Electronic Supplementary Information for

The Quantitative Pyrrole Protection of L-Phenylalanine/ L-Phenylalaninol in Aqueous Media and Rationally Updating Mechanisms of Clauson-Kaas Reaction through DFT Study

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Experimental part
General information

NMR Spectrum:

^{1}H and ^{13}C spectra were collected on 500 MHz NMR spectrometer (Bruker AVANCE). Chemical shifts for protons are reported in parts per million (ppm) downfield and are referenced to residual protium in the NMR solvent ($CHCl_3$ = δ 7.26, D_2O = δ 4.79). Chemical for carbon are reported in parts per million downfield and are referenced to the carbon resonances of solvent ($CHCl_3$ = δ 77.16). Data are represented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = double, t = triplet, q = quartet, m = multiplet, quintet using full name), coupling constants in Hertz (Hz), integration.

Apparatus:

UPH-II-20TN Ultrapure Water System, Sichuan ULUPURE Ultrapure Technology Co., Ltd. Semi-Micro Balance Precisa EP 225SM-DR, Switzerland. Himac CT15E Tabletop High-Speed Micro Centrifuges, Japan. IKA C-MAG HS 7 Control Magnetic Heating Stirrer, Germany. QiWei WFH-203B Camera obscura UV analyzer, China.

Chromatography:

Flash chromatography was conducted in glass columns using Qingdao Haiyang Chemical Co., Ltd. silica gel (160-200 mesh, Shandong, China). Analytical thin layer chromatography (TLC) was performed on precoated silica gel GF254 HPTLC plates (5 × 10 cm^2) purchased from Yantai Jiangyou Chemical Co., Ltd. (Shandong, China). The developed chromatogram was analyzed by UV lamp (254 and 365 nm). The non-UV active compounds were generally visualized through placing the plates in a sealed TLC tank containing iodine and silica gel (the 160-200 mesh mentioned above), if necessary, at the aid of a heating gun. The progress of reaction was also monitored by TLC stained with 5% v/v ethanol aqueous solution of concentrated H_2SO_4 and estimated in a concentration and time dependent manner.

Reagent and Solvent:

L-Phenylalanine (99%) was provided by Shanghai Adamas Technology Co., Ltd. 2,5-dimethoxytetrahydrofuran (DMTHF, 98%), L-Phenylalaninol (97%) were supplied by Shanghai Bidepharm. Acetic acid (AR) was obtained from Xilong Scientific Co., Ltd. Citric acid monohydrate (AR), Potassium acetate (AR), Sodium bicarbonate (AR) were purchased from Guangdong Guanghua Sci-Tech Co., Ltd. Dichloroethane (DCE, 99%), Amberlite 732 (AR) were supplied by Shanghai Macklin Biochemical Technology Co., Ltd. (S)-Methyl 2-amino-3-phenylpropanoate (97%) was bought from the Shanghai Acmec Biochemical Co., Ltd. Chloroform (AR) was offered by Sinopharm Chemical Reagent Co., Ltd.

Standard procedure for the Clauson-Kaas reaction of L-Phenylalanine.

A 5 mL reaction vial bearing sealed cup was charged with a magnetic stir bar, L-Phenylalanine (16.5 mg, 0.1 mol, 1.0 equivalent) followed by ultrapure water (300 μL, about 20 volumes), to which, 2,5-dimethoxytetrahydrofuran (DMTHF, 13.9 mg, 13.0 μl, 1.05 equivalents) was added via a micro pipette tip. The reaction vessel was sealed and heated for appropriate time at 90 °C monitored by the TLC. After the reaction (0.1 mmol scale) was finished, the aiming products were separated as oily deposition by convenient centrifugation at the speed of 8000 rpm for 5 min. The common organic solvents including EtOAc or $CHCl_3$ could be chosen to dissolve the remaining slurry, which could be washed by proper amount of water successively. Finally, the organic phase was dried over Na_2SO_4 and evaporated by vacuo pump (or air-dried) delivering targeting pyrrolyl compounds with nearly quantitative yield and perfect purity certified by crude NMR.

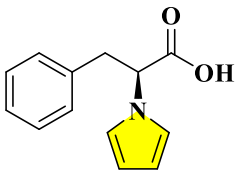
Preparation of aqueous succinaldehyde solution.

To a stirred solution of 2,5-dimethoxytetrahydrofuran (DMTHF, 1.0 g, 37.8 mmol) in H_2O (2.5 mL) was added Amberlyst-732 (10 wt%) and further heated at 70 °C for 4 h in an open flask and allow the MeOH evaporate. The resulting solution was cooled to room temperature and used directly after filtration the catalytic resins. The solutions have a value of pH about 7.0 (neutral).

Standard procedure for the Paal–Knorr reaction of L-Phenylalaninol.

A 5 mL reaction vial bearing sealed cup was charged with a magnetic stir bar, L-Phenylalaninol (13.7 mg, 0.1 mol, 1.0 equivalent) followed by ultrapure water (300 μL, about 20 volumes), to which, succinaldehyde (0.11mol, 1.1 equivalents) was added via a micro pipette tip. The reaction vessel was sealed and heated for appropriate time at 100 °C monitored by the TLC. After the reaction (0.1 mmol scale) was finished, the aiming products were separated as oily deposition by convenient centrifugation at the speed of 8000 rpm for 5 min. The common organic solvents including EtOAc or $CHCl_3$ could be chosen to dissolve the remaining slurry, which could be washed by proper amount of water successively. Finally, the organic phase was dried over Na_2SO_4 and evaporated by vacuo pump (or air-dried) delivering targeting pyrrolyl compounds with nearly quantitative yield and perfect purity certified by crude NMR.

Key characterization data for compounds 19 and 20.

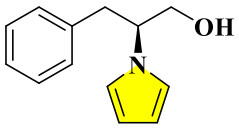


19

(*S*)-3-phenyl-2-(1H-pyrrol-1-yl)propanoic acid (Compound 19) (DMTHF, 0% CA, 90 °C, 30 min)

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.25 – 7.21 (m, 3H), 7.02 (dd, *J* = 7.6, 1.9 Hz, 2H), 6.70 (t, *J* = 2.1 Hz, 2H), 6.16 (t, *J* = 2.1 Hz, 2H), 4.78 (dd, *J* = 9.3, 5.8 Hz, 1H), 3.45 (dd, *J* = 14.0, 5.8 Hz, 1H), 3.29 (dd, *J* = 14.0, 9.4 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 175.21, 136.27, 128.92, 128.73, 127.25, 120.36, 109.00, 63.53, 39.15.



20

(*S*)-3-phenyl-2-(1H-pyrrol-1-yl)propan-1-ol (Compound 20) (Succinaldehyde, 0% CA, 100 °C, 4 h)

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.27 – 7.19 (m, 3H), 7.04 (d, *J* = 7.0 Hz, 2H), 6.70 (t, *J* = 2.2 Hz, 2H), 6.17 (t, *J* = 2.1 Hz, 2H), 4.19 (quintet, *J* = 6.2 Hz, 1H), 3.81 (d, *J* = 5.9 Hz, 2H), 3.06 (dd, *J* = 7.3, 3.6 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 137.72, 128.98, 128.64, 126.79, 119.36, 108.54, 65.41, 63.64, 38.71.

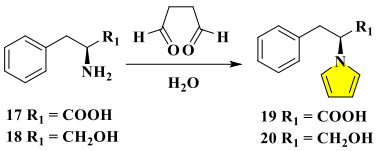


Fig. S1. Optimized Paal–Knorr procedures of L-Phenylalanine/L-Phenylalaninol with succinaldehyde in aqueous media.

When L-Phenylalaninol was tested as starting reagent, the condensation with DMTHF was inefficient perhaps due to its basicity.[S1] Even after being heated at 100 °C over 2 h in pure D_2O, the cooling mixture displayed the intact signals of starting reactants including both L-Phenylalaninol and DMTHF. This comparison of catalytic efficiency in consideration of the structural difference gives an inkling of possibly autocatalytic induction, within the architecture of L-Phenylalanine.

Because we did not detect the presence of succinaldehyde/dihydroxytetrahydrofuran as dialdehyde synthetic equivalents throughout the above reactions with DMTHF, the Paal-Knorr type of cyclization was further checked using succinaldehyde.[S2] The L-Phenylalanine could furnish the pyrrolyl ring even in room temperature overnight with only minute decrease of yield (83%), while the pyrrole protection on L-Phenylalaninol needed 4 h at 100 °C to achieve the full conversion. All the experimental phenomena prompted us to hypothesize the amino acid could probably play a much important role as a self-stimulated moiety in such systems, and envisage the possible auto-tandem process at the initiating stage (Fig. S1).

Table S1. Summary of reacting conditions and crude weights along with corresponding yields.

Chiral amine	γ-dicarbonyl or surrogate	Entry	Cat. Citric acid	*T* (℃)	time	Crude wt.	Crude yield
L-Phenylalanine (0.1 mmol)	2,5-dimethoxytetrahydrofuran (DMTHF, 1.05 eq)		3.75%	90	2 h	20.2 mg	94%
		Ent. 1	0.75%	90	1 h	20.3 mg	94%
		Ent. 2	0.75%	90	30 min	22.1 mg	103%
		Ent. 3	0.75%	90	15 min	20.1 mg	93%
		Ent. 4	0.3%	90	30 min	23.0 mg	107%
		Ent. 5	0.1%	90	30 min	20.5 mg	95%
		Ent. 6	0.05%	90	30 min	19.9 mg	92%
		Ent. 7	0.01%	90	30 min	21.4 mg	99%
		Ent. 8	0	90	30 min	20.3 mg	94%
		Ent. 9	0	90	15 min	16.6 mg	77%
L-Phenylalanine (24.2 mmol)	2,5-dimethoxytetrahydrofuran (DMTHF, 1.05 eq)		0	90	1.0 h	4750.3 mg	91%
L-Phenylalanine (0.1 mmol)	Succinaldehyde (1.05 eq)		0	r.t.	16 h	17.9 mg	83%
L-Phenylalaninol (0.1 mmol)	Succinaldehyde (1.1 eq)		0	100	4 h	23.9 mg	119%

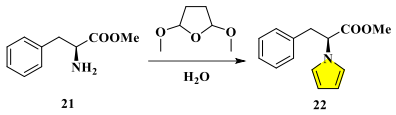


Fig. S1'. Test of Clauson-Kaas procedure for L-Phenylalanine methyl ester with DMTHF in aqueous media.

Synthetic method followed the above procedure with DMTHF

(1) about 0.1 mmol scale at 90 °C for 30 min with 0% CA in H_2O, workup by $CHCl_3$ extraction, NMR in $CDCl_3$;
(2) about 0.1 mmol scale at 90 °C for 30 min with 0.75% CA in H_2O, workup by $CHCl_3$ extraction, NMR in $CDCl_3$;
(3) about 0.1 mmol scale at 90 °C for 2 h with 10% CA in D_2O, real-time NMR in D_2O directly.

The assignment of NMR signals for mixtures in the reactants of Clauson-Kaas reaction[S3]

(1) 90 °C for 30 min with 0% CA in H_2O, NMR in $CDCl_3$;
L-Phenylalanine methyl ester (Compound 21)
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.18 (m, 5H), 3.73 (dd, *J* = 8.0, 5.2 Hz, 1H), 3.71 (s, 3H), 3.09 (dd, *J* = 13.5, 5.1 Hz, 1H), 2.86 (dd, *J* = 13.5, 7.9 Hz, 2H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 175.58, 137.30, 129.40, 128.71, 126.98, 55.92, 52.13, 41.17.

2,5-dimethoxytetrahydrofuran (DMTHF)
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.12 – 5.05 (m, 2H), 3.42 (s, 3H), 3.36 (s, 3H), 2.10 – 1.99 (m, 4H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 106.25, 105.53, 55.47, 55.12, 31.08, 30.16.

(2) 90 °C for 30 min with 0.75% CA in H_2O, NMR in $CDCl_3$;
L-Phenylalanine methyl ester (Compound 21)
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.18 (m, 5H), 3.73 (dd, *J* = 8.0, 5.1 Hz, 1H), 3.71 (s, 3H), 3.09 (dd, *J* = 13.5, 5.2 Hz, 1H), 2.86 (dd, *J* = 13.5, 7.9 Hz, 2H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 175.58, 137.30, 129.39, 128.71, 126.98, 55.92, 52.13, 41.18.

2,5-dimethoxytetrahydrofuran (DMTHF)
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.10 – 5.08 (m, 2H), 3.42 (s, 3H), 3.36 (s, 3H), 2.10 – 1.99 (m, 4H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 106.25, 105.54, 55.47, 55.12, 31.08, 30.17.

(3) 90 °C for 2 h with 10% CA in D_2O, real-time NMR in D_2O.
L-Phenylalanine methyl ester (Compound 21)
^{1}H NMR (500 MHz, D_2O) δ 7.37 – 7.22 (m, 5H), 3.91 (dd, *J* = 8.0, 5.2 Hz, 1H), 3.31 (s, 3H), 3.21 (dd, *J* = 14.6, 5.3 Hz, 2H), 3.05 (dd, *J* = 13.5, 7.9 Hz, 2H).
^{13}C NMR (126 MHz, D_2O) δ 173.85, 134.99, 129.19, 128.42, 127.62, 54.78, 48.78, 36.26.

The protonated L-Phenylalanine methyl ester (Compound 21+H^+)
^{1}H NMR (500 MHz, D_2O) δ 7.37 – 7.22 (m, 5H), 4.36 (t, *J* = 6.5 Hz 1H), 3.78 (s, 3H), 3.29-3.15 (m, 2H).
^{13}C NMR (126 MHz, D_2O) δ 170.11, 133.69, 129.29, 128.01, 54.00, 53.43, 35.56.

2,5-dimethoxytetrahydrofuran (DMTHF)
^{1}H NMR (500 MHz, D_2O) δ 5.17 – 5.12 (m, 2H), 3.34 (s, 3H), 3.28 (s, 3H), 2.08 – 1.80 (m, 4H).
^{13}C NMR (126 MHz, D_2O) δ 106.11, 105.75, 55.94, 54.95, 30.00, 29.03.

Citric acid (CA)
^{13}C NMR (126 MHz, D_2O) δ 180.33, 177.33, 74.47, 44.68.

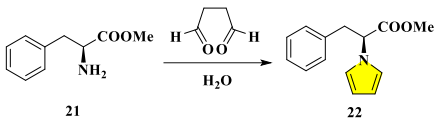


Fig. S1''. Test of Paal–Knorr procedure for L-Phenylalanine methyl ester with succinaldehyde in aqueous media.

Synthetic method followed the above procedure with succinaldehyde

(4) about 0.1 mmol scale at rt for 10 h with 0% CA in H_2O, workup by $CHCl_3$ extraction, NMR in $CDCl_3$;
(5) about 0.1 mmol scale at 90 °C for 4 h with 0% CA in H_2O, workup by $CHCl_3$ extraction, NMR in $CDCl_3$.

The assignment of NMR signals for mixtures in the reactants of Paal–Knorr reaction[S3]

(4) rt for 10 h with 0% CA in H_2O, NMR in $CDCl_3$.

L-Phenylalanine methyl ester (about 45%) (Compound 21)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.19 (m, 5H), 3.75 (dd, *J* = 7.9, 5.2 Hz, 1H), 3.72 (s, 3H), 3.10 (dd, *J* = 13.5, 5.2 Hz, 1H), 2.87 (dd, *J* = 13.5, 7.9 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 175.52, 137.23, 129.39, 128.72, 126.99, 55.86, 52.14, 41.10.

Methyl (S)-3-phenyl-2-(1H-pyrrol-1-yl)propanoate (about 55%) (Compound 22)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.17 (m, 3H), 7.06 – 6.99 (m, 2H), 6.72 (t, *J* = 2.2 Hz, 2H), 6.15 (t, *J* = 2.2 Hz, 2H), 4.75 (dd, *J* = 8.9, 6.5 Hz, 1H), 3.70 (s, 3H), 3.42 (dd, *J* = 14.7, 5.7 Hz, 1H), 3.26 (dd, *J* = 13.9, 8.8 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.75, 136.43, 128.94, 128.67, 127.15, 120.20, 108.81, 63.67, 52.69, 39.58.

Computational details

General method

All DFT calculation was performed with the Gaussian 16 (B01) program. Geometry optimization of ground-state was conducted at B3LYP-D3BJ/6-31++G(d,p) with the default polarizable continuum model (PCM) of solvation (solvent = water). Fully optimized geometries of all stationary points were further characterized by frequency calculations in order to verify that the transition states (TSs) had one and only one imaginary frequency for the desired reaction coordinate. The intrinsic reaction coordinate (IRC) analyses using the same level of theory were performed to further ensure that the TS on the potential energy surface connected to the desired minima. Single-point energy calculations were performed at M062X-D3/def2-TZVPP/SMD(water) for all optimized structures. The Gibbs free energies were summed by the single-point energy from M062X and the zero-point correction from B3LYP calculation.

