Supporting Information

N-Primary-Amine Tetrapeptide-Catalyzed Highly Asymmetric Michael Addition of Aliphatic Aldehydes to Maleimides†

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1. General Experimental Details

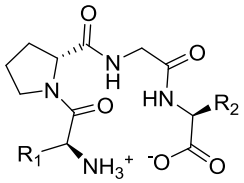
The reactions were carried out in vials and stirred with a magnetic bar without inert atmosphere unless specified. All commercial reagents were purchased with the analysis purity grade. They were used without further purification unless specified. All solvents used, mainly petroleum ether (PE) and ethyl acetate (EtOAc) were distilled. Anhydrous DCM and CH_3CN were freshly distilled from CaH_2, THF, Et_2O and toluene were freshly distilled from sodium/benzophenone before use. Anhydrous methanol and ethanol were distilled from Mg.

The reactions were monitored by TLC (thin layer chromatography) method; column and preparative TLC purifications were carried out using silica gel. Melting points were uncorrected and recorded on XT-5 melting point apparatus.

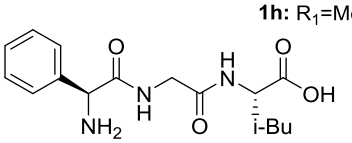
NMR spectra were acquired on a Bruker 400/600 spectrometer, running at 400/600 MHz and 100/151 MHz for ^1H and ^{13}C, respectively. NMR in $CDCl_3$, D_2O, DMSO-d_6 with TMS as an internal standard, chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CDCl_3$, 7.26 ppm for ^1H NMR and 77.00 ppm for ^{13}C NMR; D_2O, 4.80 ppm for ^1H NMR; DMSO-d_6, 2.50 ppm for ^1H NMR, 40.00 ppm for ^{13}C NMR). The following abbreviations are used to describe peak patterns when appropriate: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sept (septuplet), m (multiplet), br (broad). High resolution mass spectra (HR-MS) were measured with ESI-Orbitrap mass spectrometer.

Enantiomeric excess (ee) were decided with chiral HPLC, Waters 1525 Binary HPLC Pump/Waters 2998 Photodiode Array Detector of Lanzhou University State Key Laboratory of Applied Organic Chemistry.

2. Preparation and characterization of peptide catalysts

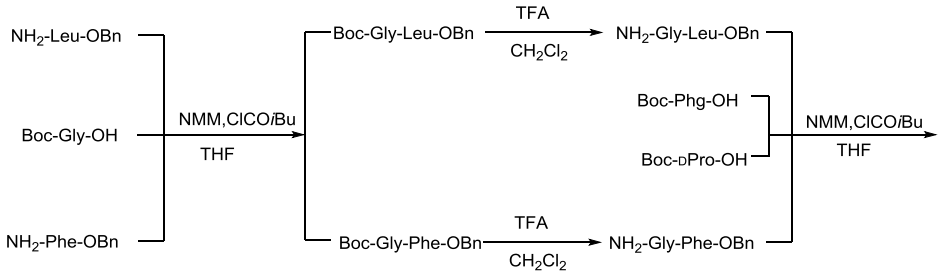


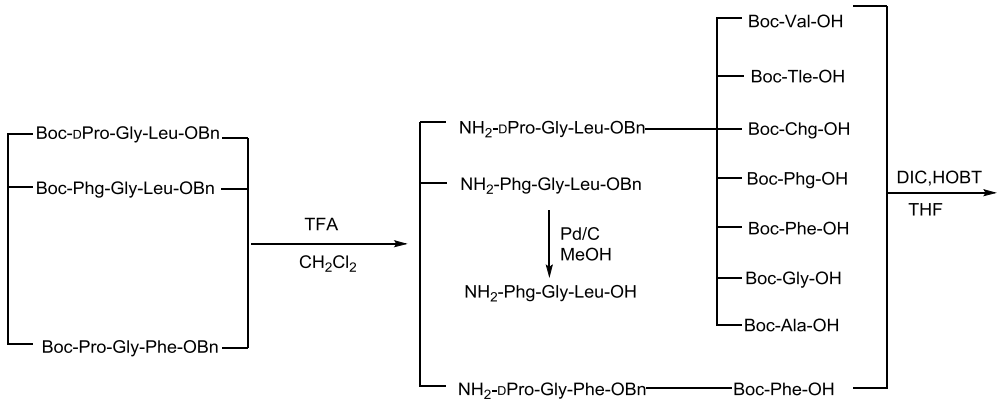
1a: R_1=*i*-Pr, R_2=*i*-Bu; NH_2-Val-DPro-Gly-Leu-OH
1b: R_1=*t*-Bu, R_2=*i*-Bu; NH_2-Tle-DPro-Gly-Leu-OH
1c: R_1=Cy, R_2=*i*-Bu; NH_2-Chg-DPro-Gly-Leu-OH
1d: R_1=Ph, R_2=*i*-Bu; NH_2-Phg-DPro-Gly-Leu-OH
1e: R_1=Bn, R_2=*i*-Bu; NH_2-Phe-DPro-Gly-Leu-OH
1f: R_1=Bn, R_2=Bn; NH_2-Phe-DPro-Gly-Phe-OH
1g: R_1=H, R_2=*i*-Bu; NH_2-Gly-DPro-Gly-Leu-OH
1h: R_1=Me, R_2=*i*-Bu; NH_2-Ala-DPro-Gly-Leu-OH

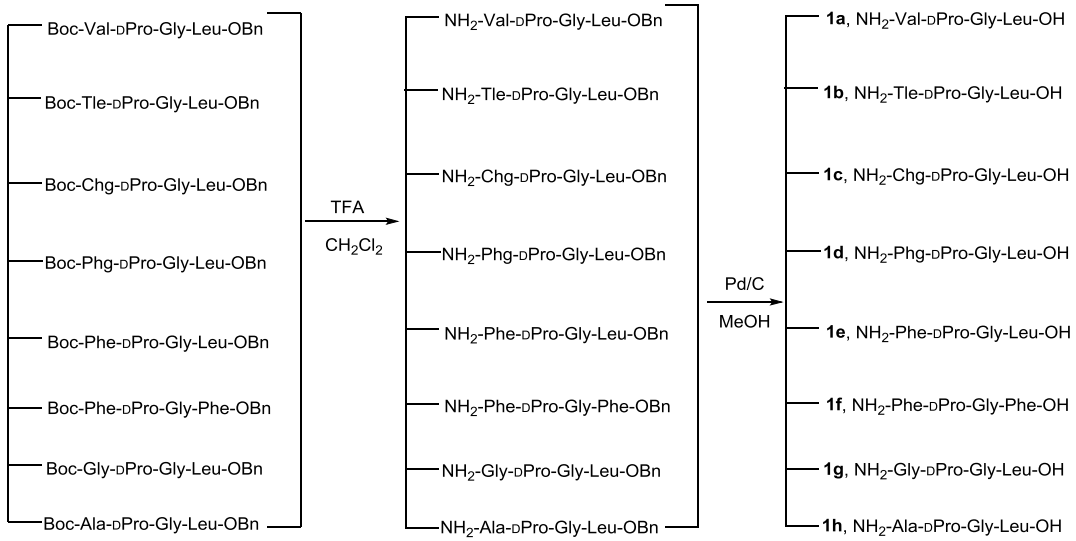


1i

1i: NH_2-Phg-Gly-Leu-OH







For the synthesis steps of the tetrapeptide catalyst, please refer to Reference [1]

1a: NH_2-Val-DPro-Gly-Leu-OH: white solid, mp 198 – 200 °C; $[\alpha]_D^{25}$ = + 36.0 (*c* 0.5, MeOH); ^{1}H NMR (600 MHz, D_2O) δ 4.53 – 4.51 (m, 1H), 4.30 – 4.25 (m, 2H), 4.05 – 4.02 (m, 1H), 3.92 – 3.83 (m, 3H), 3.77 – 3.73 (m, 1H), 2.39 – 2.34 (m, 2H), 2.12 – 2.05 (m, 3H), 1.73 – 1.63 (m, 4H), 1.13 (d, *J* = 7.2 Hz ,3H), 1.05 (d, *J* = 6.6 Hz ,3H), 0.95 (d, *J* = 6 Hz, 3H), 0.91 (d, *J* = 6 Hz, 3H); ^{13}C NMR (151 MHz, D_2O) δ 179.7, 174.3, 170.4, 168.9, 61.1, 57.1, 53.5, 48.1, 42.4, 40.5, 29.2, 28.7, 24.5, 24.3, 22.4, 20.5, 17.9, 15.9; HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ Calcd for $C_{18}H_{33}N_4O_5$ 385.2445, found: 385.2438.

1b: **NH_2-Tle-DPro-Gly-Leu-OH:** white solid, mp: 223 – 225 °C, $[\alpha]_D^{25}$ = + 4.0 (*c* 0.5, MeOH); ^{1}H NMR (600 MHz, D_2O) 4.37 – 4.34 (m, 1H), 4.10 (dd, *J* = 10.8, 3.6 Hz, 1H), 4.05 (s, 1H), 3.85 – 3.77 (m, 2H), 3.72 – 3.63 (m, 2H), 3.21 (d, *J* = 0.6 Hz, 1H), 2.23 – 2.19 (m, 1H), 1.94 – 1.88 (m, 3H), 1.58 – 1.51 (m, 1H), 1.49 – 1.44 (m, 2H), 0.97 (s, 9H), 7.78 – 7.73 (m, 6H); ^{13}C NMR (151 MHz, D_2O) δ 179.8, 174.4, 170.4, 168.2, 61.0, 59.1, 53.7, 49.0, 42.4, 40.6, 33.9, 29.3, 25.3, 24.5, 24.3, 22.4, 20.5; HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ Calcd for $C_{19}H_{31}N_4O_5$ 399.2602, found: 399.2599.

1c: NH_2-Chg-DPro-Gly-Leu-OH: white solid, mp 212 – 214 °C; $[\alpha]_D^{25}$ = + 32 (*c* 0.5, MeOH); ^{1}H NMR (600 MHz, D_2O) δ 4.51 – 4.48 (m, 1H), 4.30 – 4.23 (m, 2H), 4.07 – 4.01 (m, 1H), 3.93 – 3.72 (m, 3H), 2.41 – 2.32 (m, 1H), 2.11 – 1.96 (m, 3H), 1.83 – 1.58 (m, 7H), 1.35 – 1.12 (m, 5H), 0.96 – 0.90 (m, 6H); ^{13}C NMR (151 MHz, D_2O) δ 179.6, 174.3, 170.4, 168.9, 61.1, 56.6, 53.9, 53.4, 48.1, 42.4, 40.5, 38.5, 29.3, 28.5, 27.1, 25.1, 24.5, 24.2, 22.4, 20.5; HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ Calcd for $C_{21}H_{37}N_4O_5$ 425.2758, found: 425.2748.

1d: NH_2-Phg-DPro-Gly-Leu-OH: white solid, mp 210 – 212 ℃; $[\alpha]_D^{25}$ = + 72.0 (*c* 0.5, MeOH); ^{1}H NMR (600 MHz, D_2O) δ 7.60 – 7.44 (m, 5H), 5.47 (s, 1H), 4.50 (dd, *J* = 9.0, 3.6 Hz, 1H), 4.31 (dd, *J* = 10.2, 3.0 Hz, 1H), 4.11 – 4.08 (m, 1H), 3.90 – 3.87 (m, 1H), 3.77 – 3.73 (m, 1H), 3.05 – 3.02 (m, 1H), 2.23 – 2.16 (m, 1H), 2.02 – 1.95 (m, 2H), 1.85 – 1.73 (m, 2H), 1.68 – 1.63 (m, 2H), 0.98 – 0.87 (m, 6H); ^{13}C NMR (151 MHz, D_2O) δ 179.9, 174.3, 170.3, 167.4, 130.6, 129.9, 129.6, 129.0, 128.5, 61.5, 56.4, 53.6, 47.5, 42.4, 40.6, 29.0, 24.6, 24.2, 22.5, 20.6; HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ Calcd for $C_{21}H_{31}N_4O_5$ 419.2289, found: 419.2295.

***ent*-1d: NH_2-DPhg-Pro-Gly-DLeu-OH:** white solid, mp 210 – 212 ℃; $[\alpha]_D^{25}$ = - 72.0 (*c* 0.5, MeOH).

1e: NH_2-Phe-DPro-Gly-Leu-OH: white solid, mp 224 – 226 °C, $[\alpha]_D^{25}$ = + 60.0 (*c* 0.5, MeOH); ^{1}H NMR (600 MHz, D_2O) 7.47 – 7.41 (m, 3H), 7.35 (d, *J* = 6.6 Hz, 2H), 4.60 (dd, *J* = 9.0, 6.6 Hz, 1H), 4.37 (dd, *J* = 9.0, 4.8 Hz, 1H), 4.26 (dd, *J* = 10.2, 3.6 Hz, 1H), 4.02 – 3.99 (m, 1H), 3.90 – 3.87 (m, 1H), 3.62 – 3.58 (m, 1H), 3.28 – 3.19 (m, 2H), 2.85 – 2.81 (m, 1H), 2.16 – 2.09 (m, 1H), 1.96 – 1.85 (m, 2H), 1.72 – 1.62 (m, 4H), 0.95 – 0.89 (m, 6H); ^{13}C NMR (151 MHz, D_2O) δ 179.8, 174.1, 170.3, 168.5, 133.4, 129.4, 129.1, 128.1, 61.0, 53.6, 53.0, 47.7, 42.4, 40.5, 36.3, 29.1, 24.5, 24.0, 22.4, 20.5; HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ Calcd for $C_{22}H_{33}N_4O_5$ 433.2445, found: 433.2439.

1f: NH_2-Phe-DPro-Gly-Phe-OH: white solid, mp 203 – 205 °C, $[\alpha]_D^{25}$ = + 74.0 (*c* 0.5, MeOH); ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.42 – 8.18 (m, 2H), 7.35 – 7.12 (m, 10H), 4.36 –

4.14 (m, 3H), 3.72 – 3.68 (m, 1H), 3.48 – 3.37 (m, 2H), 3.20 – 3.12 (m, 1H), 3.02 – 2.85 (m, 3H), 1.84 – 1.68 (m, 3H), 1.39 – 1.35 (m, 1H), 1.00 (d, *J* = 6.6 Hz, 1H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 175.5, 171.5, 170.2, 168.3, 139.3, 136.0, 129.9, 129.7, 128.9, 128.3, 127.6, 126.3, 61.2, 52.9, 47.1, 42.1, 38.8, 29.4, 24.4, 23.7; HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ Calcd for $C_{25}H_{31}N_4O_5$ 467.2288, found: 467.2289.

Boc-Gly-ᴅPro-Gly-Leu-OBn: yellow oil, $[\alpha]_D^{25}$ = + 32.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 – 7.27 (m, 4H), 7.17 (d, *J* = 7.8 Hz, 1H), 7.09 (s, 1H), 5.45 (s, 1H), 5.14 (s, 2H), 4.68 – 4.65(m, 1H), 4.44 (dd, *J* = 7.8, 4.2 Hz, 1H), 4.01 – 3.92 (m, 3H), 3.82 (dd, *J* = 17.4, 3.0 Hz, 1H), 3.62 – 3.59 (m, 1H), 3.46 (dd, *J* = 16.2, 7.2 Hz, 1H), 2.22 – 2.07 (m, 3H), 2.02 – 1.98 (m, 1H), 1.72 – 1.65 (m, 3H), 1.43 (s, 9H), 0.92 (dd, *J* = 9.0, 6.0 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.1, 171.5, 169.4, 168.9, 135.4, 128.6, 128.3, 128.1, 79.8,67.0, 61.0), 50.8, 46.6, 43.1, 41.0, 28.4, 25.1, 24.8, 22.9, 21.8.

Boc-Ala-ᴅPro-Gly-Leu-OBn: yellow oil, $[\alpha]_D^{25}$ = - 7.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 – 7.35 (m, 4H), 7.21 (d, *J* =7.8 Hz, 1H), 5.37 (d, *J* = 6.0 Hz, 1H), 5.16 (d, *J* = 3.6 Hz, 2H), 4.65 – 4.62 (m 1H), 4.48 (dd, *J* = 7.8, 4.2 Hz, 1H), 4.36 – 4.32 (m, 1H), 4.12 – 4.04 (m, 1H), 3.96 (d, *J* = 12.6 Hz, 1H), 3.72 (dd, *J* = 16.8, 5.4 Hz, 1H), 3.54 (dd, *J* = 17.4, 7.8 Hz, 1H), 2.21 – 2.15 (m, 3H), 2.11 – 2.06 (m, 1H), 2.02 – 1.98 (m, 2H), 1.69 – 1.64 (m, 4H), 1.40 (s, 9H), 1.27 (d, *J* = 7.2 Hz, 3H), 0.90 (dd, *J* = 10.2, 6.0 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.0, 172.7, 171.6, 169.0, 135.7, 128.5, 128.2, 128.0, 80.4, 66.6, 61.2, 50.8, 47.5, 43.3, 41.0, 29.0, 28.3, 24.8, 24.7, 22.9, 21.8.

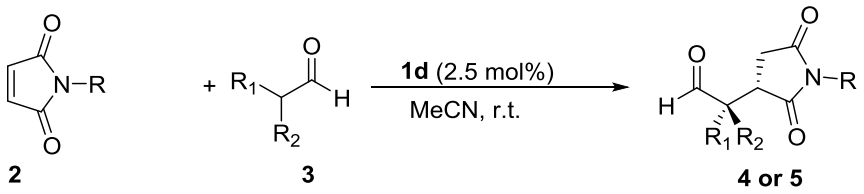
Boc-Phg-Gly-Leu-OBn: yellow oil, $[\alpha]_D^{25}$ = + 53.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (600 MHz,$CDCl_3$) δ 7.37 – 7.26 (m, 9H), 6.89 (s, 1H), 6.77 (s, 1H), 5.72 (d, *J* = 6.0 Hz, 1H), 5.17 – 5.11(m, 3H), 4.62 – 4.58 (m, 1H), 4.03 (dd, *J* = 16.8, 6.0Hz, 1H), 3.84 (dd, *J* = 16.8, 4.8Hz, 1H), 1.61 –1.54 (m, 3H), 1.41 (s, 9H), 0.86 (t, *J* = 6.0 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.5, 170.8, 168.4, 135.4, 129.1, 128.6, 128.4, 128.2, 127.3, 67.1, 51.0, 43.2, 41.1, 28.3, 24.7, 22.7, 21.8.

1g: NH_2-Gly-ᴅPro-Gly-Leu-OH: white solid, mp 167 – 169 ^{o}C, $[\alpha]_D^{25}$ = + 34.0 (*c* 1.0, MeOH); ^{1}H NMR (600 MHz, D_2O) δ 4.32 – 4.26 (m, 2H), 4.12 (dd, *J* = 10.2, 3.0 Hz, 1H), 3.88 (d, *J* = 17.4 Hz, 1H), 3.71 (d, *J* = 17.4 Hz, 1H), 3.68 – 3.65 (m, 1H), 3.54 – 3.50 (m, 1H), 2.22 – 2.19 (m, 1H), 1.96 – 1.88 (m, 2H), 1.54 – 1.46 (m, 3H), 1.38 (d, *J* = 6.6 Hz, 2H), 1.08 (s, 1H), 0.79 – 0.73 (m, 6H). ^{13}C NMR (151 MHz, D_2O) δ 182.4, 177.0, 172.9, 168.9, 63.6, 56.2, 51.2, 49.4, 44.9, 43.1, 31.9, 28.4, 26.9, 25.0, 23.2; HRMS (ESI-Orbitrap) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{26}N_4NaO_5$ 365.1795, Found 365.1807.

1h: NH_2-Ala-ᴅPro-Gly-Leu-OH: white solid, mp 234.3 – 236.2 ^{o}C, $[\alpha]_D^{25}$ = + 19.0 (*c* 1.0, MeOH); ^{1}H NMR (600 MHz, D_2O) δ 4.32 (dd, *J* = 9.0, 5.4 Hz, 1H), 4.11 (dd, *J* = 10.2, 3.6 Hz, 1H), 3.90 – 3.87 (m, 2H), 3.72 (d, *J* = 16.8 Hz, 1H), 3.53 – 3.50 (m, 1H), 3.48 – 344 (m, 1H), 3.09 (s, 1H), 2.23 – 2.20 (m, 1H), 1.94 – 1.87 (m, 3H), 1.55 – 1.46 (m, 3H), 1.08 (s, 3H), 0.76 (dd, *J* = 24.0, 6.0 Hz, 6H). ^{13}C NMR (151 MHz, D_2O) δ 179.6, 174.4, 170.4, 169.8, 61.3, 53.5, 48.3, 47.6, 42.3, 40.5, 29.2, 25.9, 24.3, 22.4, 20.5, 14.6; HRMS (ESI-Orbitrap) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{28}N_4NaO_5$ 379.1952, Found 379.1956.

1i: NH_2-Phg-Gly-Leu-OH: white solid, mp 233 – 235 °C, $[\alpha]_D^{25}$ = + 36.0 (*c* 0.5, MeOH); ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.57 (s, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 7.45 (d, *J* = 7.8 Hz, 2H), 7.34 – 7.26 (m, 3H), 4.61 (s, 1H), 4.22 – 4.19 (m, 1H), 3.78 – 3.66 (m, 2H), 1.59 – 1.56 (m, 1H), 1.51 – 1.41 (m, 2H), 0.84 (dd, *J* = 17.4, 6.6 Hz, 6H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 174.4, 171.6, 167.9, 140.0, 128.1, 127.4, 127.1, 57.8, 50.8, 42.0, 40.9, 39.8, 39.7, 39.5, 39.4, 39.3 39.1, 39.0, 24.1, 22.9, 22.0; HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ Calcd for $C_{16}H_{24}N_3O_4$ 322.1761, Found 3221764.

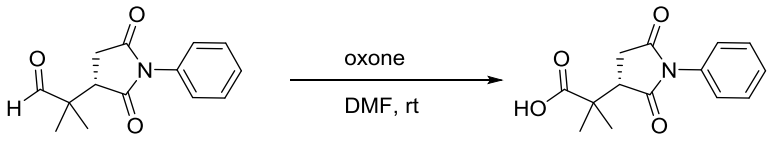
3. General procedure for the Michael addition reaction.



2 3 4 or 5

In a 5 mL round bottom flask equipped with a magnetic stirrer, the catalyst **1d** (5.2 mg, 0.0125 mmol), maleimide (0.5 mmol), aldehyde **3** (1 mmol) and acetonitrile (1.0 mL) were sequentially added and stirred at room temperature and detected by TLC. After the reaction was completed, the mixture was directly purified by column chromatography on silica gel (PE: EA=5:1) to give products.

4. Synthesis of product 6.[2]

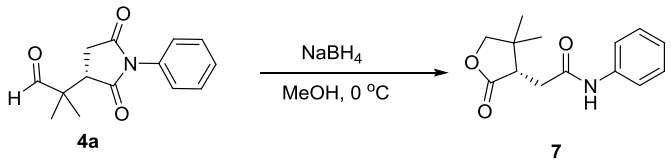


4a 6

Aldehyde **4a** (122.5 mg, 0.5 mmol) was dissolved in dry DMF (5 ml), potassium peroxymonosulfate (622 mg, 1.0 mmol) was added and the mixture was stirred at room temperature until the reaction completed. The reaction mixture was extracted with EtOAc (3 × 20 mL) and 1 M aq. HCl (20 mL). The combined organic layers were washed with 1 M aq. HCl (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered and all volatiles were removed at reduced pressure. The crude product was purified by column chromatography on silica gel (PE: EA=5:1) to give products **6** as a colorless solid (115 mg, 88% yield).

(*S*)-2-(2,5-dioxo-1-phenylpyrrolidin-3-yl)-2-methylpropanoic acid, ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.64 (s, 1H), 7.52 – 7.47 (m, 2H), 7.44 – 7.39 (m, 1H), 7.23 – 7.19 (m, 2H), 3.18 (dd, *J* = 9.6, 5.4 Hz, 1H), 2.94 (dd, *J* = 18.0, 9.6 Hz, 1H), 2.70 – 2.60 (m, 1H), 1.37 (s, 3H), 1.22 (s, 3H).

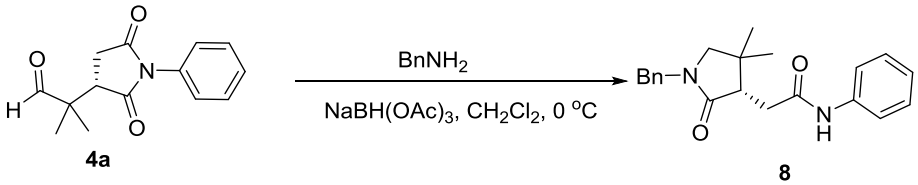
5. Synthesis of product 7.



4a 7

Aldehyde **4a** (122.5 mg, 0.5 mmol) was dissolved in dry MeOH (5.0 mL) under an argon atmosphere and the solution was cooled to 0 ℃. $NaBH_4$ (95 mg, 2.5 mmol) was added. Then the mixture was allowed to warm up to room temperature and kept stirring until the reaction completed. The reaction mixture was extracted with CH_2Cl_2 (3 × 20 mL), the combined organic layers were dried over Na_2SO_4, filtered and all volatiles were removed at reduced pressure. The crude product was purified by column chromatography on silica gel (PE: EA=5:1) to give lactone **7** as a colorless solid (94 mg, 76% yield).

6. Synthesis of product 8.

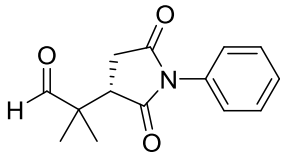


4a 8

Aldehyde **4a** (122.5 mg, 0.5 mmol) was dissolved in dry CH_2Cl_2 (5.0 mL) under an argon atmosphere and the solution was cooled to 0 ℃. AcOH (60 μL, 1 mmol), benzylamine (110 μL, 1.0 mmol) and $NaBH(OAc)_3$ (328 mg, 1.50 mmol) were added, the mixture was allowed to warm up to room temperature and kept stirring for 4 h. DIEA (175 μl, 1.0 mmol) was added and the stirring was continued for 20 h. The mixture was then extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and all volatiles were removed at reduced pressure. The crude product was purified by column chromatography on silica gel (PE: EA=5:1) to give lactam **8** as a colorless solid (104 mg, 62%).

7. Characterization of Michael addition reaction products

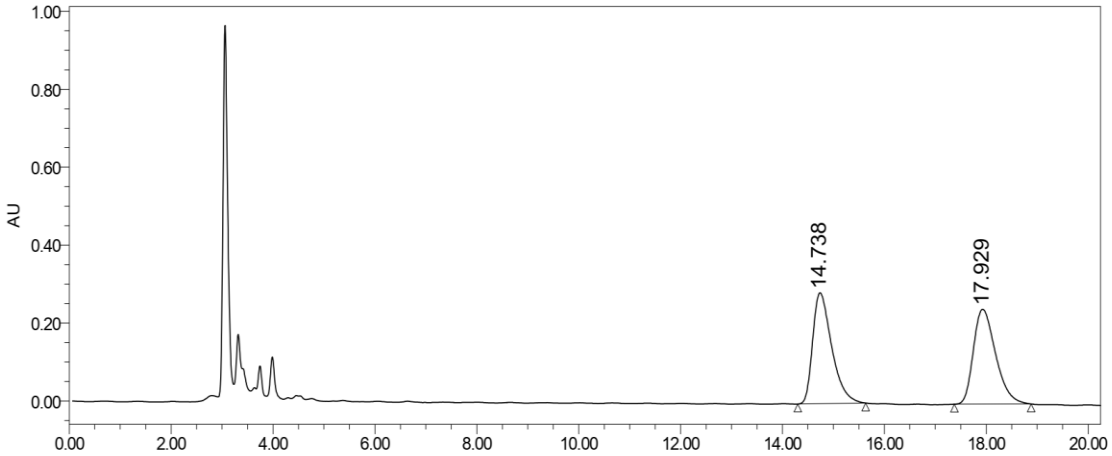
(*S*)-2-(2, 5-dioxo-1-phenylpyrrolidin-3-yl)-2-methylpropanal[3]



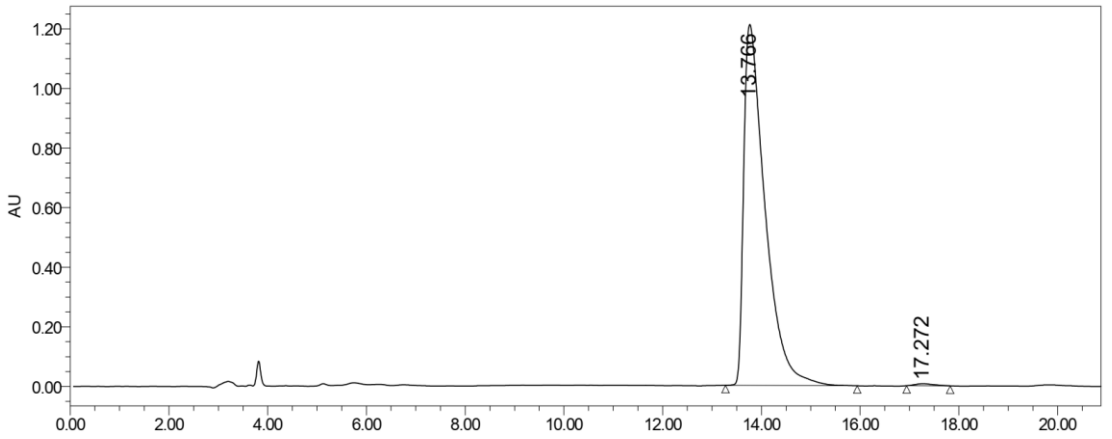
4a

4a: 120 mg, 98% yield, white solid, $[\alpha]_D^{25} = -6.0$ (*c* =1.0, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.48 – 7.44 (m, 2H), 7.40 – 7.36 (m, 1H), 7.29 – 7.25 (m, 2H), 3.14 (dd, *J* = 9.6, 5.6 Hz, 1H), 2.96 (dd, *J* = 18.6, 9.6 Hz, 1H), 2.61 (dd, *J* = 18.4, 5.6 Hz, 1H), 1.32 (s, 3H), 1.28 (s, 3H).

The ee was determined by HPLC analysis. CHIRALPAK OD-H; Hexane/2-propanol=70:30; flow rate 1.0 mL/min; 225.1 nm; retention time: 13.8 min (major) and 17.3 min (minor).

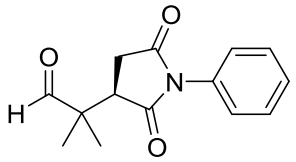


	name	Retention	Area(μV*s)	Height（μV）	% Area
1		14.738	7406303	284710	50.06
2		17.929	7387921	243519	49.94



	name	Retention	Area(μV*s)	Height（μV）	% Area
1		13.766	36286344	1210845	99.51
2		17.272	178032	6636	0.49

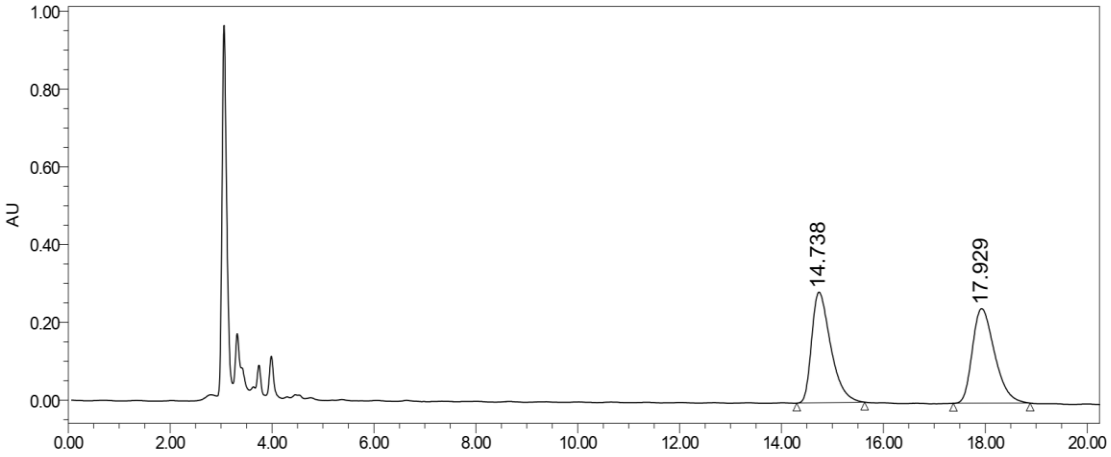
(*R*)-2-(2, 5-dioxo-1-phenylpyrrolidin-3-yl)-2-methylpropanal[3]



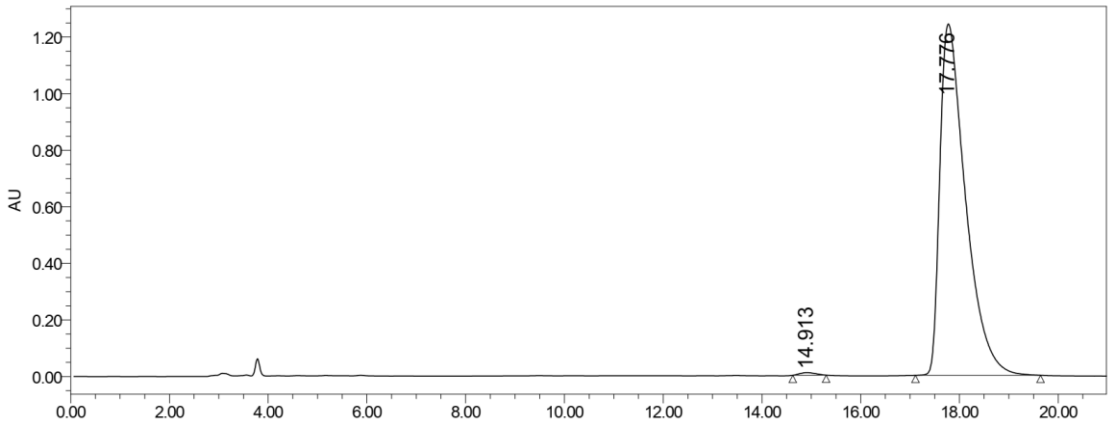
ent-**4a**

ent-**4a:** 120 mg, 98% yield, white solid, $[\alpha]_D^{25}$ = + 6.0 (*c* =1.0, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.48-7.44 (m, 2H), 7.40 – 7.36 (m, 1H), 7.29 – 7.25 (m, 2H), 3.14 (dd, *J* = 9.6, 5.6 Hz, 1H), 2.96 (dd, *J* = 18.6, 9.6 Hz, 1H), 2.61 (dd, *J* = 18.4, 5.6 Hz, 1H), 1.32 (s, 3H), 1.28 (s, 3H).

The ee was determined by HPLC analysis. CHIRALPAK OD-H; Hexane/2-propanol=70:30; flow rate 1.0 mL/min; 225.1 nm; retention time: 14.9 min (minor) and 17.8 min (major).

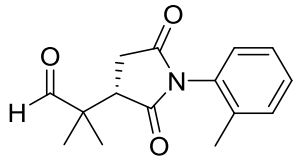


	name	Retention	Area(μV*s)	Height（μV）	% Area
1		14.738	7406303	284710	50.06
2		17.929	7387921	243519	49.94



	name	Retention	Area(μV*s)	Height（μV）	% Area
1		14.917	197953	9063	0.44
2		17.776	44754634	1242023	99.56

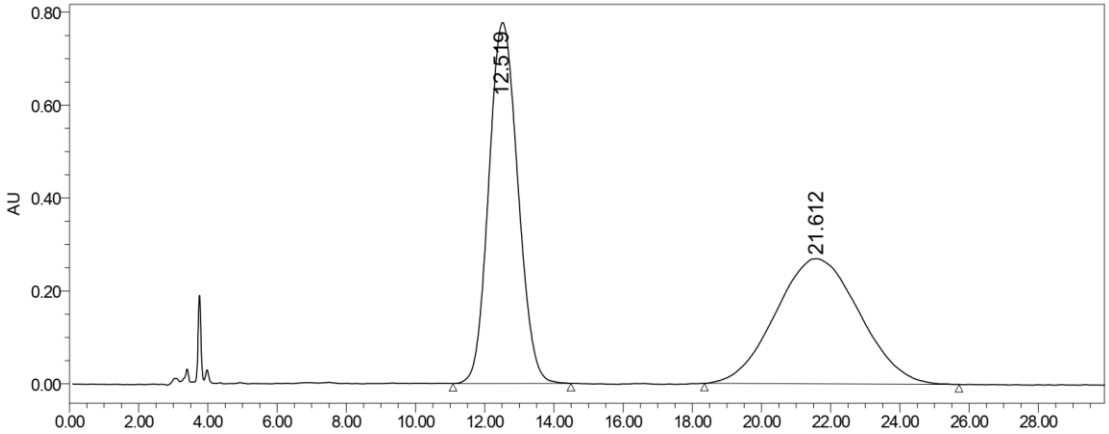
(*S*)-2-(2,5-dioxo-1-(o-tolyl)pyrrolidin-3-yl)-2-methylpropanal[4]



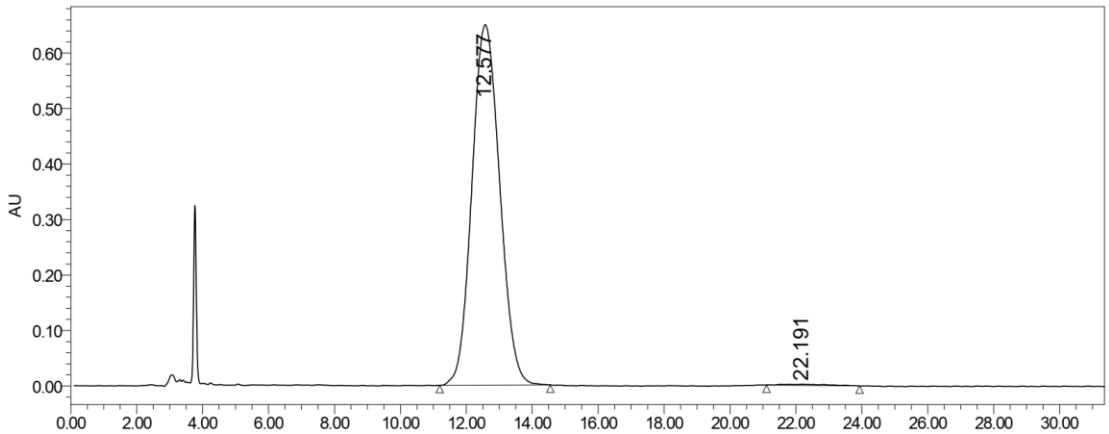
4b

4b, 106 mg, 82% yield, white solid, $[\alpha]_D^{25}$ = - 3(c =1.0, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.35 – 7.30 (m, 2H), 7.30 – 7.27 (m, 1H), 7.12 – 7.01 (m, 1H), 3.20 – 3.15 (m, 1H), 2.98 – 2.94 (m, 1H), 2.70 – 2.65 (m, 1H), 2.21(s, 2H), 2.14 (s, 1H), 1.35 (d, *J* = 5.4 Hz, 3H), 1.29 (d, *J* = 2.8 Hz, 3H).

The ee was determined by HPLC analysis. CHIRALPAK OD-H; Hexane/2-propanol=70:30; flow rate 1.0 mL/min; 223.3 nm; retention time: 12.6 min (major) and 22.2 min (minor).

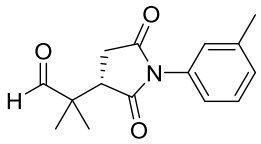


	name	Retention	Area(μV*s)	Height（μV）	% Area
1		12.519	45320859	776956	50.00
2		21.612	45317364	269059	50.00



	name	Retention	Area(μV*s)	Height（μV）	% Area
1		12.577	38033206	649569	99.50
2		22.191	190518	1917	0.50

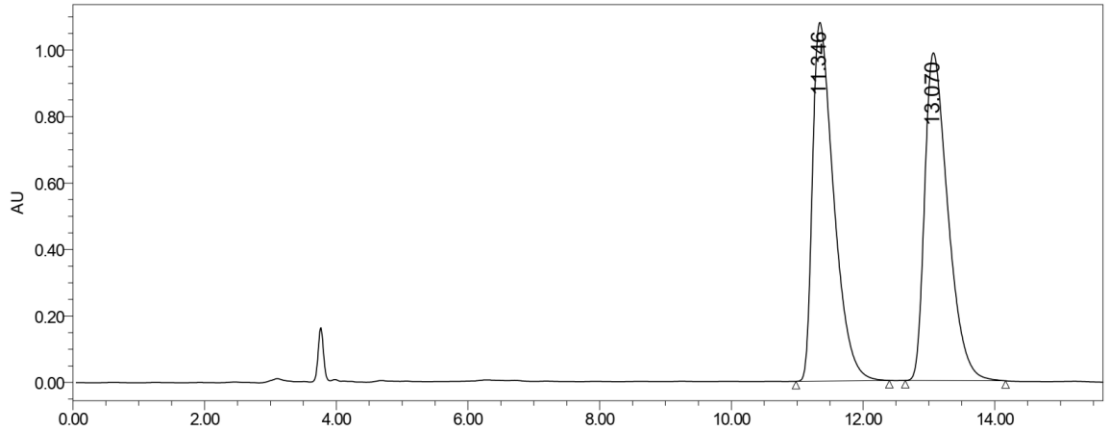
(*S*)-2-(2, 5-dioxo-1-(m-tolyl) pyrrolidin-3-yl)-2-methylpropanal



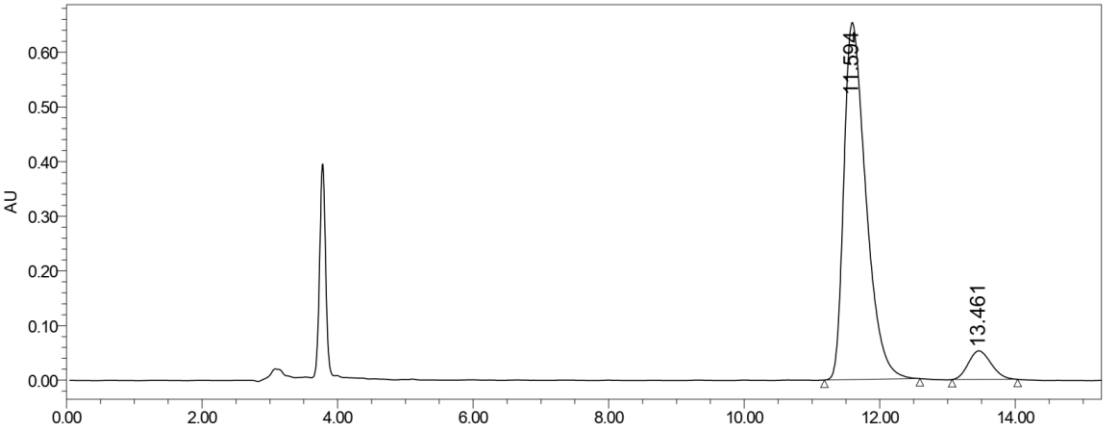
4c

4c, 116 mg, 90% yield, white solid, $[\alpha]_D^{25}$ = - 4 (c =1.0, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 9.52 (s, 1H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.20 (d, *J* = 6.6 Hz, 1H), 7.09 – 4.04 (m, 2H), 3.14 (dd, *J* = 9.6, 5.4 Hz, 1H), 2.97 (dd, *J* = 18.0, 9.6 Hz, 1H), 2.61 (dd, *J* = 18.0, 3.6 Hz, 1H), 2.38 (s, 3H), 1.32 (s, 3H), 1.28 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 202.7, 176.9, 174.8, 139.3, 131.7, 129.6, 129.0, 127.1, 123.6, 48.5, 45.0, 31.8, 21.3, 20.3, 19.6; HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ Calcd for $C_{15}H_{17}NO_3$ 260.1281, Found 261.1282.

The ee was determined by HPLC analysis. CHIRALPAK OD-H; Hexane/2-propanol=70:30; flow rate 1.0 mL/min; 218.0 nm; retention time: 11.6 min (major) and 13.5 min (minor).

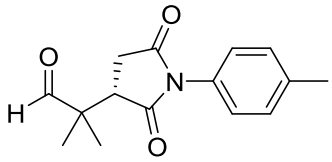


	name	Retention	Area(μV*s)	Height（μV）	% Area
1		11.346	24156091	1079047	99.50
2		13.070	24160587	986146	0.50



	name	Retention	Area(μV*s)	Height（μV）	% Area
1		11.594	14764886	653186	92.36
2		13.461	1221580	52189	7.64

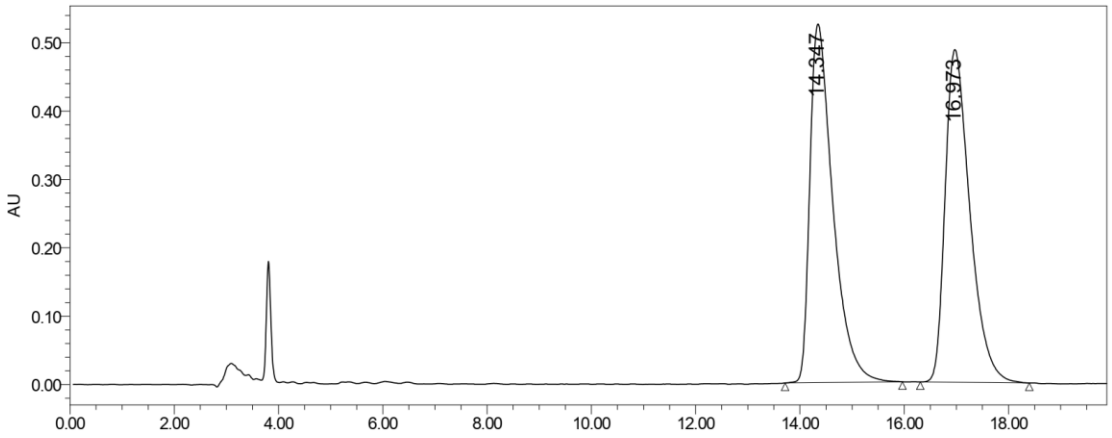
(*S*)-2-(2, 5-Dioxo-1-(p-tolyl) pyrrolidin-3-yl)-2-methylpropanal[3]



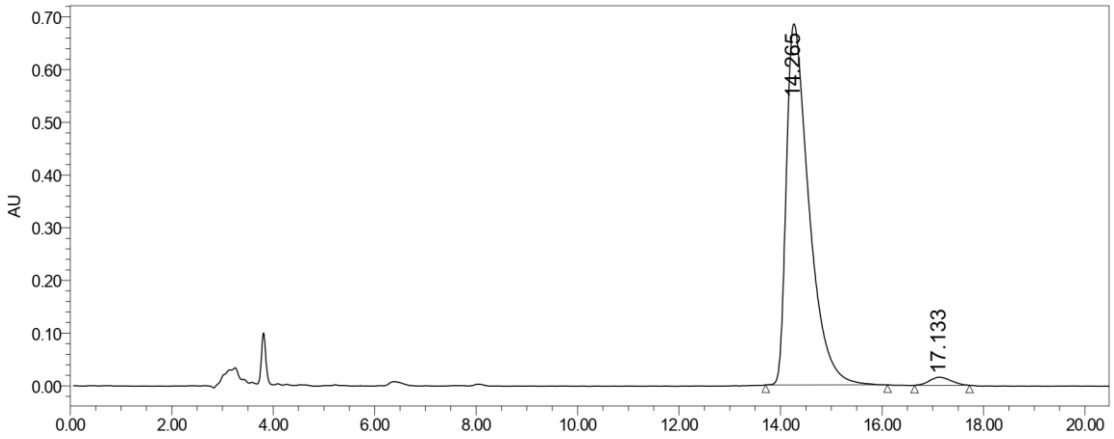
4d

4d, 116 mg, 90% yield, white solid, $[\alpha]_D^{25}$ = - 6.0 (*c* =1.0, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 9.52 (s, 1H), 7.27 (d, *J* = 7.2 Hz, 2H), 7.14 (d, *J* = 8.4 Hz, 2H), 3.14 (dd, *J* = 9.6, 5.4 Hz, 1H), 2.97 (dd, *J* = 18.4, 9.6 Hz, 1H), 2.61 (dd, *J* = 18.4, 5.6 Hz, 1H), 2.37 (s, 3H), 1.32 (s, 3H), 1.28 (s, 3H).

