**Supplementary Materials**

**Enantioselective Benzylation of Methyl 4-Oxo-3-Piperidinecarboxylate**

**with Cinchona Alkaloids Phase-Transfer Catalysts**

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**Materials and General Methods**

Melting Points were measured on SGW X-4B Melting Point Apparatus. 1H NMR spectra were recorded on a Bruker Avance 300 (300 MHz) spectrometer and 400 (400 MHz). Chemical shifts were reported in ppm from tetramethylsilane with the solvent resonance resulting from incomplete deuterium incorporation as the internal standard (CDCl3: δ 7.26 ppm). 13C NMR spectra were recorded on a Bruker Avance 300 (75 MHz) and 400 (100 MHz) spectrometer with complete proton decoupling. Chemical shifts were reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (CDCl3: δ 77.16 ppm). High-resolution mass spectrometry was performed on Thermo Orbitrap Elite. Optical rotations were measured on an Autopol IV (*d* = 589 nm, Hg lamp, 50 mm cell). The enantiomeric excess was determined by Agilent 1260 infinity series HPLC (Chiral Technologies Chiralpak AD-H column (4.6 mm x 250 mm) and Chiral Technologies Chiralpak OD-H column (4.6 mm x 250 mm)). Chemicals and solvents were purchase Linfeng and Annaiji from commercial suppliers. Silica gel plates (Qingdao Haiyang) were used for thin-layer chromatography (TLC). Purification spectrums of the product was carried out by flash column chromatography using silica gel (Yantai Jiangyou, particle size 0.100-0.075 mm).

The phase transfer catalysts **1a**-**1q** were prepared according to the literature procedures, and the structures were confirmed by their spectral properties.

**Methyl (*R*)-1,3-Dibenzyl-4-oxopiperidine-3-carboxylate (3c)**

To a 10 mL reaction tube was added methyl 1-benzyl-4-oxopiperidine- 3-carboxylate **2c** (49.5 mg, 0.2 mmol), 50% aq. KOH (112 mg, 1 mmol, 5 eq) and phase transfer catalyst **1k** (12.1 mg, 0.02 mmol, 10 mol%) followed by *p*-xylene (1 mL). After the mixture was stirred at rt for 30 min, BnBr (71.3 uL, 0.6 mmol, 3 eq) was added, and the stirring was continued at rt for additional 12 h (monitored by TLC analysis). The crude product was purified by column flash chromatography (eluting with 20:1 hexane/EtOAc) to afford **3c** (256 mg, 76% yield) as colorless transparent liquid.  -17.2º (*c* = 0.5, CH2Cl2); 73% ee; 1H NMR (300 MHz, CDCl3): *δ* 7.33-7.27 (m, 5H), 7.25-7.13 (m, 5H), 3.61 (s, 3H), 3.57 (s, 2H), 3.39 (dd, *J* = 11.4, 2.4 Hz, 1H), 3.21 (d, *J* = 13.5 Hz ,1H), 2.97-2.90 (m, 2H), 2.85-2.74 (m, 1H), 2.49-2.37 (m, 2H), 2.31 (d, *J* = 11.4 Hz, 1H); 13C NMR (75 MHz, CDCl3): *δ* 205.6, 171.2, 137.8, 136.2, 130.5, 128.9, 128.3, 128.1, 127.4, 126.8, 62.8, 61.8, 60.7, 53.1, 52.1, 40.5, 37.5; HRMS (ESI, positive): calcd for C21H23NO3 [M+H]+ 338.1751, found: 338.1749.

The enantiomeric excess of **3c** was determined by chiral HPLC analysis (column, Chiralpak OD-H, 4.6×250 mm, *n*-hexane/*i*-PrOH = 99:1; flow rate: 1 mL/min, λ = 230 nm).



**Table S1**. Optimization of the reaction conditions for **3c**a

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Entry | cat | BnBr | 50% aq. KOH | Temp/℃ | Yield (%)b | ee (%)c |
| 1 | 10 mol% | 0.6 mmol (3eq) | 0.2 mmol (1 eq) | rt. | 69 | 70 |
| 2 | 10 mol% | 1.0 mmol (5 eq) | 0.2 mmol (1 eq) | rt. | 70 | 65 |
| 3 | 10 mol% | 0.6 mmol (3 eq) | 0.6 mmol (3 eq) | rt. | 72 | 70 |
| 4 | 10 mol% | 0.6 mmol (3 eq) | 1.0 mmol (5 eq) | rt. | 76 | 73 |
| 5 | 10 mol% | 0.6 mmol (3 eq) | 1.2 mmol (6 eq) | rt. | 75 | 70 |
| 6 | 20 mol% | 0.6 mmol (3 eq) | 1.0 mmol (5 eq) | rt. | 78 | 68 |
| 7 | 5 mol% | 0.6 mmol (3 eq) | 1.0 mmol (5 eq) | rt. | 70 | 69 |
| 8 | 10 mol% | 0.6 mmol (3 eq) | 1.0 mmol (5 eq) | 0 | 64 | 70 |
| 9 | 10 mol% | 0.6 mmol (3 eq) | 1.0 mmol (5 eq) | -10 | 61 | 71 |
| 10 | 10 mol% | 0.6 mmol (3 eq) | 1.0 mmol (5 eq) | -30 | 58 | 70 |
| 11d | 10 mol% | 0.6 mmol (3 eq) | 1.0 mmol (5 eq) | rt. | 74 | 71 |
| 12e | 10 mol% | 0.6 mmol (3 eq) | 1.0 mmol (5 eq) | rt. | 70 | 69 |

Reaction conditions: a **2c** (0.2 mmol) in *p*-xylene (1 mL) b Yield of isolated product; c Determined by chiral HPLC; d the reaction was added *p*-xylene (2 mL); e the reaction was added *p*-xylene (0.5 mL).

**Methyl (R)-1-benzyl-3-(3-fluorobenzyl)-4-oxopiperidine-3-carboxylate (3d):**



Colorless liquid; Yield 65%; [*α*]22 D -24.8o (*c* = 0.5, CH2Cl2); 60% ee; 1H NMR (300 MHz, CDCl3): *δ* 7.36-7.25 (m, 5H), 7.20-7.13 (m, 1H), 6.94-6.85 (m, 3H), 3.61 (s, 3H), 3.58 (s, 2H), 3.40 (dd, *J* = 11.7, 2.7 Hz, 1H), 3.20 (d, *J* = 13.5 Hz, 1H), 2.98-2.77 (m, 3H), 2.48-2.37 (m, 2H), 2.28 (d, *J* = 11.7 Hz, 1H); 13C NMR (75 MHz, CDCl3): *δ* 205.5, 171.2, 164.4, 160.9, 138.9, 138.7, 137.7, 129.0, 128.4, 117.6, 117.3, 113.9, 113.6, 62.9, 61.8, 60.9, 53.3, 52.3, 40.6, 37.2; HRMS (ESI, positive): Calcd for C21H23FNO3 [M+H]+ 416.0856, found: 416.0859.

**Methyl (R)-1-benzyl-3-(3-chlorobenzyl)-4-oxopiperidine-3-carboxylate (3e):**



Colorless liquid; Yield 68%; [*α*]22 D -19.2º (*c* = 0.5, CH2Cl2); 67% ee; 1H NMR (300 MHz, CDCl3): *δ* 7.36-7.25 (m, 5H), 7.19-7.11 (m, 3H), 7.06-7.03 (m, 1H), 3.61 (s, 3H), 3.58 (s, 2H), 3.39 (dd, *J* = 11.4, 2.4 Hz, 1H), 3.18 (d, *J* = 13.5 Hz, 1H), 2.99-2.77 (m, 3H), 2.48-2.37 (m, 2H), 2.27 (d, *J* = 11.7 Hz, 1H); 13C NMR (75 MHz, CDCl3): *δ* 205.5, 171.1, 138.4, 137.7, 133.8, 130.6, 129.3, 129.0, 128.8, 128.4, 127.5, 127.0, 62.8, 61.8, 60.9, 53.2, 52.3, 40.5, 37.1; HRMS (ESI, positive): Calcd for C21H23ClNO3 [M+H]+ 372.1361, found: 372.1358.

**Methyl (R)-1-benzyl-3-(3-bromobenzyl)-4-oxopiperidine-3-carboxylate (3f):**



Colorless liquid; Yield 70%; [*α*]22 D -23.6º (*c* = 0.5, CH2Cl2); 66% ee; 1H NMR (300 MHz, CDCl3): *δ* 7.36-7.25 (m, 5H), 7.12-7.05 (m, 2H), 3.61 (s, 3H), 3.57 (d, *J* = 2.7 Hz, 2H), 3.39 (dd, *J* = 11.4, 9.0 Hz, 1H), 3.18 (d, *J* = 13.8 Hz, 1H), 2.99-2.92 (m, 1H), 2.87-2.76 (m, 2H), 2.48-2.37 (m, 2H), 2.27 (d, *J* = 11.7 Hz, 1H); 13C NMR (75 MHz, CDCl3): *δ* 205.5, 171.1, 138.7, 137.7, 133.5, 129.9, 129.6, 129.2, 129.0, 128.4, 127.5, 122.1, 62.8, 61.8, 60.9, 53.2, 52.2, 40.5, 37.1; HRMS (ESI, positive): Calcd for C21H23BrNO3 [M+H]+ 356.1656, found: 356.1653.

**Methyl (R)-1-benzyl-3-(3-methylbenzyl)-4-oxopiperidine-3-carboxylate (3g):**



Colorless liquid; Yield 70%; [*α*]22 D -31.2º (*c* = 0.5, CH2Cl2); 67% ee; 1H NMR (300 MHz, CDCl3): *δ* 7.34-7.24 (m, 5H), 7.13-7.08 (m, 1H), 7.00-6.92 (m, 3H), 3.61 (s, 3H), 3.57 (s, 2H), 3.39 (dd, *J* = 11.7, 9.0 Hz, 1H), 3.17 (d, *J* = 13.5 Hz, 1H), 2.93-2.88 (m, 2H), 2.83-2.75 (m, 1H), 2.47-2.37 (m, 2H), 2.32 (s, 1H), 2.28 (s, 3H); 13C NMR (75 MHz, CDCl3): *δ* 205.6, 171.3, 137.8, 137.5, 136.1, 131.3, 129.0, 128.3, 128.0, 127.5, 127.4, 62.8, 61.8, 60.8, 53.1, 52.1, 40.5, 37.4, 21.5; HRMS (ESI, positive): Calcd for C22H26NO3 [M+H]+ 352.1910, found: 352.1907.

