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Supporting Information

Stereoselective synthesis of highly substituted 1-isomorphans (1-azabicyclo[3.3.1]nonanes)

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1. Enantioselective Michael reaction optimization

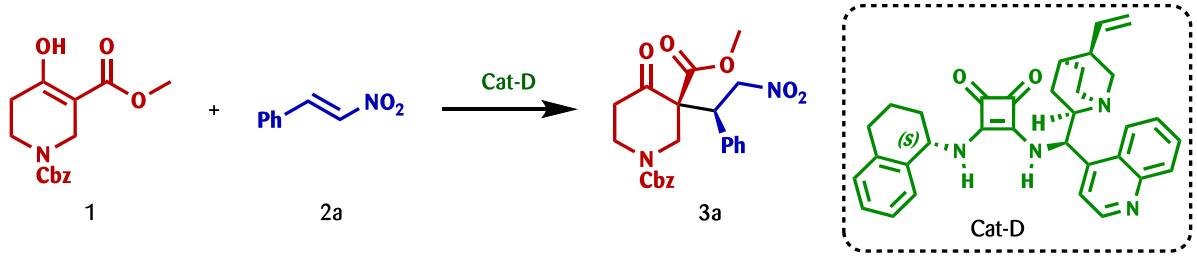


Table 1. Solvent optimization of the Michael addition of ketoester **1** to nitrostyrene **2a**.

Exp.	Solv.	Yield(%)[a]	d.r.[b]	*ee*[b]
1	PhMe	80	98:2	94
2	$PhCF_3$	76	99:1	95
3	**Acetone**	**83**	**99:1**	**95**
4	DCE	77	99:1	95
5	EtOAc	76	99:1	95
6	$CHCl_3$	78	95:5	90
7	MeCN	84	97:3	90
8	THF	75	94:6	78
9	MeOH	77	97:3	76
10	DMF	76	95:5	58
11	Brine	74	94:4	84
12	DCM/Brine	60	93:7	80

Reactions were performed with **1a** (0.1 mmol), **2a** (1 equiv.) and **Cat-D** (1 mol%) in solvent (2 M) at 20 °C [a] Isolated yield [b] e.r. and d.r. obtained by CSP-HPLC analysis. DCE: 1,2-dichloroethane, THF: tetrahydrofuran, DMF: dimethylformamide, DCM: dichloromethane.

Table 2. Product conversion at different reaction times.

Time (h)	% conversion at[a]		
	1 mol%	0.5 mol%	0.1 mol%
0.6	87	86	80
1.1	90	90	88
2.5	90	90	90
5.1	92	90	90
24	91[b]	89[c]	90[d]

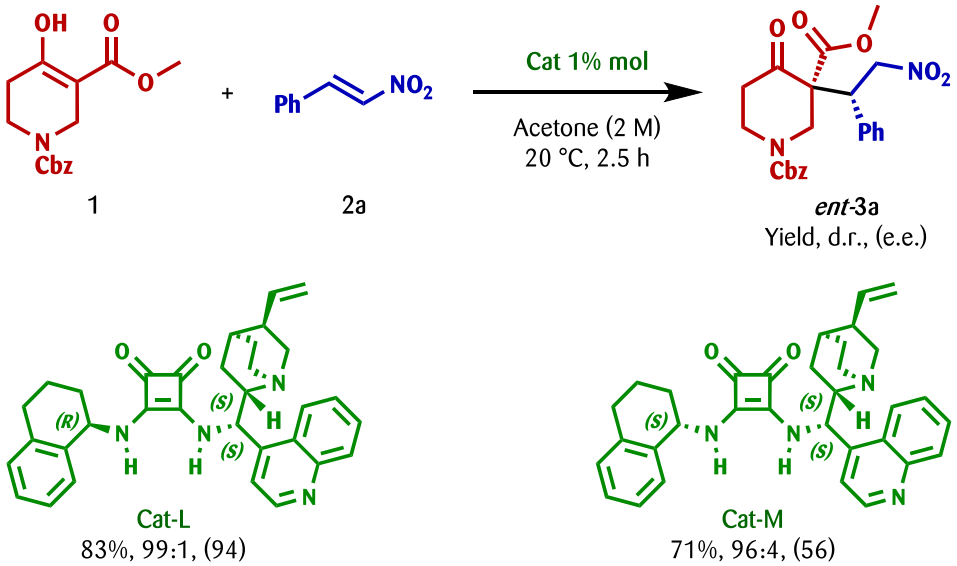
Reactions were performed with **1a** (0.5 mmol), **2a** (1 equiv.) and **Cat-D** in acetone (3.6 M) at 20 °C [a] Conversion calculated by ^{1}H NMR using 4-nitrobenzaldehyde as internal standard [b] d.r. = 97:3, e.r. = 95:5 [c] d.r. = 98:2, e.r. = 94:6 [d] d.r. = 96:4, e.r. = 88:12.

Table 3. Temperature effect on the Michael addition.

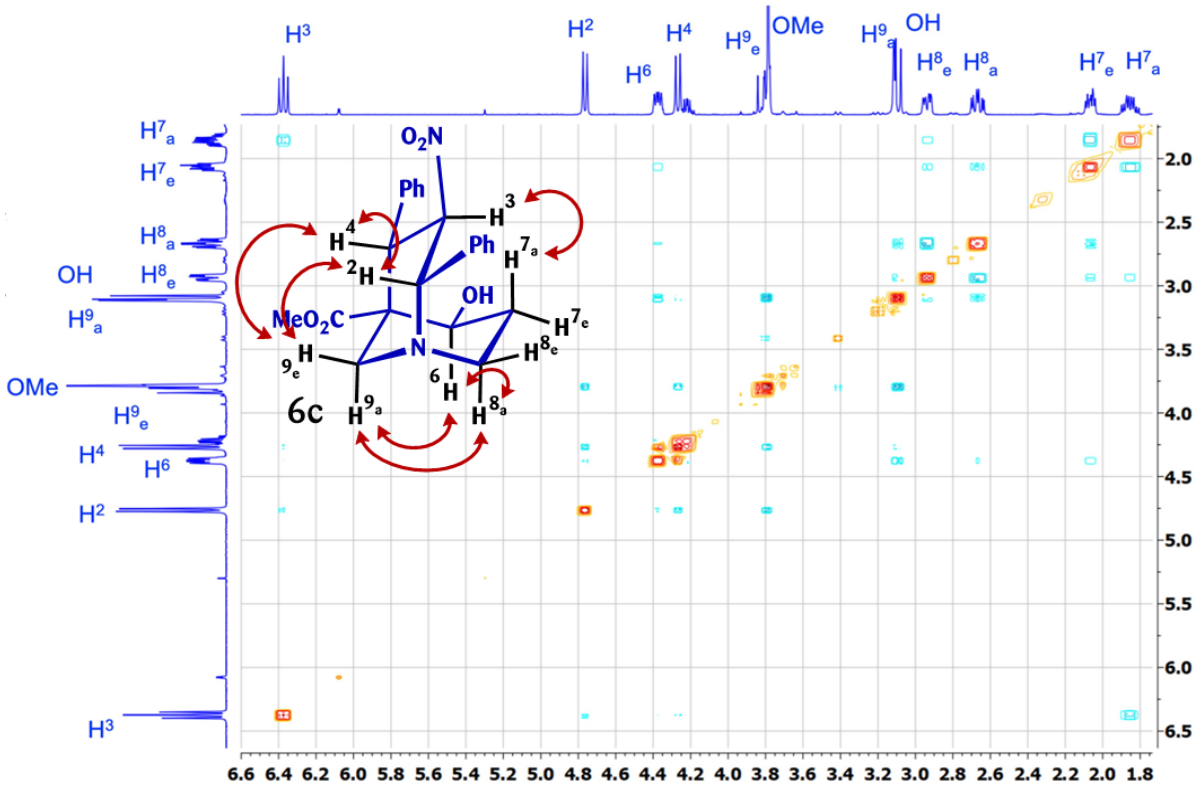
Exp.	mol%	[M]	T (°C)	Yield(%)[a]	d.r.[b]	e.r.[b]
1	1	2	0	72	97:3	96:4
2	1	2	20	84	99:1	97.5:2.5
3	1	2	35	86	99:1	98:2
4	**1**	**2**	**40**	**88**	**99:1**	**99:1**
5	1	2	45	74	99:1	99:1
6	1	2	50	65	97:3	97:3
7	1	2	60	63	96:4	96:4
8	0.5	1	50	70	98:2	96:4
9	0.5	1	60	64	97:3	96:4
10	1	1	45	77	98:2	98:2
11	1	1	50	68	99:1	98:2
12	1	1	60	68	98:2	96:4
13	1	2	40	91[c]	98:2	99:1
14	1	2	40	93[d]	97:3	99:1

Unless otherwise noted, reactions were performed with **1a** (0.1 mmol), **2a** (1 equiv.) and **Cat-D** in acetone (2 M) for 3 h.[a] Yields were determined according to obtained mass of pure product after FCC. [b] Determined by HPLC analysis using chiral column OD-H. [c] 2 equiv. of **2a** were used. [d] 2.5 of **2a** were used.

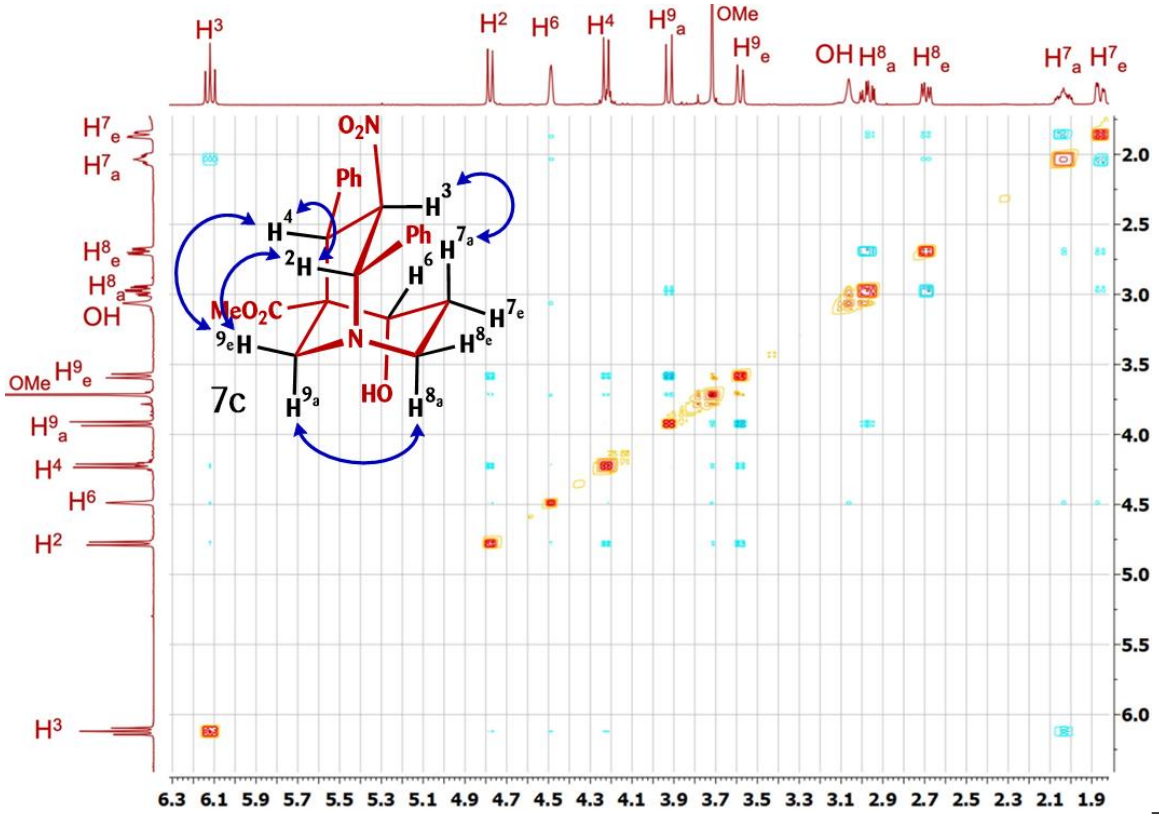
2. Enantiomer match-mismatch catalyst.



3. NOESY experiments of 6c and 7c



NOESY NMR, $CDCl_3$, 500 MHz



NOESY NMR, $CDCl_3$, 500 MHz

4. Experimental part

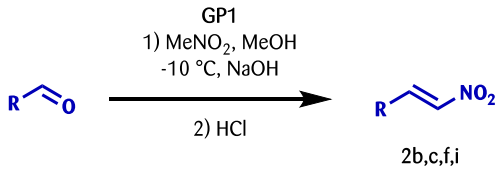
4.1 General Information

Unless stated otherwise, reactions were performed without any protective measures against moisture or air. Commercial-grade reagents and solvents were used without further purification unless otherwise stated. All reactions that require heating were conducted with a water bath/oil bath as the heat source unless otherwise noted. Thin-layer chromatography (TLC) was performed using Merck silica gel 60 GF_{254} TLC plates (0.25 mm) and visualization was done by UV light, or alternatively by I_2, basic $KMnO_4$, *p*-anisaldehyde, vanillin, phosphomolybdic acid (PMA), Seebach (PMA/$Ce(SO_4)_2$)[1], ninhydrin, $CuCl_2$, o-dianisidine, or 3,4-dinitrophenylhydrazine staining.[2] Flash column (FCC) and dry column vacuum chromatography (DCVC)[3] were performed on Sigma Aldrich 60 silica gel (230–400 mesh). ^1H and ^{13}C NMR spectra were recorded at stated temperature using Bruker Fourier-300 MHz, Jeol Eclipse-300 MHz, Bruker Avance III-400 MHz, Bruker Ascend-500 MHz, and Bruker Ascend-700 MHz spectrometers, and are referenced internally to residual solvent signals. HR-DART-MS spectra were recorded on a JEOL AccuTOF JMS-T100LC instrument. HR-FAB+-MS spectra were recorded on a JEOL JMS-700 instrument. IR spectra were measured on a Nicolet FT-IR-ATR iS-50 instrument. Optical rotations were measured with a Perkin Elmer 343 Polarimeter at the indicated temperature; concentrations are expressed in g/100 mL. Chiral high-performance liquid chromatography (HPLC) analyses were performed on either a Jasco LC-4000 Series instrument or a Waters 1525 instrument using the stated Chiral Column.

4.2 Synthesis of nitroalkenes 2

trans-β-Nitrostyrenes were purchased from Merck or synthesized according to reported methodologies.[4–7]

4.2.1 General procedure 1 (GP1) for the synthesis of nitroalkenes with an aryl group (2b,c,f,i)



2b,c,f,i

Based on literature-known procedures,[8,9] a solution of the conjugated aldehyde (1.0 equiv) and nitromethane (1.2 equiv) in methanol (0.5 M) was cooled to -10 °C in a salted ice bath. A solution of NaOH (1.2 equiv) in water (20 M) was then carefully added, keeping the internal reaction mixture temperature below 5 °C; the resulting solution was stirred for 1 h in the same ice bath. The reaction mixture was poured dropwise into a 2:3 concentrated HCl / water solution, forming a yellow precipitate. Ethyl acetate was added, and layers were separated. The organic layer was washed once with saturated $NaHCO_3$ and then with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. If not noted otherwise, the crude product was purified by recrystallization from ethanol.

(*E*)-1-Bromo-2-(2-nitrovinyl)benzene, 2b.

Following **GP1**, using 2-bromobenzaldehyde (4.17 mL, 1 equiv), nitromethane (2.37 mL, 1.2 equiv) in methanol (0.5 M, 70 mL) with NaOH (1.68 g, 1.2 equiv) in water (2.1 mL, 20 M). The crude product was purified by recrystallization from ethanol to afford the desired product as yellow needles (68%).

TLC: R_f = 0.7 (hexane/EtOAc = 6:4) [UV, $KMnO_4$]. The analytical data match those reported in the literature.[10]

(*E*)-1-Bromo-3-(2-nitrovinyl)benzene, 2c.

Following **GP1**, using 3-bromobenzaldehyde (4.21 mL, 1 equiv), nitromethane (2.37 mL, 1.2 equiv) in methanol (0.5 M, 70 mL) with NaOH (1.68 g, 1.2 equiv) in water (2.1 mL, 20 M). The crude product was purified by DCVC using a solvent gradient of 100% hexane to 92:8 hexane/EtOAc to afford the desired product as a yellow solid (45%).

TLC: R_f = 0.42 (hexane/EtOAc = 9:1) [UV, $KMnO_4$]. The analytical data match those reported in the literature.[10]

(*E*)-1-Nitro-4-(2-nitrovinyl)benzene, 2f.

Following **GP1**, using 4-nitrobenzaldehyde (0.76 g, 1 equiv), nitromethane (0.34 mL, 1.2 equiv) in methanol (0.5 M, 10 mL) with NaOH (0.29 g, 1.2 equiv) in water (0.3 mL, 20 M). The crude product was purified by recrystallization from ethanol to afford the desired product as yellow needles (50%).

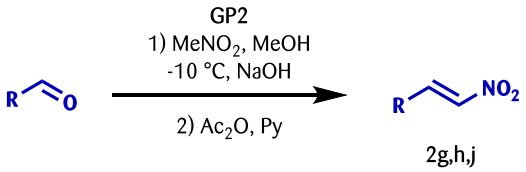
TLC: R_f = 0.58 (hexane/EtOAc = 7:3) [UV, $KMnO_4$] The analytical data match those reported in the literature.[11]

((1*E*,3*E*)-4-Nitrobuta-1,3-dien-1-yl)benzene, 2i.

Following **GP1**, using cinnamaldehyde (5.1 mL, 1 equiv), nitromethane (2.71 mL, 1.2 equiv) in methanol (0.5 M, 20 mL) with NaOH (2.4 g, 1.2 equiv) in water (2.0 mL, 24 M). The crude product was purified by DCVC using a solvent gradient of 100% hexane to 9:1 hexane/EtOAc to afford the desired product as an orange solid. Product was further purified by recrystallization from EtOH/hexane to afford the desired product as yellow needles (45%).

TLC: R_f = 0.61 (hexane/EtOAc = 8:2) [UV, Seebach]. The analytical data match those reported in the literature.[12]

4.2.2 General procedure 2 (GP2) for the synthesis of nitroalkenes with an aliphatic or pyridinyl group (2g, 2h and 2j):



2g,h,j

Based on literature procedures,[8,9] a solution of the aldehyde (1.0 equiv) and nitromethane (1.2 equiv) in methanol (0.5 M) was cooled to -10 °C in a salted ice bath. A solution of NaOH (1.2 equiv) in water (20 M) was carefully added, while ensuring that the internal temperature of the reaction mixture remained below 5 °C. The resulting solution was stirred for 1 h at the same temperature. Subsequently, glacial acetic acid (2.5 equiv) was added, and the reaction mixture was partitioned between saturated $NaHCO_3$ and ethyl acetate. The organic layer was then washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo.

Dehydration was performed by acetylation-elimination using a modified literature procedure.[13] Nitroalcohol from the first step and pyridine (3 equiv) were dissolved in THF (1 M). Acetic anhydride (6 equiv) was added dropwise, and the resulting reaction mixture was stirred at rt until completion for about 1-6 hours. For aliphatic substrates, triethylamine (3.6 equiv) was added once acetylation was complete. The reaction mixture was stirred for an additional 30 min. Ethyl acetate was added and the layers were separated. The organic layer was washed twice with saturated $NaHCO_3$, brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Crude product was purified by Dry Column Vacuum Chromatography (DCVC).

(*E*)-4-(2-Nitrovinyl)pyridine, 2h[14]

Following **GP2**, using isonicotinaldehyde (0.97 mL, 1 equiv), nitromethane (0.68 mL, 1.2 equiv) in methanol (0.5 M, 20 mL) with NaOH (0.51 g, 1.2 equiv) in water (0.5 mL, 20 M). Dehydration of nitroalcohol (0.34 g, 1 equiv) was performed with acetic anhydride (1.15 mL, 6 equiv) and pyridine (3 equiv, 0.49 mL) in THF (2 mL, 1 M). The crude product was purified by DCVC using a solvent gradient of 55:45 to 35:65 hexane/EtOAc to afford the desired product as a yellow solid.

TLC: R_f = 0.41 (hexane/EtOAc = 2:8) [UV, $KMnO_4$].
^{1}H NMR: (400 MHz, Chloroform-d) δ = 8.79 – 8.72 (m, 2H), 7.93 (d, J = 13.8 Hz, 1H), 7.67 (d, J = 13.8 Hz, 1H), 7.44 – 7.37 (m, 2H).

***tert*-Butyl (*E*)-3-(2-nitrovinyl)-1H-indole-1-carboxylate, 2g.**

Indole-derived nitroalkene was synthesized according to reported methodologies.[4,7] To a solution of (*E*)-3-(2-nitrovinyl)-1H-indole[4] (0.3 mmol) and DMAP (10 mol%) in DCM (1.15 mL, 0.25 M) was added Boc_2O (0.45 mmol, 1.5 equiv.) dissolved in 0.6 mL of DCM. The resulting reaction mixture was stirred for about 2 h until complete transformation. The crude product was adsorbed on celite and purified by flash column chromatography using a solvent gradient of 95:5 to 85:15 hexane/EtOAc to afford the desired product as a yellowish-orange solid (72 mg, 77%).

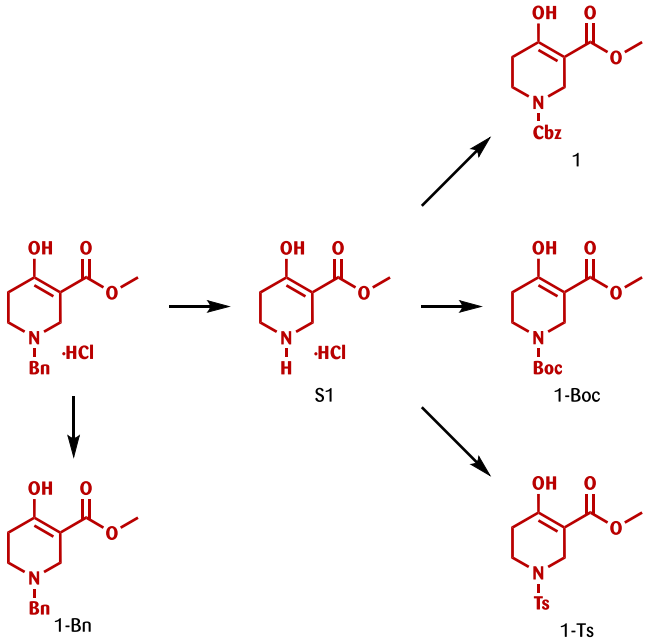
TLC: R_f = 0.66 (hexane/EtOAc = 7:3) [UV, Seebach]. The analytical data match those reported in the literature.[15]

(*E*)-(4-Nitrobut-3-en-1-yl)benzene, 2j.

Following **GP2**, using dihydrocinnamaldehyde (0.88 mL, 1 equiv), nitromethane (0.41 mL, 1.2 equiv) in methanol (0.5 M, 12 mL) with NaOH (0.29 g, 1.2 equiv) in water (0.36 mL, 20 M). Dehydration of nitroalcohol was performed with acetic anhydride (3.44 mL, 6 equiv), pyridine (3 equiv, 1.46 mL), and TEA (3 mL, 3.6 equiv) in THF (6 mL, 1 M). The crude product was purified by DCVC using a solvent gradient of 100% hexane to 92:8 hexane/EtOAc to afford the desired product as a yellow oil (48%).

TLC: (nitroalcohol) R_f = 0.31 (hexane/EtOAc = 8:2) [UV, $KMnO_4$]; (nitroalkene) R_f = 0.44 (hexane/EtOAc = 8:2) [UV, $KMnO_4$]. The analytical data match those reported in the literature.[16]

***4.3 Synthesis of piperidine ketoesters* 1.**



Methyl 4-oxopiperidine-3-carboxylate hydrochloride S1.

To a flask containing methyl 1-benzyl-4-oxo-3-piperidinecarboxylate hydrochloride (21.0 g, 70 mmol) and 5% Pd/C (2 g, 10%$_{w/w}$) under nitrogen atmosphere was added MeOH via syringe (350 mL, 0.2 M). It was purged with hydrogen and stirred for 4h. After reaction completion, the suspension was filtered through a pad of tightly compacted Celite, and the solvent evaporated. The residue was suspended in Et_2O and filtered to yield the desired product as an off-white solid (12.6 g, 92%).

^{1}H NMR: (300 MHz, DMSO-d6): δ = (enol) = 10.40 (br, 3H), 3.74 (s, 3H), 3.64 (s, 2H), 3.23 (t, *J* = 6.3 Hz, 2H), 2.59 (t, *J* = 6.3 Hz, 2H).
^{13}C NMR: (75 MHz, DMSO-d6): δ = (enol) = 169.3, 167.9, 92.6, 52.0, 39.2, 38.7, 25.4.

1-Benzyl 3-methyl 4-hydroxy-5,6-dihydropyridine-1,3(2H)-dicarboxylate, 1.

The methodology used by Hooper[17] was adapted as follows: To a solution of 1-benzyl-4-oxo-3-piperidinecarboxylate hydrochloride **S1** (8.8 g, 43.0 mmol, 1 equiv) in water (215 mL, 0.2 M) was added potassium carbonate (11.9 g, 86 mmol, 2 equiv) and Et_2O (215 mL, 0.2 M). The reaction mixture was then cooled to 0 °C and benzyl chloroformate (6.7 mL, 45.0 mmol, 1.05 equiv) was added. The reaction mixture was left to warm to RT and stirred for 16 h. The two layers were separated, and the organic layer was washed with saturated $NaHCO_3$ and then with brine (50 mL each). The solution was dried (Na_2SO_4), filtered and concentrated in vacuo. The crude product was purified by DCVC using a solvent gradient from 100% hexane to 87:13 hexane/EtOAc. It was obtained as a white amorphous solid after thorough drying under high vacuum (12.3 g, 42.14 mmol, 98%).

TLC: R_f = 0.46 (hexane/EtOAc = 75:25) [Anisaldehyde, Seebach]
^{1}H NMR: (400 MHz, Chloroform-*d*): δ = 11.97 (s, 1H), 7.36 (m, 5H), 5.16 (s, 2H), 4.14 (s, 2H), 3.78 (s, 3H), 3.68 (t, *J* = 6.0 Hz, 2H), 2.40 (s, 2H).
^{13}C NMR: (100 MHz, Chloroform-*d*): δ = 171.0, 156.1 136.7, 128.7, 128.3, 128.2, 127.1 67.5, 51.7, 40.6, 40.1, 29.0. The analytical data match those reported in the literature.[18]

1-(*tert*-Butyl) 3-methyl 4-oxopiperidine-1,3-dicarboxylate, 1-Boc.

This compound was obtained according to the reported procedure.[19] To a mixture of **S1** (10 mmol), potassium carbonate (10 mmol, 1 equiv.) and MeOH (7.35 mL, 1.36 M), was added Boc_2O (10 mmol, 1 equiv.) dissolved in MeOH (7.35 mL, 1.36 M). The resulting reaction mixture was stirred for 1 h, then quenched with water and extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by DCVC using a solvent gradient of 92:8 to 72:28 hexane/EtOAc to afford the desired product as an amorphous white solid after thorough drying (91%). The analytical data match those reported in the literature.[19]

TLC: R_f = 0.48 (hexane/EtOAc = 75:25) [Anisaldehyde, Seebach].
^{1}H NMR: (300 MHz, Chloroform-d): δ = 11.97 (s, 1H), 4.05 (s, 2H), 3.78 (s, 3H), 3.57 (t, J = 5.9 Hz, 2H), 2.37 (t, J = 5.9 Hz, 2H), 1.48 (s, 9H).
^{13}C NMR: (75 MHz, Chloroform-d): δ =171.1, 154.6, 96.1 (br), 80.2, 51.7, 40.8, 40.3, 29.0, 28.5.

Methyl 4-oxo-1-tosylpiperidine-3-carboxylate, 1-Ts.

The methodology used by Stokes[20] was adapted as follows: To a solution of 1-benzyl-4-oxo-3-piperidinecarboxylate hydrochloride **S1** (0.39 g, 2.0 mmol) in DCM (5 mL, 0.4 M) at 0 °C, were added triethylamine (0.61 mL, 2.2 equiv), DMAP (0.25 g, 0.1 equiv) and TsCl (0.38 g, 2 equiv). The reaction mixture was stirred at the same temperature for 1 h. When full conversion was reached, saturated aqueous NH_4Cl solution was added, and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by DCVC using a solvent gradient of 95:5 to 70:30 hexane/EtOAc to afford the desired product as a yellowish solid (72%).

TLC: R_f = 0.31 (hexane/EtOAc = 75:25) [Anisaldehyde, Seebach]
^{1}H NMR: (400 MHz, Chloroform-d): δ = 11.93 (s, 1H), 7.69 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 3.77 (s, 3H), 3.76 (m, 2H), 3.26 (t, J = 6.0 Hz, 2H), 2.46 (ddd, J = 7.7, 3.8, 1.6 Hz, 2H), 2.44 (s, 3H).
^{13}C NMR: (100 MHz, Chloroform-d): δ =170.6, 169.4, 144.0, 133.4, 129.9, 127.7, 95.0, 51.8, 42.4, 42.3, 29.0, 21.7.
HRMS: (DART+): [M+H]+ calcd. for $C_{14}H_{18}NO_5S$+: 312.09057, found: 312.09076.

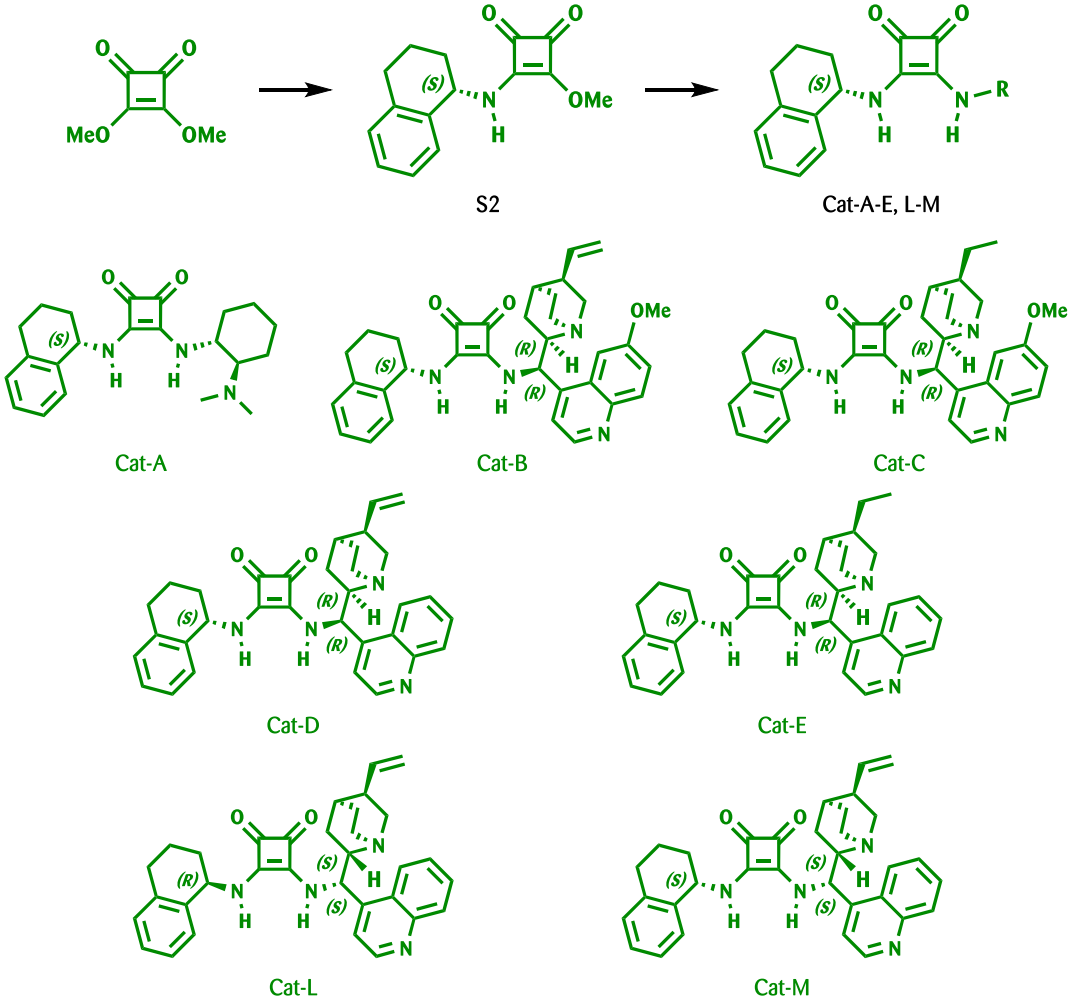
Methyl 1-benzyl-4-oxopiperidine-3-carboxylate, 1-Bn.

Methyl 1-benzyl-4-oxo-3-piperidinecarboxylate hydrochloride **S1** (0.15 g, 0.5 mmol) was dissolved in a 0.5 M Na_2CO_3 solution (17 mL). The free amine was extracted from the aqueous phase with DCM (20 mL X 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was obtained as clear oil and was used directly in Michael addition.

TLC: R_f = 0.43 (hexane/EtOAc = 75:25) [Vanillin, Ninhydrin]
^{1}H NMR: (400 MHz, Chloroform-*d*): δ = (enol) = 11.94 (s, 1H), 7.38 – 7.32 (m, 5H), 3.72 (s, 3H), 3.64 (s, 2H), 3.18 (d, *J* = 1.8 Hz, 2H), 2.62 (t, *J* = 5.8 Hz, 2H), 2.41 (tt, *J* = 6.0, 1.6 Hz, 2H).
^{13}C NMR: (101 MHz, Chloroform-*d*): δ = 204.1, 171.5, 170.5, 169.4, 138.0, 137.9, 129.2, 128.9, 128.5, 127.6, 127.4, 96.8, 62.2, 61.7, 56.6, 55.1, 53.2, 52.3, 51.5, 50.0, 48.8, 40.9, 29.5.

4.4 Preparation of organocatalysts

Reported catalysts **Cat-G**,[21] **Cat-F**,[22] **Cat-H**,[23] and **Cat-K**[24] were prepared according to literature procedures. **Cat-A-E** were obtained by the addition of the corresponding chiral amine to **S2**.



(*S*)-3-Methoxy-4-((1,2,3,4-tetrahydronaphthalen-1-yl)amino)cyclobut-3-ene-1,2-dione, S2.

(*S*)-1-Aminotetralin (0.6 mL, 4 mmol, 1 equiv), dimethylsquarate (0.58 g, 4.4 mmol, 1.1 equiv), and triethylamine (0.56 mL, 4 mmol, 1 equiv) were dissolved in DCM (20 mL, 0.2 M) and stirred at room temperature for 18 h. After reaction completion, solvent was removed in vacuo. The residue was dissolved in EtOAc and washed twice with 10% aqueous HCl and once with brine. The organic layer was dried with Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by DCVC using a solvent gradient of 60:40 to 47:53 hexane/EtOAc to afford **S2** as an off-white solid (82 %, 0.84 g).

TLC: R_f = 0.62 (hexane/EtOAc = 40:60) [vanillin, Seebach]
^{1}H NMR: (300 MHz, Chloroform-*d*): δ = 7.26 – 7.06 (m, 4H), 6.32 (br, 0.6H), 5.86 (br, 0.3H), 5.38 (br, 0.6H), 4.94 – 4.80 (m, 1H), 4.41 – 4.35 (m, 3H), 2.94 – 2.69 (m, 2H), 2.13 (s, 1H), 2.02 – 1.80 (m, 3H).
^{13}C NMR: (75 MHz, Chloroform-*d*): δ = 189.0, 183.4, 177.2, 171.4, 137.5, 134.8, 129.6, 128.4, 128.1, 126.5, 77.2, 60.6, 60.5, 53.6, 52.9, 31.6, 31.2, 29.0, 19.5, 19.3.
HRMS (DART+): $[M+H]^+$ calcd. for $C_{15}H_{16}NO_3^+$: 258.11302, found: 258.11319.

Cat-A

To a solution of *N*,*N*-dimethyl-1*R*,2*R*-diaminocyclohexane dihydrochloride[25] (544.3 mg, 2.53 mmol) and DBU (10.12 mmol, 4.0 equiv) in MeOH (17 mL, 0.15 M) was added **S2** (2.53 mmol, 1 equiv.) at room temperature. After stirring for 14 h at room temperature, the white precipitate was filtered and washed with cold methanol to yield squaramide Cat-**A** as a white powder. To maximize yield, mother liquors were filtered, and the residue was recrystallized with iPrOH/water. (781.0 mg, 84%).

^{1}H NMR: (300 MHz, DMSO-d_6): δ = 7.92 (d, *J* = 8.8 Hz, 1H), 7.36 – 7.10 (m, 5H), 5.21 (br, 1H), 3.73 (br, 1H), 2.90 – 2.66 (m, 2H), 2.36 – 2.23 (m, 1H), 2.15 (s, 6H), 2.13 – 1.54 (m, 8H), 1.33 – 1.05 (m, 4H).
^{13}C NMR: (75 MHz, DMSO): δ = 182.1, 181.9, 167.4, 166.4, 136.9, 136.4, 129.2, 129.1, 127.5, 126.3, 66.1, 54.1, 50.8, 39.9, 39.8, 34.9, 30.9, 28.4, 24.5, 24.3, 21.2, 18.3.
HRMS (FAB+): $[M+H]^+$ calcd. for $C_{22}H_{30}N_3O_2^+$: 368.2338, found: 368.2345. The analytical data match those reported in the literature.[26]

4.4.1 General procedure 3 (GP3) for the synthesis of Cinchona alkaloid-derived squaramides Cat-B-E, L-M.

Intermediate **S2** (44.8 mg, 0.17 mmol, 1 equiv.) was dissolved in 18.8 mL (0.009 M) of methanol. The corresponding amino alkaloid derivative (0.17 mmol, 1 equiv.) was added, and the reaction mixture was stirred at room temperature for 18 h. After solvent removal, the crude reaction mixture was dissolved in hot 4:6 hexane/EtOAc with a few drops of *i*-PrOH. After allowing the solution to cool to room temperature, some hexane was added to precipitate most of the catalyst, then filtrated and rinsed with 8:2 hexane/EtOAc.

Cat-B

According to **GP3**, **S2** (44.8 mg, 0.17 mmol) and the corresponding quinidine derivative[27] (55.4 mg, 0.17 mmol) afforded **Cat-B** as an orange solid (80.8 mg, 86%).

^{1}H NMR: (300 MHz, DMSO-d_6): δ = 8.76 (dd, *J* = 4.6, 1.7 Hz, 1H), 7.96 (d, *J* = 9.2 Hz, 1H), 7.88 – 7.73 (m, 3H), 7.56 (d, *J* = 4.6 Hz, 1H), 7.43 (dd, *J* = 9.2, 2.5 Hz, 1H), 7.29 (s, 1H), 7.25 – 7.17 (m, 2H), 7.17 – 7.07 (m, 1H), 6.05 (br, 1H), 5.83 (ddd, *J* = 16.9, 10.5, 5.9 Hz, 1H), 5.23 (d, *J* = 17.4 Hz, 1H), 5.16 – 5.03 (m, 2H), 3.95 (s, 3H), 3.21 (br, 2H), 3.00 – 2.59 (m, 5H), 2.23 (br, 1H), 1.97 – 1.63 (m, 4H), 1.54 (br, 3H), 1.02 (br, 1H), 0.91 – 0.75 (m, 1H).
^{13}C NMR: (75 MHz, DMSO): δ = 182.3, 181.7, 166.8, 166.3, 157.8, 147.7, 144.3, 143.9, 140.7, 136.9, 136.0, 131.5, 129.3, 129.1, 127.6, 127.4, 126.3, 122.1, 119.4, 114.5, 101.2, 58.8, 55.6, 51.0, 48.9, 45.5, 39.5, 38.5, 30.7, 28.3, 27.2, 26.1, 25.2, 18.2.
HRMS (FAB+): $[M+H]^+$ calcd. for $C_{34}H_{37}N_4O_3^+$: 549.2866, found: 549.2873.

Cat-C

According to **GP3**, **S2** (52.1 mg, 0.18 mmol) and the corresponding quinidine derivative[27] (59.6 mg, 0.18 mmol) afforded **Cat-C** as an orange solid (74.3 mg, 74%).

^{1}H NMR: (300 MHz, DMSO-d_6): δ =8.76 (dt, *J* = 4.6, 1.7 Hz, 1H), 7.96 (dt, *J* = 9.2, 2.0 Hz, 1H), 7.87 – 7.65 (m, 3H), 7.53 (d, *J* = 4.6 Hz, 1H), 7.48 – 7.37 (m, 1H), 7.34 – 7.05 (m, 4H), 6.02 (br, 1H), 5.11 (br, 1H), 3.94 (s, 3H), 3.30 – 3.17 (m, 1H), 2.95 – 2.57 (m, 6H), 1.96 – 1.61 (m, 4H), 1.58 – 1.20 (m, 6H), 0.96 (br, 1H), 0.91 – 0.69 (m, 4H).
^{13}C NMR: (75 MHz, DMSO): δ = 182.2, 181.7, 166.8, 166.2, 157.7, 147.7, 144.2, 144.2, 136.9, 136.0, 131.5, 129.2, 129.1, 127.6, 127.4, 126.2, 122.0, 119.5, 101.3, 59.0, 55.5, 50.9, 49.0, 48.2, 36.8, 30.7, 28.3, 27.0, 25.6, 25.4, 25.0, 18.2, 11.8.
HRMS (FAB+): $[M+H]^+$ calcd. For $C_{34}H_{39}N_4O_3^+$: 551.3022, found: 551.3009.

Cat-D

According to **GP3**, the cinchonine-derived amine[27] (55.4 mg, 0.27 mmol) and **S2** (44.8 mg, 0.27 mmol) afforded squaramide **Cat-D** as a white powder (95 mg, 68%).

^{1}H NMR: (300 MHz, DMSO-d_6): δ =8.94 (d, *J* = 4.3 Hz, 1H), 8.43 (d, *J* = 8.0 Hz, 1H), 8.07 (d, *J* = 8.2 Hz, 1H), 7.93 – 7.65 (m, 4H), 7.60 (d, *J* = 3.3 Hz, 1H), 7.40 – 6.96 (m, 4H), 6.24 – 5.93 (m, 1H), 5.93 – 5.67 (m, 1H), 5.26 – 4.92 (m, 3H), 3.31 – 3.00 (m, 2H), 2.98 – 2.57 (m, 5H), 2.20 (s, 1H), 2.05 – 1.59 (m, 4H), 1.50 (br, 3H), 0.92 (d, *J* = 5.4 Hz, 2H).
^{13}C NMR: (75 MHz, DMSO-D_6): δ = 182.2, 182.0, 167.0, 166.3, 150.4, 148.1, 145.6, 140.6, 136.9, 136.0, 130.0, 129.4, 129.2, 129.1, 127.6, 127.1, 126.4, 126.2, 123.3, 119.3, 114.6, 59.4, 50.9, 48.9, 45.9, 39.5, 38.7, 30.7, 28.3, 27.3, 26.0, 25.0, 18.2.
HRMS (FAB+): $[M+H]^+$ calcd. for $C_{33}H_{35}N_4O_2^+$: 519.2760, found: 519.2758.

Cat-E

According to **GP3**, **S2** (74.5 mg, 0.29 mmol) and the hydrogenated cinchonine-derived amine[27] (84.1 mg, 0.28 mmol) yield catalyst **Cat-E** as a white solid (81 mg, 55%).

^{1}H NMR: (300 MHz, DMSO-d_6): δ = 8.94 (d, *J* = 4.5 Hz, 1H), 8.45 (d, *J* = 8.5 Hz, 1H), 8.08 (d, *J* = 8.5 Hz, 1H), 7.96 – 7.66 (m, 4H), 7.61 (d, *J* = 4.6 Hz, 1H), 7.20 (m, 4H), 6.02 (br, 1H), 5.12 (br, 1H), 3.24 (br, 1H), 3.00 – 2.55 (m, 6H), 2.02 – 1.59 (m, 4H), 1.59 – 1.09 (m, 6H), 0.99 – 0.63 (m, 5H).
^{13}C NMR: (75 MHz, DMSO-D_6): δ = 182.1, 182.0, 167.0, 166.3, 150.4, 148.1, 145.7, 136.9, 136.1, 130.0, 129.4, 129.2, 129.1, 127.5, 127.1, 126.4, 126.2, 123.2, 119.4, 59.6, 50.9, 48.9, 48.4, 39.5, 36.8, 30.7, 28.3, 26.8, 25.6, 25.2, 24.8, 18.2, 11.9.
HRMS (FAB+): $[M+H]^+$ calcd. for $C_{33}H_{37}N_4O_2^+$: 521.2917, found: 521.2924.

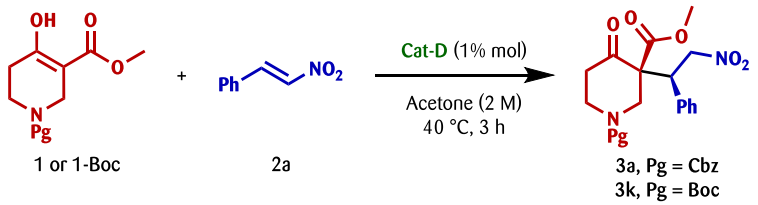
Cat-L

According to **GP3**, *ent*-**S2** (64.3 mg, 0.25 mmol) and the corresponding cinchonidine derivative[27] (0.25 mmol, 1 equiv) yield **Cat-L** as a white solid (81.7 mg, 63%).

^{1}H NMR: (400 MHz, DMSO-d_6): δ = 8.94 (d, *J* = 4.5 Hz, 1H), 8.48 (d, *J* = 8.4 Hz, 1H), 8.07 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.88 – 7.75 (m, 3H), 7.71 (ddd, *J* = 8.3, 6.8, 1.4 Hz, 1H), 7.59 (d, *J* = 4.6 Hz, 1H), 7.27 (br, 1H), 7.25 – 7.17 (m, 2H), 7.17 – 7.10 (m, 1H), 5.97 (br, 1H), 5.88 (ddd, *J* = 17.6, 10.2, 7.8 Hz, 1H), 5.13 (m, 1H), 4.99 (d, *J* = 17.2 Hz, 1H), 4.93 (d, *J* = 10.2 Hz, 1H), 3.34 – 3.23 (m, 2H), 3.16 (dd, *J* = 13.6, 10.0 Hz, 1H), 2.69 (m, 4H), 2.24 (br, 1H), 1.91 (br, 1H), 1.80 (dt, *J* = 13.3, 4.7 Hz, 1H), 1.76 – 1.64 (m, 2H), 1.61 – 1.41 (m, 3H), 1.39 – 1.25 (m, 1H), 0.67 – 0.56 (m, 1H).
^{13}C NMR: (100 MHz, DMSO): δ = 182.0, 181.9, 166.7, 166.4, 150.4, 148.1, 145.7, 142.1, 136.9, 136.0, 129.9, 129.5, 129.3, 129.1, 127.6, 127.1, 126.3, 126.3, 123.5, 114.3, 59.5, 55.5, 50.9, 40.1, 39.8, 39.3, 30.7, 28.3, 27.3, 27.2, 25.9, 18.2.

4.5 Michael addition of β-ketoesters 1 to nitroalkenes 2.

4.5.1 General procedure 4 (GP4) (enantioenriched adducts, gram scale) 3a, 3b and 3k:



To a solution of **2a** (1.3 g, 4 mmol, 1 equiv) and catalyst **Cat-D** (20.7 mg, 1 mol%) in acetone (2 mL, 2 M) was added **1** or **1-Boc** (4 mmol, 1 equiv). The solution was stirred at 40 °C in a sealed vial for 4 h. Reaction mixture was then transferred to Eppendorf tubes and centrifuged for 1 minute at 13300 RPM. The supernatant was carefully pipetted to a round bottom flask and the pellet was rinsed trice with acetone (94 % of the catalyst was recovered). The solvents used for rinsing were combined with supernatant and evaporated to dryness. The product was purified through DCVC using a gradient of hexane/EtOAc indicated to obtain the respective Michael adduct (inseparable diastereomer mixture, d.r. = 99:1, e.r. = 99:1).

1-Benzyl 3-methyl (*S*)-3-((*S*)-2-nitro-1-phenylethyl)-4-oxopiperidine-1,3-dicarboxylate, 3a.

Following **GP4** and purified by DCVC with a gradient of 85:15 to 6:4 hexane/EtOAc to obtain **3a** as a clear colorless glass (1.94 g, 88% yield).

TLC: R_f = 0.42 (hexane/EtOAc = 65:35) [Seebach]
^{1}H NMR: (400 MHz, Chloroform-*d* @ 25 °C): δ = 7.38 – 7.27 (m, 8H), 7.16 (dd, *J* = 6.4, 3.1 Hz, 2H), 5.17 – 4.96 (m, 3H), 4.83 (t, *J* = 12.3 Hz, 1H), 4.41 – 4.14 (m, 2H), 4.10 (d, *J* = 8.8 Hz, 1H), 3.65 (s, 3H), 3.37 – 3.19 (m, 1H), 3.06 (d, *J* = 13.7 Hz, 1H), 2.69 (ddd, *J* = 14.2, 10.8, 6.6 Hz, 1H), 2.62 – 2.49 (m, 1H).
^{1}H NMR: (300 MHz, Chloroform-*d* @ 47 °C): δ = 7.36 – 7.19 (m, 8H), 7.19 – 7.12 (m, 2H), 5.16 – 4.98 (m, 3H), 4.84 (dd, *J* = 13.7, 10.9 Hz, 1H), 4.34 (dd, *J* = 13.8, 2.2 Hz, 1H), 4.23 (br, 1H), 4.10 (dd, *J* = 10.7, 3.6 Hz, 1H), 3.63 (s, 3H), 3.31 (ddd, *J* = 13.4, 10.5, 4.5 Hz, 1H), 3.10 (d, *J* = 13.8 Hz, 1H), 2.70 (ddd, *J* = 14.4, 10.4, 6.5 Hz, 1H), 2.55 (dt, *J* = 14.3, 4.5 Hz, 1H).
^{13}C NMR: (100 MHz, Chloroform-*d* @ 25 °C): δ = 203.6, 168.8, 154.9, 136.2, 134.2, 129.4, 129.0, 128.8, 128.7, 128.6, 128.2, 77.3, 67.8, 63.0, 53.0, 50.8, 45.3, 44.1, 40.2.
HRMS (DART+): $[M+H]^+$ calcd. for $C_{23}H_{25}N_2O_7^+$: 441.16618, found: 441.16539.
HPLC: Chiralcel OD-H, hexane/EtOH = 8:2, flow = 1 mL/min, λ = 210 nm, t_R (major enant.) = 27.0 min, t_R (minor enant.) = 22.5 min, (e.r. = 99:1); t_R (major diast.) = 19.8 min, t_R (minor diast.) = 15.1 min, (d.r. = 99:1).
$[\alpha]_D^{20} = +60$ (c 0.2, $CHCl_3$)

1-Benzyl 3-methyl (*S*)-3-((*R*)-1-(2-bromophenyl)-2-nitroethyl)-4-oxopiperidine**-1,3-dicarboxylate, 3b.**

Following **GP4** and purified by DCVC with a gradient of 85:15 to 60:40 hexane/EtOAc to obtain **3b** as a white solid (0.94 g, 91% yield).

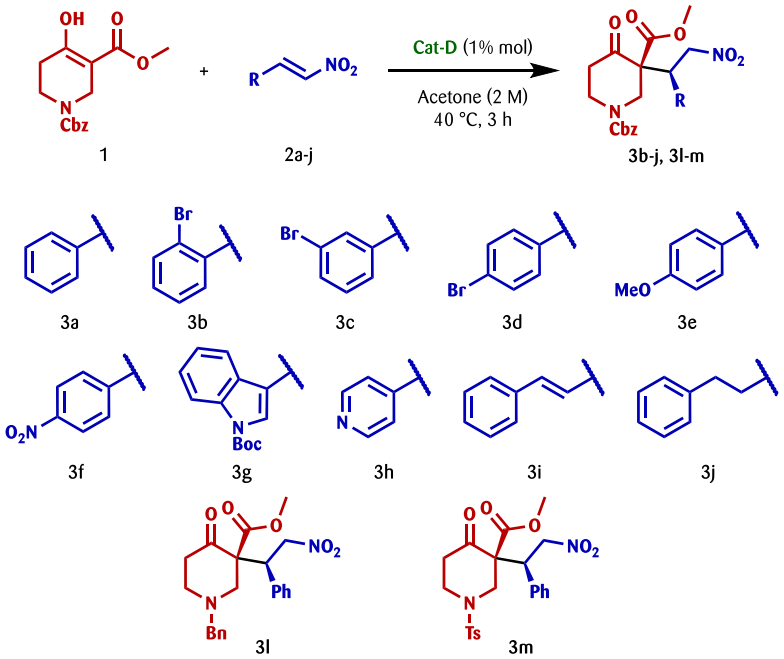
TLC: R_f = 0.41 (hexane/EtOAc = 6:4) [Seebach]
^{1}H NMR: (300 MHz, Chloroform-*d*): δ = 7.57 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.43 – 7.06 (m, 8H), 5.21 – 4.87 (m, 4H), 4.65 (dd, *J* = 13.5, 11.1 Hz, 1H), 4.51 – 4.21 (m, 2H), 3.74 – 3.52 (m, 3H), 3.28 – 3.01 (m, 2H), 2.72 (ddd, *J* = 14.3, 11.4, 6.8 Hz, 1H), 2.59 (dt, *J* = 14.3, 3.7 Hz, 1H).
^{13}C NMR: (75 MHz, Chloroform-*d*): δ = 203.0, 168.8, 154.6, 136.2, 134.2, 133.9, 130.1, 128.9, 128.7, 128.5, 128.4, 128.1, 127.1, 77.1, 67.7, 62.8, 53.0, 49.9, 44.0, 42.0, 40.2.
HRMS (DART+): $[M+H]^+$ calcd. for $C_{23}H_{24}BrN_2O_7^+$: 519.07669, found: 519.07759.
HPLC: Chiralcel OD-H, hexane/EtOH = 8:2, flow = 1.0 mL/min, λ = 210 nm, t_R (major enant.) = 15.6 min, t_R (minor enant.) = 13.6 min, (e.r. = 99:1); t_R (major diast.) = 18.2 min, t_R (minor diast.) = 20.0 min, (d.r. = 98:2).
$[\alpha]_D^{20} = +429.4$ (c 0.17, $CHCl_3$)

1-(*tert*-Butyl)-3-methyl-(*S*)-3-((*S*)-2-nitro-1-phenylethyl)-4-oxopiperidine-1,3-dicarboxylate, 3k.

Following **GP4** and purified by DCVC with a gradient of 92:8 to 72:28 hexane/EtOAc to obtain **3k** as white solid (1.454 g, 88% yield).

TLC: R_f = 0.53 (hexane/EtOAc = 65:35) [Seebach, anisaldehyde]
^{1}H NMR: (300 MHz @ 25 °C, Chloroform-*d*): δ = 7.34 – 7.27 (m, 3H), 7.20 – 7.17 (m, 2H), 5.01 (dd, *J* = 13.6, 3.6 Hz, 1H), 4.85 (dd, *J* = 13.5, 10.9 Hz, 1H), 4.28 – 4.05 (m, 3H), 3.73 (s, 3H), 3.25 (ddd, *J* = 13.4, 10.4, 4.5 Hz, 1H), 3.01 (d, *J* = 13.7 Hz, 1H), 2.68 (ddd, *J* = 14.2, 10.3, 6.5 Hz, 1H), 2.55 (dt, *J* = 14.2, 4.4 Hz, 1H), 1.39 (s, 9H).
^{1}H NMR: (300 MHz @ 55 °C, Chloroform-*d*): δ = 7.34 – 7.26 (m, 3H), 7.23 – 7.16 (m, 2H), 4.99 (dd, *J* = 13.5, 3.7 Hz, 1H), 4.85 (dd, *J* = 13.5, 10.6 Hz, 1H), 4.24 (dd, *J* = 13.8, 2.2 Hz, 1H), 4.17 – 4.01 (m, 2H), 3.71 (s, 3H), 3.25 (ddd, *J* = 13.2, 10.1, 4.6 Hz, 1H), 3.05 (d, *J* = 13.7 Hz, 1H), 2.68 (ddd, *J* = 14.4, 10.1, 6.5 Hz, 1H), 2.53 (dt, *J* = 14.4, 4.5 Hz, 1H), 1.39 (s, 9H).
^{13}C NMR: (100 MHz, Chloroform-*d*): δ = 204.2, 168.9, 154.0, 134.4, 129.5, 128.9, 128.7, 80.9, 77.4, 63.1, 52.9, 50.7, 45.3, 43.8, 40.2, 28.2.
HRMS (DART+): $[M+H]^+$ calcd. for $C_{20}H_{27}N_2O_7^+$: 407.18183, found: 407.18209.
HPLC: Chiralcel IA, hexane/EtOH = 96:4, flow = 0.8 mL/min, λ = 208 nm, t_R (major enant.) = 20.9 min, t_R (minor enant.) = 27.8.0 min, (e.r. = 99:1); t_R (enantiomeric mixture, minor diast.) = 23.5 min, (d.r. = 99:1).
$[\alpha]_D^{20} = +65$ (c 0.18, $CHCl_3$)

4.5.2 General procedure 5 (GP5) (enantioenriched adducts, milligram scale):



To a solution of **2** (0.1 mmol, 1 equiv), and **Cat-D** (0.5 mg, 1 mol%) in acetone (50 µL, 2 M) was added **1** (29.1 mg, 0.1 mmol, 1 equiv). The solution was stirred at 40 °C in a sealed vial for 4 h. Reaction mixture was then adsorbed in celite, evaporated to dryness, and purified through FCC using a gradient hexane/EtOAc to afford the respective compound **3**.

Notes: (1) Racemic standards were prepared by stirring an equimolar mixture of **1** and **2** with *rac*-**Cat-G** (5 mol%) in toluene (0.5 M) for 4 h at room temperature. (2) Decomposition of **3b** was observed when dissolved in DMSO-*d*6, so all NMR experiments at high temperature were done in $CDCl_3$.

1-Benzyl 3-methyl (*S*)-3-((*S*)-1-(3-bromophenyl)-2-nitroethyl)-4-oxopiperidine-1,3-dicarboxylate, 3c.

Using **GP5** it was purified through FCC using a solvent gradient from 85:15 to 7:3 hexane/EtOAc to give adduct **3c** as an off-white solid (inseparable diastereomer mixture, d.r. = 99:1, e.r. = 98:2, 44.6 mg, 84%).

TLC: R_f = 0.38 (hexane/EtOAc = 6:4) [Seebach]
^{1}H NMR: (300 MHz, Chloroform-*d*): δ = 7.44 (dt, *J* = 7.1, 2.0 Hz, 1H), 7.40 – 7.08 (m, 8H), 5.22 – 4.94 (m, 3H), 4.80 (dd, *J* = 13.9, 10.8 Hz, 1H), 4.40 – 4.18 (m, 2H), 4.05 (dd, *J* = 10.9, 3.5 Hz, 1H), 3.64 (s, 3H), 3.39 – 3.19 (m, 1H), 3.06 (d, *J* = 13.7 Hz, 1H), 2.71 (ddd, *J* = 14.3, 10.7, 6.6 Hz, 1H), 2.57 (dt, *J* = 14.2, 4.1 Hz, 1H).
^{1}H NMR: (300 MHz, Chloroform-*d* @ 55 °C): δ = 7.47 – 7.39 (m, 1H), 7.39 – 7.28 (m, 4H), 7.28 – 7.21 (m, 2H), 7.17 – 7.11 (m, 2H), 5.18 – 5.02 (m, 2H), 4.98 (dd, *J* = 13.8, 3.5 Hz, 1H), 4.81 (dd, *J* = 13.8, 10.6 Hz, 1H), 4.34 (dd, *J* = 13.8, 2.2 Hz, 1H), 4.29 – 4.15 (m, 1H), 4.04 (dd, *J* = 10.6, 3.6 Hz, 1H), 3.62 (s, 3H), 3.31 (ddd, *J* = 13.2, 10.4, 4.5 Hz, 1H), 3.10 (d, *J* = 13.7 Hz, 1H), 2.71 (ddd, *J* = 14.5, 10.4, 6.6 Hz, 1H), 2.55 (dt, *J* = 14.5, 4.4 Hz, 1H).
13C NMR: (75 MHz, Chloroform-*d*): δ = 203.4, 168.7, 154.8, 136.7, 136.1, 132.5, 132.0, 130.5, 128.7, 128.3, 128.2, 127.9, 123.0, 77.0, 67.9, 63.0, 53.1, 50.8, 44.9, 44.1, 40.1
HRMS (DART+): $[M+H]^+$ calcd. for $C_{23}H_{24}N_2O_7Br^+$: 519.0767, found: 519.0747.
HPLC: Chiralcel OD-H, hexane/EtOH = 9:1, flow = 1.25 mL/min, λ = 210 nm, t_R (major enant.) = 43.2 min, t_R (minor enant.) = 47.8 min, (e.r. = 98:2); t_R (major diast.) = 29.0 min, t_R (minor diast.) = 22.6 min, (d.r. = 99:1).
$[\alpha]_D^{20} = +44.4\ (c\ 0.18, CHCl_3)$

1-Benzyl 3-methyl (*S*)-3-((*S*)-1-(4-bromophenyl)-2-nitroethyl)-4-oxopiperidine-1,3-dicarboxylate, 3d.

Using **GP5** it was purified through FCC using a solvent gradient from 85:15 to 65:15 hexane/EtOAc to give adduct **3d** as an off-white solid (inseparable diastereomer mixture, d.r. = 99:1, e.r. = 99:1, 45.4 mg, 86%). Catalyst was not recovered.

TLC: R_f = 0.40 (hexane/EtOAc = 6:4) [Seebach]
^{1}H NMR: (300 MHz, Chloroform-*d*): δ = 7.46 – 7.17 (m, 7H), 7.12 – 7.02 (m, 2H), 5.19 – 4.93 (m, 3H), 4.79 (dd, *J* = 13.7, 11.0 Hz, 1H), 4.38 – 4.16 (m, 2H), 4.06 (dd, *J* = 11.0, 3.6 Hz, 1H), 3.64 (s, 3H), 3.31 (td, *J* = 11.4, 10.2, 3.8 Hz, 1H), 3.06 (d, *J* = 13.7 Hz, 1H), 2.70 (ddd, *J* = 14.2, 10.5, 6.6 Hz, 1H), 2.56 (dt, *J* = 14.0, 4.3 Hz, 1H).
^{1}H NMR: (300 MHz, Chloroform-*d* @ 55 °C): δ = 7.41 (d, *J* = 8.6 Hz, 2H), 7.37 – 7.30 (m, 3H), 7.30 – 7.21 (m, 2H), 7.08 (d, *J* = 8.5 Hz, 2H), 5.16 – 5.03 (m, 2H), 4.97 (dd, *J* = 13.7, 3.6 Hz, 1H), 4.80 (dd, *J* = 13.7, 10.7 Hz, 1H), 4.34 (dd, *J* = 13.7, 2.2 Hz, 1H), 4.27 – 4.13 (m, 1H), 4.05 (dd, *J* = 10.7, 3.6 Hz, 1H), 3.62 (s, 3H), 3.33 (ddd, *J* = 13.2, 10.2, 4.6 Hz, 1H), 3.11 (d, *J* = 13.8 Hz, 1H), 2.71 (ddd, *J* = 14.5, 10.3, 6.6 Hz, 1H), 2.55 (dt, *J* = 14.5, 4.5 Hz, 1H).
^{13}C NMR: (75 MHz, Chloroform-*d*): δ = 203.4, 168.6, 154.8, 136.0, 133.3, 132.2, 131.1, 128.7, 128.4, 127.9, 123.1, 77.0, 67.9, 62.9, 53.1, 50.7, 44.8, 44.1, 40.1.
HPLC: Chiralcel OD-H, hexane/EtOH = 8:2, flow = 1.0 mL/min, λ = 210 nm, t_R (major enant.) = 33.2 min, t_R (minor enant.) = 26.4 min, (e.r. = 99:1); t_R (major diast.) = 22.7 min, t_R (minor diast.) = 15.6 min, (d.r. = 99:1).
$[\alpha]_D^{20} = +55.4\ (c\ 0.13, CHCl_3)$

1-Benzyl 3-methyl (*S*)-3-((*S*)-1-(4-methoxyphenyl)-2-nitroethyl)-4-oxopiperidine-1,3-dicarboxylate, 3e.

Using **GP5** it was purified through FCC using a solvent gradient from 8:2 to 6:4 hexane/EtOAc to give adduct **3e** as a bright yellow solid (inseparable diastereomer mixture, d.r. = 98:2, e.r. = 98:2, 39.0 mg, 82%).

TLC: R_f = 0.32 (hexane/EtOAc = 6:4) [Seebach]

^{1}H NMR: (300 MHz, Chloroform-*d*): δ = 7.44 – 7.17 (m, 5H), 7.13 – 7.04 (m, 2H), 6.86 – 6.75 (m, 2H), 5.20 – 4.92 (m, 3H), 4.79 (dd, *J* = 13.4, 11.1 Hz, 1H), 4.40 – 4.16 (m, 2H), 4.05 (dd, *J* = 11.1, 3.6 Hz, 1H), 3.76 (s, 3H), 3.66 (s, 3H), 3.32 (t, *J* = 11.2 Hz, 1H), 3.08 (d, *J* = 13.7 Hz, 1H), 2.68 (ddd, *J* = 14.3, 10.4, 6.5 Hz, 1H), 2.56 (d, *J* = 14.0 Hz, 1H).
^{1}H NMR: (300 MHz, Chloroform-*d* @ 55 °C): δ = 7.44 – 7.17 (m, 5H), 7.13 – 7.04 (m, 2H), 6.86 – 6.75 (m, 2H), 5.20 – 4.92 (m, 3H), 4.79 (dd, *J* = 13.4, 11.1 Hz, 1H), 4.40 – 4.16 (m, 2H), 4.05 (dd, *J* = 11.1, 3.6 Hz, 1H), 3.76 (s, 3H), 3.66 (s, 3H), 3.32 (t, *J* = 11.2 Hz, 1H), 3.08 (d, *J* = 13.7 Hz, 1H), 2.68 (ddd, *J* = 14.3, 10.4, 6.5 Hz, 1H), 2.56 (d, *J* = 14.0 Hz, 1H).
^{13}C NMR: (100 MHz, Chloroform-*d*): δ = 203.7, 168.8, 159.8, 154.9, 136.1, 130.5, 128.6, 128.2, 127.6, 125.8, 114.3, 77.5, 67.8, 63.1, 55.3, 53.0, 50.8, 44.6, 44.1, 40.2.
HRMS (DART+): $[M+H]^+$ calcd. for $C_{24}H_{27}N_2O_8^+$: 471.17674, found: 471.17496.
HPLC: Chiralcel OD-H, hexane/EtOH = 8:2, flow = 1.0 mL/min, λ = 210 nm, t_R (major enant.) = 29.3 min, t_R (minor enant.) = 23.8 min, (e.r. = 98:2); t_R (major diast.) = 21.1 min, t_R (minor diast.) = 16.1 min, (d.r. = 98:2).
$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}} = +92.9$ (c 0.14, $CHCl_3$)

1-Benzyl 3-methyl (*S*)-3-((*S*)-2-nitro-1-(4-nitrophenyl)ethyl)-4-oxopiperidine-1,3-dicarboxylate, 3f.