Energy profile of reaction pathway

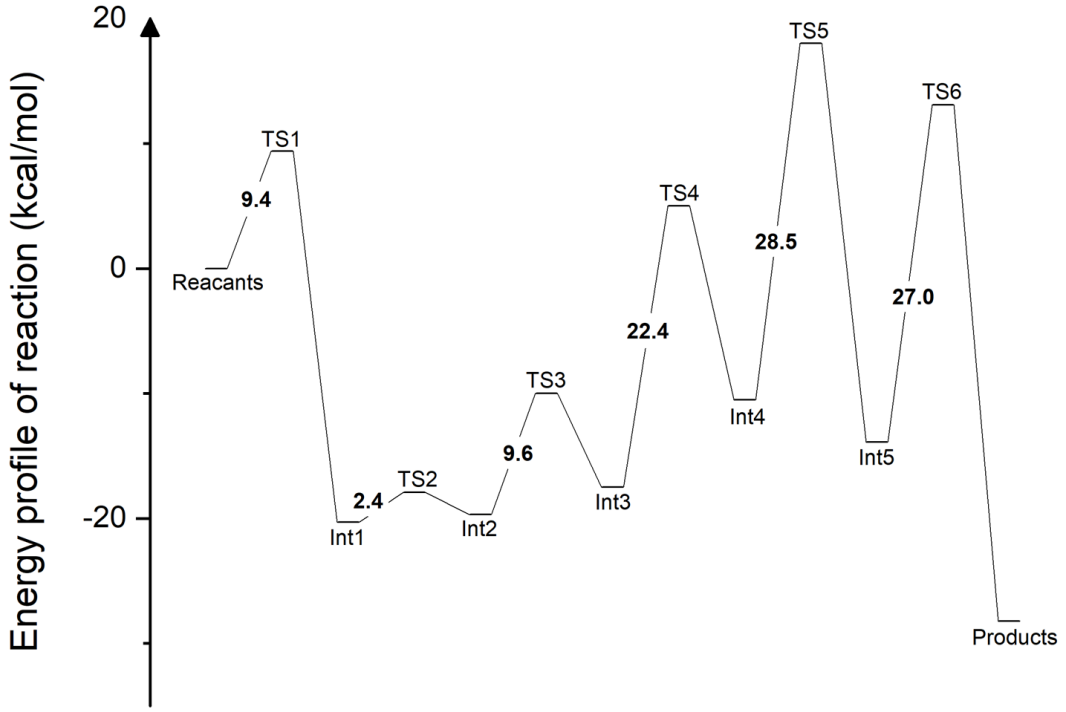


Fig. S2. Energy profile of reaction pathway

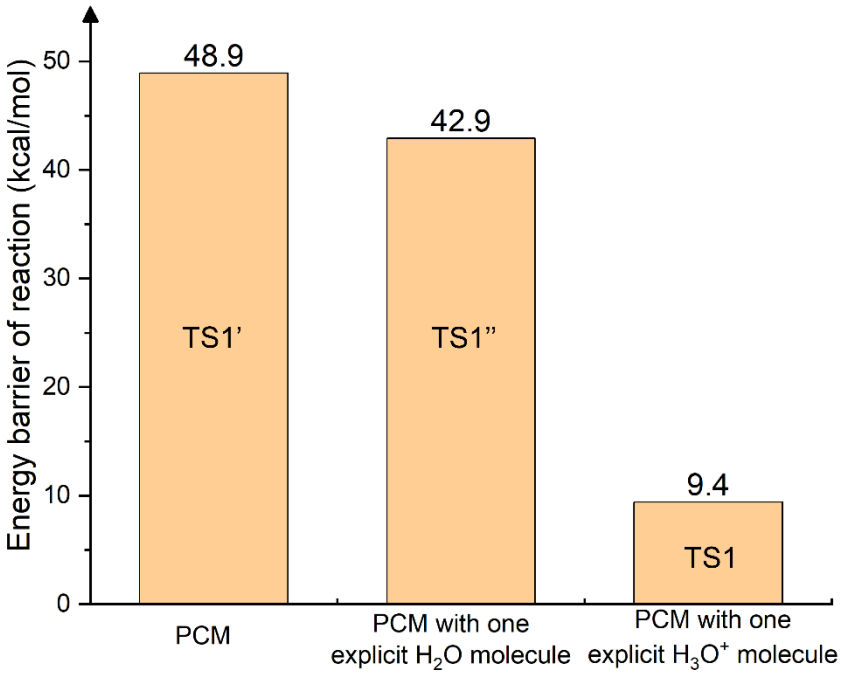


Fig. S3. Comparison of energy barriers of initiating SN_2 step for TS1', TS1" & TS1 (refer to calculations in polarizable continuum model of solvation, PCM; that containing one explicit water molecule solely, PCM+H_2O; or combined with the weak H^+, PCM+H_3O^+).

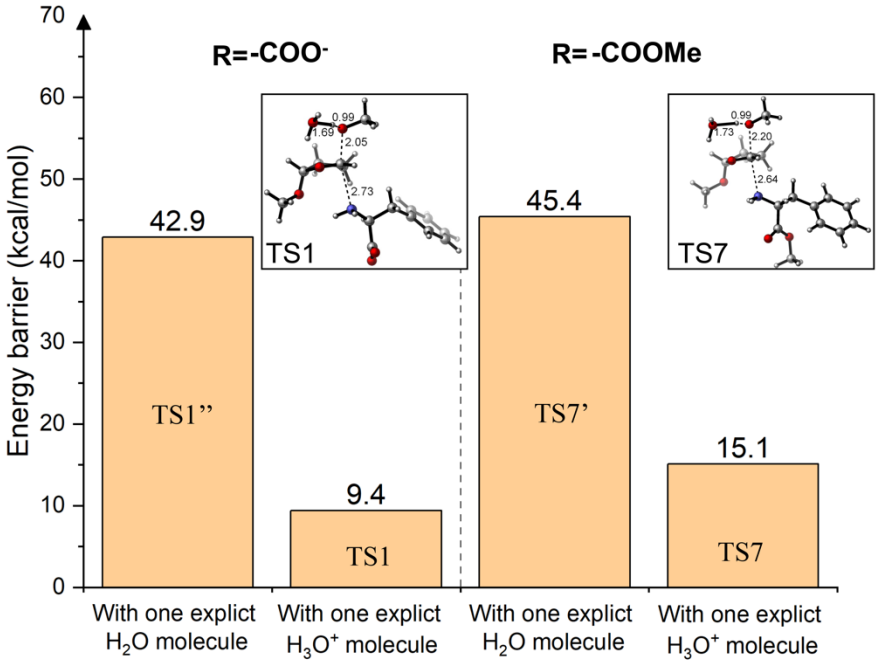


Fig. S4. Energy barriers of the first SN_2 reaction step for L-Phenylalanine (R= -COO^-) and L-Phenylalanine methyl ester (R= -COOMe).

TS1

Imagine frequency = -157.63 cm^{-1}

C	-2.11621800	0.62984100	0.09807700
H	-1.61613700	0.93140100	1.00573700
O	-3.28518900	2.30672700	0.16472900
C	-3.34411000	-0.86893200	-1.16917500
O	-2.74355300	-2.09646800	-1.25967800
C	-3.35939700	-3.13315500	-0.47287200
H	-2.85622800	-4.06012500	-0.74478100
H	-4.42666400	-3.20412200	-0.70877400
H	-3.22561500	-2.93671200	0.59457700
C	-2.71695900	0.13599000	-2.12622300
H	-3.46598100	0.87099700	-2.42486600
H	-2.33923500	-0.37158000	-3.01343800
C	-1.60810500	0.80391100	-1.29399900
H	-1.42991900	1.84987900	-1.54118800
H	-0.65708600	0.27057500	-1.36722200
O	-3.02856600	-0.28509100	0.20208300
H	-4.43504600	-0.93008300	-1.17317100
N	-0.15566600	-1.14482100	0.79192500
H	-0.58573300	-1.96065400	0.35950100
C	1.21379300	-0.97446400	0.28105300
H	1.16888100	-0.97246900	-0.81302700
C	1.73909300	0.39459600	0.76414300
C	2.16859300	-2.11978800	0.72049200
H	1.00986700	1.15517600	0.46301500
H	1.76409000	0.38063900	1.85927100
C	3.10091300	0.74966000	0.21964300
O	2.15915100	-2.40579700	1.95362100
C	4.25628300	0.59878600	0.99809300
C	3.23872000	1.21543900	-1.09699100
H	4.16528000	0.23919100	2.01933000
C	5.51827400	0.89985900	0.47633100
C	4.49621300	1.51757300	-1.62404800
H	2.35130600	1.34320300	-1.71207100
H	6.40174900	0.77678400	1.09607500
C	5.64281400	1.35939000	-0.83775200
H	4.58175600	1.87858400	-2.64490500
H	6.62148800	1.59547400	-1.24462100
O	2.87031500	-2.66869000	-0.17653500
H	-0.09363400	-1.35312700	1.78849000
O	-5.18661000	1.28564700	1.74142100
H	-4.01440600	2.01577600	0.77533500
H	-5.35906600	1.67564700	2.61009200

H	-4.91889900	0.36987800	1.90906900
C	-2.63518600	3.46843000	0.70743900
H	-2.23535500	3.26612900	1.70650700
H	-1.82069200	3.73395500	0.03210200
H	-3.34776900	4.29589000	0.75509200

TS2

Imagine frequency = -1175.94 cm^{-1}

C	-2.57280700	0.66201100	-0.99151300
H	-3.35070700	1.31409600	-1.39859600
C	-3.00953700	-1.14050300	0.45391300
O	-1.79859600	-1.67058400	0.93598900
C	-1.52475400	-1.33880300	2.30158200
H	-0.58168400	-1.82280600	2.55711000
H	-2.32159500	-1.71435800	2.95548400
H	-1.42692300	-0.25649900	2.43293200
C	-3.23948600	-1.64045900	-0.96571200
H	-4.30494200	-1.57310900	-1.20214700
H	-2.91617600	-2.67491100	-1.08919200
C	-2.42711400	-0.63801200	-1.79777300
H	-2.79822000	-0.51764900	-2.81668900
H	-1.38023400	-0.94521500	-1.85178000
O	-2.94492900	0.29083900	0.33268000
H	-3.81856300	-1.34625000	1.16243000
N	-1.35312900	1.50292900	-0.91173800
H	-1.37722100	2.40112700	-0.02226100
C	-0.13225700	0.90125100	-0.29752800
H	-0.37501500	-0.09898900	0.06475500
C	1.04442200	0.83934500	-1.28654900
C	0.12400400	1.81352900	0.93623800
H	0.67872300	0.35619200	-2.20067600
H	1.34552800	1.85560800	-1.56108200
C	2.23689900	0.07076000	-0.76379200
O	-0.74647700	2.77848800	0.99324700
C	3.47237200	0.70100900	-0.57710300
C	2.12781700	-1.29702600	-0.47165800
H	3.56947300	1.76043600	-0.79728300
C	4.57602000	-0.01379000	-0.10203700
C	3.22587200	-2.01442300	0.00641600
H	1.17902900	-1.80692900	-0.61609500
H	5.52623600	0.49273200	0.03862800
C	4.45558500	-1.37398400	0.19428900
H	3.12274500	-3.07219900	0.22948200
H	5.31040800	-1.93093300	0.56557400

O	1.04100400	1.59686000	1.72887600
H	-1.15919900	1.90889300	-1.82740100

TS3

Imagine frequency = -754.02 cm^{-1}

N	-0.73225100	-0.67508700	1.18959900
C	-1.55016300	-1.35715900	0.38340600
C	0.72110000	-0.48924900	1.03619700
C	-2.92321500	-1.72449200	0.88310400
O	-2.13348400	-0.30009200	-1.03785600
H	-1.07007200	-2.06388900	-0.28211100
H	-2.04481500	2.39895700	-0.25145300
H	-1.16639100	-0.14874700	1.93832000
C	1.18732700	-0.67983300	-0.42553600
C	1.11745200	0.91309600	1.56346700
H	1.23900600	-1.21680500	1.66751000
C	-3.89987600	-1.63837200	-0.29162200
H	-2.88048800	-2.73538100	1.30017200
H	-3.21823900	-1.04023500	1.68433200
C	-3.53166300	-0.33890600	-1.01128500
H	-1.69148100	0.85745800	-0.83036200
O	-1.27756800	1.91366700	-0.59319300
C	2.67198600	-0.44683600	-0.58449100
H	0.95177600	-1.70098200	-0.73901900
H	0.63169800	-0.00018800	-1.07659900
O	0.45606400	1.92526200	1.11660300
O	2.05402300	0.98591500	2.37313900
H	-4.94182600	-1.64909900	0.03528800
H	-3.75332700	-2.47798800	-0.97893300
O	-3.97504300	0.81625000	-0.29313200
H	-3.93058100	-0.29343800	-2.03514500
H	-0.49408300	1.86939600	0.19626500
C	3.15497100	0.77110200	-1.07989900
C	3.59233000	-1.43857500	-0.21709600
C	-5.33619900	1.16343300	-0.53885700
C	4.52878000	0.99679000	-1.20392500
H	2.45099300	1.54685200	-1.36776500
C	4.96592300	-1.21657400	-0.33670400
H	3.23089200	-2.39098800	0.16223000
H	-6.02412800	0.39081400	-0.17415400
H	-5.51192800	1.32296400	-1.61094000
H	-5.52598900	2.09194400	0.00127200
C	5.43868400	0.00390700	-0.83044400
H	4.88636900	1.94566900	-1.59247000

H	5.66564000	-1.99561500	-0.04917600
H	6.50618100	0.17689600	-0.92683000

TS4

Imagine frequency = -1269.63 cm^{-1}

N	-0.12756900	-1.36601100	-0.85989600
H	0.25776600	-1.34117500	-1.79832600
C	0.83980900	-1.20735300	0.13854100
H	0.43780800	-1.12415400	1.14418900
C	-1.41033200	-0.66096000	-0.76738600
C	2.16728900	-1.22376600	-0.06007700
H	2.55990200	-1.28826100	-1.07363200
O	3.58377000	1.20150800	0.92625600
C	-2.24126700	-1.10838500	0.44773400
C	-1.17249200	0.85088500	-0.74041400
H	-1.96096900	-0.90110700	-1.67878700
C	3.16893200	-1.18592200	1.05653600
C	4.12212400	0.00147700	1.00861600
H	4.44487000	1.93217200	0.33416400
C	-3.63764900	-0.52796300	0.41619600
H	-2.27851900	-2.20166300	0.42263300
H	-1.73839400	-0.80936600	1.37053600
O	-1.34870800	1.41791700	-1.95110000
H	-1.12385800	2.36371500	-1.88570900
O	-0.79978800	1.47728000	0.23465700
H	3.77106800	-2.10399400	1.08507900
H	2.66000800	-1.12509800	2.02683200
O	4.98869800	-0.19645500	-0.39869900
H	4.95180300	-0.10577700	1.72802700
C	-3.97092400	0.59458200	1.18605100
C	-4.61853300	-1.08732900	-0.41667800
C	6.09705700	-1.11235800	-0.32838600
C	-5.25383300	1.14726900	1.12653700
H	-3.21994500	1.03783000	1.83326200
C	-5.90114900	-0.53845200	-0.47973900
H	-4.37641800	-1.96173900	-1.01552900
H	5.71049300	-2.12460900	-0.20283800
H	6.75898700	-0.85851700	0.50608800
H	6.64249900	-1.04412100	-1.27087200
C	-6.22260900	0.58301000	0.29228300
H	-5.49516800	2.01581100	1.73208700
H	-6.64908500	-0.98685100	-1.12685200
H	-7.21979600	1.00994500	0.24597500
O	5.27453500	2.17492200	-0.44365800

H	5.31338800	0.88807100	-0.56269500
H	6.05994400	2.54119100	-0.01289200

TS5

Imagine frequency = -1559.54 cm^{-1}

N	1.91016800	-0.15171100	-0.55733800
H	2.65665100	0.71199300	-0.98658600
C	2.34439300	-1.49706500	-0.86635100
H	1.95727900	-1.96621700	-1.76167700
C	0.43603100	0.05752700	-0.59610600
C	3.24335500	-1.95303200	0.00698000
H	3.73915700	-2.91233300	-0.08244800
O	3.53252500	1.22314200	-0.06422500
C	-0.29580200	-0.69992600	0.52662500
C	0.12887000	1.55550800	-0.61271600
H	0.10358900	-0.31394200	-1.56746800
C	3.50795200	-0.96811800	1.11393000
C	2.78666900	0.31441900	0.65899700
C	-1.79700300	-0.59103500	0.37928400
H	0.01562400	-1.74742400	0.47029900
H	0.02207400	-0.31089000	1.49651000
O	0.24253600	2.12547000	0.59659700
H	0.04316500	3.07543700	0.51697700
O	-0.19127600	2.16320500	-1.61468700
H	4.57503300	-0.75240800	1.23519700
H	3.13076600	-1.33762200	2.07528800
H	2.14593200	0.75325300	1.43185800
C	-2.53522900	0.30270300	1.16627800
C	-2.47061400	-1.36364900	-0.57854800
C	-3.91822900	0.42319300	1.00089900
H	-2.02452300	0.90582900	1.91101000
C	-3.85156500	-1.24501300	-0.74714200
H	-1.91122600	-2.06611500	-1.19110000
C	-4.57985900	-0.34893300	0.04250200
H	-4.47632900	1.11818700	1.62097100
H	-4.35855700	-1.85283000	-1.49041500
H	-5.65389400	-0.25695800	-0.08633000

