Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

A Highly Enantioselective Synthetic Method towards the α_{2c}-adrenoceptor Antagonist ORM-10921

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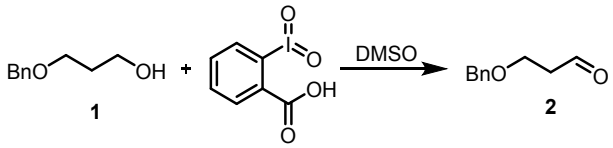
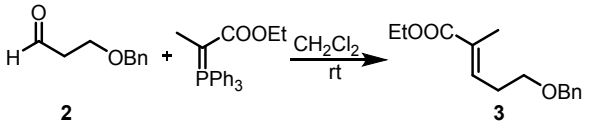
General Experimental

The chemicals and reagents were purchased from Acros, Alfa Aesar, and National Chemical Reagent Group Co. Ltd., P. R. China, and used without further purification. Anhydrous solvents (THF, MeOH, DMF, DCM, and CH_3CN) used in the reactions were dried and freshly distilled before use. Petroleum ether (PE) used had a boiling range of 60−90 °C. All the reactions were carried out under Ar atmosphere, otherwise stated else. Oxygen and/or moisture sensitive solids and liquids were transferred appropriately. Concentration of solutions in *vacuo* was accomplished using a rotary evaporator fitted with a water aspirator. Residual solvents were removed under high vacuum (0.1 - 0.2 mm Hg). The progress of the reactions was monitored by TLC (silica-coated glass plates) and visualized under UV light, and by using iodine, ceric ammonium molybdate stain or phosphomolybdic acid. Melting points were measured on a SGW X-4 microscopy melting point apparatus without correction. ^{1}H NMR and ^{13}C NMR spectra were recorded either on a 400 MHz Varian Instrument at 25 °C or 600 MHz Bruke Instrument at 25 °C, using TMS as an internal standard, respectively. Multiplicity is tabulated as s for singlet, d for doublet, dd for doublet of doublet, t for triplet, and m for multiplet. Coupling constants (J) are reported in Hertz. ^{13}C NMR spectra were completely hetero-decoupled and measured at 150 MHz. HRMS spectra were recorded on Finnigan- Mat-95 mass spectrometer, equipped with ESI source. Single crystal X-ray diffraction measurements were performed with a diffractometer working with graphite-monochromated Cu Kα radiation.

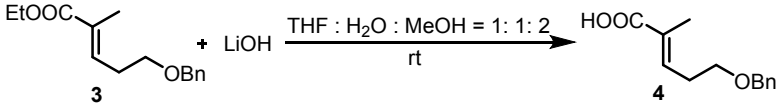
Experimental Procedures



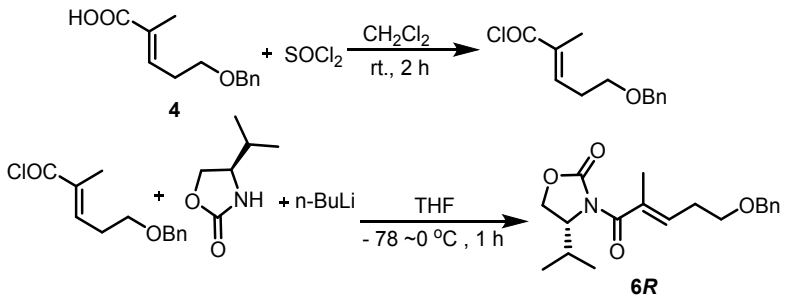
3-Benzyloxy-1-propionaldehyde (2). IBX (25.3 g, 90 mmol) was added to a solution of 3-benzyl-1-propyl alcohol (**1**, 10.0 g, 60 mmol) in DMSO (240 mL) at room temperature. After 9 h, Celite pad filtration followed dilute the filtrate with ethyl acetate (500 mL), and the organic phase was washed with H_2O (100 mL × 4), brine (100 mL), dried (Na_2SO_4), filtrated and concentrated. Purification by flash chromatography (7% ethyl acetate in petroleum ether) gave aldehyde **2** (9.00 g, 91%) as pale yellow oil. Its spectra data corresponds to those reported in the literature[1]. **TLC**: R_f = 0.25 (silica gel, 7% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.82 (t, *J* = 1.8 Hz, 1H), 7.30–7.40 (m, 5H), 4.56 (s, 2H), 3.84 (t, *J* = 6.1 Hz, 2H), 2.71 (dt, *J* = 6.1, 1.8 Hz, 2H), **ESI-MS** (*m*/*z*) 187.1 $[M+Na]^+$.



Ethyl (E)-5-(Benzyloxy)-2-methyl-2-pentenoate (3). (ethoxycarbonylethylidene) triphenyl phosphorane (16.0 g, 44 mmol) was added to a solution of the aldehyde **1** (6.00 g, 36 mmol) in CH_2Cl_2 (350 mL) at rt.. The mixture was stirred for 9 h, and then concentrated. Purification by flash chromatography (2.0% ethyl acetate in petroleum ether) gave the ester **3** (8.3 g, 91%)as colorless oil. The spectra data was consistent well with those reported in the literature[2a-b]. **TLC**: R_f = 0.25 (silica gel, 3.3% ethyl acetate in petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 – 7.25 (m, 5H), 6.78 (m, 1H), 4.53 (s, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.57 (t, *J* = 6.8 Hz, 2H), 2.49 (m, 2H), 1.85 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H). **ESI-MS** (*m*/*z*) 249.2 $[M+H]^+$.

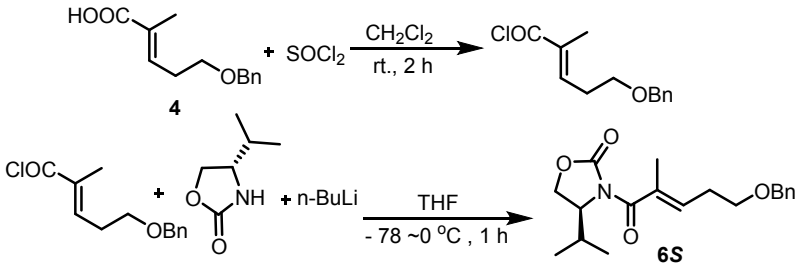


(E)-5-(benzyloxy)-2-methylpent-2-enoic acid (4). A solution of the ester **3** (10.0 g, 40 mmol) and 2.0 M LiOH (73 mL, 145 mmol) in THF/H_2O/MeOH (1/1/2) (125 mL) was stirred at rt for overnight. The mixture was acidified the pH to 2 ~ 3 with 2.0 M HCl aqueous solution at 0 ℃ and extracted with CH_2Cl_2 (250 mL × 3). And the organic phase was washed with H_2O (250 mL), brine (250 mL), dried (Na_2SO_4), filtrated and concentrated. Purification by flash chromatography (7.0% ethyl acetate in dichlormethane) gave the acid **4** (8.4 g, 95%) as colorless oil. **TLC**: R_f= 0.37 (silica gel, 10% ethyl acetate in dichlormethane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 – 7.20 (m, 5H), 6.95 (t, *J* = 7.2 Hz, 1H), 4.53 (s, 2H), 3.58 (t, *J* = 6.4 Hz, 2H), 2.52(m, 2H), 1.86 (s, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 172.7, 140.6, 137.5, 128.1, 127.8, 127.0, 72.4, 67.8, 29.0, 11.5. **HRMS** (*m*/*z*): calculated for $C_{13}H_{16}O_3Na^+$ $[M+Na]^+$: 243.0992, found: 243.0990.



(*R*)-3-(5-(benzyloxy)-2-methylpent-2-enoyl)-4-isopropyloxazolidin-2-one (6*R*). A mixture of $SOCl_2$ (25 mL) and the acid **4** (4.70 g, 21 mmol) was stirred under rt for 2 h. The solvent was removed under reduced pressure to give the acid chloride as pale yellow oil.

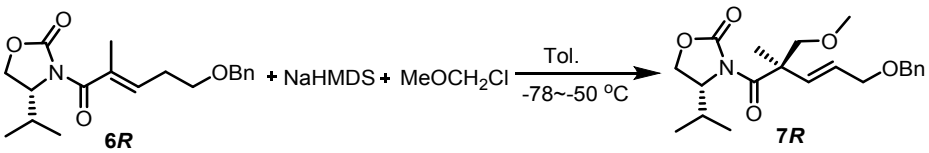
To a solution of the (R)-4-(1-methylethyl) oxazolidin-2-one (4.20 g, 32 mmol) in anhydrous THF (200 mL) at -78 °C was added 1.6 M *n*-butyllithium (14.4 mL, 23 mmol). After 30 min, the acid chloride solution (THF, 50 mL) was added. The mixture was stirred at -78 °C for 30 min and then at 0 °C for 15 min. The reaction was quenched with a saturated aqueous ammonium chloride aqueous solution (20 mL), and the resultant slurry is concentrated *in vacuo*. The residue was diluted with water (20 mL) and extracted with ethyl acetate (50 mL × 4). The organic phase was washed with the saturated $NaHCO_3$ solution (50 mL), brine (50 mL), dried (Na_2SO_4), filtrated and concentrated. Purification by flash chromatography (20% ethyl acetate in petroleum ether) gave **6*R*** (5.70 g, 83%) as colorless oil. **TLC**: R_f = 0.20 (silica gel, 20% ethyl acetate in petroleum ether); $[\alpha]_D^{20}$ = -49.5 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.26 (m, 5H), 6.11 (m, 1H), 4.52 (s, 2H), 4.52 – 4.48 (m, 1H), 4.31 (m, 1H), 4.17 (dd, *J* = 8.8 Hz, 5.2 Hz, 1H), 3.58 (t, *J* = 6.8 Hz, 2H), 2.52 (m, 2H), 2.36 (m, 1H), 1.92 (s, 3H), 0.92 – 0.89 (m, 6H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 171.6, 153.5, 138.2, 135.1, 132.3, 128.3, 127.5, 72.9, 68.5, 63.3, 58.2, 29.0, 28.2, 17.8, 15.0, 13.7. **HRMS** (*m*/*z*): calculated for $C_{19}H_{25}NO_4Na^+$ $[M+Na]^+$: 354.1676, found: 354.1664.



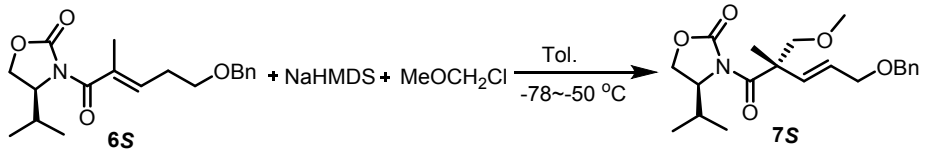
(*S*)-3-(5-(benzyloxy)-2-methylpent-2-enoyl)-4-isopropyloxazolidin-2-one (6*S*). A mixture of $SOCl_2$ (25 mL) and the acid **4** (2.00 g, 9.1 mmol) was stirred under rt for 2 h. The solvent was removed under reduced pressure to give the acid chloride as a pale yellow oil.

To a solution of the (S)-4-(1-methylethyl) oxazolidin-2-one (1.70 g, 13 mmol) in anhydrous THF (130 mL) at -78 °C is added 2.4 M *n*-butyllithium (5.70 mL, 13 mmol). After 30 min, the acid chloride solution (THF, 20 mL) was added. The mixture was stirred at -78 °C for 30 min and then at 0 °C for 15 min. The reaction was quenched with a saturated aqueous ammonium chloride solution (10 mL), and the resultant slurry was concentrated *in vacuo*. The residue was diluted with water (10 mL) and extracted with ethyl acetate (20 mL × 4). The organic phase was washed with a saturated $NaHCO_3$ solution (20 mL), brine (20 mL), dried (Na_2SO_4), filtrated and concentrated. Purification by flash chromatography (20% ethyl acetate in

petroleum ether) gave **6*S*** (2.0 g, 70%) as colorless oil. **TLC**: R_f = 0.32 (silica gel, 25% ethyl acetate in petroleum ether); $[\alpha]_D^{20}$ = 45.9 (*c* 0.80, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34 – 7.26 (m, 5H), 6.11 (m, 1H), 4.52 (s, 2H), 4.52 – 4.48 (m, 1H), 4.31 (m, 1H), 4.17 (dd, *J* = 8.8, 5.2 Hz, 1H), 3.58 (t, *J* = 6.8 Hz, 2H), 2.52 (m, 2H), 2.36 (m, 1H), 1.92 (s, 3H), 0.92 – 0.89 (m, 6H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 171.0, 153.0, 137.7, 134.6, 131.8, 127.8, 127.0, 72.4, 68.0, 62.8 57.7, 28.4, 27.7, 17.2, 14.4, 13.2. **HRMS** (*m*/*z*): calculated for $C_{19}H_{25}NO_4Na^+$ $[M+Na]^+$: 354.1676, found: 354.1664.

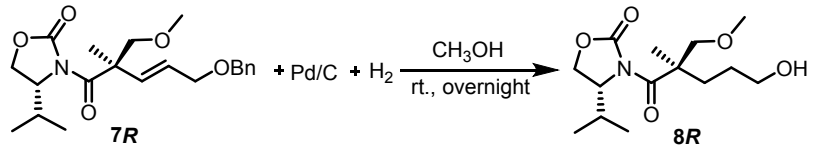


(*R*)-3-((*R*)-5-(benzyloxy)-2-(methoxymethyl)-2-methylpentanoyl)-4-isopropyloxazolidin-2-one (7*R*). To a solution of the chiral imide **6*R*** (7.70 g, 23 mmol) in toluene (250 mL) was added dropwise a solution of NaHMDS (2.0 M in THF, 23 mL, 46 mmol) at −78 °C. After stirring for 90 min at -78 °C, chloromethylmethyl ether (5.3 mL, 69 mmol) was added dropwise to the mixture, which was then stirred at -50 °C overnight. The reaction mixture was quenched with a saturated NH_4Cl solution (50 mL), and extracted with ethyl acetate (50 mL × 3). The combined organic layer was washed with brine (50 mL) and dried over Na_2SO_4. Evaporation and purification by flash column chromatography (petroleum ether/dichlormethane/ethyl acetate 10/1/1) gave **7*R*** (4.50 g, 50%) as colorless oil. **TLC**: R_f = 0.42 (silica gel, petroleum ether/dichlormethane /ethyl acetate 5/1/1); $[\alpha]_D^{20}$ = -45.9 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, CDCl3) δ 7.36 – 7.25 (m, 5H), 6.06 (d, *J* = 16.0 Hz, 1H), 5.54 (dt, *J* = 16.0, 6.0 Hz, 1H), 4.52 – 4.47 (m, 1H), 4.47 (s, 2H), 4.25 – 4.15 (m, 3H), 4.00 (d, *J* = 6.0 Hz, 2H), 3.43 (d, *J* = 8.8 Hz, 1H), 3.33 (s, 3H), 2.35 (m, 1H), 1.49 (s, 3H), 0.89 (d, *J* = 6.8 Hz, 2H), 8.86 (d, *J* = 6.8 Hz, 2H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 173.0, 152.0, 137.7, 134.0, 127.7, 127.2, 126.9, 125.5, 77.0, 71.1, 69.9, 62.5, 59.3, 58.6, 50.7, 27.6, 22.2, 17.4, 13.9. **HRMS** (*m*/*z*): calculated for $C_{21}H_{29}NO_5Na^+$ $[M+Na]^+$: 398.1938, found: 398.1940.

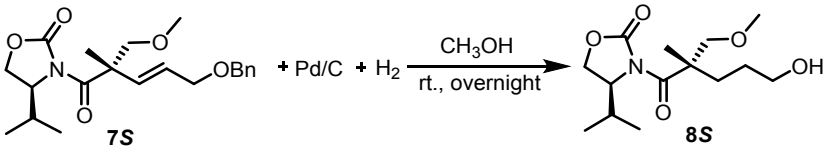


(*S*)-3-((*S*)-5-(benzyloxy)-2-(methoxymethyl)-2-methylpentanoyl)-4-isopropyloxazolidin-2-one (7*S*). To a solution of the chiral imide **6*S*** (2.00 g, 6.0 mmol) in toluene (60 mL) was added dropwise a solution of NaHMDS (2.0 M in THF, 6.3 mL, 12 mmol) at −78 °C. After stirring for 90 min at −78 °C, chloromethylmethyl ether (1.40 mL, 18 mmol) was added dropwise to the mixture, which was then stirred at -50°C for overnight. The reaction mixture was quenched with a saturated NH_4Cl solution (20 mL), and extracted with ethyl acetate (20 mL × 3). The combined organic layer was washed with brine (20 mL) and dried over Na_2SO_4. Evaporation and purification by flash column chromatography (petroleum ether/dichlormethane/ethyl acetate 10/1/1) gave **7*S*** (1.00 g, 45%) as colorless oil. **TLC**: R_f = 0.44 (silica gel, petroleum ether/dichlormethane/ethyl acetate 5/1/1); $[\alpha]_D^{20}$ = 49.7 (*c* 0.6, $CHCl_3$); **^{1}H NMR** (400 MHz, CDCl3) δ 7.36 – 7.23 (m, 5H), 6.06 (d, *J* = 16.0 Hz, 1H), 5.54 (dt, *J* = 16.0, 6.0 Hz, 1H), 4.52 – 4.47 (m, 1H), 4.47 (s, 2H), 4.25 – 4.15 (m, 3H), 4.00 (d, *J* = 6.0 Hz, 2H), 3.43 (d, *J* = 8.8 Hz, 1H), 3.33 (s, 3H), 2.35 (m, 1H), 1.49 (s, 3H), 0.89 (d, *J* = 6.8

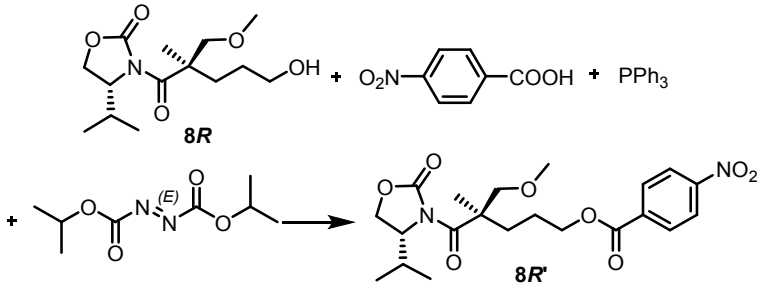
Hz, 2H), 8.86 (d, J = 6.8 Hz, 2H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 173.0, 152.0, 137.7, 134.0, 127.7, 127.2, 126.9, 125.5, 77.0, 71.1, 69.9, 62.5, 59.3, 58.6, 50.7, 27.6, 22.2, 17.4, 13.9. **HRMS** (*m*/*z*): calculated for $C_{21}H_{29}NO_5Na^+$ $[M+Na]^+$: 398.1938, found: 398.1925.



(*R*)-3-((*R*)-5-hydroxy-2-(methoxymethyl)-2-methylpentanoyl)-4-isopropyloxazolidin-2-one (8*R*). Compound **7*R*** (5.0 g, 13 mmol) was hydrogenated over 2.50 g of 10% Pd/C in 80 mL of MeOH at rt for overnight. Then the catalyst was removed by filtration, the filtrate was evaporated under reduced pressure, and the residue was dried *in vacuo*, giving **8*R*** as colorless oil. The crude product could be used in the next step without further purification. **TLC**: R_f = 0.30 (silica gel, 50% ethyl acetate in petroleum ether); **$[\alpha]_D^{20}$** = -40.5 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.54 (m, 1H), 4.28 (m, 1H), 4.19 (m, 1H), 3.99 (d, J = 9.2Hz, 1H), 3.61 (t, J = 6.4 Hz, 2H), 3.50 (d, J = 9.0 Hz, 1H), 3.31 (s, 3H), 2.31 (m, 1H), 2.11 (m, 1H), 1.78 – 1.70 (m, 2H), 1.67 (m, 1H), 1.45 (m, 1H), 1.38 (s, 3H), 0.91 – 0.88 (m, 6H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 174.7, 152.5, 76.1, 62.7, 62.3, 59.8, 58.4, 49.5, 29.5, 27.6, 27.1, 20.4, 17.4, 13.8. **HRMS** (*m*/*z*): calculated for $C_{14}H_{25}NO_5Na^+$ $[M+Na]^+$: 310.1625, found: 310.1610.

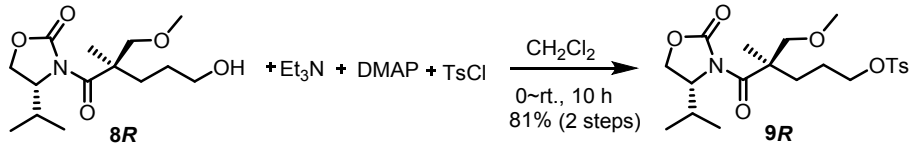


(*S*)-3-(*S*)-5-hydroxy-2-(methoxymethyl)-2-methylpentanoyl)-4-isopropyloxazolidin-2-one (8*S*). Compound **7*S*** (1.00 g, 2.6 mmol) was hydrogenated over 0.500 g of 10% Pd/C in 25 mL of MeOH at rt for overnight. After the catalyst was removed by filtration, the filtrate was evaporated under reduced pressure, and the residue was dried *in vacuo*, giving **8*S*** as colorless oil. The crude product could be used in the next step. **TLC**: R_f = 0.30 (silica gel, 50% ethyl acetate in petroleum ether); **$[\alpha]_D^{20}$** = -28.5 (*c* 0.6, $CHCl_3$); **^{1}H NMR** (400 MHz, CDCl3) δ 4.54 (m, 1H), 4.28 (m, 1H), 4.19 (m, 1H), 3.99 (d, J = 9.2Hz, 1H), 3.61 (t, J = 6.4 Hz, 2H), 3.50 (d, J = 9.0 Hz, 1H), 3.31 (s, 3H), 2.31 (m, 1H), 2.11 (m, 1H), 1.78 – 1.70 (m, 2H), 1.67 (m, 1H), 1.45 (m, 1H), 1.38 (s, 3H), 0.91 – 0.88 (m, 6H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 174.7, 152.5, 76.1, 62.7, 62.3, 59.8, 58.4, 49.5, 29.5, 27.6, 27.1, 20.4, 17.4, 13.8. **HRMS** (m/z): calculated for $C_{14}H_{25}NO_5Na^+$ $[M+Na]^+$: 310.1625, found: 310.1614.

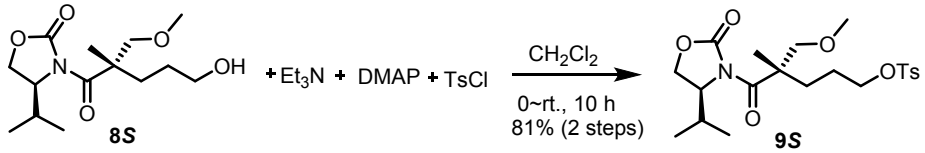


(*R*)-5-((*R*)-4-isopropyl-2-oxooxazolidin-3-yl)-4-(methoxymethyl)-4-methyl-5-oxo-pentyl 4-nitrobenzoate (8*R*'). To a stirred mixture of alcohol **8*R*** (382 mg, 1.3 mmol), *p*-nitrobenzoic acid (223mg, 1.3 mmol) and PPh_3 (367 mg, 1.4 mmol) in the THF (15 ml) was

added dropwise DIAD (0.30 mL, 1.5 mmol) at 0 °C. After addition, the resulting mixture was warmed up to rt. Once the reaction finished by monitoring the progress of reaction with TLC, the organic solvent was evaporated, and the residue was purified by column chromatography (petroleum ether/dichlormethane/ethyl acetate 7/1/1), giving **8*R'*** (464 mg, 80% into two steps) as white solid. **TLC**: R_f = 0.40 (silica gel, petroleum ether/dichlormethane /ethyl acetate 5/1/1); $[\alpha]_D^{20}$ = -36.5 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.31 – 8.29 (m, 2H), 8.23 – 8.21 (m, 2H), 4.55 (m, 1H), 4.35 (m, 2H), 4.28 (m, 1H), 4.20 (dd, *J* = 9.2, 3.2 Hz, 1H), 3.97 (d, *J* = 8.8 Hz, 1H), 3.55 (d, *J* =8.8Hz, 1H), 3.32 (s, 3H), 2.36 – 2.20 (m, 2H), 1.89 (m, 1H), 1.77 (m, 2H), 1.42 (s, 3H), 0.91 – 0.88 (m, 6H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 175.1, 164.6, 153.1, 150.5, 135.7, 130.7, 123.5, 76.5, 65.9, 63.3, 60.4, 59.0, 50.1, 30.3, 28.2, 23.9, 21.0, 18.0, 14.4. **HRMS** (*m*/*z*): calculated for $C_{21}H_{28}N_2O_8Na^+$ $[M+Na]^+$: 459.1738, found: 459.1740.

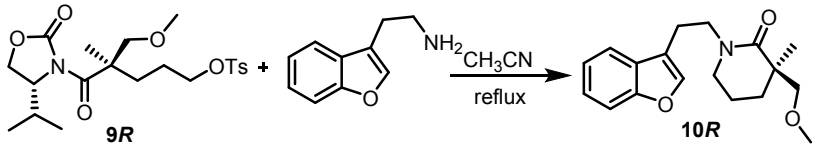


(*R*)-5-((*R*)-4-isopropyl-2-oxooxazolidin-3-yl)-4-(methoxymethyl)-4-methyl-5-oxo-pentyl 4-methylbenzenesulfonate (9*R*). To a solution of alcohol **8*R*** (648 mg, 2.3 mmol), triethylamine (1.0 mL, 6.8 mmol) and DMAP (280 mg, 0.23 mmol) in anhydrous CH_2Cl_2 (25 mL) was added tosyl chloride (860 mg, 14.5 mmol) at 0 °C in one portion and stirred for 10 min at this temperature. Then, the mixture was allowed to reach 25 °C and continued to stir until consumption of **8*R*** by checking the reaction progress with TLC. The mixture was then poured into a flask containing 20 mL of a saturated NH_4Cl solution and the aqueous phase was extracted with EtOAc (25 mL × 3). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4. Evaporation and purification by column chromatography (25% ethyl acetate in petroleum ether) gave **9*R*** (802 mg, 81% into two steps) as colorless oil. **TLC**: R_f = 0.20 (silica gel, 30% ethyl acetate in petroleum ether); $[\alpha]_D^{20}$ = -32,7 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 4.51 (m, 1H), 4.29 (m, 1H), 4.18 (dd, *J* = 9.2, 3.2 Hz, 1H), 3.99 (m, 2H), 3.87 (d, *J* = 9.0 Hz, 1H), 3.51 (d, *J* = 9.0 Hz, 1H), 3.27 (s, 3H), 2.45 (s, 3H), 2.27 (m, 1H), 2.04 (m, 1H), 1.69 – 1.53 (m, 3H), 1.32 (s, 3H), 0.90-0.86 (m, 6H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 174.9, 153.1, 144.7, 133.1, 129.8, 127.9, 76.4, 70.6, 63.4, 60.4, 59.0, 50.0, 30.2, 28.3, 24.3, 21.6, 20.8, 18.0, 14.5. **HRMS** (*m*/*z*): calculated for $C_{21}H_{31}NO_7SNa^+$ $[M+Na]^+$: 464.1713, found: 464.1702.

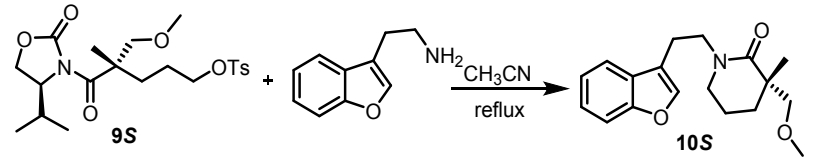


(*S*)-5-((*S*)-4-isopropyl-2-oxooxazolidin-3-yl)-4-(methoxymethyl)-4-methyl-5-oxo-pentyl-4-methylbenzenesulfonate (9*S*). To a solution of alcohol **8*S*** (765 mg, 2.6 mmol), triethylamine (1.10 mL, 7.8 mmol) and DMAP (32 mg, 0.26 mmol) in anhydrous CH_2Cl_2 (25 mL) was added tosyl chloride (977 mg, 5.12 mmol) at 0 °C in one portion and stirred for 10 min at this temperature. Then, the mixture was allowed to reach 25 °C and continued to stir until consumption of **8*S*** by checking the reaction progress with TLC. The mixture was then poured into a flask containing 20 mL of a saturated NH_4Cl solution and the aqueous phase

was extracted with EtOAc (25 mL × 3). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4. Evaporation and purification by column chromatography (25% ethyl acetate in petroleum ether) gave **9*S*** (993 mg, 87% into two steps) as colorless oil. **TLC**: R_f = 0.20 (silica gel, 30% ethyl acetate in petroleum ether); $[\alpha]_D^{20}$ = 34.1 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 4.51 (m, 1H), 4.29 (m, 1H), 4.18 (m, 1H), 3.99 (m, 2H), 3.87 (d, *J* = 9.0 Hz, 1H), 3.51 (d, *J* = 9.0 Hz, 1H), 3.27 (s, 3H), 2.45 (s, 3H), 2.27 (m, 1H), 2.04 (m, 1H), 1.69 – 1.53 (m, 3H), 1.32 (s, 3H), 0.90-0.86 (m, 6H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 174.9, 153.1, 144.7, 133.1, 129.8, 127.9, 76.4, 70.6, 63.4, 60.4, 59.0, 50.0, 30.2, 28.3, 24.3, 21.6, 20.8, 18.0, 14.5. **HRMS** (*m*/*z*): calculated for $C_{21}H_{31}NO_7SNa^+$ $[M+Na]^+$: 464.1713, found: 464.1705.

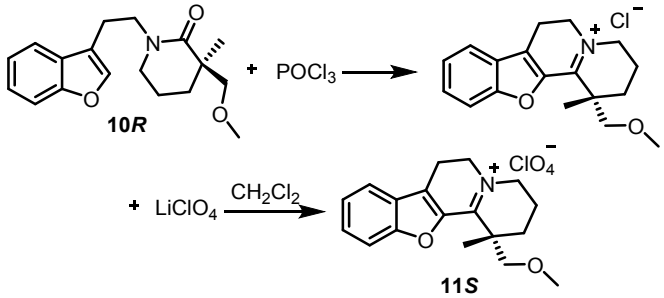


(*R*)-1-(2-(benzofuran-3-yl)ethyl)-3-(methoxymethyl)-3-methylpiperidin-2-one (10*R*). To a solution of **9*R*** (1.10 g, 2.48 mmol) in CH_3CN (3 mL) was added 2-(benzofuran-3-yl) ethanamine (0.620 g, 3.70 mmol). Then the mixture solution was refluxed for 4 h. After cooled to the rt, a solution of NaOH (1.0 M) (10 mL) and EtOAc (20 mL) containing 10% of EtOH were added to the reaction mxiture. Separation of organic phase, the aqueous phase was extracted with ethyl acetate (25 mL × 3). The combined organic phase was washed with water (20 mL), brine (20 mL) and dried over anhydrous Na_2SO_4. Evaporation and purification by column chromatography (33% ethyl acetate in petroleum ether) gave **10*R*** (0.50 g, 67%) as colorless oil. **TLC**: R_f = 0.37 (silica gel, 50% ethyl acetate in petroleum ether); $[\alpha]_D^{20}$ = 2.10 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.67 – 7.66 (m, 1H), 7.48 – 7.45 (m, 2H), 7.31 – 7.22 (m, 2H), 3.74 (d, *J* = 8.4 Hz, 1H), 3.64 (m, 2H), 3.34 (s, 3H), 3.25 (m, 1H), 3.16 – 3.11 (m, 2H), 2.95 (m, 2H), 2.08 (m, 1H), 1.75 (m, 2H), 1.50 (m, 1H), 1.14 (s, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 173.0, 154.7, 141.3, 127.5, 123.6, 121.8, 119.1, 116.8, 110.8, 79.1, 58.6, 48.7, 47.2, 42.5, 30.6, 22.4, 20.8, 19.1. **HRMS** (*m*/*z*): calculated for $C_{18}H_{24}NO_3^+$ $[M+H]^+$: 302.1751, found: 302.1752.

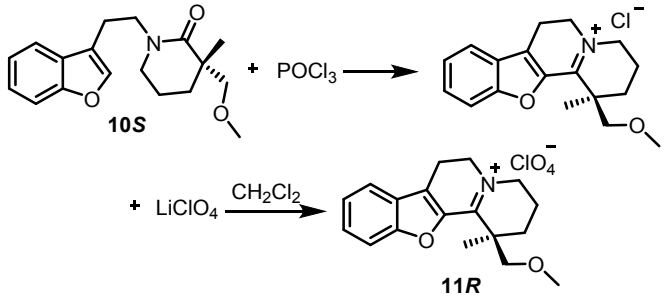


(*S*)-1-(2-(benzofuran-3-yl)ethyl)-3-(methoxymethyl)-3-methylpiperidin-2-one (10*S*). To a solution of **9*S*** (972 mg, 2.20 mmol) in CH_3CN (3 mL) was added 2-(benzofuran-3-yl)ethanamine (533 mg, 3.30 mmol). Then the mixture solution was refluxed for 4 h. After cooled to the rt, a solution of NaOH (1.0 M) (10 mL) and EtOAc (20 mL) containing 10% of EtOH were added to the reaction mxiture. Separation of organic phase, the aqueous phase was extracted with ethyl acetate (25 mL × 3). The combined organic phase was washed with water (20 mL), brine (20 mL) and dried over anhydrous Na_2SO_4. Evaporation and purification by column chromatography (33% ethyl acetate in petroleum ether) gave **10*S*** (470 mg, 71%) as a colorless oil. **TLC**: R_f = 0.37 (silica gel, 50% ethyl acetate in petroleum ether); $[\alpha]_D^{20}$ = -1.69 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.66 – 7.65 (m, 1H), 7.48 – 7.44 (m, 2H), 7.30 – 7.22 (m, 2H), 3.74 (d, *J* = 9.0 Hz, 1H), 3.63 (m, 2H), 3.34 (s, 3H), 3.25 (m, 1H), 3.14 – 3.11

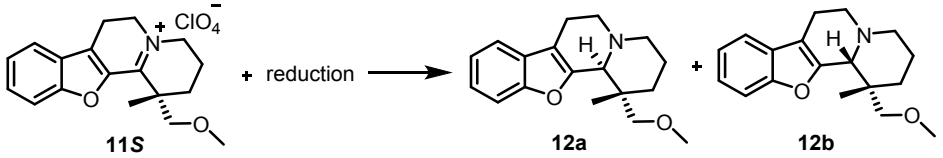
(m, 2H), 2.94 (m, 2H), 2.07 (m, 1H), 1.76 (m, 2H), 1.50 (m, 1H), 1.14 (s, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 173.0, 154.7, 141.3, 127.5, 123.6, 121.8, 119.1, 116.8, 110.8, 79.1, 58.6, 48.7, 47.2, 42.5, 30.6, 22.4, 20.8, 19.1. **HRMS** (*m/z*): calculated for $C_{18}H_{23}NO_3Na^+$ $[M+Na]^+$: 324.1570, found: 324.1561.



(*S*)-1-(methoxymethyl)-1-methyl-1,2,3,4,6,7-hexahydrobenzofuro[2,3-a]quinolizin-5-ium perchlorate (11*S*). A mixture of lactam **10*R*** (50.0 mg, 0.16 mmol) and freshly distilled $POCl_3$ (5 mL) was refluxed for 6 h. After evaporation to dryness, the brown gum obtained was dissolved in CH_2Cl_2 (15 mL) and treated by a 1 M aqueous solution of $LiClO_4$ (5.0 mL). After the mixture was stirred for 10 min, the organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (10 mL × 3). The collected organic phases were washed with an aqueous solution of $LiClO_4$, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*, gave **11*S*** as amorphous solid. Then to the next steps without further purification.



(*R*)-1-(methoxymethyl)-1-methyl-1,2,3,4,6,7-hexahydrobenzofuro[2,3-a]quinolizin-5-ium perchlorate (11*R*). A mixture of lactam **10*S*** (50.0 mg, 0.16 mmol) and freshly distilled $POCl_3$ (5 mL) was refluxed for 6 h. After evaporation to dryness, the brown gum obtained was dissolved in CH_2Cl_2 (15 mL) and treated by a 1 M aqueous solution of $LiClO_4$ (5.0 mL). After the mixture was stirred for 10 min, the organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (10 mL × 3). The collected organic phases were washed with an aqueous solution of $LiClO_4$, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*, gave **11*R*** as amorphous solid. then to the next steps without further purification.



(1*S*,12b*S*)-1-(methoxymethyl)-1-methyl-1,3,4,6,7,12b-hexahydro-2H-benzofuro[2,3-a] quinolizine (12a). TLC: R_f = 0.55 (silica gel, 50% ethyl acetate in petroleum ether); **CD** (CH_3CN, *c* 0.43 mmol·L^{-1}): λ_{max} [nm] = 229 (Δε +0.84), 208 (Δε -6.2); **$[\alpha]_D^{20}$** = -33.2 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.43 – 7.41 (m, 2H), 7.23 – 7.18 (m, 2H), 4.03 (d, *J* =

9.0 Hz, 1H), 3.47 (s, 3H), 3.43 (s, 1H), 3.36 (d, *J* = 9.0 Hz, 1H), 3.00 (m, 1H), 2.94 (m, 1H), 2.97 (m, 1H), 2.59 (m, 1H), 2.51 (m, 1H), 2.38 (m, 1H), 1.95 – 1.85 (m, 2H), 1.58 (m, 1H), 1.49 (m, 1H), 0.83 (s, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 153.9, 153.1, 127.4, 122.5, 121.6, 117.9, 112.9, 110.4, 80.3, 63.9, 58.6, 55.7, 52.9, 37.9, 34.1, 21.5, 20.6, 16.6. **HRMS** (*m/z*): calculated for $C_{18}H_{24}NO_2^+$ $[M+H]^+$: 286.1802, found: 286.1792.

(1*S*,12b*R*)-1-(methoxymethyl)-1-methyl-1,3,4,6,7,12b-hexahydro-2H-benzofuro[2,3-a]quinolizine (12b). TLC: R_f = 0.35 (silica gel, 50% ethyl acetate in petroleum ether); **CD** (CH_3CN, *c* 0.43 mmol·L^{-1}): λ_{max} [nm] = 230 (Δε -0.11), 211 (Δε +8.3); **$[\alpha]_D^{20}$** = 46.9 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.43 – 7.41 (m, 2H), 7.24 – 7.19 (m, 2H), 3.72 (d, *J* = 9.0 Hz, 1H), 3.22 (s, 3H), 3.14 (s, 1H), 3.00 – 2,97 (m, 3H), 2.84 (m, 1H), 2.55 – 2.50 (m, 2H), 2.37 (m, 1H), 2.02 (m, 1H), 1.86 (m, 1H), 1.54(m, 1H), 1.45 (s, 3H), 1.17 (m, 1H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 153.9, 152.4, 127.3, 122.7, 121.7, 117.9, 112.8, 110.6, 74.0, 68.3, 58.5, 55.9, 52.9, 37.7, 33.7, 24.8, 21.8, 20.5. **HRMS** (*m/z*): calculated for $C_{18}H_{24}NO_2^+$ $[M+H]^+$: 286.1802, found: 286.1804.

The reduction of perchlorate salt **11S** to **12a** and **12b** in different condition as follow.

