Organocatalytic regio- and stereoselective synthesis of chiral tetrasubstituted *α*-amino allenoates by *γ*-additions of *β*,*γ*-alkynyl-*α*-imino esters with pyrazolones

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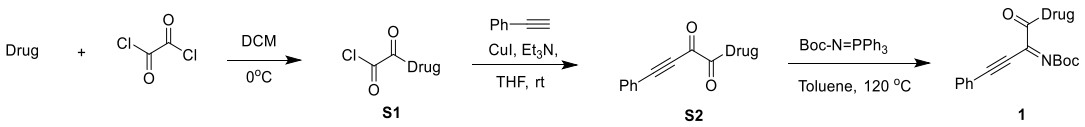
1. General information

Unless otherwise noted, materials were purchased from commercial suppliers and used without further purification. Column chromatography was performed on silica gel (200~300 mesh). Diastereomeric ratios (dr) were determined by ^{1}H NMR (400 MHz). Enantiomeric excesses (ee) were determined by HPLC using corresponding commercial chiral columns as stated at 30 °C with UV detector at 254 nm. Optical rotations were reported as follows: $[\alpha]_D^{17}$ (c g/100 mL, solvent). All ^{1}H NMR spectra were recorded on Bruker Avance II 400 MHz. ^{19}F NMR spectra were recorded on Bruker Avance II 377 MHz and. ^{13}C NMR spectra were recorded on Bruker Avance II 101 MHz with chemical shifts reported as ppm (in $CDCl_3$, TMS as internal standard). Data for ^{1}H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, br = broad singlet, dd = double doublet, coupling constants in Hz, integration). HRMS (ESI) was obtained with a HRMS/MS instrument (LTQ Orbitrap aXLTM). The absolute configuration of **3aa** was assigned by the X-ray analysis.

2. General experimental procedures

Starting Materials. All solvents, inorganic reagents were from commercial sources and used without purification unless otherwise noted. *β*,*γ*-alkynyl-*α*-imino esters and isoxazol-5(4*H*)-ones were prepared following the literature procedures.[1]

2.1 Experimental procedures and characterization of compounds 1



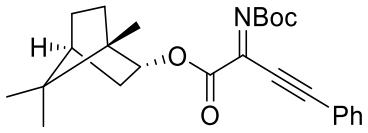
The substrates 1 containing drug fragments were prepared based on literature procedures.[2]

Into a 100 mL round-bottom flask equipped with a magnetic stir-bar was added solution of oxalyl chloride (2.0 equiv) in DCM (20 mL). The mixture was stirred at 0 °C, and a solution of an appropriate Drug (1.0 equiv) in dry DCM (0.3 M) was added drop-wise over 30 min. When the addition was completed, the mixture was allowed to warm to room temperature for 2 h. Excess oxalyl chloride was removed by vacuum distillation. The alkyloxyoxalyl chloride **S1** was used for the next step without purification.

A two necked round bottomed flask was charged with CuI (10 mol%) and THF (0.3 M), trimethylamine (2.0 equiv), alkyne (1.0 equiv) and ethyl 2 –chloro-2- oxoacetate (1.5 equiv) were added sequentially and the resulting mixture was stirred at room temperature for 24 hours. The reaction was quenched by saturated $NaHCO_3$ aqueous solution and the aqueous phase was extracted with ethyl acetate. The organic phases were combined, dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by silica gel chromatography (PE/ ethyl acetate 20:1) to give the **S2**.

An oven-dried round bottom flask was added ketoesters **S2** (1.0 equiv), *N*-Boc

triphenyliminophosphorane or *N*-Cbztriphenyliminophosphorane (1.2 equiv) and toluene. The mixture was heated to 120 °C using an oil bath and stirred for 24 - 72hrs. After cooling to room temperature, the mixture was concentrated under vacuum. The residue was purified by silica gel chromatography (PE/ ethyl acetate 10:1) to give the **(1S,2R,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl-2-((tert-butoxycarbonyl)imino)-4-phenylbut-3-ynoate (1j)**

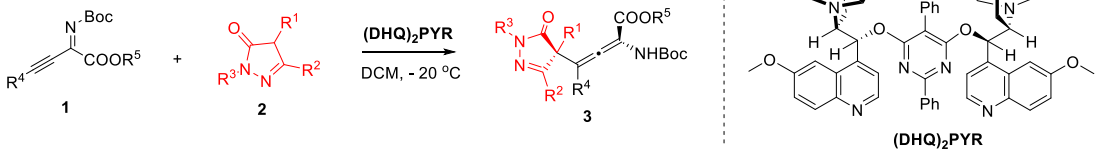


1j

The product was obtained as a white oil (23% yield); $[\alpha]_D^{17}$ = 6.480 (*c* 0.89, CH_2Cl_2);

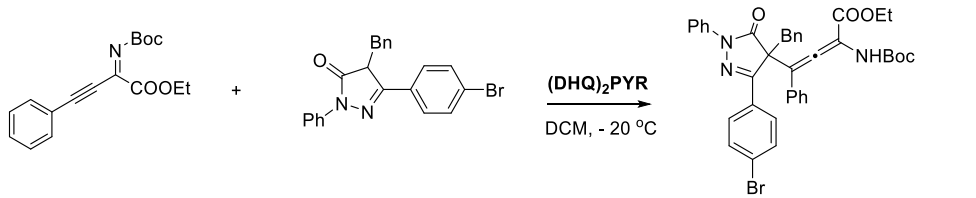
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.1 Hz, 2H), 7.48 (m, *J* = 7.5 Hz, 1H), 7.40 (m, *J* = 7.4 Hz, 2H), 5.10 (d, *J* = 9.8 Hz, 1H), 2.47 (tt, *J* = 14.1, 4.3 Hz, 1H), 2.16 (ddd, *J* = 13.1, 9.3, 4.3 Hz, 1H), 1.83 – 1.74 (m, 2H), 1.60 (s, 9H), 1.47 – 1.38 (m, 1H), 1.36 – 1.29 (m, 1H), 1.15 (dd, *J* = 14.0, 3.4 Hz, 1H), 0.96 – 0.91 (m, 9H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 160.97, 160.31, 145.18, 132.81, 131.00, 128.78, 120.09, 100.72, 84.07, 83.27, 81.29, 49.30, 48.01, 44.93, 36.57, 28.15, 27.98, 27.06, 19.69, 18.89, 13.56.
HRMS (ESI): exact mass calculated for $[M+Na]^+$($C_{25}H_{31}NO_4$+Na^+) requires m/z 432.2151, found m/z 432.2146.

2.2 General Procedure for the synthesis of products 3



To a solution of DCM (2.0 mL) were added *β*,*γ*-alkynyl-*α*-imino esters **1** (0.1 mmol), pyrazolone **2** (0.12 mmol) and catalyst **(DHQ)$_2$PYR** (0.01 mmol). The reaction mixture was stirred at -20 ºC for 12-24 h and then the solvent was removed under vacuum. The residue was purified by silica gel chromatography to yield the desired product **3**.

2.3 Gram-scale synthesis of product 3am



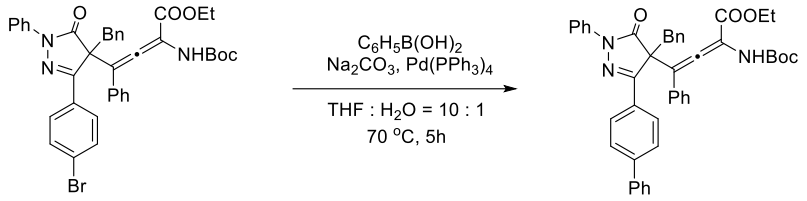
1a
2.2 mmol
662mg

2m
2.6 mmol
1066 mg

3am
1.02 g, 66% yield, >20:1 dr, 89% ee

To a solution of DCM (24.0 mL) were added β,γ-alkynyl-α-imino esters **1a** (2.2 mmol), pyrazolone **2m** (2.6 mmol) and catalyst **(DHQ)$_2$PYR** (0.22 mmol). The reaction mixture was stirred at -20 ºC for 12 h and then the solvent was removed under vacuum. The residue was purified by silica gel chromatography to yield the desired product **3am**.

2.4 Synthetic Transformations of product 4

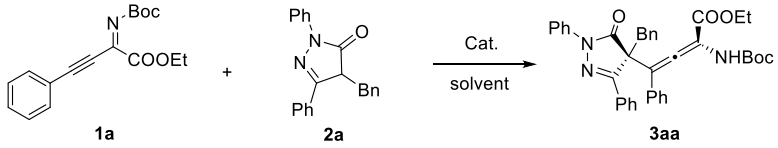


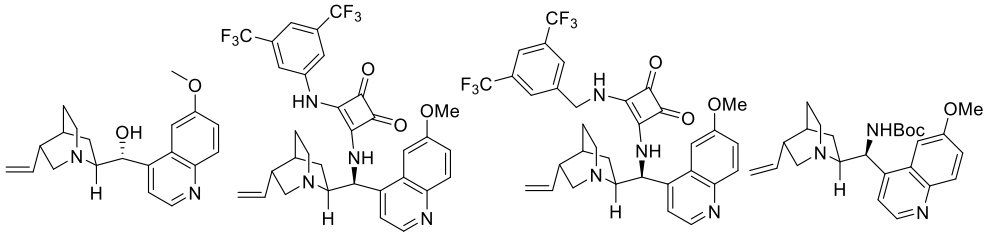
3am → **4**

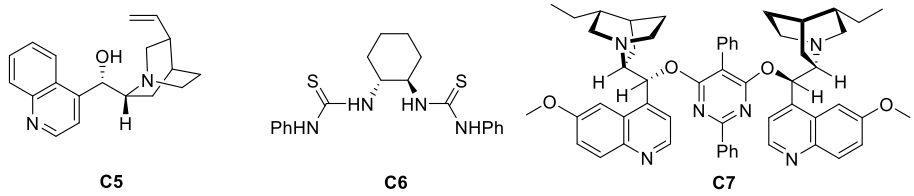
91% yield, >20:1 dr, 87% ee

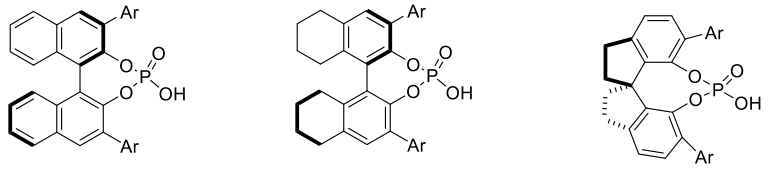
To an oven-dried round-bottom flask, equipped with a magnetic stir bar, compound **3am** (70.5 mg, 0.1 mmol, 1.0 equiv) was taken and treated with $Pd(PPh_3)_4$ (23.1 mg, 0.02 mmol, 20 mol %), phenylboronic acid (24.4 mg, 0.2 mmol, 2 equiv), and Na_2CO_3 (15.9 mg, 0.15 mmol, 1.5 equiv) in THF/H_2O (1 mL, 10:1). The reaction mixture was stirred at 70 °C for 8 h. Upon completion of the reaction, the reaction was quenched with brine and extracted with DCM. The combined organic layers were dried and concentrated under reduced pressure. Then, the reaction mixture was purified using silica gel flash column chromatography to afford the product **4** as a white solid (64.00 mg, 91% yield, 87% ee).