The ee was determined by HPLC analysis. CHIRALPAK OD-H; Hexane/2-propanol=70:30; flow rate 1.0 mL/min; 220.3 nm; retention time: 14.3 min (major) and 17.1 min (minor).

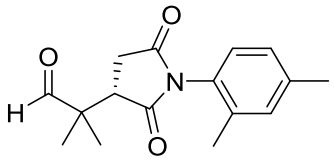


	name	Retention	Area(μV*s)	Height（μV）	% Area
1		14.347	16053191	524432	49.99
2		16.973	16059404	486643	50.01



	name	Retention	Area(μV*s)	Height（μV）	% Area
1		14.265	21219082	685034	97.96
2		17.133	442339	1512	2.04

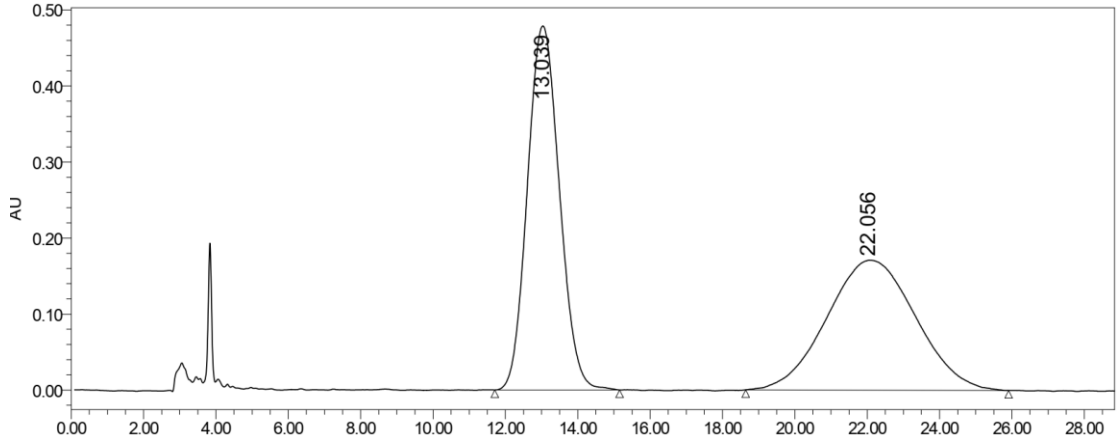
(*S*)-2-(1-(2,4-dimethylphenyl)-2,5-dioxopyrrolidin-3-yl)-2-methylpropanal



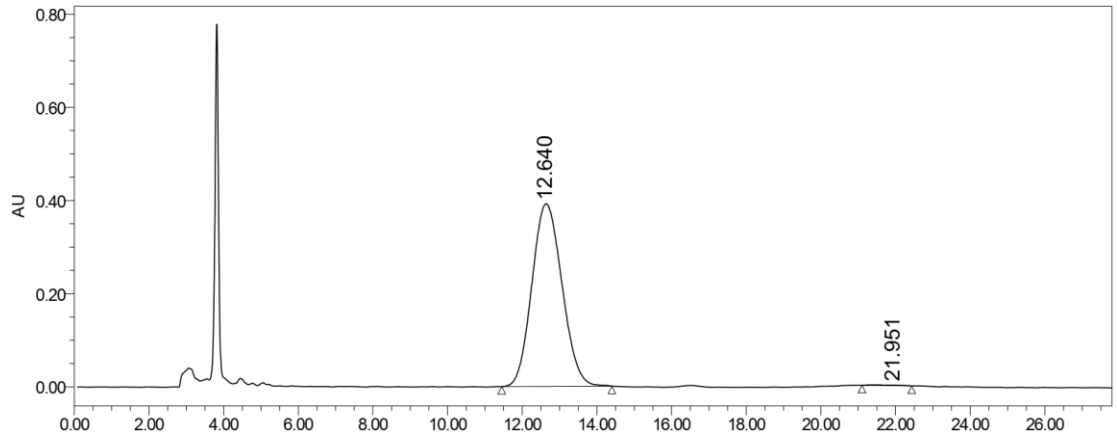
4e

4e, 93 mg, 68% yield, white solid, $[\alpha]_D^{25}$ = - 4 (*c* =1.0, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 9.52 (s, 1H), 7.14 – 7.06 (m, 2H), 6.98 – 6.91 (m, 1H), 3.22 – 3.14 (m, 1H), 3.06 – 2.94 (m, 1H), 2.72 – 7.60 (m, 1H), 2.34 (s, 3H), 2.16 – 2.04(m, 3H), 1.35 (d, *J* = 2.4 Hz, 3H), 1.30 (d, *J* = 1.8 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 203.1, 176.8, 174.7, 131.7, 129.1, 128.7, 126.6, 126.4, 51.3, 43.7, 31.1, 27.3, 15.1, 7.9; HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ Calcd for $C_{16}H_{19}NO_3$ 274.1438, Found 274.1441.

The ee was determined by HPLC analysis. CHIRALPAK OD-H; Hexane/2-propanol=70:30; flow rate 1.0 mL/min; 212.0 nm; retention time: 12.6 min (major) and 22.0 min (minor).

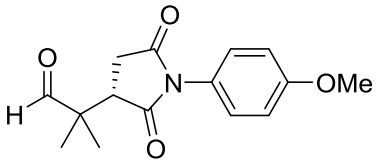


	name	Retention	Area(μV*s)	Height（μV）	% Area
1		13.039	29397550	478732	50.26
2		22.056	29088779	170963	49.74



	name	Retention	Area(μV*s)	Height（μV）	% Area
1		12.640	21988762	392149	99.72
2		21.951	61769	1212	0.28

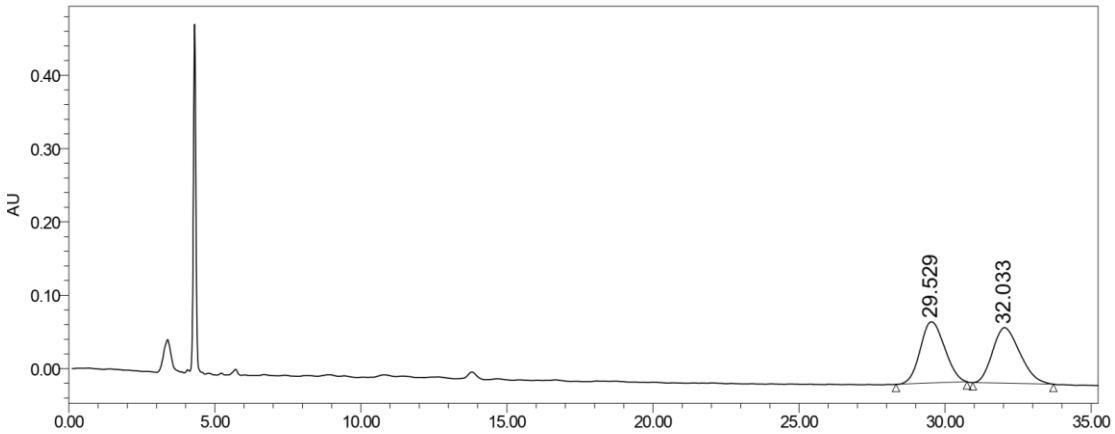
(*S*)-2-(1-(4-methoxyphenyl)-2, 5-dioxopyrrolidin-3-yl)-2-methylpropanal[3]



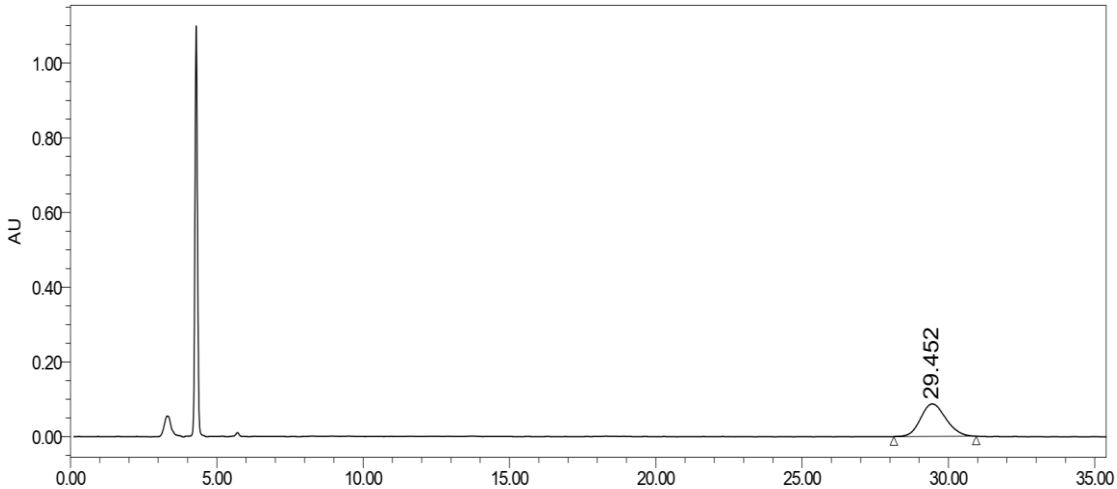
4f

4f, 135 mg, 98% yield, white solid, $[\alpha]_D^{25}$ = - 5.0 (*c* =1.0, $CHCl_3$) **;** ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.52 (s, 1H), 7.21 – 7.15 (m, 2H), 6.99 – 6.95 (m, 2H), 3.82 (s, 3H), 3.13 (dd, *J* = 9.6, 5.4 Hz, 1H), 2.96 (dd, *J* = 18.4, 9.6 Hz, 1H), 2.60 (dd, *J* = 18.6, 5.4 Hz, 1H), 1.32 (s, 3H), 1.28 (s, 3H).

The ee was determined by HPLC analysis. CHIRALPAK OD-H; Hexane/2-propanol=70:30; flow rate 1.0 mL/min; 229.8 nm; retention time: 29.5 min (major).

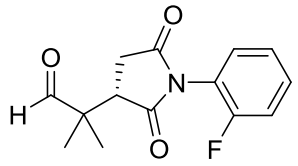


	name	Retention	Area(μV*s)	Height（μV）	% Area
1		29.529	4856022	83435	49.61
2		32.033	4931559	75842	50.39



	name	Retention	Area(μV*s)	Height（μV）	% Area
1		29.452	5210327	86838	100.00

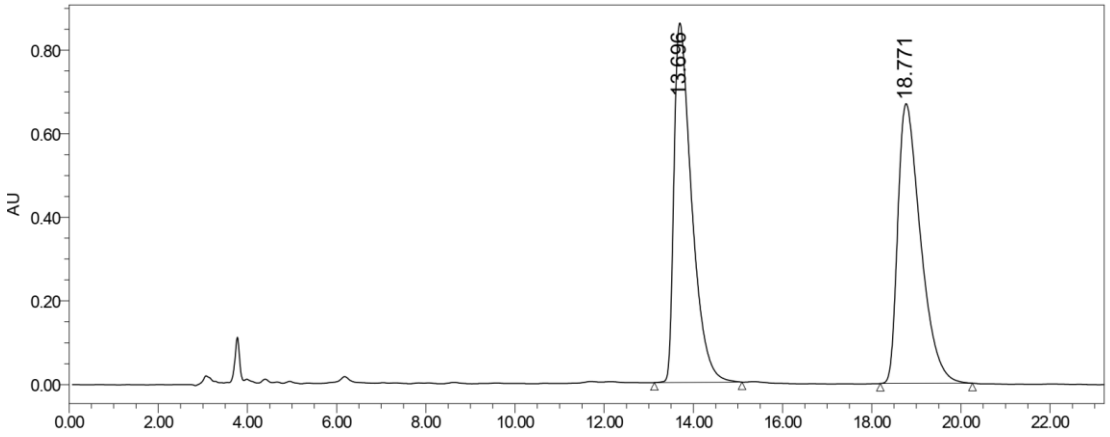
(*S*)-2-(1-(2-fluorophenyl)-2, 5-dioxopyrrolidin-3-yl)-2-methylpropanal[5]



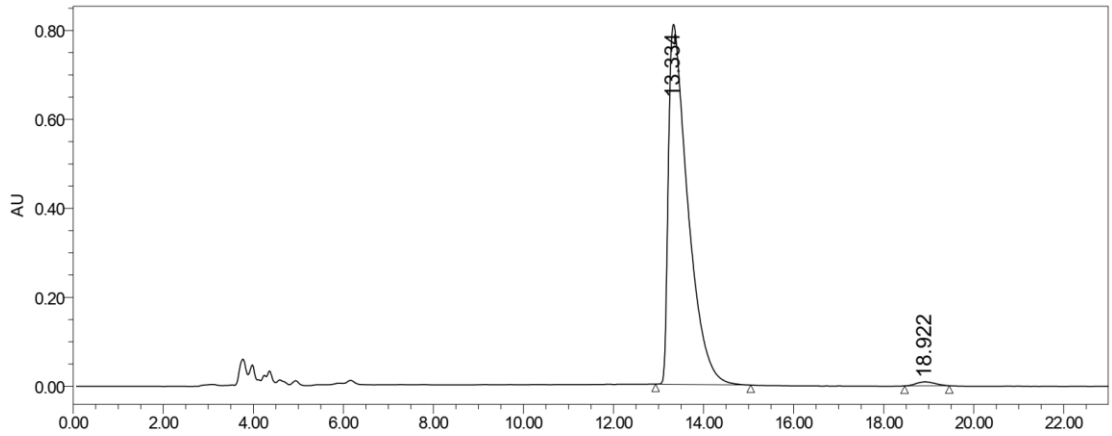
4g

4g, 121 mg, 92 % yield, white solid, $[\alpha]_D^{25}$ = - 7 (c =1.0, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 9.49 (s, 1H), 7.43 – 7.36 (m, 2H), 7.34 – 7.32 (m, 1H), 7.23 – 7.20 (m, 1H), 3.11 (dd, *J* = 9.6, 5.4Hz, 1H), 2.98 (dd, *J* = 18.0, 9.6 Hz, 1H), 2.62 (dd, *J* = 18.0, 5.4 Hz, 1H), 1.36 (s, 3H), 1.29 (s, 3H).

The ee was determined by HPLC analysis. CHIRALPAK OD-H; Hexane/2-propanol=70:30; flow rate 1.0 mL/min; 223.8 nm; retention time: 13.3 min (major) and 18.9 min (minor).

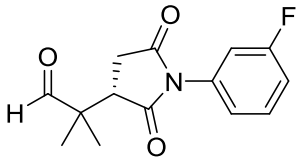


	name	Retention	Area(μV*s)	Height（μV）	% Area
1		13.696	23673680	859894	49.94
2		18.771	23727229	669416	50.06



	name	Retention	Area(μV*s)	Height（μV）	% Area
1		13.334	24205859	808994	98.94
2		18.922	258712	8824	1.06

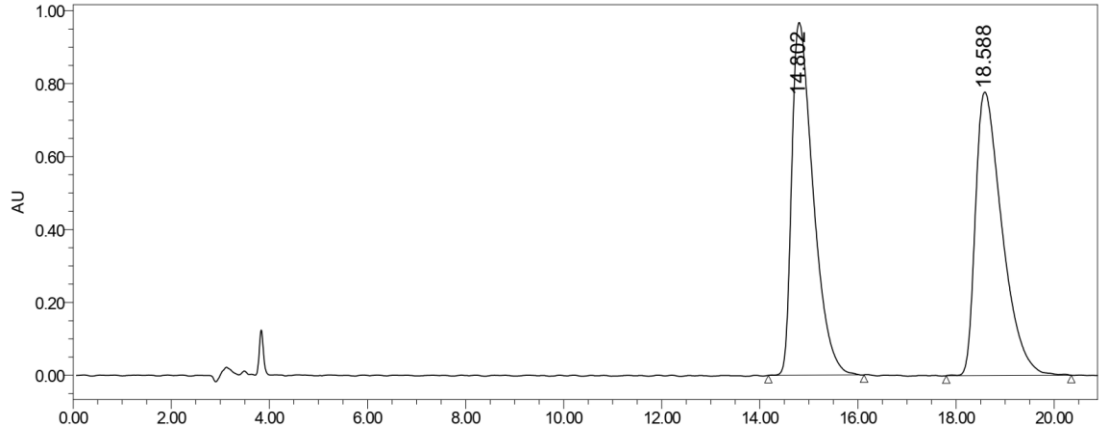
(*S*)-2-(1-(3-fluorophenyl)-2, 5-dioxopyrrolidin-3-yl)-2-methylpropanal[5]



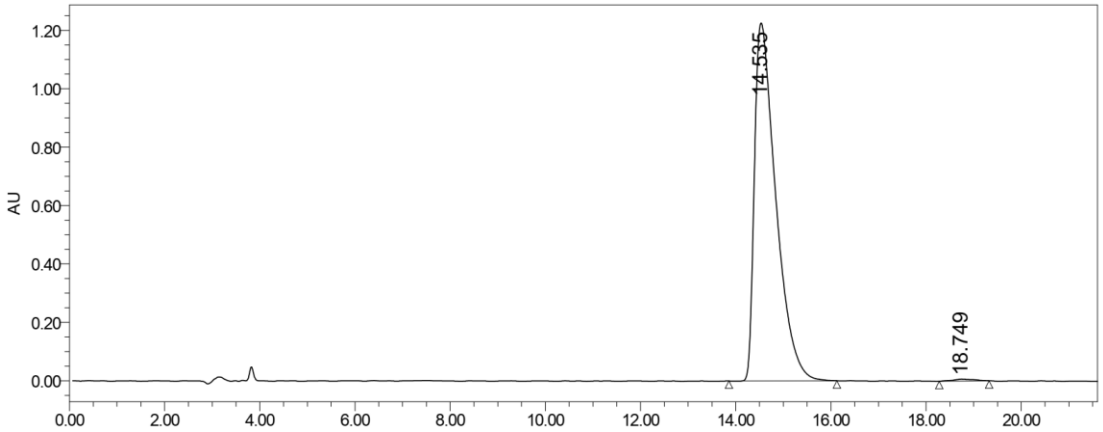
4h

4h, 124 mg, 94% yield, white solid, $[\alpha]_D^{25}$ = -4 (c =1.0, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$): δ 9.48 (s, 1H), 7.41 – 7.35 (m, 2H), 7.33 – 7.31 (m, 1H), 7.22 – 7.18 (m, 1H), 3.10 (dd, *J* = 9.6, 5.4 Hz, 1H), 2.97 (dd, *J* = 18.0, 9.6 Hz, 1H), 2.61 (dd, *J* = 18.0, 5.4 Hz, 1H), 1.35 (s, 3H), 1.28 (s, 3H).

The ee was determined by HPLC analysis. CHIRALPAK OD-H; Hexane/2-propanol=70:30; flow rate 1.0 mL/min; 223.8 nm; retention time: 13.3 min (major) and 18.9 min (minor).

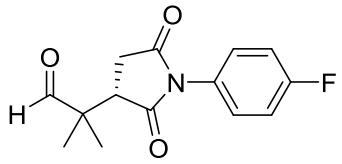


	name	Retention	Area(μV*s)	Height（μV）	% Area
1		14.802	29432165	49.98	967414
2		18.588	29452010	50.02	777518



	name	Retention	Area(μV*s)	Height（μV）	% Area
1		14.535	38169207	1225667	99.48
2		18.749	198417	6192	0.52

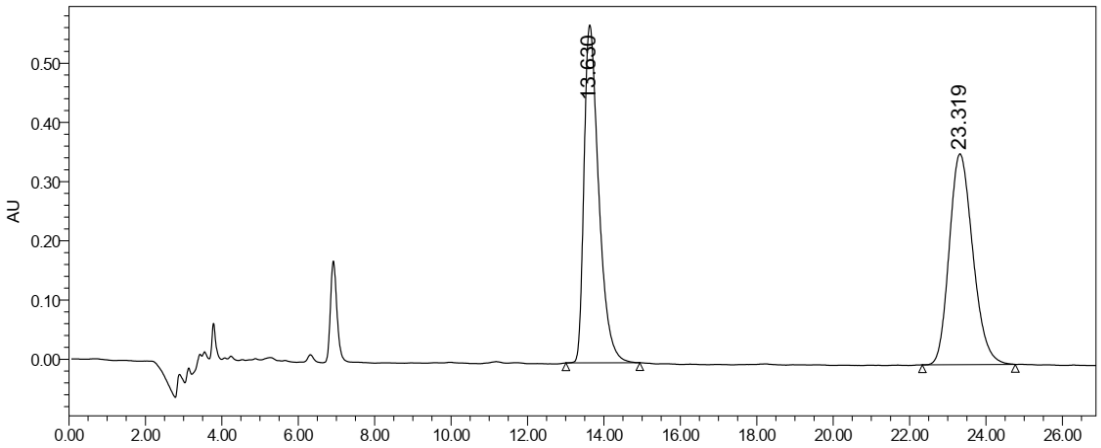
(*S*)-2-(1-(4-fluorophenyl)-2,5-dioxopyrrolidin-3-yl)-2-methylpropanal[5]



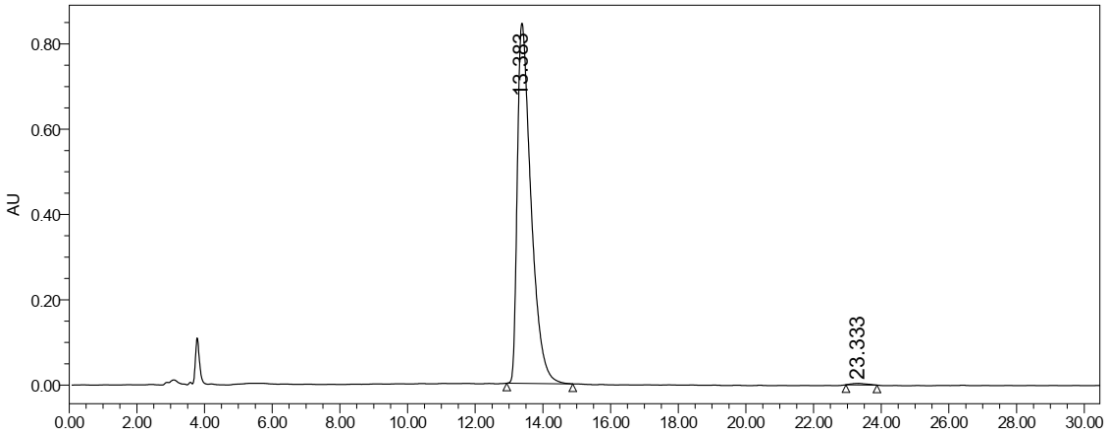
4i

4i, 125 mg, 95% yield, white solid, $[\alpha]_D^{25}$ = - 1.0 (*c* =1.0, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 9.49 (s, 1H), 7.28 – 7.24 (m, 2H), 7.17 – 7.12 (m, 2H), 3.11 (dd, *J* = 9.6, 5.4 Hz, 1H), 2.97 (dd, *J* = 18.6, 9.6 Hz, 1H), 2.61 (dd, *J* = 18.0, 5.4 Hz, 1H), 1.35 (s, 3H), 1.28 (s, 3H).

The ee was determined by HPLC analysis. CHIRALPAK OD-H; Hexane/2-propanol=70:30; flow rate 1.0 mL/min; 218.0 nm; retention time: 13.4 min (major) and 23.3 min (minor).

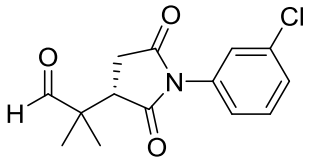


	name	Retention	Area(μV*s)	Height（μV）	% Area
1		13.630	1523591	570438	49.95
2		23.319	15267678	356054	50.05



	name	Retention	Area(μV*s)	Height（μV）	% Area
1		13.383	23734573	844120	99.53
2		23.333	112396	3383	0.47

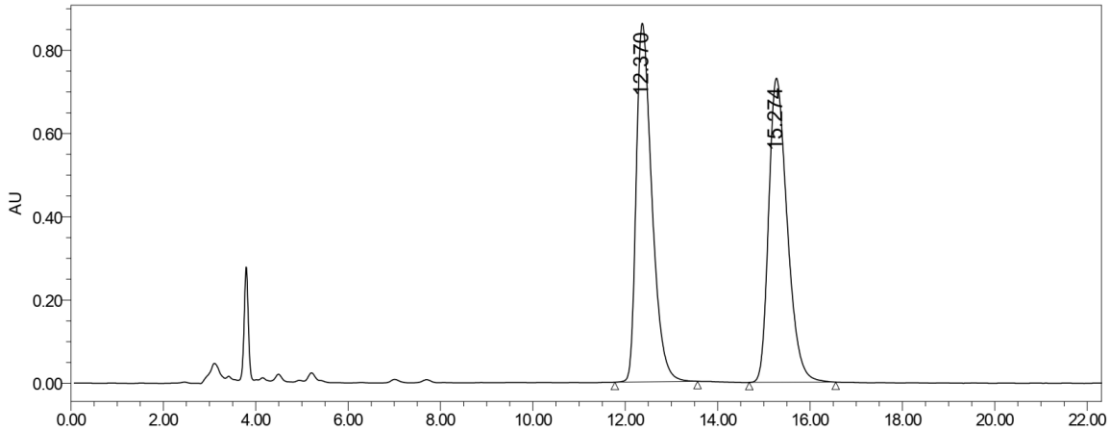
(*S*)-2-(1-(3-chlorophenyl)-2, 5-dioxopyrrolidin-3-yl)-2-methylpropanal[6]



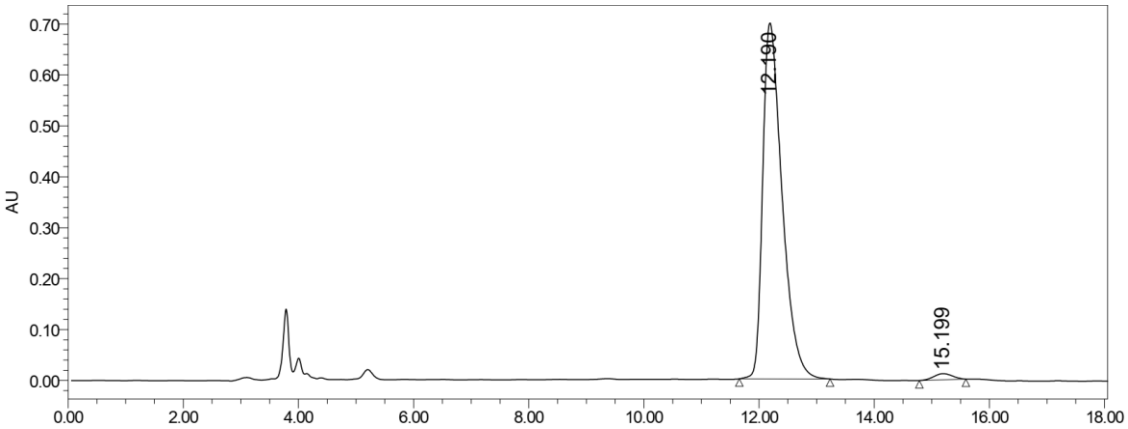
4j

4j, 124 mg, 89% yield, white solid, $[\alpha]_D^{25}$ = - 7 (c =1.0, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 9.49 (s, 1H), 7.43 – 7.36 (m, 2H), 7.33 (t, *J* = 1.8 Hz, 1H), 7.23 – 7.19 (m, 1H), 3.12 (dd, *J* = 9.6, 5.4 Hz, 1H), 2.98 (dd, *J* = 18.6, 9.6 Hz, 1H), 2.62 (dd, *J* = 18.6, 6.0 Hz, 1H), 1.37 (s, 3H), 1.30 (s, 3H).

The ee was determined by HPLC analysis. CHIRALPAK OD-H; Hexane/2-propanol=70:30; flow rate 1.0 mL/min; 212.2 nm; retention time: 12.2 min (major) and 15.2 min (minor).

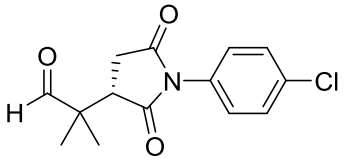


	name	Retention	Area(μV*s)	Height（μV）	% Area
1		12.370	20297233	861755	49.89
2		15.274	20385402	730525	50.11



	name	Retention	Area(μV*s)	Height（μV）	% Area
1		12.190	16328375	698710	98.37
2		15.199	271055	12055	1.63

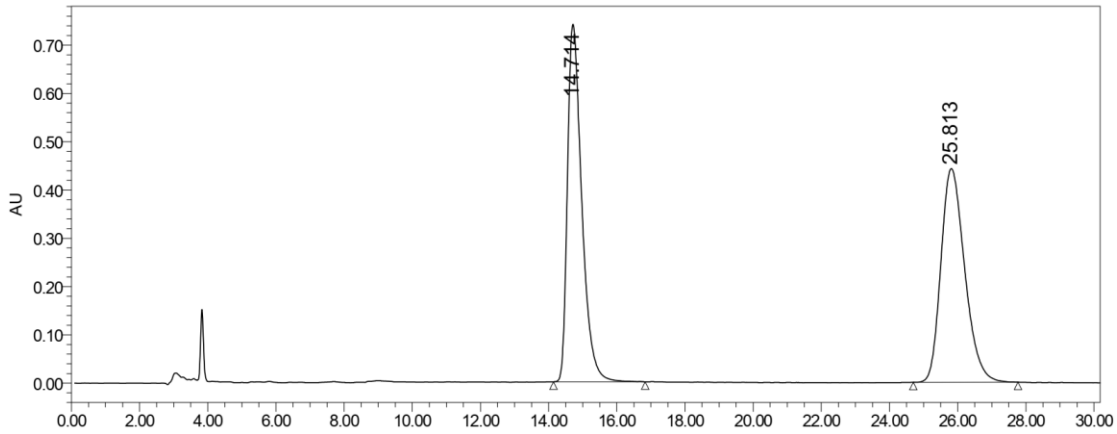
(*S*)-2-(1-(4-chlorophenyl)-2,5-dioxopyrrolidin-3-yl)-2-methylpropanal[6]



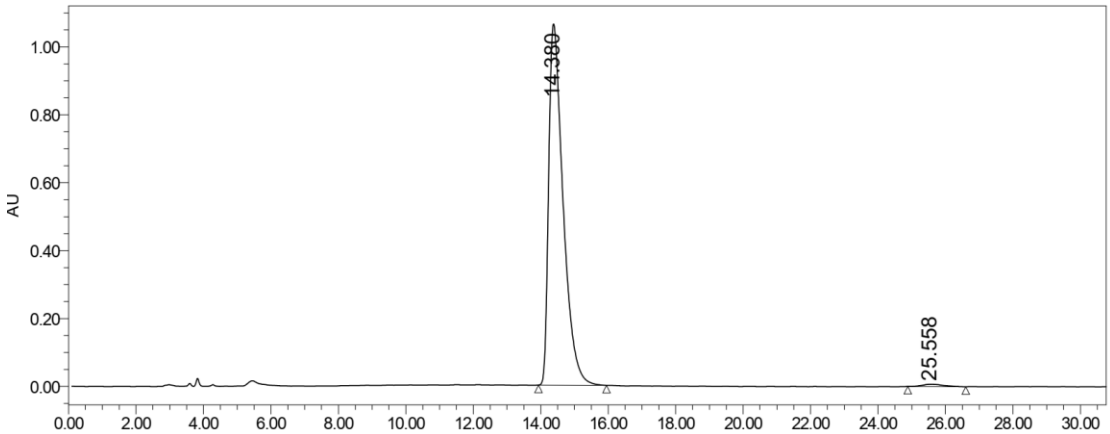
4k

4k, 125 mg, 90% yield, white solid, $[\alpha]_D^{25}$ = -3.0 (*c* =1.0, $CHCl_3$);^{1}H NMR (600 MHz, $CDCl_3$) δ 9.49 (s, 1H), 7.49 – 7.40 (m, 2H), 7.28 – 7.22 (m, 2H), 3.11 (dd, *J* = 9.6, 6.0 Hz, 1H), 2.97 (dd, *J* = 18.0, 9.6 Hz, 1H), 2.62 (dd, *J* = 18.6, 5.4 Hz, 1H), 1.36 (s, 3H), 1.29 (s, 3H).

The ee was determined by HPLC analysis. CHIRALPAK OD-H; Hexane/2-propanol=70:30; flow rate 1.0 mL/min; 225.1 nm; retention time: 14.4 min major) and 25.6 min minor).

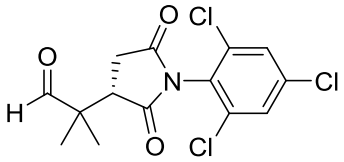


	name	Retention	Area(μV*s)	Height（μV）	% Area
1		14.714	21556192	740424	50.13
2		25.813	21442218	442328	49.87



	name	Retention	Area(μV*s)	Height（μV）	% Area
1		14.380	31438838	1063511	99.08
2		25.558	292504	6768	0.92

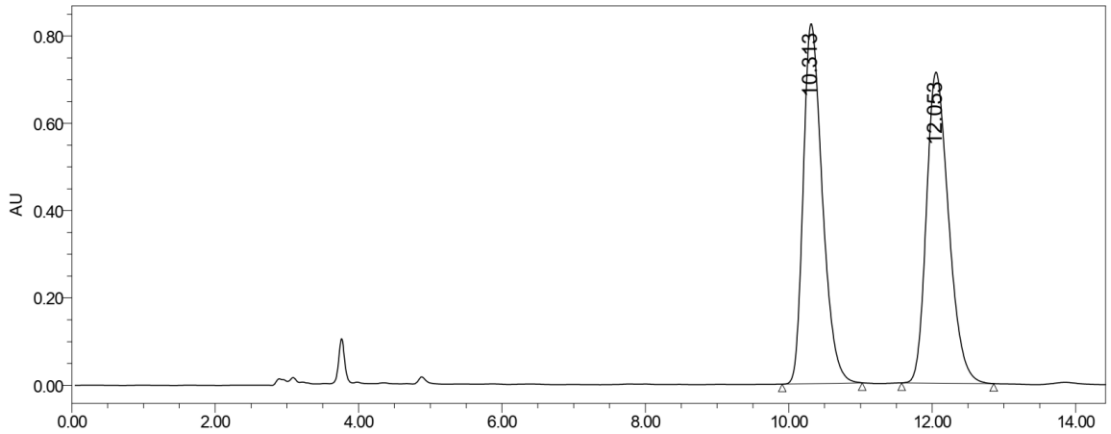
(*S*)-2-(2,5-dioxo-1-(2,4,6-trichlorophenyl)pyrrolidin-3-yl)-2-methylpropanal



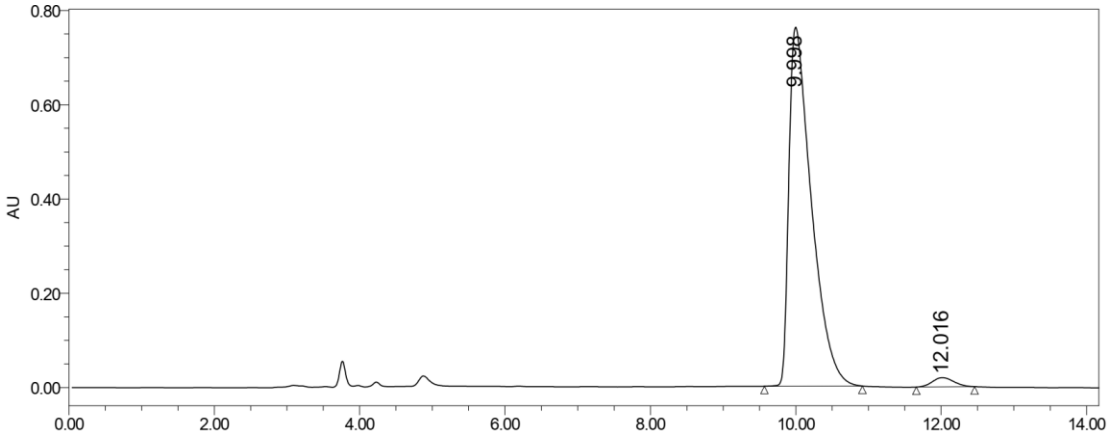
4l

4l, 170 mg,98% yield, white solid, $[\alpha]_D^{25}$ = - 10 (*c* =1.0, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 9.55 (s, 1H), 7.48 – 7.45 (m, 2H), 3.37 (dd, *J* = 9.6, 6.0 Hz, 1H), 3.12 – 3.06 (m, 1H), 2.72 (dd, *J* = 18.6, 6.0 Hz, 1H), 1.34 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 202.3, 174.8, 172.7, 136.6, 135.1, 134.9, 128.8, 127.1, 48.1, 45.5, 31.9, 19.7, 19.5; HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ Calcd for $C_{14}H_{12}Cl_3NO_3$ 347.9956, Found 347.9958.

The ee was determined by HPLC analysis. CHIRALPAK OD-H; Hexane/2-propanol=70:30; flow rate 1.0 mL/min; 210.0 nm; retention time: 10.0 min major) and 12.0 in minor).

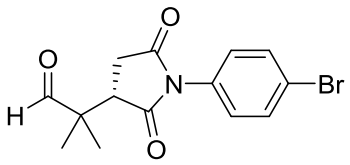


	name	Retention	Area(μV*s)	Height（μV）	% Area
1		10.313	15285758	824614	49.92
2		12.053	15334485	712551	50.08



	name	Retention	Area(μV*s)	Height（μV）	% Area
1		9.998	16340273	761631	97.61
2		12.016	400872	19664	2.39

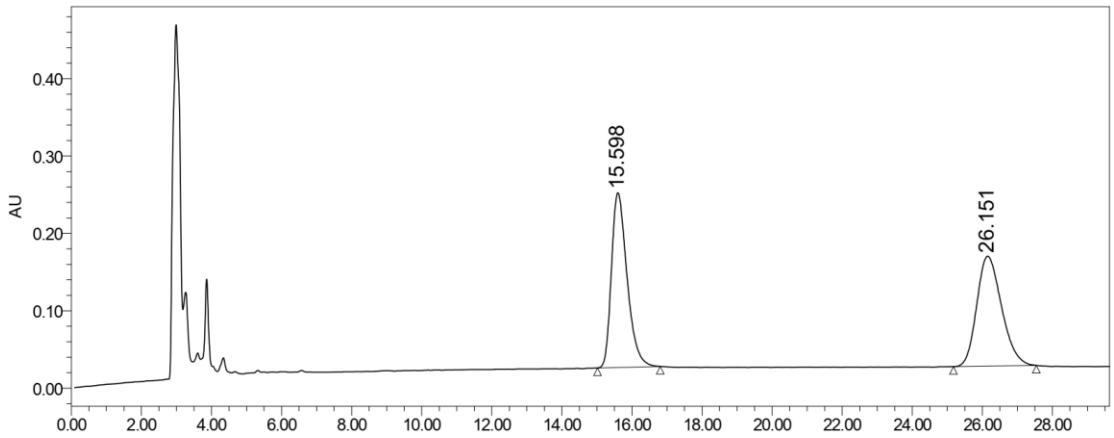
(*S*)-2-(1-(4-bromophenyl)-2, 5-dioxopyrrolidin-3-yl)-2-methylpropanal[7]



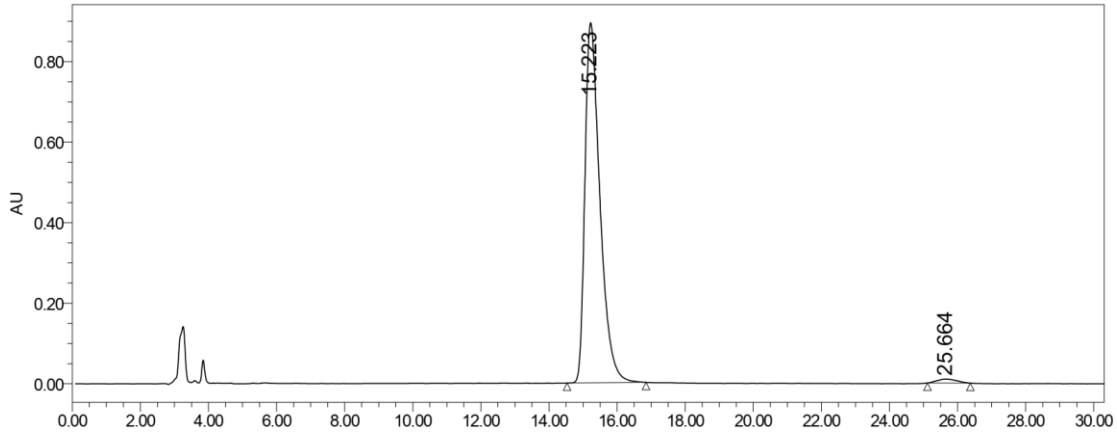
4m

4m, 153 mg, 95% yield, white solid, $[\alpha]_D^{25}$ = - 3.0 (*c* =1.0, $CHCl_3$) ;^{1}H NMR (600 MHz, $CDCl_3$) δ 9.49 (s, 1H), 7.62 – 7.57 (m, 1H), 7.23 – 7.15 (m, 2H), 3.11 (dd, *J* = 9.6, 5.4 Hz, 1H), 2.97 (dd, *J* = 18.6, 9.6 Hz, 1H), 2.62 (dd, *J* = 18.6, 6.0 Hz, 1H), 1.36 (s, 3H), 1.29 (s, 3H).

The ee was determined by HPLC analysis. CHIRALPAK OD-H; Hexane/2-propanol=70:30; flow rate 1.0 mL/min; 28.6 nm; retention time: 15.2 in major) and 25.7 min minor).

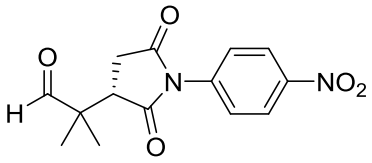


	name	Retention	Area(μV*s)	Height（μV）	% Area
1		15.598	6985385	225799	50.02
2		26.151	6979228	141996	49.98



	name	Retention	Area(μV*s)	Height（μV）	% Area
1		15.223	27322464	894400	98.58
2		25.664	392790	9770	1.42

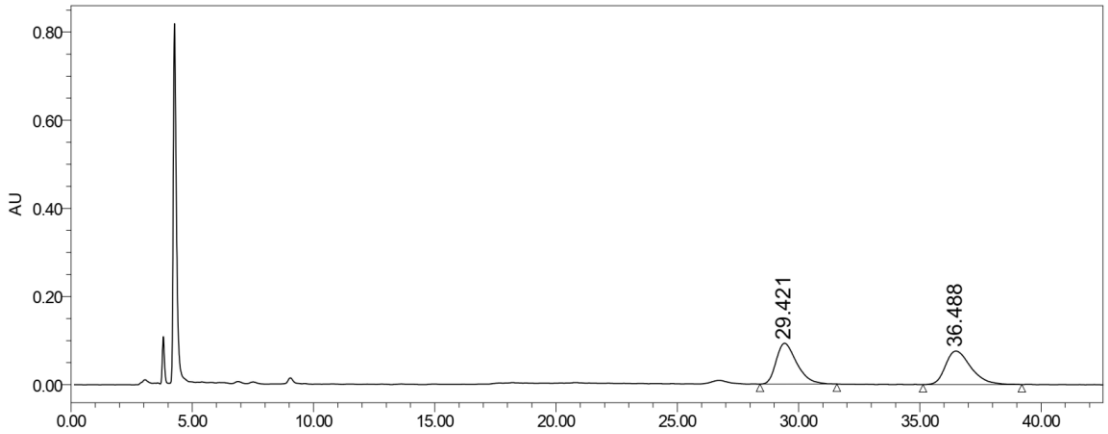
(*S*)-2-methyl-2-(1-(4-nitrophenyl)-2, 5-dioxopyrrolidin-3-yl)propanal[3]



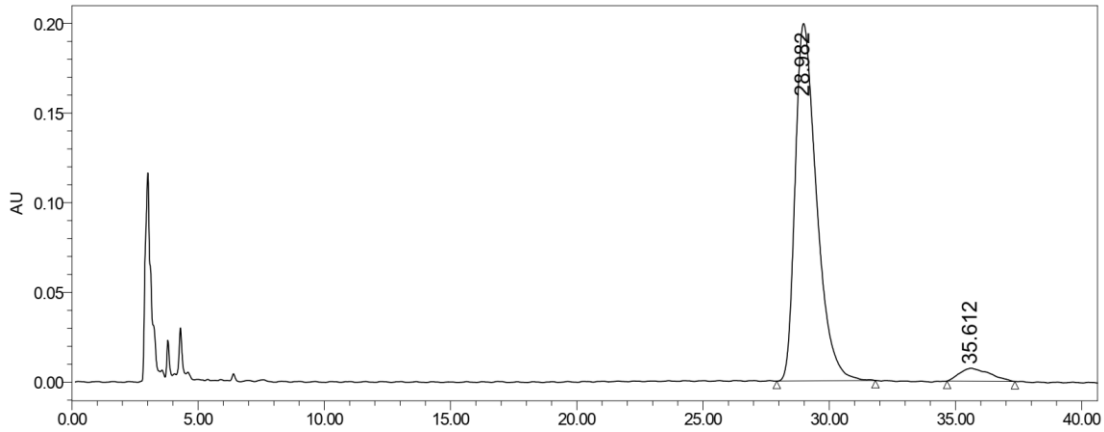
4n

4n, 116 mg, 80% yield, white solid, $[\alpha]_D^{25}$ = - 6.0 (*c* =1.0, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 9.46 (s, 1H), 8.35 – 8.29 (m, 2H), 7.61 – 7.54 (m, 2H), 3.10 (dd, *J* = 9.6, 5.4 Hz, 1H), 3.00 (dd, *J* = 18.6, 9.6 Hz, 1H), 2.65 (dd, *J* = 18.6, 5.4 Hz, 1H), 1.41 (s, 3H), 1.30 (s, 3H).

