Asymmetric Acyl-Mannich Reaction of Isoquinolines with α-(Diazomethyl)phosphonate and Diazoacetate Catalyzed by Chiral Brønsted Acids

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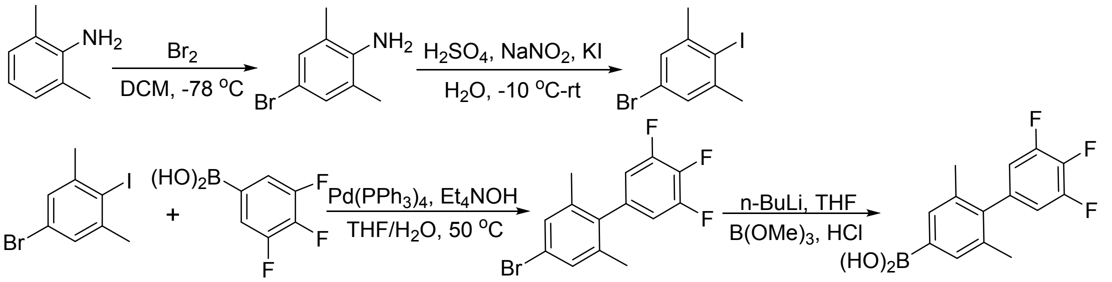
1. General methods

All solvents were purified by standard procedures and distilled prior to use. Reagents obtained from commercial source were used without further purification. Petroleum ether and ethyl acetate for flash column chromatography were distilled before use. All reactions were monitored by TLC with silica gel coated plates. Flash column chromatography was performed on silica gel H (10–40 μ). NMR spectra were recorded on 600 MHz instruments. Chemical shifts (δ) are given in ppm relative to TMS, coupling constants (*J*) in Hz. 1H NMR chemical shifts are reported in ppm relative to tetramethylsilane (TMS) with the solvent signal as the internal standard ($CDCl_3$ at 7.26 ppm). ^{13}C NMR chemical shifts are reported in ppm from tetramethylsilane (TMS) with the solvent resonance as the internal standard ($CDCl_3$ at 77.00 ppm). Melting points were determined on an X–6 digital melting-point apparatus and were uncorrected. Optical rotations were measured on a Perkin Elmer 341 Polarimeter at λ = 589 nm. Analytical high performance liquid chromatography (HPLC) was carried out on WATERS 510 instrument (2487 Dual λ Absorbance Detector and 515 HPLC Pump) using chiral column. ESI HRMS was recorded on a Bruker Apex–2.5 Å MS were purchased from J&K Chemicals and used as received (500 mesh powder).

2. Synthesis of chiral phosphoric acids

Ia-In, IIa-IIi were synthesized following the procedure described in the literature.[1]

Partial intermediates for the synthesis of chiral phosphoric acids were prepared as the following procedure:



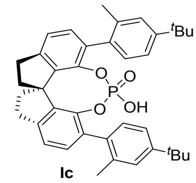
Bromine (5.38 mL, 105 mmol, 1.05 equiv.) was added slowly to the solution of 2, 6-dimethylaniline (12.3 mL, 100 mmol, 1.00 equiv.) in dried CH_2Cl_2 (250 mL) at −78 °C under argon atmosphere. After addition, the solution was allowed to warm up to room temperature. A saturated aqueous solution of Na_2SO_3 was added to the mixture to quench excess bromine in the reaction mixture. Saturated solution of Na_2CO_3 was added until the pH = 9, the organic layer was separated and the aqueous layer was extracted two times with CH_2Cl_2 (3 x 100 mL). Combined organic layers and dried over sodium sulfate, concentrated under reduce pressure. The residue was purified by column chromatography (PE/EA = 20/1) to obtain pure 4-bromo-2, 6-diethylaniline (17.9 g, 90 % yield) as a light brown solid.

4-Bromo-2, 6-diethylaniline (4.0 g, 20.0 mmol, 1.0 eq.) was suspended in 10 mL 10% aqueous H_2SO_4 and cooled to −10 °C. $NaNO_2$ (1.7 g, 25 mmol, 1.25 equiv.) in 10 mL H_2O was added dropwise, giving a pink precipitate, followed by formation of a clear red solution. After the addition, the solution was stirred for further 60 min at −10 °C, followed by dropwise addition of a solution of KI (4.5 g, 30 mmol, 1.5 equiv.) in 50 mL H_2O. Warmed to room temperature and stirred overnight. The solution was extracted with PE (4 × 50 ml). The collected organic phases were stirred over saturated aqueous Na_2SO_3 solution, until the organic phase had a light yellow color. The organic phase was then dried over $MgSO_4$ and the solvent removed under reduced pressure. The residue was purified by column chromatography (PE/EA = 100/1) to obtain pure 5-bromo-2-iodo-1,3-dimethylbenzene (2.1 g, 34 % yield).

To a round-bottomed flask, $Pd(PPh_3)_4$ (0.388 g, 0.336 mmol) was added to the mixture of (3,4,5-trifluorophenyl)boronic acid (1.182 g, 6.72 mmol), 5-bromo-2-iodo-1,3-dimethylbenzene (2.1 g, 6.72mmol) and Et_4NOH 7.7 mL (13.4 mmol, 25% of H_2O) in 30 mL degassing THF/H_2O = 3:1 (v:v) under an Ar atmosphere. Stirred at 50 °C until the starting material was disappear, then the mixture was concentrated under reduce pressure and the residue was extracted with EA, combined organic layer and washed with saturated NaCl, dried over with Na_2SO_4 and concentrated under reduce pressure, the residue was purified by flash chromatography (PE) on silica gel to give 4-bromo-3',4',5'-trifluoro-2,6-dimethyl-1,1'-biphenyl.

n-Butyllithium 1.0 mL (2.4 mmol) was slowly added to the solution of 4-bromo-3',4',5'-trifluoro-2,6-dimethyl-1,1'-biphenyl 0.7 g (2.2 mmol) in dry THF (20 mL) with stirring at −78 °C. The reaction was maintained at −78 °C until starting material was disappear, then trimethylborate 0.37 mL (3.3 mmol) was added slowly, the mixture was warmed up to rt slowly and stirred overnight. 1 N HCl was added to until pH = 1 and stirred for another 2 h. The mixture was extracted with EA, combined organic layer and washed with saturated NaCl, dried over with Na_2SO_4 and concentrated under reduce pressure, the residue was purified by flash chromatography (PE/EA = 3/1) on silica gel to afford (3',4',5'-trifluoro-2,6-dimethyl-[1,1'-biphenyl]-4-yl)boronic acid (0.275g, 45% yield).

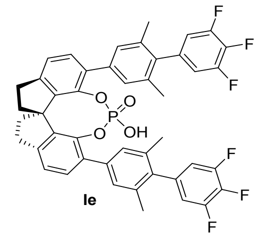
(*R*)-6, 6'-Bis((4-(tert-butyl)-2-methylphenyl)-1, 1'-spirobiindane-7, 7'-diyl phosphate (Ic)



Ic

White solid, mp 119.8–121.4 °C, [α]25 D = + 324.9° (*c* = 0.16, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 7.10 (t, *J* = 11.5 Hz, 4H), 7.05 (s, 2H), 7.01 (s, 4H), 3.17–3.08 (m, 2H), 2.89 (dd, *J* = 15.9, 7.8 Hz, 2H), 2.32 (dd, *J* = 11.7, 6.2 Hz, 2H), 2.15 (s, 2H), 2.09 (s, 6H), 1.16 (s, 18H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 149.6, 144.6, 142.6, 139.9, 135.3, 134.8, 134.3, 131.0, 130.8, 127.5, 125.6, 122.2, 59.8, 38.6, 34.1, 31.3, 30.2, 20.3 ppm. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{39}H_{43}O_4PNa^+$ 629.2797; Found 629.2795.

(*R*)-6, 6'-Bis(3', 4', 5'-trifluoro-2, 6-dimethyl-[1, 1'-biphenyl]-4-yl)-1, 1'-spirobiindane-7, 7'-diyl phosphate (Ie)

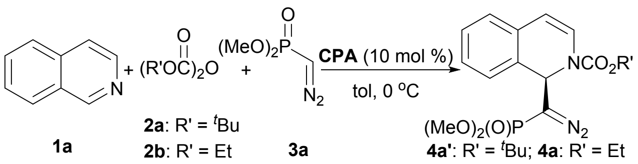


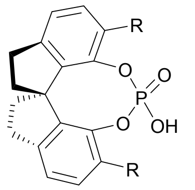
Ie

White solid, mp 215.7–217.0 °C, [α]25 D = + 479.8° (*c* = 0.20, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 7.30 (d, *J* = 7.5 Hz, 2H), 7.18 (d, *J* = 7.5 Hz, 2H), 7.10 (s, 4H), 6.63 (s, 4H), 3.19–3.09 (m, 2H), 2.91 (dd, *J* = 15.8, 7.6 Hz, 2H), 2.38 (dd, *J* = 12.0, 6.3 Hz, 2H), 2.19 (q, *J* = 10.9 Hz, 2H), 1.78 (s, 12H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 151.9, 150.2, 145.8, 142.2, 142.1, 140.6, 139.4, 137.8, 137.4, 137.3, 137.1, 135.3, 134.1, 129.9, 128.5, 122.8, 113.3, 113.2, 60.1, 38.5, 30.3, 20.5 ppm. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{45}H_{33}F_6O_4PNa^+$ 805.1918; Found 805.1913.

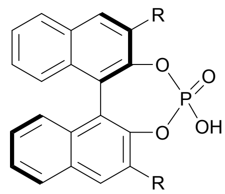
3. Screening the chiral phosphoric acids in the reaction of diazomethylphosphonate with isoquinolines and optimization the reaction conditions

Table S1. Screening the chiral phosphoric acids in the reaction of diazomethylphosphonate with isoquinoline[a]





Ia: R = Ph
Ib: R = 4-^{t}BuC$_6$H$_4$
Ic: R = 2-Me-4-^{t}BuC$_6$H$_3$
Id: R = 4-(3, 4, 5-F$_3$C$_6$H$_2$)-C$_6$H$_4$
Ie: R = 3,5-(Me)$_2$-4-(3,4,5-F$_3$C$_6$H$_2$)-C$_6$H$_2$
If: R = 4-MeOC$_6$H$_4$
Ig: R = 4-FC$_6$H$_4$
Ih: R = 4-CF$_3$C$_6$H$_4$
Ii: R = 3, 5-(CF$_3$)$_2$C$_6$H$_3$
Ij: R = 3, 4, 5-F$_3$C$_6$H$_4$
Ik: R = 4-(4-CF$_3$C$_6$H$_4$)-C$_6$H$_4$
Il: R = 4-(3, 5-(CF$_3$)$_2$C$_6$H$_3$)-C$_6$H$_4$
Im: R = 3-Me-4-(3,4,5-F$_3$C$_6$H$_2$)-C$_6$H$_3$
In: R = 3,5-(Et)$_2$-4-(3,4,5-F$_3$C$_6$H$_2$)-C$_6$H$_2$



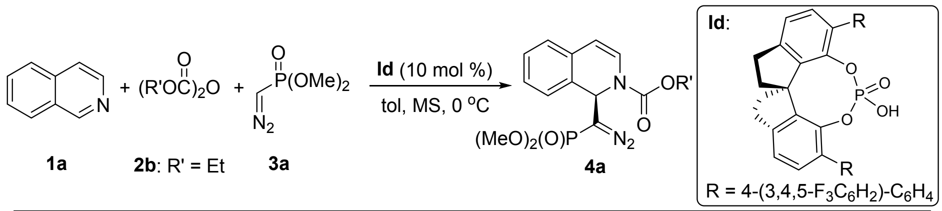
IIa: R = Ph
IIb: R =4-MeOC$_6$H$_4$
IIc: R = 4-^{t}BuC$_6$H$_4$
IId: R = 4-FC$_6$H$_4$
IIe: R =4-CF$_3$C$_6$H$_4$
IIf: R = 3,5-(CF$_3$)$_2$C$_6$H$_3$
IIg: R = 2,4,6-(^{i}Pr)$_3$C$_6$H$_2$
IIh: R = 2-Me-4-^{t}Bu-C$_6$H$_3$
IIi: R = 3,5-(Me)$_2$-4-(3,4,5-F$_3$C$_6$H$_2$)-C$_6$H$_2$

entry	**CPA**	t (h)	yield of **4a'** (%)[b]	*ee* (%)[c]
1	**Ia** (10)	96	**4a'**, 13	10
2	**Ib** (10)	120	**4a'**, 29	36
3	**Ic** (10)	96	**4a'**, 31	14
4	**Id** (10)	35	**4a'**, 32	57
5[d]	**Id** (10)	48	**4a'**, 77	75
6[d,e]	**Id** (10)	48	**4a**, 78	83
7[d,e]	**Ie** (10)	48	**4a**, 85	85
8	**If** (10)	96	**4a'**, 13	20
9	**Ig** (10)	96	**4a'**, 16	20
10	**Ih** (10)	120	**4a'**, 24	32
11	**Ii** (10)	120	**4a'**, 21	40

12	**Ij** (10)	120	**4a'**, 37	42
13	**Ik** (10)	72	**4a'**, 21	45
14	**Il** (10)	72	**4a'**, 26	48
15	**Im** (10)	48	**4a**, 87	84
16	**In** (10)	48	**4a**, 87	73
17	**IIa** (10)	120	**4a**, 58	6
18	**IIb** (10)	83	**4a**, 66	23
19	**IIc** (10)	36	**4a**, 69	20
20	**IId** (10)	18	**4a**, 61	15
21	**IIe** (10)	84	**4a**, 90	18
22	**IIf** (10)	36	**4a**, 71	39
23	**IIg** (10)	120	**4a**, 66	16
24	**IIh** (10)	68	**4a**, 63	3
25	**III** (10)	68	**4a**, 62	15

[a]Unless noted otherwise, all reactions were conducted using **1a** (0.1 mmol), **2a** (0.1 mmol), **3a** (0.1 mmol), **CPA** (10 mol %) in toluene (1.0 mL) at 0 °C. [b]Isolated yield. [c]Determined by HPLC analysis. [d]With 5 Å MS (150 mg). [e]**2b** was employed instead of **2a**.

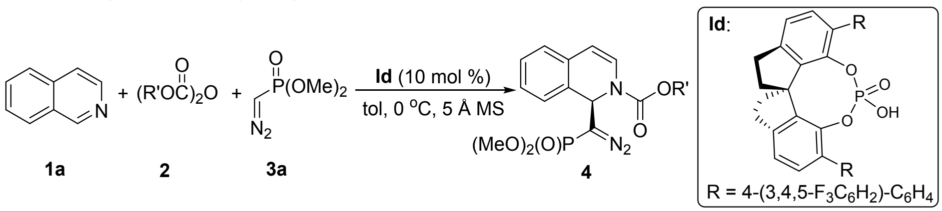
Table S2. The effect of molecular sieve on the reaction[a]



entry	MS	t (h)	yield of **4a** (%)[b]	*ee* of **4a** (%)[c]
1	--	35	32	57
2	5 Å (25 mg)	72	23	78
3	5 Å (50 mg)	72	39	83
4	5 Å (100 mg)	48	76	83
5	**5 Å (150 mg)**	**48**	**78**	**83**
6	4 Å (150 mg)	48	83	77
7	3 Å (150 mg)	48	82	75

[a]Unless noted otherwise, all reactions were conducted using **1a** (0.1 mmol), **2b** (0.1 mmol), **3a** (0.1 mmol), **Id** (10 mol %) in toluene (1.0 mL) at 0 °C under argon. [b]Isolated yield. [c]Determined by HPLC analysis.

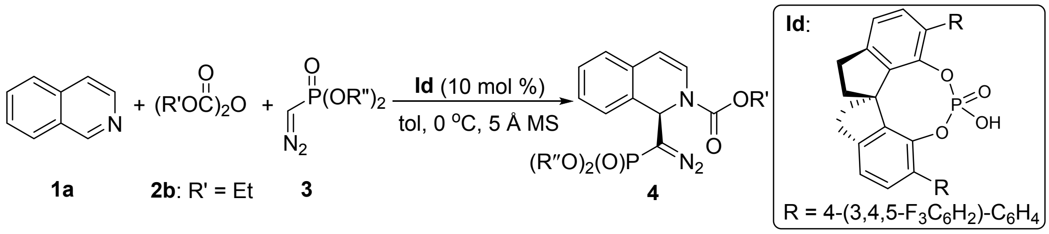
Table S3. The effect of nitrogen acylating reagent on the reaction[a]



entry	R′	yield of **4** (%)[b]	*ee* of **4** (%)[c]
1	Me	46	80
2	Et	78	83
3	^{t}Bu	77	75

[a]Unless noted otherwise, all reactions were conducted using **1a** (0.1 mmol), **2** (0.1 mmol), **3a** (0.1 mmol), 5 Å MS (150 mg), **Id** (10 mol %) in toluene (1.0 mL) at 0 °C for 48 h under argon. [b]Isolated yield. [c]Determined by HPLC analysis.

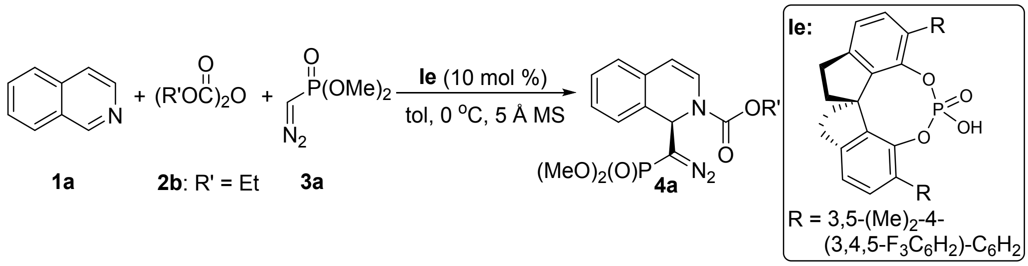
Table S4. The effect of phosphonate ester on the reaction[a]



Entry	R″	yield of **4** (%)[b]	*ee* of **4** (%)[c]
1	Me	80	83
2	Et	85	74
3	^{i}Pr	83	75
4	^{t}Bu	90	73

[a]Unless noted otherwise, all reactions were conducted using **1a** (0.1 mmol), **2b** (0.1 mmol), **3** (0.1 mmol), 5 Å MS (150 mg), **Id** (10 mol %) in toluene (1.0 mL) at 0 °C for 48 h under argon. [b]Isolated yield. [c]Determined by HPLC analysis.

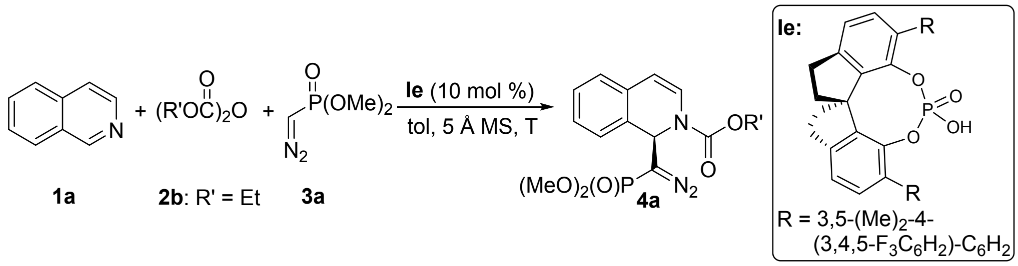
Table S5. The effect of ratio of **1a**/**2b**/**3a** on the reaction[a]



entry	**1a/2b/3a**	yield of **4a** (%)[b]	*ee* of **4a** (%)[c]
1	1.0:1.0:1.0	85	85
2	1.5:1.5:1.0	98	85
3	1.0:1.0:1.5	97	85

[a]Unless noted otherwise, all reactions were conducted using **1a**, **2b**, **3a** (0.1 mmol), 5 Å MS (150 mg), **Ie** (10 mol %) in toluene (1.0 mL) at 0 °C for 48 h under argon. [b]Isolated yield. [c]Determined by HPLC analysis.

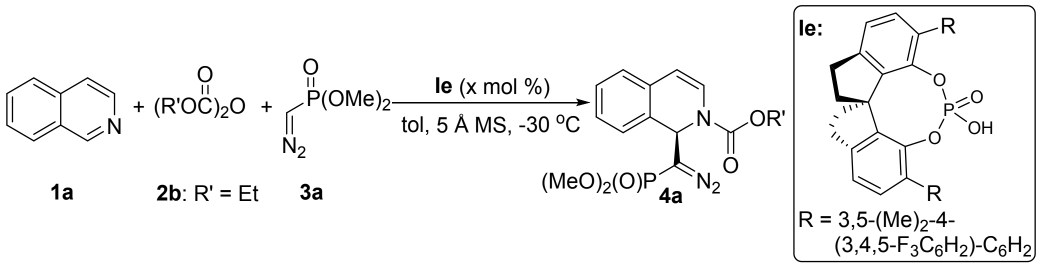
Table S6. Optimization reaction temperature[a]



Entry	T (°C)	yield of **4a** (%)[b]	*ee* of **4a** (%)[c]
1	0	98	85
2	−10	98	88
3	−20	98	89
4	**−30**	**98**	**92**
5	−40	37	92

[a]Unless noted otherwise, all reactions were conducted using **1a** (0.15 mmol), **2b** (0.15 mmol), **3** (0.1 mmol), 5 Å MS (150 mg), **Ie** (10 mol %) in toluene (1.0 mL) for 48 h under argon. [b]Isolated yield. [c]Determined by HPLC analysis.

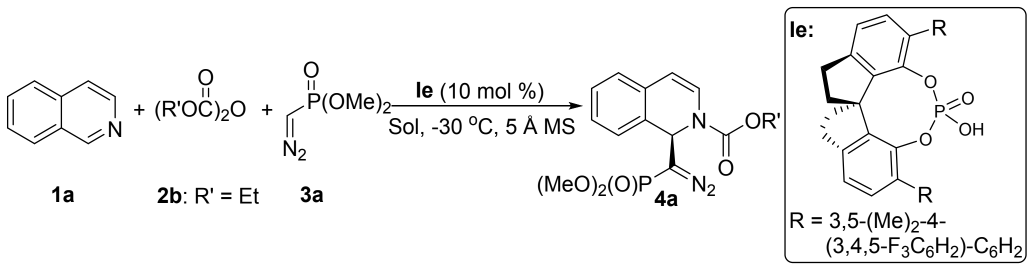
Table S7. The effect of catalyst loading **Ie** on the reaction[a]



entry	x	yield of **4a** (%)[b]	*ee* of **4a** (%)[c]
1	5	76	89
2	**10**	**98**	**92**
3	15	89	92

[a]Unless noted otherwise, all reactions were conducted using **1a** (0.15 mmol), **2b** (0.15 mmol), **3** (0.1 mmol) 5 Å MS (150 mg) in toluene (1.0 mL) at −30 °C for 48 h under argon. [b]Isolated yield. [c]Determined by HPLC analysis

Table S8. The effect of solvent on the reaction[a]

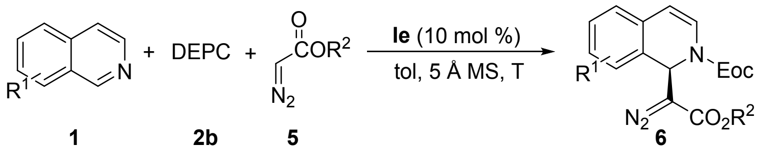


Entry	solvent	yield of **4a** (%)[b]	*ee* of **4a** (%)[c]
1	**PhMe**	**98**	**92**
2	DCM	60	83
3	THF	54	89
4	PhCl	98	91
5	PhF	98	87
6	PhEt	91	91
7	xylenes	91	92
8	mesitylene	85	92

[a]Unless noted otherwise, all reactions were conducted using **1a** (0.15 mmol), **2b** (0.15 mmol), **3** (0.1 mmol), 5 Å MS (150 mg), **Ie** (10 mol %) at −30 °C for 48 h under argon. [b]Isolated yield. [c]Determined by HPLC analysis

4. Optimization of the diazocarbonate with isoquinolines reaction conditions

Table S9. Asymmetric acyl-Mannich reaction of diazocarbonate with isoquinolines catalyzed by **Ie**[a]

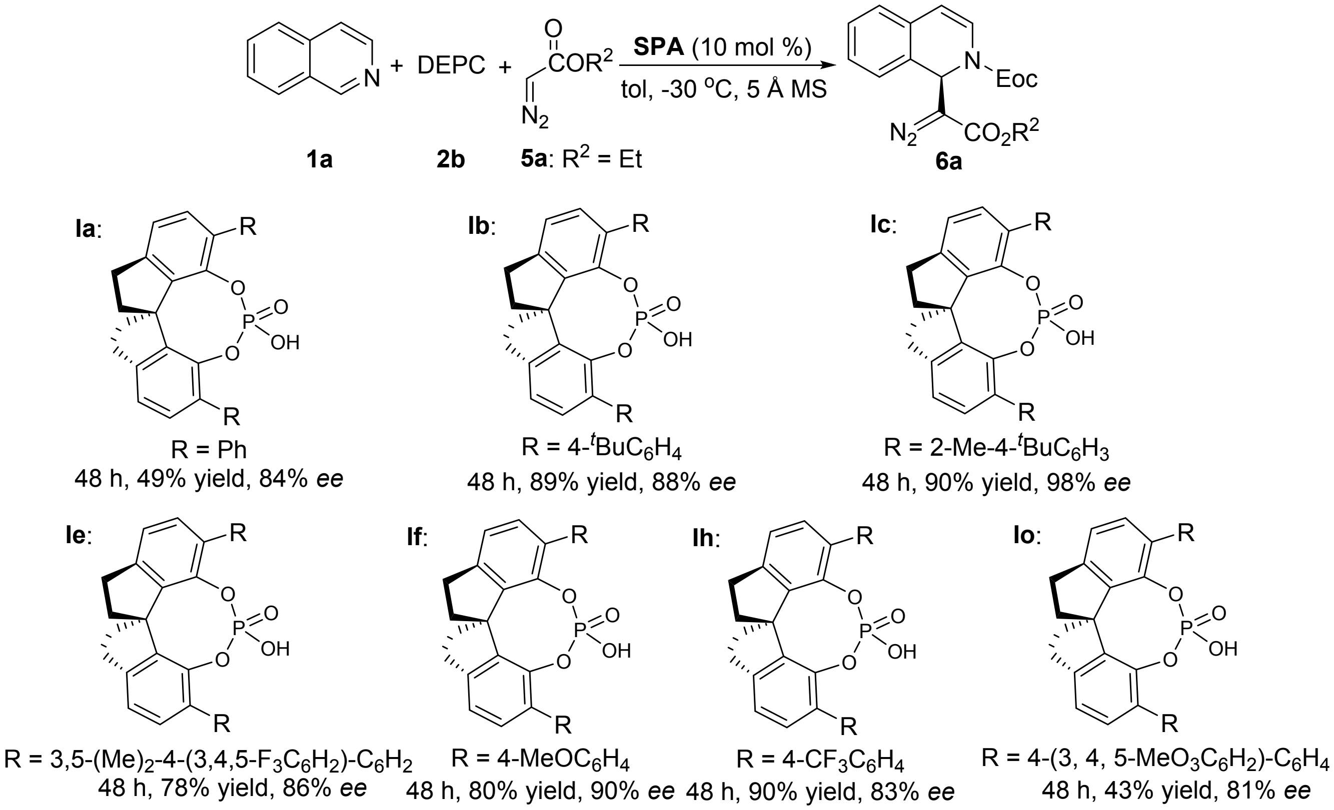


entry	R^1	R^2	T (℃)	t (h)	yield of **6** (%)[b]	*ee* of **6** (%)[c]
1	H	Me	−30	48	79	77
2	H	Et	−30	48	78	86
3	H	^{i}Pr	−30	48	72	84
4	H	^{t}Bu	−30	72	71	72

5	H	Et	−10	40	95	84
6	H	Et	−20	68	93	84
7	H	Et	−40	92	54	84
8	6-Cl	Et	−30	96	33	86
9	5-Br	Et	−30	96	45	85
10	6-Br	Et	−30	96	84	89
11	6-Me	Et	−30	96	53	87
12	6-Et	Et	−30	96	85	84
13	6-F	Et	−30	96	65	88
14	6-^{t}Bu	Et	−30	96	50	75
15	6-OMe	Et	−30	96	29	86
16	5-OMe	Et	−30	96	57	80
17	8-Br	Et	−30	96	trace	--

[a]Conditions: Unless noted otherwise, all of the reactions were carried out with **1** (0.15 mmol), **2b** (0.15 mmol), **5** (0.10mmol), **Ie** (10 mol %) and 5 Å MS (150 mg) in 1.0 mL of anhydrous toluene; [b]Isolated yield; [c]Determined by chiral HPLC

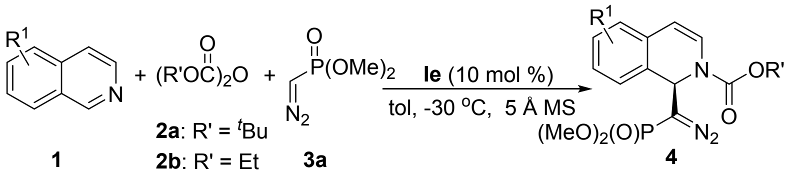
We have tried to extend the nucleophile from α-(diazomethyl)phosphonate to alkyl diazoacetate **5** under the optimized reaction conditions for α-(diazomethyl)phosphonate (Table S9). After preliminary investigated the influence of R^2 and reaction temperature on the reaction (Table S9, entries 1−7), we found that good results could be achieved when R^2 was ethyl and the reaction proceeded at −30 ℃. We also attempted to check the substrates accommodation at this conditions (Table S9, entries 8−16). These results were not satisfactory. Therefore, we further investigate other catalysts as **Ia-Ic**, **Ie**, **If, Ih** and **Io** (Scheme S1), gratifying, excellent results were observed when the reaction was catalyzed by **Ic**. So the optimized reaction conditions for ethyl diazoacetate were identified as: **Ic** (10 mol %) as catalyst in toluene at −20 °C with 5 Å MS as additive and a **1a**/**2b**/**5a** ratio of 1.5:1.5:1.



Scheme S1. Catalyst screening for the diazocarbonate with isoquinolines reaction

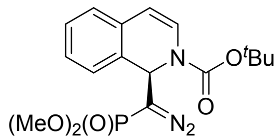
5. General procedure for asymmetric acyl-Mannich reaction

5.1. General procedure for asymmetric acyl-Mannich reaction of diazomethylphosphonate with isoquinolines



Isoquinoline **1** (0.15 mmol) and diethyl pyrocarbonate **2a** or **2b** (Boc_2O, 0.15 mmol) were added to a pre-dried tube under argon and stirred for 10 min at room temperature. Next, anhydrous toluene (1 mL), 5 Å MS (150 mg) and SPA **Ie** (0.01 mmol) was added and the system was cooled to −30 °C. The (diazomethyl)phosphonate **3a** (0.1 mmol) was then added and the mixture was stirred and monitored by TLC until **3a** had been completely consumed. The reaction mixture was then purified directly by flash chromatography on silica gel (30–50% AcOEt/petroleum ether) to obtain the corresponding product **4**.

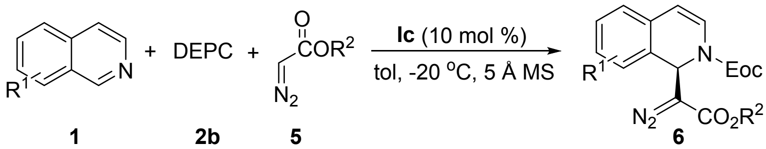
Tert-butyl (*R*)-1-(diazo(dimethoxyphosphoryl)methyl)isoquinoline-2(1H)-carboxylate (4a′)



4a′

Yellow oil, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.26 – 7.17 (m, 3H), 7.14 – 6.82 (m, 2H), 6.18 – 5.78 (m, 2H), 3.75 – 3.46 (m, 6H), 1.54 (d, *J* = 23.8 Hz, 9H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 151.5, 130.6, 128.5, 128.2, 127.4, 126.4, 125.4, 124.8, 108.2, 82.3, 52.6, 51.9, 47.2 (d, *J* = 233.1 Hz), 28.1 ppm.

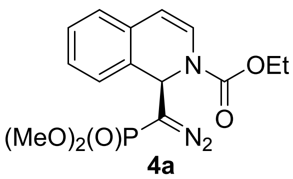
5.2. General procedure for asymmetric acyl-Mannich reaction of diazocarbonate with isoquinolines



Isoquinoline **1** (0.15 mmol) and diethyl pyrocarbonate **2b** (DEPC, 0.15 mmol) were added to a pre-dried tube under argon and stirred for 10 min at room temperature. Next, anhydrous toluene (1 mL), 5 Å MS (150 mg) and SPA **Ic** (0.01 mmol) was added and the system was cooled to −20 °C. The *α*-diazo carbonate **5** (0.1 mmol) was then added and the mixture was stirred and monitored by TLC until **5** had been completely consumed. The reaction mixture was then purified directly by flash chromatography on silica gel (5–10% AcOEt/petroleum ether) to obtain the corresponding product **6**.

6. Characterization of the acyl-Mannich reaction products

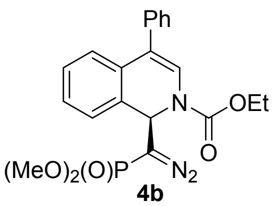
Ethyl (*R*)-1-(diazo(dimethoxyphosphoryl)methyl)isoquinoline-2(1H)-carboxylate (4a)



4a

Yellow oil, [α]25 D = +400.3° (*c* = 0.37, ^{i}PrOH); HPLC condition: chiralpak IA, 254 nm, 0.5 mL/min, n-hexane/*i*-PrOH = 70/30, t_{major} = 14.825 min, t_{minor} = 12.409 min, *ee* = 92%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25 (m, 3H), 7.15 – 6.85 (m, 2H), 6.25 – 5.78 (m, 2H), 4.38 – 4.23 (m, 2H), 3.72 (d, J = 11.7 Hz, 3H), 3.61 – 3.53 (m, 3H), 1.38-1.24 (m, 3H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 152.8, 130.3, 128.6, 128.1, 127.6, 126.5, 125.2, 125.0, 124.6, 108.9 (d, *J* = 42.5 Hz), 62.8, 53.1, 52.8, 47.4 (d, *J* = 227.4 Hz), 14.4. ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{18}N_3O_5PNa^+$ 374.0882; Found 374.0880.

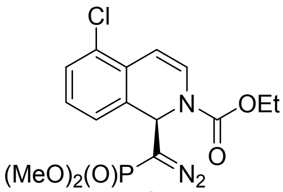
Ethyl (*R*)-1-(diazo(dimethoxyphosphoryl)methyl)-4-phenylisoquinoline-2(1H)-carboxylate (4b)



4b

Yellow oil, [α]25 D = +161.8° (*c* = 0.80, EA); HPLC condition: chiralpak IA, 254 nm, 0.5 mL/min, n-hexane/*i*-PrOH = 70/30, t_{major} = 20.259 min, t_{minor} = 17.792 min, *ee* = 94%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45 – 7.32 (m, 6H), 7.30 (t, J = 7.4 Hz, 1H), 7.23 (t, J = 7.0 Hz, 1H), 7.16 – 6.89 (m, 2H), 6.32 – 6.15 (m, 1H), 4.41 – 4.24 (m, 2H), 3.75 (d, J = 10.4 Hz, 3H), 3.62 – 3.57 (m, 3H), 1.47 – 1.28 (m, 3H). ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ 152.8, 136.8, 131.2, 128.7, 128.6, 128.4, 127.9, 127.5, 126.4, 124.3, 123.4, 122.8, 62.8, 53.3, 53.0, 52.8, 46.8 (d, *J* = 253.2 Hz), 14.4 ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{21}H_{22}N_3O_5PNa^+$ 450.1189; Found 450.1189.

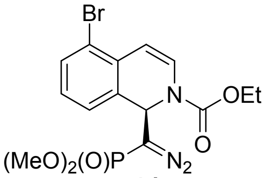
Ethyl (*R*)-5-chloro-1-(diazo(dimethoxyphosphoryl)methyl)isoquinoline-2(1H)-carboxylate (4c)



4c

Yellow oil, [α]25 D = + 76.5° (*c* = 0.44, iPrOH); HPLC condition: chiralpak IA, 254 nm, 0.5 mL/min, n-hexane/*i*-PrOH = 70/30, t_{major} = 13.255 min, t_{minor} = 10.716 min, *ee* = 93%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35–7.28 (m, 1H), 7.17 – 7.01 (m, 3H), 6.27 – 6.12 (m, 2H), 4.32 – 4.29 (m, 2H), 3.72 (d, *J* = 11.7 Hz, 3H), 3.58 (d, *J* = 15.0 Hz, 3H), 1.39 – 1.35 (m, 3H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 152.6, 130.1, 130.0, 129.4, 128.1, 126.2, 125.1, 104.9, 63.1, 52.9, 52.4, 47.5 (d, *J* = 229.3 Hz), 14.4. ppm; HRMS (ESI) m/z: [M+Na]$^+$ Calcd for $C_{15}H_{17}ClN_3O_5PNa^+$ 408.0492; Found 408.0492.

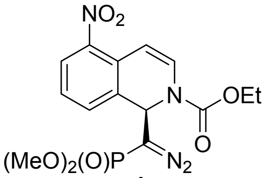
Ethyl (*R*)-5-bromo-1-(diazo(dimethoxyphosphoryl)methyl)isoquinoline-2(1H)-carboxylate (4d)



4d

Yellow oil, [α]25 D = +110.9° (*c* = 0.38, *i*PrOH); HPLC condition: chiralpak IA, 254 nm, 0.5 mL/min, n-hexane/*i*-PrOH = 70/30, t_{major} = 13.524 min, t_{minor} = 10.851 min, *ee* = 92%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.9 Hz, 1H), 7.21 (d, *J* = 7.4 Hz, 1H), 7.17–6.96 (m, 2H), 6.25 – 6.11 (m, 2H), 4.31 (dd, *J* = 13.8, 6.8 Hz, 2H), 3.70 (t, *J* = 18.6 Hz, 3H), 3.58 (d, *J* = 13.5 Hz, 3H), 1.37 – 1.34 (m, 3H). ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 152.5, 132.7, 130.04, 128.4, 127.0, 126.4, 125.8, 120.4, 107.4, 63.1, 53.1, 52.9, 52.4, 47.5 (d, *J* = 229.2 Hz), 14.4. ppm; HRMS (ESI) m/z: [M+Na]$^+$ Calcd for $C_{15}H_{17}BrN_3O_5PNa^+$ 451.9987; Found 451.9981.

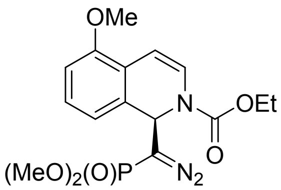
Ethyl (*R*)-1-(diazo(dimethoxyphosphoryl)methyl)-5-nitroisoquinoline-2(1H)-carboxylate (4e)



4e

Yellow oil, [α]25 D = + 3.4° (*c* = 0.24, iPrOH); HPLC condition: chiralpak IA, 254 nm, 0.5 mL/min, n-hexane/*i*-PrOH = 70/30, t_{major} = 17.264 min, t_{minor} = 14.183 min, *ee* = 92%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.2 Hz, 1H), 7.55 (d, *J* = 7.4 Hz, 1H), 7.35 (t, *J* = 7.9 Hz, 1H), 7.15 (s, 1H), 6.59 (s, 1H), 6.24 (s, 1H), 4.36 – 4.33 (m, 2H), 3.74 (d, *J* = 11.7 Hz, 3H), 3.59 (s, 3H), 1.37 (s, 3H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 152.4, 144.5, 131.8, 130.8, 129.1, 127.2, 125.2, 102.7, 63.6, 53.2, 53.0, 53.0, 47.9 (d, *J* = 230.0 Hz), 14.3 ppm; HRMS (ESI) m/z: [M+Na]$^+$ Calcd for $C_{15}H_{17}N_4O_7PNa^+$ 419.0733; Found 419.0741.

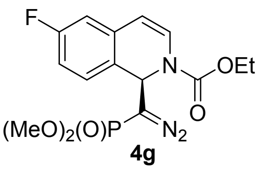
Ethyl (*R*)-1-(diazo(dimethoxyphosphoryl)methyl)-5-methoxyisoquinoline-2(1H)-carboxylate (4f)



4f

Yellow oil, [α]25 D = +28.0° (*c* = 0.74, iPrOH); HPLC condition: chiralpak IA, 254 nm, 0.5 mL/min, n-hexane/*i*-PrOH = 70/30, t_{major} = 15.823 min, t_{minor} = 13.686 min, *ee* = 89%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.20 (t, *J* = 7.9 Hz, 1H), 7.01 – 6.84 (m, 2H), 6.78 (d, *J* = 8.2 Hz, 1H), 6.34–6.02 (m, 2H), 4.40–4.22 (m, 2H), 3.84 (s, 3H), 3.74 (d, *J* = 10.7 Hz, 3H), 3.63 – 3.56 (m, 3H), 1.37 – 1.32 (m, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ 154.0, 152.8, 129.3, 128.4, 124.3, 123.7, 119.7, 118.7, 110.1, 103.7, 62.8, 55.6, 52.8, 52.1, 47.0 (d, *J* = 227.2 Hz), 14.4 ppm; HRMS (ESI) m/z: [M+Na]$^+$ Calcd for $C_{16}H_{20}N_3O_6PNa^+$ 404.0987; Found 404.0991.

Ethyl (*R*)-1-(diazo(dimethoxyphosphoryl)methyl)-6-fluoroisoquinoline-2(1H)-carboxylate (4g)



4g

Yellow solid, mp 74.9–76.0 °C, [α]25 D = +99.9° (*c* = 0.35, iPrOH); HPLC condition: chiralpak IA, 254 nm, 0.5 mL/min, n-hexane/*i*-PrOH = 70/30, t_{major} = 16.756 min, t_{minor} = 12.071 min, *ee* = 95%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25 – 6.87 (m, 3H), 6.81 (d, *J* = 8.5 Hz, 1H), 6.18 – 5.78 (m, 2H), 4.29 (d, *J* = 6.8 Hz, 2H), 3.88–3.28 (m, 6H), 1.32 (t, *J* = 39.1 Hz, 3H) ppm; ^{13}C NMR (151 MHz, CDCl3) δ 162.6 (d, *J* = 246.9 Hz), 152.7, 132.4, 128.2, 126.4, 125.8, 123.9, 114.4 (d, *J* = 22.4 Hz), 111.4 (d, J = 21.4 Hz), 107.8, 63.1, 52.8, 52.1, 47.6 (d, *J* = 229.1 Hz), 14.4 ppm. HRMS (ESI) m/z: [M+Na]$^+$ Calcd for $C_{15}H_{17}FN_3O_5PNa^+$ 392.0788; Found 392.0785.

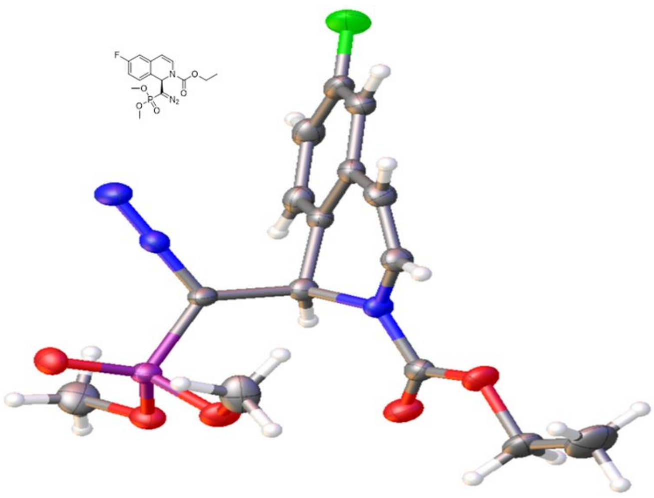
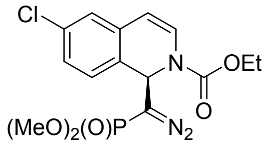


Table S10. Crystal data and structure refinement for 4g	
Empirical formula	$C_{15}H_{17}FN_3O_5P$
Formula weight	369.29
Temperature/K	149.99(10)
Crystal system	monoclinic
Space group	$P2_1$
a/Å	11.2111(2)
b/Å	6.05545(12)
c/Å	13.6909(3)
α/°	90
β/°	112.986(3)
γ/°	90
Volume/Å³	855.66(3)
Z	2
ρ_{calc}g/cm³	1.462
μ/mm⁻¹	1.831
F(000)	393.0
Crystal size/mm³	0.2 × 0.05 × 0.02
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	7.014 to 146.1
Index ranges	-13 ≤ h ≤ 13, -7 ≤ k ≤ 4, -16 ≤ l ≤ 16
Reflections collected	8887
Independent reflections	2756 [R_{int} = 0.0403, R_{sigma} = 0.0400]
Data/restraints/parameters	2756/1/229
Goodness-of-fit on F²	0.990
Final R indexes [I>=2σ (I)]	R_1 = 0.0405, wR_2 = 0.1041
Final R indexes [all data]	R_1 = 0.0425, wR_2 = 0.1070
Largest diff. peak/hole / e Å⁻³	0.27/-0.36

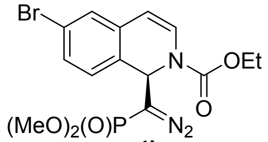
Ethyl (*R*)-6-chloro-1-(diazo(dimethoxyphosphoryl)methyl)isoquinoline-2(1H)-carboxylate (4h)



4h

Yellow oil, [α]25 D = +46.9° (*c* = 0.64, ^{i}PrOH); HPLC condition: chiralpak IA, 254 nm, 0.5 mL/min, n-hexane/*i*-PrOH = 70/30, t_{major} = 22.346 min, t_{minor} = 12.315 min, *ee* = 95%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.20 (s, 2H), 7.14–6.88 (m, 2H), 6.15 – 5.75 (m, 2H), 4.31 – 4.28 (m, 2H), 3.72 (d, *J* = 11.7 Hz, 3H), 3.58 (dd, *J* = 10.6, 5.8 Hz, 3H), 1.47–1.28 (m, 3H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 152.7, 134.4, 131.9, 127.8, 127.4, 126.4, 125.9, 124.6, 107.4, 63.1, 52.8, 52.1, 47.6 (d, *J* = 228.8 Hz), 14.4. ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{17}ClN_3O_5PNa^+$ 408.0492; Found 408.0489.

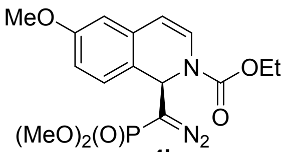
Ethyl (*R*)-6-bromo-1-(diazo(dimethoxyphosphoryl)methyl)isoquinoline-2(1H)-carboxylate (4i)



4i

Yellow oil, [α]25 D = +31.9° (*c* = 0.54, ^{i}PrOH); HPLC condition: chiralpak IA, 254 nm, 0.5 mL/min, n-hexane/*i*-PrOH = 70/30, t_{major} = 25.687 min, t_{minor} = 12.392 min, *ee* = 90%; ^{1}H NMR (600 MHz, $(CD_3)_2CO$) δ 7.45 (dd, *J* = 8.1, 2.0 Hz, 1H), 7.41 – 7.37 (m, 2H), 7.08 (s, 1H), 6.27 (d, *J* = 8.8 Hz, 1H), 5.95 (s, 1H), 4.33 – 4.28 (m, 2H), 3.70 (d, *J* = 11.7 Hz, 3H), 3.53 (d, *J* = 11.8 Hz, 3H), 1.34 (s, 3H) ppm. ^{13}C NMR (151 MHz, $(CD_3)_2CO$) δ 153.5, 133.9, 131.0, 129.6, 128.4, 128.4, 128.2, 127.3, 122.8, 107.9, 63.7, 53.3, 53.1, 48.2 (d, *J* = 223.1 Hz), 14.7 ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{17}BrN_3O_5PNa^+$ 451.9987; Found 451.9994.

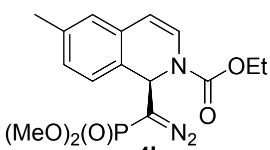
Ethyl (*R*)-1-(diazo(dimethoxyphosphoryl)methyl)-6-methoxyisoquinoline-2(1H)-carboxylate (4j)



4j

Yellow oil, [α]25 D = +41.4° (*c* = 0.46, ^{i}PrOH); HPLC condition: chiralpak IA, 254 nm, 0.5 mL/min, n-hexane/*i*-PrOH = 70/30, t_{major} = 23.653 min, t_{minor} = 12.824 min, *ee* = 84%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.17 (d, *J* = 7.6 Hz, 1H), 7.11 – 6.72 (m, 2H), 6.63 (s, 1H), 6.16 – 5.79 (m, 2H), 4.28 (d, *J* = 6.4 Hz, 2H), 3.80 (s, 3H), 3.77 – 3.52 (m, 6H), 1.38 – 1.33 (m, 3H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.8, 152.7, 131.5, 127.6, 125.6, 125.0, 120.6, 113.5, 109.8, 108.8, 62.8, 55.3, 52.8, 52.2, 47.4 (d, *J* = 228.2 Hz), 14.4 ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{20}N_3O_6PNa^+$ 404.0987; Found 404.0992.

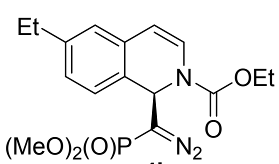
Ethyl (*R*)-1-(diazo(dimethoxyphosphoryl)methyl)-6-methylisoquinoline-2(1H)-carboxylate (4k)



4k

Yellow oil, [α]25 D = +32.6° (*c* = 0.66, ^{i}PrOH); HPLC condition: chiralpak IA, 254 nm, 0.5 mL/min, n-hexane/*i*-PrOH = 70/30, t_{major} = 20.506 min, t_{minor} = 11.930 min, *ee* = 91%; ^{1}H NMR (600 MHz, $(CD_3)_2CO$) δ 7.27 (d, *J* = 7.2 Hz, 1H), 7.12 (d, *J* = 7.7 Hz, 1H), 7.01 (d, *J* = 17.2 Hz, 2H), 6.21 (d, *J* = 7.7 Hz, 1H), 5.93 (d, *J* = 24.9 Hz, 1H), 4.35–4.20 (m, 2H), 3.71 (d, *J* = 11.4 Hz, 3H), 3.54 (d, *J* = 11.8 Hz, 3H), 2.32 (s, 3H), 1.34 (s, 3H) ppm. ^{13}C NMR (151 MHz, $(CD_3)_2CO$) δ 153.6, 139.2, 131.5, 129.2, 127.2, 126.6, 126.3, 125.8, 109.7, 63.4, 53.3, 53.2, 53.0, 48.0 (d, *J* = 222.4 Hz), 21.2, 14.7 ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{20}N_3O_5PNa^+$ 388.1038; Found 388.1041.

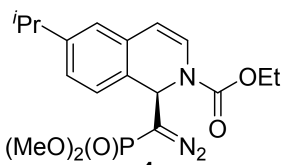
Ethyl (*R*)-1-(diazo(dimethoxyphosphoryl)methyl)-6-ethylisoquinoline-2(1H)-carboxylate (4l)



4l

Yellow oil, [α]25 D = +63.1° (*c* = 0.68, ^{i}PrOH); HPLC condition: chiralpak IA, 254 nm, 0.5 mL/min, n-hexane/*i*-PrOH = 70/30, t_{major} = 22.588 min, t_{minor} = 11.772 min, *ee* = 91%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.16 (d, *J* = 7.4 Hz, 1H), 7.07 (d, *J* = 7.5 Hz, 1H), 7.04–6.81 (m, 2H), 6.16 – 5.81 (m, 2H), 4.27 (d, *J* = 6.9 Hz, 2H), 3.72 (d, *J* = 11.7 Hz, 3H), 3.60 – 3.53 (m, 3H), 2.61 (q, *J* = 7.5 Hz, 2H), 1.37 – 1.32(m, 3H), 1.21 (t, *J* = 7.6 Hz, 3H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$)δ 152.8, 144.8, 130.1, 127.2, 126.4, 125.6, 125.1, 124.3, 109.0, 62.8, 53.0, 52.7, 52.3, 47.3 (d, *J* = 228.3 Hz), 28.5, 15.3, 14.4 ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{22}N_3O_5PNa^+$ 402.1195; Found 402.1209.

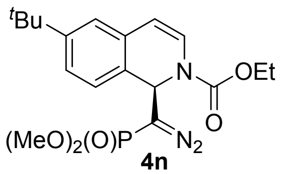
Ethyl (*R*)-1-(diazo(dimethoxyphosphoryl)methyl)-6-isopropylisoquinoline-2(1H)-carboxylate (4m)



4m

Yellow oil, [α]25 D= +43.7° (*c* = 0.56, ^{i}PrOH); HPLC condition: chiralpak IA, 254 nm, 0.5 mL/min, n-hexane/*i*-PrOH = 70/30, t_{major} = 21.760 min, t_{minor} = 11.022 min, *ee* = 90%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.17 (d, *J* = 7.6 Hz, 1H), 7.11 (d, *J* = 7.6 Hz, 1H), 7.05 – 6.85 (m, 2H), 6.17 – 5.83 (m, 2H), 4.33 – 4.28 (m, 2H), 3.76 – 3.44 (m, 6H), 2.90 – 2.85 (m, 1H), 1.37 – 1.32 (m, 3H), 1.23 (d, *J* = 6.8 Hz, 6H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 152.8, 149.5, 130.1, 126.4, 125.8, 125.0, 124.5, 123.0, 109.4, 109.1, 62.8, 53.0, 52.8, 52.4, 47.3 (d, *J* = 228.1 Hz), 33.8, 23.8, 14.4 ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{18}H_{24}N_3O_5PNa^+$ 416.1351; Found 416.1363.

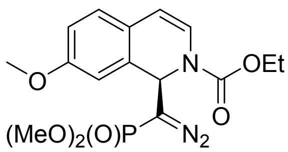
Ethyl (*R*)-6-(*tert*-butyl)-1-(diazo(dimethoxyphosphoryl)methyl)isoquinoline-2(1H)-carboxylate (4n)



4n

Yellow oil, [α]25 D = +22.1° (*c* = 0.80, ^{i}PrOH); HPLC condition: chiralpak IA, 254 nm, 0.5 mL/min, n-hexane/*i*-PrOH = 70/30, t_{major} = 20.991 min, t_{minor} = 10.496 min, *ee* = 84%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.3 Hz, 1H), 7.19 (d, *J* = 7.9 Hz, 1H), 7.13 (s, 1H), 7.08 – 6.85 (m, 1H), 6.21 – 5.89 (m, 2H), 4.45–4.21 (m, 2H), 3.77 –3.57 (m, 6H), 1.35 –1.42 (m, 12H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ 152.8, 151.8, 129.8, 126.2, 125.4, 124.7, 124.4, 121.8, 109.5, 109.3, 52.9, 52.7, 52.3, 47.3 (d, *J* = 229.1 Hz), 34.6, 31.2, 14.4 ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{19}H_{26}N_3O_5PNa^+$ 430.1508; Found 430.1514.

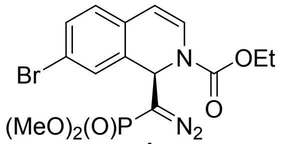
Ethyl (*R*)-1-(diazo(dimethoxyphosphoryl)methyl)-7-methoxyisoquinoline-2(1H)-carboxylate (4o)



4o

Yellow oil, [α]25 D = +80.3° (*c* = 0.26, ^{i}PrOH); HPLC condition: chiralpak IA, 254 nm, 0.5 mL/min, n-hexane/*i*-PrOH = 70/30, t_{major} = 17.229 min, t_{minor} = 13.901 min, *ee* = 73%; ^{1}H NMR (600 MHz, $(CD_3)_2CO$) 7.16 (d, *J* = 8.4 Hz, 1H), 7.02 (s, 1H), 6.95–6.83 (m, 2H), 6.20 (d, *J* = 7.6 Hz, 1H), 5.95 (d, *J* = 34.5 Hz, 1H), 4.35 – 4.22 (m, 2H), 3.83 (s, 3H), 3.78–3.68 (m, 3H), 3.57 (d, *J* = 11.8 Hz, 3H), 1.33 (d, *J* = 17.4 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $(CD_3)_2CO$) δ 160.4, 153.6, 130.6, 127.2, 123.8, 123.4, 115.5, 112.6, 109.5, 63.3, 55.9, 53.3, 53.1, 53.0, 47.7 (d, *J* = 225.4 Hz), 14.7 ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{20}N_3O_6PNa^+$ 404.0982; Found 404.0983.

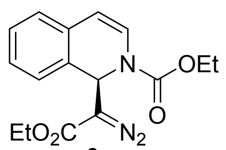
Ethyl (*R*)-7-bromo-1-(diazo(dimethoxyphosphoryl)methyl)isoquinoline-2(1H)-carboxylate (4p)



4p

Yellow oil, [α]25 D = +98.4° (*c* = 0.19, ^{i}PrOH); HPLC condition: chiralpak IA, 254 nm, 0.5 mL/min, n-hexane/*i*-PrOH = 70/30, t_{major} = 12.273 min, t_{minor} = 13.385 min, *ee* = 97%; ^{1}H NMR (600 MHz, $(CD_3)_2CO$) δ 7.63 (s, 1H), 7.47 (d, J = 8.2 Hz, 1H), 7.16 (d, J = 8.2 Hz, 1H), 7.05 (s, 1H), 6.30 (d, J = 6.4 Hz, 1H), 5.96 (d, J = 33.6 Hz, 1H), 4.34 – 4.27 (m, 2H), 3.70 (d, J = 10.9 Hz, 3H), 3.53 (d, J = 11.8 Hz, 3H), 1.34 (s, 3H) ppm. ^{13}C NMR (151 MHz, $(CD_3)_2CO$) δ 153.6, 132.4, 131.4, 130.5, 127.5, 126.8, 126.5, 120.7, 108.1, 63.7, 53.3, 53.0, 48.3 (d, *J* = 223.8 Hz), 14.7 ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{17}BrN_3O_5PNa^+$ 451.9981; Found 451.9982.

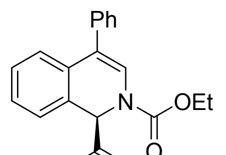
Ethyl (*R*)-1-(1-diazo-2-ethoxy-2-oxoethyl)isoquinoline-2(1H)-carboxylate (6a)



6a

Yellow oil, [α]25 D = + 164.3° (*c* = 0.52, EA); HPLC condition: chiralpak IA, 254 nm, 0.5 mL/min, n-hexane/*i*-PrOH = 90/10, t_{major} = 15.992 min, t_{minor} = 13.286 min, *ee* = 98%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25 – 7.21 (m, 3H), 7.13 – 6.31 (m, 3H), 5.81 (s, 1H), 4.37 – 4.13 (m, 4H), 1.34 (s, 3H), 1.23 (s, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.8, 152.8, 130.1, 128.7, 128.4, 127.6, 126.3, 125.3, 124.9, 108.2, 62.8, 60.9, 51.3, 14.4 ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{17}N_3O_4Na^+$ 338.1117; Found 338.1118.

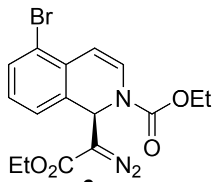
Ethyl (*R*)-1-(1-diazo-2-ethoxy-2-oxoethyl)-4-phenylisoquinoline-2(1H)-carboxylate (6b)



6b

Yellow oil, [α]25 D = +242.5° (*c* = 0.77, EA); HPLC condition: chiralpak IA, 254 nm, 0.5 mL/min, n-hexane/*i*-PrOH = 90/10, t_{major} = 13.381 min, t_{minor} = 11.378 min, *ee* = 98%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 (t, *J* = 7.4 Hz, 2H), 7.40–7.33 (m, 4H), 7.29 (t, *J* = 7.4 Hz, 1H), 7.24 (t, *J* = 7.5 Hz, 1H), 7.17–6.91 (m, 2H), 6.54 (d, *J* = 48.2 Hz, 1H), 4.35 (d, *J* = 6.0 Hz, 2H), 4.25 (d, *J* = 6.9 Hz, 2H), 1.37 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.8, 152.8, 136.8, 131.0, 129.3, 128.9, 128.8, 128.7, 128.6, 128.3, 128.0, 127.5, 126.3, 124.2, 123.7, 123.4, 122.2, 62.8, 61.0, 51.2, 14.4 ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{22}H_{21}N_3O_4Na^+$ 414.1430; Found 414.1428.

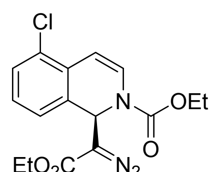
Ethyl (*R*)-5-bromo-1-(1-diazo-2-ethoxy-2-oxoethyl)isoquinoline-2(1H)-carboxylate (6c)



6c

Yellow oil, [α]25 D = + 161.2° (*c* = 0.63, EA); HPLC condition: chiralpak IC, 254 nm, 0.5 mL/min, n-hexane/*i*-PrOH = 90/10, t_{major} = 21.258 min, t_{minor} = 16.897 min, *ee* = 98%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 8.0, 0.7 Hz, 1H), 7.19 (d, *J* = 5.3 Hz, 1H), 7.15–6.95 (m, 2H), 6.41 (s, 1H), 6.16 (d, *J* = 5.5 Hz, 1H), 4.37–4.26 (m, 2H), 4.19 (dd, *J* = 13.4, 6.5 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.23 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.7, 152.7, 132.5, 130.7, 129.8, 128.4, 126.6, 125.6, 120.3, 106.7, 63.1, 61.0, 51.3, 14.4 ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{16}BrN_3O_4Na^+$ 416.0222; Found 416.0223.

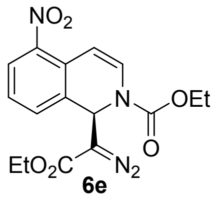
Ethyl (*R*)-5-chloro-1-(1-diazo-2-ethoxy-2-oxoethyl)isoquinoline-2(1H)-carboxylate (6d)



6d

Yellow oil, [α]25 D = + 156.9° (*c* = 0.64, EA); HPLC condition: chiralpak IC, 254 nm, 0.5 mL/min, n-hexane/*i*-PrOH = 90/10, t_{major} = 19.826 min, t_{minor} = 16.341 min, *ee* = 98%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.18–6.97 (m, 3H), 6.41 (s, 1H), 6.18 (s, 1H), 4.36 – 4.27 (m, 2H), 4.20 – 4.17 (m, 2H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.7, 152.7, 130.6, 129.9, 129.2, 128.1, 128.1, 126.4, 124.9, 104.2, 63.0, 61.0, 51.2, 14.3 ppm. HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{16}ClN_3O_4Na^+$ 372.0727; Found 372.0725.

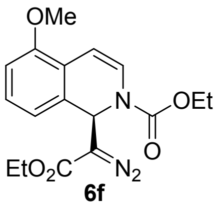
Ethyl (*R*)-1-(1-diazo-2-ethoxy-2-oxoethyl)-5-nitroisoquinoline-2(1H)-carboxylate (6e)



6e

Yellow oil, [α]25 D = + 83.4° (*c* = 0.67, EA); HPLC condition: chiralpak IC, 254 nm, 0.5 mL/min, n-hexane/*i*-PrOH = 90/10, t_{major} = 24.060 min, t_{minor} = 32.787 min, *ee* = 96%,^{1}H NMR (600 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.1 Hz, 1H), 7.51 (d, *J* = 6.7 Hz, 1H), 7.31 (t, *J* = 7.9 Hz, 1H), 7.17 (d, *J* = 7.7 Hz, 1H), 6.56 (d, *J* = 7.1 Hz, 1H), 6.46 (s, 1H), 4.38 – 4.28 (m, 2H), 4.19 (dd, *J* = 14.1, 7.0 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.23 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.5, 152.4, 144.4, 131.6, 131.4, 129.3, 127.2, 125.2, 125.0, 102.1, 63.5, 61.2, 51.2, 14.3 ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{16}N_4O_6Na^+$ 383.0968; Found 383.0965.

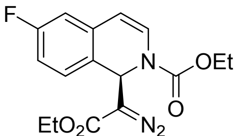
Ethyl (*R*)-1-(1-diazo-2-ethoxy-2-oxoethyl)-5-methoxyisoquinoline-2(1H)-carboxylate (6f)



6f

Yellow oil, [α]25 D = + 103.1° (c = 0.62, EA); HPLC condition: chiralpak IA, 254 nm, 0.5 mL/min, n-hexane/*i*-PrOH = 90/10, t_{major} = 17.381 min, t_{minor} = 14.147 min, *ee* = 99%, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.17 (t, *J* = 7.9 Hz, 1H), 7.01 – 6.85 (m, 2H), 6.77 (d, *J* = 8.2 Hz, 1H), 6.39 (d, *J* = 53.2 Hz, 1H), 6.18 (s, 1H), 4.35 – 4.25 (m, 2H), 4.24–4.14 (m, 2H), 3.84 (s, 3H), 1.39–1.29 (m, 3H), 1.24 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.9, 153.9, 129.9, 128.3, 127.9, 123.9, 119.5, 118.5, 109.9, 102.9, 62.7, 60.9, 55.6, 50.9, 14.4 ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{19}N_3O_5Na^+$ 368.1222; Found 368.1223.

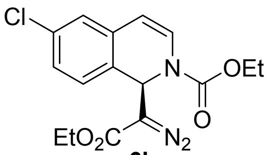
Ethyl (*R*)-1-(1-diazo-2-ethoxy-2-oxoethyl)-6-fluoroisoquinoline-2(1H)-carboxylate (6g)



6g

Yellow oil, [α]25 D = + 73.1° (*c* = 0.58, EA); HPLC condition: chiralpak IC, 254 nm, 0.5 mL/min, n-hexane/*i*-PrOH = 90/10, t_{major} = 18.172 min, t_{minor} = 16.829 min, *ee* = 97%, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.21 (s, 1H), 7.14–6.93 (m, 1H), 6.90 (td, *J* = 8.5, 2.4 Hz, 1H), 6.78 (dd, *J* = 9.1, 2.4 Hz, 1H), 6.41 (s, 1H), 5.75 (s, 1H), 4.39–4.27 (m, 2H), 4.19 (dd, *J* = 13.5, 6.6 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.23 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.8, 162.6 (d, *J* = 246.4 Hz)., 152.9, 132.2 (d, *J* = 8.6 Hz), 128.0 (d, *J* = 8.4 Hz), 126.0, 124.5 (d, *J* = 2.8 Hz), 114.3 (d, *J* = 22.3 Hz), 111.3 (d, *J* = 22.5 Hz), 107.3 (d, *J* = 2.1 Hz), 63.0, 61.0, 51.0, 14.4 ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{16}FN_3O_4Na^+$ 356.1023; Found 356.1021.

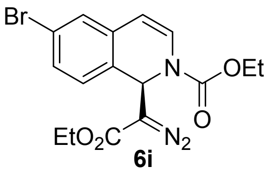
Ethyl (*R*)-6-chloro-1-(1-diazo-2-ethoxy-2-oxoethyl)isoquinoline-2(1H)-carboxylate (6h)



6h

Yellow oil, [α]25 D = + 85.1° (*c* = 0.64, EA); HPLC condition: chiralpak IC, 254 nm, 0.5 mL/min, n-hexane/*i*-PrOH = 90/10, t_{major} = 18.533 min, t_{minor} = 17.139 min, *ee* = 97%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.17 (s, 2H), 7.12–6.91 (m, 2H), 6.39 (s, 1H), 5.73 (s, 1H), 4.37 – 4.25 (m, 2H), 4.21 – 4.17 (m, 2H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.23 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.7, 152.8, 134.2, 131.8, 127.6, 127.4, 127.0, 126.1, 124.6, 106.9, 63.0, 61.0, 51.0, 14.4 ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{16}ClN_3O_4Na^+$ 372.0727; Found 372.0726.

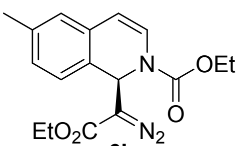
Ethyl (*R*)-6-bromo-1-(1-diazo-2-ethoxy-2-oxoethyl)isoquinoline-2(1H)-carboxylate (6i)



6i

Yellow oil, [α]25 D = + 80.6° (*c* = 0.69, EA); HPLC condition: chiralpak IC, 254 nm, 0.5 mL/min, n-hexane/*i*-PrOH = 90/10, t_{major} = 18.870 min, t_{minor} = 17.596 min, *ee* = 98%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.1 Hz, 1H), 7.23 (s, 1H), 7.12 – 6.97 (m, 2H), 6.36 (d, *J* = 25.7 Hz, 1H), 5.73 (s, 1H), 4.39 – 4.26 (m, 2H), 4.26–4.15 (m, 2H), 1.34 (t, *J* = 6.9 Hz, 3H), 1.24 (t, *J* = 6.6 Hz, 3H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.6, 152.7, 132.1, 130.3, 127.9, 127.5, 127.5, 126.1, 122.2, 106.7, 63.0, 61.0, 51.1, 14.4 ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{16}BrN_3O_4Na^+$ 416.0222; Found 416.0223.

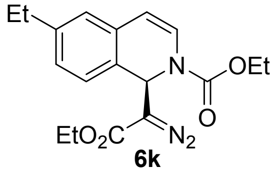
Ethyl (*R*)-1-(1-diazo-2-ethoxy-2-oxoethyl)-6-methylisoquinoline-2(1H)-carboxylate (6j)



6j

Yellow oil, [α]25 D = +55.0° (*c* = 0.47, EA); HPLC condition: chiralpak IC, 254 nm, 0.5 mL/min, n-hexane/*i*-PrOH = 90/10, t_{major} = 25.037 min, t_{minor} = 23.242 min, *ee* = 98%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.13 (s, 1H), 7.07–6.86 (m, 3H), 6.38 (d, *J* = 43.8 Hz, 1H), 5.77 (s, 1H), 4.33–4.24 (m, 2H), 4.20 (s, 2H), 2.32 (s, 3H), 1.33 (s, 3H), 1.24 (t, *J* = 6.7 Hz, 3H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.9, 152.9, 138.2, 129.9, 128.4, 126.2, 126.0, 125.5, 124.7, 108.3, 62.8, 60.9, 51.2, 21.1, 14.4 ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{19}N_3O_4Na^+$ 352.1273; Found 352.1270.

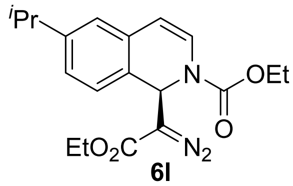
Ethyl (*R*)-1-(1-diazo-2-ethoxy-2-oxoethyl)-6-ethylisoquinoline-2(1H)-carboxylate (6k)



6k

Yellow oil, [α]25 D = +104.8° (c = 0.67, EA); HPLC condition: chiralpak IA, 254 nm, 0.5 mL/min, n-hexane/i-PrOH =90/10, t_{major} = 17.727 min, t_{minor} = 13.646 min, ee = 98%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.16 (s, 1H), 7.06 – 6.90 (m, 3H), 6.39 (d, J = 45.1 Hz, 1H), 5.79 (s, 1H), 4.35 – 4.26 (m, 2H), 4.24 – 4.15 (m, 2H), 2.62 (q, J = 7.6 Hz, 2H), 1.34 (d, J = 5.8 Hz, 3H), 1.23 (dd, J = 14.3, 6.8 Hz, 6H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.9, 152.9, 144.6, 130.0, 127.2, 126.2, 126.2, 125.2, 124.8, 124.3, 108.5, 62.8, 60.9, 51.1, 28.5, 15.3, 14.4 ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{18}H_{21}N_3O_4Na^+$ 366.1430; Found 366.1431.

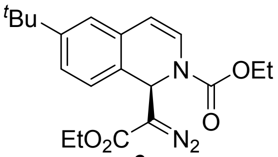
Ethyl (*R*)-1-(1-diazo-2-ethoxy-2-oxoethyl)-6-isopropylisoquinoline-2(1H)-carboxylate (6l)



6l

Yellow oil, [α]25 D = +82.8° (c = 0.56, EA); HPLC condition: chiralpak IA, 254 nm, 0.5 mL/min, n-hexane/i-PrOH = 90/10, t_{major} = 17.267 min, t_{minor} = 13.358 min, ee = 97%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.17 (s, 1H), 7.09 (dd, J = 7.8, 1.4 Hz, 1H), 7.06 – 6.86 (m, 2H), 6.39 (d, J = 42.0 Hz, 1H), 5.79 (s, 1H), 4.33 – 4.28 (m, 2H), 4.25–4.14 (m, 2H), 2.93 – 2.81 (m, 1H), 1.33 (t, J = 6.5 Hz, 3H), 1.23 (t, J = 5.8 Hz, 9H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.9, 152.8, 149.2, 129.9, 126.3, 126.2, 125.8, 125.4, 124.8, 122.9, 108.5, 62.7, 60.8, 51.1, 33.8, 23.8, 14.4 ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{19}H_{23}N_3O_4Na^+$ 380.1586; Found 380.1587.

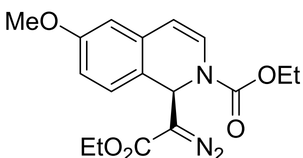
Ethyl (*R*)-6-(tert-butyl)-1-(1-diazo-2-ethoxy-2-oxoethyl)isoquinoline-2(1H)-carboxylate (6m)



6m

Yellow oil, [α]25 D = +96.4° (c = 0.56, EA); HPLC condition: chiralpak IA, 254 nm, 0.5 mL/min, n-hexane/i-PrOH = 90/10, t_{major} = 17.314 min, t_{minor} = 12.137 min, ee = 95%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.26 – 7.24 (m, 1H), 7.19 (s, 1H), 7.13 – 6.85 (m, 2H), 6.39 (d, J = 45.1 Hz, 1H), 5.81 (s, 1H), 4.35 – 4.25 (m, 2H), 4.25 – 4.15 (m, 2H), 1.31 (s, 9H), 1.24 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.9, 152.8, 151.5, 129.6, 126.0, 126.0, 125.1, 124.8, 124.6, 121.8, 108.8, 62.7, 60.8, 51.0, 34.6, 31.2, 14.4 ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{20}H_{25}N_3O_4Na^+$ 394.1743; Found 394.1740.

