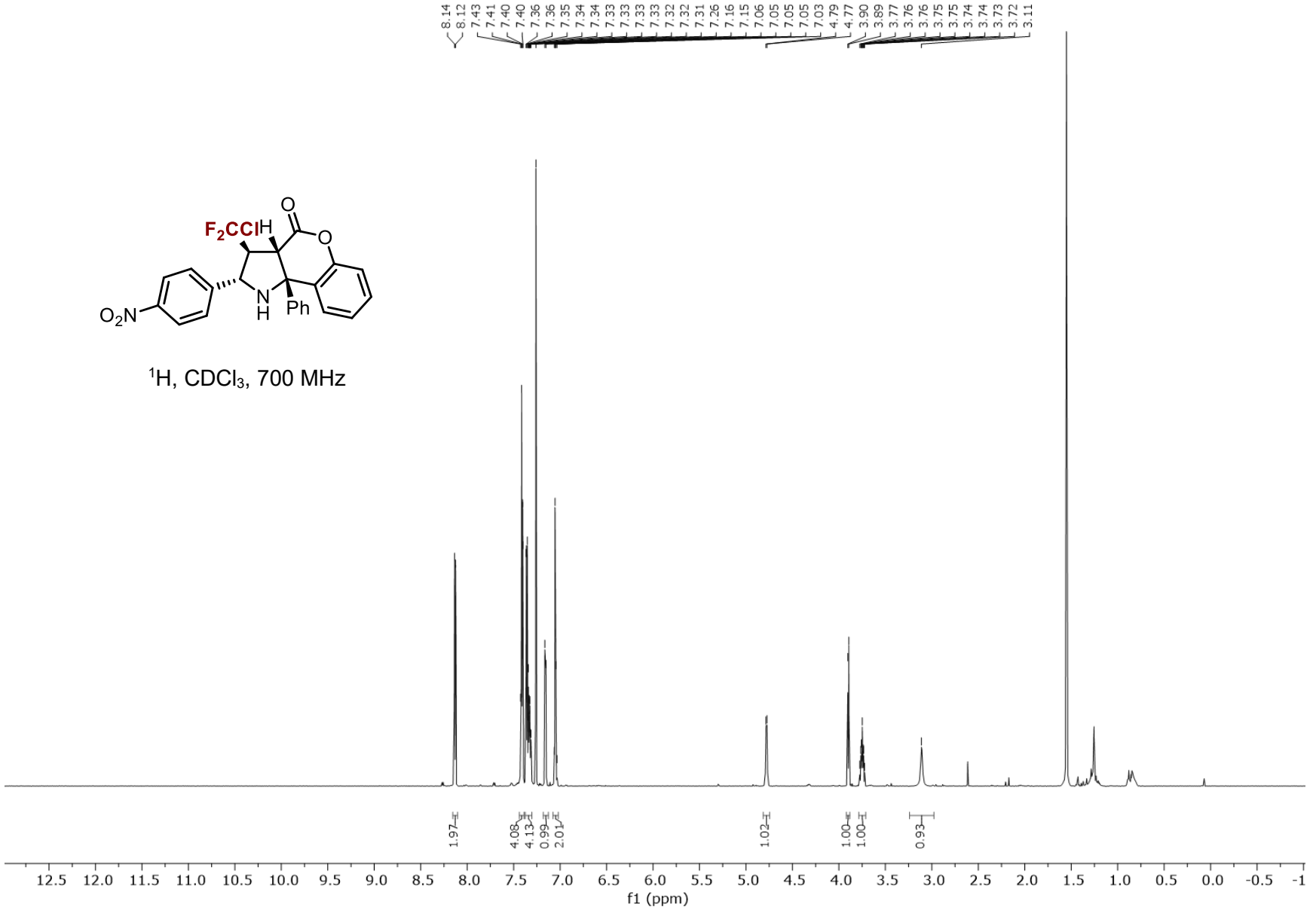
<Chromatogram>

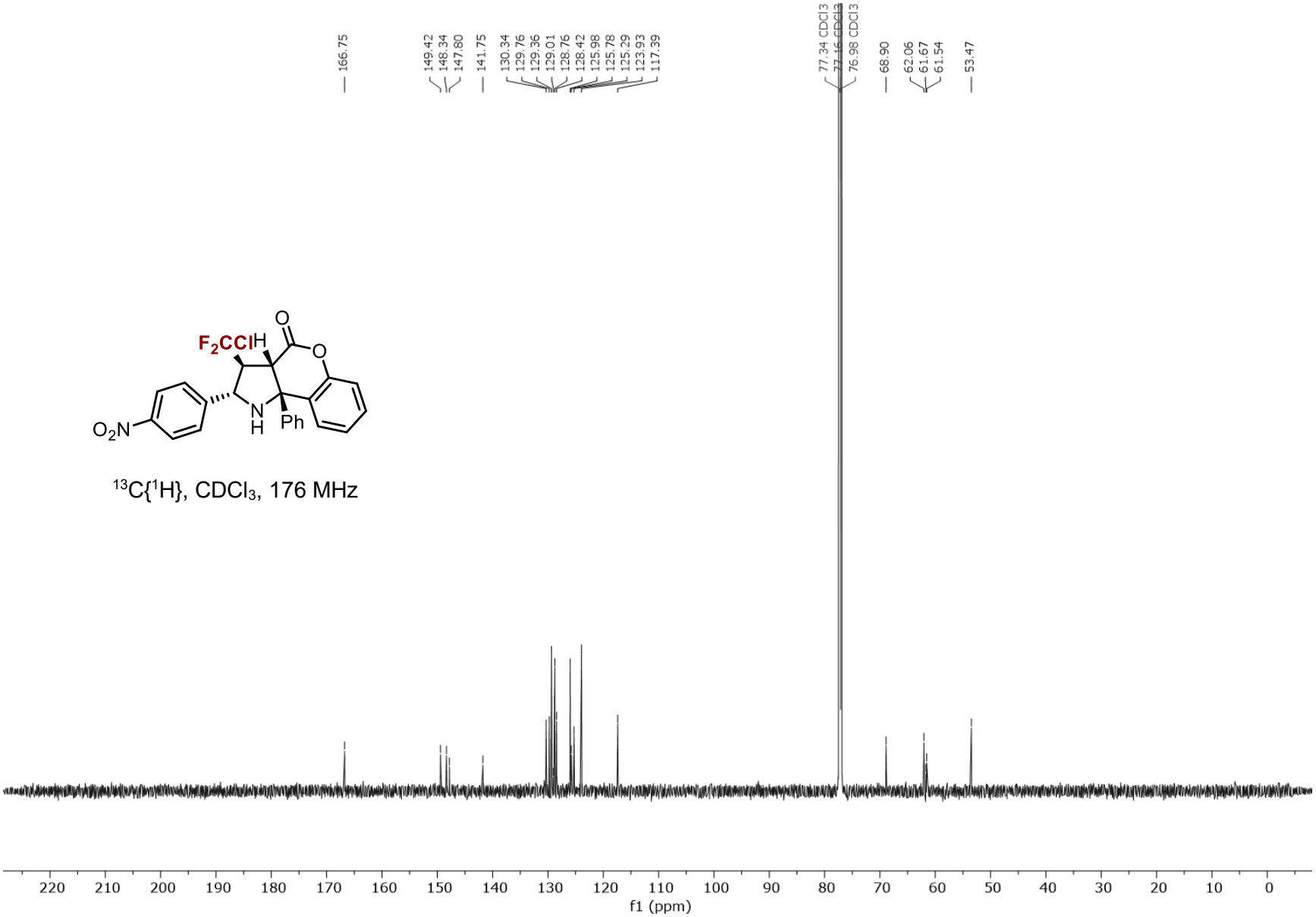


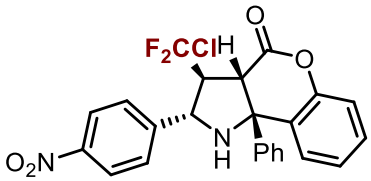
(2*S*,3*S*,3a*S*,9b*S*)-3-(chlorodifluoromethyl)-2-(4-nitrophenyl)-9b-phenyl-2,3,3a,9b-tetrahydrochromeno[4,3-*b*]pyrrol-4(1*H*)-one (34)



Following **General Procedure G**, 4-nitrophenyl (*E*)-4-chloro-4,4-difluorobut-2-enoate (55.4 mg, 0.20 mmol), (*E*)-*N*-4-nitrobenzyl-2-hydroxybenzophenoneimine (99.6 mg, 0.30 mmol), and (2*S*,3*R*)-8-MeO-HyperSe (8.0 mg, 0.02 mmol), and dimethylformamide (2 mL) were stirred for 23 h at 50 °C. The mixture was concentrated *in vacuo*, diluted with CH_2Cl_2, and washed successively with water (× 3). Further purification by flash column chromatography (2:3 CH_2Cl_2:Hexane) gave the title compound as colourless oil (23 mg, 30%). $[\alpha]_D^{20}$ −172.5 (*c* 0.2, $CDCl_3$); **Chiral HPLC analysis** Chiralpak IB (95:5 Hexane:^{i}PrOH, flow rate 1 mL·min^{-1}, 270 nm, 30 °C) t_R(2*R*,3*R*,3a*R*,9b*R*): 33.0 min, t_R(2*S*,3*S*,3a*S*,9b*S*): 40.8 min, 1:99 er; **IR** ν_{max} (thin film): 3344 (Ar-H), 2924 (C-H), 1751 (C=O), 1521 (asymm. NO_2), 1346 (symm. NO_2), 1213 (CF_3), 1107 (C-O); **^{1}H NMR** (700 MHz, $CDCl_3$), δ_H: 3.75 (1H, app tdd, $^3J_{HF}$ = 10.7, 7.4, 7.1, C(3)*H*), 3.90 (1H, d, $^3J_{HH}$ = 7.1, C(3a)*H*), 4.78 (1H, d, $^3J_{HH}$ = 7.4, C(2)*H*), 7.03−7.07 (2H, m, ArC(8,9)*H*), 7.16 (1H, d, $^3J_{HH}$ = 8.2, ArC(6)*H*), 7.31−7.38 (4H, m, ArC(7)*H* and PhC(2,4,6)*H*), 7.39−7.44 (4H, m, PhC(3,5)*H* and O_2N-ArC(2,6)*H*), 8.11−8.15 (2H, m, O_2N-ArC(3,5)*H*); **^{13}C{^{1}H} NMR** (176 MHz, $CDCl_3$), δ_C: 53.8 (*C*(3a)H), 61.5 (app t, $^2J_{CF}$ = 23.6, *C*(3)H), 62.1 (*C*(2)H), 68.9 (*C*(9b)), 117.4 (Ar*C*(6)H), 123.9 (O_2N-Ar*C*(3,5)H), 125.3 (Ar*C*(8)H), 125.8 (Ar*C*(9a)), 126.0 (Ph*C*(2,6)H), 128.4 (Ph*C*(4)H), 128.8 (O_2N-Ar*C*(2,6)H), 129.0 (app t, $^1J_{CF}$ = 293.5, ClF_2C), 129.4 (Ph*C*(3,5)H), 129.8 (Ar*C*(9)H), 130.3 (Ar*C*(7)H), 141.8 (PhC(1)), 147.8 (O_2N-Ar*C*(4)), 148.3 (O_2N-Ar*C*(1)), 149.4 (*C*(5a)), 166.8 (O*C*(4)-O); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$), δ_F: −51.52 (1F, d, $^2J_{FF}$ = 168.4, Cl$F_a$$F_b$C), −52.60 (1F, d, $^2J_{FF}$ = 168.4, Cl$F_a$$F_b$C); **HRMS** (ESI$^+$) $C_{24}ClH_{17}F_2N_2NaO_4^+$ ([M+Na]$^+$) requires 493.0737, found 493.0734 (−0.63 ppm).