3. Optimization of reaction conditions









C8, Ar = 2,4,6-$^{i}Pr_3CH_2$
C9, Ar = 3,5-$(CF_3)_2$-C_6H_3

C10, Ar = 9-phenanthryl
C11, Ar = 9-pyrenyl
C12, Ar = 9-anthryl

C13, Ar = 2-naphthyl

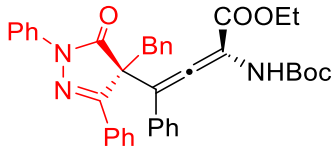
Entry[a]	**Cat.**	Solvent	t[h]	Yield[%][b]	dr[c]	ee[%][d]
1	**DPP**	DCE	72	49	5:1	--
2	**C1**	DCE	12	72	>20:1	-36
3	**C2**	DCE	12	68	10:1	58
4	**C3**	DCE	12	71	>20:1	54
5	**C4**	DCE	12	66	>20:1	51
6	**C5**	DCE	12	36	1.1:1	32
7	**C5**	DCE	12	74	>20:1	64
8	**C7**	DCE	10	94	>20:1	78
9	**C8**	DCE	72	45	3:1	6
10	**C9**	DCE	72	43	5:1	6
11	**C10**	DCE	72	47	2:1	22
12	**C11**	DCE	72	42	5:1	30
13	**C12**	DCE	72	45	5:1	34
14	**C13**	DCE	72	46	1:1	-10
15	**C7**	DCM	9	78	>20:1	80
16	**C7**	EtOAc	10	94	>20:1	79

17	**C7**	THF	12	84	>20:1	75
18[h]	**C7**	DCM	10	80	>20:1	70
19[i]	**C7**	DCM	11	91	>20:1	82
20[f]	**C7**	DCM	12	77	>20:1	81
21[g]	**C7**	DCM	10	80	>20:1	81
22[j]	**C7**	DCM	11	84	>20:1	84
23[je]	**C7**	DCM	11	93	>20:1	84
24[k]	**C7**	DCM	12	87	>20:1	87
25[kg]	**C7**	DCM	12	93	>20:1	88
26[kf]	**C7**	DCM	12	88	>20:1	90
27[ki]	**C7**	DCM	21	85	>20:1	90
28[kfi]	**C7**	DCM	21	85	>20:1	88
29[kl]	**C7**	DCM	16	86	>20:1	90

[a] The reaction was conducted with **1a** (0.1 mmol), **2a** (0.12 mmol) and **Cat.** (10 mol %) in solvent (1.0 mL) at rt. [b] Isolated yield. [c] Determined by 1H NMR of the crude mixture. [d] Detected by chiral HPLC analysis. [e] 2a (1.5 equiv) was added. [f] DCM (2.0 mL) was used. [g] DCM (0.5 mL) was used. [h] catalyst (20 mol%) was used. [i] catalyst (5 mol%) was used. [j] The temperature is 0 °C. [k] The temperature is -20 °C. [l] DCM (4 mL) was used.

4. Characterization Data

ethyl(R)-4-((S)-4-benzyl-5-oxo-1,3-diphenyl-4,5-dihydro-1H-pyrazol-4-yl)-2-((tert-butoxycarbonyl)a-mino)-4-phenylbuta-2,3-dienoate (3aa)

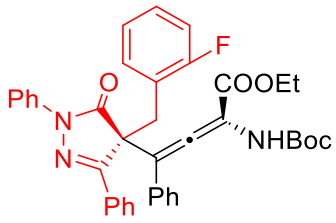


3aa

yellow solid, 88% yield, dr > 20:1, mp 95.3-96.5 °C; $[\alpha]_D^{17}$ = 30.488 (*c* 0.57, CH_2Cl_2);

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 – 8.16 (m, 2H), 7.43 (d, *J* = 7.3 Hz, 2H), 7.38 – 7.31 (m, 3H), 7.24 – 7.17 (m, 4H), 7.06 – 6.99 (m, 4H), 6.91 (m, *J* = 14.5, 7.0 Hz, 3H), 6.73 (d, *J* = 6.7 Hz, 2H), 6.41 (s, 1H), 4.38 (dq, *J* = 10.6, 7.1 Hz, 1H), 4.24 (dq, *J* = 10.6, 7.1 Hz, 1H), 3.50 – 3.40 (m, 2H), 1.49 (s, 9H), 1.38 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 202.68, 172.72, 164.76, 157.91, 151.72, 137.64, 134.72, 134.26, 131.17, 130.34, 129.85, 128.74, 128.50, 128.23, 127.86, 127.80, 127.67, 127.38, 127.23, 125.62, 120.27, 115.96, 105.62, 81.00, 63.46, 62.85, 42.27, 28.42, 14.39.
HRMS (ESI): exact mass calculated for $[M+Na]^+$($C_{39}H_{37}N_3O_5$+Na^+) requires m/z 650.2631, found m/z 650.2624. The enantiomeric excess was determined to be 90% by HPLC. [IE+ID column, 254 nm, *n*-hexane:^{i}PrOH = 75:1, 0.8 mL/min]: 14.4 min (minor), 19.5 min (major).

ethyl (R)-2-((tert-butoxycarbonyl)amino)-4-((S)-4-(2-fluorobenzyl)-5-oxo-1,3-diphenyl-4,5-dihydro-1H-pyrazol-4-yl)-4-phenylbuta-2,3-dienoate (3ab)

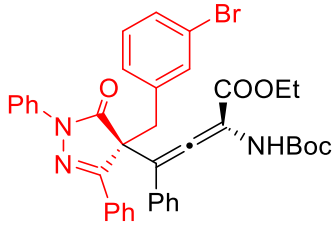


3ab

white solid, 84% yield, dr > 20:1, mp 93.3-93.9 °C; $[\alpha]_D^{17}$ = 45.310 (*c* 0.76, CH_2Cl_2);

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (dd, *J* = 6.7, 2.9 Hz, 2H), 7.60 (d, *J* = 8.1 Hz, 2H), 7.45 – 7.38 (m, 3H), 7.34 – 7.26 (m, 4H), 7.13 (dd, *J* = 19.4, 5.7 Hz, 4H), 6.98 (m, *J* = 14.8, 7.1 Hz, 2H), 6.75 (q, *J* = 9.0, 8.0 Hz, 2H), 6.51 (s, 1H), 4.52 – 4.43 (m, 1H), 4.37 – 4.28 (m, 1H), 3.74 (d, *J* = 13.2 Hz, 1H), 3.56 (d, *J* = 13.5 Hz, 1H), 1.58 (s, 9H), 1.48 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 202.64, 172.57, 164.72, 164.67, 162.30, 159.84, 158.01, 151.70, 137.69, 134.61, 134.56, 131.90, 131.86, 130.85, 130.29, 129.11, 129.03, 128.78, 128.49, 128.23, 127.83, 127.36, 125.55, 123.49, 121.69, 121.53, 120.04, 115.97, 115.24, 115.02, 105.77, 81.05, 62.88, 62.78, 34.81, 28.40, 14.34.
^{19}F NMR (377 MHz, $CDCl_3$) δ -114.34.
HRMS (ESI): exact mass calculated for $[M+Na]^+$($C_{39}H_{36}FN_3O_5$+Na^+) requires m/z 668.2531, found m/z 668.2527. The enantiomeric excess was determined to be 71% by HPLC. [IE+ID column, 254 nm, *n*-hexane:^{i}PrOH = 75:1, 0.8 mL/min]: 16.2 min (minor), 20.4 min (major).

ethyl (R)-4-((S)-4-(3-bromobenzyl)-5-oxo-1,3-diphenyl-4,5-dihydro-1H-pyrazol-4-yl)-2-((tert-butoxycarbonyl)amino)-4-phenylbuta-2,3-dienoate (3ad)



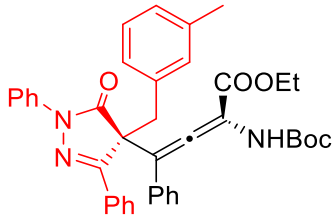
3ac

yellow solid, 78% yield, dr > 20:1, mp 152.5-152.8 °C; $[\alpha]_D^{17}$ = 25.68 (*c* 1.17, CH_2Cl_2);

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 – 8.16 (m, 2H), 7.47 (d, *J* = 7.4 Hz, 2H), 7.36 (dd, *J* = 5.3, 2.0 Hz, 3H), 7.25 (m, *J* = 7.8 Hz, 2H), 7.19 (dd, *J* = 6.7, 3.0 Hz, 2H), 7.09 (d, *J* = 7.4 Hz, 2H), 7.05 – 7.01 (m, 3H), 6.84 (s, 1H), 6.76 (m, *J* = 7.8 Hz, 1H), 6.66 (d, *J* = 7.7 Hz, 1H), 6.41 (s, 1H), 4.38 (dq, *J* = 10.6, 7.1 Hz, 1H), 4.26 (dq, *J* = 10.6, 7.1 Hz, 1H), 3.44 – 3.35 (m, 2H), 1.50 (s, 9H), 1.38 (d, *J* = 14.3 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 202.55, 172.49, 164.64, 157.76, 151.70, 137.45, 136.64, 134.55, 132.85, 130.97, 130.52, 130.35, 129.38, 128.86, 128.81, 128.52, 128.44,

128.30, 127.77, 127.35, 125.78, 121.77, 120.31, 115.64, 105.68, 81.08, 77.43, 77.11, 76.79, 63.20, 62.89, 41.62, 28.41, 14.36.
HRMS (ESI): exact mass calculated for $[M+Na]^+$($C_{39}H_{36}BrN_3O_5$+Na^+) requires m/z 728.1731, found m/z 728.1726. The enantiomeric excess was determined to be 82% by HPLC. [ID+IF column, 254 nm, *n*-hexane:^{i}PrOH = 75:1, 0.8 mL/min]: 18.1 min (minor), 21.7 min (major).

ethyl (R)-2-((tert-butoxycarbonyl)amino)-4-((S)-4-(3-methylbenzyl)-5-oxo-1,3-diphenyl-4,5-dihydro-1H-pyrazol-4-yl)-4-phenylbuta-2,3-dienoate (3ac)

