Supporting Information

Asymmetric Reduction of Aromatic α-Dehydroamino Acid Esters with Water as Hydrogen Source

Yuze Dai,[a] Jingchao Chen,[a]* Zheting Wang,[a] Ting Wang,[a] Lin Wang,[a] Yong Yang,[b] Xingfang Qiao,[b] and Baomin Fan[ab]*

[a] Key Laboratory of Chemistry in Ethnic Medicinal Resources (Yunnan Minzu University), State Ethnic Affairs Commission & Ministry of Education, Yunnan Minzu University, Kunming 650504, Yunnan, China. E-mail: chenjingchao84@163.com (J. C. Chen), adams.bmf@hotmail.com (B. M. Fan)

[b] Chongqing Key Laboratory of traditional Chinese medicine health, Chongqing Accademy of Chinese Materia Medica, Chongqing 400065, China.

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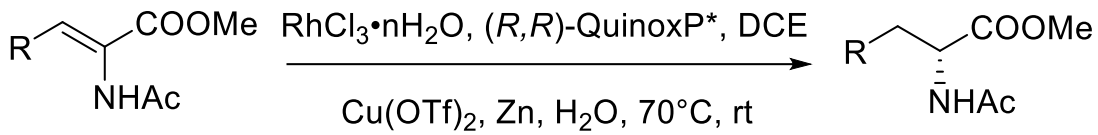
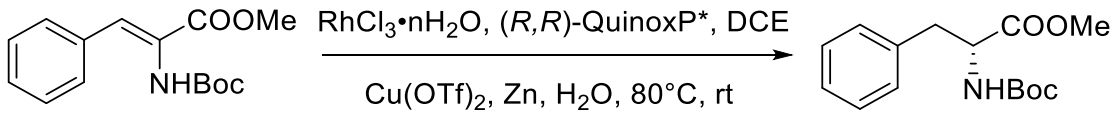
A: General Information

Unless otherwise noted, all reagents and solvents were purchased from commercial suppliers, used without further purification and the workup was carried out in air. The reactions and manipulations were performed under an atmosphere of argon by using standard Schlenk techniques and Drybox (Mikrouna, Supper 1220/750). Anhydrous DCE (Dichloroethane) was distilled from calcium hydride and stored under argon. All commercially available reagents were obtained from commercial suppliers and used without further purification. All catalytic experiments were carried out using standard techniques. Chromatography was carried out over silica gel (Innochem 200– 300 mesh) and TLC was performed using silica gel 60 F254 (Merck) plates. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker NMR spectrometer in $CDCl_3$ using TMS as an internal reference with chemical shift values reported in ppm. Abbreviations used in the NMR follow-up experiments: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. The enantioselective excesses were determined by Agilent 1260 Series HPLC using Daicel OD-H chiral columns eluted with a mixture of isopropyl alcohol and hexane or chiral GC Analysis on GC column (CP-Chirasil-V-Val for Optical Isomers 25m 0.25mm 0.12μm P/N: CP7495).

B: Procedure for the Reactions

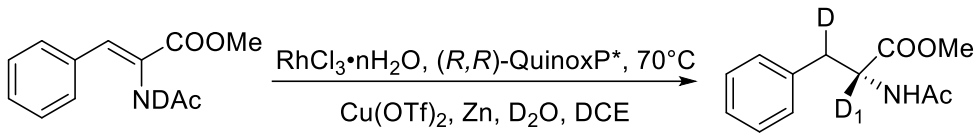


$RhCl_3 \cdot nH_2O$ (5.4 mg, 0.01 mmol), (*R*,*R*)-QuinoxP* (4.0 mg, 0.012 mmol) and 1 mL 1,2-dichloroethane were added to a Schlenk tube under argon atmosphere. The resulting solution was stirred at 1000 revolutions per minute at room temperature for 30 minutes, then $Cu(OTf)_2$ (7.3 mg, 0.02 mmol) was added and stirred for additional 10 min. Zinc powder (39 mg, 0.6 mmol) was added to the above mixture. And **1a** (43.8 mg, 0.2 mmol) in 1,2-dichloroethane (1.0 mL) was added to the above mixture. After the addition of H_2O (36 μL, 2 mmol), the mixture was stirred at 70 °C by an oil bath under argon atmosphere with TLC monitoring and liquid quality detection until the complete consumption of **1a**. The residue was purified by chromatography on a silica gel column to afford the desired product **2a** (42.4 mg, 96% yield)

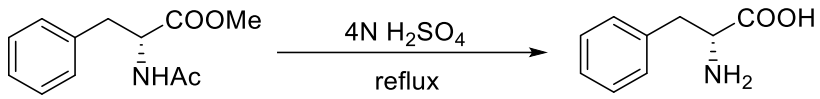


$RhCl_3 \cdot nH_2O$ (10.8 mg, 0.02 mmol), (*R*,*R*)-QuinoxP* (8.0mg, 0.024 mmol) and 1 mL 1,2-dichloroethane were added to a Schlenk tube under argon atmosphere. The resulting solution was stirred at 1000 revolutions per minute at room temperature for 30 minutes, then $Cu(OTf)_2$ (14.6 mg, 0.02 mmol) was added and stirred for additional 10 min. Zinc powder (39 mg,

0.6 mmol) was added to the above mixture. And **1l** (55.4 mg, 0.2 mmol) in 1,2-dichloroethane (1.0 mL) was added to the above mixture. After the addition of H_2O (36 μL, 2 mmol), the mixture was stirred at 70 °C by an oil bath under argon atmosphere with TLC monitoring and liquid quality detection until the complete consumption of **1l**. The residue was purified by chromatography on a silica gel column to afford the desired product **2l** (50.2 mg, 90% yield)

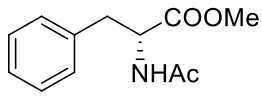


$RhCl_3 \cdot nH_2O$ (5.4 mg, 0.01 mmol), (*R*,*R*)-QuinoxP* (4.0 mg, 0.012 mmol) and 1.0 mL 1,2-dichloroethane were added to a Schlenk tube under argon atmosphere. The resulting solution was stirred at 1000 revolutions per minute at room temperature for 30 minutes, then $Cu(OTf)_2$ (7.3 mg, 0.02 mmol) was added and stirred for additional 10 min. Zinc powder (39 mg, 0.6 mmol) was added to the above mixture. And **1a'** (44 mg, 0.2 mmol) in 1,2-dichloroethane (1.0 mL) was added to the above mixture. After the addition of D_2O (40 μL, 2 mmol), the mixture was stirred at 70 ℃ by an oil bath under argon atmosphere with TLC monitoring and liquid quality detection until the complete consumption of **1a**'. The residue was purified by chromatography on a silica gel column to afford the desired product **2a'** (40 mg, 90% yield)



After **2a** (221mg) was added to the round bottom flask, 4N H_2SO_4 reflux was added and reflux by heated with an oil bath overnight, and LCMS was used to detect the reaction. After completion, the mixture was neutralized to PH 5.5 with 4 N NaOH and concentrated. After adding concentrated NaOH, the slurry was stirred for a while and filtrated. Then the filtrate was concentrated to afford **3a** with 85% yield (140.2 mg) and retained *ee* (determined by the **2a**).

C: Characterization Data of Products

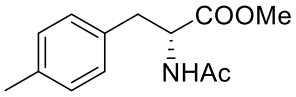


2a

(*R*)-2-Acetamido-3-phenylpropionic acid methyl ester (2a)[1]

White solid. Purified by silica gel column chromatography (ethyl acetate/petroleum ether, 1/2), 42.4 mg, 96% yield, 91% *ee*, $[\alpha]_D^{20} = -100$ (c 1.1, CH_3OH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (d, J = 7.8 Hz, 1H), 7.24 (dd, J = 25.2, 7.1 Hz, 5H), 4.43 (dt, J = 9.7, 5.0 Hz, 1H), 3.58 (s, 3H), 2.93 (ddd, J = 57.1, 13.9, 7.6 Hz, 2H), 1.78 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 172.27, 169.38, 137.30, 129.05, 128.29, 126.58, 53.66, 51.83, 36.74, 22.26. The *ee* of **2a** was determined by HPLC analysis using a Daicel Chiralcel OD-H column (25 cm × 0.46 cm ID), conditions: n-hexane/i-PrOH = 90/10, 1.0 mL/min, 220 nm; t_{major} = 12.0 min, t_{minor} = 16.4

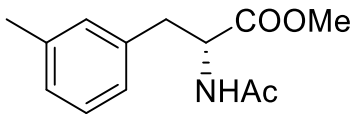
min.



2b

Methyl (*R*)-2-acetamido-3-(*p*-tolyl) propanoate (2b)[2]

White solid. Purified by silica gel column chromatography (ethyl acetate/petroleum ether, 1/2), 45.1 mg, 96% yield, 91% *ee*, $[\alpha]_D^{20}$ = −82 (c 1.0, CH_3OH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (d, *J* = 7.7 Hz, 1H), 7.09 (s, 4H), 4.40 (ddd, *J* = 9.3, 7.7, 5.5 Hz, 1H), 3.59 (s, 3H), 2.95 (dd, *J* = 13.7, 5.6 Hz, 1H), 2.81 (dd, *J* = 13.7, 9.3 Hz, 1H), 2.25 (s, 3H), 1.79 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 172.3, 169.4, 135.6, 134.2, 128.9, 128.9, 53.8, 51.8, 36.4, 22.3, 20.7. The *ee* of **2b** was determined by GC analysis using a Agilent J&W GC column (CP-Chirasil-V-Val for Optical Isomers 25m 0.25mm 0.12μm P/N: CP7495), conditions: t_{major} = 19.0 min, t_{minor} = 19.9 min.

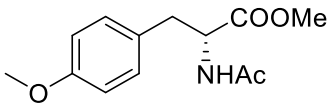


2c

Methyl (*R*)-2-acetamido-3-(m-tolyl) propanoate (2c)[3]

White solid. Purified by silica gel column chromatography (ethyl acetate/petroleum ether, 1/2), 45.2 mg, 96% yield, 95% *ee*, $[\alpha]_D^{20}$ = −95 (c 0.9, CH_3OH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.32 (d, *J* = 7.7 Hz, 1H), 7.39 – 6.71 (m, 4H), 4.43 (ddd, *J* = 9.2, 7.7, 5.6 Hz, 1H), 3.59 (s, 3H), 2.96 (dd, *J* = 13.7, 5.7 Hz, 1H), 2.83 (dd, *J* = 13.7, 9.2 Hz, 1H), 2.27 (s, 3H),

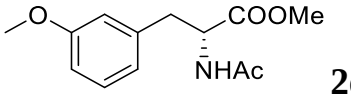
1.80 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) δ 172.2, 169.3, 137.2, 137.2, 129.6, 128.1, 127.2, 126.0, 53.7, 51.7, 36.7, 22.2, 20.9. The *ee* of **2c** was determined by GC analysis using a Agilent J&W GC column (CP-Chirasil-V-Val for Optical Isomers 25m 0.25mm 0.12μm P/N: CP7495), conditions: t_{major} = 20.4 min, t_{minor} = 21.6 min.



2d

Methyl (*R*)-2-acetamido-3-(4-methoxyphenyl) propanoate (2d)[4]

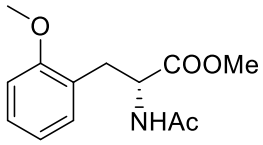
White solid. Purified by silica gel column chromatography (ethyl acetate/petroleum ether, 1/2), 45.7 mg, 91% yield, 96% *ee*, $[\alpha]_D^{20}$ = −95 (c 1.1, CH_3OH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 (d, *J* = 7.7 Hz, 1H), 7.21 (ddd, *J* = 8.2, 7.4, 1.8 Hz, 1H), 7.10 (dd, *J* = 7.4, 1.8 Hz, 1H), 6.95 (dd, *J* = 8.3, 1.1 Hz, 1H), 6.85 (td, *J* = 7.4, 1.1 Hz, 1H), 3.78 (s, 3H), 3.55 (s, 3H), 1.77 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) δ 172.5, 169.3, 157.3, 130.6, 128.2, 124.9, 120.1, 110.6, 55.3, 52.0, 51.6, 31.9, 22.2. The *ee* of **2d** was determined by GC analysis using a Agilent J&W GC column (CP-Chirasil-V-Val for Optical Isomers 25m 0.25mm 0.12μm P/N: CP7495), conditions: t_{major} = 24.9 min, t_{minor} = 25.8 min.



2e

(*R*)-Methyl 2-acetylamino-3-(3-methoxyphenyl) propanoate (2e)[4]

White solid. Purified by silica gel column chromatography (ethyl acetate/petroleum ether, 1/2), 49.2 mg, 90% yield, 98% *ee*, $[\alpha]_D^{20}$ = −97 (c 1.3, CH_3OH). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.33 (d, *J* = 7.8 Hz, 1H), 7.19 (td, *J* = 7.5, 1.0 Hz, 1H), 6.78 (dt, *J* = 9.0, 1.4 Hz, 3H), 4.44 (ddd, *J* = 9.4, 7.7, 5.4 Hz, 1H), 3.72 (s, 3H), 3.60 (s, 3H), 2.98 (dd, *J* = 13.7, 5.5 Hz, 1H), 2.84 (dd, *J* = 13.7, 9.4 Hz, 1H), 1.79 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 172.2, 169.4, 159.2, 138.8, 129.3, 121.2, 114.7, 112.1, 54.9, 53.6, 51.9, 36.7, 22.2. The *ee* of **2e** was determined by GC analysis using a Agilent J&W GC column (CP-Chirasil-V-Val for Optical Isomers 25m 0.25mm 0.12μm P/N: CP7495), conditions: t_{major} = 20.4 min, t_{minor} = 21.6 min.

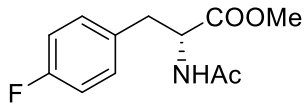


2f

Methyl (*R*)-2-acetamido-3-(2-methoxyphenyl) propanoate (2f) [4]

White solid. Purified by silica gel column chromatography (ethyl acetate/petroleum ether, 1/2), 46.2 mg, 92% yield, 92% *ee*, $[\alpha]_D^{20}$ = −113 (c 1.2, CH_3OH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 (d, *J* = 7.7 Hz, 1H), 7.21 (ddd, *J* = 8.2, 7.4, 1.8 Hz, 1H), 7.10 (dd, *J* = 7.4, 1.8 Hz, 1H), 6.95 (dd, *J* = 8.3, 1.1 Hz, 1H), 6.85 (td, *J* = 7.4, 1.1 Hz, 1H), 3.78 (s, 3H), 3.55 (s, 3H), 1.77 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 172.5, 169.3, 157.3, 130.6, 128.2, 124.9, 120.1, 110.6, 55.3, 52.0, 51.6, 31.9, 22.2. The

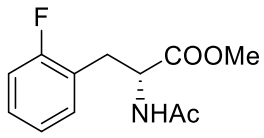
ee of **2f** was determined by GC analysis using a Agilent J&W GC column (CP-Chirasil-V-Val for Optical Isomers 25m 0.25mm 0.12μm P/N: CP7495), conditions: t_{major} = 23.3 min, t_{minor} = 23.7 min.



2g

Methyl (*R*)-2-acetamido-3-(4-fluorophenyl) propanoate (2g) [4]

White solid. Purified by silica gel column chromatography (ethyl acetate/petroleum ether, 1/2), 45.4 mg, 95% yield, 75% *ee*, $[\alpha]_D^{20}$ = −108 (c 1.3, CH_3OH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.34 (d, *J* = 7.8 Hz, 1H), 7.29 – 7.04 (m, 4H), 3.59 (s, 3H), 2.89 – 2.78 (m, 1H), 1.79 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 172.1, 169.2, 162.3, 159.9, 133.4 (d, *J* = 3.1 Hz), 130.9 (d, *J* = 8.1 Hz), 115.0, 114.8, 53.6, 51.8, 35.9, 22.2. The *ee* of **2g** was determined by GC analysis using a Agilent J&W GC column (CP-Chirasil-V-Val for Optical Isomers 25m 0.25mm 0.12μm P/N: CP7495), conditions: t_{major} = 16.3 min, t_{minor} = 17.3 min.

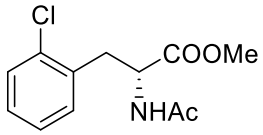


2h

Methyl (*R*)-2-acetamido-3-(2-fluorophenyl) propanoate (2h)[5]

White solid. Purified by silica gel column chromatography (ethyl acetate/petroleum ether, 1/2), 44.9 mg, 94% yield, 93% *ee*, $[\alpha]_D^{20}$ = −120 (c 1.1, CH_3OH). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.25 – 7.16 (m, 1H), 7.16 – 6.93 (m, 3H), 6.14 (d, *J* = 7.9 Hz, 1H), 4.85 (dt, *J* = 7.8, 6.0 Hz, 1H),

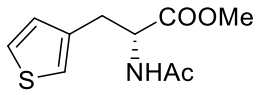
3.71 (d, J = 1.0 Hz, 3H), 3.19 (dd, J = 13.9, 5.9 Hz, 1H), 3.10 (dd, J = 14.0, 6.2 Hz, 1H), 1.95 (d, J = 0.9 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-d) δ 172.09, 169.86, 162.65, 160.21, 131.73 (d, J = 4.5 Hz), 129.12 (d, J = 8.1 Hz), 124.28 (d, J = 3.6 Hz), 123.08 (d, J = 15.9 Hz), 115.45 (d, J = 22.3 Hz), 52.54 (d, J = 2.4 Hz), 31.47 (d, J = 1.5 Hz), 23.09. The *ee* of **2h** was determined by GC analysis using a Agilent J&W GC column (CP-Chirasil-V-Val for Optical Isomers 25m 0.25mm 0.12μm P/N: CP7495), conditions: t_{major} = 22.2 min, t_{minor} = 23.2 min.



2i

methyl (*R*)-2-acetamido-3-(2-chlorophenyl) propanoate (2i)[2]

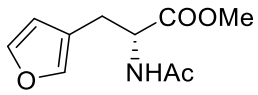
White solid. Purified by silica gel column chromatography (ethyl acetate/petroleum ether, 1/2), 48.9 mg, 96% yield, 91% *ee*, $[\alpha]_D^{20}$ = −119 (c 1.0, CH_3OH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (d, J = 7.9 Hz, 1H), 7.39 – 7.25 (m, 3H), 7.23 – 7.12 (m, 1H), 4.46 (ddd, J = 9.6, 7.8, 5.4 Hz, 1H), 3.60 (s, 3H), 3.03 (dd, J = 13.7, 5.4 Hz, 1H), 2.86 (dd, J = 13.8, 9.6 Hz, 1H), 1.78 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) δ 172.0, 169.4, 139.9, 132.8, 130.1, 129.0, 127.8, 126.6, 53.3, 51.9, 36.2, 22.2. The *ee* of **2i** was determined by GC analysis using a Agilent J&W GC column (CP-Chirasil-V-Val for Optical Isomers 25m 0.25mm 0.12μm P/N: CP7495), conditions: t_{major} = 27.3 min, t_{minor} = 28.2 min.



2j

(*R*)-(*R*)-Methyl 2-acetylamino-3-(2-thienyl) propanoate (2j) [6]

White solid. Purified by silica gel column chromatography (ethyl acetate/petroleum ether, 1/2), 42.2 mg, 94% yield, 93% *ee*, $[\alpha]_D^{20}$ = −93 (c 0.9, CH_3OH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90 (d, *J* = 7.7 Hz, 1H), 7.02 (dd, *J* = 4.9, 3.0 Hz, 1H), 6.80 (dd, *J* = 2.9, 1.2 Hz, 1H), 6.57 (dd, *J* = 4.9, 1.3 Hz, 1H), 4.02 (ddd, *J* = 9.1, 7.7, 5.5 Hz, 1H), 2.65 – 2.56 (m, 1H), 2.49 (dd, *J* = 14.4, 9.1 Hz, 1H), 1.39 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 172.1, 169.3, 137.4, 128.5, 125.8, 122.4, 53.0, 51.8, 31.3, 22.2. The *ee* of **2j** was determined by GC analysis using a Agilent J&W GC column (CP-Chirasil-V-Val for Optical Isomers 25m 0.25mm 0.12μm P/N: CP7495), conditions: t_{major} = 19.3 min, t_{minor} = 20.0 min.

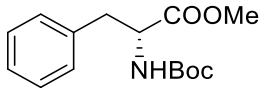


2k

methyl (*R*)-2-acetamido-3-(furan-3-yl) propanoate (2k) [6]

White solid. Purified by silica gel column chromatography (ethyl acetate/petroleum ether, 1/2), 39.2 mg, 93% yield, 98% *ee*, $[\alpha]_D^{20}$ = −101 (c 1.1, CH_3OH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 (d, *J* = 7.9 Hz, 1H), 7.35 (dd, *J* = 5.1, 1.3 Hz, 1H), 7.23 – 6.73 (m, 2H), 4.46 (ddd, *J* = 8.9, 7.9, 5.3 Hz, 1H), 3.62 (s, 3H), 3.26 (ddd, *J* = 14.9, 5.2, 0.8 Hz, 1H), 3.12 (ddd, *J* = 14.8, 8.9, 0.9 Hz, 1H), 1.84 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 171.6, 169.4, 139.0, 126.9, 126.4, 124.8, 53.6, 52.0, 31.0, 22.3. The

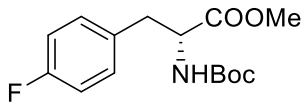
ee of **2k** was determined by GC analysis using a Agilent J&W GC column (CP-Chirasil-V-Val for Optical Isomers 25m 0.25mm 0.12μm P/N: CP7495), conditions: t_{major} = 13.9 min, t_{minor} = 15.0 min.



2l

(*R*)-2-*tert*-Butoxycarbonylamino-3-phenylpropanoic acid methyl ester (2l) [6]

White solid. Purified by silica gel column chromatography (ethyl acetate/petroleum ether, 1/2), 50.2 mg, 90% yield, 96% *ee*, $[\alpha]_D^{20}$ = −91 (c 1.3, CH_3OH). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.33 – 7.24 (m, 1H), 7.15 – 7.08 (m, 1H), 4.97 (d, *J* = 8.3 Hz, 0H), 4.58 (q, *J* = 7.1, 6.6 Hz, 0H), 3.70 (s, 3H), 3.07 (qd, *J* = 13.9, 6.0 Hz, 2H), 1.41 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 172.5, 155.2, 136.2, 129.4, 128.7, 127.2 80.1, 54.6, 52.3, 38.51, 28.4. The *ee* of **2l** was determined by HPLC analysis using a Daicel Chiralcel OJ-H column (25 cm × 0.46 cm ID), conditions: n-hexane/i-PrOH = 97/3, 1.0 mL/min, 220 nm; t_{major} = 10.2 min, t_{minor} = 12.2 min.

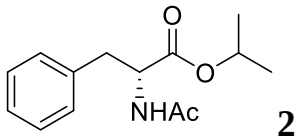


2m

***N*-[(1,1-dimethylethoxy)carbonyl]-4-fluoro-D-phenylalanine methyl ester (2m)**[6]

White solid. Purified by silica gel column chromatography (ethyl acetate/petroleum ether, 1/2), 49.3 mg, 83% yield, 95% *ee*, $[\alpha]_D^{20}$ = −103

(c 1.3, CH_3OH). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.12 – 7.04 (m, 2H), 7.02 – 6.92 (m, 2H), 5.00 (d, *J* = 8.3 Hz, 1H), 4.55 (q, *J* = 6.5 Hz, 1H), 3.70 (s, 3H), 3.09 (dd, *J* = 13.9, 5.8 Hz, 1H), 3.00 (dd, *J* = 14.0, 6.2 Hz, 1H), 1.41 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-d) δ 172.18, 163.22, 160.78, 155.02, 131.78 (d, *J* = 3.3 Hz), 130.78 (d, *J* = 8.0 Hz), 115.37 (d, *J* = 21.3 Hz), 80.00, 54.44, 52.23, 37.63, 28.26. The *ee* of **2m** was determined by HPLC analysis using a Daicel Chiralcel OD-H column (25 cm × 0.46 cm ID), conditions: n-hexane/i-PrOH = 90/10, 1.0 mL/min, 220 nm; t_{major} = 7.9 min, t_{minor} = 8.9 min.

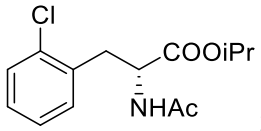


2n

Isopropyl (*R*)-α-acetylamido-3-phenylpropanoate (2n) [9]

White solid. Purified by silica gel column chromatography (ethyl acetate/petroleum ether, 1/2), 45.3 mg, 91% yield, 93% *ee*, $[\alpha]_D^{20}$ = −121 (c 1.3, CH_3OH). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.35 – 7.17 (m, 3H), 7.16 – 7.08 (m, 2H), 6.12 (d, *J* = 7.9 Hz, 1H), 5.00 (p, *J* = 6.3 Hz, 1H), 4.83 (dt, *J* = 7.9, 6.0 Hz, 1H), 3.10 (dd, *J* = 6.0, 4.2 Hz, 2H), 1.98 (s, 3H), 1.21 (dd, *J* = 11.3, 6.3 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-d) δ 171.33, 169.72, 136.05, 129.45, 128.51, 127.09, 69.44, 53.30, 37.99, 23.19, 21.82, 21.73. The *ee* of **2n** was determined by GC analysis using a Agilent J&W GC column (CP-Chirasil-V-Val for Optical Isomers 25m 0.25mm

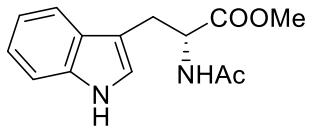
0.12μm P/N: CP7495), conditions: t_{major} = 21.0 min, t_{minor} = 21.9 min.



2o

Isopropyl (*R*)-2-acetamido-3-(2-chlorophenyl)propanoate (2o) [6]

White solid. Purified by silica gel column chromatography (ethyl acetate/petroleum ether, 1/2), 50.9 mg, 90% yield, 92% *ee*, $[\alpha]_D^{20}$ = −133 (c 1.3, CH_3OH). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.24 – 7.14 (m, 2H), 7.10 (d, *J* = 1.3 Hz, 1H), 7.00 (ddd, *J* = 5.1, 3.8, 1.7 Hz, 1H), 6.19 (d, *J* = 7.6 Hz, 1H), 4.99 (p, *J* = 6.3 Hz, 1H), 4.78 (dt, *J* = 7.7, 5.9 Hz, 1H), 3.05 (t, *J* = 6.0 Hz, 2H), 1.97 (s, 3H), 1.20 (dd, *J* = 7.9, 6.3 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-d) δ 171.05, 169.74, 138.24, 134.25, 129.75, 129.67, 127.63, 127.26, 69.74, 53.24, 37.69, 23.17, 21.82, 21.73. The *ee* of **2o** was determined by GC analysis using a Agilent J&W GC column (CP-Chirasil-V-Val for Optical Isomers 25m 0.25mm 0.12μm P/N: CP7495), conditions: t_{major} = 20.5 min, t_{minor} = 21.5 min.

