Electronic Supplementary Material (ESI) for ChemComm.

Supporting Information

Chemoselective amide reductions by heteroleptic fluoroaryl boron Lewis acids

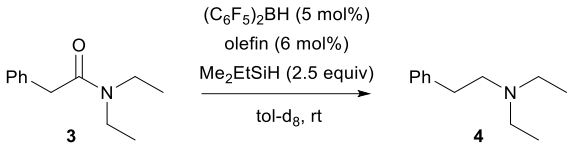
Michael T. Peruzzi, Qiong Qiong Mei, Stephen J. Lee, and Michel R. Gagné

Table of Contents

General Methods

Unless otherwise stated, all commercially available reagents were used as received. Dichloromethane and toluene were passed through a column of alumina before use. 1,2-dichloroethane was distilled from CaH_2 and stored over 4Å molecular sieves before use. Deuterated solvents (Cambridge isotope laboratories) were stored over 3Å sieves before use. All solvents were subjected to 3 freeze-pump-thaw cycles before use. All reactions were performed under an atmosphere of nitrogen unless otherwise stated. Thin layer chromatography (TLC) was performed on SiliCycle Silica Gel 60 F254 plates and was visualized with UV light and KMnO4 stain. NMR spectra were recorded on a Bruker Avance 600 MHz, 500 MHz, or 400 MHz spectrometer. The residual solvent protons (^{1}H) or the solvent carbons (^{13}C) were used as internal standards. ^{1}H NMR data are presented as follows: chemical shift in ppm (δ) downfield from tetramethylsilane (multiplicity, coupling constant, integration). The following abbreviations are used in reporting NMR data: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; dt, doublet of triplets; ddd, doublet of doublet of doublets; m, multiplet. Samples were analyzed with a Q Exactive HF-X (ThermoFisher, Bremen, Germany) mass spectrometer. Samples were introduced via a heated electrospray source (HESI) at a flow rate of 10 µL/min. 100 time domain transients were averaged in the mass spectrum. ESI source conditions were set as: vaporizer temperature 35 °C, sheath gas (nitrogen) 8 arb, auxillary gas (nitrogen) 0 arb, sweep gas (nitrogen) 0 arb, capillary temperature 320 °C, capillary voltage 320 V and funnel Rf level 35 V. The mass range was set to 150-2000 m/z. All measurements were recorded at a resolution setting of 120,000. Solutions were analyzed at 0.1 mg/mL or less based on responsiveness to the ESI mechanism. Xcalibur (ThermoFisher, Breman, Germany) was used to analyze the data. Molecular formula assignments were determined with Molecular Formula Calculator (v 1.2.3). All observed species were singly charged, as verified by unit *m/z* separation between mass spectral peaks corresponding to the ^{12}C and $^{13}C^{12}C_{c-1}$ isotope for each elemental composition.

Measurement of initial rates



In a nitrogen filled glove box, $HB(C_6F_5)_2$ (1.7 mg, 0.05 mmol) was added to a dram vial, and suspended in toluene-d_8 (200 µL). Olefin (0.06 mmol) was then added to the vial. After complete dissolution of the mixture (c.a. 5 min), Me_2EtSiH (33 µL, 0.25 mmol) was added. This solution was then transferred to a vial containing **3** (19.0 mg, 0.1 mmol) and DCE (internal standard, 8 µL, 0.1 mmol) dissolved in toluene-d_8 (200 µL). The solution was lightly agitated and transferred to a J-Young NMR tube. The vials were rinsed with a single aliquot of toluene-d_8 (100 µL) and subsequently transferred to the J-Young before monitoring by ^{1}H-NMR.

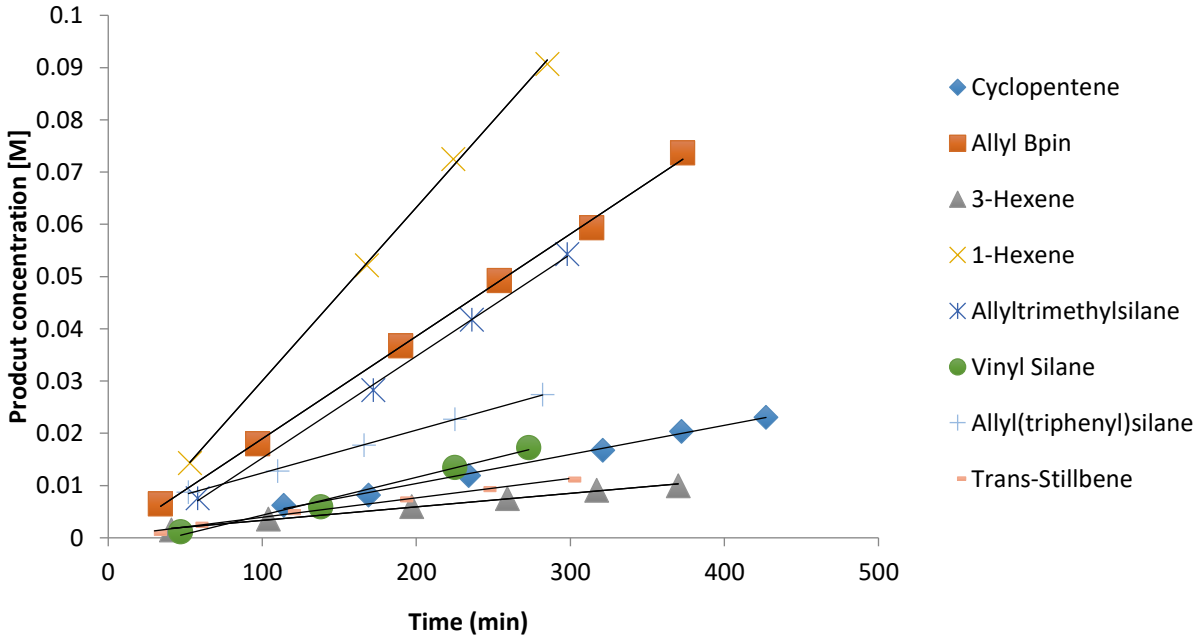


Figure S1: Plot for the rate of reduction of **3** to **4** by various in-*situ* derived heteroleptic boron catalysts

Olefin	Equation	R^2
Cyclopentene	y = 0.0000557x - 0.0007450	0.995
Allyl Bpin	y = 0.000196x - 0.000627	0.999
3-Hexene	y = 0.000026x + 0.000749	0.995
1-Hexene	y = 0.000332x - 0.003131	0.999
Allyltrimethylsilane	y = 0.000195x - 0.004223	0.999
Vinyl Silane	y = 0.000072x - 0.002911	0.987
Allyl(triphenyl)silane	y = 0.000082x + 0.004197	0.999
Trans-Stillbene	y = 0.000037x + 0.000217	0.995

Table S1: Linear regressions and R^2 coefficient for data in Figure S1

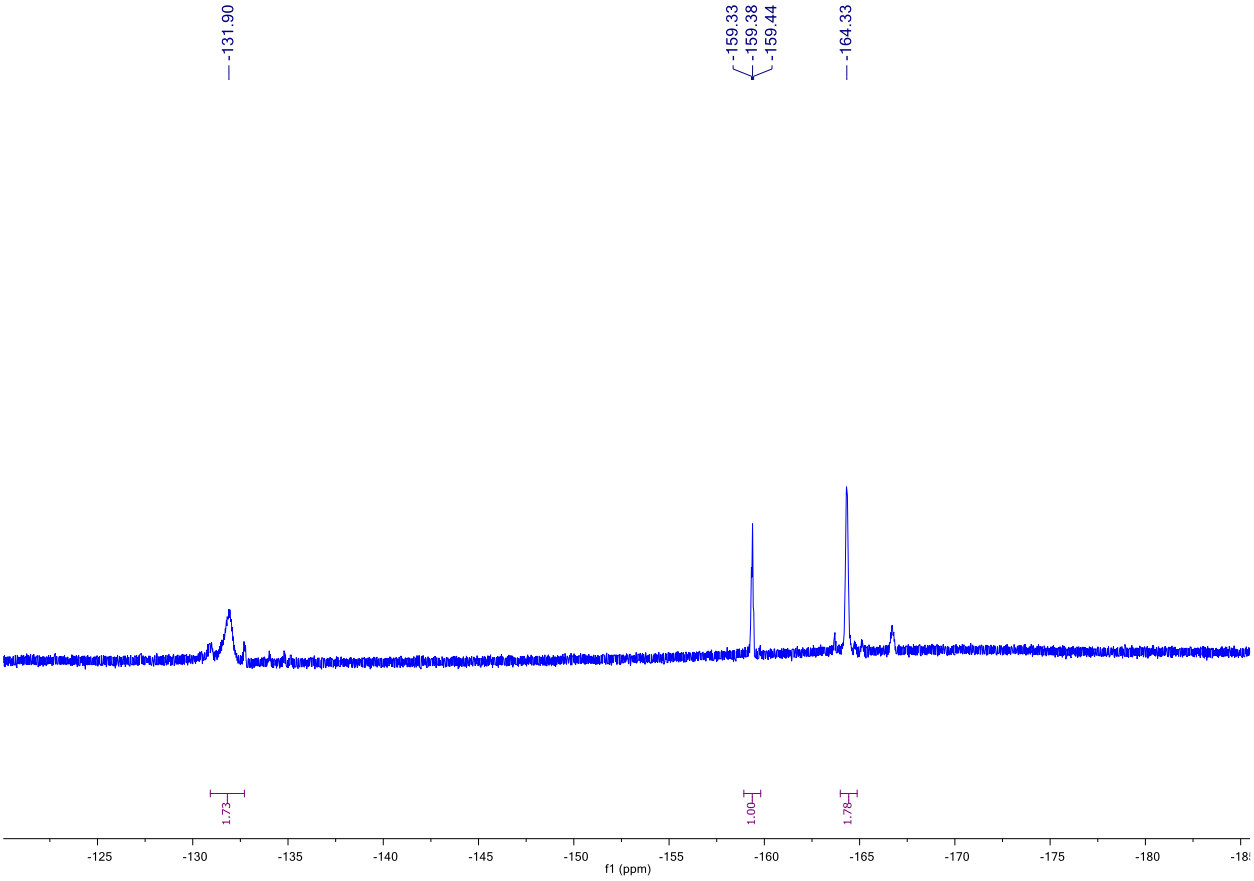


Figure S2: In-*situ* ^{19}F-NMR for the reduction of **3** by catalyst **7**. The spectrum was acquired at approximately ~20% conversion for the reduction of **3** to **4** and indicates that the catalyst exists as a single major species. The lack of change indicates that under these conditions chain walking of the borane is minimal for catalyst **7**.

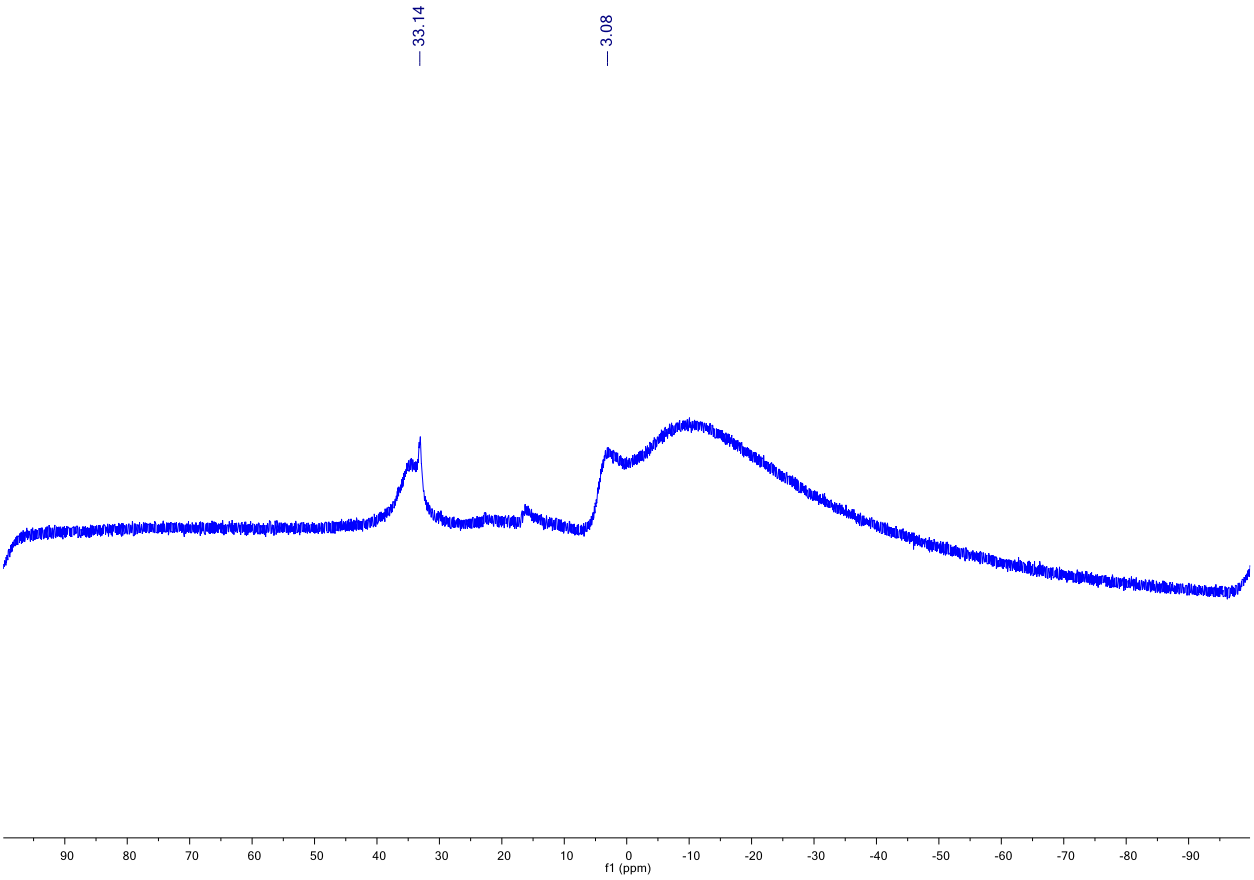
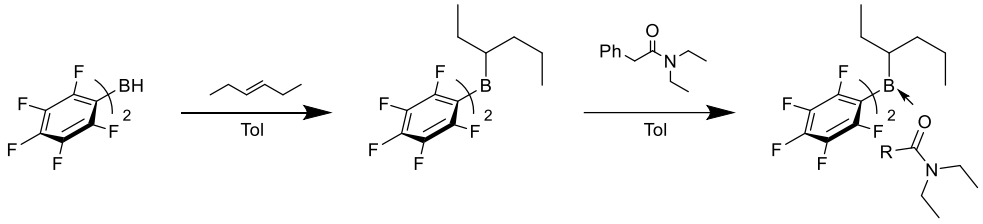


Figure S3: In-*situ* ^{11B}-NMR for the reduction of **3** by catalyst **7**. The spectrum was acquired at approximately ~20% conversion for the reduction of **3** to **4** and indicates that the catalyst exists as a single major species.



To gain insight into the results of the in-situ ^{11}B-NMR experiment, the following experiment was performed.

In a nitrogen filled glovebox, a suspension of $(C_6F_5)_2BH$[1] (0.0068 g, 0.02 mmol) in 250 µL toluene was prepared. 3-Hexene (2.3 µL, 0.023 mmol) was added and the solution allowed to stand until complete dissolution of the borane was observed (c.a. 5 min). The solution was then transferred to a septum sealed NMR tube, and the vial rinsed with an additional 100 µL toluene, before capping and removing from the glovebox. After acquiring an ^{11}B-NMR (160 MHz, δ)

[1] D. J. Parks, W. E. Piers and G. P. Yap, *Organometallics*, 1998, **17**, 5492–5503.

spectrum, **3** (0.0037 g) was added. After shaking for ~1 minute a second ^{11}B-NMR spectrum was acquired.

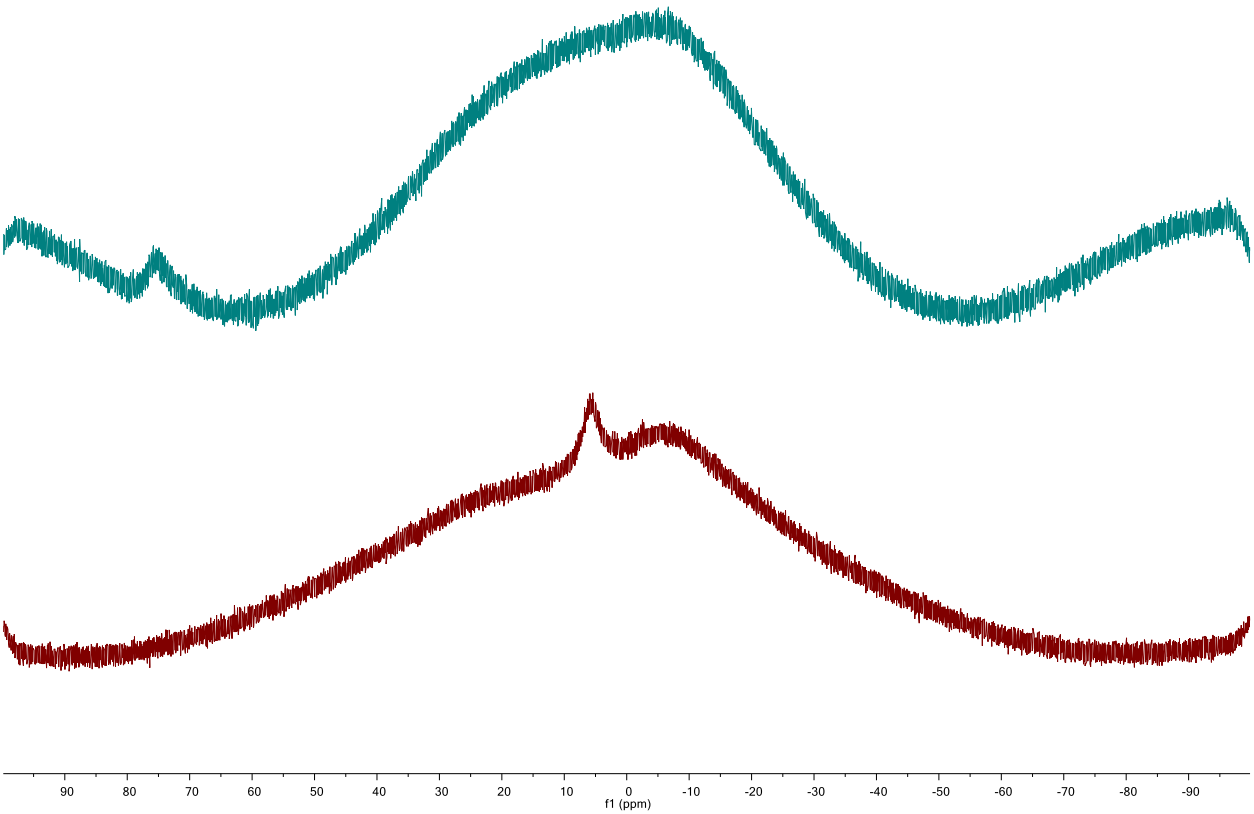
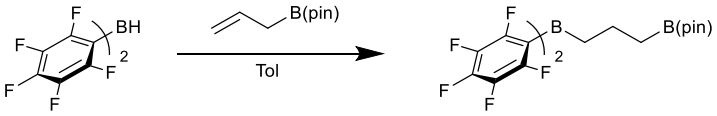


Figure S4: ^{11}B-NMR **2** in toluene (green) followed by the addition of 1 eqv. **3** (red). The results show that upon coordination of the amide the boron resonance shifts upfield.

In-situ catalyst preparation



In a nitrogen filled glovebox, a suspension of $(C_6F_5)_2BH$[1] (0.0068 g, 0.02 mmol) in 250 µL toluene was prepared. Allyl pinacol borane (4.4 µL, 0.023 mmol) was added and the solution allowed to stand until complete dissolution of the borane was observed (c.a. 5 min). The solution was then transferred to a J-Young NMR tube, and the vial rinsed with an additional 250 µL toluene, before capping and removing from the glovebox.

^{1}H NMR (500 MHz, Toluene-d_8) δ 1.74 (t, J = 7.2 Hz, 2H), 1.57 (p, J = 7.2 Hz, 2H), 1.05 – 1.00 (m, 2H), 0.92 (s, 12H).

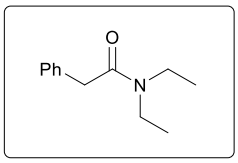
^{13}C NMR (151 MHz, Toluene-d_8) δ 147.37 (m, $^{1}J_{C\text{-}F}$ = 244 Hz), 141.969 (m, $^{1}J_{C\text{-}F}$ = 256 Hz), 137.3 (m, $^{1}J_{C\text{-}F}$ = 256 Hz), 115.88 (m), 86.20, 30.51 (br, s), 23.97, 18.56, 12.88 (br, s).

^{11}B NMR (160 MHz, Toluene- d_8) δ 46.9, 33.7.

^{19}F NMR (376 MHz, Toluene- d_8) δ -130.16 (m), -151.03(m), -161.91 (m).

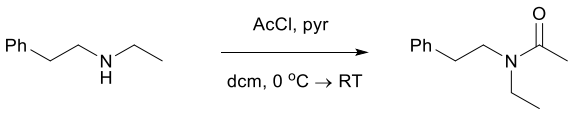
Preparation of alkyl amide starting materials

N,N-diethyl-2-phenylacetamide (3)



Prepared according to literature procedure[2]

N-ethyl-N-phenethylacetamide (S1)



To a 0 °C solution of N-ethyl-2-phenethylamine (0.463 g, 3.11 mmol) and pyridine (0.5 mL, 6.22 mmol) in 10 mL of dcm was added acetyl chloride (0.27 mL, 3.73 mmol) dropwise. After warming to RT overnight, the solution was quenched with 1 M HCl. The organic layer was then washed with saturated $NaHCO_3$, and brine before drying over Na_2SO_4, and concentrating *en vacuo*. The residue was then purified by column chromatography (SiO_2, 1:0 → 98:2 → 95:5 dcm:MeOH) to give the title compound as a clear oil (0.328 g, 55%).

(1.2:1 mixture of rotamers) 1D-NOESY analysis (see below) aided in the assignment of rotameric resonances in the ^{1}H NMR spectrum. Rotamers are not able to be distinguished in the $^{13}C\{^1H\}$ NMR spectrum.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.36 – 7.29 (R1&2, m, 4H), 7.28 – 7.17 (R1&2, m, 6H), 3.57 – 3.52 (R1, m, 2H), 3.51 – 3.47 (R2, m, 2H), 3.43 (R1, q, *J* = 7.1 Hz, 2H), 3.21 (R1, q, *J* = 7.2 Hz, 2H), 2.88 (R2, m, 4H), 2.12 (R1, s, 3H), 1.94 (R2, s, 2H), 1.15 (R1&2, m, 6H).

$^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 170.2, 170.1, 139.6, 138.4, 129.0, 128.9, 128.9, 128.6, 126.9, 126.4, 50.1, 47.7, 44.1, 40.5, 35.6, 34.4, 21.6, 21.5, 14.2, 13.1.

HRMS (ESI) calcd for $C_{12}H_{17}NO(M+H)^+$: 192.13884. Found: 192.13781.

[2] V. Rathore, M. Sattar, R. Kumar and S. Kumar, *J. Org. Chem.*, 2016, **81**, 9206–9218.

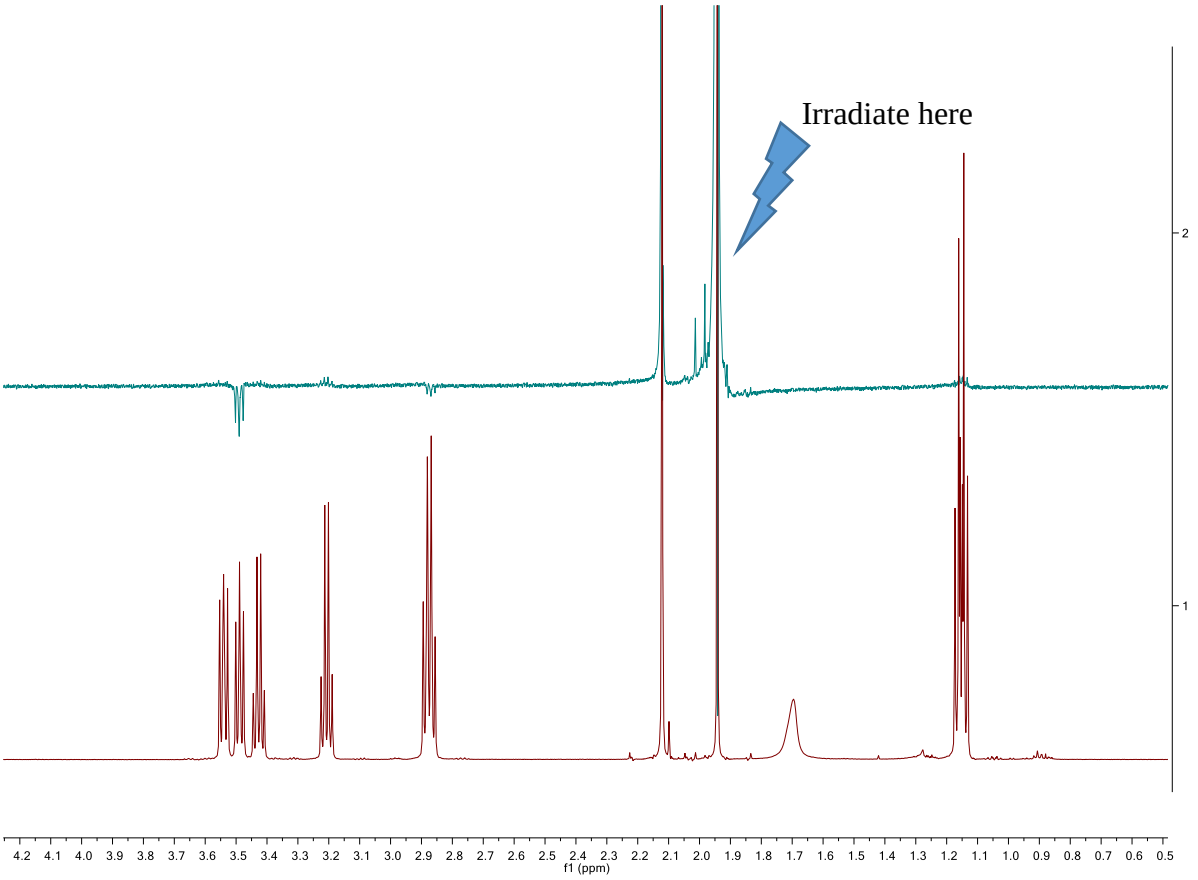
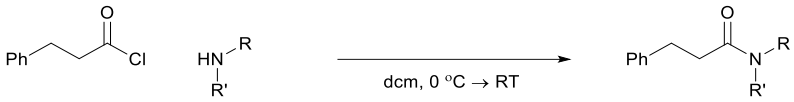
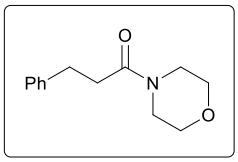


Figure S3 1D-NOESY analysis of **S1**. Irradiation of the acetyl group in a 1D-NOE experiment reveals two methyls of the same phase. This suggests the methyl peaks correspond to the two rotamers of **S1**.[3]



To a 0 °C stirring solution of amine (12.0 mmol) in dcm (10 mL) was added hydrocinnamoyl chloride (0.59 mL, 4.0 mmol) dropwise. After warming to RT overnight, the solution was quenched with 1 M HCl. The organic layer was then washed with saturated $NaHCO_3$, and brine before drying over Na_2SO_4, and concentrating *in vacuo*. The residue was then purified by column chromatography.

1-morpholino-3-phenylpropan-1-one (S2)



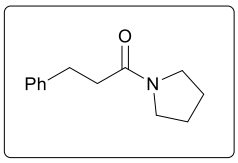
Derived from morpholine (SiO_2, 98:2 dcm:MeOH)

Clear oil, 0.683 g, 78%

[3] D. X. Hu, P. Grice and S. V. Ley, *J. Org. Chem.*, 2012, **77**, 5198–5202.

Spectra matches those previously reported.[4]

3-phenyl-1-(pyrrolidin-1-yl)propan-1-one (S3)

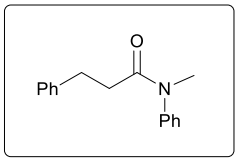


Derived from pyrolidine (SiO_2, 1:0 → 98:2 → 95:5 dcm:MeOH)

Yellow oil, 0.636 g, 78%

Spectra matches those previously reported.[5]

N-methyl-N,3-diphenylpropanamide (S4)

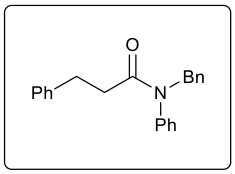


Derived from N-Me aniline (SiO_2, 1:0 → 98:2 → 95:5 dcm:MeOH)

Yellow oil, 0.776 mg, 83%

Spectra matches those previously reported.[6]

N-benzyl-N,3-diphenylpropanamide (S5)



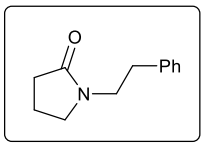
Derived from N-Bn aniline (SiO_2, 1:0 → 98:2 dcm:MeOH)

Yellow oil, 0.262 g, 21%

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.28 – 7.25 (m, 3H), 7.25 – 7.20 (m, 5H), 7.19 – 7.12 (m, 3H), 7.09 – 7.04 (m, 2H), 6.82 – 6.77 (m, 2H), 4.87 (s, 2H), 2.95 (t, *J* = 7.7 Hz, 2H), 2.37 (t, *J* = 7.7 Hz, 2H).

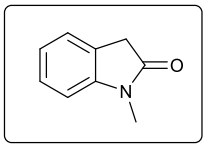
^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 172.1, 142.4, 141.3, 137.6, 129.6, 128.9, 128.7, 128.66, 128.53, 128.4, 128.0, 127.4, 126.2, 53.2, 36.3, 31.9.