The enantiomeric excess of **3d-3g** was determined by chiral HPLC analysis (column, Chiralpak IB, 4.6×250 mm, n-hexane/*i*-PrOH = 98:2; flow rate: 1 mL/min, λ = 254 nm).

**Ethyl (*R*)-1,3-Dibenzyl-4-oxopiperidine-3-carboxylate (3h)**

To an oven-dried 100 mL round-bottom flask was sequentially added 1-benzyl-3-ethoxycarbonyl-4-piperidone hydrochloride (1.2 g, 4 mmol), 50% aq. KOH (2.7 g, 24 mmol, 6 eq), *O*-allyl-*N*-9-anthracenemethylcindexnine bromide (**1k**) (242 mg, 0.4 mmol, 10 mol%) and *p*-xylene (20 mL). After the mixture was stirred at rt for 30 min, BnBr (1.4 mL, 12 mmol, 3 eq) was introduced, and the stirring was continued at rt for additional 12 h. The solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography (eluting with 20:1 hexane/EtOAc) to give **3h** (983 mg, 70% yield) as colorless liquid.  -43.6º (*c* = 0.5, CH2Cl2); 76% ee; 1H NMR (400 MHz, CDCl3) δ 7.34-7.27 (m, 5H), 7.22-7.16 (m, 5H), 4.14-4.00 (m, 2H), 3.60 (d, *J* = 13.2 Hz, 1H), 3.54 (d, *J* = 13.2 Hz, 1H), 3.42 (dd, *J* = 11.6, 2.4 Hz, 1H), 3.22 (d, *J* = 13.6 Hz, 1H), 2.98-2.91 (m, 2H), 2.86-2.78 (m, 1H), 2.47-2.35 (m, 2H), 2.30 (d, *J* = 11.6 Hz, 1H), 1.11 (t, *J* = 7.2 Hz, 3H); 13C NMR (100 MHz, CDCl3): δ 205.9, 170.9, 138.0, 136.4, 130.7, 129.0, 128.4, 128.1, 127.4, 126.6, 62.8, 61.9, 61.3, 61.2, 53.2, 40.7, 37.6, 14.0; HRMS (ESI, positive): calcd. for C23H25NO5 [M+H]+ 352.1907, found: 352.1906.

The enantiomeric excess of **3h** was determined by chiral HPLC analysis (column, Chiralpak AD-H, 4.6×250 mm, *n*-hexane/*i*-PrOH=99:1; flow rate: 1 mL/min, λ = 230 nm).

**Ethyl (*R*)-3-benzyl-4-oxopiperidine-3-carboxylate (4)**

To a 50 mL round-bottom flask were sequentially added **3h** (351mg, 1 mmol), 10% Pd/C (70 mg) and EtOH (10 mL), and the mixture was stirred at rt and under hydrogen atmosphere for 12 h. The reaction mixture was filtered through a celite pad, the filtrate was concentrated under reduced pressure, and the crude product was purified by flash column chromatography (eluting with DCM/MeOH, 50:1 to 20:1) to afford **4** (225mg, 86% yield) as light yellow oil.  -150.8º (*c* = 0.5, CH2Cl2). 1H NMR (400 MHz, CDCl3): δ 7.27-7.20 (m, 3H), 7.10-7.06 (m, 2H), 4.18-4.08 (m, 2H), 3.70-3.67 (m, 1H), 3.41-3.36 (m, 2H), 2.93-2.86 (m, 1H), 2.82 (d, *J* = 14.0 Hz, 1H), 2.63 (d, *J* = 13.6 Hz, 1H), 2.48-2.42 (m, 2H), 1.87 (s, 1H), 1.20 (t, *J* = 7.2 Hz, 3H); 13C NMR (75 MHz, CDCl3): δ 204.6, 170.6, 136.0, 130.1, 128.2, 126.8, 64.4, 61.6, 55.3, 48.0, 43.5, 37.5, 14.0; HRMS (ESI, positive): calcd for C15H19NO3 [M+H]+ 262.1438, found: 262.1438.

**Ethyl (*R*)-3-benzyl-1-(*tert*-butyl)-4-oxopiperidine-1,3-dicarboxylate (5)**

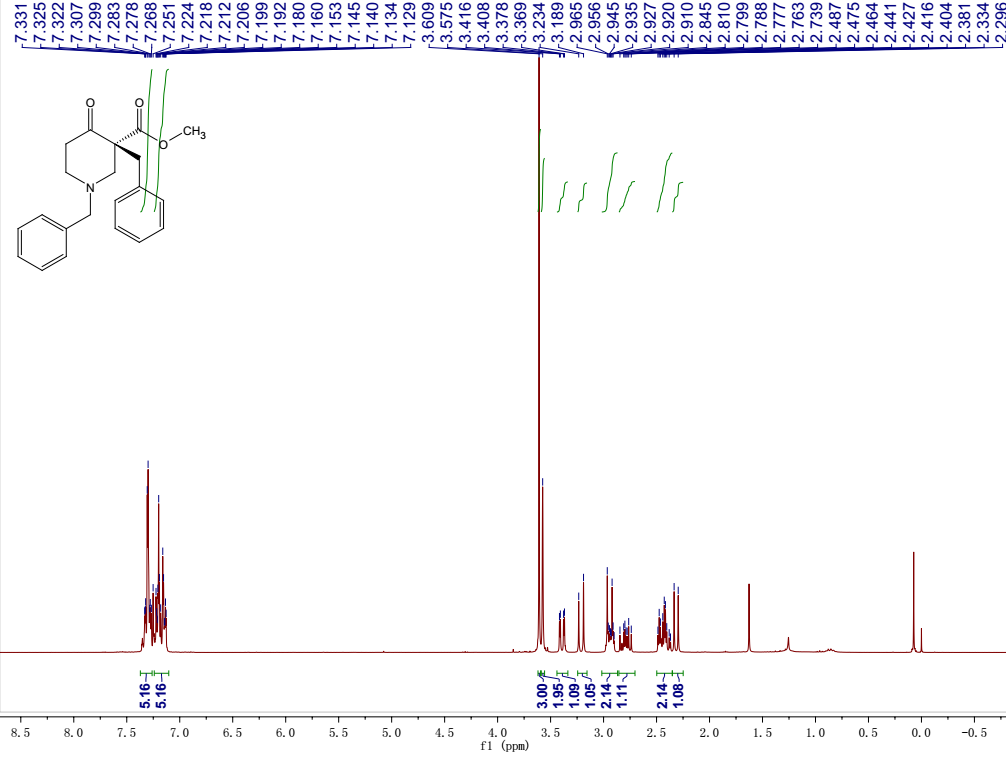
**4** (120 mg, 0.46 mmol) was dissolved in anhydrous CH2Cl2 (5 mL), triethylamine (0.13 mL, 0.92 mmol, 2 eq), 4-dimethylaminopyridine (6 mg, 0.046 mmol, 0.1 eq) and di-(*tert*-butyl) pyrocarbonate (0.11 mL, 0.46 mmol, 1 eq) were added successively at 0 ℃，and the reaction mixture was stirred at rt for 15 min. After completion of the reaction monitored by TLC, the reaction was quenched by the addition of saturated aqueous NaHCO3 (3 mL), and the resulting mixture was extracted with DCM (25 mL×3). The combined organic phases were washed with brine (30 mL), dried over anhydrous Na2SO4, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (eluting with 20:1 hexane/EtOAc) to afford **5** (122 mg, 87% yield) as white solid. mp 89-91℃;  -53.5º (*c* = 3, CH2Cl2) [Lit.[6] -45.8º (*c* = 3, CH2Cl2)]; 66% ee; 1H NMR (300 MHz, CDCl3): δ 7.28-7.15 (m, 5H), 4.62 (s, 1H), 4.17 (bs, 1H), 4.11-4.06 (m, 2H), 3.26 (d, *J* = 13.8 Hz, 1H), 3.19-3.11 (m, 1H), 3.01 (d, *J* = 13.5 Hz, 2H), 2.75-2.65 (m, 1H), 2.44 (d, *J* = 14.4 Hz, 1H), 1.45 (s, 9H), 1.15 (t, *J* = 7.2 Hz, 3H); 13C NMR (75 MHz, CDCl3): δ 204.6, 169.8, 154.3, 135.7, 130.5, 128.3, 127.0, 80.5, 62.3, 61.8, 50.4, 43.2, 40.1, 37.4, 28.3, 14.0; HRMS (ESI, positive): calcd. for C20H27NNaO5 [M+Na]+ 384.1781, found: 384.1781.

The enantiomeric excess of **5** was determined by chiral HPLC analysis (column, Chiralpak OD-H, 4.6×250 mm, *n*-hexane/*i*-PrOH = 99:1; flow rate: 1 mL/min, λ = 230 nm).

**3α*R*-Benzyl-1-(*tert*-butyl)oxycarbonyl-2-methyl-4,5,6,7-tetrahydro-2*H*-pyrazolo- [4,3-c]pyridine-3(3αH)-one (6)**

A solution of **5** (940 mg, 2.6 mmol), methylhydrazinium sulphate (750 mg, 5.2 mmol, 2 eq) and sodium acetate (854 mg, 10.4 mmol, 4 eq) in EtOH (35 mL) was heated at 80 ℃ under nitrogen atmosphere for 12 h. After the reaction is complete, the reaction mixture was cooled to rt, and concentrated in vacuo. The crude residue was diluted with DCM (100 mL), and was washed with saturated aqueous NaHCO3 (30 mL) and brine (30 mL), and dried (anhydrous Na2SO4). The crude product was purified by flash column chromatography (eluting with hexane/EtOAc, 5:1 to 3:1) to give **6** (620mg, 70% yield) as white solid. mp 123-125℃;  44.8o (*c* = 1, CH2Cl2); 69 % ee; 1H NMR (300 MHz, CDCl3): δ 7.18-7.09 (m, 3H), 7.02-6.97 (m, 2H), 4.60 (bs, 1H), 4.39 (d, *J* = 12.6 Hz, 1H), 3.17 (d, *J* = 13.2 Hz, 1H), 3.00 (s, 3H), 2.95 (d, *J* = 13.5 Hz, 1H), 2.64 (bs, 3H), 2.49 (d, *J* = 9.6 Hz, 1H), 1.47 (s, 9H); 13C NMR (75 MHz, CDCl3): δ 174.5, 162.0, 154.6, 134.7, 128.6, 128.3, 127.2, 81.0, 60.3, 56.7, 50.8, 45.5, 37.9, 30.7, 28.3; HRMS (ESI, positive): calcd. for C19H25N3NaO3 [M+Na]+ 366.1788, found: 366.1791.

