Supporting Information

Enantioselective Formal Total Syntheses of (-)-Cephalotaxine and (-)-Amathaspiramide F through a Key Ir/Cu Dual Catalysis

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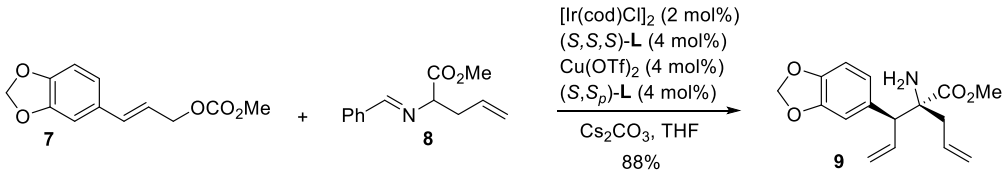
1. General Information

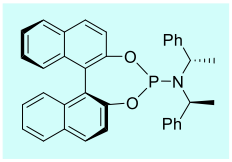
Unless otherwise stated, all oxygen or moisture-sensitive reactions were conducted in flame-dried glassware under a nitrogen atmosphere. All solvents were purified and dried according to standard methods prior to use. Reagents were purchased from commercial sources and were used without further purification.

Chromatographic purification of products was accomplished using forced-flow chromatography on 200-300 mesh silica gel. The TLC glass plates were performed on 0.20 mm silica gel GF254 plates and visualized with UV light (254 nm). Visualization was performed using ultraviolet light (254 nm) and potassium permanganate ($KMnO_4$) in water.

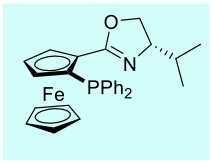
^1H and ^{13}C NMR spectra were acquired on Bruker Avance III-400 spectrometer and Bruker Avance III-600 MHz spectrometer, and TMS was used as the internal standard. Chemical shifts were given in parts per million (ppm) with reference to residual solvent signals [^1H NMR: $CDCl_3$ (7.26); ^{13}C NMR: $CDCl_3$ (77.0)]. Peak multiplicities were recorded as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or unresolved, br = broad singlet. Infrared (IR) spectra were recorded on a Thermo Nicolet iS10 Infrared spectrometer with ATR ITX-DIAMOND disks. High-resolution mass spectral (HRMS) data were obtained at the mass spectrometry service operated at Agilent 6540 Q-TOF LC/MS spectrometer for electrospray ionisation (ESI) and were reported as (*m/z*). Optical rotations were measured on an Automatic Polarimeter APVI-6W 91058.

2. Experimental Procedures and Data





(*S*,*S*,*S*)-**L**



(*S*,*S*$_p$)-**L**

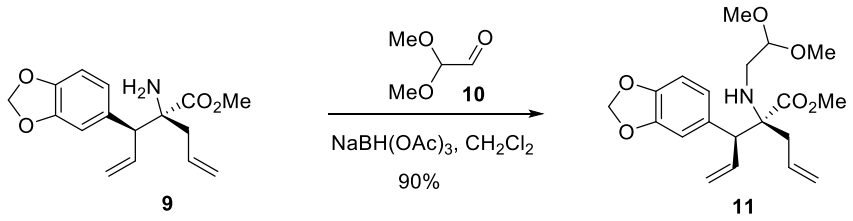
The preparation of Ir catalyst: A 25 mL flame-dried flask was cooled to room temperature and transferred to a nitrogen-filled glove box. To this flask were added $[Ir(cod)Cl]_2$ (134 mg, 0.2 mmol, 0.02 equiv), (*S*, *S*, *S*)-**L** (215 mg, 0.4 mmol, 0.04 equiv), THF (4 mL) and *n*-propylamine (0.5 mL). The flask was filled with N_2 and removed from the glove box. The reaction mixture was stirred at 50 ºC for 30 min, and then the volatile solvents were removed under a vacuum to give a pale-yellow solid. The **Ir** catalyst was prepared after adding THF (20 mL).

The preparation of Cu catalyst: $Cu(OTf)_2$ (144 mg, 0.4 mmol, 0.04 equiv), (*S*, *S*$_p$)-**L** (192 mg, 0.4 mmol, 0.04 equiv) were stirred in THF (20 mL) in a Schlenk flask under nitrogen atmosphere at room temperature for 1 h.

Synthesis of 9:

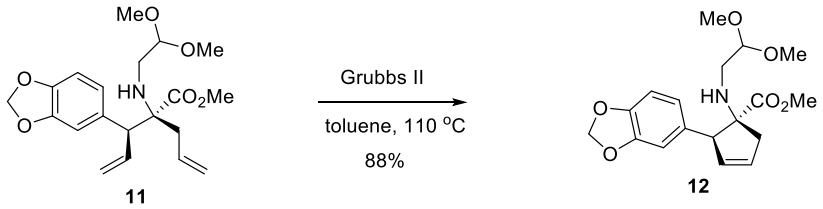
A 100 mL flame-dried flask was cooled to room temperature and filled with N_2. To this flask were added aldimine Schiff base **8** (3.05 g, 14 mmol, 1.4 equiv), Cs_2CO_3 (4.56 g, 14 mmol, 1.4 equiv), Cu catalyst (20 mL), and Ir catalyst (20 mL) was then added. Allylic carbonate **7** (2.37 g, 10 mmol, 1.0 equiv) was then added, and the reaction mixture was stirred at room temperature for 12 h. To the reaction mixture was added a 10% citric acid solution (20 mL) at room temperature and stirred for 2 h. After being washed with ethyl acetate, the mixture was neutralized with solid K_2CO_3 and extracted with ethyl acetate (40 mL x 3). The combined extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was then purified by column chromatography (petroleum ether/ethyl acetate = 4:1) to give the desired products **9** (2.55 g, 88%). The product was analyzed by HPLC to determine the enantiomeric excess: 96% ee (Chiralpak AD-H, *i*-propanol /hexane = 5/95, flow rate 1.0 mL/min, λ = 210 nm).

$\mathbf{R}_f$ = 0.28 (petroleum ether/ethyl acetate = 4:1). **IR** (KBr): *v* 3072, 1731, 1502, 1485, 1246, 1210, 1036, 925 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.74 (s, 1H), 6.70 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.62 (dd, *J* = 8.0 Hz, 1.6 Hz,1H), 6.36 – 6.19 (m, 1H), 5.99 – 5.81 (m, 2H), 5.70 – 5.48 (m, 1H), 5.30 – 4.99 (m, 4H), 3.61 (s, 3H), 3.58 (d, *J* = 10.6 Hz, 1H), 2.58 (dd, *J* = 13.7, 8.8 Hz, 1H), 2.30 (dd, *J* = 13.7, 8.8 Hz, 1H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$): δ 176.4, 147.7, 146.6, 136.5, 134.1, 132.9, 121.6, 119.9, 118.1, 108.8, 108.3, 101.0, 64.4, 57.4, 52.0, 43.0 ppm. **HRMS** (ESI^+): calcd for $C_{16}H_{20}NO_4$ $[M+H]^+$ 290.1387, found 290.1386. $[\alpha]_D^{25.9}$ = +84.51 (*c* = 2.74, $CHCl_3$).



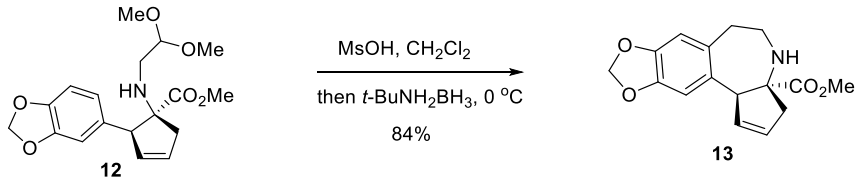
Synthesis of 11: To a solution of compound **9** (580 mg, 2.0 mmol, 1.0 equiv) in dry dichloromethane was added 2,2-dimethoxyethanal **10** (60% in H_2O) (0.4 mL, 3.0 mmol, 1.5 equiv), $NaBH(OAc)_3$ (636 mg, 3.0 mmol, 1.5 equiv), magnesium sulfate anhydrous (241 mg, 4.0 mmol, 2.0 equiv). The reaction mixture was stirred at room temperature for 6 h and then was quenched with saturated $NaHCO_3$ aqueous solution (10 mL). The aqueous layer was extracted with dichloromethane (30 mL x 3). The combined organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography (petroleum ether/ethyl acetate = 5:1) to afford compound **11** (678 mg, 90% yield) as a yellow oil.

$\mathbf{R}_f$ = 0.48 (petroleum ether/ethyl ether = 4:1). **IR** (KBr): *v* 2950, 1726, 1504, 1488, 1443, 1247, 1130, 1040, 924 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.70 (d, J = 8.0 Hz, 1H), 6.63 (s, 1H), 6.57 (d, J = 8.0 Hz, 1H), 6.22 (m, 1H), 5.90 (s, 2H), 5.88 – 5.82 (m, 1H), 5.25 – 5.04 (m, 4H), 4.44 (dd, J = 6.7, 4.4 Hz, 1H), 3.64 (s, 3H), 3.50 (d, J = 10.0 Hz, 1H), 3.36 (s, 3H), 3.35 (s, 3H), 2.70 (dd, J = 11.2, 6.7 Hz, 1H), 2.58 (dd, J = 11.2, 6.7 Hz, 1H), 2.50 (dd, J = 15.8, 7.8 Hz, 1H), 2.41 (dd, J = 15.8, 7.8 Hz, 1H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$): δ 174.7, 147.6, 146.5, 136.6, 133.9, 133.7, 122.0, 118.5, 118.2, 109.0, 108.1, 104.1, 101.0, 67.0, 56.8, 54.2, 53.0, 51.6, 44.8, 36.5 ppm. **HRMS** (ESI^+): calcd for $C_{20}H_{28}NO_6$ $[M+H]^+$ 378.1911, found 378.1913. $[\alpha]_D^{25.2}$ = +90.61 (c = 2.93, $CHCl_3$).



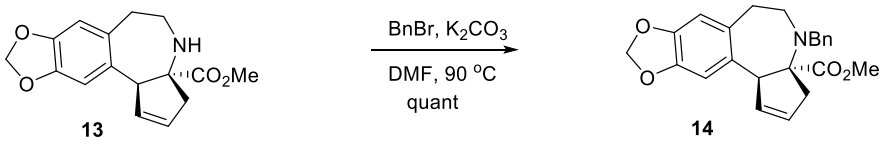
Synthesis of 12: To a solution of compound **11** (143 mg, 0.38 mmol, 1.0 equiv) in dry toluene (7.6 mL) was added Grubbs II (16.2 mg, 0.02 mmol, 0.05 equiv). The reaction mixture was stirred at 100 °C for 4 h. After cooling to room temperature; the reaction mixture was directly concentrated *in vacuo* and subjected to flash column chromatography (petroleum ether/ethyl acetate = 3:1) to afford the desired product **12** (117 mg, 88% yield) as a yellow oil.

$\mathbf{R}_f$= 0.21 (petroleum ether/ethyl acetate = 4:1). **IR** (KBr): *v* 2950, 1728, 1503, 1487, 1442, 1248, 1232, 1195, 1132, 1039, 931 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.81 – 6.59 (m, 3H), 5.92 (s, 2H), 5.89 – 5.85 (m, 1H), 5.69 – 5.65 (m, 1H), 4.24 – 4.18 (m, 1H), 4.13 (m, 1H), 3.77 (s, 3H), 3.24 (s, 3H), 3.17 (s, 3H), 3.14 – 3.06 (m, 1H), 2.56 – 2.48 (m, 1H), 2.42 (m, 2H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$): δ 176.5, 147.4, 146.7, 132.0, 131.5, 129.5, 122.9, 110.1, 107.8, 104.2, 100.9, 71.0, 59.0, 54.0, 53.6, 52.2, 46.2, 41.4 ppm. **HRMS** (ESI^+): calcd for $C_{18}H_{24}NO_6$ $[M+H]^+$ 350.1598, found 350.1600. $[\alpha]_D^{27.2}$ = -102.07 (c = 0.42, $CHCl_3$).



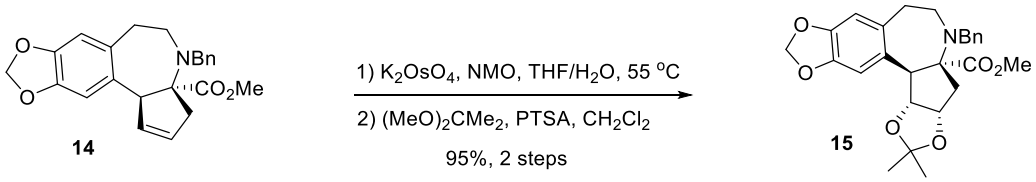
Synthesis of 13: MsOH (0.4 mL, 7.25 mmol, 25.0 equiv) was dropwise added to an ice-cooled solution of compound **12** (100 mg, 0.29 mmol, 1.0 equiv) in dry dichloromethane (5.7 mL). After the addition, the reaction mixture was warmed to room temperature and stirred for 14 h. The resulting mixture was then added *t*-$BuNH_2BH_3$ (75 mg, 0.87 mmol, 3.0 equiv) at 0 °C and stirred for 30 min. Finally, the reaction mixture was quenched with saturated $NaHCO_3$ aqueous solution (20 mL), and the aqueous layer was extracted with dichloromethane (10 mL x 3). The combined organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography (petroleum ether/ethyl acetate = 1:1) to afford compound **13** (70 mg, 84% yield) as a pale yellow oil.

R_f = 0.23 (petroleum ether/ethyl acetate = 1:1). **IR** (KBr): *v* 3382, 2936, 2788, 1717, 1653, 1483, 1453, 1271, 1223, 1042, 932 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.64 (s, 1H), 6.63 (s, 1H), 5.95 – 5.90 (m, 1H), 5.91 – 5.85 (m, 2H), 5.85 – 5.78 (m, 1H), 4.52 – 4.50 (m, 1H), 3.79 (s, 3H), 2.95 – 2.77 (m, 3H), 2.77 – 2.66 (m, 1H), 2.58 (m, 1H), 2.34 (m, 1H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$): δ 175.6, 146.3, 146.3, 132.3, 131.9, 130.7, 128.9, 109.3, 107.7, 100.8, 69.3, 53.3, 52.5, 44.3, 42.2, 32.3 ppm. **HRMS** (ESI^+): calcd for $C_{16}H_{18}NO_4$ $[M+H]^+$ 288.1230, found 288.1228. **$[\alpha]_D^{27.1}$** = -95.65 (*c* = 0.30, $CHCl_3$).



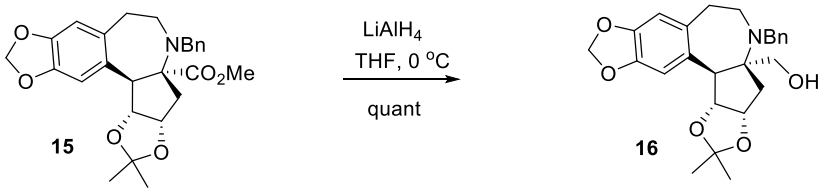
Synthesis of 14: To a solution of compound **13** (286 mg, 1.0 mmol, 1.0 equiv) in dry DMF (1 mL) was added K_2CO_3 (207.3 mg, 1.5 mmol, 1.6 equiv), BnBr (0.1mL, 1.0 mmol, 1.0 equiv). After the addition, the reaction mixture was stirred at 90 °C for 3 h, and TLC analysis indicated complete consumption of the starting material. The mixture was then quenched with H_2O (4 mL), and the aqueous layer was extracted with ethyl acetate (10 mL x 4). Next, the combined organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Finally, the crude residue was purified by column chromatography (petroleum ether/ethyl acetate = 6:1) to afford compound **14** (372 mg, 99% yield) as a colorless oil.

R_f = 0.88 (petroleum ether/ethyl acetate = 2:1). **IR** (KBr): *v* 2952, 1720, 1482, 1453, 1361, 1262, 1228, 1171, 1064, 936 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.12 (dd, *J* = 4.5, 2.1 Hz, 3H), 6.77 (dd, *J* = 4.5, 2.1 Hz, 2H), 6.73 (d, *J* = 2.1 Hz, 1H), 6.62 (d, *J* = 1.7 Hz, 1H), 5.99 (m, 1H), 5.95 (m, 3H), 4.64 (d, *J* = 2.9 Hz, 1H), 3.99 (dd, *J* = 15.7, 2.2 Hz, 1H), 3.84 (s, 3H), 3.30 (dd, *J* = 15.7, 2.2 Hz, 1H), 3.19 – 3.08 (m, 1H), 3.01 (dd, *J* = 15.6, 2.8 Hz, 1H), 2.63 – 2.53 (m, 1H), 2.52 – 2.43 (m, 2H), 2.35 (dt, *J* = 15.6, 2.8 Hz, 1H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$): δ 173.9, 146.0, 145.8, 140.9, 132.4, 132.3, 131.9, 130.1, 128.2, 127.2, 126.5, 108.8, 106.9, 100.7, 75.0, 56.8, 52.2, 51.7, 48.3, 41.3, 31.8 ppm. **HRMS** (ESI^+): calcd for $C_{23}H_{24}NO_4$ $[M+H]^+$ 378.1700, found 378.1705. **$[\alpha]_D^{25.8}$** = -116.59 (*c* = 3.15, $CHCl_3$).