Using **GP5** it was purified through FCC using a solvent gradient from 8:2 to 6:4 hexane/EtOAc to give adduct **3f** as an off-white solid (inseparable diastereomer mixture, d.r. = >99:1, e.r. = 98:2, 40.9 mg, 83%).

TLC: R_f = 0.32 (hexane/EtOAc = 6:4) [Seebach]
^{1}H NMR: (300 MHz, DMSO-d_6 @ 120 °C): δ = 8.14 (d, *J* = 8.8 Hz, 2H), 7.64 (d, *J* = 8.9 Hz, 2H), 7.39 – 7.23 (m, 5H), 5.22 (dd, *J* = 14.2, 3.7 Hz, 1H), 5.16 – 5.07 (m, 1H), 5.06 (s, 2H), 4.27 (dd, *J* = 10.4, 3.6 Hz, 1H), 4.19 (dd, *J* = 13.5, 2.1 Hz, 1H), 4.06 (dddd, *J* = 13.2, 6.7, 4.6, 2.1 Hz, 1H), 3.64 (s, 3H), 3.47 (d, *J* = 13.5 Hz, 1H), 3.39 (ddd, *J* = 13.0, 9.9, 4.7 Hz, 1H), 2.73 (ddd, *J* = 15.3, 9.8, 6.7 Hz, 1H), 2.57 (dt, *J* = 15.1, 4.7 Hz, 1H).
^{13}C NMR: (75 MHz, DMSO-d_6 @ 120 °C): δ = 202.3, 167.7, 153.7, 147.0, 142.5, 135.9, 130.5, 127.5, 127.1, 126.6, 122.3, 76.0, 66.2, 61.6, 52.1, 48.8, 44.1, 42.1, 38.7.
HRMS (DART+): $[M+H]^+$ calcd. for $C_{23}H_{24}N_3O_9^+$: 486.1513, found: 486.1497.
HPLC: Chiralcel OD-H, hexane/EtOH = 6:4, flow = 1.25 mL/min, λ = 210 nm, t_R (major enant.) = 20.4 min, t_R (minor enant.) = 15.0 min, (e.r. = 98:2); t_R (enantiomeric mixture, diast.) = 10.5 min. (d.r. = >99:1).
$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}} = +83.7$ (c 0.19, $CHCl_3$)

1-Benzyl-3-methyl-(*S*)-3-((*S*)-1-(1-(*tert*-butoxycarbonyl)-1*H*-indol-3-yl)-2-nitroethyl)-4-oxopiperidine-1,3-dicarboxylate, 3g.

Using **GP5** it was purified through FCC using a solvent gradient from 75:25 to 5:5 hexane/EtOAc to give adduct **3g** as a white solid (inseparable diastereomer mixture, d.r. = 96:4, e.r. = 82:18, 7.7 mg, 13%).

TLC: R_f = 0.21 (hexane/EtOAc = 7:3) [Seebach (revealed instantly)]
^{1}H NMR: (300 MHz, Chloroform-*d* @ 25 °C): δ = 8.08 (d, *J* = 8.1 Hz, 1H), 7.71 – 7.44 (m, 2H), 7.46 – 6.88 (m, 7H), 5.39 (t, *J* = 12.2 Hz, 0.3H), 5.25 – 4.95 (m, 2.4H), 4.92 – 4.30 (m, 3.3H), 4.28 – 4.04 (m, 1H), 3.74 – 2.93 (m, 5H), 2.90 – 2.32 (m, 2H), 1.68 (d, *J* = 1.7 Hz, 9H).
^{1}H NMR: (300 MHz, Chloroform-*d* @ 55 °C): δ = 8.09 (d, *J* = 8.0 Hz, 1H), 7.67 – 7.56 (m, 1H), 7.55 – 7.47 (m, 1H), 7.39 – 7.18 (m, 6H), 7.15 (s, 1H), 5.34 (dd, *J* = 14.0, 10.0 Hz, 0.2H), 5.15 – 4.98 (m, 2.1H), 4.84 (dd, *J* = 13.6, 9.9 Hz, 1.2H), 4.74 (dd, *J* = 13.9, 3.0 Hz, 0.6H), 4.54 – 4.38 (m, 1.7H), 4.19 (dddd, *J* = 13.2, 6.7, 4.6, 1.9 Hz, 1H), 3.65 (s, 0.8H), 3.59 (s, 2.2H), 3.42 (ddd, *J* = 13.6, 10.2, 4.6 Hz, 0.8H), 3.28 (d, *J* = 13.8 Hz, 0.8H), 3.14 – 2.98 (m, 0.5H), 2.79 (ddt, *J* = 12.2, 10.0, 5.0 Hz, 1H), 2.64 (dt, *J* = 10.2, 4.7 Hz, 0.7H), 2.42 (dt, *J* = 14.5, 4.3 Hz, 0.3H), 1.68 (s, 9H).
^{13}C NMR: (75 MHz, Chloroform-*d*): δ = 203.9, 169.1, 149.4, 134.9, 130.7, 130.2, 128.7, 128.6, 128.4, 128.2, 127.8, 125.8, 125.4, 125.2, 125.1, 123.3, 123.1, 118.7, 115.5, 84.5, 77.8, 67.9, 67.7, 64.5, 63.5, 53.5, 53.0, 50.4, 50.0, 44.0, 40.0, 39.9, 35.6, 28.3.

HPLC: Chiralcel IA, hexane/EtOH = 85:15, flow = 1.25 mL/min, λ = 210 nm, $\lambda_{(CD)}$ = 280 nm, t_R (major enant.) = 11.4 min, t_R (minor enant.) = 13.1 min, (e.r. = 82:18); t_R (Major diast.) = 12.6 min, t_R (minor diast.) = 10.1 min (d.r. = 96:4).

1-Benzyl 3-methyl (*S*)-3-((*S*)-2-nitro-1-(pyridin-4-yl)ethyl)-4-oxopiperidine-1,3-dicarboxylate, 3h.

Using **GP5** it was purified through FCC using a solvent gradient from 6:4 to 35:65 hexane/EtOAc to give adduct **3h** as an orange solid (minor diastereomer was not detected in HPLC. d.r. = >99:1, e.r. = 98:2, 26.7 mg, 66%).

TLC: R_f = 0.47 (hexane/EtOAc = 2:8) [Seebach]
^{1}H NMR: (300 MHz, Chloroform-*d*): δ = 8.59 – 8.50 (m, 2H), 7.42 – 7.19 (m, 5H), 7.19 – 7.10 (m, 2H), 5.19 – 4.93 (m, 3H), 4.85 (dd, *J* = 14.0, 10.7 Hz, 1H), 4.44 – 4.19 (m, 2H), 4.06 (dd, *J* = 10.8, 3.5 Hz, 1H), 3.62 (s, 3H), 3.38 – 3.20 (m, 1H), 3.10 (d, *J* = 13.7 Hz, 1H), 2.74 (ddd, *J* = 14.5, 10.7, 6.7 Hz, 1H), 2.58 (dt, *J* = 14.4, 4.1 Hz, 1H).
^{1}H NMR: (300 MHz, Chloroform-*d* @ 55 °C): δ = 8.58 – 8.49 (m, 2H), 7.40 – 7.21 (m, 5H), 7.18 – 7.10 (m, 2H), 5.18 – 5.02 (m, 2H), 4.97 (dd, *J* = 14.0, 3.7 Hz, 1H), 4.85 (dd, *J* = 14.0, 10.3 Hz, 1H), 4.38 (dd, *J* = 13.7, 2.2 Hz, 1H), 4.30 – 4.16 (m, 1H), 4.05 (dd, *J* = 10.3, 3.7 Hz, 1H), 3.60 (s, 3H), 3.32 (ddd, *J* = 13.4, 10.4, 4.5 Hz, 1H), 3.14 (d, *J* = 13.7 Hz, 1H), 2.74 (ddd, *J* = 14.6, 10.4, 6.6 Hz, 1H), 2.56 (dt, *J* = 14.6, 4.4 Hz, 1H).
^{13}C NMR: (75 MHz, Chloroform-*d*): δ = 203.1, 168.4, 154.8, 150.4, 143.7, 136.0, 128.7, 128.5, 128.0, 124.6, 76.4, 68.0, 62.7, 53.2, 50.7, 44.7, 44.0, 40.1.
HPLC: Chiralcel OD-H, hexane/EtOH = 6:4, flow = 1.25 mL/min, λ = 210 nm, $\lambda_{(CD)}$ = 240 nm, t_R (major enant.) = 7.2 min, t_R (minor enant.) = 8.1 min, (e.r. = 98:2); Minor diastereomer was not detected.
$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}} = +29.2$ (c 0.12, $CHCl_3$)

1-Benzyl 3-methyl (*S*)-3-((*S,E*)-1-nitro-4-phenylbut-3-en-2-yl)-4-oxopiperidine-1,3-dicarboxylate, 3i.

Using **GP5** it was purified through FCC using a solvent gradient from 85:15 to 7:3 hexane/EtOAc to give adduct **3i** as a white solid (diastereomer mixture, d.r. = 96:4, e.r. = 96:4, 35.4 mg, 76%). Catalyst was not recovered.

TLC: (Major diast) R_f = 0.32, (minor diast.) R_f = 0.36 (Plate was eluted twice in hexane/EtOAc = 8:2, then once in hexane/EtOAc = 7:3) [Seebach]
^{1}H NMR: (300 MHz, Chloroform-*d*): δ = 7.43 – 7.16 (m, 10H), 6.51 (d, *J* = 15.7 Hz, 1H), 6.07 (dd, *J* = 15.8, 9.9 Hz, 1H), 5.27 – 5.01 (m, 2H), 4.73 (dd, *J* = 12.7, 3.2 Hz, 1H), 4.66 – 4.39 (m, 2H), 4.23 – 4.02 (m, 1H), 3.74 – 3.25 (m, 6H), 2.77 (ddd, *J* = 14.6, 9.6, 6.4 Hz, 1H), 2.59 (dt, *J* = 14.7, 4.8 Hz, 1H).
^{1}H NMR: (300 MHz, Chloroform-*d* @ 55 °C): δ = 7.35 – 7.21 (m, 10H), 6.51 (d, *J* = 15.8 Hz, 1H), 6.06 (dd, *J* = 15.8, 9.8 Hz, 1H), 5.24 – 5.05 (m, 2H), 4.72 (dd, *J* = 12.8, 3.3 Hz, 1H), 4.60 – 4.42 (m, 2H), 4.15 – 4.03 (m, 1H), 3.68 (s, 3H), 3.58 (td, *J* = 9.9, 3.2 Hz, 1H), 3.50 (td, *J* = 9.4, 4.9 Hz, 1H), 3.42 (d, *J* = 13.9 Hz, 1H), 2.77 (ddd, *J* = 14.7, 9.4, 6.4 Hz, 1H), 2.58 (dt, *J* = 14.8, 5.1 Hz, 1H).
^{13}C NMR: (75 MHz, Chloroform-*d*): δ = 203.9, 168.9, 155.0, 137.5, 135.8, 128.7, 128.7, 128.5, 128.4, 128.1, 126.9, 121.9, 77.0, 68.1, 62.6, 53.1, 50.3, 44.0, 43.9, 40.0.
HRMS (DART+): $[M+H]^+$ calcd. for $C_{25}H_{27}N_2O_7^+$: 467.18183, found:467.18167.
HPLC: Chiralcel OD-H, hexane/EtOH = 8:2, flow = 1.0 mL/min, λ = 210 nm, $\lambda_{(CD)}$ = 235 nm, t_R (major enant.) = 28.1 min, t_R (minor enant.) = 24.2 min, (e.r. = 94:6); t_R (Major diast.) = 18.8 min, t_R (minor diast.) = 16.7 min (d.r. = 96:4).
$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}} = +30.8$ (c 0.12, $CHCl_3$)

1-Benzyl 3-methyl (*S*)-3-((*S*)-1-nitro-4-phenylbutan-2-yl)-4-oxopiperidine-1,3-dicarboxylate, 3j.

Using **GP5** it was purified through FCC using a solvent gradient from 9:1 to 7:3 hexane/EtOAc to give adduct **3j** as an off-white solid (inseparable diastereomer mixture, d.r. = 99:1, e.r. = 98:2, 81%). Catalyst was not recovered.

TLC: R_f = 0.30 (hexane/EtOAc = 7:3) [Seebach]
^{1}H NMR: (300 MHz, Chloroform-*d* @ 25 °C): δ = 7.44 – 6.96 (m, 10H), 5.31 – 5.03 (m, 2H), 4.70 – 3.70 (m, 5H), 3.64 (s, 4H), 2.89 (bs, 1H), 2.78 – 2.35 (m, 4H), 2.05 – 1.66 (m, 2H).

^{1}H NMR: (300 MHz, Chloroform-*d* @ 55 °C): δ = 7.42 – 7.03 (m, 10H), 5.20 (q, *J* = 12.3 Hz, 2H), 4.60 (dd, *J* = 14.6, 4.2 Hz, 1H), 4.50 (dd, *J* = 14.6, 5.7 Hz, 1H), 4.40 – 4.23 (m, 1H), 3.64 (s, 6H), 2.98 – 2.83 (m, 1H), 2.75 – 2.42 (m, 4H), 1.98 – 1.65 (m, 2H).
^{13}C NMR: (75 MHz, Chloroform-*d*): δ = 204.4, 169.2, 155.1, 140.7, 136.2, 128.8, 128.7, 128.6, 128.5, 128.2, 126.4, 77.4, 68.1, 65.0, 52.9, 48.4, 43.6, 39.3, 38.7, 34.0, 32.9.
HPLC: Chiralpak IA, hexane/EtOH = 6:4, flow = 1.0 mL/min, λ = 210 nm, t_R (major enant.) = 11.75 min, t_R (minor enant.) = 8.32 min, (e.r. = 98:2); t_R (enantiomeric mixture, diast.) = 9.96 min (d.r. = >99:1).
$[\alpha]_D^{20} = -38.0$ (c 0.15, $CHCl_3$)

Methyl (S)-1-benzyl-3-((S)-2-nitro-1-phenylethyl)-4-oxopiperidine-3-carboxylate, 3l.

Using **GP5** with **2a** (35.4 mg, 0.15 mmol) and **1-Bn** (19.3 mg, 0.15 mmol). It was purified through FCC using a solvent gradient from 9:1 to 75:25 hexane/EtOAc to give adduct **3l** as an orange solid (inseparable diastereomer mixture, d.r. = 99:1, e.r. = 99:1, 44.4 mg, 87%).

TLC: R_f = 0.22 (hexane/EtOAc = 8:2) [vanillin, ninhydrin]
^{1}H NMR: (400 MHz, Chloroform-*d*): δ = 7.28 (d, *J* = 28.2 Hz, 10H), 5.02 (dd, *J* = 13.6, 11.2 Hz, 1H), 4.78 (dd, *J* = 13.6, 3.2 Hz, 1H), 4.26 (dd, *J* = 11.2, 3.2 Hz, 1H), 3.67 (s, 3H), 3.58 – 3.44 (m, 2H), 3.03 (dd, *J* = 11.9, 1.8 Hz, 1H), 2.78 (ddt, *J* = 8.4, 4.1, 2.2 Hz, 1H), 2.75 – 2.67 (m, 1H), 2.67 – 2.56 (m, 2H), 2.50 – 2.41 (m, 1H).
^{13}C NMR: (100 MHz, Chloroform-*d*): δ = 205.6, 169.7, 137.3, 134.9, 129.6, 129.1, 128.7, 128.5, 127.7, 77.6, 64.5, 61.8, 60.5, 52.8, 52.5, 45.9, 40.4.
HRMS (DART+): $[M+H]^+$ calcd. for $C_{22}H_{25}N_2O_5^+$: 397.17635, found: 397.17569.
HPLC: Chiralcel OD-H, hexane/EtOH = 60:40, flow = 1.0 mL/min, λ = 210 nm, t_R (major enant.) = 14.5 min, t_R (minor enant.) = 5.9 min, (e.r. = 90:10); diastereomer was not observed (d.r. = 99:1).
$[\alpha]_D^{20} = +1.1$ (c 0.18, $CHCl_3$)

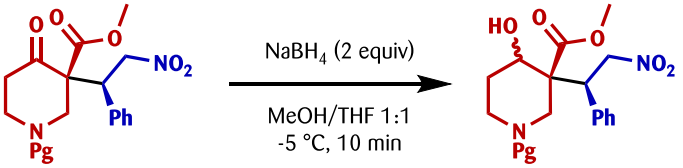
Methyl (*S*)-3-((*S*)-2-nitro-1-phenylethyl)-4-oxo-1-tosylpiperidine-3-carboxylate, 3m.

Using **GP5** with **2a** (31.8 mg, 0.1 mmol) and **1-Ts** (19.3 mg, 0.1 mmol). It was purified through FCC using a solvent gradient from 85:15 to 62:38 hexane/EtOAc to give adduct **3m** as an off-white solid (inseparable diastereomer mixture, d.r. = 97:3, e.r. = 94:6, 27.7 mg, 59%).

TLC: R_f = 0.28 (hexane/EtOAc = 65:35) [PMA, anisaldehyde]
^{1}H NMR: (300 MHz, Chloroform-*d*): δ = 7.51 (d, *J* = 8.3 Hz, 2H), 7.38 – 7.28 (m, 5H), 7.29 – 7.19 (m, 2H), 4.92 (dd, *J* = 13.6, 10.8 Hz, 1H), 4.80 (dd, *J* = 13.6, 3.7 Hz, 1H), 4.18 (dd, *J* = 10.7, 3.7 Hz, 1H), 3.76 (s, 3H), 3.64 (dd, *J* = 12.2, 2.1 Hz, 1H), 3.56 (dddd, *J* = 10.3, 8.2, 5.1, 2.3 Hz, 1H), 3.09 – 2.94 (m, 1H), 2.82 (ddd, *J* = 14.3, 9.3, 5.9 Hz, 1H), 2.76 – 2.65 (m, 2H), 2.43 (s, 3H).
^{13}C NMR: (75 MHz, Chloroform-*d*): δ = 202.7, 168.4, 144.6, 133.7, 132.3, 130.1, 129.7, 129.1, 129.0, 127.8, 77.2, 62.9, 53.2, 47.1, 45.3, 39.5, 21.7, 14.2.
HRMS (DART+): $[M+H]^+$ calcd. for $C_{22}H_{25}N_2O_7S^+$: 461.13825, found: 461.13750.
HPLC: Chiralcel OD-H, hexane/EtOH = 6:4, flow = 1.25 mL/min, λ = 210 nm, $\lambda_{(CD)}$ = 240 nm, t_R (major enant.) = 9.3 min, t_R (minor enant.) = 6.3 min, (e.r. = 94:6); t_R (major diast.) = 6.9 min, t_R (minor diast.) = 5.6 min, (d.r. = 97:3).
$[\alpha]_D^{20} = -30.6$ (c 0.17, $CHCl_3$)

4.6 Synthesis of 1-isomorphans

4.6.1 General procedure 6 (GP6) to reduce ketone 3k and 3a



3a, Pg = Cbz
3k, Pg = Boc

4-Boc
4-Cbz

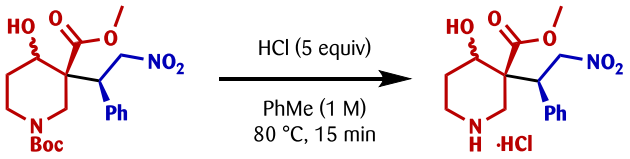
To a suspension of **3k** (1.27 g, 3.1 mmol) in a 1:1 mixture of THF/MeOH (0.2 M, 15.6 mL) was added sodium borohydride (0.24 g, 6.2 mmol) in small amounts at 0 °C. After adding the borohydride, the suspension turns into a clear colorless solution which was stirred for 10 minutes in an open flask. EtOAc (50 mL) was added to the reaction mixture and washed twice with a saturated ammonium chloride solution, then once with brine. The solution was dried (Na_2SO_4), filtered and concentrated in vacuo.

1-(*tert*-Butyl) 3-methyl (3*S*)-4-hydroxy-3-((*S*)-2-nitro-1-phenylethyl)piperidine-1,3-dicarboxylate (4-Boc)
Product **4-Boc** was obtained as a white solid (inseparable diastereomeric mixture, d.r. = 0.55:0.45, 1.24 g, 98%).

TLC: R_f = 0.43 (hexane/EtOAc = 1:1), [Seebach, Anisaldehyde]
^{1}H NMR: (300 MHz, DMSO-d_6 @ 120 °C): δ = 7.35 – 7.26 (m, 3H), 7.21 – 7.10 (m, 2H), 5.22 (ddd, *J* = 13.4, 4.1, 2.4 Hz, 1H), 5.14 – 4.95 (m, 1.5H), 4.87 (d, *J* = 5.2 Hz, 0.5H), 4.25 (s, 0.5H), 4.14 (q, *J* = 4.9 Hz, 0.5H), 3.93 – 3.80 (m, 1.5H), 3.76 – 3.61 (m, 2.6H), 3.58 (s, 1.4H), 3.41 (d, *J* = 13.5 Hz, 0.5H), 3.31 (d, *J* = 13.7 Hz, 0.5H), 3.21 (ddd, *J* = 12.9, 10.9, 3.9 Hz, 0.5H), 3.05 (td, *J* = 12.8, 3.3 Hz, 0.5H), 2.96 (d, *J* = 13.2 Hz, 0.5H), 1.89 (dddd, *J* = 13.9, 10.9, 5.2, 2.8 Hz, 0.5H), 1.75 – 1.62 (m, 1H), 1.56 – 1.47 (m, 0.5H), 1.44 (s, 5H), 1.30 (s, 4H).
^{13}C NMR: (75 MHz, DMSO-D_6 @ 120 °C) **Both epimers:** δ = 171.3, 152.9, 135.5, 135.3, 128.4, 128.1, 127.5, 127.4, 127.1, 78.5, 77.7, 76.4, 75.9, 66.4, 64.0, 53.1, 53.0, 50.6, 45.4, 44.4, 43.6, 42.1, 39.5, 37.8, 36.3, 29.6, 27.8, 27.5, 27.4.
HRMS (DART+): $[M+H]^+$ calcd. for $C_{20}H_{29}N_2O_7^+$: 409.19748, found: 409.19602.

1-Benzyl 3-methyl (3*S*)-4-hydroxy-3-((*S*)-2-nitro-1-phenylethyl)piperidine-1,3-dicarboxylate (4-Cbz)
TLC: R_f = 0.44 (hexane/EtOAc = 1:1), [Seebach, Anisaldehyde]
^{1}H NMR: (300 MHz, Chloroform-*d*): δ = 7.48 – 7.14 (m, 8H), 7.14 – 6.93 (m, 2H), 5.25 – 4.83 (m, 4H), 4.36 (bs, 0.5H), 4.26 – 2.71 (m, 9H), 2.01 – 1.51 (m, 2.5H).
^{1}H NMR: (300 MHz, Chloroform-*d* @ 55 °C): δ = 7.45 – 6.97 (m, 10H), 5.20 – 4.86 (m, 4H), 4.36 (d, *J* = 3.6 Hz, 0.5H), 4.19 – 3.65 (m, 3.5H), 3.55 (s, 1.2H), 3.43 (s, 1.8H), 3.31 – 2.88 (m, 2H), 2.61 (s, 1H), 1.99 – 1.85 (m, 0.5H), 1.80 – 1.52 (m, 2H).

Methyl (3*S*)-4-hydroxy-3-((*S*)-2-nitro-1-phenylethyl)piperidine-3-carboxylate hydrochloride (5) 4.6.2 from 4-Boc

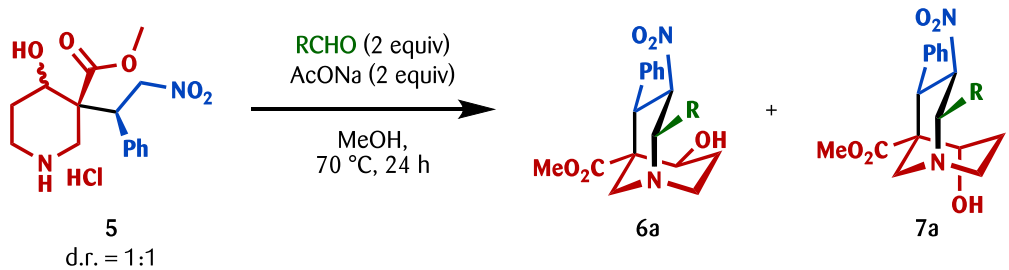


4-Boc 5

To a solution of **4-Boc** (726.4 mg. 1.8 mmol) in toluene (1.8 mL, 1 M) in an oil bath at 80 °C, was added concentrated HCl (0.75 mL, 5 equiv.). Reaction mixture was stirred until reactant was no longer detected by TLC for about 15 minutes. After completion, a small amount of MeOH was added to dissolve the precipitate. Solvent was removed under vacuum, and remaining solvent was thoroughly removed by azeotropic distillation with ethyl acetate. Product was then filtered and washed with ethyl ether to obtain the desired product as a white-off solid (inseparable diastereomeric mixture, d.r. = 0.55:0.45, 600.1 mg, 98%).

TLC: (Starting material **4-Boc**) R_f = 0.43 (hexane/EtOAc = 1:1), [Seebach, Anisaldehyde]
^{1}H NMR (700 MHz, DMSO-d_6) **Both epimers:** δ = 9.96 – 9.21 (m, 1.5H), 7.73 (s, 0.5H), 7.43 – 7.28 (m, 4H), 7.17 – 7.12 (m, 1H), 6.22 – 6.15 (m, 0.5H), 5.81 (dt, *J* = 6.0, 3.0 Hz, 0.5H), 5.43 – 5.34 (m, 1H), 5.21 (dd, *J* = 13.7, 11.8 Hz, 0.5H), 5.03 (ddd, *J* = 13.6, 12.0, 1.5 Hz, 0.5H), 4.30 – 4.23 (m, 1H), 4.17 (s, 0.5H), 3.84 (dd, *J* = 12.0, 3.8 Hz, 0.5H), 3.69 (s, 1.5H), 3.67 (s, 1.5H), 3.17 (d, *J* = 13.6 Hz, 0.5H), 3.14 – 3.00 (m, 2H), 2.96 (dt, *J* = 11.2, 3.4 Hz, 0.5H), 2.73 (d, *J* = 13.0 Hz, 0.5H), 2.61 (d, *J* = 13.4 Hz, 0.5H), 2.11 – 2.03 (m, 0.5H), 1.87 (dq, *J* = 15.1, 3.0 Hz, 0.5H), 1.80 – 1.74 (m, 0.5H), 1.54 (td, *J* = 15.2, 4.1 Hz, 0.5H).
^{13}C NMR: (100 MHz, DMSO) **Both epimers:** δ = 171.2, 170.8, 135.3, 134.5, 128.6, 128.3, 128.2, 76.1, 75.4, 64.1, 62.0, 52.9, 52.3, 52.1, 51.6, 45.5, 43.0, 42.5, 41.0, 37.4, 37.1, 27.4, 25.4.
HRMS (DART+): $[M+H]^+$ calcd. for $C_{15}H_{21}N_2O_5^+$: 309.14505, found: 309.14513.

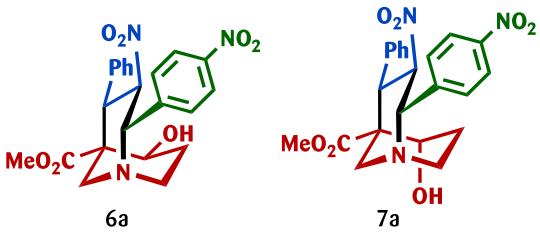
4.6.4 General procedure 7 (GP7) for the syntheses of isomorphans



5 d.r. = 1:1 6a 7a

To a solution of **5** (35.1 mg. 0.1 mmol) and the corresponding aldehyde (0.2 mmol, 2 equiv.) in methanol (0.5 mL, 0.2 M) was added NaOAc (16.8 mg, 0.2 mmol, 2 equiv). The reaction mixture was stirred in a sealed vial at 70 °C for 24 h. Water (2 mL) was added to the reaction mixture and the product was extracted with ethyl acetate (3 mL). Phases were separated and the organic phase was then washed twice with saturated $NaHCO_3$. Isomorphans were purified through FCC using a DCM/EtOAc solvent gradient to give products **6** and **7.**

Methyl (1*R*,2*S*,3*R*,4*S*,5*S*,6*S and 6R*)-6-hydroxy-3-nitro-2-(4-nitrophenyl)-4-phenyl-1-azabicyclo[3.3.1]nonane-5-carboxylate (6a & 7a)

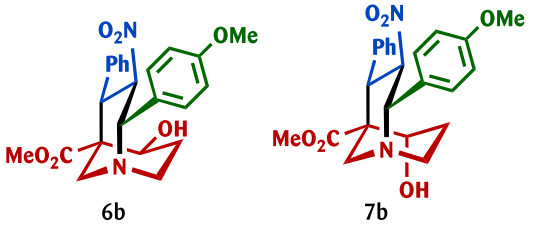


Following **GP7** the compounds were purified using FCC using a solvent gradient from 1:0 to 7:3 DCM/EtOAc to give products **6a** (13.2 mg, 30%) and **7a** (21.7 mg, 48%) as yellow solids (total yield = 34.9 mg, 78%).

TLC: R_f (**7a**) = 0.24 (DCM/EtOAc = 9:1), [UV, $CuCl_2$]; R_f (**6a**) = 0.39 (DCM/EtOAc = 9:1), [UV, $CuCl_2$]
^{1}H NMR (6a): (300 MHz, Chloroform-*d*): δ = 8.27 (d, *J* = 8.8 Hz, 2H), 7.71 (d, *J* = 8.7 Hz, 2H), 7.44 – 7.36 (m, 2H), 7.34 – 7.21 (m, 3H), 6.36 (dd, *J* = 12.2, 11.1 Hz, 1H), 4.84 (d, *J* = 11.1 Hz, 1H), 4.38 (dd, *J* = 12.3, 6.5 Hz, 1H), 4.26 (d, *J* = 12.2 Hz, 1H), 3.83 – 3.74 (m, 4H), 3.15 – 3.05 (m, 2H), 2.83 – 2.57 (m, 2H), 2.15 – 2.00 (m, 1H), 1.79 (dtd, *J* = 14.5, 12.3, 7.5 Hz, 1H).
^{13}C NMR (6a): (75 MHz, Chloroform-*d*): δ = 174.0, 142.3, 134.3, 130.4, 129.7, 128.6, 128.1, 124.2, 86.4, 72.9, 67.4, 59.4, 53.4, 52.7, 51.4, 45.0, 31.7.

^{1}H NMR (7a): (300 MHz, Chloroform-*d*): δ = 8.26 (d, *J* = 8.7 Hz, 2H), 7.70 (d, *J* = 8.8 Hz, 2H), 7.43 – 7.30 (m, 3H), 7.21 – 7.10 (m, 2H), 6.10 (t, *J* = 11.5 Hz, 1H), 4.86 (d, *J* = 11.2 Hz, 1H), 4.49 (s, 1H), 4.22 (d, *J* = 11.9 Hz, 1H), 3.93 (d, *J* = 13.5 Hz, 1H), 3.71 (s, 3H), 3.57 (d, *J* = 13.4 Hz, 1H), 3.08 – 2.92 (m, 2H), 2.50 (dd, *J* = 15.0, 5.8 Hz, 1H), 2.07 – 1.79 (m, 2H).
^{13}C NMR (7a): (75 MHz, Chloroform-*d*): δ = 173.7, 148.2, 142.7, 133.7, 129.6, 129.3, 129.1, 128.4, 124.1, 87.0, 66.9, 64.8, 53.8, 52.5, 52.4, 50.1, 40.9, 30.8.
HRMS (DART+): $[M+H]^+$ calcd. for $C_{22}H_{24}N_3O_7^+$: 442.16142, found: 442.16048.
$[\alpha]_D^{20}$ (**6a**) $= -70.0$ (c 0.12, $CHCl_3$); $[\alpha]_D^{20}$ (**7a**) $= -47.4$ (c 0.19, $CHCl_3$)

Methyl (1*R*,2*S*,3*R*,4*S*,5*S*, 6*S and 6R*)-6-hydroxy-2-(4-methoxyphenyl)-3-nitro-4-phenyl-1-azabicyclo[3.3.1]nonane-5-carboxylate (6b & 7b).

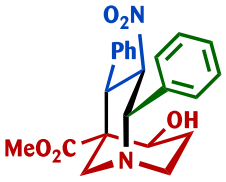


Following **GP7** the compounds were purified using FCC using a solvent gradient from 93:7 to 7:3 DCM/EtOAc to give products **6b** (12.4 mg, 29%) and **7b** (18.5 mg, 43%) as off-white solids (total yield =30.9 mg, 72%).

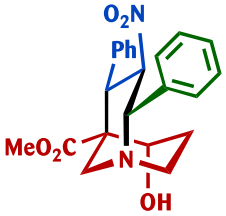
TLC: R_f (**7b**) = 0.15 (DCM/EtOAc = 9:1), [UV, $CuCl_2$]; R_f (**6b**) = 0.31 (DCM/EtOAc = 9:1), [UV, $CuCl_2$]
^{1}H NMR (6b): (300 MHz, Chloroform-*d*): δ = 7.46 – 7.33 (m, 4H), 7.31 – 7.18 (m, 3H), 6.98 – 6.86 (m, 2H), 6.30 (t, *J* = 11.7 Hz, 1H), 4.70 (d, *J* = 11.1 Hz, 1H), 4.36 (dd, *J* = 12.1, 6.4 Hz, 1H), 4.25 (d, *J* = 12.2 Hz, 1H), 3.88 – 3.68 (m, 7H), 3.14 – 3.01 (m, 2H), 2.96 (dd, *J* = 15.0, 6.1 Hz, 1H), 2.65 (td, *J* = 14.1, 4.9 Hz, 1H), 2.11 – 1.98 (m, 1H), 1.83 (ddt, *J* = 19.7, 13.6, 6.2 Hz, 1H).
^{13}C NMR (6b): (75 MHz, Chloroform-*d*): δ = 174.4, 160.0, 134.9, 130.4, 129.9, 128.3, 128.0, 127.1, 114.4, 86.9, 73.2, 67.7, 59.3, 55.4, 53.4, 52.5, 51.4, 44.6, 31.7.

^{1}H NMR (7b): (300 MHz, Chloroform-*d*): δ = 7.43 – 7.29 (m, 5H), 7.16 (dd, *J* = 7.8, 1.9 Hz, 2H), 6.98 – 6.86 (m, 2H), 6.05 (t, *J* = 11.6 Hz, 1H), 4.71 (d, *J* = 11.2 Hz, 1H), 4.47 (bks, 1H), 4.21 (d, *J* = 11.9 Hz, 1H), 3.91 (d, *J* = 13.4 Hz, 1H), 3.80 (s, 3H), 3.70 (s, 3H), 3.55 (d, *J* = 13.4 Hz, 1H), 3.11 – 2.89 (m, 2H), 2.71 (dd, *J* = 14.8, 6.0 Hz, 1H), 2.01 (ddd, *J* = 19.6, 12.6, 5.8 Hz, 1H), 1.85 (dd, *J* = 15.2, 5.1 Hz, 1H).
^{13}C NMR (7b): (75 MHz, Chloroform-*d*): δ = 174.1, 159.9, 134.2, 129.8, 129.2, 128.9, 128.4, 127.4, 114.3, 87.5, 67.2, 65.1, 55.4, 53.6, 52.4, 50.1, 40.5, 30.8.
HRMS (DART+): $[M+H]^+$ calcd. for $C_{23}H_{27}N_2O_6^+$: 427.18691, found: 427.18799.
$[\alpha]_D^{20}$ (**6b**) $= -48.3$ (c 0.12, $CHCl_3$); $[\alpha]_D^{20}$ (**7b**) $= -52.1$ (c 0.14, $CHCl_3$)

Methyl (1*R*,2*S*,3*R*,4*S*,5*S*,6*S* and 6*R*)-6-hydroxy-3-nitro-2,4-diphenyl-1-azabicyclo[3.3.1]nonane-5-carboxylate (6c & 7c)



6c



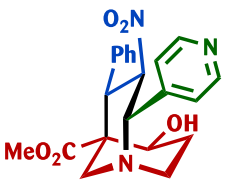
7c

Following **GP7** the compounds were purified using FCC using a solvent gradient from 9:1 to 10:0 DCM/hexane, then from 10:0 to 8:2 DCM/EtOAc to give products **6c** (10.8 mg, 27%) and **7c** (16.1 mg, 40%) as off-white solids (total yield = 26.9 mg, 67%).

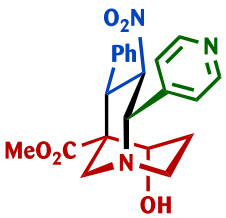
TLC: R_f (**7c**) = 0.14 (DCM/EtOAc = 9:1), [UV, $CuCl_2$]; R_f (**6c**) = 0.33 (DCM/EtOAc = 9:1), [UV, $CuCl_2$]
^{1}H NMR (6c): (500 MHz, Chloroform-*d*): δ = 7.52 – 7.47 (m, 2H), 7.41 (t, *J* = 7.5 Hz, 4H), 7.38 – 7.29 (m, 2H), 7.29 – 7.21 (m, 2H), 6.37 (t, *J* = 11.7 Hz, 1H), 4.76 (d, *J* = 11.1 Hz, 1H), 4.38 (dd, *J* = 12.1, 6.3 Hz, 1H), 4.27 (d, *J* = 12.3 Hz, 1H), 3.81 – 3.77 (m, 4H), 3.11 (d, *J* = 2.3 Hz, 1H), 3.09 (d, *J* = 13.7 Hz, 1H), 2.94 (ddd, *J* = 15.0, 6.0, 2.1 Hz, 1H), 2.67 (td, *J* = 15.0, 14.5, 4.9 Hz, 1H), 2.07 (dt, *J* = 14.3, 5.6 Hz, 1H), 1.85 (tdd, *J* = 13.9, 12.0, 6.2 Hz, 1H).
^{13}C NMR (6c): (125 MHz, Chloroform-*d*): δ = 174.3, 135.0, 134.8, 130.4, 129.0, 128.7, 128.4, 128.0, 86.5, 73.1, 68.2, 59.4, 53.4, 52.6, 51.4, 44.7, 31.7.

^{1}H NMR (7c): (500 MHz, Chloroform-*d*): δ = 7.50 – 7.46 (m, 2H), 7.43 – 7.29 (m, 6H), 7.20 – 7.15 (m, 2H), 6.12 (t, *J* = 11.6 Hz, 1H), 4.78 (d, *J* = 11.3 Hz, 1H), 4.49 (s, 1H), 4.22 (d, *J* = 11.8 Hz, 1H), 3.92 (d, *J* = 13.3 Hz, 1H), 3.72 (s, 3H), 3.58 (dt, *J* = 13.3, 1.8 Hz, 1H), 3.06 (s, 1H), 2.97 (td, *J* = 14.2, 5.0 Hz, 1H), 2.69 (dd, *J* = 14.9, 6.1 Hz, 1H), 2.08 – 1.99 (m, 1H), 1.86 (ddd, *J* = 15.4, 4.8, 2.0 Hz, 1H).
^{13}C NMR (7c): (75 MHz, Chloroform-*d*): δ = 174.0, 135.4, 134.2, 129.2, 129.0, 128.9, 128.9, 128.6, 128.4, 87.2, 67.7, 65.0, 53.8, 52.4, 50.1, 40.6, 30.8.
HRMS (DART+): $[M+H]^+$ calcd. for $C_{22}H_{25}N_2O_5^+$: 397.17635, found: 397.17561.
$[\alpha]_D^{20}$ (**6c**) $= -30.8$ (c 0.12, $CHCl_3$); $[\alpha]_D^{20}$ (**7c**) $= -27.1$ (c 0.14, $CHCl_3$)

Methyl (1*R*,2*S*,3*R*,4*S*,5*S*,6*S* and 6*R*)-6-hydroxy-3-nitro-4-phenyl-2-(pyridin-4-yl)-1-azabicyclo[3.3.1]nonane-5-carboxylate (6d & 7d)



6d



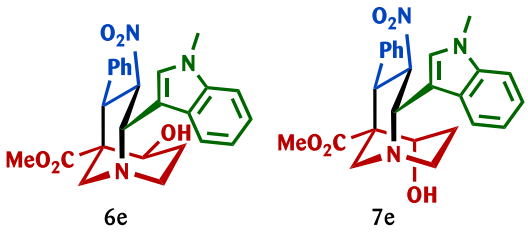
7d

Following **GP7** the compounds were purified using FCC using a solvent gradient from 99:1 to 9:1 DCM/EtOH to give products **6d** (12.6 mg, 26%) as an off-white solid and **7d** (18.5 mg, 38%) as a dull yellow solid (total yield = 31.1 mg, 64%).

TLC: R_f (**7d**) = 0.24 (DCM/EtOH = 95:5), [UV, $CuCl_2$]; R_f (**6d**) = 0.32 (DCM/EtOH = 95:5), [UV, $CuCl_2$]
^{1}H NMR (6d): (400 MHz, Chloroform-*d*): δ = 8.67 (d, *J* = 5.0 Hz, 2H), 7.49 – 7.36 (m, 4H), 7.31 – 7.23 (m, 3H), 6.33 (dd, *J* = 12.3, 11.1 Hz, 1H), 4.75 (d, *J* = 11.0 Hz, 1H), 4.37 (dd, *J* = 12.1, 6.4 Hz, 1H), 4.25 (d, *J* = 12.2 Hz, 1H), 3.79 (s, 4H), 3.15 – 3.06 (m, 2H), 2.78 (dd, *J* = 15.3, 6.5 Hz, 1H), 2.69 (ddd, *J* = 15.2, 13.3, 4.8 Hz, 1H), 2.12 – 2.01 (m, 1H), 1.87 – 1.72 (m, 1H).
^{13}C NMR (6d): (75 MHz, Chloroform-*d*): δ = 174.0, 150.7, 144.1, 134.3, 130.4, 128.5, 128.1, 123.4, 86.0, 73.0, 67.0, 59.4, 53.3, 52.7, 51.4, 45.1, 31.7.

^{1}H NMR (7d): (400 MHz, Chloroform-*d*): δ = 8.66 (d, *J* = 5.4 Hz, 2H), 7.46 – 7.32 (m, 5H), 7.19 – 7.13 (m, 2H), 6.07 (t, *J* = 11.5 Hz, 1H), 4.77 (d, *J* = 11.1 Hz, 1H), 4.51 – 4.45 (m, 1H), 4.20 (d, *J* = 11.9 Hz, 1H), 3.92 (d, *J* = 13.5 Hz, 1H), 3.71 (s, 3H), 3.56 (dt, *J* = 13.5, 1.8 Hz, 1H), 3.14 – 2.93 (m, 2H), 2.53 (dd, *J* = 15.0, 5.9 Hz, 1H), 1.96 (dddd, *J* = 16.9, 13.3, 6.0, 4.0 Hz, 1H), 1.91 – 1.80 (m, 1H).
^{13}C NMR (7d): (75 MHz, Chloroform-*d*): δ = 173.7, 150.6, 144.5, 133.8, 129.3, 129.1, 128.4, 123.3, 86.6, 66.4, 64.8, 53.8, 52.5, 52.4, 50.1, 41.0, 30.8.
HRMS (DART+): $[M+H]^+$ calcd. for $C_{21}H_{24}N_3O_5^+$: 398.17160, found: 398.17259.
$[\alpha]_D^{20}$ (**6d**) $= -6.2$ (*c* 0.13, $CHCl_3$); $[\alpha]_D^{20}$ (**7b**) $= -12.0$ (*c* 0.15 , $CHCl_3$)

Methyl (1*R*,2*S*,3*R*,4*S*,5*S*,6*S*)-6-hydroxy-2-(1-methyl-1*H*-indol-3-yl)-3-nitro-4-phenyl-1-azabicyclo[3.3.1]nonane-5-carboxylate (6e & 7e)

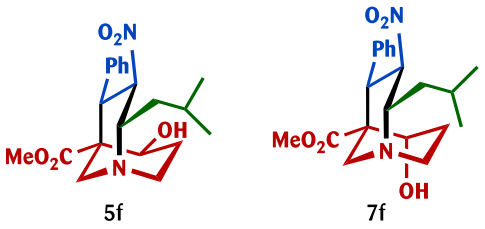


Following **GP7** the compounds were purified using FCC using a solvent gradient from 9:1 to 1:0 DCM/hexane, then from 1:0 to 8:2 DCM/EtOAc to give products **6e** (16.8 mg, 19%) as a dull orange solid and **7e** (32.0 mg, 36%) as a dull yellow solid (total yield = 48.8 mg, 55%).

TLC: R_f (**7e**) = 0.23, R_f (**6e**) = 0.42, (DCM/EtOAc = 9:1) [Seebach, $CuCl_2$]
^{1}H NMR (6e): (300 MHz, Chloroform-*d*): δ = 7.73 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.47 – 7.38 (m, 2H), 7.34 – 7.21 (m, 6H), 7.14 (ddd, *J* = 8.0, 6.7, 1.4 Hz, 1H), 6.19 (dd, *J* = 12.3, 10.9 Hz, 1H), 5.14 (d, *J* = 10.9 Hz, 1H), 4.42 – 4.26 (m, 2H), 3.88 – 3.75 (m, 7H), 3.17 – 3.06 (m, 2H), 3.00 (dd, *J* = 14.9, 6.4 Hz, 1H), 2.64 (td, *J* = 14.1, 4.9 Hz, 1H), 1.99 (ddd, *J* = 14.2, 6.6, 3.2 Hz, 1H), 1.77 (qd, *J* = 13.3, 6.1 Hz, 1H).
^{13}C NMR (6e): (75 MHz, Chloroform-*d*): δ = 174.6, 137.5, 135.1, 130.5, 128.3, 128.0, 127.5, 127.1, 122.6, 120.1, 119.8, 109.7, 109.5, 88.4, 73.3, 61.6, 58.5, 53.6, 52.5, 51.4, 44.9, 33.1, 31.7.

^{1}H NMR (7e): (300 MHz, Chloroform-*d*): δ = 7.76 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.42 – 7.08 (m, 9H), 5.95 (t, *J* = 11.5 Hz, 1H), 5.15 (d, *J* = 10.9 Hz, 1H), 4.51 – 4.43 (m, 1H), 4.26 (d, *J* = 11.9 Hz, 1H), 3.95 (d, *J* = 13.4 Hz, 1H), 3.76 (s, 3H), 3.72 (s, 3H), 3.63 (d, *J* = 13.8 Hz, 1H), 3.06 (br, 1H), 2.96 (td, *J* = 14.0, 5.0 Hz, 1H), 2.75 (dd, *J* = 14.7, 6.1 Hz, 1H), 1.96 (ddt, *J* = 18.6, 13.3, 4.4 Hz, 1H), 1.77 (dd, *J* = 15.5, 4.8 Hz, 1H).
^{13}C NMR (7e): (75 MHz, Chloroform-*d*): δ = 174.3, 137.5, 134.4, 129.2, 128.8, 128.4, 127.5, 126.8, 122.6, 120.3, 119.8, 110.3, 109.4, 89.0, 65.2, 61.2, 52.7, 52.4, 49.9, 40.8, 33.1, 30.8.
HRMS (DART+): $[M+H]^+$ calcd. for $C_{25}H_{28}N_3O_5^+$: 450.20290, found: 450.20295.
$[\alpha]_D^{20}$ (**6e**) $= +1.0$ (*c* 0.1, $CHCl_3$); $[\alpha]_D^{20}$ (**7e**) $= -6.3$ (*c* 0.16, $CHCl_3$)

Methyl (1*R*,2*S*,3*R*,4*S*,5*S*,6*S* and 6*R*)-6-hydroxy-2-isobutyl-3-nitro-4-phenyl-1-azabicyclo[3.3.1]nonane-5-carboxylate (6f & 7f)

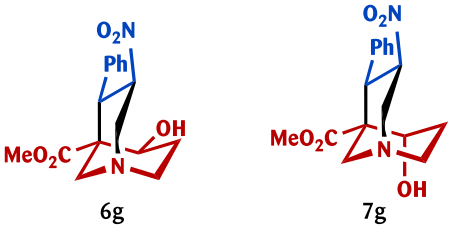


Following **GP7** the compounds were purified using FCC using a solvent gradient from 80:20 to 1:0 DCM/hexane, then from 1:0 to 85:15 DCM/EtOAc to give products **6f** (26.4 mg, 35%) as a white solid and **7f** (43.8 mg, 59%) as a pale-yellow wax (total yield = 70.2 mg, 94%).

TLC: R_f (**7f**) = 0.19, R_f (**6f**) = 0.34, (DCM/EtOAc = 9:1) [UV, $CuCl_2$]
^{1}H NMR (6f): (300 MHz, Chloroform-*d*): δ = 7.32 – 7.16 (m, 5H), 5.49 (dd, *J* = 12.4, 10.4 Hz, 1H), 4.29 (dd, *J* = 12.1, 6.5 Hz, 1H), 4.17 (d, *J* = 12.5 Hz, 1H), 3.76 (s, 3H), 3.57 – 3.42 (m, 2H), 3.27 (dd, *J* = 15.4, 5.6 Hz, 1H), 3.02 – 2.90 (m, 2H), 2.82 (ddd, *J* = 15.0, 13.6, 4.8 Hz, 1H), 2.03 (dt, *J* = 14.1, 5.6 Hz, 1H), 1.84 – 1.59 (m, 3H), 1.17 – 1.06 (m, 1H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.86 (d, *J* = 6.4 Hz, 3H).
^{13}C NMR (6f): (75 MHz, Chloroform-*d*): δ = 174.5, 135.2, 130.1, 128.1, 128.0, 90.8, 73.1, 62.0, 59.3, 52.5, 51.6, 44.0, 38.3, 31.6, 23.8, 23.7, 20.9.

^{1}H NMR (7f): (300 MHz, Chloroform-*d*): δ = 7.31 – 7.20 (m, 3H), 7.10 – 6.99 (m, 2H), 5.22 (dd, *J* = 12.1, 10.4 Hz, 1H), 4.34 – 4.27 (m, 1H), 4.11 (d, *J* = 12.1 Hz, 1H), 3.77 (d, *J* = 13.4 Hz, 1H), 3.67 (s, 3H), 3.48 (td, *J* = 10.7, 3.8 Hz, 1H), 3.26 (dt, *J* = 13.5, 1.7 Hz, 1H), 3.20 – 2.91 (m, 3H), 1.91 – 1.61 (m, 4H), 1.12 (ddd, *J* = 14.2, 10.3, 3.5 Hz, 1H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.84 (d, *J* = 6.4 Hz, 3H).
^{13}C NMR (7f): (75 MHz, Chloroform-*d*): δ = 174.2, 134.4, 129.1, 128.7, 128.3, 91.5, 65.1, 61.6, 53.5, 52.3, 51.8, 50.0, 40.1, 38.8, 30.7, 23.8, 23.7, 20.9.
HRMS (DART+): $[M+H]^+$ calcd. for $C_{20}H_{29}N_2O_5^+$: 377.20765, found: 377.20678.
$[\alpha]_D^{20}$ (**6f**) $= +14.3$ (c 0.14, $CHCl_3$); $[\alpha]_D^{20}$ (**7f**) $= -2.9$ (c 0.17, $CHCl_3$)

Methyl (1*R*,3*R*,4*S*,5*S*,6*S*)-6-hydroxy-3-nitro-4-phenyl-1-azabicyclo[3.3.1]nonane-5-carboxylate (6g & 7g)

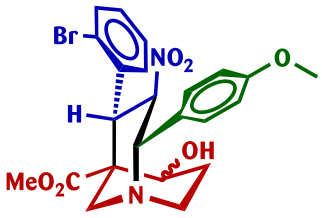


Following **GP7**, using **5** (82.7. 0.2 mmol), formalin (36 µL, 2.0 equiv.), and NaOAc (40.1 mg, 2.0 equiv) in methanol (0.5 mL, 0.5 M). Products were purified through FCC using 99:1:0.1 DCM/MeOH/NH_4OH as mobile phase to give products **6g** (32.2 mg, 42%) and **7g** (21.8 mg, 29%) as off-white solids (total yield = 54.0 mg, 71%).

TLC: R_f (**7g**) = 0.36, R_f (**6g**) = 0.49, (DCM/MeOH/NH_4OH = 95:5:0.5) [UV, $CuCl_2$]
^{1}H NMR (6g): (400 MHz, Chloroform-*d*): δ = 7.33 – 7.19 (m, 5H), 5.90 (ddd, *J* = 12.6, 11.0, 6.1 Hz, 1H), 4.31 (dd, *J* = 12.1, 6.4 Hz, 1H), 4.18 (d, *J* = 12.5 Hz, 1H), 3.77 (s, 3H), 3.67 (ddd, *J* = 13.7, 6.0, 1.6 Hz, 1H), 3.50 – 3.39 (m, 2H), 3.25 – 3.17 (m, 1H), 3.11 (td, *J* = 14.3, 13.9, 5.1 Hz, 1H), 3.02 (s, 1H), 2.85 (d, *J* = 13.6 Hz, 1H), 2.11 (dt, *J* = 14.5, 5.7 Hz, 1H), 1.90 (dddd, *J* = 14.5, 13.4, 12.1, 6.7 Hz, 1H).
^{13}C NMR (6g): (100 MHz, Chloroform-*d*): δ = 174.3, 135.5, 130.0, 128.1, 84.6, 72.9, 57.5, 57.2, 52.5, 51.5, 51.3, 51.2, 31.5.

^{1}H NMR (7g): (400 MHz, Chloroform-*d*): δ = 7.35 – 7.27 (m, 3H), 7.11 – 7.06 (m, 2H), 5.61 (ddd, *J* = 12.2, 11.0, 6.5 Hz, 1H), 4.35 (bs, 1H), 4.18 (d, *J* = 12.2 Hz, 1H), 3.72 – 3.65 (m, 5H), 3.49 – 3.32 (m, 2H), 3.22 (dt, *J* = 13.4, 1.8 Hz, 1H), 3.03 – 2.91 (m, 2H), 2.07 (dddd, *J* = 13.3, 9.3, 6.4, 4.1 Hz, 1H), 1.91 (ddd, *J* = 15.5, 4.9, 1.8 Hz, 1H).
^{13}C NMR (7g): (100 MHz, Chloroform-*d*): δ = 174.0, 134.8, 129.2, 128.7, 128.2, 85.0, 64.9, 56.8, 52.4, 51.5, 50.2, 49.9, 47.4, 30.5.
HRMS (DART+): $[M+H]^+$ calcd. for $C_{16}H_{21}N_2O_5^+$: 321.14505, found: 321.14419.
$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ $(\mathbf{6g}) = +2.3$ $(c\ 0.13, CHCl_3)$; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ $(\mathbf{7g}) = -18.7$ $(c\ 0.15, CHCl_3)$

Methyl (2*R*,3*R*,5*S*,6*R*)-4-(2-bromophenyl)-6-hydroxy-2-(4-methoxyphenyl)-3-nitro-1-azabicyclo[3.3.1]nonane-5-carboxylate (6h & 7h) Scheme 7.



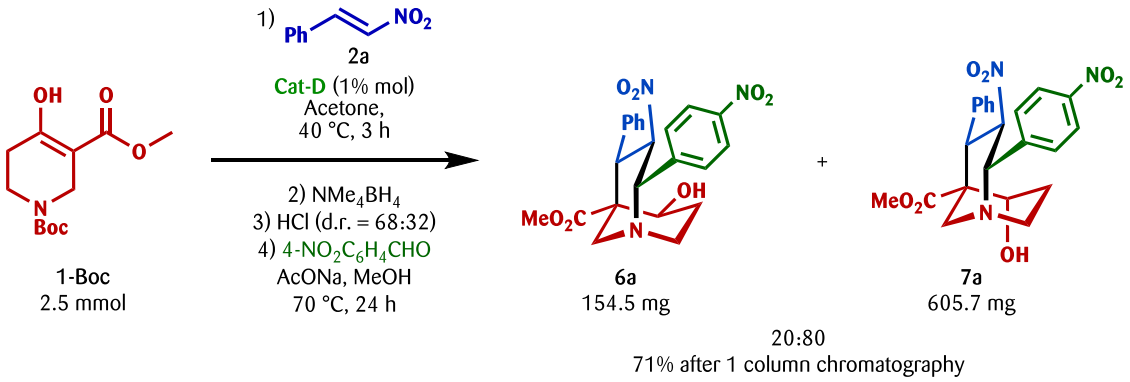
6h/7h

The Michael addition to obtain **3b** was performed in 2 mmol scale as reported previously in the ESI. The product **3b** (870.2 mg, 1.7 mmol) was suspended in MeOH (0.1 M, 16.7 mL) and sodium borohydride (134.4 mg, 3.35 mmol) was added in small amounts at 0 °C. After adding the borohydride, the suspension turned into a clear colorless solution which was stirred for 10 minutes in an open flask. EtOAc (25 mL) was added to the reaction mixture and washed twice with a saturated ammonium chloride solution, then once with brine. The solution was dried (Na_2SO_4), filtered and concentrated in vacuo. Then, a flask containing **4b** (815.8 mg, 1.6 mmol), conc. HCl (0.27 mL, 2.1 equiv.) and 5% Pd/C (83.7 mg, 10%$_{w/w}$) under a nitrogen atmosphere, MeOH was added via a syringe (7.82 mL, 0.2 M). It was purged with hydrogen and stirred for 2h. After reaction completion, the suspension was filtered through a pad of tightly compacted Celite, and the solvent evaporated to dryness. The residue was suspended in 5% EtOAc in Et_2O and filtered to yield hydrochloride **5b** as a white solid (mixture of diastereomers, d.r. nearly 1:1). Finally, to a solution of crude **5b** (631.2 mg, 1.49 mmol) and anisaldehyde (0.4 mL, 2.97 mmol, 2 equiv.) in methanol (3 mL, 0.5 M), was added NaOAc (256.0 mg, 2.97 mmol, 2 equiv). The reaction mixture was stirred in a sealed vial at 70 °C for 24 h. Water (10 mL) was added to the reaction mixture, and the product was extracted with ethyl acetate (25 mL). Phases were separated, and the organic phase was washed twice with saturated $NaHCO_3$. Isomorphans were purified through DCVC using a solvent from 7:3 to 6:4 hexane/acetone to give products **6h** (335.9 mg, 41% from **3b**) and **7h** (274.8 mg, 33% from **3b**).

TLC: R_f (**7h**) = 0.19, R_f (**6h**) = 0.28, (hexane/EtOAc = 1:1) [UV, $CuCl_2$]
^{1}H NMR (7h): (400 MHz, Chloroform-*d*): δ = 7.58 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.47 – 7.37 (m, 4H), 7.19 (ddd, *J* = 8.1, 6.6, 2.3 Hz, 1H), 6.93 (d, *J* = 8.8 Hz, 2H), 5.92 (t, *J* = 11.5 Hz, 1H), 4.86 (d, *J* = 11.6 Hz, 1H), 4.77 (d, *J* = 11.2 Hz, 1H), 4.64 (bs, 1H), 3.93 (d, *J* = 13.8 Hz, 1H), 3.82 (s, 3H), 3.75 – 3.66 (m, 4H), 2.99 (td, *J* = 14.1, 5.0 Hz, 1H), 2.75 (dd, *J* = 14.9, 6.2 Hz, 1H), 2.42 (d, *J* = 4.0 Hz, 1H), 2.14 – 2.00 (m, 1H), 1.89 (ddd, *J* = 15.2, 4.5, 1.9 Hz, 1H).
^{13}C NMR (7h): (75 MHz, Chloroform-*d*): δ = 173.0, 160.0, 134.2, 130.0, 129.7, 128.7, 127.9, 127.2, 126.4, 114.4, 88.4, 67.0, 65.7, 55.4, 53.2, 52.7, 49.5, 48.2, 40.3, 31.2.

^{1}H NMR (6h): (300 MHz, Chloroform-*d*): δ = 8.05 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.45 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.38 (d, *J* = 8.7 Hz, 2H), 7.31 (td, *J* = 7.7, 1.3 Hz, 1H), 7.08 (ddd, *J* = 8.0, 7.3, 1.6 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 6.18 (t, *J* = 11.6 Hz, 1H), 4.81 (d, *J* = 12.0 Hz, 1H), 4.72 (d, *J* = 11.1 Hz, 1H), 4.22 (dd, *J* = 11.8, 6.4 Hz, 1H), 3.93 (bs, 1H), 3.89 (dd, *J* = 14.0, 2.2 Hz, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.14 (d, *J* = 14.1 Hz, 1H), 2.96 (dd, *J* = 15.1, 6.1 Hz, 1H), 2.68 (ddd, *J* = 15.0, 13.3, 4.9 Hz, 1H), 2.08 (dt, *J* = 14.0, 5.6 Hz, 1H), 1.87 (ddt, *J* = 14.1, 12.0, 6.9 Hz, 1H).
^{13}C NMR (6h): (75 MHz, Chloroform-*d*): δ = 174.4, 160.0, 133.9, 133.5, 132.9, 129.8, 126.9, 126.7, 126.3, 114.3, 88.1, 74.1, 67.5, 58.4, 55.4, 52.9, 51.1, 48.4, 44.4, 32.1.
HRMS (DART+): $[M+H]^+$ calcd. for $C_{23}H_{26}BrN_2O_6^+$: 505.09742, found: 505.09795.
$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ **(6h)** $= -62.1$ (c 0.14 , $CHCl_3$); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ **(7h)** $= -44.2$ (c 0.12, $CHCl_3$)

Preparative scale of 6a and 7a (Scheme 7)



Michael addition: Following **GP4**, **1-Boc** (645.0 mg, 2.5 mmol), **2a** (371.2 mg, 2.49 mmol) and catalyst **Cat-D** (13.2 mg, 1 mol%) in acetone (1.25 mL, 2 M) reacted for 3 h. The reaction mixture was diluted and centrifuged for 10 minutes at 3400 RPM. The supernatant was carefully pipetted to a round bottom flask, and the pellet was rinsed and centrifuged trice with acetone. The solvents used for rinsing were combined with supernatant and evaporated to dryness. [Circa 2% (19.5 mg) of crude product was purified through FCC to assess stereoselectivity (e.r. = 96:4, d.r. = 98:2)].

Ketone reduction: To a suspension of crude **3k** (991.9 mg, 2.44 mmol) in MeOH (0.1 M, 25 mL) was added tetramethylammonium borohydride (467.5 mg, 5.0 mmol) in small amounts at 0 °C. After adding the borohydride, the suspension turned into a clear colorless solution, then stirred for 10 minutes in an open flask. EtOAc (25 mL) was added to the reaction mixture and washed twice with a saturated ammonium chloride solution, then once with brine. The solution was dried (Na_2SO_4), filtered and concentrated in vacuo, attaining the crude product **4-Boc** as a white solid.

Boc removal: To a flask containing crude **4-Boc** (974.1 mg. 2.4 mmol) in toluene (2.5 mL, 1 M) in an oil bath at 80 °C, was added concentrated HCl (1.04 mL, 12.5 mmol.). Upon HCl addition, the reaction mixture turned orange, and a precipitate was quickly formed; thus, to have an efficient agitation, it was added an extra 3 mL of toluene. The reaction mixture was stirred until the reactant was no longer seen in TLC (about 10 minutes). The solvent was carefully removed under vacuum, and the remaining water was thoroughly removed by azeotropic distillation, first with toluene and then EtOAc. Crude product **5** was suspended in the minimum amount of MeOH and precipitated with Et_2O. It was filtered and washed with ethyl ether to obtain **5** as a white-off solid (mixture of diastereomers, d.r. = 68:32).

Nitro-Mannich: To a solution of crude **5** (712.0 mg, 2.07 mmol) and 4-nitrobenzaldehyde (770.9 mg, 5 mmol) in methanol (4 mL, 0.5 M), was added NaOAc (417.2 mg, 5 mmol). The reaction mixture was stirred in a sealed vial at 70 °C for 24 h. Water (10 mL) was added to the reaction mixture and the product was extracted with ethyl acetate (25 mL). Phases were separated and the organic phase was then washed twice with saturated $NaHCO_3$ and once with brine.

7a·HCl isolation: Crude mixture of **6a** & **7a** was dissolved in 5 mL of 10% MeOH in EtOAc, then concentrated HCl (0.22 mL, 2.62 mL) was added. Solvent was concentrated in vacuo, and the remaining oily residue was diluted with 15 mL EtOAc and concentrated under vacuum twice. The remaining oily residue was diluted with 0.5 mL of EtOAc, and the hydrochloride precipitated with 10 mL of toluene, and 20 mL of diethyl ether. It was filtered, and the solid was rinsed with diethyl ether. Up to this point, the precipitate consisted predominantly of **7a** and was slightly contaminated with 4-nitrobenzaldehyde and **6a** (as can be examined by TLC, 9:1 DCM/EtOAc). Hence, the precipitate was dissolved in minimum MeOH, diluted with 15 mL EtOAc and concentrated under vacuum twice to form again an oily residue. Precipitation and filtration of **7a·HCl** was repeated as previously described to yield pure **7a·HCl** as a yellow solid. Optically pure **7a·HCl** is soluble to some extent in EtOAc, and slightly soluble in ethyl ether. It was liberated from the salt by washing an EtOAc solution of the hydrochloride with saturated $NaHCO_3$ to obtain 416.9 mg of free **7a** (39% yield from **1-Boc**).

Purification of remaining 6a & 7a: Mother liquors from both filtrations were concentrated to dryness, and the oil was dissolved in ethyl acetate (15 mL). The solution was washed twice with saturated $NaHCO_3$ and once with brine. Organic phase was dried (Na_2SO_4), filtered and concentrated *in vacuo*. Crude product mixture was adsorbed on celite and purified through DCVC using a solvent gradient from 1:0 to 7:3 DCM/EtOAc to give products **6a** (154.5 mg, 14% yield from **1-Boc**) and **7a** (188.8 mg, 18% yield from **1-Boc**) as yellow solids (total yield = 760.2 mg, d.r. = 8:2, 71% yield from **1-Boc**).