1-phenethylpyrrolidin-2-one (S6)



Prepared according to literature procedure.[7]

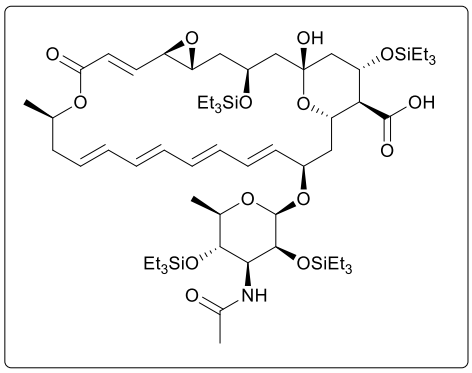
1-methylindolin-2-one (S7)



Prepared according to literature procedure.[8]

[4] R. W. M. Davidson and M. J. Fuchter, *Chem. Commun.*, 2016, **52**, 11638–11641.
[5] S. L. Zultanski, J. Zhao and S. S. Stahl, *J. Am. Chem. Soc.*, 2016, **138**, 6416–6419.
[6] D. Ameen and T. J. Snape, *Tetrahedron Lett.*, 2015, **56**, 1816–1819.
[7] B. Fanté, Y. Soro, S. Siaka, J. Marrot and J.-M. Coustard, *Synth. Commun.*, 2014, **44**, 2377–2385.
[8] Q.-B. Zhang, W.-L. Jia, Y.-L. Ban, Y. Zheng, Q. Liu and L.-Z. Wu, *Chem. - A Eur. J.*, 2016, **22**, 2595–2598.

N-acetyl-O-triethylsilane natamycin (1)



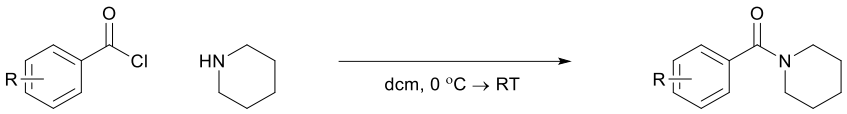
Made according to literature procedure[9] with the following modification:

TES-Cl was added as a solution in THF (15 mL) via syringe pump over a period of 30 minutes.

White solid, 1.16 g, 36%

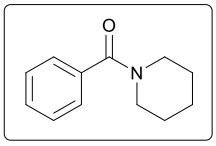
[9]T. A. Bender, P. R. Payne and M. R. Gagné, *Nat. Chem.*, 2017, **10**, 85–90.

Preparation of N-Benzoyl starting materials



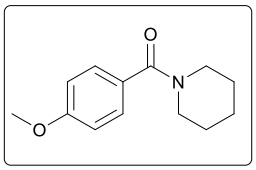
To a 0 °C stirring solution of piperidine (0.4 mL, 4.0 mmol) in 10 mL dcm was added the aryl chloride (0.14 mL, 1.2 mmol) dropwise. After warming to RT overnight, the solution was quenched with 1 M HCl. The organic layer was then washed with saturated $NaHCO_{3(aq)}$, and brine before drying over Na_2SO_4, and concentrating *in vacuo*. The residue was then purified by column chromatography.

Phenyl(piperidin-1-yl)methanone (S8)



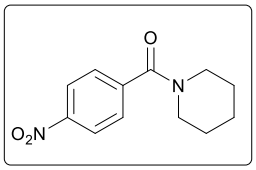
(SiO_2, 3:2 Hexanes:EtOAc)
Viscous oil, 0.197 g, 87%
Spectra matches those previously reported.[10]

(4-methoxyphenyl)(piperidin-1-yl)methanone (S9)



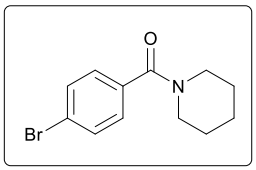
(SiO_2, 3:2 Hexanes:EtOAc)
White solid, 0.250 g, 97%
Spectra matches those previously reported.[10]

(4-nitrophenyl)(piperidin-1-yl)methanone (S10)



(SiO_2, 3:2 Hexanes:EtOAc)
White solid, 0.288 g, 99%
Spectra matches those previously reported.[11]

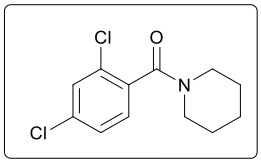
(4-bromophenyl)(piperidin-1-yl)methanone (S11)



(SiO_2, 3:2 Hexanes:EtOAc)
White solid, 0.247 g, 46%
Spectra matches those previously reported.[10]

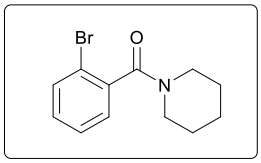
[10] J. A. Fernández-Salas, S. Manzini and S. P. Nolan, *Chem. Commun.*, 2013, **49**, 9758.
[11] G.-L. Li, K. K.-Y. Kung and M.-K. Wong, *Chem. Commun.*, 2012, **48**, 4112.

(2,4-dichlorophenyl)(piperidin-1-yl)methanone (S12)



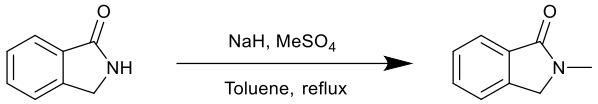
(SiO_2, 3:2 Hexanes:EtOAc)
Viscous oil, 0.825 g, 79%
Spectra matches those previously reported.[12]

(2-bromophenyl)(piperidin-1-yl)methanone (S13)



(SiO_2, 98:2 dcm:MeOH)
Viscous oil, 0.524 g, 49%
Spectra matches those previously reported.[13]

2-methylisoindolin-1-one (S14)



According to a modified literature procedure.[8] To a solution of isoindolin-1-one[14] (0.160 g, 1.2 mmol) in toluene (3 mL) was added sodium hydride (0.053 g, 1.3 mmol). The solution was then heated to 60 °C for 20 minutes (caution: $H_{2(g)}$ evolution). Dimethyl sulfate (0.14 mL, 1.4 mmol) was then added and the solution heated at reflux for four hours. After cooling to RT, the solution was filtered and concentrated. The residue was purified by column chromatography (SiO_2, 2:1→1:1 hexanes:EtOAc) to yield the title compound as a white solid (0.140 g, 80% yield).

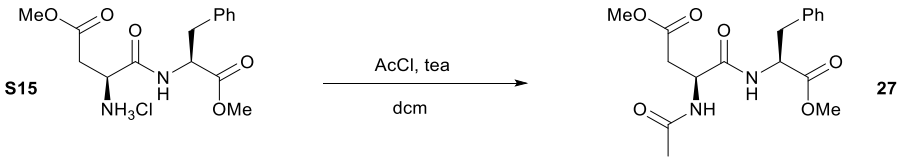
Spectra matched those previously reported.[15]

[12] M. Mitzlaff, K. Warning and H. Jensen, *Justus Liebigs Ann. Chem.*, **1978**, 1713–1733.
[13] Y. Long, Z. She, X. Liu and Y. Chen, *J. Org. Chem.*, 2013, **78**, 2579–2588.
[14] K. Y. Koltunov, G. K. S. Prakash, G. Rasul and G. A. Olah, *European J. Org. Chem.*, 2006, 4861–4866.
[15] Y. Du, T. K. Hyster and T. Rovis, *Chem. Commun.*, 2011, **47**, 12074.

Preparation of oligo-amide starting materials

In the majority of cases, the oligo-amide starting materials exist as rotameric mixtures. All major rotameric resonances are indicated. Minor rotameric resonances are indicated only when clearly distinguished.

Methyl (S)-3-acetamido-4-(((S)-1-methoxy-1-oxo-3-phenylpropan-2-yl)amino)-4-oxobutanoate (27)



To a solution of **S15**[16] (0.344 g, 1.0 mmol) and Et_3N (0.28 mL, 2.0 mmol) in dcm (12 mL) was added acetyl chloride (0.071 mL, 1.0 mmol). The solution was then allowed to stir overnight before washing with brine and drying over Na_2SO_4. The resulting residue was purified by column chromatography (SiO_2, 98:2 dcm:MeOH) to give **27** as a white solid (0.247 mg, 70%)

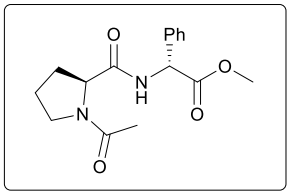
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.30 (dd, *J* = 8.1, 6.5 Hz, 2H), 7.26 – 7.23 (m, 1H), 7.13 (dd, *J* = 7.1, 1.7 Hz, 2H), 6.98 (d, *J* = 7.7 Hz, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 4.83 – 4.67 (m, 2H), 3.72 (s, 3H), 3.69 (s, 3H), 3.15 (dd, *J* = 14.0, 5.5 Hz, 1H), 3.04 (dd, *J* = 14.0, 7.0 Hz, 1H), 2.93 (dd, *J* = 17.1, 4.0 Hz, 1H), 2.57 (dd, *J* = 17.1, 6.7 Hz, 1H), 1.95 (s, 3H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 172.9, 171.6, 170.3, 170.2, 135.8, 129.4, 128.7, 127.3, 53.6, 52.6, 52.3, 49.1, 37.7, 35.2, 23.3.

HRMS (ESI) calcd for $C_{17}H_{23}N_2O_6$ $(M+H)^+$: 351.15561. Found: 351.15442.

The remaining dipeptides were synthesized according to the methods of Beller et. al.[17]

Methyl (R)-2-((S)-1-acetylpyrrolidine-2-carboxamido)-2-phenylacetate (S16)



N-acetyl-L-proline and D-phenylglycine methyl ester hydrochloride
(SiO_2, 96:4 dcm:MeOH)
White solid, 1.093 g, 72%
(6:1 mixture of rotamers)

Major: ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.07 (d, *J* = 6.9 Hz, 1H), 7.39 – 7.27 (m, 6H), 5.46 (d, *J* = 6.9 Hz, 1H), 4.67 (dd, *J* = 8.2, 1.9 Hz, 1H), 3.70 (s, 3H), 3.51 (ddd, *J* = 10.7, 8.5, 2.8 Hz, 1H), 3.40 (td, *J* = 9.7, 7.0 Hz, 1H), 2.42 (ddt, *J* = 12.0, 6.7, 2.4 Hz, 1H), 2.07 (s & overlapping m, 4H), 1.96 (dddd, *J* = 12.5, 9.8, 7.0, 2.8 Hz, 1H), 1.90 – 1.81 (m, 1H).

[16] P. Ding, X. Li, G. Qing, T. Sun and X. Liang, *Chem. Commun.*, 2015, **51**, 16111–16114.
[17] S. Das, Y. Li, C. Bornschein, S. Pisiewicz, K. Kiersch, D. Michalik, F. Gallou, K. Junge and M. Beller, *Angew. Chemie - Int. Ed.*, 2015, **54**, 12389–12393.

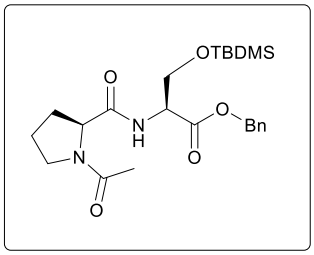
$^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 171.14, 171.06, 170.8, 136.3, 129.0, 128.5, 127.3, 59.5, 57.0, 52.8, 48.4, 27.4, 25.1, 22.5.

Minor: ^{1}H NMR (600 MHz, Chloroform-*d*) δ 6.79 (d, *J* = 7.5 Hz, 1H), 5.56 (d, *J* = 7.5 Hz, 1H), 4.33 (dd, *J* = 8.7, 2.7 Hz, 1H), 3.60 – 3.54 (m, 2H), 2.26 (dddd, *J* = 12.9, 11.0, 8.7, 6.8 Hz, 1H), 2.21 – 2.12 (m, 1H).

$^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 171.5, 170.98, 170.95, 135.7, 129.4, 127.3, 62.2, 56.6, 53.0, 46.9, 32.1, 23.1.

HRMS (ESI) calcd for $C_{16}H_{21}N_2O_4$ $(M+H)^+$: 305.15013. Found: 305.14893

Benzyl N-(acetyl-L-prolyl)-O-(tert-butyldimethylsilyl)-L-serinate (S17)



N-acetyl-L-proline and benzyl O-(tert-butyldimethylsilyl)-L-serinate[18]
(SiO_2, 95:5 dcm:MeOH)
Viscous oil, 2.138 g, 99%
(2.9:1 mixture of rotamers)

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.45 (d, *J* = 7.9 Hz, 2H), 7.37 – 7.28 (m, 5H), 5.18 (d, *J* = 12.3 Hz, 1H), 5.15 (d, *J* = 12.6 Hz, 1H), 4.61 (dd, *J* = 14.0, 8.2 Hz, 2H), 4.05 (dd, *J* = 10.0, 3.0 Hz, 1H), 3.83 (dd, *J* = 10.1, 3.3 Hz, 1H), 3.56 – 3.53 (m, 1H), 3.42 (td, *J* = 9.5, 6.8 Hz, 1H), 2.39 – 2.29 (m, 1H), 2.29 – 2.17 (m, 1H), 2.08 (d, *J* = 1.1 Hz, 3H), 1.99 – 1.76 (m, 2H), 0.83 (s, 9H), 0.00 (s, 3H), -0.03 (s, 3H).

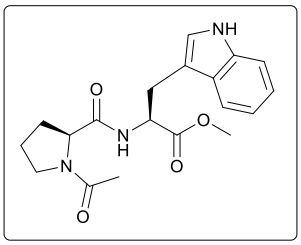
^{13}C NMR (151 MHz, $CDCl_3$) δ 171.4, 170.6, 170.2, 135.6, 128.6, 128.40, 128.36, 67.2, 63.4, 59.7, 54.8, 48.3, 28.0, 25.8, 25.0, 22.5, 18.3, -5.5, -5.6.

Minor: ^{1}H NMR (600 MHz, Chloroform-*d*) δ 6.76 (d, *J* = 8.6 Hz, 1H), 5.13 (d, *J* = 9.2 Hz, 1H), 4.67 (dt, *J* = 8.8, 3.0 Hz, 1H), 4.30 (dd, *J* = 8.4, 2.7 Hz, 1H), 4.11 (ddd, *J* = 10.1, 2.6, 1.1 Hz, 1H), 3.79 (dd, *J* = 10.1, 3.2 Hz, 1H), 2.01 (s, 3H), 0.82 (s, 12H), -0.00 (s, 5H).

$^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 171.9, 170.9, 169.8, 135.1, 128.8, 128.7, 67.7, 62.3, 54.2, 46.8, 32.1, 25.8, 25.7, 23.0, 18.2, -5.55, -5.58.

HRMS (ESI) calcd for $C_{23}H_{37}N_2O_5Si$ $(M+H)^+$: 449.24717. Found: 449.24570.

Methyl acetyl-L-prolyl-L-tryptophanate (S18)

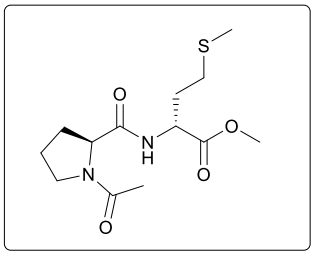


N-acetyl-L-proline and L-tryptophan methyl ester hydrochloride
(SiO_2, 96:4 dcm:MeOH)
White solid, 1.011g, 94%

[18] P. Wipf and Y. Uto, *J. Org. Chem.*, 2000, **65**, 1037–1049.

Spectra matches those previously reported.[19]

Methyl acetyl-L-prolyl-D-methioninate (S19)



N-acetyl-L-proline and D-methionine methyl ester hydrochloride
(SiO_2, 1:0 → 98:2 → 95:5 dcm:MeOH)
White solid, 0.681 g, 75%
(6.2:1 mixture of rotamers)

Major: ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.72 (d, *J* = 8.0 Hz, 1H), 4.67 – 4.60 (m, 2H), 3.72 (s, 3H), 3.58 (ddd, *J* = 10.8, 8.4, 2.6 Hz, 1H), 3.44 (td, *J* = 9.8, 7.0 Hz, 1H), 2.52 (t, *J* = 7.4 Hz, 2H), 2.45 – 2.40 (m, 1H), 2.13 (s, 4H), 2.09 (s, 4H), 1.99 (ddt, *J* = 14.5, 11.4, 7.3 Hz, 2H), 1.86 (tt, *J* = 12.1, 7.5 Hz, 1H).

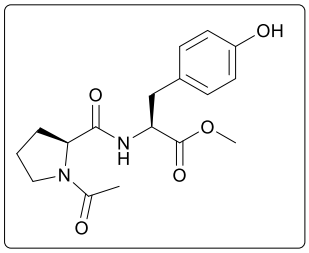
^{13}C NMR (151 MHz, $CDCl_3$) δ 172.3, 171.3, 171.3, 59.7, 52.5, 51.7, 48.4, 31.5, 30.2, 27.5, 25.1, 22.6, 15.6.

Minor: ^{1}H NMR (600 MHz, Chloroform-*d*) δ 6.91 (d, *J* = 8.3 Hz, 1H), 4.77 (q, *J* = 7.5 Hz, 0H), 4.35 (d, *J* = 8.0 Hz, 1H), 3.78 (s, 3H), 2.09 (s, 4H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 172.1, 171.9, 170.5, 62.4, 52.7, 51.8, 46.9, 32.2, 30.5, 30.3, 22.8, 15.4.

HRMS (ESI) calcd for $C_{13}H_{23}N_2O_4S$ $(M+H)^+$: 303.13785. Found: 303.13003.

Methyl acetyl-L-prolyl-L-tyrosinate (S20)



N-acetyl-L-proline and L-tryptophan methyl ester hydrochloride
(SiO_2, 1:0 → 98:2 → 95:5 dcm:MeOH)
White foam, 0.621 g, 62%
(5.3:1 mixture of rotamers)

Major: ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.32 (d, *J* = 7.9 Hz, 1H), 6.97 – 6.94 (m, 2H), 6.71 – 6.68 (m, 2H), 4.80 (ddd, *J* = 7.9, 6.6, 5.3 Hz, 1H), 4.55 (dd, *J* = 8.2, 2.1 Hz, 1H), 3.73 (s, 3H), 3.50 – 3.45 (m, 1H), 3.38 (td, *J* = 9.6, 7.1 Hz, 1H), 3.10 (dd, *J* = 14.1, 5.2 Hz, 1H), 2.96 (dd, *J* = 14.1, 6.7 Hz, 1H), 2.35 – 2.27 (m, 1H), 2.05 (s, 3H), 2.02 (ddd, *J* = 9.4, 5.3, 2.8 Hz, 0H), 1.94 (dddd, *J* = 12.9, 10.1, 6.8, 3.0 Hz, 1H), 1.87 – 1.78 (m, 1H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 172.0, 171.4, 171.0, 155.8, 130.5, 127.2, 115.5, 59.6, 53.6, 52.5, 48.4, 37.1, 27.7, 25.0, 22.4.

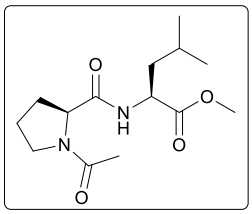
Minor: ^{1}H NMR (600 MHz, Chloroform-*d*) δ 6.94 – 6.91 (m, 2H), 6.78 – 6.75 (m, 2H), 6.28 (d, *J* = 8.4 Hz, 1H), 4.24 (dd, *J* = 8.8, 2.3 Hz, 1H), 3.76 (s, 3H), 3.15 (dd, *J* = 14.3, 5.3 Hz, 1H), 2.19 – 2.11 (m, 1H), 1.56 – 1.47 (m, 1H).

[19] S. Das, Y. Li, L. Q. Lu, K. Junge and M. Beller, *Chem. - A Eur. J.*, 2016, **22**, 7050–7053.

$^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 171.8, 171.6, 130.1, 127.2, 116.0, 62.3, 52.8, 52.7, 46.9, 36.8, 31.9, 22.7, 22.3.

HRMS (ESI) calcd for $C_{17}H_{23}N_2O_5$ $(M+H)^+$: 335.16070. Found: 335.15940.

Methyl acetyl-L-prolyl-L-leucinate (S21)



N-acetyl-L-proline and L-tyrosine methyl ester hydrochloride
(SiO_2, 1:0 → 98:2 → 95:5 dcm:MeOH)
Viscous oil, 0.620 g, 62%
(4.3:1 mixture of rotamers)

Major: ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.38 (d, *J* = 7.5 Hz, 1H), 4.57 (dd, *J* = 8.2, 1.9 Hz, 1H), 4.46 – 4.41 (m, 1H), 3.69 (s, 3H), 3.54 – 3.49 (m, 1H), 3.40 (td, *J* = 9.7, 7.0 Hz, 1H), 2.38 (ddt, *J* = 12.1, 6.8, 2.4 Hz, 1H), 2.28 – 2.16 (m, 1H), 2.07 (s, 3H), 1.99 – 1.92 (m, 1H), 1.81 (dddd, *J* = 12.5, 11.2, 8.1, 7.0 Hz, 1H), 1.68 – 1.47 (m, 3H), 0.90 (d, *J* = 6.2 Hz, 3H), 0.87 (d, *J* = 6.2 Hz, 3H).

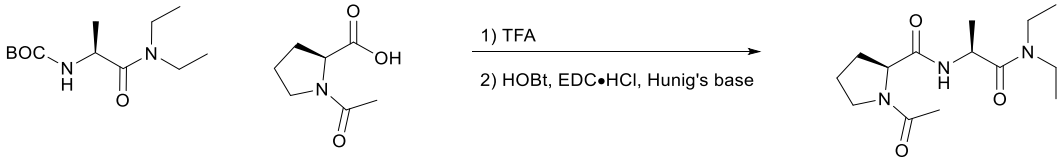
$^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 173.3, 171.1, 170.9, 59.4, 52.3, 51.2, 48.3, 41.2, 27.3, 25.1, 25.0, 22.8, 22.5, 22.0.

Minor: ^{1}H NMR (600 MHz, Chloroform-*d*) δ 6.53 (d, *J* = 8.7 Hz, 1H), 4.63 (dt, *J* = 9.2, 4.7 Hz, 1H), 4.32 (dd, *J* = 8.7, 2.6 Hz, 1H), 3.66 – 3.57 (m, 2H), 0.94 (d, *J* = 6.3 Hz, 3H).

$^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 172.9, 171.9, 62.2, 52.3, 50.6, 46.8, 40.6, 32.1, 25.1, 23.0, 22.9, 21.4.

HRMS (ESI) calcd for $C_{14}H_{25}N_2O_4$ $(M+H)^+$: 285.18143. Found: 285.18032.

(S)-1-acetyl-N-((S)-1-(diethylamino)-1-oxopropan-2-yl)pyrrolidine-2-carboxamide (S22)



To a solution of N,N-Diethyl-(N-Boc)-alanine amide[20] (0.366g, 1.5 mmol) in 14 mL dcm was added 1.4 mL TFA. After two hours the solution was concentrated *in vacuo* and the residue dried overnight under high vac at 50 °C. N-acetyl proline (0.236 g, 1.5 mmol), HOBt (0.260 g, 1.9 mmol), and EDC•HCl (0.377 g, 1.9 mmol) were then added to the flask. The solids were then dissolved in dcm (10 mL) and Hunig's base was added (0.32 mL, 1.8 mmol). After stirring at RT overnight, the reaction mixture was diluted with dcm and washed with $NH_4Cl_{(aq)}$, $NaHCO_{3(aq)}$, and $brine_{(aq)}$. After drying over Na_2SO_4 and concentrating *in vacuo*, the residue was purified by column

[20] J. C. Anderson and S. Skerratt, *J. Chem. Soc. Perkin Trans. 1*, 2002, **30**, 2871–2879.

chromatography (SiO_2, 1:0 → 98:2 → 95:5 dcm:MeOH) to give the title compound as a viscous oil (0.398 g, 94%)

(4:1 mixture of rotamers)

Major: ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.20 (d, *J* = 7.4 Hz, 1H), 4.73 (p, *J* = 6.9 Hz, 1H), 4.46 (dd, *J* = 8.2, 2.9 Hz, 1H), 3.60 (ddd, *J* = 9.8, 7.9, 3.4 Hz, 1H), 3.52 – 3.41 (m, 2H), 3.32 (qd, *J* = 7.3, 3.6 Hz, 2H), 3.21 (dqd, *J* = 14.1, 7.1, 3.8 Hz, 1H), 2.18 (tdt, *J* = 12.8, 6.5, 3.3 Hz, 1H), 2.09 (s, 3H), 2.08 – 2.02 (m, 1H), 1.99 – 1.91 (m, 2H), 1.30 (d, *J* = 6.8 Hz, 3H), 1.20 (t, *J* = 7.2 Hz, 3H), 1.09 (t, *J* = 7.1 Hz, 3H).

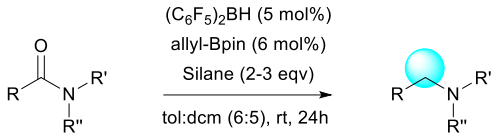
^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 171.5, 170.8, 170.3, 60.1, 48.3, 45.5, 41.7, 40.3, 28.8, 25.0, 22.6, 19.1, 14.6, 12.9.

Minor: ^{1}H NMR (600 MHz, Chloroform-*d*) δ 6.91 (d, *J* = 7.7 Hz, 1H), 4.78 (p, *J* = 7.0 Hz, 1H), 4.23 (dd, *J* = 8.7, 2.8 Hz, 1H), 2.01 (s, 3H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 171.3, 171.1, 170.5, 62.2, 46.8, 40.4, 32.2, 23.1, 22.5, 19.2.

HRMS (ESI) calcd for $C_{14}H_{25}N_3O_3$ $(M+H)^+$: 284.19742. Found: 84.19622.

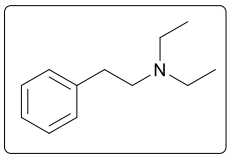
Amide reduction products



Representative procedure for the reduction of amides

In a nitrogen filled glovebox, a dram vial containing H–B(C_6F_5)$_2$ (1.7 mg, 0.05 mmol) was diluted with 200 µL toluene before adding allyl-Bpin (1.1 µL, 0.06 mmol). After complete dissolution of the suspension (c.a 5 min), silane (see below) was added and the solution transferred to a separate vial containing the amide (0.1 mmol) dissolved in 250 µL dcm. The vial which contained the catalyst/silane mixture was rinsed with an additional 100 µL toluene and transferred to the reaction flask. After capping the vial with a screw top septum lid (PTFE), the vial was allowed to stir outside of the glovebox for 24h. After the allotted time, the solution was concentrated in *vacuo* before purifying by column chromatography.

N,N-diethyl-2-phenylethan-1-amine (4 & 13)



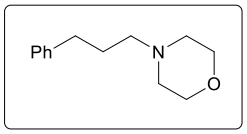
Me_2EtSiH (40 µL, 0.3 mmol), (SiO_2, 7:1:0.2 hexanes:EtOAc:Et_3N)

Clear oil, 0.0129 g, 73%

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29 (td, *J* = 7.2, 1.6 Hz, 2H), 7.22 – 7.17 (m, 3H), 2.79 – 2.73 (m, 2H), 2.73 – 2.68 (m, 2H), 2.62 (q, *J* = 7.2 Hz, 4H), 1.07 (t, *J* = 7.2 Hz, 6H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 140.7, 128.8, 128.5, 126.1, 54.9, 46.9, 33.3, 11.8.

4-(3-phenylpropyl)morpholine (14)



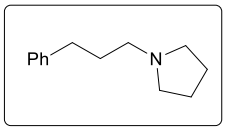
Me_2EtSiH (40 µL, 0.3 mmol), (SiO_2, 7:1:0.2 hexanes:EtOAc:Et_3N)

Clear oil, 0.0206 g, 98%

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.25 (m, 2H), 7.19 (dt, *J* = 9.4, 3.0 Hz, 3H), 3.72 (t, *J* = 4.7 Hz, 4H), 2.64 (t, *J* = 7.7 Hz, 2H), 2.43 (t, *J* = 4.6 Hz, 4H), 2.39 – 2.33 (m, 2H), 1.82 (tt, *J* = 9.4, 6.7 Hz, 2H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 142.2, 128.5, 128.4, 125.9, 67.1, 58.5, 53.8, 33.7, 28.4.

1-(3-phenylpropyl)pyrrolidine (15)



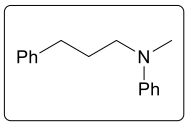
Me_2EtSiH (40 µL, 0.3 mmol), (SiO_2, 7:1:0.2 hexanes:EtOAc:Et_3N)

Yellow oil, 0.0180 g, 92%

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28 (t, *J* = 7.7 Hz, 2H), 7.19 (dt, *J* = 7.7, 2.9 Hz, 3H), 2.68 – 2.63 (m, 2H), 2.53 – 2.45 (m, 6H), 1.86 (tt, *J* = 9.6, 6.8 Hz, 2H), 1.81 – 1.75 (m, 4H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 142.3, 128.5, 128.4, 125.9, 56.2, 54.3, 34.0, 30.7, 23.5.

N-methyl-N-(3-phenylpropyl)aniline (16)



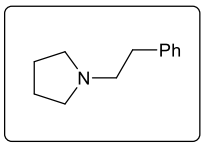
Me_2EtSiH (40 μL, 0.3 mmol), (SiO_2, 7:1:0.2 hexanes:EtOAc:Et_3N)

Clear oil, 0.0210 g, 95%

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 8.2, 7.0 Hz, 2H), 7.29 – 7.22 (m, 6H), 6.75 – 6.69 (m, 3H), 3.42 – 3.35 (m, 2H), 2.97 (s, 3H), 2.73 – 2.68 (m, 2H), 2.02 – 1.90 (m, 2H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 149.4, 141.9, 129.3, 128.50, 128.47, 126.0, 116.1, 112.3, 52.4, 38.4, 33.5, 28.3.