The enantiomeric excess of **6** was determined by chiral HPLC analysis (column, Chiralpak AD-H, 4.6 × 250 mm, *n*-hexane/*i*-PrOH = 99:1; flow rate: 1 mL/min, λ = 254 nm).



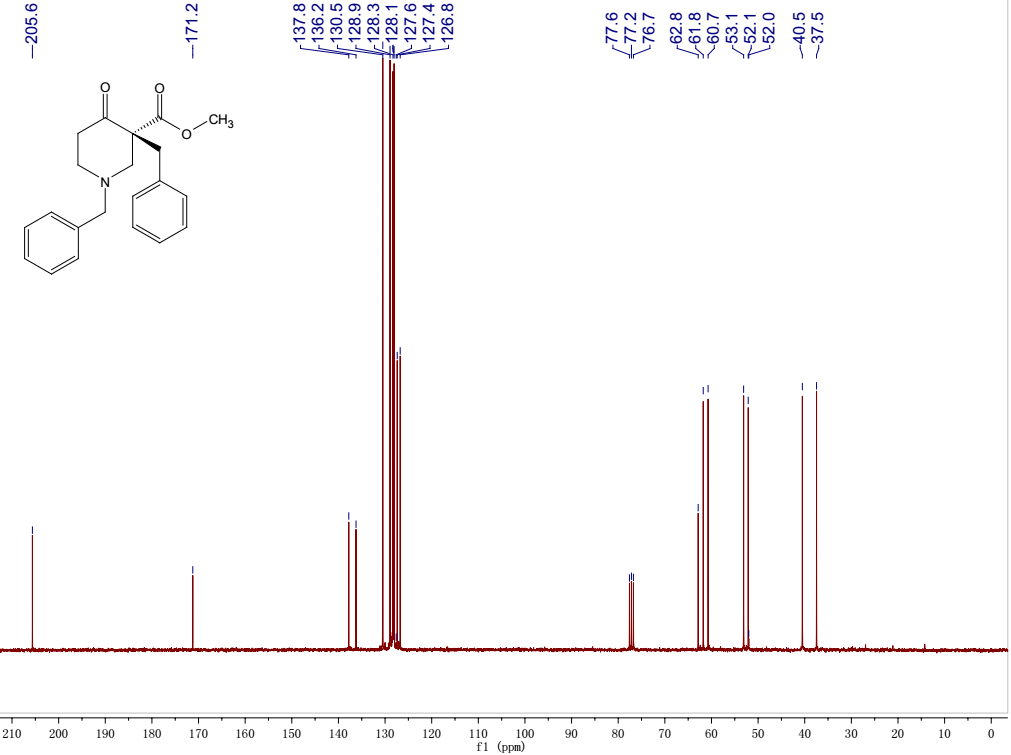
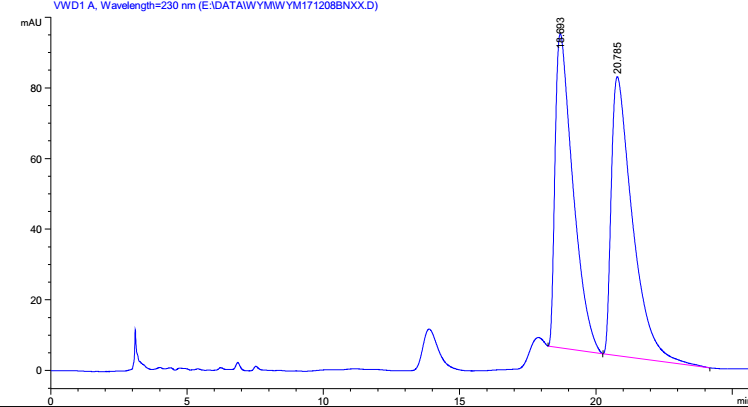
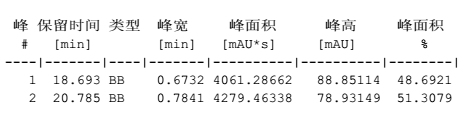
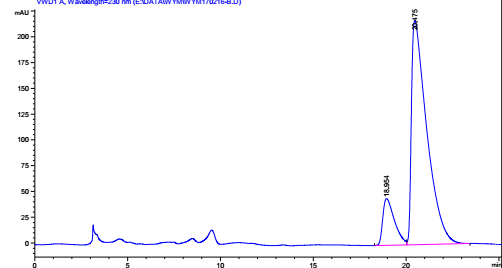


Fig 1: 1H NMR and 13C NMR spectra of **3c**







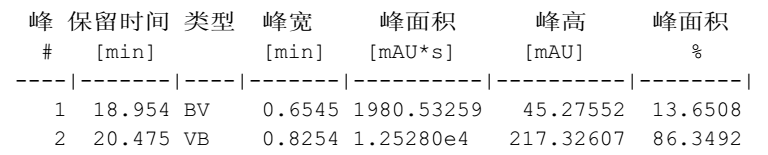
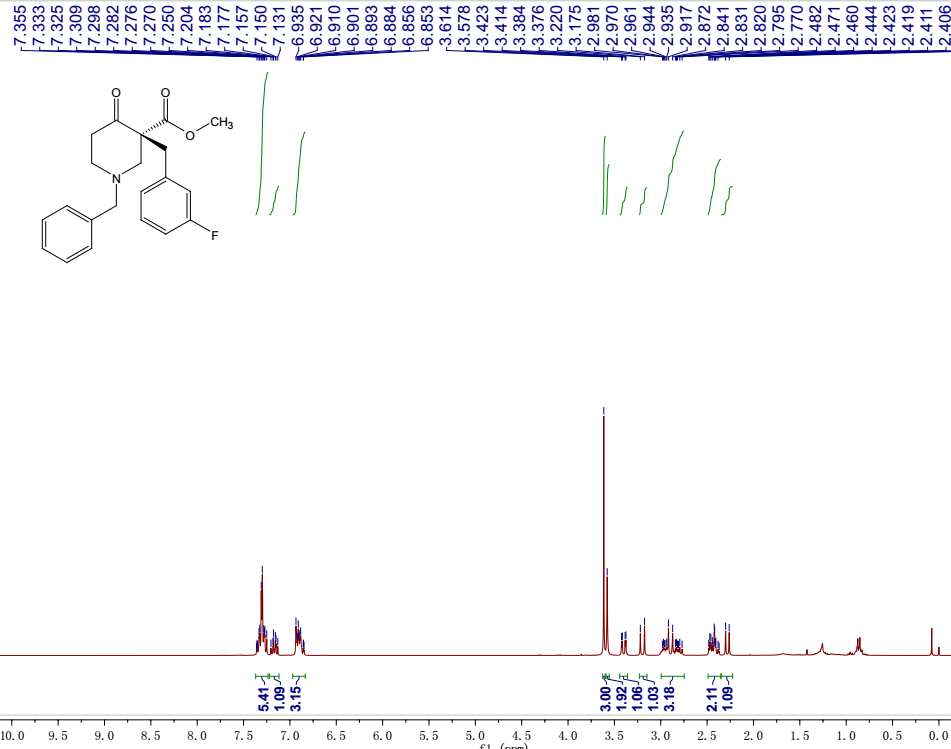


Fig 2: HPLC chromatogram of **3c** comparing to the racemic mixture



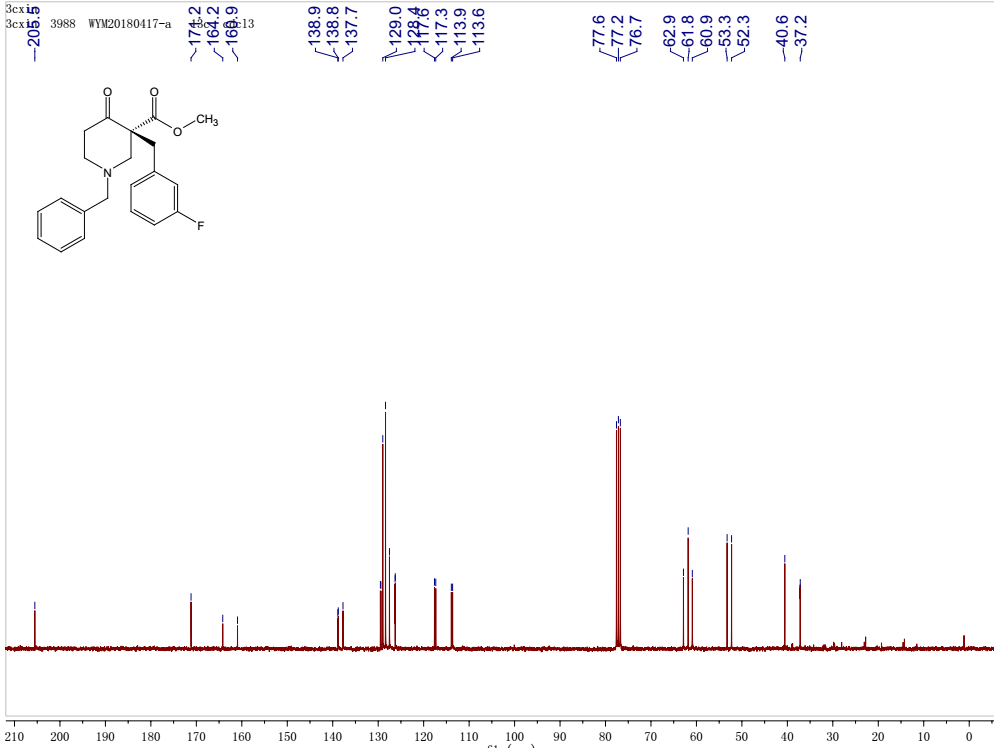
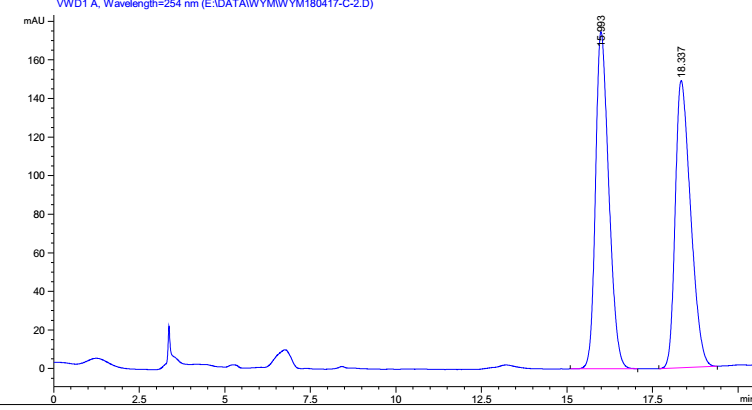
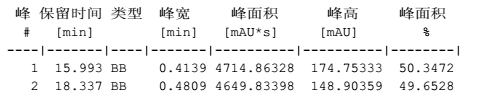
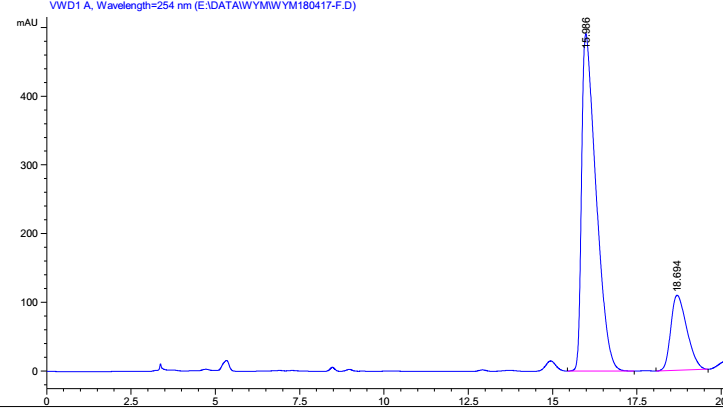


