Supporting Information

A Unified Total Synthesis of Benzo[*d*][1,3]dioxole-type Benzylisoquinoline Alkaloids of Aporphines, Coptisines, and Dibenzopyrrocolines

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General Information

Unless stated otherwise, all reagents and solvents were obtained from commercial suppliers and used without purification. Anhydrous acetonitrile (CH_3CN) was purchased from *J&K Scientific*. Anhydrous tetrahydrofuran (THF), *N*,*N*-dimethylformamide (DMF), and toluene were distilled from sodium and benzophenone. Dichloromethane was distilled from calcium hydride. Analytical thin layer chromatography (TLC) was performed on pre-coated silica gel 60 GF_{254} plates (Qingdao Haiyang Chemical, Qingdao, China). Flash column chromatography was performed using Tsingdao silica gel (60, particle size 0.040-0.063 mm, Qingdao Haiyang Chemical, Qingdao, China). Visualization on TLC was achieved by use of 254 nm UV light. Optical rotations were measured on a JASCO P-2000 polarimeter. Melting points were measured on an XT_{5B} melting instrument and uncorrected. IR spectra were recorded on a Nicolet 5700 FT-IR microscope instrument (FT-IR microscope transmission). NMR spectra were recorded on a Varian Mercury-400 NMR spectrometer or a Bruker AVANCE-III 500 NMR spectrometer or a Varian VNS-600 NMR spectrometer in $CDCl_3$ or DMSO-d_6 with tetramethylsilane (TMS) as internal standard; Data for ^1H NMR were reported as follows: Chemical shift (δ, ppm), multiplicity (s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; br = broad), coupling constant (Hz), and integration. Data for ^{13}C NMR were reported in terms of chemical shift (δ, ppm). The enantiomeric excess values were determined using chiral HPLC with a Shimadzu LC 20A instrument for compounds *rac*-**8** and (*S*)-**8**, *rac*-**18** and (*S*)-**18**, *rac*-**24** and (*S*)-**24**, and **25**, or an Agilent 1260 instrument for

compounds *rac*-**16** and (*S*)-**16** and *rac*-**17** and (*S*)-**17**, or a Shimadzu LC-20AT instrument for compounds **22** and **23**, over Daicel CHIRALPAK column. High resolution mass spectroscopy (HRMS) analyses were performed on a Q-Exactive (Thermo Scientific) Inc mass instrument (HESI).

I. Screening of the (*S*)-Tetrahydropapaverine Substrates (10-14) for Arylation Reaction[1]

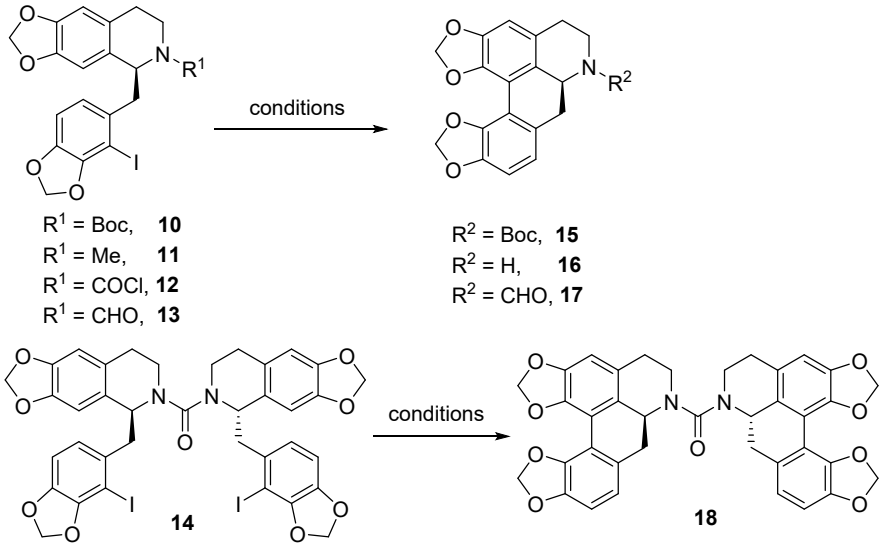


Table S1. Optimization of substrates for constructing the aporphine systems[a]

Entries	Substrates	Ligands	Products	Yields (%)[b]
1	**10**	PhDavePhos	**15**	95
2	**10**	XPhos	**15**	70
3[c]	**10**	PCy_3•HBF_4	**15**	83
4	**11**	PhDavePhos	messy	---
5	**11**	XPhos	messy	---
6[c]	**11**	PCy_3•HBF_4	messy	---
7	**12**	PhDavePhos	messy	---
8	**12**	XPhos	messy	---
9[c]	**12**	PCy_3•HBF_4	messy	---
10	**13**	PhDavePhos	**17**	81
11	**13**	XPhos	**17**	72
12[c]	**13**	PCy_3•HBF_4	**17**	87
13[d]	**14**	PhDavePhos	**18**	79
14[d]	**14**	XPhos	**18**	83
15[c, d]	**14**	PCy_3•HBF_4	**18**	76

[a]Reaction conditions: Substrate (0.1 mmol), $Pd(OAc)_2$ (10 mol%), Ligand (40 mol%), and K_2CO_3 (2.5 eq) in anhydrous DMF (4.0 mL) at 110°C under argon for 12h, unless

noted otherwise; [b]Isolated yields; [c]The reaction employed silver carbonate (0.5 eq) as the additive; [d]Substrate (0.2 mmol), anhydrous DMF (8.0 mL).

General procedure of arylation: using the preparation of compound 15 from compound 10 as an example.

To a suspension of compound **10** (53.7 mg, 0.1 mmol) and K_2CO_3 (34.5 mg, 0.25 mmol) in anhydrous DMF (4.0 mL, 0.025M, degassed by purging with argon in an ultrasonic bath) was sequentially added PhDave-Phos (15.3 mg, 0.04 mmol) and $Pd(OAc)_2$ (2.3 mg, 0.01 mmol) under argon. The mixture was heated to 110°C for 12 h, then gradually cooled to r.t., poured into sat. $NaHCO_3/H_2O$ (v/v, 1/1, 10 mL) and extracted with CH_2Cl_2 (10 mL). The aqueous layer was extracted using CH_2Cl_2 (10 mL×2), and the combined CH_2Cl_2 extract was washed using H_2O (10 mL×3) and brine (10 mL×2), respectively, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified using flash chromatography (mobile phase of *n*-hexane/EtOAc = 3/1) to afford product **15** (39 mg, 95.3% yield) as white solid.

A scale-up using compound **10** (5.0 g, 9.31 mmol) and K_2CO_3 (3.2 g, 23.27 mmol), PhDave-Phos (1.4 g, 3.73 mmol) and $Pd(OAc)_2$ (0.2 g, 0.93 mmol) in anhydrous DMF (186 mL, 0.05M) gave the arylation product **15** (3.7g, 98% yield). Compound **15** can be followed up without fine purification.

II. Optimization of Conditions for Heck Coupling Reaction[2]

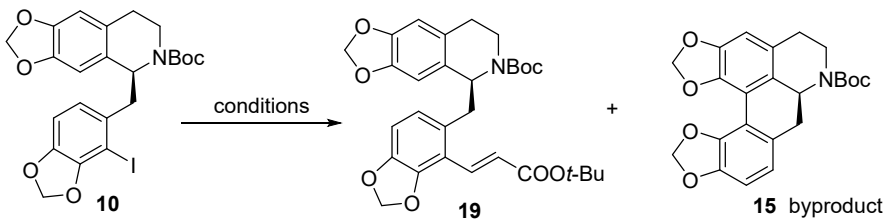


Table S2. Optimization conditions for Heck coupling reaction of compound 10 [a]

Entries	Ligands	Additive	Bases	Solvents (4.0 mL)	Time (h)	**19** (%)[b]	**15** (%)[b]
1[c]	P(*o*-tollyl)$_3$	none	Et_3N	MeCN/Et_3N (2:1)	12	53	0
2[d]	P(*o*-tollyl)$_3$	none	Et_3N	Et_3N	12	68	11
3[d]	P(*o*-tollyl)$_3$	none	Et_3N	Et_3N	18	70	15
4[e]	PPh_3	none	K_2CO_3	DMF/*tert*-butyl acrylate (4:1)	7	60	27
5[e]	P(*o*-tollyl)$_3$	none	K_2CO_3	DMF/*tert*-butyl acrylate (4:1)	7	68	12
6[e]	none	TBAC	$NaHCO_3$	DMF/*tert*-butyl acrylate (4:1)	7	99	trace
7[e]	none	TBAC	K_2CO_3	DMF/*tert*-butyl acrylate (4:1)	7	82	trace

[a]Reaction conditions: Substrate **10** (0.1 mmol), *tert*-butyl acrylate (0.5 mmol), $Pd(OAc)_2$ (10 mol%), Ligand (40 mol%) or additive (2.0 eq), and base (2.5 eq) in solvents (4.0 mL), unless noted otherwise; [b]Isolated yields; [c]The reaction temperature was 70°C; [d]The reaction temperature was 90°C; [e]The reaction temperature was 120°C.

General procedure for Heck coupling reaction of compound 10

Method A for Entries 1-5. Compound **10** (53.7 mg, 0.1 mmol), P(*o*-tollyl)$_3$ (12.2 mg, 0.04 mmol) or PPh_3 (10.5 mg, 0.04 mmol), and $Pd(OAc)_2$ (2.3 mg, 0.01 mmol) were successively added to MeCN/Et_3N (v/v, 2:1, 4.0 mL) or Et_3N (4.0 mL), or anhydrous

DMF/*tert*-butyl acrylate (v/v, 4/1, 4.0 mL, 0.025M). All solvents utilized were degassed by purging with argon in an ultrasonic bath. *Tert*-butyl acrylate (0.5 mmol, 72.6 uL), was then added (Entries 1-3), heated to 70°C (Entry 1) or 90°C (Entries 2-3) or 120°C (Entries 4-5) for the stated hours. After that, the reaction mixture was cooled to r.t., poured into sat. $NaHCO_3$ solution (10 mL), and extracted using CH_2Cl_2 (10 mL×3). The combined organic layer was washed using H_2O (10 mL×2) and brine (10 mL×2), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Compound **15** and **19** was isolated by silica gel chromatography (mobile phase of *n*-hexane/EtOAc 7/1) in the stated yields.

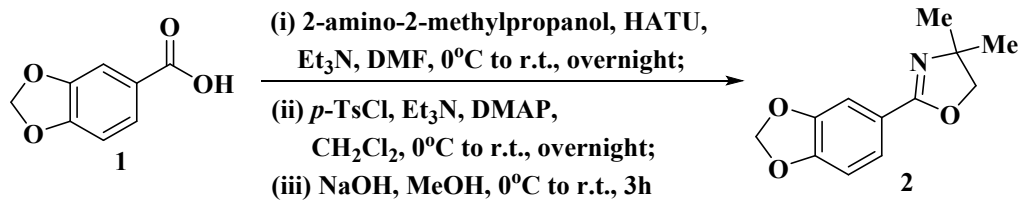
Note: we did not determine the compound **10** not transformed for Entries 1-3, since it was difficult to separate compound **10** and **19** using silica gel chromatography.

Method B for Entries 6-7. Compound **10** (53.7 mg, 0.1 mmol), anhydrous $NaHCO_3$ (21.0 mg, 0.25 mmol) or anhydrous K_2CO_3 (34.5 mg, 0.25 mmol), *n*-$Bu_4N^+Cl^-$ (TBAC, 55.6 mg, 0.2 mmol), and $Pd(OAc)_2$ (2.3 mg, 0.01 mmol) were successively added to DMF (anhydrous)/*tert*-butyl acrylate (v/v, 4/1, 4.0 mL, 0.025M, degassed by purging with argon in an ultrasonic bath), then heated to 120°C for 7 h. After that, the reaction mixture was cooled to r.t., poured into sat. $NaHCO_3$ solution (10 mL), and extracted using CH_2Cl_2 (10 mL×3). The combined organic layer was washed using H_2O (10 mL×2) and brine (10 mL×3), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (mobile phase of *n*-hexane/EtOAc 5/1).

A scale-up using compound **10** (2.5 g, 4.65 mmol), $NaHCO_3$ (0.98 g, 11.63 mmol), *n*-$Bu_4N^+Cl^-$ (TBAC, 2.6 g, 9.3 mmol), and $Pd(OAc)_2$ (0.1 g, 0.46 mmol) in anhydrous DMF/*tert*-butyl acrylate (v/v, 4/1, 50 mL, 0.1M) was conducted. The crude product was purified by silica gel chromatography (mobile phase of *n*-hexane/EtOAc 5/1 to 3/1) to give compound **19** (2.43 g, 4.52 mmol) in 97% yield.

III. Experimental procedures

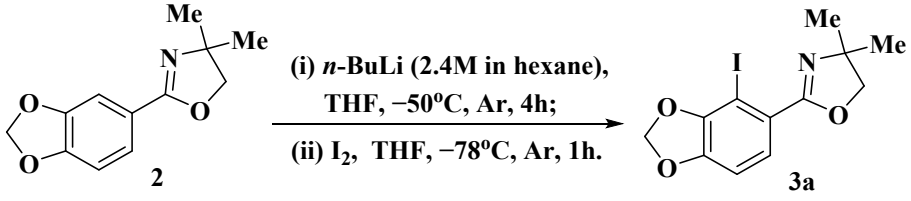
2-(benzo[d][1,3]dioxol-5-yl)-4,4-dimethyl-4,5-dihydrooxazole (2).



(*i*) To a stirred solution of piperonylic acid **1** (98.0 g, 590.2 mmol) in DMF (1300 mL) was dropped 2-amino-2-methyl-1-propanol (563 mL) at 0°C, followed by the addition of triethylamine (410 mL) at the same temperature. After stirring at 0°C for 15 min, HATU (269.2 g, 707.9 mmol) was added in such a way that the reaction temperature was kept below 5°C. After the addition, the reaction mixture was stirred at 0°C for 1 h before being allowed to warm to r.t., and then stirred overnight. The reaction mixture was divided into two approximately equivalent portions for workup for convenience. The workup procedure for both portion was the same and as follows. H_2O was added to the solution and the mixture was extracted using CH_2Cl_2 (400 mL×3). The organic layer was washed using H_2O (600 mL×2), 2N HCl (600 mL×2), H_2O (600 mL×2), sat. $NaHCO_3$ (600 mL×2), and brine (600 mL), respectively, dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to afford 122.8 g of white solid which was used in the next step without further purification. (*ii*) To a stirred solution of this crude intermediate in CH_2Cl_2 (1200 mL) was sequentially added *p*-TsCl (246.1 g, 1290.8 mmol), triethylamine (360 mL, 2582.9 mmol), and DMAP (6.3 g, 51.6 mmol) at 0°C. The reaction mixture was stirred at 0°C for 1 h

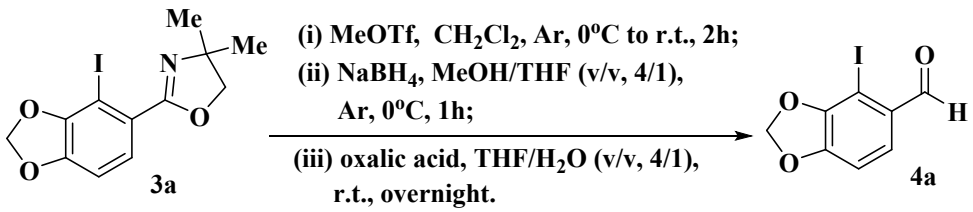
before being allowed to warm to r.t. and stirred overnight. The reaction mixture was washed using H_2O (600 mL), sat. $NaHCO_3$ (600 mL×2), and brine (600 mL), respectively, dried over anhydrous Na_2SO_4, and filtered and evaporated under reduced pressure. The obtained crude material of brown oil was used in the next step without further purification. (*iii*) To a stirred solution of this crude oil in MeOH (1200 mL) was added, portionwise, NaOH solid particles (70.8 g, 1770.6 mmol) at 0°C over 20 min. The reaction mixture was allowed to warm to r.t. and stirred for 3 h. H_2O (200 mL) was added to the solution and the mixture was evaporated to remove approximately 800 mL of solvent. H_2O (800 mL) was added to the residue, which was extracted using CH_2Cl_2 (500 mL×3). The organic layer was collected and then washed using brine (600 mL×2), dried over anhydrous Na_2SO_4, and filtered and evaporated under reduced pressure. The residue was purified using flash chromatography (mobile phase of *n*-hexane/EtOAc = 100/1 to 15/1) to give compound **2** (87.5 g, 69% over three steps) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (dd, J = 8.1, 1.7 Hz, 1H), 7.36 (d, J = 1.7 Hz, 1H), 6.76 (d, J = 8.1 Hz, 1H), 5.94 (s, 2H), 4.02 (s, 2H), 1.31 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 150.0, 147.5, 123.0, 122.0, 108.3, 107.9, 101.4, 79.0, 67.4, 28.3 (2×C). HRESIMS *m/z*: calcd for $C_{12}H_{14}O_3N$ $[M+H]^+$, 220.0968; found, *m/z* 220.0969.

2-(4-iodobenzo[d][1,3]dioxol-5-yl)-4,4-dimethyl-4,5-dihydrooxazole (3a).



To a −50°C solution of oxazoline **2** (37.0 g, 168.88 mmol) in THF (560 mL) was added, dropwise, a solution of *n*-BuLi (2.4 M in hexane, 115.0 mL, 270.21 mmol) over 30 min under argon so that the internal temperature was maintained between −45°C and −50°C. The reaction mixture was stirred for 4 h and then cooled to −78°C. A solution of iodine (107.0 g, 422.20 mmol) in THF (210 mL) was slowly added in such a way that the internal temperature was kept below −70°C. This solution was stirred at −78°C for 1 h. The reaction was quenched using sat. $Na_2S_2O_3$ (100 mL), allowed to reach ambient temperature, and stirred overnight. The mixture was concentrated *in vacuo* and approximately 700 mL of solvent was removed. Sat. $Na_2S_2O_3$ (500 mL) was poured into the residue, which was extracted using EtOAc (400 mL×3). The organic layer was collected and washed using brine (600 mL×2) and was concentrated to obtain 200 mL of residue, allowing large amount of solid to crystallize at ambient temperature. After filtration and washing using a mixture of *n*-hexane and EtOAc, compound **3a** (48.1 g, 82.7% yield) was collected as white solid. M.p. 78–79°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, J = 8.1 Hz, 1H), 6.75 (d, J = 8.1 Hz, 1H), 6.06 (s, 2H), 4.10 (s, 2H), 1.40 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.9, 150.2, 147.3, 126.5, 125.2, 107.8, 100.8, 79.1, 72.2, 68.0, 28.3 (2×C). HRESIMS *m/z*: calcd for $C_{12}H_{13}INO_3$ $[M+H]^+$, 345.9935; found, *m/z* 345.9934.

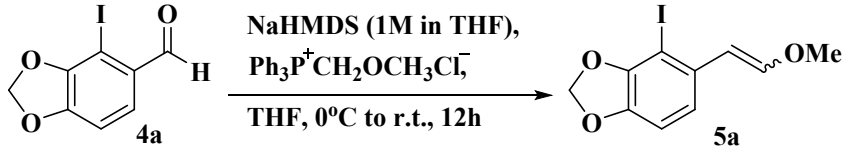
4-iodobenzo[d][1,3]dioxole-5-carbaldehyde (4a).



To a solution of compound **3a** (34.5 g, 100 mmol) in CH_2Cl_2 (350 mL) was added methyl trifluoromethanesulfonate (23.7 mL, 210 mmol) at 0°C under argon. The mixture was stirred at r.t. for 2 h. The mixture was cooled to 0°C and a solution of $NaBH_4$ (9.8 g, 260 mmol) in THF: MeOH (v/v, 1/4, 500 mL) was slowly added with argon pumping. *Note: be careful for the foaming phenomenon during the addition.* After the addition, the mixture was stirred at this condition for 1 h before being quenched using sat. NH_4Cl (50 mL). The resulting mixture was re-warmed to r.t. and stirred for 30 min, after which the mixture was evaporated *in vacuo* to remove approximately 600 mL of solvents. The residue was poured into the sat. NH_4Cl (400 mL) and extracted using CH_2Cl_2 (250 mL×3). The combined organic extract was washed using brine (150 mL×2), treated with Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting material was dissolved in THF: H_2O (4:1, 600 mL), and oxalic acid dihydrate (78.4 g, 622.9 mmol) was added. The reaction mixture was stirred at r.t. overnight and then H_2O (100 mL) was added. The resultant was concentrated to approximate 300 mL of the residue. Sat. NH_4Cl (200 mL) was poured into this residue, which was extracted using EtOAc (250 mL×3). The combined organic extract was washed using H_2O (150 mL×3), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The obtained crude aldehyde was purified using flash chromatography (mobile phase of *n*-hexane/EtOAc = 10/1 to 5/1), affording the aldehyde **4a** (22.9 g, 83% yield, within three steps) as white solid. M.p. 131–133°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.90 (s, 1H), 7.53 (d, J = 8.1 Hz, 1H), 6.85 (d, J = 8.1 Hz, 1H), 6.15 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.8, 151.0, 150.4, 128.9,

127.6, 108.4, 101.6, 76.1. HRESIMS *m/z*: calcd for $C_8H_6O_3I$ $[M+H]^+$, 276.9356; found, *m/z* 276.9357.

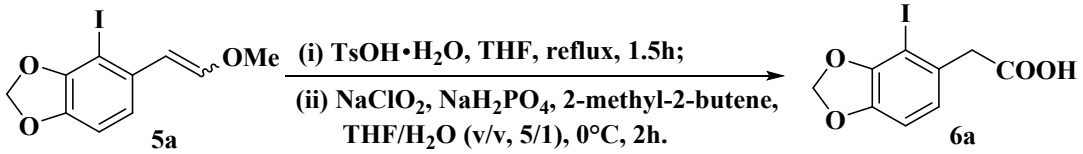
4-iodo-5-(2-methoxyvinyl)benzo[d][1,3]dioxole (5a).



NaHMDS (1M in THF, 164.0 mL, 163.2 mmol) was added to a stirred suspension of (methoxymethyl)triphenylphosphonium chloride (59.1 g, 172.5 mmol) in THF (650 mL) at 0°C under argon over 30 min. The red mixture was stirred in this condition for another 40 min before aldehyde **4a** (25 g, 96 mmol) was added, portionwise, over 30 min at an argon atmosphere at 0°C. The resulting light yellow suspension was allowed to warm to r.t. and stirred overnight. The reaction mixture was quenched using sat. $NaHCO_3$ (50 mL) and concentrated to remove approximately 600 mL of solvents. The residue was diluted using sat. $NaHCO_3$ (400 mL) and extracted using CH_2Cl_2 (250 mL×3). The combined organic layer was washed using brine (150 mL×2), dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified over silica gel chromatography (mobile phase of EtOAc/*n*-hexane 1:50 to 1:35) to give enol ether **5a** as colorless oil (27.5 g, 17:3 mixture of *E:Z* isomers, 96% yield,). ^{1}H NMR (400 MHz, $CDCl_3$, *E:Z* 17:3) δ 7.56 (minor, d, J = 8.0 Hz, 0.15H), 6.82 – 6.78 (m, 1.7H), 6.73 (minor, d, J = 8.0 Hz, 0.15H), 6.69 (major, d, J = 8.0 Hz, 0.85H), 6.18 (minor, d, J = 7.2 Hz, 0.15H), 6.00 (major, s, 1.7H), 5.99 (s, 0.3H), 5.89 (major, d, J = 12.6 Hz, 0.85H), 5.38 (minor, d, J = 7.2 Hz, 0.15H), 3.76 (s, 0.45H), 3.71 (major, s, 2.55H). HRESIMS *m/z*: calcd for $C_{10}H_{10}O_3I$ $[M+H]^+$,

304.9669; found, *m/z* 304.9668.

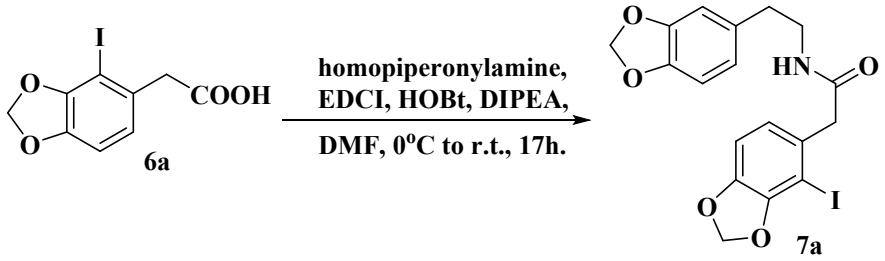
2-(4-iodobenzo[d][1,3]dioxol-5-yl)acetic acid (6a).



A solution of the enol ether **5a** (12.5 g, 50 mmol) in THF (500 mL) was degassed by purging with argon in an ultrasonic bath for 5 min and then cooled to 0°C. To this solution, *p*-toluenesulfonic acid monohydrate (*p*-TsOH·H_2O, 19.1 g, 100 mmol)[20] was added under argon and the reaction mixture was stirred at 0°C for 15 min. This mixture was gradually heated to reflux for 1.5 h and then gradually cooled to r.t., then cooled to 0°C. 2-Methyl-2-butene (53 mL, 500 mmol) and sodium hydrogen phosphate (13.8 g, 115 mmol) was sequentially added at 0°C under argon. The stirring was continued for 15 min before a solution of sodium chlorite (15.8 g, 175 mmol) in H_2O (100 mL) was added slowly in such a way that the internal temperature was kept below 5°C. The reaction mixture was stirred for 2 h,[21] quenched using sat. NH_4Cl (50 mL), and concentrated to remove excess THF (approximately 350 mL). The residue was poured into sat. NH_4Cl/H_2O (v/v, 1/1, 350 mL) and extracted using EtOAc (250 mL×3). The combined extract was washed using brine (300 mL), dried over anhydrous Na_2SO_4, and concentrated. The residue upon work up was chromatographed on silica gel using *n*-hexane/EtOAc (6:1 to 1/1) as eluent to afford carboxylic acid **6a** (9.4 g, 75% yield, within two steps) as a white pale yellow solid. M.p. 192–193°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 (d, J = 8.0 Hz, 1H), 6.73 (d, J = 8.0 Hz, 1H), 6.03 (s, 2H), 3.77 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$)

δ 177.1, 150.1, 145.5, 129.9, 123.8, 108.2, 101.0, 77.9, 44.2. HRESIMS $[M+Na]^+$: Calcd for $C_9H_7O_4INa$: 328.9281, found: *m/z* 328.9283.

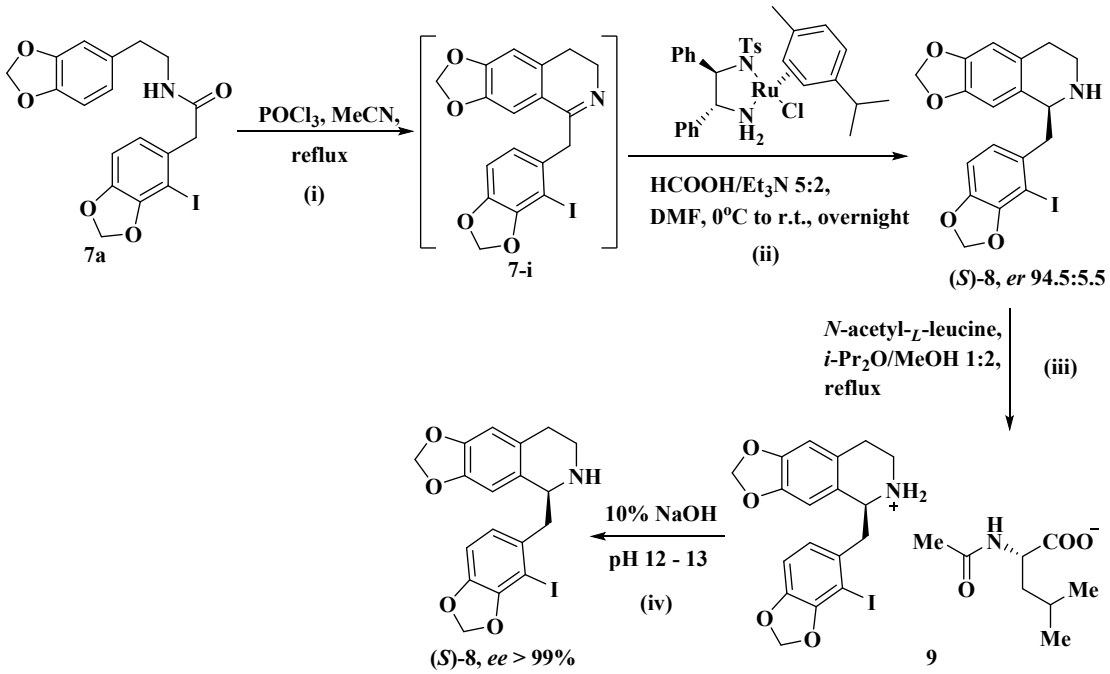
N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-2-(4-iodobenzo[d][1,3]-dioxol-5-yl)acetamide (7a).



An 1L three-necked flask was ovenly dried and successively charged with anhydrous DMF (500 mL), acid **6a** (15.0 g, 49.03 mmol), homopiperonylamine (10.0 mL, 73.5 mmol), EDCI (14.1 g, 73.5 mmol), and HOBt (7.29 g, 53.39 mmol). The suspension was stirred at 0°C under argon, and continued to stir at this condition for 1 h after DIPEA (17 mL, 98.06 mmol) was added. The mixture was allowed to warm to r.t. and stirred for 17 h. The reaction mixture was poured into H_2O (700 mL) and extracted using CH_2Cl_2 (450 mL×3). The combined organic layer was sequentially washed using H_2O (400 mL), 2N HCl (400 mL), H_2O (400 mL), sat. $NaHCO_3$ (400 mL), and brine (400 mL), respectively. The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The white crude was stirred in a slurry of EtOH (150 mL) for 3 h, the mixture was filtered and washed using EtOH (15 mL×2). The collected white solid was dried under air and weighed 20.6 g (**7a**, 93.5% yield). M.p. 103–105°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75 (d, J = 8.0 Hz, 1H), 6.70 (d, J = 8.0 Hz, 1H), 6.66 (d, J = 8.0 Hz, 1H), 6.54 (brs, 1H), 6.49 (br d, J = 8.0 Hz, 1H), 6.06 (s, 2H),

5.92 (s, 2H), 5.31 (br, 1H), 3.59 (s, 2H), 3.42 (td, J = 6.4, 6.4 Hz, 2H), 2.66 (t, J = 6.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8 (s), 150.3 (s), 147.9 (s), 146.3 (s), 145.5 (s), 132.4 (s), 131.0 (s), 123.9 (d), 121.8 (d), 109.1 (d), 108.4 (d), 108.3 (d), 101.1 (t), 101.0 (t), 77.9 (s), 46.9 (t), 40.8 (t), 35.1 (t). HRESIMS $[M+H]^+$: Calcd for $C_{18}H_{17}O_5NI$: 454.0146, found: *m/z* 454.0147.

(*S*)-5-((4-iodobenzo[*d*][1,3]dioxol-5-yl)methyl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-*g*]isoquinoline ((*S*)-8, *ee* > 99%)[3]



(i) To a suspension of amide **7a** (15.0 g, 33.11 mmol) in anhydrous CH_3CN (700 mL) was added $POCl_3$ (25 mL, 264.88 mmol) at r.t. over 15 min with argon continuously purging throughout the reaction. The reaction mixture was gradually heated to reflux and a clear brown solution was obtained. After 1.5 h of refluxing, the solution was allowed to cool to 40°C – 50°C and concentrated to remove excess CH_3CN and

$POCl_3$. The residue was separated between CH_2Cl_2 (150 mL) and H_2O (300 mL). The pH value of the aqueous layer was adjusted to 7 – 8 using sat. $NaHCO_3$. The aqueous layer was further extracted using CH_2Cl_2 (150 mL×3). The combined organic solution was washed using brine (200 mL×2), dried over anhydrous Na_2SO_4, and concentrated to obtain **7-i** (13.4 g, 93% yield) as light yellow solid which was used for next procedure without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (s, 1H), 6.68 (d, J = 8.0 Hz, 1H), 7.67 (s, 1H), 6.65 (d, J = 8.0 Hz, 1H), 6.02 (s, 2H), 5.96 (s, 2H), 4.03 (s, 2H), 3.67 (t, J = 7.2 Hz, 2H), 2.65 (t, J = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 149.9, 149.1, 146.5, 144.8, 133.8, 133.5, 123.1, 122.5, 108.2, 108.1, 106.1, 101.4, 100.7, 78.3, 47.3, 45.8, 26.5.

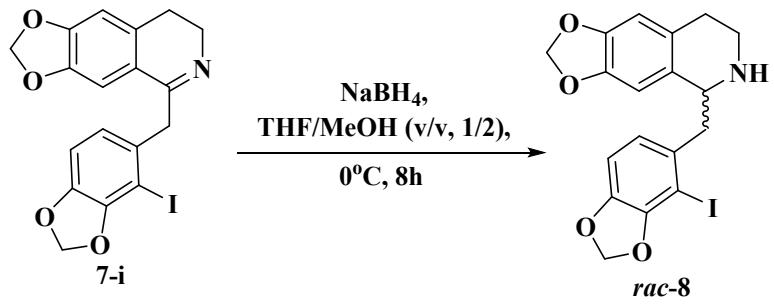
(ii) The prepared 3,4-dihydroisoquinoline intermediate **7-i** (kept under argon) was dissolved in anhydrous DMF (660 mL, 0.05 M), which was degassed by purging with argon in an ultrasonic bath for 5 min. RuCl[(*R*,*R*)-TsDPEN(*p*-cymene)] (1.05 g, 1.66 mmol, 5 mol%) was added at 0°C followed by the addition of formic acid/trimethylamine azeotrope (5:2, 22.0 mL) over a period of 40 min while argon was bubbled through the mixture. The reaction mixture was allowed to warm to r.t. (argon was still purging for the first 2 h at r.t.) and stirred overnight under argon before being partitioned between sat. K_2CO_3/brine (v/v, 1/1, 600 mL) and CH_2Cl_2 (600 mL). The aqueous layer was extracted using CH_2Cl_2 (400 mL×2). The combined organic layer was washed using H_2O (400 mL×3) and brine (400 mL×3), respectively, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified over silica gel chromatography (mobile phase of *n*-hexane/EtOAc/CH_2Cl_2/Et_3N = 4/1/1/0.06) to

afford 10.9 g of amine (*S*)-**8** as white solid in an overall yield of 75.5% within two steps. $[\alpha]_D^{20}$ +24.5 (c 0.4，$CHCl_3$), which was analyzed via Chiral HPLC (Chiralpak AD-H, eluent of *n*-Hexane/Ethanol/Diethylamine = 70/30/0.1(v/v/v), 1.0 mL/min, 35°C, λ = 254nm, t_s (*S*-enantiomer) = 9.737 min, t_R (*R*-enantiomer) = 15.798 min, *er* (*S/R*) = 94.5388/5.4612.

(iii) To a suspension of amine (*S*)-**8** (8.0 g, 18.3 mmol, 94.5388/5.4612 *er*) in *i*-Pr_2O/MeOH (v/v, 1/2, 400 mL) was added (–)-*N*-acetyl-*L*-leucine (3.2 g, 18.3 mmol). The reaction mixture was heated to reflux for 5 h, then gradually cooled to r.t., and kept temperature between 2°C and 8°C overnight. A white solid was precipitated and collected via filtration, giving 7.13 g (67.3% yield based on isomer content) of leucinate salt **9**. $[\alpha]_D^{20}$ +17.6 (c 0.5，MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 (d, *J* = 7.6 Hz, 1H), 6.85 (d, *J* = 8.0 Hz, 1H), 6.84 (s, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 6.66 (s, 1H), 6.08 (brs, 1H), 6.07 (brs, 1H), 5.94 (s, 2H), 4.18 (m, 1H), 4.00 (dd, *J* = 10.0, 3.6 Hz, 1H), 3.14 –3.07 (m, 1H), 3.05 (dd, *J* = 14.0, 3.6 Hz, 1H), 2.88 (dd, *J* = 14.0, 10.0 Hz, 1H), 2.81 (ddd, *J* = 12.4, 5.6, 6.6 Hz, 1H), 2.64 – 2.60 (m, 2H), 1.83 (s, 3H), 1.67 – 1.57 (m, 1H), 1.49 – 1.46 (m, 2H), 0.88 (d, *J* = 6.6 Hz, 3H), 0.84 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.4 (s), 169.1 (s), 149.2 (s), 145.5 (s), 145.3 (s), 144.2 (s), 134.2 (s), 131.4 (s), 128.2 (s), 124.0 (d), 108.6 (d), 107.7 (d), 106.1 (d), 100.5 (t), 100.4 (t), 78.7 (s), 55.0 (d), 50.3 (d), 44.5 (t), 40.2 (t), 38.9 (t), 29.0 (t), 24.3 (d), 22.9 (q), 22.4 (q), 21.4 (q). HRESIMS $[M+H–(N\text{-acetyl-}L\text{-leucine})]^+$: Calcd for $C_{18}H_{17}O_4NI$: 438.0197, found: *m/z* 438.0186.

(iv) A suspension of leucinate salt **9** (7.0 g, 11.18 mmol) in H_2O/MeOH (v/v, 4/1, 700 mL) was heated to 70°C – 80°C to obtain a clear solution, then gradually cooled to 50°C and adjusted to pH = 12 –13 using 10% NaOH. An increasing amount of white solid was precipitated and the mixture suspension was stirred at r.t. for 2 h. White solid was collected by filtration and washed using H_2O (50 mL×2), affording (*S*)-**8** (4.75 g, 95% yield). Specific rotation: $[\alpha]_D^{20}$ +32 (*c* 1.0, $CHCl_3$) for an enantiomerically enriched sample (*S*)-**8**. Enantiomeric purity of (*S*)-**8** was determined through HPLC analysis in comparison with authentic racemic material (Chiralpak AD-H, eluent of *n*-Hexane/Ethanol/Diethylamine = 70/30/0.1(v/v/v), 1.0 mL/min, 35°C, λ = 254nm, t_S (*S*-enantiomer) = 9.738 min, t_R (*R*-enantiomer) = 15.744 min, *ee* > 99%). M.p. 172–173°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (s, 1H), 6.75 (d, *J* = 8.0, 1H), 6.73 (d, *J* = 8.0, 1H), 6.58 (s, 1H), 6.05 (d, *J* = 1.4 Hz, 1H), 6.04 (d, *J* = 1.4 Hz, 1H), 5.92 (d, *J* = 1.4 Hz, 1H), 5.91 (d, *J* = 1.4 Hz, 1H), 4.15 (dd, *J* = 10.4, 3.2 Hz, 1H), 3.24 – 3.18 (m, 2H), 2.96 – 2.90 (m, 2H), 2.76 – 2.73 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 146.1, 145.8, 144.9, 134.5, 131.5, 128.4, 123.8, 108.9, 108.0, 106.6, 100.8, 100.7, 77.7, 55.4, 45.4, 40.1, 30.1. HRESIMS $[M+H]^+$: Calcd for $C_{18}H_{17}O_4NI$: 438.0197, found: *m/z* 438.0198.

5-((4-iodobenzo[*d*][1,3]dioxol-5-yl)methyl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-*g*]-isoquinoline (*rac*-8)



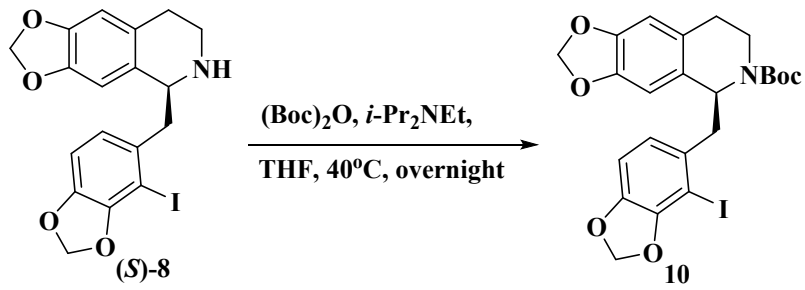
7-i

rac-8

The crude 3,4-dihydroisoquinoline intermediate **7-i** (2.0 g, 4.6 mmmol) was dissolved in THF/MeOH (v/v, 1/2, 150 mL) and treated with $NaBH_4$ (0.35 g, 9.2 mmol) at 0°C under argon. The reaction mixture was continued to stir at this condition for 8 h and quenched using sat. $NaHCO_3$ (30 mL), then concentrated to remove approximately 100 mL of mixed solvents. The residue was then partitioned between sat. $NaHCO_3$ (80 mL) and CH_2Cl_2 (60 mL). The aqueous layer was extracted using CH_2Cl_2 (60 mL×2). The combined organic layer was washed using brine (80 mL), dried over anhydrous Na_2SO_4, and concentrated to give the crude product which was purified by a slurry with MeOH or silica gel chromatography (mobile phase of *n*-hexane/CH_2Cl_2 1/1 to *n*-hexane/CH_2Cl_2/MeOH 3/30/2) to afford racemic amine **8** (1.83 g, 4.19 mmol) as white solid in 91% yield.

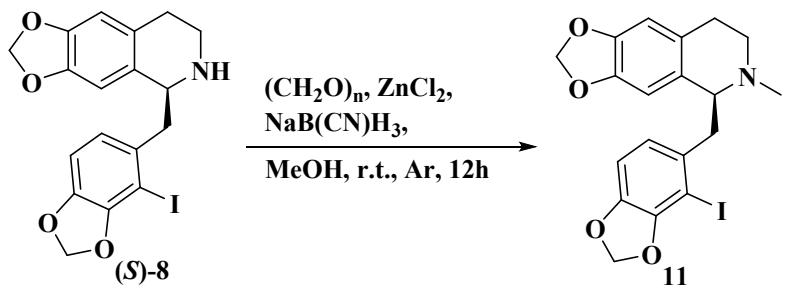
HPLC conditions: Enantiomeric proportion of racemic amine was determined by HPLC analysis (Chiralpak AD-H, eluent *n*-Hexane/Ethanol/Diethylamine = 70/30/0.1 (v/v/v), 1.0 mL/min, 35°C, λ = 254nm, t_S (*S*-enantiomer) = 9.783 min, t_R (*R*-enantiomer) = 16.002 min, *er* (*S*/*R*) = 45.8930/54.1070).

tert-butyl (S)-5-((4-iodobenzo[d][1,3]dioxol-5-yl)methyl)-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinoline-6(5H)-carboxylate (10).



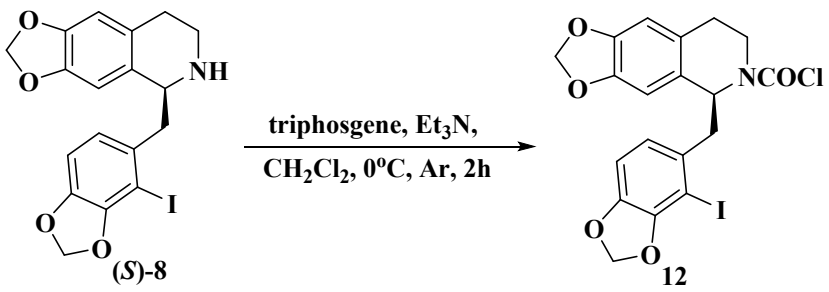
A mixed solution of tetrahydroisoquinoline (*S*)-**8** (5.0 g, 11.44 mmol), $(Boc)_2O$ (5.0 g, 22.88 mmol), and DIPEA (5.0 mL, 28.6 mmol) in THF (200 mL) was stirred at 40°C for 5 h. The reaction mixture was concentrated under reduced pressure and purified via flash chromatography (mobile phase of *n*-hexane/EtOAc = 3/1 to 2/1) to provide compound **10** (6.1 g) as white solid in quantitative yield. $[\alpha]_D^{20}$ +42 (c 1.0, $CHCl_3$). M.p. 156–158°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (s, 0.8H), 6.70 – 6.66 (m, 1.4H), 6.60 – 6.55 (m, 1.8H), 6.03 – 6.00 (m, 2H), 5.94 – 5.90 (m, 2H), 5.30 – 5.21 (m, 1H), 4.36 – 4.31 (m, 0.8H), 3.94 – 3.88 (m, 0.2H), 3.43 – 3.36 (m, 0.2H), 3.26 – 3.19 (m, 0.8H), 3.11 – 2.96 (m, 2H), 2.92 – 2.84 (m, 0.8H), 2.82 – 2.74 (m, 0.2H), 2.67 – 2.61 (m, 1H), 1.35 (s, 1.8H), 1.15 (s, 7.2H). ^{13}C NMR (100 MHz, $CDCl_3$, major rotamer). δ 154.4 (s), 149.5 (s), 146.6 (s), 146.2 (s), 145.0 (s), 134.1 (s), 130.2 (s), 127.8 (s), 123.7 (d), 108.8 (d), 108.2 (d), 107.0 (d), 101.0 (t), 100.7 (t), 79.5 (s), 78.5 (s) 54.3 (d), 45.2 (t), 36.3 (t), 28.8 (t), 28.3 (q, 3×C). HRESIMS $[M+Na]^+$: Calcd for $C_{23}H_{24}O_6NINa$: 560.0197, found: *m/z* 560.0198.

(S)-5-((4-iodobenzo[d][1,3]dioxol-5-yl)methyl)-6-methyl-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-g]isoquinoline (11).



A mixture suspension of amine **8** (0.8 g, 1.83 mmol), paraformaldehyde (0.33 g, 10.98 mmol), anhydrous $ZnCl_2$ (0.5 g, 3.66 mmol), and $Na(CN)BH_3$ (0.29 g, 4.58 mmol) in MeOH (80 mL) was stirred at r.t. under an argon atmosphere overnight. *Note: relatively large amount of solvent was necessary because of the poor solubility of amine in MeOH*. The reaction mixture was heated to reflux for 3h to drive the reaction to completion before being concentrated under reduced pressure, and the resultant residue was then purified using flash chromatography (mobile phase of *n*-hexane/EtOAc/Et_3N = 4/1/0.05 to EtOAc/CH_2Cl_2 = 1/1), yielding the amine **11** (0.71 g, 86%) as white solid. $[\alpha]_D^{20}$ +62.8 (c 1.0, $CHCl_3$). M.p. 148–150°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.67 (d, J = 8.0 Hz, 1H), 6.59 (d, J = 8.0 Hz, 1H), 6.56 (s, 1H), 6.23 (s, 1H), 6.03 (s, 2H), 5.87 (brs, 1H), 5.85 (brs, 1H), 3.78 (t, J = 7.2 Hz, 1H), 3.33 – 3.26 (m, 1H), 3.14 (dd, J = 14.0, 7.2 Hz, 1H), 2.94 – 2.86 (m, 2H), 2.84 – 2.79 (m, 1H), 2.57 (br d, J = 17.8 Hz, 1H), 2.45 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.5 (s), 146.2 (s), 145.4 (s), 144.5 (s), 135.0 (s), 129.9 (s), 127.2 (s), 124.2 (d), 108.6 (d), 108.3 (d), 107.9 (d), 100.7 (t), 100.6 (t), 78.2 (s), 63.4 (d), 45.8 (t), 44.4 (t), 42.6 (q), 24.8 (t). HRESIMS $[M+H]^+$: Calcd for $C_{19}H_{19}O_4NI$: 452.0353, found: *m/z* 452.0346.

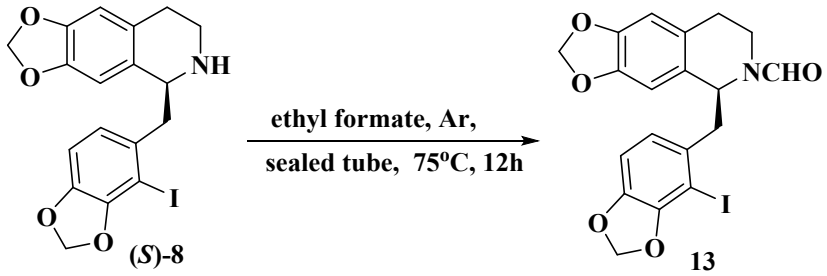
(S)-5-((4-iodobenzo[d][1,3]dioxol-5-yl)methyl)-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinoline-6(5H)-carbonyl chloride (12).



A solution of triphosgene (0.326 g, 1.1 mmol) in CH_2Cl_2 (10 mL) was added dropwise to the solution of (*S*)-**8** (0.437 g, 1.0 mmol) in anhydrous mixed solvent of CH_2Cl_2/Et_3N (v/v, 9/1, 10 mL) at 0°C in an argon atmosphere. After the addition, the mixture was stirred at the same condition for 2h before being quenched by aqueous sat. NH_4Cl (10 mL) followed by addition of H_2O (10 mL). The reaction mixture was warmed to r.t. and stirred for another 30 min, then separated in a separatory funnel. The aqueous layer was extracted using CH_2Cl_2 (10 mL), and the combined organic extract was washed using H_2O (10 mL) and brine (10 mL), respectively, dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified using flash chromatography with CH_2Cl_2 as eluent, providing compound **12** (0.45g, 90.7% yield) as white solid. $[\alpha]_D^{20}$ +66.9 (c 1.0, $CHCl_3$). M.p. 157–158°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (s, 0.5H), 6.71 (d, J = 8.0 Hz, 0.5H), 6.69 (d, J = 8.0 Hz, 0.5H), 6.62 – 6.56 (m, 2.5H), 6.04 (s, 1H), 6.04 (d, J = 1.6 Hz, 0.5H), 6.03 (d, J = 1.6 Hz, 0.5H), 5.96 (d, J = 1.2 Hz, 0.5H), 5.95 (d, J = 1.2 Hz, 0.5H), 5.94 (d, J = 1.2 Hz, 0.5H), 5.93 (d, J = 1.2 Hz, 0.5H), 5.45 – 5.41 (m, 1H), 4.38 (dddd, J = 13.2, 6.0, 3.3, 1.2 Hz, 0.5H), 4.15 (ddd, J = 13.2, 5.2, 5.2 Hz, 0.5H), 3.71 (ddd, J = 13.6, 9.2, 4.4 Hz, 0.5H), 3.46 (ddd, J = 15.6, 10.8, 4.4 Hz, 0.5H), 3.25 – 3.19 (m, 1H), 3.13 (dd, J = 14.0, 2.4 Hz, 0.5H), 3.11 (dd, J = 14.0, 4.0 Hz, 0.5H), 3.00 – 2.86 (m, 1H), 2.82 – 2.73 (m, 1H). ^{13}C NMR (100 MHz,

$CDCl_3$) δ 149.9 (149.8) (s), 149.2 (148.7) (s), 147.2 (147.1) (s), 146.6 (146.5) (s), 145.3 (145.1) (s), 132.6 (132.1) (s), 128.3 (128.2) (s), 127.0 (126.8) (s), 123.7 (123.4) (d), 108.6 (108.5) (d), 108.3 (108.1) (d), 107.3 (106.9) (d), 101.3 (101.2) (t), 100.8 (100.8) (t), 78.5 (78.2) (s), 59.3 (58.3) (d), 45.2 (44.4) (t), 43.9 (40.7) (t), 28.7 (28.4) (t). HRESIMS $[M+H]^+$: Calcd for $C_{19}H_{16}O_5NClI$: 496.0252, found: *m/z*: 496.0248.

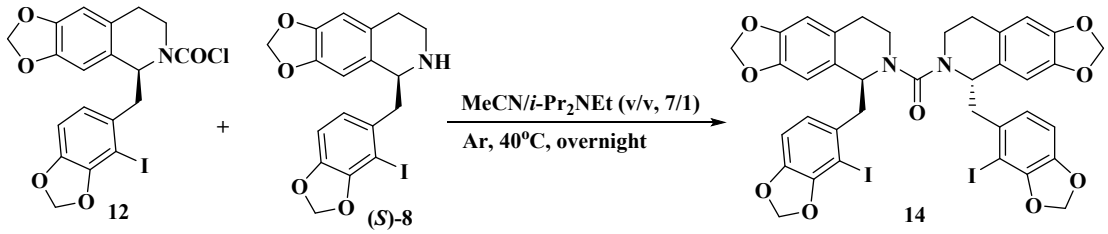
(S)-5-((4-iodobenzo[d][1,3]dioxol-5-yl)methyl)-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinoline-6(5H)-carbaldehyde (13).



A solution of amine (*S*)-**8** (2.5 g, 5.72 mmol) in ethyl formate (110 mL) was heated to 75°C with oil bath in a sealed tube under argon for 12 h. The mixture was cooled to r.t.. The reaction mixture was concentrated, filtered, dried under reduced pressure, and used in the next step without further purification. The white solid **13** (2.08 g, 4.48 mmol) was obtained in 78.3% yield. $[\alpha]_D^{20}$ +60.7 (c 1.0, $CHCl_3$). M.p. 171–173°C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (minor, s, 0.23H), 7.49 (major, s, 0.77H), 6.92 (major, s, 0.77H), 6.71 – 6.69 (m, 1H), 6.66 (minor, d, *J* = 7.9 Hz, 0.23H), 6.62 – 6.61 (m, 1H), 6.55 (minor, s, 0.23H), 6.51 (major, d, *J* = 7.9 Hz, 0.77H)., 6.06 – 6.01 (m, 2H), 5.95 – 5.92 (m, 2H), 5.58 (minor, dd, *J* = 9.4, 4.8 Hz, 0.23H), 4.69 (major, dd, *J* = 10.7, 3.5 Hz, 0.77H), 4.46 (major, ddd, *J* = 13.2, 6.2, 2.6 Hz, 0.77H), 3.64 – 3.61 (m, 0.46H), 3.23 – 3.14 (m, 1.77H), 3.07 – 3.01 (m, 1H), 2.91 – 2.81 (m, 1H), 2.76 – 2.70

(m, 1H). ^{13}C NMR (150 MHz, DMSO, major rotamer) δ 160.6 (d), 149.4 (s), 146.3 (s), 145.7 (s), 144.5 (s), 132.7 (s), 128.8 (s), 127.1 (s), 124.1 (d), 108.6 (d), 107.8 (d), 106.3 (d), 100.9 (t), 100.6 (t), 78.5 (s), 56.5 (d), 44.5 (t), 33.7 (t), 27.4 (t). HRESIMS $[M+H]^+$: Calcd for $C_{19}H_{17}O_5NI$: 466.0146, found: *m/z* 466.0138.

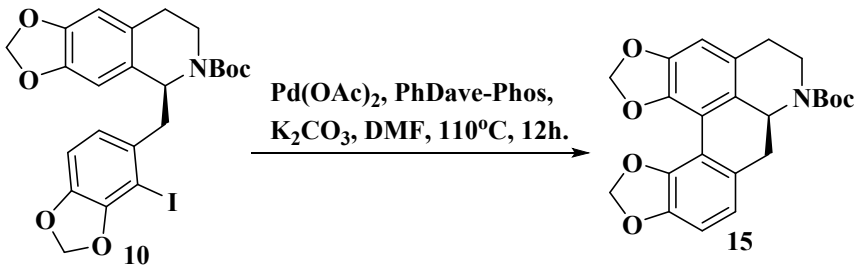
bis((S)-5-((4-iodobenzo[d][1,3]dioxol-5-yl)methyl)-7,8-dihydro[1,3]dioxolo[4,5-g]isoquinolin-6(5H)-yl)methanone (14).



A suspension of **12** (0.3 g, 0.6 mmol) in anhydrous MeCN (30 mL) was added dropwise to the solution of (*S*)-**8** (0.218 g, 0.5 mmol) in anhydrous mixed solvent of MeCN/*i*-Pr_2NEt (v/v, 7/1, 20 mL) at 0°C in an argon atmosphere. After the addition, the mixture was gradually warmed to 40°C and stirred overnight. H_2O (80 mL) was added, then the mixture was extracted using CH_2Cl_2 (50 mL×3). The combined organic extract was washed using H_2O (50 mL×2) and brine (50 mL), respectively, dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified over flash chromatography (mobile phase of *n*-hexane/CH_2Cl_2/MeOH = 15/20/1). The eluate containing product was dried at 80°C for 1 h in an argon atmosphere using oil pump to remove residual CH_2Cl_2 and afforded **14** (0.37 g, 82.6% yield) as white solid. M.p. 123–125°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 (s, 2H), 6.65 (d, J = 8.0 Hz, 2H), 6.62 (d, J = 8.0 Hz, 2H), 6.46 (s, 2H), 6.00 (brs, 2H), 5.98 (brs, 2H), 5.89 (s, 4H),

4.94 (dd, *J* = 10.4, 4.4 Hz, 2H), 3.50 (m, 2H), 3.38 (ddd, *J* = 12.0, 12.0, 4.0 Hz, 2H), 3.01 (dd, *J* = 14.0, 10.4 Hz, 2H), 2.90 (dd, *J* = 14.0, 4.4 Hz, 2H), 2.38 (dd, *J* = 16.0, 4.0 Hz, 2H), 2.09 (dd, *J* = 16.0, 12.0, 6.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4 (s), 149.4 (s), 146.6 (s), 146.0 (s), 144.6 (s), 134.1 (s), 130.0 (s), 127.2 (s), 123.8 (d), 108.6 (d), 108.0 (d), 107.0 (d), 100.8 (t), 100.6 (t), 78.3 (s), 56.3 (d), 45.0 (t), 40.2 (t), 28.2 (t). HRESIMS $[M+H]^+$: Calcd for $C_{37}H_{31}O_9N_2I_2$: 901.0113, found: *m/z* 901.0104.

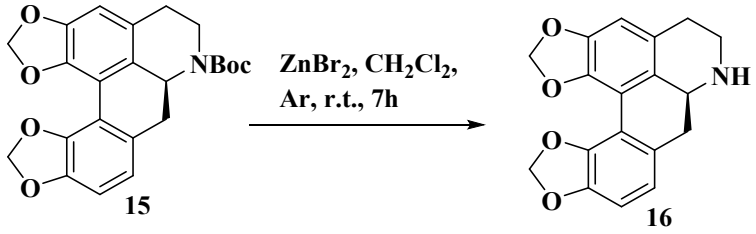
tert-butyl (S)-5,6,7a,8-tetrahydro-7H-[1,3]dioxolo[4',5':4,5]-benzo[1,2,3-de][1,3]dioxolo[4',5':5,6]benzo[1,2-g]quinoline-7-carboxylate (15).



See 'General Procedure of Arylation for Constructing Aporphine Systems' and **Table S1** in the supplementary information for more details. A scale-up to synthesize **15** was conducted from **10** (5.0 g, 9.31 mmol), K_2CO_3 (3.2 g, 23.27 mmol), PhDave-Phos (1.4 g, 3.73 mmol), and $Pd(OAc)_2$ (0.2 g, 0.93 mmol) in anhydrous DMF (186 mL, 0.05M). The crude product was purified using flash chromatography (mobile phase of *n*-hexane/EtOAc = 3/1) to give the arylation product **15** (3.7g, 98% yield). $[\alpha]_D^{20}$ +178 (*c* 1.0, $CHCl_3$). M.p. 203–205°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (d, *J* = 8.0 Hz, 1H), 6.73 (d, *J* = 8.0 Hz, 1H), 6.61 (s, 1H), 6.08 (br, s, 1H), 6.07 (br, s, 1H), 5.95 (br, s, 1H), 5.92 (br, s, 1H), 4.64 (d, *J* = 12.2 Hz, 1H), 4.38 (d, *J* = 10.2 Hz,

1H), 2.99 – 2.75 (m, 3H), 2.70 (t, J = 13.3 Hz, 1H), 2.60 (m, 1H), 1.49 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7 (s), 147.2 (s), 147.0 (s), 144.3 (s), 143.1 (s), 130.7 (s), 127.4 (s), 126.8 (s), 120.8 (d), 113.2 (s), 113.1 (s), 108.1 (d), 107.7 (d), 100.9 (t), 100.9 (t), 80.02 (s), 52.1 (d), 38.7 (t), 35.4 (t), 30.5 (t), 28.7 (q, 3×C). HRESIMS $[M+Na]^+$: Calcd for $C_{23}H_{23}O_6NNa$: 423.1418, found: *m/z* 423.1407.