Reduction with $NaBH_4$. The amorphous solid **11*S*** was dissolved in MeOH (10 mL) and cooled to 0 °C, and sodium borohydride (172 mg, 0.57 mmol) was added dropwise. The reaction mixture was stirred for overnight and quenched with aqueous sodium sulfate. The mixture was extracted with ethyl acetate (15 mL × 4), and the combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Determined the crude product by ^{1}H-NMR spectroscopy (1,3,5-trimethoxybenzene as an internal standard). Afford **12a** and **12b** (82% into two steps, **12a**/**12b** 1.0/1.8) as viscous yellow oil.

Reduction with $Zn(BH_4)_2$. Preparation of $Zn(BH_4)_2$ (ca. 0.25 M ethereal solution). This procedure was carried out under an argon atmosphere in a round bottom flask, to a vigorously stirred suspension of $NaBH_4$ (398 mg, 10.5 mmol, powder – as dry as possible) in dry Et_2O (13 mL), was added a suspension of $ZnCl_2$ (681 mg, 5.0 mmol) in dry Et_2O (5 mL) dropwise over a period of 10 min at rt. The resulting mixture was stirred for 24 h. After this time, the solids were allowed to sediment. The clear solution was collected with a syringe and used immediately in the next step.

Asymmetric Reduction. The amorphous solid **11*S*** was dissolved in CH_2Cl_2 (2 mL) and cooled to -78 °C, and the freshly prepared solution of $Zn(BH_4)_2$ (0.25 M in Et_2O, 6 mL, 1.65 mmol) was added dropwise. The reaction mixture was stirred for 3.5 h, then the reaction was carefully quenched (violent evolution of gas) with MeOH (5.0 mL). Concentrated *in vacuo*. Determined the crude product by ^{1}H-NMR spectroscopy (1,3,5-trimethoxybenzene as an internal standard). Afford **12a** and **12b** (59% into two steps, **12a**/**12b** 1.0/2.0) as viscous yellow oil.

Reduction with $LiBHEt_3$. A round bottom flask charged with argon atmosphere, the amorphous solid **11*S*** was dissolved in CH_2Cl_2 (10 mL), The solution was cooled to -78 °C, and $LiEt_3BH$ (0.8 mL, 1.0 M solution in THF) was added via syringe. After being stirred at -78 °C for 1 h, the reaction mixture was cautiously quenched with satd. NH_4Cl (1.0 mL) and warmed to rt. The solution was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (10 mL

× 3), and the combined organic phases were washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated. Determined the crude product by ^{1}H-NMR spectroscopy (1,3,5-trimethoxybenzene as an internal standard). Afford **12a** and **12b** (81% into two steps, **12a**/**12b** 1.0/2.0) as a viscous yellow oil.

Reduction with L-selectride. A solution of L-selectride (0.33 mL, 1.0 M in THF) was added dropwise to a cold (−78 °C) solution of the amorphous solid **11*S*** in 4.0 mL THF, and the stirring was continued at that temperature for 4 h, there are start material residual by TLC, prolong reaction time to overnight, there is no obvious change by TLC. The reaction mixture was cautiously quenched with satd. NH_4Cl (1 mL) and warmed to rt. Dilute the reaction solution with 10 mL water, Separation of organic phase, the aqueous phase was extracted with ethyl acetate (10 mL × 3). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated. Determined the crude product by ^{1}H-NMR spectroscopy (1,3,5-trimethoxybenzene as an internal standard). Afford **12a** and **12b** (38% into two steps, **12a**/**12b** 1.0/1.9) as viscous yellow oil.

Reduction with catecholborane. A round bottom flask charged with argon atmosphere, the amorphous solid **11*S*** was dissolved in THF (3.0 mL), The solution was cooled to -78 °C, and catecholborane (99 mg, 0.8 mmol) was added, warm to room temperature. And then stirring at room temperature for overnight, there is no target compounds was detected by TLC. To this mixture was added 1.0 mL of CH_3OH and 1.0 mL of a saturated solution of sodium potassium tartrate. The resulting mixture was stirred for 1 h, washed with brine, and the brine layer was extracted with EtOAc (10 mL × 3). The combined organic portions were dried over anhydrous Na_2SO_4, filtered, and concentrated. Determined the residue by ^{1}H-NMR, the result is same as by TLC.

Reduction with BH_3·SMe_2. A round bottom flask charged with argon atmosphere, the amorphous solid **11*S*** was dissolved in THF (2.5 mL), The solution was cooled to -78 °C, and BH_3·SMe_2 (0.08 mL, 10.0 M solution in THF) was added via syringe. After being stirred at -78 °C for 2 h. To this mixture was added 5.0 mL of CH_3OH, stirred 0.5 h, then warmed to room temperature and concentrated. Determined the crude product by ^{1}H-NMR spectroscopy (1,3,5-trimethoxybenzene as an internal standard). Afford **12a** and **12b** (98% into two steps, **12a**/**12b** 1.0/1.8) as viscous yellow oil.

Reduction with BH_3·SMe_2/(*R*)-CBS. To a solution of (*R*)-Me-CBS (0.17 mL, 1.0 M solution in THF) was added BH_3·SMe_2 (0.08 mL, 10.0 M solution in THF) and the mixture was stirred under a nitrogen atmosphere at room temperature, then cooled to -78 °C. Then the amorphous solid **11*S*** was added. The reaction mixture was stirred for 4 h. To this mixture was added 5.0 mL of CH_3OH, stirred 0.5 h, then warmed to room temperature and concentrated. Determined the crude product by ^{1}H-NMR spectroscopy (1,3,5-trimethoxybenzene as an internal standard). Afford **12a** and **12b** (97% into two steps, **12a**/**12b** 1.0/2.8) as viscous yellow oil.

Reduction with BH_3·SMe_2/(*S*)-CBS. To a solution of (*S*)-Me-CBS (0.17 mL, 1.0 M solution in THF) was added BH_3·SMe_2 (0.08 mL, 10.0 M solution in THF) and the mixture was stirred

under a nitrogen atmosphere at room temperature, then cooled to -78 °C. Then the amorphous solid **11*S*** was added. The reaction mixture was stirred for 4 h. To this mixture was added 5.0 mL of CH_3OH, stirred 0.5 h, then warmed to room temperature and concentrated. Determined the crude product by ^{1}H-NMR spectroscopy (1,3,5-trimethoxybenzene as an internal standard). Afford **12a** and **12b** (95% into two steps, **12a**/**12b** 1.0/3.8) as viscous yellow oil.

Reduction with Et_3SiH. A round bottom flask charged with argon atmosphere, the amorphous solid **11*S*** was dissolved in 4.0 mL of CH_2Cl_2/TFA (3/1). The solution was cooled to -78 °C, and Et_3SiH (40.0 uL, 0.25 mmol) was added, stirring at this temperature for 2.0 h, there is no target compounds was detected by TLC. Then warm to -50 °C, stirred overnight, no target compounds was detected by TLC. Then warm to room temperature, stirred overnight, no target compounds was detected by TLC. The reaction mixture was then diluted with 15.0 mL of CH_2Cl_2 and washed with 5% (w/w) aq. $NaHCO_3$ (10.0 mL). The layers were separated and the organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*.

Reduction with $PhMe_2SiH$. A round bottom flask charged with argon atmosphere, the amorphous solid **11*S*** was dissolved in 4.0 mL of CH_2Cl_2/TFA (3/1). The solution was cooled to 0 °C, and $PhMe_2SiH$ (40.0 uL, 0.25 mmol) was added. Then warm to room temperature, stirred overnight, no target compounds was detected by TLC. The reaction mixture was then diluted with 15.0 mL of CH_2Cl_2 and washed with 5% (w/w) aq. $NaHCO_3$ (10.0 mL). The layers were separated and the organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*.

Reduction with H_2/(Pd/C). A round bottom flask charged with argon atmosphere, the amorphous solid **11*S*** was dissolved in 3.0 mL of DMF. Pd/C (10%, 80 mg) was added, and the resulting suspension was stirred under hydrogen atmosphere (1.0 atm) for 4.5 h. The reaction mixture was filtered through Celite and the solid residue washed with ethyl acetate. The filtrate was evaporated, and the crude residue was treated with a 30% ammonia solution. The mixture was extracted with CH_2Cl_2 (20 mL × 3), and the collected organic phases were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Determined the crude product by ^{1}H-NMR spectroscopy (1,3,5-trimethoxybenzene as an internal standard). Afford **12a** and **12b** (73% into two steps, **12a**/**12b** 1.0/2.4) as viscous yellow oil.

Reduction with H_2/Crabtree's catalyst. A round bottom flask charged with argon atmosphere, the amorphous solid **11*S*** was dissolved in 3.0 mL of CH_2Cl_2. To this mixture was added Crabtree's catalyst (6.60 mg, 0.008 mmol). The flask was evacuated, refilled with hydrogen three times, placed under an atmosphere of hydrogen (1.0 atm) and stirring for overnight. No target compounds was detected by TLC. The flask was evacuated and the solvent was removed under reduced pressure.

Reduction with H_2/(*R*)-TsDPEN-Ru^{II} catalyst.

Method A. A round bottom flask charged with argon atmosphere, the amorphous solid **11*S*** was dissolved in 3.0 mL of CH_3OH at room temperature, To this mixture was added (*R*)-

TsDPEN-Ru^{II} catalyst (11.0 mg, 0.016 mmol). The flask was evacuated, refilled with hydrogen three times, placed under an atmosphere of hydrogen (1.0 atm) and stirring for overnight. No target compounds was detected by TLC. The flask was evacuated and the solvent was removed under reduced pressure.

Method B. A round bottom flask charged with argon atmosphere, the amorphous solid **11*S*** was dissolved in 3.0 mL of DMF at room temperature, To this mixture was added (*R*)-TsDPEN-Ru^{II} catalyst (11.0 mg, 0.016 mmol). The flask was evacuated, refilled with hydrogen three times, placed under an atmosphere of hydrogen (1.0 atm) and stirring for overnight. Then reaction mixture was cooled to 0 °C and quenched with $NaHCO_3$ (50 mL, sat. aq.). The resulting mixture was extracted with EtOAc (50 mL × 4) and the combined organic extracts were dried over anhydrous MgSO4) and concentrated *in vacuo*. Determined the crude product by ^{1}H-NMR spectroscopy (1,3,5-trimethoxybenzene as an internal standard). Afford **12a** and **12b** (68% into two steps, **12a**/**12b** 1.0/2.4) as viscous yellow oil.

Reduction with $LiAlH_4$. The amorphous solid **11*S*** was added to a mixture of lithium aluminum hydride (63.0 mg, 1.65 mmol) and trimethylaluminum (0.83 mL, 2.0 M in Toluene, 1.65 mmol) in THF (5.0 mL) at –78 °C under nitrogen. The suspension was stirred at -78 °C for 1.0 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL), then add 30 mL of Et_3N/CH_3OH/EtOAc(3/10/87). This mixture stirring 0.5 h. The precipitate was filtered off. The solution was extracted with EtOAc (20 mL × 3), combined organic phase ,washed with brine (20 mL), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. Determined the crude product by ^{1}H-NMR spectroscopy (1,3,5-trimethoxybenzene as an internal standard). Afford **12a** and **12b** (25% into two steps, **12a**/**12b** 1.0/1.8) as viscous yellow oil.

Reduction with $LiAlH(OBu^t)_3$. A round bottom flask charged with argon atmosphere, the amorphous solid **11*S*** was dissolved in 2.0 mL of THF. The solution was cooled to 0 °C, and $LiAlH(OBu^t)_3$ (135 mg, 0.53 mmol) was added, stirring at this temperature for 0.5 h. At this time, the reaction was quenched by addition of satd. aqueous Na_2SO_4 and CH_2Cl_2. The mixture added 5.0 mL of HCl (2.0 M), stirred 5.0 min. Adjusted pH 8 ~ 9 by Na_2CO_3. The resulting mixture was extracted with CH_2Cl_2 (10 mL × 4) and the combined organic extracts washed with satd. aqueous NaCl, dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. Determined the crude product by ^{1}H-NMR spectroscopy (1,3,5-trimethoxybenzene as an internal standard). Afford **12a** and **12b** (85% into two steps, **12a**/**12b** 1.0/2.5) as viscous yellow oil.

Reduction with Red-Al. A round bottom flask charged with argon atmosphere, the amorphous solid **11*S*** was dissolved in 4.0 mL of THF. The solution was cooled to -78 °C. A solution of sodium bis(2-methoxyethoxy)aluminum hydride (0.10 mL, 0.36 mmol, 3.5 M in toluene) was added dropwise. Once the addition was complete, stirred at this temperature for 1.0 h. Then aqueous saturated ammonium chloride (1.0 mL) added. The flask warmed to room temperature. Diluted with 10 mL of water, the layers were separated and the aqueous phase was extracted with EtOAc (10 mL × 3), combined organic phase, washed with brine (10 mL), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. Determined

the crude product by ^{1}H-NMR spectroscopy (1,3,5-trimethoxybenzene as an internal standard). Afford **12a** and **12b** (97% into two steps, **12a**/**12b** 1.0/3.2) as viscous yellow oil.

Reduction with $LiAlH_4$/(*R*)-BINAL-H. Preparation of (*R*)-BINAL-H reagents. A round bottom flask charged with argon atmosphere, 0.6 mL of $LiAlH_4$ (1.0 M in THF) was introduced via a syringe, and then at room temperature an alcohol in THF (2.0 M, 1.0 equiv) was added in a dropwise manner over a period of ca. 10 min with stirring. Subsequently a THF solution of optically pure (*R*)-binaphthol (172 mg, 0.6 mmol,) was added, and the resulting mixture was stirred usually for an additional 30 min at room temperature and used for the asymmetric reduction. Notably the BINAL-H reagent (R'O = simple alkoxyl) thus formed in THF was cloudy but a near-solution which contained only a very small amount of suspension. If a large quantity ofprecipitate separates out for some reason, one should repeat the preparation from the beginning.

Asymmetric Reduction. The (*R*)-BINAL-H reagent in THF was cooled to -90 °C. Subsequently the amorphous solid **11*S*** was added, The mixture was stirred for an additional 1.0 h at this temperature. After addition of methanol (1.0 mL), the mixture added 5.0 mL of HCl (2.0 M), stirred 5.0 min. Adjusted pH 8 ~ 9 by Na_2CO_3. The resulting mixture was extracted with CH_2Cl_2 (10 mL × 4) and the combined organic extracts washed with satd. aqueous NaCl, dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. Determined the crude product by ^{1}H-NMR spectroscopy (1,3,5-trimethoxybenzene as an internal standard). Afford **12a** and **12b** (95% into two steps, **12a**/**12b** 1.0/1.9) as viscous yellow oil.

Reduction with $LiAlH_4$/(*S*)-BINAL-H. Preparation of (*S*)-BINAL-H Reagents. A round bottom flask charged with argon atmosphere, 0.6 mL of $LiAlH_4$ (1.0 M in THF) was introduced via a syringe, and then at room temperature an alcohol in THF (2.0 M, 1.0 equiv) was added in a dropwise manner over a period of ca. 10 min with stirring. Subsequently a THF solution of optically pure (*S*)-binaphthol (172 mg, 0.6 mmol) was added, and the resulting mixture was stirred usually for an additional 30 min at room temperature and used for the asymmetric reduction. Notably the BINAL-H reagent (R'O = simple alkoxyl) thus formed in THF was cloudy but a near-solution which contained only a very small amount of suspension. If a large quantity ofprecipitate separates out for some reason, one should repeat the preparation from the beginning.

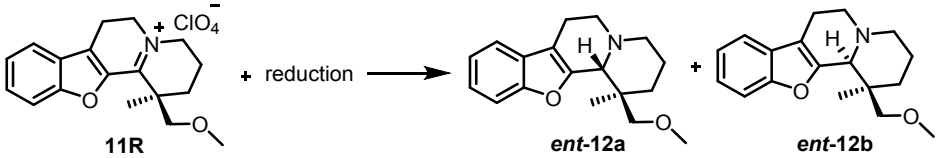
Asymmetric Reduction. The (*S*)-BINAL-H reagent in THF was cooled to -90 °C. Subsequently the amorphous solid **11*S*** was added, the mixture was stirred for an additional 1.0 h at this temperature. After addition of methanol (1.0 mL), the mixture added 5.0 mL of HCl (2.0 M), stirred 5.0 min. Adjusted pH 8 ~ 9 by Na_2CO_3. The resulting mixture was extracted with CH_2Cl_2 (10 mL × 4) and the combined organic extracts washed with satd. aqueous NaCl, dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. Determined the crude product by ^{1}H-NMR spectroscopy (1,3,5-trimethoxybenzene as an internal standard). Afford **12a** and **12b** (98% into two steps, **12a**/**12b** 1.0/1.6) as viscous yellow oil.

Reduction with DIBALH.

Method A. A round bottom flask charged with argon atmosphere, the amorphous solid **11*S*** was dissolved in 5.0 mL of CH_2Cl_2. The solution was cooled to -78 °C. Neat DIBALH (0.15

mL, 0.2 mmol, 1.5 M in toluene) was added dropwise, the mixture was stirred for an additional 1.0 h at this temperature. The reaction was quenched by dropwise addition of H_2O, till coagulation occurred. The suspension was diluted with 1.0 M aqueous HCl solution and then stirred 5.0 min. Adjusted pH 8 ~ 9 by 1.0 M aqueous Na_2CO_3, The resulting mixture was extracted with CH_2Cl_2 (10 mL × 4) and the combined organic extracts washed with satd. aqueous NaCl, dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. Determined the crude product by ^{1}H-NMR spectroscopy (1,3,5-trimethoxybenzene as an internal standard). Afford **12a** and **12b** (98% into two steps, **12a**/**12b** 2.2/1.0) as viscous yellow oil. Purification by column chromatography (petroleum ether / ethyl acetate / acetone = 200/5/1) gave **12a** and **12b** (89% into two steps, **12a**: 62%, **12b**: 27%) as colorless oil.

Method B. A round bottom flask charged with argon atmosphere, the amorphous solid **11*S*** was dissolved in 3.0 mL of CH_2Cl_2. Added $Yb(OTf)_3$ (113mg, 0.16 mmol) , the mixture was stirred at room temperature for 30 min. Neat DIBALH (0.17 mL, 0.25 mmol, 1.5 M in toluene) was added dropwise, the resulting solution was stirred for 1 h and the mixture was quenched with 1.5 mL of methanol. The solvent was evaporated *in vacuo*, and the residue was diluted with 10% HCl, extracted with CH_2Cl_2 (5.0 mL × 4), and dried ($MgSO_4$) and the solvent was evaporated. Determined the crude product by ^{1}H-NMR spectroscopy (1,3,5-trimethoxybenzene as an internal standard). Afford **12a** and **12b** (95% into two steps, **12a**/**12b** 2.0/1.0) as viscous yellow oil.

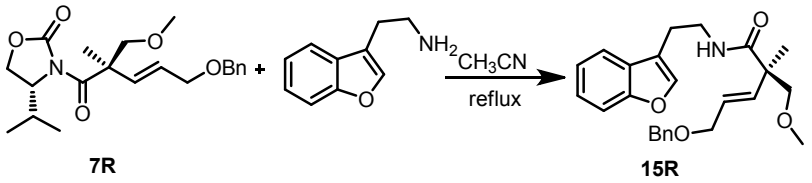


(1*R*,12b*R*)-1-(methoxymethyl)-1-methyl-1,3,4,6,7,12b-hexahydro-2H-benzofuro[2,3-a]quinolizine (*ent*-12a). TLC: R_f = 0.55 (silica gel, 50% ethyl acetate in petroleum ether); **[α]$_D^{20}$** = 23.9 (*c* 0.5, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.42 – 7.41 (m, 2H), 7.21-7.20 (m, 2H), 4.04 (d, *J* = 9.0 Hz, 1H), 3.47 (s, 3H), 3.43 (s, 1H), 3.36 (d, *J* = 9.0 Hz, 1H), 3.00 – 2.85 (m, 3H), 2.60-2.53 (m, 2H), 2.37 (m, 1H), 1.96 – 1.83 (m, 2H), 1.59 – 1.49 (m, 2H), 0.83 (s, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 154.1, 153.8, 128.1, 122.6, 121.7, 117.9, 112.9, 110.4, 80.1, 63.9, 58.5, 55.6, 52.9, 37.9, 33.9, 21.2, 20.3, 16.5. **HRMS** (*m/z*): calculated for $C_{18}H_{24}NO_2^+$ $[M+H]^+$: 286.1802, found: 286.1803.

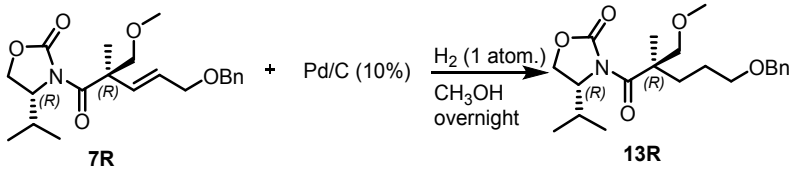
(1*R*,12b*S*)-1-(methoxymethyl)-1-methyl-1,3,4,6,7,12b-hexahydro-2H-benzofuro[2,3-a] quinolizine (*ent*-12b). TLC: R_f = 0.35 (silica gel, 50% ethyl acetate in petroleum ether); **[α]$_D^{20}$** = -56.5 (*c* 0.5, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.42 (m, 2H), 7.21 (m, 2H), 3.72 (d, *J* = 9.0 Hz, 1H), 3.22 (s, 3H), 3.14 (s, 1H), 3.00 – 2,97 (m, 3H), 2.84 (m, 1H), 2.55 – 2.50 (m, 2H), 2.37 (m, 1H), 2.02 (m, 1H), 1.86 (m, 1H), 1.54(m, 1H), 1.45 (s, 3H), 1.17 (m, 1H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 153.9, 152.3, 127.2, 122.8, 121.7, 117.9, 112.8, 110.6, 73.9, 68.3, 58.7, 55.9, 52.9, 37.8, 33.6, 24.7, 21.6, 20.3. **HRMS** (*m/z*): calculated for $C_{18}H_{24}NO_2^+$ $[M+H]^+$: 286.1802, found: 286.1801.

Reduction with $NaBH_4$.The amorphous solid **11*R*** was dissolved in MeOH (10 mL) and cooled to 0 °C, and sodium borohydride (207 mg, 5.47 mmol) was added dropwise. The reaction mixture was stirred for overnight and quenched with aqueous sodium sulfate. The mixture was extracted with ethyl acetate (15 mL × 4), and the combined organic phases were

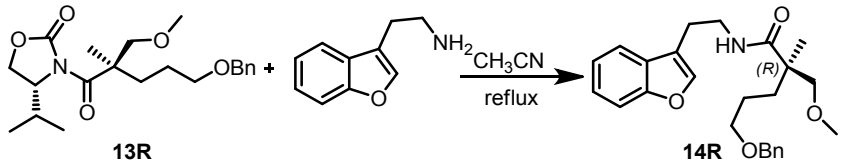
washed with brine, dried with anhydrous Na_2SO_4, and concentrated *in vacuo*. Determined the crude product by ^{1}H-NMR spectroscopy (1,3,5-trimethoxybenzene as an internal standard). Afford ***ent*-12a** and ***ent*-12b** (79% into two steps, ***ent*-12a**/***ent*-12b** 1.0/1.8) as viscous yellow oil. Purification by column chromatography (petroleum ether / ethyl acetate / acetone = 200/5/1) gave ***ent*-12a** and ***ent*-12b** (75% into two steps, ***ent*-12a**: 26%, ***ent*-12b**: 49%) as colorless oil.



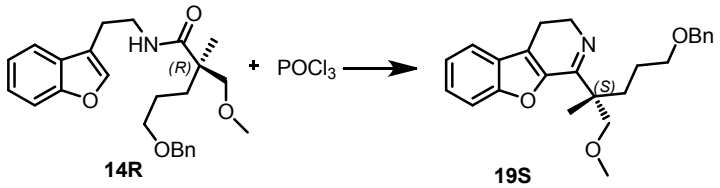
(R)-N-(2-(benzofuran-3-yl)ethyl)-5-(benzyloxy)-2-(methoxymethyl)-2-methylpent-3-enamide (15R). To a solution of 2-(benzofuran-3-yl) ethanamine (121 mg, 0.75 mmol) in CH_3CN (8 mL) was added **7R** (188 mg, 0.50 mmol). Then the mixture solution was refluxed for 2 h. After cooled to the rt, a solution of NaOH (1.0 M) (10 mL) and EtOAc (20 mL) containing 10% of EtOH were added to the reaction mxiture. Separation of organic phase, the aqueous phase was extracted with ethyl acetate (20 mL × 3). The combined organic phase was washed with water (20 mL), brine (20 mL) and dried over anhydrous Na_2SO_4. Evaporation and purification by column chromatography (40% ethyl acetate in petroleum ether) gave **15R** (179 mg, 88%) as colorless oil. **TLC**: R_f = 0.50 (silica gel, petroleum ether/ethyl acetate = 1/1); $[\alpha]_D^{20}$ = 1.80 (*c* 1.0, $CHCl_3$);**^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.8 Hz, 1H), 7.46-7.45 (m, 2H), 7.35 – 7.22 (m, 7H), 6.53 (s, 1H), 5.90 (d, *J* = 15.6 Hz, 1H), 5.73 (dt, *J* = 15.6, 5.4 Hz, 1H), 4.48 (s, 2H), 3.98 (d, *J* = 5.4 Hz, 2H), 3.58 (m, 2H), 3.46 (d, *J* = 9.0 Hz, 1H), 3.33 (d, *J* = 9.0 Hz, 1H), 3.24 (s, 3H), 2.88 (m, 2H), 1.21 (s, 3H). ^{13}C NMR (150 MHz, CDCl3) δ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.4, 155.4, 141.9, 138.2, 134.5, 128.4, 127.8, 127.7, 127.7, 124.4, 122.5, 119.6, 117.4, 111.5, 78.1, 72.3, 70.6, 59.1, 48.7, 38.9, 23.7, 20.3. **HRMS** (*m*/*z*): calculated for $C_{25}H_{30}NO_4^+$ [M+H]$^+$: 408.2169, found: 408.2166.



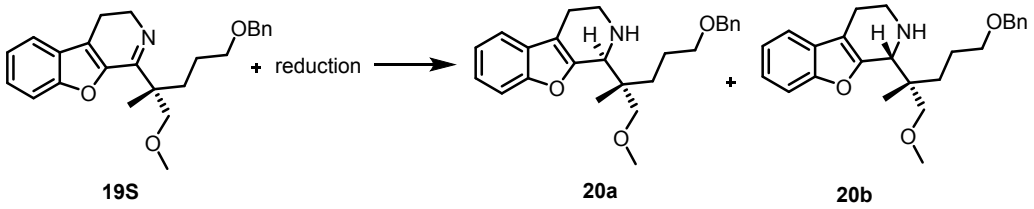
(R)-3-((R)-5-(benzyloxy)-2-(methoxymethyl)-2-methylpentanoyl)-4-isopropyloxazolidin-2-one (13R). Compound **7R** (635 mg, 1.69 mmol) was hydrogenated over 31 mg of 10% Pd/C in 25 mL of MeOH at rt for 0.5 h. Then the catalyst was removed by filtration, the filtrate was evaporated under reduced pressure, and the residue purified by column chromatography (10% ethyl acetate in petroleum ether) gave **13R** (533 mg, 84%) as colorless oil. **TLC**: R_f= 0.60 (silica gel, petroleum ether / dichlormethane /ethyl acetate = 5/1/1); $[\alpha]_D^{20}$ = -46.2 (*c* 1.0, $CHCl_3$);**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.26 (m, 5H), 4.52 (m, 1H), 4.48 (s, 2H), 4.23 (m, 1H), 4.17 (m, 1H), 4.05 (d, J = 8.9 Hz, 1H), 3.47 – 3,42 (m, 3H), 3.30 (s, 3H), 2.30 (m, 1H), 2.13 (m, 1H), 1.76 – 1.58 (m, 3H), 1.48 (m, 1H), 1.37 (s, 3H), 0.89 – 0.87 (m, 6H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 174.7, 152.5, 137.9, 127.7, 127.0, 126.9, 72.3, 69.9, 62.6, 59.8, 58.4, 49.7, 29.7, 27.6, 24.3, 20.6, 17.4, 13.8. **HRMS** (*m*/*z*): calculated for $C_{21}H_{32}NO_5^+$ [M+H]$^+$: 378.2275, found: 378.2268.



(R)-N-(2-(benzofuran-3-yl)ethyl)-5-(benzyloxy)-2-(methoxymethyl)-2-methylpentan amide (14R). To a solution of 2-(benzofuran-3-yl) ethanamine (593 mg, 3.68 mmol) in CH_3CN (8 mL) was added **13R** (925 mg, 2.45 mmol). Then the mixture solution was refluxed for overnight. After cooled to the rt, a solution of NaOH (1.0 M) (30 mL) and EtOAc (60 mL) containing 10% of EtOH were added to the reaction mxiture. Separation of organic phase, the aqueous phase was extracted with ethyl acetate (30 mL × 3). The combined organic phase was washed with water (20 mL), brine (20 mL) and dried over anhydrous Na_2SO_4. Evaporation and purification by column chromatography (20% ethyl acetate in petroleum ether) gave **14R** (921 mg, 92%) as colorless oil. **TLC**: R_f = 0.33 (silica gel, petroleum ether / dichlormethane /ethyl acetate = 5/1/1); $[\alpha]_D^{20}$ = 1.60 (*c* 1.0, $CHCl_3$);**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.59 (d, J = 7.2 Hz, 1H), 7.47-7.45 (m, 2H), 7.35 – 7.22 (m, 7H), 6.87 (s, 1H), 4.46 (s, 2H), 3.56 (q, J = 6.4 Hz, 2H), 3.41 (t, J = 5.6 Hz, 2H), 3.31 (d, J = 9.2 Hz, 1H), 3.21 (d, J = 9.2 Hz, 1H), 3.18 (s, 3H), 2.86 (t, J = 6.8 Hz, 2H), 1.67– 1.48 (m, 4H), 1.08 (s, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) 13C NMR (151 MHz, CDCl3) δ 175.6, 154.8, 141.2, 137.9, 127.7, 127.3, 127.0, 126.9, 123.7, 121.8, 119.0, 116.9, 110.9, 77.5, 72.3, 70.0, 58.4, 45.1, 37.9, 32.5, 24.0, 23.2, 19.5. **HRMS** (*m*/*z*): calculated for $C_{25}H_{32}NO_4^+$ $[M+H]^+$: 410.2326, found: 410.2322.



(S)-1-(5-(benzyloxy)-1-methoxy-2-methylpentan-2-yl)-3,4-dihydrobenzofuro[2,3-c] pyridine (19S). To a solution of amide **14R** (168 mg, 0.41 mmol) in CH_3CN (5 mL) was added freshly distilled $POCl_3$ (0.13 ml, 1.43 mmol) was refluxed for 6 h. After evaporation to dryness, the brown gum obtained was dissolved in CH_2Cl_2 (10 mL), and adjusted pH 8 ~ 9 by satd. $NaHCO_3$, the organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (10 mL × 3). The collected organic phases were washed with a brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*, gave **19S** as colorless oil. Then to the next steps without further purification.



(S)-1-((S)-5-(benzyloxy)-1-methoxy-2-methylpentan-2-yl)-1,2,3,4-tetrahydrobenzofuro [2,3-c]pyridine (20a). TLC: R_f = 0.08 (silica gel, petroleum ether/ethyl acetate = 1/1); $[\alpha]_D^{20}$ = -63.2 (*c* 1.0, $CHCl_3$);**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45-7,40 (m, 2H), 7.31 – 7.19 (m, 7H), 4.47 (s, 2H), 4.10 (s, 1H), 3.45 – 3.40 (m, 3H), 3.34 – 3.23 (m, 5H), 2.85 (m, 1H), 2.73 – 2.58

(m, 2H), 2.14 (s, 1H), 1.72 – 1.60 (m, 2H), 1.59 – 1.50 (m, 2H), 1.17 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 153.7, 153.5, 138.0, 127.7, 127.6, 127.0, 126.9, 122.7, 121.7, 117.9, 113.8, 110.5, 78.2, 72.2, 70.6, 58.6, 58.4, 42.8, 40.6, 30.4, 23.4, 22.3, 19.5. **HRMS** (*m/z*): calculated for $C_{25}H_{32}NO_3^+$ $[M+H]^+$: 394.2377, found: 394.2374.

(R)-1-((S)-5-(benzyloxy)-1-methoxy-2-methylpentan-2-yl)-1,2,3,4-tetrahydrobenzofuro [2,3-c]pyridine (20b). TLC: R_f = 0.17 (silica gel, petroleum ether/ethyl acetate = 1/1); **$[\alpha]_D^{20}$** = 53.5 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45-7,40 (m, 2H), 7.36 – 7.19 (m, 7H), 4.52 (s, 2H), 4.06 (s, 1H), 3.54 – 3.51 (m, 2H), 3.35 – 3.26 (m, 3H), 3.24 (s, 1H), 2.82 (m, 1H), 2.72 – 2.59 (m, 2H), 2.08 (s, 1H), 1.83 (m, 1H), 1.77 – 1.65 (m, 3H), 1.04 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 153.8, 153.5, 138.1, 127.7, 127.6, 127.1, 126.9, 122.7, 121.6, 117.9, 113.9, 110.5, 77.2, 72.3, 70.7, 58.8, 58.5, 42.8, 40.5, 30.9, 23.4, 22.4, 19.2. **HRMS** (*m/z*): calculated for $C_{25}H_{32}NO_3^+$ $[M+H]^+$: 394.2377, found: 394.2380.

The reduction of imine **19S** to **20a** and **20b** in different condition as follow.

Reduction with H_2/(Pd/C). A round bottom flask charged with argon atmosphere, **19S** was dissolved in 3.0 mL of CH_3OH. 10% Pd/C (24 mg, 50wt%) was added, and the resulting suspension was stirred under hydrogen atmosphere (1.0 atm) for 2.0 h. The reaction mixture was filtered through Celite and the solid residue washed with methanol. The filtrate was concentrated *in vacuo*. Determined the crude product by ^{1}H-NMR spectroscopy (1,3,5-trimethoxybenzene as an internal standard). Afford **20a** and **20b** (72% into two steps, **12SS**/**12SR** 3.0/1.0) as viscous yellow oil.

Reduction with $NaBH_4$. A round bottom flask charged with argon atmosphere, **19S** was dissolved in MeOH (2 mL) and cooled to 0 °C, and sodium borohydride (5.1 mg, 0.13 mmol) was added dropwise. The reaction mixture was stirred for 2.0 h and quenched with satd. $NaHCO_3$, evaporate off of methanol, Dilute the residue with ethyl acetate, the organic layer was separated and the aqueous phase extracted with ethyl acetate (15 mL × 3), and the combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Determined the crude product by ^{1}H-NMR spectroscopy (1,3,5-trimethoxybenzene as an internal standard). Afford **20a** and **20b** (81% into two steps, **20a**/**20b** 3.2/1.0) as viscous yellow oil.

Reduction with L-selectride. A solution of L-selectride (0.25 mL, 1.0 M in THF) was added dropwise to a cold (−78 °C) solution of **19S** in 3.0 mL THF, and the stirring was continued at that temperature for 1.0 h, there are much start material residual by TLC, warm to rt., prolong reaction time to overnight, there is no obvious change by TLC. The reaction mixture was cautiously quenched with satd. NH_4Cl (5 mL). Dilute the reaction solution with 10 mL water, Separation of organic phase, the aqueous phase was extracted with ethyl acetate (20 mL × 3). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated.

Reduction with 9-BBN. A round bottom flask charged with argon atmosphere, **19S** was dissolved in THF (3.0 mL), The solution was cooled to -78 °C, and 9-BBN (0.73 mL, 0.5 M in THF, 0.37 mmol) was added via syringe. After being stirred at -78 °C for 4.0 h. There are

much start material residual by TLC, warm to -50 °C for 4.0 h, no obvious change. Then warm to rt., prolong reaction time to overnight, there is no obvious change by TLC. The reaction mixture was cautiously quenched with methanol (5 mL), evaporate to dryness.

Reduction with Catecholborane. A round bottom flask charged with argon atmosphere, **19S** was dissolved in THF (3.0 mL), The solution was cooled to -78 °C, and catecholborane (44.0 mg, 0.37 mmol) was added. After being stirred at -78 °C for 1.0 h. The reaction mixture was cautiously quenched with methanol (5 mL), evaporate to dryness. Determined the crude product by ^{1}H-NMR spectroscopy (1,3,5-trimethoxybenzene as an internal standard). Afford **20a** and **20b** (quantity into two steps, **20a**/**20b** 3.0/1.0) as viscous yellow oil.

Reduction with (S)-BINOL-borane. Preparation of (*S*)-BINOL-H Reagents. A round bottom flask charged with argon atmosphere, (*S*)-binaphthol (105mg, 0.37mmol) was dissolved in THF (2.0 mL), The solution was cooled to 0 °C, BH3/THF (0.37mL, 1M in THF, 0.37mmol) was added at 0 °C. The reaction mixture was stirred for 2 h at the same temperature and used for the asymmetric reduction

Asymmetric Reduction. A round bottom flask charged with argon atmosphere, **19S** was dissolved in THF (3.0 mL), The solution was cooled to -78 °C, and the solution of (S)-BINOL-borane in THF was added. After being stirred at -78 °C for 1.0 h. There are much start material residual by TLC, warm to -50 °C for 1.0 h, start material has been a significant decrease, prolong reaction time to overnight, there is no obvious change by TLC. Then the reaction mixture was cautiously quenched with methanol (5 mL), evaporate to dryness. Determined the crude product by ^{1}H-NMR spectroscopy (1,3,5-trimethoxybenzene as an internal standard). No target compounds was found.

Reduction with DIBALH. A round bottom flask charged with argon atmosphere, **19S** was dissolved in 5.0 mL of CH_2Cl_2. The solution was cooled to -78 °C. Neat DIBALH (0.32 mL, 0.49 mmol, 1.5 M in toluene) was added dropwise, the mixture was stirred for an additional 1.0 h at this temperature. The reaction was quenched by dropwise addition of H_2O, till coagulation occurred. The suspension was diluted with 1.0 M aqueous HCl solution and then stirred 5.0 min. Adjusted pH 8 ~ 9 by 1.0 M aqueous $NaHCO_3$, The resulting mixture was extracted with CH_2Cl_2 (20 mL × 4) and the combined organic extracts washed with satd. aqueous NaCl, dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. Determined the crude product by ^{1}H-NMR spectroscopy (1,3,5-trimethoxybenzene as an internal standard). Afford **20a** and **20b** (90% into two steps, **20a**/**20b** >97.0/3.0) as viscous yellow oil. Purification by column chromatography (50% ethyl acetate in petroleum ether) gave **20a** and **20b** (71% into two steps, **20a**/**20b** >98.0/2.0) as colorless oil.

Reduction with (*R*)-BINAL-H. Preparation of (*R*)-BINAL-H reagents. A round bottom flask charged with argon atmosphere, 0.43 mL of $LiAlH_4$ (1.0 M in THF) was introduced via a syringe, and then at room temperature an alcohol in THF (2.0 M, 1.0 equiv) was added in a dropwise manner over a period of ca. 10 min with stirring. Subsequently a THF solution of optically pure (*R*)-binaphthol (123 mg, 0.43 mmol,) was added, and the resulting mixture was stirred usually for an additional 30 min at room temperature and used for the asymmetric

reduction. Notably the BINAL-H reagent (R'O = simple alkoxyl) thus formed in THF was cloudy but a near-solution which contained only a very small amount of suspension. If a large quantity of precipitate separates out for some reason, one should repeat the preparation from the beginning.

