Organocatalytic Cascade Reaction of 2-Nitrocyclohexanone and α, β-Unsaturated Aldehydes with Unusual Regioselectivity

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(A) General details

^{1}H and ^{13}C NMR spectrum were recorded on a Bruker Advance 400 MHz spectrometer as solutions in $CDCl_3$. Chemical shifts are reported in ppm relative to residual solvent signals (CDCl3, 7.26 ppm for ^{1}H NMR, $CDCl_3$, 77.0 ppm for ^{13}C NMR), Coupling constants are reported in Hertz (abbreviated for Hz). The following abbreviations are used to designate chemical shift mutiplicities: s= singlet, d= doublet, m= multiplet, br=broad. High-resolution mass spectrum were obtained with Shimadazu LCMS-IT-TOF mass spectrometer. Optical rotations were measured using a 1 mL cell with a 1 dm path length on a Perkin-Elmer 341 digital polarimeter and are reported as follows: $[\alpha]_D^{20}$ (*c* in gram per 100 mL of solvent). The flash column chromatography was carried out over silica gel (230–400 mesh), purchased from Qingdao Haiyang Chemical Co., Ltd. Melting points were recorded on an electrothermal digital melting point apparatus and were uncorrected. TLC analysis was performed on precoated silica gel GF_{254} slides, and visualised by either UV irradiation or I_2 staining. Infrared (IR) spectrum were recorded on a Bruker Tensor 37 spectrophotometer. Data are represented as frequency of absorption (cm^{-1}). Unless otherwise stated, all reagents were obtained from commercial sources and used as received. The solvents were used as commercial anhydrous grade without further purification. 2-Nitrocyclohexanone[1] and 2-methyl-6-nitrocyclohexanone[2] were prepared according to the literature procedure respectively. Enantiomeric excesses were determined by HPLC using a Daicel Chiralcel AD-H column (4.6 mm × 25 cm) and eluting with *n*-hexane/*i*-PrOH solution.

(B) Screening of additives for the reaction of 2-nitrocyclohexanone and cinnamaldehyde.

Table 1 Screening of additives[a]

entry	time (h)	additive	yield (%)[b]	dr[c]	ee (%)[d]
1	19	PhCOOH	25	85:15	98
2	9	Na_2CO_3	15	85:15	-
3	9	K_2CO_3	24	83:17	-
4	9	KOAc	23	81:19	-
5	9	Et_3N	84	85:15	99
6	9	DMAP[e]	89	85:15	99
7	9	N-methyl-pyrrolidine	90	86:14	99
8	3	DABCO[f]	96	88:12	99
9	9	DIPEA[g]	35	81:19	99
10	9	NMM[h]	23	82:18	-
11	9	2,6-lutidine	4	-	-

[a] Unless otherwise stated, all reactions were performed with **1** (0.24 mmol), **2a** (0.2 mmol), **3c** (0.02 mmol) and additive (0.02 mmol) in THF (0.5 mL). [b] Determined by HPLC analysis. [c] Determined by ^1H NMR analysis of the crude mixture. [d] Values of the major diastereoisomers and were determined by chiral HPLC. [e] 4-Dimethylaminopyridine. [f] 1, 4-Diazabicyclo[2.2.2]octane. [g] *N,N*-Diisopropylethylamine. [h] *N*-methyl-morpholine.

(C) General experimental procedure for the reaction of 2-nitrocyclohexanone and α, β-unsaturated aldehydes.

To a solution of α, β-unsaturated aldehyde (0.2 mmol) in THF (0.5 mL) was added catalyst **3c** (7.2 mg, 0.02 mmol, 10 mol %), DABCO (2.2 mg, 0.02 mmol) at room temperature. After the reaction mixture was stirred for 10 minutes, 2-nitrocyclohexanone (**1**, 34 mg, 0.24 mmol, 1.2 eq) was added. The mixture was stirred at room temperature for 3h. Then it was concentrated under vacuum and purified by flash column chromatography using ethyl acetate / petrol ether as eluent.

The racemic product was obtained by mixing equal amounts of **4** and ent-**4** independently obtained by using catalyst **3c** and its enatiomer.

(D) Mechanism investigation

To the three portions of solution of **1** (14 mg, 0.1 mmol) in 2.5 mL $CDCl_3$was added one equivalent of **3c**, DABCO, DABCO and **3c** respectively. After stirring for 0.5 h, the mixtures were subjected to NMR analysis.

(E) Elaboration of 4a and 4g

Synthesis of **8a**:

The solution of **4a** (27.5 mg, 0.1 mmol) in 1 mL CH_3OH was refluxed for 3h. Then it was concentrated under vacuum and the residue was purified by flash column chromatography using ethyl acetate / petrol ether as eluent. **8a** was obtained as a white solid.

According to the same procedure, **8g** was also obtained.

Synthesis of **10a**:

To a solution of **8a** (29 mg, 0.1 mmol) in 2.5 mL THF was added Zinc powder (169 mg, 2.6 mmol) and HOAc (162 μL, 2.8 mmol). After the mixture was stirred overnight, it was diluted with EtOAc (30 mL). The organic layer was washed with saturated Na_2CO_3 (10 mL × 2,) and brine (10 mL). The organic layer was dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by flash column chromatography.

(F) X-ray Structure of 8g

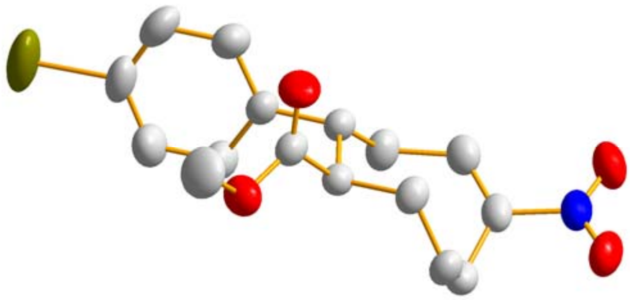
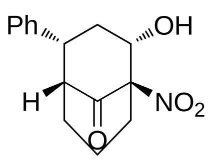
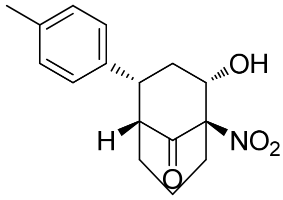


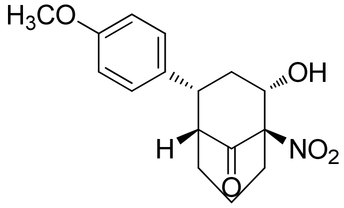
Figure 1. X-ray Structure of 8g



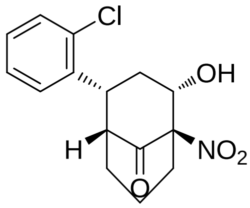
(*1R,2S,4R,5R*)-2-hydroxy-1-nitro-4-phenylbicyclo[3.3.1]nonan-9-one , sticky pale yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 - 7.37(m, 2H), 7.32-7.25(m, 3H),δ 5.05 (ddd, J = 11.4, 6.8, 1.6 Hz, 1H), 3.24 (dt, J = 14.0, 4.8 Hz, 1H), 2.95-2.80(m, 3H), 2.70 (td, J = 14.0, 11.4 Hz, 1H), 2.62 (shift to 2.79 in concentrated solution, br, 1H,), 2.47-2.40 (m, 1H), 2.23-2.10 (m, 1H), 1.94-1.84 (m, 2H), 1.83-1.73 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.79, 138.75, 128.91, 127.47, 127.44, 101.32, 72.37, 51.89, 41.10, 32.61, 31.24, 26.91, 20.14; IR (KBr) ν/cm^{-1}: 3446, 2937, 1733, 1550, 1033; HRMS (ESI) calcd for $C_{15}H_{16}NO_4$(M - H)$^-$: 274.1085, found: 274.1098; $[\alpha]_D^{20}$ = + 106.6 (c = 1.0, $CHCl_3$); The enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (4.6 mm × 25 cm) (*n*-hexane/*i*-PrOH = 90/10, λ = 220 nm, 0.8 mL/min); t_R (minor enantiomer) = 20.1 min, t_R (major enantiomer) = 31.8 min, 99% ee.



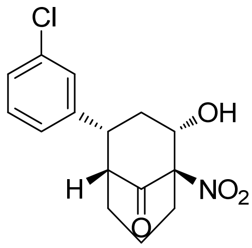
(*1R,2S,4R,5R*)-2-hydroxy-1-nitro-4-(p-tolyl)bicyclo[3.3.1]nonan-9-one , sticky pale yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (q, *J* = 8.2 Hz, 4H), 5.04 (ddd, *J* = 11.4, 6.6, 1.5 Hz, 1H), 3.20 (dt, *J* = 14.0, 4.8 Hz, 1H), 2.94 – 2.80 (m, 4H), 2.67 (td, *J* = 14.0, 11.4 Hz, 1H), 2.44 – 2.37 (m, 1H), 2.35 (s, 3H), 2.20-2.10 (m, 1H), 1.94 – 1.88 (m, 1H), 1.85 – 1.71 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.98, 137.10, 135.69, 129.53, 127.31, 101.33, 72.39, 51.94, 40.72, 32.77, 31.22, 26.92, 26.88, 20.94, 20.12; IR (KBr) ν/cm^{-1}: 3526, 2926, 1734, 1550, 1079, 1041; HRMS (ESI) calcd for $C_{16}H_{18}NO_4$(M - H)$^-$: 288.1241, found: 288.1249; $[\alpha]_D^{20}$ = + 99.0 (c = 1.1, $CHCl_3$); The enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (4.6 mm × 25 cm) (*n*-hexane/*i*-PrOH = 90/10, λ = 230 nm, 0.8 mL/min); t_R (minor enantiomer) = 16.5 min, t_R (major enantiomer) = 31.3 min, 99% ee.



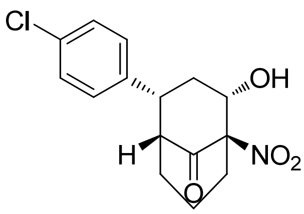
(*1R,2S,4R,5R*)-2-hydroxy-4-(4-methoxyphenyl)-1-nitrobicyclo[3.3.1]nonan-9-one, sticky pale yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, *J* = 8.5 Hz, 2H), 6.91 (d, *J* = 8.5 Hz, 2H), 5.05 – 5.01 (m, 1H), 3.81 (s, 3H), 3.19 (dt, *J* = 13.8, 4.3 Hz, 1H), 2.92 – 2.80 (m, 3H), 2.64 (q, *J* = 13.8Hz, 1H), 2.44 – 2.37(m, 1H); 2.20 -2.09 (m, 1H), 1.89 – 1.83 (m, 2H), 1.80 - 1.74 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.01, 158.81, 130.69, 128.43, 114.25, 101.30, 72.35, 55.30, 52.05, 40.38, 32.94, 31.22, 26.86, 20.12; IR (KBr) ν/cm^{-1}: 3447, 2935, 1734, 1550, 1514, 1253, 1034; HRMS (ESI) calcd for $C_{16}H_{18}NO_5$(M - H)$^-$: 304.1190, found: 304.1188; $[\alpha]_D^{20}$ = + 84.8 (c = 0.9, $CHCl_3$); The enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (4.6 mm × 25 cm) (*n*-hexane/*i*-PrOH = 90/10, λ = 230 nm, 0.8 mL/min); t_R (minor enantiomer) = 27.5min, t_R (major enantiomer) = 47.7 min, 99% ee.



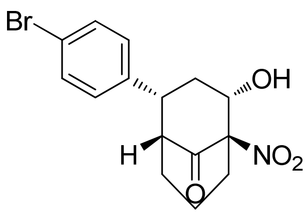
(*1R,2S,4R,5R*)-4-(2-chlorophenyl)-2-hydroxy-1-nitrobicyclo[3.3.1]nonan-9-one , sticky pale yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.38 (m, 2H), 7.36 – 7.32 (m, 1H), 7.29 – 7.24 (m, 1H), 5.09 (ddd, *J* = 11.3, 6.6, 1.6 Hz, 1H), 3.67 (dt, *J* = 14.0, 4.5 Hz, 1H), 3.00 (q, *J* = 4.5 Hz, 1H), 2.97 – 2.83 (m, 3H), 2.76 (td, *J* = 14.0, 11.3 Hz, 1H), 2.31 (dt, *J* = 14.0, 6.0 Hz, 1H), 2.24 – 2.17 (m, 1H), 1.87 – 1.82 (m, 2H), 1.81 – 1.74 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.13, 135.92, 134.18, 130.42, 128.66, 128.00, 126.99, 101.27, 76.70, 76.68, 72.17, 48.17, 37.73, 32.51, 31.20, 26.95, 20.05; IR (KBr) ν/cm^{-1}: 3512, 2927, 1734, 1551, 1531, 1082, 1033; HRMS (ESI) calcd for $C_{15}H_{15}ClNO_4$ (M - H)$^-$: 308.0695, found: 308.0709; $[\alpha]_D^{20}$ = + 116.1 (c = 1.2, $CHCl_3$); The enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (4.6 mm × 25 cm) (*n*-hexane/*i*-PrOH = 90/10, λ = 220 nm, 0.8 mL/min); t_R (minor enantiomer) = 20.1 min, t_R (major enantiomer) = 32.1 min, 99% ee.



(*1R,2S,4R,5R*)-4-(3-chlorophenyl)-2-hydroxy-1-nitrobicyclo[3.3.1]nonan-9-one , sticky pale yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.26 (m, 3H), 7.16 – 7.15 (m, 1H), 5.04 (dd, *J* = 11.3, 6.6 Hz, 1H), 3.21 (dt, *J* = 13.9, 4.9 Hz, 1H), 2.94 – 2.80 (m, 4H), 2.65 (td, *J* = 13.9, 11.3 Hz, 1H), 2.46 – 2.39 (m, 1H), 2.22 – 2.06 (m, 1H), 1.91 – 1.85 (m, 2H), 1.83 – 1.75 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.34, 140.90, 134.90, 130.14, 127.66, 125.66, 101.16, 72.17, 51.58, 40.71, 32.50, 31.16, 26.88, 20.10; IR (KBr) *ν*/cm^{-1}: 3447, 2928, 1734, 1596, 1549, 1081, 1042; HRMS (ESI) calcd for $C_{15}H_{15}ClNO_4$ (M - H)$^-$: 308.0695, found: 308.0712; $[\alpha]_D^{20}$ = + 107.6 (c = 0.9, $CHCl_3$); The enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (4.6 mm × 25 cm) (*n*-hexane/*i*-PrOH = 90/10, λ = 220 nm, 0.8 mL/min); t_R (minor enantiomer) = 19.9 min, t_R (major enantiomer) =22.6 min, 99% ee.

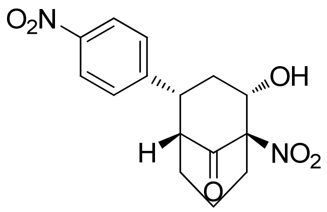


(*1R,2S,4R,5R*)-4-(4-chlorophenyl)-2-hydroxy-1-nitrobicyclo[3.3.1]nonan-9-one , sticky pale yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.5 Hz, 2H), 7.20 (d, *J* = 8.5 Hz, 2H), 5.09 – 4.99 (m, 1H), 3.22 (dt, *J* = 14.0, 4.8 Hz, 1H), 2.94 – 2.78 (m, 4H), 2.64 (td, *J* = 14.0, 11.2 Hz, 1H), 2.41 (dt, *J* = 14.0, 6.1 Hz, 1H), 2.17 – 2.07 (m, 1H), 1.89 – 1.84 (m, 2H), 1.82 – 1.74 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.50, 137.24, 133.32, 129.05, 128.76, 101.17, 72.20, 51.68, 40.49, 32.63, 31.16, 26.83, 20.08; IR (KBr) *ν*/cm^{-1}: 3503, 2928, 1734, 1549, 1493, 1092; HRMS (ESI) calcd for $C_{15}H_{15}ClNO_4$ (M - H)$^-$: 308.0695, found: 308.0690; $[\alpha]_D^{20}$ = + 96.1 (c = 0.9, $CHCl_3$); The enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (4.6 mm × 25 cm) (*n*-hexane/*i*-PrOH = 90/10, λ = 230 nm, 0.8 mL/min); t_R (minor enantiomer) = 25.0 min, t_R (major enantiomer) = 32.6 min, 99% ee.

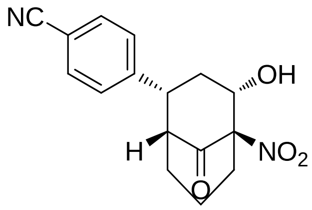


(*1R,2S,4R,5R*)-4-(4-bromophenyl)-2-hydroxy-1-nitrobicyclo[3.3.1]nonan-9-one , sticky pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.3 Hz, 2H), 7.14 (d, *J* =

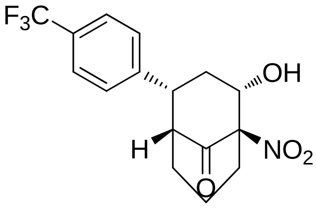
8.3 Hz, 2H), 5.04 (ddd, *J* = 11.3, 6.7, 1.6 Hz, 1H), 3.20 (dt, *J* = 14.0, 4.8 Hz, 1H), 2.93 – 2.75 (m, 4H), 2.64 (td, *J* = 14.0, 11.3 Hz, 1H), 2.41 (dt, *J* = 14.0, 6.0 Hz, 1H), 2.17 – 2.07 (m, 1H), 1.89 – 1.84 (m, 2H), 1.82 – 1.74 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.56, 137.79, 131.98, 129.13, 121.33, 101.17, 72.17, 51.62, 40.50, 32.58, 31.13, 26.85, 20.06; IR (KBr) ν/cm^{-1}:3448, 2928, 1733, 1549, 1489, 1454, 1077; HRMS (ESI) calcd for $C_{15}H_{15}BrNO_4$ (M - H)$^-$: 352.0190, found: 352.0179; $[\alpha]_D^{20}$ = + 87.7 (c = 1.0, $CHCl_3$); The enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (4.6 mm × 25 cm) (*n*-hexane/*i*-PrOH = 90/10, λ = 220 nm, 0.8 mL/min); t_R (minor enantiomer) = 26.2 min, t_R (major enantiomer) = 33.7 min, 99% ee.



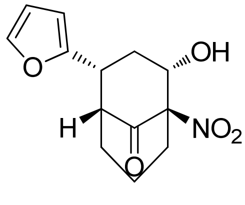
(*1R,2S,4R,5R*)-2-hydroxy-1-nitro-4-(4-nitrophenyl)bicyclo[3.3.1]nonan-9-one , sticky pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.8 Hz, 2H), 7.46 (d, *J* = 8.8 Hz, 2H), 5.07 (ddd, *J* = 11.2, 6.7, 1.7 Hz, 1H), 3.35 (dt, *J* = 13.9, 4.7 Hz, 1H), 2.96 – 2.82 (m, 4H), 2.72 (td, *J* = 13.9, 11.2 Hz, 1H), 2.51 – 2.45 (m, 1H), 2.23 – 2.09 (m, 1H), 1.95 – 1.87 (m, 1H), 1.85 – 1.76 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.82, 147.27, 146.25, 128.40, 124.10, 101.01, 72.01, 51.31, 40.91, 32.37, 31.10, 26.83, 20.06; IR (KBr) ν/cm^{-1}:3445, 2922, 2851, 1719, 1551, 1520, 1347, 1054; HRMS (ESI) calcd for $C_{15}H_{15}N_2O_6$ (M - H)$^-$: 319.0936, found: 319.0955; $[\alpha]_D^{20}$ = + 80.9 (c = 0.6, $CHCl_3$); The enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (4.6 mm × 25 cm) (*n*-hexane/*i*-PrOH = 80/20, λ = 254 nm, 0.8 mL/min); t_R (minor enantiomer) = 25.7 min, t_R (major enantiomer) = 33.6 min, 99% ee.



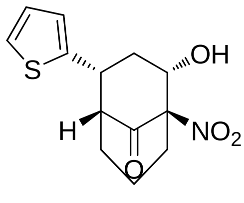
4-((*1R,2R,4S,5R*)-4-hydroxy-5-nitro-9-oxobicyclo[3.3.1]nonan-2-yl)benzonitrile , sticky pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.2 Hz, 2H), 7.39 (d, *J* = 8.2 Hz, 2H), 5.06 (ddd, *J* = 11.3, 6.7, 1.6 Hz, 1H), 3.29 (dt, *J* = 14.0, 4.8 Hz, 1H), 2.94 – 2.79 (m, 4H), 2.68 (td, *J* = 14.0, 11.3 Hz, 1H), 2.48 – 2.41 (m, 1H), 2.20 – 2.06 (m, 1H), 1.94 – 1.85 (m, 1H), 1.84 – 1.76 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.10, 144.31, 132.67, 128.30, 118.33, 111.39, 101.03, 71.98, 51.32, 40.95, 32.32, 31.04, 26.88, 20.01; IR (KBr) ν/cm^{-1}: 3442, 1734, 1638, 1551, 1082; HRMS (ESI) calcd for $C_{16}H_{15}N_2O_4$ (M - H)$^-$: 299.1037, found: 299.1026; $[\alpha]_D^{20}$ = + 90.3 (c = 1.0, $CHCl_3$); The enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (4.6 mm × 25 cm) (*n*-hexane/*i*-PrOH = 90/10, λ = 230 nm, 0.8 mL/min); t_R (minor enantiomer) = 22.9 min, t_R (major enantiomer) = 30.5 min, 99% ee.



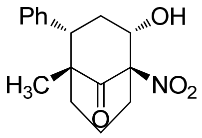
(*1R,2S,4R,5R*)-2-hydroxy-1-nitro-4-(4-(trifluoromethyl)phenyl)bicyclo[3.3.1]nonan-9-one , sticky pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.0 Hz, 2H), 7.40 (d, *J* = 8.0 Hz, 2H), 5.09 – 5.05 (m, 1H), 3.31 (dt, *J* = 14.0, 4.8 Hz, 1H), 2.96 – 2.81 (m, 4H), 2.71 (td, *J* = 14.0, 11.3 Hz, 1H), 2.45 (dt, *J* = 14.0, 6.1 Hz, 1H), 2.21– 2.09 (m, 1H), 1.93 – 1.83 (m, 2H), 1.82 –1.73 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.29, 142.88, 129.99, 129.67, 127.87, 125.86 (q, *J* = 3.9 Hz), 125.28, 122.57, 101.15, 72.17, 51.54, 40.85, 32.47, 31.15, 26.89, 20.08; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.63; IR (KBr) ν/cm^{-1}: 3525, 2943, 1735, 1551, 1328, 1167, 1124, 1069; HRMS (ESI) calcd for $C_{16}H_{15}F_3NO_4$ (M - H)$^-$: 342.0959, found: 342.0950; $[\alpha]_D^{20}$ = + 75.3 (c = 1.0, $CHCl_3$); The enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (4.6 mm × 25 cm) (*n*-hexane/*i*-PrOH = 90/10, λ = 230 nm, 0.8 mL/min); t_R (minor enantiomer) = 19.8 min, t_R (major enantiomer) = 21.4 min, 95% ee.



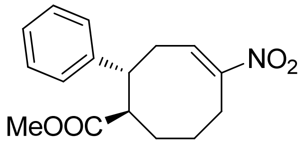
(*1R,2S,4R,5R*)-4-(furan-2-yl)-2-hydroxy-1-nitrobicyclo[3.3.1]nonan-9-one , sticky pale yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 1.8 Hz, 1H), 6.35 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.20 (d, *J* = 3.3 Hz, 1H), 5.04 – 4.99 (m, 1H), 3.29 (td, *J* = 9.8, 4.6 Hz, 1H), 3.06 – 3.03 (m, 1H), 2.88 – 2.77 (m, 3H), 2.53 – 2.49 (m, 2H), 2.14 – 2.04 (m, 1H), 1.97 – 1.86 (m, 2H), 1.78 – 1.71 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.28, 152.80, 142.25, 110.27, 106.73, 101.28, 71.94, 49.26, 35.67, 31.86, 31.14, 27.91, 19.90; IR (KBr) ν/cm^{-1}: 3542, 2948, 2921, 1737, 1545, 1083, 1009; HRMS (ESI) calcd for $C_{13}H_{14}NO_5$ (M - H)$^-$: 264.0877, found: 264.0883; $[\alpha]_D^{20}$ = + 93.1 (c = 0.8, $CHCl_3$); The enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (4.6 mm × 25 cm) (*n*-hexane/*i*-PrOH = 90/10, λ = 230 nm, 0.8 mL/min); t_R (minor enantiomer) = 18.1 min, t_R (major enantiomer) = 24.8 min, 99% ee.



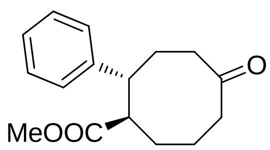
(*1R,2S,4R,5R*)-2-hydroxy-1-nitro-4-(thiophen-2-yl)bicyclo[3.3.1]nonan-9-one , pale yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.26 (m, 1H), 7.02 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.93 (dt, *J* = 3.6, 1.1 Hz, 1H), 5.04 – 4.99 (m, 1H), 3.53 – 3.47 (m, 1H), 2.95 – 2.90 (m, 1H), 2.90 – 2.81 (m, 2H), 2.63 – 2.57 (m, 2H), 2.18 – 1.90 (m, 4H), 1.81 – 1.73 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.47, 142.56, 127.06, 124.58, 124.43, 101.16, 71.84, 52.13, 37.08, 34.47, 31.13, 27.36, 19.90; IR (KBr) ν/cm^{-1}: 3582, 2942, 1731, 1545, 1077; HRMS (ESI) calcd for $C_{13}H_{14}NO_4S$ (M - H)$^-$: 280.0649, found: 280.0638; $[\alpha]_D^{20}$ = + 107.1 (c = 1.1, $CHCl_3$); The enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (4.6 mm × 25 cm) (*n*-hexane/*i*-PrOH = 90/10, λ = 230 nm, 0.8 mL/min); t_R (minor enantiomer) = 20.5 min, t_R (major enantiomer) = 28.9 min, 99% ee.