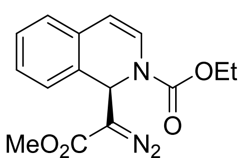
Ethyl (*R*)-1-(1-diazo-2-ethoxy-2-oxoethyl)-6-methoxyisoquinoline-2(1H)-carboxylate (6n)



6n

Yellow oil, [α]25 D = + 68.2° (c = 0.28, EA); HPLC condition: chiralpak IA, 254 nm, 0.5 mL/min, n-hexane/i-PrOH = 90/10, t_{major} = 25.037 min, t_{minor} = 14.508 min, ee = 97%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.17 – 6.93 (m, 2H), 6.77 (dd, J = 8.4, 2.6 Hz, 1H), 6.61 (d, J = 2.5 Hz, 1H), 6.37 (d, J = 36.1 Hz, 1H), 5.77 (s, 1H), 4.35 – 4.25 (m, 2H), 4.25 – 4.14 (m, 2H), 3.80 (s, 3H), 1.34 (t, J = 6.9 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H). ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.6, 131.4, 127.4, 125.3, 121.2, 113.5, 109.7, 108.2, 62.8, 60.9, 55.3, 51.1, 14.4 ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{19}N_3O_5Na^+$ 368.1222; Found 368.1226.

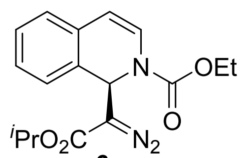
Ethyl (*R*)-1-(1-diazo-2-methoxy-2-oxoethyl)isoquinoline-2(1H)-carboxylate (6o)



6o

Yellow oil, [α]25 D = +142.6° (c = 0.59, EA); HPLC condition: chiralpak IA, 254 nm, 0.5 mL/min, n-hexane/i-PrOH = 90/10, t_{major} = 16.943 min, t_{minor} = 14.009 min, ee = 95%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.26–7.18 (m, 3H), 7.09-6.92 (m, 2H), 6.45-6.39 (m, 1H), 5.81 (s, 1H), 4.37–4.24 (m, 2H), 3.74 (s, 3H), 1.34 (t, J = 6.6 Hz, 3H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.2, 152.8, 130.0, 128.6, 128.5, 127.6, 126.3, 124.9, 108.2, 62.8, 51.9, 51.2, 14.4 ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{15}N_3O_4Na^+$ 324.0960; Found 324.1215.

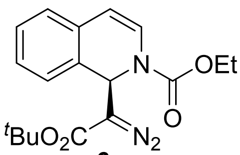
Ethyl (*R*)-1-(1-diazo-2-isopropoxy-2-oxoethyl)isoquinoline-2(1H)-carboxylate (6p)



6p

Yellow oil, [α]25 D = +145.0° (c = 0.61, EA); HPLC condition: chiralpak IA, 254 nm, 0.5 mL/min, n-hexane/i-PrOH = 90/10, t_{major} = 14.290 min, t_{minor} = 12.163 min, ee = 98%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33–7.26 (m, 3H), 7.15-6.97 (m, 2H), 6.50-6.44 (m, 1H), 5.87 (s, 1H), 5.13 (dt, J = 12.4, 6.2 Hz, 1H), 4.44–4.29 (m, 2H), 1.40 (s, 3H), 1.30 (d, J = 6.0 Hz, 3H), 1.24 (d, J = 6.1 Hz, 3H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.5, 152.9, 130.2, 128.9, 128.4, 127.6, 126.3, 125.3, 124.9, 108.3, 68.6, 62.8, 51.4, 22.0, 21.9, 14.4 ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{19}N_3O_4Na^+$ 352.1273; Found 352.1275.

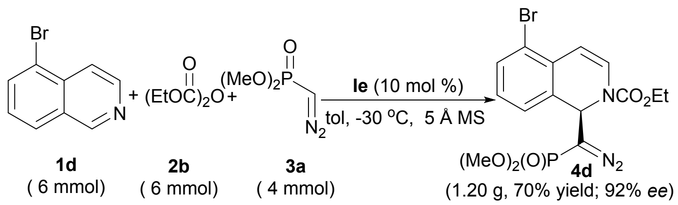
Ethyl (*R*)-1-(2-(*tert*-butoxy)-1-diazo-2-oxoethyl)isoquinoline-2(1H)-carboxylate (6q)



6q

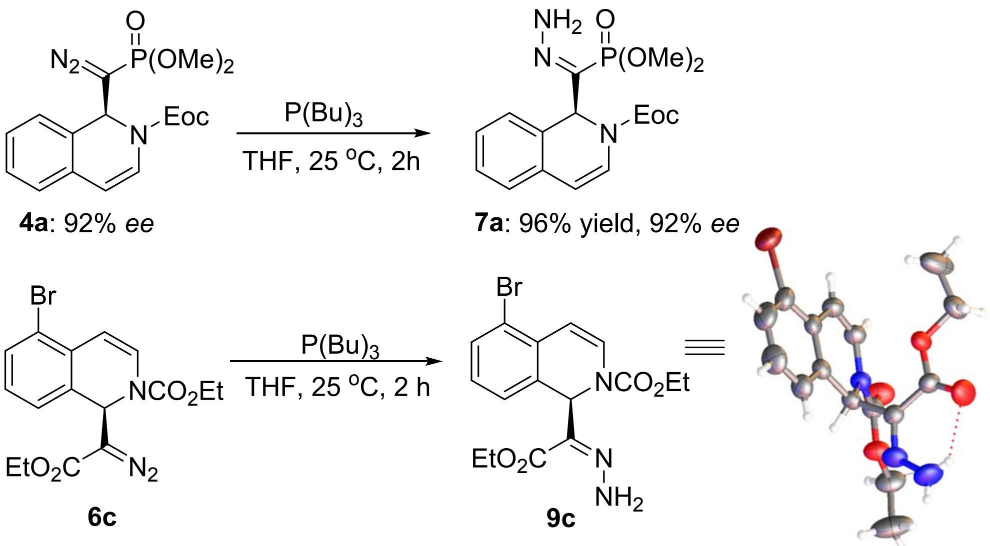
Yellow oil, [α]25 D = +133.3° (c = 0.62, EA); HPLC condition: chiralpak IC, 254 nm, 0.5 mL/min, n-hexane/i-PrOH = 90/10, t_{major} = 12.094 min, t_{minor} = 12.550 min, ee = 98%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27–7.18 (m, 3H), 7.08-6.92 (m, 2H), 6.39-6.33 (m, 1H), 5.79 (d, *J* = 7.4 Hz, 1H), 4.38–4.22 (m, 2H), 1.45 (s, 9H), 1.34 (s, 3H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.1, 152.7, 130.0, 129.1, 128.3, 127.6, 126.2, 125.2, 124.9, 108.2, 81.7, 62.8, 51.3, 28.3, 14.4 ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{18}H_{21}N_3O_4Na^+$ 366.1430; Found 366.1431.

7. Gram-scale reaction to obtain product 4d.



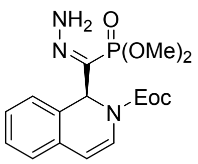
To evaluate its potential synthetic utility, the reaction was also performed on a larger scale (4 mmol), affording α-diazo-β-isoquinoline-phosphonate **4d** in 70% yield with enantioselectivity (92% *ee*) similar to that obtained in the 0.1-mmol-scale reaction with 10 mol % catalyst

8. Synthesis of 7a, 8a and 9c from 4a and 7c



$P(Bu)_3$ (68 uL, 0.3 mmol) was added to the solution of **4a** (35.1 mg, 0.1 mmol) in THF (2.0 mL) under nitrogen atmosphere and stirred at rt. The reaction mixture was stirred overnight at the same temperature until **4a** had been completely consumed by TLC, then, the mixture was purified directly by flash chromatography on silica gel (30–50% AcOEt/petroleum ether) to give the corresponding product **7a** (33.9 mg, 96% yield, 92% *ee*). **9c** was prepared according to the procedure of **7a**

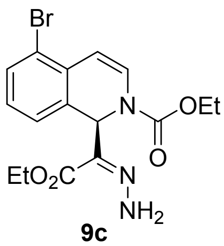
Ethyl (*S*, *Z*)-1-((dimethoxyphosphoryl)(hydrazono)methyl)isoquinoline-2(1H)-carboxylate (7a)



7a

Colourless oil, [α]25 D = +14.6° (*c* = 0.37, ^{i}PrOH); HPLC condition: chiralpak IA, 254 nm, 0.5 mL/min, n-hexane/*i*-PrOH = 70/30, t_{major} = 16.348 min, t_{minor} = 13.699 min, *ee* = 92%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.61 (s, 2H), 7.26–7.09 (m, *3*H), 7.08–6.88 (m, 2H), 6.16-6.08 (m, 1H), 5.73 (d, *J* = 20.0 Hz, 1H), 4.26 (dd, *J* = 6.8, 2.7 Hz, 2H), 3.45 (dd, *J* = 101.9, 10.5 Hz, 6H), 1.31 (t, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 153.0, 130.8, 129.5, 127.9, 127.4, 126.5, 125.8, 124.6, 106.8, 62.4, 60.9, 59.8, 58.5, 52.0 (d, *J* = 4.7 Hz), 14.5 ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{20}N_3O_5PNa^+$ 376.1038; Found 376.10387.

Ethyl (*R*, *Z*)-5-bromo-1-(2-ethoxy-1-hydrazono-2-oxoethyl)isoquinoline-2(1H)-carboxylate (9c)



9c

White solid, mp 90.5–92.1 °C, [α]25 D = +893.9° (*c* = 0.23, ^{i}PrOH); HPLC condition: chiralpak IA, 254 nm, 0.5 mL/min, n-hexane/*i*-PrOH = 70/30, t_{major} = 12.439 min, t_{minor} = 9.891 min, *ee* = 99%; ^{1}H NMR (600 MHz, $(CD_3)_2CO$) δ 8.95 (s, 2H), 7.43 (d, *J* = 7.9 Hz, 1H), 7.31 (s, 1H), 7.12 (s, 1H), 7.04 (t, *J* = 7.6 Hz, 1H), 6.38 (s, 1H), 5.99 (d, *J* = 7.9 Hz, 1H), 4.36–4.27 (m, 2H), 4.25-4.18 (m, 2H), 1.38 (t, *J* = 7.1 Hz, 3H), 1.27 (s, 3H) ppm; ^{13}C NMR (151 MHz, $(CD_3)_2CO$) δ 162.3, 132.4, 131.0, 129.6, 128.5, 127.1, 120.5, 104.8, 63.1, 61.1, 56.3, 14.7, 14.6 ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{18}BrN_3O_4Na^+$ 418.0373; Found 418.0371.

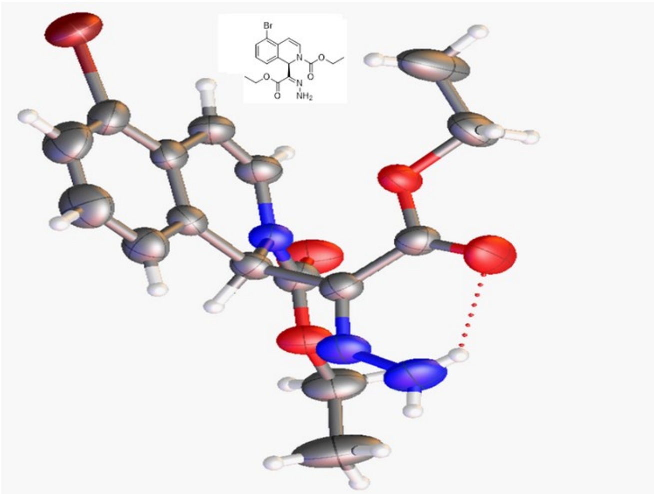
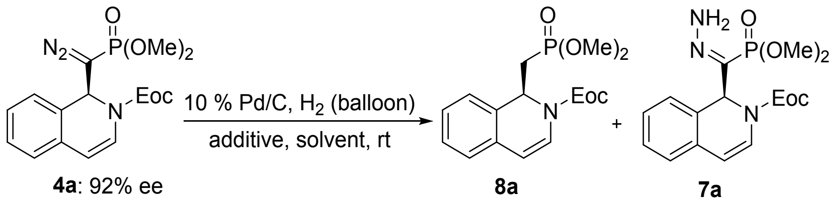


Table S11. Crystal data and structure refinement for **9c**	
Empirical formula	$C_{16}H_{18}BrN_3O_4$
Formula weight	396.24
Temperature/K	294.0(3)
Crystal system	monoclinic
Space group	$P2_1$
a/Å	7.32373(10)
b/Å	15.62333(14)
c/Å	8.25080(10)
α/°	90
β/°	112.6346(15)
γ/°	90
Volume/Å^3	871.35(2)
Z	2
ρ_{calc}g/cm^3	1.510
μ/mm^{-1}	3.440
F(000)	404.0
Crystal size/mm^3	0.2 × 0.2 × 0.2
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	11.328 to 143.384
Index ranges	-8 ≤ h ≤ 8, -18 ≤ k ≤ 19, -9 ≤ l ≤ 10
Reflections collected	9511
Independent reflections	3335 [R_{int} = 0.0177, R_{sigma} = 0.0158]

Data/restraints/parameters	3335/2/227
Goodness-of-fit on F^2	1.041
Final R indexes [I>=2σ (I)]	R_1 = 0.0383, wR_2 = 0.1058
Final R indexes [all data]	R_1 = 0.0386, wR_2 = 0.1063
Largest diff. peak/hole / e Å^{-3}	0.43/-0.67

Table S12. Optimization of the reaction conditions from **4a** to **8a**[a]

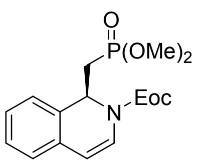


entry	solvent/0.04M	additive/equiv.	t (h)	Pd/C (%)	yield of **7a** (%)[b]	yield of **8a** (%)[b]
1	MeOH	--	24	5	--	confusion
2	EA	--	24	5	--	confusion
3	MeOH	DBU (1.0)	12	5	80	trace
4	MeOH	DBU (1.0)	12	1	--	31
5	EA	DBU (1.0)	12	1	0	0
6	MeOH/EA= 1/4	DBU (1.0)	12	1	22	49
7	MeOH/EA= 1/4	DBU (0.5)	12	1	16	55
8	MeOH/EA= 1/9	DBU (1.0)	12	1	37	53
9	MeOH/EA= 1/4	Et_3N (0.5)	48	1	trace	trace
10	MeOH/EA= 1/4	DBN (1.0)	48	1	20	49
14	MeOH/EA= 1/4	DBU (0.5)	48	1	12	70
15	MeOH/EA= 1/4	DBU (0.2)	60	1	trace	82

[a]Unless noted otherwise, all reactions were conducted using **4a** (0.1 mmol), 10% Pd/C at rt under 1 atm of H_2 (balloon). [b]Isolated yield.

10% Pd/C (1.06 mg, 1 mol %) was added to the solution of **4a** (35.3 mg, 0.1 mmol) in EA:MeOH = 4:1 (2.5 mL). The reaction vessel was purged with H_2 (3 times), DBU (3.0 uL, 0.02mmol) was added to the mixture then stirred under 1 atm of H_2 (balloon). After the reaction completed, filtrated through a plug of celite, then the filtrate was concentrated under vacuum, the residue was purified by flash chromatography on silica gel (50–100% AcOEt/petroleum ether) to give the title compound **8a** in 82% yield (26.6 mg, 92% *ee*).

Ethyl (*S*)-1-((dimethoxyphosphoryl)methyl)isoquinoline-2(1H)-carboxylate (8a)



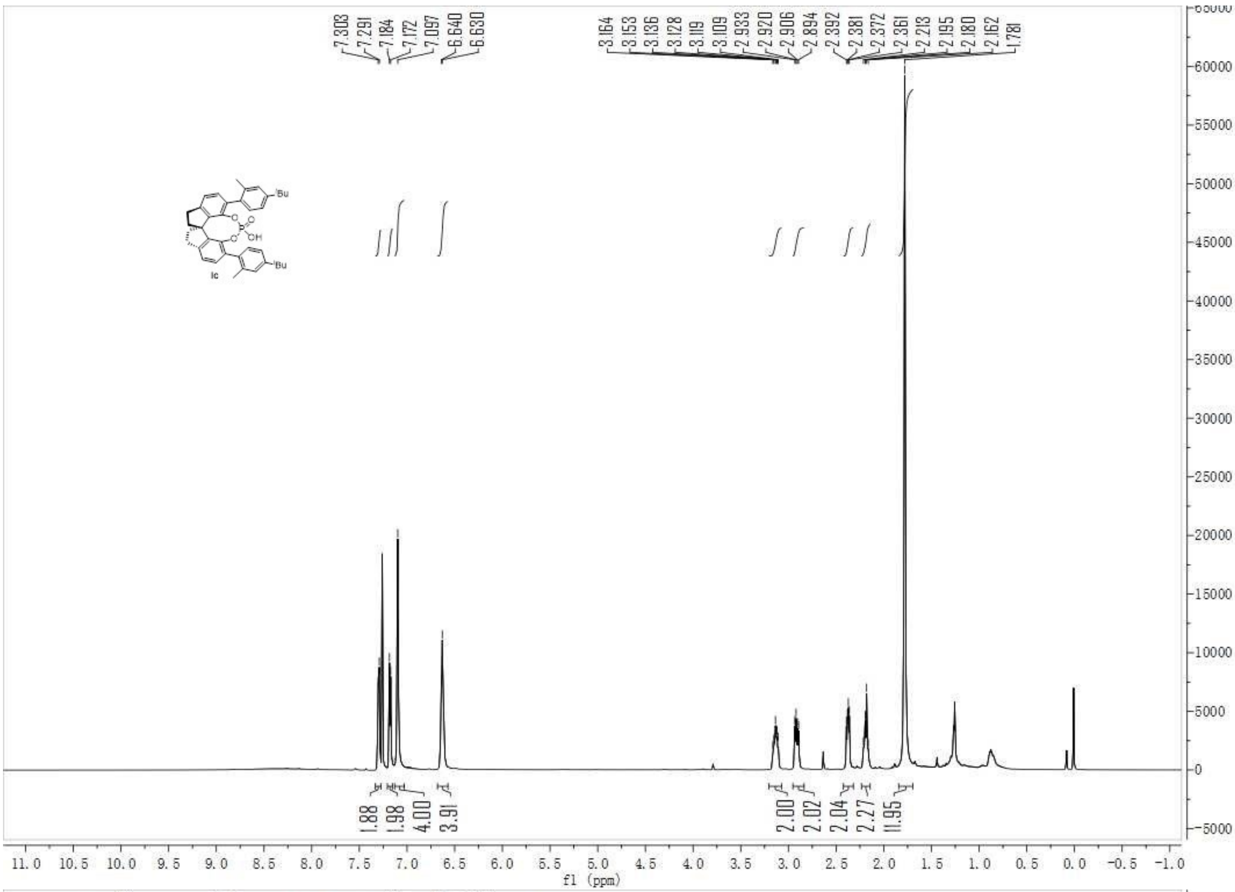
8a

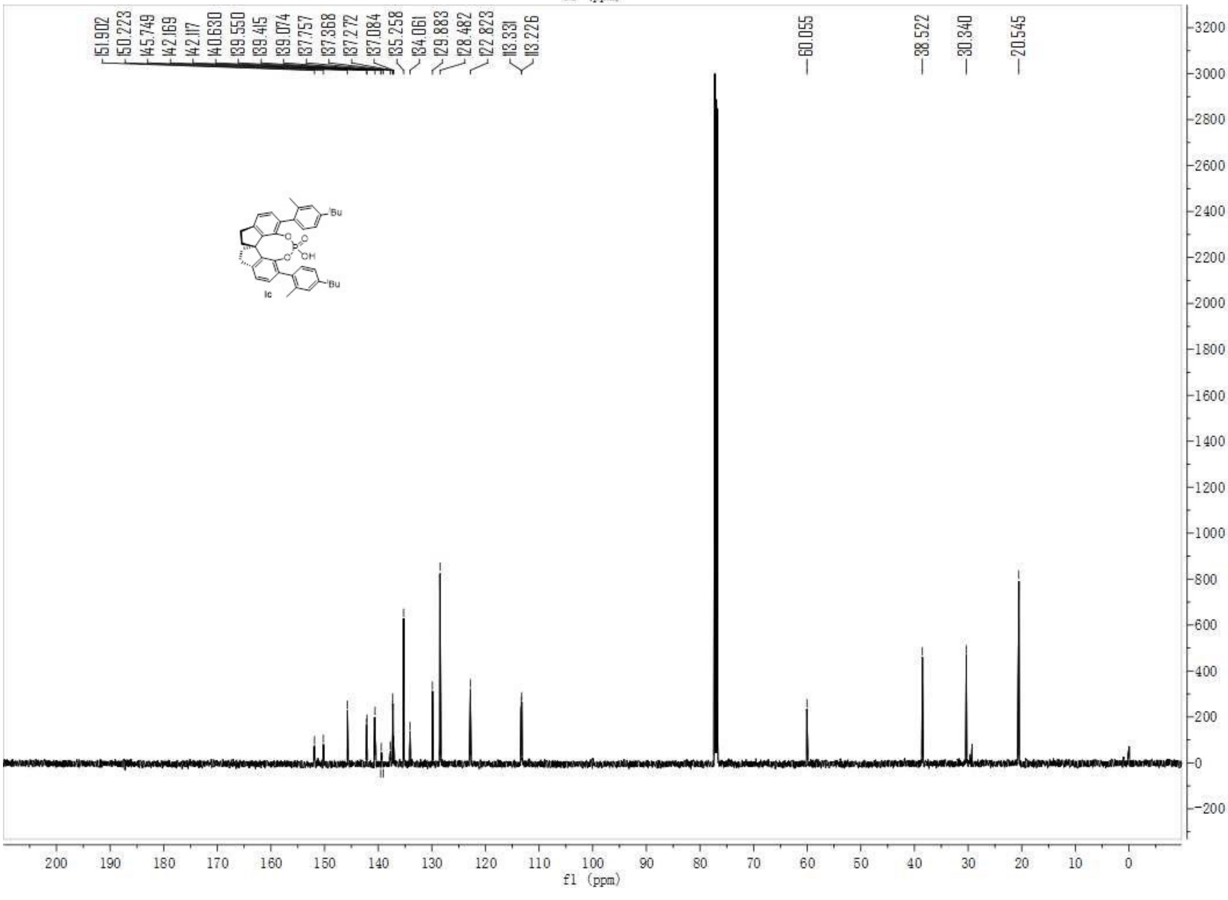
Colourless oil, [α]25 D = +597.0° (*c* = 0.20, ^{i}PrOH); HPLC condition: chiralpak IC, 230 nm, 1.0 mL/min, n-hexane/*i*-PrOH = 70/30, t_{major} = 29.220 min, t_{minor} = 39.308 min, *ee* = 92%; ^{1}H NMR (600 MHz, $(CD_3)_2CO$) δ 7.33-7.30 (m, 1H), 7.26-7.20 (m, 2H), 7.15 (d, *J* = 7.3 Hz, 1H), 6.92-6.85 (m, 1H), 6.08-6.00 (m, 1H), 5.74 (dd, *J* = 14.9, 7.5 Hz, 1H), 4.24 (d, *J* = 5.6 Hz, 2H), 3.59 (t, *J* = 13.8 Hz, 3H), 3.52 (d, *J* = 10.6 Hz, 3H), 2.24–2.06 (m, 2H), 1.39–1.26 (m, 3H) ppm; ^{13}C NMR (151 MHz, $(CD_3)_2CO$) δ 153.1, 131.2, 128.9, 127.7, 127.6, 127.4, 125.5, 125.3, 109.7, 109.5, 63.0, 52.3, 51.4, 29.9 (d, *J* = 175.9 Hz), 14.8 ppm; HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{20}NO_5PNa^+$ 348.0971; Found 348.0971.

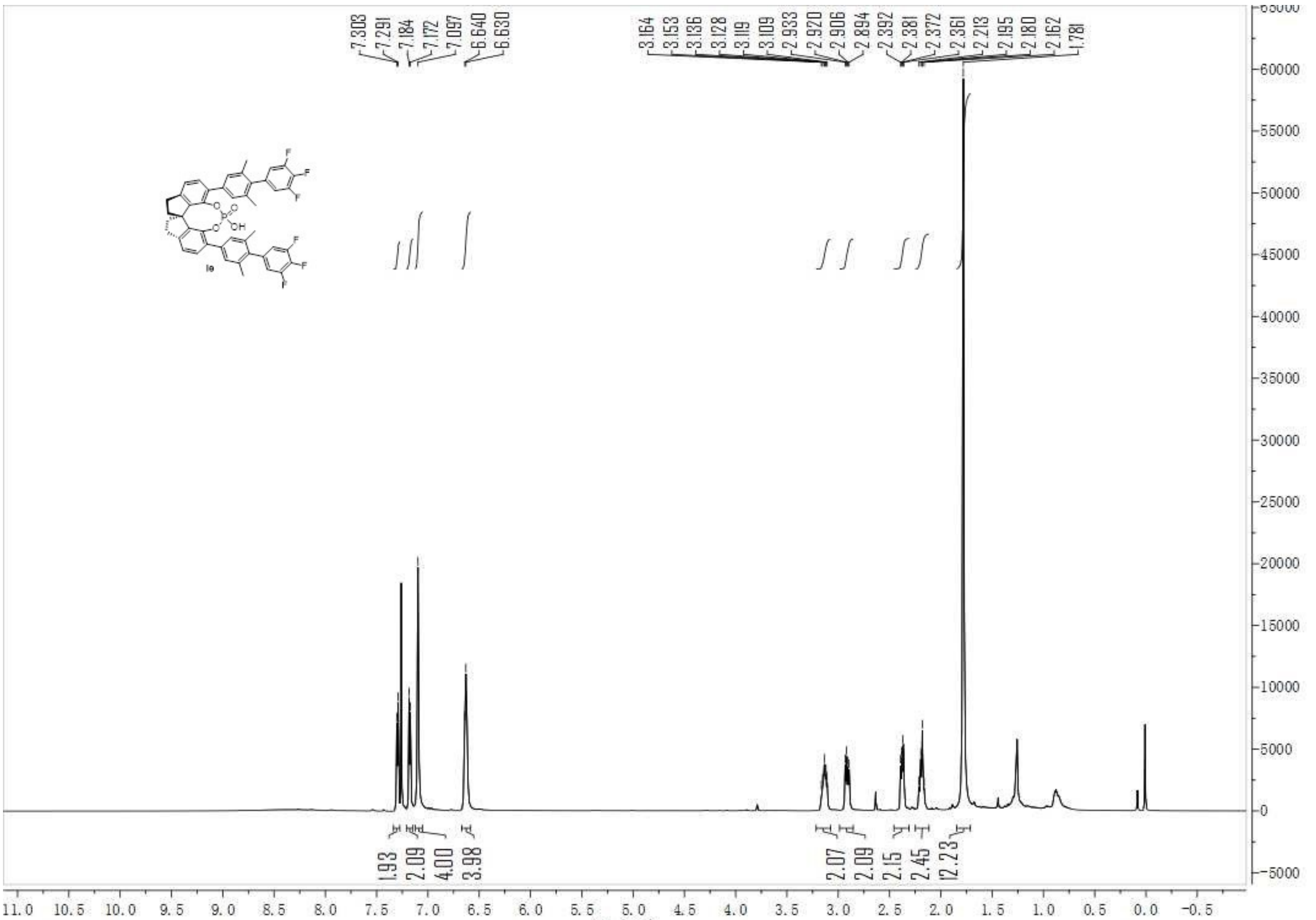
9. References

[1] a) F. X. Xu, D. Huang, C. Han, W. Shen, X. F. Lin, Y. G. Wang, *J. Org. Chem.* **2010**, *75*, 8677; b) B. Zheng, H. H. Chen, L. Zhu, X. Q. Hou, Y. Wang, Y. Lan, Y. G. Peng, *Org. Lett.* **2019***, 21*, 593. c) B. Xu, S. F. Zhu, X. L. Xie, J. J. Shen, Q. L. Zhou, *Angew. Chem. Int. Ed.* **2011***, 50,* 11483. d) Y. X. Jia, J. Zhong, S. F. Zhu, C. M. Zhang, Q. L. Zhou, *Angew. Chem. Int. Ed.* **2007***, 46*, 5565.

10. NMR spectra and HPLC for SPAs and asymmetric acyl-Mannich reaction products.



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2.933
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2.381
2.372
2.361
2.213
2.195
2.180
2.162
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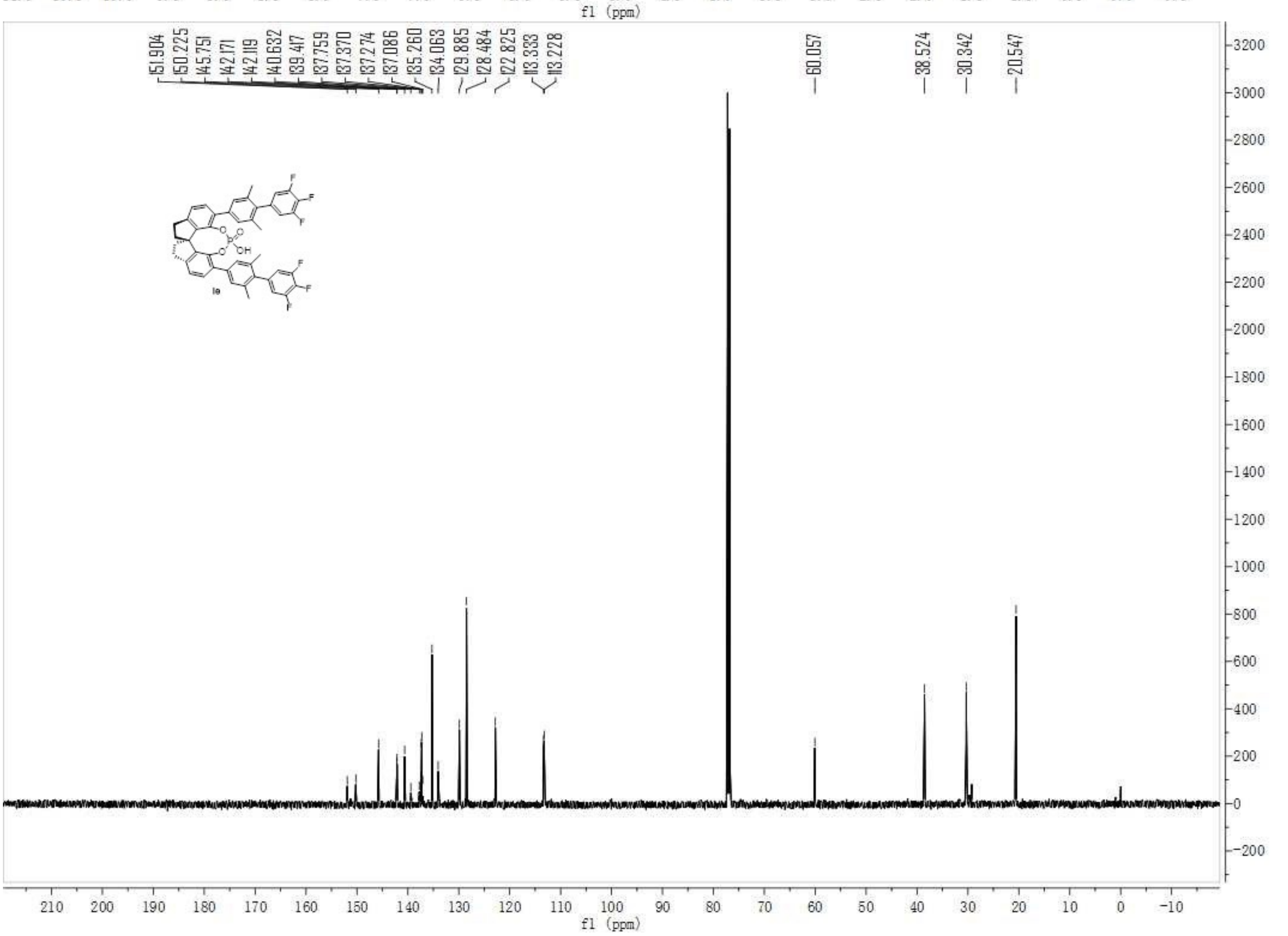
1.93
2.09
4.00
3.98
2.07
2.09
2.15
2.45
12.23
f1 (ppm)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128.484
122.825
113.333
113.228
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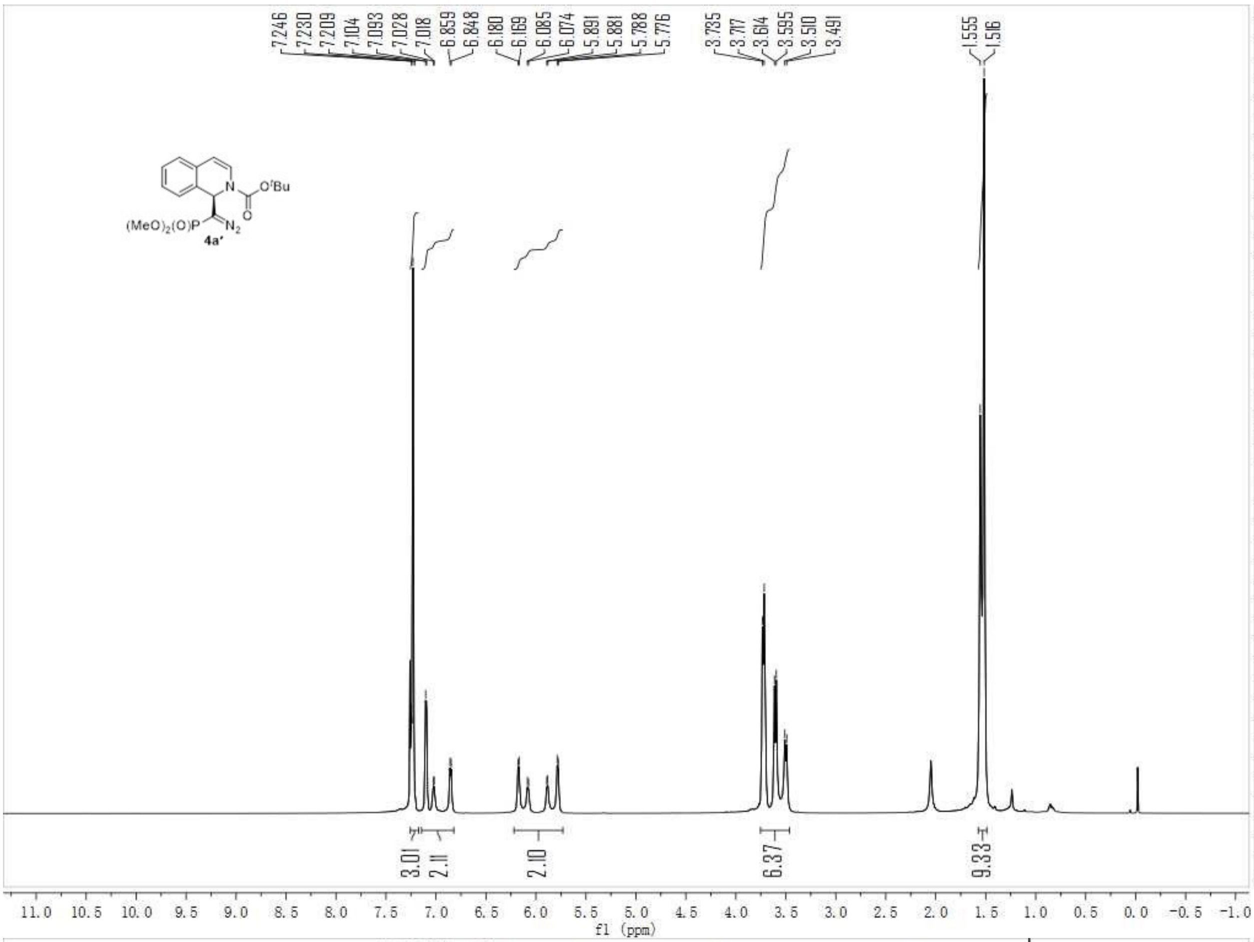
30.342
20.547
f1 (ppm)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5.881
5.788
5.776
3.735
3.717
3.614
3.595
3.510
3.491
1.555
1.516
O^tBu
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N2
4a′
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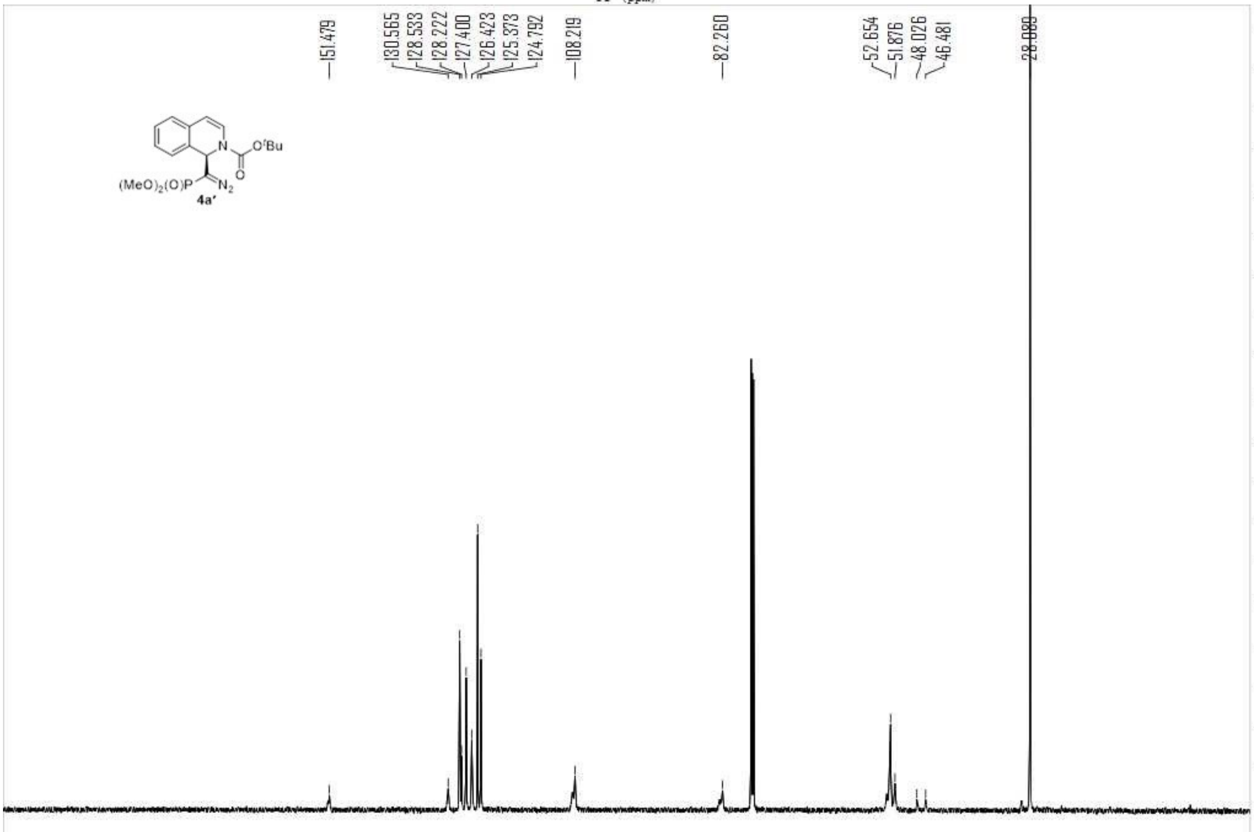
2.11
2.10
6.37
9.33
f1 (ppm)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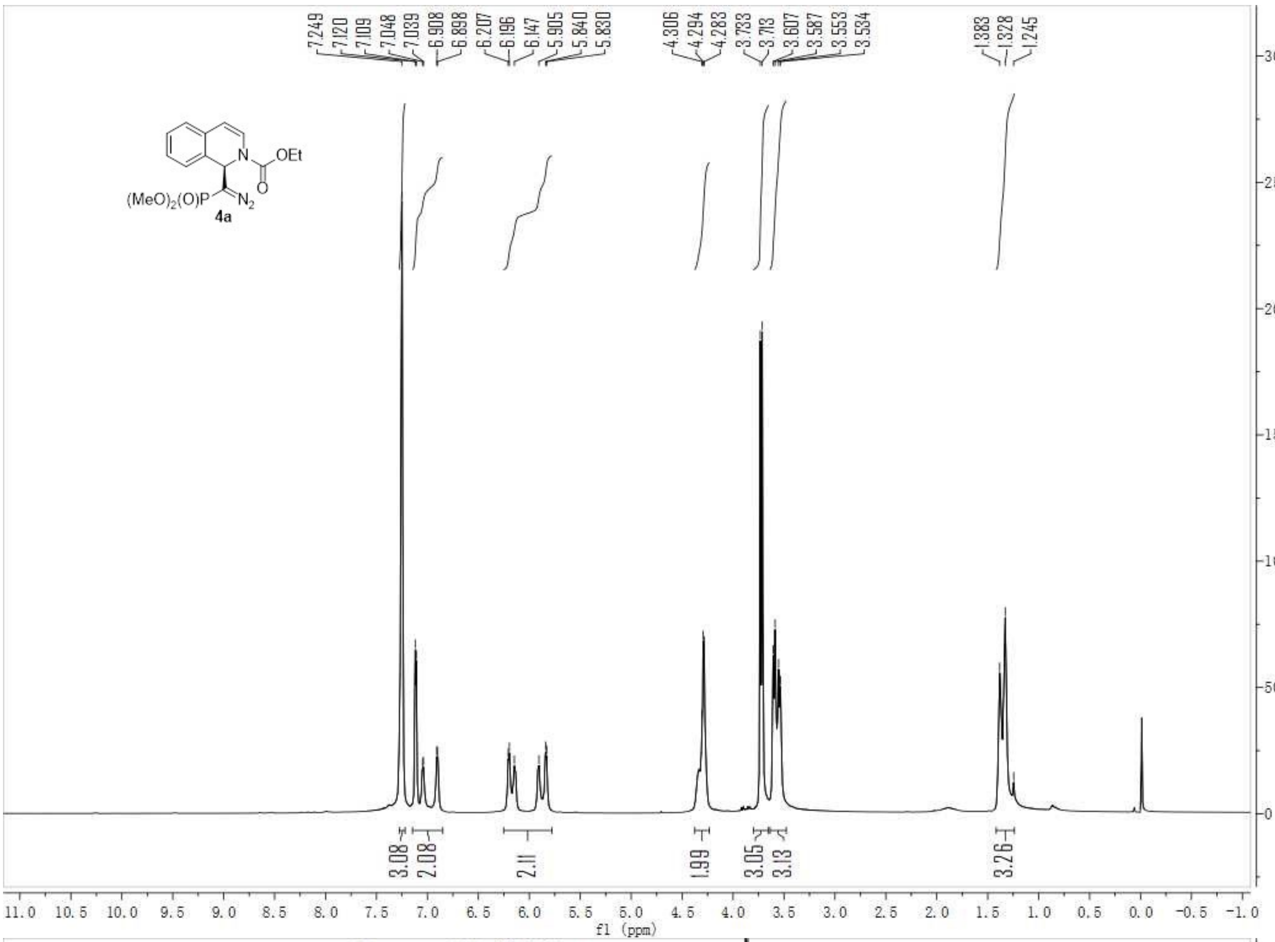
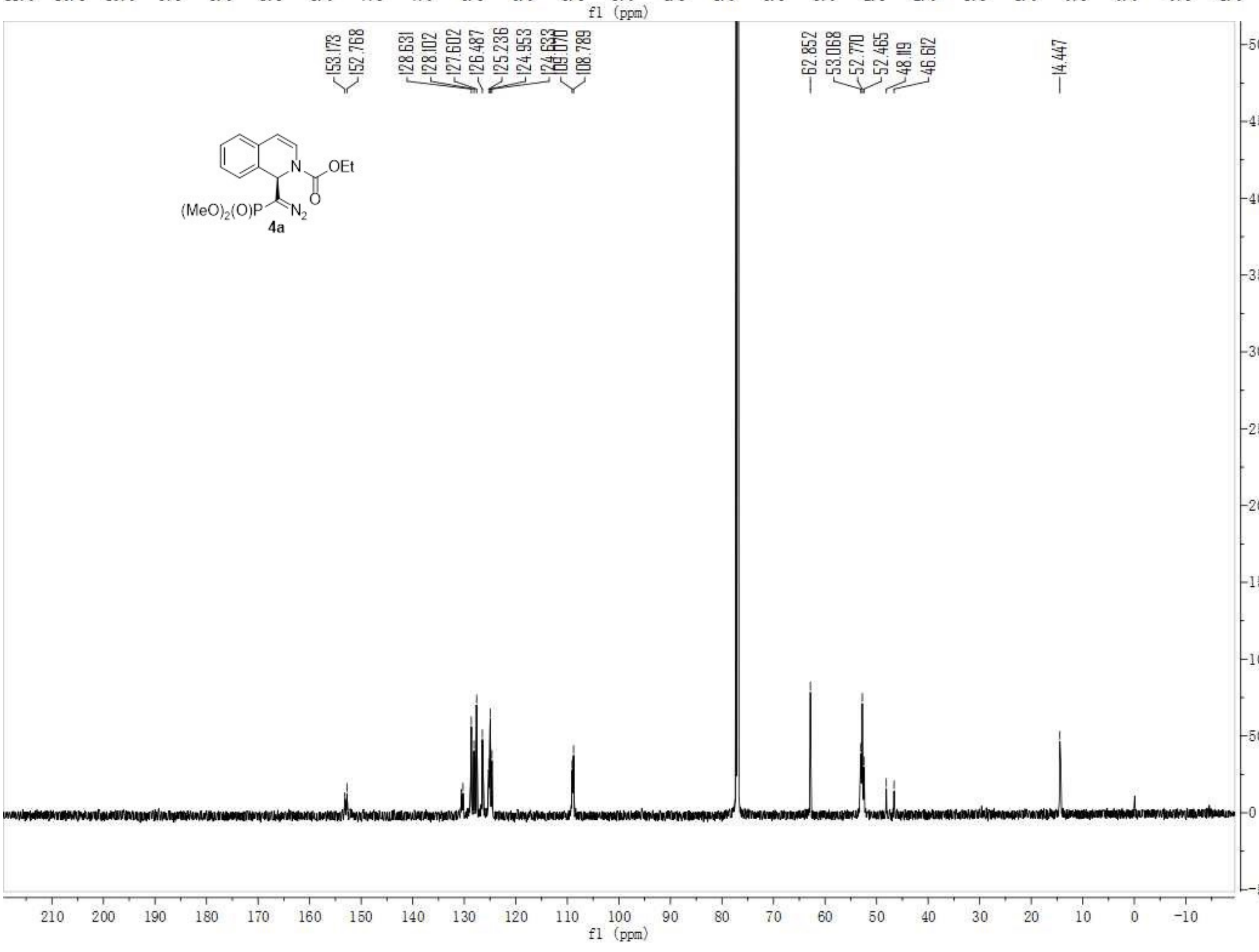
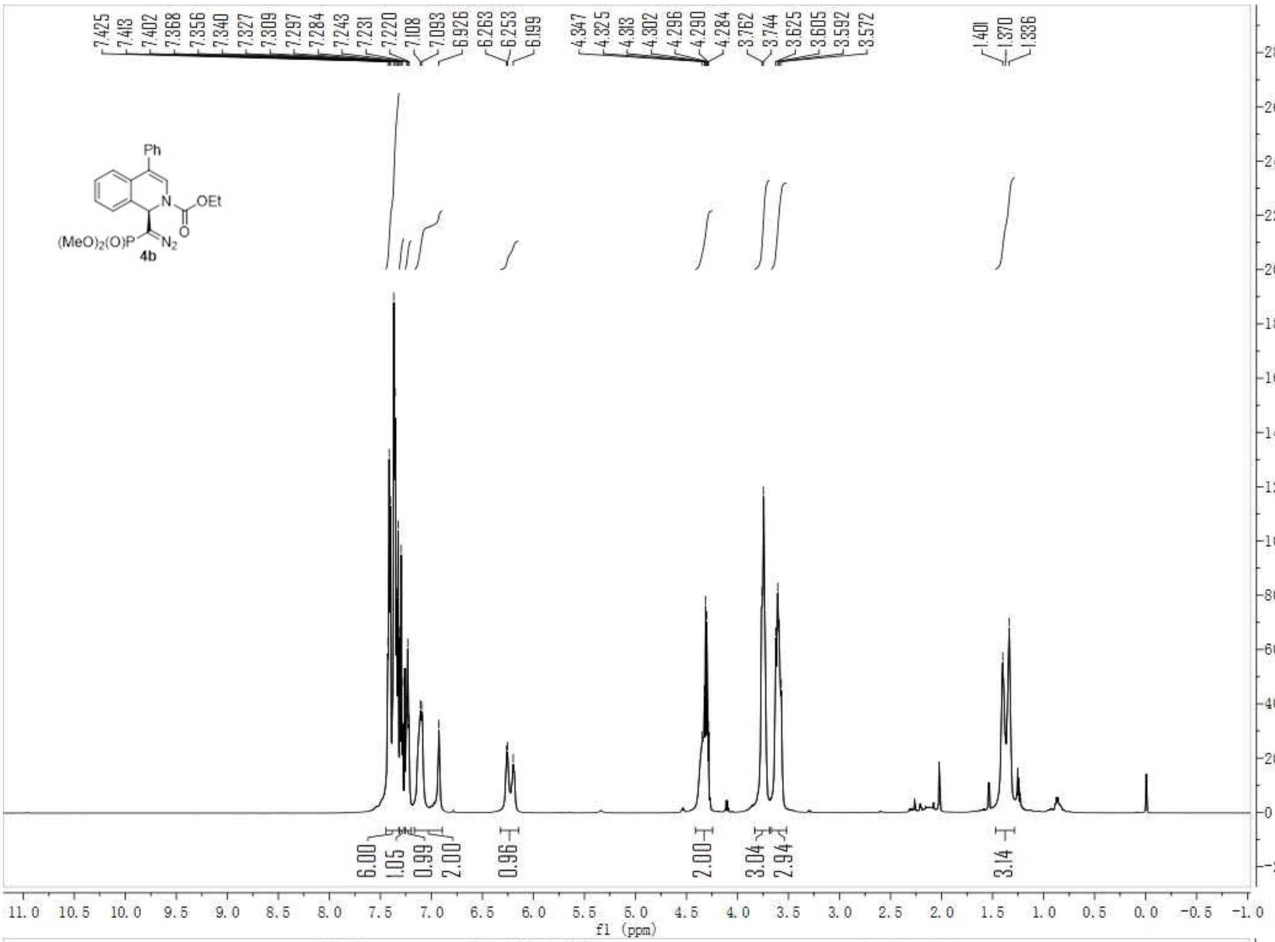
N2
4a′
f1 (ppm)



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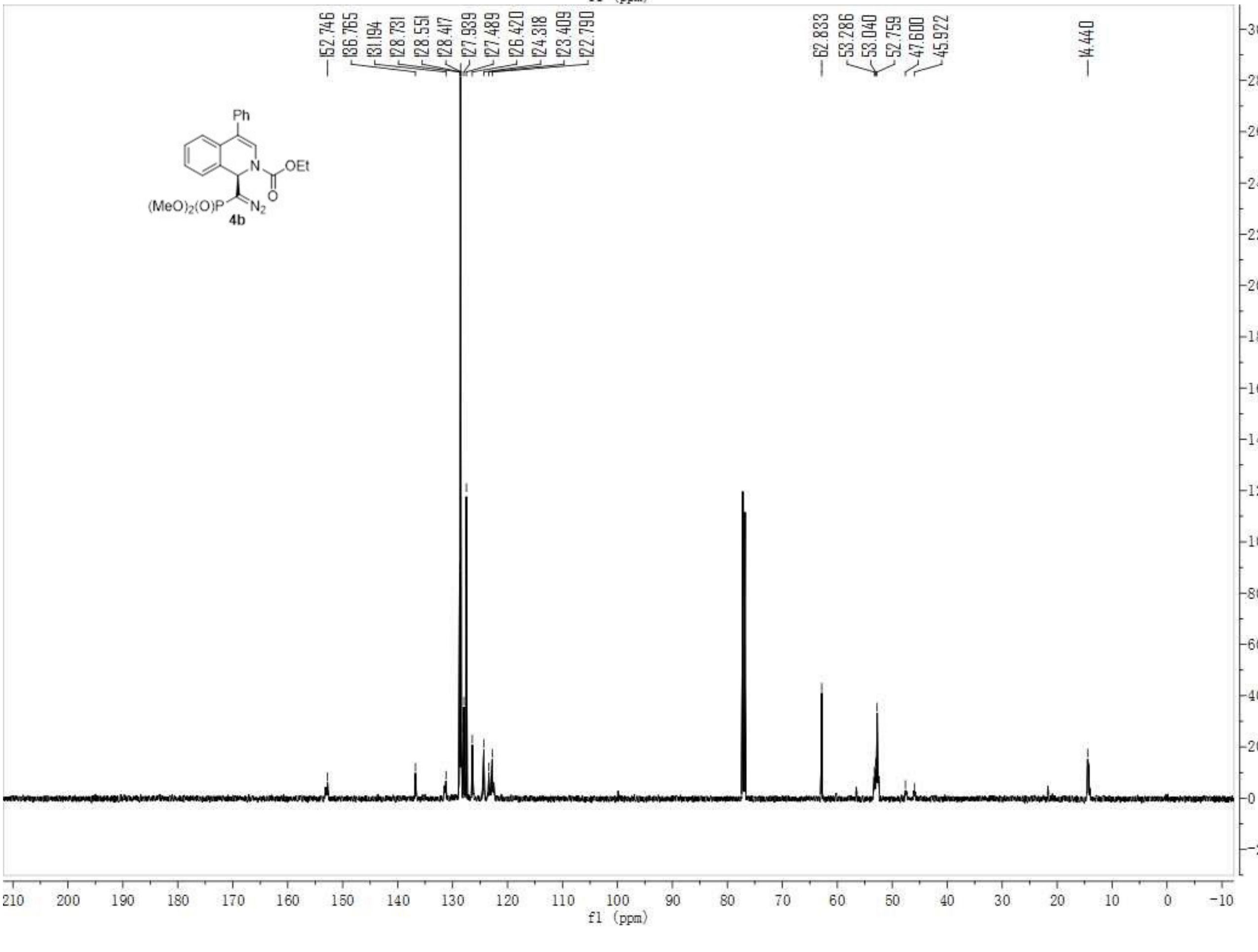
1.401 1.370 1.336
Ph
N
OEt
O
(MeO)2(O)P
N2
4b
6.00 1.05 0.99 2.00 0.96 2.00 3.04 2.94 3.14
f1 (ppm)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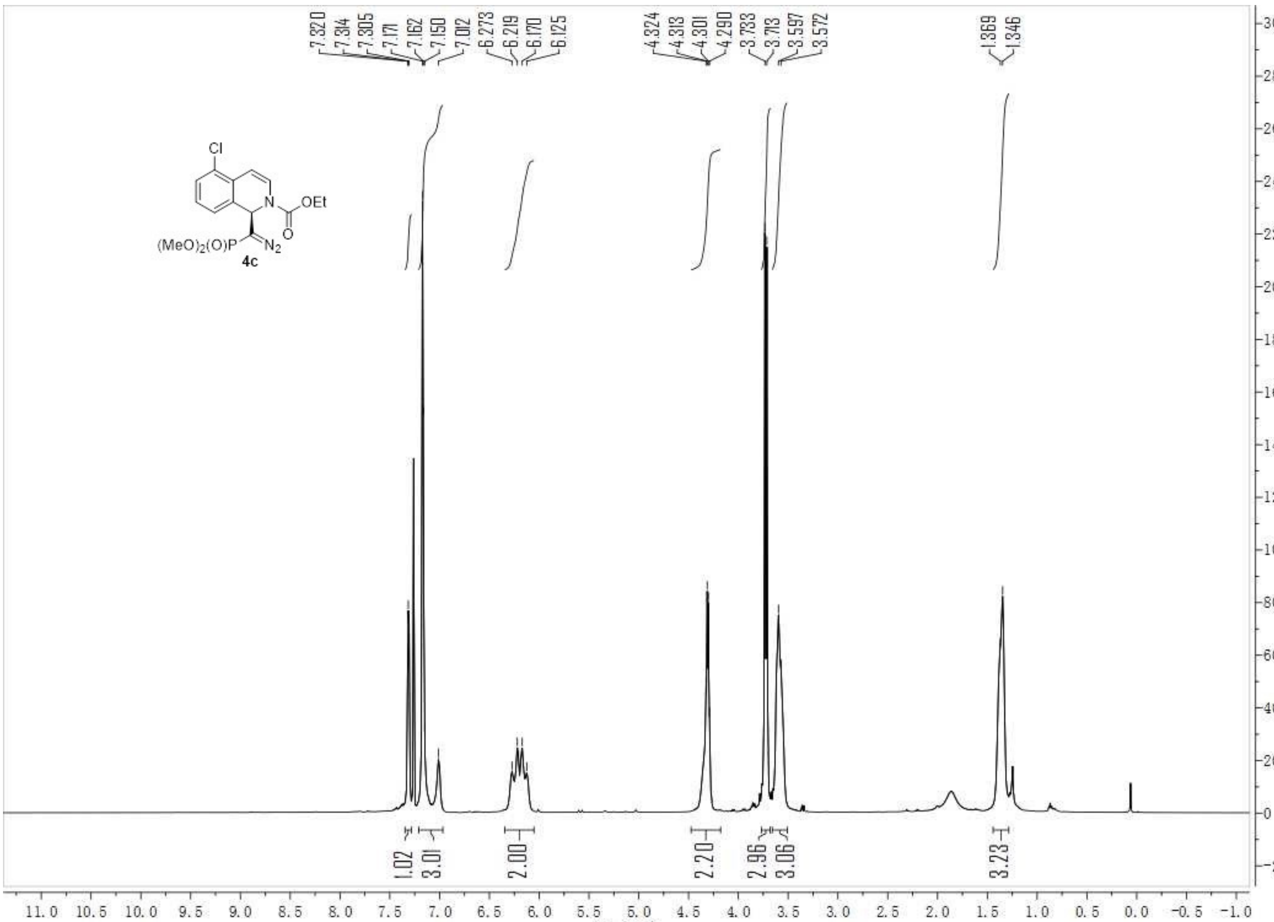
62.833 53.286 53.040 52.759 47.600 45.922
14.440
Ph
N
OEt
O
(MeO)2(O)P
N2
4b
f1 (ppm)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3.713
3.597
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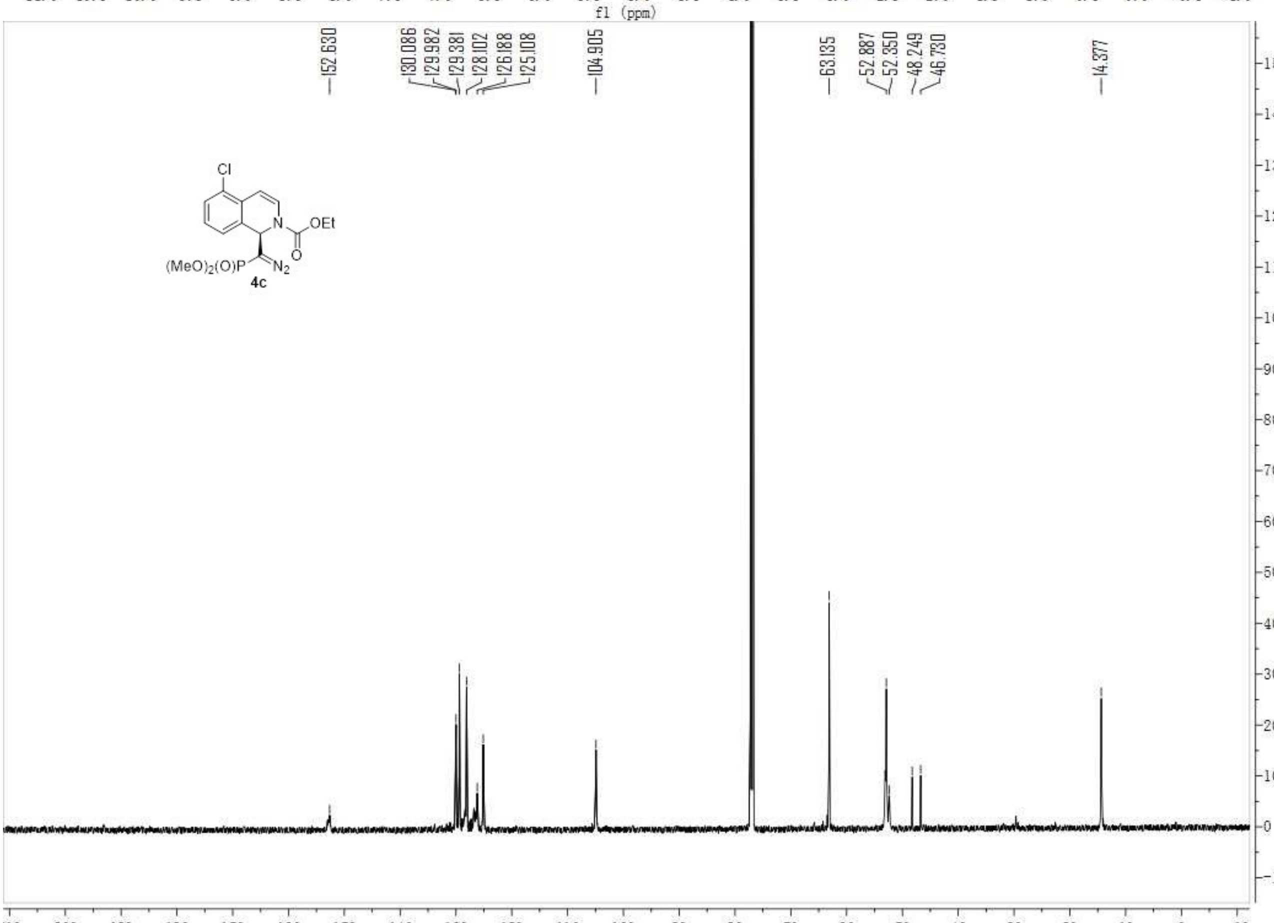
1.346
Cl
N
OEt
O
(MeO)2(O)P
N2
4c
1.02
3.01
2.00
2.20
2.96
3.06
3.23
f1 (ppm)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129.982
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128.102
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125.108
104.905
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52.887
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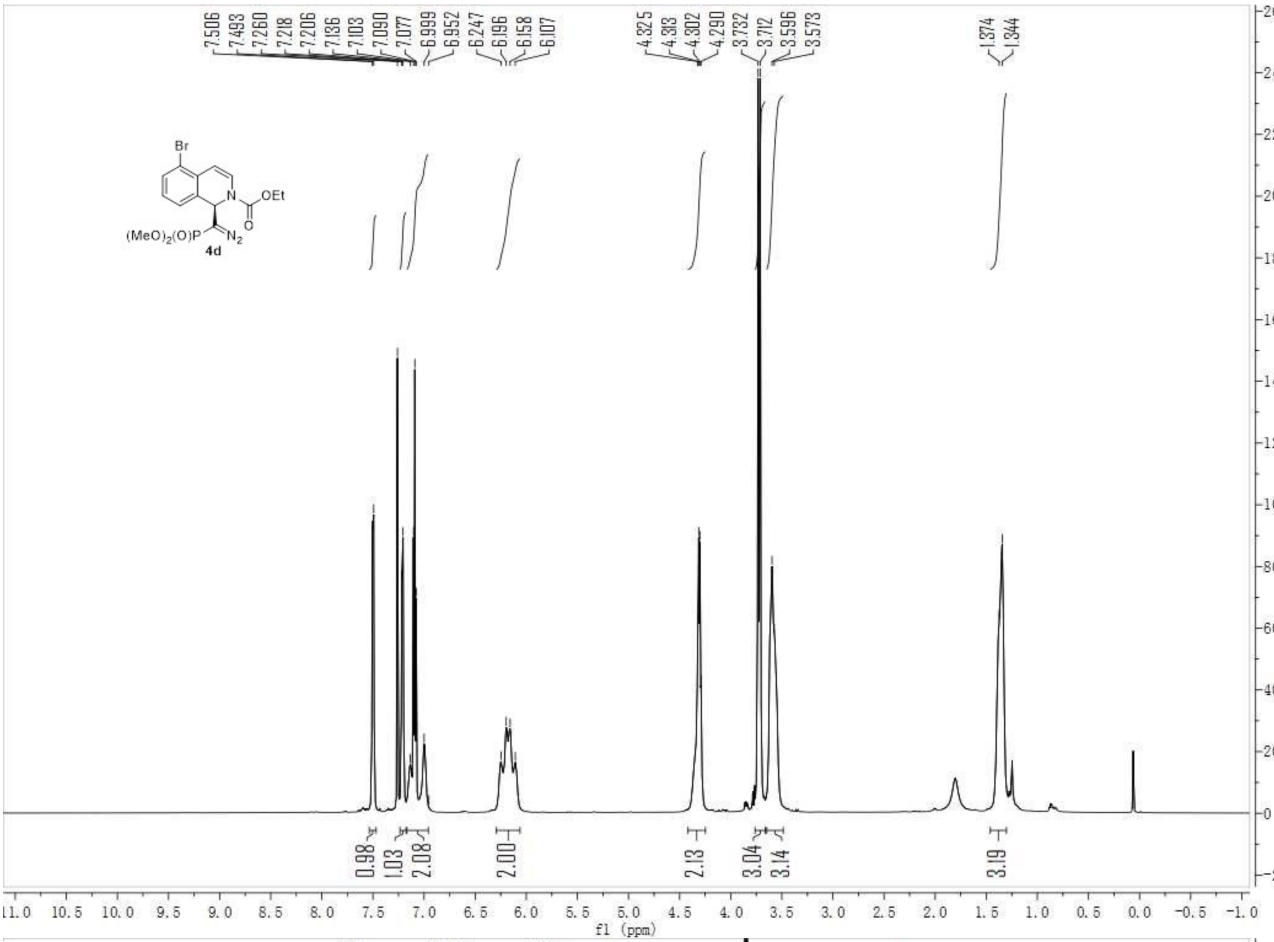
46.730
14.377
Cl
N
OEt
O
(MeO)2(O)P
N2
4c
f1 (ppm)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7.260
7.218
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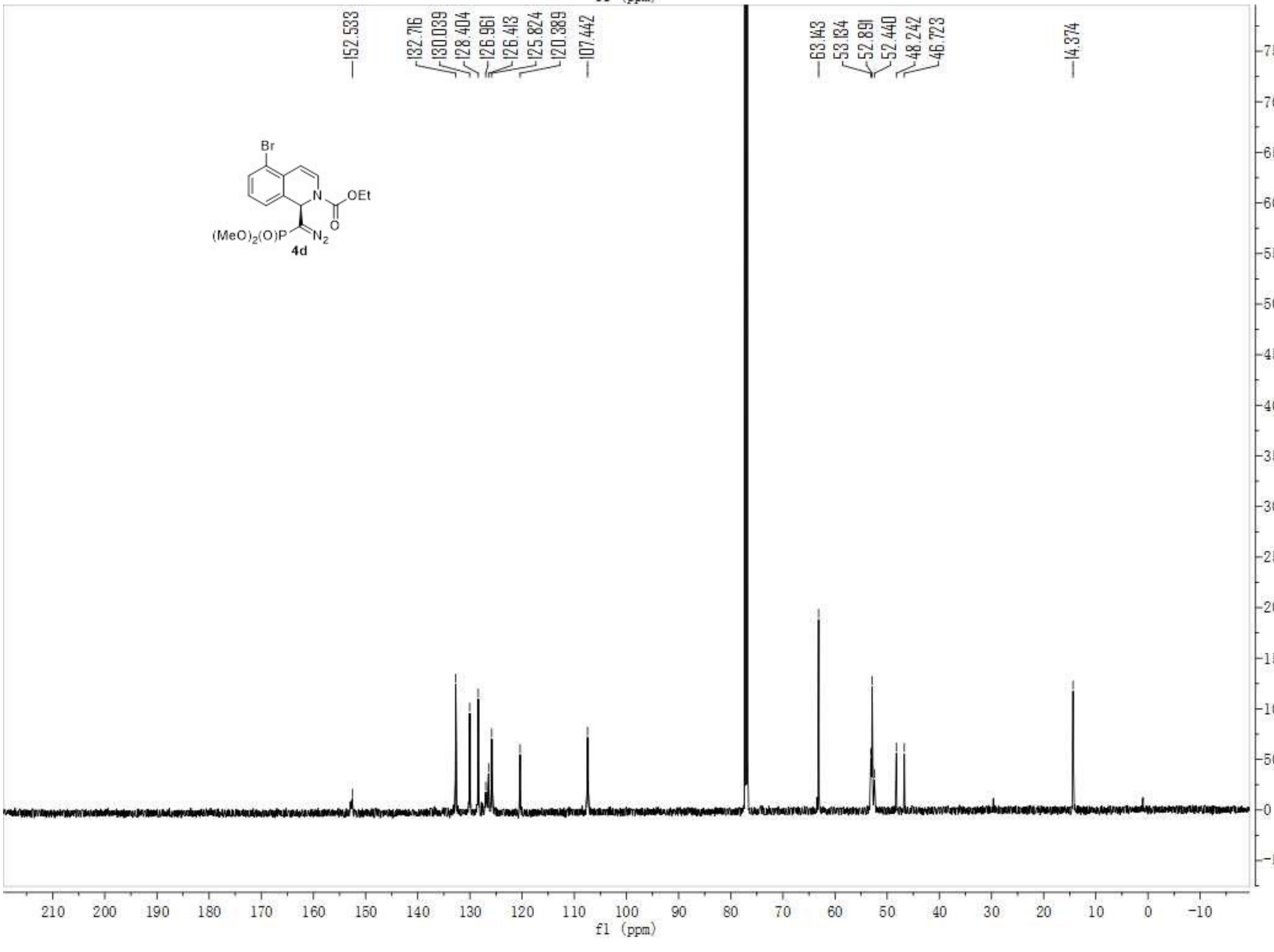
7.136
7.103
7.090
7.077
6.999
6.952
6.247
6.196
6.158
6.107
4.325
4.313
4.302
4.290
3.732
3.712
3.596
3.573
1.374
1.344
Br
N
OEt
O
(MeO)2(O)P
N2
4d
0.98
1.03
2.08
2.00
2.13
3.04
3.14
3.19
f1 (ppm)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53.134
52.891
52.440
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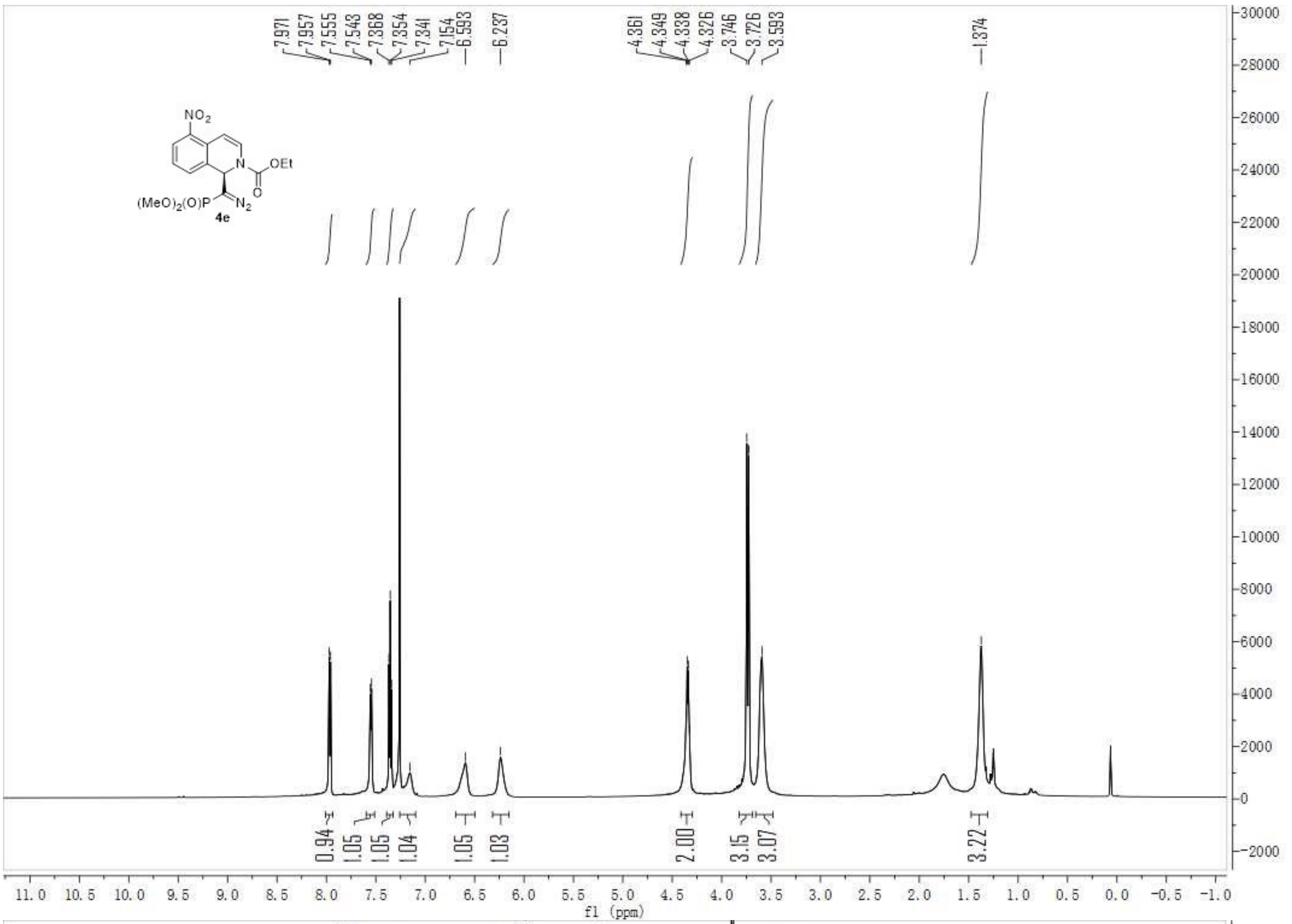
46.723
14.374
Br
N
OEt
O
(MeO)2(O)P
N2
4d
f1 (ppm)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7.154
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6.237
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4.338
4.326
3.746
3.726
3.593
1.374
NO2
N
OEt
O
(MeO)2(O)P
N2
4e
0.94
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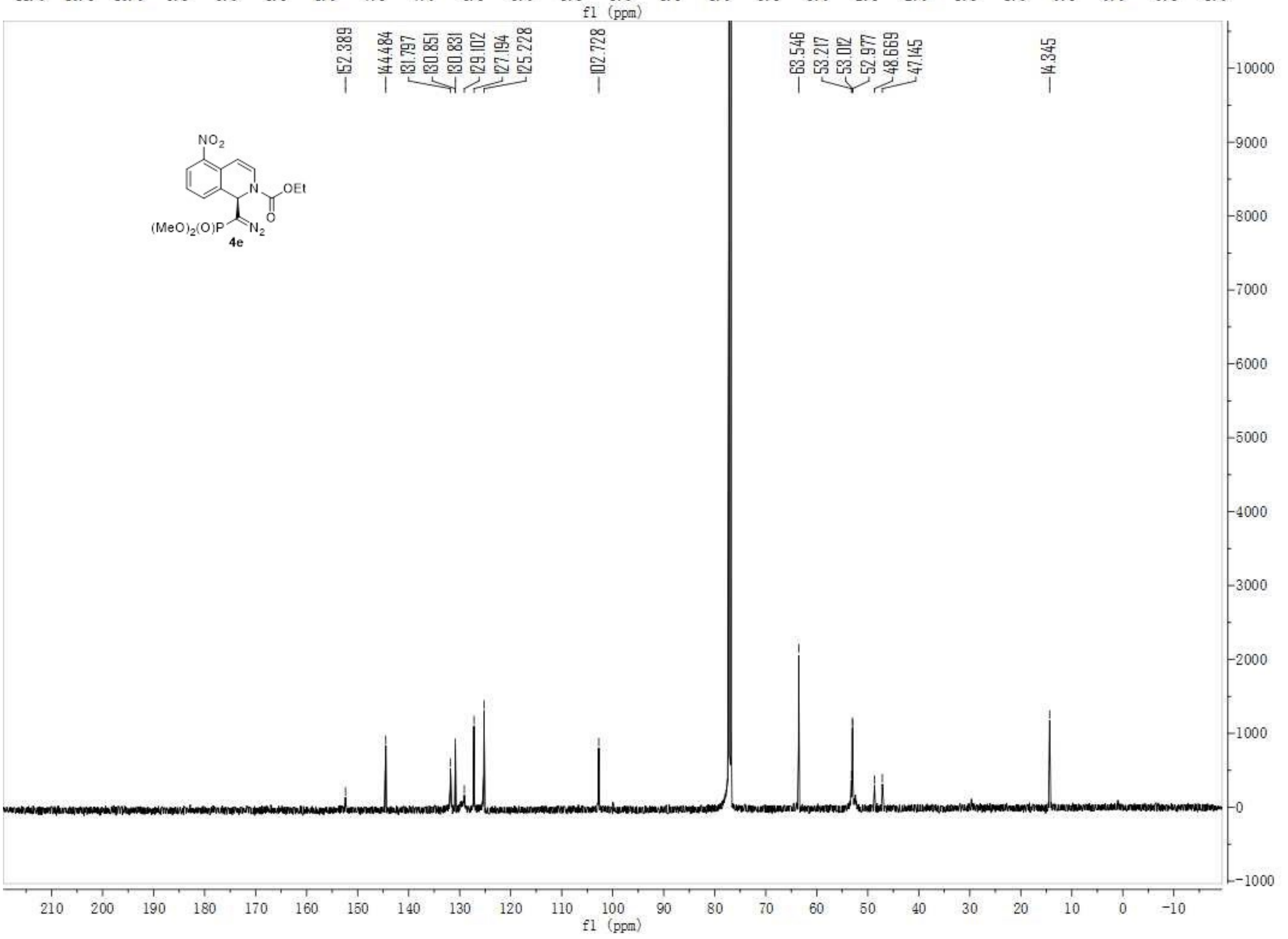
1.05
1.04
1.05
1.03
2.00
3.15
3.07
3.22
f1 (ppm)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127.194
125.228
102.728
63.546
53.217
53.012
52.977
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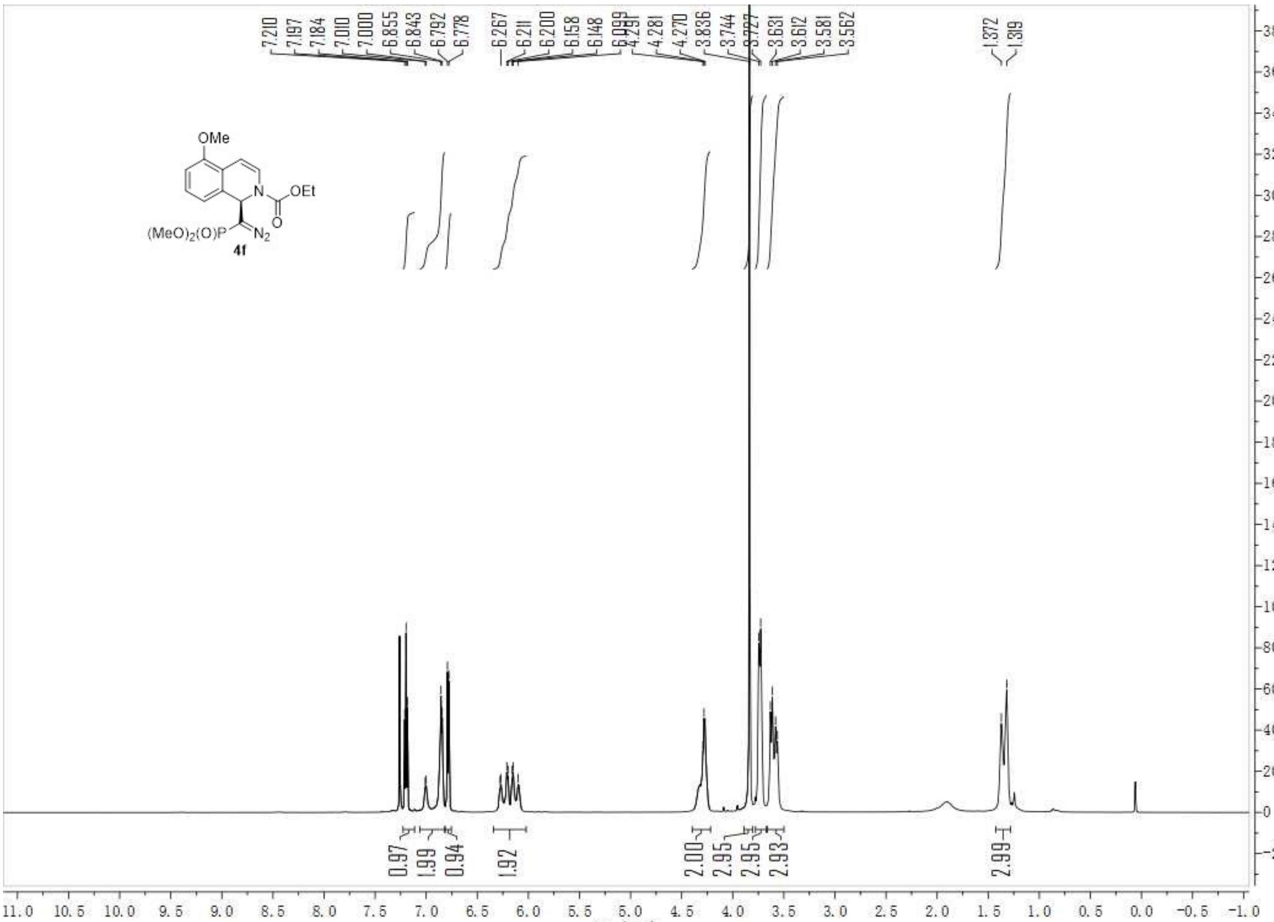
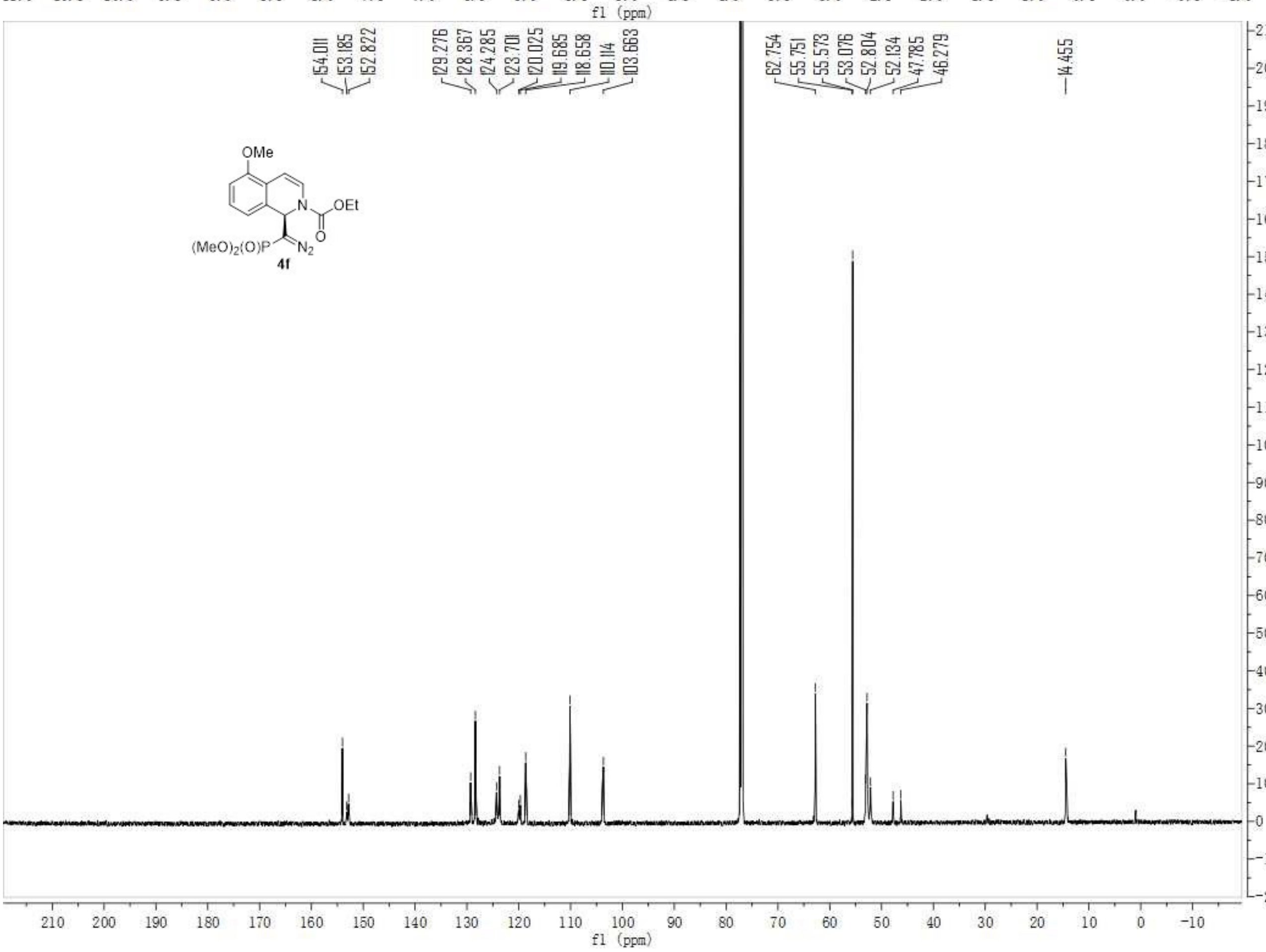
47.145
14.345
NO2
N
OEt
O
(MeO)2(O)P
N2
4e
f1 (ppm)