Asymmetric Reduction. The (*R*)-BINAL-H reagent in THF was cooled to -78 °C. Subsequently **19S** was added, the mixture was stirred for an additional 1.0 h at this temperature. There are much start material residual by TLC, warm to rt. for overnight, there is no obvious change by TLC. The reaction was quenched with methanol (5 mL), the mixture was added 5.0 mL of HCl (2.0 M), stirred 5.0 min. Adjusted pH 8 ~ 9 by Na_2CO_3. The resulting mixture was extracted with CH_2Cl_2 (20 mL × 4) and the combined organic extracts washed with satd. aqueous NaCl, dried with anhydrous Na_2SO_4 and concentrated *in vacuo*.

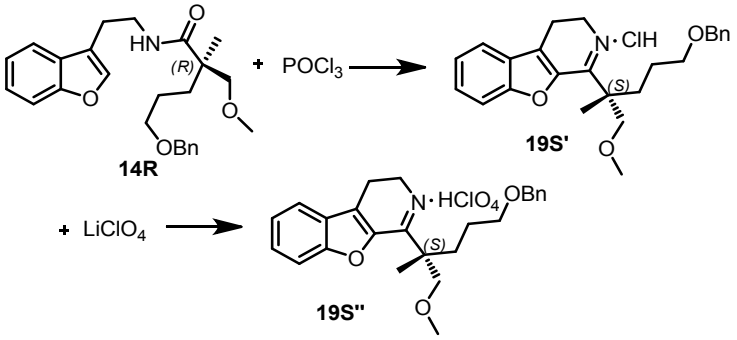
Reduction with (*S*)-BINAL-H. Preparation of (*S*)-BINAL-H reagents. A round bottom flask charged with argon atmosphere, 0.43 mL of $LiAlH_4$ (1.0 M in THF) was introduced via a syringe, and then at room temperature an alcohol in THF (2.0 M, 1.0 equiv) was added in a dropwise manner over a period of ca. 10 min with stirring. Subsequently a THF solution of optically pure (*S*)-binaphthol (123 mg, 0.43 mmol,) was added, and the resulting mixture was stirred usually for an additional 30 min at room temperature and used for the asymmetric reduction. Notably the BINAL-H reagent (R'O = simple alkoxyl) thus formed in THF was cloudy but a near-solution which contained only a very small amount of suspension. If a large quantity of precipitate separates out for some reason, one should repeat the preparation from the beginning.

Asymmetric Reduction. The (*S*)-BINAL-H reagent in THF was cooled to -78 °C. Subsequently **19S** was added, the mixture was stirred for an additional 1.0 h at this temperature. There are much start material residual by TLC, warm to rt. for overnight, there is no obvious change by TLC. The reaction was quenched with methanol (5 mL), the mixture was added 5.0 mL of HCl (2.0 M), stirred 5.0 min. Adjusted pH 8 ~ 9 by Na_2CO_3. The resulting mixture was extracted with CH_2Cl_2 (20 mL × 4) and the combined organic extracts washed with satd. aqueous NaCl, dried with anhydrous Na_2SO_4 and concentrated *in vacuo*.

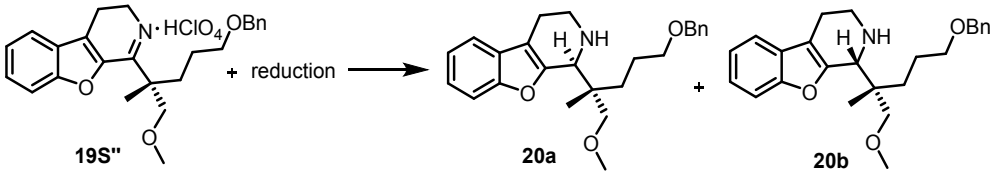
Reduction with H_2/(*R*)-TsDPEN-Ru^{II} catalyst. A round bottom flask charged with argon atmosphere, **19S** was dissolved in 2.0 mL of DMF at room temperature, HCOOH/Et_3N (V/V 5/2) 0.14 mL was added to the solution, then (*R*)-TsDPEN-Ru^{II} catalyst (2.35 mg, 0.0037 mmol) was added, stirring for overnight. The target compounds was less than 10% detected by TLC. Then reaction mixture was cooled to 0 °C and quenched with $NaHCO_3$ (20 mL, sat. aq.). The resulting mixture was extracted with EtOAc (20 mL × 3) and the combined organic extracts were dried over anhydrous MgSO4 and concentrated *in vacuo*.

Reduction with H_2/(*S*)-TsDPEN-Ru^{II} catalyst. A round bottom flask charged with argon atmosphere, **19S** was dissolved in 2.0 mL of DMF at room temperature, HCOOH/Et_3N (V/V 5/2) 0.14 mL was added to the solution, then (*S*)-TsDPEN-Ru^{II} catalyst (2.35 mg, 0.0037 mmol) was added, stirring for overnight. No target compounds was found by TLC. Then reaction mixture was cooled to 0 °C and quenched with $NaHCO_3$ (20 mL, sat. aq.). The resulting mixture was extracted with EtOAc (20 mL × 3) and the combined organic extracts

were dried over anhydrous MgSO4 and concentrated *in vacuo*.



(S)-1-(5-(benzyloxy)-1-methoxy-2-methylpentan-2-yl)-3,4-dihydrobenzofuro[2,3-c] pyridine-2-ium perchlorate (19S''). To a solution of amide **14R** (168 mg, 0.41 mmol) in CH_3CN (5 mL) was added freshly distilled $POCl_3$ (0.13 ml, 1.43 mmol) was refluxed for 6 h. After evaporation to dryness, the brown gum obtained was dissolved in CH_2Cl_2 (15 mL), and treated by a 1 M aqueous solution of $LiClO_4$ (5.0 mL). After the mixture was stirred for 30 min, the organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (20 mL × 3). The collected organic phases were washed with an aqueous solution of $LiClO_4$, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*, gave **19S''** as yellow oil. Then to the next steps without further purification.

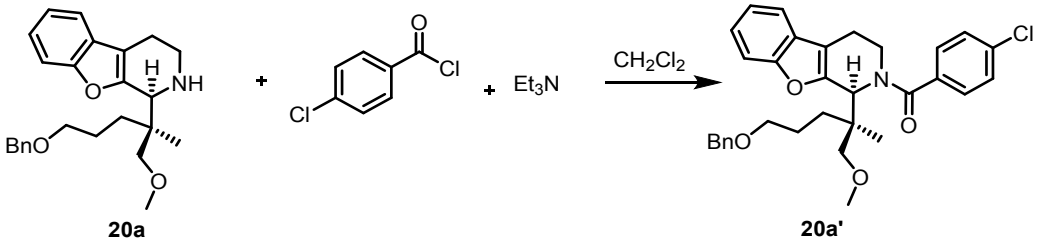


The reduction of perchlorate salt **19SS''** to **20a** and **20b** in different condition as follow.

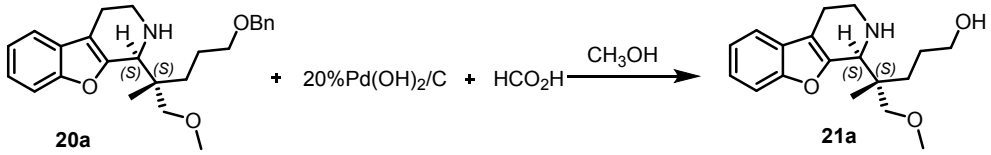
Reduction with $NaBH_4$. A round bottom flask charged with argon atmosphere, **19SS''** was dissolved in MeOH (2 mL) and cooled to 0 °C, and sodium borohydride (5.1 mg, 0.13 mmol) was added dropwise. The reaction mixture was stirred for 2.0 h and quenched with satd. $NaHCO_3$, evaporate off of methanol, Dilute the residue with ethyl acetate, the organic layer was separated and the aqueous phase extracted with ethyl acetate (15 mL × 3), and the combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Determined the crude product by ^{1}H-NMR spectroscopy (1,3,5-trimethoxybenzene as an internal standard). Afford **20a** and **20b** (quantity into two steps, **20a**/**20b** 3.3/1.0) as viscous yellow oil.

Reduction with DIBALH. A round bottom flask charged with argon atmosphere, **19SS''** was dissolved in 2.0 mL of CH_2Cl_2. The solution was cooled to -78 °C. Neat DIBALH (0.18 mL, 0.3 mmol, 1.5 M in toluene) was added dropwise, the mixture was stirred for an additional 1.0 h at this temperature. The reaction was quenched by dropwise addition of H_2O, till coagulation occurred. The suspension was diluted with 1.0 M aqueous HCl solution and then stirred 5.0 min. Adjusted pH 8 ~ 9 by 1.0 M aqueous $NaHCO_3$, The resulting mixture was extracted with CH_2Cl_2 (10 mL × 4) and the combined organic extracts washed with satd. aqueous NaCl, dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. Determined the crude product by ^{1}H-NMR spectroscopy (1,3,5-trimethoxybenzene as an internal standard).

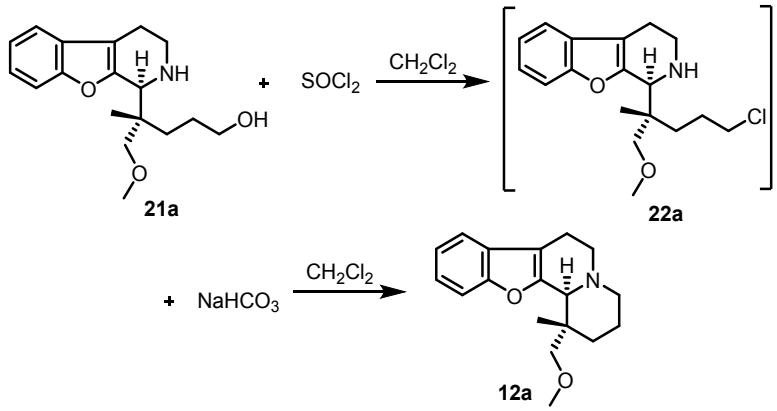
Afford **20a** and **20b** (80% into two steps, **20a**/**20b** >97.0/3.0) as viscous yellow oil.



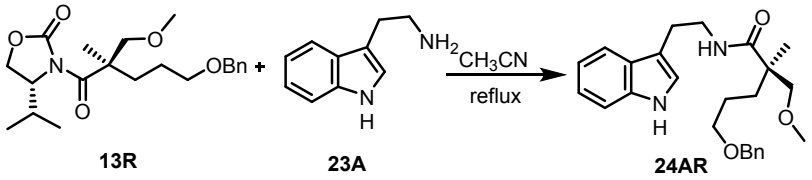
((S)-1-((S)-5-(benzyloxy)-1-methoxy-2-methylpentan-2-yl)-3,4-dihydrobenzofuro[2,3-c]pyridin-2(1H)-yl)(4-chlorophenyl)methanone (20a'). A round bottom flask charged with argon atmosphere, **20a** (143mg, 0.36 mmol) was dissolved in CH2Cl2 (4 mL) and Et3N (0.08 mL, 0.54 mmol) was added to the solution. Then cooled to 0 ºC, 4-chlorobenzoyl chloride (0.05 ml, 0.36 mmol) was added dropwise at 0 ºC and after continued stirring at 0 ºC for 30 min the mixture was allowed to warm to room temperature (23 ºC). After additional stirring for 24 h, the mixture was concentrated and the residue was dissolved in EtOAc (20 mL). The solution was transferred into a separation funnel and washed with satd. $NaHCO_3$ (10 mL) followed by brine (10 mL). The organic layer was separated, dried over anhydrous Na_2SO_4. Evaporation and purification by column chromatography (10% ethyl acetate in petroleum ether) gave **20a'** (180 mg, 94%) as white needle-like solids. **TLC**: R_f = 0.48 (silica gel, petroleum ether / ethyl acetate = 5/1); $[\alpha]_D^{20}$ = 84.2 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) ^{1}H NMR (400 MHz, cdcl$_3$) δ 7.52 – 7.20 (m, 13H), 6.07 (s, 1H), 4.50 (s, 2H), 3.90 (m, 1H), 3.77 (m, 1H), 3.52-3.49 (m, 3H), 3.28(s, 1H), 3.24 (d, *J* = 9.6 Hz, 1H), 2.59 (m, 2H), 1.86-1.75 (m, 3H), 1.61 (m, 1H), 1.11 (s, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 170.2, 154.0, 150.6, 138.7, 134.8, 134.7, 128.2, 127.7, 127.5, 127.0, 126.8, 126.7, 123.3, 122.0, 118.0, 111.6, 110.7, 76.9, 72.2, 70.5, 58.4, 53.8, 43.4, 42.7, 31.2, 23.5, 21.3, 19.5. **HRMS** (*m/z*): calculated for $C_{32}H_{35}NO_3^+$ $[M+H]^+$: 532.2249, found: 532.2233.



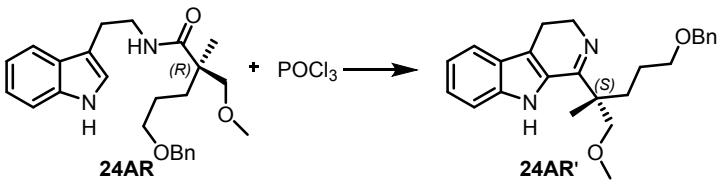
(S)-5-methoxy-4-methyl-4-((S)-1,2,3,4-tetrahydrobenzofuro[2,3-c]pyridin-1-yl)pentan-1-ol (21a). A round bottom flask charged with argon atmosphere, **20a** (210mg, 0.53 mmol) was dissolved in CH_3OH (5 mL) and 20% $Pd(OH)_2$/C (315 mg, 150wt%) was added to the solution. Followed HCOOH (0.53 mL, 1 mL/mmol) was added, then reflux for 6 h, the catalyst was removed by filtration, the filtrate was evaporated under reduced pressure, and the residue was dissolved in CH_2Cl_2 (20 mL). Added satd. $NaHCO_3$ (5 mL), after additional stirring for 5 min, separation of organic phase, the aqueous phase was extracted with CH_2Cl_2 (10 mL × 3). The combined organic phase was washed with brine (20 mL) and dried over anhydrous Na_2SO_4. Evaporated under reduced pressure, then to the next steps without further purification.



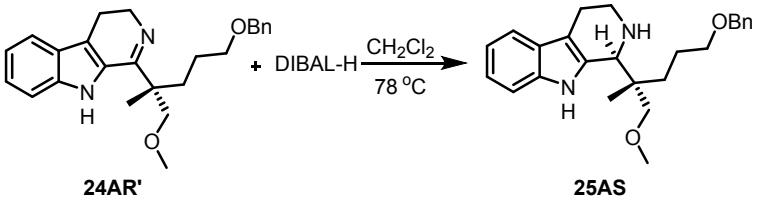
(1*S*,12b*S*)-1-(methoxymethyl)-1-methyl-1,3,4,6,7,12b-hexahydro-2H-benzofuro[2,3-a] quinolizine (12a). A round bottom flask charged with argon atmosphere, a solution of **21a** in CH_2Cl_2 (6.0 mL) was cooled to 0 ºC, and thionyl chloride (0.23 mL, 3.8 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 2.0 h, evaporation to dryness, the residue was dissolved in CH_2Cl_2 (6.0 mL), saturated $NaHCO_3$ (14 mL, 25 mL/mmol) was added slowly. After being stirred for another 2.0 h, separation of organic phase, the aqueous phase was extracted with CH_2Cl_2 (15 mL × 3). The combined organic phase was washed with brine (20 mL) and dried over anhydrous Na_2SO_4. Evaporation and purification by column chromatography (10% ethyl acetate in petroleum ether) gave **12a** (111 mg, 73% into three steps) as colorless oil.



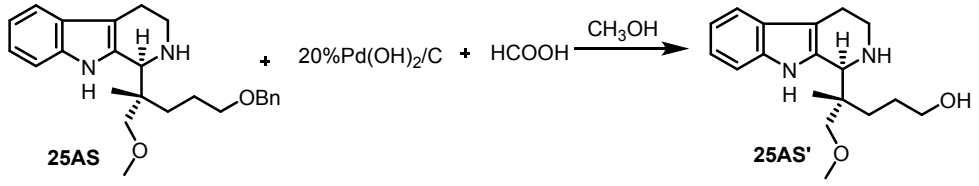
(R)-N-(2-(1H-indol-3-yl)ethyl)-5-(benzyloxy)-2-(methoxymethyl)-2-methylpentanamide (24AR). To a solution of 2-(1H-indol-3-yl)ethan-1-amine (339 mg, 2.12 mmol) in CH_3CN (14 mL) was added **13R** (533 mg, 1.41 mmol). Then the mixture solution was refluxed for overnight. After cooled to the rt, a solution of NaOH (15 mL, 1.0 M) and EtOAc (30 mL) containing 10% of EtOH were added to the reaction mxiture. Separation of organic phase, the aqueous phase was extracted with ethyl acetate (30 mL × 3). The combined organic phase was washed with brine (20 mL) and dried over anhydrous Na_2SO_4. Evaporation and purification by column chromatography (petroleum ether / diethyl ether /ethyl acetate = 5/1/1) gave **24AR** (524 mg, 91%) as colorless oil. **TLC**: R_f = 0.53 (silica gel, dichloromethane/ethyl acetate = 5/1/1); $[\alpha]_D^{20}$ = 7.50 (*c* 1.0, $CHCl_3$);**^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.37 – 7.26 (m, 6H), 7.18 (m, 1H), 7.11 (m, 1H), 7.00 (s, 1H), 6.74 (s, 1H), 4.47 (s, 2H), 3.57 (m, 2H), 3.41 (t, *J* = 5.2 Hz, 2H), 3.30 (d, *J* = 9.2 Hz, 1H), 3.20 (d, *J* = 9.2 Hz, 1H), 3.14 (s, 3H), 2.94 (t, *J* = 6.8 Hz, 2H), 1.65 – 1.47 (m, 4H), 1.07 (s, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 176.0, 138.6, 136.3, 128.4, 127.7, 127.6, 127.4, 122.1, 122.0, 119.3, 118.8, 113.2, 111.1, 78.1, 72.9, 70.8, 59.0, 45.7, 39.5, 33.2, 25.3, 24.6, 20.1. **HRMS** (*m/z*): calculated for $C_{25}H_{33}N_2O_3^+$ $[M+H]^+$: 409.2486, found: 409.2483.



(S)-1-(5-(benzyloxy)-1-methoxy-2-methylpentan-2-yl)-4,9-dihydro-3H-pyrido[3,4-b]indole (24AR'). To a solution of amide **24AR** (524 mg, 1.28 mmol) in CH_3CN (15 mL) was added freshly distilled $POCl_3$ (0.55 ml, 4.48 mmol) was refluxed for 6 h. After evaporation to dryness, the brown gum obtained was dissolved in CH_2Cl_2 (15 mL), and adjusted pH 8 ~ 9 by satd. $NaHCO_3$, the organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (20 mL × 3). The collected organic phases were washed with a brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*, gave **24AR'** as colorless oil. Then to the next steps without further purification.

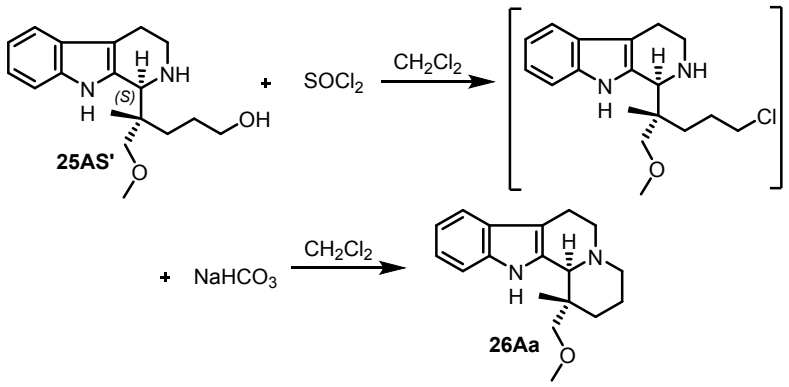


(S)-1-((S)-5-(benzyloxy)-1-methoxy-2-methylpentan-2-yl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (25AS). A round bottom flask charged with argon atmosphere, **24AR'** was dissolved in 15 mL of CH_2Cl_2. The solution was cooled to -78 °C. Neat DIBALH (1.0 mL, 2.1 mmol, 1.5 M in toluene) was added dropwise, the mixture was stirred for an additional 1.0 h at this temperature. The reaction was quenched by dropwise addition of H_2O, till coagulation occurred. The suspension was diluted with 1.0 M aqueous HCl solution and then stirred 5.0 min. Adjusted pH 8 ~ 9 by 1.0 M aqueous $NaHCO_3$, The resulting mixture was extracted with CH_2Cl_2 (20 mL × 4) and the combined organic extracts washed with satd. aqueous NaCl, dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (50% ethyl acetate in petroleum ether) gave **25AS** (84% into two steps, dr: >98:2) as colorless oil. **TLC**: R_f = 0.48 (silica gel, dichloromethane/ methyl alcohol = 20/1); $[\alpha]_D^{20}$ = -39.9 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.09 (s, 1H), 7.47 (m, 1H), 7.37 – 7.30 (m, 5H), 7.05-7.03 (m, 2H), 6.92 (m, 1H), 4.59 (s, 2H), 4.23 (s, 1H), 3.61 (m, 1H), 3.48 (m, 1H), 3.37 – 3.33 (m, 5H), 3.20 (d, *J* = 9.6 Hz, 1H), 2.84 (m, 1H), 2.74-2.69 (m, 2H), 2.42 (s, 1H), 1.79 – 1.74 (m, 3H), 1.59 (m, 1H), 1.06 (s, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 137.6, 135.1, 132.6, 128.0, 127.4, 127.3, 127.2, 126.5, 120.6, 118.2, 117.1, 110.8, 110.1, 79.2, 72.7, 70.1, 58.5, 57.4, 43.1, 41.1, 32.8, 23.4, 22.5, 19.2. **HRMS** (*m/z*): calculated for $C_{25}H_{33}N_2O_2^+$ $[M+H]^+$: 393.2537, found: 393.2533.

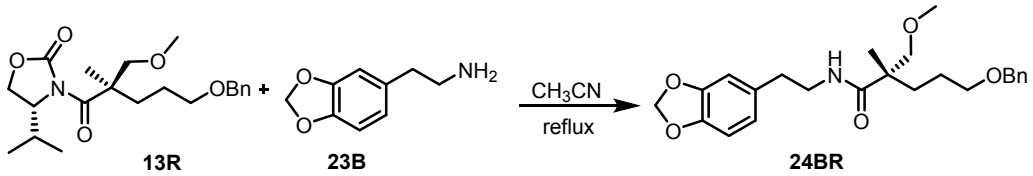


(S)-5-methoxy-4-methyl-4-((S)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)pentan-1-ol (25AS'). A round bottom flask charged with argon atmosphere, **25AS** (373mg, 0.95 mmol) was dissolved in CH_3OH (10 mL) and 20% $Pd(OH)_2/C$ (560 mg, 150wt%) was added to the

solution. Followed HCOOH (0.95 mL, 1 mL/mmol) was added, then reflux for 6 h, the catalyst was removed by filtration, the filtrate was evaporated under reduced pressure, and the residue was dissolved in CH_2Cl_2 (20 mL). Added satd. $NaHCO_3$ (5 mL), after additional stirring for 5 min, separation of organic phase, the aqueous phase was extracted with CH_2Cl_2 (10 mL × 3). The combined organic phase was washed with brine (20 mL) and dried over anhydrous Na_2SO_4. Evaporated under reduced pressure, then to the next steps without further purification.

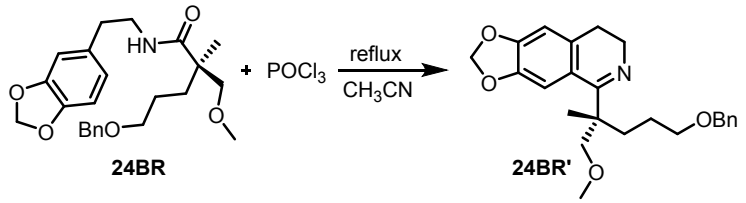


(1S,12bS)-1-(methoxymethyl)-1-methyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine (26Aa). A round bottom flask charged with argon atmosphere, a solution of **25AS'**in CH_2Cl_2 (10 mL) was cooled to 0 ºC, and thionyl chloride (0.41 mL, 5.7 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 2.0 h, evaporation to dryness, the residue was dissolved in CH_2Cl_2 (10 mL), saturated $NaHCO_3$ (24 mL, 25 mL/mmol) was added slowly. After being stirred for another 2.0 h, separation of organic phase, the aqueous phase was extracted with CH_2Cl_2 (25 mL × 3). The combined organic phase was washed with brine (40 mL) and dried over anhydrous Na_2SO_4. Evaporation and purification by column chromatography (petroleum ether / ethyl acetate / methyl alcohol = 10/2/1) gave **26Aa** (189 mg, 70% into three steps) as colorless oil. **TLC**: R_f = 0.18 (silica gel, petroleum ether / ethyl acetate / methyl alcohol = 10/2/1); $[\alpha]_D^{20}$ = -54.4 (*c* 1.0, $CHCl_3$);**^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.77 (s, 1H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.28 (d, *J* = 8.4 Hz, 1H), 7.10 (m, 1H), 7.05 (m, 1H), 3.55 (s, 3H), 3.41 (s, 2H), 3.31 (s, 1H), 3.05 – 2.92 (m, 3H), 2.64 (m, 1H), 2.56 (m, 1H), 2.33 (m, 1H), 1.97 (m, 1H), 1.56 (m, 1H), 1.50 (m, 1H), 1.44 (m, 1H), 0.91 (s, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 135.3, 133.2, 126.5, 120.2, 118.1, 117.2, 110.3, 109.7, 82.2, 68.1, 58.8, 56.2, 54.1, 38.1, 35.9, 21.3, 21.2, 15.7. **HRMS** (*m/z*): calculated for $C_{18}H_{25}N_2O^+$ $[M+H]^+$: 285.1961, found: 285.1962.

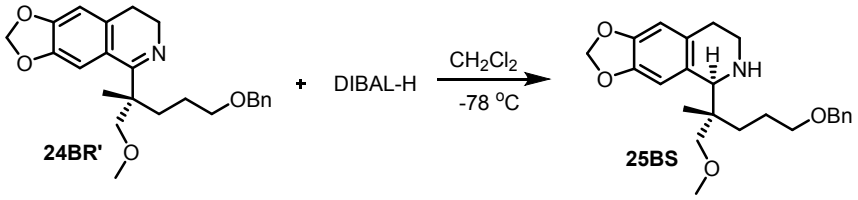


(S)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-5-(benzyloxy)-2-(methoxymethyl)-2-methyl pentanamide (24BR). To a solution of 2-(benzo[d][1,3]dioxol-5-yl)ethan-1-amine (66 mg, 0.40 mmol) in CH_3CN (2 mL) was added **13R** (100 mg, 0.26 mmol). Then the mixture solution was refluxed for overnight. After cooled to the rt, a solution of NaOH (1.0 M) (10 mL) and EtOAc (20 mL) containing 10% of EtOH were added to the reaction mxiture.

Separation of organic phase, the aqueous phase was extracted with ethyl acetate (10 mL × 3). The combined organic phase was washed with water (10 mL), brine (10 mL) and dried over anhydrous Na_2SO_4. Evaporation and purification by column chromatography (petroleum ether / diethyl ether /ethyl acetate = 5/1/1) gave **24BR** (104 mg, 95%) as colorless oil. **TLC**: R_f = 0.21 (silica gel, petroleum ether / diethyl ether /ethyl acetate = 5/1/1); $[\alpha]_D^{20}$ = 2.30 (*c* 1.0, $CHCl_3$);**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29 (m, 5H), 6.74 – 6.61 (m, 4H), 5.90 (s, 2H), 4.47 (s, 2H), 3.42 (m, 4H), 3.33 (d, *J* = 8.8 Hz, 1H), 3.24 (m, 4H), 2.69 (m, 2H), 1.60 – 1.51 (m, 4H), 1.08 (s, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) ^{13}C NMR (151 MHz, $CDCl_3$) δ 175.4, 147.1, 145.4, 137.9, 132.4, 127.7, 127.0, 126.96, 121.1, 108.5, 107.6, 100.2, 77.5, 72.3, 70.1, 58.5, 45.1, 39.9, 34.8, 32.6, 23.9, 19.5. **HRMS** (*m/z*): calculated for $C_{24}H_{32}NO_5^+$ $[M+H]^+$: 414.2275, found: 414.2285.

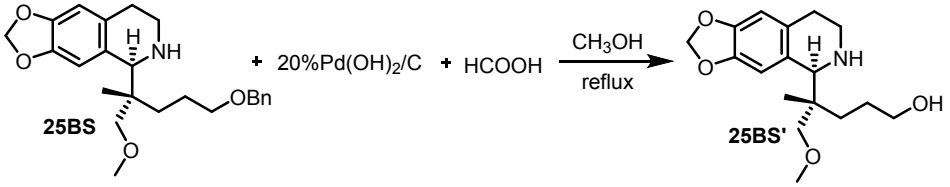


(S)-5-(5-(benzyloxy)-1-methoxy-2-methylpentan-2-yl)-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinoline (24BR'). To a solution of amide **24BR** (352 mg, 0.85 mmol) in CH_3CN (10 mL) was added freshly distilled $POCl_3$ (0.27 ml, 2.98 mmol) was refluxed for 6 h. After evaporation to dryness, the brown gum obtained was dissolved in CH_2Cl_2 (10 mL), and adjusted pH 8 ~ 9 by satd. $NaHCO_3$, the organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (10 mL × 3). The collected organic phases were washed with a brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*, gave **24BR'** as colorless oil. Then to the next steps without further purification.

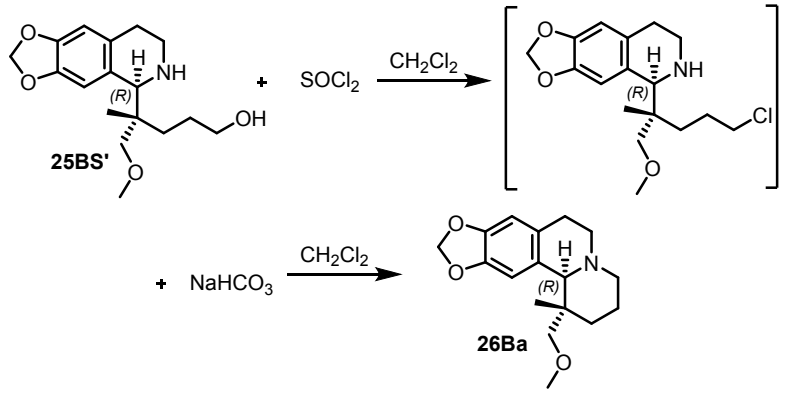


(R)-5-((S)-5-(benzyloxy)-1-methoxy-2-methylpentan-2-yl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline (25BS). A round bottom flask charged with argon atmosphere, **18bR'** was dissolved in 8.0 mL of CH_2Cl_2. The solution was cooled to -78 °C. Neat DIBALH (0.68 mL, 1.02 mmol, 1.5 M in toluene) was added dropwise, the mixture was stirred for an additional 1.0 h at this temperature. The reaction was quenched by dropwise addition of H_2O, till coagulation occurred. The suspension was diluted with 1.0 M aqueous HCl solution and then stirred 5.0 min. Adjusted pH 8 ~ 9 by 1.0 M aqueous $NaHCO_3$, The resulting mixture was extracted with CH_2Cl_2 (20 mL × 4) and the combined organic extracts washed with satd. aqueous NaCl, dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (dichloromethane/ methyl alcohol = 40/1) gave **25BS** (92% into two steps, dr: >98.0/2.0) as colorless oil. **TLC**: R_f = 0.25 (silica gel, dichloromethane/ methyl alcohol = 30/1); $[\alpha]_D^{20}$ = -73.1 (*c* 1.0, $CHCl_3$);**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31 (m, 5H), 6.65 (s, 1H), 6.57 (s, 1H), 5.91 (s, 2H), 5.14 (s, 1H), 4.48 (s, 2H), 4.35 (s, 1H), 3.46 – 3.43 (m, 3H), 3.31 (s, 3H), 3.17– 3.11 (m, 2H), 2.82 – 2.71 (m, 2H), 2.52 (m, 1H), 1.61 – 1.50 (m, 3H), 1.42 (m, 1H), 0.92 (s, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ

145.5, 145.2, 138.0, 130.5, 127.7, 127.0,127.0, 126.9, 125.7, 108.4, 108.0, 100.2, 77.0, 72.2, 70.3, 59.9, 58.2, 42.3, 41.7, 30.0, 29.1, 23.4, 18.6. **HRMS** (*m/z*): calculated for $C_{22}H_{32}NO_4^+$ $[M+H]^+$: 398.2326, found: 398.2325.



(S)-5-methoxy-4-methyl-4-((R)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)pentan-1-ol (25BS'). A round bottom flask charged with argon atmosphere, **25BS** (295 mg, 0.74 mmol) was dissolved in CH_3OH (7.5 mL) and 20% $Pd(OH)_2/C$ (443 mg, 150wt%) was added to the solution. Followed HCOOH (0.75 mL, 1 mL/mmol) was added, then reflux for 6 h, the catalyst was removed by filtration, the filtrate was evaporated under reduced pressure, and the residue was dissolved in CH_2Cl_2 (20 mL). Added satd. $NaHCO_3$ (5 mL), after additional stirring for 5 min, separation of organic phase, the aqueous phase was extracted with CH_2Cl_2 (10 mL × 3). The combined organic phase was washed with brine (20 mL) and dried over anhydrous Na_2SO_4. Evaporated under reduced pressure, then to the next steps without further purification.



(1S,12bR)-1-(methoxymethyl)-1-methyl-1,3,4,6,7,12b-hexahydro-2H-[1,3]dioxolo[4,5-g]pyrido[2,1-a]isoquinoline (26Ba). A round bottom flask charged with argon atmosphere, a solution of **25BS'** in CH_2Cl_2 (8 mL) was cooled to 0 ºC, and thionyl chloride (0.32 mL, 4.4 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 2.0 h, evaporation to dryness, the residue was dissolved in CH_2Cl_2 (8 mL), saturated $NaHCO_3$ (19 mL, 25 mL/mmol) was added slowly. After being stirred for another 2.0 h, separation of organic phase, the aqueous phase was extracted with CH_2Cl_2 (25 mL × 3). The combined organic phase was washed with brine (40 mL) and dried over anhydrous Na_2SO_4. Evaporation and purification by column chromatography (petroleum ether / ethyl acetate / methyl alcohol = 50/5/1) gave **26Ba** (137 mg, 64% into three steps) as colorless oil. **TLC**: R_f = 0.24 (silica gel, petroleum ether / ethyl acetate / methyl alcohol = 20/2/1); $\mathbf{[\alpha]_D^{20}}$ = -92.2 (*c* 1.0, $CHCl_3$);**^{1}H NMR** (400 MHz, $CDCl_3$) ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.74 (s, 1H), 6.55 (s, 1H), 5.92– 5.90 (m, 2H), 3.63 (s, 1H), 3.49 (d, *J* = 9.6 Hz, 1H), 3.42 (s, 3H), 3.00 – 2.85 (m, 4H), 2.55 – 2.51 (m, 3H), 2.06 (m, 1H), 1.92 (m, 1H), 1.52 (m, 1H), 1.43 (m, 1H), 0.67 (s, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 144.7, 144.6, 130.8, 128.3, 107.8, 107.7, 99.9, 80.0, 65.9, 58.0, 56.0, 50.6, 39.5, 35.4, 31.1, 21.7, 16.3. **HRMS** (*m/z*): calculated for $C_{17}H_{24}NO_3^+$ $[M+H]^+$:

290.1751, found: 290.1758.

Determine the Absolute Configuration of 12a and 12b

As the endeavor for getting high quality homochiral crystal was unsuccessful, we applied electronic circular dichroism (ECD) measurement coupled with theoretical prediction to determine the absolute configuration. It has been proved to be reliable for the absolute configuration assignment by the ECD method coupled with ab initio calculation.[S3] Conformational analysis at the molecular mechanics (MM) level was carried out. The B3LYP (Becke, 3-parameter, Lee-Yang-Parr) functional was adopted for geometry optimization to search the most stable conformers at the 6-31G* basis set level. The ECD spectrum was calculated with the TDDFT (time-dependent density functional theory) level of theory with the B3LYP function based on the DFT/B3LYP/TZVP (Valence triple-zeta plus polarization) optimized geometries. Effect of acetonitrile solvent was taken into account by the polarizable continuum model (PCM) at room temperature. The theoretical estimated ECDs are consistent with experiment value (see Figure 1), indicating the absolute configuration is SS-configuration. All the quantum chemistry calculations are performed with Gaussian09.[S4]

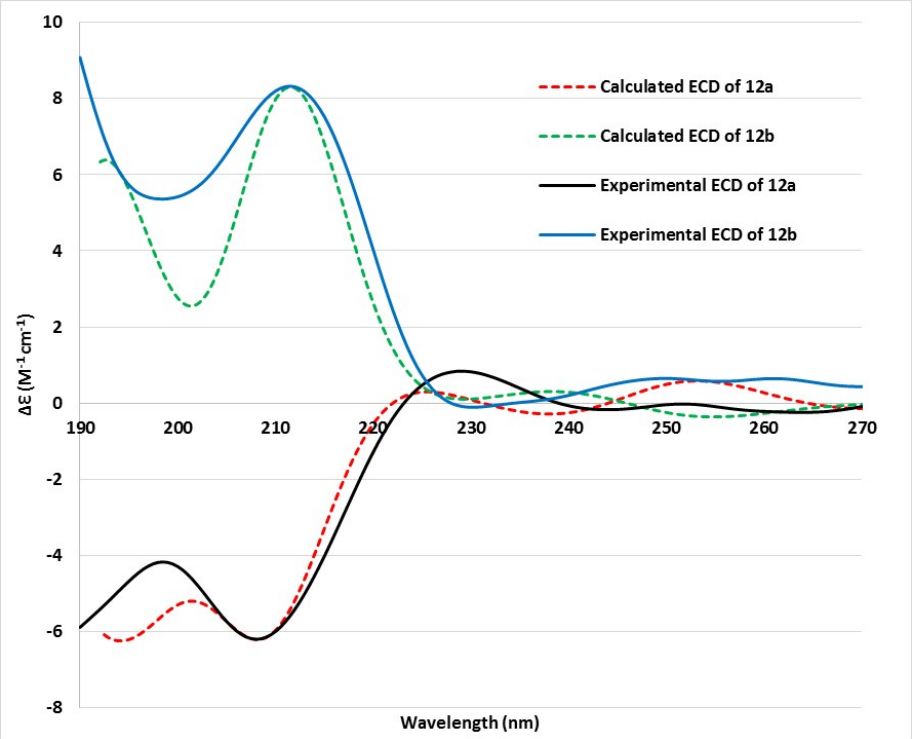
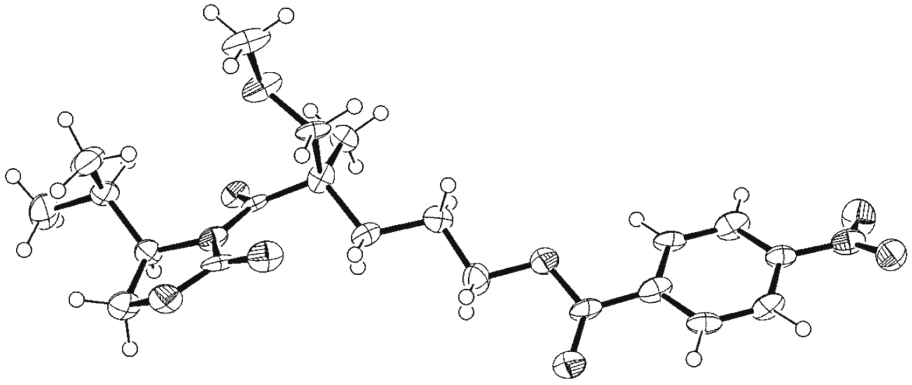
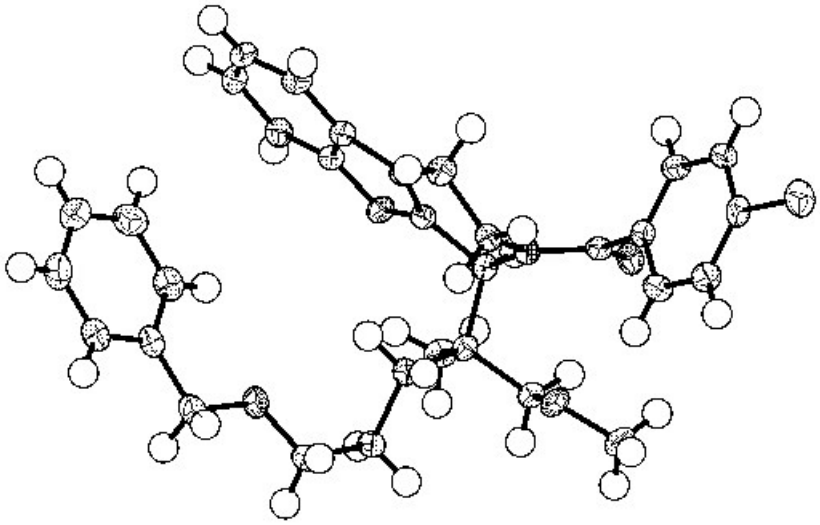


Fig 1 Calculated ECD spectra of **12a** [(1*S*,12b*S*)-12] (red line), **12b** [(1*S*,12b*R*)-12] (green line) and experimental ECD spectra of **12a** [(1*S*,12b*S*)-12] (black line), **12b** [(1*S*,12b*R*)-12] (blue line)

The X-ray Single Crystal Analysis of 8R' (CCDC 1812609)



The X-ray Single Crystal Analysis of 20a' (CCDC 1868095)



Reference

S1. *Tetrahedron*, 2007, **63**, 11325.