F2CClH
O
O
N
H
Ph
O2N
1H, CDCl3, 700 MHz
8.14
8.12
7.43
7.41
7.40
7.40
7.36
7.36
7.35
7.34
7.34
7.33
7.33
7.33
7.33
7.32
7.32
7.31
7.26
7.16
7.15
7.06
7.05
7.05
7.05
7.03
4.79
4.77
3.90
3.89
3.77
3.76
3.76
3.75
3.75
3.74
3.74
3.73
3.72
3.11
1.97
4.08
4.13
0.99
2.01
1.02
1.00
1.00
0.93
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)


166.75
149.42
148.34
147.80
141.75
130.34
129.76
129.36
129.01
128.76
128.42
125.98
125.78
125.29
123.93
117.39
77.34 CDCl3
77.16 CDCl3
76.98 CDCl3
68.90
62.06
61.67
61.54
53.47
F2CClH
O
O
N
H
Ph
O2N
13C{1H}, CDCl3, 176 MHz
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

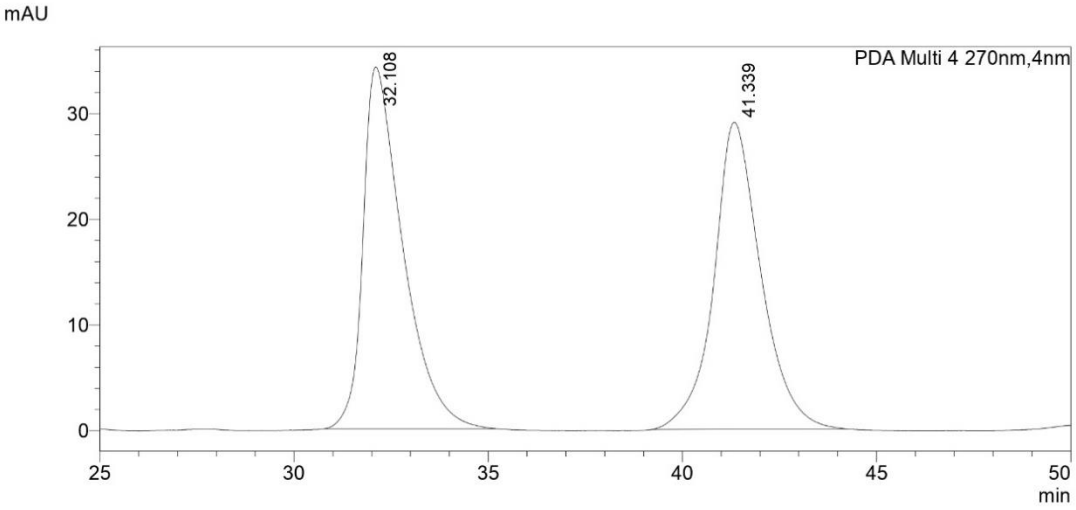


$^{19}F\{^{1}H\}$, $CDCl_3$, 376 MHz

<Peak Table>

PDA Ch4 270nm

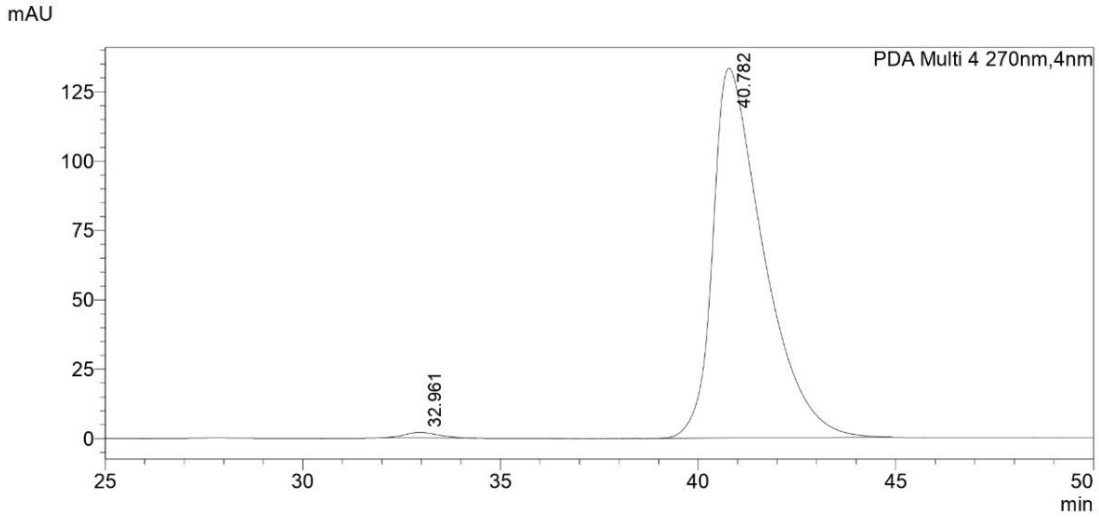
Peak#	Ret. Time	Area%
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2	41.339	50.088
Total		100.000



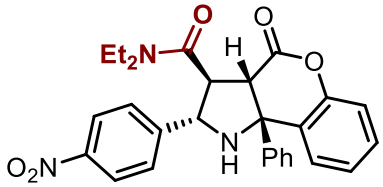
<Peak Table>

PDA Ch4 270nm

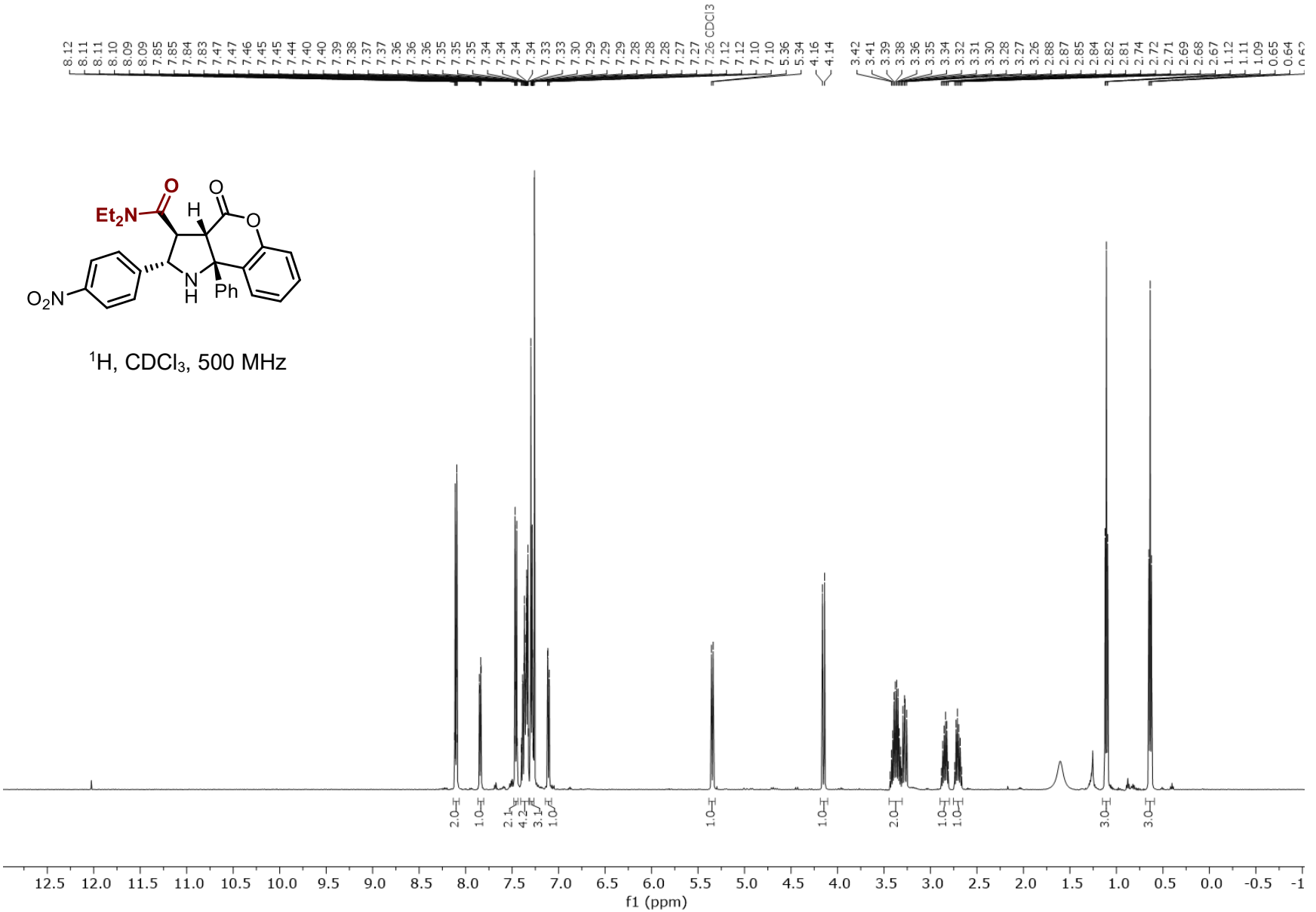
Peak#	Ret. Time	Area%
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2	40.782	98.973
Total		100.000

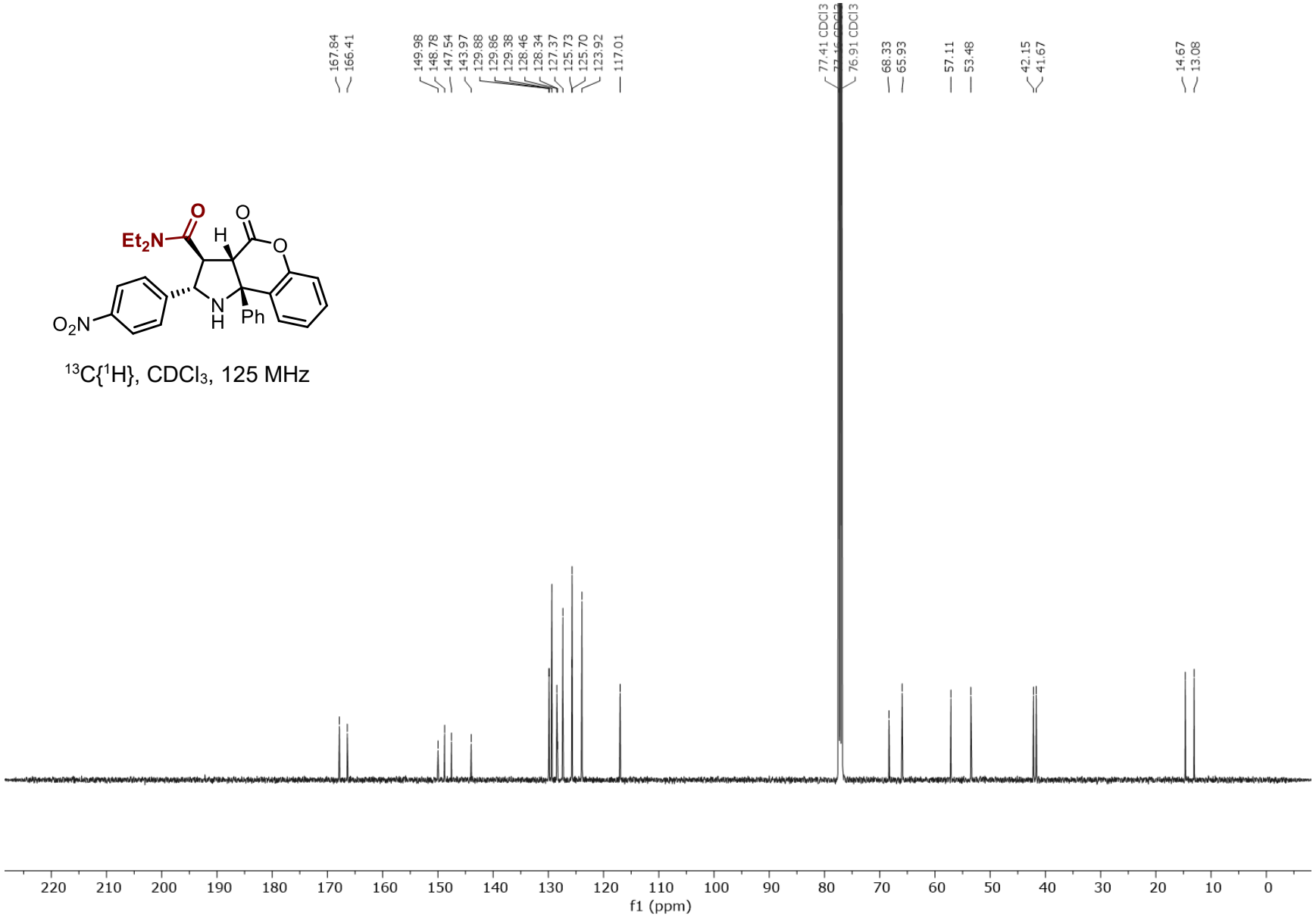


(2S,3S,3aS,9bS)-*N*,*N*-diethyl-2-(4-nitrophenyl)-4-oxo-9b-phenyl-1,2,3,3a,4,9b-hexahydrochromeno[4,3-b]pyrrole-3-carboxamide (35)