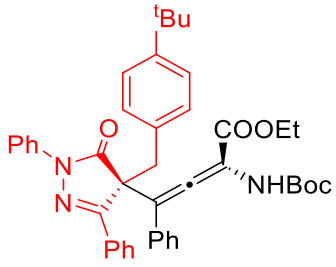


3ad

white solid, 86% yield, dr > 20:1, mp 139.8-140.5 °C; $[\alpha]_D^{17}$ = 30.610 (*c* 0.97, CH_2Cl_2);

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 – 8.23 (m, 2H), 7.57 – 7.52 (m, 2H), 7.42 (dd, *J* = 5.2, 2.0 Hz, 3H), 7.34 – 7.27 (m, 4H), 7.17 – 7.09 (m, 4H), 6.90 – 6.82 (m, 2H), 6.62 – 6.56 (m, 2H), 6.50 (s, 1H), 4.46 (dq, *J* = 10.7, 7.1 Hz, 1H), 4.35 (dq, *J* = 10.6, 7.1 Hz, 1H), 3.49 (d, *J* = 2.2 Hz, 2H), 1.99 (s, 3H), 1.58 (s, 9H), 1.47 (t, *J* = 7.1 Hz, 3H);
^{13}C NMR (101 MHz, $CDCl_3$) δ 203.11, 173.28, 165.12, 158.45, 152.07, 138.04, 137.67, 135.11, 134.43, 131.66, 130.89, 130.64, 129.07, 129.04, 128.86, 128.57, 128.26, 128.15, 128.02, 127.76, 127.19, 125.94, 120.62, 116.31, 105.95, 81.33, 63.78, 63.19, 42.63, 28.77, 21.43, 14.74.
HRMS (ESI): exact mass calculated for $[M+Na]^+$($C_{40}H_{39}N_3O_5$+Na^+) requires m/z 664.2782, found m/z 664.2784. The enantiomeric excess was determined to be 90% by HPLC. [IF+IG column, 254 nm, *n*-hexane:^{i}PrOH = 75:1, 0.8 mL/min]: 13.4 min (minor), 15.2 min (major).

ethyl (R)-2-((tert-butoxycarbonyl)amino)-4-((S)-4-(4-(tert-butyl)benzyl)-5-oxo-1,3-diphenyl-4,5-dihydro-1H-pyrazol-4-yl)-4-phenylbuta-2,3-dienoate (3ae)



3ae

white solid, 82% yield, dr > 20:1, mp 145.3-145.8 °C; $[\alpha]_D^{17}$ = 40.467 (*c* 0.77, CH_2Cl_2);

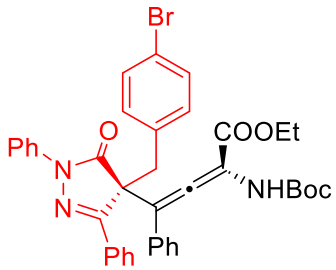
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 – 8.24 (m, 2H), 7.42 – 7.33 (m, 5H), 7.27 – 7.20 (m, 4H), 7.10 – 7.04 (m, 4H), 6.96 (d, *J* = 8.0 Hz, 2H), 6.73 (d, *J* = 8.4 Hz, 2H), 6.47

(s, 1H), 4.44 (dq, *J* = 10.5, 7.1 Hz, 1H), 4.28 (dq, *J* = 10.5, 7.1 Hz, 1H), 3.53 – 3.39 (m, 2H), 1.53 (s, 9H), 1.42 (t, *J* = 7.1 Hz, 3H), 1.11 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 202.88, 172.78, 164.78, 157.95, 151.73, 150.00, 137.61, 134.81, 131.35, 131.14, 131.03, 130.29, 129.59, 128.75, 128.66, 128.52, 128.21, 127.76, 127.39, 125.72, 124.68, 120.70, 115.97, 105.69, 80.97, 63.47, 62.84, 41.93, 34.37, 31.29, 28.43, 14.41.

HRMS (ESI): exact mass calculated for $[M+Na]^+$($C_{43}H_{45}N_3O_5$+Na^+) requires m/z 706.3251, found m/z 706.3256. The enantiomeric excess was determined to be 89% by HPLC. [IF+IE column, 254 nm, *n*-hexane:^{i}PrOH = 75:1, 0.8 mL/min]: 13.7 min (minor), 15.5 min (major).

ethyl (R)-4-((S)-4-(4-bromobenzyl)-5-oxo-1,3-diphenyl-4,5-dihydro-1H-pyrazol-4-yl)-2-((tert-butoxycarbonyl)amino)-4-phenylbuta-2,3-dienoate (3af)



3af

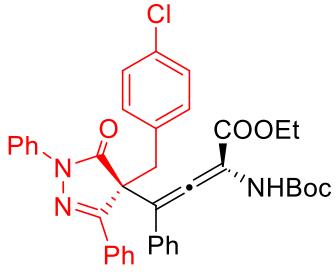
white solid, 86% yield, dr > 20:1, mp 98.4-98.9 °C; $[\alpha]_D^{17}$ = 31.289 (*c* 1.29, CH_2Cl_2);

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (dd, *J* = 6.9, 2.9 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 6.6 Hz, 3H), 7.24 (m, *J* = 7.8 Hz, 2H), 7.17 (dd, *J* = 6.8, 3.0 Hz, 2H), 7.10 – 6.99 (m, 6H), 6.59 (d, *J* = 8.0 Hz, 2H), 6.41 (s, 1H), 4.37 (dq, *J* = 10.6, 7.1 Hz, 1H), 4.24 (dq, *J* = 10.9, 7.1 Hz, 1H), 3.40 (q, *J* = 13.0 Hz, 2H), 1.49 (s, 9H), 1.38 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 202.53, 172.51, 164.65, 157.70, 151.72, 137.50, 134.56, 133.41, 131.57, 130.98, 130.95, 130.50, 128.83, 128.51, 128.29, 127.77, 127.32, 125.77, 121.37, 120.16, 115.73, 105.66, 81.06, 63.23, 62.87, 41.50, 28.41, 14.36.

HRMS (ESI): exact mass calculated for $[M+Na]^+$($C_{39}H_{36}BrN_3O_5$+Na^+) requires m/z 728.1731, found m/z 728.1727. The enantiomeric excess was determined to be 90% by HPLC. [IC column, 254 nm, *n*-hexane:^{i}PrOH = 75:1, 0.8 mL/min]: 6.0 min (major), 7.2 min (minor).

ethyl (R)-2-((tert-butoxycarbonyl)amino)-4-((S)-4-(4-chlorobenzyl)-5-oxo-1,3-diphenyl-4,5-dihydro-1H-pyrazol-4-yl)-4-phenylbuta-2,3-dienoate (3ag)

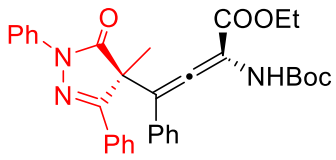


3ag

white solid, 65% yield, dr > 20:1, mp 93.0-93.8 °C; $[\alpha]_D^{17}$ = 11.000 (*c* 0.10, CH_2Cl_2);

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 – 8.16 (m, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 5.4 Hz, 3H), 7.24 (m, *J* = 7.8 Hz, 2H), 7.20 – 7.14 (m, 2H), 7.09 – 6.99 (m, 4H), 6.87 (d, *J* = 8.0 Hz, 2H), 6.65 (d, *J* = 8.0 Hz, 2H), 6.41 (s, 1H), 4.36 (dq, *J* = 14.4, 7.0 Hz, 1H), 4.24 (dq, *J* = 14.2, 7.6 Hz, 1H), 3.42 (q, *J* = 13.0 Hz, 2H), 1.49 (s, 9H), 1.38 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 202.55, 172.54, 164.66, 157.73, 151.73, 137.53, 134.57, 133.14, 132.90, 131.21, 130.97, 130.50, 128.83, 128.52, 128.29, 128.03, 127.77, 127.33, 125.75, 120.13, 115.75, 105.66, 81.06, 63.31, 62.87, 41.46, 28.41, 14.36.
HRMS (ESI): exact mass calculated for $[M+Na]^+$($C_{39}H_{36}ClN_3O_5$+Na^+) requires m/z 684.2241, found m/z 684.2229. The enantiomeric excess was determined to be 91% by HPLC. [IC column, 254 nm, *n*-hexane:^{i}PrOH = 75:1, 0.8 mL/min]: 5.8 min (major), 6.8 min (minor).

ethyl (R)-2-((tert-butoxycarbonyl)amino)-4-((S)-4-methyl-5-oxo-1,3-diphenyl-4,5-dihydro-1H-pyrazol-4-yl)-4-phenylbuta-2,3-dienoate (3ah)

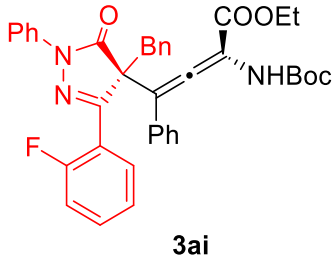


3ah

white solid, 89% yield, dr > 20:1, mp 134.8-135.8 °C; $[\alpha]_D^{17}$ = 96.167 (*c* 0.86, CH_2Cl_2);

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (dd, *J* = 7.4, 2.3 Hz, 2H), 7.99 – 7.95 (m, 2H), 7.44 – 7.39 (m, 5H), 7.25 – 7.19 (m, 3H), 7.11 (dd, *J* = 5.1, 1.9 Hz, 3H), 6.46 (s, 1H), 4.45 – 4.36 (m, 1H), 4.35 – 4.26 (m, 1H), 1.74 (s, 3H), 1.55 (s, 9H), 1.42 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 202.89, 173.87, 164.75, 160.26, 151.62, 138.31, 134.66, 130.43, 130.13, 128.94, 128.66, 128.52, 128.19, 127.51, 127.46, 125.34, 119.38, 116.31, 105.45, 80.89, 62.78, 57.45, 28.36, 22.94, 14.24.
HRMS (ESI): exact mass calculated for $[M+Na]^+$($C_{33}H_{33}N_3O_5$+Na^+) requires m/z 574.2318, found m/z 574.2310. The enantiomeric excess was determined to be 91% by HPLC. [IE column, 254 nm, *n*-hexane:^{i}PrOH = 75:1, 0.8 mL/min]: 9.6 min (minor), 10.6 min (major).

ethyl (R)-4-((S)-4-benzyl-3-(2-fluorophenyl)-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)-2-((tert-butoxycarbonyl)amino)-4-phenylbuta-2,3-dienoate (3aj)

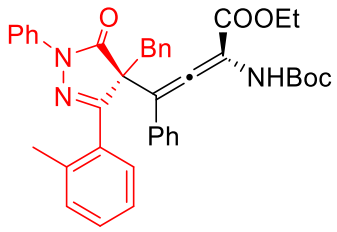


3ai

white solid, 86% yield, dr > 20:1, mp 82.5-83.3 °C; $[\alpha]_D^{17}$ = 3.810 (*c* 1.05, CH_2Cl_2);