S2. a) *J. Org. Chem.*, 1988, **53**, 1437; b) *Tetrahedron Letters*, 2007, **48**, 5177.

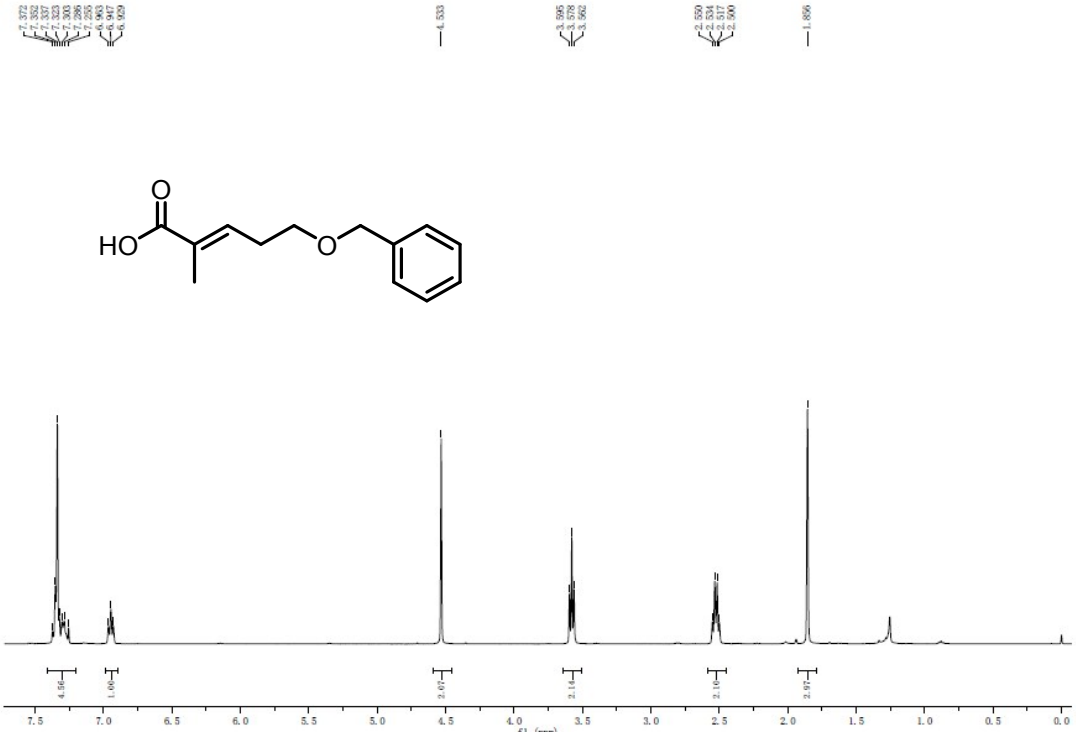
S3. a) *Tetrahedron Letters*, 2015, **56**, 913; b) *Tetrahedron,* 2016, **72**, 1276; c) *Chem. Soc. Rev.*, 2007, **36**, 914; d) *J. Am. Chem. Soc.,* 2009, **131**, 3183.

S4. Frisch, M. J. et al GAUSSIAN 09, Revision A.02; Gaussian: Wallingford, CT, 2009.

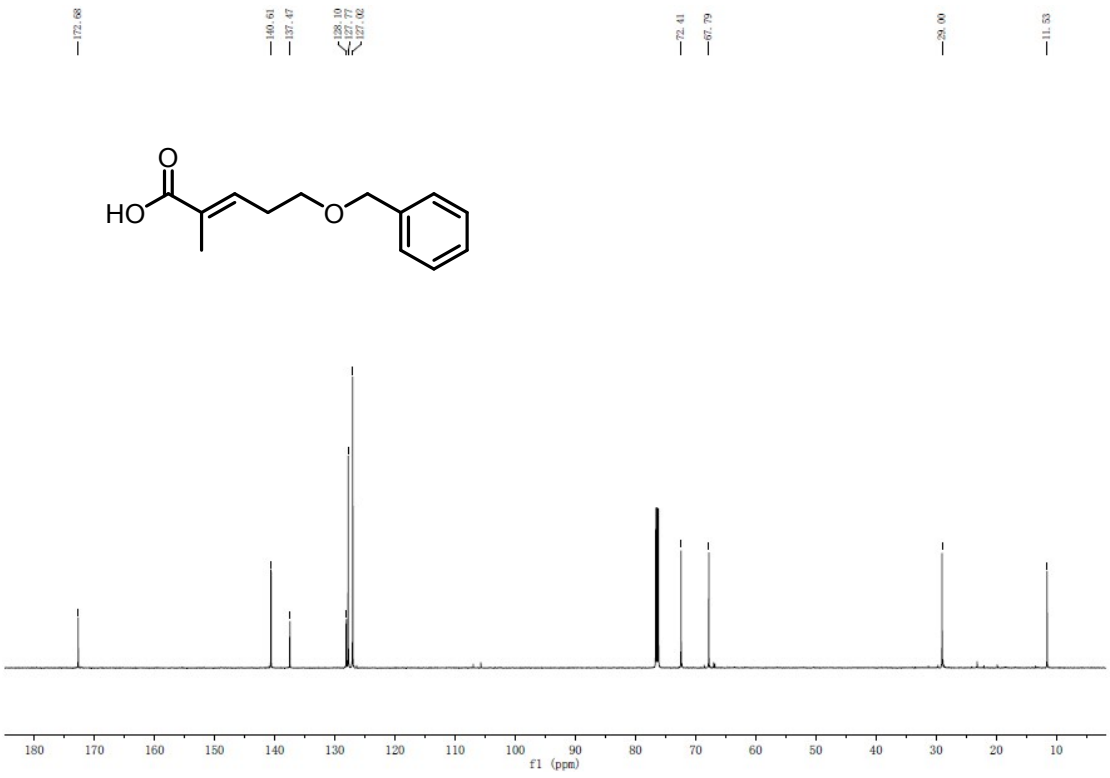
^{1}H NMR spectrum of compound 2 (400 MHz, $CDCl_3$):

^{1}H NMR spectrum of compound 3 (400 MHz, $CDCl_3$):

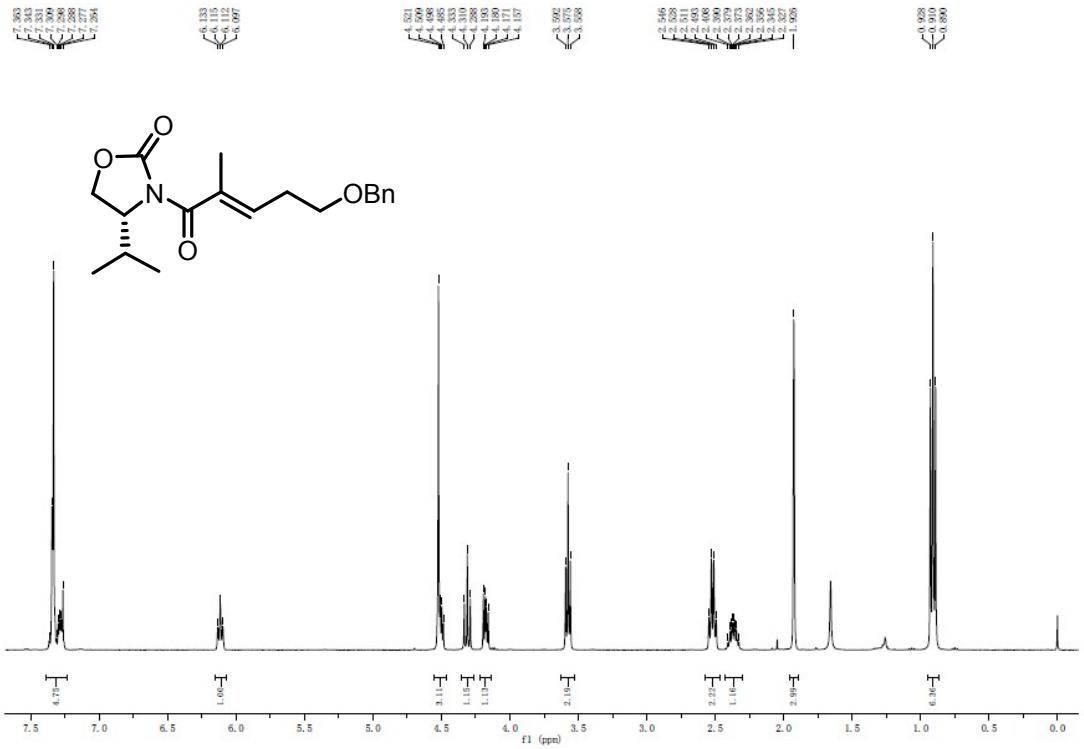
^{1}H-NMR spectrum of compound 4 (400 MHz, $CDCl_3$):



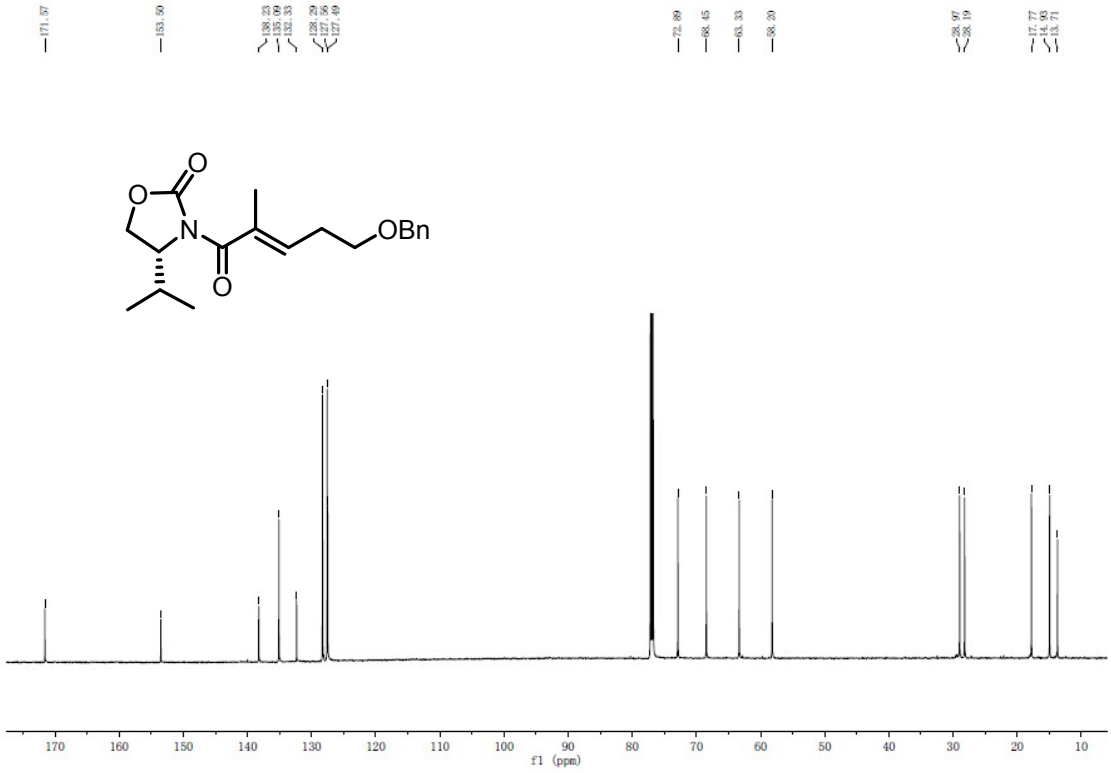
^{13}C-NMR spectrum of compound 4 (150 MHz, $CDCl_3$):



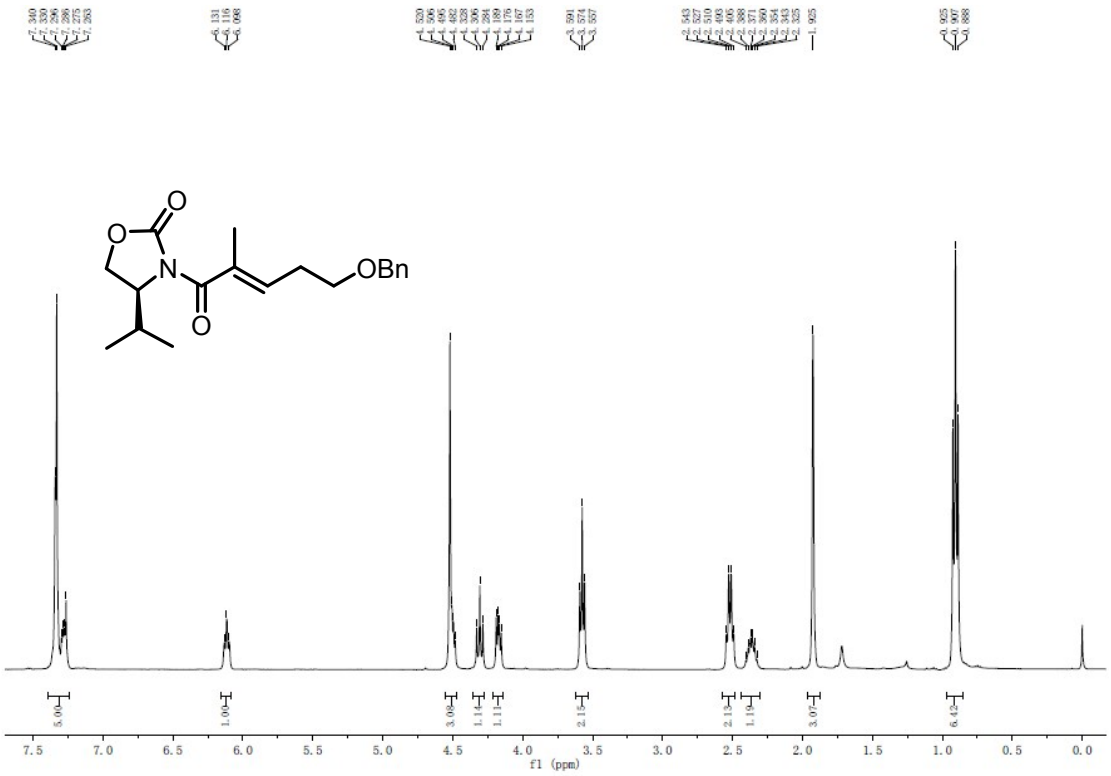
^{1}H-NMR spectrum of compound 6R (400 MHz, $CDCl_3$):



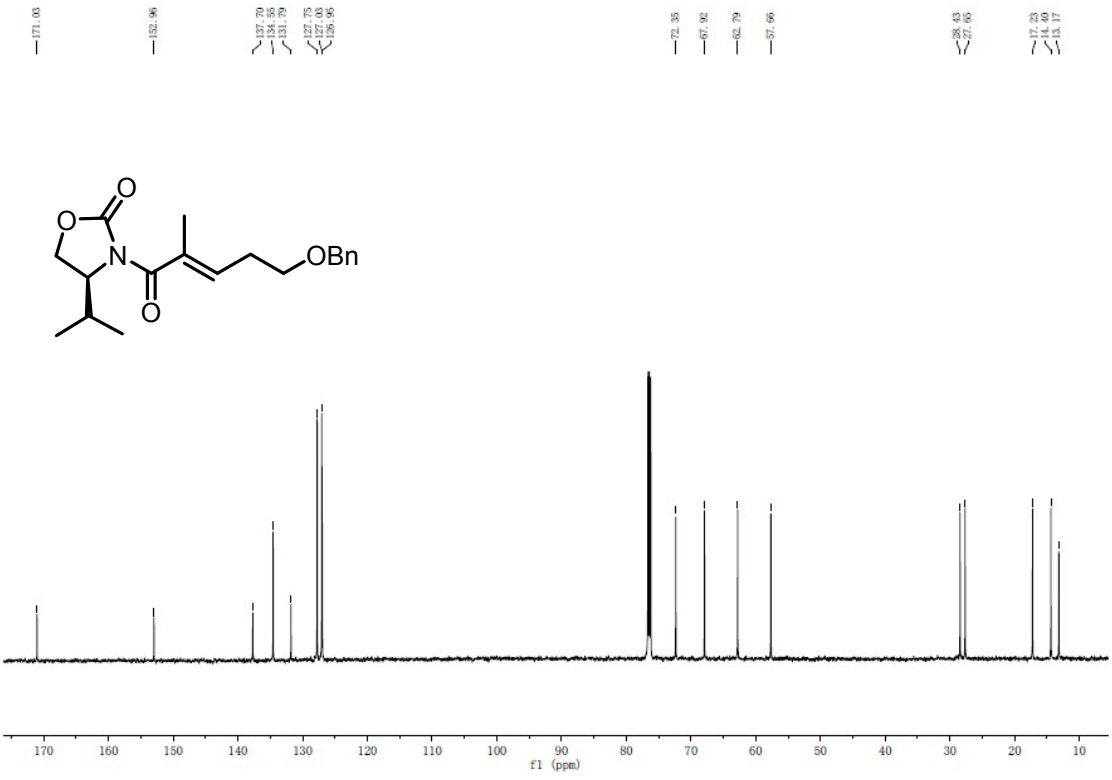
^{13}C-NMR spectrum of compound 6R (150 MHz, $CDCl_3$):



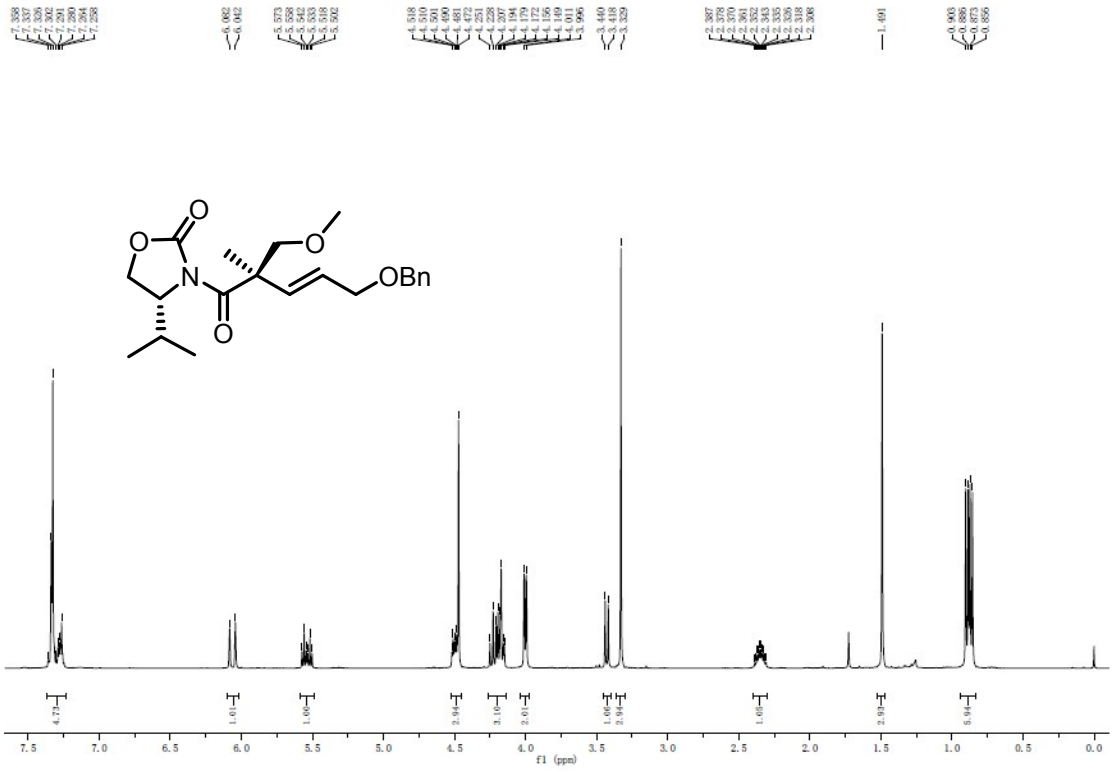
^{1}H-NMR spectrum of compound 6S (400 MHz, $CDCl_3$):



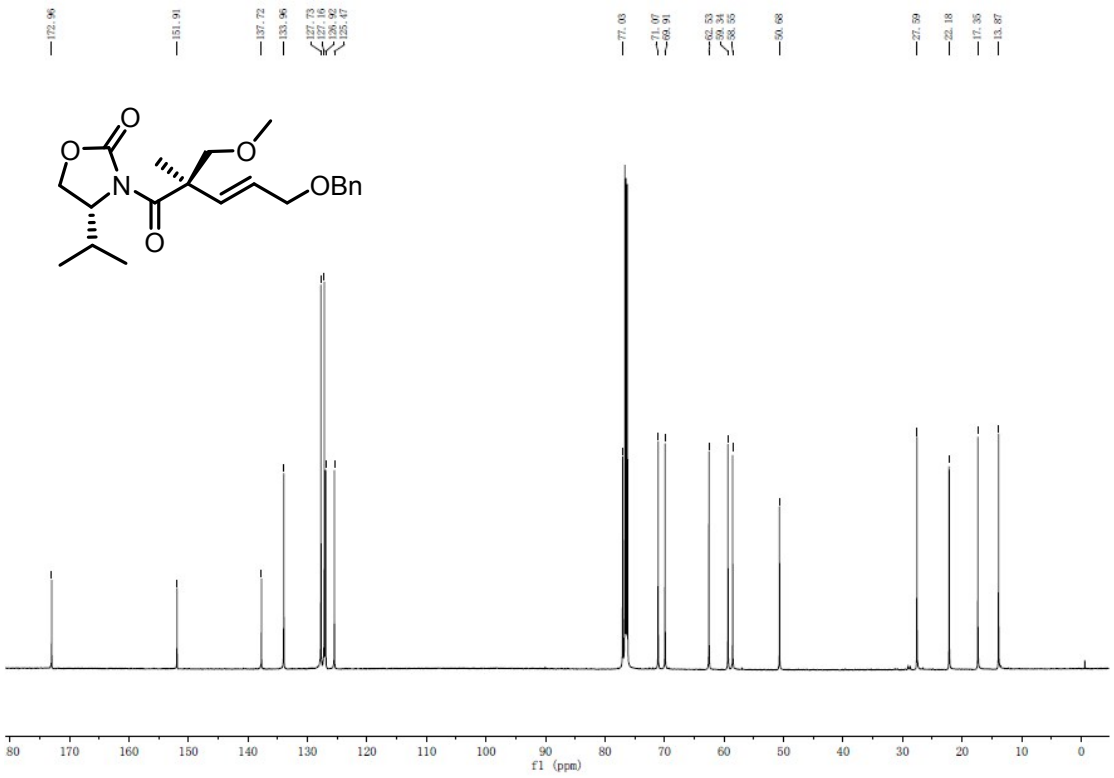
^{13}C-NMR spectrum of compound 6S (150 MHz, $CDCl_3$):



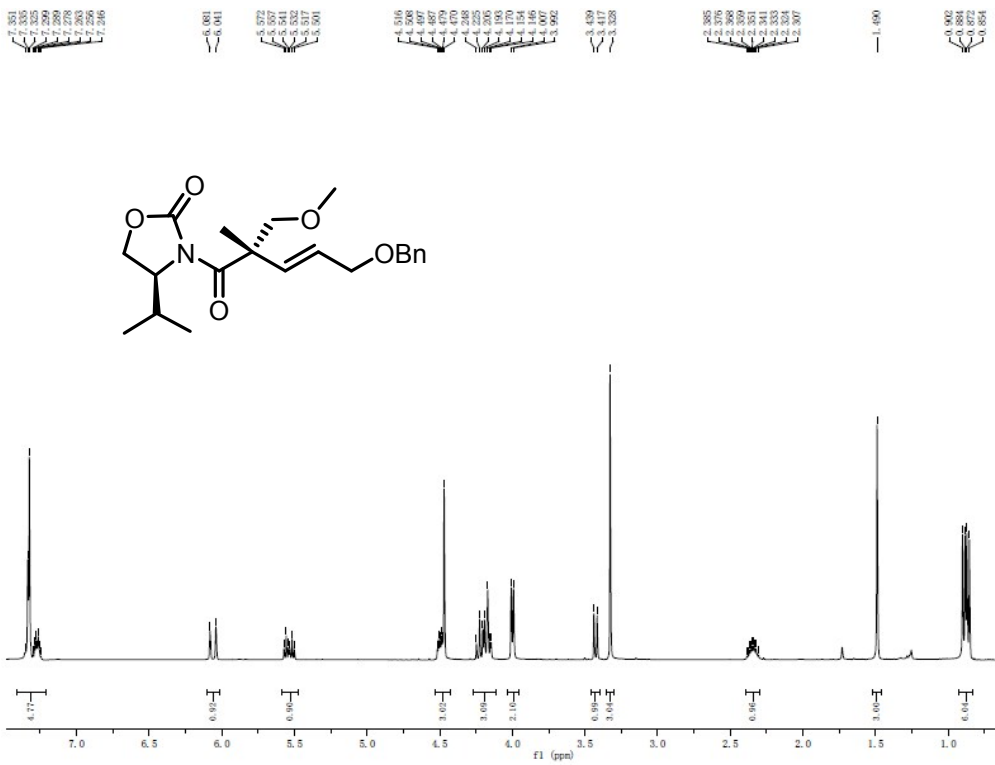
^{1}H-NMR spectrum of compound 7R (400 MHz, $CDCl_3$):



^{13}C-NMR spectrum of compound 7R (150 MHz, $CDCl_3$):

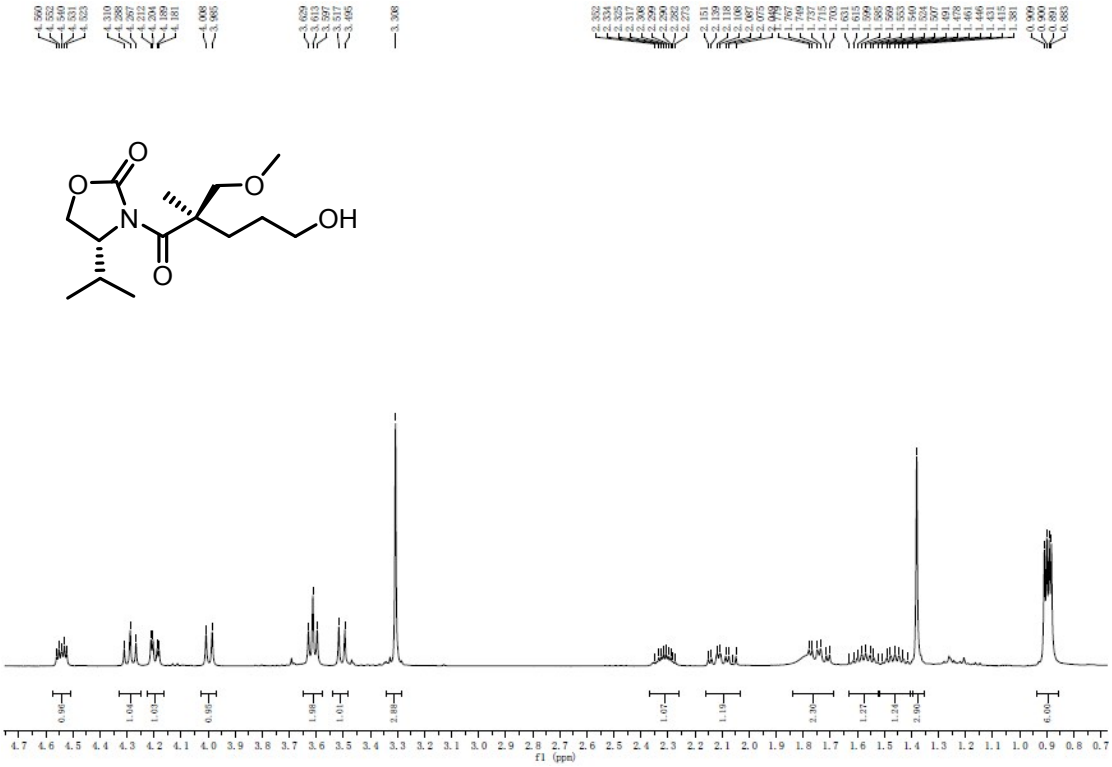


^{1}H-NMR spectrum of compound 7S (400 MHz, $CDCl_3$):

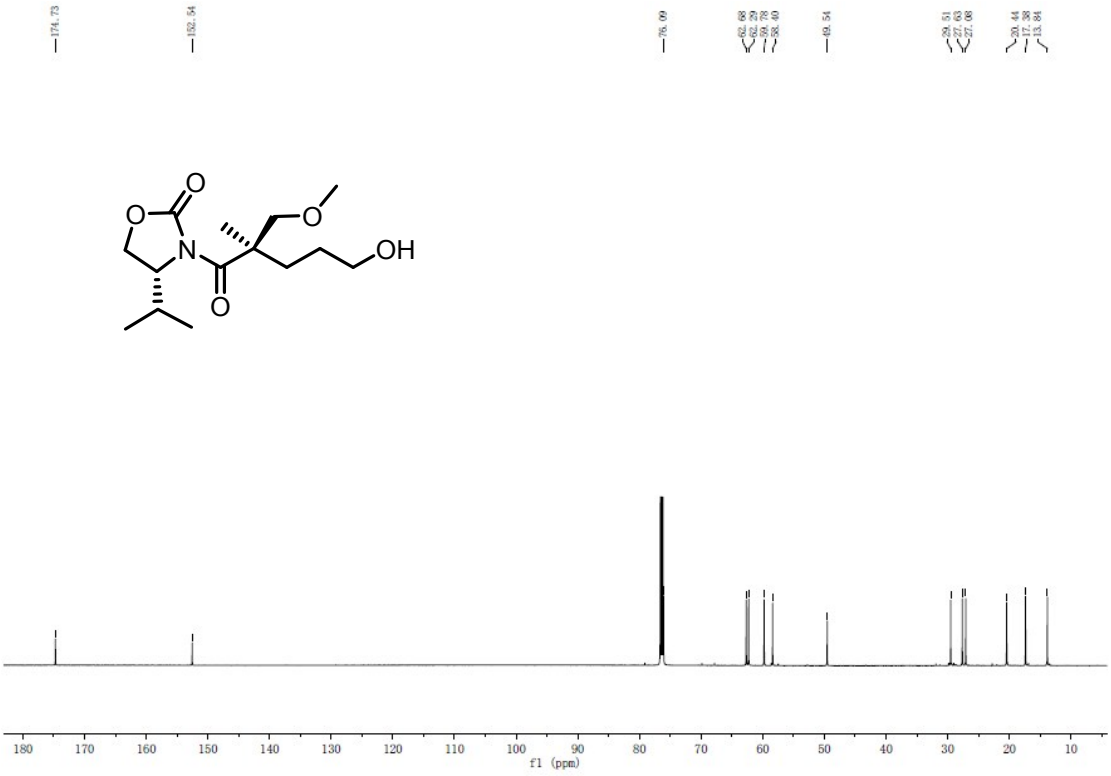


^{13}C-NMR spectrum of compound 7R (150 MHz, $CDCl_3$):

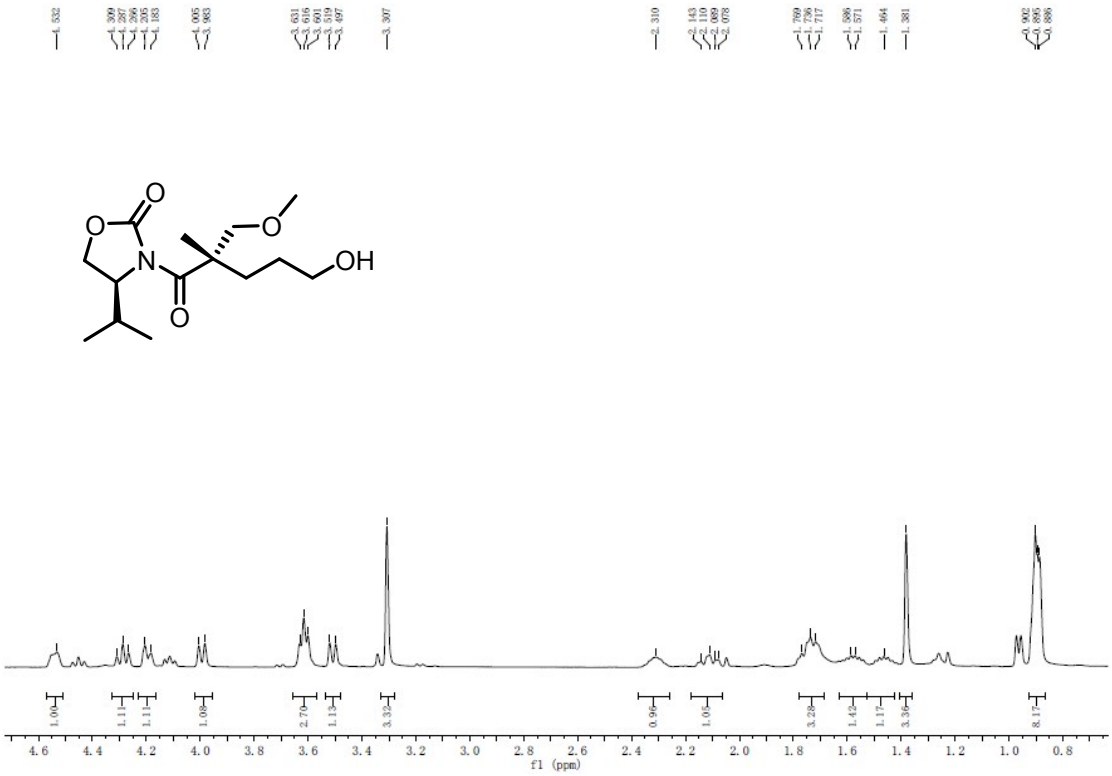
^{1}H-NMR spectrum of compound 8R (400 MHz, $CDCl_3$):



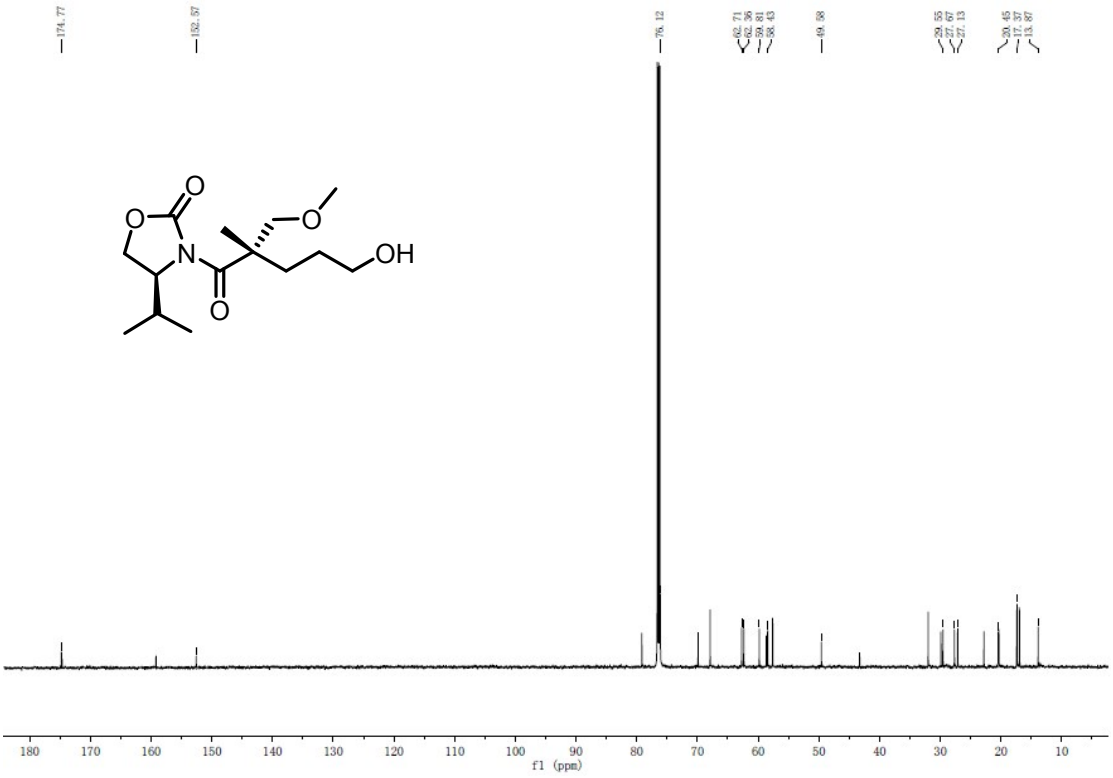
^{13}C-NMR spectrum of compound 8R (150 MHz, $CDCl_3$):