7.210
7.197
7.184
7.010
7.000
6.855
6.843
6.792
6.778
6.267
6.211
6.200
6.158
6.148
4.291
4.281
4.270
3.836
3.744
3.727
3.631
3.612
3.581
3.562
1.372
1.319
OMe
N
OEt
O
(MeO)2(O)P
N2
4f
0.97
1.99
0.94
1.92
2.00
2.95
2.95
2.93
2.99
f1 (ppm)



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153.185
152.822
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119.685
118.658
110.114
103.663
62.754
55.751
55.573
53.076
52.804
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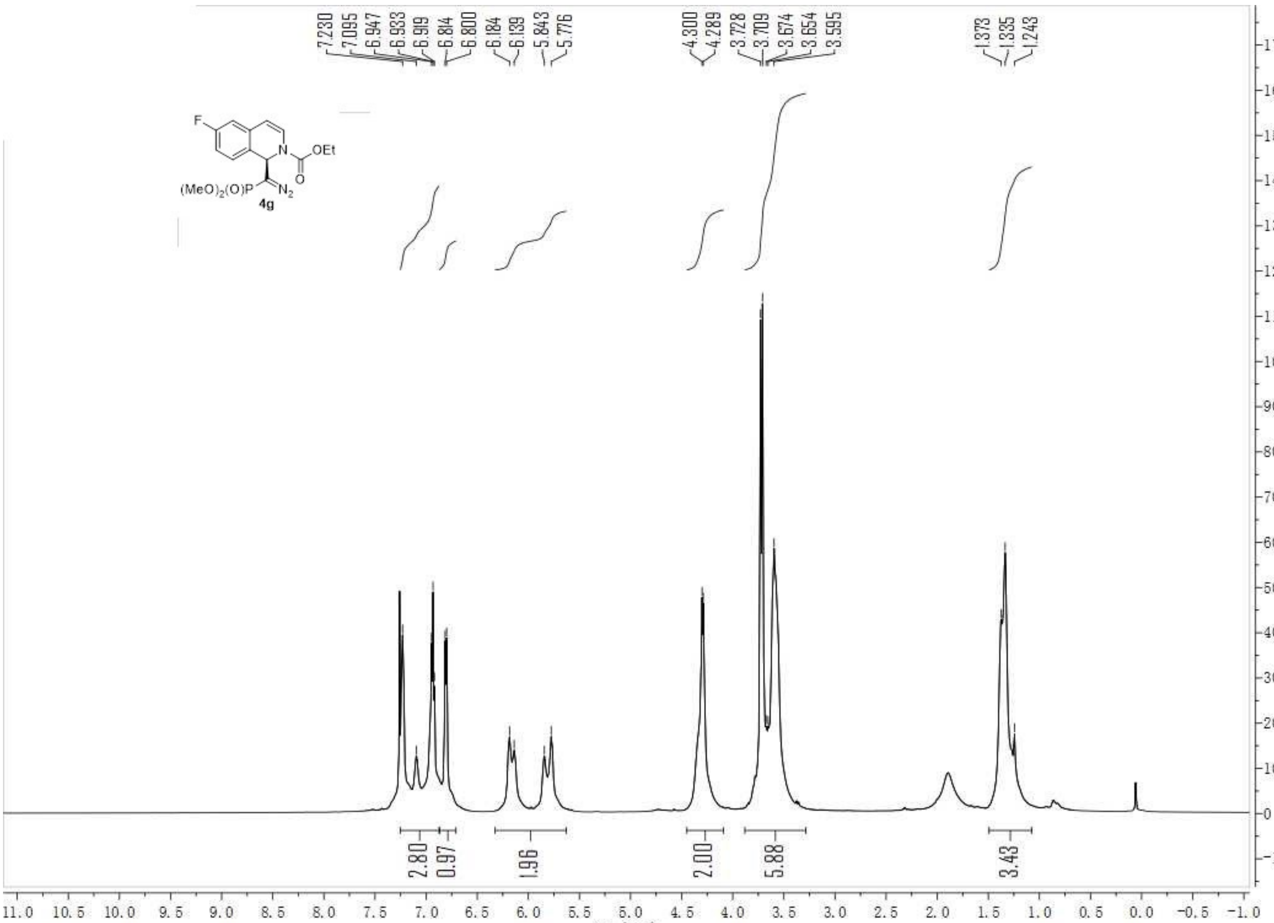
46.279
14.455
OMe
N
OEt
O
(MeO)2(O)P
N2
4f
f1 (ppm)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7.095
6.947
6.933
6.919
6.814
6.800
6.184
6.139
5.843
5.776
4.300
4.289
3.728
3.709
3.674
3.654
3.595
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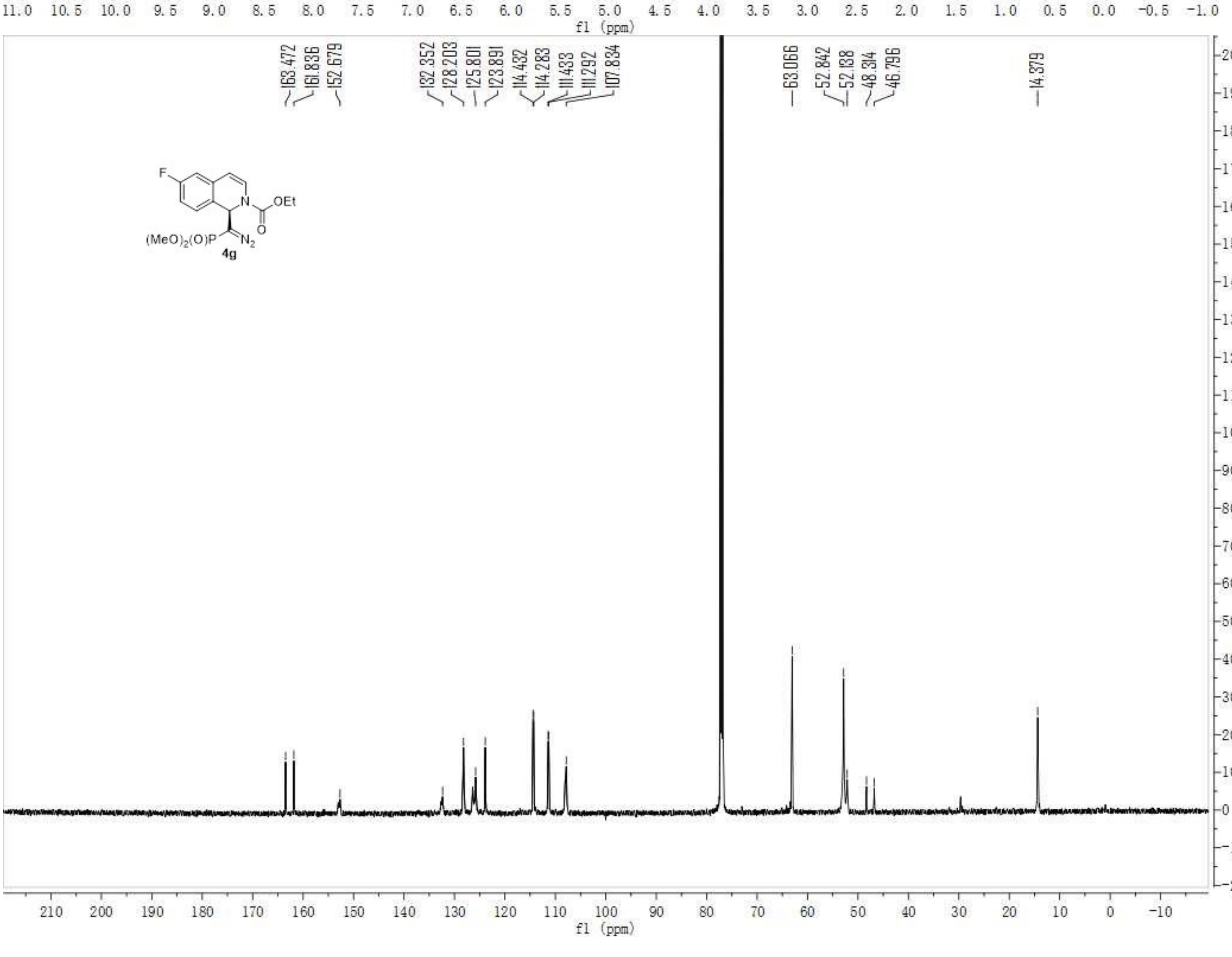
1.335
1.243
4g
2.80
0.97
1.96
2.00
5.88
3.43
f1 (ppm)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123.891
114.432
114.283
111.433
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107.834
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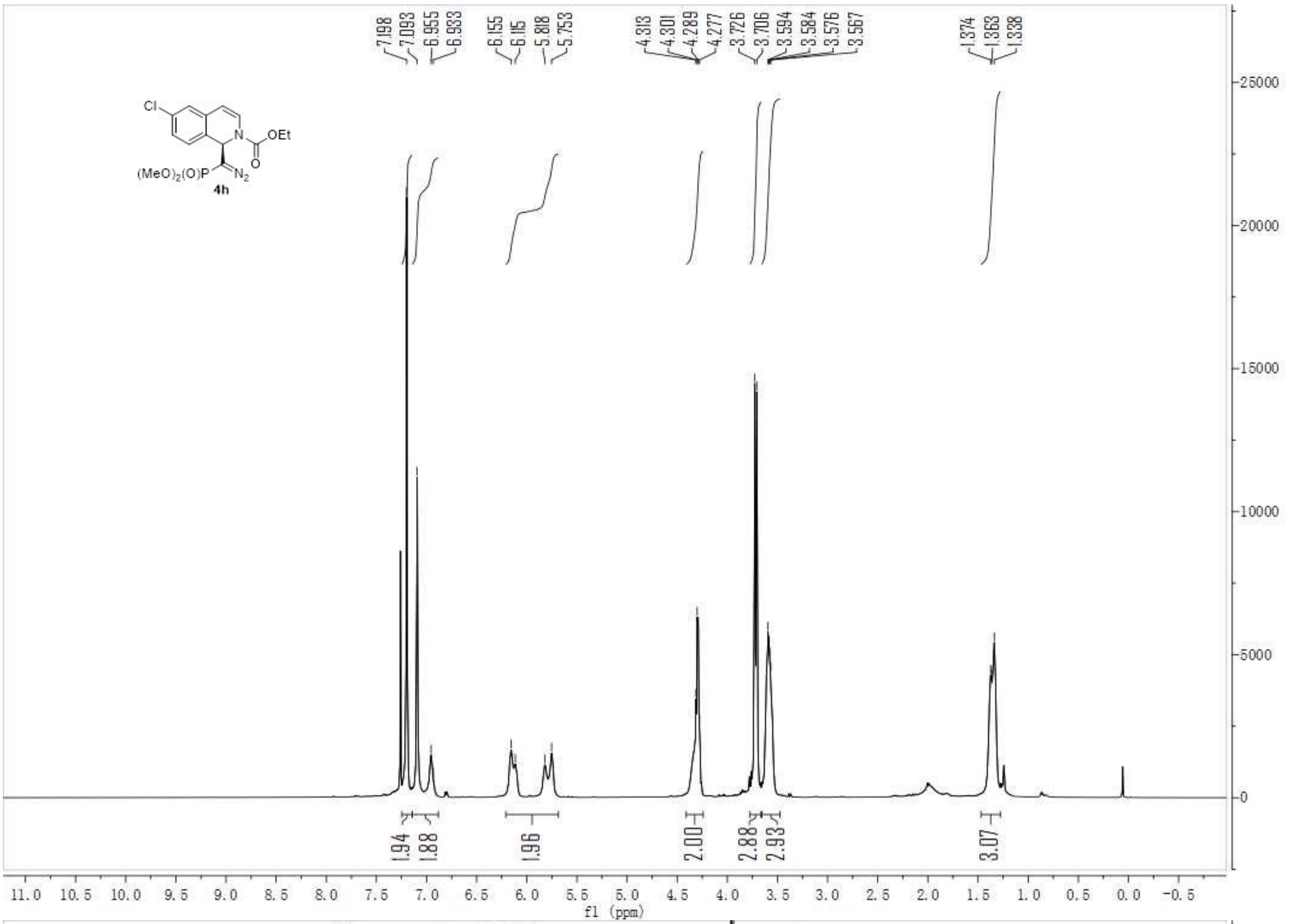
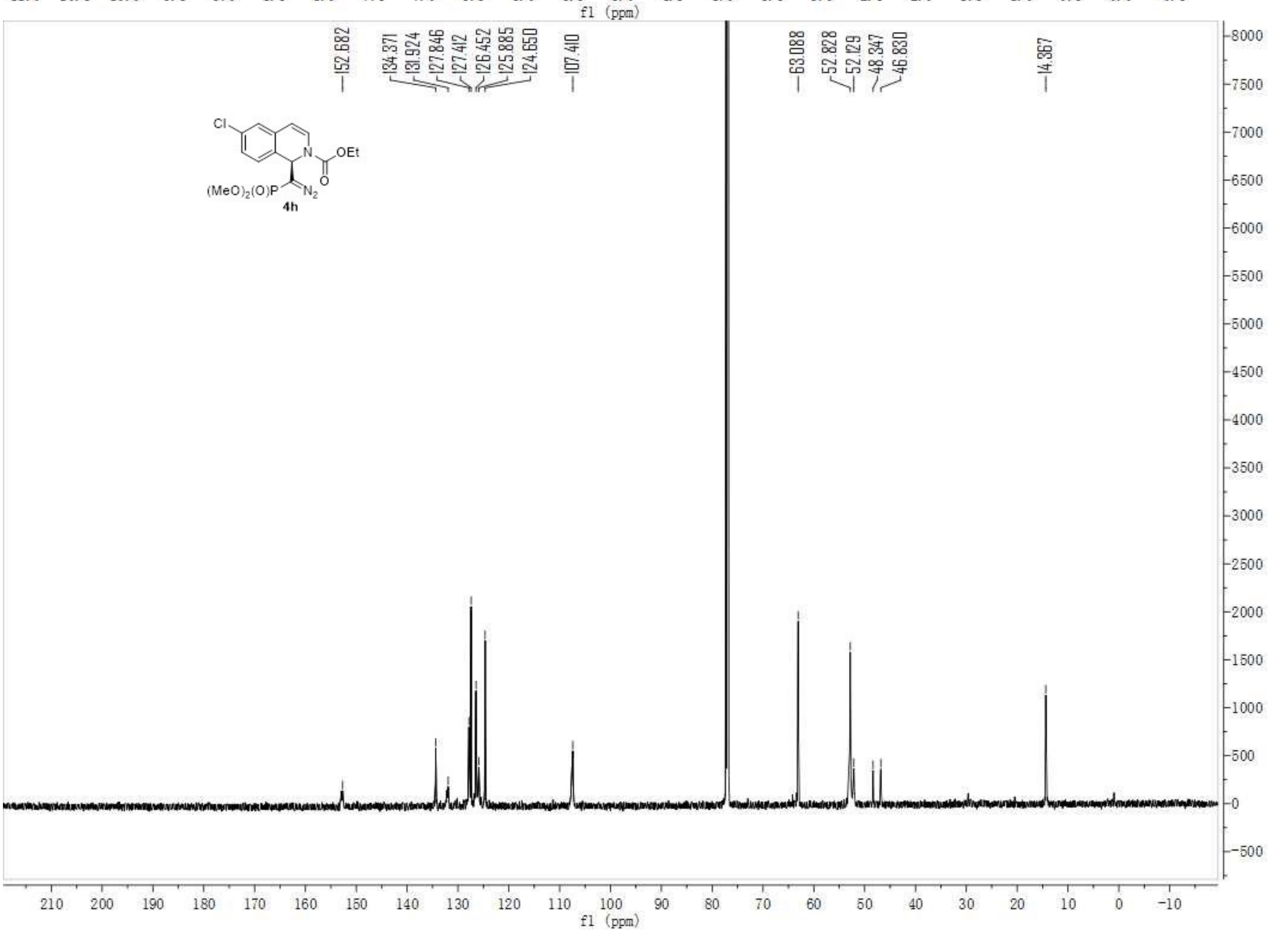
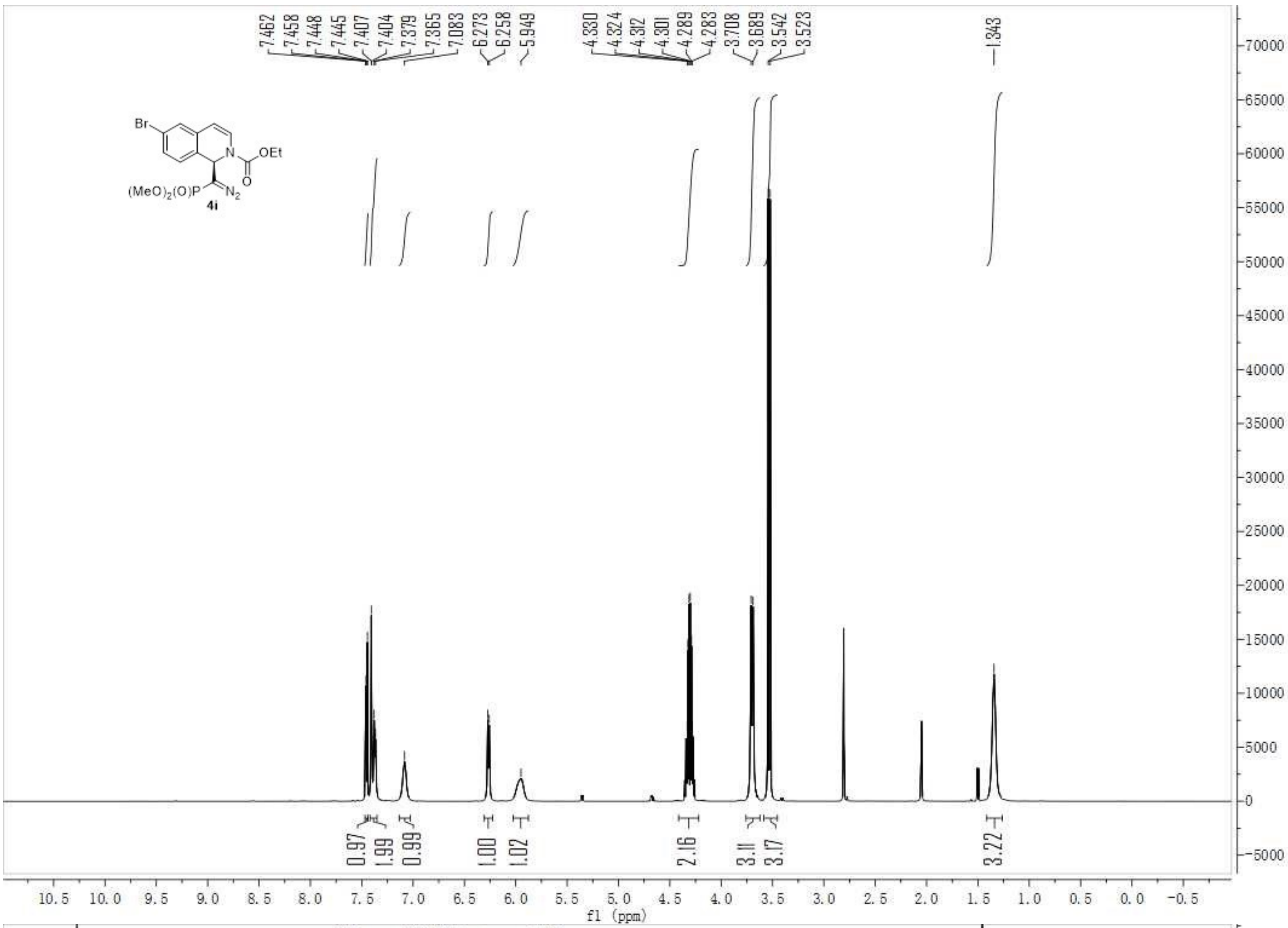
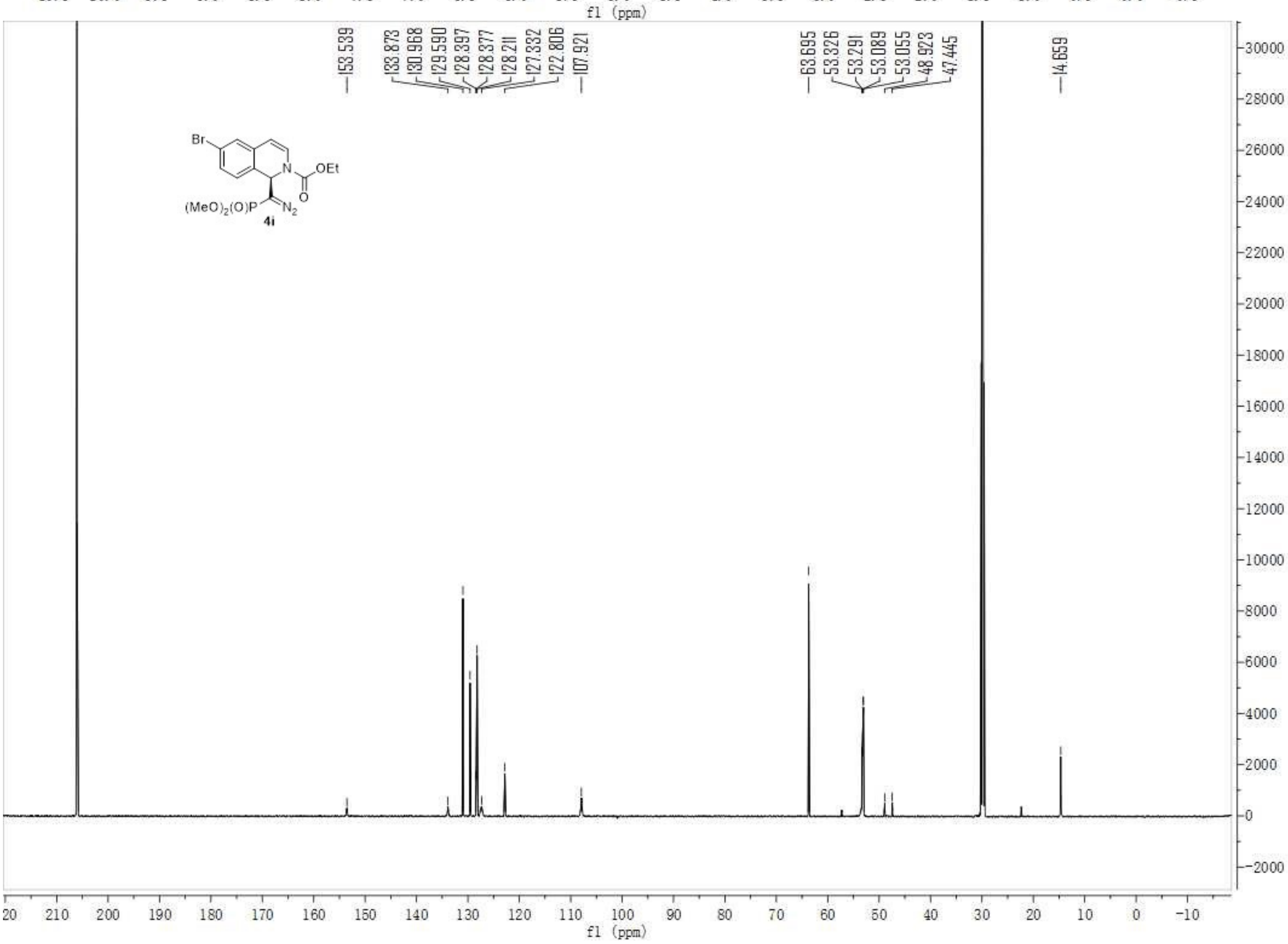
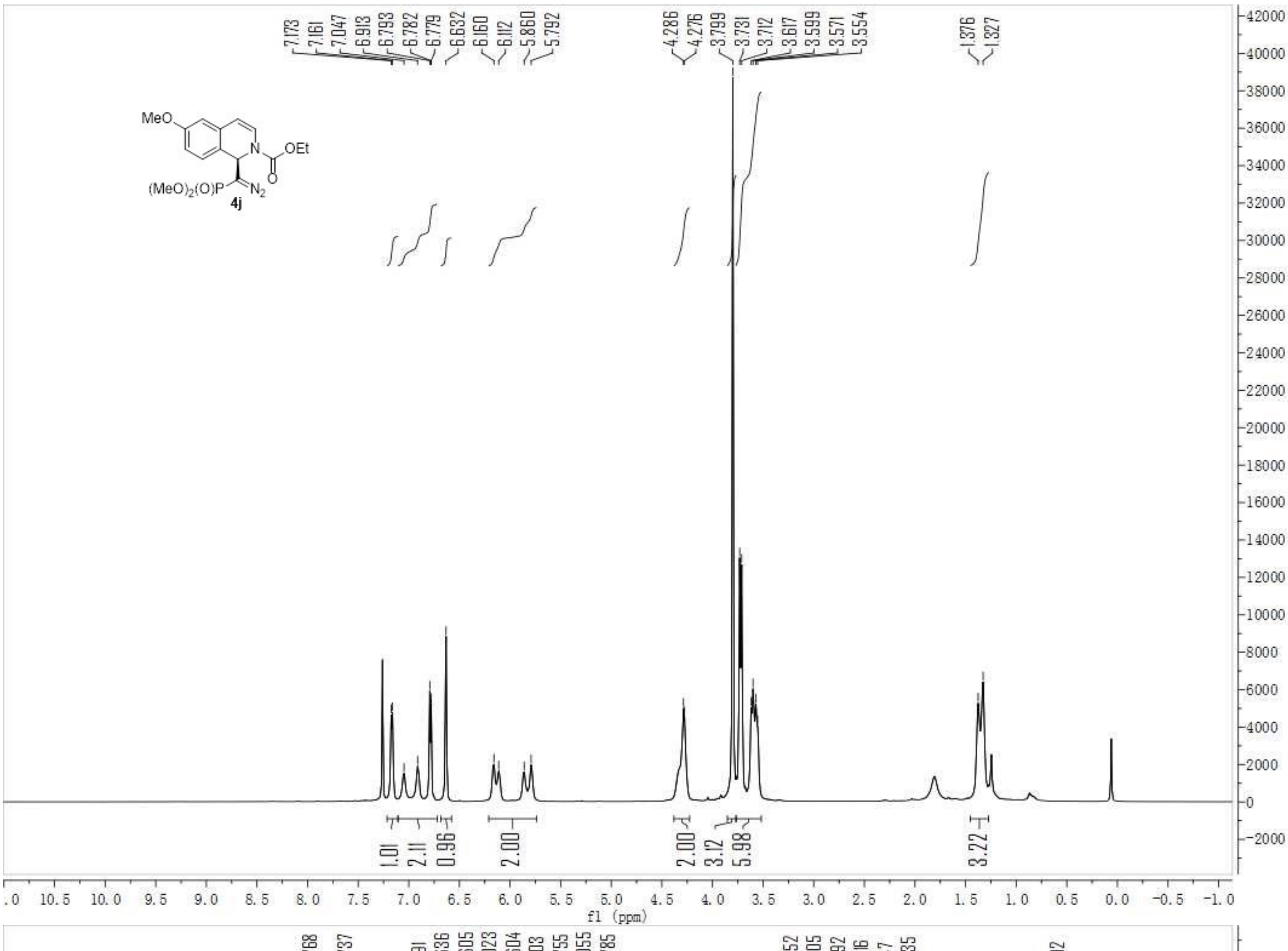
52.842
52.138
48.314
46.796
14.379
4g
f1 (ppm)



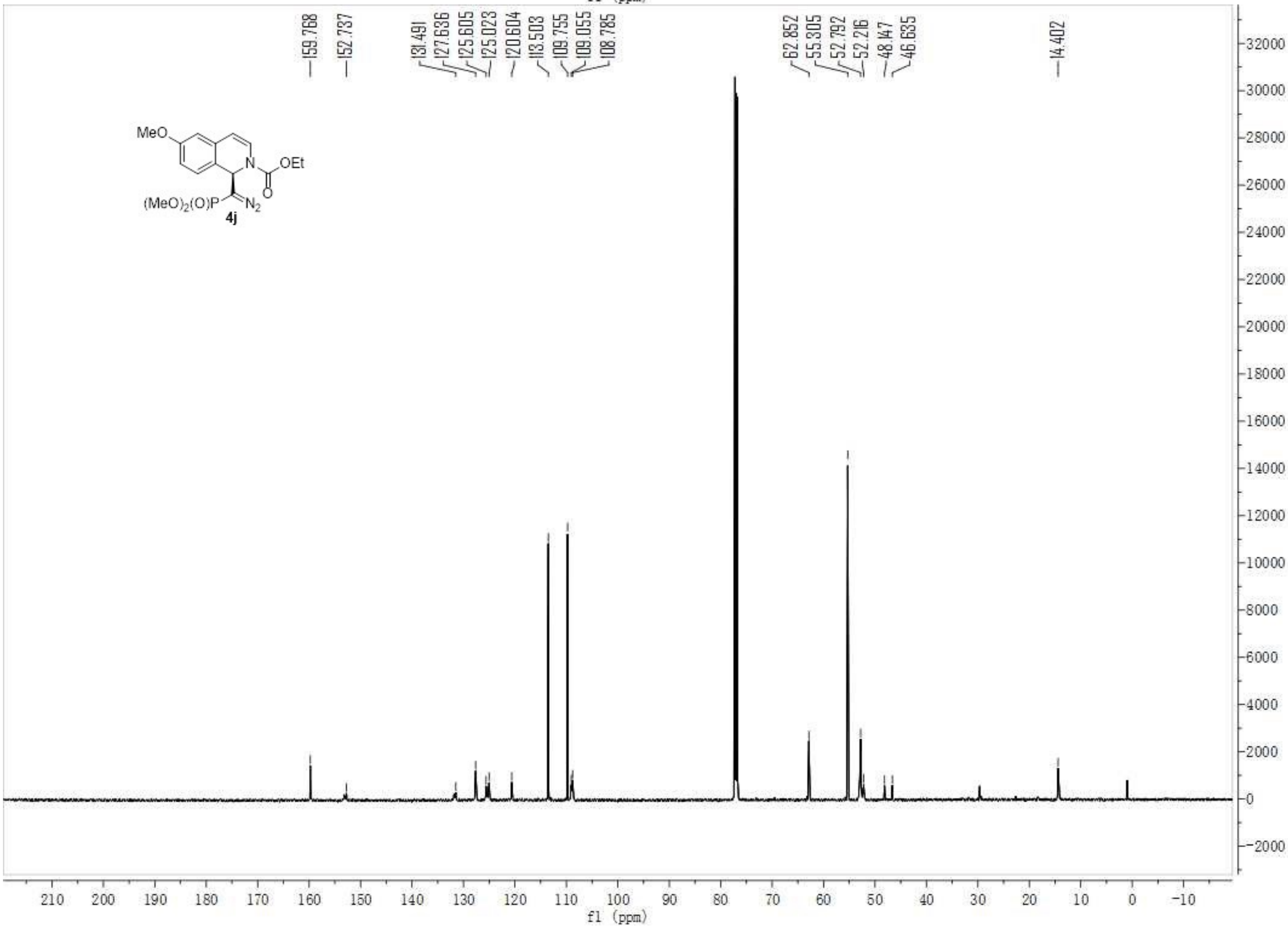








7.173
7.161
7.047
6.913
6.793
6.782
6.779
6.632
6.160
6.112
5.860
5.792
4.286
4.276
3.799
3.731
3.712
3.617
3.599
3.571
3.554
1.376
1.327
MeO
N
OEt
O
(MeO)2(O)P
N2
4j
1.01
2.11
0.96
2.00
2.00
3.12
5.98
3.22
f1 (ppm)



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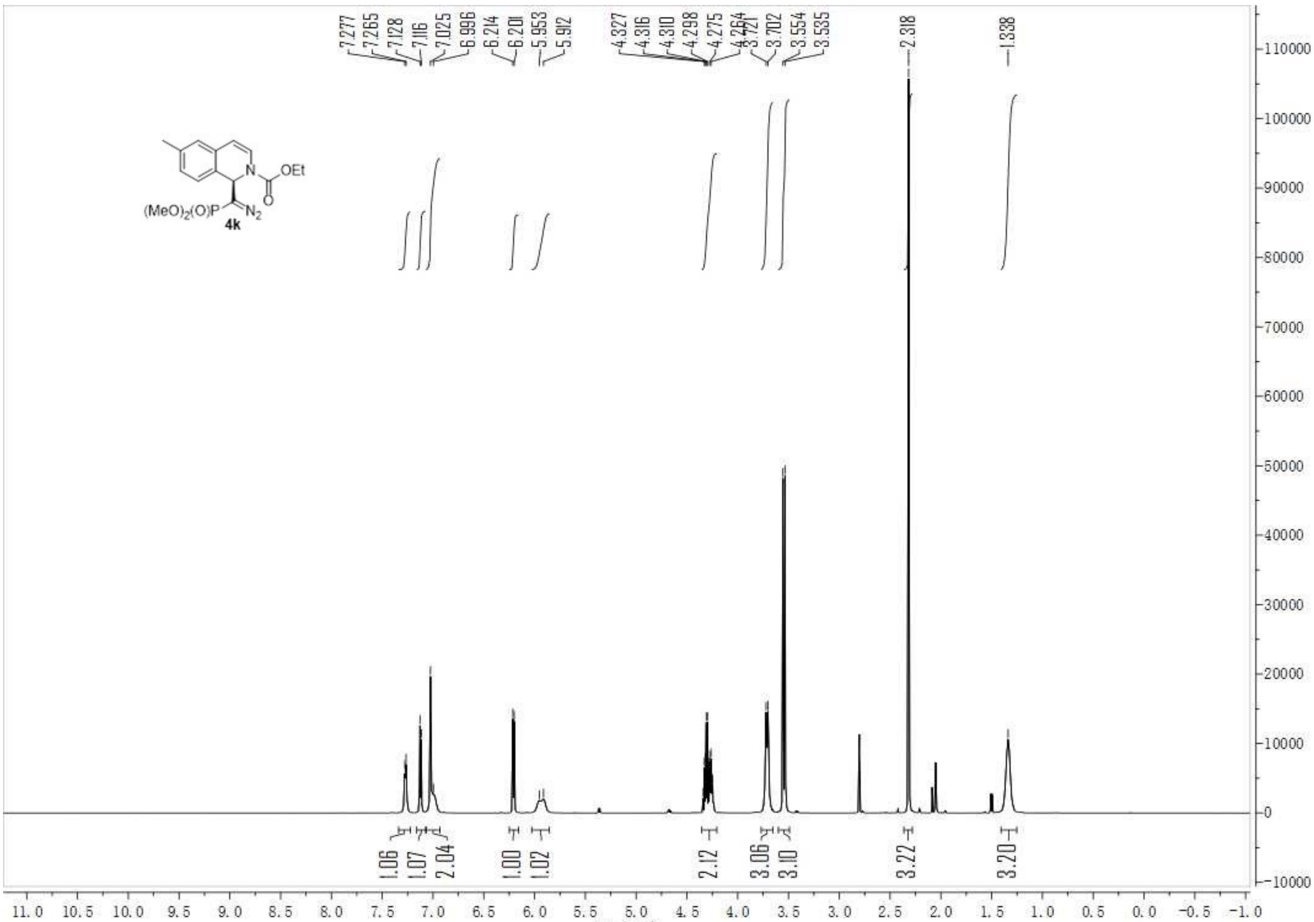
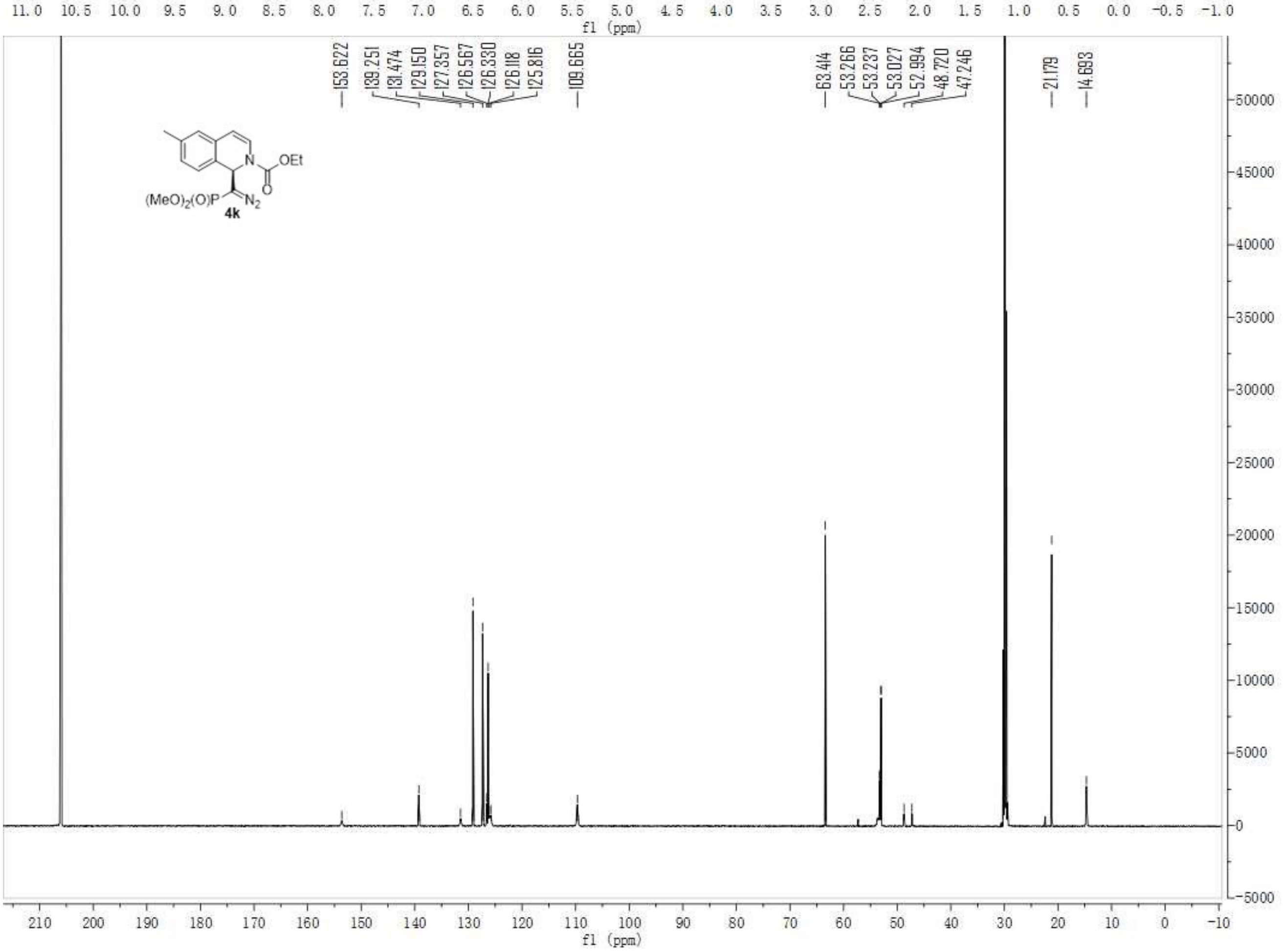
131.491
127.636
125.605
125.023
120.604
113.503
109.755
109.055
108.785
62.852
55.305
52.792
52.216
48.147
46.635
14.402
MeO
N
OEt
O
(MeO)2(O)P
N2
4j
f1 (ppm)



7.277
7.265
7.128
7.116
7.025
6.996
6.214
6.201
5.953
5.912
4.327
4.316
4.310
4.298
4.275
4.264
3.721
3.702
3.554
3.535
2.318
1.338
OEt
(MeO)2(O)P
N2
4k
1.06
1.07
2.04
1.00
1.02
2.12
3.06
3.10
3.22
3.20
f1 (ppm)



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126.567
126.330
126.118
125.816
109.665
63.414
53.266
53.237
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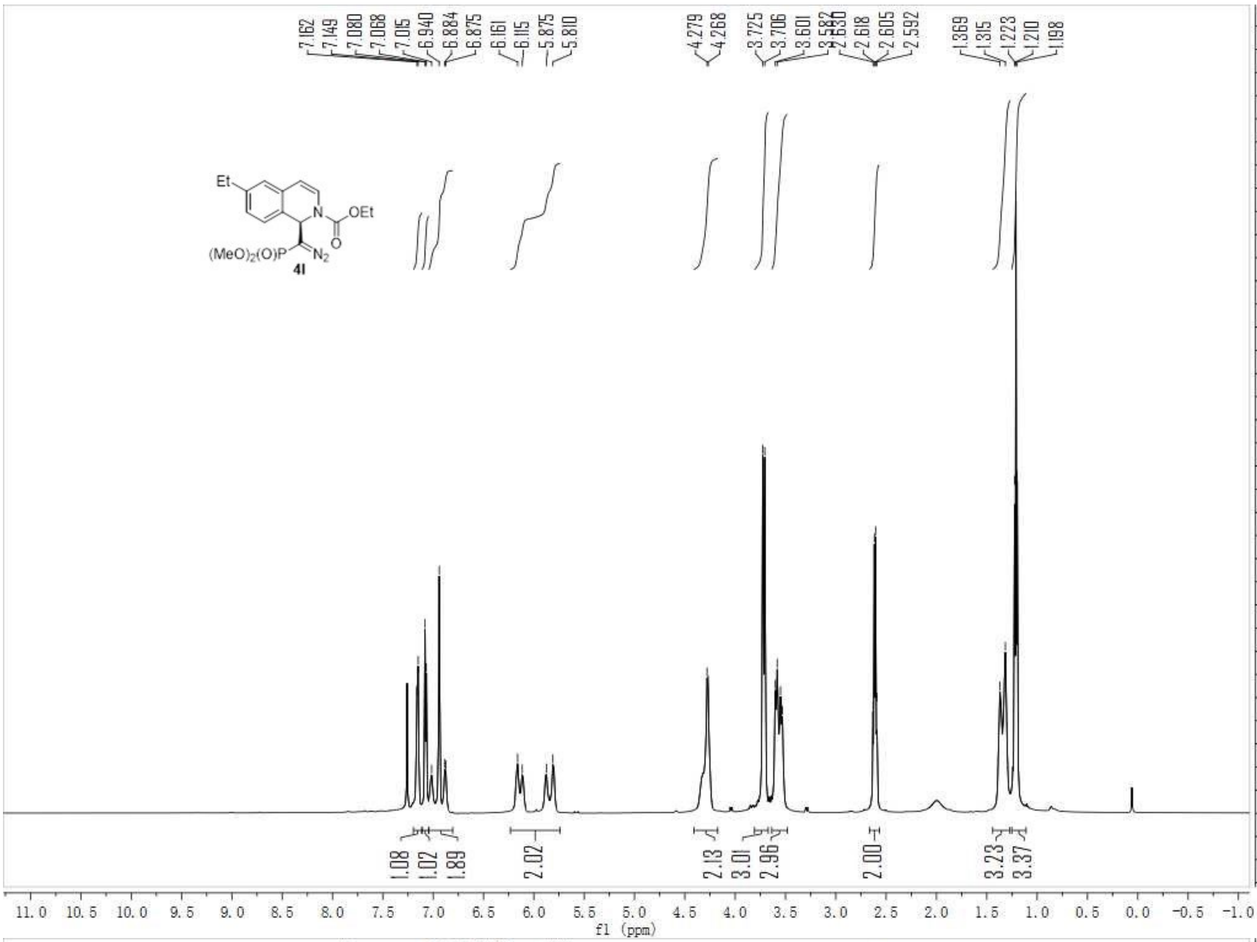
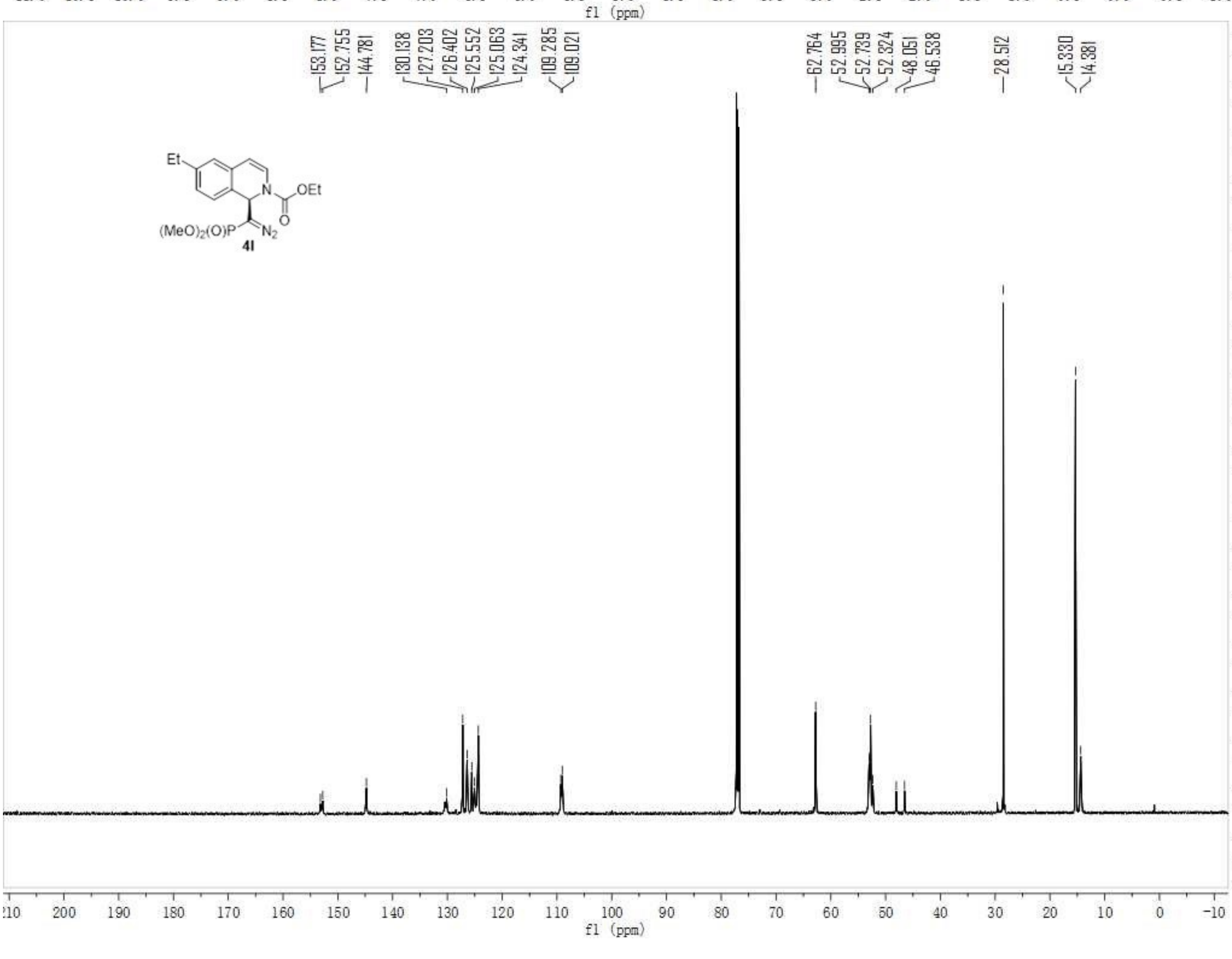
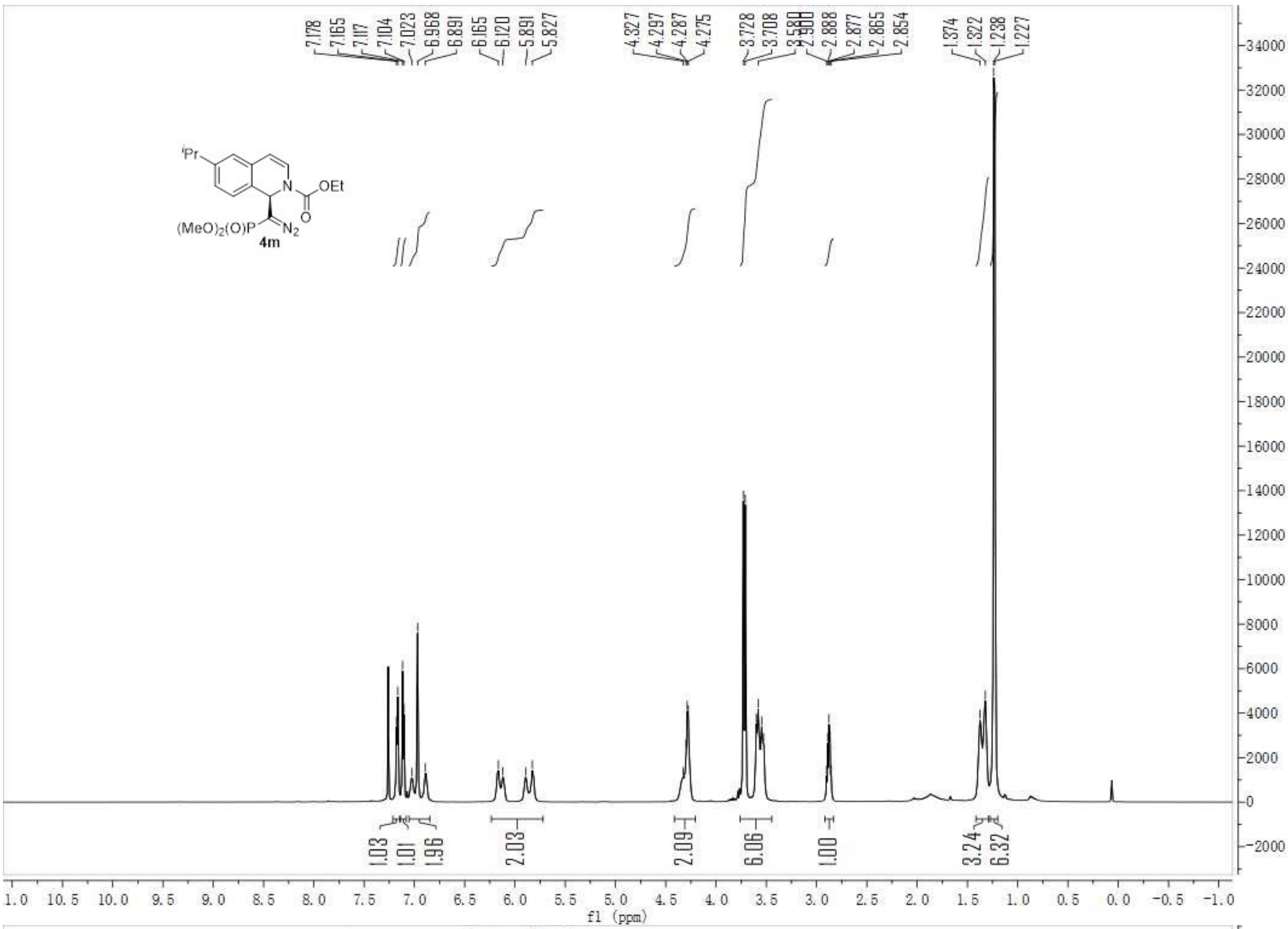
48.720
47.246
21.179
14.693
OEt
(MeO)2(O)P
N2
4k
f1 (ppm)