Fig 3: 1H NMR and 13C NMR spectra of **3d**







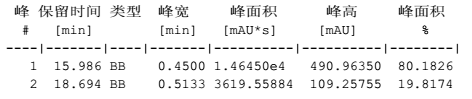
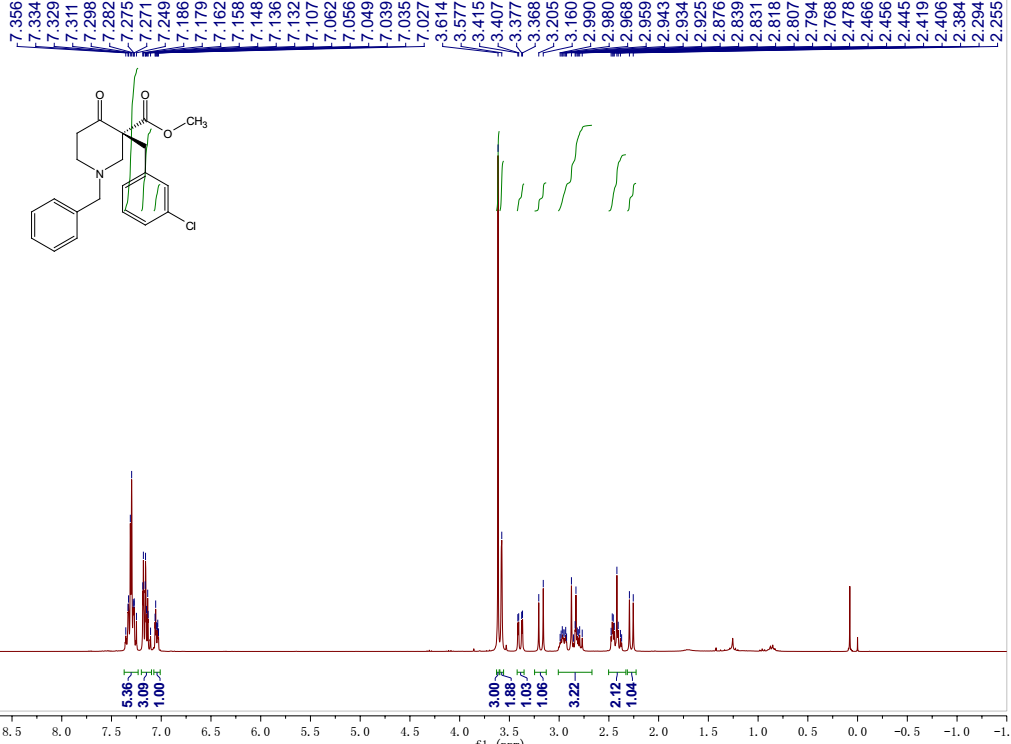


Fig 4: HPLC chromatogram of **3d** comparing to the racemic mixture



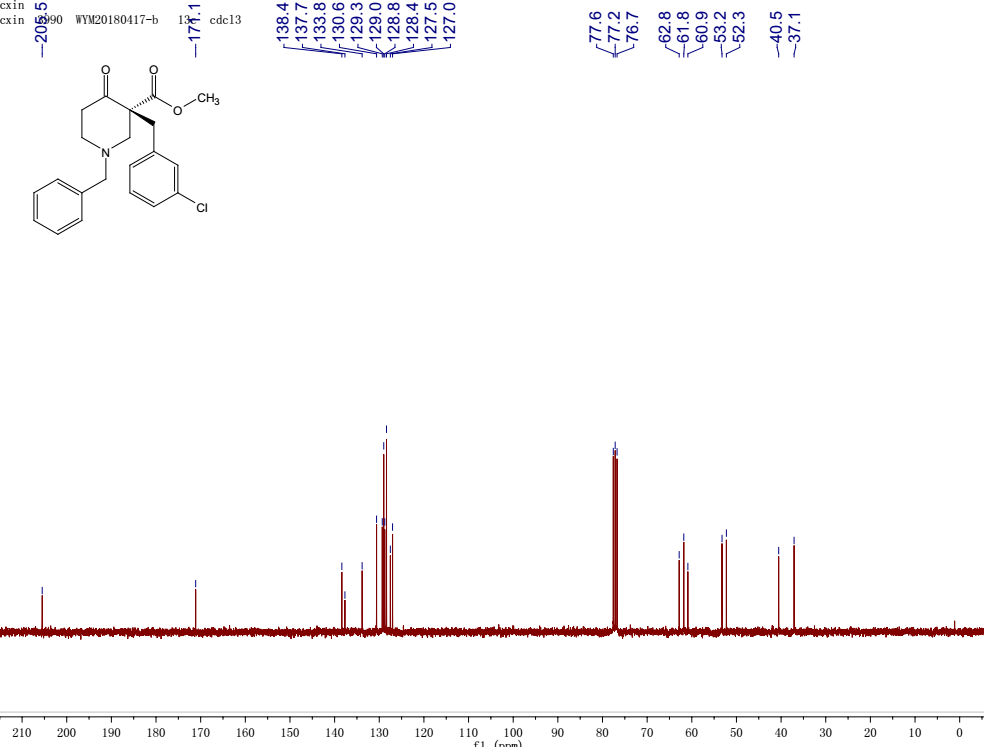
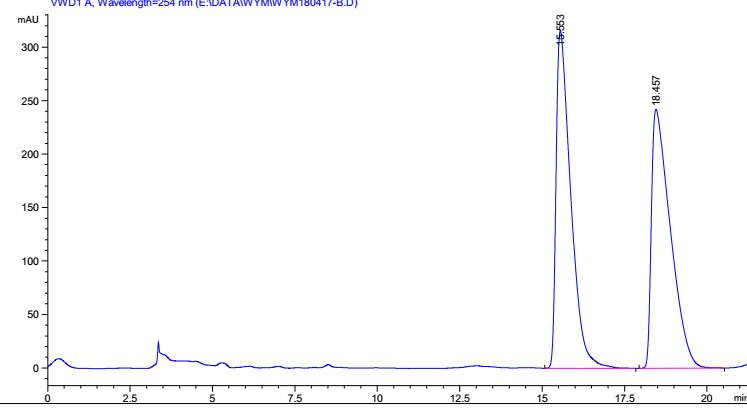
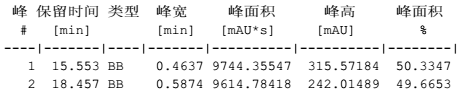
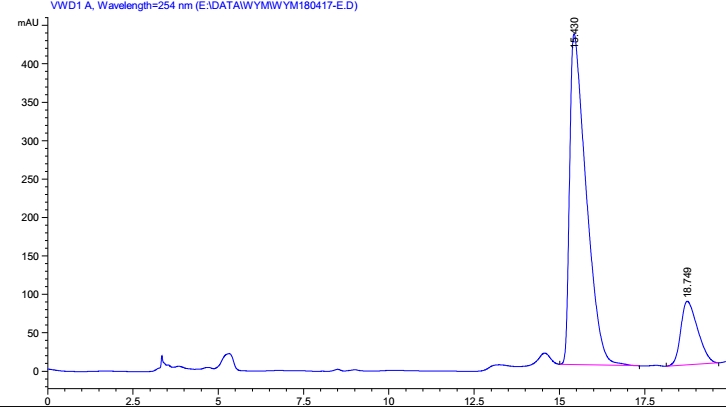


Fig 5: 1H NMR and 13C NMR spectra of **3e**







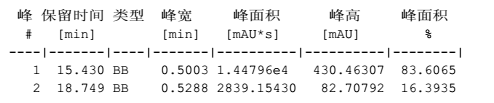
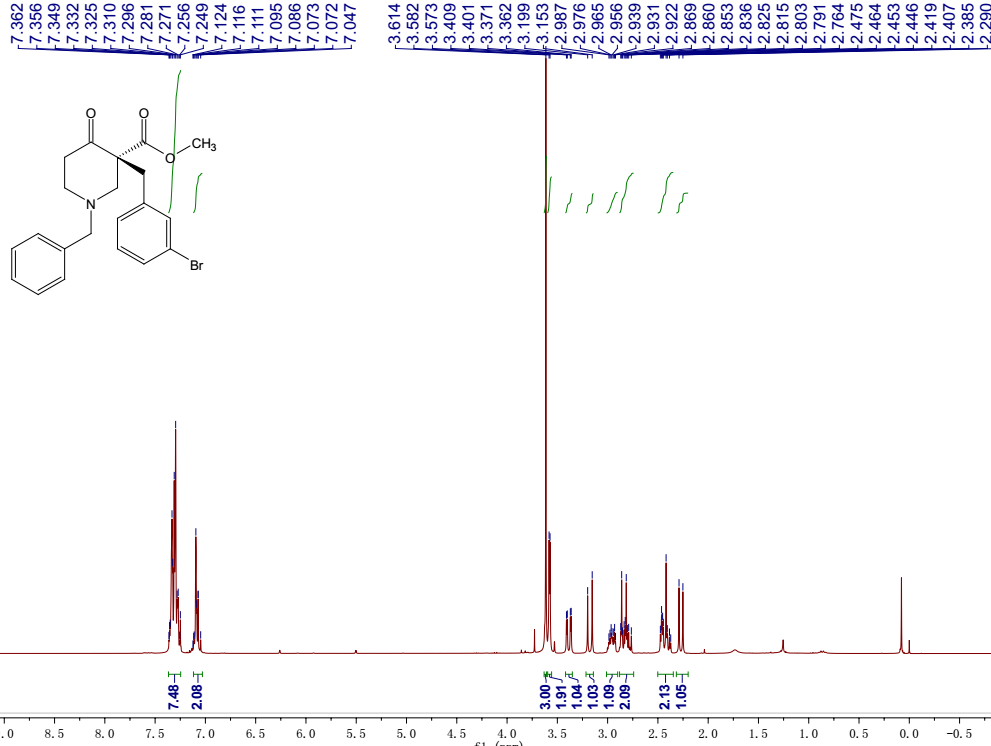