The ee was determined by HPLC analysis. CHIRALPAK OD-H; Hexane/2-propanol=70:30; flow rate 1.0 mL/min; 212.1 nm; retention time: 29.0 min (major) and 35.6 min (minor).

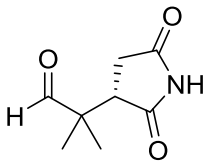


	name	Retention	Area(μV*s)	Height（μV）	% Area
1		29.421	5436178	92445	49.57
2		36.488	5530446	76010	50.43



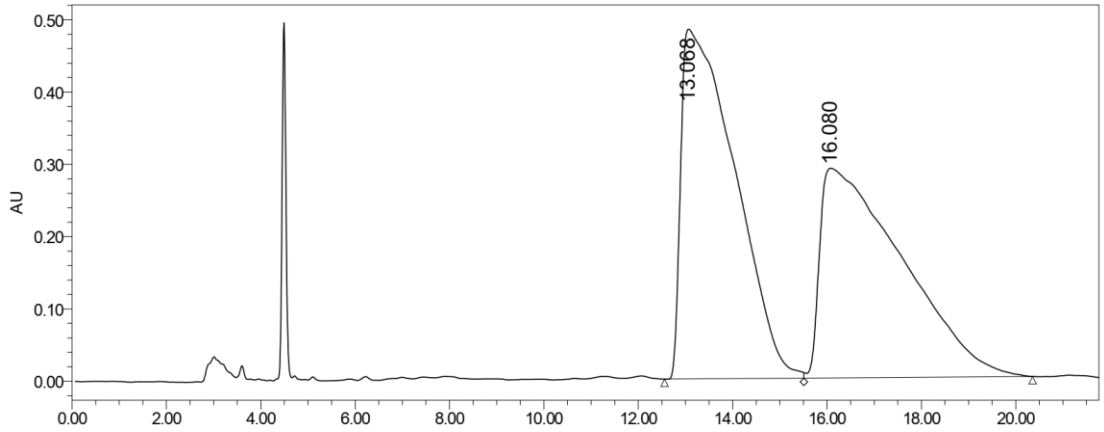
	name	Retention	Area(μV*s)	Height（μV）	% Area
1		28.982	11731075	199118	95.17
2		35.612	595682	7185	4.83

(S)-2-(2,5-dioxopyrrolidin-3-yl)-2-methylpropanal[5]

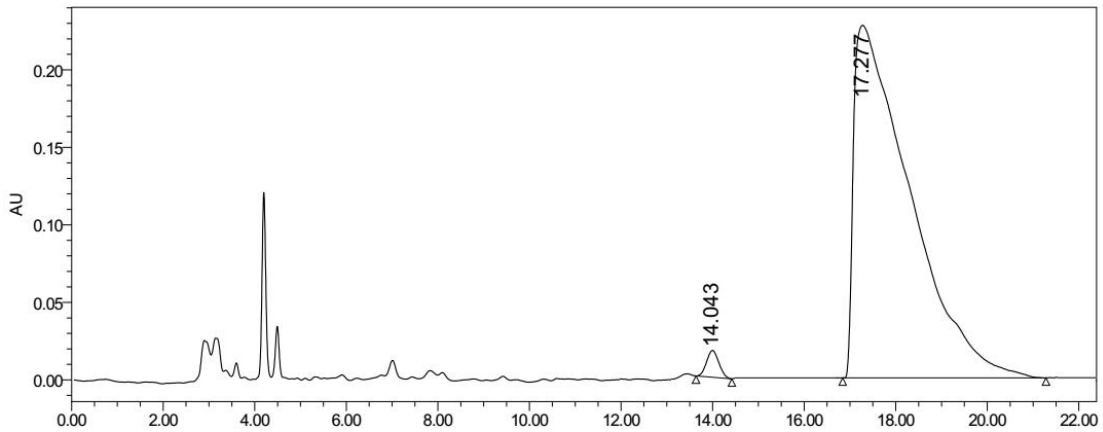


4o

4o, 72 mg, 85% yield, white solid, $[\alpha]_D^{25}$ = + 5.0 (*c* =1.0, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 9.46 (s, 1H), 8.81 (s, 1H), 3.07 (dd, *J* = 9.6, 5.4 Hz, 1H), 2.83 (dd, *J* = 18.4, 9.6 Hz, 1H), 2.48 (dd, *J* = 18.4, 5.4 Hz, 1H), 1.21 (d, *J* = 6.9 Hz, 6H).
The ee was determined by HPLC analysis. CHIRALPAK AD-H; Hexane/2-propanol=80:20; flow rate 1.0 mL/min; 220.3 nm; retention time: 14.0 min minor) and 17.3 min major).

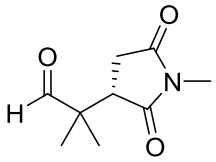


	name	Retention	Area(μV*s)	Height（μV）	% Area
1		13.068	38543440	483879	52.17
2		16.080	35198786	290053	47.73



	name	Retention	Area(μV*s)	Height（μV）	% Area
1		14.043	320458	17256	1.62
2		17.277	19429310	227407	98.38

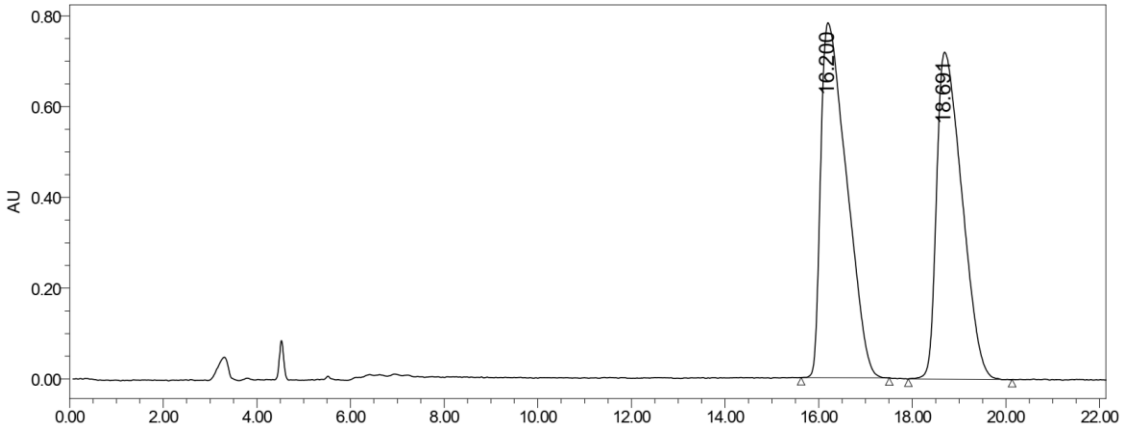
(S)-2-methyl-2-(1-methyl-2, 5-dioxopyrrolidin-3-yl)propanal[2]



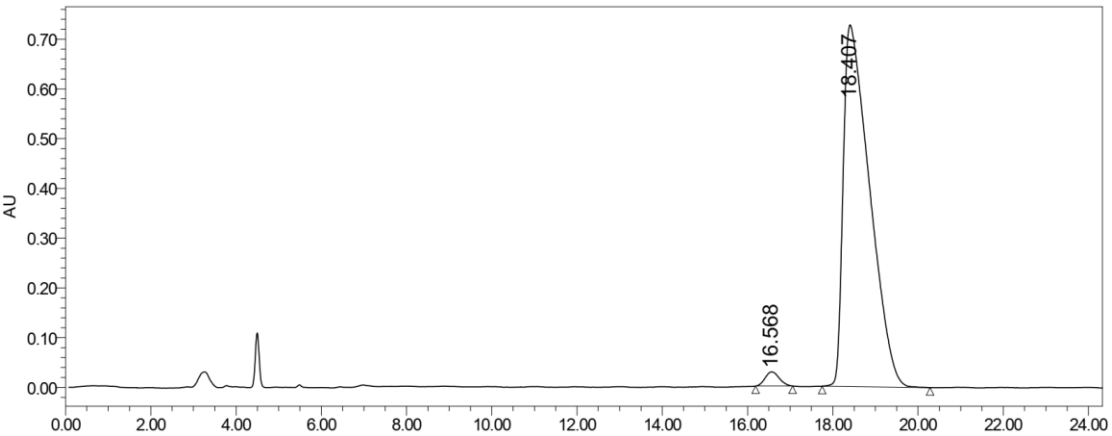
4p

4p, 82.4 mg, 90% yield, white solid, $[\alpha]_D^{25}$ = + 9.0 (*c* =1.0, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 9.51 (s, 1H), 3.04 (dd, *J* = 9.6, 5.4 Hz, 1H), 2.99 (s, 3H), 2.82 (q, *J* = 9.0 Hz, 1H), 2.45 (dd, *J* = 18.0, 5.4 Hz, 1H), 1.22 (d, *J* = 6.6 Hz, 6H).

The ee was determined by HPLC analysis. CHIRALPAK AS-H; Hexane/2-propanol=80:20; flow rate 1.0 mL/min; 212.1 nm; retention time: 16.6 min minor) and 18.4 min major).

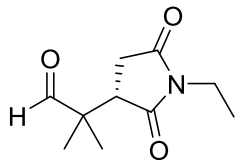


	name	Retention	Area(μV*s)	Height（μV）	% Area
1		16.200	29854019	781752	52.45
2		18.691	27068928	720472	47.55



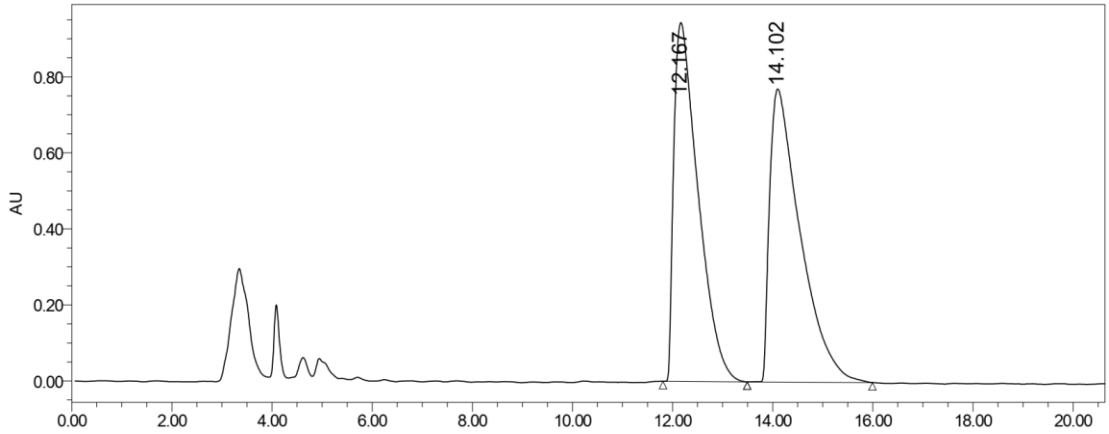
	name	Retention	Area(μV*s)	Height（μV）	% Area
1		16.568	654216	28479	2.06
2		18.407	31129546	726944	97.94

(*S*)-2-(1-ethyl-2, 5-dioxopyrrolidin-3-yl)-2-methylpropanal[8]

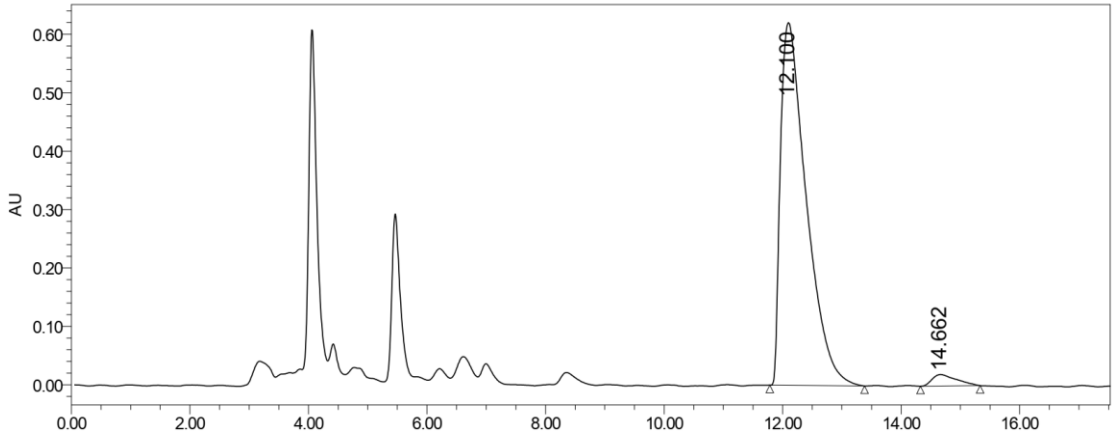


4q

4q, 79 mg, 80% yield, white solid, $[\alpha]_D^{25}$ = + 7 (*c* =1.0, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 9.52 (s, 1H), 3.56 (q, *J* = 7.2 Hz, 2H), 3.02 (dd, *J* = 9.0, 5.4 Hz, 1H), 2.83 – 2.77 (m, 1H), 2.43 (dd, *J* = 18.0, 4.8 Hz, 1H), 1.21 (d, *J* = 6.6 Hz, 6H), 1.17 (t, *J* = 7.2 Hz, 3H).
The ee was determined by HPLC analysis. CHIRALPAK OJ-H; Hexane/2-propanol=80:20; flow rate 1.0 mL/min;. 210 nm; retention time: 12.1 min major) and 14.7 min minor).

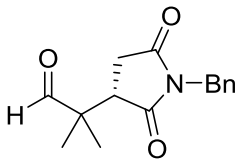


	name	Retention	Area(μV*s)	Height（μV）	% Area
1		12.167	31823887	943579	49.29
2		14.102	32746661	770825	50.71



	name	Retention	Area(μV*s)	Height（μV）	% Area
1		12.100	18777285	620673	97.12
2		14.662	557040	19547	2.88

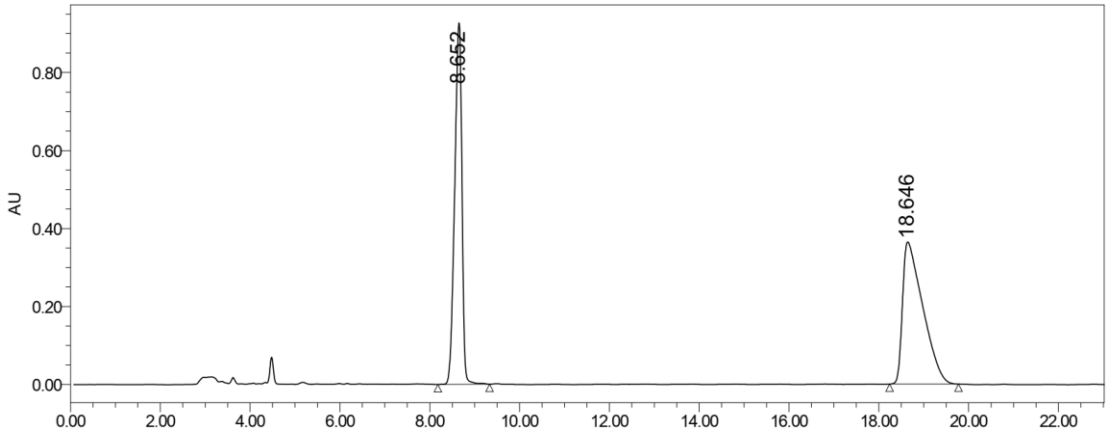
(*S*)-2-(1-benzyl-2,5-dioxopyrrolidin-3-yl)-2-methylpropanal[2]



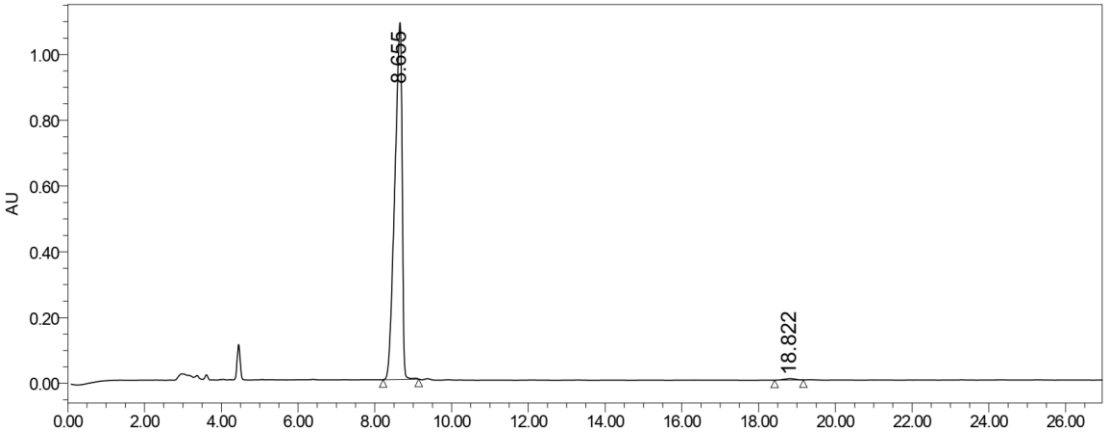
4r

4r, 119 mg, 92% yield, white solid, $[\alpha]_D^{25}$ = +14.0 (*c* =1.0, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 9.48 (s, 1H), 7.37 – 7.34 (m, 2H), 7.31 – 7.28 (m, 3H), 4.65 (q, *J* = 13.8 Hz, 2H), 3.03 (dd, *J* = 9.6, 5.4 Hz, 1H), 2.81 (q, *J* = 9.0 Hz, 1H), 2.45 (dd, *J* = 18.0, 5.4 Hz, 1H), 1.16 (d, *J* = 2.4 Hz, 6H).

The ee was determined by HPLC analysis. CHIRALPAK AD-H; Hexane/2-propanol=80:20; flow rate 1.0 mL/min; 218.0 nm; retention time: 8.7 min major) and 18.8 min minor).

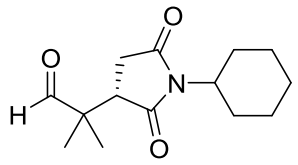


	name	Retention	Area(μV*s)	Height（μV）	% Area
1		8.652	10389220	927047	47.72
2		18.646	11381536	364637	52.28



	name	Retention	Area(μV*s)	Height（μV）	% Area
1		8.655	14293091	1085770	99.48
2		18.822	74212	3734	0.52

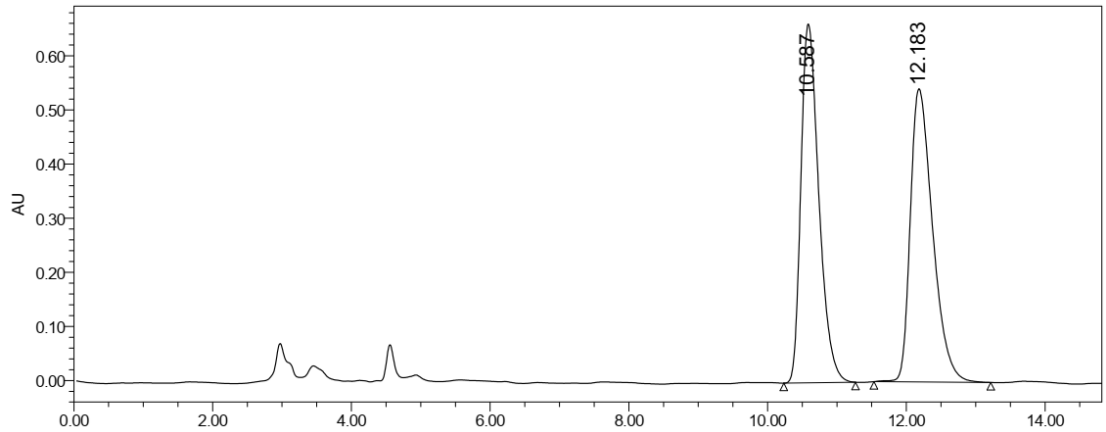
(*S*)-2-(1-cyclohexyl-2,5-dioxopyrrolidin-3-yl)-2-methylpropanal[2]



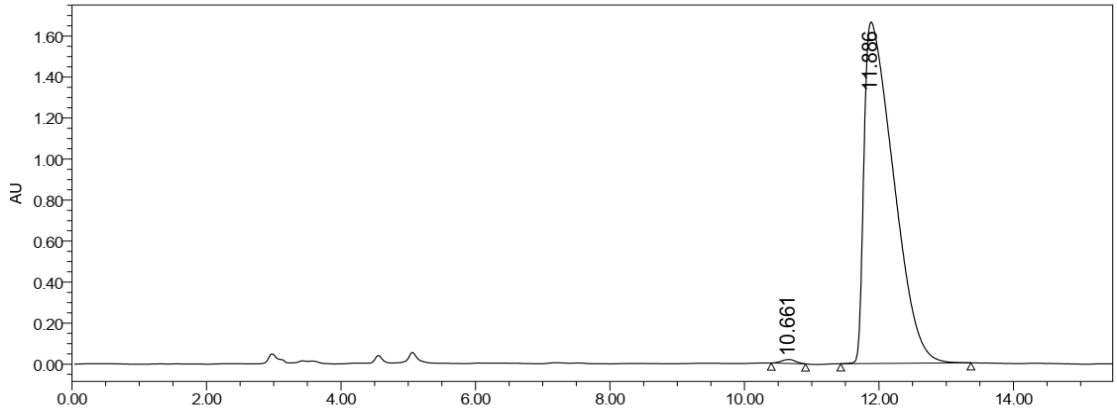
4s

4s, 119 mg, 95% yield, white solid, $[\alpha]_D^{25}$ = + 14(*c* =1.0, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 9.51 (s, 1H), 3.98 – 3.91 (m, 1H), 2.97 (dd, *J* = 9.6, 5.4 Hz, 1H), 2.74 (dd, *J* = 18.0, 9.6 Hz, 1H), 2.37 (dd, *J* = 18.0, 4.8 Hz, 1H), 2.16 – 2.08 (m, 2H), 1.85 – 1.74 (m, 2H), 1.66 – 1.53 (m, 3H), 1.32 – 1.23 (m, 2H), 1.23 – 1.12 (m, 7H).

The ee was determined by HPLC analysis. CHIRALPAK OD-H; Hexane/2-propanol=90:10; flow rate 1.0 mL/min; 290.2 nm; retention time: 10.7 min (minor) and 11.9 min (major).

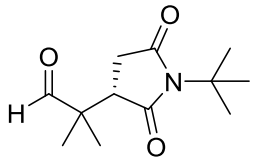


	name	Retention	Area(μV*s)	Height（μV）	% Area
1		10.587	11934680	663317	49.66
2		12.183	12098579	541826	50.34



	name	Retention	Area(μV*s)	Height（μV）	% Area
1		10.661	280595	19525	0.55
2		11.886	50534272	1665170	99.45

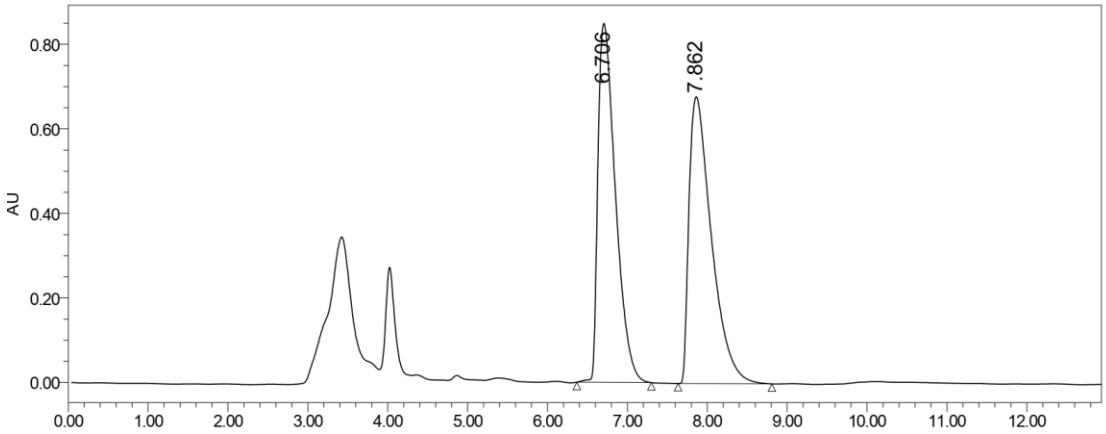
(S)-2-(1-(tert-butyl)-2,5-dioxopyrrolidin-3-yl)-2-methylpropanal[8]



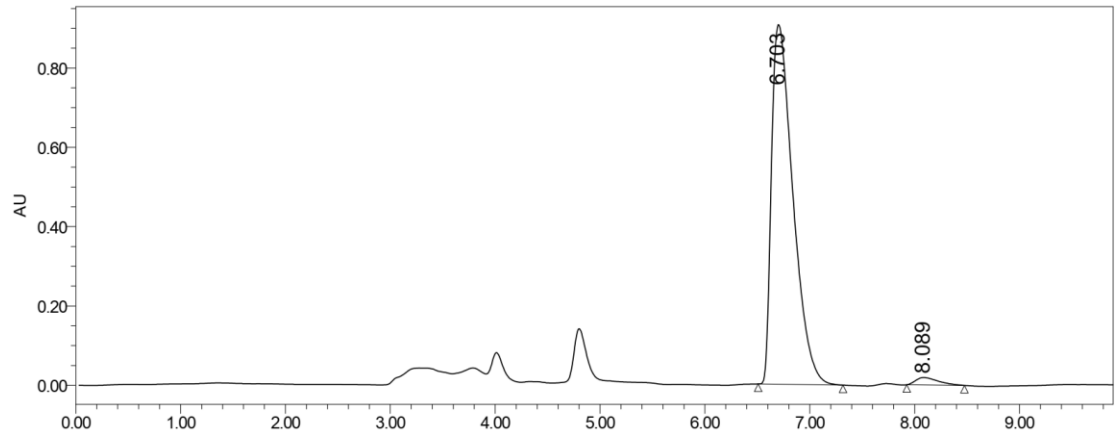
4t

4t, 82 mg, 73% yield, white solid, $[\alpha]_D^{25}$ = + 10 (*c* = 1.0, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 9.56 (s, 1H), 2.97 (dd, *J* =10.2, 6.0 Hz, 1H), 2.69 (dd, *J* = 18.0, 9.6 Hz, 1H), 2.36 (dd, *J* = 18.0, 5.4 Hz, 1H), 1.56 (s, 9H), 1.14 (s, 6H).

The ee was determined by HPLC analysis. CHIRALPAK OJ-H; Hexane/2-propanol=80:20; flow rate 1.0 mL/min; 210.0 nm; retention time: 6.7 min major) and 8.1 min minor).

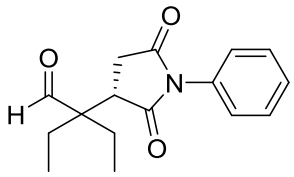


	name	Retention	Area(μV*s)	Height（μV）	% Area
1		6.706	12948637	849527	49.45
2		7.862	13237067	679032	50.55



	name	Retention	Area(μV*s)	Height（μV）	% Area
1		6.703	12896817	907287	97.87
2		8.089	281095	18706	2.13

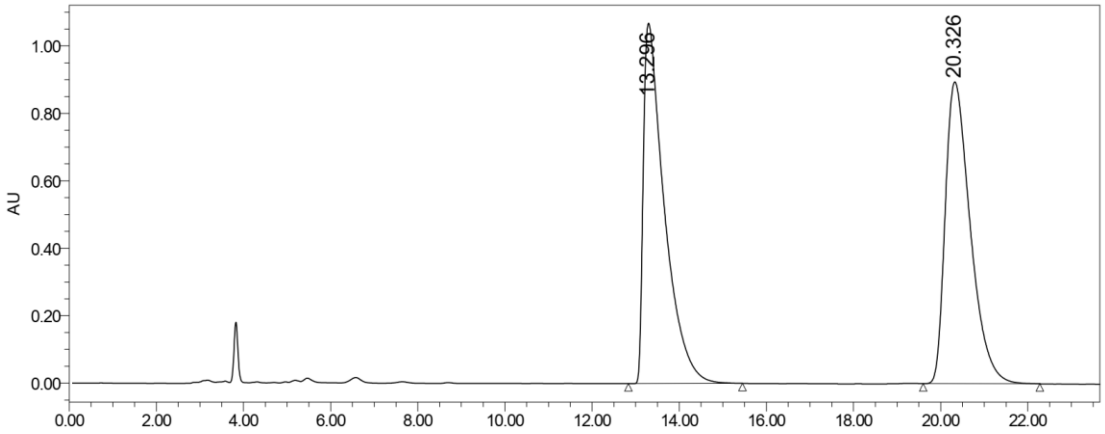
(*S*)-2-(2,5-dioxo-1-phenylpyrrolidin-3-yl)-2-ethylbutanal[2]



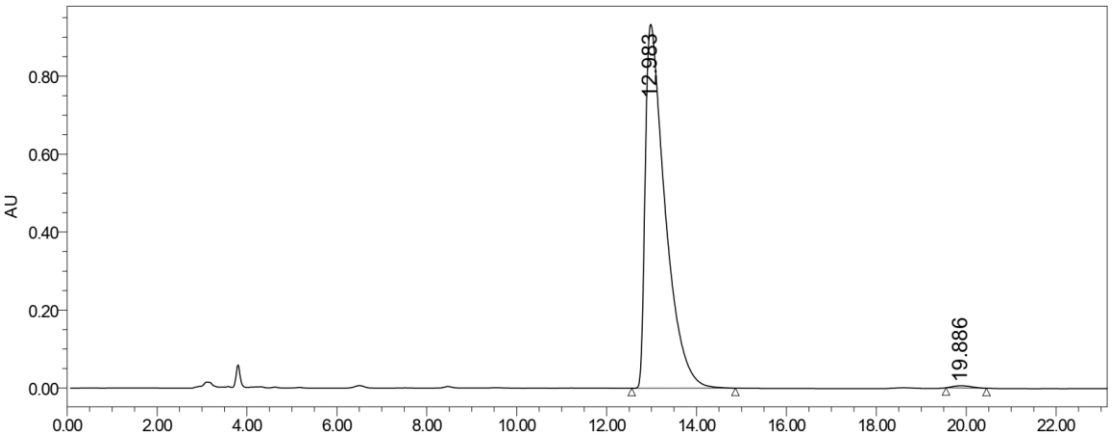
5a

5a, 129 mg, 95% yield, white solid, $[\alpha]_D^{25}$ = +10.0 (c =1.0, $CHCl_3$); 1H NMR (600 MHz, $CDCl_3$) δ 9.63 (s, 1H), 7.49 – 7.44 (m, 2H), 7.41 – 7.37 (m, 1H), 7.29 – 7.25 (m, 2H), 3.25 (dd, *J* = 9.6, 6.0 Hz, 1H), 2.97 (dd, *J* = 18.0, 9.6 Hz, 1H), 2.69 (dd, *J* = 18.0, 5.4 Hz, 1H), 2.02 – 1.83 (m, 3H), 1.78 – 1.70 (m, 1H), 1.03 – 0.97 (m, 6H).

The ee was determined by HPLC analysis. CHIRALPAK OD-H; Hexane/2-propanol=70:30; flow rate 1.0 mL/min; 218.0 nm; retention time: 13.0 min (major) and 19.9 min (minor).

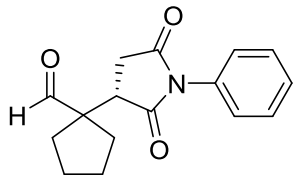


	name	Retention	Area(μV*s)	Height（μV）	% Area
1		13.296	35676433	1068439	49.97
2		20.326	35714472	894901	50.03



	name	Retention	Area(μV*s)	Height（μV）	% Area
1		12.983	28573658	933141	99.47
2		19.886	153340	5426	0.53

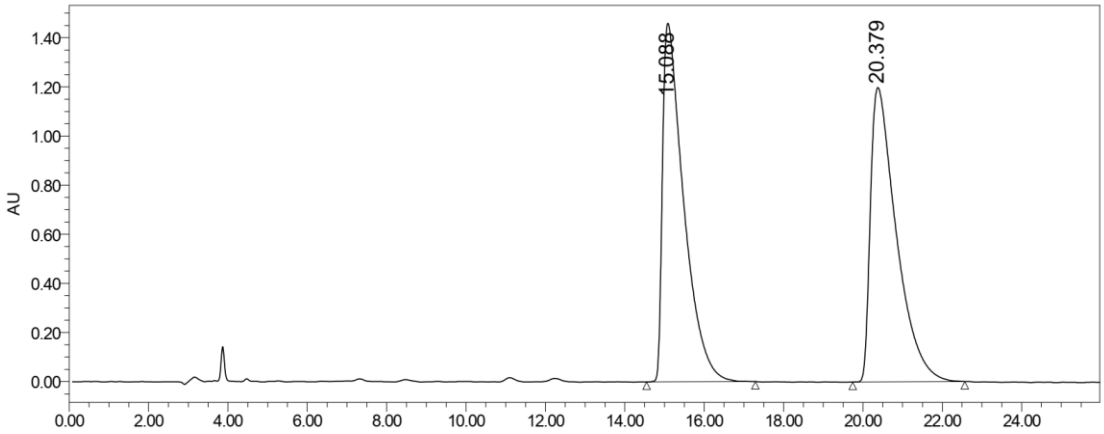
(S)-1-(2,5-dioxo-1-phenylpyrrolidin-3-yl)cyclopentanecarbaldehyde[2]



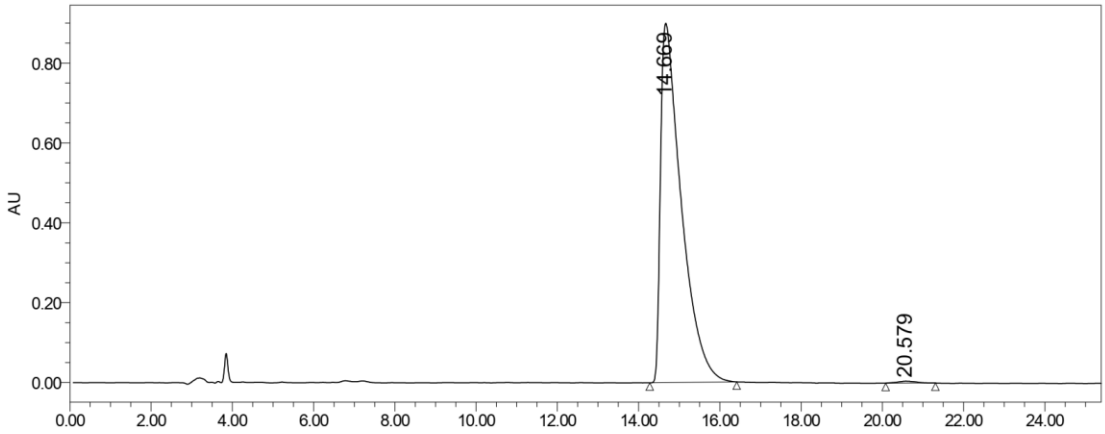
5b

5b, 129 mg, 95% yield, white solid, $[\alpha]_D^{25}$ = + 40.0 (*c* = +1.0, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 9.39 (s, 1H), 7.49 – 7.46 (m, 2H), 7.40 – 7.37 (m, 1H), 7.34 – 7.29 (m, 2H), 3.05 – 2.94 (m, 2H), 2.58 (dd, *J* = 18.0, 5.4 Hz, 1H), 2.37 – 2.27 (m, 1H), 2.14 – 2.03 (m, 2H), 1.88 – 1.69 (m, 5H).

The ee was determined by HPLC analysis. CHIRALPAK OD-H; Hexane/2-propanol=70:30; flow rate 1.0 mL/min; 226.2 nm; retention time: 14.7 min (major) and 20.6 min (minor).

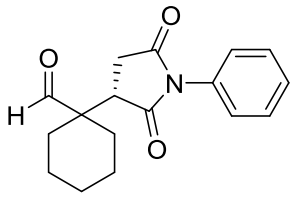


	name	Retention	Area(μV*s)	Height（μV）	% Area
1		15.088	54063092	1459676	49.88
2		20.379	54324113	1198482	50.12



	name	Retention	Area(μV*s)	Height（μV）	% Area
1		14.669	31923243	899692	99.54
2		20.579	146400	4608	0.46

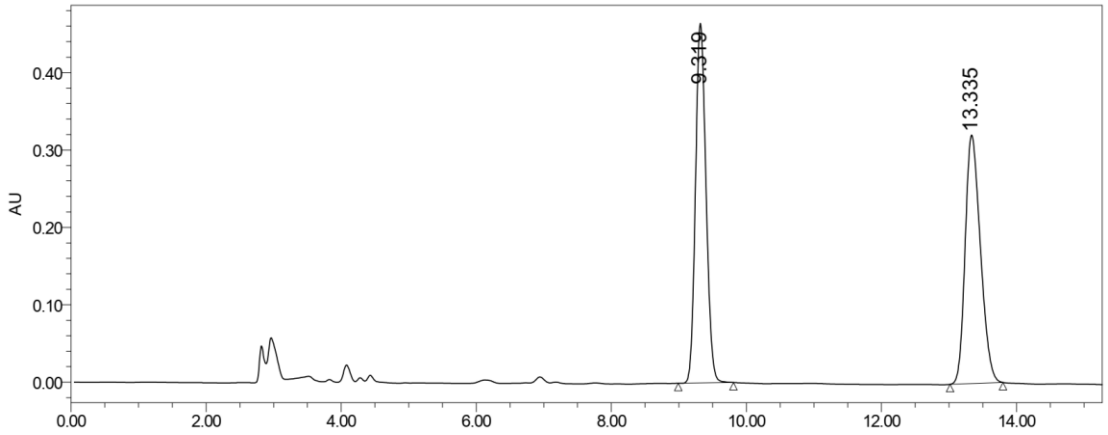
(S)-1-(2,5-dioxo-1-phenylpyrrolidin-3-yl)cyclohexanecarbaldehyde[2]



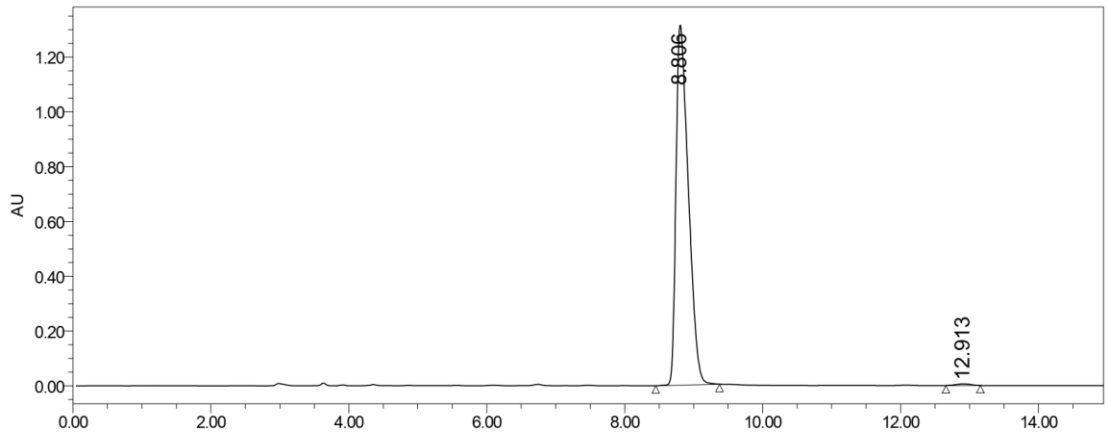
5c

5c, 136 mg, 96% yield, white solid, $[\alpha]_D^{25}$ = + 5.0 (*c* =1.0, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 9.55 (s, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.40 – 7.38 (m, 1H), 7.31 – 7.27 (m, 2H), 3.22 (dd, *J* = 9.0, 6.0 Hz, 1H), 2.87 (dd, *J* = 18.0, 9.6 Hz, 1H), 2.68 (dd, *J* = 18.2, 5.9 Hz, 1H), 1.99 – 1.85 (m, 3H), 1.67 – 1.49 (m, 6H).

The ee was determined by HPLC analysis. CHIRALPAK OD-H; Hexane/2-propanol=70:30; flow rate 1.0 mL/min; 220.3 nm; retention time: 8.8 min (major) and 12.9 min (minor).

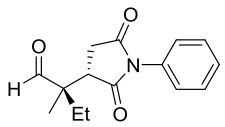


	name	Retention	Area(μV*s)	Height（μV）	% Area
1		9.319	5017953	464718	49.94
2		13.335	5030511	321217	50.06



	name	Retention	Area(μV*s)	Height（μV）	% Area
1		8.806	16338010	1314746	99.48
2		12.913	86170	5932	0.52

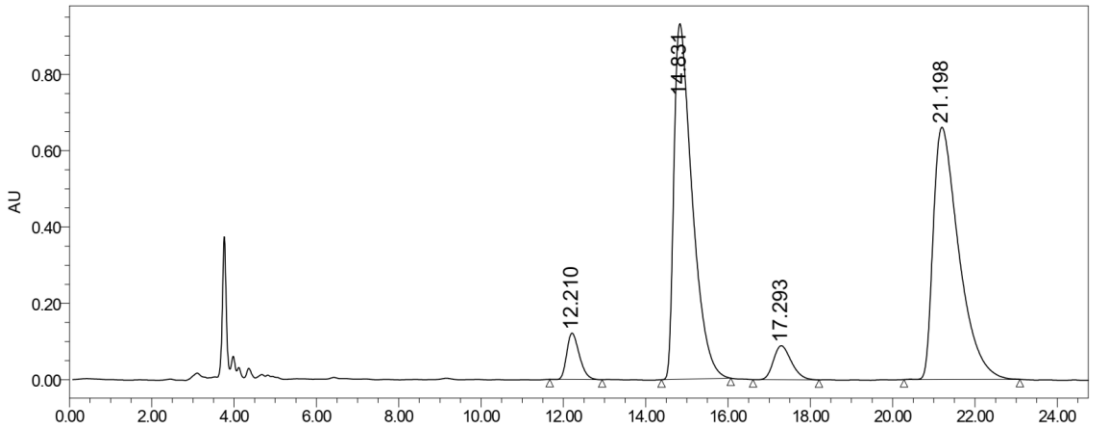
(*R*)-2-((*S*)-2,5-dioxo-1-phenylpyrrolidin-3-yl)-2-methylbutanal[9]



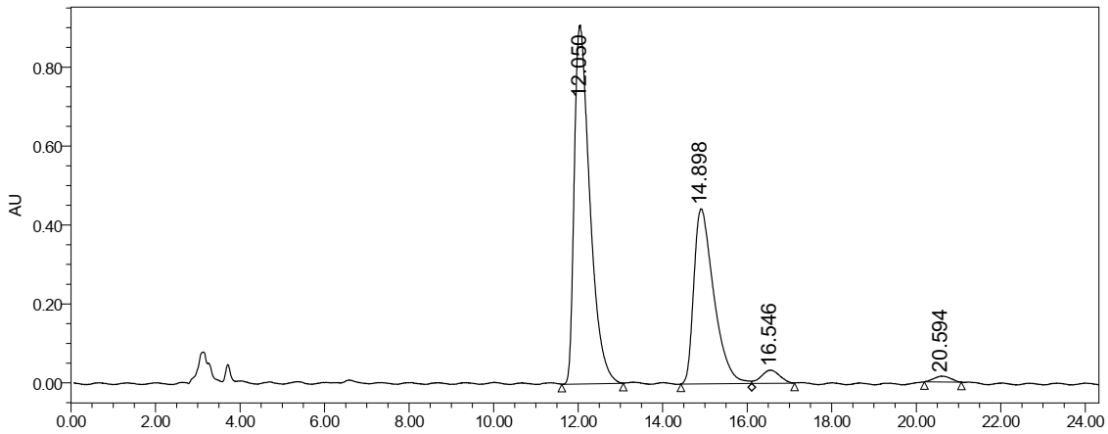
5d

5d, 136 mg, 96% yield, white solid, $[\alpha]_D^{25}$ = -14.0 (*c* =1.0, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 9.62 (s, 1H), 7.48 – 7.44 (m, 2H), 7.41 – 7.39 (m, 1H), 7.29 – 7.25 (m, 2H), 3.35 (dd, *J* = 9.6, 60 Hz, 1H), 2.95 (dd, *J* = 18.0, 9.6 Hz, 1H), 2.66 (dd, *J* = 18.0, 6.0 Hz, 1H), 1.80 – 1.70 (m, 2H), 1.19 (s, 3H), 0.95 (t, *J* = 7.8 Hz, 3H).

The ee was determined by HPLC analysis. CHIRALPAK OD-H; Hexane/2-propanol=70:30; flow rate 1.0 mL/min; 220.3 nm; retention time: major diastereomer: 12.0 min (major), 16.5 min (minor); minor diastereomer: 14.9min (major), 20.6 min (minor).

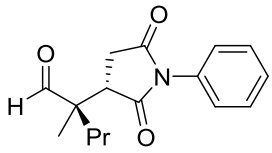


	name	Retention	Area(μV*s)	Height（μV）	% Area
1		12.210	2577136	121500	4.12
2		14.831	28705401	931709	45.90
3		17.293	2694091	88966	4.31
4		21.198	28557600	660957	45.67



	name	Retention	Area(μV*s)	Height（μV）	% Area
1		12.050	23290734	909416	59.31
2		14.898	14567566	443655	37.10
3		16.546	1004142	33616	2.56
4		20.594	403927	14784	1.03

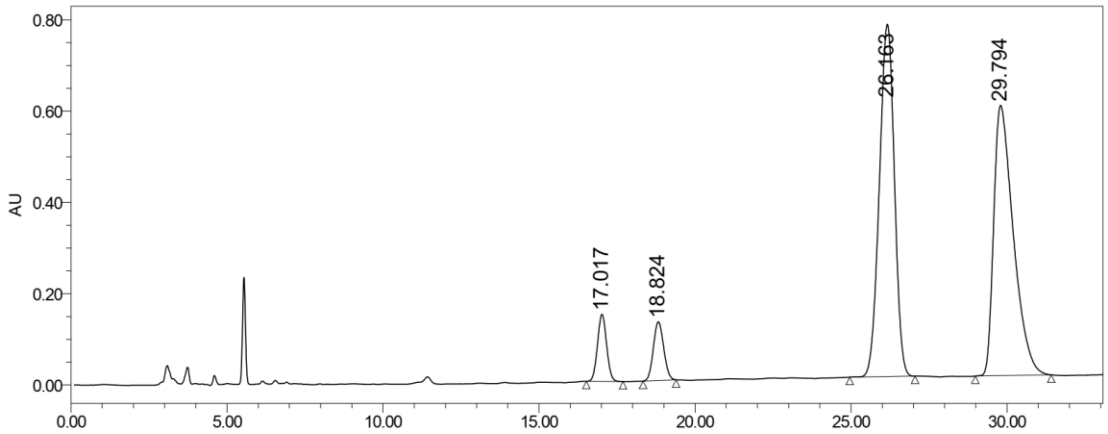
(*R*)-2-((*S*)-2, 5-dioxo-1-phenylpyrrolidin-3-yl)-2-methylpentanal[2]



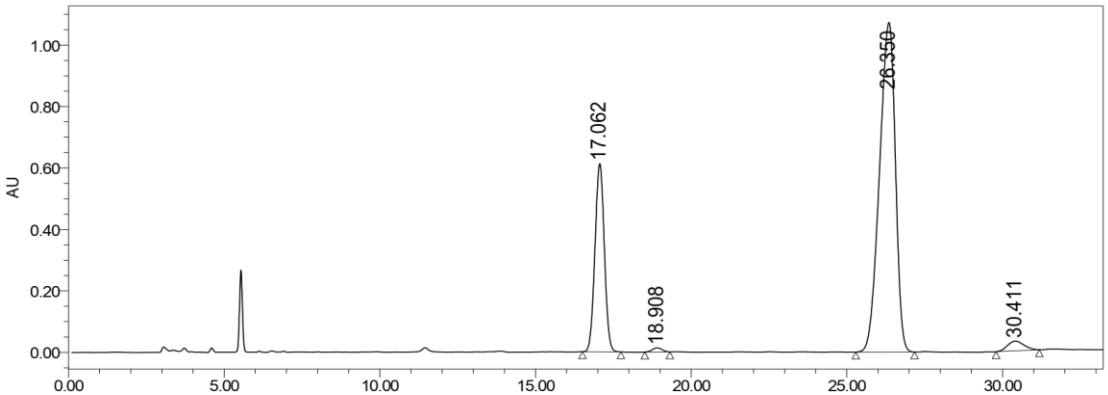
5e

5e, 136 mg, 96% yield, white solid, $[\alpha]_D^{25}$ = - 5.0 (*c* =1.0, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 9.62 (s, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 7.39 (t, *J* = 7.4 Hz, 1H), 7.29 – 7.25 (m, 2H), 3.34 (dd, *J* = 9.6, 60. Hz, 1H), 2.94 (dd, *J* = 18.0, 9.6 Hz, 1H), 2.66 (dd, *J* = 18.0, 6.0 Hz, 1H), 1.70 – 1.57 (m, 2H), 1.45 – 1.36 (m, 1H), 1.31 – 1.22 (m, 1H), 1.19 (s, 3H), 0.95 (t, *J* = 7.2 Hz, 3H).