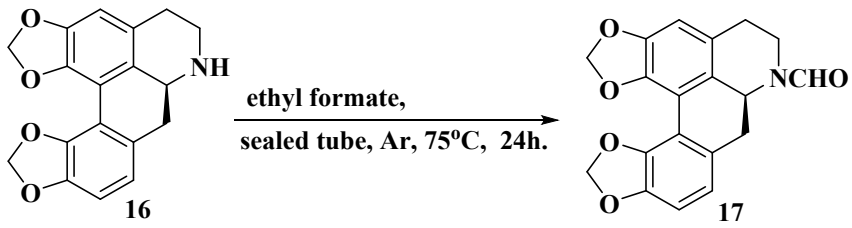
(S)-(+)-Ovigerine (16).



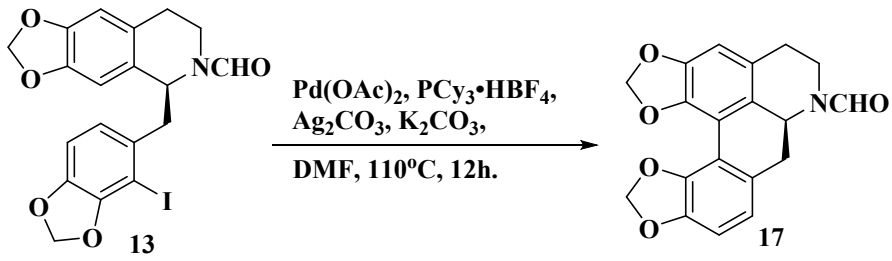
$ZnBr_2$ (2.2 g, 9.78 mmol) was added to a solution of compound **15** (1.0 g, 2.44 mmol) in CH_2Cl_2 (49 mL, 0.05M) under argon. The mixture was stirred at r.t. for 7 h before being separated using sat. $NaHCO_3$ (30 mL). The biphasic solution was partitioned, and the aqueous layer was extracted using CH_2Cl_2 (30 mL×2). The combined organic extract was washed using brine (40 mL×2), dried over anhydrous Na_2SO_4, concentrated *in vacuo*, recrystallized from a mixed solvent of *n*-hexane and CH_2Cl_2, providing (*S*)-(+)-ovigerine **16** (0.69 g, 91.6% yield) as white solid. Enantiomeric purity of **16** was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AD-H, eluent *n*-Hexane/Ethanol = 82/18 (v/v), 1.0 mL/min, 25°C, λ = 254nm, t_R (*R*-enantiomer) = 18.214 min, t_S (*S*-enantiomer) = 20.336 min, *ee* > 99%). $[\alpha]_D^{20}$ +223 (c 1.0, $CHCl_3$)[lit.[4a] $[\alpha]_D^{20}$ +217 (c 1.0, $CHCl_3$)]. M.p. 146–148°C. IR (neat): 3325, 2943, 2910, 2882, 1059, 940, 814, 781, 671, 583,

517 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 6.73 (br, 2H), 6.60 (s, 1H), 6.08(brs, 1H), 6.05 (brs, 1H), 5.93 (brs, 1H), 5.90 (brs, 1H), 3.81 (dd, J = 13.6, 4.0 Hz, 1H), 3.40 – 3.32 (m, 1H), 3.02 – 2.93 (m, 2H), 2.85 (dd, J = 14.0, 4.0 Hz, 1H), 2.70 – 2.58 (m, 2H), 2.46 (brs, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.2 (s), 147.1 (s), 144.2 (s), 142.5 (s), 129.9 (s), 129.1 (s), 126.5 (s), 120.4 (d), 113.6 (s), 112.2 (s), 108.3 (d), 107.4 (d), 100.9 (t), 100.7 (t), 54.2 (d), 43.3 (t), 37.5 (t), 29.3 (t). HRESIMS $[M+H]^+$: Calcd for $C_{18}H_{16}O_4N$: 310.1074, found: *m/z* 310.1068.

(S)-(+)-N-formylovigerine (17).



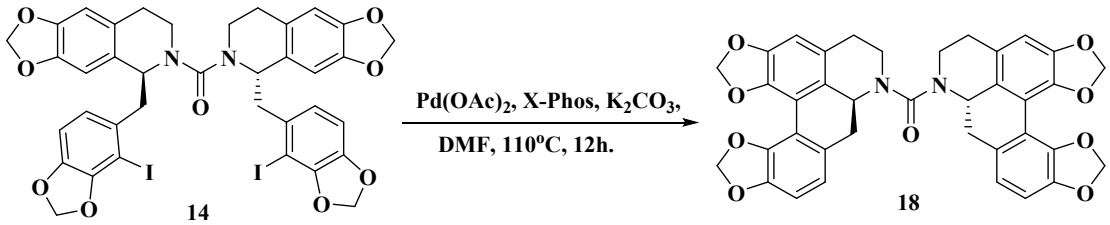
Method A: A solution of (*S*)-(+)-ovigerine **16** (0.3 g, 0.97 mmol) in ethyl formate (15 mL) in a sealed 25 mL vessel was heated at 75°C on oil bath under argon for 24 h. The reaction mixture was concentrated *in vacuo*. The resultant residue was purified using flash chromatography (mobile phase of CH_2Cl_2/MeOH = 50/1), yielding (*S*)-(+)-*N*-formylovigerine **17** (0.21 g, 61% yield) as white solid.



Method B: A scale-up to synthesize **17** was conducted from **13** (1.5 g, 3.22 mmol) and K_2CO_3 (1.1 g, 8.06 mmol) in anhydrous DMF (65 mL, 0.05M), along with

PCy_3•HBF_4 (0.47 g, 1.29 mmol), silver carbonate (0.44 g, 1.61 mmol), and $Pd(OAc)_2$ (0.14 g, 0.64 mmol). See 'General Procedure of Arylation for Constructing Aporphine Systems' and **Table S1** in the supplementary information for more details. The crude product was purified using flash chromatography (mobile phase of CH_2Cl_2/MeOH = 50/1), giving (*S*)-(+)-*N*-formylovigerine **17** (0.98 g, 2.92 mmol) in 90.5% yield. Enantiomeric purity of **17** was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AD-H, eluent of *n*-Hexane/Ethanol = 82/18 (v/v), 1.0 mL/min, 35°C, λ = 254nm, t_R (*R*-enantiomer) = 11.754 min, t_S (*S*-enantiomer) = 19.592 min, *ee* > 99%). $[\alpha]_D^{20}$ +330 (c 0.11, $CHCl_3$)[lit.[4c] $[\alpha]_D^{20}$ +321 (c 0.11，$CHCl_3$)]. M.p. 104–106°C. IR (neat): 3438, 2892, 1669, 1057, 935, 806, 788, 468 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ 8.34 (s, 0.26H, minor), 8.23 (s, 0.74H, major), 6.88 – 6.80 (m, 3H), 6.08 (m, 2H), 6.02 – 5.99 (m, 2H), 4.63 (dd, *J* = 13.2, 3.1 Hz, 0.74H, major), 4.52 (dd, *J* = 12.0, 5.6 Hz, 0.26H, minor), 4.24 (dt, *J* = 12.6, 3.7 Hz, 0.26H, minor), 3.92 (d, *J* = 12.3 Hz, 0.74H, major), 3.23 (td, *J* = 12.6, 11.3, 4.8 Hz, 0.74H, major), 3.03 – 2.93 (m, 0.26H, minor), 2.93 – 2.82 (m, 1.26H), 2.80 – 2.69 (m, 1.48H), 2.68 – 2.54 (m, 1.26H). ^{13}C NMR (126 MHz, DMSO-d_6, major rotamer) δ 162.3 (d), 146.8 (s, 2×C), 144.0 (s), 142.9 (s), 129.6 (s), 126.8 (s), 125.0 (s), 120.8 (d), 112.3 (s, 2×C), 108.2 (d), 107.6 (d), 100.8 (t), 100.7 (t), 48.7 (d), 41.1 (t), 33.5 (t), 30.1 (t). HRESIMS $[M+H]^+$: Calcd for $C_{19}H_{16}O_5N$: 338.1023, found: *m/z* 338.1017.

(+)-Ovigeridimerine (18).



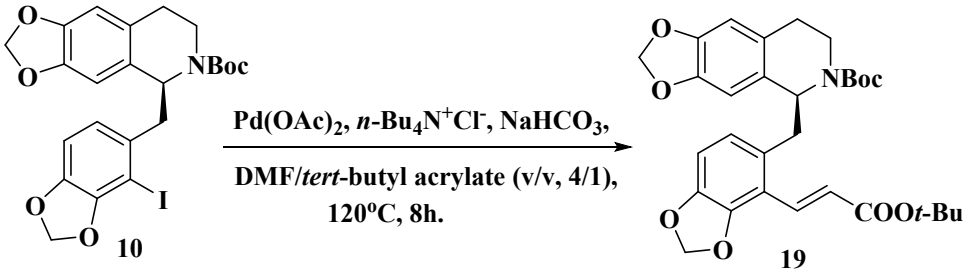
14 18

See 'General Procedure of Arylation for Constructing Aporphine Systems' and **Table S1** in the supplementary information for more details. The white solid of **18** (107.8 mg, 83.7% yield) was prepared from compound **14** (180 mg, 0.2 mmol), purified using flash chromatography (mobile phase of petroleum ether/CH_2Cl_2/MeOH = 25/30/1), dried at 80°C for 1 h in an argon atmosphere using oil pump to remove residual CH_2Cl_2. $[\alpha]_D^{20}$ +208 (*c* 0.12，$CHCl_3$)[lit.[4b] $[\alpha]_D^{20}$ +197 (*c* 0.12，$CHCl_3$)]. Enantiomeric purity of **18** was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak IB00CE-RD026, eluent of *n*-Hexane/Ethanol/Diethylamine = 70/30/0.1 (v/v/v), 1.0 mL/min, 35°C, λ = 220nm, t_{RR} (*R*,*R*-enantiomer) = 8.210 min, t_{SS} (*S*,*S*-enantiomer) = 17.260 min, *ee* > 99%). M.p. 211–214°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (d, *J* = 8.0, 2H), 6.71 (d, *J* = 8.0, 2H), 6.62 (s, 2H), 6.08 (d, *J* = 1.6Hz, 2H), 6.07 (d, *J* = 1.6Hz, 2H), 5.95 (d, *J* = 1.2 Hz, 2H), 5.94 (d, *J* = 1.2 Hz, 2H), 4.72 (dd, *J* = 13.2, 3.6 Hz, 2H), 3.78 – 3.73 (m, 2H), 3.29 – 3.23 (m, 2H), 3.05 (dd, *J* = 13.6, 4.0 Hz, 2H), 2.85 – 2.73 (m, 4H), 2.58 (t, *J* = 13.1, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4 (s), 147.2 (s), 147.0 (s), 144.2 (s), 143.1 (s), 130.3 (s), 127.3 (s), 126.4 (s), 120.9 (d), 113.2 (s), 113.1 (s), 107.7 (d), 107.7 (d), 100.9 (×2) (t), 53.0 (d), 44.3 (t), 35.5 (t), 30.3 (t). HRESIMS $[M+H]^+$: Calcd for $C_{37}H_{29}O_9N_2$: 645.1868, found: *m/z* 645.1860.

The crystal for compound **18** was prepared by treating **18** with a mixture of methanol and water.

The structure of **18** was also confirmed by single-crystal X-ray analysis. The crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as deposition No. CCDC 2074178. Copies of the data can be obtained free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: +44 1223 336 033, or e-mail: deposit@ccdc.cam.ac.uk].

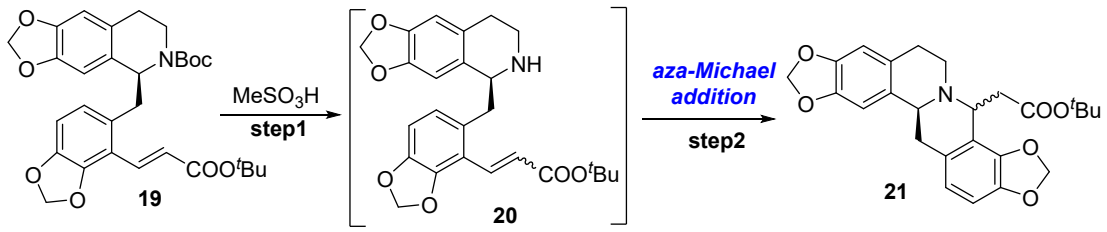
tert-butyl (S)-5-((4-(3-(tert-butoxy)-3-oxoprop-1-en-1-yl)benzo-[d][1,3]dioxol-5-yl)methyl)-7,8-dihydro-[1,3]dioxolo[4,5-g]iso-quinoline-6(5H)-carboxylate (19).



See the optimization of the Heck coupling to avoid the formation of arylation byproduct **15** in **Table S2** in the Supporting information for more details. A scale-up to synthesize **19** was conducted from **10** (2.5 g, 4.65 mmol), $NaHCO_3$ (0.98 g, 11.63 mmol), *n*-$Bu_4N^+Cl^-$ (2.6 g, 9.3 mmol), and $Pd(OAc)_2$ (0.2 g, 0.93 mmol) in DMF/*tert*-butyl acrylate (v/v, 4/1, 50 mL, 0.1M). The crude product was purified using silica gel chromatography (mobile phase of *n*-hexane/EtOAc/CH_2Cl_2 = 16/1/1) to give compound **19** (2.43 g, 4.52 mmol) in 97% yield. M.p. 119–122°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 16.0 Hz, 0.7H), 7.36 (d, J = 16.0 Hz, 0.3H), 6.79 – 6.29

(m, 5H), 6.05 – 5.86 (m, 4H), 5.07 – 4.99 (m, 1H), 4.17 – 4.13 (m, 0.7H), 3.70 – 3.64 (m, 0.3H), 3.54 – 3.47 (m, 0.3H), 3.34 – 3.27 (m, 0.7H), 3.18 – 2.94 (m, 2H), 2.88 – 2.80 (m, 0.7H), 2.74 – 2.63 (m, 1.3H), 1.56 (s, 6.3H), 1.53 (s, 2.7H), 1.39 (s, 2.7H), 1.18 (s, 6.3H). ^{13}C NMR (100 MHz, $CDCl_3$, major rotamer) δ 166.6 (C=O, s), 154.4 (N-C=O, s), 146.8 (s), 146.7 (s), 146.7 (s), 146.3 (s), 134.9 (d), 131.9 (s), 129.8 (s), 128.0 (s), 124.8 (d), 124.0 (d), 117.1 (s), 109.3 (d), 108.8 (d), 107.2 (d), 101.4 (t), 101.0 (t), 80.6 (s), 79.6 (s), 56.7 (d), 39.6 (t), 37.1 (t), 28.6 (t), 28.4 (9×C, q), 28.2 (9×C, q). HRESIMS $[M+H]^+$: Calcd for $C_{30}H_{36}O_8N$: 538.2435, found: *m/z* 538.2428.

tert-butyl 2-((12bS)-6,7,12b,13-tetrahydro-4H-[1,3]dioxolo-[4',5':7,8]isoquinolino[3,2-a][1,3]dioxolo[4,5-g]isoquinolin-4-yl)acetate (21).



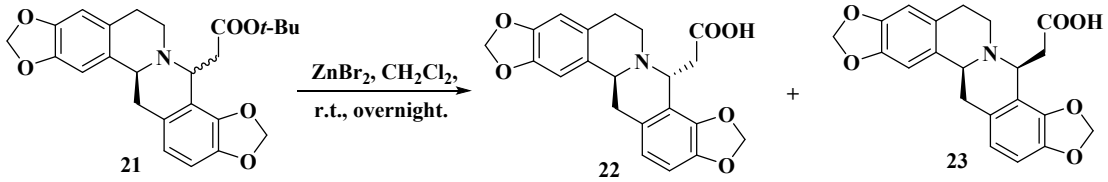
(i) $MeSO_3H$ (2.7 mL, 41.89 mmol) was added to a solution of compound **19** (1.5 g, 2.79 mmol) in a mixed solvent of *t*-BuOAc/CH_2Cl_2 (v/v, 3/1, 110 mL, 0.025M) at 0°C under argon, then the mixture was stirred at r.t. for 3 h. Sat. $NaHCO_3$ was slowly added at 0°C to achieve pH = 7 – 8, and CH_2Cl_2 (40 mL) was then added. The biphase was partitioned and the aqueous layer was extracted using CH_2Cl_2 (40 mL×2). The combined organic extract was sequentially washed using sat. $NaHCO_3$ (70 mL×2), H_2O (70 mL×2), and brine (70 mL×2), respectively, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*, treated with *n*-hexane (30mL), then filtered, washed with

n-hexane (10 mL), dried under reduced pressure in an argon atmosphere to afford crude product **20** as white solid, which was used in the next step without further purification. HRESIMS $[M+H]^+$: Calcd for $C_{25}H_{28}O_6N$: 438.1911, found: *m/z* 438.1903.

(ii) A solution of crude product **20** prepared above in *t*-BuOH (50 mL) was reflux under argon for 3 h. The reaction mixture was concentrated *in vacuo*, and the residue was purified using flash chromatography (mobile phase of *n*-hexane/EtOAc/CH_2Cl_2 = 40/1/1) to afford **21** (0.84 g, 2.9:1 mixture of *anti:syn* isomers, 68.5% yield within two steps) as white solid. M.p.182–184°C. ^{1}H NMR (600 MHz, $CDCl_3$, *dr* 2.9:1) δ 6.73 (s, 0.26H), 6.70 – 6.68 (m, 1H), 6.63 – 6.61 (m, 1H), 6.58 – 6.57 (m, 1.74H), 5.99 – 5.98 (m, 1H), 5.93 (major, dd, *J* = 1.5 Hz, 0.74H), 5.91 – 5.90 (m, 2.26H), 4.50 (major, dd, *J* = 10.2, 4.2 Hz, 0.74H), 4.16 (major, dd, *J* = 11.4, 5.4 Hz, 0.74H), 4.13 – 4.11 (minor, m, 0.26H), 3.67 (minor, d, *J* = 11.4 Hz, 0.26H), 3.35 – 4.32 (minor, m, 0.26H), 3.09 (td, *J* = 11.3, 9.1, 4.5 Hz, 1H), 3.04 – 3.01 (m, 0.26H), 2.95 – 2.88 (m, 1.26H), 2.84 – 2.77 (m, 2.26H), 2.74 (d, *J* = 4.8 Hz, 0.26H), 2.68 (td, *J* = 14.1, 13.3, 4.1 Hz, 1.74H), 2.62 (dd, *J* = 15.5, 5.2 Hz, 0.74H), 2.48 (minor, ddd, *J* = 11.4, 11.4, 3.0 Hz, 0.26H), 1.40 (major, s, 6.75H), 1.32 (minor, s, 2.25H). ^{13}C NMR (150 MHz, $CDCl_3$, major *anti* isomer) δ 171.3 (s), 146.2 (s), 145.8 (s), 145.3 (s), 143.8 (s), 132.3 (s), 128.2 (s), 127.5 (s), 121.4 (d), 119.7 (s), 108.8 (d), 107.2 (d), 106.7 (d), 101.2 (t), 100.8 (t), 80.3 (s), 57.5 (d), 51.1 (d), 46.2 (t), 40.0 (t), 32.0 (t), 30.2 (t), 28.2 (3×C, q). HRESIMS $[M+H]^+$: Calcd for $C_{25}H_{28}O_6N$: 438.1911, found: *m/z* 438.1903.

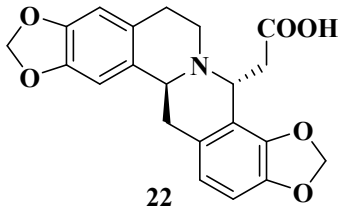
2-((4R,12bS)-6,7,12b,13-tetrahydro-4H-[1,3]dioxolo-[4',5':7,8]isoqui-nolino[3,2-

a][1,3]dioxolo[4,5-g]isoquinolin-4-yl)acetic acid (anti product, 22) and ***2-((4S,12bS)-6,7,12b,13-tetrahydro-4H-[1,3]dioxolo[4',5':7,8]-isoquinolino[3,2-a][1,3]dioxolo[4,5-g]isoquinolin-4-yl)acetic acid (syn product, 23).***



To a solution of *tert*-butyl ester **21** (0.8 g, 1.83 mmol) in CH_2Cl_2 (50 mL) was added $ZnBr_2$ (4.1 g, 18.3 mmol) at r.t. under argon.[27b] The mixture was stirred overnight before being diluted using CH_2Cl_2 (20 mL) and poured into phosphate buffer solution (0.2 mol/L, pH = 7, 80 mL). The two phases were separated and the aqueous layer was extracted using CH_2Cl_2 (40 mL×3). The collective organic solution was washed using brine (40 mL), dried over anhydrous Na_2SO_4, then concentrated under reduced pressure. The crude product was purified using flash chromatography (mobile phase of petroleum ether/EtOAc/MeOH = 6/7/1), providing, respectively, **22** (0.46 g, 65.6% yield) and **23** (0.15 g, 22% yield), in 87.6% total yield as white solids.

Compound **22**.



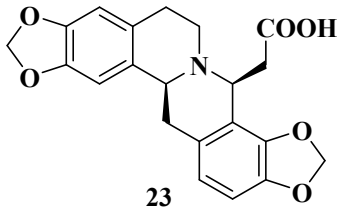
The product was analyzed by HPLC to determine the enantiomeric excess (CHIRALPAK OZ-H, MeOH/AcOH =100/0.1(v/v), flow rate = 1.0 mL/min, λ = 214 nm, t_{anti} = 7.329 min). It has the *ee* value larger than 99%. M.p. 162–163°C. ^{1}H NMR

(400 MHz, $CDCl_3$) δ 6.74 (d, J = 8.0 Hz, 1H), 6.60 (d, J = 8.0 Hz, 1H), 6.60 (s, 1H), 6.57 (s, 1H), 6.00 (d, J = 1.2 Hz, 1H), 5.96 (d, J = 1.2 Hz, 1H), 5.93 (s, 2H), 4.33 – 4.26 (m, 2H), 3.33 – 3.19 (m, 2H), 3.02 – 2.98 (m, 1H), 2.94 – 2.86 (m, 3H), 2.83 – 2.80 (m, 1H), 2.70 – 2.66 (dd, J = 16.8, 12.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4 (s), 147.3 (s), 146.4 (s), 146.0 (s), 144.2 (s), 129.2 (s), 125.1 (s), 125.0 (s), 121.6 (d), 115.4 (s), 108.9 (d), 108.4 (d), 106.7 (d), 101.7 (t), 101.2 (t), 56.9 (d), 50.3 (d), 45.0 (t), 35.9 (t), 30.6 (t), 28.5 (t). HRESIMS $[M+H]^+$: Calcd for $C_{21}H_{20}O_6N$: 382.1285, found: *m/z* 382.1281.

The crystal for hydrochloride salt of **22** (**22**•HCl) was prepared by treating **22** with 4N HCl in a mixture of MeCN, acetone and water.

The structure of hydrochloride salt of **22** (**22**•HCl) was also confirmed by single-crystal X-ray analysis. The crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as deposition No. CCDC 2101275. Copies of the data can be obtained free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: +44 1223 336 033, or e-mail: deposit@ccdc.cam.ac.uk].

Compound **23**.

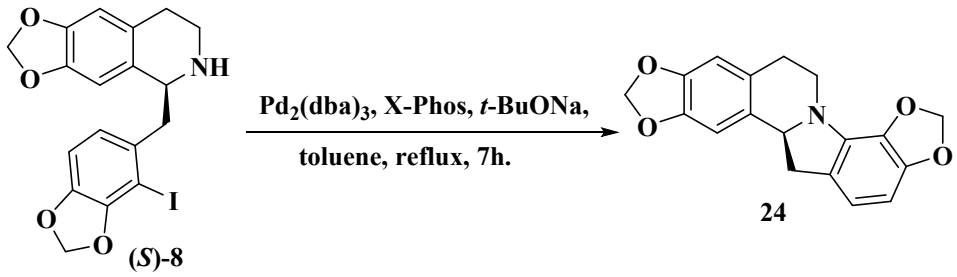


23

The product was analyzed by HPLC to determine the enantiomeric excess (CHIRALPAK OZ-H, MeOH/AcOH =100/0.1(v/v), flow rate = 1.0 mL/min, λ = 214

nm, t_{syn} = 6.475 min). It has the *ee* value larger than 99%. M.p. 163–164°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (s, 1H), 6.74 (d, J = 8.0 Hz, 1H), 6.67 (d, J = 8.0 Hz, 1H), 6.62 (s, 1H), 6.04 (d, J = 1.2 Hz, 1H), 5.95 (s, 2H), 5.95 (d, J = 1.2 Hz, 1H), 4.22 (d, J = 3.8 Hz, 1H), 3.93 (d, J = 11.2 Hz, 1H), 3.58 (dd, J = 10.4, 4.1 Hz, 1H), 3.34 (dd, J = 17.2, 2.0 Hz, 1H), 3.25 – 3.16 (m, 2H), 3.11 – 2.98 (m, 2H), 2.80 – 2.70 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3 (s), 147.0 (s), 147.0 (s), 146.5 (s), 144.0 (s), 128.4 (s), 128.2 (s), 126.8 (s), 121.7 (d), 116.3 (s), 108.5 (d), 108.3 (d), 105.7 (d), 101.5 (t), 101.3 (t), 59.4 (d), 57.9 (d), 35.8 (t), 33.9 (t), 29.8 (t), 29.3 (t). HRESIMS $[M+H]^+$: Calcd for $C_{21}H_{20}O_6N$: 382.1285, found: *m/z* 382.1281.

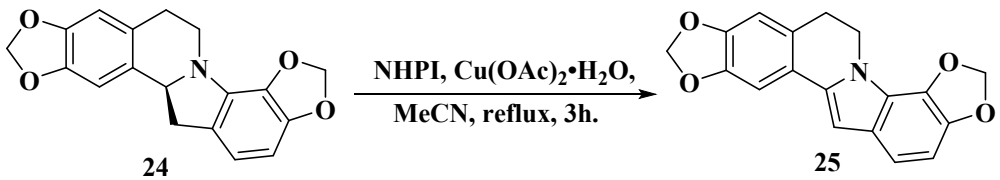
(S)-7,8,13b,14-tetrahydro-[1,3]dioxolo[4',5':6,7]indolo[2,1-a][1,3]dioxolo[4,5-g]isoquinoline (24).



X-Phos (0.31 g, 0.65 mmol), $Pd_2(dba)_3$ (0.075 g, 0.08 mmol), and *t*-BuONa (0.39 g, 4.04 mmol) was sequentially added to a solution of compound (*S*)-**8** (0.5 g, 1.62 mmol) in toluene (33 mL, 0.05M, degassed by purging with argon in an ultrasonic bath) under an argon atmosphere. The mixture was heated to reflux for 7 h, then gradually cooled to r.t., and poured into sat. $NaHCO_3/H_2O$ (v/v, 1/1, 70 mL). The organic layer was collected and washed using brine (40 mL). The aqueous layer was extracted using CH_2Cl_2 (30 mL×2), and the combined extract was washed using H_2O

(30 mL×1) and brine (30 mL×1), respectively. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified using flash chromatography (mobile phase of petroleum ether/CH_2Cl_2/MeOH 75/20/1) to afford amination product **24** (0.29 g, 82.7% yield) as yellow amorphous solid. Enantiomeric purity of **24** was determined through HPLC analysis in comparison with authentic racemic material (Chiralpak AD-H, eluent of *n*-Hexane/Ethanol = 85/15 (v/v), 1.0 mL/min, 35°C, λ = 254nm, t_R (*R*-enantiomer) = 8.384 min, t_S (*S*-enantiomer) = 10.524 min, *ee* = 98.7%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.63 (s, 1H), 6.53 (d, J = 7.6 Hz, 1H), 6.47 (s, 1H), 6.23 (d, J = 7.6 Hz, 1H), 5.89 (d, J = 1.2 Hz, 1H), 5.88 (d, J = 1.2 Hz, 1H), 5.87 (2×d, J = 1.2 Hz, 2H), 4.81 (dd, J = 8.8, 0.8 Hz, 1H), 4.12 (ddd, J = 13.6, 5.2, 1.6 Hz, 1H), 3.46 (ddd, J = 14.8, 8.8, 1.2 Hz, 1H), 3.27 (ddd, J = 16.4, 12.4, 4.0 Hz, 1H), 3.03 (dd, J = 15.2, 2.8 Hz, 1H), 2.99 – 2.90 (m, 1H), 2.47 (dddd, J = 16.4, 3.6, 2.0, 2.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.1 (s), 146.5 (s), 146.1 (s), 133.6 (s), 131.9 (s), 131.4 (s), 128.5 (s), 125.3 (s), 117.5 (d), 108.6 (d), 106.2 (d), 100.8 (t), 100.6 (t), 99.1 (d), 63.7 (d), 43.7 (t), 37.8 (t), 26.6 (t). HRESIMS $[M+H]^+$: Calcd for $C_{18}H_{16}O_4N$: 310.1074, found: *m/z* 310.1066.

7,8-dihydro-[1,3]dioxolo[4',5':6,7]indolo[2,1-a][1,3]dioxolo-[4,5-g]isoquinoline (25).

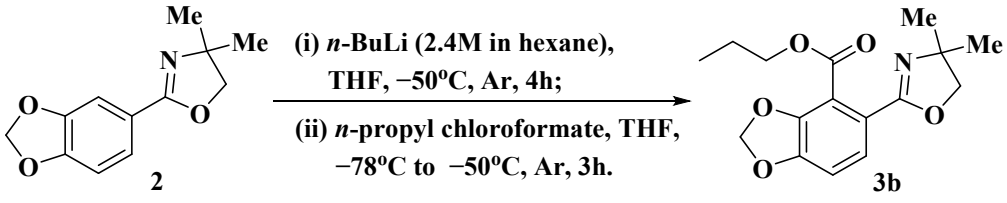


24 25

To a solution of amine **24** (0.2 mmol, 61.9 mg) in acetonitrile (7 mL) was added *N*-

hydroxyphthalimide (NHPI, 0.04 mmol, 6.6 mg) and $Cu(OAc)_2•H_2O$ (0.01 mmol, 2.0 mg), followed by heating to reflux for 3 h, then gradually cooled to r.t., filtered through a pad of silica gel. The filtrate was then concentrated, the residue was purified using flash chromatography (mobile phase of petroleum ether/CH_2Cl_2/MeOH = 80/20/1) to afford oxidation product **25** (22.3 mg, 36.3% yield) as white solid. The product was analyzed by HPLC to determine the oxidized byproduct **25** contained in compound **24**: Chiralpak AD-H, eluent of *n*-Hexane/Ethanol = 85/15 (v/v), 1.0 mL/min, 35°C, λ = 254nm, t_{25} = 16.241 min. M.p. 208–209°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (s, 1H), 7.06 (d, J = 8.4 Hz, 1H), 6.75 (d, J = 8.4 Hz, 1H), 6.72 (s, 1H), 6.64 (s, 1H), 6.00 (s, 2H), 5.97 (s, 2H), 4.36 (t, J = 6.4 Hz, 2H), 3.08 (t, J = 6.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.2 (s), 147.1 (s), 143.0 (s), 136.0 (s), 130.9 (s), 126.9 (s), 126.2 (s), 122.7 (s), 122.5 (s), 112.9 (d), 108.7 (d), 104.5 (d), 103.4 (d), 101.2 (t), 100.9 (t), 96.6 (d), 42.4 (t), 29.7 (t). HRESIMS $[M+H]^+$: Calcd for $C_{18}H_{14}O_4N$: 308.0917, found: *m/z* 308.0910.

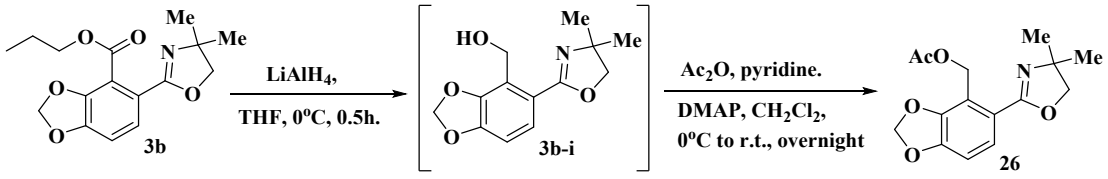
Propyl 5-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)benzo[d][1,3]-dioxole-4-carboxylate (3b).



The synthesis procedure for preparing **3b** from oxazoline **2** (35.5 g, 161.9 mmol) was based on the method for preparing **3a** from **2**, with the reaction mixture being allowed to warm to –50°C after the addition of *n*-propyl chloroformate at –78°C, and

stirred at –50°C for further 3h. The crude product was purified using silica gel column chromatography (mobile phase of *n*-hexane/EtOAc = 20/1 to 5/1) to give **3b** (37.7 g, 76.2% yield) as white solid. M.p. 42–43°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 8.0 Hz, 1H), 6.86 (d, J = 8.0 Hz, 1H), 6.08 (s, 2H), 4.27 (t, J = 6.8 Hz, 2H), 4.05 (s, 2H), 1.76 (qt, J = 6.8, 6.8 Hz, 2H), 1.35 (s, 6H), 0.99 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 161.0, 150.0, 146.0, 124.1, 120.4, 115.5, 109.1, 102.3, 79.4, 67.7, 67.3, 28.2 (2×C), 21.9, 10.5. HRESIMS $[M+H]^+$: Calcd for $C_{16}H_{20}O_5N$: 306.1336, found: *m/z* 306.1336.

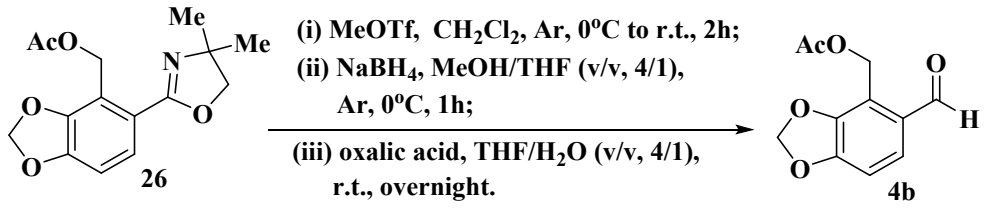
(5-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)benzo[d][1,3]dioxol-4-yl)methyl acetate (26).



(*i*) A solution of compound **3b** (20.0 g, 65.5 mmol) in anhydrous THF (400 mL) was cooled to 0°C. $LiAlH_4$ (3.8 g, 100.1 mmol) was added slowly. The suspension was stirred at 0°C for 0.5 h before being quenched by dropwise adding of sat. $NaHCO_3$ (50 mL). *Note: extreme care should be practiced during the quenching process. As this process is exothermic and generates flammable hydrogen gas. it is highly advisable to add aqueous solution of $NaHCO_3$ cautiously.* The mixture was filtered through Celite, followed by rinsing using THF (25 mL×2). The filtrate was concentrated to remove 350 mL of solution. The residue was diluted with sat. $NaHCO_3$ (300 mL) and extracted using CH_2Cl_2 (200 mL×3). The combined organic

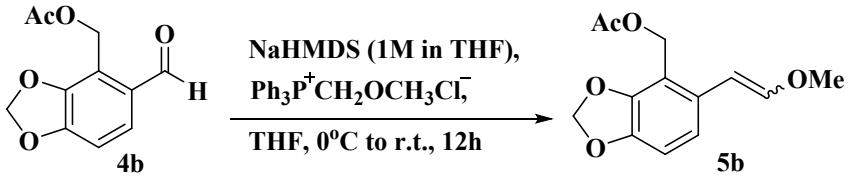
layer was washed using H_2O (200 mL) and brine (200 mL) one by one, dried over anhydrous Na_2SO_4, filtered, and concentrated. The reduction product **3b-i** was obtained (14.5 g, 88.5% yield), and was used in the next step without further purification. M.p. 87–88°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 8.0 Hz, 1H), 6.79 (brs, 1H, OH), 6.75 (d, J = 8.0 Hz, 1H), 6.02 (s, 2H), 4.69 (s, 2H), 4.09 (s, 2H), 1.38 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 149.9, 146.4, 125.1, 123.5, 121.0, 107.0, 101.6, 78.8, 67.9, 55.8, 28.6 (2×C). (*ii*) To a stirred solution of compound **3b-i** (14.0 g, 56 mmol) in anhydrous CH_2Cl_2 (250 mL) was sequentially added Ac_2O (13.0 mL, 137.5 mmol), pyridine (11.3 mL), and 4-(dimethylamino)pyridine (DMAP, 3.4 g, 27.8 mmol) at 0°C. The reaction mixture was allowed to warm to r.t. and stirred overnight. CH_2Cl_2 (250 mL) was added to dilute the solution which was poured into a separatory funnel and then sequentially washed using H_2O (300 mL×2), sat. $NaHCO_3$ (300 mL×2), and brine (300 mL×2), respectively, dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was treated with *n*-hexane (150 mL). The suspension was stirred for 0.5 h and then filtered, rinsed using *n*-hexane (15 mL×2), providing compound **26** (15.6 g, 95.6% yield) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 8.4 Hz, 1H), 6.79 (d, J = 8.4 Hz, 1H), 6.04 (s, 2H), 5.47 (s, 2H), 4.03 (s, 2H), 2.05 (s, 3H), 1.34 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 161.3, 149.4, 147.8, 125.0, 122.0, 117.2, 108.2, 101.9, 78.9, 67.9, 58.7, 28.4 (2×C), 21.1. HRESIMS $[M+H]^+$: Calcd for $C_{15}H_{18}NO_5$: 292.1180, found: *m/z* 292.1179.

(5-formylbenzo[d][1,3]dioxol-4-yl)methyl acetate (4b).



The synthesis procedure for preparing compound **4b** from **26** (11.4 g, 51.5 mmol) was based on the method for preparing **4a** from **3a**. The crude product was purified using silica gel column chromatography (mobile phase of *n*-hexane/EtOAc = 8/1 to 4/1) to afford **4b** (8.62 g, 75.3% yield). M.p. 115–116°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.97 (s, 1H), 7.45 (d, J = 8.0 Hz, 1H), 6.93 (d, J = 8.0 Hz, 1H), 6.12 (s, 2H), 5.49 (s, 2H), 2.08 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.6, 170.8, 152.4, 148.1, 130.9, 129.6, 117.5, 108.3, 102.6, 57.2, 20.9. HRESIMS $[M+Na]^+$: Calcd for $C_{11}H_{10}O_5Na$: 245.0420, found: *m/z* 245.0424.

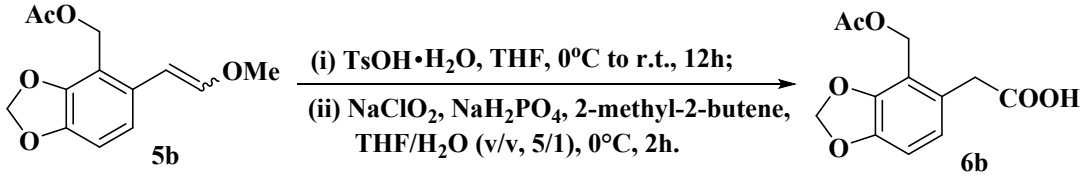
(5-(2-methoxyvinyl)benzo[d][1,3]dioxol-4-yl)methyl acetate (5b).



The synthesis procedure for preparing enol ether **5b** from aldehyde **4b** (18.5 g, 83.31 mmol) was based on the method for preparing **5a** from **4a**. The crude product was purified using silica gel column chromatography (mobile phase of *n*-hexane/EtOAc = 40/1 to 20/1) to afford **5b** (17.8 g, 7:3 mixture of *E:Z* isomers, 85.6% yield). ^{1}H NMR (400 MHz, $CDCl_3$, *E:Z* 7:3) δ 7.46 (minor, d, J = 8.3 Hz, 0.3H), 6.80 – 6.76 (m, 1.7H), 6.73 (major, d, J = 8.1 Hz, 0.7H), 6.15 (minor, d, J = 7.2 Hz, 0.3H), 5.96 (major, brs, 1.4H), 5.95 (minor, brs, 0.6H), 5.89 (major, d, J = 12.7 Hz, 0.7H),

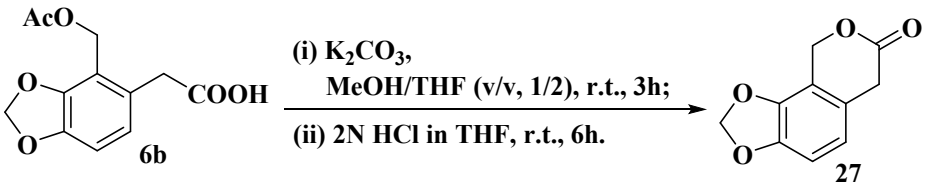
5.27 (minor, d, J = 7.2 Hz, 0.3H), 5.15 (major, s, 1.4 H), 5.14 (minor, s, 0.6 H), 3.74 (minor, s, 0.9H), 3.66 (major, s, 2.1H), 2.08 (major, s, 2.1H), 2.07 (minor, s, 0.9H). ^{13}C NMR (100 MHz, $CDCl_3$, major *E* isomer) δ 171.0, 149.7, 145.8, 130.7, 122.9, 118.7, 114.3, 109.0, 101.4, 101.4, 58.2, 56.6, 21.0. HRESIMS $[M+Na]^+$: Calcd for $C_{13}H_{14}O_5Na$: 273.0733, found: *m/z* 273.0727.

2-(4-(acetoxymethyl)benzo[d][1,3]dioxol-5-yl)acetic acid (6b).



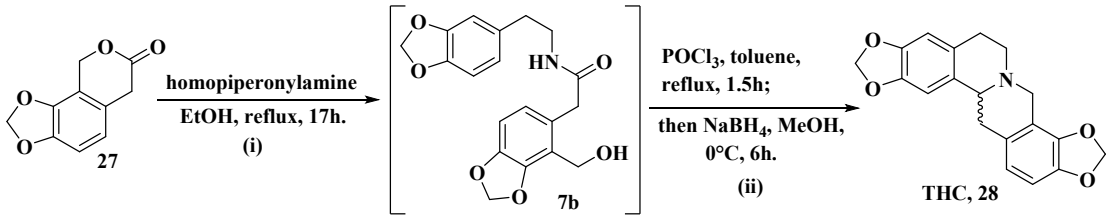
The synthesis procedure for preparing compound **6b** from **5b** (12.5 g, 49.98 mmol) was based on the method for preparing **6a** from **5a**, but with *p*-toluenesulfonic acid monohydrate (*p*-TsOH·H_2O, 19.0 g, 99.97 mmol) being added at 0°C under argon. The reaction mixture was stirred at 0°C for 15 min. The reaction mixture was allowed to warm to r.t., and then stirred for 15 h. The crude acid was chromatographed on silica gel using *n*-hexane/EtOAc (v/v, 3:1 to 1/1) as eluent to afford carboxylic acid **6b** (7.9 g, 62.7% yield, over two steps) as a white pale yellow solid. M.p. 135–136°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (d, J = 8.0 Hz, 1H), 6.74 (d, J = 8.0 Hz, 1H), 6.00 (s, 2H), 5.15 (s, 2H), 3.70 (s, 2H), 2.04 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 170.9, 147.6, 147.1, 126.7, 124.1, 116.4, 108.8, 101.7, 58.2, 37.7, 20.9. HRESIMS $[M+Na]^+$: Calcd for $C_{12}H_{12}O_6Na$: 275.0526, found: *m/z* 275.0526.

6,9-dihydro-7H-[1,3]dioxolo[4,5-h]isochromen-7-one (27).



To a solution of the acid material **6b** (5.0 g, 19.84 mmol) in a mixed solvent of MeOH/THF (v/v, 1/2, 150 mL) was added K_2CO_3 (5.5 g, 39.68 mmol). The reaction mixture was stirred at r.t. for 3 h. and then concentrated *in vacuo*. To this residue was added H_2O (150 mL) and it was treated with 2N HCl until pH = 4. The aqueous solution was extracted using CH_2Cl_2 (100 mL×3) and the combined organic layer was washed using H_2O (100 mL) and brine (100 mL), sequentially. This CH_2Cl_2 solution was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was dissolved in 2N HCl in THF (15 mL) and stirred at r.t. for 6 h. The reaction mixture was poured into H_2O (150 mL) and extracted using CH_2Cl_2 (120 mL×3). The combined organic layer was washed using H_2O (100 mL), sat. $NaHCO_3$ (100 mL), and brine (100 mL), respectively, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography using *n*-hexane/EtOAc = 4/1 as eluent provided lactone **27** (3.16 g, 83% yield) as white solid. M.p. 131–132°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75 (d, J = 8.0 Hz, 1H), 6.63 (d, J = 8.0 Hz, 1H), 5.98 (s, 2H), 5.28 (s, 2H), 3.62 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 146.9, 143.2, 124.8, 119.6, 113.0, 108.6, 101.8, 64.4, 35.9. HRESIMS $[M+H]^+$: Calcd for $C_{10}H_9O_6$: 193.0495, found: *m/z* 193.0496.

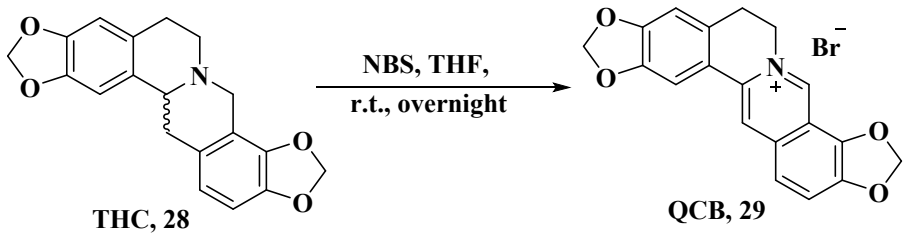
N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-2-(4-(hydroxymethyl)-benzo[d][1,3]dioxol-5-yl)acetamide (7b) and ***Tetrahydrocoptisine (THC, 28).***



(*i*) A solution of lactone **27** (2.5 g, 13.02 mmol) and homopiperonylamine (2.65 mL, 19.53 mmol) in EtOH (65 mL) was reflux for 17 h. After cooling to r.t., the precipitates were collected by filtration, rinsed using EtOH (5 mL×2), and dried *in vacuo* to afford amide **7b** (4.28 g, 92% yield) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (brs, 1H), 6.80 – 6.74 (m, 3H), 6.68 (d, J = 8.0 Hz, 1H), 6.61 (d, J = 8.0 Hz, 1H), 5.99 (s, 2H), 5.96 (s, 2H), 5.31 (brs, 1H), 4.45 (s, 2H), 3.47 (s, 2H), 3.24 – 3.19 (m, 2H), 2.60 (t, J = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.0, 147.2, 145.9, 145.5, 145.5, 133.1, 129.4, 122.8, 122.1, 121.6, 109.1, 108.1, 107.3, 100.8, 100.7, 54.6, 40.6, 38.7, 34.6. HRESIMS $[M+H]^+$: Calcd for $C_{19}H_{20}NO_6$: 358.1285, found: *m/z* 358.1286. (*ii*) A solution of phosphoryl chloride (14.0 mL) in dry toluene (35.0 mL) was added at r.t. over 10 min to a stirred solution of amide **7b** (3.5 g, 9.8 mmol) in dry toluene (90.0 mL) under an argon atmosphere. The reaction mixture was heated under reflux for 1.5 h, and then cooled to about 40°C. Excess phosphoryl chloride and toluene were evaporated *in vacuo*. The residue obtained was dissolved in MeOH (60 mL). After cooling the solution to 0°C, sodium borohydride (0.74 g, 19.6 mmol) was added in small portions over a period of 15 min. The solution was kept at 0°C for 6 h. The reaction mixture was quenched using sat. $NaHCO_3$ (80 mL), and then extracted using CH_2Cl_2 (50 mL×3). The combined

organic layer was washed using H_2O (80 mL), and brine (80 mL), respectively, dried over anhydrous Na_2SO_4. After removal of the solvent, the crude product was purified using flash chromatography using *n*-hexane/EtOAc/CH_2Cl_2 = 2/0.25/0.75 as eluent to provide **28** (3.21 g, 76.3% yield, within two steps) as pale yellow solid. M.p. 216–218°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (s, 1H), 6.68 (d, J = 8.0 Hz, 1H), 6.63 (d, J = 8.0 Hz, 1H), 6.59 (s, 1H), 5.96 (d, J = 1.4 Hz, 1H), 5.93 – 5.92 (m, 3H), 4.12 (d, J = 15.2 Hz, 1H), 3.62 (brd, J = 16.0 Hz, 1H), 3.59 (d, J = 15.2 Hz, 1H), 3.24 (dd, J = 16.0, 3.6 Hz, 1H), 3.19 – 3.10 (m, 2H), 2.84 (dd, J = 16.4, 11.6 Hz, 1H), 2.69 – 2.63 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.4 (s), 146.2 (s), 145.2 (s), 143.5 (s), 130.4 (s), 128.4 (s), 127.7 (s), 121.2 (d), 116.5 (s), 108.6 (d), 107.0 (d), 105.6 (d), 101.2 (t), 101.2 (t), 59.9 (d), 52.9 (t), 51.3 (t), 36.4 (t), 29.5 (t). HRESIMS $[M+H]^+$: Calcd for $C_{19}H_{18}O_4N$: 324.1230, found: *m/z* 324.1233.

Quaternary Coptisine Bromide (QCB, 29).

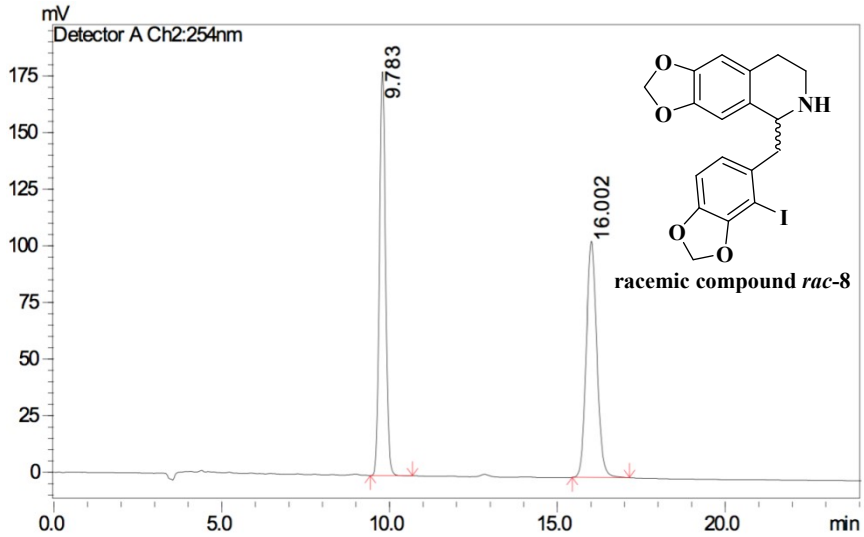


To a clear solution of THC **28** (0.3 g, 0.93 mmol) in THF (60 mL) was added NBS (0.27 g, 1.50 mmol). The suspension was stirred at r.t. overnight, filtered, washed using THF (8 mL×2) and H_2O (15 mL×3), respectively, dried under air to afford QCB **29** (0.28 g, 75.1% yield) as yellow solid. M.p. 202–203°C. IR (neat): 3456, 3074, 3049, 2997, 2910, 2781, 1916, 1831, 1714, 1641, 1618, 1603, 1571, 1504, 1476, 1432,

1408, 1386, 1361, 1323, 1286, 1258, 1234, 1215, 1193, 1139, 1108, 1059, 1036, 999, 931, 897, 871, 821, 772, 750, 707, 648, 628, 615, 565, 508, 483, 455, 424 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.94 (s, 1H), 8.96 (s, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.83 (d, J = 8.4 Hz, 1H), 7.79 (s, 1H), 7.08 (s, 1H), 6.54 (s, 2H), 6.17 (s, 2H), 4.88 (t, J = 6.4 Hz, 2H), 3.20 (t, J = 6.4 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 149.8 (s), 147.8 (s), 147.1 (s), 144.6 (d), 143.9 (s), 136.9 (s), 132.4 (s), 130.6 (s), 121.8 (d), 121.1 (d), 121.0 (d), 120.6 (s), 111.7 (s), 108.5 (d), 105.4 (d), 104.5 (t), 102.2 (t), 55.2 (t), 26.3 (t). HRESIMS $[M+H-Br]^{+}$: Calcd for $C_{19}H_{14}O_4N$: 320.0917, found: *m/z* 320.0918.

IV. HPLC Methods and Chromatograms

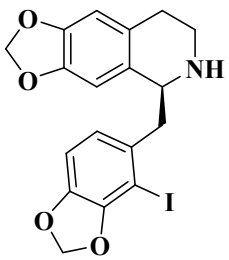
HPLC profile for racemic compound *rac*-8



Peak No.	Time	Area	Area%	Plate number	Tailing	Resolution
1	9.783	13617457	45.8930	9414.710	1.119	--
2	16.002	16054733	54.1070	10404.542	1.157	12.065

(*S*)-5-((4-iodobenzo[*d*][1,3]dioxol-5-yl)methyl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-*g*]isoquinoline ((*S*)-8, *ee* = 89%)
and (*S*)-5-((4-iodobenzo[*d*][1,3]dioxol-5-yl)methyl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-*g*]isoquinoline ((*S*)-8, *ee* > 99%)[3]

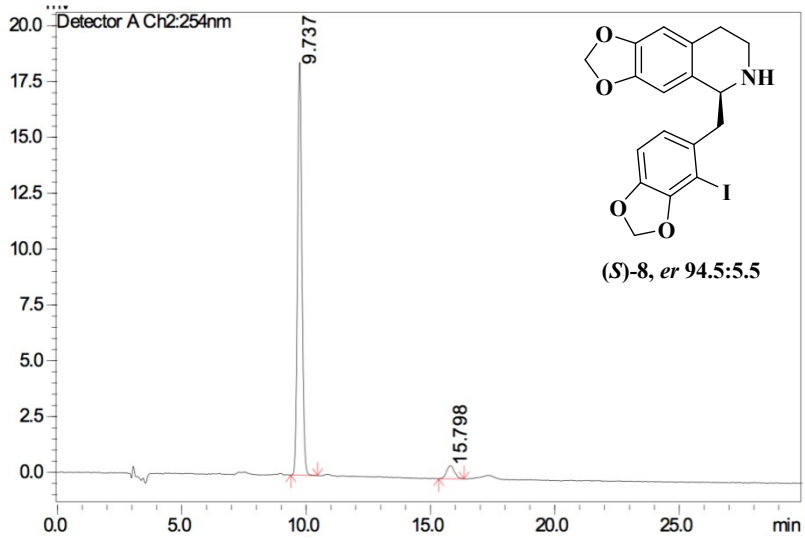
(*S*)-5-((4-iodobenzo[*d*][1,3]dioxol-5-yl)methyl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-*g*]isoquinoline ((*S*)-8, *ee* = 89%)



(*S*)-8, *er* 94.5:5.5

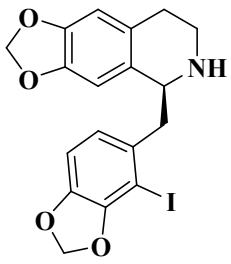
HPLC conditions: Enantiomeric purity of Noyori asymmetric hydrogenation product (*S*)-**8** (89% *ee*) was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AD-H, eluent *n*-Hexane/Ethanol/Diethylamine = 70/30/0.1(v/v/v), 1.0 mL/min, 35°C, λ = 254nm, t_S (*S*-enantiomer) = 9.783 min, t_R (*R*-enantiomer) = 16.002 min, ***ee* = 89%**.

HPLC profile for chiral product (*S*)-8 (*er* 94.5:5.5)



Peak No.	Time	Area	Area%	Plate number	Tailing	Resolution
1	9.737	227724	94.5388	12521.570	1.125	--
2	15.798	13155	5.4612	11657.948	1.147	12.989

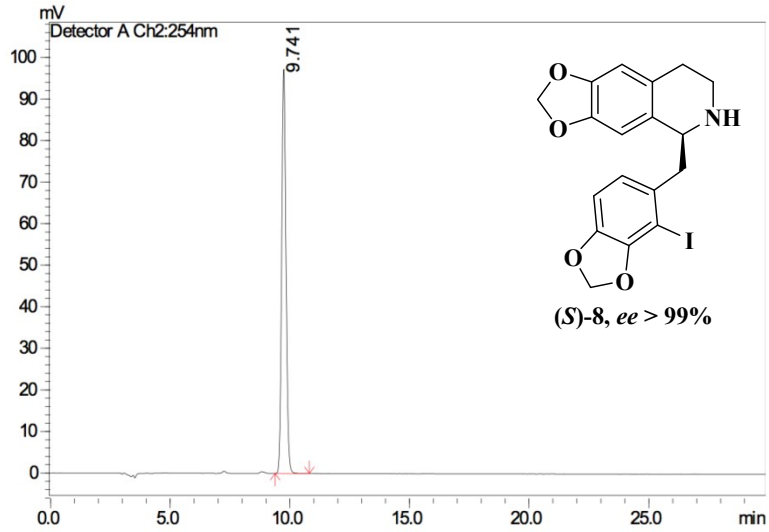
(*S*)-5-((4-iodobenzo[*d*][1,3]dioxol-5-yl)methyl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-*g*]isoquinoline ((*S*)-8, *ee* > 99%)



(*S*)-8, *ee* > 99%

HPLC conditions: Enantiomeric purity of (*S*)-**8** (*ee* > 99%) after resolution with (–)-*N*-acetyl-*L*-leucine was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AD-H, eluent *n*-Hexane/Ethanol/Diethylamine = 70/30/0.1(v/v/v), 1.0 mL/min, 35°C, λ = 254nm, t_S (*S*-enantiomer) = 9.783 min, t_R (*R*-enantiomer) = 16.002 min, *ee* > 99%.

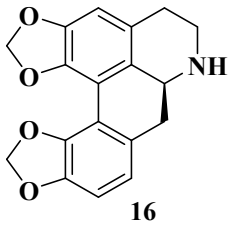
HPLC profile for chiral product (*S*)-8 (*ee* > 99%)



(*S*)-8, *ee* > 99%

Peak No.	Time	Area	Area%	Plate number	Tailing	Resolution
1	9.741	1215133	100.0000	12154.839	1.131	--

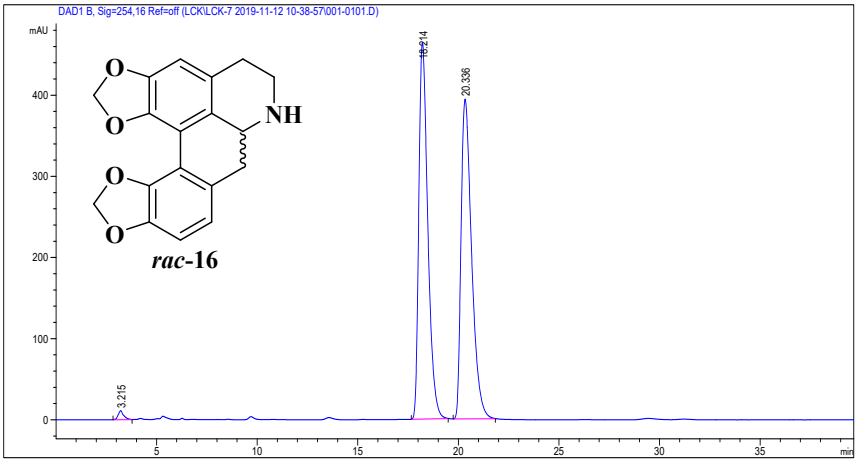
(*S*)-(+)-Ovigerine (16)



16

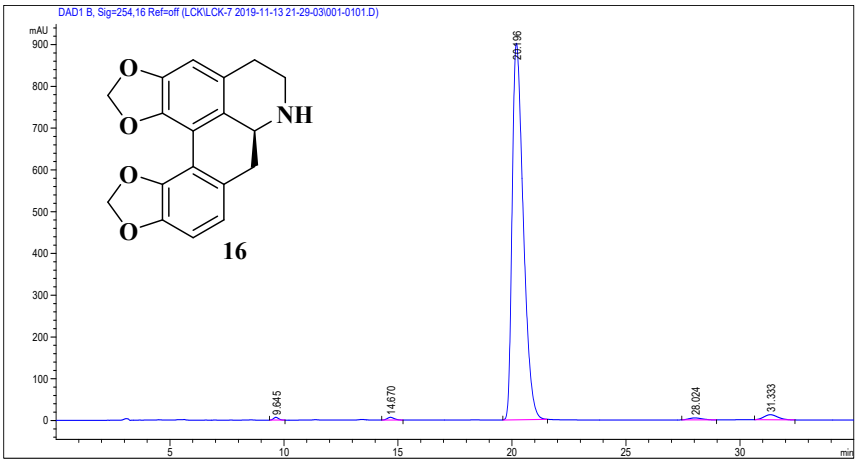
HPLC conditions: Enantiomeric purity of **16** was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AD-H, eluent *n*-Hexane/Ethanol = 82/18 (v/v), 1.0 mL/min, 25°C, λ = 254nm, t_R (*R*-enantiomer) = 18.214 min, t_S (*S*-enantiomer) = 20.336 min, *ee* > 99%.