Following **General Procedure G**, *N*,*N*-diethyl (4-nitrophenyl) fumarate (116.8 mg, 0.40 mmol), (*E*)-*N*-4-nitrophenyl-2-hydroxybenzophenoneimine (199.2 mg, 0.60 mmol), and (2*S*,3*R*)-8-MeO-HyperSe (16.0 mg, 0.04 mmol), and dimethylformamide (4 mL) were stirred for 23 h at 50 °C. The mixture was then concentrated *in vacuo* and stirred in 1 M HCl (1 mL) and THF (2 mL) for one hour. The mixture was concentrated *in vacuo*, diluted with CH_2Cl_2, and washed successively with saturated $NaHCO_3$ and water (× 3). Further purification by flash column chromatography (pure toluene) gave the title compound as a colourless oil (113 mg, 58%). $[\alpha]_D^{20}$ −60.6 (*c* 0.5, $CHCl_3$); **Chiral HPLC analysis** Chiralpak IB (95:5 Hexane:^{i}PrOH, flow rate 1 mL·min^{-1}, 220 nm, 30 °C) t_R(2*S*,3*S*,3a*S*,9b*S*): 23.0 min, t_R(2*R*,3*R*,3a*R*,9b*R*): 56.0 min, 97:3 er; **IR** ν_{max} (thin film): 3346 (Ar-H), 2978, 2933 and, 2873 (sp^{3}C-H), 1761 (C=O, ester), 1634 (C=O, amide) 1520 (asymm. NO_2), 1344 (symm. NO_2), **^{1}H NMR** (500 MHz, $CDCl_3$), equal ratio of rotamers was observed, δ_H: 0.64 (3H, t, $^3J_{HH}$ = 7.1, N(CH$_a$H$_b$)$_2$(C*H*$_3$)$_2$, rota. 1), 1.11 (3H, t, $^3J_{HH}$ = 7.1, N(CH$_a$H$_b$)$_2$(C*H*$_3$)$_2$, rota. 2), 2.70 (1H, dq, $^2J_{HH}$ = 14.5, $^3J_{HH}$ = 7.1, N(C*H*$_a$H$_b$)$_2$(C*H*$_3$)$_2$, rota. 1), 2.85 (1H, dq, $^2J_{HH}$ = 14.5, $^3J_{HH}$ = 7.1, N(CH$_a$*H*$_b$)$_2$(C*H*$_3$)$_2$, rota. 1), 3.28 (1H, dd, $^3J_{HH}$ = 11.4, 9.2, C(3)*H*), 3.30–3.44 (2H, m, N(C*H*$_a$*H*$_b$)$_2$(C*H*$_3$)$_2$, rota. 2), 4.15 (1H, d, $^3J_{HH}$ = 11.4, C(3a)*H*), 5.35 (1H, d, $^3J_{HH}$ = 9.2, C(2)*H*), 7.11 (1H, dd, $^3J_{HH}$ = 7.7, $^4J_{HH}$ = 1.60, ArC(6)*H*), 7.27−7.31 (3H, m, PhC*H*), 7.32−7.41 (4H, m, ArC(7,8)*H* and PhC*H*), 7.44–7.49 (2H, m, O$_2$N-ArC(2,6)*H*), 7.84 (1H, dd, $^3J_{HH}$ = 7.4, $^4J_{HH}$ = 2.0, C(9)*H*), 8.08–8.13 (2H, m, O$_2$N-ArC(3,5)*H*); **^{13}C{^{1}H} NMR** (125 MHz, $CDCl_3$), δ_C: 13.1 (N(CH$_a$H$_b$)$_2$(*C*H$_3$)$_2$, rota.1), 14.7 (N(CH$_a$H$_b$)$_2$(*C*H$_3$)$_2$, rota.2), 41.7 (N(*C*H$_a$H$_b$)$_2$(CH$_3$)$_2$, rota.1), 42.2 (N(*C*H$_a$H$_b$)$_2$(CH$_3$)$_2$, rota.2) 53.5 (*C*(3)H), 57.1 (*C*(3a)H), 65.9 (*C*(2)H), 68.3 (*C*(9b)), 117.0 (Ar*C*(6)H), 123.9 (O$_2$N-Ar*C*(3,5)H), 125.7^0 (Ph*C*(2,6)H), 125.7^3, 127.4 (O$_2$N-Ar*C*(2,6)H), 128.3, 128.5, 129.4 (Ph*C*(3,5)H), 129.8^6 and 129.8^8 (Ar*C*(9)H and Ar*C*(7)H), 144.0 (Ph*C*(1)), 147.5 (O$_2$N-Ar*C*(4)), 148.8 (Ar*C*(5a)), 150.0 (O$_2$N-Ar*C*(1)), 166.4 (O*C*(4)-O), 167.8 (CH$_3$)$_2$(CH$_2$)$_2$N*C*O); **HRMS** (ESI$^+$) $C_{28}H_{27}N_3NaO_5^+$ ([M+Na]$^+$) requires 508.1842, found 508.1839 (−0.76 ppm).


Et2N
O
O
H
O
N
H
Ph
O2N
1H, CDCl3, 500 MHz
f1 (ppm)

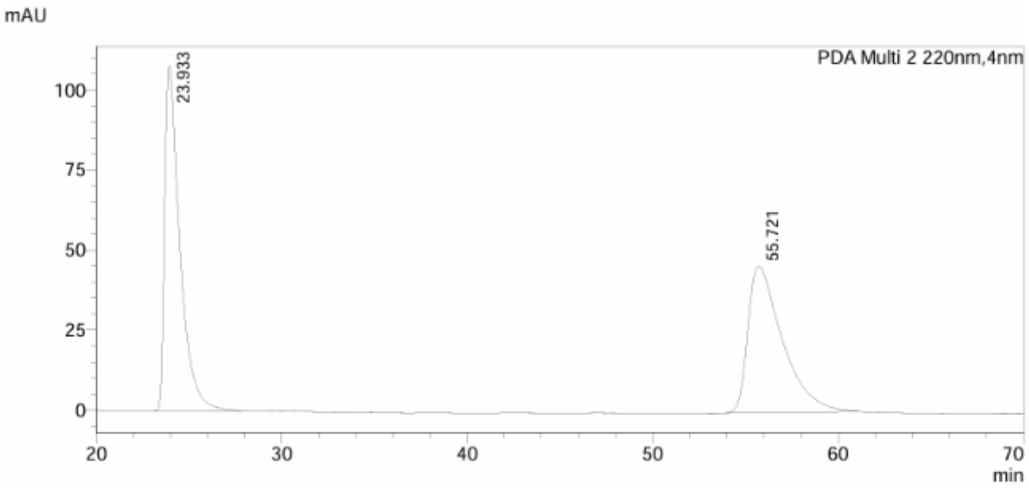

167.84
166.41
149.98
148.78
147.54
143.97
129.88
129.86
129.38
128.46
128.34
127.37
125.73
125.70
123.92
117.01
77.41 CDCl3
76.91 CDCl3
68.33
65.93
57.11
53.48
42.15
41.67
14.67
13.08
Et2N
O
O
H
O
N
H
Ph
O2N
13C{1H}, CDCl3, 125 MHz
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

<Peak Table>

PDA Ch2 220nm

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2	55.721	49.034
Total		100.000

<Chromatogram>

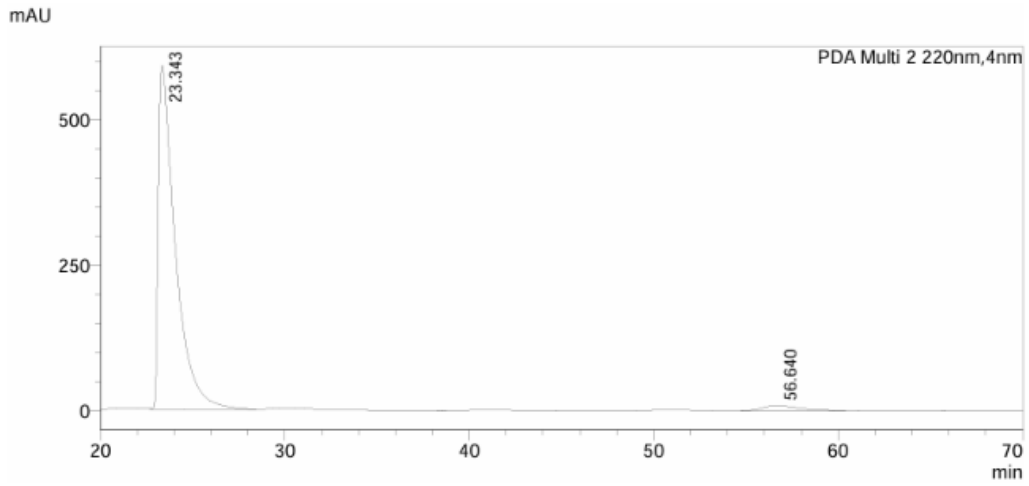


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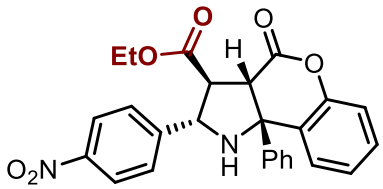
PDA Ch2 220nm

Peak#	Ret. Time	Area%
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2	56.640	2.997
Total		100.000