5. References:

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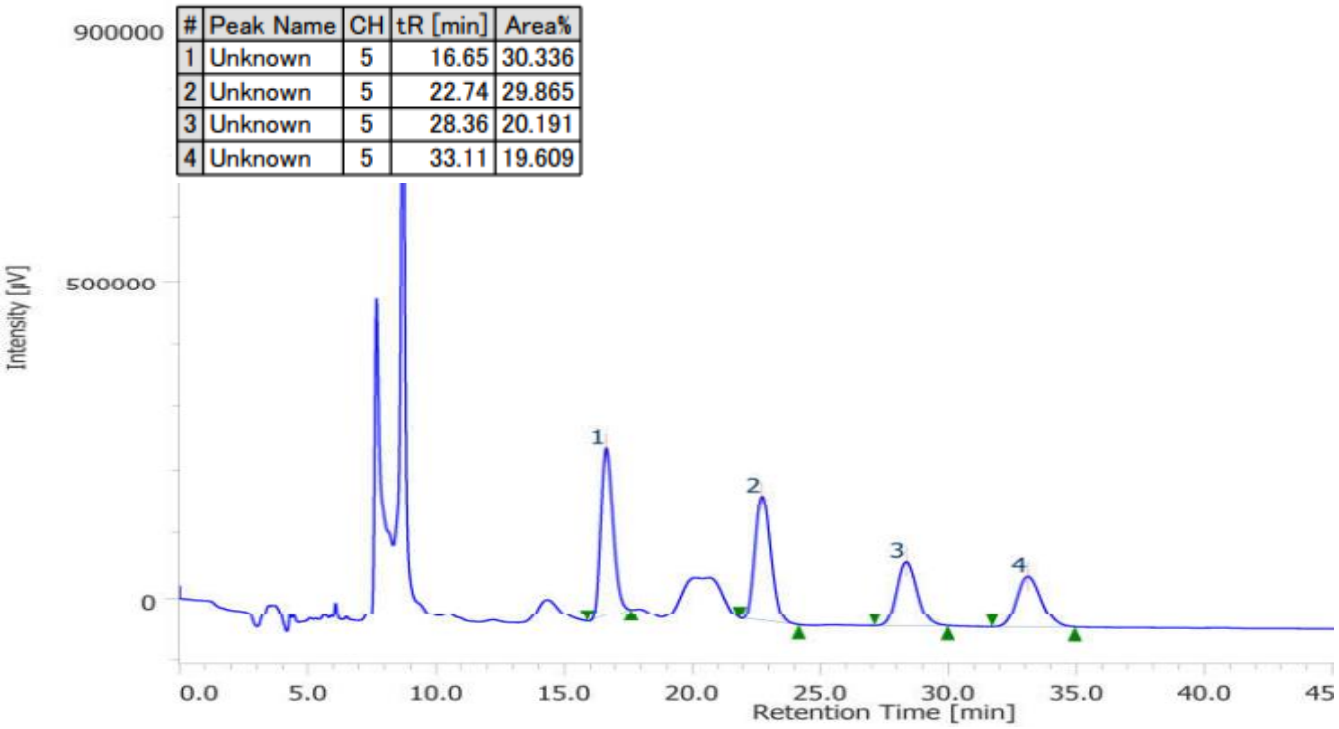
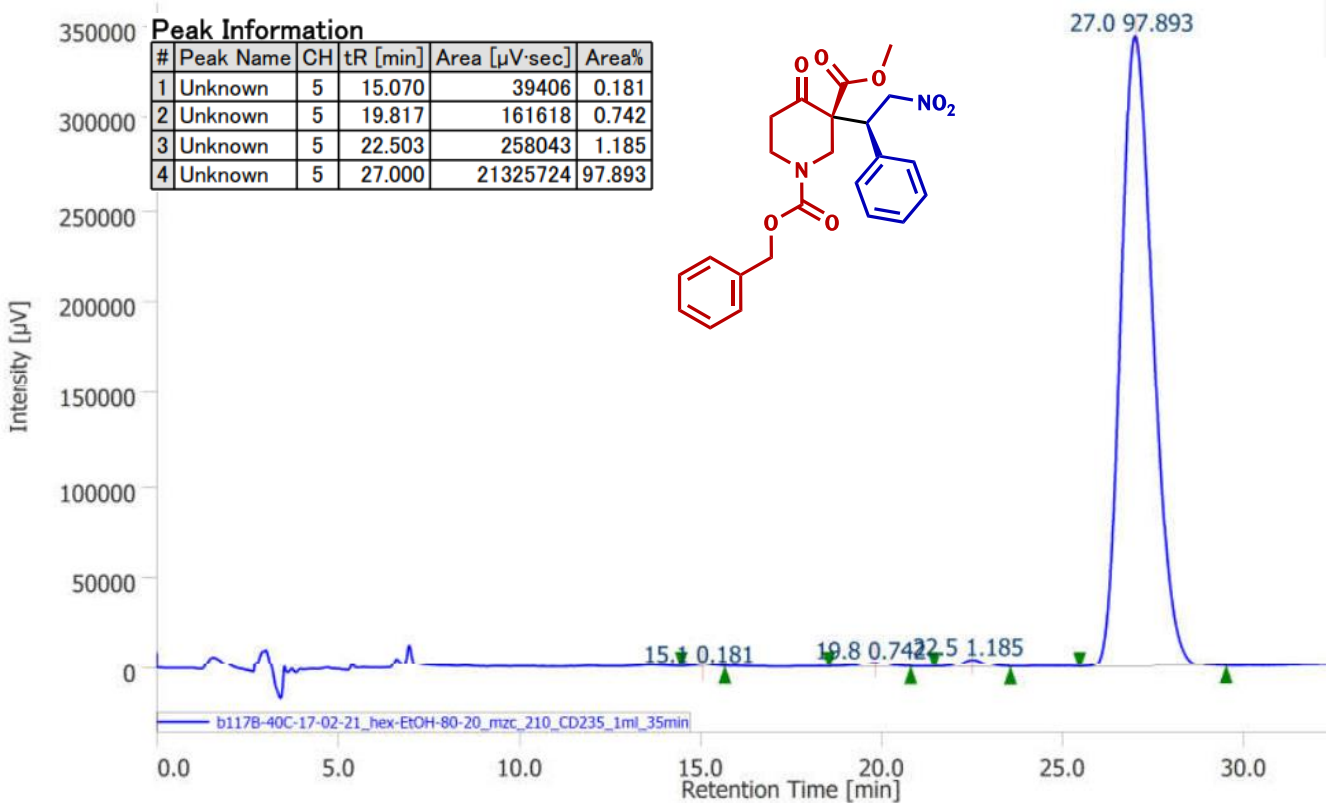
6. Chiral stationary phase HPLC chromatograms

Compound **3a** (98 ee, 99:1 d.r.) HPLC Chiralpak OD-H, hexane/EtOH 80:20, 1 mL/min, 210 nm.



#	Peak Name	CH	tR [min]	Area%
1	Unknown	5	16.65	30.336
2	Unknown	5	22.74	29.865
3	Unknown	5	28.36	20.191
4	Unknown	5	33.11	19.609

Racemic



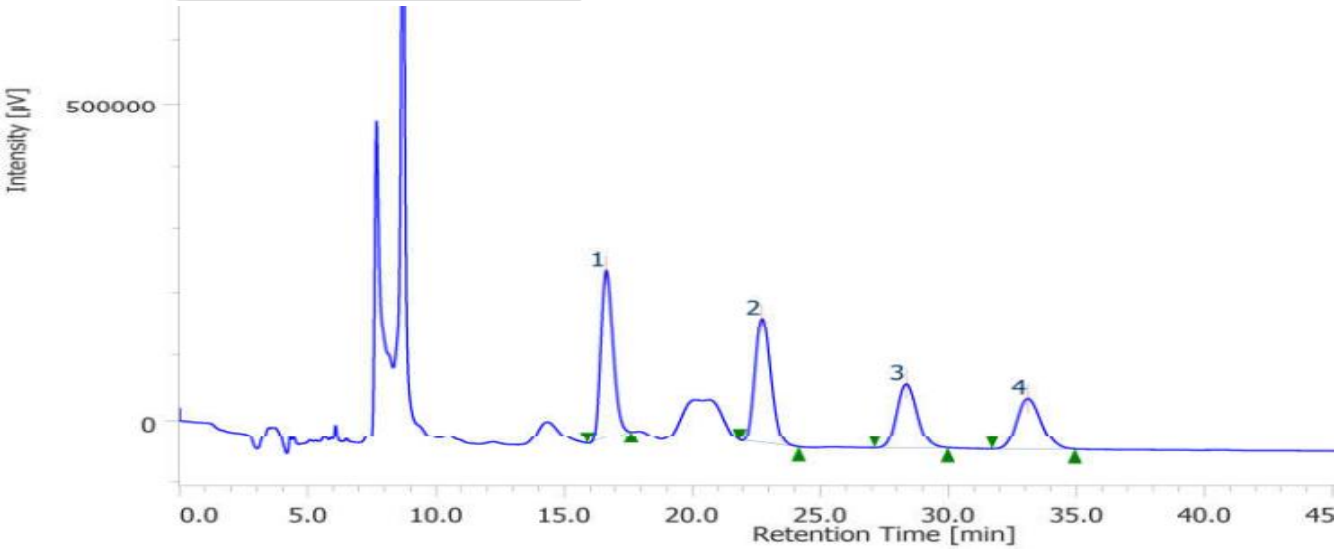
Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Area%
1	Unknown	5	15.070	39406	0.181
2	Unknown	5	19.817	161618	0.742
3	Unknown	5	22.503	258043	1.185
4	Unknown	5	27.000	21325724	97.893

Enantiomerically enriched

Compound *ent*-**3a** (97 ee, 99:1 d.r.) HPLC Chiralpak OD-H, hexane/EtOH 80:20, 1 mL/min, 210 nm.

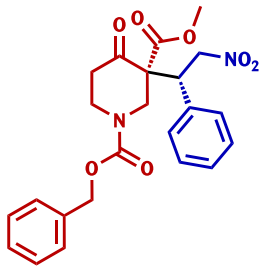
#	Peak Name	CH	tR [min]	Area%
1	Unknown	5	16.65	30.336
2	Unknown	5	22.74	29.865
3	Unknown	5	28.36	20.191
4	Unknown	5	33.11	19.609



Racemic

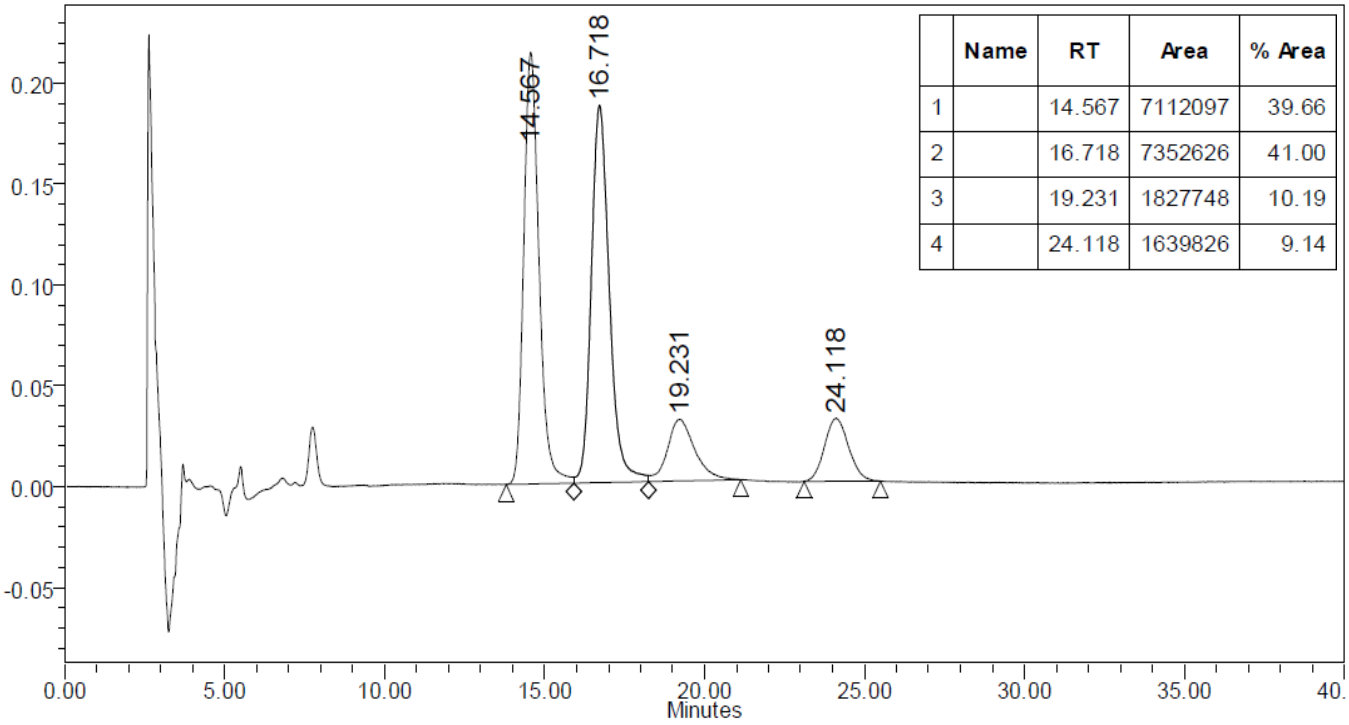
Peak Information

#	Peak Name	CH	tR [min]	Area [μV·sec]	Area%
1	Unknown	5	19.090	387223	0.938
2	Unknown	5	26.227	134474	0.326
3	Unknown	5	32.173	39621947	95.967
4	Unknown	5	38.200	1143199	2.769



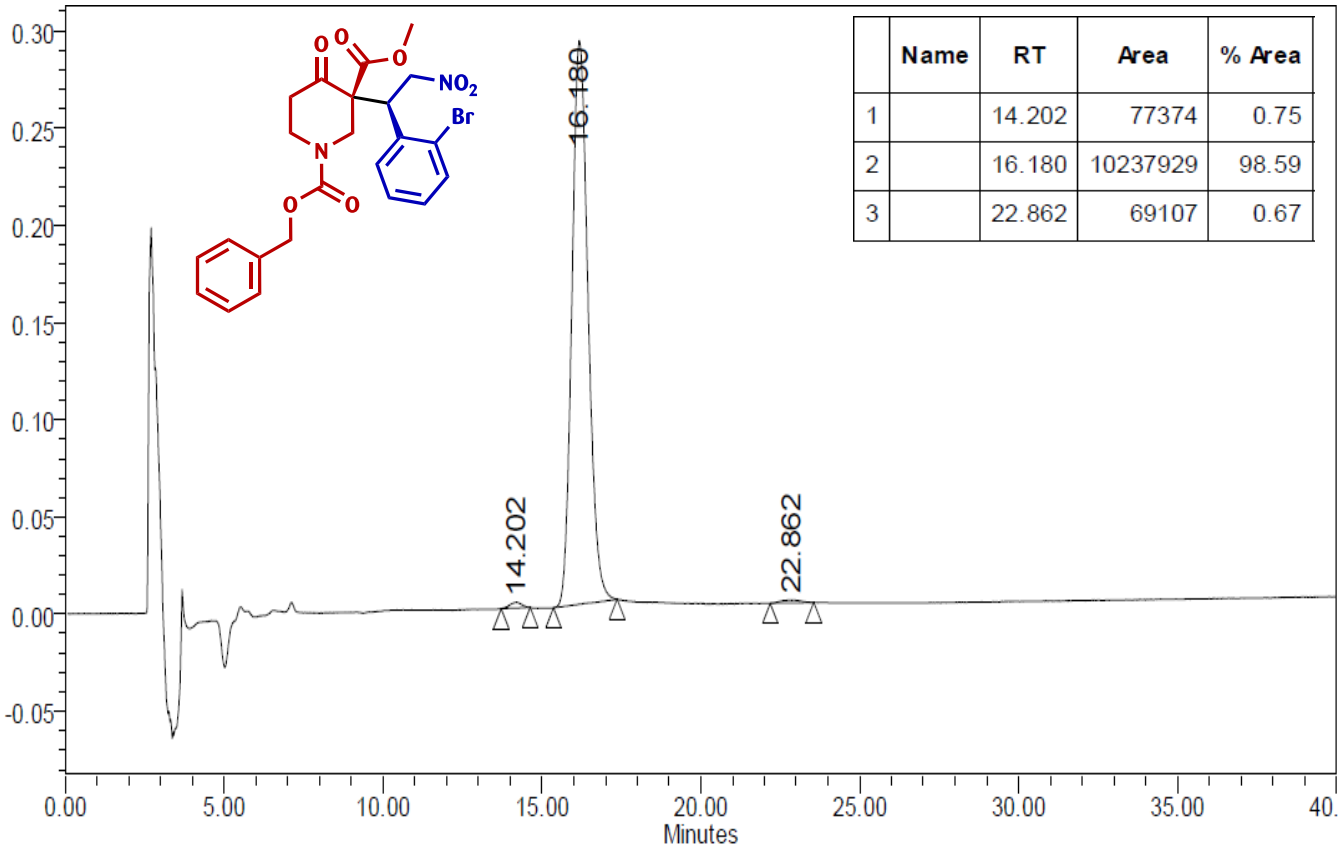
Enantiomerically enriched

Compound **3b** (98 ee, 98:2 d.r.) HPLC Chiralcel OD-H 250 x 4.6 mm 5µm, hexane/EtOH 80:20, 1 mL/min, 210 nm.



	Name	RT	Area	% Area
1		14.567	7112097	39.66
2		16.718	7352626	41.00
3		19.231	1827748	10.19
4		24.118	1639826	9.14

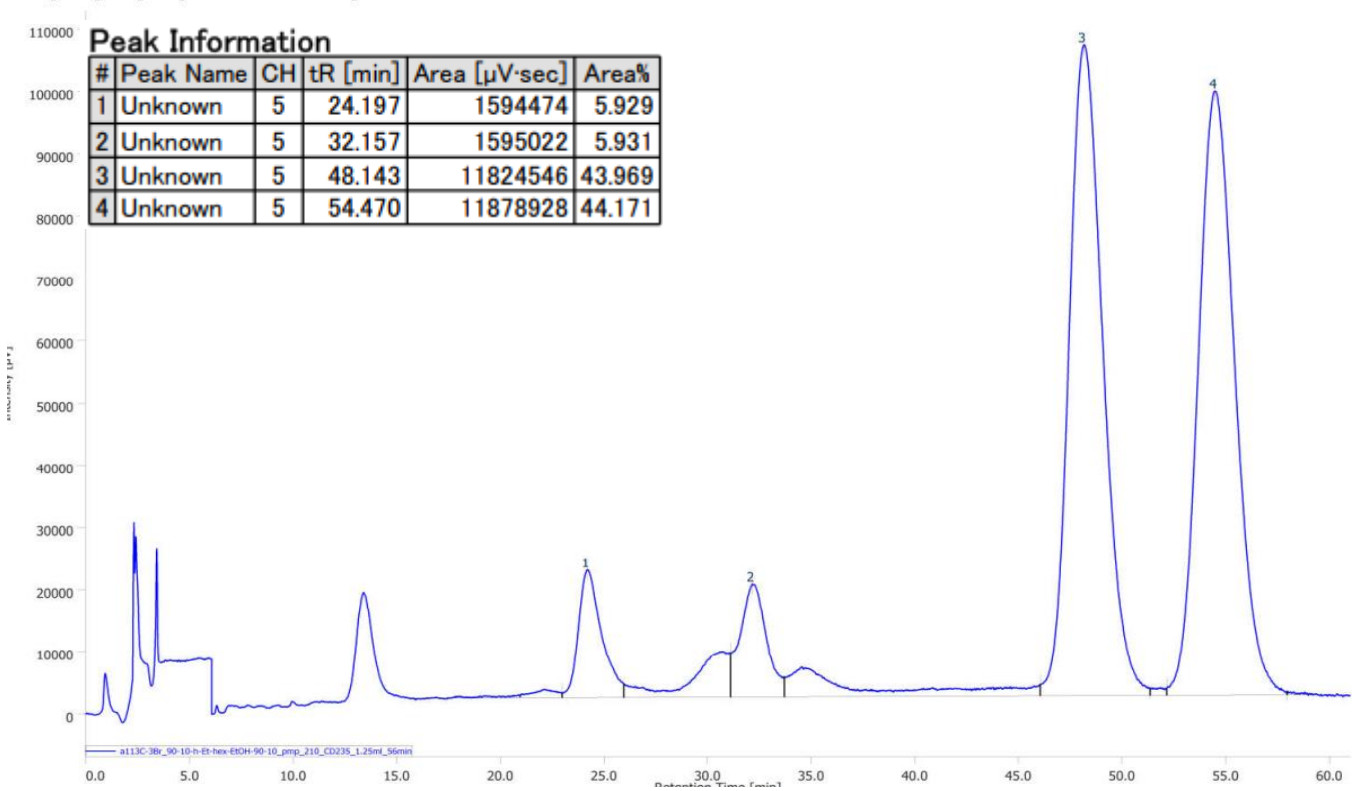
Racemic



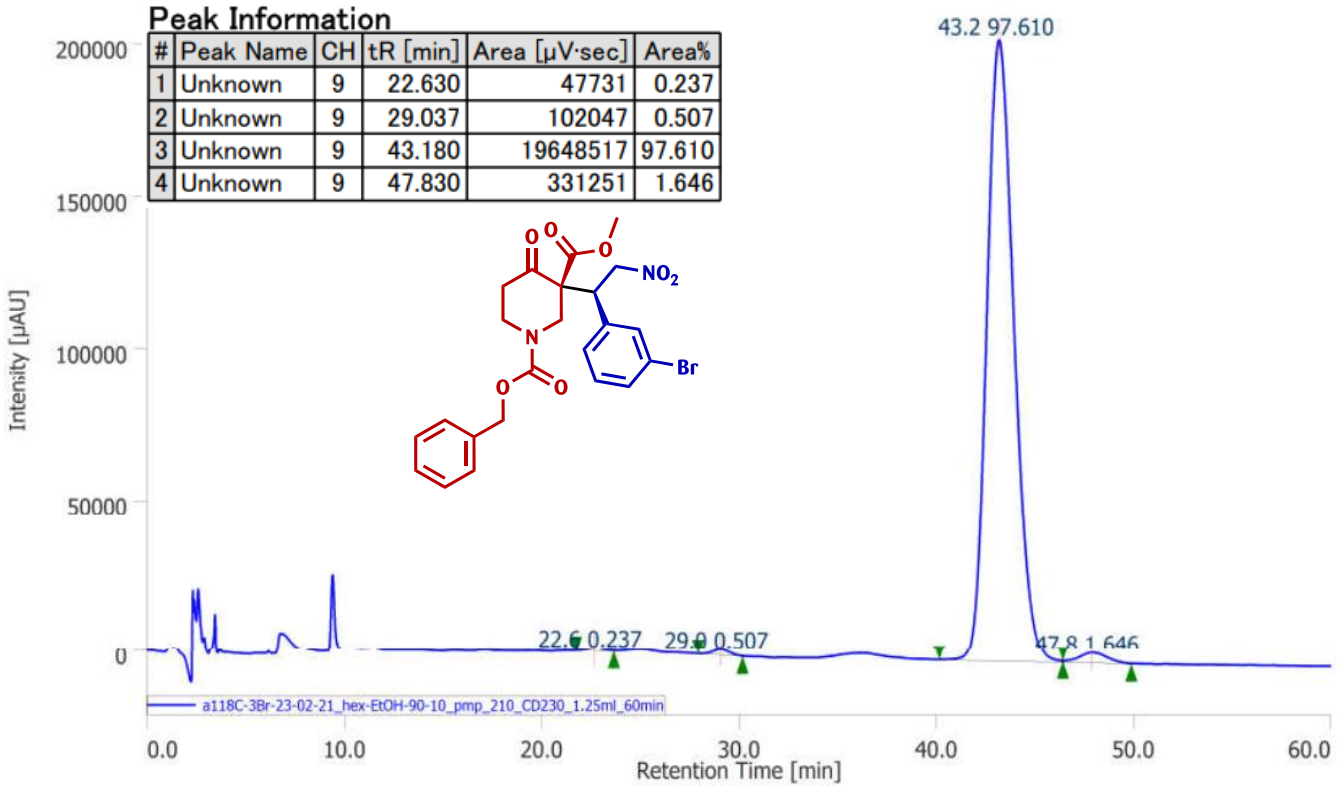
	Name	RT	Area	% Area
1		14.202	77374	0.75
2		16.180	10237929	98.59
3		22.862	69107	0.67

Enantiomerically enriched

Compound **3c** (98 ee, 99:1 d.r.) HPLC Chiralpak OD-H, hexane/EtOH 90:10, 1.25 mL/min, 210 nm.

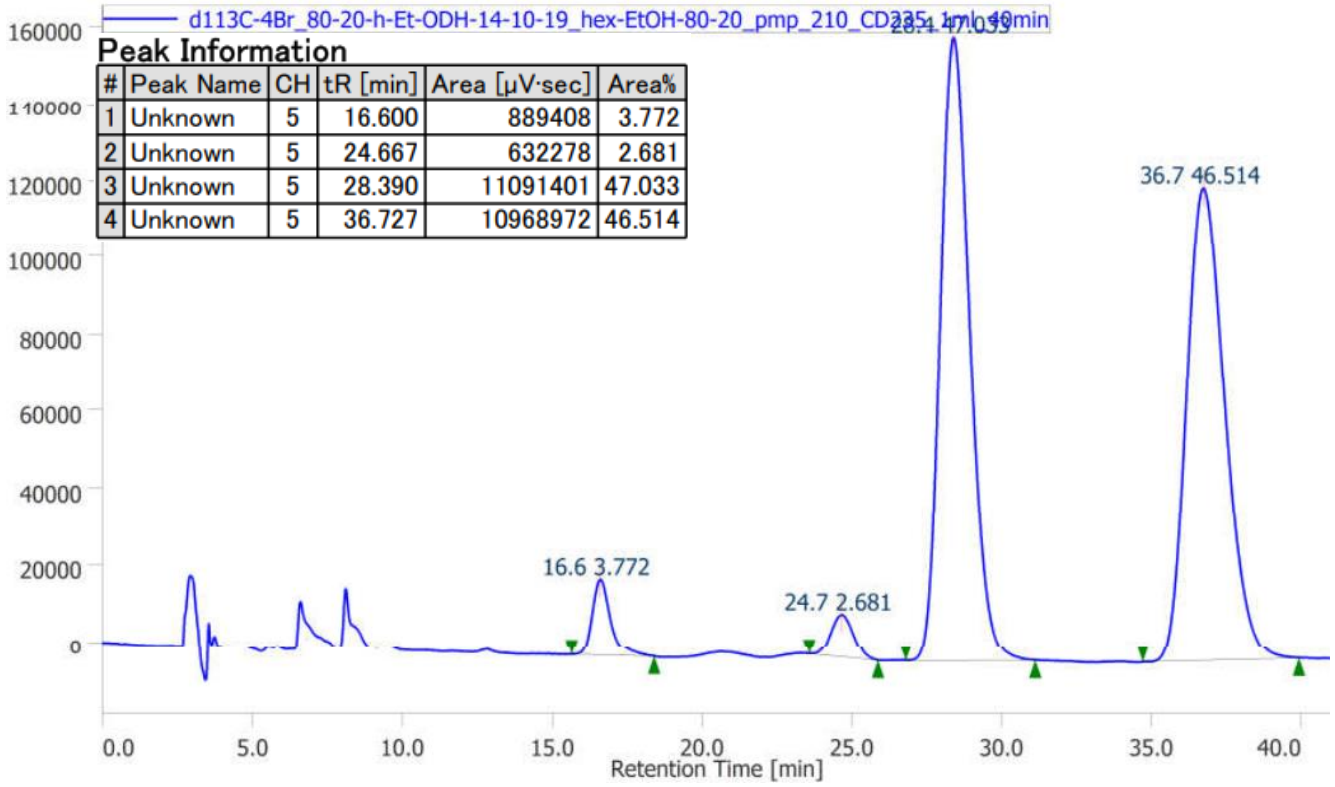


Racemic

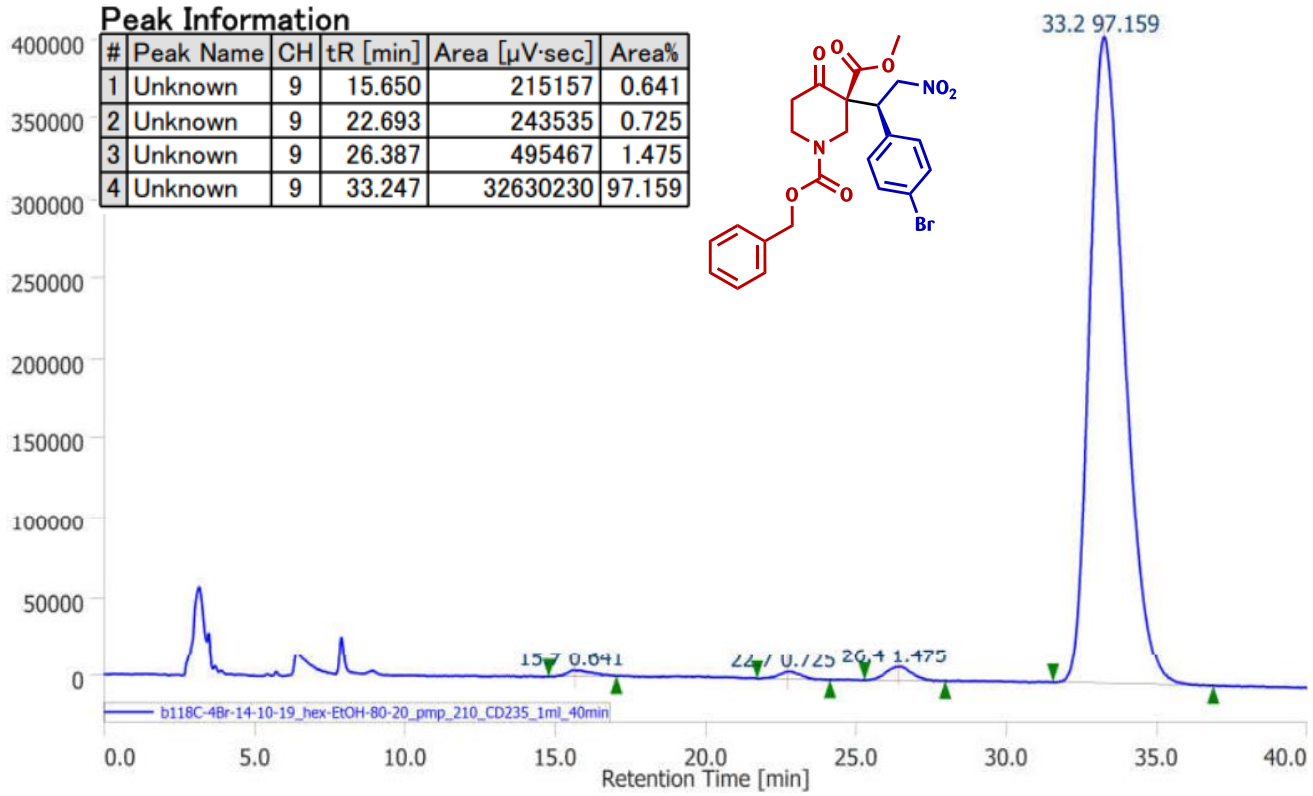


Enantiomerically enriched

Compound **3d** (98 ee, 99:1 d.r.) HPLC Chiralpak OD-H, hexane/EtOH 80:20, 1 mL/min, 210 nm.

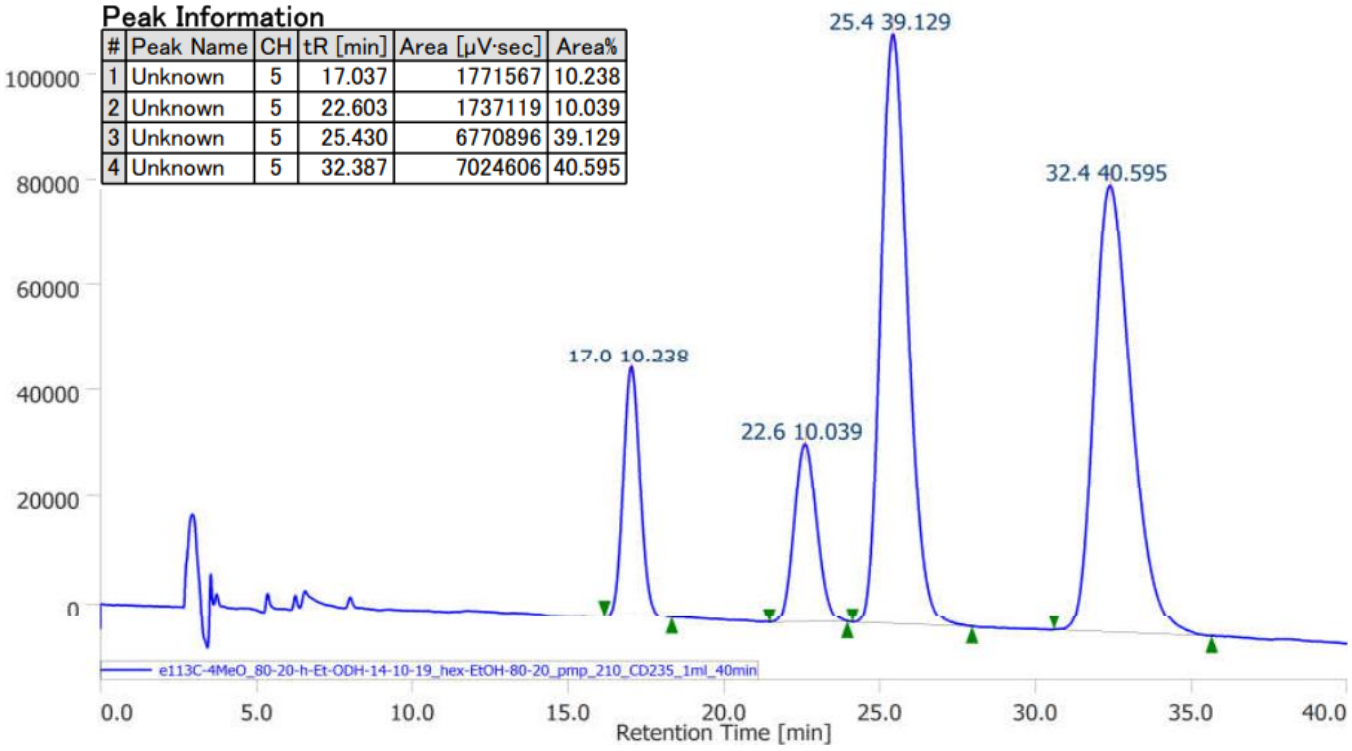


Racemic

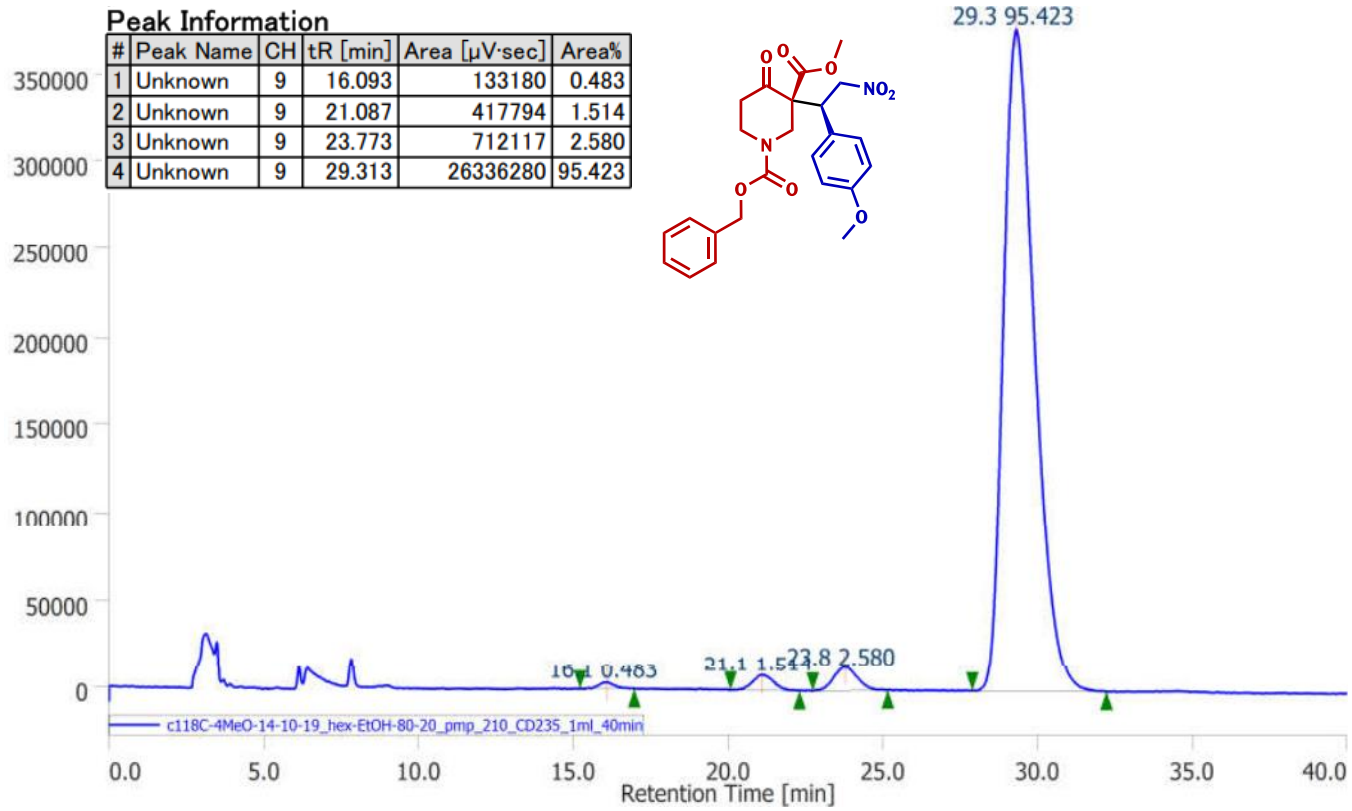


Enantiomerically enriched

Compound **3e** (96 ee, 98:2 d.r.) HPLC Chiralpak OD-H, hexane/EtOH 80:20, 1 mL/min, 210 nm.

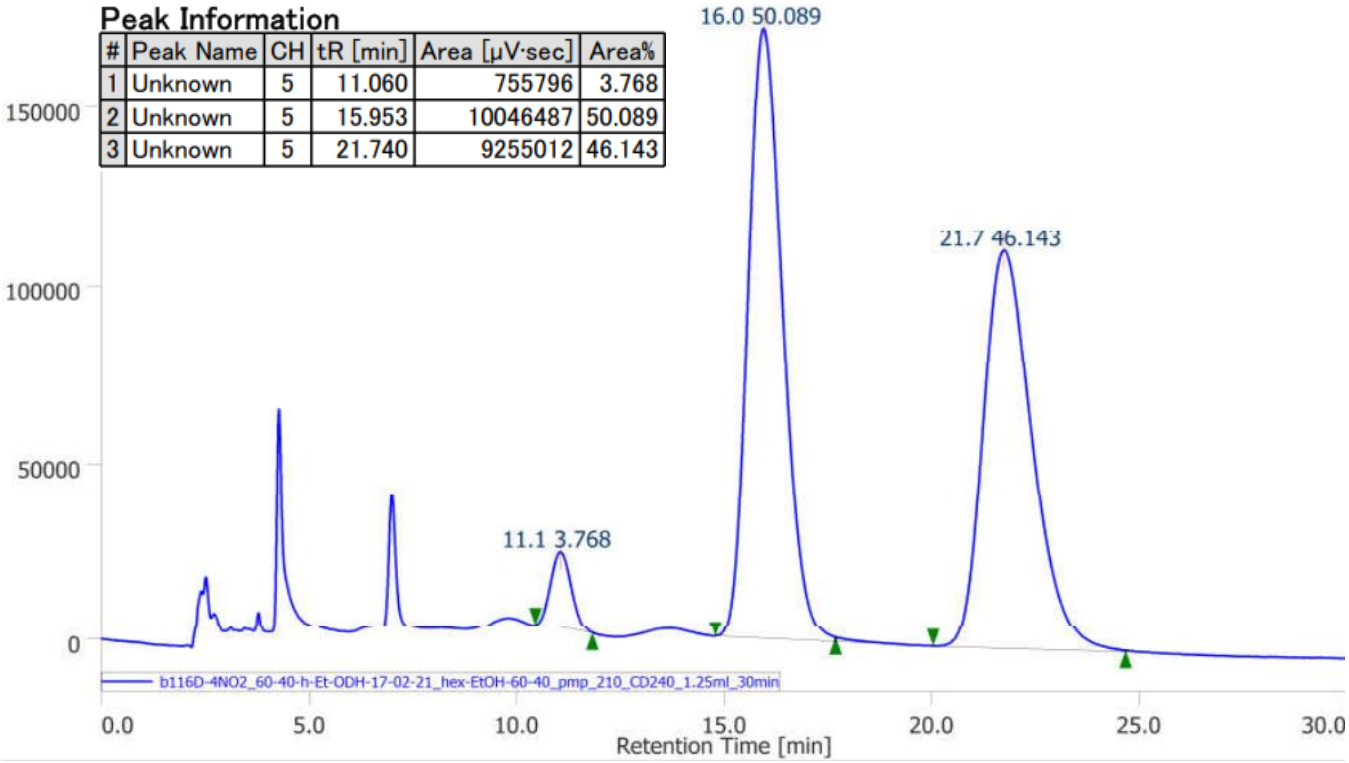


Racemic

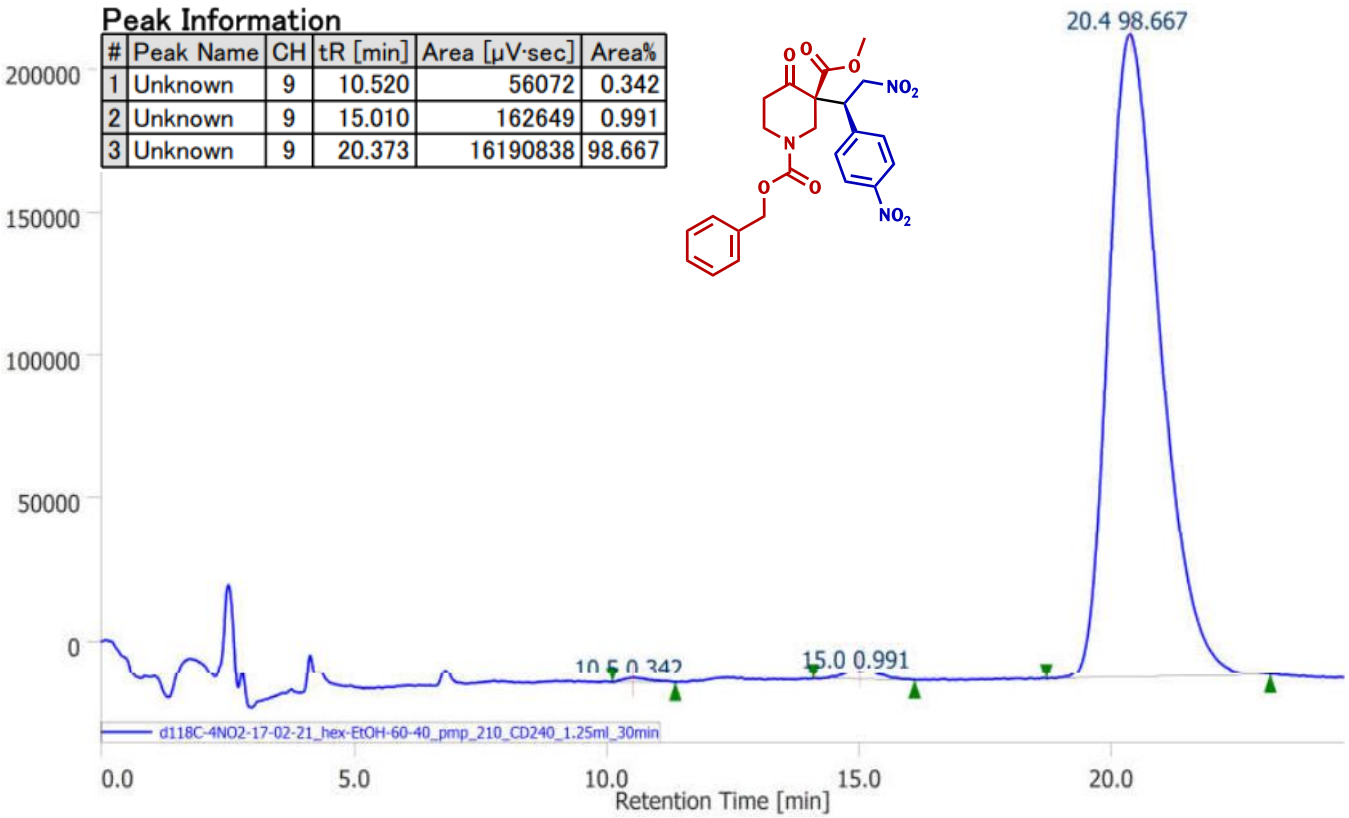


Enantiomerically enriched

Compound **3f** (98 ee, 99:1 d.r.) HPLC Chiralpak OD-H, hexane/EtOH 90:10, 1.25 mL/min, 210 nm.

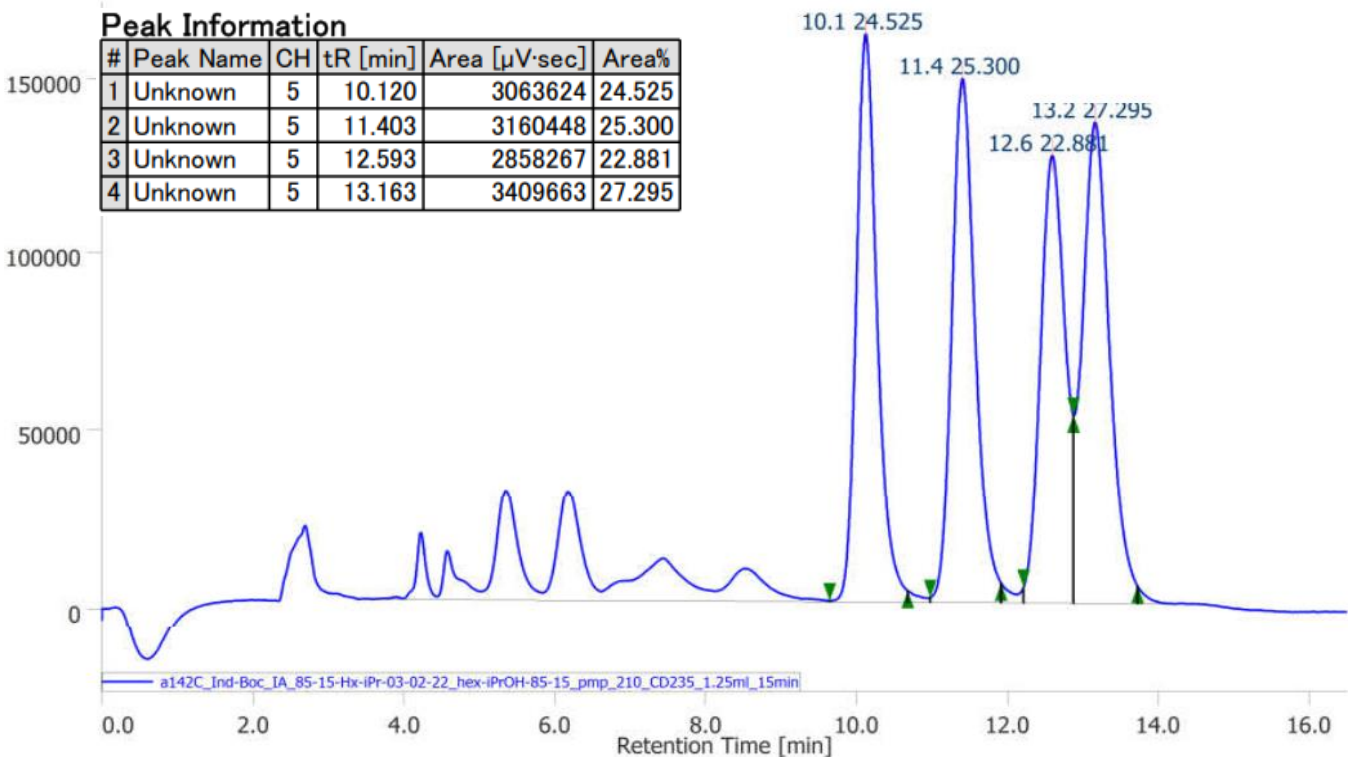


Racemic

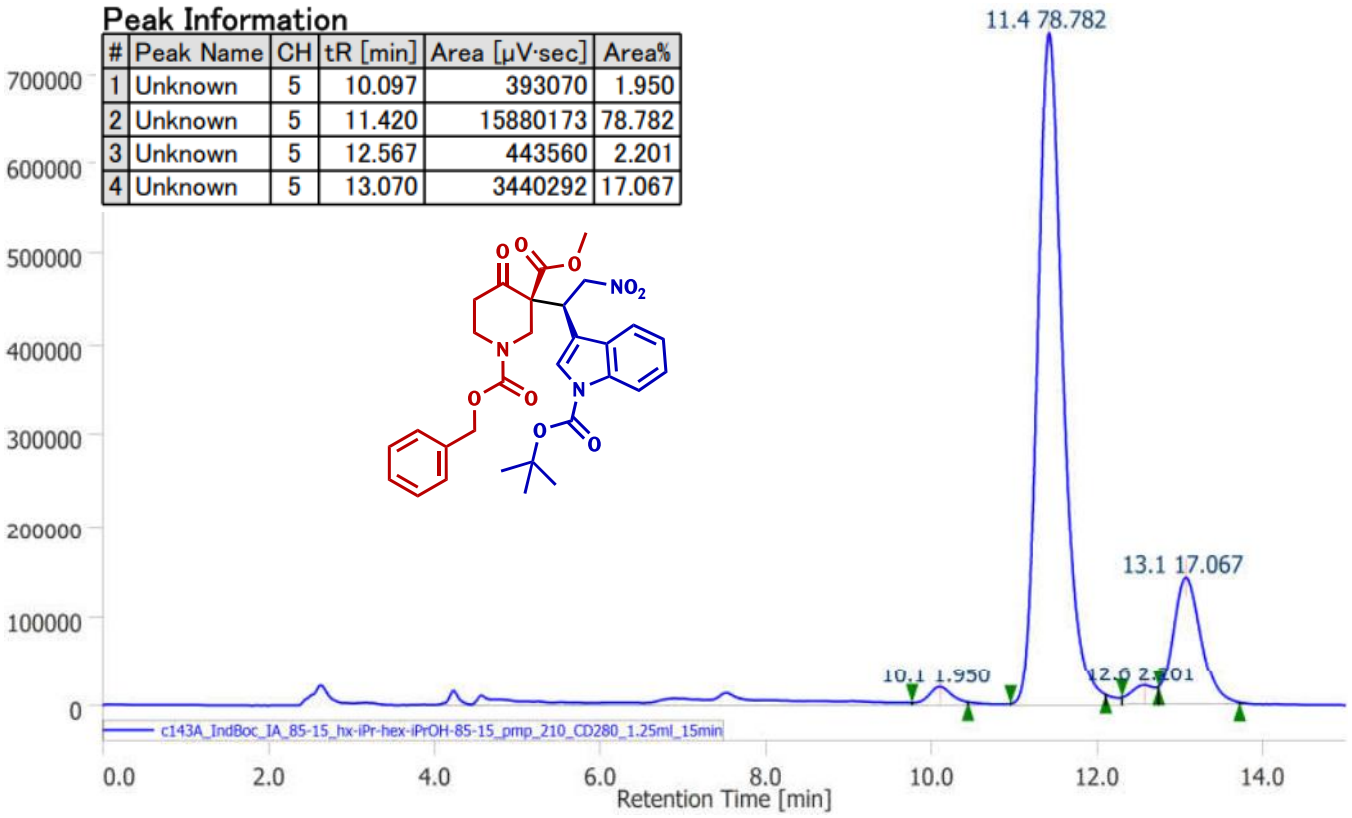


Enantiomerically enriched

Compound **3g** (74 ee, 96:4 d.r.) HPLC Chiralpak IA, hexane/isopropanol 85:15, 1.25 mL/min, 210 nm.

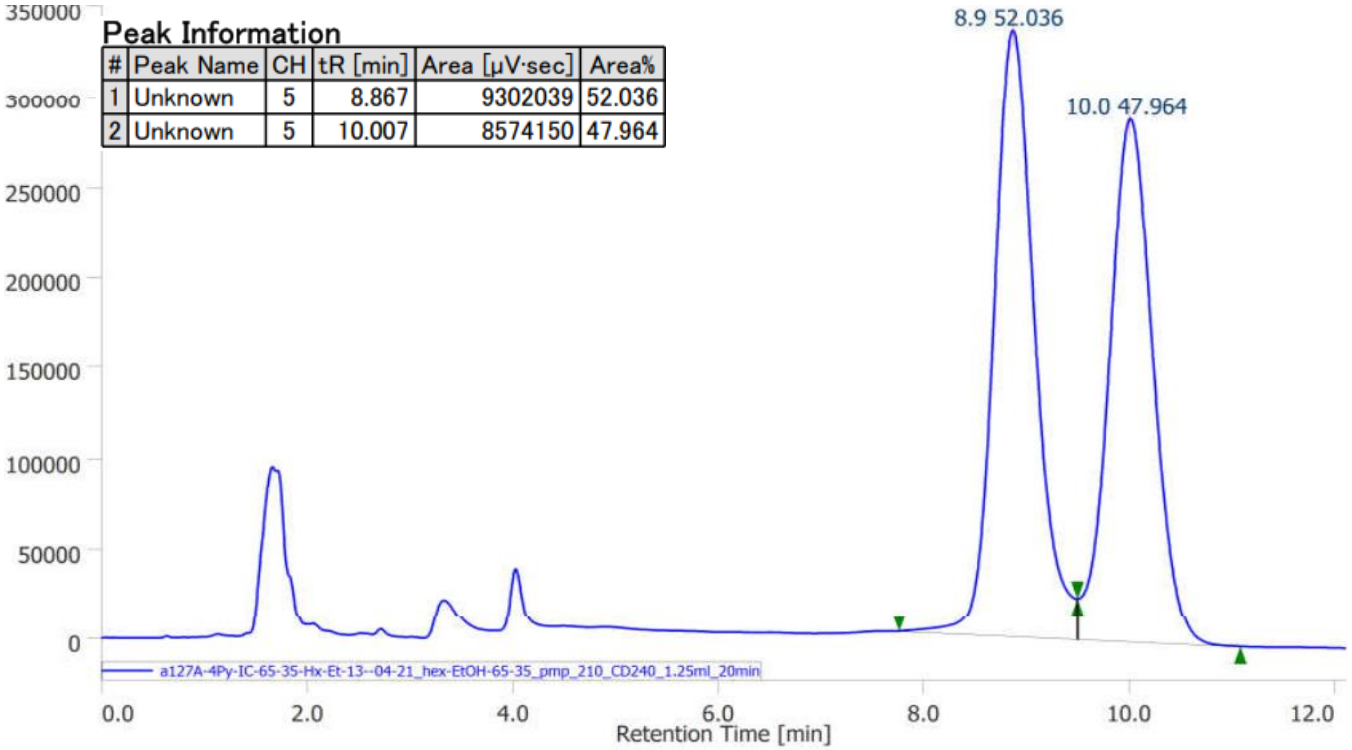


Racemic

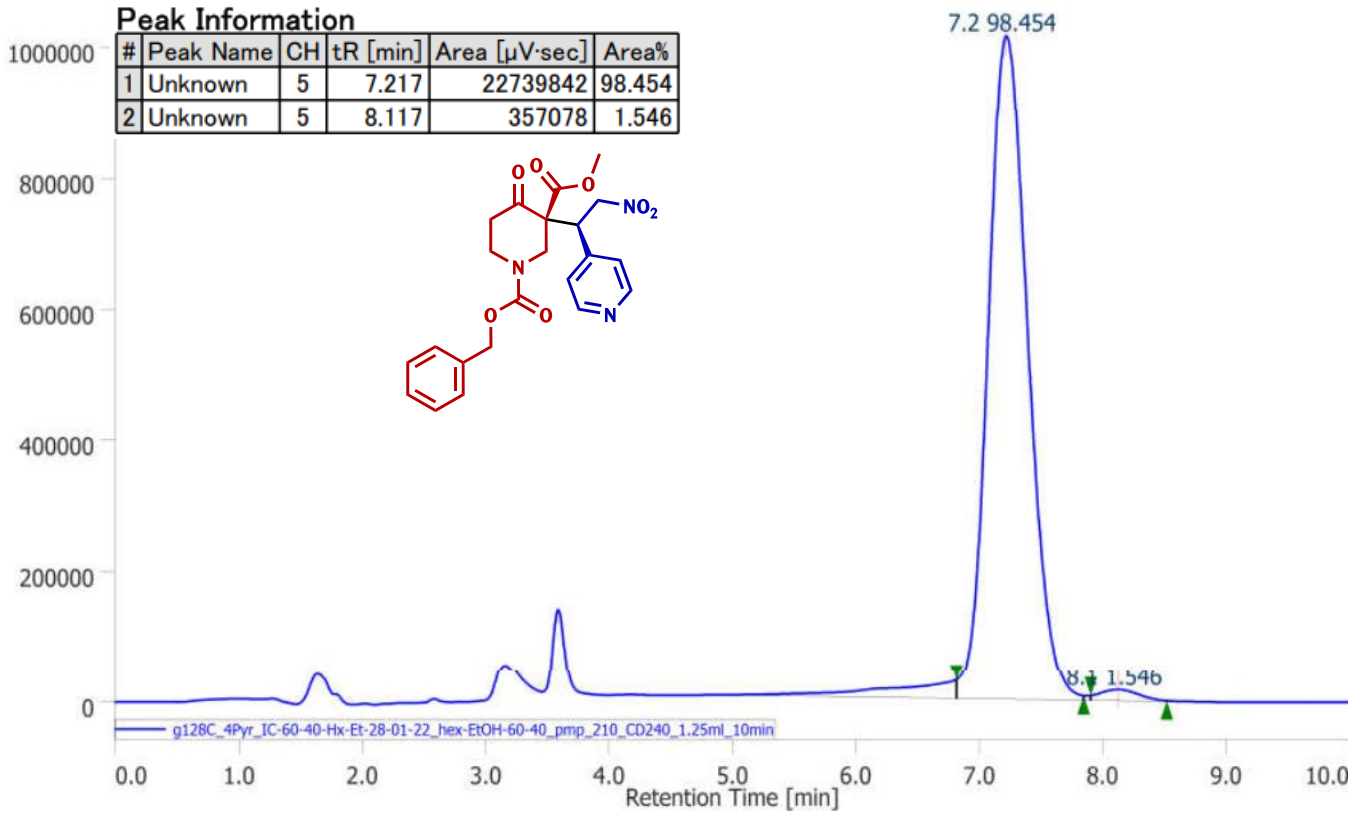


Enantiomerically enriched

Compound **3h** (97 ee, 99:1 d.r.) HPLC Chiralpak IC, hexane/EtOH 65:35, 1.25 mL/min, 210 nm.

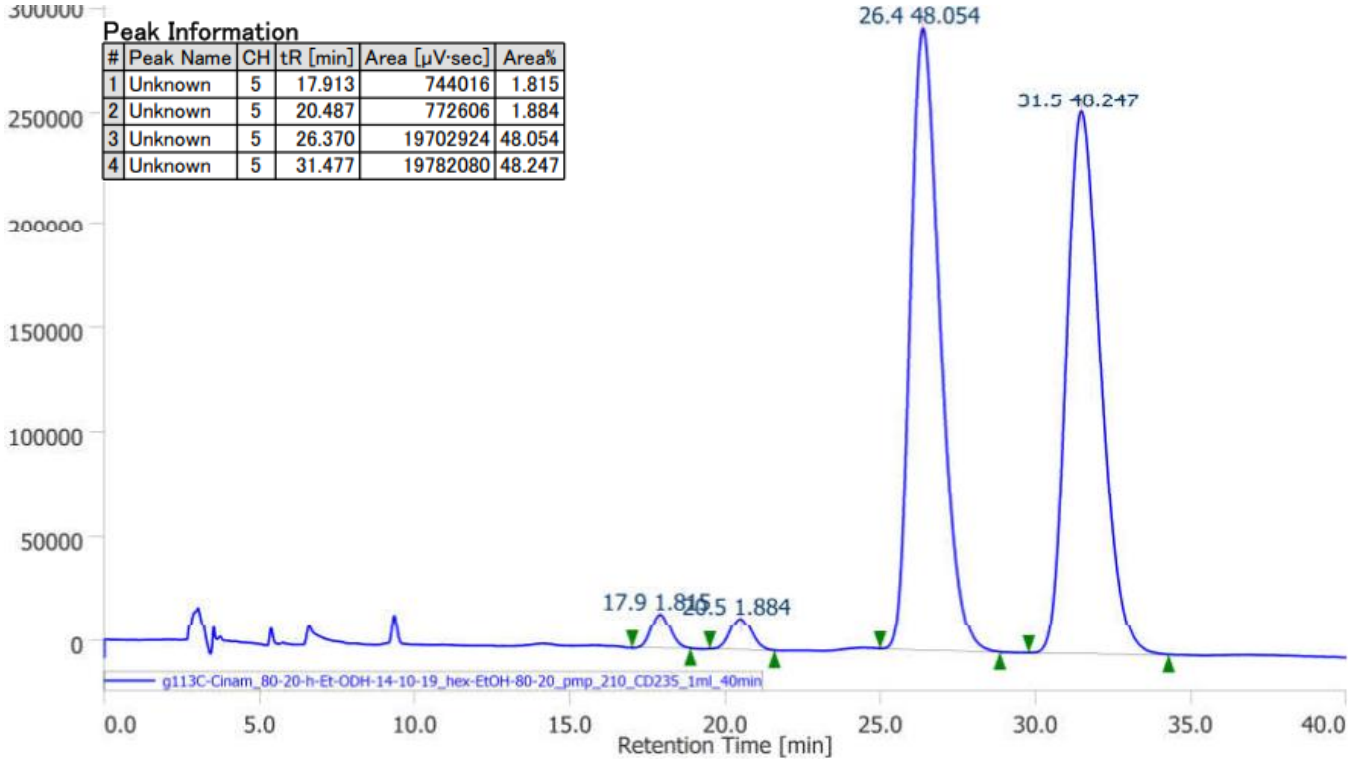


Racemic

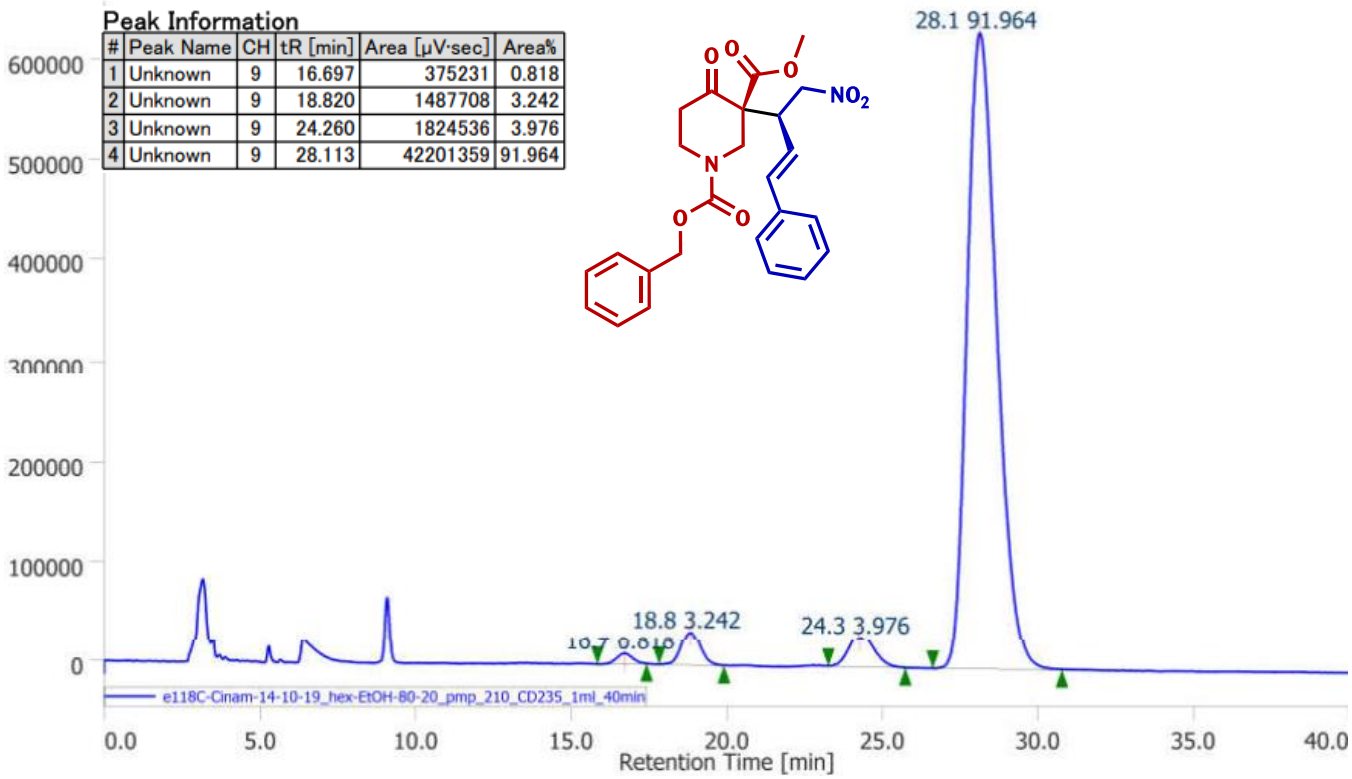


Enantiomerically enriched

Compound **3i** (92 ee, 96:4 d.r.) HPLC Chiralpak OD-H, hexane/EtOH 80:20, 1 mL/min, 210 nm.