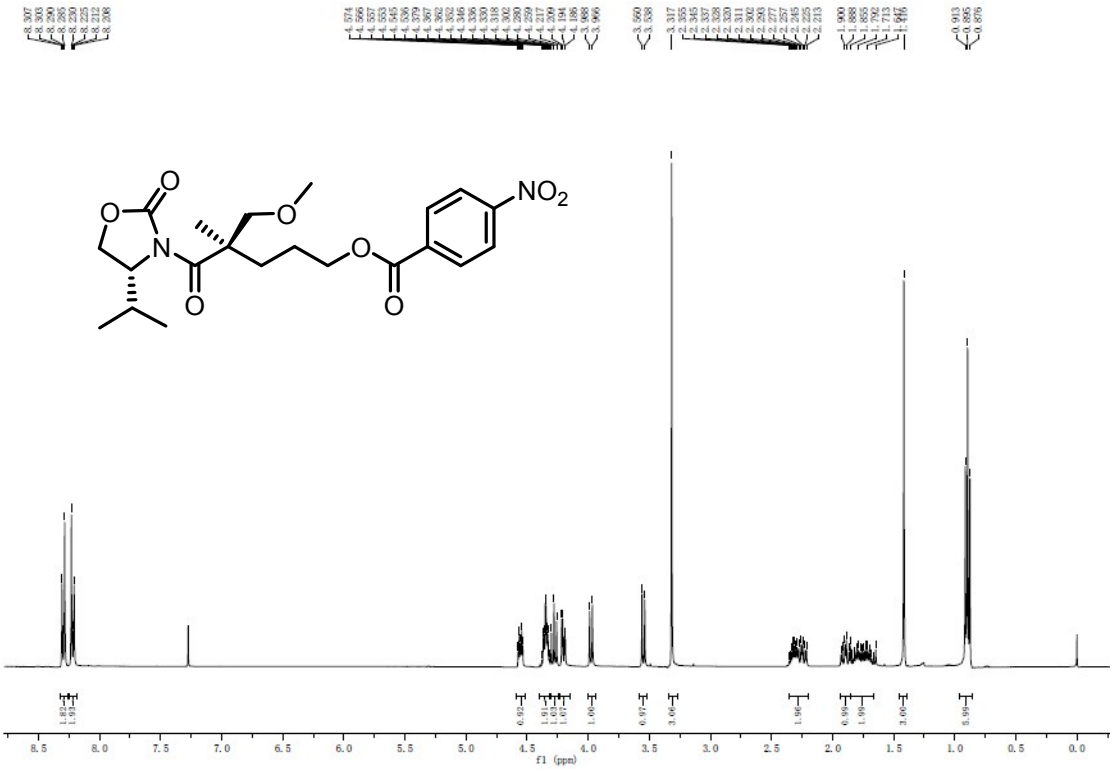
^{1}H-NMR spectrum of compound 8S (400 MHz, $CDCl_3$):



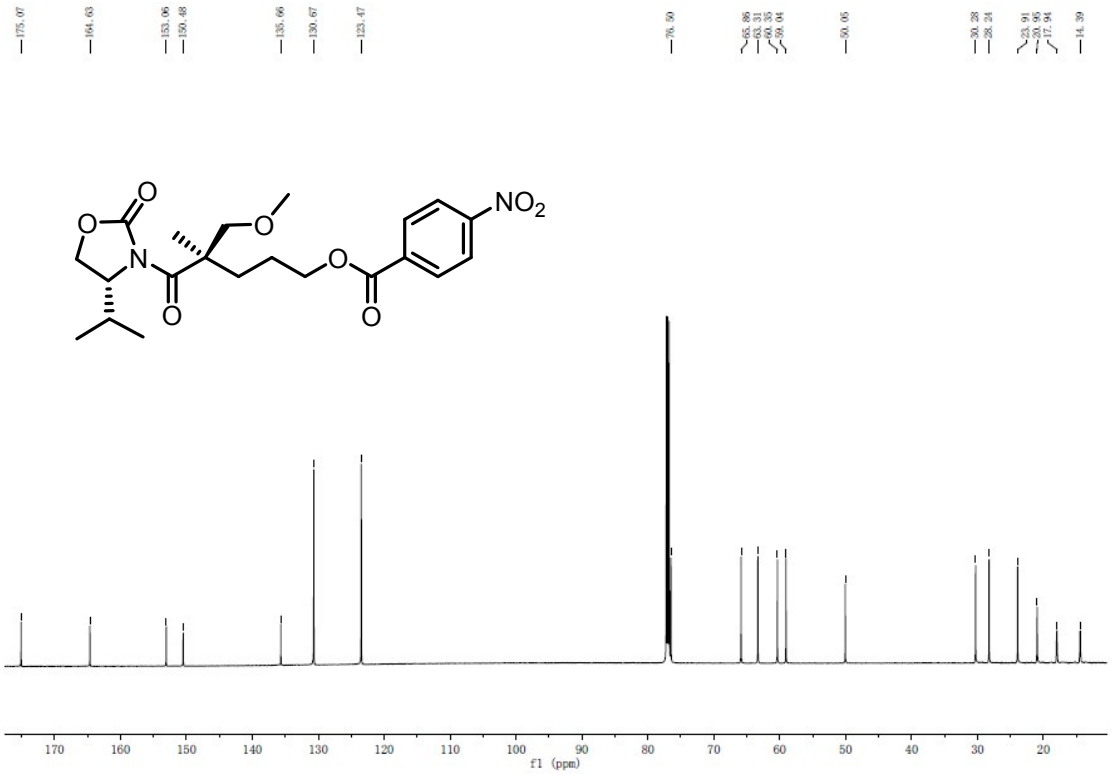
^{13}C-NMR spectrum of compound 8S (150 MHz, $CDCl_3$):



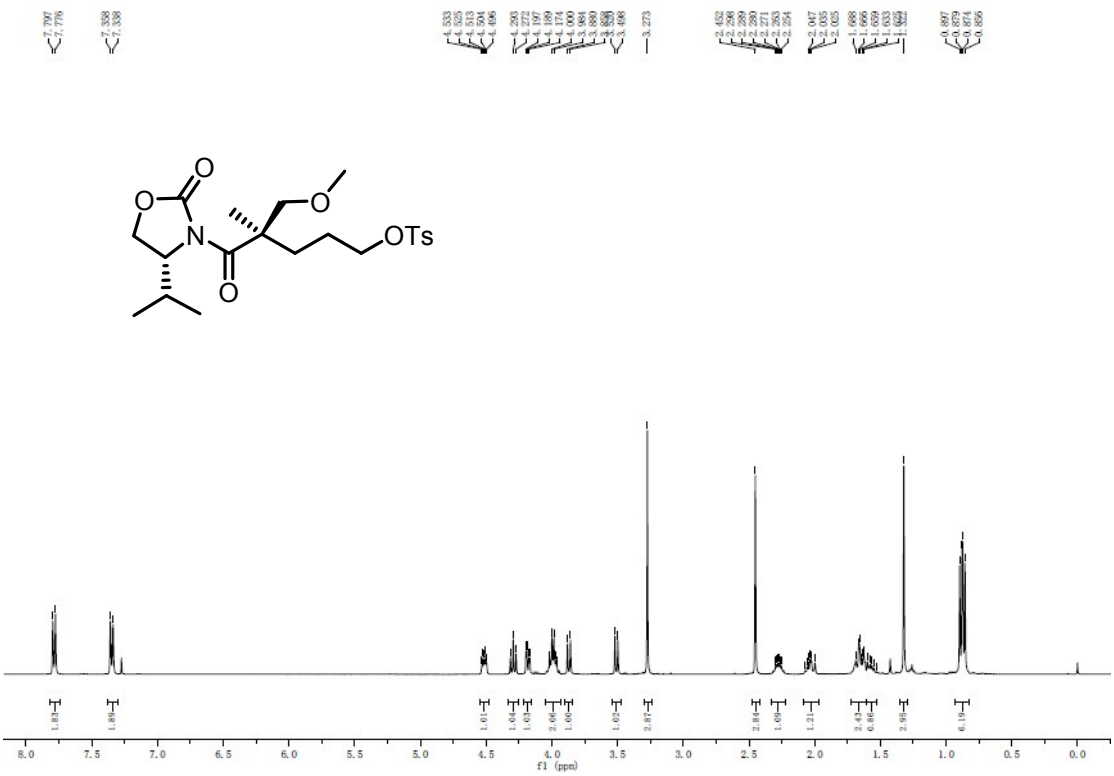
^{1}H-NMR spectrum of compound 8R' (400 MHz, $CDCl_3$):



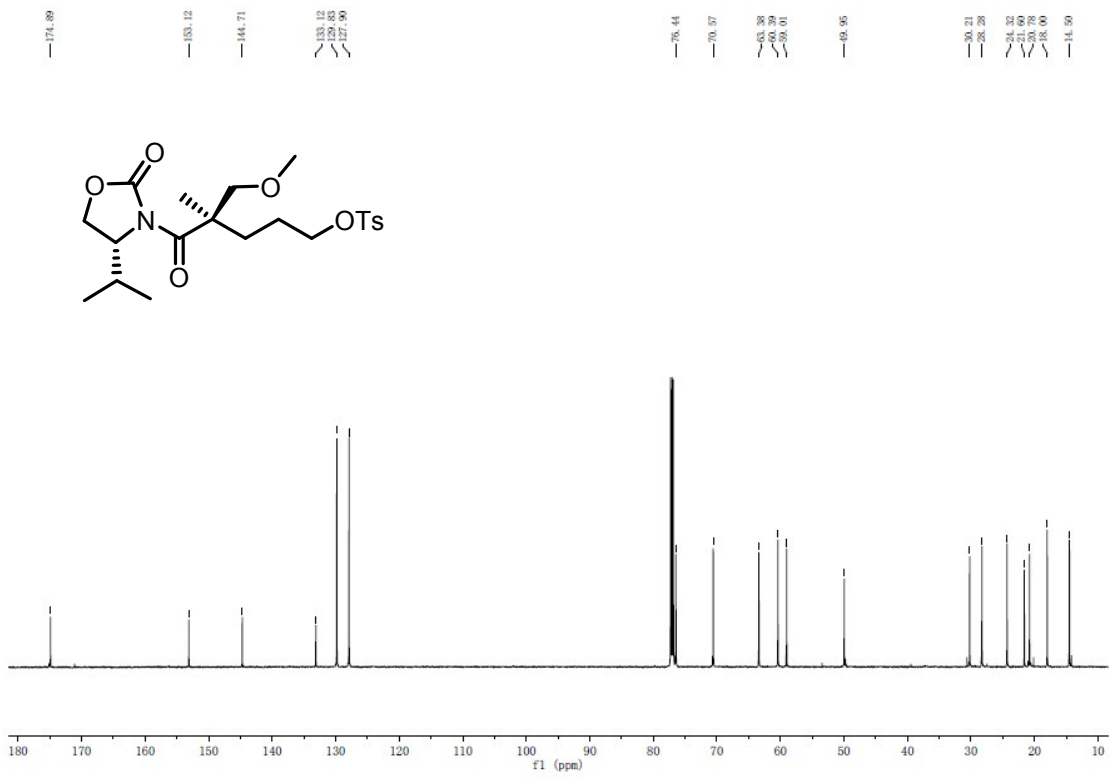
^{13}C-NMR spectrum of compound 8R' (150 MHz, $CDCl_3$):



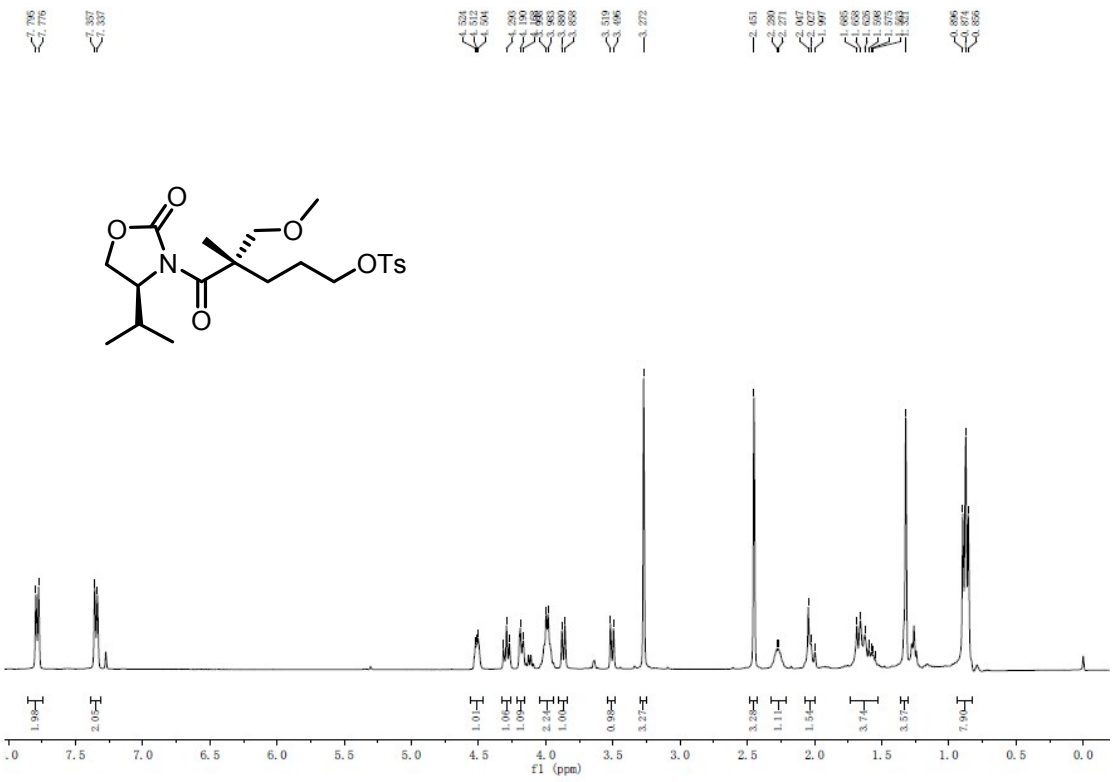
^{1}H-NMR spectrum of compound 9R (400 MHz, $CDCl_3$):



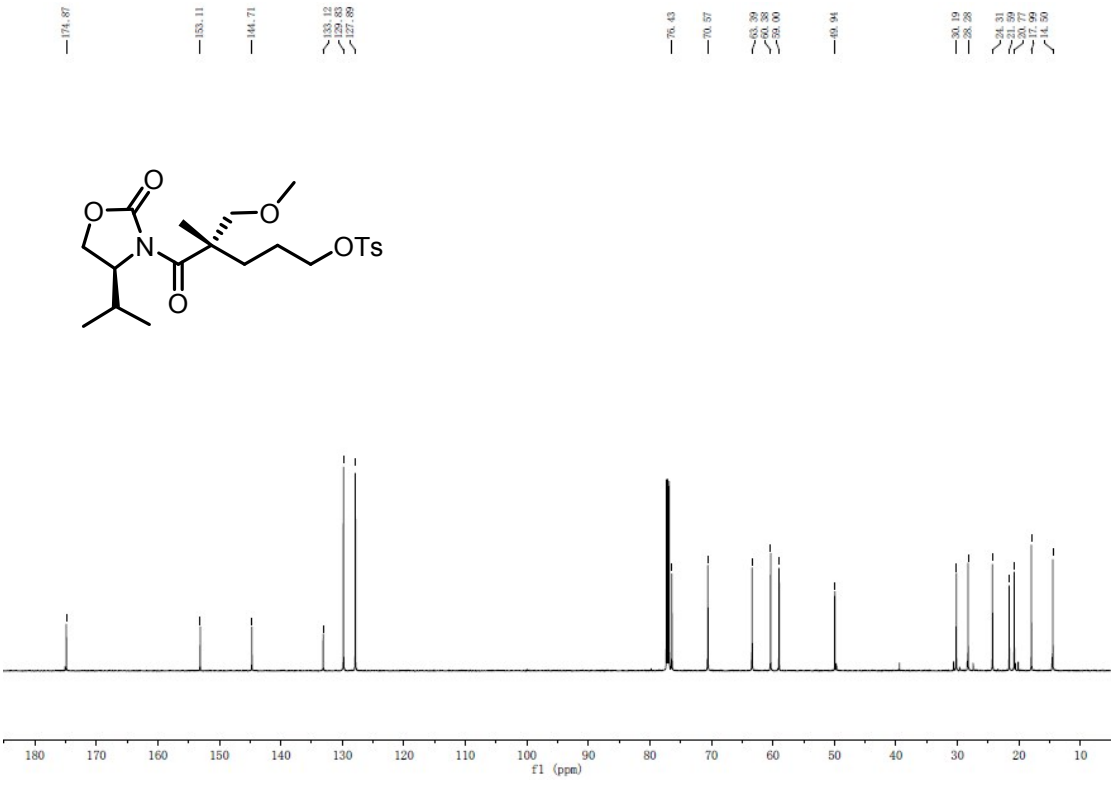
^{13}C-NMR spectrum of compound 9R (150 MHz, $CDCl_3$):



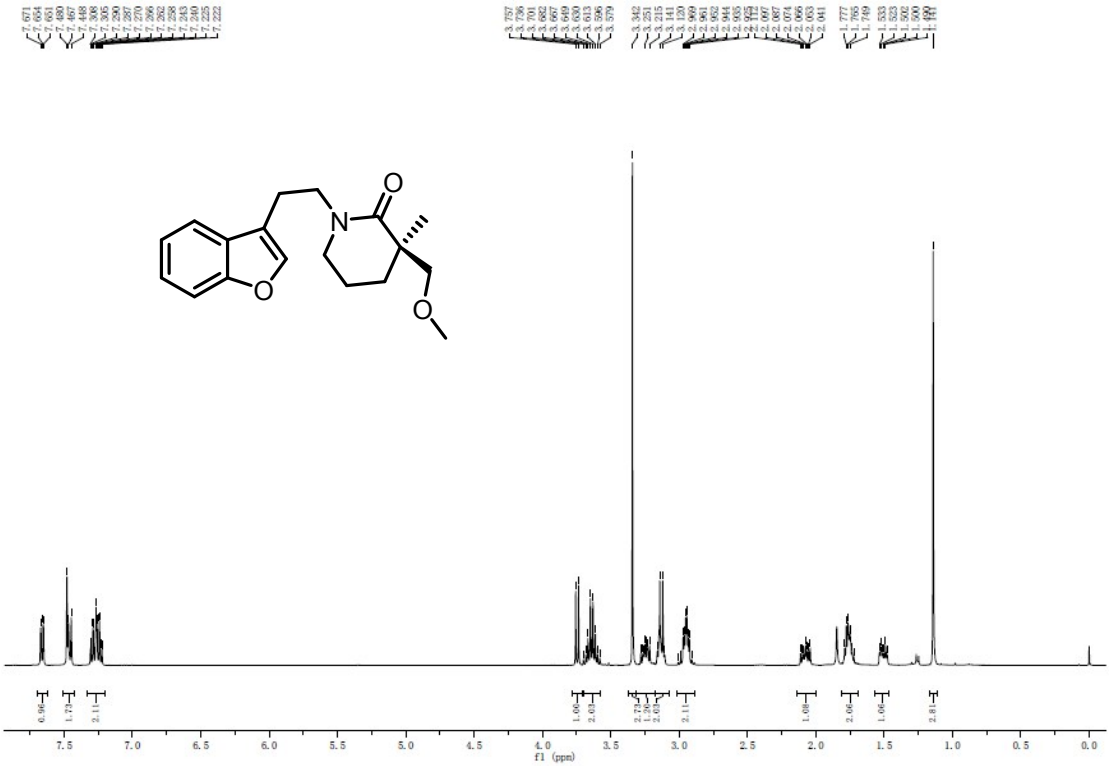
^{1}H-NMR spectrum of compound 9S (400 MHz, $CDCl_3$):



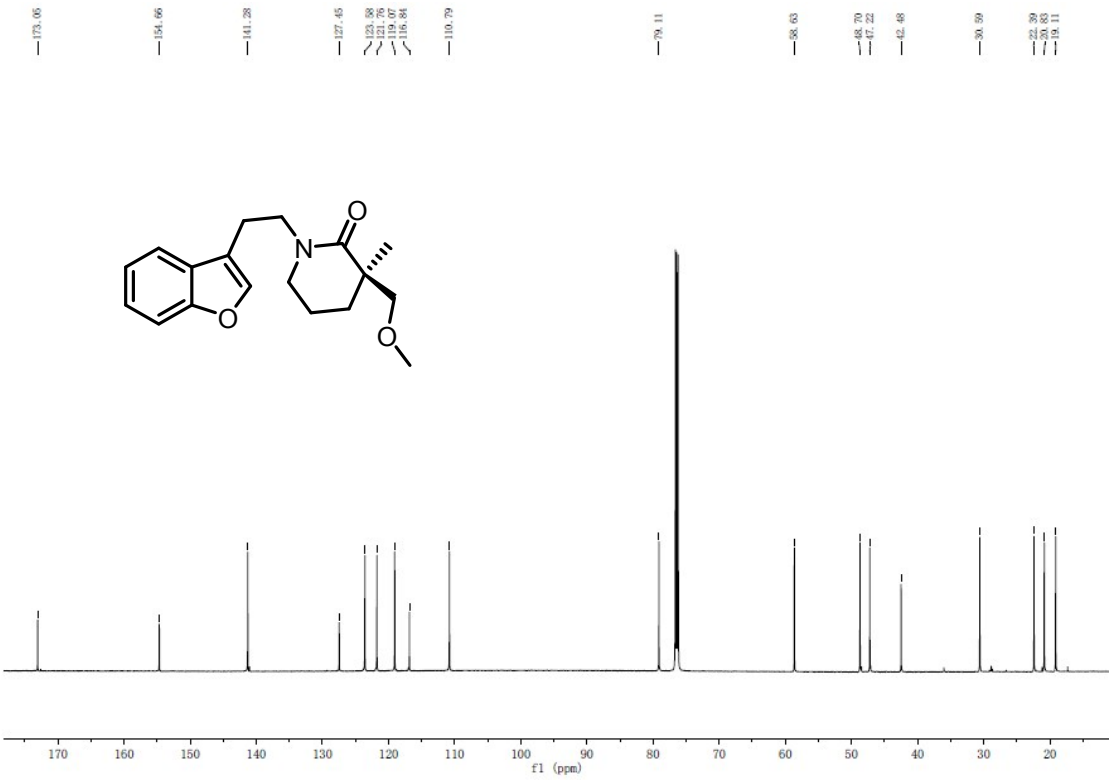
^{13}C-NMR spectrum of compound 9S (150 MHz, $CDCl_3$):



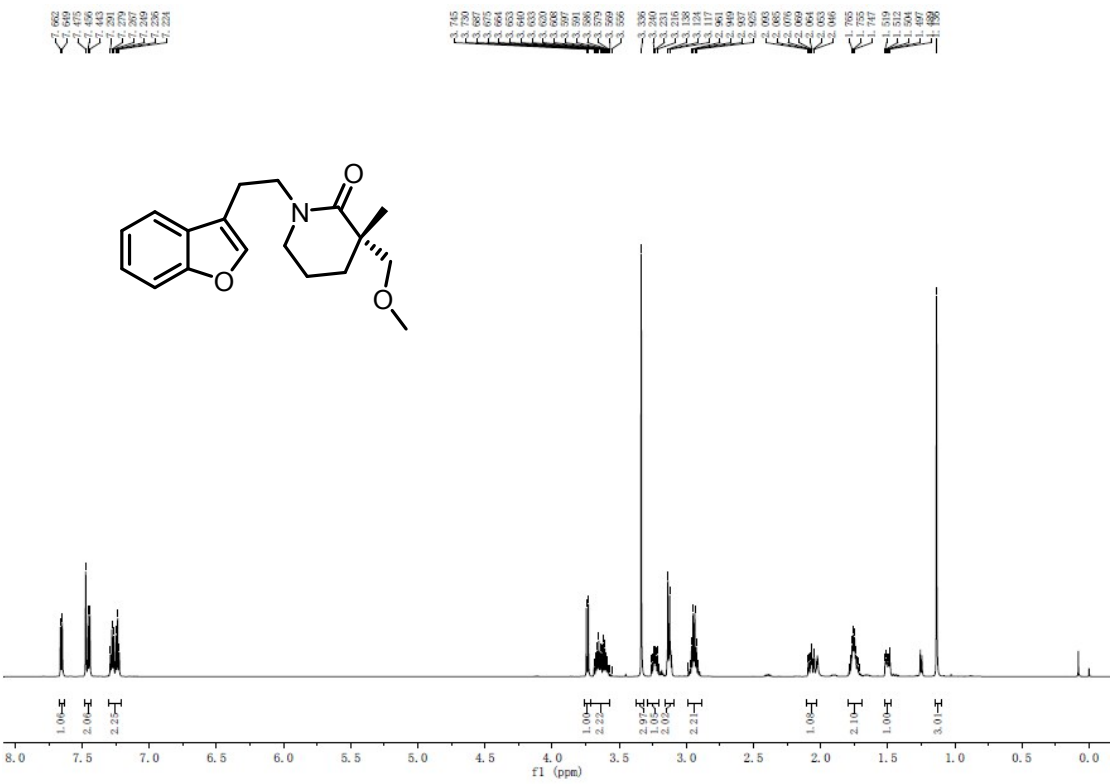
^{1}H-NMR spectrum of compound 10R (400 MHz, $CDCl_3$):



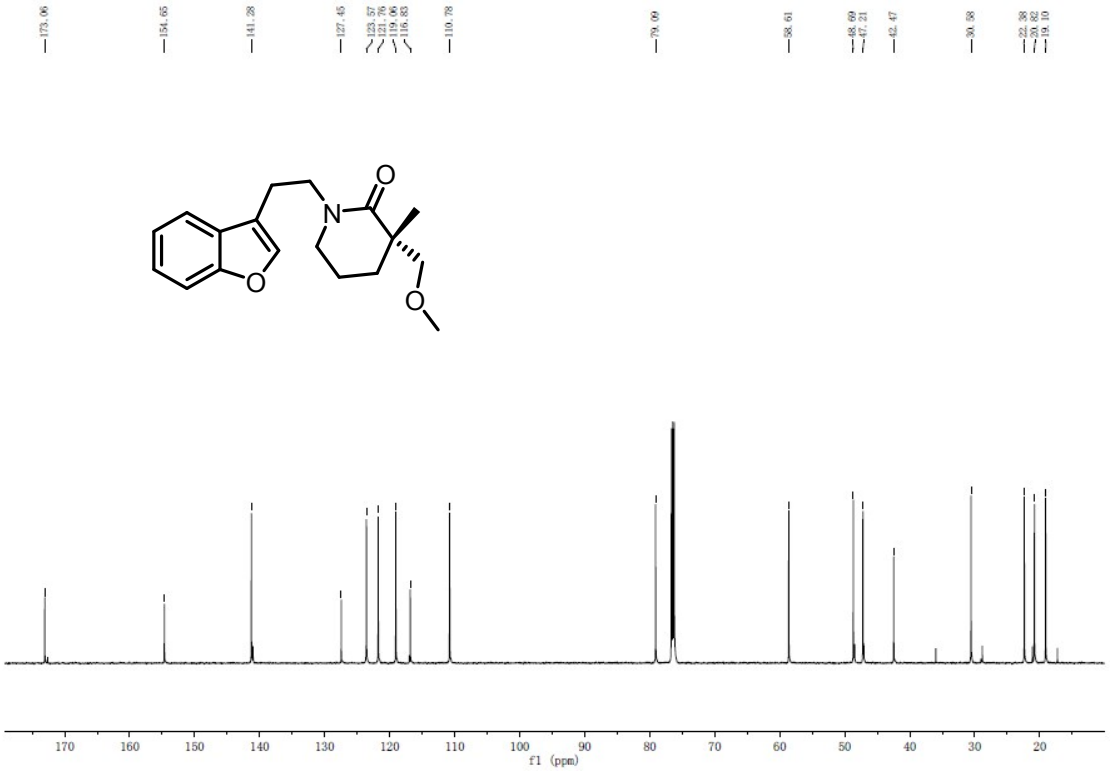
^{13}C-NMR spectrum of compound 10R (150 MHz, $CDCl_3$):



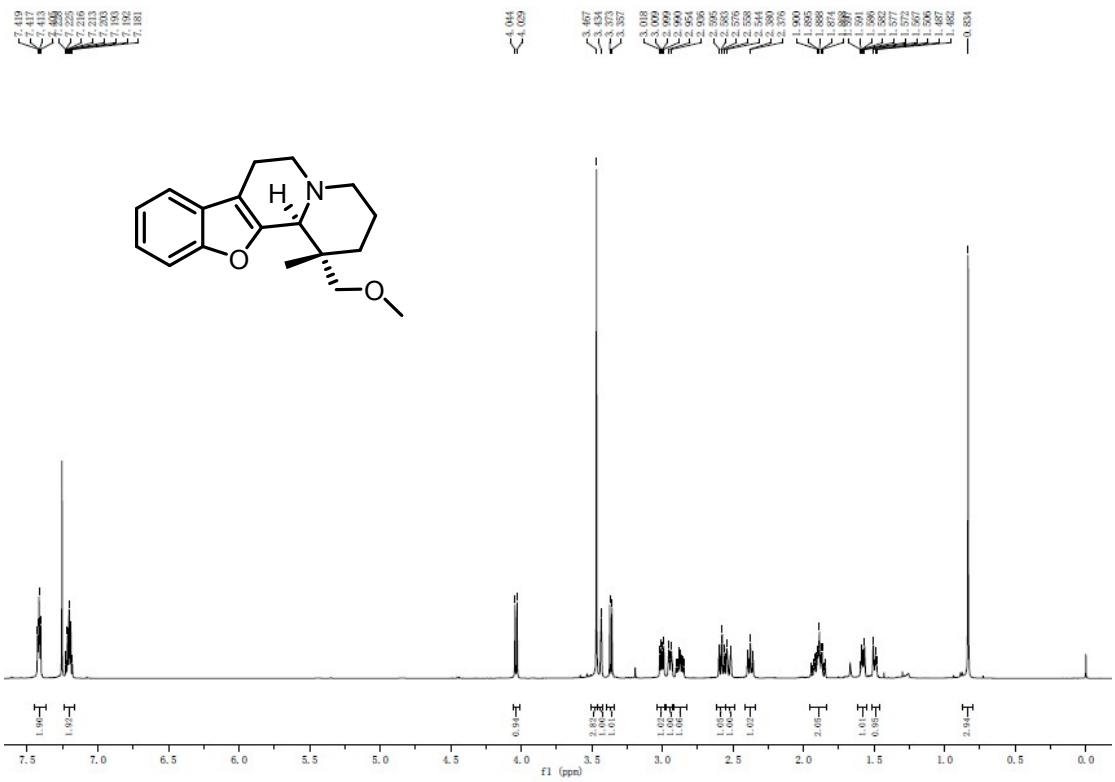
^{1}H-NMR spectrum of compound 10S (600 MHz, $CDCl_3$):



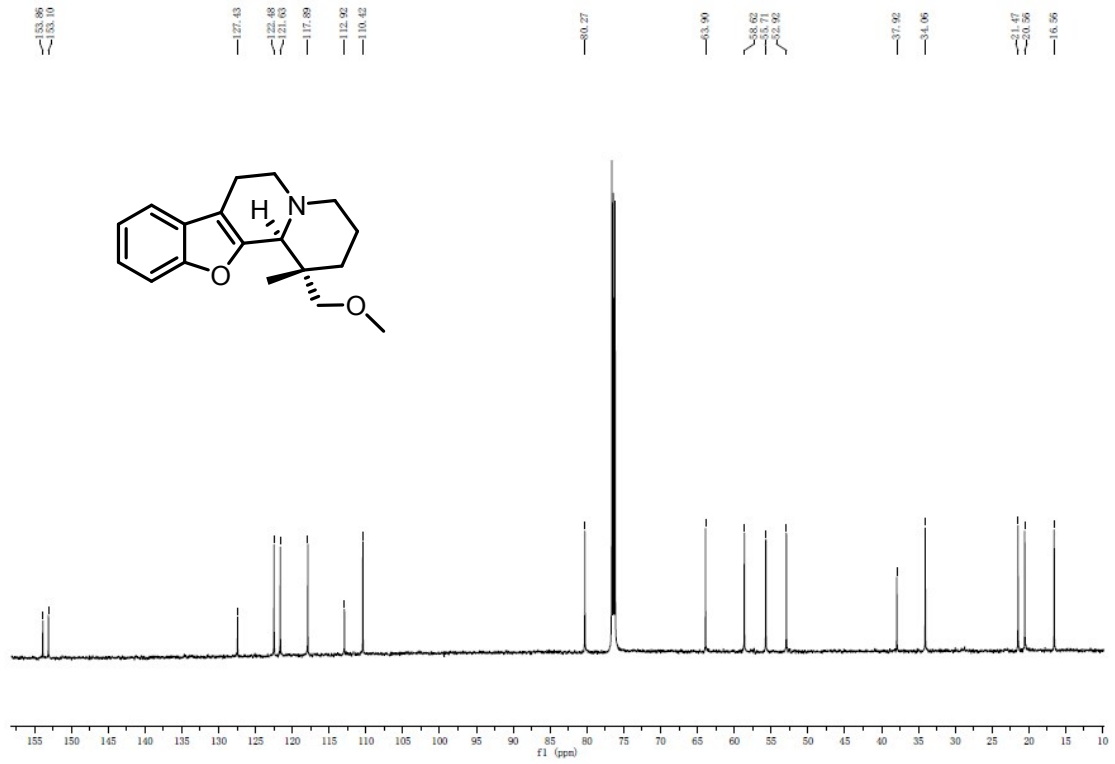
^{13}C-NMR spectrum of compound 10S (150 MHz, $CDCl_3$):



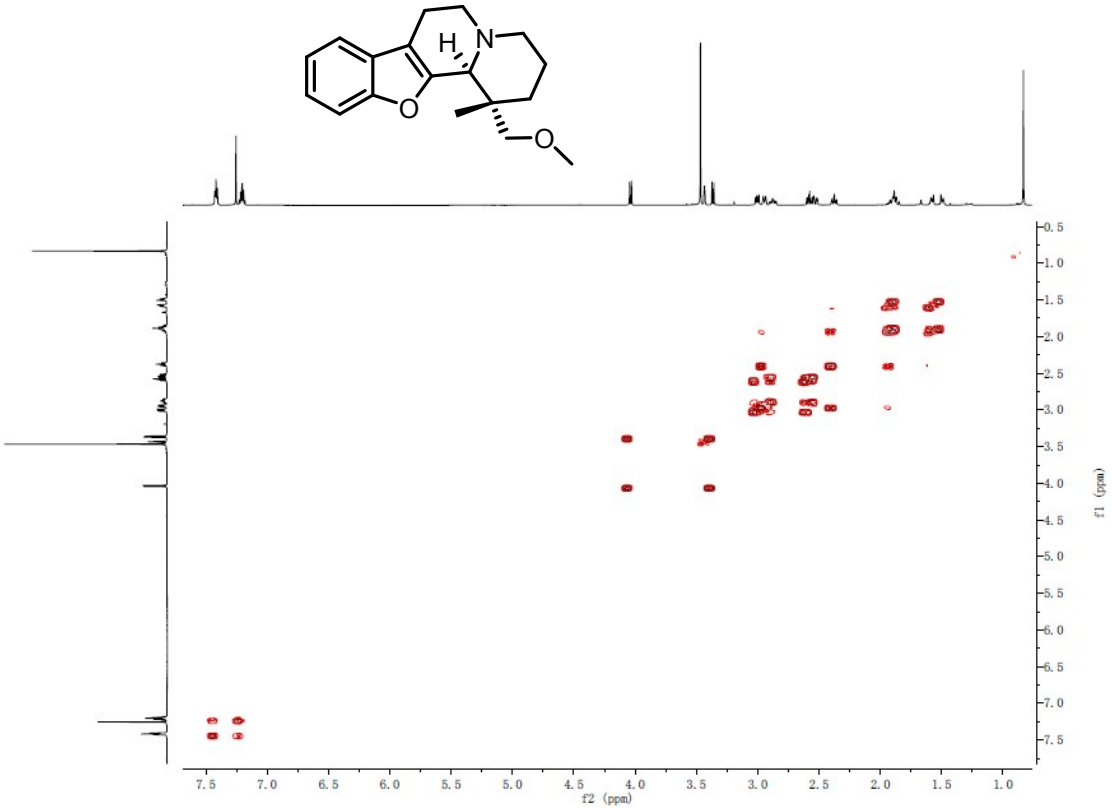
^{1}H-NMR spectrum of compound 12a (600 MHz, $CDCl_3$):



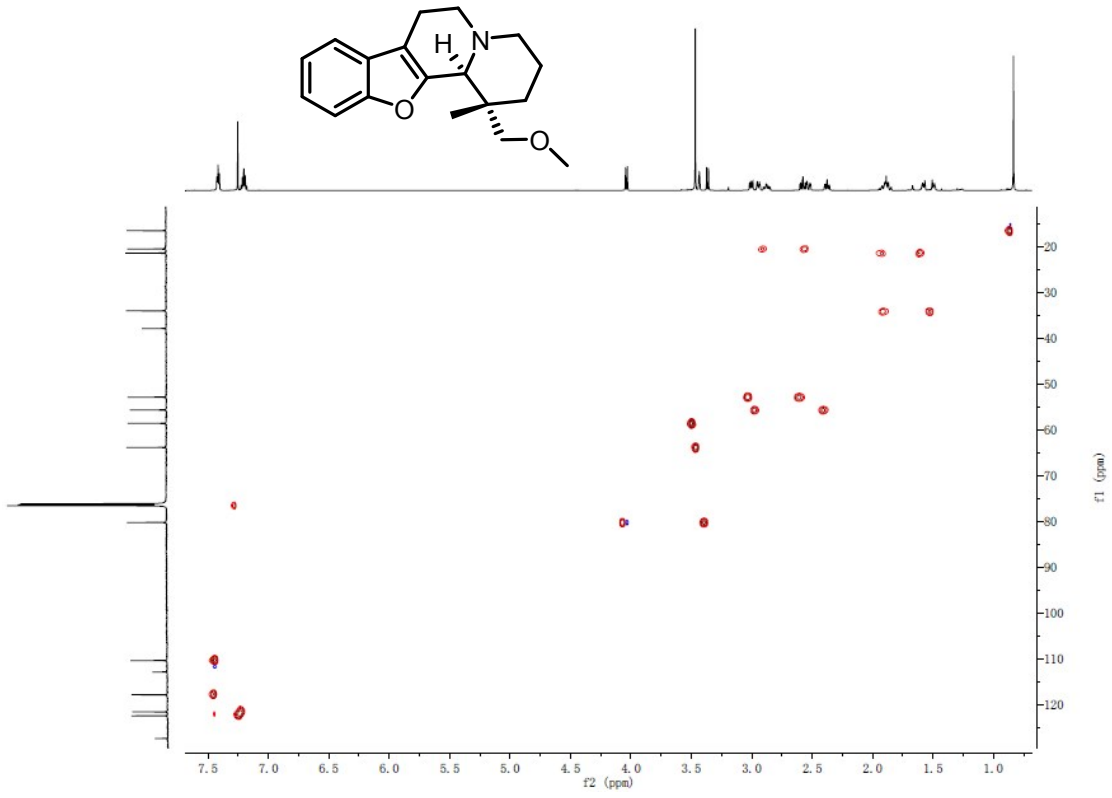
^{13}C-NMR spectrum of compound 12a (150 MHz, $CDCl_3$):