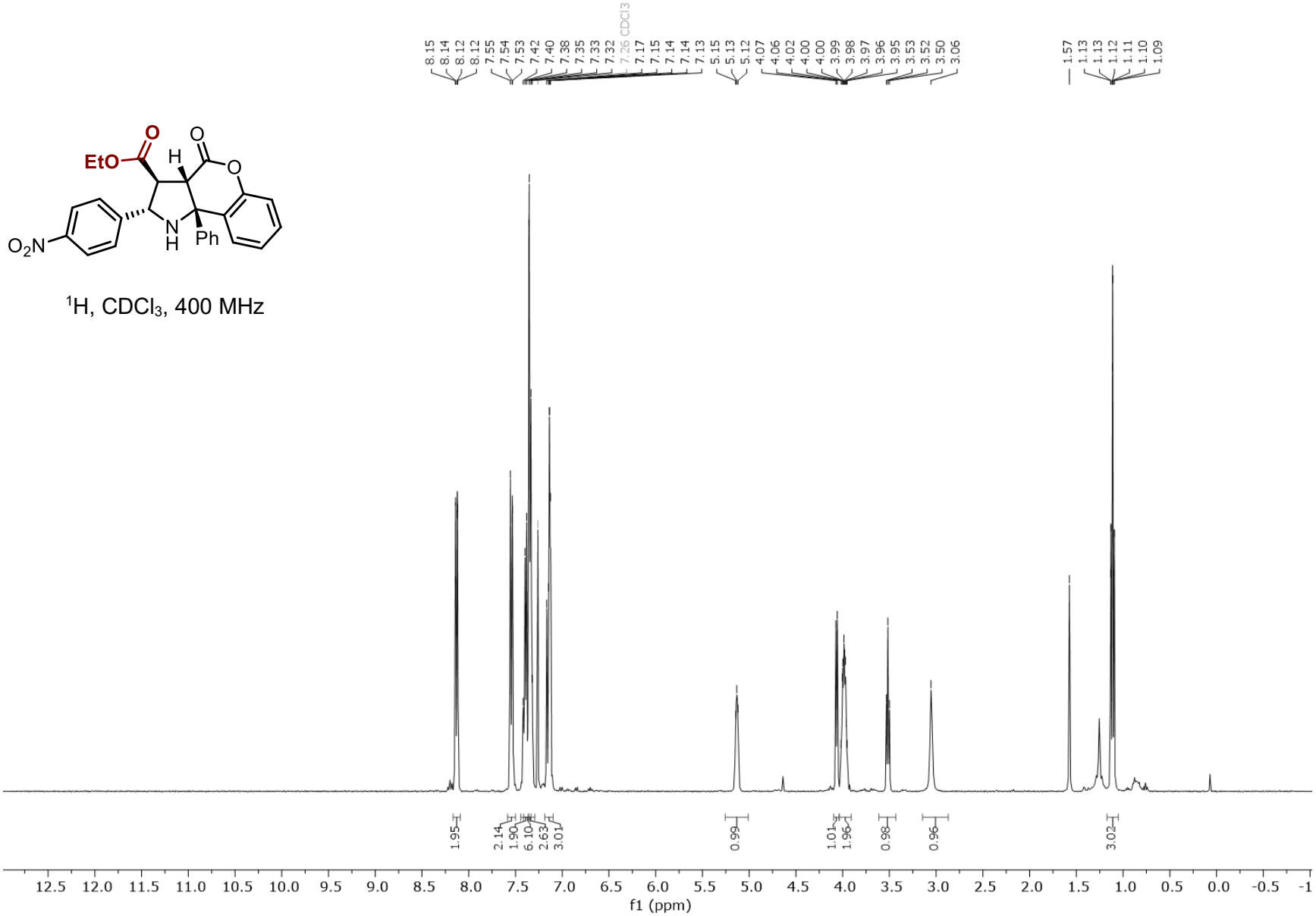
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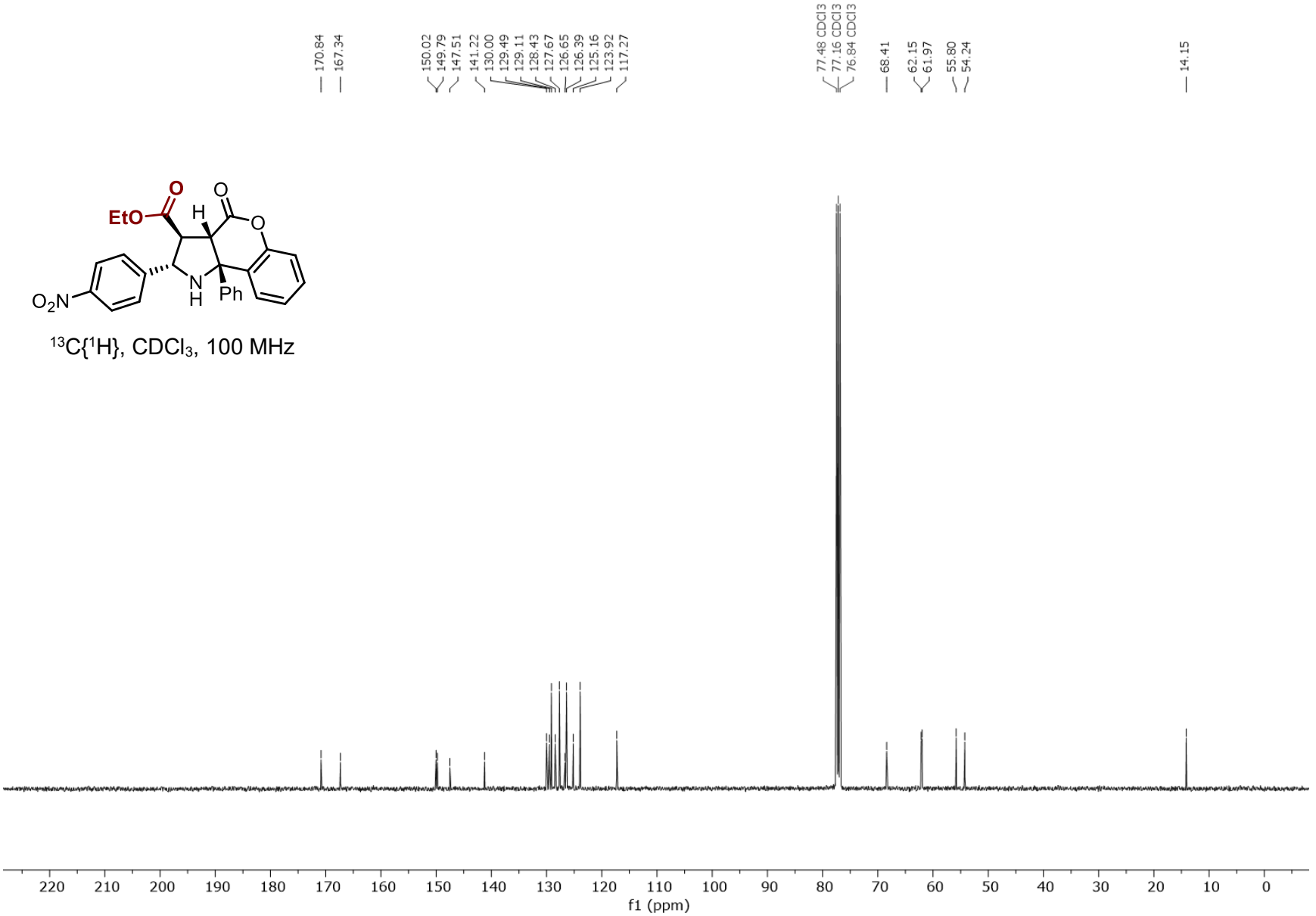
Ethyl (2*S*,3*S*,3a*S*,9b*S*)-2-(4-nitrophenyl)-4-oxo-9b-phenyl-1,2,3,3a,4,9b-hexahydrochromeno[4,3-*b*]pyrrole-3-carboxylate (36)



Following **General Procedure G**, ethyl (4-nitrophenyl) fumarate (53.2 mg, 0.20 mmol), (*E*)-*N*-4-nitrophenyl-2-hydroxybenzophenoneimine (99.6 mg, 0.30 mmol), and (2*S*,3*R*)-8-MeO-HyperSe (8.0 mg, 0.02 mmol), and dimethylformamide (2 mL) were stirred for 23 h at 50 °C. The mixture was then concentrated *in vacuo* and stirred in 1 M HCl (1 mL) and THF (2 mL) for one hour. The mixture was concentrated *in vacuo*, diluted with CH_2Cl_2, and washed successively with saturated $NaHCO_3$ and water (× 3). Further purification by flash column chromatography (2:8 CH_2Cl_2:Hexane) gave the title compound as a colourless oil (72 mg, 40%). $[\alpha]_D^{20}$ −26.5 (*c* 0.4, $CDCl_3$); **Chiral HPLC analysis** Chiralpak OD-H (95:5 Hexane:^{i}PrOH, flow rate 1 mL·min^{-1}, 211 nm, 30 °C) t_R(2*S*,3*S*,3a*S*,9b*S*): 41.0 min, t_R(2*R*,3*R*,3a*R*,9b*R*): 51.0 min, 94:6 er; **IR** ν_{max} (thin film): 3348 (Ar-H), 2926 (C-H), 1732 (C=O), 1519 (asymm. NO_2), 1346 (symm. NO_2), 1220 and 1111 (C-O); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H: 1.11 (3H, dd, $^3J_{HH}$ = 7.0$_9$, 7.0$_7$, CH_3CH$_a$H$_b$), 3.06 (1H, broad s, N*H*), 3.52 (1H, dd, $^3J_{HH}$ = 6.6, 6.4, C(3)*H*), 3.92−4.04 (2H, m, CH$_3$CH_aH$_b$), 4.07 (1H, d, $^3J_{HH}$ = 6.4, C(3a)*H*), 5.13 (1H, app t, $^3J_{HH}$ = 5.2, C(2)*H*), 7.10−7.18 (3H, m, ArC(6,8,9)*H*), 7.30−7.45 (6H, m, ArC(7)*H*, PhC(2,3,4,5,6)*H*), 7.50−7.58 (2H, m, O_2N-ArC(2,6)*H*), 8.09−8.16 (2H, m, O_2N-ArC(2,5)*H*); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$), δ_C: 14.2 (H$_3$C H$_a$H$_b$C), 54.2 (*C*(3a)H), 55.8 (*C*(3)H), 62.0 (H$_3$CH$_a$H$_b$*C*), 62.2 (*C*(2)H), 68.4 (*C*(9b)), 117.3 (Ar*C*(6)H), 123.9 (O_2N-Ar*C*(3,5)H), 125.2 (Ar*C*(8)H), 126.4 (Ph*C*(2,6)H), 126.6 (Ar*C*(9a)), 128.4 (Ph*C*(4)H), 129.1 (Ph*C*(3,5)H), 129.5 (Ar*C*(9)H), 130.0 (Ar*C*(7)H), 141.2 (Ph*C*(1)), 147.5 (O_2N-Ar*C*(4)), 149.8 (Ar*C*(5a)), 150.0 (O_2N-Ar*C*(1)), 167.3 (O*C*(4)-O), 170.8 (H$_3$CH$_2$CO*C*O); **HRMS** (ESI$^+$) $C_{26}H_{22}N_2NaO_6^+$ ([M+Na]$^+$) requires 481.1370, found 481.1371 (0.1 ppm).