1-phenethylpyrrolidine (17)



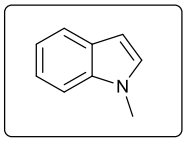
Me_2EtSiH (40 μL, 0.3 mmol), (SiO_2, 7:1:0.2 hexanes:EtOAc:Et_3N)

Clear oil, 0.011 g, 62%

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.23 (m, 4H), 7.24 (d, *J* = 1.8 Hz, 1H), 2.99 – 2.86 (m, 2H), 2.87 – 2.78 (m, 2H), 2.74 (s, 3H), 1.91 (h, *J* = 3.1 Hz, 4H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 140.6, 128.8, 128.5, 126.2, 58.5, 54.4, 35.9, 23.6.

1-methyl-1H-indole (S23)



Derived from **S7**

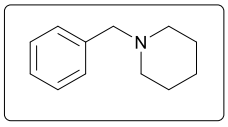
Me_2EtSiH (40 μL, 0.3 mmol), (SiO_2, 30:1 hexanes:EtOAc) Caution: rapid gas evolution.

Clear oil, 0.0123 g, 94%

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.9 Hz, 1H), 7.34 (d, *J* = 1.2 Hz, 1H), 7.25 (d, *J* = 8.7 Hz, 1H), 7.13 (s, 1H), 7.07 (d, *J* = 3.1 Hz, 1H), 6.51 (dd, *J* = 3.1, 0.9 Hz, 1H), 3.81 (s, 3H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 128.9, 1216, 121.0, 119.4, 109.3, 101.0, 33.0.

1-benzylpiperidine (20)



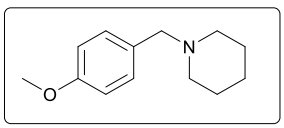
Et_2SiH_2 (32 μL, 0.25 mmol), (SiO_2, 7:1:0.2 hexanes:EtOAc:Et_3N)

Clear oil, 0.0148 g, 85%

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 – 7.29 (m, 4H), 7.26 – 7.22 (m, 1H), 3.48 (s, 2H), 2.38 (s, 4H), 1.62 – 1.53 (m, 4H), 1.46 – 1.38 (m, 2H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 138.7, 129.4, 128.2, 126.9, 64.0, 54.6, 26.1, 24.5.

1-(4-methoxybenzyl)piperidine (21)



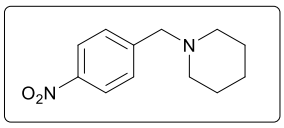
Et_2SiH_2 (32 μL, 0.25 mmol), (SiO_2, 7:1:0.2 hexanes:EtOAc:Et_3N)

Clear oil, 0.0190 g, 93%

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 3.80 (s, 3H), 3.41 (s, 2H), 2.35 (s, 4H), 1.56 (p, *J* = 5.7 Hz, 4H), 1.47 – 1.38 (m, 2H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 158.7, 130.7, 130.5, 113.6, 63.4, 55.4, 54.5, 26.1, 24.6.

1-(4-nitrobenzyl)piperidine (22)



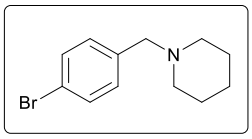
Et_2SiH_2 (32 μL, 0.25 mmol), (SiO_2, 7:1:0.2 hexanes:EtOAc:Et_3N)

Yellow oil, 0.0236g, 99%

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 3.53 (s, 2H), 2.37 (s, 4H), 1.57 (p, *J* = 5.7 Hz, 4H), 1.49 – 1.37 (m, 2H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 147.14, 147.08, 129.6, 123.5, 63.1, 54.8, 26.1, 24.3.

1-(4-bromobenzyl)piperidine (23)



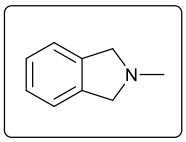
Et_2SiH_2 (32 μL, 0.25 mmol), (SiO_2, 7:1:0.2 hexanes:EtOAc:Et_3N)

Clear oil, 0.0246 g, 92%

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49 – 7.42 (m, 2H), 7.26 – 7.19 (m, 2H), 3.46 (s, 2H), 2.40 (s, 4H), 1.60 (p, *J* = 5.7 Hz, 4H), 1.46 (p, *J* = 5.9 Hz, 2H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 137.9, 131.3, 130.9, 120.7, 63.2, 54.6, 26.1, 24.5.

2-methylisoindoline (26)



Et_2SiH_2 (32 μL, 0.25 mmol), (SiO_2, 95:5 dcm:MeOH)

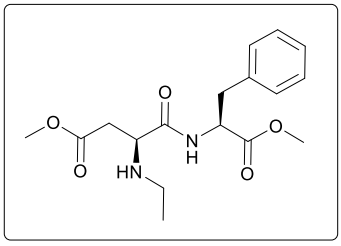
Yellow oil, 0.010 g, 75%

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (s, 4H), 3.99 (s, 4H), 2.64 (s, 3H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 139.9, 127.1, 122.4, 61.0, 42.6.

Methyl (S)-3-(ethylamino)-4-(((S)-1-methoxy-1-oxo-3-phenylpropan-2-yl)amino)-4-oxobutanoate (28)

Me_2EtSiH (33 μL, 0.25 mmol), (SiO_2, 1:0 → 98:2 → 95:5 dcm:MeOH)



White solid, 0.0287 g, 85%

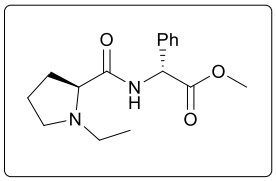
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.5 Hz, 1H), 7.30 – 7.26 (m, 2H), 7.25 – 7.21 (m, 1H), 7.15 – 7.10 (m, 2H), 4.84 (ddd, *J* = 8.5, 6.7, 5.7 Hz, 1H), 3.71 (s, 3H), 3.67 (s, 3H), 3.41 (dd, *J* = 8.5, 4.0 Hz, 1H), 3.15 (dd, *J* = 13.9, 5.7 Hz, 1H), 3.07 (dd, *J* = 13.9, 6.7 Hz, 1H), 2.72 (dd, *J* = 16.6, 4.0 Hz, 1H), 2.59 – 2.45 (m, 3H), 1.73 – 1.63 (m, 1H), 1.01 (t, *J* = 7.1 Hz, 3H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 172.7, 172.2, 172.0, 136.1, 129.3, 128.6, 127.2, 58.8, 52.7, 52.4, 52.0, 42.4, 38.1, 36.0, 15.5.

HRMS (ESI) calcd for $C_{17}H_{25}N_2O_5$ $(M+H)^+$: 337.17635. Found: 337.17485.

Methyl (R)-2-((S)-1-ethylpyrrolidine-2-carboxamido)-2-phenylacetate (29)

Me_2EtSiH (33 μL, 0.25 mmol), (SiO_2, 1:0 → 98:2 → 95:5 dcm:MeOH)



Yellow oil, 0.0261 g, (90 %)

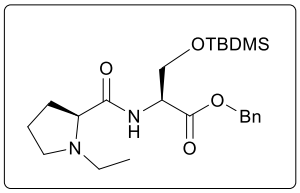
^1H NMR (600 MHz, $CDCl_3$) δ 8.43 (d, *J* = 8.1 Hz, 1H), 7.42 – 7.28 (m, 5H), 5.58 (d, *J* = 8.1 Hz, 1H), 3.72 (s, 3H), 3.22 (ddd, *J* = 9.0, 6.7, 1.8 Hz, 1H), 3.07 (dd, *J* = 10.3, 4.6 Hz, 1H), 2.77 (dq, *J* = 11.9, 7.3 Hz, 1H), 2.52 (dq, *J* = 12.0, 7.1 Hz, 1H), 2.31 (ddd, *J* = 10.5, 9.0, 6.1 Hz, 1H), 2.12 (dtd, *J* = 13.2, 10.1, 7.8 Hz, 1H), 1.81 – 1.60 (m, 2H), 1.16 (t, *J* = 7.2 Hz, 3H).

$^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 175.0, 171.5, 136.9, 129.1, 128.5, 127.2, 67.2, 55.8, 53.8, 52.8, 49.9, 30.6, 24.4, 14.5.

HRMS (ESI) calcd for $C_{16}H_{23}N_2O_3$ $(M+H)^+$: 291.17087. Found: 291.16927.

Benzyl O-(tert-butyldimethylsilyl)-N-(ethyl-L-prolyl)-L-serinate (30)

Me_2EtSiH (33 μL, 0.25 mmol), (SiO_2, 1:0 → 98:2 → 95:5 dcm:MeOH)



Clear oil, 0.0412 g, 91%

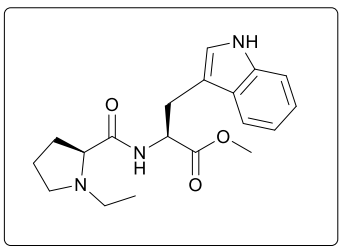
^1H NMR (600 MHz, $CDCl_3$) δ 8.29 (d, *J* = 9.2 Hz, 1H), 7.37 – 7.27 (m, 5H), 5.17 (d, *J* = 12.2 Hz, 1H), 5.14 (d, *J* = 12.2 Hz, 1H), 4.68 (dt, *J* = 9.2, 2.8 Hz, 1H), 4.13 (dd, *J* = 9.9, 2.4 Hz, 1H), 3.76 (dd, *J* = 9.9, 3.1 Hz, 1H), 3.17 (ddd, *J* = 8.9, 6.6, 2.1 Hz, 1H), 3.04 (dd, *J* = 10.4, 4.6 Hz, 1H), 2.69 (dq, *J* = 11.9, 7.3 Hz, 1H), 2.40 (dq, *J* = 11.9, 7.1 Hz, 1H), 2.31 – 2.22 (m, 1H), 2.21 – 2.08 (m, 1H), 1.88 – 1.64 (m, 2H), 1.01 (t, *J* = 7.2 Hz, 3H), 0.85 (s, 9H), 0.01 (s, 3H), -0.02 (s, 3H).

$^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 175.3, 170.4, 135.5, 128.6, 128.41, 128.40, 67.22, 67.17, 63.9, 53.7, 53.5, 49.7, 30.7, 25.7, 24.4, 18.2, 14.2, -5.5, -5.6.

HRMS (ESI) calcd for $C_{23}H_{39}N_2O_4Si$ $(M+H)^+$: 435.26791. Found: 435.26602.

Methyl ethyl-L-prolyl-L-tryptophanate (31)

Me_2EtSiH (33 μL, 0.25 mmol), (SiO_2, 1:0 → 98:2 → 95:5 dcm:MeOH)



Clear oil, 0.0327 g, 95%

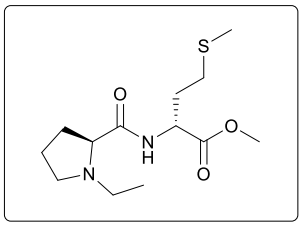
^1H NMR (600 MHz, $CDCl_3$) δ 8.40 (s, 1H), 8.03 (d, *J* = 8.8 Hz, 1H), 7.59 – 7.52 (m, 1H), 7.34 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.17 (ddd, *J* = 8.3, 7.1, 1.2 Hz, 1H), 7.10 (ddd, *J* = 7.9, 7.0, 1.0 Hz, 1H), 6.97 (d, *J* = 2.4 Hz, 1H), 4.93 (dt, *J* = 8.8, 5.8 Hz, 1H), 3.68 (s, 3H), 3.35 – 3.27 (m, 2H), 3.02 – 2.94 (m, 2H), 2.57 (dq, *J* = 11.9, 7.3 Hz, 1H), 2.35 (dq, *J* = 12.0, 7.1 Hz, 1H), 2.18 (ddd, *J* = 10.7, 8.9, 6.1 Hz, 1H), 2.06 (dtd, *J* = 12.8, 10.3, 7.8 Hz, 1H), 1.75 – 1.58 (m, 1H), 1.43 (dtdd, *J* = 11.9, 10.2, 8.1, 6.6 Hz, 1H), 0.88 (t, *J* = 7.2 Hz, 3H).

$^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 175.4, 172.6, 136.2, 127.8, 122.7, 122.2, 119.5, 118.6, 111.3, 110.3, 67.1, 53.5, 52.5, 52.3, 49.6, 30.6, 27.8, 24.3, 14.1.

HRMS (ESI) calcd for $C_{19}H_{26}N_3O_3$ $(M+H)^+$: 344.19742. Found: 344.19596.

Methyl ethyl-L-prolyl-D-methioninate (32)

Me_2EtSiH (33 μL, 0.25 mmol), (SiO_2, 1:0 → 98:2 → 95:5 dcm:MeOH)



Yellow oil, 0.0288 g, 99%

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.0 Hz, 1H), 4.66 (ddd, *J* = 8.8, 7.8, 5.0 Hz, 1H), 3.72 (s, 3H), 3.20 (ddd, *J* = 8.8, 4.7, 3.1 Hz, 1H), 3.05 (dd, *J* = 10.3, 4.4 Hz, 1H), 2.63 (ddd, *J* = 14.6, 9.7, 6.1 Hz, 1H), 2.53 – 2.45 (m, 3H), 2.31 (q, *J* = 8.6 Hz, 1H), 2.20 – 2.09 (m, 2H), 2.07 (s, 3H), 2.02 – 1.94 (m, 1H), 1.92 – 1.82 (m, 1H), 1.75 (ddt, *J* = 10.6, 6.8, 3.8 Hz, 2H), 1.07 (t, *J* = 7.2 Hz, 3H).

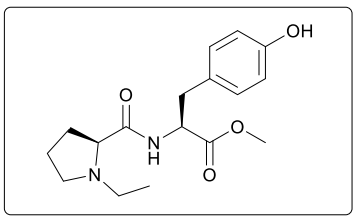
$^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 175.4, 172.5, 67.2, 53.9, 52.5, 51.0, 49.9, 32.0, 30.8, 30.2, 24.4, 15.6, 14.5.

HRMS (ESI) calcd for $C_{13}H_{25}N_2O_3S$ $(M+H)^+$: 289.15859. Found: 289.15715.

Methyl ethyl-L-prolyl-L-tyrosinate (33)

After the allotted reaction time, the solution was concentrated *in vacuo*. With no precautions to avoid air or moisture, the residue was taken up in 1 mL 19:1 ACN:MeOH and 15 μL DBU added. After stirring for 5 minutes, the solution was again concentrated *in vacuo* and before purifying by column chromatography.

Me_2EtSiH (46 μL, 0.45 mmol), (SiO_2, 1:0 → 98:2 → 95:5 dcm:MeOH)



Clear oil, 0.0232 g, 76%

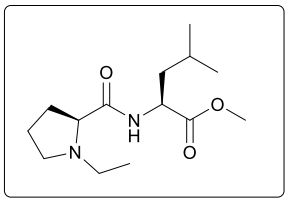
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.01 (d, *J* = 9.7 Hz, 1H), 7.01 – 6.92 (m, 2H), 6.75 – 6.66 (m, 2H), 4.98 (dt, *J* = 9.6, 4.8 Hz, 1H), 3.76 (s, 3H), 3.23 (dd, *J* = 14.1, 4.9 Hz, 1H), 3.09 (t, *J* = 7.8 Hz, 1H), 2.97 (dd, *J* = 10.7, 4.2 Hz, 1H), 2.81 (dd, *J* = 14.1, 9.4 Hz, 1H), 2.59 (dq, *J* = 11.9, 7.3 Hz, 1H), 2.46 (dq, *J* = 12.0, 7.1 Hz, 1H), 2.23 (dt, *J* = 16.1, 7.5 Hz, 1H), 1.93 (dtd, *J* = 13.0, 10.5, 7.8 Hz, 1H), 1.58 (td, *J* = 7.2, 3.7 Hz, 1H), 1.41 (ddd, *J* = 20.7, 13.0, 7.7 Hz, 1H), 1.32 (d, *J* = 11.1 Hz, 1H), 1.04 (t, *J* = 7.2 Hz, 3H).

$^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 176.0, 172.4, 156.0, 130.2, 126.9, 115.5, 66.6, 53.9, 52.5, 52.3, 49.7, 37.9, 30.5, 24.2, 14.2.

HRMS (ESI) calcd for $C_{17}H_{25}N_2O_4$ $(M+H)^+$: 321.18143. Found: 321.18003.

Methyl ethyl-L-prolyl-L-leucinate (34)

Me_2EtSiH (33 μL, 0.25 mmol), (SiO_2, 1:0 → 98:2 → 95:5 dcm:MeOH)



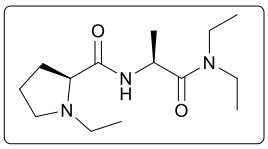
Clear oil, 0.0129 g, 70%

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.81 (d, *J* = 9.3 Hz, 1H), 4.63 (td, *J* = 9.2, 4.9 Hz, 1H), 3.71 (s, 3H), 3.20 (ddd, *J* = 8.8, 6.7, 1.8 Hz, 1H), 3.02 (dd, *J* = 10.2, 4.6 Hz, 1H), 2.70 (dq, *J* = 11.9, 7.3 Hz, 1H), 2.49 (dq, *J* = 11.9, 7.1 Hz, 1H), 2.31 (ddd, *J* = 10.4, 9.0, 6.2 Hz, 1H), 2.16 (dtd, *J* = 13.2, 10.3, 8.0 Hz, 1H), 1.86 – 1.74 (m, 1H), 1.72 – 1.53 (m, 4H), 1.11 (t, *J* = 7.2 Hz, 3H), 0.93 (dd, *J* = 6.3, 1.4 Hz, 6H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 175.2, 173.6, 67.2, 53.8, 52.2, 50.0, 49.8, 41.8, 30.9, 25.2, 24.4, 23.1, 22.0, 14.3.

HRMS (ESI) calcd for $C_{14}H_{27}N_2O_3$ $(M+H)^+$: 271.20217. Found: 271.20080.

(S)-N-((S)-1-(diethylamino)-1-oxopropan-2-yl)-1-ethylpyrrolidine-2-carboxamide (35)



Me_2EtSiH (33 μL, 0.25 mmol) (SiO_2, 1:0 → 98:2 → 95:5 dcm:MeOH)

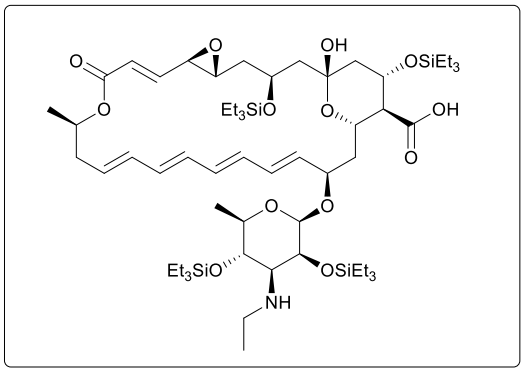
Clear oil, 0.0253 g, 96%

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.4 Hz, 1H), 4.82 (dq, *J* = 8.6, 6.8 Hz, 1H), 3.46 (dq, *J* = 14.1, 7.1 Hz, 1H), 3.35 (qd, *J* = 7.2, 2.1 Hz, 2H), 3.26 (dq, *J* = 14.0, 7.1 Hz, 1H), 3.19 (ddd, *J* = 9.0, 6.4, 2.3 Hz, 1H), 2.98 (dd, *J* = 10.6, 4.5 Hz, 1H), 2.61 (dq, *J* = 14.2, 7.3, 6.0 Hz, 1H), 2.47 (dt, *J* = 12.3, 7.1 Hz, 1H), 2.36 – 2.23 (m, 1H), 2.13 (dtd, *J* = 13.0, 10.0, 7.9 Hz, 1H), 1.86 – 1.66 (m, 3H), 1.29 (d, *J* = 6.8 Hz, 3H), 1.21 (t, *J* = 7.1 Hz, 3H), 1.09 (t, *J* = 7.1 Hz, 3H), 1.06 (t, *J* = 7.2 Hz, 3H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 174.7, 171.7, 67.2, 53.8, 49.8, 44.4, 41.8, 40.3, 30.9, 24.3, 19.5, 14.7, 14.2, 12.9.

HRMS (ESI) calcd for $C_{14}H_{28}N_3O_2$ $(M+H)^+$: 270.21815. Found: 270.21677.

N-ethyl-O-triethylsilane natamycin (36)



100 % toluene, Et_2SiH_2 (29 μL, 0.22 mmol), 20h

After the reaction time, the solution was diluted with dcm and added to a separatory funnel containing pH=7 buffer. The aqueous phase was then washed with dcm (x4). The combined organics were dried over Na_2SO_4 and concentrated in *vacuo* before purification by silica gel chromatography.

(SiO_2, 1:0 → 20:1 → 15:1 → 10:1 → 8:1 → 5:1 → 3:1 →1:1 hexanes:EtOAc)

White solid, 0.0423 g, 75%

Matched previously recorded spectra[9]

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.28 (dd, *J* = 15.7, 8.1 Hz, 1H), 6.17 (m, 3H), 6.07 – 6.01 (m, 3H), 5.98 – 5.93 (m, 1H), 5.59 (dd, *J* = 14.0, 9.1 Hz, 1H), 5.49 (ddd, *J* = 15.2, 10.4, 5.1 Hz, 1H), 5.09 – 5.02 (m, 1H), 4.48 (s, 1H), 4.39 – 4.23 (m, 5H), 4.10 (ddd, *J* = 10.6, 7.2, 3.4 Hz, 1H), 3.93 (s, 1H), 3.19 (s, 1H), 3.15 – 3.07 (m, 2H), 2.91 (d, *J* = 8.3 Hz, 1H), 2.78 (s, 1H), 2.44 – 2.32 (m, 3H), 2.24 – 2.18 (m, 1H), 2.10 (dt, *J* = 13.3, 10.7 Hz, 1H), 2.00 (ddd, *J* = 14.0, 7.2, 4.1 Hz, 1H), 1.93 (ddd, *J* = 14.2, 7.3, 2.6 Hz, 1H), 1.86 (ddd, *J* = 23.1, 13.1, 6.1 Hz, 3H), 1.73 (ddd, *J* = 14.0, 11.7, 8.2 Hz, 2H), 1.33 (d, *J* = 6.3 Hz, 3H), 1.24 (d, *J* = 6.4 Hz, 1H), 1.20 (t, *J* = 8.4 Hz, 3H), 1.12 – 1.04 (m, 3H), 1.01 – 0.85 (m, 40H), 0.60 (m, 24H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 177.5, 166.1, 143.7, 135.1, 134.4, 133.0, 132.5, 132.4, 132.2, 129.3, 125.8, 99.9, 96.6, 78.0, 74.2, 73.8 70.0, 69.3, 67.4, 66.8, 64.3, 56.54, 56.49, 46.4, 43.8, 41.4, 39.8, 37.4, 20.4, 18.8, 15.4, 7.2, 7.1, 7.0, 6.9, 5.7, 5.4, 5.1, 5.0.

HRMS (ESI) calcd for $C_{59}H_{108}NO_{13}Si_4$ $(M+H)^+$: 1150.68977. Found: 1150.68772.

References

1 D. J. Parks, W. E. Piers and G. P. Yap, *Organometallics*, 1998, **17**, 5492–5503.

2 V. Rathore, M. Sattar, R. Kumar and S. Kumar, *J. Org. Chem.*, 2016, **81**, 9206–9218.

3 D. X. Hu, P. Grice and S. V. Ley, *J. Org. Chem.*, 2012, **77**, 5198–5202.

4 R. W. M. Davidson and M. J. Fuchter, *Chem. Commun.*, 2016, **52**, 11638–11641.

5 S. L. Zultanski, J. Zhao and S. S. Stahl, *J. Am. Chem. Soc.*, 2016, **138**, 6416–6419.

6 D. Ameen and T. J. Snape, *Tetrahedron Lett.*, 2015, **56**, 1816–1819.

7 B. Fanté, Y. Soro, S. Siaka, J. Marrot and J.-M. Coustard, *Synth. Commun.*, 2014, **44**, 2377–2385.

8 Q.-B. Zhang, W.-L. Jia, Y.-L. Ban, Y. Zheng, Q. Liu and L.-Z. Wu, *Chem. - A Eur. J.*, 2016, **22**, 2595–2598.

9 T. A. Bender, P. R. Payne and M. R. Gagné, *Nat. Chem.*, 2017, **10**, 85–90.

10 J. A. Fernández-Salas, S. Manzini and S. P. Nolan, *Chem. Commun.*, 2013, **49**, 9758.

11 G.-L. Li, K. K.-Y. Kung and M.-K. Wong, *Chem. Commun.*, 2012, **48**, 4112.

12 M. Mitzlaff, K. Warning and H. Jensen, *Justus Liebigs Ann. Chem.*, 1978, **1978**, 1713–1733.

13 Y. Long, Z. She, X. Liu and Y. Chen, *J. Org. Chem.*, 2013, **78**, 2579–2588.

14 K. Y. Koltunov, G. K. S. Prakash, G. Rasul and G. A. Olah, *European J. Org. Chem.*, 2006, 4861–4866.

15 Y. Du, T. K. Hyster and T. Rovis, *Chem. Commun.*, 2011, **47**, 12074.

16 P. Ding, X. Li, G. Qing, T. Sun and X. Liang, *Chem. Commun.*, 2015, **51**, 16111–16114.

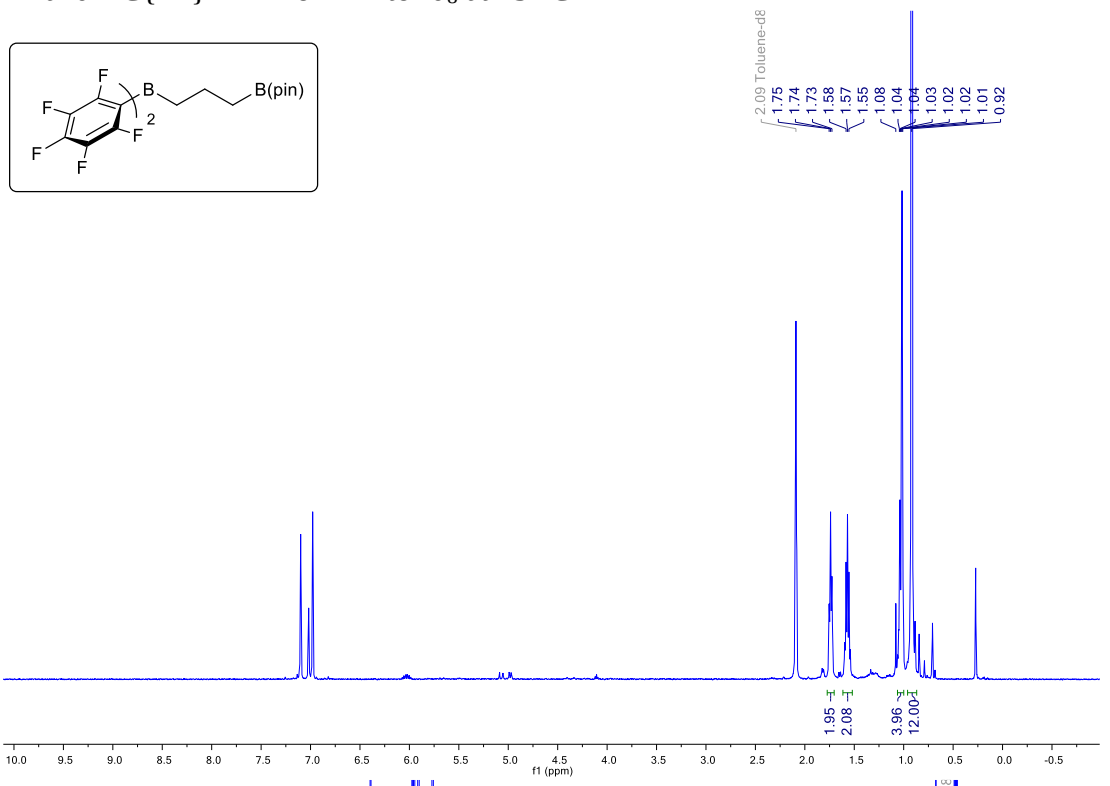
17 S. Das, Y. Li, C. Bornschein, S. Pisiewicz, K. Kiersch, D. Michalik, F. Gallou, K. Junge and M. Beller, *Angew. Chemie Int. Ed.*, 2015, **54**, 12389–12393.

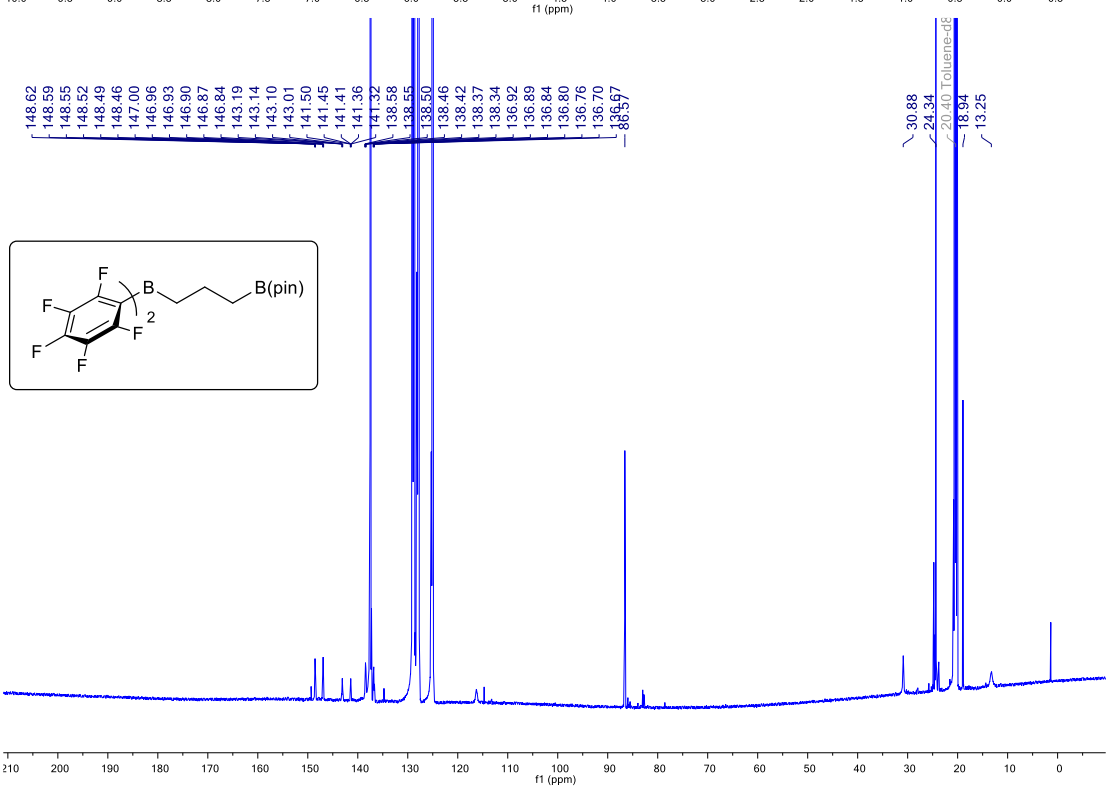
18 P. Wipf and Y. Uto, *J. Org. Chem.*, 2000, **65**, 1037–1049.