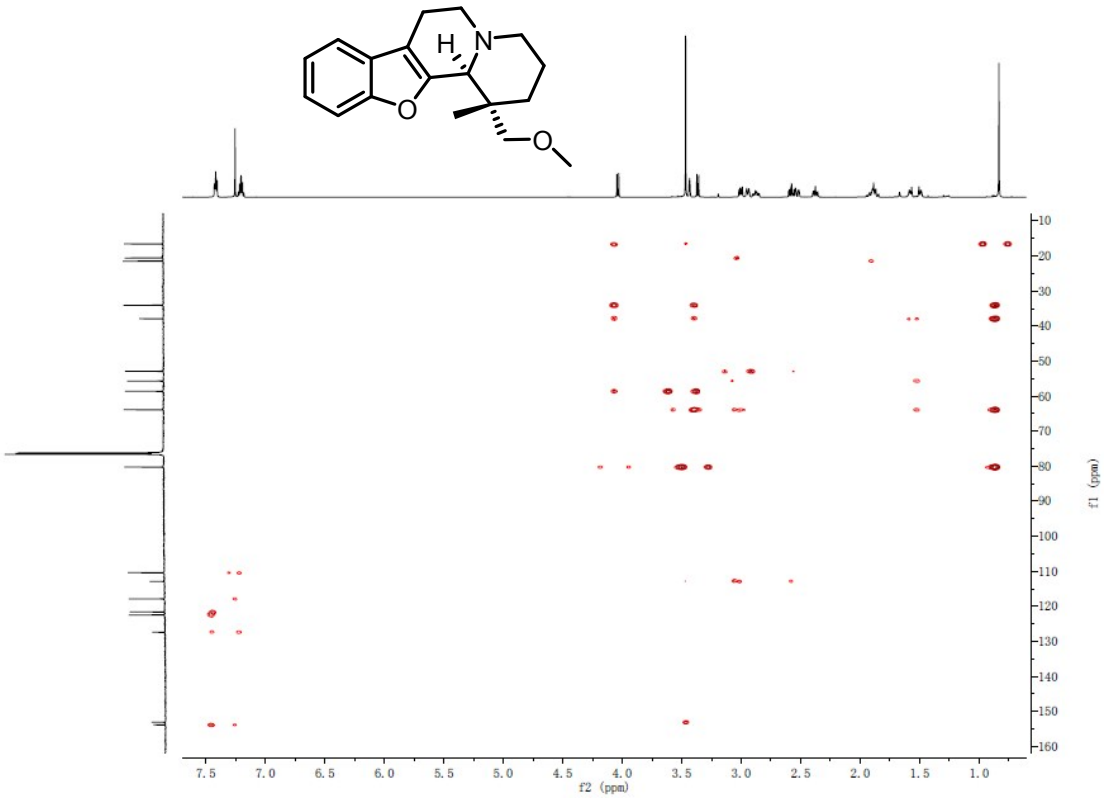
^{1}H-^{1}H COSY spectrum of compound 12a (600 MHz, $CDCl_3$):



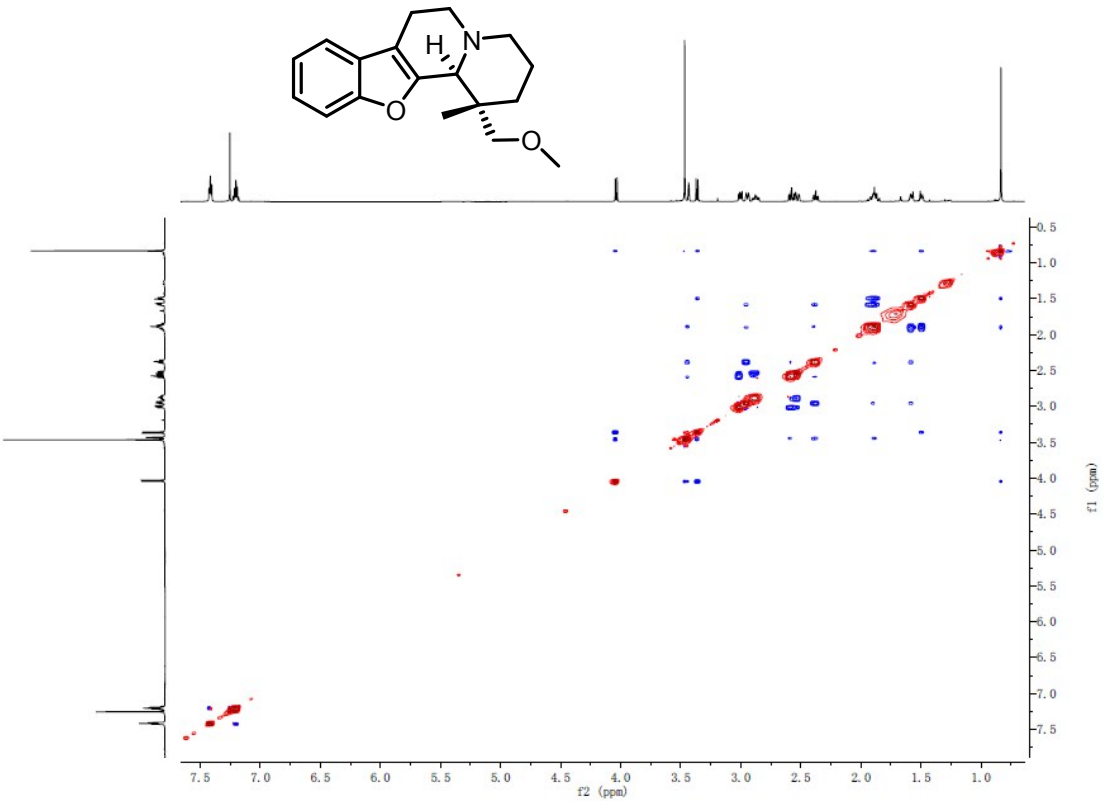
HSQC spectrum of compound 12a (600 MHz, $CDCl_3$):



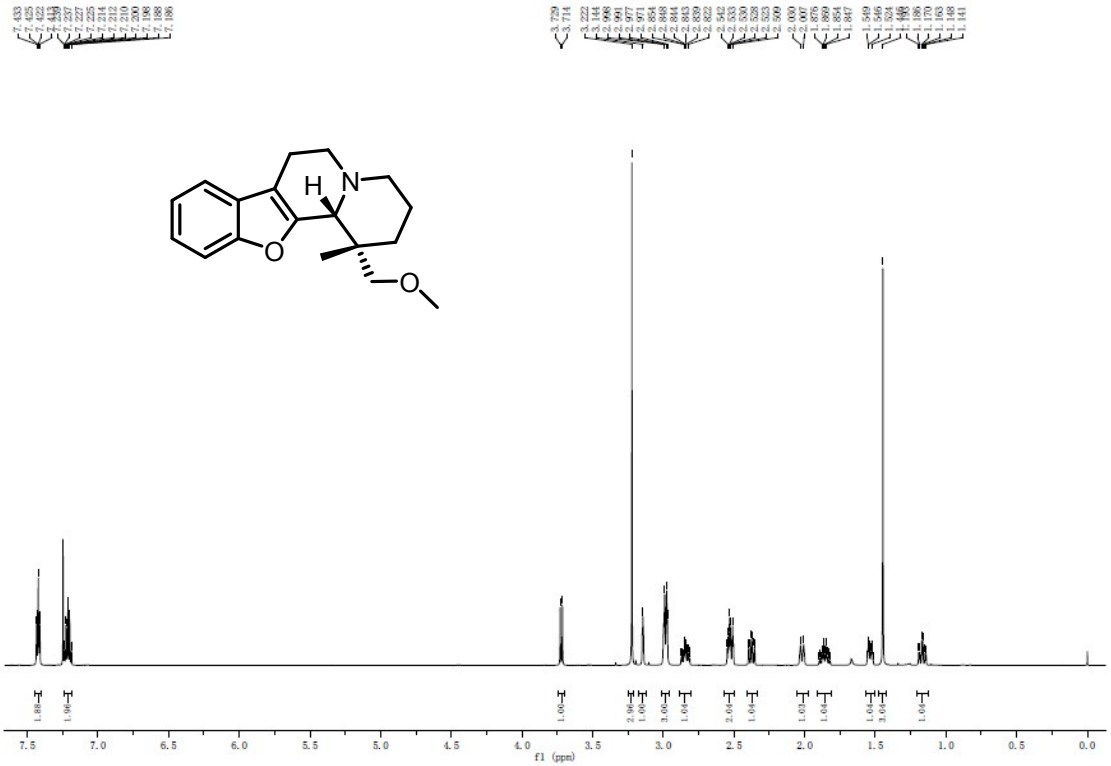
HMBC spectrum of compound 12a (600 MHz, $CDCl_3$):



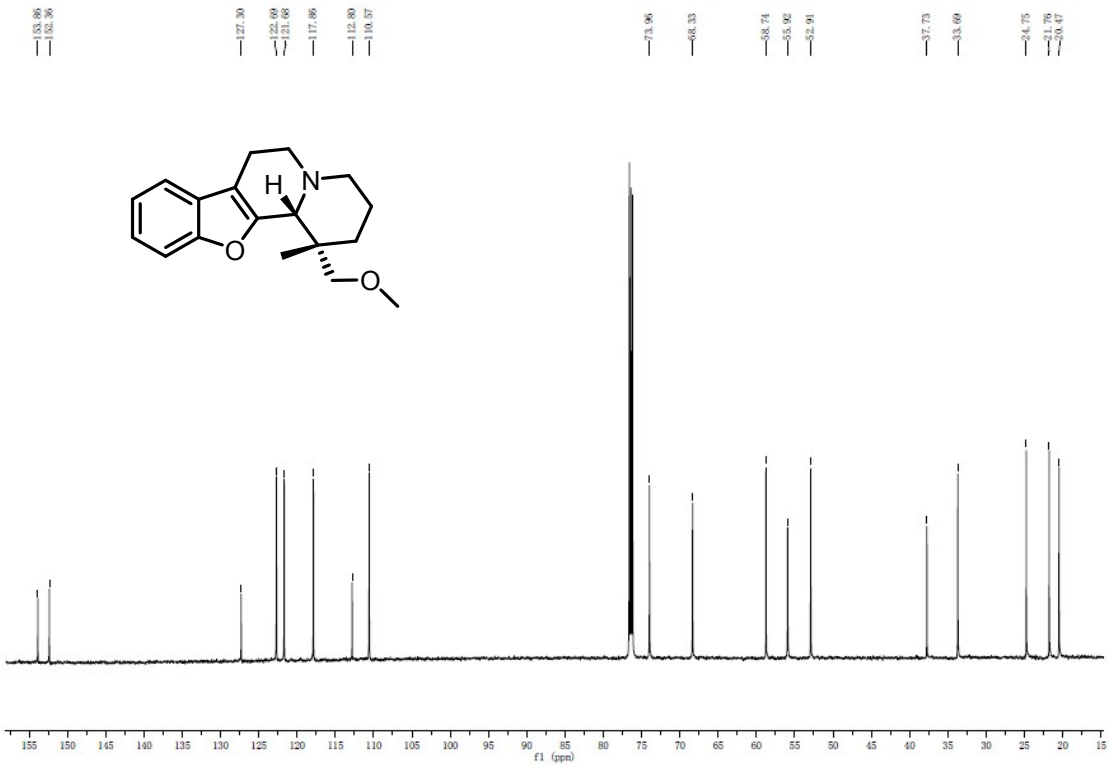
NOESY spectrum of compound 12a (600 MHz, $CDCl_3$):



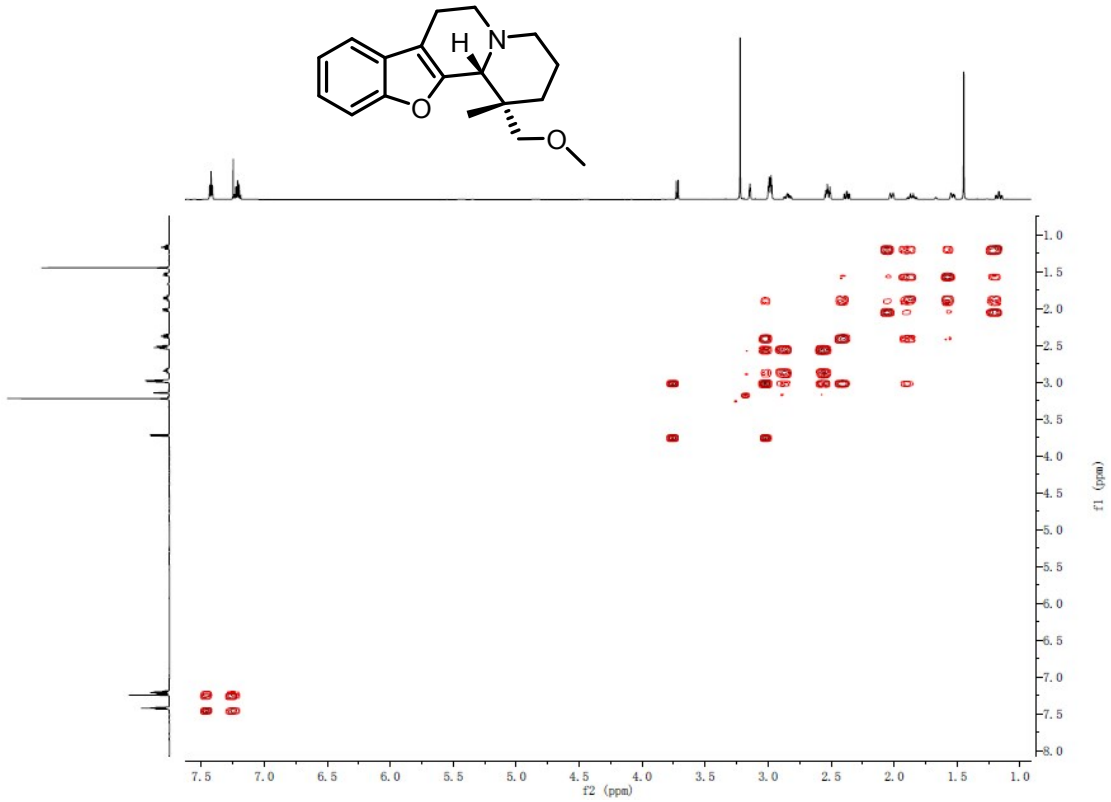
^{1}H-NMR spectrum of compound 12b (600 MHz, $CDCl_3$):



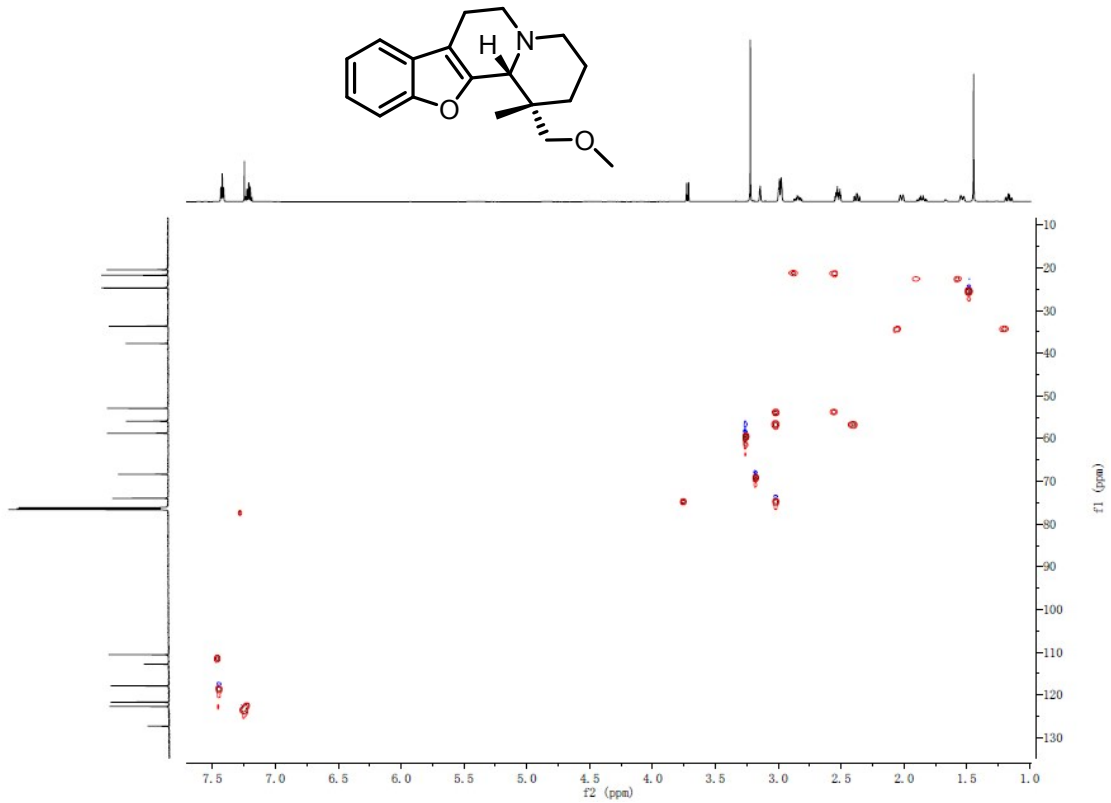
^{13}C-NMR spectrum of compound 12b (150 MHz, $CDCl_3$):



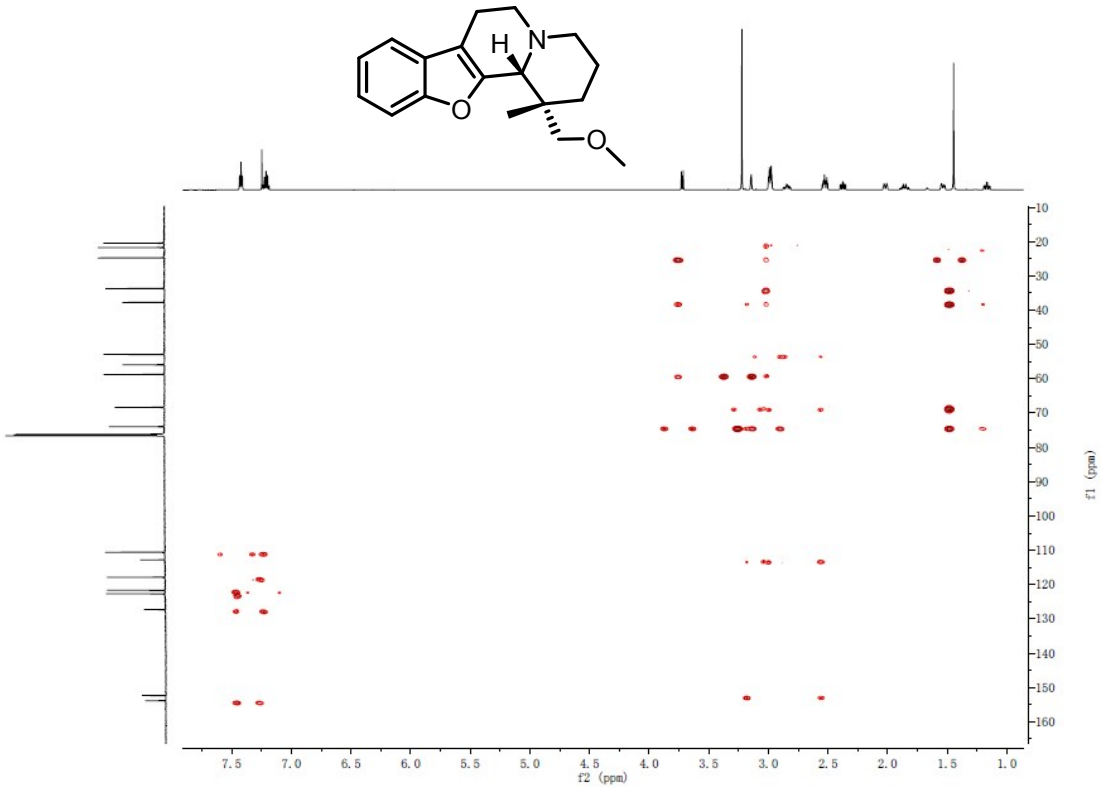
^{1}H-^{1}H COSY spectrum of compound 12b (600 MHz, $CDCl_3$):



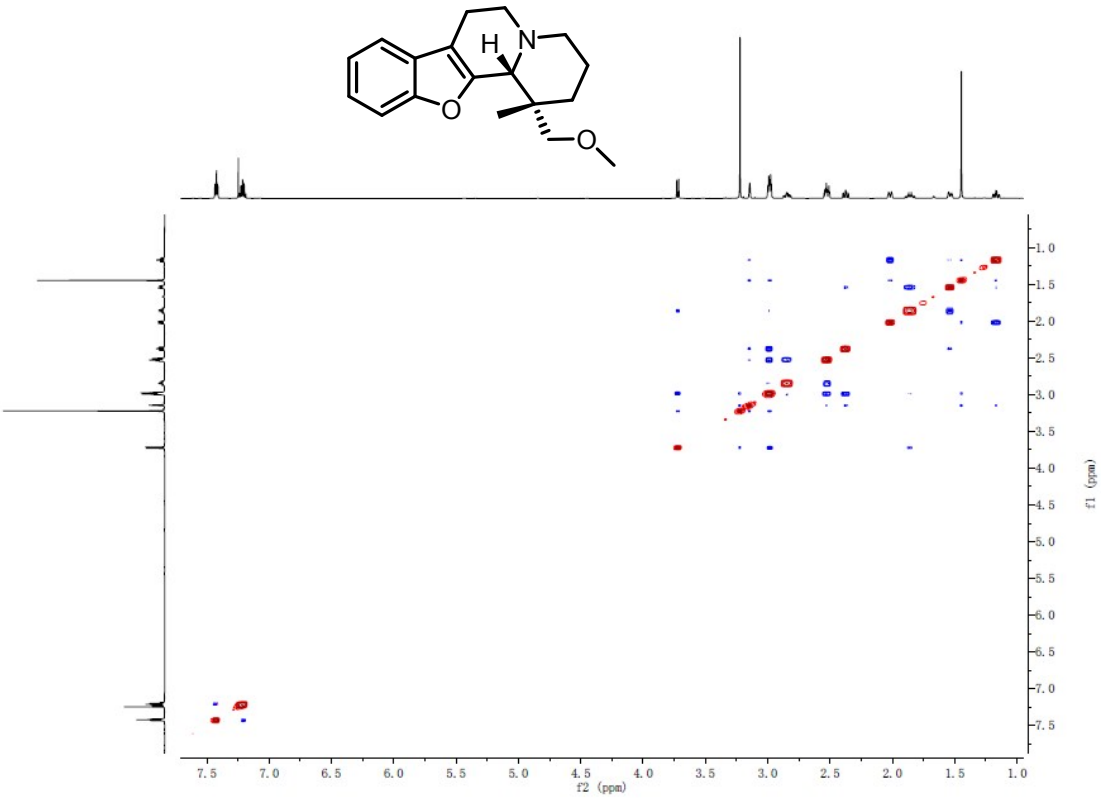
HSQC spectrum of compound 12b (600 MHz, $CDCl_3$):



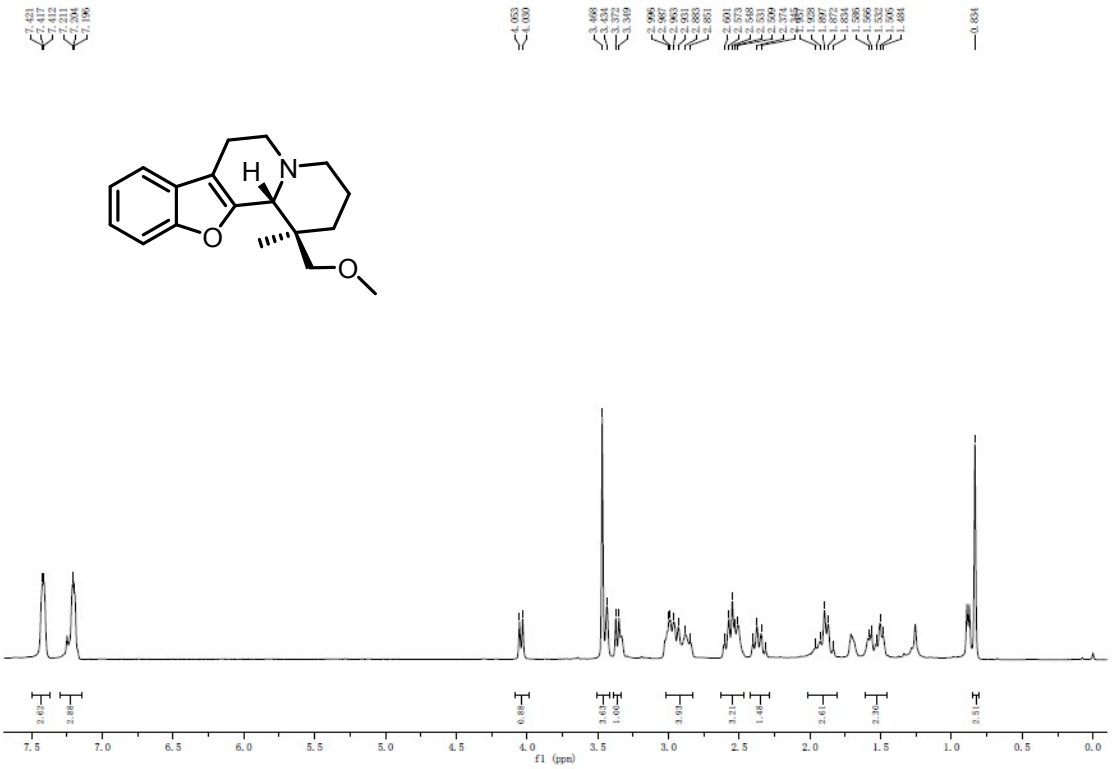
HMBC spectrum of compound 12b (600 MHz, $CDCl_3$):



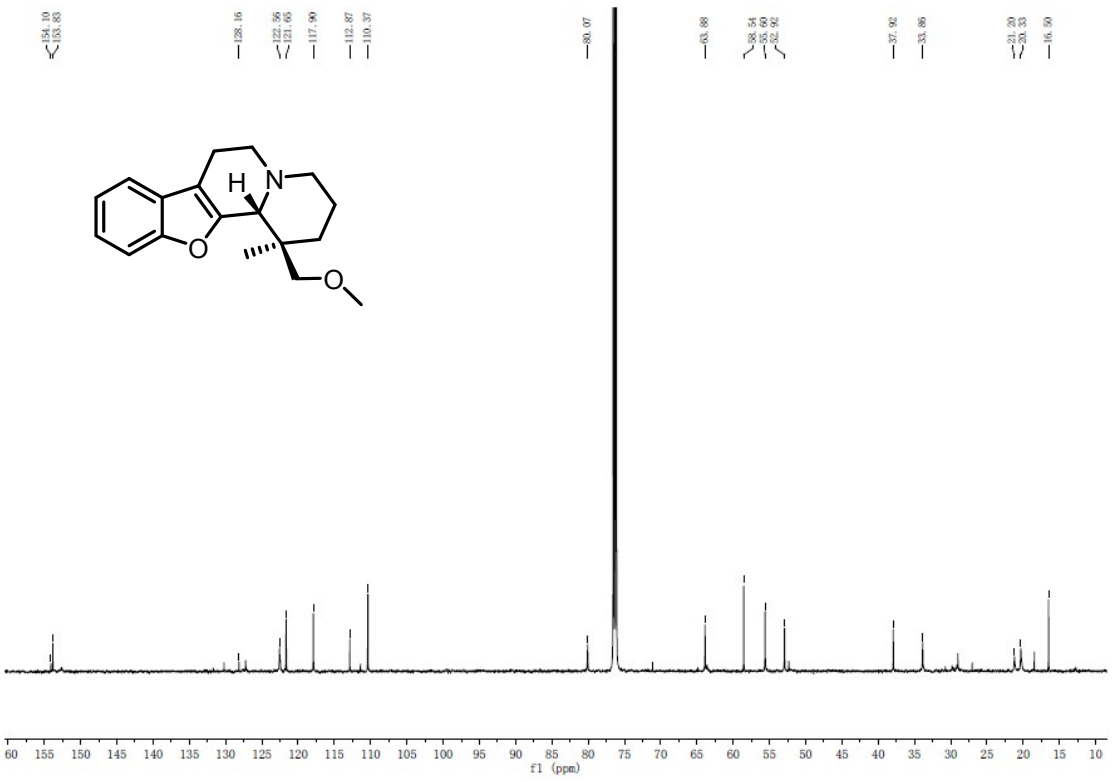
NOESY spectrum of compound 12b (600 MHz, $CDCl_3$):



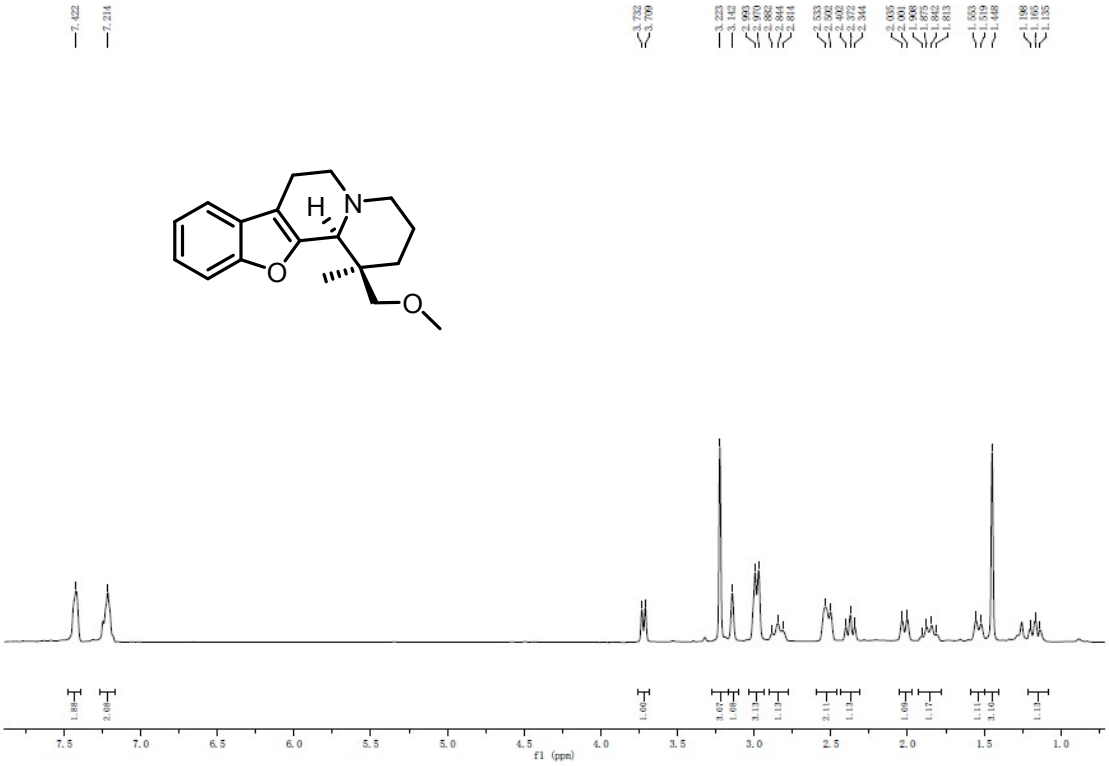
^{1}H-NMR spectrum of compound ent-12a (400 MHz, $CDCl_3$):



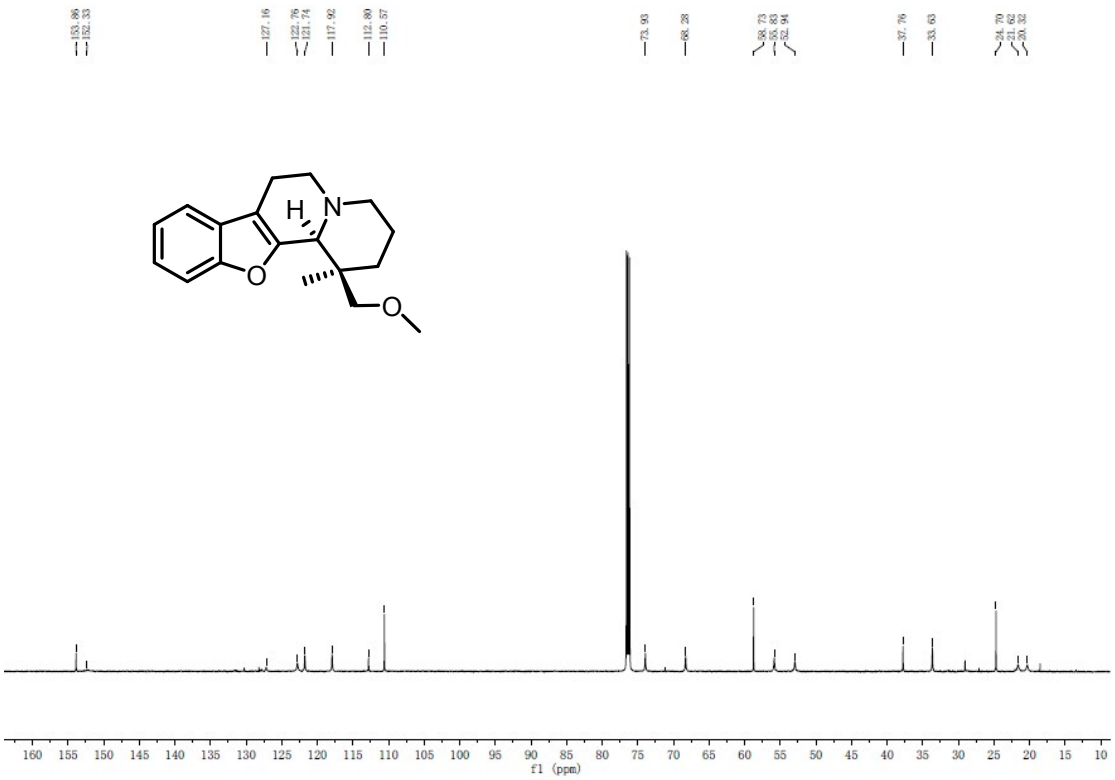
^{13}C-NMR spectrum of compound ent-12a (150 MHz, $CDCl_3$):



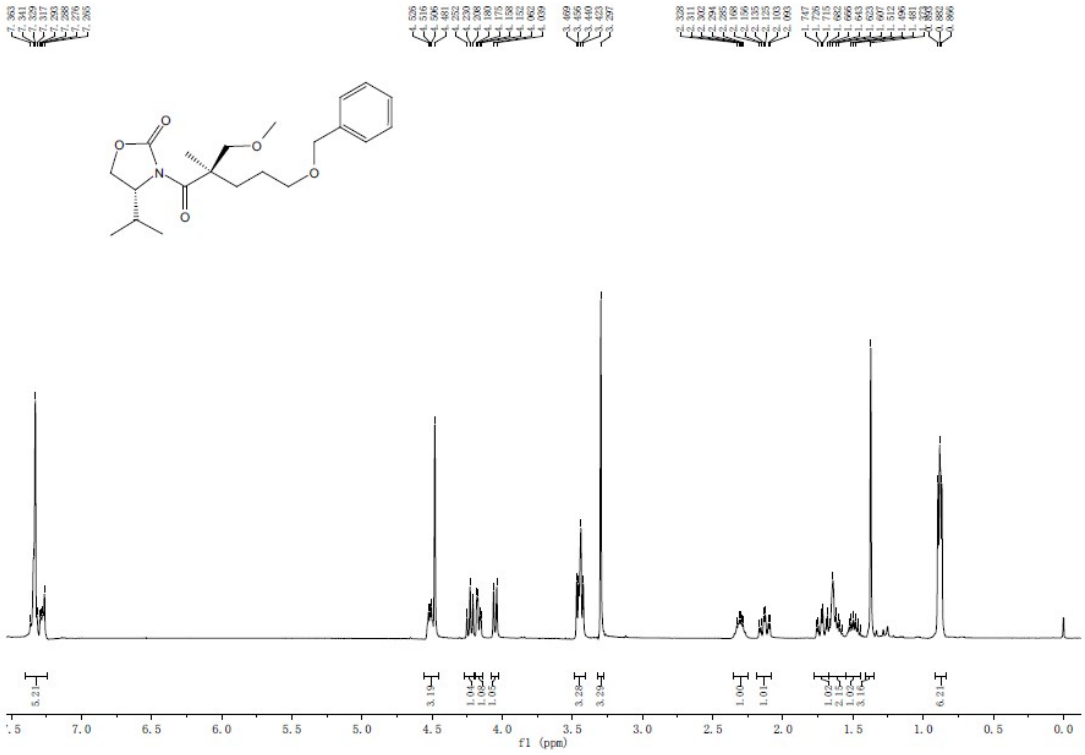
^{1}H-NMR spectrum of compound ent-12b (400 MHz, $CDCl_3$):



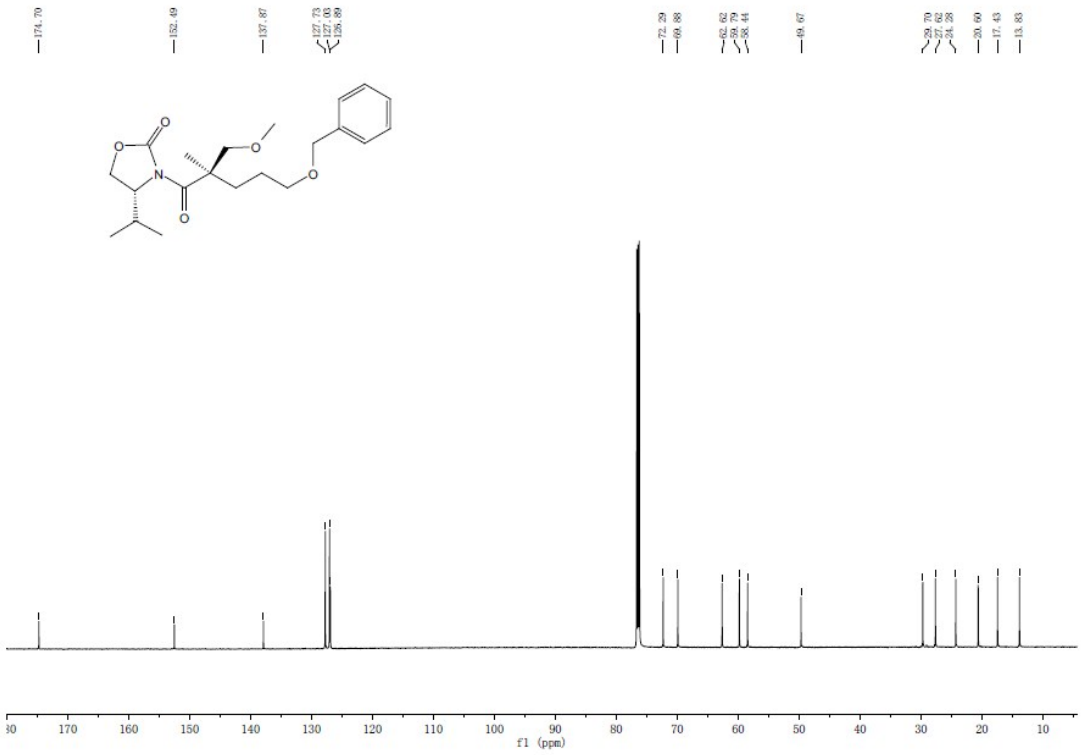
^{13}C-NMR spectrum of compound ent-12b (150 MHz, $CDCl_3$):