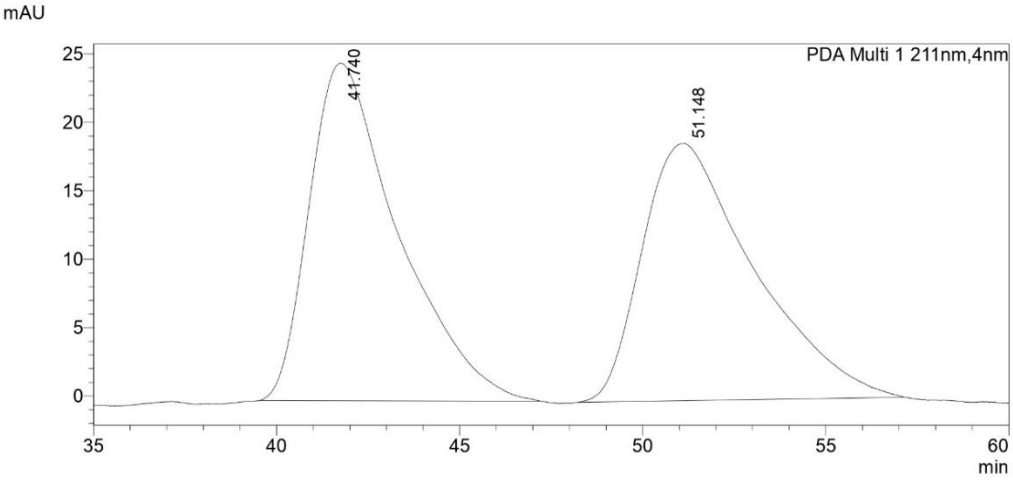
^{1}H, $CDCl_3$, 400 MHz

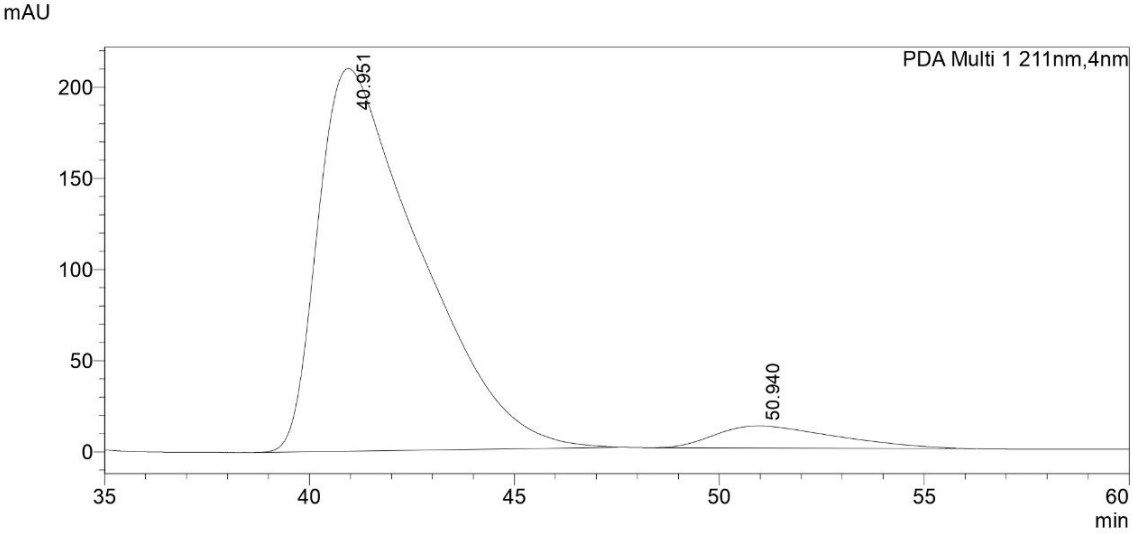

170.84
167.34
150.02
149.79
147.51
141.22
130.00
129.49
129.11
128.43
127.67
126.65
126.39
125.16
123.92
117.27
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
68.41
62.15
61.97
55.80
54.24
14.15
EtO
O
O
H
O
N
H
Ph
O2N
13C{1H}, CDCl3, 100 MHz
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

<Peak Table>

PDA Ch1 211nm

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2	51.148	48.820
Total		100.000



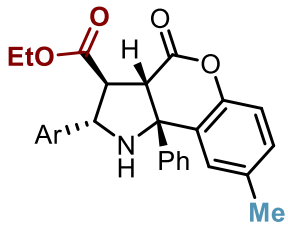


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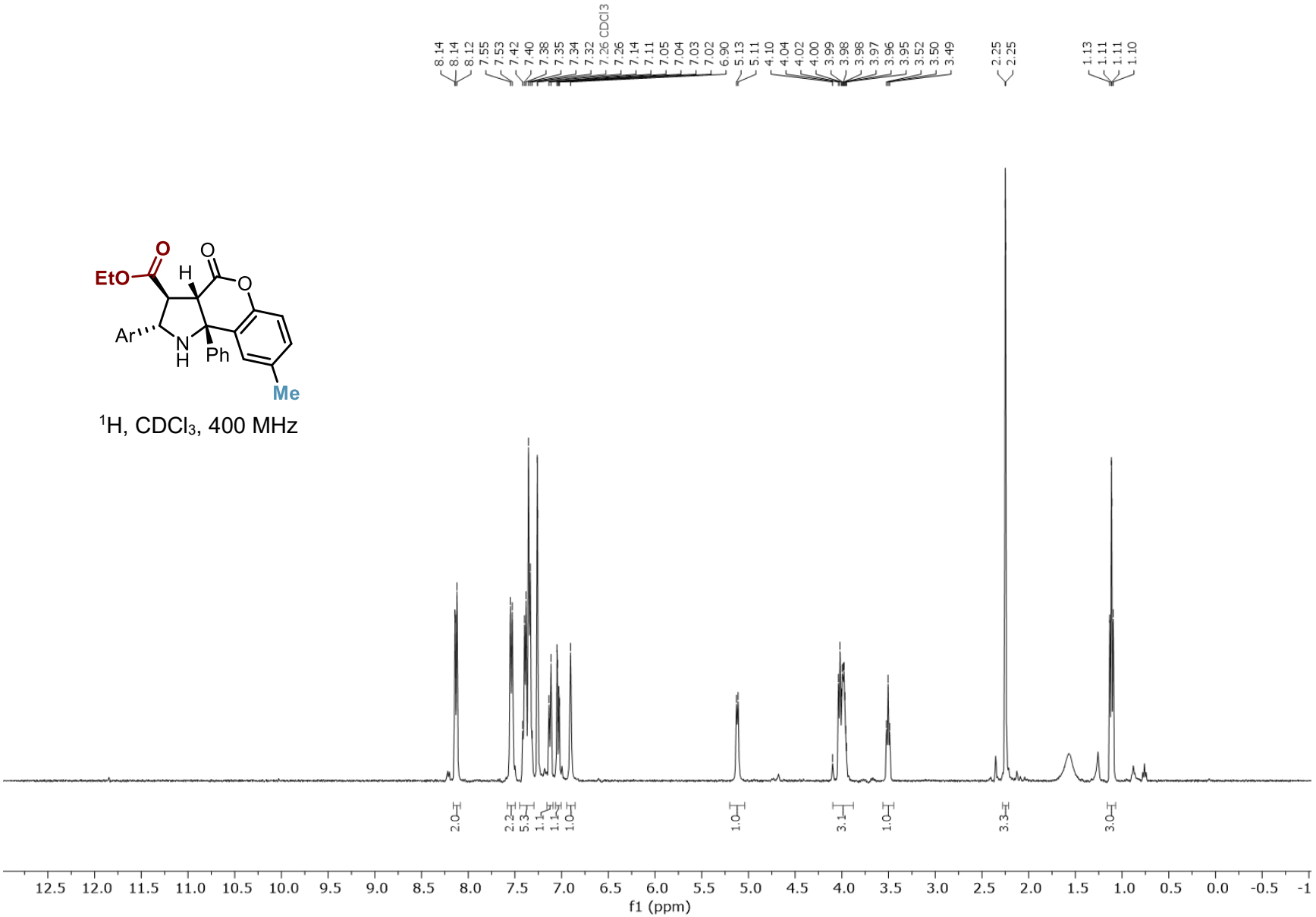
PDA Ch1 211nm

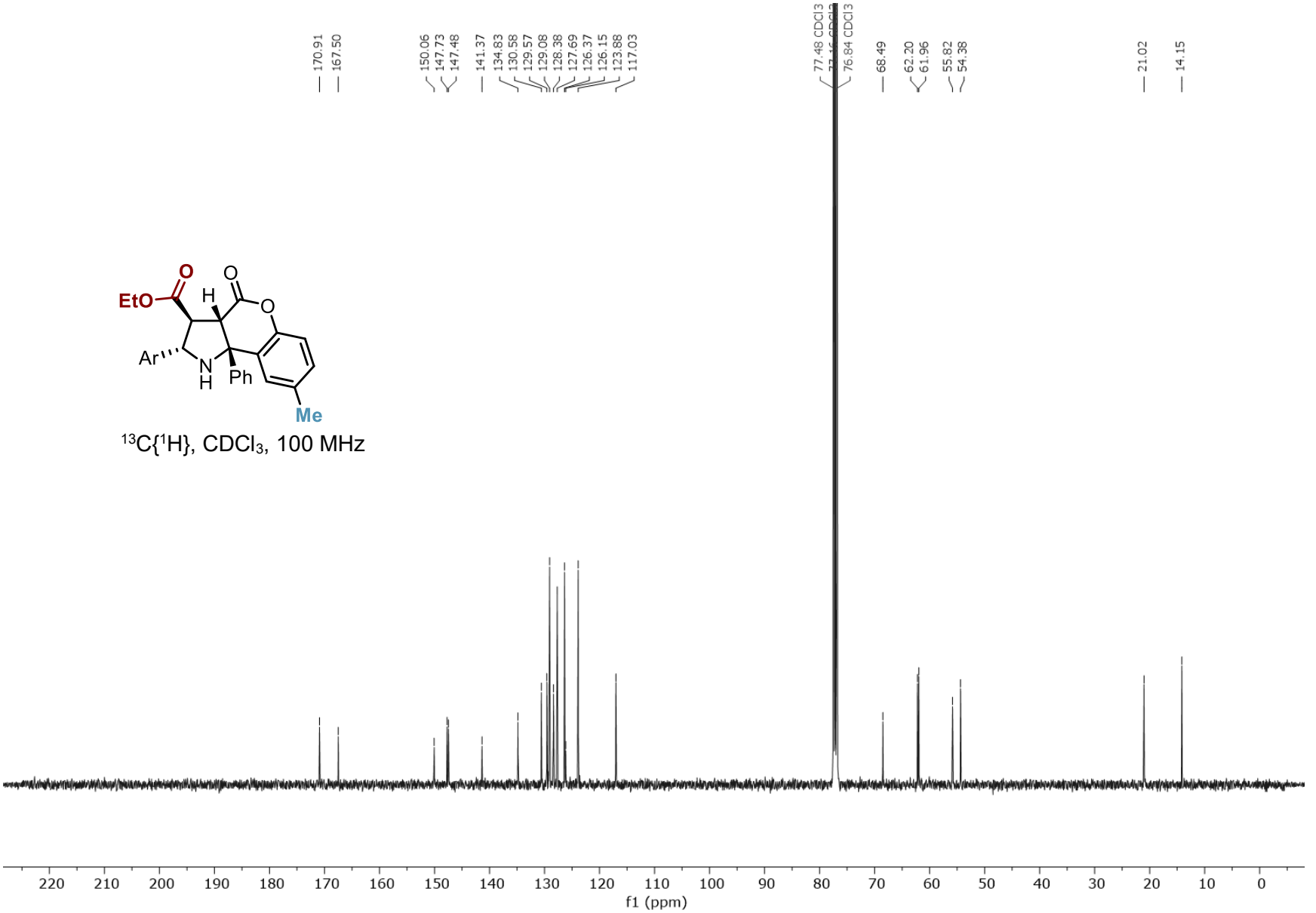
Peak#	Ret. Time	Area%
1	40.951	93.595
2	50.940	6.405
Total		100.000

Ethyl (2*S*,3*S*,3a*S*,9b*S*)-8-methyl-2-(4-nitrophenyl)-4-oxo-9b-phenyl-1,2,3,3a,4,9b-hexahydrochromeno[4,3-*b*]pyrrole-3-carboxylate (37)