The ee was determined by HPLC analysis. CHIRALPAK OD-H; Hexane/2-propanol=70:30; flow rate 1.0 mL/min; 220.3 nm; retention time: major diastereomer: 26.4 min (major), 30.4 min (minor); minor diastereomer: 17.1 min (major), 18.9 min (minor).

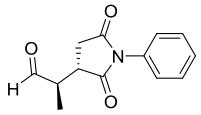


	name	Retention	Area(μV*s)	Height（μV）	% Area
1		17.017	2982732	147014	5.17
2		18.824	2958456	128667	5.13
3		26.163	25835572	771670	44.81
4		29.794	25882733	592250	44.89



	name	Retention	Area(μV*s)	Height（μV）	% Area
1		17.062	12776146	612211	24.48
2		18.908	287380	13313	0.55
3		26.350	37954470	1071984	72.73
4		30.411	1164083	31614	2.23

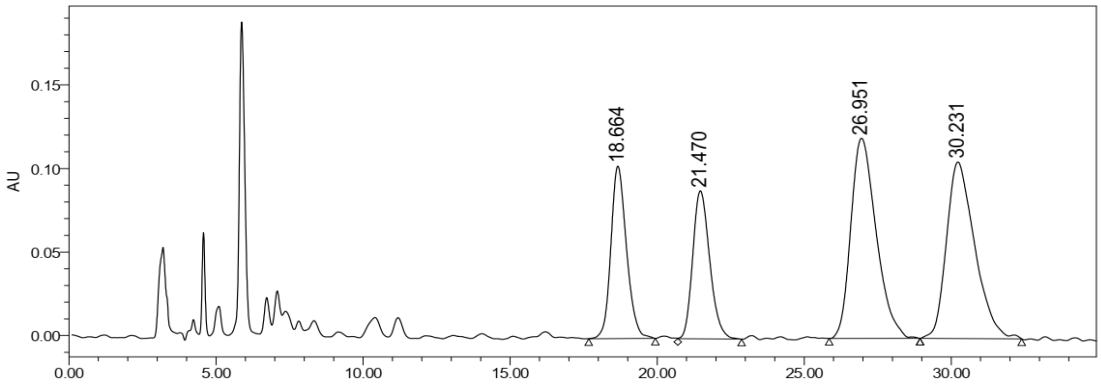
(*R*)-2-((*S*)-2,5-dioxo-1-phenylpyrrolidin-3-yl)propanal[3]



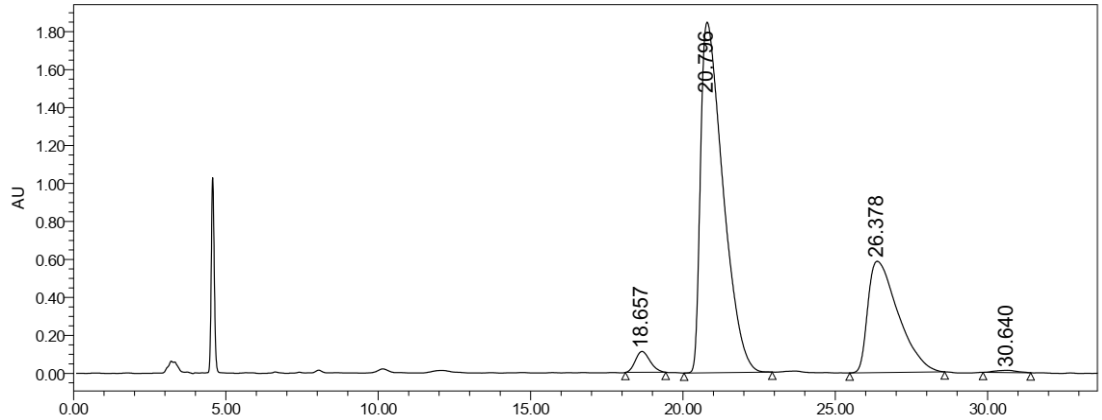
5f

5f, 101 mg, 88% yield, white solid, $[\alpha]_D^{25}$ = - 20.0 (*c* =1.0, $CHCl_3$);^{1}H NMR (600 MHz, $CDCl_3$) δ 9.63 (s, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 7.40 (t, *J* = 7.2 Hz, 1H), 7.34 – 7.28 (m, 2H), 3.31-3.26 (m, 1H), 3.12 – 3.06 (m, 1H), 2.93 (dd, *J* = 18.0, 9.6 Hz, 1H), 2.60 (dd, *J* = 18.0, 5.6 Hz, 1H), 1.40 (d, *J* = 7.8 Hz, 3H).

The ee was determined by HPLC analysis. CHIRALPAK OJ-H; Hexane/2-propanol=80:20; flow rate 0.5 mL/min; 218.0 nm; retention time: major diastereomer: 20.8 min (major), 18.7 min (minor); minor diastereomer: 26.4 min (major), 30.64 min (minor).

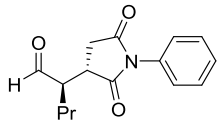


	name	Retention	Area(μV*s)	Height（μV）	% Area
1		18.664	3816535	103126	17.64
2		21.470	3561165	88535	16.46
3		26.951	7193182	119784	33.25
4		30.231	7064967	105669	32.65



	name	Retention	Area(μV*s)	Height（μV）	% Area
1		18.657	3678015	110374	2.64
2		20.796	94439714	1846632	67.80
3		26.378	40579281	586647	29.13
4		30.640	587258	12131	0.42

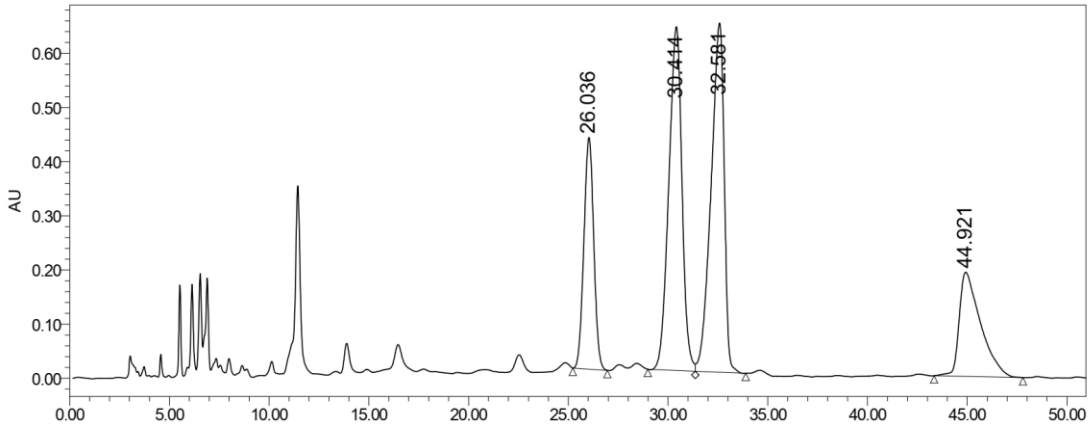
(*R*)-2-((*S*)-2, 5-dioxo-1-phenylpyrrolidin-3-yl) pentanal[10]



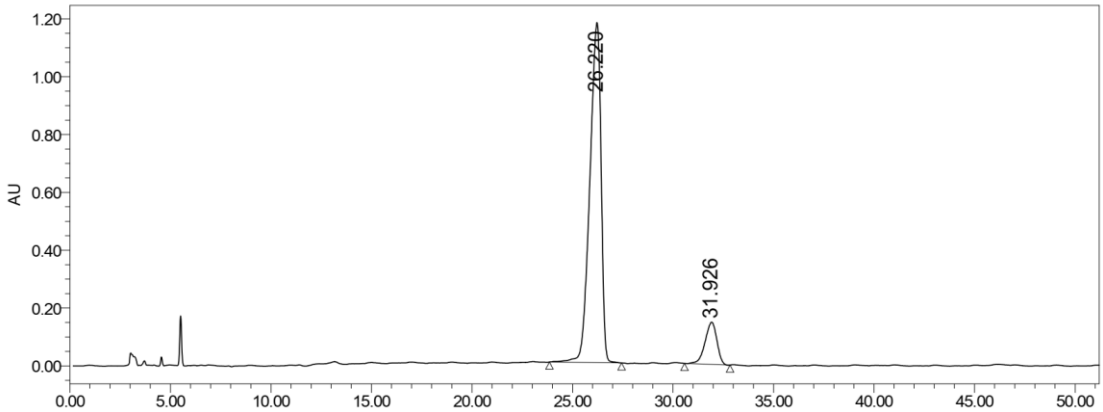
5g

5g, 124 mg, 96% yield, white solid, $[\alpha]_D^{25}$ = - 15.0 (*c* =1.0, $CHCl_3$);^{1}H NMR (600 MHz, $CDCl_3$) δ 9.76 (s, 1H), 7.50 – 7.46 (m, 2H), 7.42 – 7.38 (m, 1H), 7.33 – 7.28 (m, 2H), 3.37 – 3.32 (m, 1H), 3.04 – 3.01 (m, 1H), 2.59 (d, *J* = 5.4 Hz, 1H), 2.56 (d, *J* = 6.0 Hz, 1H), 1.94 – 1.85 (m, 1H), 1.69 – 1.60 (m, 1H), 1.58 – 1.52 (m, 2H), 1.01 (t, *J* = 7.2 Hz, 3H).

The ee was determined by HPLC analysis. CHIRALPAK AD-H; Hexane/2-propanol=90:10; flow rate 0.5 mL/min; 210.0 nm; retention time: major diastereomer: 26.2 min (major); minor diastereomer: 31.9 min (major)

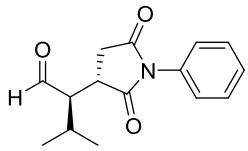


	name	Retention	Area(μV*s)	Height（μV）	% Area
1		26.036	14709735	427889	16.79
2		30.414	29140350	634860	33.27
3		32.581	29434013	644808	33.60
4		44.921	14316356	192471	16.34



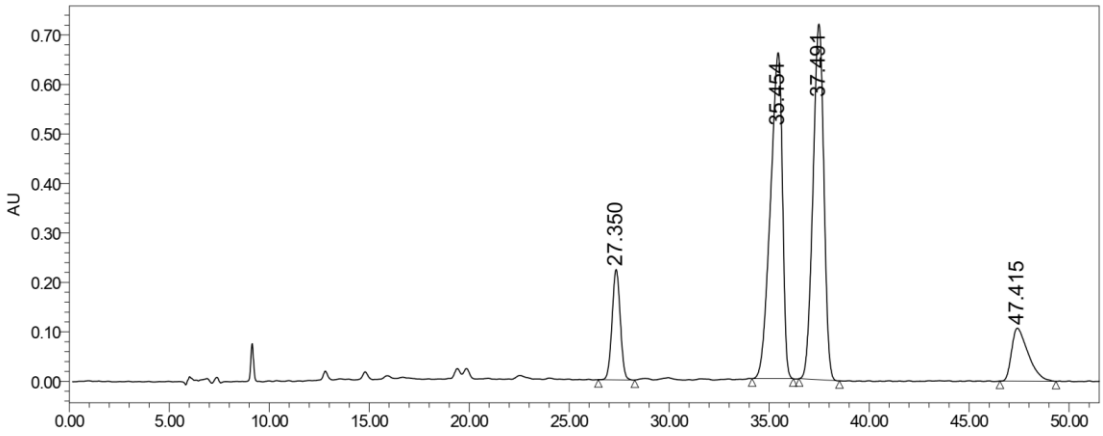
	name	Retention	Area(μV*s)	Height（μV）	% Area
1		26.220	45575639	1175894	88.45
2		31.926	5954041	145867	11.55

(*R*)-2-((*S*)-2,5-dioxo-1-phenylpyrrolidin-3-yl)-3-methylbutanal[11]

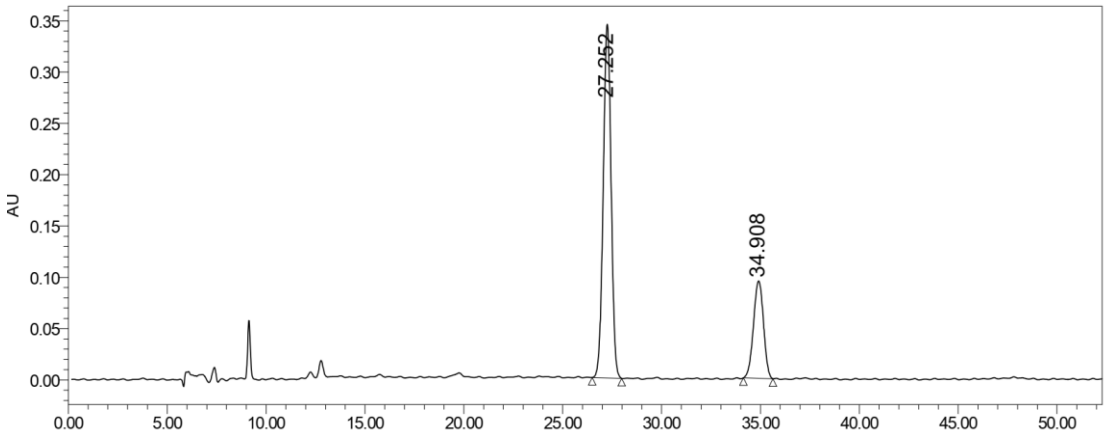


5h

5h, 109 mg, 84% yield, white solid, $[\alpha]_D^{25}$ = - 16.0 (*c* =1.0, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 9.78 (s, 1H), 7.50 – 7.45 (m, 2H), 7.41 – 7.36 (m, 1H), 7.31 – 7.28 (m, 2H), 3.17 (dd, *J* = 7.2, 3.7 Hz, 1H), 3.11 – 2.99 (m, 1H), 2.87 (dd, *J* = 18.0, 9.6 Hz, 1H), 2.73 (dd, *J* = 18.0, 6.0 Hz, 1H), 2.36 – 2.28 (m, 1H), 1.26 (d, *J* = 6.6 Hz, 3H), 1.10 (d, *J* = 6.6 Hz, 3H).
The ee was determined by HPLC analysis. CHIRALPAK AD-H; Hexane/2-propanol=80:20; flow rate 0.5 mL/min; 218.0 nm; retention time: major diastereomer: 27.3 min (major); minor diastereomer: 34.9 min (major).

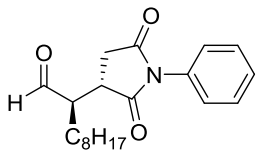


	name	Retention	Area(μV*s)	Height（μV）	% Area
1		27.350	6333296	223022	9.43
2		35.454	27486087	658934	40.94
3		37.491	27193226	718723	40.50
4		47.415	6125187	106781	9.12



	name	Retention	Area(μV*s)	Height（μV）	% Area
1		26.220	45575639	1175894	88.45
2		31.926	5954041	145867	11.55

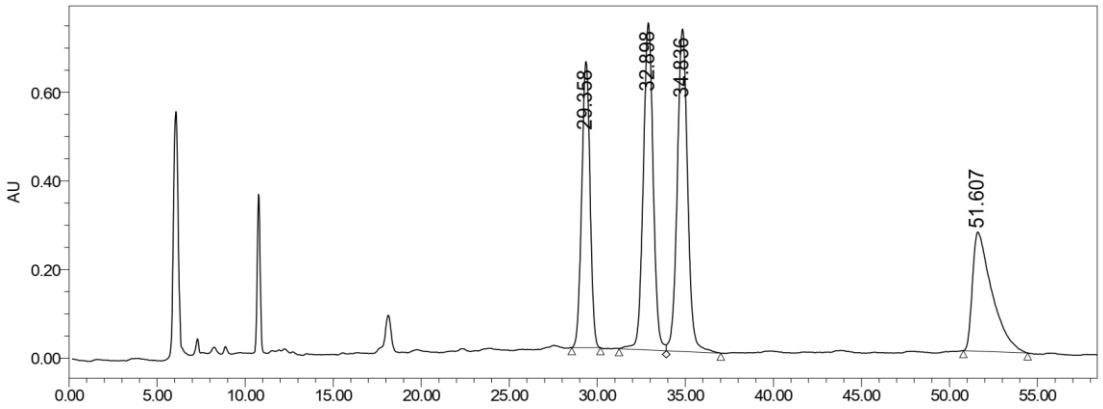
(*R*)-2-((*S*)-2, 5-dioxo-1-phenylpyrrolidin-3-yl)decanal[3]



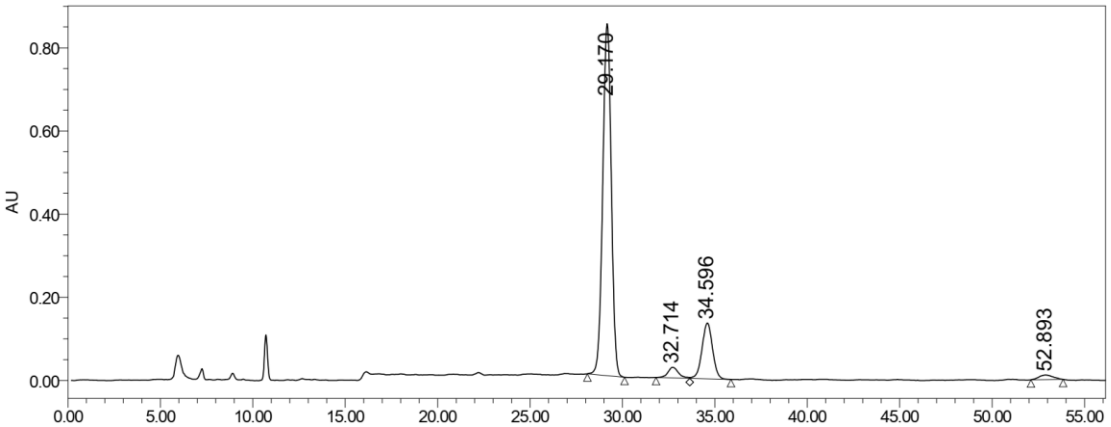
5i

5i, 99 mg, 60% yield, white solid, $[\alpha]_D^{25}$ = - 16(*c* =1.0, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 9.64 (s, 1H), 7.51 – 7.45 (m, 2H), 7.42 – 7.38 (m, 1H), 7.36 – 7.27 (m, 2H), 3.25 - 3.23 (m 1H), 3.10 – 3.07 (m, 1H), 2.87 (dd, *J* = 18.0, 9.6 Hz, 1H), 2.63 - 2.59 (m, 1H), 1.52 – 1.51 (m, 3H), 1.33 – 1.26 (m, 11H), 1.37-1.35 (m, 1H), 1.33 – 1.22 (m, 9H), 0.91 – 0.89 (m, 3H).

The ee was determined by HPLC analysis. CHIRALPAK AD-H; Hexane/2-propanol=90:10; flow rate 0.5 mL/min; 218.0 nm; retention time: major diastereomer: 29.2 min (major), 52.9 min (minor); minor diastereomer: 32.7 min (minor), 34.6 min (major).

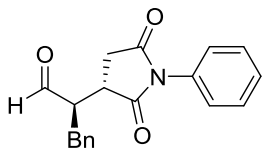


	name	Retention	Area(μV*s)	Height（μV）	% Area
1		29.358	21132529	646341	21.05
2		32.898	28846605	738850	28.73
3		34.836	29761359	728217	29.64
4		51.607	20666740	269134	20.58



	name	Retention	Area(μV*s)	Height（μV）	% Area
1		29.170	27195805	846185	79.67
2		32.714	1019143	25341	2.99
3		34.596	5336611	134240	15.63
4		52.893	585811	11016	1.72

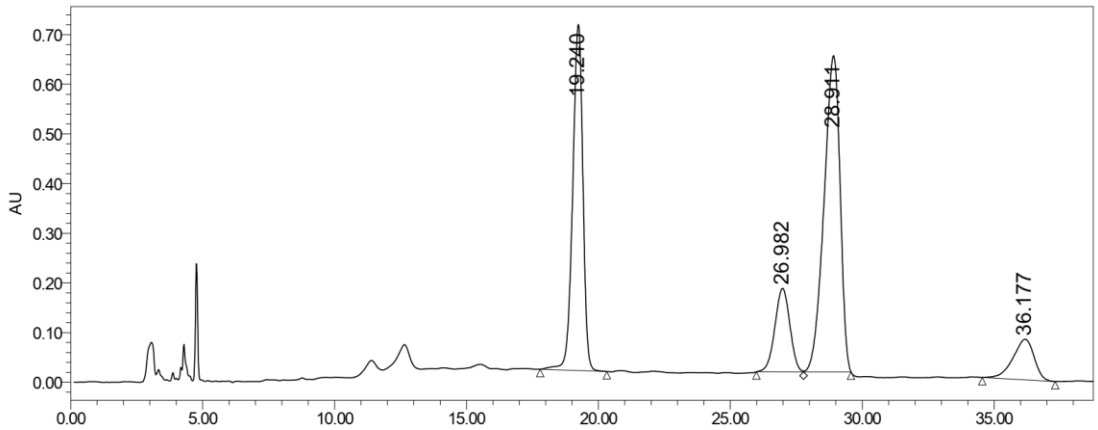
(*R*)-2-((*S*)-2,5-dioxo-1-phenylpyrrolidin-3-yl)-3-phenylpropanal[11]



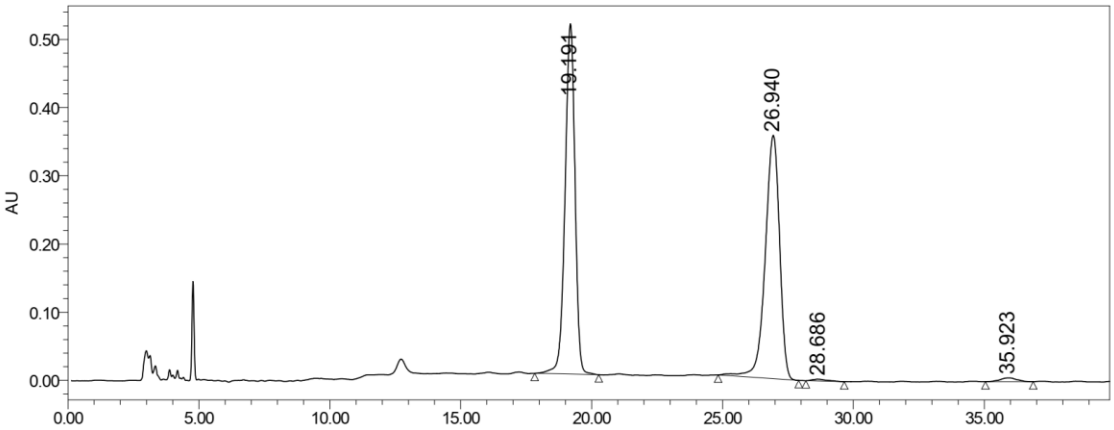
5j

5j, 115 mg, 75% yield, white solid, $[\alpha]_D^{25}$ = + 25 (*c* =1.0, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 9.72 (s, 1H), 7.49 – 7.44 (m, 2H), 7.41 – 7.33 (m, 3H), 7.33 – 7.23 (m, 5H), 3.65 – 3.59 (m, 1H), 3.40 (dd, *J* = 13.8, 5.4 Hz, 1H), 2.97 – 2.85 (m, 1H), 2.85 – 2.73(m, 2H), 2.65 – 2.58 (m, 1H).

The ee was determined by HPLC analysis. CHIRALPAK AD-H; Hexane/2-propanol=85:15; flow rate 1.0 mL/min; 218.0 nm; retention time: 19.2 min (major), 28.7 min (minor); 26.9 min (major), 36.0 min (minor).

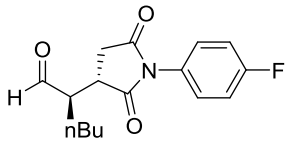


	name	Retention	Area(μV*s)	Height（μV）	% Area
1		19.240	18741327	696903	33.02
2		26.982	6613330	168048	11.56
3		28.911	26848588	636749	47.30
4		36.177	4561387	81732	8.04



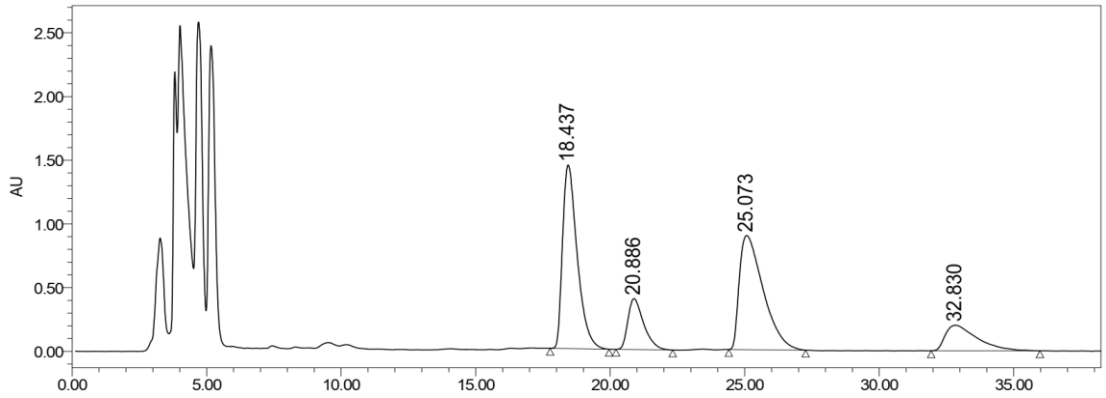
	name	Retention	Area(μV*s)	Height（μV）	% Area
1		19.191	13549609	513686	49.29
2		26.940	13577878	356879	49.39
3		28.686	110853	2685	0.40
4		35.923	250091	5573	0.91

(*R*)-2-((*S*)-1-(4-fluorophenyl)-2,5-dioxopyrrolidin-3-yl) hexanal

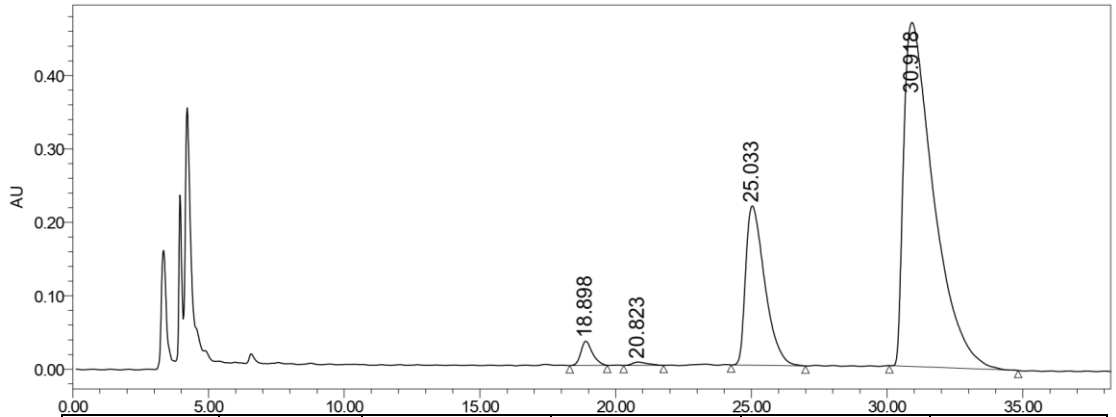


5k

5k, 108 mg, 74% yield, white solid, $[\alpha]_D^{25}$ = - 33(*c* =1.0, $CHCl_3$);^{1}H NMR (600 MHz, $CDCl_3$) δ 9.62 (s, 1H), 7.34 – 7.28 (m, 2H), 7.19 – 7.13 (m, 2H), 3.29 – 3.20 (m, 1H), 3.10 – 3.02 (m, 1H), 2.86 (dd, *J* = 18.0, 9.6 Hz, 1H), 2.60 (dd, *J* = 18.0, 6.0 Hz, 1H), 1.54 – 1.49 (m, 6H), 0.97 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 201.4, 177.3, 174.7, 134.5, 130.3, 129.4, 127.7, 52.9, 38.5, 32.6, 29.8, 26.1, 22.6, 13.8; HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ Calcd for $C_{16}H_{18}FNO_3$ 292.1343, Found 292.1342. The ee was determined by HPLC analysis. CHIRALPAK OJ-H; Hexane/2-propanol=70:30; flow rate 1.0 mL/min; 218.0 nm; retention time: minor diastereomer: 18.9 min (minor), 25.0 min (major); major diastereomer: 20.8 min (minor), 30.9 min (major).

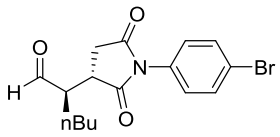


	name	Retention	Area(μV*s)	Height（μV）	% Area
1		18.437	54503368	1441505	38.28
2		20.886	16247313	399884	11.41
3		25.073	55171543	896028	38.75
4		32.830	16449307	200484	11.55



	name	Retention	Area(μV*s)	Height（μV）	% Area
1		18.898	987578	33041	2.07
2		20.823	183482	4644	0.38
3		25.033	10621657	216792	22.22
4		30.918	36009583	468405	75.33

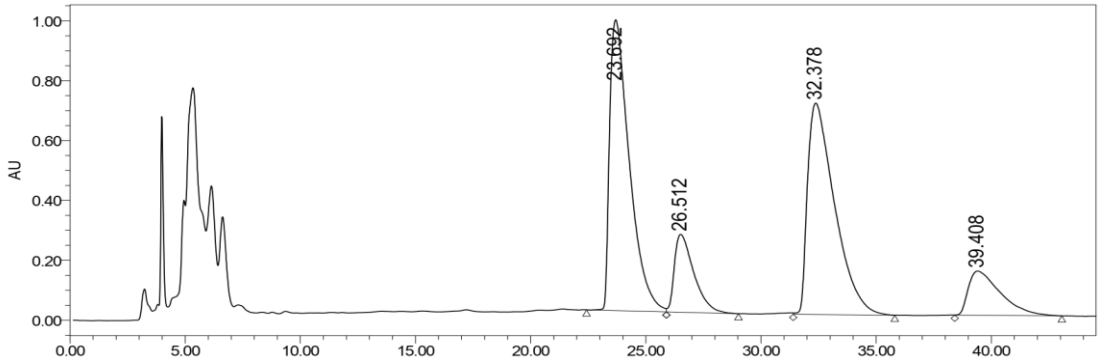
(*R*)-2-((*S*)-1-(4-bromophenyl)-2, 5-dioxopyrrolidin-3-yl)hexanal



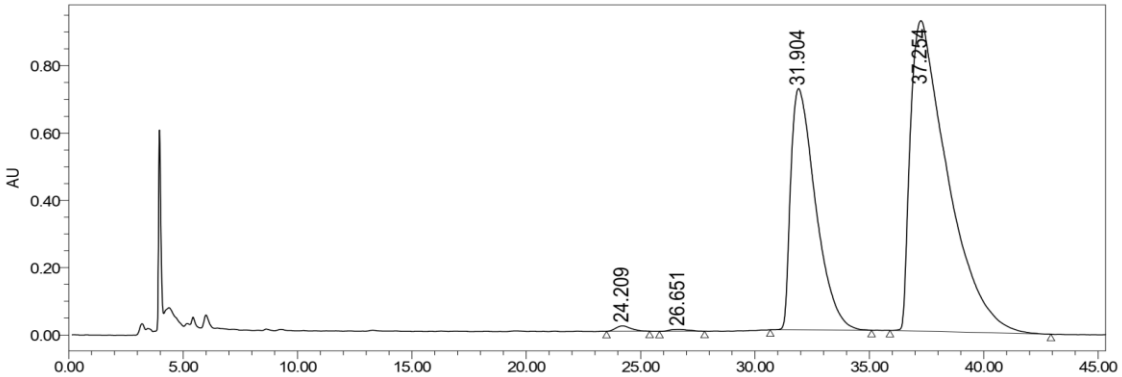
5l

5l, 125 mg, 71% yield, white solid, $[\alpha]_D^{25}$ = - 80.0(*c* =1.0, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.74 (s, 1H), 7.63 – 7.57 (m, 2H), 7.23 – 7.18 (m, 2H), 3.33 – 3.28(m, 1H), 3.05 – 2.95 (m, 2H), 2.56 (dd, *J* = 18.6, 6.0 Hz, 1H), 1.96 – 1.89 (m, 1H), 1.73 – 1.65 (m, 1H), 1.53 – 1.46 (m, 2H), 1.45 – 1.36(m, 2H), 0.94 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 201.4, 177.3, 174.7, 132.3, 130.9, 128.0, 52.9, 38.5, 32.6, 29.8, 26.1, 22.6, 13.8; HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ Calcd for $C_{16}H_{18}BrNO_3$ 352.0543, Found 352.0545.

The ee was determined by HPLC analysis. CHIRALPAK OJ-H; Hexane/2-propanol=80:20; flow rate 1.0 mL/min; 218.0 nm; retention time: minor diastereomer: 24.2 min (minor),31.9 min (major); major diastereomer: 26.7 min (minor), 37.3 min (major).

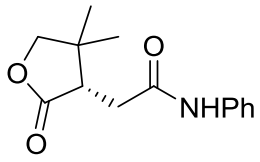


	name	Retention	Area(μV*s)	Height（μV）	% Area
1		23.692	57922665	970904	39.89
2		26.512	15277246	259945	10.52
3		32.378	57702904	705713	39.73
4		39.408	14318756	147908	9.86



	name	Retention	Area(μV*s)	Height（μV）	% Area
1		24.209	729962	15913	0.46
2		26.651	320285	5675	0.20
3		31.904	54219721	717455	33.89
4		37.254	104708543	922576	65.45

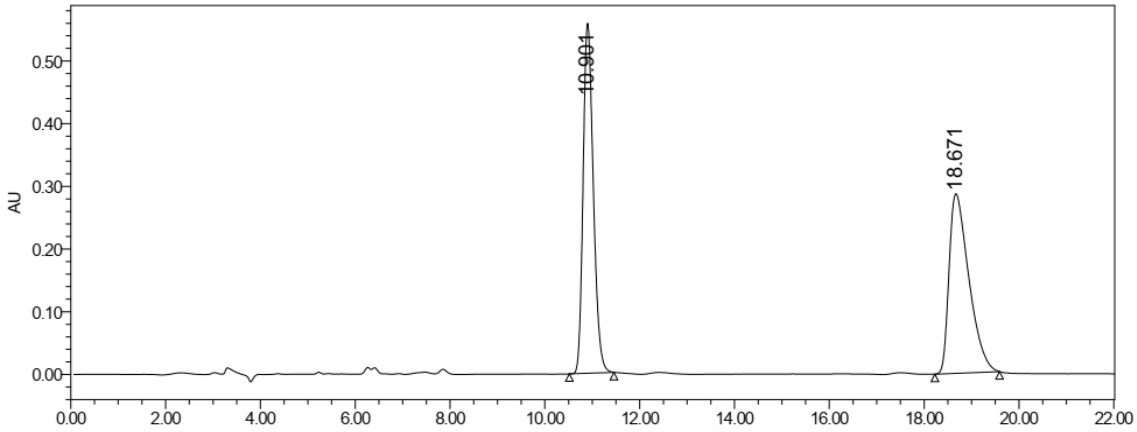
(*S*)-2-(4,4-dimethyl-2-oxotetrahydrofuran-3-yl)-N-phenylacetamide[2]



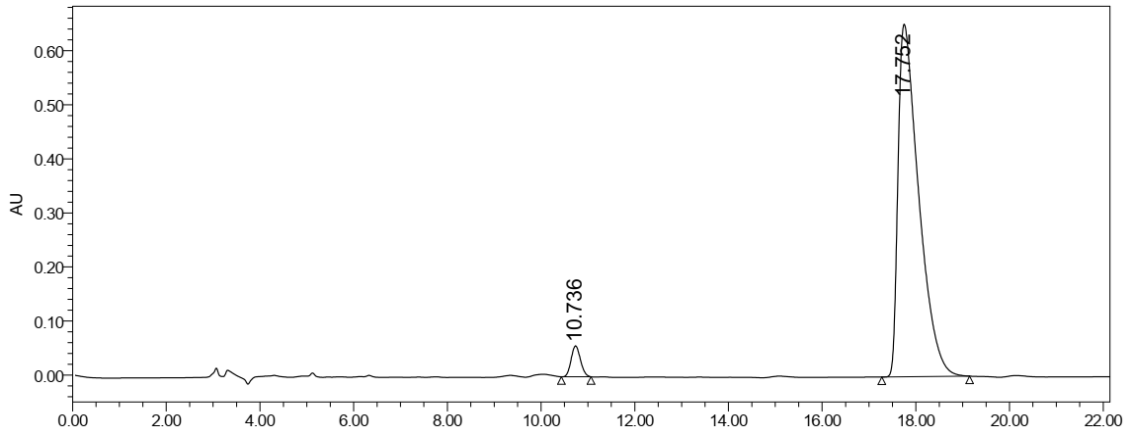
7

7, 94 mg, 76% yield, white solid, $[\alpha]_D^{25}$ = + 9.0 (*c* =1.0, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 8.64 (s, 1H), 7.53 (d, *J* = 7.8 Hz, 2H), 7.32 – 7.26 (m, 2H), 7.09 (t, *J* = 7.2 Hz, 1H), 4.01 (d, *J* = 9.0 Hz, 1H), 3.97 (d, *J* = 9.0 Hz, 1H), 2.92 (dd, *J* = 8.4, 4.2 Hz, 1H), 2.68 (dd, *J* = 15.0, 8.4 Hz, 1H), 2.38 (dd, *J* = 15.0, 4.2 Hz, 1H), 1.19 (s, 3H), 1.01 (s, 3H).

The ee was determined by HPLC analysis. CHIRALPAK OJ-H; Hexane/2-propanol=80:20; flow rate 1.0 mL/min; 220.0 nm; retention time: 10.7 min (minor) and 17.8 min(major).

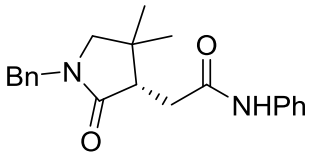


	name	Retention	Area(μV*s)	Height（μV）	% Area
1		10.901	8338189	557996	50.12
2		18.671	8296957	286207	49.88



	name	Retention	Area(μV*s)	Height（μV）	% Area
1		10.736	791378	57027	3.81
2		17.752	19955672	651974	96.19

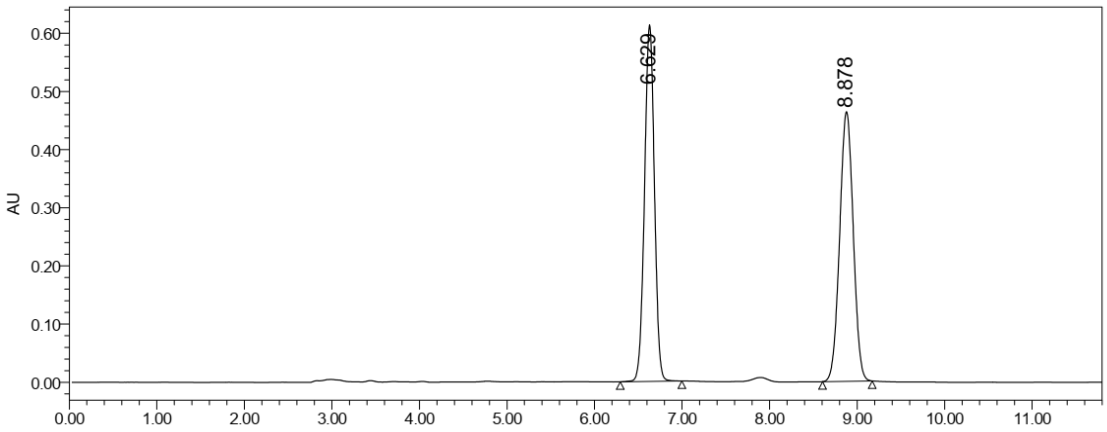
(*S*)-2-(1-benzyl-4,4-dimethyl-2-oxopyrrolidin-3-yl)-N-phenylacetamide[2]



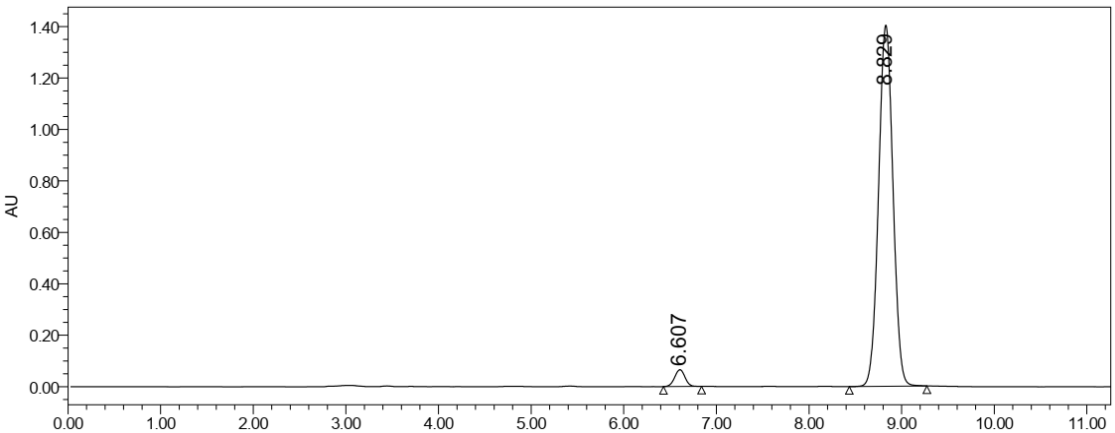
8

8, 104 mg, 62% yield, white solid, $[\alpha]_D^{25}$ = - 40 (*c* =1.0, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 10.43 (s, 1H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.35 – 7.20 (m, 7H), 7.05 (t, *J* = 7.2 Hz, 1H), 4.58 (d, *J* = 15.0 Hz, 1H), 4.37 (d, *J* = 15.0 Hz, 1H), 3.09 (d, *J* = 9.6 Hz, 1H), 2.85 (d, *J* = 9.6 Hz, 1H), 2.78 – 2.66 (m, 2H), 2.32 – 2.29 (m, 1H), 1.13 (s, 3H), 0.87 (s, 3H).

The ee was determined by HPLC analysis. CHIRALPAK AD-H; Hexane/2-propanol=75:25; flow rate 1.0 mL/min; 218.0 nm; retention time: 6.6 min (minor) and 8.8 min(major).