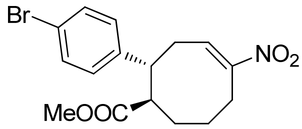
(*1R,2S,4S,5R*)-2-hydroxy-5-methyl-1-nitro-4-phenylbicyclo[3.3.1]nonan-9-one, sticky pale yellow oil,^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.30 (m, 3H), 7.28 – 7.22 (m, 2H), 5.07 – 5.01 (m, 1H), 3.02 – 2.96 (m, 1H), 2.93 – 2.85 (m, 1H), 2.83 – 2.71 (m, 3H), 2.51 – 2.33 (m, 2H), 2.18 (ddd, *J* = 12.5, 5.7, 2.9 Hz, 1H), 1.90 – 1.81 (m, 1H), 1.64 – 1.55 (m, 1H), 0.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.77, 138.05, 129.20, 128.52, 127.68, 101.97, 72.01, 50.64, 48.37, 35.25, 31.31, 22.41, 20.07. IR (KBr) *ν*/cm^{-1}: 2931, 1720, 1547, 1456, 1287, 1037, 770; HRMS (ESI) calcd for $C_{16}H_{18}NO_4$ (M - H)$^-$: 288.1241, found: 288.1236; $[\alpha]_D^{20}$ = + 66.3 (c = 1.1, $CHCl_3$); The enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (4.6 mm × 25 cm) (*n*-hexane/*i*-PrOH = 90/10, λ = 220 nm, 0.8 mL/min); t_R (minor enantiomer) = 15.7 min, t_R (major enantiomer) = 28.9 min, 86% ee.



(*1R,2R*)-methyl 5-nitro-2-phenylcyclooct-4-enecarboxylate , white solid ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 3H), 7.23 – 7.19 (m, 1H), 7.15 (d, *J* = 7.4 Hz, 2H), 3.36 (s, 4H), 3.05 – 2.99 (m, 1H), 2.82 – 2.75 (m, 3H), 2.57 (dt, *J* = 14.1, 7.4 Hz, 1H), 2.02 – 1.98 (m, 2H), 1.83 – 1.81 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.31, 152.57, 142.92, 133.80, 128.67, 127.13, 127.07, 51.46, 49.67, 48.23, 33.25, 30.04, 27.67, 25.36; mp: 98~99 °C; IR (KBr) *ν*/cm^{-1}: 2946, 2855, 1730, 1521, 1437, 1367, 1332,1162; HRMS (ESI) calcd for $C_{16}H_{18}NO_4$ (M - H)$^-$: 288.1241, found: 288.1233; $[\alpha]_D^{20}$ = – 44.9 (c = 1.0, $CHCl_3$); The enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (4.6 mm × 25 cm) (*n*-hexane/*i*-PrOH = 98/2, λ = 254 nm, 0.8 mL/min); t_R (minor enantiomer) = 14.5 min, t_R (major enantiomer) = 15.7 min, 99% ee.



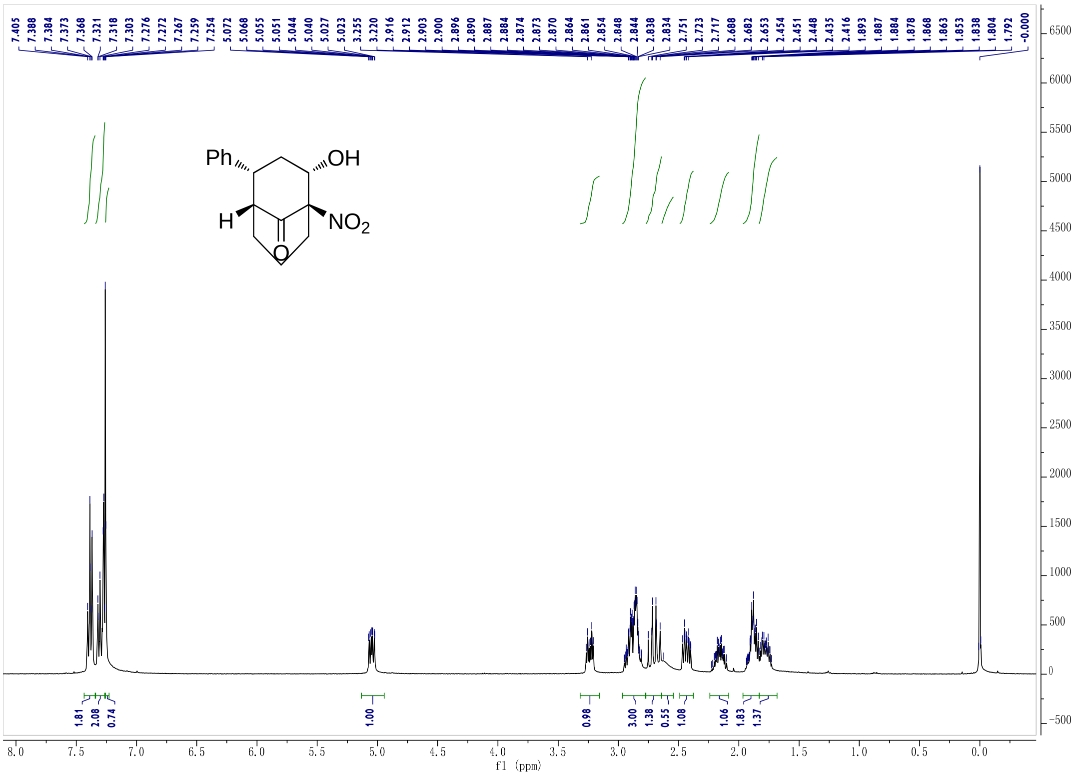
(*1R,2R*)-methyl 5-oxo-2-phenylcyclooctanecarboxylate , white solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.24 (m, 2H), 7.22 – 7.15 (m, 3H), 3.32 (s, 3H), 3.12 – 3.01 (m, 2H), 2.85 – 2.80 (m, 1H), 2.51 – 2.44 (m, 1H), 2.41 – 2.26 (m, 2H), 2.16 (ddd, *J* = 16.1, 7.9, 3.3 Hz, 1H), 2.07 – 1.81 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.05, 162.64, 144.16, 128.22, 127.76, 126.37, 51.27, 48.26, 47.05, 31.90, 29.77, 29.57, 27.17, 24.85. mp: 88~90 °C; IR (KBr) *ν*/cm^{-1}: 3062, 3028, 2923, 1735, 1434, 1162, 962; HRMS (ESI) calcd for $C_{16}H_{19}O_3$ (M - H)$^-$: 259.1340, found: 259.1348; $[\alpha]_D^{20}$ = + 2.6 (c = 0.5, $CHCl_3$); The enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (4.6 mm × 25 cm) (*n*-hexane/*i*-PrOH = 85/15, λ = 208 nm, 0.8 mL/min); t_R (minor enantiomer) = 16.3 min, t_R (major enantiomer) = 17.1 min, 99% ee.

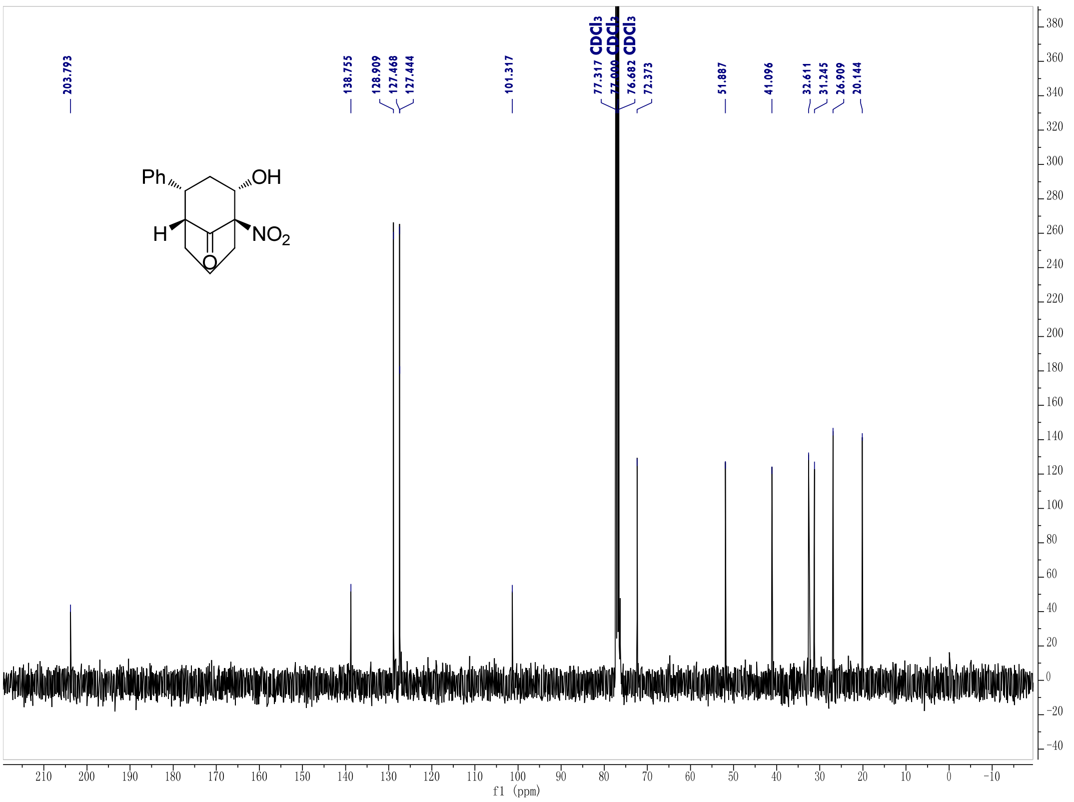
 (1R,2R)-methyl 2-(4-bromophenyl)-5-nitrocyclooct-4-enecarboxylate, white solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.4 Hz, 2H), 7.25 (dd, *J* = 9.8, 7.4 Hz, 1H), 7.04 (d, *J* = 8.4 Hz, 2H), 3.40 (s, 3H), 3.35 (ddd, *J* = 11.3, 7.1, 4.2 Hz, 1H), 3.06 – 2.99 (m, 1H), 2.81 – 2.73 (m, 3H), 2.53 (dt, *J* = 14.2, 7.4 Hz, 1H), 2.05 – 1.97 (m, 2H), 1.85 – 1.78 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.07, 152.75, 141.89, 133.24, 131.82, 128.85, 120.90, 51.67, 49.42, 47.54, 33.04, 30.05, 27.66, 25.35. mp: 107~109 °C; IR (KBr) ν/cm^{-1}: 2947, 2870, 1720, 1522, 1436, 1333, 1158, 1010; HRMS (ESI) calcd for $C_{16}H_{17}BrNO_4$ $(M - H)^-$: 366.0346, found: 366.0340; $[\alpha]_D^{20}$ = – 80.9 (c = 1.0, $CHCl_3$); The enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (4.6 mm × 25 cm) (*n*-hexane/*i*-PrOH = 95/5, λ = 230 nm, 0.8 mL/min); t_R (minor enantiomer) = 14.9 min, t_R (major enantiomer) = 17.2 min, 99% ee.

Reference:

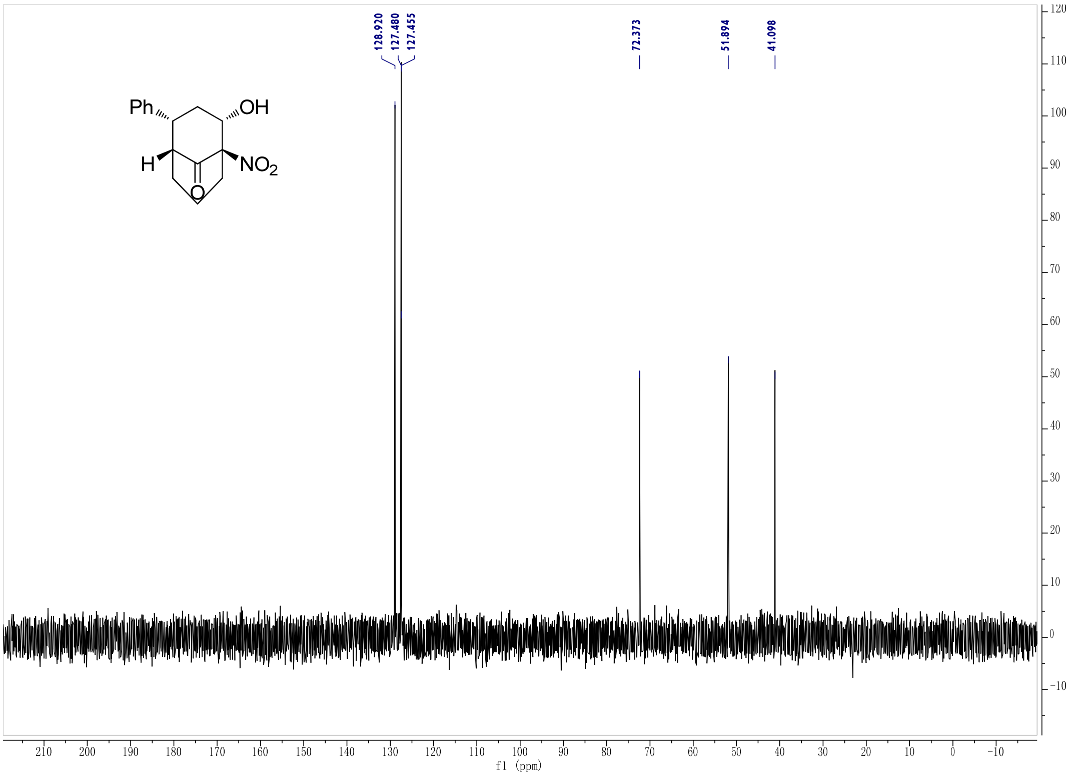
1 P. Dampawan and W. W. Zajac, Jr., *Synthesis*, 1983, 545.
2 R. Ballini, G. Bartoli, R. Castagnani, E. Marcantoni and M. Petrini, *Synlett*, 1992, 64.