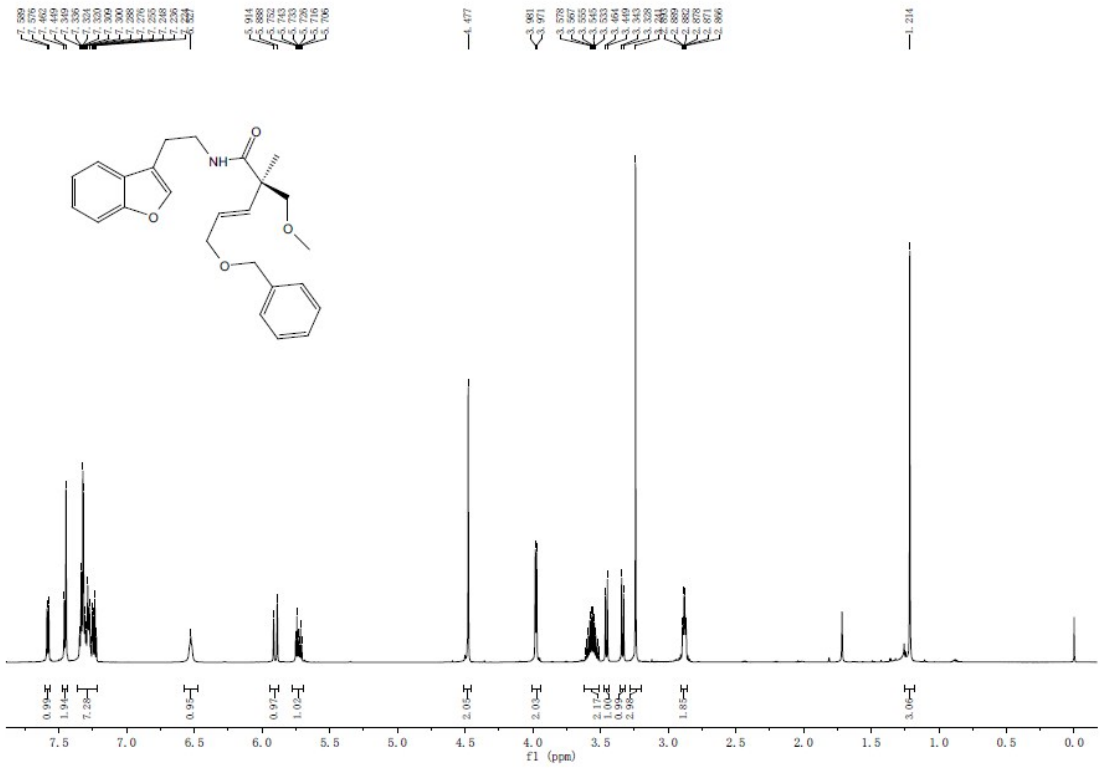
^{1}H NMR spectrum of compound 13R (400 MHz, $CDCl_3$):



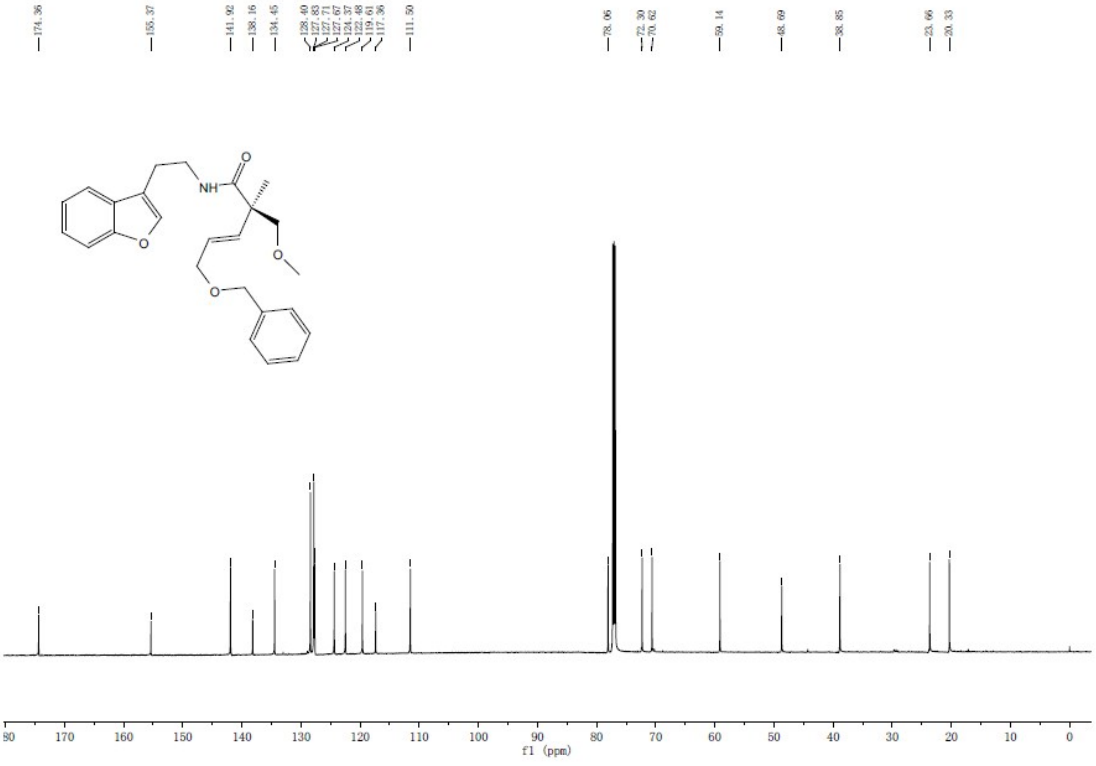
^{13}C-NMR spectrum of compound 13R (150 MHz, $CDCl_3$):



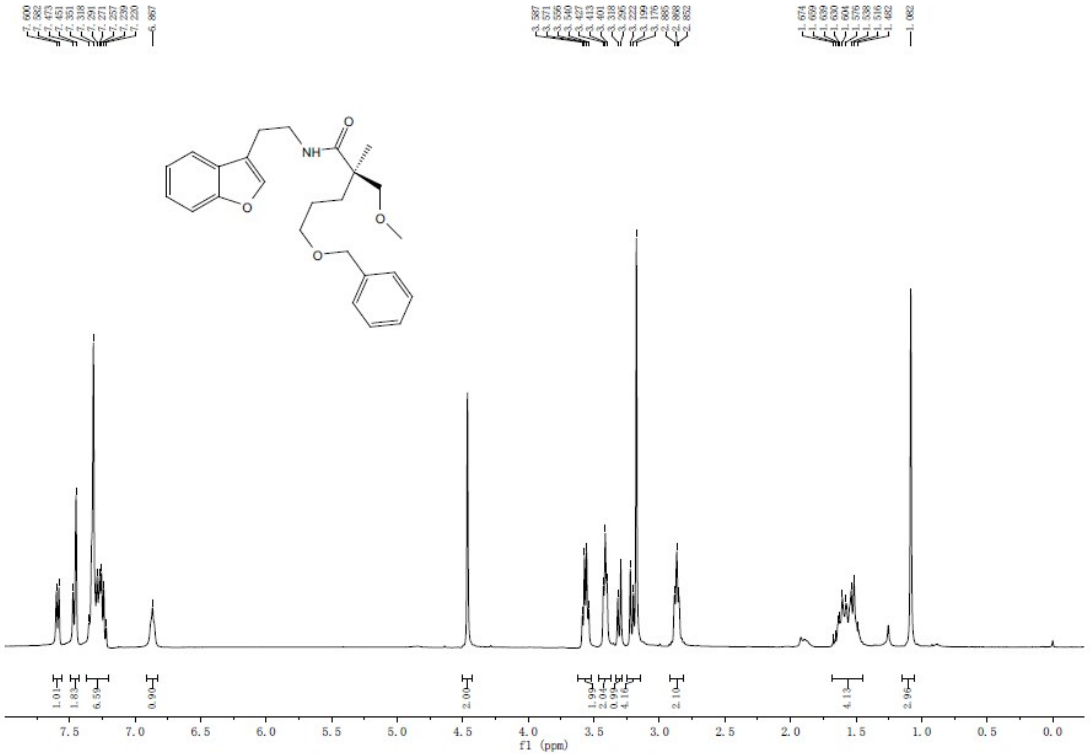
^{1}H NMR spectrum of compound 15R (600 MHz, $CDCl_3$):



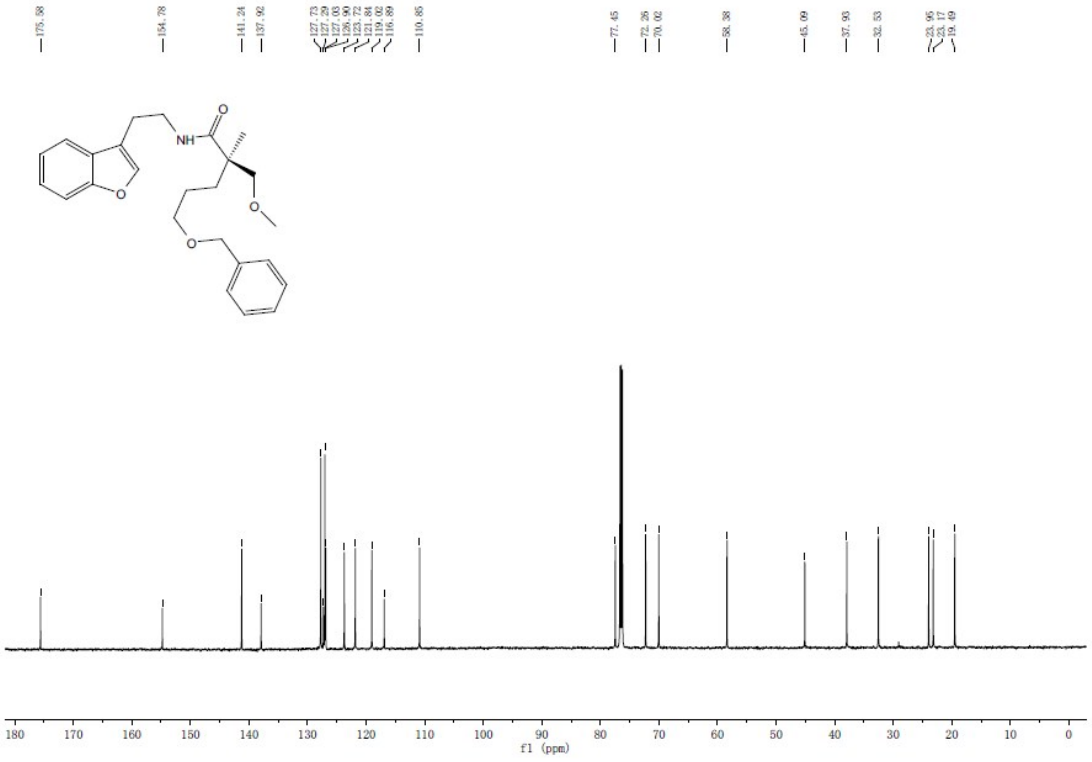
^{13}C-NMR spectrum of compound 15R (150 MHz, $CDCl_3$):



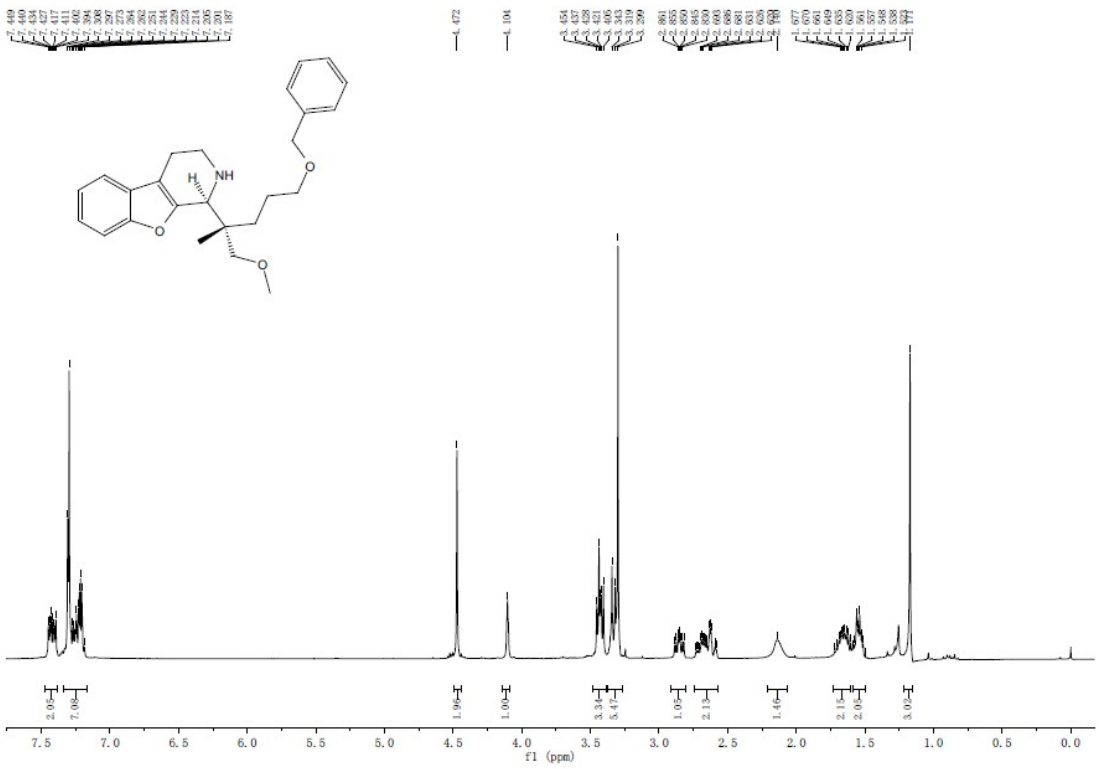
^{1}H NMR spectrum of compound 14R (400 MHz, $CDCl_3$):



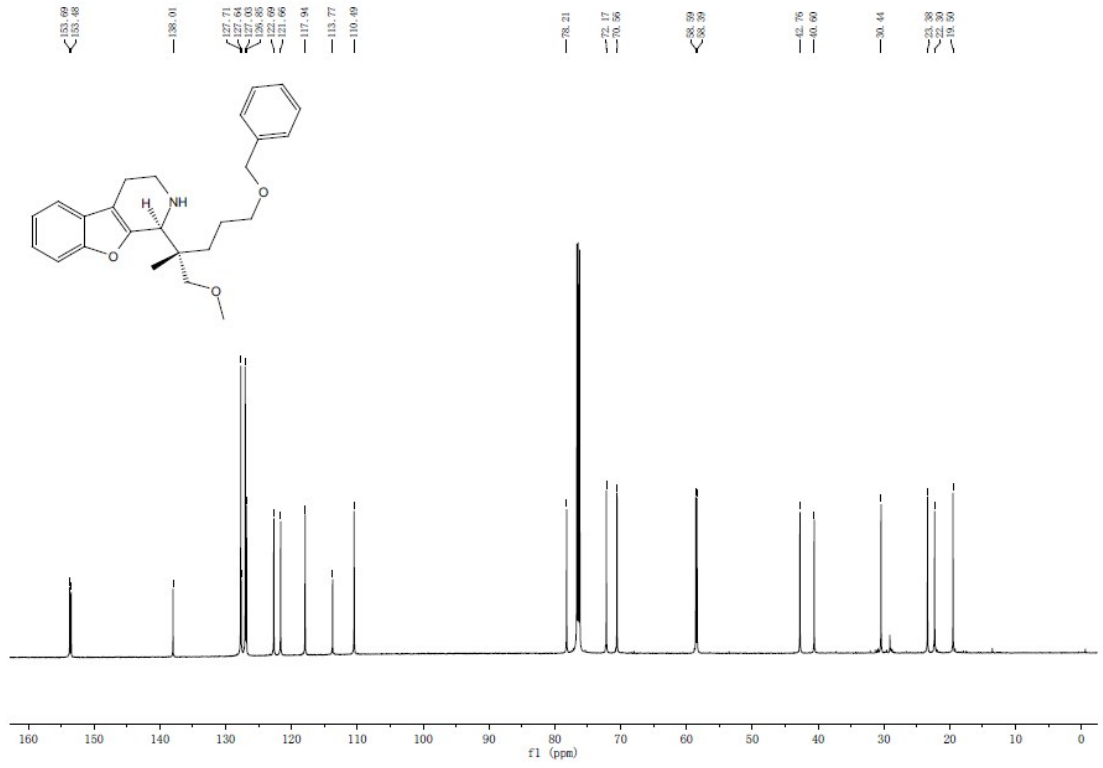
^{13}C-NMR spectrum of compound 14R (150 MHz, $CDCl_3$):



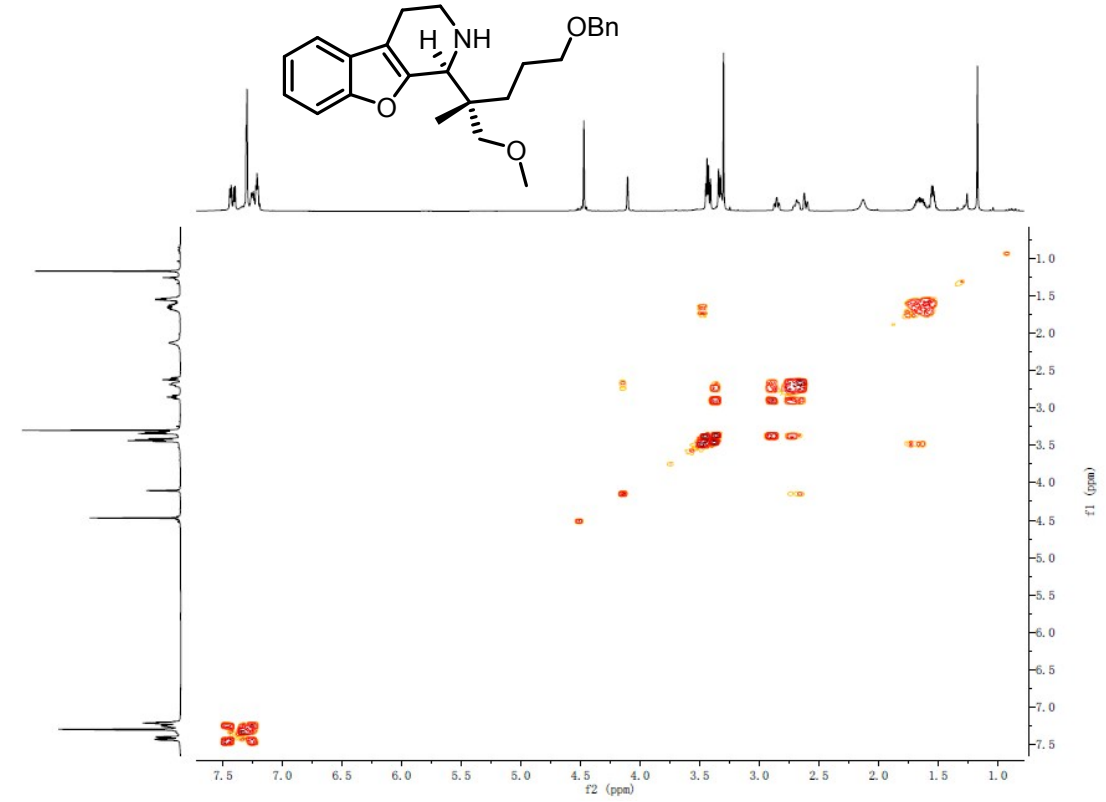
^{1}H NMR spectrum of compound 20a (400 MHz, $CDCl_3$):



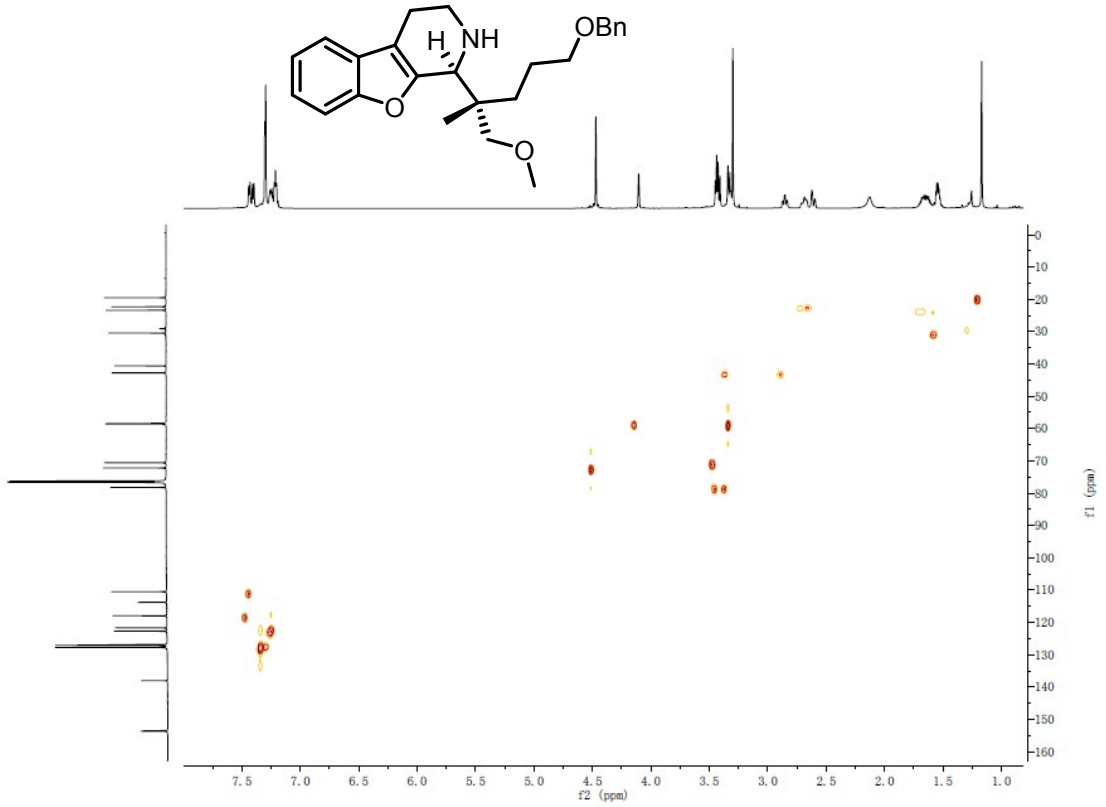
^{13}C-NMR spectrum of compound 20a (150 MHz, $CDCl_3$):



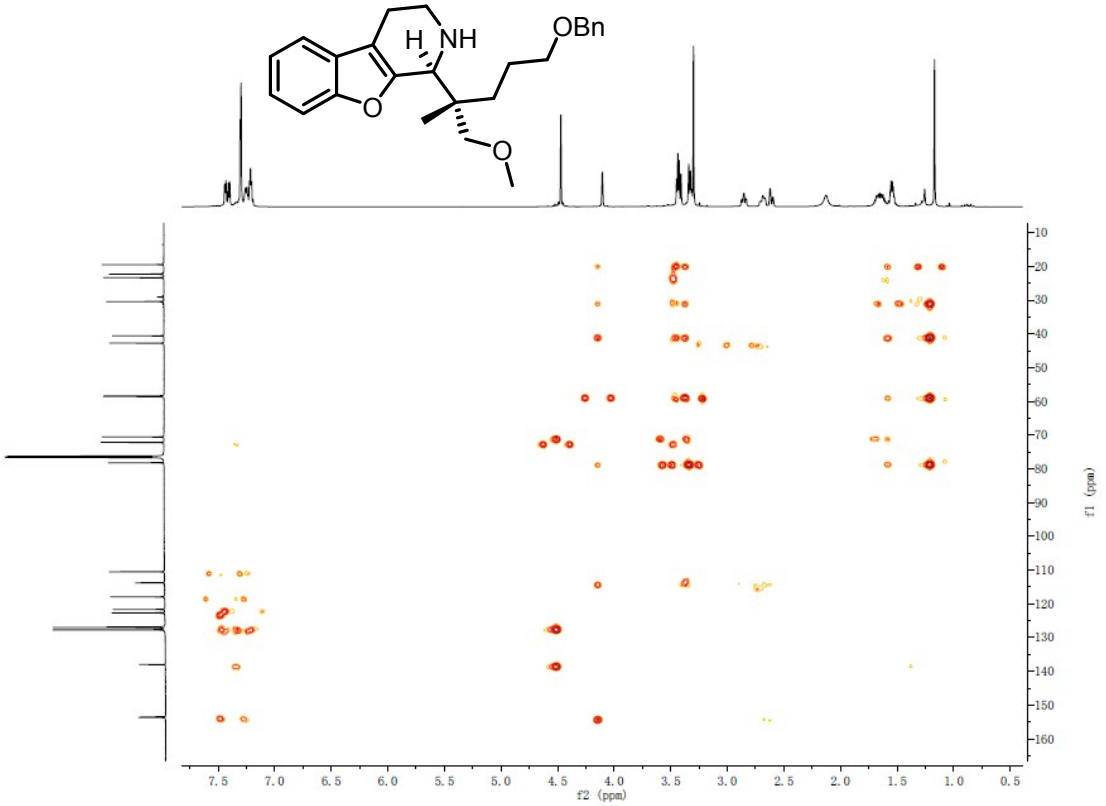
^{1}H-^{1}H COSY spectrum of compound 20a (600 MHz, $CDCl_3$):



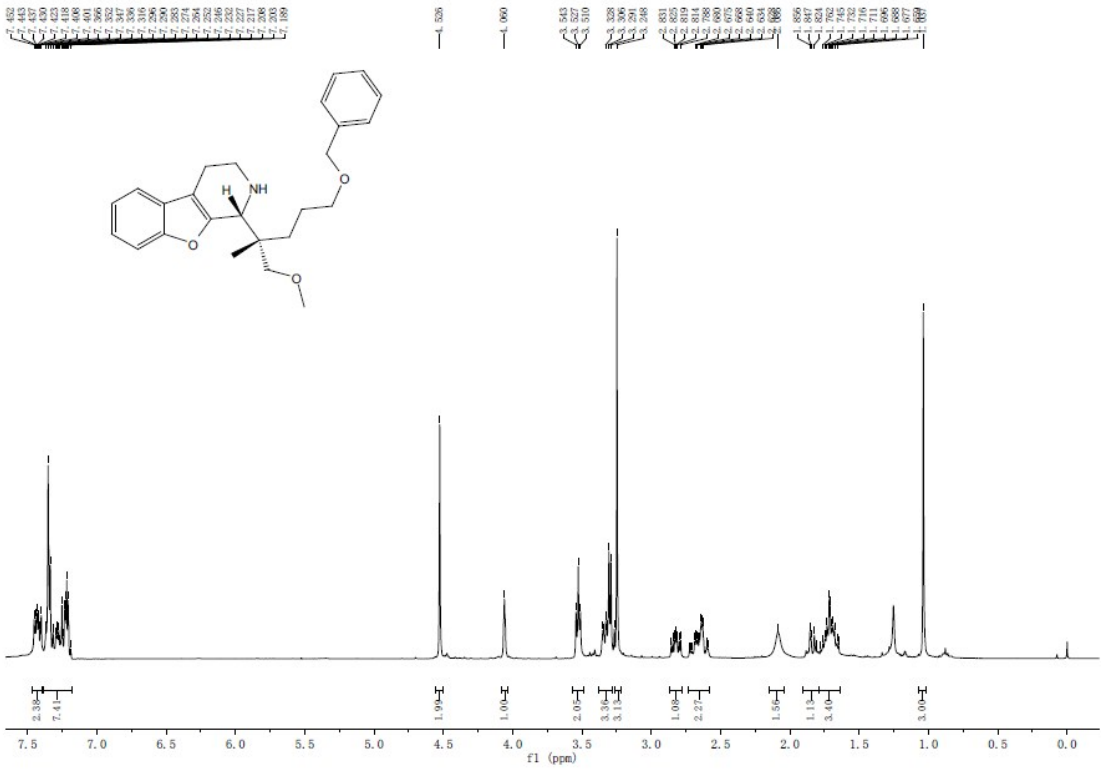
HSQC spectrum of compound 20a (600 MHz, $CDCl_3$):



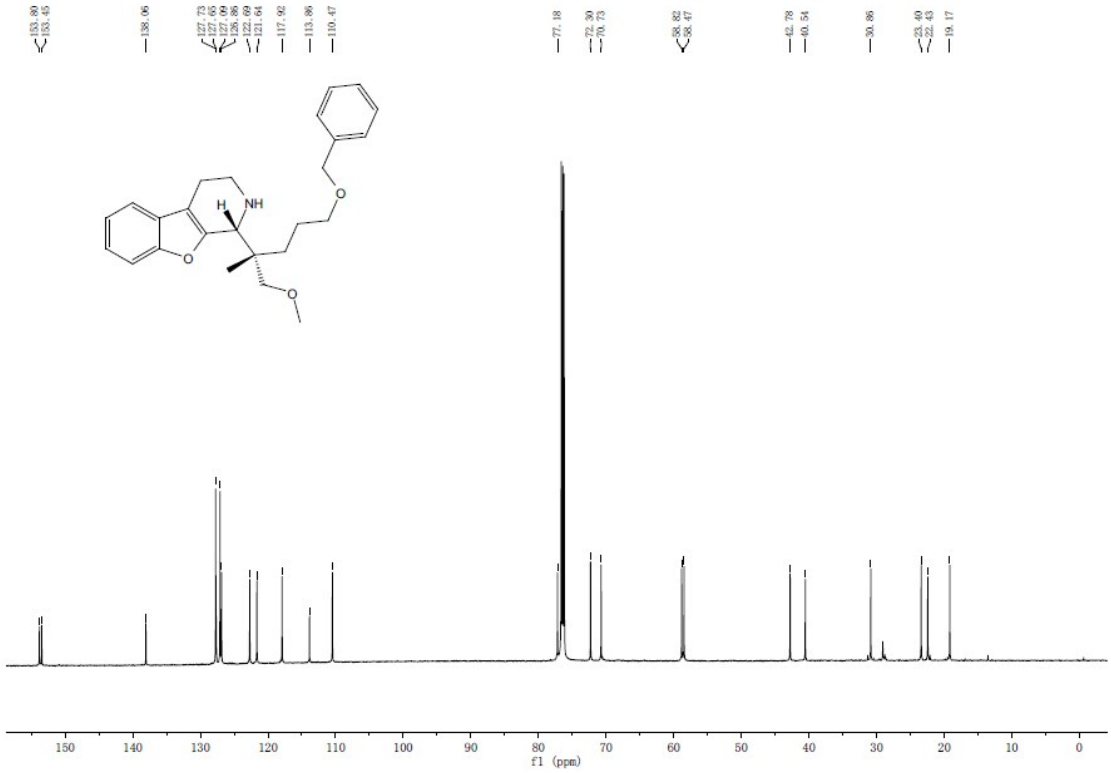
HMBC spectrum of compound 20a (600 MHz, $CDCl_3$):



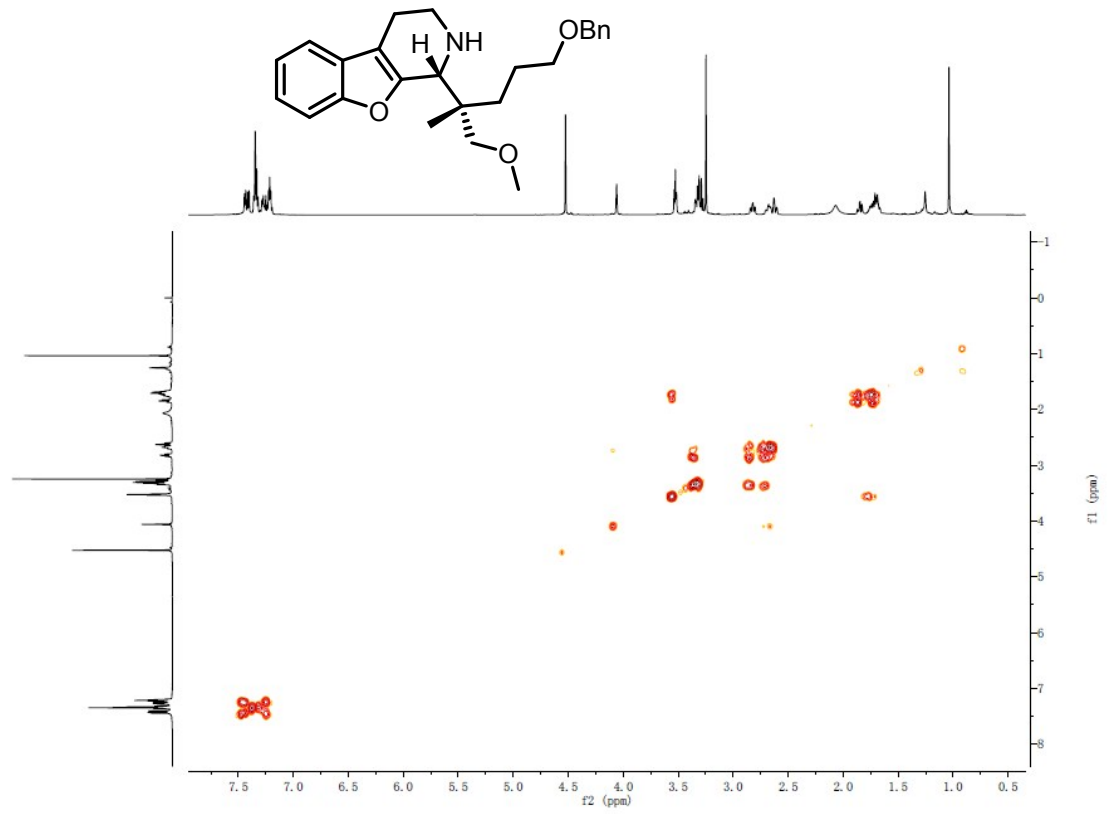
^{1}H NMR spectrum of compound 20b (400 MHz, $CDCl_3$):



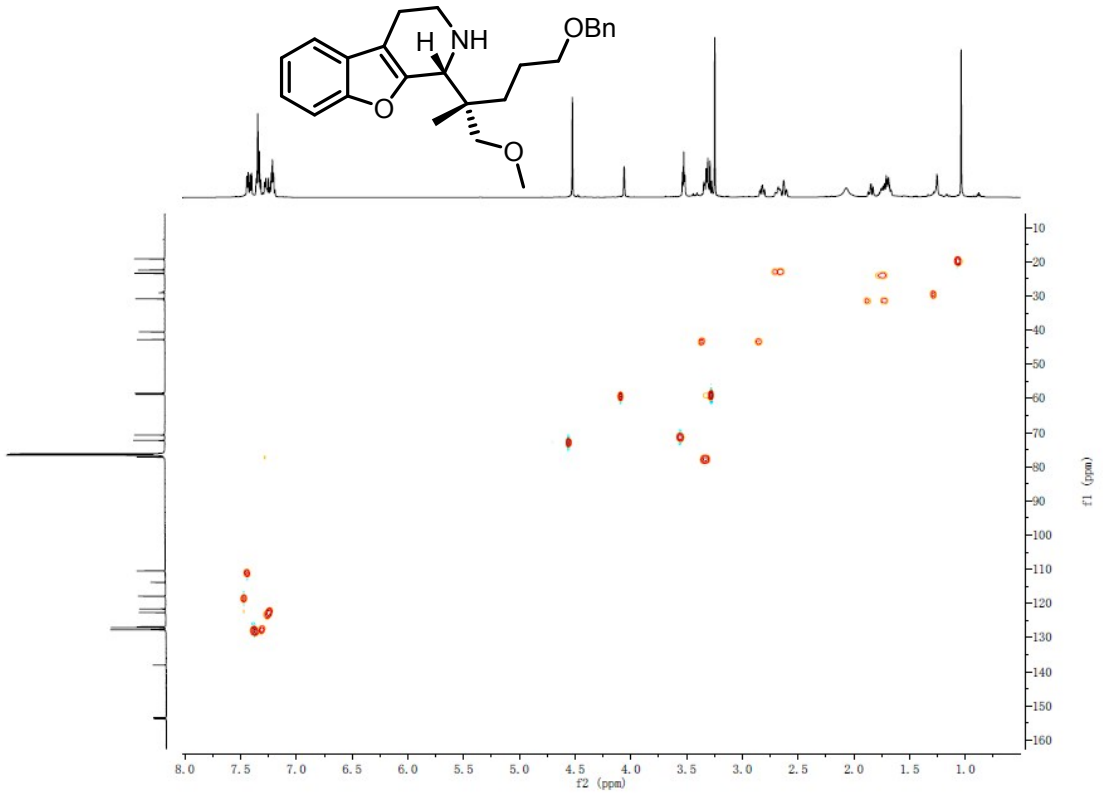
^{13}C-NMR spectrum of compound 20b (150 MHz, $CDCl_3$):



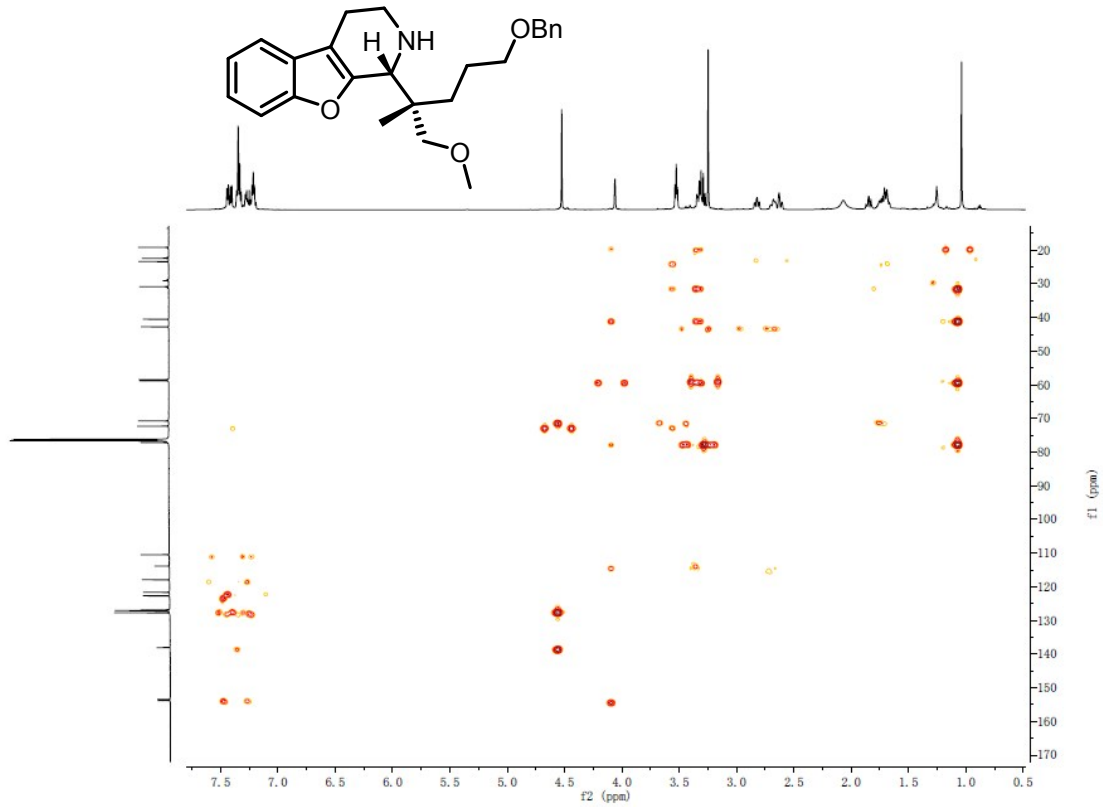
^{1}H-^{1}H COSY spectrum of compound 20b (600 MHz, $CDCl_3$):