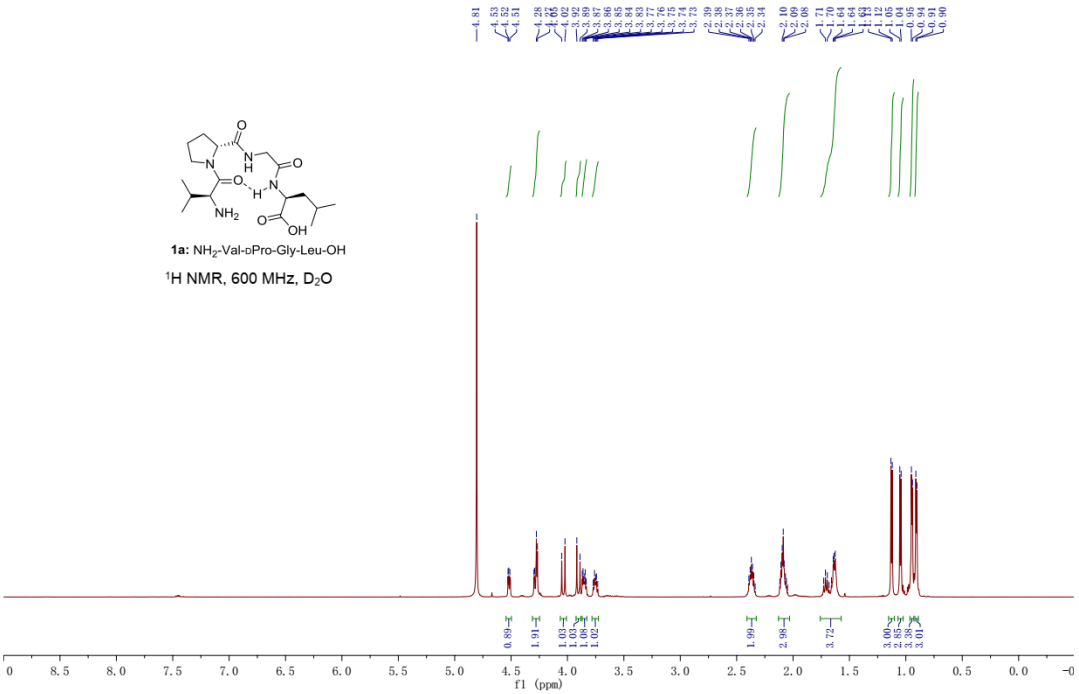


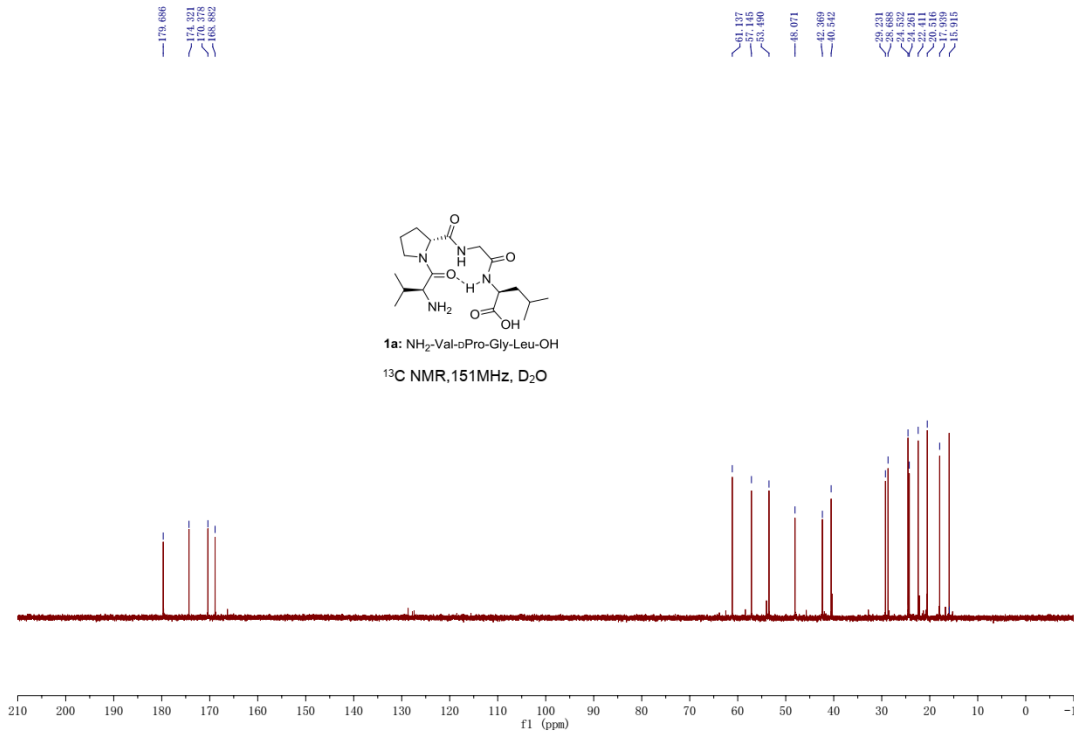
	name	Retention	Area(μV*s)	Height（μV）	% Area
1		6.629	4808190	612913	49.04
2		8.878	4995451	463276	50.96

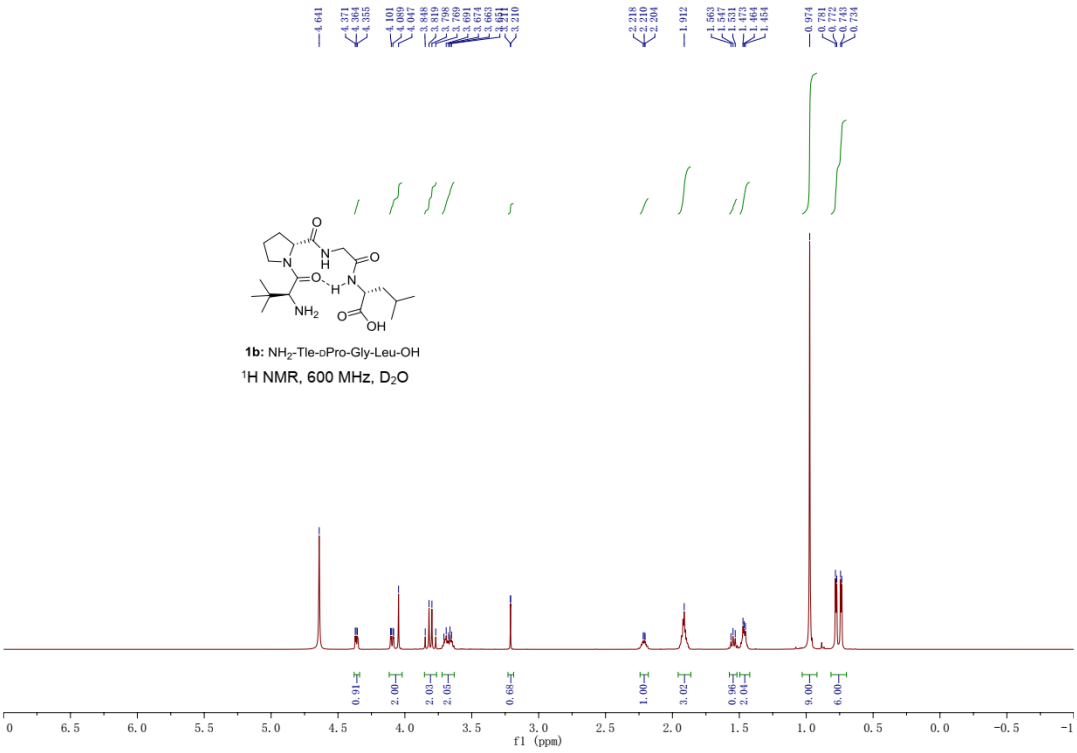


	name	Retention	Area(μV*s)	Height（μV）	% Area
1		6.607	503647	65314	3.21
2		8.829	15166967	1403681	96.79

8. Copies of NMR spectra

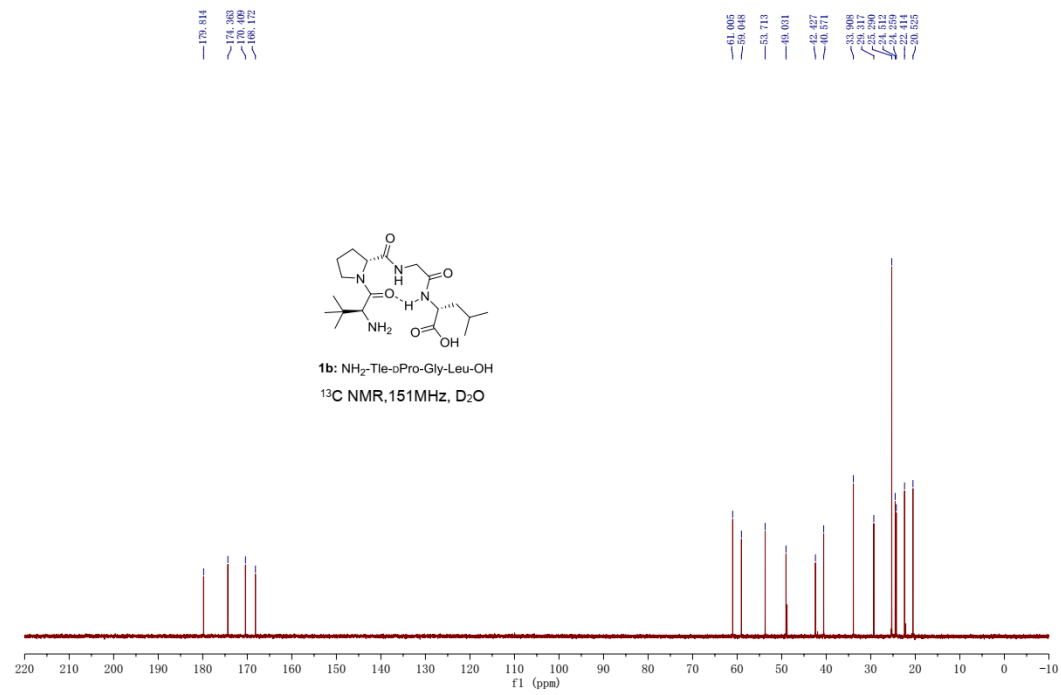






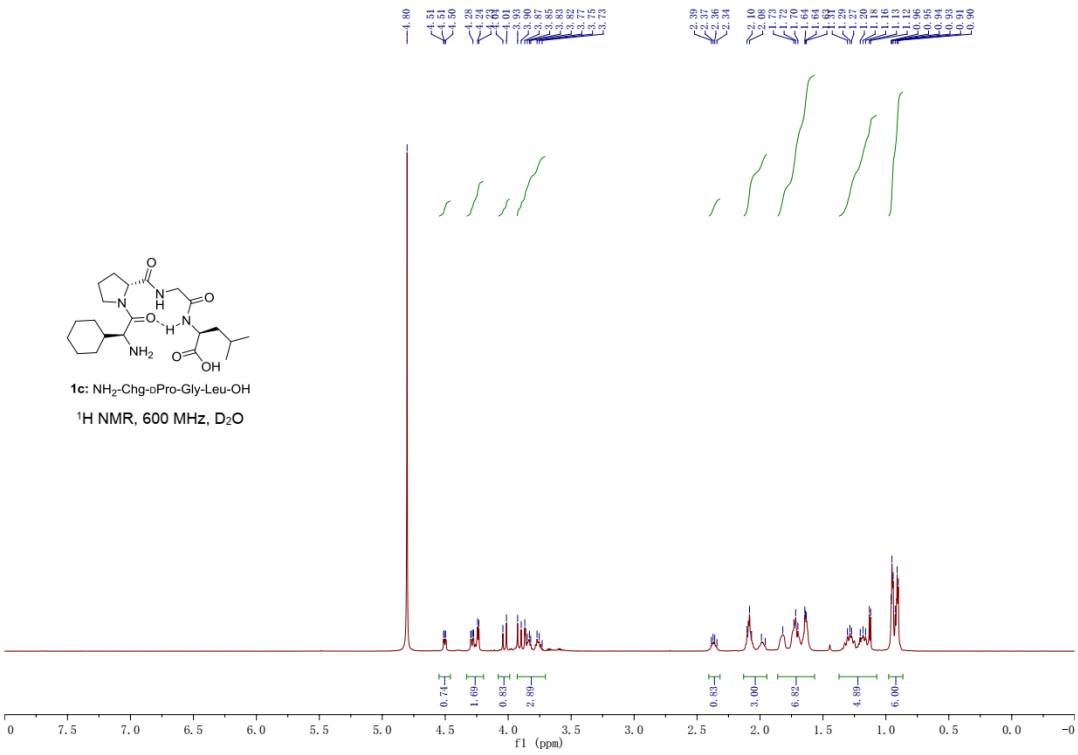
1b: NH_2-Tle-D-Pro-Gly-Leu-OH

^{1}H NMR, 600 MHz, D_2O



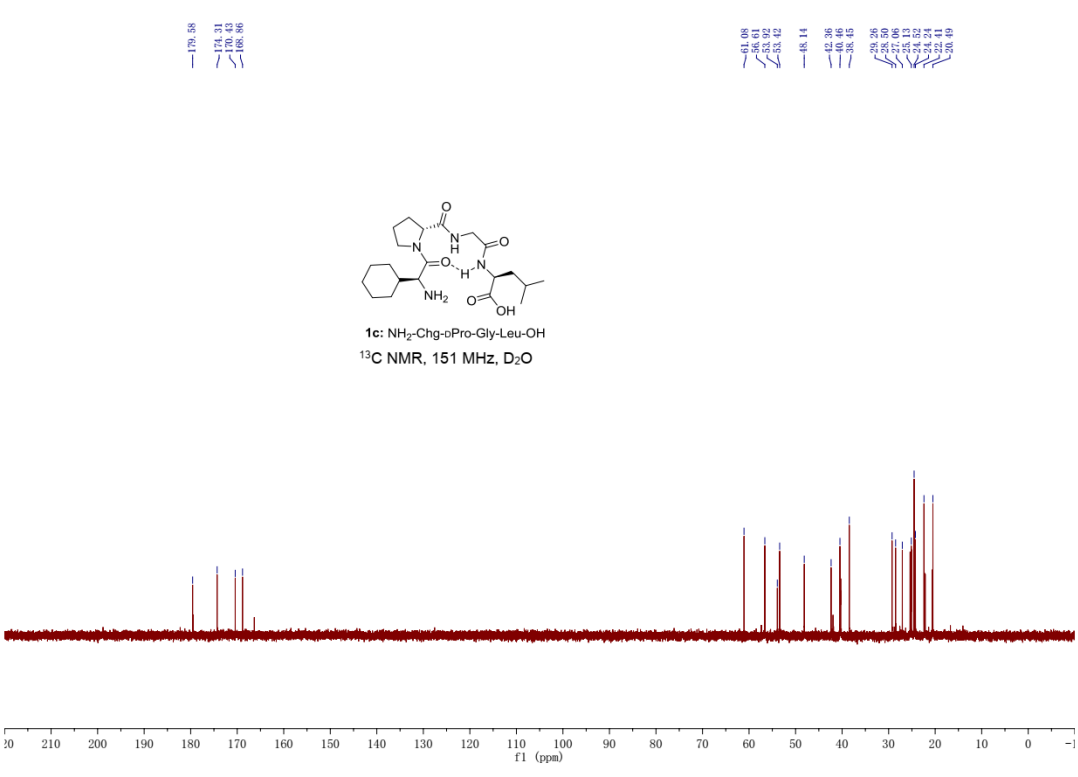
1b: NH_2-Tle-D-Pro-Gly-Leu-OH

^{13}C NMR,151MHz, D_2O



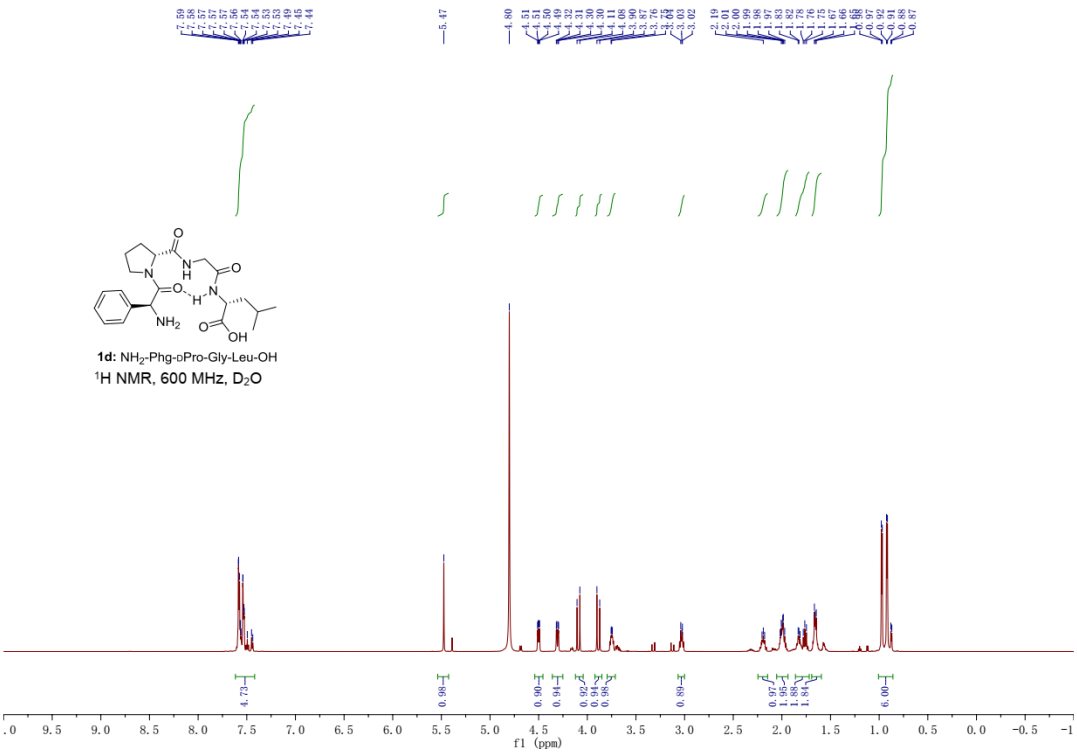
1c: NH_2-Chg-dPro-Gly-Leu-OH

^{1}H NMR, 600 MHz, D_2O



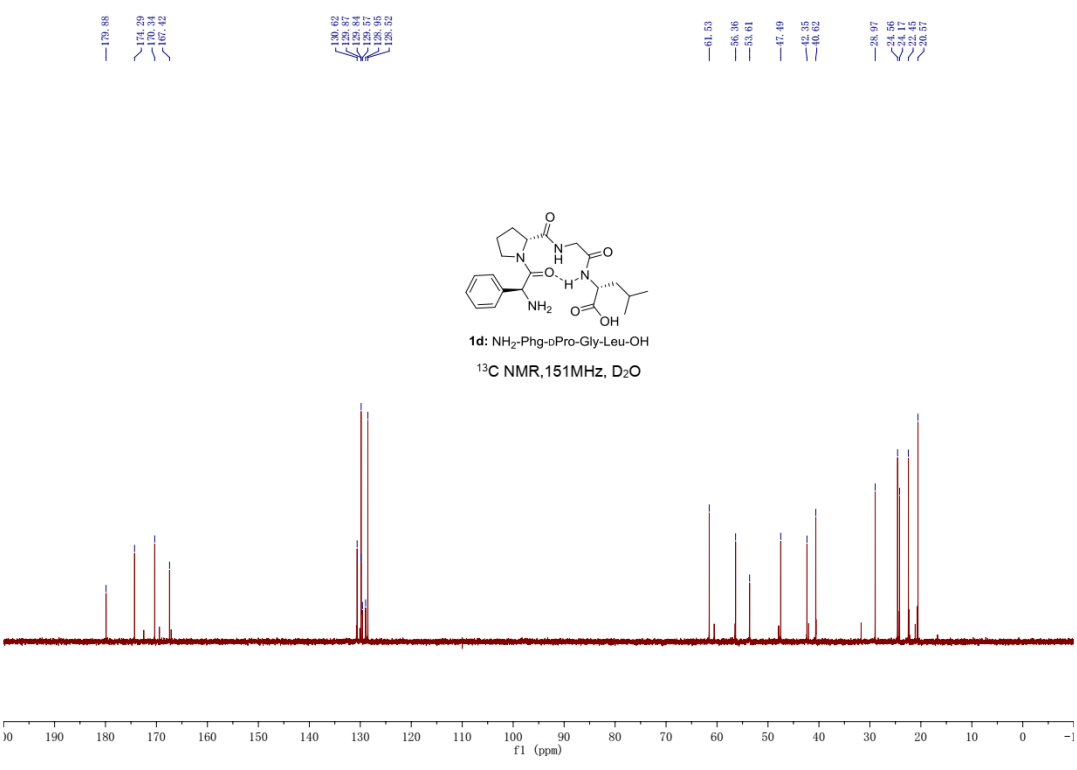
1c: NH_2-Chg-dPro-Gly-Leu-OH

^{13}C NMR, 151 MHz, D_2O



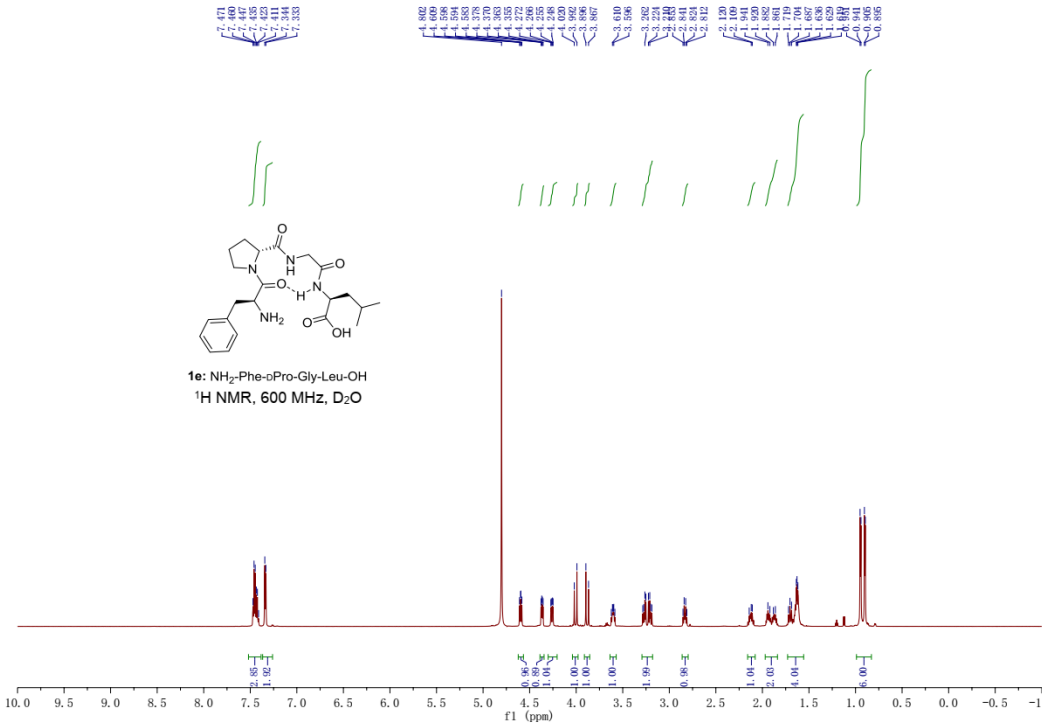
1d: NH_2-Phg-ᴅPro-Gly-Leu-OH

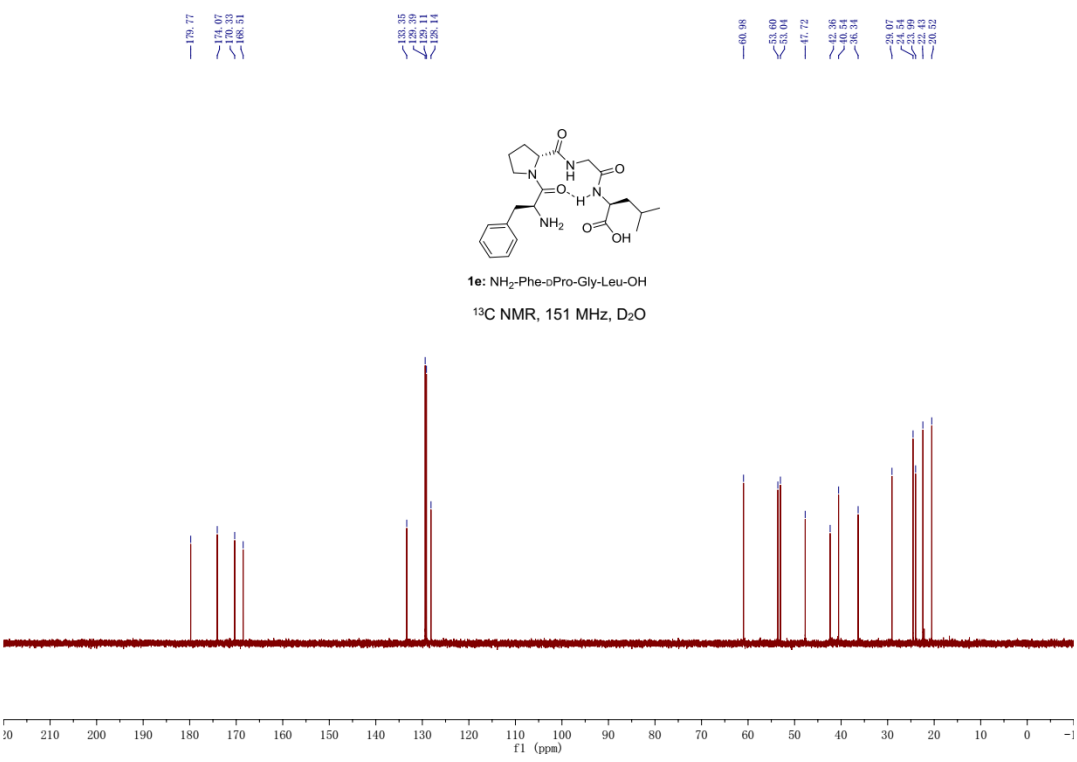
^{1}H NMR, 600 MHz, D_2O

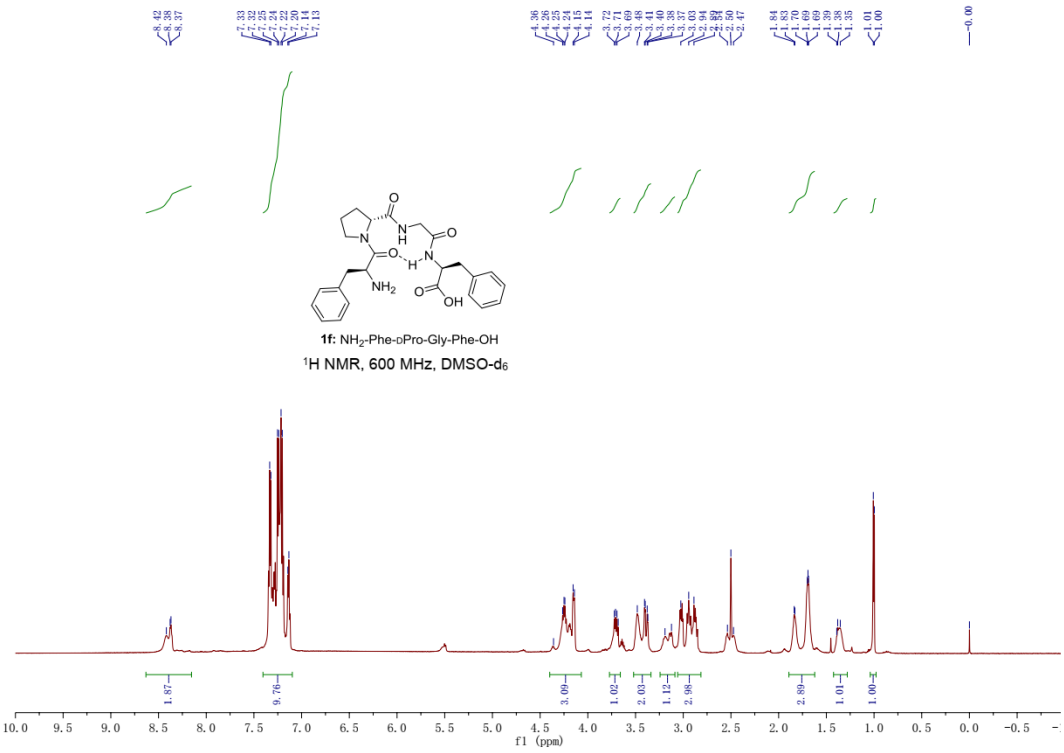


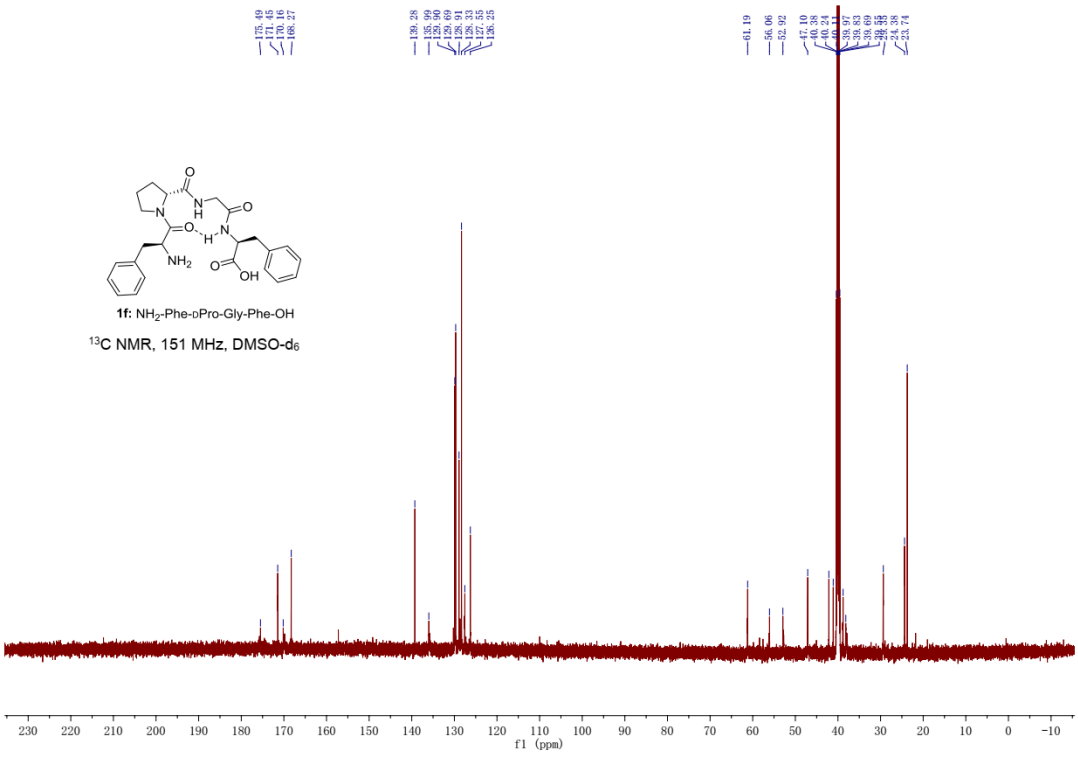
1d: NH_2-Phg-ᴅPro-Gly-Leu-OH

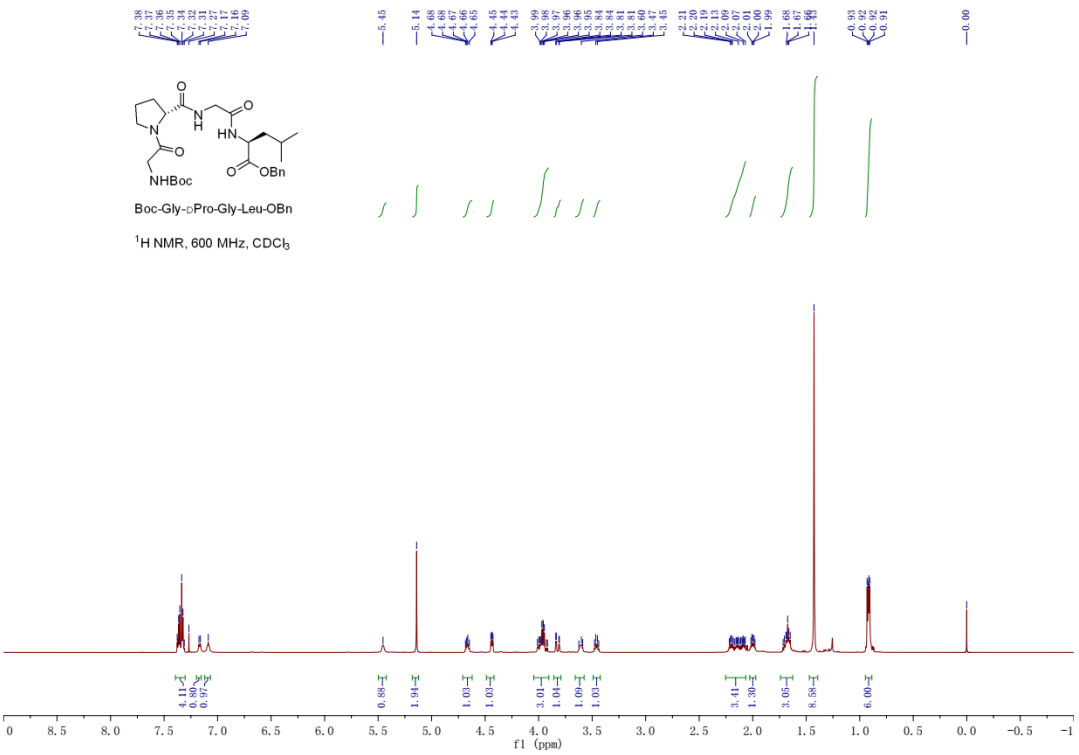
^{13}C NMR,151MHz, D_2O

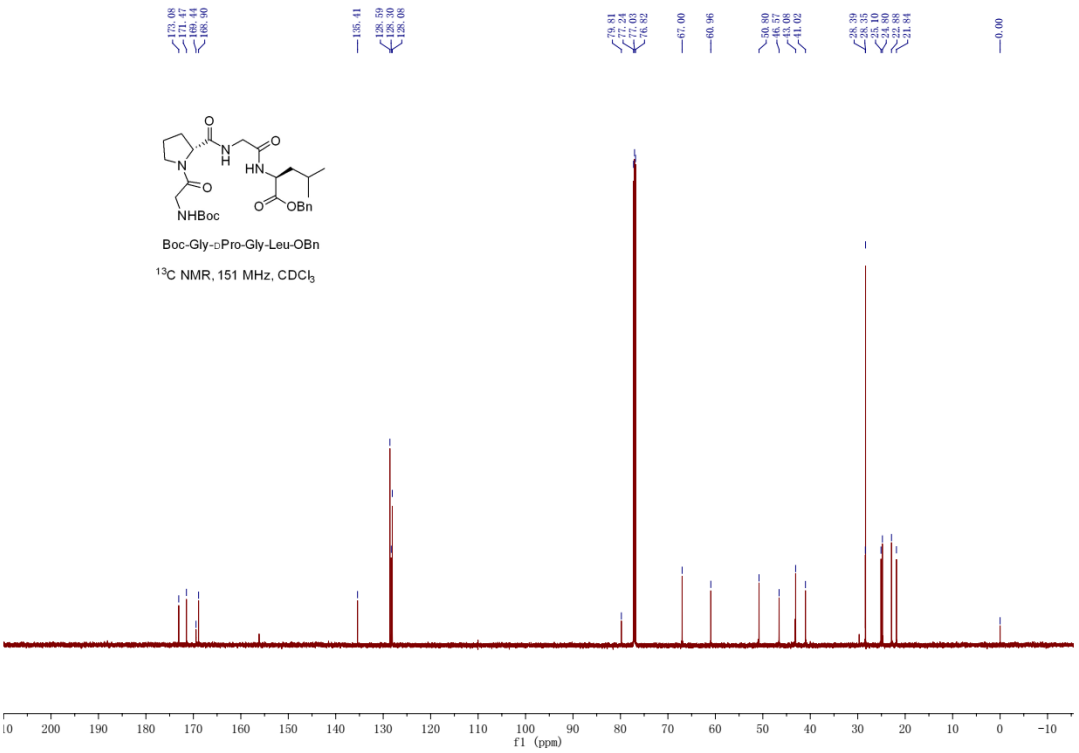

1e: NH2-Phe-dPro-Gly-Leu-OH
1H NMR, 600 MHz, D2O
f1 (ppm)

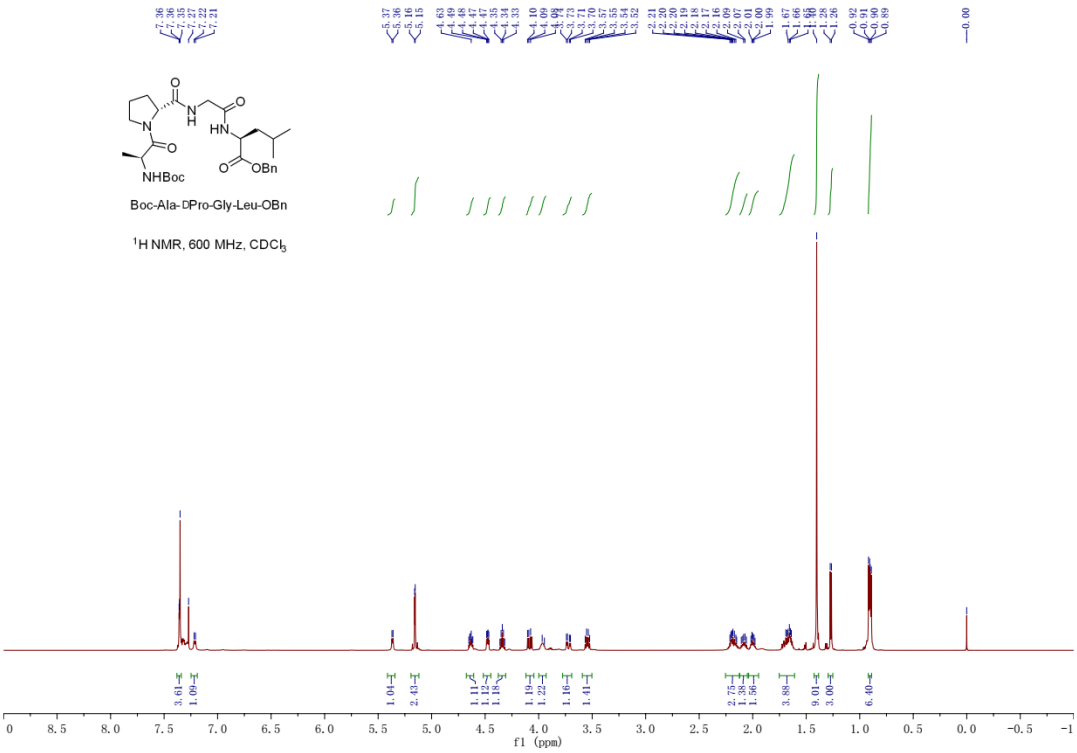

1e: NH2-Phe-dPro-Gly-Leu-OH
13C NMR, 151 MHz, D2O
f1 (ppm)

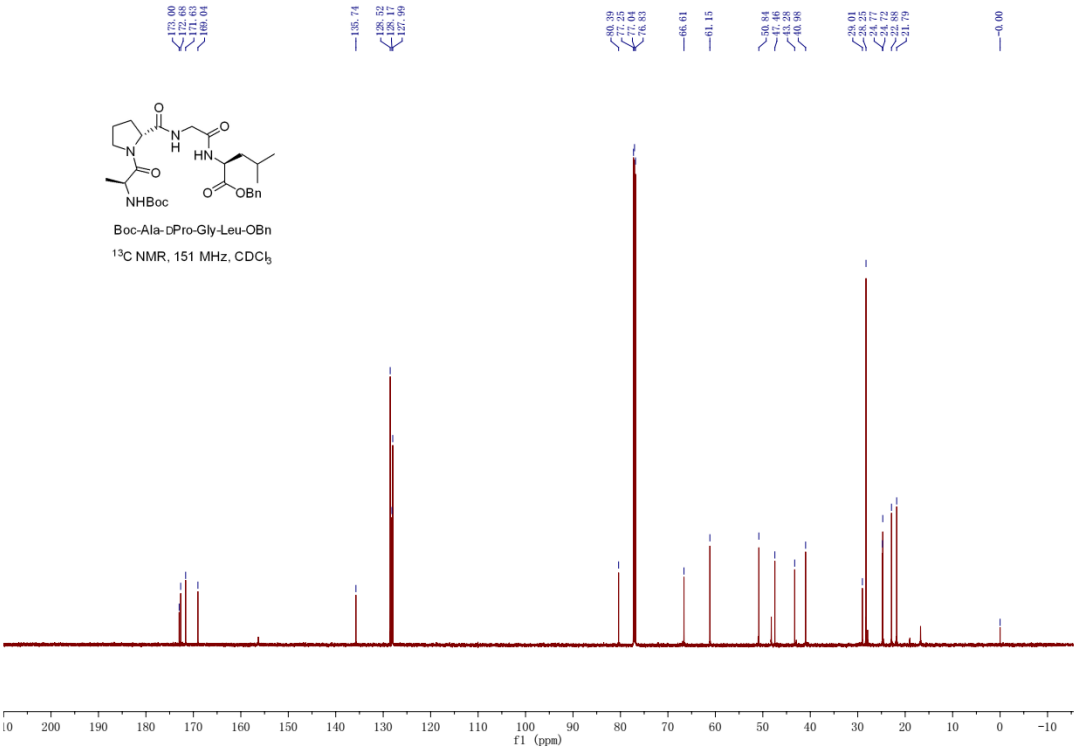

1f: NH2-Phe-DPro-Gly-Phe-OH
1H NMR, 600 MHz, DMSO-d6
f1 (ppm)

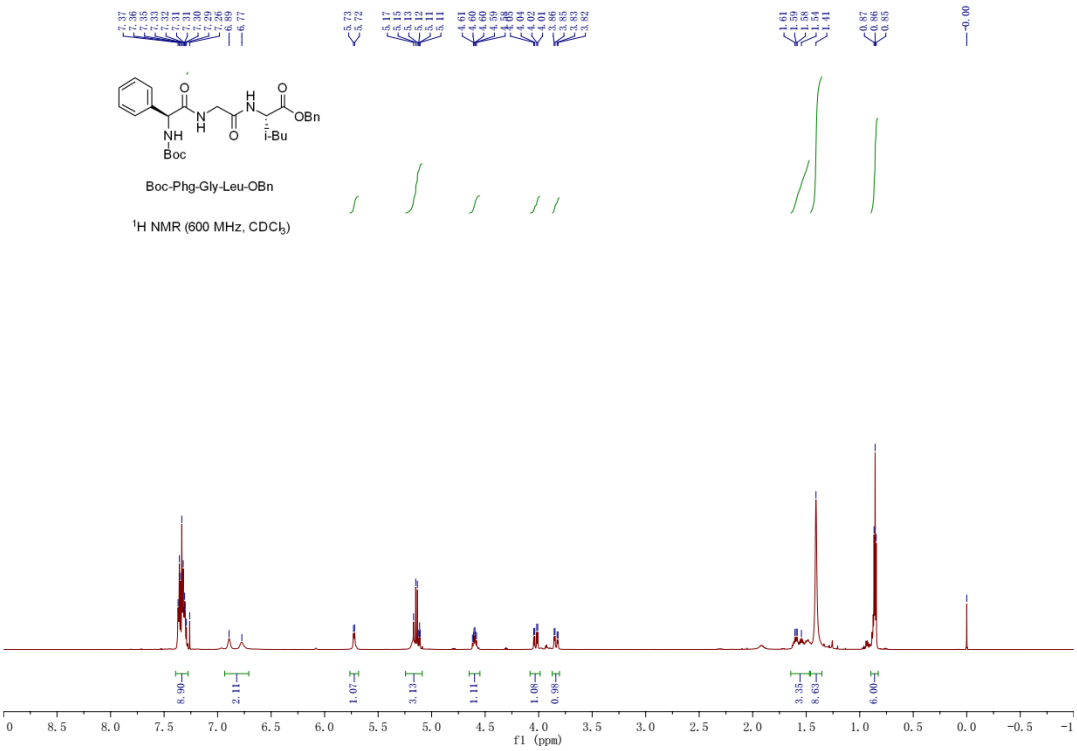

1f: NH2-Phe-DPro-Gly-Phe-OH
13C NMR, 151 MHz, DMSO-d6
f1 (ppm)

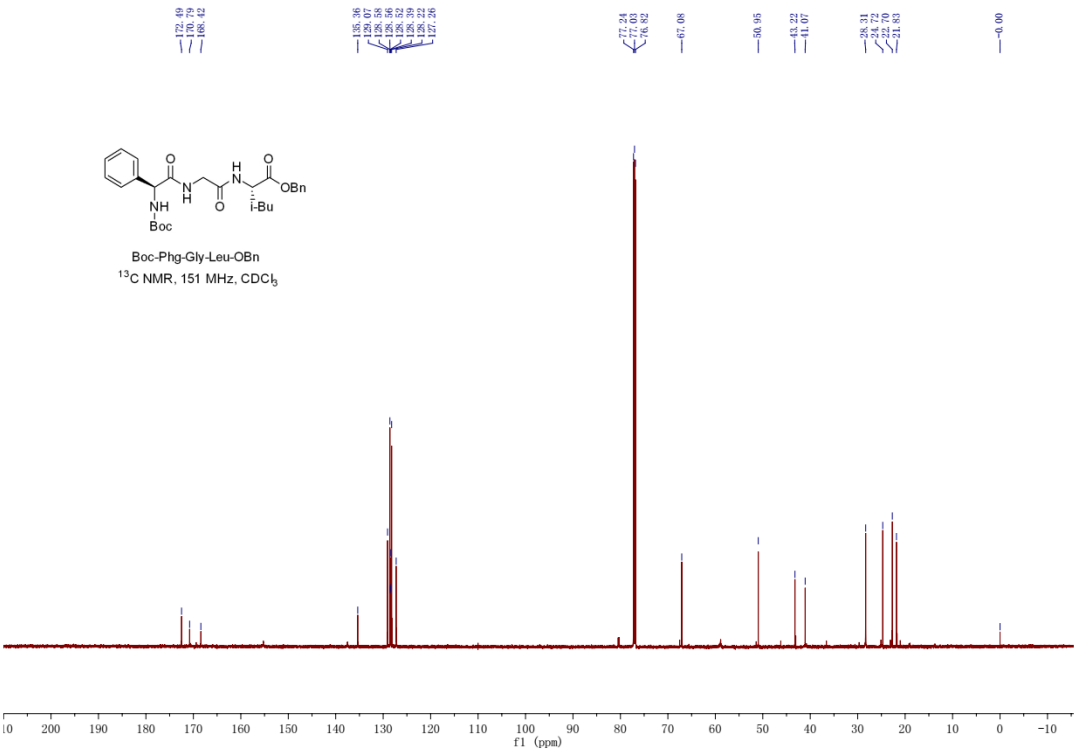

Boc-Gly-D-Pro-Gly-Leu-OBn
1H NMR, 600 MHz, CDCl3
f1 (ppm)

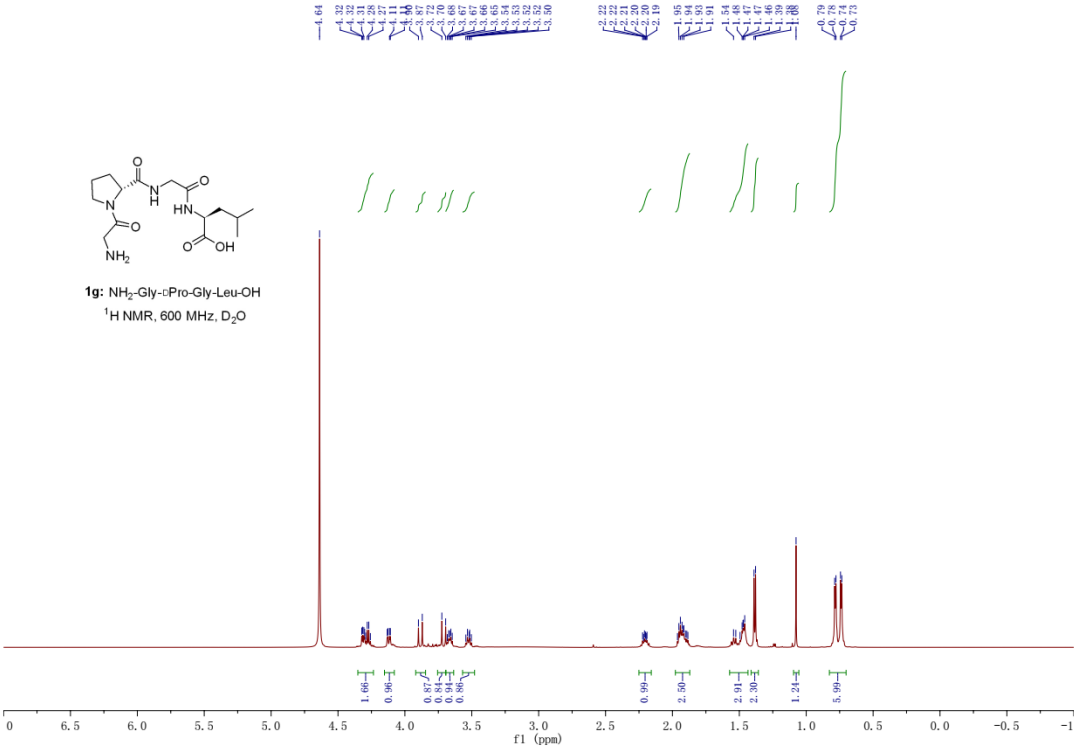

Boc-Gly-D-Pro-Gly-Leu-OBn
13C NMR, 151 MHz, CDCl3
f1 (ppm)