Following **General Procedure G**, ethyl (4-nitrophenyl) fumarate (106.4 mg, 0.40 mmol), (*E*)-*N*-4-nitrophenyl-2-hydroxy-5-methylbenzophenoneimine (207.0 mg, 0.60 mmol), and (2*S*,3*R*)-8-MeO-HyperSe (16.0 mg, 0.04 mmol), and dimethylformamide (4 mL) were stirred for 23 h at 50 °C. The mixture was then concentrated *in vacuo* and stirred in 1 M HCl (2 mL) and THF (1 mL) for one hour. The mixture was concentrated *in vacuo*, diluted with CH_2Cl_2, and washed successively with saturated $NaHCO_3$ and water (× 3). Further purification by flash column chromatography (1:19 Et_2O:Toluene) gave the title compound as a colourless oil (58 mg, 32%). $[\alpha]_D^{20}$ −54.8 (*c* 0.5, $CHCl_3$); **Chiral HPLC analysis** Chiralpak OD-H (95:5 Hexane:^{i}PrOH, flow rate 1 mL·min^{-1}, 220 nm, 30 °C) t_R(2*S*,3*S*,3a*S*,9b*S*): 38.0 min, t_R(2*R*,3*R*,3a*R*,9b*R*): 49.0 min, 94:6 er; **IR** ν_{max} (thin film): 3346 (Ar-H), 2983 and 2929 (sp^{3}C-H),1747 and 1732 (C=O), 1517 (asymm. NO_2), 1344 (symm. NO_2), 1219 and 1166 (C-O); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H: 1.11 (3H, dd, $^3J_{HH}$ = 6.8, 6.6, CH_3CH$_a$H$_b$), 2.25 (3H, d, $^4J_{HH}$ = 2.2, C(8)CH_3), 3.50 (1H, app.t, $^3J_{HH}$ = 6.9, 6.7, C(3)*H*), 3.91−4.06 (3H, m, CH$_3$CH_aH$_b$, C(3a)*H*), 5.12 (1H, d, $^3J_{HH}$ = 6.9, C(2)*H*), 6.90 (1H, s, ArC(9)*H*), 7.04 (1H, dd, $^3J_{HH}$ = 8.3, $^4J_{HH}$ = 2.2, ArC(7)*H*), 7.12 (1H, d, $^3J_{HH}$ = 8.3, ArC(6)*H*), 7.30−7.43 (5H, m, PhC(2,3,4,5,6)*H*), 7.50−7.58 (2H, m, O_2N-ArC(2,6)*H*), 8.09−8.16 (2H, m, O_2N-ArC(3,5)*H*); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ_C: 14.2 (H$_3$C H$_a$H$_b$C), 21.0 (C(8)C H$_3$), 54.4 (*C*(3a)H), 55.8 (*C*(3)H), 62.0 (H$_3$CH$_a$H$_b$*C* or *C*(2)H), 62.2 (H$_3$CH$_a$H$_b$*C* or *C*(2)H), 68.5 (*C*(9b)), 117.0 (Ar*C*(7)H), 123.9 (O_2N-Ar*C*(3,5)H), 126.2 (Ar*C*(9a)), 126.4 (Ph*C*(2,6)H), 127.7 (O_2N-Ar*C*(2,6)H), 128.4 (Ph*C*(4)H), 129.1 (Ph*C*(3,5)H), 129.6 (Ar*C*(9)H), 130.6 (Ar*C*(6)H), 134.8 (Ar*C*(8)), 141.4 (Ph*C*(1)), 147.5 (O_2N-Ar*C*(4)), 147.7 (Ar*C*(5a)), 150.0 (O_2N-Ar*C*(1)), 167.5 (O*C*(4)-O), 170.9 (H$_3$CH$_a$H$_b$CO*C*O); **HRMS** (ESI$^+$) $C_{27}H_{24}N_2NaO_6^+$ ([M+Na]$^+$) requires 495.1537, found 495.1515 (−4.55 ppm).


EtO
O
H
O
O
Ar
N
H
Ph
Me
^{1}H, CDCl$_3$, 400 MHz
8.14
8.14
8.12
7.55
7.53
7.42
7.40
7.38
7.35
7.34
7.32
7.26 CDCl3
7.26
7.14
7.11
7.05
7.04
7.03
7.02
6.90
5.13
5.11
4.10
4.04
4.02
4.00
3.99
3.98
3.98
3.97
3.96
3.95
3.52
3.50
3.49
2.25
2.25
1.13
1.11
1.11
1.10
2.0
2.2
5.3
1.5
1.1
1.0
1.0
3.1
1.0
3.3
3.0
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)



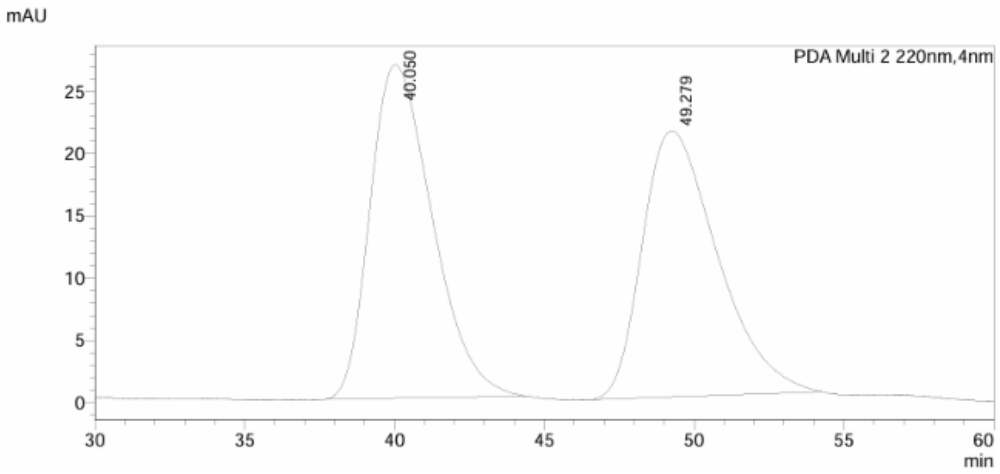
$^{13}C\{^{1}H\}$, $CDCl_3$, 100 MHz

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PDA Ch2 220nm

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Total		100.000

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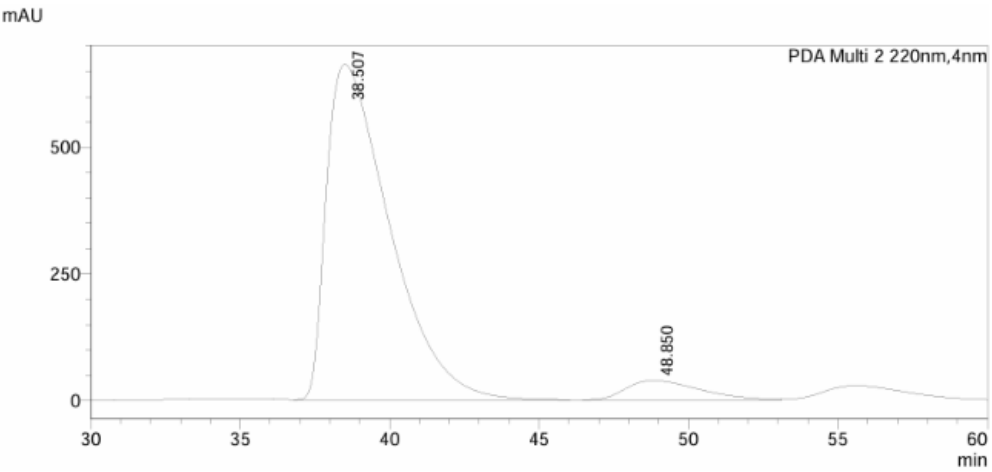


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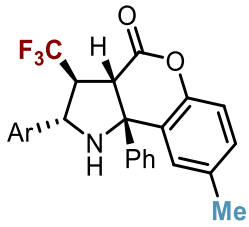
PDA Ch2 220nm

Peak#	Ret. Time	Area%
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2	48.850	6.226
Total		100.000

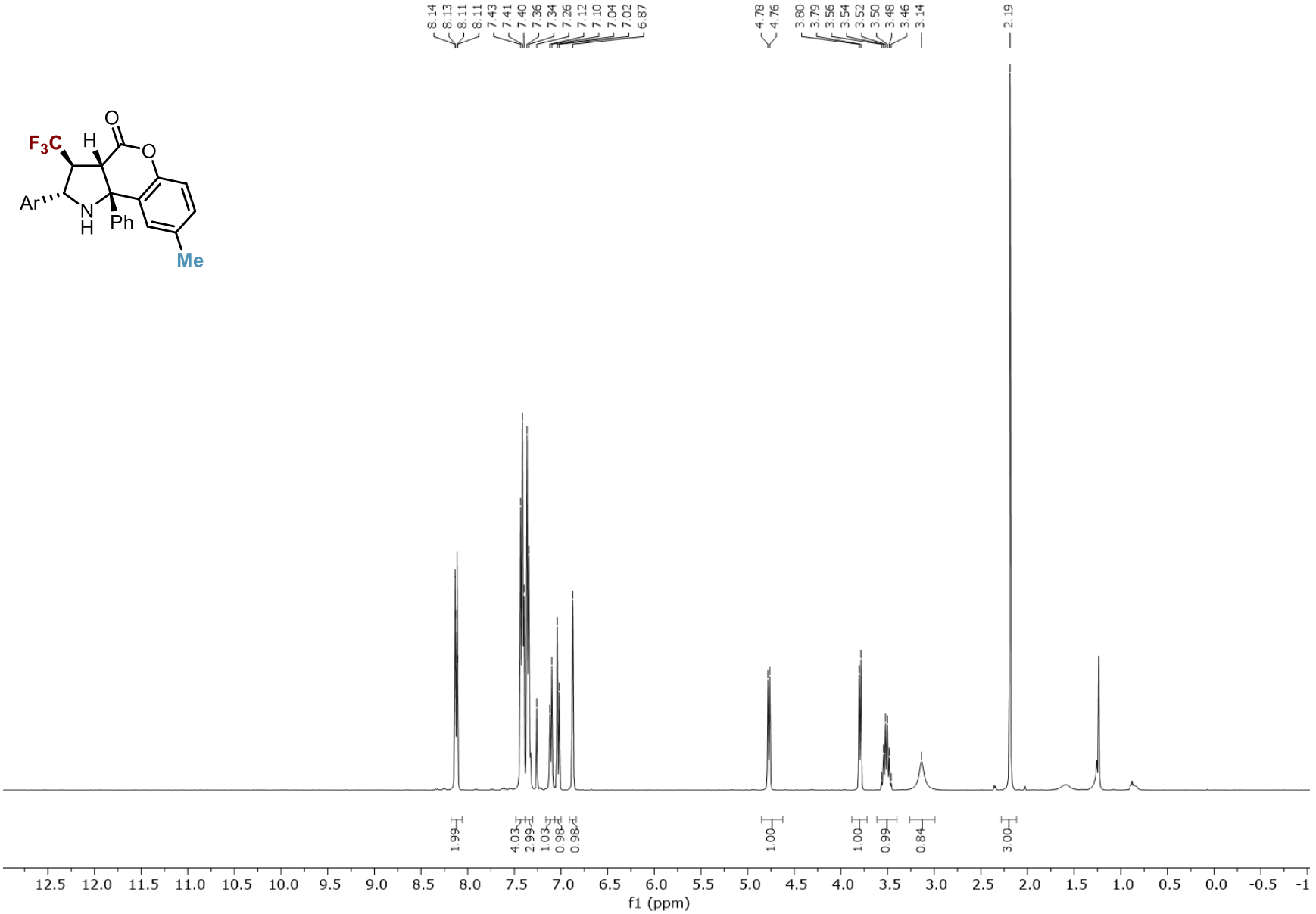
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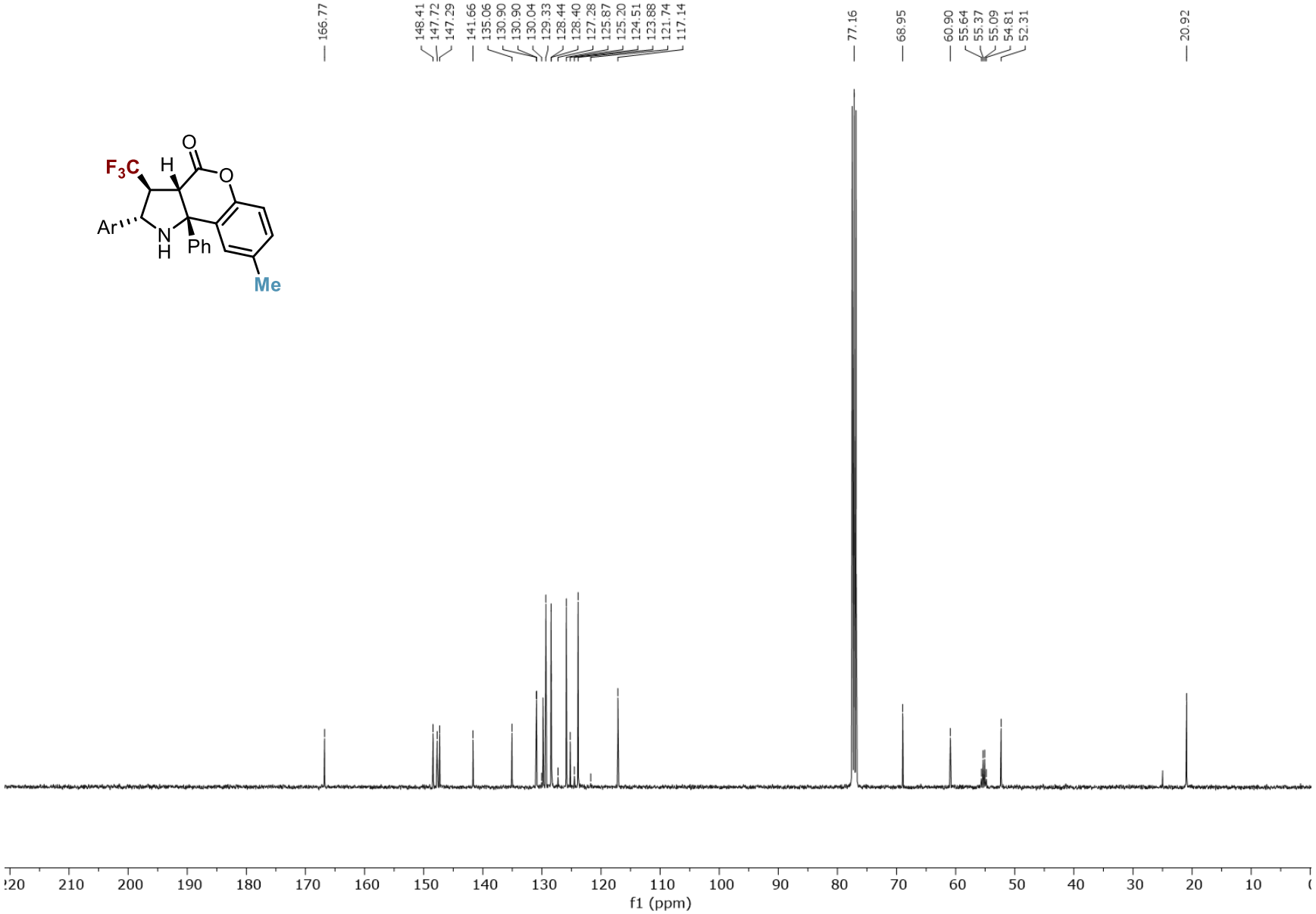