19 S. Das, Y. Li, L. Q. Lu, K. Junge and M. Beller, *Chem. - A Eur. J.*, 2016, **22**, 7050–7053.

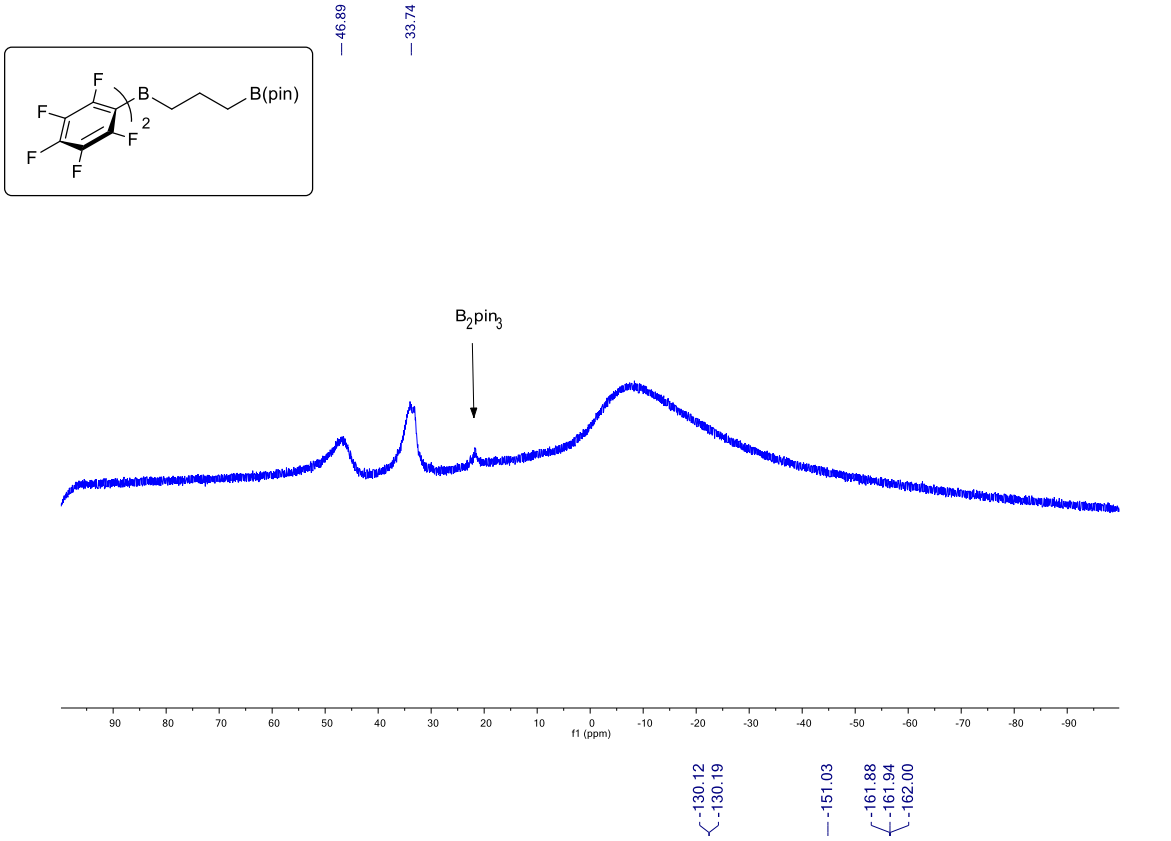
20 J. C. Anderson and S. Skerratt, *J. Chem. Soc. Perkin Trans. 1*, 2002, **30**, 2871–2879.

^{1}H and $^{13}C\{^{1}H\}$ NMR of **7** in tol-d_8 at 25 °C

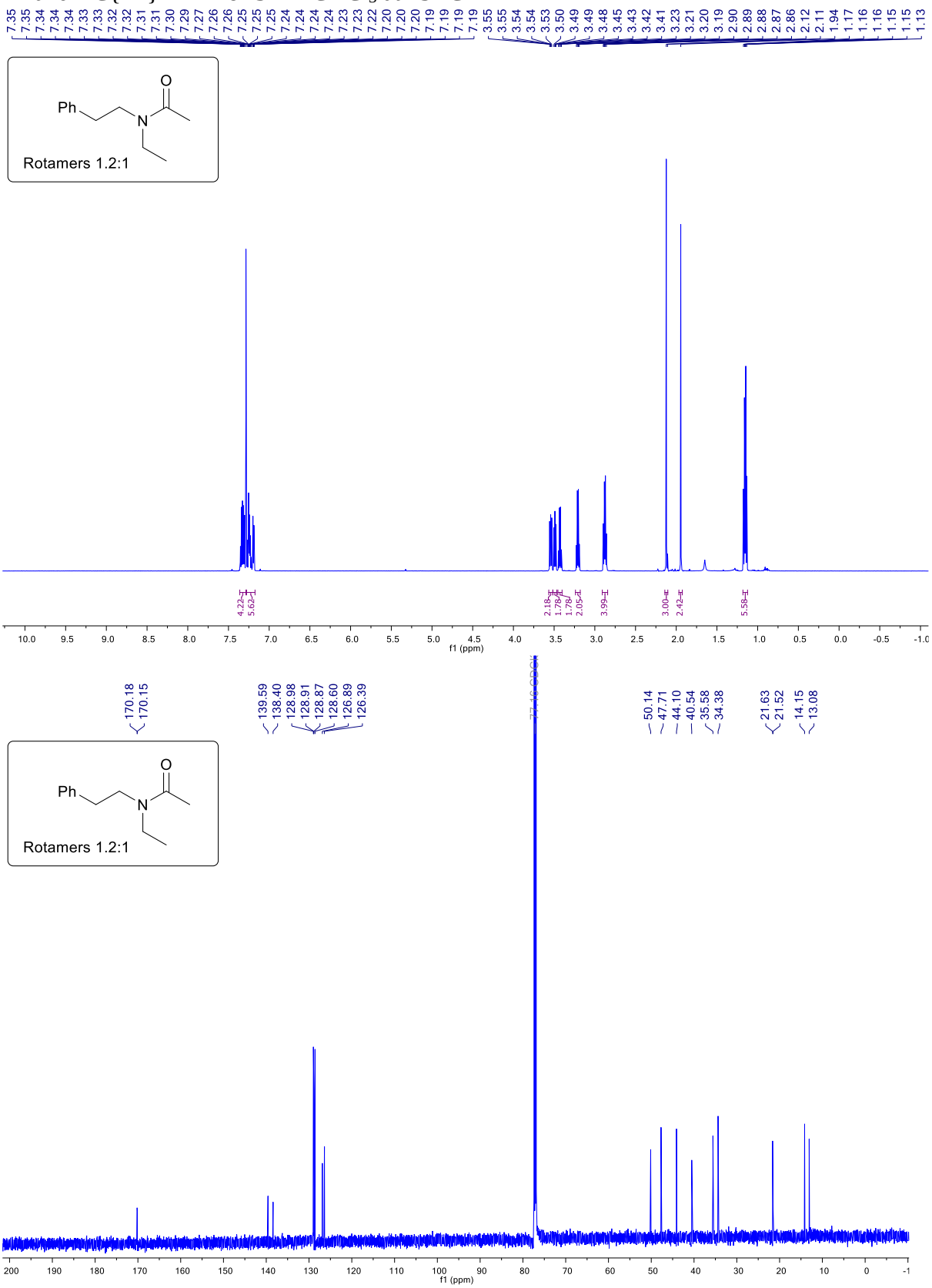




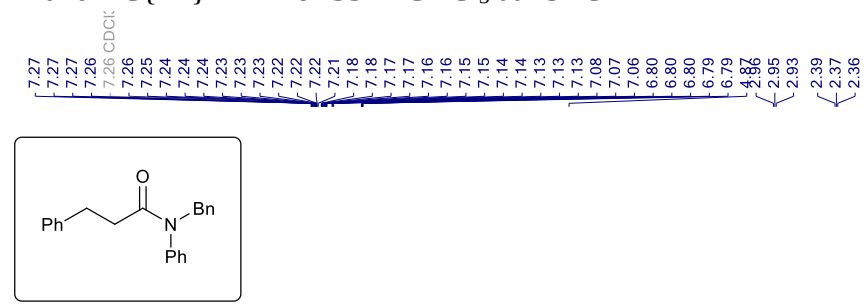
^{11}B and $^{19}F\{^{1}H\}$ NMR of **7** in tol-d_8 at 25 °C

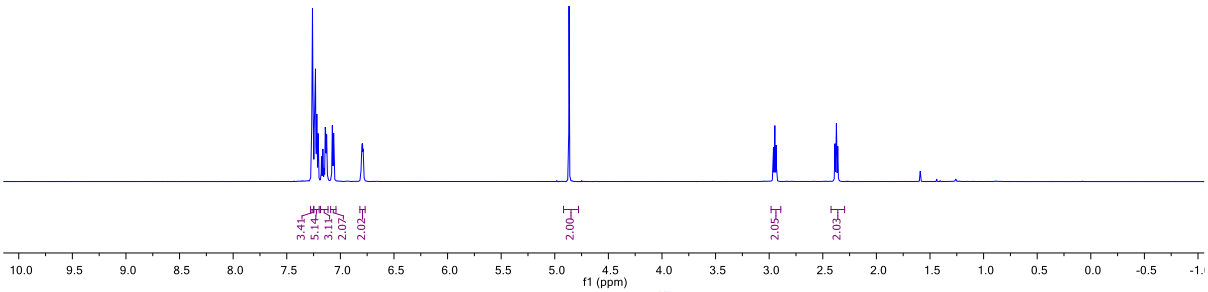


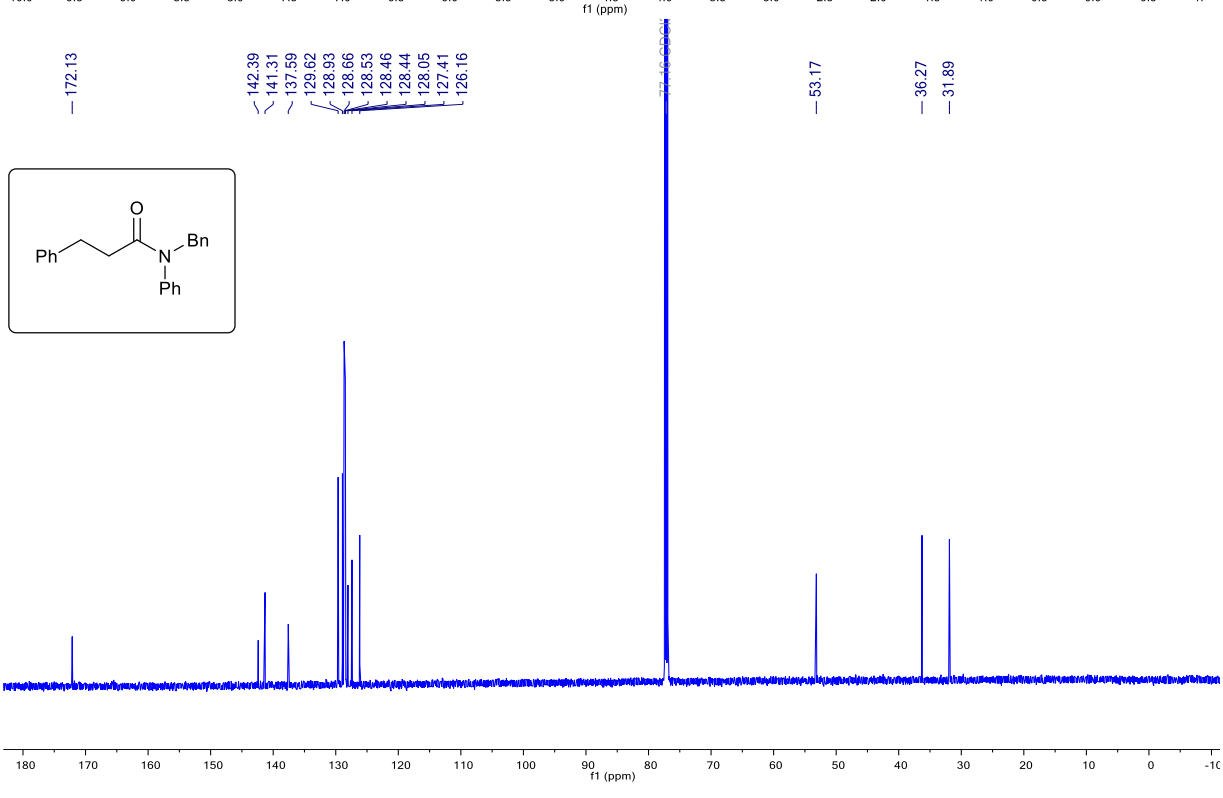
^{1}H and $^{13}C\{^{1}H\}$ NMR of **S1** in $CDCl_3$ at 25 °C



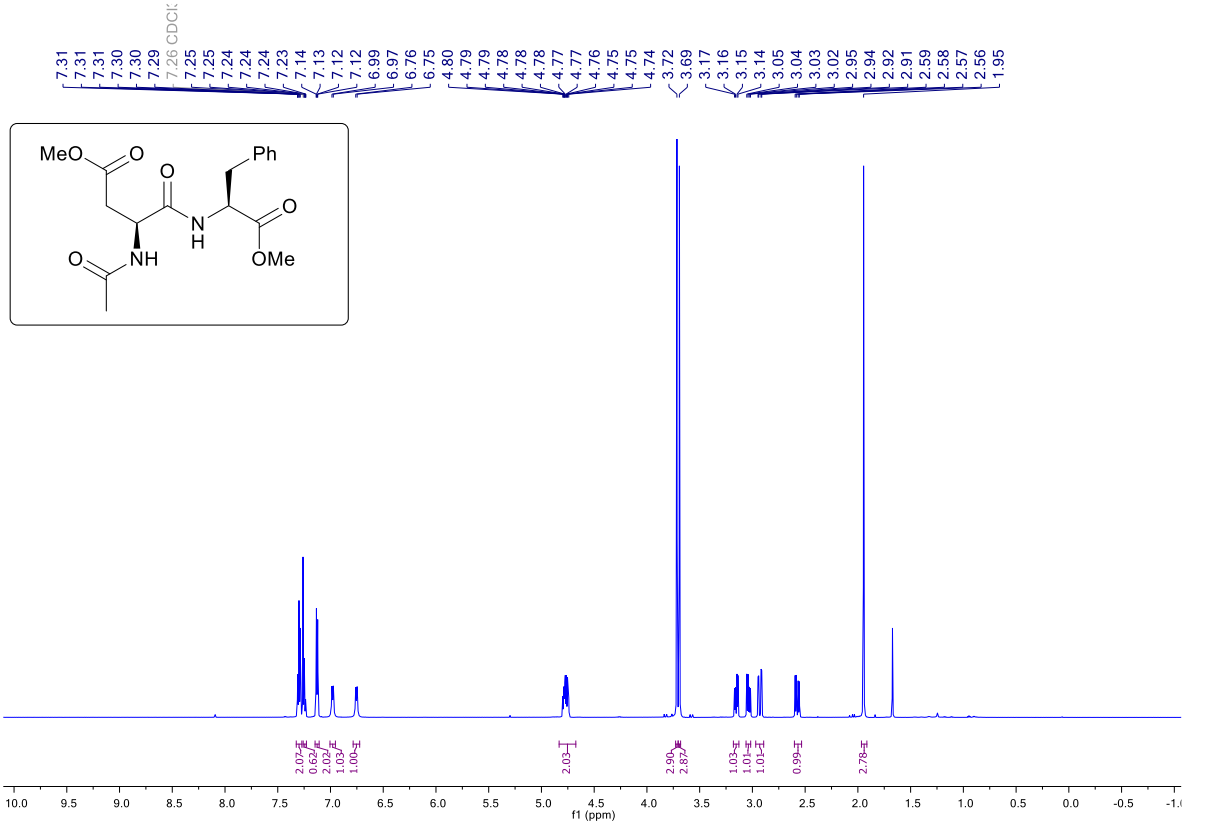
^{1}H and $^{13}C\{^{1}H\}$ NMR of **S5** in $CDCl_3$ at 25 °C

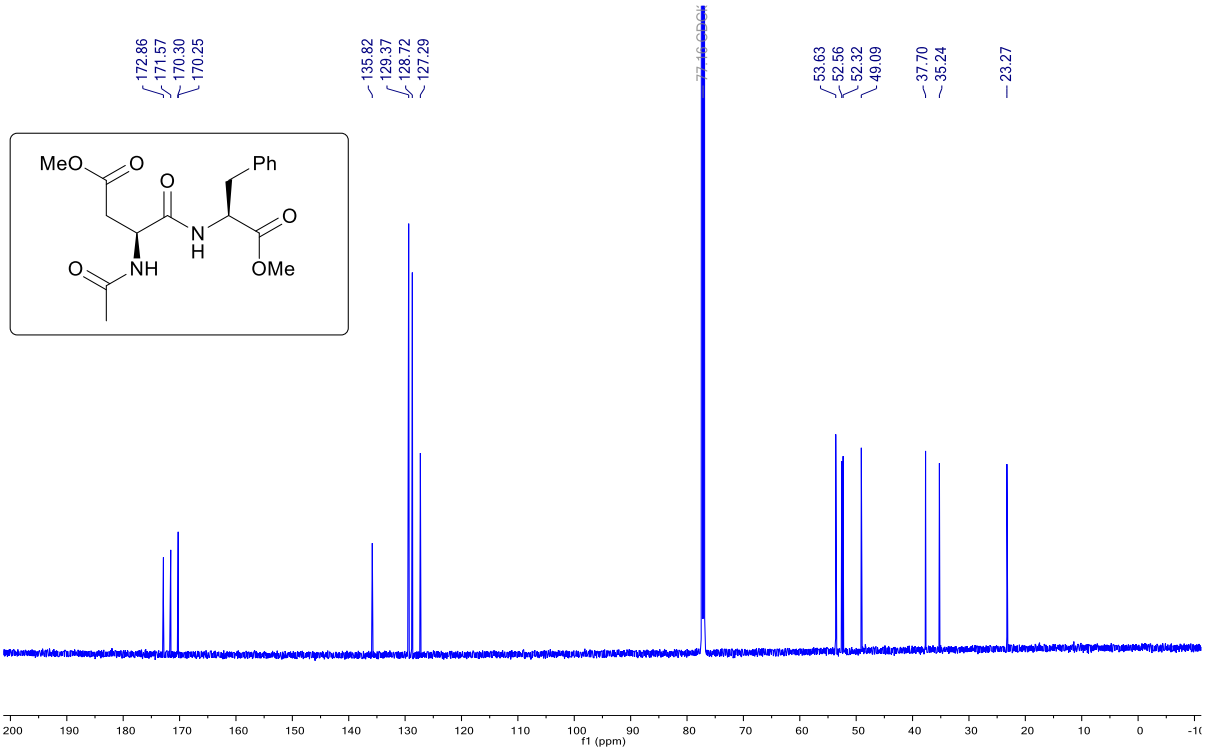




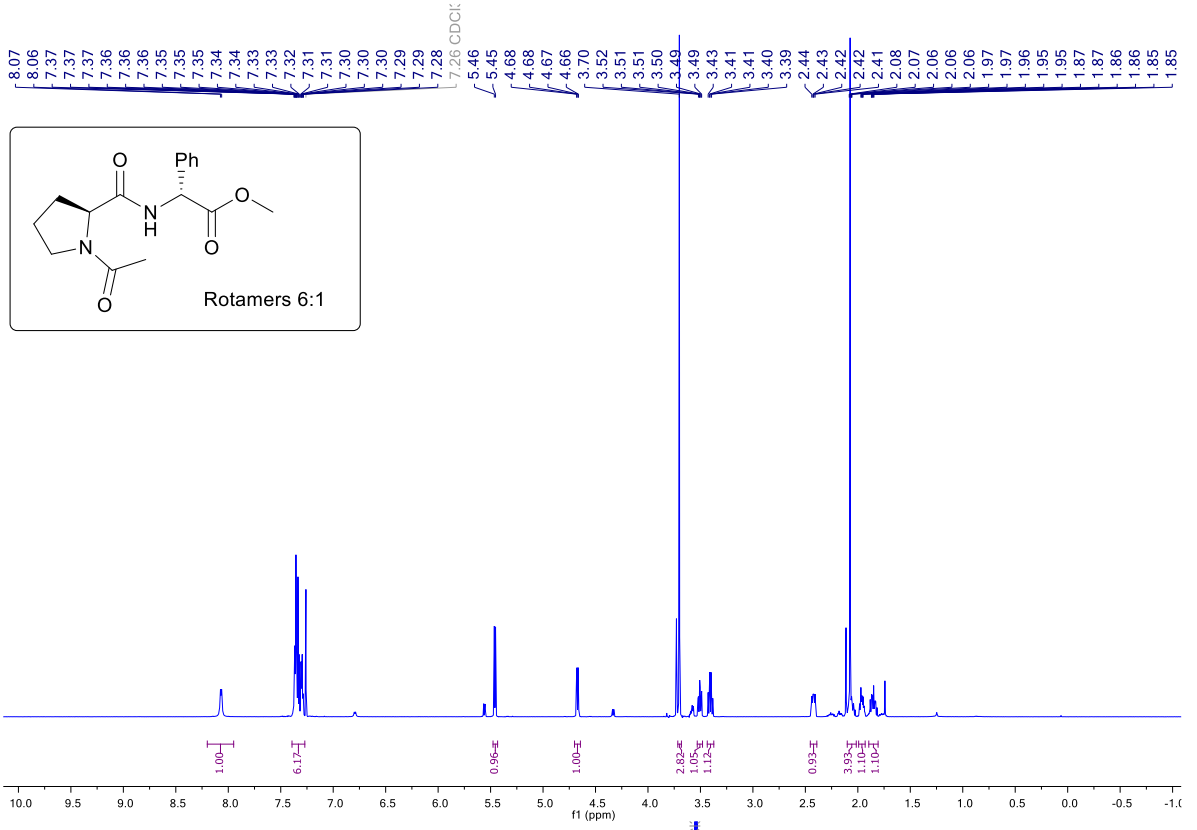


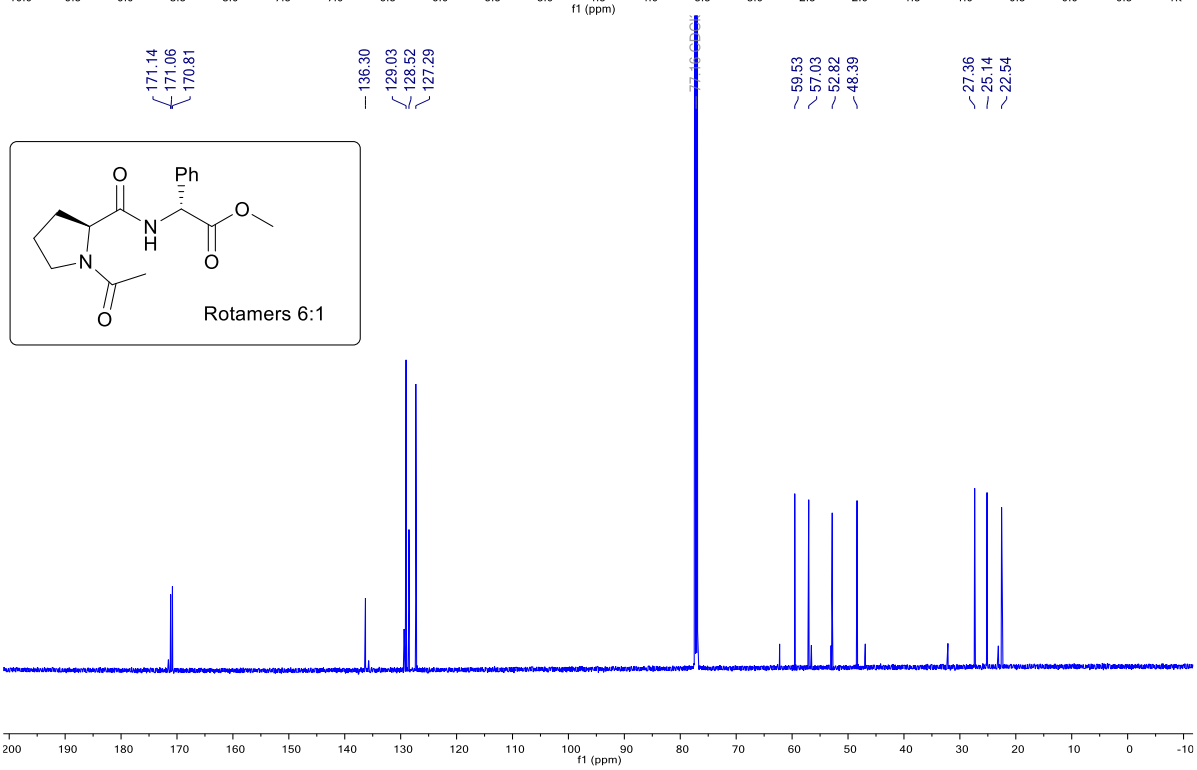
^{1}H and $^{13}C\{^{1}H\}$ NMR of **27** in $CDCl_3$ at 25 °C