HPLC profile for racemic product *rac*-16



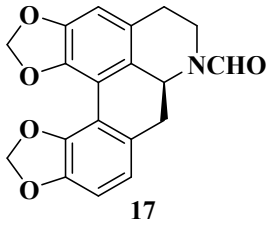
Peak No.	Time	Area	Peak height	Peak Width	Tailing	Area%
1	18.214	14400.4	464	0.476	0.622	50.058
2	20.336	14367.2	394	0.5614	0.573	49.942

HPLC profile for chiral product 16 (*ee* > 99%)



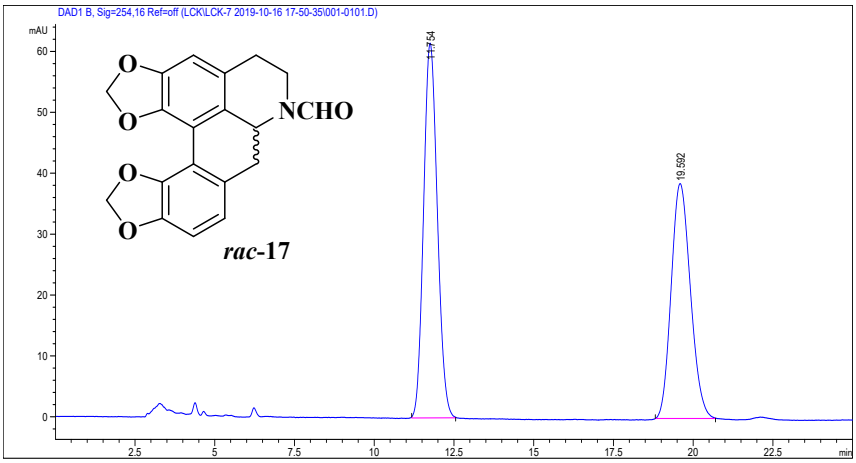
Peak No.	Time	Area	Peak height	Peak Width	Tailing	Area%
1	20.196	30602.1	901.7	0.5239	0.575	100.000

(*S*)-(+)-*N*-formylovigerine (17)



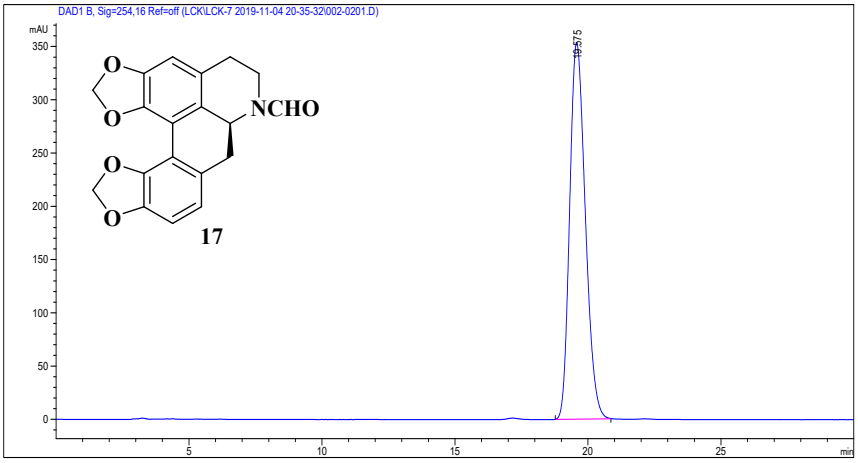
HPLC conditions: Enantiomeric purity of **17** was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AD-H, eluent *n*-Hexane/Ethanol = 82/18 (v/v), 1.0 mL/min, 35°C, λ = 254nm, t_R (*R*-enantiomer) = 11.754 min, t_S (*S*-enantiomer) = 19.592 min, *ee* > 99%.

HPLC profile for racemic product *rac*-17



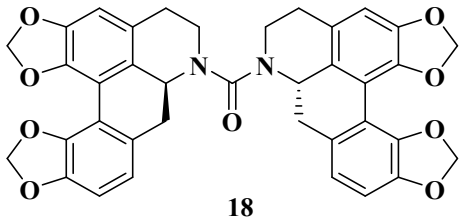
Peak No.	Time	Area	Peak height	Peak Width	Tailing	Area%
1	11.754	1844.3	61.5	0.4636	0.868	53.327
2	19.592	1614.2	38.6	0.6403	0.831	46.673

HPLC profiles for chiral product 17 (*ee* > 99%)



Peak No.	Time	Area	Peak height	Peak Width	Tailing	Area%
1	19.575	14473.4	353.7	0.6373	0.758	100.000

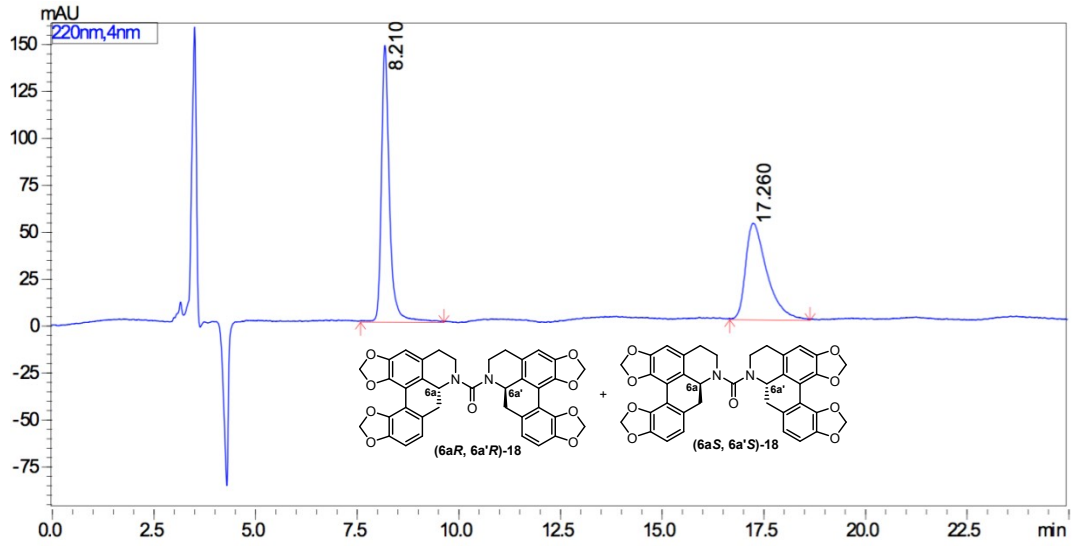
(+)-Ovigeridimerine, 18



18

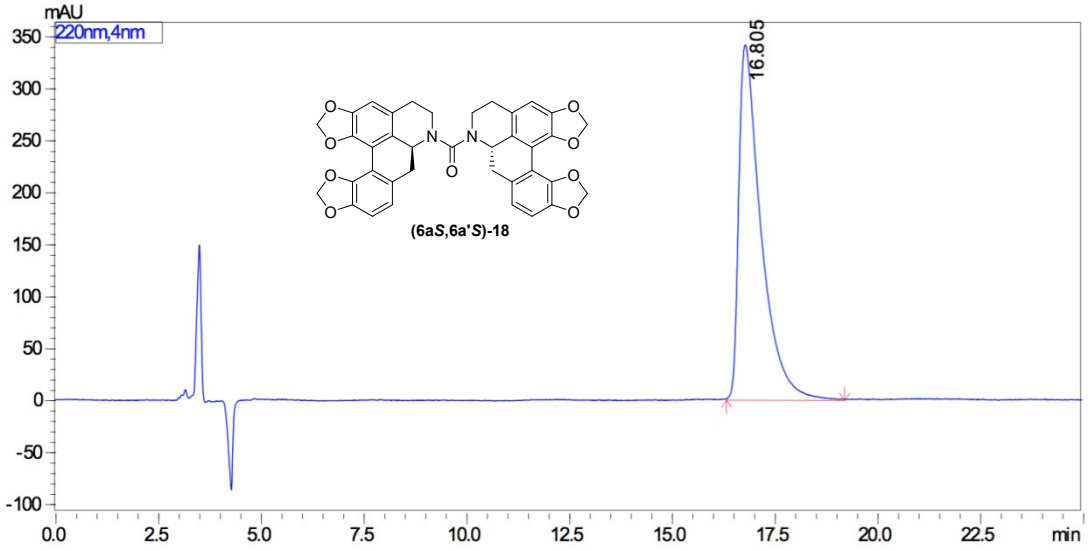
HPLC conditions: Enantiomeric purity of **18** was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak IB00CE-RD026, eluent *n*-Hexane/Ethanol/Diethylamine = 70/30/0.1 (v/v/v), 1.0 mL/min, 35°C, λ = 220nm, t_{RR} (*R,R*-enantiomer) = 8.210 min, t_{SS} (*S,S*-enantiomer) = 17.260 min, *ee* > 99%.

HPLC profile for racemic product *rac*-18



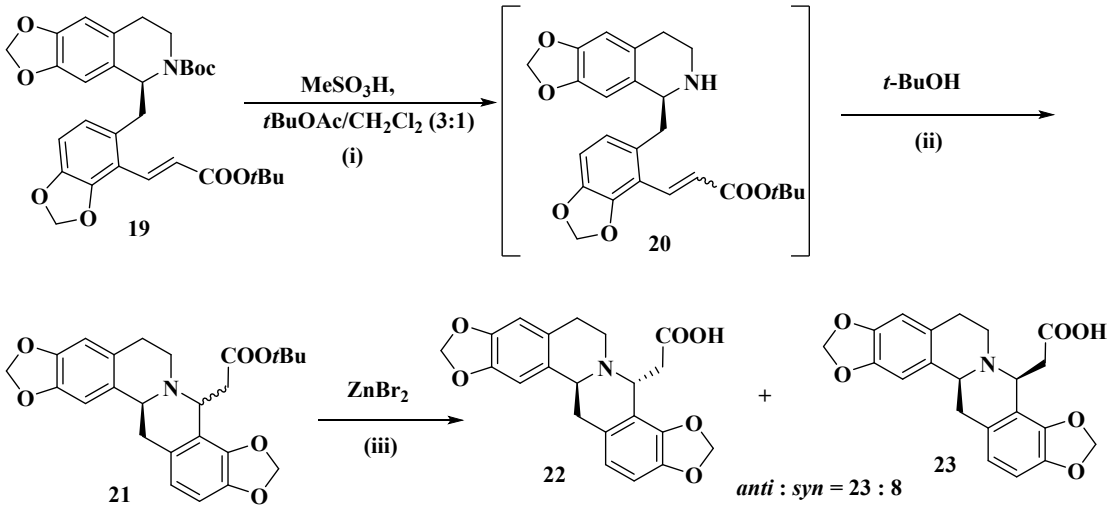
Peak No.	Time	Area	Plate number	Tailing	Area%
1	8.210	1974071	9273	1.358	52.011
2	17.260	1821436	5643	1.702	47.989

HPLC profile for chiral product 18 (*ee* > 99%)

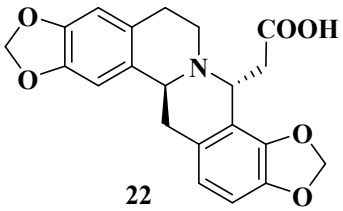


Peak No.	Time	Area	Plate number	Tailing	Area%
1	16.805	12634967	5290	2.247	100.000

2-((4*R*,12b*S*)-6,7,12b,13-tetrahydro-4*H*-[1,3]dioxolo[4',5':7,8]isoquinolino[3,2-*a*][1,3]dioxolo[4,5-*g*]isoquinolin-4-yl)acetic acid (22) and 2-((4*S*,12b*S*)-6,7,12b,13-tetrahydro-4*H*-[1,3]dioxolo[4',5':7,8]isoquinolino[3,2-*a*][1,3]dioxolo[4,5-*g*]isoquinolin-4-yl)acetic acid (23)



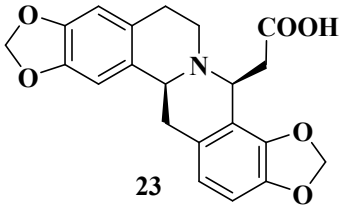
2-((4*R*,12b*S*)-6,7,12b,13-tetrahydro-4*H*-[1,3]dioxolo[4',5':7,8]isoquinolino[3,2-*a*][1,3]dioxolo[4,5-*g*]isoquinolin-4-yl)acetic acid (*anti* product, 22)



22

HPLC conditions: Enantiomeric purity of **22** (*ee* > 99%) was determined by HPLC analysis in comparison with crude racemic materials of both **22** and **23**. CHIRALPAK OZ-H, MeOH/HAC =100/0.1(v/v), flow rate = 1.0 mL/min, λ = 214 nm, $t_{ena\text{-}23}$ = 5.636 min, t_{23} = 6.617 min, t_{22} = 7.539 min, $t_{ena\text{-}22}$ = 10.303 min, *ee* > 99%.

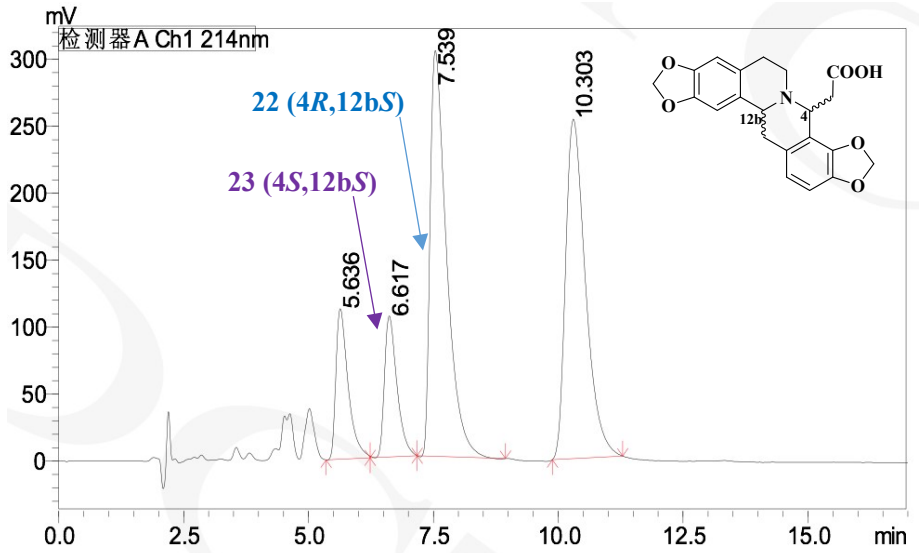
2-((4*S*,12b*S*)-6,7,12b,13-tetrahydro-4*H*-[1,3]dioxolo[4',5':7,8]isoquinolino[3,2-*a*][1,3]dioxolo[4,5-*g*]isoquinolin-4-yl)acetic acid (*syn* product, 23)



23

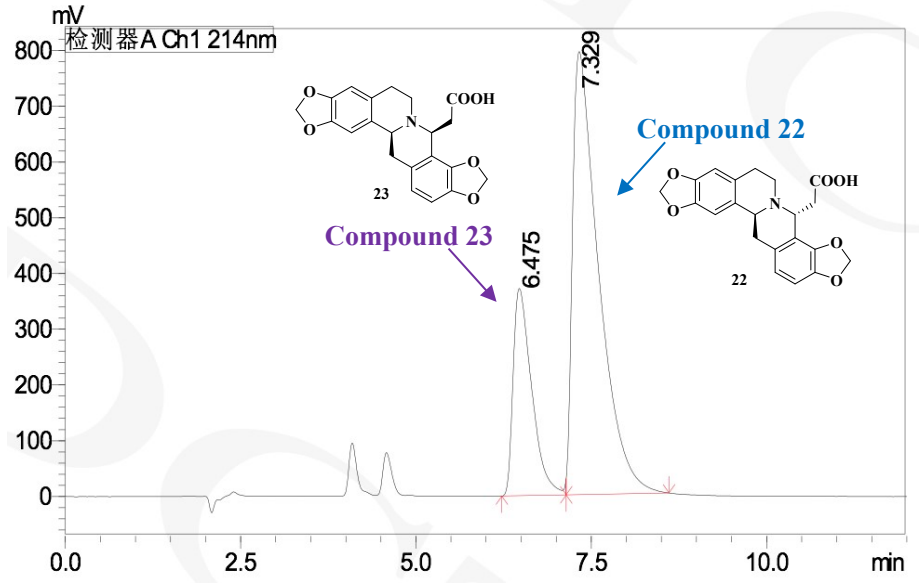
HPLC conditions: Enantiomeric purity of **23** (*ee* > 99%) was determined by HPLC analysis in comparison with crude racemic materials of both **22** and **23**. CHIRALPAK OZ-H, MeOH/HAC =100/0.1(v/v), flow rate = 1.0 mL/min, λ = 214 nm, $t_{ena\text{-}23}$ = 5.636 min, t_{23} = 6.617 min, t_{22} = 7.539 min, $t_{ena\text{-}22}$ = 10.303 min, *ee* > 99%.

HPLC profile for diastereoisomers of crude racemic materials of both 22 and 23



Peak No.	Time	Area	Area%	Plate number	Tailing	Resolution
1	5.636	1919552	10.820	2676	1.803	--
2	6.617	1825412	10.289	3407	1.555	2.206
3	7.539	6953508	39.195	2600	2.028	1.766
4	10.303	7042163	39.695	3265	1.529	4.211

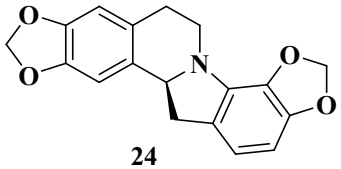
HPLC profile for crude chiral products 22 and 23



Peak No.	Time	Area	Area%	Plate number	Tailing	Resolution
1	6.475	6887376	25.031	2846	1.873	--

2	7.329	20628206	74.969	1889	2.603	1.473

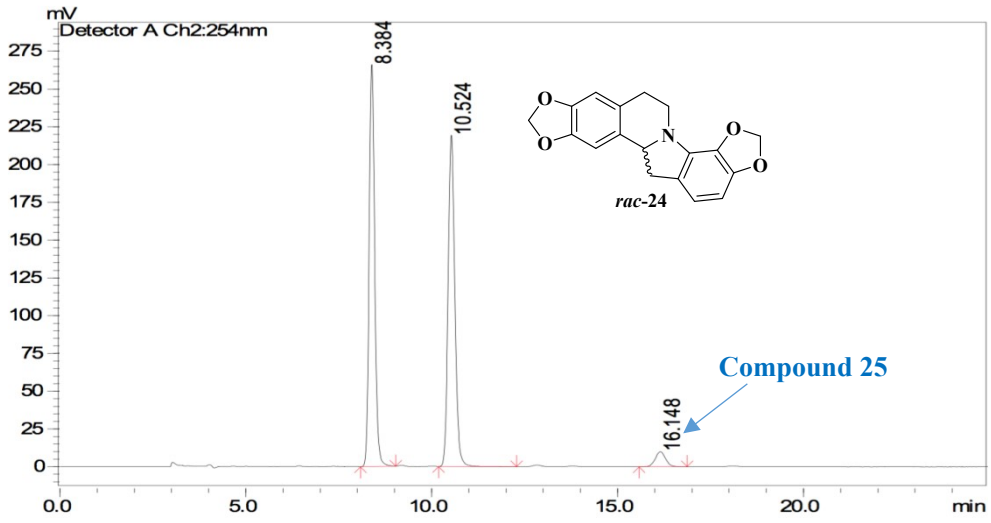
(*S*)-7,8,13b,14-tetrahydro-[1,3]dioxolo[4',5':6,7]indolo[2,1-*a*][1,3]dioxolo[4,5-*g*]isoquinoline (24)



24

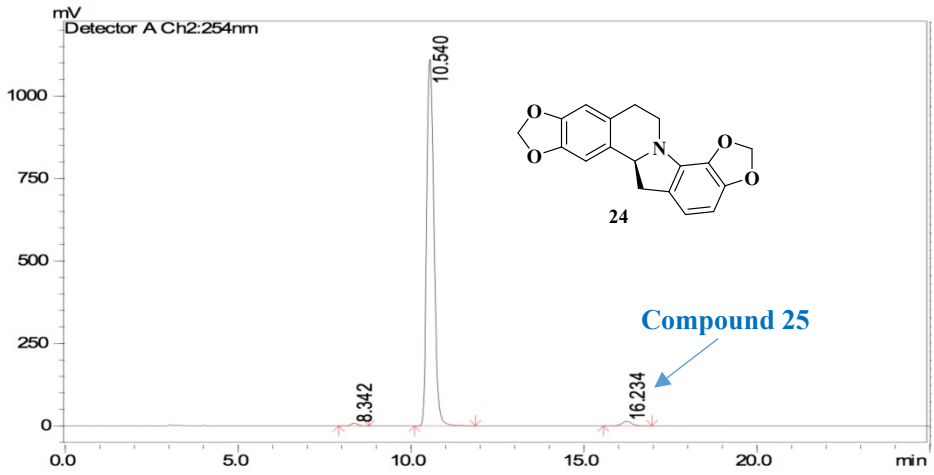
HPLC conditions: Enantiomeric purity of **24** was determined by HPLC analysis in comparison with authentic racemic material (Chiralpak AD-H, eluent *n*-Hexane/Ethanol = 85/15 (v/v), 1.0 mL/min, 35°C, λ = 254nm, t_R (*R*-enantiomer) = 8.384 min, t_S (*S*-enantiomer) = 10.524 min, *ee* = 98.7%.

HPLC profile for racemic product *rac*-24



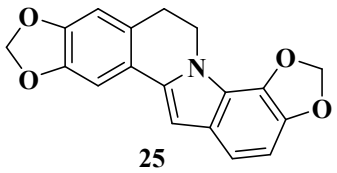
Peak No.	Time	Area	Plate number	Tailing	Area%
1	8.384	2754099	14740.037	1.170	48.1717
2	10.524	2769913	15839.555	1.151	48.4483
3	16.148	193247	15896.174	1.058	3.3801

HPLC profile for chiral product 24 (*ee* = 98.7%)



Peak No.	Time	Area	Plate number	Tailing	Area%
1	8.342	106570	8693.801	1.248	0.6388
2	10.540	16301802	12548.643	1.273	97.7181
3	16.234	274112	16125.606	1.076	1.6431

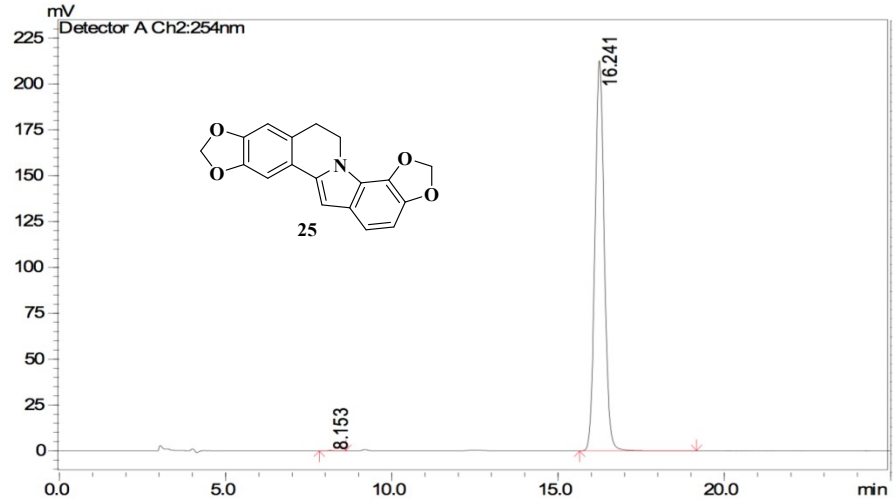
7,8-dihydro-[1,3]dioxolo[4',5':6,7]indolo[2,1-*a*][1,3]dioxolo[4,5-*g*]isoquinoline (25)



25

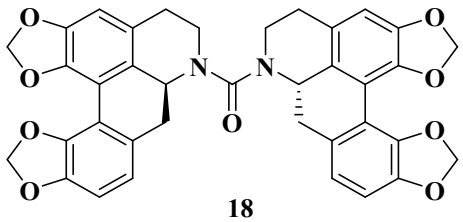
HPLC conditions: This product was analyzed by HPLC to determine the oxidized byproduct **25** contained in compound **24.** Chiralpak AD-H, eluent *n*-Hexane/Ethanol = 85/15 (v/v), 1.0 mL/min, 35°C, λ = 254nm, t_{25} = 16.241 min.

HPLC profile for compound 25

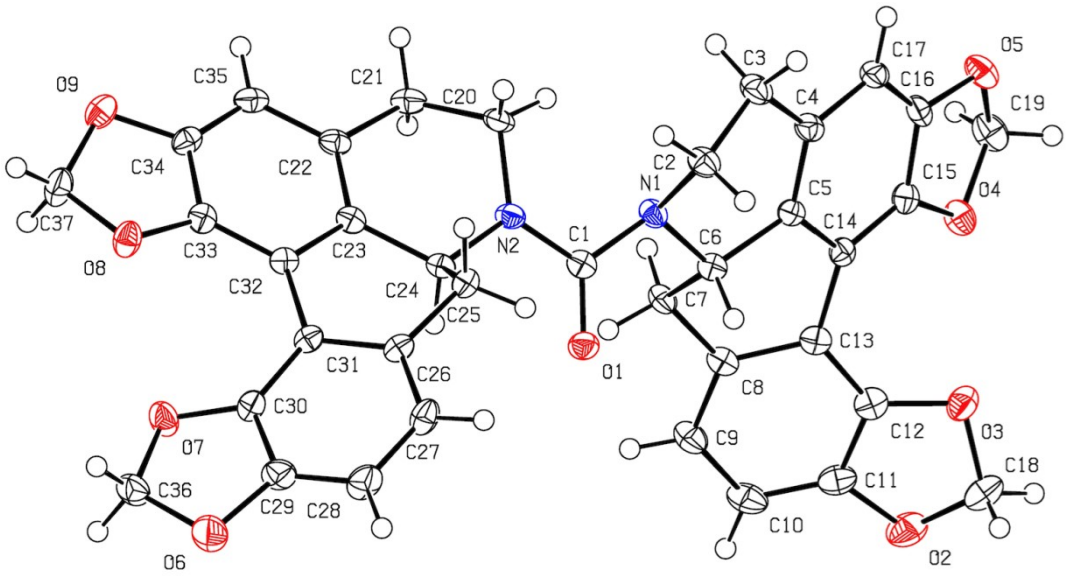

mV
Detector A Ch2:254nm
225
200
175
150
125
100
75
50
25
0
16.241
8.153
0.0
5.0
10.0
15.0
20.0
min
O
O
N
O
O
25

V. X-Ray Structure and Crystal Data

Figure S1. X-ray crystal structure of compound 18



18

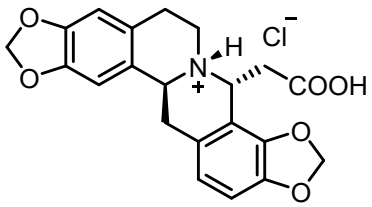


The structure of **18** was also confirmed by single-crystal X-ray analysis. The crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as deposition No. CCDC 2074178. Copies of the data can be obtained free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: +44 1223 336 033, or e-mail: deposit@ccdc.cam.ac.uk].

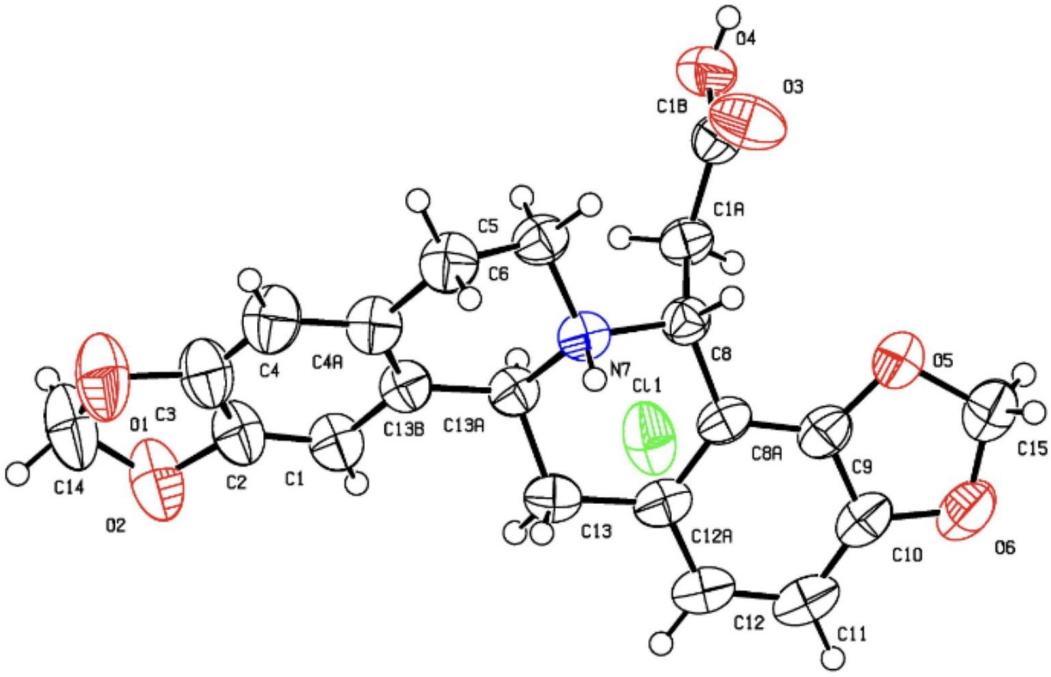
Table S3. Crystal data and structure refinement for compound 18

Identification code	**exp_7093**
Empirical formula	$C_{37}H_{28}N_2O_9$
Formula weight	644.61
Temperature	112.65 K
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 8.37408(12) Å $\alpha = 90^\circ$.
	b = 26.0423(3) Å $\beta = 94.8115(14)^\circ$.
	c = 13.33213(18) Å $\gamma = 90^\circ$.
Volume	2897.23(7) $Å^3$
Z	4
Density (calculated)	1.478 mg/mm^3
Absorption coefficient	0.887 mm^{-1}
F(000)	1344
Crystal size	0.410 × 0.400 × 0.350
2^Θ range for data collection	7.47 to 142.328°
Index ranges	-10 <= h <= 10,
	-31 <= k <= 31,
	-10 <= l <= 16
Reflections collected	20464
Independent reflections	10928[R(int) = 0.0342 (inf-0.9Å)]
Data/restraints/parameters	10928/1/865
Goodness-of-fit on F^2	1.022
Final R indexes	R_1 = 0.0392, wR_2 = 0.0956
[I > 2σ (I) i.e. $F_o > 4\sigma (F_o)$]	
Final R indexes [all data]	R_1 = 0.0410, wR_2 = 0.0977
Largest diff. peak/hole / e $Å^{-3}$	0.219/-0.212
Flack Parameters	0.07(9)
Completeness	0.9991

Figure S2. X-ray crystal structure of hydrochloride salt of compound 22 (22•HCl)



22• HCl



The structure of **22•HCl** was also confirmed by single-crystal X-ray analysis. The crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as deposition No. CCDC 2101275. Copies of the data can be obtained free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: +44 1223 336 033, or e-mail: deposit@ccdc.cam.ac.uk].

Table S4. Crystal data and structure refinement for hydrochloride salt of compound 22 (22•HCl)

Identification code	**P20210630a**
Empirical formula	$C_{21}H_{20}ClNO_6$
Formula weight	417.83
Temperature	294.15 K
Crystal system	Orthorhobic
Space group	$C222_1$
Unit cell dimensions	a = 11.64130(10) Å $\alpha = 90^{\circ}$.
	b = 12.87260(10) Å $\beta = 90^{\circ}$.
	c = 25.5684(4) Å $\gamma = 90^{\circ}$.
Volume	3831.52(7) $Å^3$
Z	8
Density (calculated)	1.449 mg/mm^3
Absorption coefficient	2.117 mm^{-1}
F(000)	1744
Crystal size	0.16 × 0.14 × 0.1
Radiation	CuKα (λ = 54184)
2^{Θ} range for data collection	6.914 to 174.3°
Index ranges	-14 <= h <= 14,
	-16 <= k <= 16,
	-32 <= l <= 32
Reflections collected	19537
Independent reflections	4122 [R_{int} = 0.0577, R_{sigma} = 0.0327]
Data/restraints/parameters	4122/0/265
Goodness-of-fit on F^2	1.195
Final R indexes	R_1 = 0.0453, wR_2 = 0.1057
[I > 2σ (I) i.e. F_o > 4σ (F_o)]	
Final R indexes [all data]	R_1 = 0.0582, wR_2 = 0.1225
Largest diff. peak/hole / e $Å^{-3}$	0.18/-0.19
Flack Parameters	0.002(7)

VI. NMR data Comparison of Natural and Synthetic Products

Table S5. NMR data Comparison of Natural and Synthetic (*S*)-(+)-Ovigerine

^{1}H NMR [δ H (ppm), *J* (Hz)]		**^{13}C NMR [δ C (ppm)]**	
Natural sample[5a]	Synthetic sample ($CDCl_3$, 400Hz)	Natural sample[5b] ($CDCl_3$, 75Hz)	Synthetic sample ($CDCl_3$, 100Hz)
	6.73 br	147.0	147.2 (s)
	6.60 s	146.7	147.1 (s)
	6.08 brs	143.8	144.2 (s)
6.01	6.05 brs	142.2	142.5 (s)
5.88	5.93 brs	129.6	129.9 (s)
	5.90 brs	128.8	129.1 (s)
	3.81 dd (13.6, 4.0)	126.2	126.5 (s)
	3.40 – 3.32 m	120.1	120.4 (d)
	3.02 – 2.93 m	113.3	113.6 (s)
	2.85 dd (14.0, 4.0)	111.9	112.2 (s)
	2.70 – 2.58 m	108.3	108.3 (d)
	2.46 brs	107.1	107.4 (d)
		100.6	100.9 (t)
		100.4	100.7 (t)
		53.8	54.2 (d)
		42.9	43.3 (t)
		37.1	37.5 (t)
		28.9	29.3 (t)

Table S6. NMR data Comparison of Natural and Synthetic (6a*S,6a'S*)-(+)-Ovigeridimerine

^{1}H NMR [δ H (ppm), *J* (Hz)]		**^{13}C NMR [δ C (ppm)]**
Natural sample[4c] ($CDCl_3$, 200Hz)	Synthetic sample ($CDCl_3$, 400Hz)	Synthetic sample ($CDCl_3$, 100Hz)
6.73 s	6.73 d (8.0)	164.4 (s)
6.62 s	6.71 d (8.0)	147.2 (s)
6.09 d (1.4)	6.62 s	147.0 (s)
6.08 d (1.4)	6.08 d (1.6)	144.2 (s)
5.96	6.07 d (1.6)	143.1 (s)
5.94	5.95 d (1.2)	130.3 (s)
4.72 dd (13.1, 3.6)	5.94 d (1.2)	127.3 (s)
3.76 m	4.72 dd (13.2, 3.6)	126.4 (s)
3.26 m	3.78 – 3.73 m	120.9 (d)
3.05 dd (13.1, 3.6)	3.29 – 3.23 m	113.2 (s)
2.80 m	3.05 dd (13.6, 4.0)	113.1 (s)
2.58 t (13.1)	2.85 – 2.73 m	107.7 (d)
	2.58 t (13.1)	107.7 (d)
		100.9 (t)
		53.0 (d)
		44.3 (t)
		35.5 (t)
		30.3 (t)

Table S7. NMR data Comparison of Natural and Synthetic Impatien B

^{1}H NMR [δ H (ppm), *J* (Hz)]			**^{13}C NMR [δ C (ppm)]**		
Natural sample[6] ($CDCl_3$, 300Hz)	Synthetic sample Compound **22** ($CDCl_3$, 400Hz)	Synthetic sample Compound **23** ($CDCl_3$, 400Hz)	Natural sample[6] ($CDCl_3$, 75Hz)	Synthetic sample Compound **22** ($CDCl_3$, 100Hz)	Synthetic sample Compound **23** ($CDCl_3$, 100Hz)
6.78 d (8.0)	6.74 d (8.0)	6.76 s	176.9 (s)	172.4 (s)	172.3 (s)
6.74 s	6.60 d (8.0)	6.74 d (8.0)	149.1 (s)	147.3 (s)	147.0 (s)
6.70 d (8.0)	6.60 s	6.67 d (8.0)	148.1 (s)	146.4 (s)	147.0 (s)
6.67 s	6.57 s	6.62 s	147.5 (s)	146.0 (s)	146.5 (s)
6.00 d	6.00 d (1.2)	6.04 d (1.2)	145.3 (s)	144.2 (s)	144.0 (s)
5.91 d	5.96 d (1.2)	5.95 s	129.0 (s)	129.2 (s)	128.4 (s)
4.70 t (5.0, 15.9)	5.93 s	5.95 d (1.2)	125.7 (s)	125.1 (s)	128.2 (s)
			125.3 (s)	125.0 (s)	126.8 (s)
3.54 d (6.6)	4.33 – 4.26 m	4.22 d (3.8)	122.9 (d)	121.6 (d)	121.7 (d)
			115.3 (s)	115.4 (s)	116.3 (s)
3.34 d (6.6)	3.33 – 3.19 m	3.93 d (11.2)	109.6 (d)	108.9 (d)	108.5 (d)
			109.5 (d)	108.4 (d)	108.3 (d)
3.15 d (5.0)	3.02 – 2.98 m	3.58 dd (10.4, 4.1)	107.6 (d)	106.7 (d)	105.7 (d)
2.98 d (5.0)	2.94 – 2.86 m	3.34 dd, (17.2, 2.0)	103.2 (t)	101.7 (t)	101.5 (t)
2.79 t (5.0, 15.9)	2.83 – 2.80 m	3.25 – 3.16 m	102.6 (t)	101.2 (t)	101.3 (t)
	2.70 – 2.66 dd (16.8, 12.4)	3.11 – 2.98 m	59.1 (d)	56.9 (d)	59.4 (d)
		2.80 – 2.70 m	52.0 (d)	50.3 (d)	57.9 (d)
			45.7 (t)	45.0 (t)	35.8 (t)

			36.7 (t)	35.9 (t)	33.9 (t)
			32.2 (t)	30.6 (t)	29.8 (t)
			28.1 (t)	28.5 (t)	29.3 (t)

Table S8. NMR data Comparison of reported Synthetic 2,3:8,9-Bis(methylenedioxy)-5,6-dihydroindolo[2,1-*a*]isoquinoline (25) and compound 25 synthesized by a different method in this paper

^{1}H NMR [δ H (ppm), *J* (Hz)]		**^{13}C NMR [δ C (ppm)]**
Reported Synthetic sample[7] ($CDCl_3$, 270Hz)	Synthetic sample in this paper ($CDCl_3$, 400Hz)	Synthetic sample in this paper ($CDCl_3$, 100Hz)
7.16 s	7.16 s	147.2 (s)
7.06 d (8.3)	7.06 d (8.4)	147.1 (s)
6.75	6.75 d (8.4)	143.0 (s)
6.72 s	6.72 s	136.0 (s)
6.64	6.64 s	130.9 (s)
5.99 s	6.00 s	126.9 (s)
5.97	5.97 s	126.2 (s)
4.37	4.36 t (6.4)	122.7 (s)
3.08	3.08 t (6.4)	122.5 (s)
		112.9 (d)
		108.7 (d)
		104.5 (d)
		103.4 (d)
		101.2 (t)
		100.9 (t)
		96.6 (d)
		42.4 (t)
		29.7 (t)

Table S9. NMR data Comparison of Natural and Synthetic Tetrahydrocoptisine (THC)

^{1}H NMR [δ H (ppm), J (Hz)]		**^{13}C NMR [δ C (ppm)]**	
Natural sample[8] ($CDCl_3$, 400Hz)	Synthetic sample ($CDCl_3$, 400Hz)	Natural sample[7] ($CDCl_3$, 100Hz)	Synthetic sample ($CDCl_3$, 100Hz)
6.73 s	6.72 s	146.2	146.4 (s)
6.68 d (8.0)	6.68 d (8.0)	146.0	146.2 (s)
6.63 d (8.0)	6.63 d (8.0)	145.0	145.2 (s)
6.59 s	6.59 s	143.3	143.5 (s)
5.94 d (15.2)	5.96 d (1.4)	130.7	130.4 (s)
5.92 s	5.93 – 5.92 m	128.6	128.4 (s)
4.09 d (15.2)	4.12 d (15.2)	127.8	127.7 (s)
3.55 t (12.4)	3.62 d (16.0)	121.1	121.2 (d)
3.23 dd (15.9, 3.5)	3.59 d (15.2)	116.9	116.5 (s)
3.19 – 3.05 m	3.24 dd (16.0, 3.6)	108.4	108.6 (d)
2.80 dd (15.8, 11.4)	3.19 – 3.10 m	106.8	107.0 (d)
2.70 – 2.58 m	2.84 dd (16.4, 11.6)	105.5	105.6 (d)
	2.69 – 2.63 m	101.0	101.2 (t)
		100.8	101.2 (t)
		59.8	59.9 (d)
		52.9	52.9 (t)
		51.2	51.3 (t)
		36.5	36.4 (t)
		29.6	29.5 (t)

Table S10. NMR data Comparison of Natural Coptisine Chloride (QCC) and Synthetic Coptisine Bromide (QCB)

^{1}H NMR [δ H (ppm), J (Hz)]		**^{13}C NMR [δ C (ppm)]**	
Natural sample[9] (DMSO-d_6, 300Hz)	Synthetic sample (DMSO-d_6, 400Hz)	Natural sample[8] (CD_3OD, 100Hz)	Synthetic sample (DMSO-d_6, 100Hz)
9.91 s	9.94 s	149.8	149.8 (s)
8.92 s	8.96 s	147.7	147.8 (s)
8.02 d (8.0)	8.03 d (8.4)	147.1	147.1 (s)
7.81 d (8.0)	7.83 d (8.4)	144.6	144.6 (d)
7.77 s	7.79 s	143.9	143.9 (s)
7.07 s	7.08 s	136.9	136.9 (s)
6.52 s	6.54 s	132.4	132.4 (s)
6.16 s	6.17 s	130.6	130.6 (s)
4.86 m	4.88 t (6.4)	121.8	121.8 (d)
3.18 m	3.20 t (6.4)	121.1	121.1 (d)
		120.5	121.0 (d)
		121.0	120.6 (s)
		111.7	111.7 (s)
		108.5	108.5 (d)
		105.4	105.4 (d)
		104.1	104.5 (t)
		102.1	102.2 (t)
		55.2	55.2 (t)
		26.3	26.3 (t)

VII. Supplementary References

[1] (a) L.-C. Campeau, M. Parisien, A. Jean and K. Fagnou, *J. Am. Chem. Soc*. 2006, ***128***, 581–590; (b) S. Chaudhary, S. Ponnala, O. LeGendre, J. A. Gonzales, H. A. Navarro and W. W. Harding, *Bioorgan. Med. Chem.* 2011, ***19***, 5861–5868; (c) J. R. Butler, C. Wang, J.-W. Bian and J. M. Ready, *J. Am. Chem. Soc*. 2011, ***133***, 9956–9959; (d) M. Hellal, S. Singh and G. D. Cuny, *Tetrahedron.* 2012, ***68***, 1674–1681; (e) R. Jangir and N. P. Argade, *Synthesis.* 2017, ***49***, 1655–1663.