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7.117
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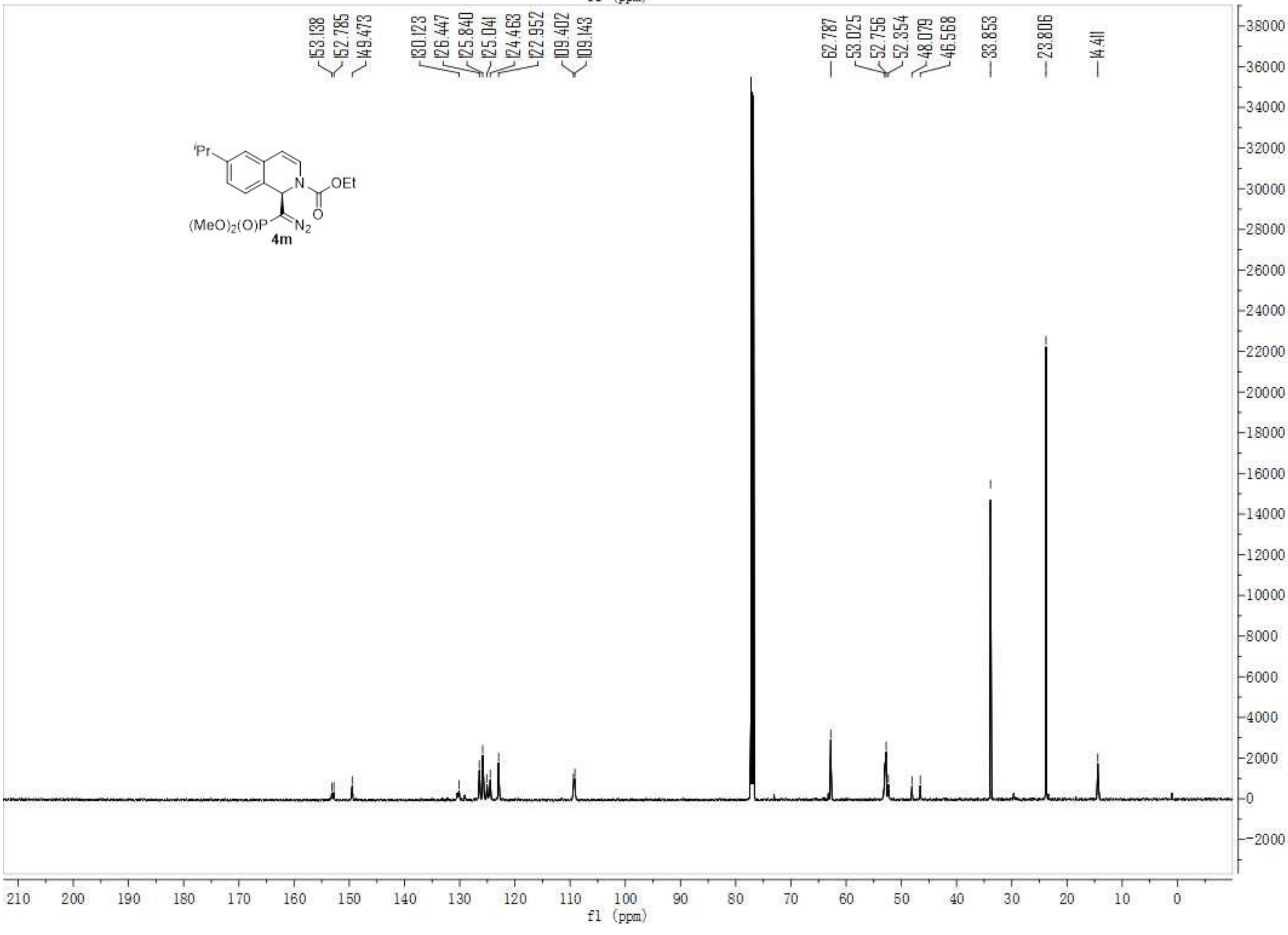
7.023
6.968
6.891
6.165
6.120
5.891
5.827
4.327
4.297
4.287
4.275
3.728
3.708
2.888
2.877
2.865
2.854
1.374
1.322
1.238
1.227
iPr
N
OEt
O
(MeO)2(O)P
N2
4m
1.03
1.01
1.96
2.03
2.09
6.06
1.00
3.24
6.32
f1 (ppm)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124.463
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109.402
109.143
62.787
53.025
52.756
52.354
48.079
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23.806
14.411
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N
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O
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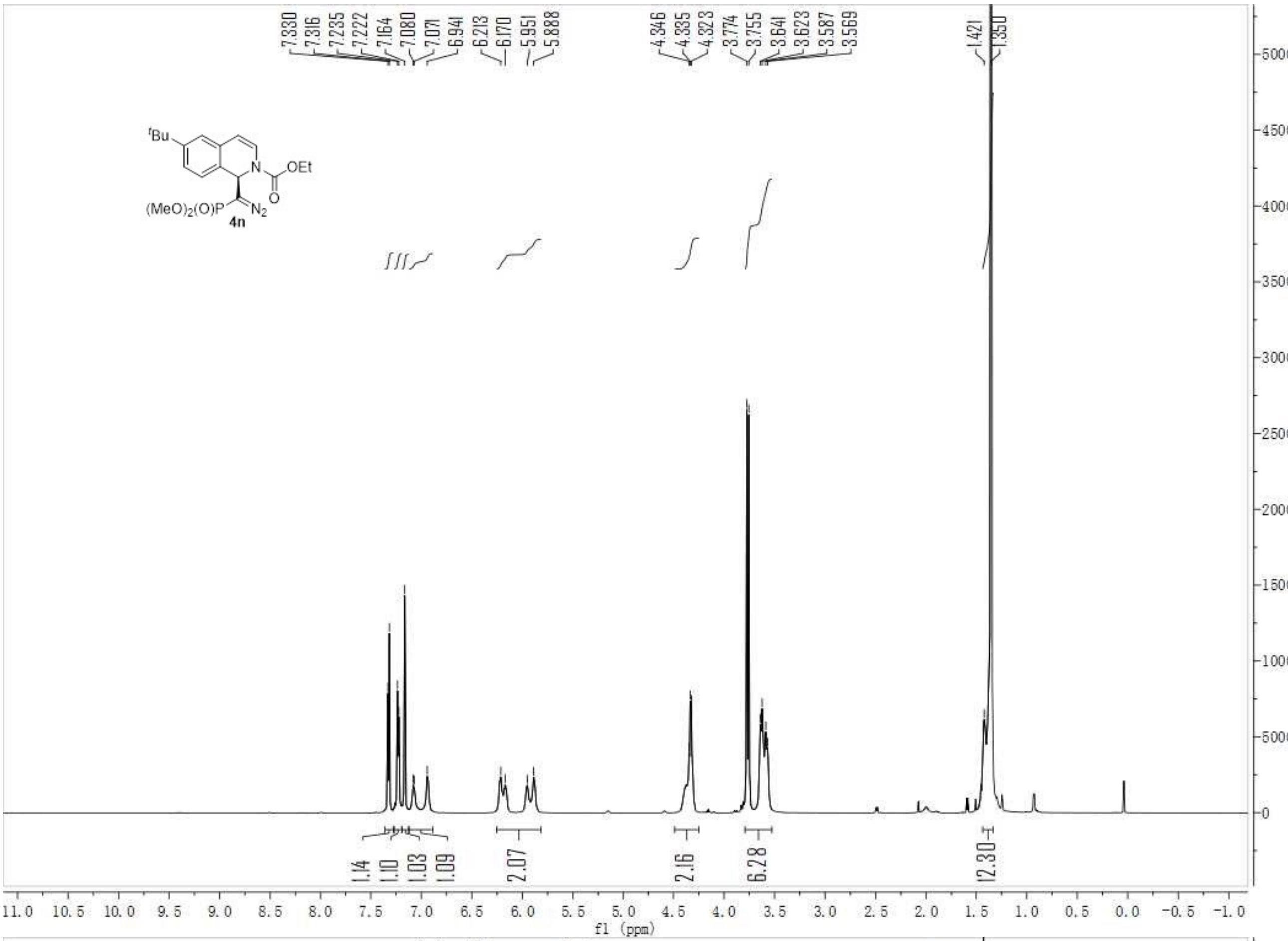
N2
4m
f1 (ppm)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7.164
7.080
7.071
6.941
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6.170
5.951
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4.346
4.335
4.323
3.774
3.755
3.641
3.623
3.587
3.569
1.421
1.350
tBu
OEt
(MeO)2(O)P
N2
4n
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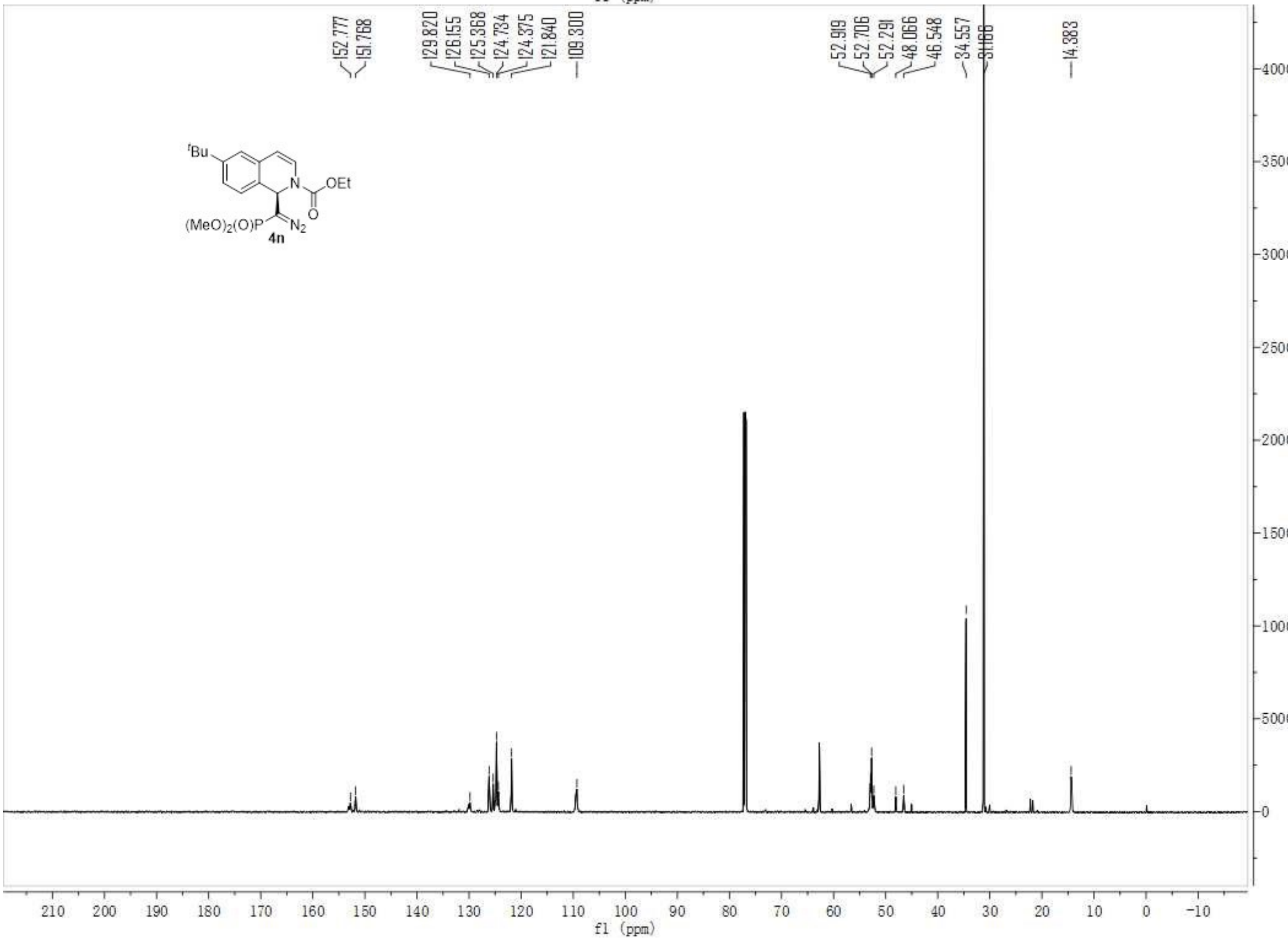
1.03
1.09
2.07
2.16
6.28
12.30
fl (ppm)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34.557
31.168
14.383
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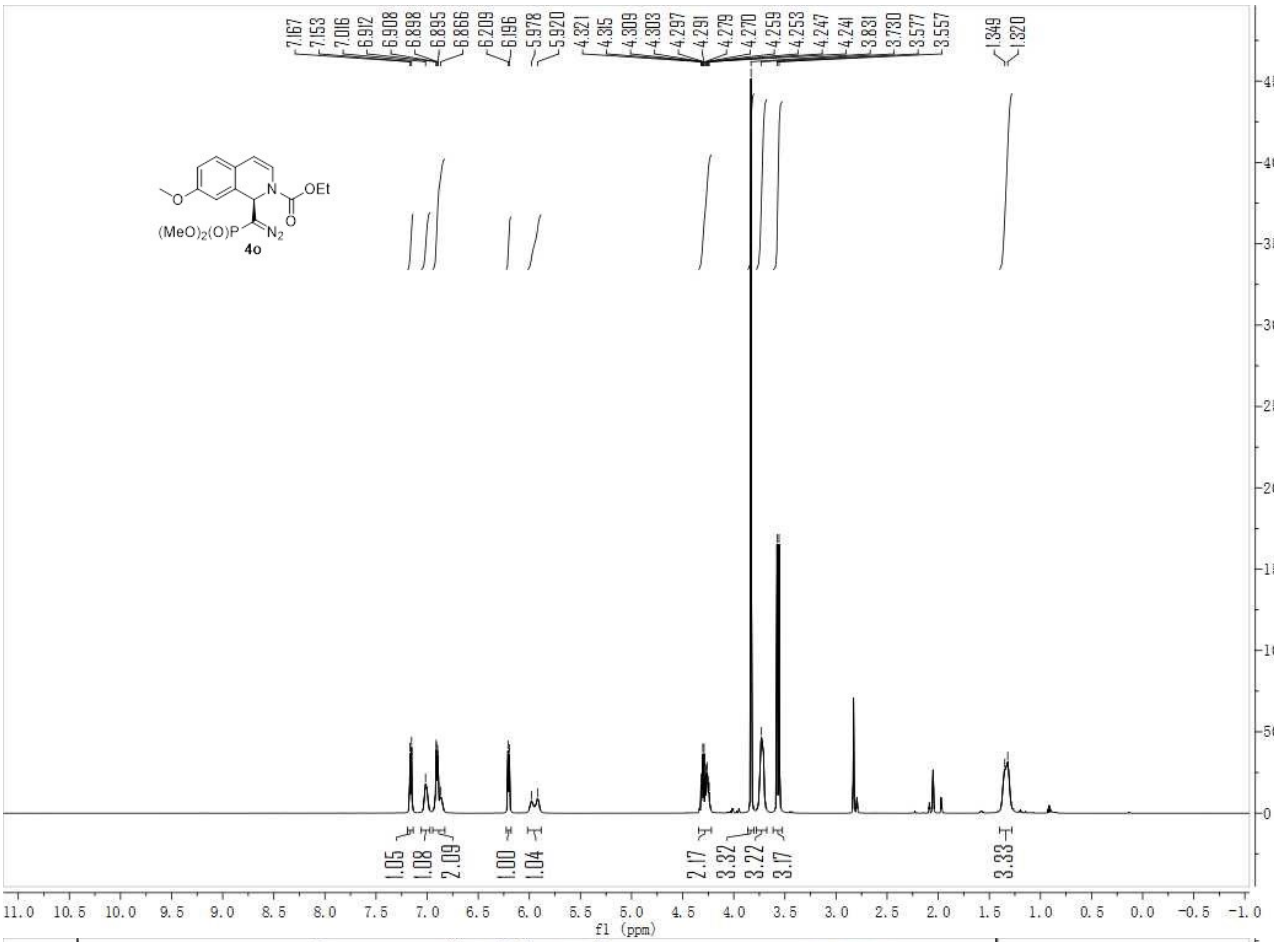
OEt
(MeO)2(O)P
N2
4n
fl (ppm)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4.315
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4.303
4.297
4.291
4.279
4.270
4.259
4.253
4.247
4.241
3.831
3.730
3.577
3.557
1.349
1.320
OEt
(MeO)2(O)P
N2
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1.04
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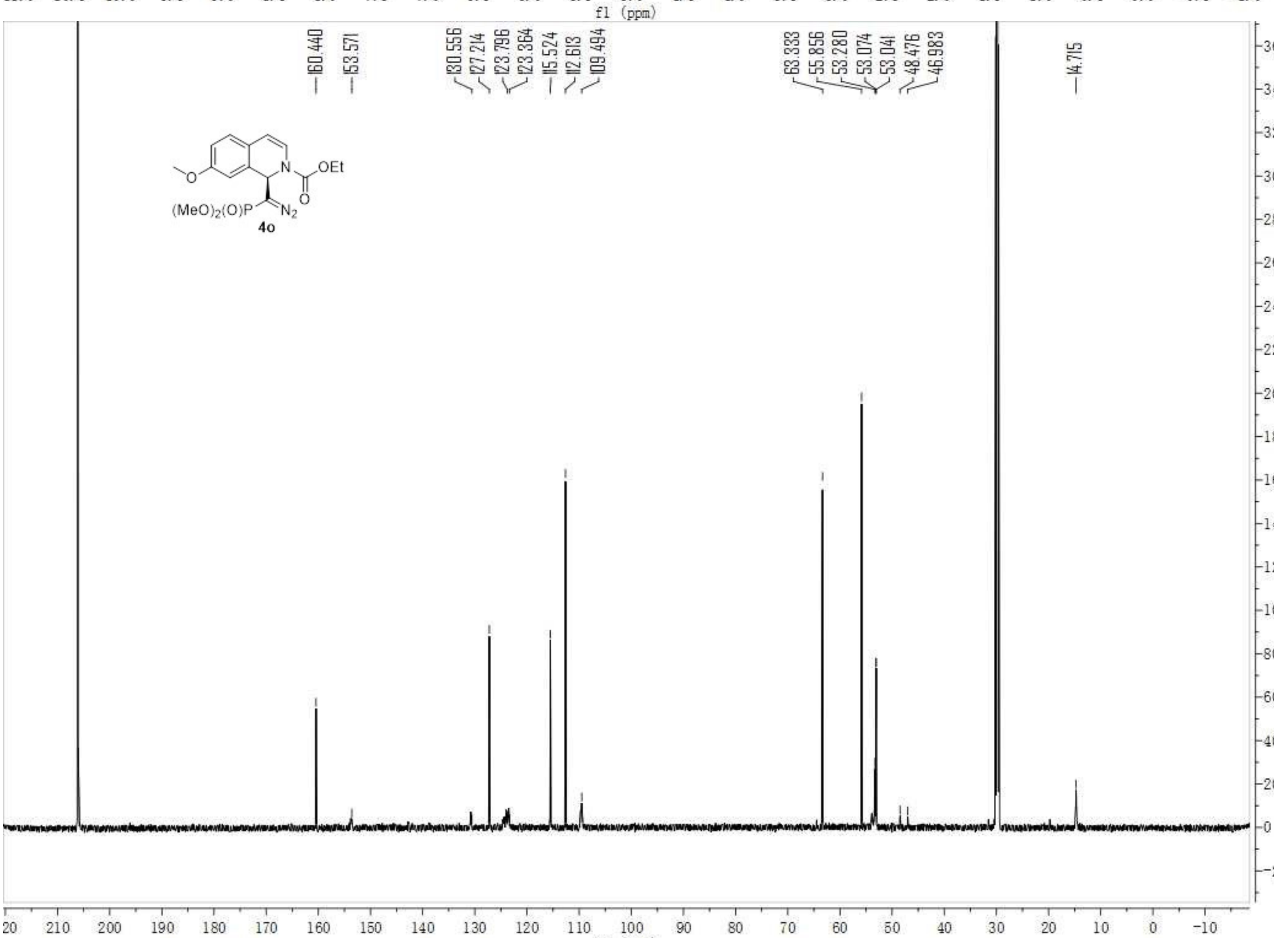
3.22
3.17
3.33
f1 (ppm)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112.613
109.494
63.333
55.856
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48.476
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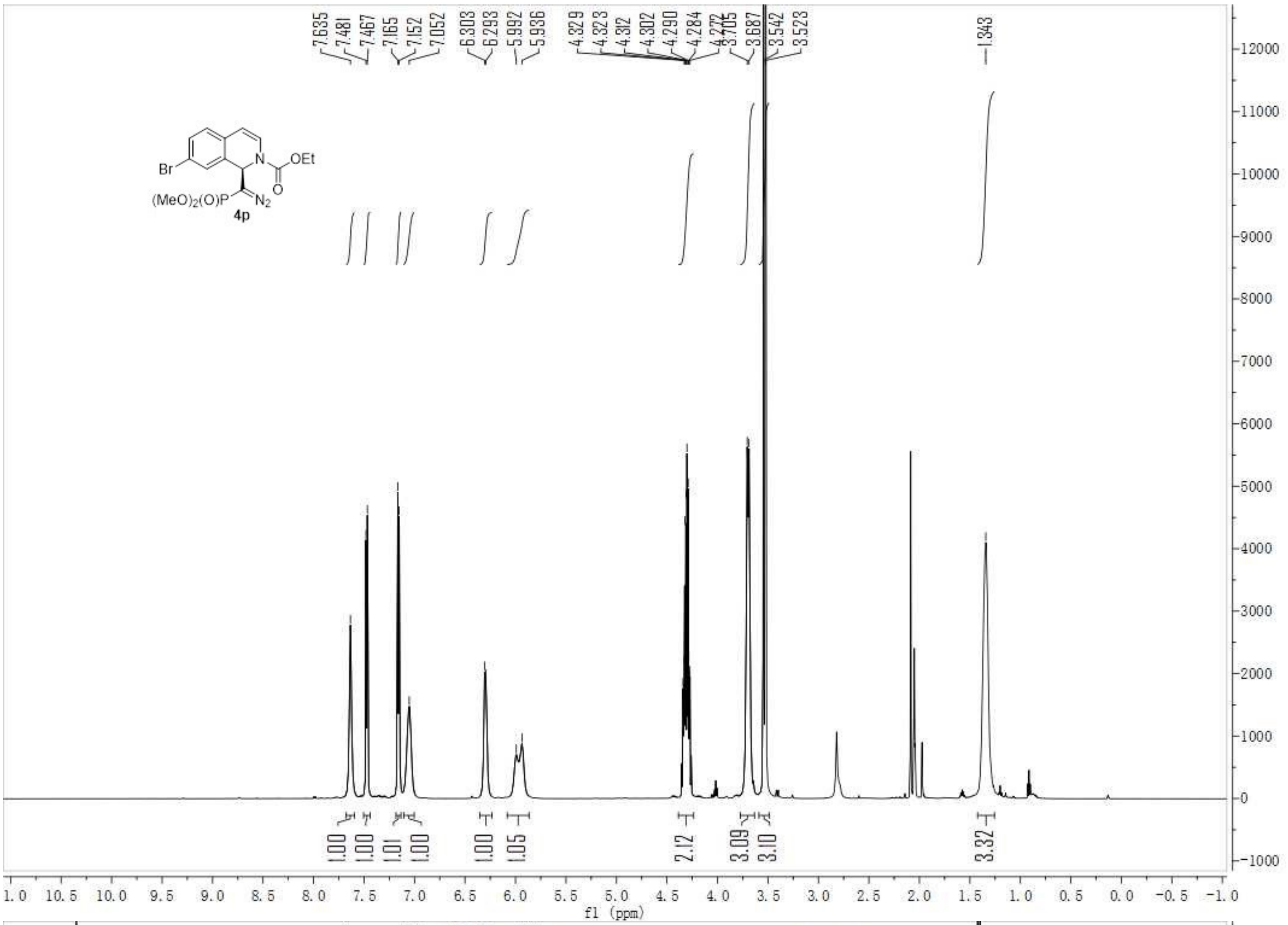
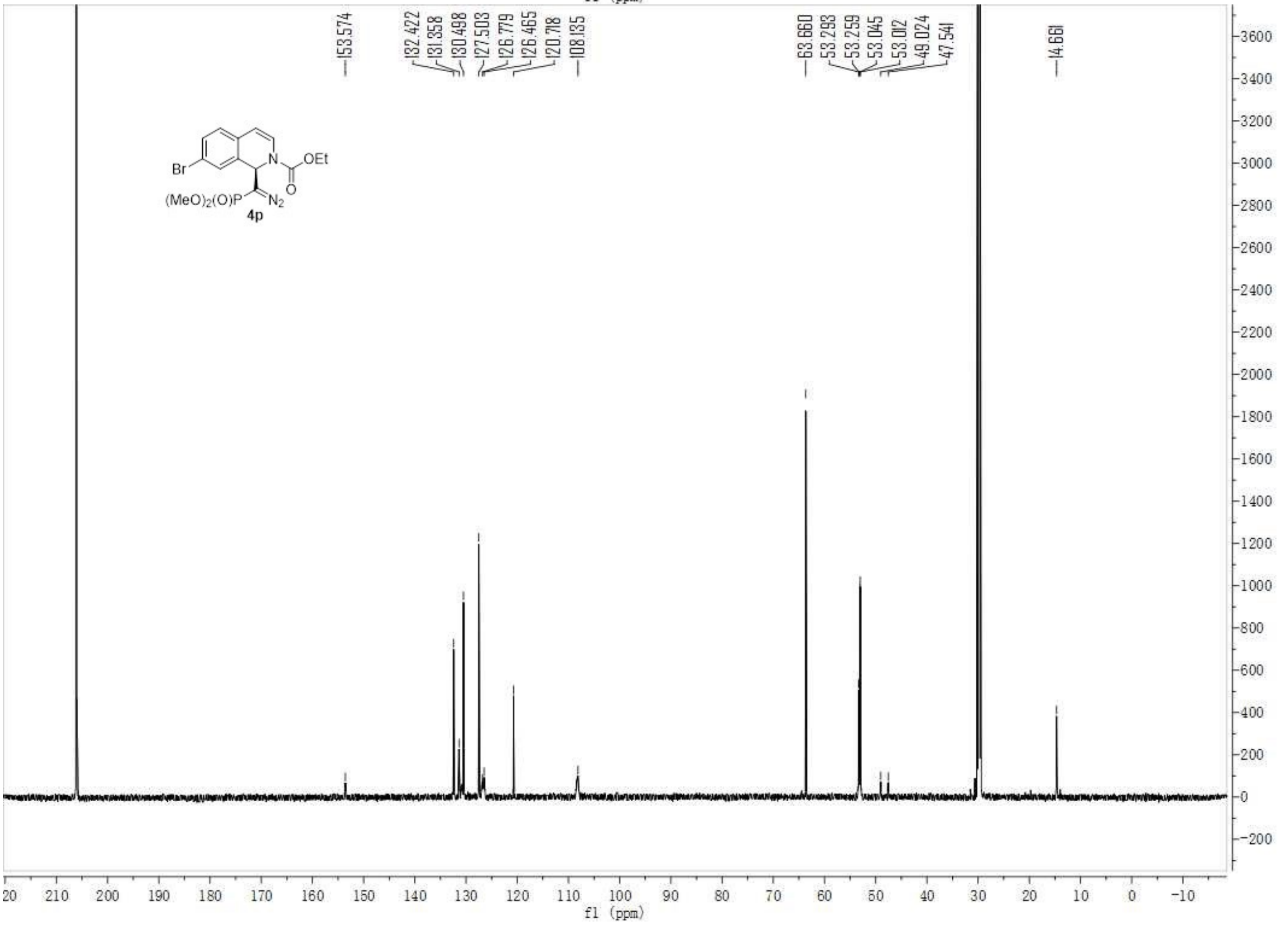
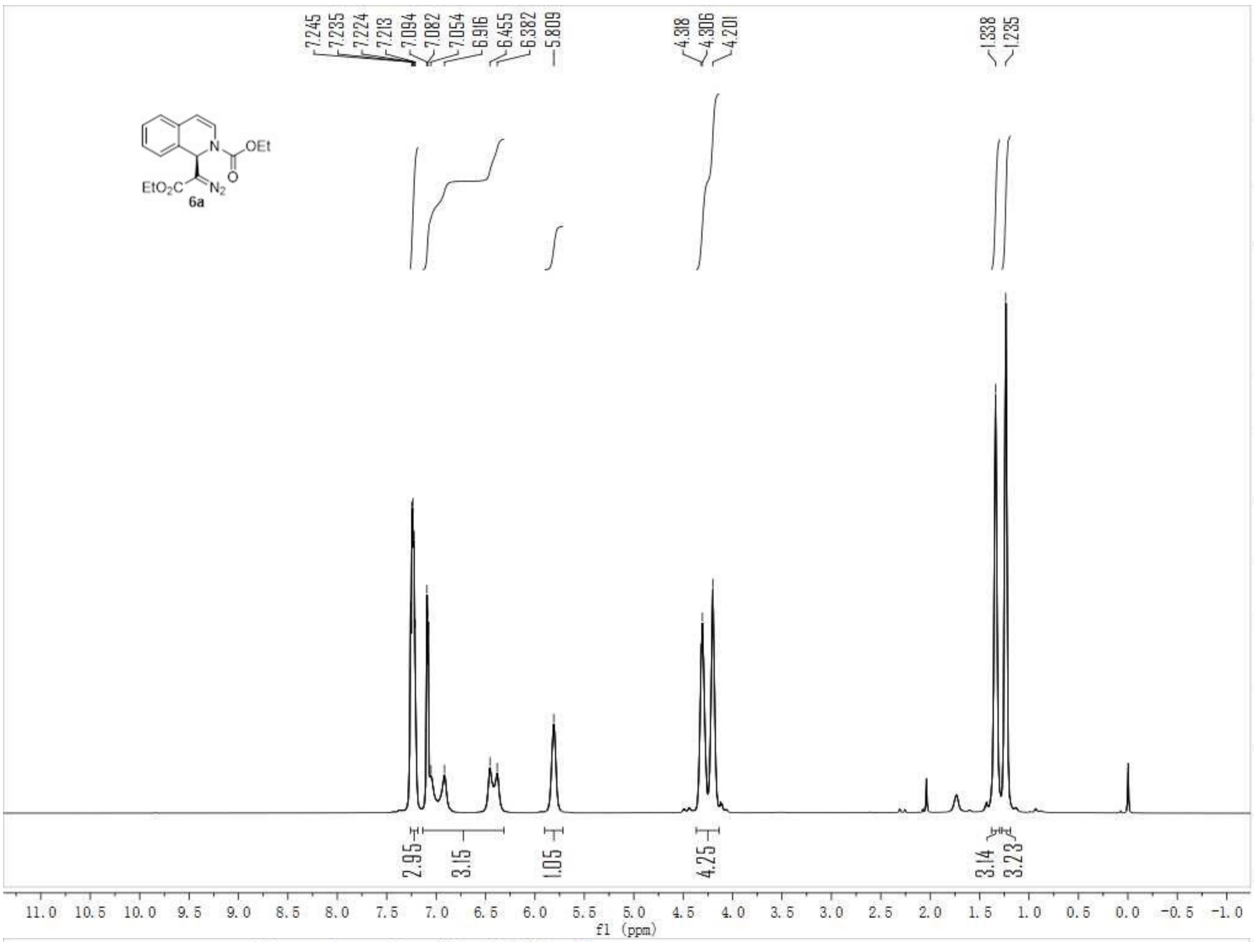
(MeO)2(O)P
N2
4o
f1 (ppm)



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6.382
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4.306
4.201
1.338
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N2
OEt
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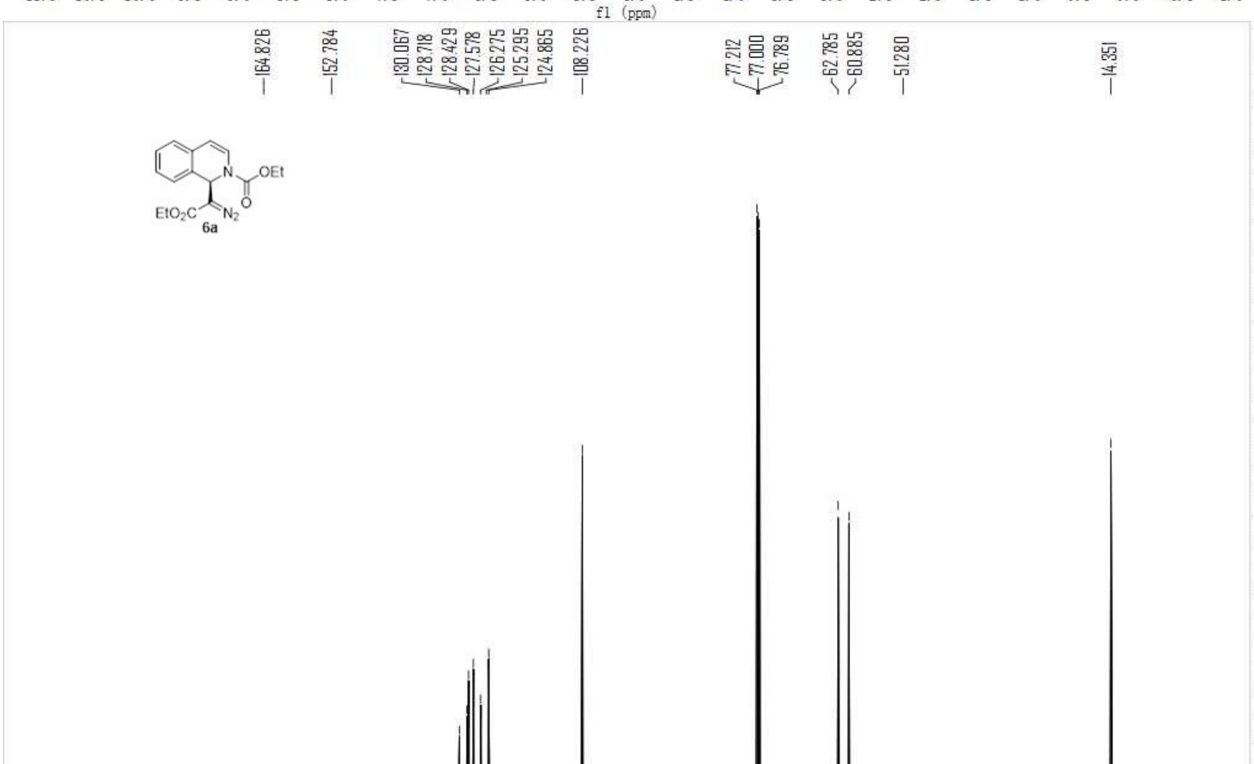
2.95
3.15
1.05
4.25
3.14
3.23
f1 (ppm)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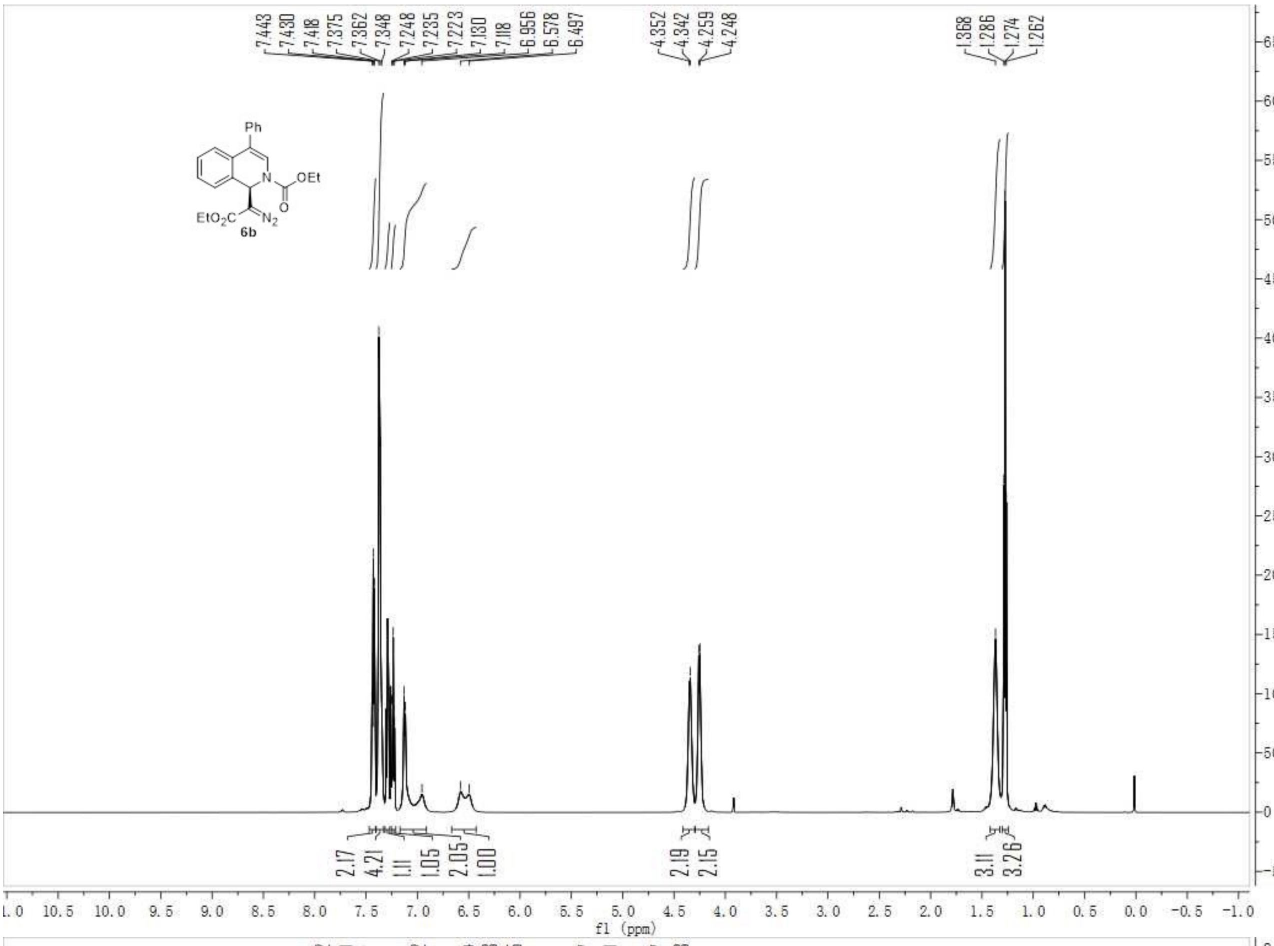
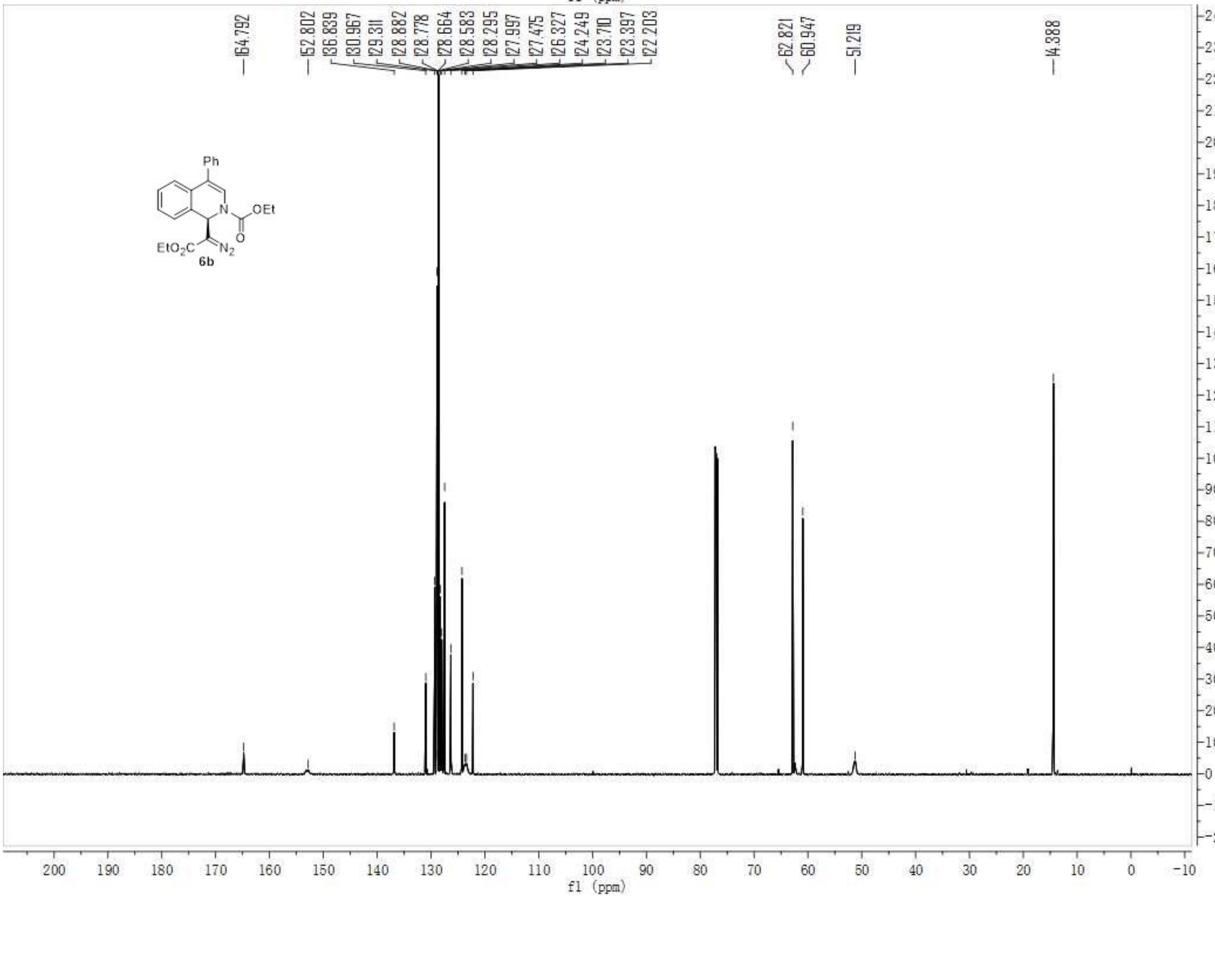
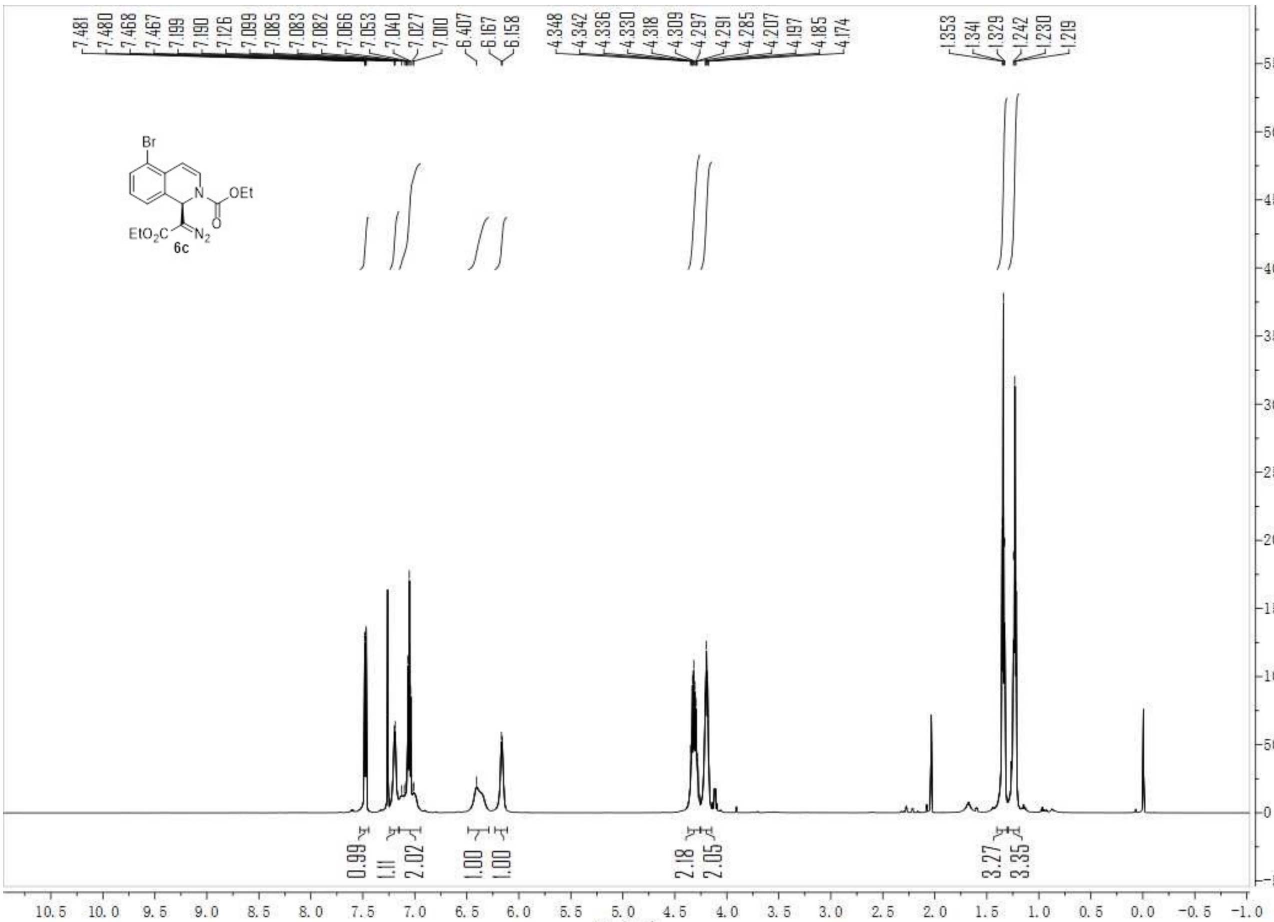
EtO2C
N2
OEt
6a
f1 (ppm)



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7.099
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7.040
7.027
7.010
6.407
6.167
6.158
4.348
4.342
4.336
4.330
4.318
4.309
4.297
4.291
4.285
4.207
4.197
4.185
4.174
1.353
1.341
1.329
1.242
1.230
1.219
Br
N
OEt
O
EtO2C
N2
6c
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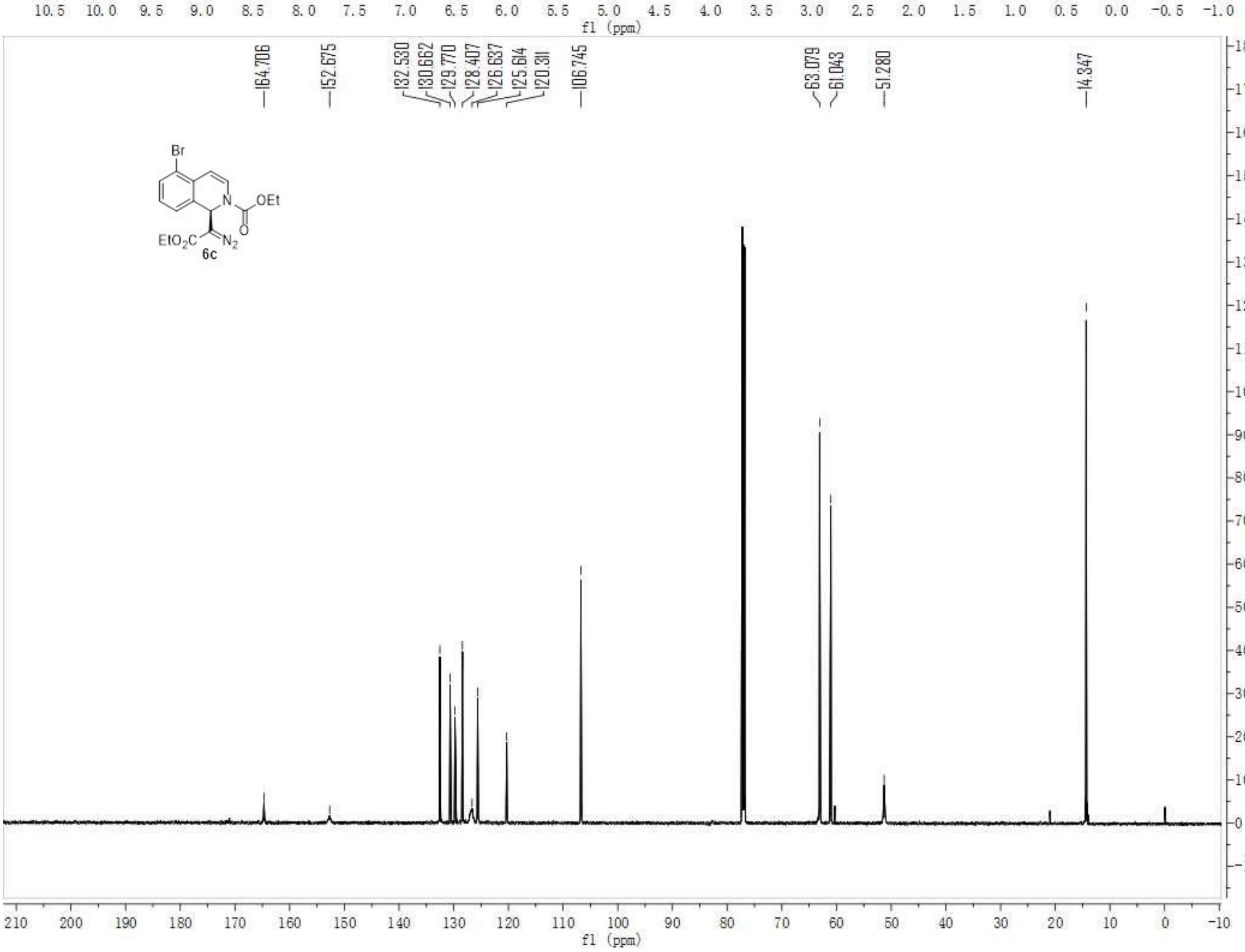
3.35
f1 (ppm)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Br
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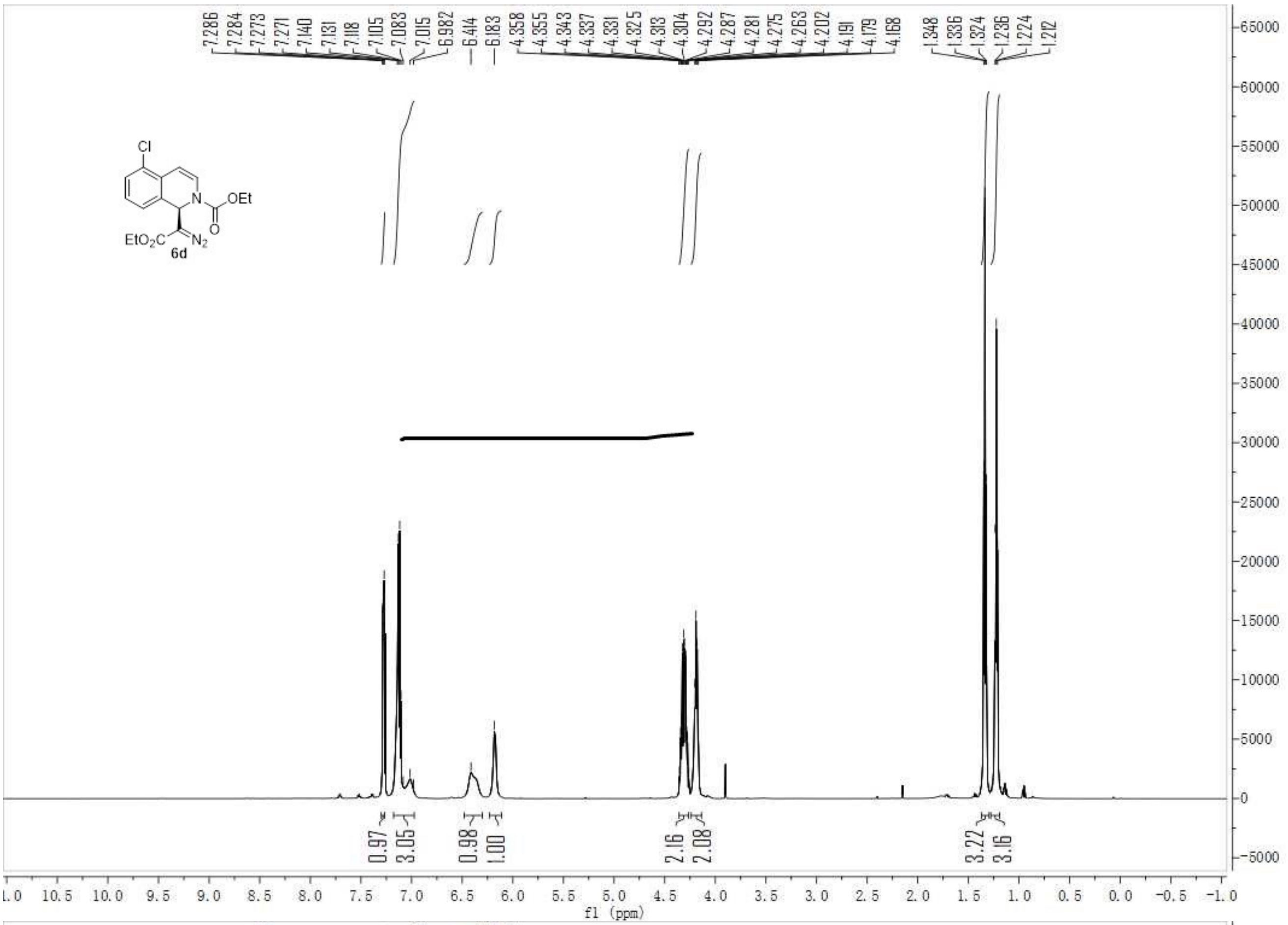
O
EtO2C
N2
6c
f1 (ppm)



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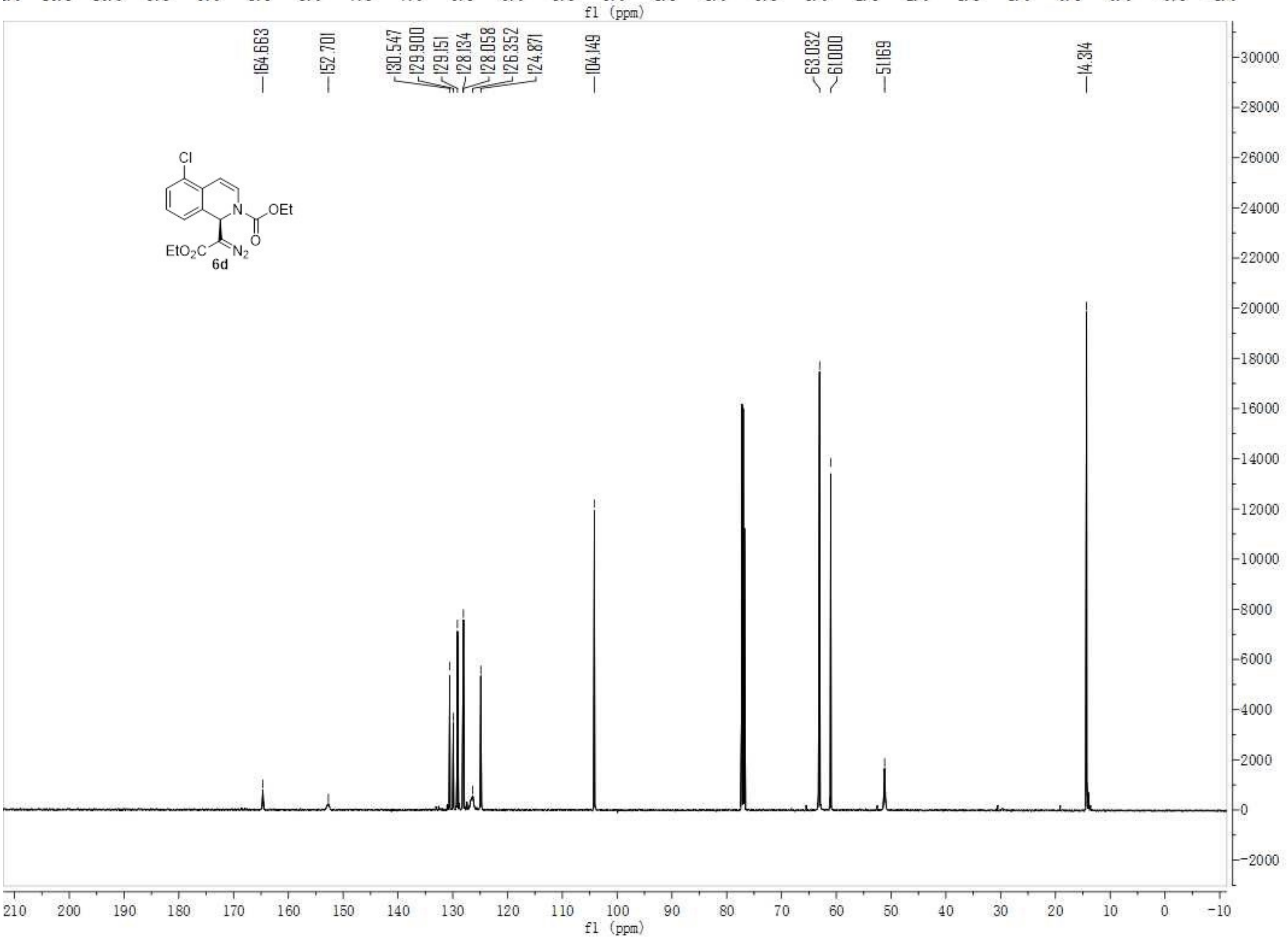
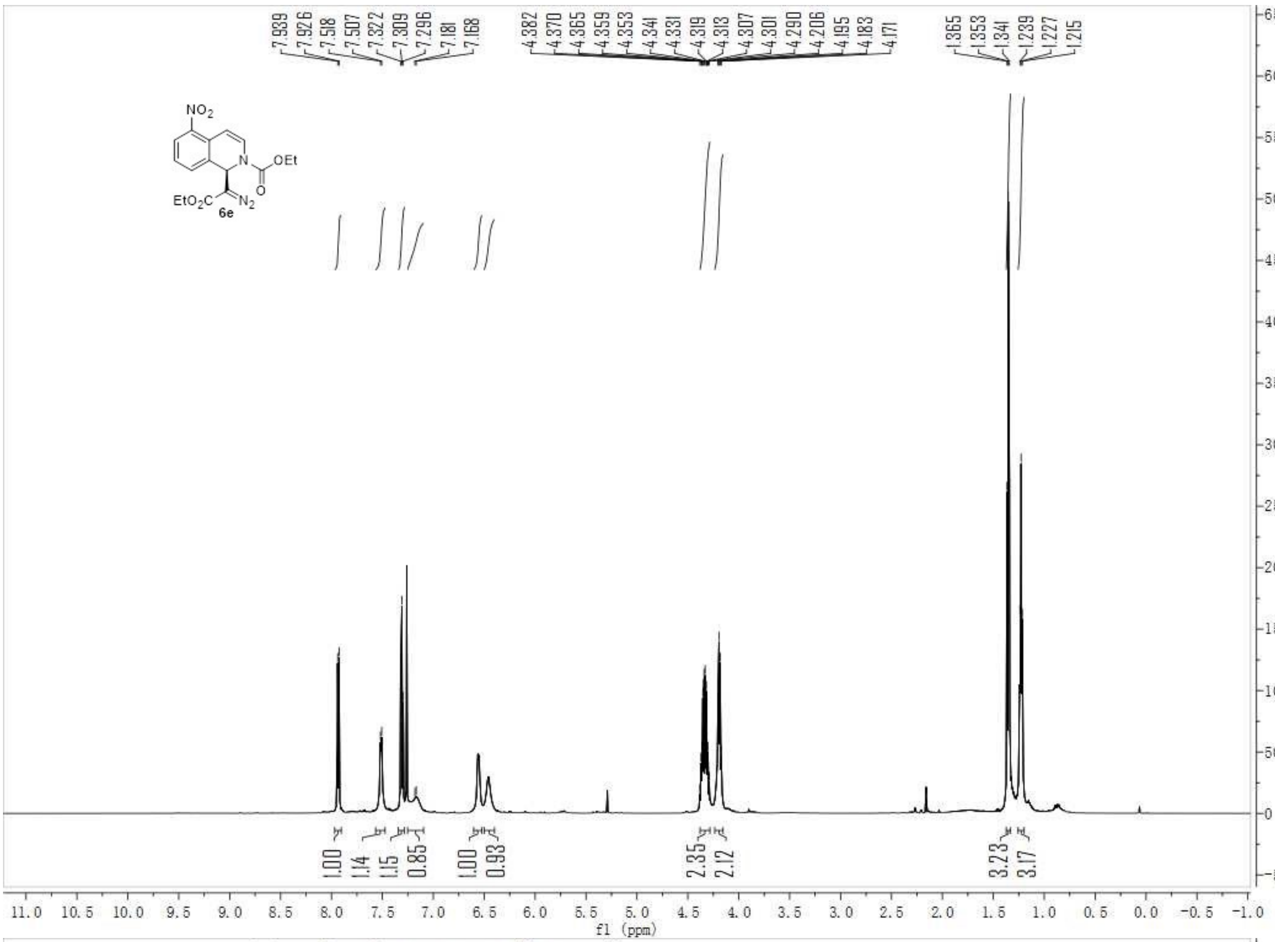
Cl
OEt
EtO2C
N2
6d
0.97 3.05 0.98 1.00 2.16 2.08 3.22 3.16
f1 (ppm)



164.663 152.701 130.547 129.900 129.151 128.134 128.058 126.352 124.871 104.149 63.032 61.000 51.169 14.314
Cl
OEt
EtO2C
N2
6d
f1 (ppm)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4.365
4.359
4.353
4.341
4.331
4.319
4.313
4.307
4.301
4.290
4.206
4.195
4.183
4.171
1.365
1.353
1.341
1.239
1.227
1.215
NO2
N
OEt
O
EtO2C
N2
6e
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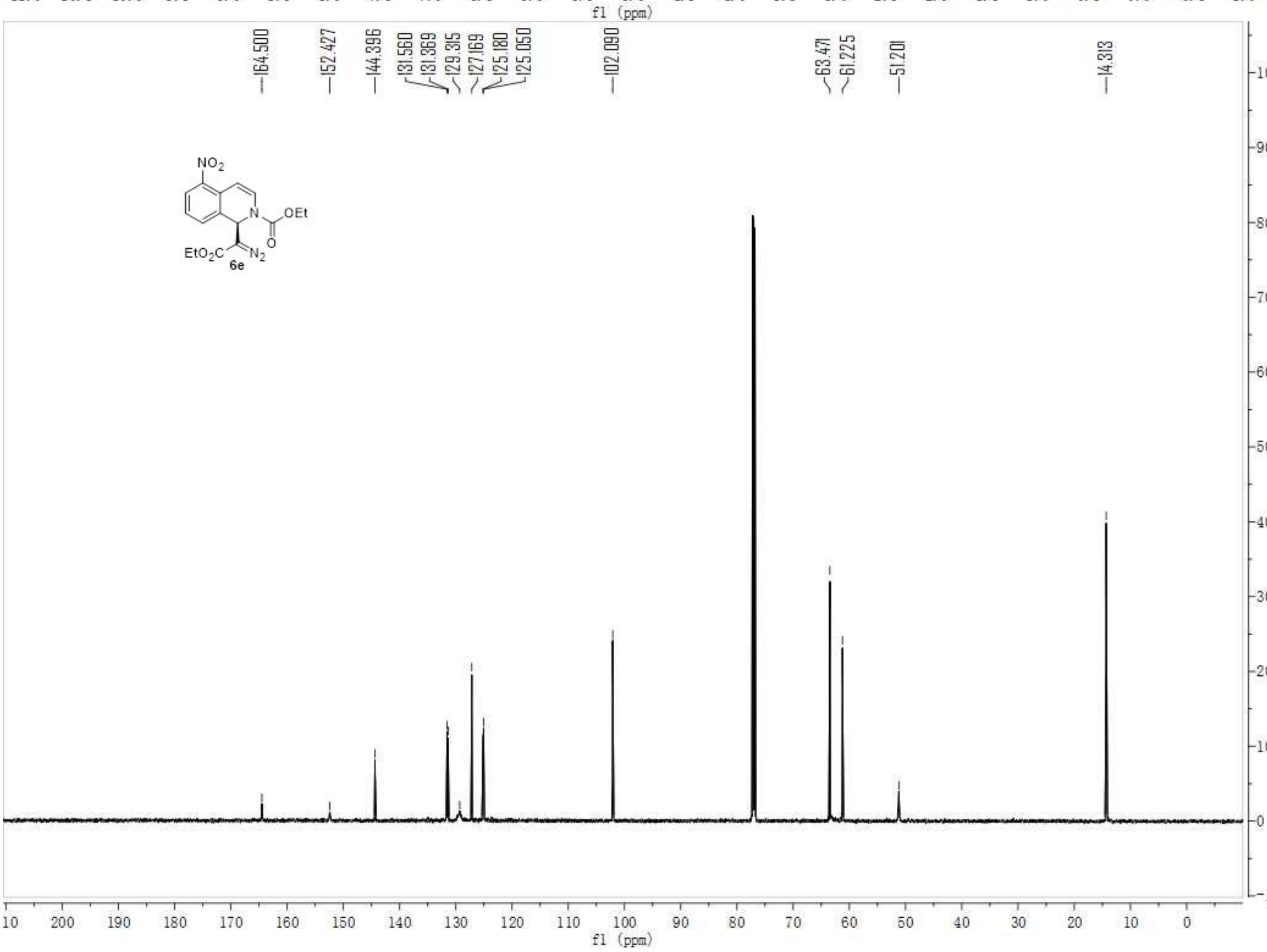
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125.180
125.050
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51.201
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NO2
N
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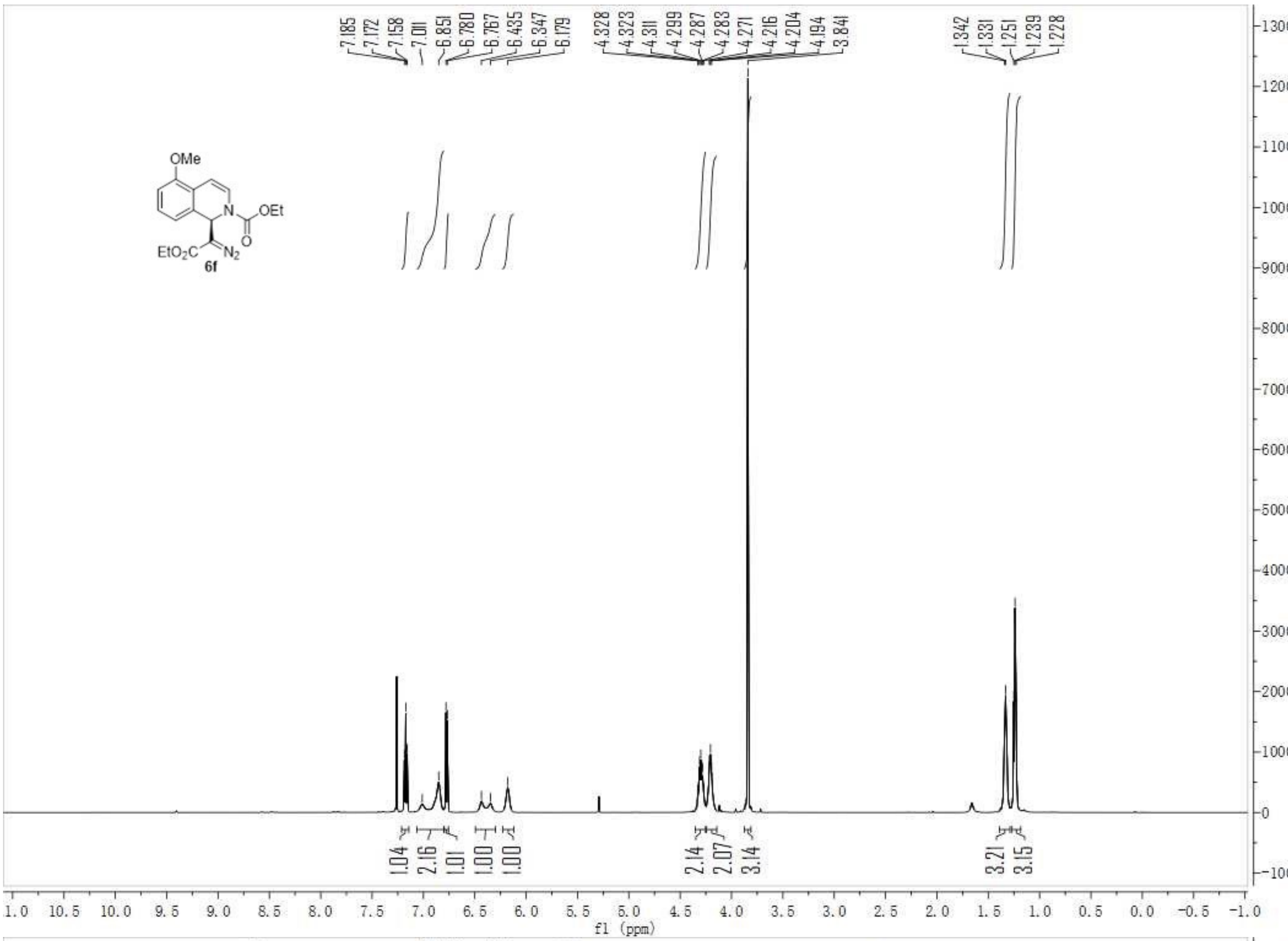
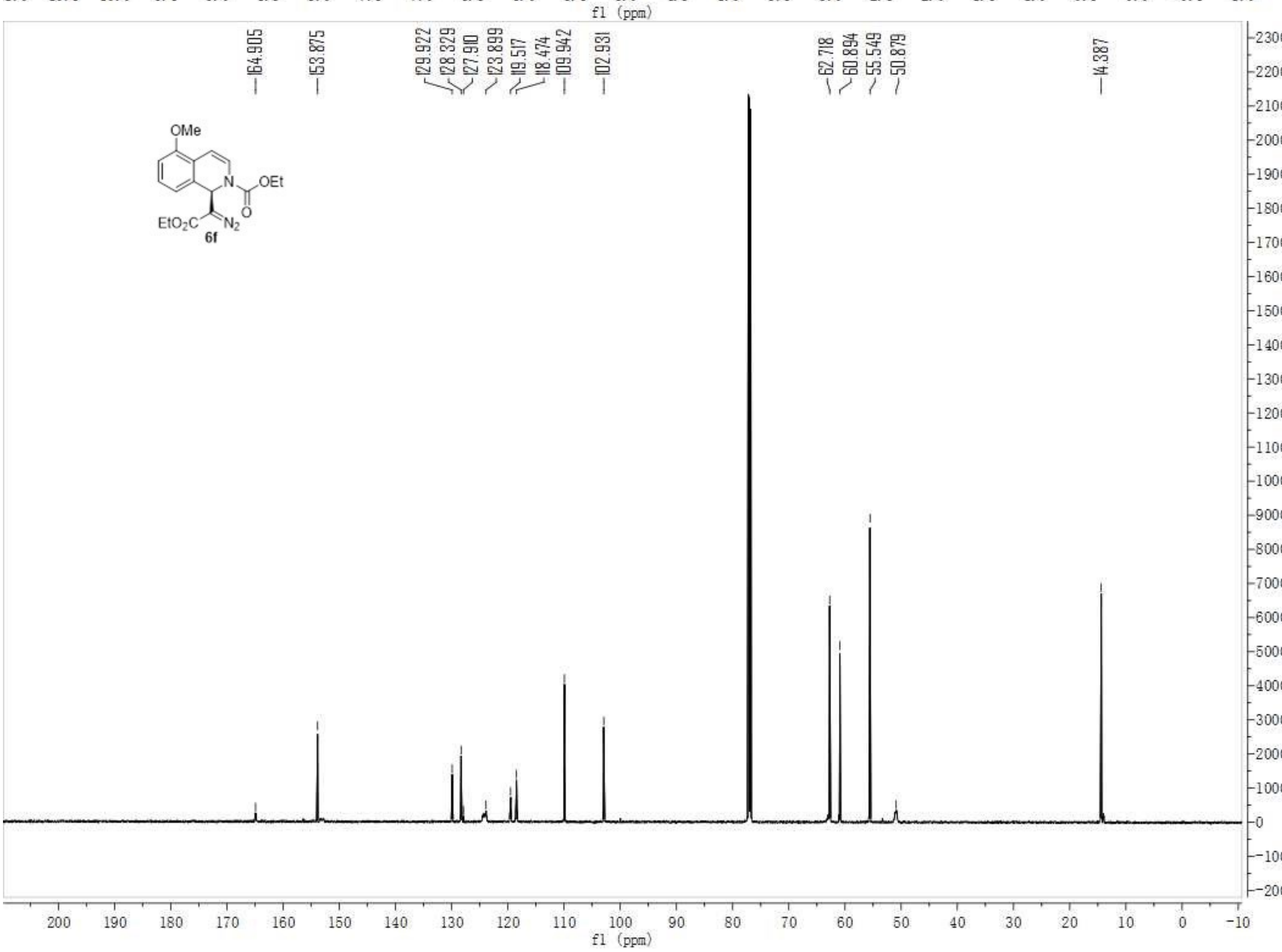
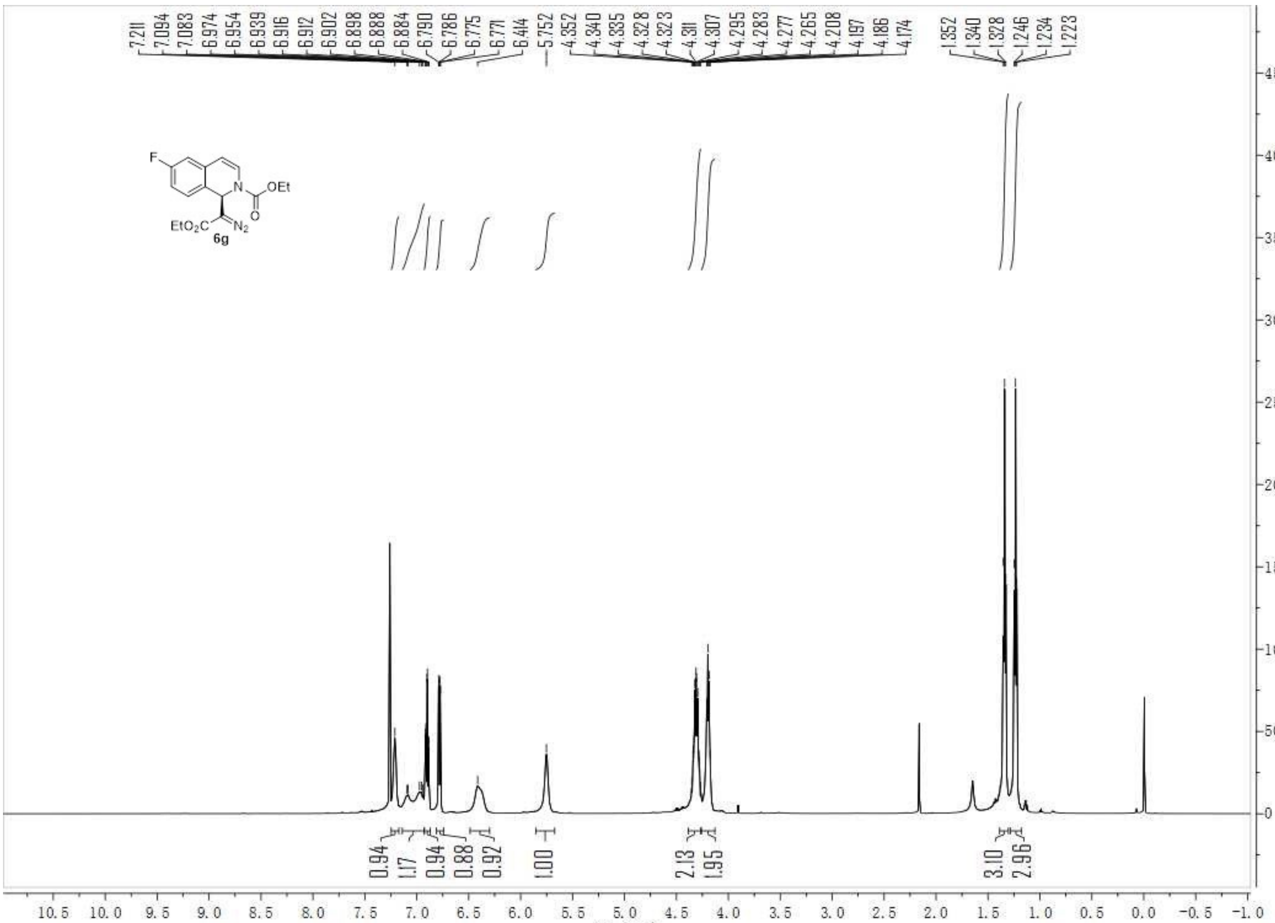
O
EtO2C
N2
6e
f1 (ppm)







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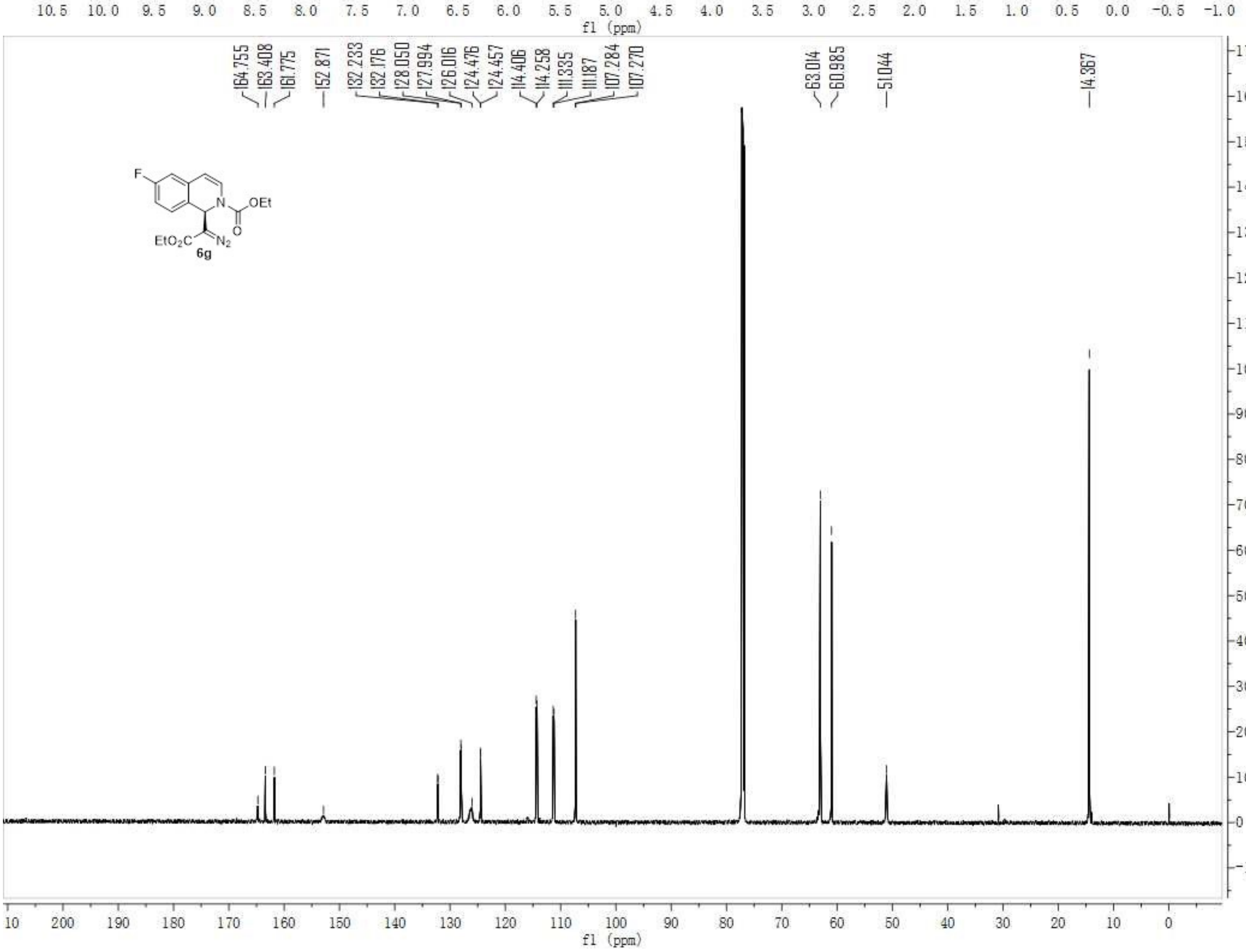

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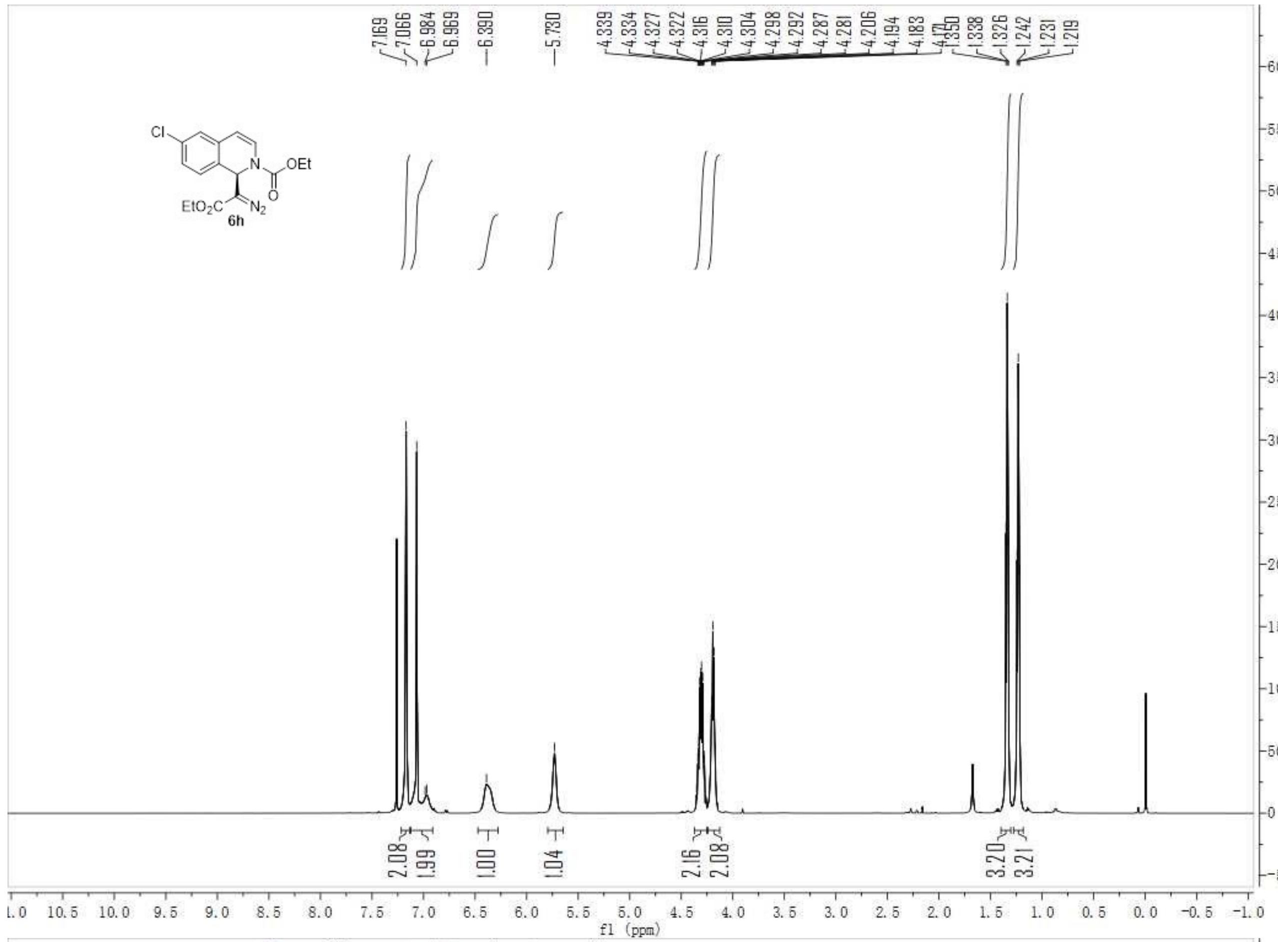
f1 (ppm)