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (m, *J* = 8.7 Hz, 1H), 7.45 (d, *J* = 7.3 Hz, 2H), 7.33 – 7.28 (m, 1H), 7.25 – 7.20 (m, 5H), 7.07 – 7.03 (m, 4H), 7.02 – 6.90 (m, 4H), 6.73 (d, *J* = 6.9 Hz, 2H), 6.39 (s, 1H), 4.36 (dq, *J* = 10.5, 7.1 Hz, 1H), 4.25 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.41 (d, *J* = 2.8 Hz, 2H), 1.47 (s, 9H), 1.38 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 202.62, 172.10, 164.65, 161.72, 159.13, 154.60, 154.54, 151.68, 137.55, 134.52, 134.12, 131.51, 131.42, 131.12, 129.55, 128.75, 128.56, 128.32, 128.03, 127.82, 127.33, 125.70, 124.53, 124.49, 120.29, 119.37, 119.28, 116.82, 116.61, 115.82, 105.61, 80.98, 63.91, 62.85, 41.93, 28.39, 14.35.
^{19}F NMR (377 MHz, $CDCl_3$) δ -107.68.
HRMS (ESI): exact mass calculated for $[M+Na]^+$($C_{39}H_{36}FN_3O_5$+Na^+) requires m/z 668.2531, found m/z 668.2526. The enantiomeric excess was determined to be 80% by HPLC. [IE column, 254 nm, *n*-hexane:^{i}PrOH = 75:1, 0.8 mL/min]: 11.1 min (minor), 13.0 min (major).

ethyl (R)-4-((S)-4-benzyl-5-oxo-1-phenyl-3-(o-tolyl)-4,5-dihydro-1H-pyrazol-4-yl)-2-((tert-butoxycarbonyl)amino)-4-phenylbuta-2,3-dienoate (3ai)

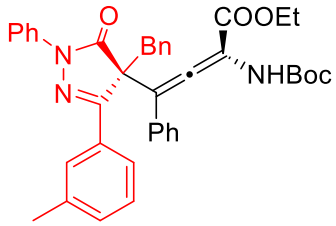


3aj

white solid, 80% yield, dr > 20:1, mp 124.5-125.1 ºC; $[\alpha]_D^{17}$ = 37.822 (*c* 0.85, CH_2Cl_2);

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 7.8 Hz, 1H), 7.84 (s, 1H), 7.45 (d, *J* = 7.3 Hz, 2H), 7.24 (dd, *J* = 9.8, 7.6 Hz, 3H), 7.20 – 7.16 (m, 2H), 7.13 (d, *J* = 7.2 Hz, 1H), 7.07 – 7.00 (m, 4H), 6.95 – 6.88 (m, 3H), 6.75 (d, *J* = 6.7 Hz, 2H), 6.42 (s, 1H), 4.38 (dq, *J* = 10.6, 7.1 Hz, 1H), 4.24 (dq, *J* = 10.5, 7.1 Hz, 1H), 3.52 – 3.39 (m, 2H), 2.34 (s, 3H), 1.48 (s, 9H), 1.38 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 202.74, 172.68, 164.83, 158.10, 151.66, 138.41, 137.67, 134.90, 134.33, 131.25, 131.04, 129.89, 128.74, 128.66, 128.46, 128.15, 127.83, 127.73, 127.20, 127.04, 125.59, 124.95, 120.27, 116.05, 105.56, 80.86, 63.39, 62.84, 42.44, 28.37, 21.47, 14.35.
HRMS (ESI): exact mass calculated for $[M+Na]^+$($C_{40}H_{39}N_3O_5$+Na^+) requires m/z 664.2782, found m/z 664.2789. The enantiomeric excess was determined to be 89% by HPLC. [IE+ID column, 254 nm, *n*-hexane:^{i}PrOH = 75:1, 0.8 mL/min]: 13.9 min (minor), 15.3 min (major).

ethyl (R)-4-((S)-4-benzyl-5-oxo-1-phenyl-3-(m-tolyl)-4,5-dihydro-1H-pyrazol-4-yl)-2-((tert-butoxycarbonyl)amino)-4-phenylbuta-2,3-dienoate (3ak)

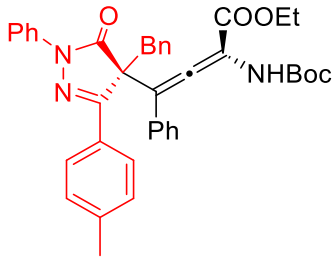


3ak

white solid, 82% yield, dr > 20:1, mp 123.6-124.1 °C; $[\alpha]_D^{17}$ = 35.445 (*c* 0.82, CH_2Cl_2);

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 7.8 Hz, 1H), 7.84 (s, 1H), 7.45 (d, *J* = 8.8 Hz, 2H), 7.22 (dq, *J* = 16.6, 8.5, 8.1 Hz, 5H), 7.13 (d, *J* = 7.6 Hz, 1H), 7.06 – 6.99 (m, 4H), 6.91 (m, *J* = 14.1, 6.9 Hz, 3H), 6.78 – 6.72 (m, 2H), 6.42 (d, *J* = 2.2 Hz, 1H), 4.42 – 4.33 (m, 1H), 4.24 (dq, *J* = 10.6, 7.1 Hz, 1H), 3.46 (q, *J* = 12.9 Hz, 2H), 2.33 (s, 3H), 1.47 (s, 9H), 1.37 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 202.76, 172.69, 164.83, 158.10, 151.67, 138.42, 137.68, 134.91, 134.34, 131.26, 131.05, 129.90, 128.74, 128.67, 128.47, 128.17, 127.84, 127.74, 127.21, 127.04, 125.59, 124.96, 120.27, 116.06, 105.57, 80.87, 63.41, 62.85, 42.46, 28.38, 21.48, 14.36.
HRMS (ESI): exact mass calculated for $[M+Na]^+$($C_{40}H_{39}N_3O_5$+Na^+) requires m/z 664.2782, found m/z 664.2783. The enantiomeric excess was determined to be 88% by HPLC. [IE+IF column, 254 nm, *n*-hexane:^{i}PrOH = 75:1, 0.8 mL/min]: 14.1 min (minor), 15.8 min (major).

ethyl (R)-4-((S)-4-benzyl-5-oxo-1-phenyl-3-(p-tolyl)-4,5-dihydro-1H-pyrazol-4-yl)-2-((tert-butoxycarbonyl)amino)-4-phenylbuta-2,3-dienoate (3al)



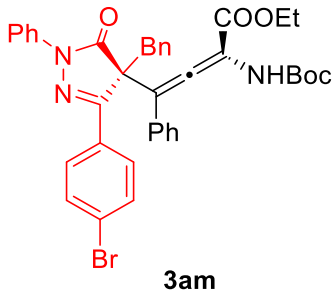
3al

yellow solid, 96% yield, dr > 20:1, mp 184.2-184.8 °C; $[\alpha]_D^{17}$ = 43.783 (*c* 1.13, CH_2Cl_2);

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 7.9 Hz, 2H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.25 – 7.12 (m, 7H), 7.04 (dd, *J* = 10.3, 5.7 Hz, 4H), 6.92 (m, *J* = 14.6, 7.1 Hz, 3H), 6.75 (d, *J* = 7.4 Hz, 2H), 6.40 (s, 1H), 4.39 (dq, *J* = 14.1, 7.2 Hz, 1H), 4.30 – 4.21 (m, 1H), 3.44 (q, *J* = 12.8 Hz, 2H), 2.31 (s, 3H), 1.51 (s, 9H), 1.39 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 202.68, 172.63, 164.78, 157.94, 151.68, 140.45, 137.67, 134.74, 134.31, 129.87, 129.48, 128.69, 128.46, 128.16, 127.79, 127.28, 127.16, 125.51, 120.26, 116.03, 105.54, 80.92, 63.41, 62.81, 42.29, 28.41, 21.71, 14.37.
HRMS (ESI): exact mass calculated for $[M+Na]^+$($C_{40}H_{39}N_3O_5$+Na^+) requires m/z 664.2782, found m/z 664.2778. The enantiomeric excess was determined to be 91% by

HPLC. [IE column, 254 nm, *n*-hexane:^{i}PrOH = 75:1, 0.8 mL/min]: 6.1 min (major), 7.3 min (minor).

ethyl (R)-4-((S)-4-benzyl-3-(4-bromophenyl)-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)-2-((tert-butoxycarbonyl)amino)-4-phenylbuta-2,3-dienoate (3am)



3am

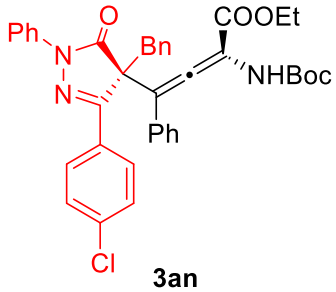
yellow solid, 74% yield, dr > 20:1, mp 185.9-186.5 °C; $[\alpha]_D^{17}$ = 63.405 (*c* 0.70, CH_2Cl_2);

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 7.4 Hz, 2H), 7.22 (m, *J* = 7.9 Hz, 2H), 7.14 (m, *J* = 4.7, 2.9 Hz, 2H), 7.08 – 7.02 (m, 4H), 6.93 (m, *J* = 14.4, 7.0 Hz, 3H), 6.73 (d, *J* = 7.5 Hz, 2H), 6.43 (s, 1H), 4.38 (dq, *J* = 10.5, 7.1 Hz, 1H), 4.24 (dq, *J* = 10.6, 7.1 Hz, 1H), 3.43 (s, 2H), 1.50 (s, 9H), 1.38 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 201.58, 171.50, 163.49, 155.87, 150.70, 136.38, 133.50, 132.93, 131.77, 130.93, 128.95, 128.64, 127.74, 127.67, 127.46, 127.21, 126.82, 126.54, 126.23, 124.67, 123.71, 119.16, 114.59, 104.65, 80.06, 62.11, 61.78, 41.25, 27.33, 13.25.