Fig 6: HPLC chromatogram of **3e** comparing to the racemic mixture



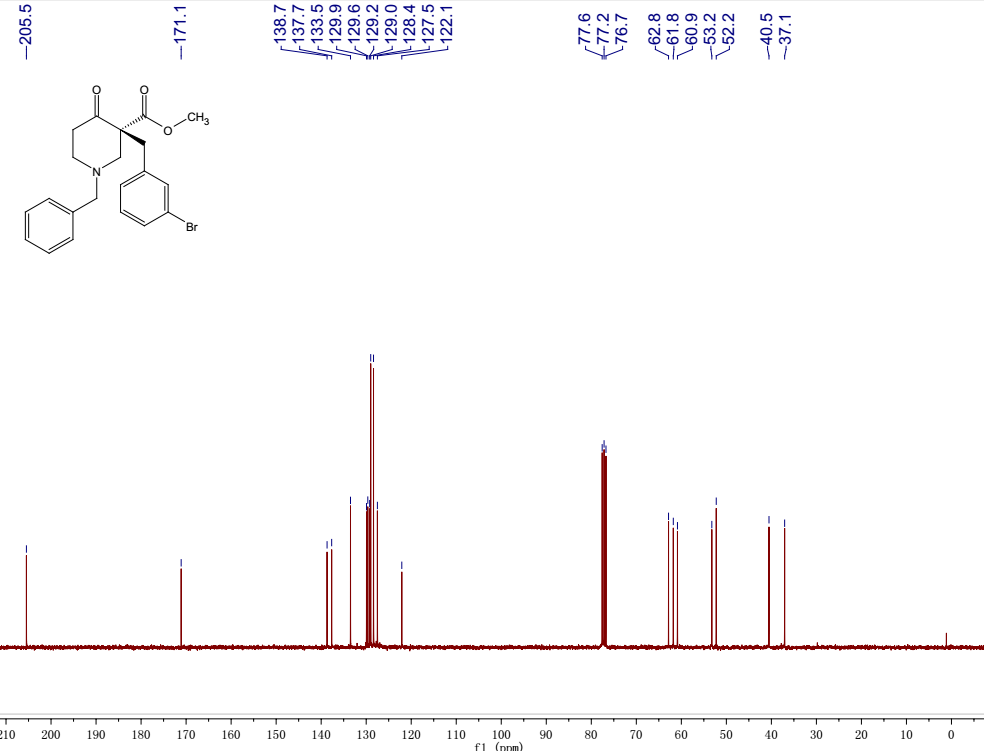
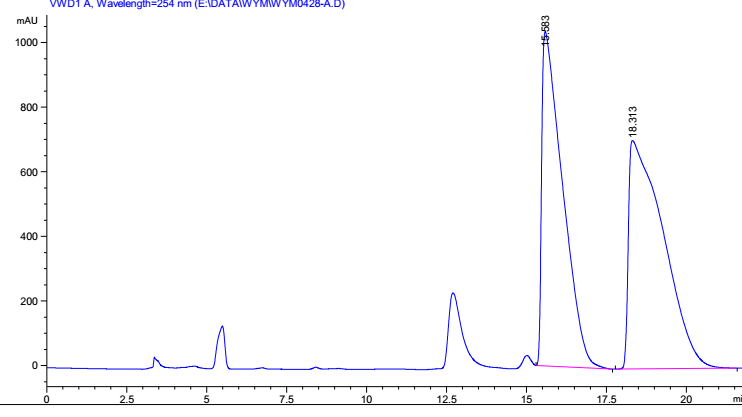
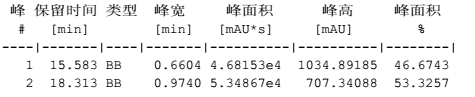
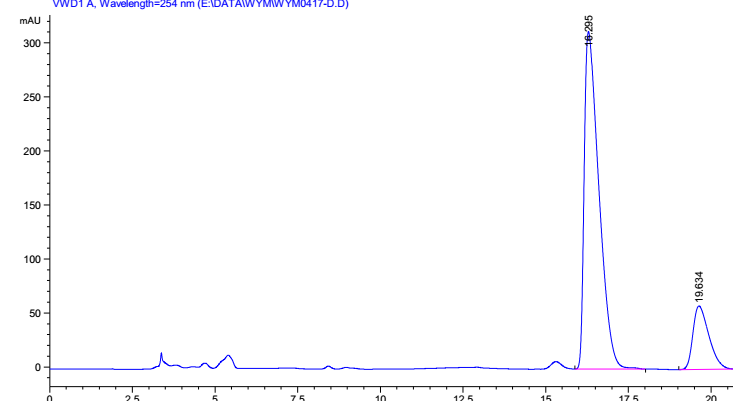


Fig 7: 1H NMR and 13C NMR spectra of **3f**







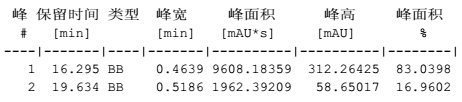
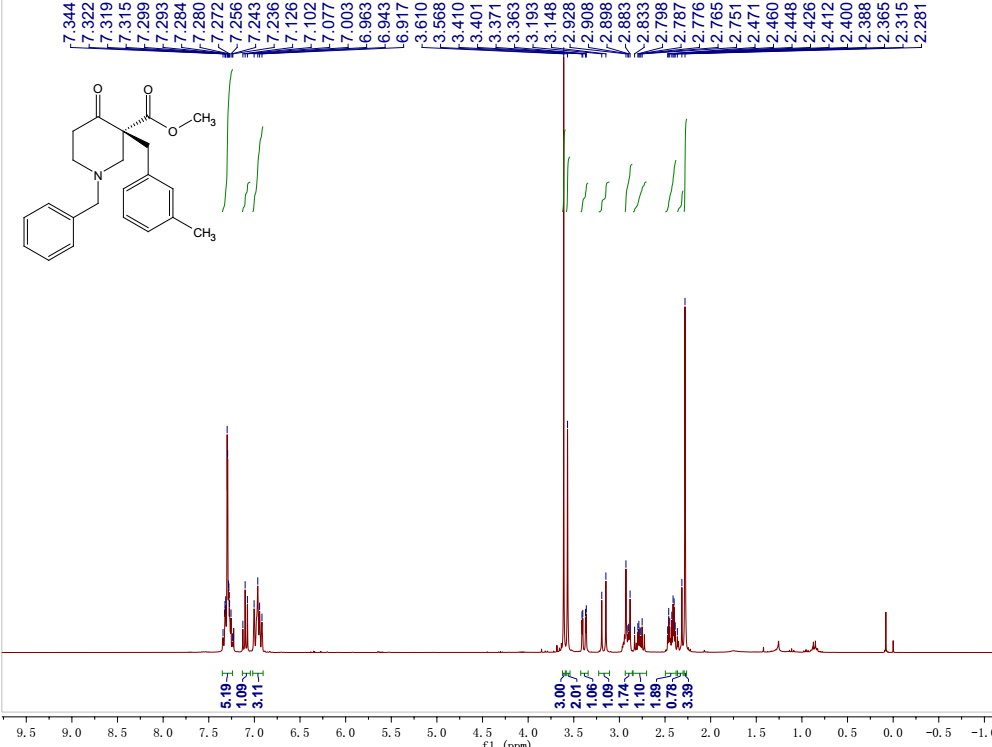


Fig 8: HPLC chromatogram of **3f** comparing to the racemic mixture



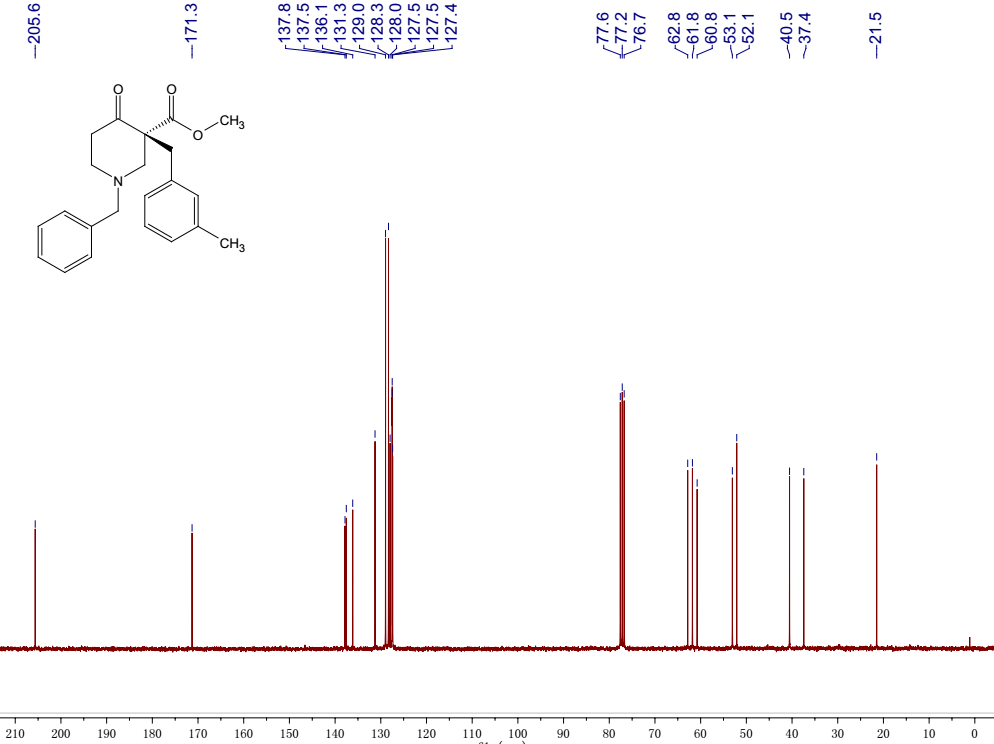
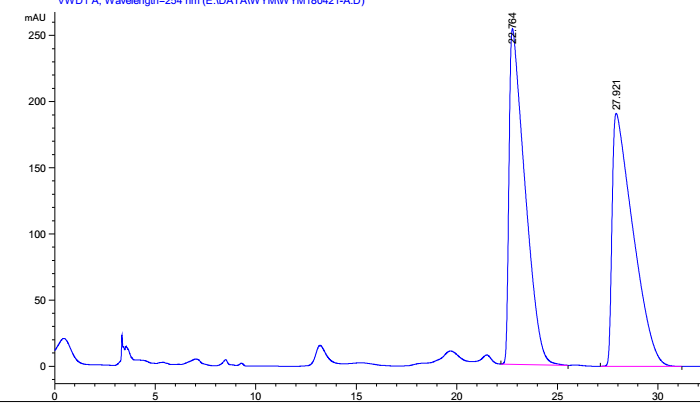
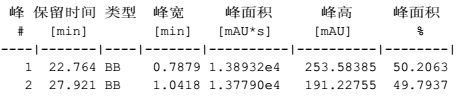
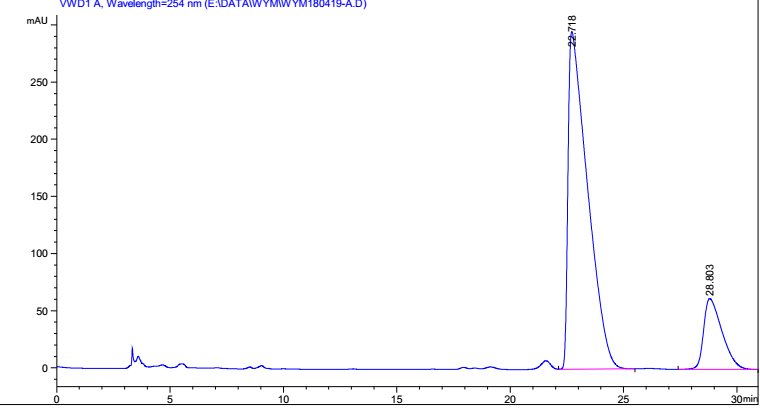