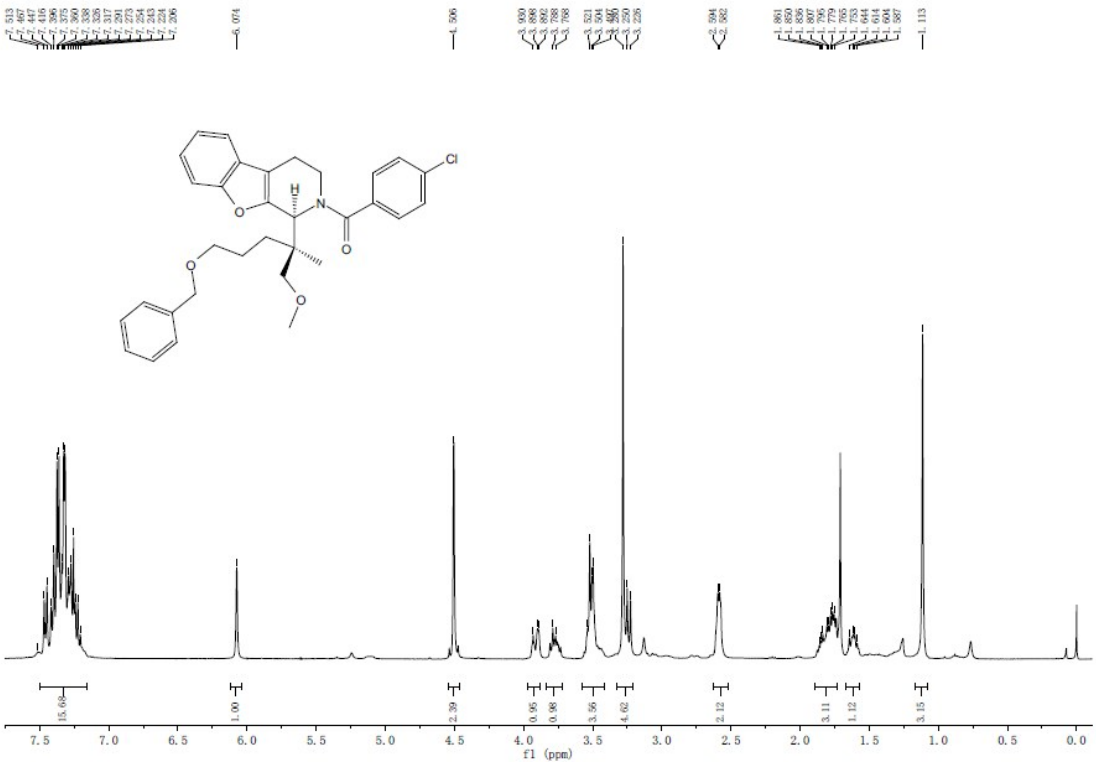
HSQC spectrum of compound 20b (600 MHz, $CDCl_3$):



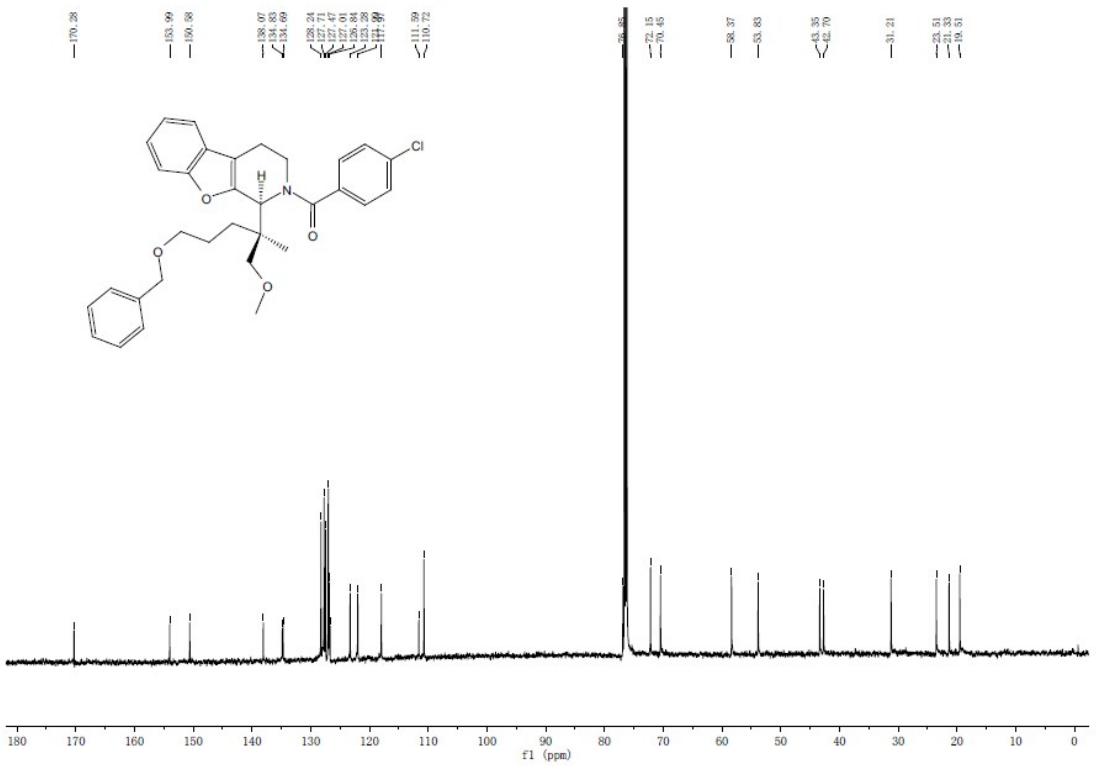
HMBC spectrum of compound 20b (600 MHz, $CDCl_3$):



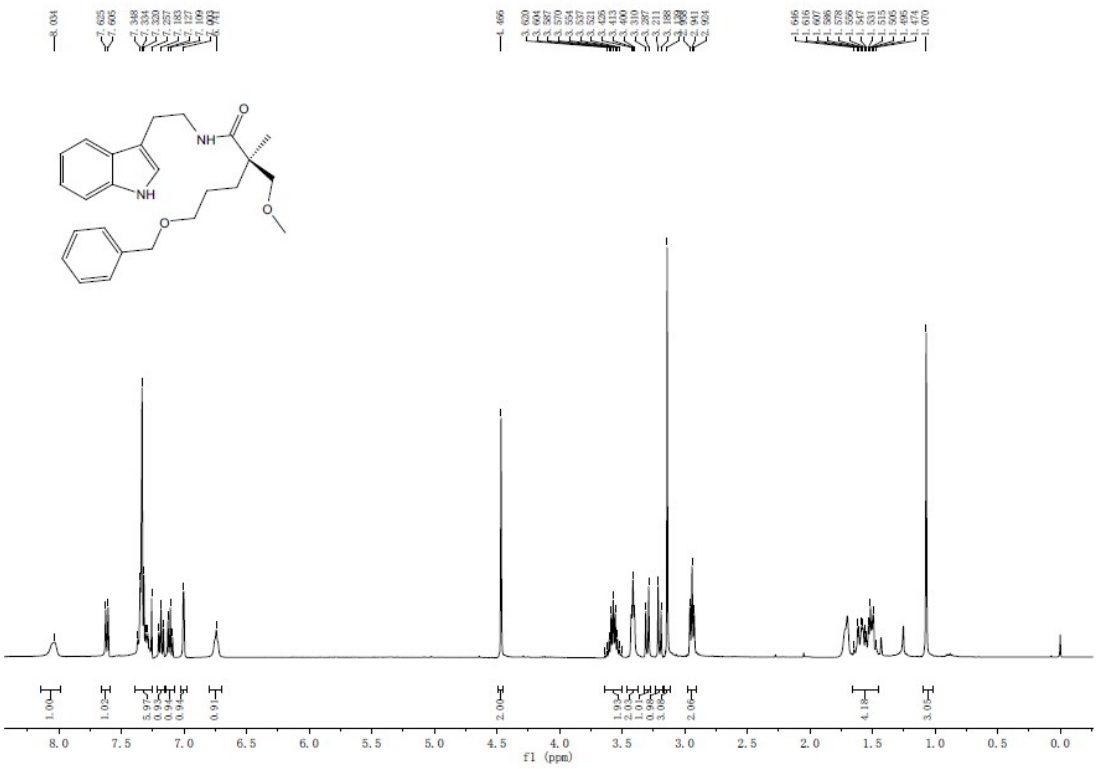
^{1}H NMR spectrum of compound 20a' (400 MHz, $CDCl_3$):



^{13}C-NMR spectrum of compound 20a' (150 MHz, $CDCl_3$):

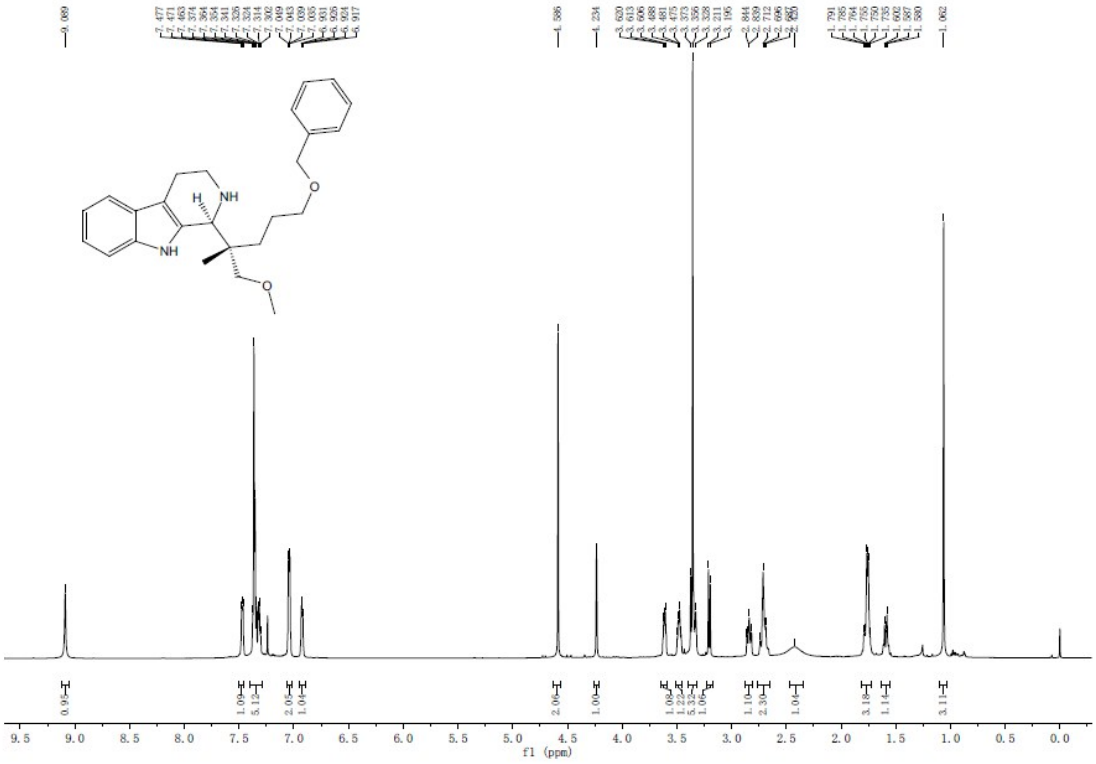


^{1}H-NMR spectrum of compound 24AR (400 MHz, $CDCl_3$):

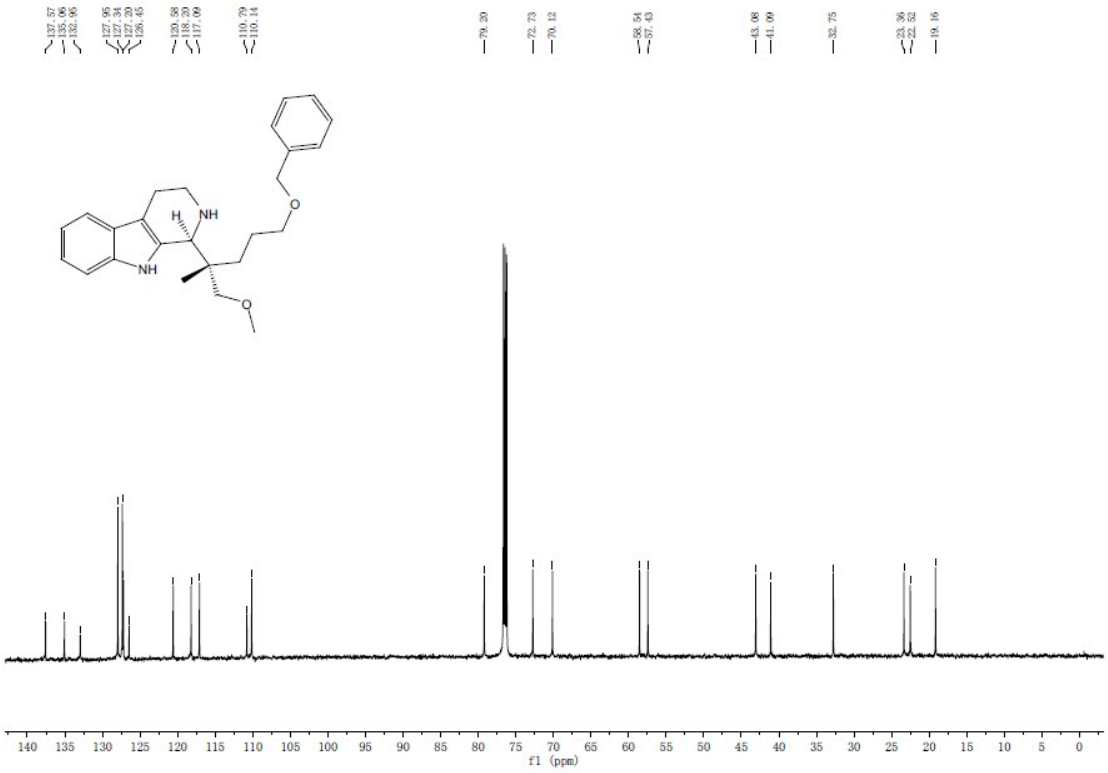


^{13}C-NMR spectrum of compound 24AR (150 MHz, $CDCl_3$):

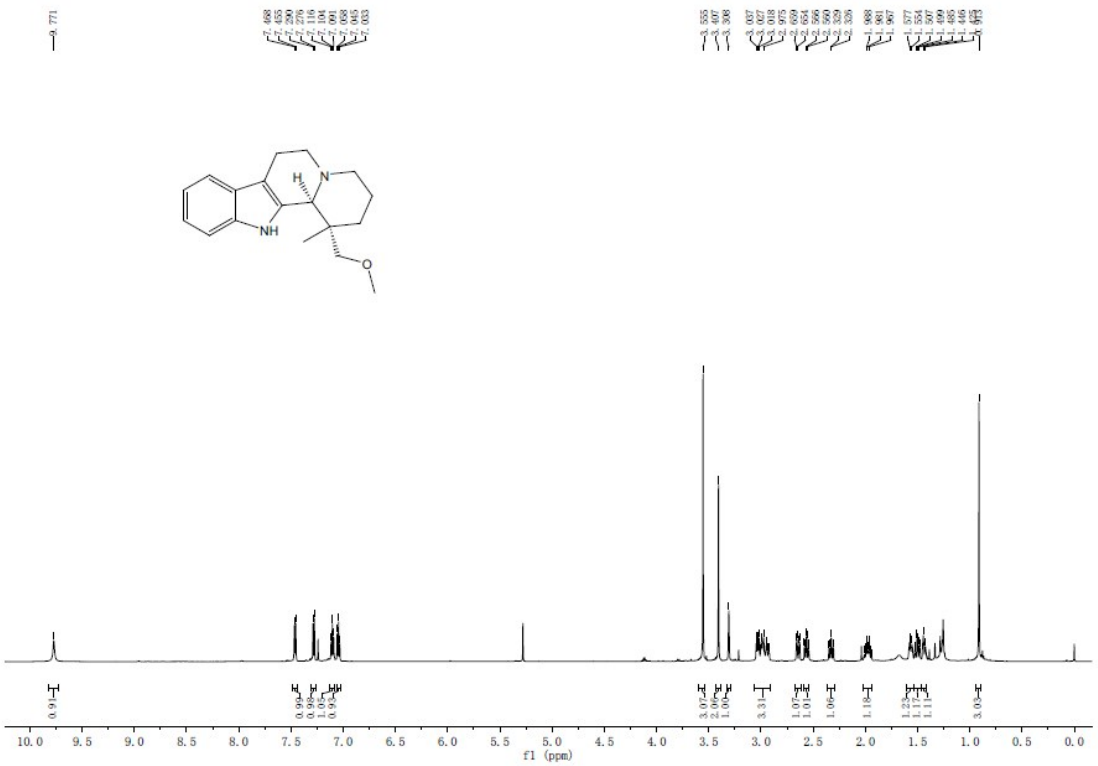
^{1}H-NMR spectrum of compound 25AS (600 MHz, $CDCl_3$):



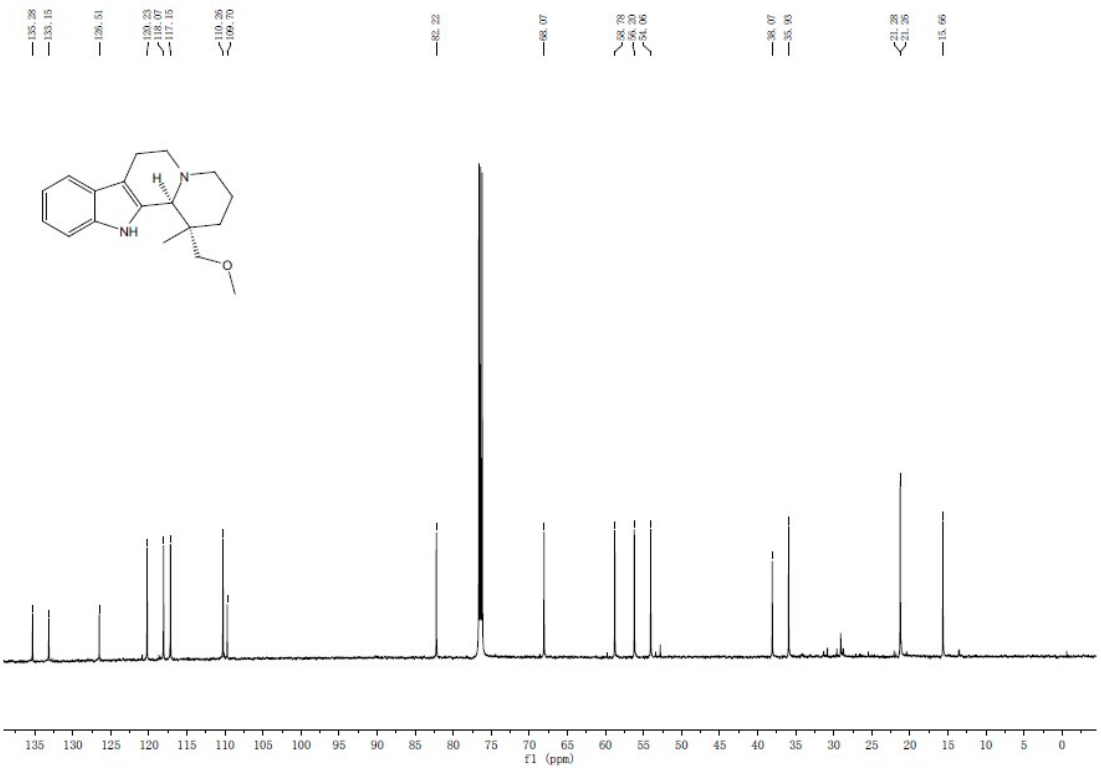
^{13}C-NMR spectrum of compound 25AS (150 MHz, $CDCl_3$):



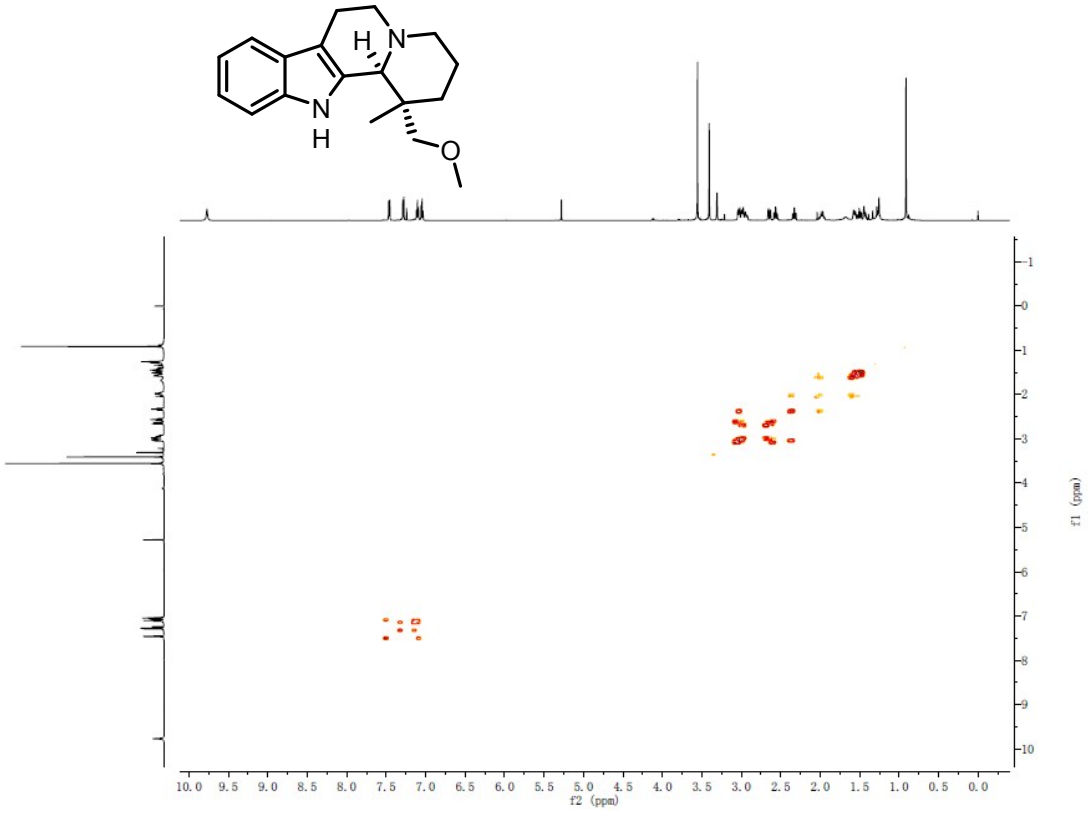
^{1}H-NMR spectrum of compound 26Aa (600 MHz, $CDCl_3$):



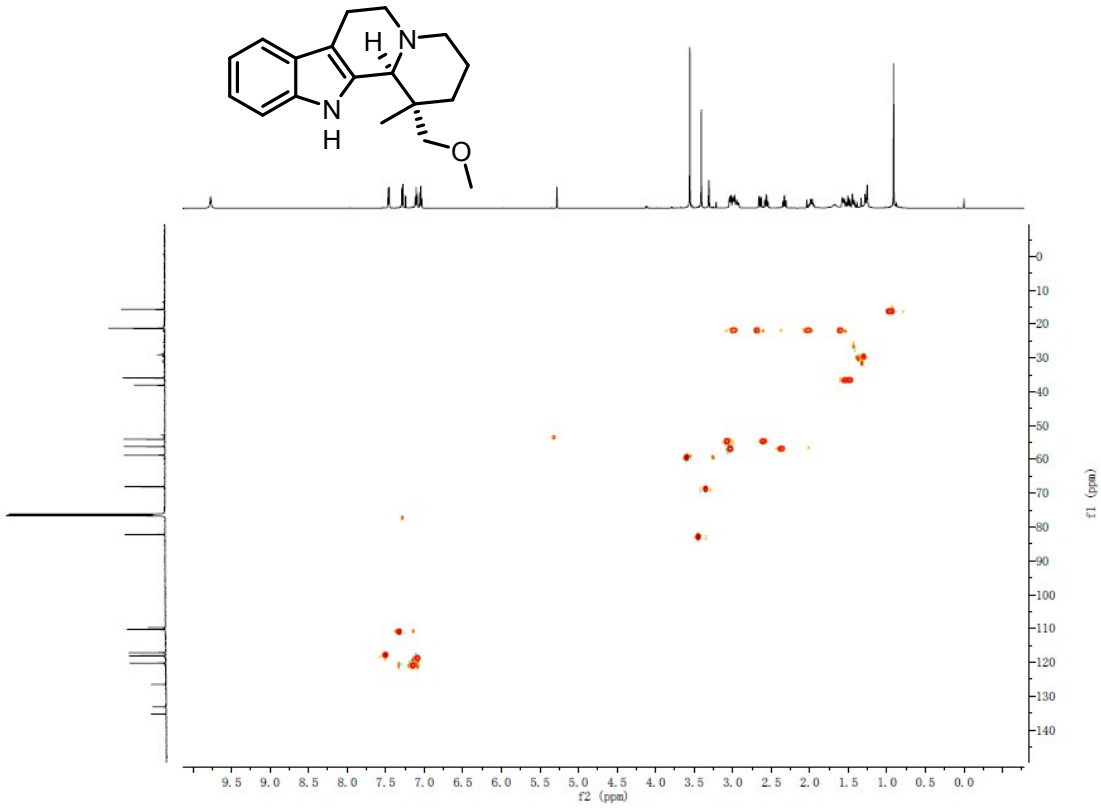
^{13}C-NMR spectrum of compound 26Aa (150 MHz, $CDCl_3$):



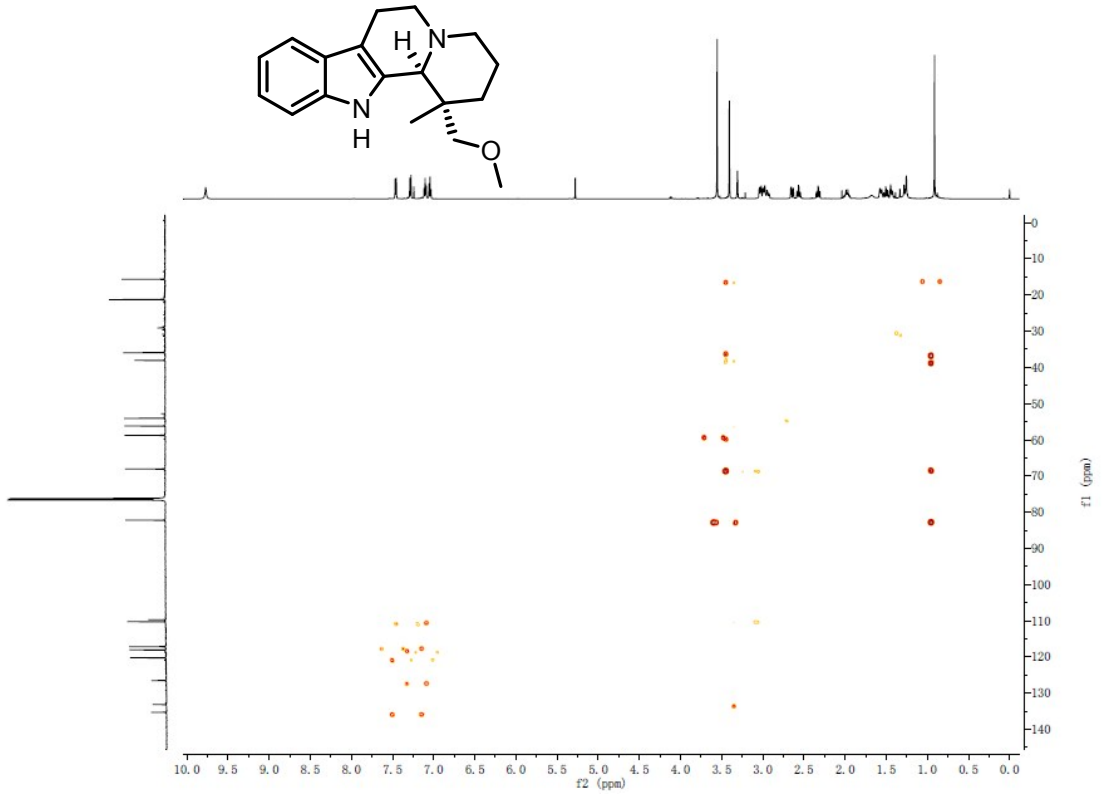
^{1}H-^{1}H COSY spectrum of compound 26Aa (600 MHz, $CDCl_3$):



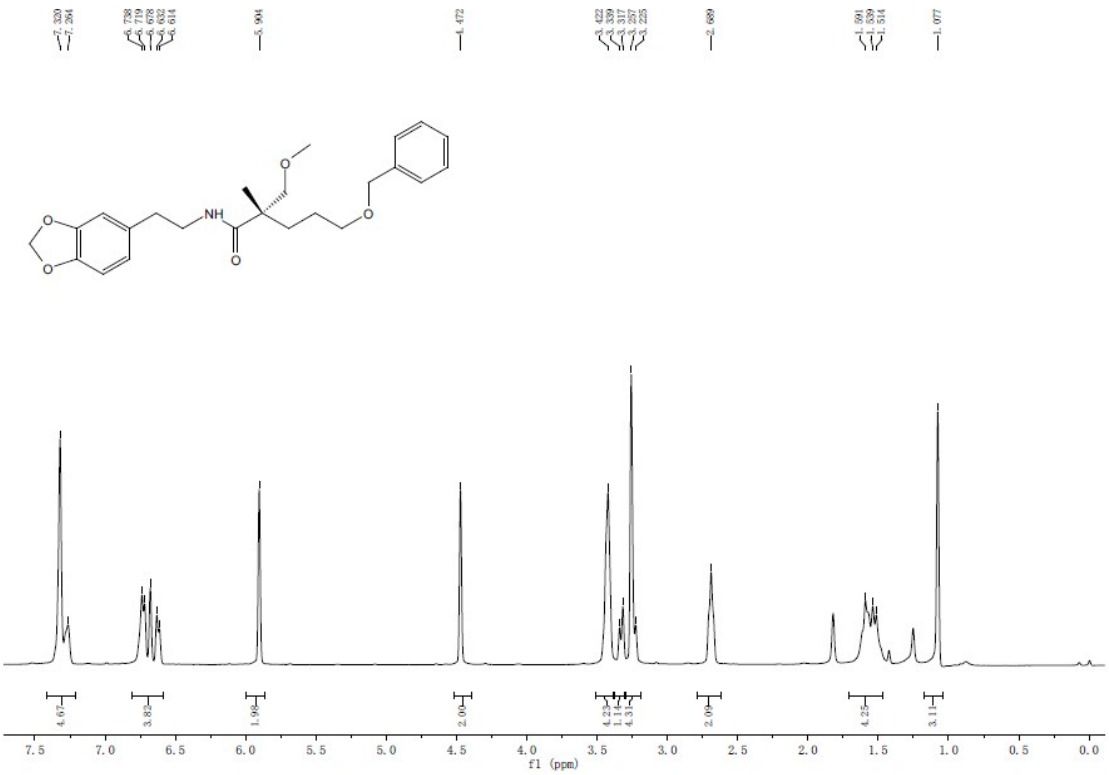
HSQC spectrum of compound 26Aa (600 MHz, $CDCl_3$):



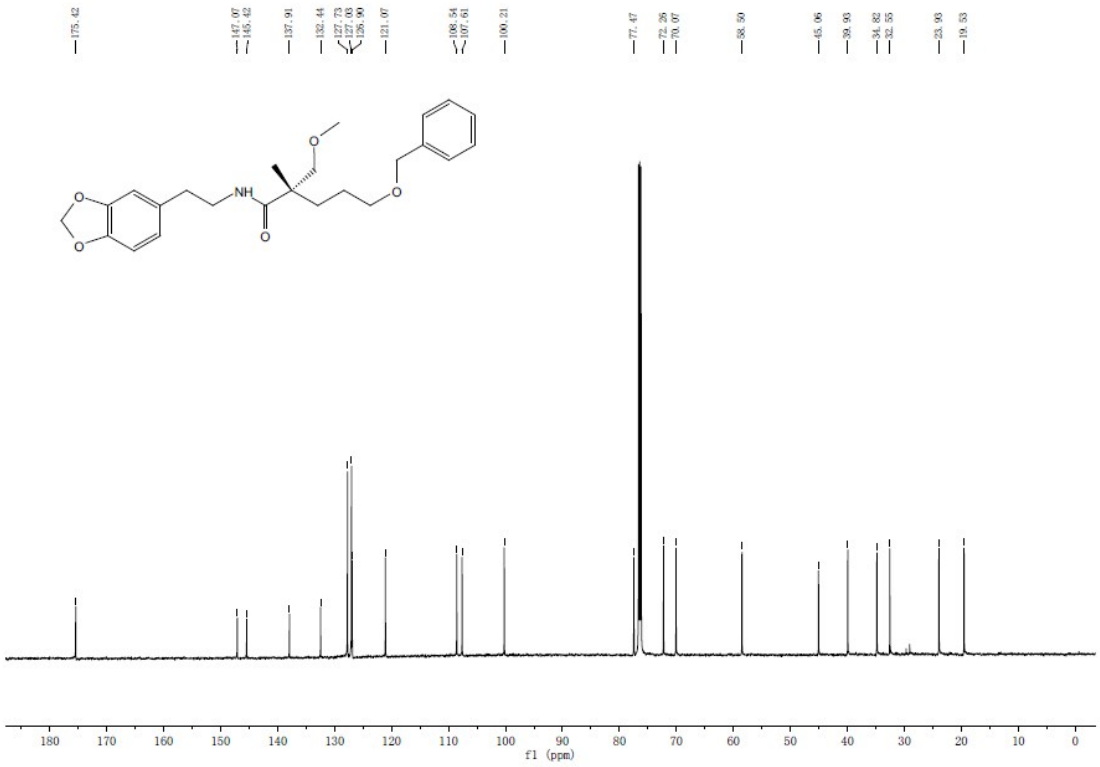
HMBC spectrum of compound 26Aa (600 MHz, $CDCl_3$):



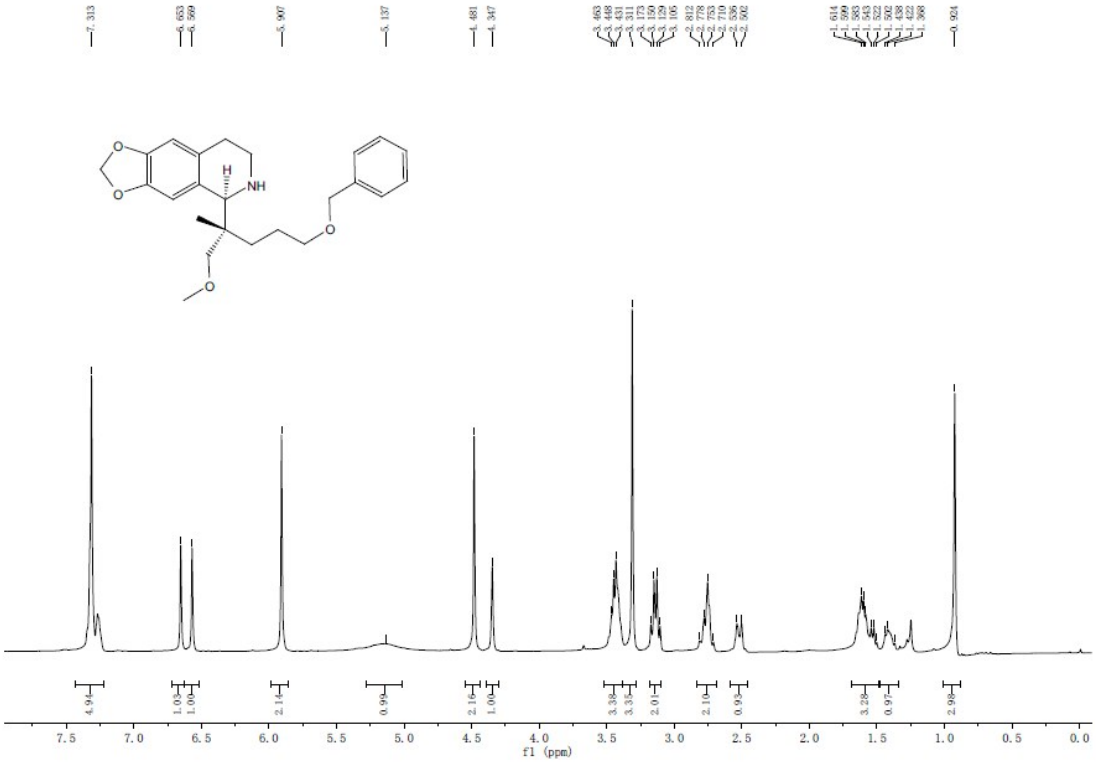
^{1}H NMR spectrum of compound 24BR (400 MHz, $CDCl_3$):



^{13}C-NMR spectrum of compound 24BR (150 MHz, $CDCl_3$):

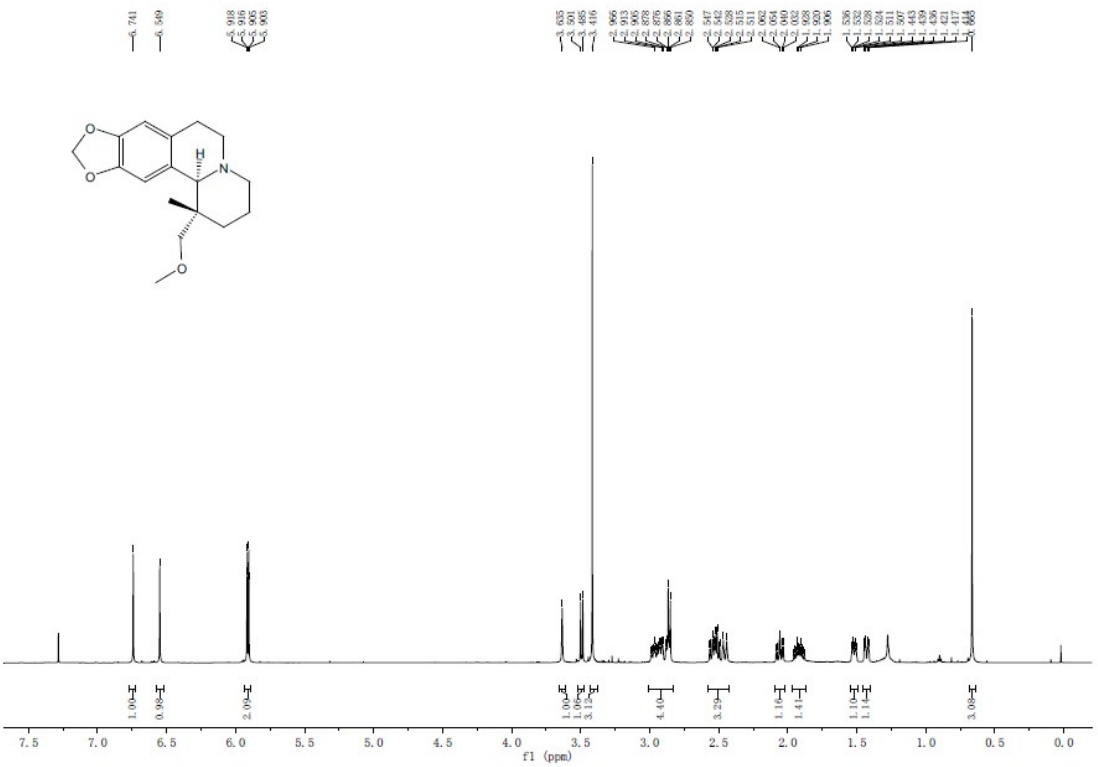


^{1}H NMR spectrum of compound 25BS (400 MHz, $CDCl_3$):



^{13}C-NMR spectrum of compound 25BS (150 MHz, $CDCl_3$):

^{1}H NMR spectrum of compound 26Ba (600 MHz, $CDCl_3$):



^{13}C-NMR spectrum of compound 26Ba (150 MHz, $CDCl_3$):