Boc-Ala-DPro-Gly-Leu-OBn
1H NMR, 600 MHz, CDCl3
f1 (ppm)


Boc-Ala-DPro-Gly-Leu-OBn
13C NMR, 151 MHz, CDCl3
f1 (ppm)

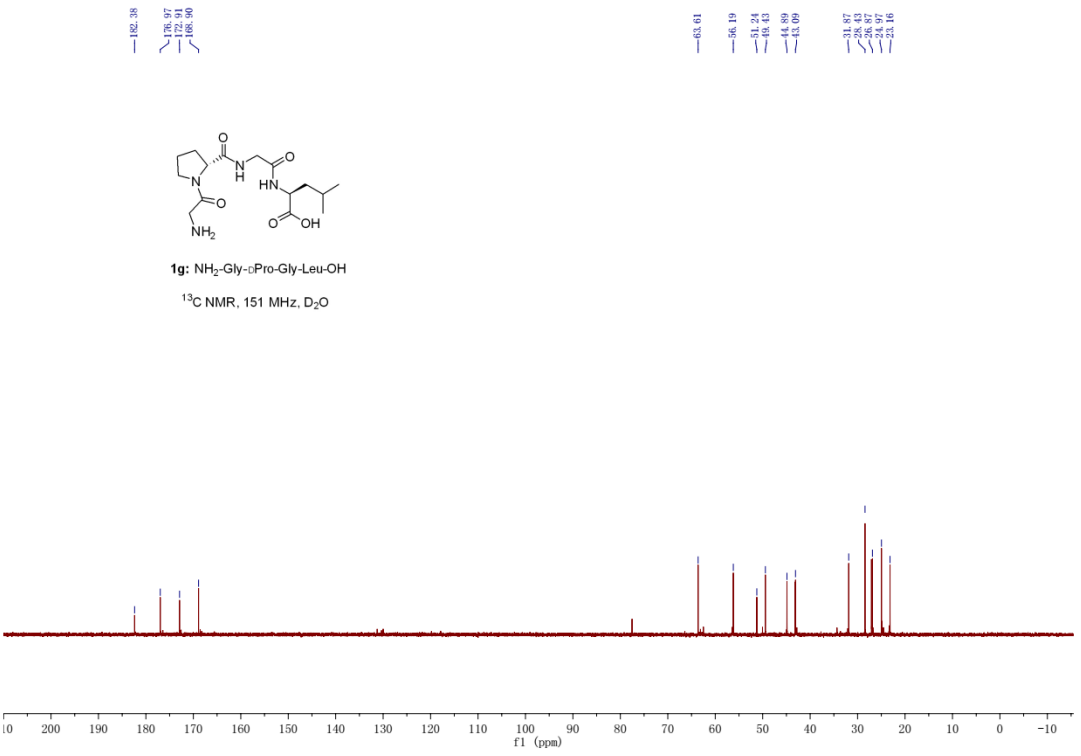

Boc-Phg-Gly-Leu-OBn
^{1}H NMR (600 MHz, $CDCl_3$)
f1 (ppm)


Boc-Phg-Gly-Leu-OBn
^{13}C NMR, 151 MHz, $CDCl_3$
f1 (ppm)



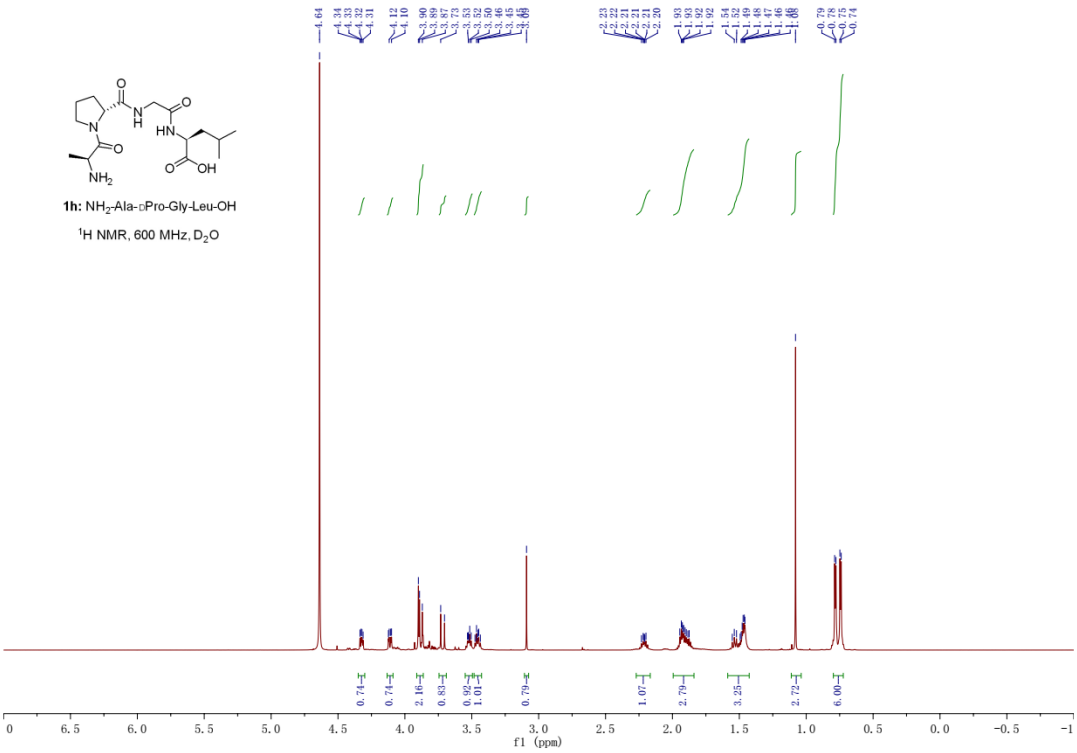
1g: NH_2-Gly-ᴅPro-Gly-Leu-OH

^{1}H NMR, 600 MHz, D_2O



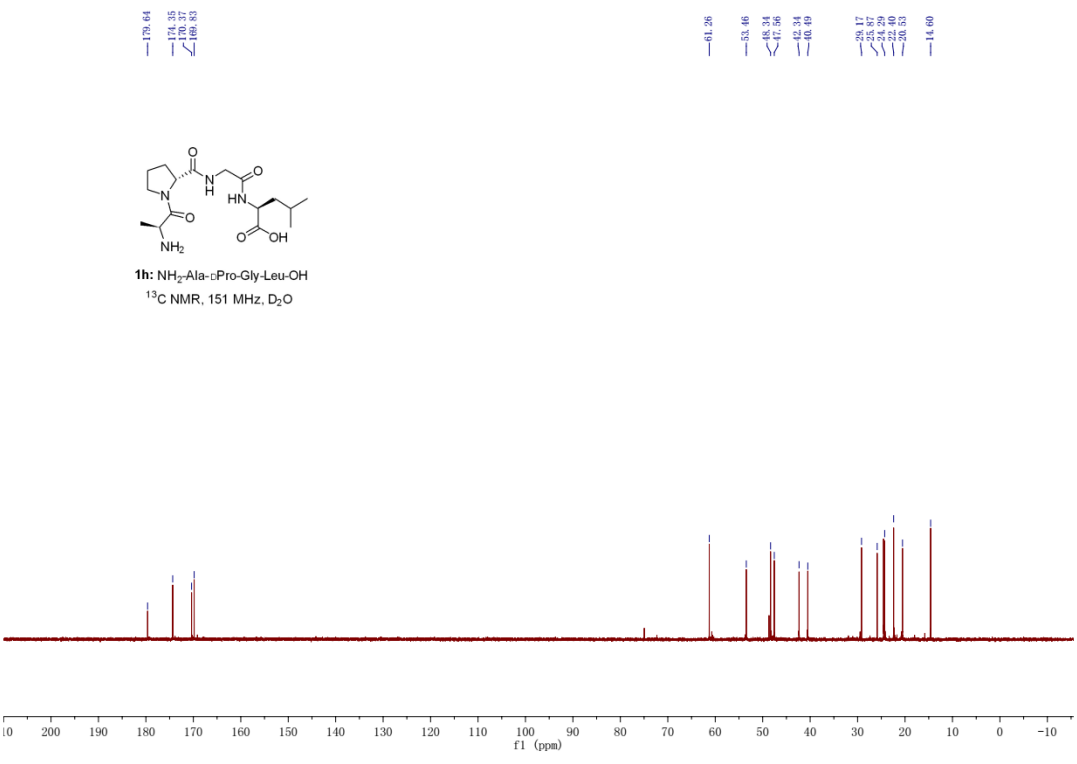
1g: NH_2-Gly-ᴅPro-Gly-Leu-OH

^{13}C NMR, 151 MHz, D_2O



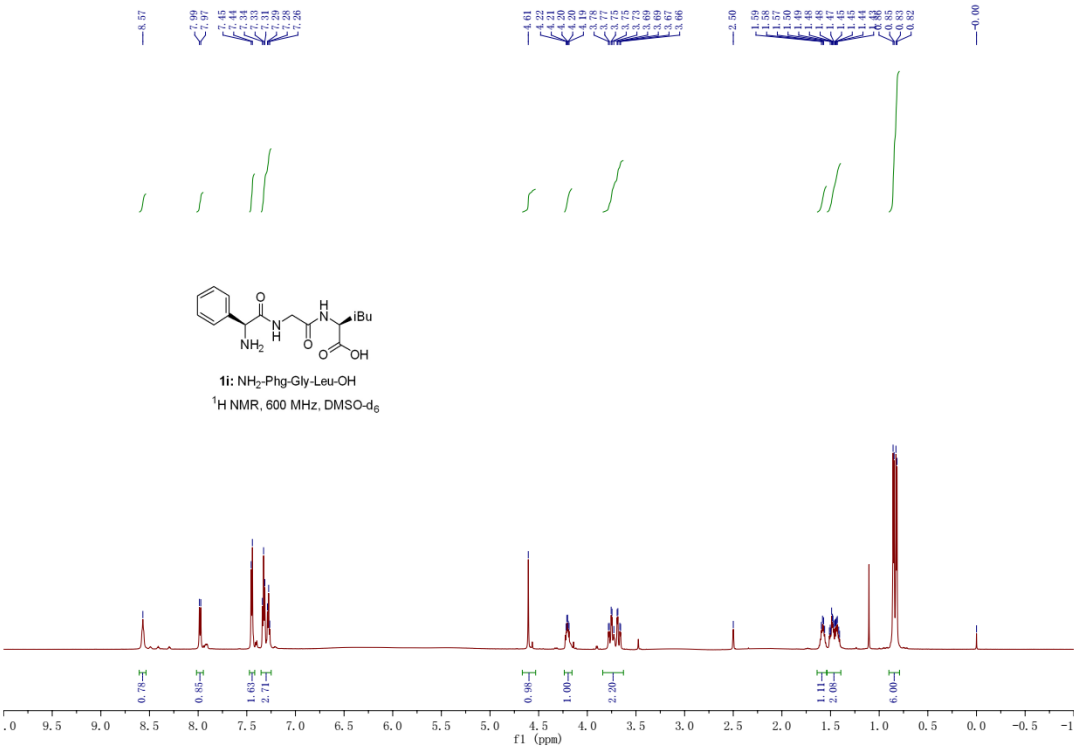
1h: NH_2-Ala-□Pro-Gly-Leu-OH

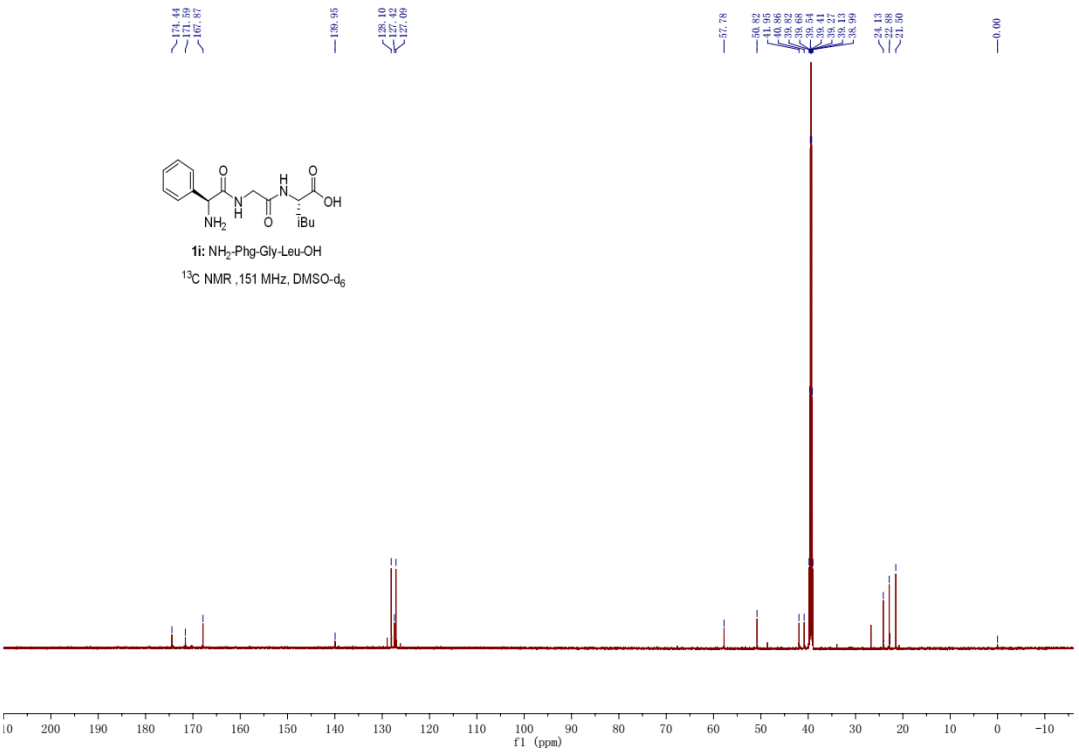
^{1}H NMR, 600 MHz, D_2O

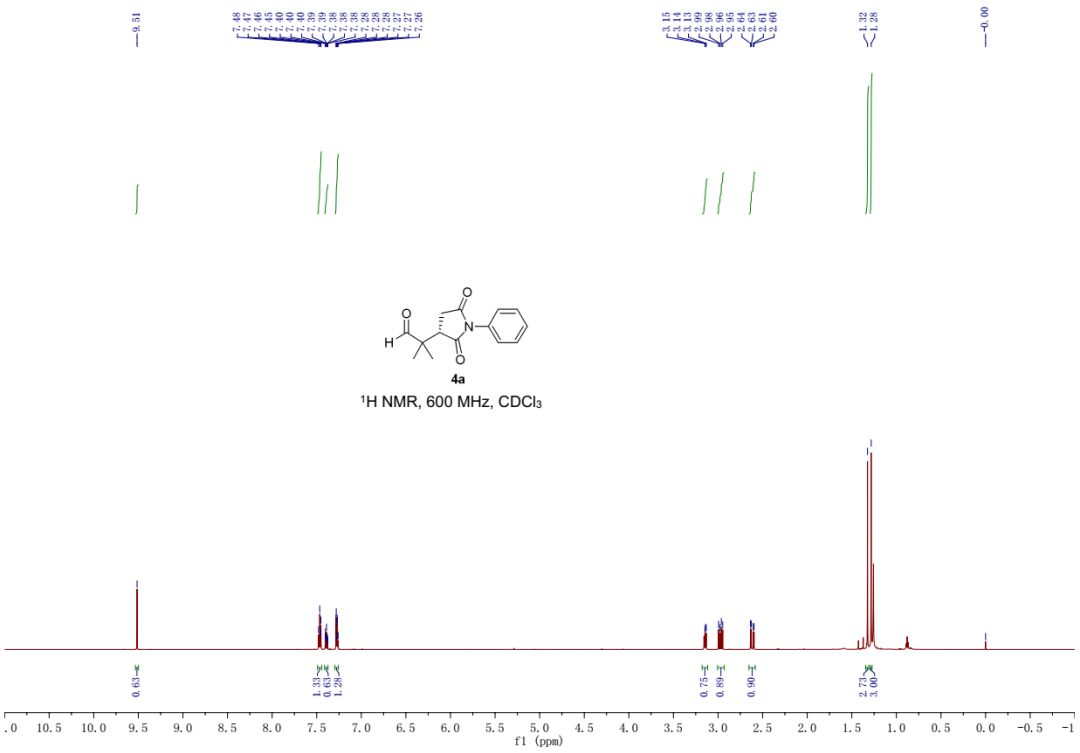


1h: NH_2-Ala-□Pro-Gly-Leu-OH

^{13}C NMR, 151 MHz, D_2O

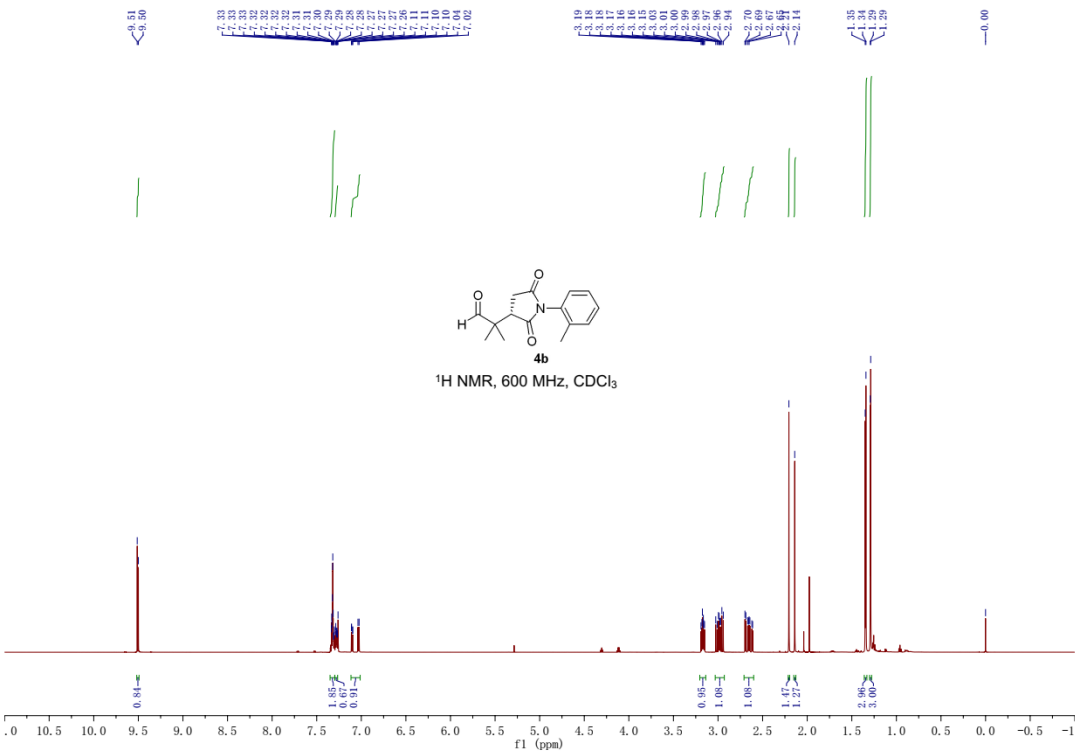

8.57
7.99
7.97
7.45
7.44
7.34
7.33
7.31
7.29
7.28
7.26
4.61
4.22
4.21
4.20
4.19
4.19
3.78
3.77
3.75
3.75
3.73
3.69
3.67
3.66
2.50
1.59
1.58
1.57
1.50
1.49
1.48
1.48
1.47
1.45
1.45
1.44
0.86
0.85
0.83
0.82
0.00
iBu
NH2
OH
1i: NH2-Phg-Gly-Leu-OH
1H NMR, 600 MHz, DMSO-d6
0.78
0.85
1.63
2.71
0.98
1.00
2.20
1.11
2.08
6.00
f1 (ppm)


174.44
171.59
167.87
139.95
128.10
127.42
127.09
57.78
50.62
41.85
40.86
39.82
39.68
39.54
39.41
39.27
38.13
38.99
24.13
22.88
21.50
0.00
NH2
OH
iBu
1i: NH2-Phg-Gly-Leu-OH
13C NMR ,151 MHz, DMSO-d6
f1 (ppm)



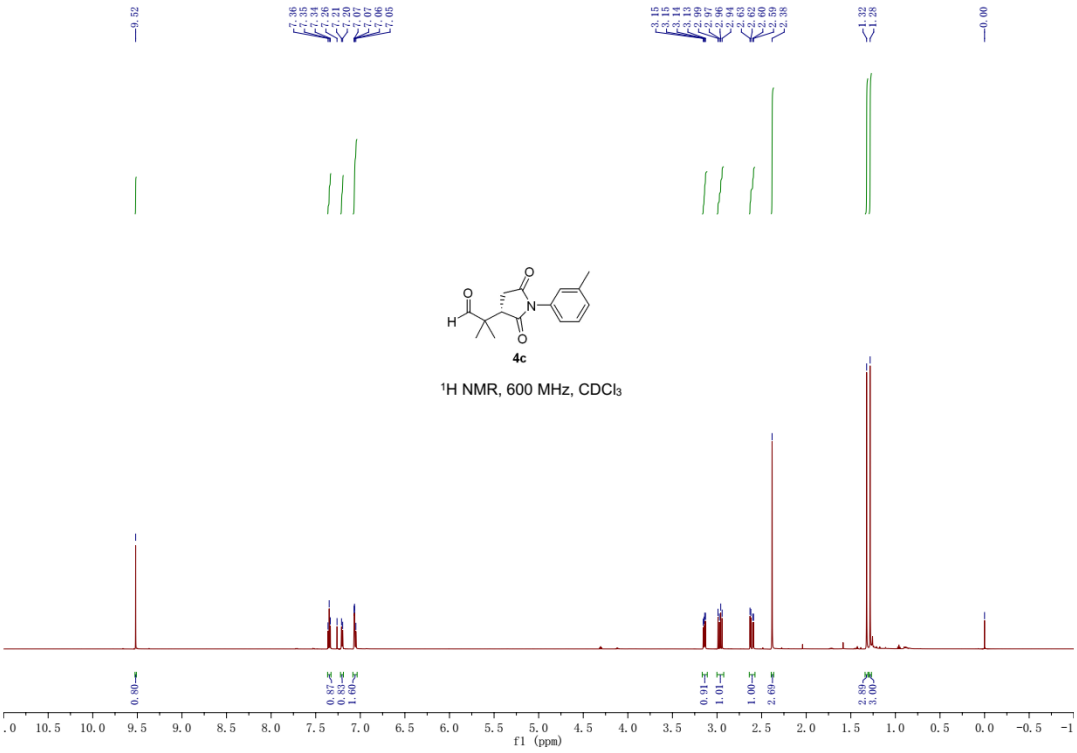
4a

^{1}H NMR, 600 MHz, $CDCl_3$



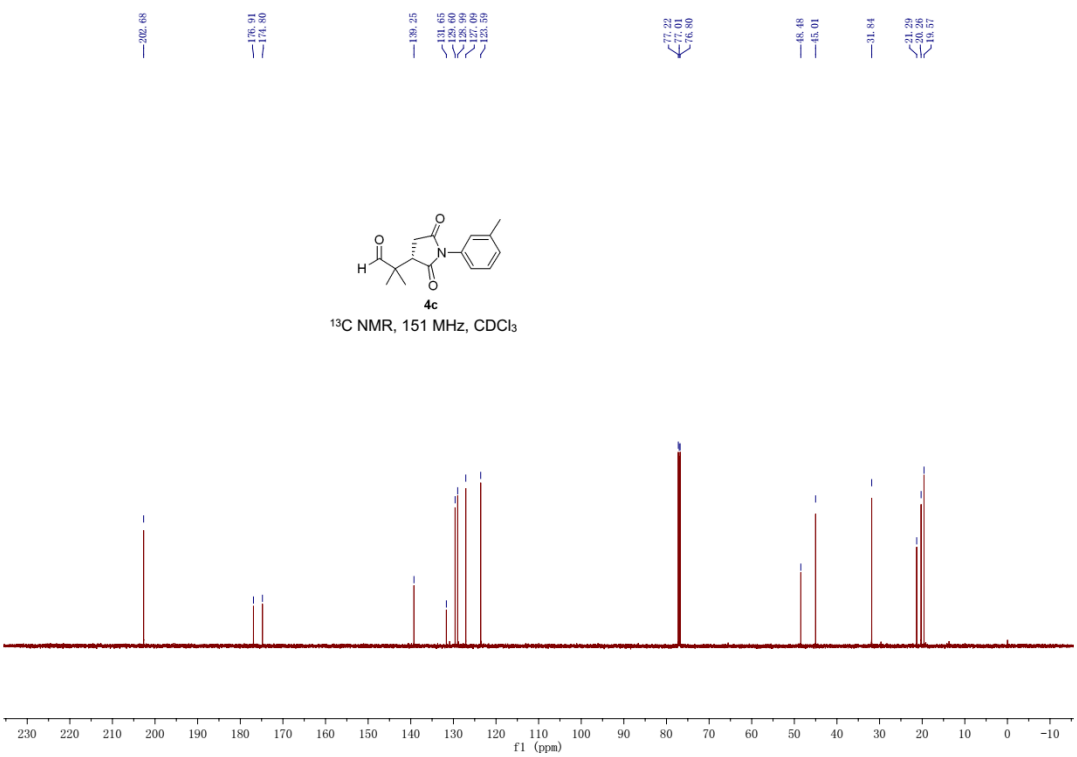
4b

^{1}H NMR, 600 MHz, $CDCl_3$



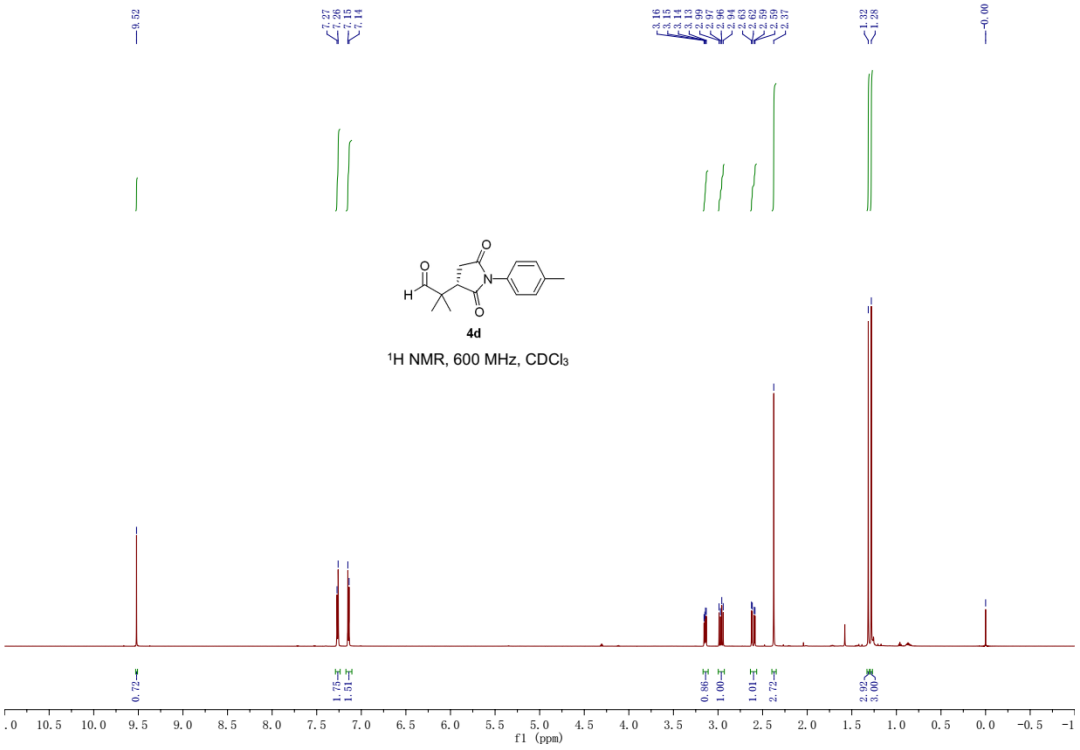
4c

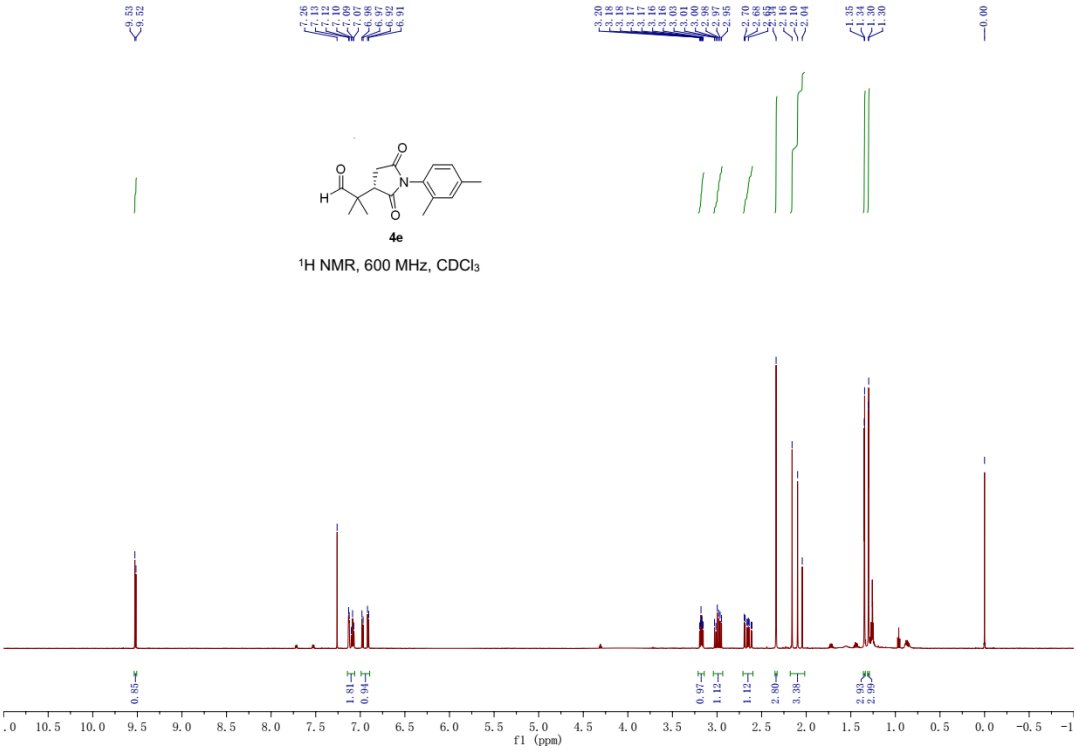
^{1}H NMR, 600 MHz, $CDCl_3$



4c

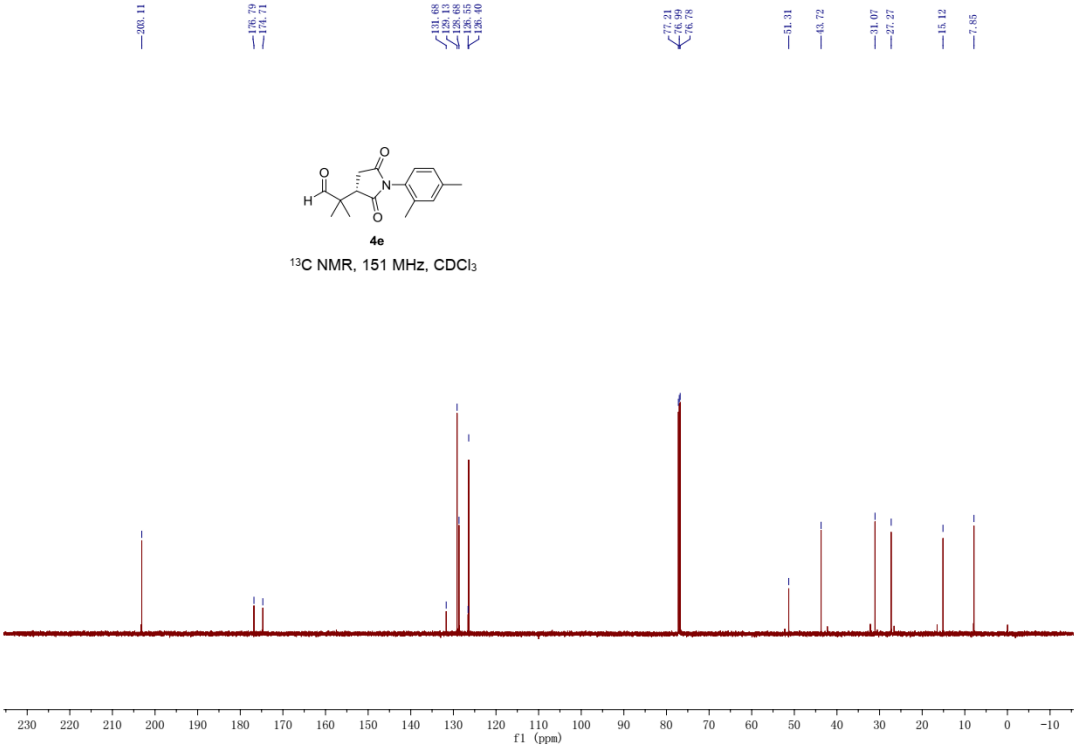
^{13}C NMR, 151 MHz, $CDCl_3$


9.52
7.27
7.26
7.15
7.14
3.16
3.15
3.14
3.13
2.99
2.97
2.96
2.94
2.63
2.62
2.59
2.59
2.37
1.32
1.28
0.00
4d
¹H NMR, 600 MHz, CDCl3
0.72
1.75
1.51
0.86
1.00
1.01
2.72
2.92
3.00
f1 (ppm)



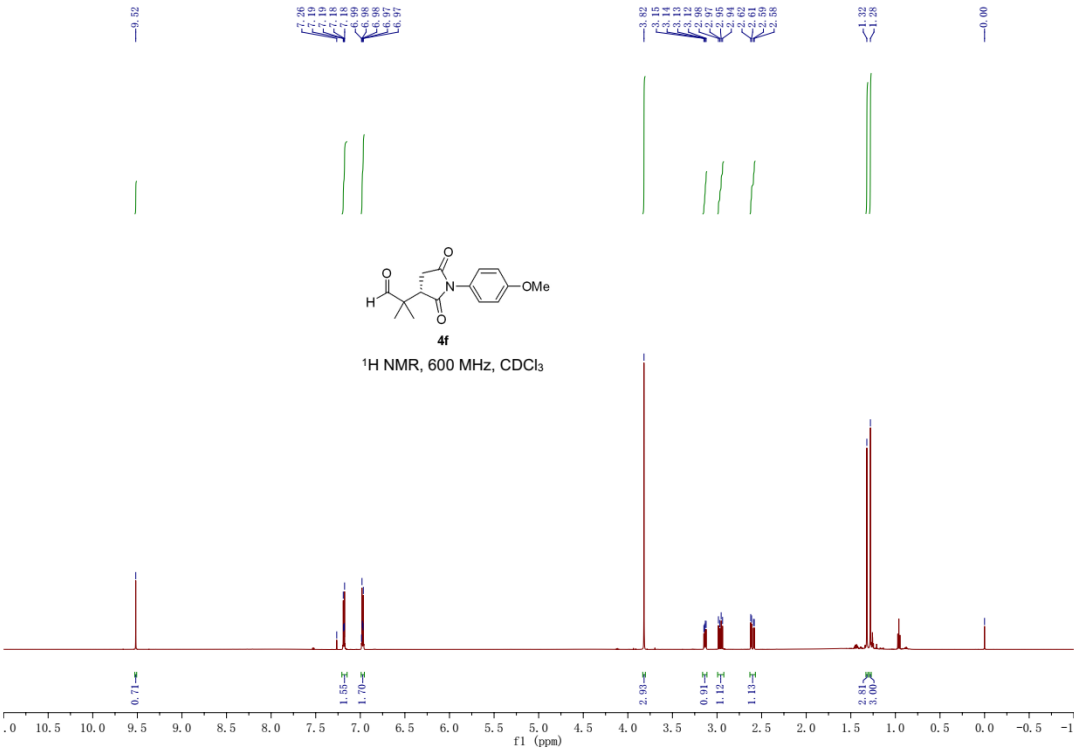
4e

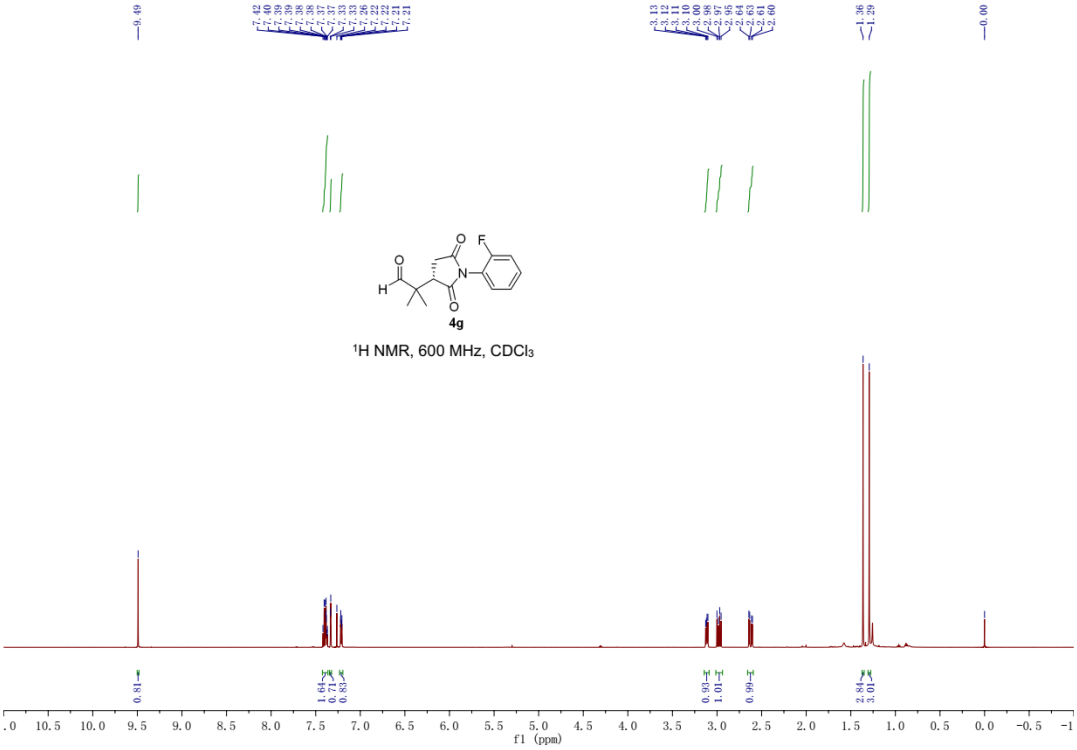
^{1}H NMR, 600 MHz, $CDCl_3$

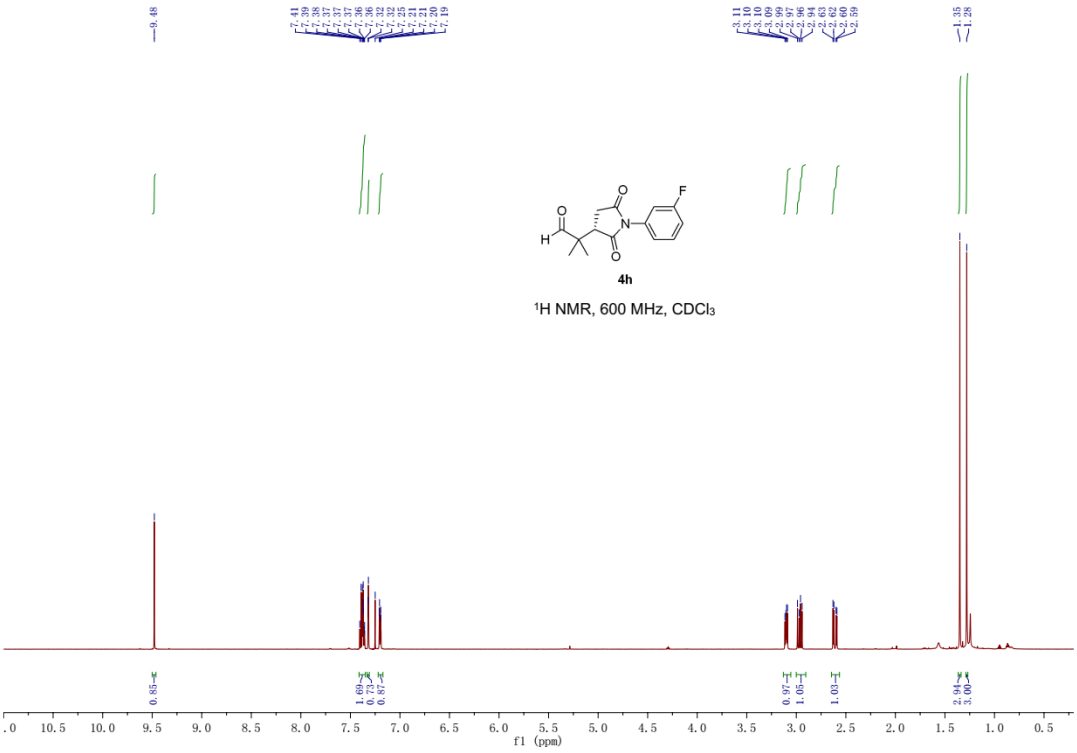


4e

^{13}C NMR, 151 MHz, $CDCl_3$

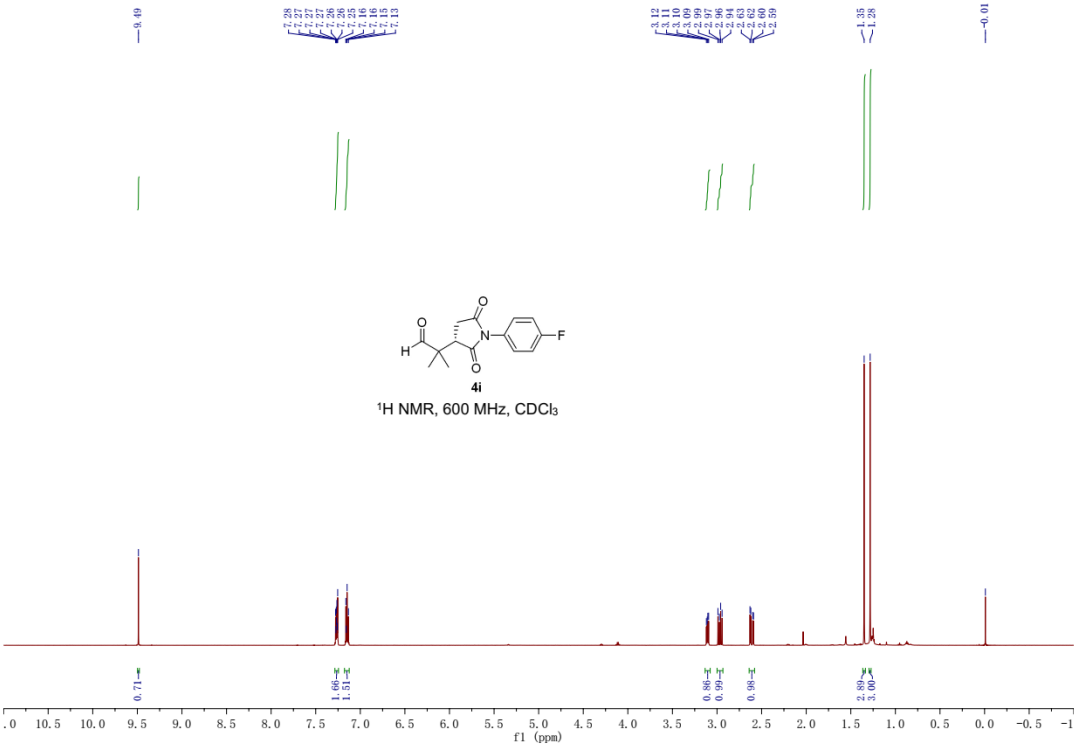

9.52
7.26
7.19
7.19
7.18
7.18
6.99
6.98
6.98
6.97
6.97
3.82
3.15
3.14
3.13
3.12
2.98
2.97
2.95
2.94
2.62
2.61
2.59
2.58
1.32
1.28
0.00
O
O
H
N
OMe
O
4f
1H NMR, 600 MHz, CDCl3
0.71
1.55
1.70
2.93
0.91
1.12
1.13
2.81
3.00
f1 (ppm)


9.49
7.42
7.40
7.39
7.39
7.38
7.38
7.37
7.37
7.33
7.33
7.26
7.22
7.22
7.21
7.21
3.13
3.12
3.11
3.10
2.98
2.97
2.95
2.64
2.63
2.61
2.60
1.36
1.29
0.00
O
F
O
H
N
O
4g
1H NMR, 600 MHz, CDCl3
0.81
1.69
1.72
0.83
0.93
1.01
0.99
2.84
3.01
f1 (ppm)