TS6

Imagine frequency = -618.86 cm^{-1}

O	3.18757500	0.96014700	-0.84953100
H	2.78178500	1.48438500	-0.14373800
H	4.09208500	0.38795100	-0.40630400
C	0.72476900	-0.99186000	1.21838300

C	1.74854200	-1.85584200	1.25833500
H	0.00691900	-0.69709800	1.96667200
C	2.43576000	-1.85159000	-0.07383700
H	2.05272800	-2.44410500	2.11185400
C	1.65704800	-0.85134500	-0.83665200
H	3.50420800	-1.52397500	-0.00733700
H	2.43874700	-2.82418200	-0.58439900
H	1.71804000	-0.62616900	-1.88853400
O	5.00280200	-0.34969200	0.08852100
N	0.65774000	-0.42010500	-0.09190300
C	-0.34507000	0.55667100	-0.52372400
H	-0.18621700	0.69871800	-1.59676500
H	5.70151300	-0.47987300	-0.56656300
C	-1.76025100	0.04881100	-0.29951000
C	-2.43133100	0.26212800	0.91203600
C	-2.38283700	-0.68520300	-1.31670800
C	-3.71148200	-0.26044300	1.10452700
H	-1.96791100	0.83939400	1.70702000
C	-3.66190400	-1.20787200	-1.12250300
H	-1.86559500	-0.84857000	-2.25737500
C	-4.32704200	-0.99667100	0.08888200
H	-4.22535500	-0.08968500	2.04469000
H	-4.13870700	-1.77379400	-1.91606500
H	-5.32298600	-1.40074100	0.23914800
C	-0.06253500	1.91885700	0.13378700
O	0.89045700	2.13955600	0.84766200
O	-0.93335200	2.89386600	-0.16320300
H	-1.67529700	2.57362800	-0.70466900

TS1’ (without one explicit H_3O^+ molecule)

Imagine frequency = -405.74 cm^{-1}

C	1.99326400	0.72439000	-0.44372900
H	1.43146000	1.13125500	-1.26125700
O	2.84283000	2.78183600	-1.02016800
C	1.81914300	3.70146900	-0.93581200
H	0.81558400	3.27385800	-1.18861400
H	1.94227000	4.56499300	-1.62482400
H	1.69227100	4.15075900	0.07897500
C	3.85159900	-0.23232700	0.48794100
O	3.52198100	-1.52283600	0.90893300
C	4.07388300	-2.56542700	0.09114000
H	3.79986400	-3.50796900	0.56513500
H	5.16579900	-2.47796600	0.04647900
H	3.66159000	-2.52901500	-0.92226200

C	3.35328300	0.79658000	1.49491700
H	3.97844600	1.68791900	1.43209900
H	3.39114800	0.39663500	2.50865400
C	1.92346200	1.11488000	1.01314700
H	1.66243700	2.16544300	1.12042900
H	1.18222000	0.52081700	1.55100600
O	3.12865400	0.08914500	-0.74556800
H	4.91025800	-0.16463100	0.22255000
N	0.76894300	-0.94648600	-0.41513000
H	1.31578200	-1.59196800	0.15449500
C	-0.62915200	-0.88311000	0.05028900
H	-0.62172600	-0.75676400	1.13555900
C	-1.31890100	0.33233300	-0.60537700
C	-1.37754900	-2.20554500	-0.29275600
H	-0.75185100	1.23180900	-0.34533300
H	-1.26438100	0.21289500	-1.69286800
C	-2.75445100	0.50726900	-0.17396700
O	-1.19560000	-2.64361300	-1.46496800
C	-3.81168100	0.07001700	-0.98250600
C	-3.05537300	1.09436400	1.06403000
H	-3.59241500	-0.38671000	-1.94358900
C	-5.13847100	0.21005200	-0.56475800
C	-4.37882000	1.23563800	1.48718900
H	-2.24555600	1.44467500	1.69922700
H	-5.94497900	-0.13390000	-1.20572100
C	-5.42654400	0.79203300	0.67299100
H	-4.59256400	1.69405400	2.44832000
H	-6.45636300	0.90303600	0.99880400
O	-2.09482000	-2.71043300	0.61190400
H	0.77160700	-1.31231600	-1.36886100

TS1'' (with one explicit water molecule)

Imagine frequency = -379.18 cm^{-1}

C	-1.84735000	-0.53887300	-0.03032600
H	-1.34648600	-1.07173900	-0.81523100
O	-2.90624200	-2.56520700	-0.10224300
C	-3.53077300	0.73813500	0.85603400
O	-3.07745900	2.04377100	1.01271800
C	-3.62531700	2.97646400	0.06749100
H	-3.25212200	3.95966600	0.35344600
H	-4.72029000	2.96755200	0.11472400
H	-3.29869800	2.73895500	-0.94973400
C	-3.02106900	-0.14820300	1.98509100
H	-3.71889100	-0.97344200	2.13091000

H	-2.93092800	0.42059300	2.91077600
C	-1.67350800	-0.68251400	1.45894800
H	-1.49725900	-1.72310600	1.72374700
H	-0.83377100	-0.08634700	1.81908400
O	-2.93259200	0.14977300	-0.35851600
H	-4.60860200	0.70874400	0.67543400
N	-0.45046500	1.05957600	-0.36832100
H	-0.90688200	1.82636300	0.12475600
C	0.97047300	0.95994500	0.00730700
H	1.04097900	1.01122900	1.09688100
C	1.51720800	-0.39962400	-0.47951900
C	1.78575500	2.13980800	-0.59984100
H	0.90811300	-1.19256100	-0.03342800
H	1.38368100	-0.45286700	-1.56544600
C	2.96656800	-0.62544300	-0.12403600
O	1.55240800	2.39259600	-1.81689600
C	3.98282900	-0.42490700	-1.06739700
C	3.32497200	-1.02070000	1.17342600
H	3.71913300	-0.11938400	-2.07610000
C	5.32565900	-0.60904800	-0.72455300
C	4.66473200	-1.20535300	1.52193300
H	2.54709500	-1.18737000	1.91448800
H	6.09939600	-0.44985300	-1.46994400
C	5.67138000	-0.99853100	0.57251200
H	4.92288700	-1.51351600	2.53089800
H	6.71350900	-1.14390000	0.84055700
O	2.60134500	2.72684700	0.16103900
H	-0.50259400	1.27261600	-1.36573700
O	-4.16477600	-1.93446800	-2.22361200
H	-3.65930900	-2.22509200	-1.36770200
H	-4.11737900	-0.97000600	-2.19401000
C	-1.92727200	-3.53267400	-0.30315500
H	-1.40145100	-3.42594900	-1.27641100
H	-1.13803200	-3.50430900	0.47734500
H	-2.33602500	-4.56070500	-0.28445900

TS7

Imagine frequency = -126.39 cm^{-1}

C	-2.39390400	-0.59716100	0.04559900
H	-1.88679400	-1.15863000	-0.72406700
O	-3.87517800	-2.22117700	0.06999500
C	-3.59461200	1.19090400	0.88956200
O	-2.85519800	2.33966100	0.87399800

C	-3.25817200	3.31444600	-0.11009900
H	-2.65965500	4.20336600	0.08340600
H	-4.32184100	3.54665900	0.00384700
H	-3.06063400	2.94420600	-1.11972700
C	-3.23104300	0.29128500	2.06271900
H	-4.10662900	-0.28760700	2.35950900
H	-2.89572700	0.89260800	2.90723900
C	-2.13533600	-0.63935200	1.51155900
H	-2.18154100	-1.65818300	1.89522200
H	-1.12699000	-0.25960400	1.69397300
O	-3.18033100	0.34862900	-0.32636700
H	-4.65903800	1.36337200	0.71738200
N	-0.27994800	0.86876600	-0.53235500
H	-0.63124700	1.70782600	-0.07435100
C	1.07672700	0.55695800	-0.09265500
H	1.07888900	0.46601000	0.99700100
C	1.52160100	-0.78963400	-0.71291600
C	2.08384000	1.64093400	-0.47666700
H	0.79792600	-1.54465900	-0.39175700
H	1.44912300	-0.70368100	-1.80259100
C	2.92107400	-1.19218000	-0.31255500
O	2.12667300	2.16902400	-1.57548300
C	4.01339900	-0.91800200	-1.14657900
C	3.15767600	-1.79832800	0.92948600
H	3.84417700	-0.45056100	-2.11278500
C	5.31498200	-1.23420400	-0.74694700
C	4.45618300	-2.11750200	1.33252900
H	2.31895700	-2.02006800	1.58440900
H	6.14983500	-1.01436300	-1.40561100
C	5.54033600	-1.83316000	0.49550000
H	4.62178500	-2.58830800	2.29695100
H	6.55038000	-2.08054400	0.80752000
O	2.92905800	1.92091800	0.52236300
H	-0.29314200	1.04778100	-1.53507600
O	-5.37230200	-1.20411200	-1.94515700
H	-4.45535000	-1.95041200	-0.68302000
H	-5.53112200	-1.71322200	-2.75238200
H	-4.92289800	-0.39426400	-2.22770500
C	-3.36269000	-3.53846500	-0.16646500
H	-2.82506400	-3.59246800	-1.11970300
H	-2.67664000	-3.77403900	0.64945000
H	-4.17890300	-4.26753800	-0.16656200
C	3.99356400	2.85586600	0.22775600
H	3.57628400	3.81817700	-0.07334100

H	4.55680700	2.95167400	1.15385600
H	4.62516900	2.45711200	-0.56834800

TS7'

Imagine frequency = -332.49 cm^{-1}

C	2.02075000	-0.53028100	0.03372800
H	1.55754700	-1.08864500	0.82598300
O	3.25570700	-2.56301400	0.37801300
C	3.65941400	0.80365200	-0.85023400
O	3.08093400	2.03132500	-1.14796800
C	3.49871300	3.10825300	-0.29067200
H	3.02189900	4.00911900	-0.67587000
H	4.58791000	3.22014700	-0.32695600
H	3.17926600	2.93301100	0.74125600
C	3.32578700	-0.22770700	-1.91931900
H	4.10695700	-0.98866100	-1.93347400
H	3.25670400	0.24139900	-2.90079200
C	1.99705700	-0.84706500	-1.43938300
H	1.95709200	-1.92478600	-1.58312800
H	1.13667900	-0.39739400	-1.93743900
O	3.03260300	0.25245800	0.37391000
H	4.71684400	0.90578000	-0.59541300
N	0.51800800	0.90948700	0.14186700
H	0.92521000	1.65689600	-0.42142800
C	-0.85037300	0.57857700	-0.28161700
H	-0.83699300	0.38522900	-1.35590000
C	-1.35038400	-0.67647400	0.46671900
C	-1.80987400	1.75251200	-0.07795800
H	-0.69546000	-1.50920700	0.19554200
H	-1.24780300	-0.50827500	1.54309900
C	-2.78283300	-1.01289200	0.12293100
O	-1.79262900	2.17517600	1.19189500
C	-3.83067800	-0.64381300	0.97658600
C	-3.08846200	-1.66103000	-1.08236900
H	-3.60600400	-0.14315500	1.91419600
C	-5.15855000	-0.91412400	0.63331500
C	-4.41363600	-1.93248800	-1.42879500
H	-2.28409500	-1.95665100	-1.75096900
H	-5.95920100	-0.62404500	1.30690400
C	-5.45353000	-1.55777700	-0.57139600
H	-4.63420100	-2.43765500	-2.36426500
H	-6.48410300	-1.76951400	-0.83913600
O	-2.50634000	2.23071300	-0.95343500
H	0.53918500	1.20608300	1.11689500

O	4.34289600	-1.59404400	2.44802500
H	3.90243800	-2.02372100	1.60682100
H	4.21111000	-0.64658700	2.31359900
C	2.30642600	-3.54286500	0.64277500
H	1.79991800	-3.40879600	1.62328700
H	1.49601500	-3.56517800	-0.11829700
H	2.73265200	-4.56512100	0.65514900
C	-2.67914500	3.26882300	1.52873300
H	-2.50579700	3.46404500	2.58485500
H	-2.43478000	4.14521400	0.92640700
H	-3.71450900	2.97133000	1.35421500

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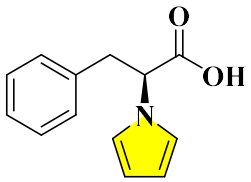

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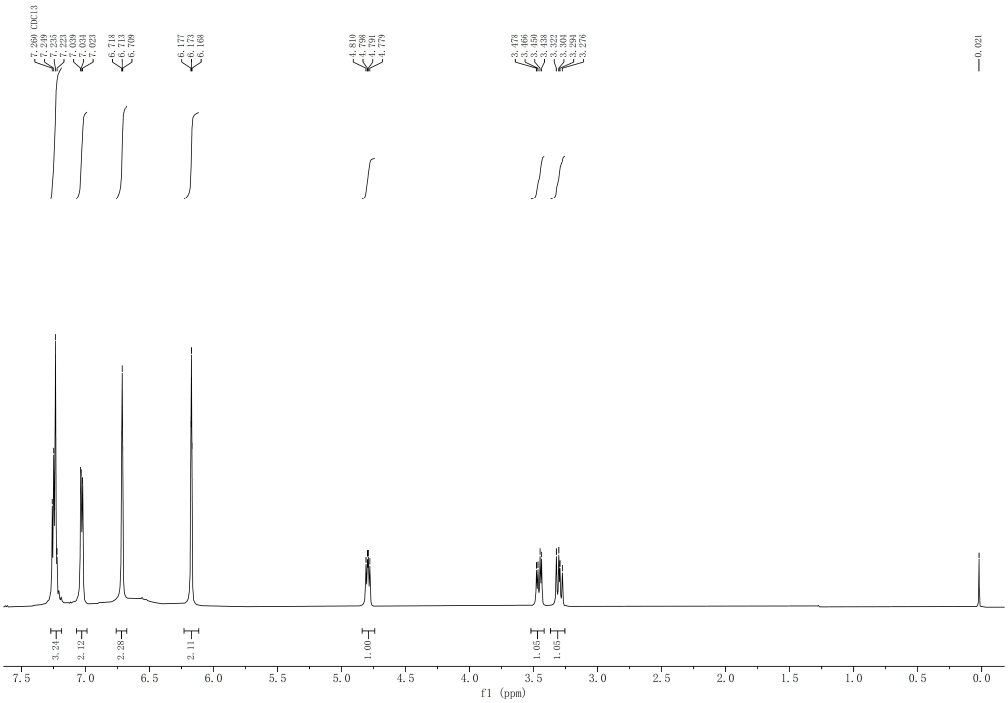
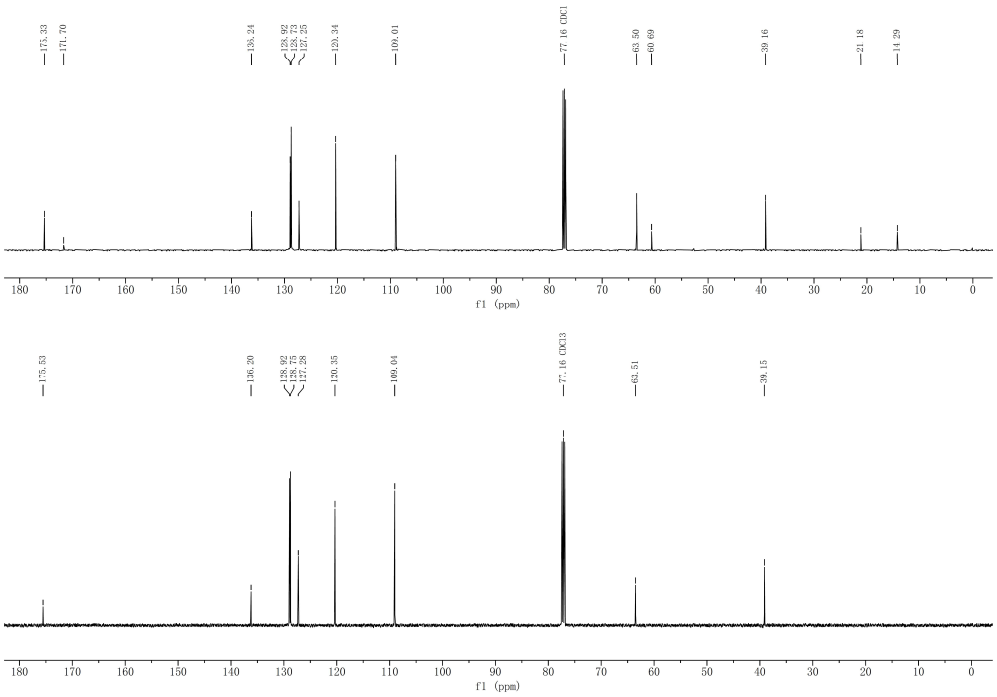
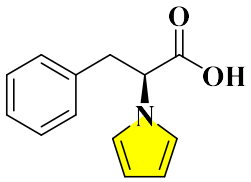