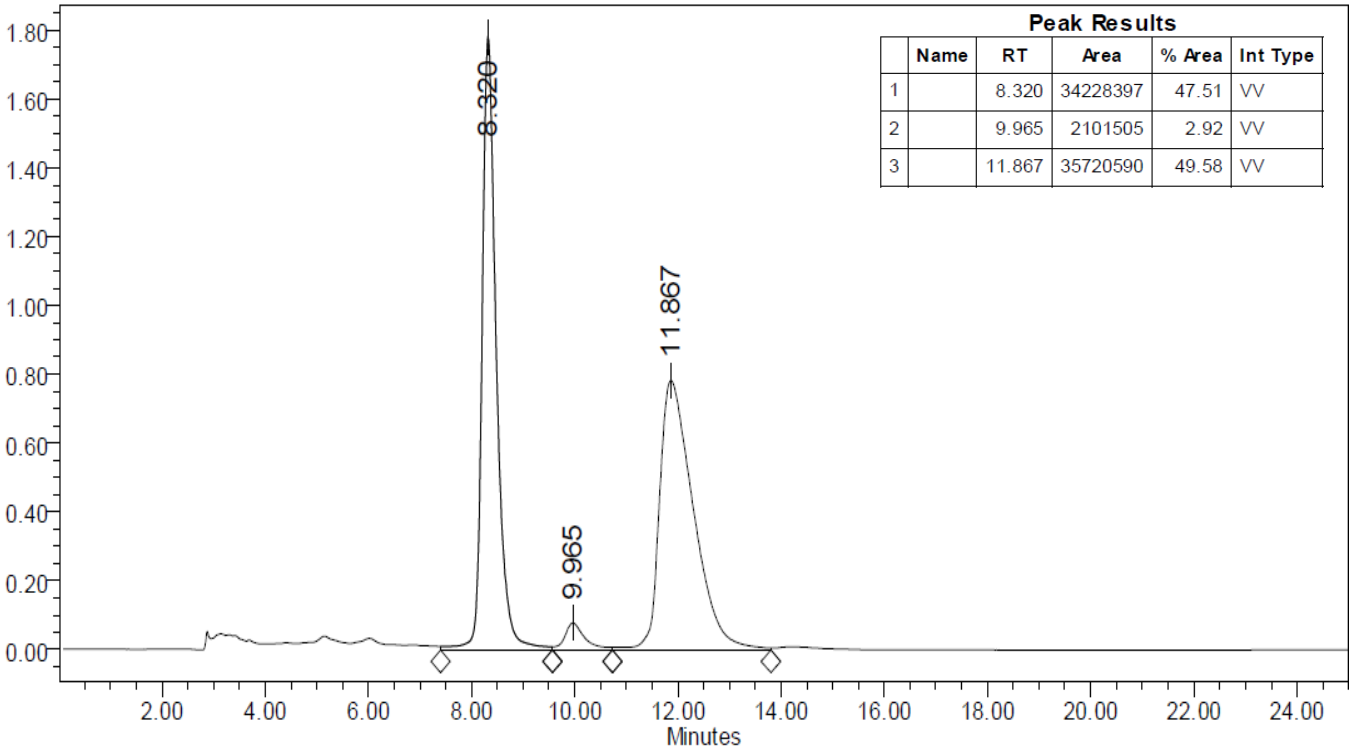


Racemic

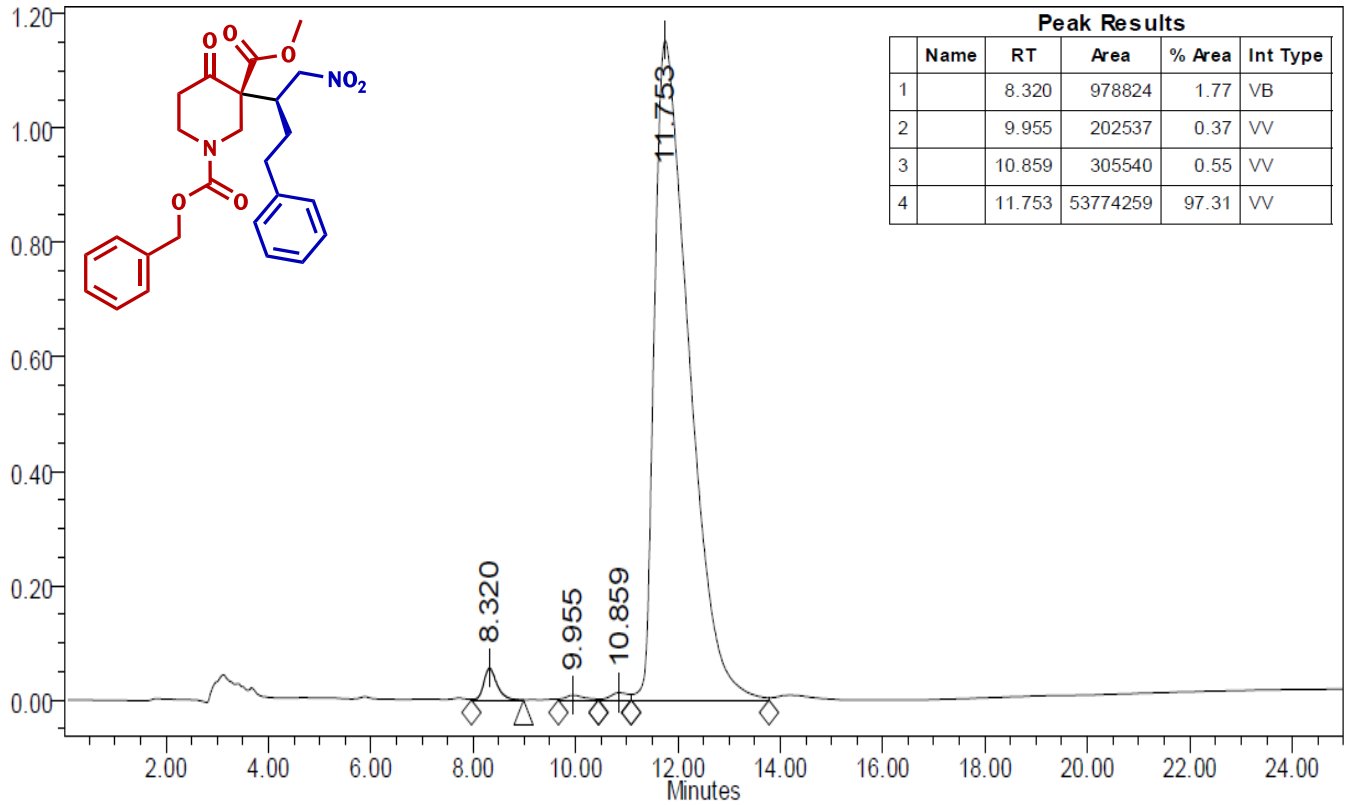


Enantiomerically enriched

Compound **3j** (94 ee, 97:3 d.r.) HPLC Chiralpak IA, hexane/EtOH 60:40, 1 mL/min, 210 nm.

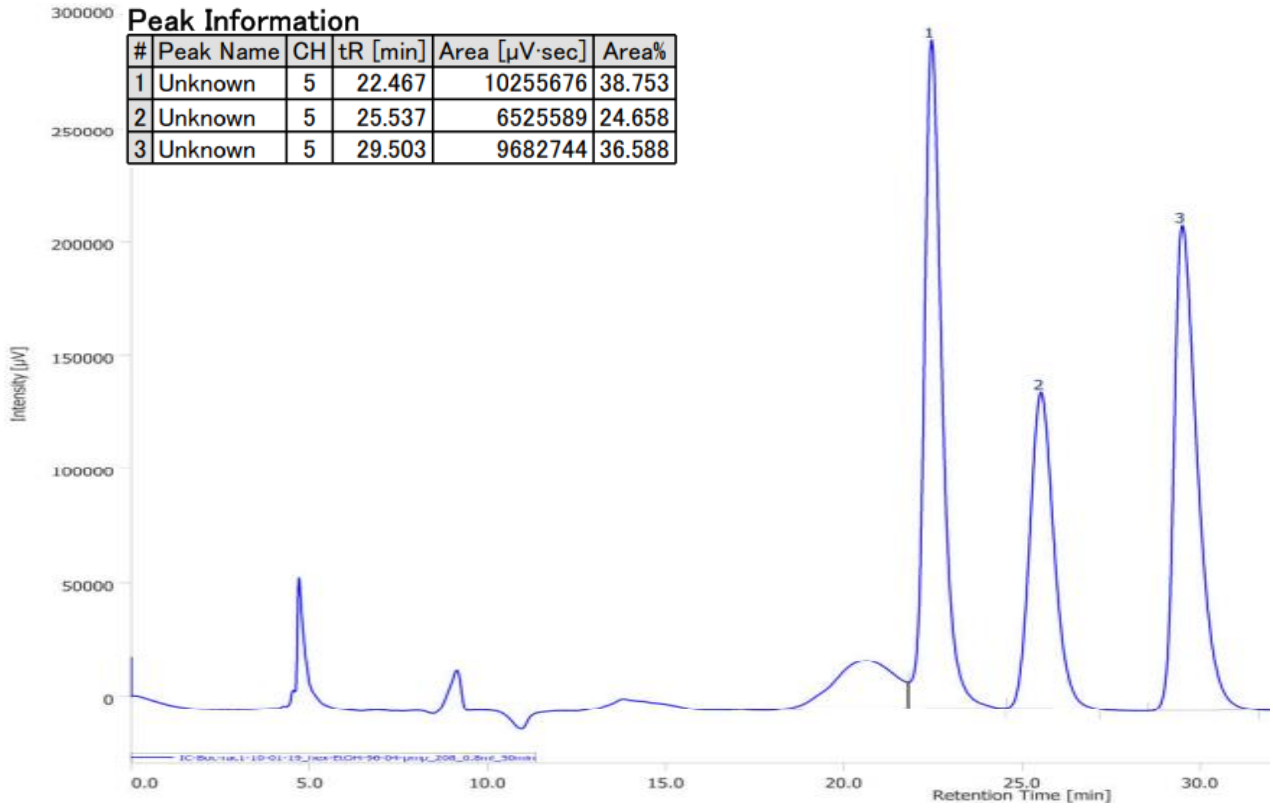


Racemic

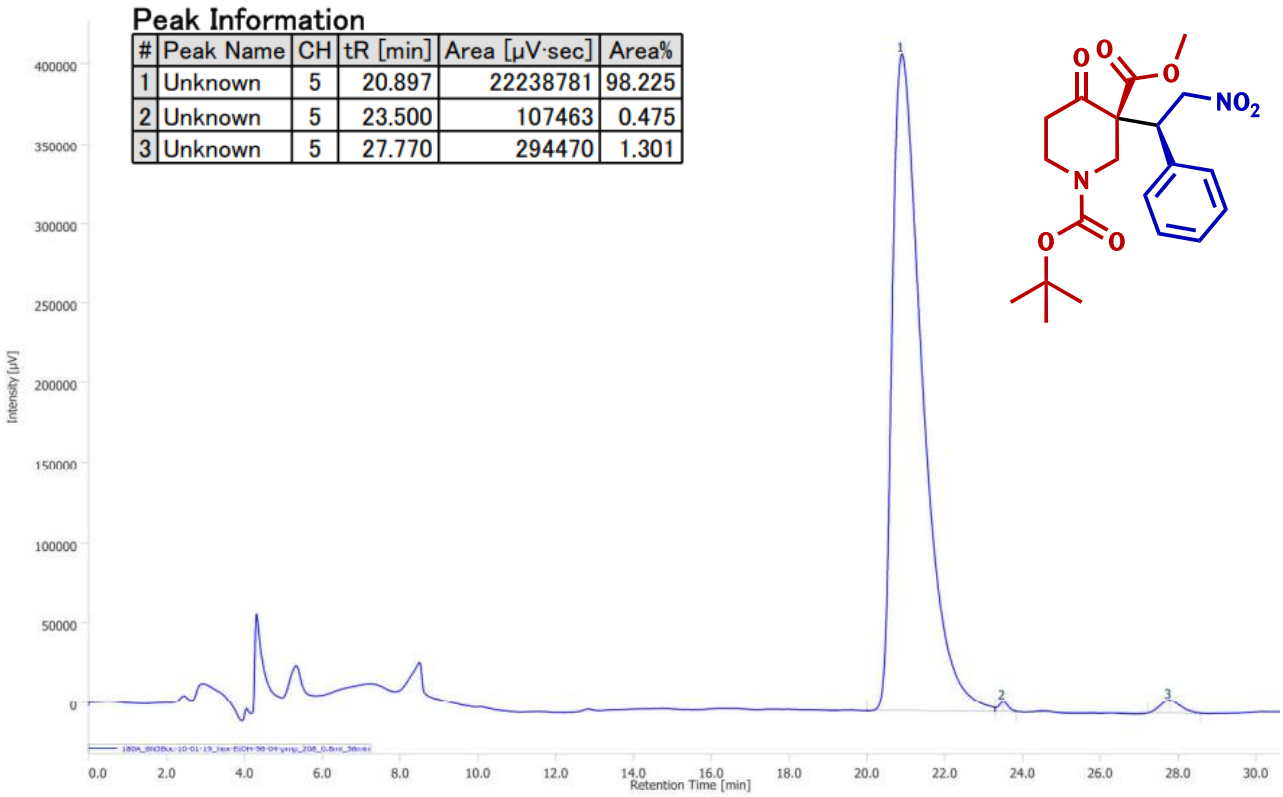


Enantiomerically enriched

Compound **3k** (97 ee, >99:1 d.r.) HPLC Chiralpak IA, hexane/EtOH 96:04, 0.8 mL/min, 208 nm.

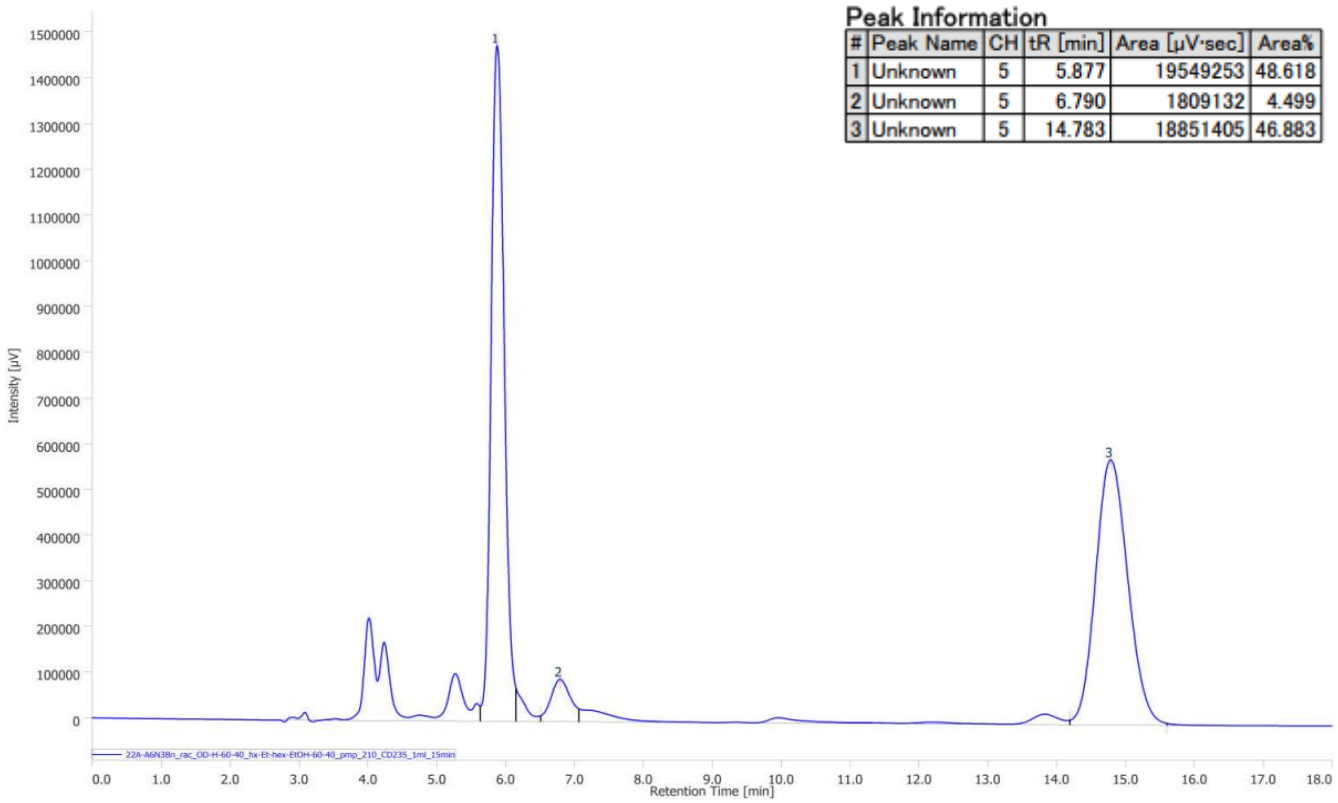


Racemic

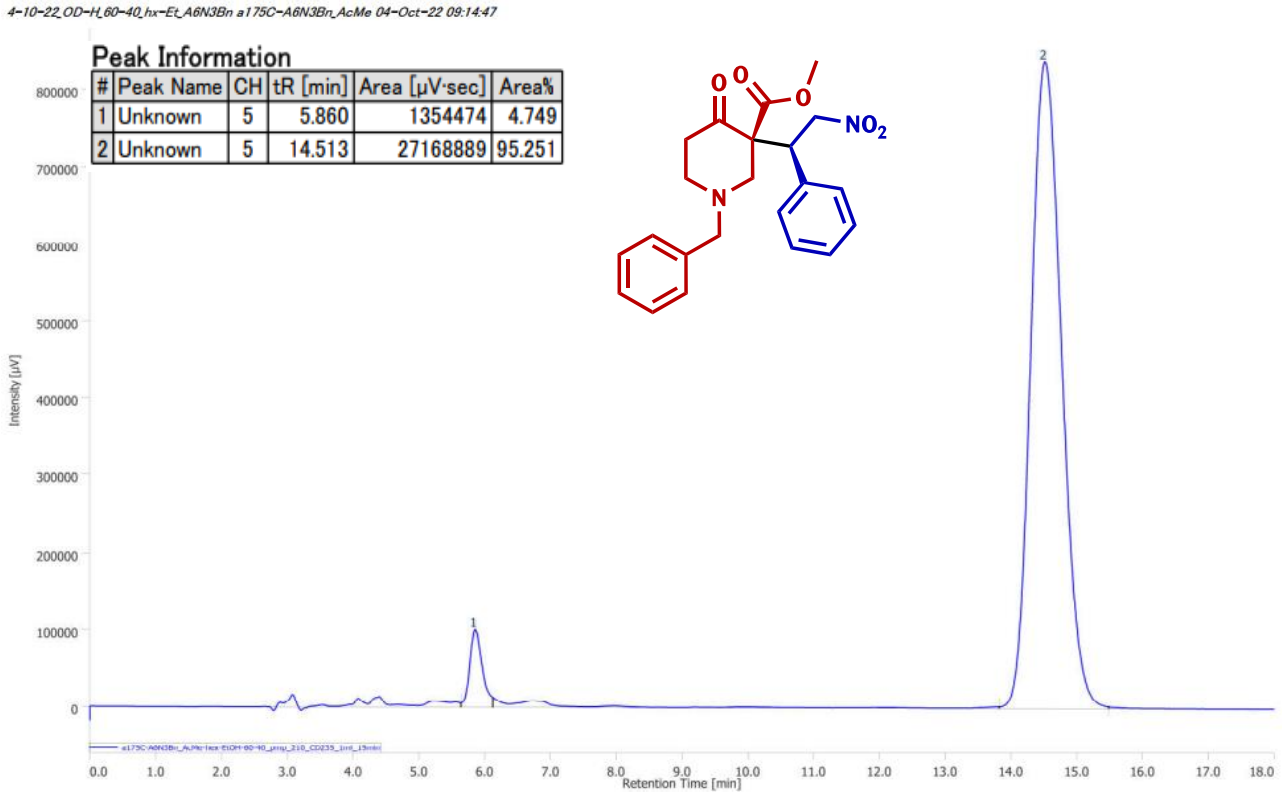


Enantiomerically enriched

Compound **3l** (90 ee, 99:1 d.r.) HPLC Chiralpak OD-H, hexane/EtOH 60:40, 1 mL/min, 210 nm.

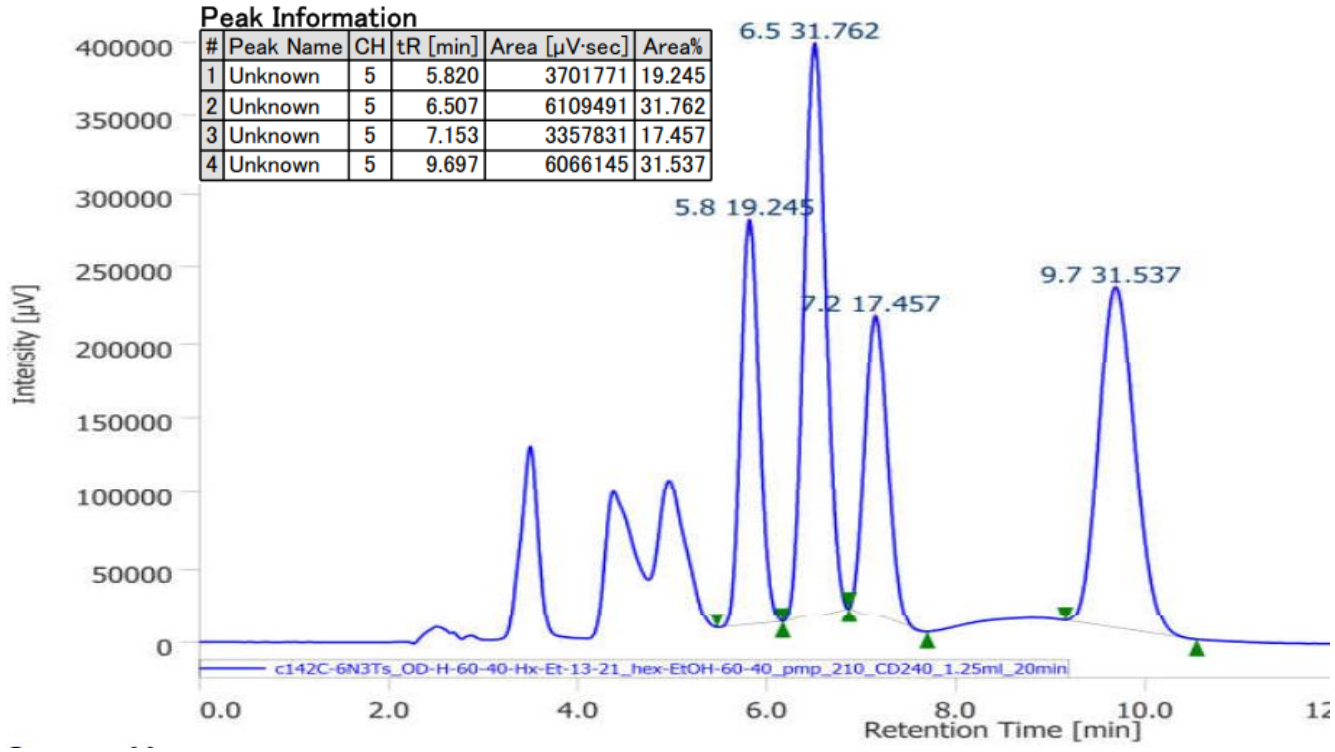


Racemic

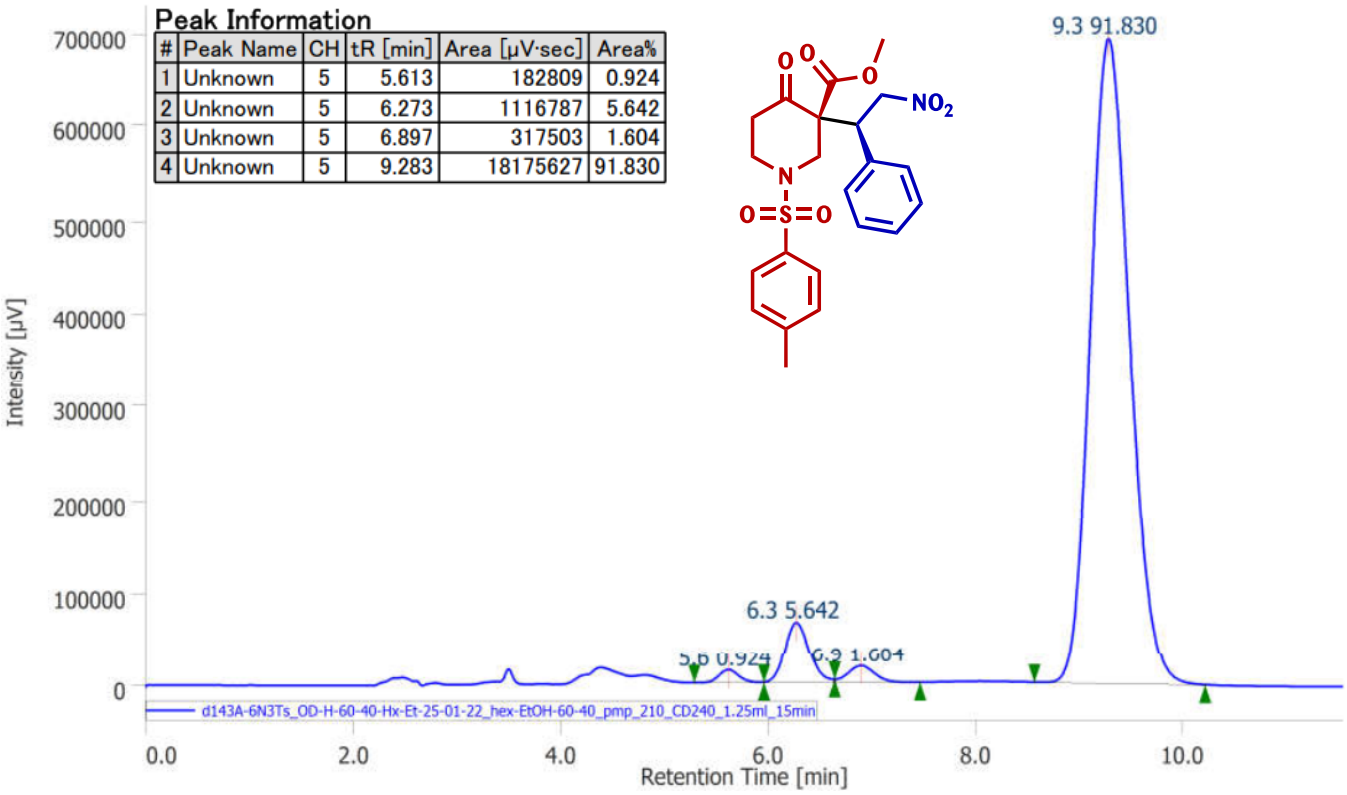


Enantiomerically enriched

Compound **3m** (88 ee, 97:3 d.r.) HPLC Chiralpak OD-H, hexane/EtOH 60:40, 1.25 mL/min, 210 nm.



Racemic

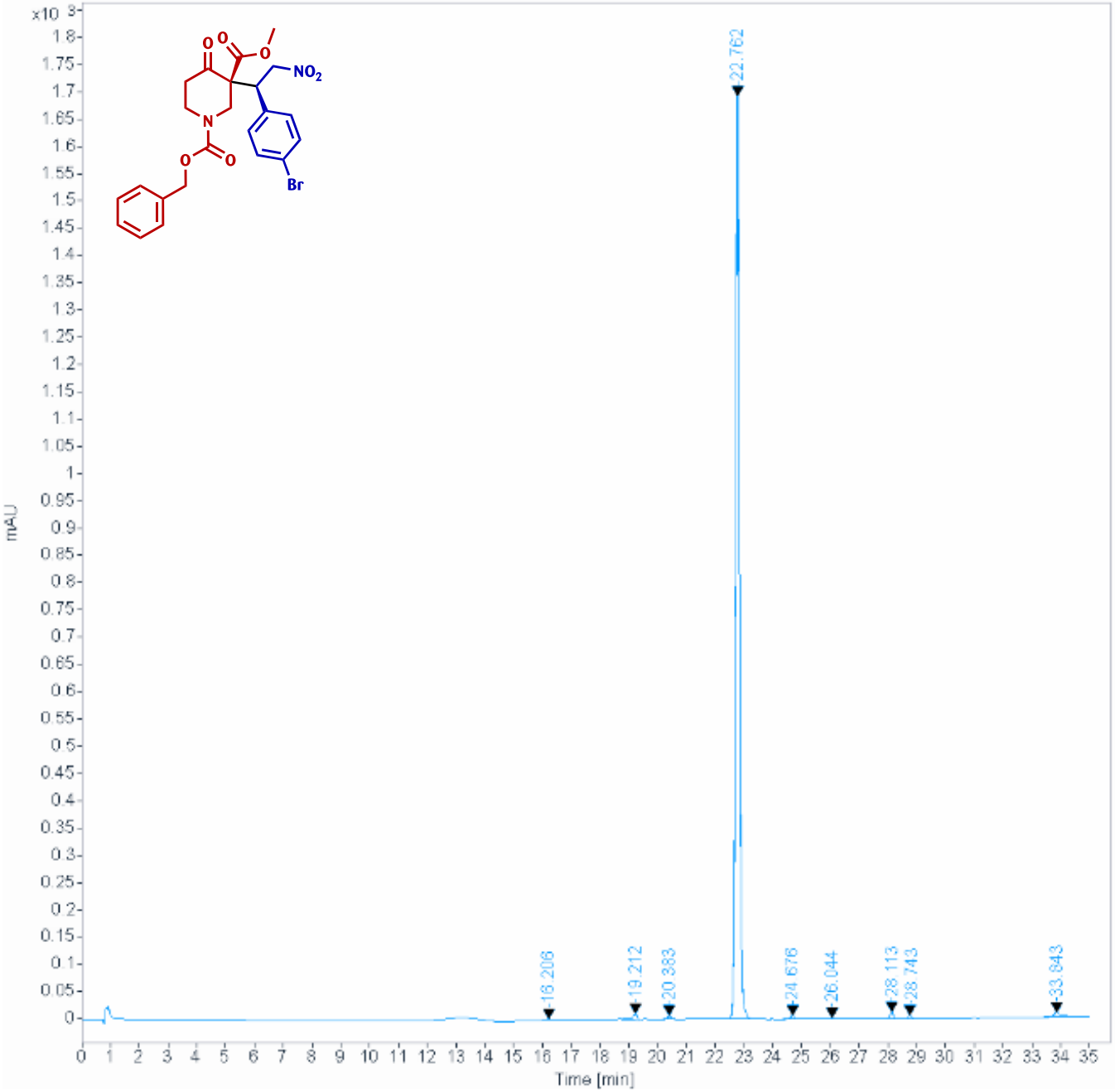


Enantiomerically enriched

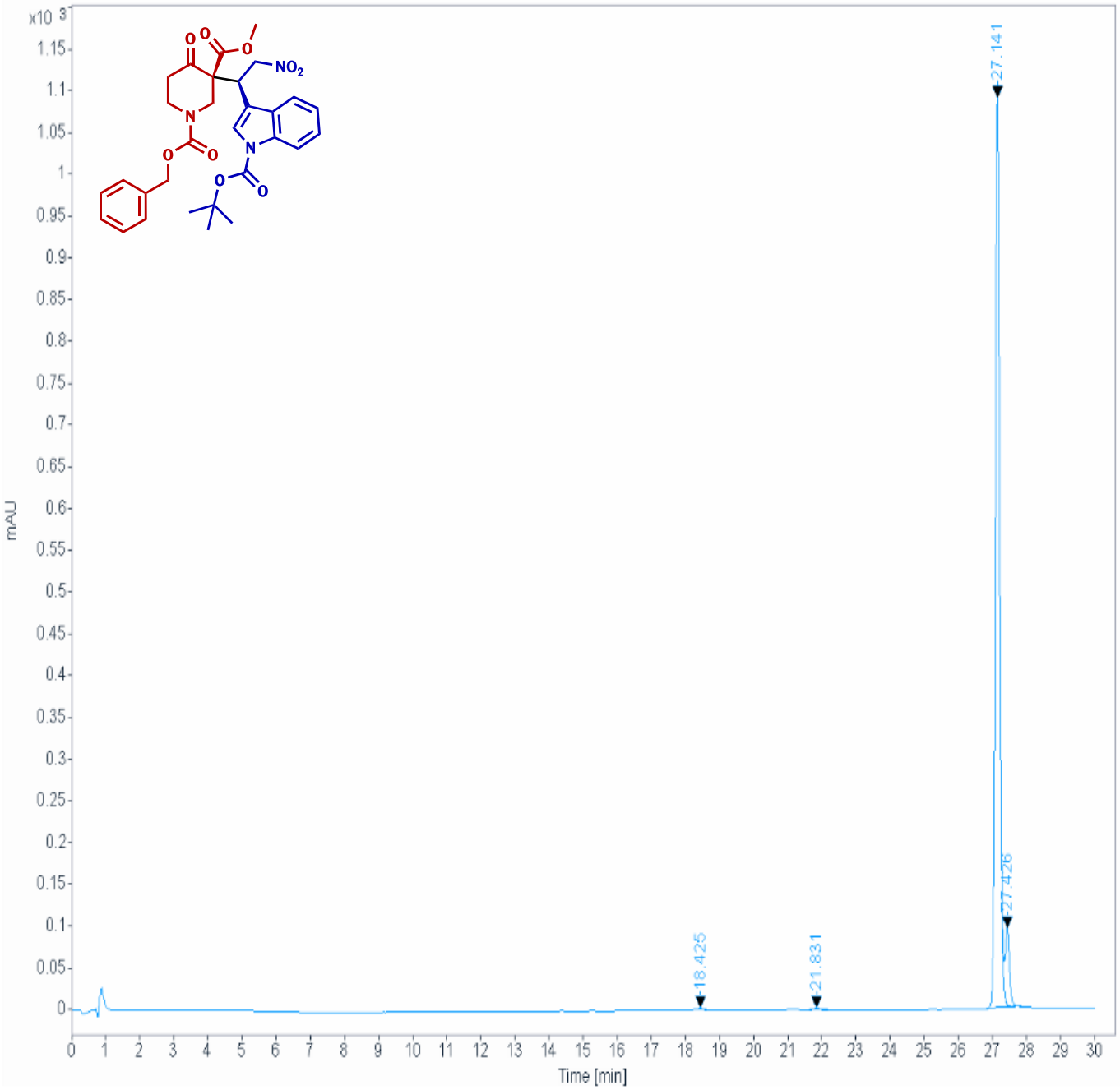
7. Inverse-phase HPLC chromatograms

Purity for compounds **3d, 3g, 3h**, and **3j** was assessed by inverse-phase HPLC using the following conditions: Eclipse XDB-C18 5.0 x 2.1 mm, water/acetonitrile gradient: 9:1 for 25 min, then pure acetonitrile; flow = 0.2 mL/min, λ = 220 nm.

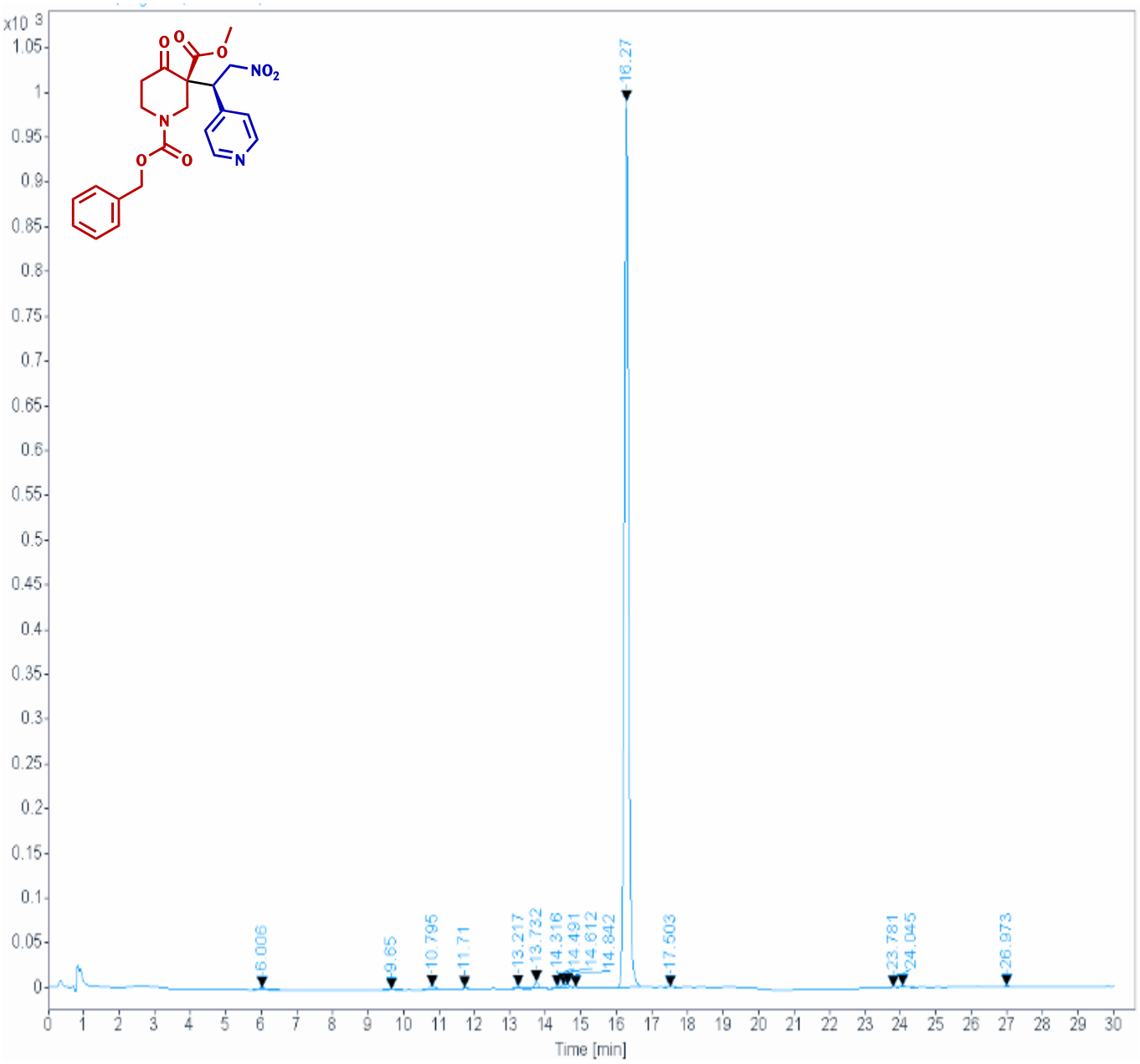
Compound 3d:



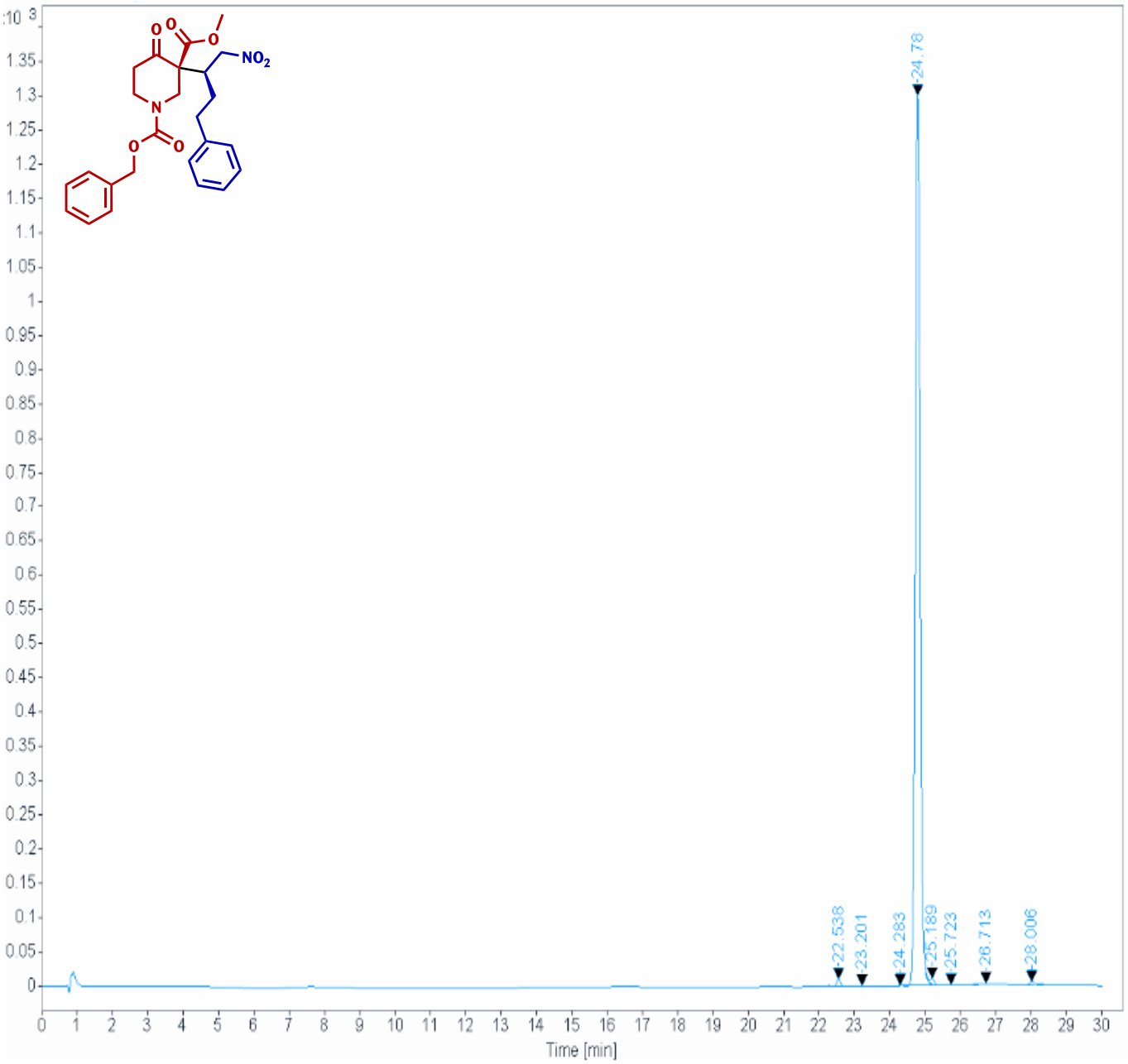
Compound 3g:



Compound 3h:

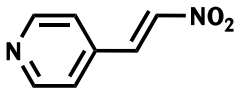

x10 3
1.05
1
0.95
0.9
0.85
0.8
0.75
0.7
0.65
0.6
0.55
0.5
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
O
O
O
NO2
N
O
O
N
16.27
6.006
9.65
10.795
11.71
13.217
13.732
14.316
14.491
14.612
14.842
17.503
23.781
24.045
26.973
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30
Time [min]

Compound 3j:

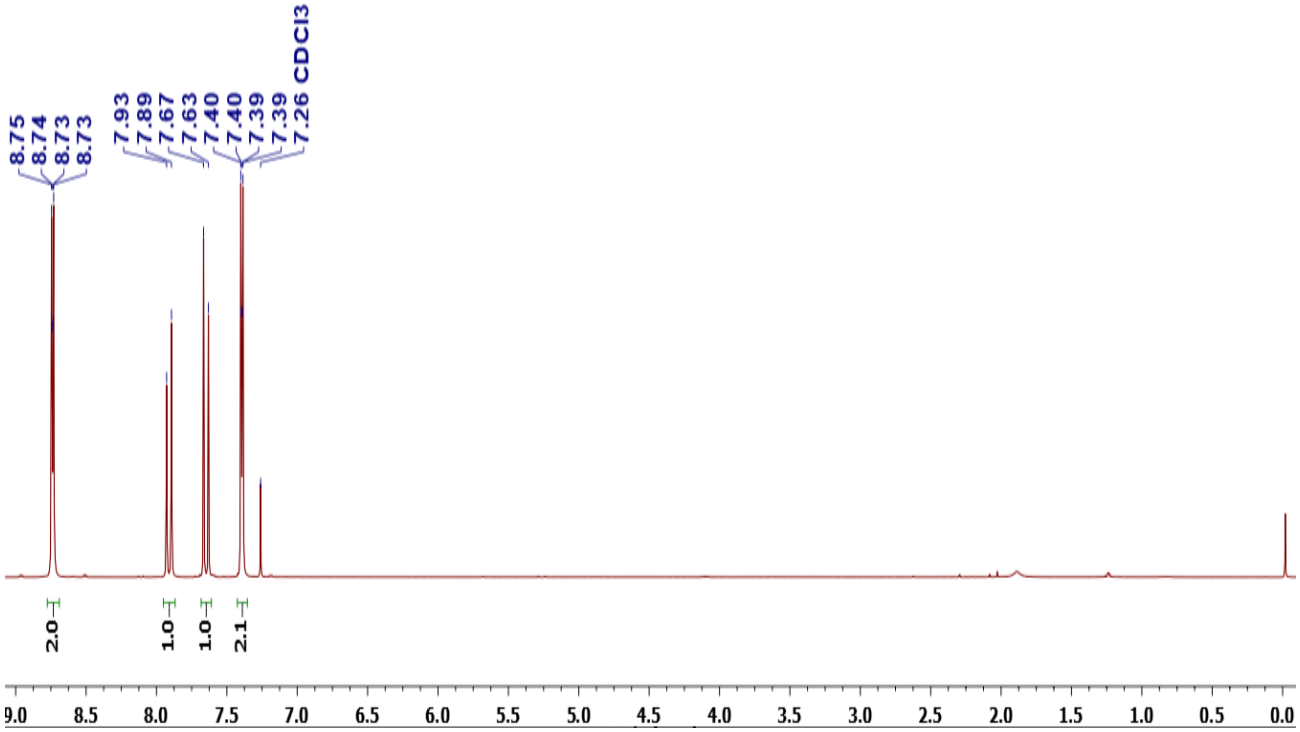

10 3
1.35
1.3
1.25
1.2
1.15
1.1
1.05
1
0.95
0.9
0.85
0.8
0.75
0.7
0.65
0.6
0.55
0.5
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
O
O
O
NO2
N
O
O
24.78
22.538
23.201
24.283
25.189
25.723
26.713
28.006
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30
Time [min]

8. NMR Spectra

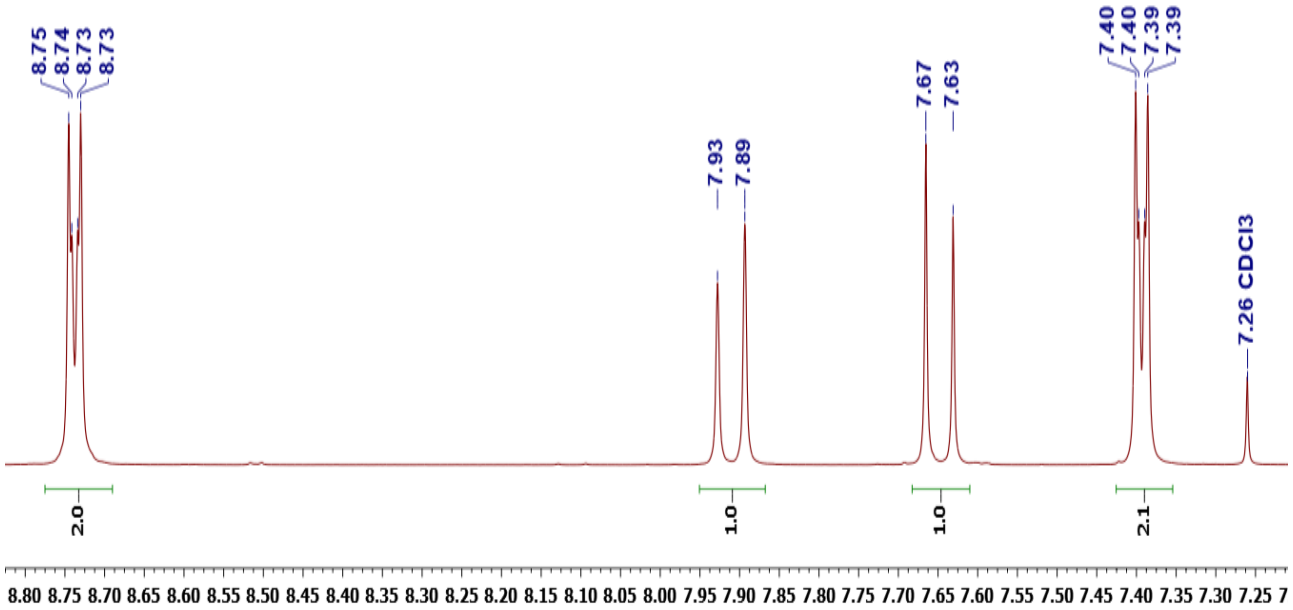
8.1 Nitroalkenes



Compound **2h**.

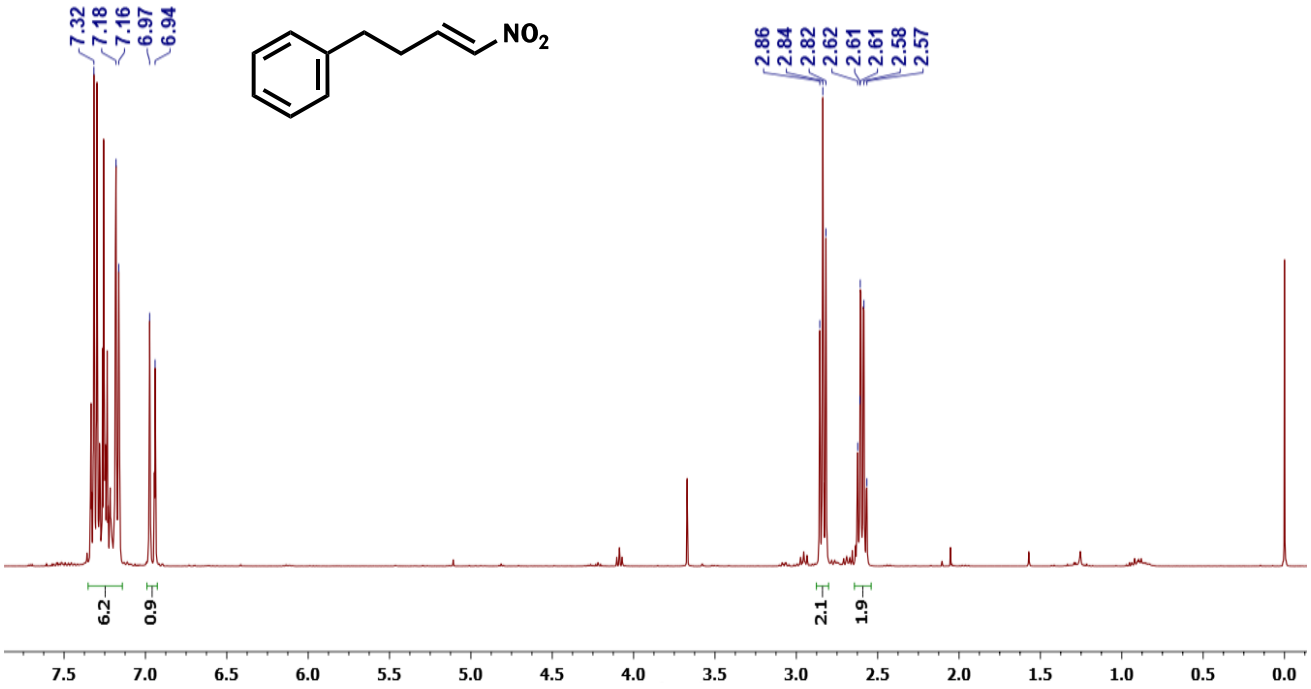


^{1}H NMR, $CDCl_3$, 400 MHz @ 25 °C

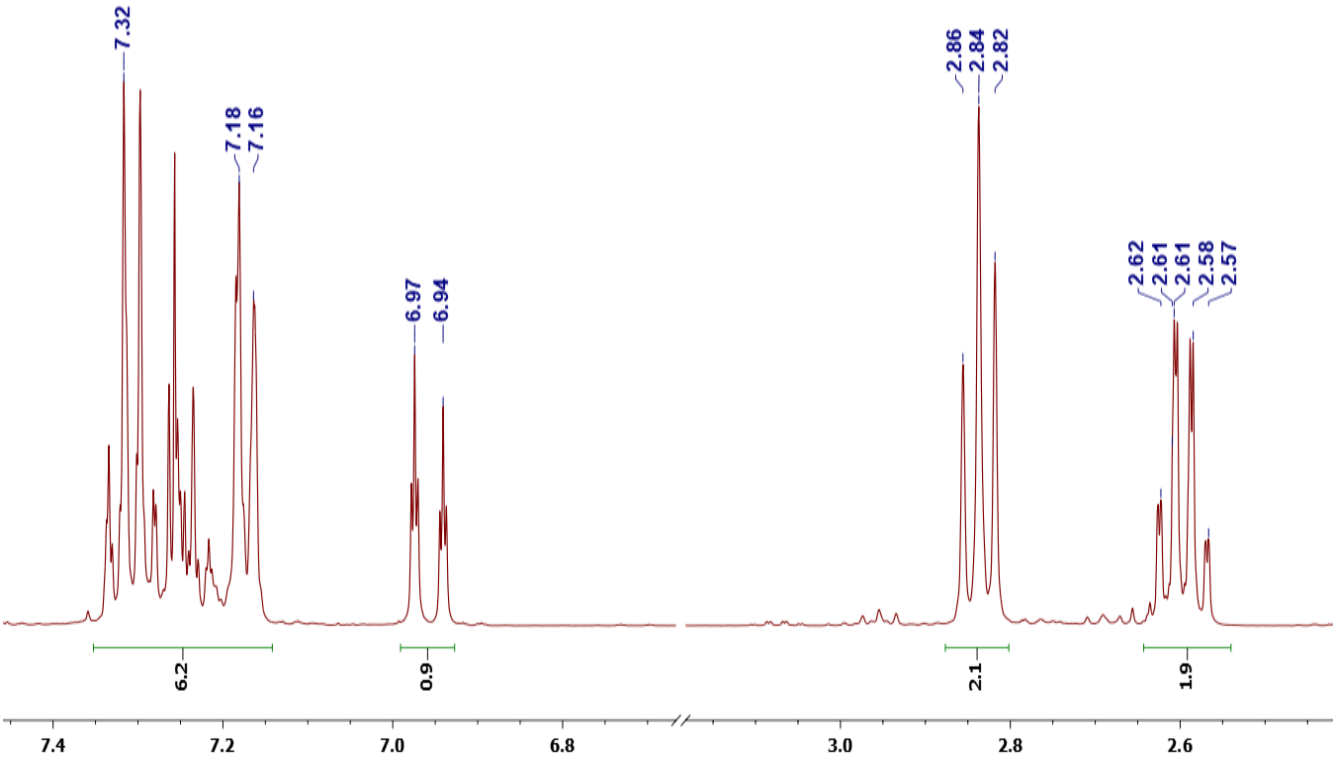


^{1}H NMR, $CDCl_3$, 400 MHz @ 25 °C

Compound **2j**.