HRMS (ESI): exact mass calculated for $[M+Na]^+$($C_{39}H_{36}BrN_3O_5$+Na^+) requires m/z 728.1731, found m/z 728.1727. The enantiomeric excess was determined to be 90% by HPLC. [IE column, 254 nm, *n*-hexane:^{i}PrOH = 75:1, 0.8 mL/min]: 5.6 min (major), 6.4 min (minor).

ethyl (R)-4-((S)-4-benzyl-3-(4-chlorophenyl)-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)-2-((tert-butoxycarbonyl)amino)-4-phenylbuta-2,3-dienoate (3an)



3an

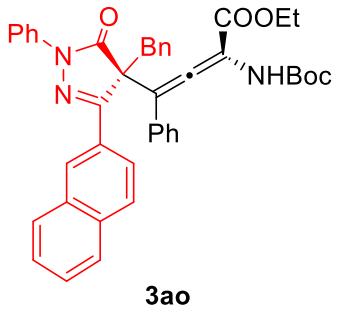
white solid, 87% yield, dr > 20:1, mp 181.4-181.9 °C; $[\alpha]_D^{17}$ = 69.522 (*c* 1.11, CH_2Cl_2);

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.7 Hz, 2H), 7.42 (d, *J* = 7.4 Hz, 2H), 7.31 (d, *J* = 8.7 Hz, 2H), 7.24 (m, *J* = 7.9 Hz, 2H), 7.17 – 7.13 (m, 2H), 7.10 – 7.03 (m, 4H), 6.94 (m, *J* = 14.5, 7.0 Hz, 3H), 6.74 (d, *J* = 6.7 Hz, 2H), 6.43 (s, 1H), 4.39 (dq, *J* = 10.6, 7.1 Hz, 1H), 4.25 (dq, *J* = 10.6, 7.1 Hz, 1H), 3.43 (s, 2H), 1.51 (s, 9H), 1.39 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 202.65, 172.59, 164.59, 156.89, 151.78, 137.47, 136.23, 134.59, 134.03, 129.72, 129.60, 129.04, 128.76, 128.62, 128.54, 128.29, 127.90, 127.64, 127.31, 125.75, 120.26, 115.68, 105.72, 81.14, 63.23, 62.88, 42.32, 28.42, 14.33.

HRMS (ESI): exact mass calculated for $[M+Na]^+$($C_{39}H_{36}ClN_3O_5$+Na^+) requires m/z 684.2241, found m/z 684.2239. The enantiomeric excess was determined to be 90% by HPLC. [IC column, 254 nm, *n*-hexane:^{i}PrOH = 75:1, 0.8 mL/min]: 5.5 min (major), 6.3 min (minor).

ethyl (R)-4-((S)-4-benzyl-3-(naphthalen-2-yl)-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)-2-((tert-butoxycarbonyl)amino)-4-phenylbuta-2,3-dienoate (3ao)



3ao

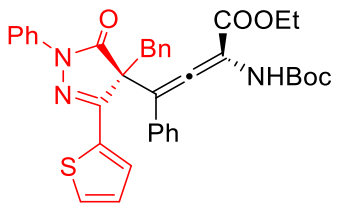
white solid, 85% yield, dr > 20:1, mp 110.2-110.9 °C; $[\alpha]_D^{17}$ = 135.910 (*c* 0.84, CH_2Cl_2);

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (s, 1H), 8.41 (d, *J* = 7.0 Hz, 1H), 7.98 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.70 (m, *J* = 7.9 Hz, 2H), 7.50 (d, *J* = 7.2 Hz, 2H), 7.44 – 7.37 (m, 2H), 7.26 – 7.18 (m, 4H), 7.09 – 7.04 (m, 1H), 6.99 – 6.90 (m, 4H), 6.86 (m, *J* = 7.4 Hz, 2H), 6.73 (d, *J* = 6.9 Hz, 2H), 6.51 (s, 1H), 4.39 (dq, *J* = 10.6, 7.1 Hz, 1H), 4.25 (dq, *J* = 10.5, 7.1 Hz, 1H), 3.63 – 3.47 (m, 2H), 1.55 (s, 9H), 1.38 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 202.78, 172.74, 164.85, 157.91, 151.90, 137.74, 135.05, 134.26, 134.19, 133.76, 132.89, 129.95, 129.88, 128.81, 128.55, 128.28, 128.17, 128.05, 127.88, 127.64, 127.60, 127.26, 127.22, 125.96, 125.67, 123.35, 120.29, 116.43, 105.68, 80.98, 63.40, 62.95, 43.04, 28.45, 14.37.

HRMS (ESI): exact mass calculated for $[M+Na]^+$($C_{43}H_{39}N_3O_5$+Na^+) requires m/z 700.2787, found m/z 700.2787. The enantiomeric excess was determined to be 88% by HPLC. [IE+IF column, 254 nm, *n*-hexane:^{i}PrOH = 75:1, 0.8 mL/min]: 14.8 min (minor), 16.5 min (major).

ethyl (R)-4-((S)-4-benzyl-5-oxo-1-phenyl-3-(thiophen-2-yl)-4,5-dihydro-1H-pyrazol-4-yl)-2-((tert-butoxycarbonyl)amino)-4-phenylbuta-2,3-dienoate (3ap)

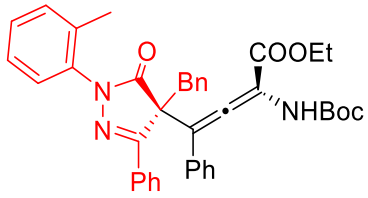


3ap

yellow solid, 85% yield, dr > 20:1, mp 92.8-93.5 °C; $[\alpha]_D^{17}$ = 28.893 (*c* 1.02, CH_2Cl_2);

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, *J* = 3.8 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 5.0 Hz, 1H), 7.22 – 7.17 (m, 4H), 7.07 – 7.01 (m, 5H), 6.96 (q, *J* = 7.4, 6.4 Hz, 3H), 6.82 (d, *J* = 5.8 Hz, 2H), 6.40 (s, 1H), 4.38 (dq, *J* = 10.5, 7.1 Hz, 1H), 4.23 (dt, *J* = 10.6, 7.1 Hz, 1H), 3.47 – 3.39 (m, 2H), 1.47 (s, 9H), 1.38 (t, *J* = 7.2 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 203.07, 172.14, 164.64, 154.48, 151.76, 137.35, 134.62, 134.53, 134.02, 130.97, 129.81, 128.70, 128.56, 128.46, 128.25, 128.10, 127.98, 127.78, 127.33, 125.66, 120.35, 115.54, 105.63, 81.08, 63.83, 62.85, 42.74, 28.33, 14.36.
HRMS (ESI): exact mass calculated for $[M+Na]^+$($C_{37}H_{35}N_3O_5S$+Na^+) requires m/z 656.2195, found m/z 656.2188. The enantiomeric excess was determined to be 91% by HPLC. [IC column, 254 nm, *n*-hexane:^{i}PrOH = 75:1, 0.8 mL/min]: 6.9 min (major), 12.1 min (minor).

ethyl (R)-4-((S)-4-benzyl-5-oxo-3-phenyl-1-(o-tolyl)-4,5-dihydro-1H-pyrazol-4-yl)-2-((tert-butoxycarbonyl)amino)-4-phenylbuta-2,3-dienoate (3aq)

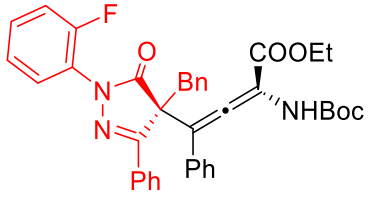


3aq

white solid, 88% yield, dr > 20:1, mp 85.0-85.6 °C; $[\alpha]_D^{17}$ = 9.323 (*c* 1.14, CH_2Cl_2);

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (dd, *J* = 7.5, 2.2 Hz, 2H), 7.43 – 7.37 (m, 3H), 7.28 (dd, *J* = 6.7, 3.0 Hz, 2H), 7.09 (dd, *J* = 5.1, 1.9 Hz, 3H), 7.06 – 6.92 (m, 6H), 6.81 (d, *J* = 6.9 Hz, 2H), 6.43 – 6.33 (m, 2H), 4.41 (dq, *J* = 10.6, 7.1 Hz, 1H), 4.28 (dq, *J* = 10.6, 7.1 Hz, 1H), 3.58 – 3.36 (m, 2H), 1.53 (s, 3H), 1.48 (s, 9H), 1.41 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 202.31, 172.71, 164.93, 157.36, 135.64, 135.31, 134.80, 134.70, 131.66, 130.98, 130.35, 130.29, 128.94, 128.49, 128.45, 128.35, 128.27, 128.09, 127.38, 127.25, 126.35, 126.22, 115.79, 105.03, 80.92, 62.84, 41.30, 28.41, 17.71, 14.44.
HRMS (ESI): exact mass calculated for $[M+Na]^+$($C_{40}H_{39}N_3O_5$+Na^+) requires m/z 664.2782, found m/z 664.2781. The enantiomeric excess was determined to be 80% by HPLC. [ID+IG column, 254 nm, *n*-hexane:^{i}PrOH = 75:1, 0.8 mL/min]: 18.2 min (minor), 21.3 min (major).

ethyl (R)-4-((S)-4-benzyl-1-(2-fluorophenyl)-5-oxo-3-phenyl-4,5-dihydro-1H-pyrazol-4-yl)-2-((tert-butoxycarbonyl)amino)-4-phenylbuta-2,3-dienoate (3ar)

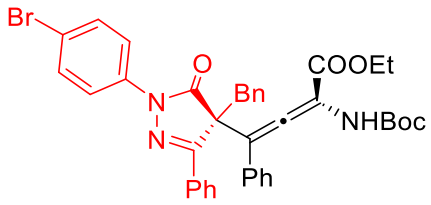


3ar

white solid, 92% yield, dr > 20:1, mp 98.0-98.7 °C; $[\alpha]_D^{17}$ = 43.762 (*c* 1.07, CH_2Cl_2);

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (dd, *J* = 6.6, 2.9 Hz, 2H), 7.38 – 7.27 (m, 5H), 7.15 – 7.04 (m, 5H), 6.96 (m, *J* = 27.7, 7.5 Hz, 4H), 6.80 (d, *J* = 7.1 Hz, 2H), 6.57 – 6.50 (m, 1H), 6.42 (s, 1H), 4.37 (dq, *J* = 10.4, 7.1 Hz, 1H), 4.22 (dq, *J* = 10.6, 7.1 Hz, 1H), 3.55 – 3.39 (m, 2H), 1.50 (s, 9H), 1.36 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 202.55, 172.78, 164.78, 158.51, 158.33, 155.80, 151.70, 134.64, 134.33, 131.10, 130.35, 130.18, 129.61, 129.54, 128.77, 128.44, 128.26, 128.01, 127.96, 127.51, 127.31, 127.26, 124.69, 124.57, 124.26, 124.22, 116.78, 116.59, 115.82, 105.58, 80.98, 62.82, 62.55, 41.98, 28.42, 14.39.
^{19}F NMR (377 MHz, $CDCl_3$) δ -118.41.
HRMS (ESI): exact mass calculated for $[M+Na]^+$($C_{39}H_{36}FN_3O_5$+Na^+) requires m/z 668.2531, found m/z 668.2527. The enantiomeric excess was determined to be 82% by HPLC. [IC column, 254 nm, *n*-hexane:^{i}PrOH = 75:1, 0.8 mL/min]: 7.8 min (major), 12.4 min (minor).