(G) NMR spectrum

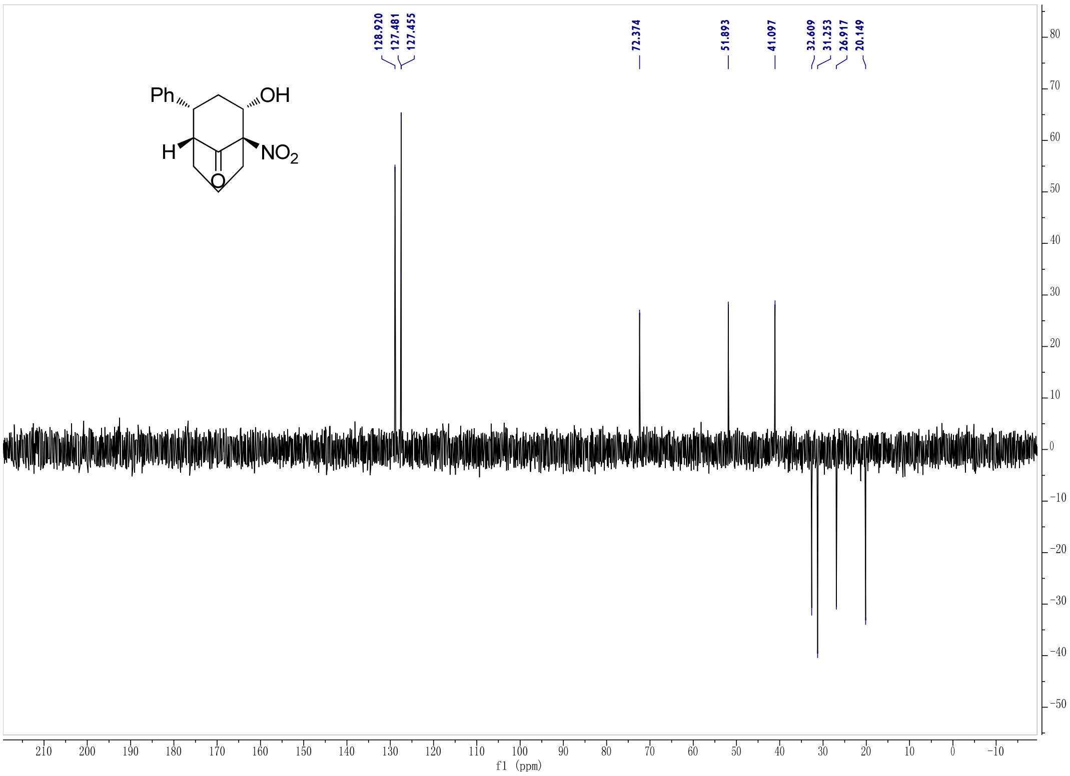




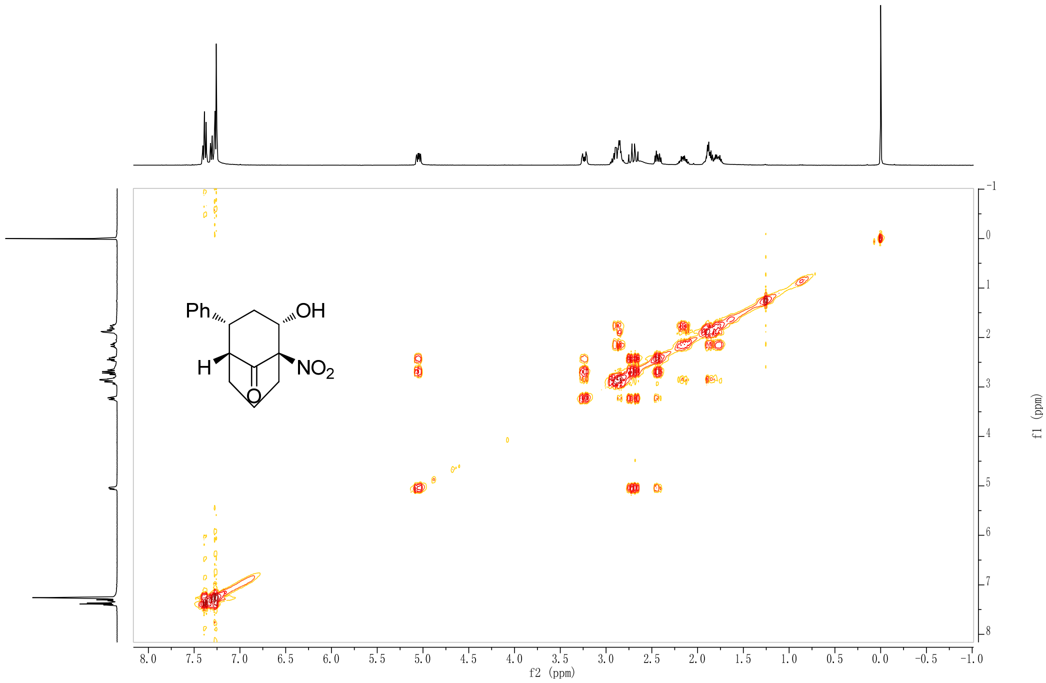
Dept 90 spectrum



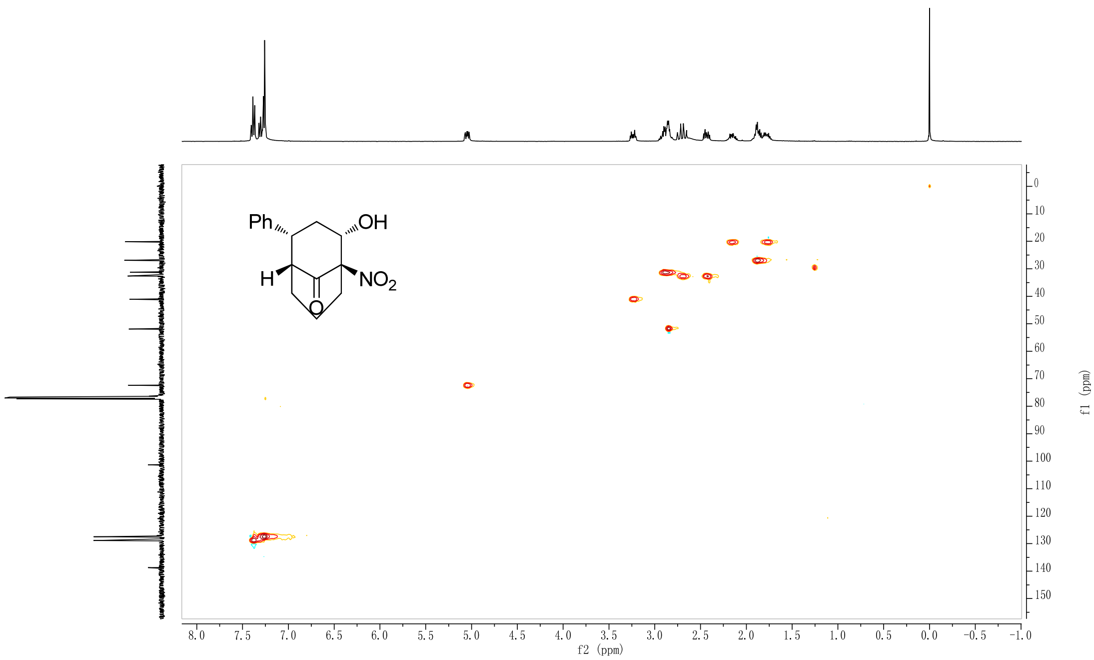
Dept 135 spectrum



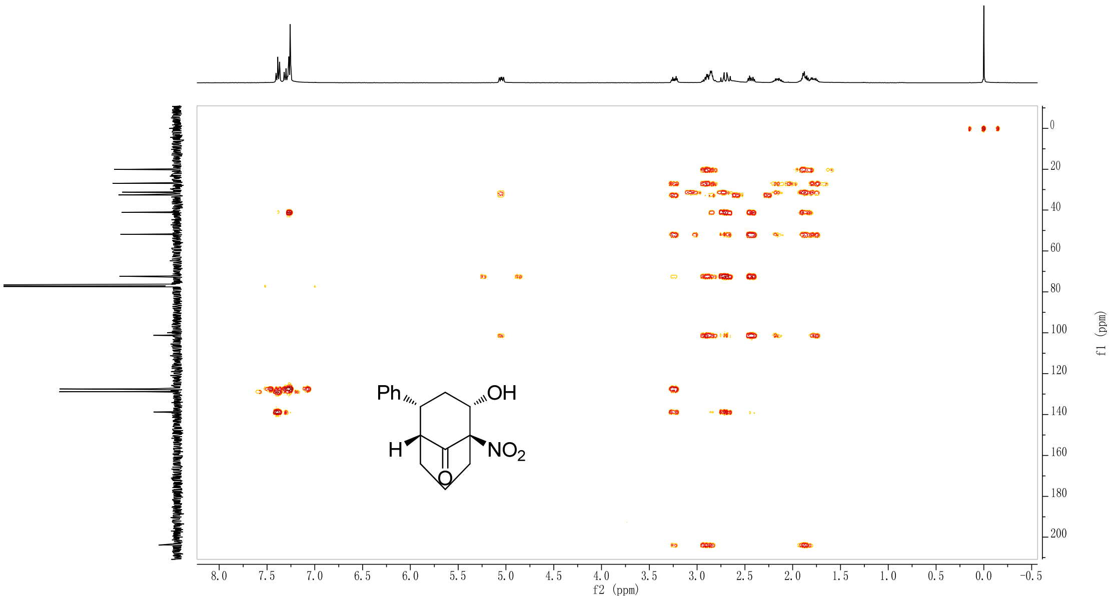
H, H-Cosy spectrum



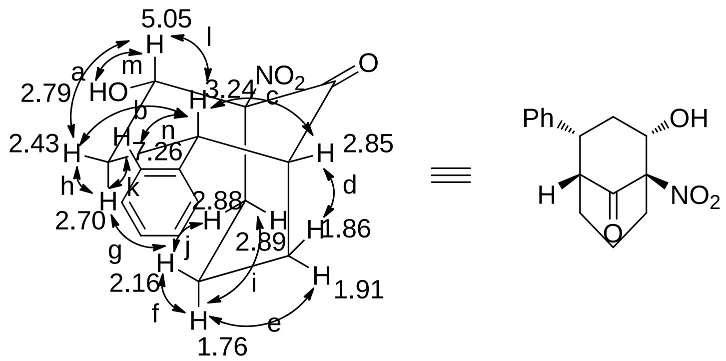
HMQC spectrum

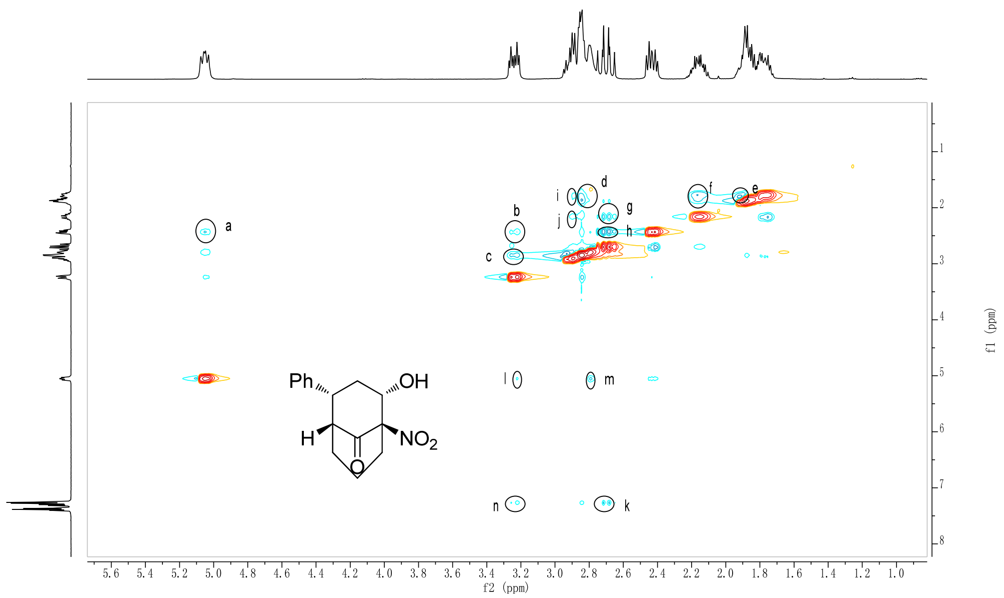


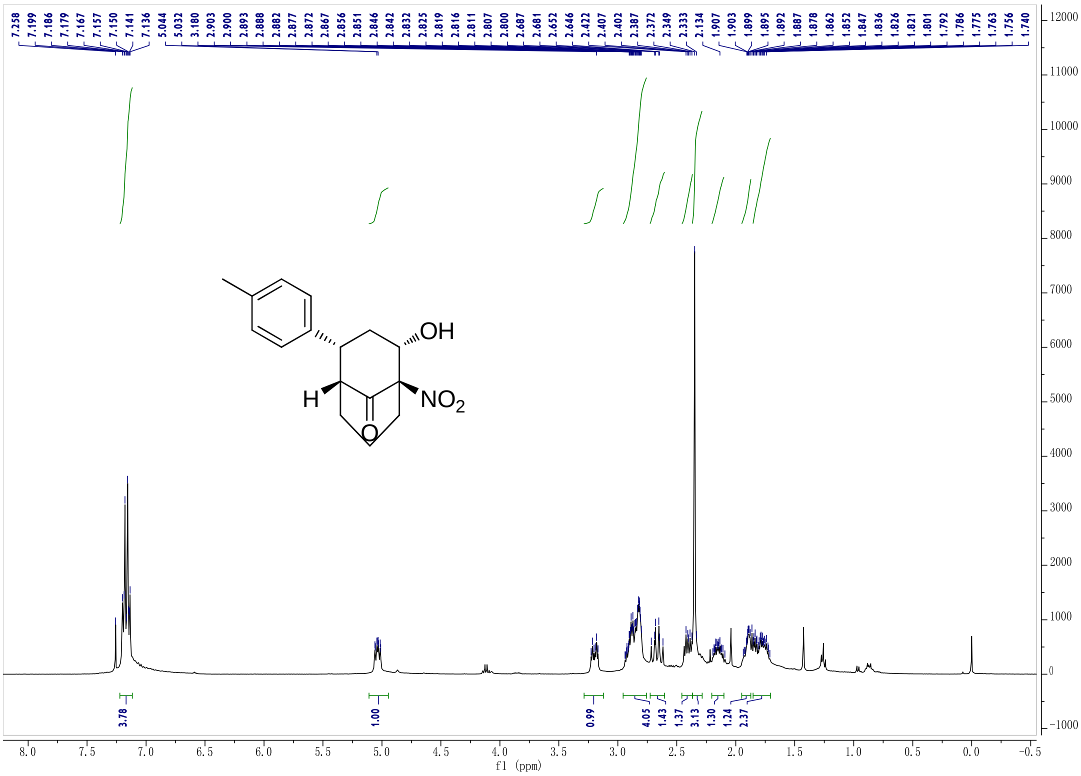
HMBC spectrum

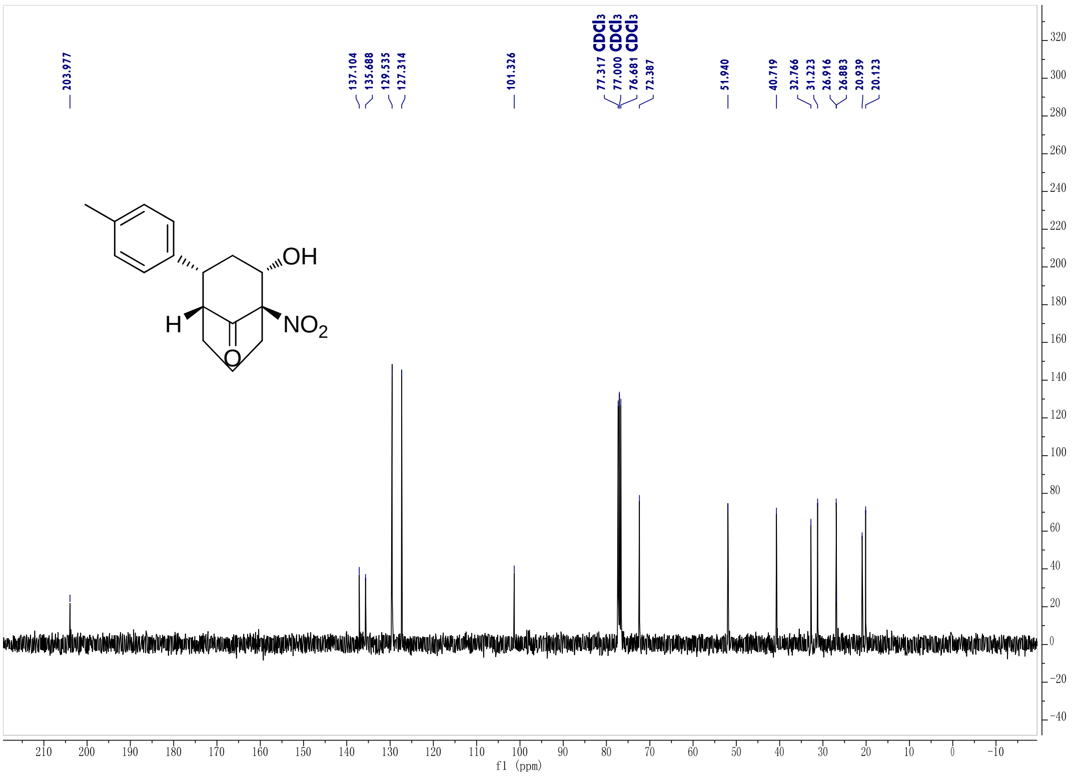


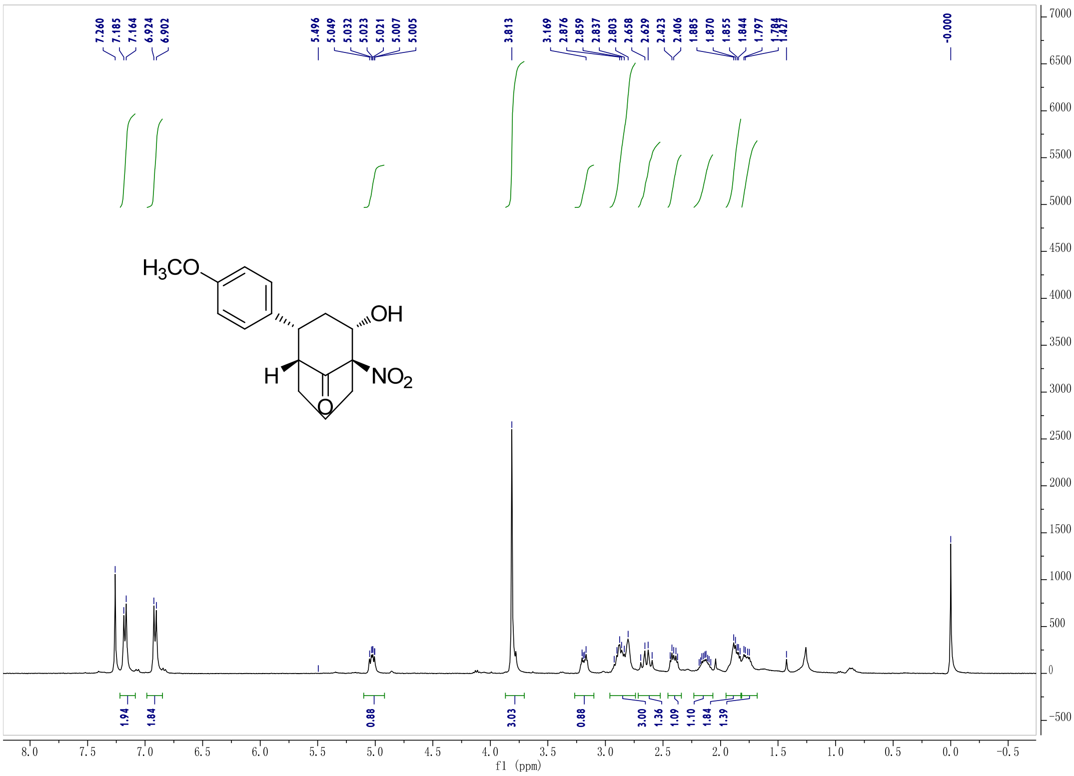
NOE spectrum







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3.813
3.169
2.876
2.859
2.837
2.803
2.658
2.629
2.423
2.406
1.885
1.870
1.855
1.844
1.797
1.784
-0.000
H_3CO
OH
H
NO_2
O
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3.03
0.88
3.00
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1.09
1.10
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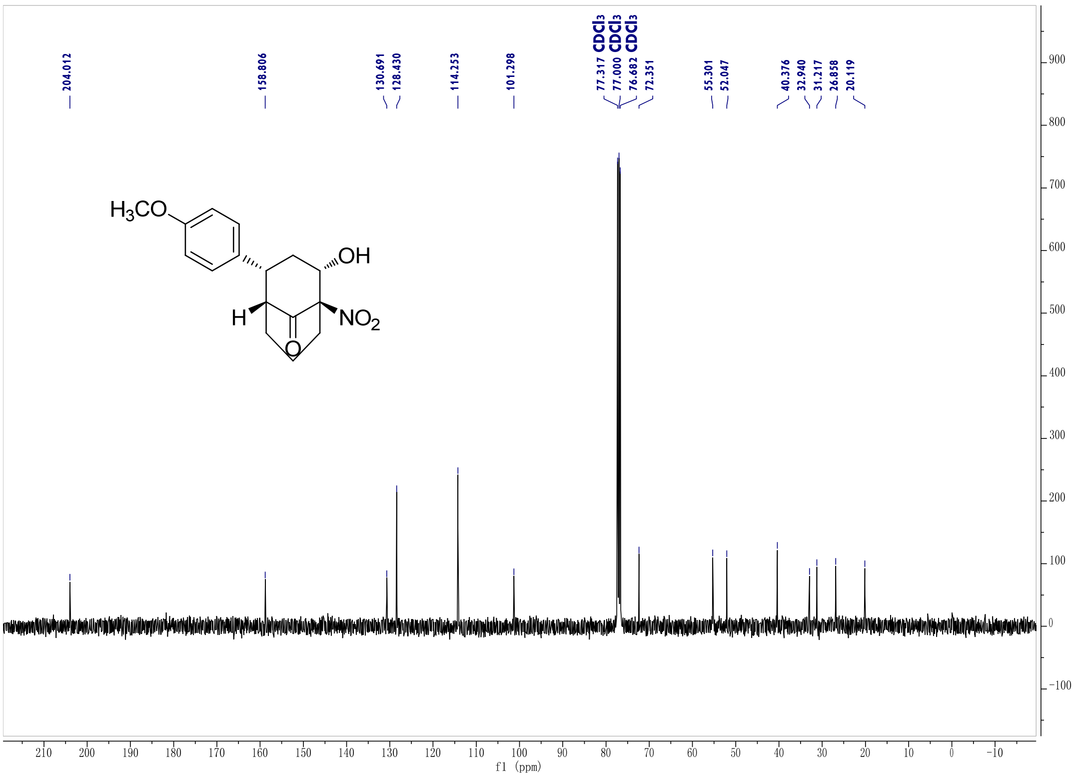
1.39
f1 (ppm)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OH
H
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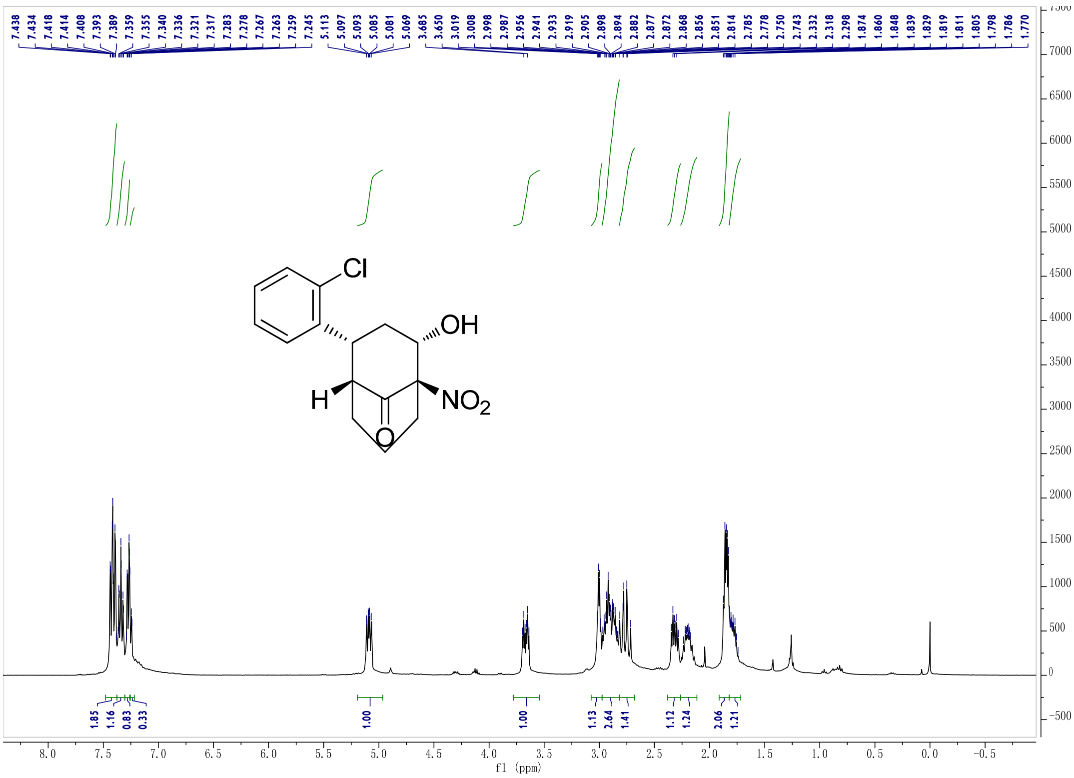
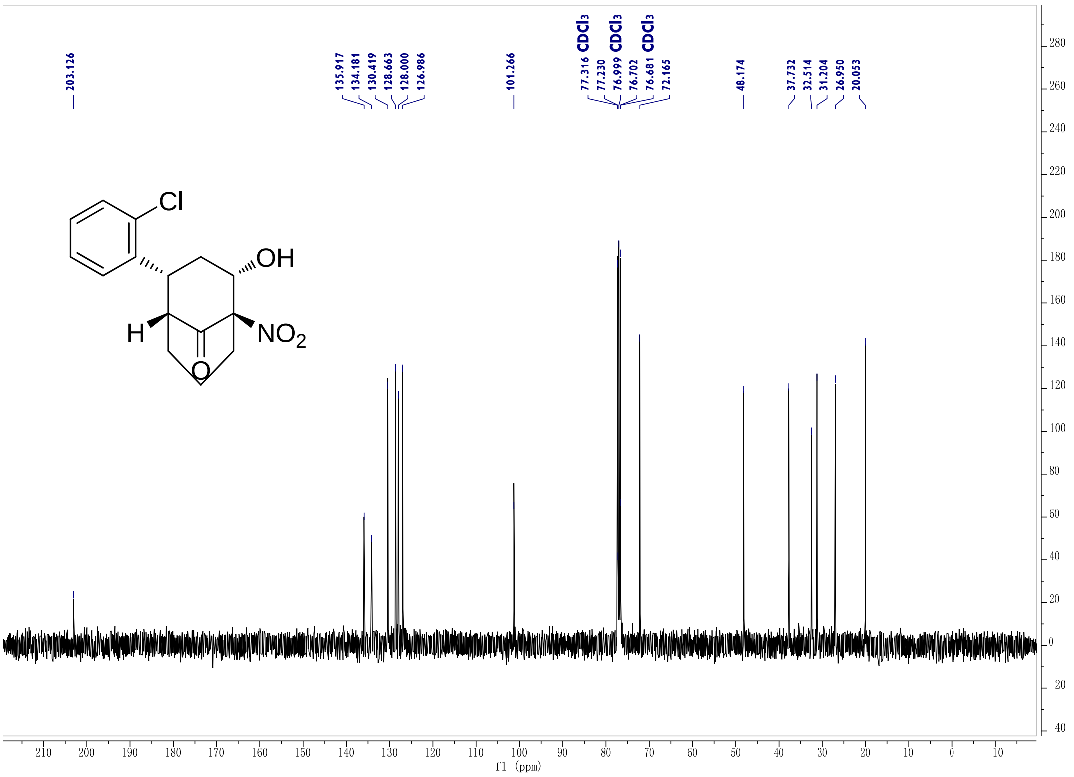
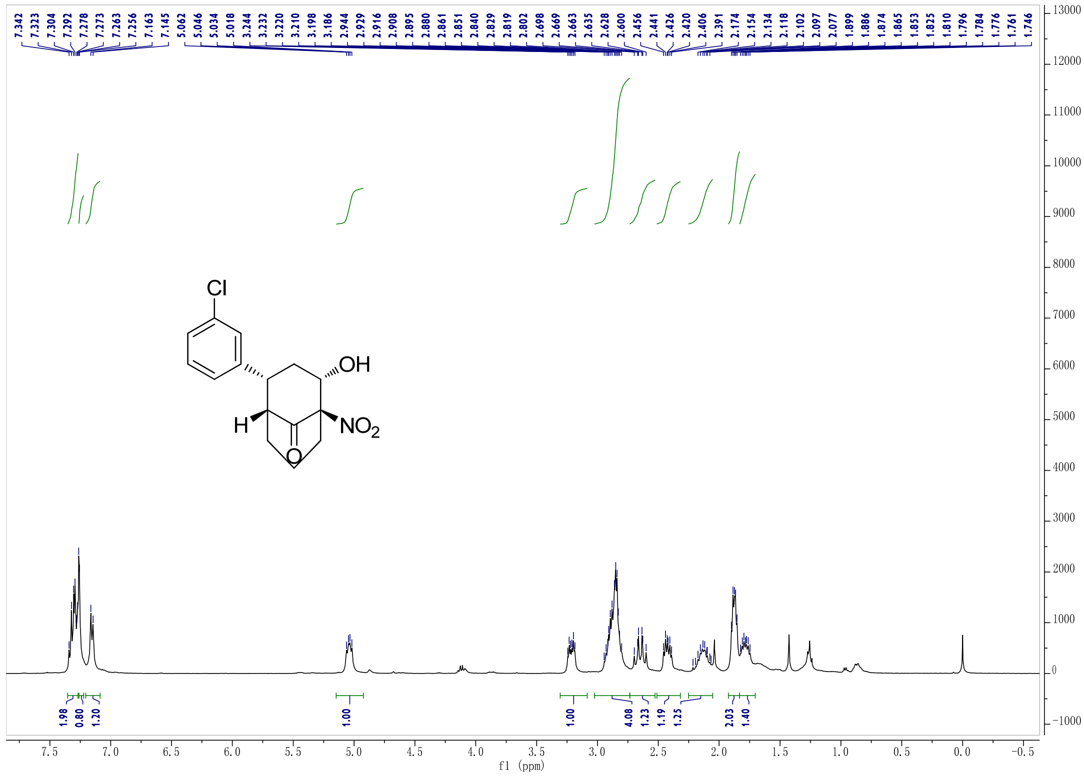
O
f1 (ppm)