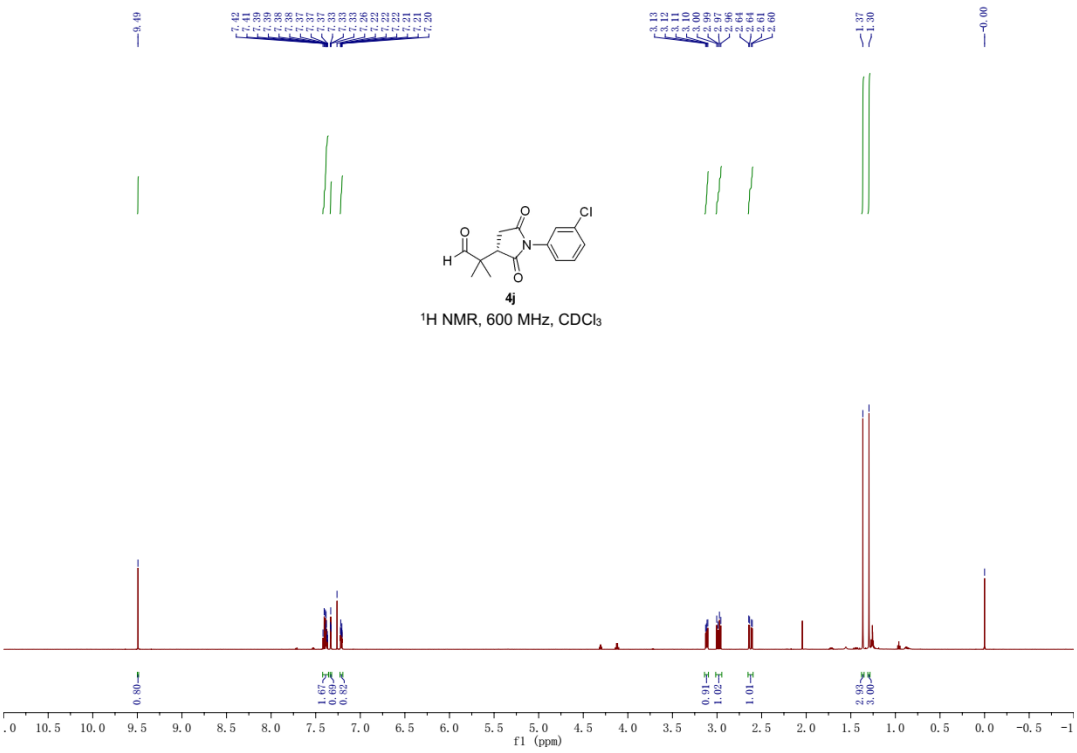
4h

^{1}H NMR, 600 MHz, $CDCl_3$



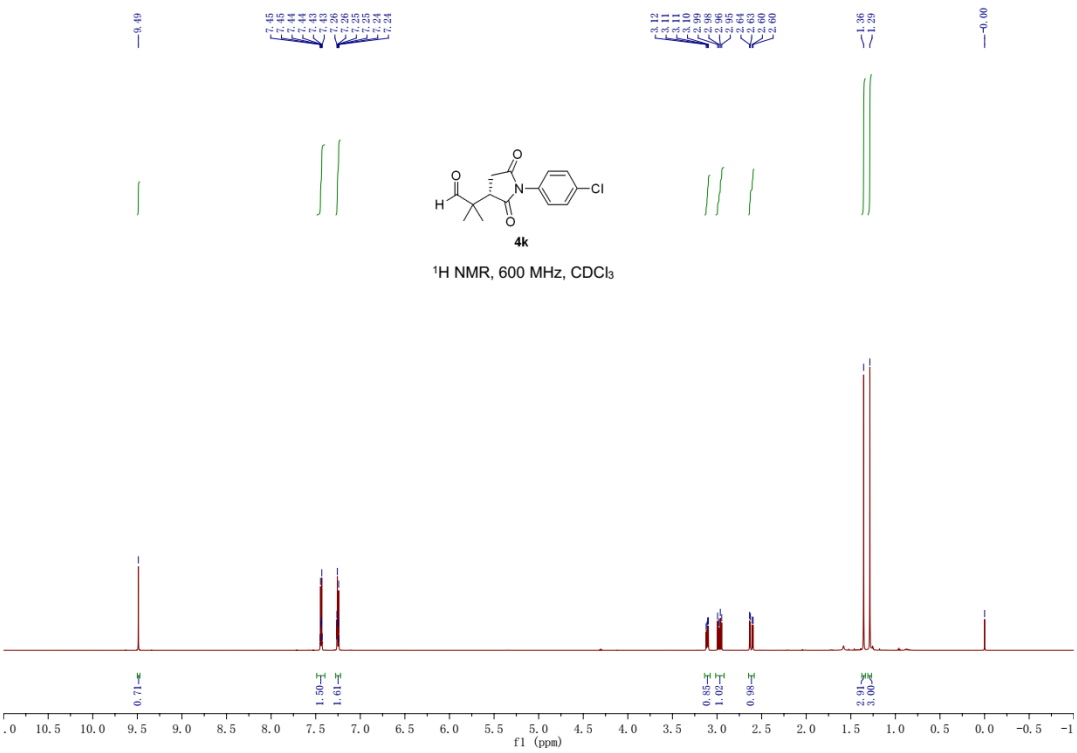
4i

^{1}H NMR, 600 MHz, $CDCl_3$



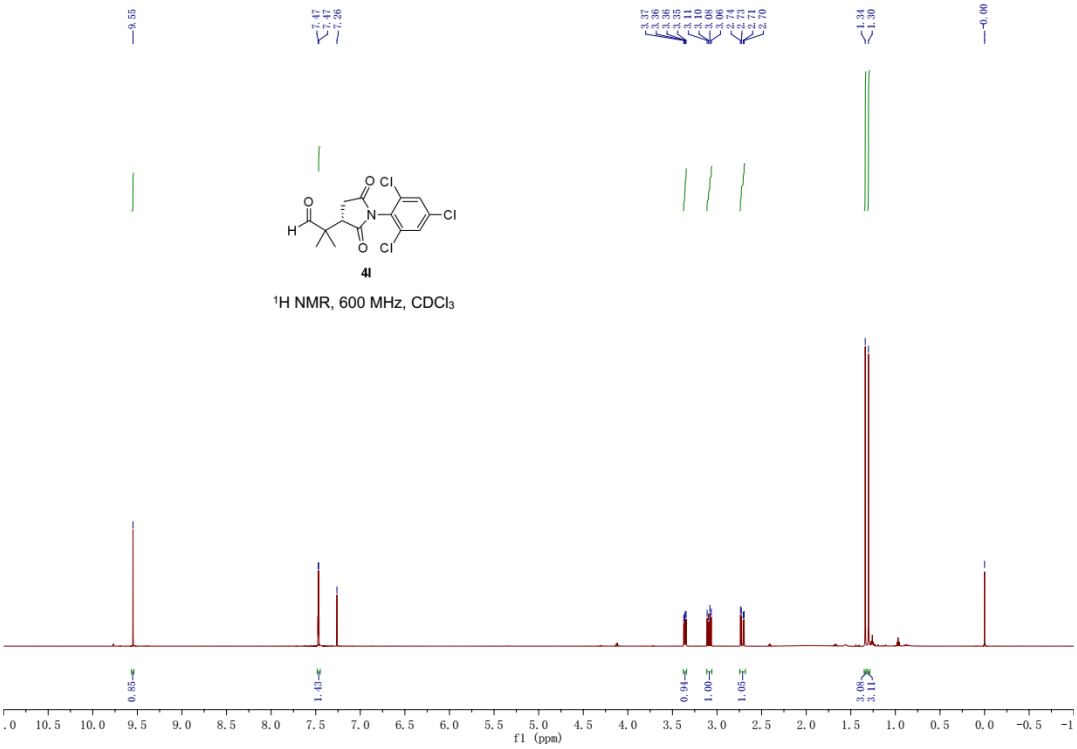
4j

^{1}H NMR, 600 MHz, $CDCl_3$



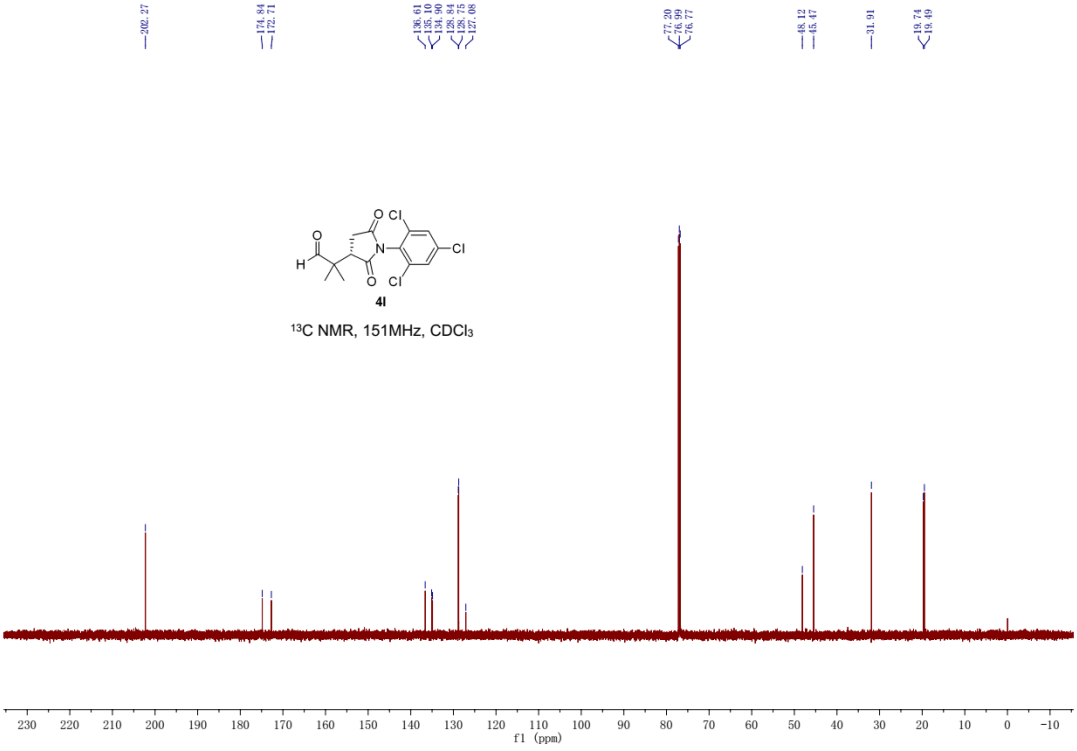
4k

^{1}H NMR, 600 MHz, $CDCl_3$



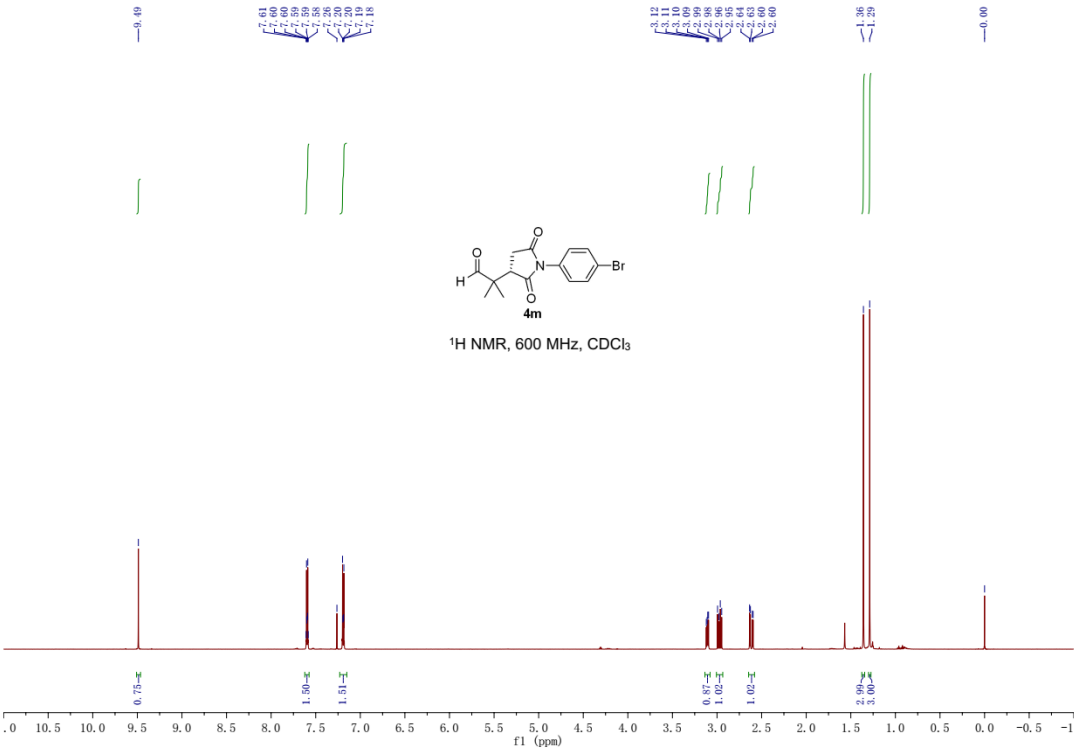
4l

^{1}H NMR, 600 MHz, $CDCl_3$

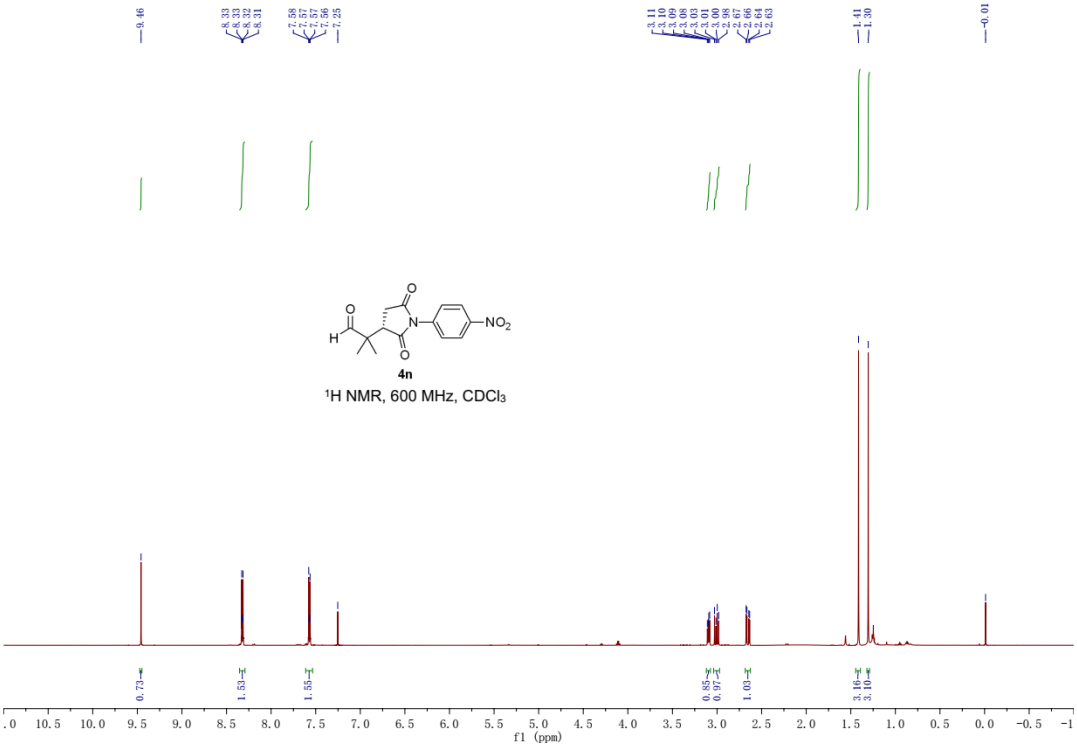


4l

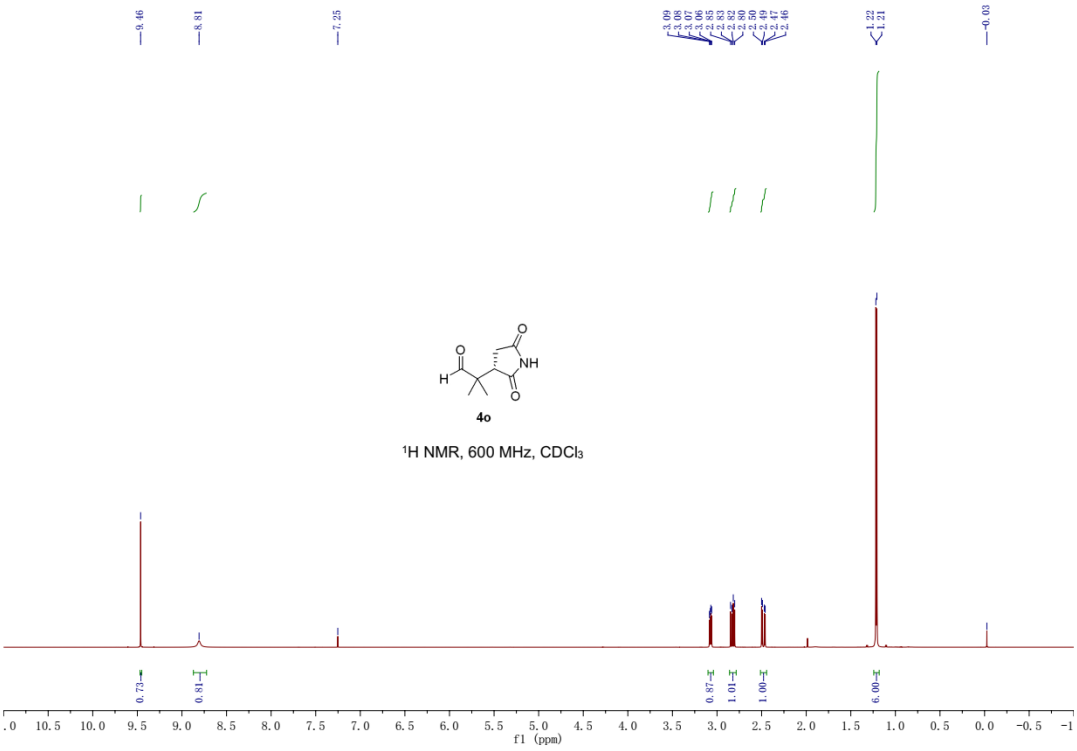
^{13}C NMR, 151MHz, $CDCl_3$



^{1}H NMR, 600 MHz, $CDCl_3$

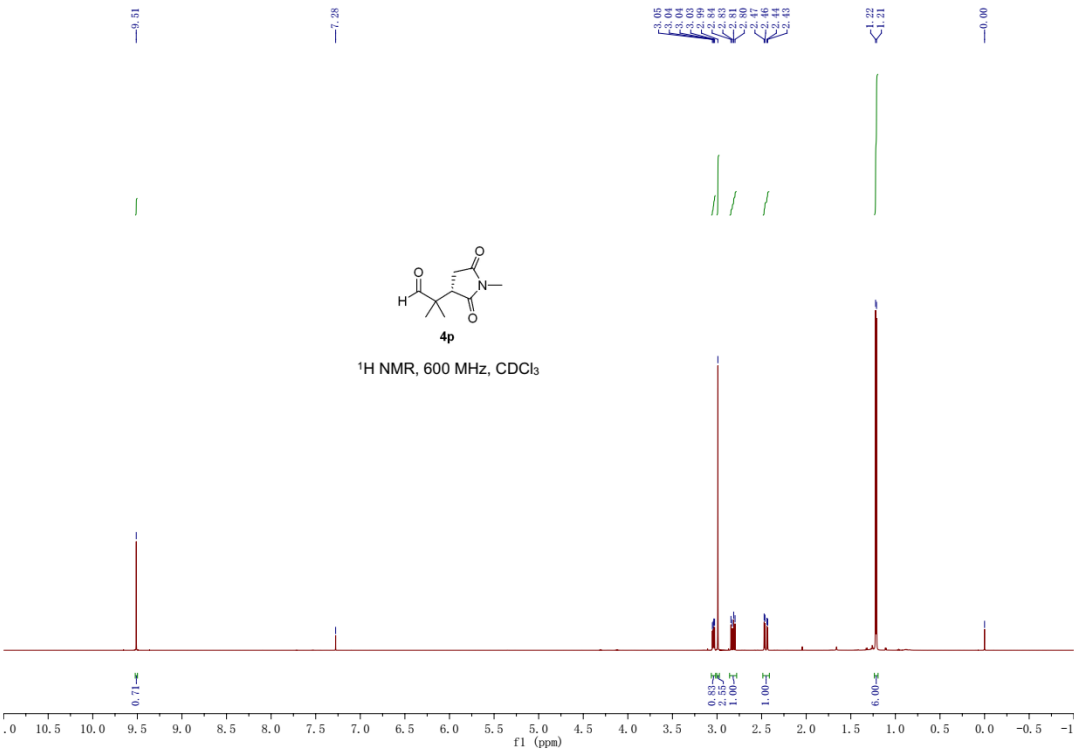


^{1}H NMR, 600 MHz, $CDCl_3$



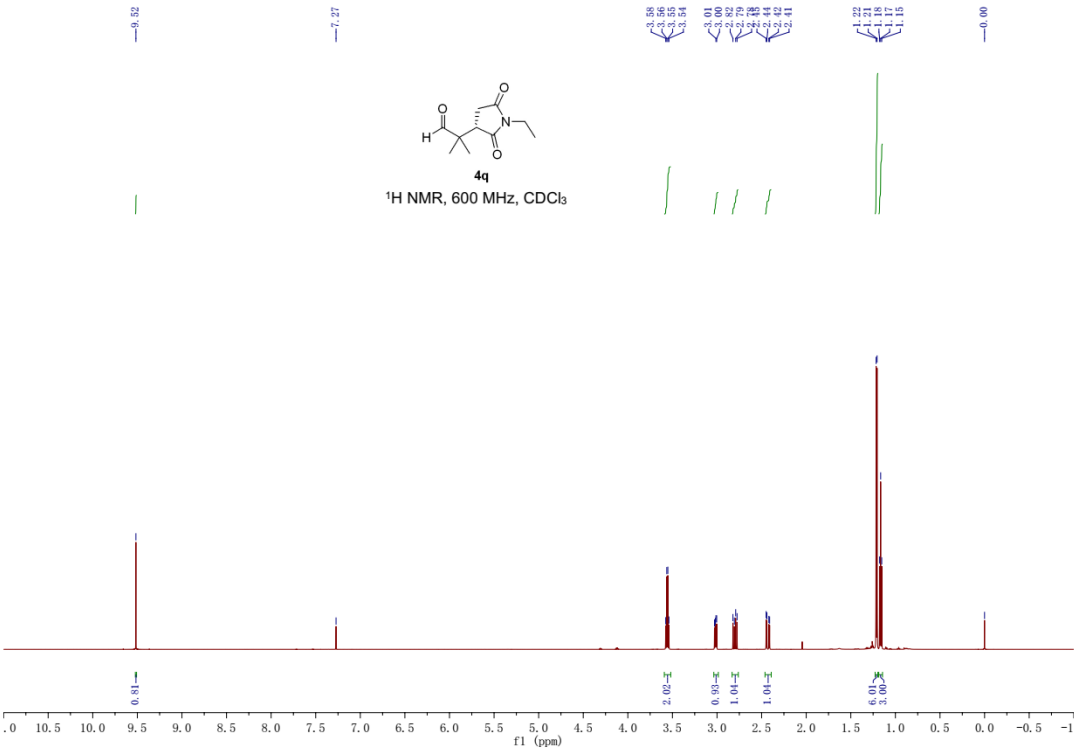
4o

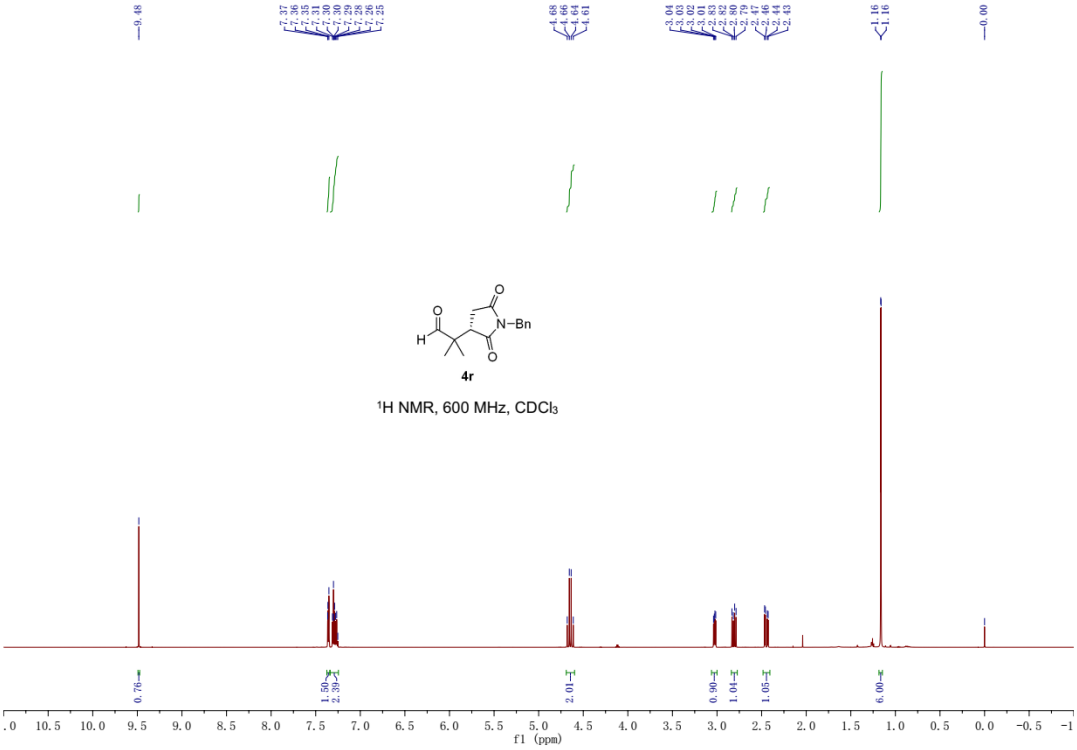
^{1}H NMR, 600 MHz, $CDCl_3$

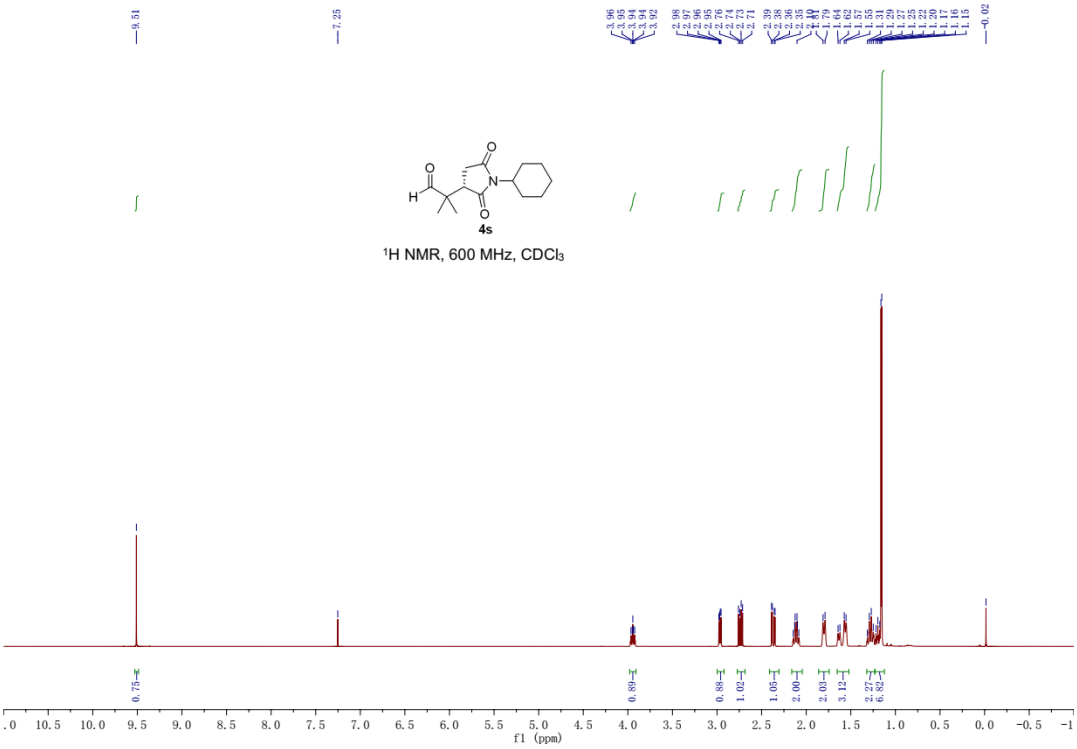


4p

^{1}H NMR, 600 MHz, $CDCl_3$

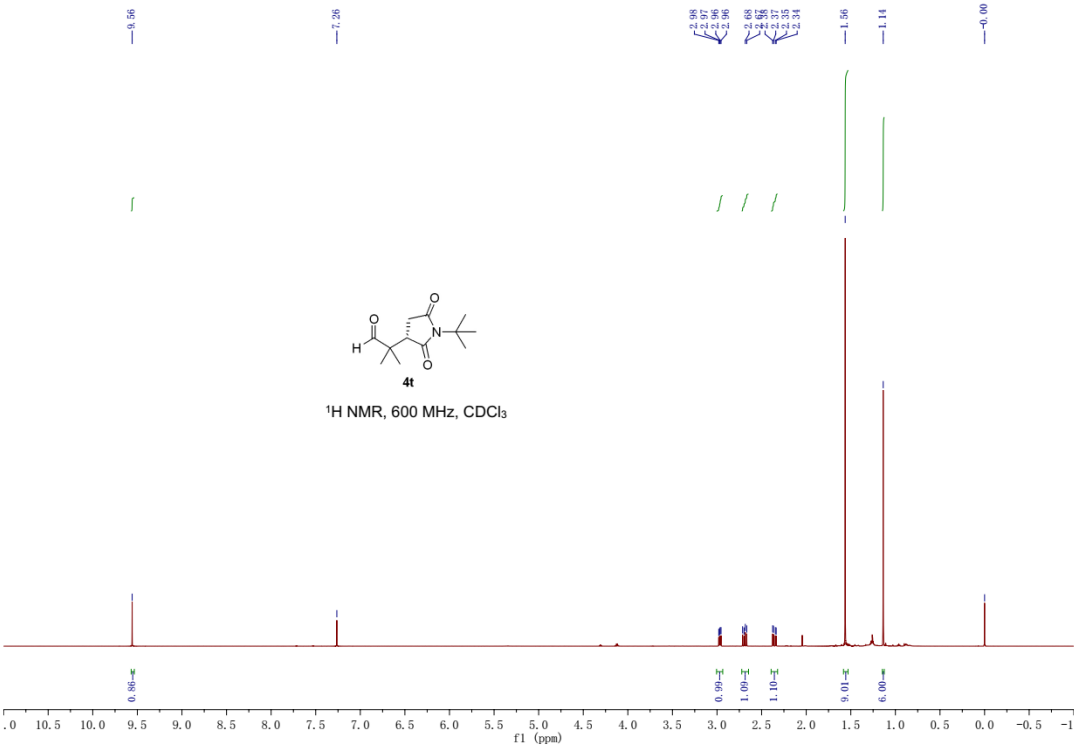

9.52
7.27
3.58
3.56
3.55
3.54
3.01
3.00
2.82
2.79
2.48
2.44
2.42
2.41
1.22
1.21
1.18
1.17
1.15
0.00
4q
¹H NMR, 600 MHz, CDCl₃
0.81
2.02
0.93
1.04
1.04
6.01
3.00
f1 (ppm)


9.48
7.37
7.36
7.35
7.31
7.30
7.30
7.29
7.28
7.26
7.25
4.68
4.66
4.64
4.61
3.04
3.03
3.02
3.01
2.83
2.82
2.80
2.79
2.47
2.46
2.44
2.43
1.16
1.16
0.00
4r
¹H NMR, 600 MHz, CDCl₃
0.76
1.50
2.39
2.01
0.90
1.04
1.05
6.00
f1 (ppm)