DMTHF, 10% CA, 90 °C, 2 h for ^{1}H NMR of purified Compound **19** (500 MHz, $CDCl_3$)



DMTHF, 0.75% CA, u-crude vs 10% CA, d-purified, 90 °C, 2 h, ^{13}C NMR-**19** (126 MHz, $CDCl_3$)



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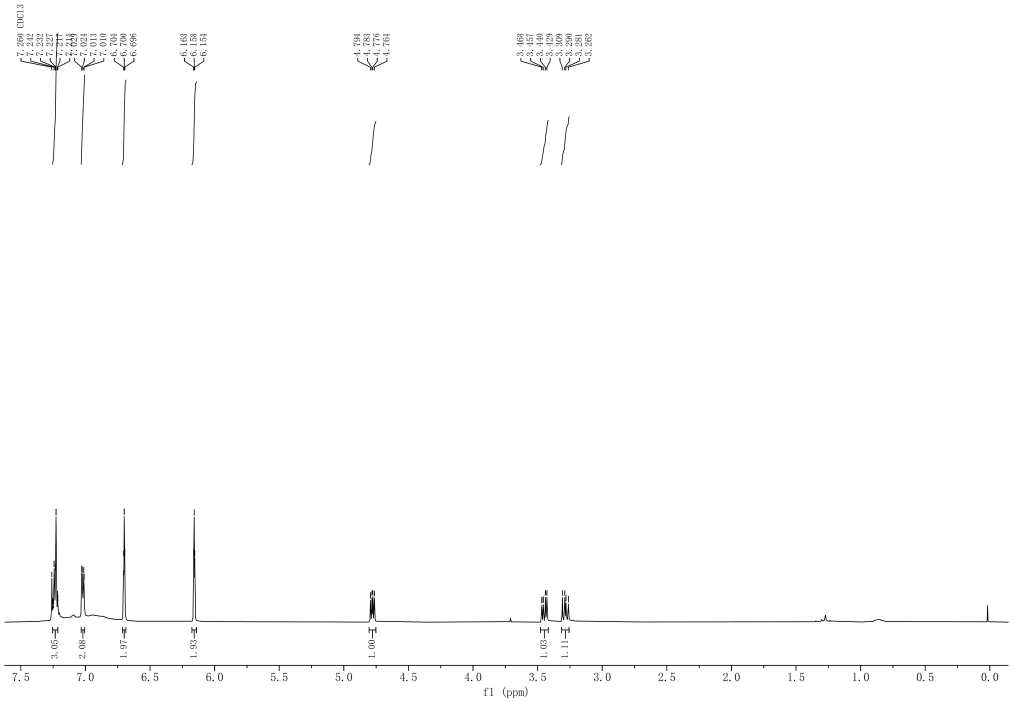
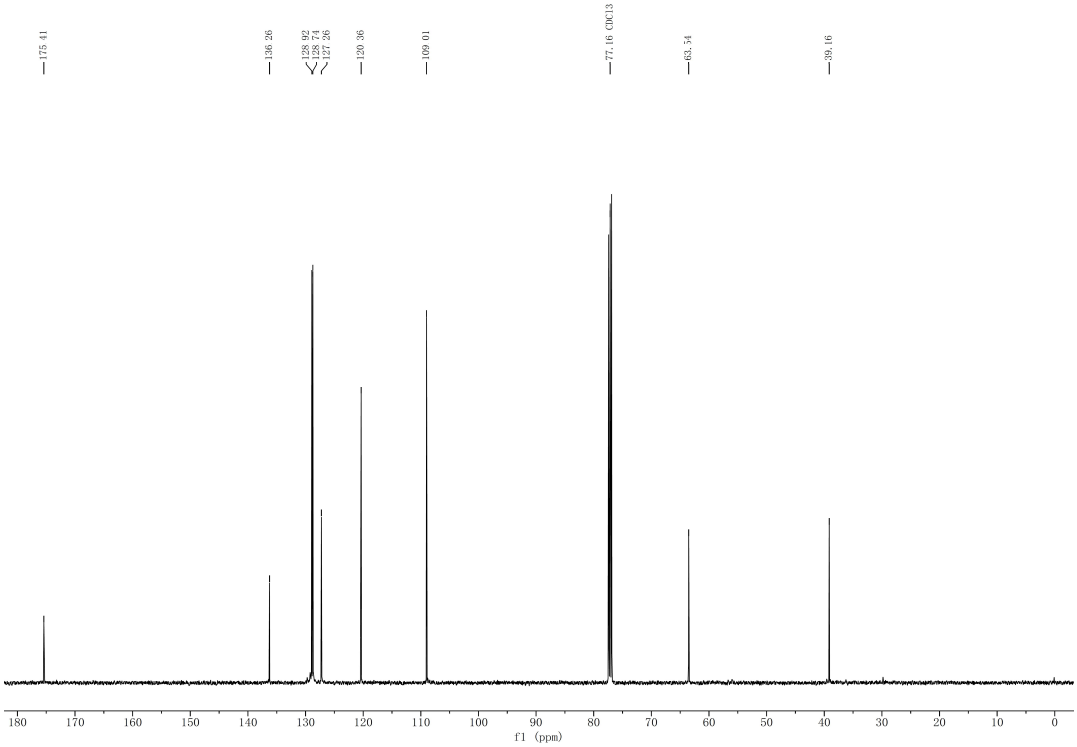


DMTHF, 0.75% CA, 90 °C, 1 h for crude ^{1}H NMR of Compound **19** (500 MHz, $CDCl_3$)



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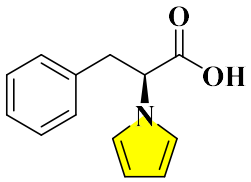

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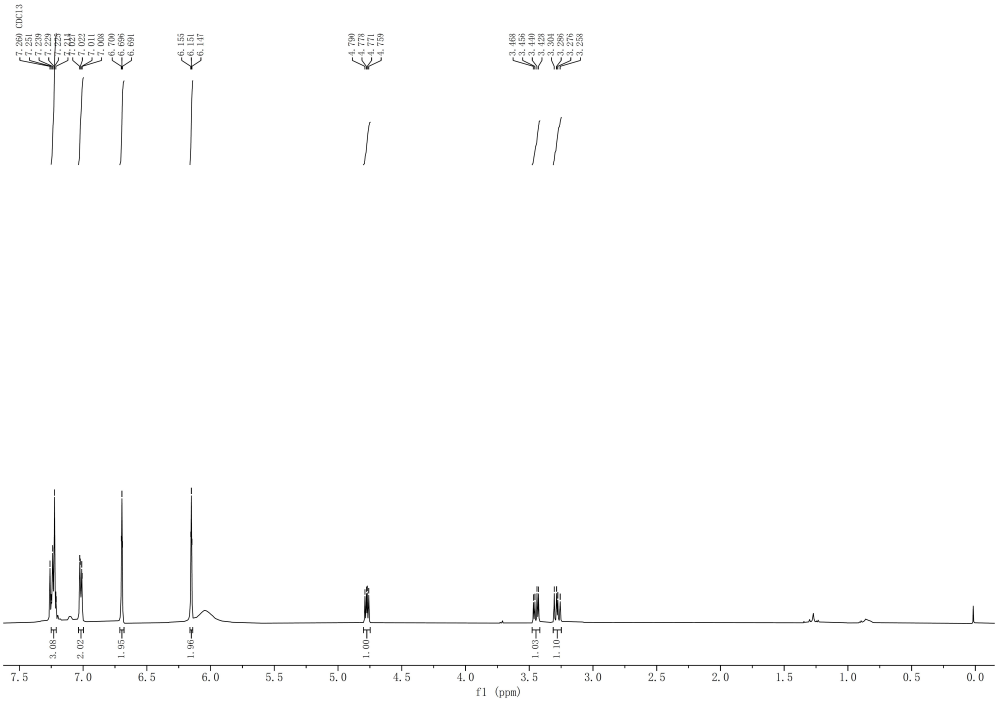

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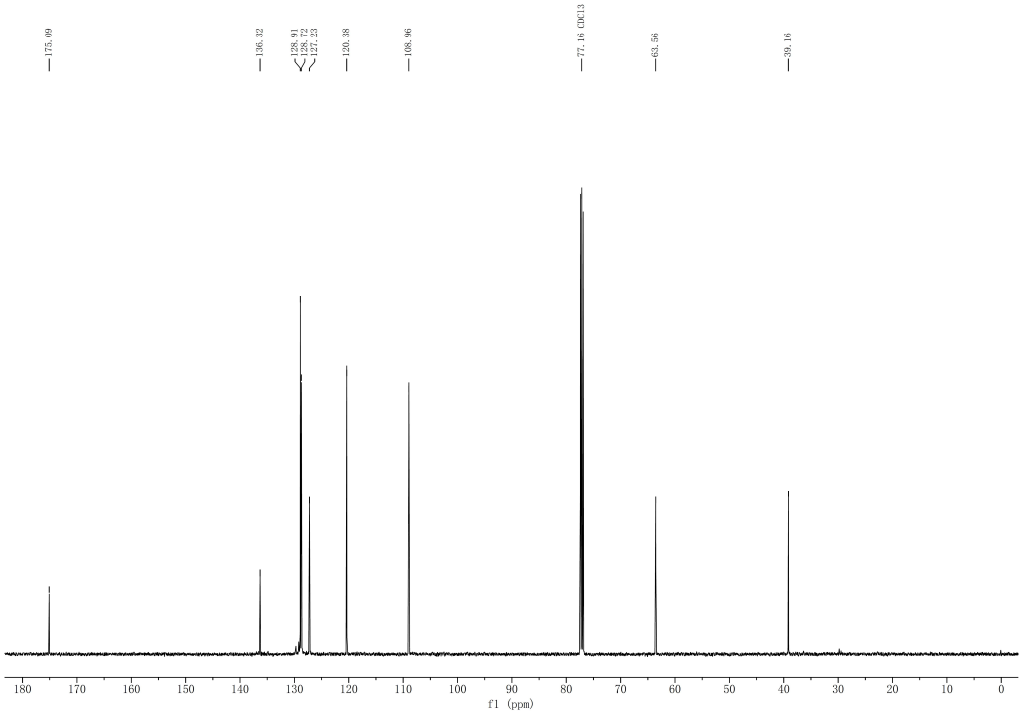
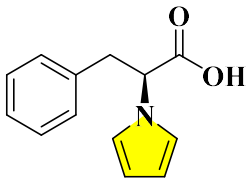


DMTHF, 0.75% CA, 90 °C, 30 min for crude ^{13}C NMR of Compound **19** (126 MHz, $CDCl_3$)



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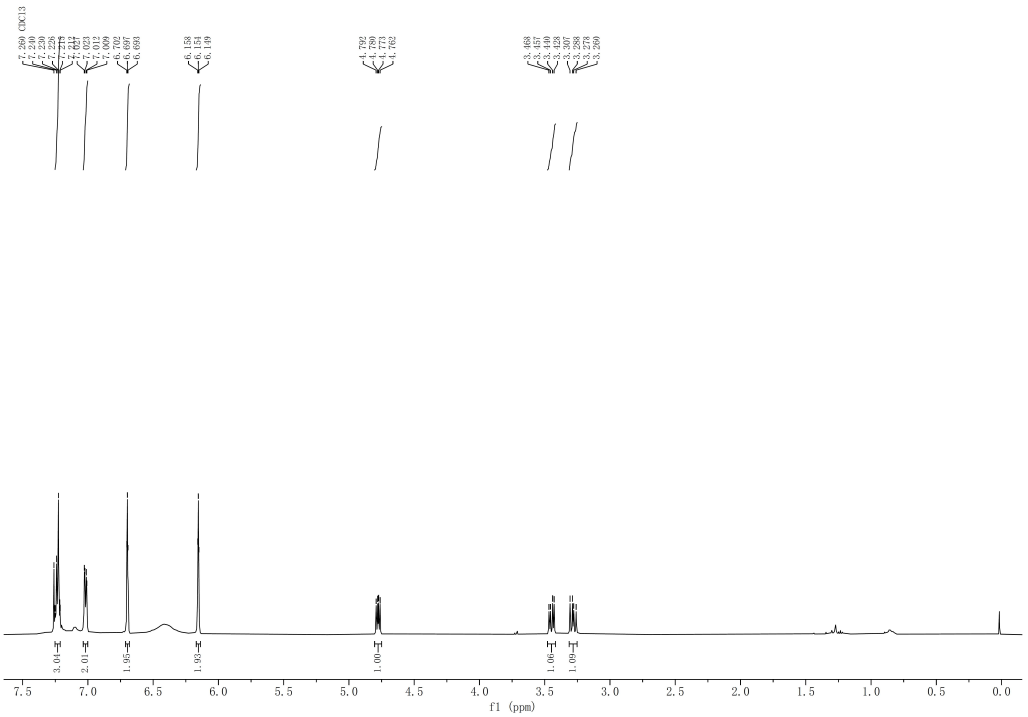

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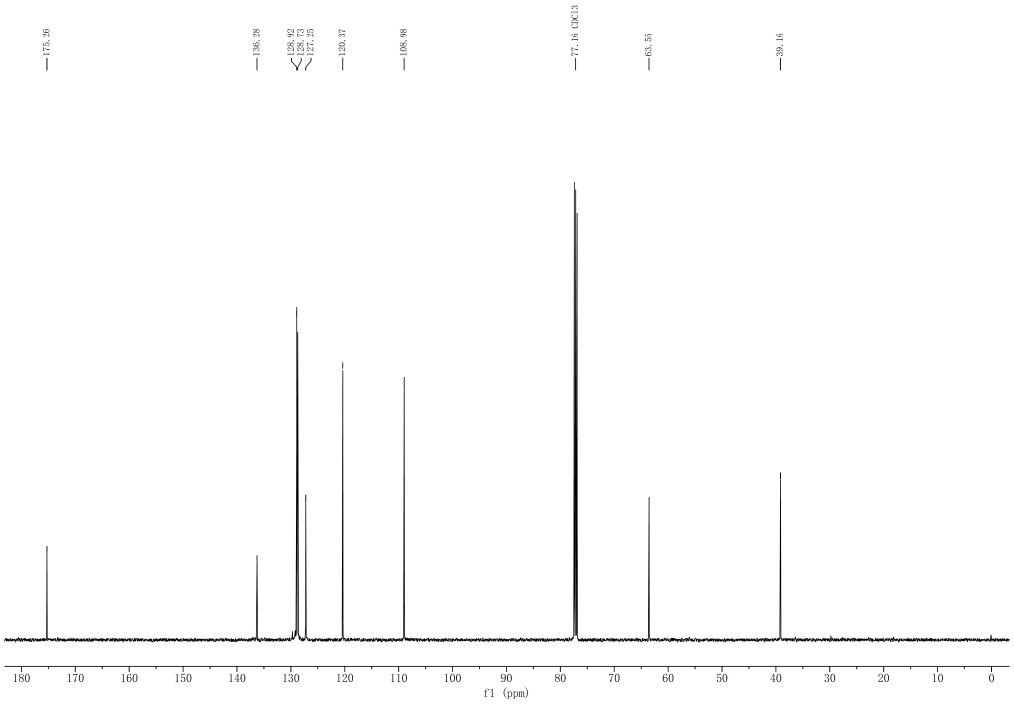

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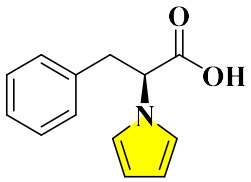