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3.198
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2.916
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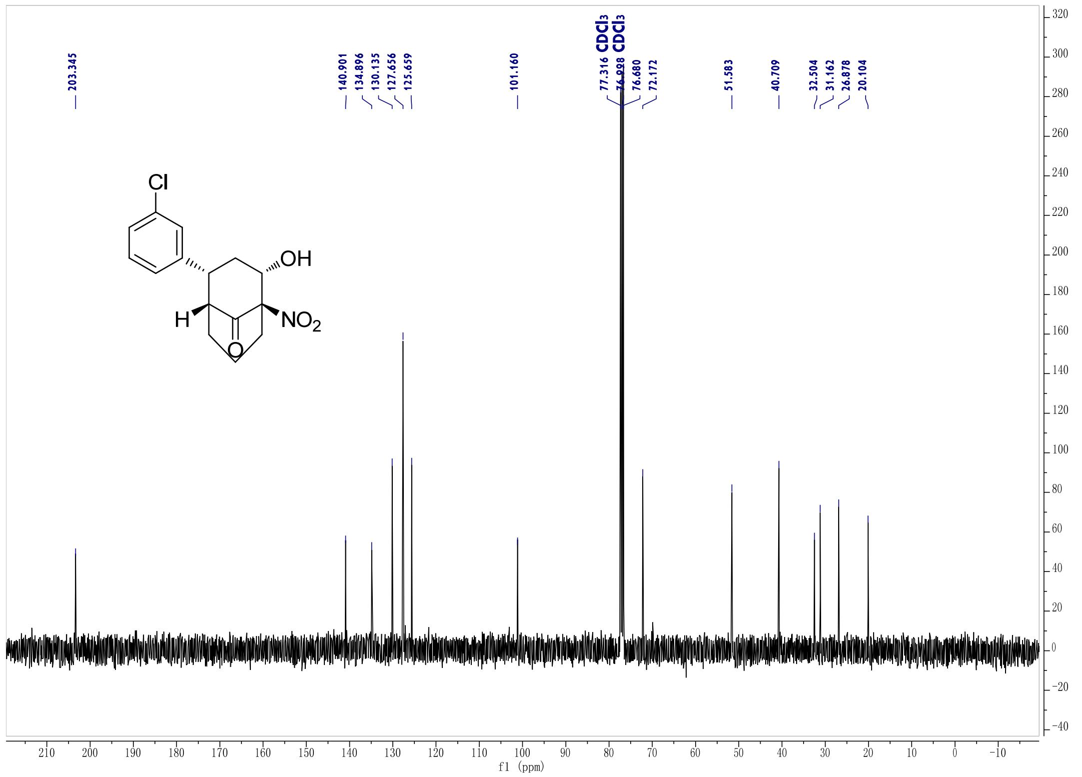
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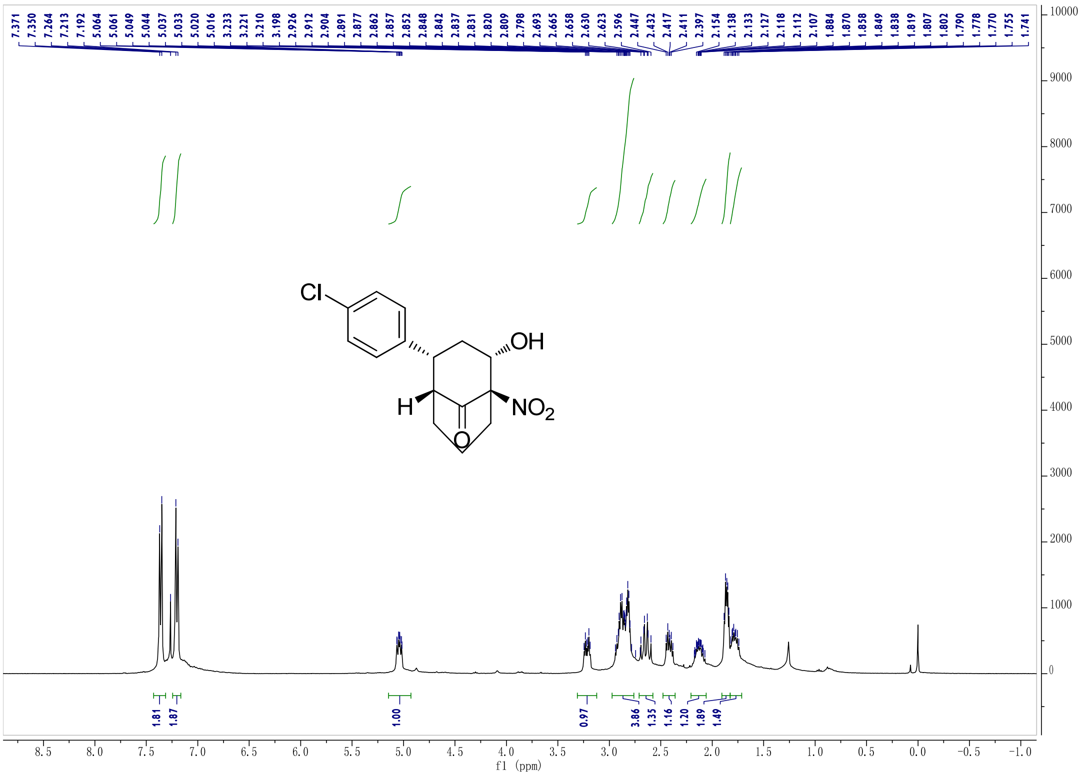
f1 (ppm)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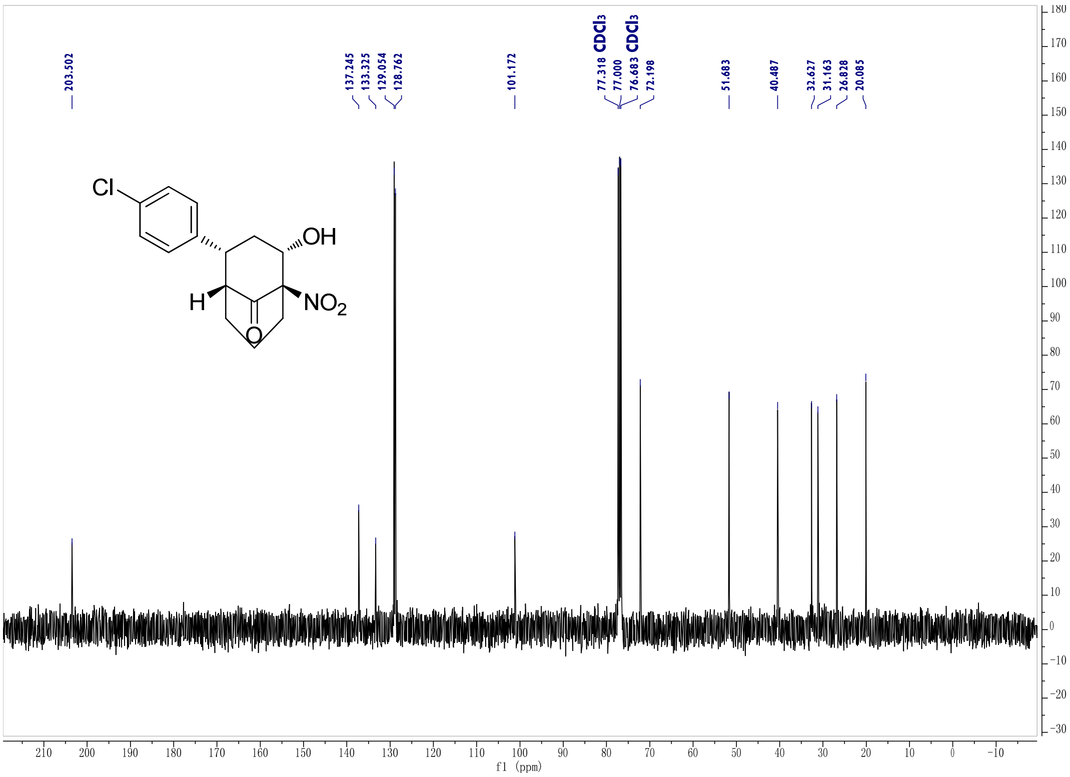
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Cl
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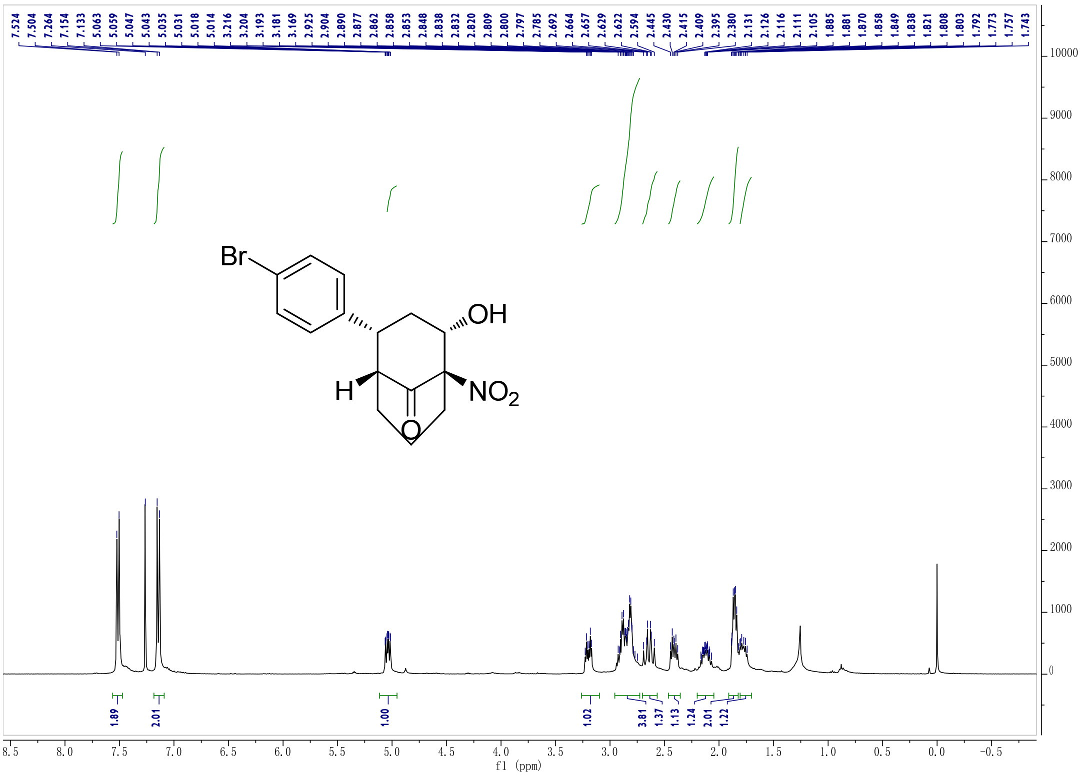
H
NO2
O
f1 (ppm)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H
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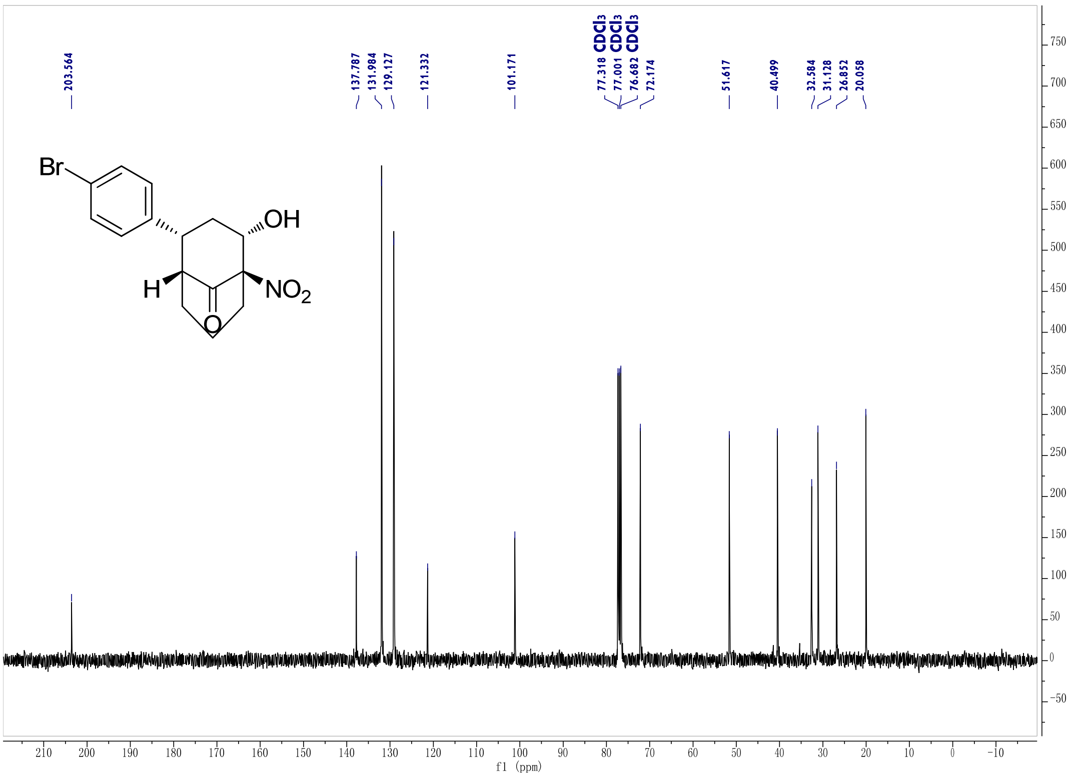
1.24
2.01
1.22
f1 (ppm)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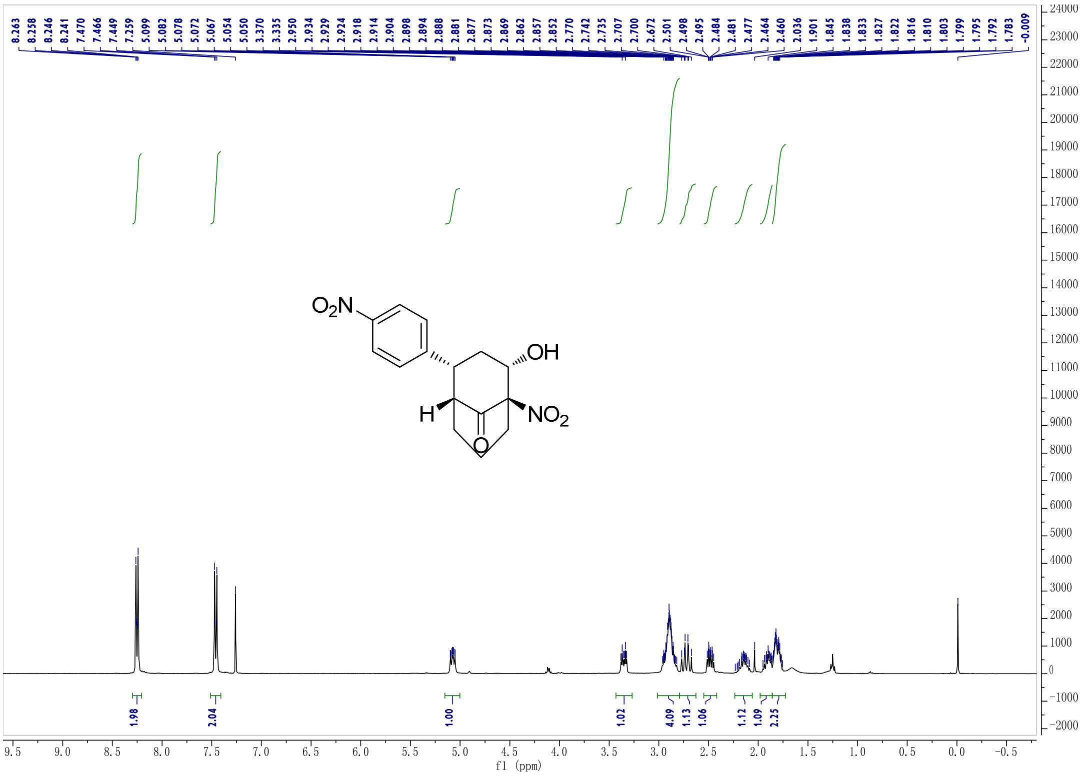
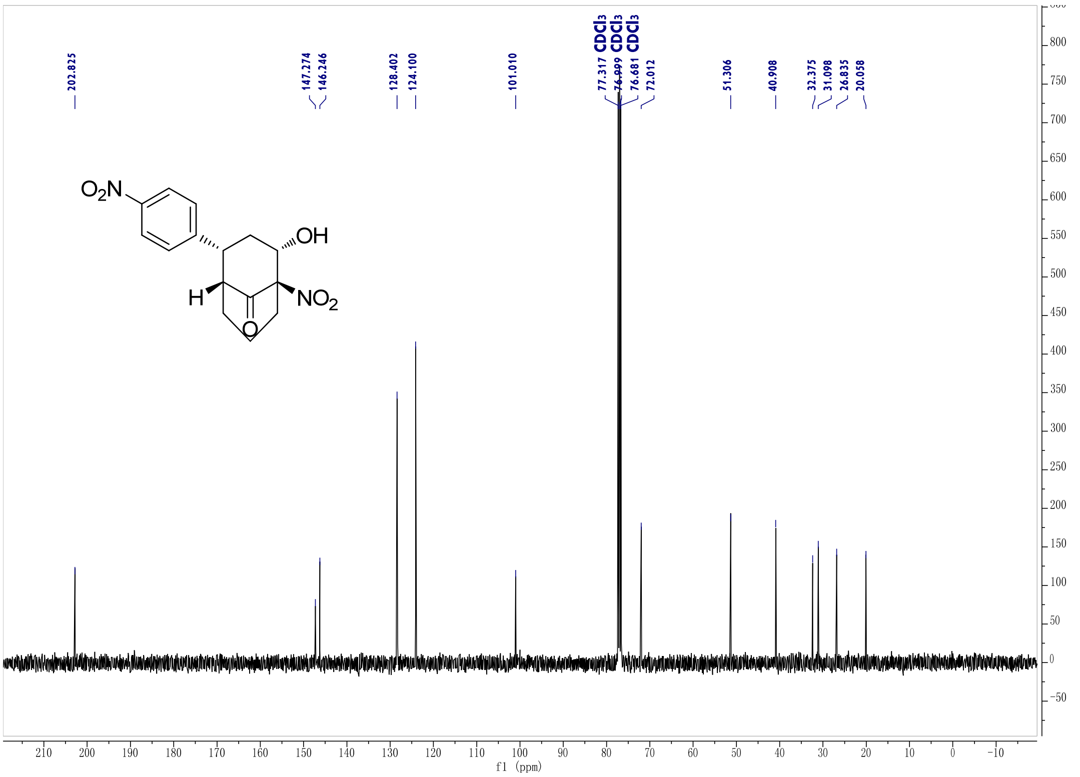
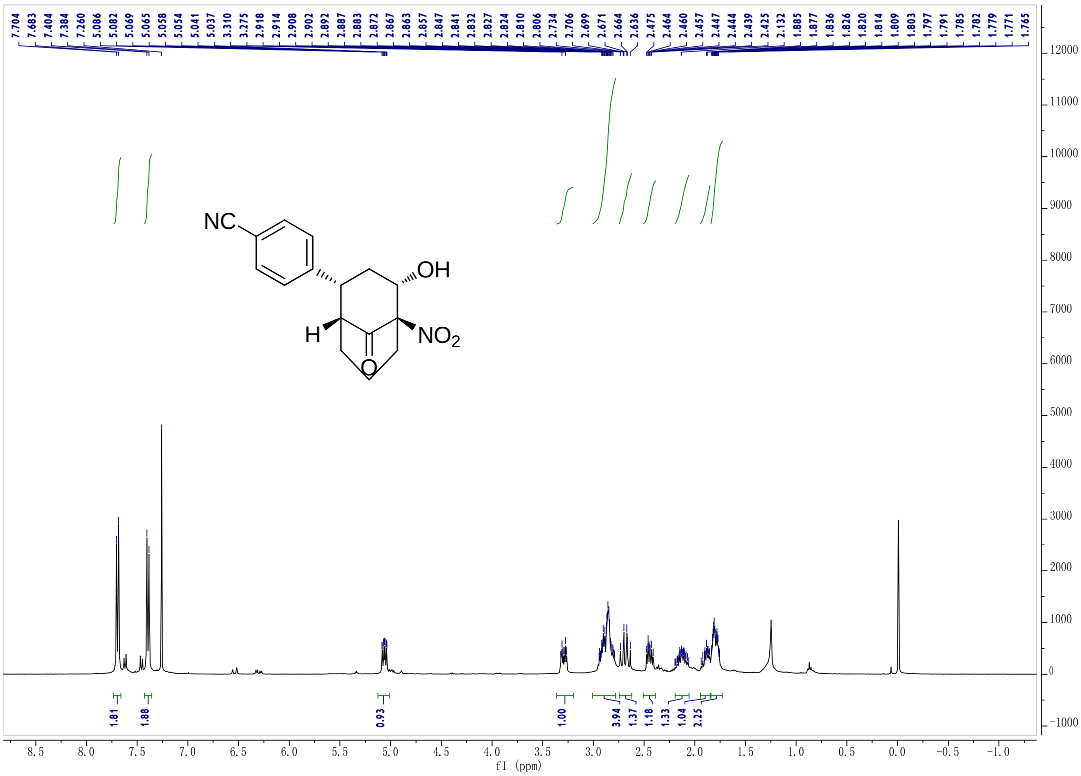
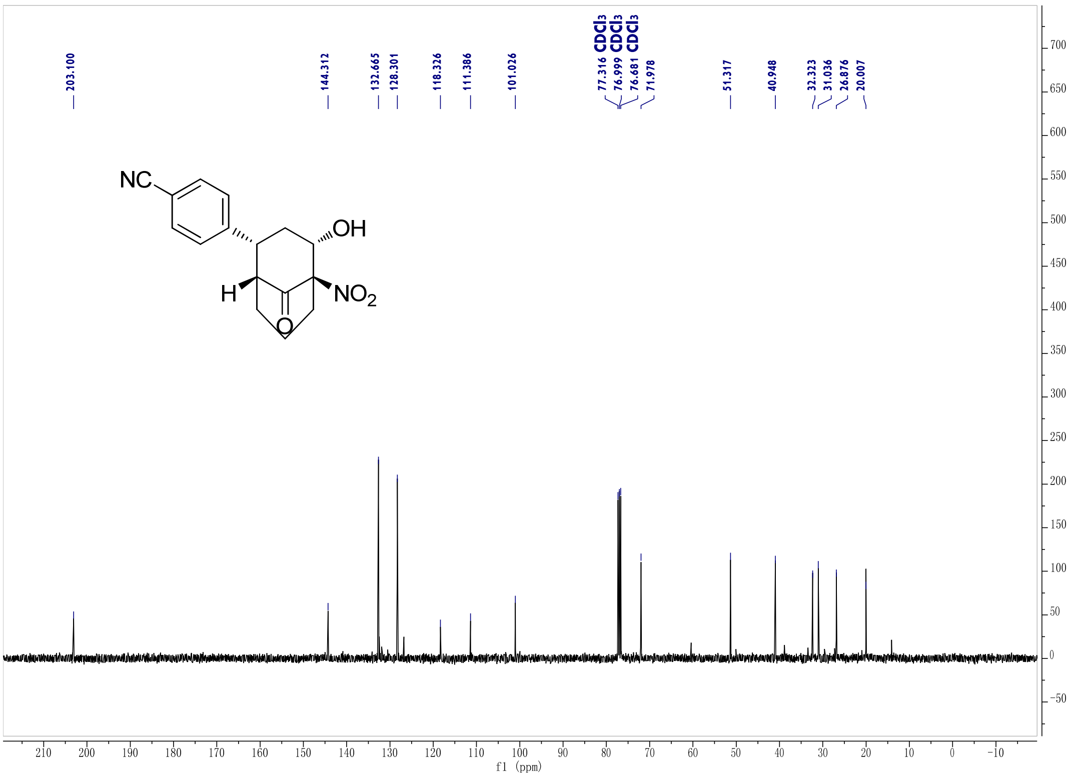
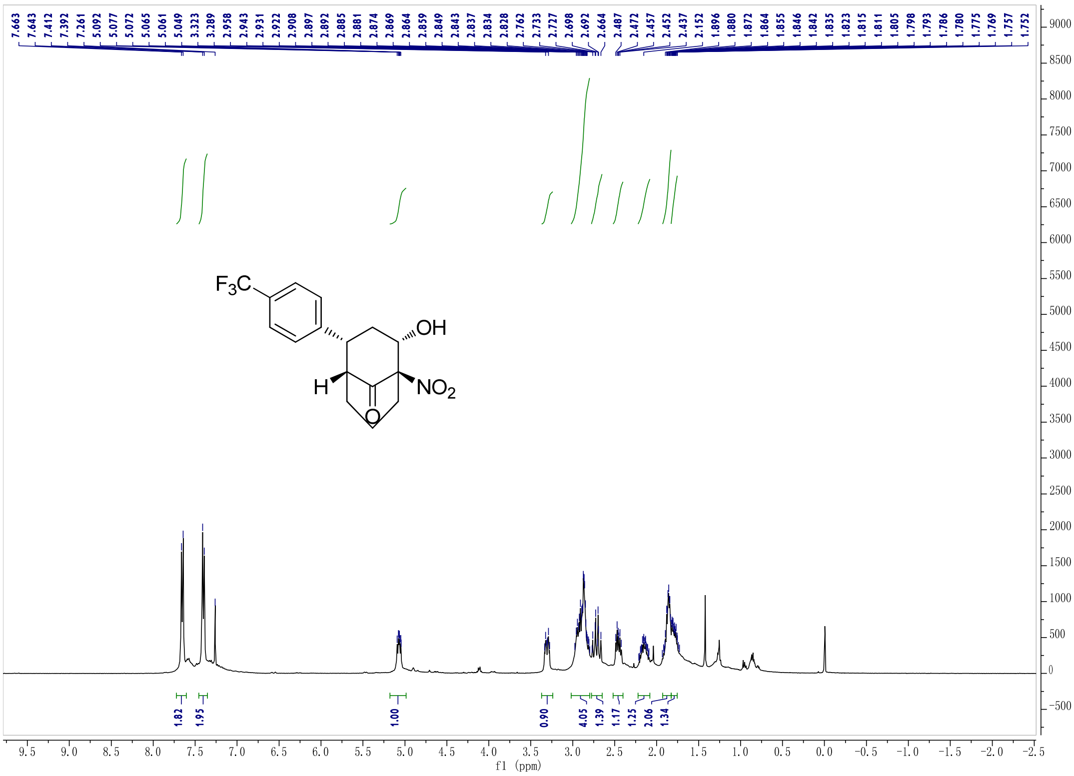
f1 (ppm)