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VIII. Supplementary Figures

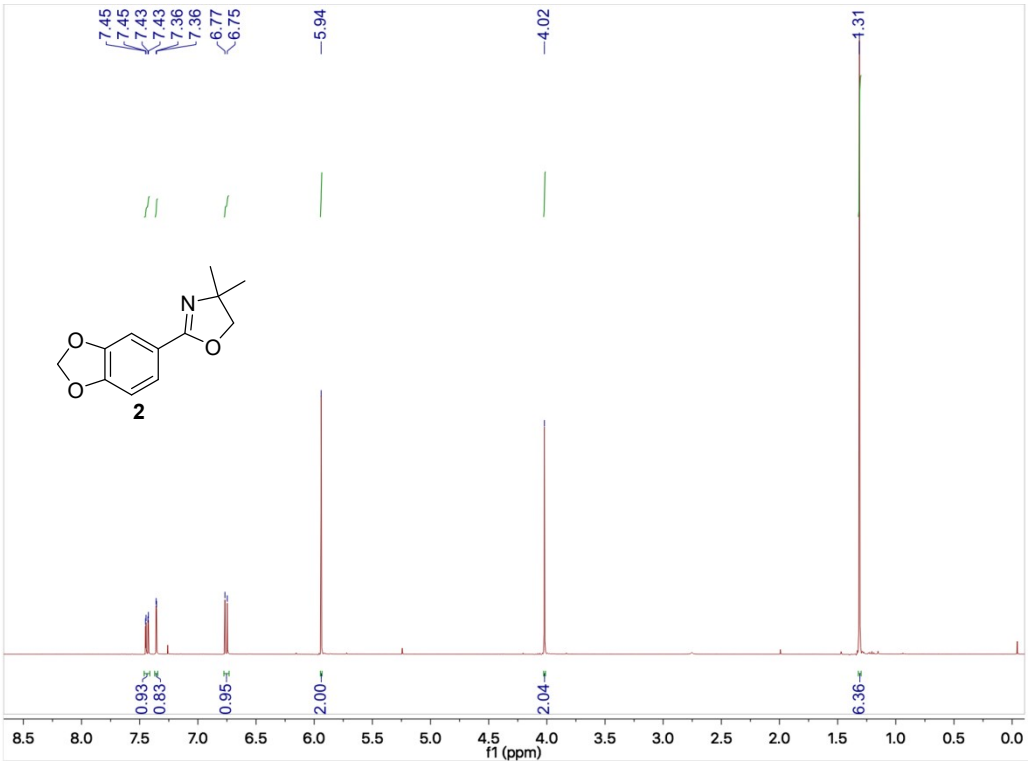

Figure S3. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **2**

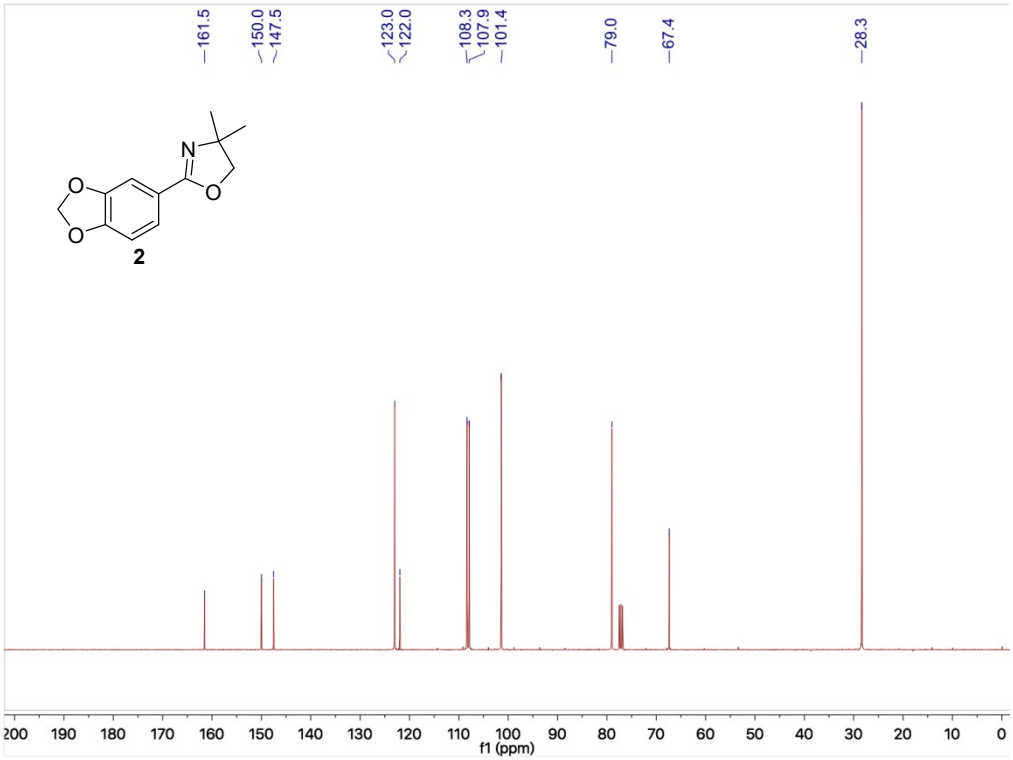

Figure S4. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **2**

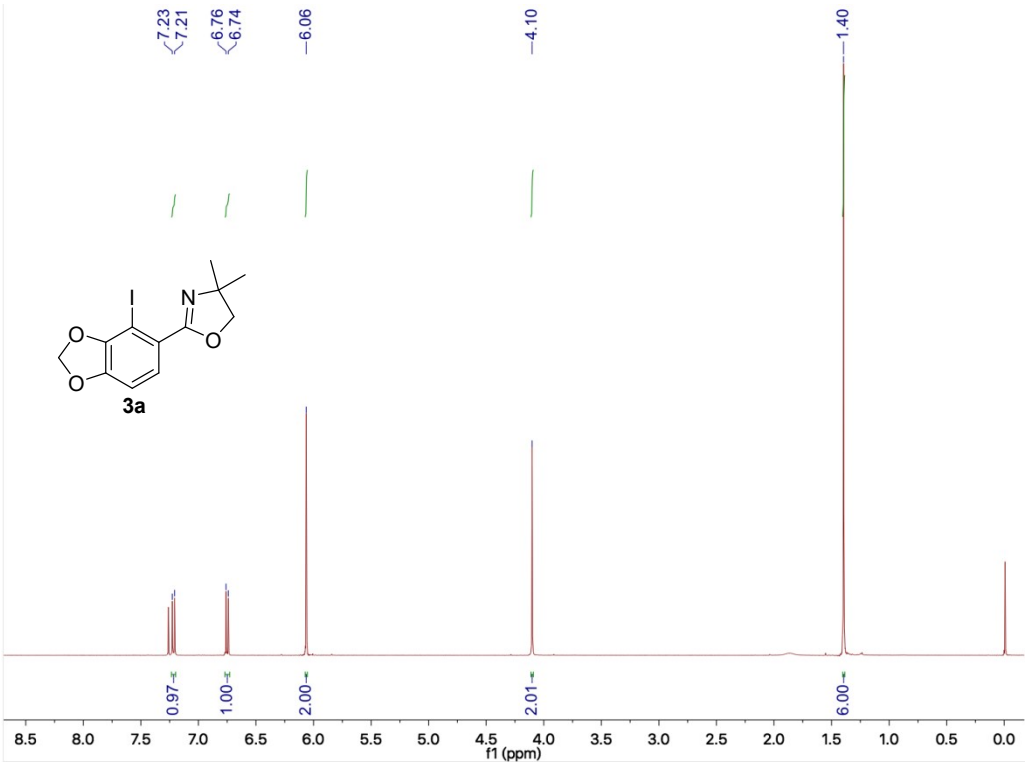

Figure S5. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **3a**

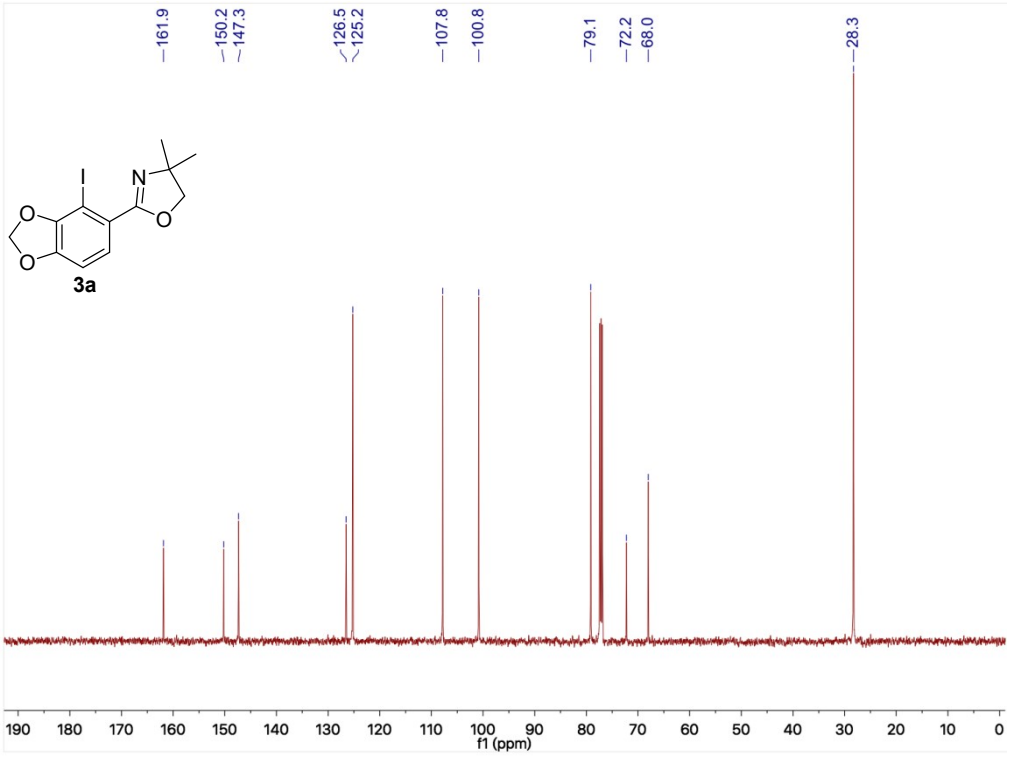

Figure S6. ^{13}C NMR spectrum (126 MHz, $CDCl_3$) of compound **3a**

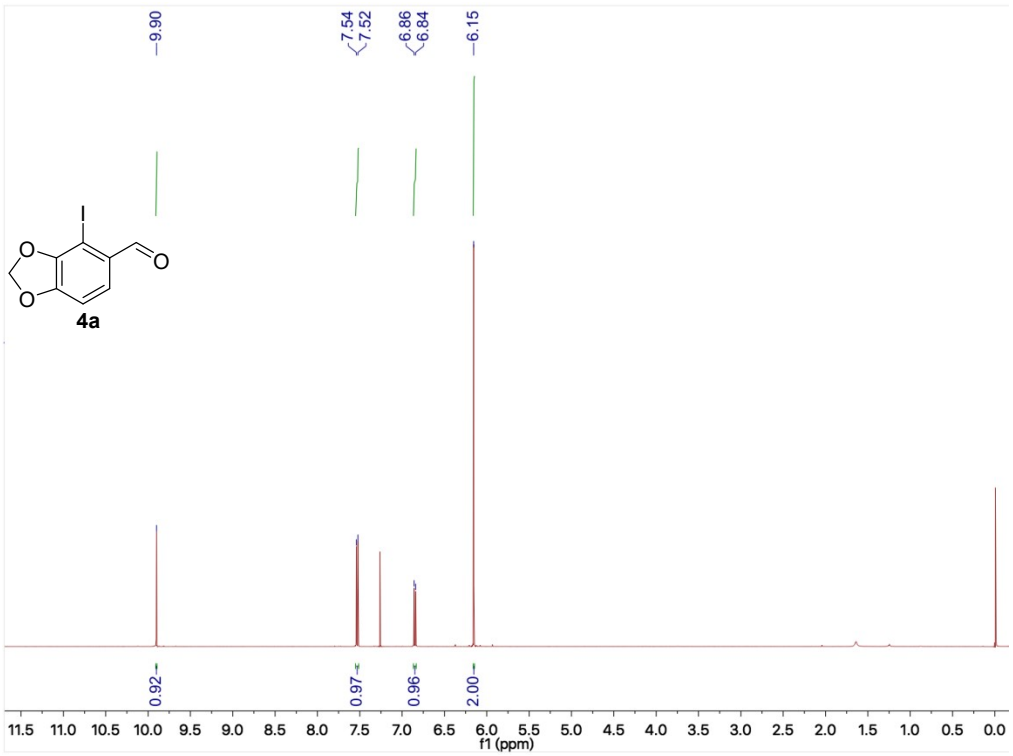

Figure S7. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **4a**

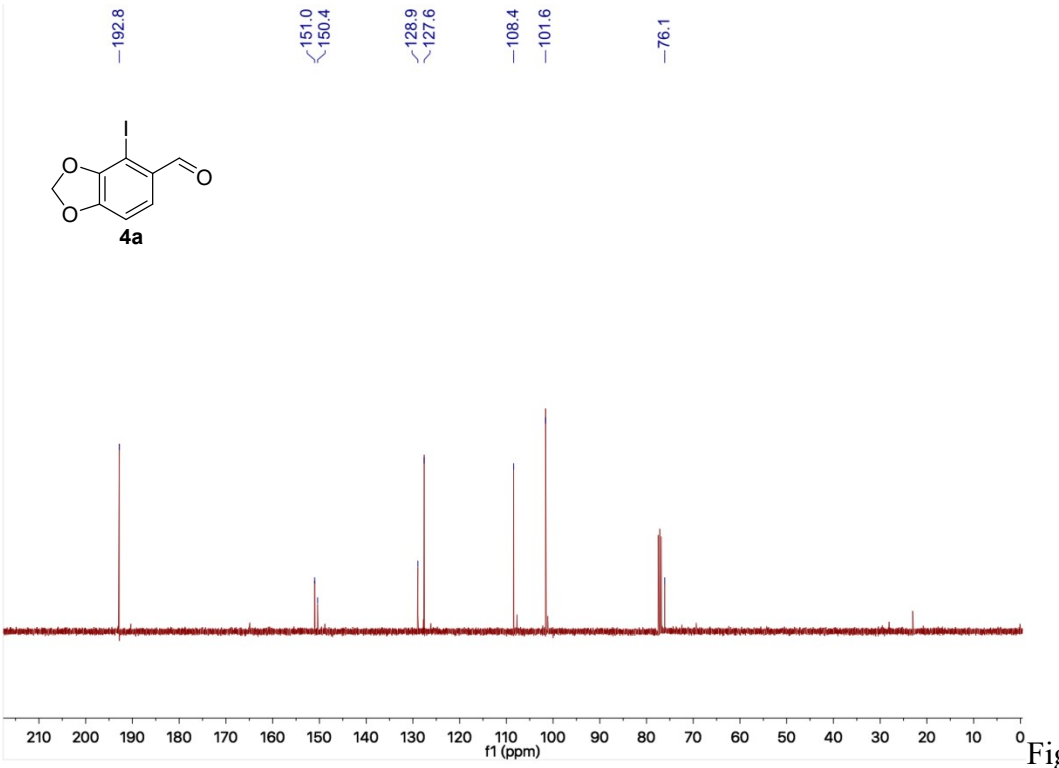

Figure S8. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **4a**

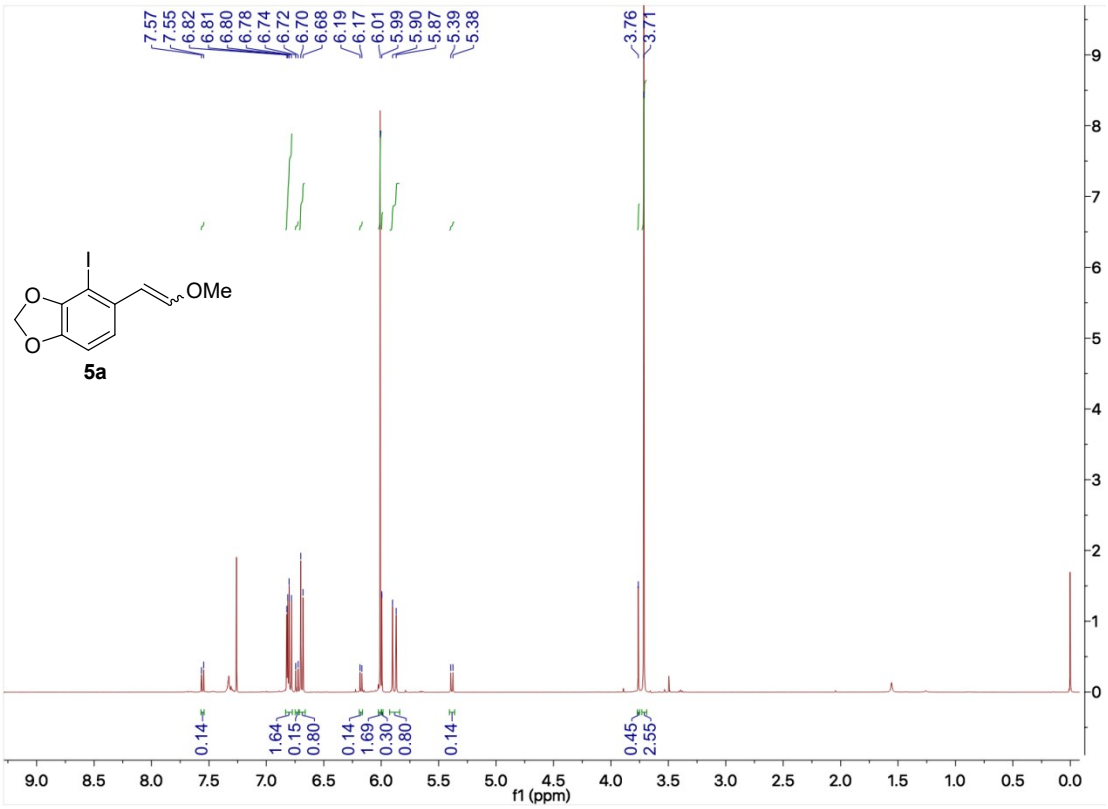

Figure S9. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **5a**

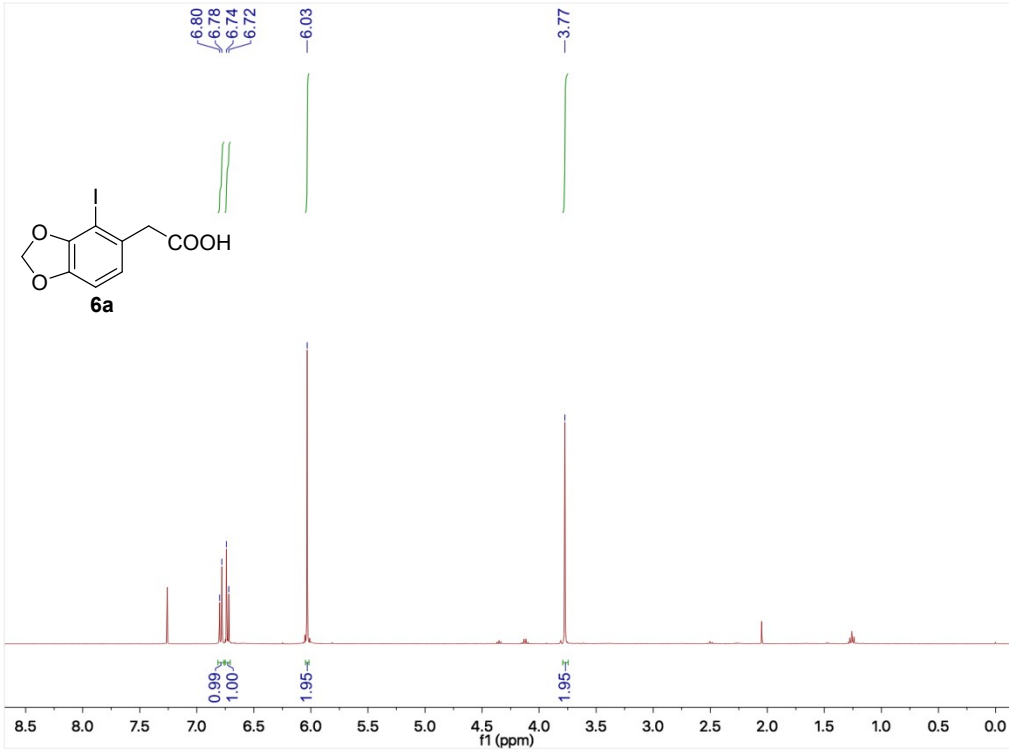

Figure S10. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **6a**

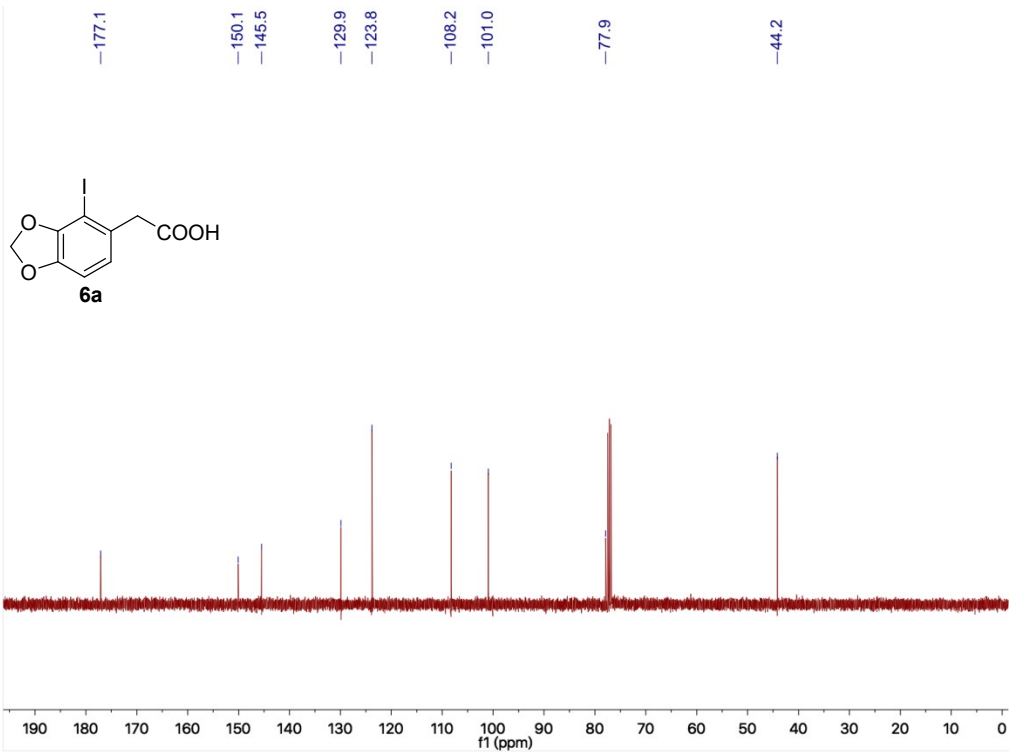

Figure S11. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **6a**

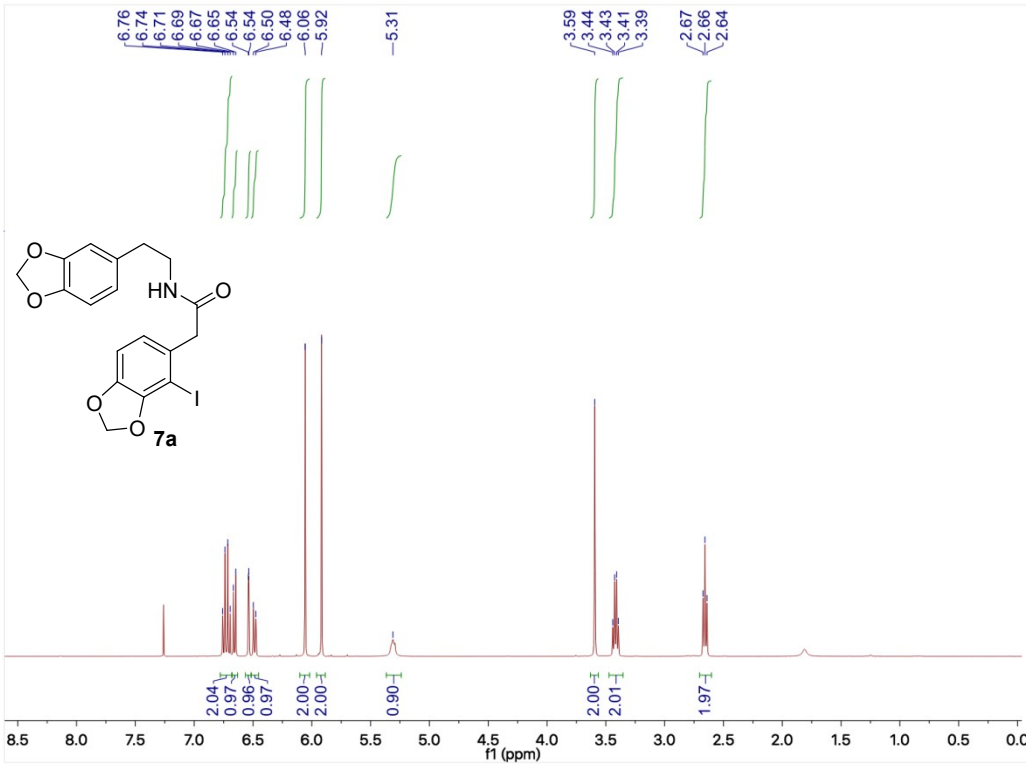

Figure S12. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **7a**

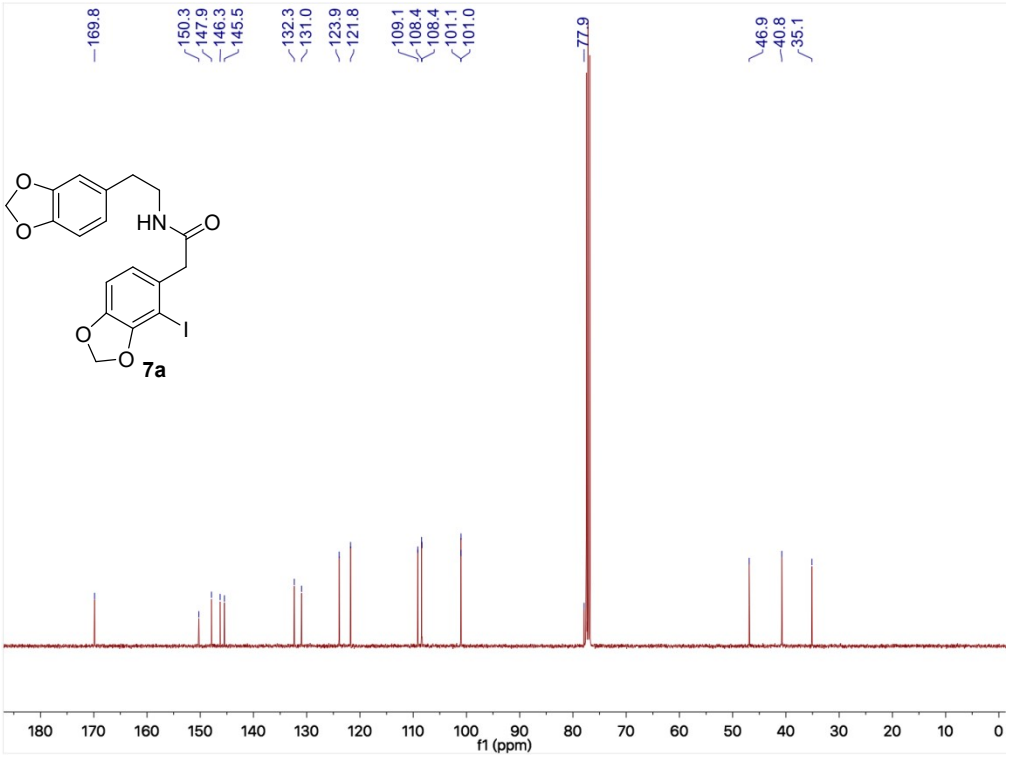

Figure S13. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **7a**

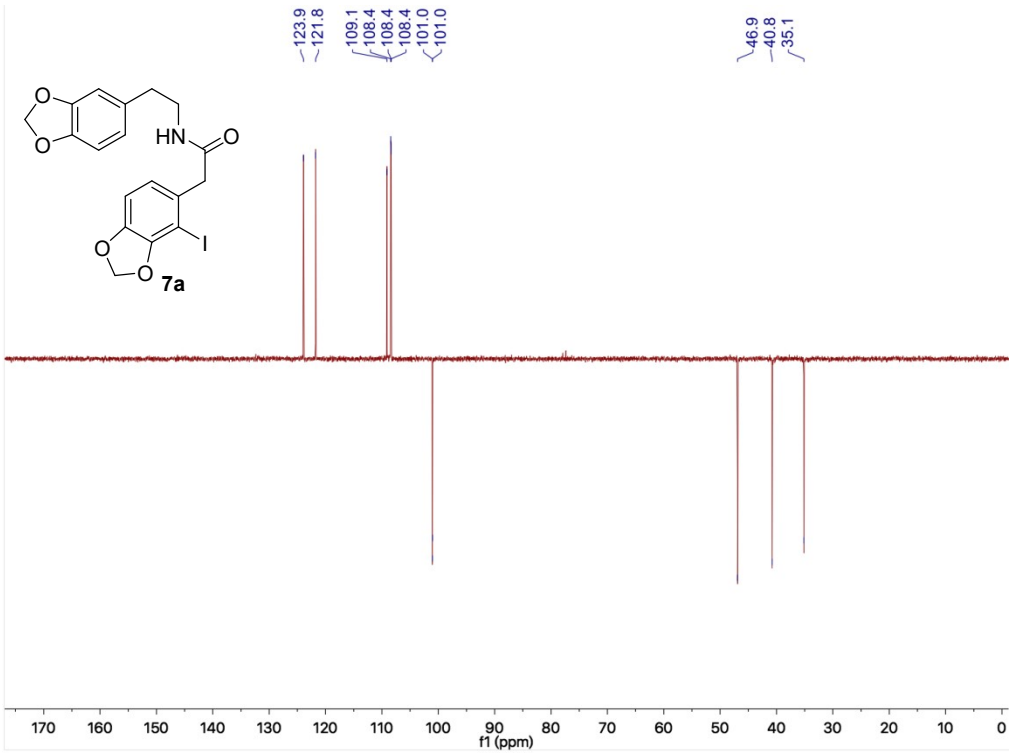

Figure S14. DEPT135 spectrum (100 MHz, $CDCl_3$) of compound **7a**

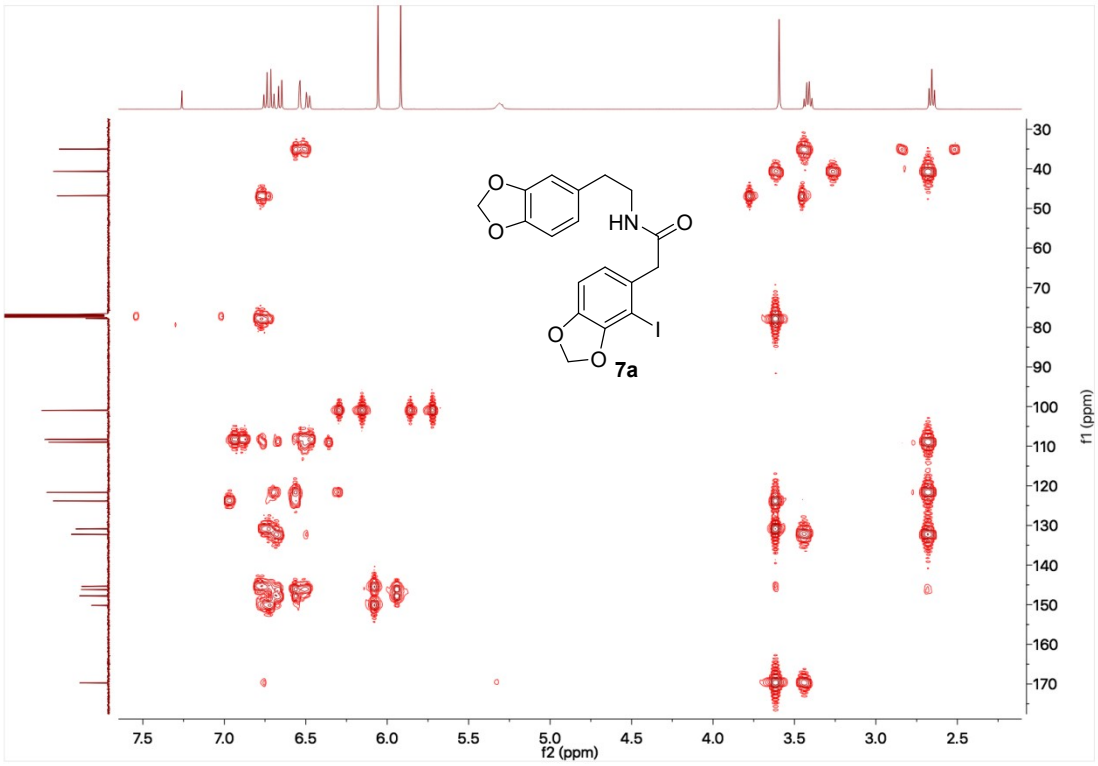

Figure S15. HMBC spectrum (400 MHz, $CDCl_3$) of compound **7a**

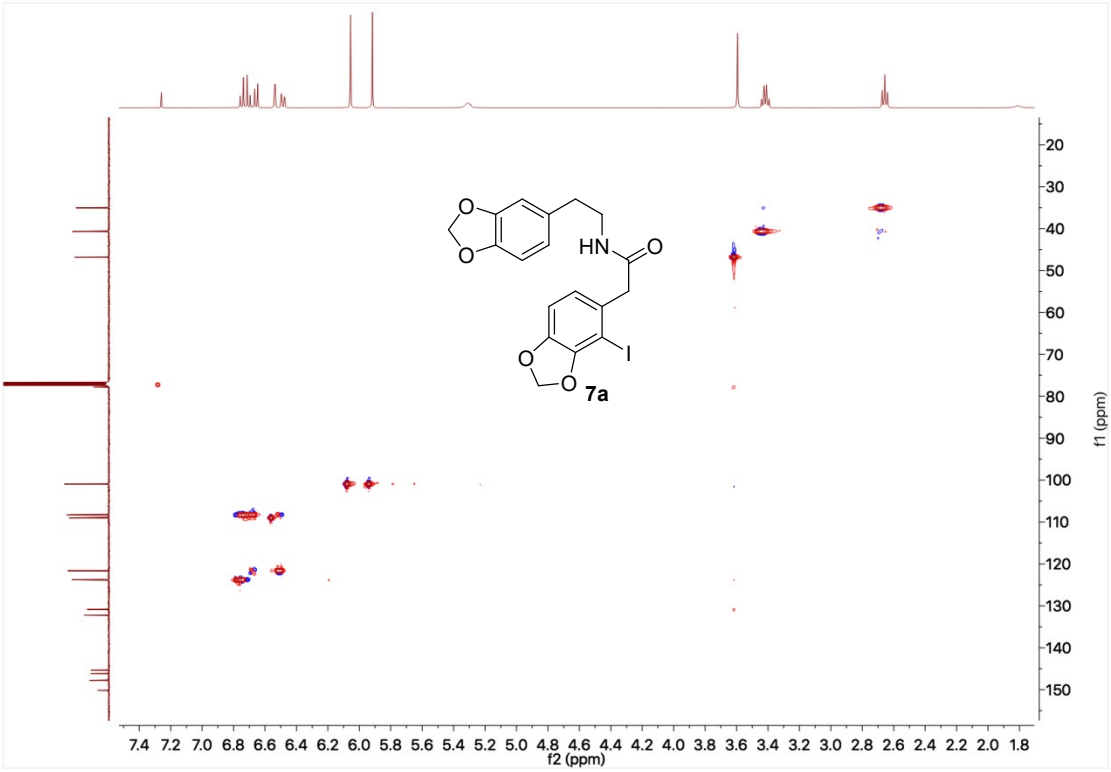

Figure S16. HSQC spectrum (400 MHz, $CDCl_3$) of compound **7a**

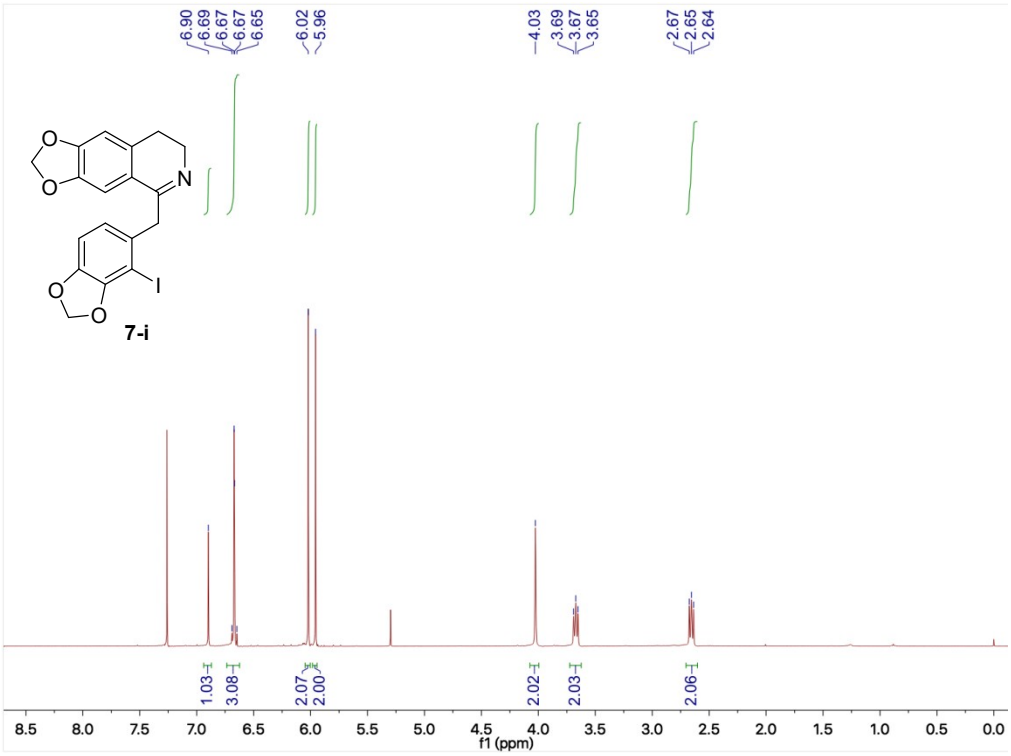

Figure S17. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **7-i**

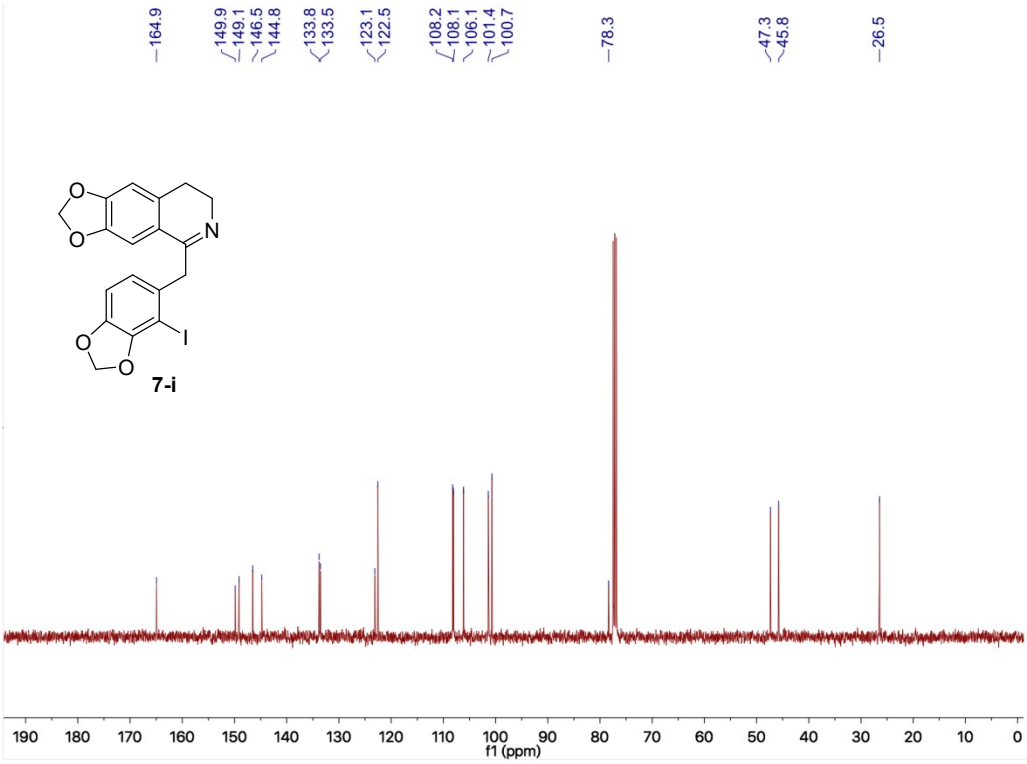

Figure S18. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **7-i**

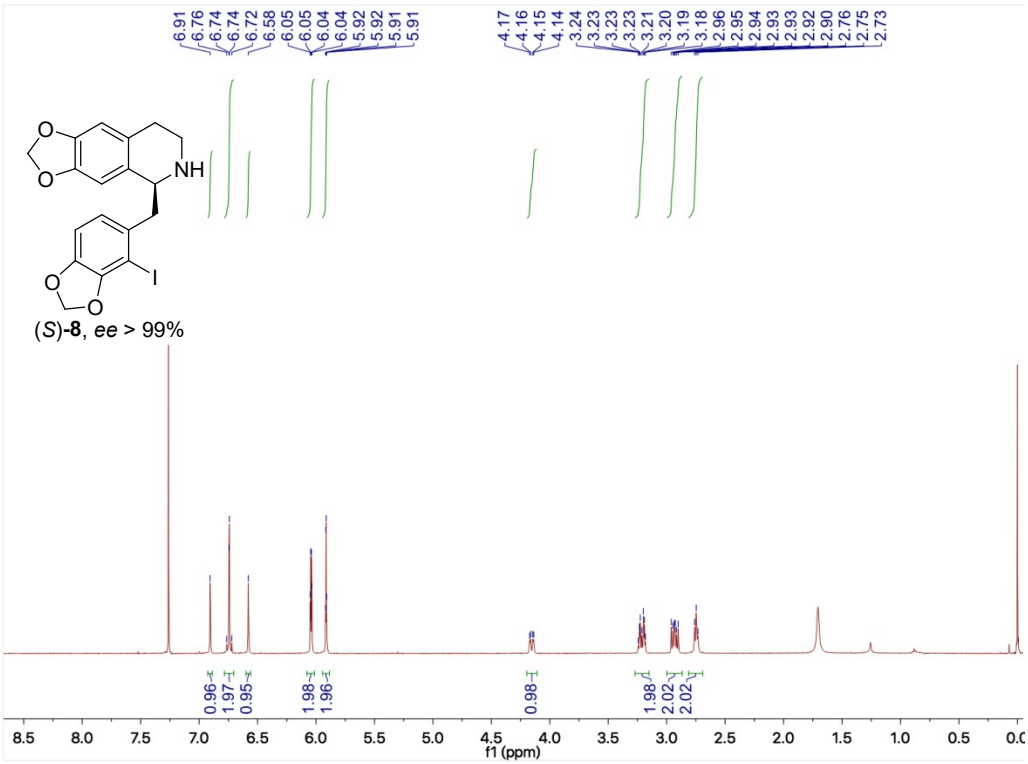

Figure S19. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound (*S*)-**8**

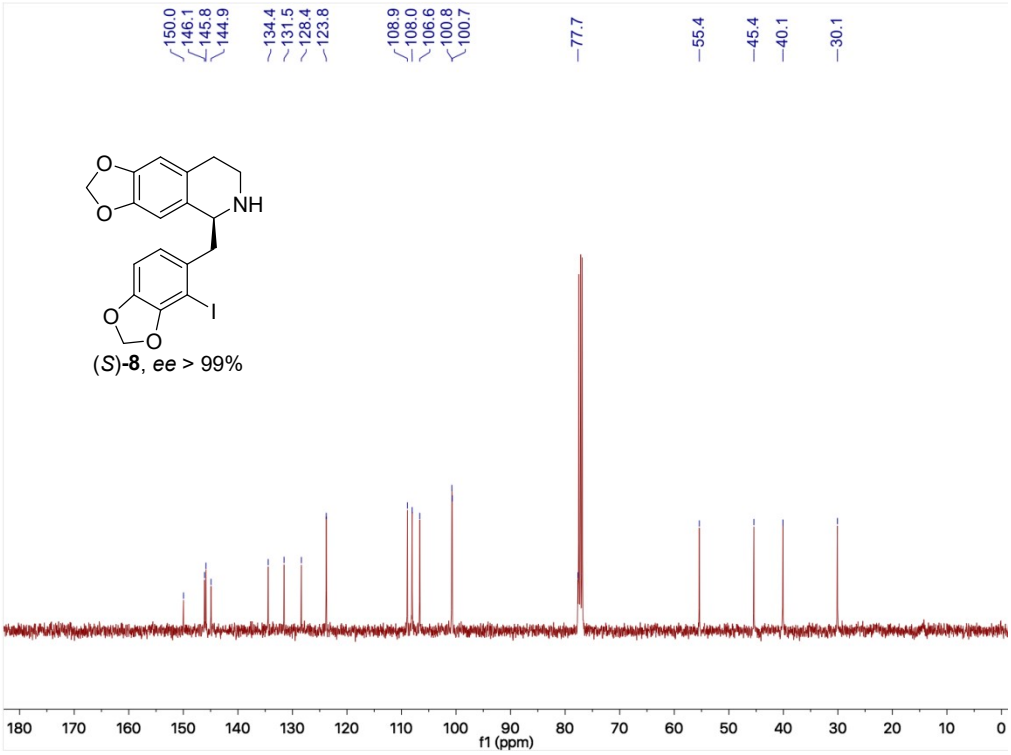

Figure S20. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound (*S*)-**8**

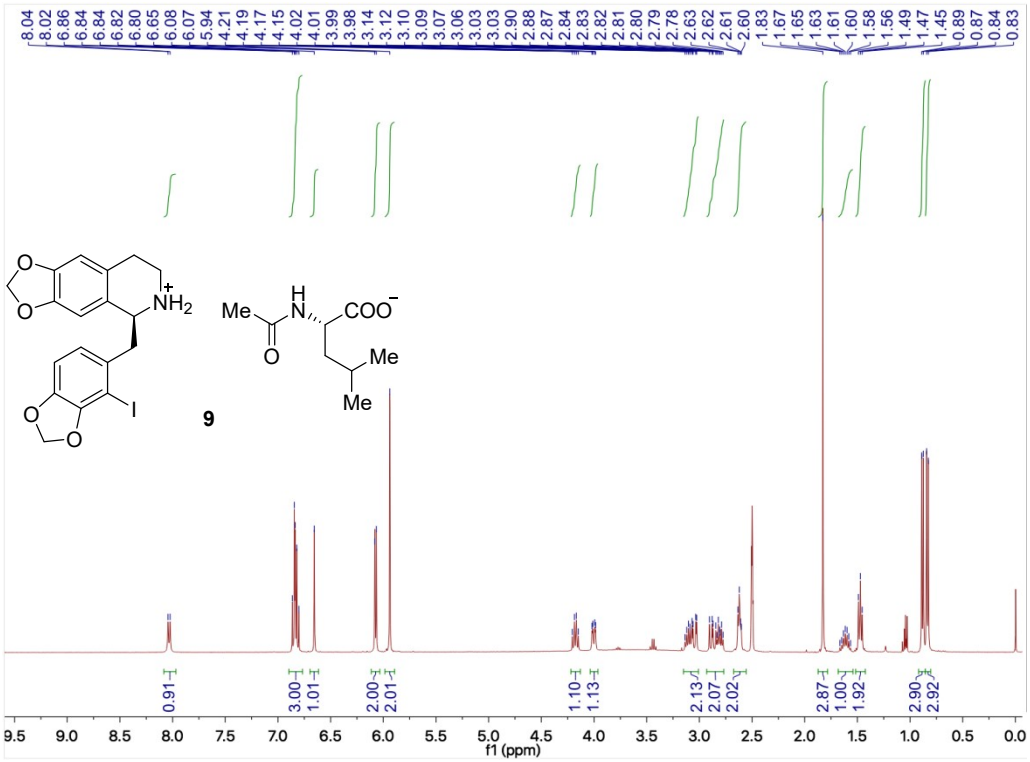

Figure S21. ^{1}H NMR spectrum (400 MHz, DMSO-d_6) of compound **9**

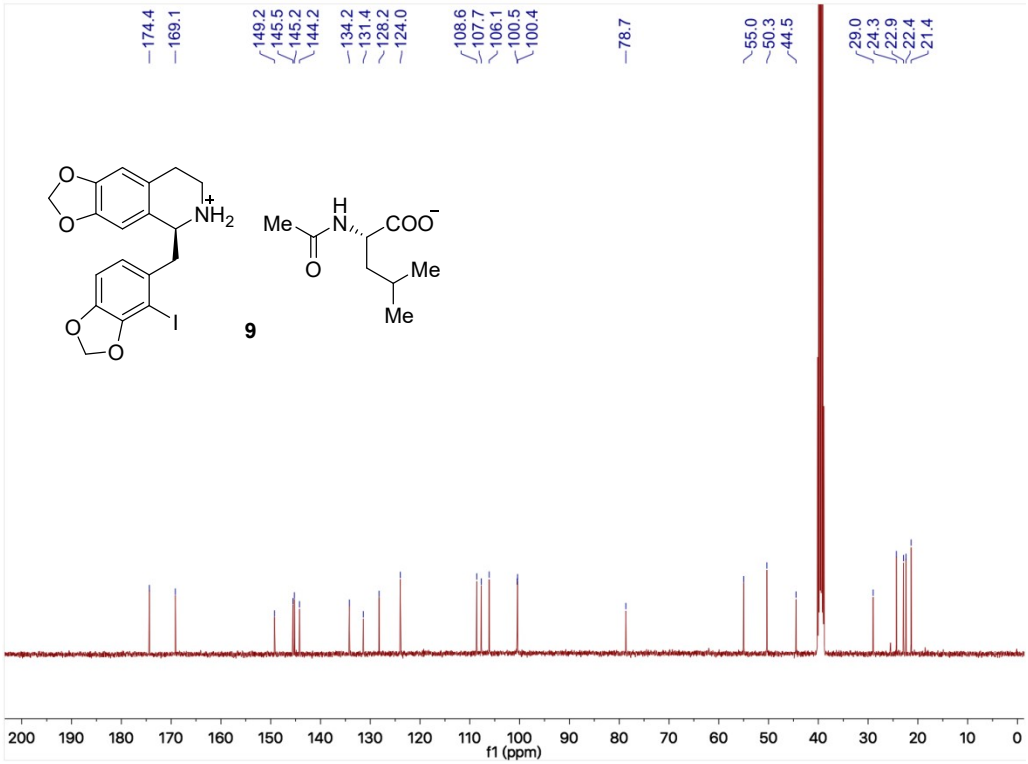

Figure S22. ^{13}C NMR spectrum (100 MHz, DMSO-d_6) of compound **9**

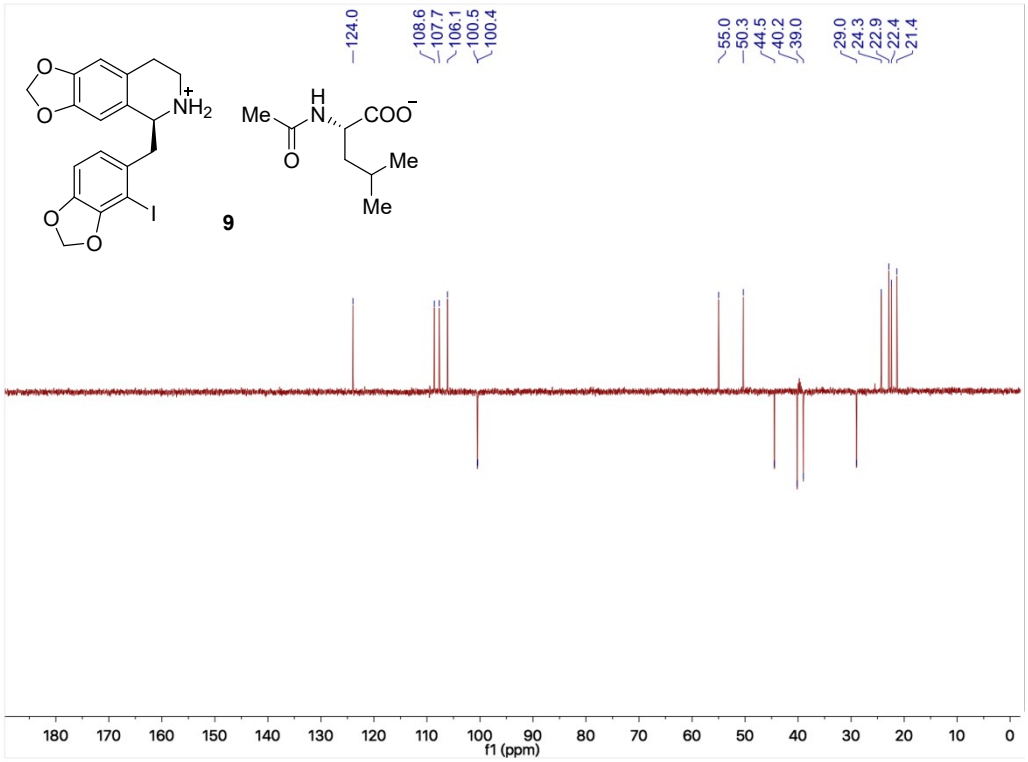

Figure S23. DEPT 135 spectrum (100 MHz, DMSO-d_6) of compound **9**

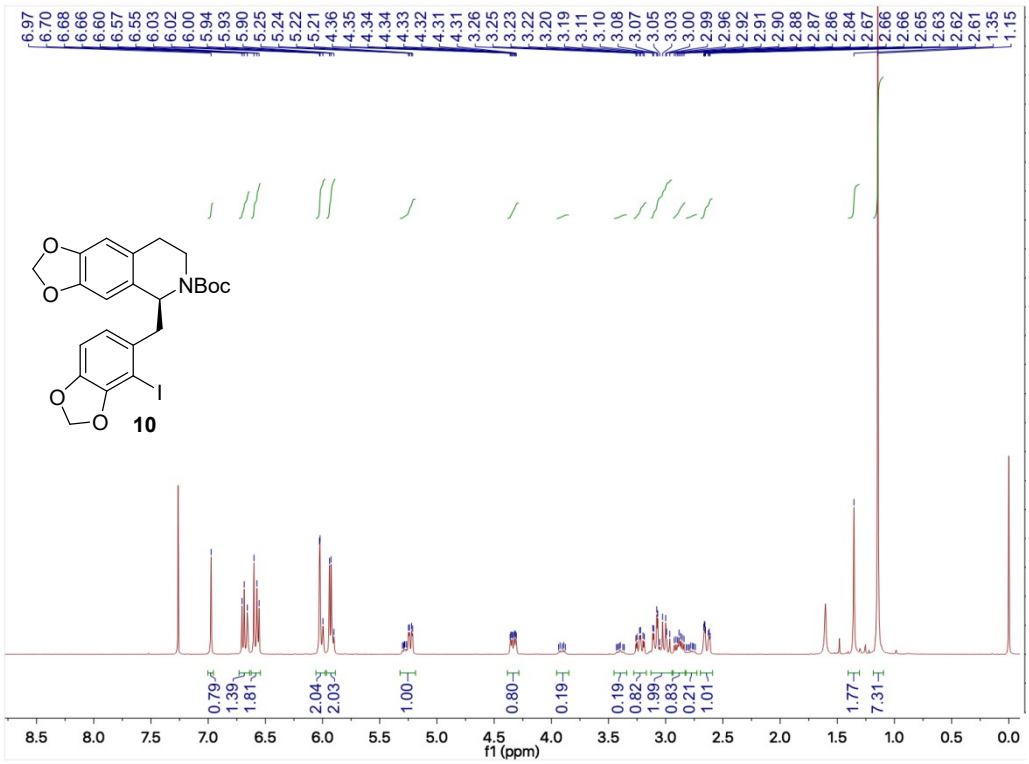

Figure S24. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **10**

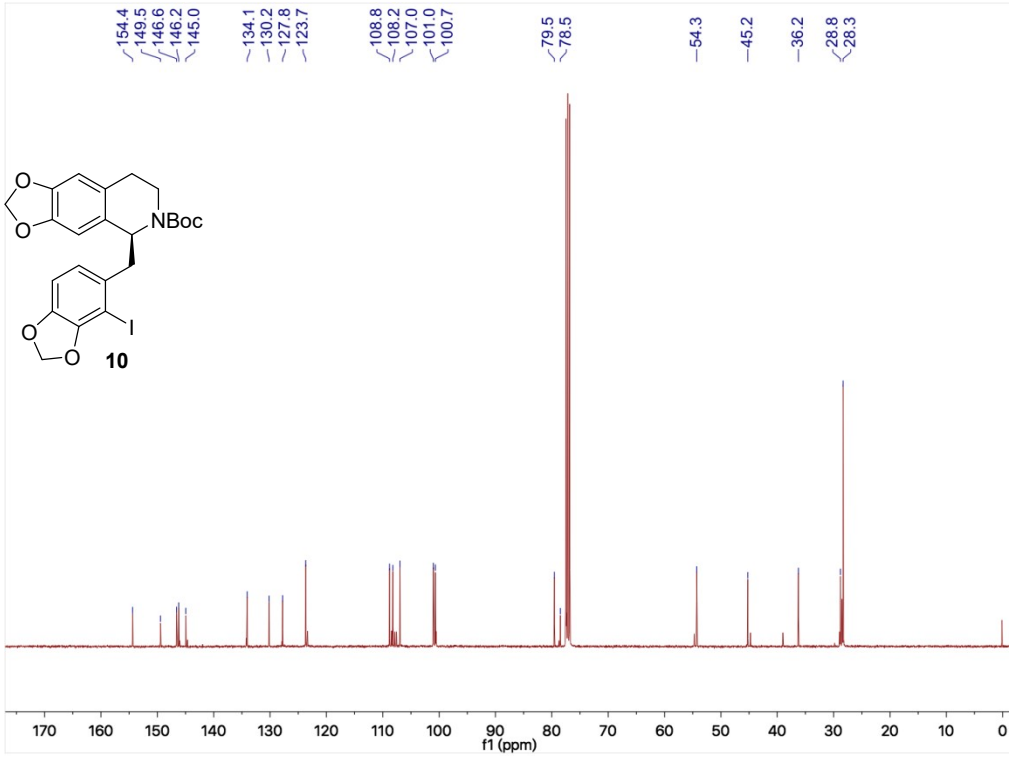

Figure S25. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **10**

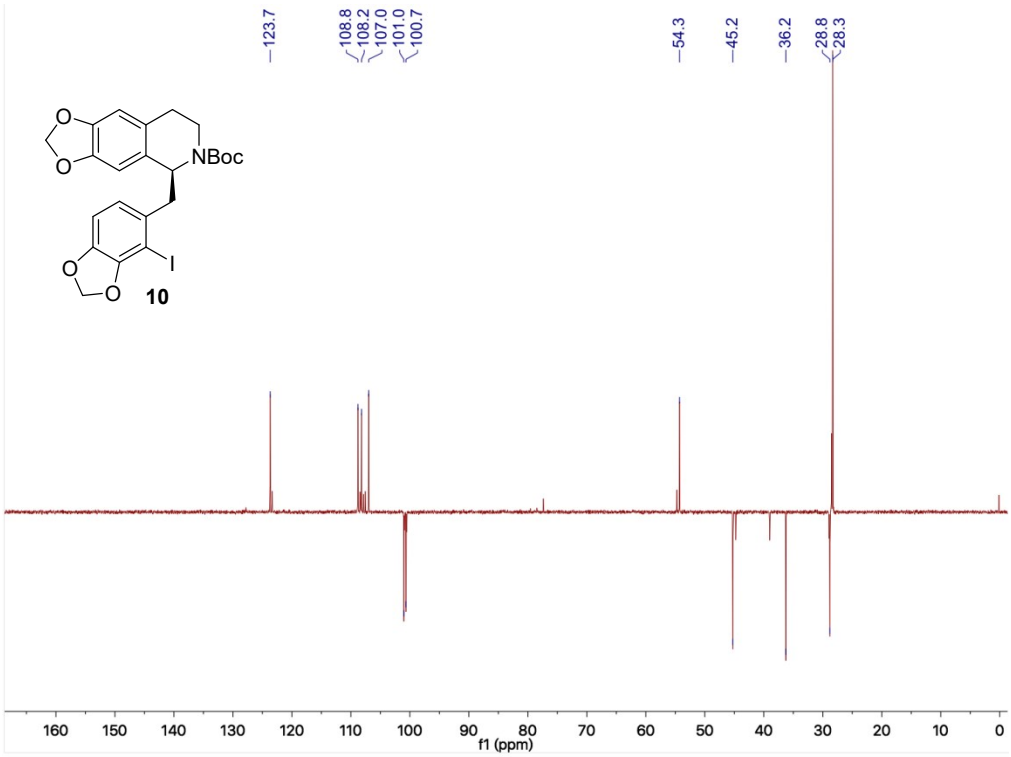

Figure S26. DEPT 135 spectrum (100 MHz, $CDCl_3$) of compound **10**

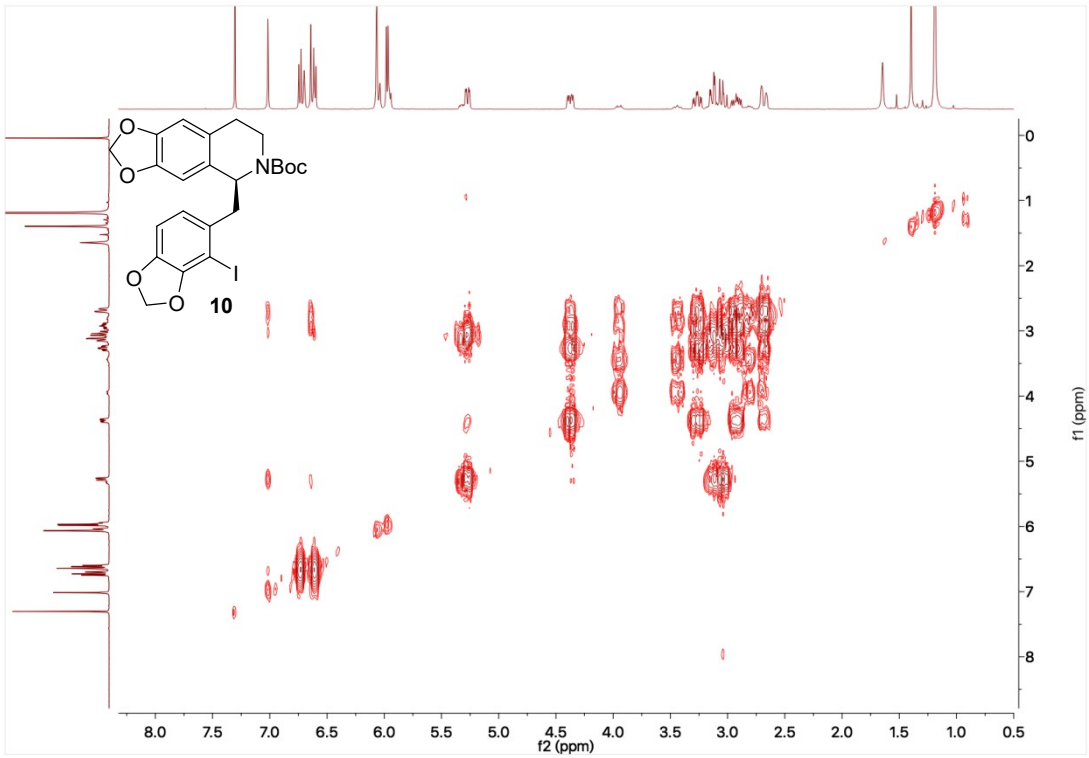