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4.292
4.287
4.281
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4.183
1.338
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1.231
1.219
Cl
N
OEt
O
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6h
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1.00
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2.08
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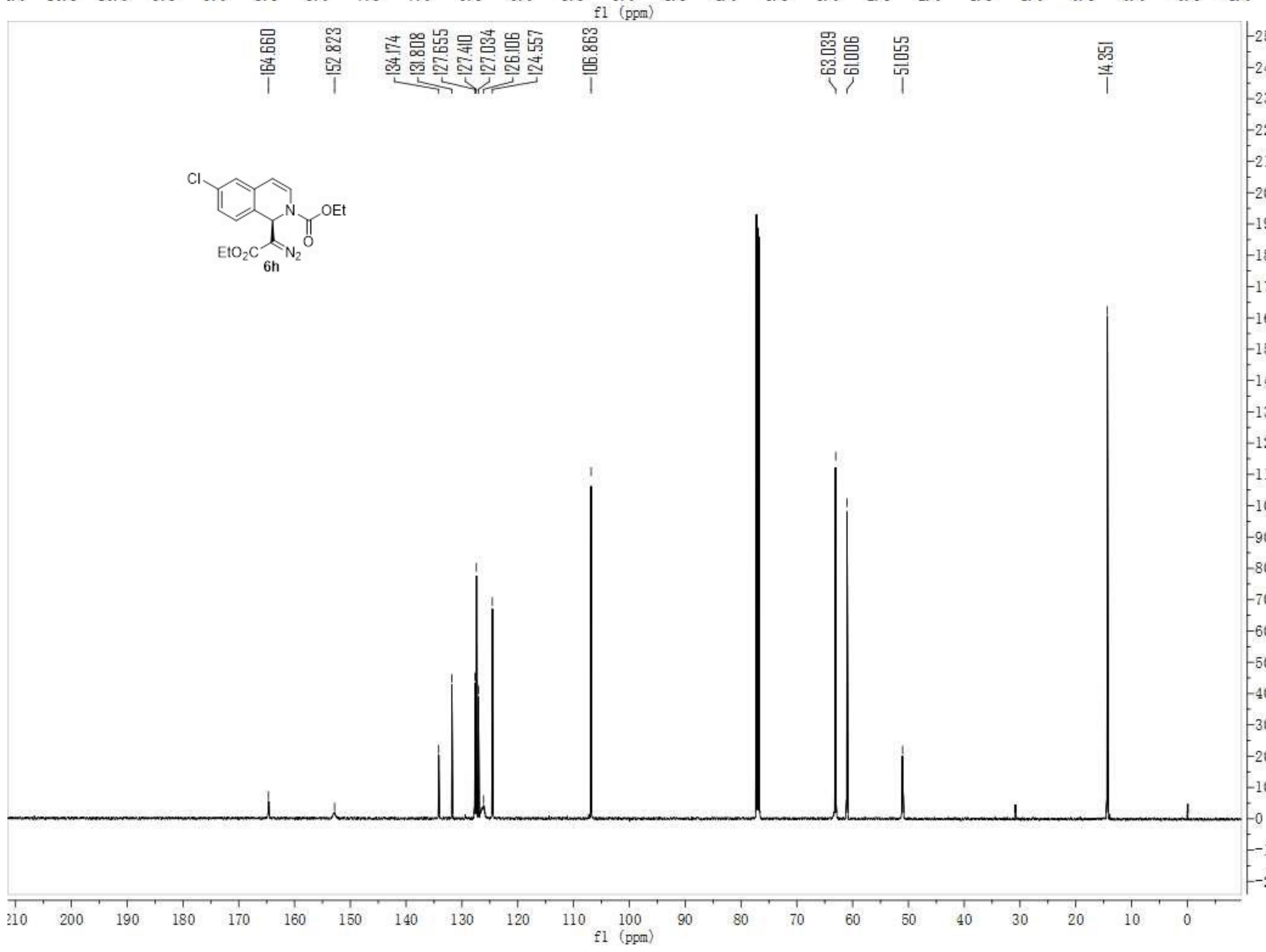
3.21
f1 (ppm)



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Cl
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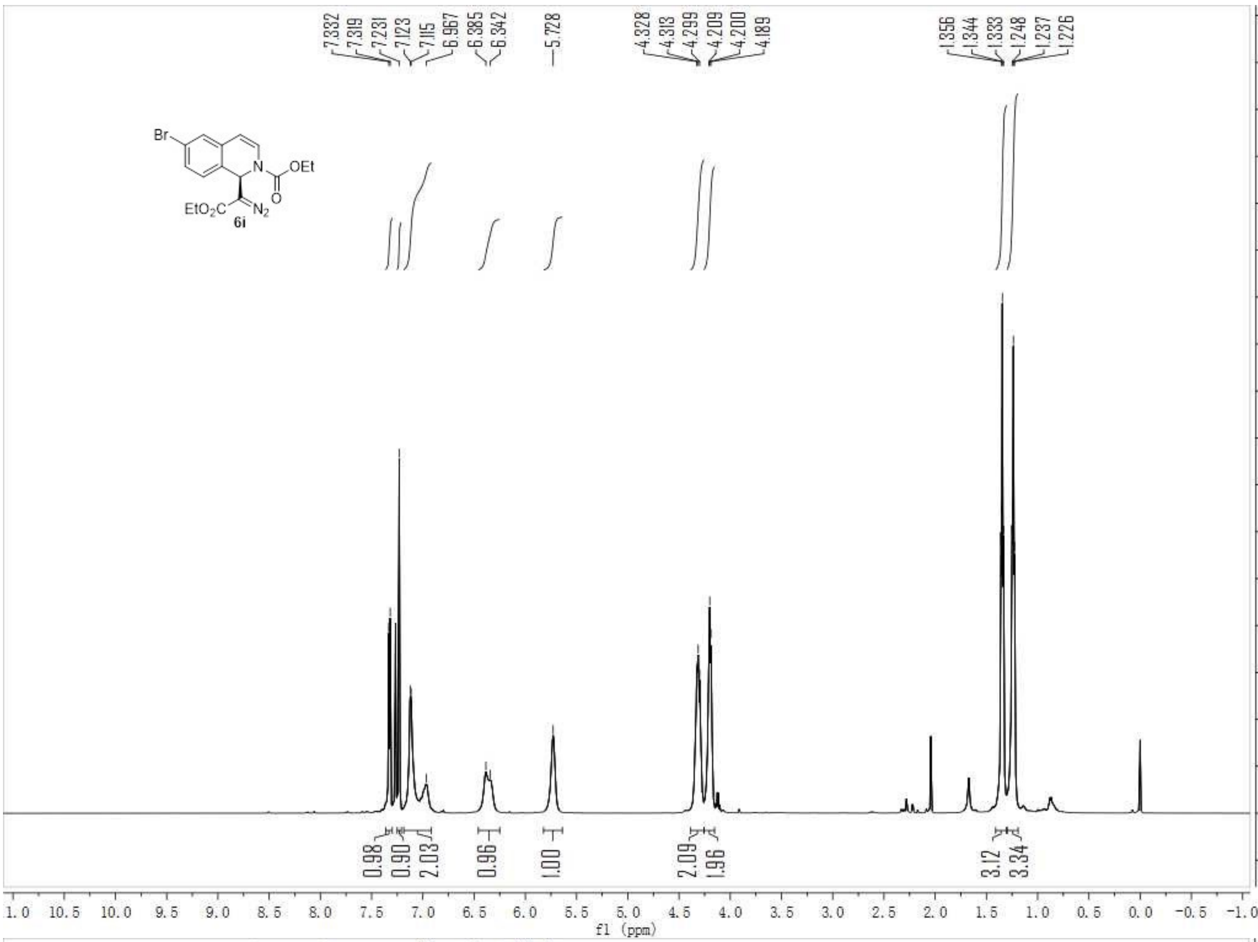
OEt
O
EtO2C
N2
6h
f1 (ppm)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1.344
1.333
1.248
1.237
1.226
Br
N
OEt
O
EtO2C
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1.00
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1.96
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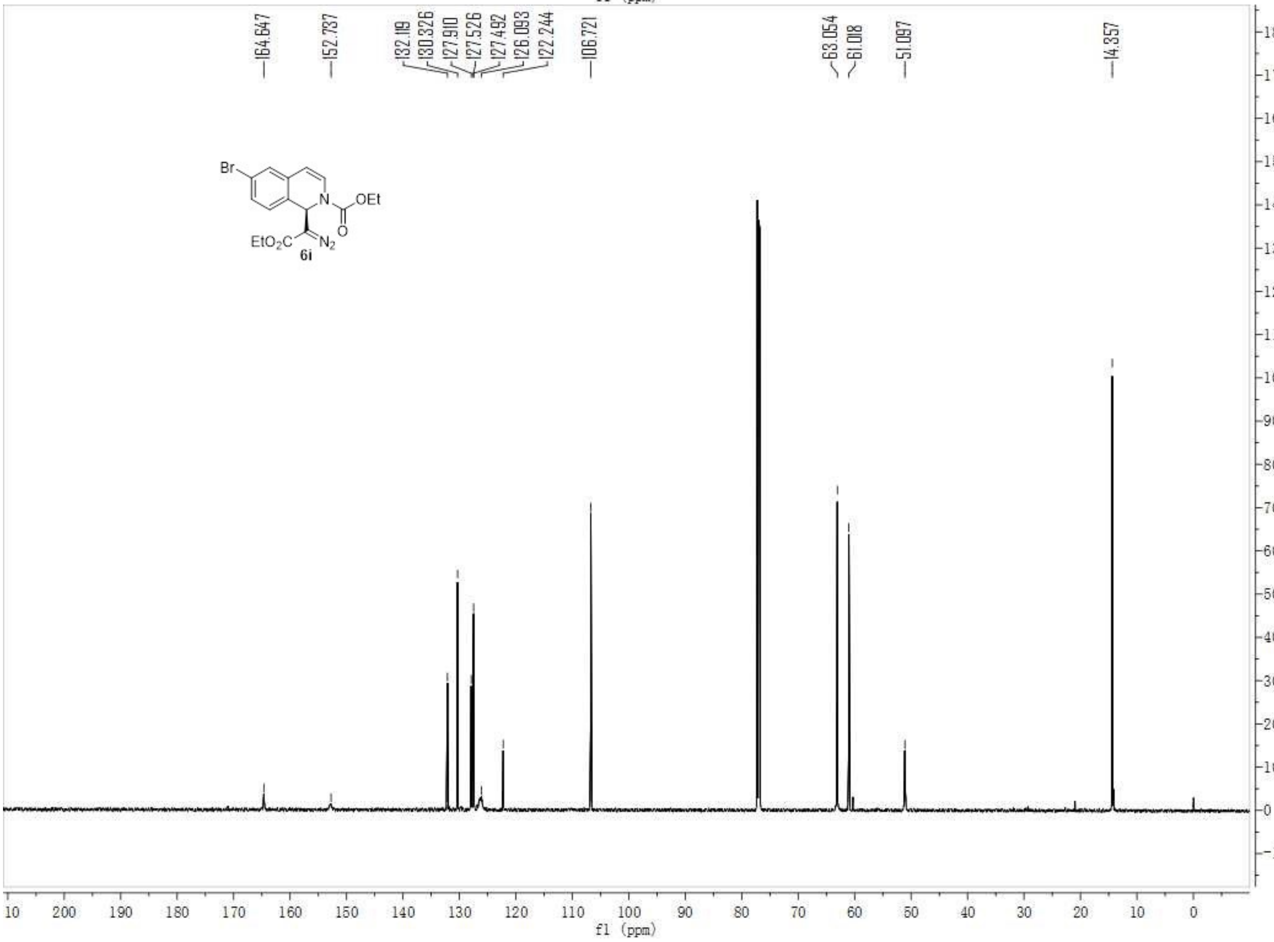
3.34
f1 (ppm)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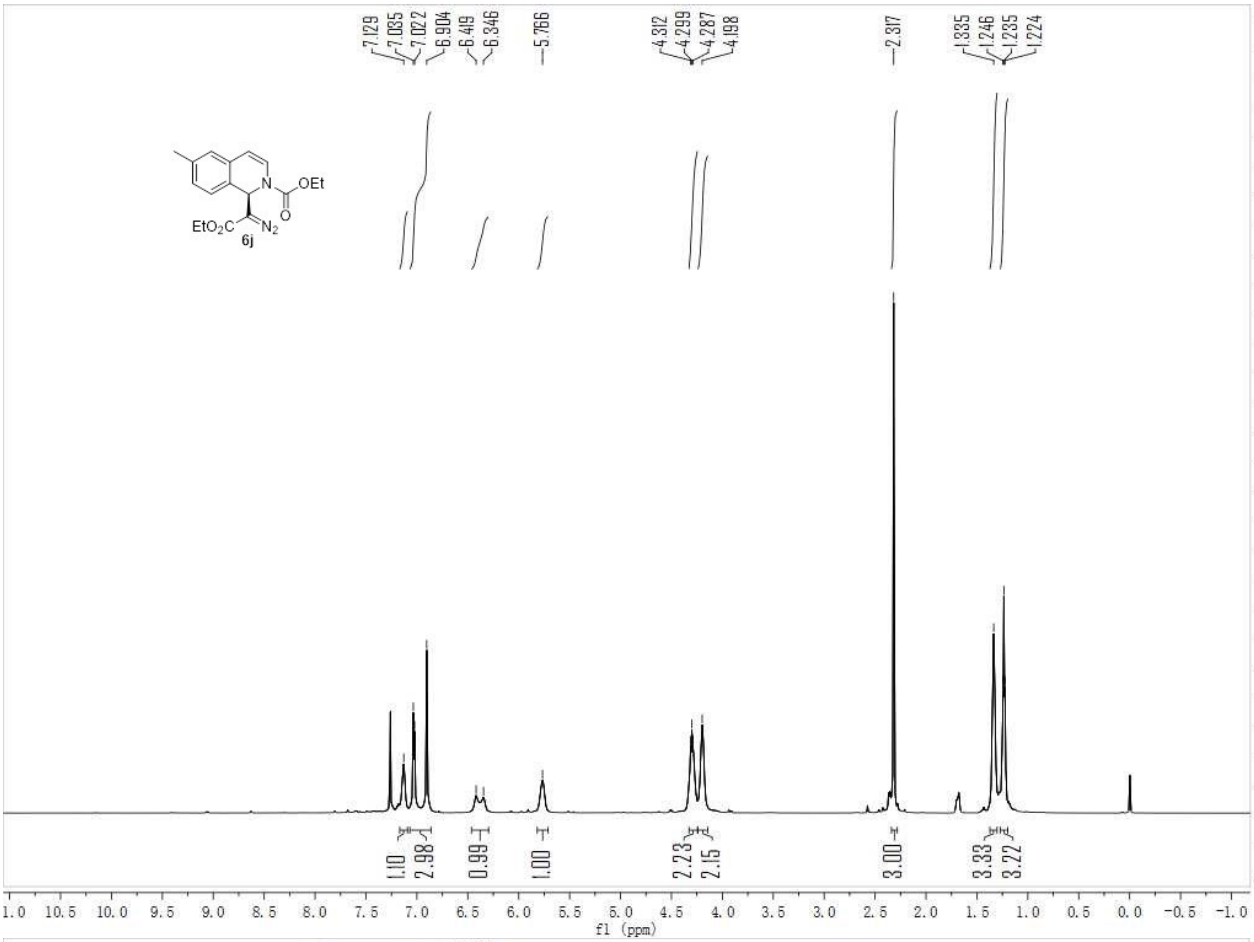
O
EtO2C
N2
6i
f1 (ppm)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1.246
1.235
1.224
OEt
N
EtO2C
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1.00
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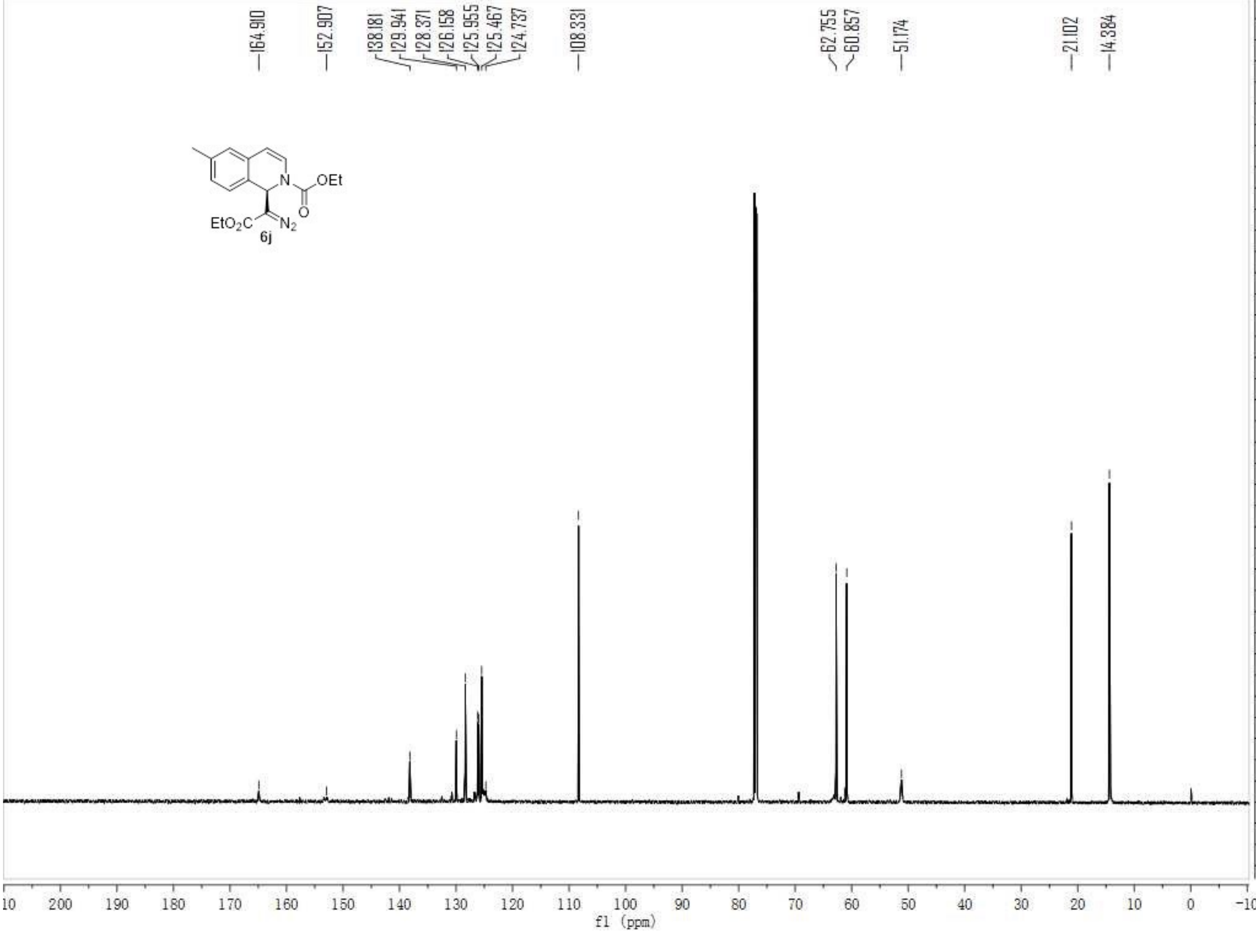
3.22
f1 (ppm)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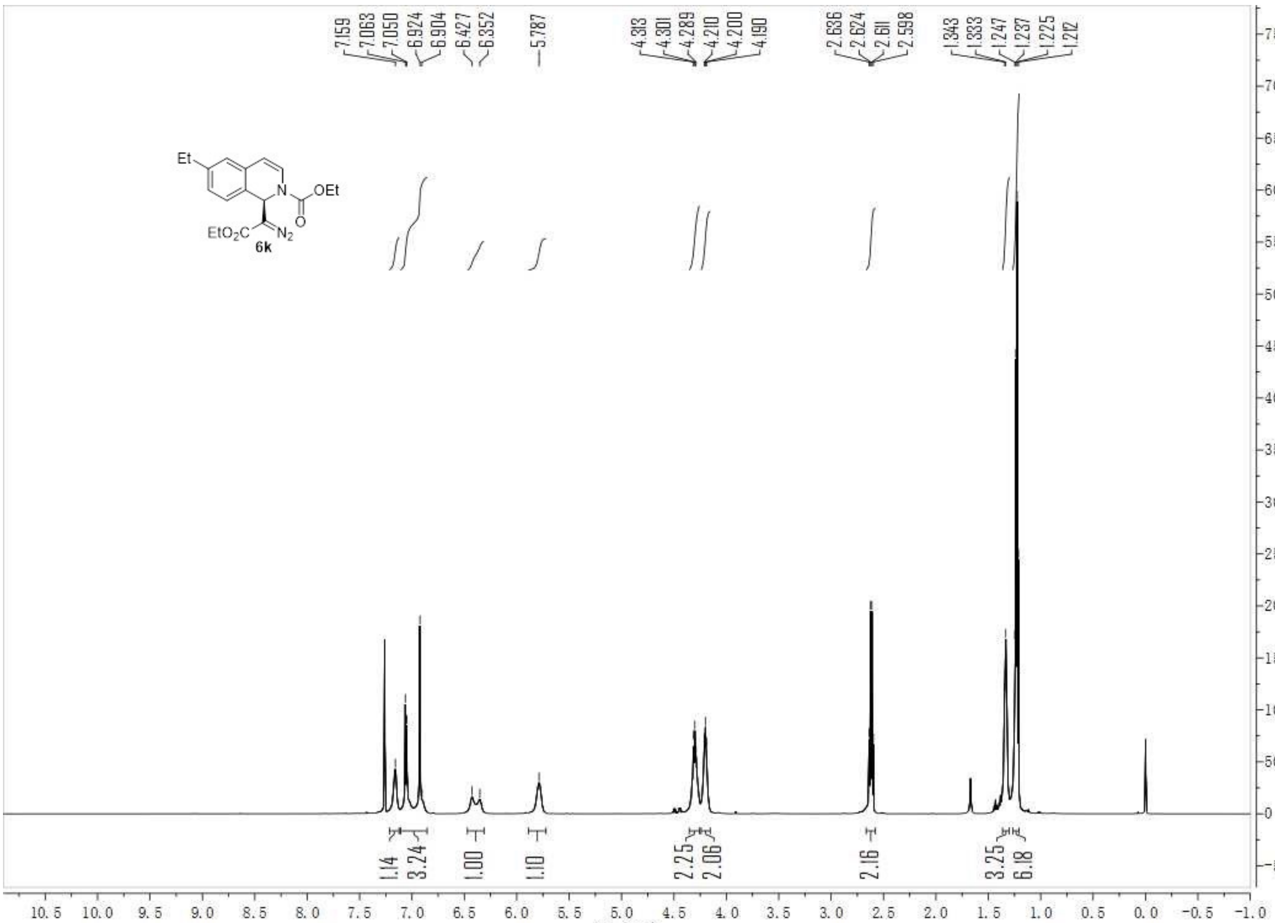
f1 (ppm)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4.190
2.636
2.624
2.611
2.598
1.343
1.333
1.247
1.237
1.225
1.212
Et
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OEt
O
EtO2C
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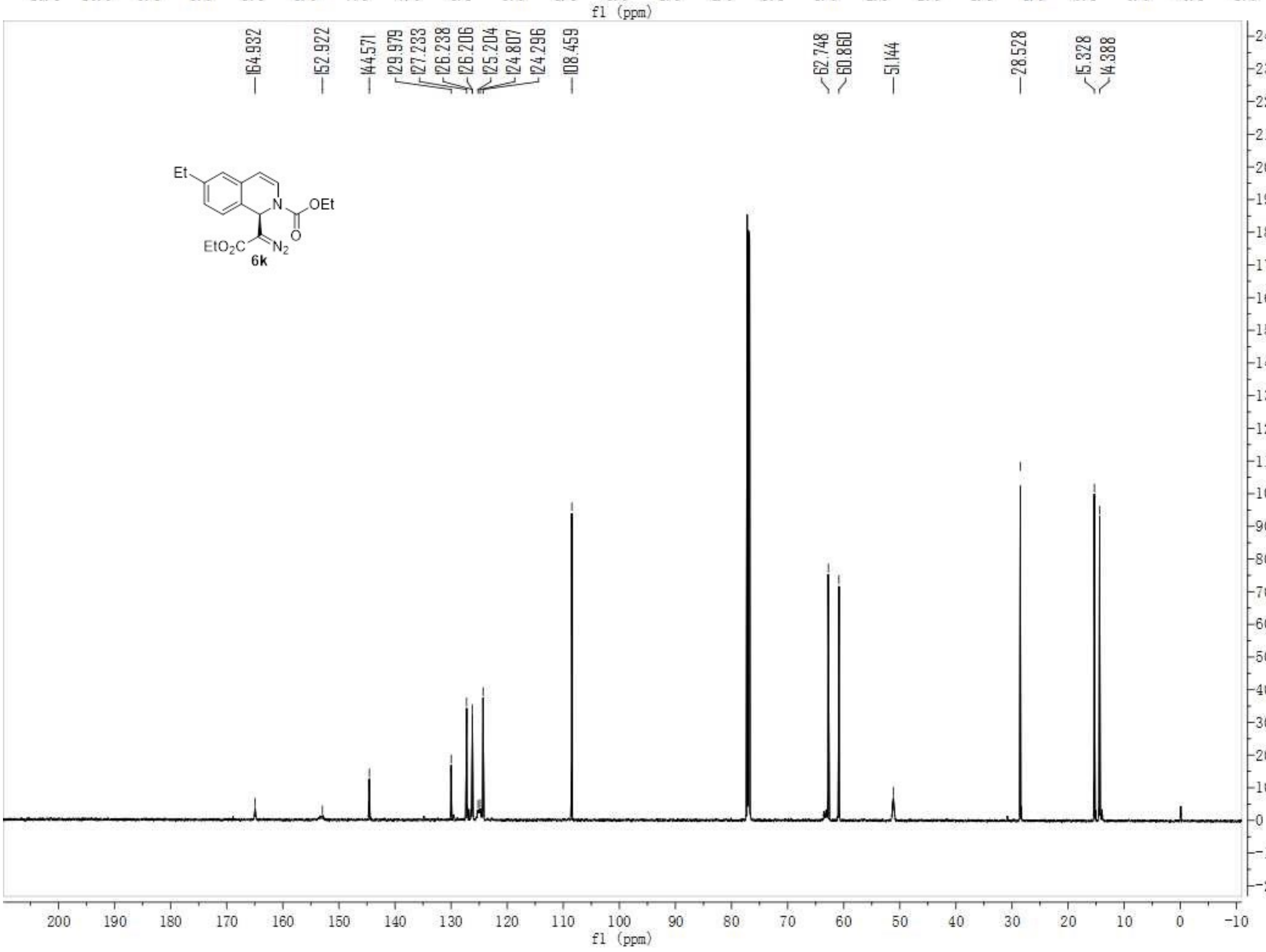
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O
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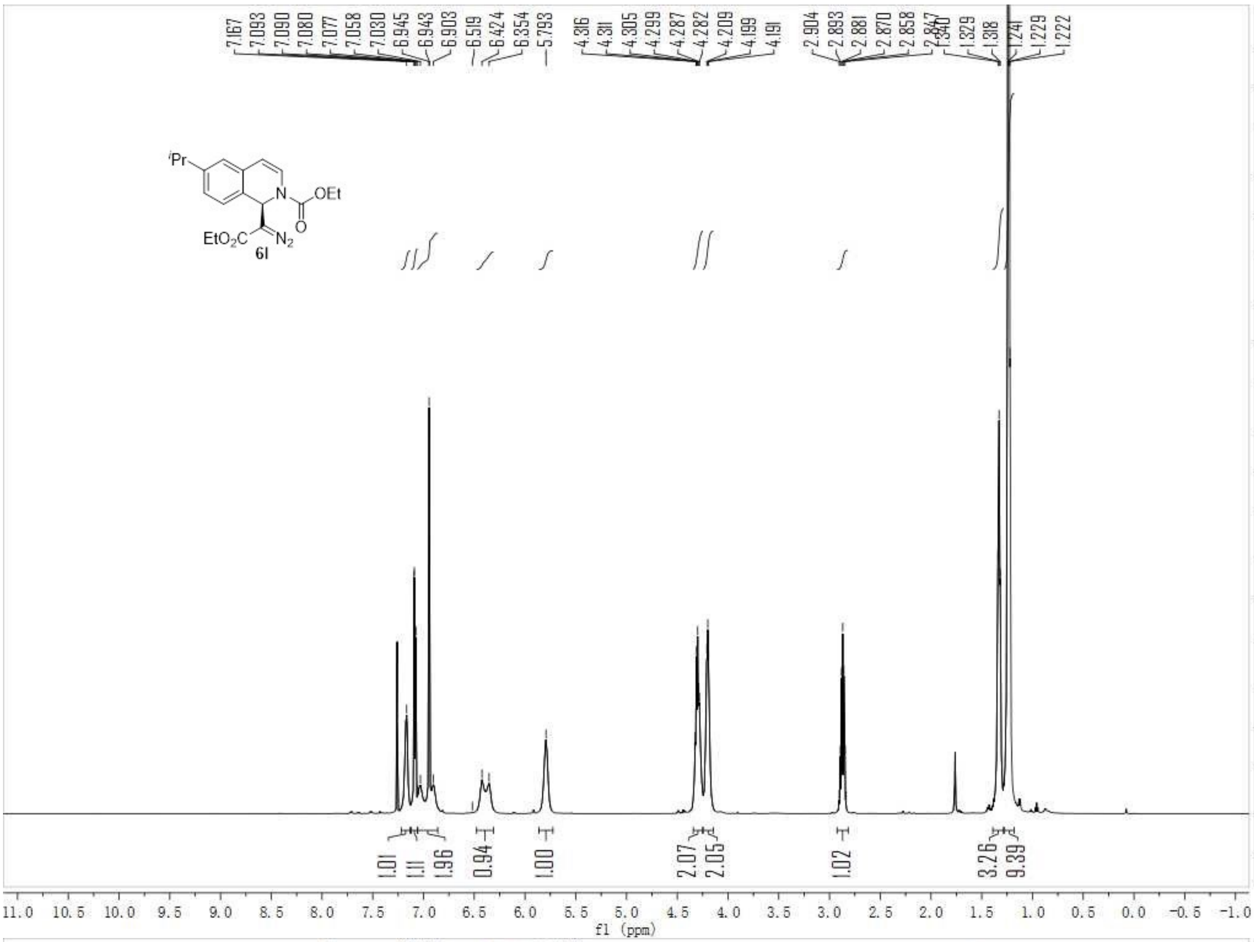
N2
6k
f1 (ppm)



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iPr
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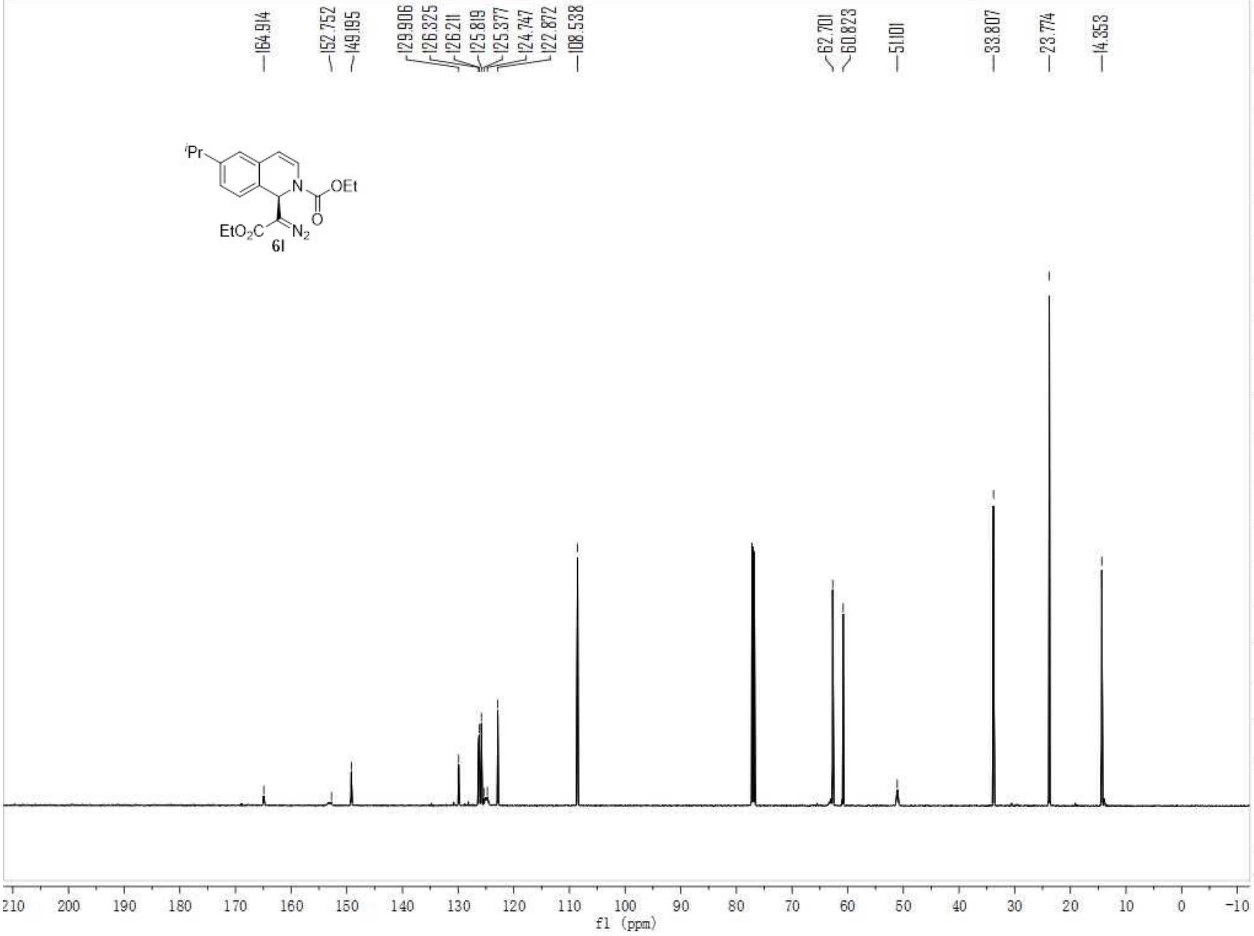
OEt
O
EtO2C
N2
6l
1.01 1.11 1.96 0.94 1.00 2.07 2.05 1.02 3.26 9.39
f1 (ppm)



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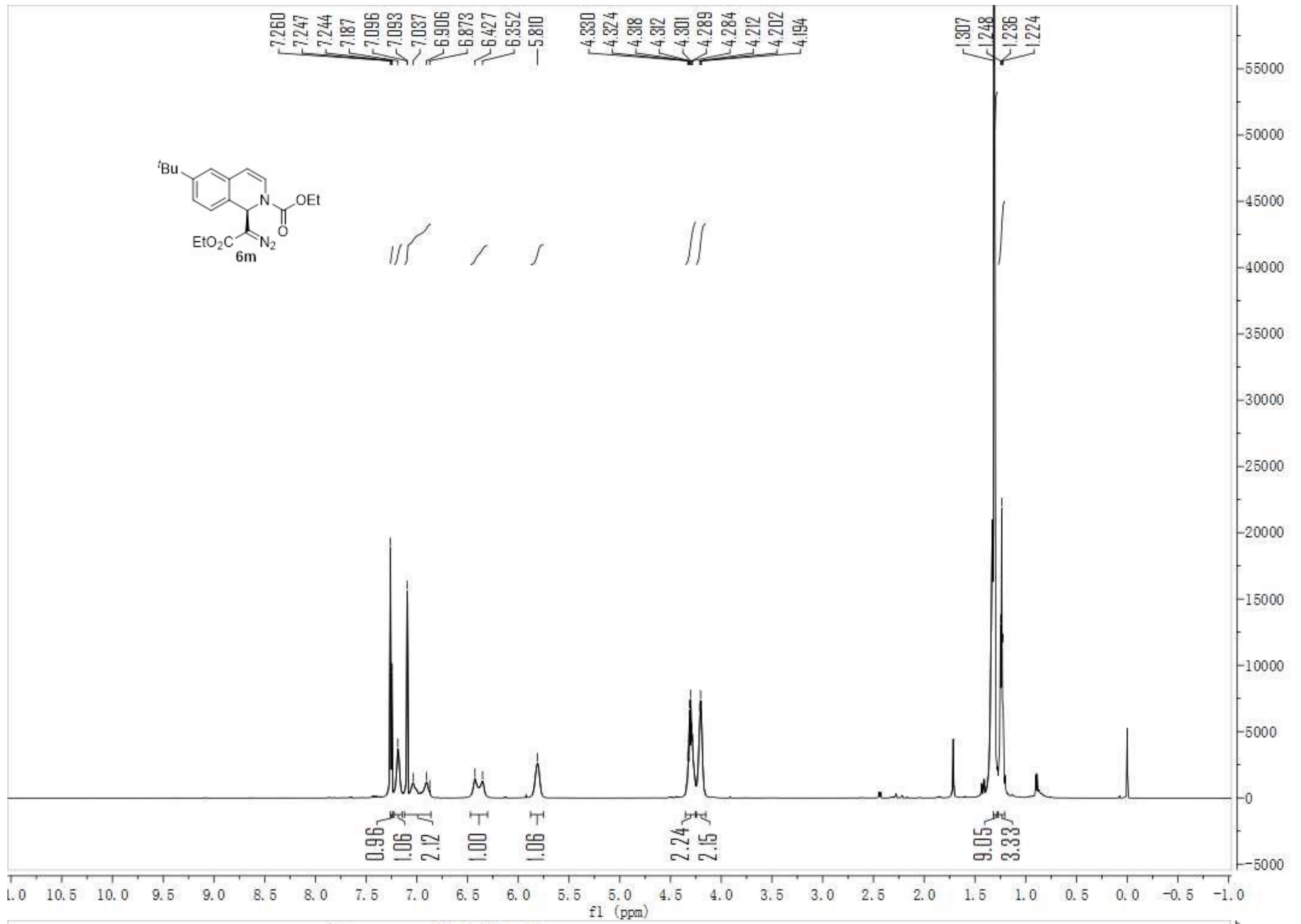
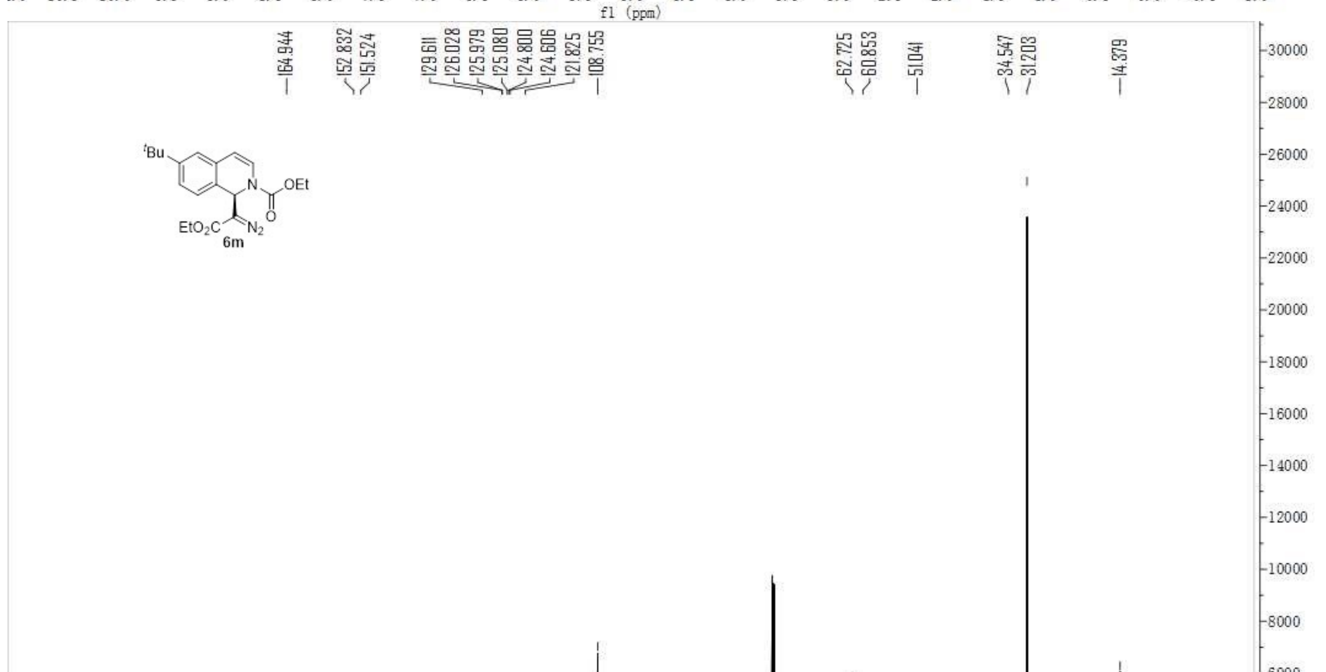
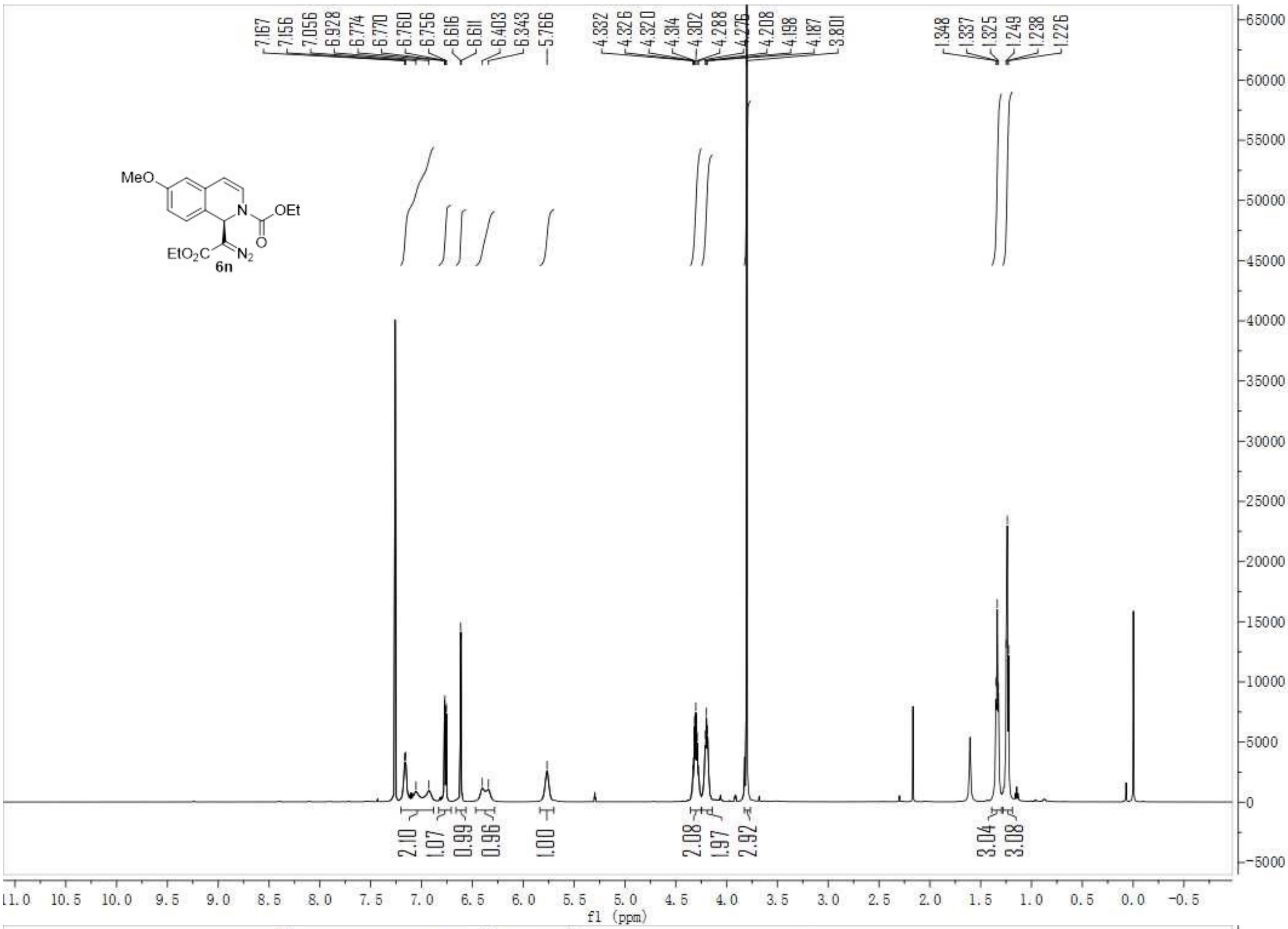
EtO2C
N2
6l
f1 (ppm)



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4.326
4.320
4.314
4.302
4.288
4.276
4.208
4.198
4.187
3.801
1.348
1.337
1.325
1.249
1.238
1.226
MeO
N
OEt
O
EtO2C
N2
6n
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1.00
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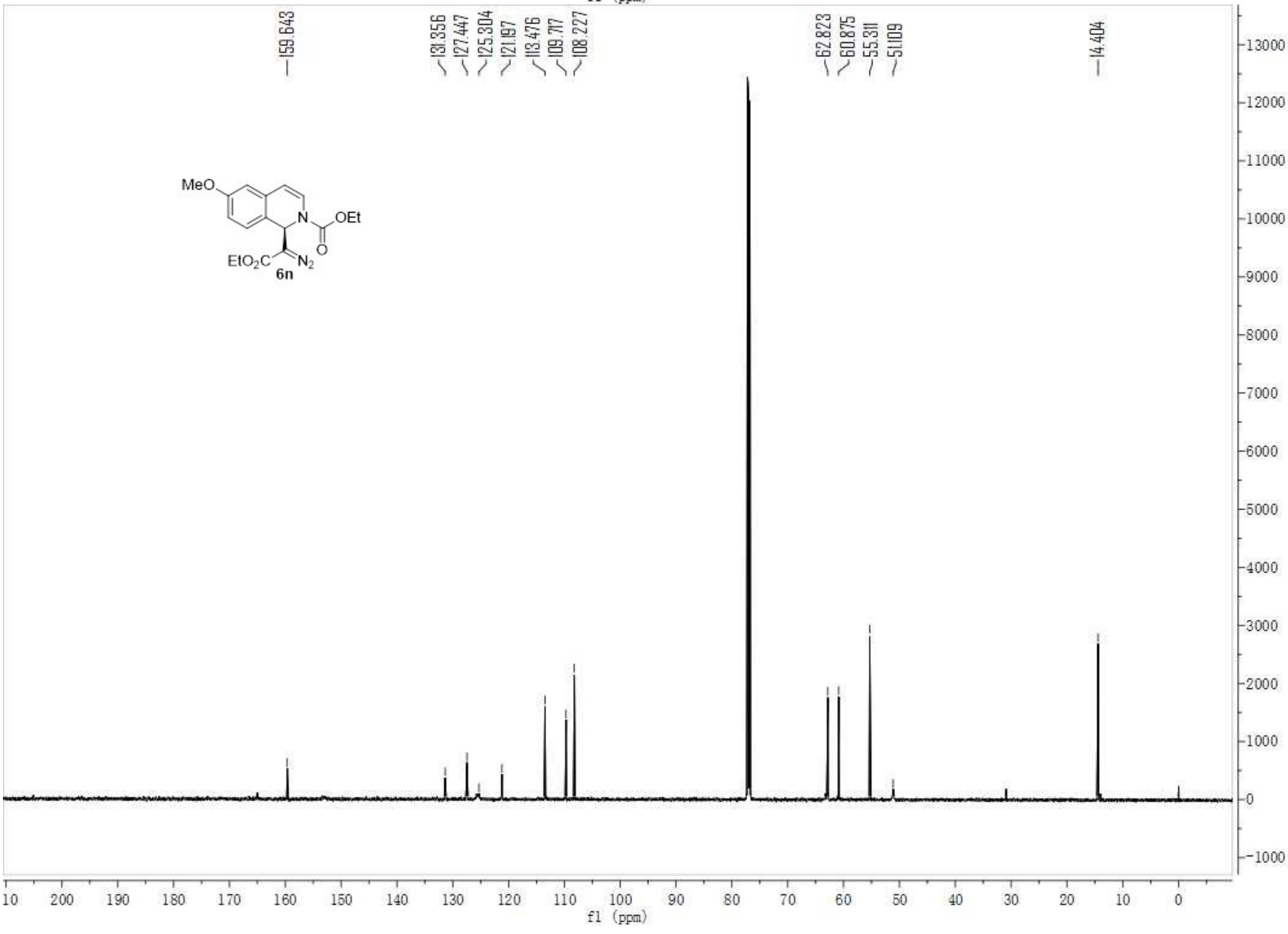
2.92
3.04
3.08
f1 (ppm)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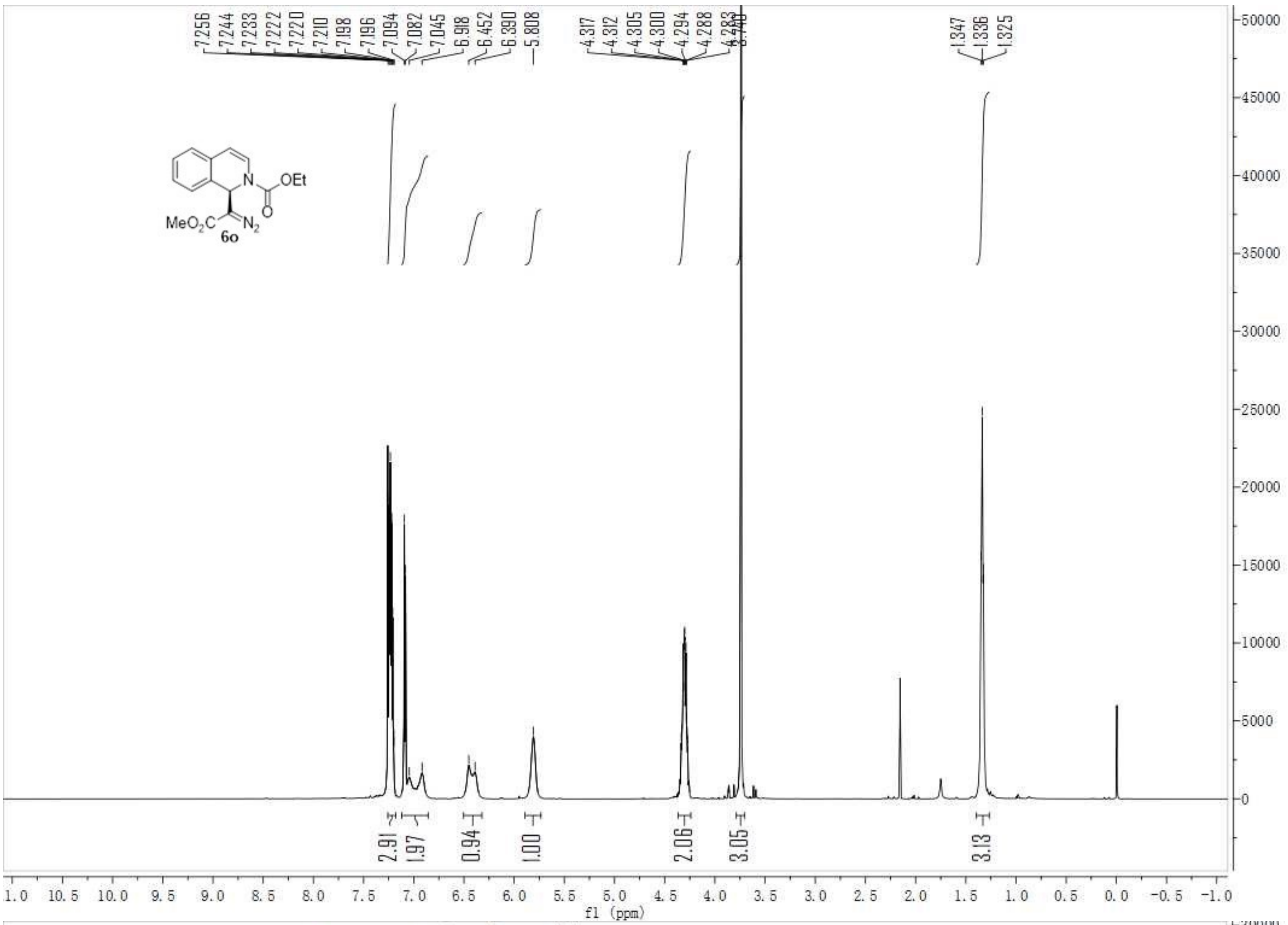
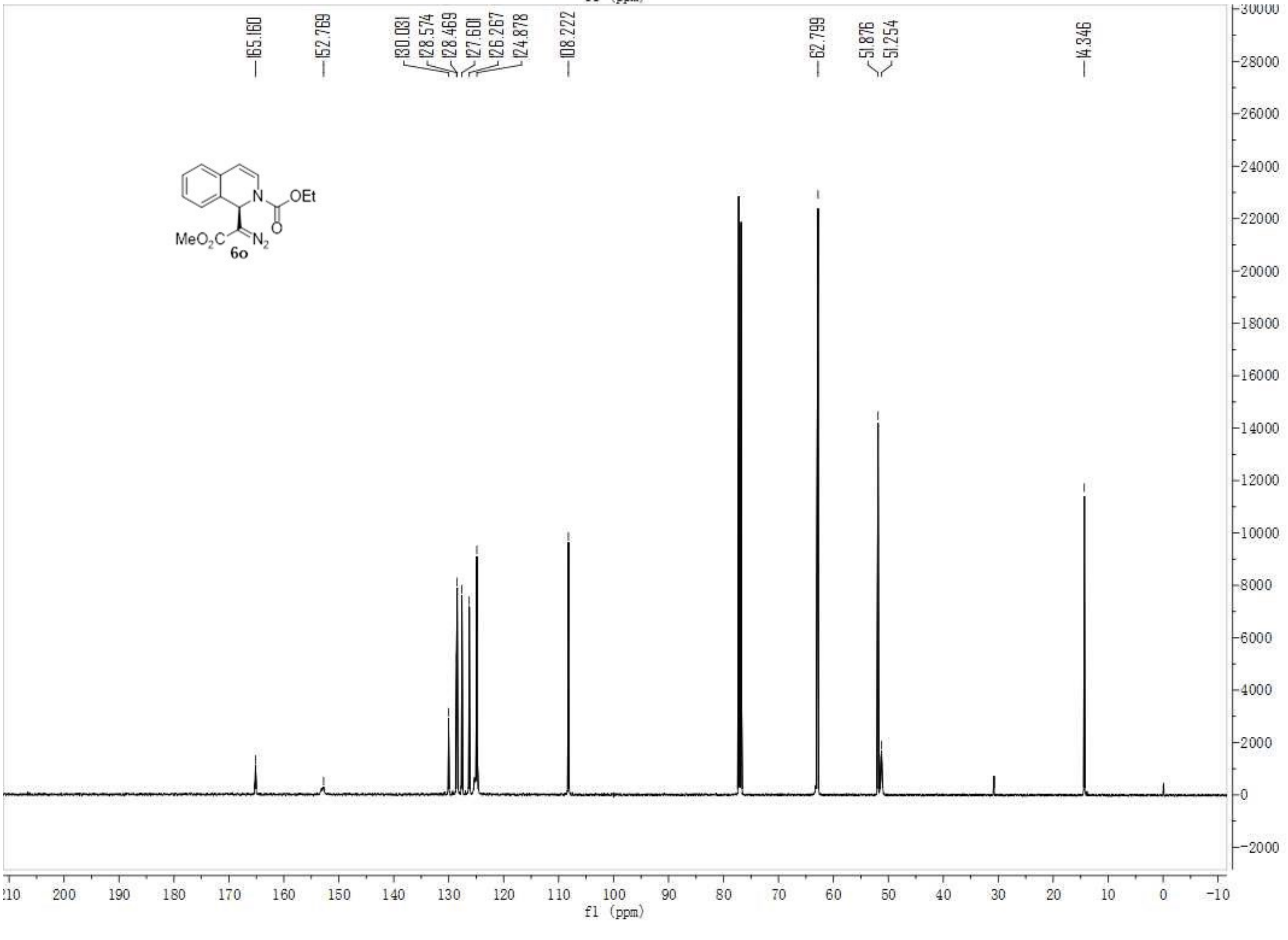
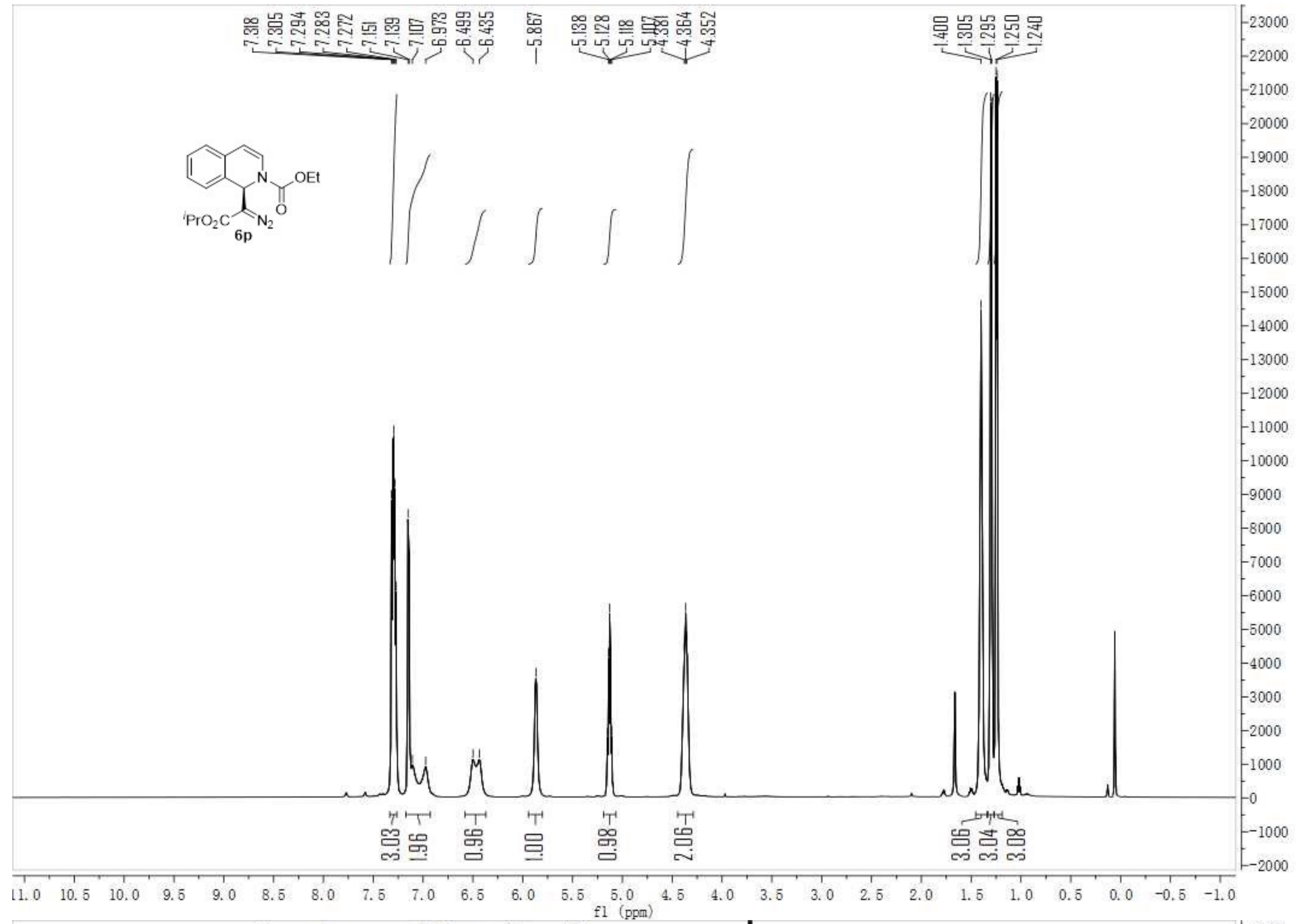
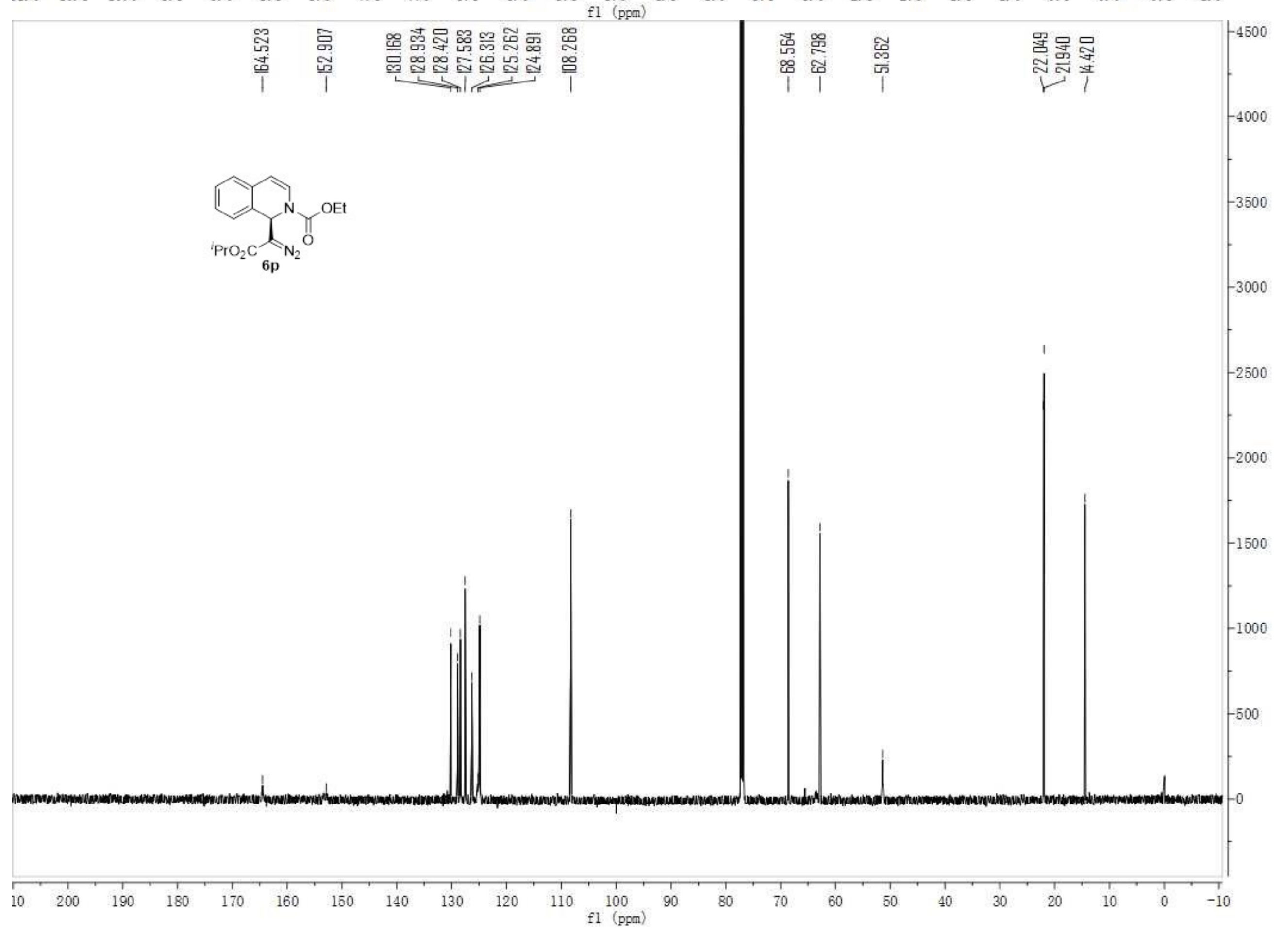
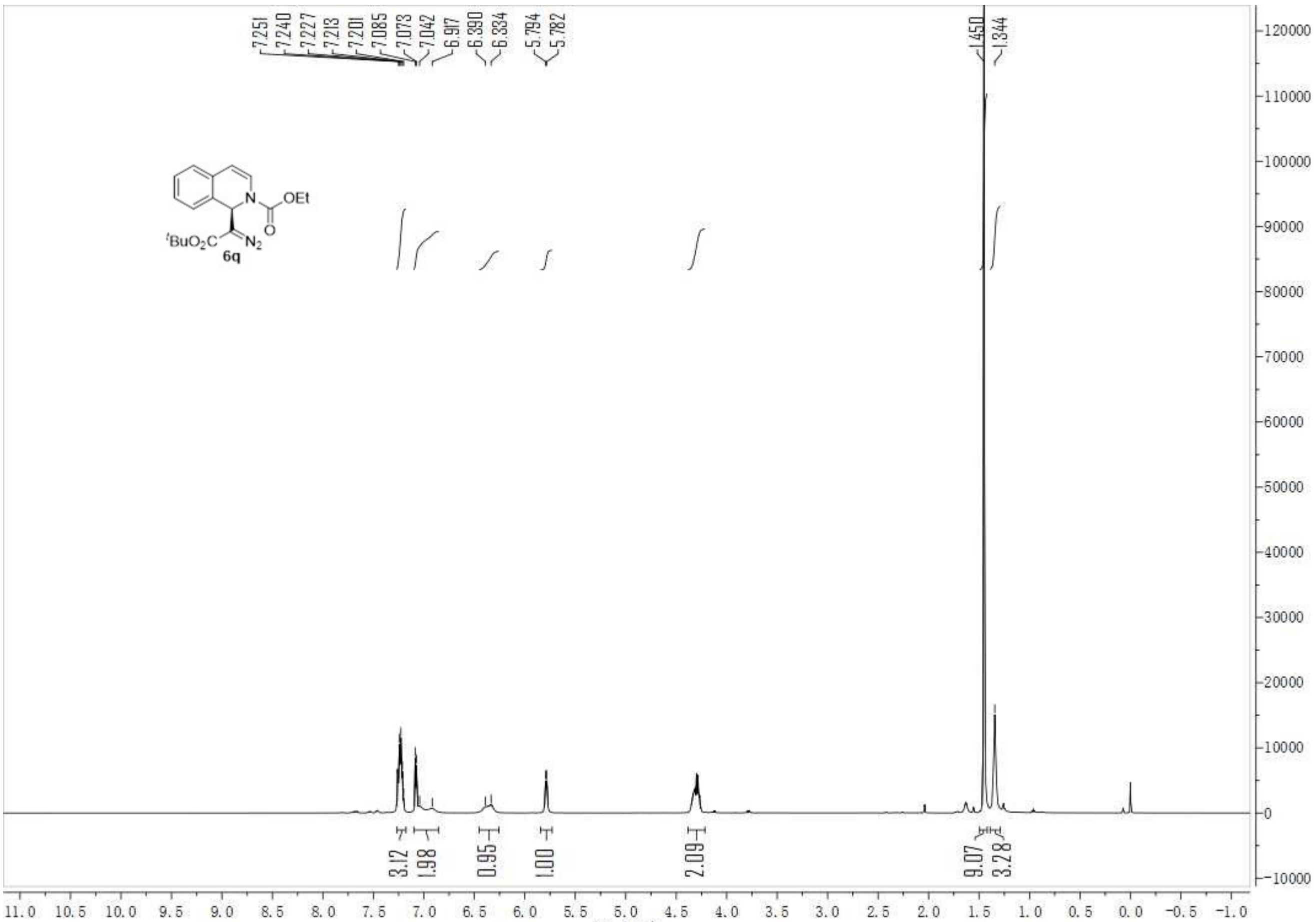
OEt
O
EtO2C
N2
6n
f1 (ppm)











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5.782
1.450
1.344
OEt
N
O
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6q
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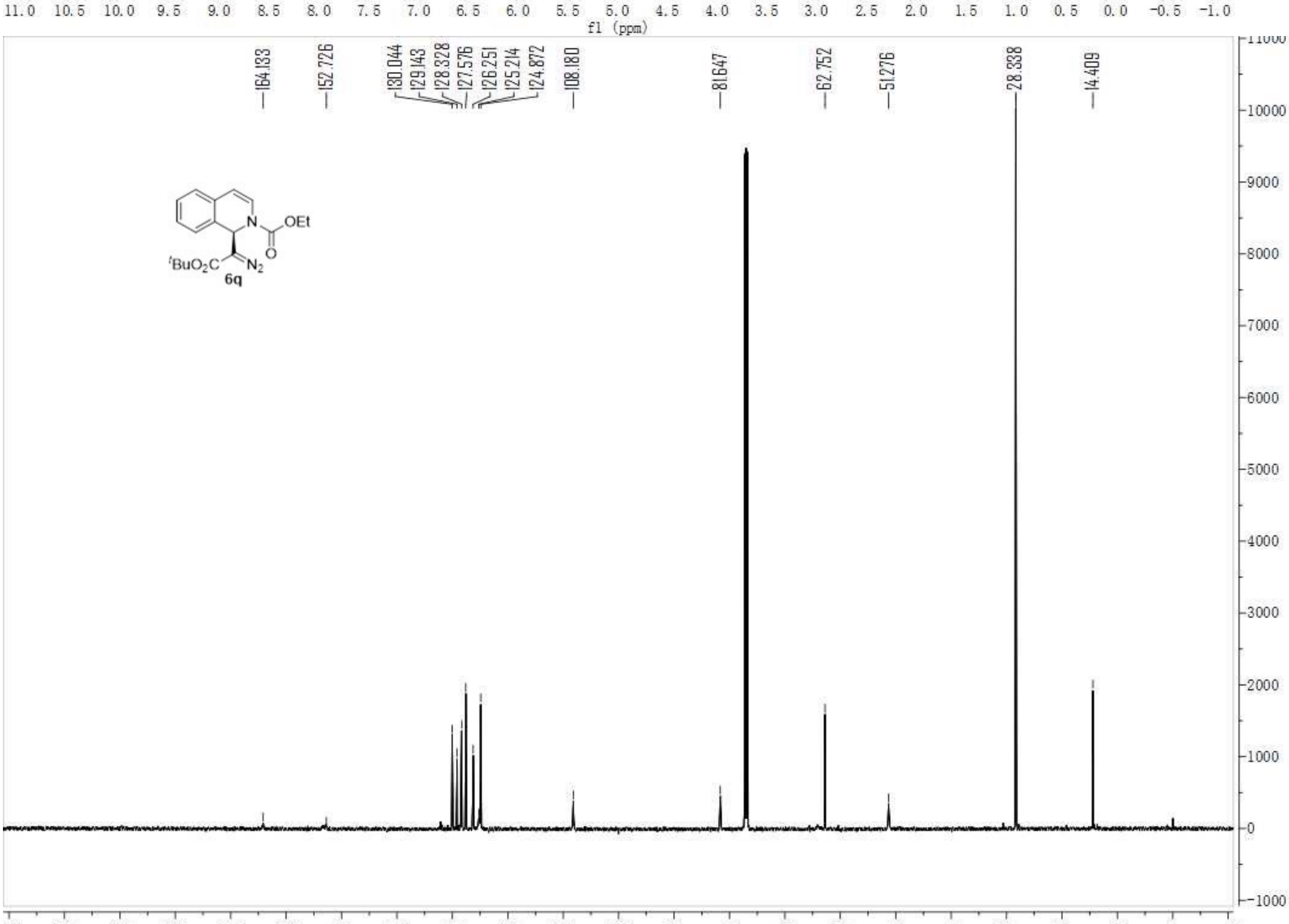
3.28
f1 (ppm)