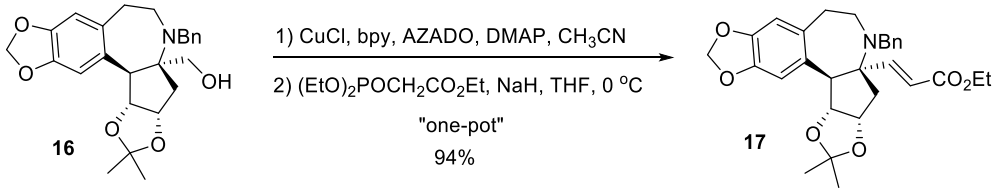
Synthesis of 15: To a solution of compound **14** (377 mg, 1.0 mmol, 1.0 equiv) in THF/H_2O (4:1) (5 mL) was added K_2OsO_4 (0.06 M in H_2O, 0.8 mL, 0.05 mmol, 0.05 equiv), NMO (4.8 M in H_2O, 0.6 mL，3.0 mmol, 3.0 equiv). The reaction mixture was stirred at 55 °C for 12 h and then quenched with H_2O (4 mL), and the aqueous layer was extracted with ethyl acetate (20 mL x 4). The combined organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product is directly used for the next step without purification. The crude product was dissolved in dry dichloromethane, 2,2-dimethoxypropane (1.2 mL, 10.0 mmol, 10 equiv), and PTSA (95.1 mg, 0.5 mmol, 0.5 equiv) was added. The reaction mixture was stirred for 30 min at room temperature, and TLC analysis indicated complete consumption of the starting material. The mixture was then quenched with saturated $NaHCO_3$ aqueous solution (2 mL), and the aqueous layer was extracted with dichloromethane (10 mL x 3). The combined organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography (petroleum ether/ethyl acetate = 10:1) to afford the desired product **15** (429 mg, 95% yield, two steps) as a pale yellow oil.

R_f = 0.65 (petroleum ether/ethyl acetate = 2:1). **IR** (KBr): *v* 3424, 3060, 1621, 1603, 974, 823, 803, 775, 670, 638, 585, 436, 416 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.16 – 7.08 (m, 3H), 6.80 – 6.73 (m, 2H), 6.61 (s, 1H), 6.54 (s, 1H), 5.97 (d, J = 3.3 Hz, 2H), 5.17 (d, J = 5.9 Hz, 1H), 4.87 (t, J = 6.4 Hz, 1H), 4.26 (s, 1H), 3.89 (d, J = 15.7 Hz, 1H), 3.85 (s, 3H), 3.13 (d, J = 15.7 Hz, 1H), 3.09 – 3.02 (m, 1H), 2.75 (d, J = 14.0 Hz, 1H), 2.53 (m, 3H), 1.81 (m, 1H), 1.44 (s, 3H), 1.35 (s, 3H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$): δ 170.6, 146.1, 146.0, 140.6, 133.4, 129.7, 128.3, 127.2, 126.7, 109.8, 109.1, 106.1, 100.9, 83.6, 77.9, 72.7, 56.3, 51.3, 47.2, 41.6, 32.4, 25.6, 23.9 ppm. **HRMS** (ESI^+): calcd for $C_{26}H_{30}NO_6$ $[M+H]^+$ 452.2068, found 452.2066. **$[\alpha]_D^{19.5}$** = -21.33 (c = 1.79, $CHCl_3$).



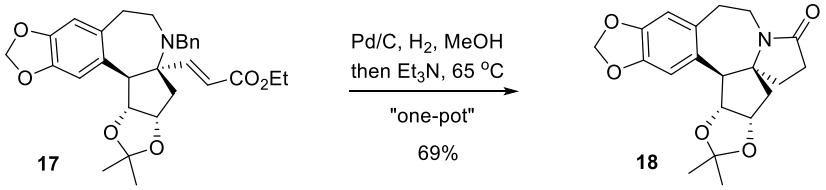
Synthesis of 16: $LiAlH_4$ (76 mg, 2.0 mmol, 2.0 equiv) was added in portions to an ice-cooled solution of compound **15** (451 mg, 1.0 mmol, 1.0 equiv) in dry THF (5 mL). After the addition, the reaction mixture was left stirring for 0.5 h at 0 °C. The reaction mixture was quenched with H_2O (2 mL), and 1 *N* NaOH (5 mL) was added. The resulting mixture was stirred intensely and filtered by diatomite washing with ethyl acetate. The organic phase was concentrated *in vacuo*. Finally, the crude residue was purified by column chromatography (petroleum ether/ethyl acetate = 4:1) to afford compound **16** (422 mg, quant. yield) as a pale yellow oil.

R_f = 0.52 (petroleum ether/ethyl acetate = 2:1). **IR (KBr)**: *v* 3081, 3060, 2713, 1723, 804, 770, 673, 642, 617, 596, 484, 437 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.22 – 7.11 (m, 3H), 6.89 (m, 2H), 6.62 (s, 1H), 6.59 (s, 1H), 6.00 – 5.86 (m, 2H), 5.21 (dd, *J* = 6.8, 3.4 Hz, 1H), 4.90 (td, *J* = 6.8, 2.3 Hz, 1H), 4.02 (s, 2H), 3.91 (d, *J* = 15.5 Hz, 1H), 3.51 – 3.39 (d, *J* = 15.5 Hz, 2H), 2.91 (dt, *J* = 12.4, 5.0 Hz, 1H), 2.86 – 2.76 (m, 1H), 2.71 (dt, *J* = 14.5, 6.3Hz, 1H), 2.55 (dd, *J* = 12.4, 6.3 Hz, 1H), 2.16 (dd, *J* = 14.5, 2.3 Hz, 1H), 2.07 – 1.93 (m, 1H), 1.58 (s, 3H), 1.38 (s, 3H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$): δ 146.1, 145.9, 141.5, 133.7, 130.8, 128.3, 127.3, 126.6, 110.9, 109.5, 108.1, 100.9, 83.7, 78.4, 70.9, 62.9, 56.1, 47.1, 40.0, 33.7, 26.4, 24.0 ppm. **HRMS** (ESI^+): calcd for $C_{25}H_{30}NO_5$ $[M+H]^+$ 424.2118, found 424.2124. $[\alpha]_D^{19.4}$ = +25.48 (*c* = 2.05, $CHCl_3$).

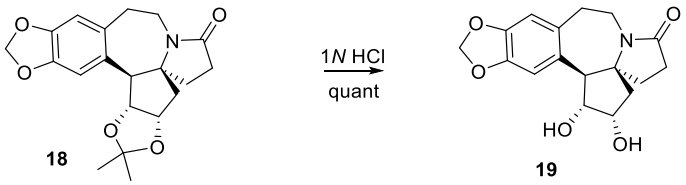


Synthesis of 17: The compound **16** (285 mg, 0.67 mmol, 1.0 equiv) was dissolved in acetonitrile (3 mL). To the solution were added 2,2'-bipyridine (5.3 mg, 0.05 mmol, 0.05 equiv), DMAP (8.2 mg, 0.1 mmol, 0.1 equiv), CuCl (3.3 mg, 0.05 mmol, 0.05 equiv) and azaadamantane-*N*-oxyl (5.1 mg, 0.05 mmol, 0.05 equiv). The reaction was stirred at room temperature for 3 h. The resulting mixture was concentrated *in vacuo,* and the crude product was directly used for the next step without purification. NaH (60% in mineral oil 129 mg, 3.2 mmol, 4.5 equiv) was added in portions to an ice-cooled solution of triethyl phosphonoacetate (0.6 mL, 3.3 mmol, 1.0 equiv) in dry THF (5 mL). The reaction mixture was stirred for 30 min at 0 °C, and the crude product dissolved in dry THF (4 mL) was added. The resulting mixture was stirred at room temperature for 4 h, and TLC analysis indicated complete consumption of the starting material. The mixture was then quenched with saturated NH_4Cl aqueous solution (5 mL), and the aqueous layer was extracted with ethyl acetate (20 mL x 4). The combined organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography (petroleum ether/ethyl acetate = 8:1) to afford compound **17** (310 mg, 95% yield, two steps) as a colorless oil.

R_f = 0.44 (petroleum ether/ethyl acetate = 15:1). **IR (KBr)**: *v* 3081, 3061, 2829, 1715, 822, 797, 671, 632, 569, 502, 461, 436 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.22 (m, 3H), 7.14 (d, *J* = 16.1 Hz, 1H), 7.01 (m, 2H), 6.59 (s, 1H), 6.57 (s, 1H), 6.00 (d, *J* = 16.1 Hz, 1H), 5.94 (dd, *J* = 10.5, 1.5 Hz, 2H), 5.20 (dd, *J* = 6.8, 4.7 Hz, 1H), 4.92 (td, *J* = 6.8, 3.4 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.87 (d, *J* = 15.1 Hz, 1H), 3.40 (d, *J* = 4.7 Hz, 1H), 3.18 (d, *J* = 15.1 Hz, 1H), 2.82 (m, 1H), 2.75 (m, 1H), 2.67 (m, 1H), 2.57 (m, 1H), 2.32 (m, 1H), 2.15 (m, 1H), 1.48 (s, 3H), 1.33 (s, 3H), 1.33 – 1.25 (q, 3H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.6, 147.6, 146.5, 146.1, 140.4, 134.1, 129.7, 128.4, 127.6, 126.9, 121.8, 111.7, 109.6, 101.0, 83.3, 78.0, 69.9, 60.6, 59.1, 56.0, 47.7, 43.4, 34.6, 26.4, 24.5, 14.4 ppm. **HRMS** (ESI): *m/z* calcd for $C_{29}H_{34}NO_6$ $[M+H]^+$ 492.2381, found 492.2382. $[\alpha]_D^{19.4}$ = +61.44 (*c* = 2.28, $CHCl_3$).



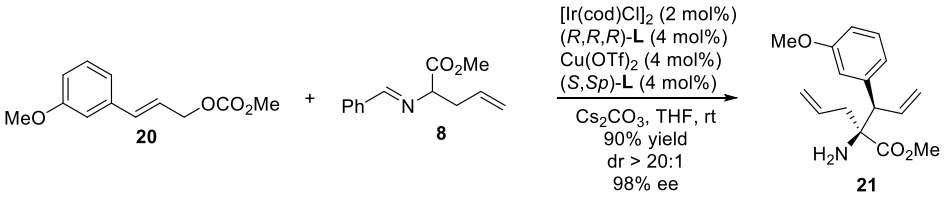
Synthesis of 18: 10% Pd/C (111 mg, 0.1 mmol, 0.1 equiv) was added to the solution of compound **17** (500 mg, 1.05 mmol, 1.0 equiv) in absolute MeOH (10 mL). The reaction mixture was stirred under hydrogen for a further 24 h. The resulting mixture was filtered by diatomite washing with ethyl acetate. The organic phase was concentrated *in vacuo,* and the crude product was directly used for the next step without purification. The crude product was dissolved in absolute MeOH (10 mL), and triethylamine (0.7 mL, 5 mmol, 5.0 equiv) was added. The reaction mixture was refluxed until TLC analysis indicated complete consumption of the starting material. The resulting mixture was concentrated *in vacuo.* Finally, the crude residue was purified by column chromatography (petroleum ether/ethyl acetate = 1:3) to afford compound **18** (259 mg, 69% yield, two steps) as a white solid. m.p. 204-206 °C. $\mathbf{R}_f$= 0.18 (petroleum ether/ethyl acetate = 1:1). **IR** (KBr): *v* 3434, 3358, 2783, 1731, 1318, 980, 909, 828, 751, 737, 713, 636, 581，410 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.64 (s, 1H), 6.62 (s, 1H), 5.90 (s, 2H), 4.80 (td, *J* = 5.7, 2.7 Hz, 1H), 4.68 (t, *J* = 5.4 Hz, 1H), 4.10 (ddd, *J* = 13.8, 11.9, 7.0 Hz, 1H), 3.17 (d, *J* = 5.3 Hz, 1H), 3.04 (ddd, *J* = 13.9, 6.8, 1.9 Hz, 1H), 2.81 (ddd, *J* = 15.1, 11.9, 6.7 Hz, 1H), 2.72 – 2.53 (m, 2H), 2.29 – 2.20 (m, 4H), 2.19 – 2.11 (m, 1H), 1.60 (s, 3H), 1.32 (s, 3H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$): δ 174.8, 147.1, 146.6, 131.2, 128.8, 111.5, 111.3, 110.1, 101.1, 87.7, 79.8, 70.7, 65.1, 41.2, 38.9, 38.0, 30.5, 30.0, 28.1, 25.5 ppm. **HRMS** (ESI): *m/z* calcd for $C_{20}H_{24}NO_5$ $[M+H]^+$ 358.1649, found 358.1648. $[\alpha]_D^{20}$ = +78.87 (*c* = 1.8, $CHCl_3$).

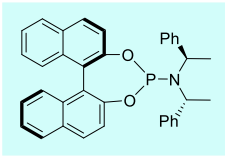


Synthesis of 19: 1 *N* HCl (1.4 mL, 5.0 equiv) was added to the solution of compound **18** (100 mg, 0.28 mmol, 1.0 equiv) in THF (1 mL). The reaction mixture was stirred at 50 °C until TLC analysis indicated complete consumption of the starting material. The resulting mixture was concentrated *in vacuo* and neutralized by 2*N* NaOH, and the aqueous layer was extracted with dichloromethane (20 mL x 4). The combined organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Finally, the crude residue was purified by column chromatography (dichloromethane/methanol = 20:1) to afford compound **19** (88 mg, quant) as a white solid. m.p. 185-186 °C.

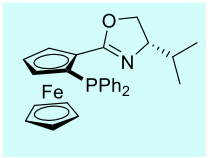
$\mathbf{R}_f$= 0.22 (dichloromethane/methanol = 20:1). **IR** (KBr): *v* 3430, 2923, 1677, 976, 824, 806, 787, 710, 519, 484, 445, 412 cm^{-1}. **^{1}H NMR** (400 MHz, MeOD): δ 6.60 (s, 1H), 6.58 (s, 1H), 5.77 (d, *J* = 3.0 Hz, 2H), 4.27 (dd, *J* = 9.8, 3.9 Hz, 1H), 4.07 (t, *J* = 3.8 Hz, 1H), 3.95 – 3.82 (m, 1H), 3.12 – 2.96 (m, 3H), 2.61 – 2.50 (m, 1H), 2.45 (dd, *J* = 14.5, 3.9 Hz, 1H), 2.33 – 2.21 (m, 1H), 2.20 – 2.10 (m, 1H), 2.11 – 1.96 (m, 2H), 1.81 (d, *J* = 14.5 Hz, 1H) ppm. **^{13}C NMR** (150 MHz, MeOD): δ 178.1, 148.4, 148.0,

133.2, 131.3, 113.4, 111.7, 102.4, 79.7, 73.2, 69.6, 62.6, 48.7, 42.0, 40.8, 39.8, 31.0 ppm. **HRMS** (ESI): *m/z* calcd for $C_{17}H_{20}NO_5$ $[M+H]^+$ 318.1336, found 318.1339. $[\alpha]_D^{21.2}$ = +45.45 (*c* = 0.11, CH_3OH).





(*R,R,R*)-**L**



(*S,S*$_p$)-**L**

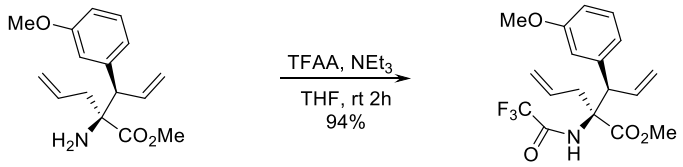
The preparation of **Ir catalyst:** A 25 mL flame-dried flask was cooled to room temperature and transferred to a nitrogen-filled glove box. To this flask were added $[Ir(cod)Cl]_2$ (134 mg, 0.2 mmol, 0.02 equiv), (*R*, *R*, *R*)-**L** (216 mg, 0.4 mmol, 0.04 equiv), THF (1 mL) and *n*-propylamine (1 mL). The flask was filled with N_2 and removed from the glove box. The reaction mixture was heated at 50 ºC for 30 min, and then the volatile solvents were removed under a vacuum to give a pale-yellow solid. The **Ir** catalyst was prepared after adding THF (10 mL).

The preparation of **Cu catalyst:** $Cu(OTf)_2$ (145mg, 0.4 mmol, 0.04 equiv), (*S*, *S*$_p$)-**L** (192 mg, 0.4 mmol, 0.04 equiv) were stirred in THF (10 mL) in a Schlenk flask under nitrogen atmosphere at room temperature for 1 h.

Synthesis of 21:

A flame-dried 100 mL flask was cooled to room temperature and filled with N_2. To this flask were added aldimine Schiff base **8** (3.052 g, 14 mmol, 1.4 equiv), Cs_2CO_3 (4.56 g, 14 mmol, 1.4 equiv), Cu catalyst (10 mL) and Ir catalyst (10 mL) were then added. Allylic carbonate **20** (2.2 g, 10 mmol, 1 equiv) was then added, and the reaction mixture was stirred at room temperature for 12 h. To the reaction mixture was added a 10% citric acid solution (20 mL) at room temperature and stirred for 2 h. After being washed with ethyl acetate, the mixture was neutralized with solid K_2CO_3 and extracted with ethyl acetate (100 mL x 3). The combined extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was then purified by column chromatography (petroleum ether/ethyl acetate = 5:1) to give the desired products **21** (2.48 g, 90%). The product was analyzed by HPLC to determine the enantiomeric excess: 98% ee (Chiralpak AD-H, *i*-propanol /hexane = 5/95, flow rate 1.0 mL/min, λ = 210 nm).