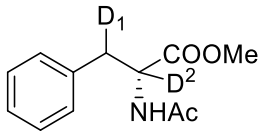


2p

Methyl *L*-N-acetyltryptophanate(2p) [7]

White solid. Purified by silica gel column chromatography (ethyl acetate/petroleum ether, 1/2), 46.8 mg, 90% yield, 99% *ee*, $[\alpha]_D^{20}$ = −100 (c 0.9, CH_3OH). ^{1}H NMR (400 MHz, DMSO-d6) δ 10.89 – 10.85 (m, 1H),

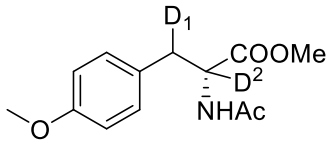
8.32 (d, *J* = 7.5 Hz, 1H), 7.49 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.35 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.03 (dddd, *J* = 32.1, 8.0, 7.0, 1.1 Hz, 2H), 4.51 (td, *J* = 8.1, 5.8 Hz, 1H), 3.58 (s, 3H), 3.19 – 3.10 (m, 1H), 3.03 (dd, *J* = 14.4, 8.2 Hz, 1H), 1.82 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d6) δ 172.57, 169.37, 136.12, 127.09, 123.63, 120.98, 118.42, 117.98, 111.45, 109.53, 53.16, 51.75, 27.13, 22.31. The *ee* of **2p** was determined by HPLC analysis using a Daicel Chiralcel AS-H column (25 cm × 0.46 cm ID), conditions: n-hexane/i-PrOH = 70/30, 1.0 mL/min, 220 nm; t_{minor} = 13.3 min, t_{major} = 15.8.



2a'

Methyl(3*R*)-[2,3-2D]-*N*-acetyl-phenylalaninate (2a')[9]

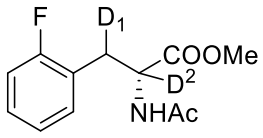
White solid. Purified by silica gel column chromatography (ethyl acetate/petroleum ether, 1/2), 41.1 mg, 93% yield, 91% *ee*, $[\alpha]_D^{20}$ = −103 (c 1.1, CH_3OH). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.38 – 7.19 (m, 3H), 7.14 – 7.07 (m, 2H), 6.13 (d, *J* = 5.1 Hz, 1H), 4.88 (dd, *J* = 7.8, 5.8 Hz, 0.1H), 3.72 (s, 3H), 3.09 (d, *J* = 24.2 Hz, 1.08H), 1.98 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*) δ 172.2, 169.8, 135.9, 129.3, 128.7, 127.2, 52.4, 23.2. The *ee* of **2a'** was determined by GC analysis using a Agilent J&W GC column (CP-Chirasil-V-Val for Optical Isomers 25m 0.25mm 0.12μm P/N: CP7495), conditions: t_{major} = 15.9 min, t_{minor} = 16.7 min.



2d'

Methyl 2-acetamido-3-(4-methoxyphenyl)propanoate-2,3-d_2 (2d')

White solid. Purified by silica gel column chromatography (ethyl acetate/petroleum ether, 1/2), 45.1 mg, 90% yield, 96% *ee*, $[\alpha]_D^{20}$ = −99 (c 1.1, CH_3OH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.33 (s, 1H), 7.12 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 4.37 (dd, *J* = 9.3, 7.7 Hz, 0.09H), 3.71 (s, 3H), 3.58 (s, 3H), 2.92 (d, *J* = 13.8 Hz, 0.1H), 2.77 (s, 1H), 1.79 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 172.25, 169.31, 157.97, 130.01, 129.05, 113.65, 54.93, 53.85, 51.71, 35.94, 22.21. HRMS (ESI$^+$): m/z calculated for $C_{13}H_{15}D_2NO_4$ [M]$^+$: 254.1351. Found 254.1356. The *ee* of **2d'** was determined by GC analysis using a Agilent J&W GC column (CP-Chirasil-V-Val for Optical Isomers 25m 0.25mm 0.12μm P/N: CP7495), conditions: t_{major} = 24.9 min, t_{minor} = 25.8 min.

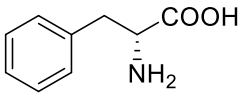


2h'

Methyl 2-acetamido-3-(2-fluorophenyl) propanoate-2,3-d2 (2h')

White solid. Purified by silica gel column chromatography (ethyl acetate/petroleum ether, 1/2), 44.5 mg, 93% yield,93% *ee*, $[\alpha]_D^{20}$ = −125 (c 1.1, CH_3OH). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.32 – 7.17 (m, 1H), 7.19 – 6.96 (m, 3H), 6.11 (s, 1H), 4.84 (dd, *J* = 7.9, 6.1 Hz, 0.1H), 3.72 (s, 3H), 3.30 (d, *J* = 13.7 Hz, 0.07H), 3.13 (d, *J* = 34.1 Hz, 1H), 1.96 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-d) δ 172.09, 169.86, 162.65, 160.21, 131.73 (d, *J* = 4.5 Hz), 129.12 (d, *J* = 8.1 Hz), 124.28 (d, *J* = 3.6 Hz),

123.08 (d, J = 15.9 Hz), 115.45 (d, J = 22.3 Hz), 52.54 (d, J = 2.4 Hz), 31.47 (d, J = 1.5 Hz), 23.09. HRMS (ESI^+): m/z calculated for $C_{12}H_{12}D_2FNO_3$ $[M]^+$: 242.1157. Found 242.1156. The *ee* of **2h**' was determined by GC analysis using a Agilent J&W GC column (CP-Chirasil-V-Val for Optical Isomers 25m 0.25mm 0.12μm P/N: CP7495), conditions: t_{major} = 22.2 min, t_{minor} = 23.2 min.



3a

***D*-Phenylalanine (3a)[1]**

White solid, $[\alpha]_D^{20}$ = (+20 (c 1.1, H_2O) ^1H NMR (400 MHz, Deuterium Oxide) δ 7.41 – 7.23 (m, 5H), 3.93 (dd, J = 7.9, 5.1 Hz, 1H), 3.25 (s, 1H), 3.06 (dd, J = 14.5, 8.0 Hz, 1H), 2.89 – 2.81 (m, 1H), 1.70 (dtd, J = 10.8, 8.1, 5.3 Hz, 1H), 0.59 – 0.55 (m, 1H).

D: Reference

[1] Hu, Y.; Chen, J.; Li, B.; Zhang, Z.; Gridnev, I. D.; Zhang, W. *Angew. Chem. Int. Ed* **2020**, 59, 5371.

[2] Luo, Y.; Ouyang, G.; Tang, Y.; He, Y. M.; Fan, Q. H. *J Org Chem.* **2020**, 85, 8176.

[3] Jia, J.; Ling, Z.; Zhang, Z.; Tamura, K.; Gridnev, I. D.; Imamoto, T.; Zhang, W. *Advanced Synthesis & Catalysis* **2018**, 360, 738.

[4] Hong, J.; Wenqiang, Z.; Xing K.; Ziping, C.; Xu, C.; Yan, L.; Yong, C. *J. Am. Chem. Soc*. **2020**, 142, 9642.

[5] Zhang, C.; Hu, H.; Chen, F.; Fang, Q.; Yang, Y.; Lu, B.; Xie, J.; Wu, J.; Li, S.; Fang, W. *Chem Sci.* **2016**, 7, 4594.

[6] Navarre, L.; Martinez, R.; Genet, J.-P.; Darses, S. *J. Am. Chem. Soc.* **2008**, 130, 6159.

[7] Angelini, E.; Balsamini, C.; Bartoccini, F.; Lucarini, S.; Piersanti, G. *J Org Chem.* **2008**, 73, 5654.

[8] Amir-Heidari, B.; Thirlway, J.; Micklefield, J. *Org. Lett.* **2007**, 9, 1513.

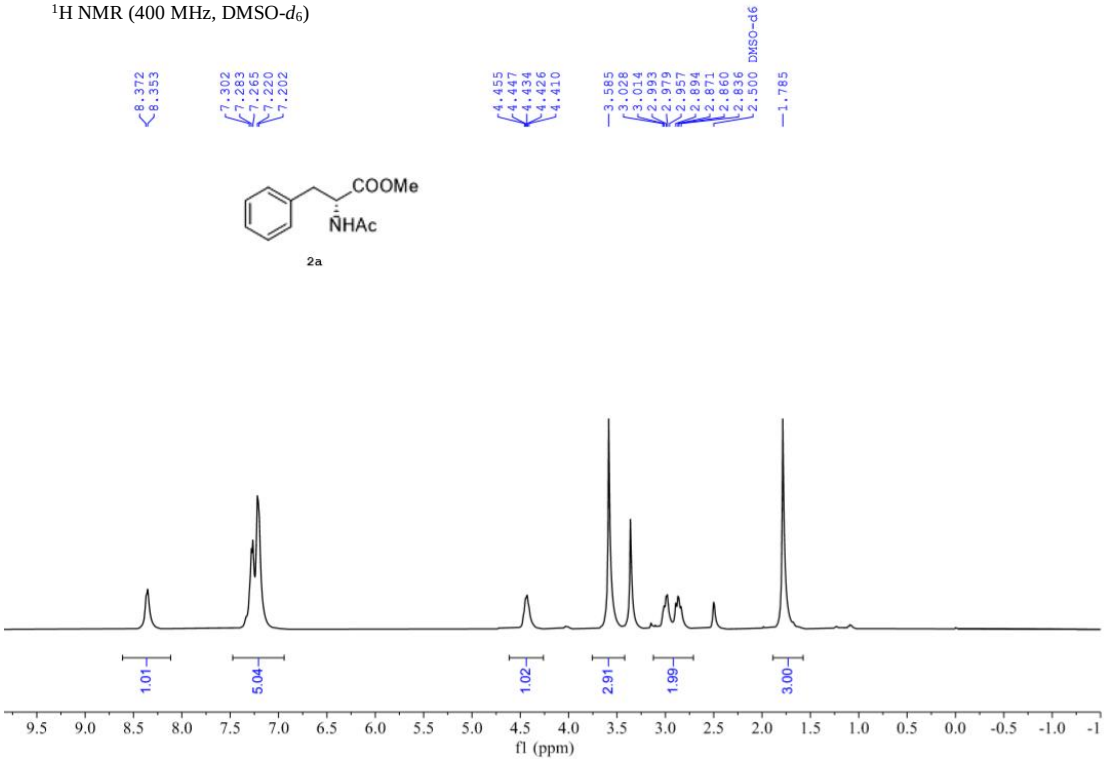
[9] Yang, P.; Xu, H.; Zhou, J. S. *Angew. Chem. Int. Ed.* **2014**, 53, 12210.

[10] Oki, H.; Oura, I.; Nakamura, T.; Ogata, K.; Fukuzawa, S.-i. Tetrahedron:

Asymmetry 2009, 20, 2185.

E: NMR Spectra of Products

^{1}H NMR (400 MHz, DMSO-d_6)



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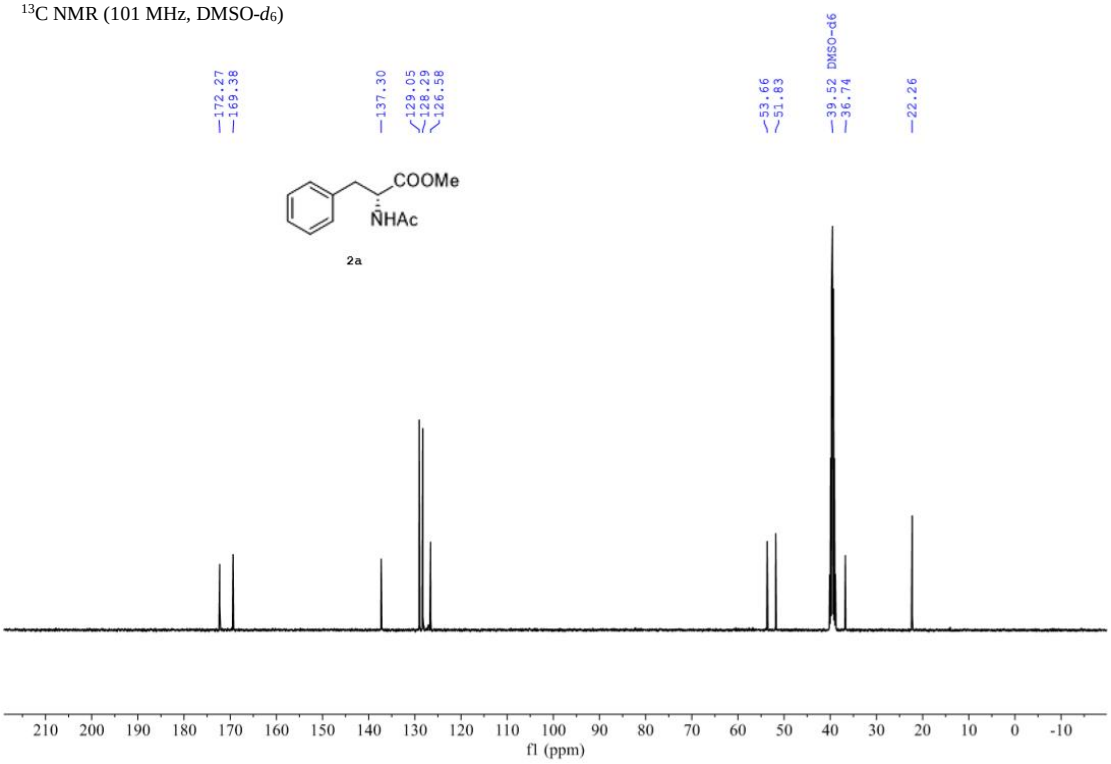

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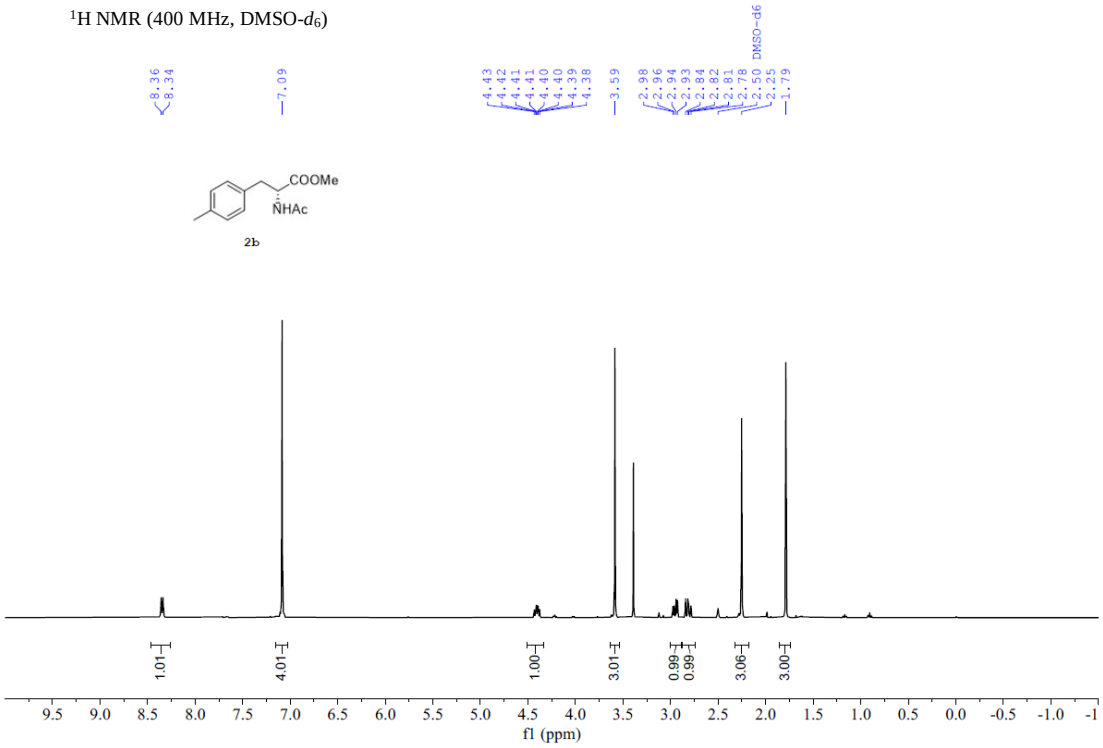

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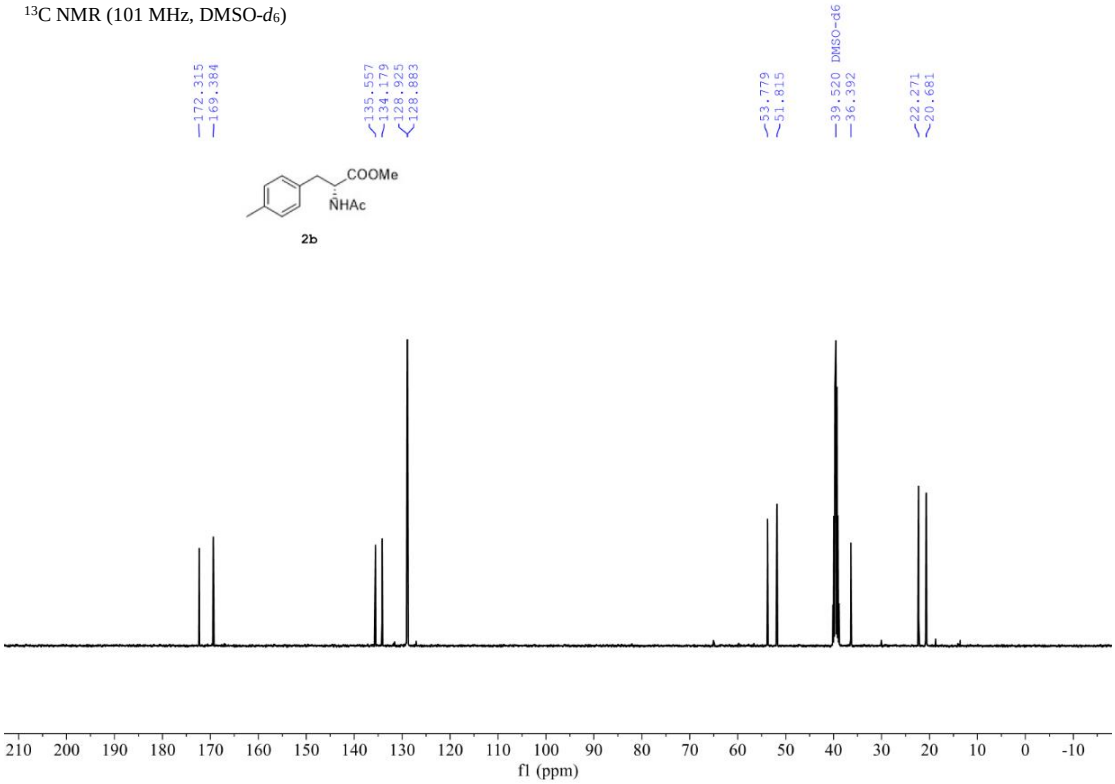

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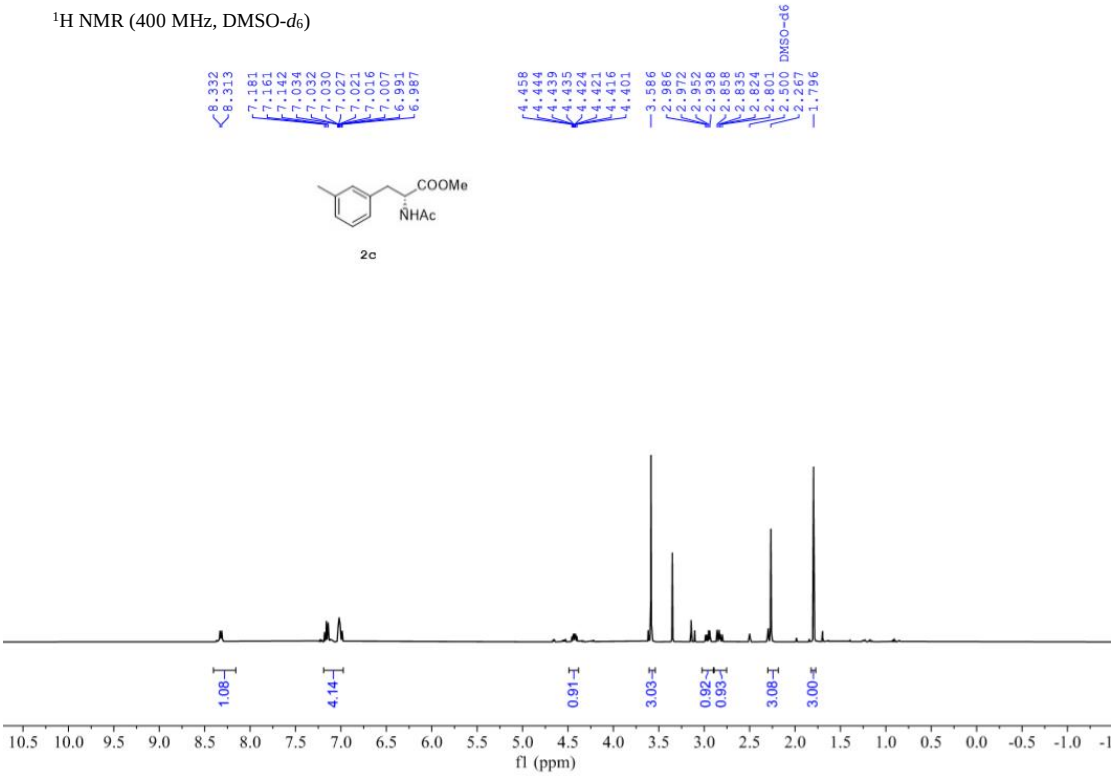

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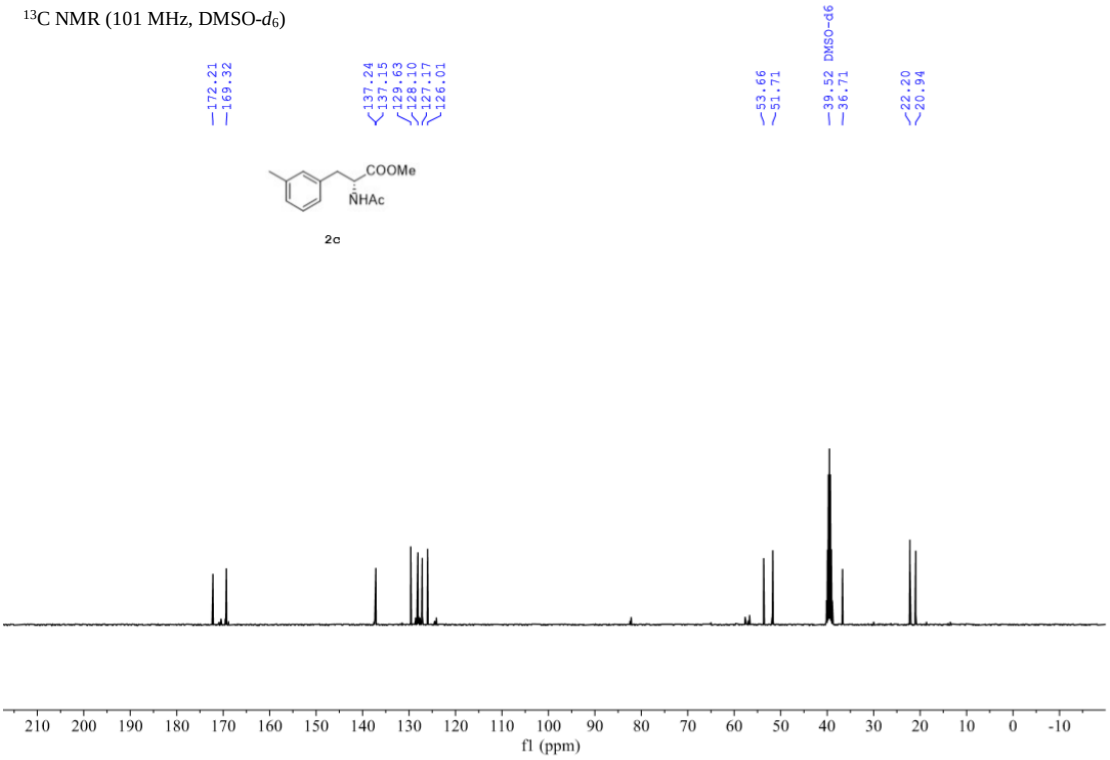

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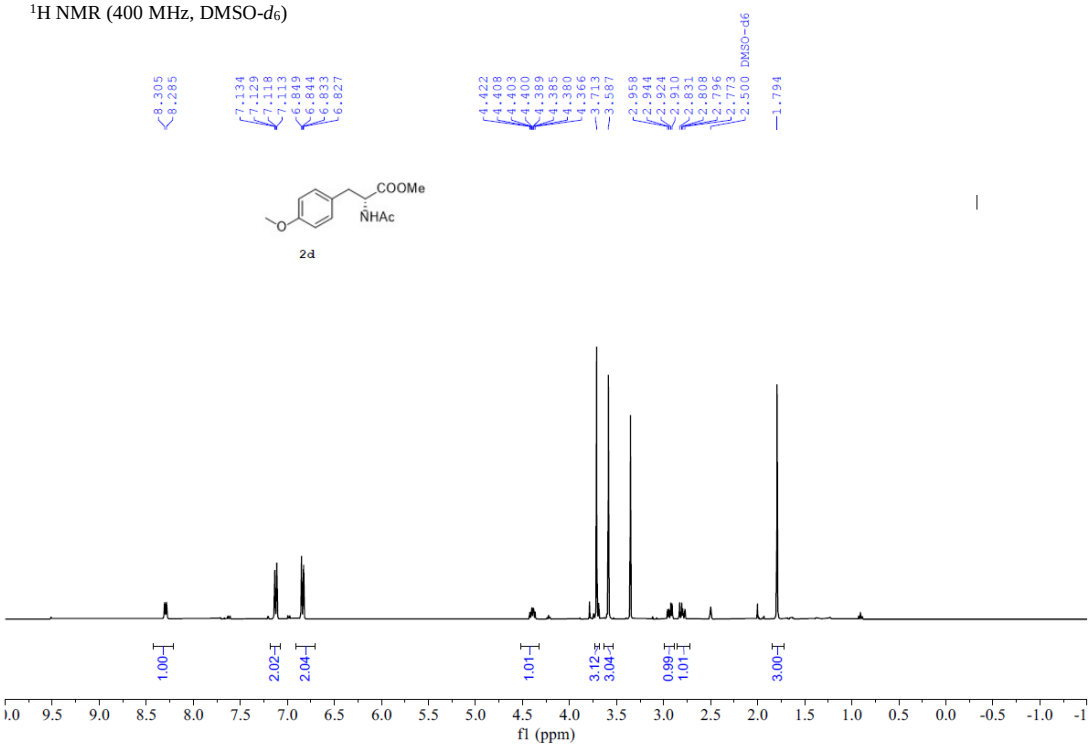