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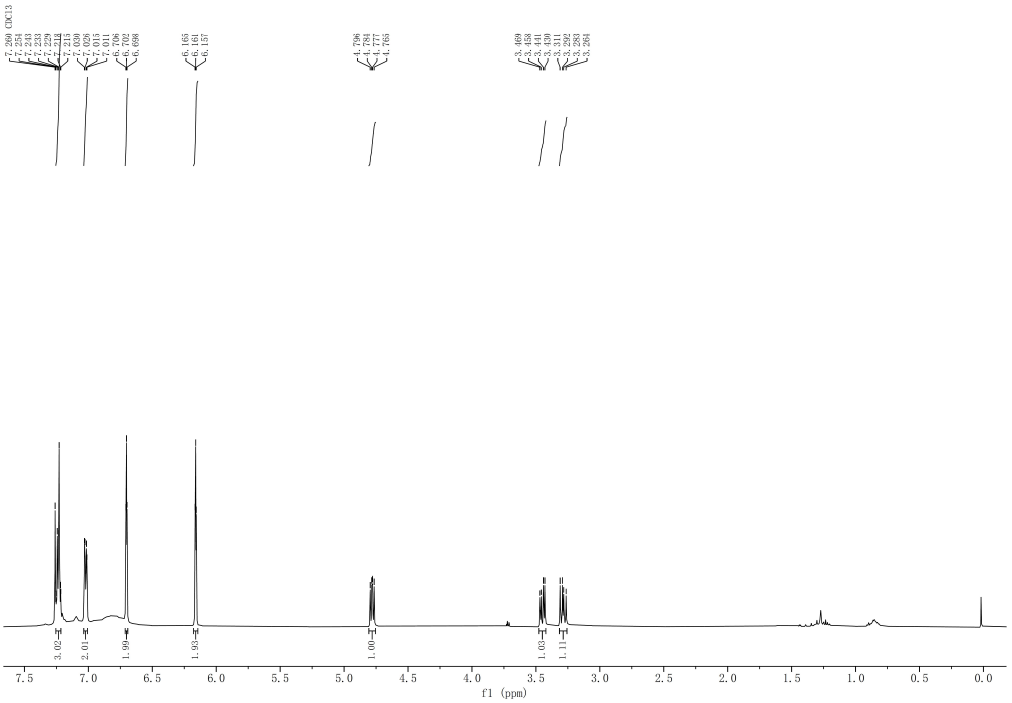
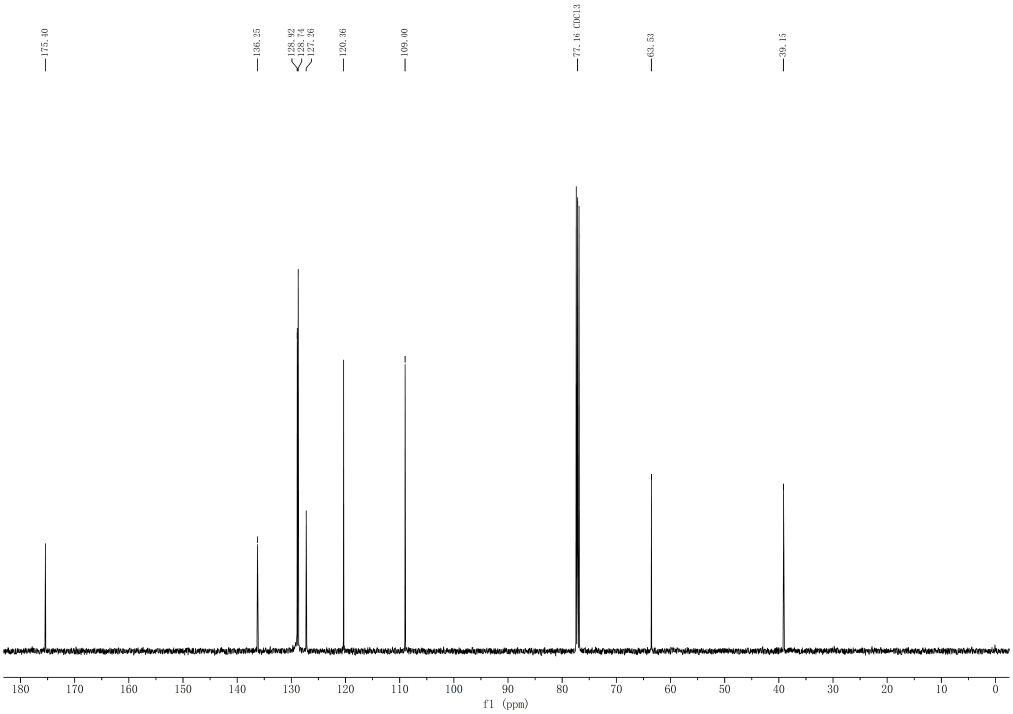
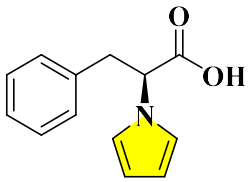


DMTHF, 0.3% CA, 90 °C, 30 min for crude ^{1}H NMR of Compound **19** (500 MHz, $CDCl_3$)



DMTHF, 0.3% CA, 90 °C, 30 min for crude ^{13}C NMR of Compound **19** (126 MHz, $CDCl_3$)



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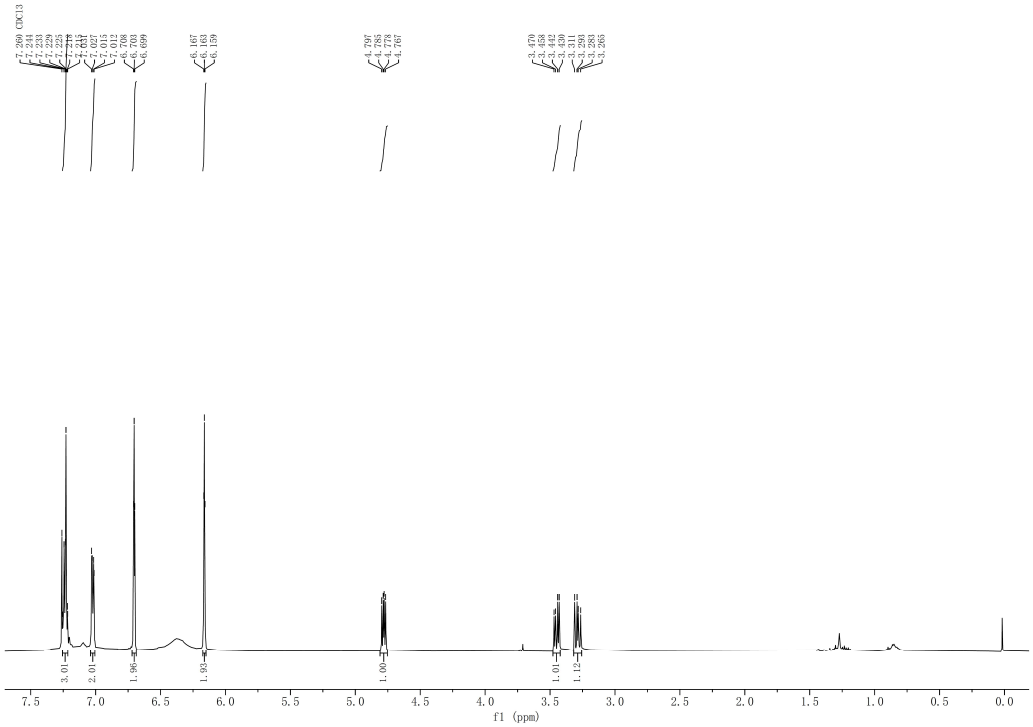

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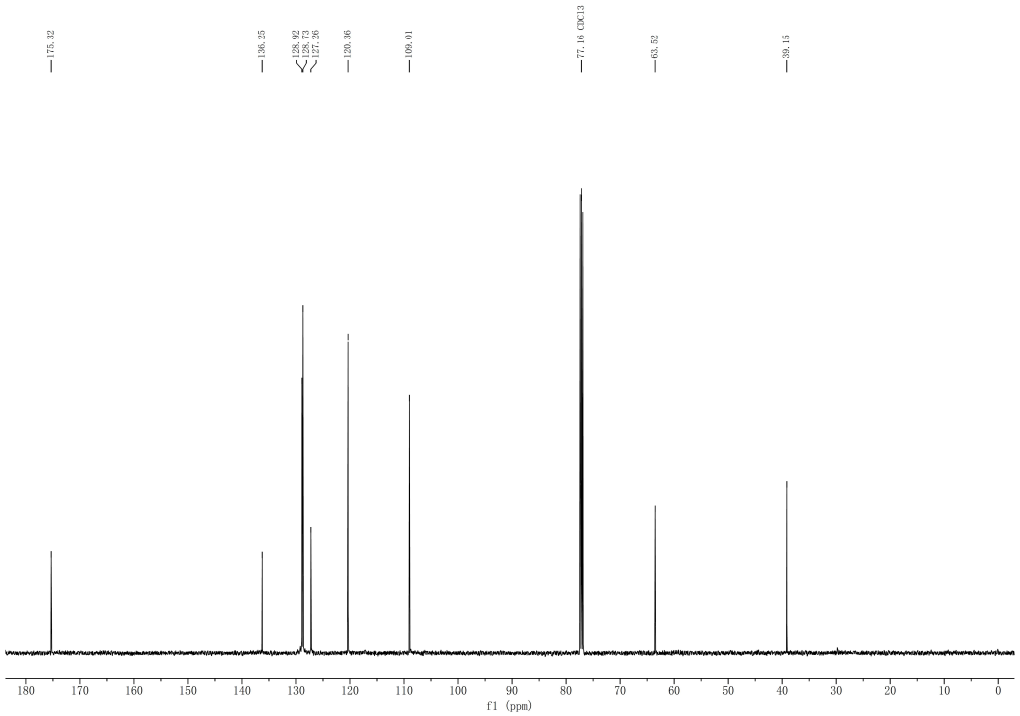
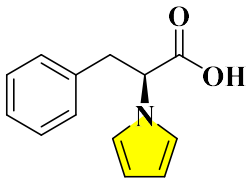


DMTHF, 0.1% CA, 90 °C, 30 min for crude ^{13}C NMR of Compound **19** (126 MHz, $CDCl_3$)



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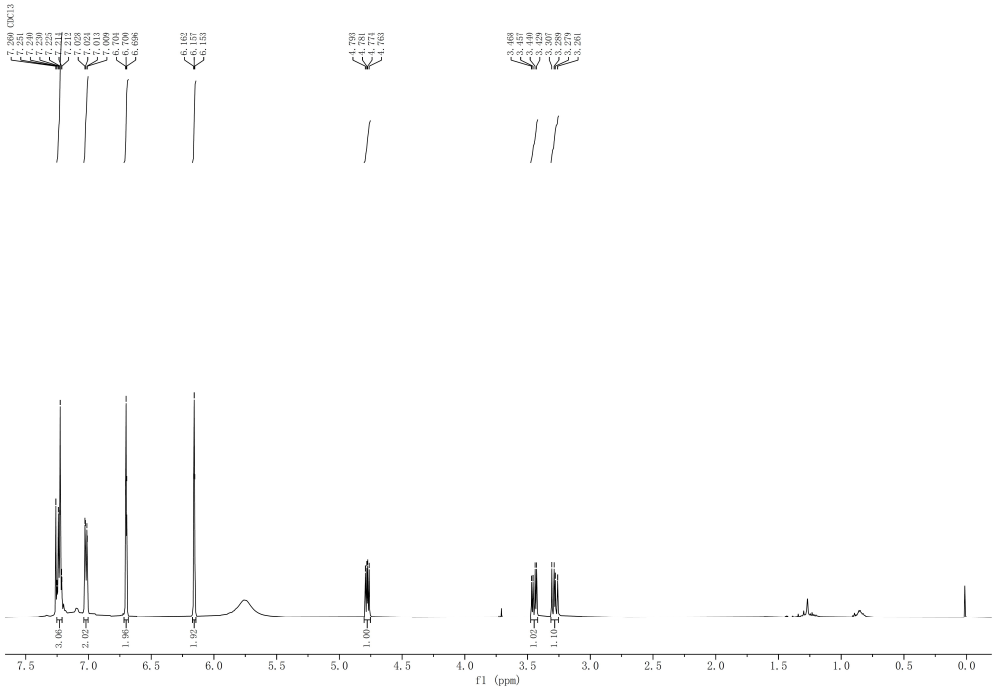

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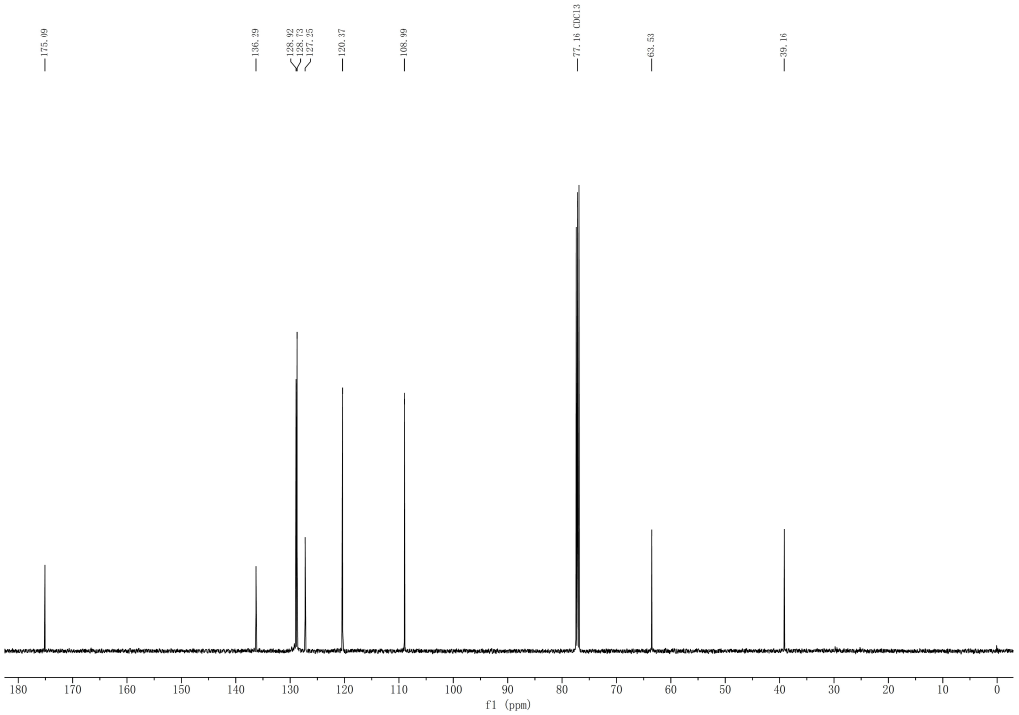
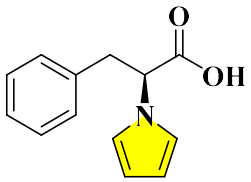


DMTHF, 0.05% CA, 90 °C, 30 min for crude ^{13}C NMR of Compound **19** (126 MHz, $CDCl_3$)



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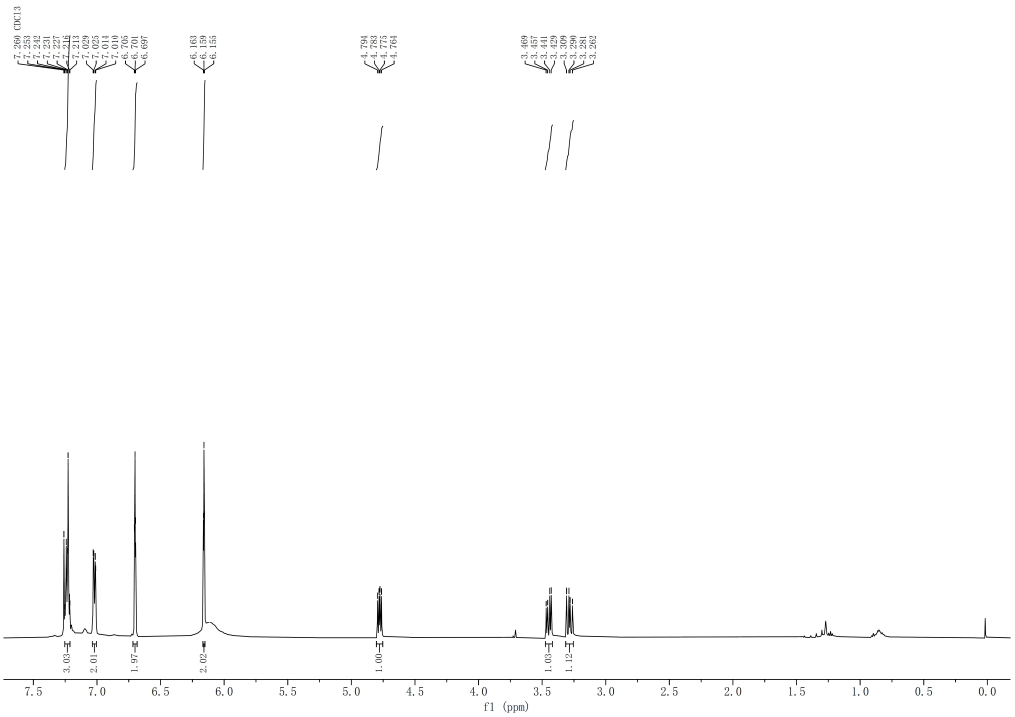