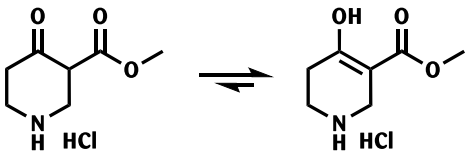
^{1}H NMR, $CDCl_3$, 400 MHz @ 25 °C



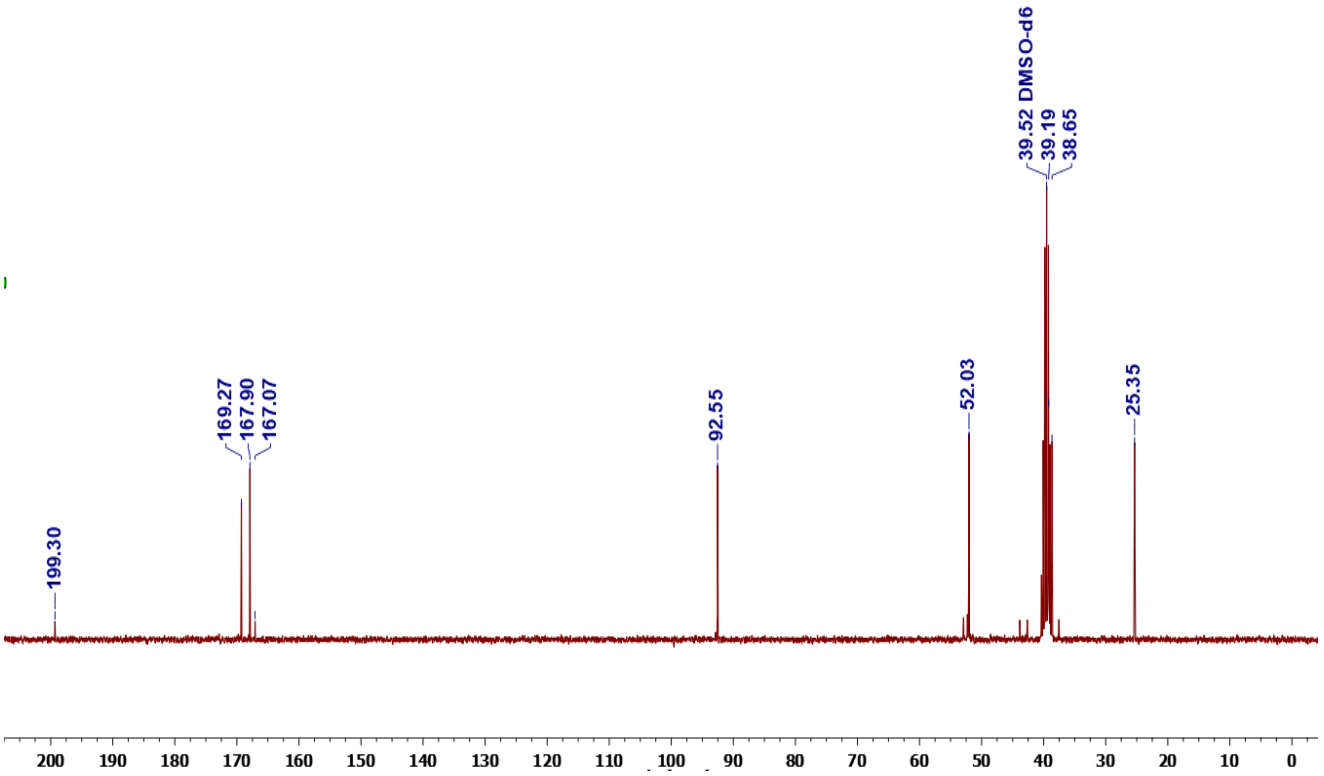
^{1}H NMR, $CDCl_3$, 400 MHz @ 25 °C

8.2 β-ketoesters

Compound **S1**

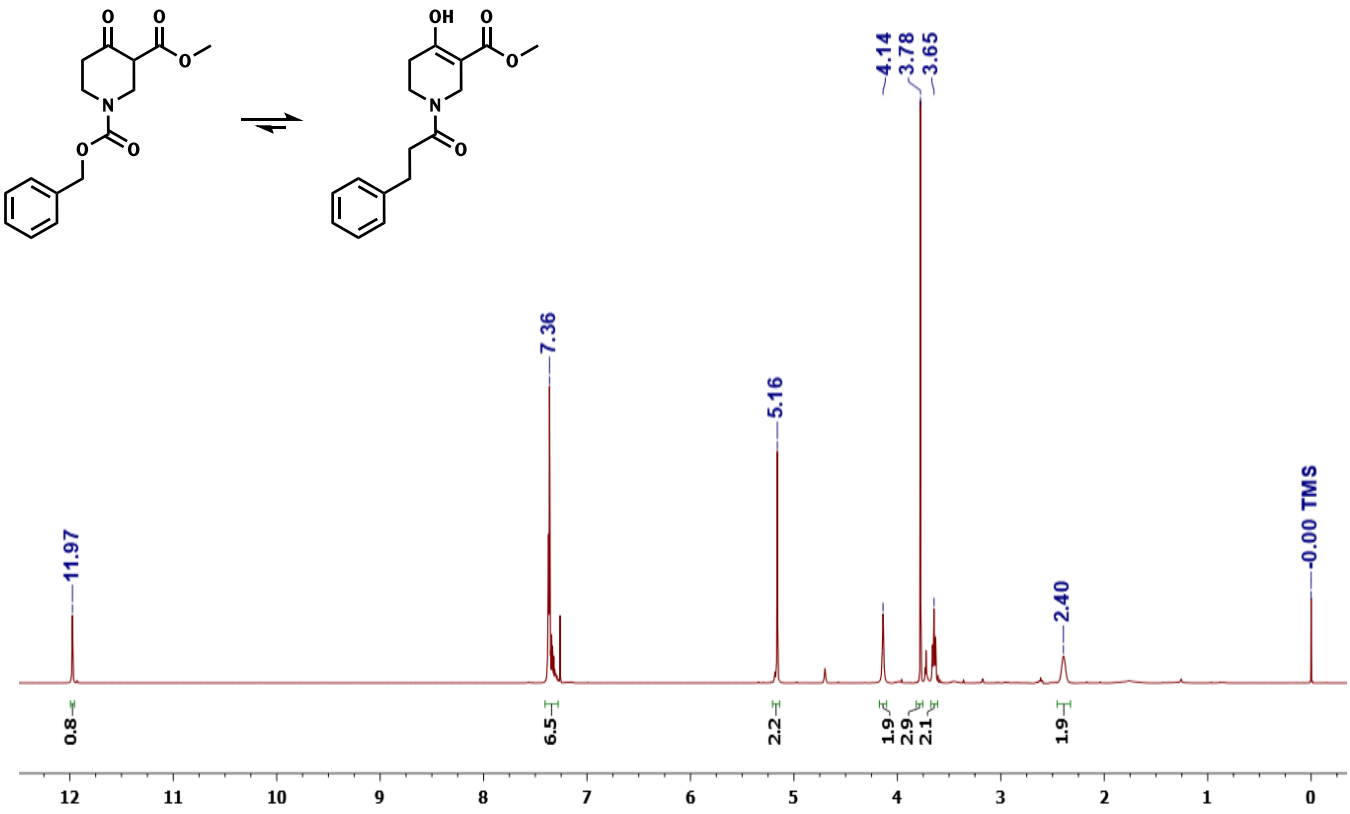


^{1}H NMR, DMSO-*d6*, 300 MHz @ 25 °C

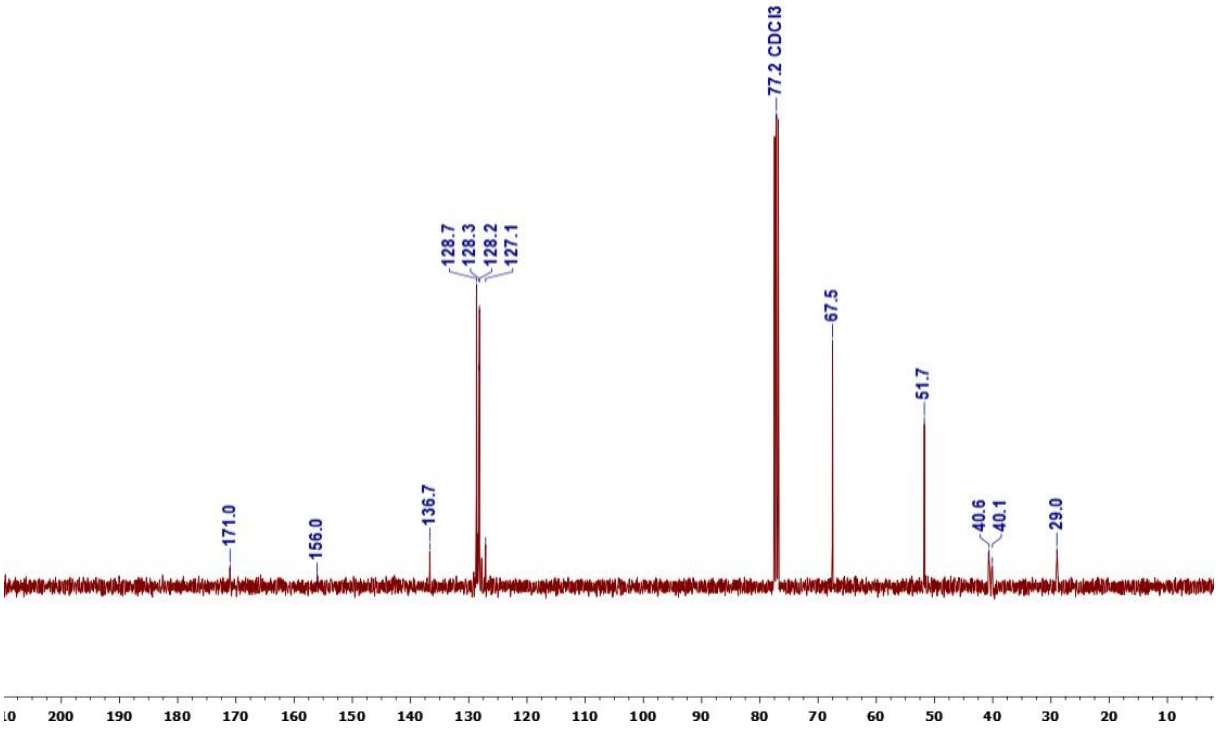


^{13}C NMR, DMSO-d6, 75 MHz @ 25 °C

Compound **1**

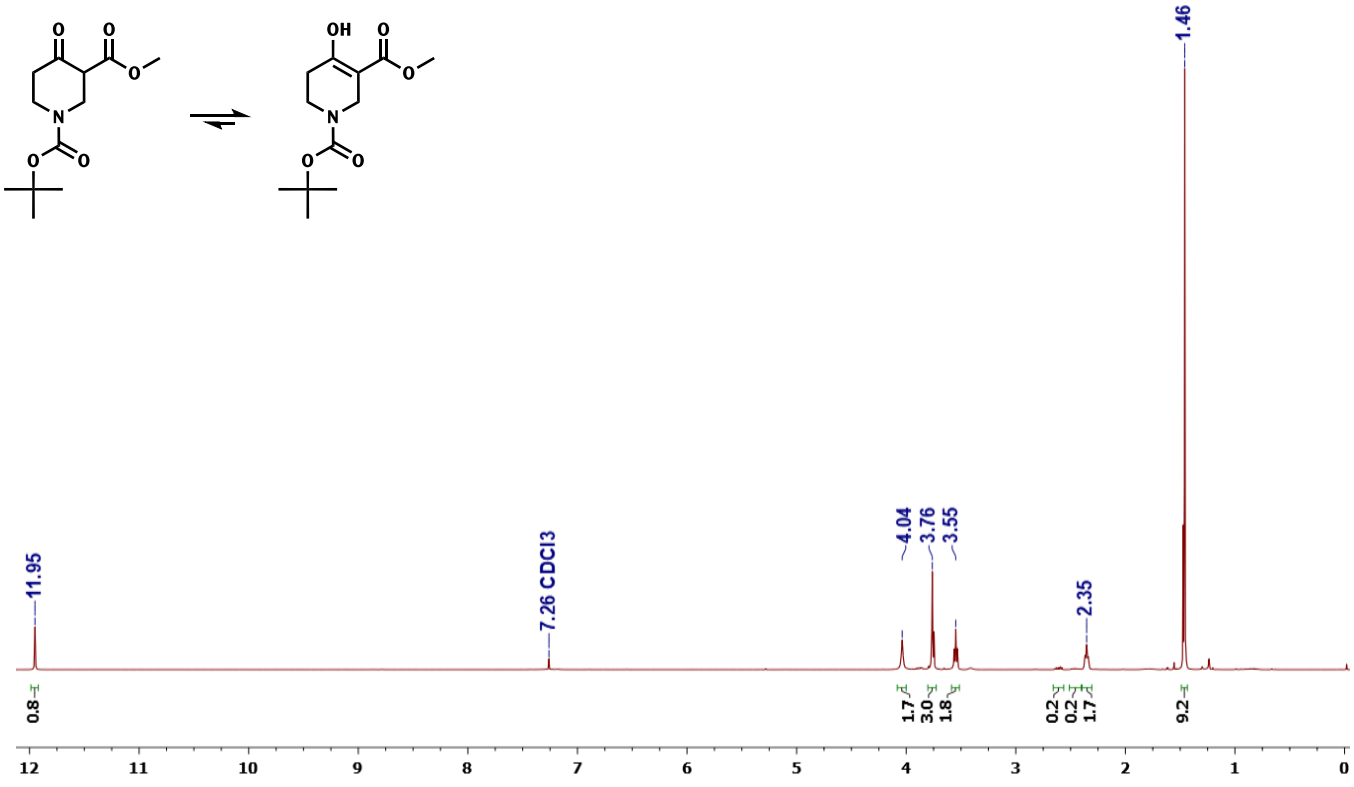


^{1}H NMR, $CDCl_3$, 300 MHz @ 25 °C

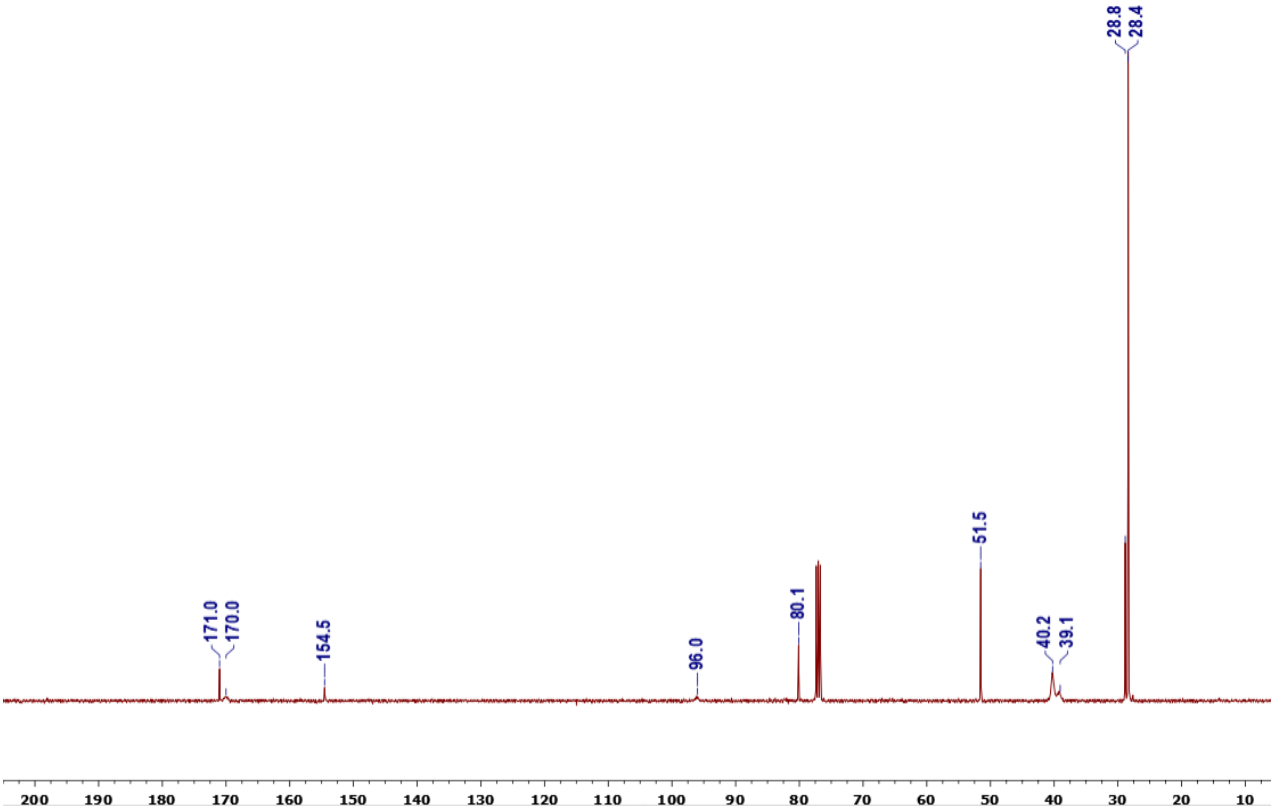


^{13}C NMR, $CDCl_3$, 100 MHz @ 25 °C

Compound **1-Boc**

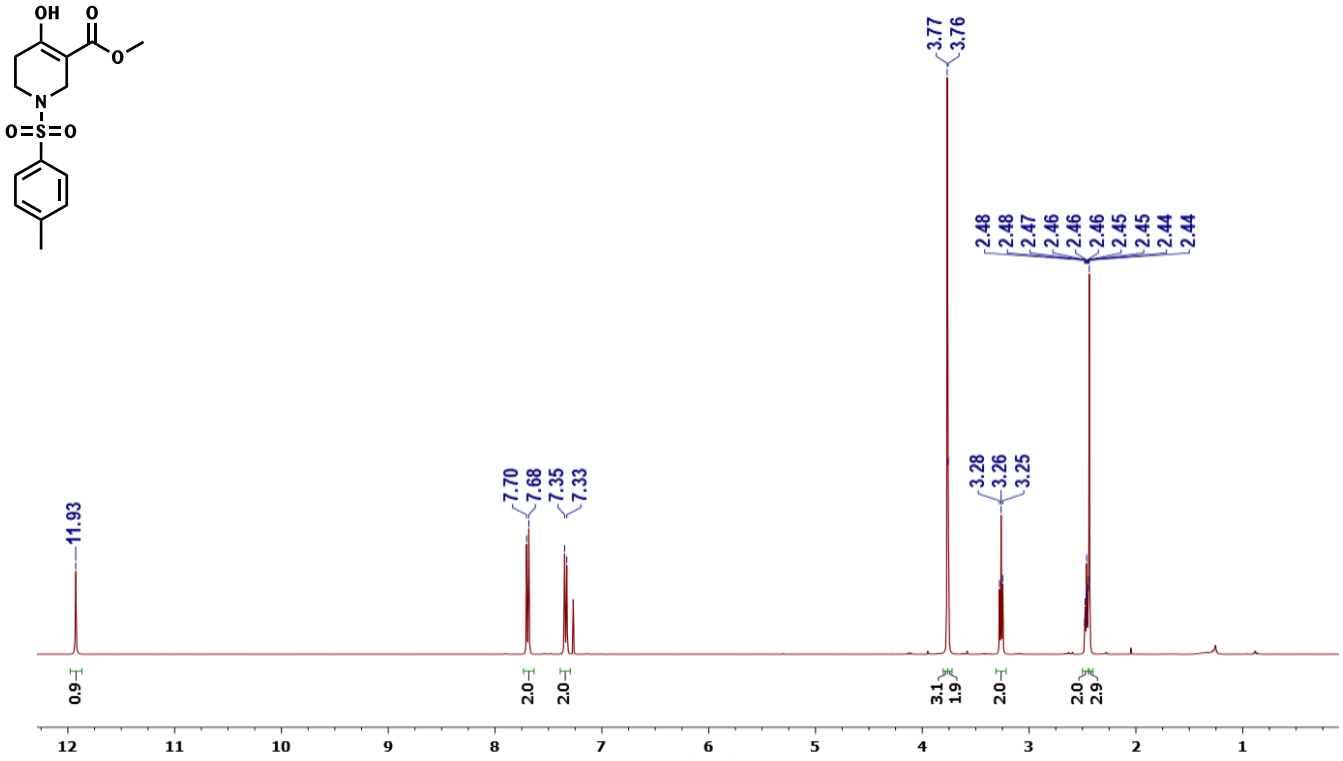


^{1}H NMR, $CDCl_3$, 300 MHz @ 25 °C

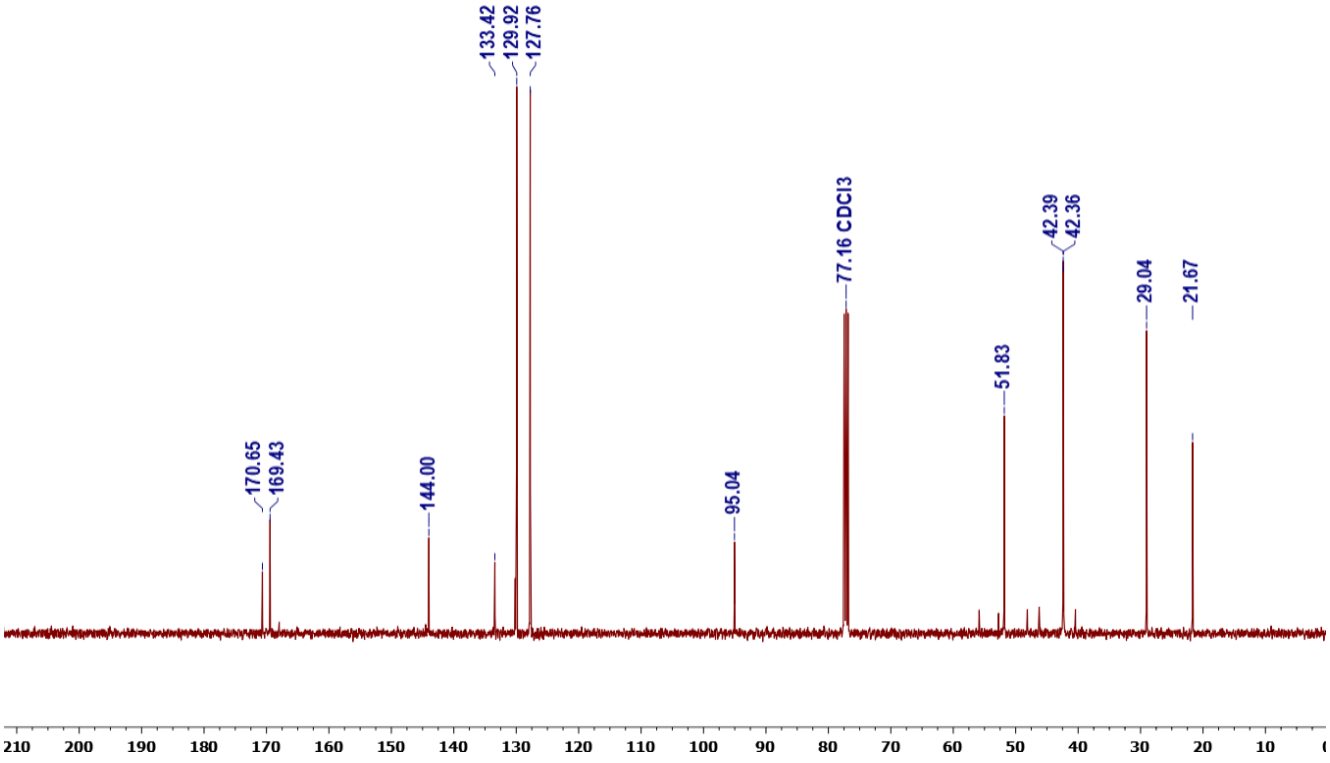


^{13}C NMR, $CDCl_3$, 100 MHz @ 25 °C

Compound **1-Ts.**

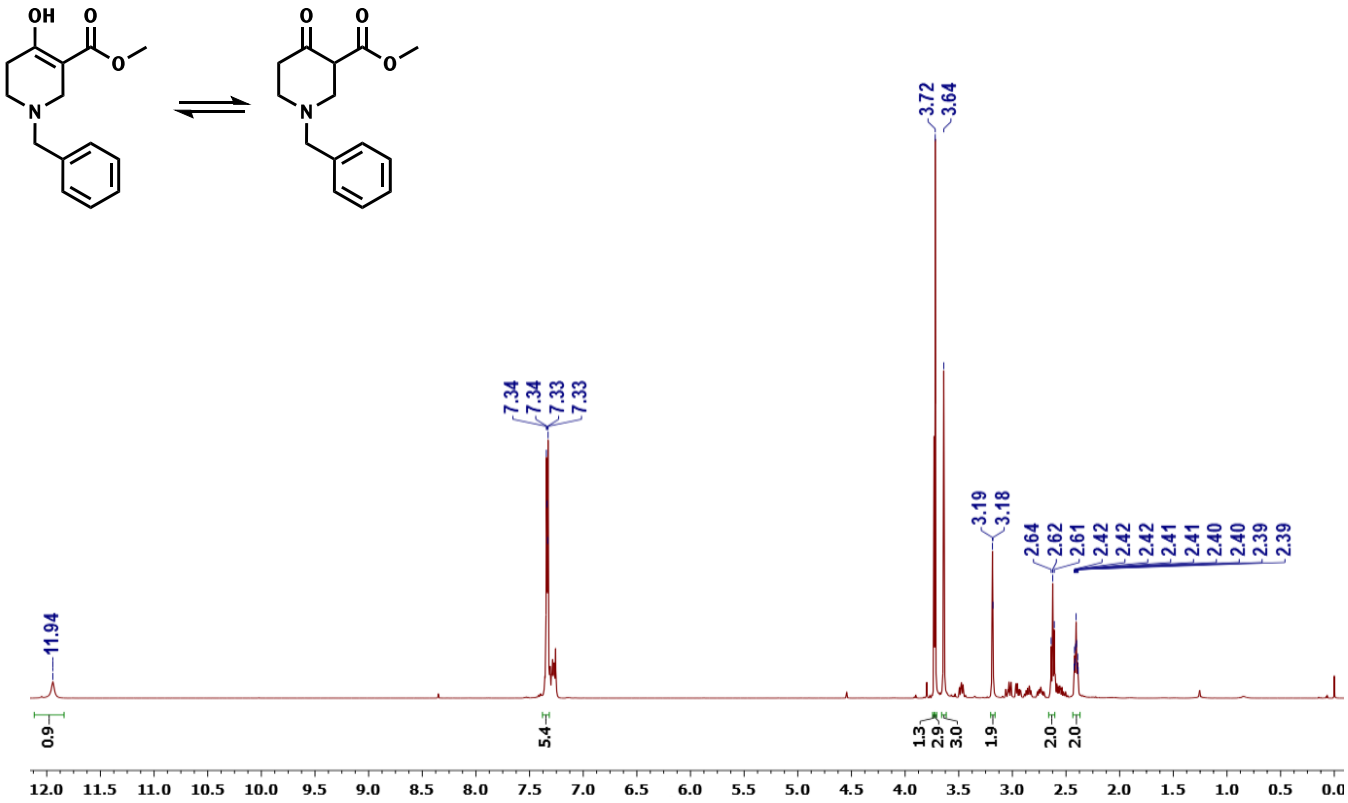


^{1}H NMR, $CDCl_3$, 400 MHz @ 25 °C

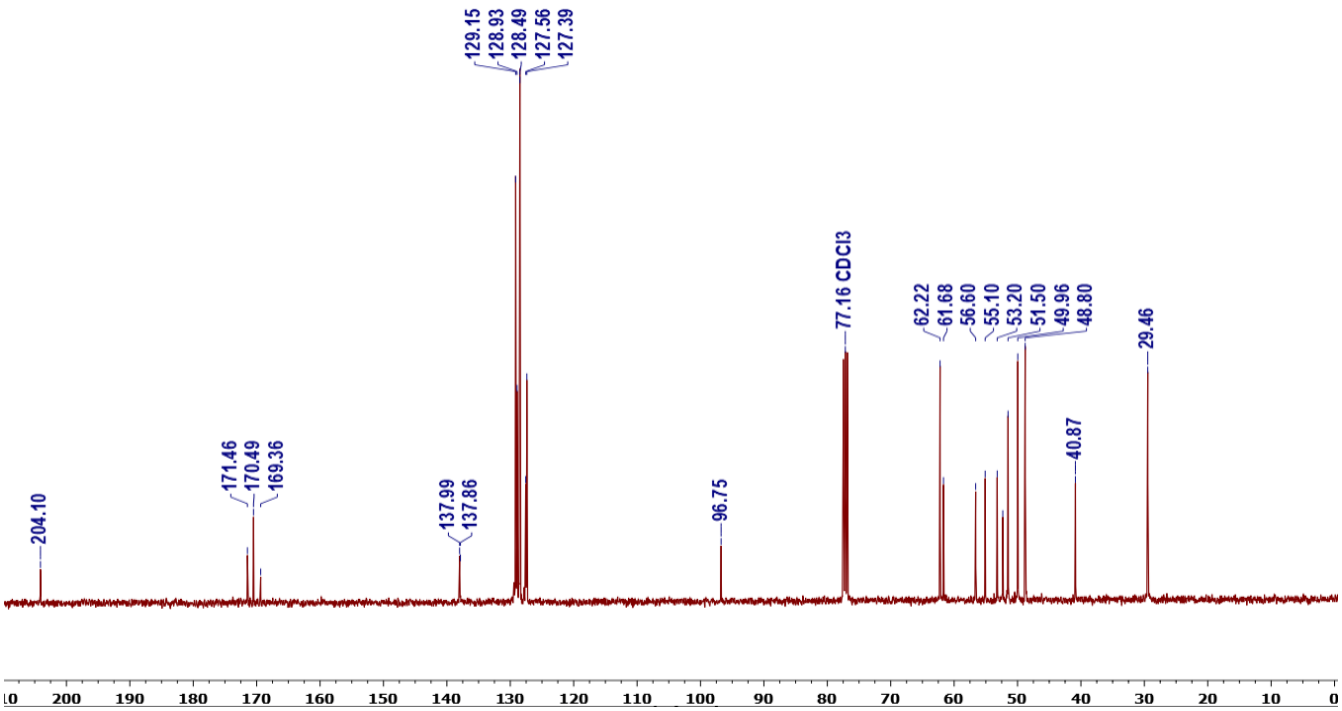


^{13}C NMR, $CDCl_3$, 100 MHz @ 25 °C

Compound **1-Bn**.

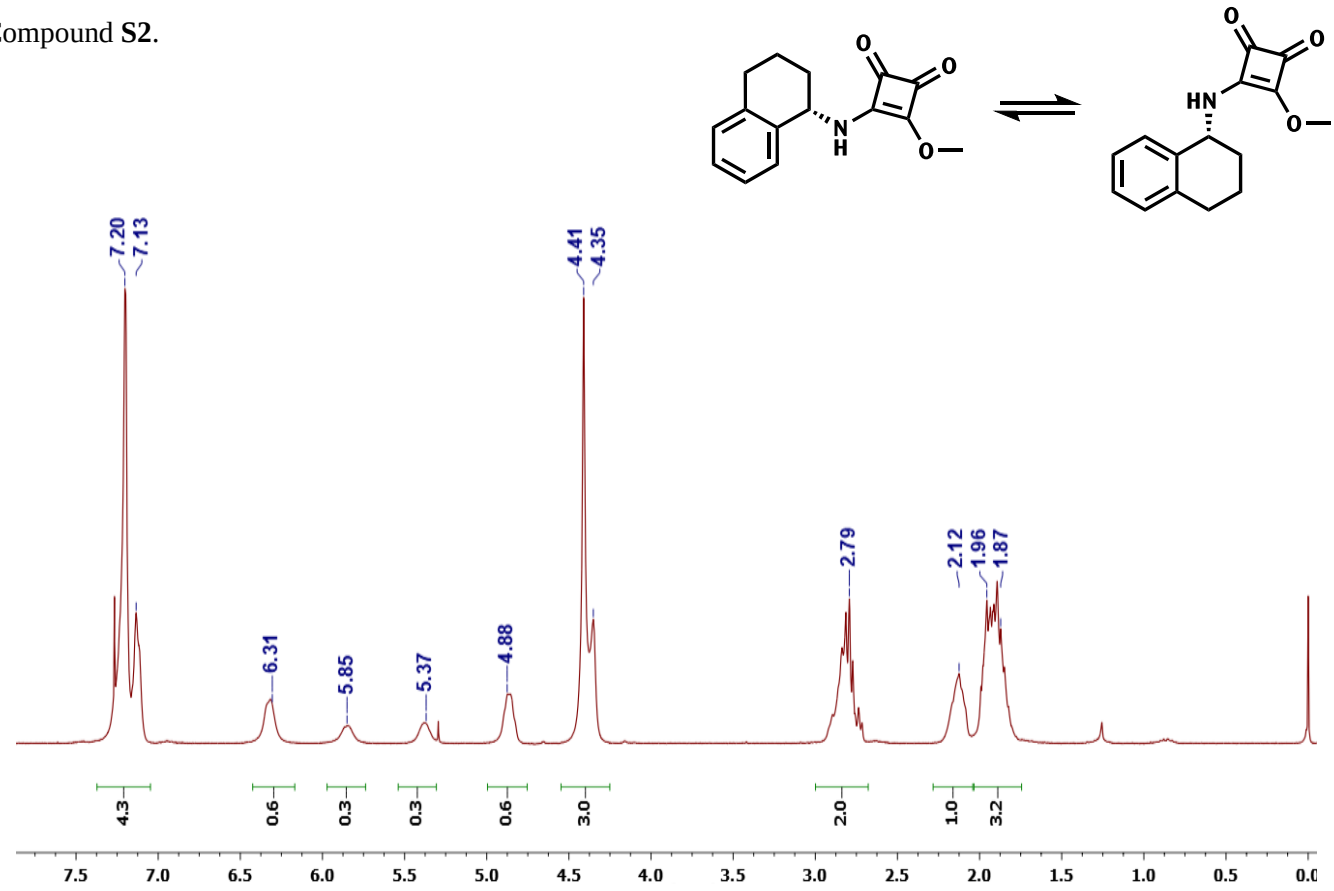


^{1}H NMR, $CDCl_3$, 400 MHz @ 25 °C

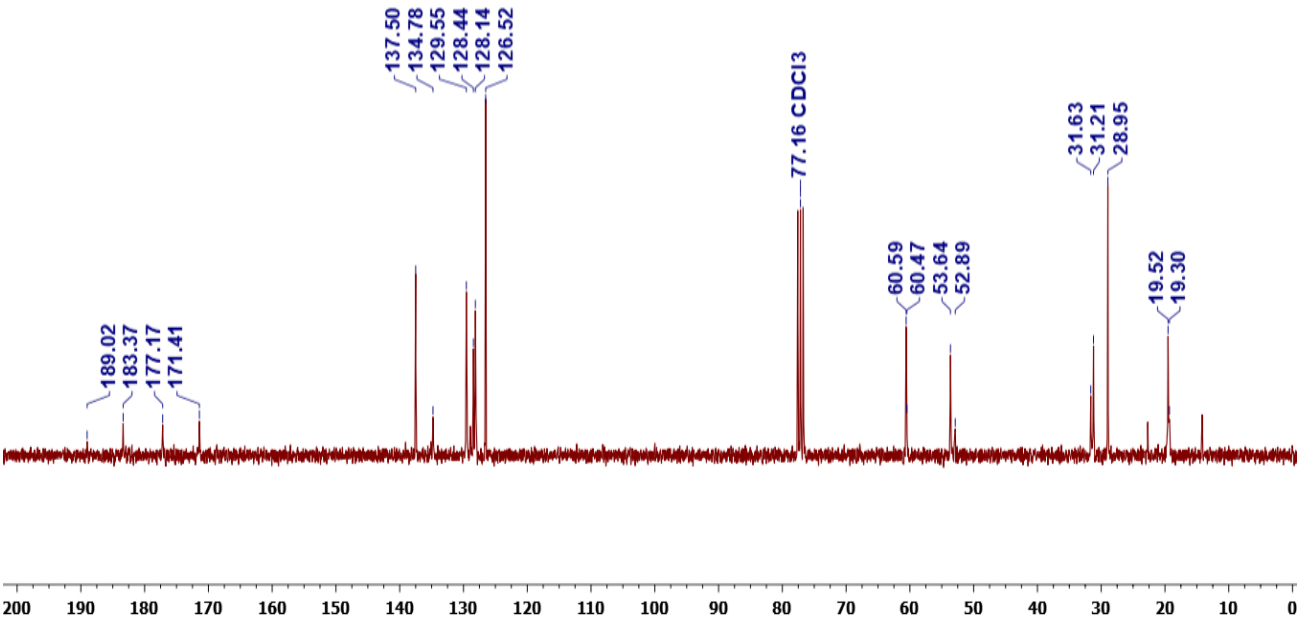


^{13}C NMR, $CDCl_3$, 100 MHz @ 25 °C

Compound **S2**.



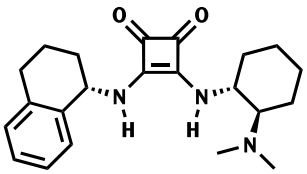
^{1}H NMR, $CDCl_3$, 300 MHz @ 25 °C



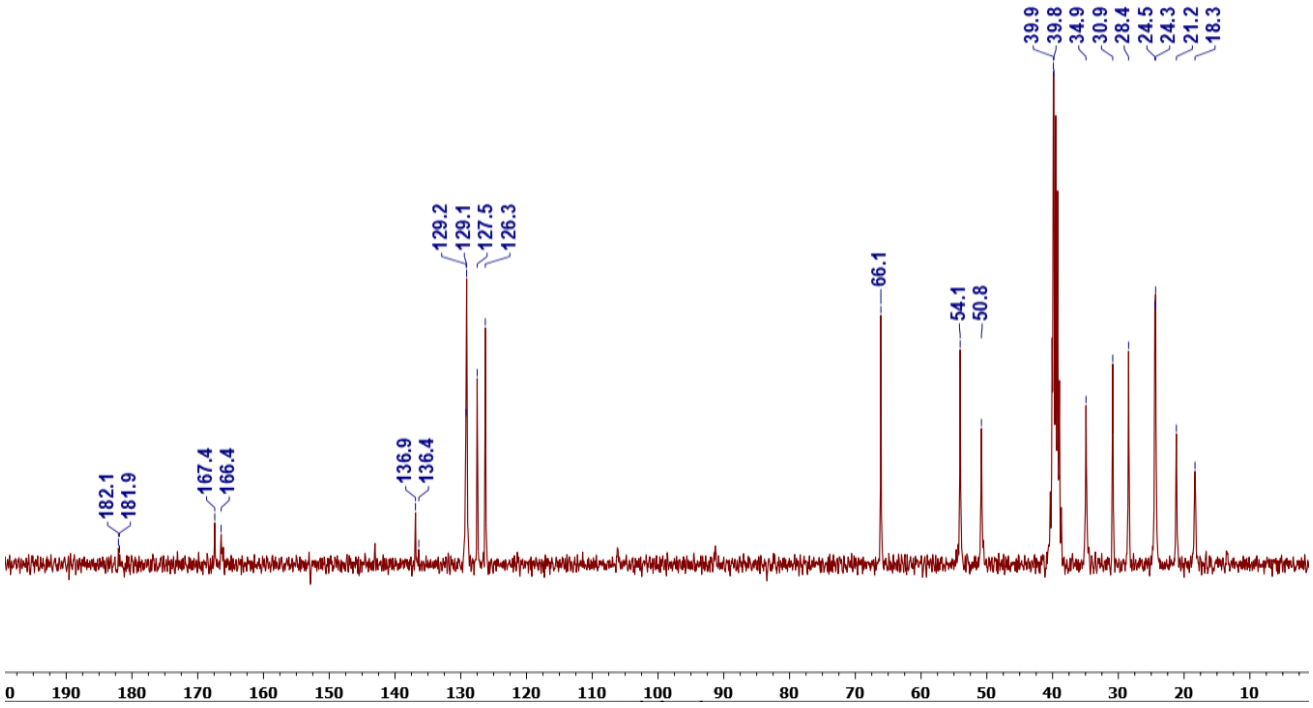
^{13}C NMR, $CDCl_3$, 75 MHz @ 25 °C

8.3 Catalysts

Catalyst **A**.

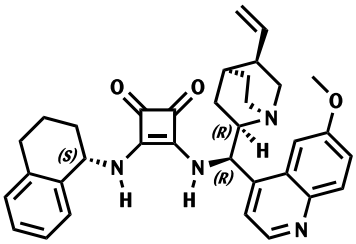


^{1}H NMR, DMSO-d6, 300 MHz @ 25 °C

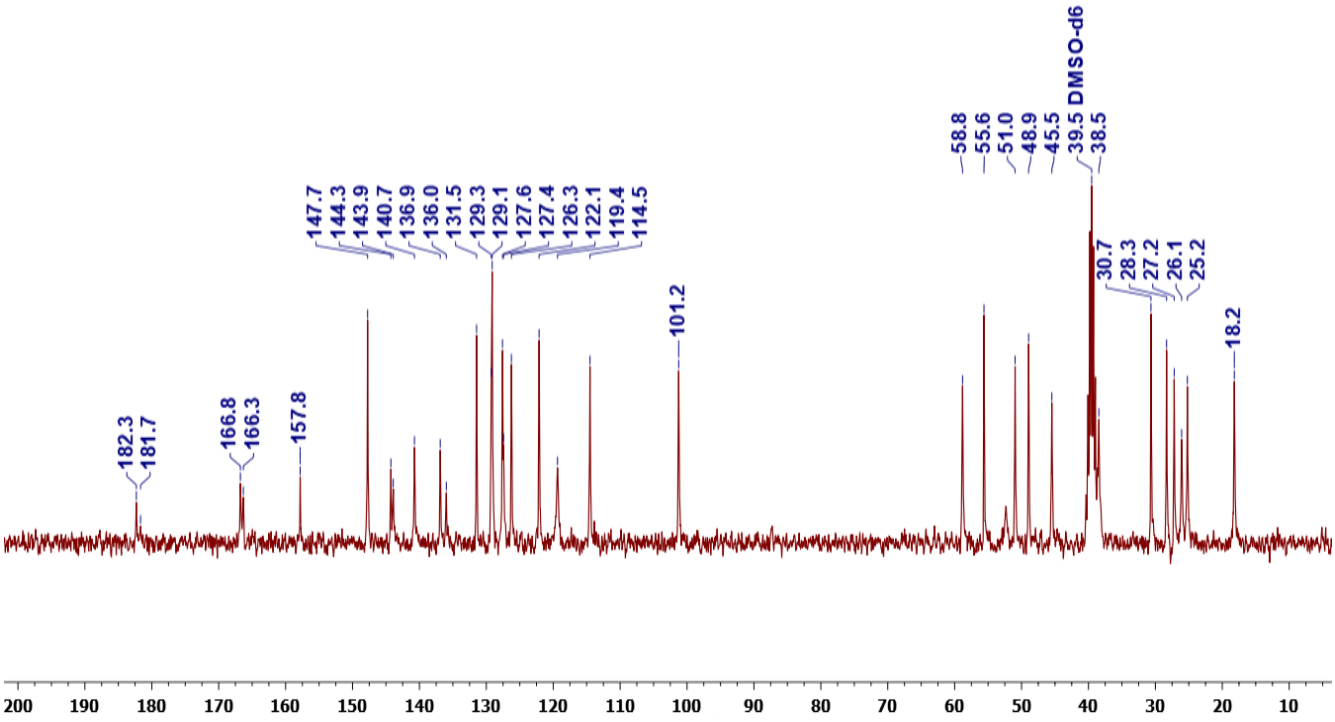


^{13}C NMR, DMSO-d6, 75 MHz @ 25 °C

Catalyst **B**.

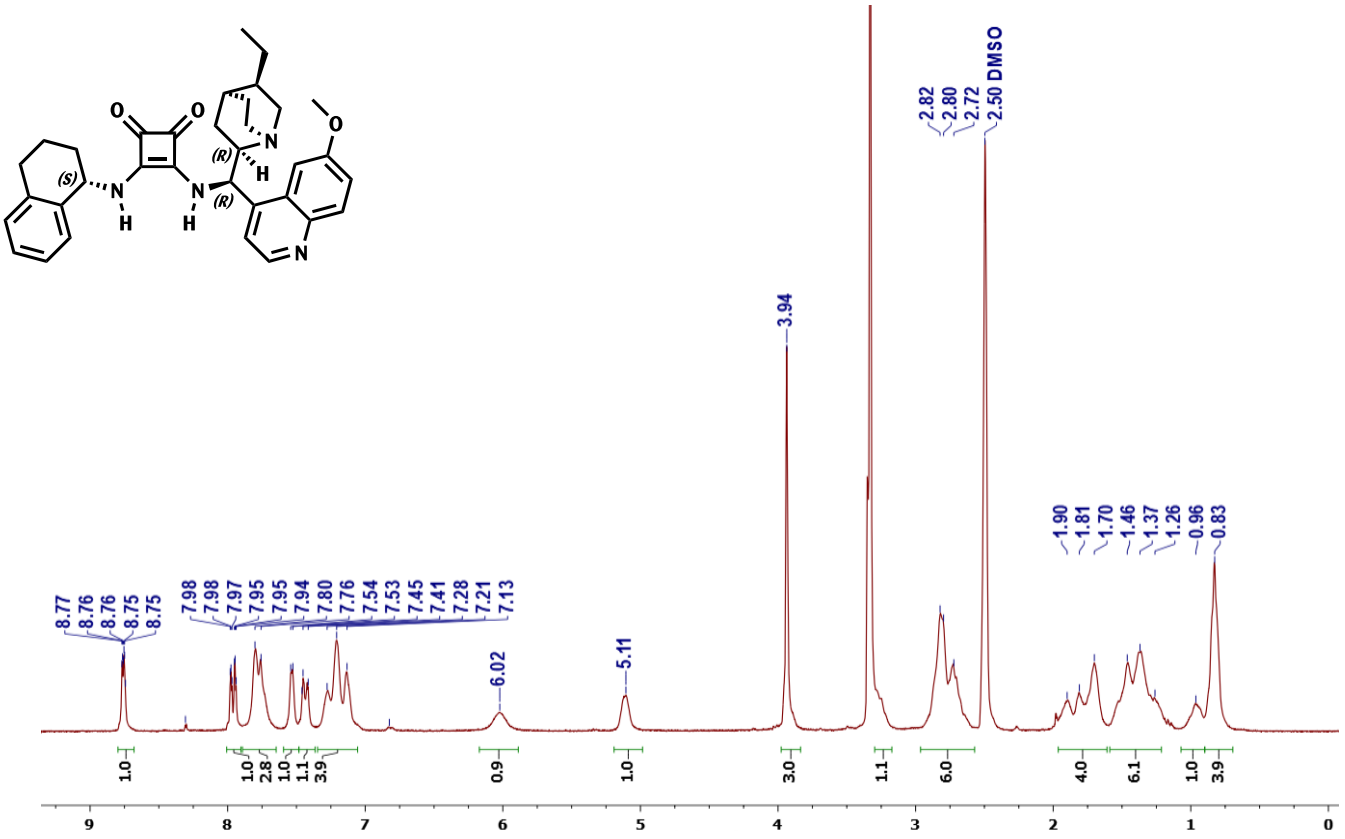


^{1}H NMR, DMSO-d6, 300 MHz @ 25 °C

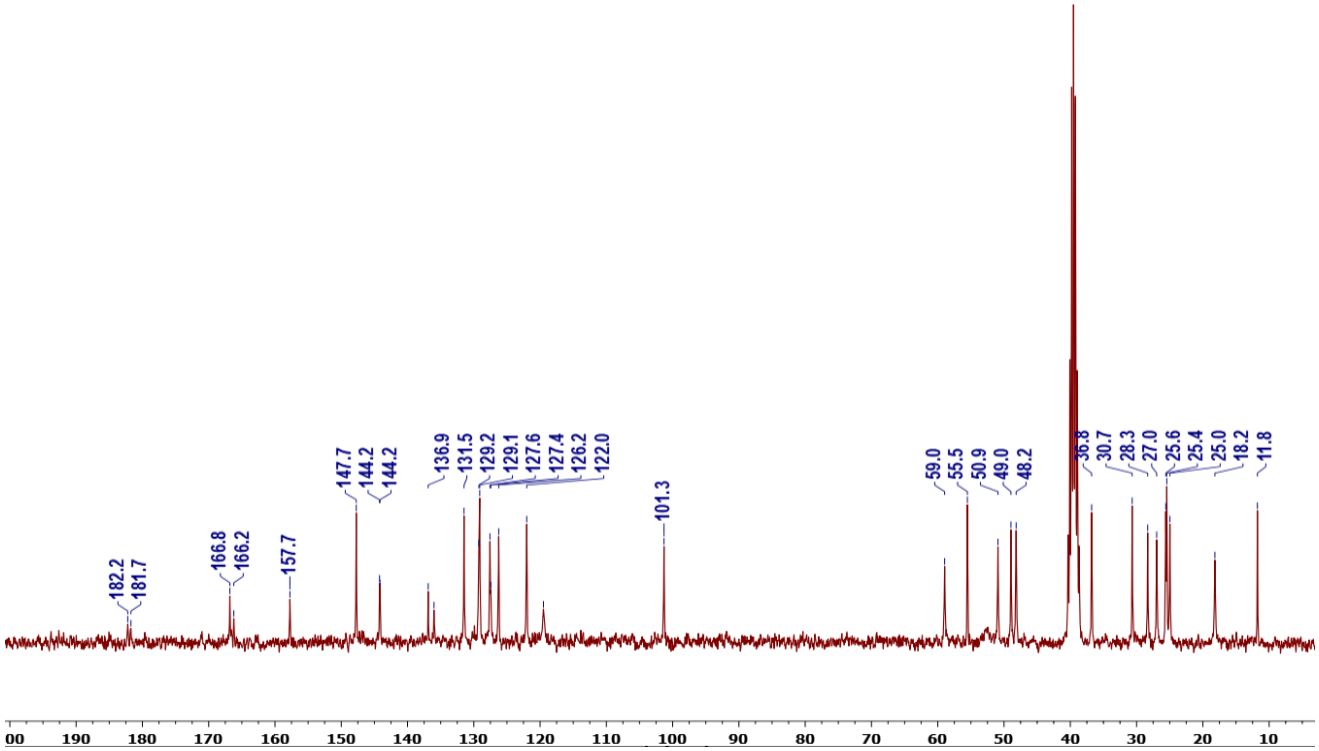


^{13}C NMR, DMSO-d6, 75 MHz @ 25 °C

Catalyst **C**.

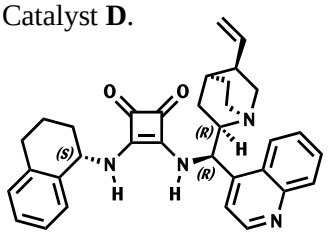


^{1}H NMR, DMSO-d6, 300 MHz @ 25 °C

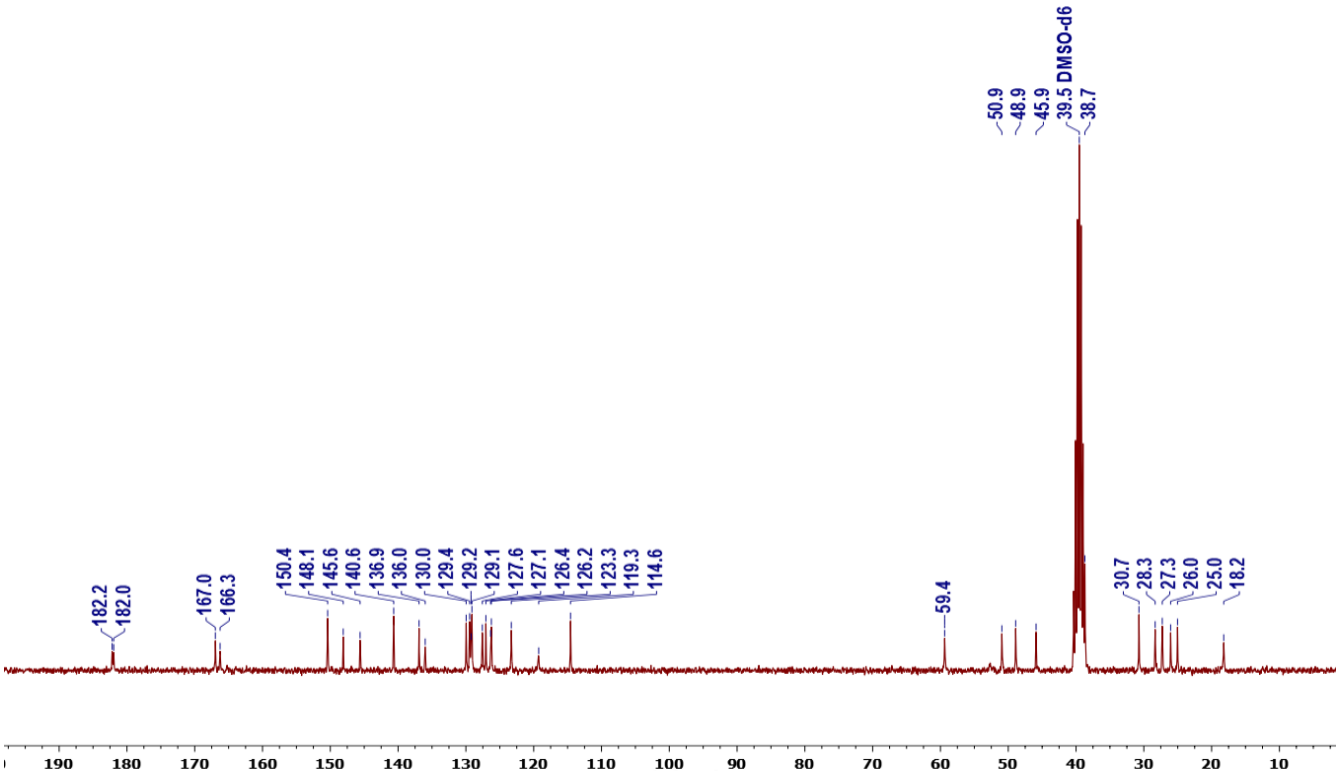


^{13}C NMR, DMSO-d6, 75 MHz @ 25 °C

Catalyst **D**.

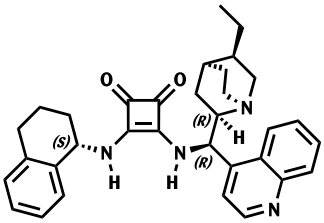


^{1}H NMR, DMSO-d6, 300 MHz @ 25 °C

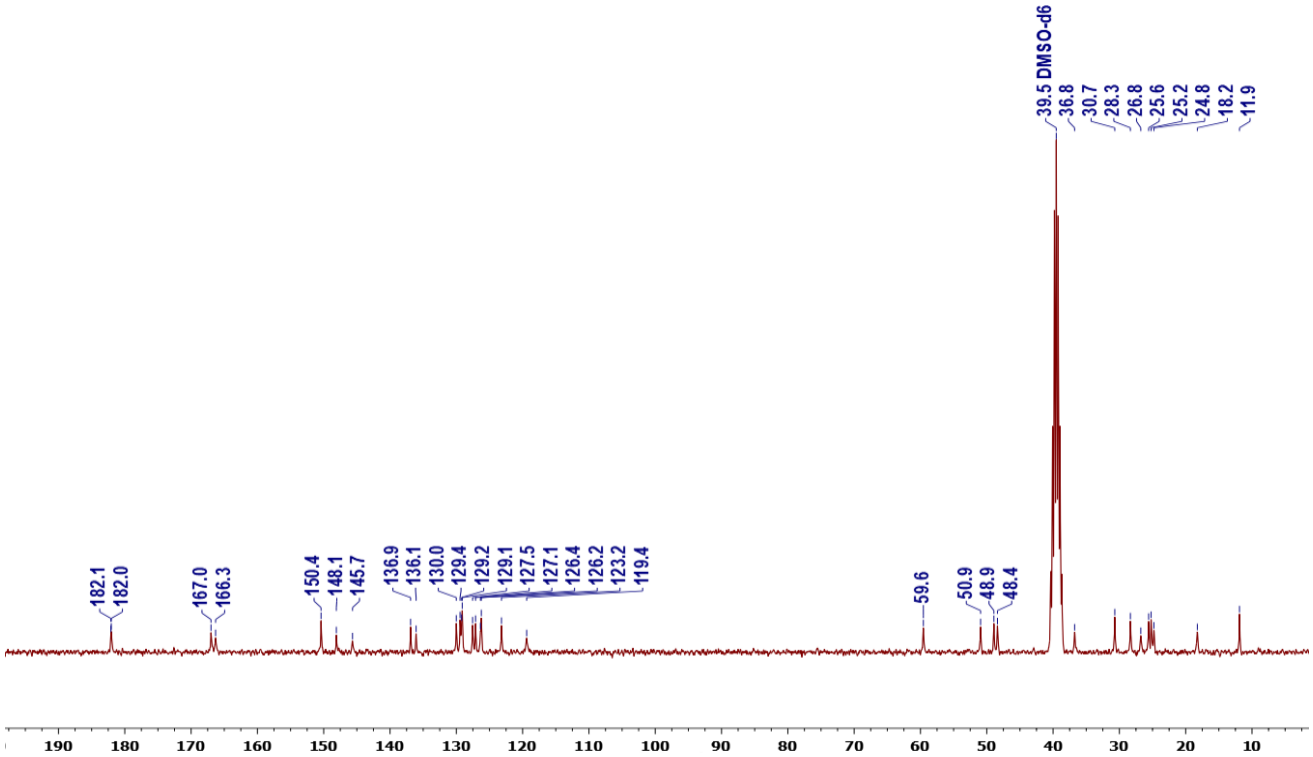


^{13}C NMR, DMSO-d6, 75 MHz @ 25 °C

Catalyst **E**.

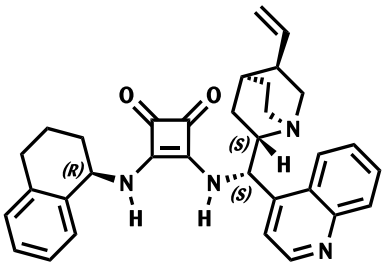


^{1}H NMR, DMSO-d6, 300 MHz @ 25 °C

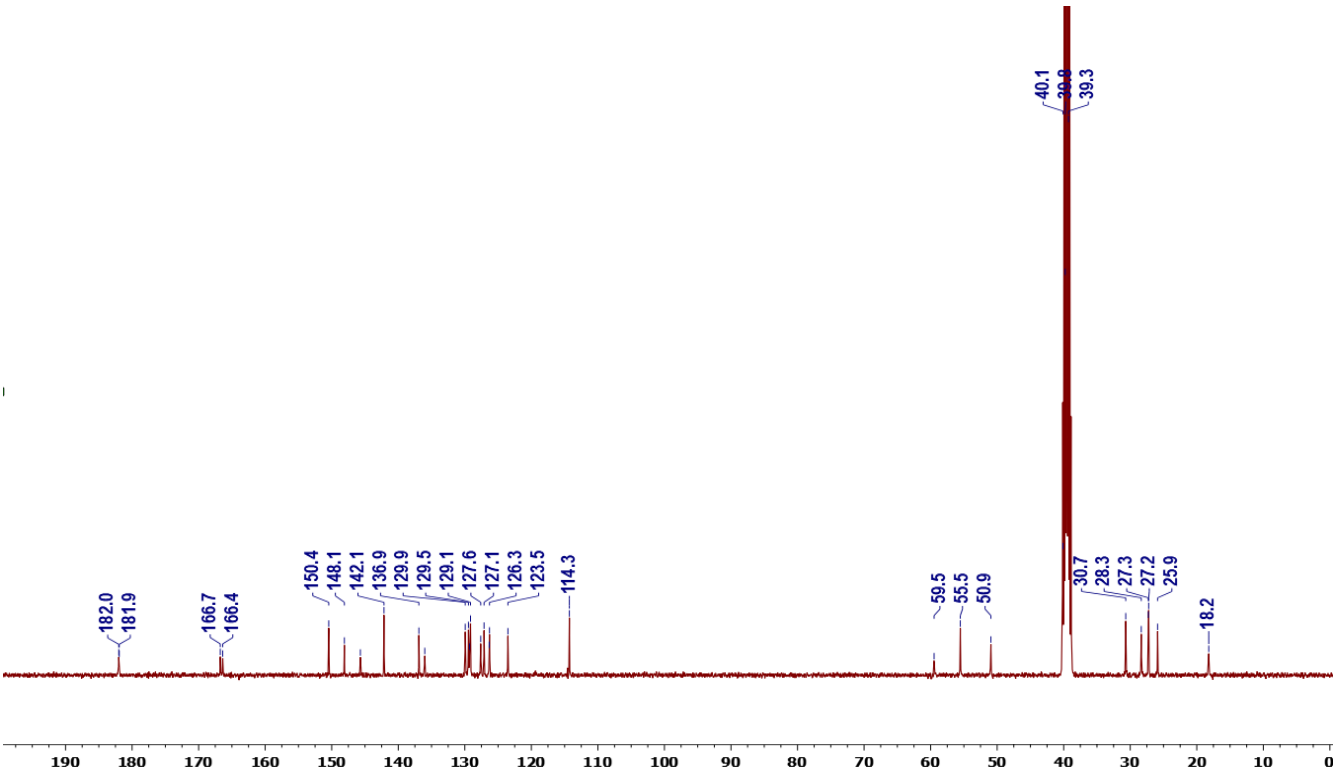


^{13}C NMR, DMSO-d6, 75 MHz @ 25 °C

Catalyst **L**.



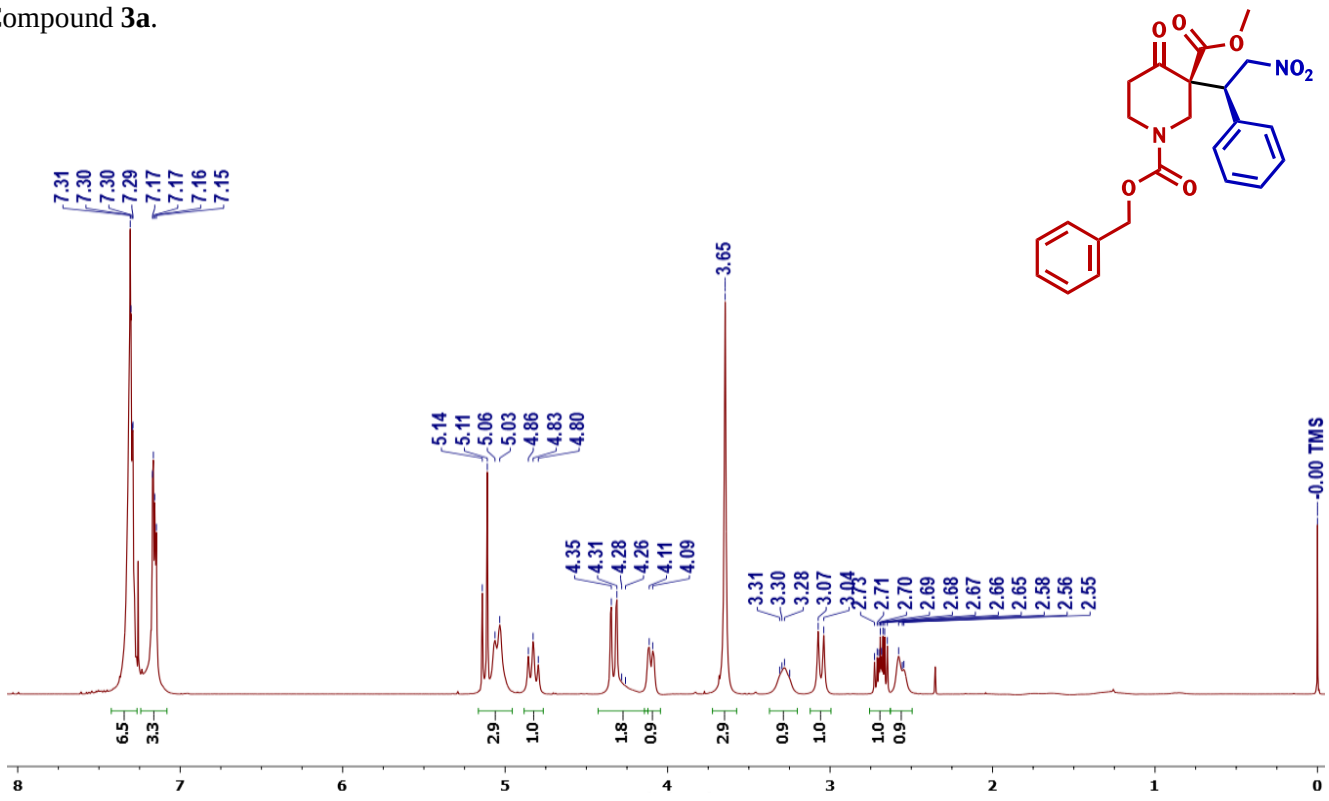
^{1}H NMR, DMSO-d6, 300 MHz @ 25 °C



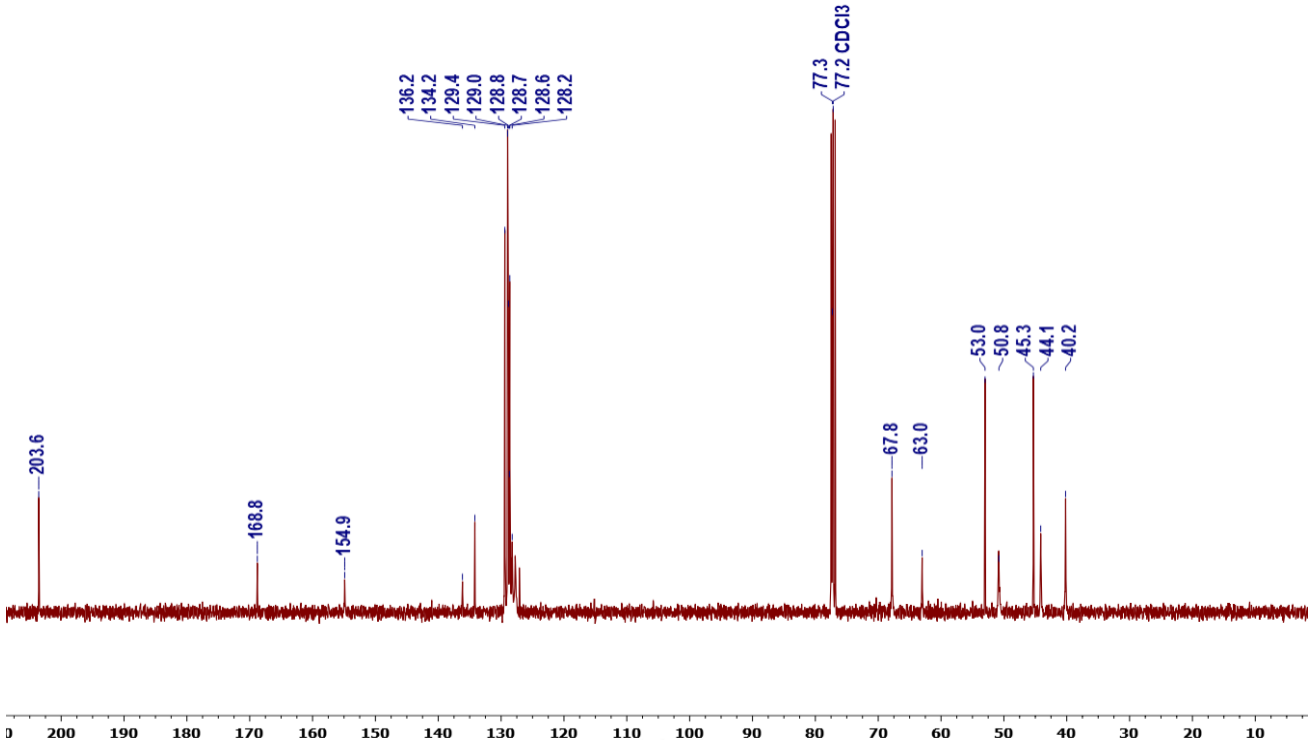
^{13}C NMR, DMSO-d6, 75 MHz @ 25 °C

8.4 Michael adducts

Compound **3a**.

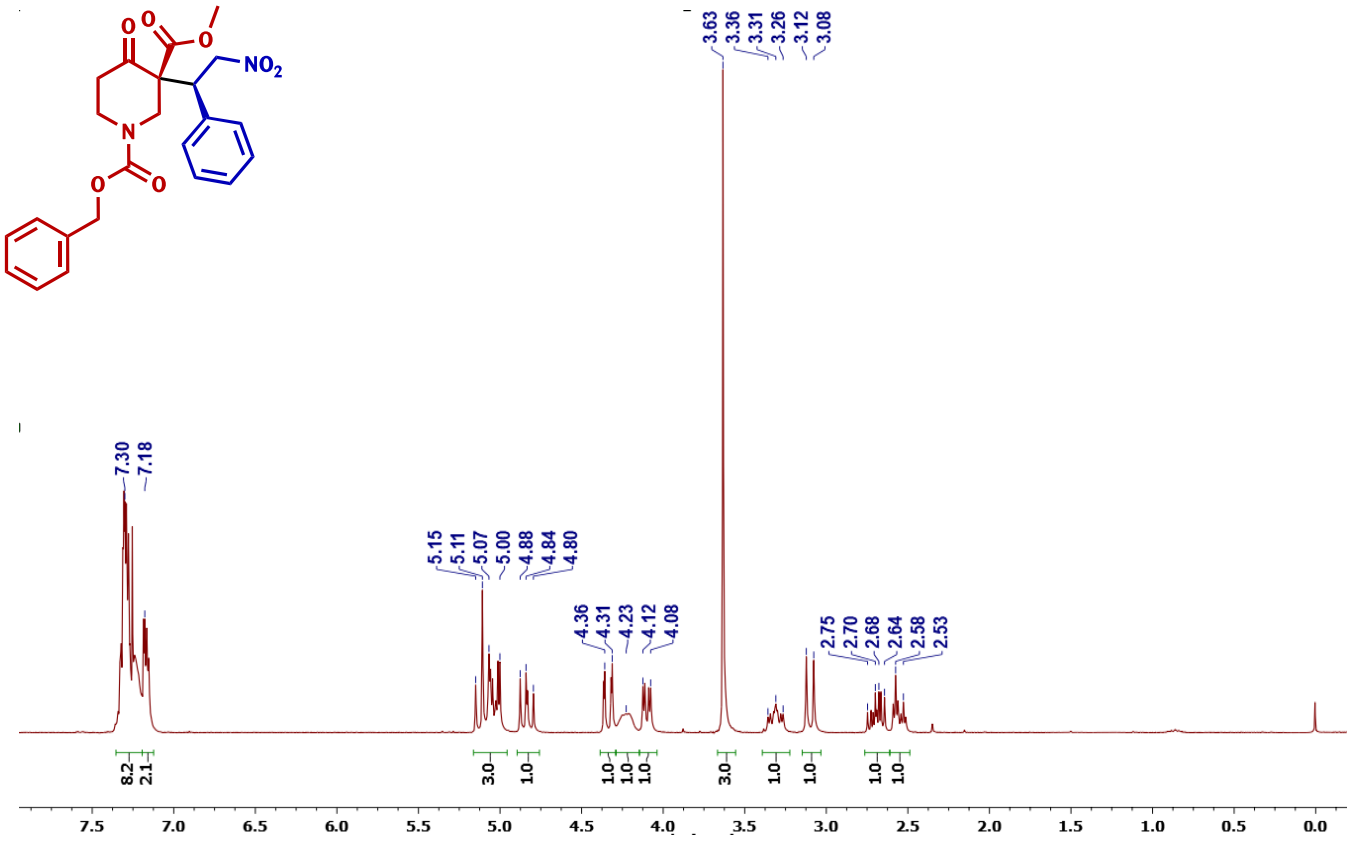


^{1}H NMR, $CDCl_3$, 400 MHz @ 25 °C

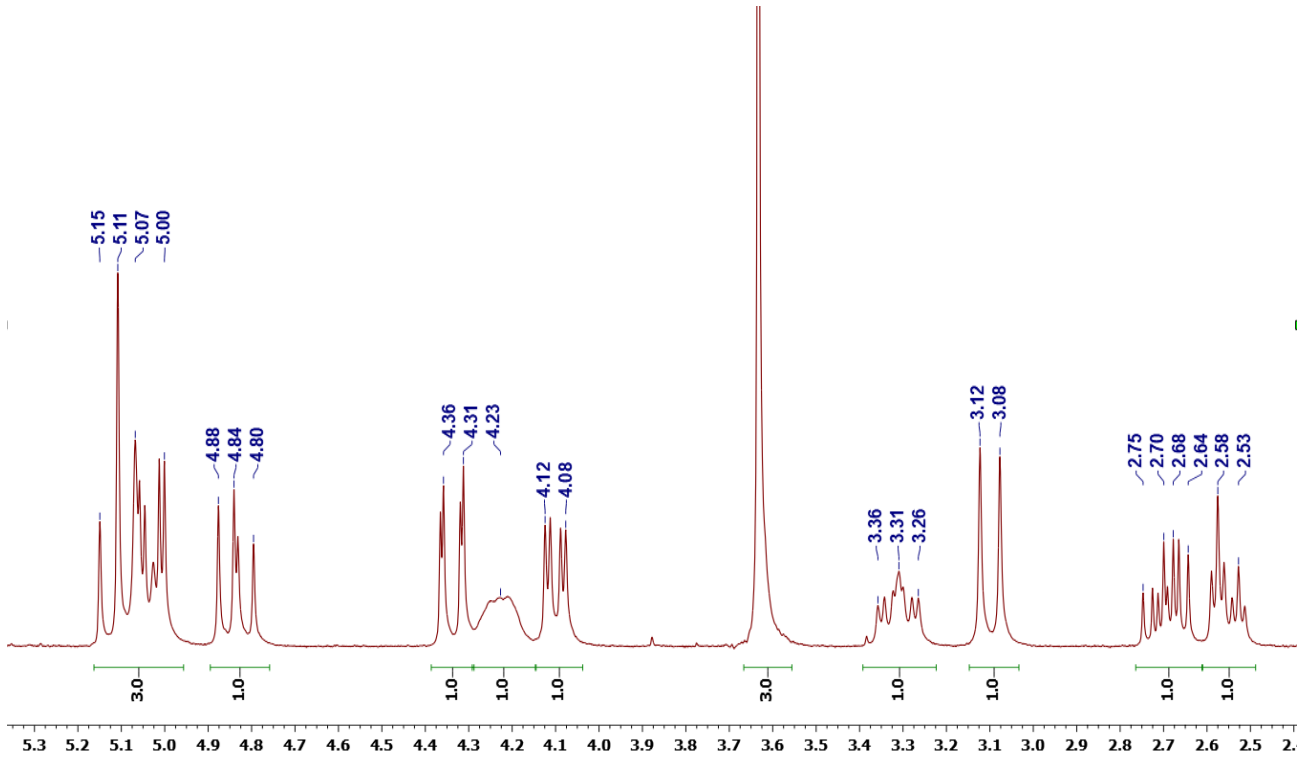


^{13}C NMR, $CDCl_3$, 100 MHz @ 25 °C

Compound **3a**.

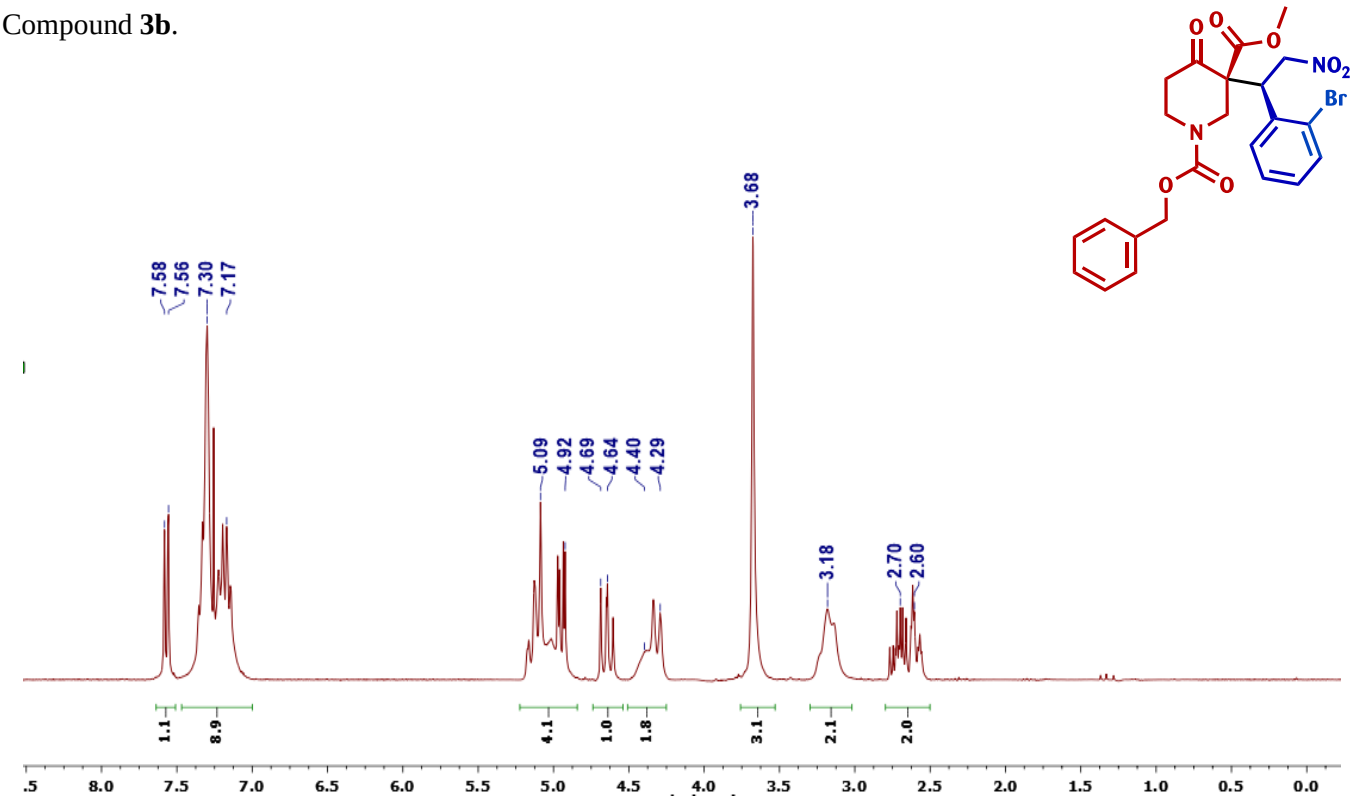


^{1}H NMR, $CDCl_3$, 300 MHz @ 47 °C

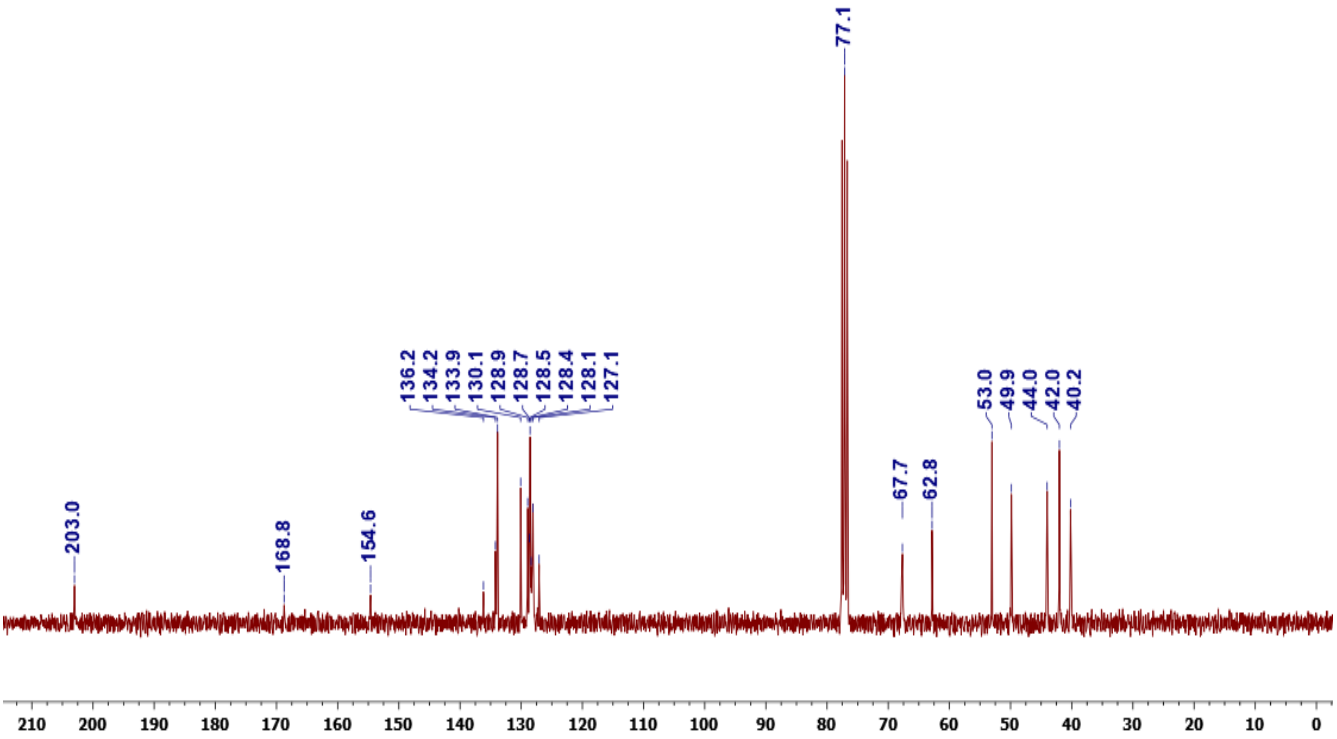


^{1}H NMR, $CDCl_3$, 300 MHz @ 47 °C

Compound **3b**.