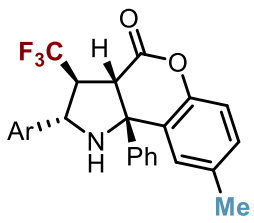
(2*S*,3*S*,3a*S*,9b*S*)-8-methyl-2-(4-nitrophenyl)-9b-phenyl-3-(trifluoromethyl)-2,3,3a,9b-tetrahydrochromeno[4,3-*b*]pyrrol-4(1*H*)-one (38)



Following **General Procedure G**, 4-nitrophenyl (*E*)-4,4,4-trifluorobut-2-enoate (104 mg, 0.40 mmol), (*E*)-*N*-4-nitrobenzyl-2-hydroxy-4-methylbenozophenoneimine (207 mg, 0.60 mmol), and (2*S*,3*R*)-8-MeO-HyperSe (16 mg, 0.04 mmol), and dimethylformamide (4 mL) were stirred for 23 h at 50 °C. The mixture was then concentrated *in vacuo* and stirred in 1 M HCl (2 mL) and THF (4 mL) for one hour. The mixture was concentrated *in vacuo*, diluted with CH_2Cl_2, and washed successively with saturated $NaHCO_3$ and water (× 3). Further purification by flash column chromatography (2:3 CH_2Cl_2:Hexane) gave the title compound as a colourless oil (32 mg, 17%). $[\alpha]_D^{20}$ −80.2 (*c* 0.4, $CDCl_3$); **Chiral HPLC analysis** Chiralpak IB (95:5 Hexane:^{i}PrOH, flow rate 1 mL·min^{-1}, 211 nm, 30 °C) t_R(2*R*,3*R*,3a*R*,9b*R*): 24.9 min, t_R(2*S*,3*S*,3a*S*,9b*S*): 33.7 min, 1:99 er; **IR** ν_{max} (thin film): 3346 (Ar-H), 2924 (C-H), 1749 (C=O), 1519 (asymm. NO_2), 1346 (symm. NO_2), 1165 and 1070 (C-O), 1122 (CF_3); **^{1}H NMR** (400 MHz, $CDCl_3$), δ_H: 2.19 (3H, s, C*H*$_3$), 3.14 (1H, broad s, N*H*), 3.51 (1H, ddt, $^3J_{HF}$ = 8.1, $^3J_{HH}$ = 7.7, 7.4, C(3)*H*), 3.79 (1H, d, $^3J_{HH}$ = 7.4, C(3a)*H*), 4.77 (1H, d, $^3J_{HH}$ = 7.7, C(2)*H*), 6.87 (1H, s, ArC(9)*H*), 7.03 (1H, d, $^3J_{HH}$ = 8.4, ArC(6)*H*), 7.11 (1H, d, $^3J_{HH}$ = 8.4, ArC(7)*H*), 7.31−7.38 (3H, m, PhC(2,4,6)*H*), 7.38−7.46 (4H, m, O_2N-ArC(2,6)*H* and PhC(3,5)*H*), 8.09−8.16 (2H, m, O_2N-ArC(3,5)*H*); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ_C: 20.9 (*C*H$_3$), 52.3 (*C*(3a)H), 55.2 (q, $^2J_{CF}$ = 28.0, *C*(3)H), 60.9 (*C*(2)H), 68.9 (*C*(9b)), 117.1 (Ar*C*(6)H), 123.9 (O_2N-Ar*C*(3,5)H), 125.2 (Ar*C*(9a)), 125.9 (Ph*C*(2,6)H), 125.9 (q, $^1J_{CF}$ = 278.6, *C*F$_3$) , 128.4 (Ph*C*(4)H), 128.4 (O_2N-Ar*C*(2,6)H), 129.3 (Ph*C*(3,5)H), 129.8 (Ar*C*(9)H), 130.9 (Ar*C*(7)H), 135.1 (Ar*C*(8)CH$_3$), 141.7 (Ph*C*(1)), 147.3 (Ar*C*(5a)), 147.7 (O_2N-Ar*C*(4)), 148.4 (O_2N-Ar*C*(1)), 166.8 (O*C*(4)-O); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) δ_F: −67.7 (3F, s, C*F*$_3$); **HRMS** (ESI$^+$) $C_{25}H_{19}F_3N_2NaO_4^+$ $[M+Na]^+$requires, 491.1189 found 491.1188 (−0.3 ppm).


8.14
8.13
8.11
8.11
7.43
7.41
7.40
7.36
7.34
7.26
7.12
7.10
7.04
7.02
6.87
4.78
4.76
3.80
3.79
3.56
3.54
3.52
3.50
3.48
3.46
3.14
2.19
F3C
H
O
O
Ar
N
H
Ph
Me
1.99
4.03
2.99
1.03
0.98
0.98
1.00
1.00
0.99
0.84
3.00
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)


166.77
148.41
147.72
147.29
141.66
135.06
130.90
130.90
130.04
129.33
128.44
128.40
127.28
125.87
125.20
124.51
123.88
121.74
117.14
77.16
68.95
60.90
55.64
55.37
55.09
54.81
52.31
20.92
F3C
H
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f1 (ppm)


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O
Ar
N
H
Ph
Me

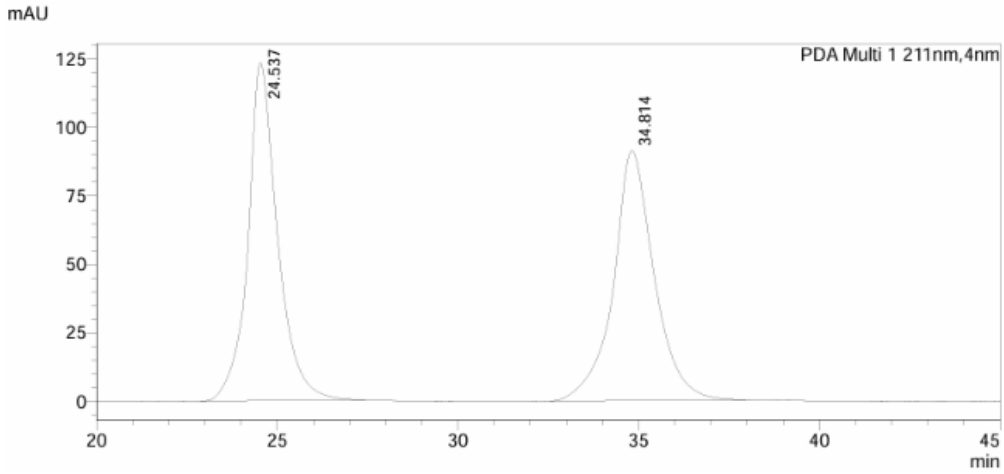
-67.67
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
f1 (ppm)

<Peak Table>

PDA Ch1 211nm

Peak#	Ret. Time	Area%
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2	34.814	50.450
Total		100.000

<Chromatogram>

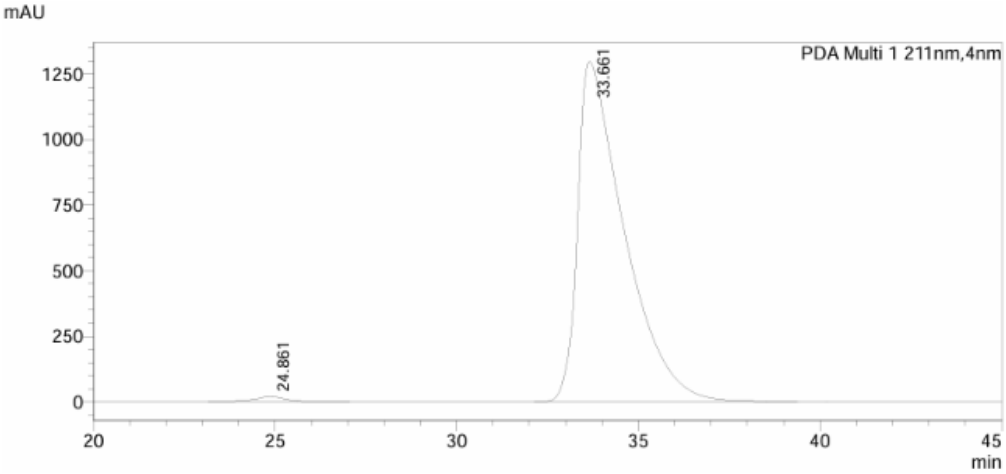


<Peak Table>

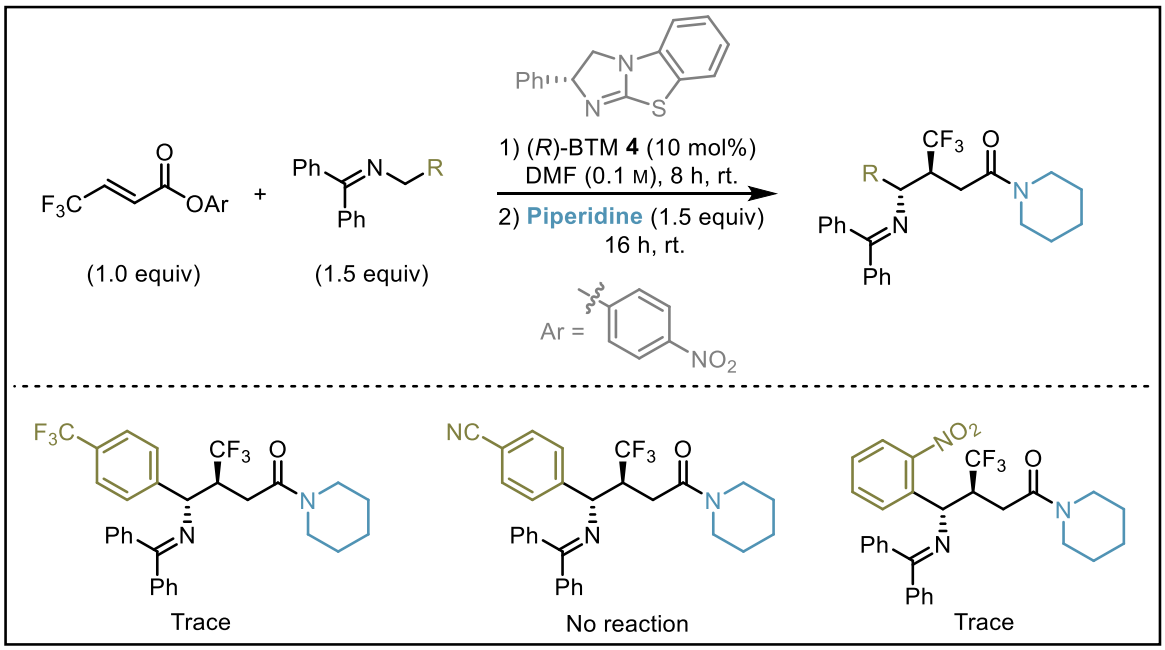
PDA Ch1 211nm

Peak#	Ret. Time	Area%
1	24.861	1.074
2	33.661	98.926
Total		100.000

<Chromatogram>



6. Limitations for Michael addition products



7. Absolute configuration

7.1 X-ray studies

X-ray diffraction data for compounds **11** and **24** were collected at 173 K using a Rigaku MM-007HF High Brilliance RA generator/confocal optics [Cu Kα radiation (λ = 1.54187 Å)] with XtaLAB P100 diffractometer. Intensity data for both compounds were collected (using a calculated strategy) and processed (including correction for Lorentz, polarization and absorption) using CrysAlisPro [20]. Structures were solved by dual-space methods (SHELXT [21]) and refined by full-matrix least-squares against F^2 (SHELXL-2025/1 [22]). Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were refined using a riding model except for NH hydrogens which were located from the difference Fourier map and refined isotropically subject to a distance restraint. All calculations were performed using the Olex2 [23] interface. Selected crystallographic data are presented in Table 2. CCDC 2574454-2574455 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