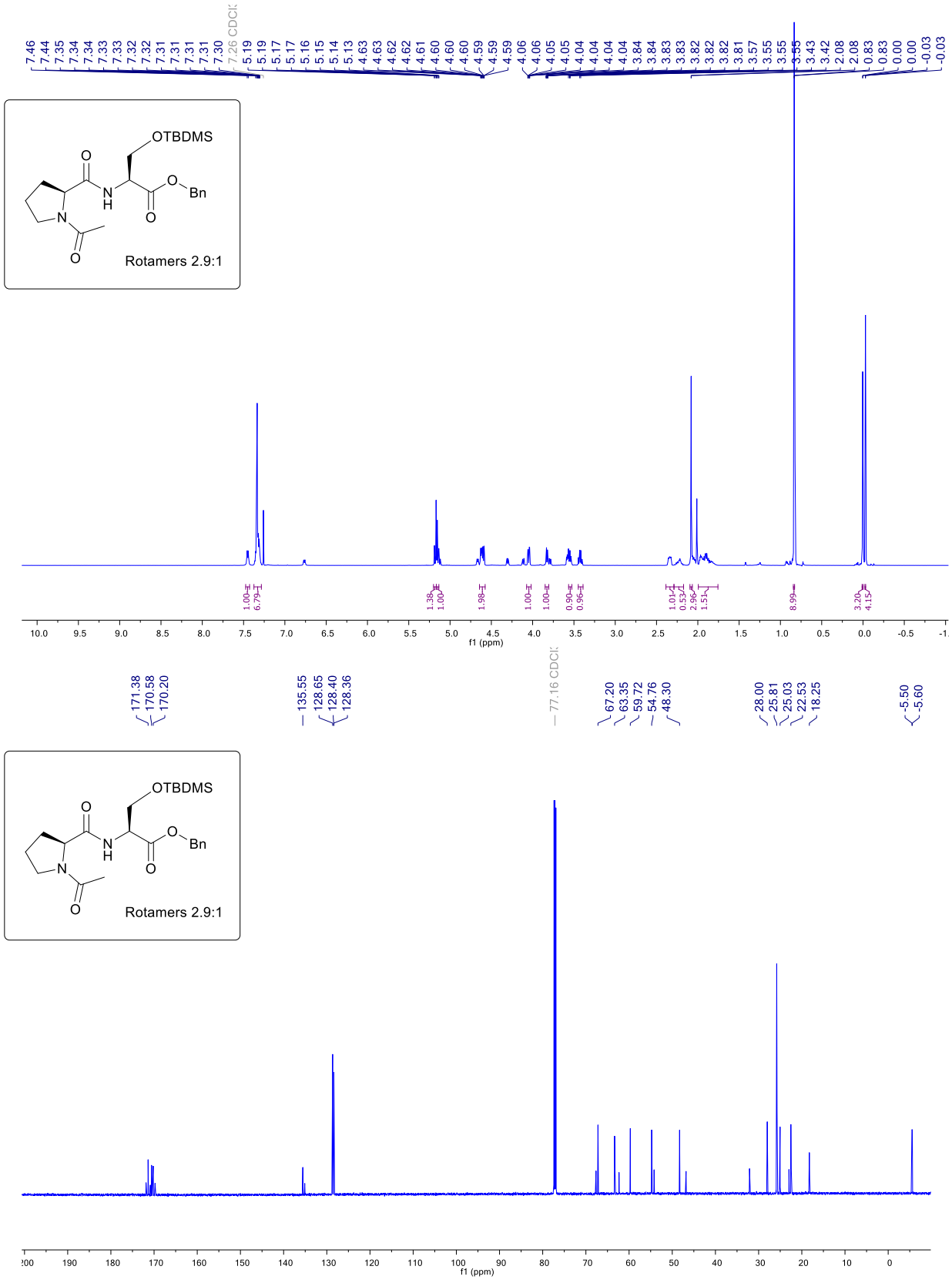


^{1}H and $^{13}C\{^{1}H\}$ NMR of **S16** in $CDCl_3$ at 25 °C

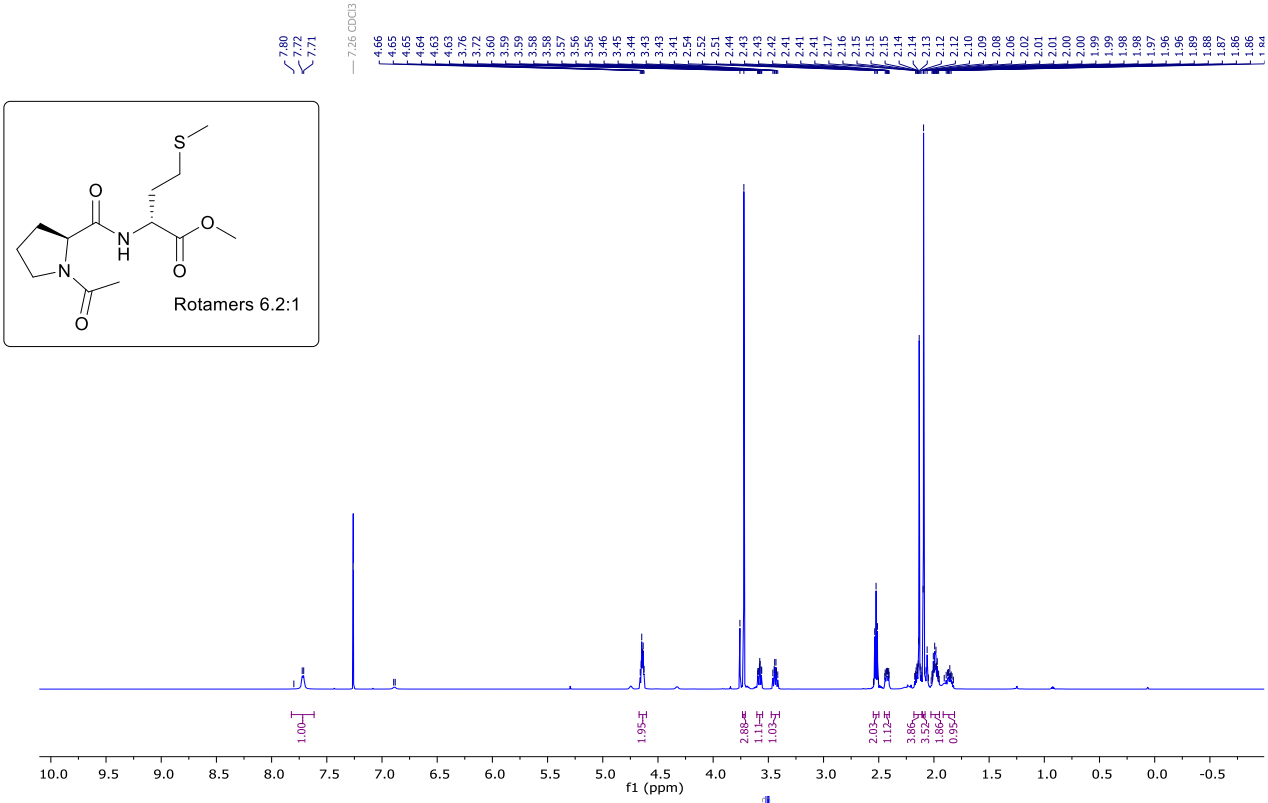


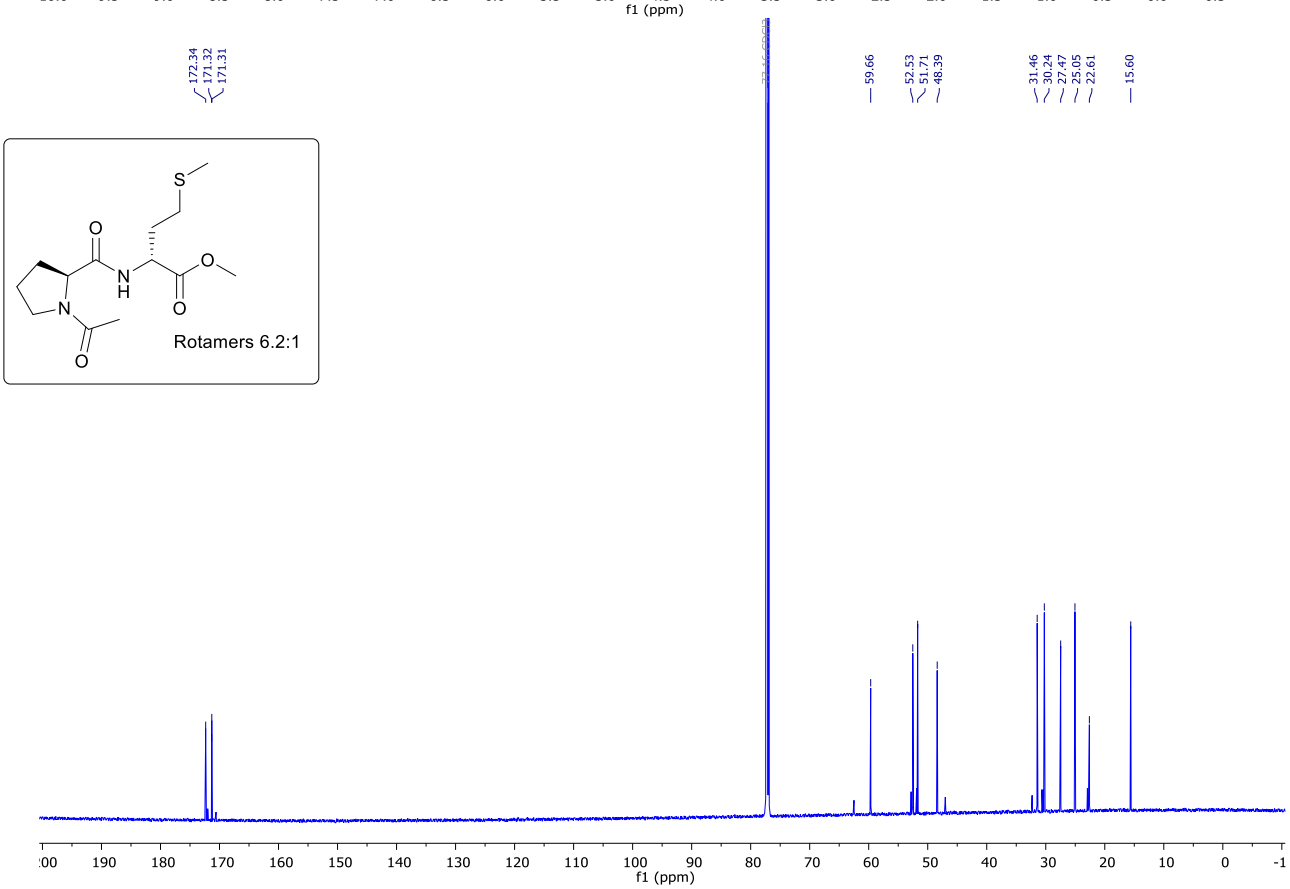


^{1}H and $^{13}C\{^{1}H\}$ NMR of **S17** in $CDCl_3$ at 25 °C

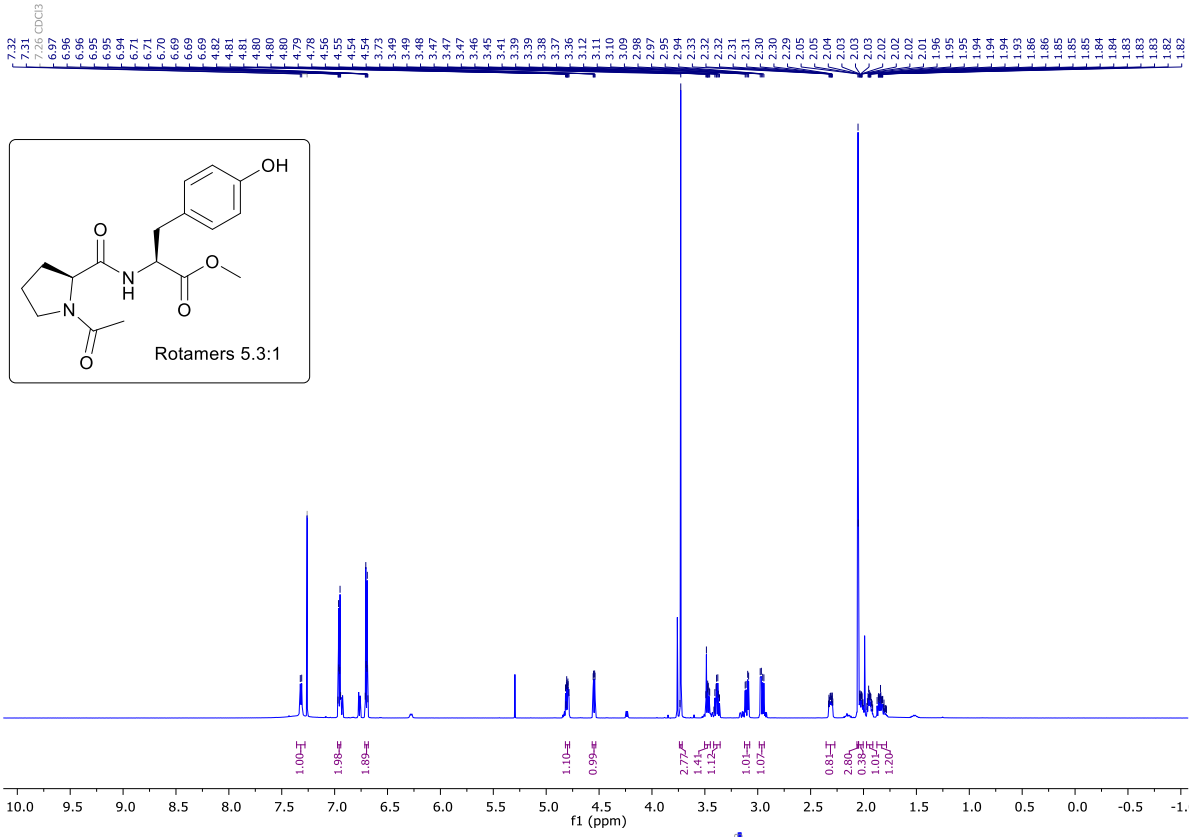


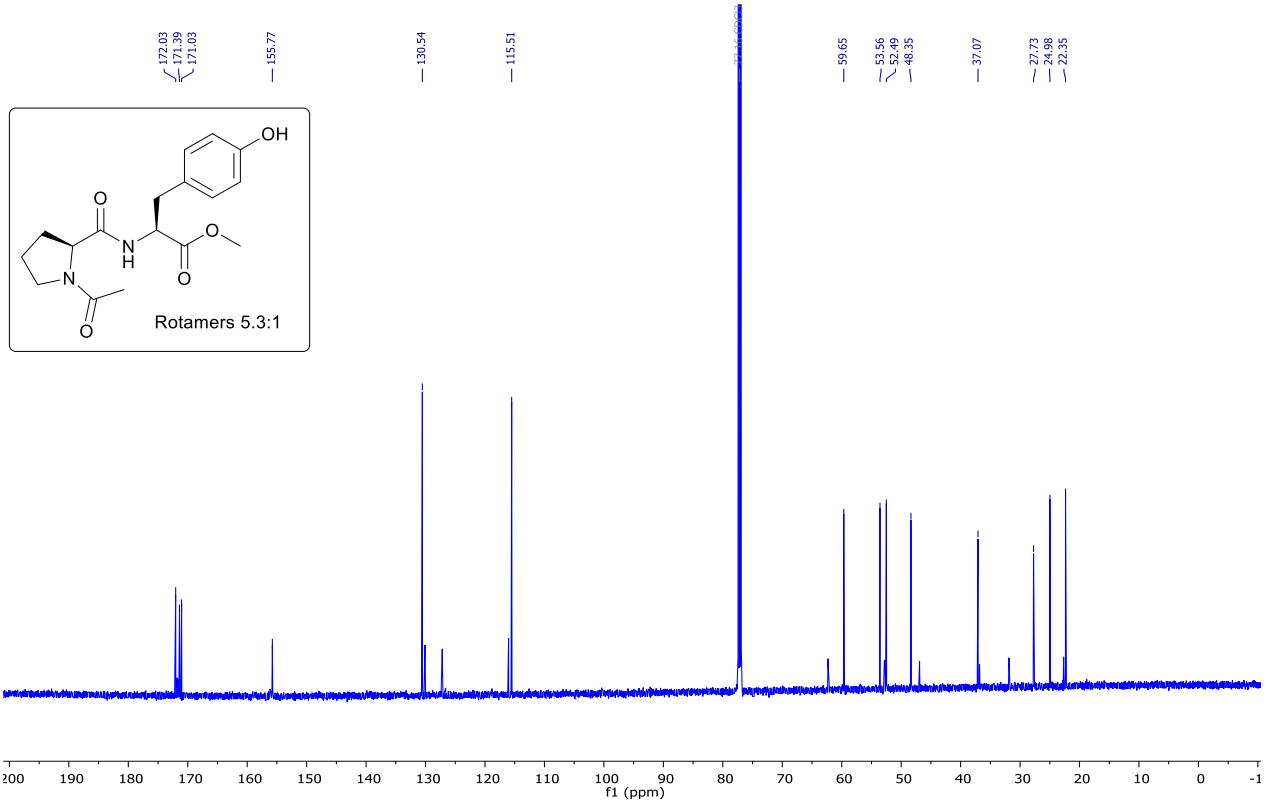
^{1}H and $^{13}C\{^{1}H\}$ NMR of **S19** in $CDCl_3$ at 25 °C



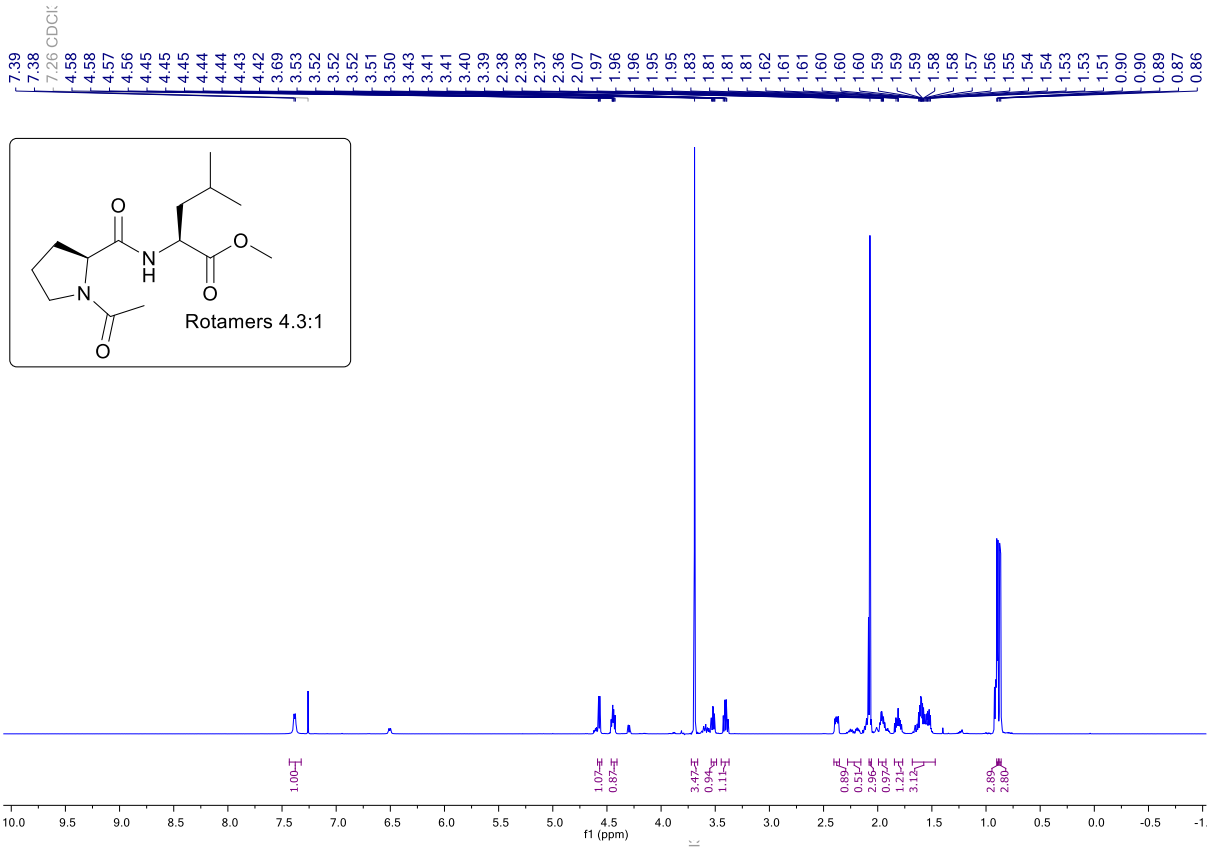


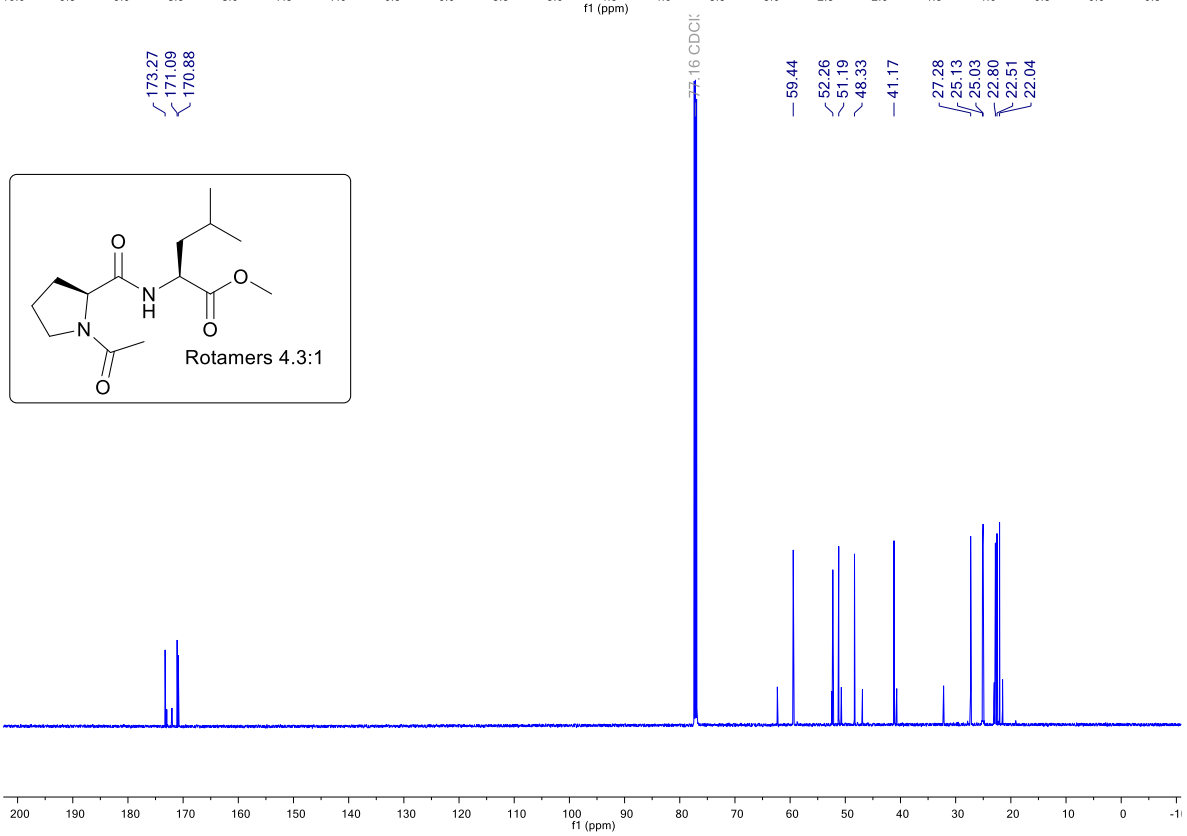
^{1}H and $^{13}C\{^{1}H\}$ NMR of **S20** in $CDCl_3$ at 25 °C



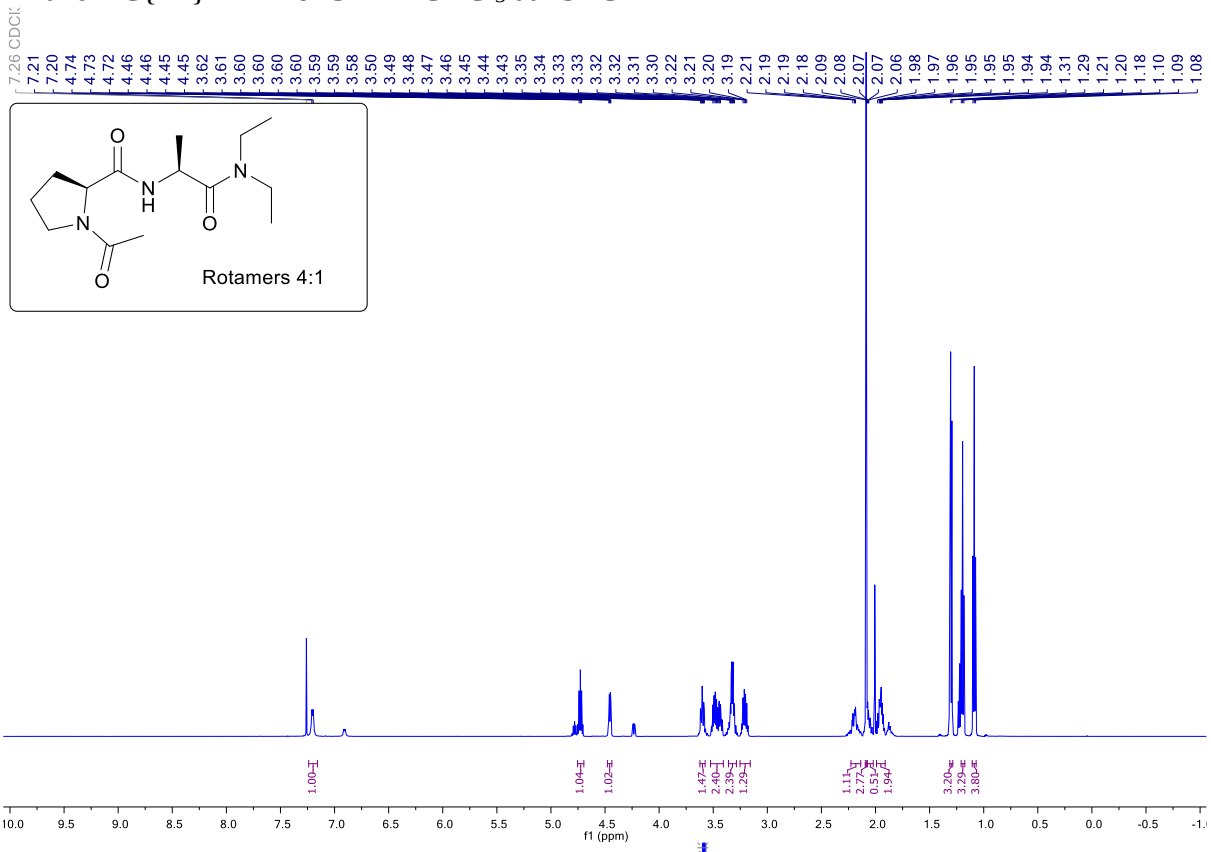


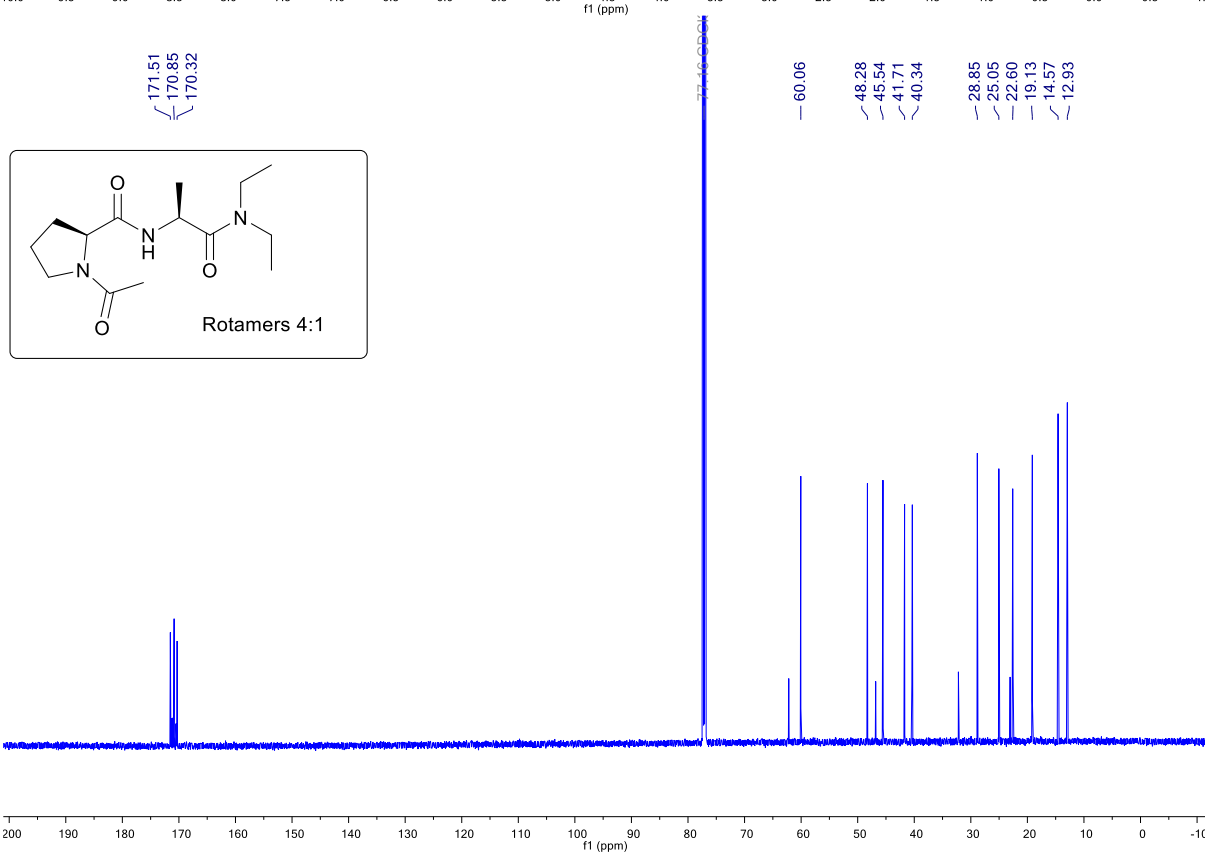
^{1}H and $^{13}C\{^{1}H\}$ NMR of **S21** in $CDCl_3$ at 25 °C