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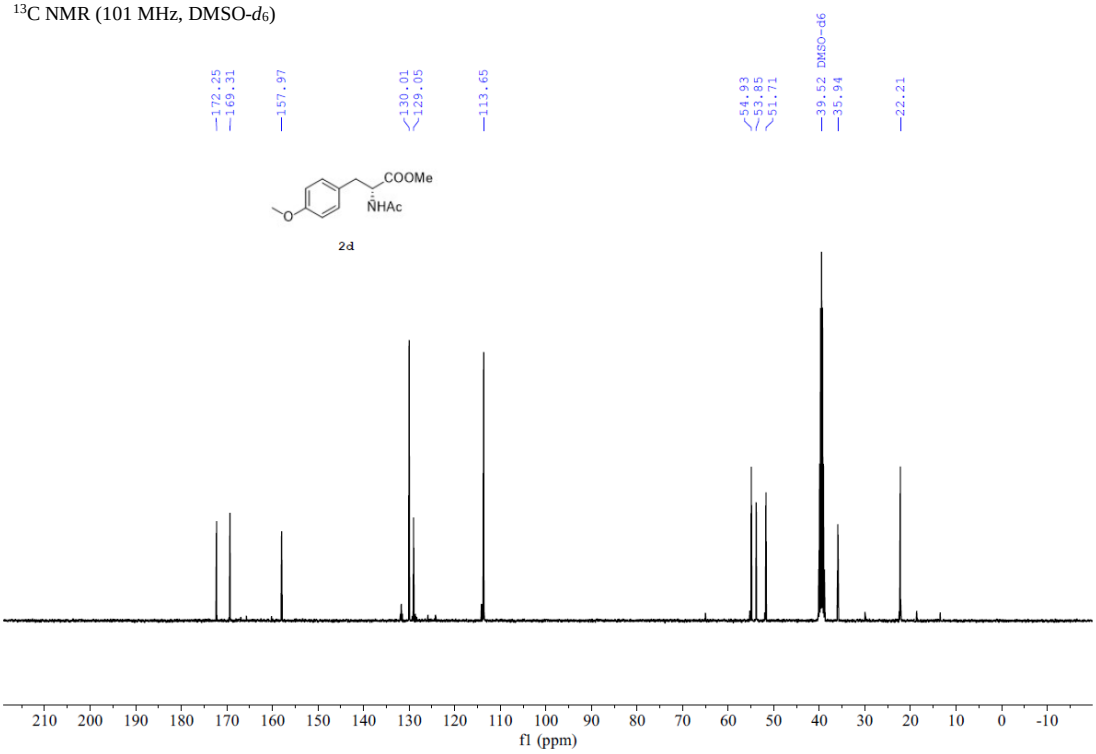

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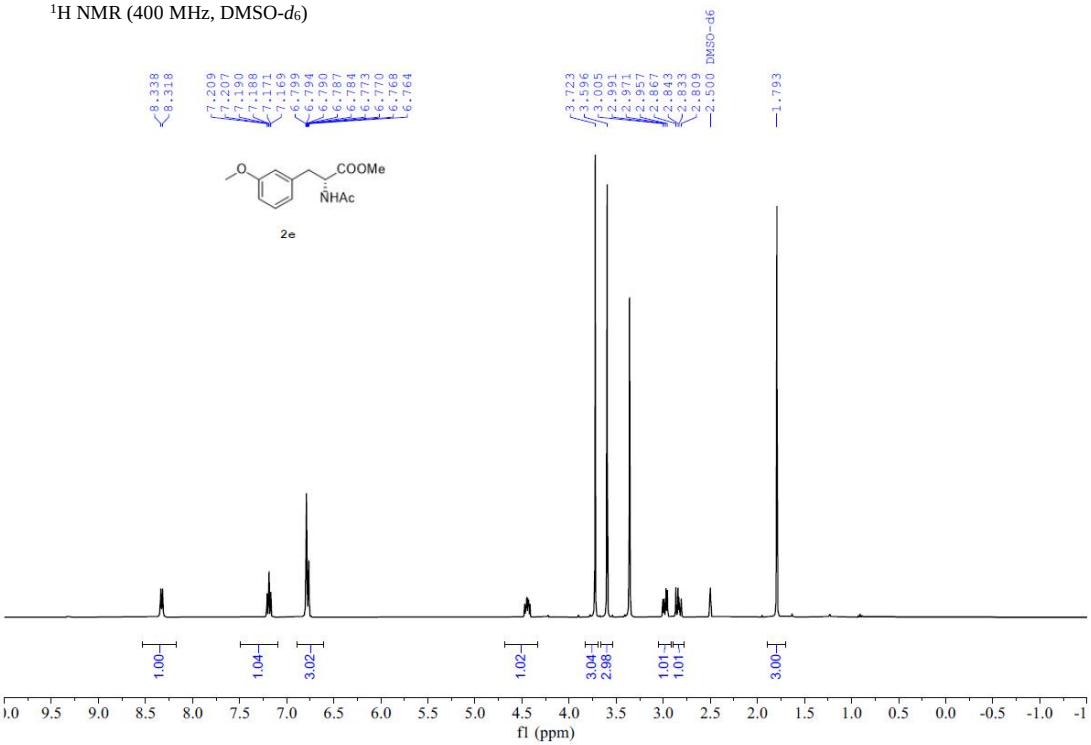

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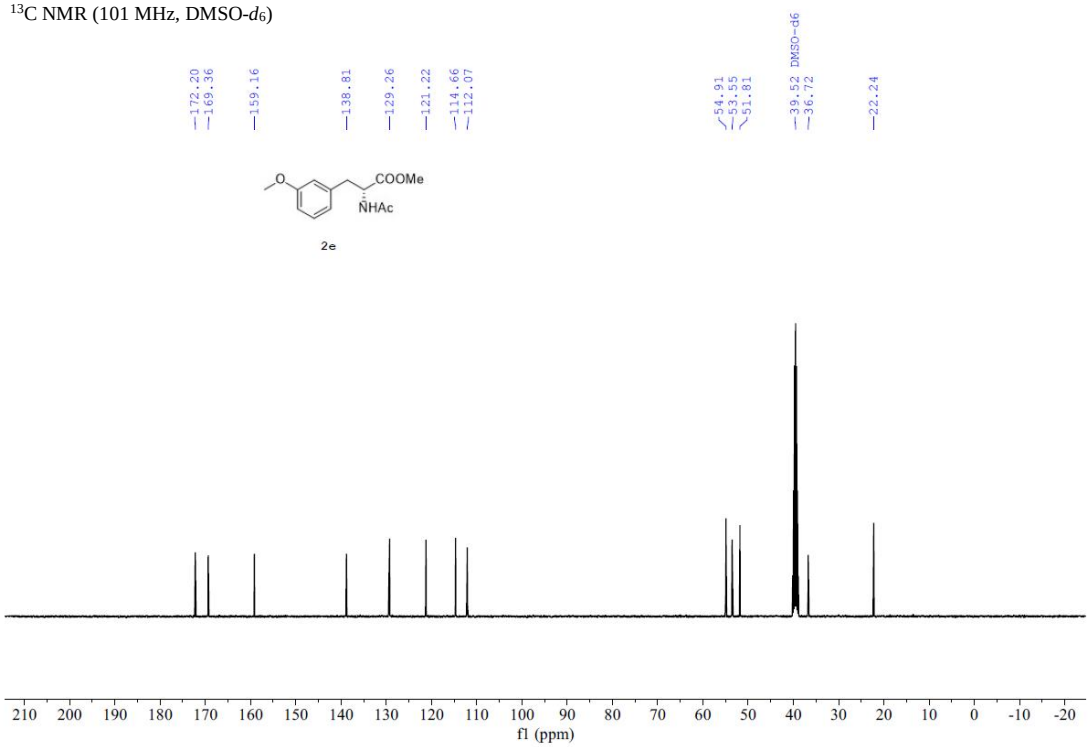

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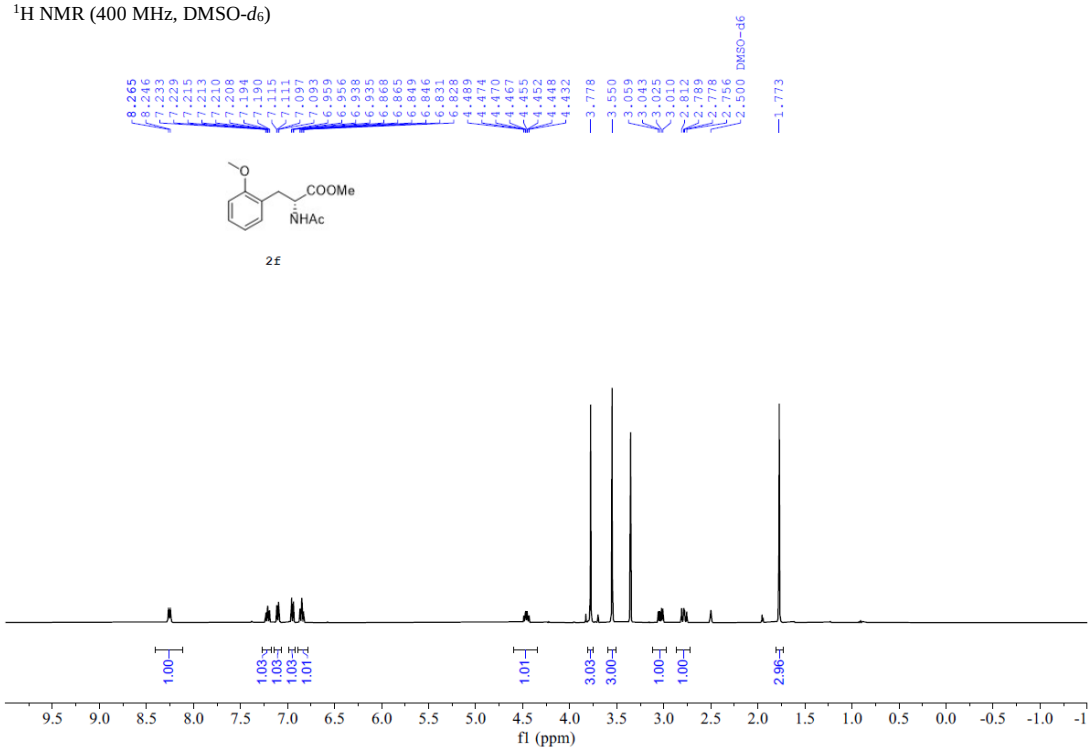

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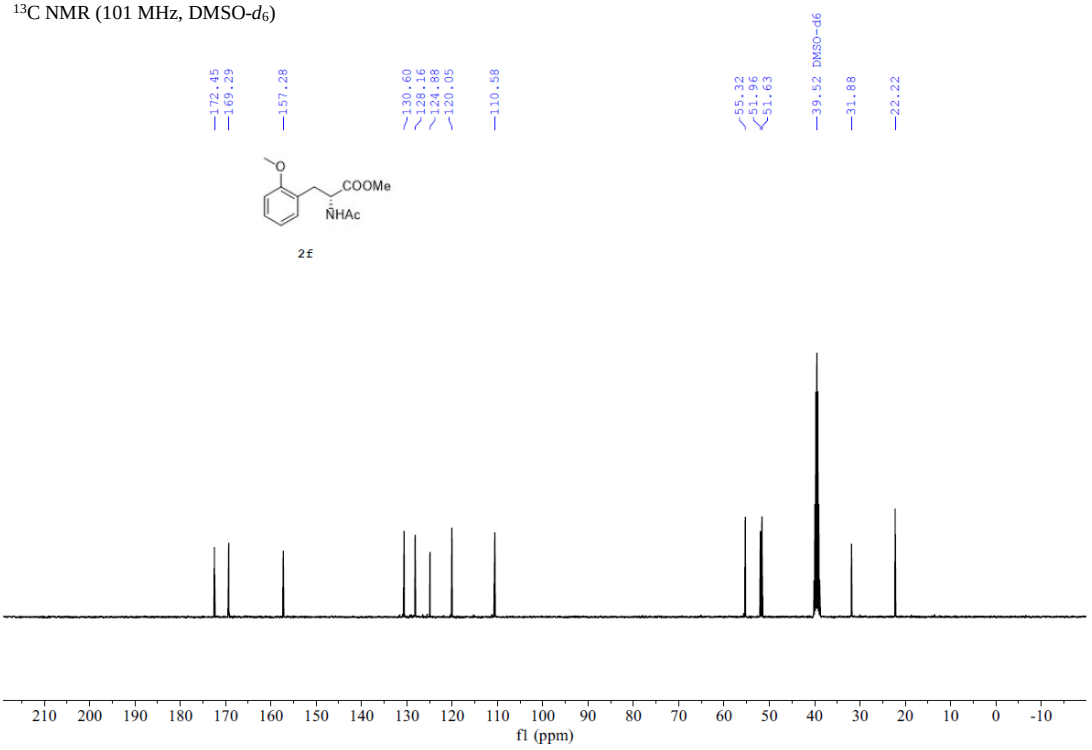

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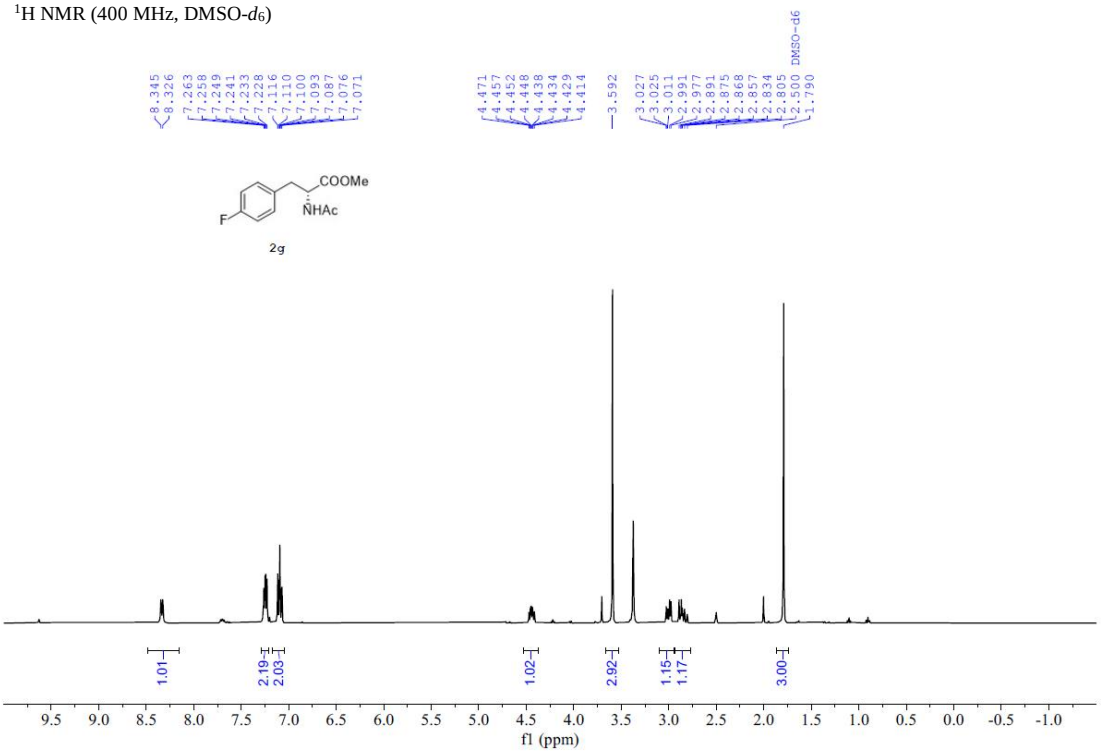

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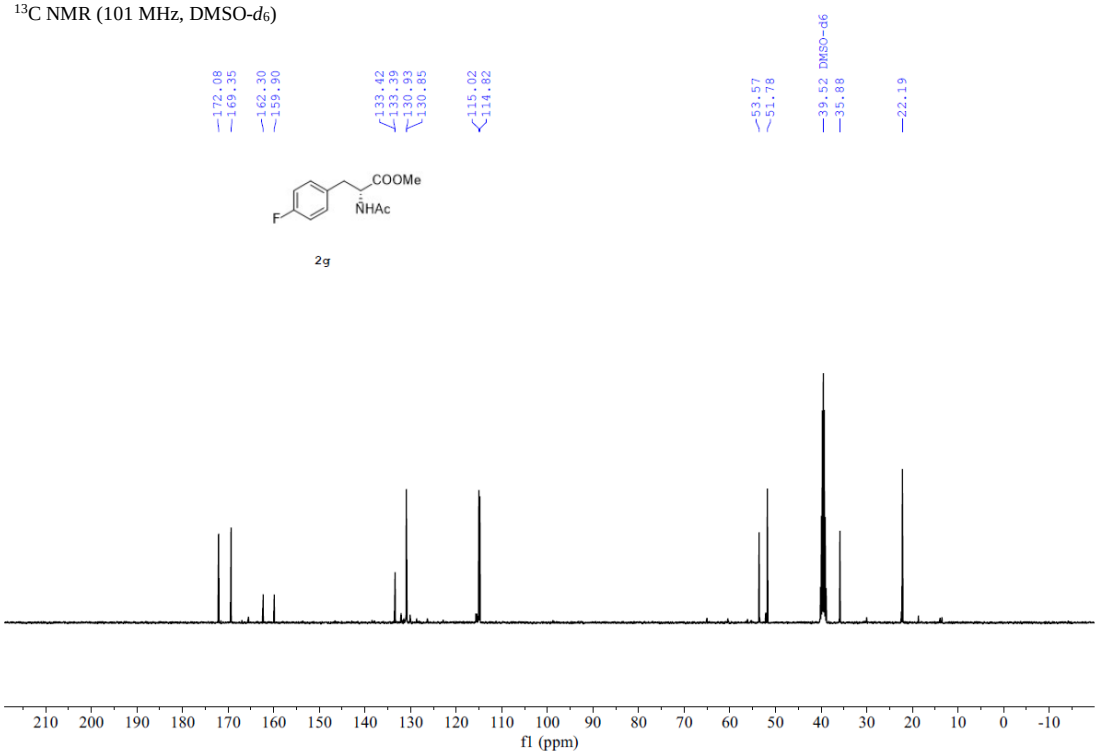

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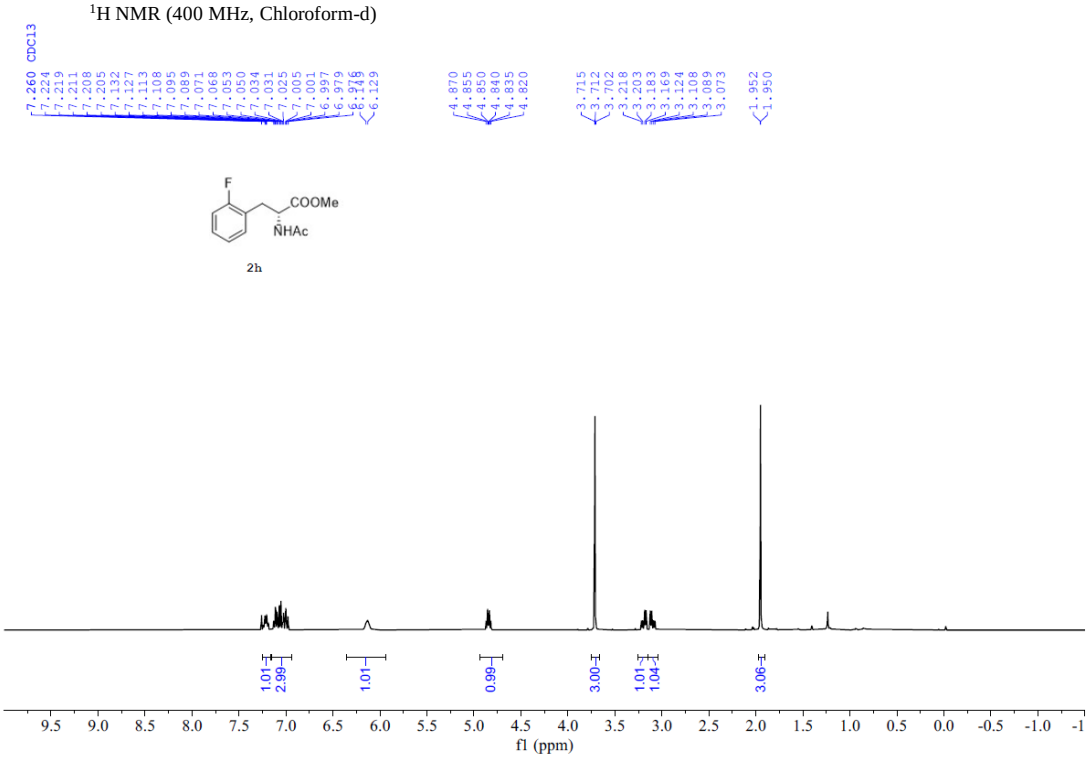

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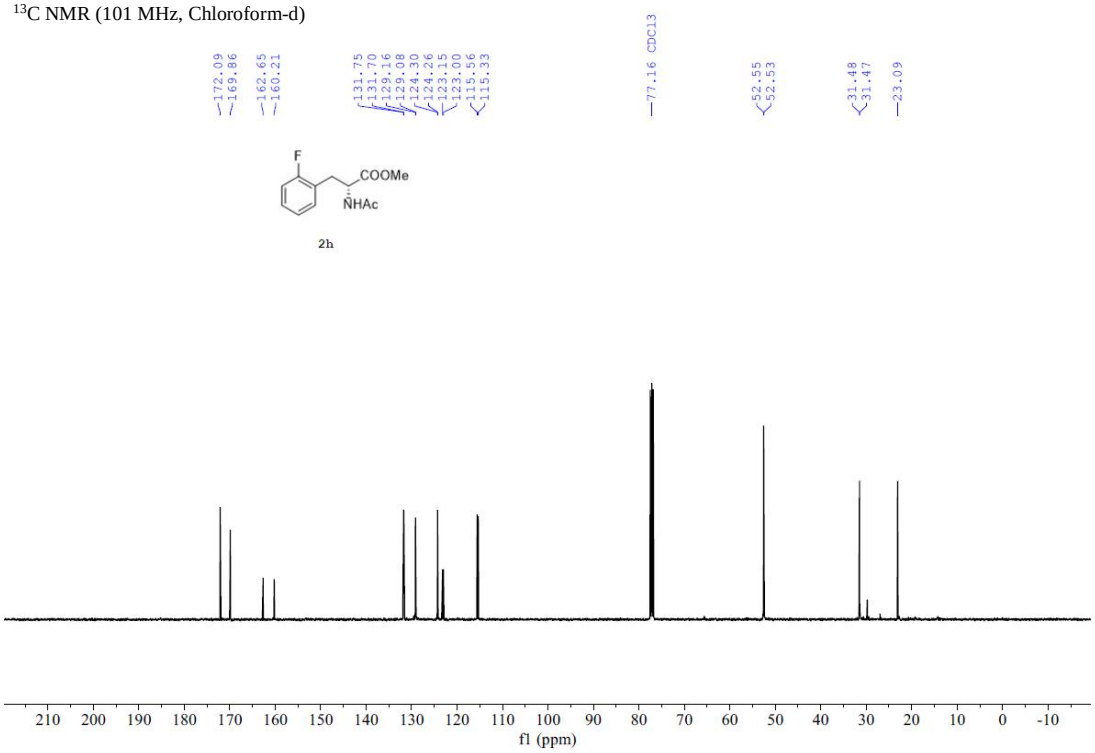

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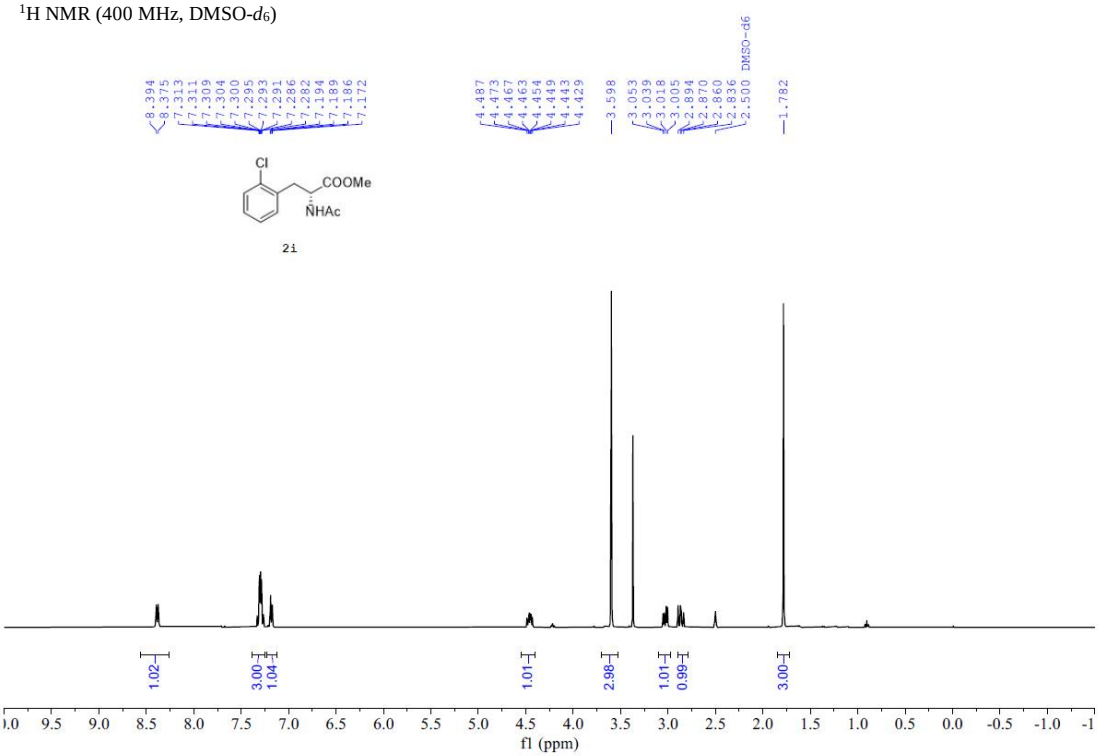