Figure S27. ^1H-^1H COSY spectrum (400 MHz, $CDCl_3$) of compound **10**

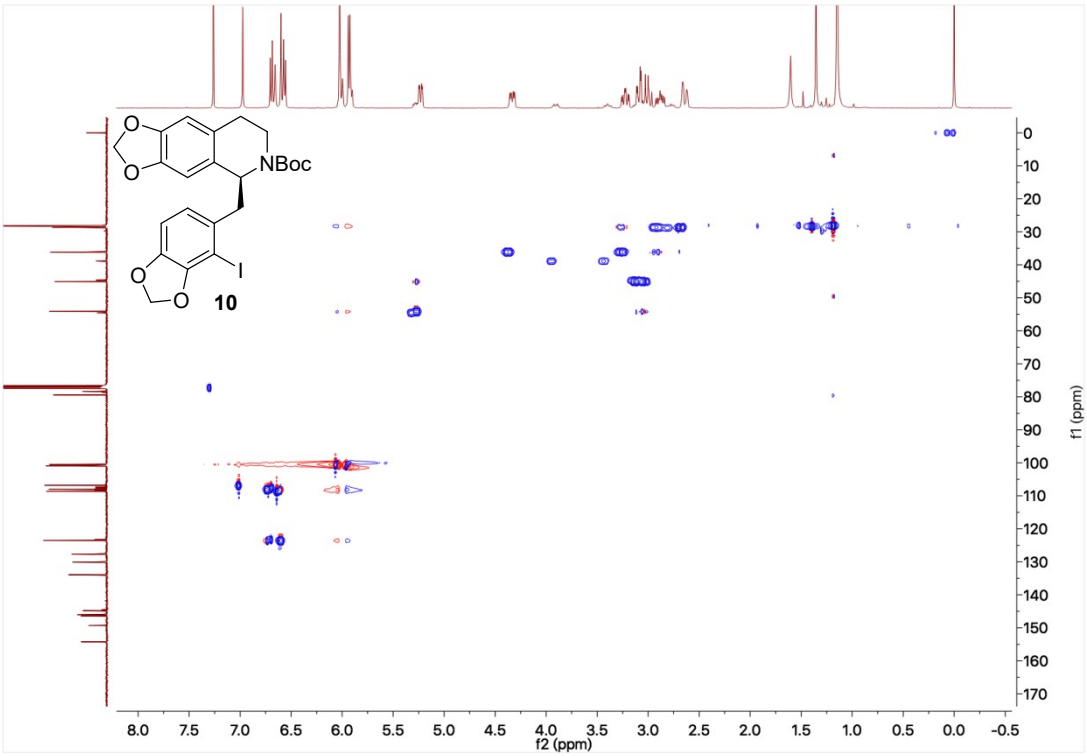

Figure S28. HSQC spectrum (400 MHz, $CDCl_3$) of compound **10**

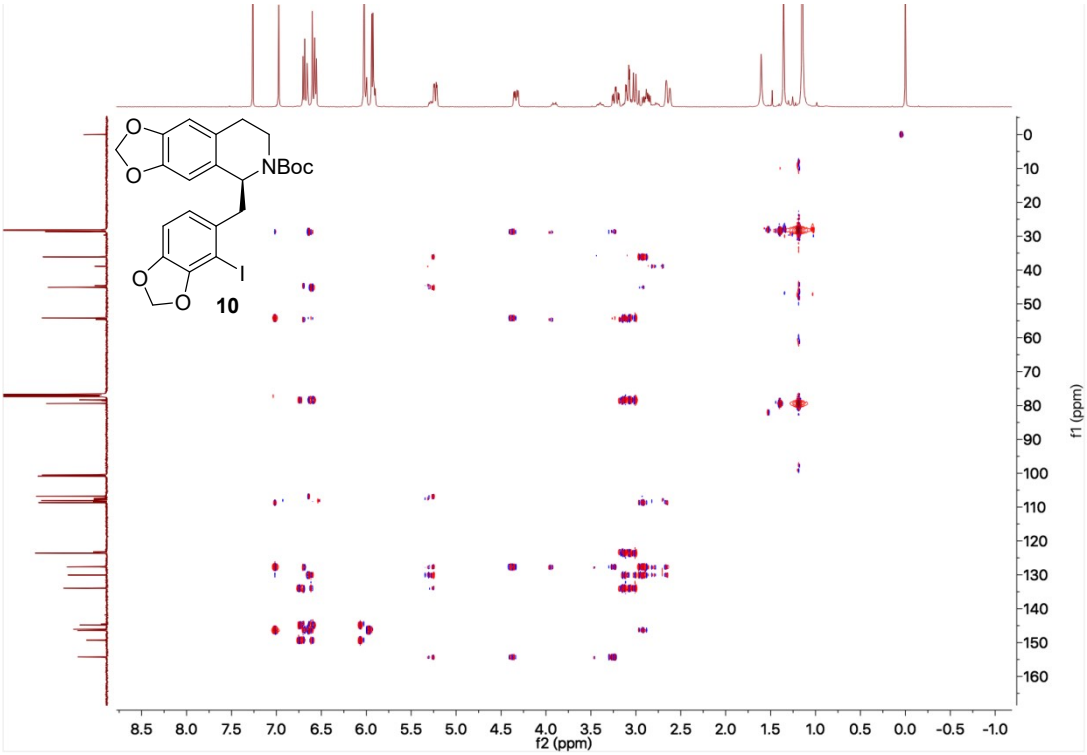

Figure S29. HMBC spectrum (400 MHz, $CDCl_3$) of compound **10**

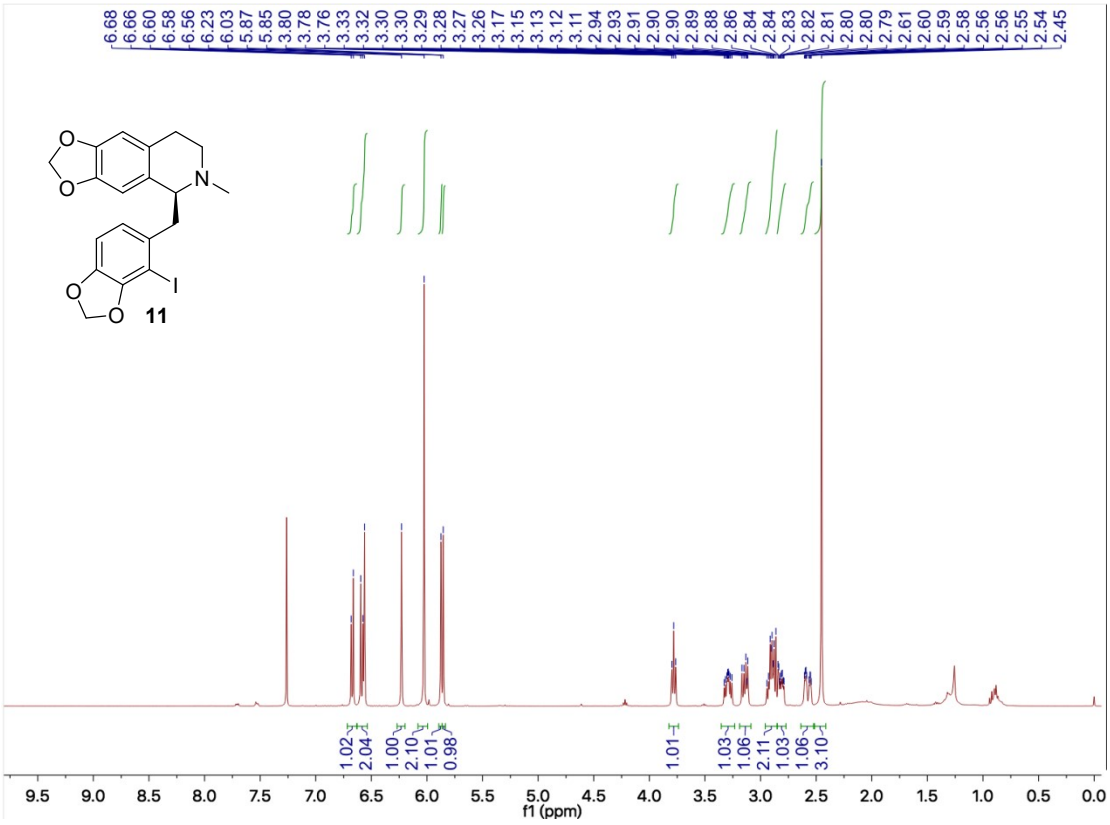

Figure S30. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **11**

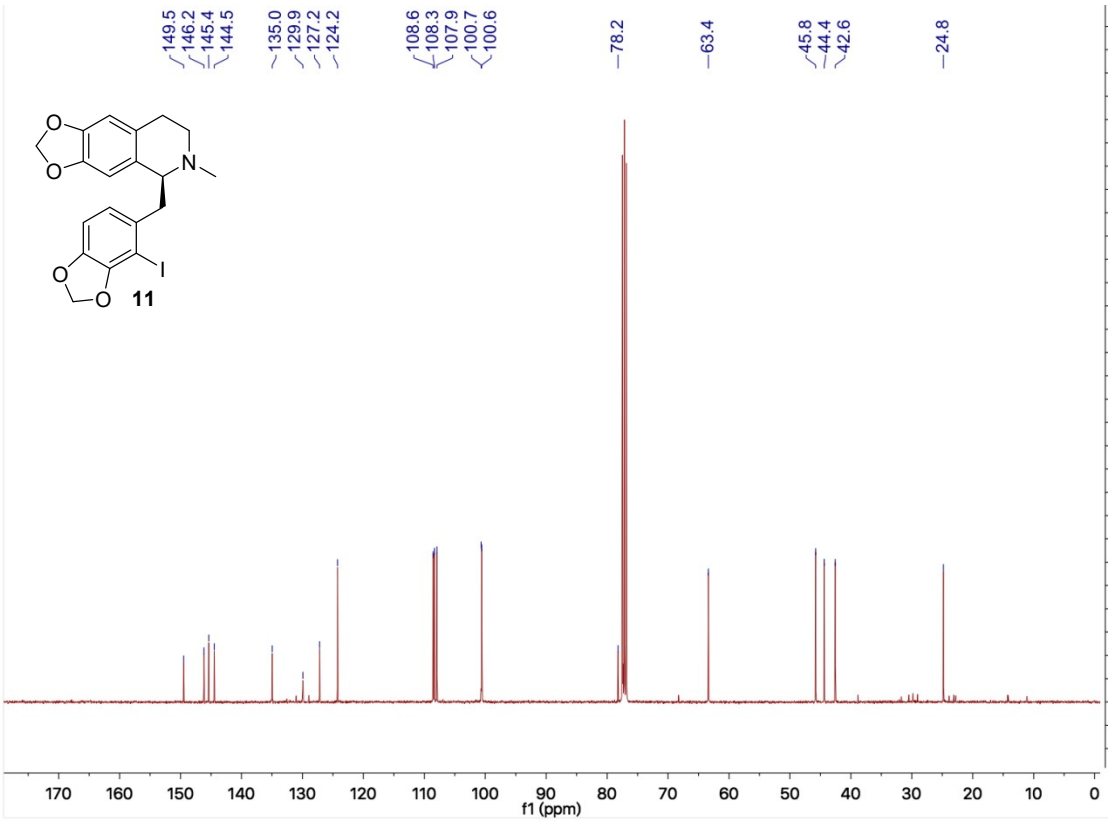

Figure S31. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **11**

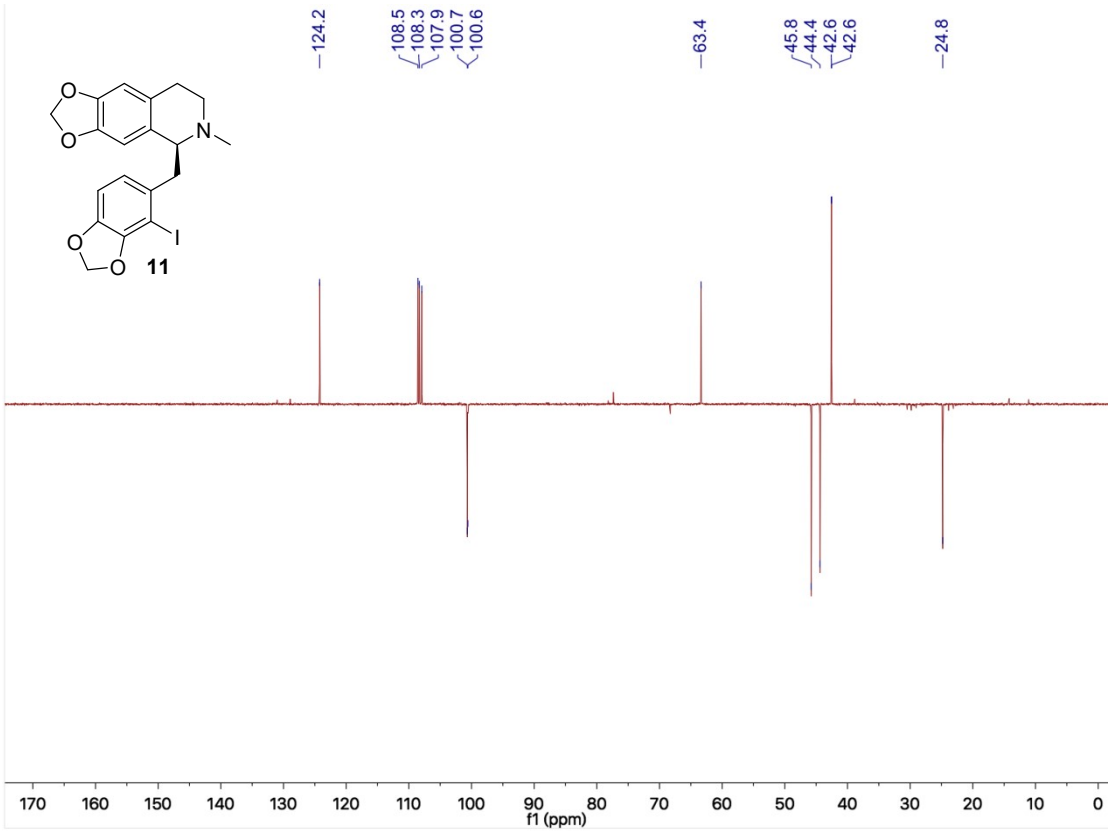

Figure S32. DEPT 135 spectrum (100 MHz, $CDCl_3$) of compound **11**

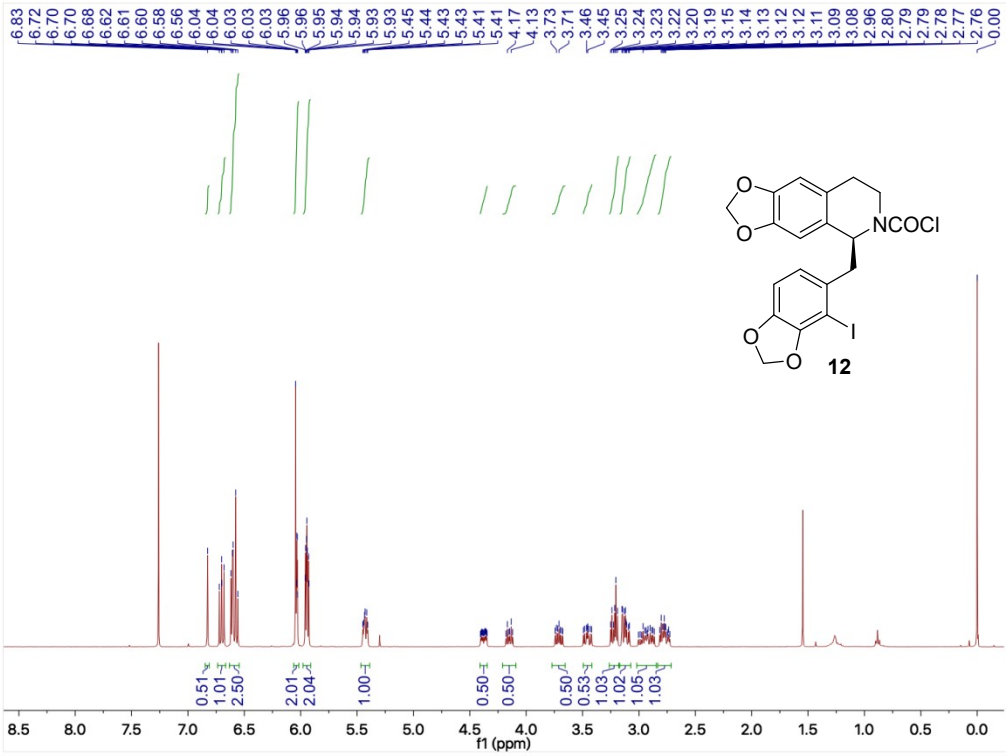

Figure S33. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **12**

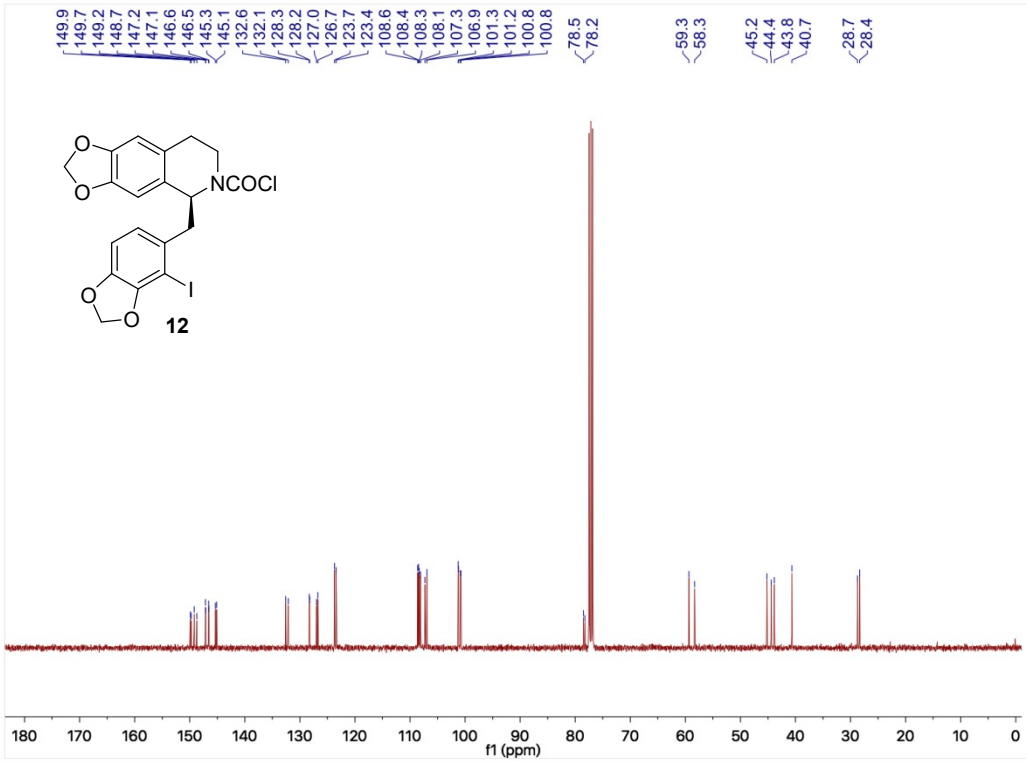

Figure S34. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **12**

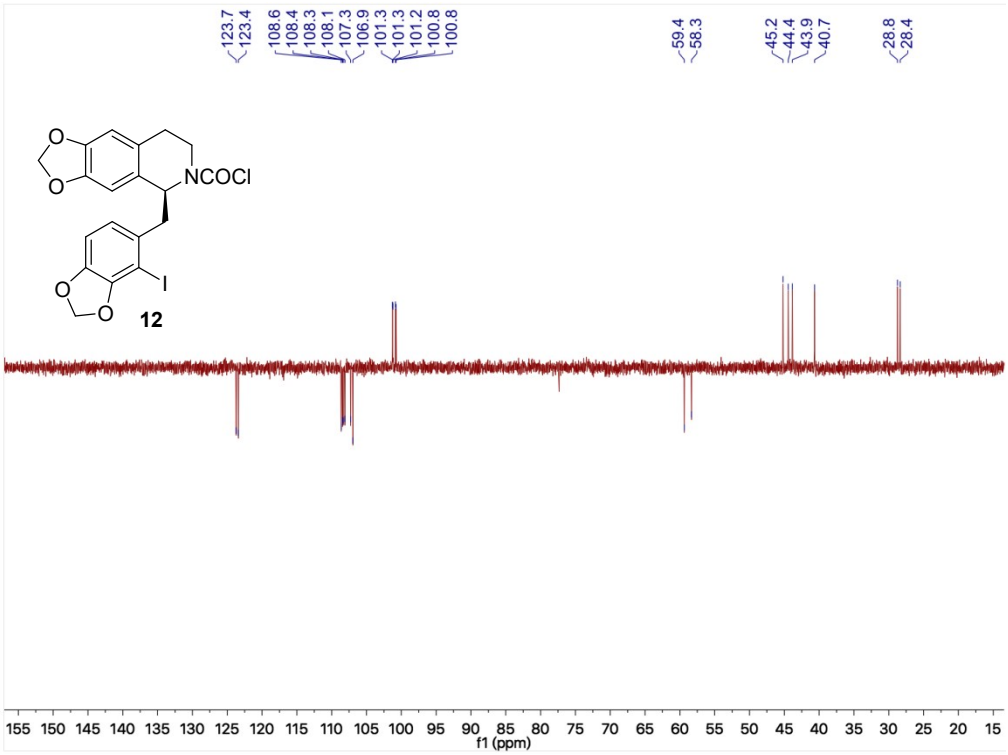

Figure S35. DEPT 135 spectrum (100 MHz, $CDCl_3$) of compound **12**

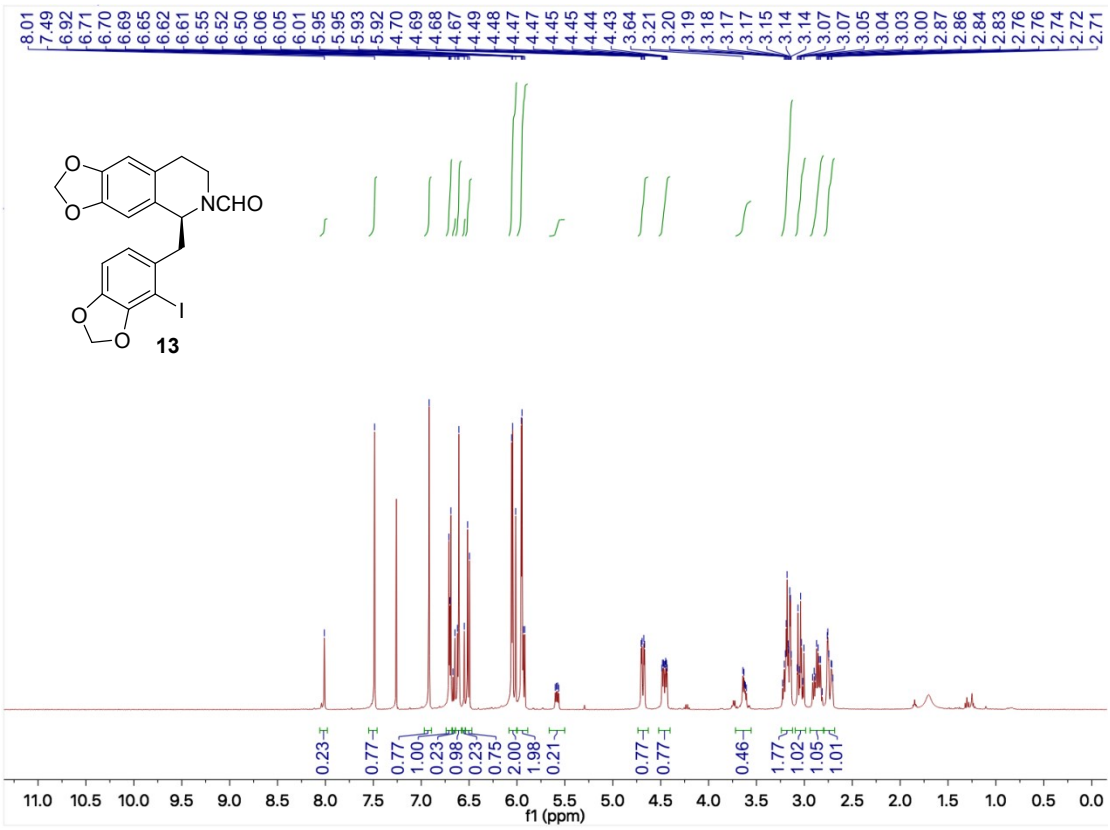

Figure S36. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **13**

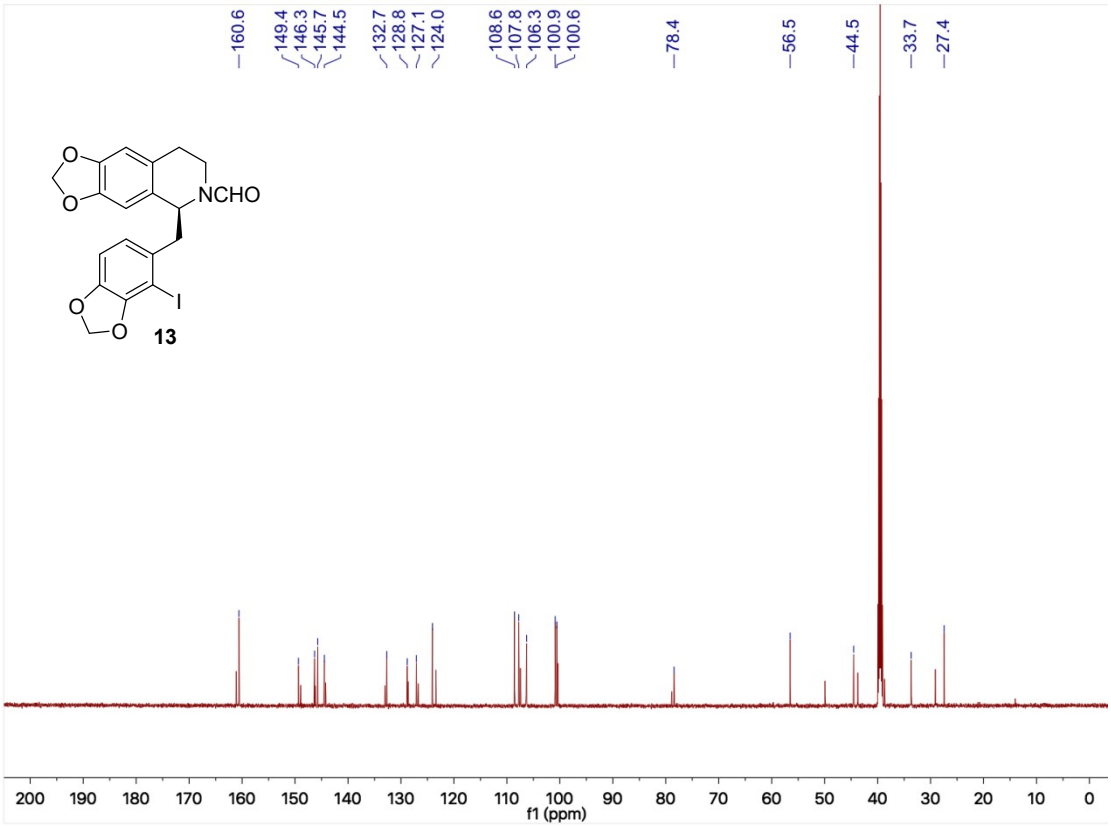

Figure S37. ^{13}C NMR spectrum (150 MHz, DMSO-d_6) of compound **13**

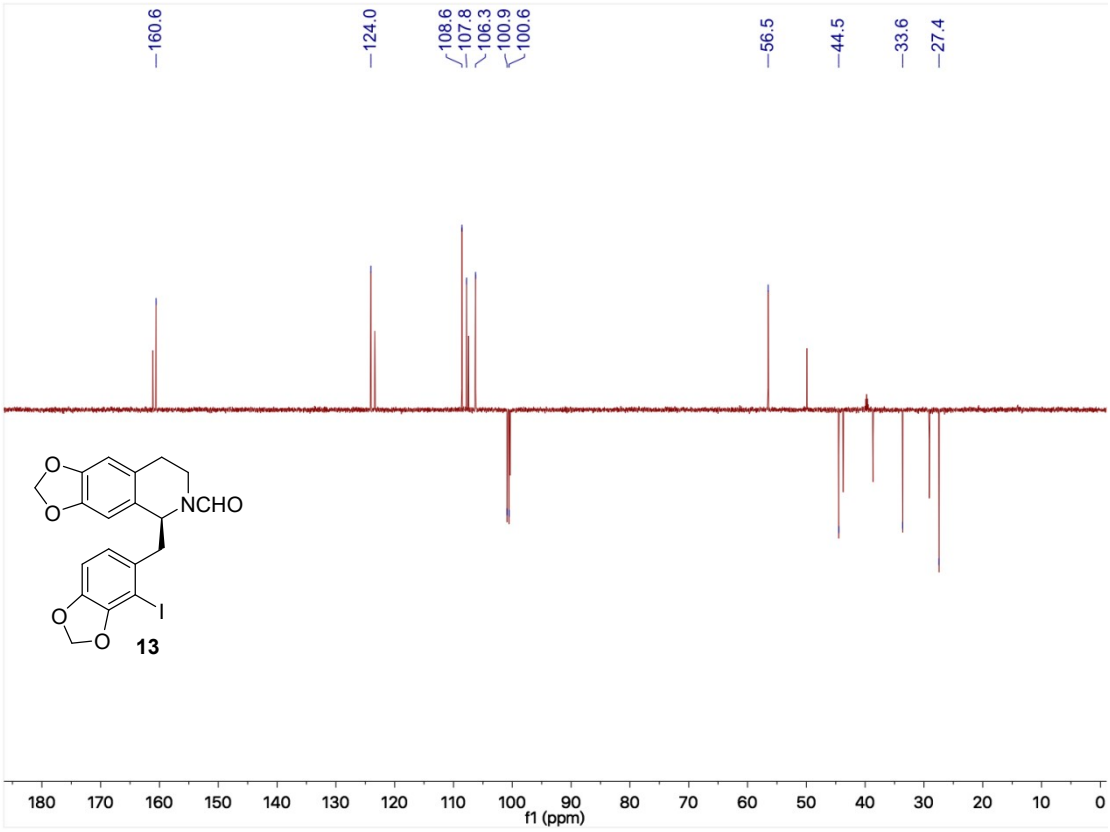

Figure S38. DEPT 135 spectrum (150 MHz, DMSO-d_6) of compound **13**

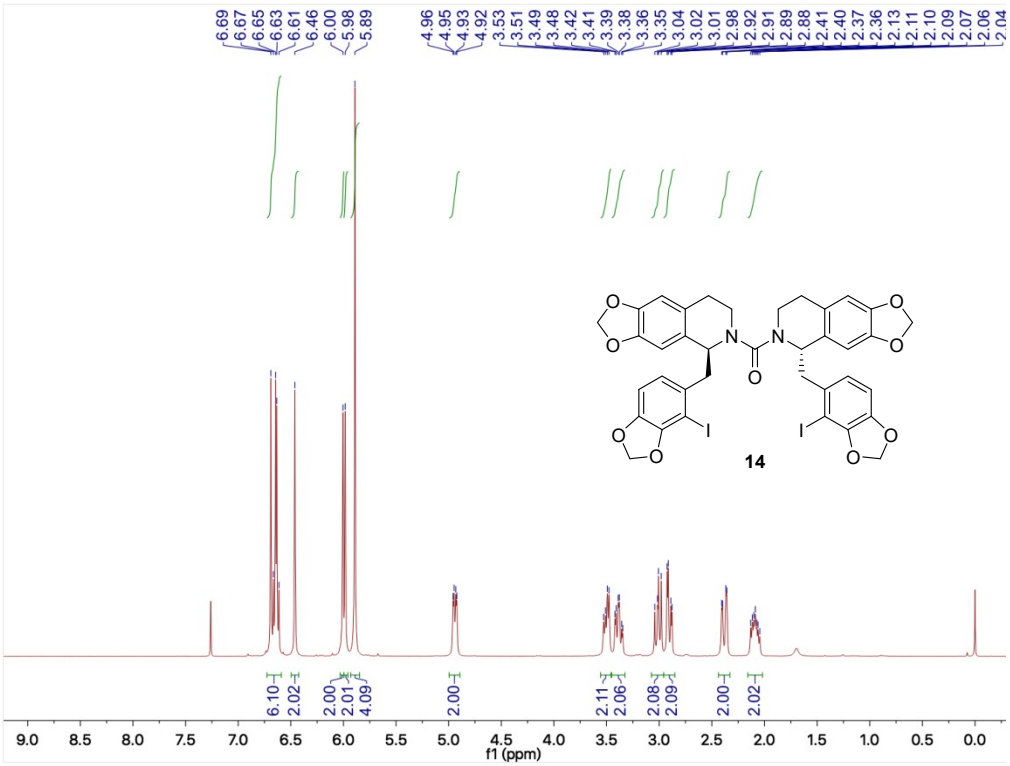

Figure S39. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **14**

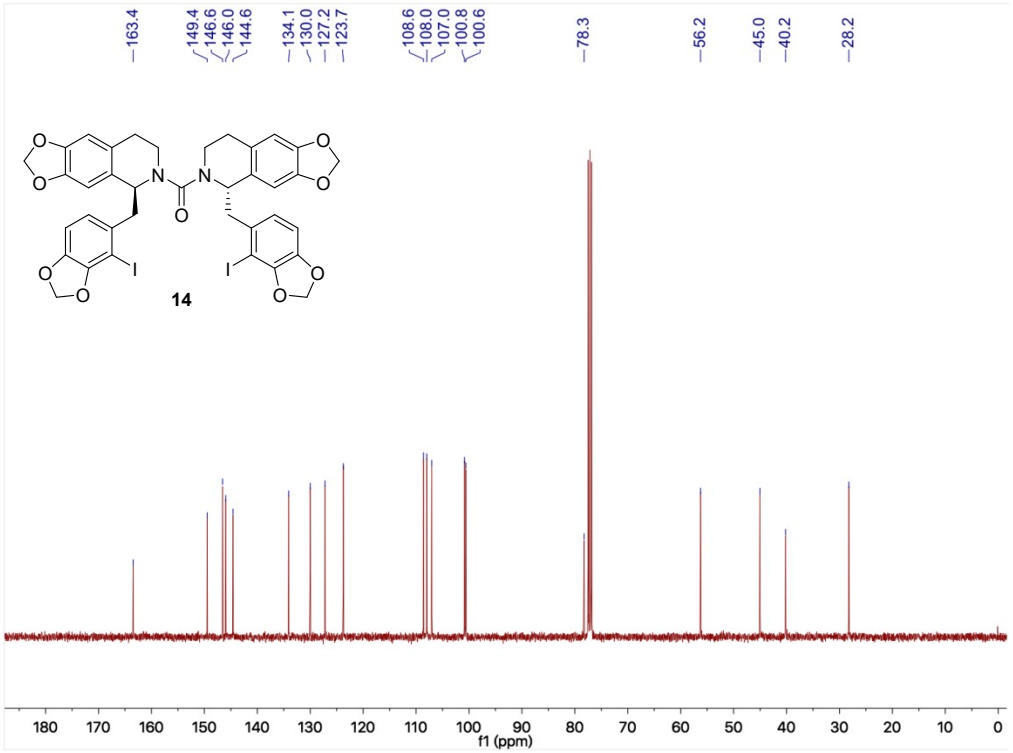

Figure S40. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **14**

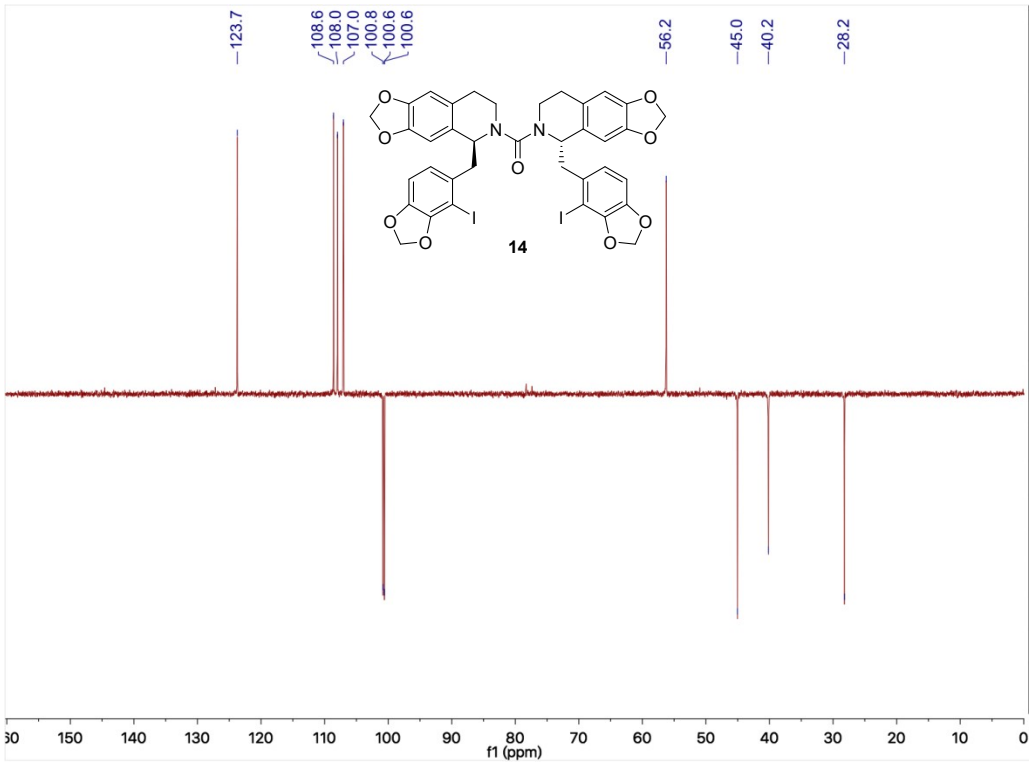

Figure S41. DEPT 135 spectrum (100 MHz, $CDCl_3$) of compound **14**

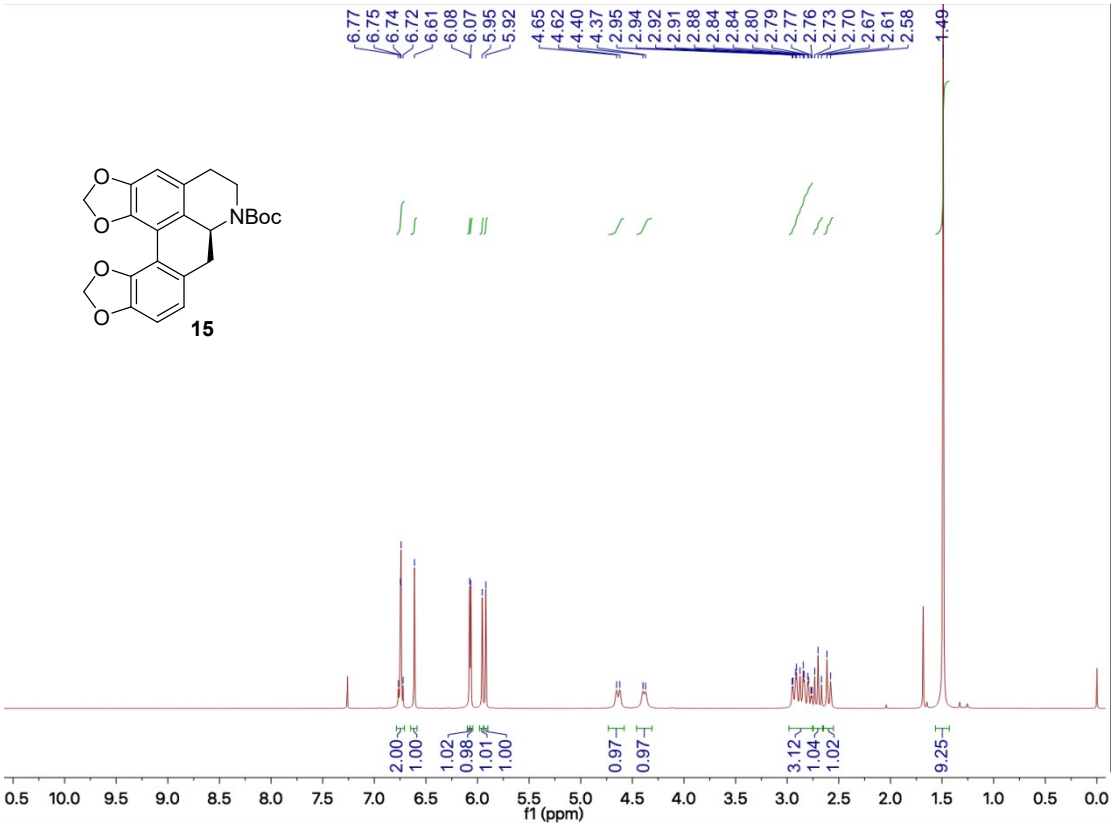

Figure S42. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **15**

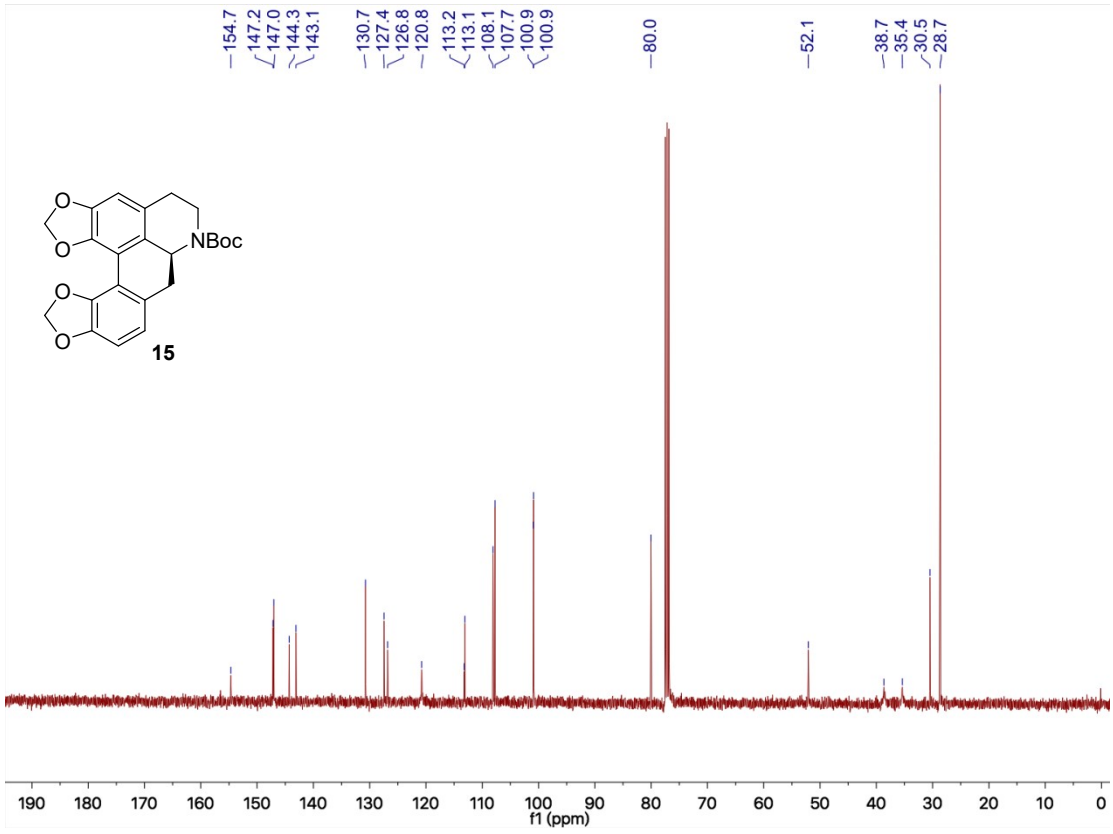

Figure S43. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **15**

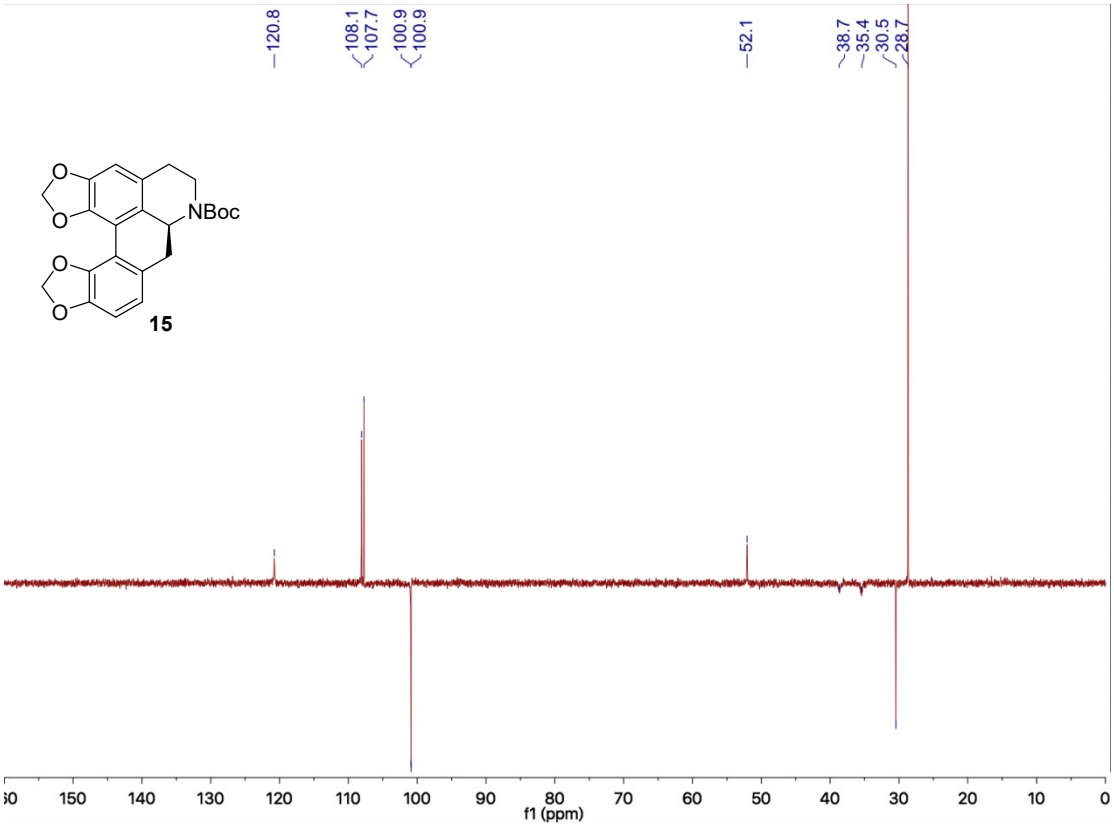

Figure S44. DEPT 135 spectrum (100 MHz, $CDCl_3$) of compound **15**

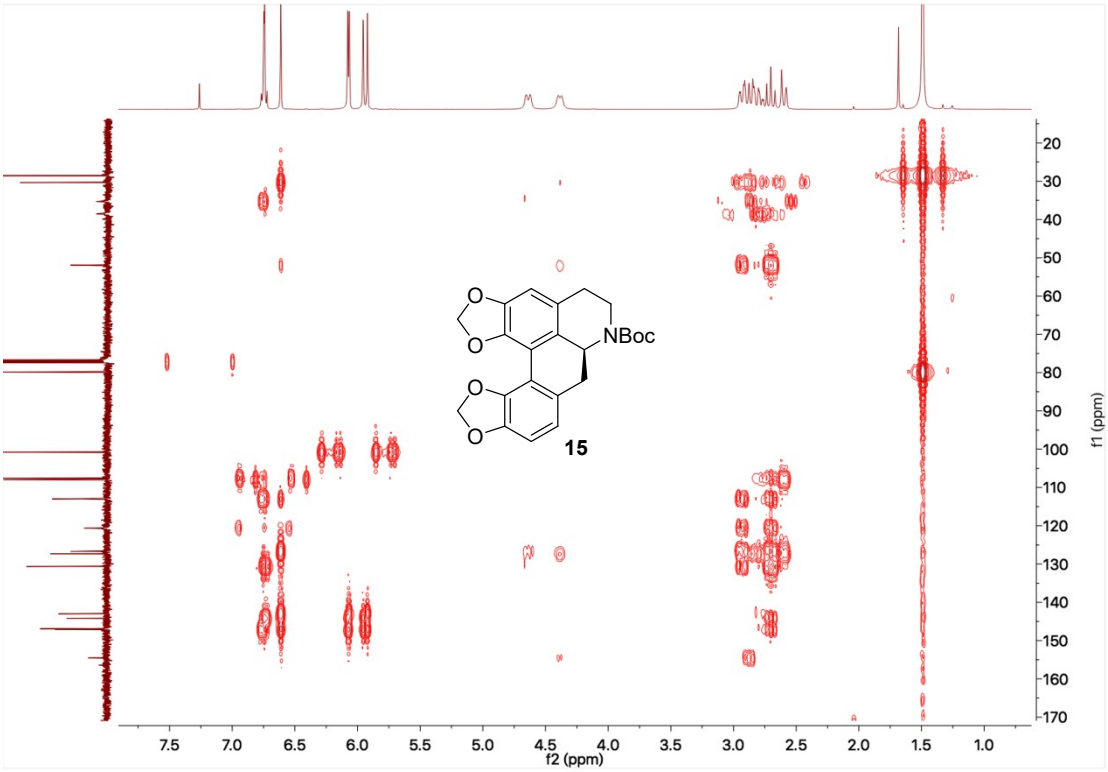

Figure S45. HMBC spectrum (400 MHz, $CDCl_3$) of compound **15**

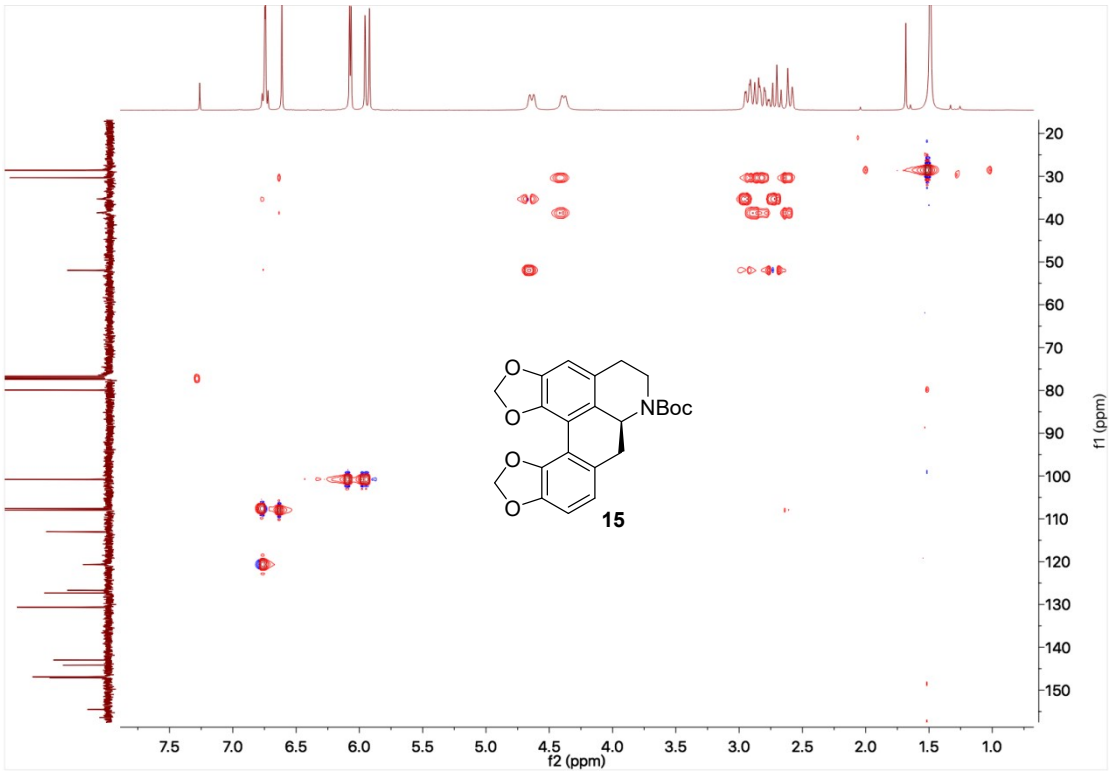

Figure S46. HSQC spectrum (400 MHz, $CDCl_3$) of compound **15**

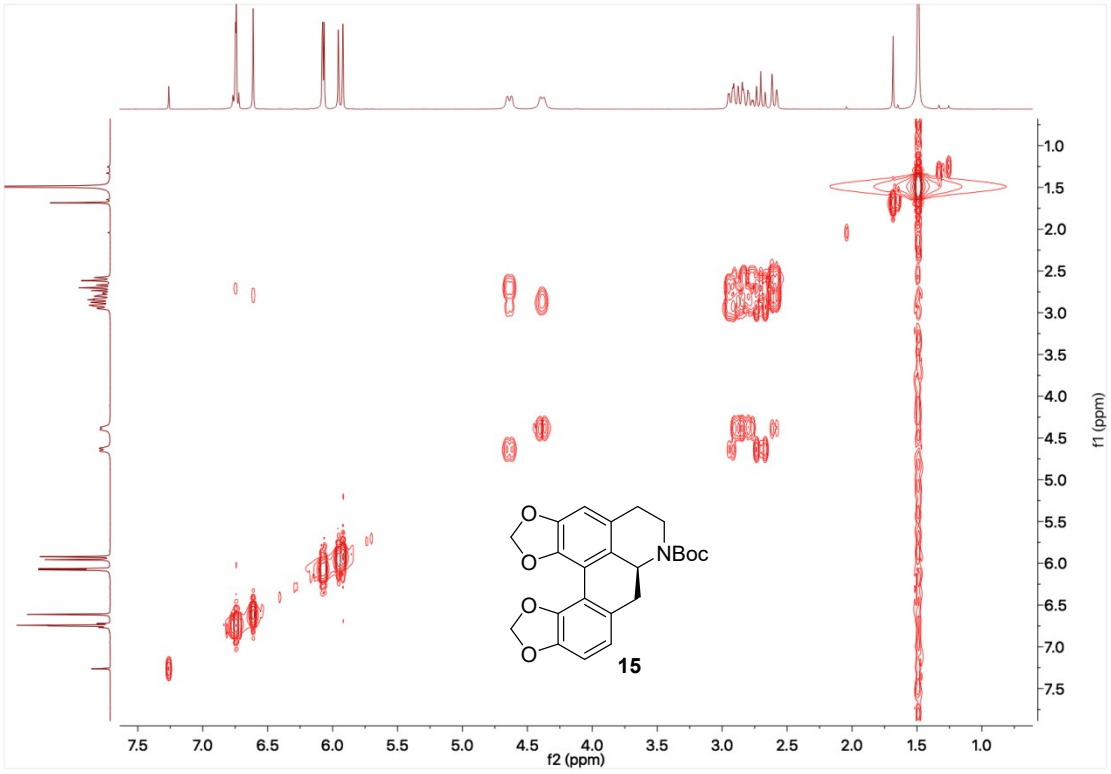

Figure S47. ^{1}H-^{1}H COSY spectrum (400 MHz, $CDCl_3$) of compound **15**

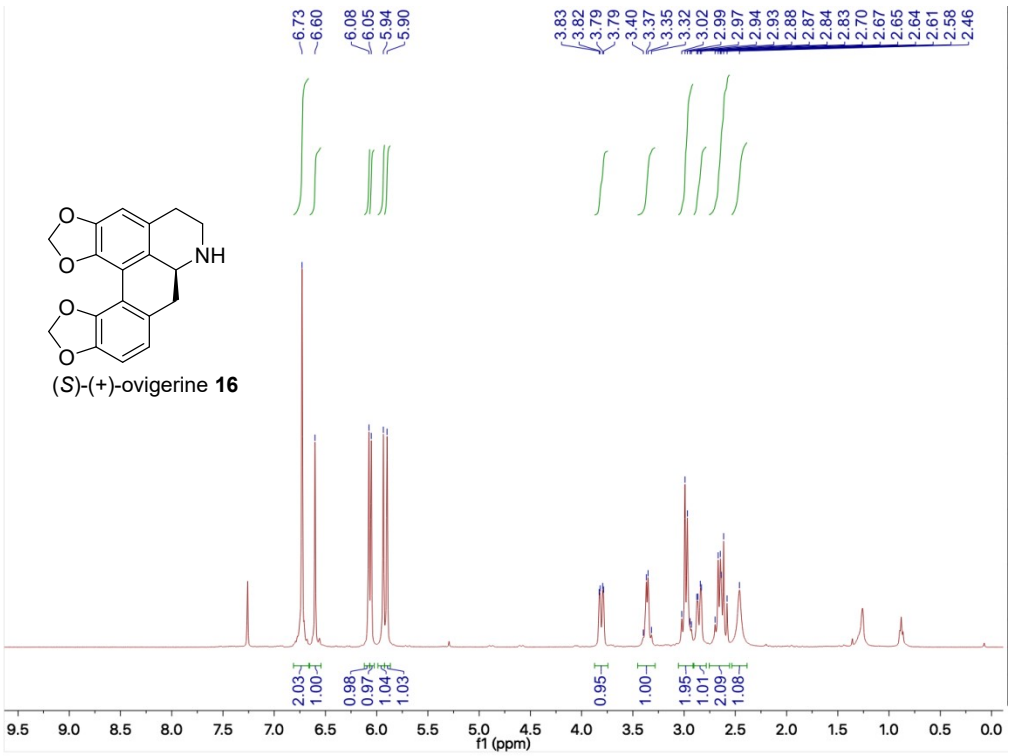

Figure S48. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **16**

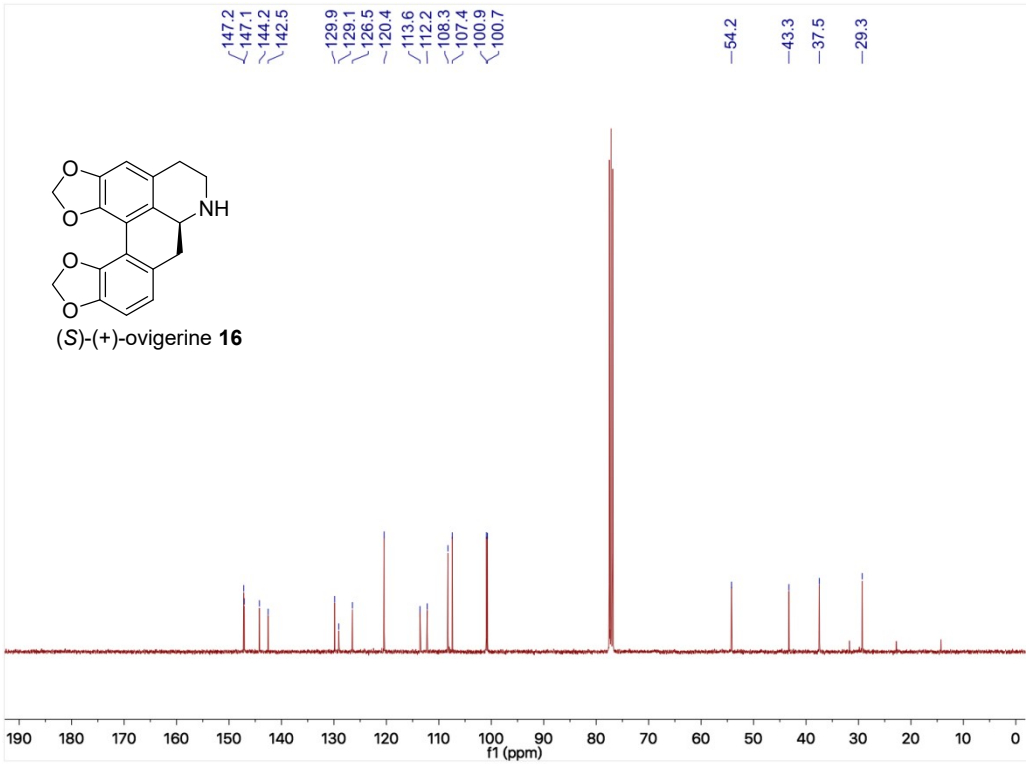

Figure S49. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **16**

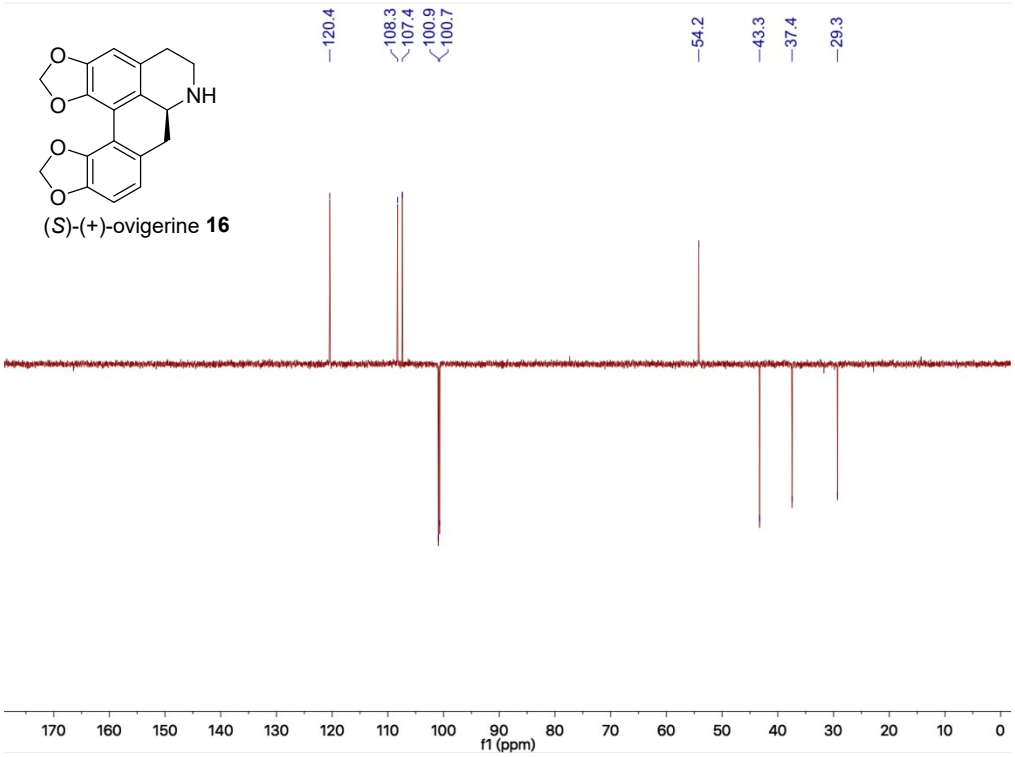

Figure S50. DEPT 135 spectrum (100 MHz, $CDCl_3$) of compound **16**

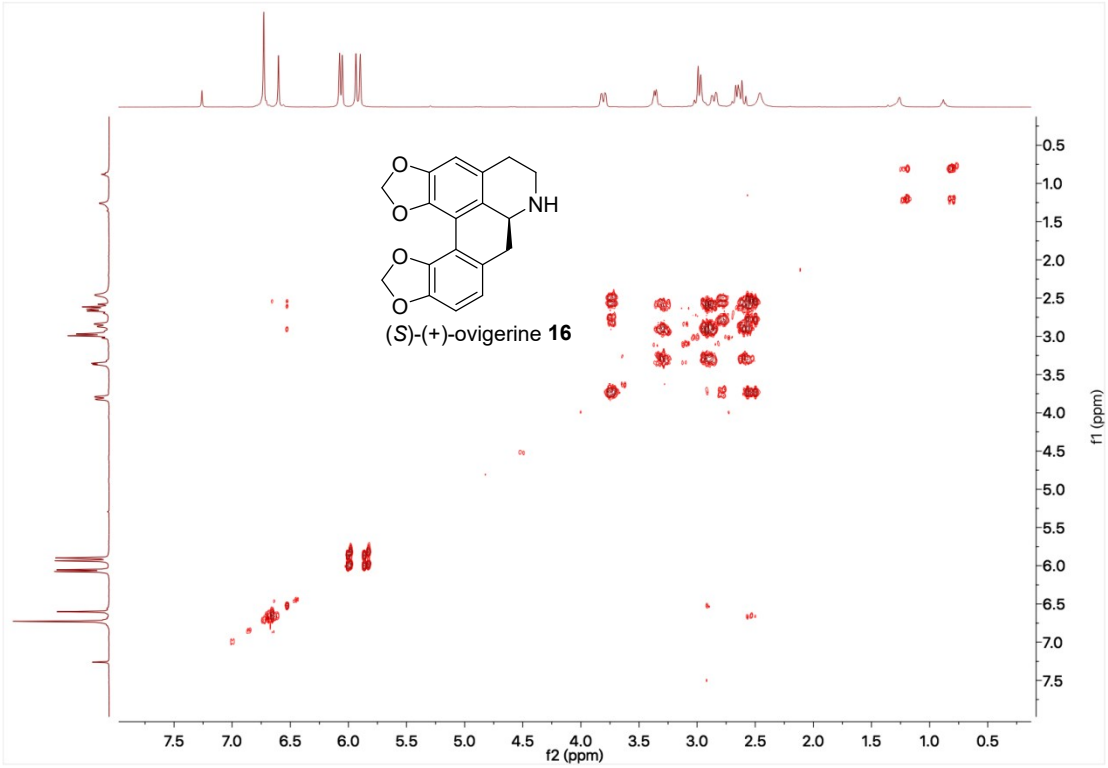

Figure S51. ^1H-^1H COSY spectrum (400 MHz, $CDCl_3$) of compound **16**

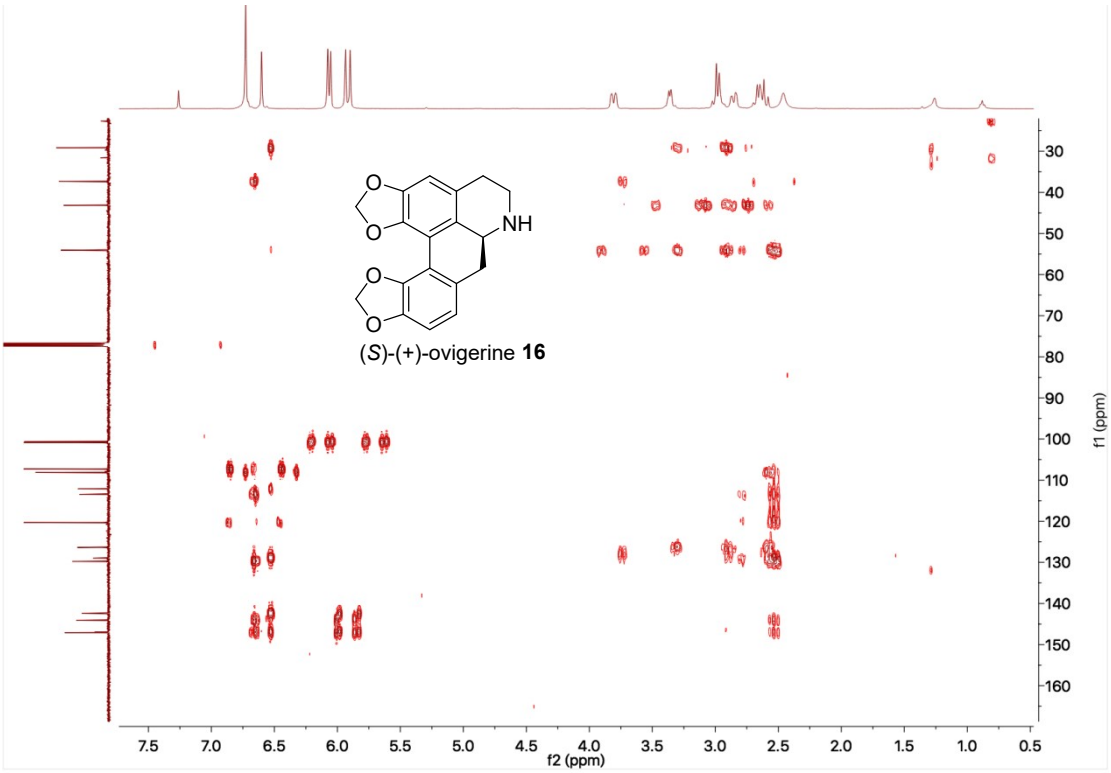