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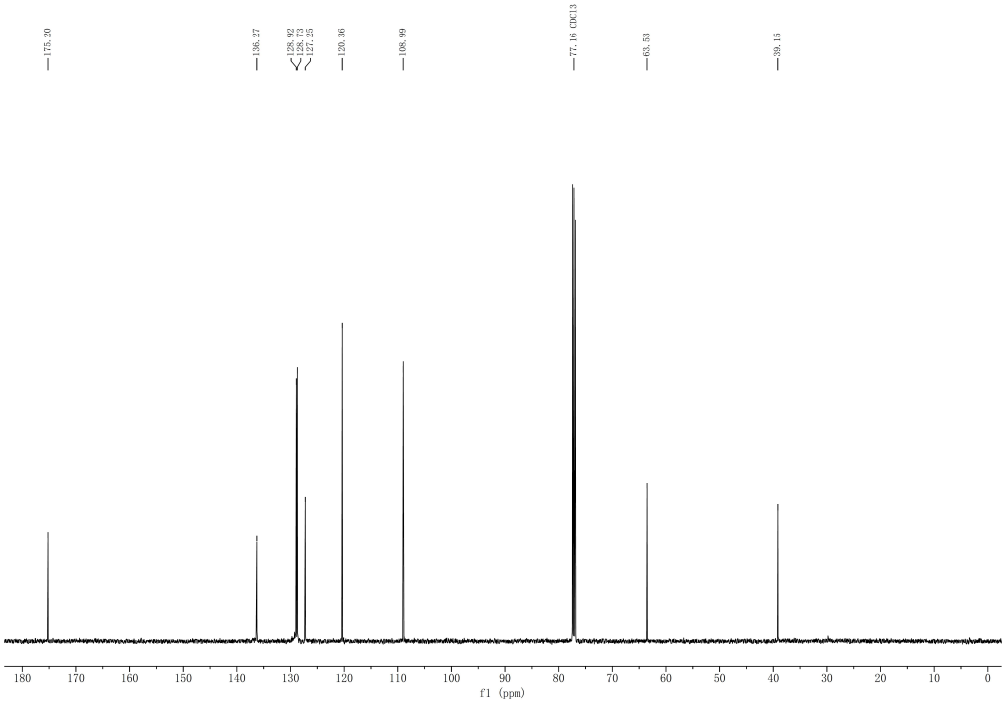

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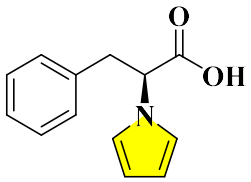

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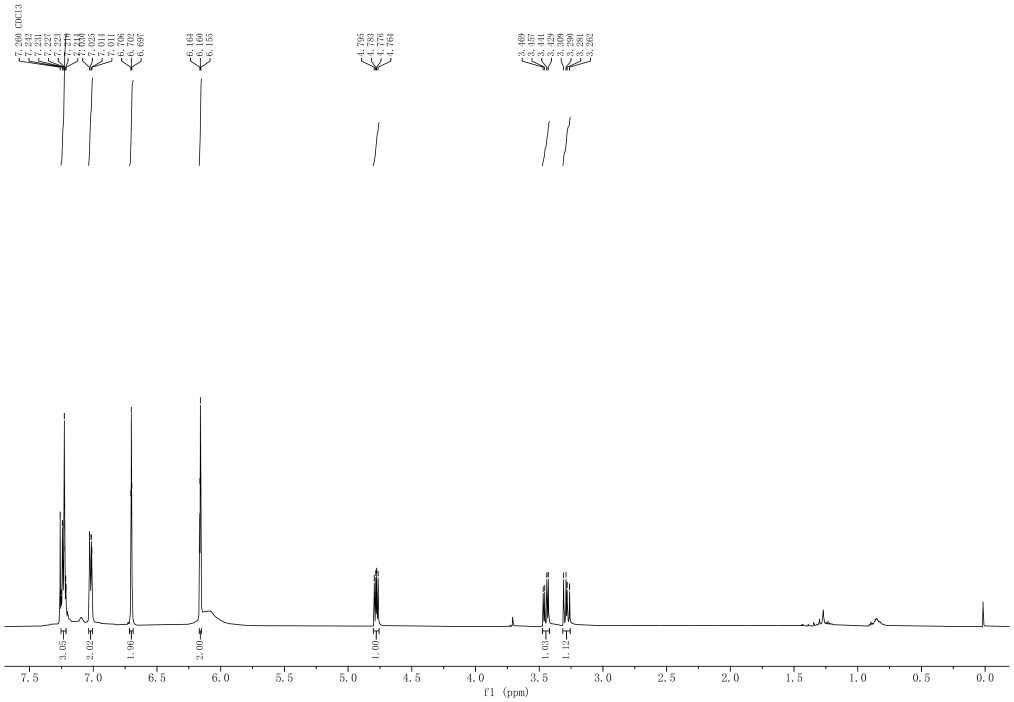
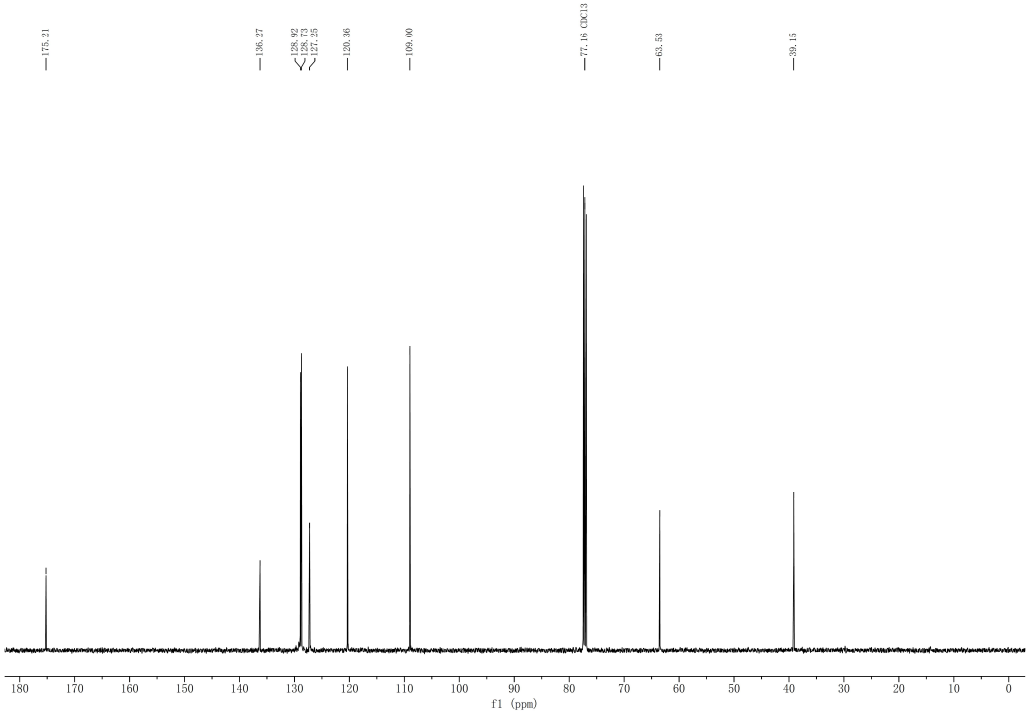


DMTHF, 0% CA, 90 °C, 30 min for crude ^{1}H NMR of Compound **19** (500 MHz, $CDCl_3$)



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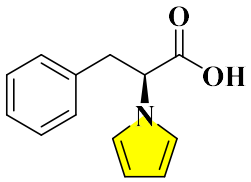

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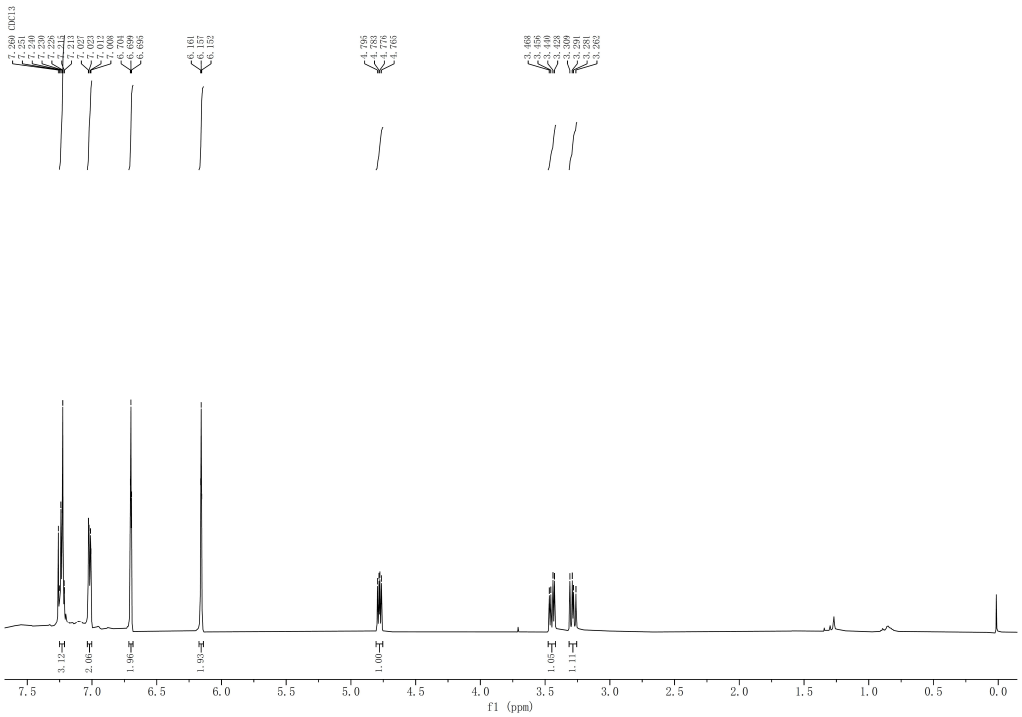
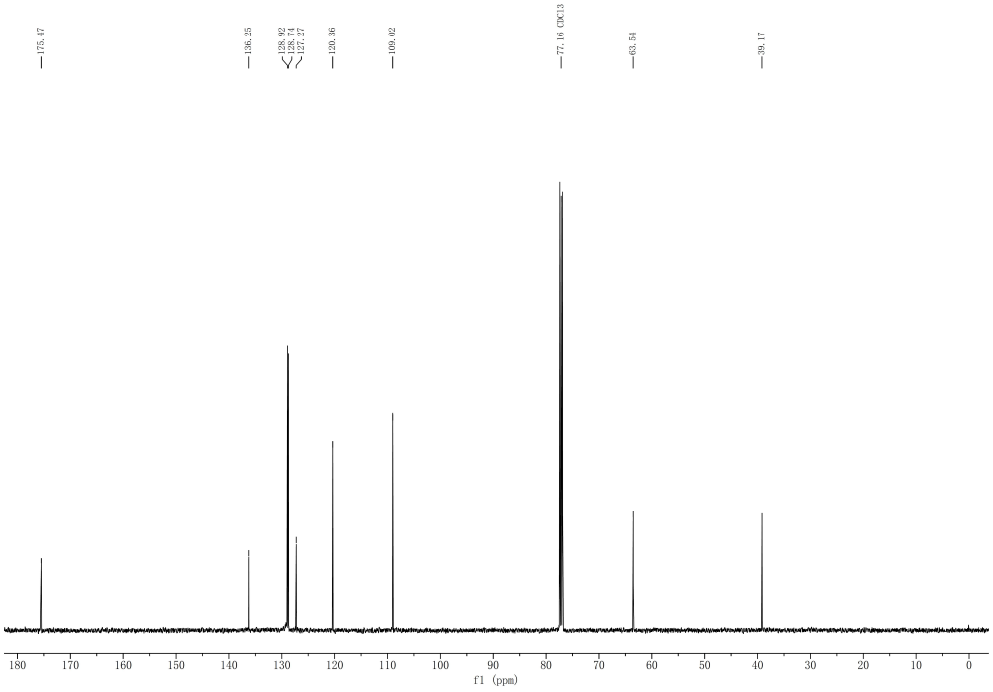


DMTHF, 0% CA, 90 °C, 15 min for crude ^{1}H NMR of Compound **19** (500 MHz, $CDCl_3$)



DMTHF, 0% CA, 90 °C, 15 min for crude ^{13}C NMR of Compound **19** (126 MHz, $CDCl_3$)

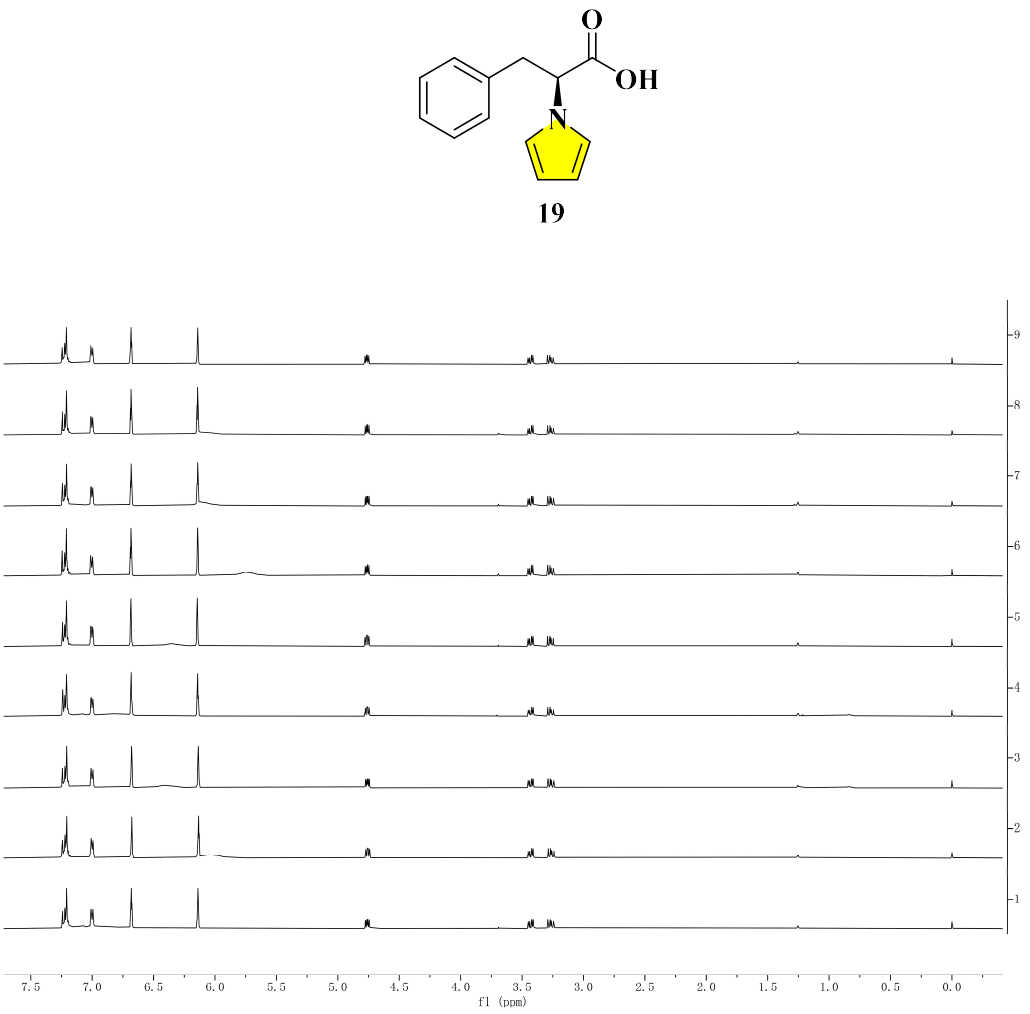
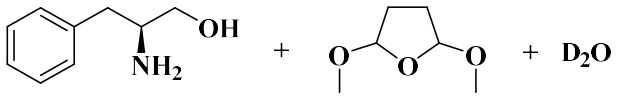
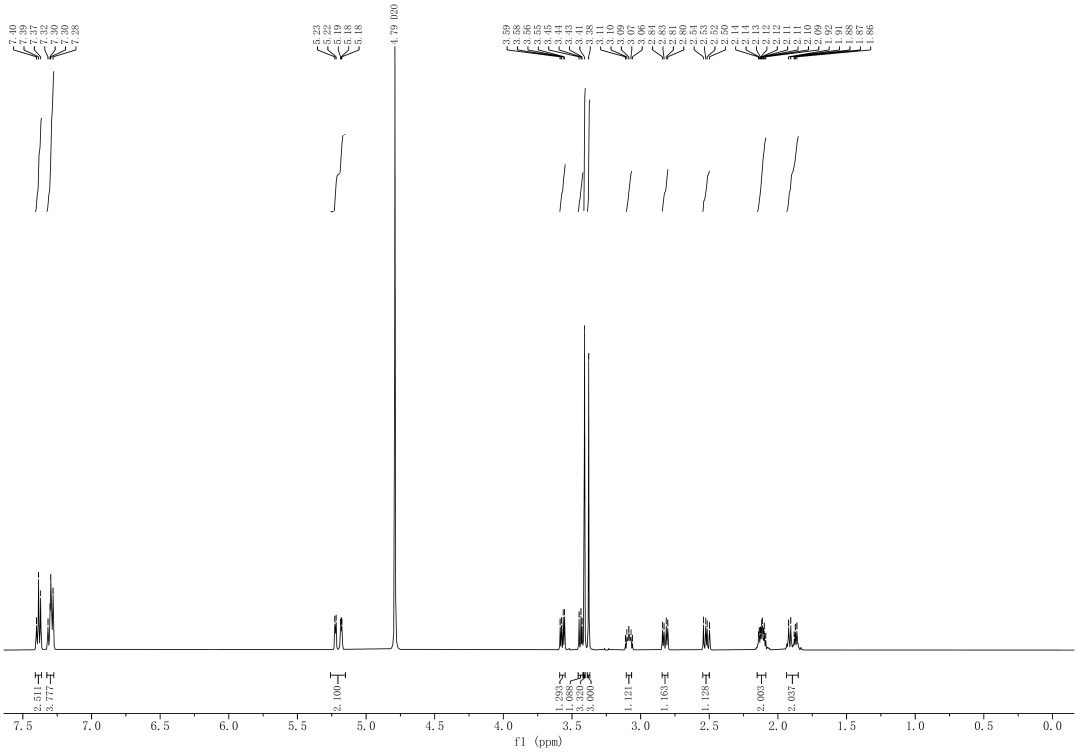
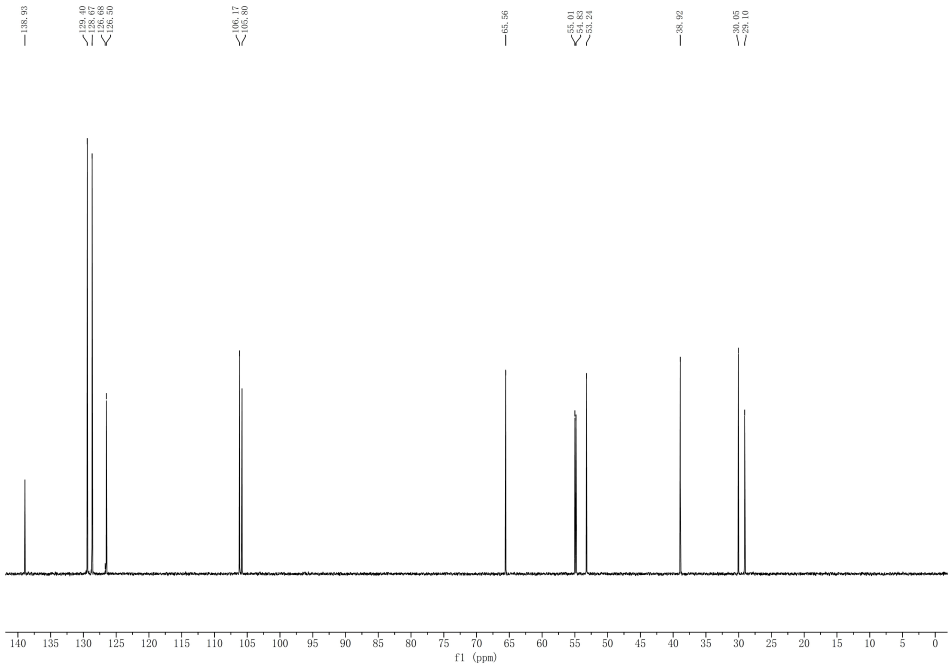