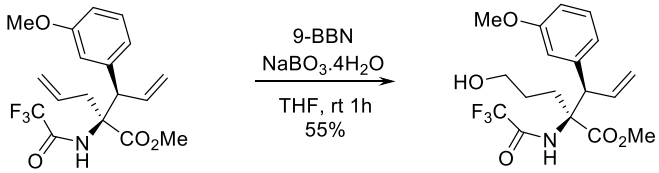
R$_f$ = 0.2 (petroleum ether/ethyl acetate = 8:1). **IR** (KBr): *v* 3565, 3521, 3508, 3325, 3217, 1376, 1081, 816, 670, 567 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 7.22 (d, *J* = 8.4 Hz, 1H), 6.90 (d, *J* = 6.2 Hz, 2H), 6.80 (d, *J* = 8.4 Hz, 1H), 6.30 – 6.20 (m, 1H), 5.67 – 5.50 (m, 1H), 5.08 (m, 4H), 3.80 (s, 3H), 3.72 (s, 3H), 3.62 (d, *J* = 9.4 Hz, 1H), 2.61 (dd, *J* = 13.6, 6.4 Hz, 1H), 1.92 (dd, *J* = 13.6, 6.4 Hz, 1H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 175.9, 159.4, 140.8, 137.0, 132.5, 129.2, 121.8, 119.6, 117.5, 115.4, 112.2, 64.9, 58.5, 55.1, 52.1, 43.3 ppm. **HRMS** (ESI): *m/z* calcd for $C_{16}H_{22}NO_3$ $[M+H]^+$ 276.1594, found 276.1593. $[\alpha]_D^{27.4}$ = +1.04 (*c* = 0.31, $CHCl_3$).



21 22

Synthesis of 22: A 100 mL flame-dried flask equipped with a stir bar was charged with compound **21** (1090 mg, 3.9 mmol, 1.0 equiv) and triethylamine (2.4 mL, 17 mmol, 4.4 equiv) followed by the addition of dry THF (39 mL) and cooled down to 0 ºC. Trifluoroacetic anhydride (1.2 mL, 8.6 mmol, 2.2 equiv) was added dropwise via a syringe. The resulting mixture was warmed to room temperature and stirred for 2 h, upon which TLC analysis indicated complete consumption of the starting material. The mixture was then quenched with saturated NH_4Cl aqueous solution (20 mL), and the aqueous layer was extracted with dichloromethane (100 mL x 3). The combined organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Finally, the crude residue was purified by column chromatography (petroleum ether/ethyl acetate = 4:1) to afford compound **22** (1360 mg, 96% yield) as a colorless oil.

R_f = 0.21 (petroleum ether/ethyl ether = 20:1). **IR** (KBr): *v* 3434, 3081, 3006, 2982, 2838, 1641, 1367, 1090, 976, 826, 811, 640, 605, 566, 527 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.26 – 7.09 (m, 2H), 6.79 (dd, *J* = 8.4, 2.5 Hz, 1H), 6.60 – 6.55 (m, 1H), 6.54 (t, *J* = 2.1 Hz, 1H), 6.41–6.31 (m, 1H), 5.50 – 5.43 (m, 1H), 5.34 – 5.23 (m, 2H), 5.17 – 5.07 (m, 2H), 4.34 (d, *J* = 10.0 Hz, 1H), 3.88 (s, 3H), 3.75 (s, 3H), 3.32 (dd, *J* = 14.2, 7.8 Hz, 1H), 2.84 (dd, *J* = 14.2, 7.8 Hz, 1H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$): δ 171.5, 159.7, 155.9, 140.0, 135.3, 131.0, 129.6, 120.1, 119.9, 119.4, 116.8 113.6, 113.1, 68.5, 55.0, 53.9, 53.2, 37.2 ppm. **HRMS** (ESI): *m/z* calcd for $C_{18}H_{21}F_3NO_4$ $[M+H]^+$ 372.1417, found 372.1421. **[α]** $_D^{27.5}$ = +6.75 (*c* = 0.85, $CHCl_3$).

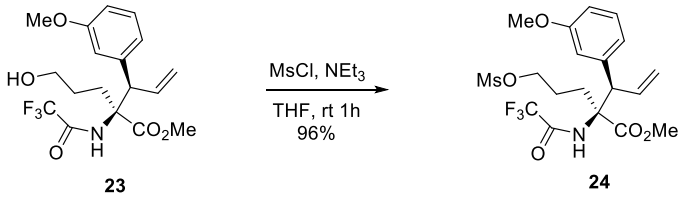


22 23

Synthesis of 23: 9-BBN (5.9 mL, 2.96 mmol, 1.1 equiv) was dropwise added to an ice-cooled solution of compound **22** (1000 mg, 2.7 mmol, 1.0 equiv) in dry THF (26 mL). The resulting mixture was warmed to room temperature and stirred for 1 h. Sodium perborate tetrahydrate (1690 mg, 10 mmol, 4 equiv) was added, and the suspension was stirred for 3 h. The mixture was extracted with ethyl acetate (100 mL x 3). The combined organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography (petroleum ether/ethyl acetate = 2:1) to afford compound **23** (577 mg, 55% yield) as a colorless oil, and starting material **22** recovered (390 mg, 90% based on recovered starting material).

R_f= 0.23 (petroleum ether/ethyl acetate = 2:1). **IR** (KBr): *v* 3547, 3428, 3080, 3005, 2884, 2839, 1637, 1377, 1355, 975, 905, 827, 677, 644, 629 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.25 – 7.16 (m, 2H), 6.79 (dd, *J* = 8.3, 2.6 Hz, 1H), 6.56 (d, *J* = 7.6 Hz, 1H), 6.52 (t, *J* = 2.1 Hz, 1H), 6.35 (dt, *J* = 16.9, 10.0

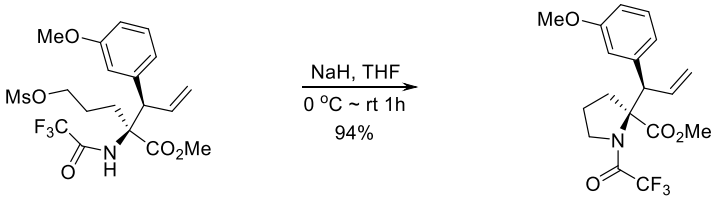
Hz, 1H), 5.35 – 5.18 (m, 2H), 4.28 (d, J = 10.0 Hz, 1H), 3.88 (s, 3H), 3.75 (s, 3H), 3.62 (m, 2H), 2.67 – 2.59 (m, 1H), 2.24 – 2.16 (m, 1H), 1.51 – 1.34 (m, 2H), 1.27 – 1.19 (m, 1H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$): δ 171.9, 159.7, 155.9, 140.0, 135.2, 129.6, 120.1, 119.4, 116.8, 113.7, 113.2, 68.7, 62.0, 55.0, 54.4, 53.4, 29.5, 27.4 ppm. **HRMS** (ESI): *m/z* calcd for $C_{18}H_{22}F_3NO_5Na$ $[M+Na]^+$ 412.1342, found 412.1343. $[\alpha]_D^{26.9}$ = +25.17 (c = 1.86, $CHCl_3$).



23 **24**

Synthesis of 24: A solution of compound **23** (1200 mg, 3.08 mmol, 1.0 eq.) and triethylamine (0.85 mL, 6.1 mmol, 2.0 equiv) in dry THF (30 ml) was cooled to 0 °C. Methanesulfonyl chloride (0.35 mL, 4.6 mmol, 1.5 equiv) was added. After the addition was complete, the reaction mixture was warmed to room temperature and stirred for 1h, upon which TLC analysis indicated complete consumption of the starting material. The mixture was then quenched with saturated $NaHCO_3$ aqueous solution (20 mL), and the aqueous layer was extracted with ethyl acetate (100 mL x 3). The combined organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography (petroleum ether/ethyl acetate = 4:1) to afford compound **24** (1.380 g, 96% yield) as a colorless oil.

R_f = 0.21 (petroleum ether/ethyl acetate = 3:1). **IR** (KBr): ν 3638, 3566, 3080, 3028, 2840, 1637, 1090, 678, 645, 629, 607, 548 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.24 – 7.17 (m, 2H), 6.80 (dd, J = 8.2, 2.5 Hz, 1H), 6.56 – 6.51 (m, 2H),6.40 – 6.26 (m, 1H), 5.35 – 5.22 (m, 2H), 4.26 – 4.17 (m, 3H), 3.90 (s, 3H), 3.78 (s, 3H), 3.01 (s, 3H), 2.68 (td, J = 14.4, 12.9, 4.5 Hz, 1H), 2.27 (td, J = 14.4, 12.9, 4.5 Hz, 1H), 1.67 – 1.59 (m, 1H), 1.47 – 1.41 (m, 1H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$): δ 171.5, 159.7, 155.7, 139.6, 134.9, 129.7, 119.9, 119.7, 116.2, 113.7, 113.2, 68.7, 68.3, 55.0, 54.4, 53.6, 37.4, 29.1, 24.3 ppm. **HRMS**(ESI): *m/z* calcd for $C_{19}H_{24}F_3NO_7SNa$ $[M+Na]^+$ 490.1118, found 490.1120. $[\alpha]_D^{26.9}$ = +23.04 (c = 1.87, $CHCl_3$).

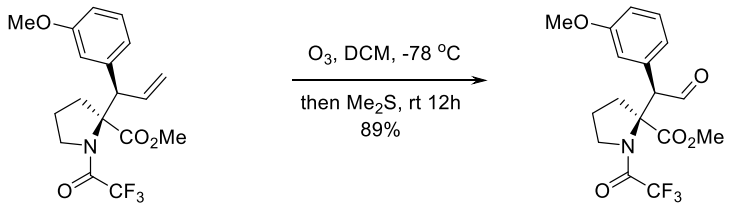


24 **25**

Synthesis of 25: Sodium hydride (60% in mineral oil 177 mg, 4.4 mmol, 1.5 equiv) was added in portions to an ice-cooled solution of compound **24** (1380 mg, 2.95 mmol, 1.0 equiv) in dry THF (29 mL). After the addition was complete, the reaction mixture was warmed to room temperature and stirred for 10 min, upon which TLC analysis indicated complete consumption of the starting material. The mixture was then quenched with saturated $NaHCO_3$ aqueous solution (20 mL), and the aqueous layer was extracted with ethyl acetate (100 mL x 3). Next, the combined organic phase was washed

with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Finally, the crude residue was purified by column chromatography (petroleum ether/ethyl acetate = 4:1) to afford compound **25** (1029 mg, 94% yield) as a colorless oil.

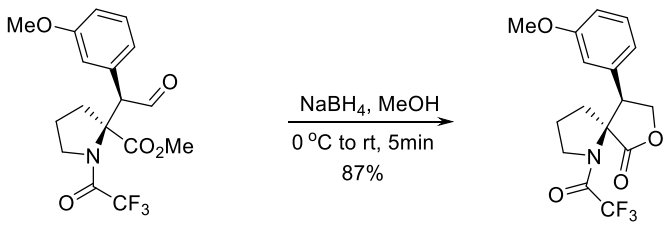
R_f= 0.31 (petroleum ether/ethyl acetate = 8:1). **IR** (KBr): *v* 3081, 2894, 2838, 1637, 1351, 1336, 969, 877, 824, 733, 641 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.21 (t, *J* = 8.2 Hz, 1H), 6.99 – 6.90 (m, 2H), 6.79 (dd, *J* = 8.2, 2.5 Hz, 1H), 6.16 (dt, *J* = 16.8, 9.1 Hz, 1H), 5.12 – 5.03 (m, 2H), 4.55 (d, *J* = 9.1 Hz, 1H), 3.92 – 3.90 (m, 1H), 3.79 (s, 3H), 3.68 (s, 3H), 3.55 – 3.48 (m, 1H), 2.41– 2.34 (m, 1H), 2.11 – 1.96 (m, 2H), 1.78 – 1.63 (m, 1H) ppm. **^{13}C NMR** (100MHz, $CDCl_3$): δ 171.5, 159.3, 155.9, 141.1, 136.2, 129.0, 122.3, 117.7, 116.0, 112.1, 73.5, 55.1, 52.6, 52.5, 49.0, 49.0, 34.1, 23.9 ppm. **HRMS** (ESI): *m/z* calcd for $C_{18}H_{21}F_3NO_4$ $[M+H]^+$ 372.1417, found 372.1415. **$[\alpha]_D^{26.6}$** = -100.58 (*c* = 1.78, $CHCl_3$).



25 **26**

Synthesis of 26: Compound **25** (1100 mg, 2.96 mmol, 1.0 equiv) was dissolved in dry dichloromethane (60 mL) and cooled to -78 °C. An O_3-O_2 stream was passed through the solution for 10 min, upon which TLC analysis indicated complete consumption of the starting material. After the solution was purged with oxygen for 15 min, Me_2S (21 mL, 296 mmol, 100 equiv) was added. The reaction mixture was warmed to room temperature and stirred for 8 h. Finally, the solution was concentrated *in vacuo*. The crude product was purified by silica gel flash chromatography (petroleum ether/ethyl acetate = 4:1) to afford the desired product **26** (983 mg, 89% yield) as a white solid. m.p. 96-97 °C.

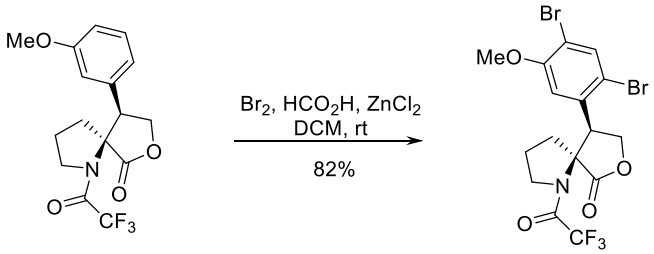
R_f= 0.21 (petroleum ether/ethyl acetate = 4:1). **IR** (KBr): *v* 3003, 2893, 2840, 2737, 2581, 2073, 2048, 2022, 2001, 1983, 1966, 1938, 1520, 949, 924, 824, 738, 651, 623, 587, 565, 530 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.90 (d, *J* = 4.7 Hz, 1H), 7.37 – 7.26 (m, 1H), 6.90 (d, *J* = 7.9 Hz, 1H), 6.77 – 6.67 (m, 2H), 4.37 (s, 1H), 3.86 – 3.75 (m, 7H), 3.41 (q, *J* = 8.2 Hz, 1H), 2.40 – 2.30 (m, 1H), 2.17 (dt, *J* = 13.1, 6.6 Hz, 1H), 1.85 (dq, *J* = 14.2, 7.4, 6.6 Hz, 1H), 1.39 (dp, *J* = 13.1, 6.6 Hz, 1H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$): δ 196.3, 170.9, 159.7, 156.7, 133.5, 129.6, 123.5, 117.5, 116.8, 113.9, 72.0, 61.7, 55.1, 53.2, 49.0, 36.4, 23.1 ppm. **HRMS** (ESI): *m/z* calcd for $C_{17}H_{19}F_3NO_5$ $[M+H]^+$ 374.1210, found 374.1207. **$[\alpha]_D^{26.9}$** = -155.59 (*c* = 1.03, $CHCl_3$).



26 **27**

Synthesis of 27: A solution of compound **26** (100 mg, 0.27 mmol, 1.0 equiv) in dry MeOH (2 mL) was cooled to 0 °C. To the mixture, $NaBH_4$ (8 mg, 0.22 mmol, 0.8 equiv) was added in small portions to control the rate of the gas evolution. After the addition was complete, the reaction mixture was left stirring for 0.5 h, warmed to room temperature, and quenched by adding H_2O (1 mL). The resulting mixture was concentrated, diluted with water (10 mL), and extracted with dichloromethane (50 mL × 3). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate = 4:1) to afford compound **27** (80.6 mg, 87% yield) as a white solid. m.p. 97-98 °C.

R_f = 0.28 (petroleum ether/ethyl acetate = 4:1). **IR** (KBr): *v* 3545, 3360, 3138, 3077, 3011, 2943, 2926, 2905, 2880, 2841, 2751, 2640, 2323, 1548, 1514, 1383, 1352, 1338, 1329, 1320, 996, 923, 884, 824, 728, 713, 670, 646, 631, 616, 588, 577, 555, 526 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.27 (t, J = 8.0 Hz, 1H), 6.88 (dd, J = 8.0, 2.1 Hz, 1H), 6.81 (dd, J = 7.5, 1.7 Hz, 1H), 6.77 (t, J = 2.1 Hz, 1H), 4.83 (dd, J = 10.8, 8.7 Hz, 1H), 4.60 (t, J = 8.7 Hz, 1H), 3.78 (s, 3H), 3.76 – 3.63 (m, 2H), 3.04 (m, 1H), 2.60 (m, 1H), 2.23 (m, 1H), 2.15 – 2.02 (m, 1H), 1.98 – 1.87 (m, 1H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$): δ 174.4, 159.9, 156.5, 135.1, 129.9, 121.0, 117.3, 114.2, 114.0, 71.1, 69.1, 55.1, 53.4, 48.2, 39.4, 24.2 ppm. **HRMS** (ESI): *m/z* calcd for $C_{16}H_{16}F_3NO_4Na$ $[M+Na]^+$ 366.0924, found 366.0924. **$[\alpha]_D^{26.6}$** = -180.12 (c = 2.29, $CHCl_3$).