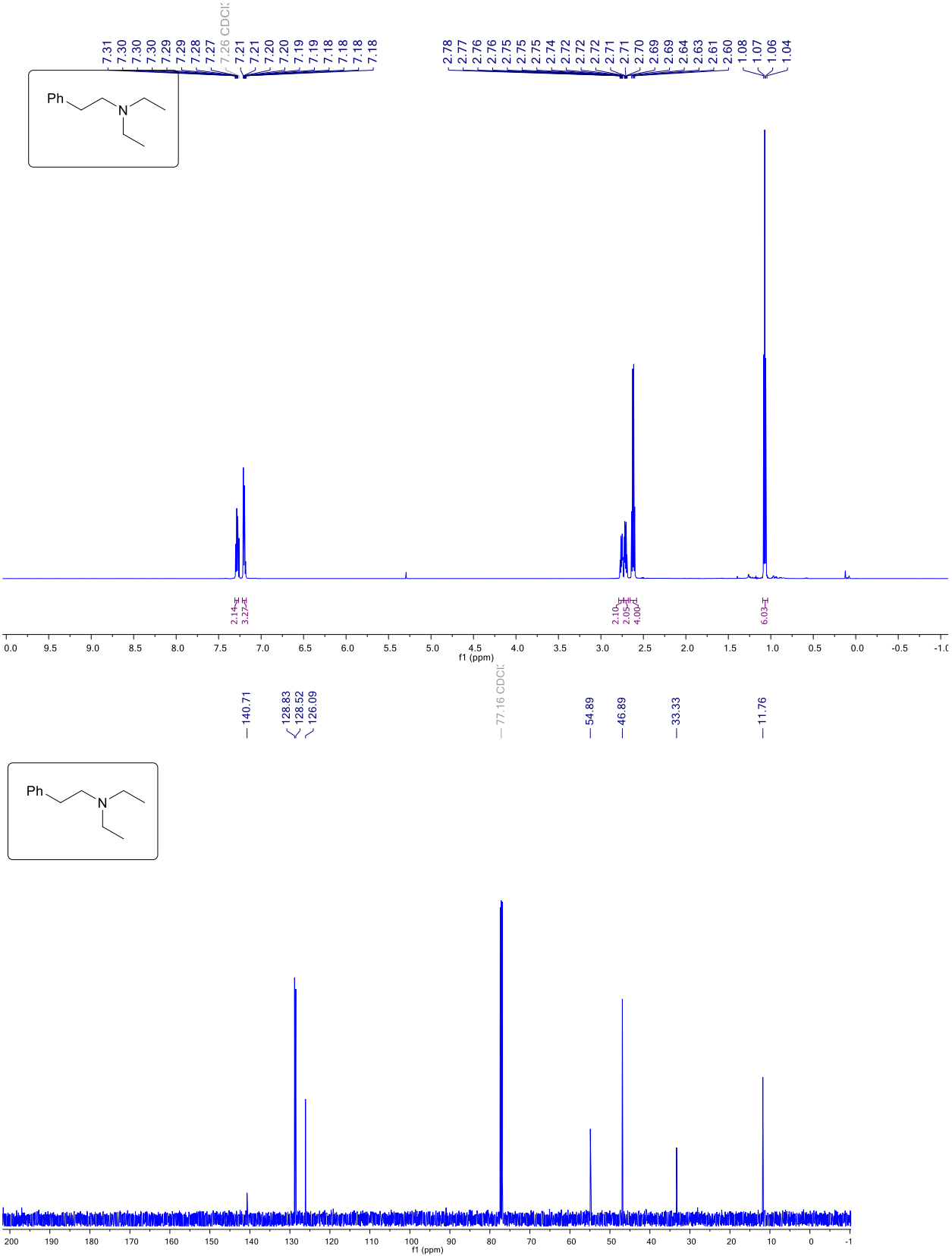


^{1}H and $^{13}C\{^{1}H\}$ NMR of **S22** in $CDCl_3$ at 25 °C

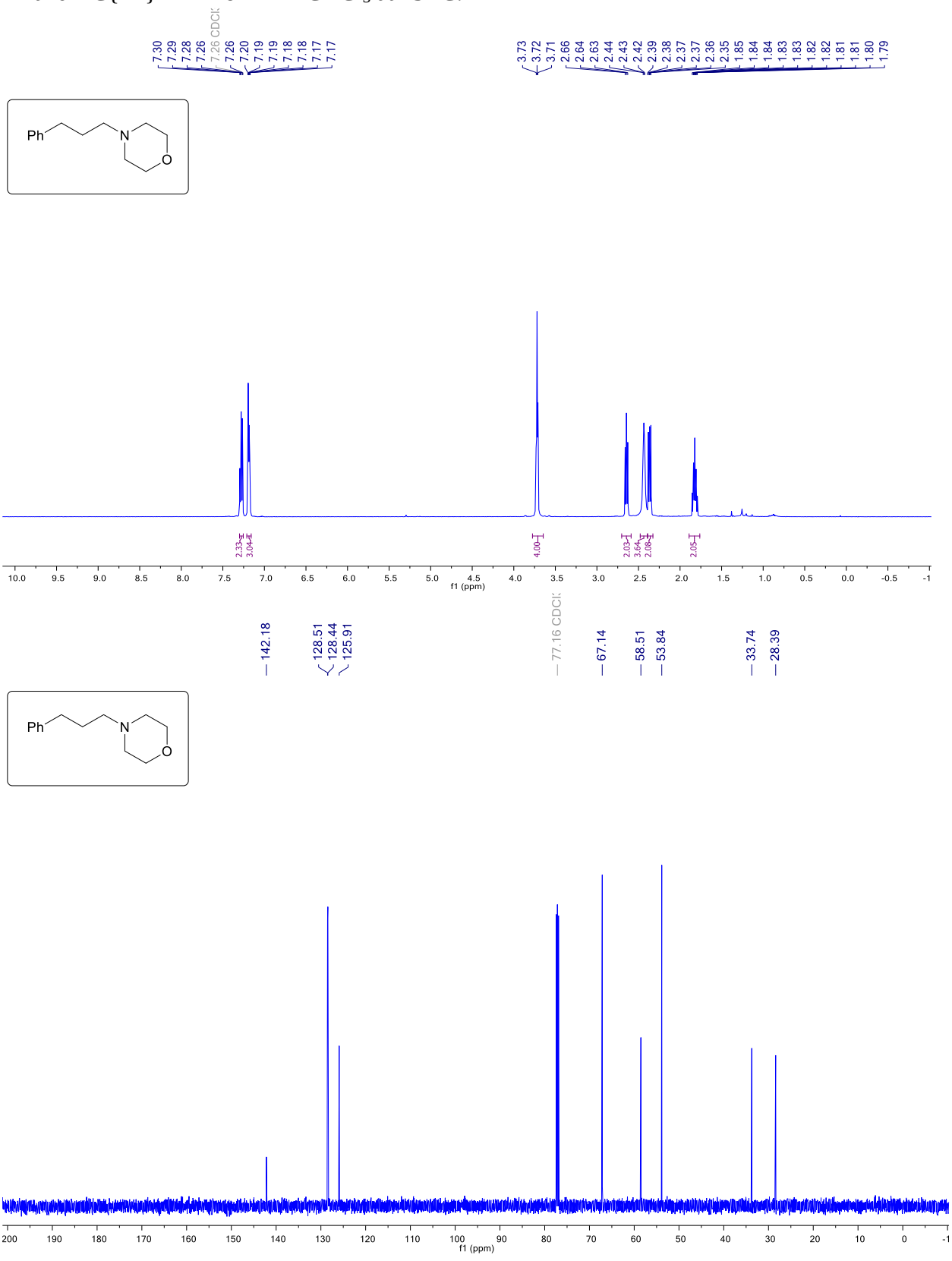




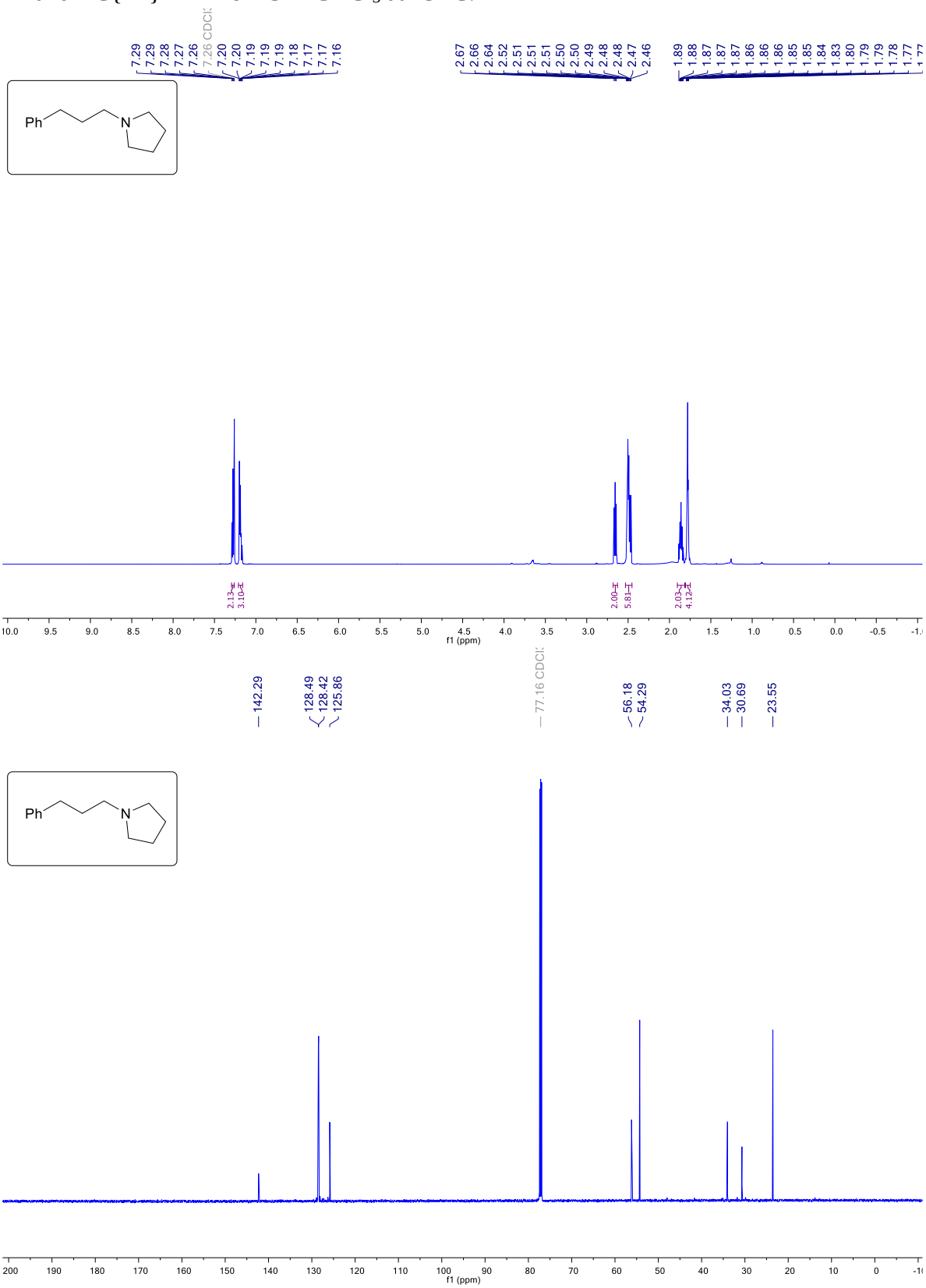
^{1}H and $^{13}C\{^{1}H\}$ NMR of **4 & 13** in $CDCl_3$ at 25 °C.



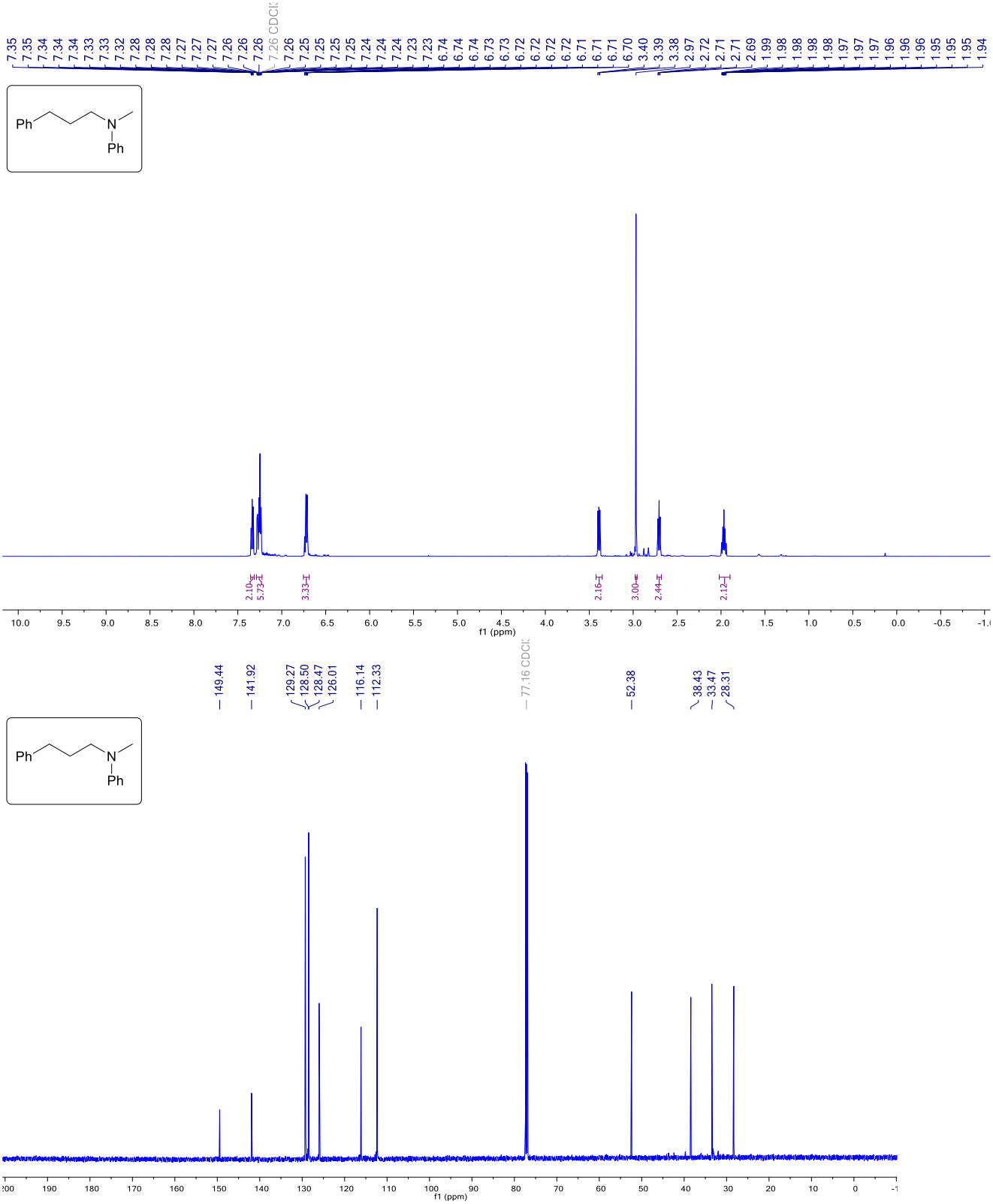
^{1}H and $^{13}C\{^{1}H\}$ NMR of **14** in $CDCl_3$ at 25 °C.



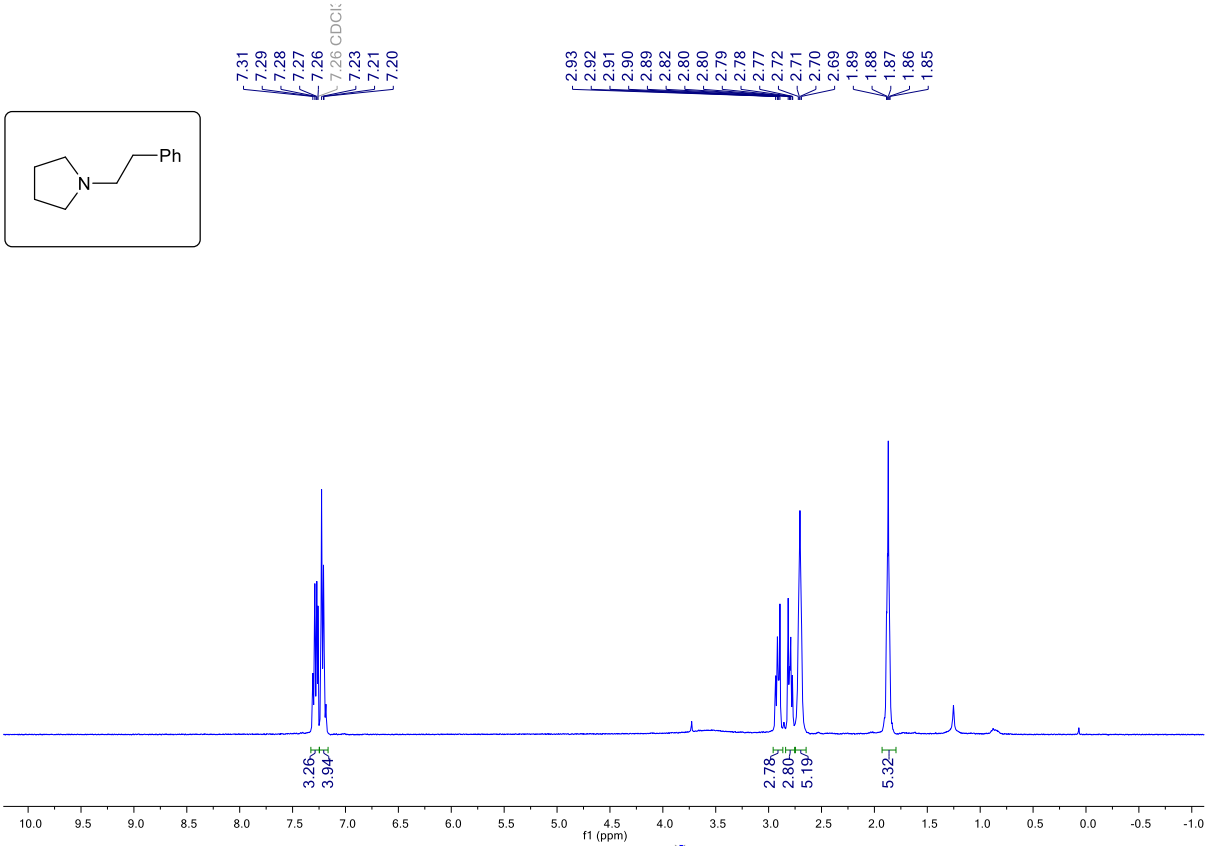
^{1}H and $^{13}C\{^{1}H\}$ NMR of **15** in $CDCl_3$ at 25 °C.

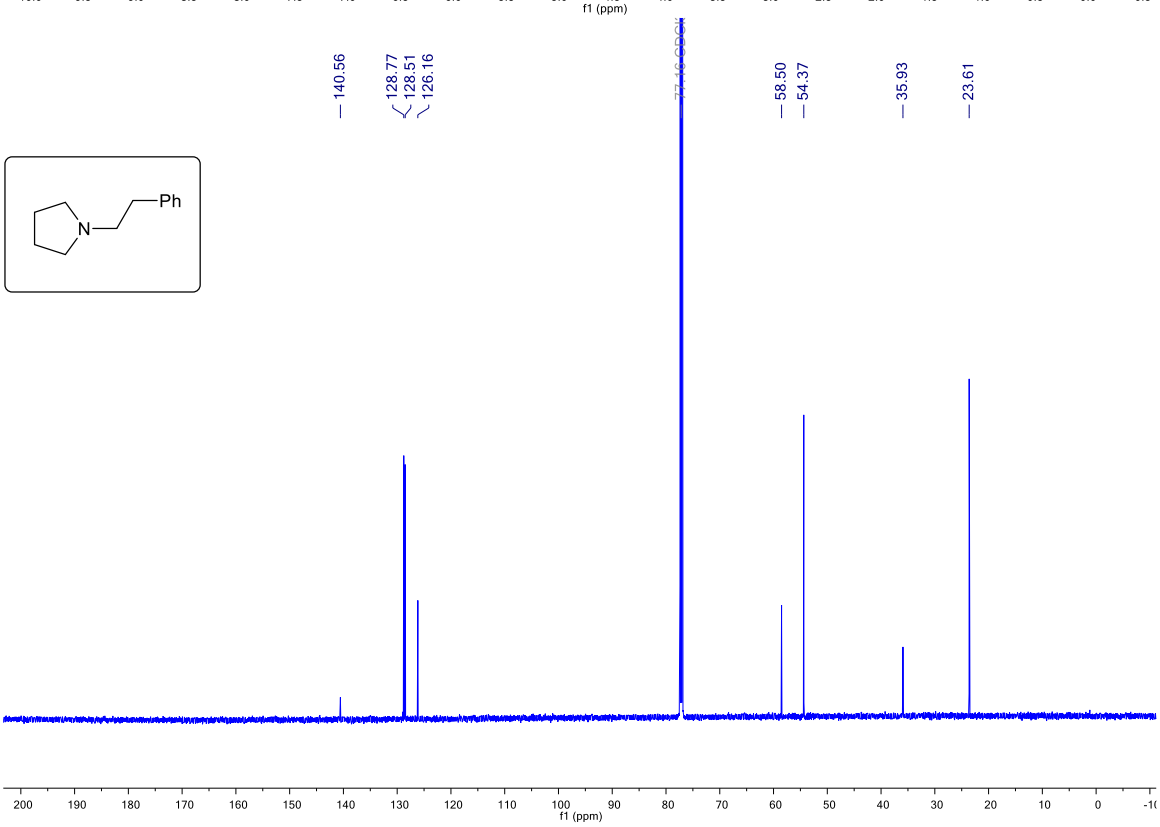


^{1}H and $^{13}C\{^{1}H\}$ NMR of **16** in $CDCl_3$ at 25 °C.

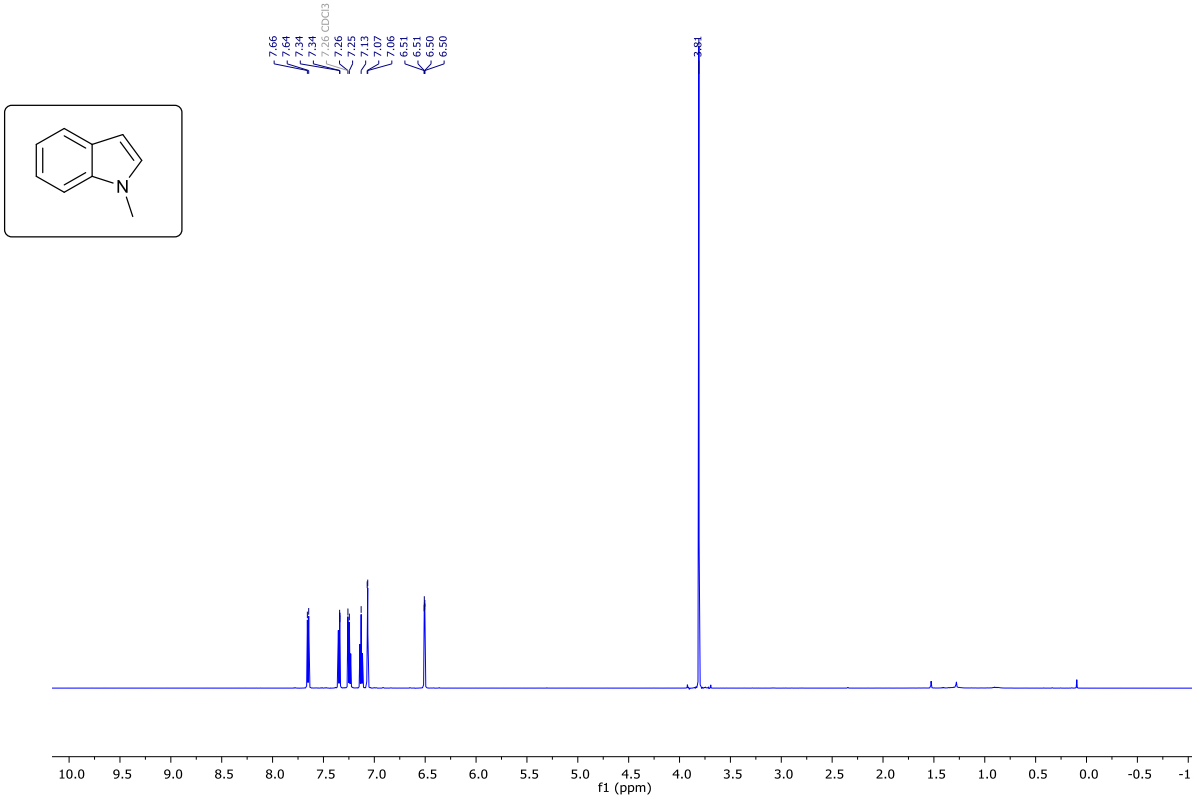


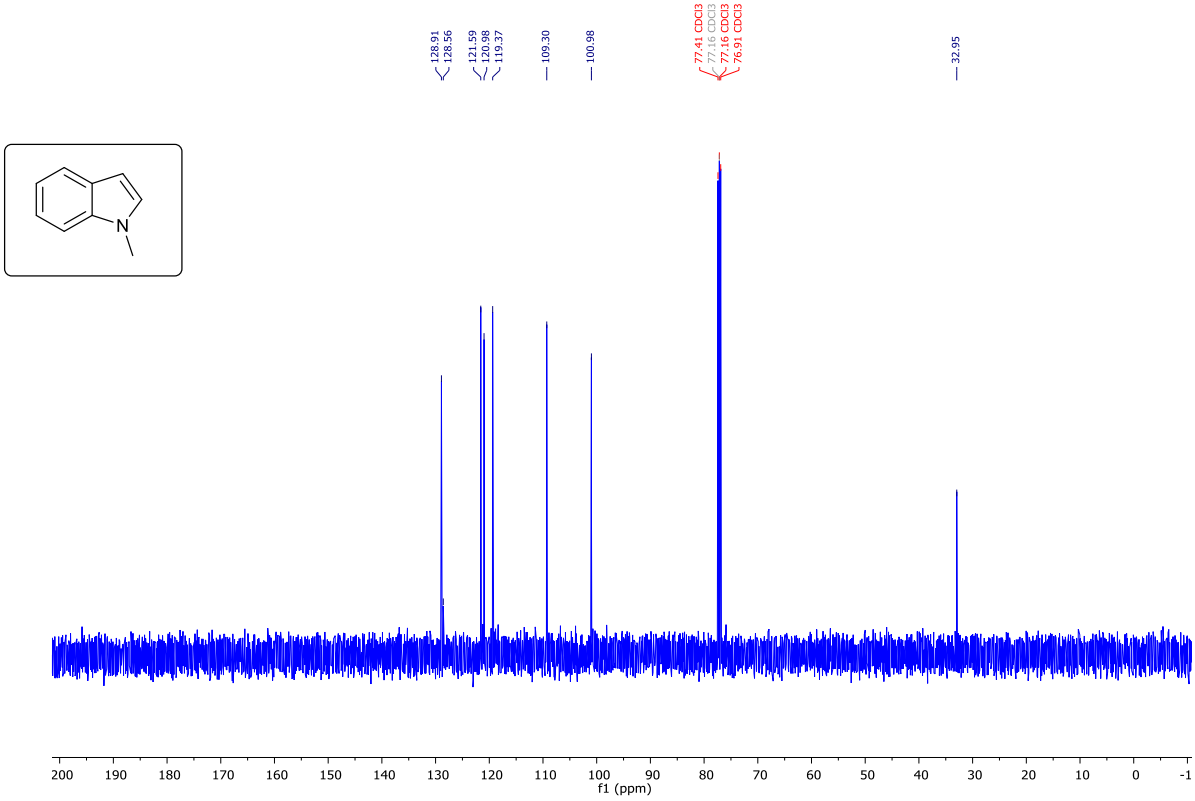
^{1}H and $^{13}C\{^{1}H\}$ NMR of **17** in $CDCl_3$ at 25 °C