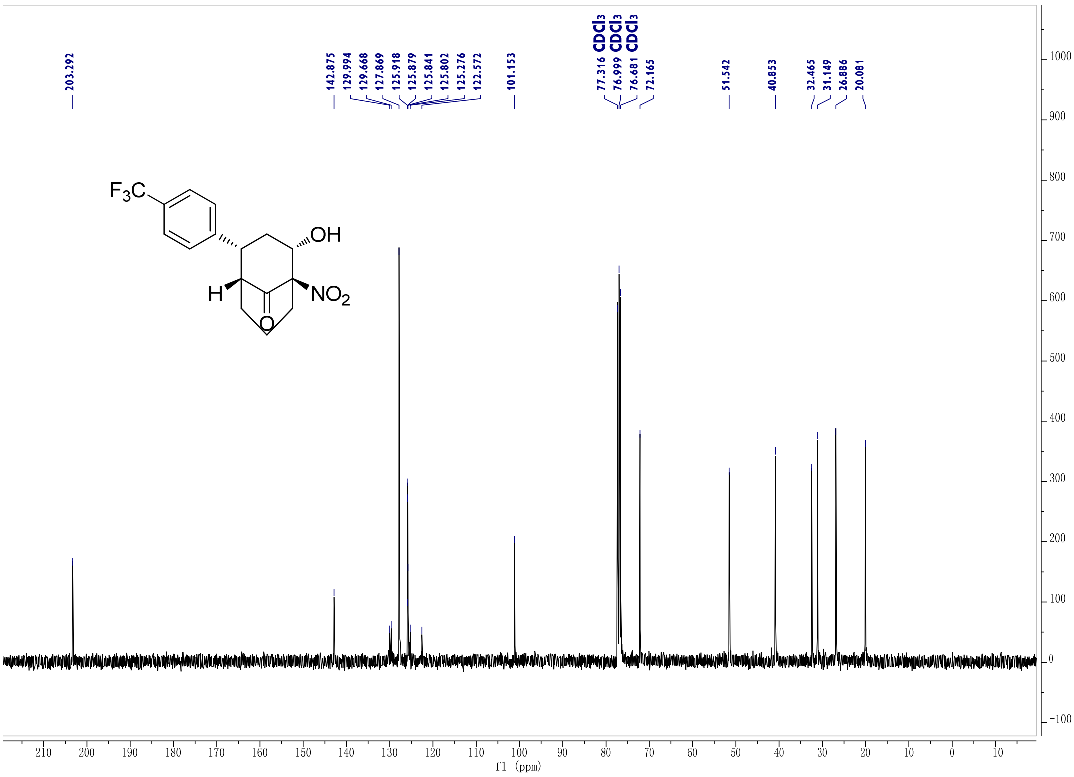




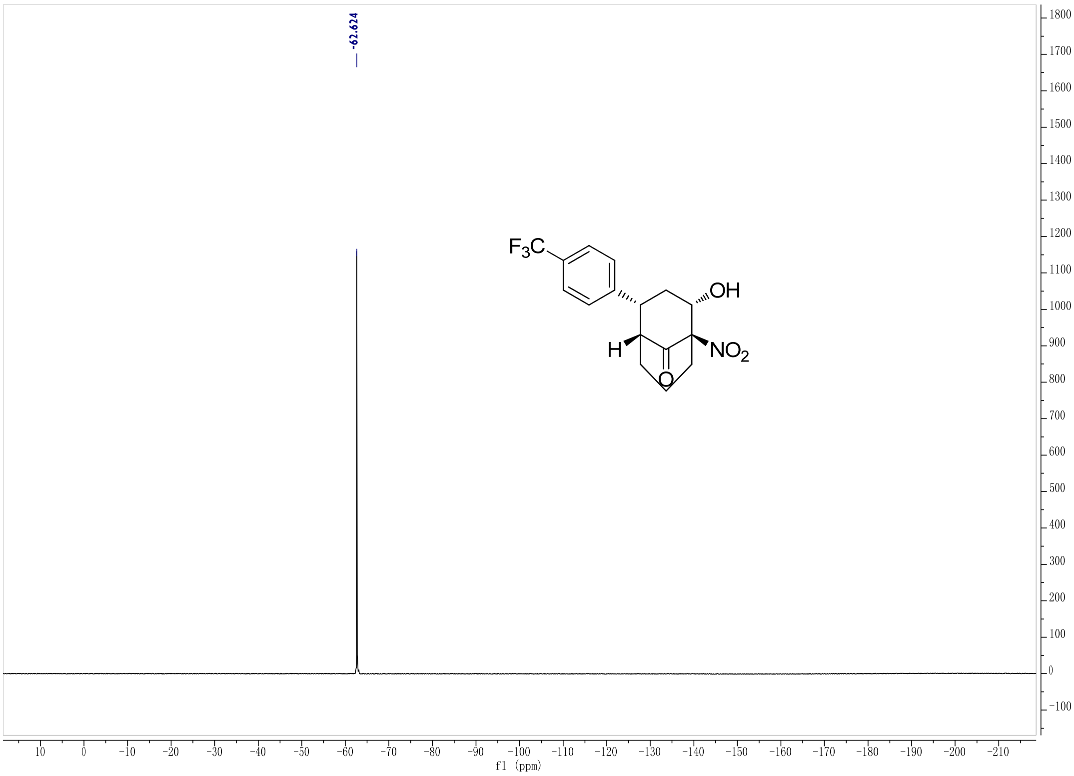


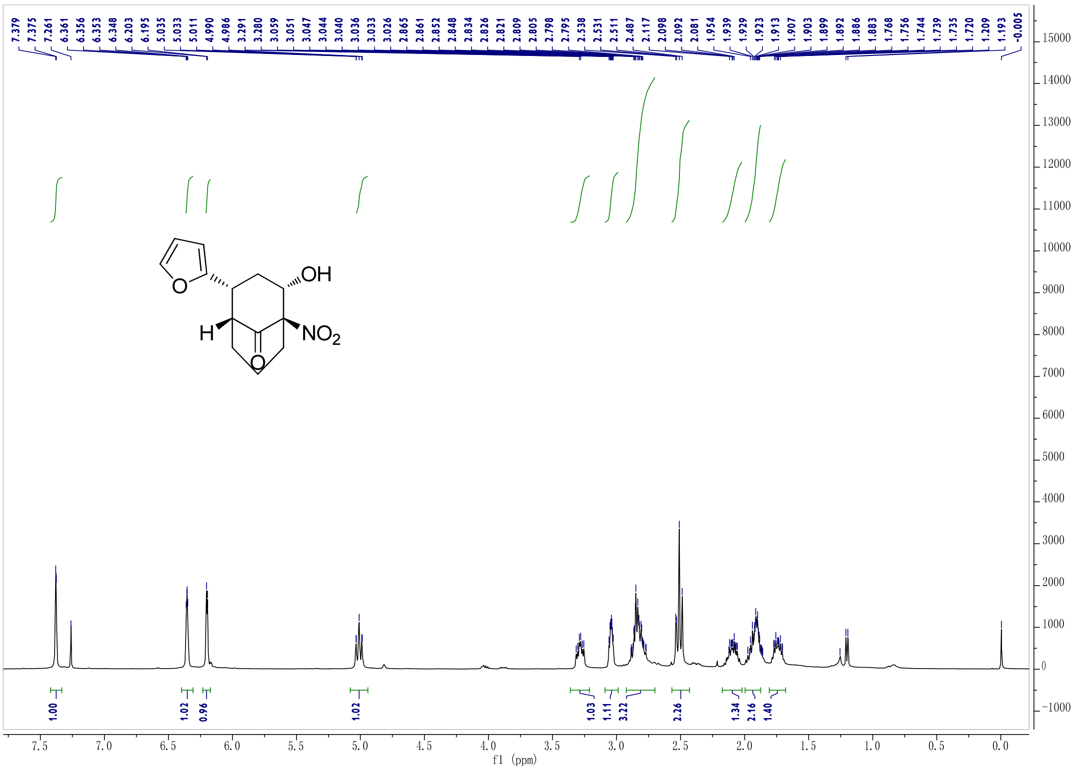




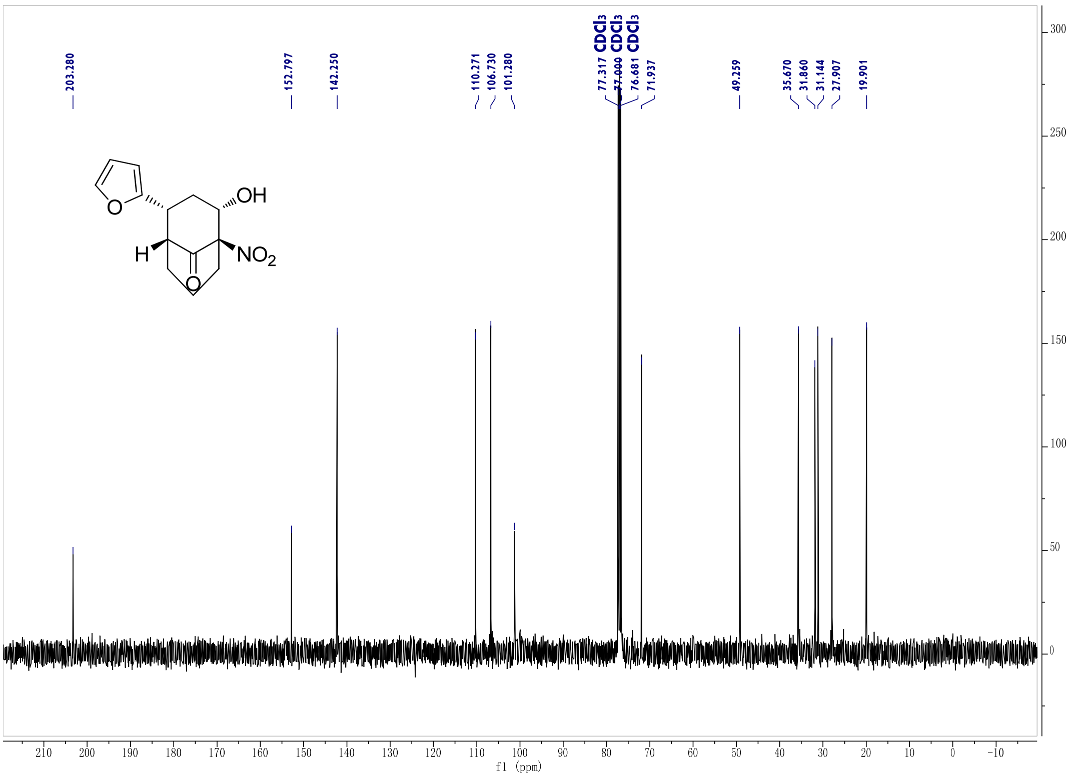


^{19}F spectrum

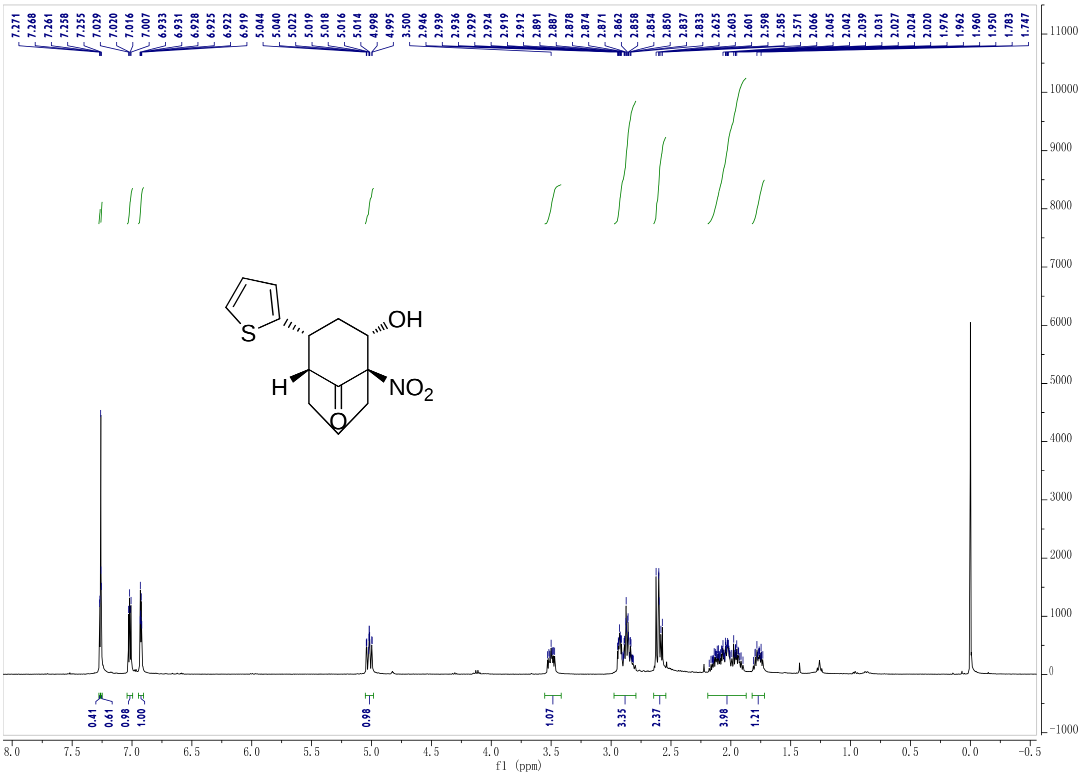


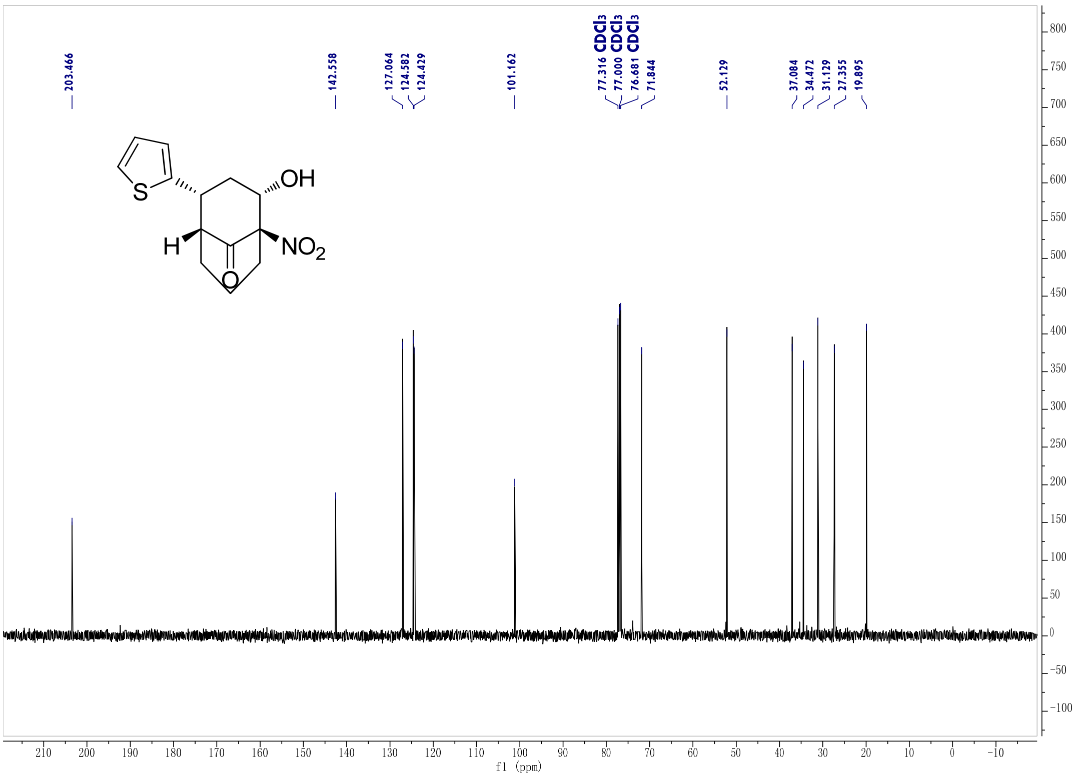


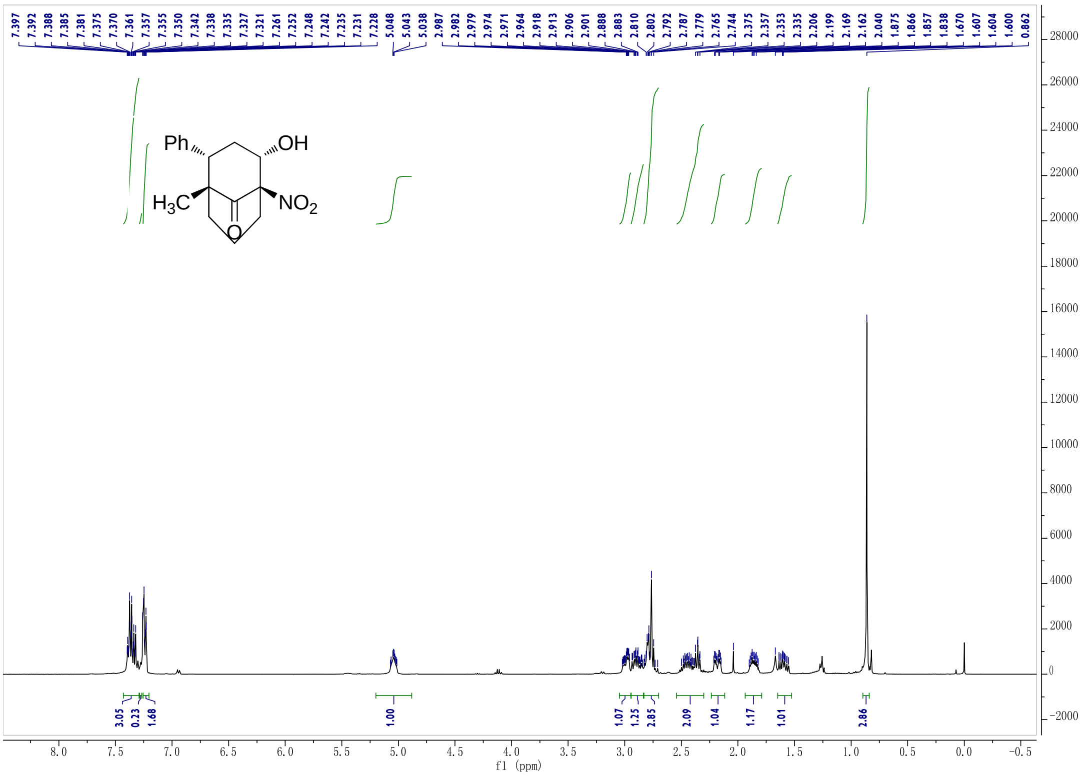
OH
H
NO2
O
f1 (ppm)

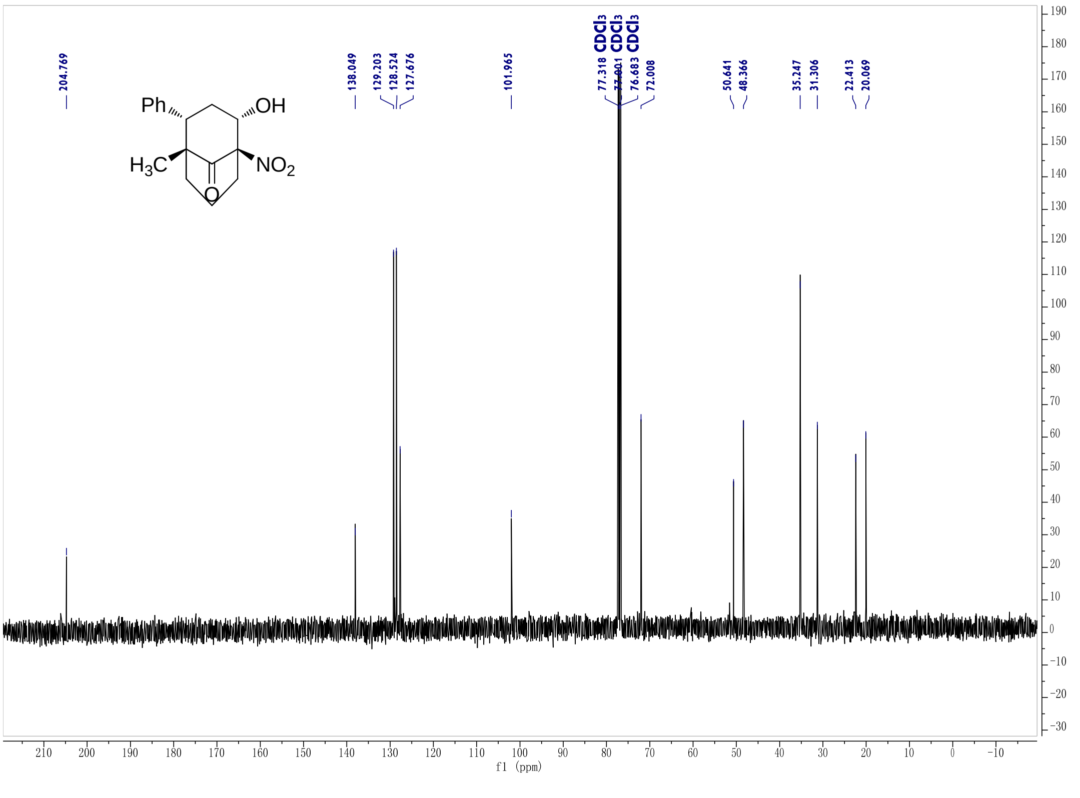


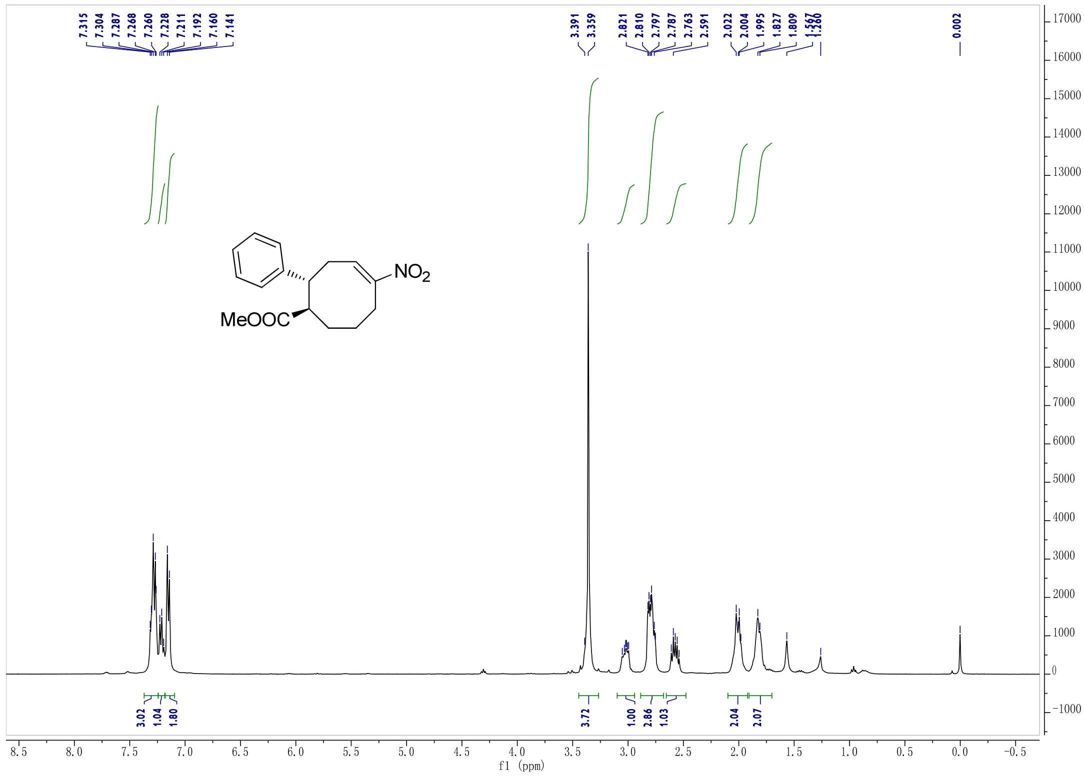
203.280
152.797
142.250
110.271
106.730
101.280
77.317 CDCl3
77.000 CDCl3
76.681 CDCl3
71.937
49.259
35.670
31.860
31.144
27.907
19.901
OH
H
NO2
O
f1 (ppm)

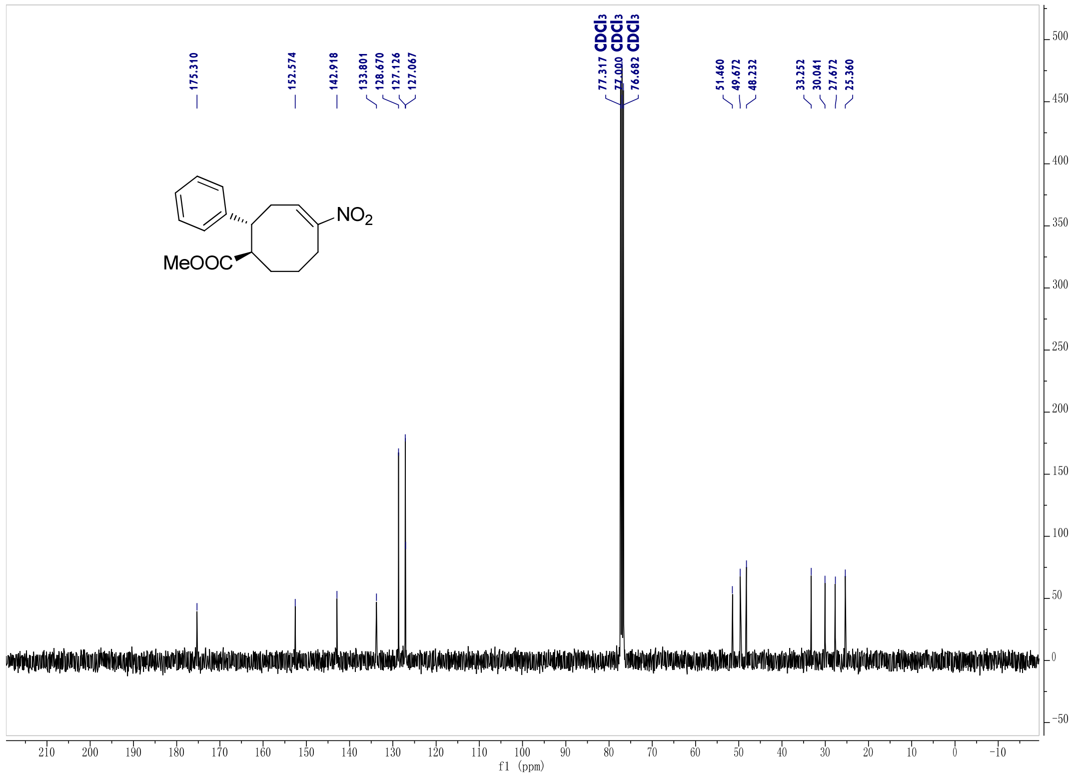


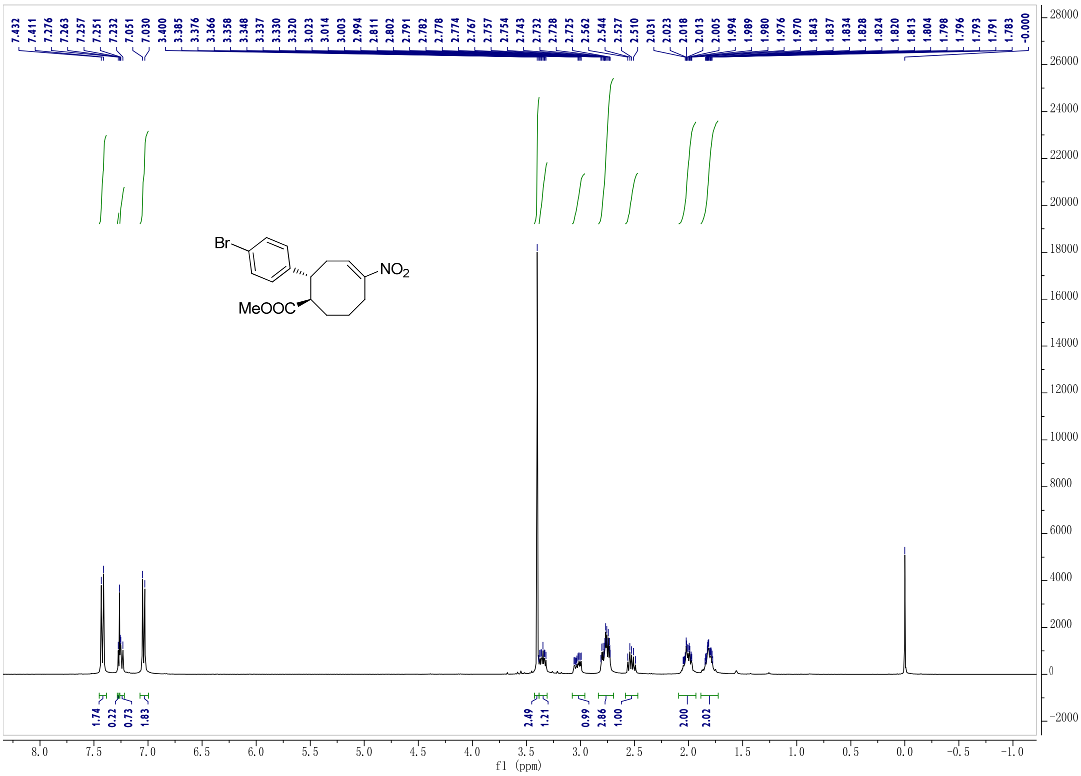


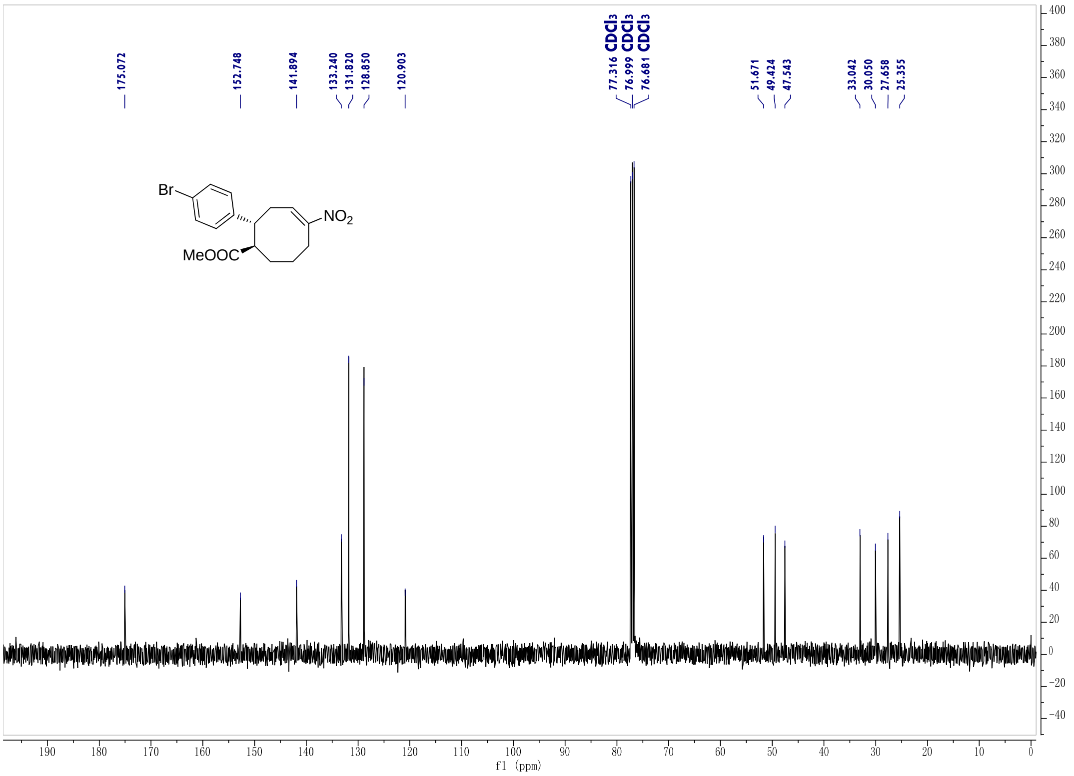

7.397 7.392 7.388 7.385 7.381 7.375 7.370 7.361 7.357 7.355 7.350 7.342 7.338 7.335 7.327 7.321 7.261 7.252 7.248 7.242 7.235 7.231 7.228 5.048 5.043 5.038 2.987 2.982 2.979 2.974 2.971 2.964 2.918 2.913 2.906 2.901 2.888 2.883 2.810 2.802 2.792 2.787 2.779 2.765 2.744 2.375 2.357 2.353 2.335 2.206 2.199 2.169 2.162 2.040 1.875 1.866 1.857 1.838 1.670 1.607 1.604 1.600 0.862
Ph
OH
H_3C
NO_2
O
3.05
0.23
1.68
1.00
1.07
1.25
2.85
2.09
1.04
1.17
1.01
2.86
f1 (ppm)