Fig. S5. Crude parallel ^{1}H NMR spectra for the N-protected products of L-Phenylalanine after simplified centrifugal isolation. Reaction temperature was 90 °C for all entries. 0.75% CA, 1 h (Entry 1); 0.75% CA, 30 min (Entry 2); 0.75% CA, 15 min (Entry 3); 0.3% CA, 30 min (Entry 4); 0.1% CA, 30 min (Entry 5); 0.05% CA, 30 min (Entry 6); 0.01% CA, 30 min (Entry 7); 0% CA, 30 min (Entry 8); 0% CA, 15 min (Entry 9).

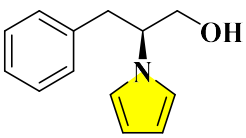




DMTHF, 0% CA, 100 °C, 2 h for ^{1}H NMR of crude reactants (500 MHz, D_2O)



DMTHF, 0% CA, 100 °C, 2 h for ^{13}C NMR of crude reactants (126 MHz, D_2O)



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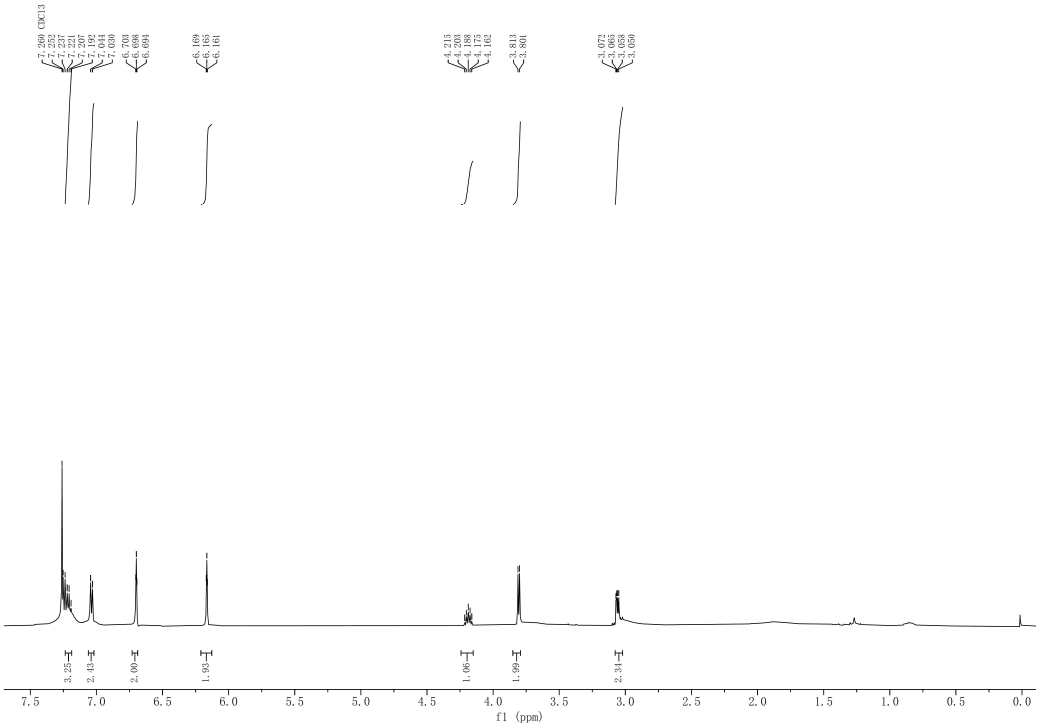
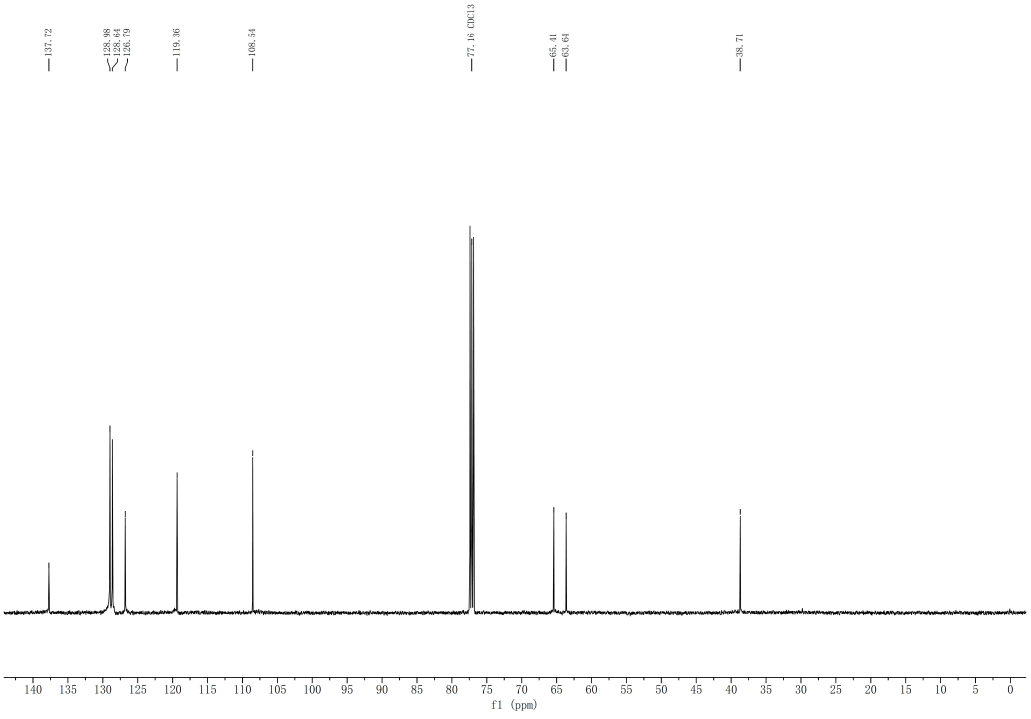
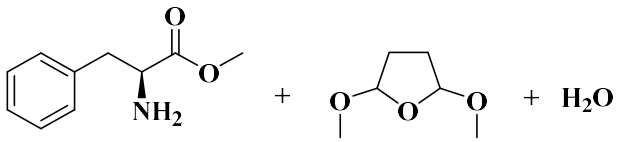
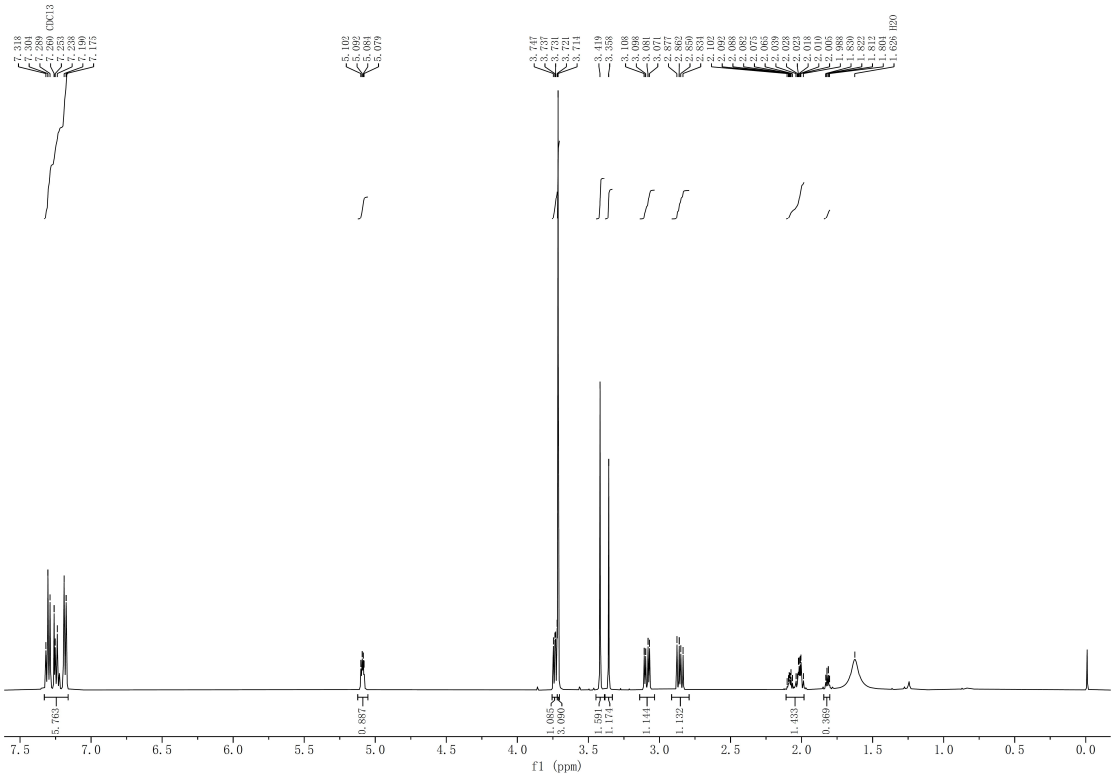


Succinaldehyde, 0% CA, 100 °C, 4 h for crude ^{1}H NMR of Compound **20** (500 MHz, $CDCl_3$)

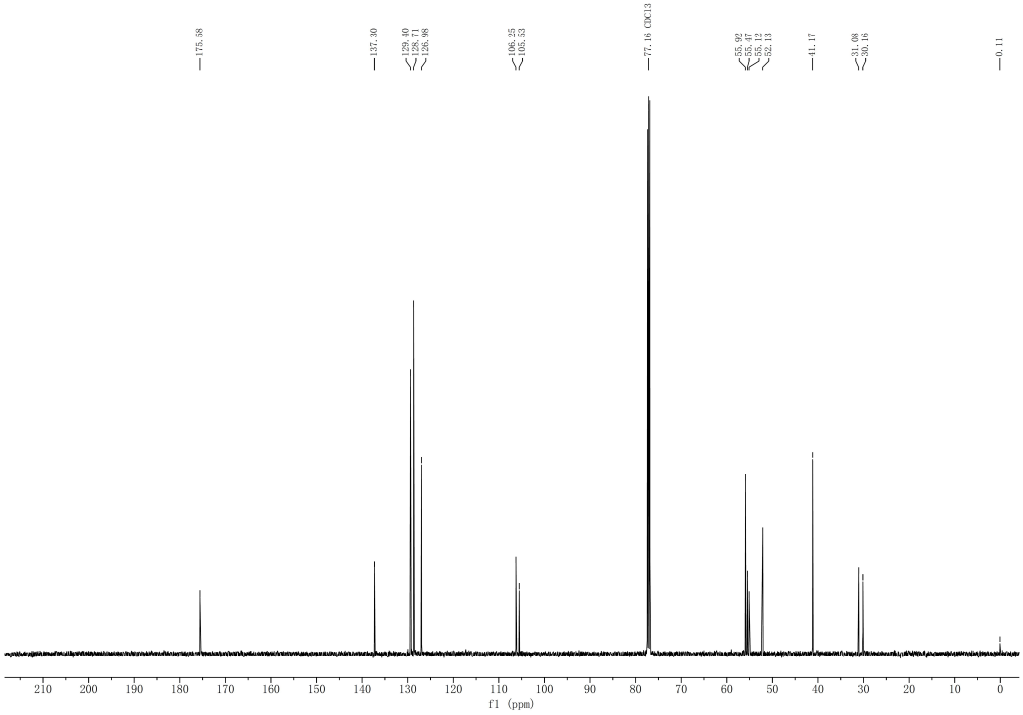


Succinaldehyde, 0% CA, 100 °C, 4 h for crude ^{13}C NMR of Compound **20** (126 MHz, $CDCl_3$)