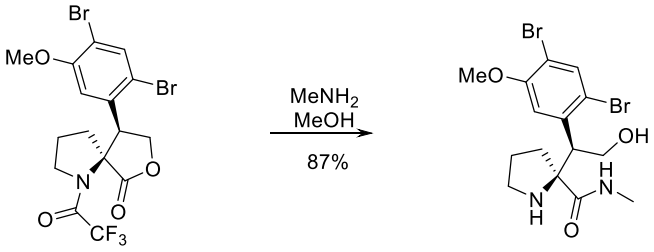


27 **28**

Synthesis of 28: The compound **27** (63 mg, 0.18 mmol, 1.0 equiv) was dissolved in dry dichloromethane (0.9 mL). To the solution were added zinc chloride (147 mg, 1.08 mmol, 6.0 equiv), formate (0.10 mL, 2.7 mmol, 15.0 equiv), and bromine (0.029 mL, 0.54 mmol, 3.0 equiv). The reaction was stirred at room temperature for 4 h, upon which TLC analysis indicated complete consumption of the starting material. The resulting mixture was cooled to 0 ºC and quenched by the addition of saturated Na_2SO_3 aqueous solution (1 mL) and saturated $NaHCO_3$ aqueous solution (1 mL) and extracted with dichloromethane (20 mL x 3). The combined organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography (petroleum ether/ethyl acetate = 2:1) to afford compound **28** (74 mg, 82% yield) as a white solid. m.p. 170 -171°C.

R_f = 0.27 (petroleum ether/ethyl acetate = 8:1). **IR** (KBr): *v* 3104, 3075, 2986, 2950, 2920, 2854, 1651, 1556, 1519, 1328, 1308, 992, 945, 932, 884, 831, 769, 758, 729, 706, 650, 634, 603, 592, 580, 526 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.79 (s, 1H), 6.81 (s, 1H), 4.70 – 4.57 (m, 2H), 4.42 (dd, J = 10.5, 8.7 Hz, 1H), 3.81 (s, 3H), 3.73 (td, J = 9.9, 7.0 Hz, 1H), 3.34 (ddd, J = 10.9, 8.2, 3.1 Hz, 1H), 2.60 – 2.47 (m, 2H), 2.17 – 2.13 (m, 1H), 2.03 – 1.88 (m, 1H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$): δ 173.7, 157.5,

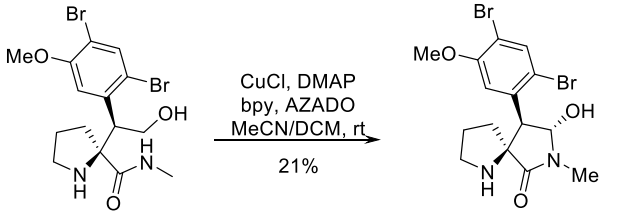
155.7, 136.8, 133.9, 117.3, 115.8, 112.6, 112.2, 71.5, 70.0, 56.1, 50.6, 48.5, 39.0, 24.3 ppm. **HRMS** (ESI): *m/z* calcd for $C_{16}H_{14}Br_2F_3NO_4Na$ $[M+Na]^+$ 521.9134, found 521.9131. $[\alpha]_D^{26.6}$ = -198.56 (*c* = 4.25, $CHCl_3$).



28 **29**

Synthesis of 29: The compound **28** (109.4 mg, 0.22 mmol, 1.0 equiv) was dissolved in methylamine (12 mL, 30-33 wt. % in methanol). The reaction was stirred at room temperature for 15 h, upon which TLC analysis indicated complete consumption of the starting material. The resulting mixture was concentrated *in vacuo*. The crude residue was purified by column chromatography (petroleum ether/ethyl acetate 1:4) to afford compound **29** (83 mg, 87% yield) as a white solid. m.p. 165-167 °C.

$\mathbf{R}_f$ = 0.21 (petroleum ether/ethyl acetate = 1:2). **IR** (KBr): *v* 3107, 3013, 2991, 2069, 1294, 980, 935, 820, 781, 755, 718, 673, 624, 610, 589, 567, 528 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.09 (s, 1H), 7.74 (s, 1H), 6.96 (s, 1H), 4.21 (dd, *J* = 12.2, 4.7 Hz, 1H), 3.84 (dd, *J* = 12.2, 4.7 Hz, 1H), 3.80 (s, 3H), 3.54 (t, *J* = 4.7 Hz, 1H), 3.05 (dd, *J* = 9.6, 6.8 Hz, 1H), 2.90 (ddd, *J* = 10.1, 7.0, 3.8 Hz, 1H), 2.79 (d, *J* = 5.1 Hz, 3H), 2.34 (ddd, *J* = 11.6, 7.0, 3.8 Hz, 1H), 2.09 (ddd, *J* = 13.1, 10.1, 7.4 Hz, 1H), 1.87 (ddt, *J* = 10.1, 7.4, 3.8 Hz, 1H), 1.69 (dd, *J* = 20.6, 8.7 Hz, 2H) ppm. **^{13}C NMR** (150 MHz, $CDCl_3$): δ 177.6, 155.4, 139.0, 136.1, 116.5, 113.2, 111.5, 72.2, 63.8, 56.4, 54.1, 46.6, 38.0, 26.3, 25.9 ppm. **HRMS** (ESI): *m/z* calcd for $C_{15}H_{21}Br_2N_2O_3$ $[M+H]^+$ 434.9913, found 434.9911. $[\alpha]_D^{26.8}$ = +5.31 (*c* = 1.03, $CHCl_3$).

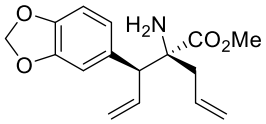


29 **(-)-amathaspiramide F**

Synthesis of (-)-amathaspiramide F: The compound **29** (43 mg, 0.18 mmol, 1.0 equiv) was dissolved in acetonitrile (1.5 mL) and dichloromethane (0.5 mL). To the solution were added 2,2'-bipyridine (1.5 mg, 0.01 mmol, 0.1 equiv), DMAP (2.4 mg, 0.02 mmol, 0.2 equiv), CuCl (1.0 mg, 0.01 mmol, 0.1 equiv) and azaadamantane-*N*-oxyl (1.5 mg, 0.01 mmol, 0.1 equiv). The reaction was stirred at room temperature for 3 h. The resulting mixture was concentrated *in a vacuum*. The crude residue was purified by column chromatography (dichloromethane/methanol = 10:1) to afford **(-)-amathaspiramide F** (9 mg, 21% yield) as a white solid and recovered starting material **29** (31 mg, 0.07mmol). m.p. 169-170 °C.

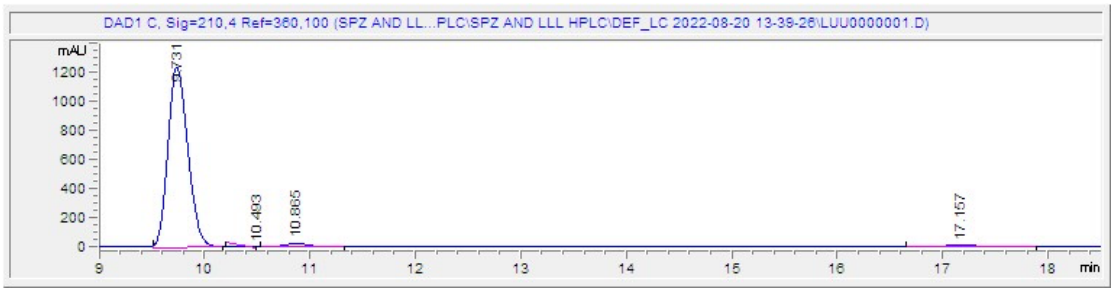
R_f = 0.28 (dichloromethane/methanol = 10:1). **IR** (KBr): *v* 3279, 3102, 3017, 2978, 2892, 2850, 2797, 2616, 2239, 1558, 1518, 971, 958, 864, 825, 801, 766, 752, 645, 623, 607, 572 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.75 (s, 1H), 6.73 (s, 1H), 5.06 (d, J = 2.7 Hz, 1H), 3.82 (s, 3H), 3.72 (d, J = 2.7 Hz, 1H), 3.04 (dd, J = 10.5, 6.9 Hz, 1H), 3.00 (s, 3H), 2.59 (ddd, J = 10.5, 7.7, 5.8 Hz, 1H), 2.19 (dt, J = 12.7, 8.3 Hz, 1H), 2.09 (ddd, J = 12.7, 7.7, 5.2 Hz, 1H), 1.91 – 1.83 (m, 1H), 1.82 – 1.76 (m, 1H) ppm. **^{13}C NMR** (150 MHz, $CDCl_3$): δ 176.7, 155.4, 137.5, 136.2, 116.4, 111.7, 111.4, 87.8, 70.2, 57.7, 56.4, 47.5, 38.8, 27.4, 26.1 ppm. **HRMS** (ESI): *m/z* calcd for $C_{15}H_{19}Br_2N_2O_3$ $[M+H]^+$ 432.9757, found 432.9756. **$[\alpha]_D^{25.8}$** = -30.88 (*c* = 0.12, $CHCl_3$).

3. HPLC and NMR spectra



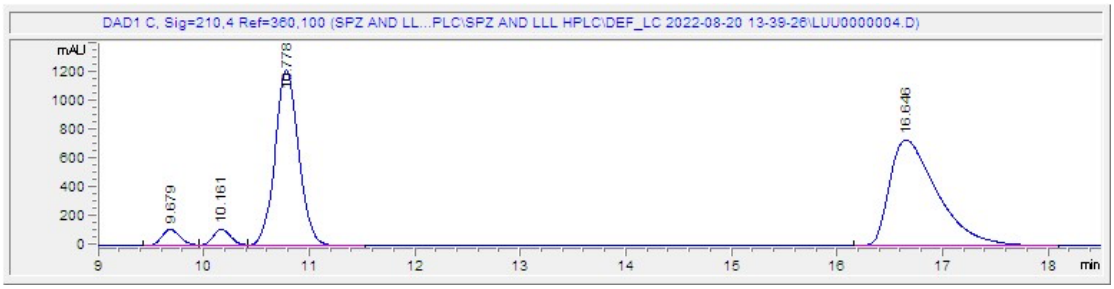
9

Enantioenriched mixture of compound **9**

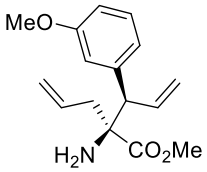


#	Time	Area	Height	Width	Area%	Symmetry
1	9.731	16291.3	1232.3	0.2203	96.209	0.804
2	10.493	20.1	8.8	0.0379	0.119	0
3	10.865	407.5	25.9	0.2398	2.406	0.976
4	17.157	214.3	6.9	0.4738	1.266	0.724

Racemate of compound **9**

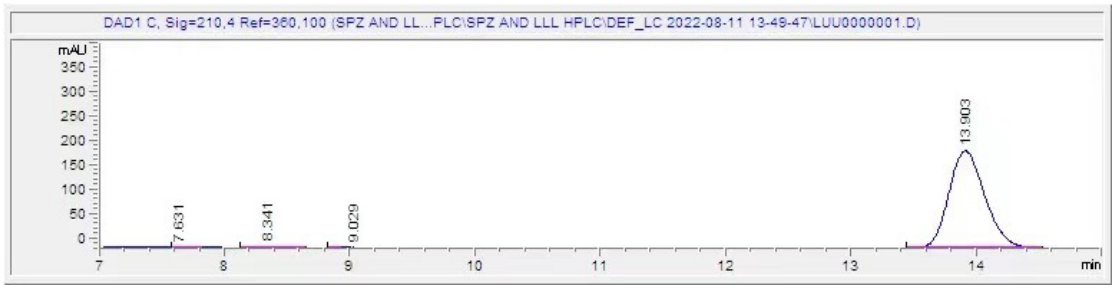


#	Time	Area	Height	Width	Area%	Symmetry
1	9.679	1326.2	111.4	0.1829	3.000	0.817
2	10.161	1292.5	111.8	0.1789	2.924	0.82
3	10.778	18784.8	1210.2	0.2391	42.490	0.899
4	16.646	22805.9	729.4	0.4728	51.586	0.479



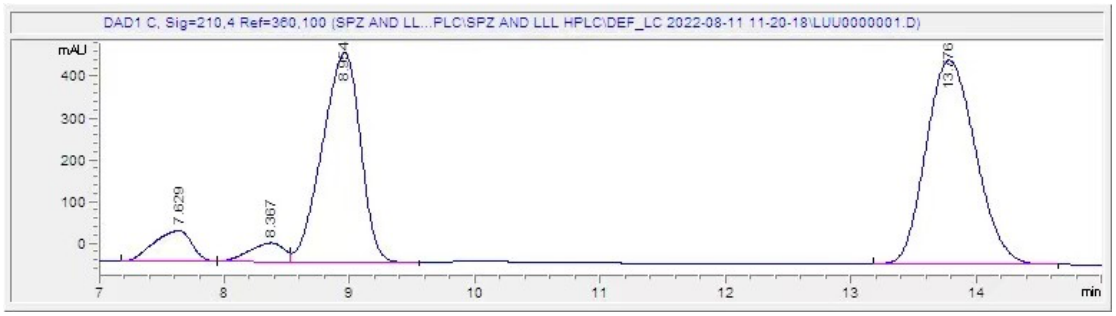
21

Enantioenriched mixture of compound **21**

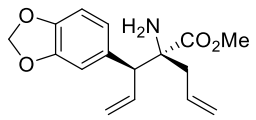


#	Time	Area	Height	Width	Area%	Symmetry
1	7.631	22.8	1.9	0.1962	0.567	0.284
2	8.341	19.9	1.7	0.1775	0.495	0.852
3	9.029	13.3	2.2	0.099	0.330	0.247
4	13.903	3970	198.2	0.3096	98.608	0.792

Racemate of compound **21**

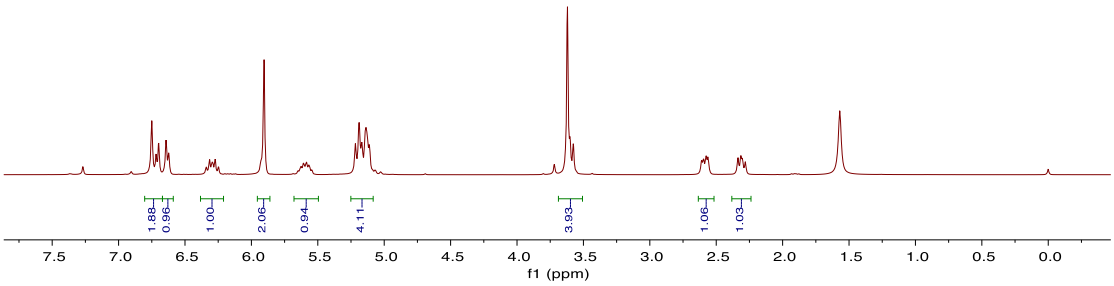


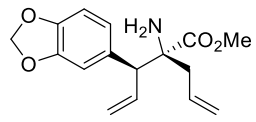
#	Time	Area	Height	Width	Area%	Symmetry
1	7.629	1633	75.9	0.3631	6.122	1.783
2	8.367	934.5	46.7	0.3093	3.503	1.728
3	8.954	10657.2	501.9	0.3337	39.956	1.361
4	13.776	13447.9	488.7	0.435	50.419	0.842