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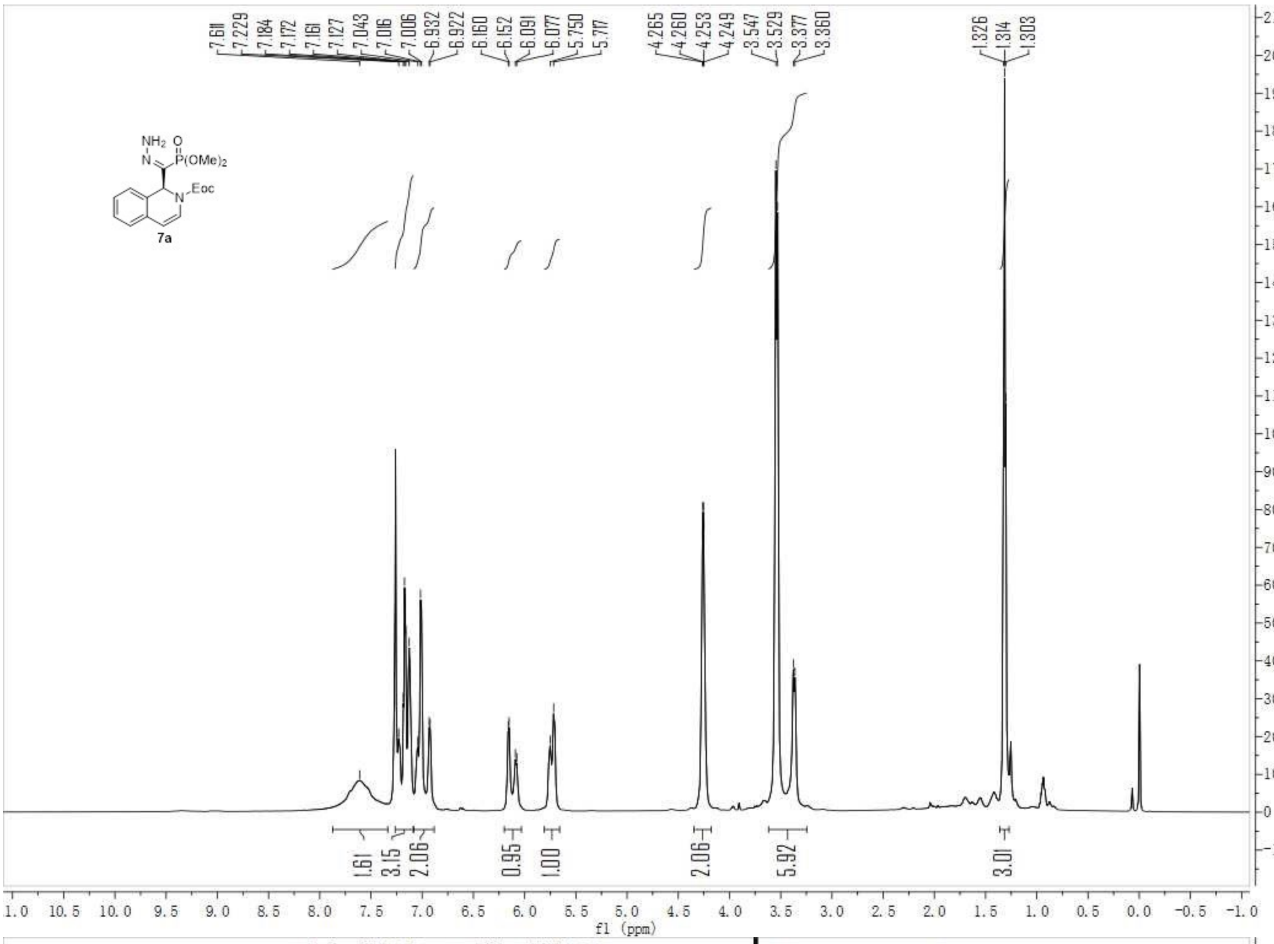
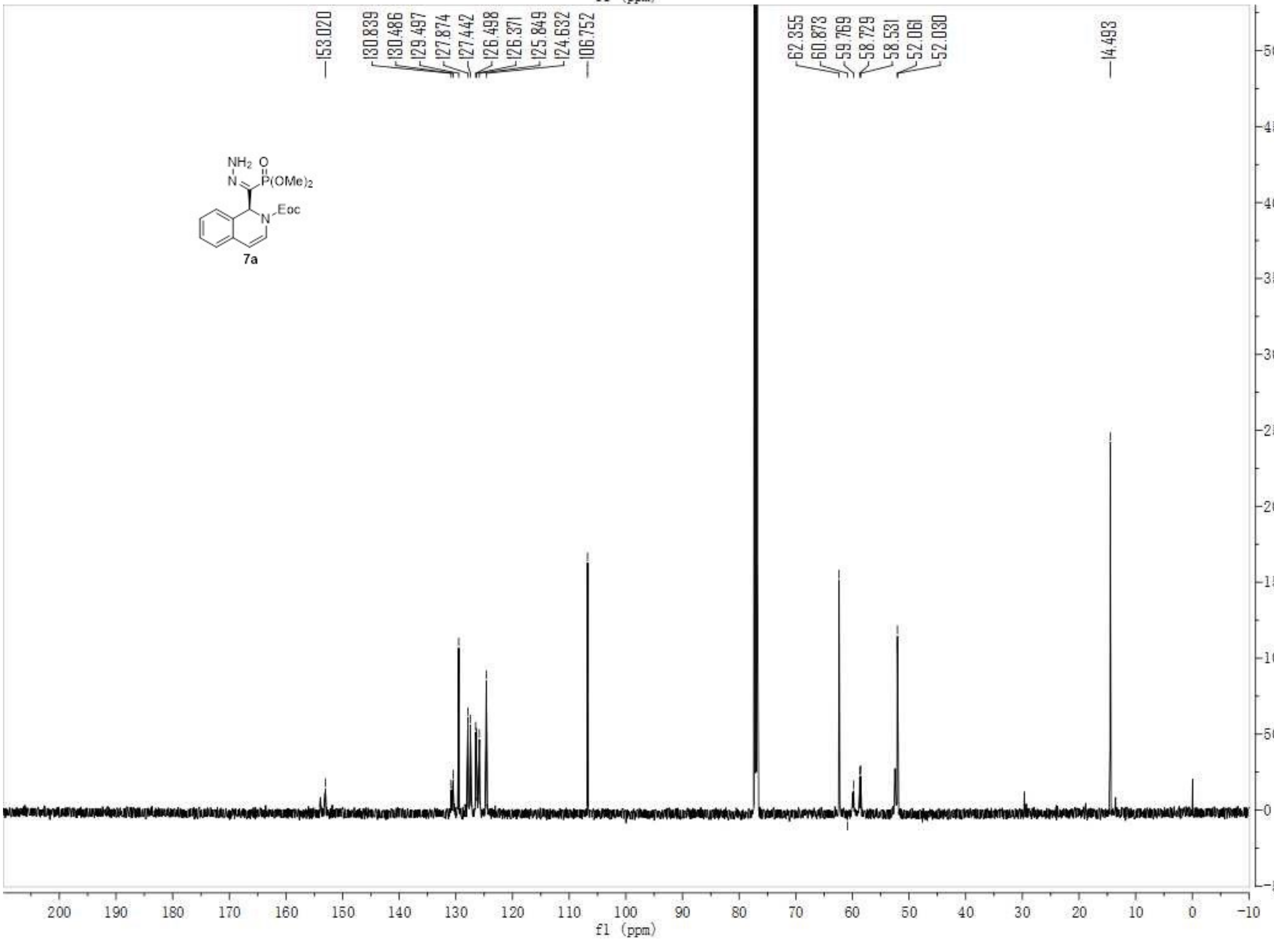
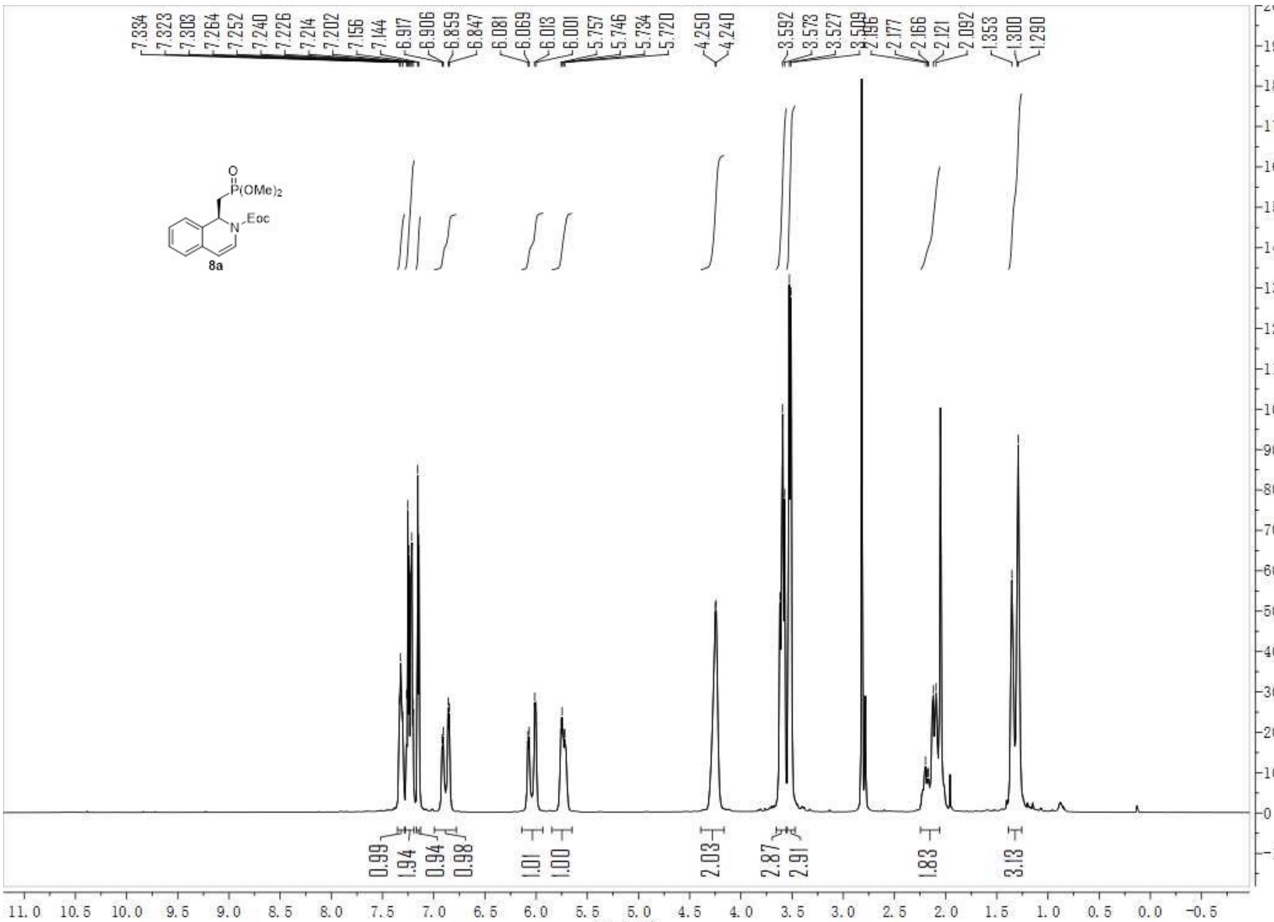
f1 (ppm)



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3.573
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2.177
2.166
2.121
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1.300
1.290
P(OMe)2
Eoc
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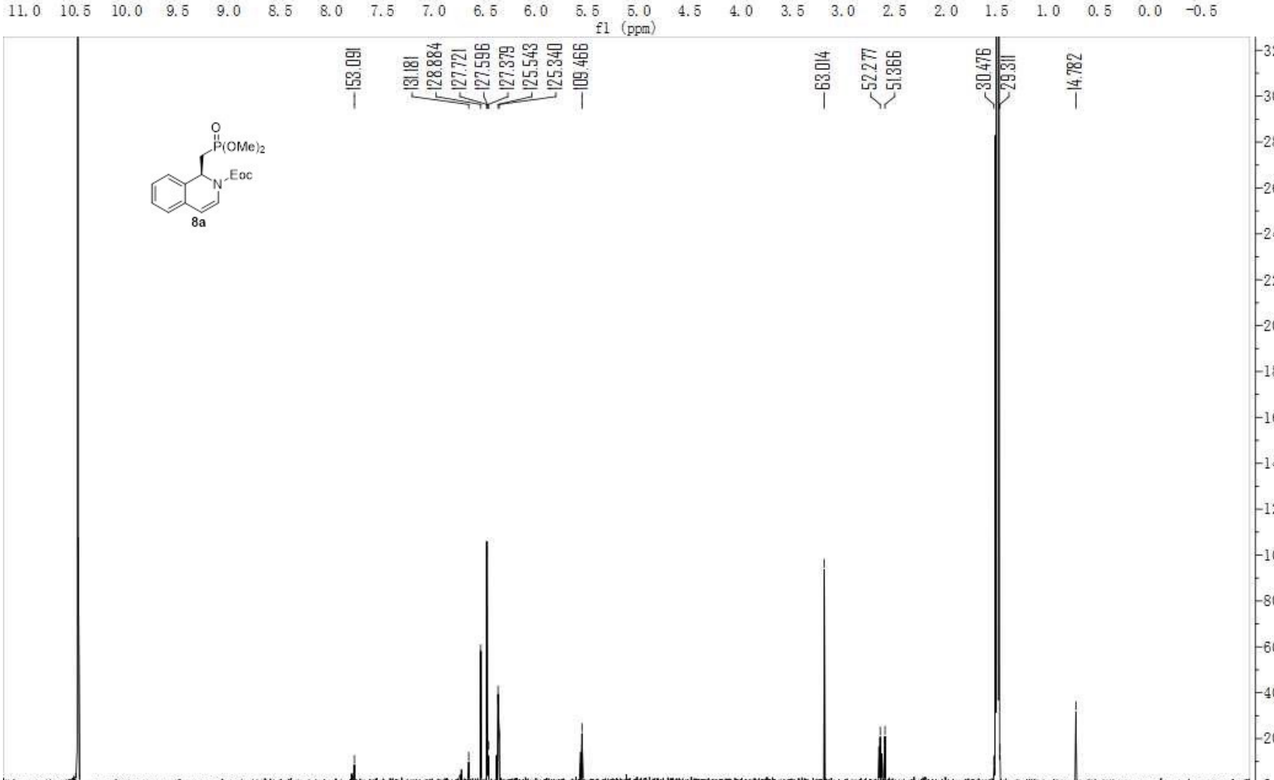
f1 (ppm)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P(OMe)2
Eoc
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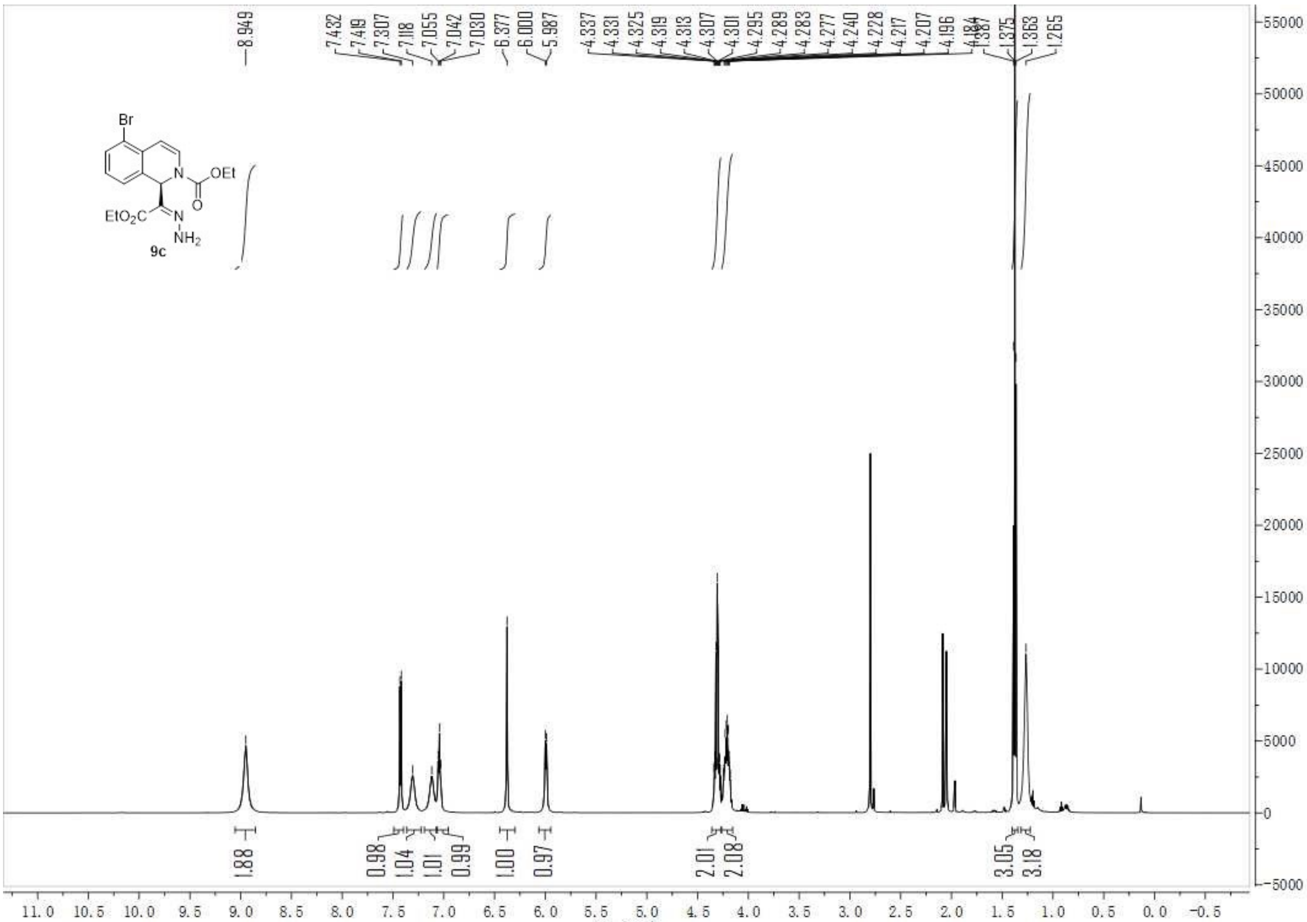
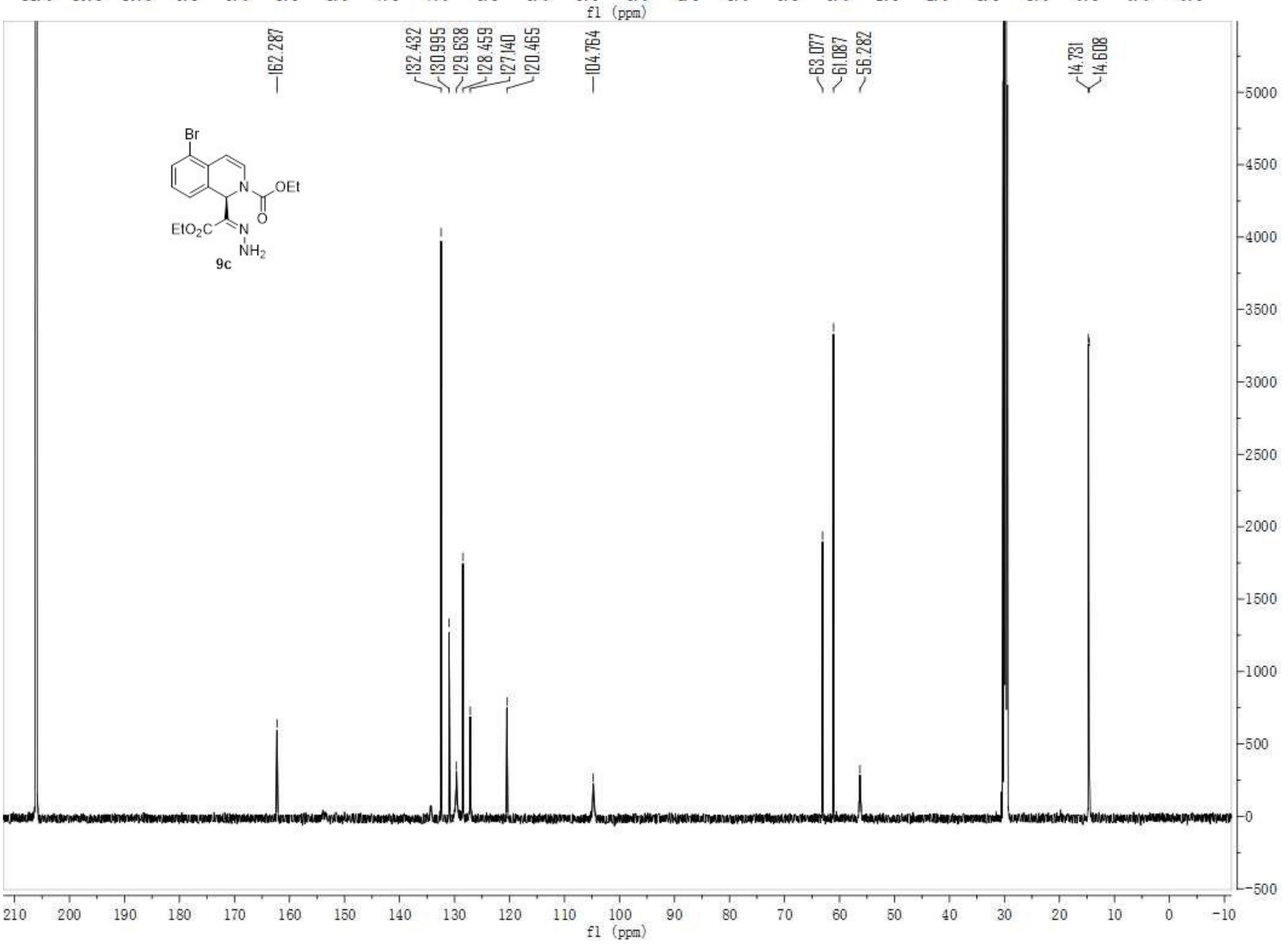
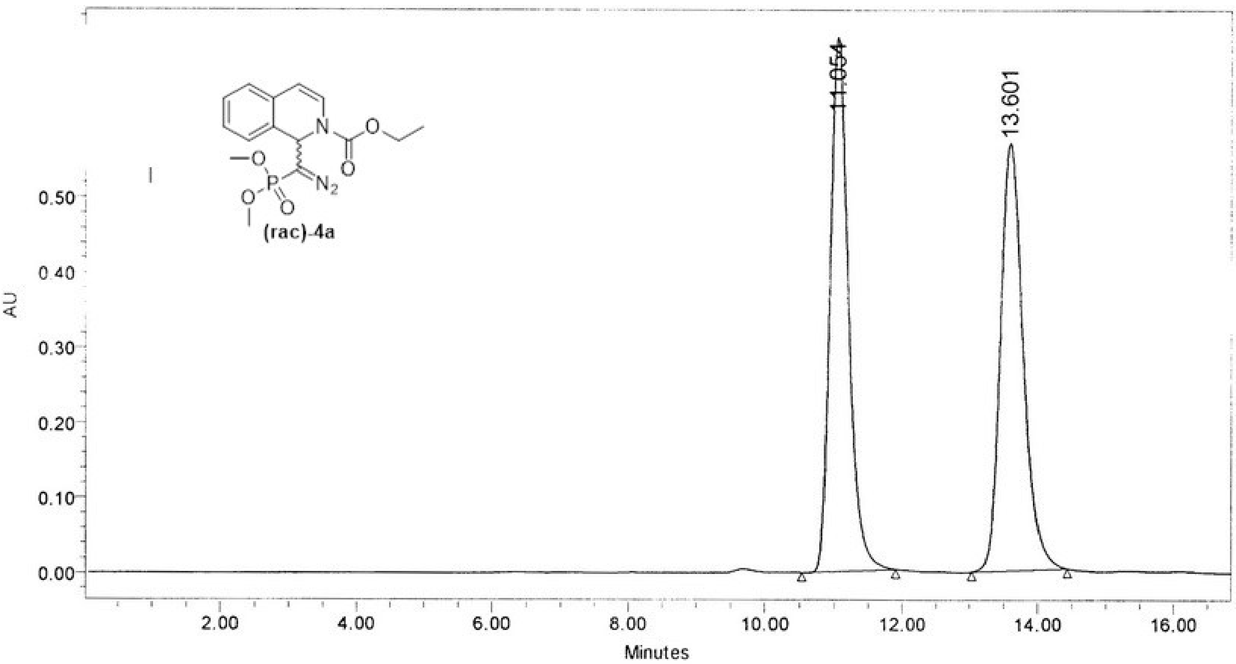
f1 (ppm)







	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
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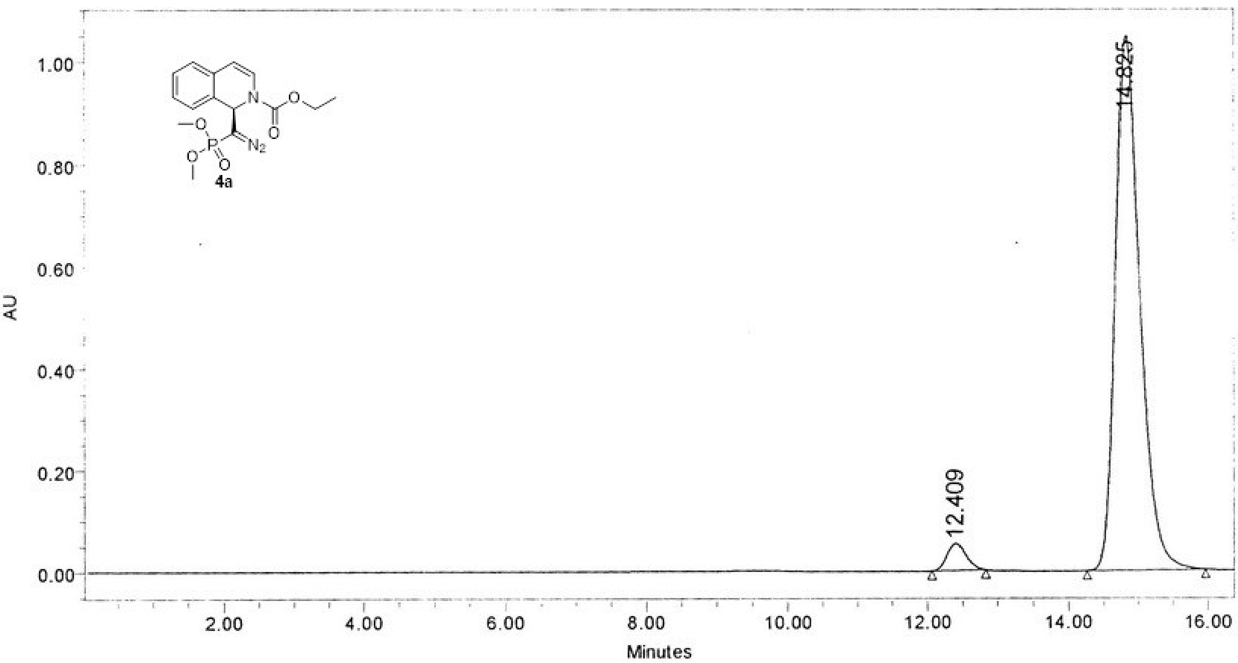
2	13.601	13304806	50.21	569822	44.52



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
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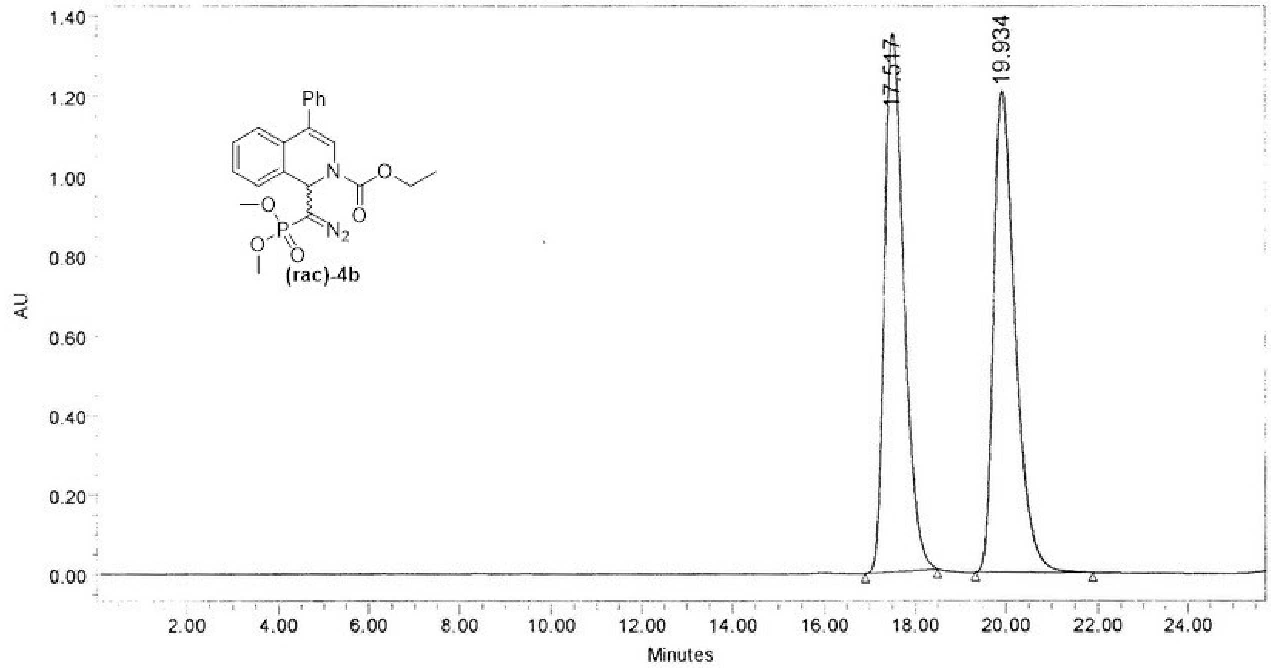
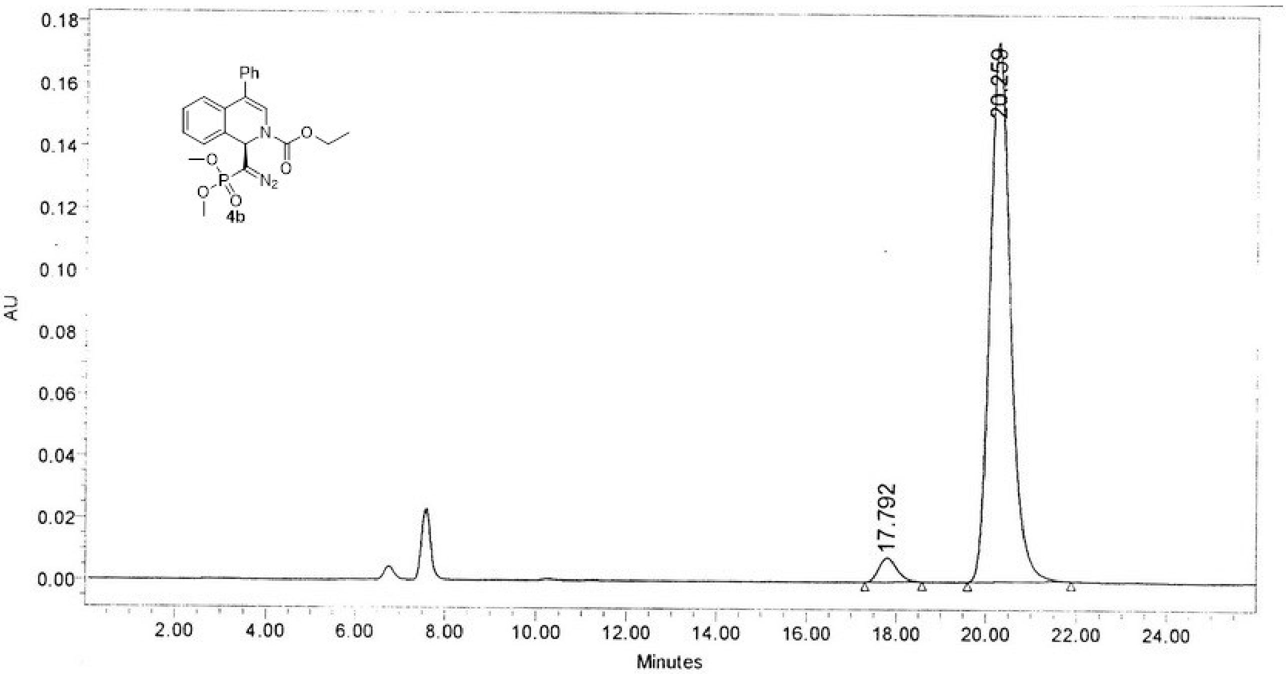
2	14.825	25599217	96.25	1048642	95.14



	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	17.517	39999054	50.11	1351118	52.75
2	19.934	39825023	49.89	1210460	47.25



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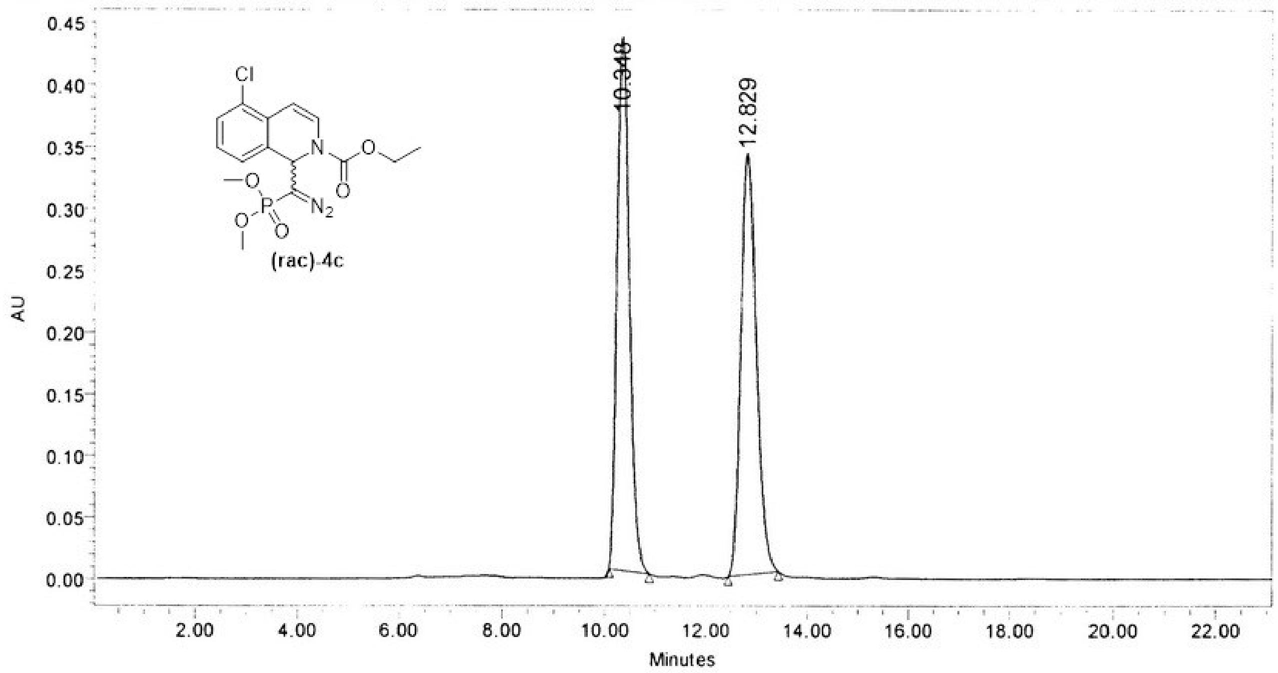

	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
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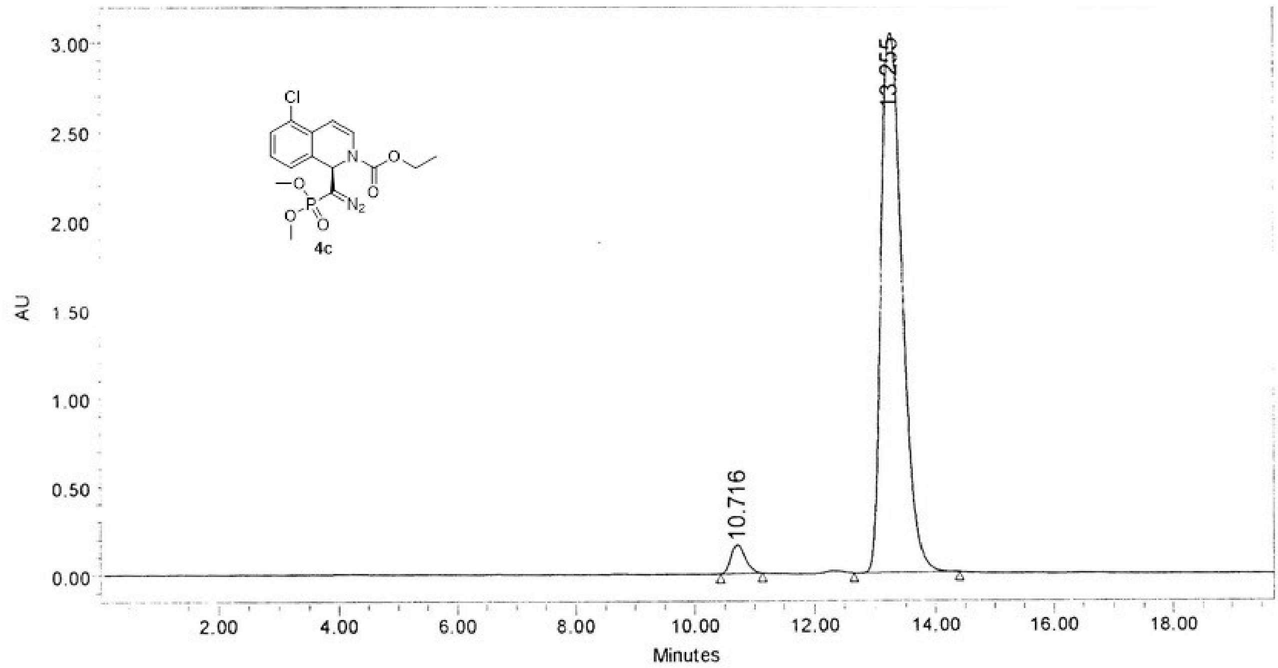
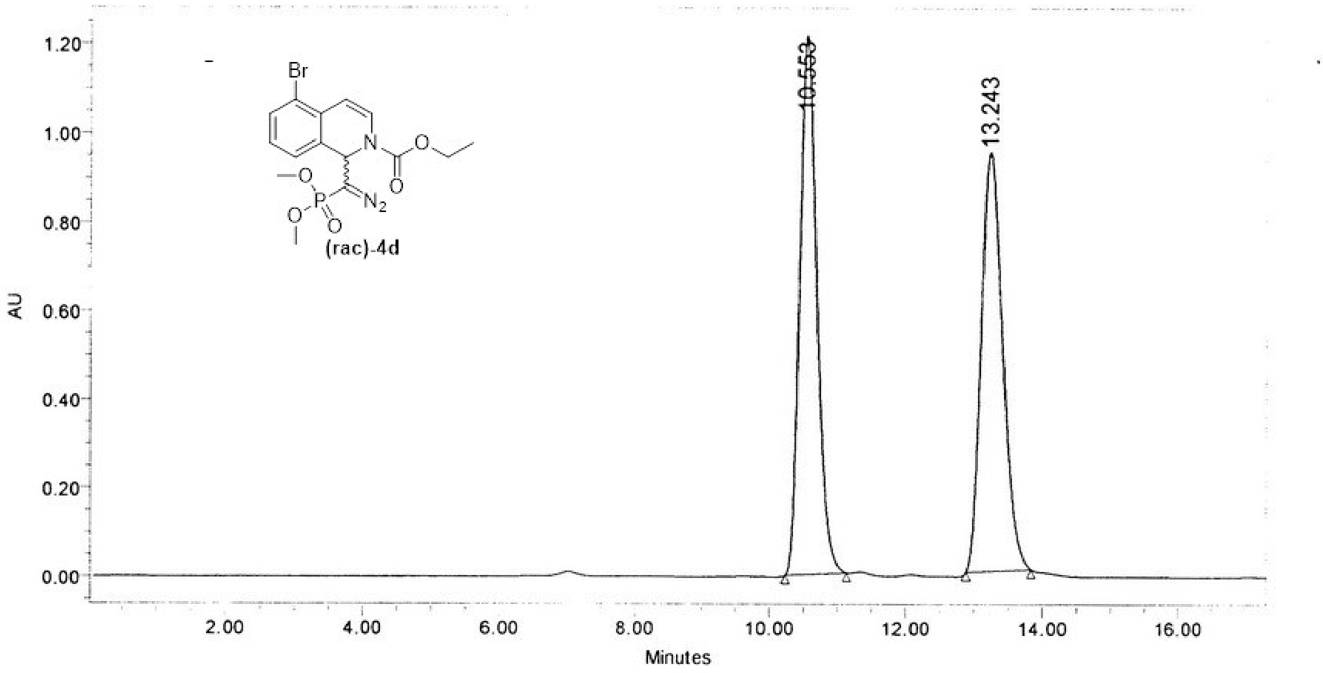
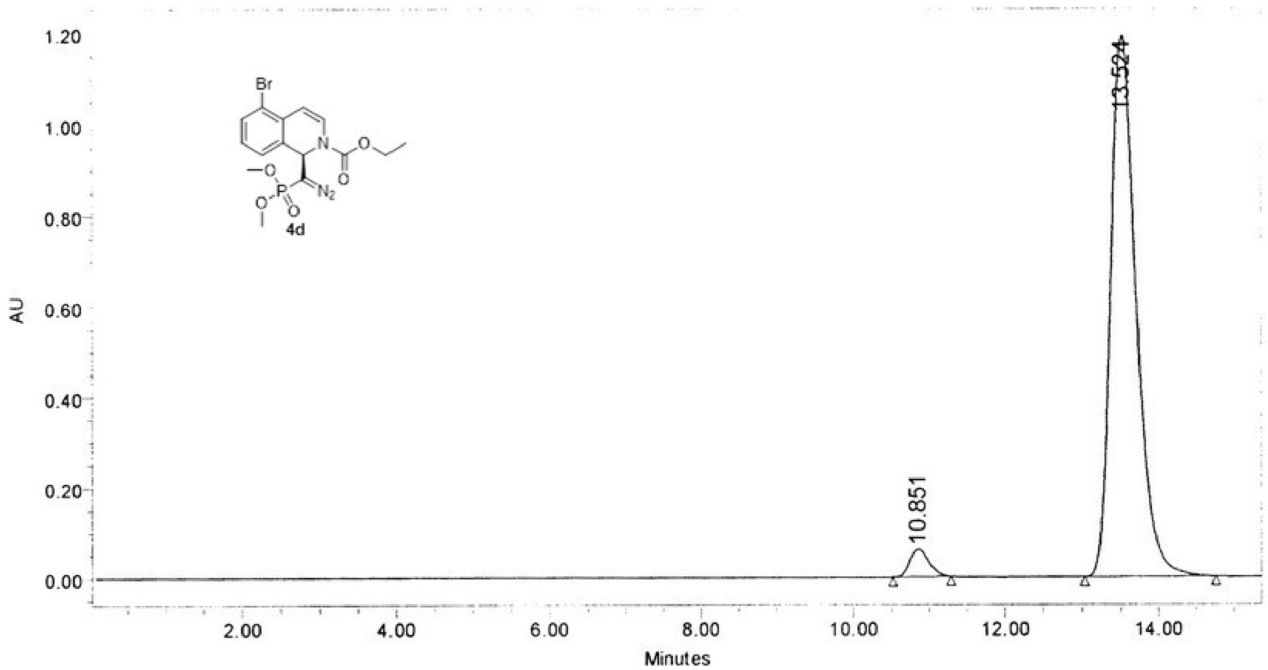


	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	10.716	2701230	3.53	161159	5.03
2	13.255	73774243	96.47	3040776	94.97



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	10.553	21075258	50.59	1214532	56.18
2	13.243	20579773	49.41	947423	43.82



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
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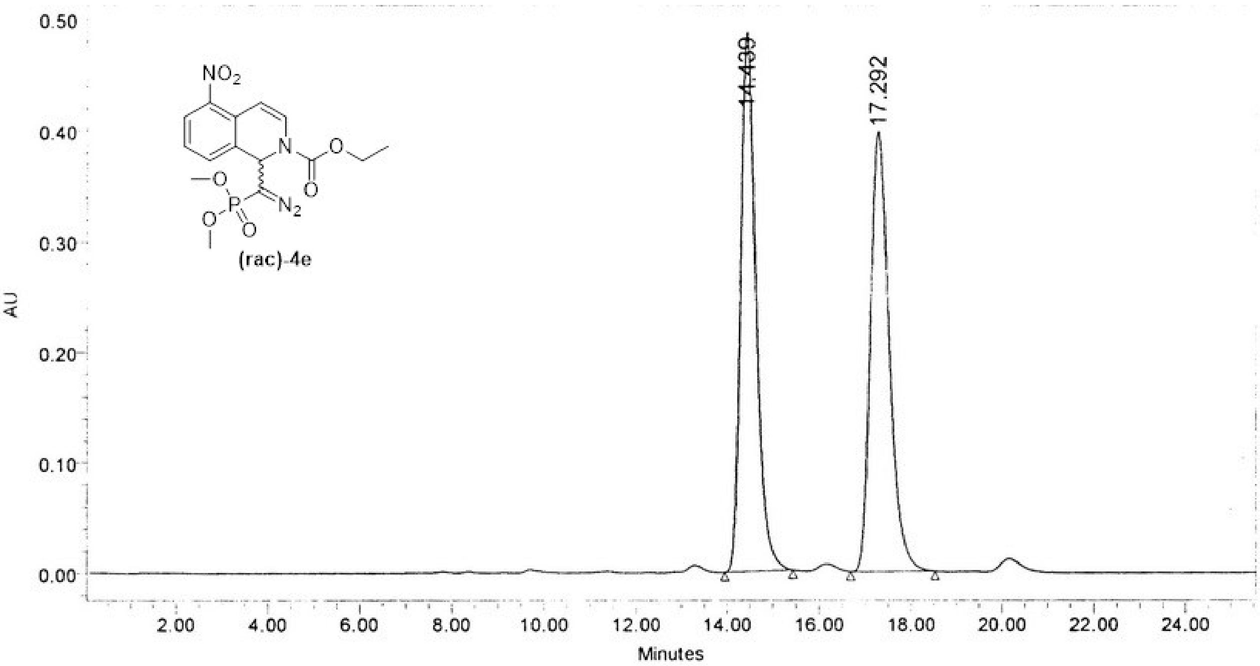
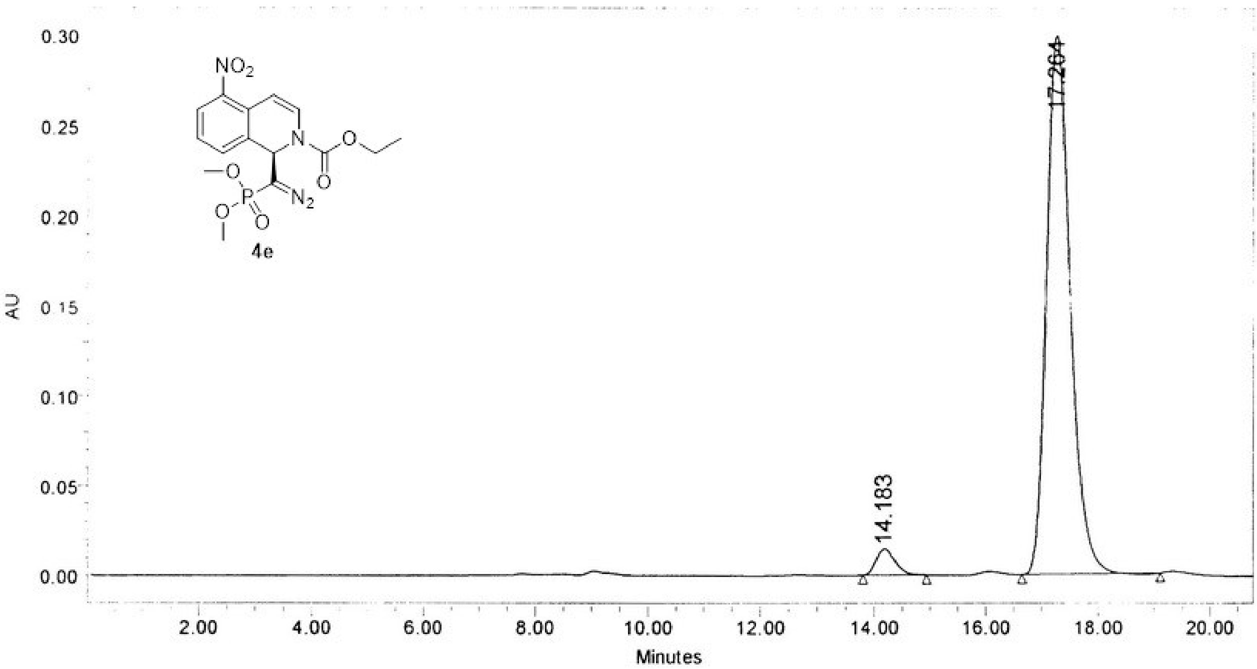
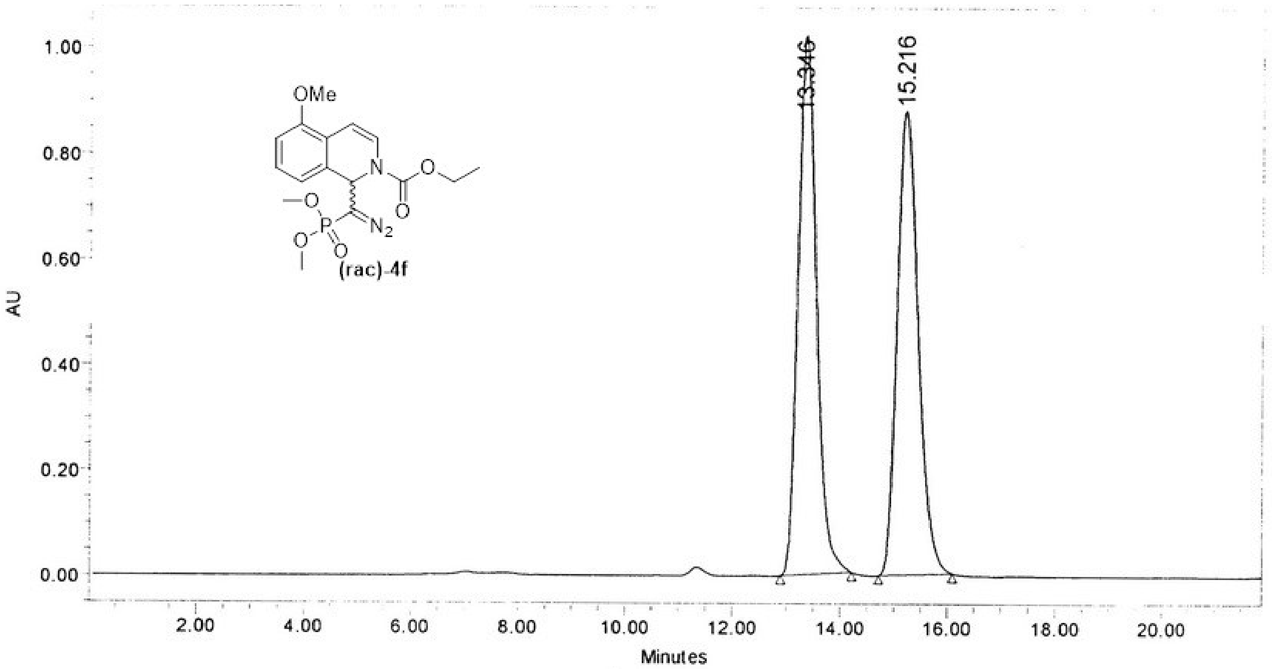
2	13.524	27679184	96.27	1193869	95.11



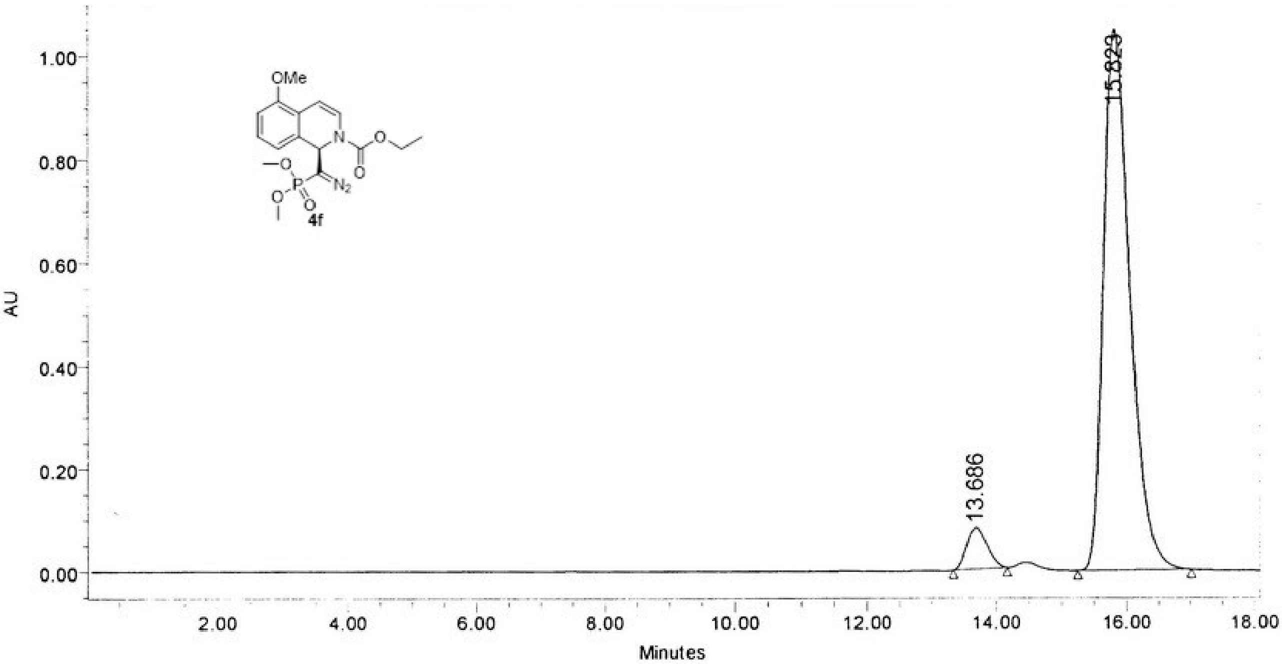
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	14.439	11312528	50.06	487374	55.01
2	17.292	11287424	49.94	398636	44.99



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	14.183	339604	3.74	14573	4.64
2	17.264	8741220	96.26	299416	95.36



	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	13.346	24253423	50.15	1022125	53.73
2	15.216	24108178	49.85	880314	46.27



	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
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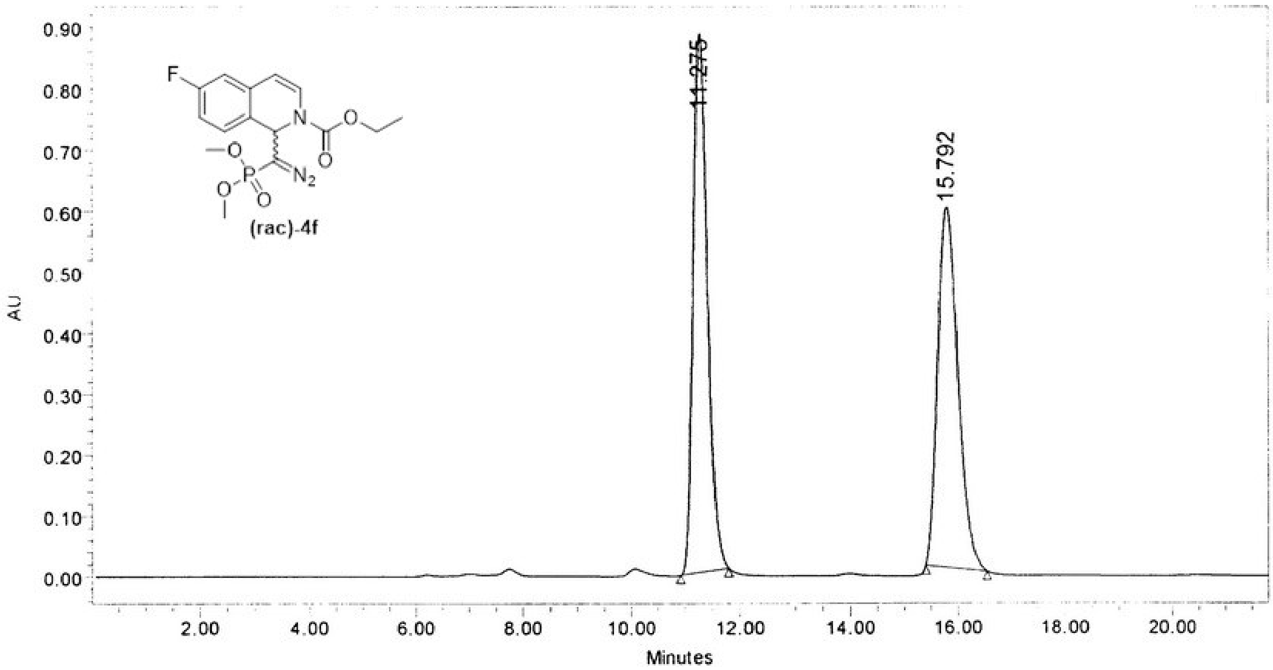
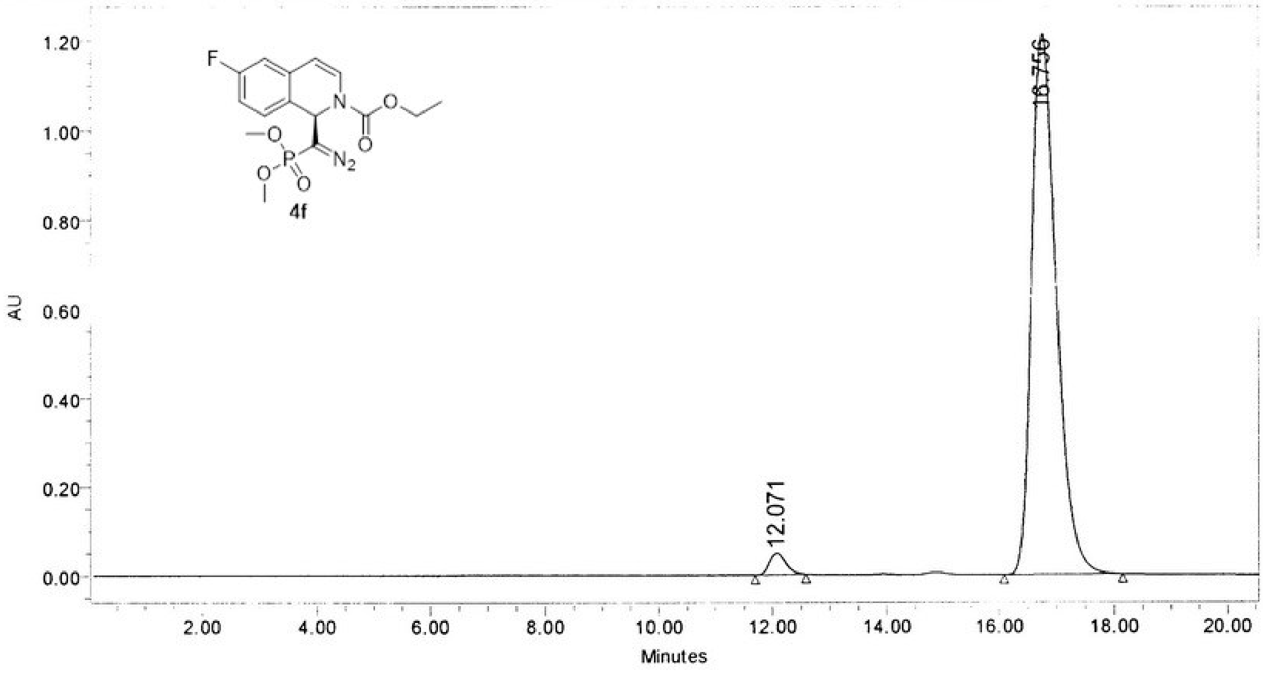
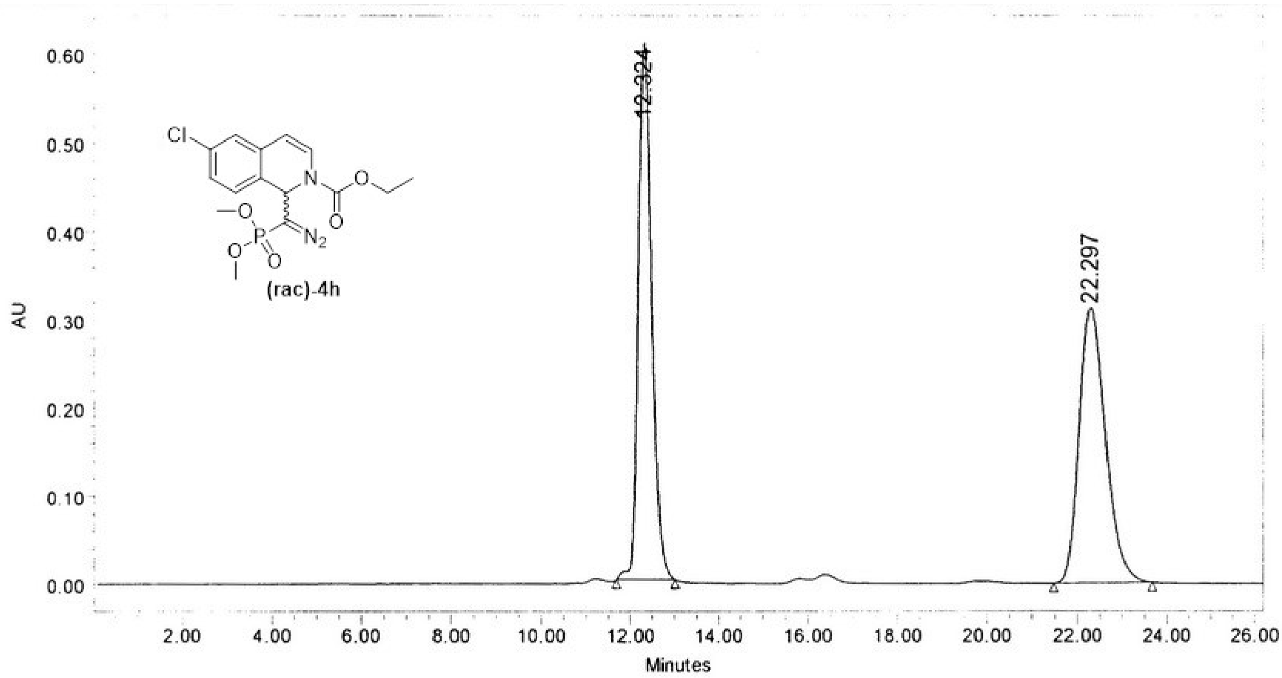
2	15.823	29869425	94.42	1048852	92.88



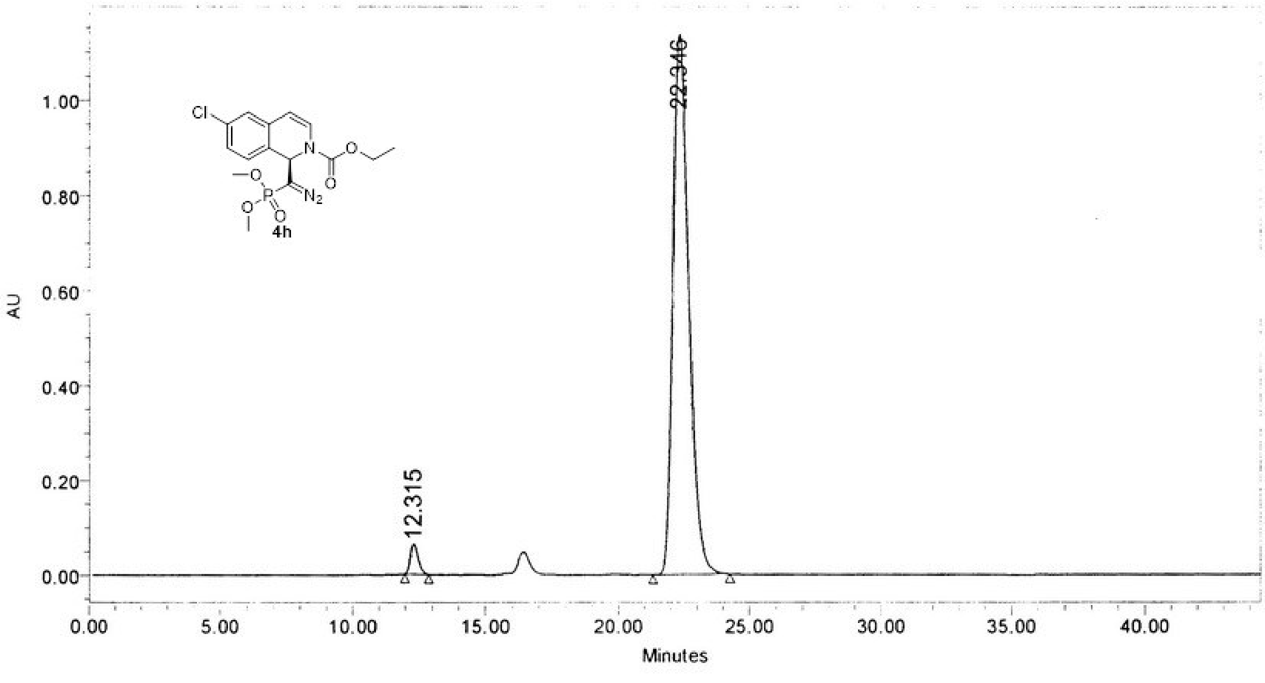
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	11.275	15991773	50.53	884588	59.87
2	15.792	15657718	49.47	592980	40.13



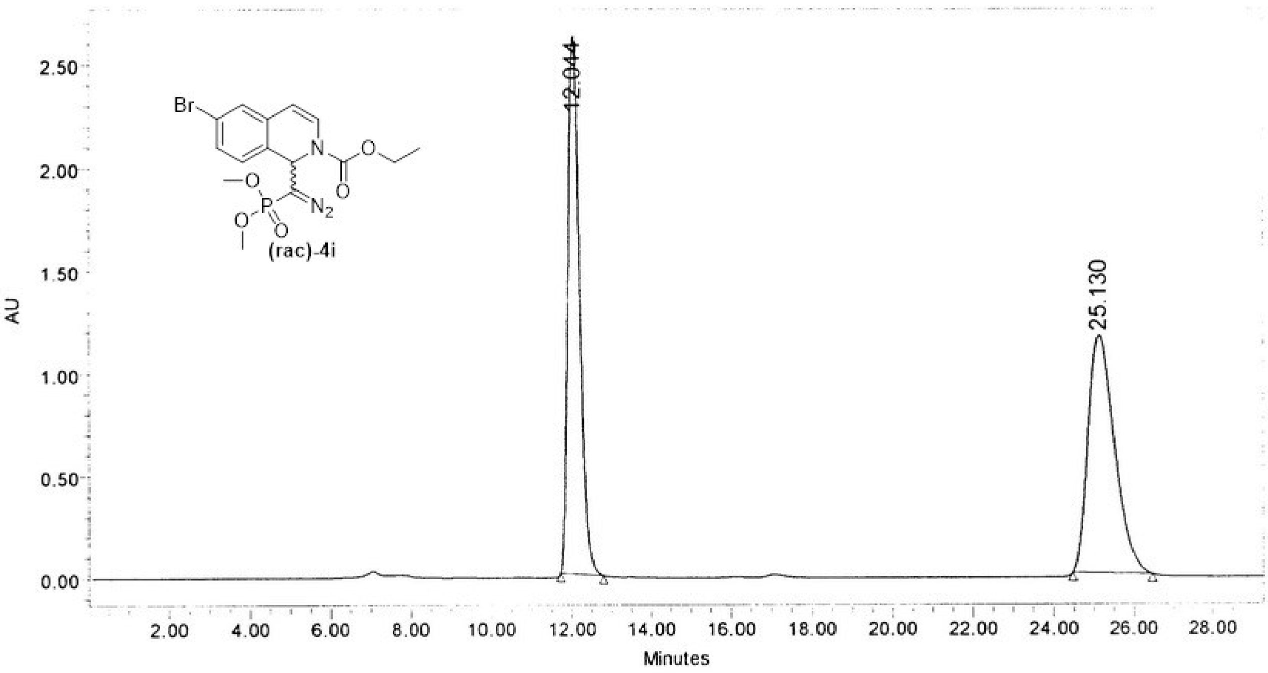
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	12.071	958661	2.59	48424	3.84
2	16.756	36053163	97.41	1213574	96.16



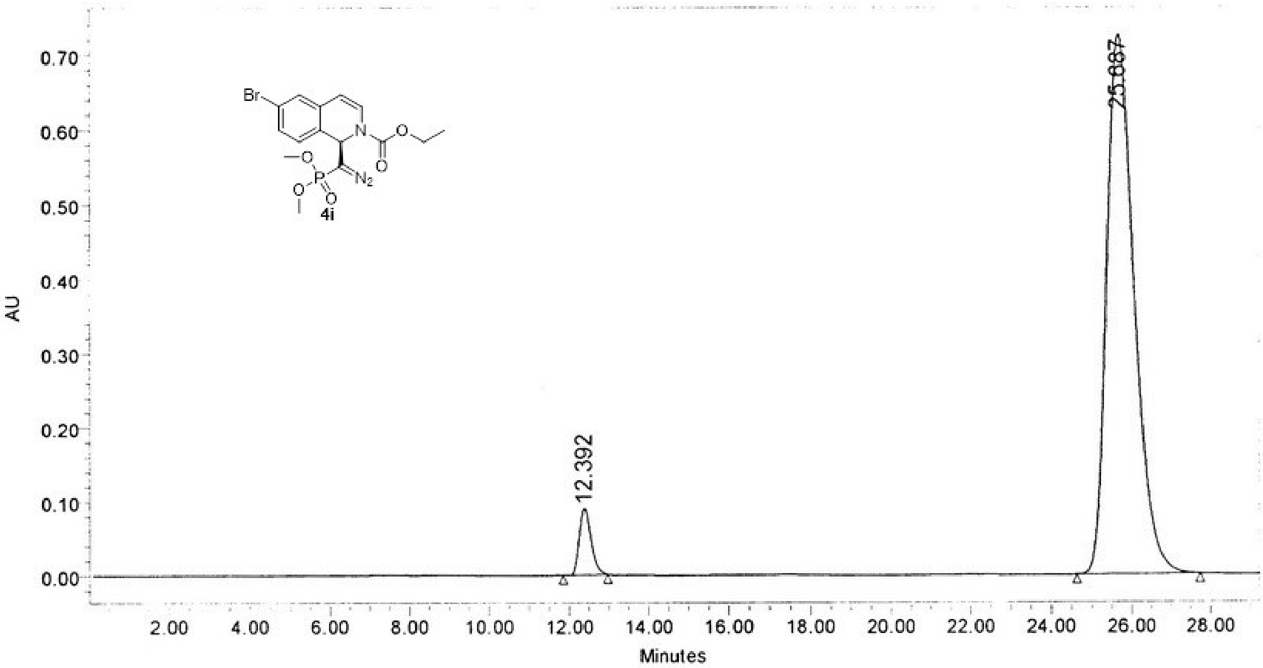
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	12.324	12654519	49.93	608416	66.08
2	22.297	12688128	50.07	312298	33.92



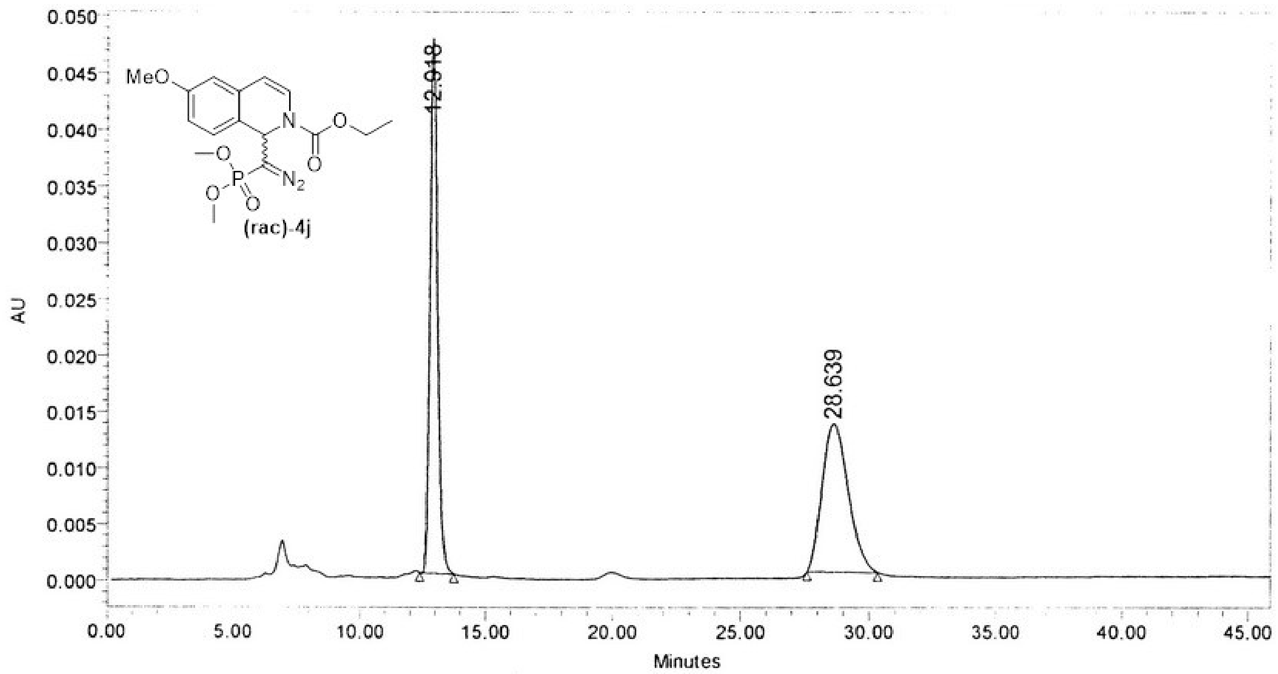
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	12.315	1275955	2.59	63506	5.29
2	22.346	47979687	97.41	1137018	94.71



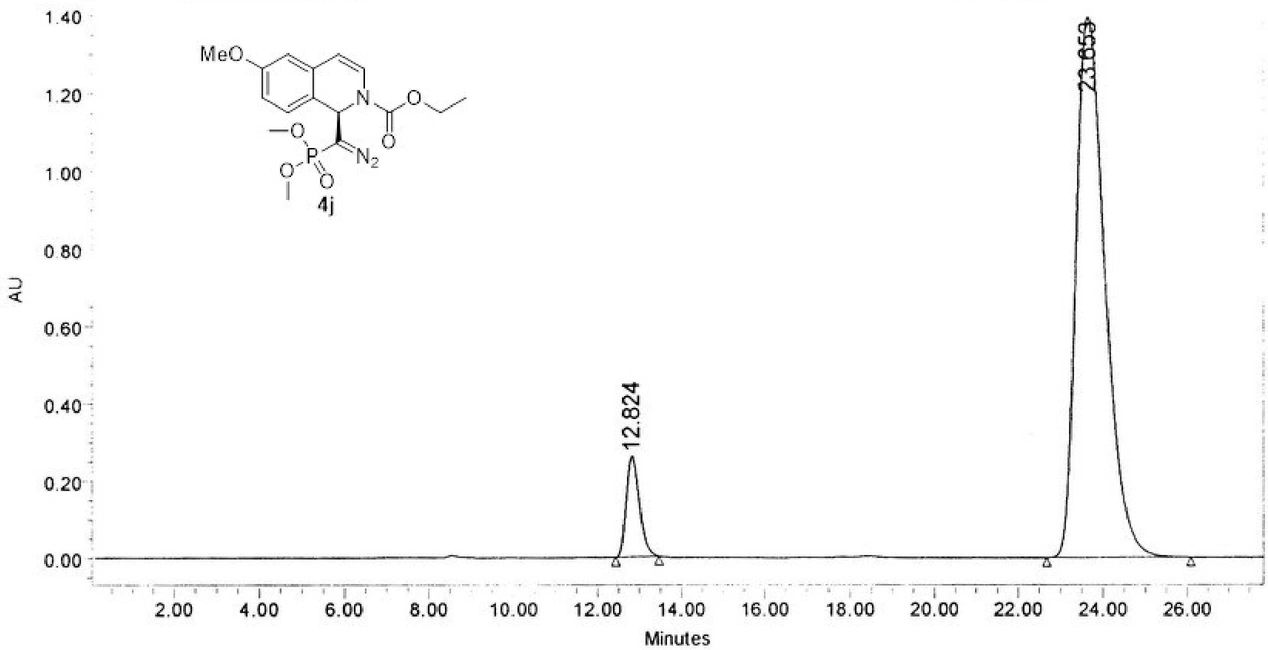
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	12.044	53157029	49.71	2615496	69.29
2	25.130	53767155	50.29	1159302	30.71