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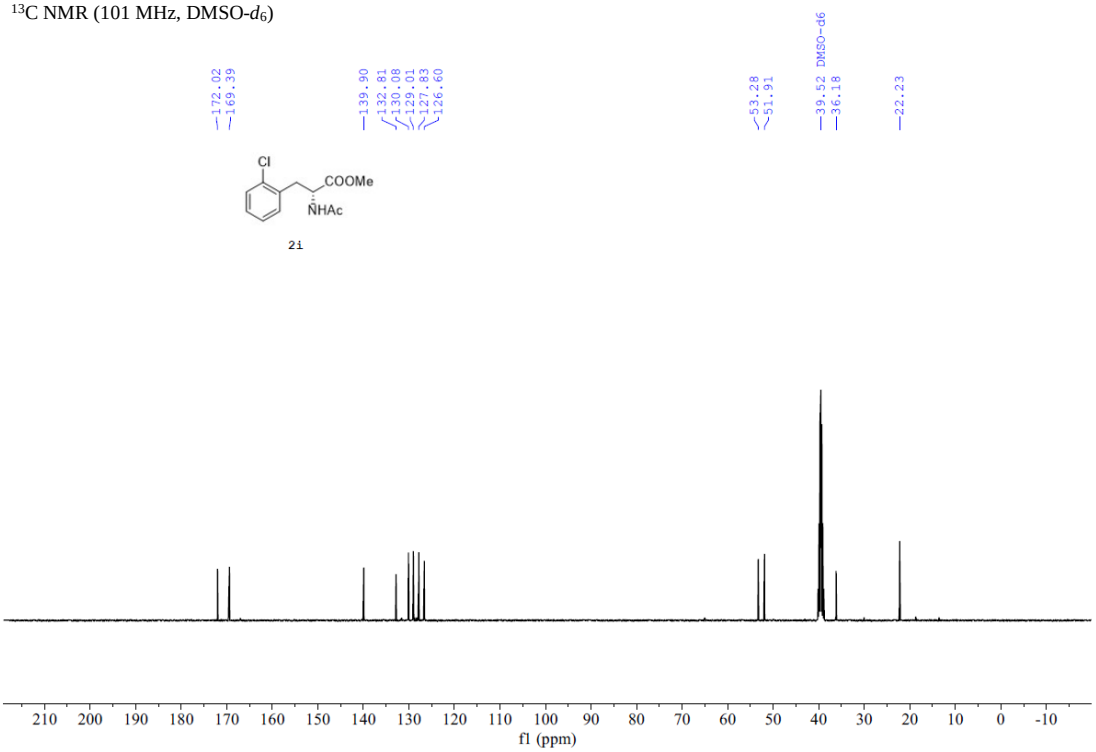

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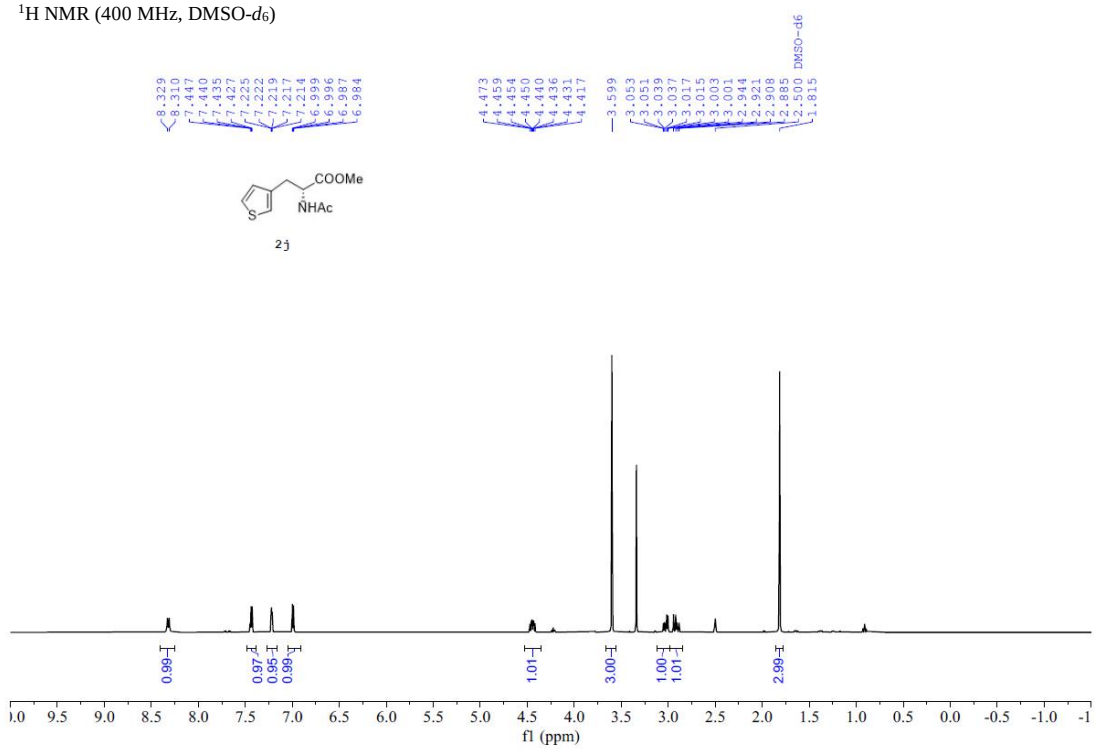
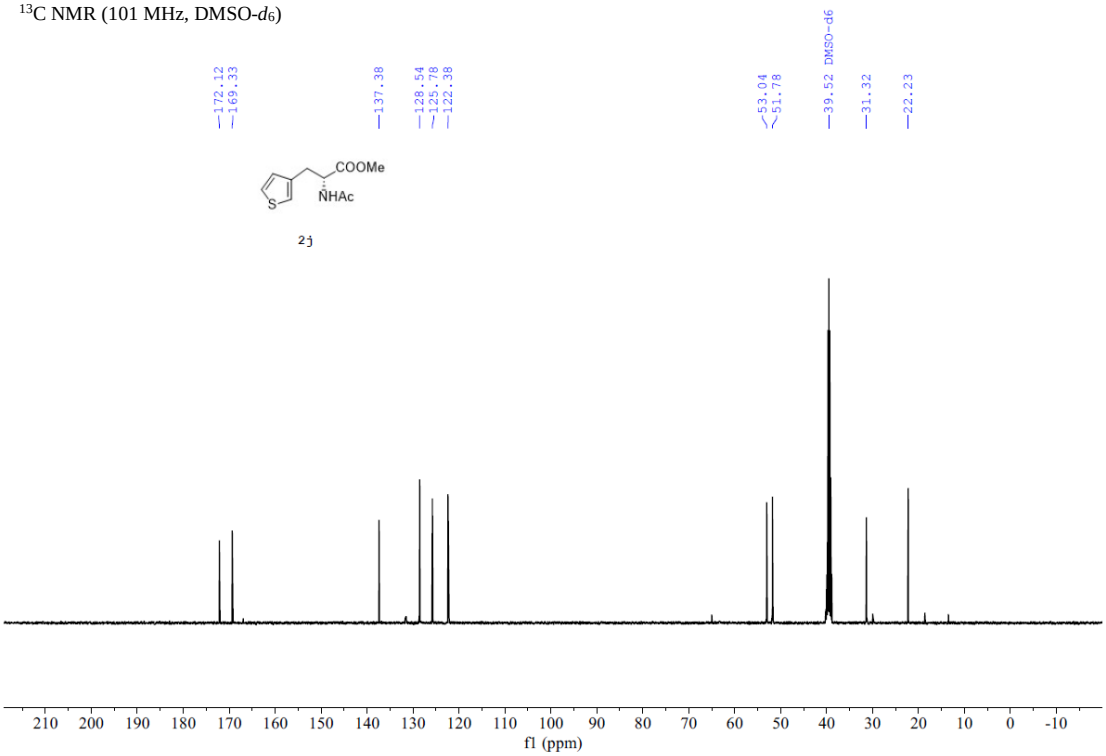
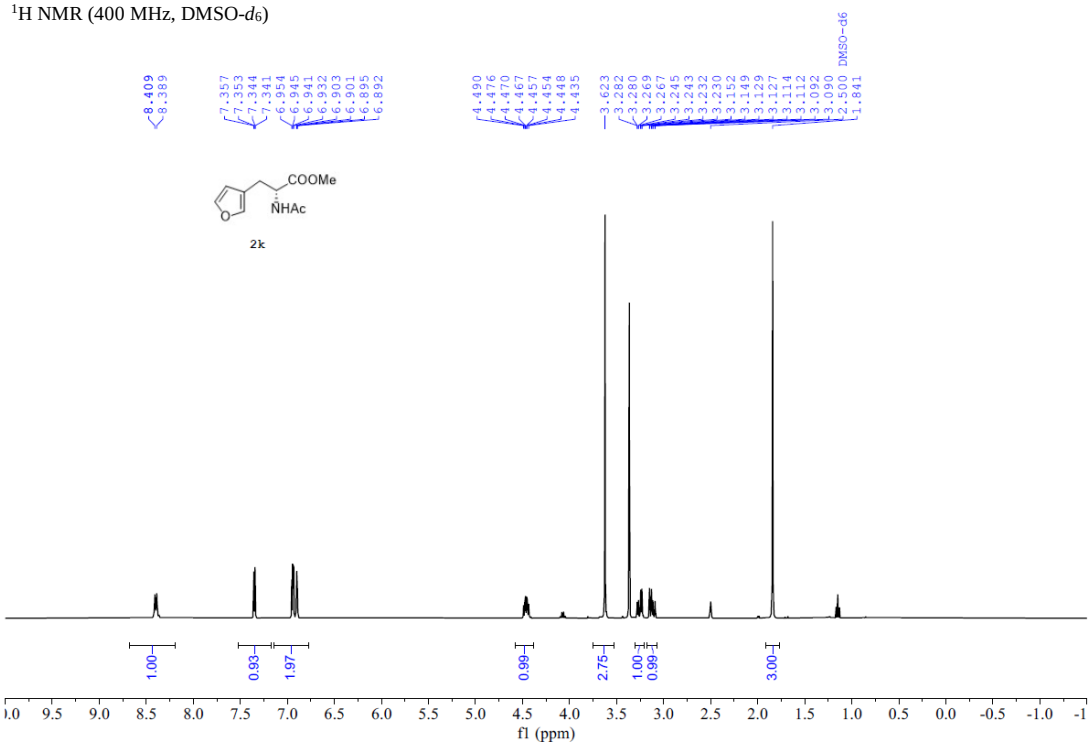


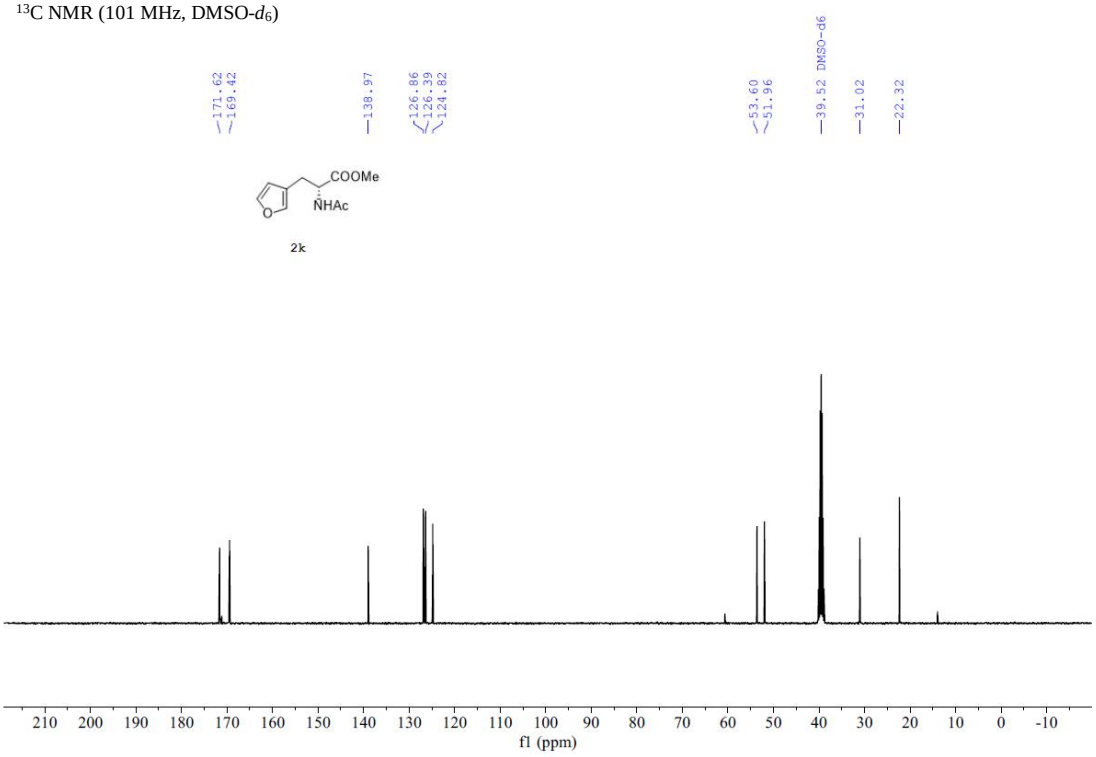
^{13}C NMR (101 MHz, DMSO-d_6)



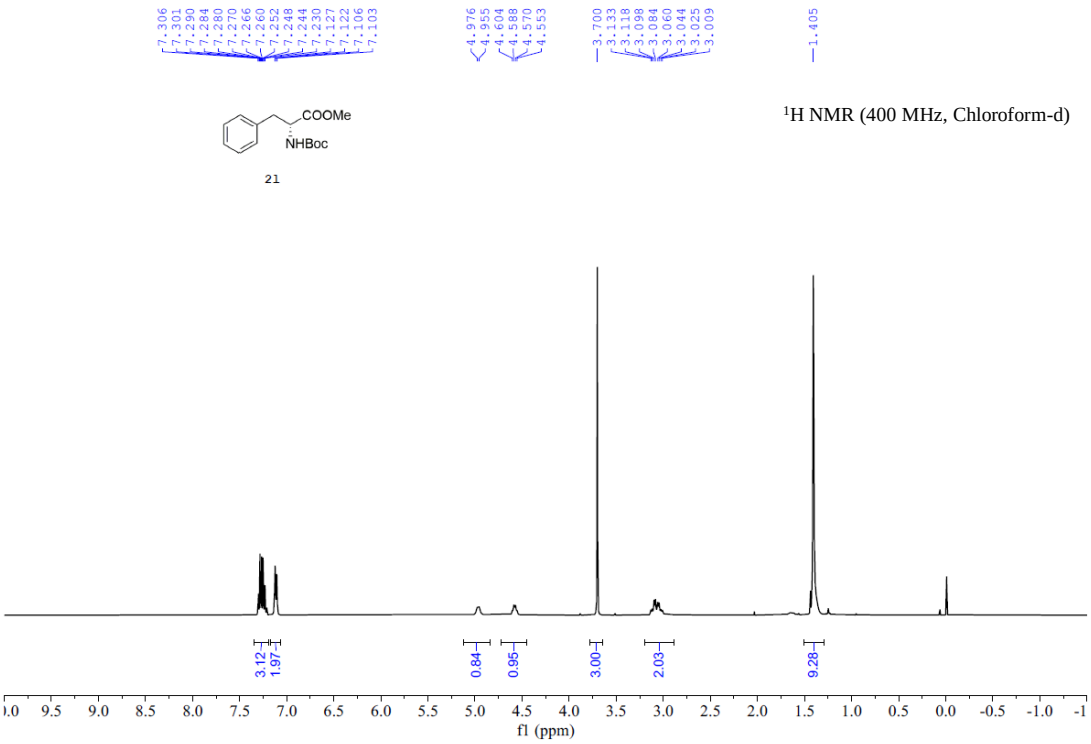
^{1}H NMR (400 MHz, DMSO-d_6)



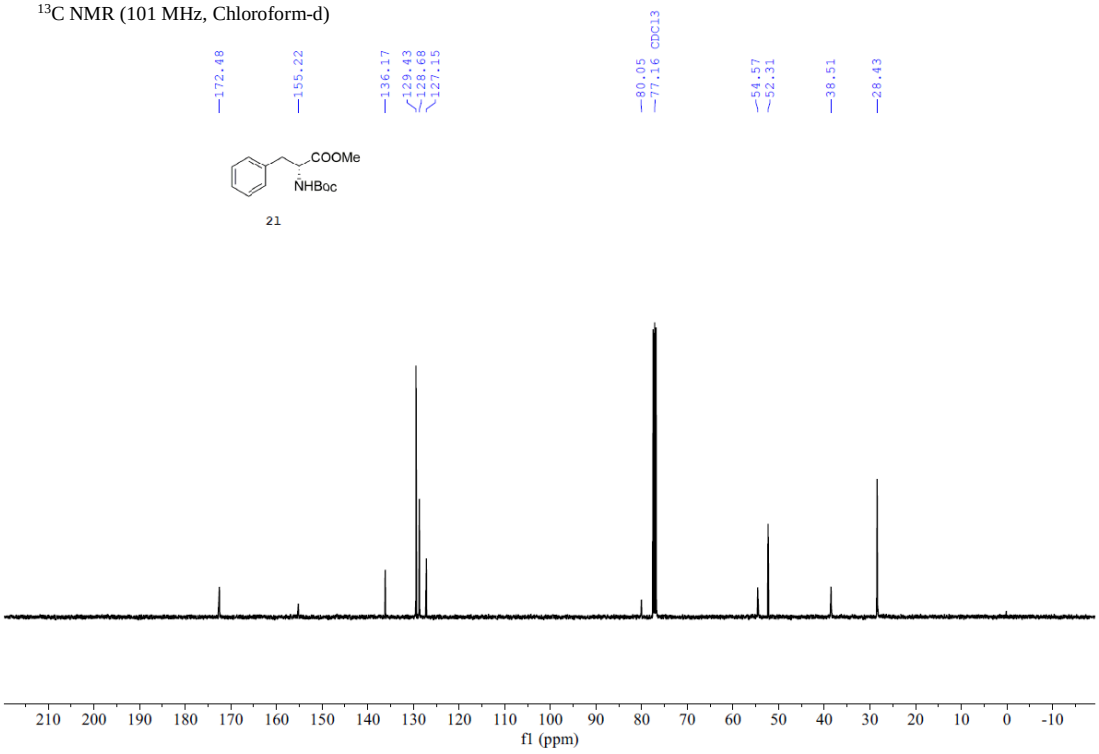
^{13}C NMR (101 MHz, DMSO-d_6)



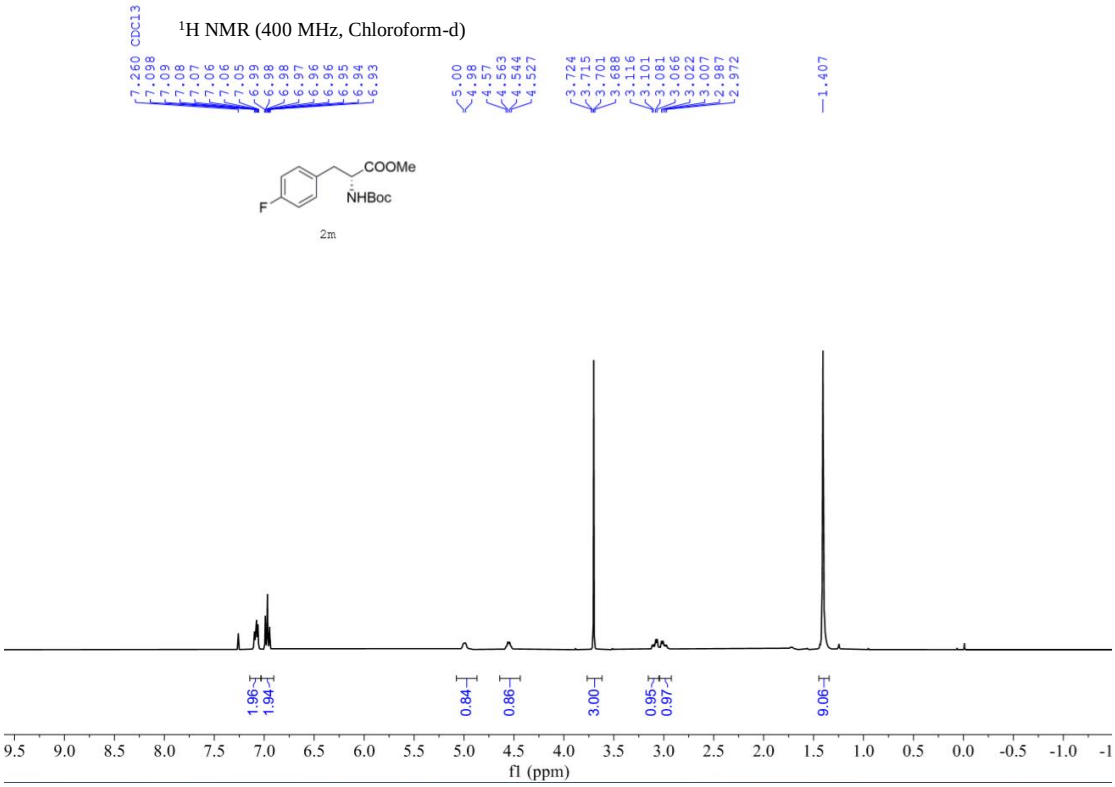
^{1}H NMR (400 MHz, Chloroform-d)



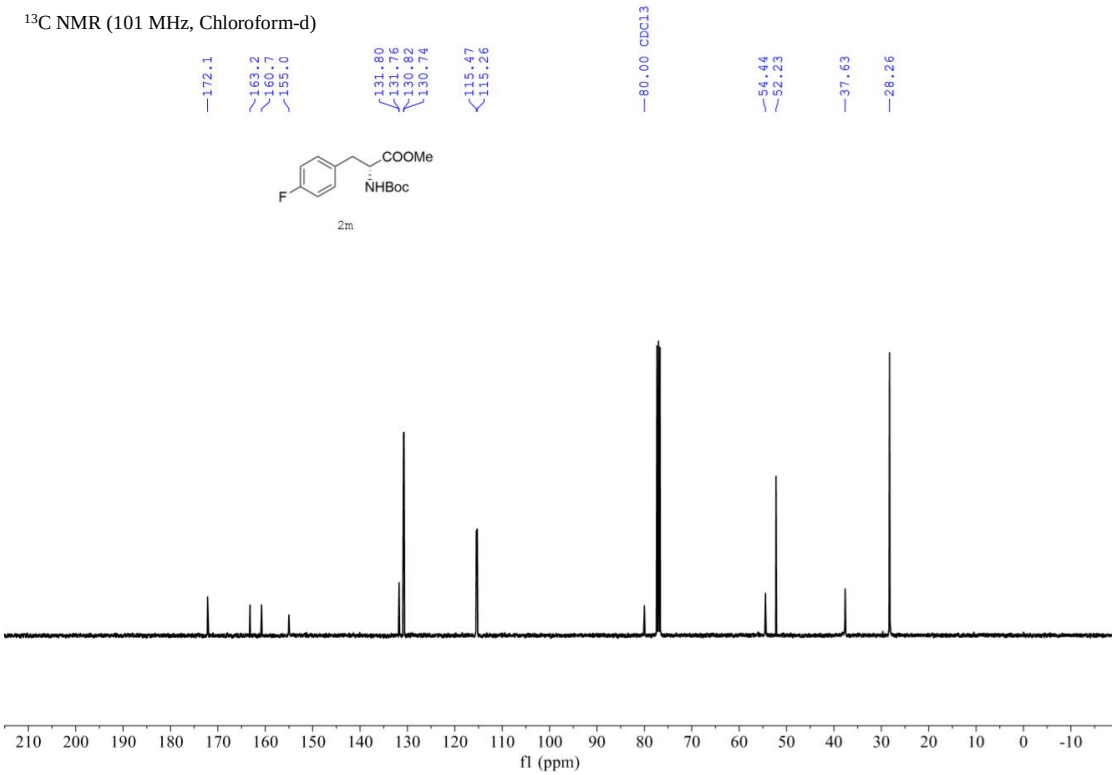
^{13}C NMR (101 MHz, Chloroform-d)



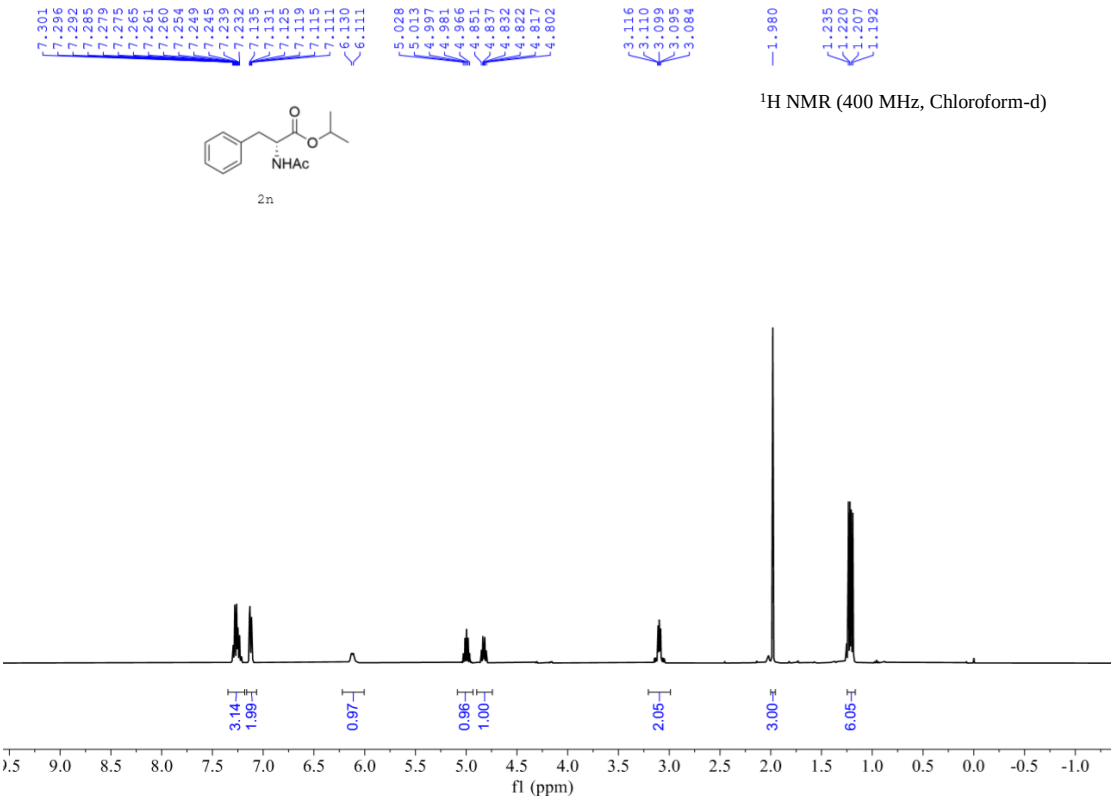
^{1}H NMR (400 MHz, Chloroform-d)