9

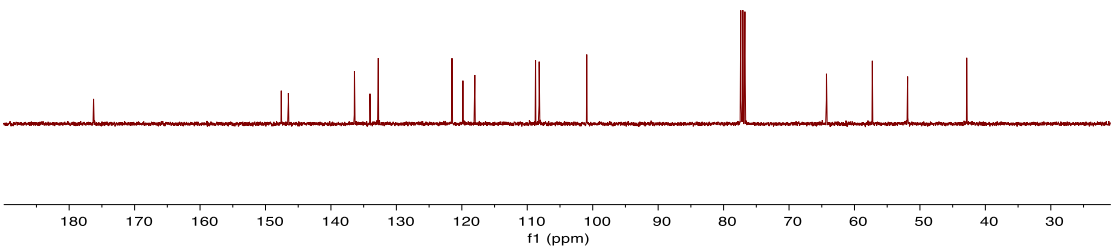
^{1}H NMR, 400 MHz, $CDCl_3$

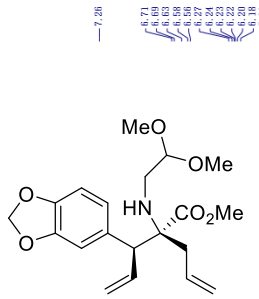




9

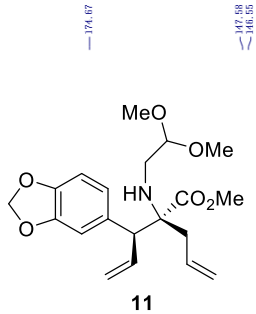
^{13}C NMR, 100 MHz, $CDCl_3$





11

^{1}H NMR, 400 MHz, $CDCl_3$



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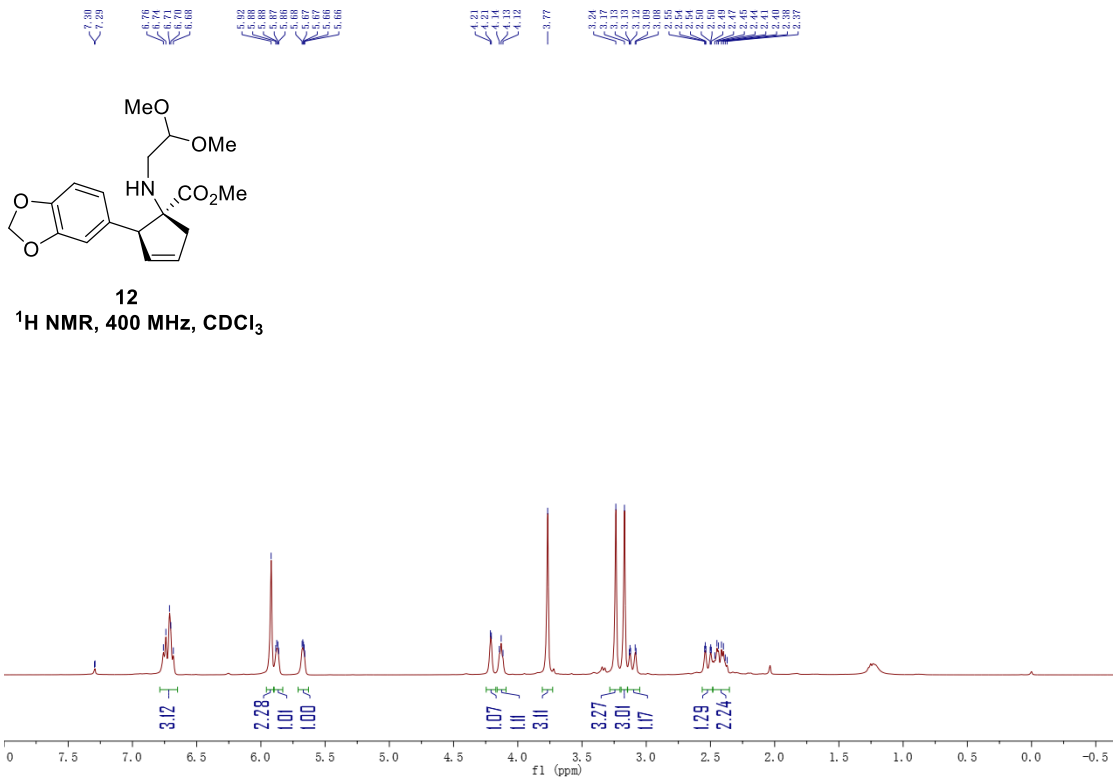
^{13}C NMR, 100 MHz, $CDCl_3$



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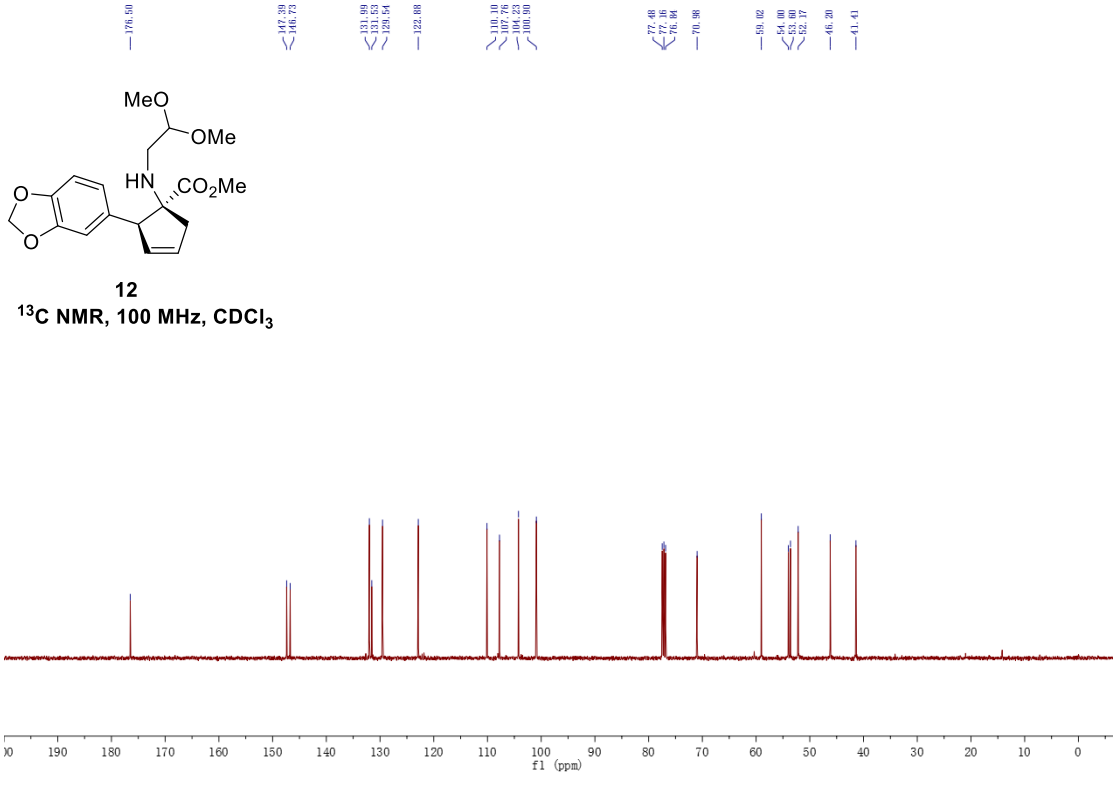

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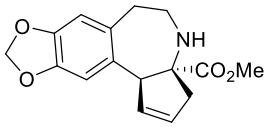

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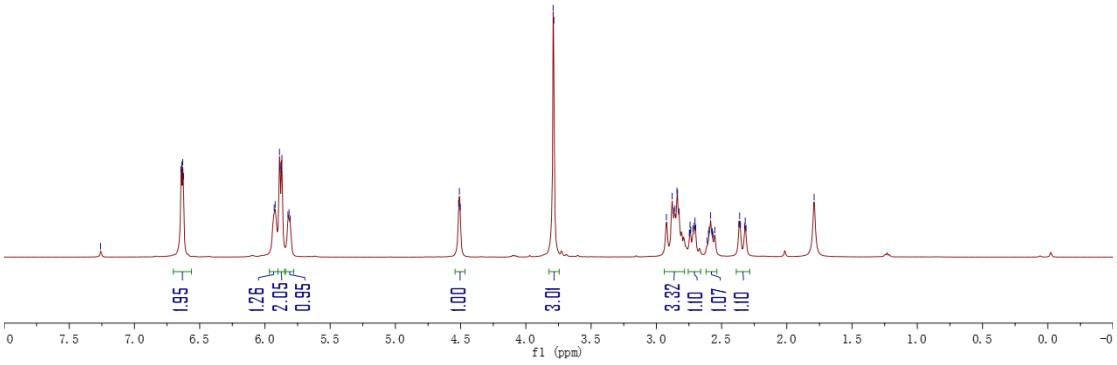
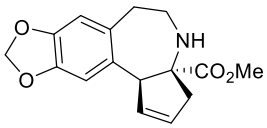
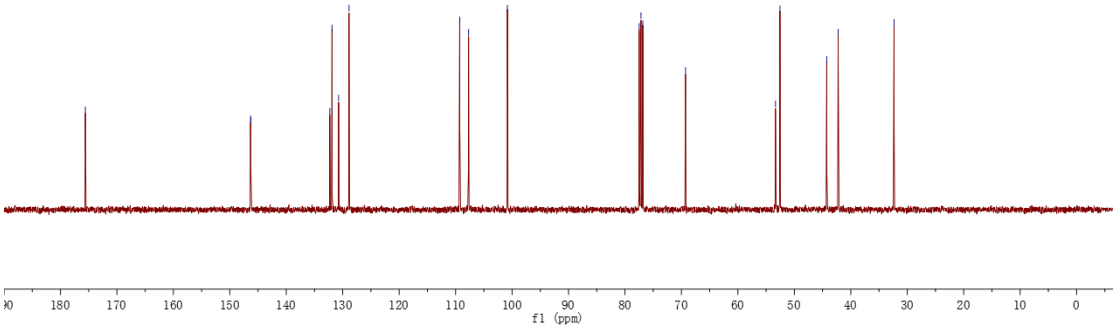
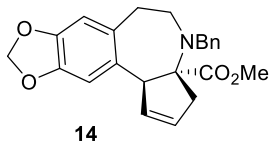




13

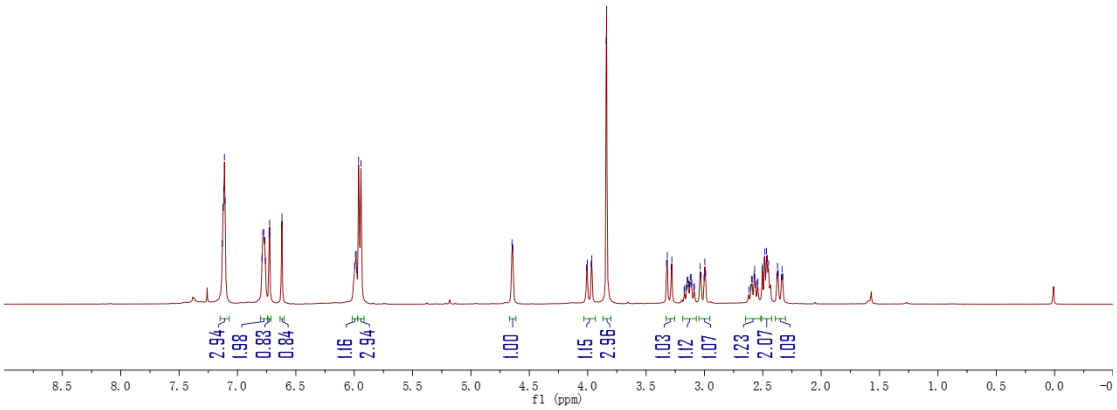
^{13}C NMR, 100 MHz, $CDCl_3$

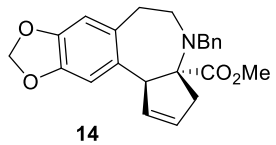




14

^{1}H NMR, 400 MHz, $CDCl_3$





14

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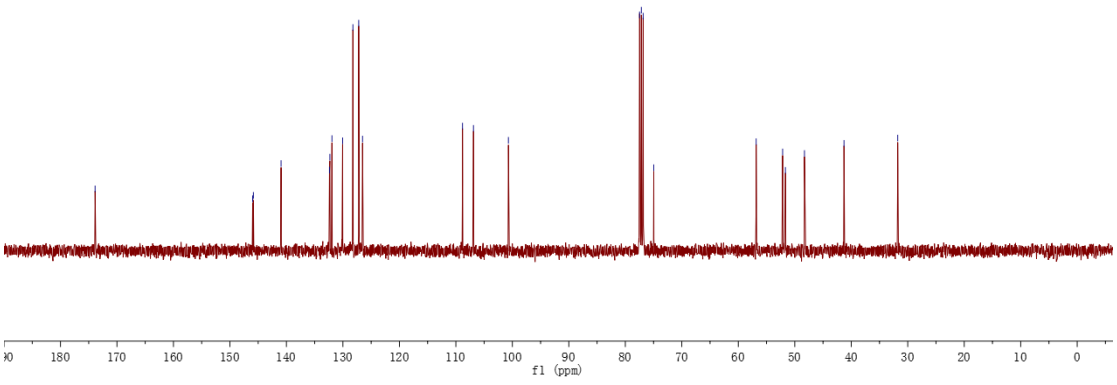
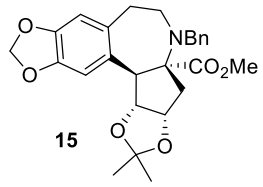
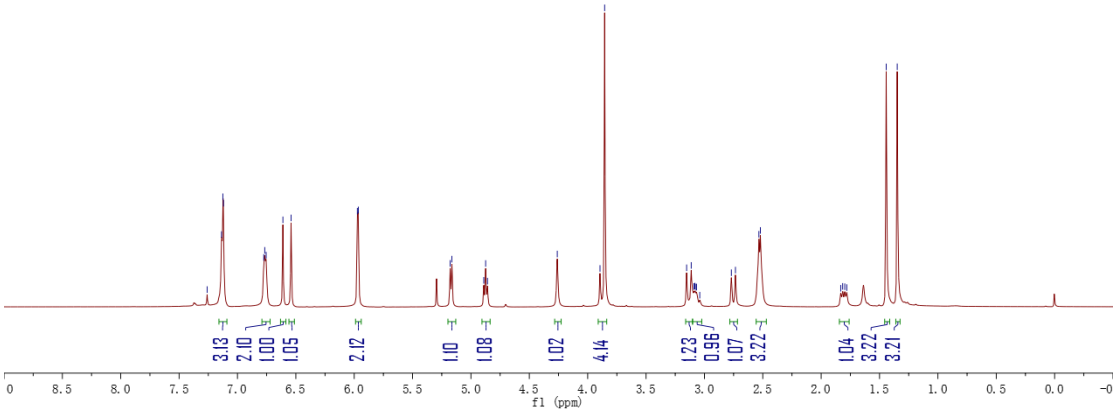
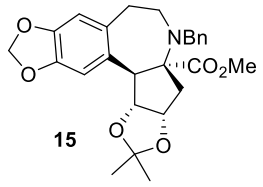