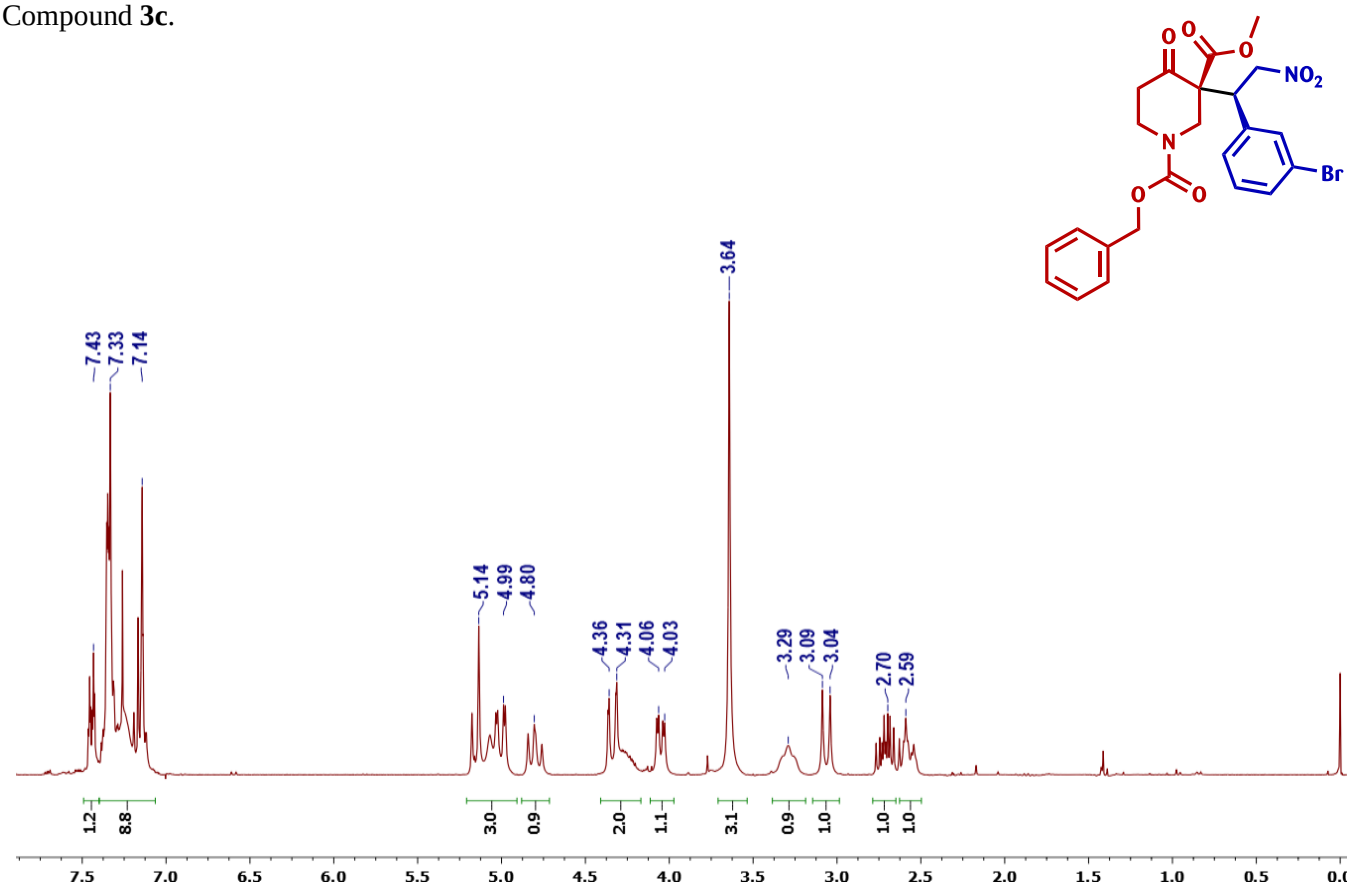


^{1}H NMR, $CDCl_3$, 300 MHz @ 25 °C

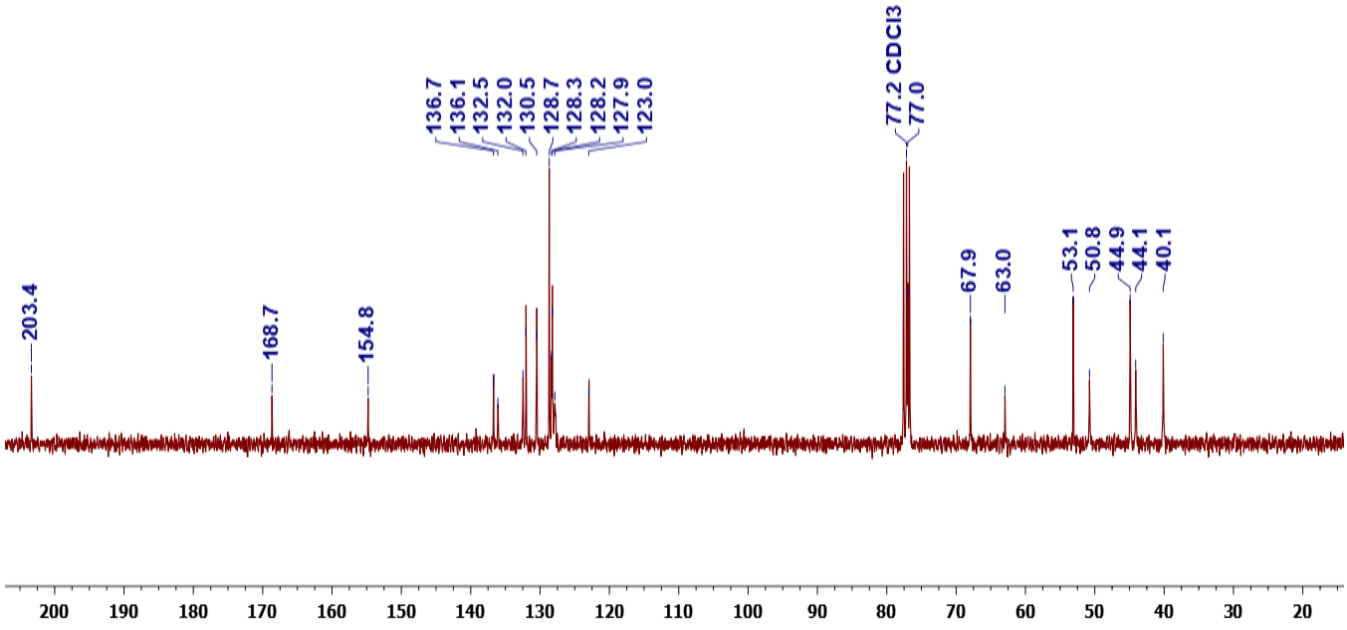


^{13}C NMR, $CDCl_3$, 75 MHz @ 25 °C

Compound **3c**.

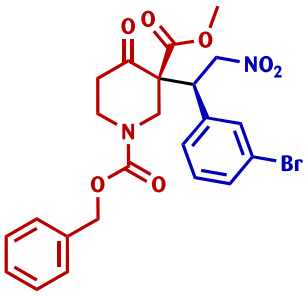


^{1}H NMR, $CDCl_3$, 300 MHz @ 25 °C

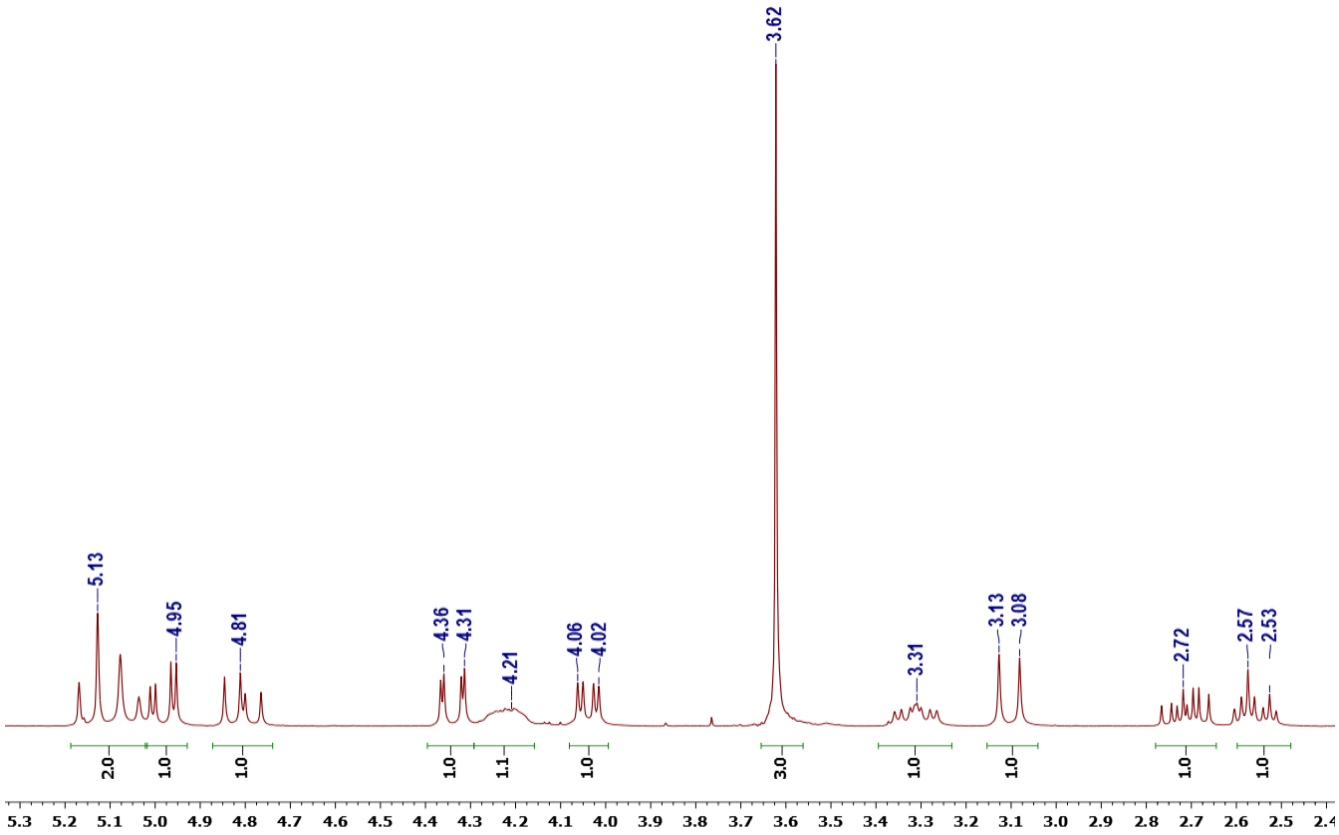


^{13}C NMR, $CDCl_3$, 75 MHz @ 25 °C

Compound **3c**.

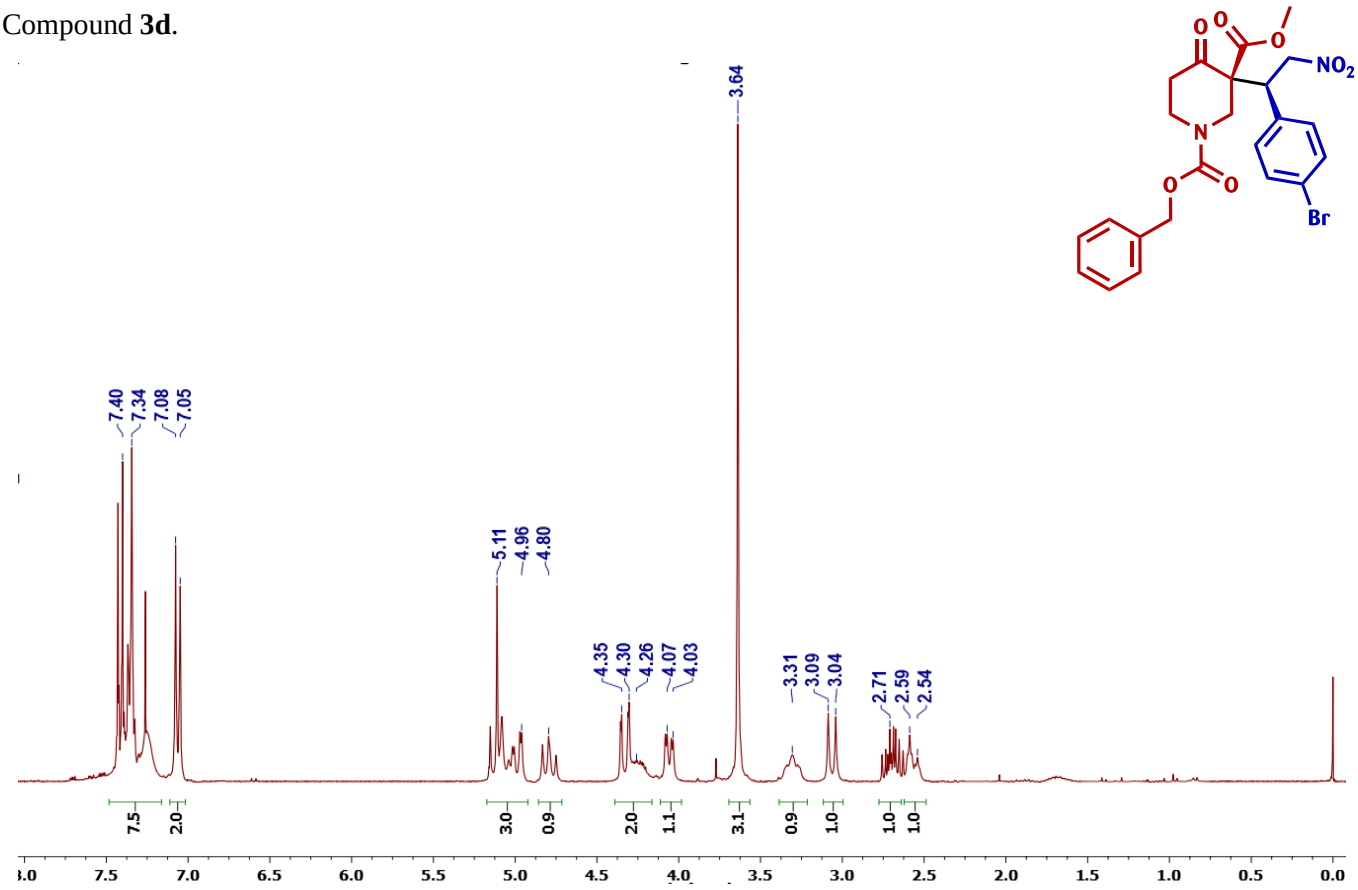


^{1}H NMR, $CDCl_3$, 300 MHz @ 55 °C

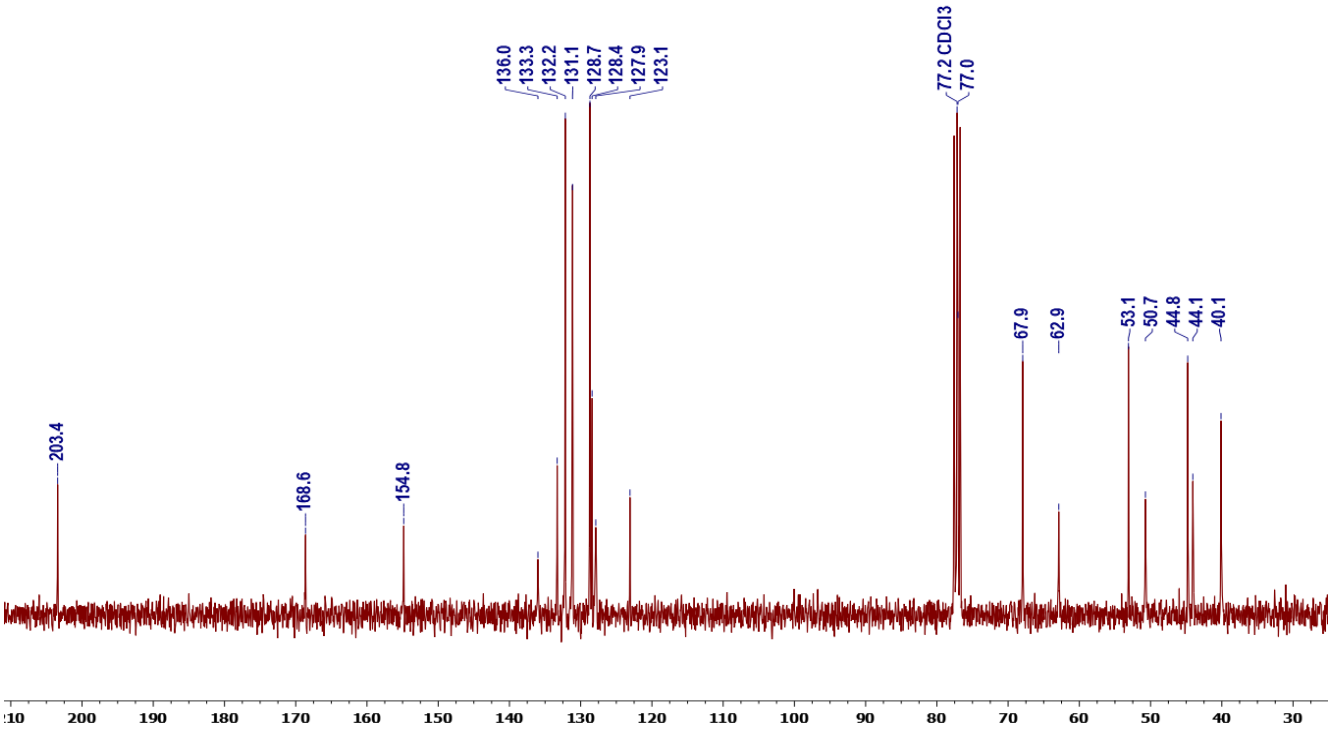


^{1}H NMR, $CDCl_3$, 300 MHz @ 55 °C

Compound **3d**.

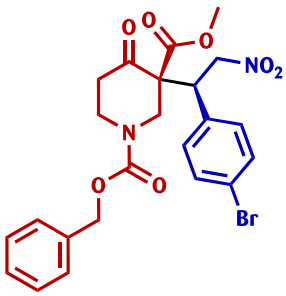


^{1}H NMR, $CDCl_3$, 300 MHz @ 25 °C

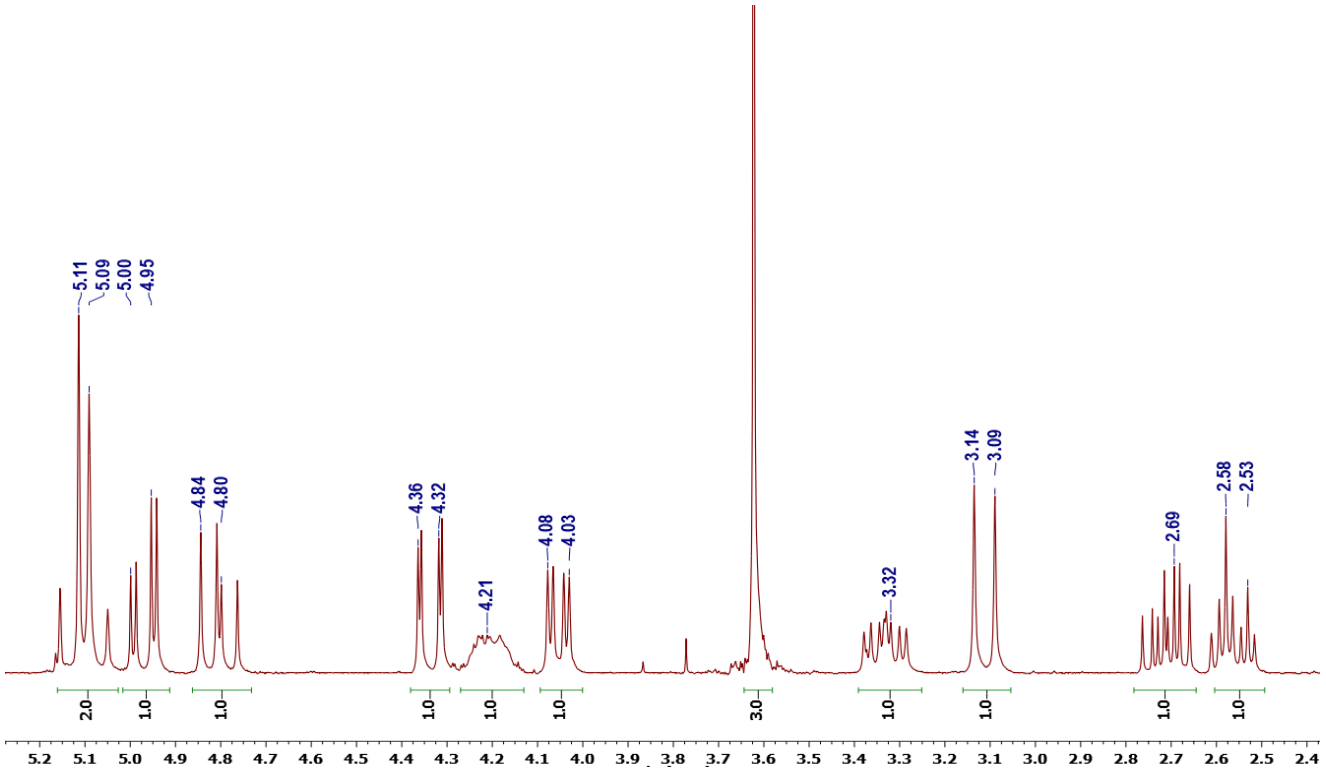


^{13}C NMR, $CDCl_3$, 75 MHz @ 25 °C

Compound **3d**.

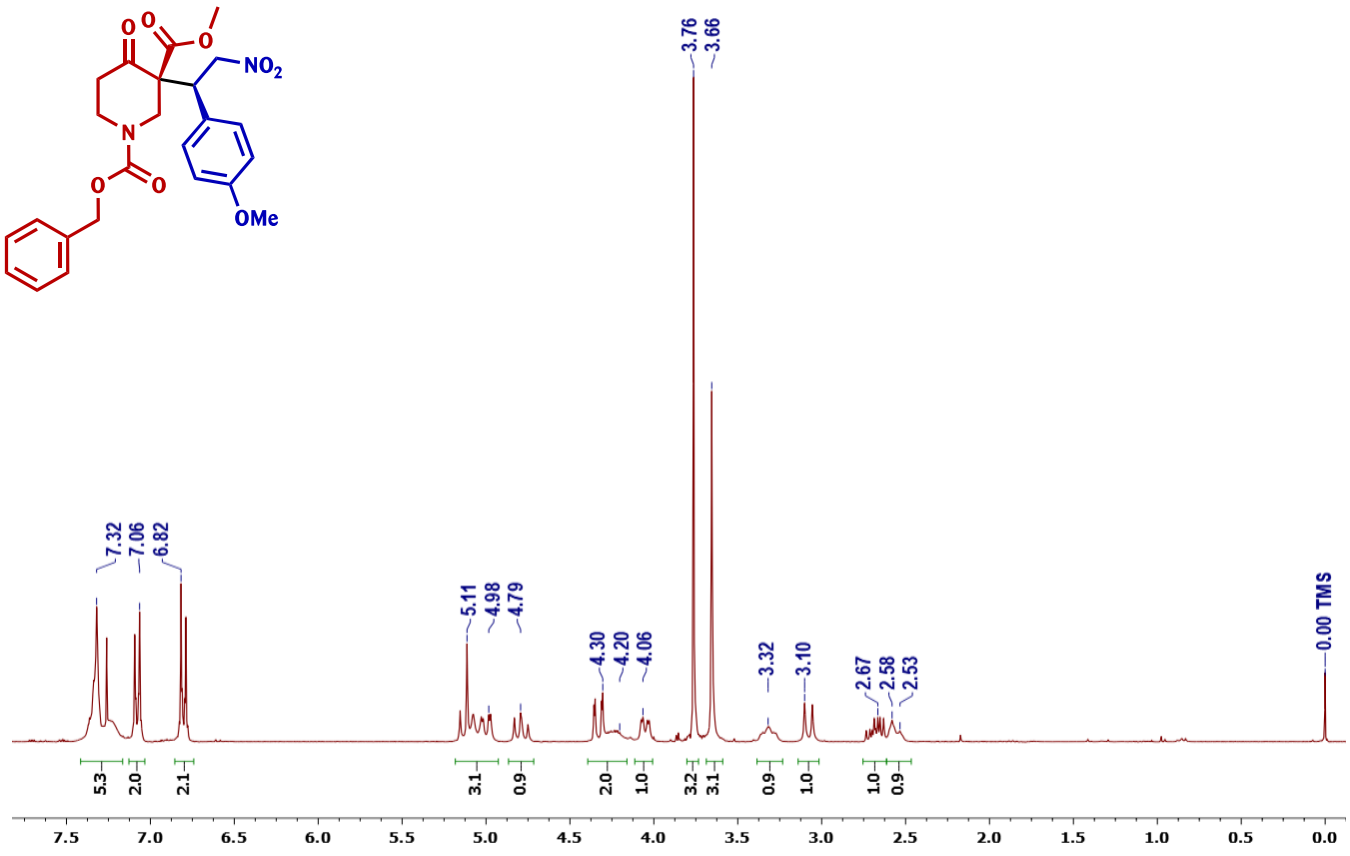


^{1}H NMR, $CDCl_3$, 300 MHz @ 55 °C

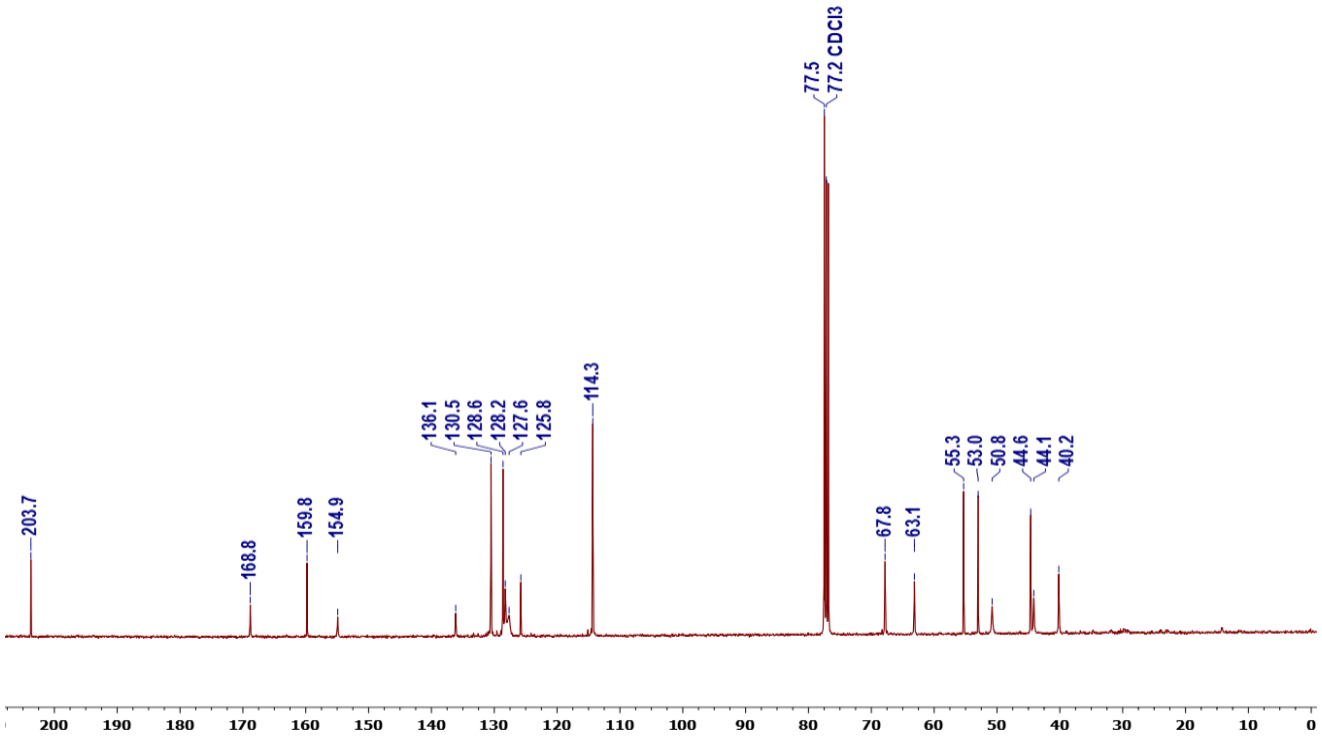


^{1}H NMR, $CDCl_3$, 300 MHz @ 55 °C

Compound **3e**.

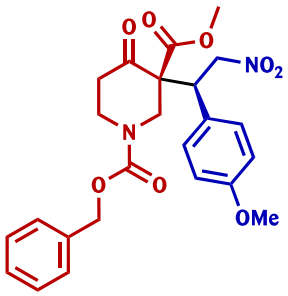


^{1}H NMR, $CDCl_3$, 300 MHz @ 25 °C

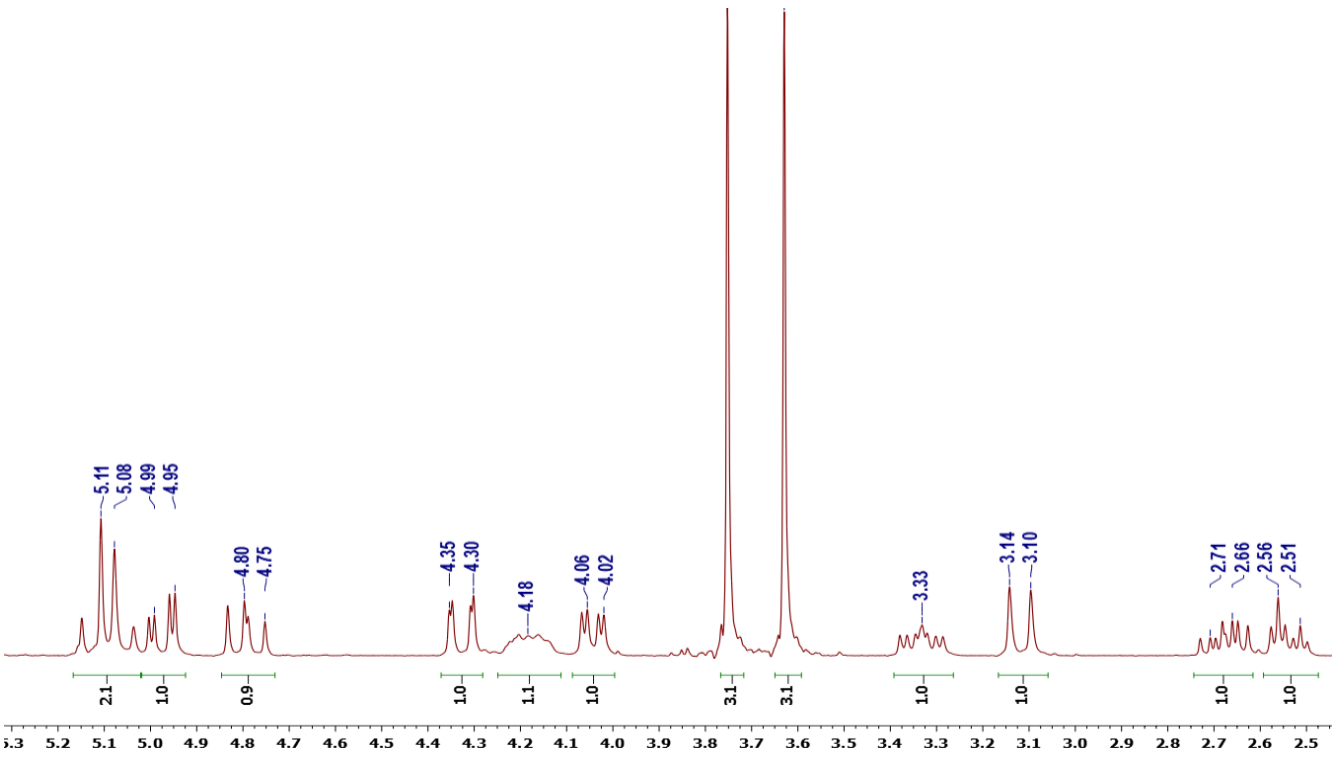


^{13}C NMR, $CDCl_3$, 100 MHz @ 25 °C

Compound **3e**.

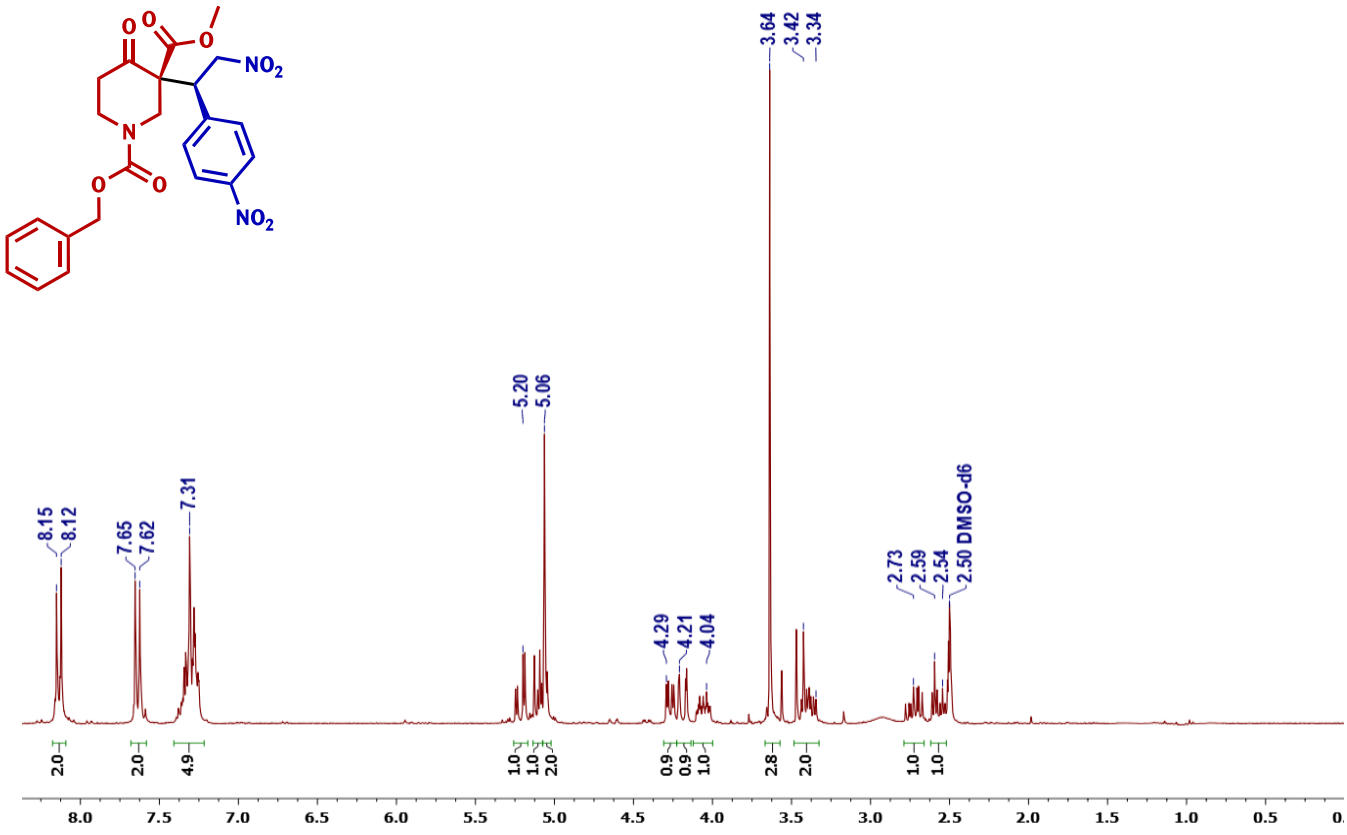


^{1}H NMR, $CDCl_3$, 300 MHz @ 55 °C

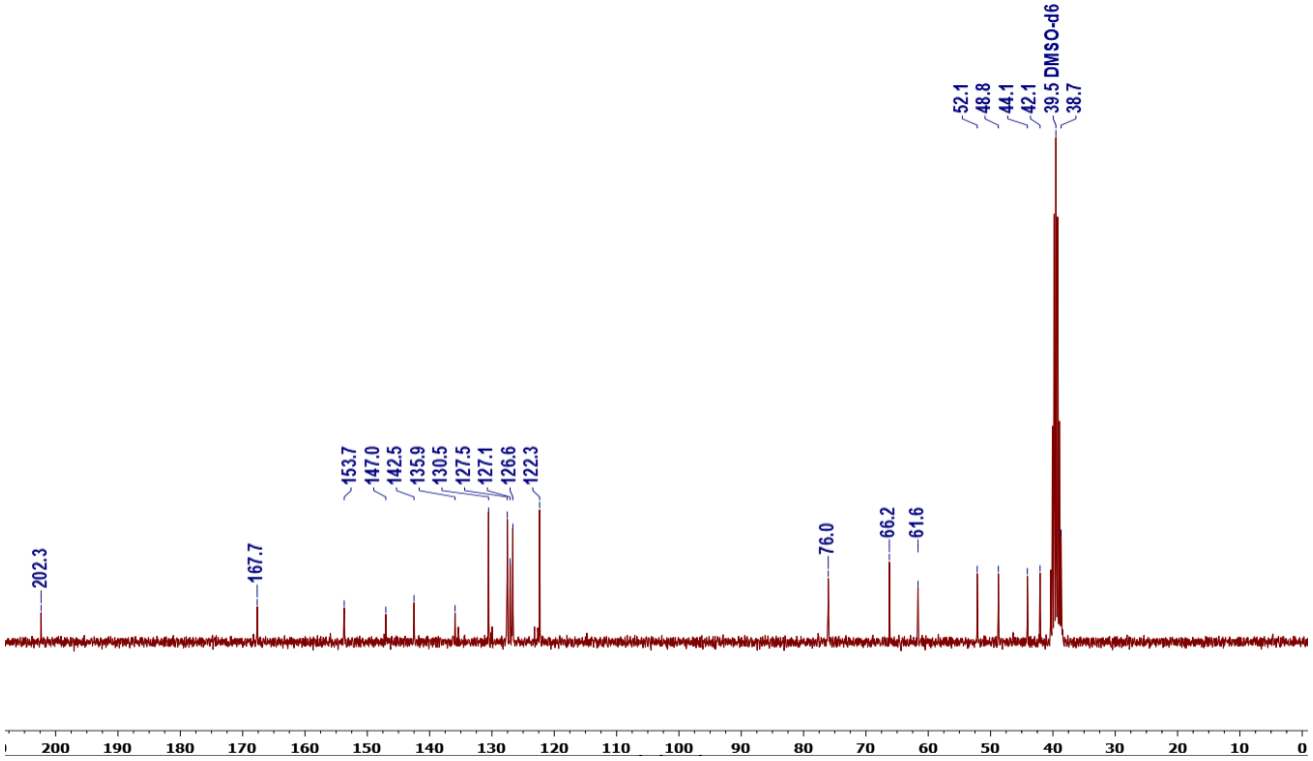


^{1}H NMR, $CDCl_3$, 300 MHz @ 55 °C

Compound **3f**.

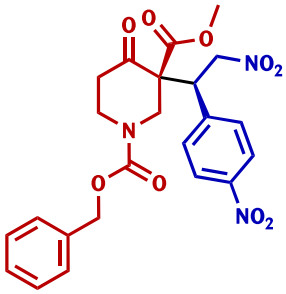


^{1}H NMR, DMSO-d_6, 300 MHz @ 120 °C

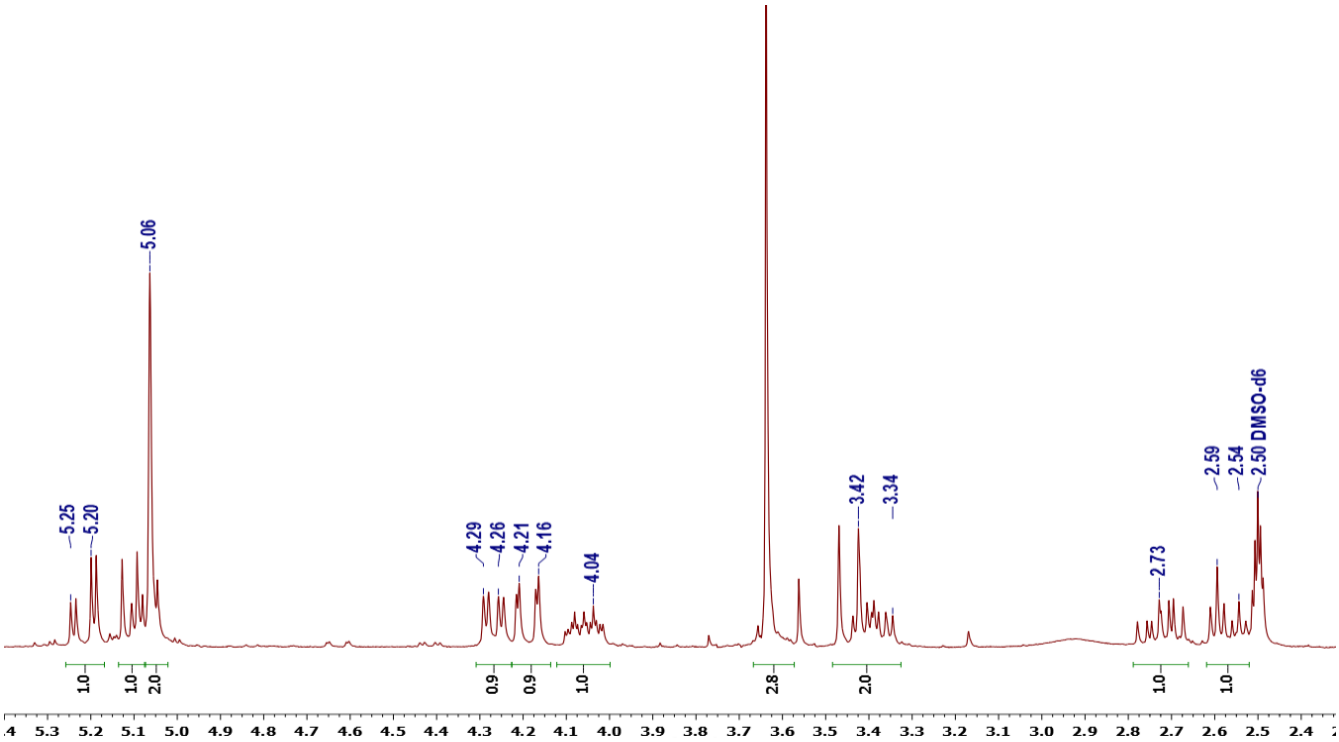


^{13}C NMR, DMSO-d_6, 75 MHz @ 120 °C

Compound **3f**.

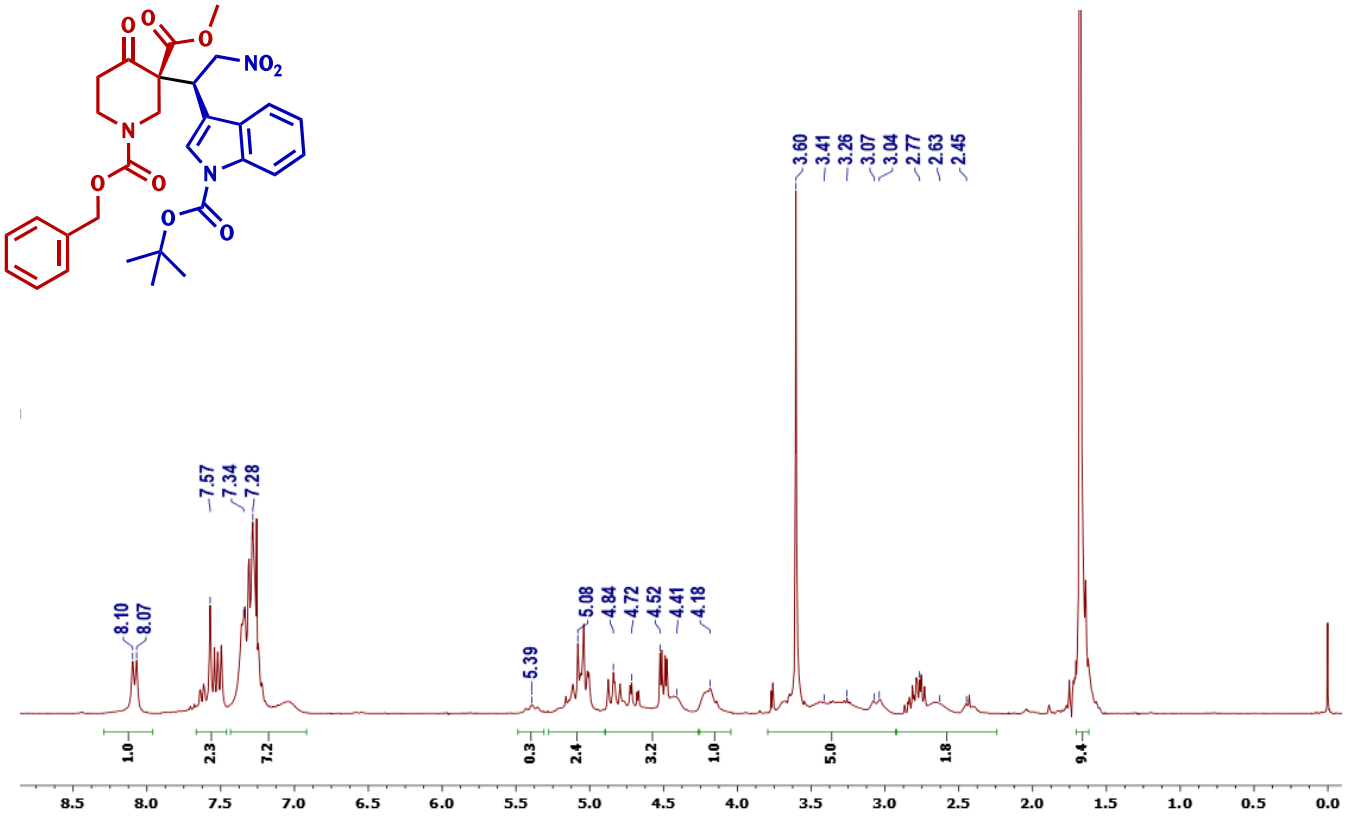


^{13}C NMR, DMSO-d_6, 75 MHz @ 120 °C

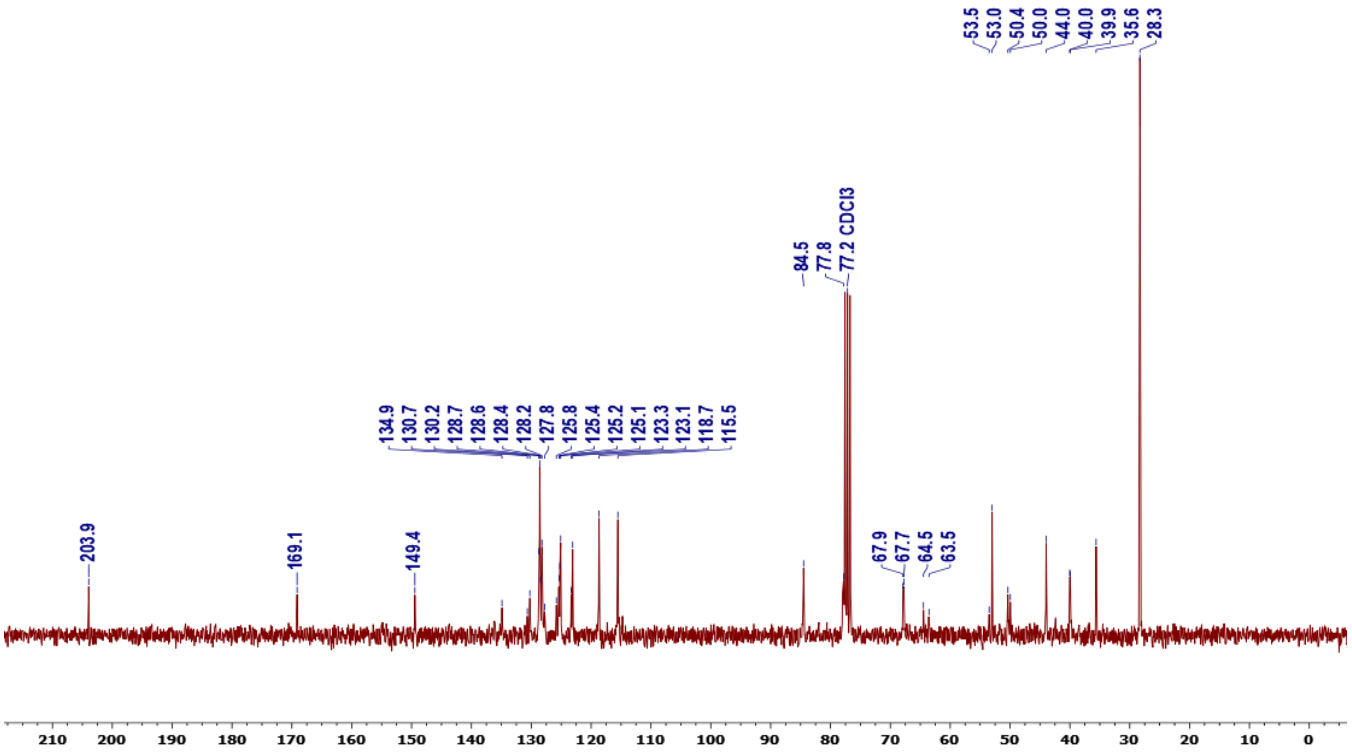


^{1}H NMR, DMSO-d_6, 300 MHz @ 120 °C

Compound **3g**.

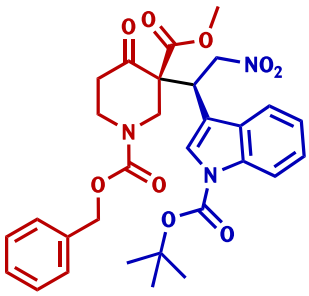


^{1}H NMR, $CDCl_3$, 300 MHz @ 25 °C

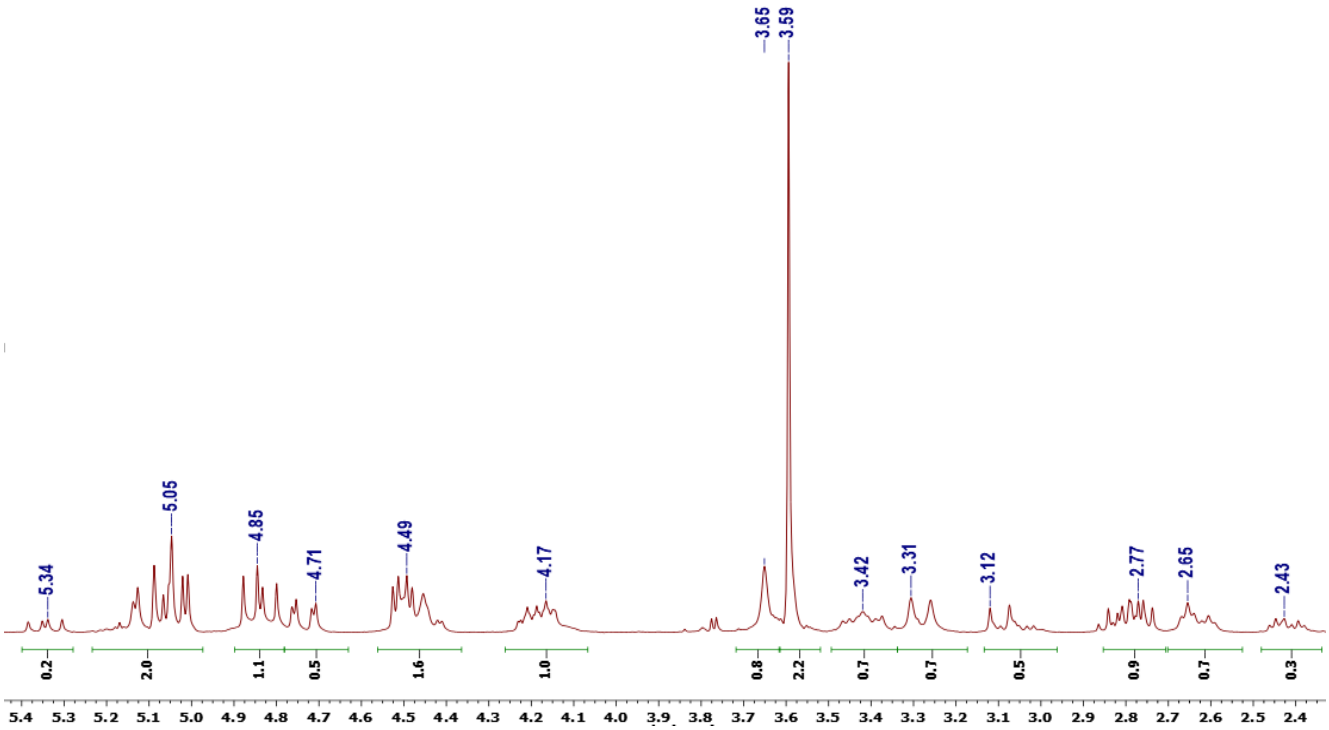


^{13}C NMR, $CDCl_3$, 75 MHz @ 25 °C

Compound **3g**.

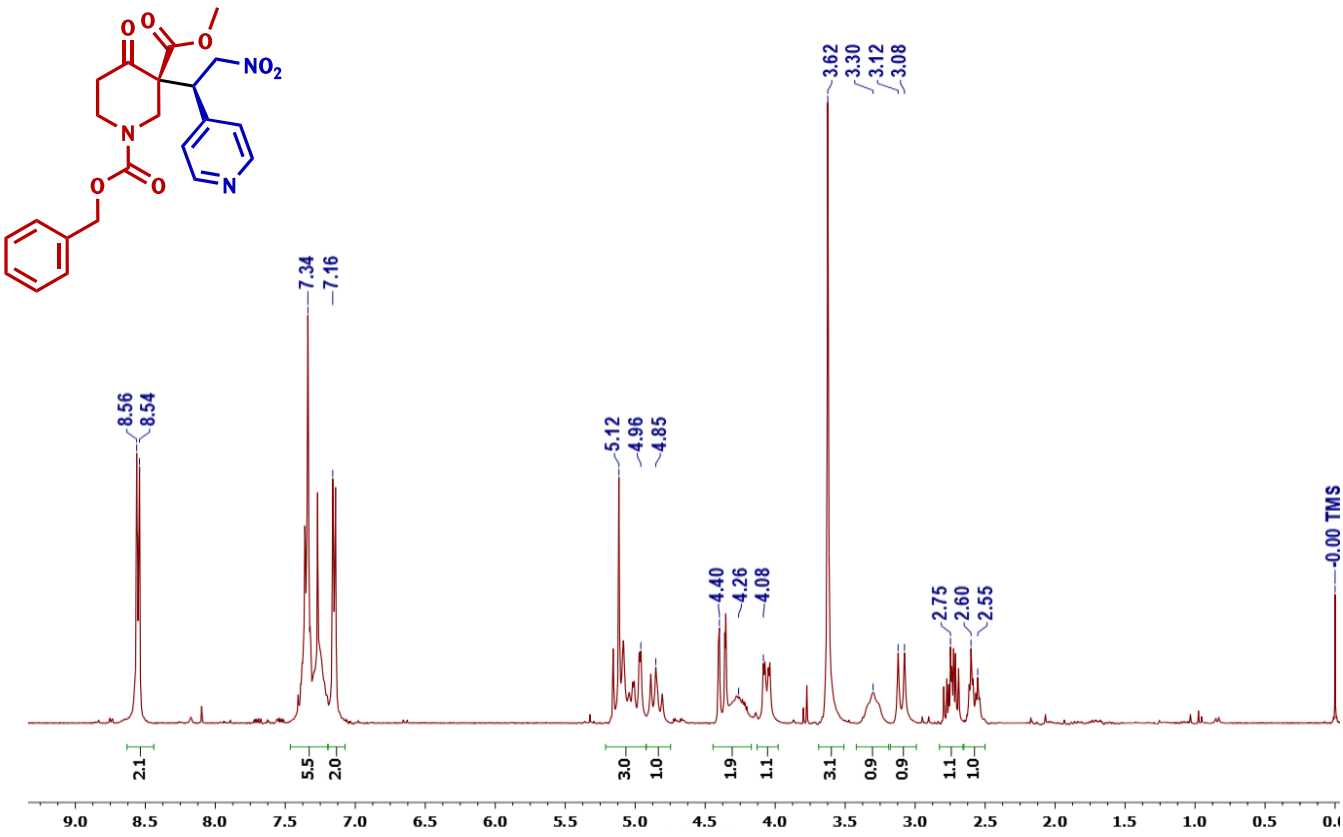


^{1}H NMR, $CDCl_3$, 300 MHz @ 55 °C

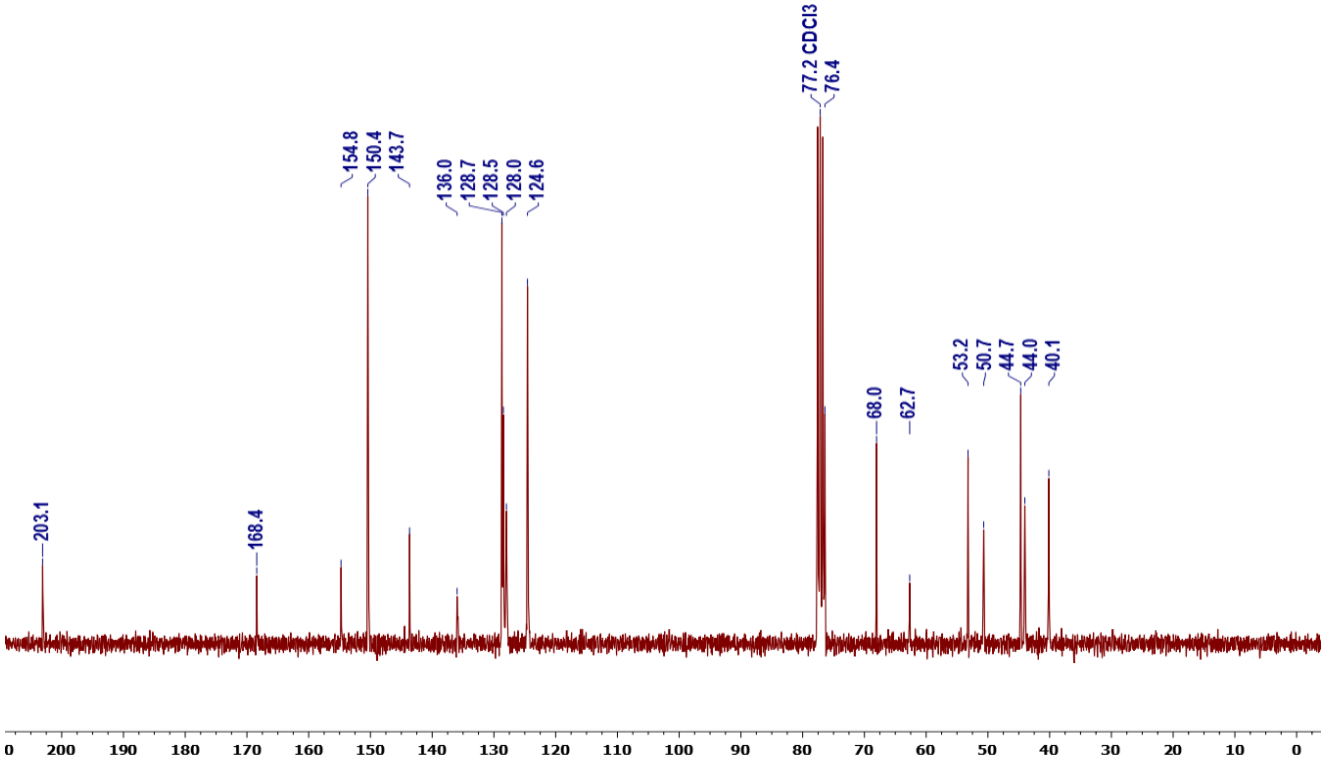


^{1}H NMR, $CDCl_3$, 300 MHz @ 55 °C

Compound **3h**.

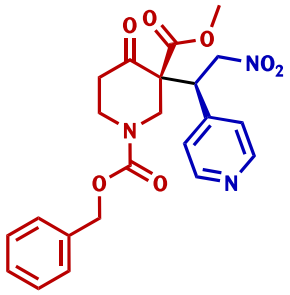


^{1}H NMR, $CDCl_3$, 300 MHz @ 25 °C

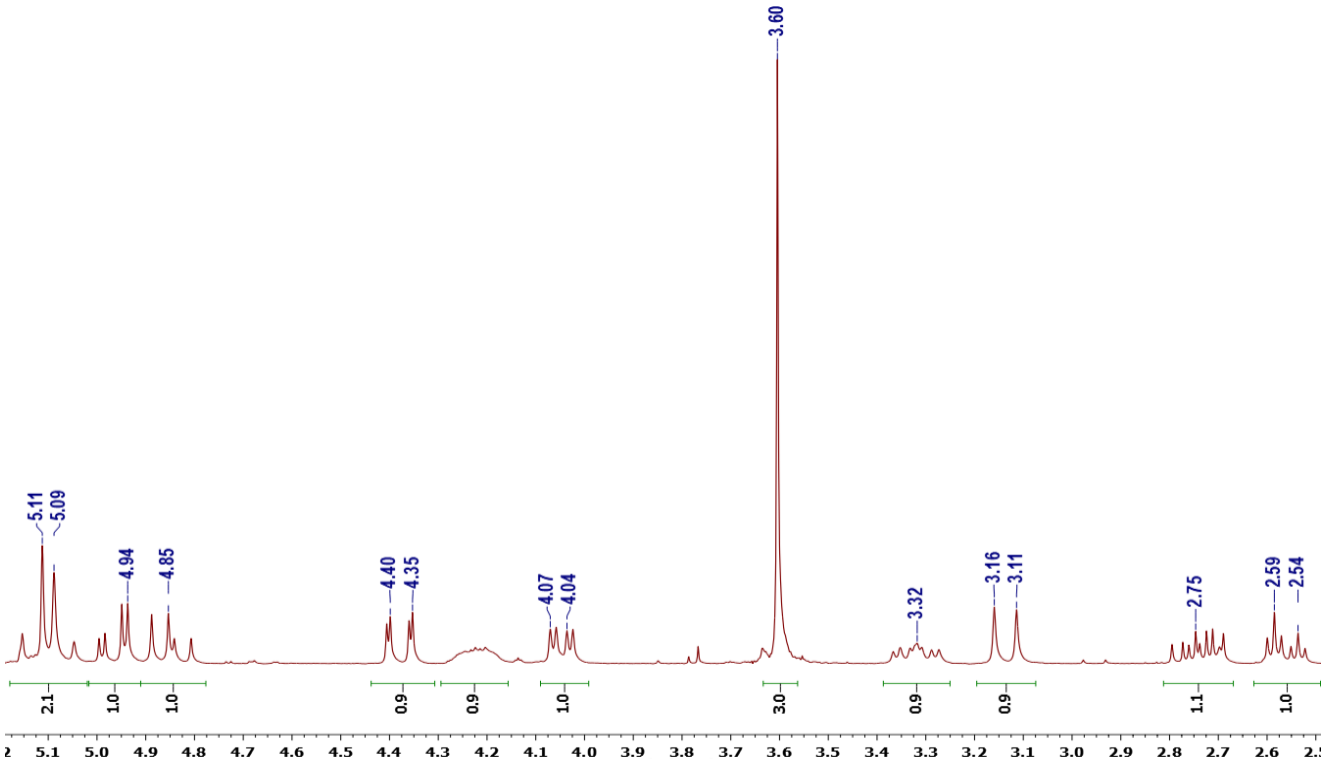


^{13}C NMR, $CDCl_3$, 75 MHz @ 25 °C

Compound **3h**.