ethyl (R)-4-((S)-4-benzyl-1-(4-bromophenyl)-5-oxo-3-phenyl-4,5-dihydro-1H-pyrazol-4-yl)-2-((tert-butoxycarbonyl)amino)-4-phenylbuta-2,3-dienoate (3as)

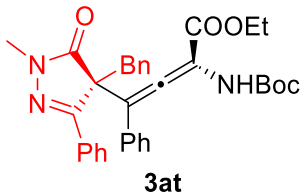


3as

white solid, 65% yield, dr > 20:1, mp 175.6-176.3 ºC; $[\alpha]_D^{17}$ = 2.906 (*c* 0.93, CH_2Cl_2);

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (dd, *J* = 6.7, 3.0 Hz, 2H), 7.51 – 7.40 (m, 7H), 7.24 (ddd, *J* = 8.5, 5.6, 3.2 Hz, 2H), 7.13 – 7.09 (m, 3H), 7.03 (m, *J* = 7.3 Hz, 1H), 6.98 (m, *J* = 7.4 Hz, 2H), 6.79 (d, *J* = 7.1 Hz, 2H), 6.49 (s, 1H), 4.47 (dq, *J* = 10.5, 7.1 Hz, 1H), 4.34 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.59 – 3.46 (m, 2H), 1.58 (s, 9H), 1.48 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 202.69, 172.68, 164.64, 158.25, 151.68, 136.68, 134.62, 134.11, 134.08, 131.71, 130.91, 130.52, 129.75, 128.77, 128.50, 128.40, 128.25, 128.18, 127.85, 127.72, 127.41, 127.27, 126.91, 121.24, 118.38, 115.67, 105.66, 81.03, 63.58, 62.85, 42.28, 28.39, 14.35.
HRMS (ESI): exact mass calculated for $[M+Na]^+$($C_{39}H_{36}BrN_3O_5$+Na^+) requires m/z 728.1731, found m/z 728.1734. The enantiomeric excess was determined to be 88% by HPLC. [IC+IC column, 254 nm, *n*-hexane:^{i}PrOH = 75:1, 0.8 mL/min]: 14.8 min (major), 17.2 min (minor).

ethyl (R)-4-((S)-4-benzyl-1-methyl-5-oxo-3-phenyl-4,5-dihydro-1H-pyrazol-4-yl)-2-((tert-butoxycarbonyl)amino)-4-phenylbuta-2,3-dienoate (3at)

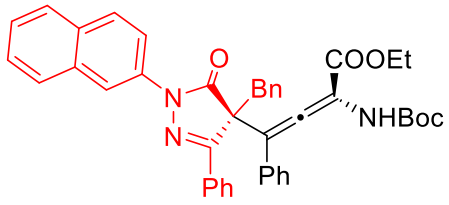


3at

yellow solid, 66% yield, dr > 20:1, mp 78.3-78.9 °C; $[\alpha]_D^{17}$ = 87.387 (*c* 0.44, CH_2Cl_2);

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 – 8.14 (m, 2H), 7.40 (dd, *J* = 5.2, 1.9 Hz, 3H), 7.25 – 7.21 (m, 2H), 7.16 – 7.03 (m, 6H), 6.79 (d, *J* = 6.9 Hz, 2H), 6.46 (s, 1H), 4.47 (dq, *J* = 10.6, 7.1 Hz, 1H), 4.33 (dq, *J* = 10.5, 7.0 Hz, 1H), 3.50 – 3.35 (m, 2H), 3.04 (s, 3H), 1.57 (s, 9H), 1.49 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 202.54, 174.05, 164.79, 157.37, 151.63, 134.75, 134.44, 131.24, 129.98, 129.80, 128.68, 128.39, 128.10, 127.72, 127.68, 127.11, 126.97, 115.81, 105.38, 80.89, 62.76, 62.30, 41.87, 31.24, 28.37, 14.32.
HRMS (ESI): exact mass calculated for $[M+Na]^+$ ($C_{34}H_{35}N_3O_5$+Na^+) requires m/z 588.2474, found m/z 588.2474. The enantiomeric excess was determined to be 79% by HPLC. [IE column, 254 nm, *n*-hexane:^{i}PrOH = 75:1, 0.8 mL/min]: 13.4 min (major), 16.4 min (minor).

ethyl (R)-4-((S)-4-benzyl-1-(naphthalen-2-yl)-5-oxo-3-phenyl-4,5-dihydro-1H-pyrazol-4-yl)-2-((tert-butoxycarbonyl)amino)-4-phenylbuta-2,3-dienoate (3au)

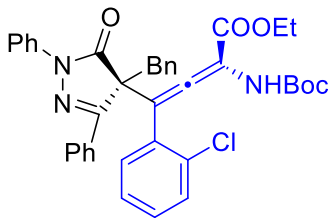


3au

white solid, 75% yield, dr > 20:1, mp 94.7-95.3 °C; $[\alpha]_D^{17}$ = -14.811 (*c* 1.01, CH_2Cl_2);

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 6.9 Hz, 2H), 7.99 (s, 1H), 7.68 (dq, *J* = 17.4, 8.7 Hz, 4H), 7.39 – 7.29 (m, 5H), 7.25 – 7.19 (m, 2H), 7.06 – 6.98 (m, 3H), 6.90 (m, *J* = 14.3, 6.6 Hz, 3H), 6.76 (d, *J* = 6.4 Hz, 2H), 6.42 (s, 1H), 4.40 (m, *J* = 9.9, 7.3, 3.7 Hz, 1H), 4.28 (m, *J* = 14.6, 7.1, 3.5 Hz, 1H), 3.55 – 3.38 (m, 2H), 1.50 (s, 9H), 1.42 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 202.73, 172.94, 164.74, 158.10, 151.71, 135.26, 134.71, 134.24, 133.42, 131.33, 131.14, 130.41, 130.13, 129.84, 128.78, 128.53, 128.24, 128.06, 127.88, 127.79, 127.63, 127.45, 127.24, 126.37, 125.48, 119.35, 117.30, 115.96, 105.67, 81.02, 63.60, 62.87, 42.36, 28.42, 14.42.
HRMS (ESI): exact mass calculated for $[M+Na]^+$($C_{43}H_{39}N_3O_5$+Na^+) requires m/z 700.2787, found m/z 700.2786. The enantiomeric excess was determined to be 88% by HPLC. [IC column, 254 nm, *n*-hexane:^{i}PrOH = 75:1, 0.8 mL/min]: 9.8 min (major), 8.7 min (minor).

ethyl (R)-4-((S)-4-benzyl-5-oxo-1,3-diphenyl-4,5-dihydro-1H-pyrazol-4-yl)-2-((tert-butoxycarbonyl)amino)-4-(2-chlorophenyl)buta-2,3-dienoate (3ba)

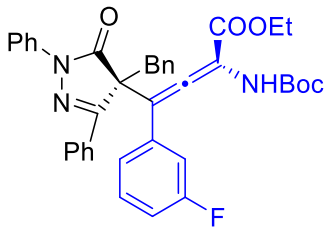


3ba

yellow solid, 81% yield, dr > 20:1, mp 129.5-130.1 °C; $[\alpha]_D^{17}$ = 66.635 (*c* 1.04, CH_2Cl_2);

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 – 8.14 (m, 2H), 7.53 (d, *J* = 7.5 Hz, 2H), 7.34 – 7.29 (m, 3H), 7.26 – 7.20 (m, 3H), 7.16 – 7.12 (m, 1H), 7.04 (m, *J* = 7.4 Hz, 1H), 6.97 – 6.85 (m, 5H), 6.77 (d, *J* = 6.6 Hz, 2H), 6.20 (s, 1H), 4.20 (pq, *J* = 7.7, 4.4, 3.5 Hz, 2H), 3.86 (d, *J* = 13.2 Hz, 1H), 3.45 (d, *J* = 13.2 Hz, 1H), 1.39 (s, 9H), 1.31 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 204.38, 172.51, 164.53, 157.53, 151.41, 137.77, 134.46, 133.21, 132.79, 131.05, 130.28, 130.16, 129.90, 129.23, 128.67, 128.36, 127.86, 127.55, 127.10, 126.53, 125.39, 120.02, 111.29, 105.63, 80.81, 63.19, 62.61, 41.50, 28.23, 14.24.
HRMS (ESI): exact mass calculated for $[M+Na]^+$($C_{39}H_{36}ClN_3O_5$+Na^+) requires m/z 684.2241, found m/z 684.2237. The enantiomeric excess was determined to be 88% by HPLC. [IE column, 254 nm, *n*-hexane:^{i}PrOH = 75:1, 0.8 mL/min]: 10.0 min (minor), 12.2 min (major).

ethyl (R)-4-((S)-4-benzyl-5-oxo-1,3-diphenyl-4,5-dihydro-1H-pyrazol-4-yl)-2-((tert-butoxycarbonyl)amino)-4-(3-fluorophenyl)buta-2,3-dienoate (3ca)



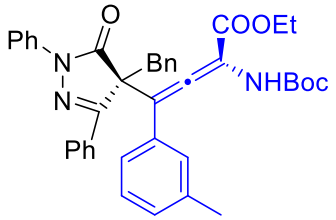
3ca

yellow solid, 73% yield, dr > 20:1, mp 139.6-140.1 °C; $[\alpha]_D^{17}$ = 31.230 (*c* 0.92, CH_2Cl_2);

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (dd, *J* = 6.7, 3.0 Hz, 2H), 7.44 (d, *J* = 7.6 Hz, 2H), 7.35 (dd, *J* = 5.1, 1.9 Hz, 3H), 7.23 (m, *J* = 7.8 Hz, 2H), 7.06 (m, *J* = 7.4 Hz, 1H), 6.99 – 6.89 (m, 6H), 6.73 (d, *J* = 7.5 Hz, 3H), 6.43 (s, 1H), 4.40 (dq, *J* = 10.6, 7.1 Hz, 1H), 4.30 – 4.24 (m, 1H), 3.47 – 3.38 (m, 2H), 1.50 (s, 9H), 1.39 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 203.10, 172.56, 164.46, 163.73, 161.28, 157.75, 151.71, 137.50, 136.93, 136.85, 134.00, 130.97, 130.46, 130.03, 129.95, 129.81, 128.81, 128.76, 127.87, 127.29, 127.26, 125.73, 123.12, 123.09, 120.29, 115.36, 115.32, 115.13, 115.11, 114.95, 114.93, 106.03, 81.22, 63.21, 62.97, 42.36, 28.38, 14.35.
^{19}F NMR (377 MHz, $CDCl_3$) δ -112.45.
HRMS (ESI): exact mass calculated for $[M+Na]^+$($C_{39}H_{36}FN_3O_5$+Na^+) requires m/z 668.2531, found m/z 668.2534. The enantiomeric excess was determined to be 86% by