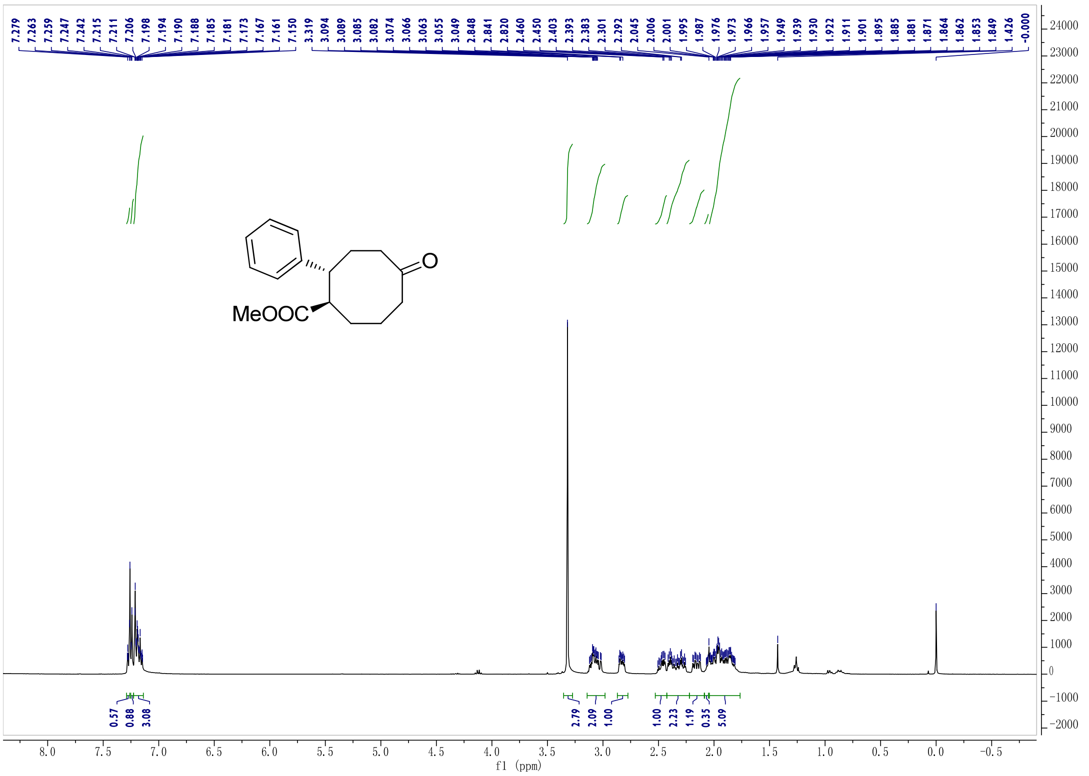

204.769
138.049
129.203
128.524
127.676
101.965
77.318 CDCl3
77.001 CDCl3
76.683 CDCl3
72.008
50.641
48.366
35.247
31.306
22.413
20.069
Ph
OH
H_3C
NO_2
O
f1 (ppm)

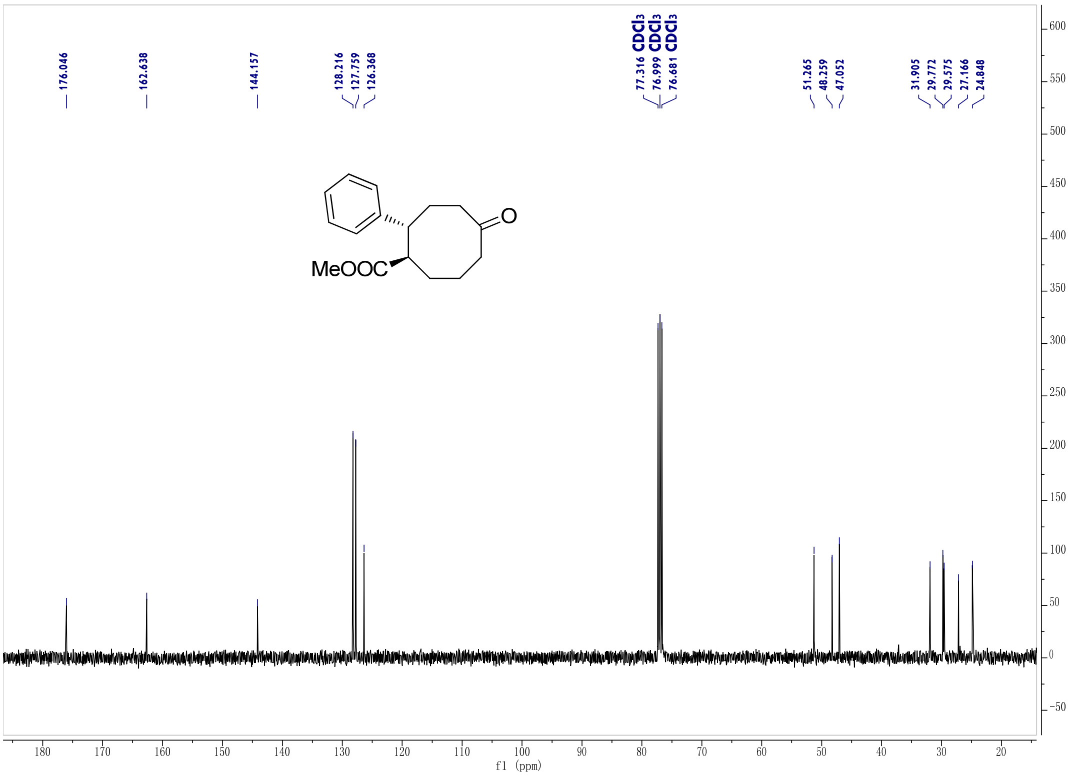




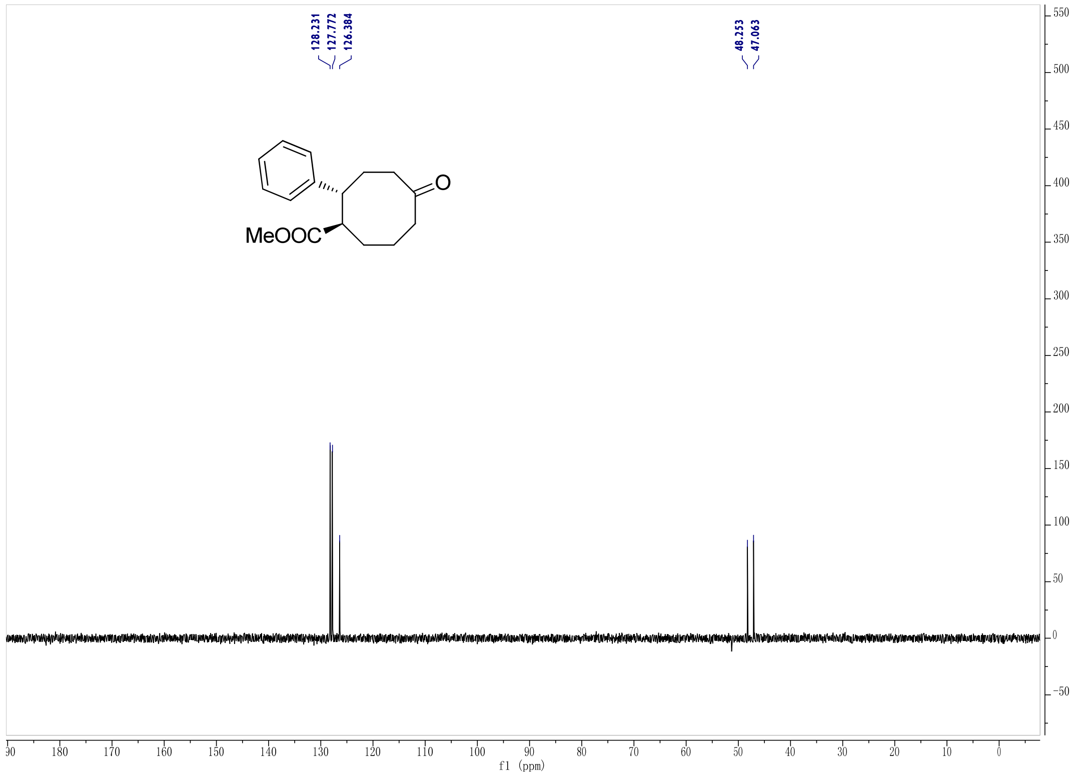

Br
NO2
MeOOC
f1 (ppm)


175.072
152.748
141.894
133.240
131.820
128.850
120.903
77.316 CDCl3
76.999 CDCl3
76.681 CDCl3
51.671
49.424
47.543
33.042
30.050
27.658
25.355
Br
NO2
MeOOC
f1 (ppm)

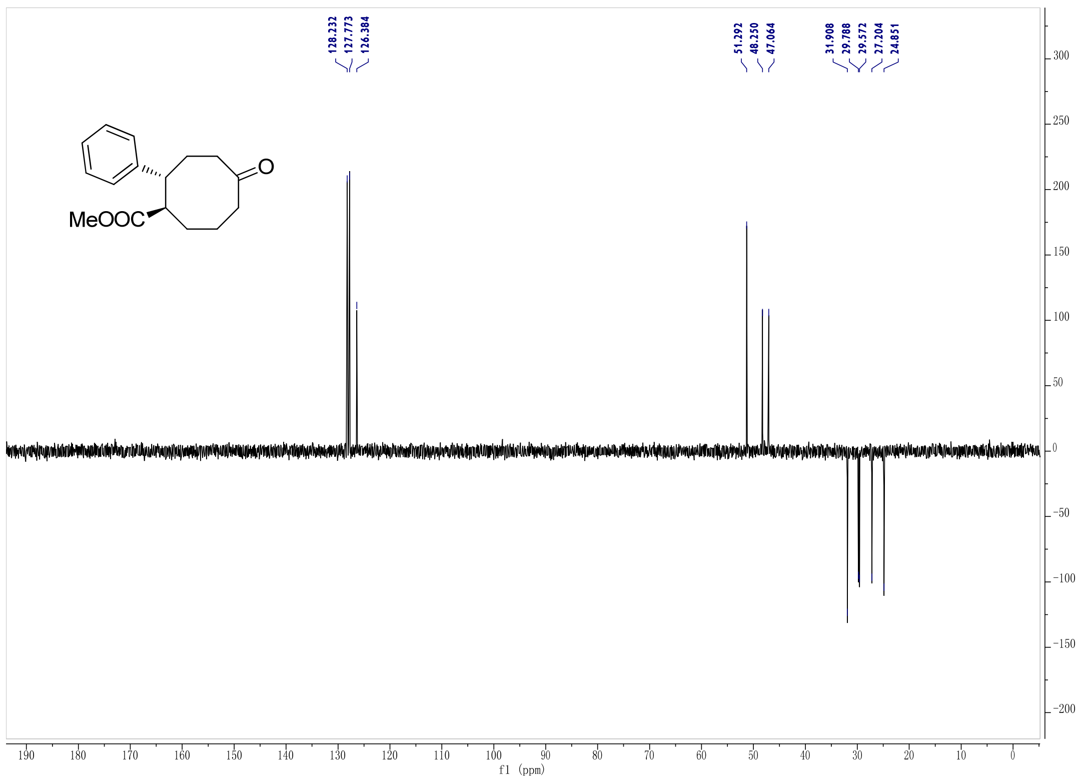

7.279 7.263 7.259 7.247 7.242 7.215 7.211 7.206 7.198 7.194 7.190 7.188 7.185 7.181 7.173 7.167 7.161 7.150 3.319 3.094 3.089 3.085 3.082 3.074 3.066 3.063 3.055 3.049 2.848 2.841 2.820 2.460 2.450 2.403 2.393 2.383 2.301 2.292 2.045 2.006 2.001 1.995 1.987 1.976 1.973 1.966 1.957 1.949 1.939 1.930 1.922 1.911 1.901 1.895 1.885 1.881 1.871 1.864 1.862 1.853 1.849 1.426 -0.000
MeOOC
O
0.57 0.88 3.08 2.79 2.09 1.00 1.00 2.23 1.19 0.35 5.09
f1 (ppm)


176.046 162.638 144.157 128.216 127.759 126.368 77.316 CDCl3 76.999 CDCl3 76.681 CDCl3 51.265 48.259 47.052 31.905 29.772 29.575 27.166 24.848
MeOOC
O
f1 (ppm)

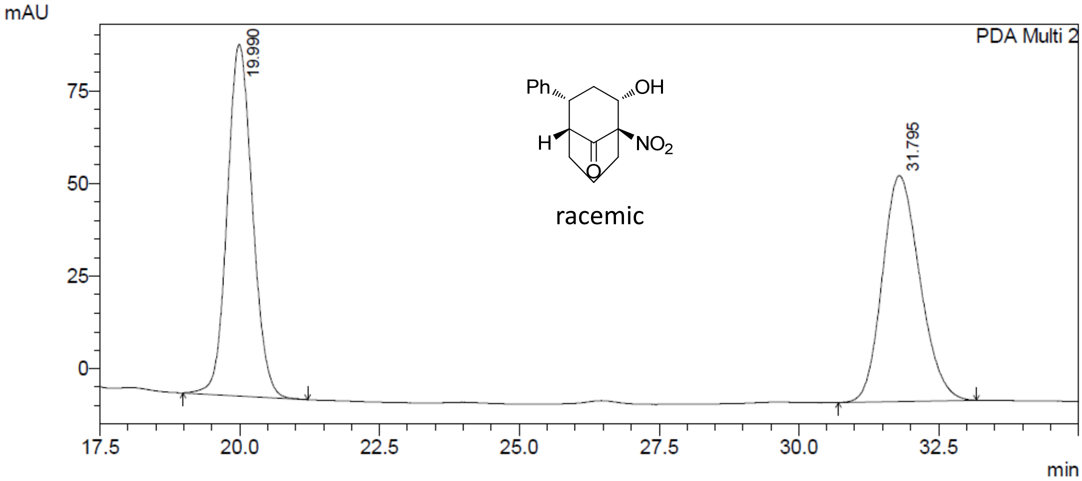
Dept 90 spectrum



Dept 135 spectrum



(H) HPLC chromatogram

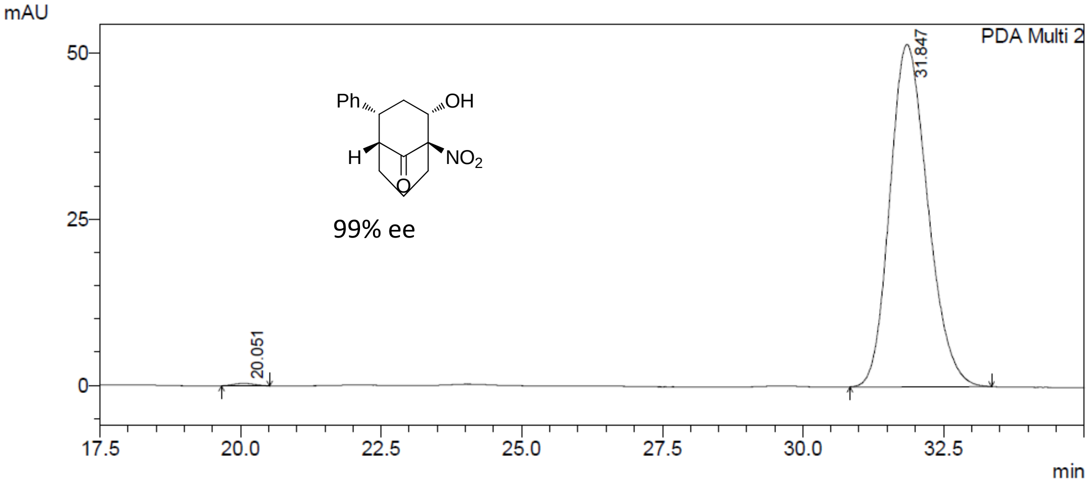


1 PDA Multi 2/220nm 4nm

PeakTable

PDA Ch2 220nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	19.990	2979531	94909	51.137	60.879
2	31.795	2847004	60988	48.863	39.121
Total		5826535	155897	100.000	100.000

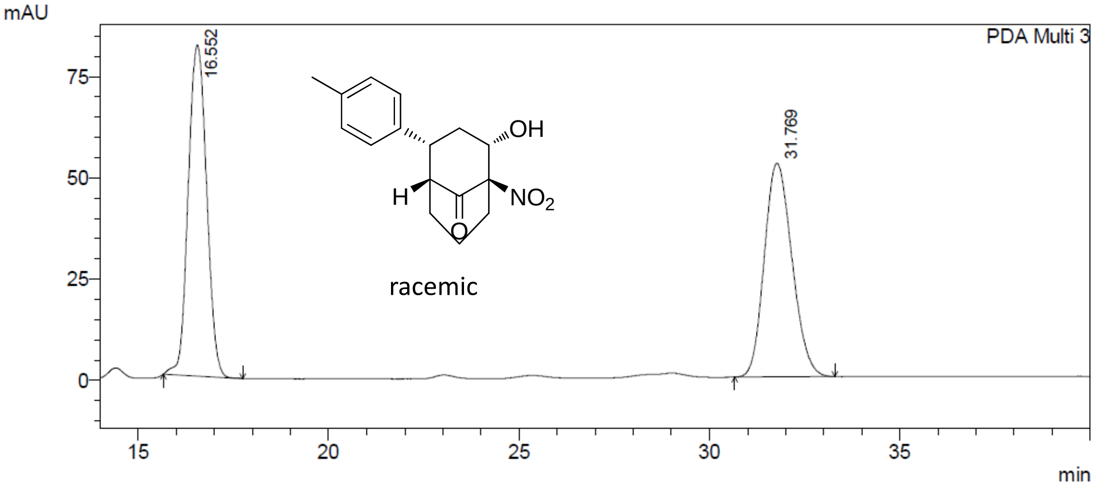


1 PDA Multi 2/220nm 4nm

PeakTable

PDA Ch2 220nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	20.051	10298	396	0.424	0.764
2	31.847	2416659	51496	99.576	99.236
Total		2426957	51893	100.000	100.000

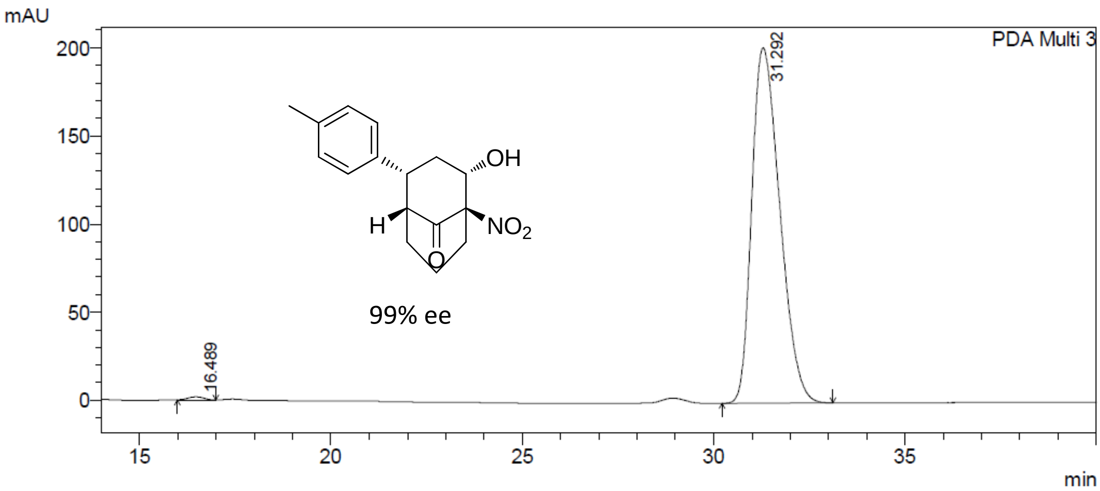


1 PDA Multi 3/230nm 4nm

PeakTable

PDA Ch3 230nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	16.552	2746242	81720	50.683	60.784
2	31.769	2672242	52724	49.317	39.216
Total		5418485	134445	100.000	100.000

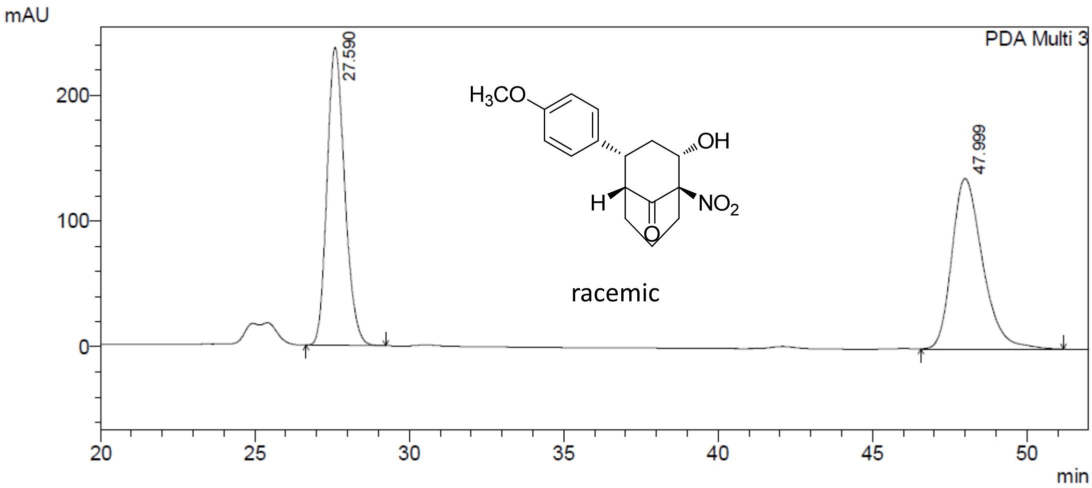


1 PDA Multi 3/230nm 4nm

PeakTable

PDA Ch3 230nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	16.489	51615	1806	0.500	0.888
2	31.292	10279551	201622	99.500	99.112
Total		10331167	203427	100.000	100.000

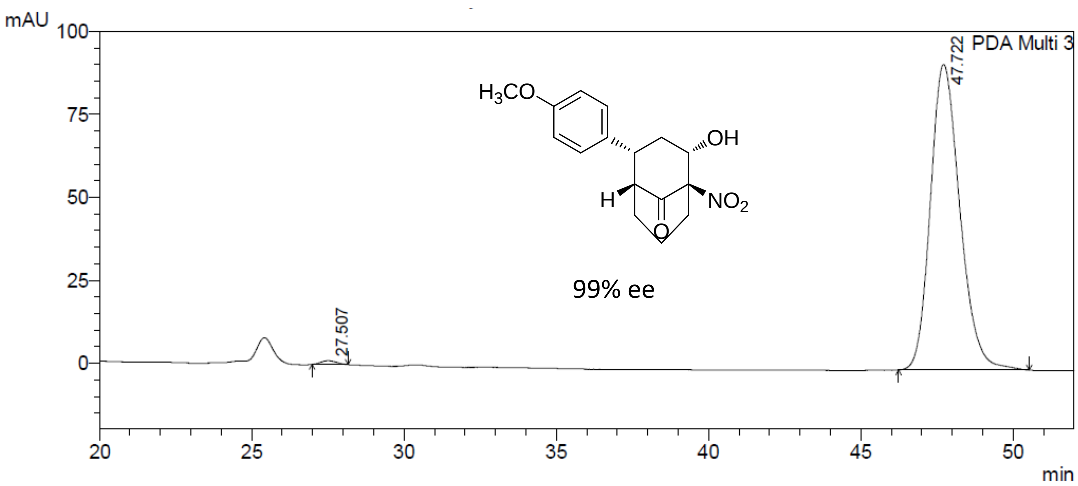


1 PDA Multi 3/230nm 4nm

PeakTable

PDA Ch3 230nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	27.590	9468371	237180	50.182	63.635
2	47.999	9399630	135539	49.818	36.365
Total		18868001	372719	100.000	100.000