Figure S52. HMBC spectrum (400 MHz, $CDCl_3$) of compound **16**

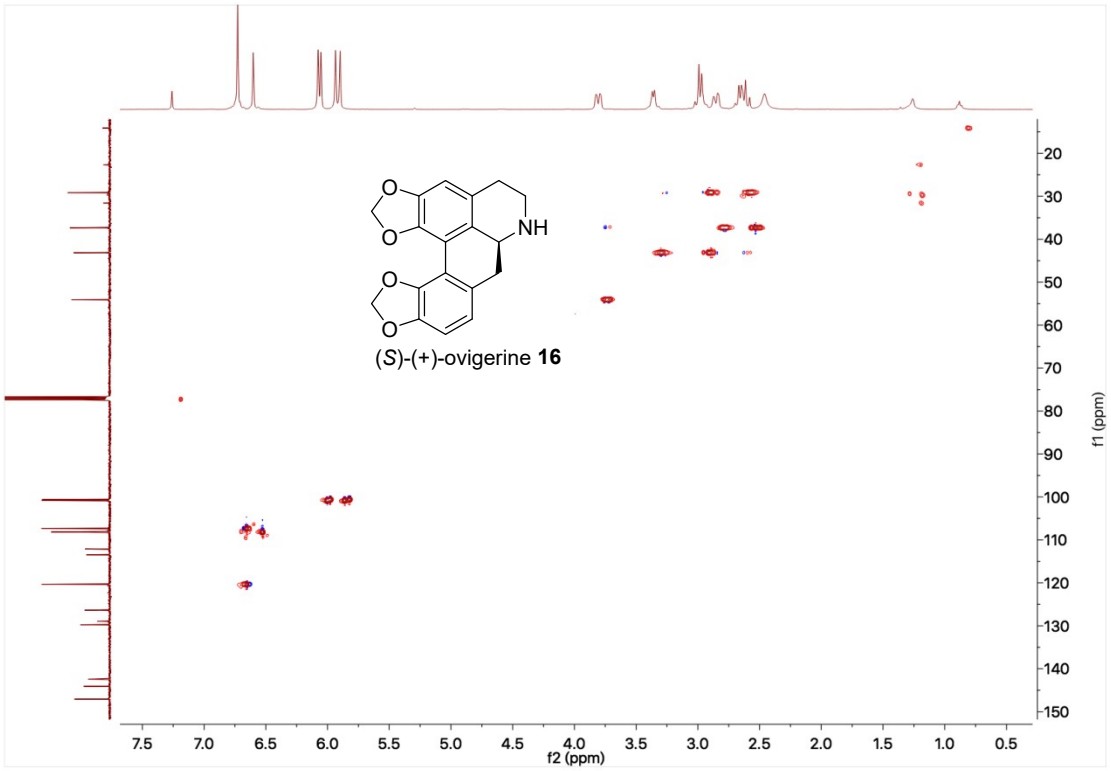

Figure S53. HSQC spectrum (400 MHz, $CDCl_3$) of compound **16**

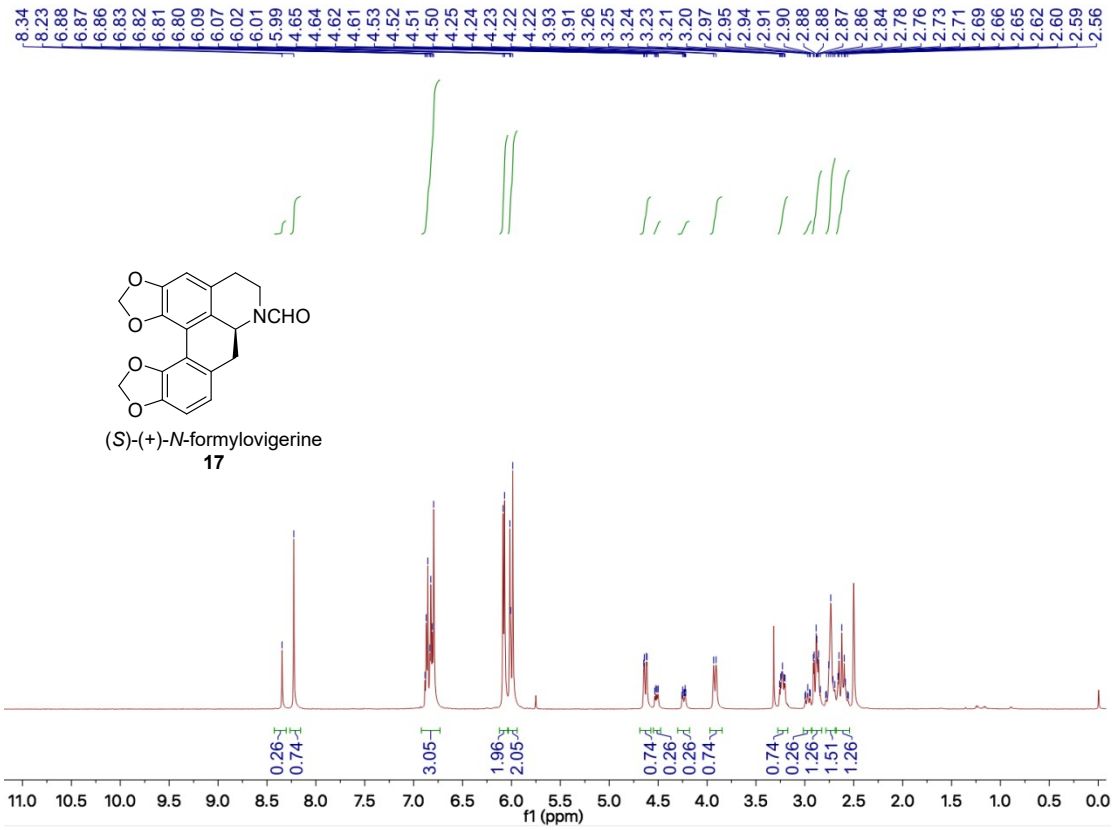

Figure S54. ^{1}H NMR spectrum (500 MHz, DMSO-d_6) of compound **17**

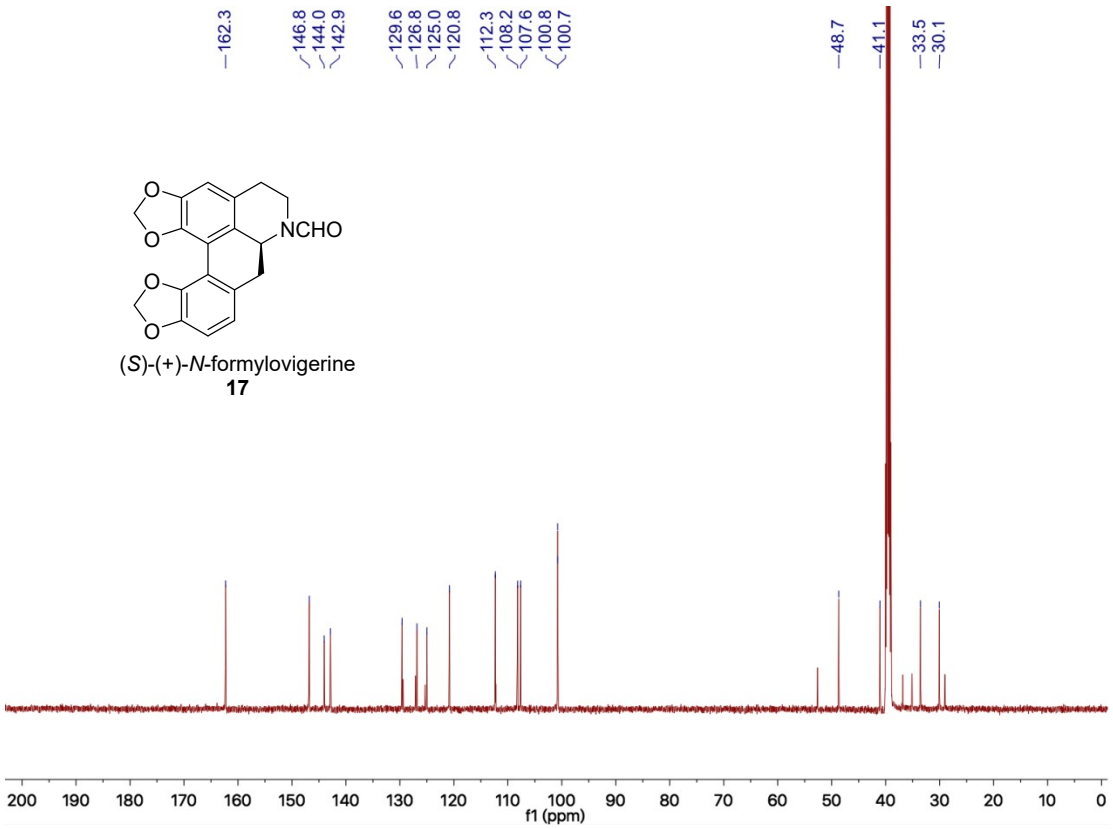

Figure S55. ^{13}C NMR spectrum (126 MHz, $CDCl_3$) of compound **17**

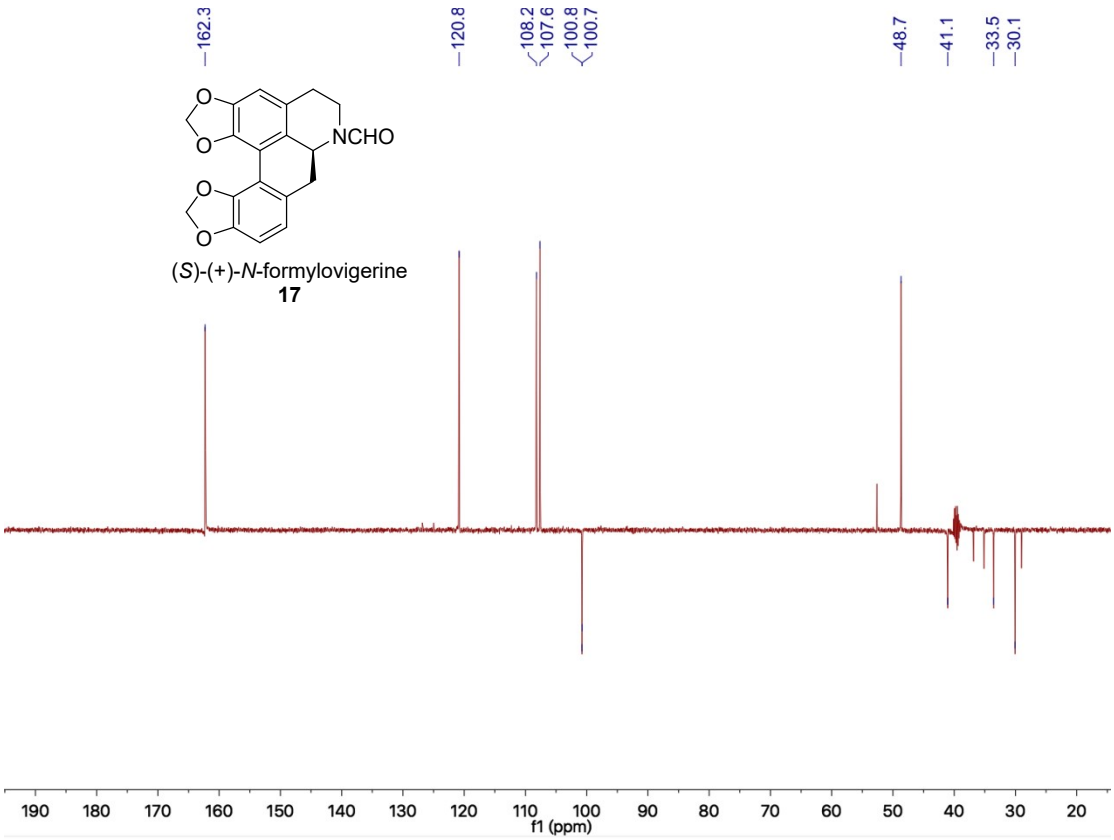

Figure S56. DEPT 135 spectrum (126 MHz, $CDCl_3$) of compound **17**

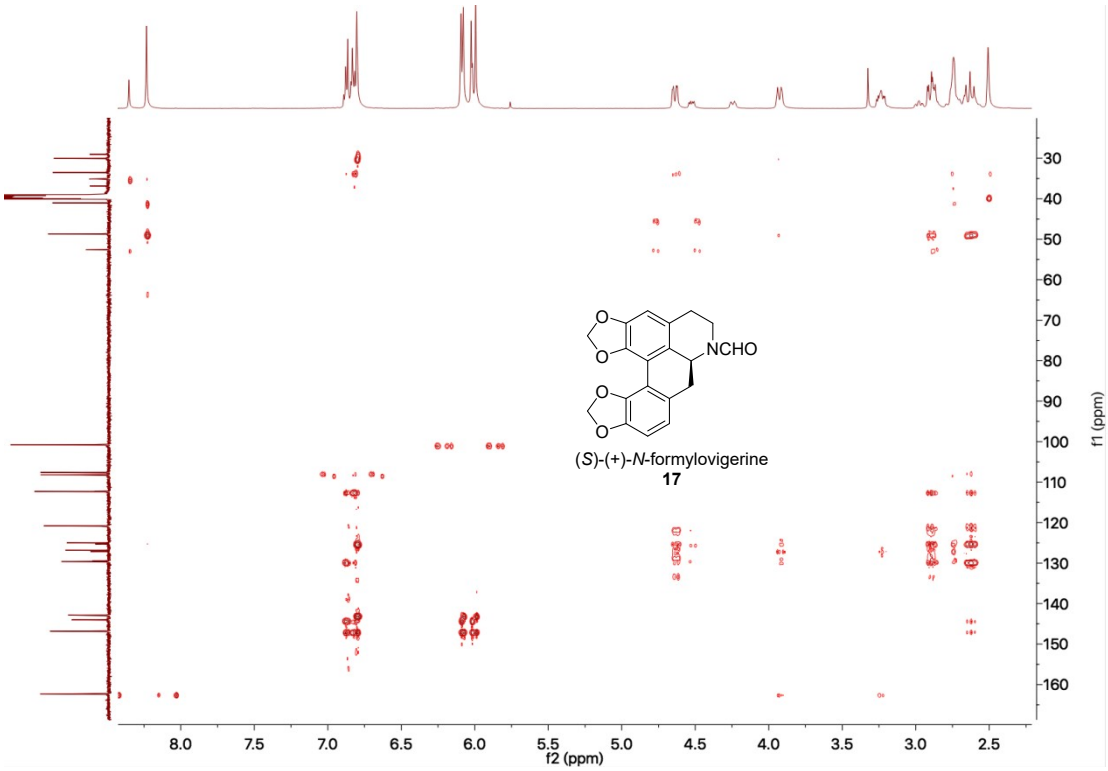

Figure S57. HMBC spectrum (500 MHz, $CDCl_3$) of compound **17**

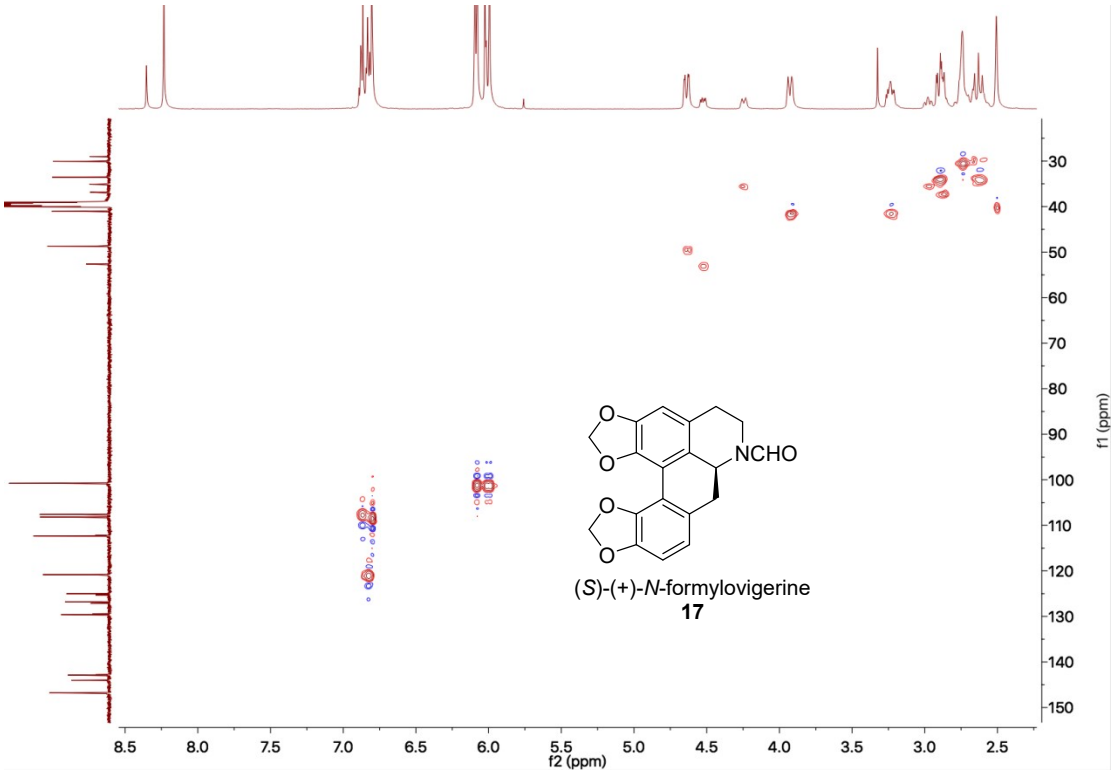

Figure S58. HSQC spectrum (500 MHz, $CDCl_3$) of compound **17**

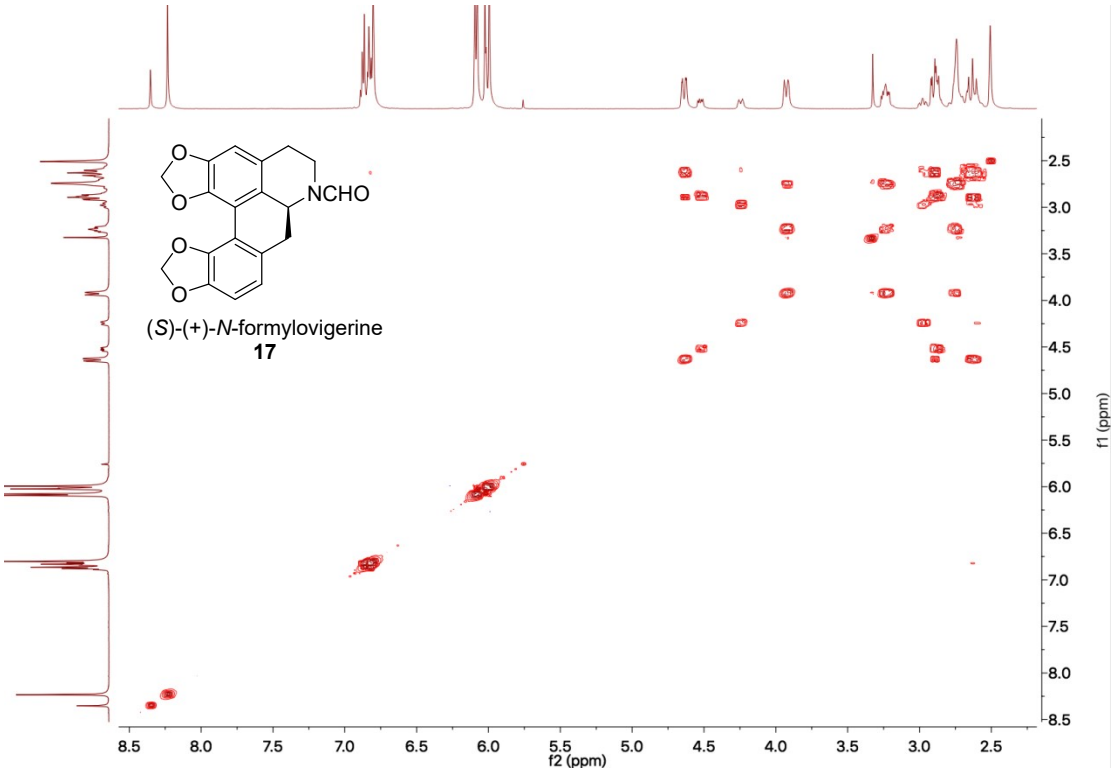

Figure S59. ^1H-^1H COSY spectrum (500 MHz, $CDCl_3$) of compound **17**

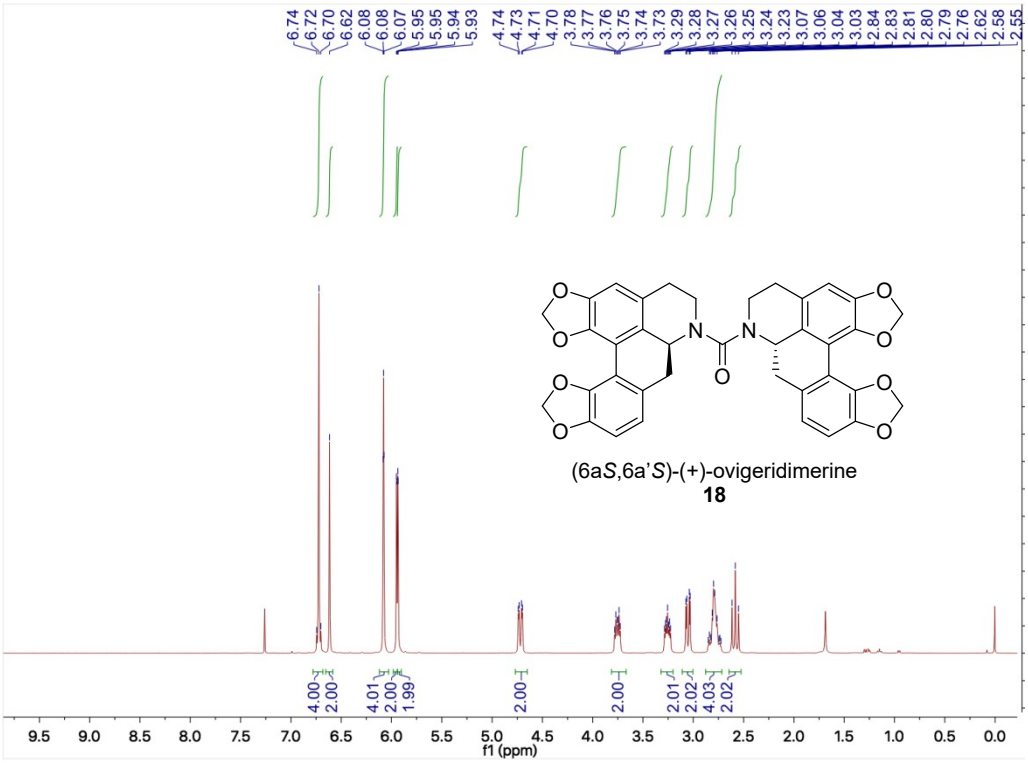

Figure S60. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **18**

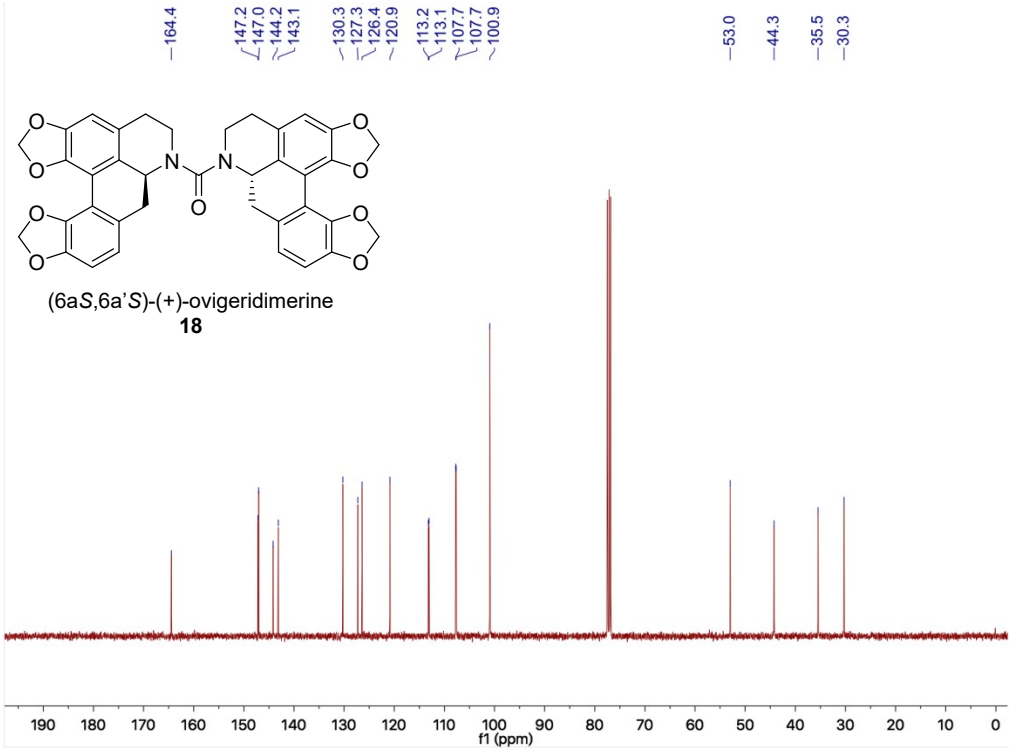

Figure S61. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **18**

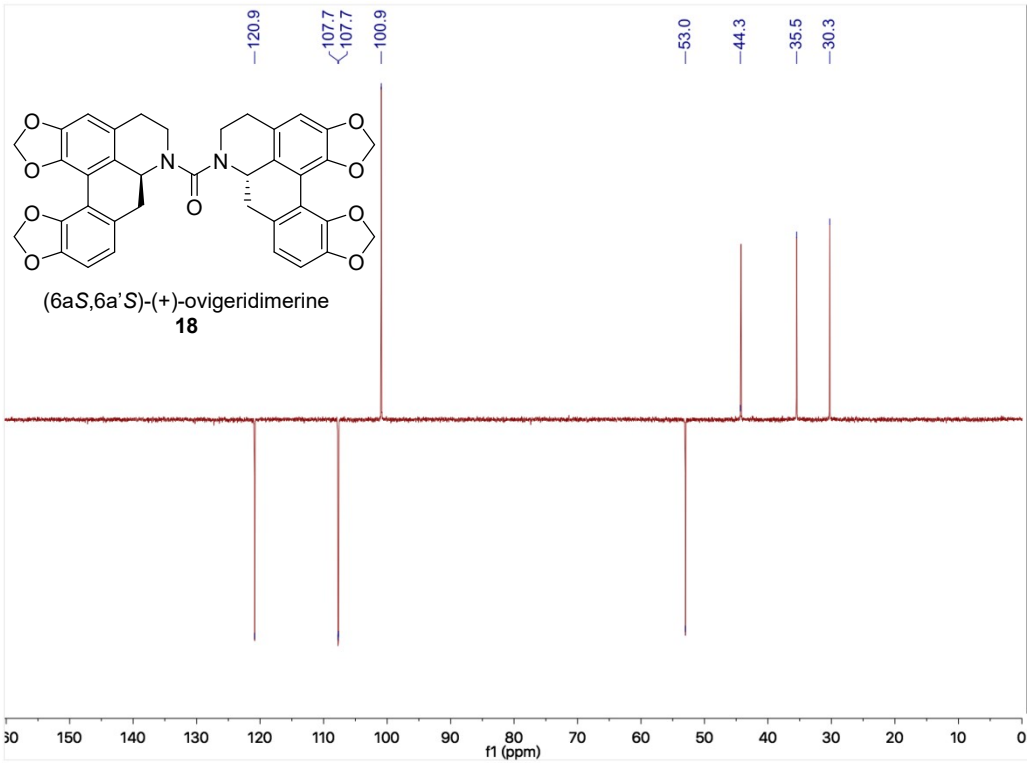

Figure S62. DEPT 135 spectrum (100 MHz, $CDCl_3$) of compound **18**

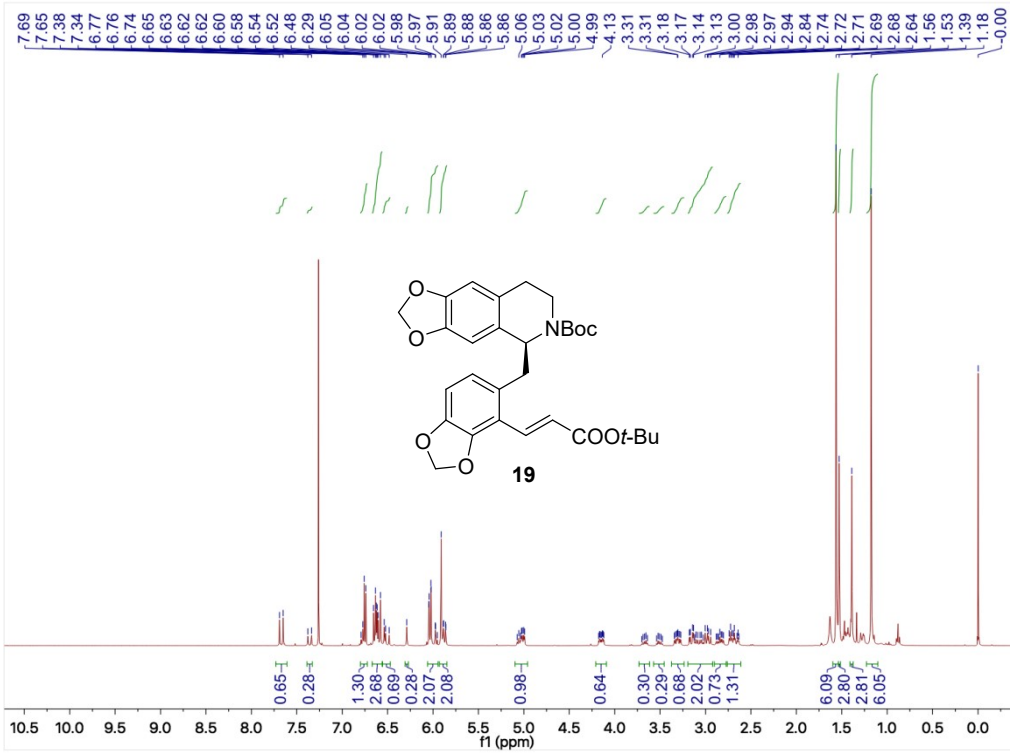

Figure S63. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **19**

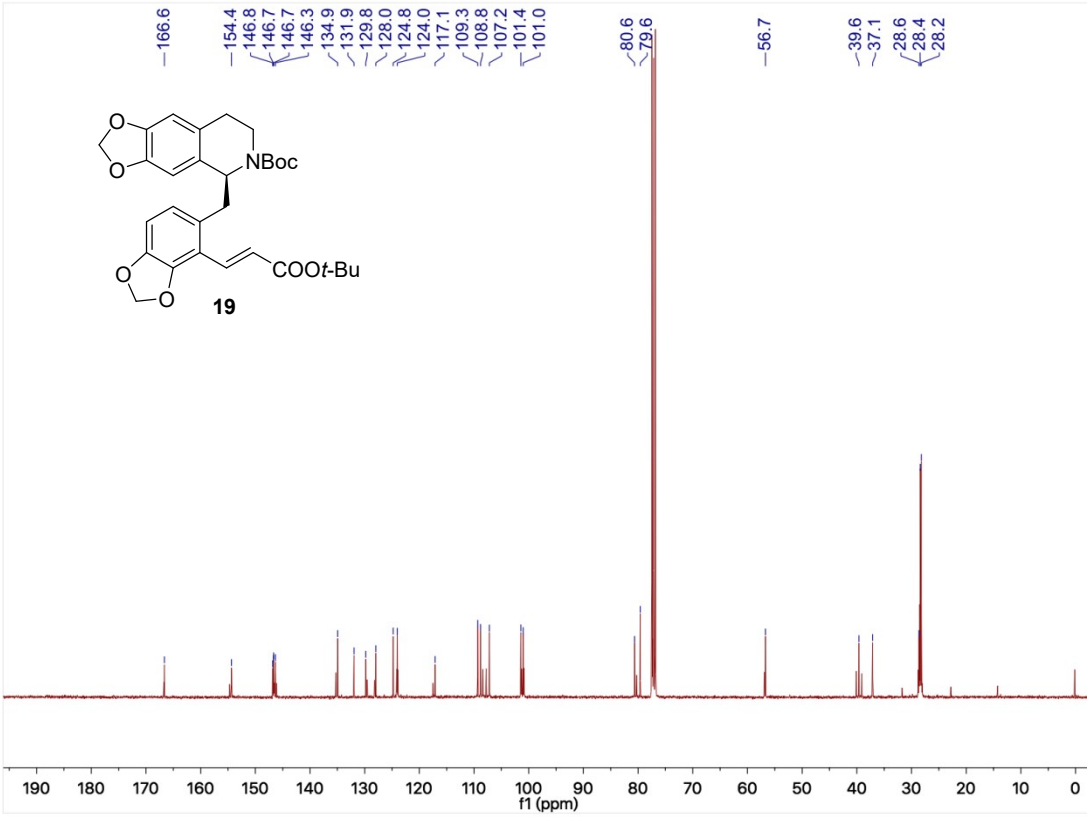

Figure S64. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **19**

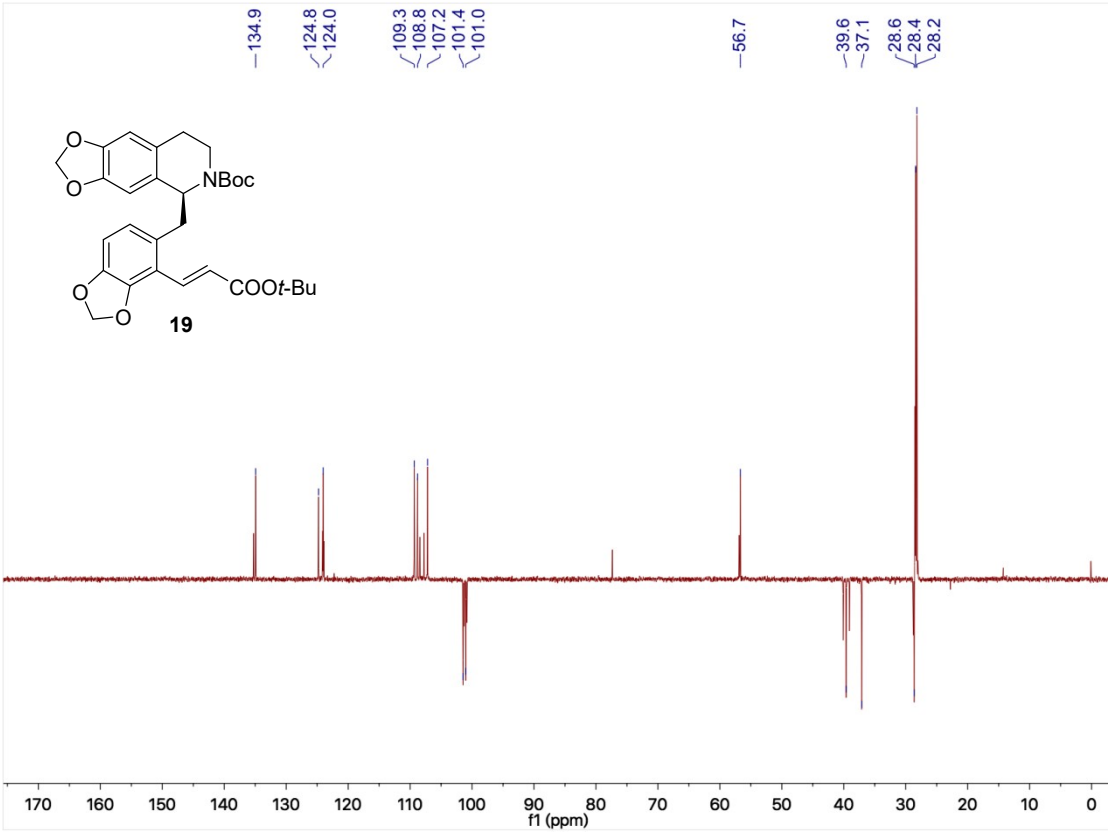

Figure S65. DEPT 135 spectrum (100 MHz, $CDCl_3$) of compound **19**

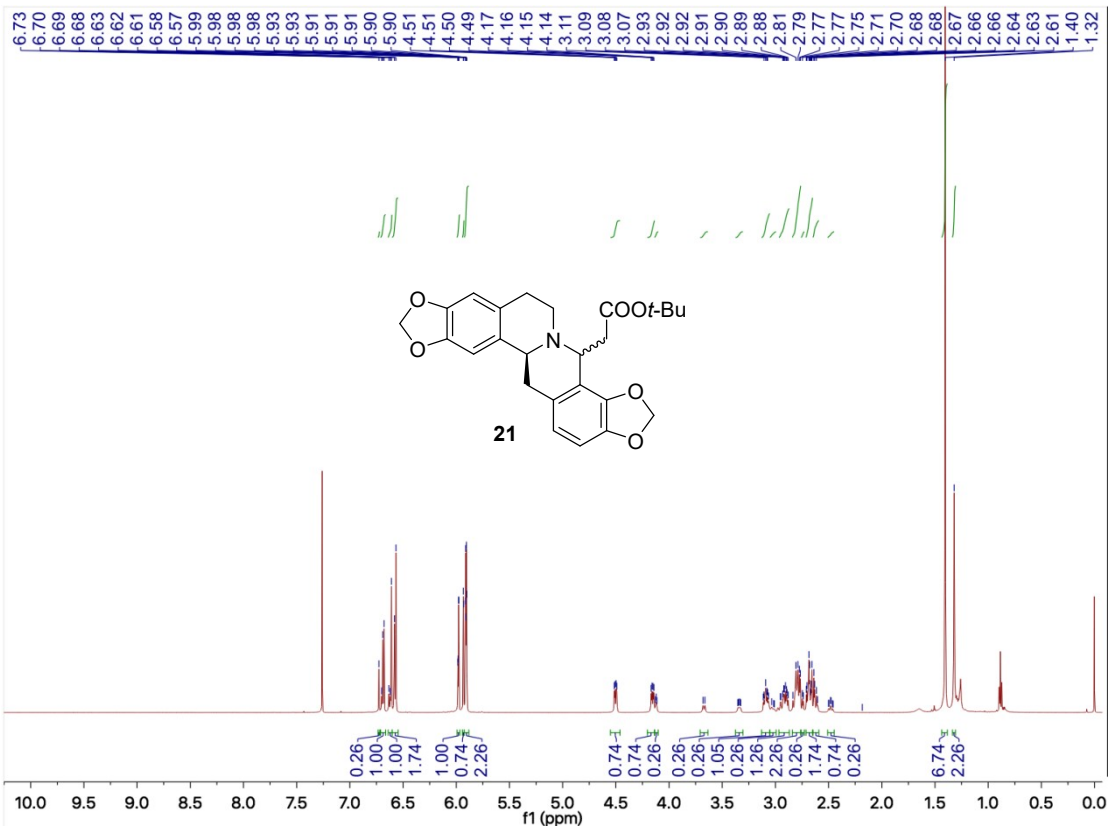

Figure S66. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of compound **21** (*anti*/*syn* 23/8)

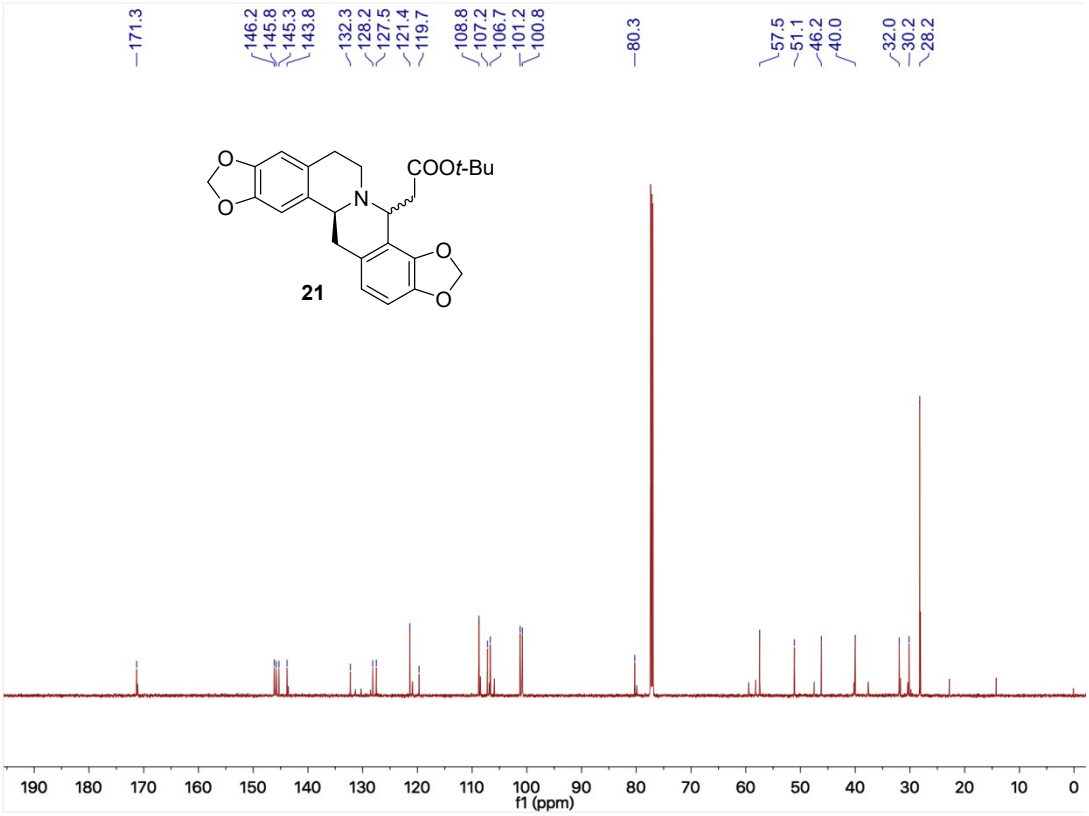

Figure S67. ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of compound **21** (*anti*/*syn* 23/8)

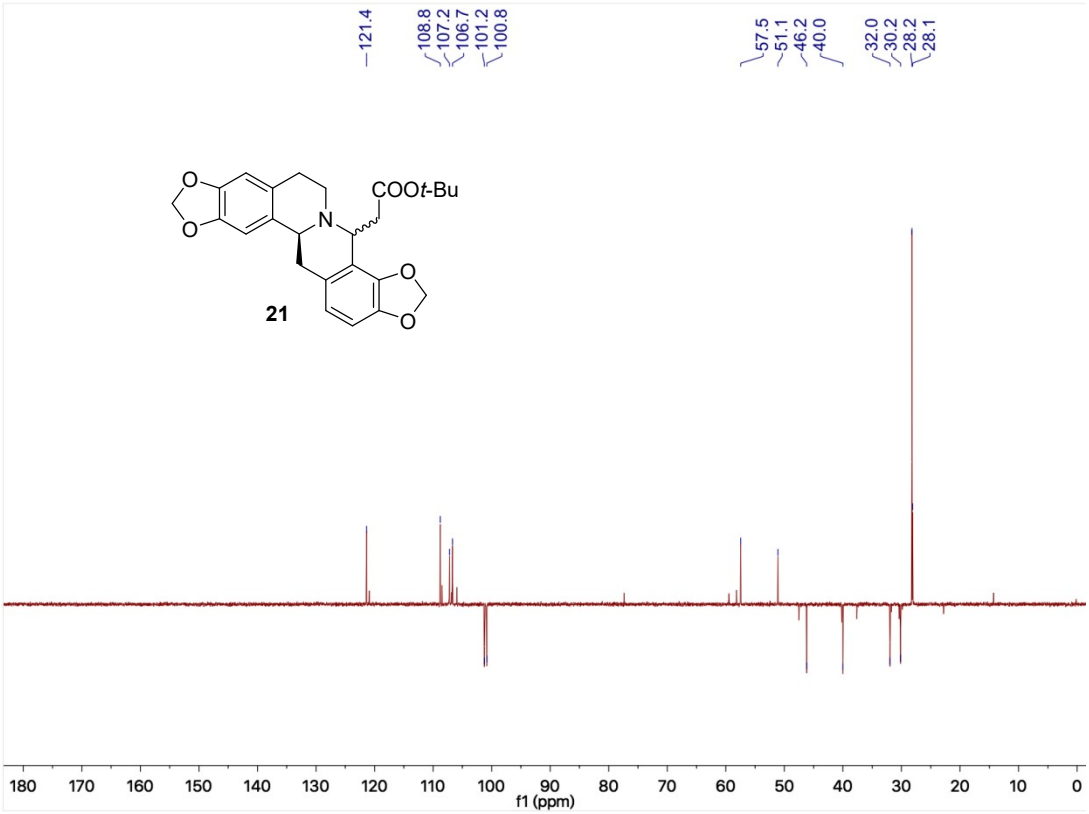

Figure S68. DEPT 135 spectrum (150 MHz, $CDCl_3$) of compound **21** (*anti*/*syn* 23/8)

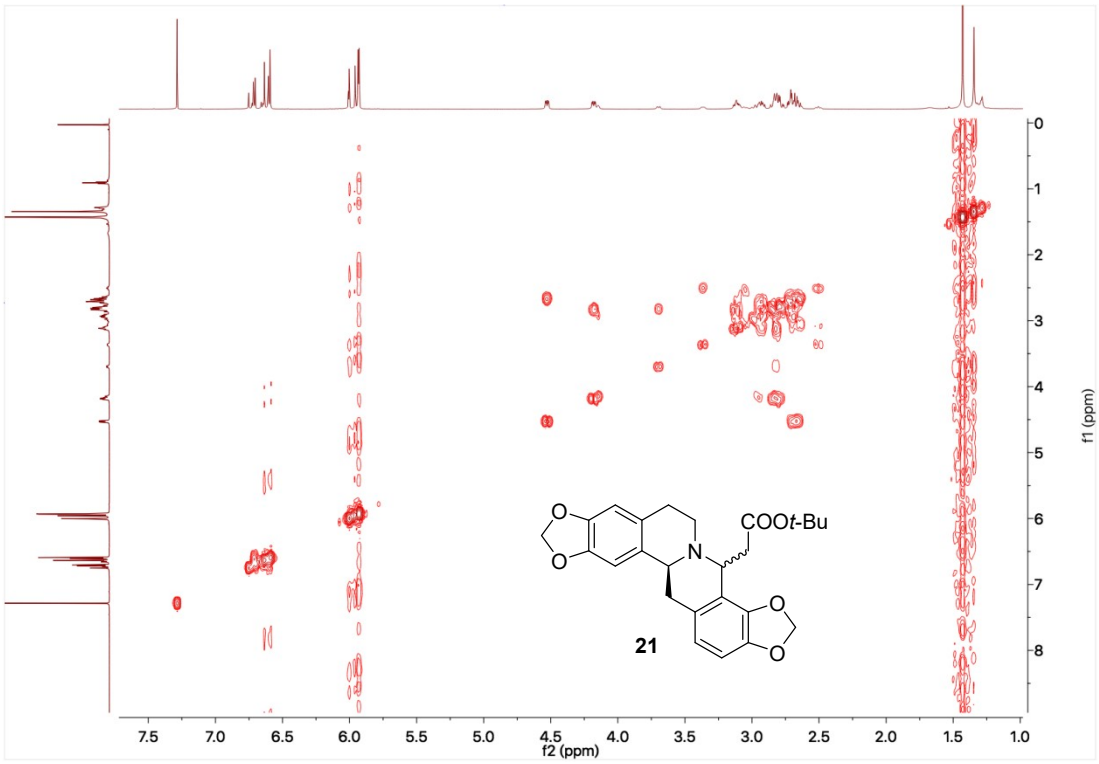

Figure S69. ^{1}H-^{1}H COSY spectrum (600 MHz, $CDCl_3$) of compound **21**

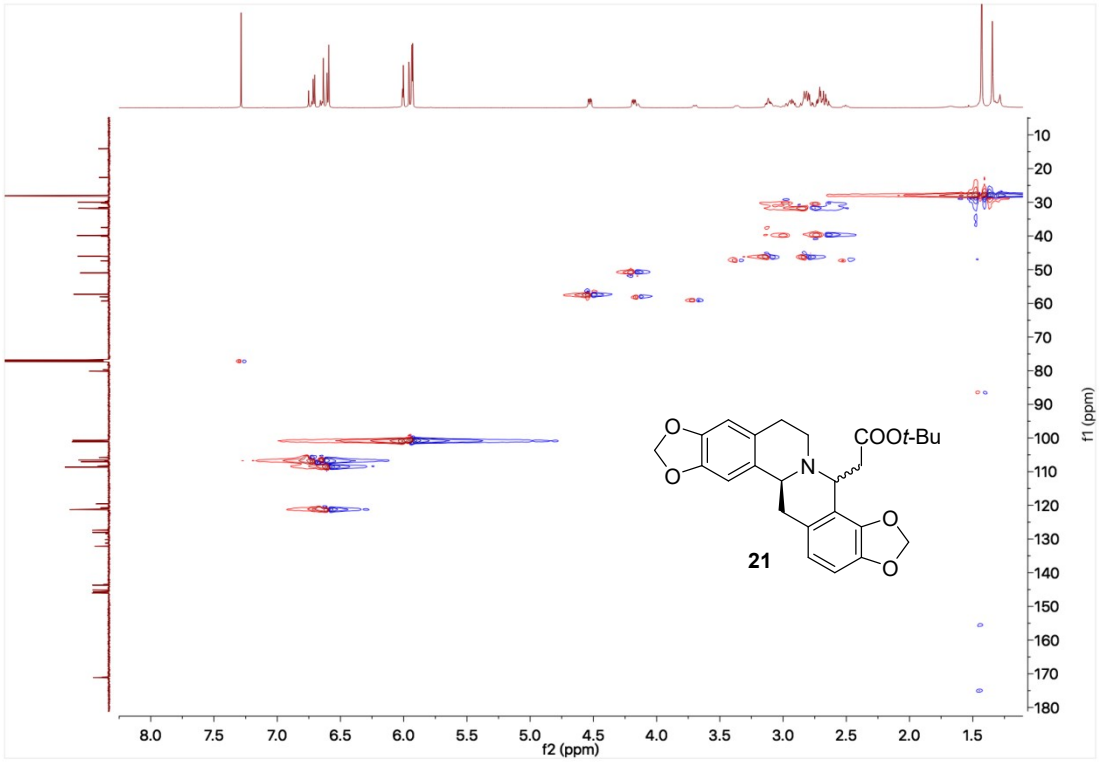

Figure S70. HSQC spectrum (600 MHz, $CDCl_3$) of compound **21** (*anti*/*syn* 23/8)

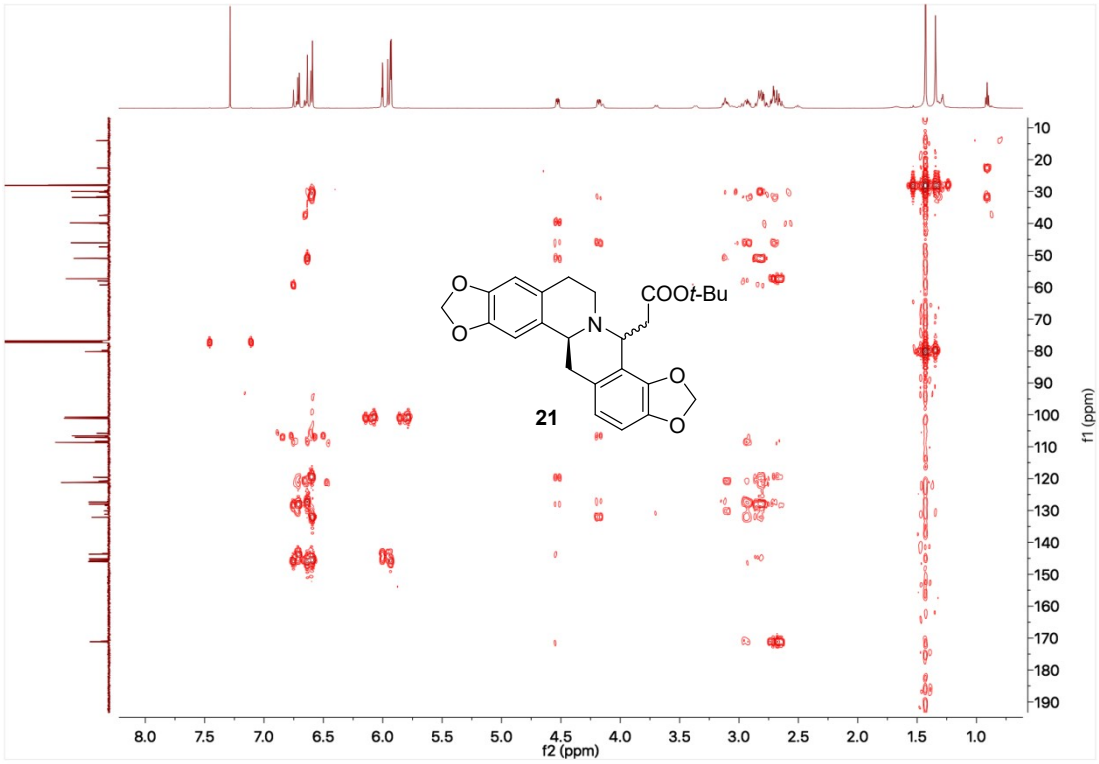

Figure S71. HMBC spectrum (600 MHz, $CDCl_3$) of compound **21** (*anti*/*syn* 23/8)

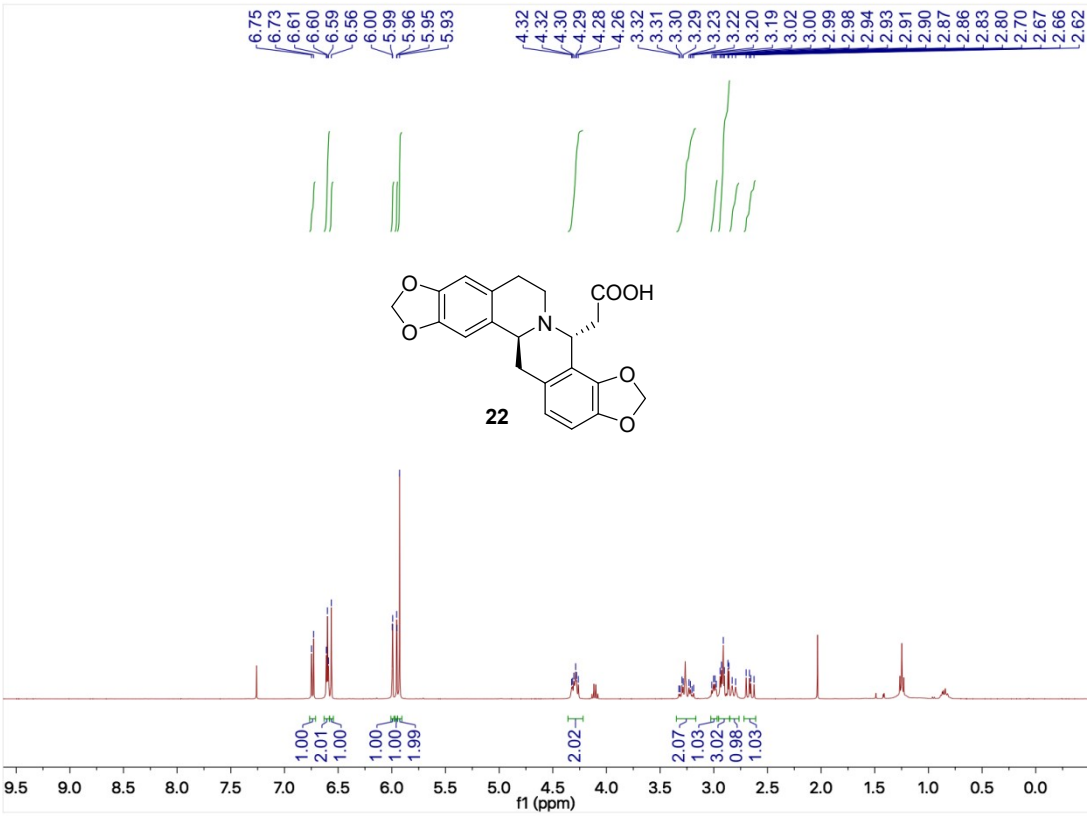

Figure S72. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **22** (*anti*)

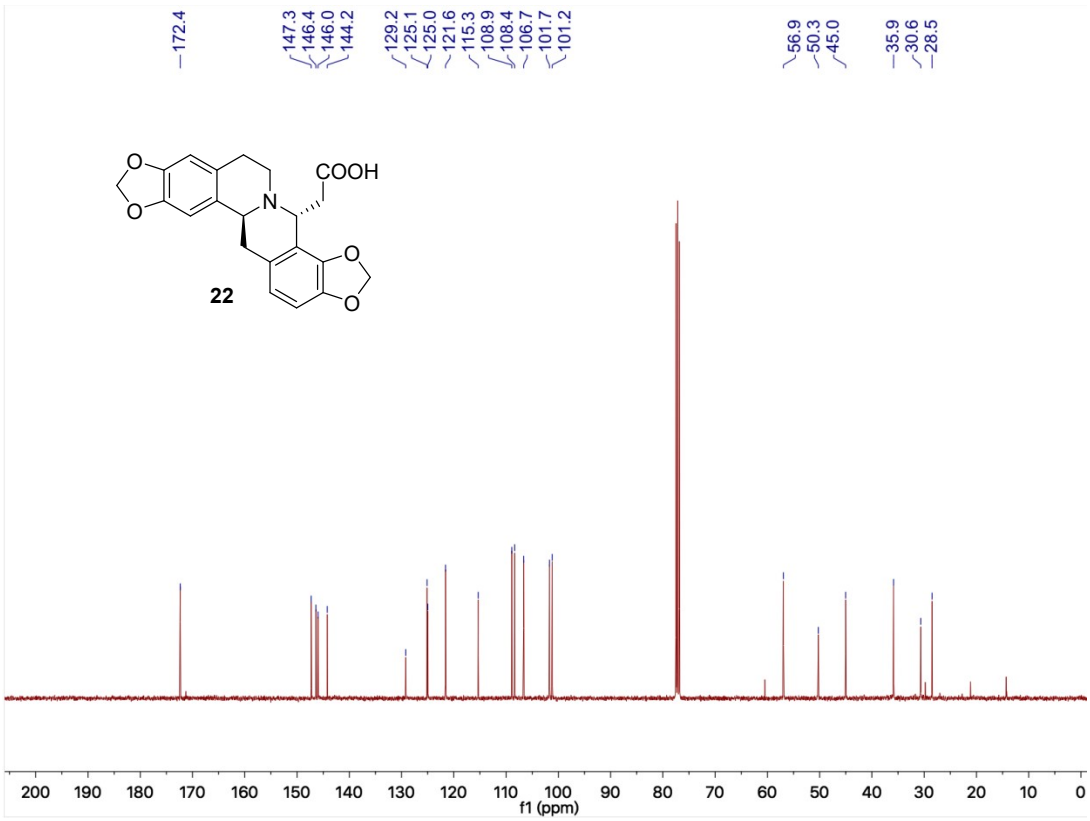

Figure S73. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **22** (*anti*)

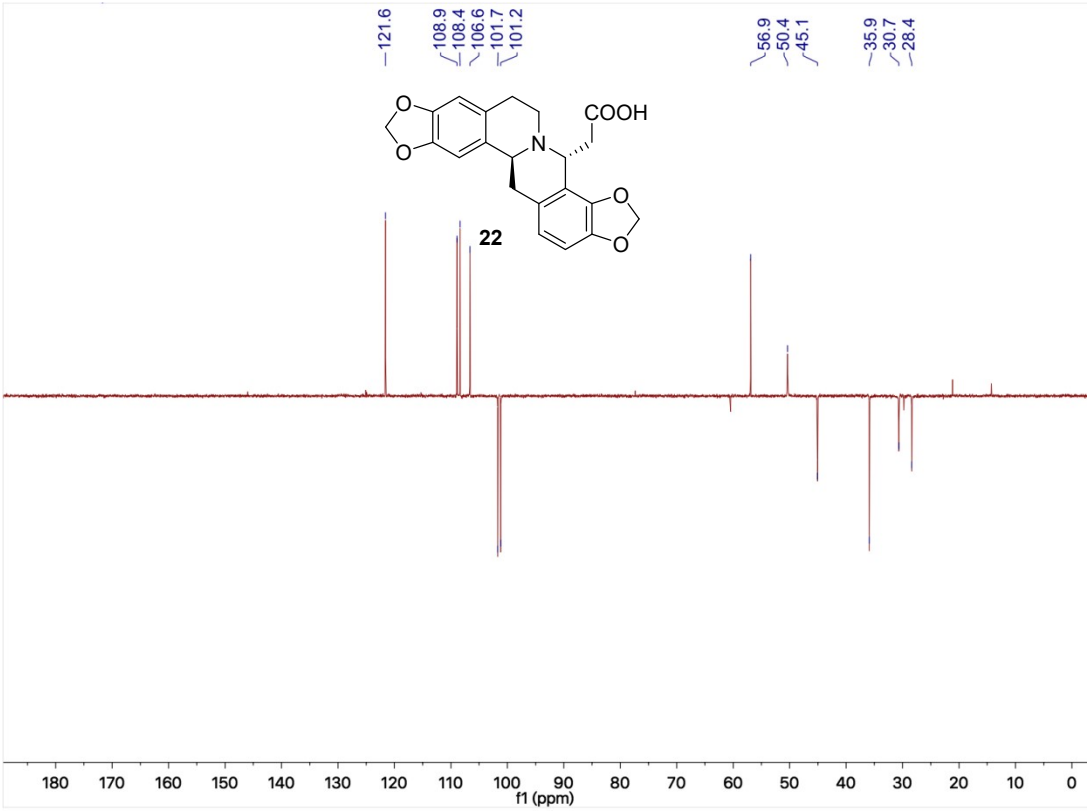

Figure S74. DEPT 135 spectrum (100 MHz, $CDCl_3$) of compound **22** (*anti*)

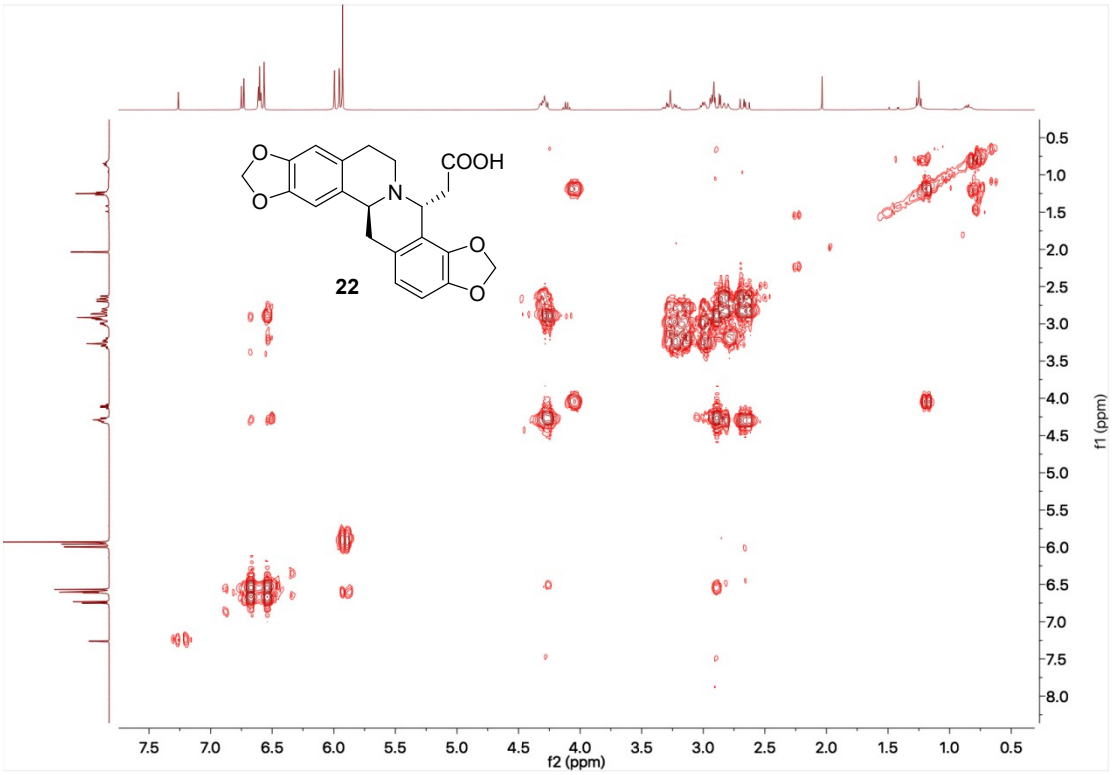

Figure S75. ^1H-^1H COSY spectrum (400 MHz, $CDCl_3$) of compound **22** (*anti*)