HPLC. [IE column, 254 nm, *n*-hexane:^{i}PrOH = 75:1, 0.8 mL/min]: 7.0 min (minor), 7.8 min (major).

ethyl (R)-4-((S)-4-benzyl-5-oxo-1,3-diphenyl-4,5-dihydro-1H-pyrazol-4-yl)-2-((tert-butoxycarbonyl)amino)-4-(m-tolyl)buta-2,3-dienoate (3da)



3da

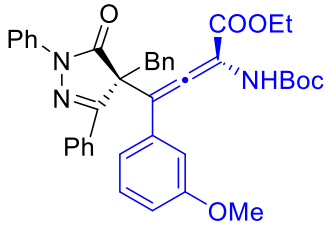
yellow solid, 79% yield, dr > 20:1, mp 140.6-141.1 °C; $[\alpha]_D^{17}$ = 31.010 (*c* 1.12, CH_2Cl_2);

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 – 8.16 (m, 2H), 7.44 (d, *J* = 7.4 Hz, 2H), 7.33 (dd, *J* = 5.0, 2.4 Hz, 3H), 7.23 (d, *J* = 7.8 Hz, 2H), 7.07 – 6.98 (m, 3H), 6.91 (dd, *J* = 21.0, 7.0 Hz, 4H), 6.81 (d, *J* = 7.6 Hz, 1H), 6.74 (d, *J* = 6.5 Hz, 2H), 6.41 (s, 1H), 4.38 (dq, *J* = 10.5, 7.1 Hz, 1H), 4.24 (dq, *J* = 10.6, 7.1 Hz, 1H), 3.49 – 3.39 (m, 2H), 2.01 (s, 3H), 1.49 (s, 9H), 1.38 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 202.55, 172.81, 164.80, 158.03, 151.73, 137.92, 137.66, 134.54, 134.32, 131.20, 130.95, 130.28, 129.86, 129.03, 128.74, 128.70, 128.45, 128.36, 127.85, 127.42, 127.20, 125.63, 124.86, 120.34, 116.05, 105.55, 80.95, 63.38, 62.80, 42.20, 28.40, 21.42, 14.40.

HRMS (ESI): exact mass calculated for $[M+Na]^+$($C_{40}H_{39}N_3O_5$+Na^+) requires m/z 664.2782, found m/z 664.2783. The enantiomeric excess was determined to be 90% by HPLC. [IE column, 254 nm, *n*-hexane:^{i}PrOH = 75:1, 0.8 mL/min]: 8.0 min (minor), 9.3 min (major).

ethyl (R)-4-((S)-4-benzyl-5-oxo-1,3-diphenyl-4,5-dihydro-1H-pyrazol-4-yl)-2-((tert-butoxycarbonyl)amino)-4-(3-methoxyphenyl)buta-2,3-dienoate (3ea)



3ea

white solid, 88% yield, dr > 20:1, mp 93.7-94.3 °C; $[\alpha]_D^{17}$ = 39.386 (*c* 1.14, CH_2Cl_2);

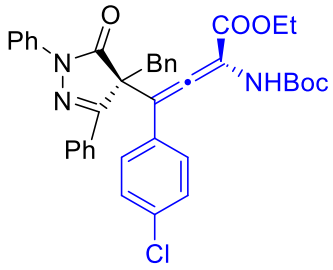
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 – 8.17 (m, 2H), 7.47 (d, *J* = 7.3 Hz, 2H), 7.34 (d, *J* = 5.6 Hz, 3H), 7.22 (m, *J* = 7.8 Hz, 2H), 7.05 (m, *J* = 7.4 Hz, 1H), 6.96 – 6.88 (m, 4H), 6.82 (s, 1H), 6.76 (dd, *J* = 11.7, 7.5 Hz, 3H), 6.56 (d, *J* = 5.8 Hz, 1H), 6.42 (s, 1H), 4.39 (dq, *J* = 10.5, 7.1 Hz, 1H), 4.24 (dt, *J* = 10.6, 7.1 Hz, 1H), 3.43 (d, *J* = 17.0 Hz, 5H), 1.50 (s, 9H), 1.39 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 202.59, 172.71, 164.69, 159.35, 157.92, 151.75, 137.68, 135.94, 134.22, 131.14, 130.31, 129.82, 129.44, 128.73, 128.69, 127.85, 127.37,

127.22, 125.56, 120.11, 119.86, 115.88, 114.78, 112.94, 105.63, 81.00, 63.43, 62.84, 54.91, 42.28, 28.39, 14.37.

HRMS (ESI): exact mass calculated for $[M+Na]^+$($C_{40}H_{39}N_3O_6$+Na^+) requires m/z 680.2737, found m/z 680.2729. The enantiomeric excess was determined to be 88% by HPLC. [IE column, 254 nm, *n*-hexane:^{i}PrOH = 75:1, 0.8 mL/min]: 9.1 min (minor), 12.1 min (major).

ethyl (R)-4-((S)-4-benzyl-5-oxo-1,3-diphenyl-4,5-dihydro-1H-pyrazol-4-yl)-2-((tert-butoxycarbonyl)amino)-4-(4-chlorophenyl)buta-2,3-dienoate (3fa)



3fa

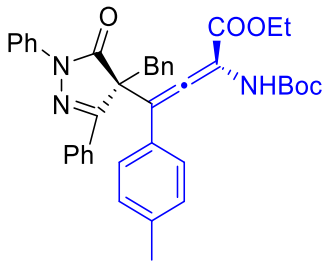
yellow solid, 65% yield, dr > 20:1, mp 194.8-195.1 °C; $[\alpha]_D^{17}$ = 41.678 (*c* 0.74, CH_2Cl_2);

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (dd, *J* = 6.7, 3.0 Hz, 2H), 7.45 (d, *J* = 7.5 Hz, 2H), 7.38 – 7.34 (m, 3H), 7.24 (m, *J* = 7.9 Hz, 2H), 7.13 (d, *J* = 8.6 Hz, 2H), 7.08 (m, *J* = 7.4 Hz, 1H), 7.01 (d, *J* = 8.5 Hz, 2H), 6.93 (m, *J* = 14.5, 7.0 Hz, 3H), 6.73 (d, *J* = 7.1 Hz, 2H), 6.42 (s, 1H), 4.40 (dq, *J* = 10.6, 7.1 Hz, 1H), 4.26 (dq, *J* = 10.4, 7.0 Hz, 1H), 3.47 – 3.39 (m, 2H), 1.51 (s, 9H), 1.39 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 202.84, 172.55, 164.48, 157.73, 151.70, 137.50, 134.19, 134.01, 133.24, 130.95, 130.46, 129.78, 129.11, 128.80, 128.77, 128.73, 127.87, 127.28, 127.24, 125.71, 120.16, 114.93, 105.90, 81.16, 63.32, 62.93, 42.29, 28.38, 14.35.

HRMS (ESI): exact mass calculated for $[M+Na]^+$($C_{39}H_{36}ClN_3O_5$+Na^+) requires m/z 684.2241, found m/z 684.2233. The enantiomeric excess was determined to be 86% by HPLC. [IE column, 254 nm, *n*-hexane:^{i}PrOH = 75:1, 0.8 mL/min]: 7.0 min (minor), 8.3 min (major).

ethyl (R)-4-((S)-4-benzyl-5-oxo-1,3-diphenyl-4,5-dihydro-1H-pyrazol-4-yl)-2-((tert-butoxycarbonyl)amino)-4-(p-tolyl)buta-2,3-dienoate (3ga)

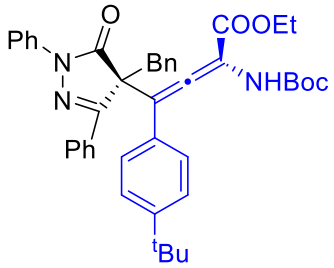


3ga

white solid, 94% yield, dr > 20:1, mp 98.1-98.9 °C; $[\alpha]_D^{17}$ = 28.231 (*c* 0.59, CH_2Cl_2);

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 – 8.18 (m, 2H), 7.46 (d, *J* = 7.2 Hz, 2H), 7.35 (dd, *J* = 5.2, 2.0 Hz, 3H), 7.23 (m, *J* = 7.9 Hz, 2H), 7.08 (m, *J* = 7.3 Hz, 3H), 6.92 (m, *J* = 14.4, 7.0 Hz, 3H), 6.84 (d, *J* = 7.9 Hz, 2H), 6.73 (d, *J* = 6.7 Hz, 2H), 6.40 (s, 1H), 4.39 (dq, *J* = 10.6, 7.1 Hz, 1H), 4.25 (dq, *J* = 10.6, 7.1 Hz, 1H), 3.49 – 3.38 (m, 2H), 2.09 (s, 3H), 1.50 (s, 9H), 1.40 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 202.50, 172.76, 164.80, 157.99, 151.67, 138.02, 137.66, 134.28, 131.71, 131.16, 130.27, 129.83, 129.23, 128.71, 127.80, 127.58, 127.38, 127.17, 125.54, 120.24, 115.91, 105.43, 80.90, 63.38, 62.77, 42.27, 28.40, 21.13, 14.36.
HRMS (ESI): exact mass calculated for $[M+Na]^+$($C_{40}H_{39}N_3O_5$+Na^+) requires m/z 664.2782, found m/z 664.2777. The enantiomeric excess was determined to be 88% by HPLC. [IE column, 254 nm, *n*-hexane:^{i}PrOH = 75:1, 0.8 mL/min]: 9.8 min (minor), 11.7 min (major).

ethyl (R)-4-((S)-4-benzyl-5-oxo-1,3-diphenyl-4,5-dihydro-1H-pyrazol-4-yl)-2-((tert-butoxycarbonyl)amino)-4-(4-(tert-butyl)phenyl)buta-2,3-dienoate (3ha)

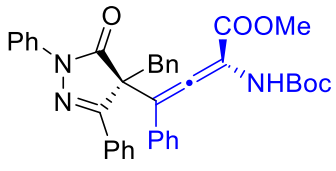


3ha

yellow solid, 94% yield, dr > 20:1, mp 96.9-97.3 °C; $[\alpha]_D^{17}$ = 30.333 (*c* 1.02, CH_2Cl_2);