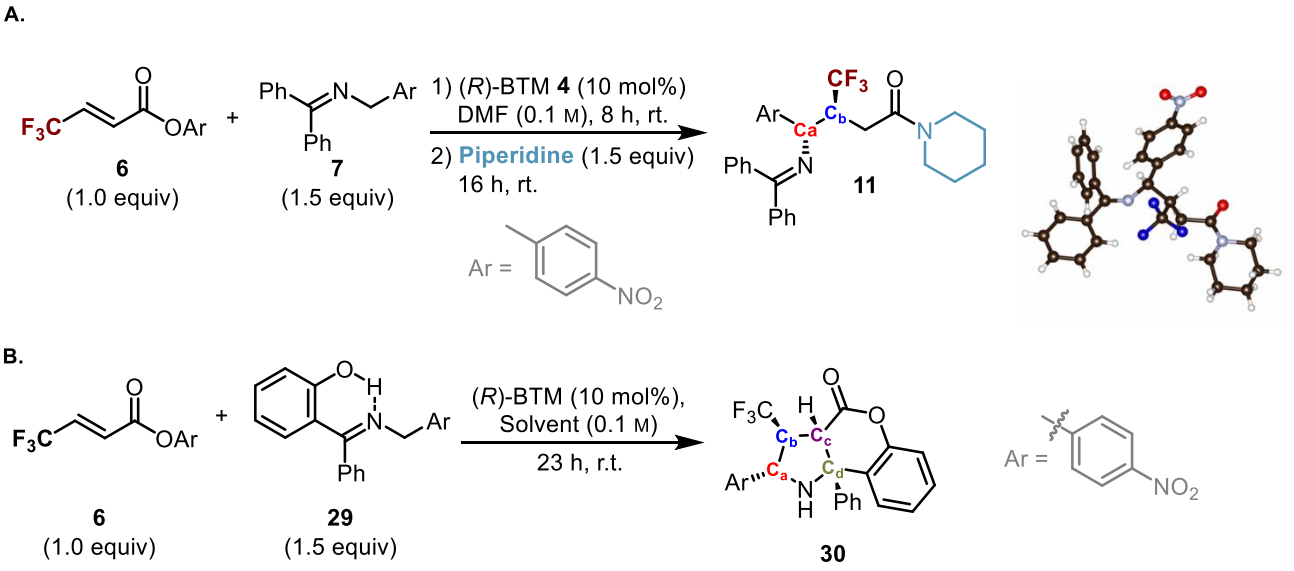
Table 2. Selected crystallographic data.

	11	24
formula	$C_{29}H_{28}F_3N_3O_3$	$C_{11}H_9F_3N_2O_3$
fw	523.54	274.20
crystal description	Colourless prism	Colourless prism
crystal size [mm^3]	0.18 × 0.08 × 0.06	0.14 × 0.08 × 0.02
space group	$P6_1$	$P2_1$
***a* [Å]**	9.41750(10)	7.36770(10)
***b* [Å]**		13.1883(2)
***c* [Å]**	51.0090(9)	12.33899(18)
***β* [°]**		99.2737(14)
vol [Å]^3	3917.86(11)	1183.27(3)
Z	6	4
***ρ* (calc) [g/cm^3]**	1.331	1.539
***μ* [mm^{-1}]**	0.850	1.267
F(000)	1644	560
reflections collected	128891	18190
independent reflections (R_{int})	4872 (0.0803)	4161 (0.0281)
parameters, restraints	343, 1	351, 3
GoF on F^2	1.429	1.057
R_1 [$I > 2\sigma(I)$]	0.0551	0.0263
wR_2 (all data)	0.1083	0.0729
largest diff. peak/hole [e/Å^3]	0.205/−0.202	0.185/−0.178
Flack parameter	0.01(3)	0.03(3)

7.2 NOESY experiments

Crystals of chromeno-pyrrolidine product **30** suitable for single-crystal X-ray diffraction studies were not obtained. However, the absolute configuration was assigned with the help of the known absolute configuration of Michael addition product **11** and Nuclear Overhauser effect (NOE) analysis of chromeno-pyrrolidine **30**.

It is hypothesized that chromeno-pyrrolidine product **30** is formed through three consecutive reactions e.g. (i) Michael addition, (ii) cyclization (Mannich reaction), and (iii) lactonization. According to this hypothesis, it can be rationalized that the stereochemistry of carbon C_a and C_b in Michael addition product **11** would be the same as that of carbon C_a and C_b in chromeno-pyrrolidine product **30**.



The stereochemistry of C_c and C_d was determined through the hypothesized stereochemistry of C_a and C_b and NOE analysis. The selective irradiation of proton $\mathbf{H_b}$ (3.55 ppm) gave a strong correlation with proton $\mathbf{H_e}$ (7.45 ppm), as shown in **Figure 1. B.** This result parallels the hypothesised stereochemistry of C_a and C_b, suggesting that $\mathbf{H_b}$ (3.55 ppm) and 4-nitrophenyl ring are on the same face of the pyrrolidine ring of chromeno-pyrrolidine **30**. Selective irradiation of proton $\mathbf{H_c}$ (3.86 ppm) showed a strong correlation with protons $\mathbf{H_d}$ (7.38 ppm) suggesting that phenyl ring on C_d and $\mathbf{H_d}$ (7.38 ppm) are on the same face of the pyrrolidine ring of chromeno-pyrrolidine **30** (**Figure 1. C.**). Then, the selective irradiation of proton $\mathbf{H_a}$ (4.80 ppm) showed a strong correlation with protons $\mathbf{H_e}$ (7.45 ppm) of 4-nitrophenyl ring on C_a and $\mathbf{H_d}$ (7.38 ppm) of the phenyl ring, this result suggests that phenyl ring on C_d and and proton $\mathbf{H_a}$ (4.80 ppm) are on the same face of pyrrolidine ring of chromeno-pyrrolidine **30** (**Figure 1. D.**). The absolute configuration of C_a (*S*) and relative configuration of C_a and C_d suggest the configuration of C_d (*S*). Similarly, the configuration of C_c can be assigned as (*S*) from the absolute configuration of C_d(*S*) and from the relative configuration of C_c and C_d.

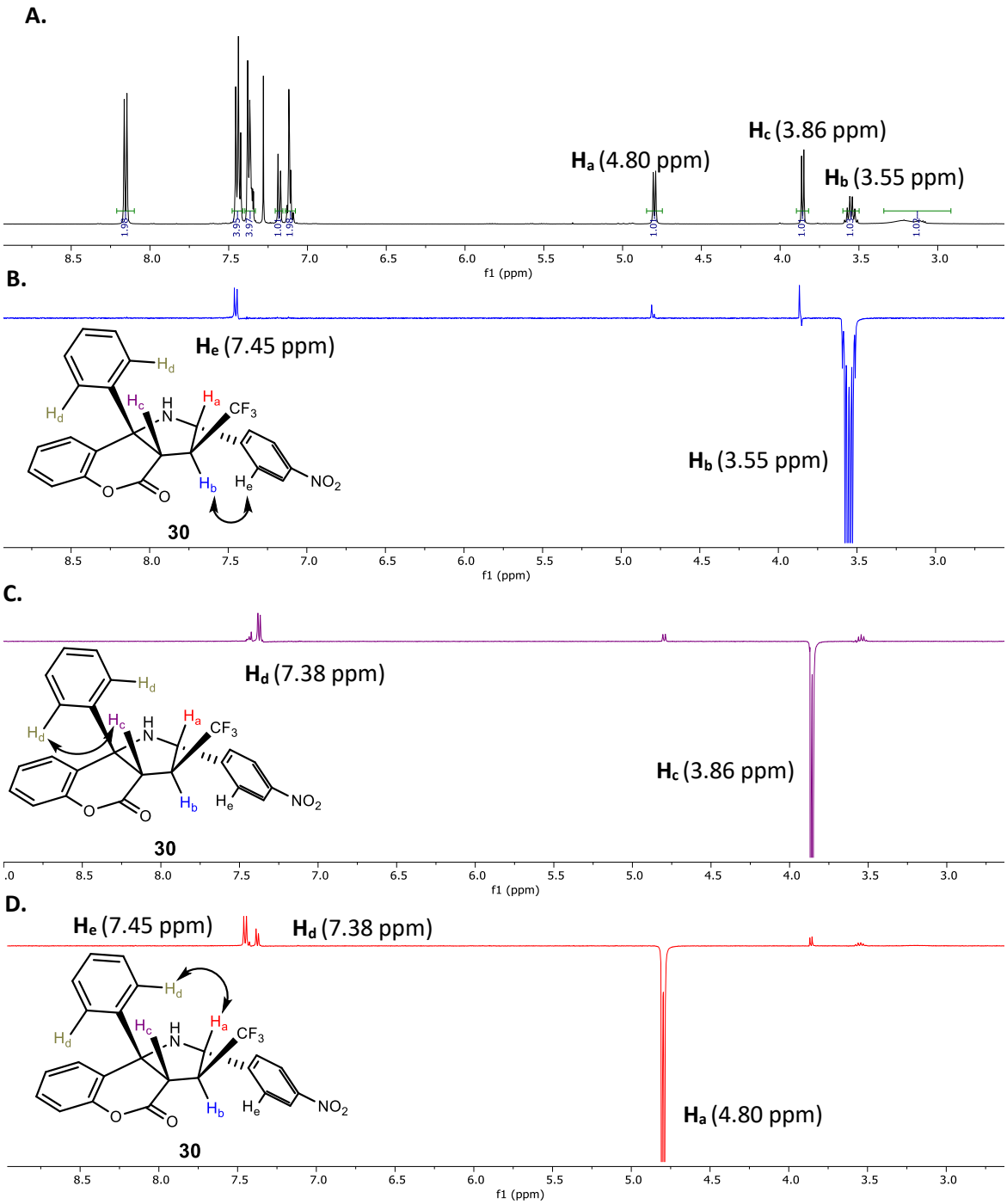


Figure 1. (A) 1H NMR spectrum of chromeno-pyrrolidine **30**, 1D ^{1}H NMR NOE experiments of the chromeno-pyrrolidine product **30** selectively irradiated protons; **(B) H_b** (3.55 ppm); **(C) H_c**.3.86 ppm, and **(D) H_a** 4.80 ppm.

8. References

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