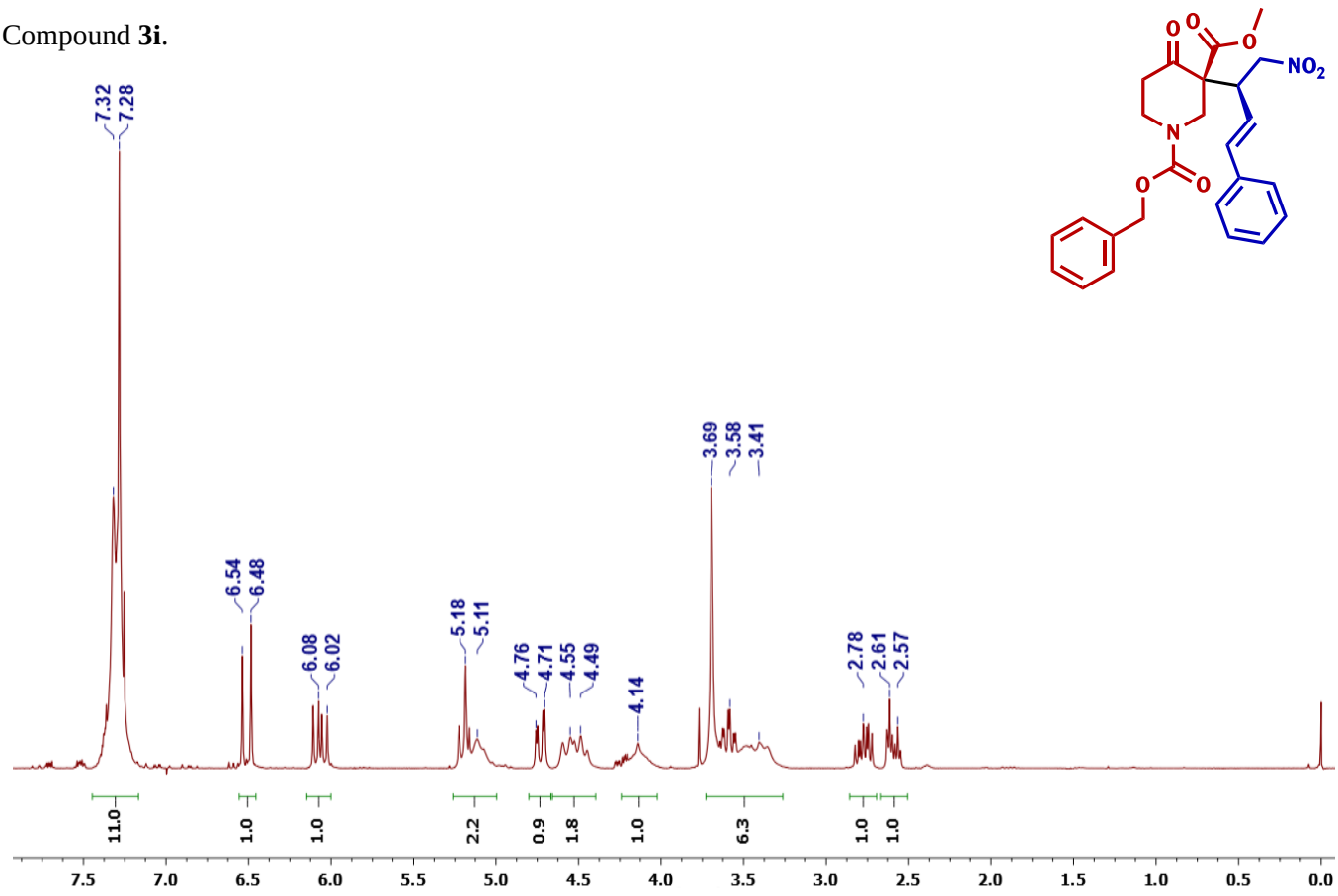


^{1}H NMR, $CDCl_3$, 300 MHz @ 55 °C

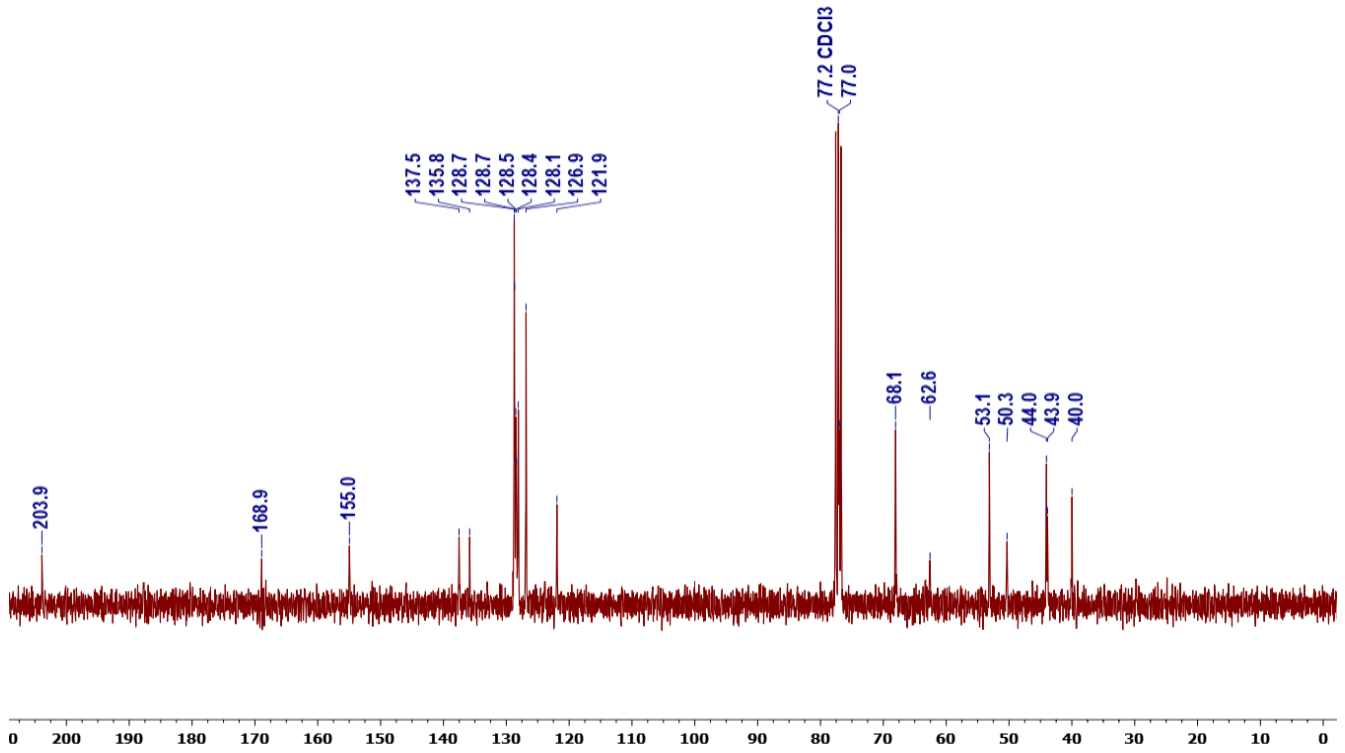


^{1}H NMR, $CDCl_3$, 300 MHz @ 55 °C

Compound **3i**.

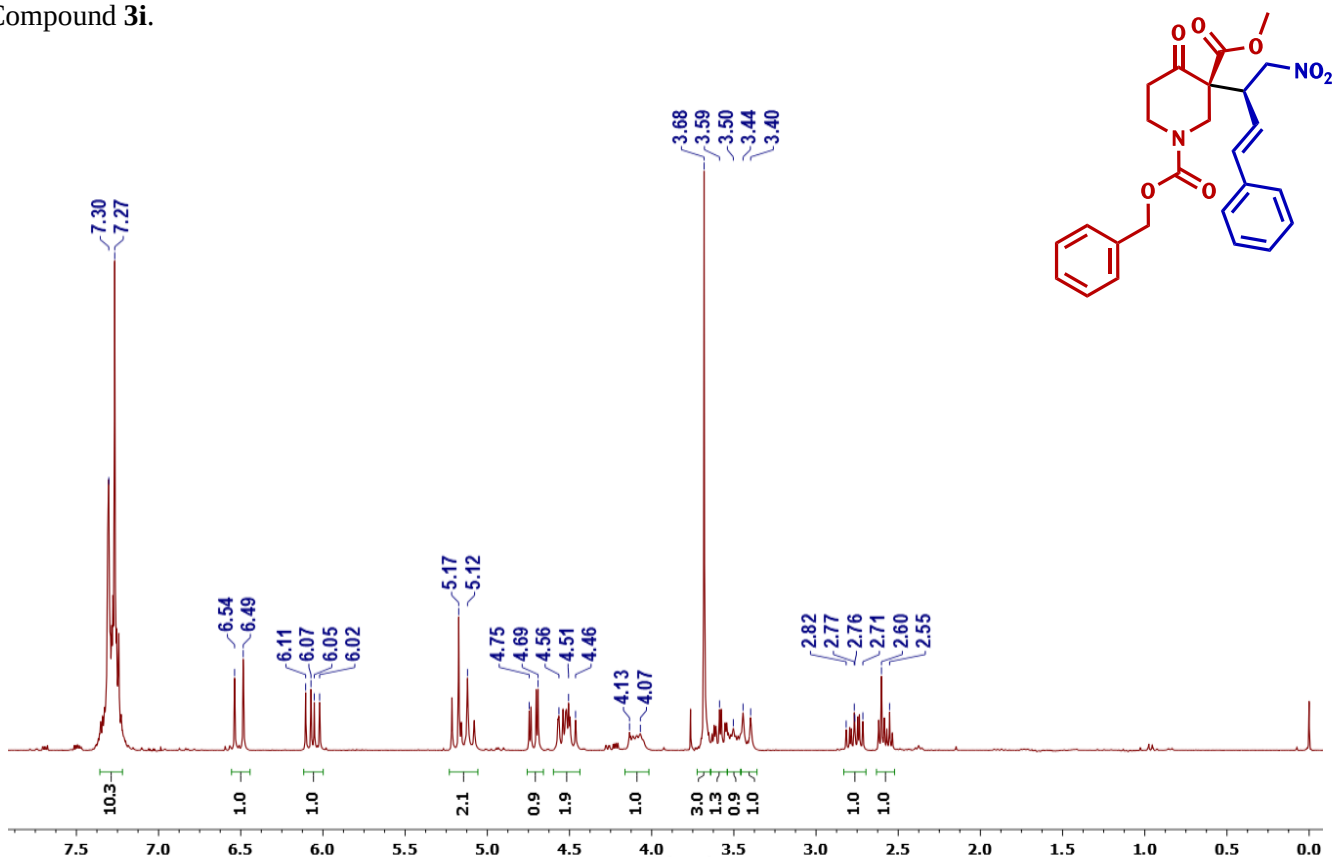


^{1}H NMR, $CDCl_3$, 300 MHz @ 25 °C

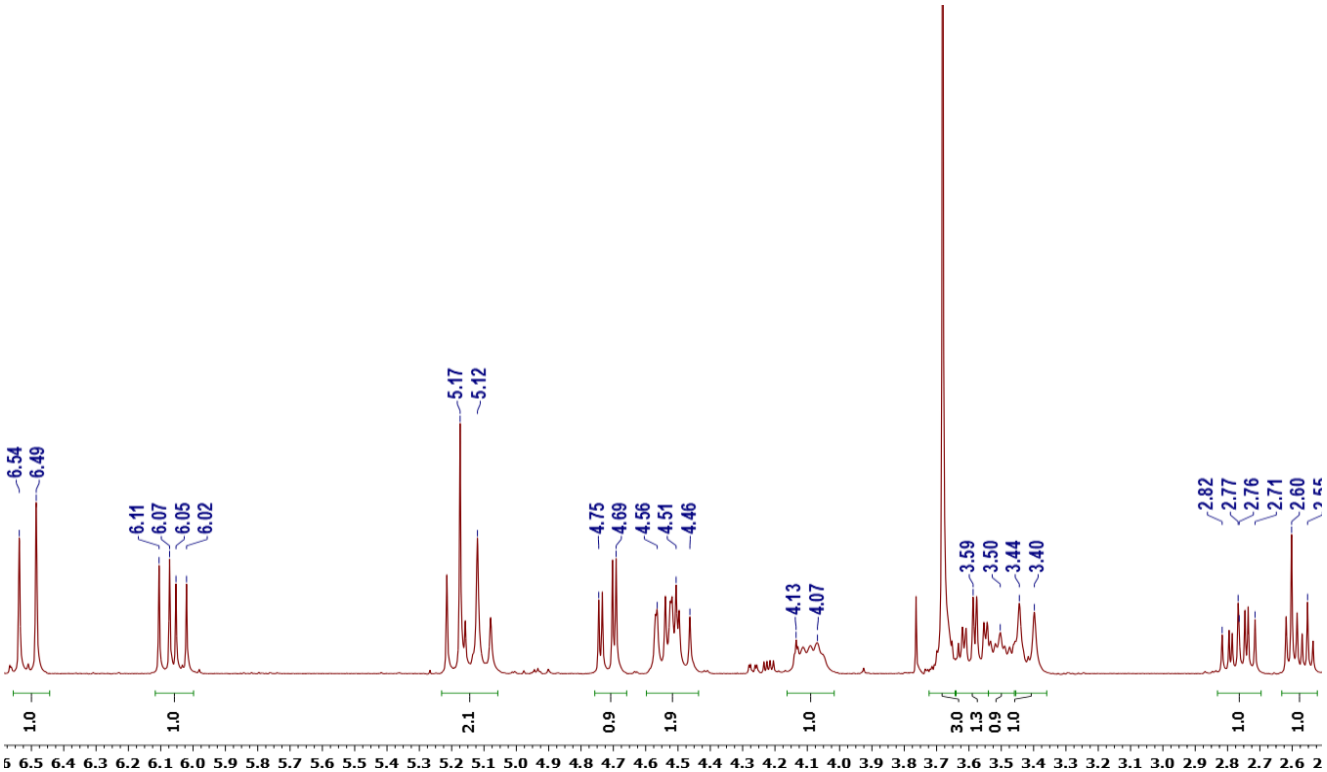


^{13}C NMR, $CDCl_3$, 75 MHz @ 25 °C

Compound **3i**.

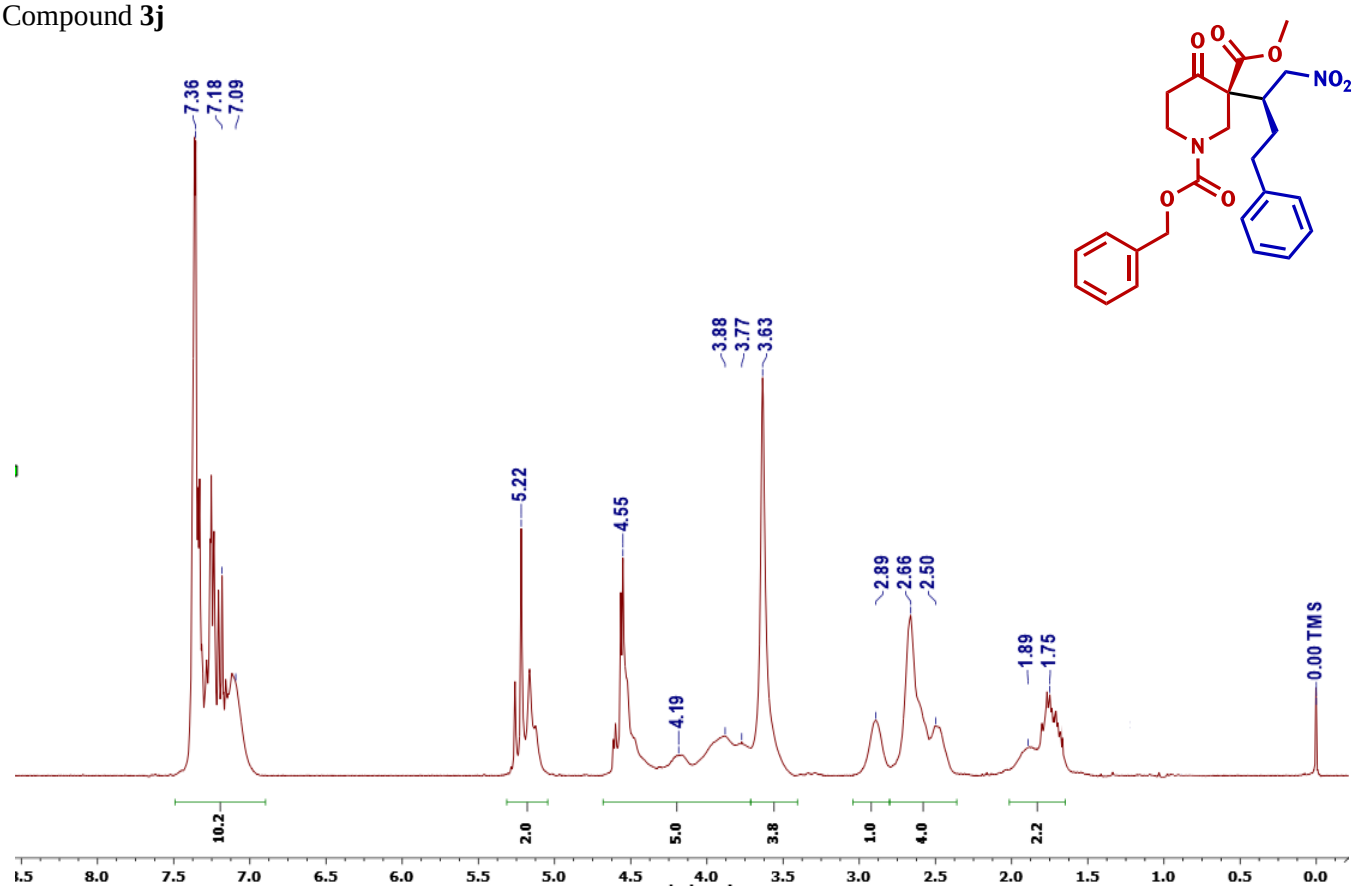


^{1}H NMR, $CDCl_3$, 300 MHz @ 55 °C

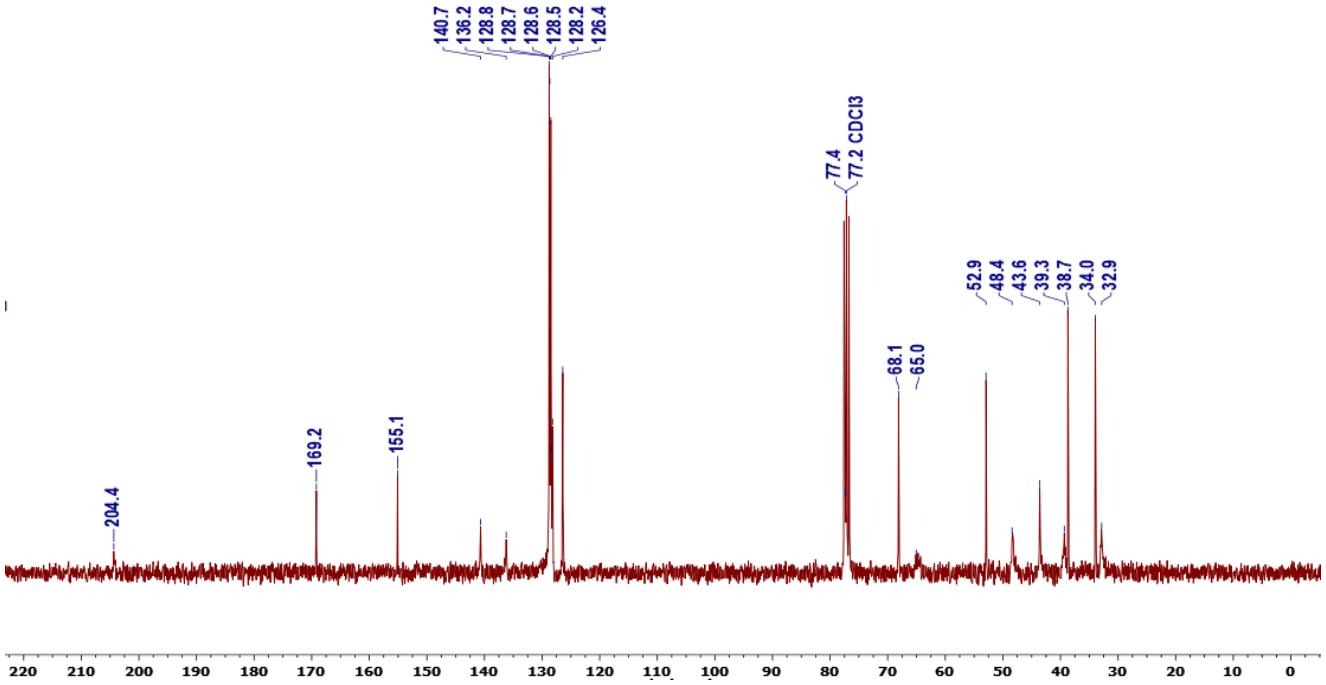


^{1}H NMR, $CDCl_3$, 300 MHz @ 55 °C

Compound **3j**

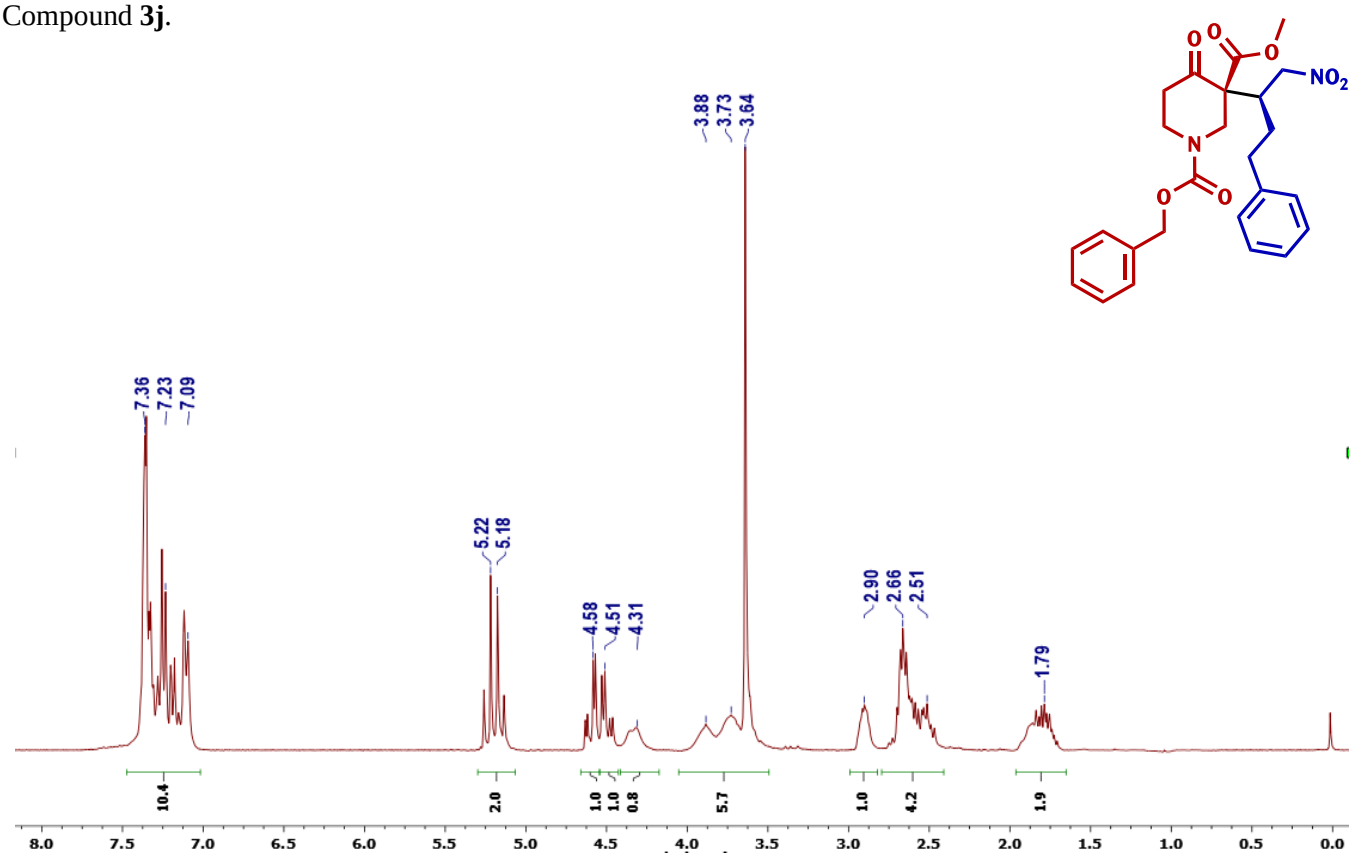


^{1}H NMR, $CDCl_3$, 300 MHz @ 25 °C

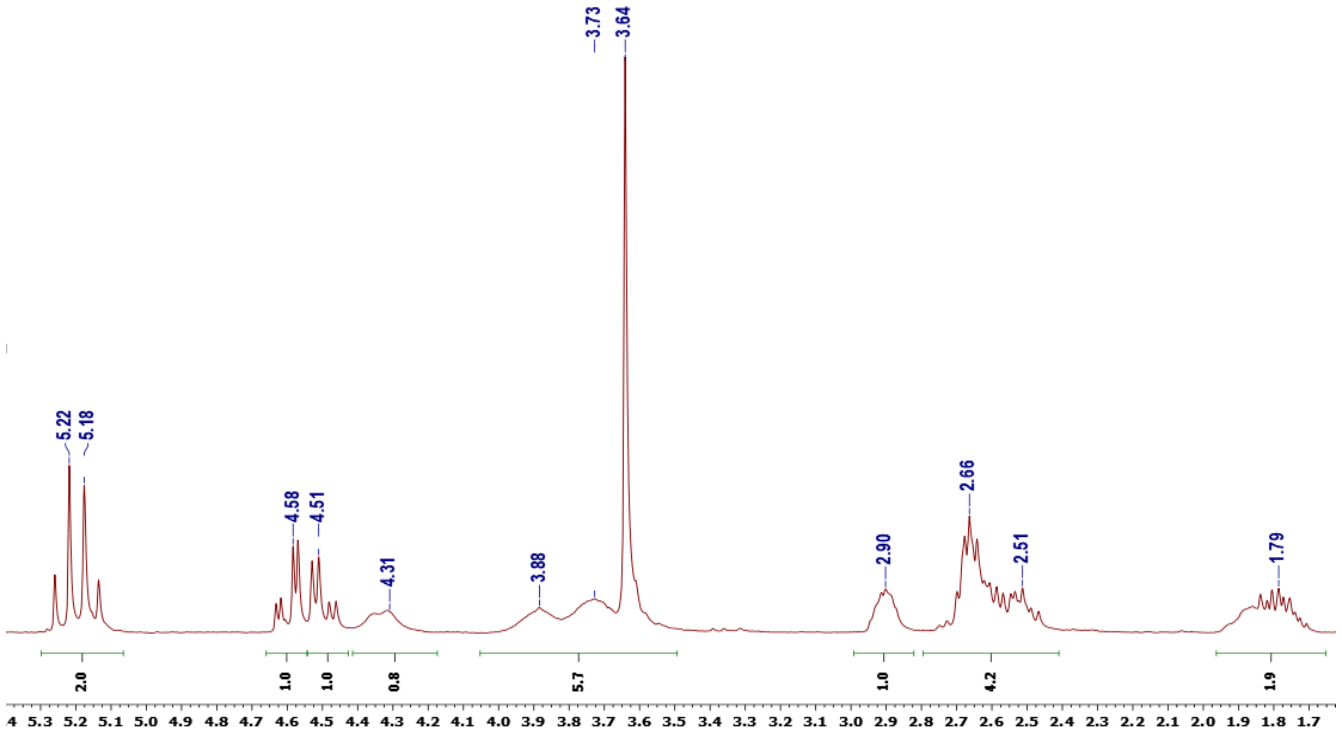


^{13}C NMR, $CDCl_3$, 75 MHz @ 25 °C

Compound **3j**.

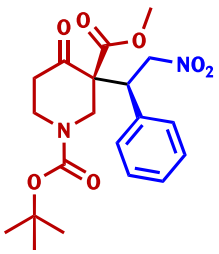


^{1}H NMR, $CDCl_3$, 300 MHz @ 55 °C

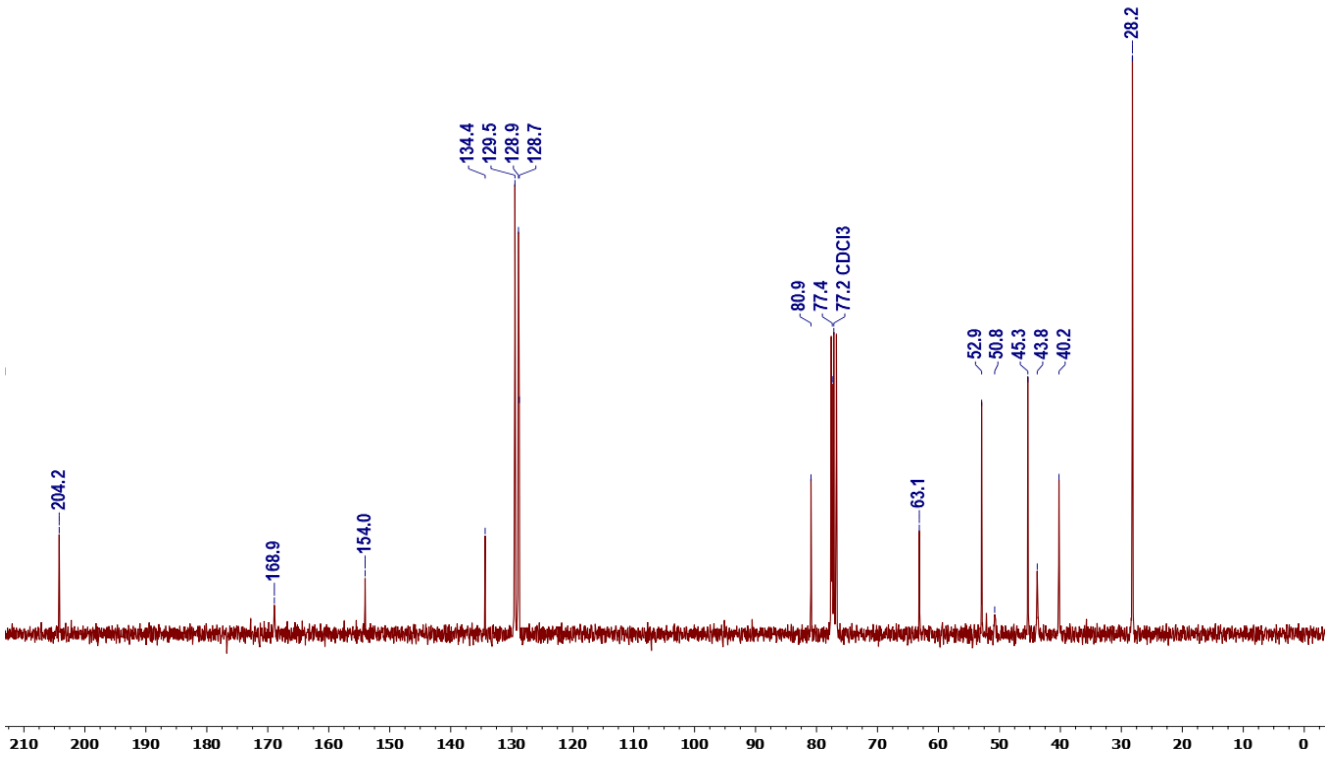


^{1}H NMR, $CDCl_3$, 300 MHz @ 55 °C

Compound **3k**.

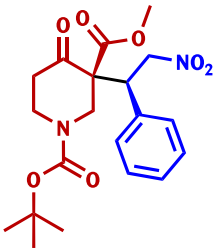


^{1}H NMR, $CDCl_3$, 300 MHz @ 25 °C

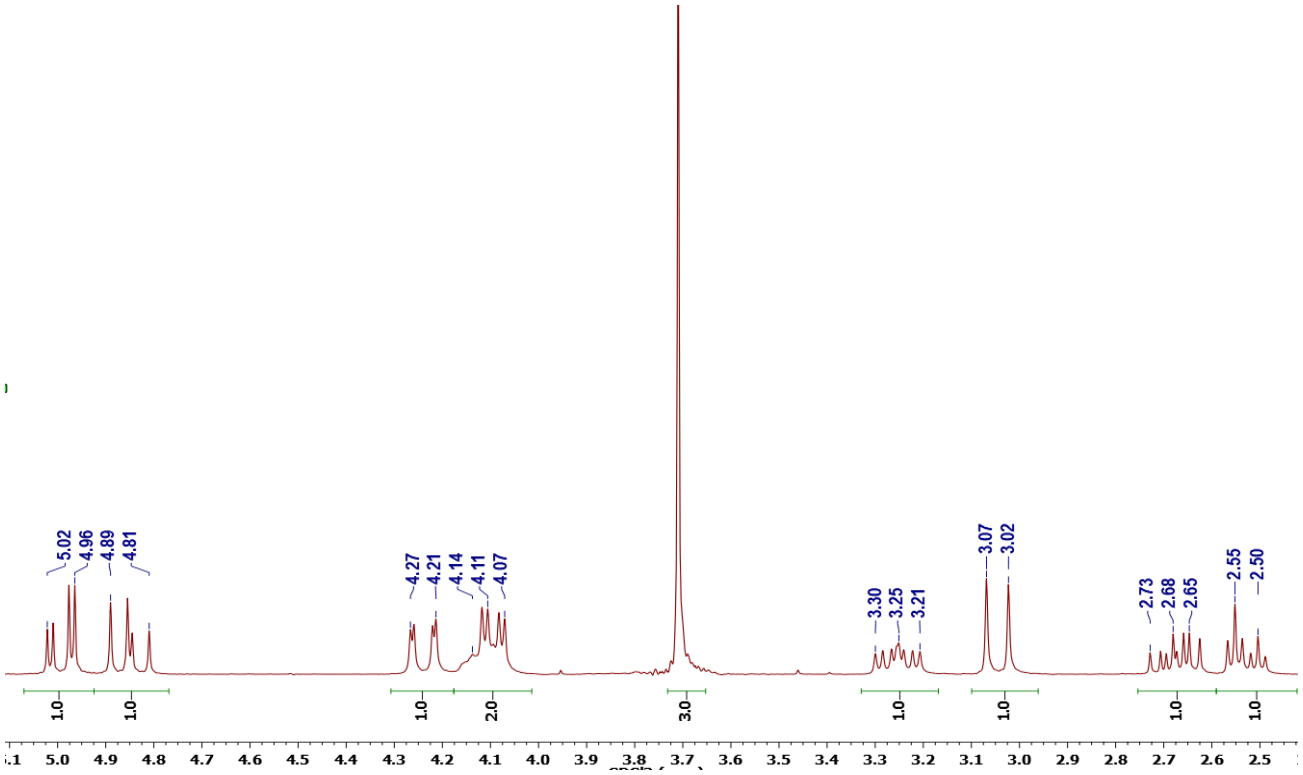


^{13}C NMR, $CDCl_3$, 75 MHz @ 25 °C

Compound **3k**.

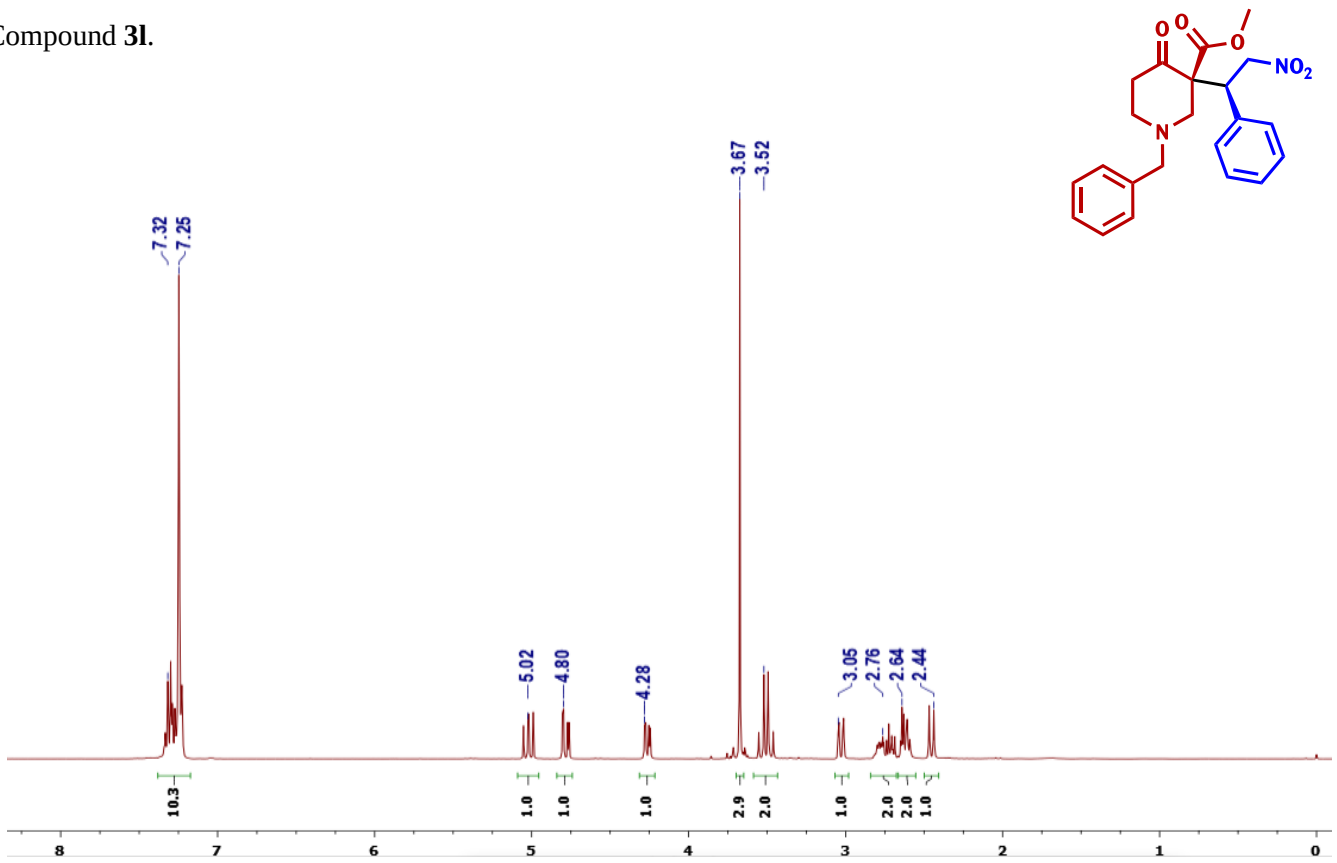


^{1}H NMR, $CDCl_3$, 300 MHz @ 55 °C

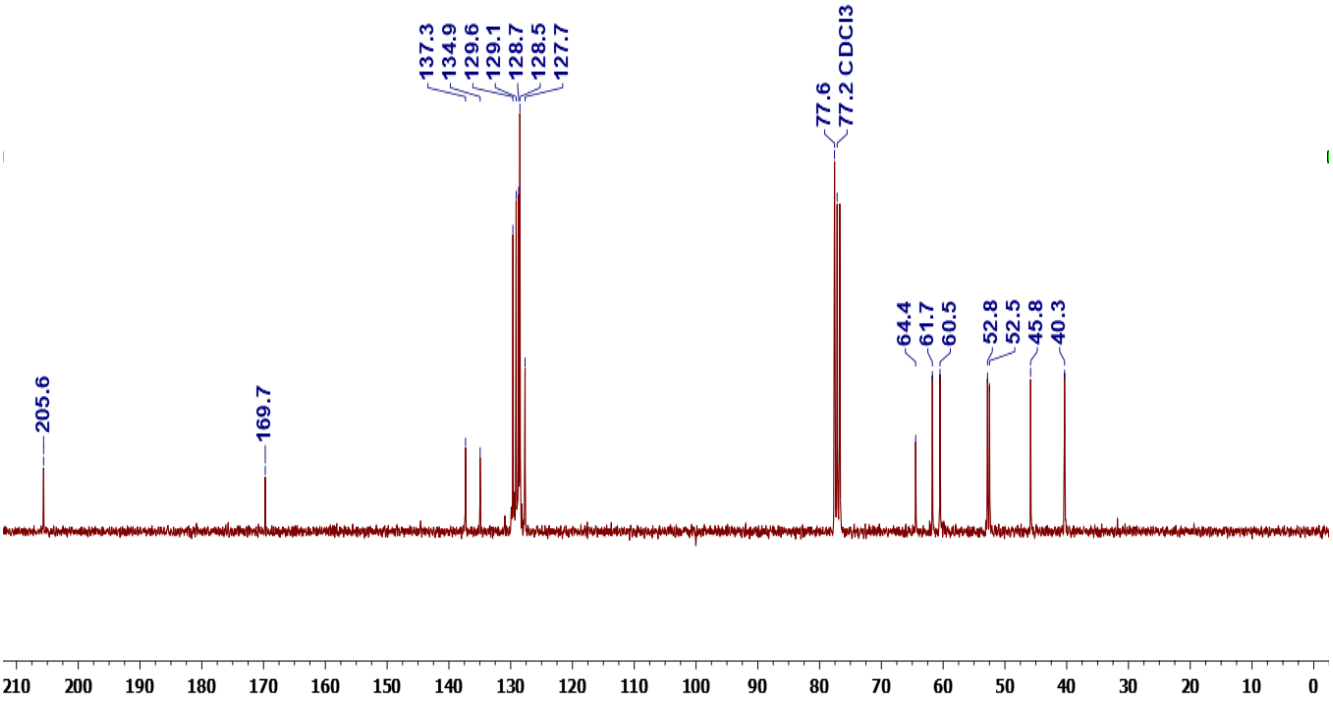


^{1}H NMR, $CDCl_3$, 300 MHz @ 55 °C

Compound **3l**.

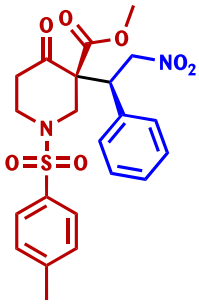


^{1}H NMR, $CDCl_3$, 400 MHz @ 25 °C

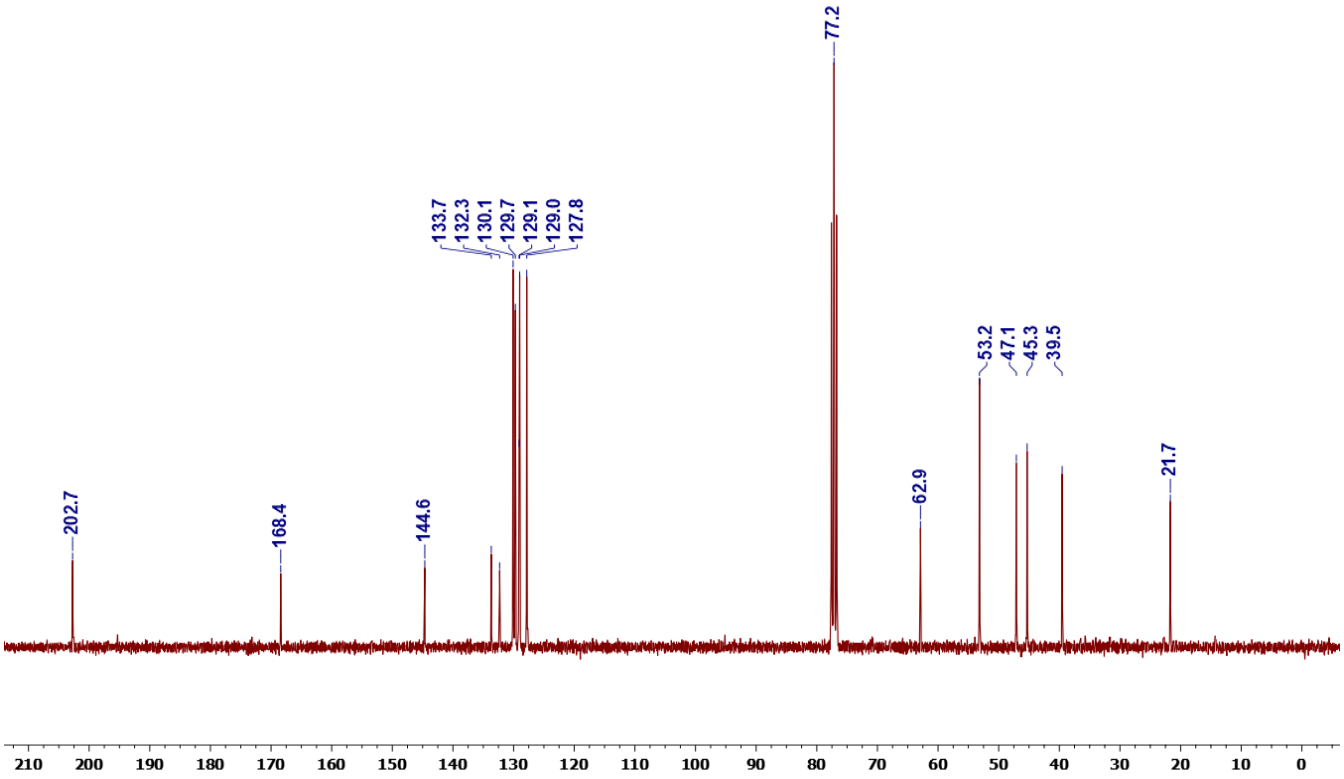


^{13}C NMR, $CDCl_3$, 75 MHz @ 25 °C

Compound **3m**.