15

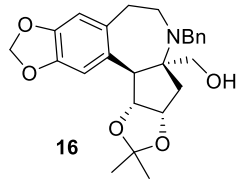
^{1}H NMR, 400 MHz, $CDCl_3$





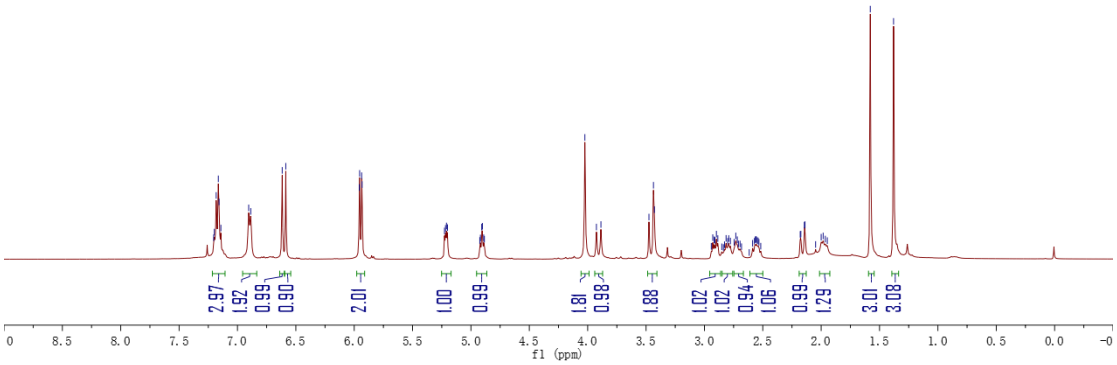
15

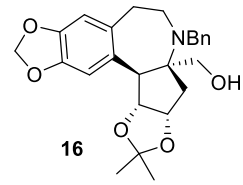
^{13}C NMR, 100 MHz, $CDCl_3$



16

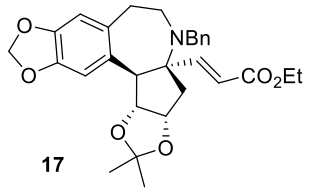
^{1}H NMR, 400 MHz, $CDCl_3$





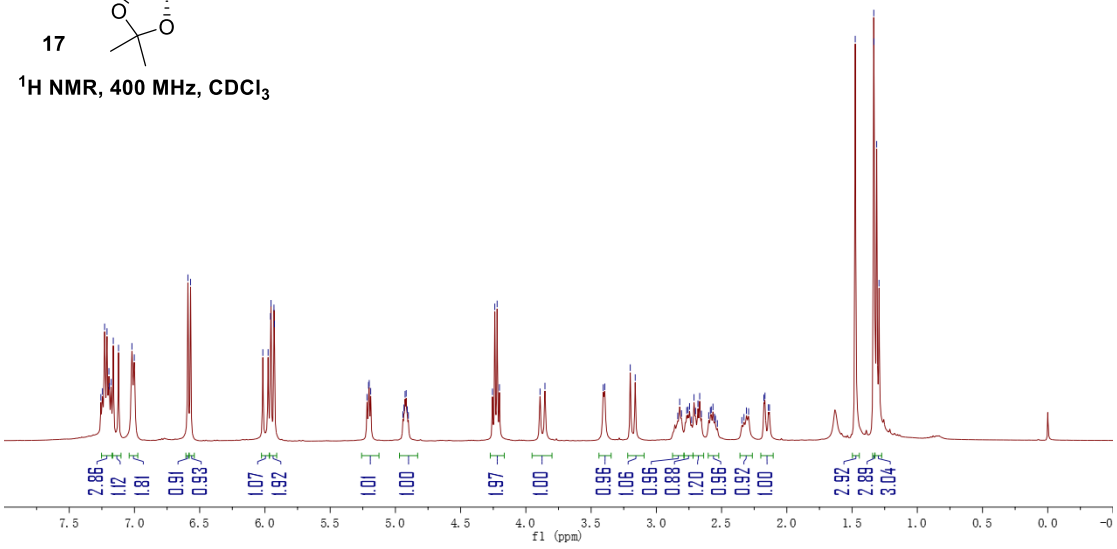
16

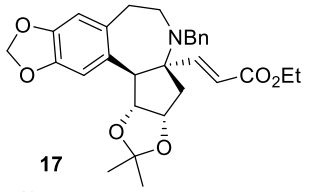
^{13}C NMR, 100 MHz, $CDCl_3$



17

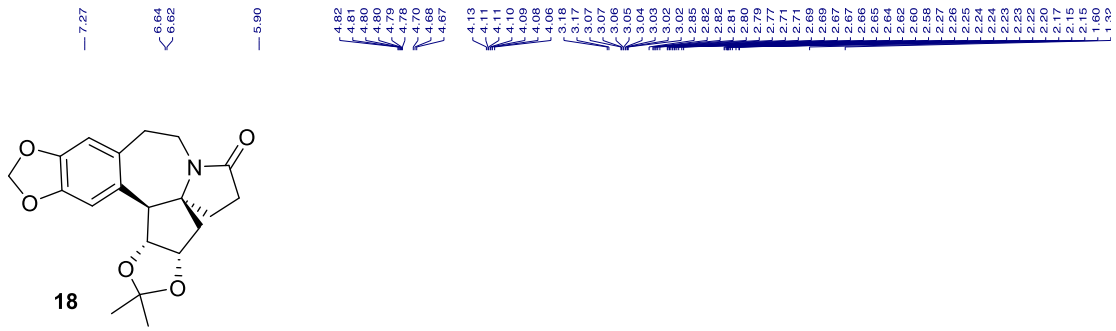
^{1}H NMR, 400 MHz, $CDCl_3$





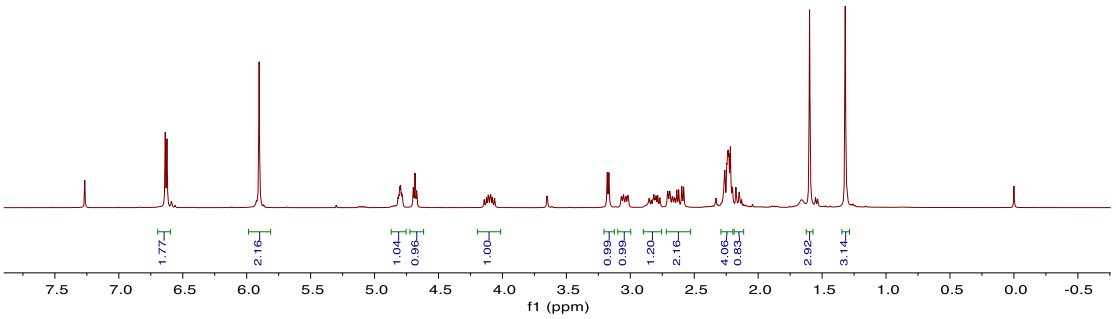
17

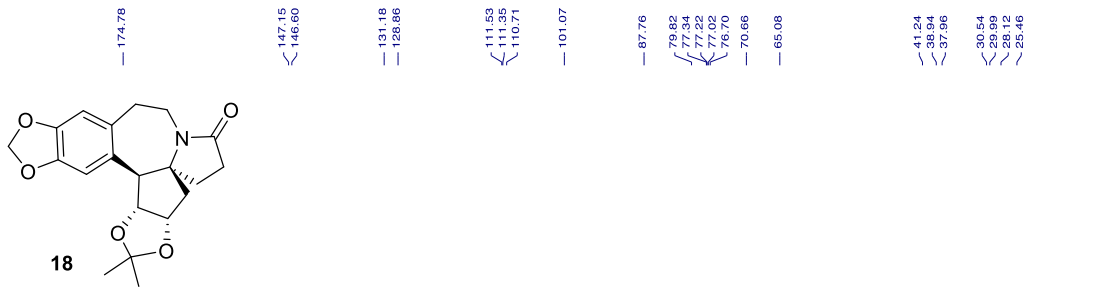
^{13}C NMR, 100 MHz, $CDCl_3$



18

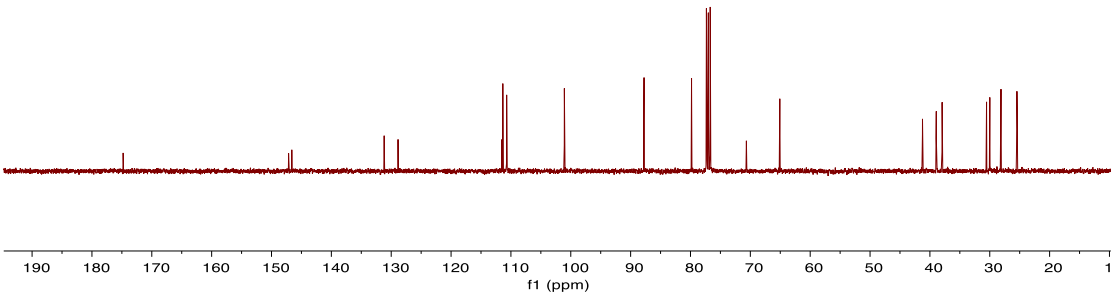
^{1}H NMR, 400 MHz, $CDCl_3$

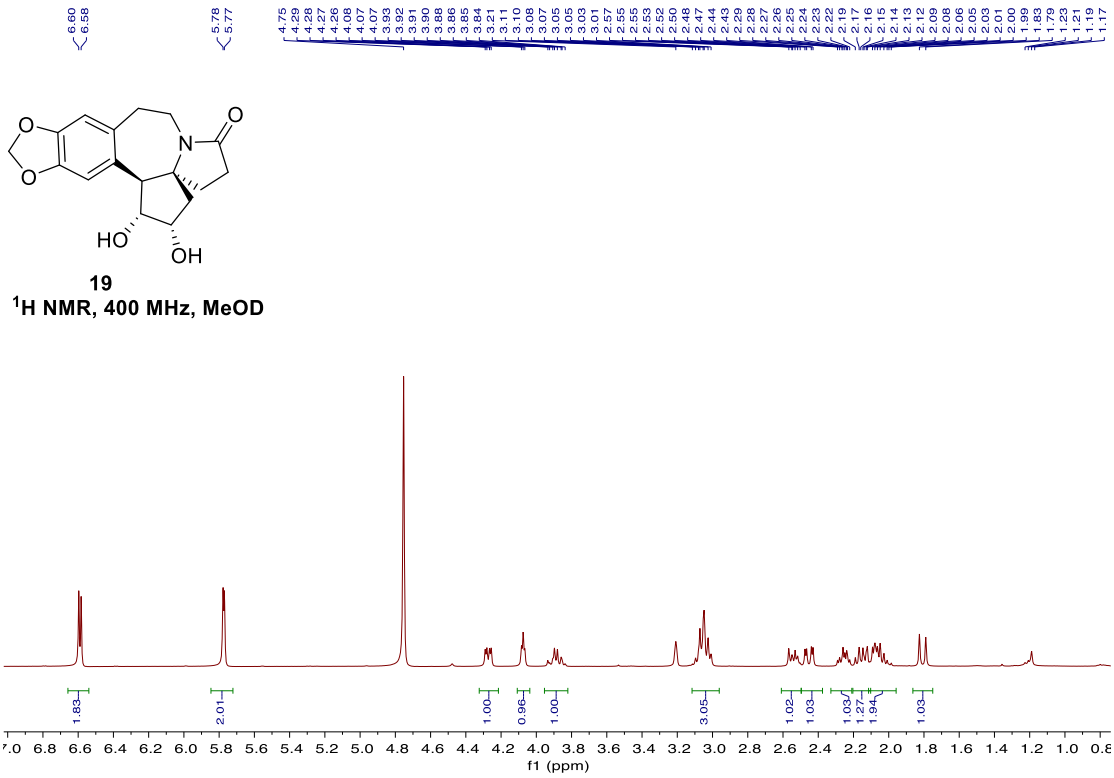




18

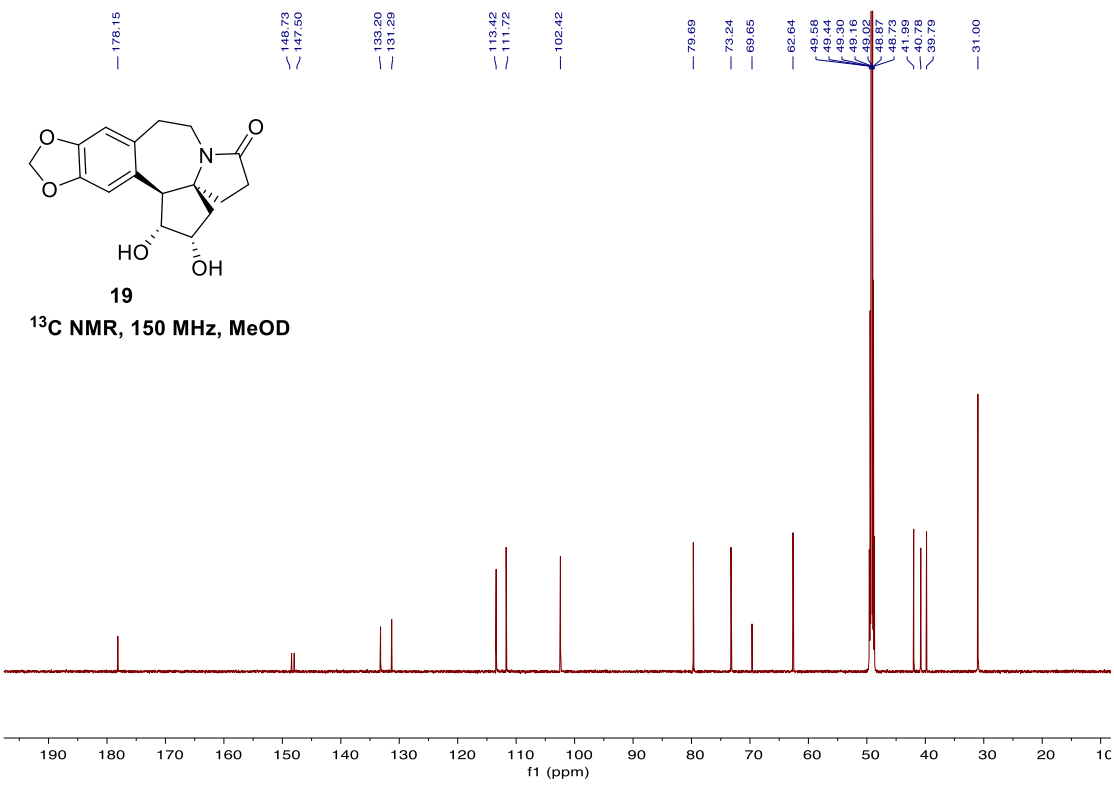
^{13}C NMR, 100 MHz, $CDCl_3$





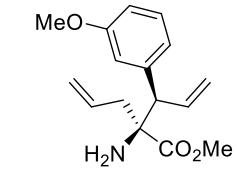
19

^{1}H NMR, 400 MHz, MeOD



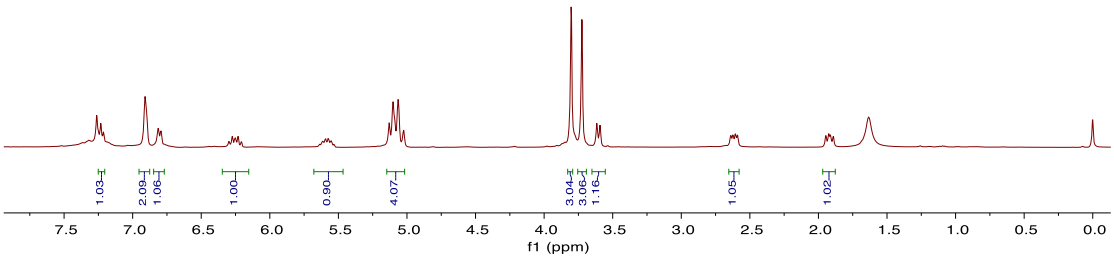
19

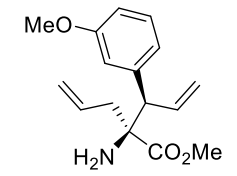
^{13}C NMR, 150 MHz, MeOD



21

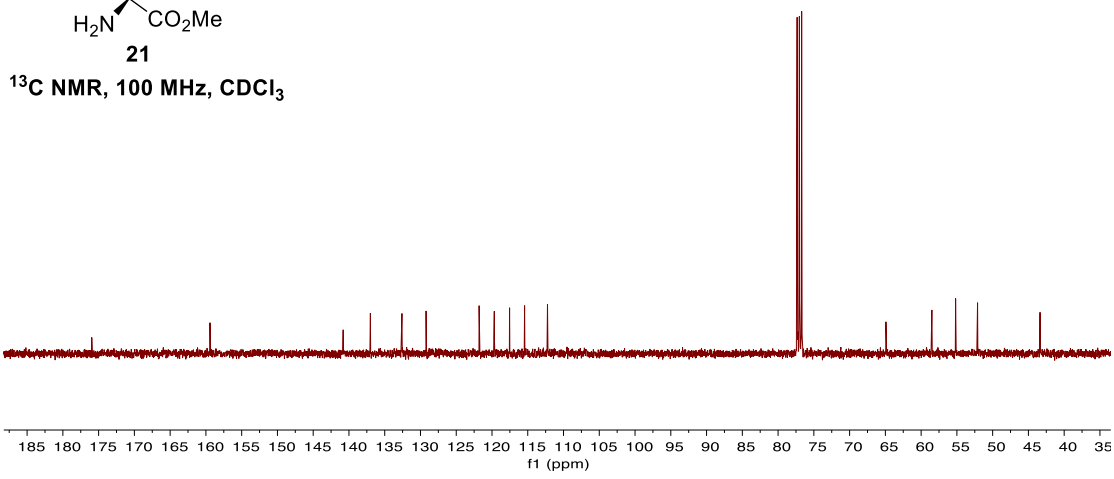
^{1}H NMR, 400 MHz, $CDCl_3$