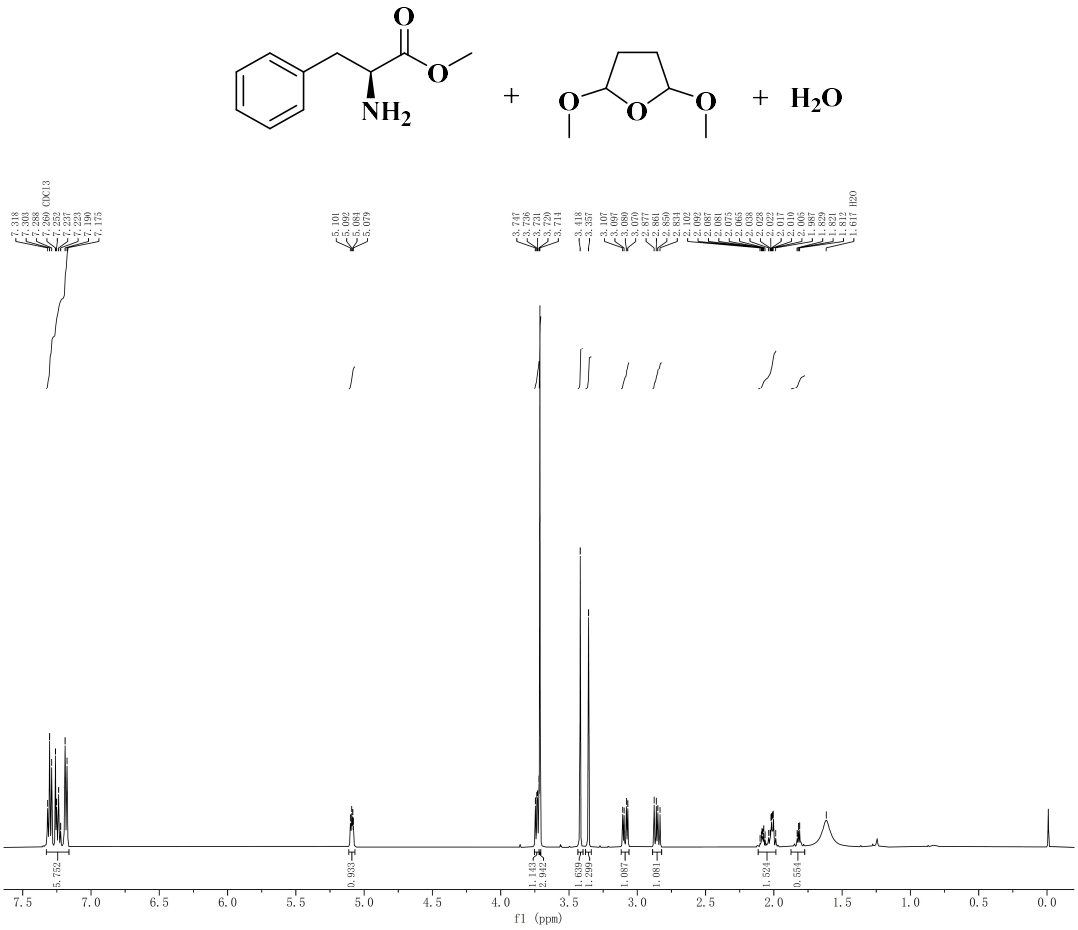




DMTHF, 0% CA, 90 °C, 30 min for ^{1}H NMR of crude reactants (500 MHz, $CDCl_3$)



DMTHF, 0% CA, 90 °C, 30 min for ^{13}C NMR of crude reactants (126 MHz, $CDCl_3$)



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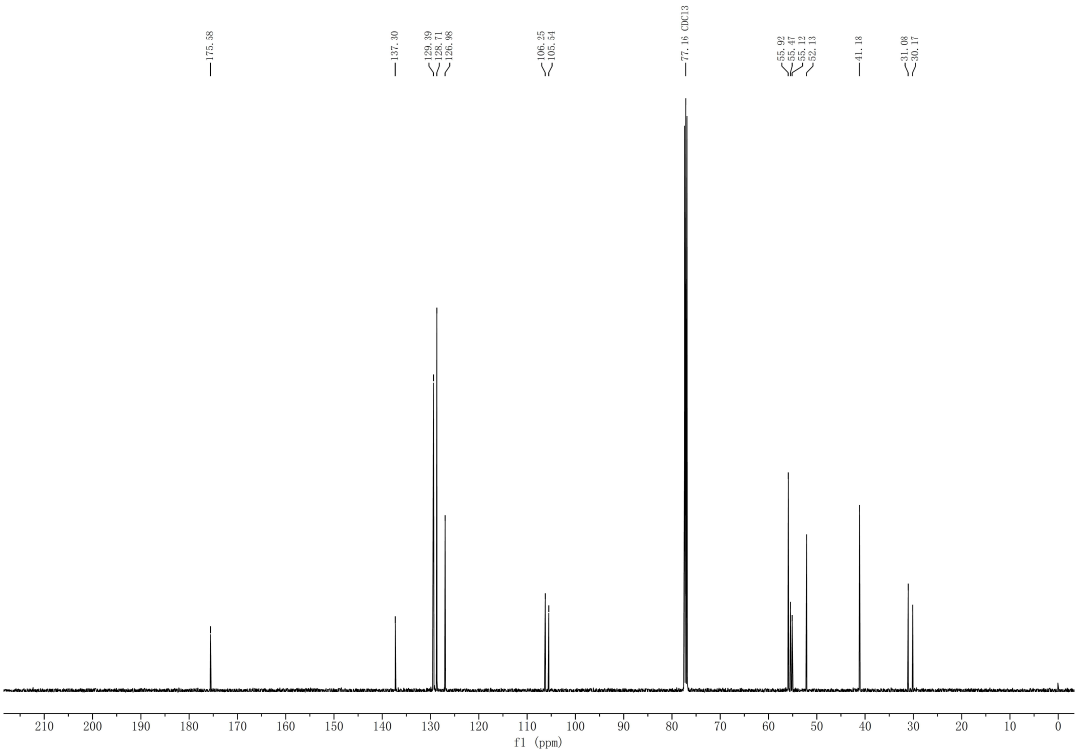
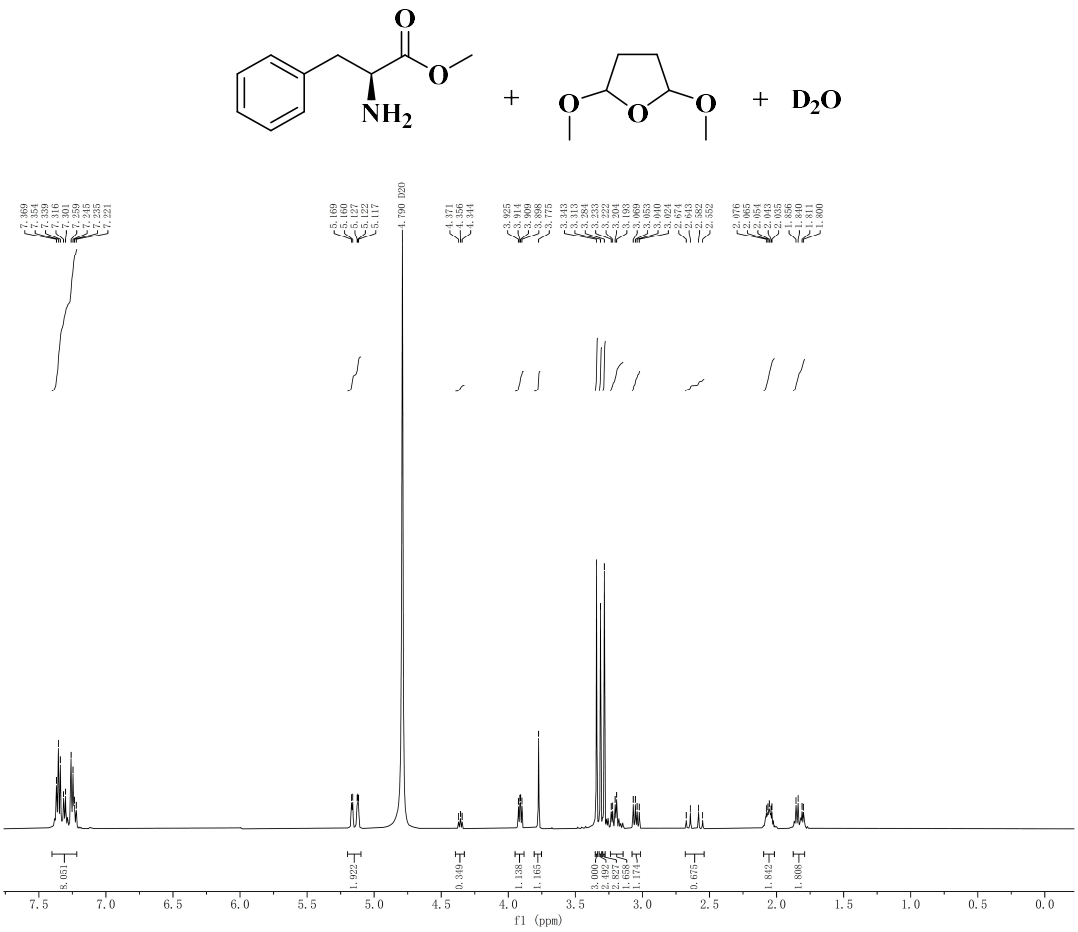
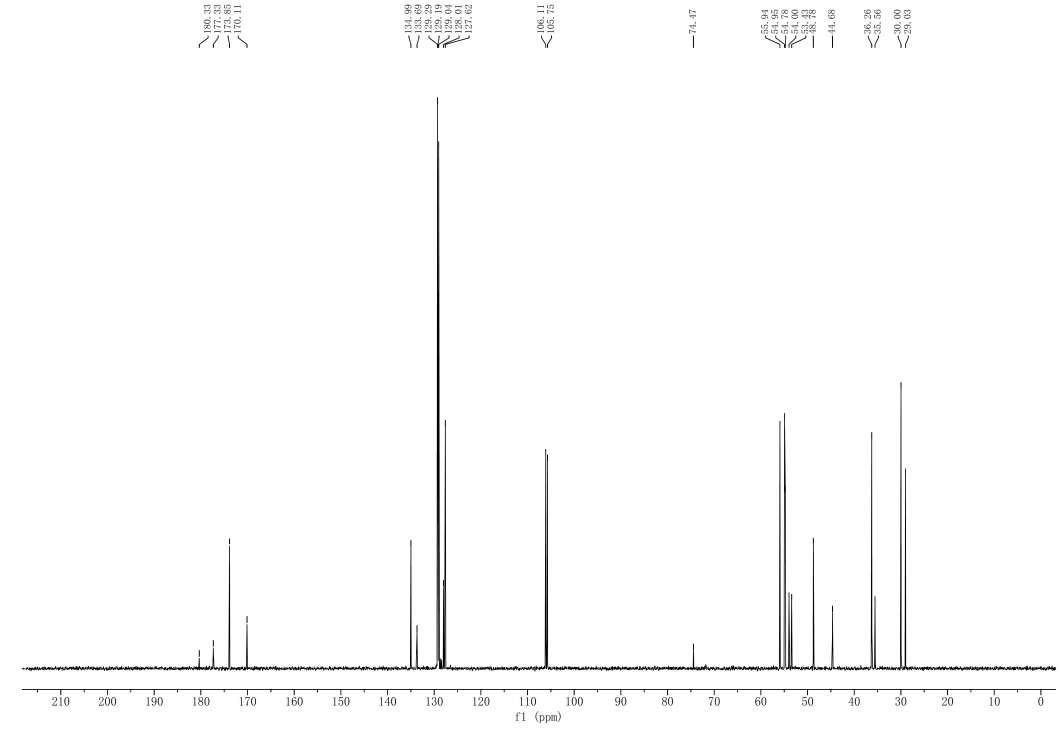


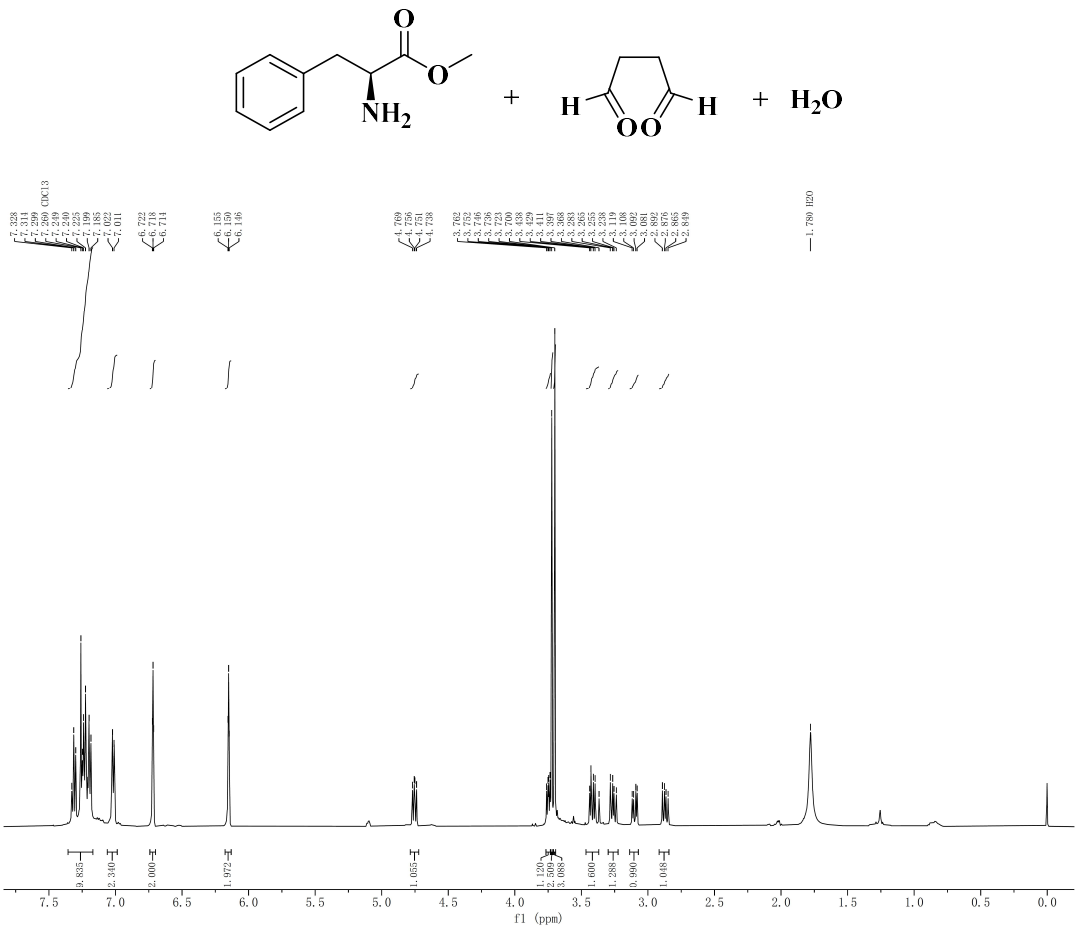
DMTHF, 0.75% CA, 90 °C, 30 min for ^{13}C NMR of crude reactants (126 MHz, $CDCl_3$)



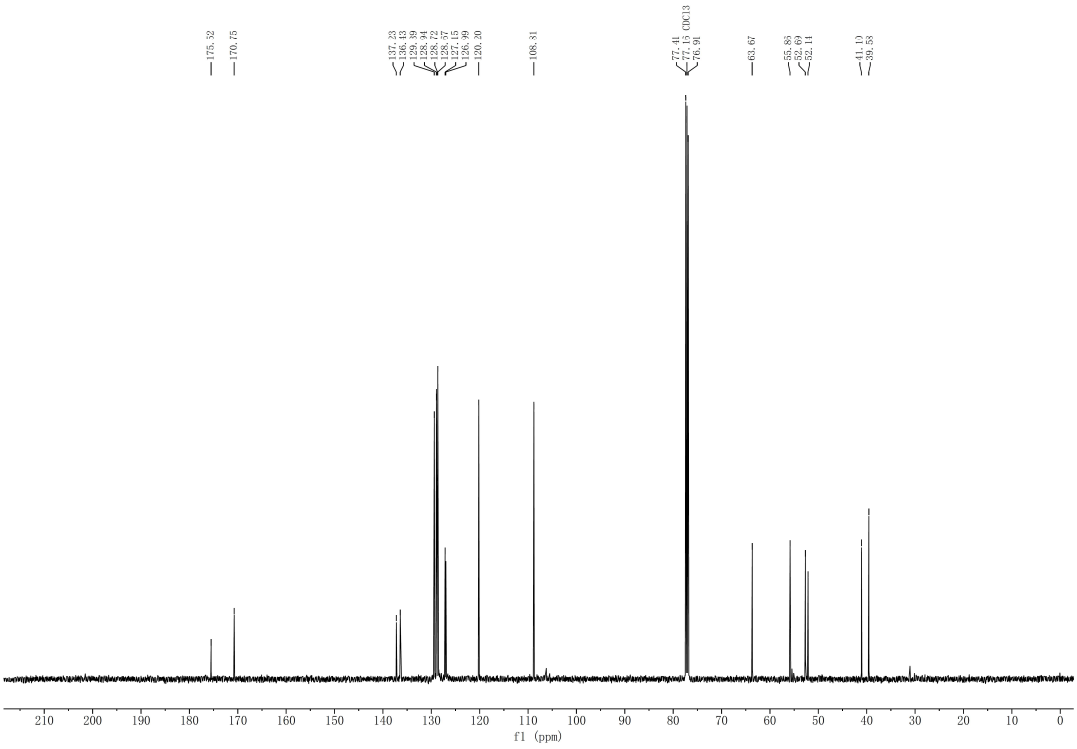
DMTHF, 10% CA, 90 °C, 2 h for ^{1}H NMR of crude reactants (500 MHz, D_2O)



DMTHF, 10% CA, 90 °C, 2 h for ^{13}C NMR of crude reactants (126 MHz, D_2O)



Succinaldehyde, 0% CA, rt, 10 h for ^{1}H NMR of crude reactants (500 MHz, $CDCl_3$)



Succinaldehyde, 0% CA, rt, 10 h for ^{13}C NMR of crude reactants (126 MHz, $CDCl_3$)