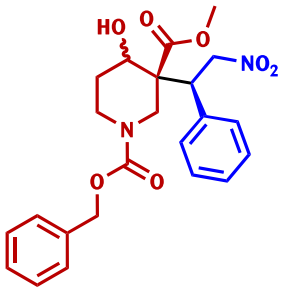
^{1}H NMR, $CDCl_3$, 300 MHz @ 25 °C

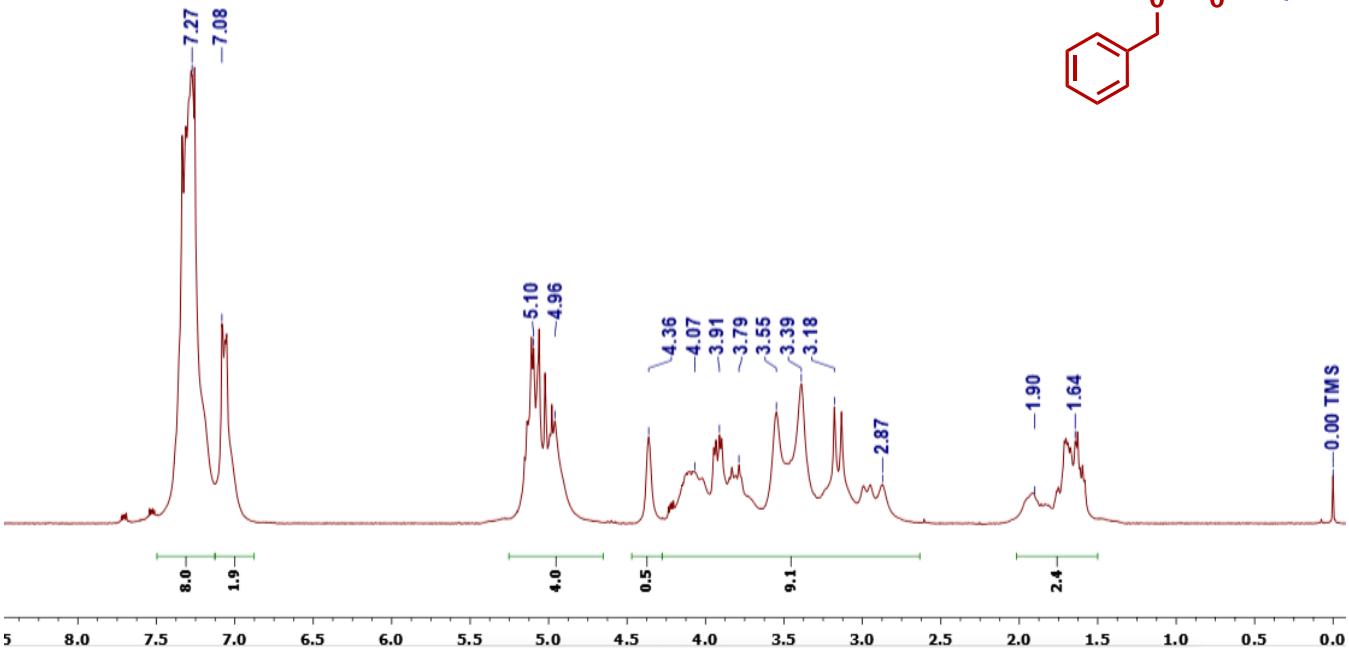


^{13}C NMR, $CDCl_3$, 75 MHz @ 25 °C

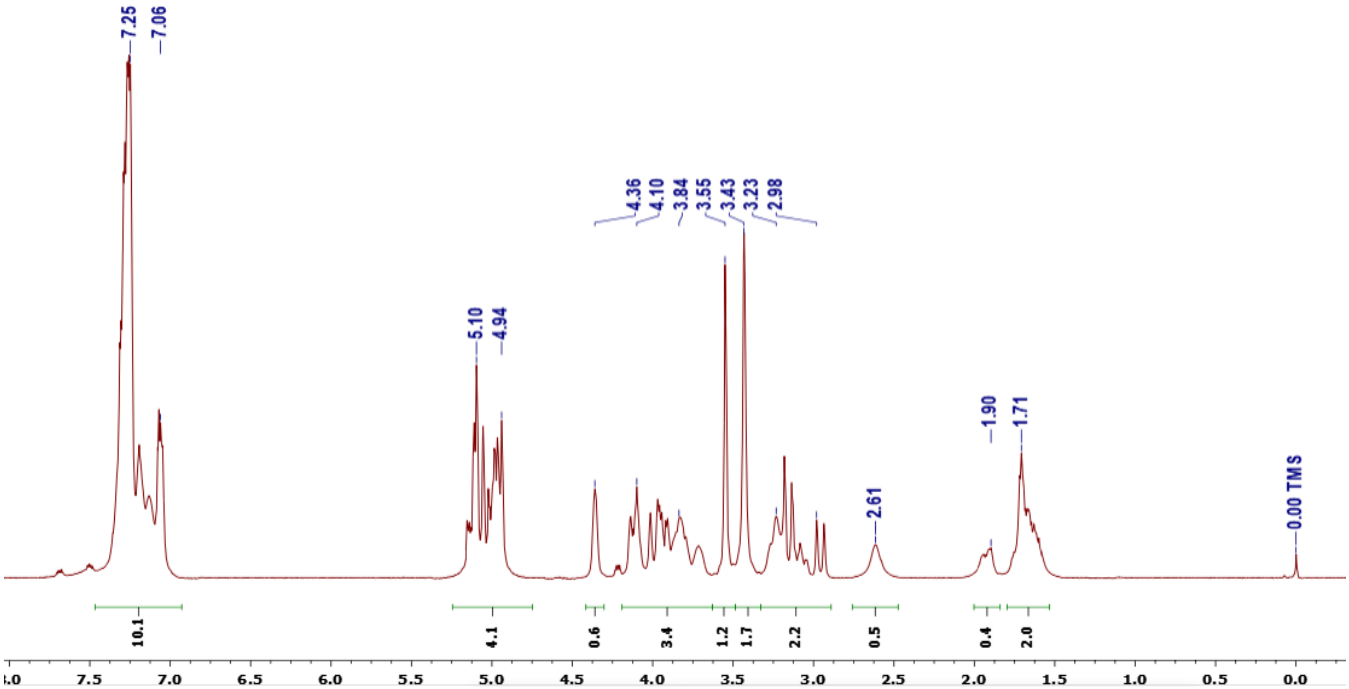
8.5 Isomorphan intermediates

Compound **4-Cbz**



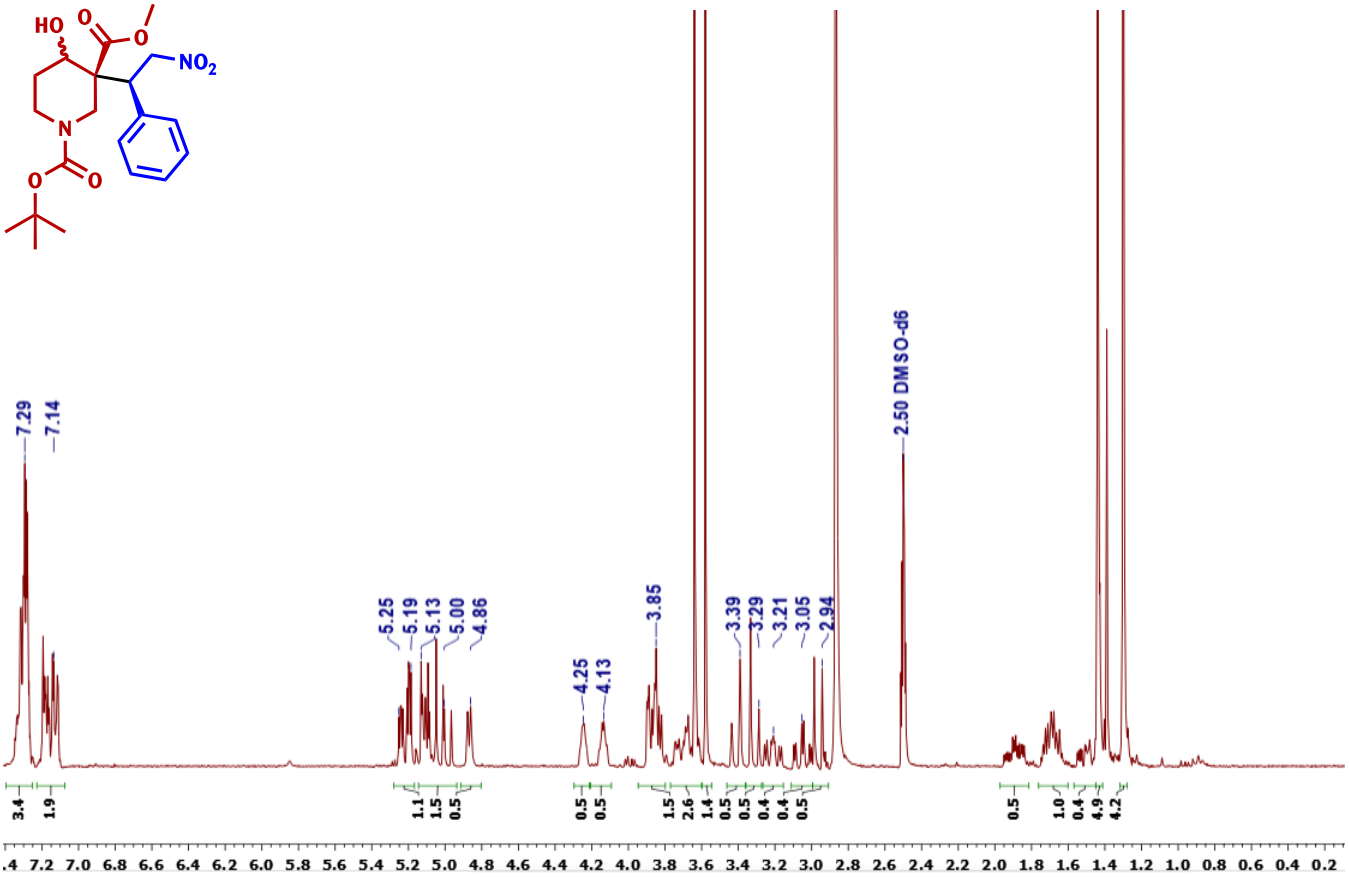


^{1}H NMR, $CDCl_3$, 300 MHz @ 25 °C

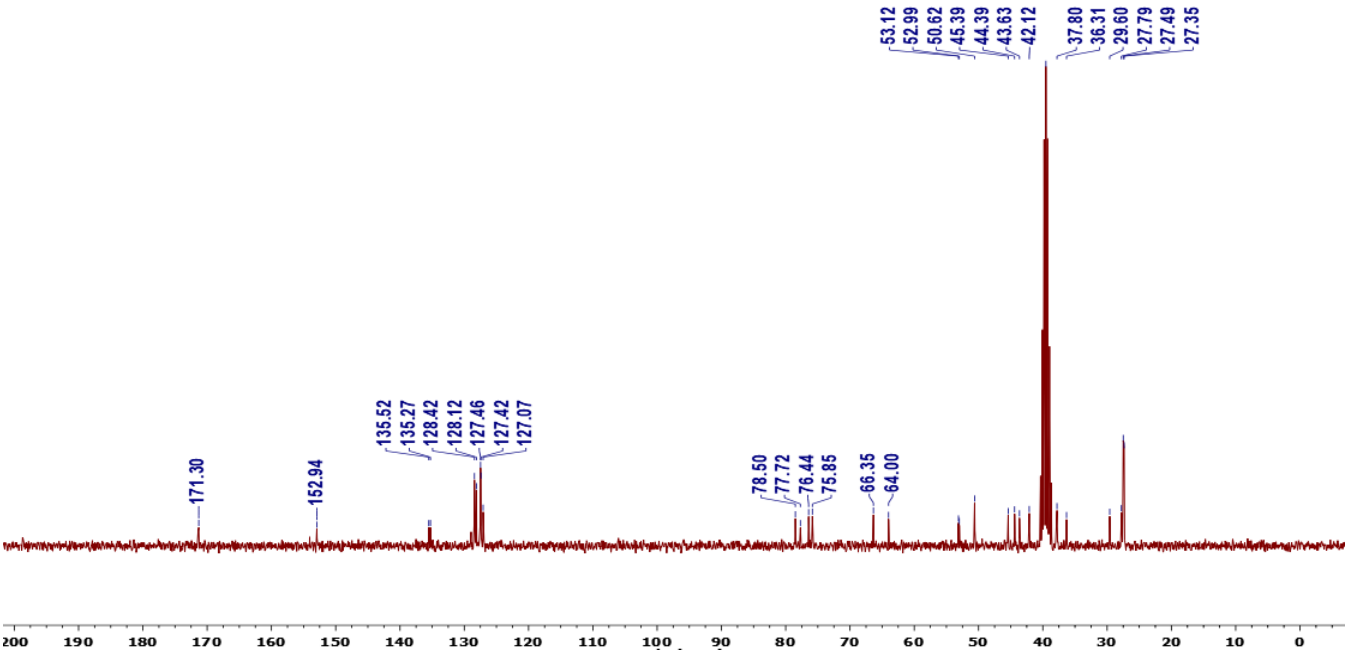


^{1}H NMR, $CDCl_3$, 300 MHz @ 55 °C

Compound **4-Boc**

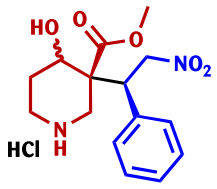


^{1}H NMR, DMSO-*d6*, 300 MHz @ 120 °C

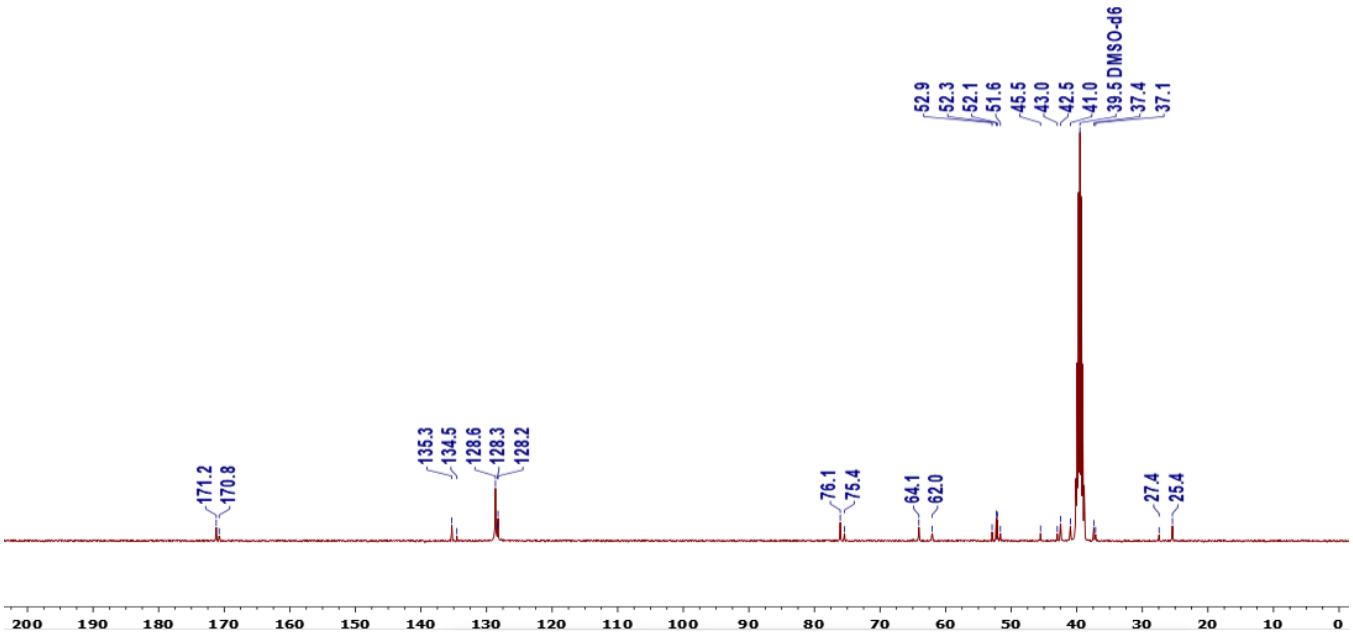


^{13}C NMR, DMSO-*d6*, 75 MHz @ 120 °C

Compound **5**



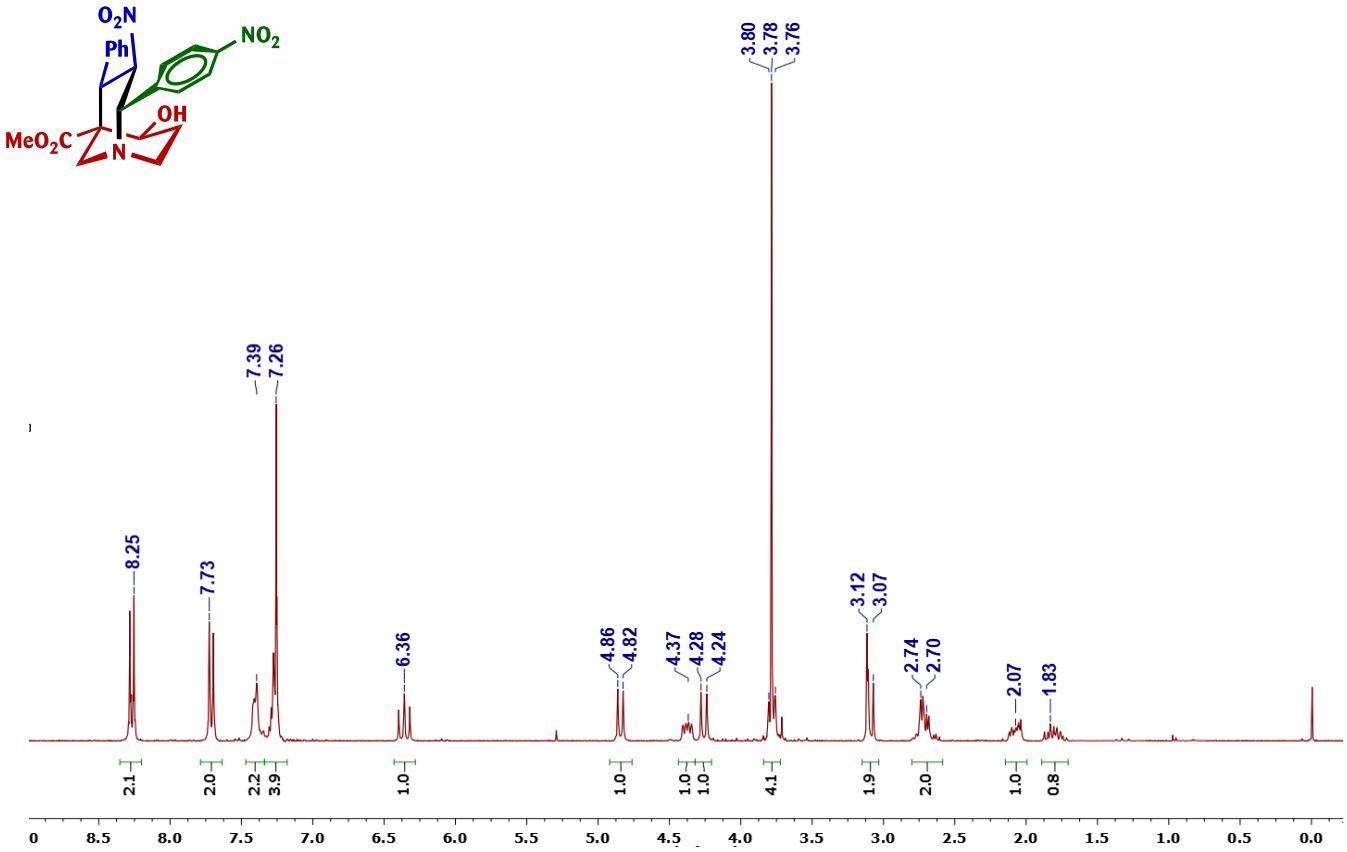
^{1}H NMR, DMSO-*d6*, 700 MHz @ 25 °C



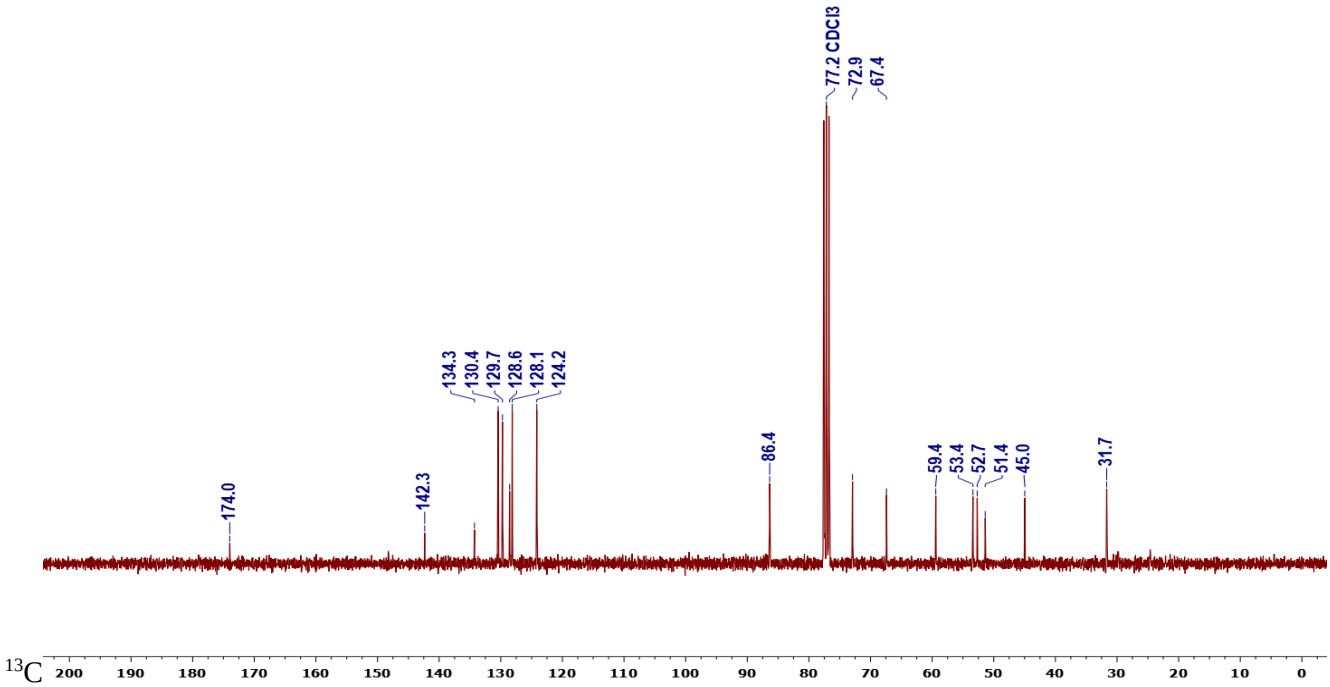
^{13}C NMR, DMSO-*d6*, 100 MHz @ 25 °C

8.6 Isomorphans

Compound **6a**

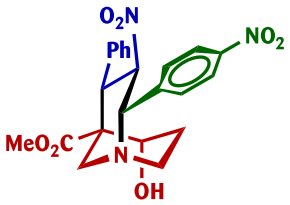


^{1}H NMR, $CDCl_3$, 300 MHz @ 25 °C

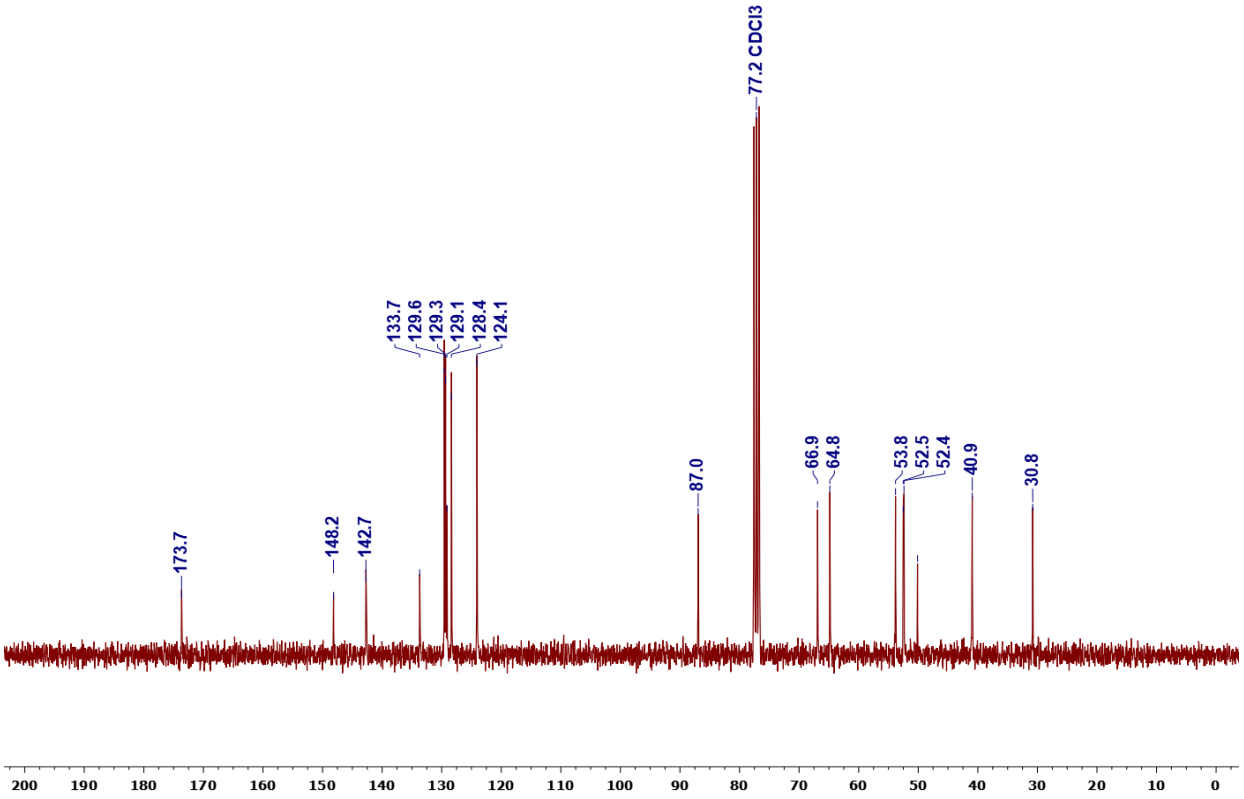


NMR, $CDCl_3$, 75 MHz @ 25 °C

Compound **7a**

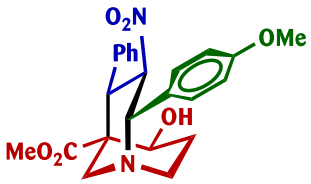


^{1}H NMR, $CDCl_3$, 300 MHz @ 25 °C

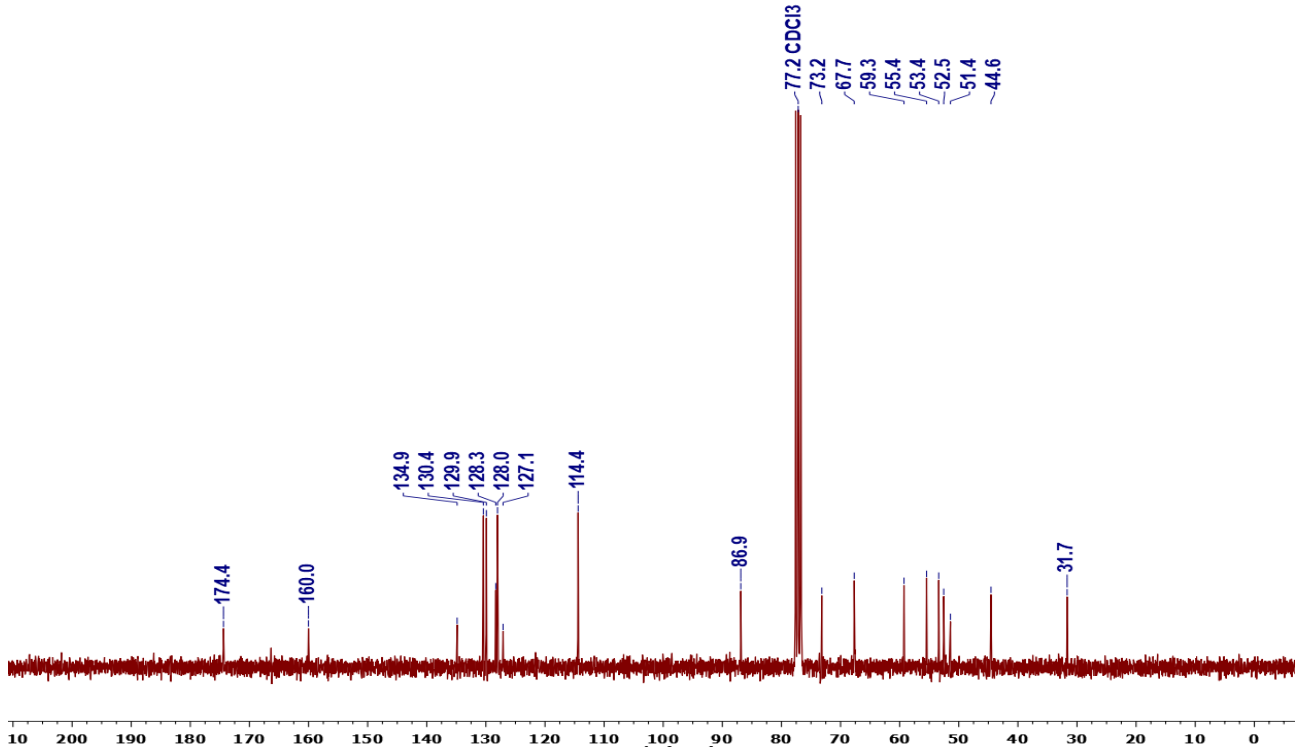


^{13}CNMR, $CDCl_3$, 75 MHz @ 25 °C

Compound **6b**

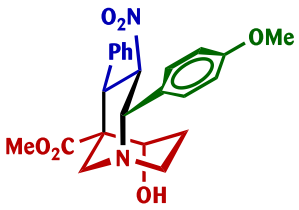


^{1}H NMR, $CDCl_3$, 300 MHz @ 25 °C

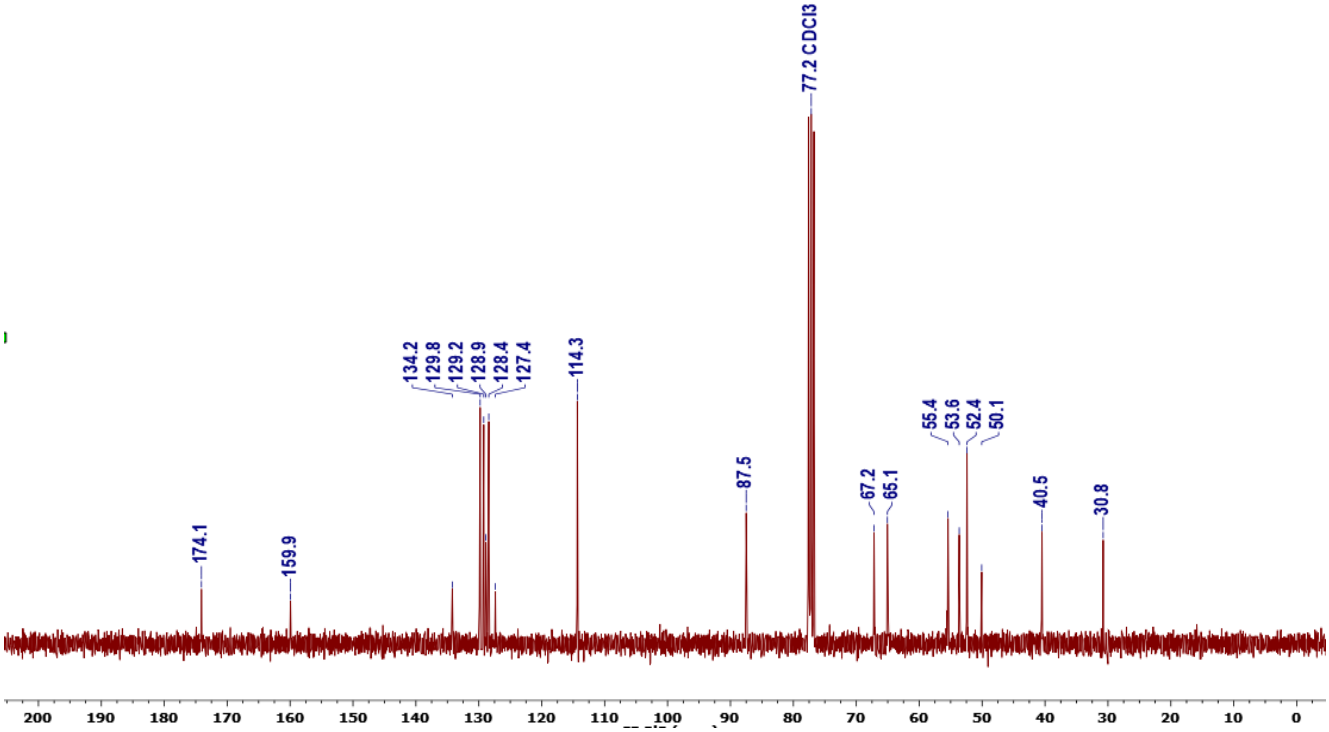


^{13}C NMR, $CDCl_3$, 75 MHz @ 25 °C

Compound **7b**

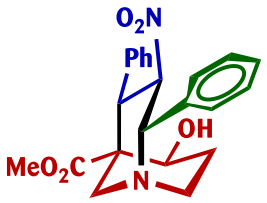


^{1}H NMR, $CDCl_3$, 300 MHz @ 25 °C

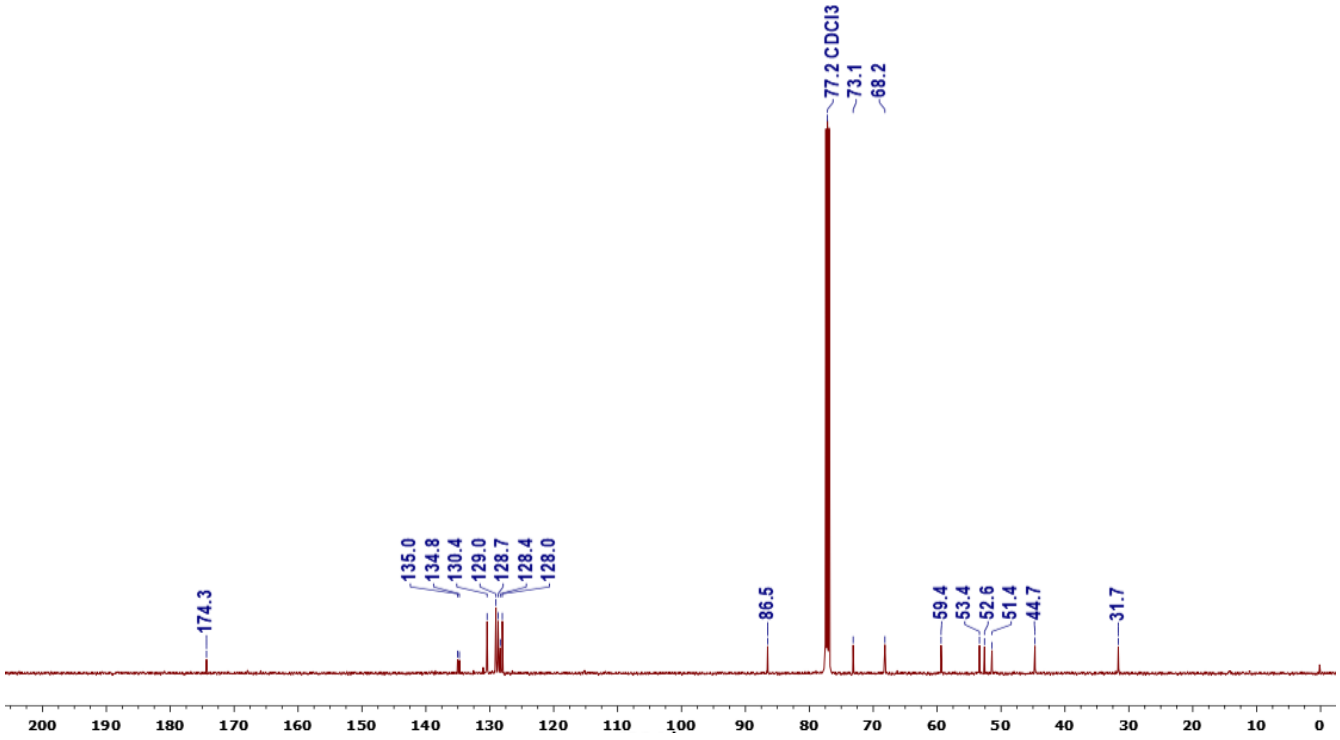


^{13}CNMR, $CDCl_3$, 75 MHz @ 25 °C

Compound **6c**

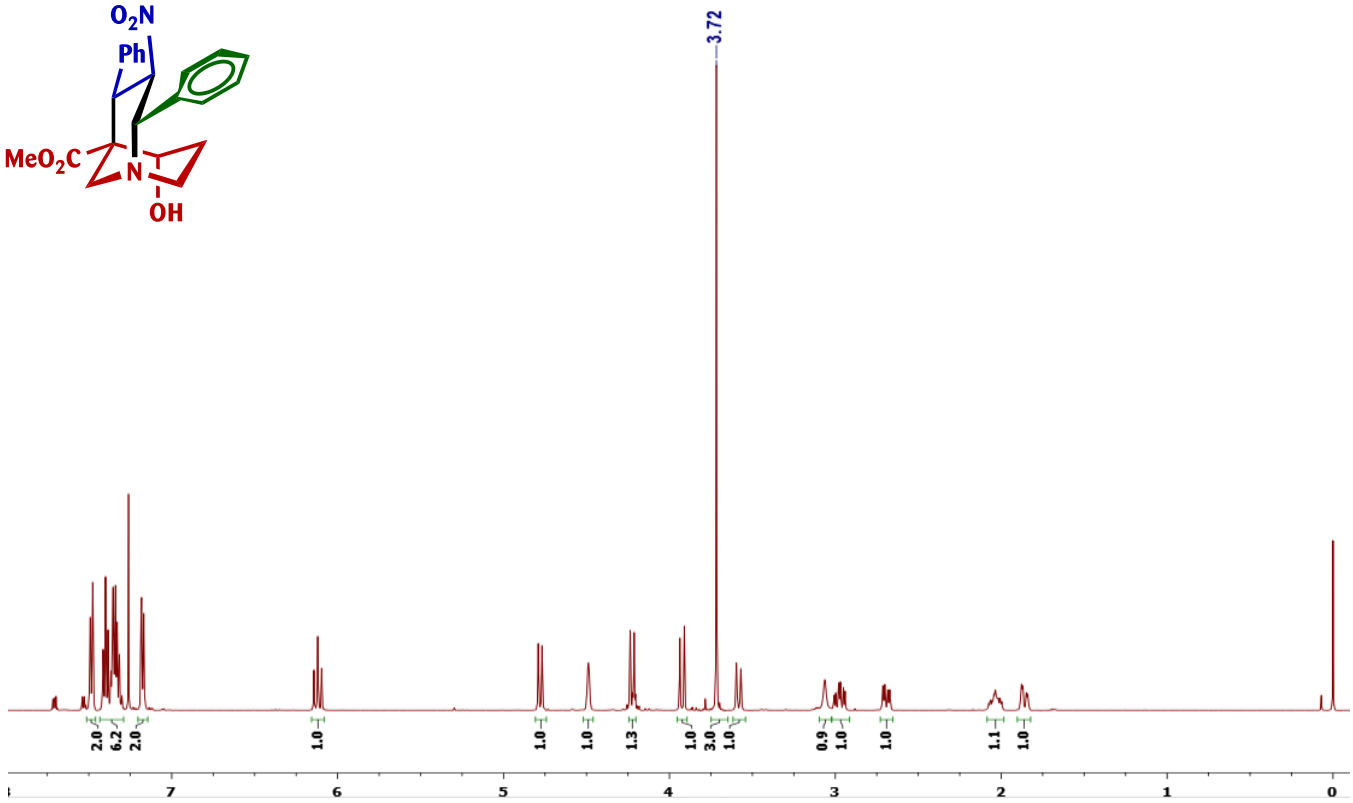


^{1}H NMR, $CDCl_3$, 500 MHz @ 25 °C

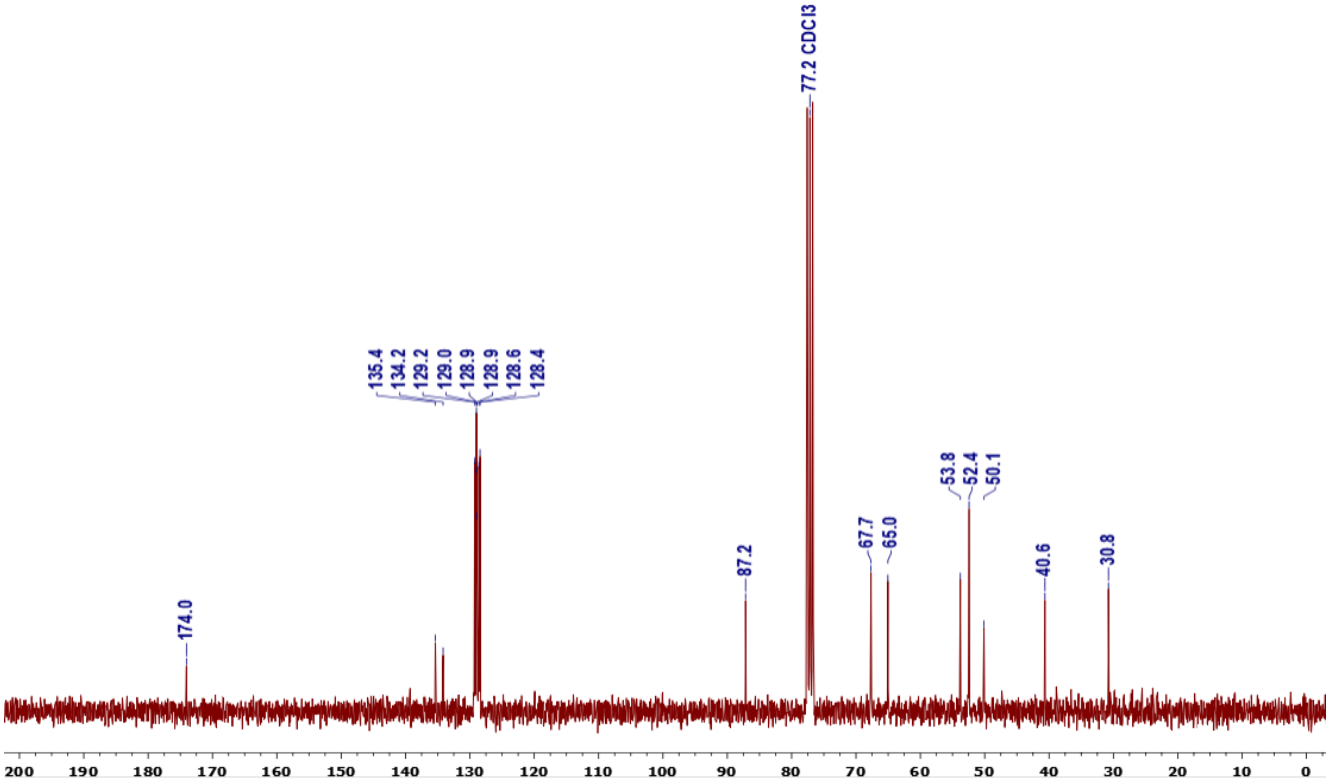


^{13}C NMR, $CDCl_3$, 125 MHz @ 25 °C

Compound **7c**

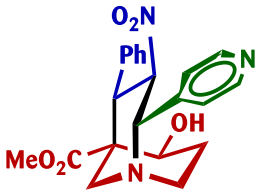


^{1}H NMR, $CDCl_3$, 500 MHz @ 25 °C

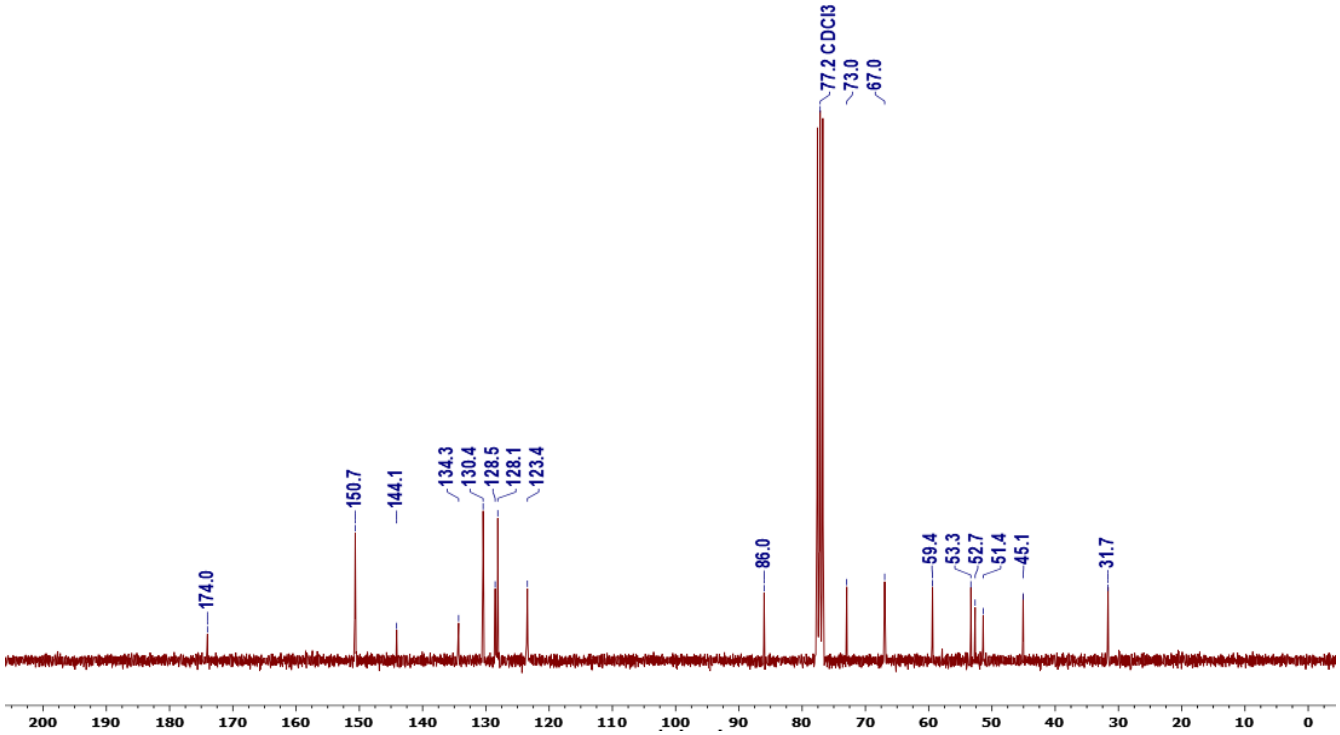


^{13}CNMR, $CDCl_3$, 75 MHz @ 25 °C

Compound **6d**

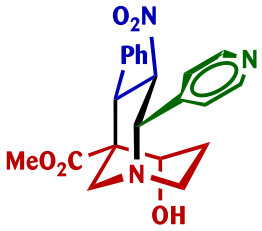


^{1}H NMR, $CDCl_3$, 400 MHz @ 25 °C

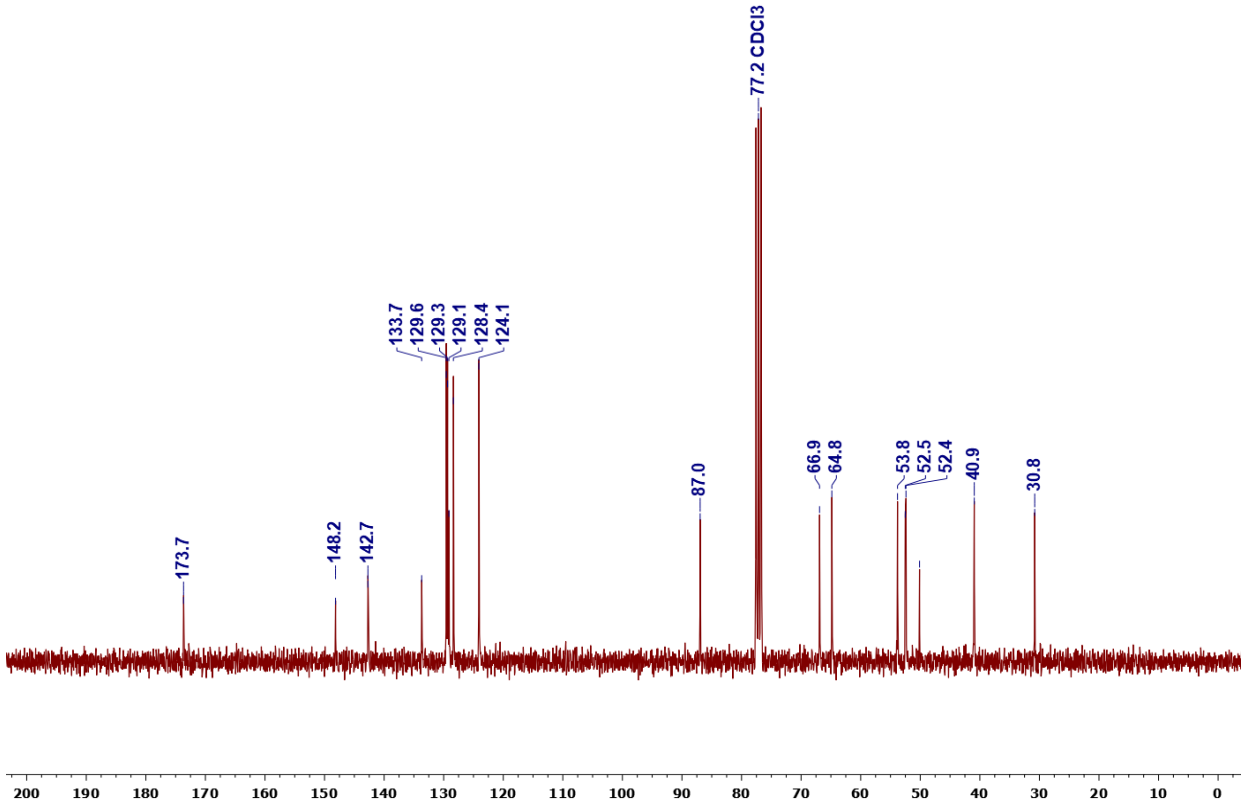


^{13}C NMR, $CDCl_3$, 75 MHz @ 25 °C

Compound **7d**

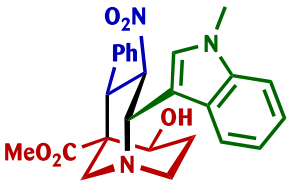


^{1}H NMR, $CDCl_3$, 400 MHz @ 25 °C

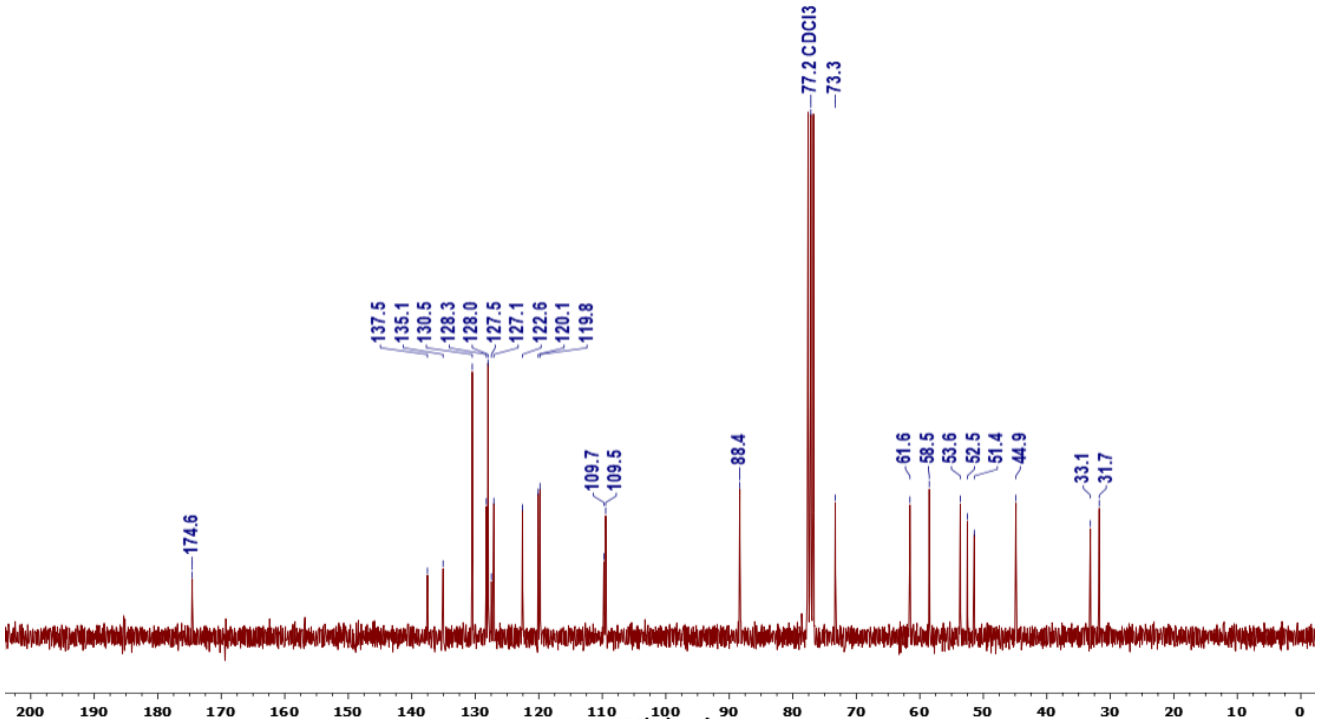


^{13}CNMR, $CDCl_3$, 75 MHz @ 25 °C

Compound **6e**

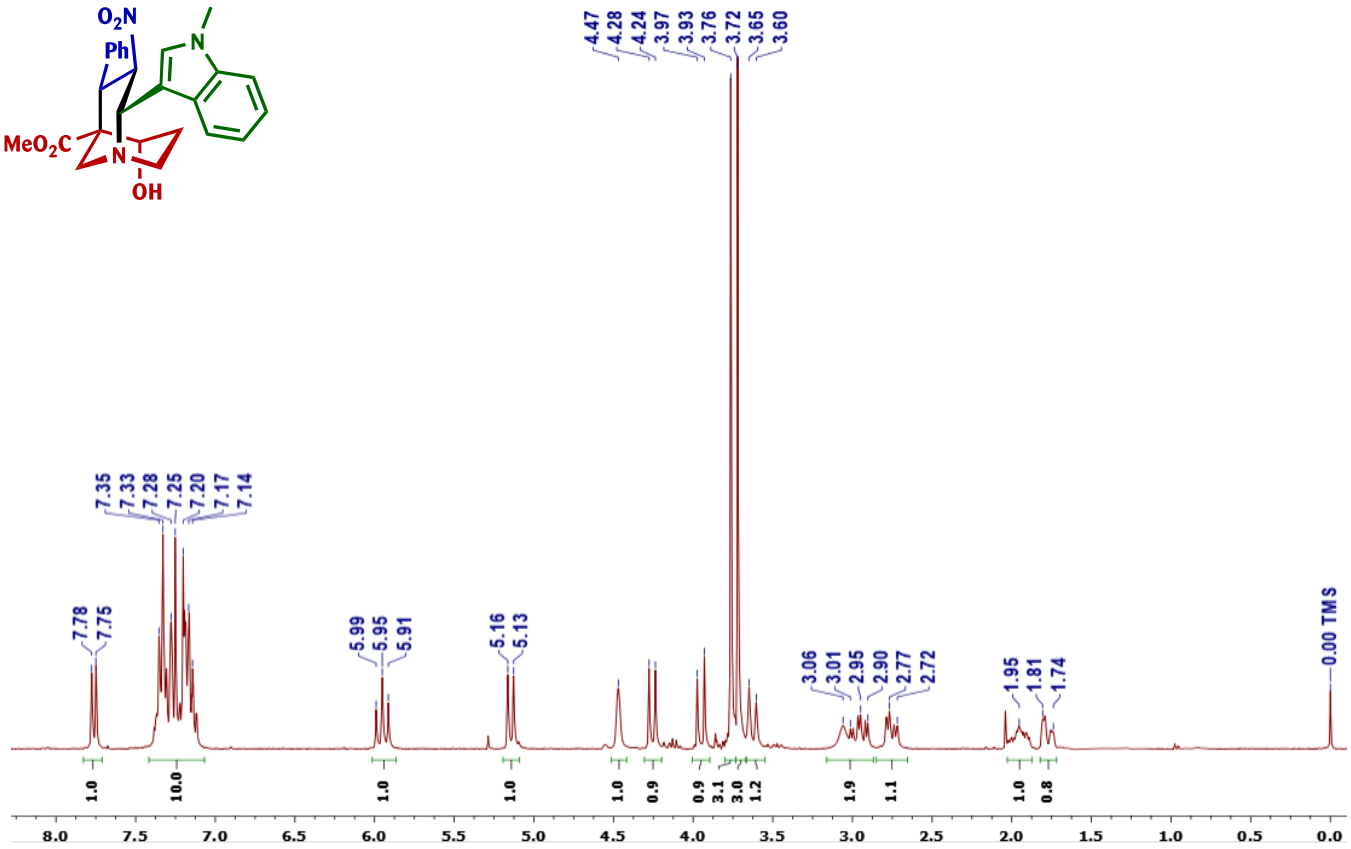


^{1}H NMR, $CDCl_3$, 300 MHz @ 25 °C

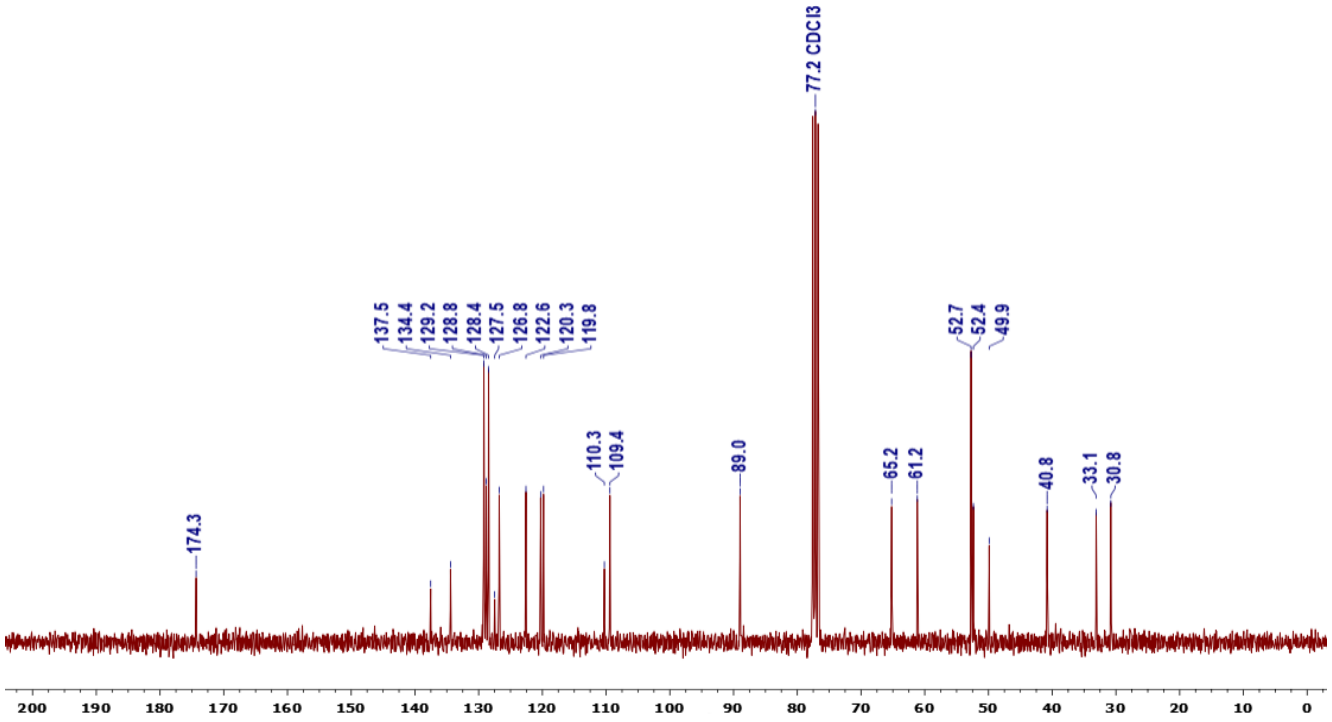


^{13}C NMR, $CDCl_3$, 75 MHz @ 25 °C

Compound **7e**

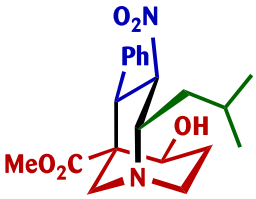


^{1}H NMR, $CDCl_3$, 300 MHz @ 25 °C

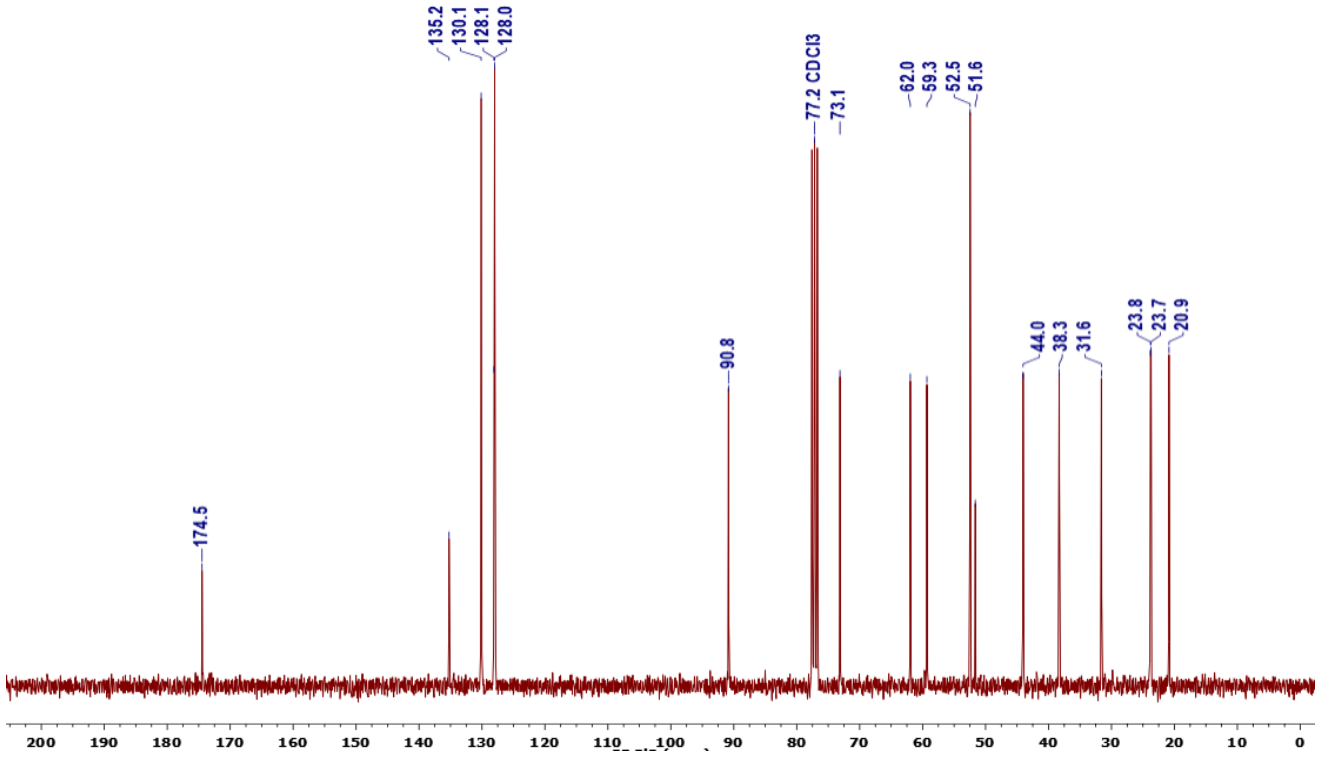


^{13}CNMR, $CDCl_3$, 75 MHz @ 25 °C

Compound **6f**

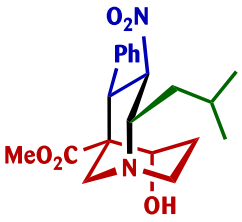


^{1}H NMR, $CDCl_3$, 300 MHz @ 25 °C

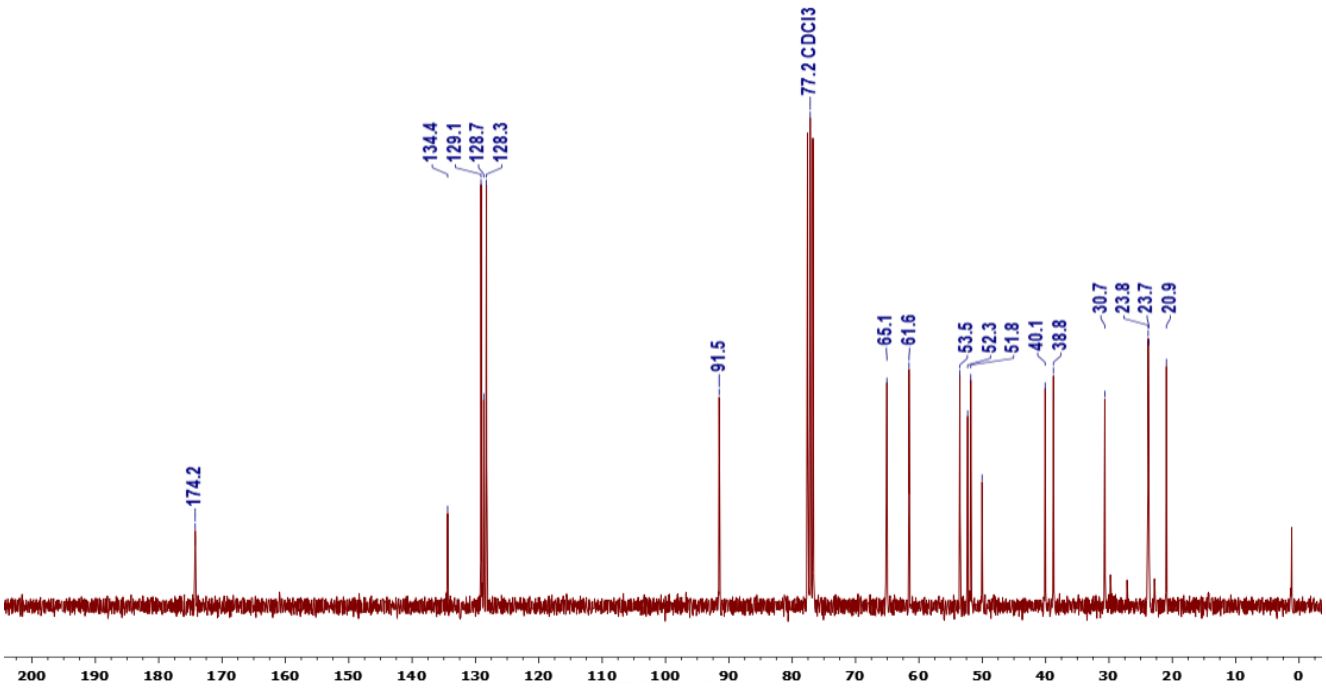


^{13}C NMR, $CDCl_3$, 75 MHz @ 25 °C

Compound **7f**

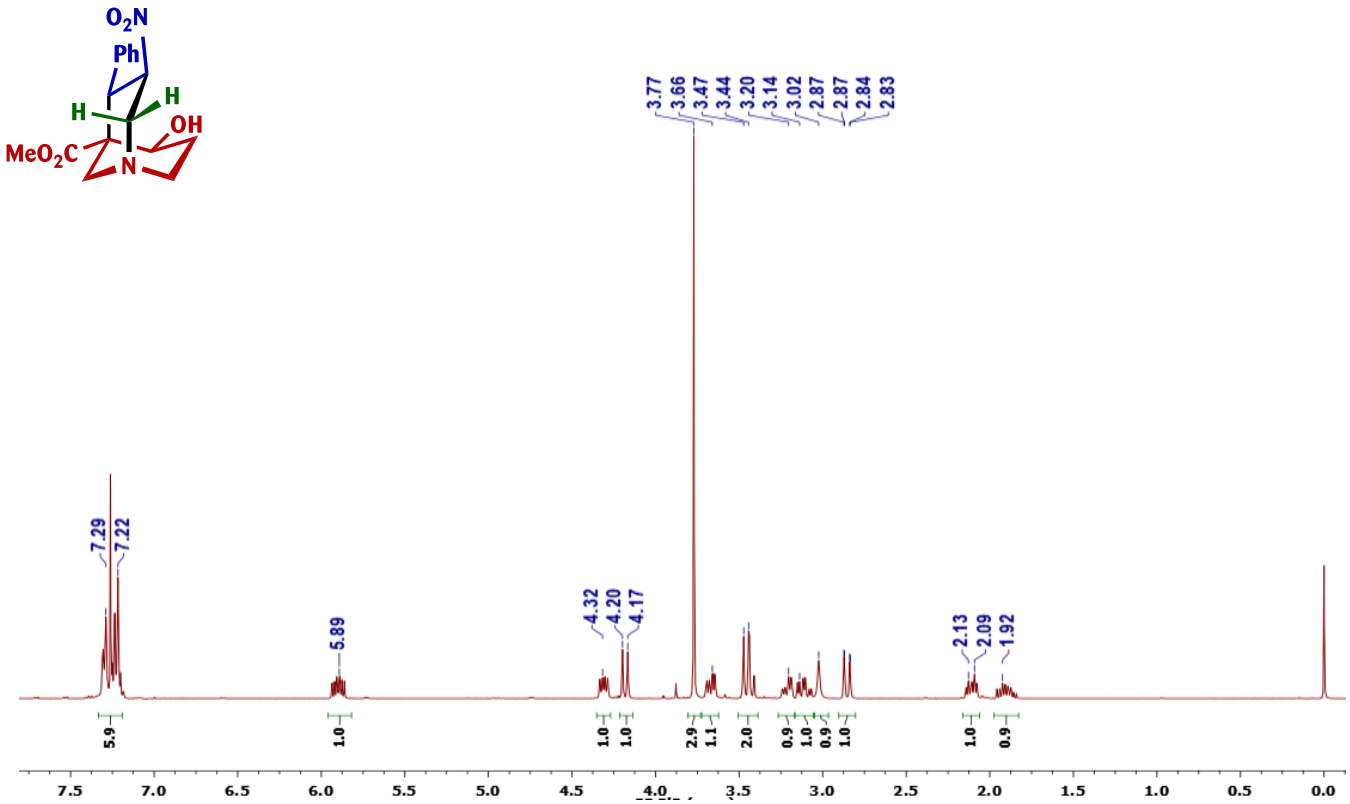


^{1}H NMR, $CDCl_3$, 300 MHz @ 25 °C

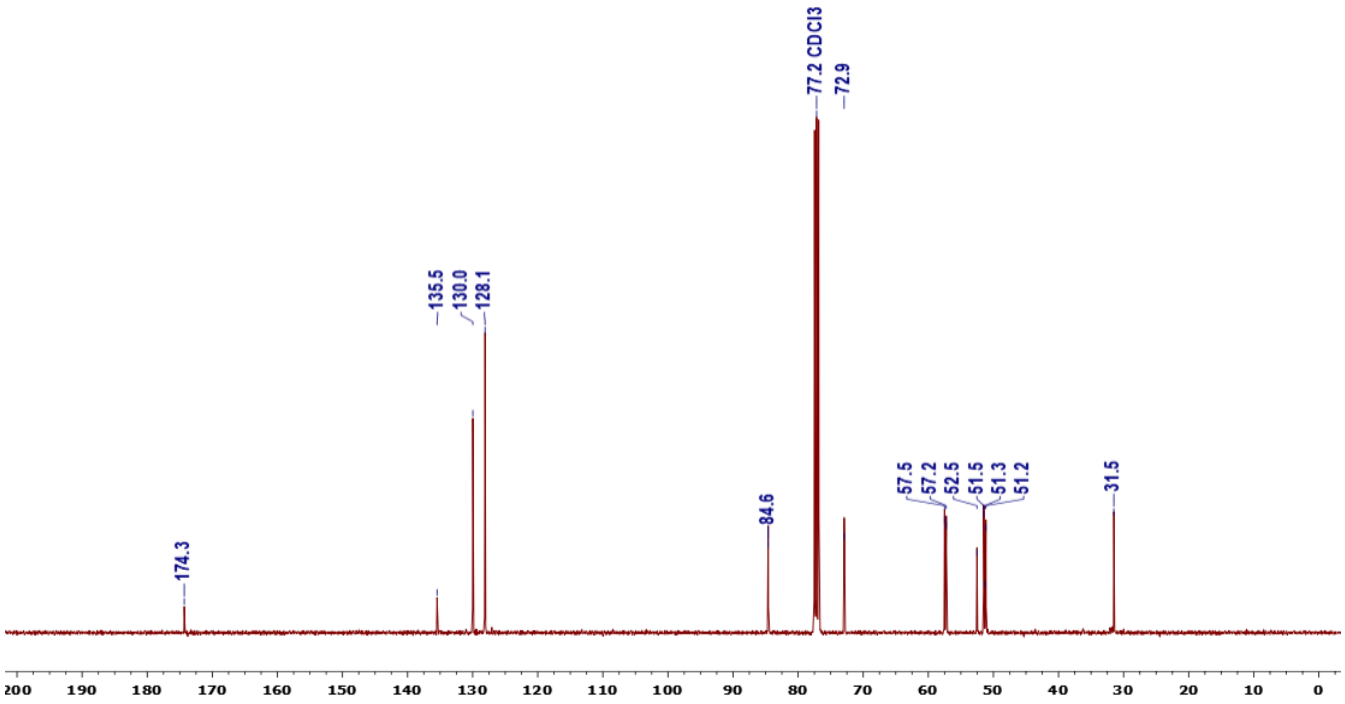


^{13}CNMR, $CDCl_3$, 75 MHz @ 25 °C

Compound **6g**

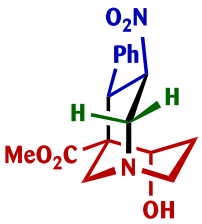


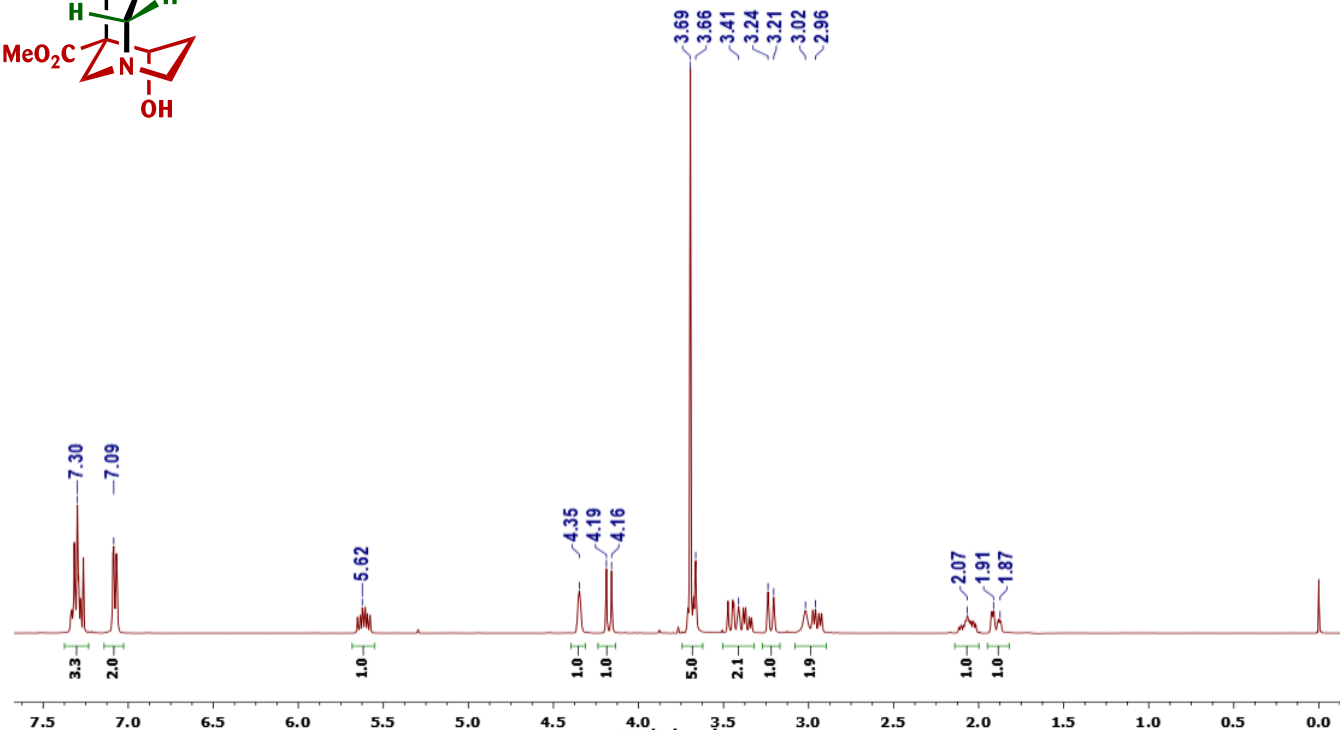
^{1}H NMR, $CDCl_3$, 400 MHz @ 25 °C



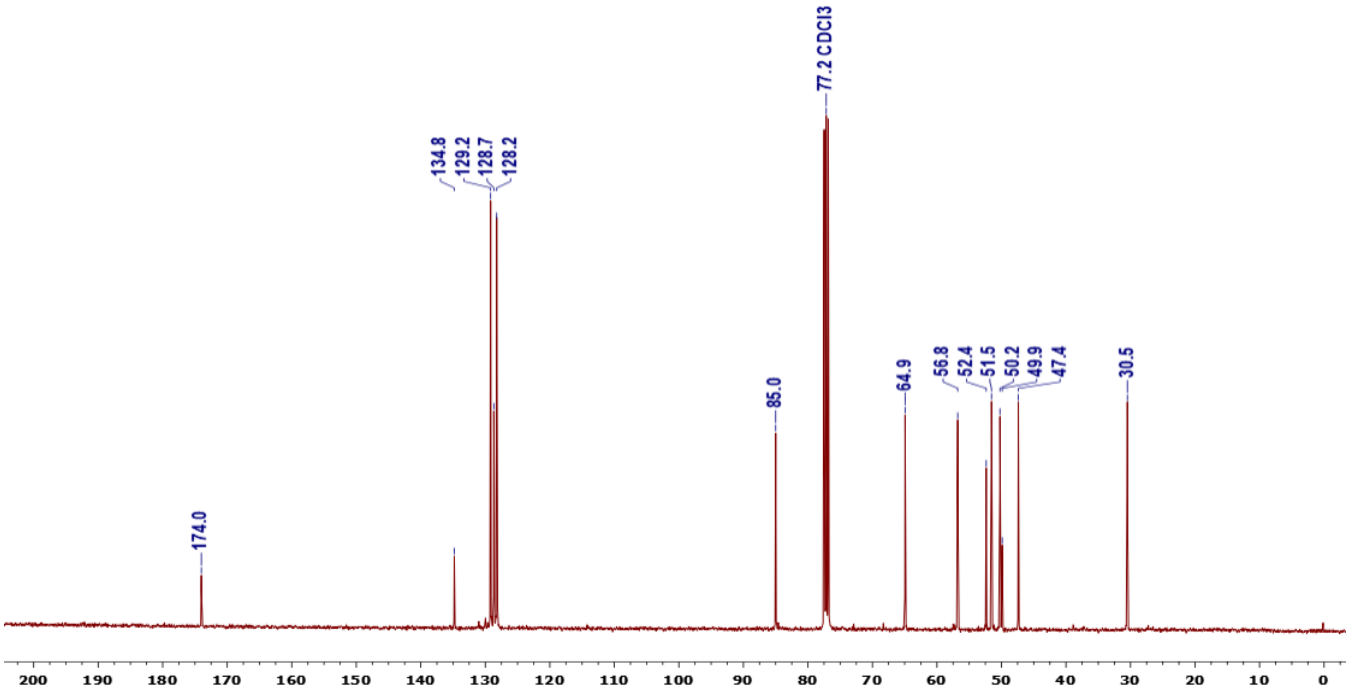
^{13}C NMR, $CDCl_3$, 100 MHz @ 25 °C

Compound **7g**



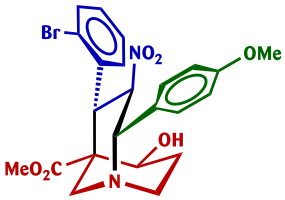


^{1}H NMR, $CDCl_3$, 400 MHz @ 25 °C

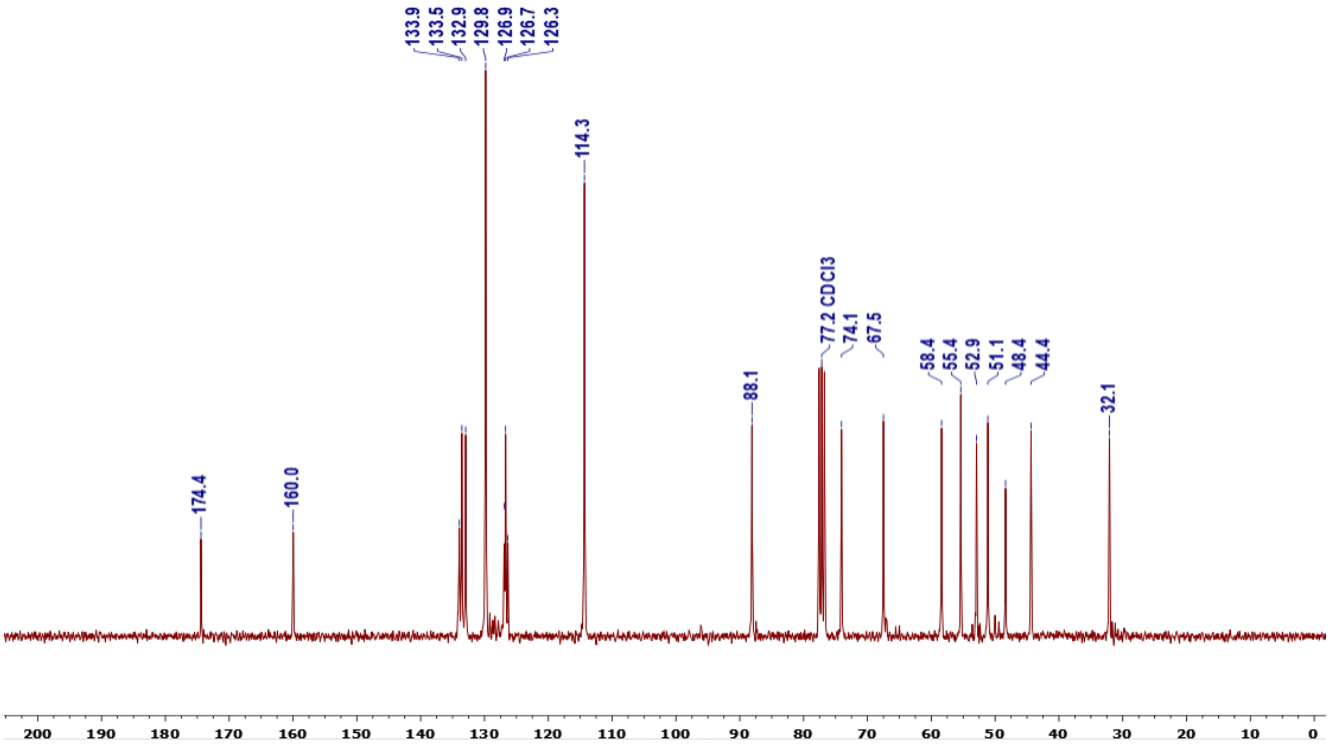


^{13}CNMR, $CDCl_3$, 100 MHz @ 25 °C

Compound **6h**

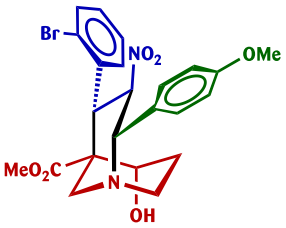


^{1}H NMR, $CDCl_3$, 300 MHz @ 25 °C

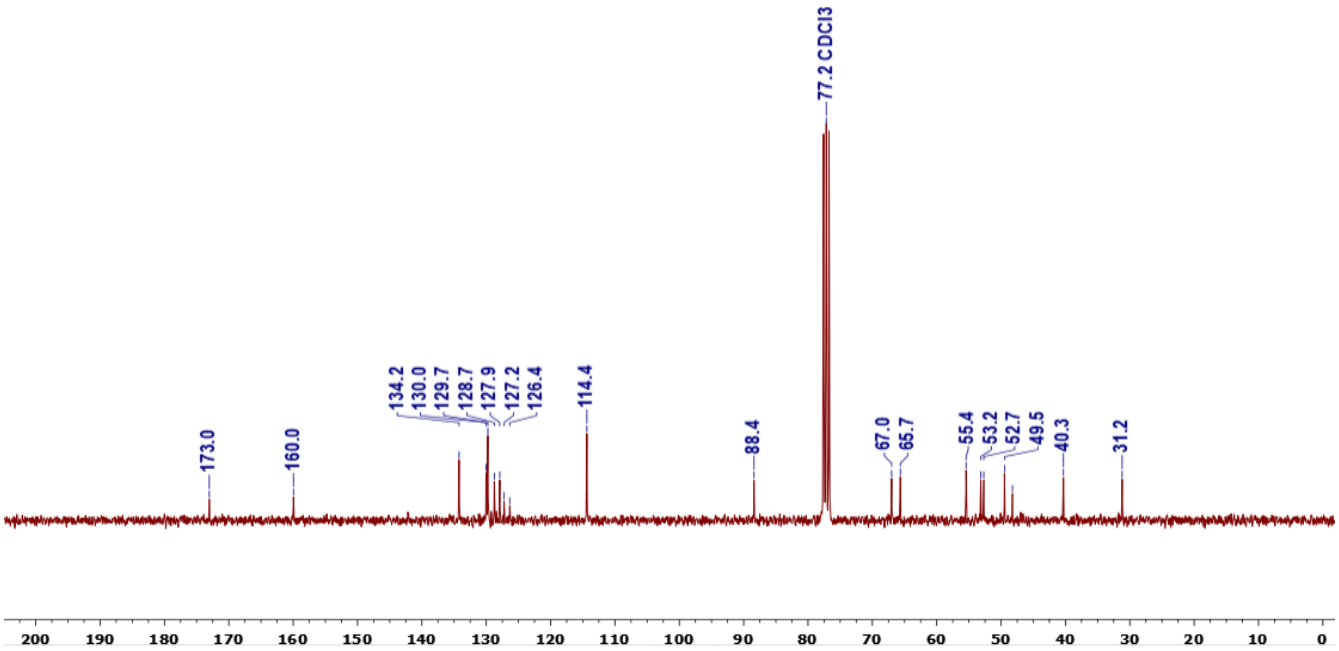


^{13}C NMR, $CDCl_3$, 75 MHz @ 25 °C

Compound **7h**



^{1}H NMR, $CDCl_3$, 400 MHz @ 25 °C



^{13}CNMR, $CDCl_3$, 75 MHz @ 25 °C