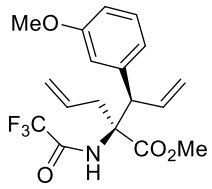




21

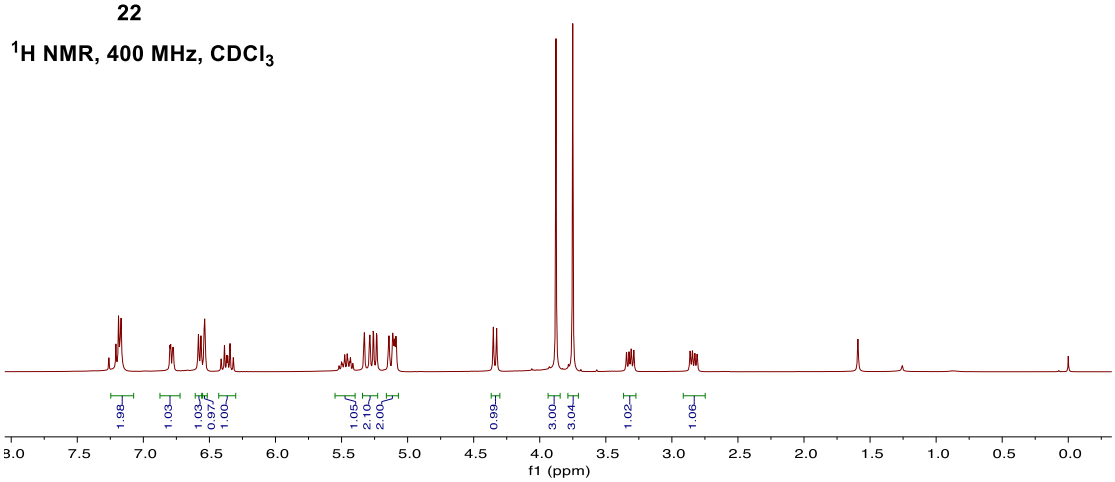
^{13}C NMR, 100 MHz, $CDCl_3$

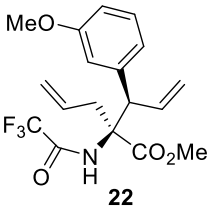




22

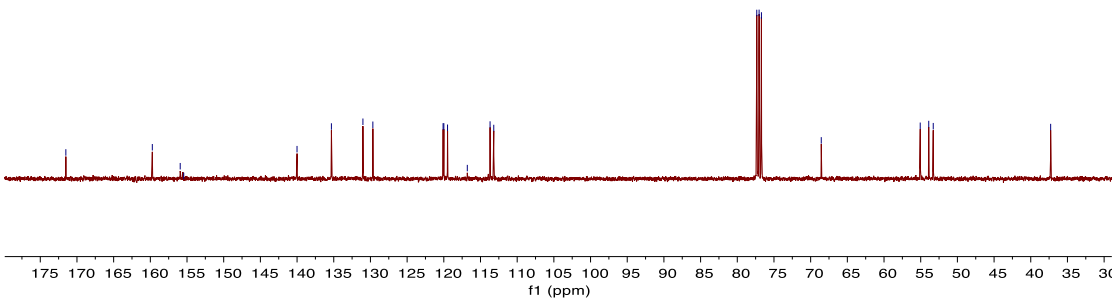
^{1}H NMR, 400 MHz, $CDCl_3$

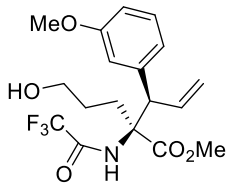




22

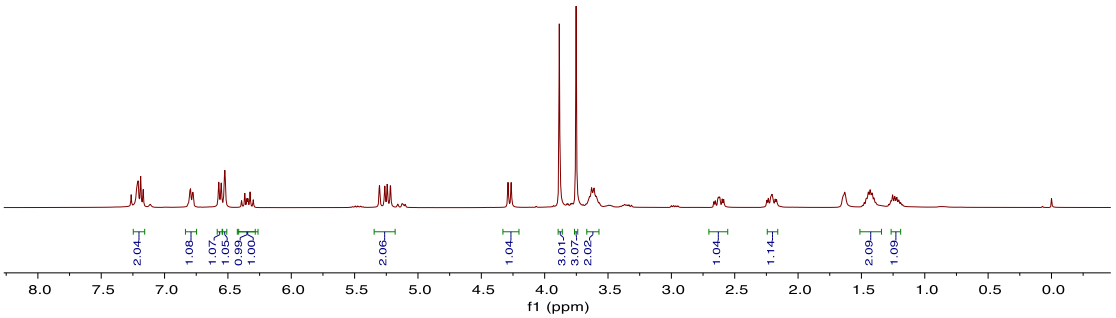
^{13}C NMR, 100 MHz, $CDCl_3$

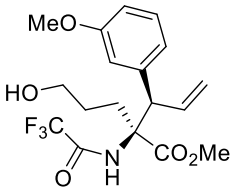




23

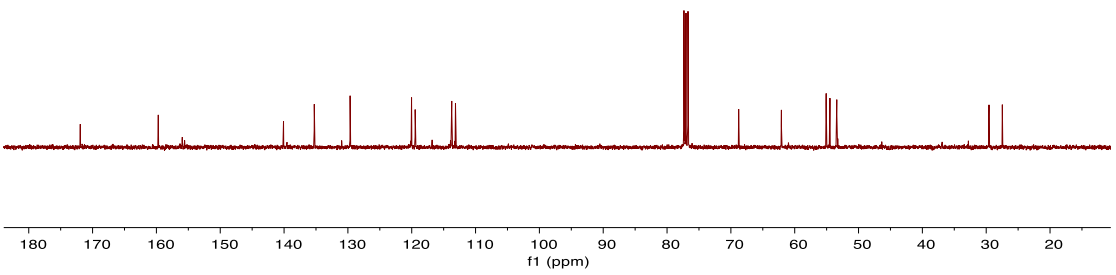
^{1}H NMR, 400 MHz, $CDCl_3$

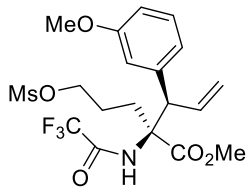




23

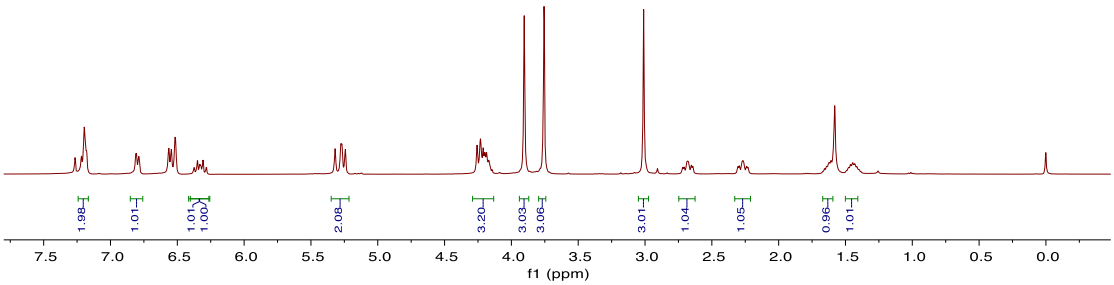
^{13}C NMR, 100 MHz, $CDCl_3$

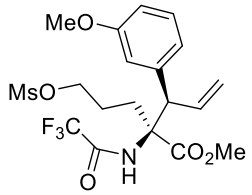




24

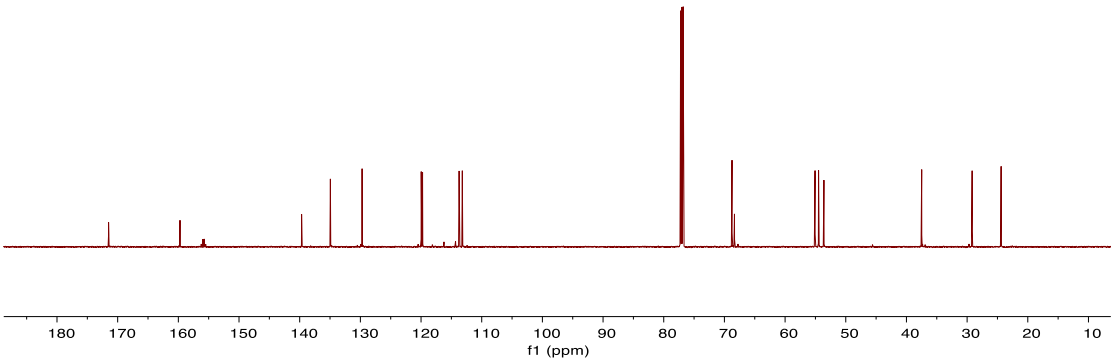
^{1}H NMR, 400 MHz, $CDCl_3$

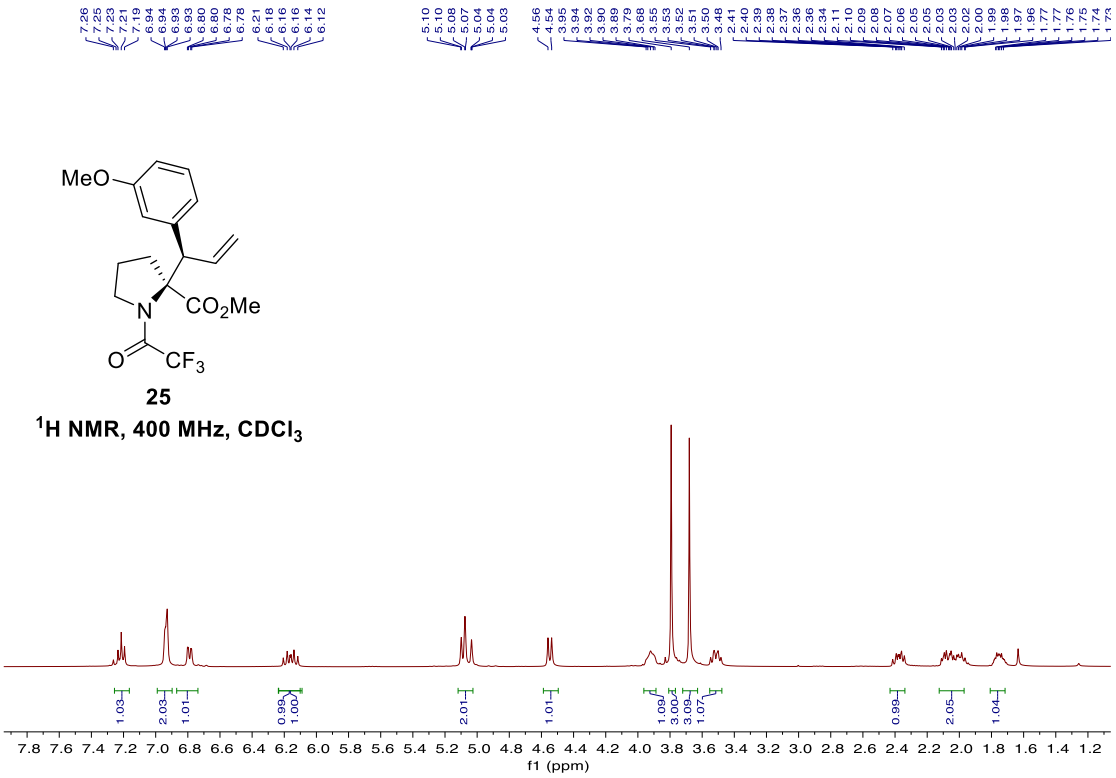


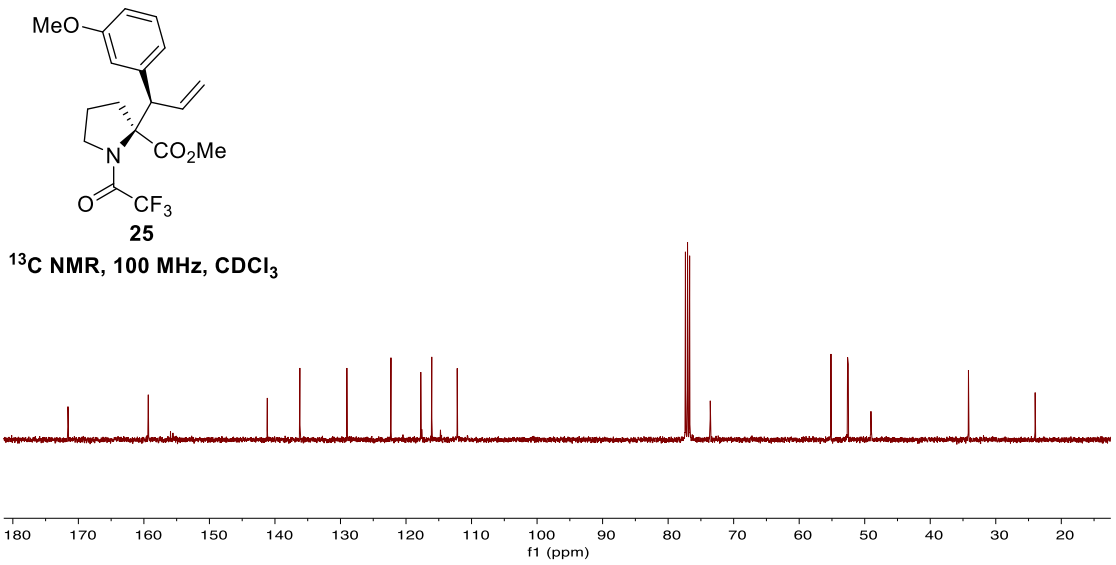


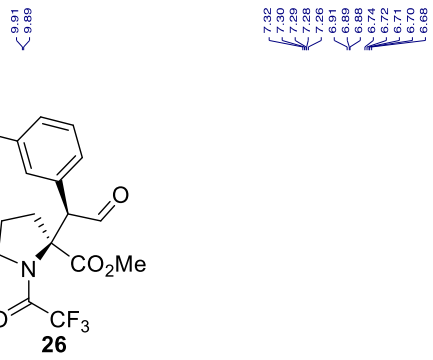
24

^{13}C NMR, 100 MHz, $CDCl_3$



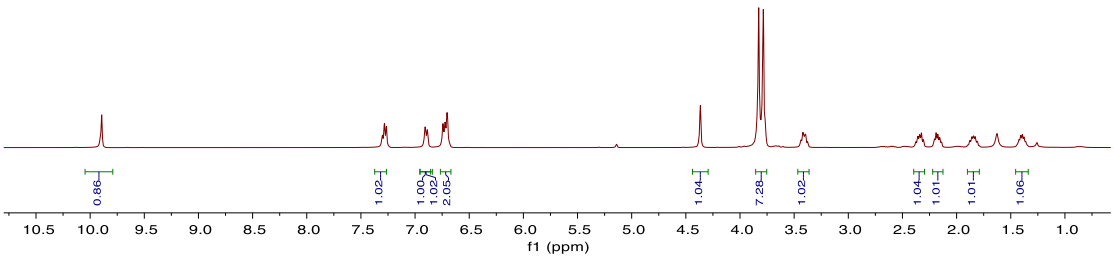

MeO
N
CO2Me
O
CF3
25
1H NMR, 400 MHz, CDCl3
f1 (ppm)

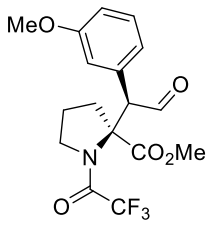

MeO
N
CO2Me
O
CF3
25
13C NMR, 100 MHz, CDCl3
f1 (ppm)