Fig 9: 1H NMR and 13C NMR spectra of **3g**







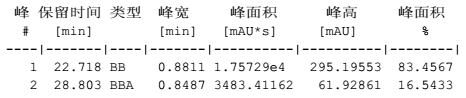
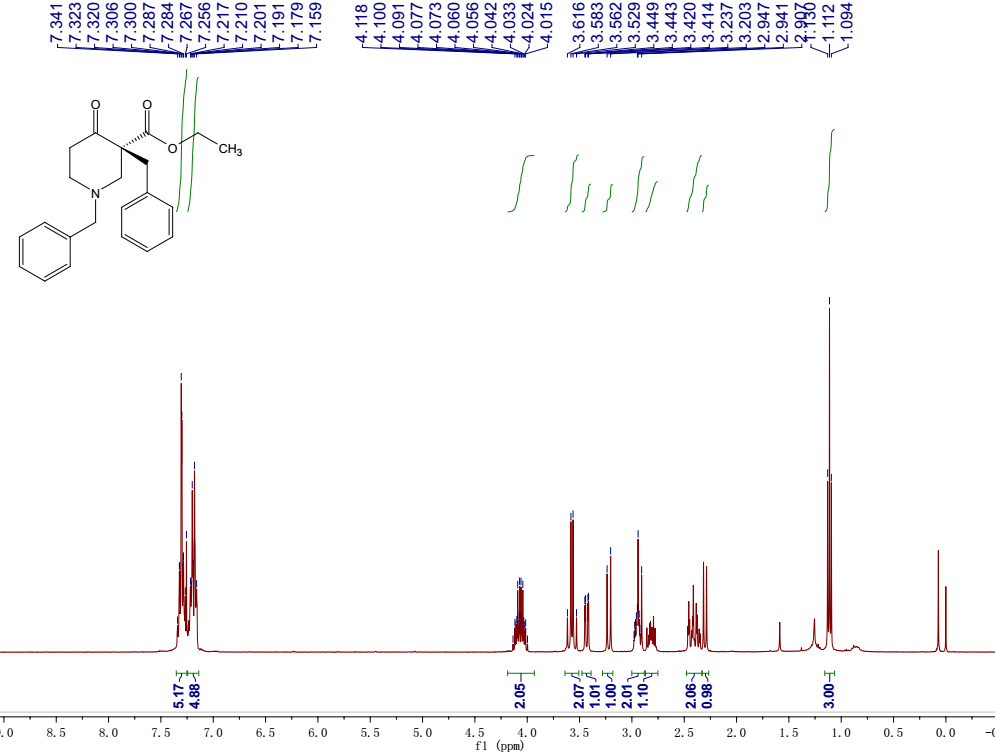


Fig 10: HPLC chromatogram of **3g** comparing to the racemic mixture



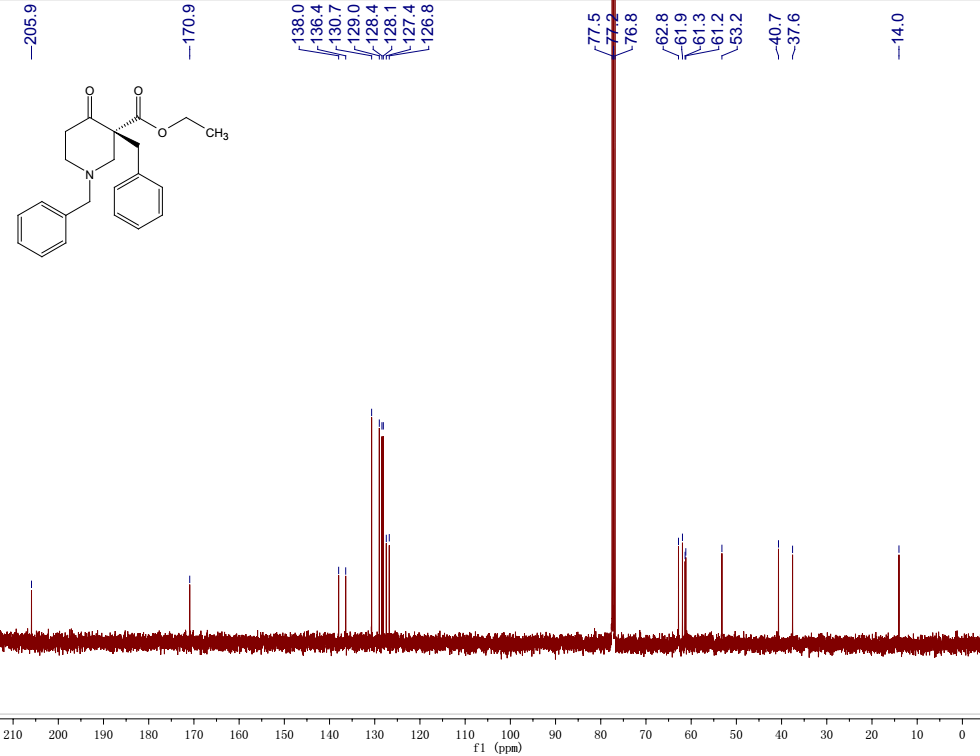
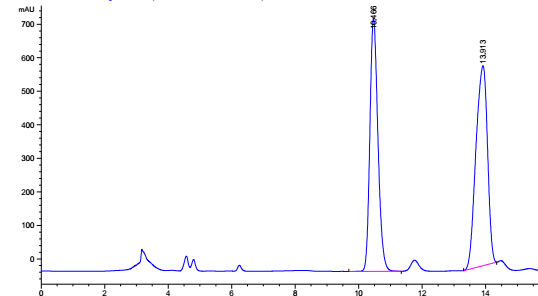
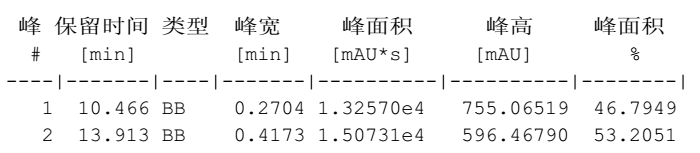
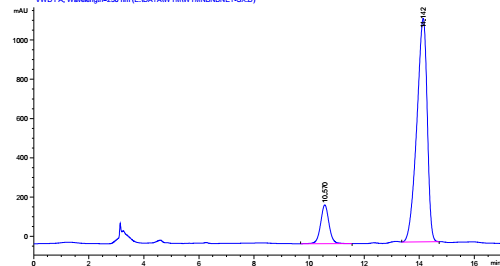


Fig 11: 1H NMR and 13C NMR spectra of **3h**







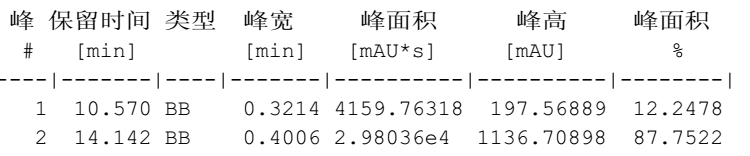
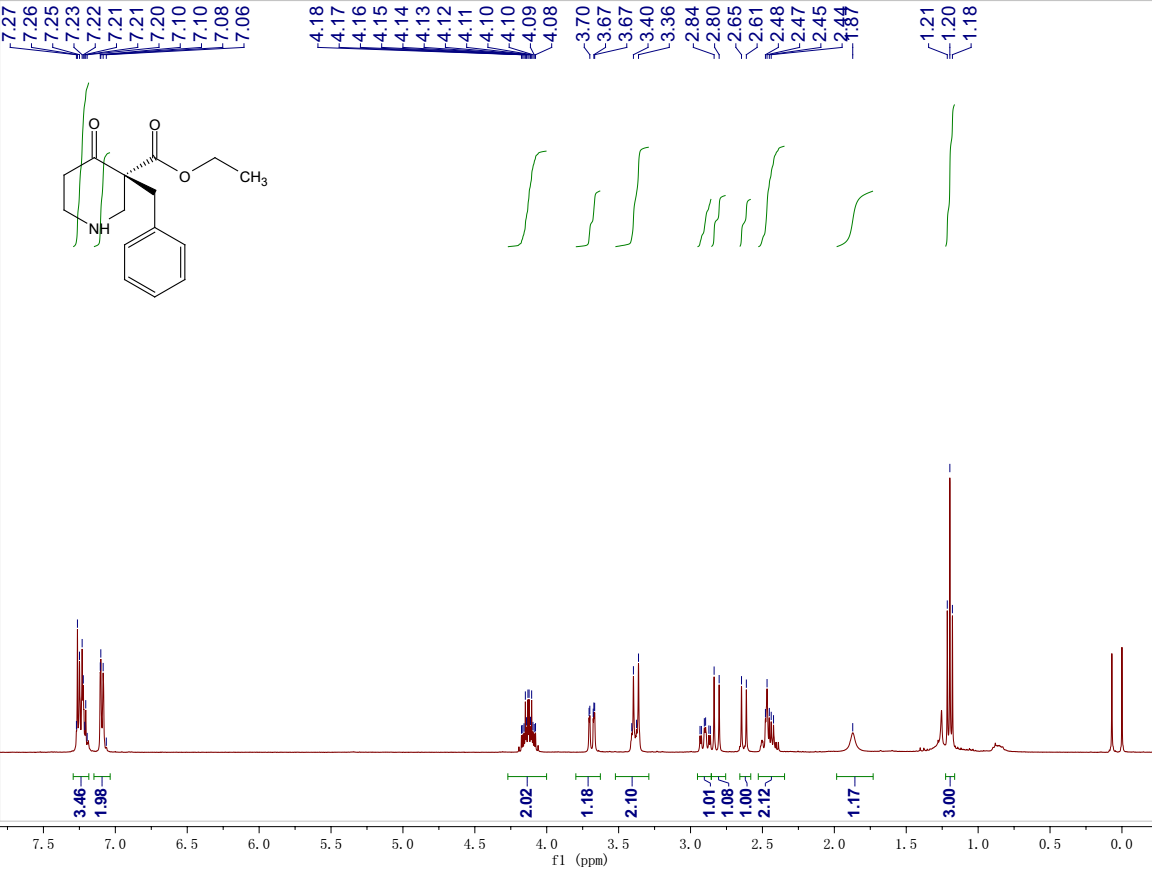