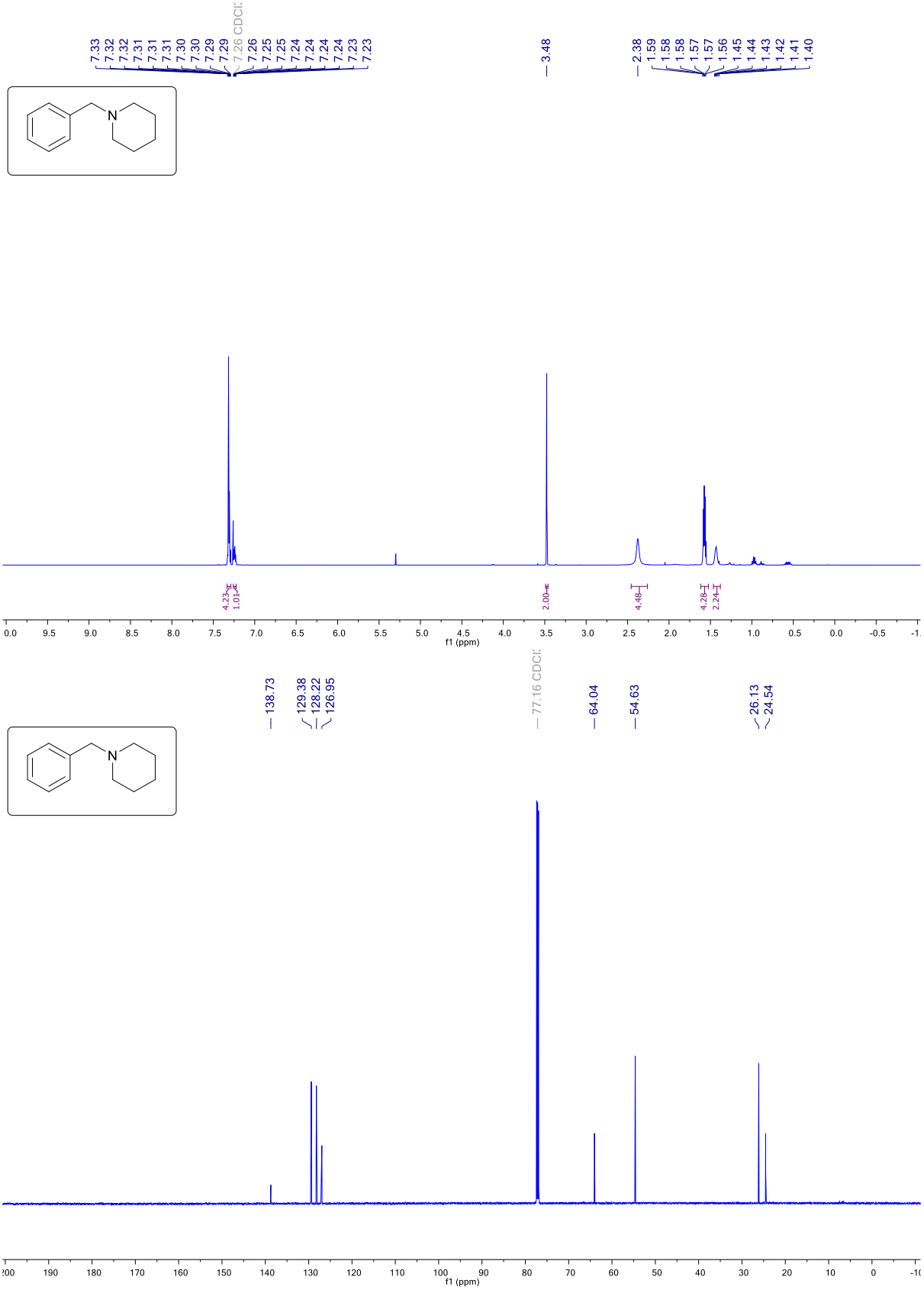


^{1}H and $^{13}C\{^{1}H\}$ NMR of **S23** in $CDCl_3$ at 25 °C

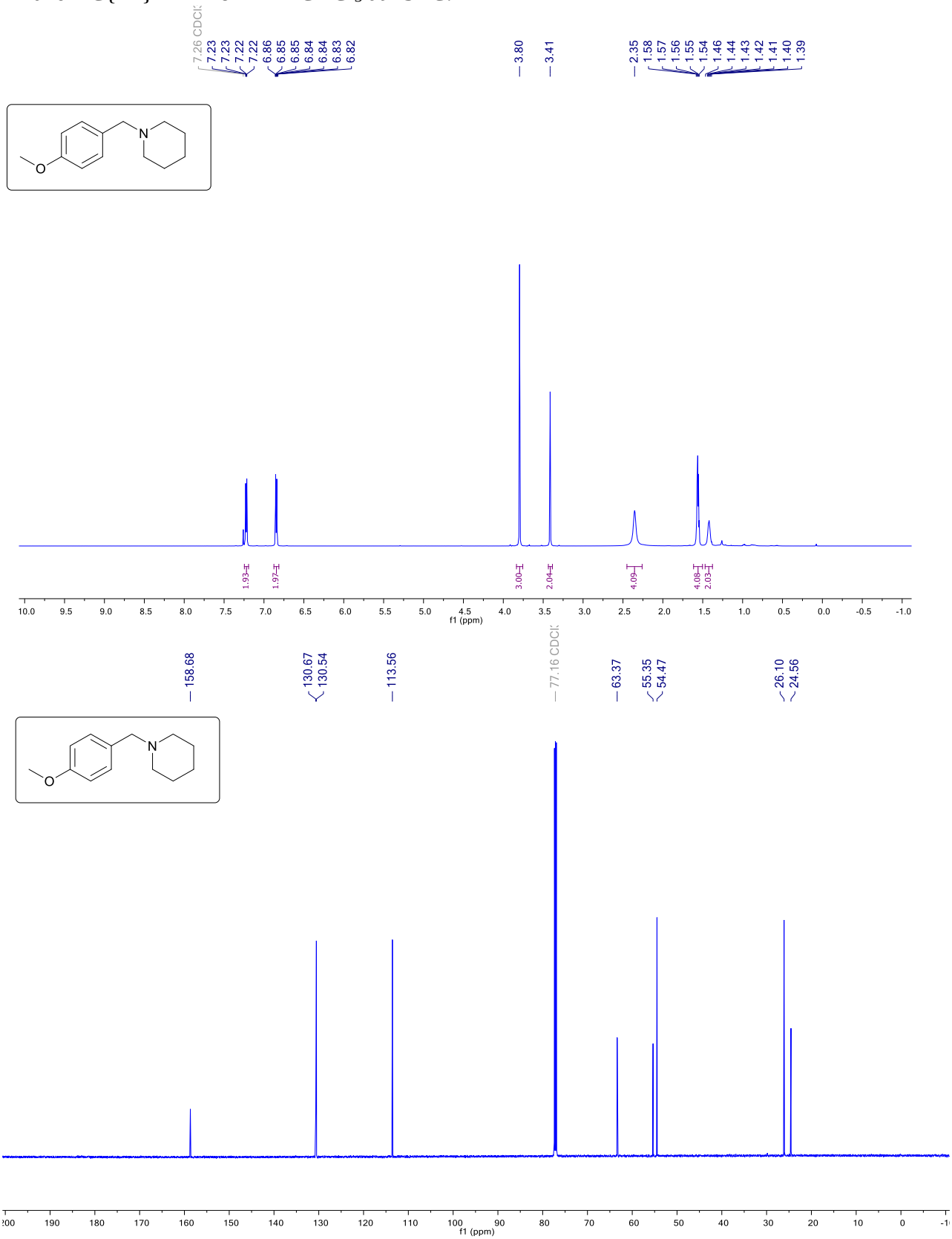




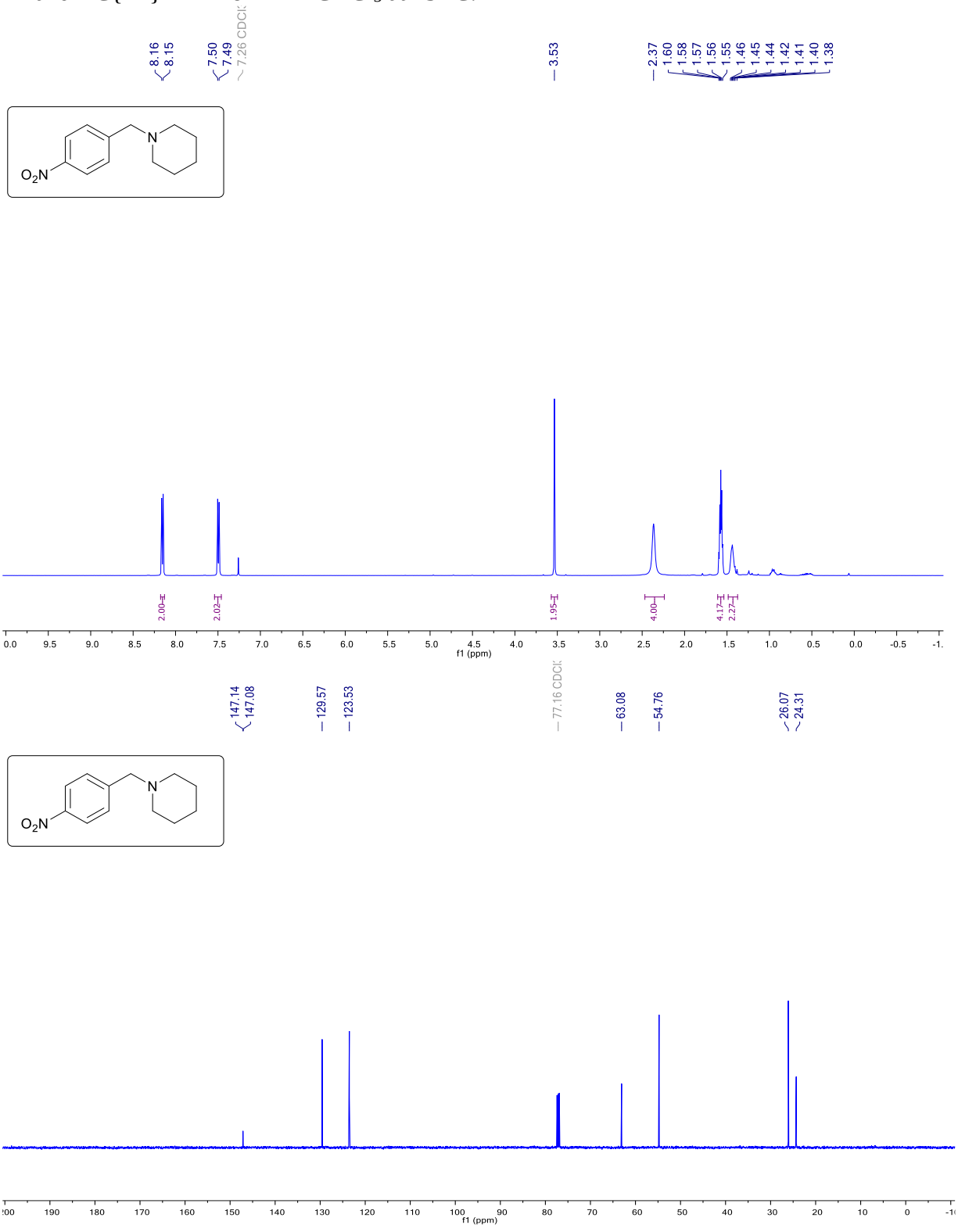
^{1}H and $^{13}C\{^{1}H\}$ NMR of **20** in $CDCl_3$ at 25 °C.



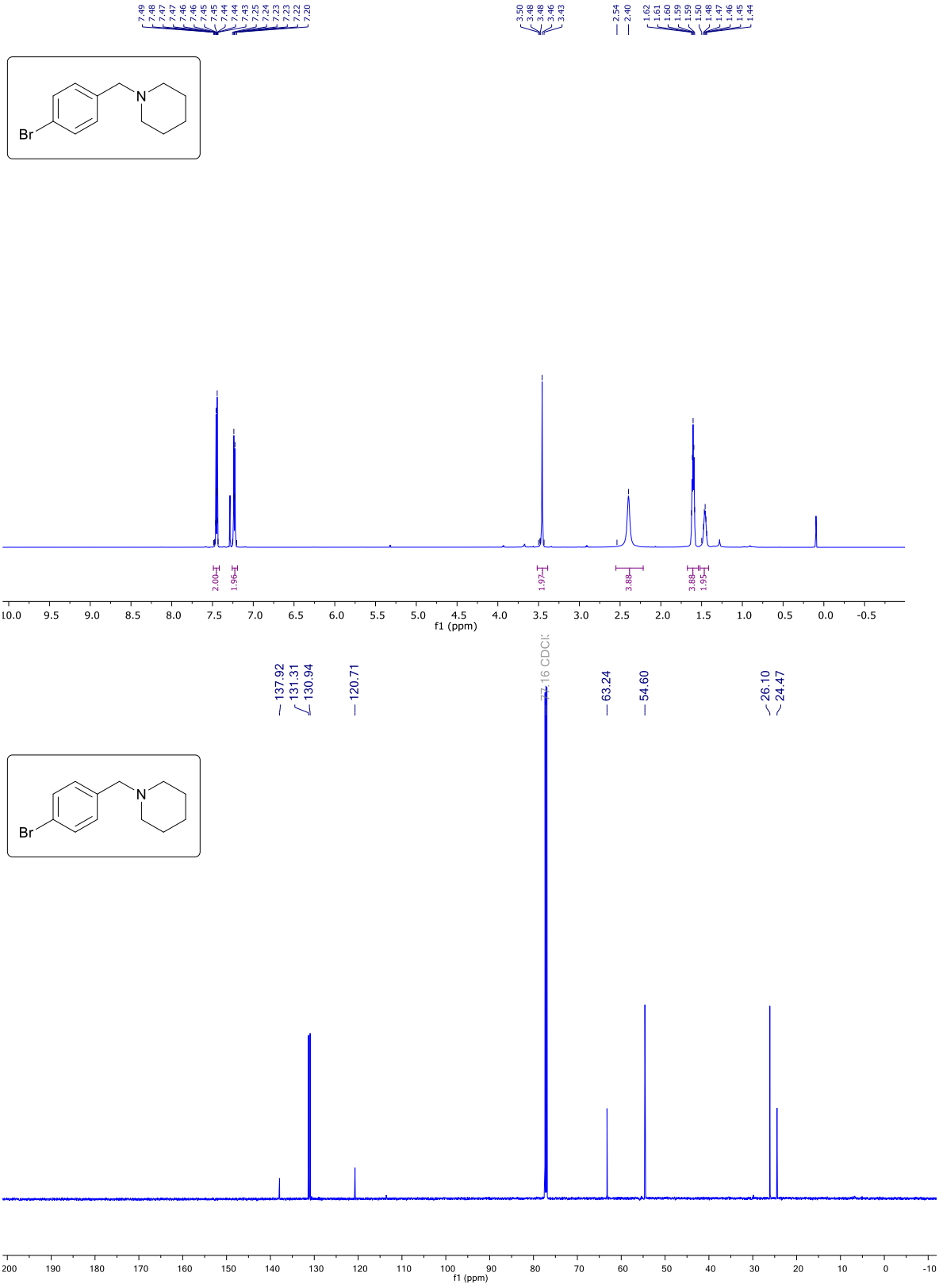
^{1}H and $^{13}C\{^{1}H\}$ NMR of **21** in $CDCl_3$ at 25 °C.



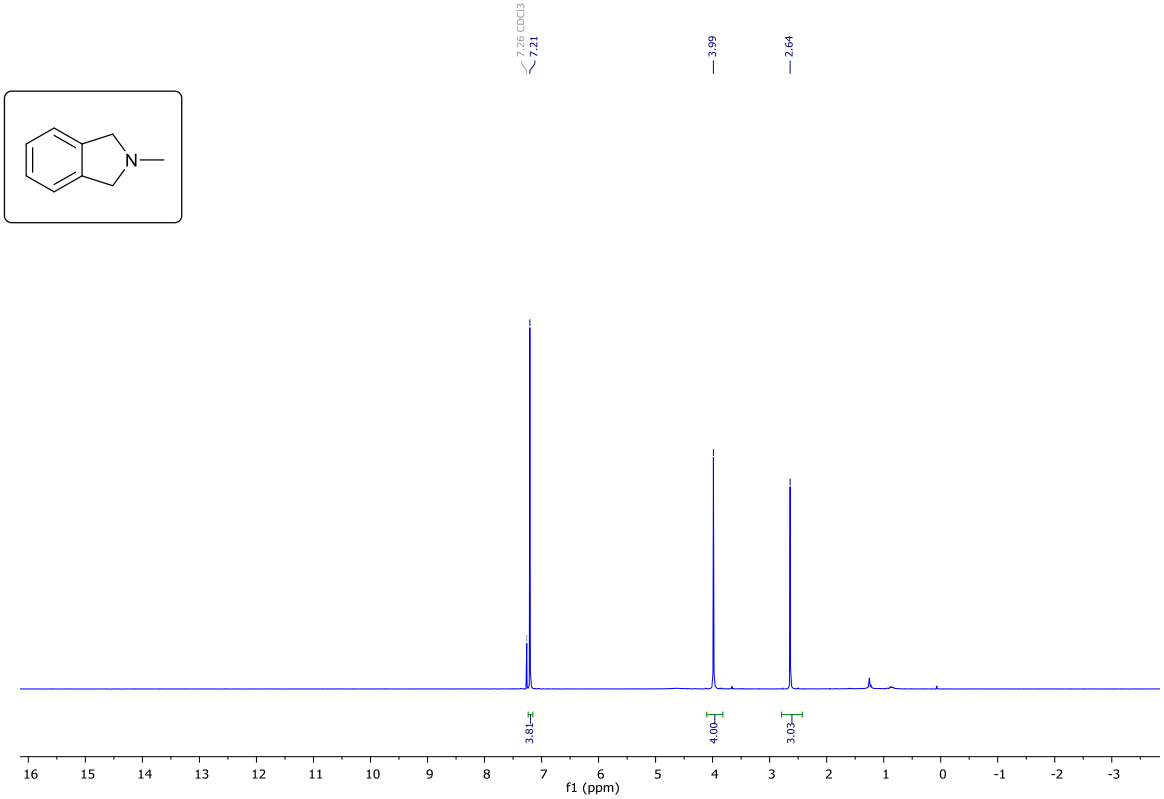
^{1}H and $^{13}C\{^{1}H\}$ NMR of **22** in $CDCl_3$ at 25 °C.

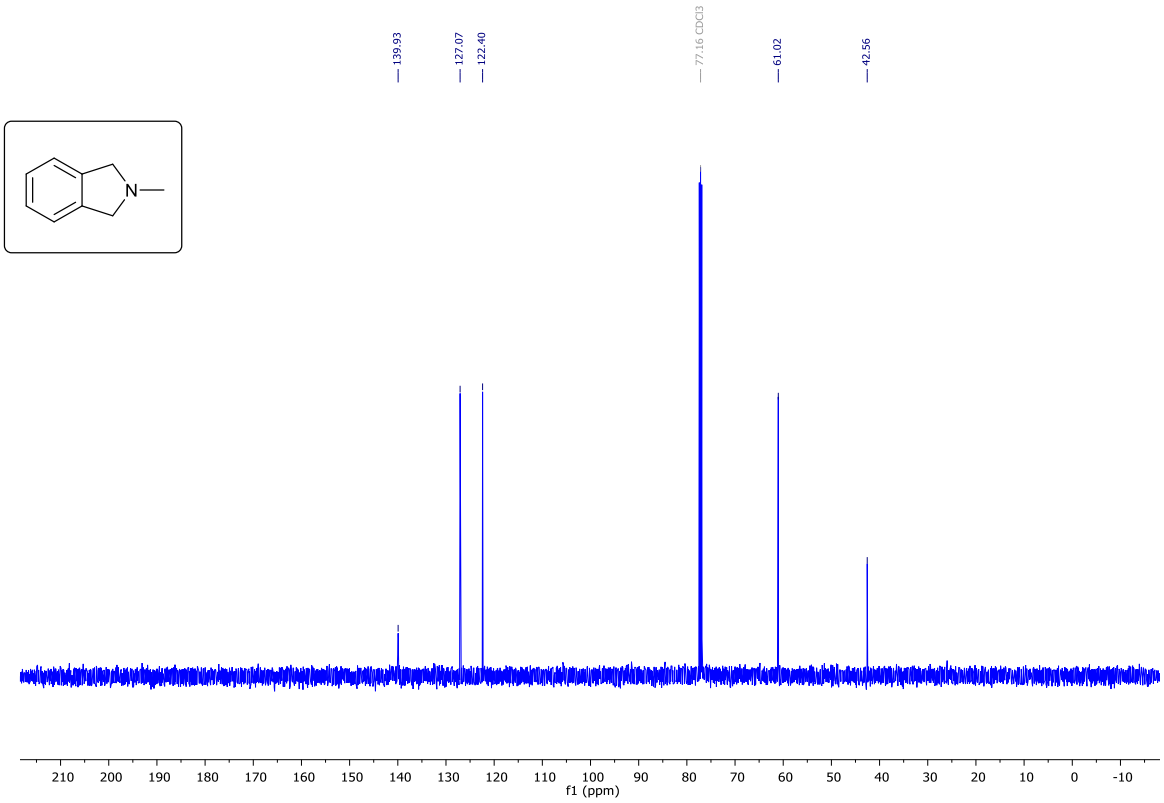


^{1}H and $^{13}C\{^{1}H\}$ NMR of **23** in $CDCl_3$ at 25 °C.

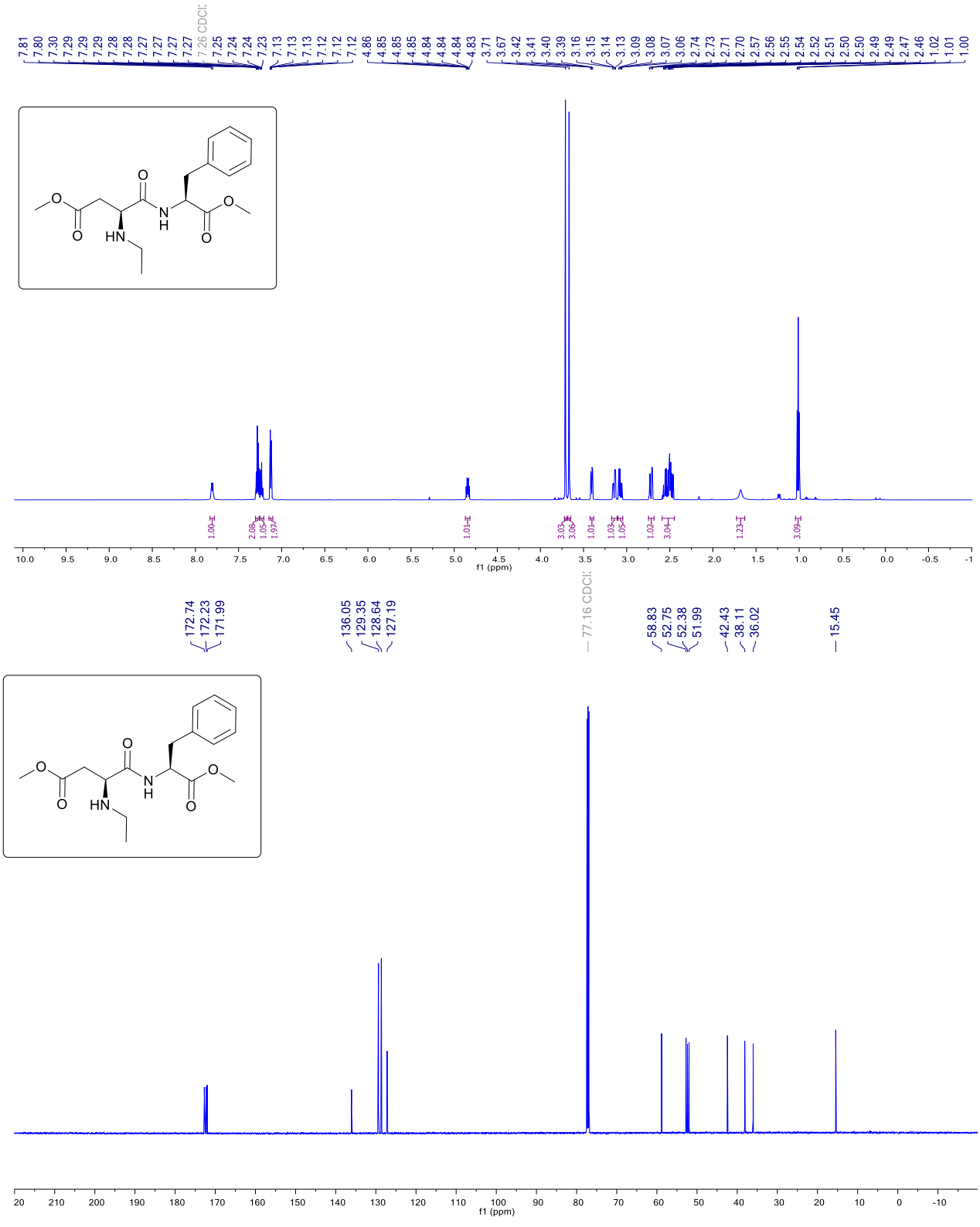


^{1}H and $^{13}C\{^{1}H\}$ NMR of **26** in $CDCl_3$ at 25 °C.

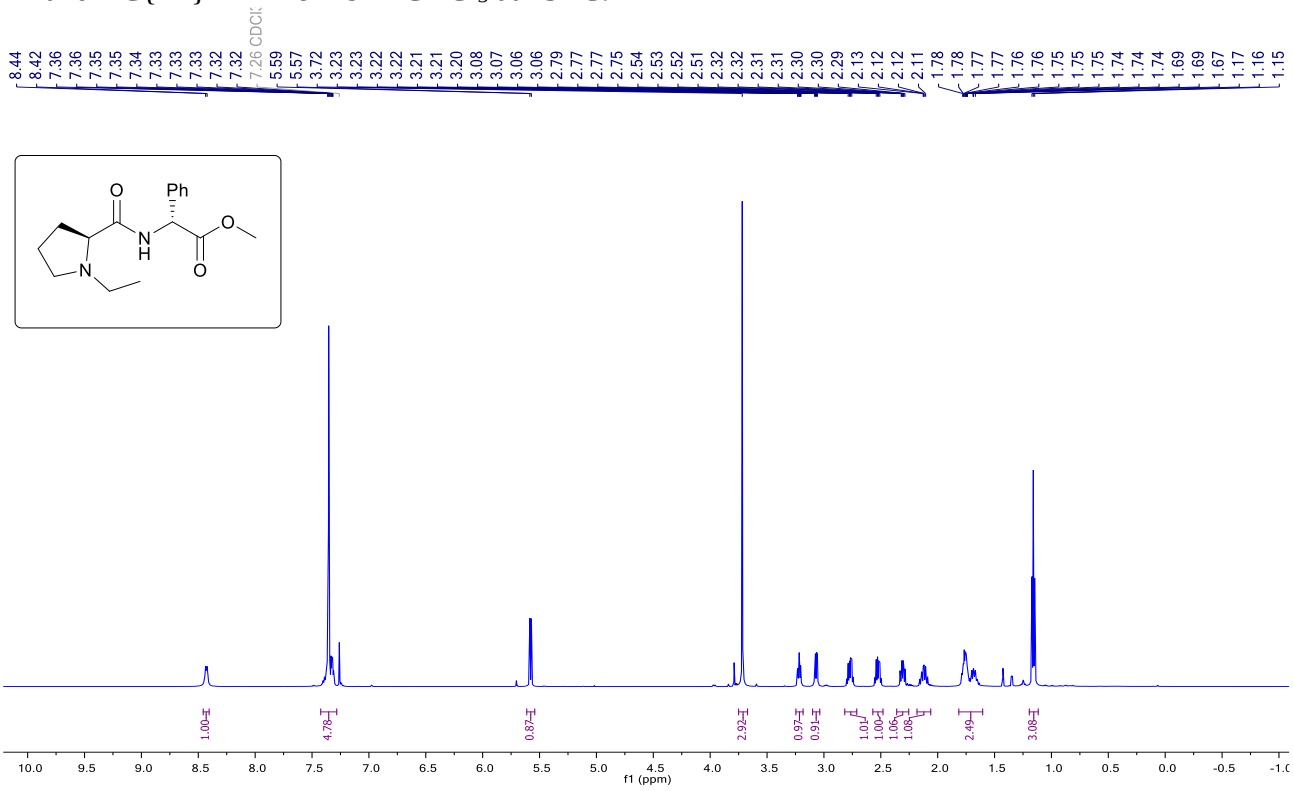


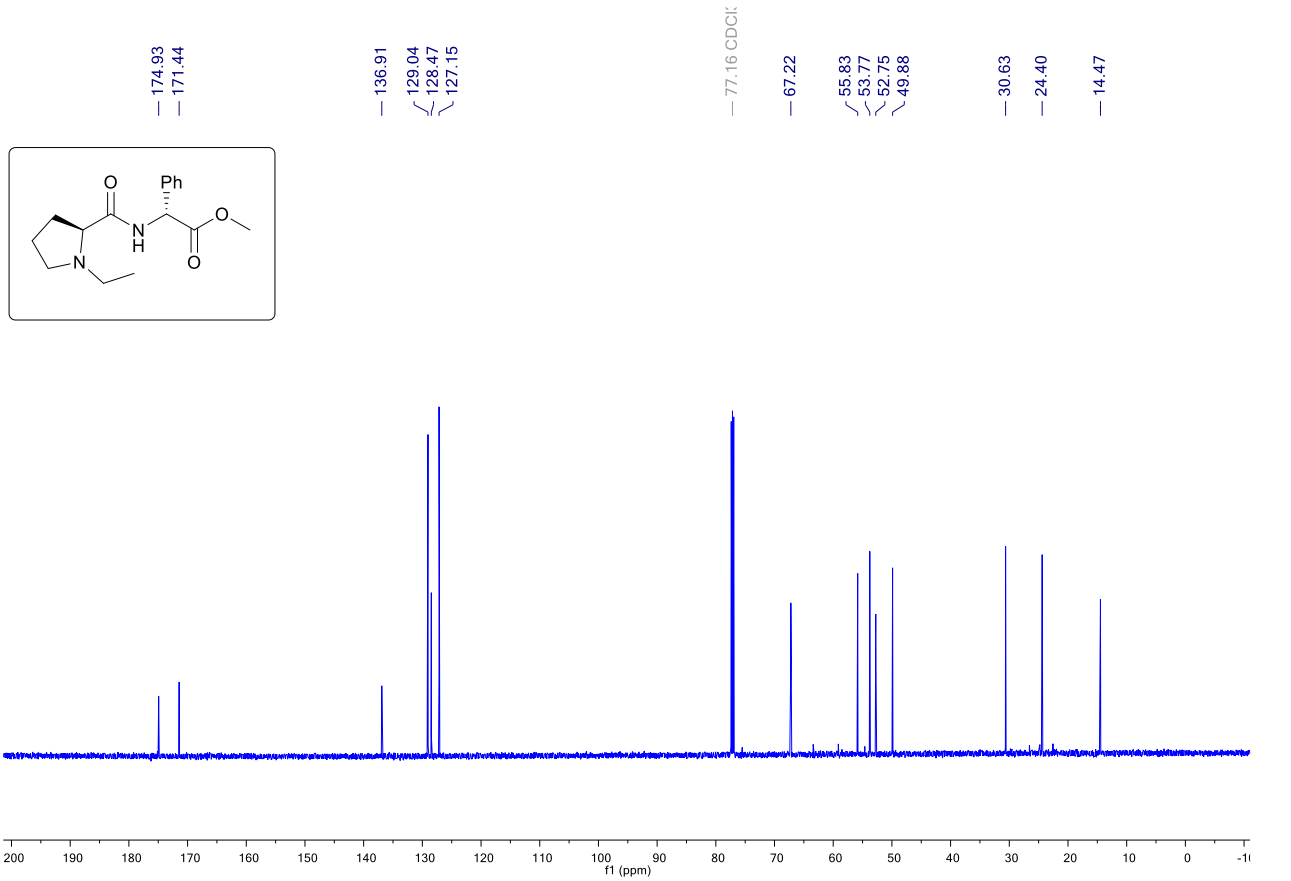


^{1}H and $^{13}C\{^{1}H\}$ NMR of **28** in $CDCl_3$ at 25 °C.

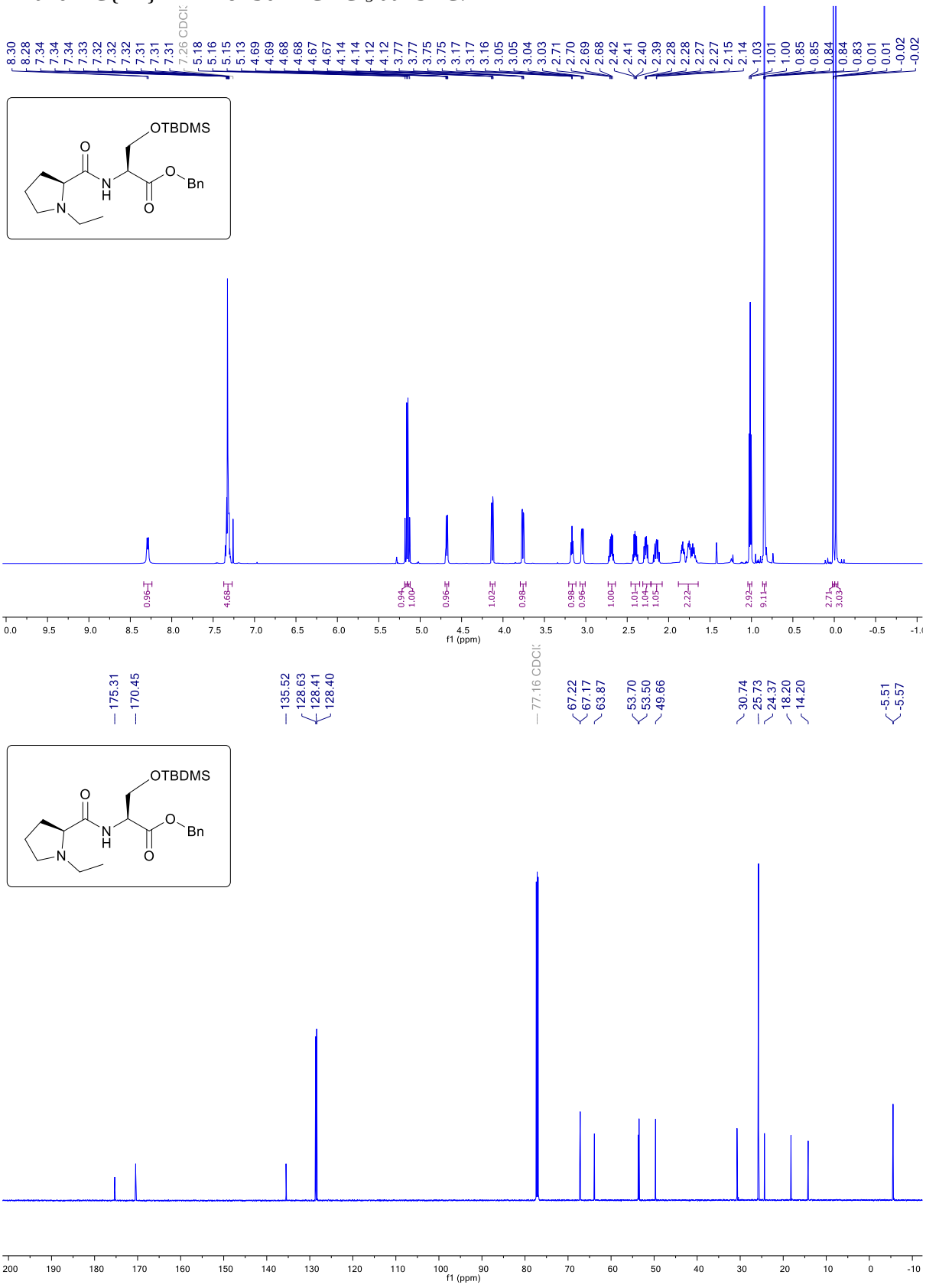


^{1}H and $^{13}C\{^{1}H\}$ NMR of **29** in $CDCl_3$ at 25 °C.