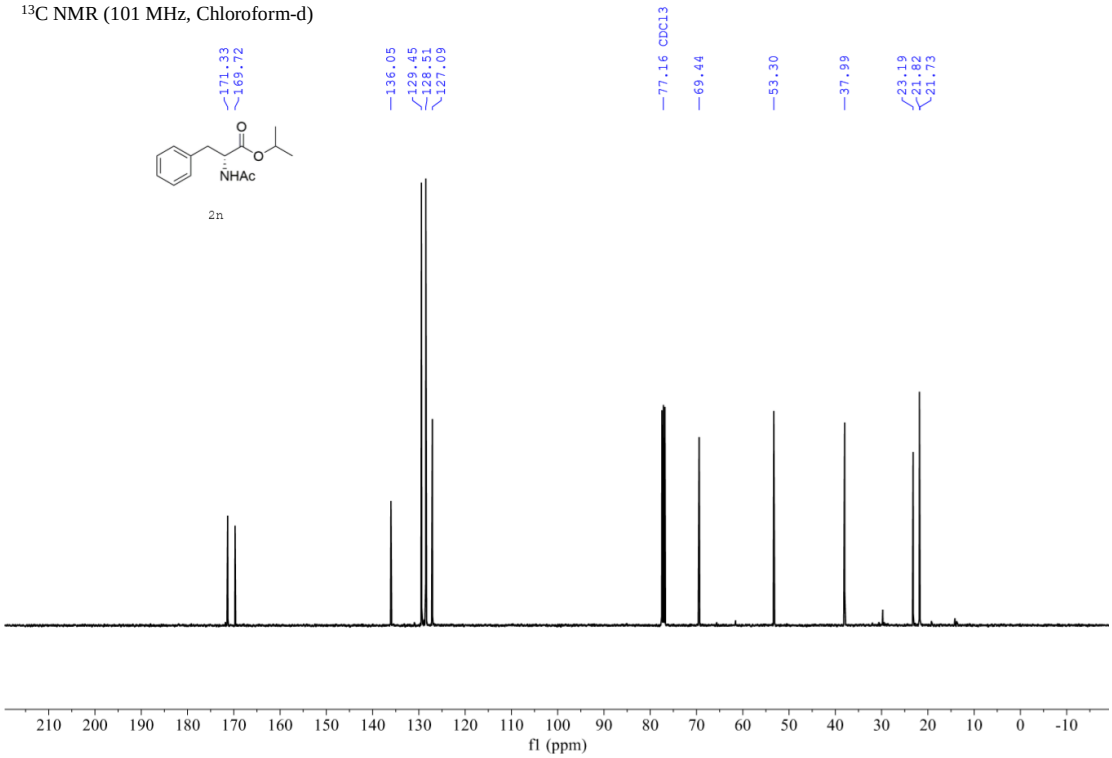
^{13}C NMR (101 MHz, Chloroform-d)



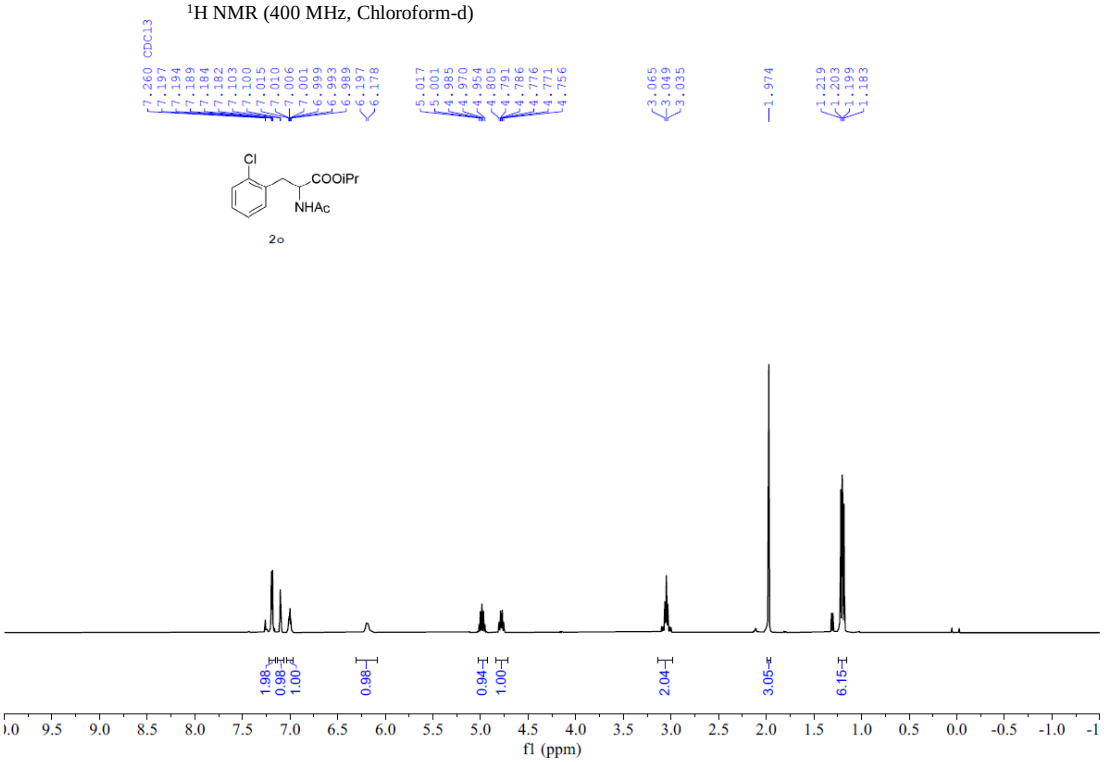
^{1}H NMR (400 MHz, Chloroform-d)



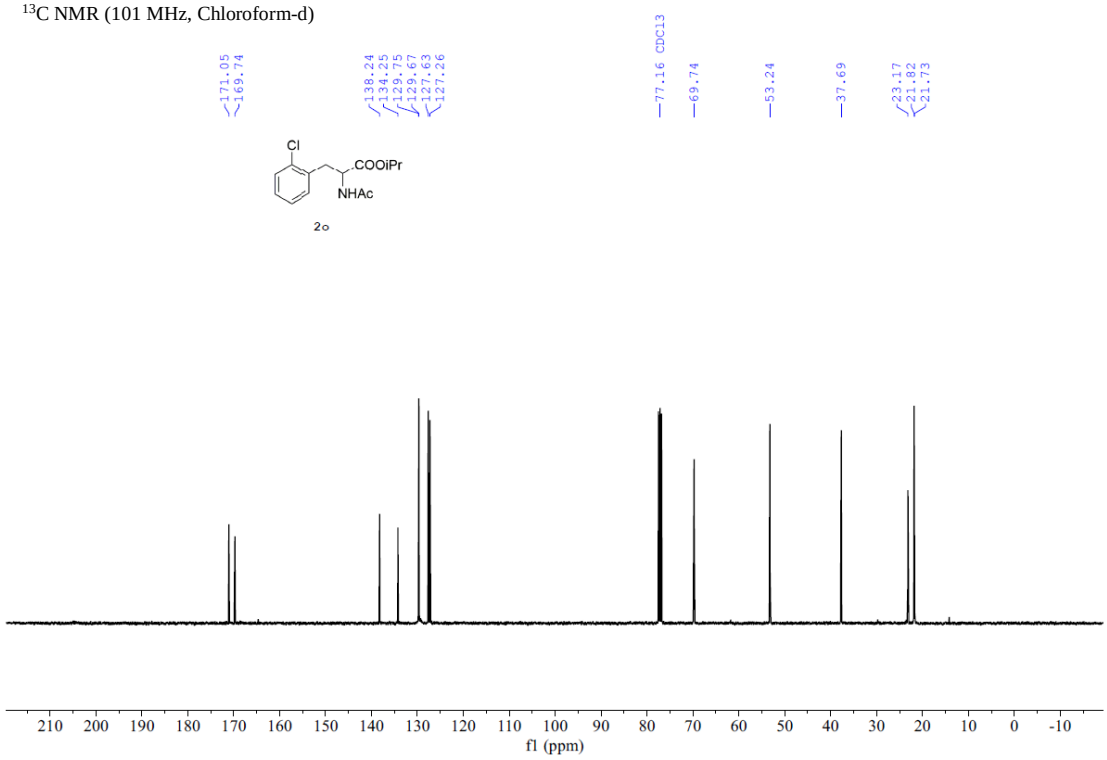
^{13}C NMR (101 MHz, Chloroform-d)



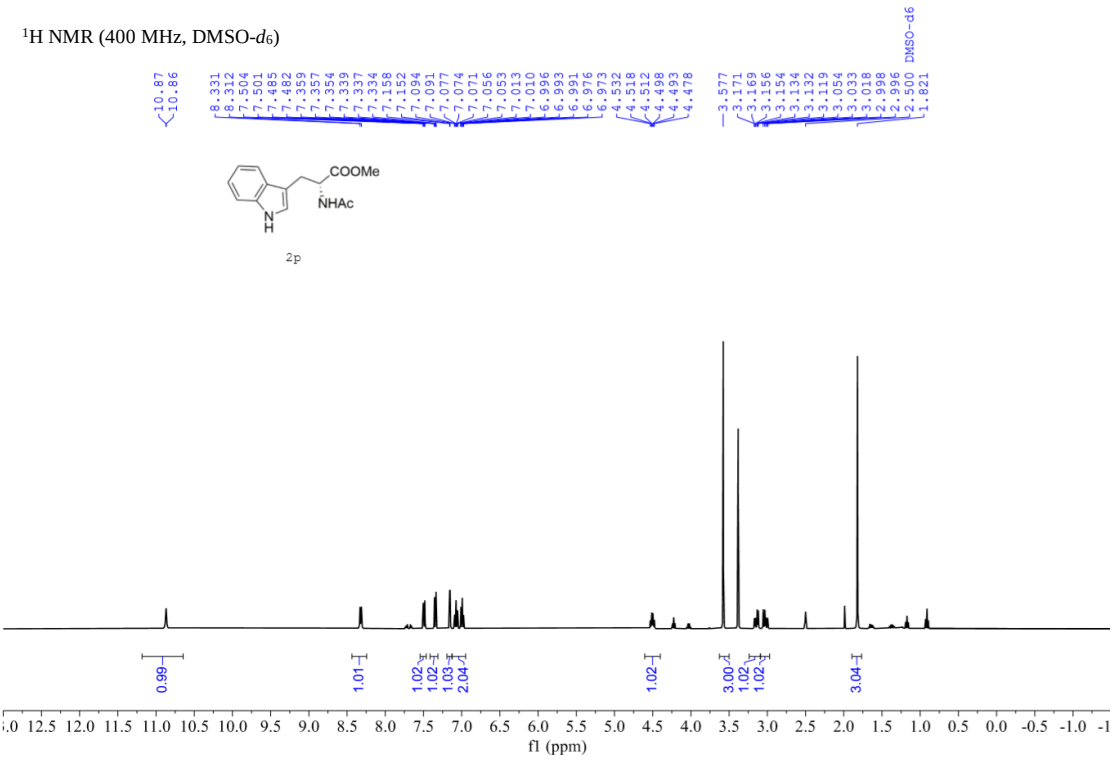
^{1}H NMR (400 MHz, Chloroform-d)



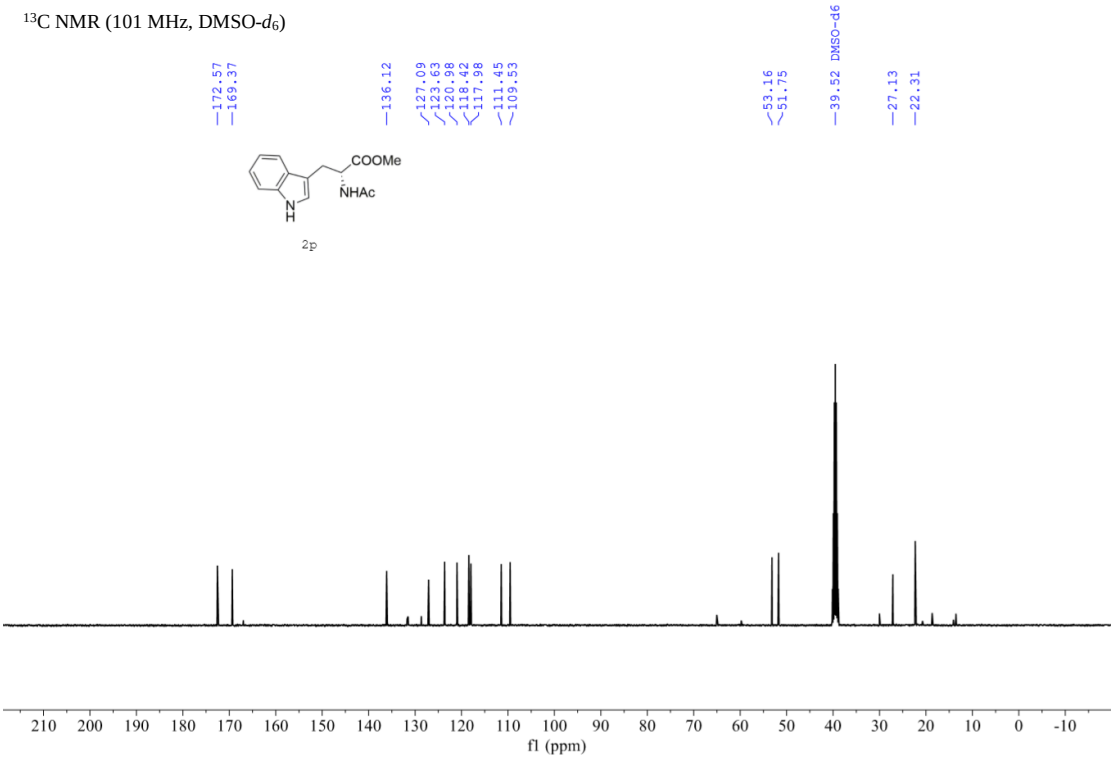
^{13}C NMR (101 MHz, Chloroform-d)



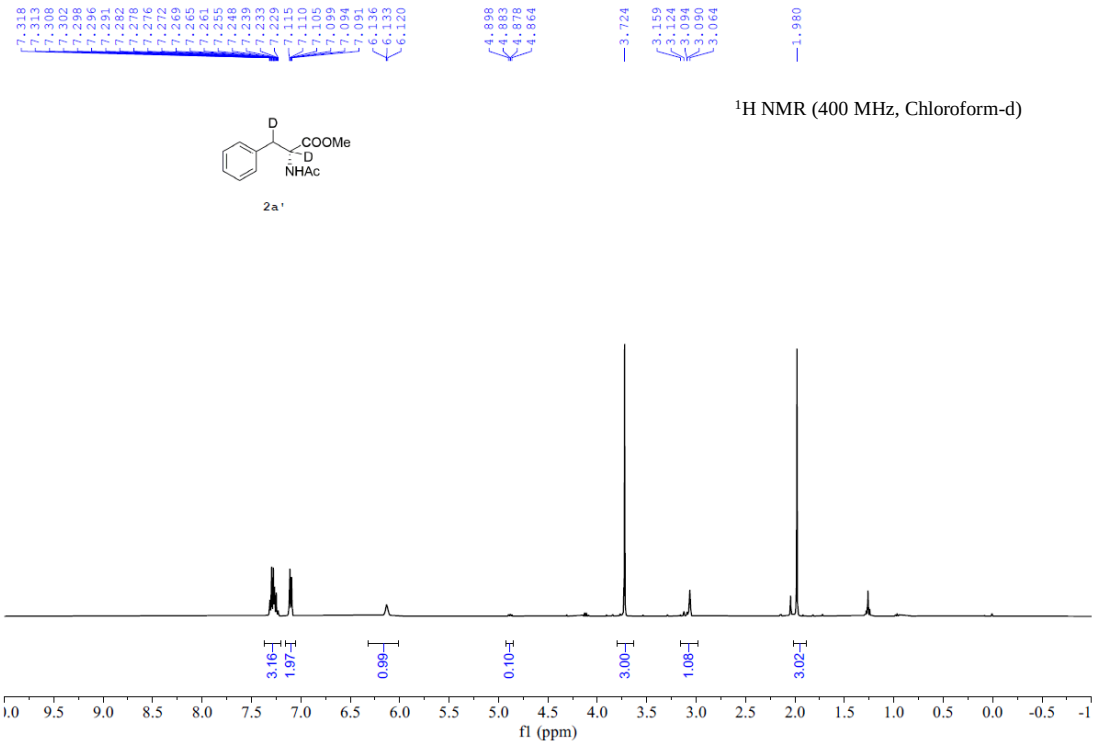
^{1}H NMR (400 MHz, DMSO-d_6)



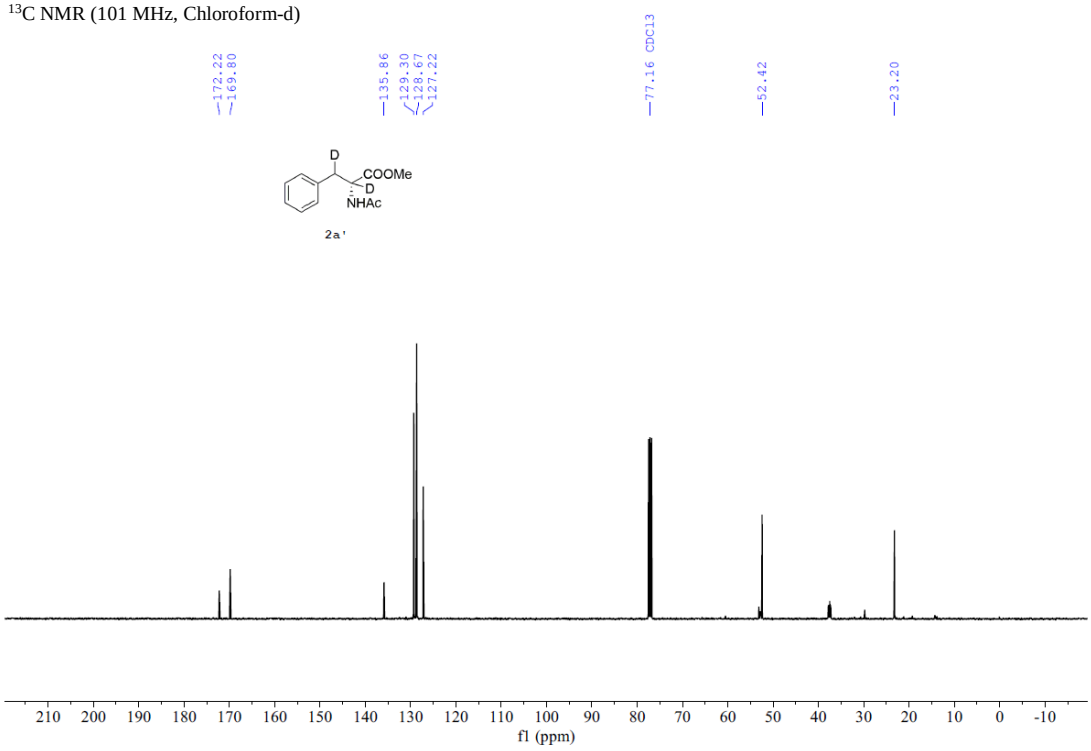
^{13}C NMR (101 MHz, DMSO-d_6)



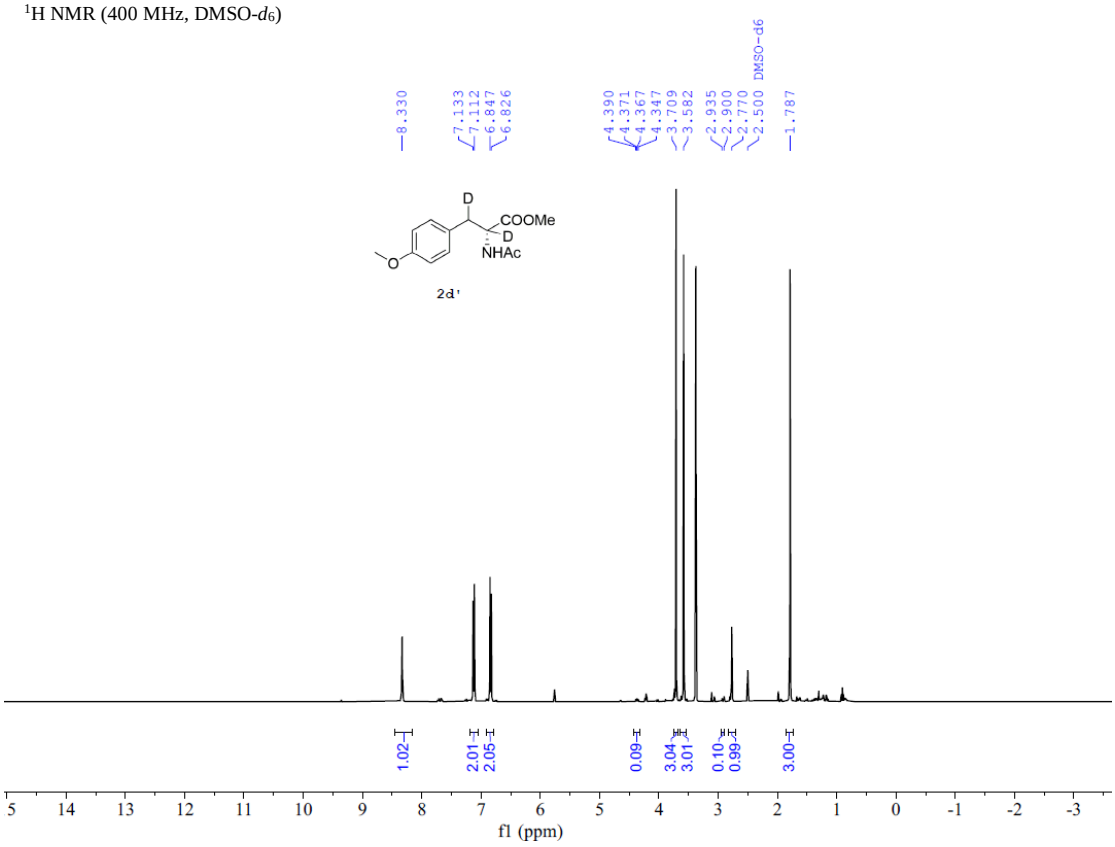
^{1}H NMR (400 MHz, Chloroform-d)



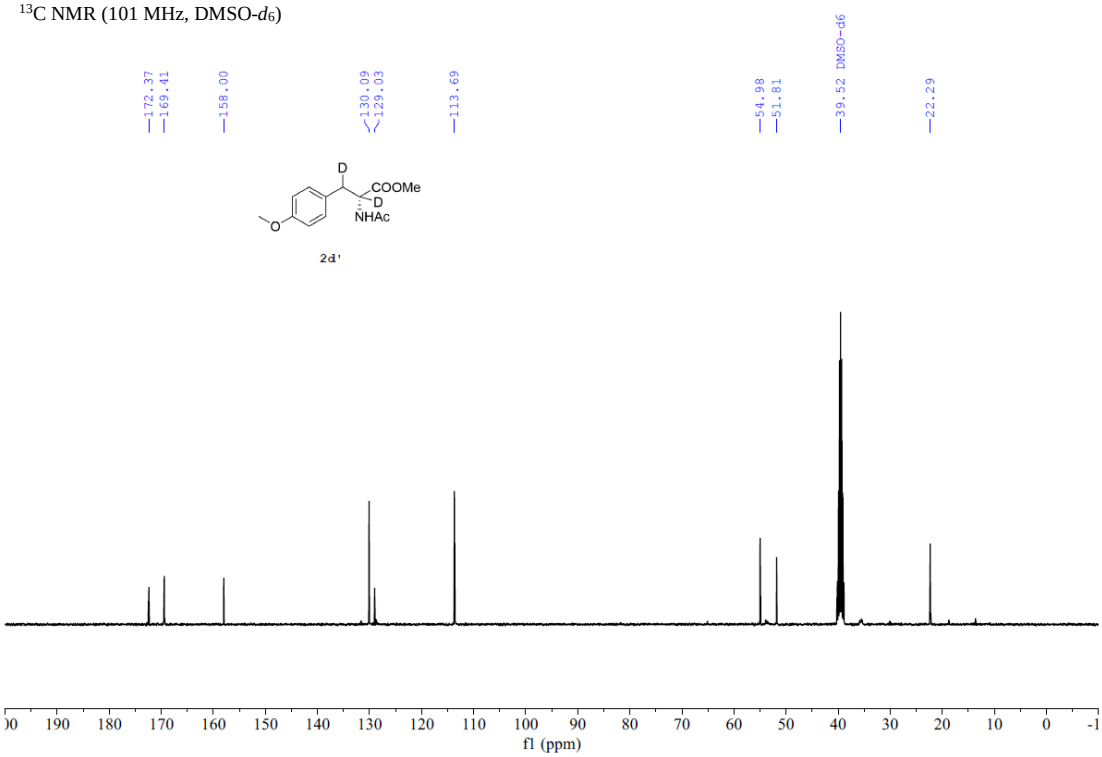
^{13}C NMR (101 MHz, Chloroform-d)



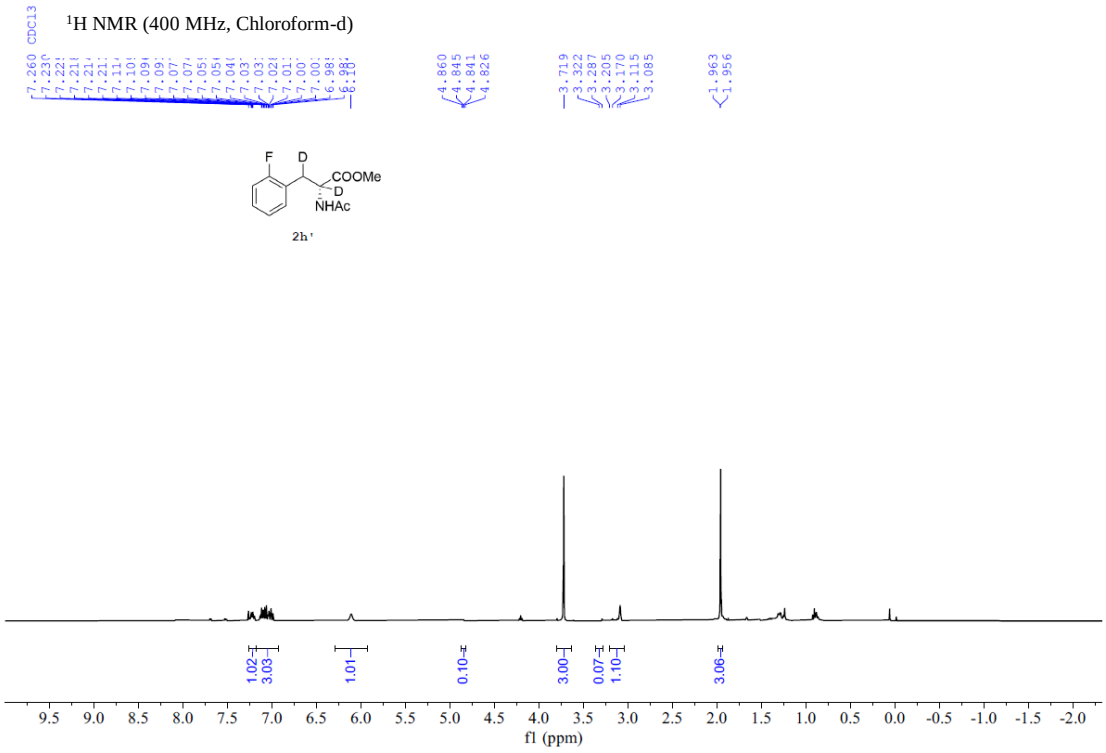
^{1}H NMR (400 MHz, DMSO-d_6)