Fig 12: HPLC chromatogram of **3h** comparing to the racemic mixture



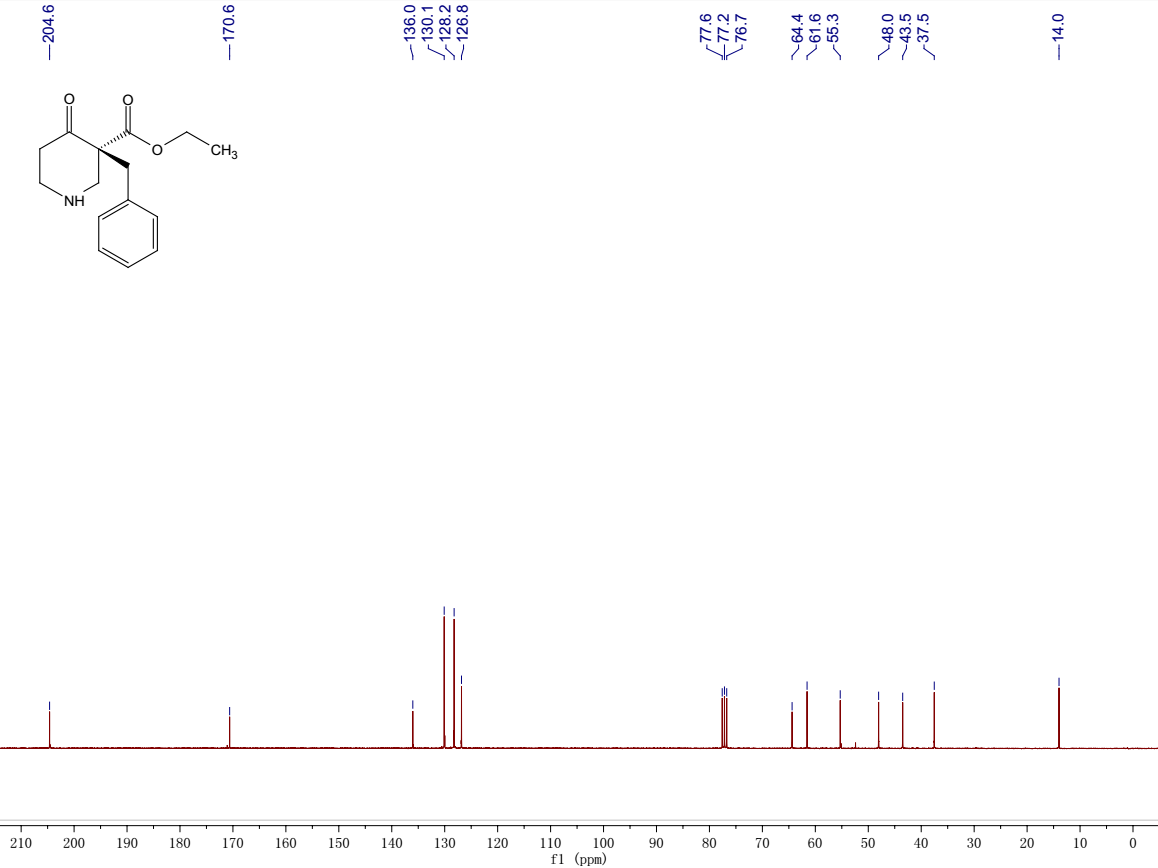
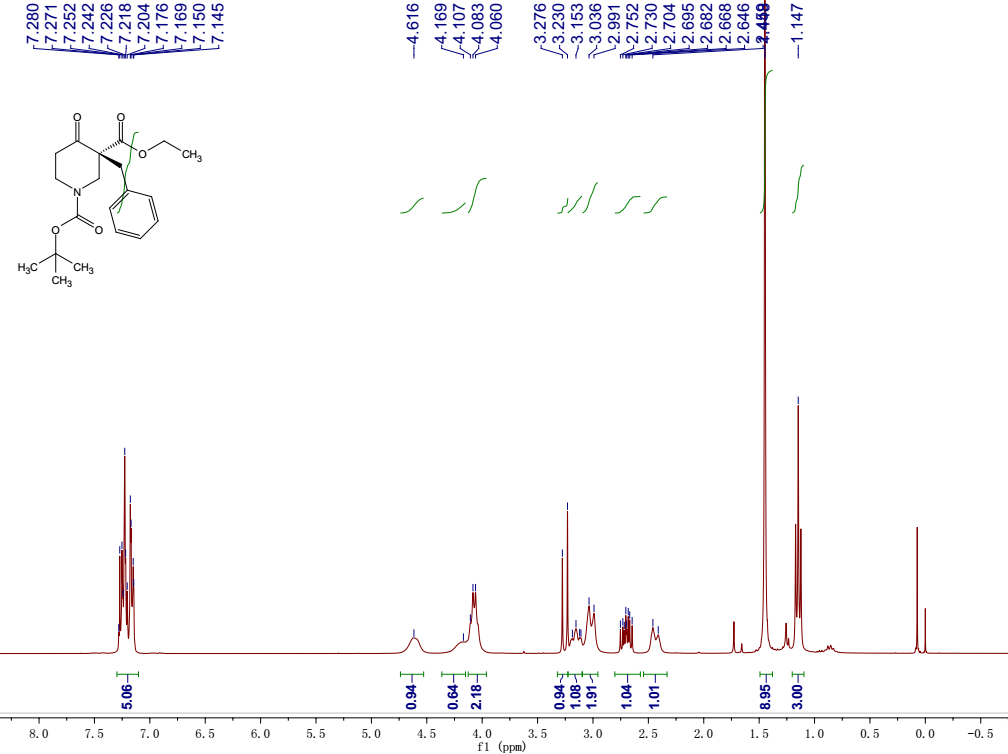


Fig 13: 1H NMR and 13C NMR spectra of **4**



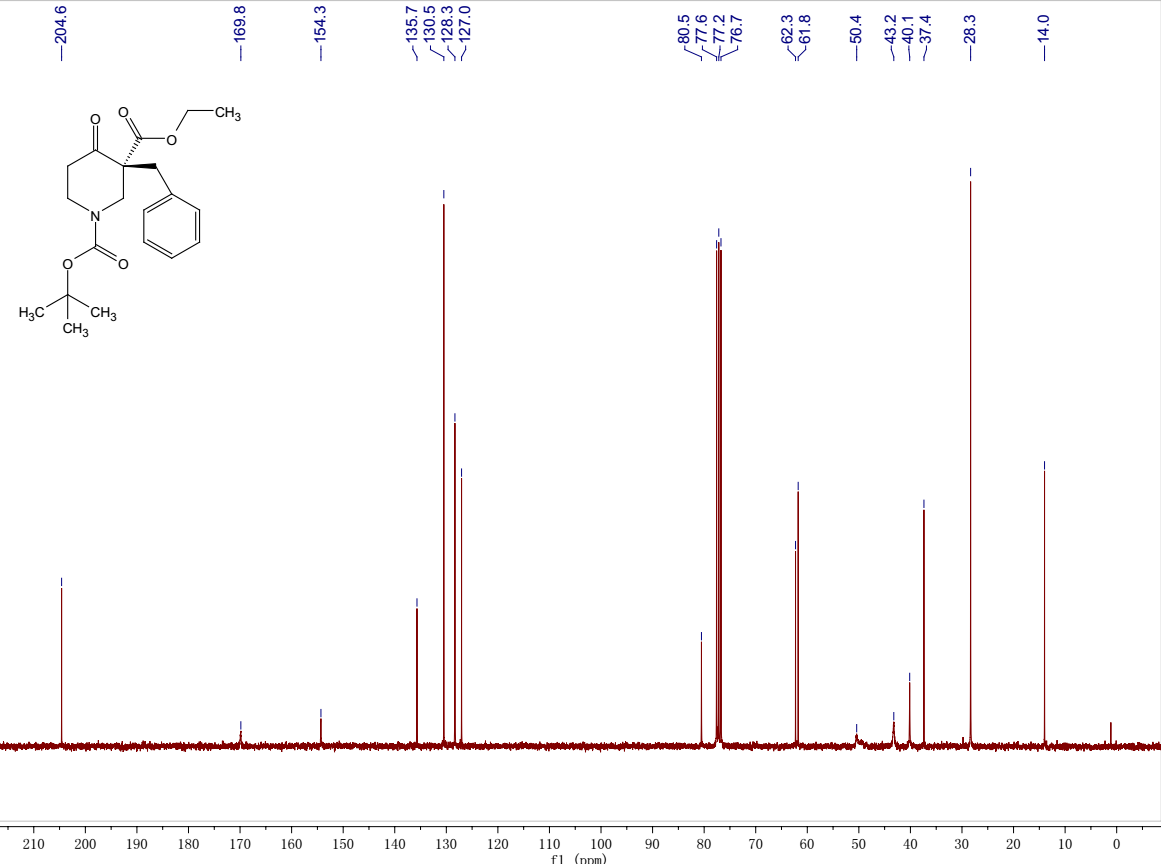
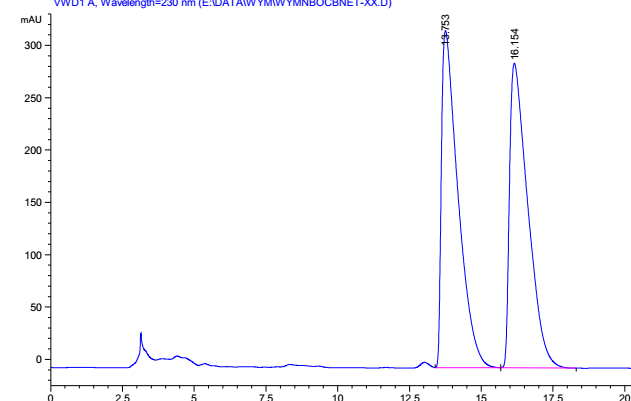
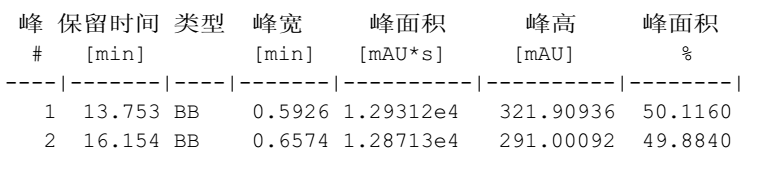
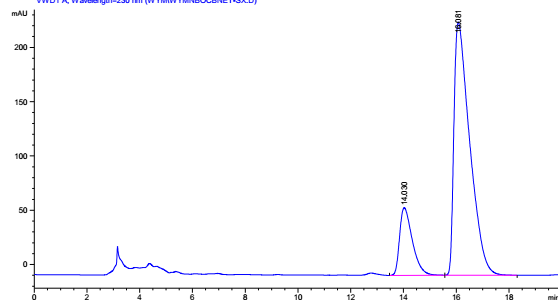