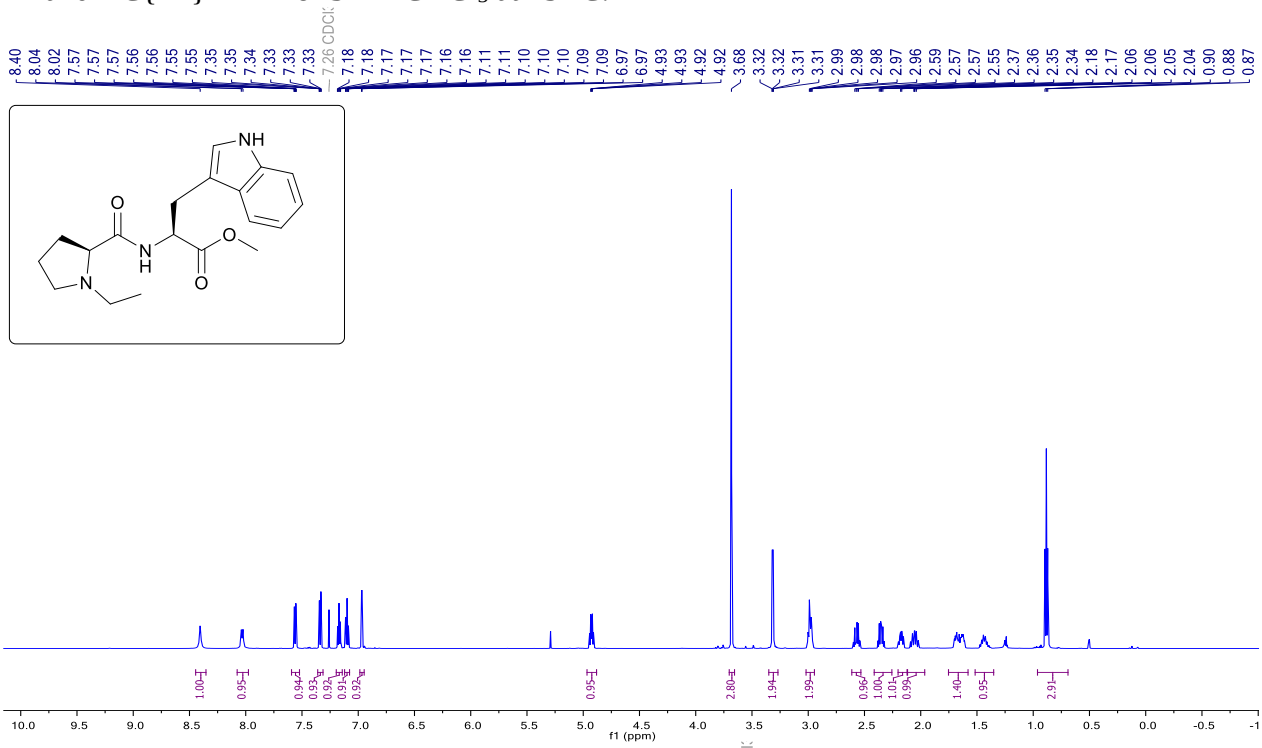


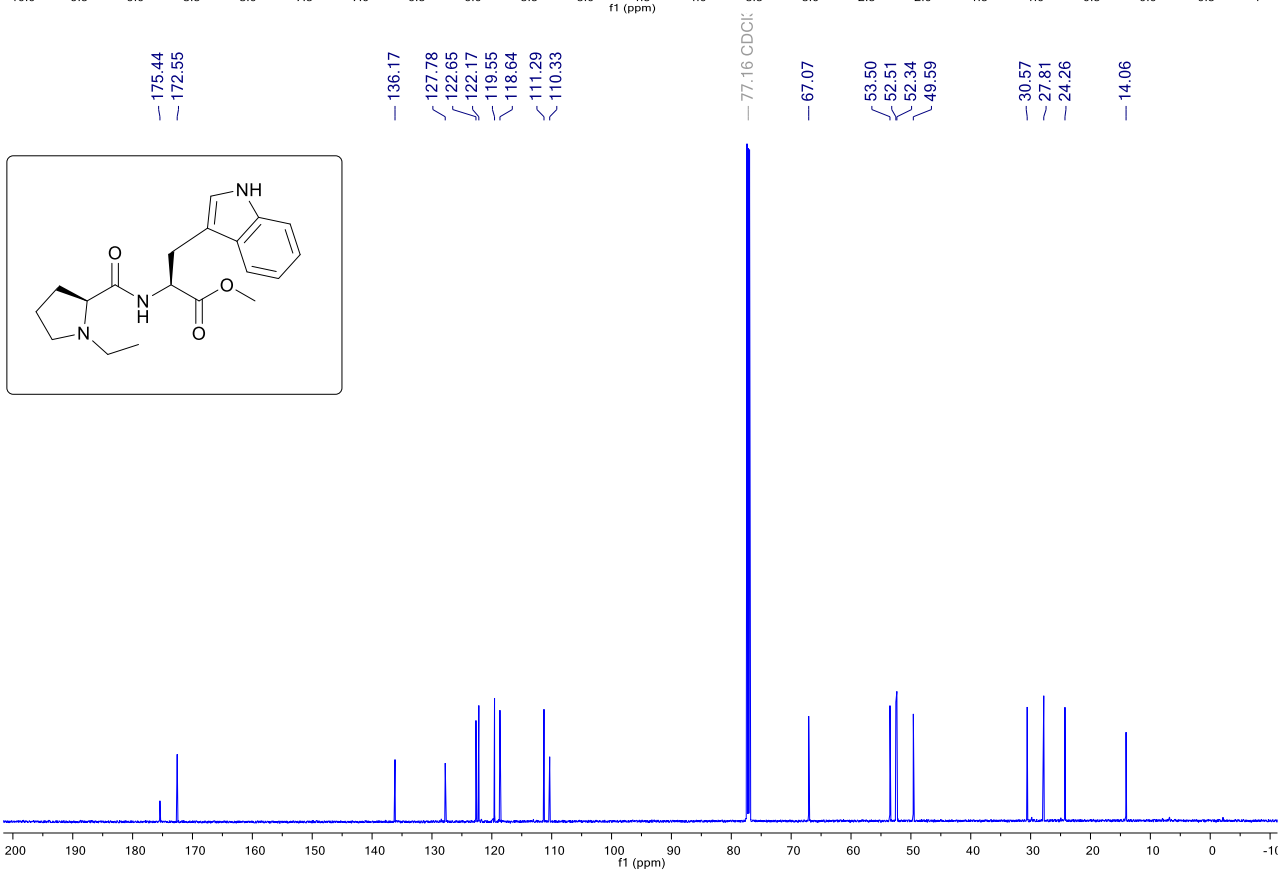


^{1}H and $^{13}C\{^{1}H\}$ NMR of **30** in $CDCl_3$ at 25 °C.

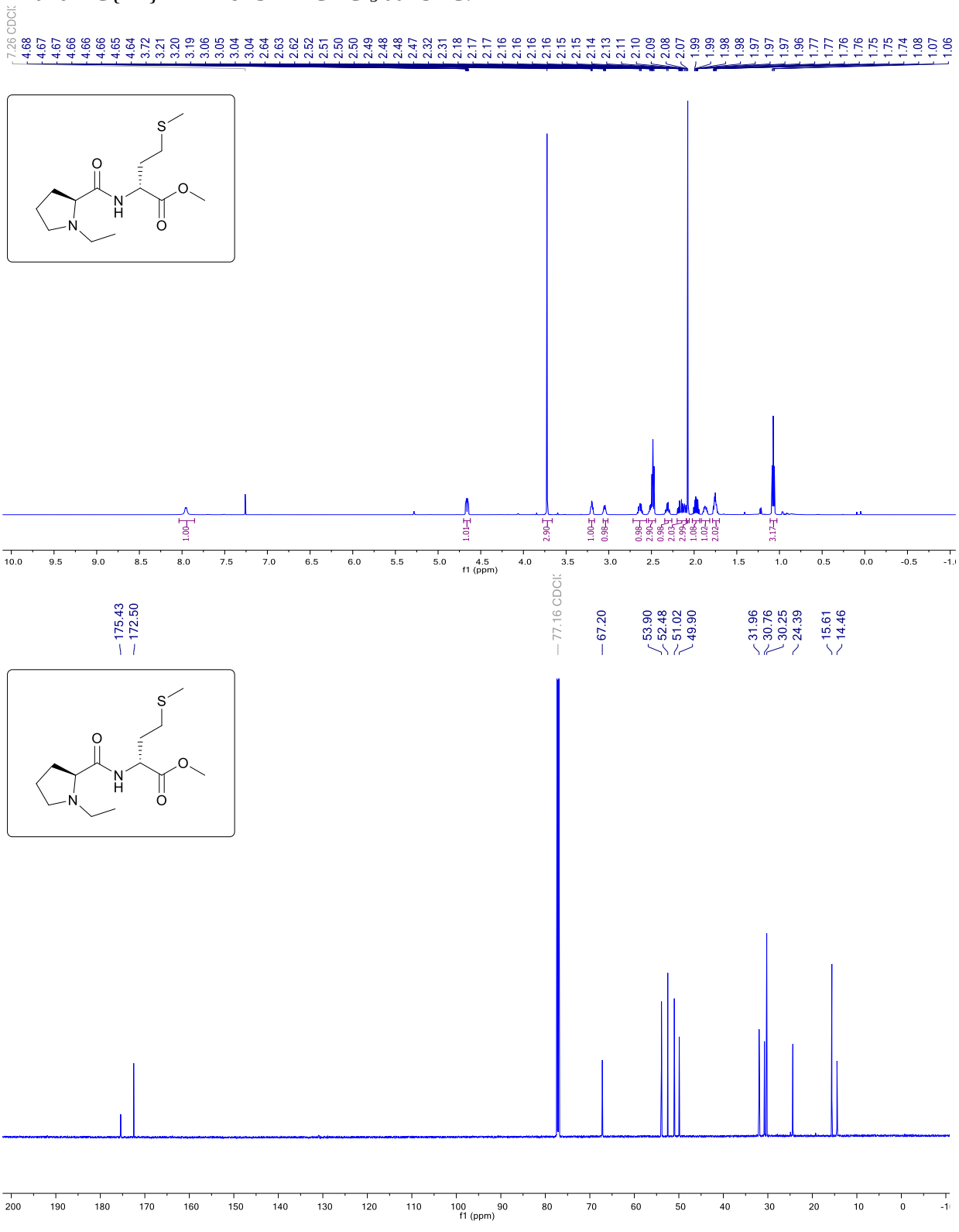


^{1}H and $^{13}C\{^{1}H\}$ NMR of **31** in $CDCl_3$ at 25 °C.

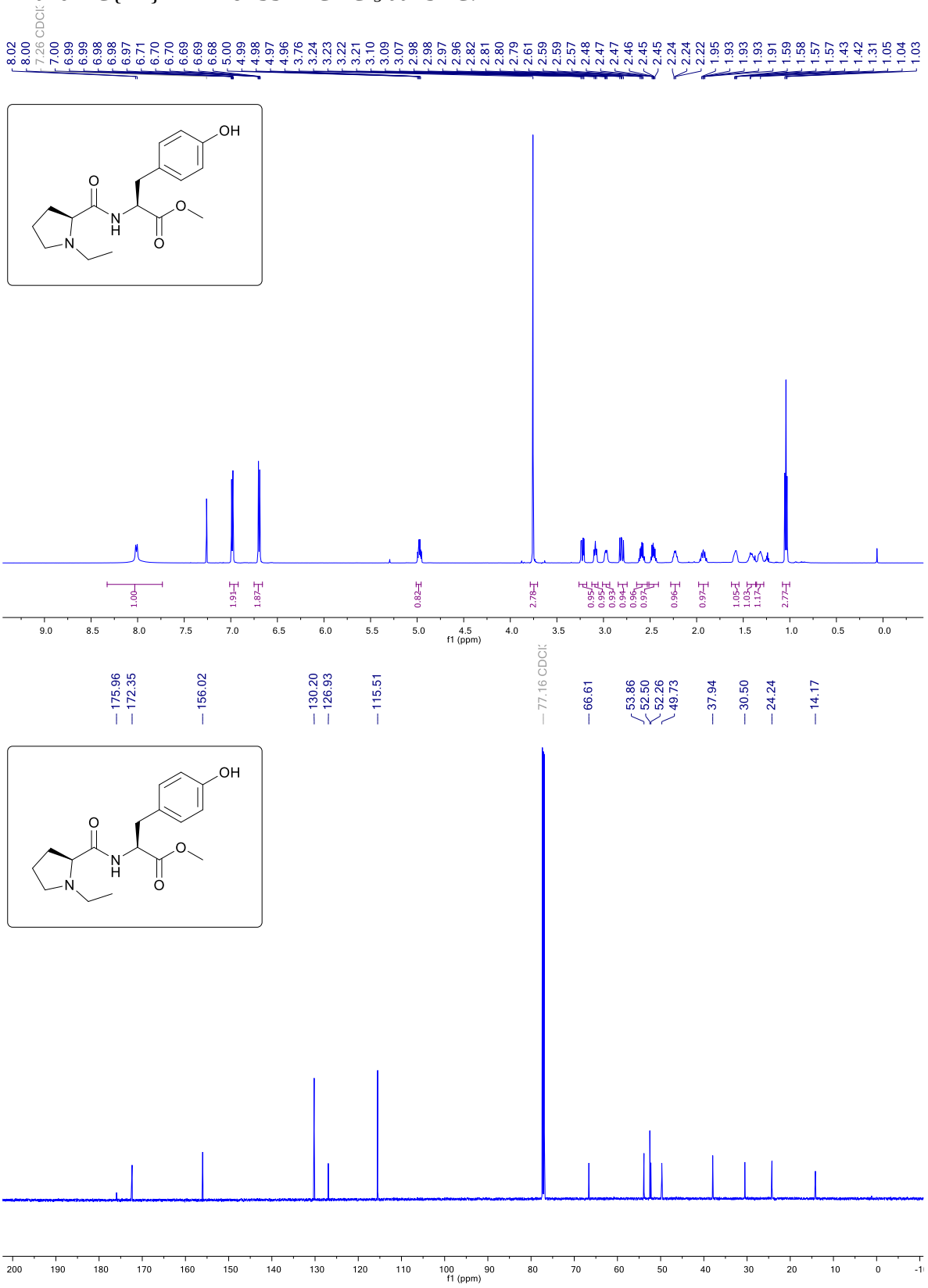




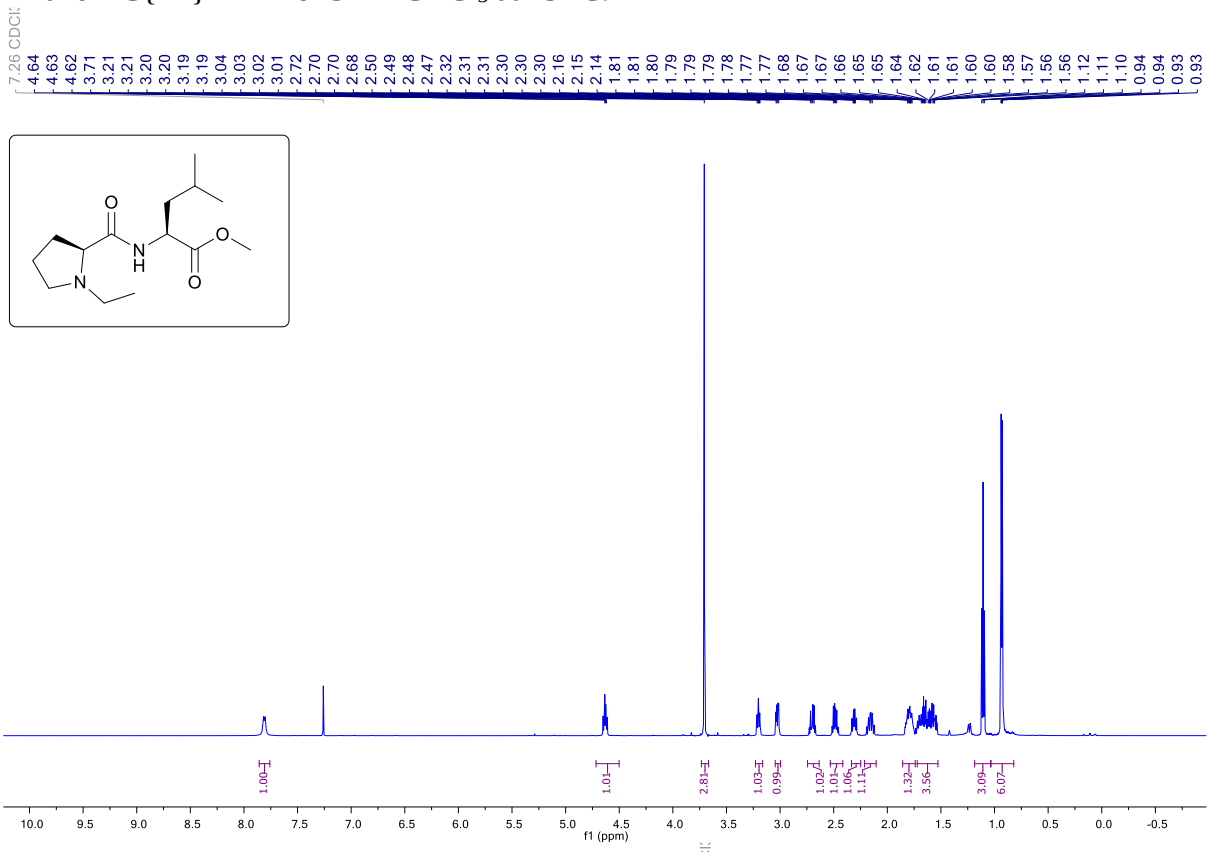
^{1}H and $^{13}C\{^{1}H\}$ NMR of **32** in $CDCl_3$ at 25 °C.

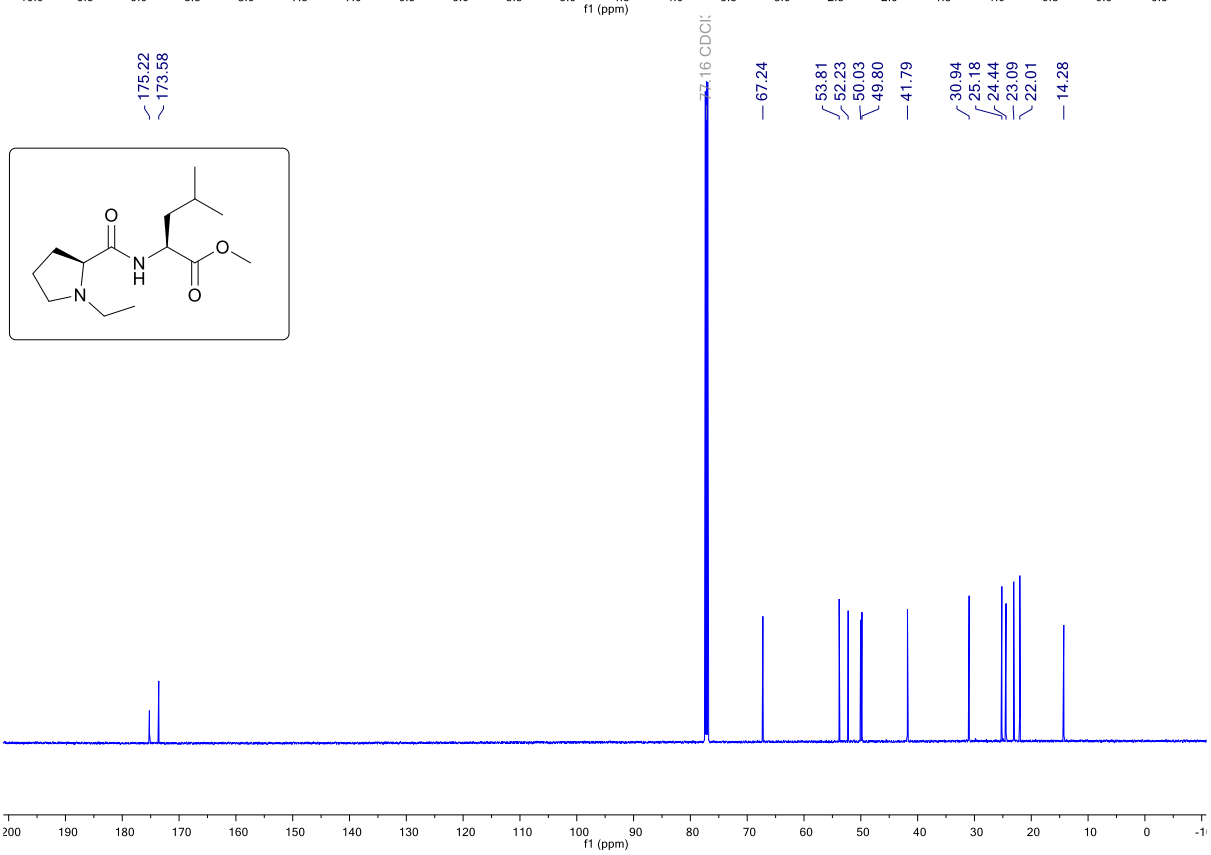


^{1}H and $^{13}C\{^{1}H\}$ NMR of **33** in $CDCl_3$ at 25 °C.

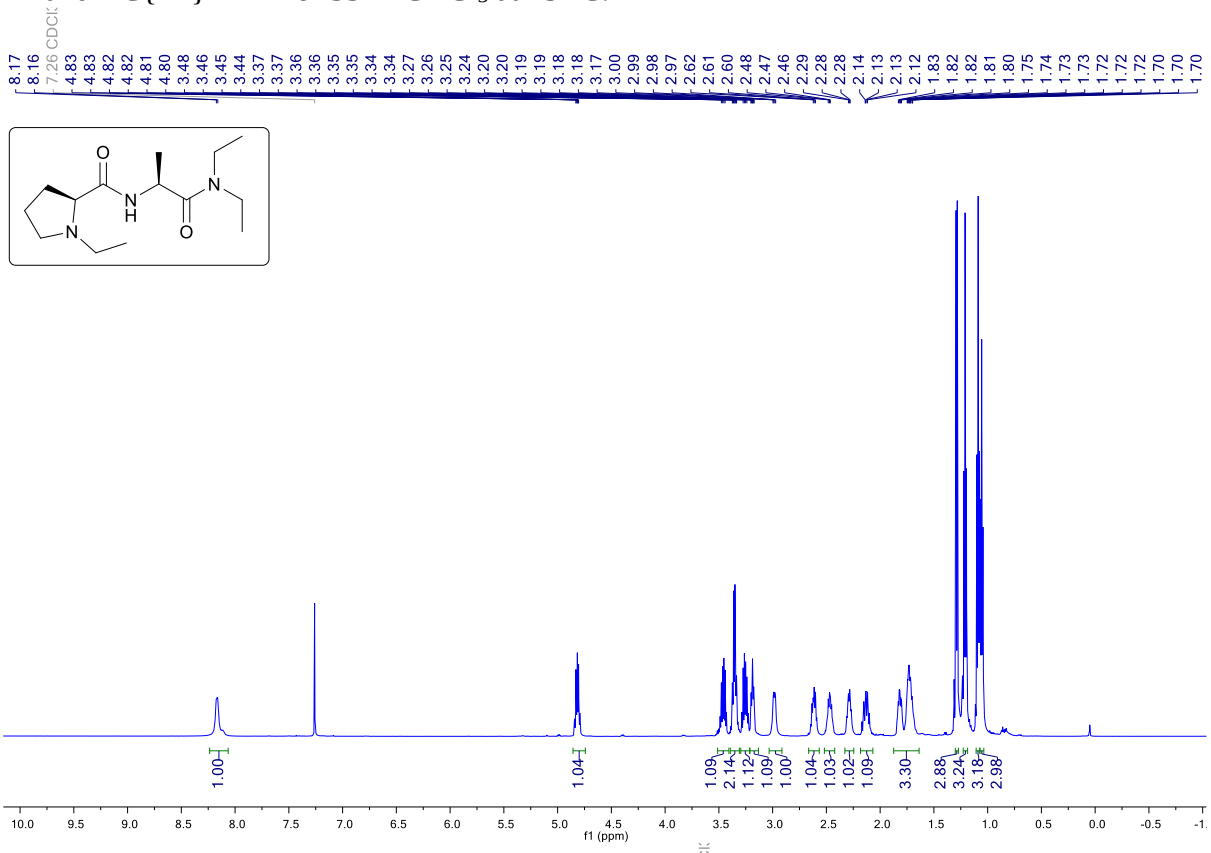


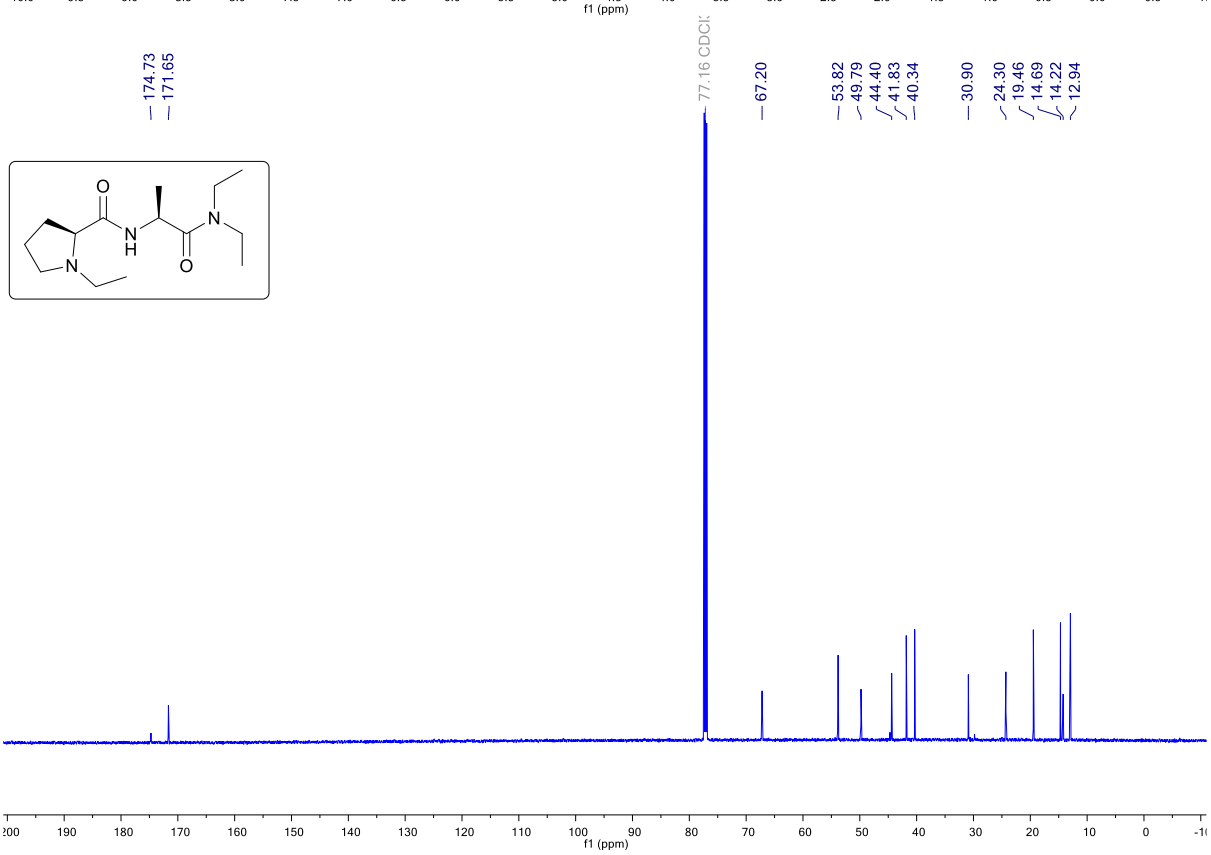
^{1}H and $^{13}C\{^{1}H\}$ NMR of **34** in $CDCl_3$ at 25 °C.





^{1}H and $^{13}C\{^{1}H\}$ NMR of **35** in $CDCl_3$ at 25 °C.





^{1}H and $^{13}C\{^{1}H\}$ NMR of **36** in $CDCl_3$ at 25 °C.