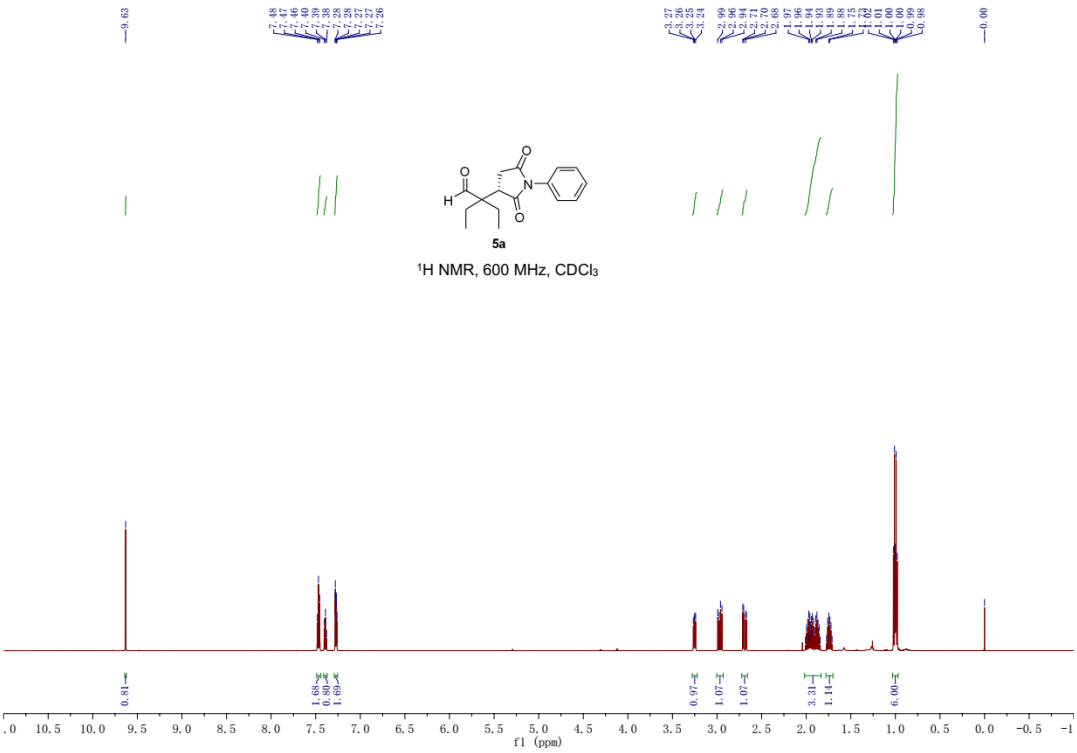
4s

^{1}H NMR, 600 MHz, $CDCl_3$



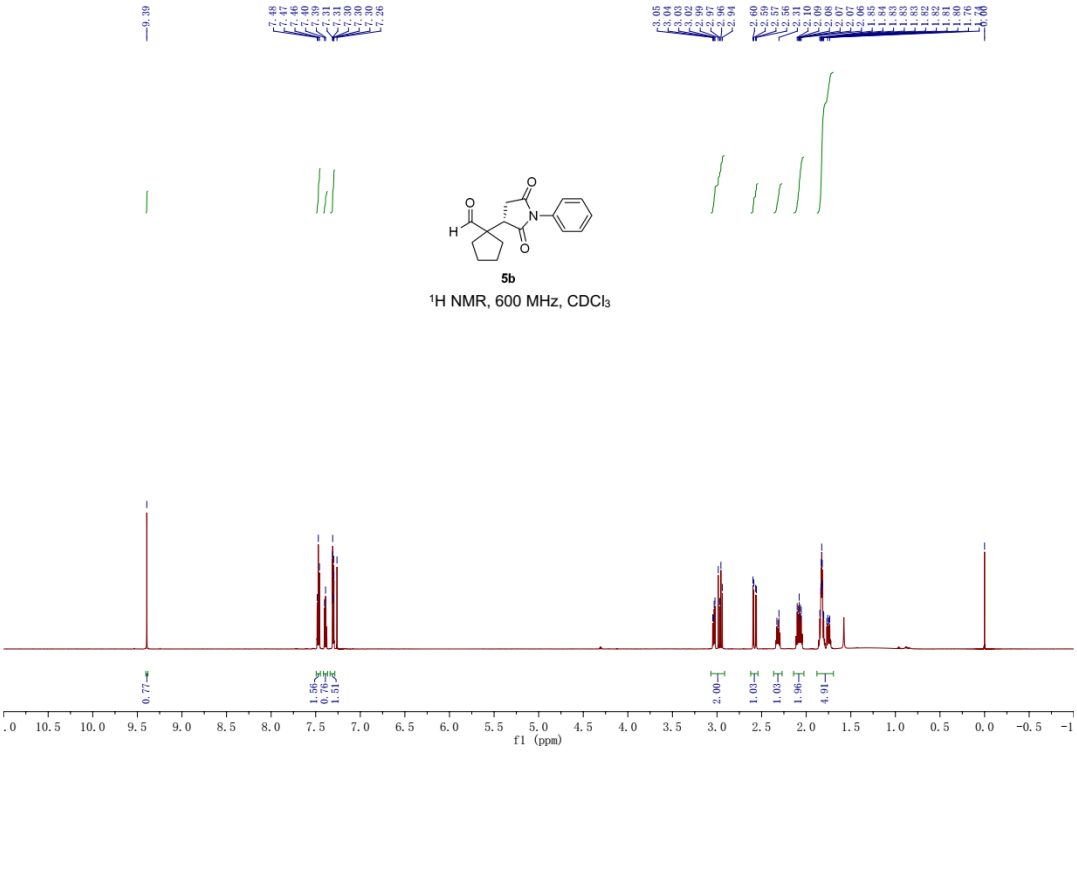
4t

^{1}H NMR, 600 MHz, $CDCl_3$



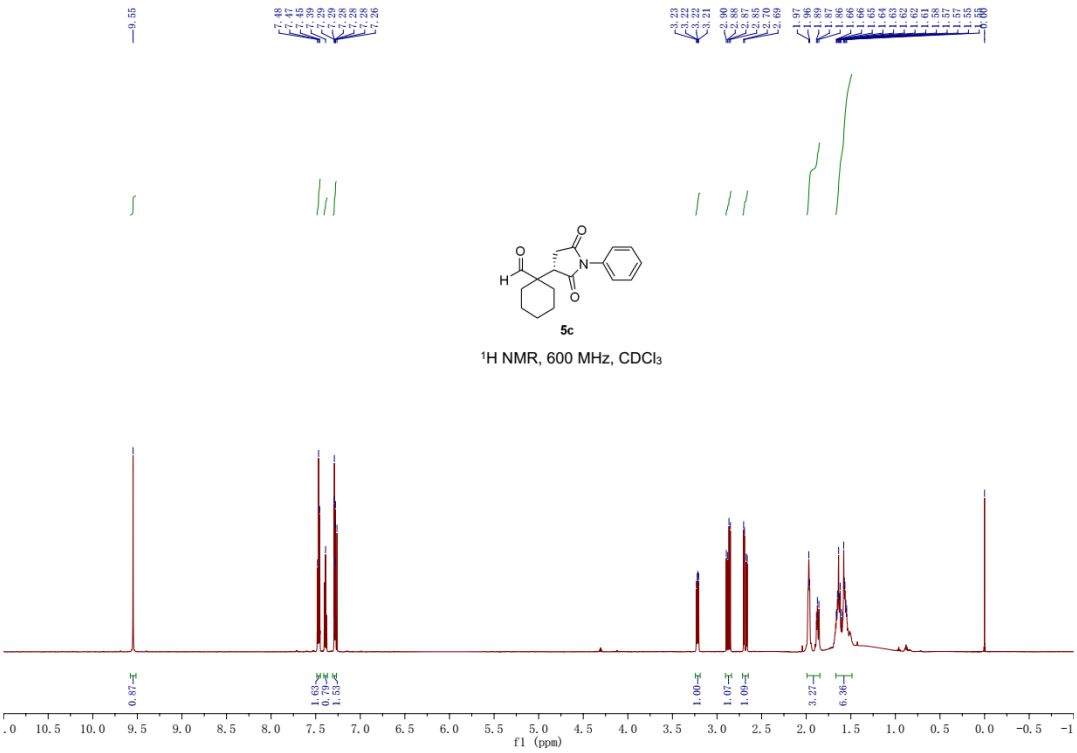
5a

^{1}H NMR, 600 MHz, $CDCl_3$



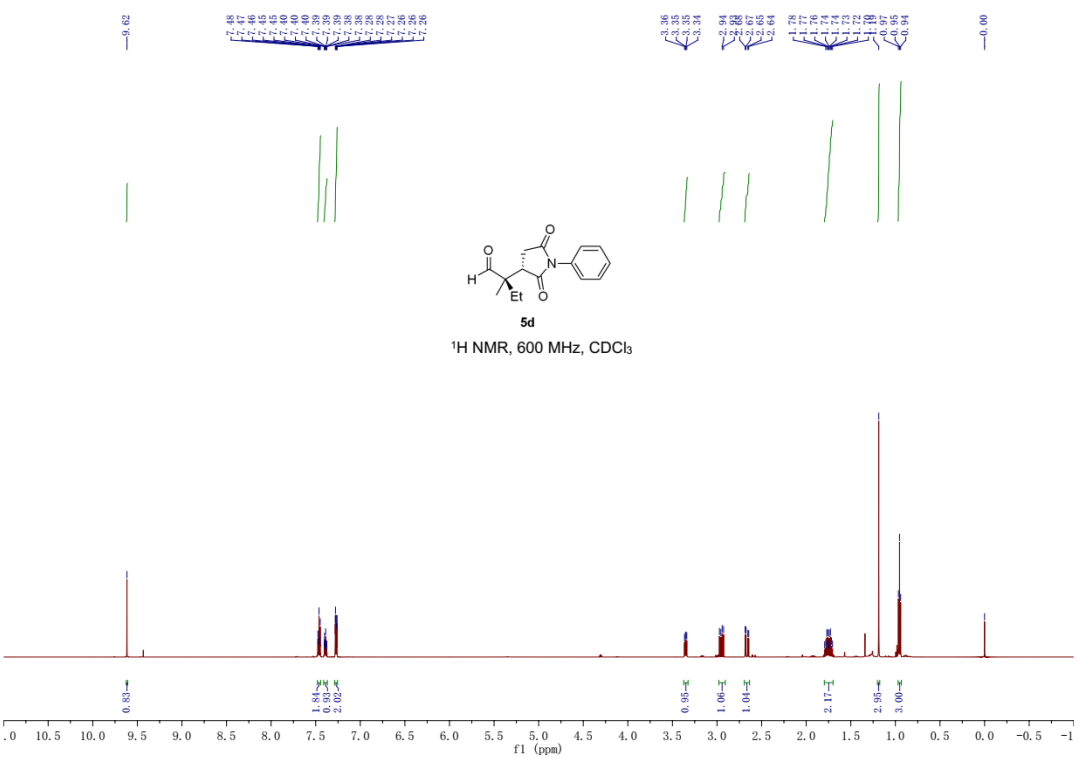
5b

^{1}H NMR, 600 MHz, $CDCl_3$



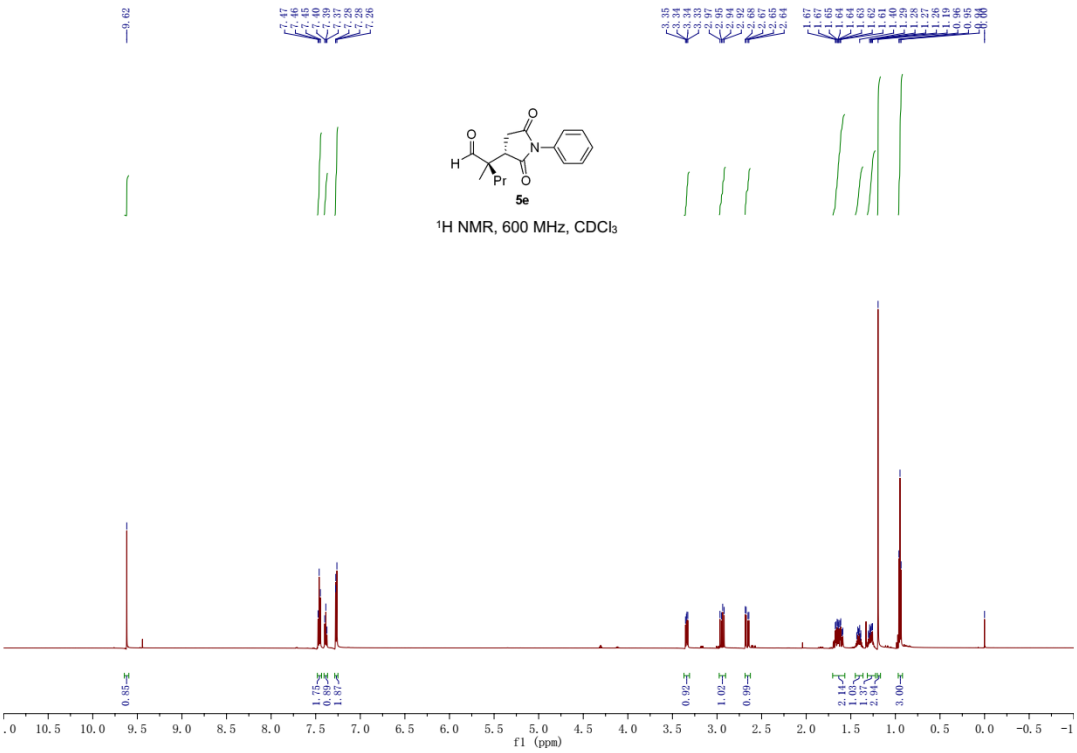
5c

^{1}H NMR, 600 MHz, $CDCl_3$



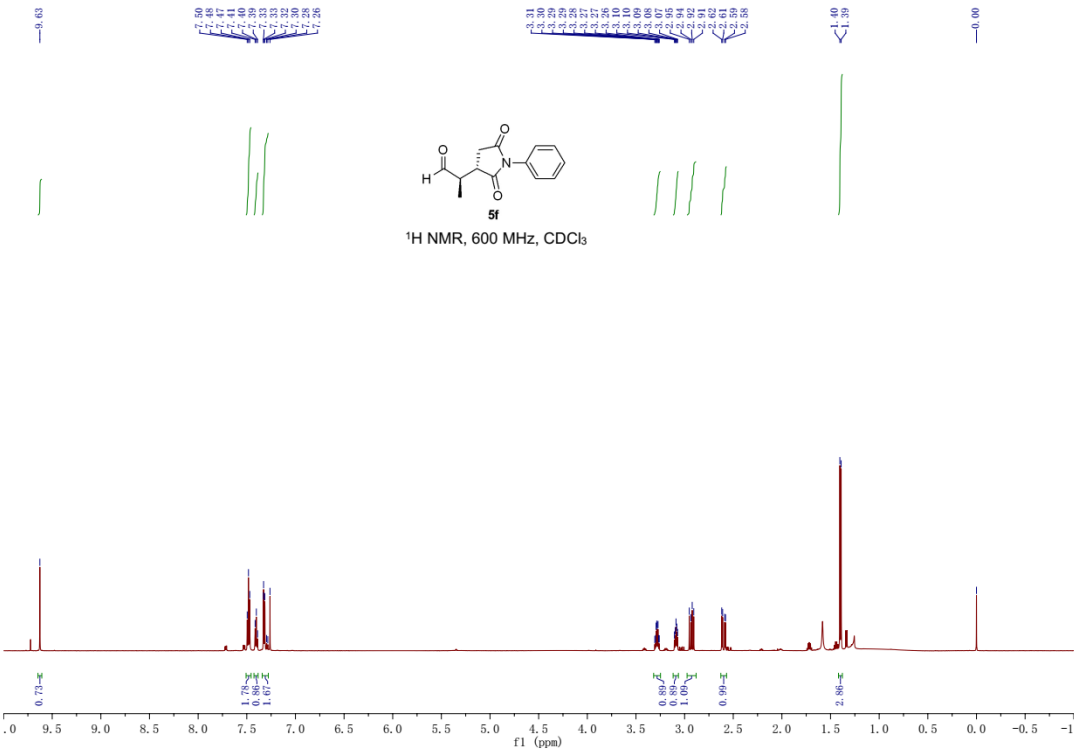
5d

^{1}H NMR, 600 MHz, $CDCl_3$



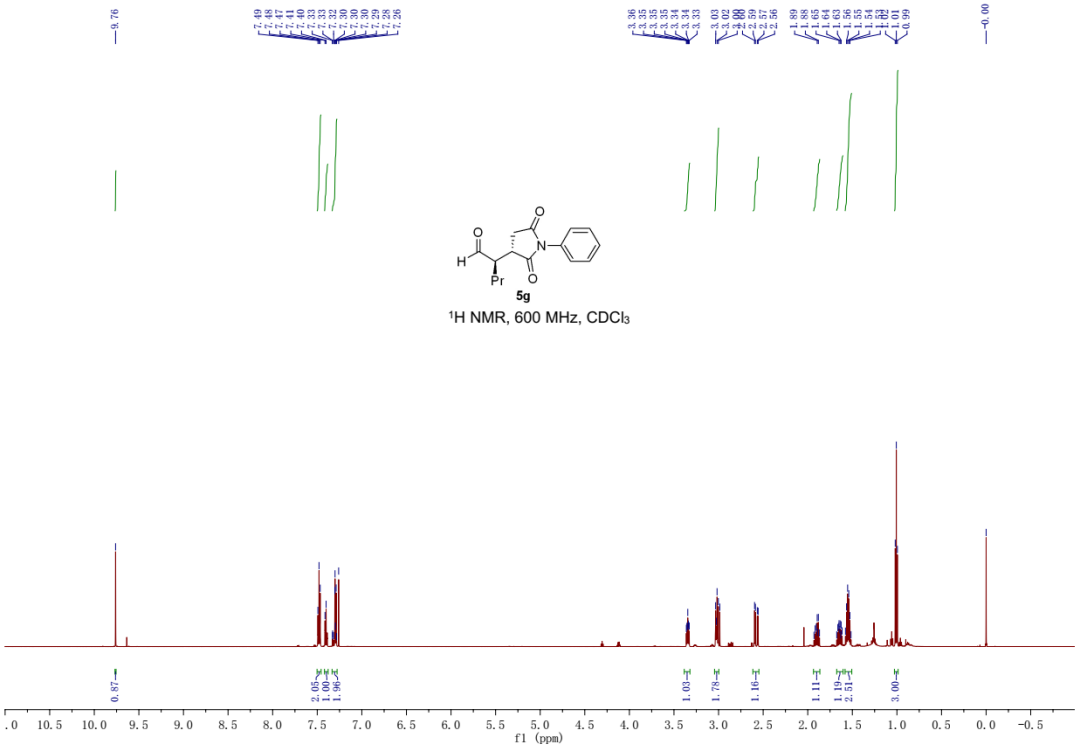
5e

^{1}H NMR, 600 MHz, $CDCl_3$



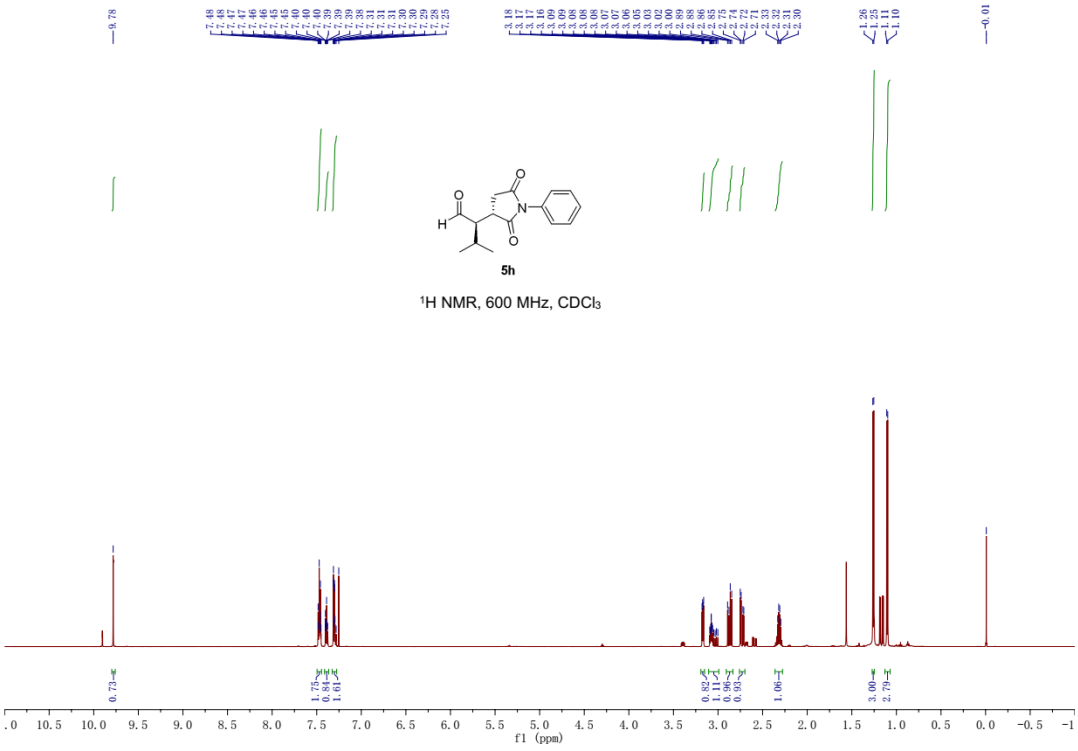
5f

^{1}H NMR, 600 MHz, $CDCl_3$



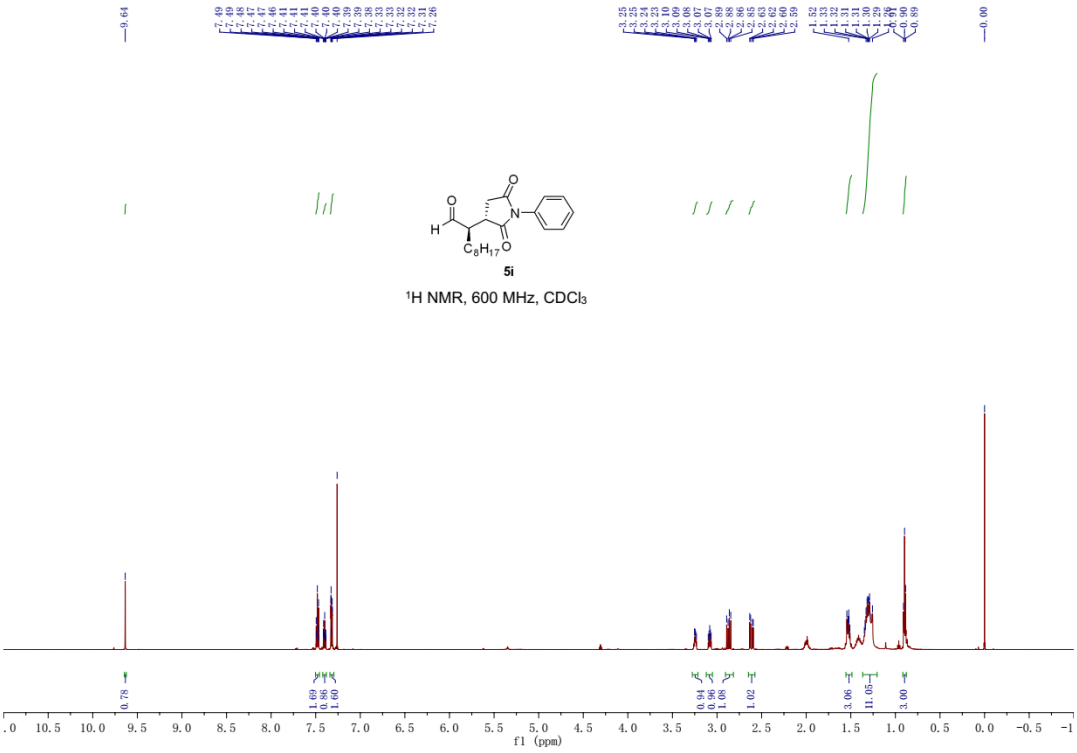
5g

^{1}H NMR, 600 MHz, $CDCl_3$



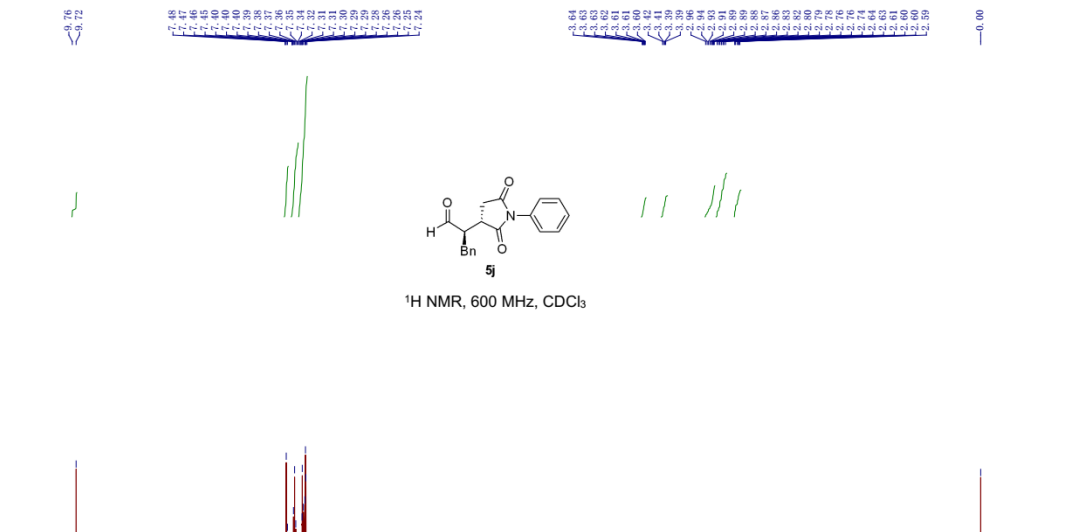
5h

^{1}H NMR, 600 MHz, $CDCl_3$



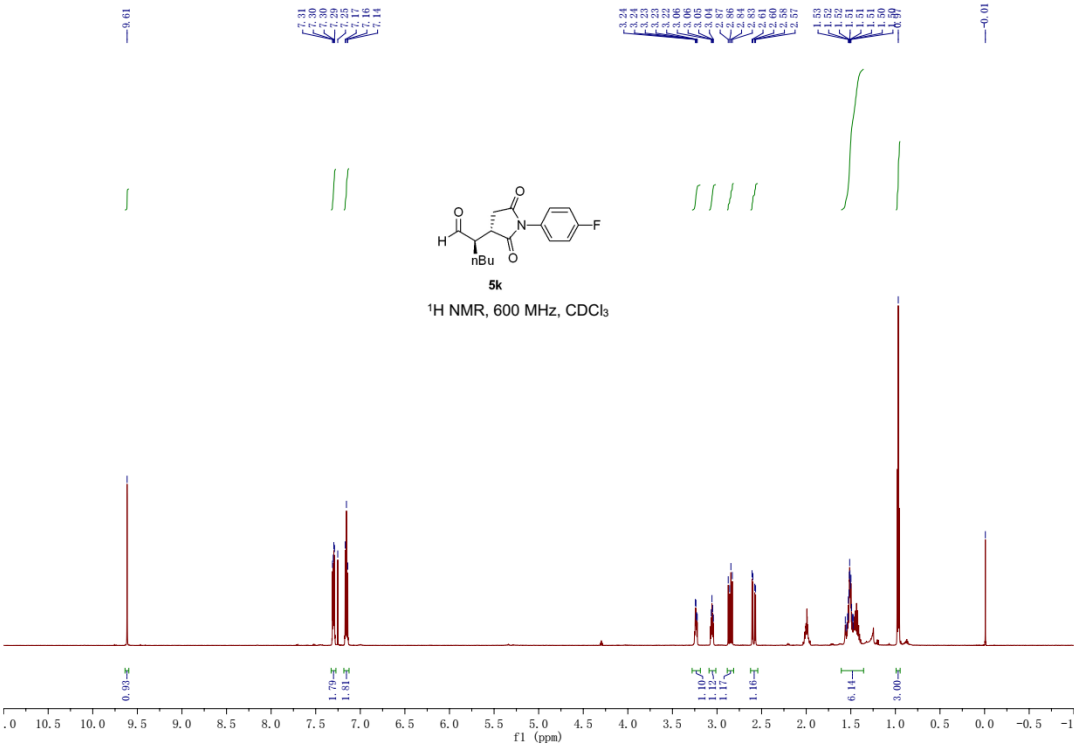
5i

^{1}H NMR, 600 MHz, $CDCl_3$



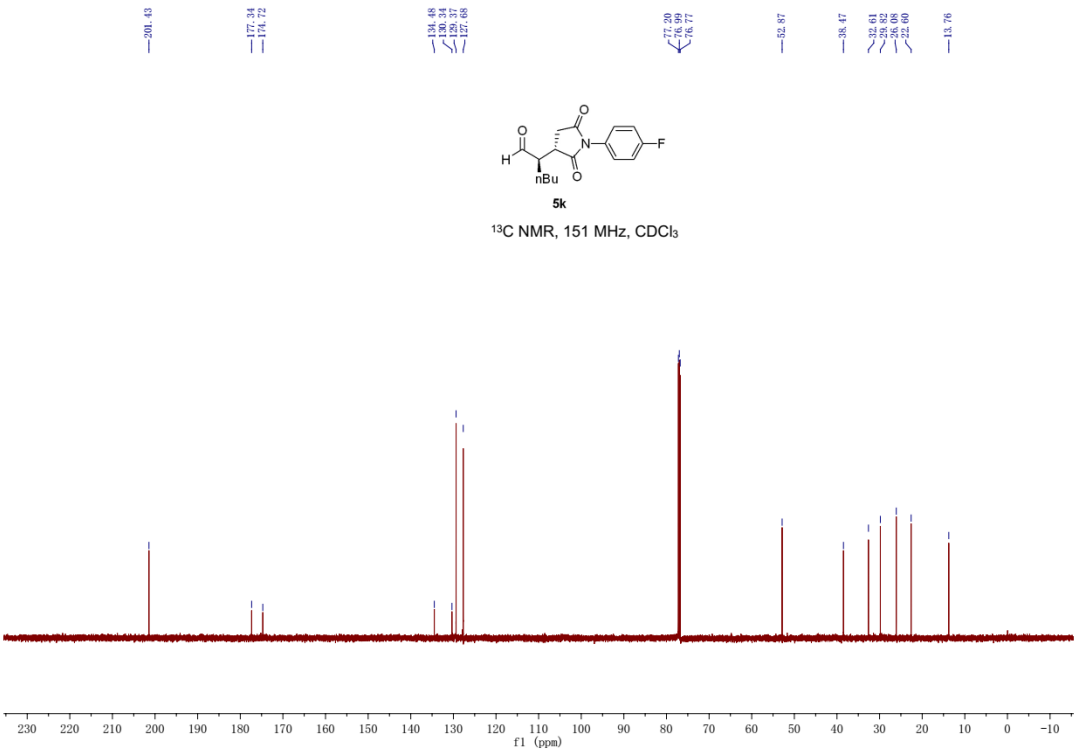
5j

^{1}H NMR, 600 MHz, $CDCl_3$



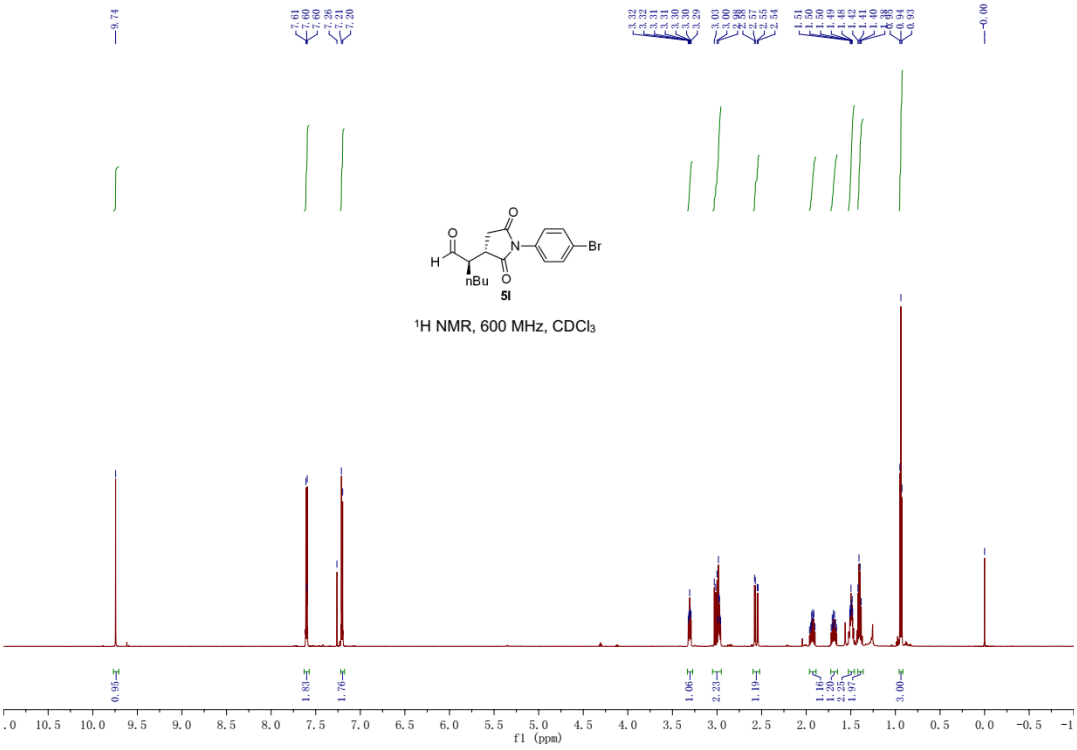
5k

^{1}H NMR, 600 MHz, $CDCl_3$

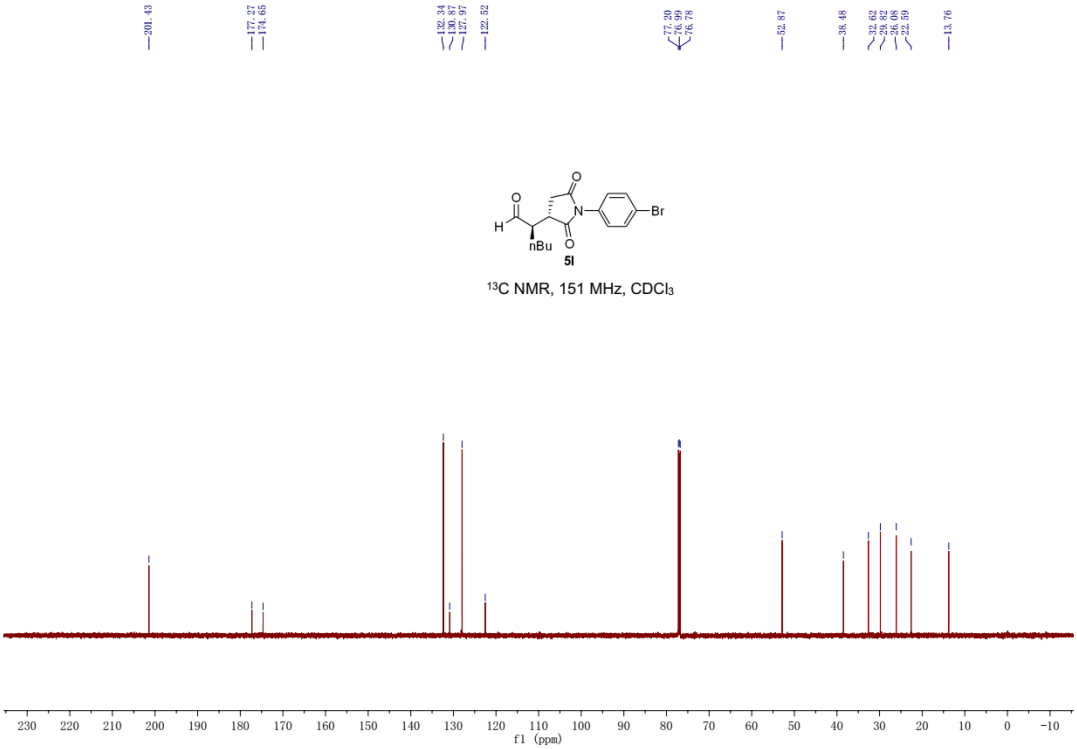


5k

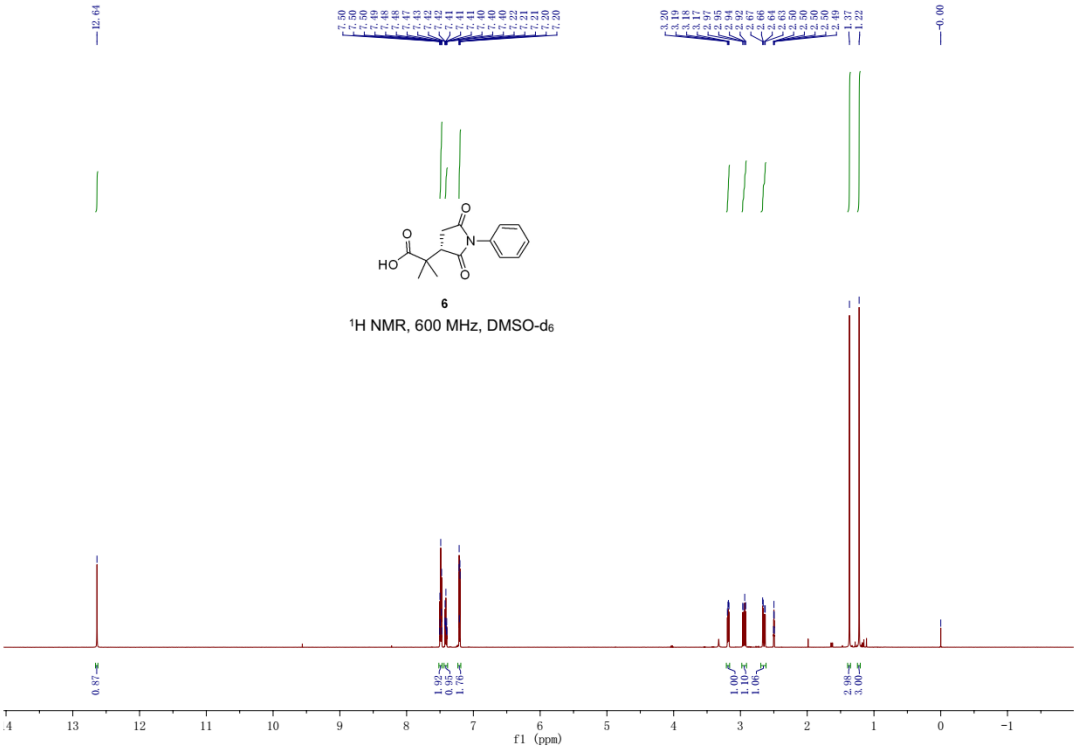
^{13}C NMR, 151 MHz, $CDCl_3$



^{1}H NMR, 600 MHz, $CDCl_3$

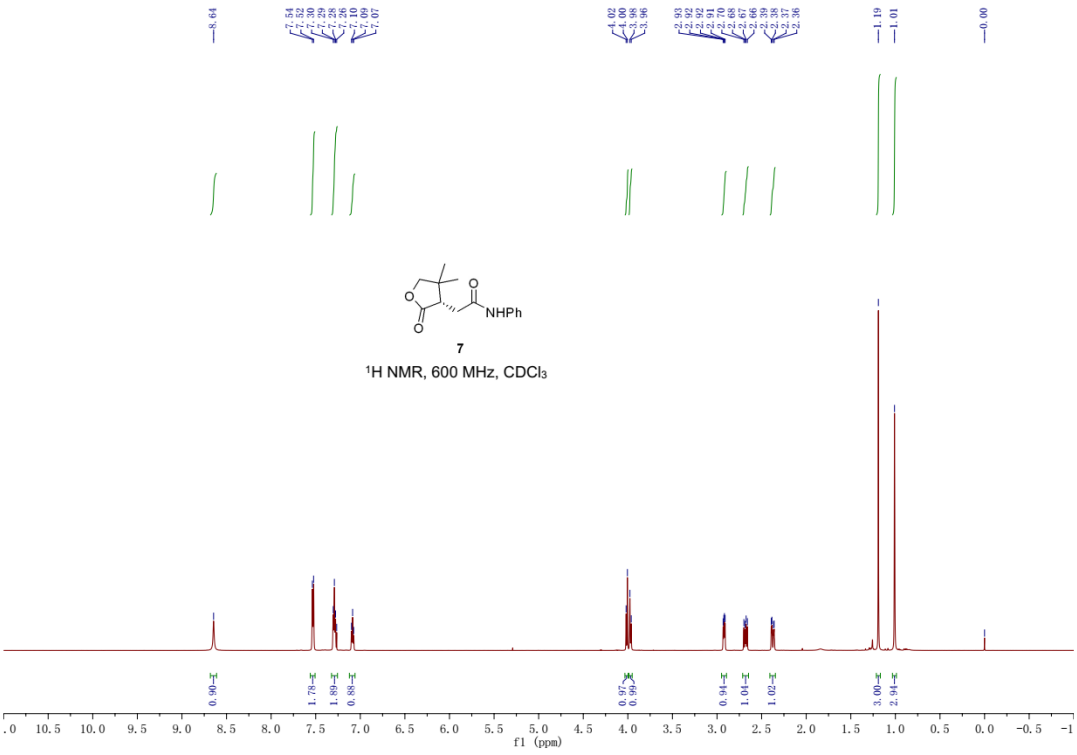


^{13}C NMR, 151 MHz, $CDCl_3$



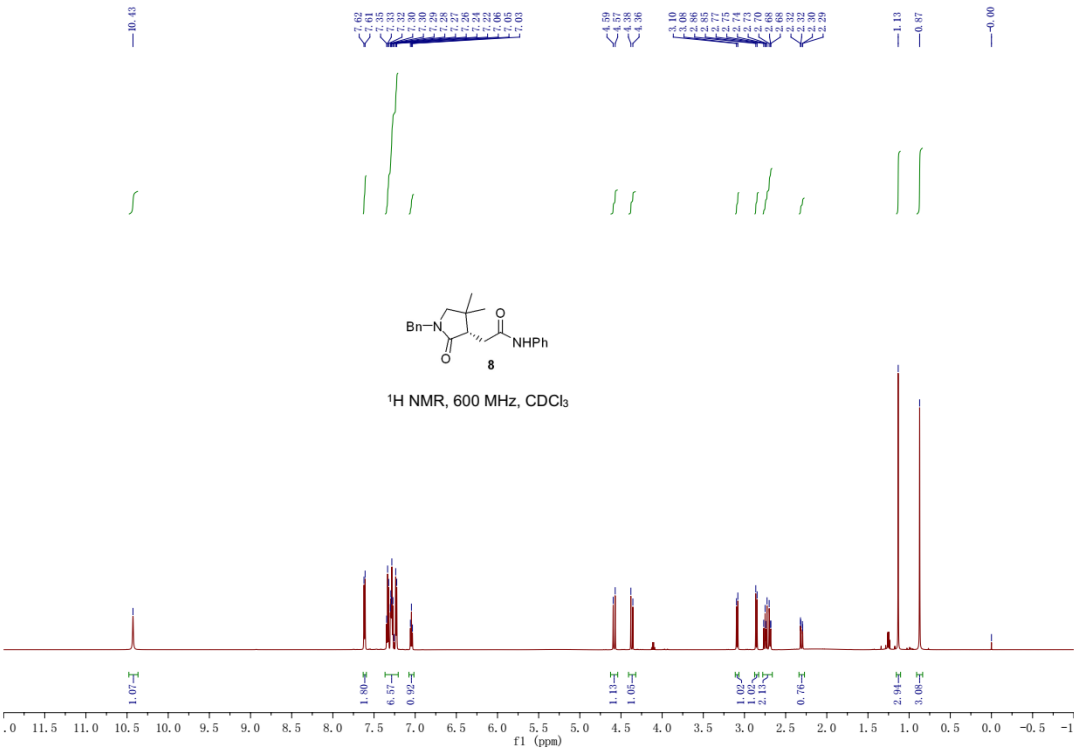
6

^{1}H NMR, 600 MHz, DMSO-d_6



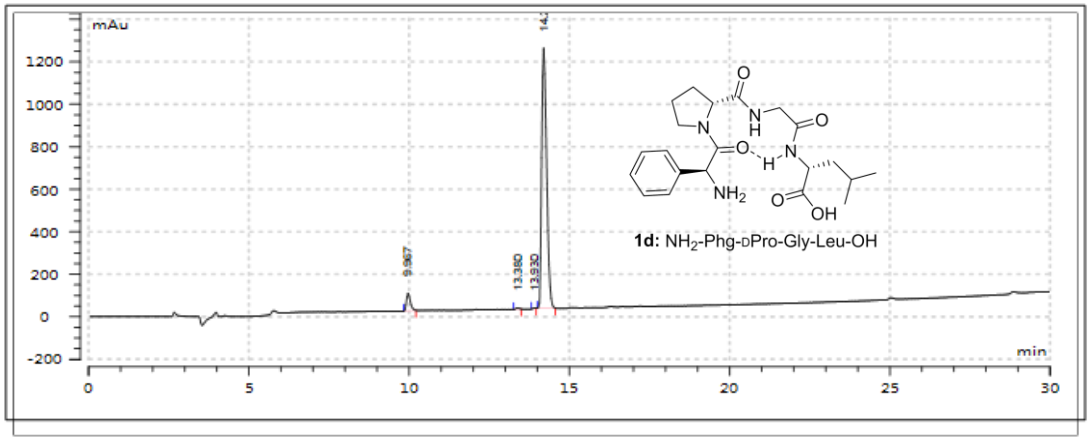
7

^{1}H NMR, 600 MHz, $CDCl_3$

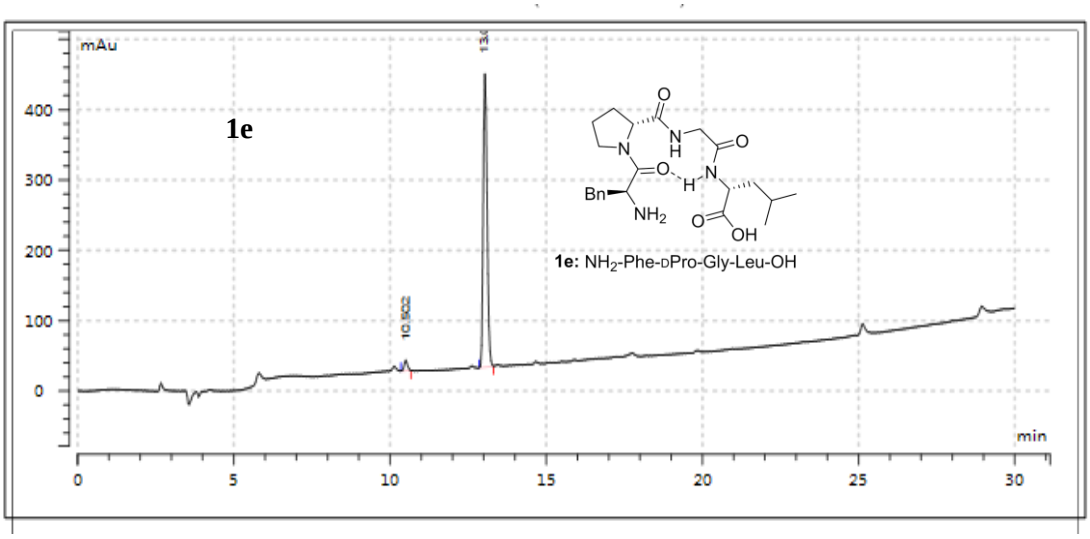

Bn—N
O
NHPh
O
8
¹H NMR, 600 MHz, CDCl₃
f1 (ppm)

9. HPLC analytical of the tetrapeptides 1d and 1e

Tetrapeptides **1d** and **1e** have passed HPLC purity analysis, and used C18 reversed phase column gradient elution, acetonitrile/ (0.1% TFA in water) = 10: 90 to 90: 10, 1mL/min. λ_{max} = 220nm.



No	name	Retention	Area(μV*s)	Height（μV）	% Area
1	N.A.	9.967	699.50797	82.804	5.034
2	N.A.	13.380	45.30635	6.571	0.326
3	N.A.	13.930	12.72706	2.292	0.092
4	N.A.	14.200	13138.91413	1224.438	94.549



No	name	Retention	Area(μV*s)	Height（μV）	% Area
1	N.A.	10.502	111.03011	15.070	3.000
2	N.A.	13.038	3590.04890	418.667	97.000

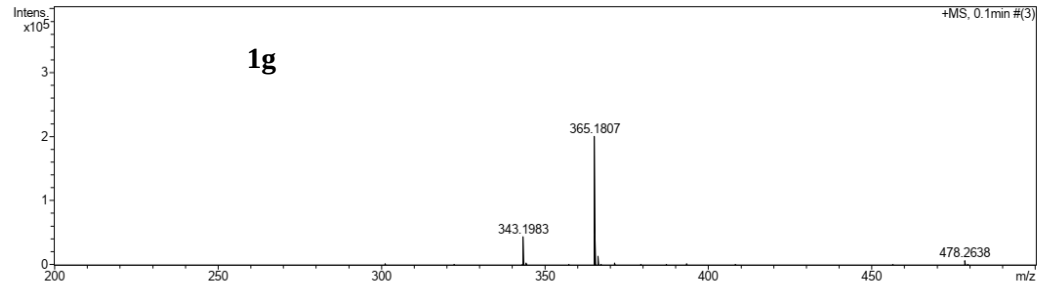
10. Images of the HR-MS of the new compounds

Analysis Info

Analysis Name	D:\Data\202008\20200804hanzhijian02.d	Acquisition Date	8/4/2020 10:25:54 AM
Method	POS_TuneLow_NaTFACal_100-1200.m	Operator	BDAL@DE
Sample Name	< No Sample >	Instrument / Ser#	maXis 4G 20204
Comment			

Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.3 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	180 °C
Scan Begin	100 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	1200 m/z	Set Collision Cell RF	1500.0 Vpp	Set Divert Valve	Source



Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
365.1807	1	C 15 H 26 N 4 Na O 5	100.00	365.1795	-1.1	-3.1	62.4	4.5	even	ok

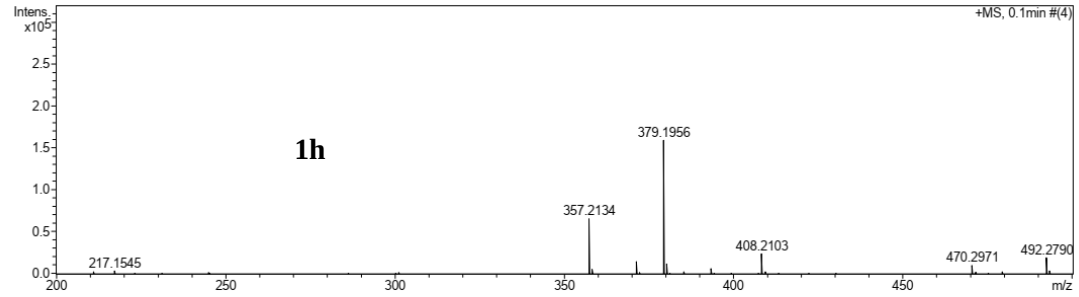
Mass Spectrum SmartFormula Report

Analysis Info

Analysis Name	D:\Data\202008\20200804hanzhijian03.d	Acquisition Date	8/4/2020 10:26:56 AM
Method	POS_TuneLow_NaTFACal_100-1200.m	Operator	BDAL@DE
Sample Name	< No Sample >	Instrument / Ser#	maXis 4G 20204
Comment			

Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.3 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	180 °C
Scan Begin	100 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	1200 m/z	Set Collision Cell RF	1500.0 Vpp	Set Divert Valve	Source



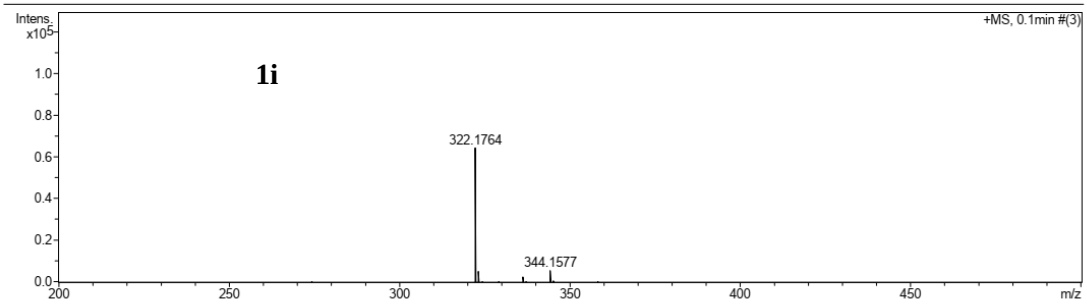
Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
379.1956	1	C 16 H 28 N 4 Na O 5	100.00	379.1952	-0.4	-1.0	64.2	4.5	even	ok

Analysis Info

Analysis Name	D:\Data\202008\20200804hanzhijian01.d	Acquisition Date	8/4/2020 10:24:00 AM
Method	POS_TuneLow_NaTFACal_100-1200.m	Operator	BDAL@DE
Sample Name	< No Sample >	Instrument / Ser#	maXis 4G 20204
Comment			

Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.3 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	180 °C
Scan Begin	100 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	1200 m/z	Set Collision Cell RF	1500.0 Vpp	Set Divert Valve	Source



Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
322.1764	1	C 16 H 24 N 3 O 4	100.00	322.1761	-0.3	-0.8	59.4	6.5	even	ok

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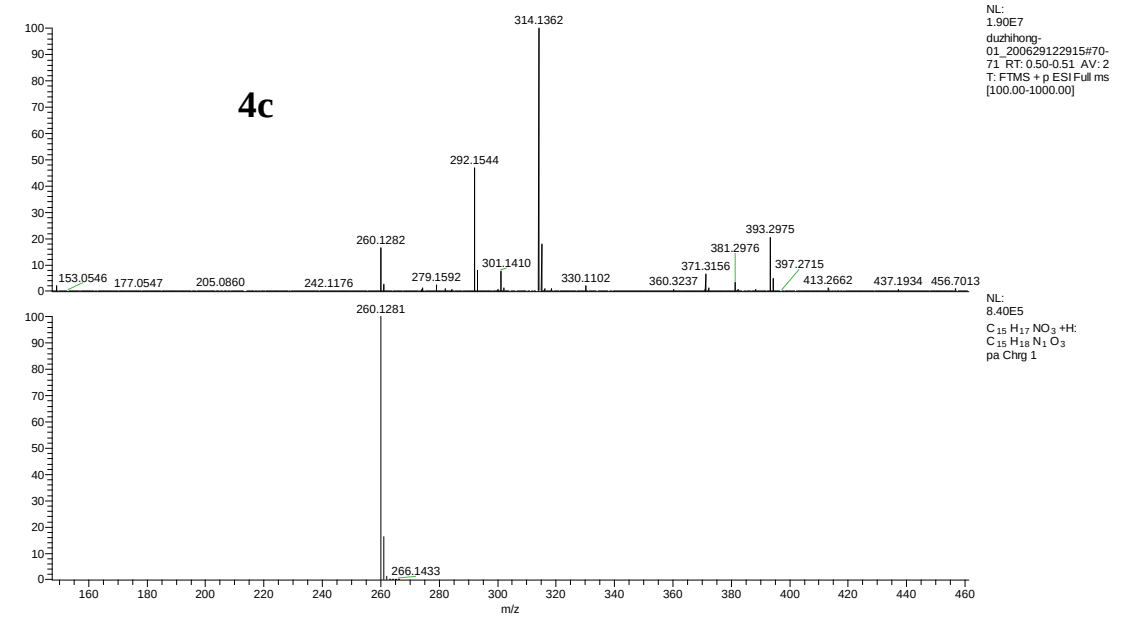

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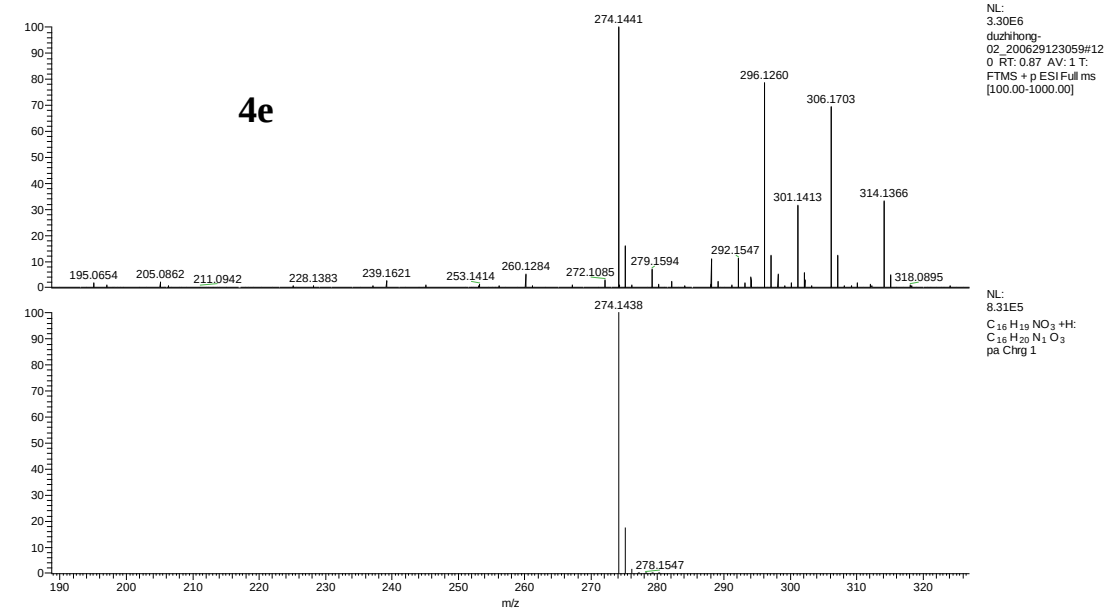

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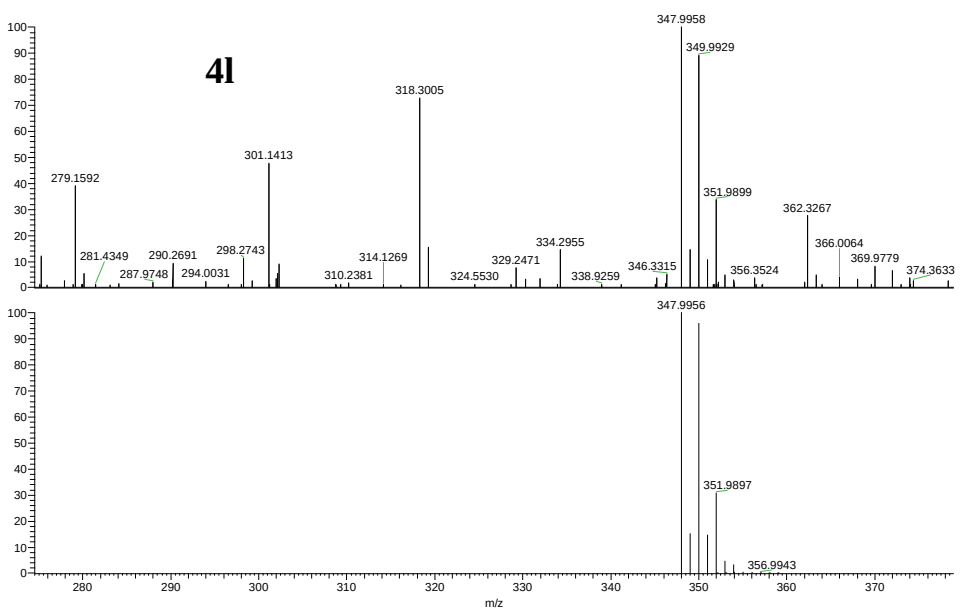

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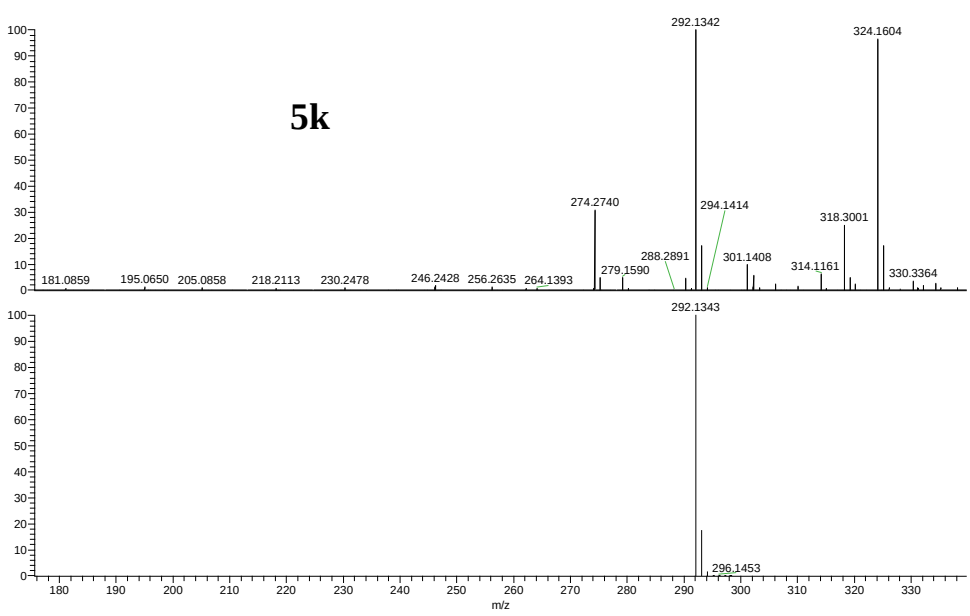

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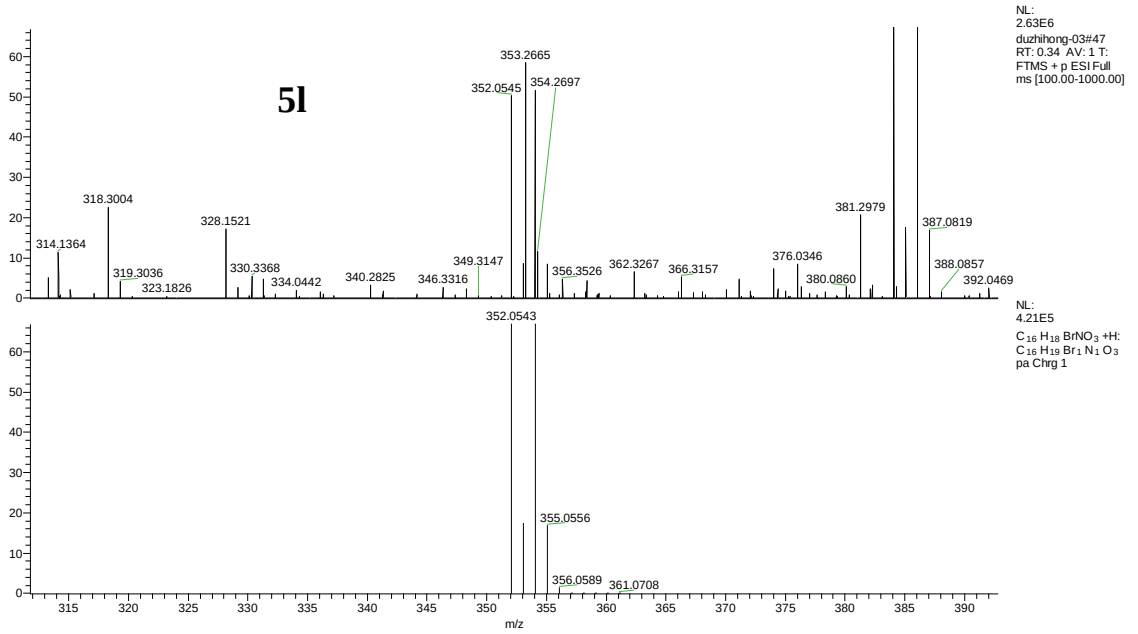

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