26

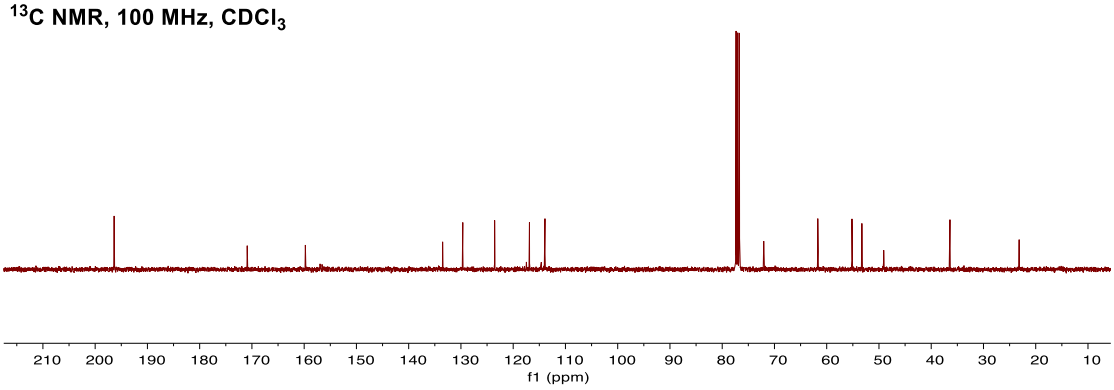
^{1}H NMR, 400 MHz, $CDCl_3$

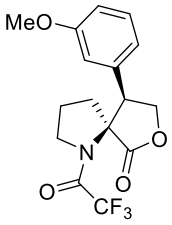




26

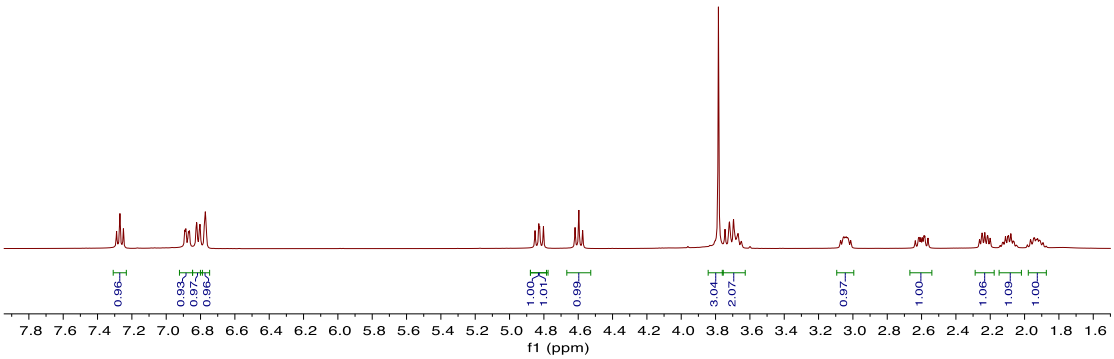
^{13}C NMR, 100 MHz, $CDCl_3$

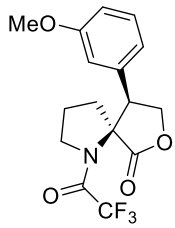




27

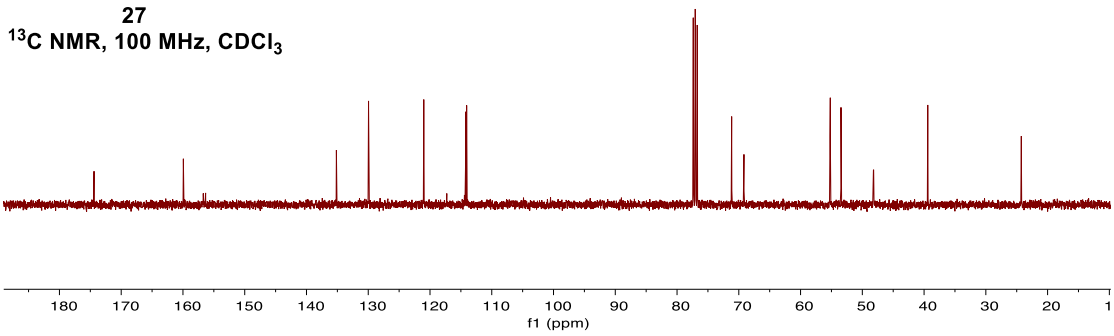
^{1}H NMR, 400 MHz, $CDCl_3$

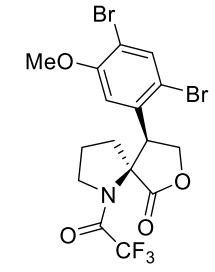




27

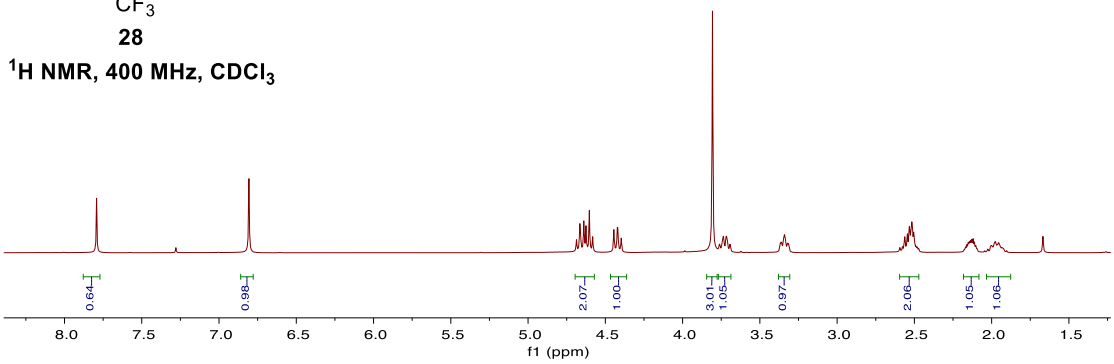
^{13}C NMR, 100 MHz, $CDCl_3$

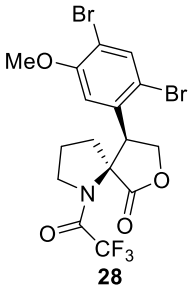




28

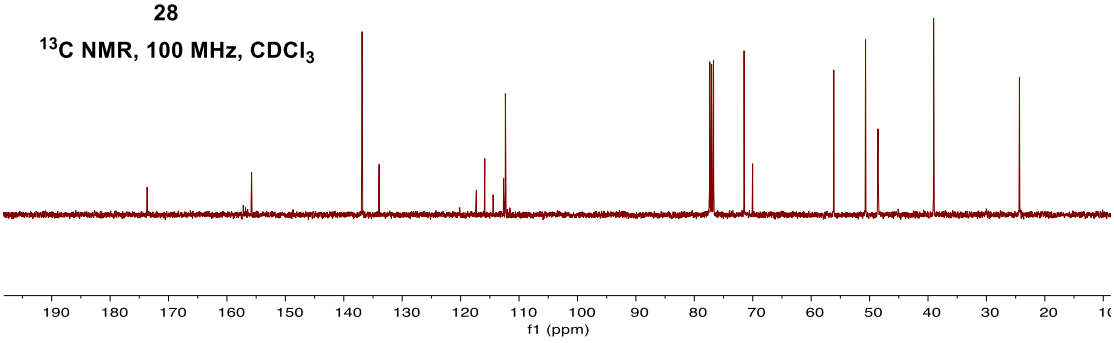
^{1}H NMR, 400 MHz, $CDCl_3$

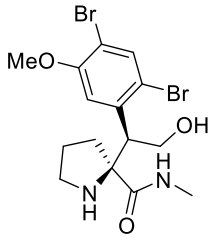




28

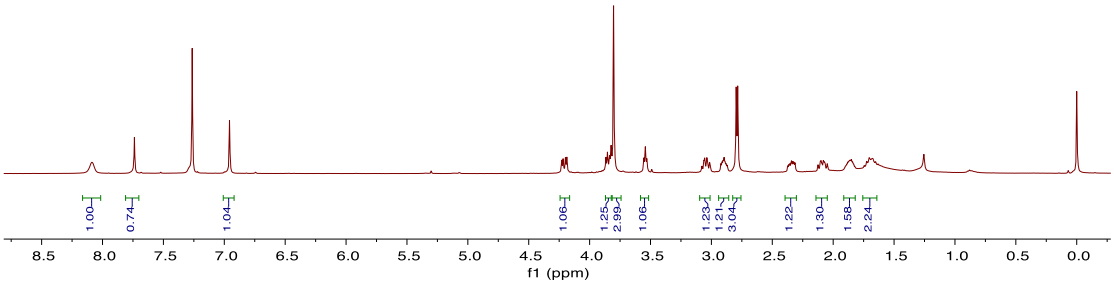
^{13}C NMR, 100 MHz, $CDCl_3$

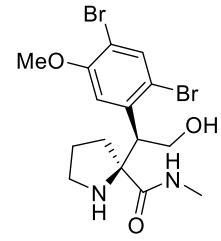




29

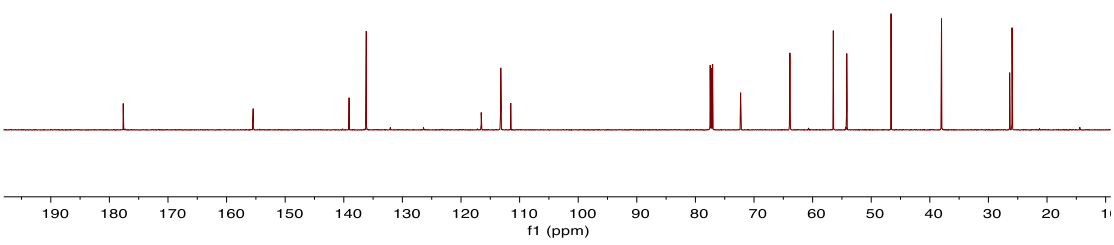
^{1}H NMR, 400 MHz, $CDCl_3$

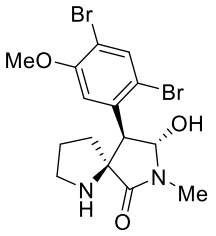




29

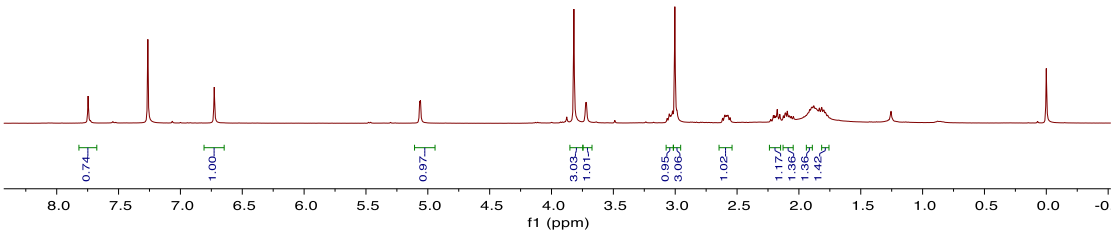
^{13}C NMR, 150 MHz, $CDCl_3$

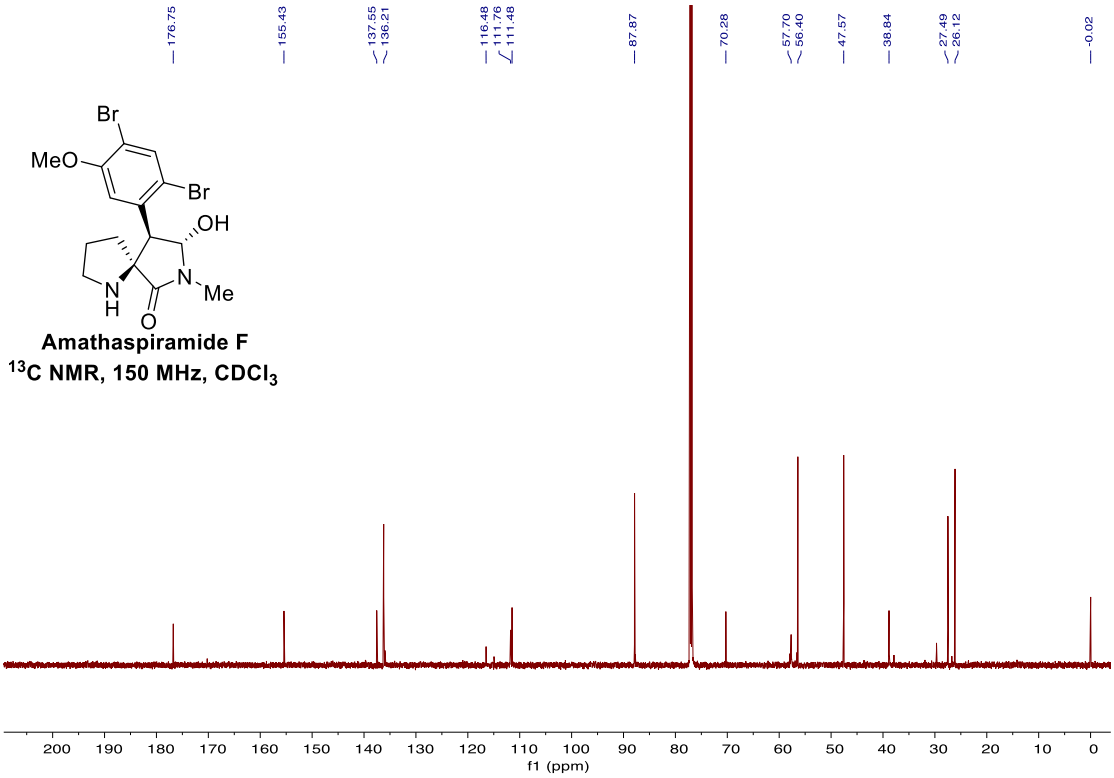




Amathaspiramide F

^{1}H NMR, 400 MHz, $CDCl_3$



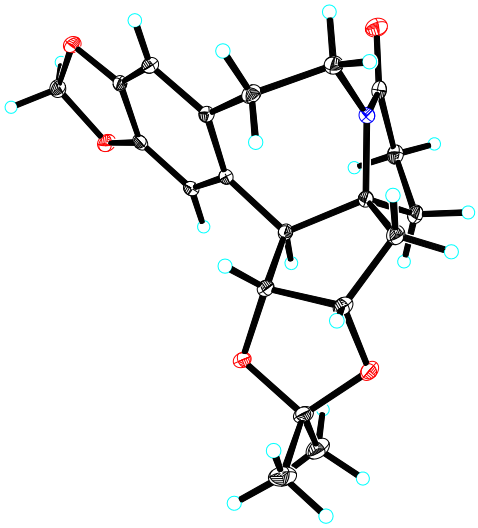


Amathaspiramide F

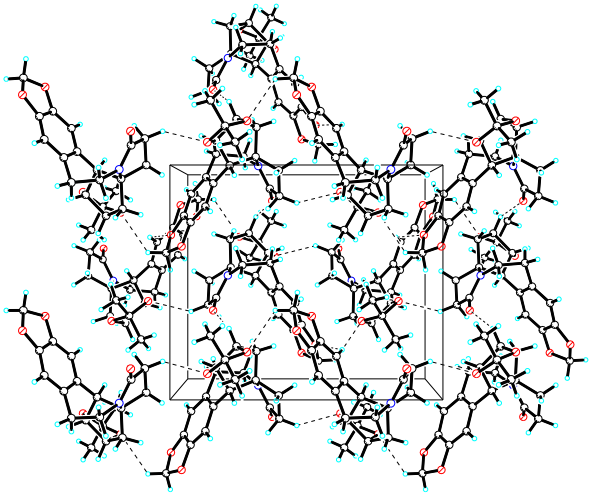
^{13}C NMR, 150 MHz, $CDCl_3$

4. X-Ray Structure and Analysis Data

Crystal data for **18**: $C_{20}H_{23}NO_5$, M = 357.39, a = 11.0160(2) Å, b = 11.7054(3) Å, c = 13.6481(3) Å, α = 90°, β = 90°, γ = 90°, V = 1759.88(7) Å^3, T = 100.(2) K, space group $P212121$, Z = 4, μ(Cu Kα) = 0.797 mm^{-1}, 11329 reflections measured, 3426 independent reflections (R_{int} = 0.0360). The final R_1 values were 0.0337 ($I > 2\sigma(I)$). The final $wR(F^2)$ values were 0.0896 ($I > 2\sigma(I)$). The final R_1 values were 0.0339 (all data). The final $wR(F^2)$ values were 0.0898 (all data). The goodness of fit on F^2 was 1.081. Flack parameter = 0.09(5).



View of a molecule of **18** with the atom-labelling scheme.
Displacement ellipsoids are drawn at the 30% probability level.

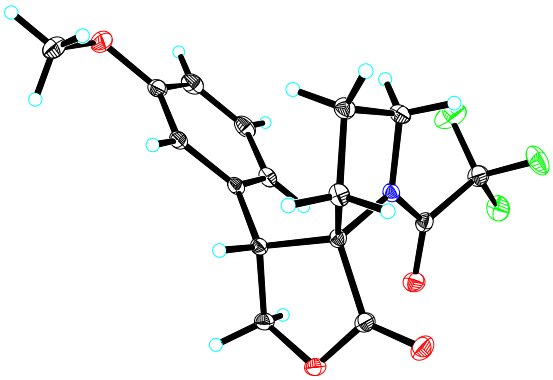


View of the pack drawing of **18**.
Hydrogen-bonds are shown as dashed lines.

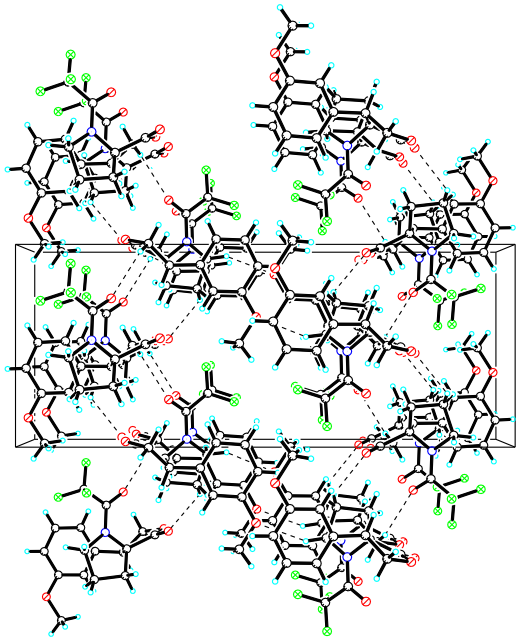
Table 1. Crystal data and structure refinement for **18**.

Identification code	global	
Empirical formula	C20 H23 N O5	
Formula weight	357.39	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 11.0160(2) Å	□= 90°.
	b = 11.7054(3) Å	□= 90°.
	c = 13.6481(3) Å	□ = 90°.
Volume	1759.88(7) $Å^3$	
Z	4	
Density (calculated)	1.349 Mg/m^3	
Absorption coefficient	0.797 mm^{-1}	
F(000)	760	
Crystal size	0.550 x 0.440 x 0.330 mm^3	
Theta range for data collection	5.16 to 72.19°.	
Index ranges	-13<=h<=11, -14<=k<=11, -14<=l<=16	
Reflections collected	11329	
Independent reflections	3426 [R(int) = 0.0360]	
Completeness to theta = 72.19°	99.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.78 and 0.65	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3426 / 0 / 237	
Goodness-of-fit on F^2	1.081	
Final R indices [I>2sigma(I)]	R1 = 0.0337, wR2 = 0.0896	
R indices (all data)	R1 = 0.0339, wR2 = 0.0898	
Absolute structure parameter	0.09(5)	
Largest diff. Peak and hole	0.677 and -0.183 e.$Å^{-3}$	

Crystal data for **27**: $C_{16}H_{16}F_3NO_4$, M = 343.30, a = 7.1715(3) Å, b = 9.3959(4) Å, c = 23.0426(9) Å, α = 90°, β = 90°, γ = 90°, V = 1552.67(11) $Å^3$, T = 100.(2) K, space group $P212121$, Z = 4, μ(Cu Kα) = 1.116 mm^{-1}, 15643 reflections measured, 3052 independent reflections (R_{int} = 0.0541). The final R_1 values were 0.0315 ($I > 2\sigma(I)$). The final $wR(F^2)$ values were 0.0799 ($I > 2\sigma(I)$). The final R_1 values were 0.0318 (all data). The final $wR(F^2)$ values were 0.0802 (all data). The goodness of fit on F^2 was 1.062. Flack parameter = 0.02(5).



View of a molecule of **27** with the atom-labelling scheme.
Displacement ellipsoids are drawn at the 30% probability level.



View of the pack drawing of **27**.
Hydrogen-bonds are shown as dashed lines.

Table 1. Crystal data and structure refinement for **27**

Identification code	global
Empirical formula	C16 H16 F3 N O4
Formula weight	343.30
Temperature	100(2) K
Wavelength	1.54178 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$

Unit cell dimensions	a = 7.1715(3) Å	□= 90°.
	b = 9.3959(4) Å	□= 90°.
	c = 23.0426(9) Å	□ = 90°.
Volume	1552.67(11) $Å^3$	
Z	4	
Density (calculated)	1.469 Mg/m^3	
Absorption coefficient	1.116 mm^{-1}	
F(000)	712	
Crystal size	0.750 x 0.600 x 0.320 mm^3	
Theta range for data collection	5.08 to 72.43°.	
Index ranges	-8<=h<=7, -11<=k<=11, -28<=l<=28	
Reflections collected	15643	
Independent reflections	3052 [R(int) = 0.0541]	
Completeness to theta = 72.43°	99.2 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.72 and 0.45	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3052 / 0 / 218	
Goodness-of-fit on F^2	1.062	
Final R indices [I>2sigma(I)]	R1 = 0.0315, wR2 = 0.0799	
R indices (all data)	R1 = 0.0318, wR2 = 0.0802	
Absolute structure parameter	0.02(5)	
Largest diff. Peak and hole	0.267 and -0.286 $e.Å^{-3}$	

5. References

[1] Huo, X. H.; Zhang, J. C.; Fu, J. K.; He, R.; Zhang, W. B. Ir/Cu Dual Catalysis: Enantio- and Diastereodivergent Acess to α,α-Disubstituted α-Amino Acids Bearing Vicinal Stereocenters *J. Am. Chem. Soc.* **2018**, *140*, 2080-2084.