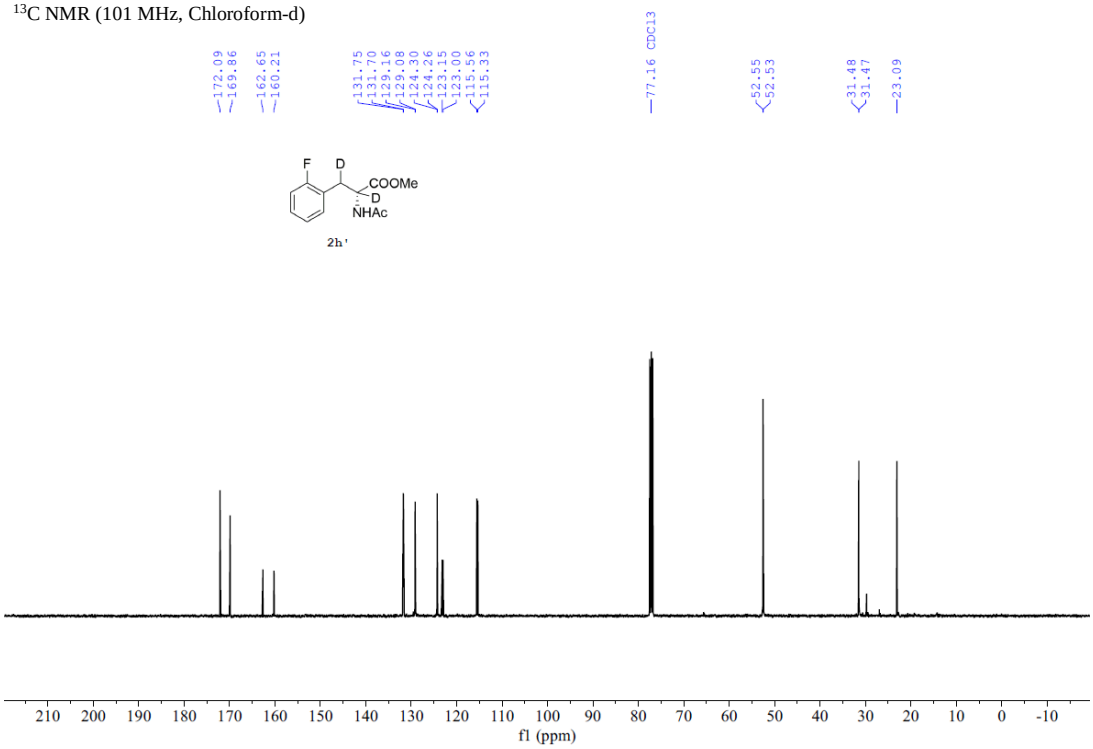
^{13}C NMR (101 MHz, DMSO-d_6)

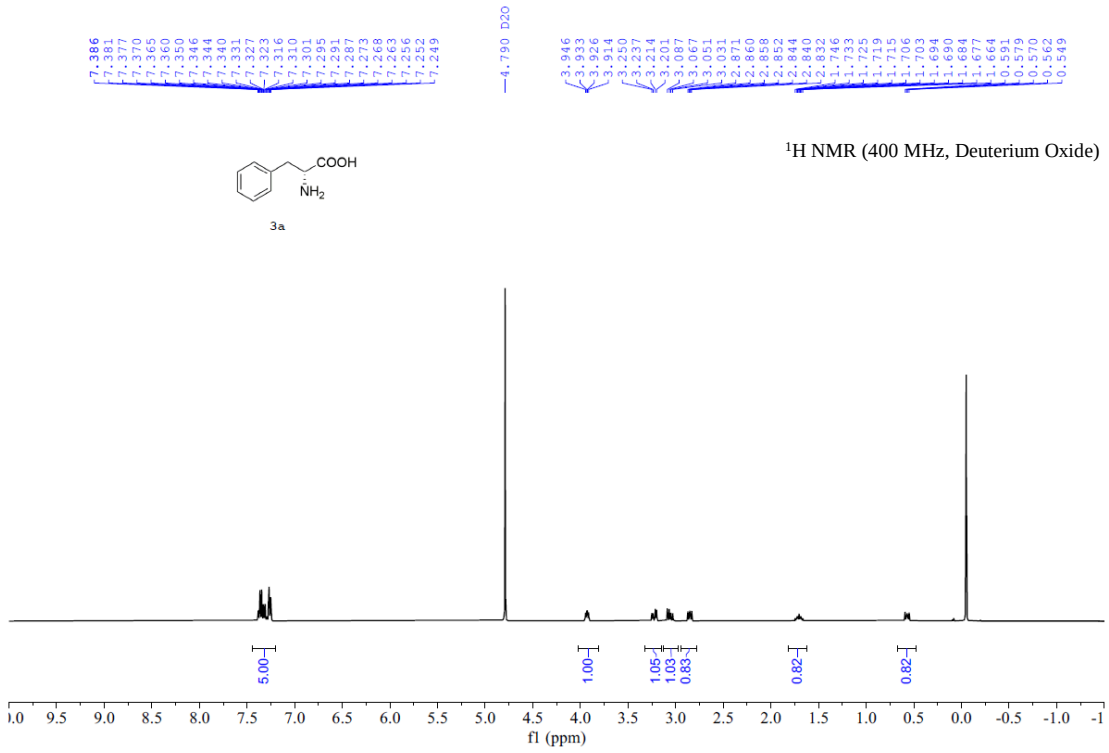


^{1}H NMR (400 MHz, Chloroform-d)

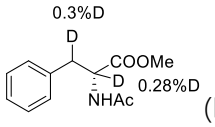


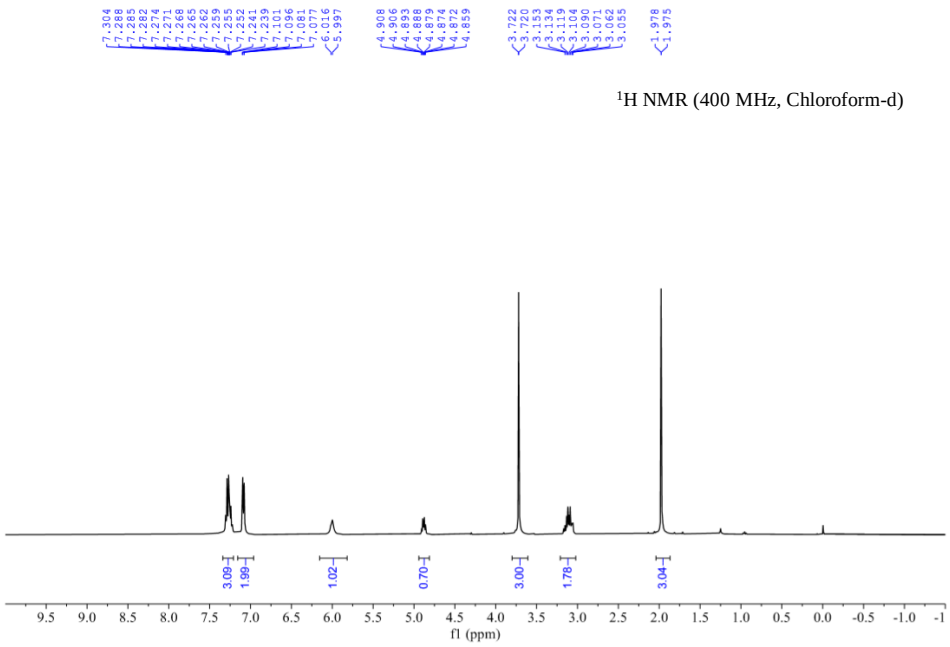
^{13}C NMR (101 MHz, Chloroform-d)





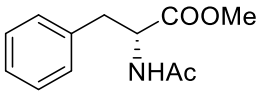
^{1}H NMR (400 MHz, Deuterium Oxide)





^{1}H NMR (400 MHz, Chloroform-d)

F: HPLC or GC Spectra of Products



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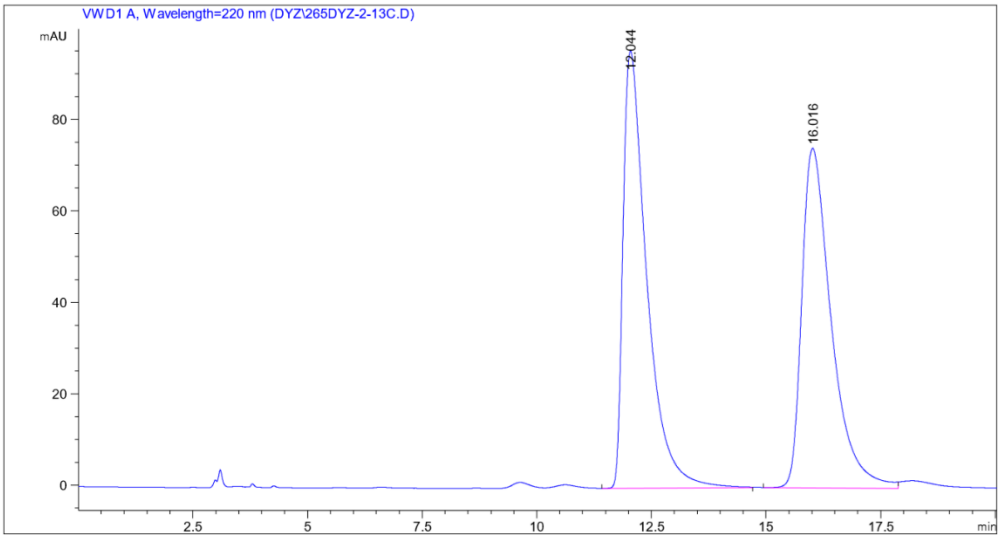
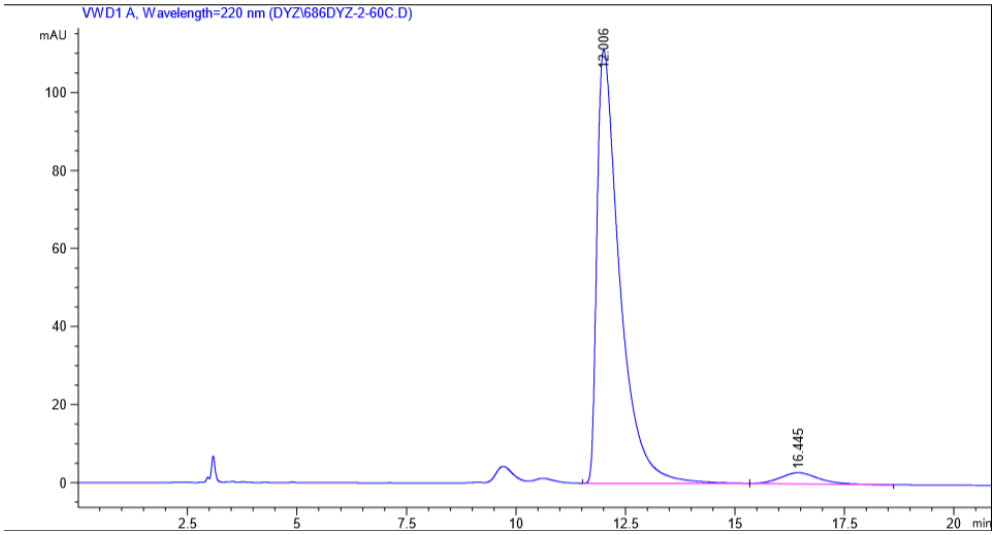
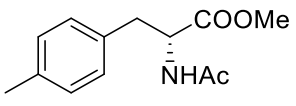


Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	12.044	MM	0.5993	3441.18408	95.69855	50.8886
2	16.016	MM	0.7453	3321.00269	74.26982	49.1114



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	12.006	BB	0.5328	4008.36938	111.12948	95.8459
2	16.445	BB	0.8301	173.73067	2.86638	4.1541



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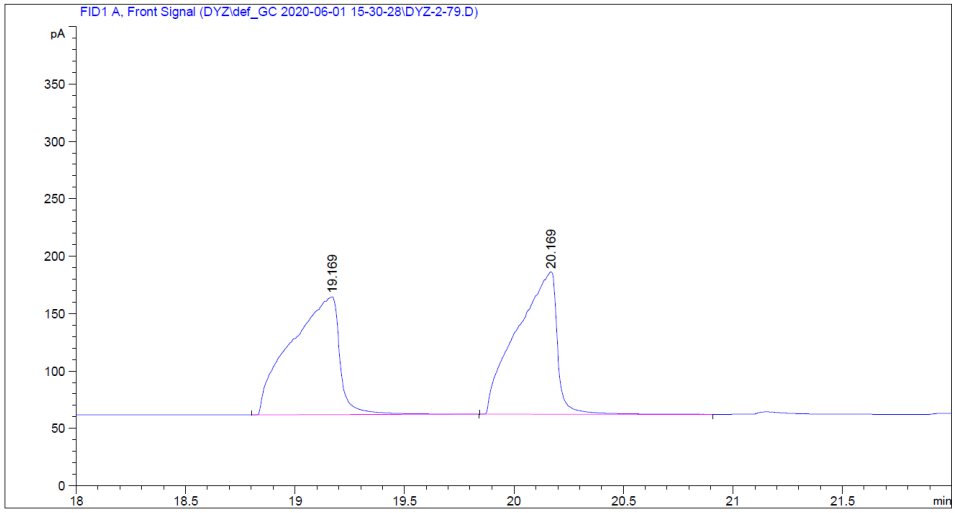

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
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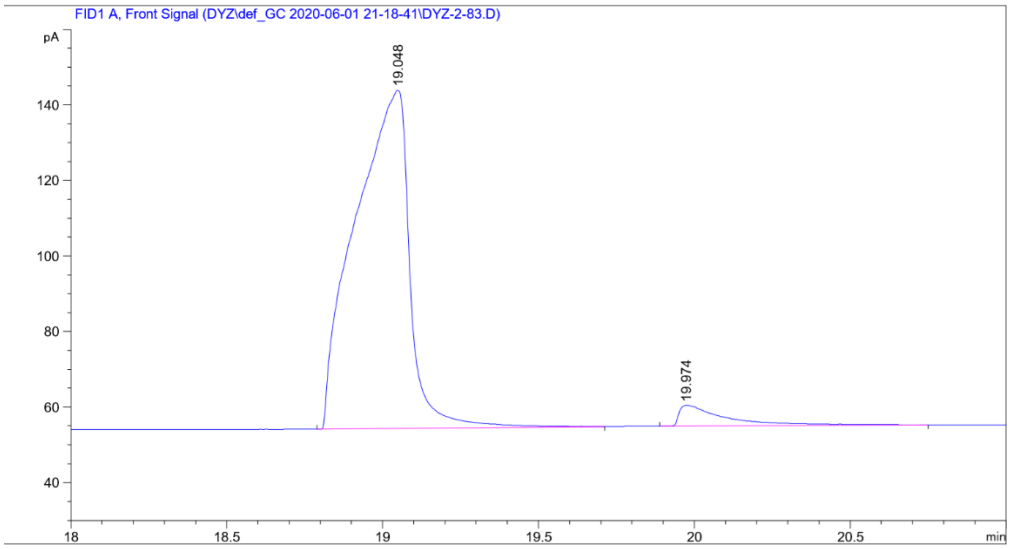
2	20.169	BB	0.1635	1588.60669	123.94453	49.90834



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
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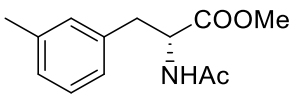
2	19.974	MM	0.1717	56.69831	5.50253	4.96020



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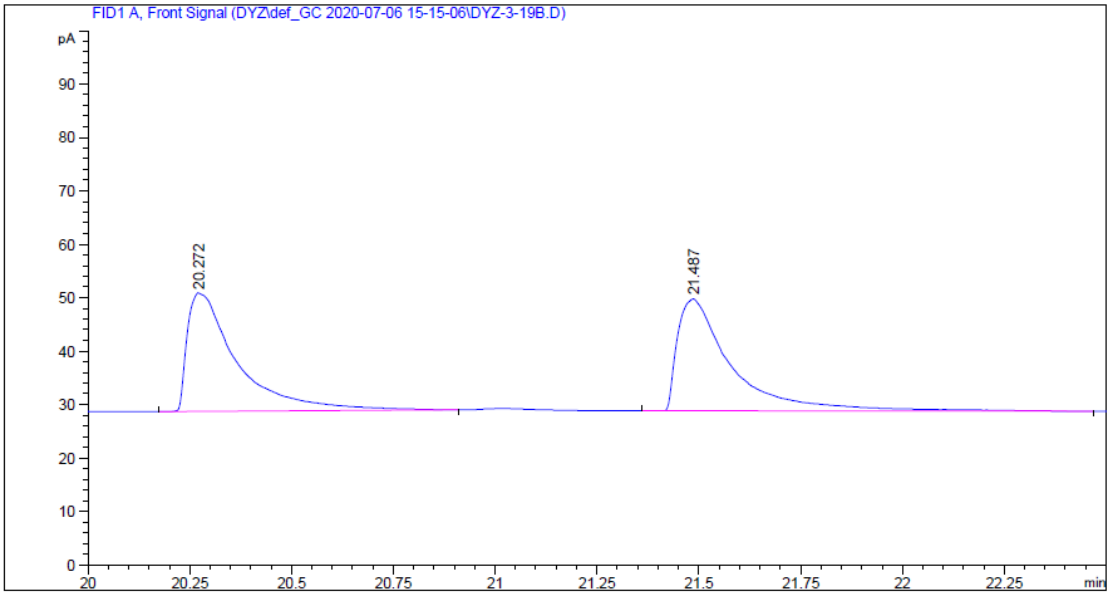
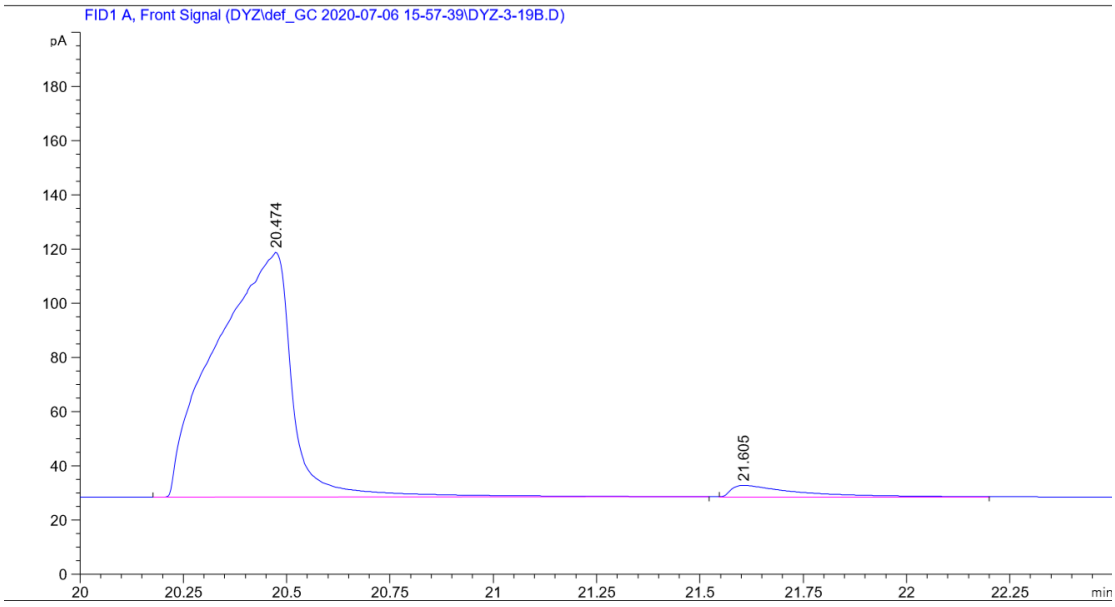


Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	20.272	BB	0.1125	188.81664	22.14335	49.24214
2	21.487	BB	0.1353	194.62862	20.97442	50.75786



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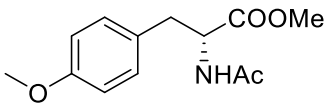
1	20.474	BB	0.1611	1161.61389	90.31393	96.04564
2	21.605	MM	0.1868	47.82564	4.26808	3.95436



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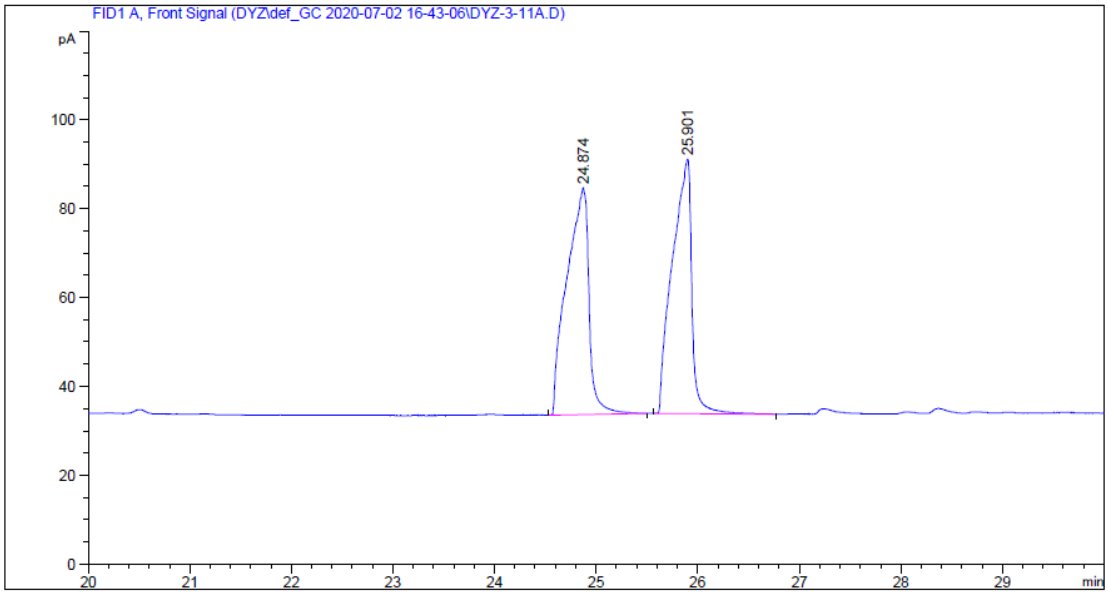
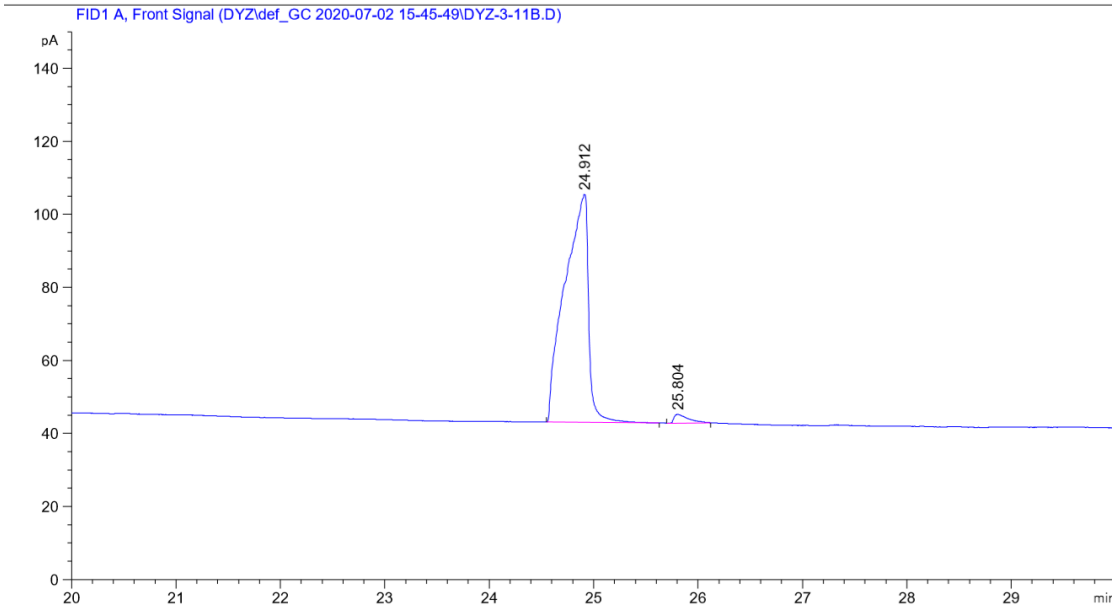
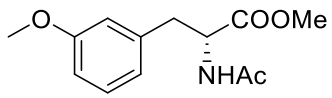


Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	24.874	BB	0.1850	775.00537	51.09440	50.38363
2	25.901	BB	0.1704	763.20331	57.31199	49.61637



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	24.912	BB	0.1858	983.03680	62.38900	97.74159
2	25.804	MM	0.1588	22.71397	2.38464	2.25841



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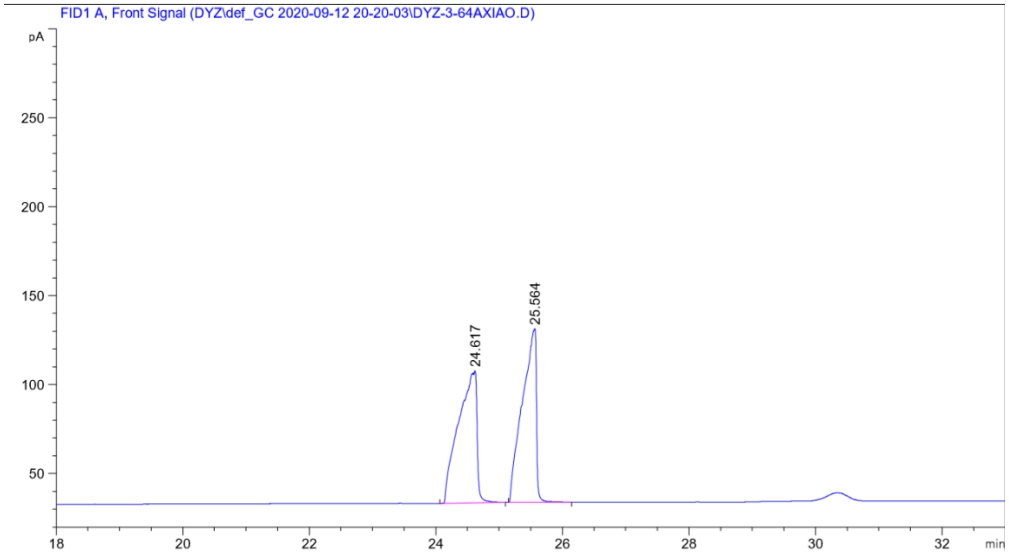