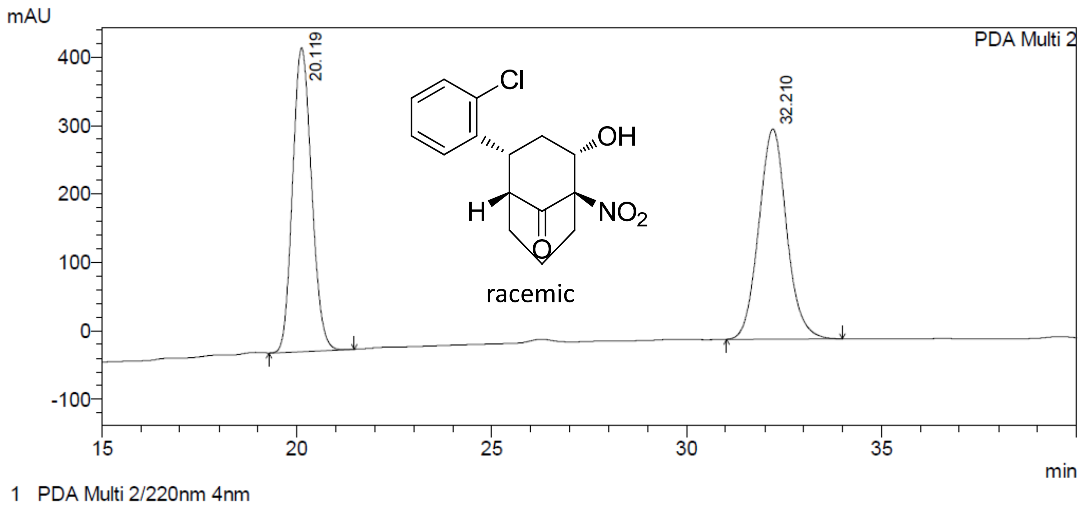


1 PDA Multi 3/230nm 4nm

PeakTable

PDA Ch3 230nm 4nm

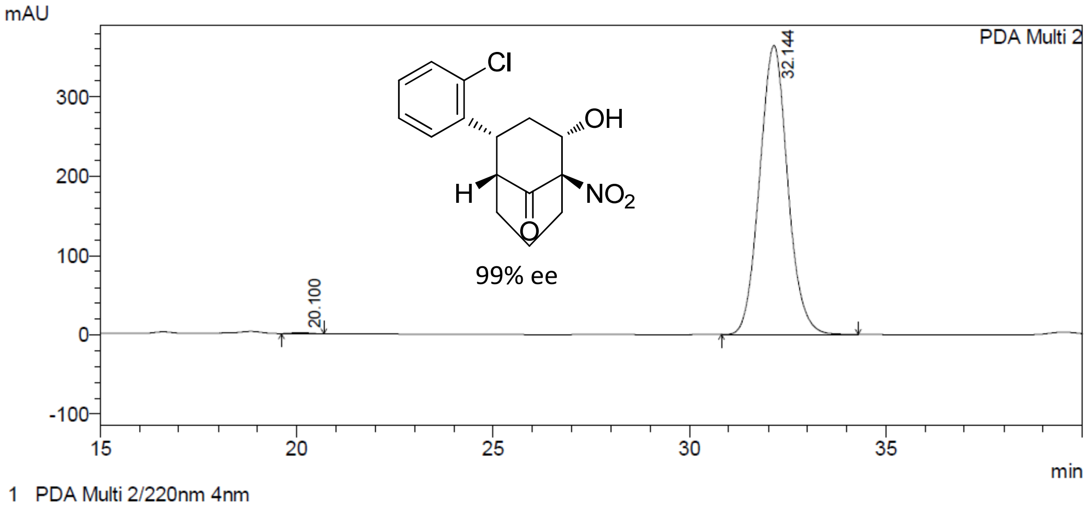
Peak#	Ret. Time	Area	Height	Area %	Height %
1	27.507	40418	1141	0.645	1.223
2	47.722	6226576	92152	99.355	98.777
Total		6266994	93294	100.000	100.000



PeakTable

PDA Ch2 220nm 4nm

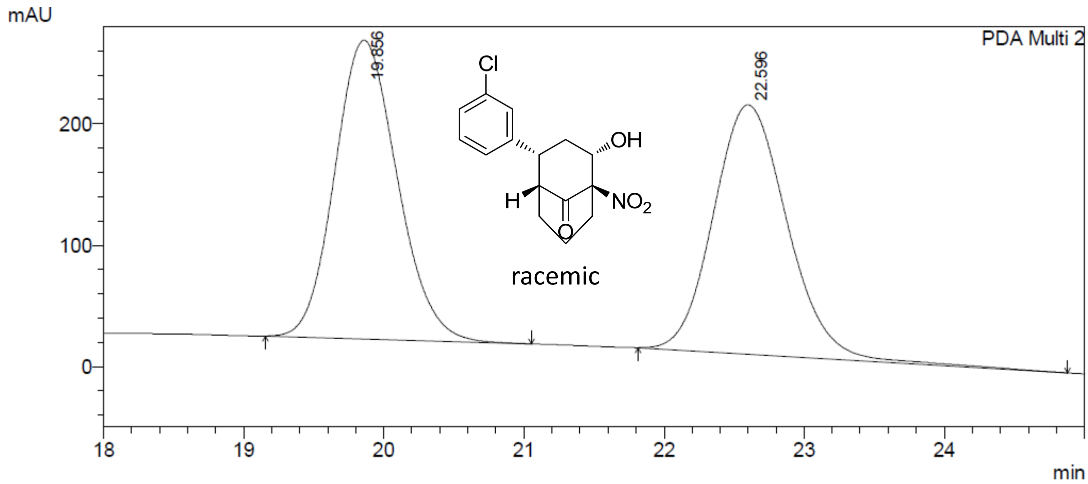
Peak#	Ret. Time	Area	Height	Area %	Height %
1	20.119	15058615	443708	49.694	59.111
2	32.210	15244168	306924	50.306	40.889
Total		30302783	750631	100.000	100.000



PeakTable

PDA Ch2 220nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	20.100	42731	1407	0.235	0.385
2	32.144	18136069	364487	99.765	99.615
Total		18178801	365895	100.000	100.000

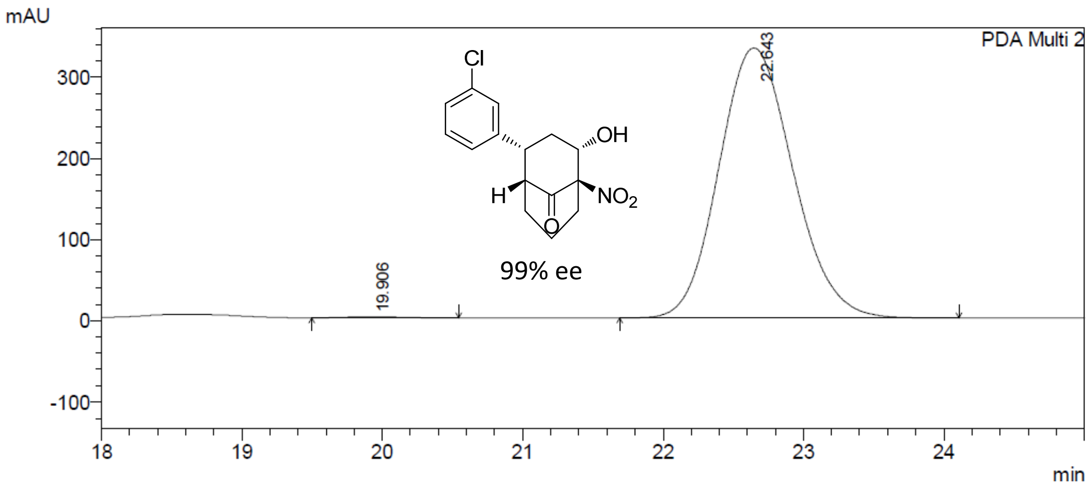


1 PDA Multi 2/220nm 4nm

PeakTable

PDA Ch2 220nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	19.856	7651067	246040	50.306	54.517
2	22.596	7557944	205265	49.694	45.483
Total		15209011	451305	100.000	100.000

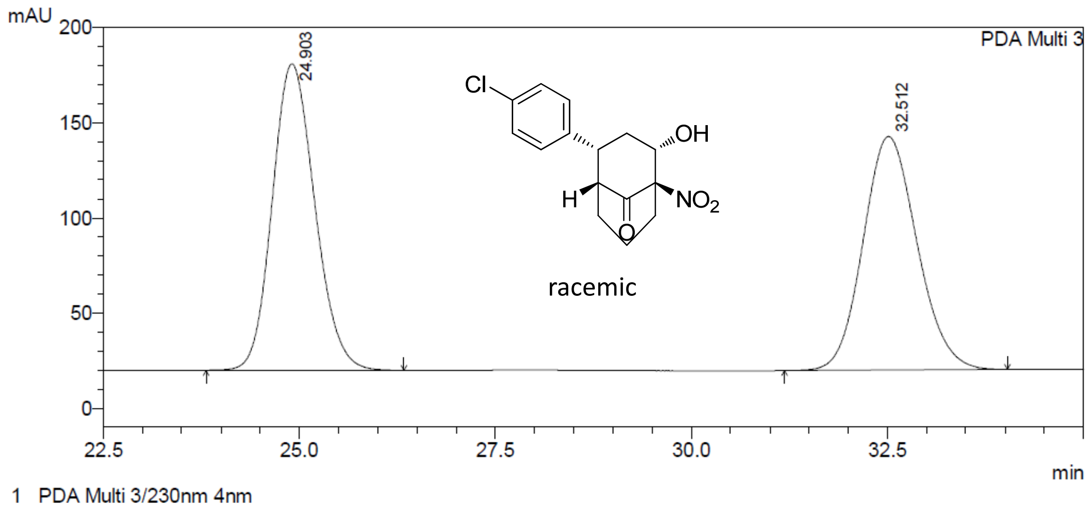


1 PDA Multi 2/220nm 4nm

PeakTable

PDA Ch2 220nm 4nm

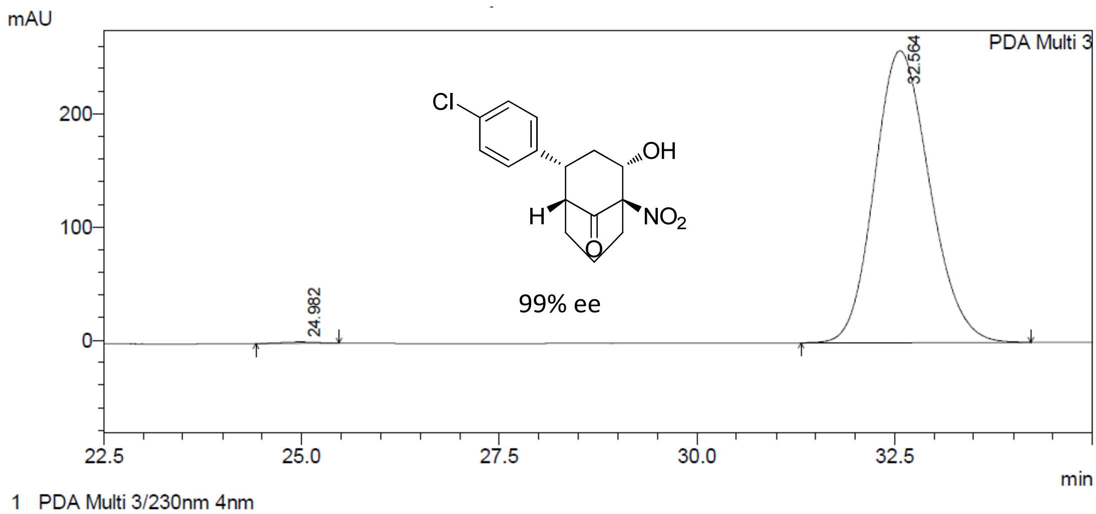
Peak#	Ret. Time	Area	Height	Area %	Height %
1	19.906	42510	1482	0.346	0.443
2	22.643	12231349	332966	99.654	99.557
Total		12273859	334448	100.000	100.000



PeakTable

PDA Ch3 230nm 4nm

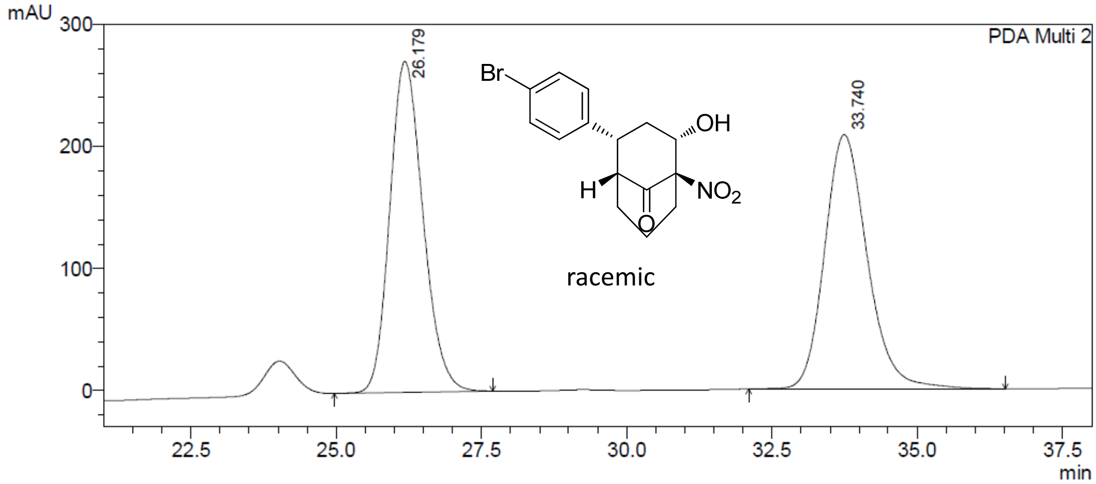
Peak#	Ret. Time	Area	Height	Area %	Height %
1	24.903	6097521	160967	50.874	56.752
2	32.512	5887942	122665	49.126	43.248
Total		11985463	283631	100.000	100.000



PeakTable

PDA Ch3 230nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	24.982	33199	1099	0.263	0.424
2	32.564	12572322	258104	99.737	99.576
Total		12605521	259203	100.000	100.000

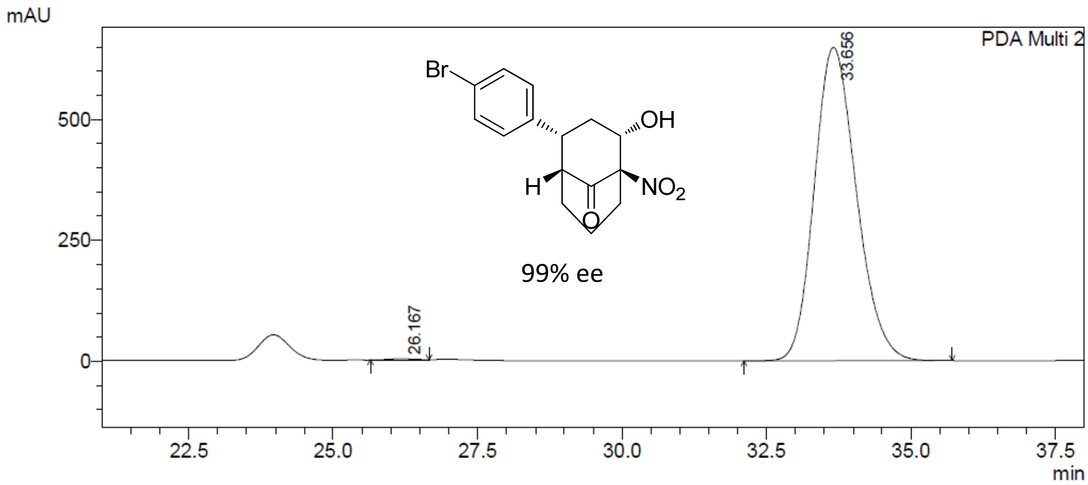


1 PDA Multi 2/220nm 4nm

PeakTable

PDA Ch2 220nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	26.179	10806832	271325	50.314	56.568
2	33.740	10671816	208322	49.686	43.432
Total		21478649	479646	100.000	100.000

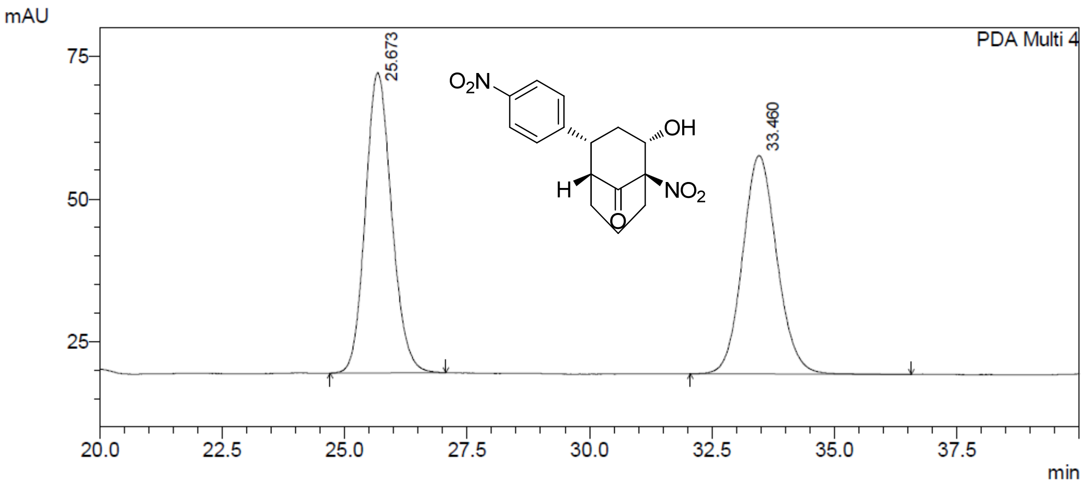


1 PDA Multi 2/220nm 4nm

PeakTable

PDA Ch2 220nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	26.167	65254	2244	0.198	0.345
2	33.656	32972173	648673	99.802	99.655
Total		33037426	650917	100.000	100.000

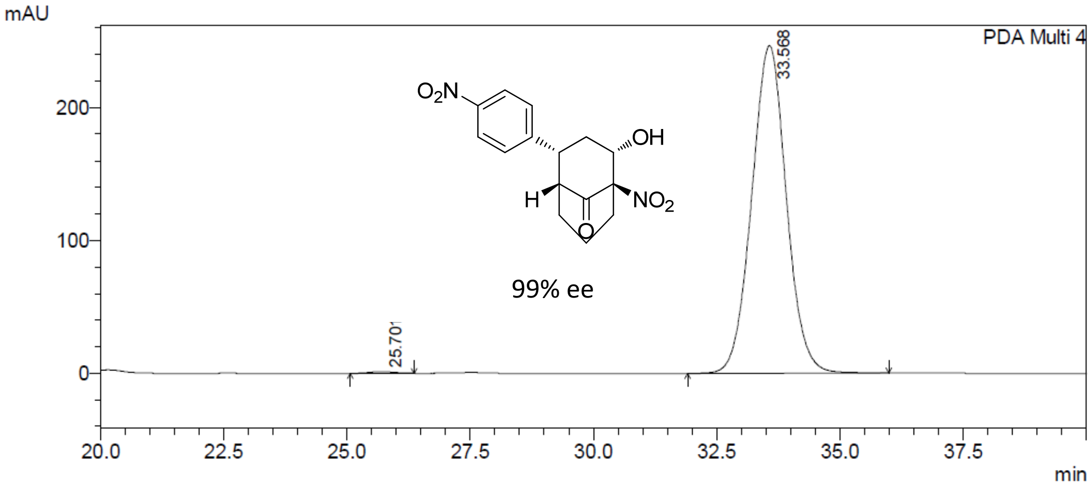


1 PDA Multi 4/254nm 4nm

PeakTable

PDA Ch4 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	25.673	1966665	52590	51.437	57.912
2	33.460	1856801	38221	48.563	42.088
Total		3823466	90811	100.000	100.000

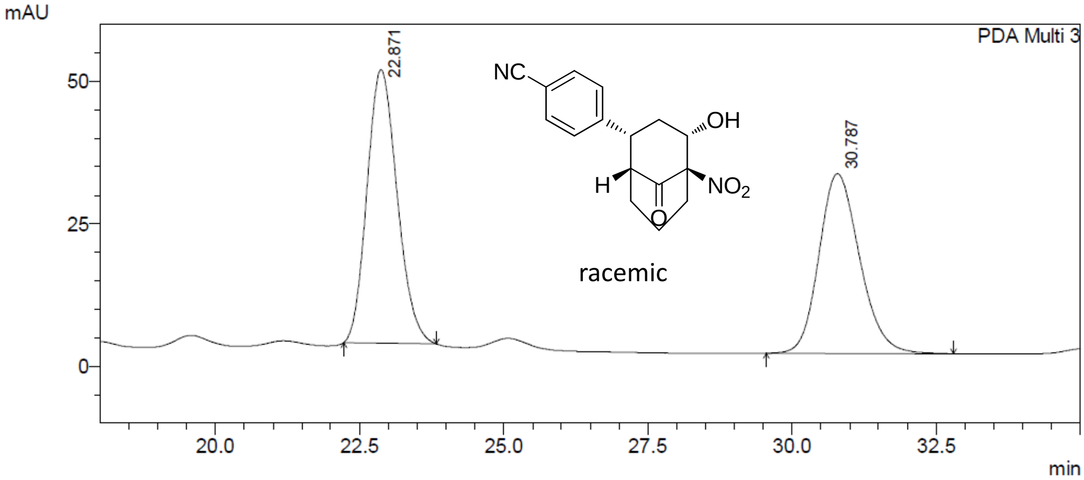


1 PDA Multi 4/254nm 4nm

PeakTable

PDA Ch4 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	25.701	43917	1246	0.363	0.503
2	33.568	12057281	246532	99.637	99.497
Total		12101198	247778	100.000	100.000

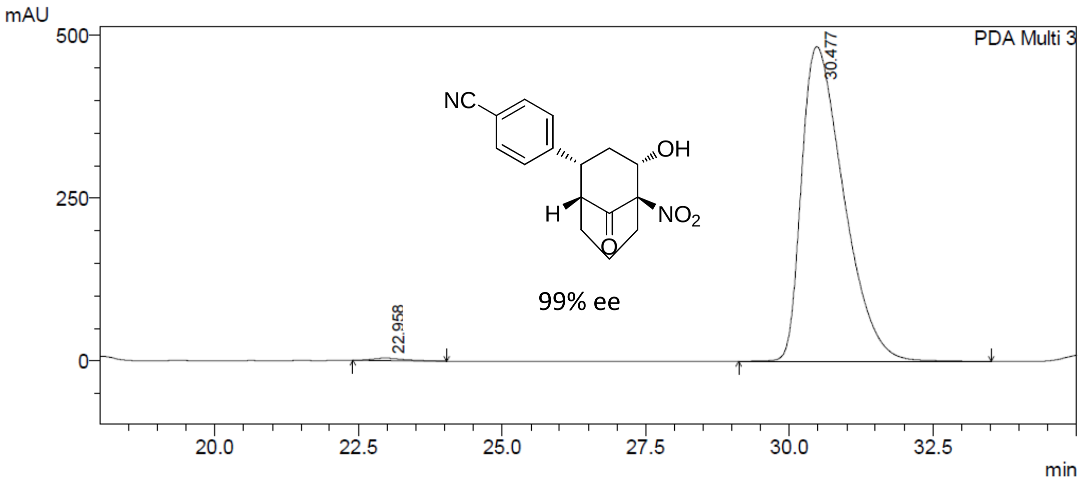


1 PDA Multi 3/230nm 4nm

PeakTable

PDA Ch3 230nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	22.871	1747479	47960	53.065	60.350
2	30.787	1545603	31510	46.935	39.650
Total		3293082	79470	100.000	100.000

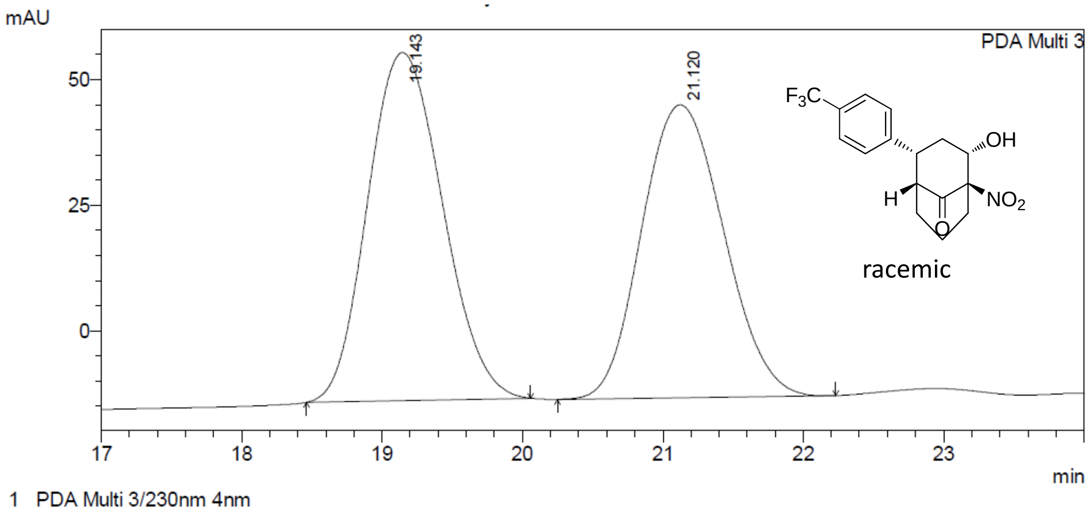


1 PDA Multi 3/230nm 4nm

PeakTable

PDA Ch3 230nm 4nm

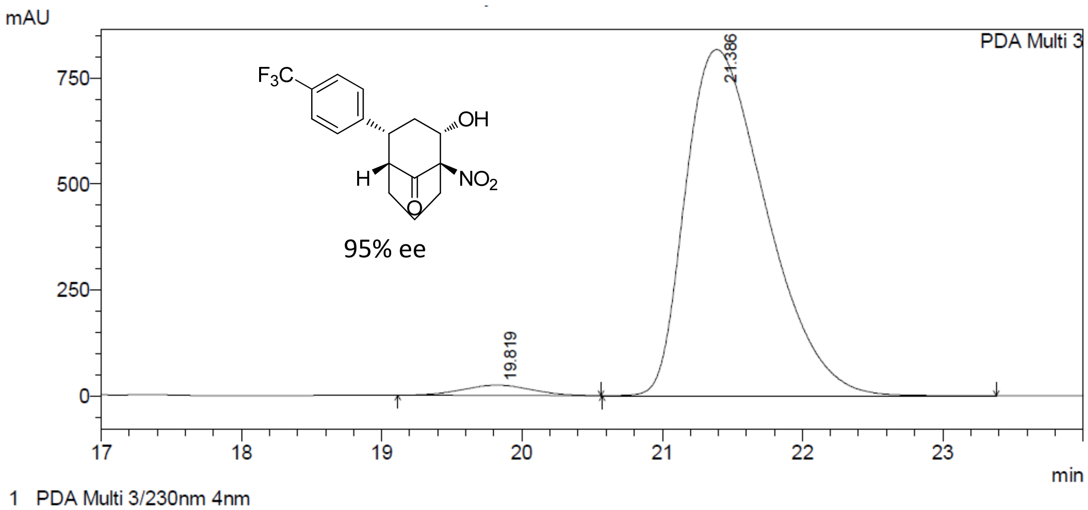
Peak#	Ret. Time	Area	Height	Area %	Height %
1	22.958	132165	3520	0.531	0.723
2	30.477	24738079	483277	99.469	99.277
Total		24870244	486797	100.000	100.000