Fig 14: 1H NMR and 13C NMR spectra of **5**







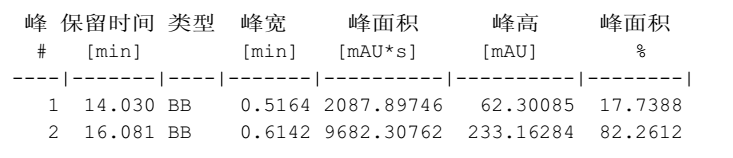
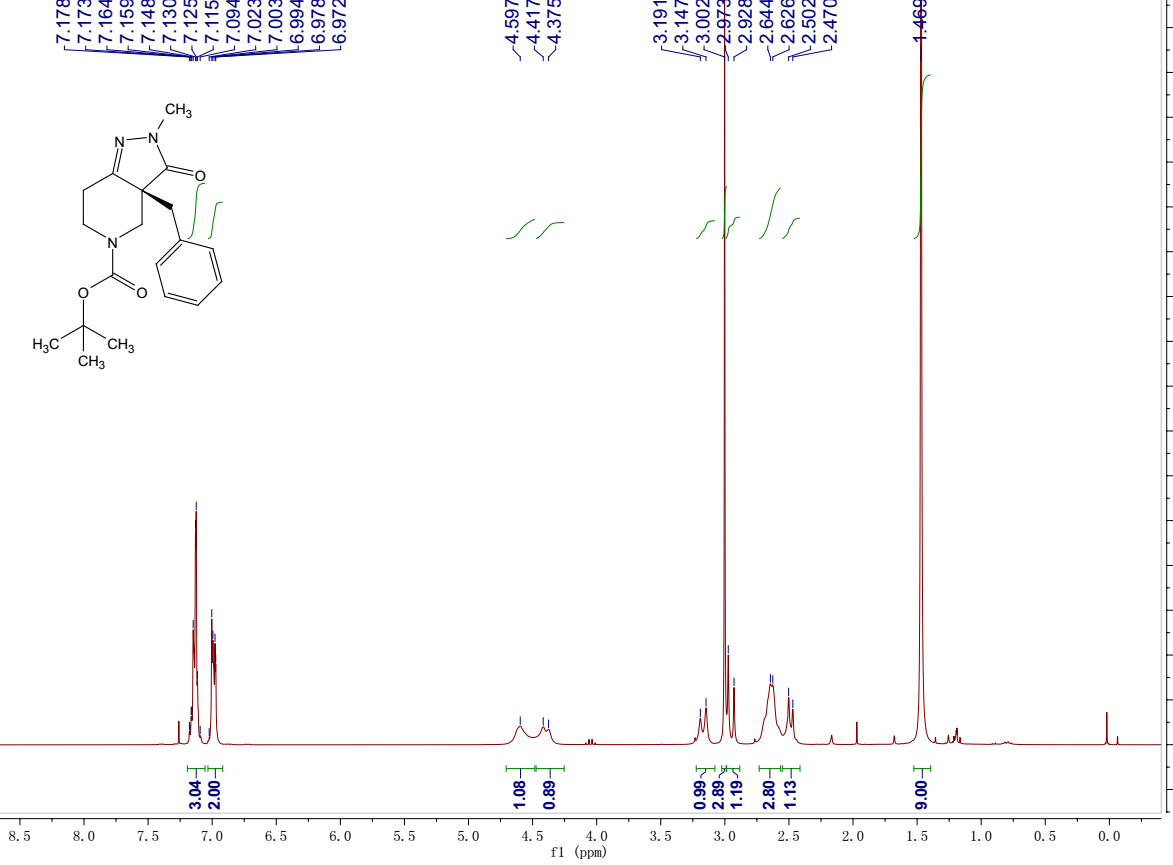


Fig 15: HPLC chromatogram of **5** comparing to the racemic mixture.



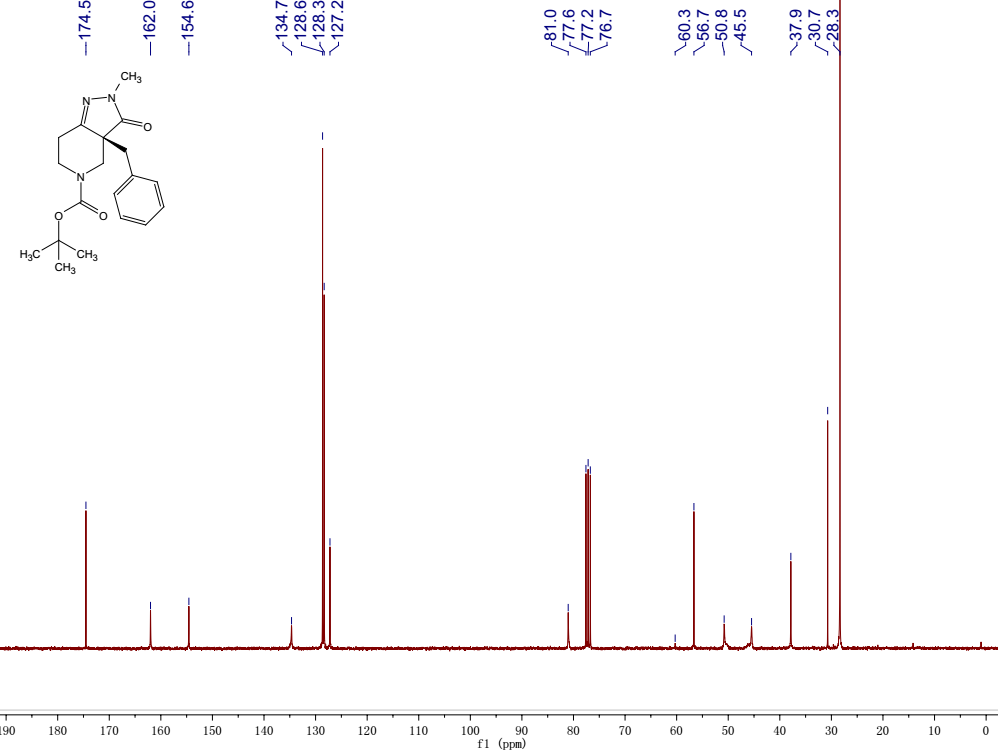
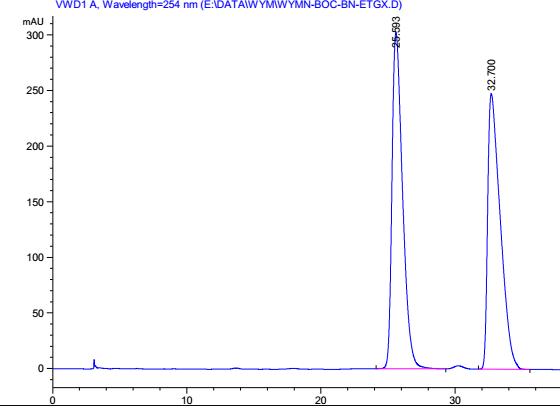
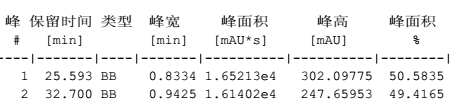
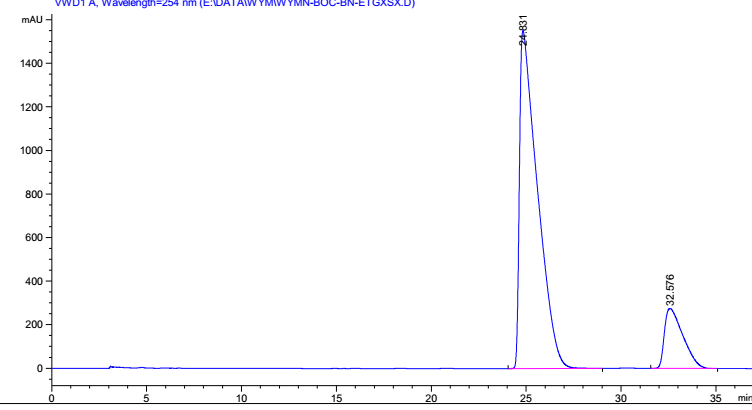


Fig.16. 1H NMR and 13C NMR spectra of **6**







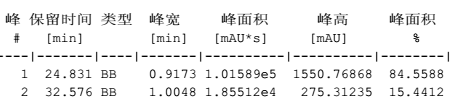


Fig 17: HPLC chromatogram of **6** comparing to the racemic mixture.