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
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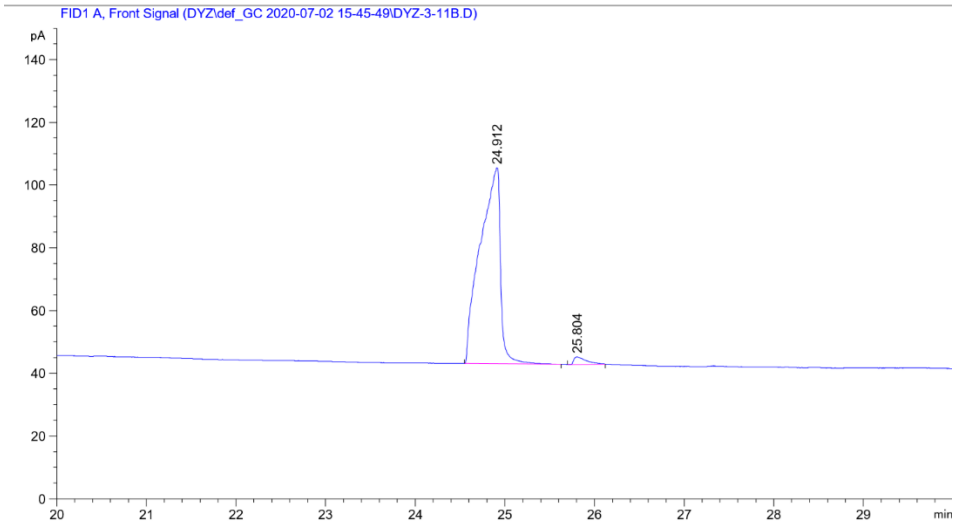
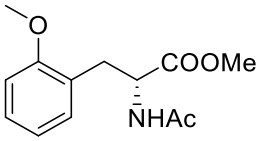
2	25.564	BB	0.1909	1504.17456	97.53384	49.93373



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	24.912	BB	0.1858	983.03680	62.38900	97.74159
2	25.804	MM	0.1588	22.71397	2.38464	2.25841



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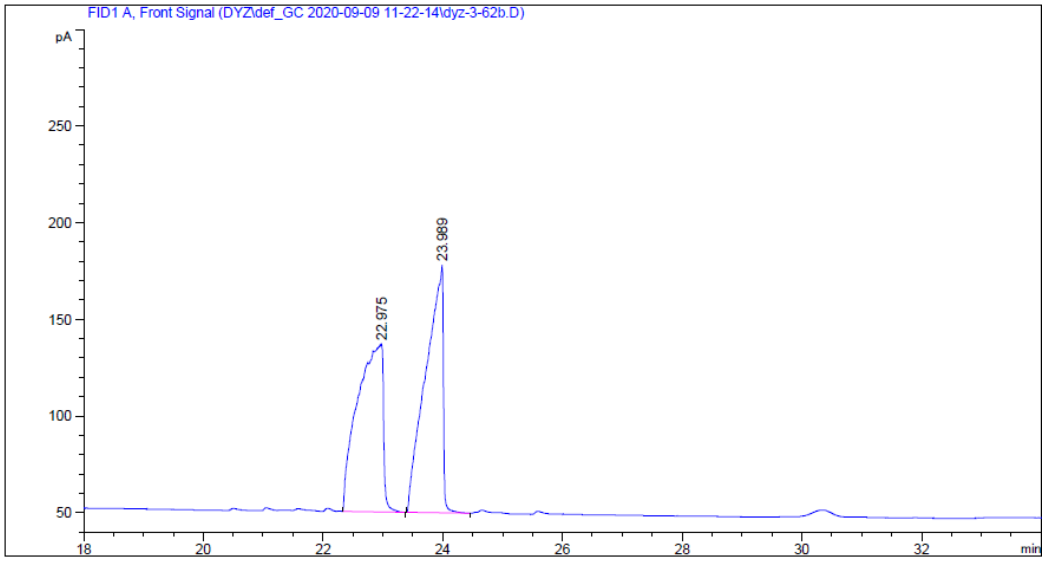

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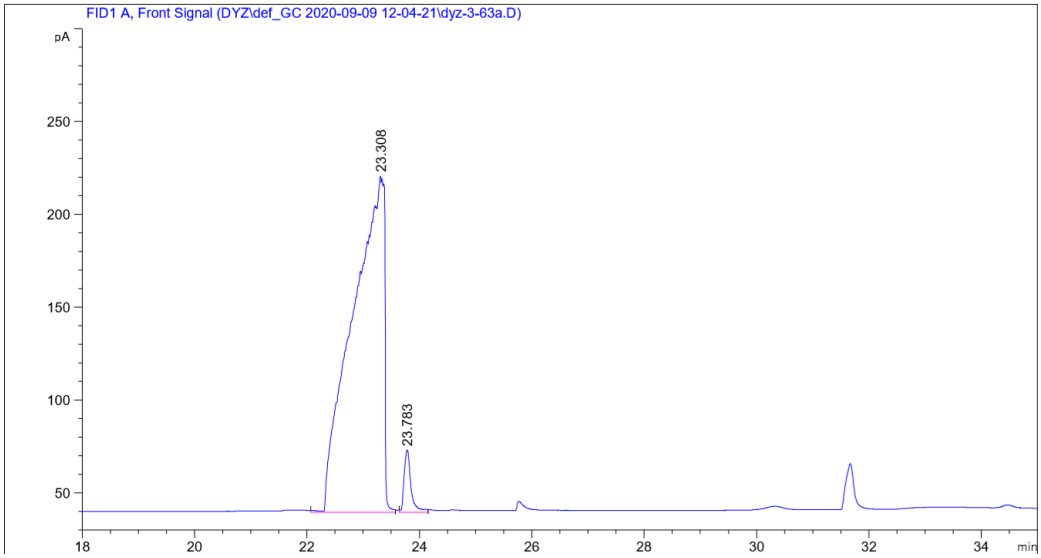
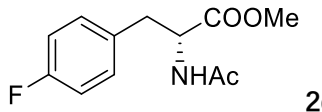
1	22.975	BB	0.3585	2586.81787	86.83775	50.01477
2	23.989	BB	0.2440	2585.28955	128.36943	49.98523



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	23.308	MM	0.6520	7085.14893	181.11177	96.13635
2	23.783	MM	0.1419	284.74719	33.45419	3.86365



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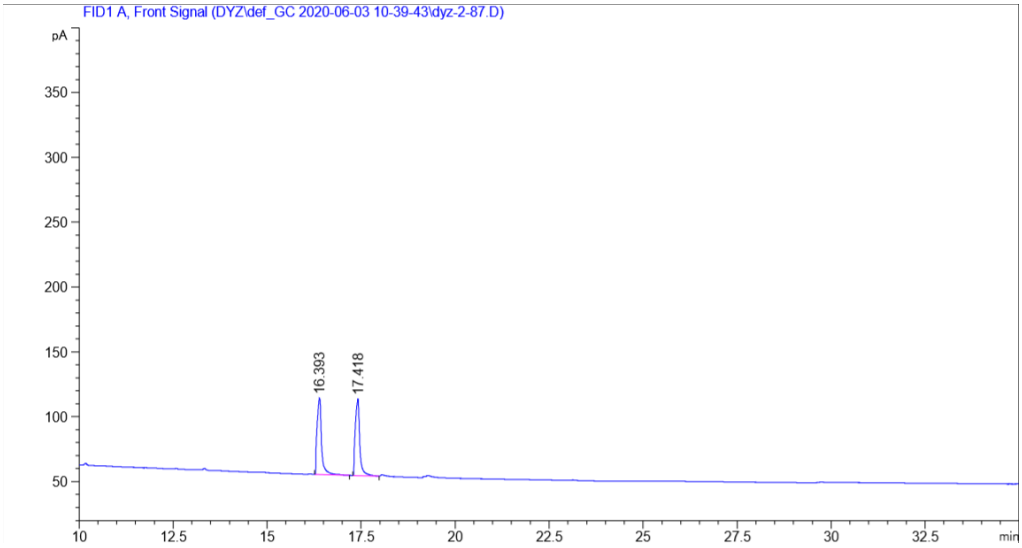

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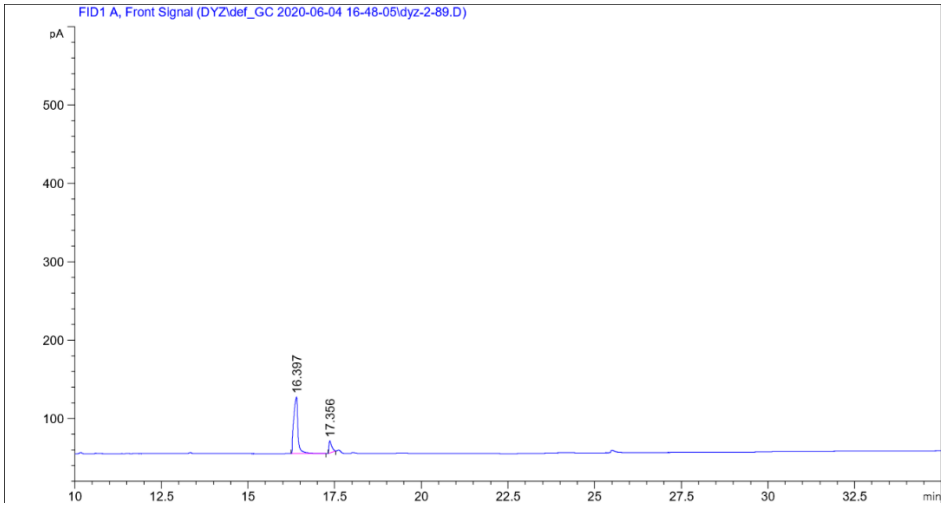

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
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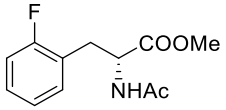

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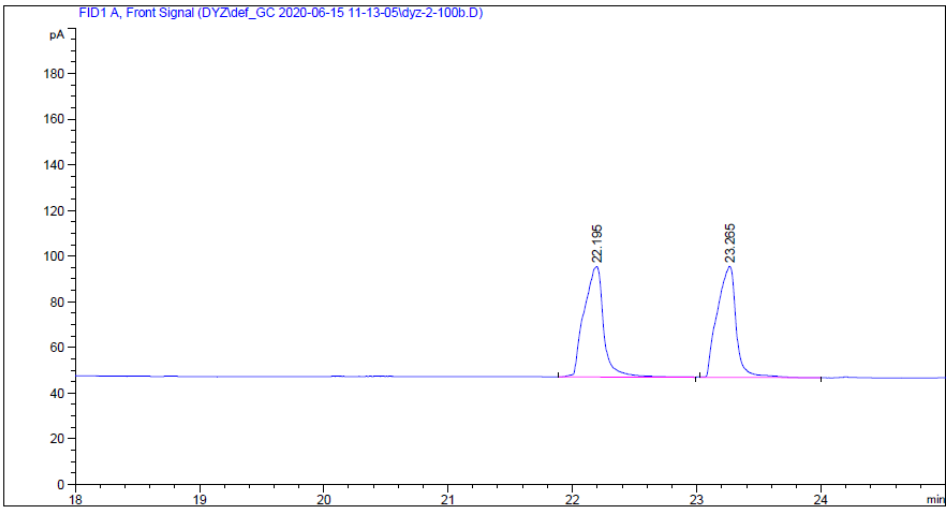

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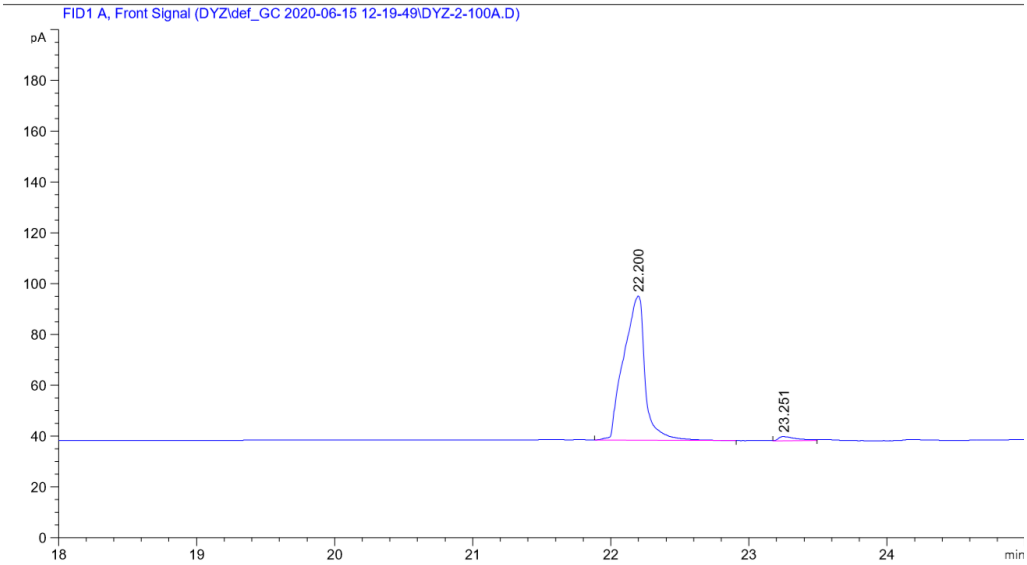
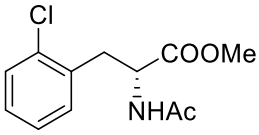
1	22.195	BB	0.1512	526.74738	48.32098	50.71864
2	23.265	BB	0.1399	511.82022	48.60297	49.28136



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	22.200	BB	0.1373	609.61768	56.76505	97.54092
2	23.251	MM	0.1542	15.36890	1.66061	2.45908



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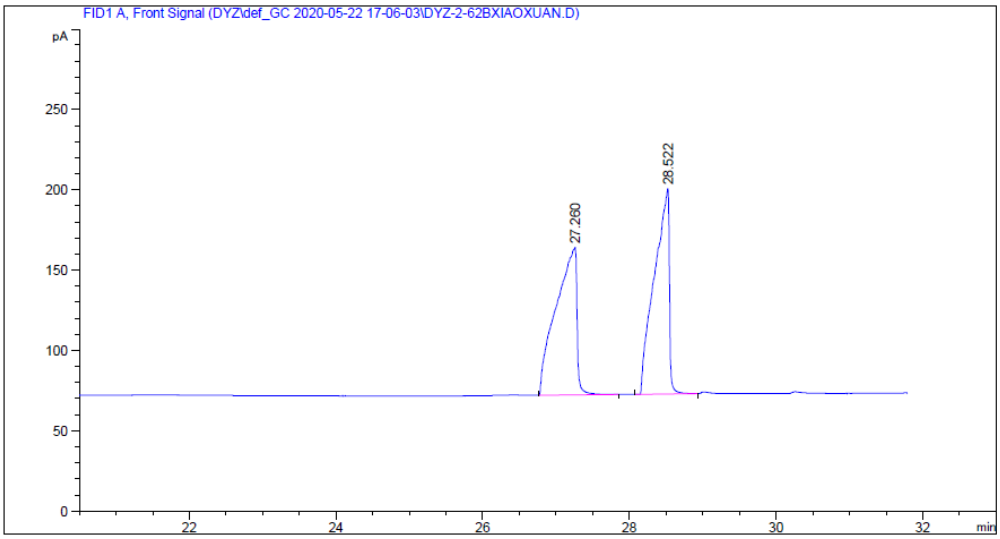
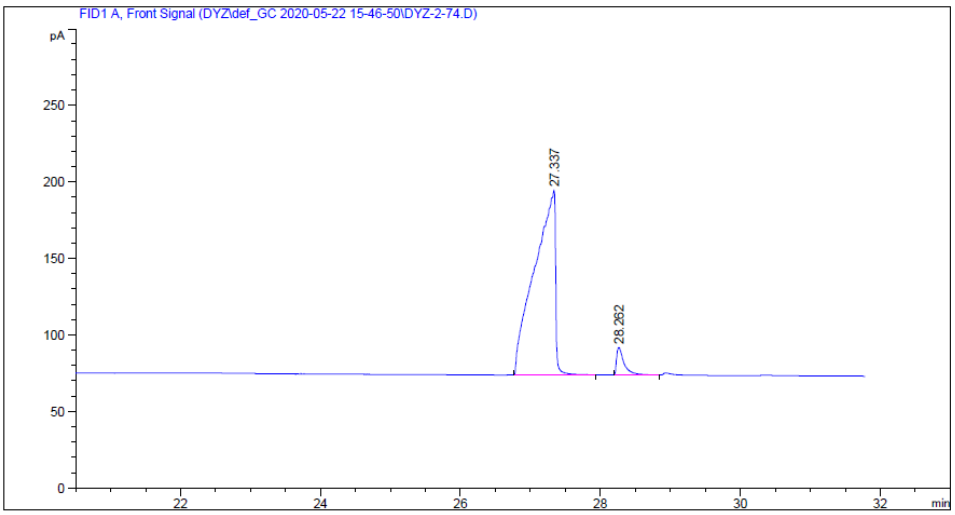
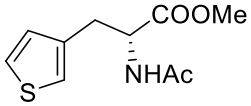


Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	27.260	BB	0.2393	1815.08447	91.94624	50.07011
2	28.522	BB	0.1740	1810.00110	127.99702	49.92989



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	27.337	BB	0.2536	2506.21069	120.53541	94.91247
2	28.262	BB	0.1122	134.33881	17.96441	5.08753



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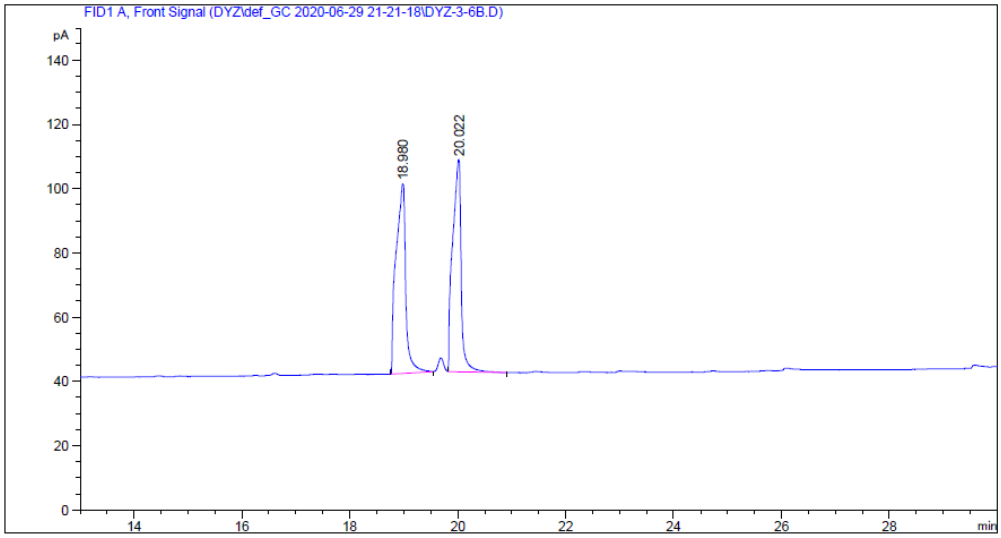
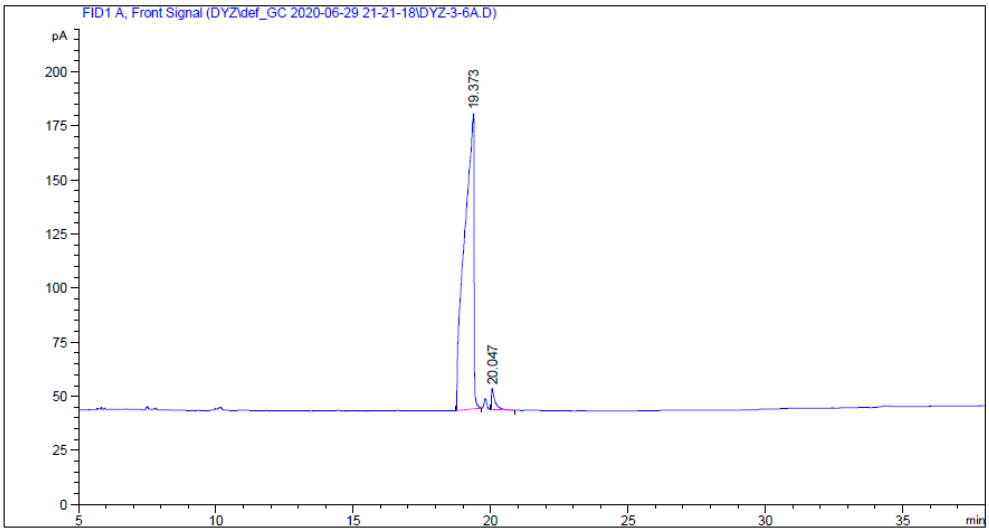
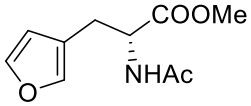


Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	18.980	BB	0.1639	737.13007	58.95929	50.18764
2	20.022	VB	0.1453	731.61823	66.03623	49.81236



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	19.373	BB	0.2864	3260.59399	136.66290	97.45380
2	20.047	BB	0.1156	85.19030	9.77859	2.54620



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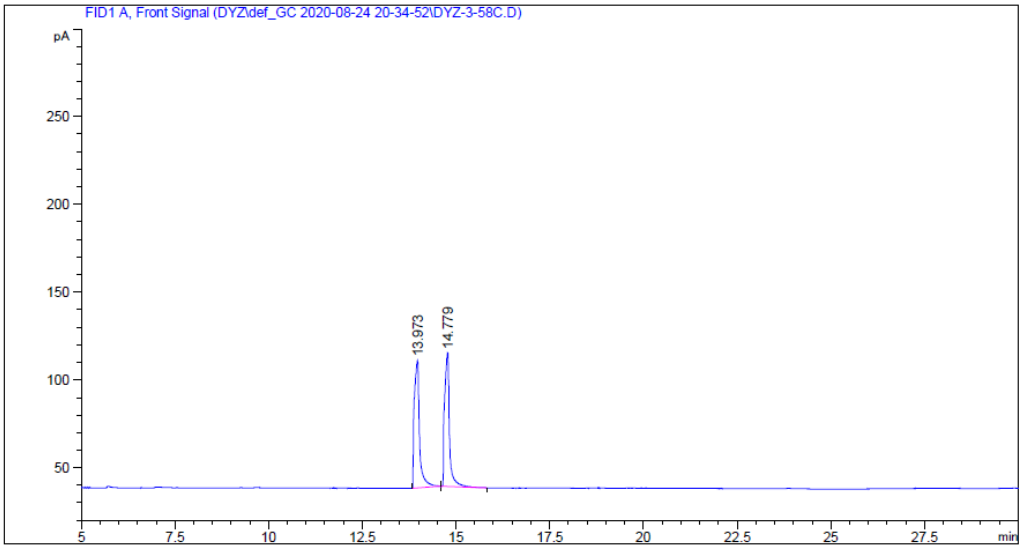
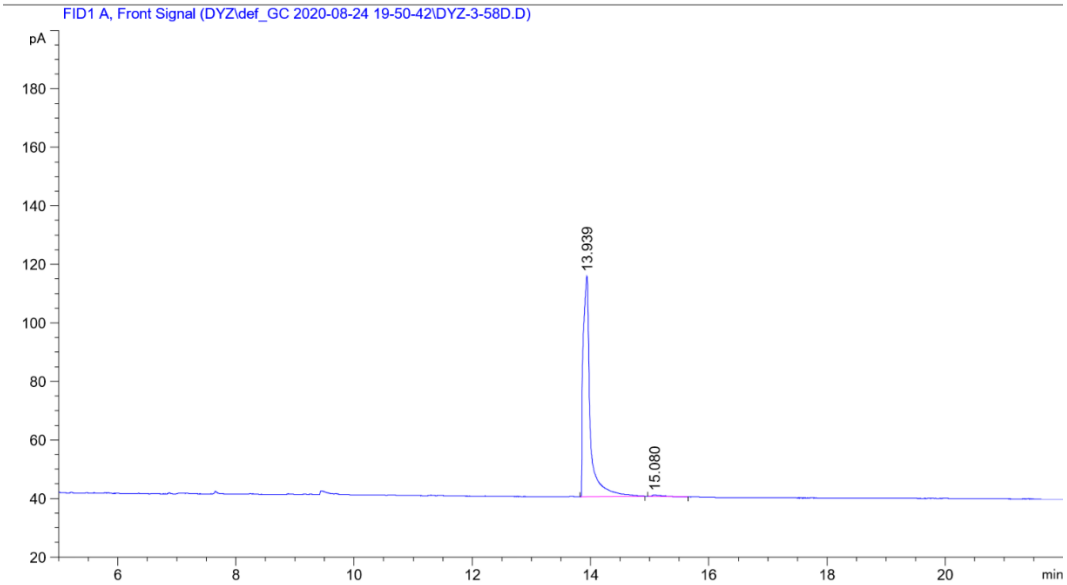
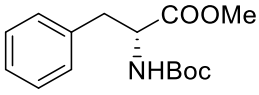


Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	13.973	BB	0.1294	700.33264	72.66418	50.52497
2	14.779	BB	0.1200	685.77930	76.16316	49.47503



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	13.939	BB	0.1121	634.52740	75.48859	99.19528
2	15.080	MM	0.1842	5.14760	4.65713e-1	0.80472