PeakTable

PDA Ch3 230nm 4nm

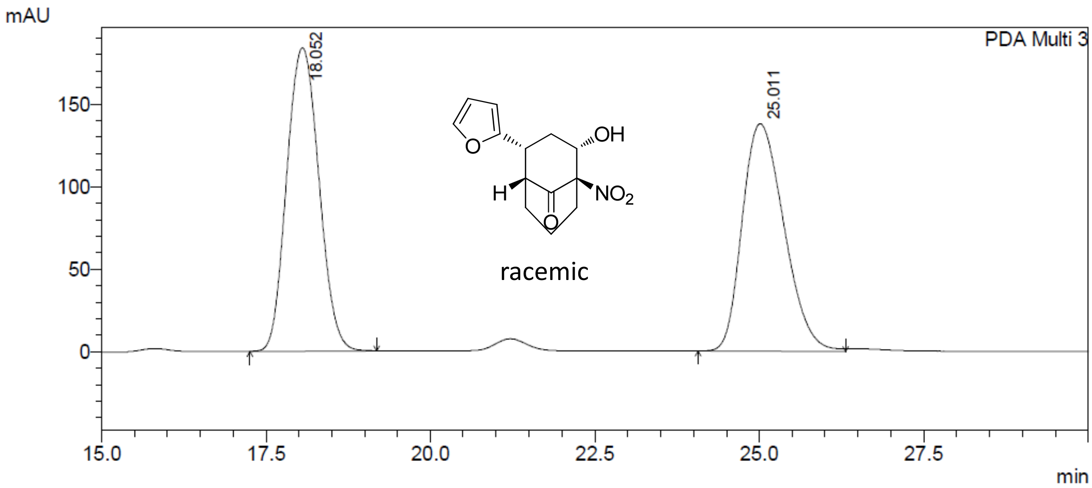
Peak#	Ret. Time	Area	Height	Area %	Height %
1	19.143	2573969	69387	52.093	54.317
2	21.120	2367146	58356	47.907	45.683
Total		4941115	127743	100.000	100.000



PeakTable

PDA Ch3 230nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	19.819	830115	24156	2.471	2.870
2	21.386	32765677	817521	97.529	97.130
Total		33595792	841677	100.000	100.000

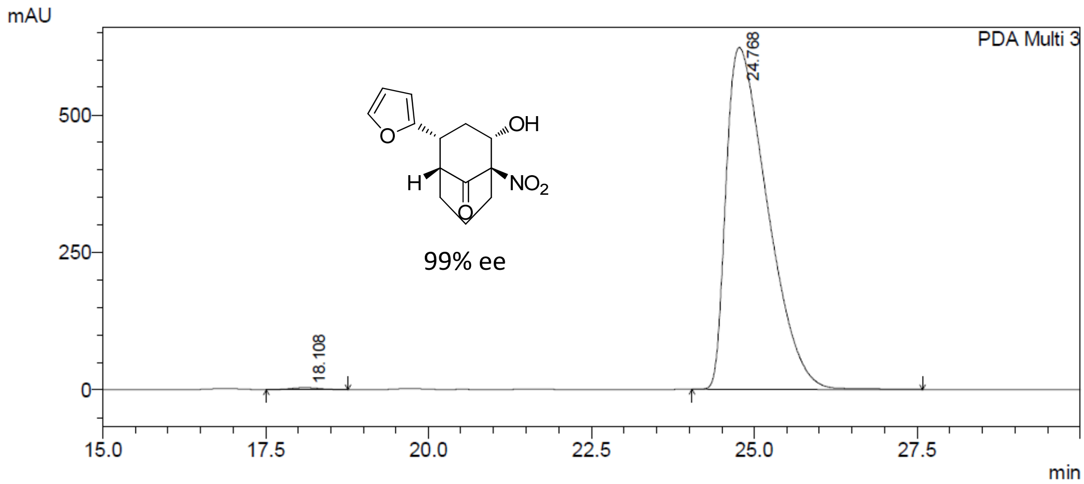


1 PDA Multi 3/230nm 4nm

PeakTable

PDA Ch3 230nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	18.052	6275865	183853	50.652	57.131
2	25.011	6114239	137954	49.348	42.869
Total		12390104	321807	100.000	100.000

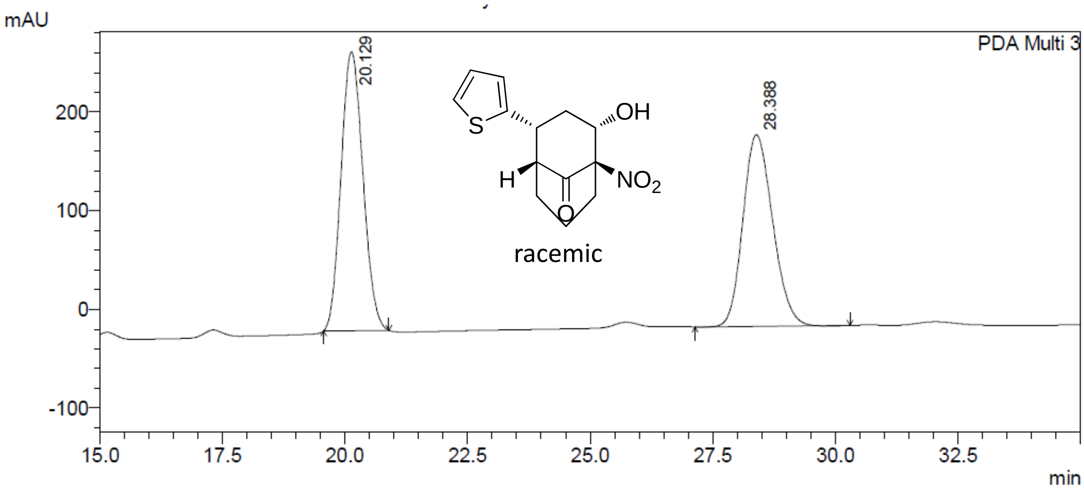


1 PDA Multi 3/230nm 4nm

PeakTable

PDA Ch3 230nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	18.108	113606	3851	0.411	0.615
2	24.768	27496088	621959	99.589	99.385
Total		27609694	625810	100.000	100.000

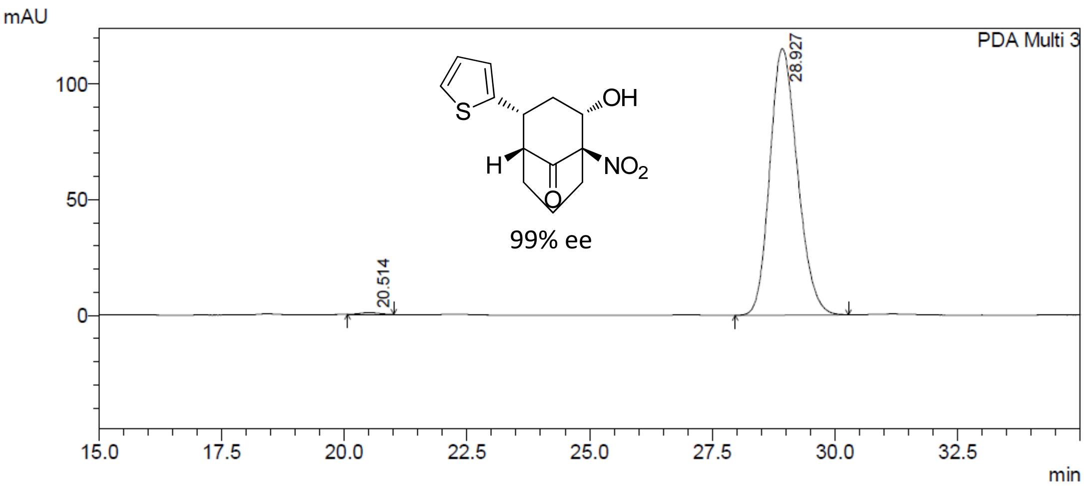


1 PDA Multi 3/230nm 4nm

PeakTable

PDA Ch3 230nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	20.129	8797882	282595	51.788	59.282
2	28.388	8190224	194099	48.212	40.718
Total		16988106	476694	100.000	100.000

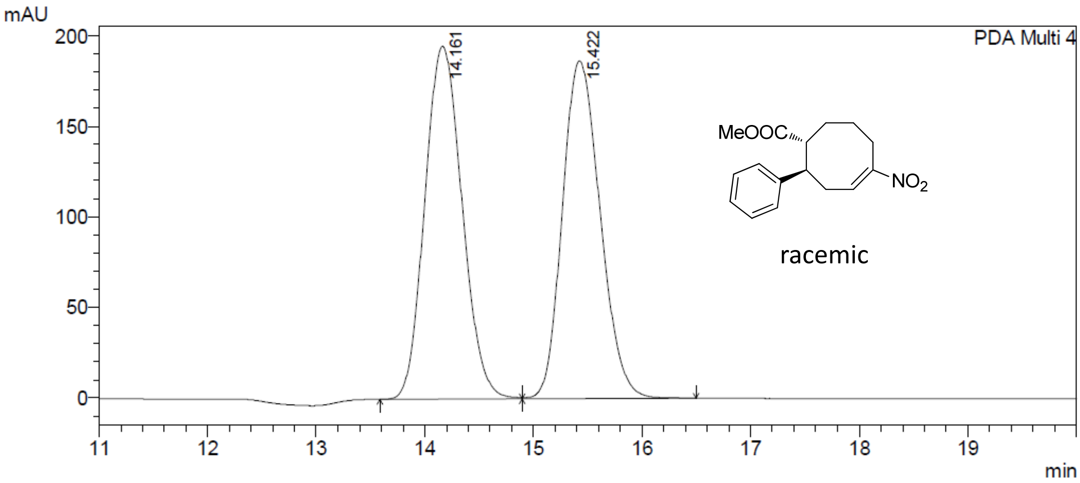


1 PDA Multi 3/230nm 4nm

PeakTable

PDA Ch3 230nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	20.514	23823	864	0.523	0.744
2	28.927	4533673	115322	99.477	99.256
Total		4557496	116186	100.000	100.000

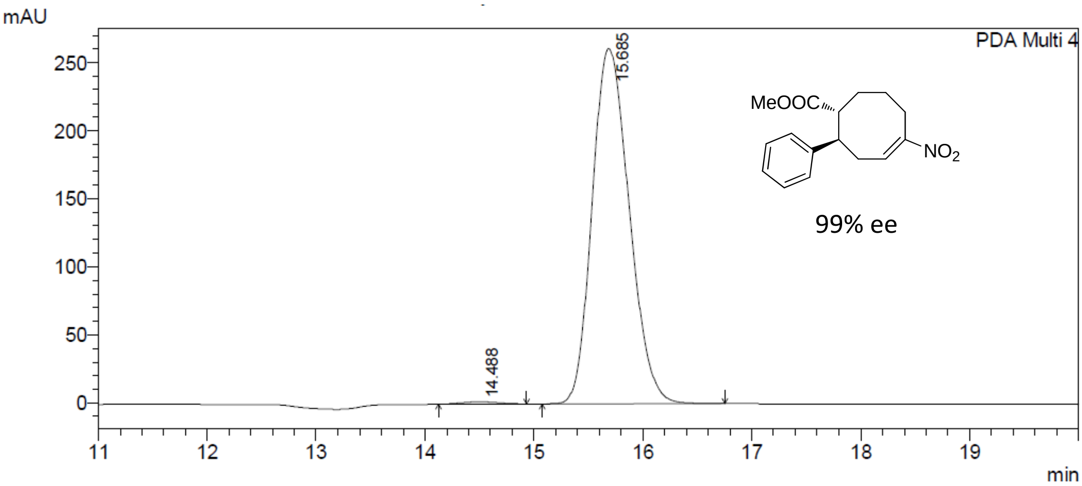


1 PDA Multi 4/254nm 4nm

PeakTable

PDA Ch4 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	14.161	4656505	194889	50.798	51.097
2	15.422	4510169	186520	49.202	48.903
Total		9166673	381408	100.000	100.000

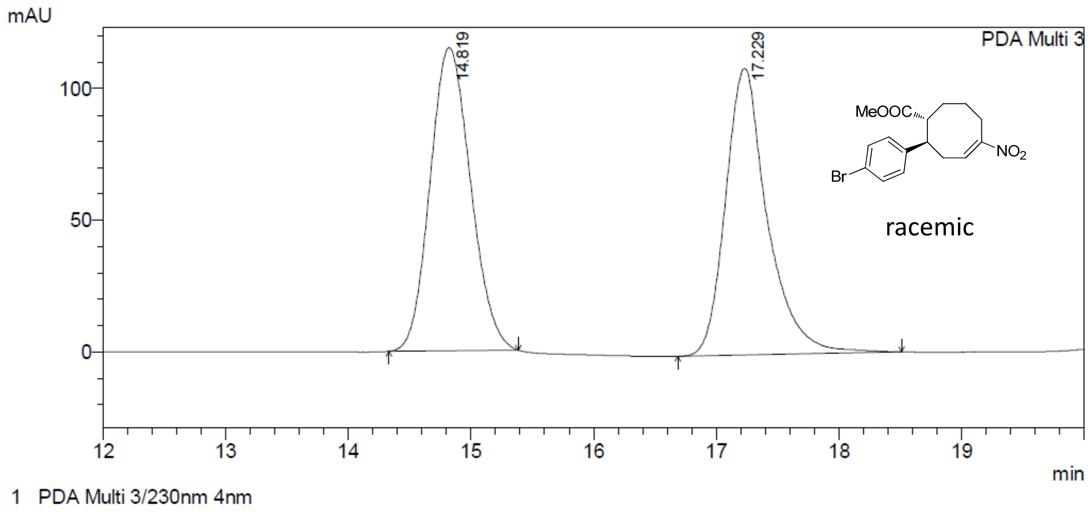


1 PDA Multi 4/254nm 4nm

PeakTable

PDA Ch4 254nm 4nm

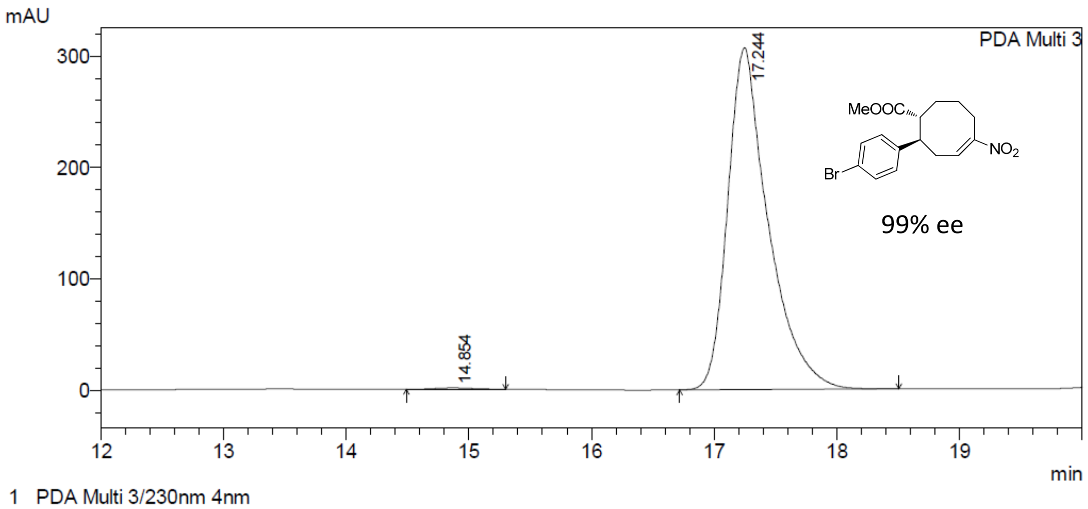
Peak#	Ret. Time	Area	Height	Area %	Height %
1	14.488	36529	1627	0.588	0.620
2	15.685	6171052	260967	99.412	99.380
Total		6207581	262594	100.000	100.000



PeakTable

PDA Ch3 230nm 4nm

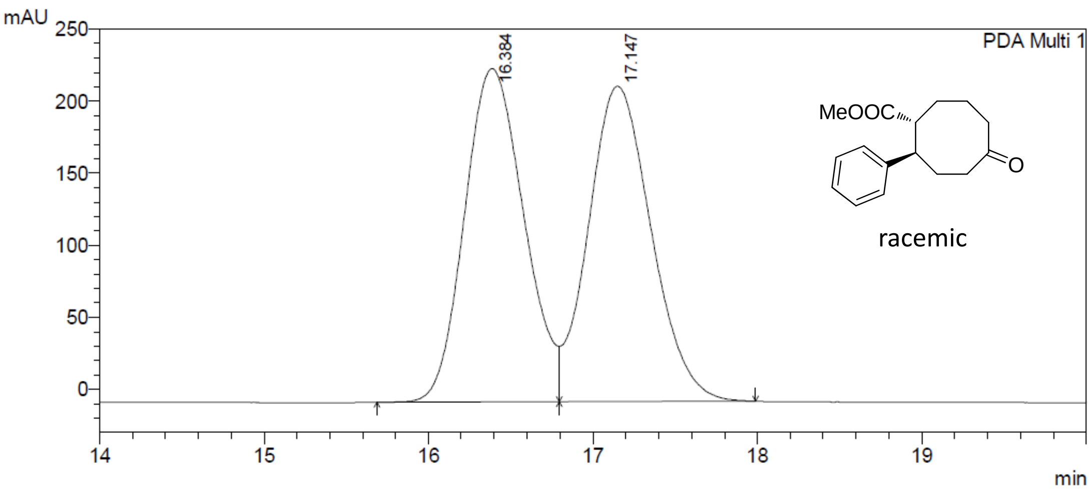
Peak#	Ret. Time	Area	Height	Area %	Height %
1	14.819	2653593	115173	50.589	51.385
2	17.229	2591844	108963	49.411	48.615
Total		5245437	224136	100.000	100.000



PeakTable

PDA Ch3 230nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	14.854	28029	1329	0.396	0.432
2	17.244	7058363	306572	99.604	99.568
Total		7086392	307901	100.000	100.000

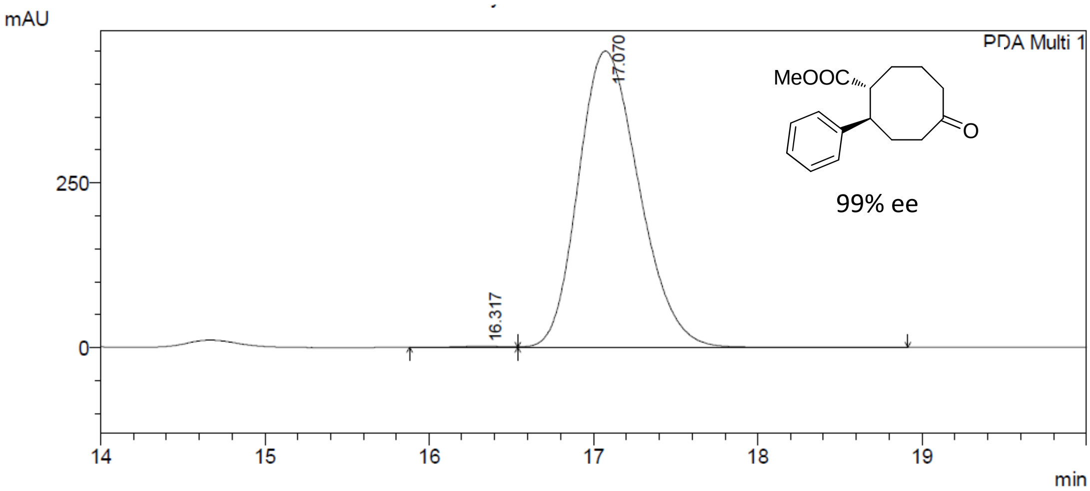


1 PDA Multi 1/208nm 4nm

PeakTable

PDA Ch1 208nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	16.384	5806583	231247	49.952	51.383
2	17.147	5817629	218796	50.048	48.617
Total		11624213	450043	100.000	100.000

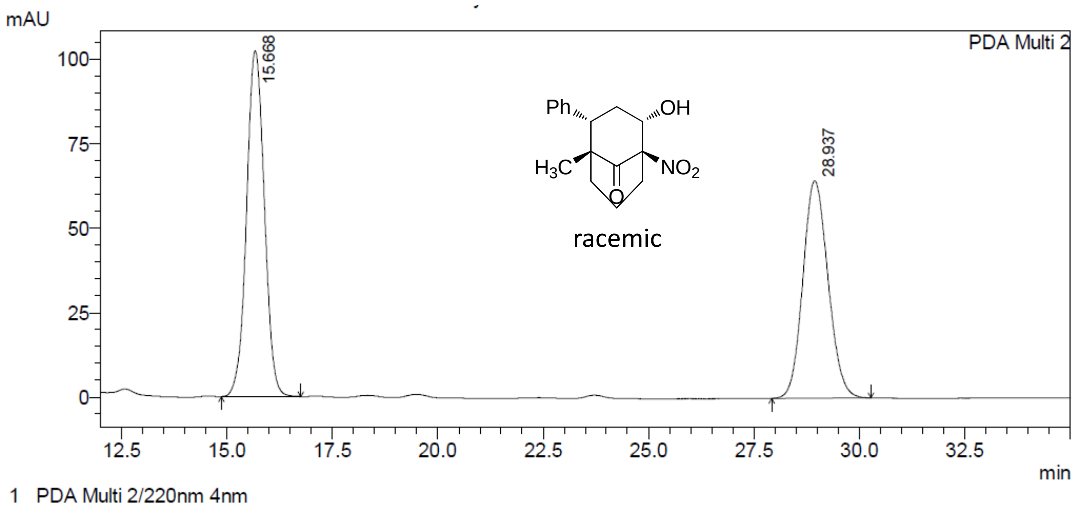


1 PDA Multi 1/208nm 4nm

PeakTable

PDA Ch1 208nm 4nm

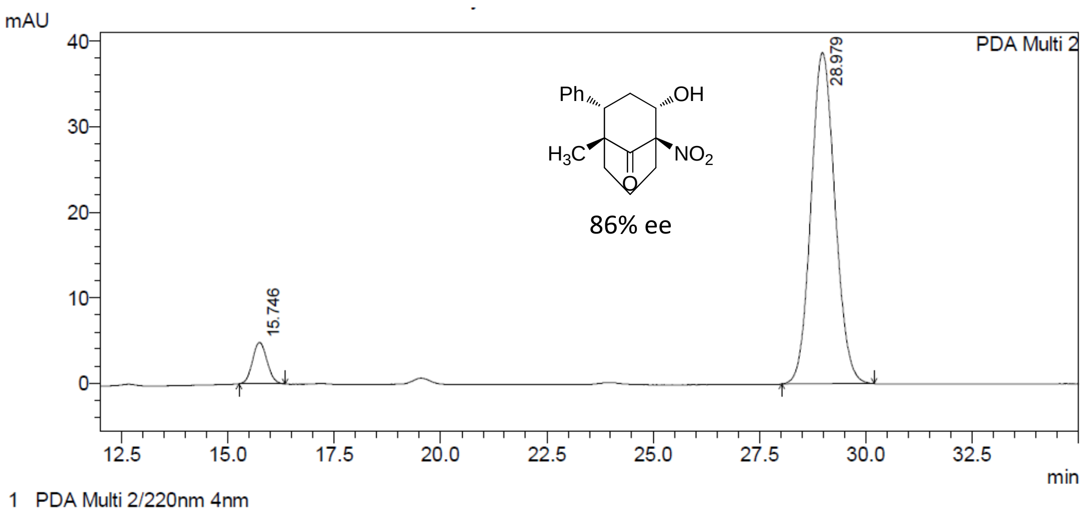
Peak#	Ret. Time	Area	Height	Area %	Height %
1	16.317	39370	1904	0.339	0.422
2	17.070	11569675	449729	99.661	99.578
Total		11609045	451632	100.000	100.000



PeakTable

PDA Ch2 220nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	15.668	3009582	102287	52.979	61.389
2	28.937	2671156	64334	47.021	38.611
Total		5680738	166620	100.000	100.000



PeakTable

PDA Ch2 220nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	15.746	115538	4852	7.059	11.139
2	28.979	1521195	38704	92.941	88.861
Total		1636733	43555	100.000	100.000