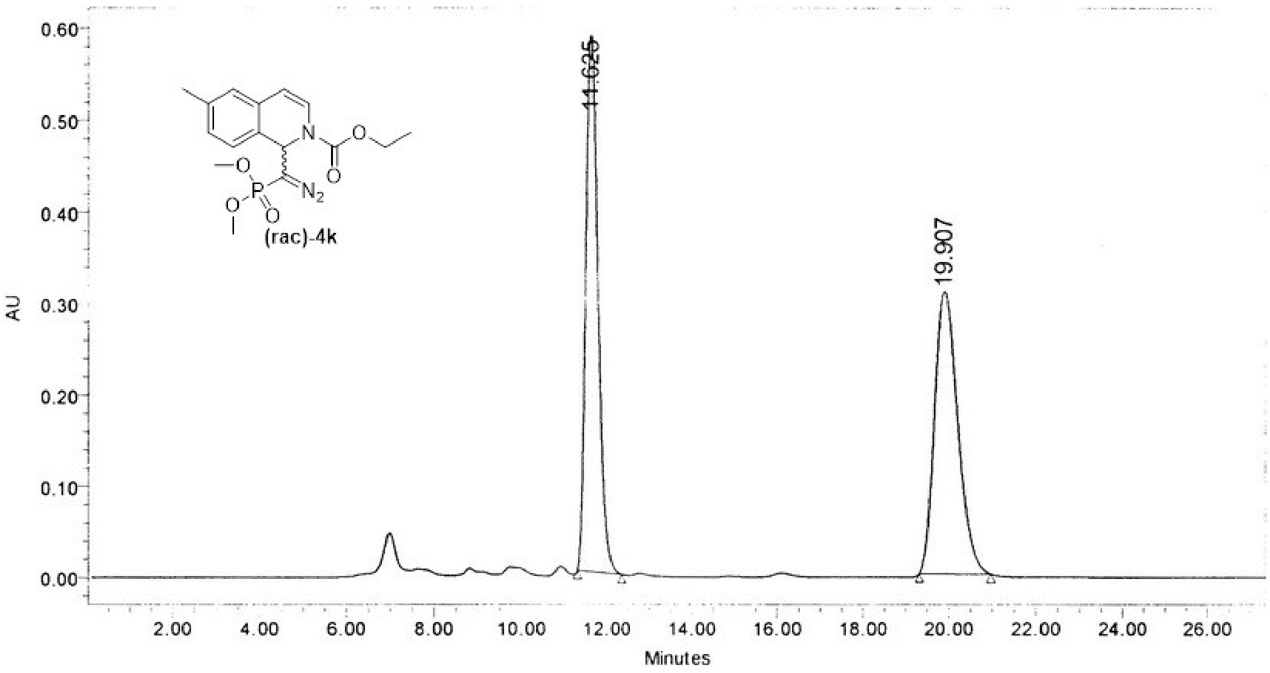
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	12.392	1819405	4.98	89553	10.98
2	25.687	34745156	95.02	725987	89.02



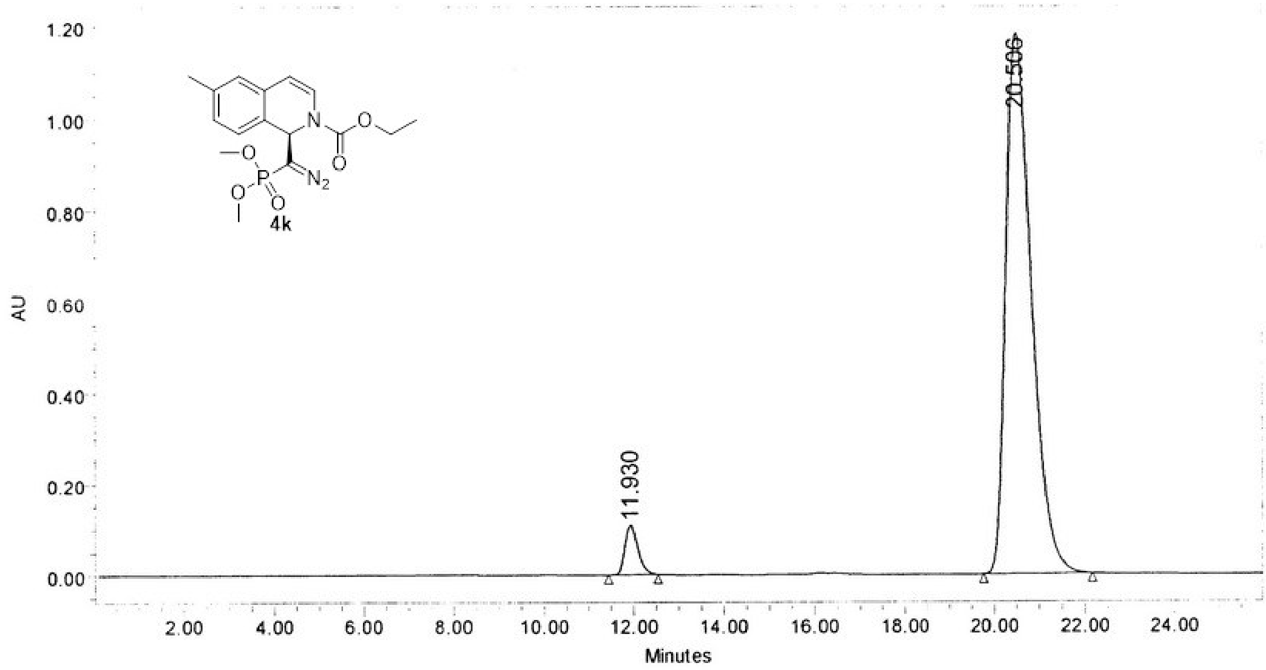
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	12.918	1013269	52.20	47338	78.23
2	28.639	927761	47.80	13173	21.77



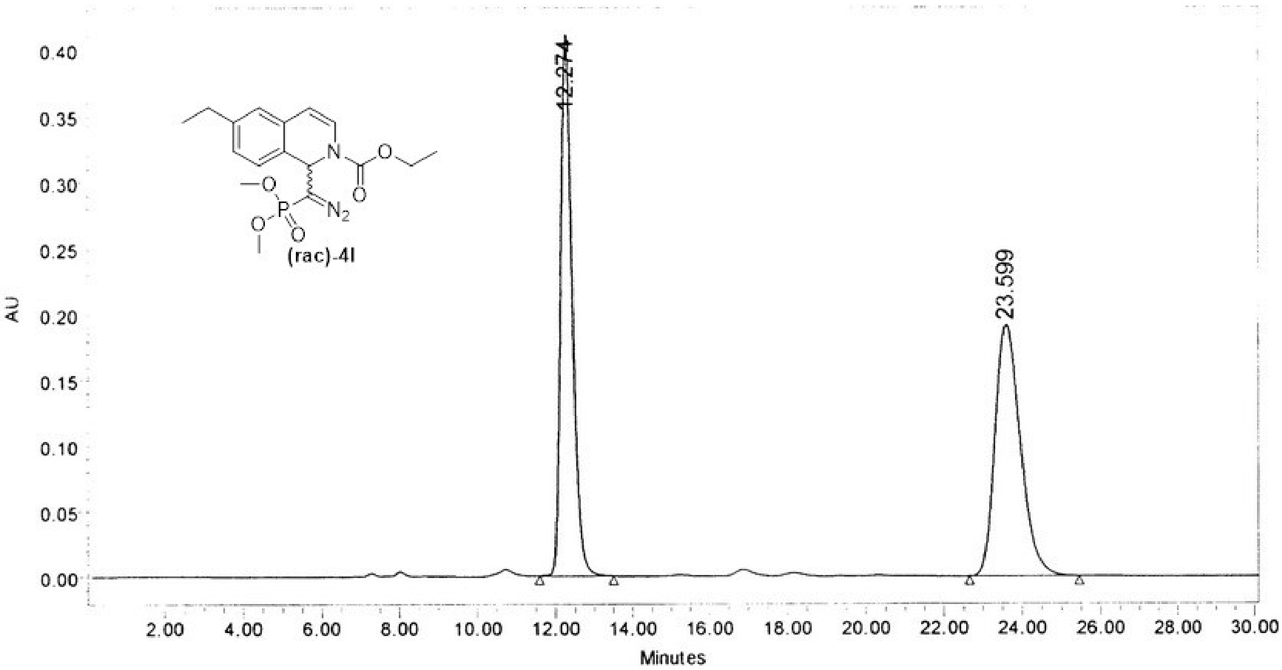
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	12.824	5703693	7.97	261177	15.77
2	23.653	65882670	92.03	1395001	84.23



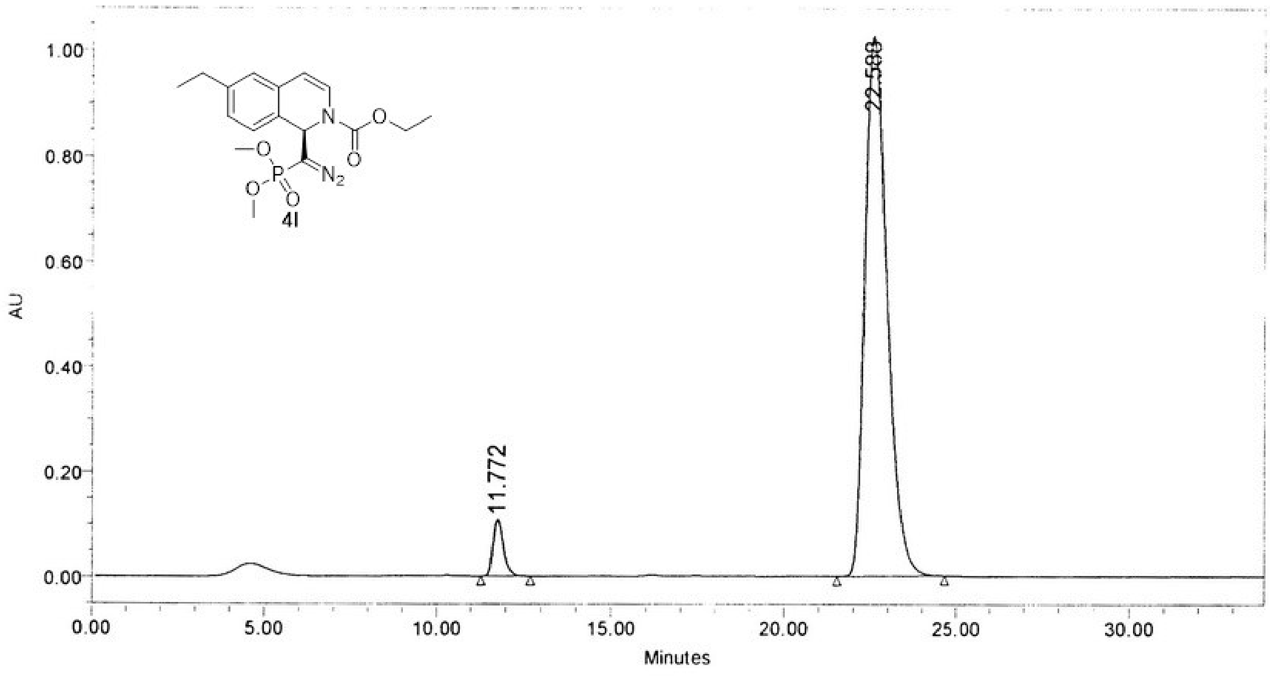
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	11.625	11674668	50.26	587484	65.47
2	19.907	11555853	49.74	309824	34.53



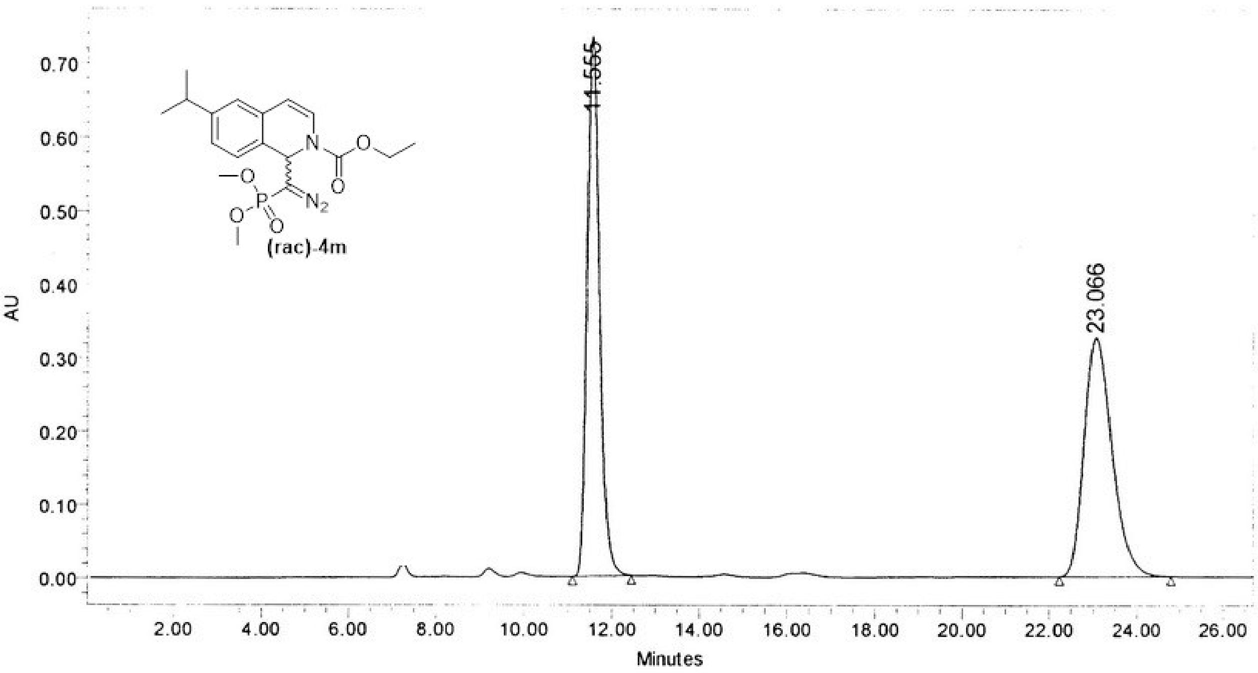
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	11.930	2183601	4.48	108976	8.44
2	20.506	46578094	95.52	1182839	91.56



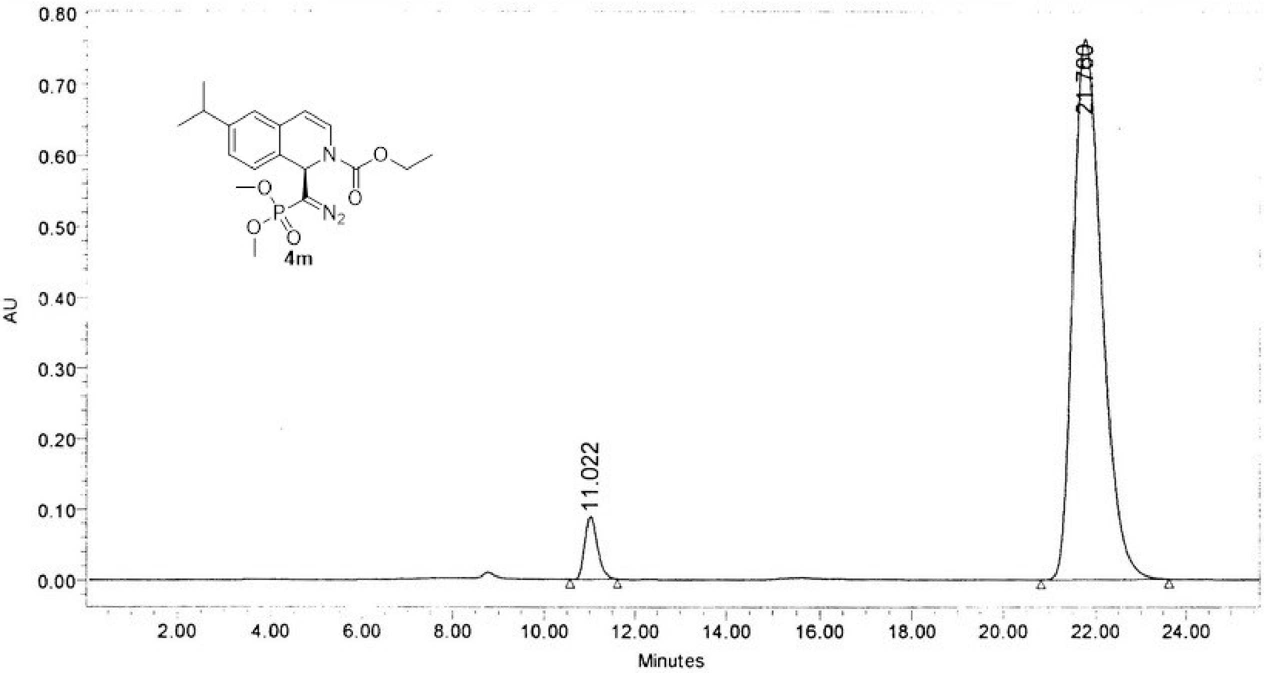
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	12.274	8627774	50.02	411151	68.22
2	23.599	8621528	49.98	191569	31.78



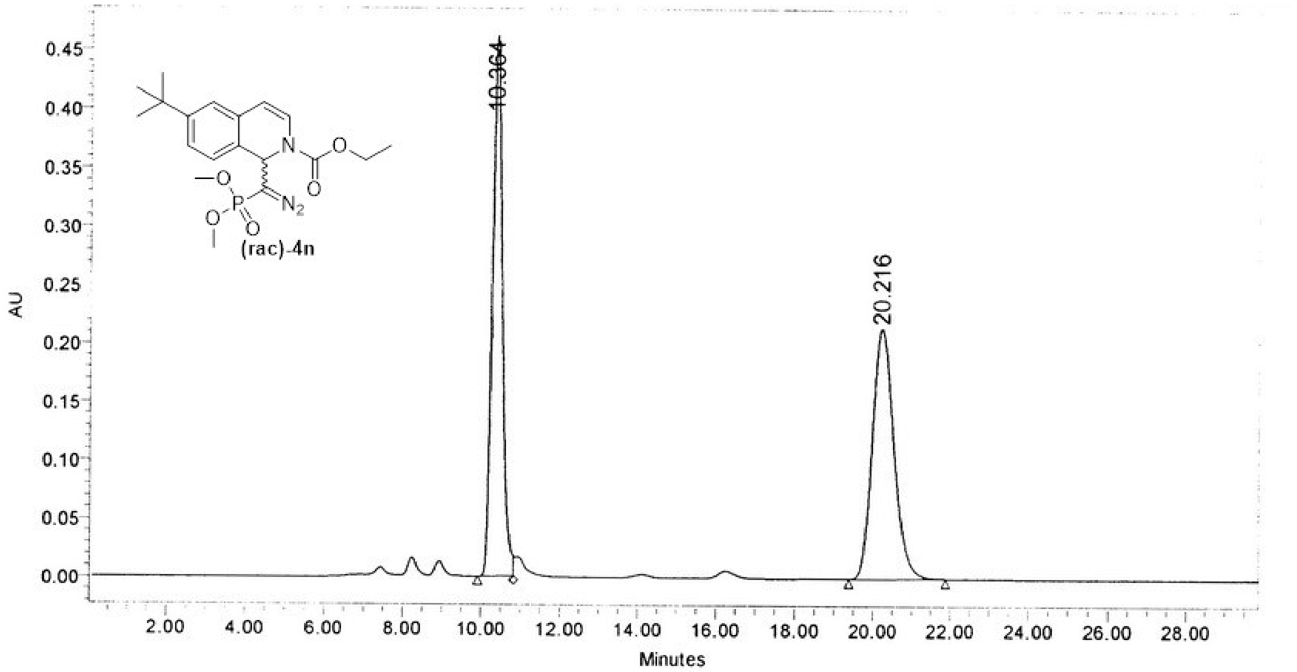
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	11.772	2233014	4.63	108058	9.53
2	22.588	46024133	95.37	1025979	90.47



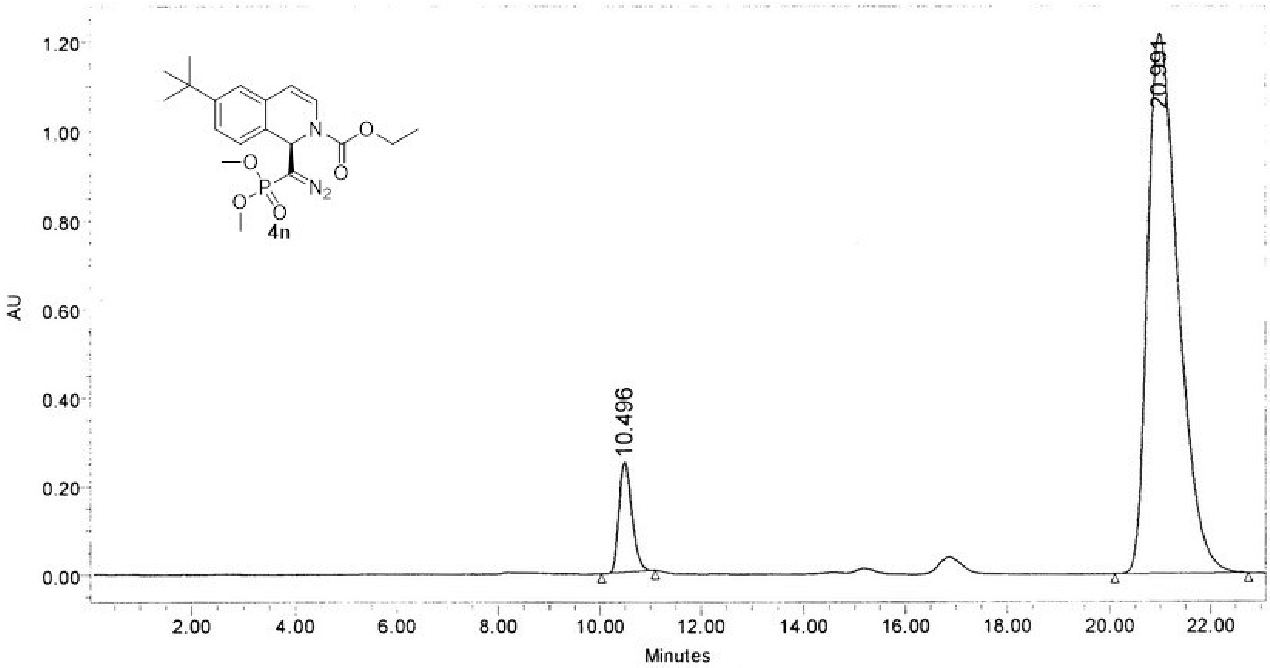
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	11.555	14438790	49.82	734375	69.26
2	23.066	14545772	50.18	325887	30.74



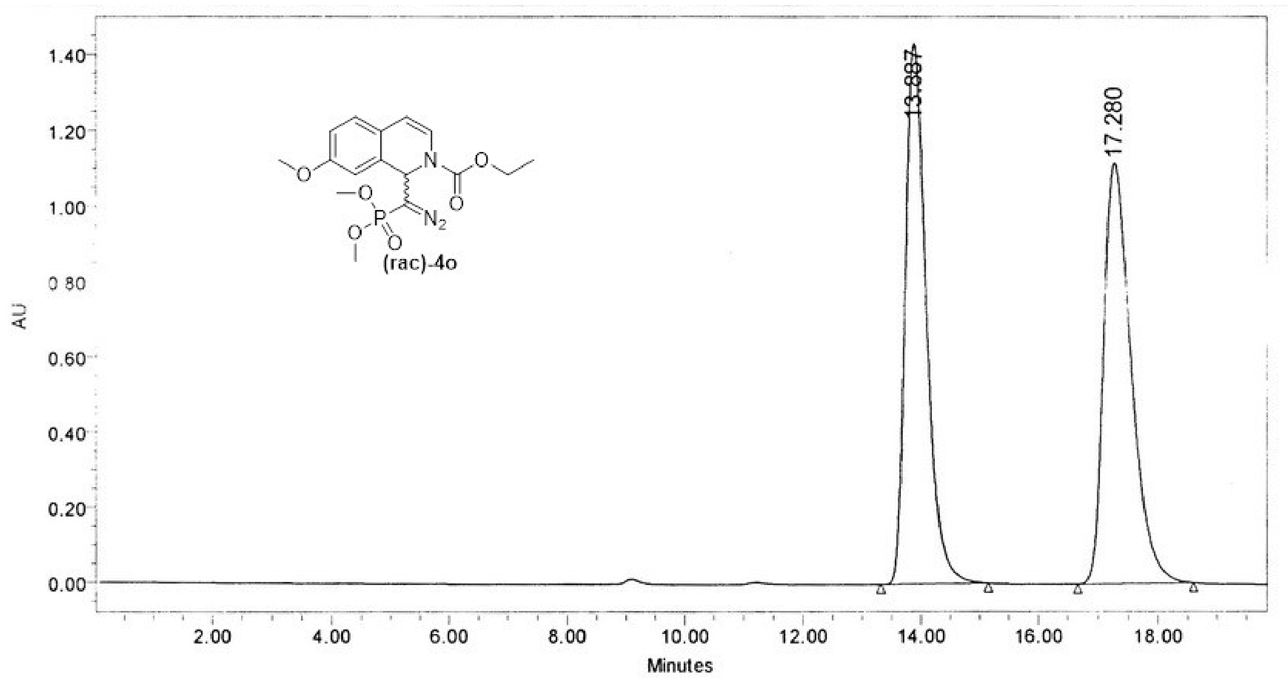
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	11.022	1713911	4.89	88569	10.40
2	21.760	33322932	95.11	763434	89.60



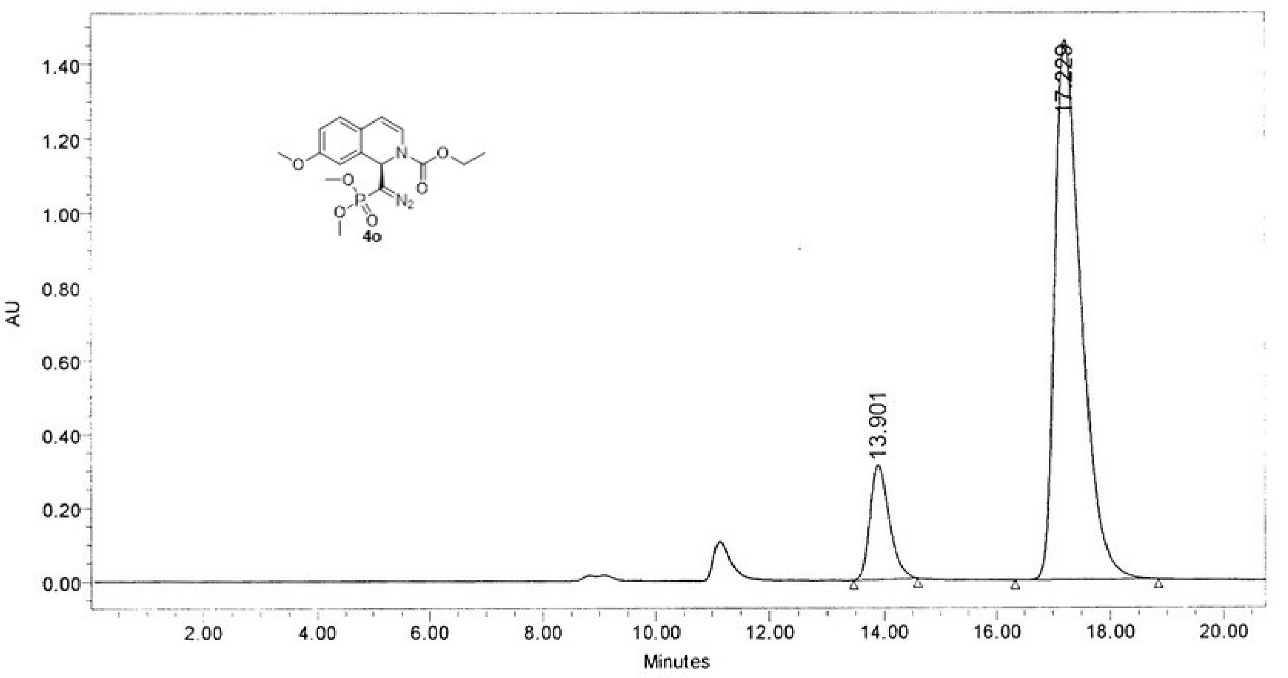
	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	10.364	8139966	49.58	461399	68.26
2	20.216	8277166	50.42	214498	31.74



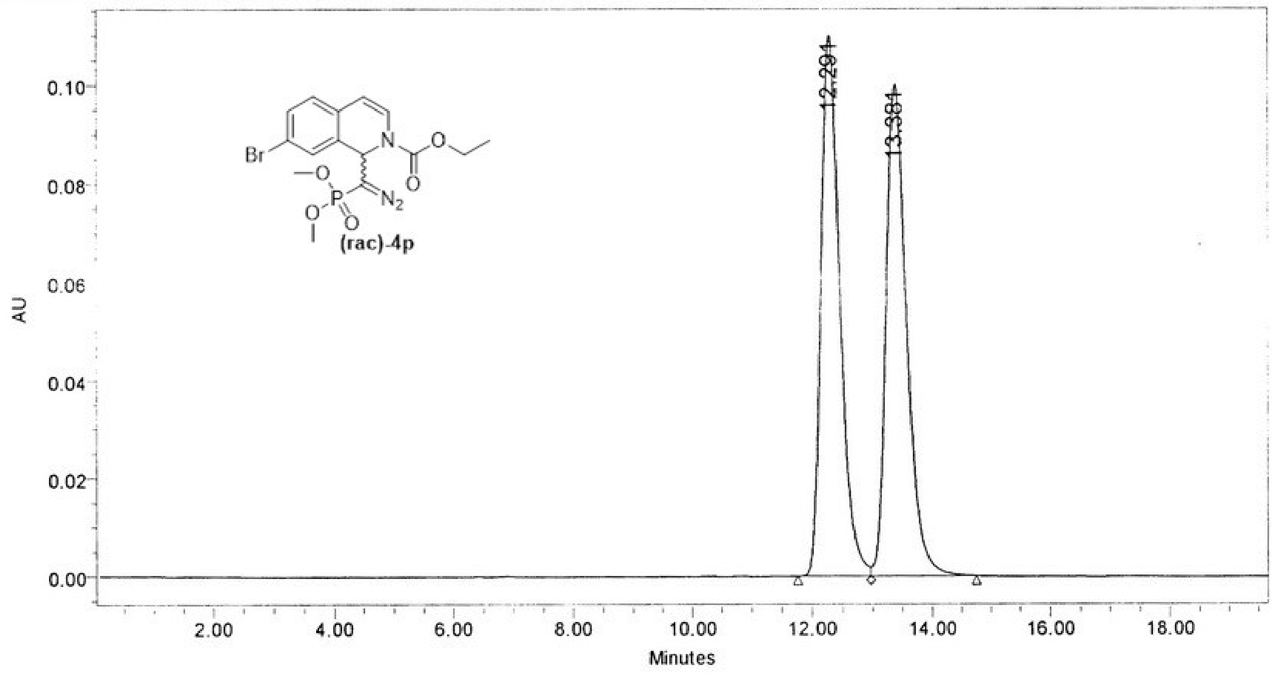
	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	10.496	4467983	7.93	249473	17.01
2	20.991	51893896	92.07	1217015	82.99



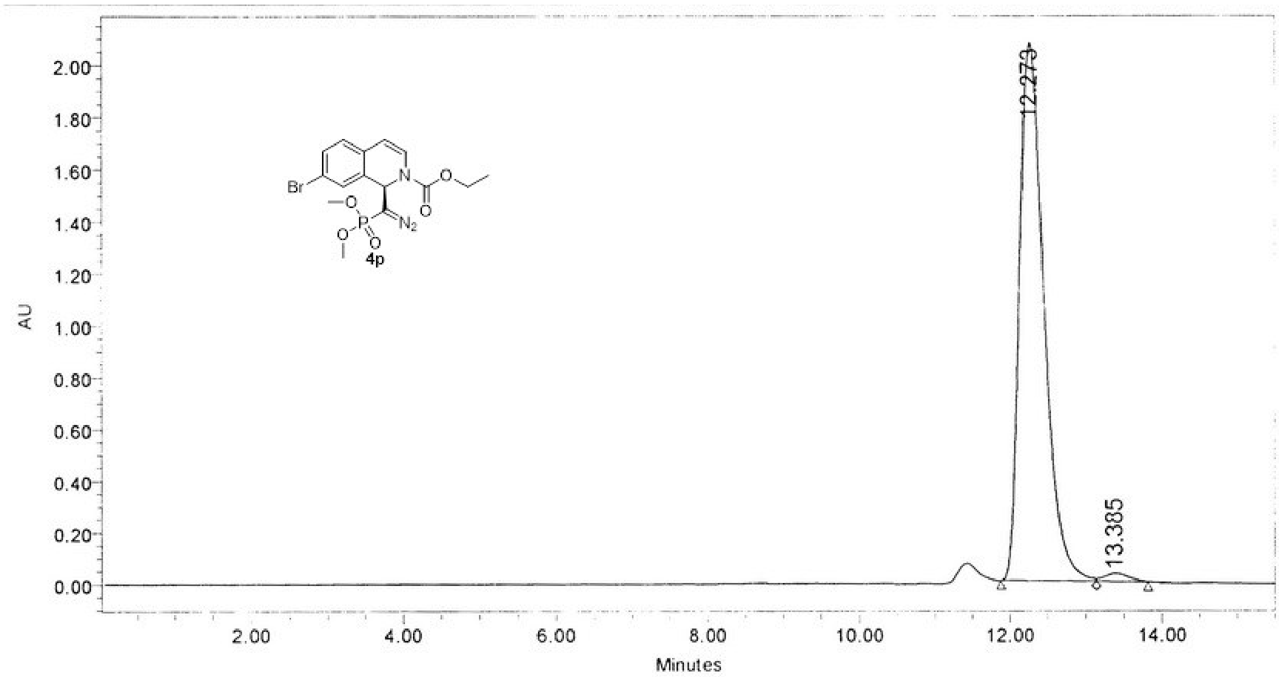
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	13.887	35595878	50.07	1433369	56.16
2	17.280	35499389	49.93	1119014	43.84



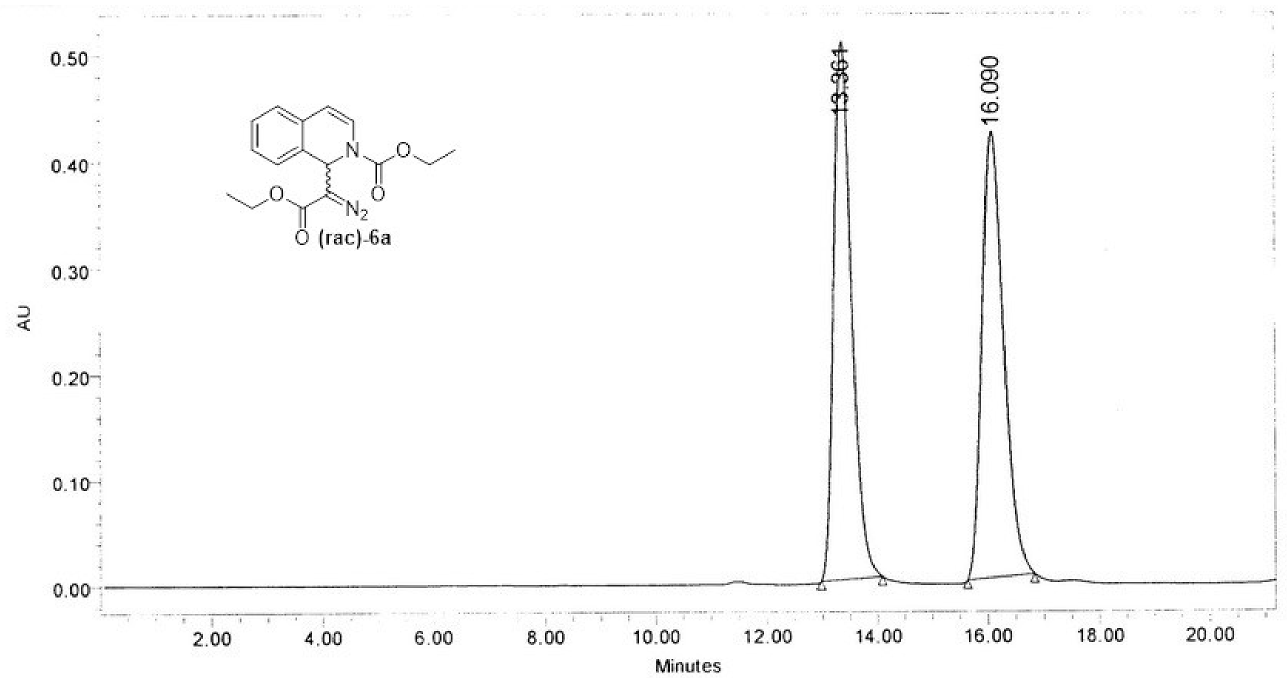
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	13.901	7333411	13.50	311193	17.56
2	17.229	46968304	86.50	1461238	82.44



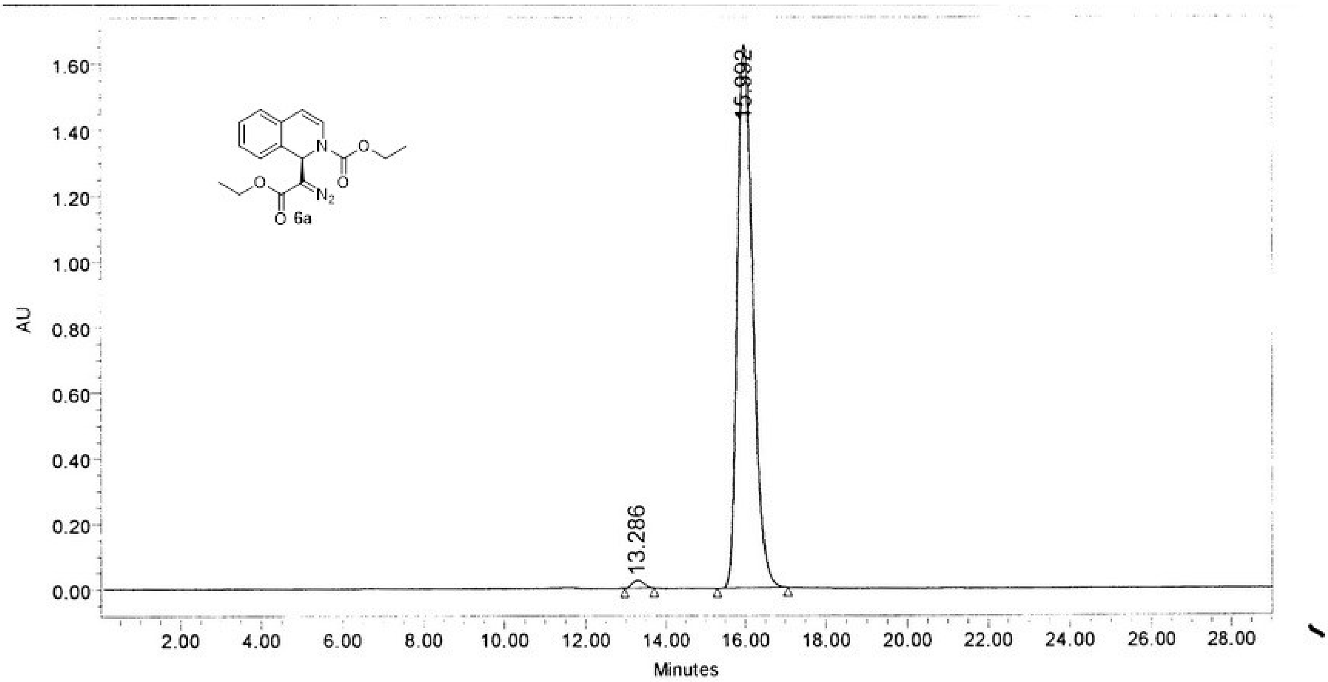
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	12.291	2373655	49.66	110079	52.37
2	13.381	2405857	50.34	100129	47.63



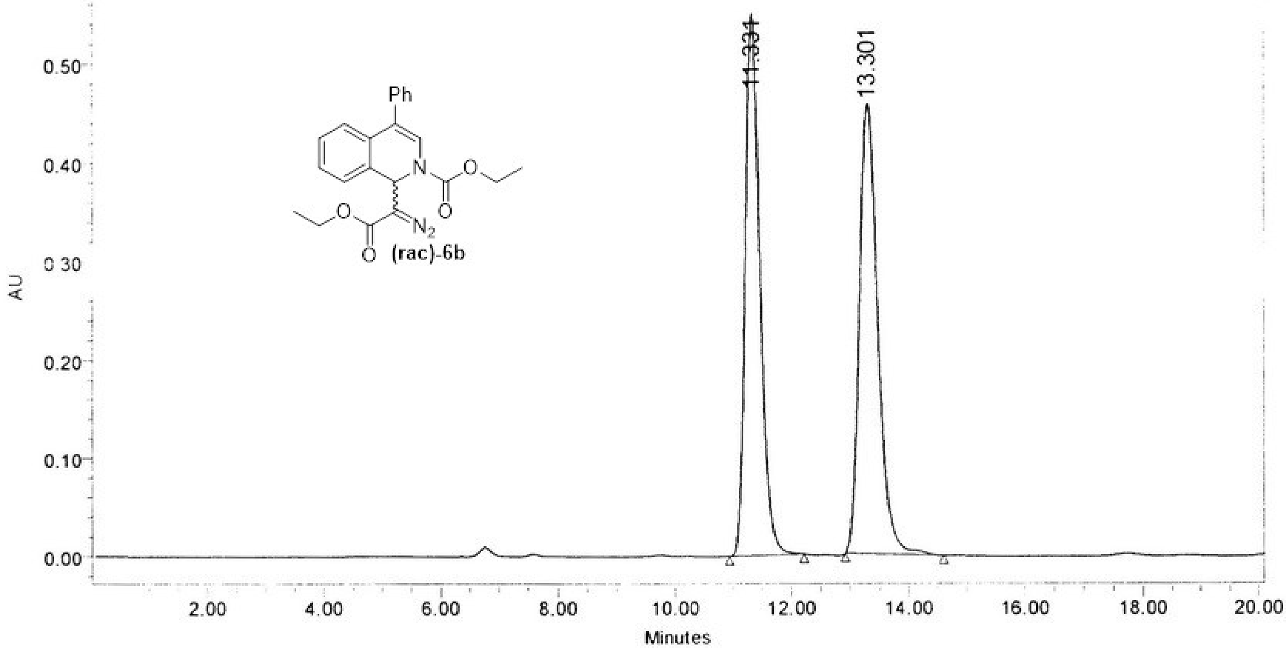
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	12.273	46513641	98.56	2072708	98.56
2	13.385	681511	1.44	30384	1.44



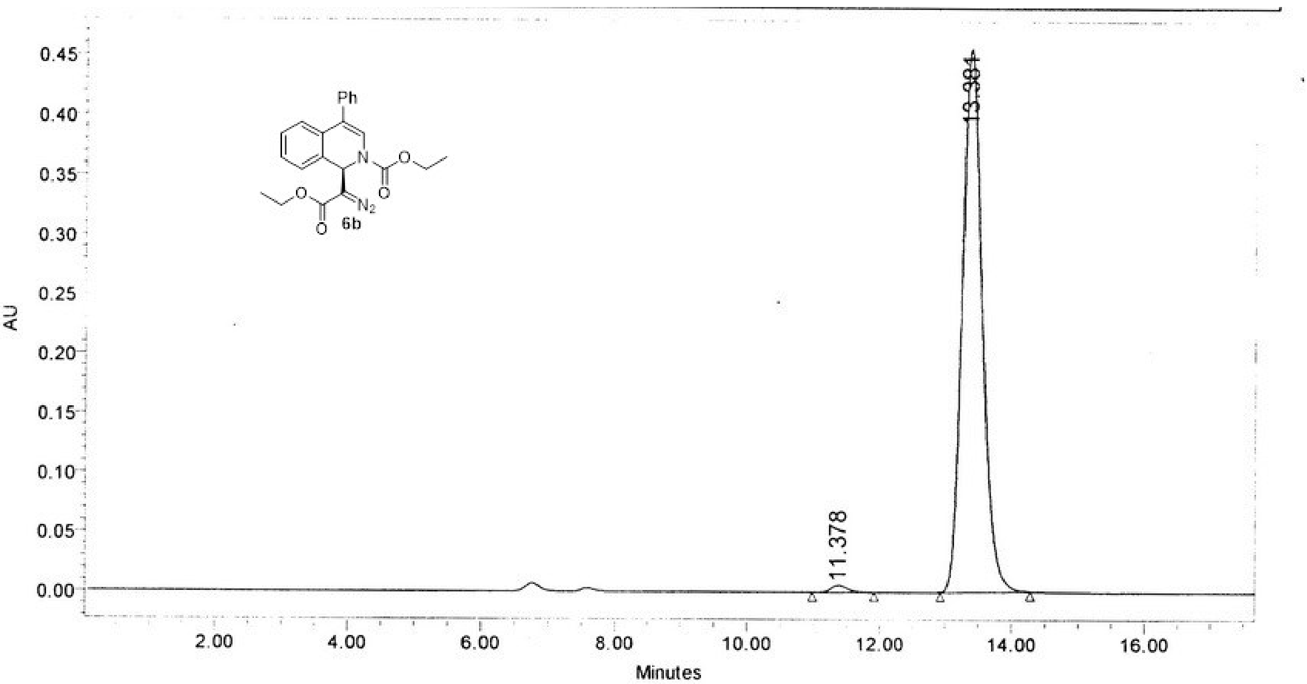
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	13.361	11454136	50.20	507403	54.68
2	16.090	11361018	49.80	420594	45.32



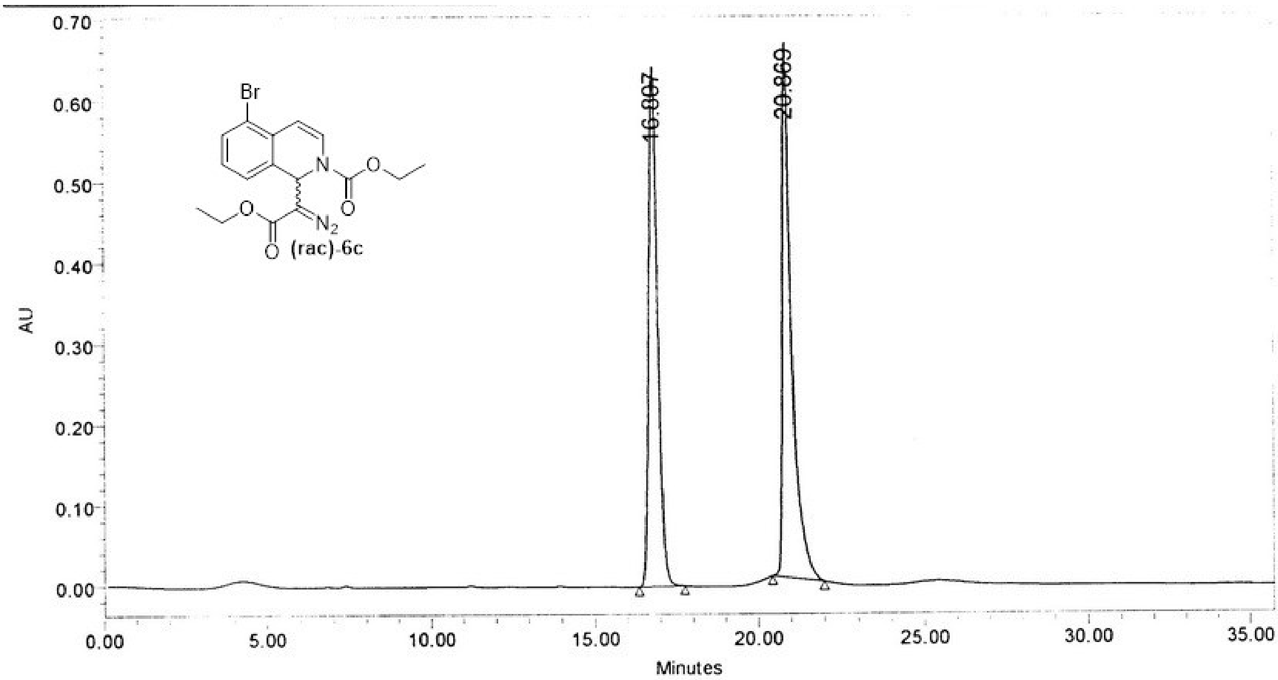
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	13.286	493901	1.08	24392	1.45
2	15.992	45137226	98.92	1656874	98.55



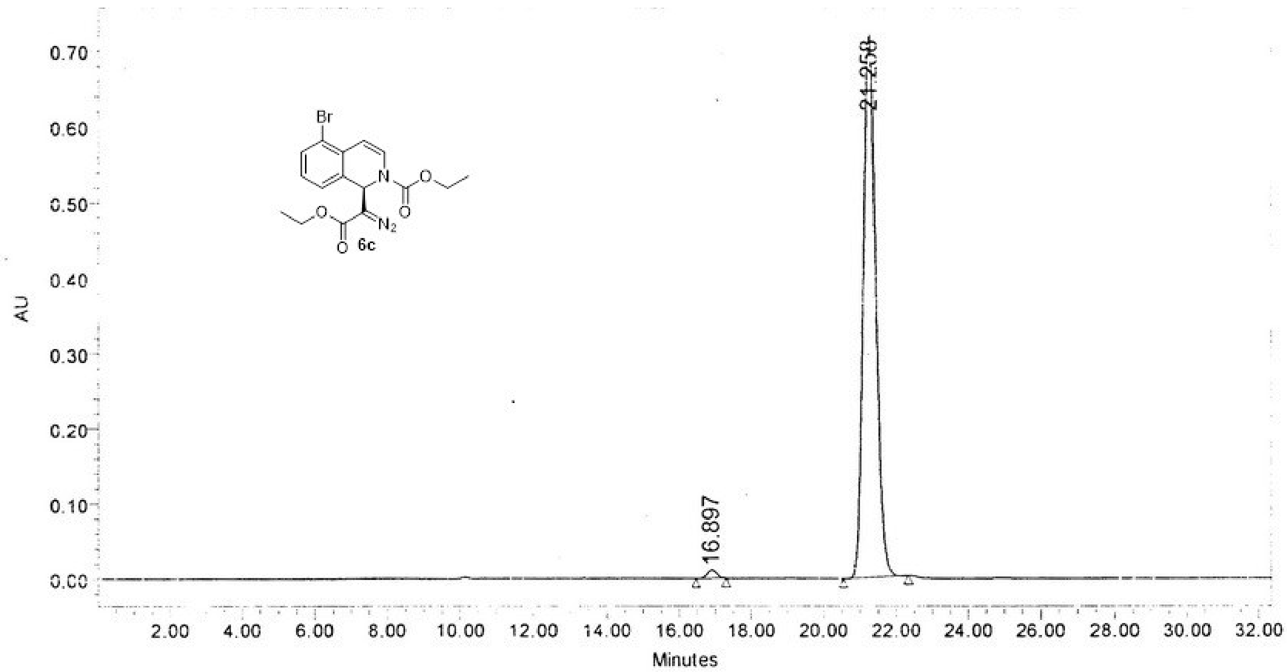
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	11.331	9727330	49.37	551205	54.62
2	13.301	9974435	50.63	457866	45.38



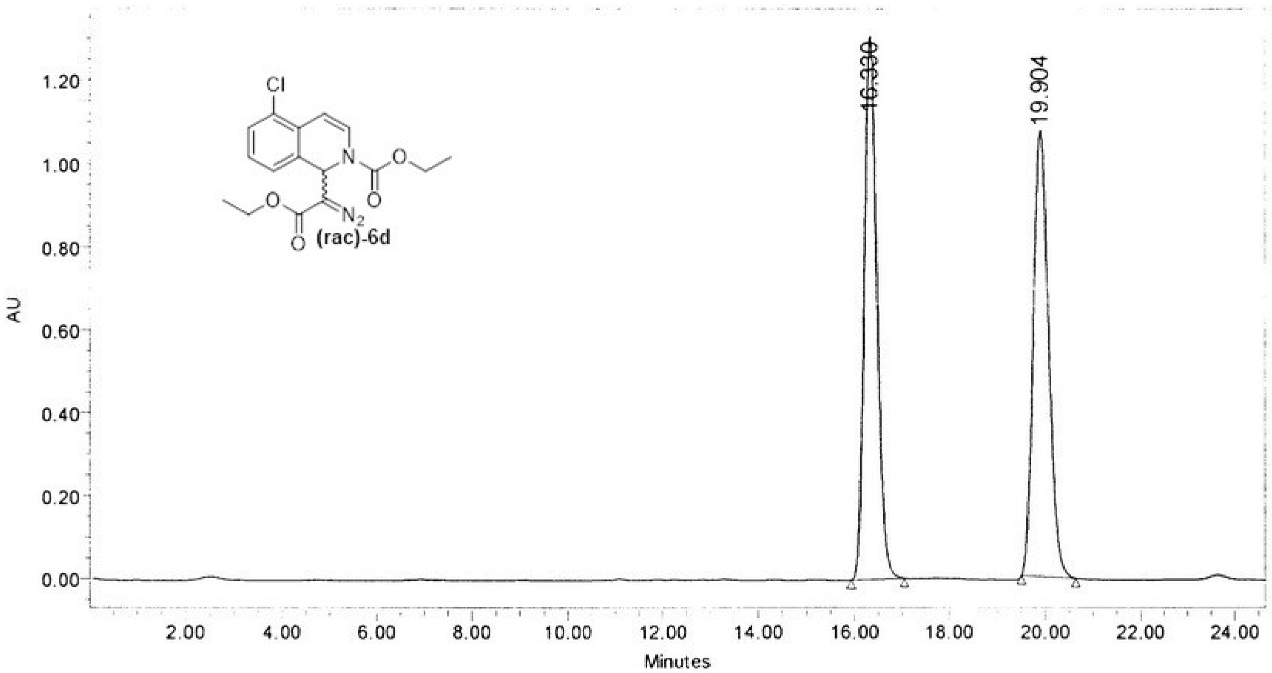
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	11.378	101717	1.05	5688	1.23
2	13.381	9620576	98.95	456375	98.77



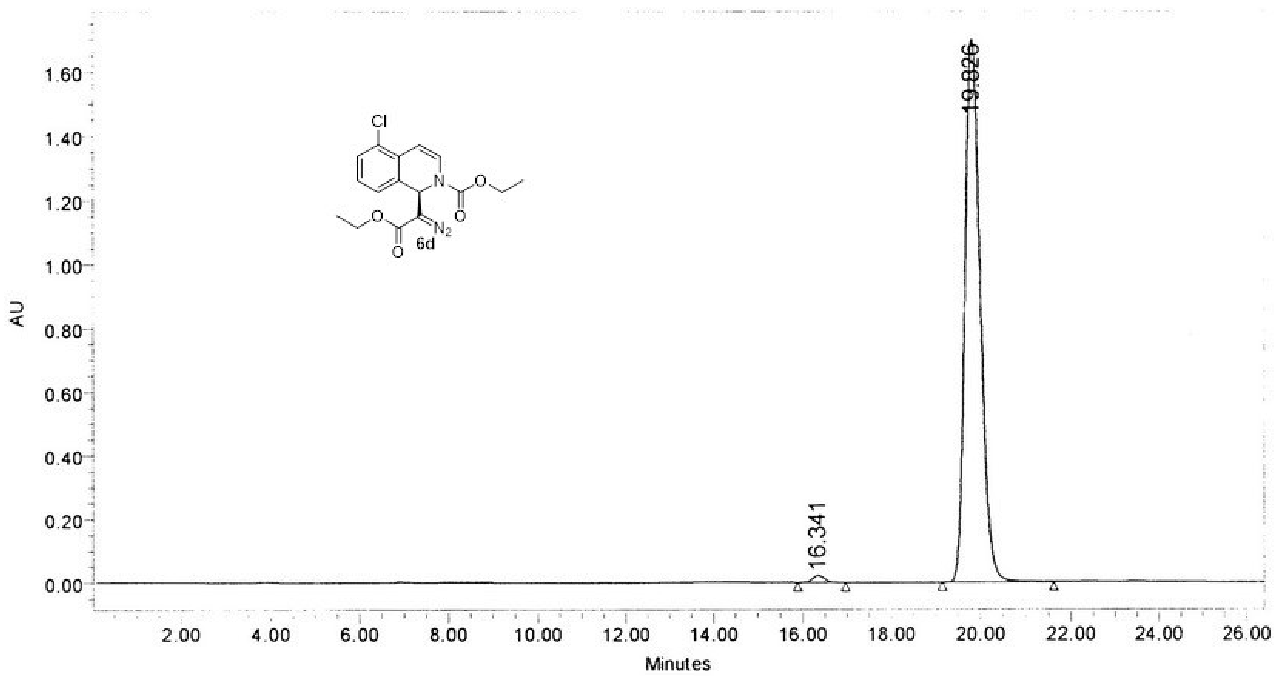
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	16.807	12203049	49.28	643810	49.37
2	20.869	12561965	50.72	660201	50.63



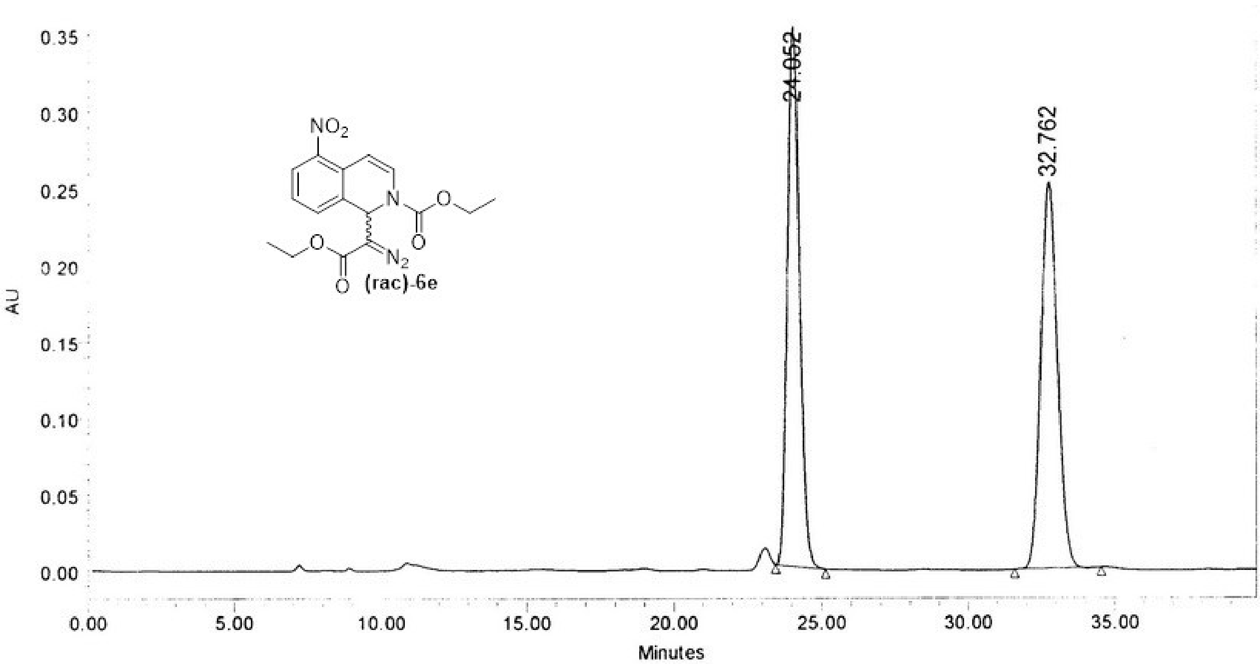
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	16.897	201393	1.16	11088	1.52
2	21.258	17198209	98.84	720149	98.48



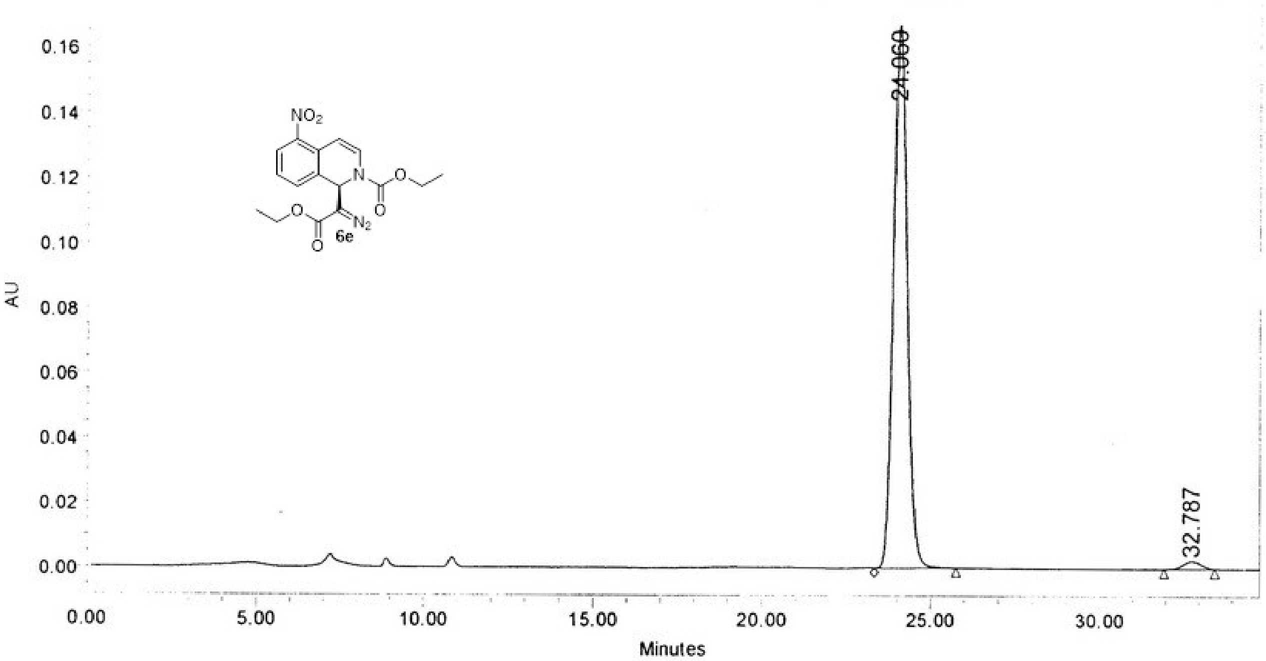
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	16.330	23984921	50.64	1307728	54.86
2	19.904	23376633	49.36	1075998	45.14



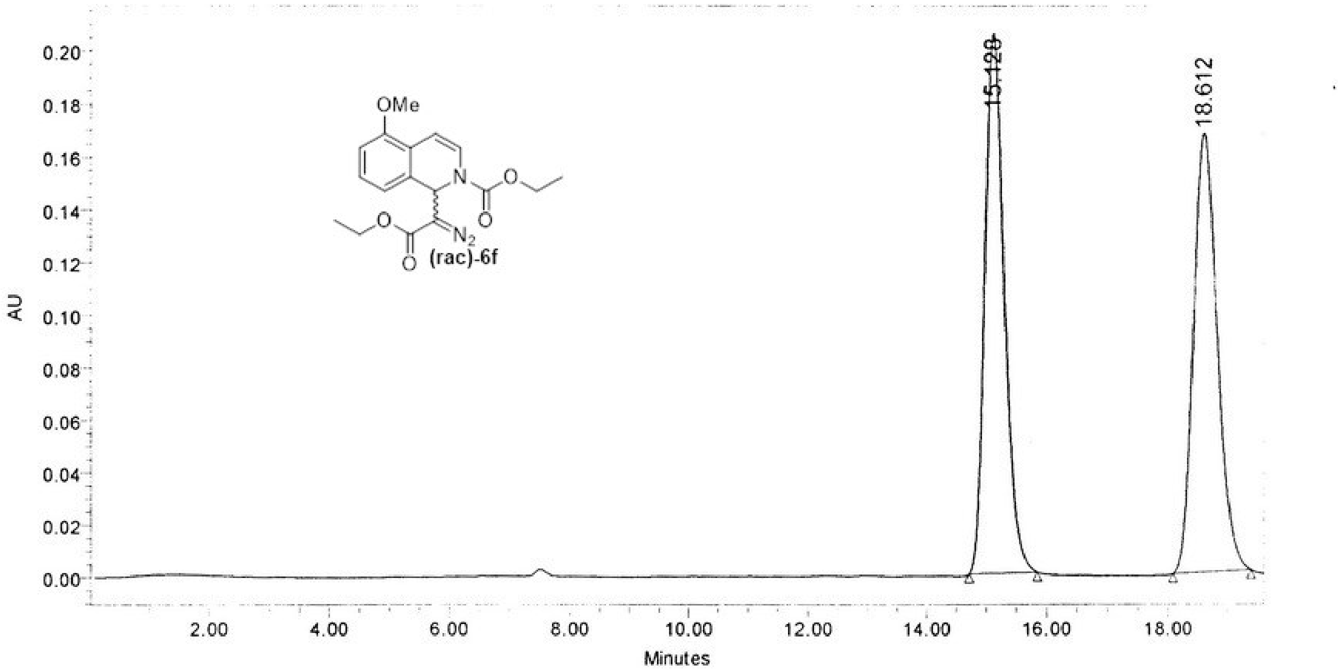
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	16.341	423487	1.05	22742	1.32
2	19.826	40018345	98.95	1702831	98.68



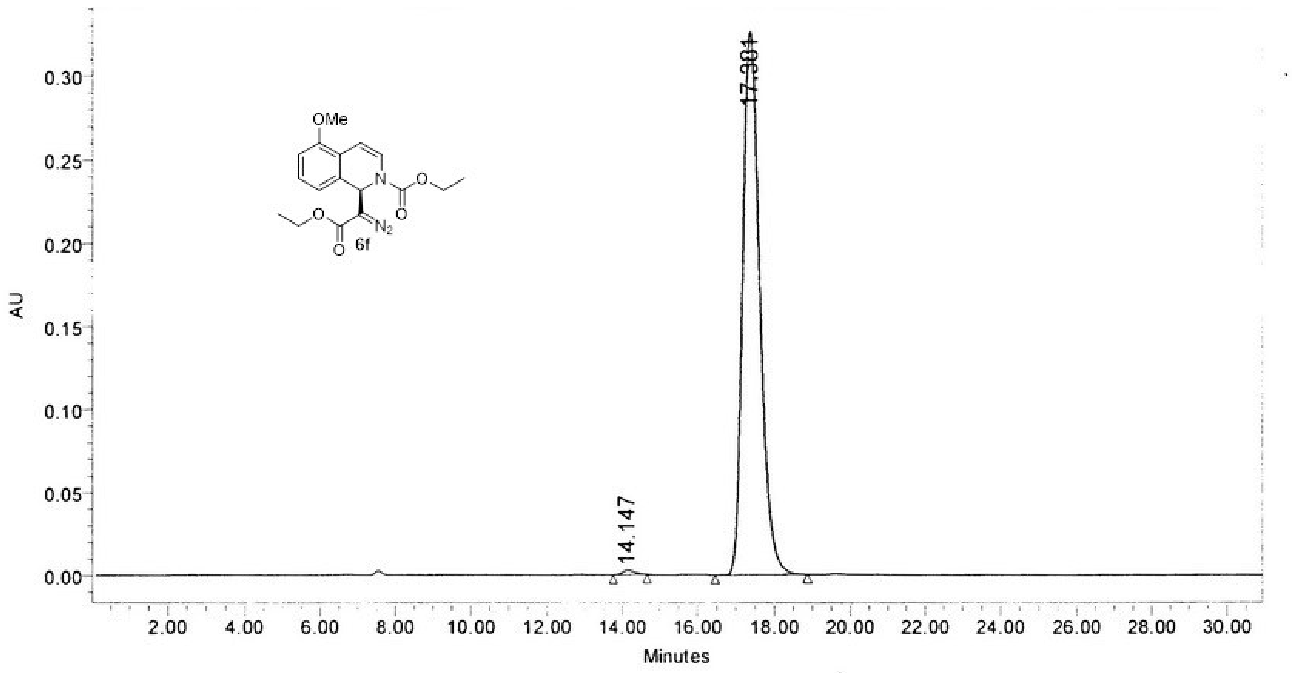
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	24.052	9928021	49.88	352861	58.21
2	32.762	9977732	50.12	253345	41.79



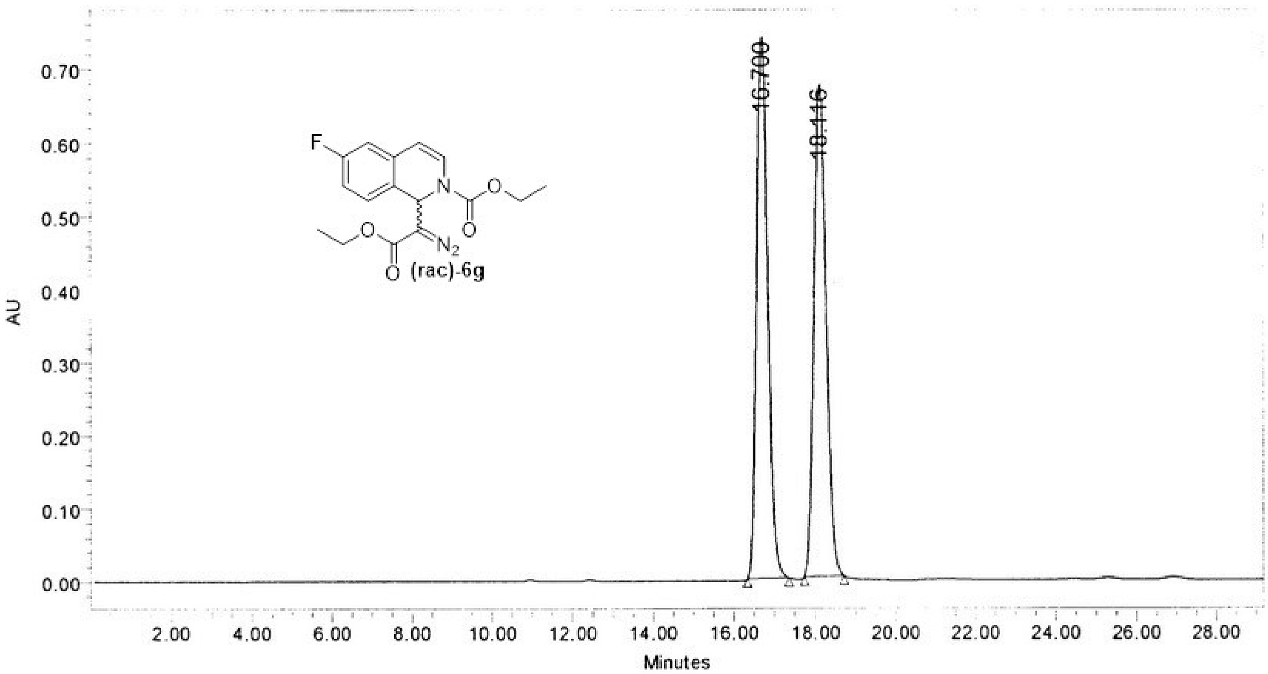
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	24.060	4761808	98.10	167443	98.56
2	32.787	92329	1.90	2446	1.44



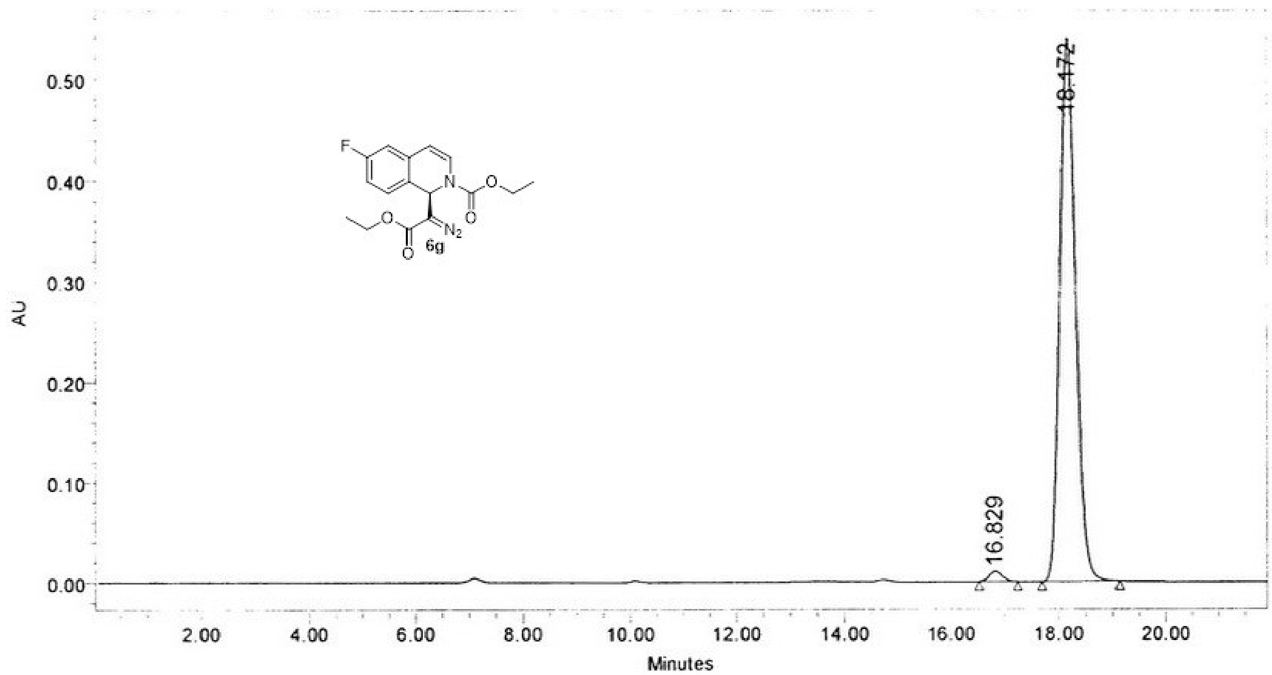
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	15.128	4608930	49.71	205288	55.11
2	18.612	4663159	50.29	167248	44.89