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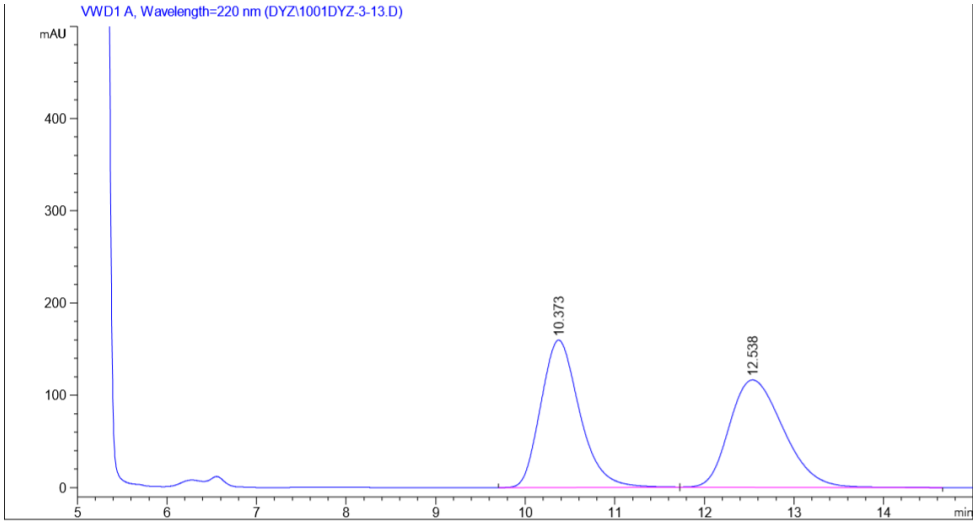
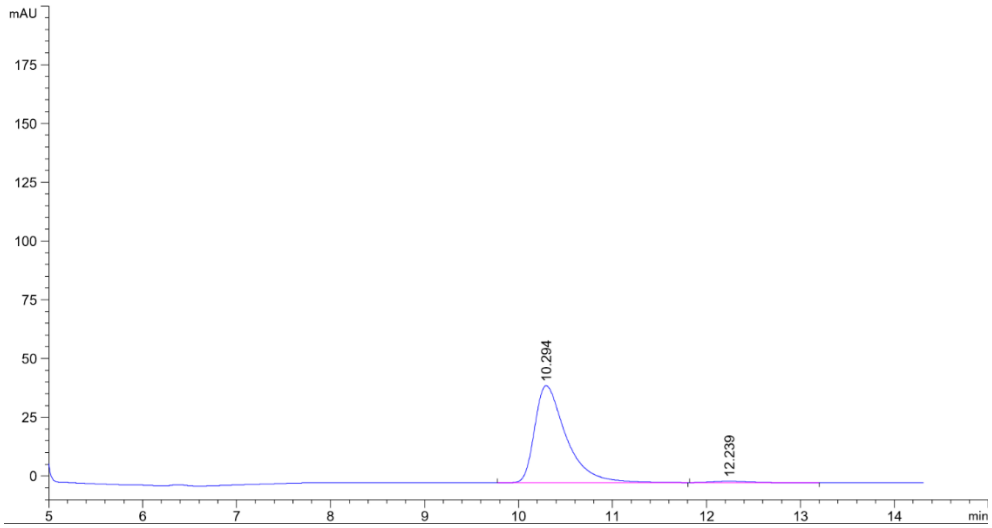
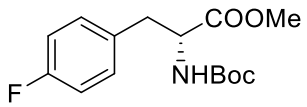


Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	10.373	BB	0.4640	4790.47363	159.69540	49.6872
2	12.538	BB	0.6578	4850.78076	116.24332	50.3128



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	10.294	BB	0.3474	959.46680	41.24044	97.9420
2	12.239	MM	0.4968	20.16089	6.76395e-1	2.0580



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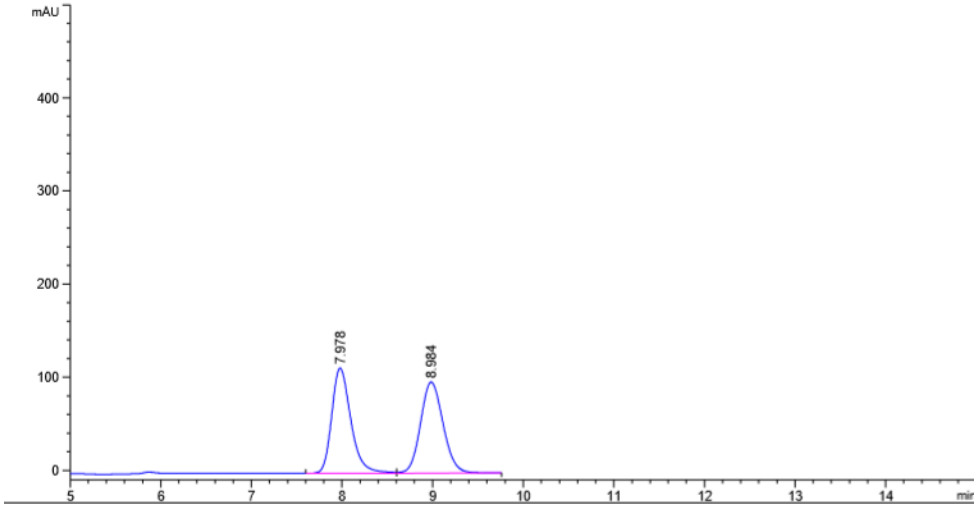
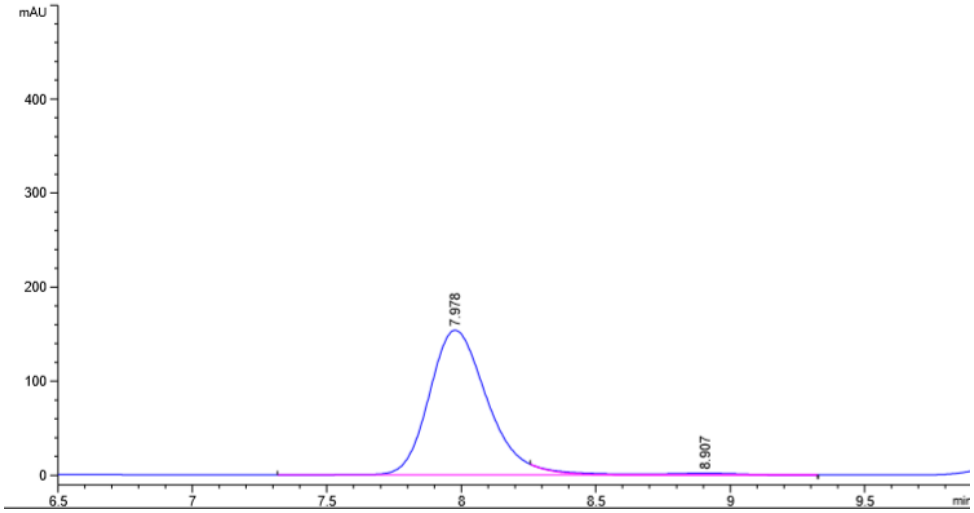
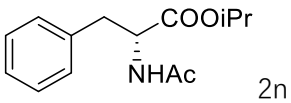


Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	7.978	BV	0.2245	1658.52649	112.83984	49.5618
2	8.984	VBA	0.2686	1687.85156	97.69234	50.4382



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	7.978	BV R	0.2314	2315.38916	154.01122	97.7145
2	8.907	VB E	0.4122	54.15570	1.81994	2.2855



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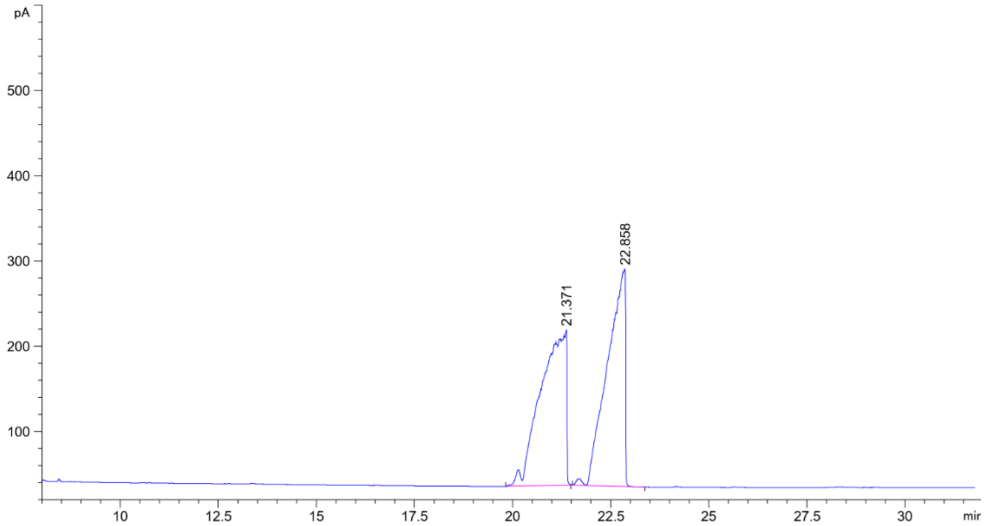
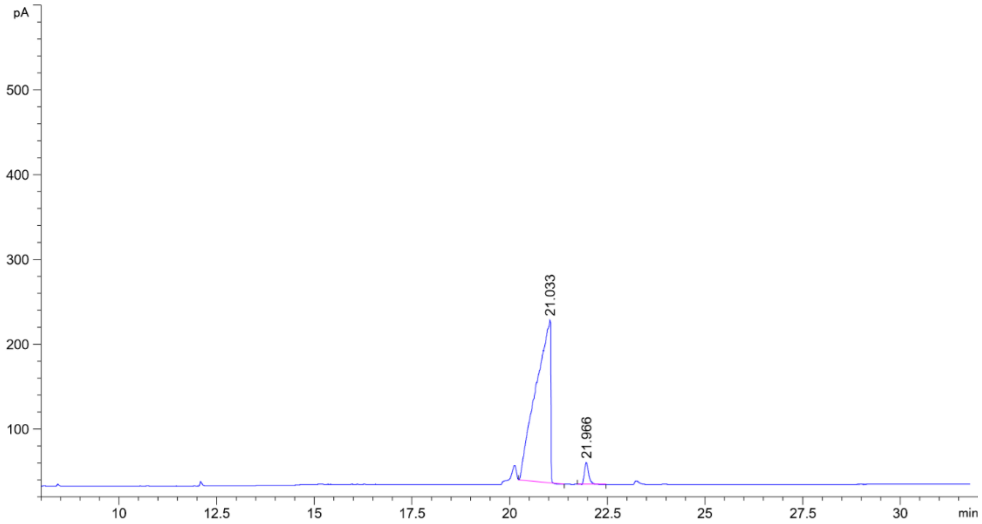
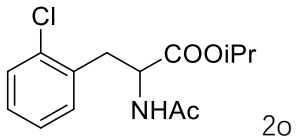


Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	21.371	MM	0.7538	8227.65137	181.92204	50.53497
2	22.858	MM	0.5264	8053.45215	254.96251	49.46503



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	21.033	MM	0.4365	5032.72021	192.17944	96.43120
2	21.966	MM	0.1229	186.25497	25.25395	3.56880



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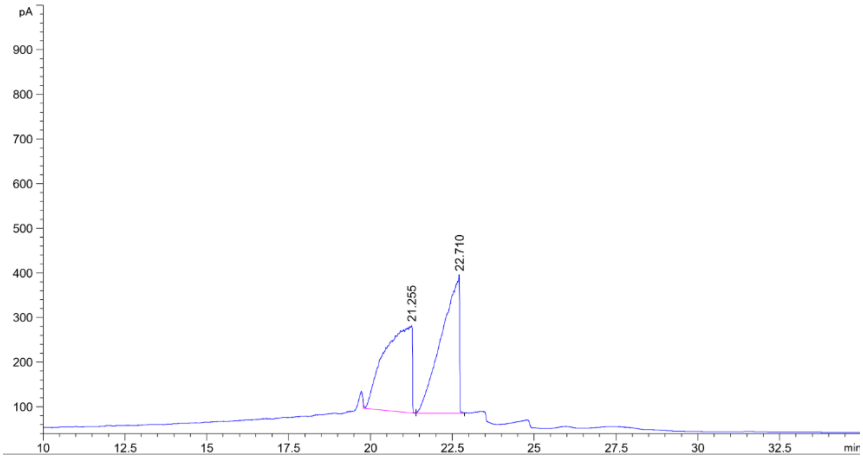
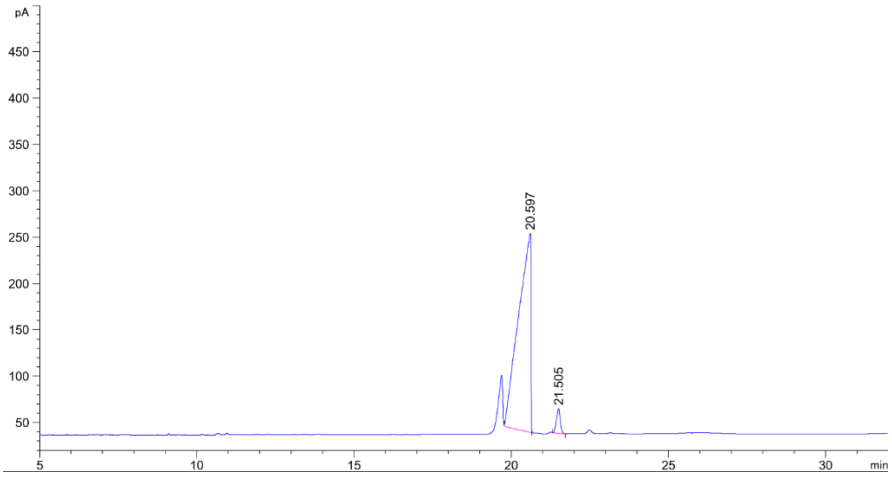
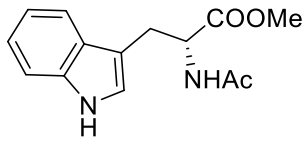


Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	21.255	MM	0.9560	1.12600e4	196.30672	49.06141
2	22.710	MM	0.6273	1.16909e4	310.62085	50.93859



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	20.597	MM	0.4533	5834.33398	214.52913	96.32856
2	21.505	BB	0.1208	222.36789	26.52867	3.67144



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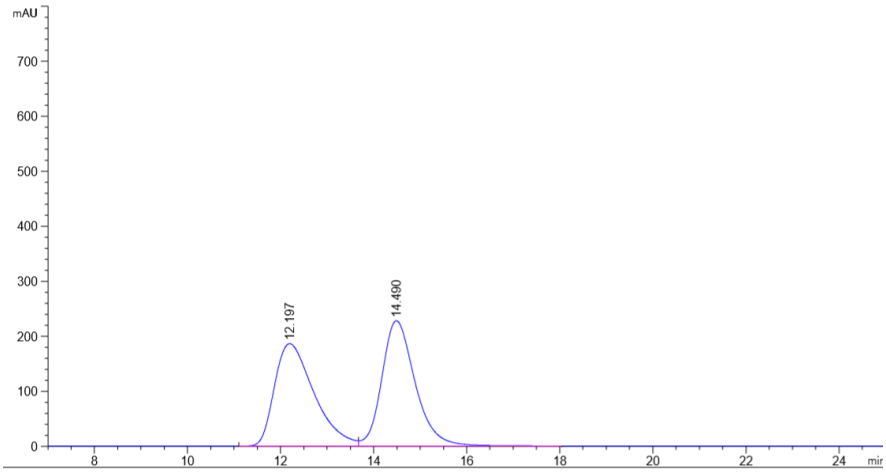
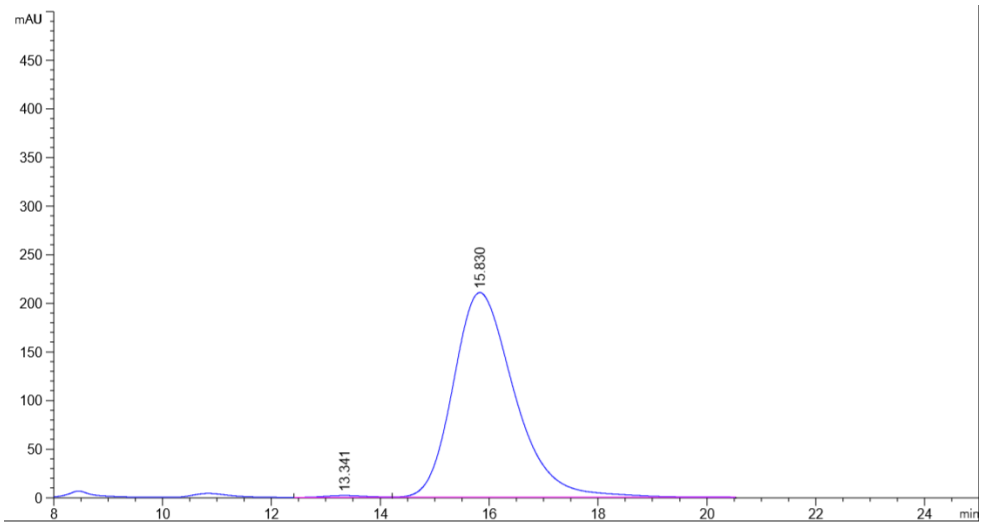
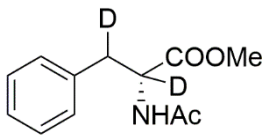


Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	12.197	BV	0.9028	1.09301e4	185.93152	49.1741
2	14.490	VB	0.7572	1.12972e4	227.56946	50.8259



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	13.341	BB	0.5962	82.42096	1.73829	0.4992
2	15.830	BBA	1.1934	1.64288e4	210.31090	99.5008



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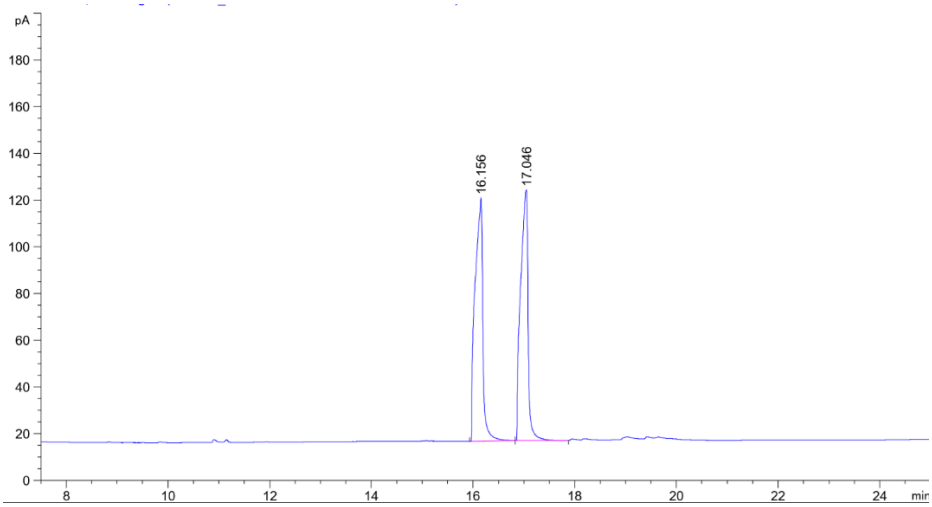
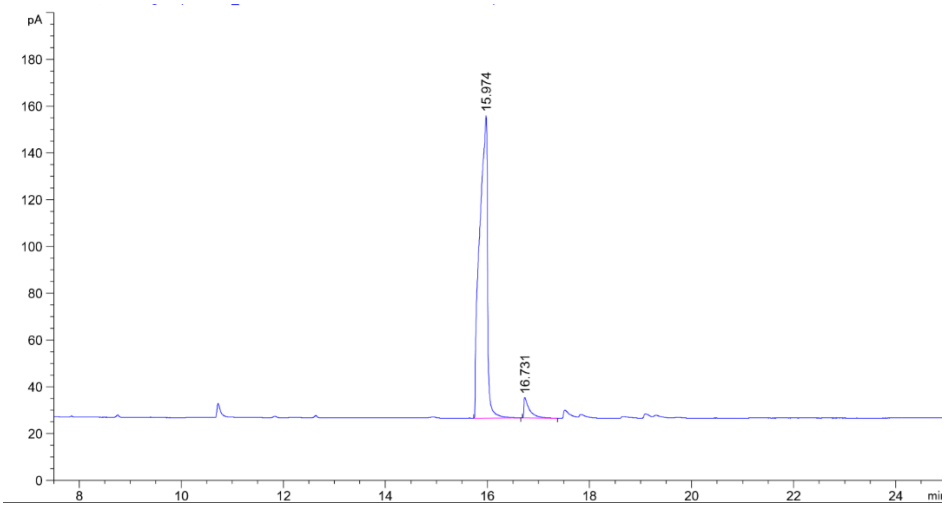
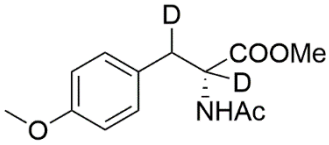


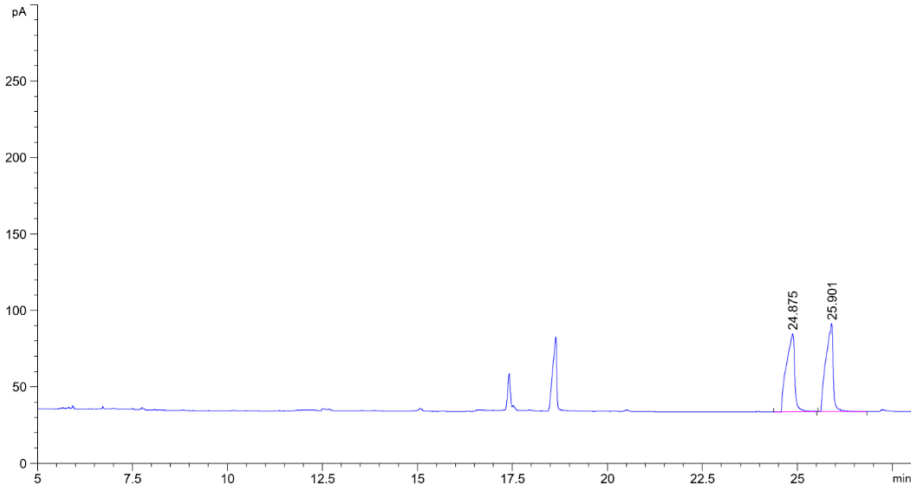
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	16.156	BB	0.1381	1106.37390	104.04253	50.15611
2	17.046	BB	0.1346	1099.48669	107.23270	49.84389



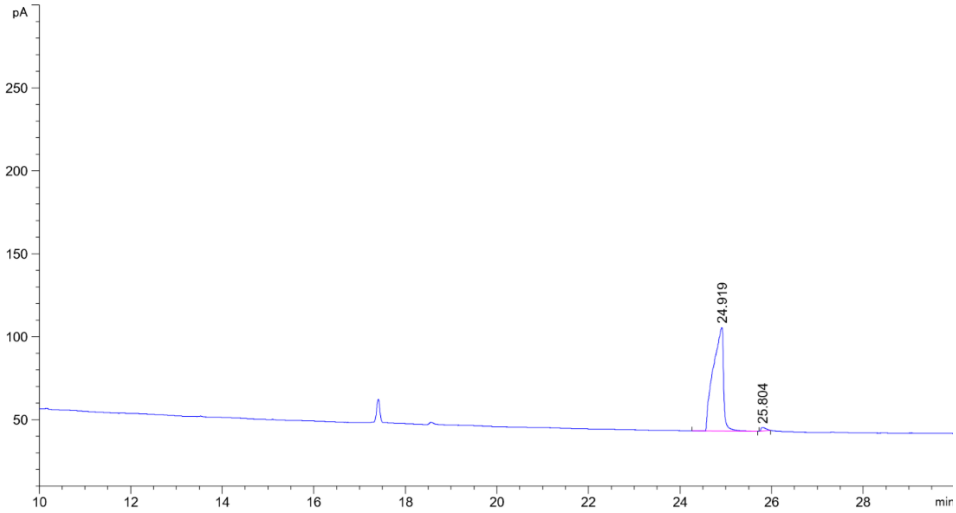
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	15.974	BB	0.1393	1400.90930	129.39996	95.47094
2	16.731	BB	0.1011	66.45798	8.70607	4.52906



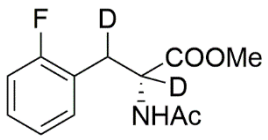
2d'



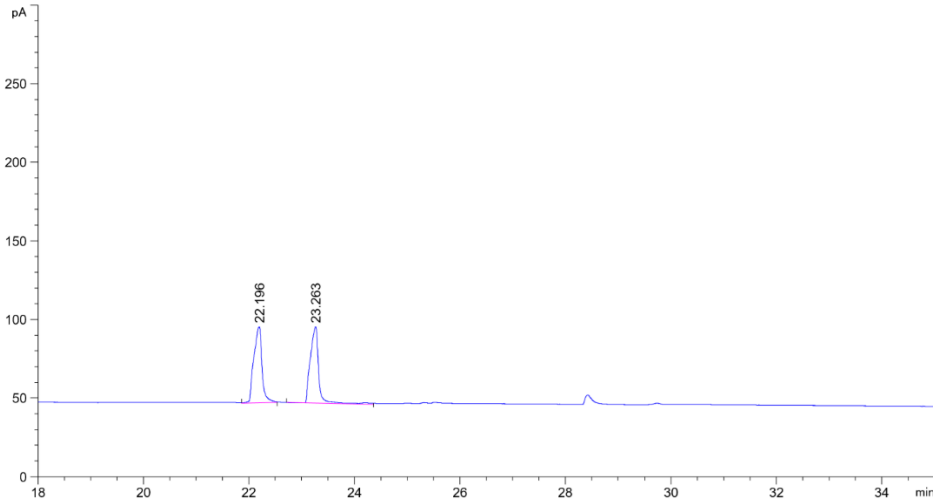
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	24.875	MM	0.2524	773.25079	51.06961	50.31317
2	25.901	MM	0.2220	763.62482	57.32741	49.68683



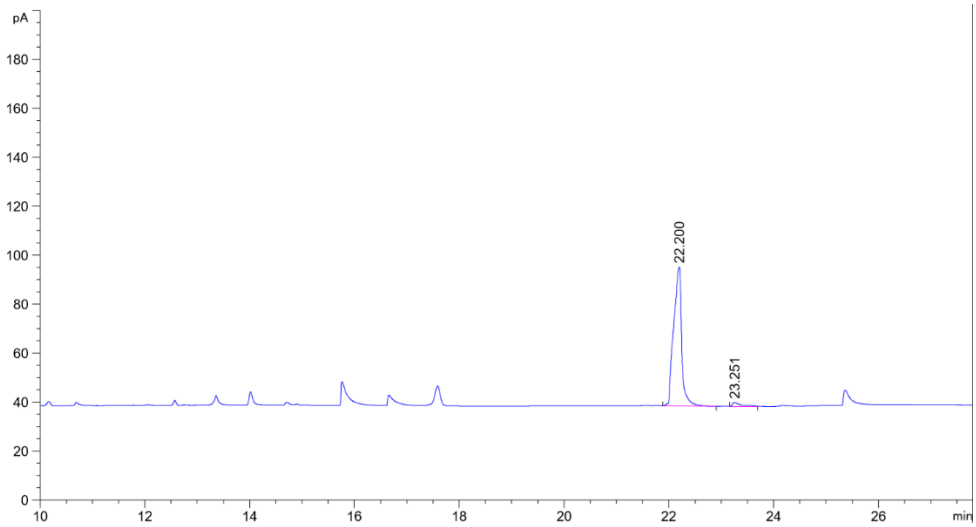
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	24.919	MM	0.2627	985.16986	62.49469	98.38940
2	25.804	MM	0.1198	16.12684	2.24411	1.61060



2h'



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	22.196	MM	0.1805	524.09381	48.39197	49.42517
2	23.263	MM	0.1836	536.28448	48.68873	50.57483



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	22.200	BB	0.1373	609.61768	56.76505	96.89772
2	23.251	MM	0.2006	19.51754	1.62132	3.10228