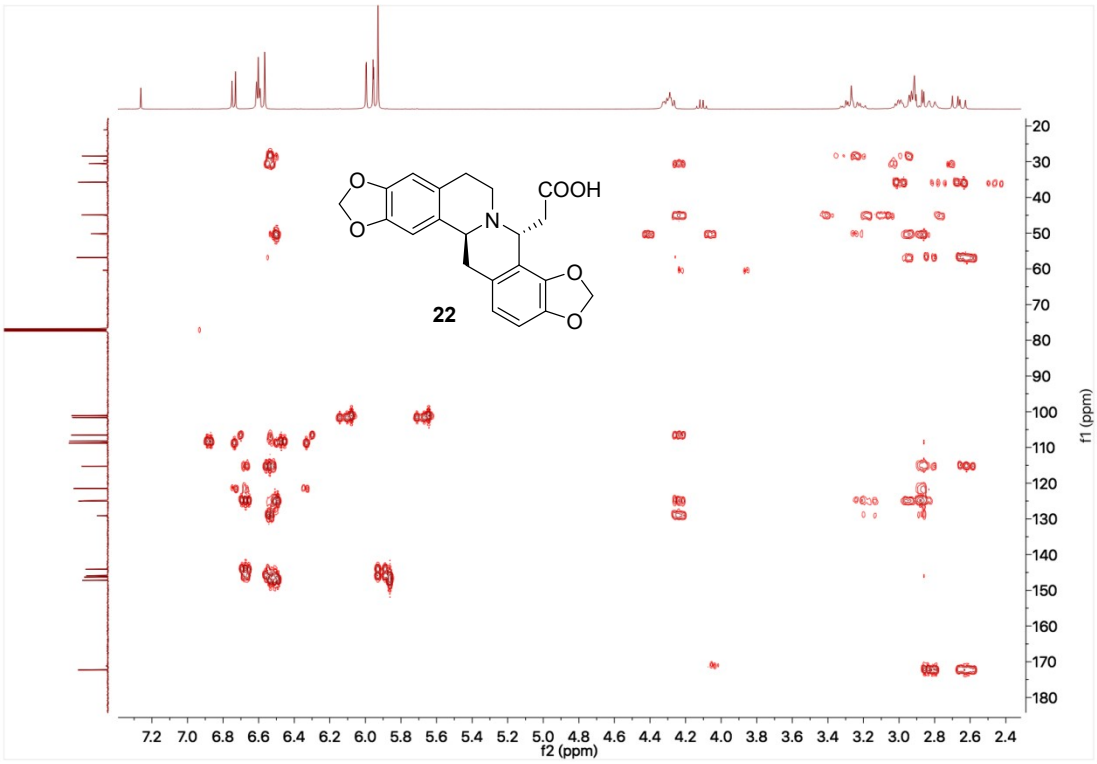

Figure S76. HMBC spectrum (400 MHz, $CDCl_3$) of compound **22** (*anti*)

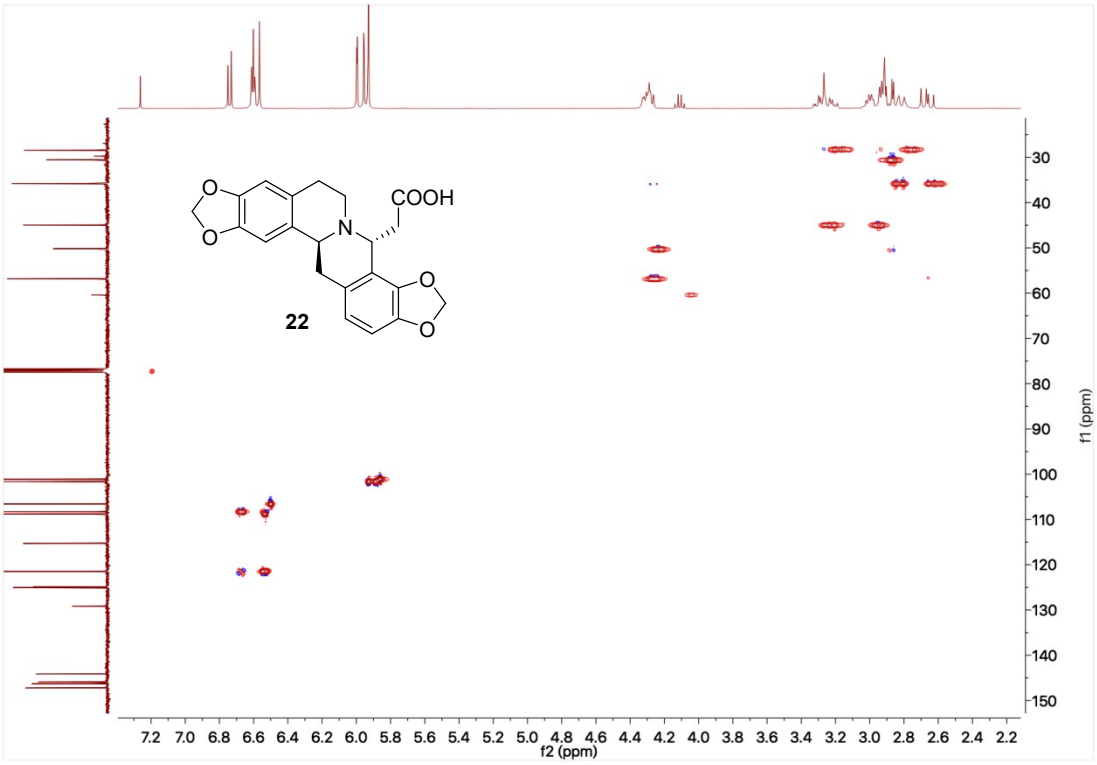

Figure S77. HSQC spectrum (400 MHz, $CDCl_3$) of compound **22** (*anti*)

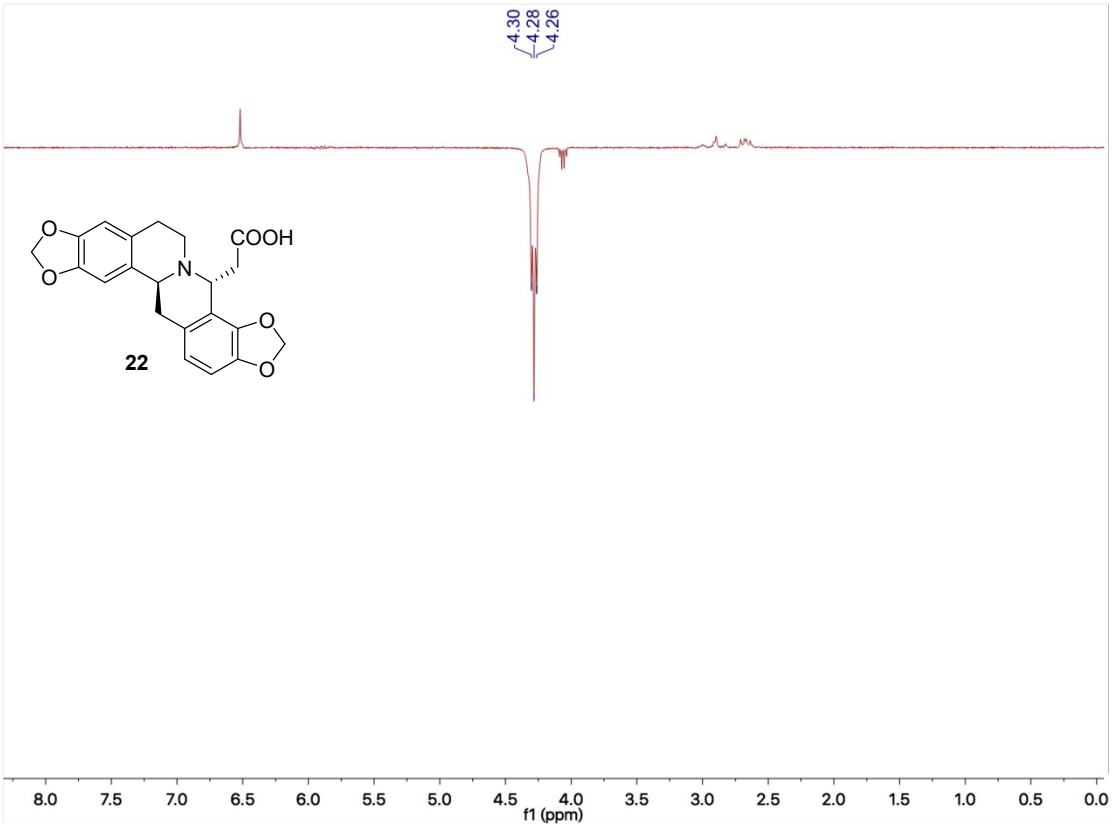

Figure S78. NOE spectrum (400 MHz, $CDCl_3$, irradiation at 4.32 – 4.26) of compound **22** (*anti*)

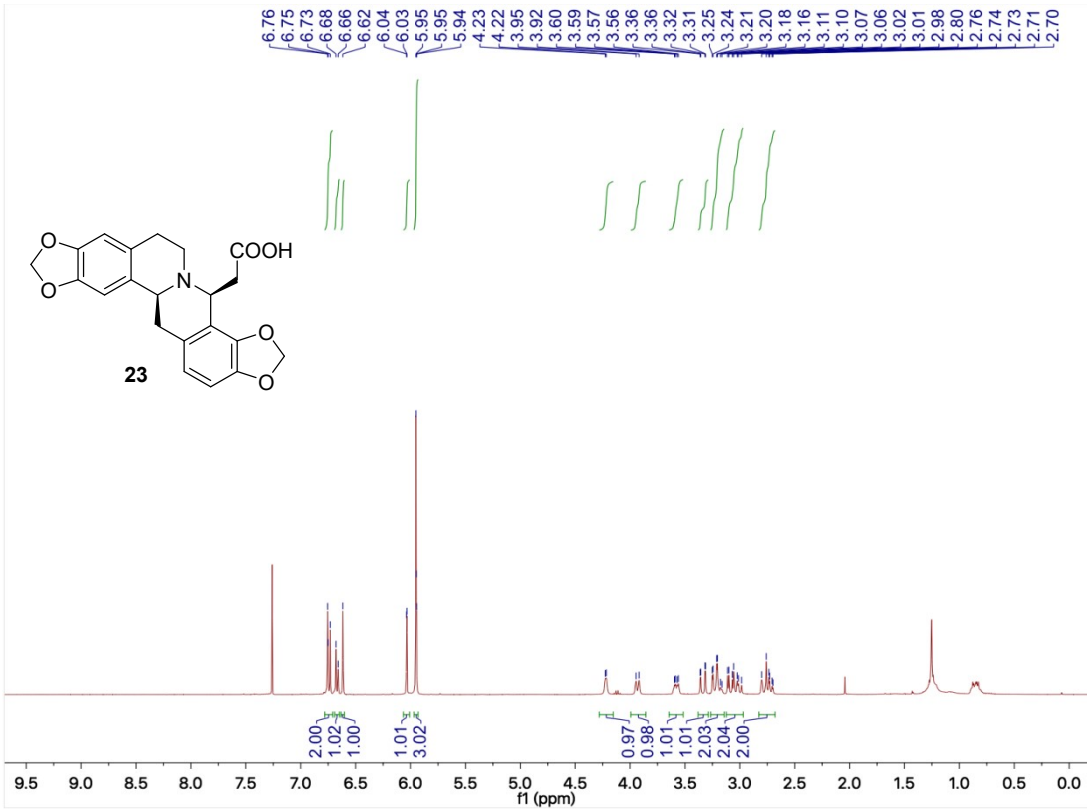

Figure S79. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **23** (*syn*)

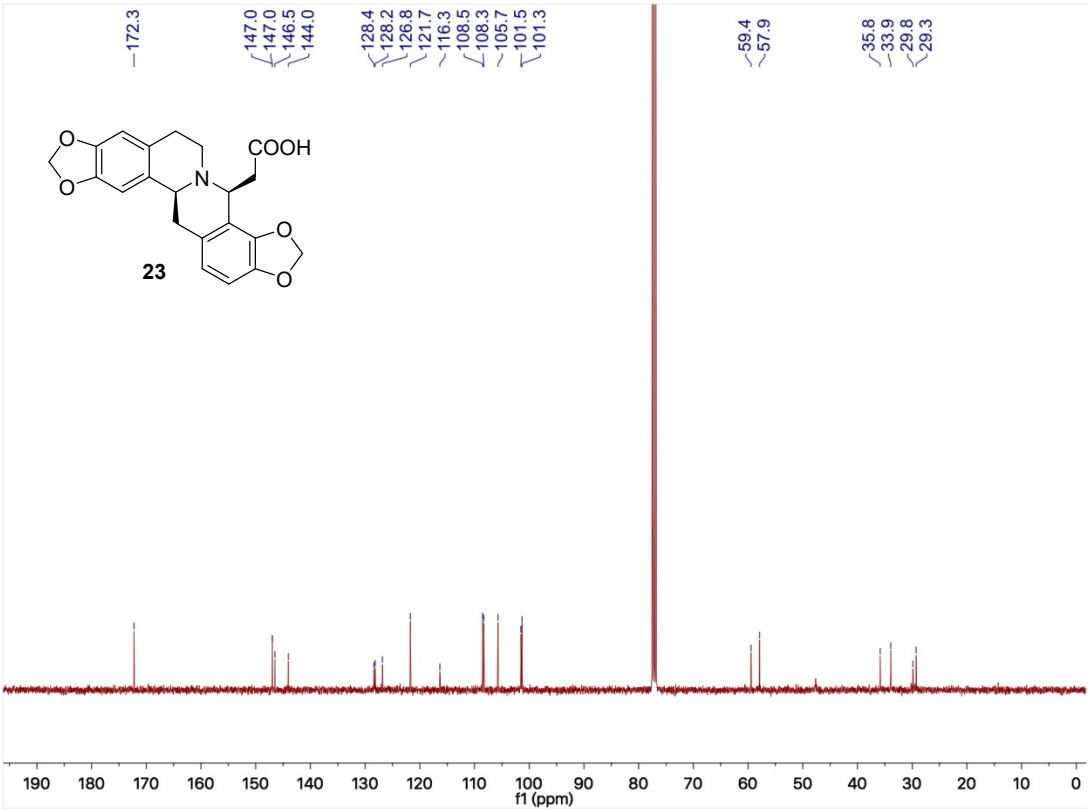

Figure S80. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **23** (*syn*)

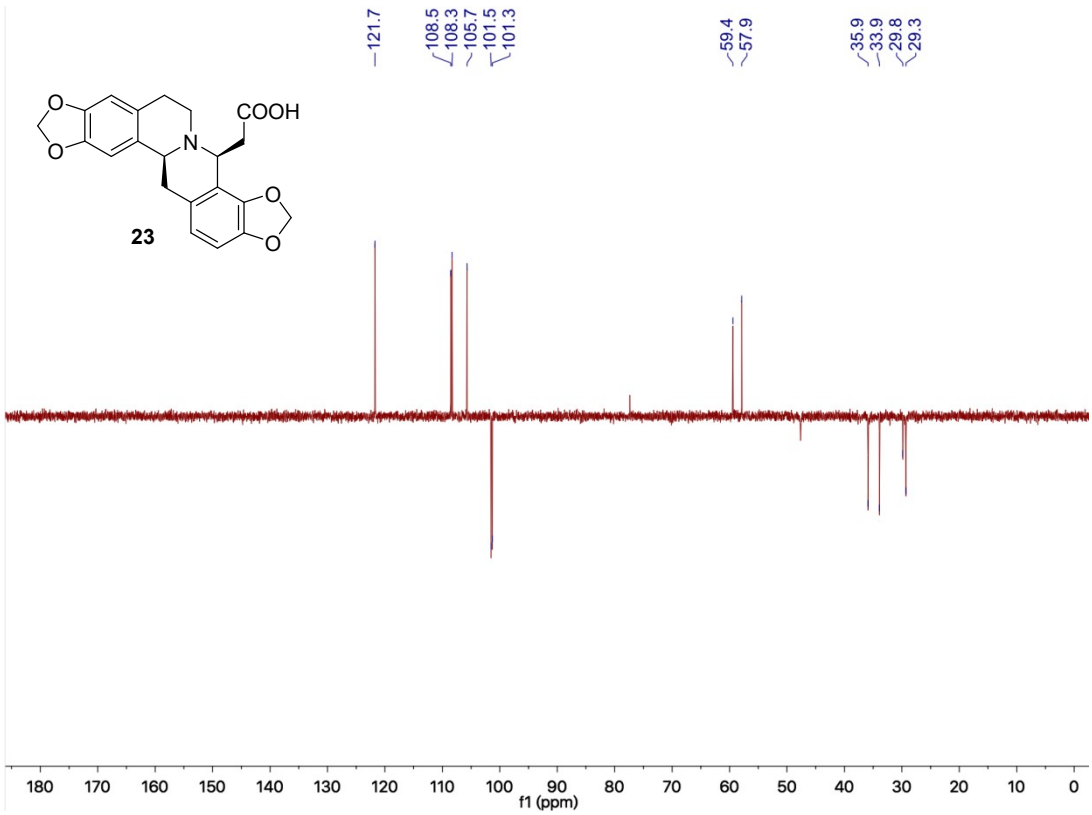

Figure S81. DEPT 135 spectrum (100 MHz, $CDCl_3$) of compound **23** (*syn*)

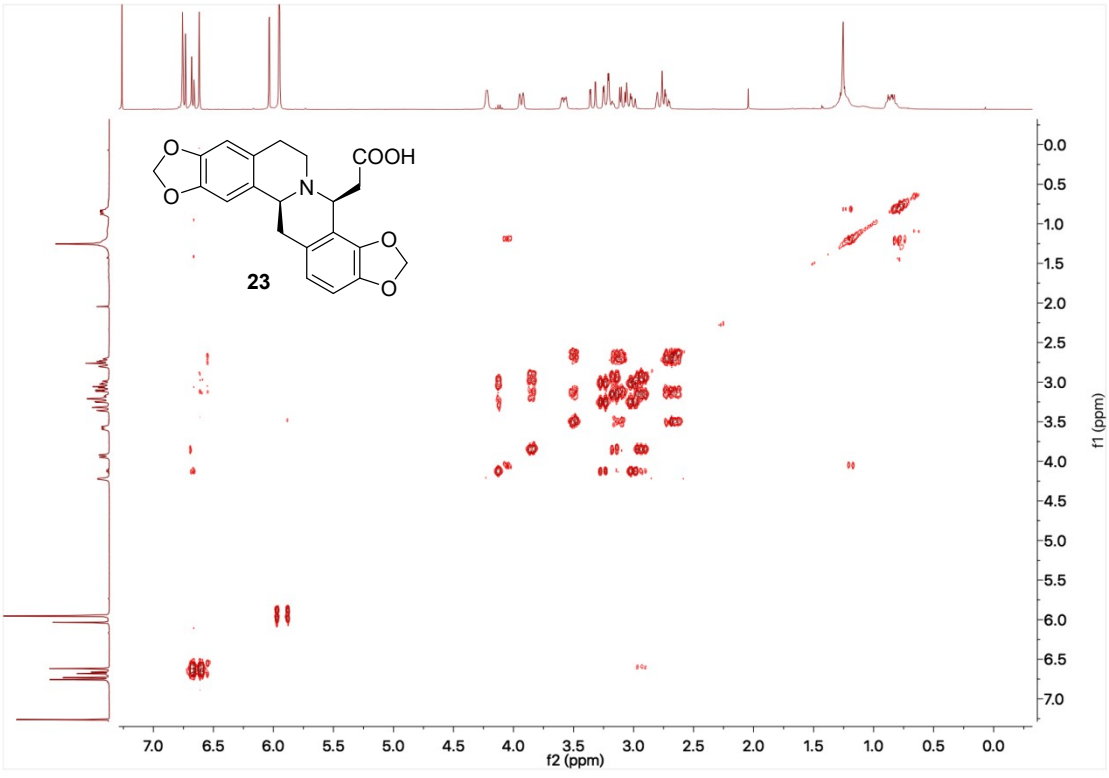

Figure S82. ^1H-^1H COSY spectrum (400 MHz, $CDCl_3$) of compound **23** (*syn*)

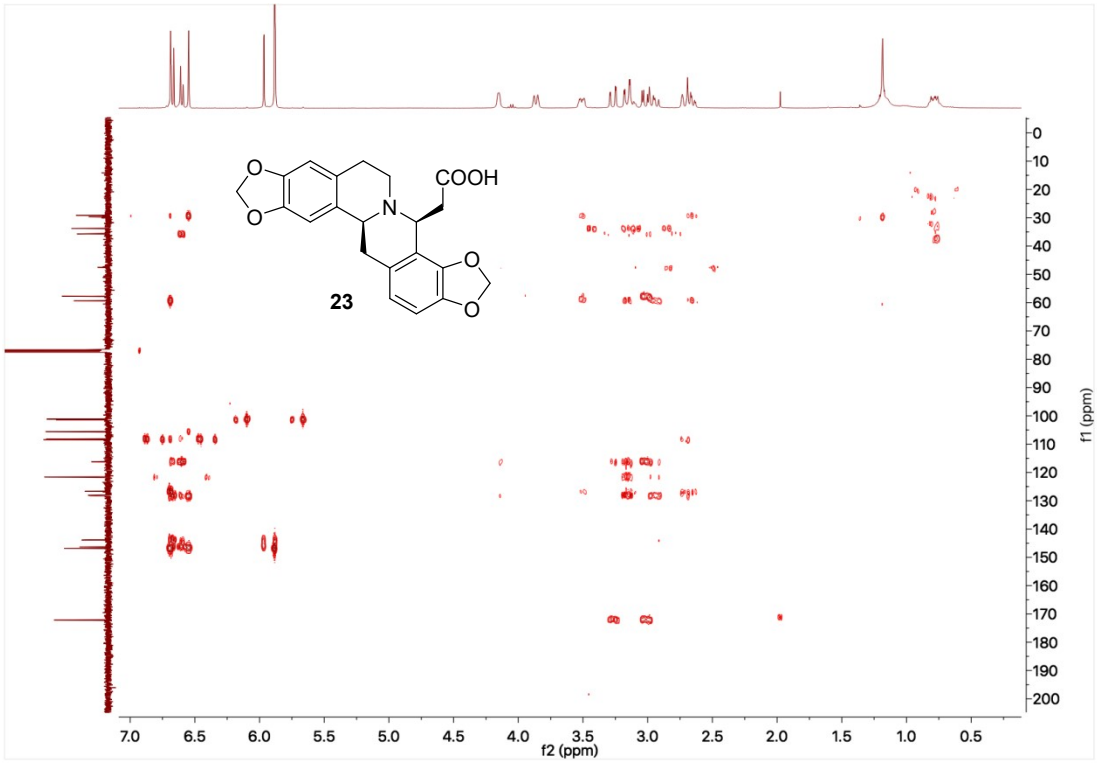

Figure S83. HMBC spectrum (400 MHz, $CDCl_3$) of compound **23** (*syn*)

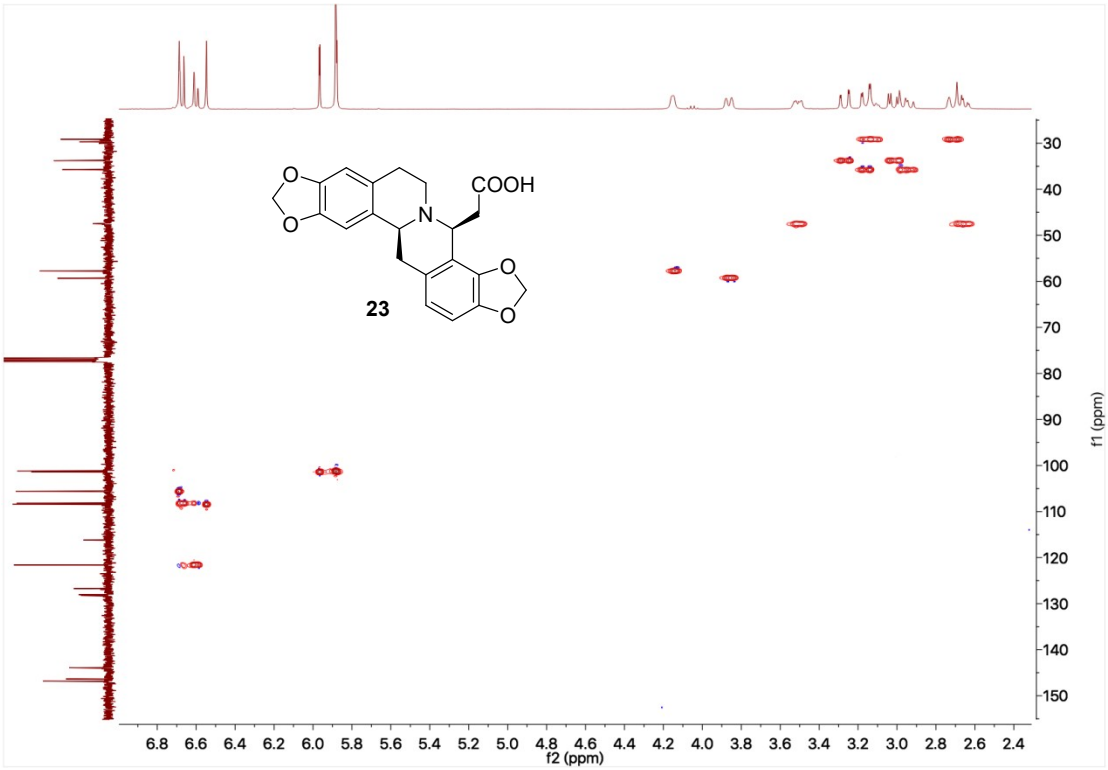

Figure S84. HSQC spectrum (400 MHz, $CDCl_3$) of compound **23** (*syn*)

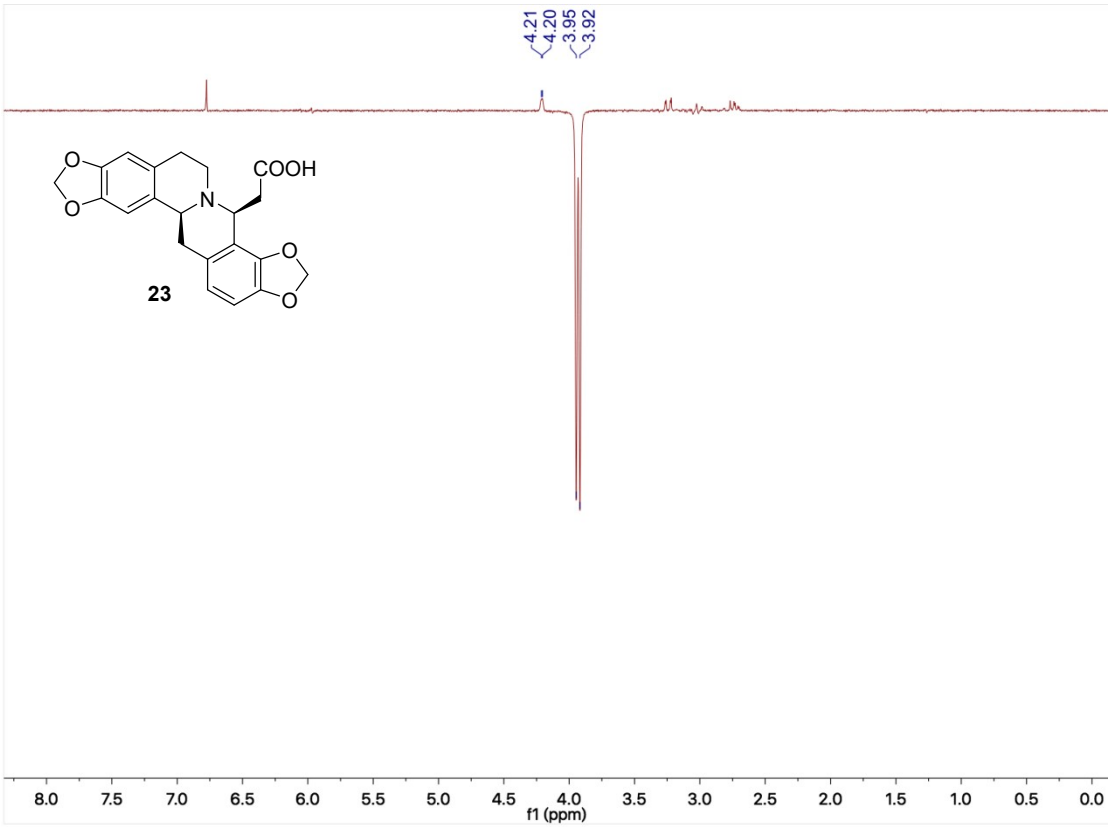

Figure S85. NOE spectrum (400 MHz, $CDCl_3$, irradiation at 3.95 – 3.92) of compound **23** (*syn*)