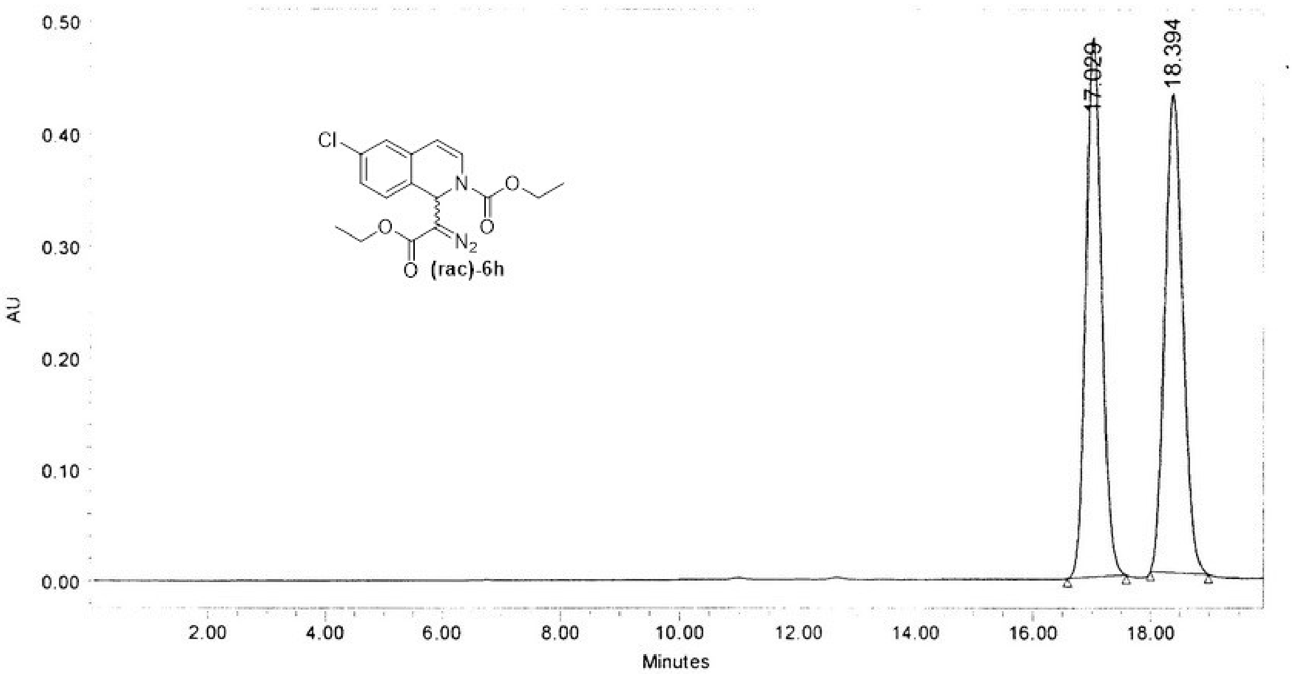
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	14.147	63189	0.63	2581	0.78
2	17.381	9997091	99.37	326318	99.22



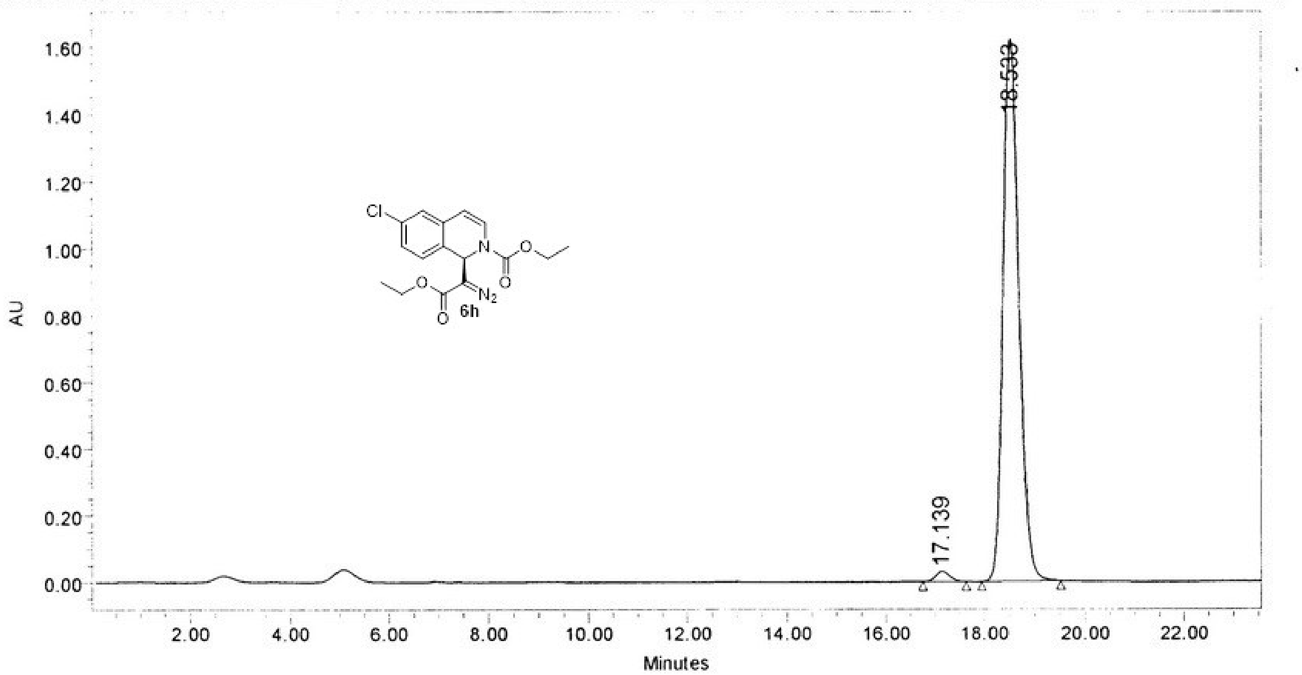
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	16.700	14010233	50.13	738788	52.35
2	18.116	13938529	49.87	672516	47.65



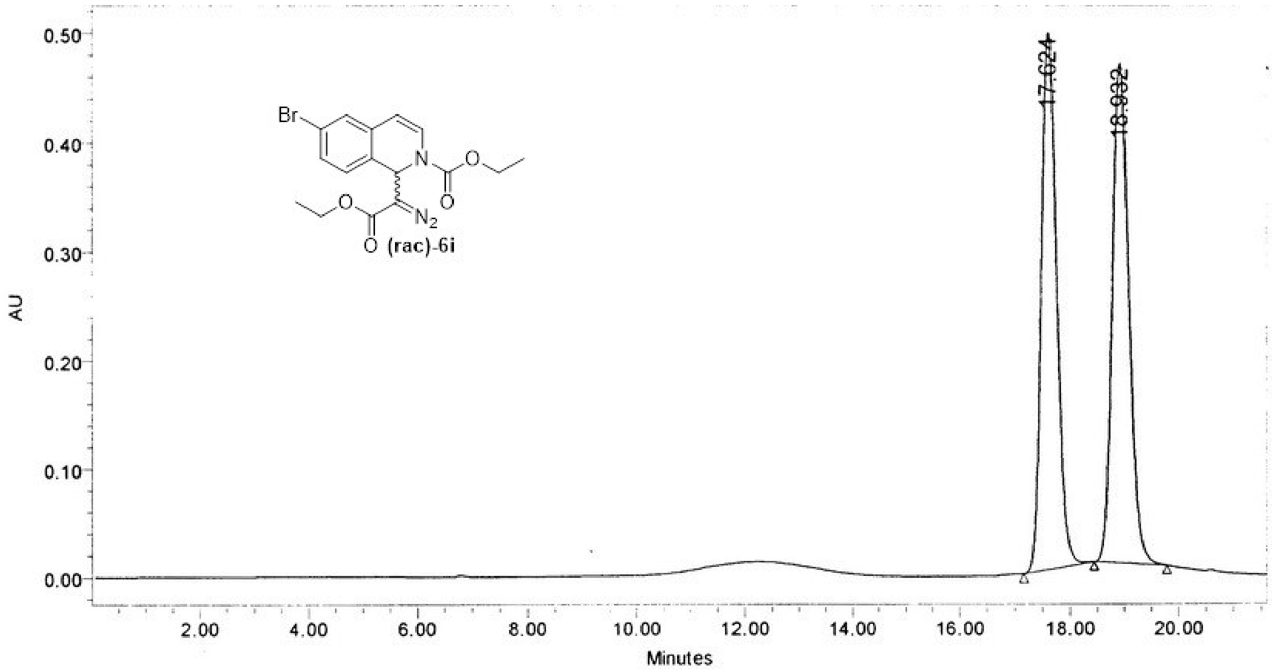
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	16.829	178371	1.62	10351	1.88
2	18.172	10864583	98.38	540093	98.12



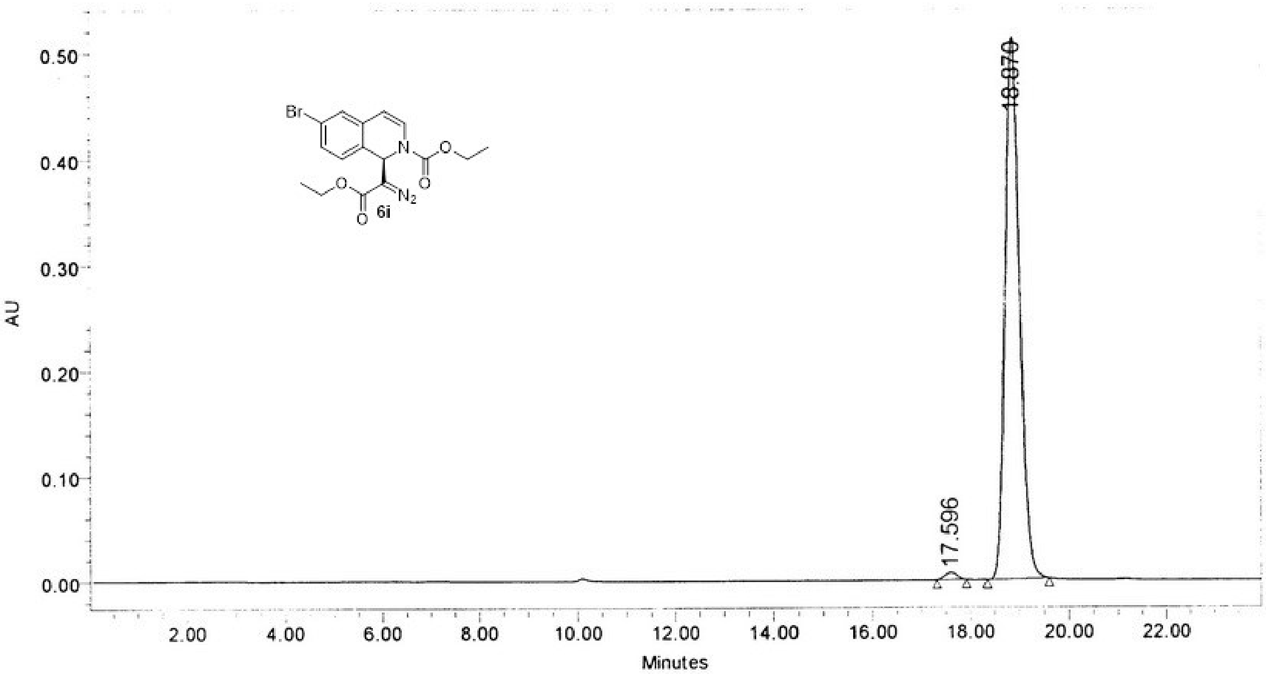
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	17.029	9034135	49.75	483158	52.95
2	18.394	9126318	50.25	429396	47.05



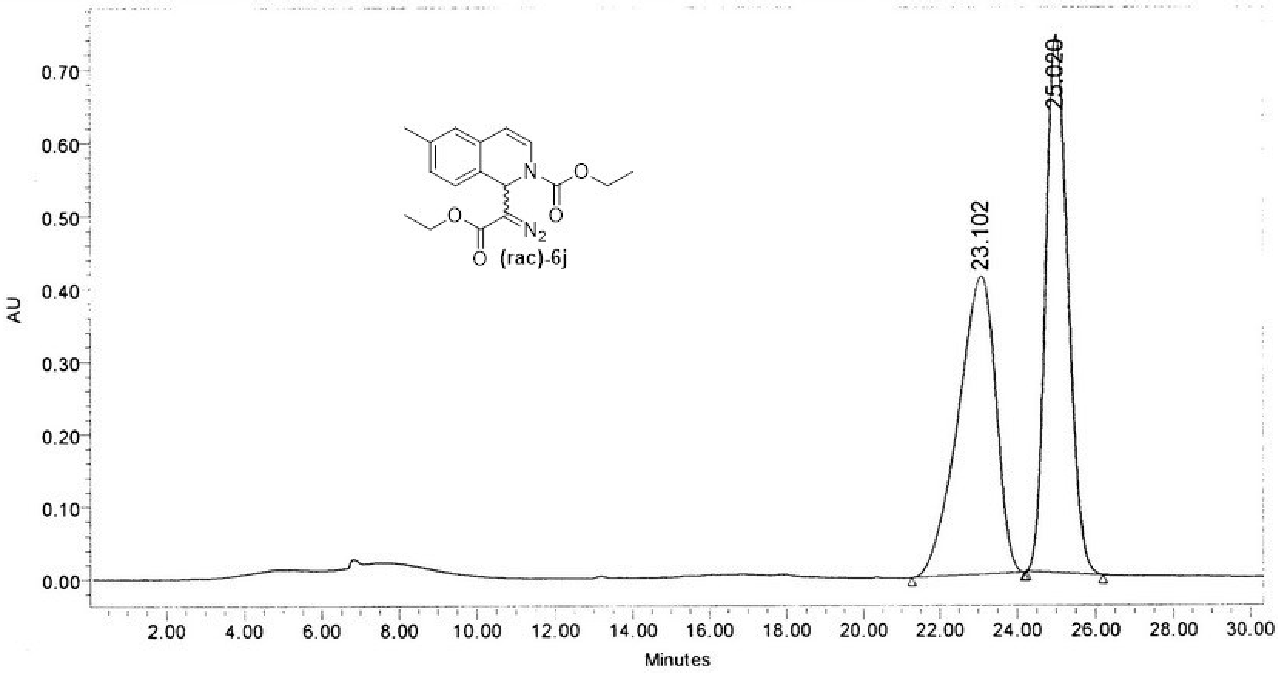
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	17.139	607700	1.69	31077	1.88
2	18.533	35306742	98.31	1622149	98.12



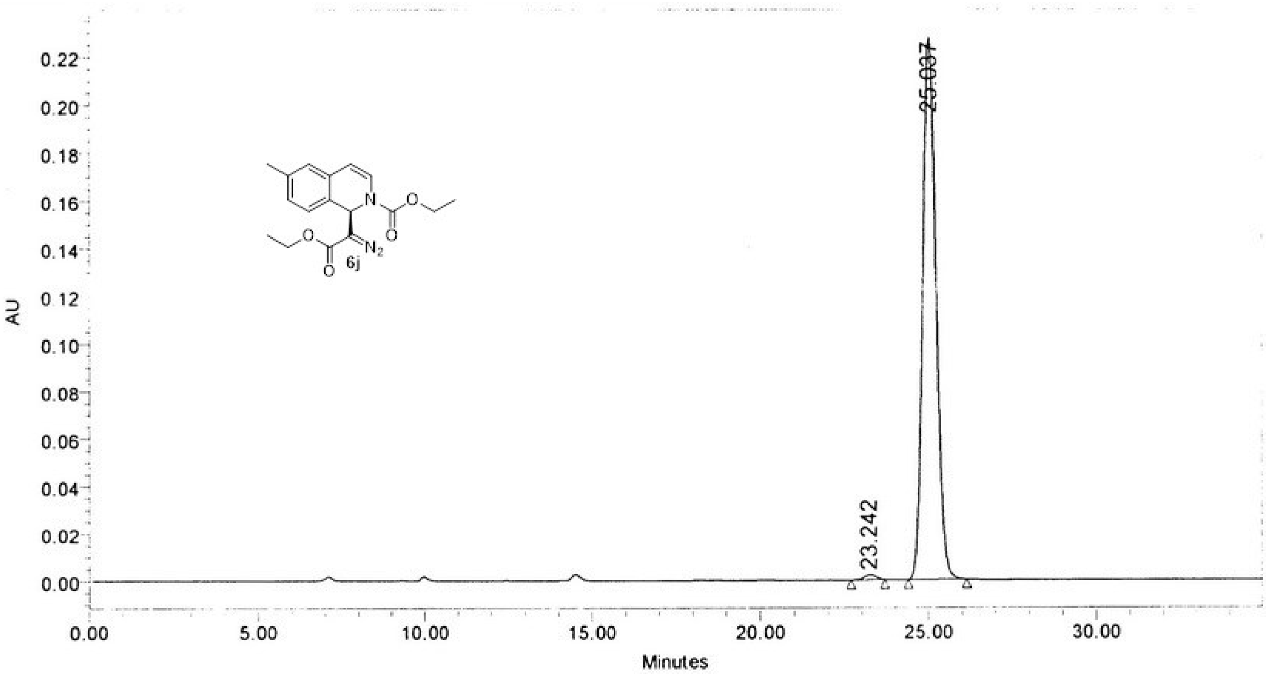
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	17.624	9384376	49.20	494071	51.83
2	18.932	9690075	50.80	459149	48.17



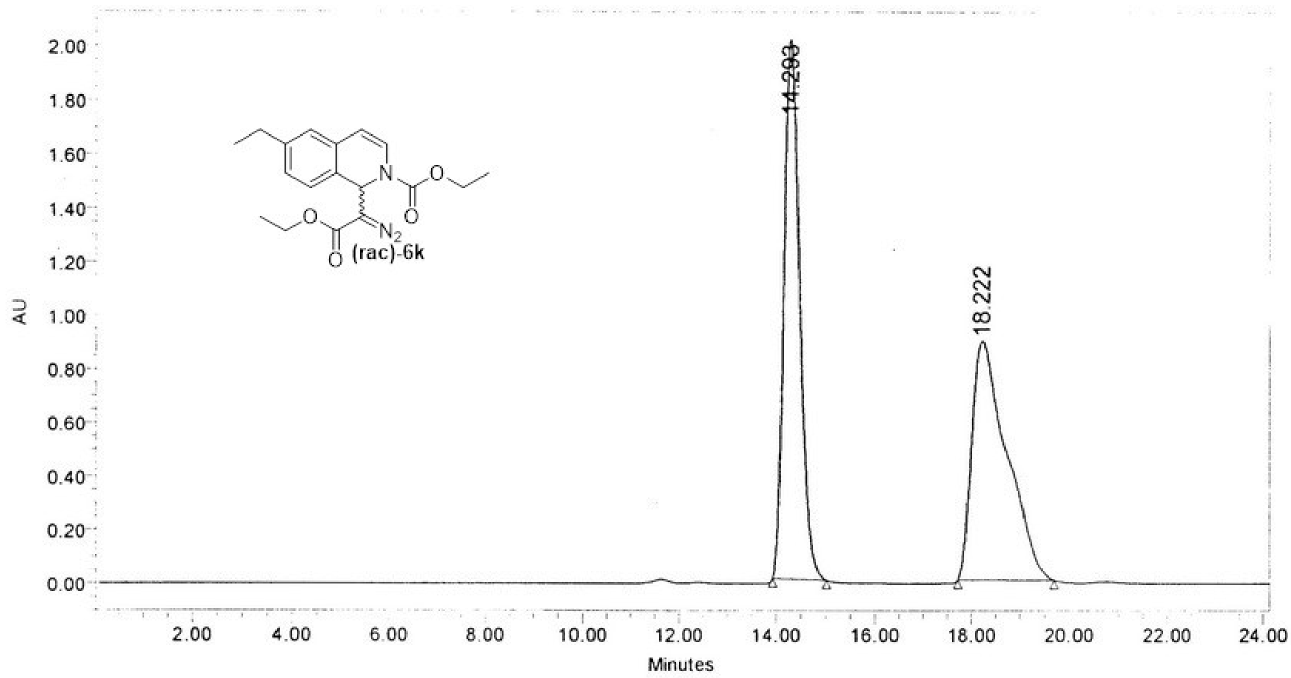
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	17.596	113604	1.07	6613	1.27
2	18.870	10517923	98.93	513970	98.73



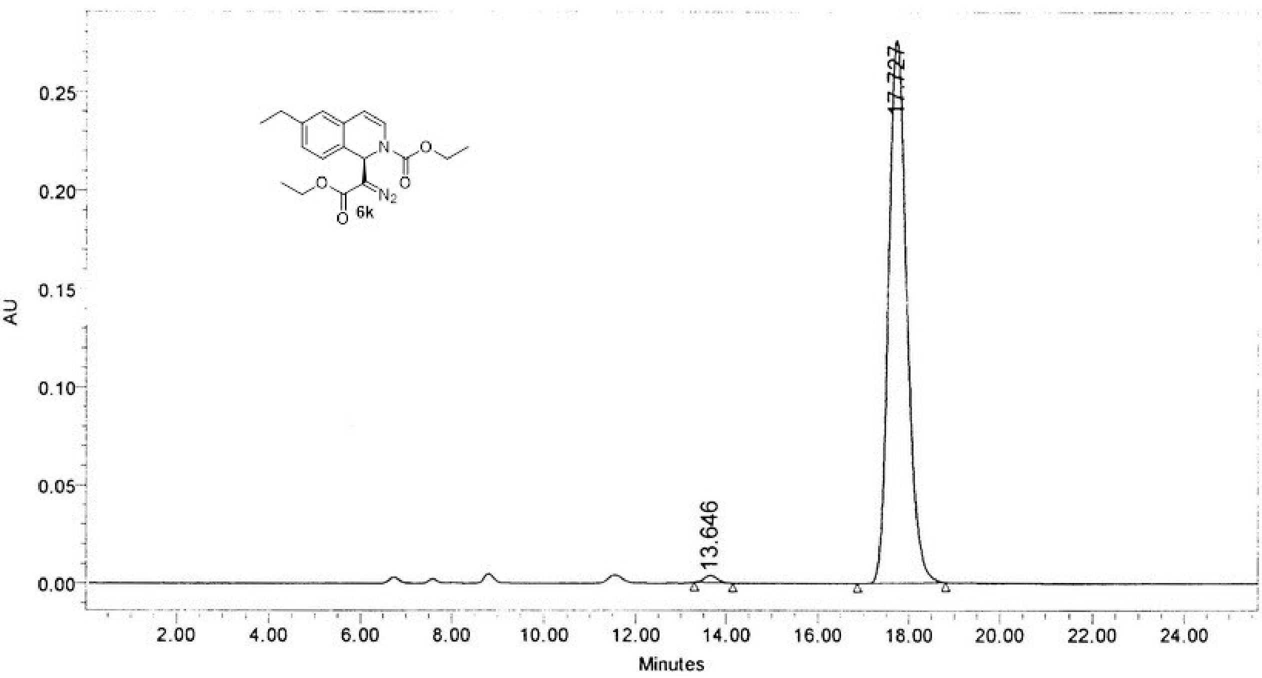
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	23.102	27965601	49.30	410479	35.72
2	25.020	28758419	50.70	738653	64.28



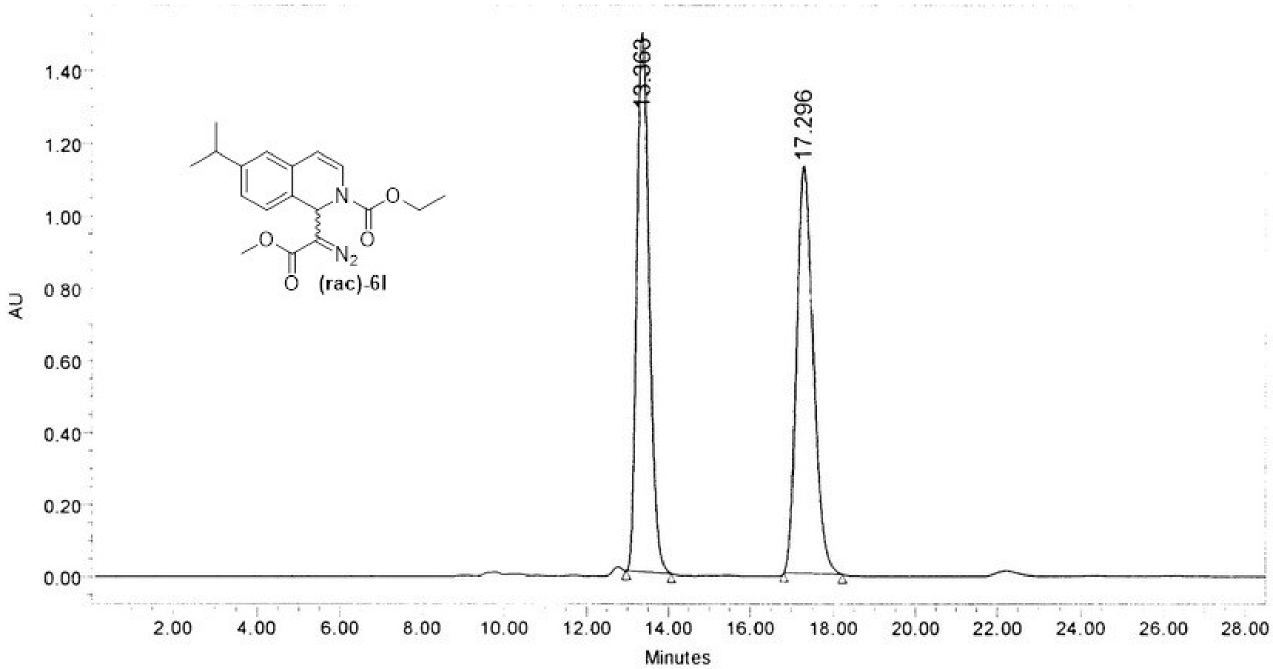
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	23.242	56462	0.89	2205	0.96
2	25.037	6274140	99.11	227884	99.04



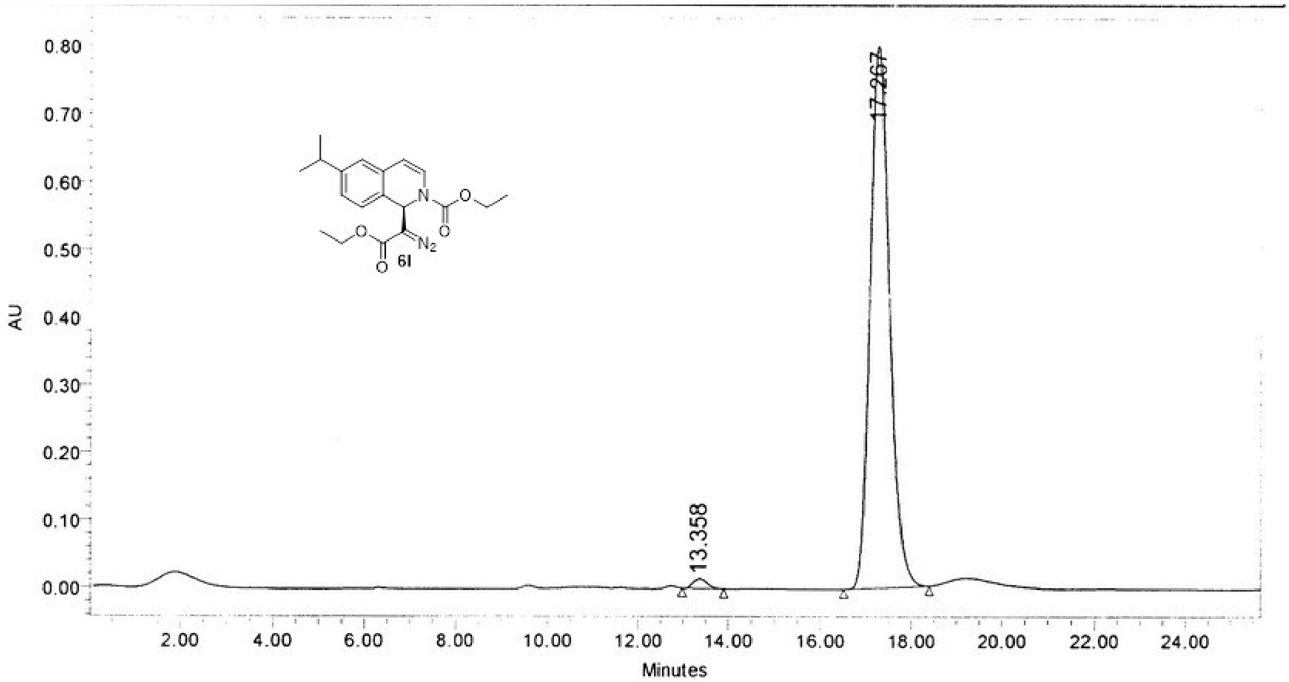
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	14.293	44475449	50.07	2010122	69.29
2	18.222	44355248	49.93	890967	30.71



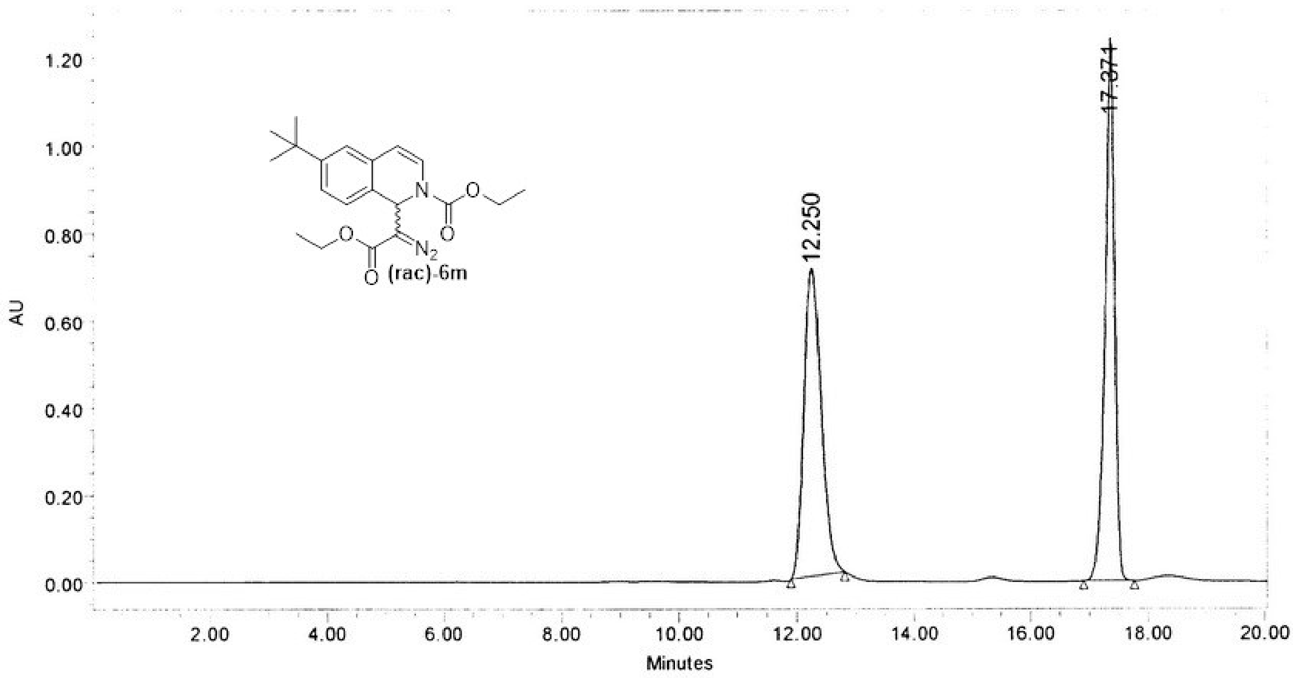
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	13.646	66298	0.85	3312	1.18
2	17.727	7727879	99.15	276517	98.82



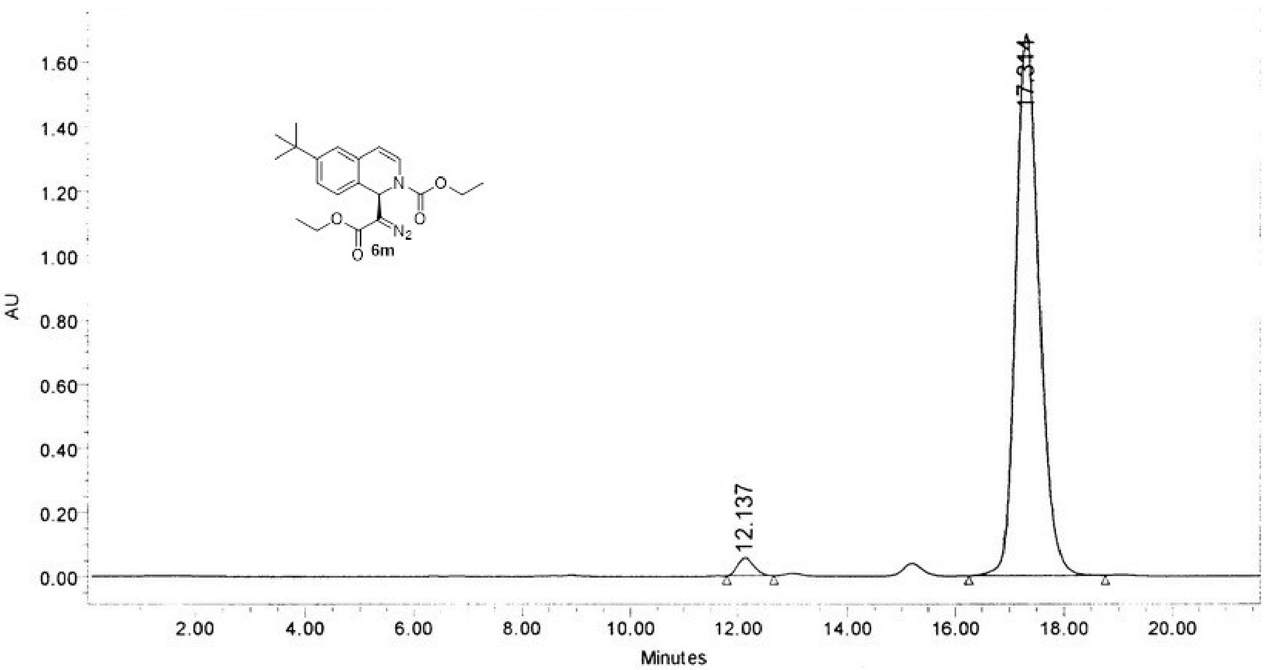
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	13.363	31382016	49.87	1492045	56.89
2	17.296	31551354	50.13	1130418	43.11



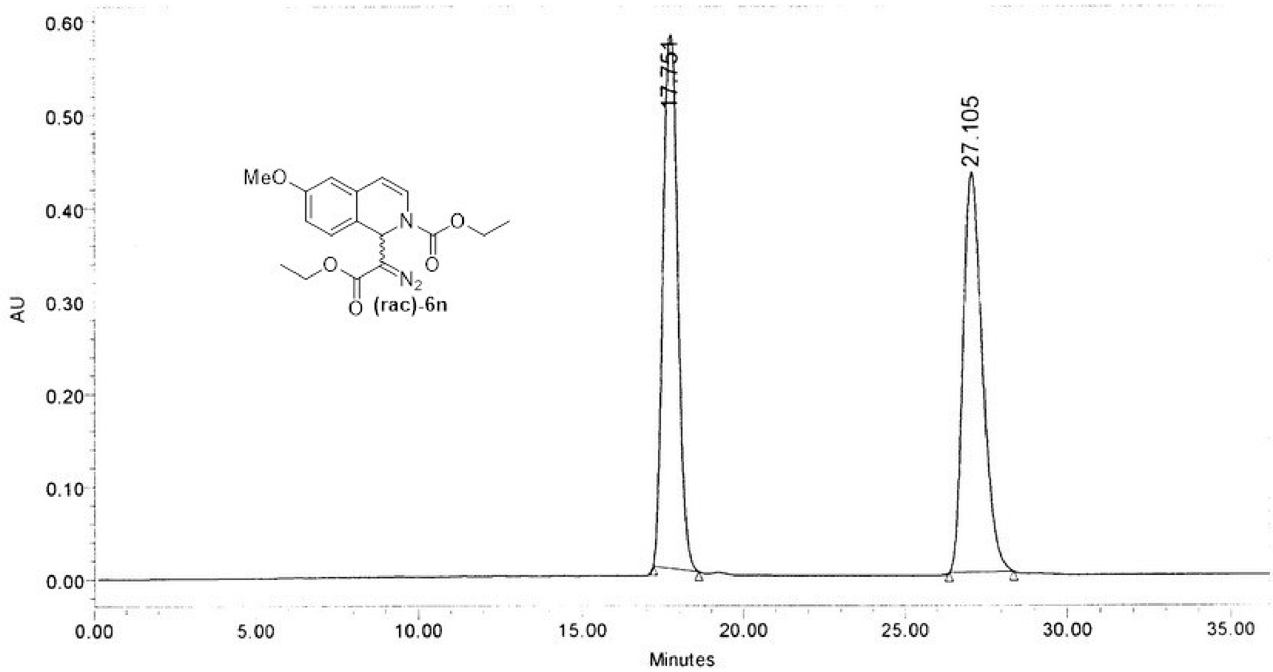
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	13.358	310268	1.28	14643	1.79
2	17.267	23877777	98.72	801696	98.21



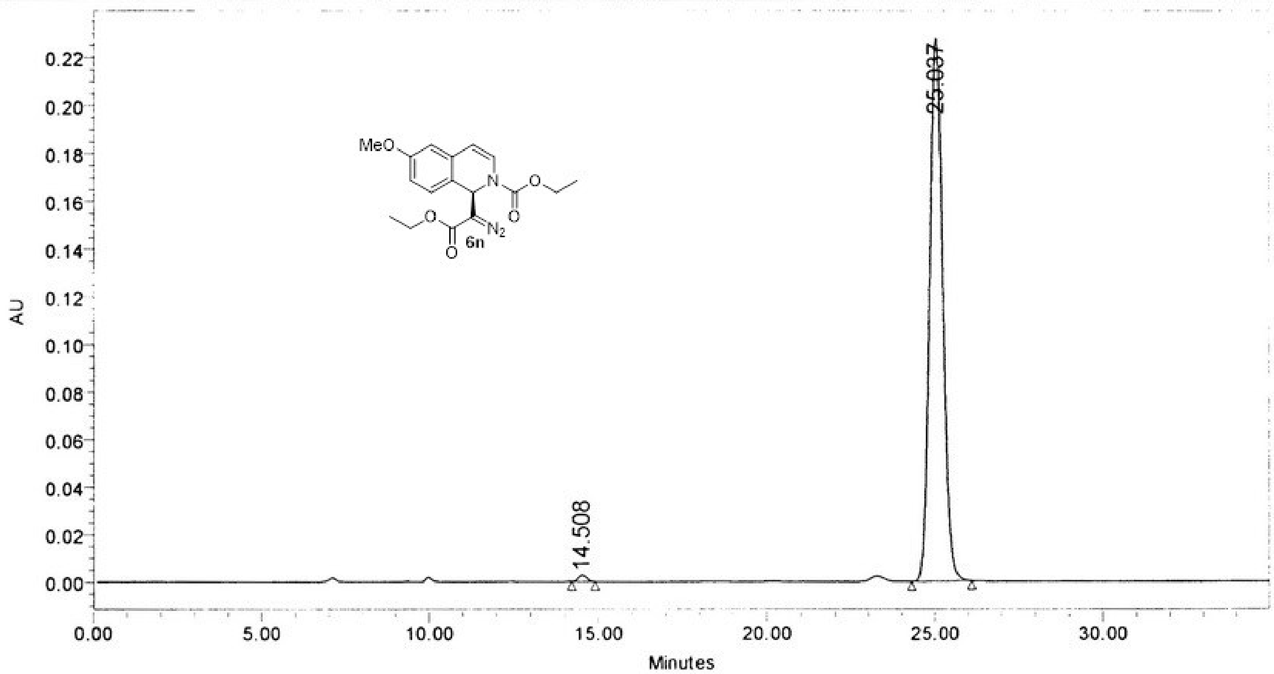
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	12.250	14317564	50.36	707179	36.28
2	17.371	14110141	49.64	1242188	63.72



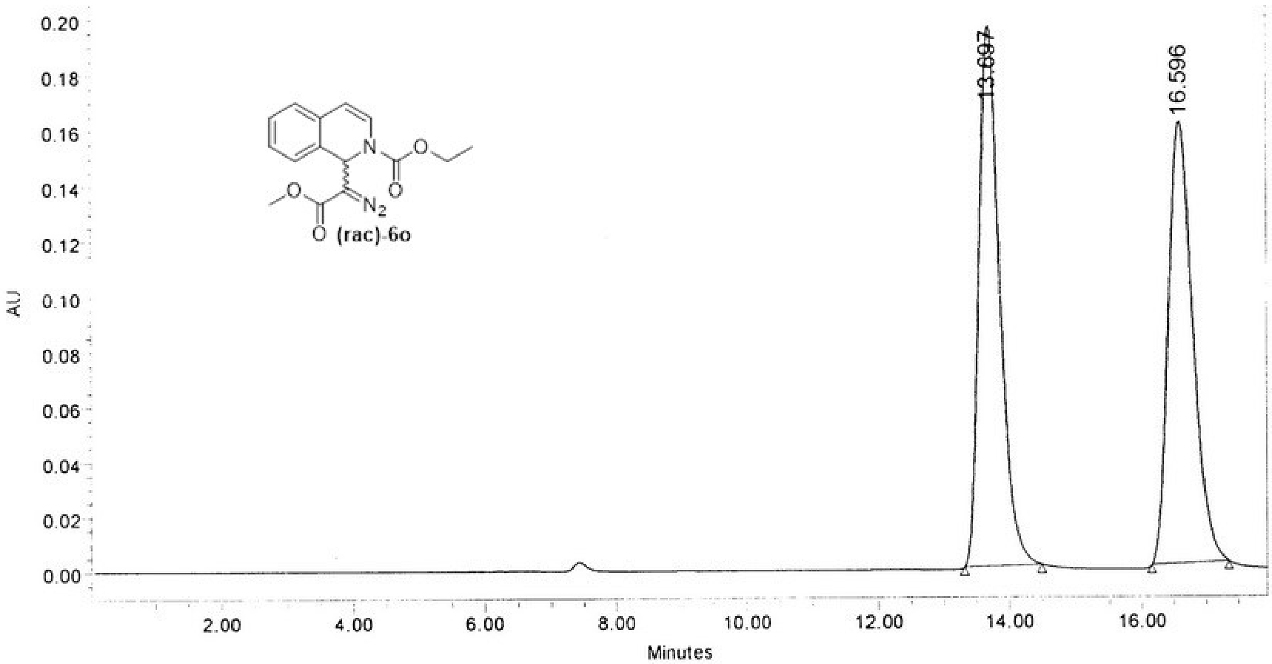
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	12.137	1150303	2.24	55697	3.20
2	17.314	50094114	97.76	1686883	96.80



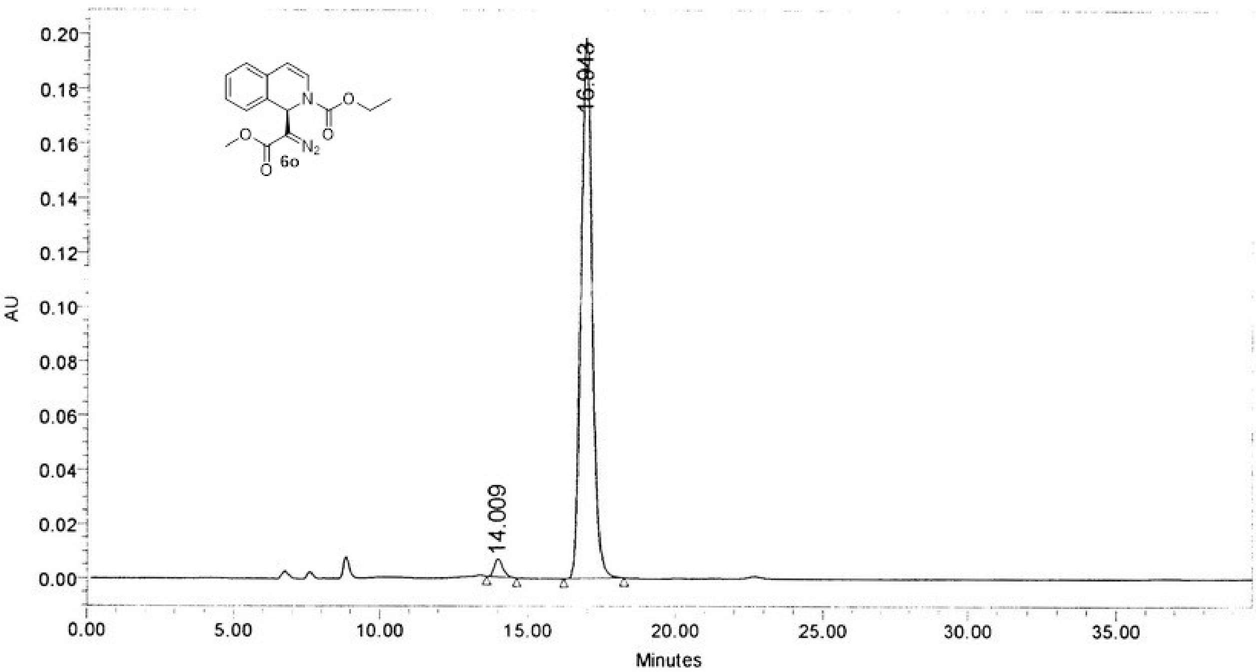
	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	17.751	18442260	50.51	574738	57.12
2	27.105	18073143	49.49	431443	42.88



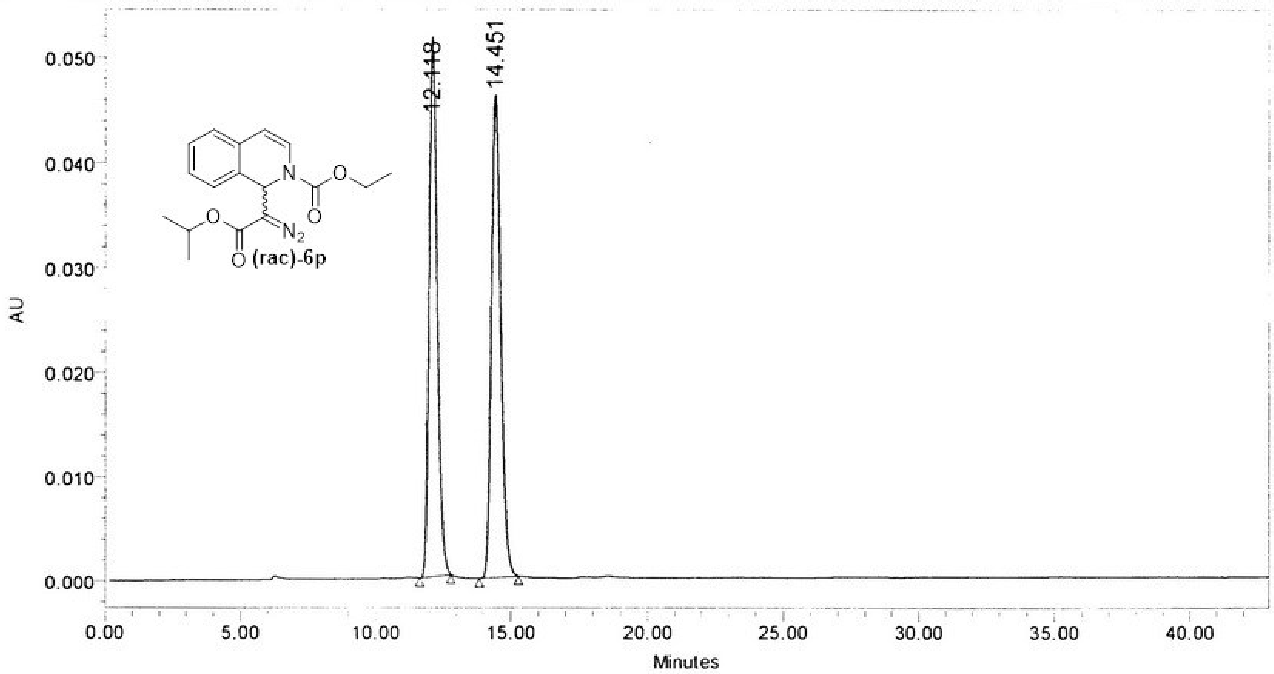
	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	14.508	45554	0.72	2681	1.16
2	25.037	6280013	99.28	227961	98.84



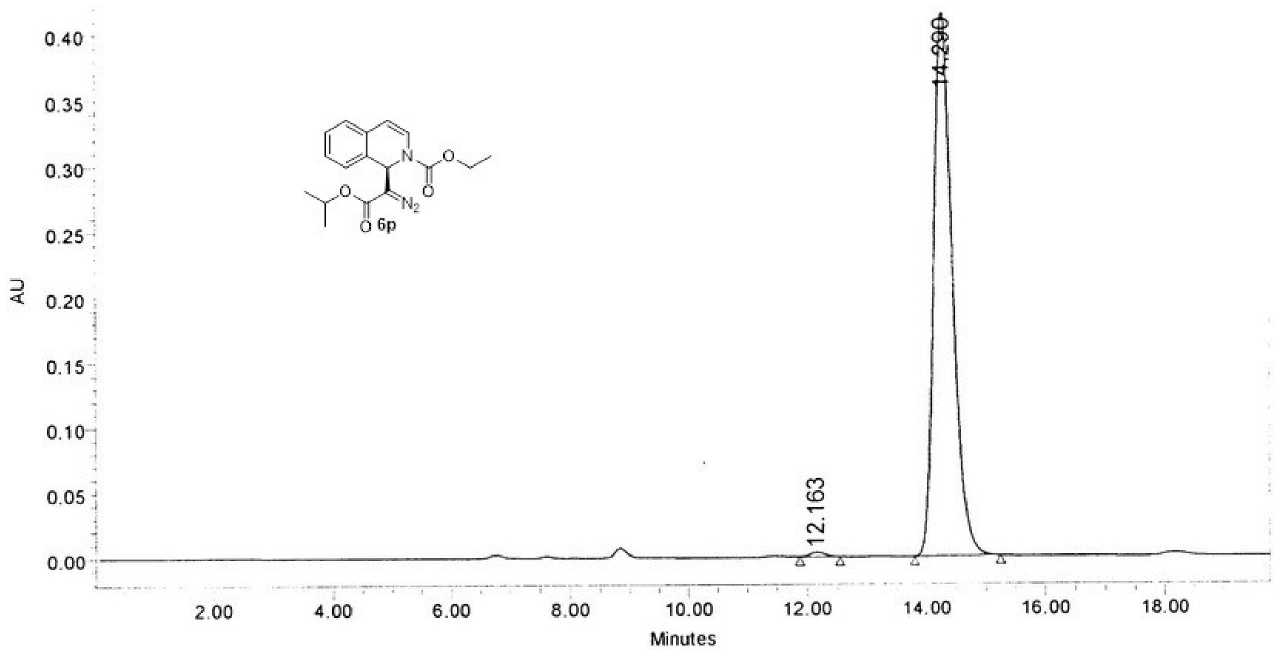
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	13.697	4271697	50.19	195902	55.00
2	16.596	4240163	49.81	160305	45.00



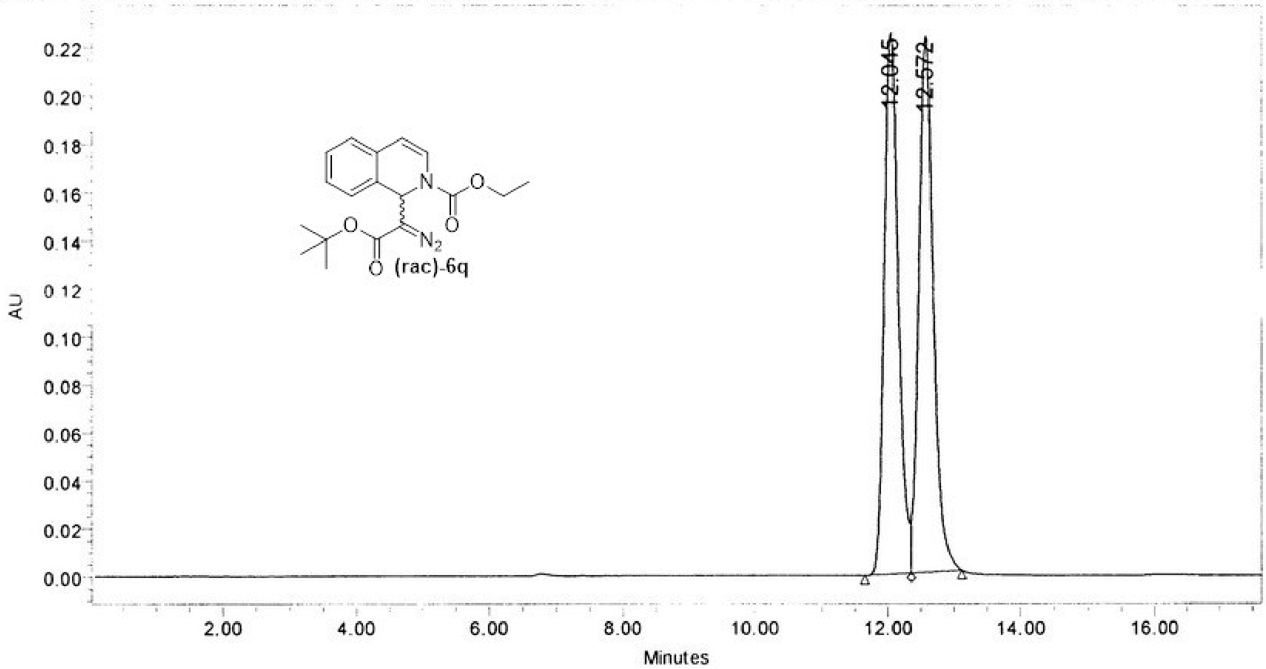
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	14.009	135296	2.54	6587	3.21
2	16.943	5200033	97.46	198926	96.79



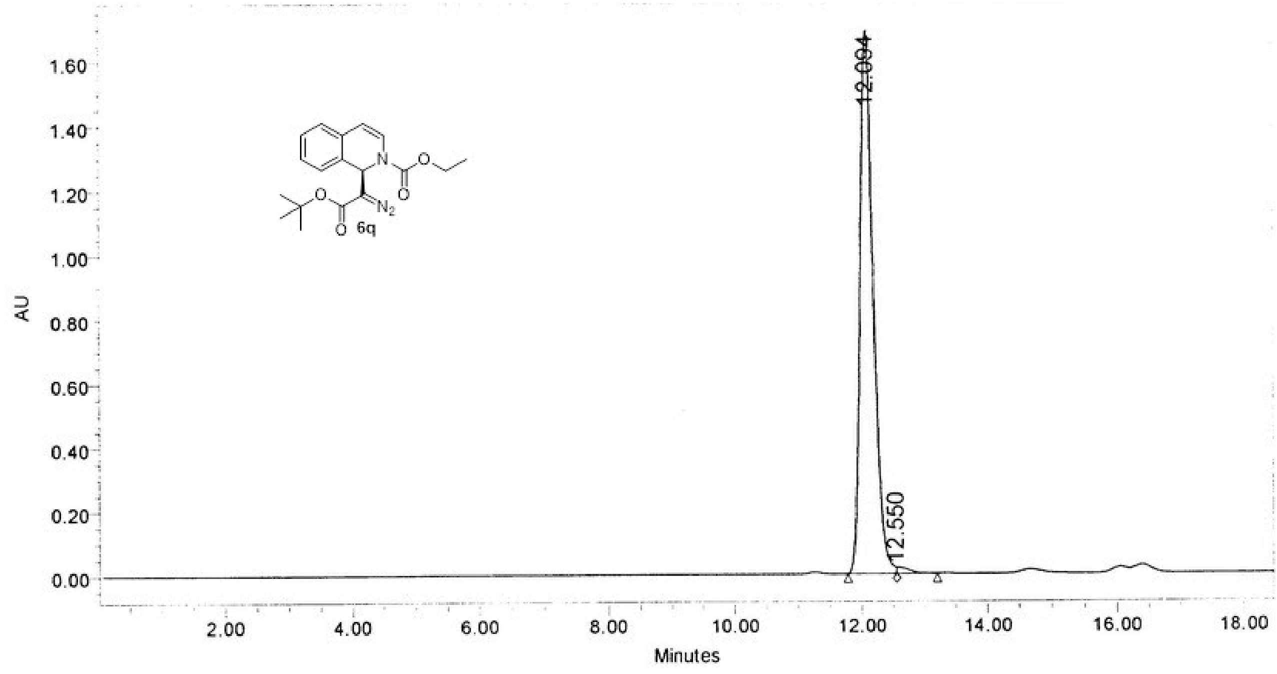
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	12.118	1088025	49.46	51554	52.75
2	14.451	1111687	50.54	46177	47.25



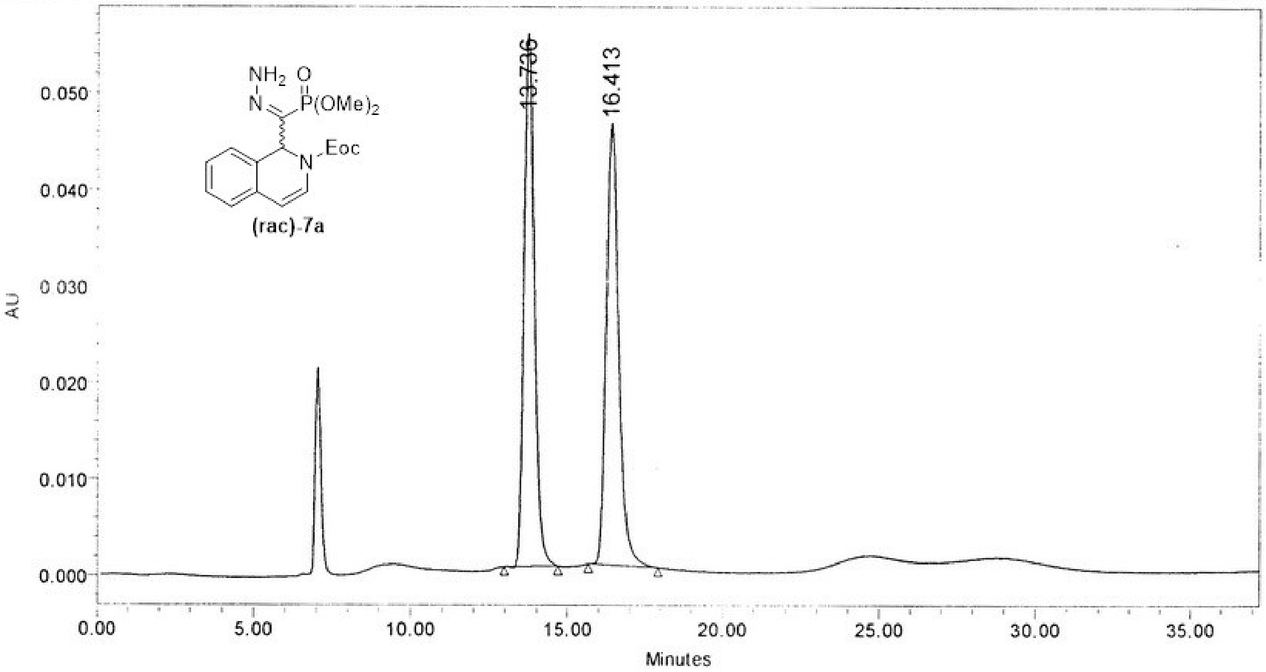
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	12.163	57432	0.63	3253	0.78
2	14.290	9078872	99.37	415437	99.22



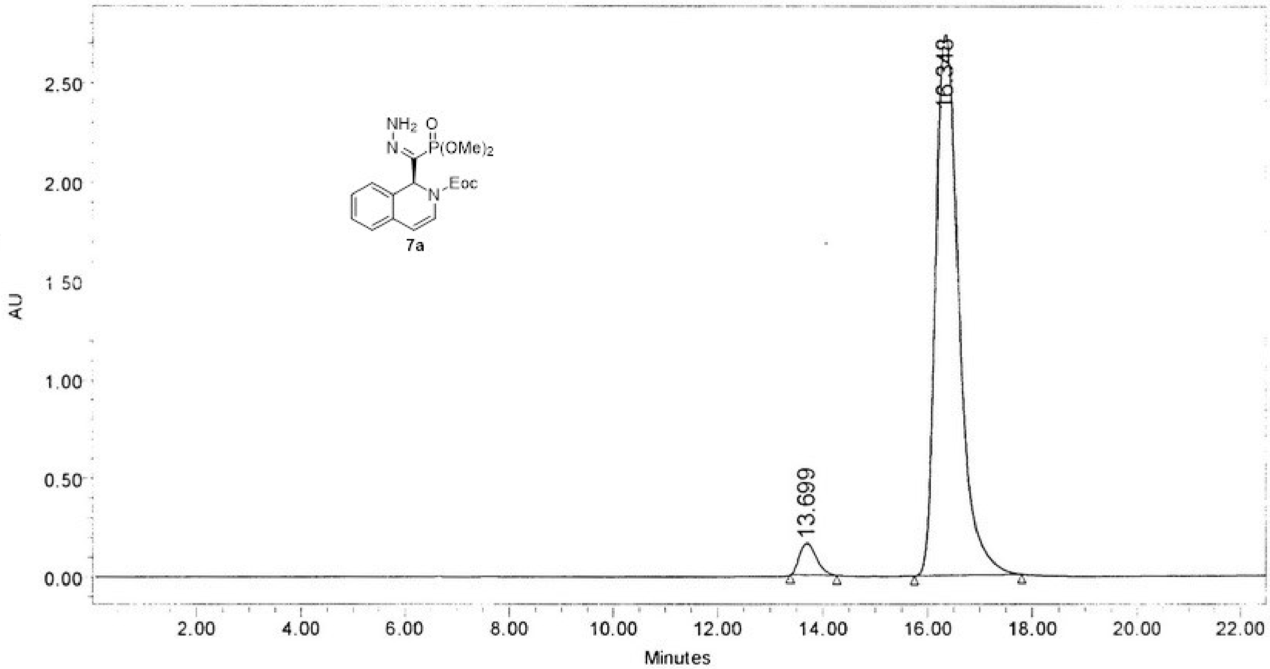
	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	12.045	3338791	49.17	225506	50.25
2	12.572	3450930	50.83	223302	49.75



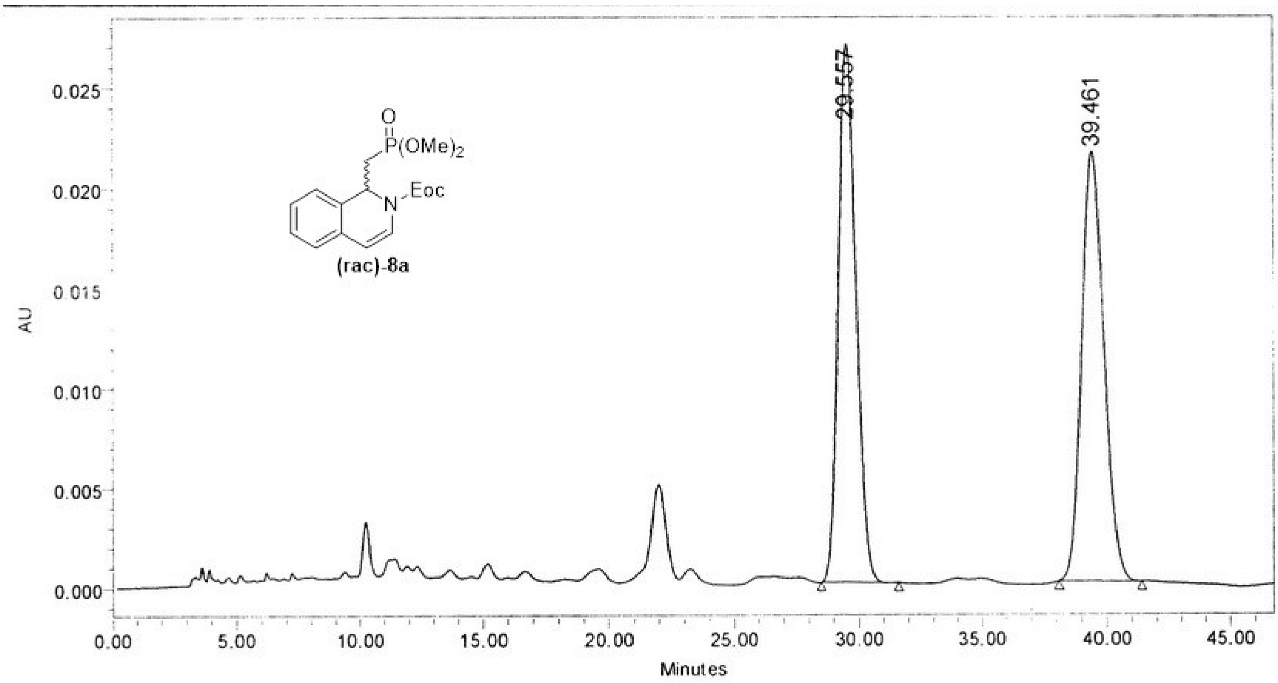
	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	12.094	24603527	98.94	1693988	98.90
2	12.550	262911	1.06	18839	1.10



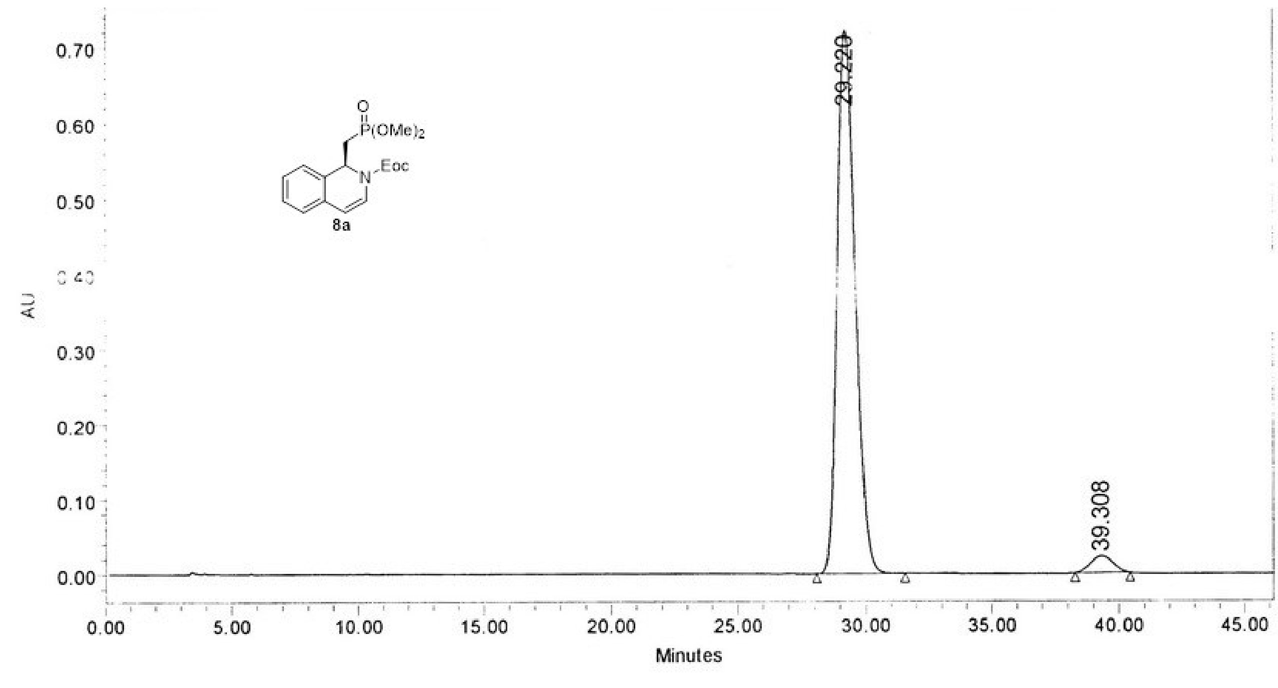
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	13.736	1244649	49.22	55109	54.57
2	16.413	1284160	50.78	45871	45.43



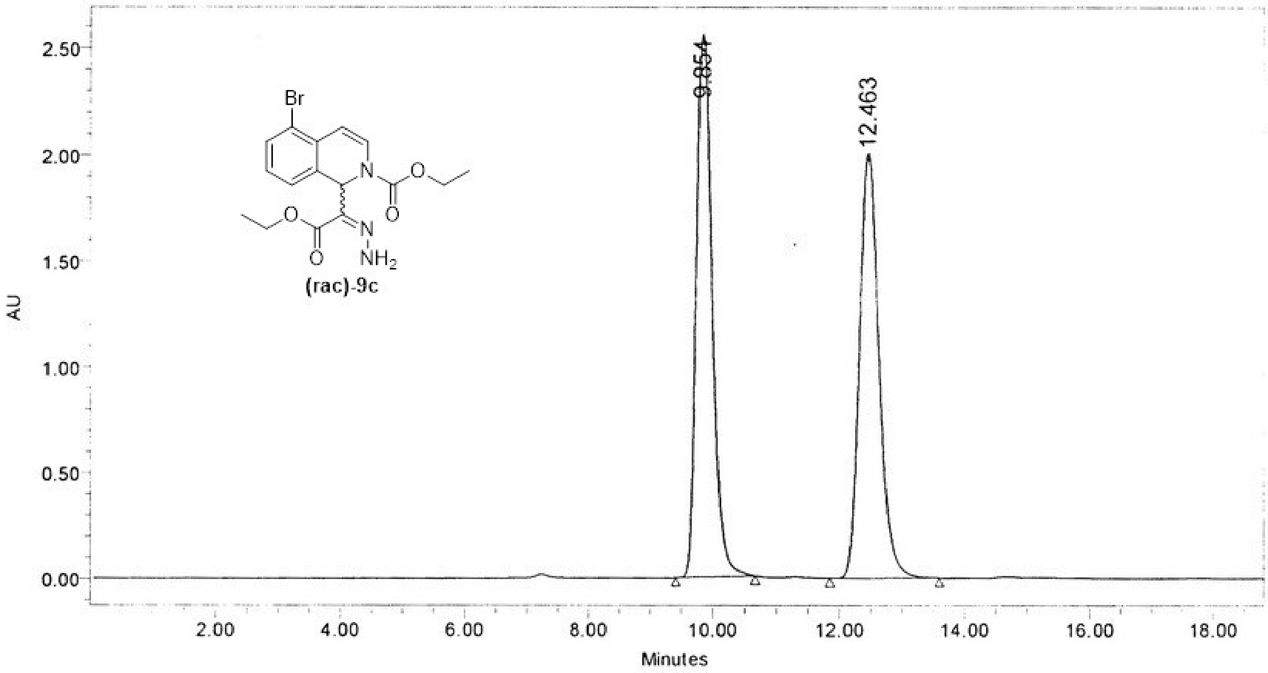
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	13.699	3571008	4.04	161269	5.55
2	16.348	84732688	95.96	2741976	94.45



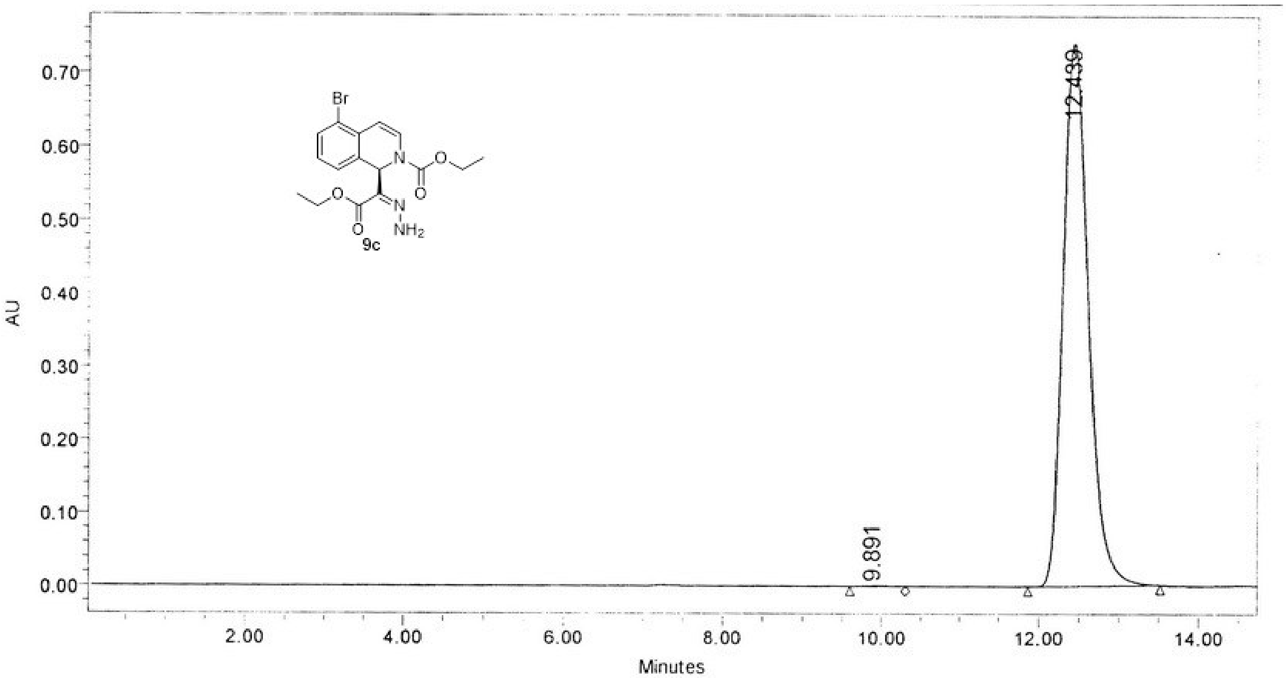
	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	29.557	1318423	50.11	26887	55.59
2	39.461	1312839	49.89	21483	44.41



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	29.220	35266490	96.30	722292	97.01
2	39.308	1354715	3.70	22248	2.99



	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	9.854	44790690	50.83	2556705	56.01
2	12.463	43323513	49.17	2008355	43.99



	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	9.891	14372	0.09	855	0.12
2	12.439	16195637	99.91	742200	99.88