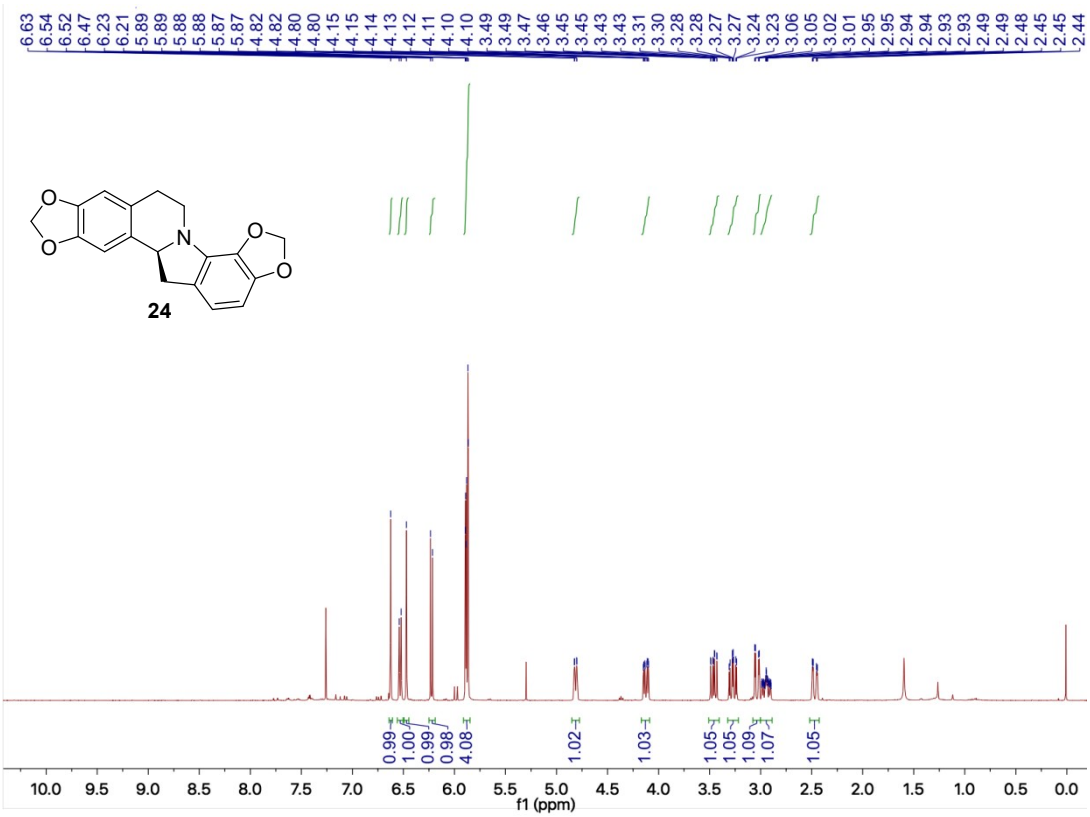

Figure S86. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **24**

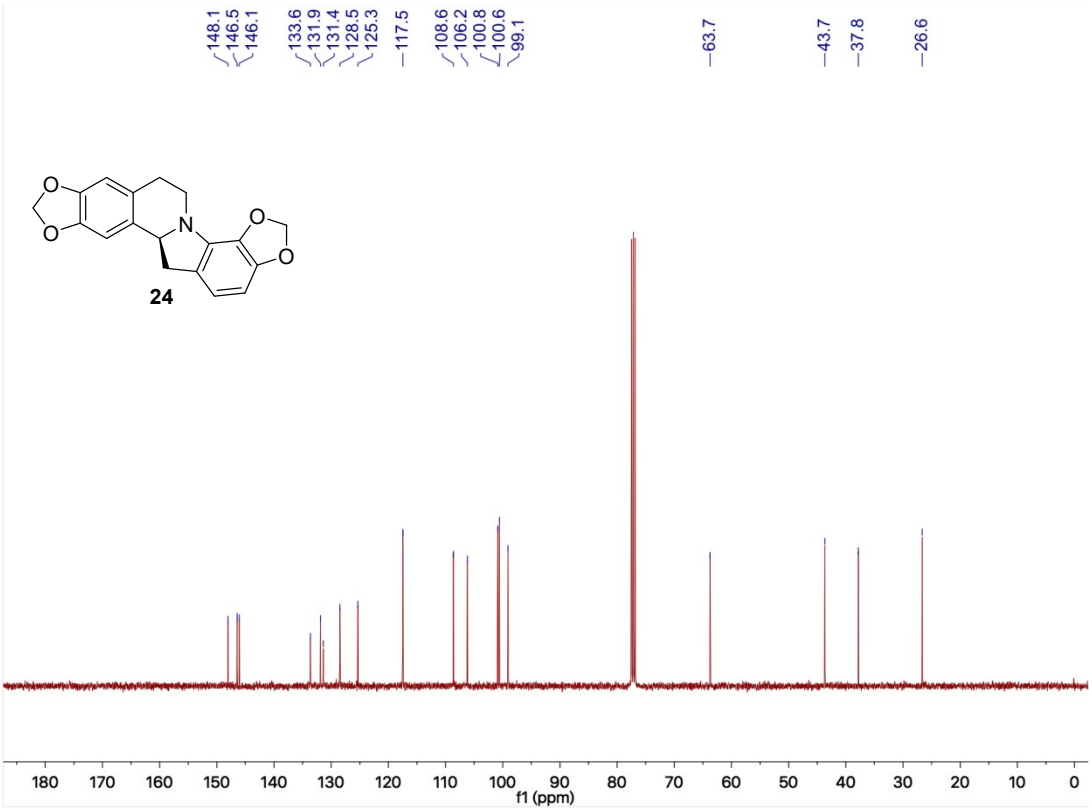

Figure S87. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **24**

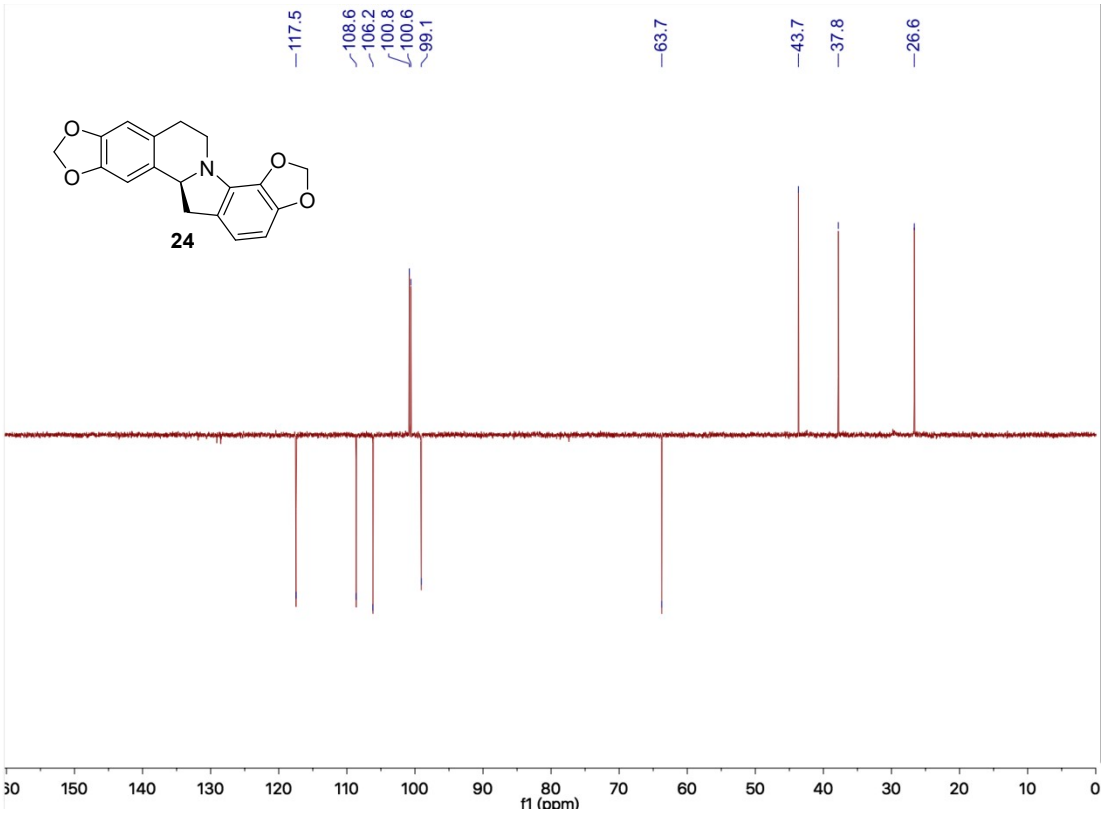

Figure S88. DEPT135 spectrum (100 MHz, $CDCl_3$) of compound **24**

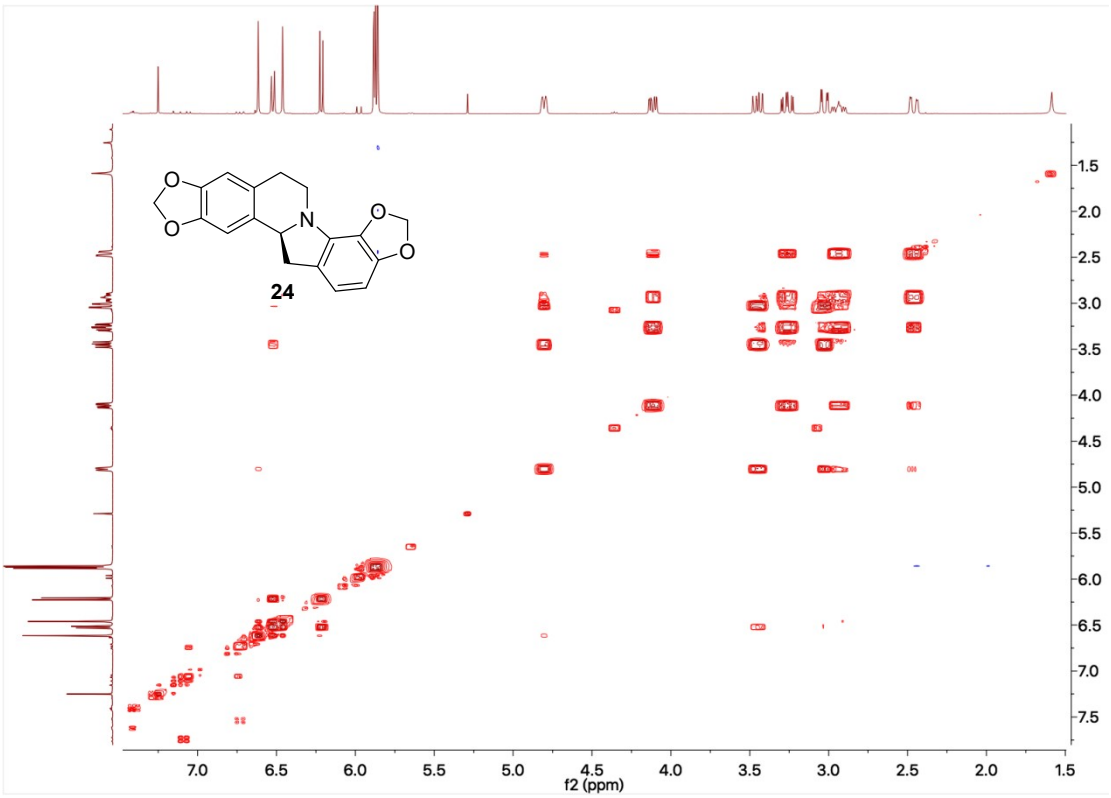

Figure S89. ^1H-^1H COSY spectrum (400 MHz, $CDCl_3$) of compound **24**

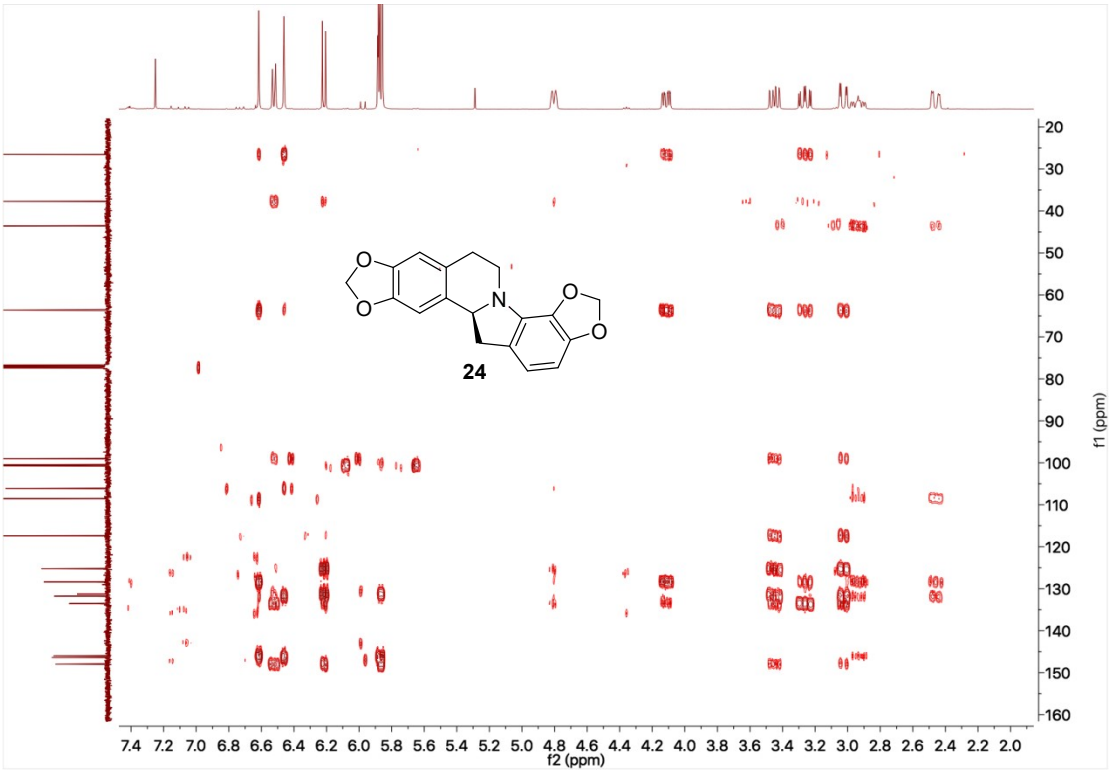

Figure S90. HMBC spectrum (400 MHz, $CDCl_3$) of compound **24**

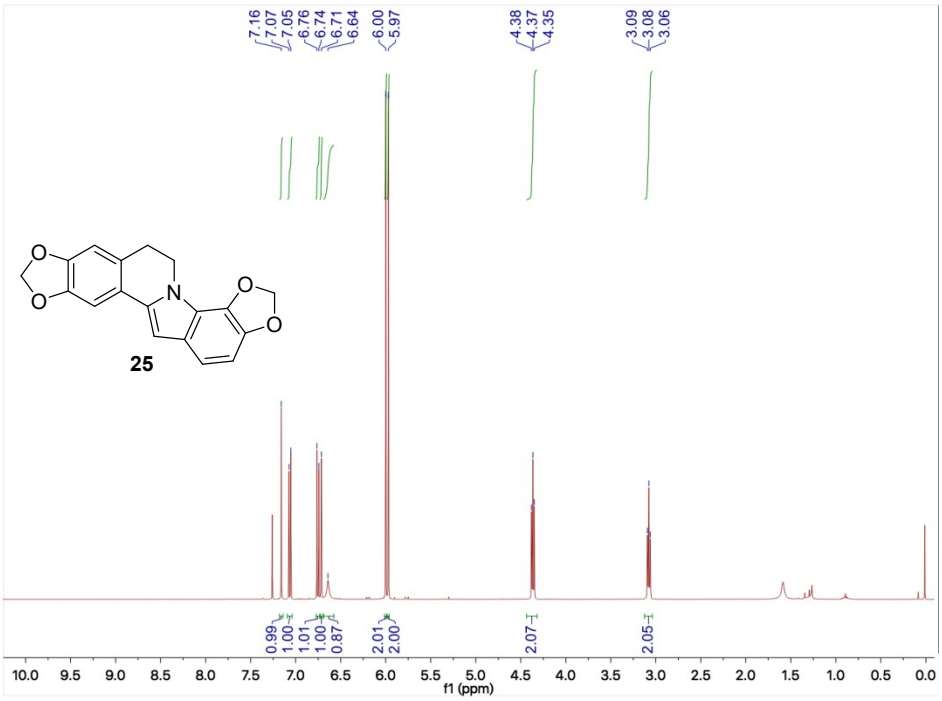

Figure S91. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **25**

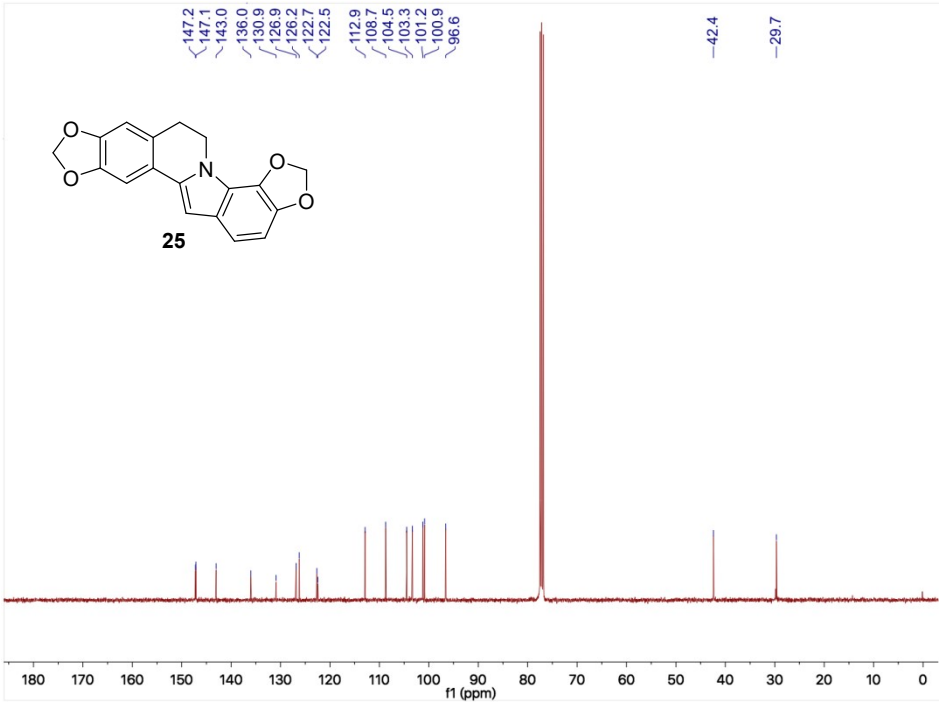

Figure S92. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **25**

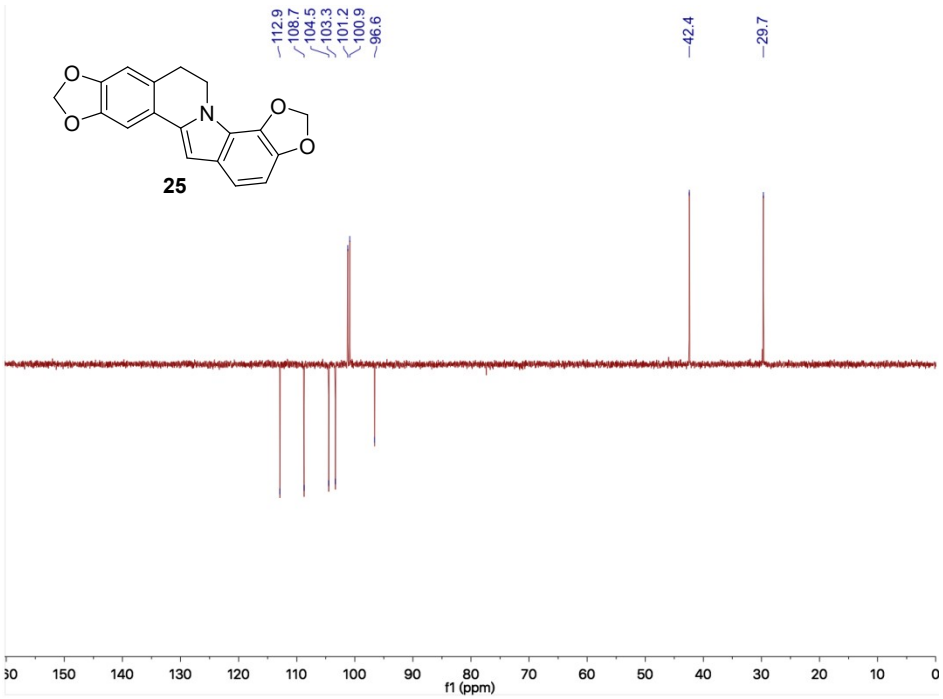

Figure S93. DEPT135 spectrum (100 MHz, $CDCl_3$) of compound **25**

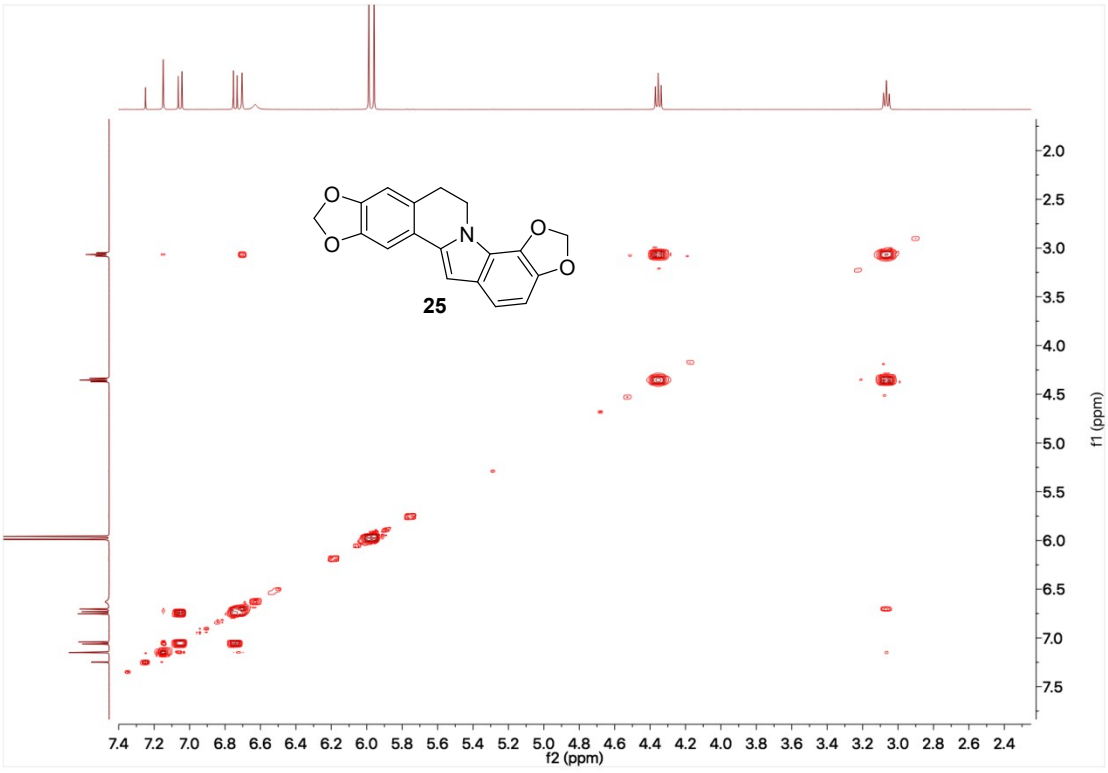

Figure S94. ^1H-^1H COSY spectrum (400 MHz, $CDCl_3$) of compound **25**

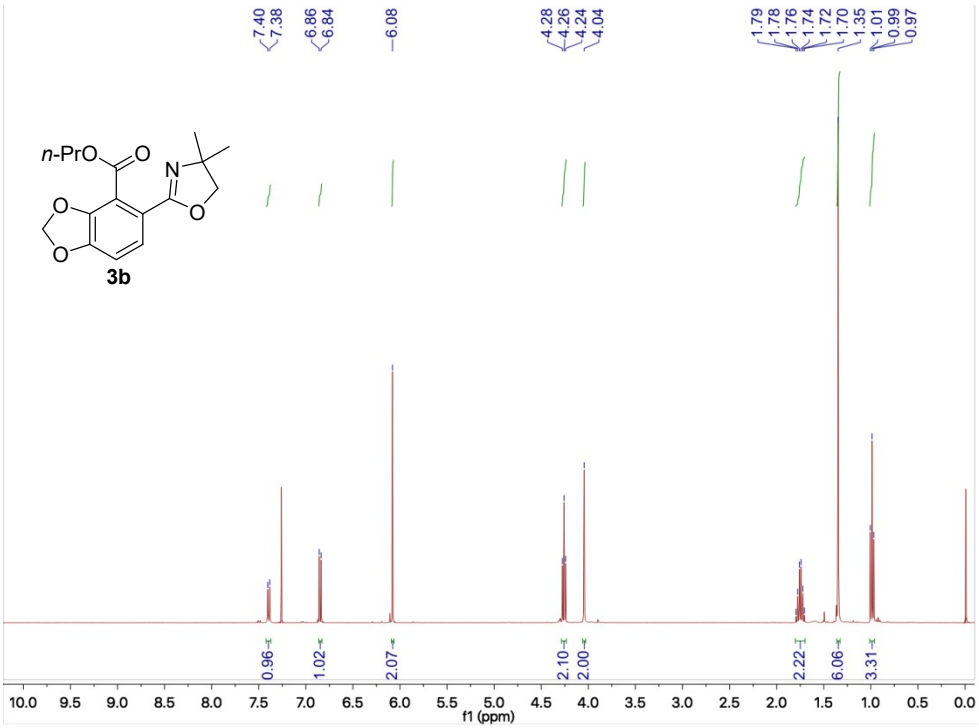

Figure S95. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **3b**

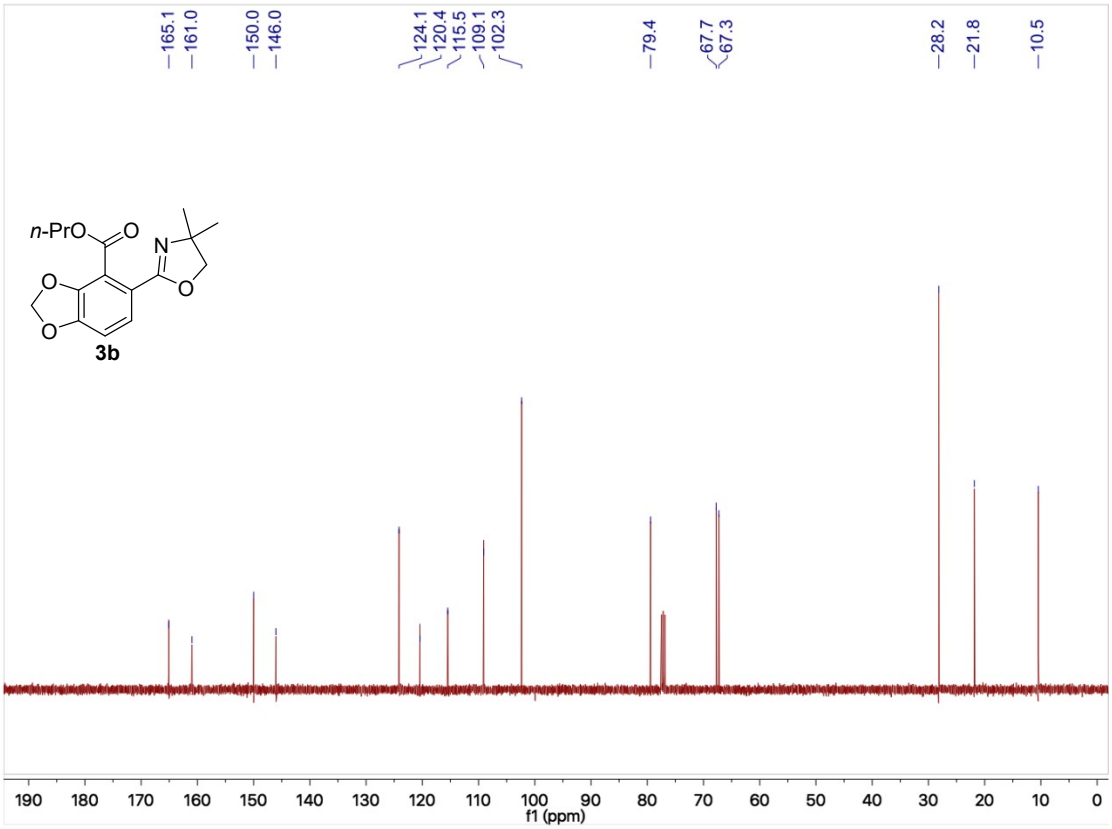

Figure S96. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **3b**

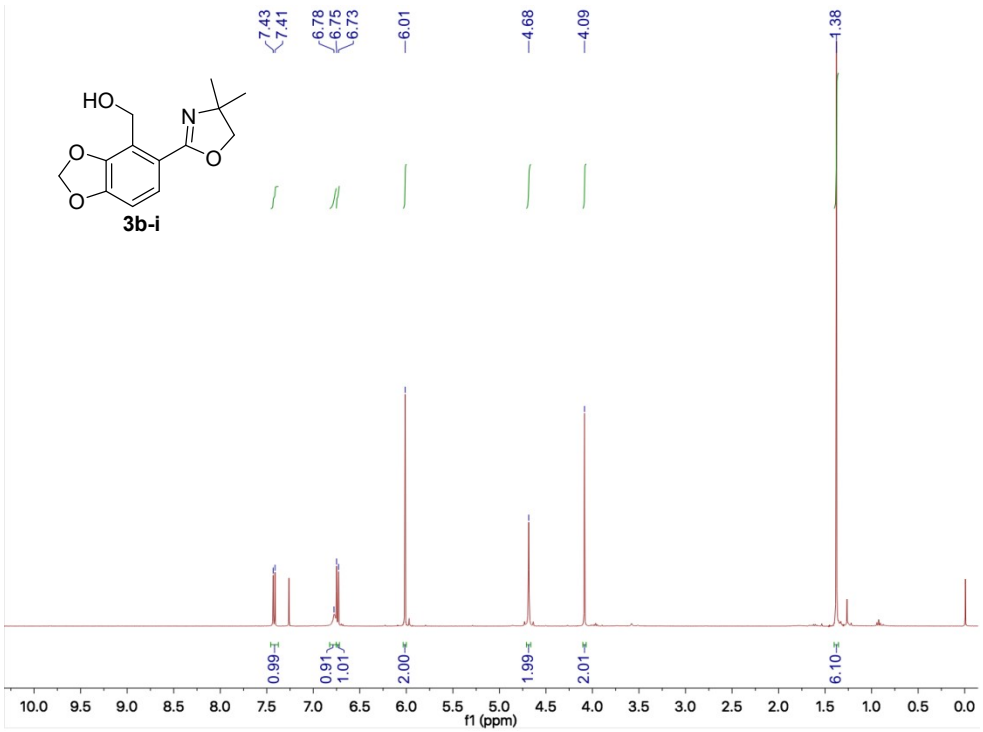

Figure S97. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **3b-i**

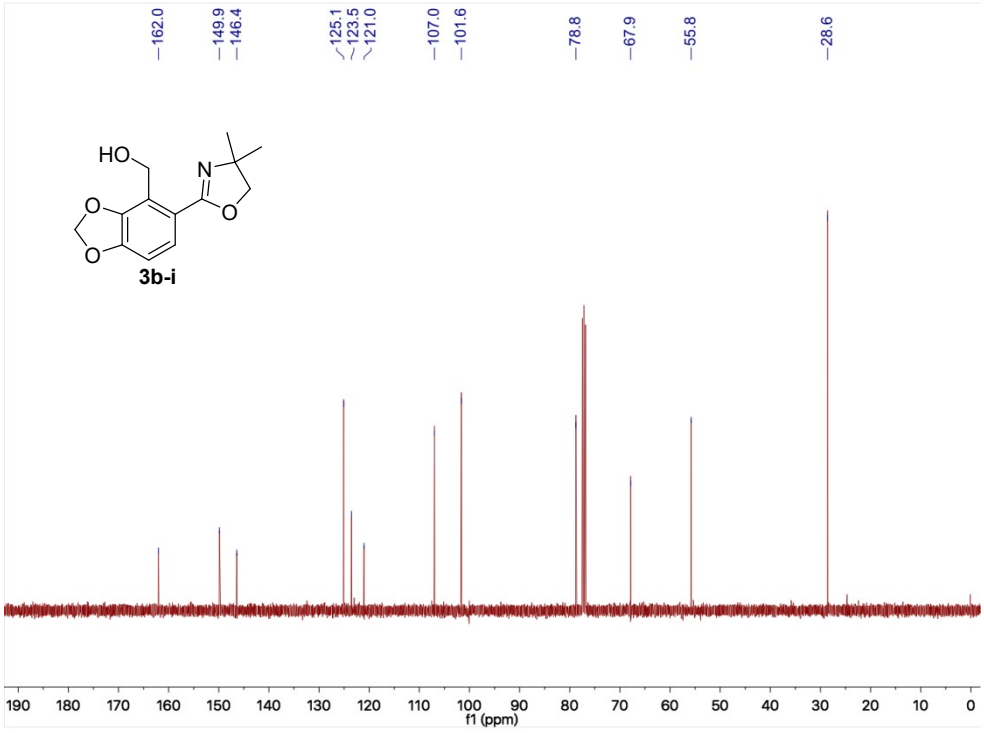

Figure S98. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **3b-i**

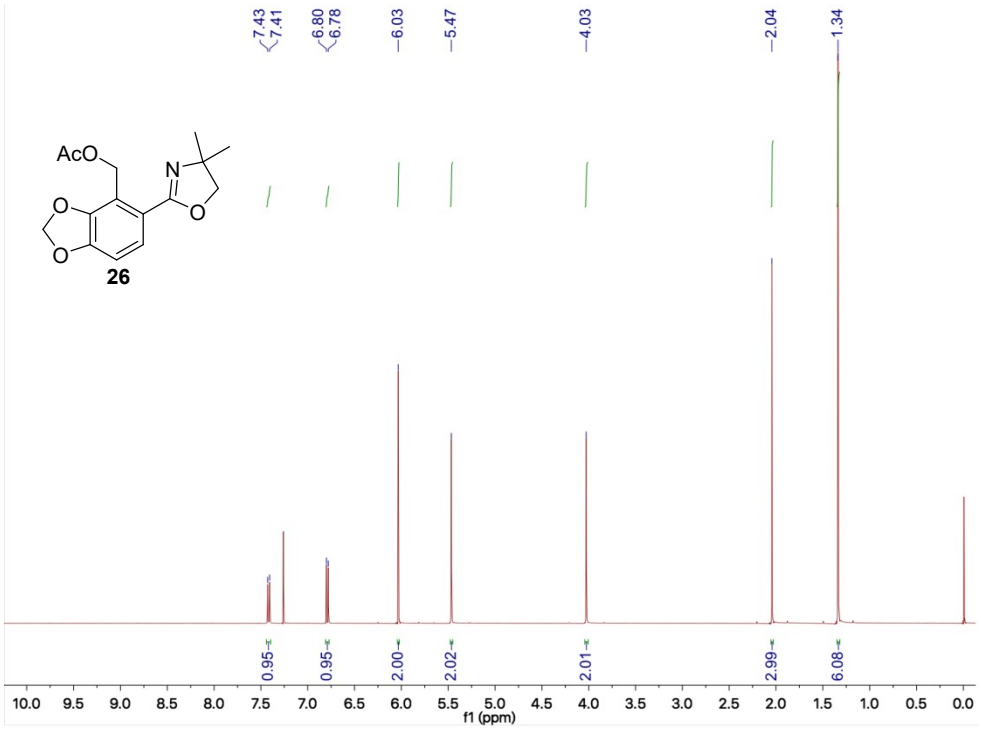

Figure S99. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **26**

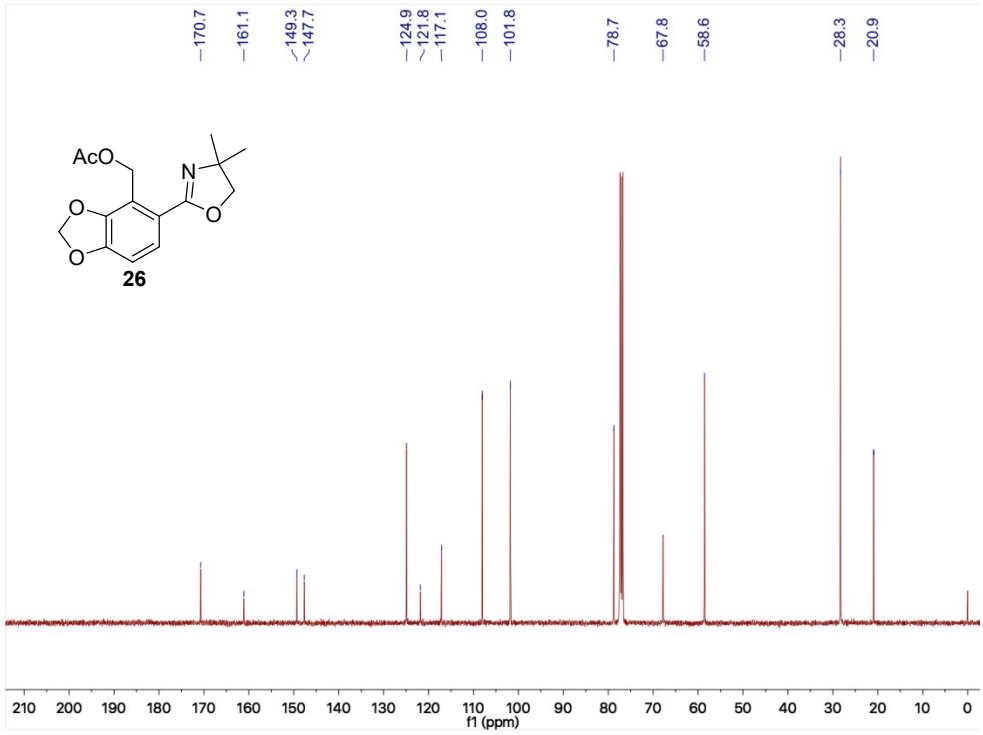

Figure S100. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **26**

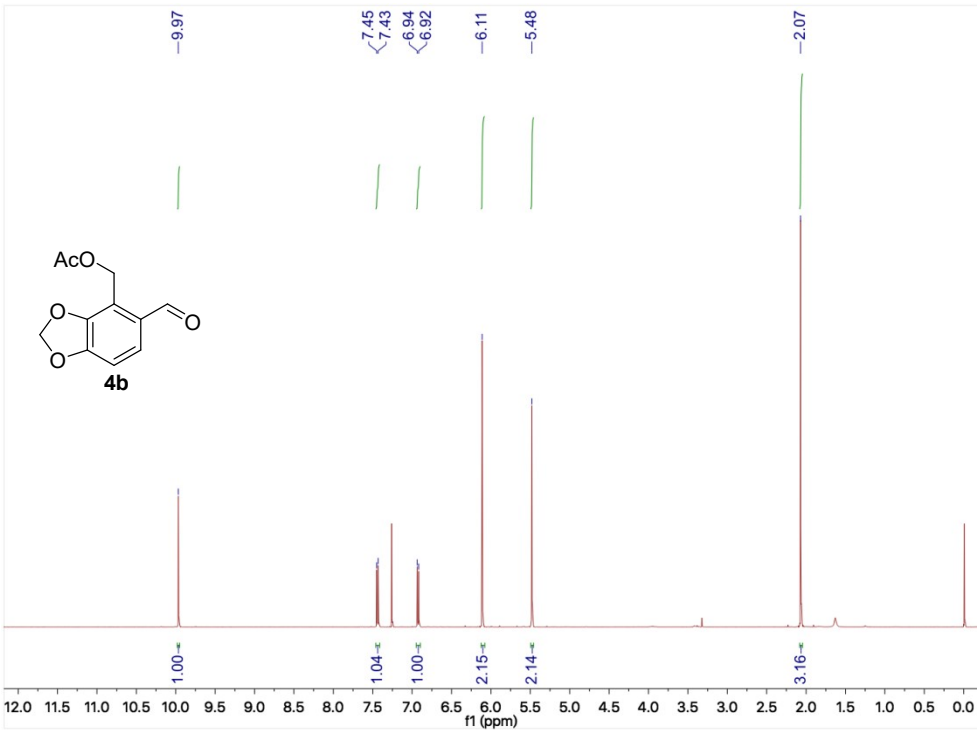

Figure S101. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **4b**

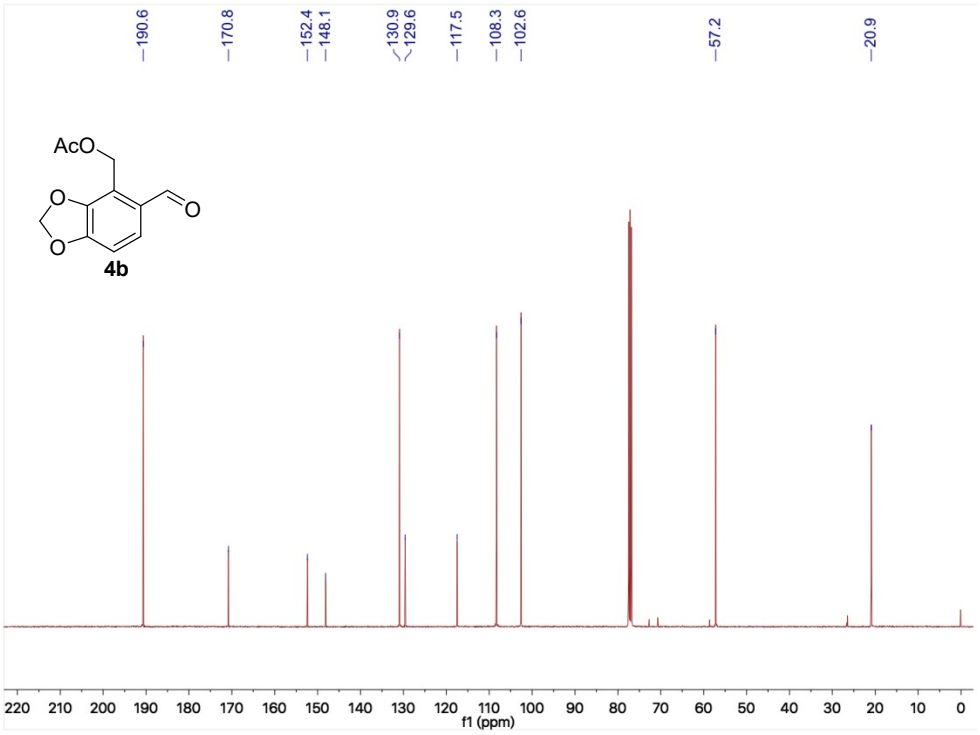

Figure S102. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **4b**

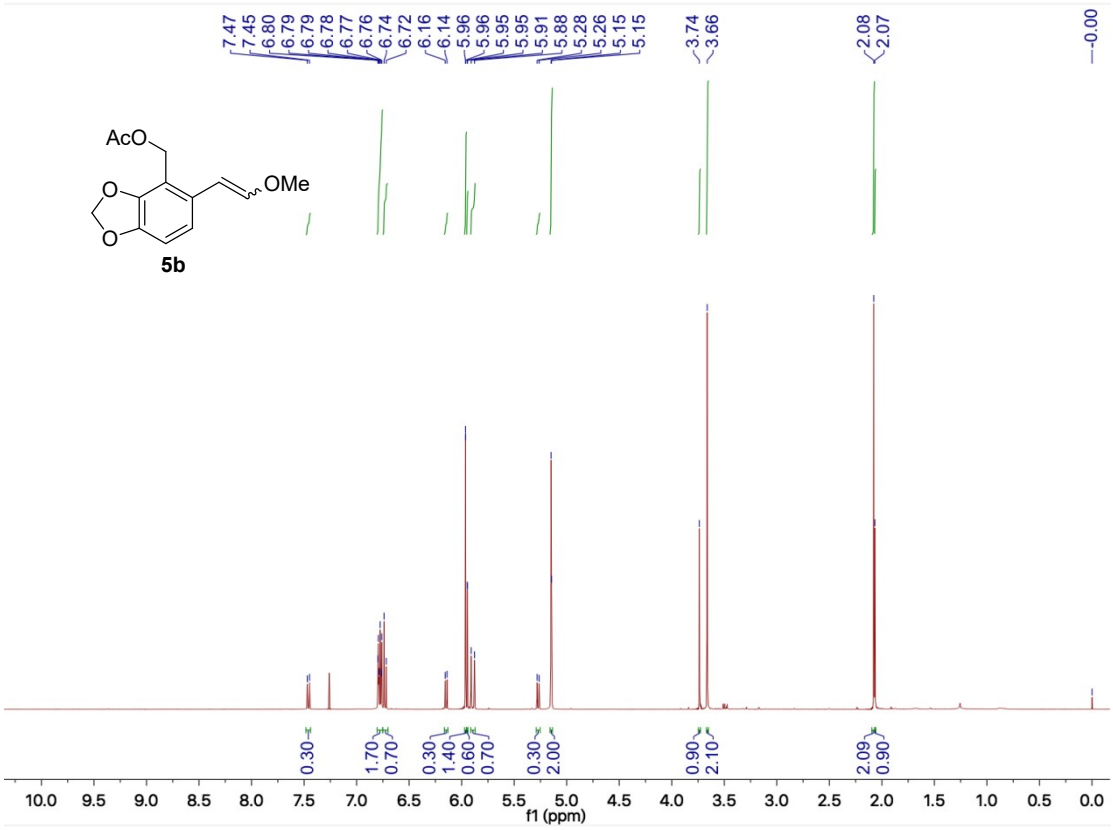

Figure S103. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **5b**

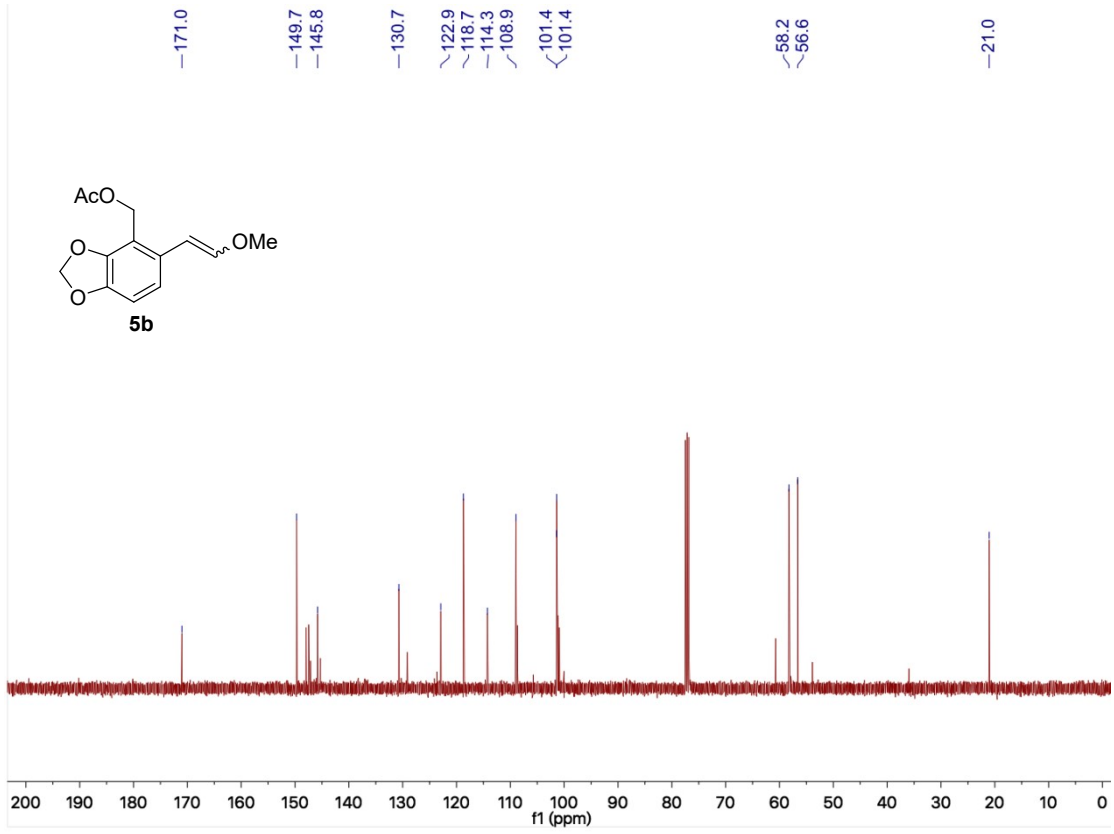

Figure S104. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **5b**

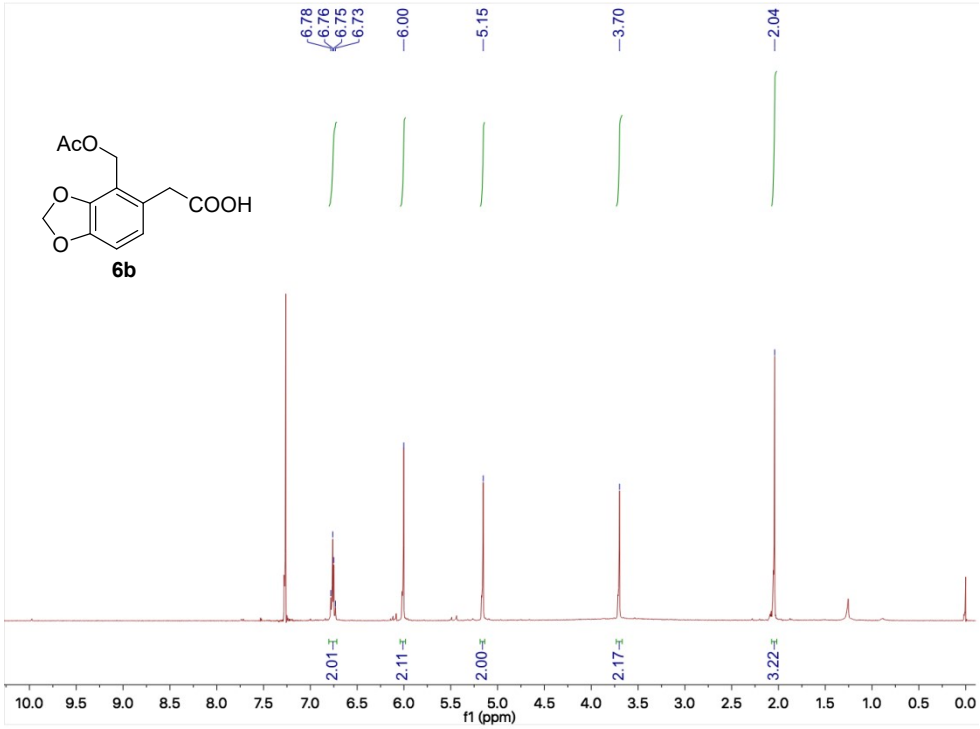

Figure S105. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **6b**

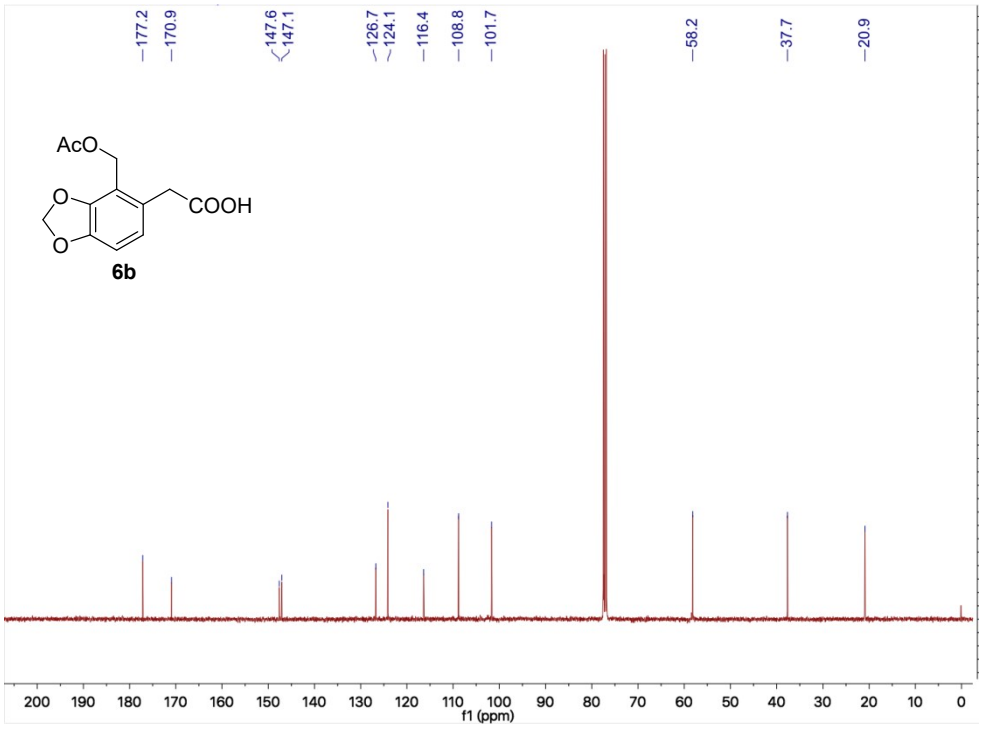

Figure S106. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **6b**

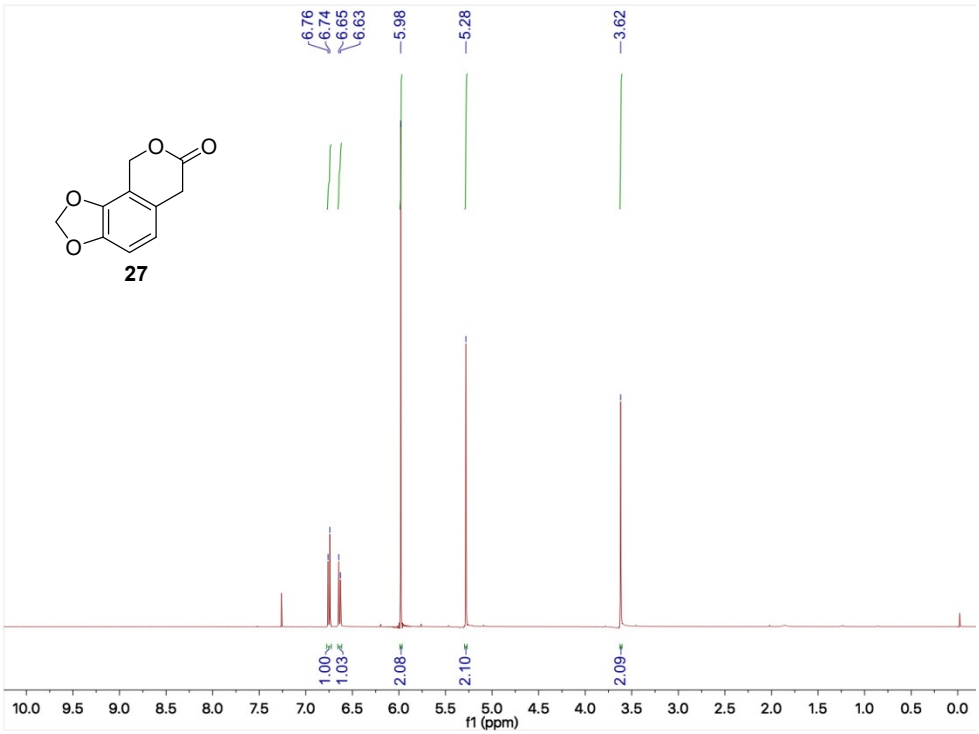

Figure S107. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **27**

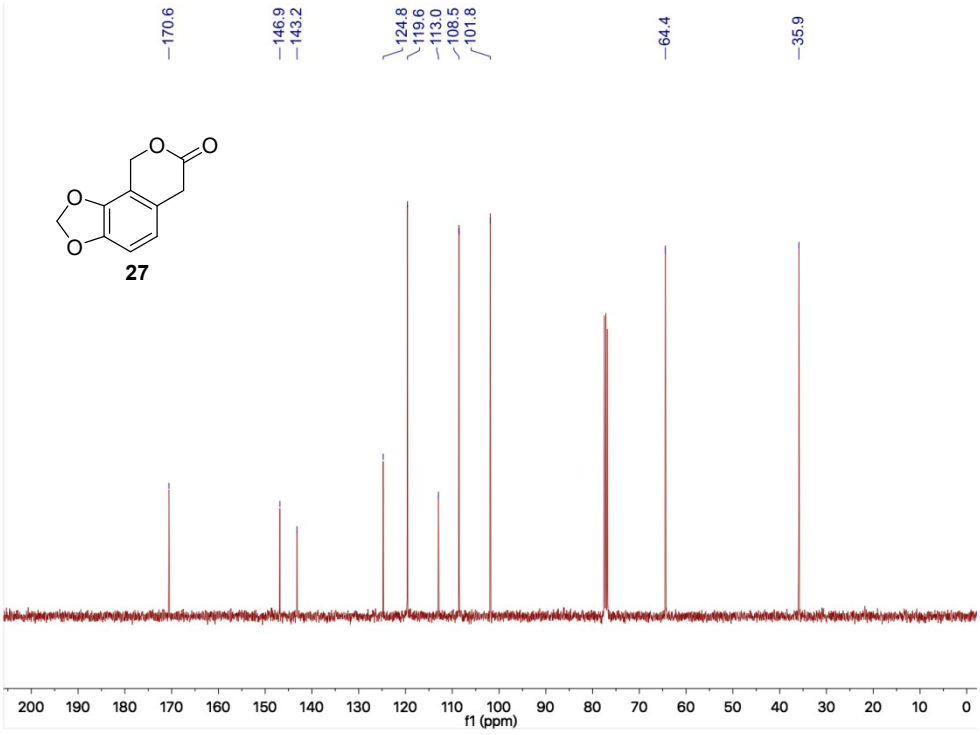

Figure S108. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **27**

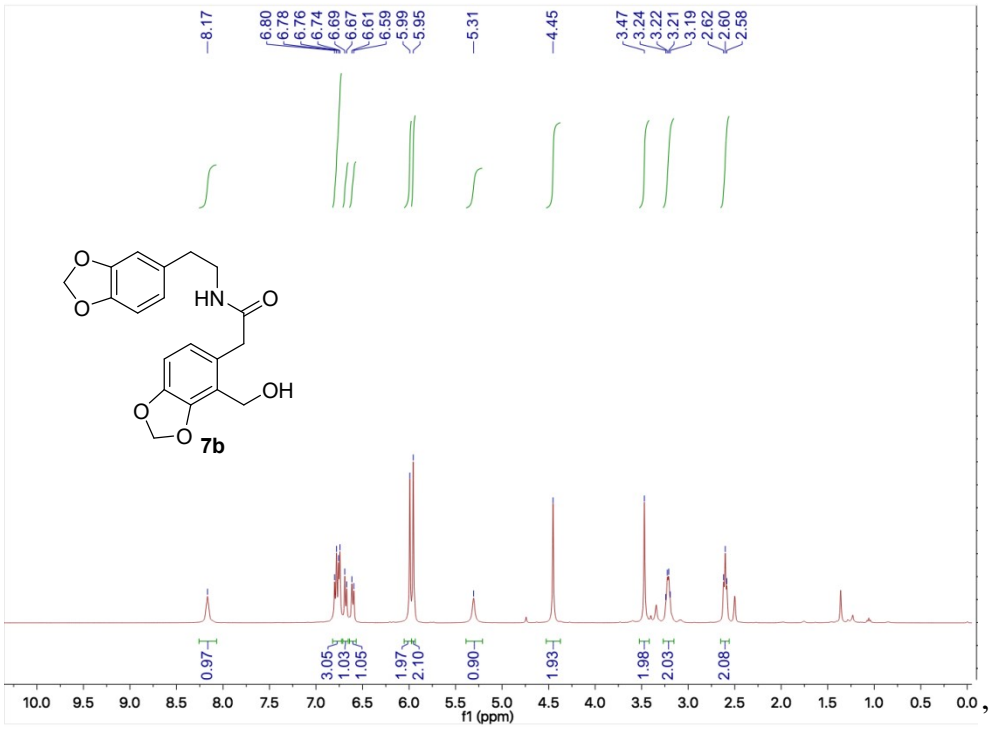

Figure S109. ^{1}H NMR spectrum (400 MHz, DMSO-d_6) of compound **7b**

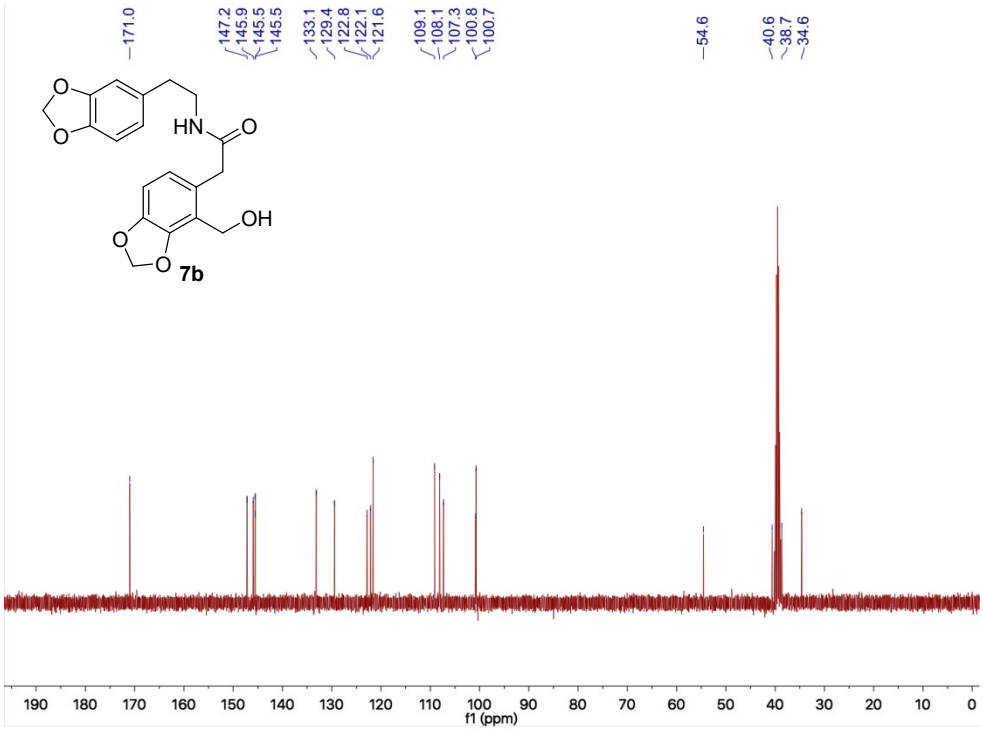

Figure S110. ^{13}C NMR spectrum (100 MHz, DMSO-d_6) of compound **7b**

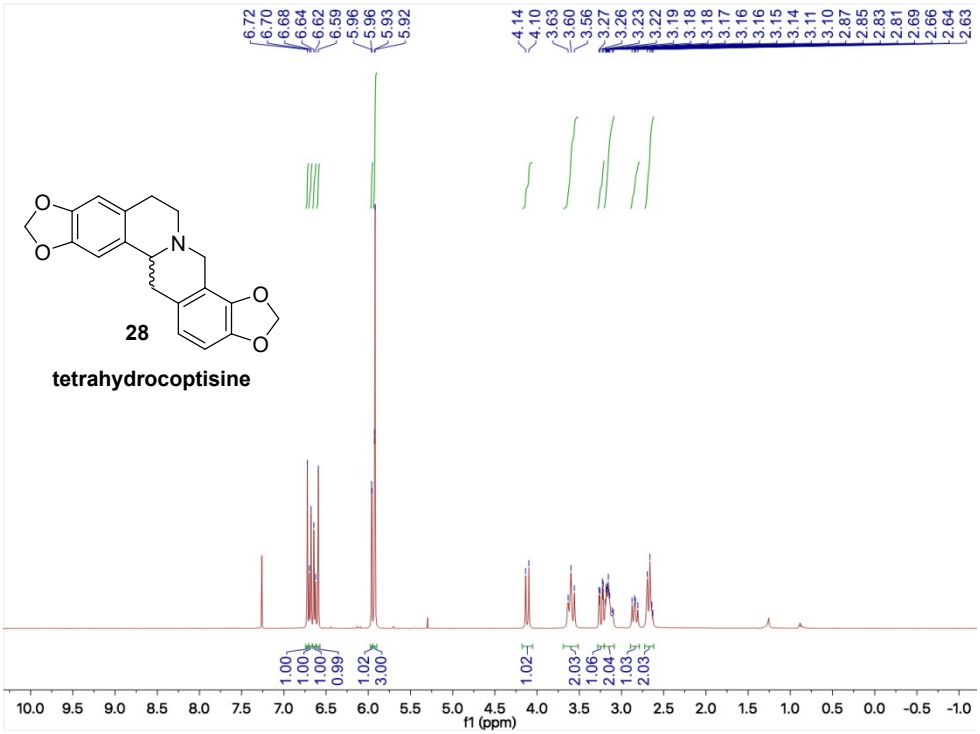

Figure S111. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **28**

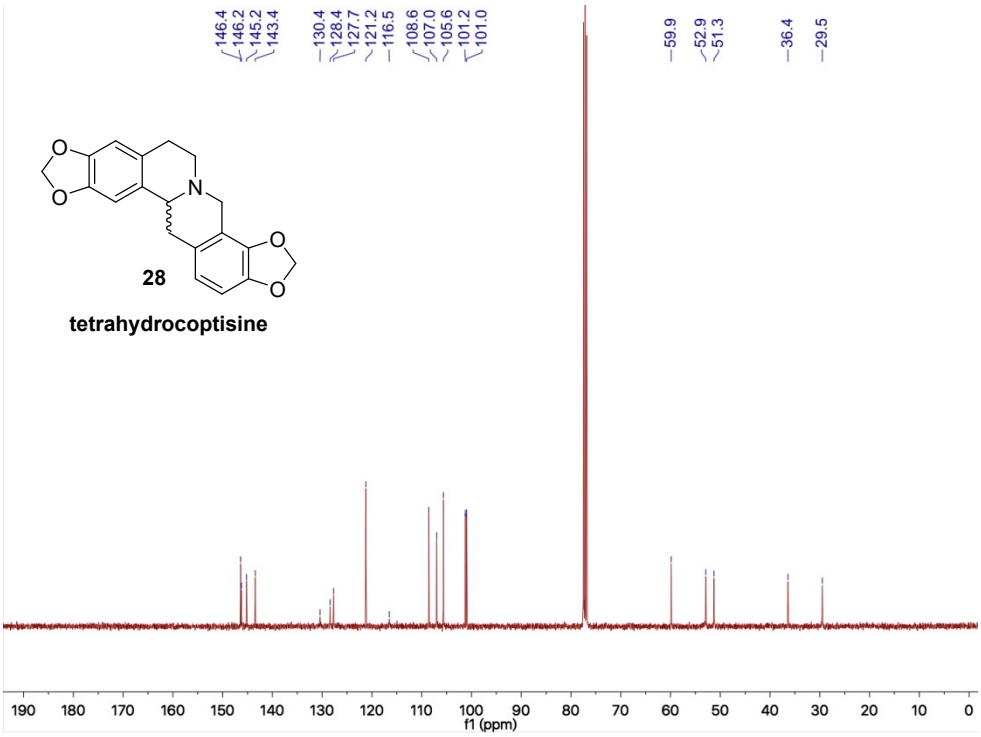

Figure S112. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **28**

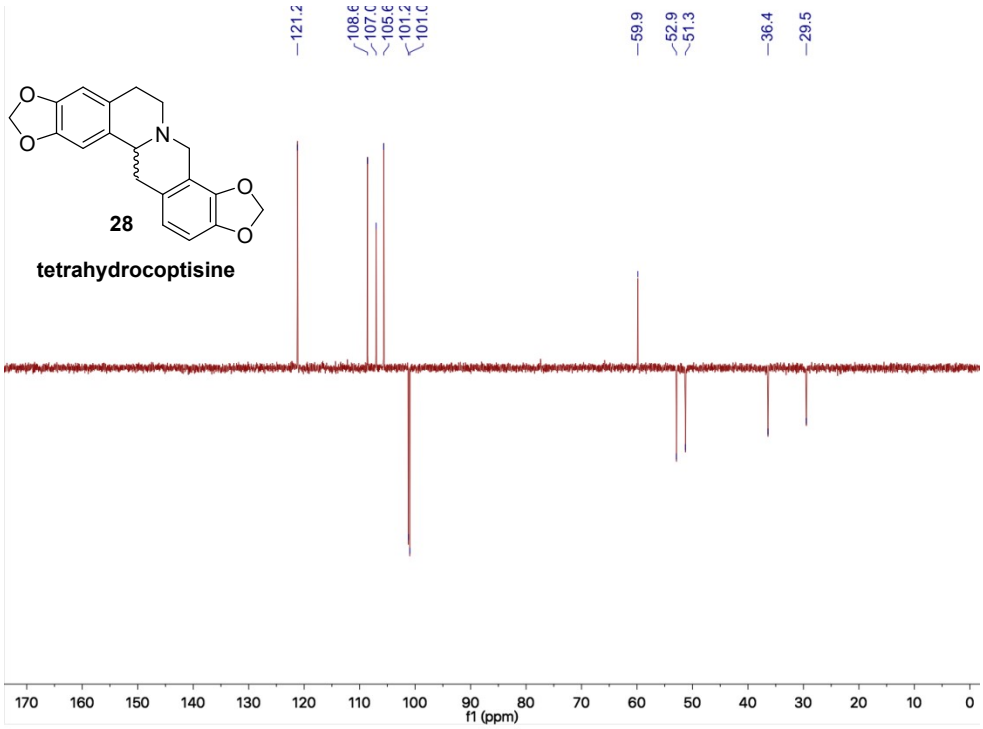

Figure S113. DEPT135 spectrum (100 MHz, $CDCl_3$) of compound **28**

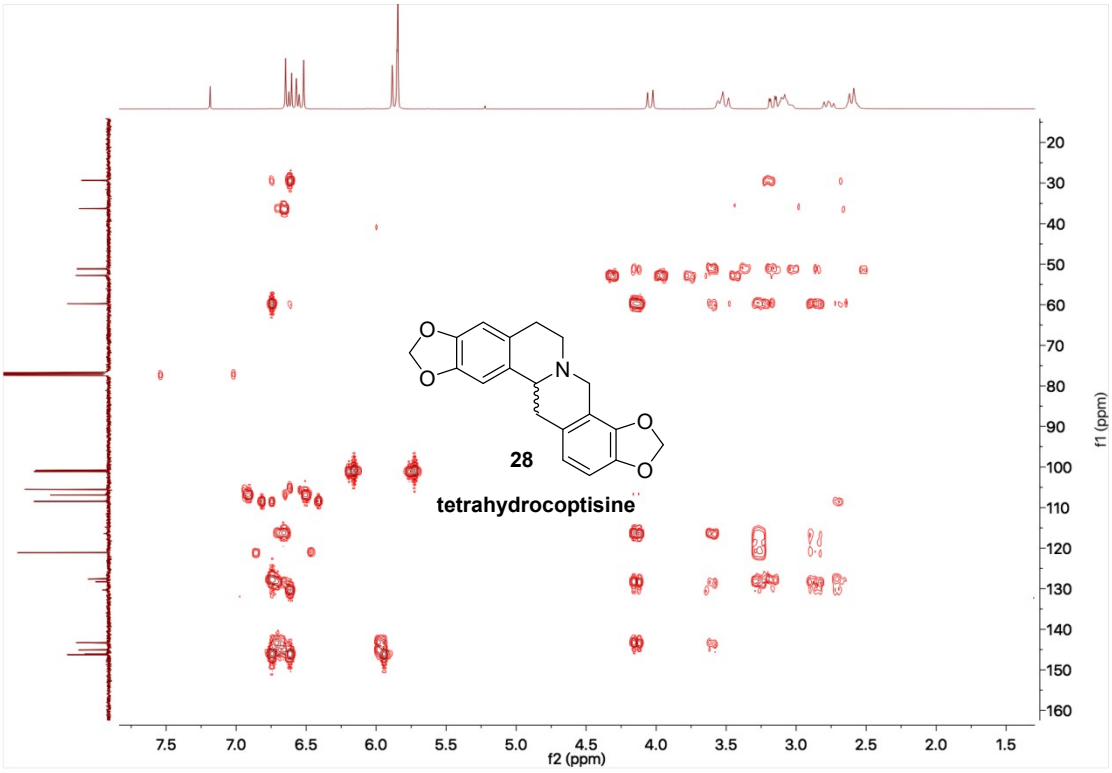

Figure S114. HMBC spectrum (400 MHz, $CDCl_3$) of compound **28**

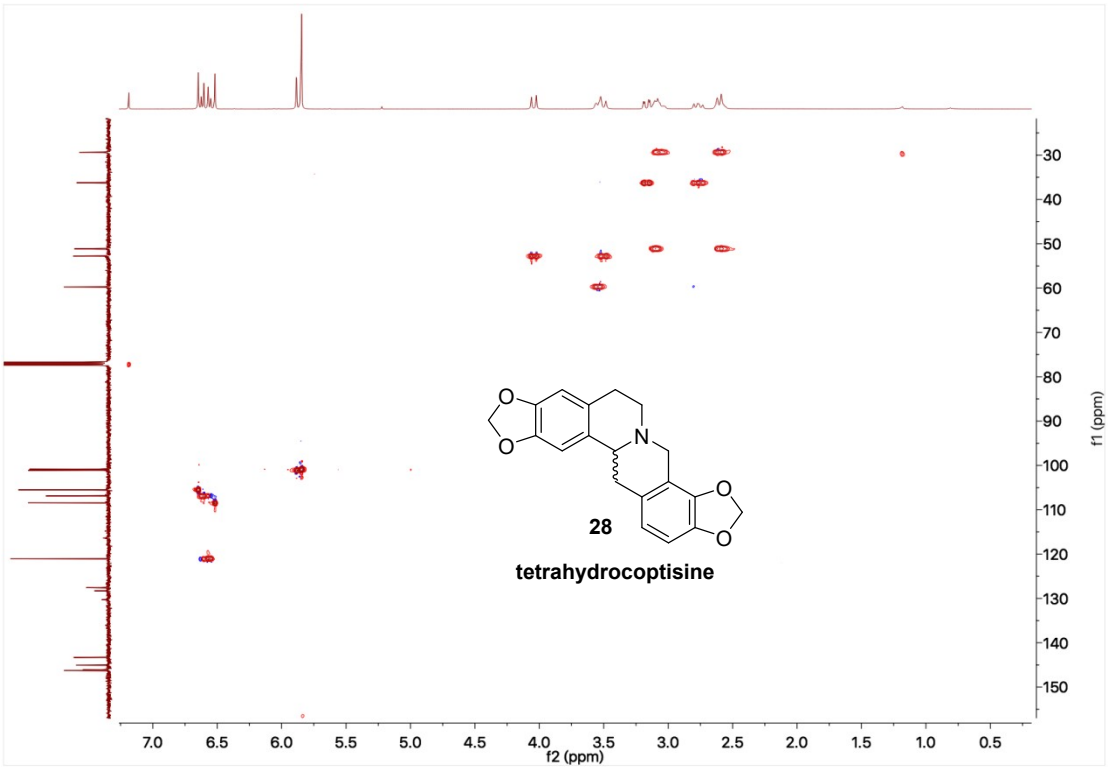

Figure S115. HSQC spectrum (400 MHz, $CDCl_3$) of compound **28**

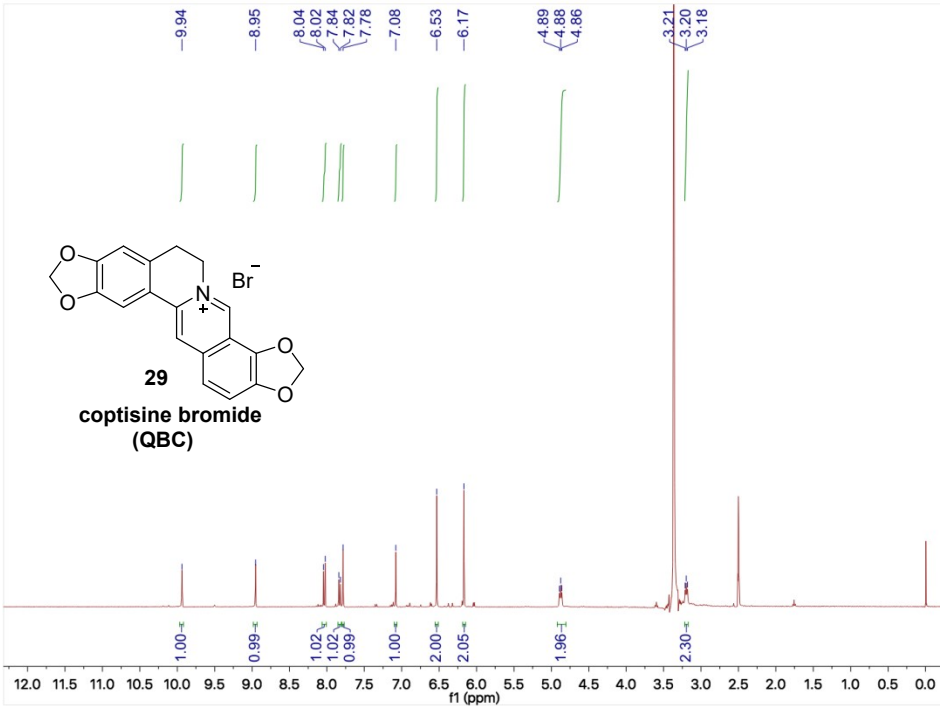

Figure S116*. ^{1}H NMR spectrum (400 MHz, DMSO-d_6) of compound **29**

*QCB is a compound that is very easy to crystallize and purify. In this study, the compound was not purified by crystallization.

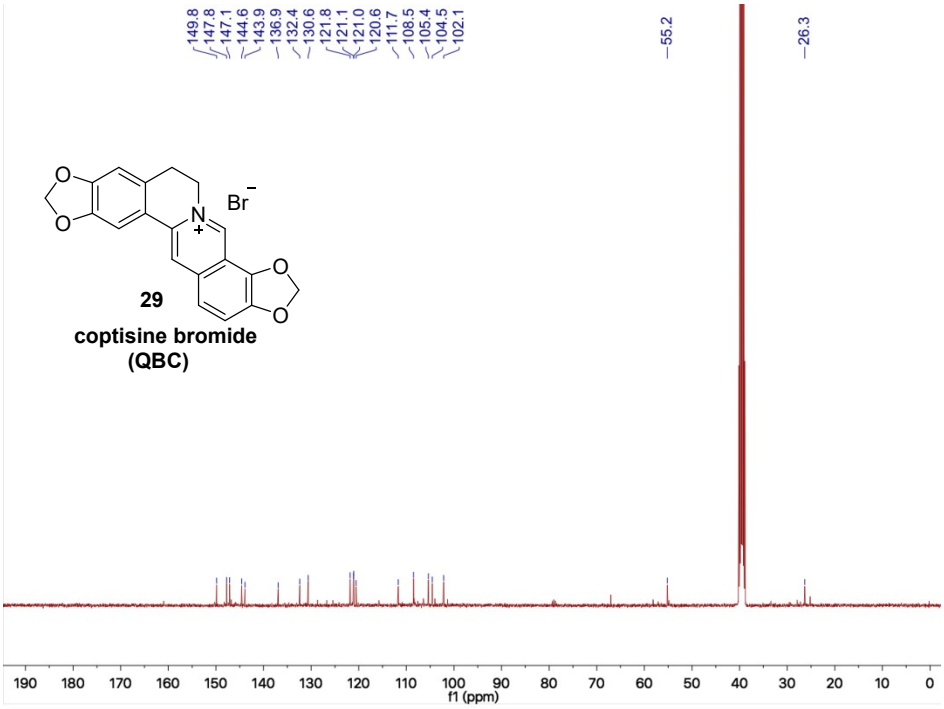

Figure S117*. ^{13}C NMR spectrum (100 MHz, DMSO-d_6) of compound **29**

*QCB is a compound that is very easy to crystallize and purify. In this study, the compound was not purified by crystallization.

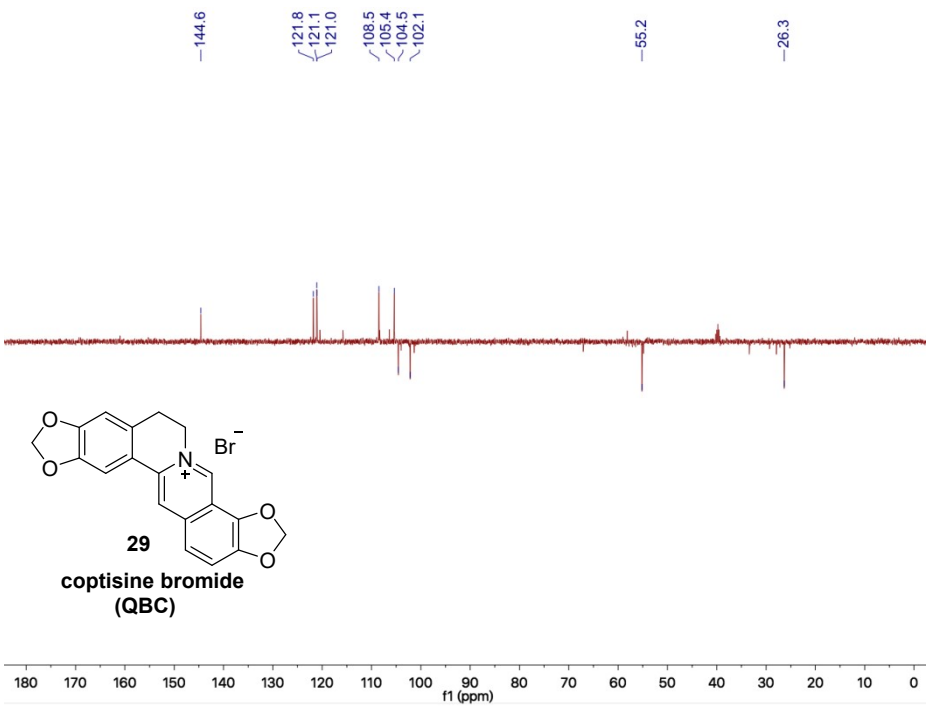

Figure S118. DEPT135 spectrum (100 MHz, DMSO-d_6) of compound **29**

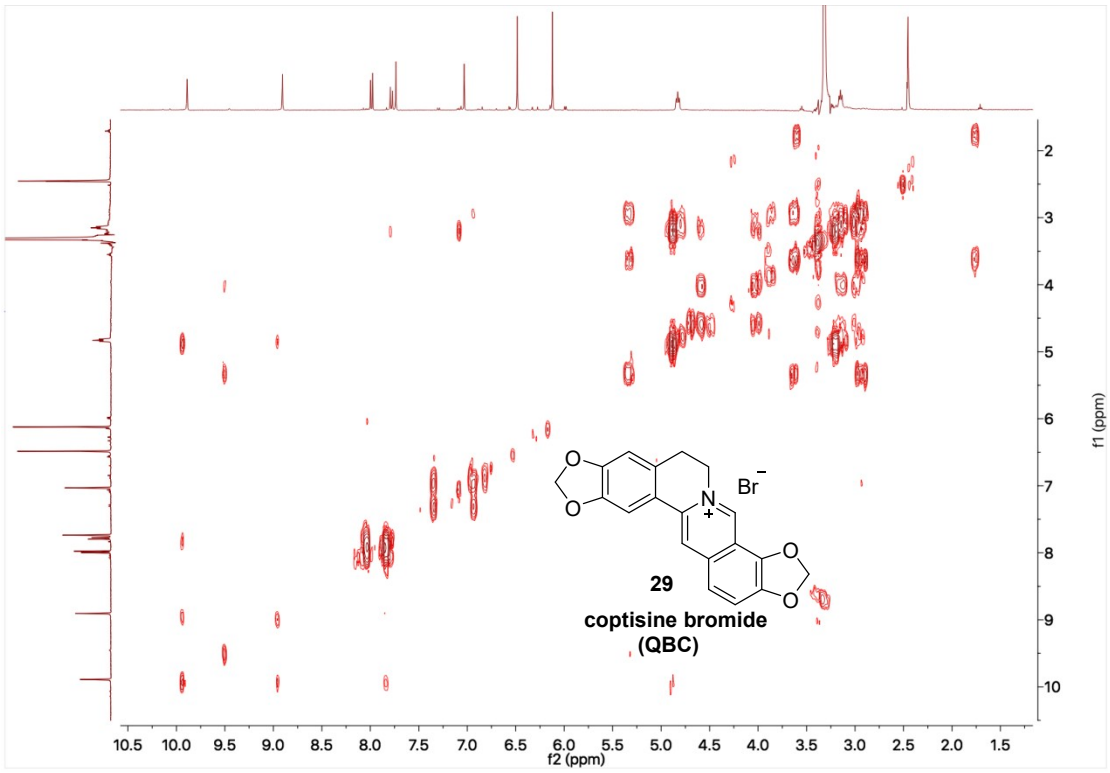

Figure S119. ^{1}H-^{1}H COSY spectrum (400 MHz, DMSO-d_6) of compound **29**

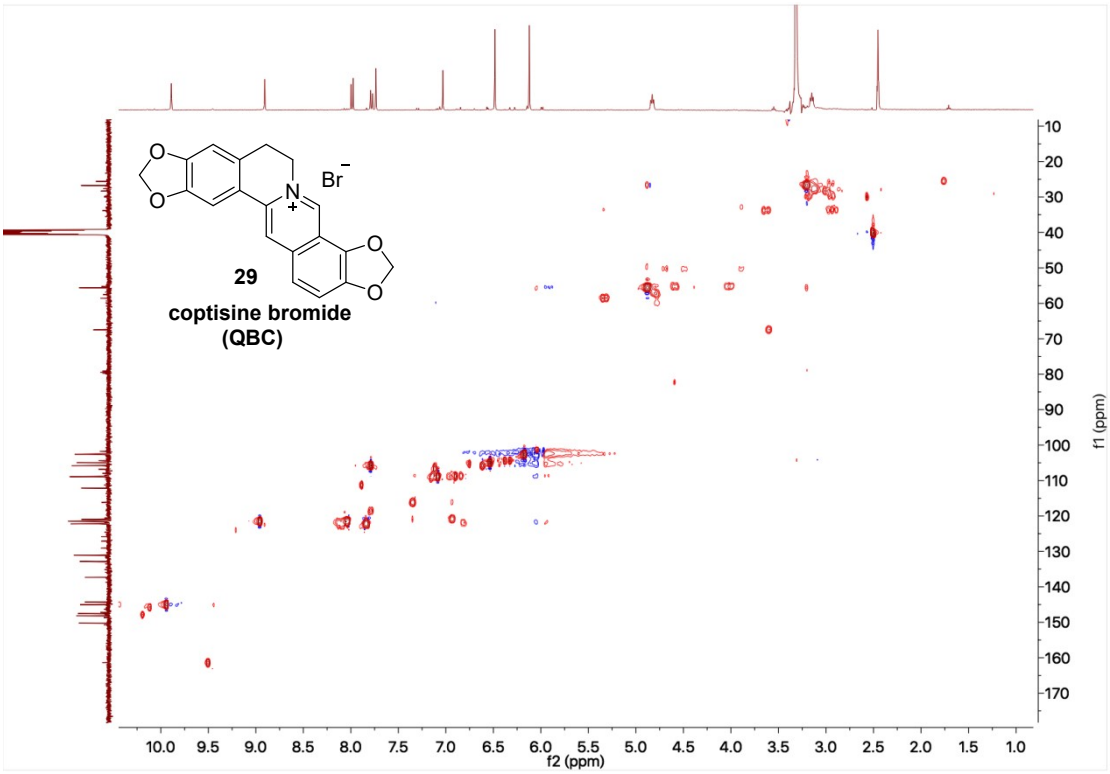

Figure S120. HSQC spectrum (400 MHz, DMSO-d_6) of compound **29**

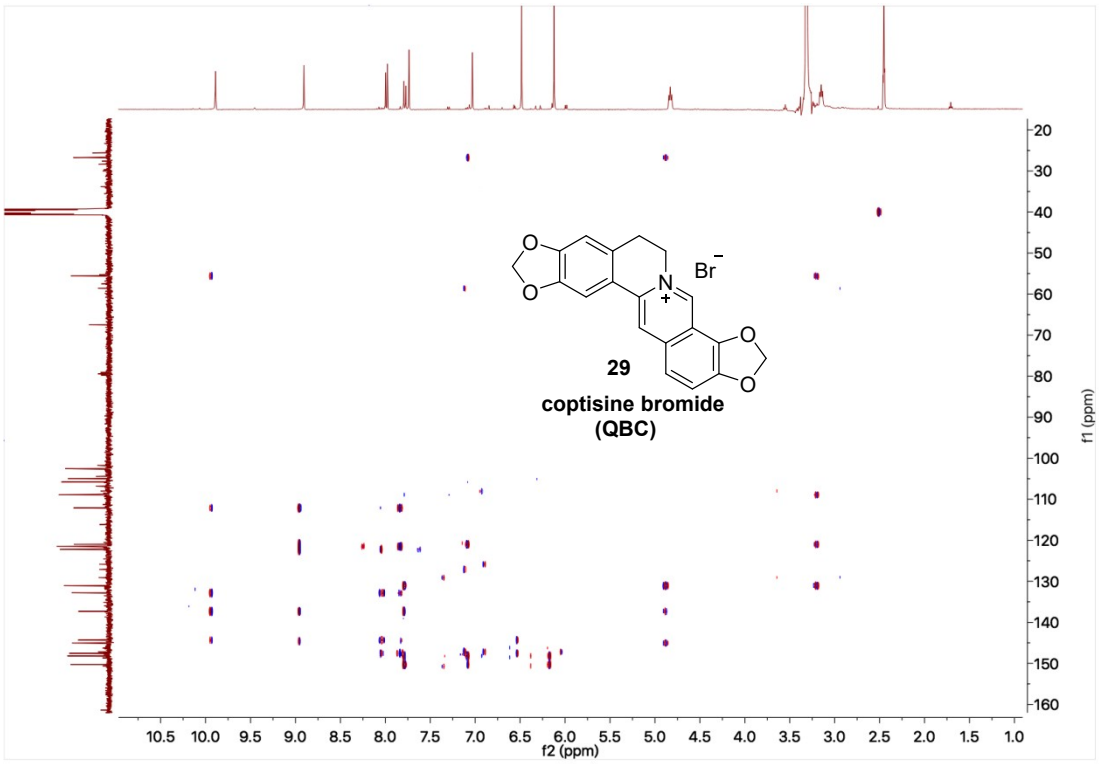

Figure S121. HMBC spectrum (400 MHz, DMSO-d_6) of compound **29**