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 – 8.18 (m, 2H), 7.43 – 7.39 (m, 2H), 7.36 (dd, *J* = 5.3, 1.9 Hz, 3H), 7.22 (m, *J* = 7.9 Hz, 2H), 7.15 (d, *J* = 8.5 Hz, 2H), 7.09 – 7.03 (m, 3H), 6.96 (m, *J* = 7.3 Hz, 1H), 6.90 (m, *J* = 7.2 Hz, 2H), 6.73 (d, *J* = 6.8 Hz, 2H), 6.40 (s, 1H), 4.41 (dq, *J* = 10.6, 7.1 Hz, 1H), 4.30 – 4.22 (m, 1H), 3.48 – 3.38 (m, 2H), 1.50 (s, 9H), 1.41 (t, *J* = 7.1 Hz, 3H), 1.09 (s, 9H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 202.67, 172.79, 164.82, 158.07, 151.67, 151.05, 137.63, 134.25, 131.46, 131.26, 130.28, 129.84, 128.74, 128.69, 127.79, 127.44, 127.38, 127.17, 125.60, 125.51, 120.40, 115.98, 105.45, 80.89, 63.30, 62.79, 42.24, 34.50, 31.17, 28.40, 14.40.
HRMS (ESI): exact mass calculated for $[M+Na]^+$($C_{43}H_{45}N_3O_5$+Na^+) requires m/z 706.3251, found m/z 706.3252. The enantiomeric excess was determined to be 88% by HPLC. [IE column, 254 nm, *n*-hexane:^{i}PrOH = 75:1, 0.8 mL/min]: 6.8 min (major), 7.8 min (minor).

methyl (R)-4-((S)-4-benzyl-5-oxo-1,3-diphenyl-4,5-dihydro-1H-pyrazol-4-yl)-2-((tert-butoxycarbonyl)amino)-4-phenylbuta-2,3-dienoate (3ia)

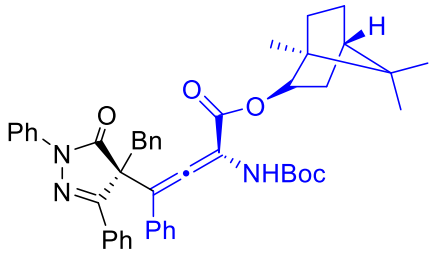


3ia

yellow solid, 87% yield, dr > 20:1, mp 151.5-151.9 °C; $[\alpha]_D^{17}$ = 41.772(*c* 1.34, CH_2Cl_2);

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (dd, *J* = 6.7, 2.9 Hz, 2H), 7.47 (d, *J* = 8.1 Hz, 2H), 7.33 (dd, *J* = 5.3, 2.0 Hz, 3H), 7.26 – 7.17 (m, 4H), 7.08 – 7.00 (m, 4H), 6.91 (m, *J* = 14.5, 7.0 Hz, 3H), 6.74 (d, *J* = 7.0 Hz, 2H), 6.42 (s, 1H), 3.86 (s, 3H), 3.51 – 3.40 (m, 2H), 1.50 (s, 9H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 202.85, 172.92, 165.29, 158.13, 151.70, 137.58, 134.60, 134.12, 131.00, 130.35, 129.83, 128.75, 128.70, 128.53, 128.28, 127.84, 127.70, 127.34, 127.25, 125.67, 120.23, 116.09, 105.59, 81.06, 63.30, 53.73, 42.49, 28.40.
HRMS (ESI): exact mass calculated for $[M+Na]^+$($C_{38}H_{35}N_3O_5$+Na^+) requires m/z 636.2474, found m/z 636.2468. The enantiomeric excess was determined to be 88% by HPLC. [IE column, 254 nm, *n*-hexane:^{i}PrOH = 75:1, 0.8 mL/min]: 10.5 min (minor), 12.7 min (major).

(1S,2S,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl (R)-4-((S)-4-benzyl-5-oxo-1,3-diphenyl-4,5-dihydro-1H-pyrazol-4-yl)-2-((tert-butoxycarbonyl)amino)-4-phenylbuta-2,3-dienoate (3ja)

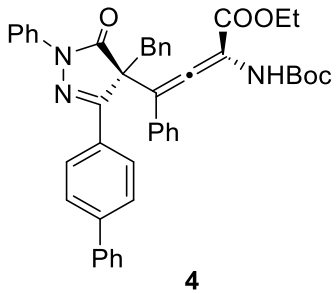


3ja

white solid, 87% yield, dr > 20:1, mp 120.3-120.9 °C; $[\alpha]_D^{17}$ = -18.841 (*c* 0.28, CH_2Cl_2);

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (dd, *J* = 6.7, 3.1 Hz, 2H), 7.46 (dd, *J* = 8.3, 3.4 Hz, 2H), 7.36 (dd, *J* = 5.3, 2.2 Hz, 3H), 7.25 – 7.17 (m, 4H), 7.07 – 6.99 (m, 4H), 6.97 – 6.88 (m, 3H), 6.74 (d, *J* = 7.0 Hz, 2H), 6.44 (s, 1H), 5.13 – 4.92 (m, 1H), 3.59 – 3.42 (m, 2H), 2.30 (m, *J* = 15.8, 11.6, 4.9 Hz, 2H), 1.70 – 1.61 (m, 2H), 1.49 (s, 9H), 1.34 (dt, *J* = 10.8, 5.5 Hz, 2H), 1.03 (d, *J* = 3.8 Hz, 2H), 0.86 (d, *J* = 11.5 Hz, 6H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 202.41, 172.26, 165.25, 157.53, 151.72, 137.75, 134.87, 134.36, 131.34, 130.26, 129.85, 128.72, 128.68, 128.44, 128.15, 127.85, 127.78, 127.46, 127.16, 125.37, 119.97, 116.20, 105.88, 83.53, 80.89, 63.61, 49.39, 48.26, 44.96, 42.09, 36.54, 28.42, 27.94, 27.11, 19.90, 19.01, 13.82.
HRMS (ESI): exact mass calculated for $[M+Na]^+$($C_{47}H_{49}N_3O_5$+Na^+) requires m/z 758.3570, found m/z 758.3562.

ethyl (R)-4-((S)-3-([1,1'-biphenyl]-4-yl)-4-benzyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)-2-((tert-butoxycarbonyl)amino)-4-phenylbuta-2,3-dienoate (4)

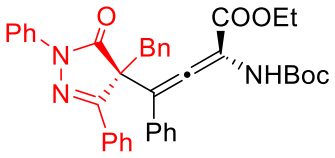


4

white solid, 91% yield, dr > 20:1, mp 180.8-181.3 °C; $[\alpha]_D^{17}$ = 111.335 (*c* 1.04, CH_2Cl_2);

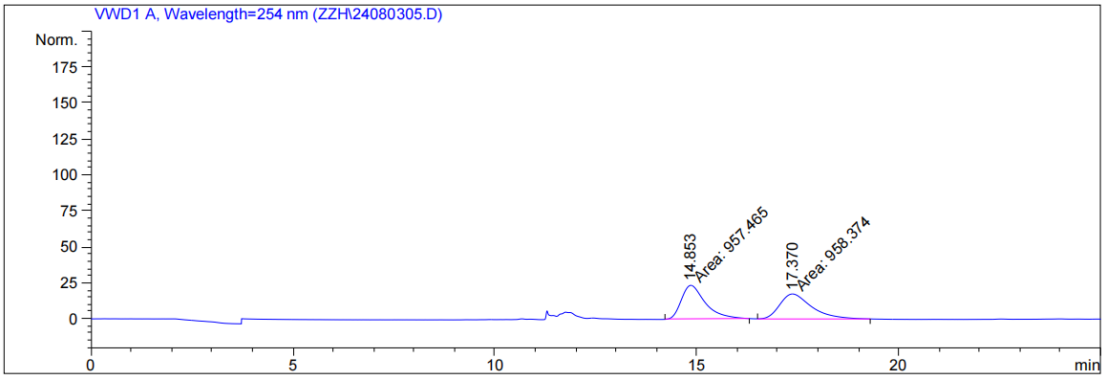
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.1 Hz, 2H), 7.59 (dd, *J* = 13.8, 7.6 Hz, 4H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.36 (m, *J* = 7.6 Hz, 2H), 7.29 – 7.19 (m, 5H), 7.08 – 7.02 (m, 4H), 6.93 (m, *J* = 14.2, 7.0 Hz, 3H), 6.78 (d, *J* = 7.1 Hz, 2H), 6.43 (s, 1H), 4.39 (dq, *J* = 10.5, 7.1 Hz, 1H), 4.25 (dq, *J* = 10.3, 7.0 Hz, 1H), 3.48 (q, *J* = 12.9 Hz, 2H), 1.51 (s, 9H), 1.39 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 202.80, 172.77, 164.77, 157.69, 151.79, 142.64, 140.52, 137.62, 134.73, 134.25, 130.15, 129.90, 129.58, 128.97, 128.77, 128.56, 128.28, 127.90, 127.83, 127.34, 127.28, 127.03, 125.70, 120.37, 115.98, 115.42, 105.69, 81.05, 63.48, 62.89, 42.37, 28.45, 14.40.
HRMS (ESI): exact mass calculated for $[M+Na]^+$($C_{45}H_{41}N_3O_5$+Na^+) requires m/z 726.2944, found m/z 726.2937. The enantiomeric excess was determined to be 87% by HPLC. [IE column, 254 nm, *n*-hexane:^{i}PrOH = 75:1, 0.8 mL/min]: 9.1 min (minor), 10.9 min (major).

5. HPLC Analysis

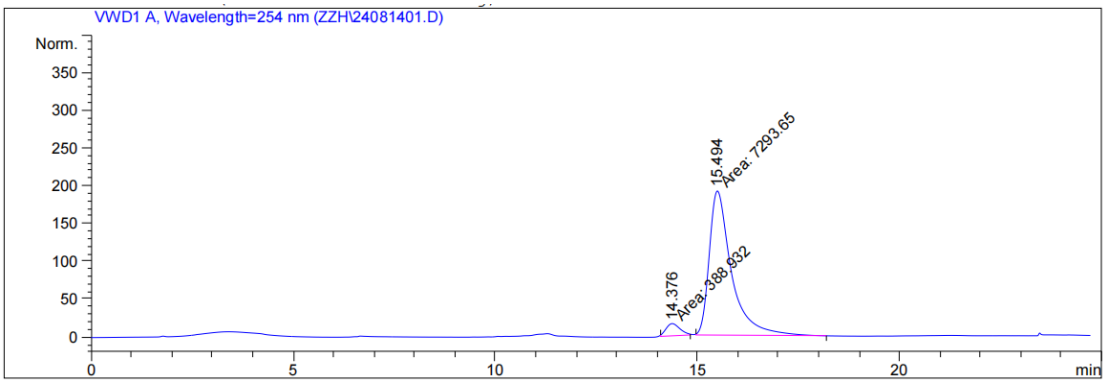


3aa

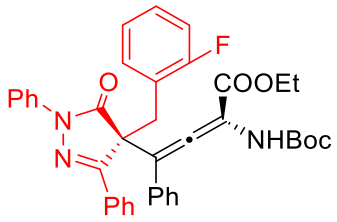
HPLC using an IE-H + ID-H column, n-hexane / ^{i}PrOH = 75/1, flow rate = 0.8 mL/min



Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	14.853	MM	0.6845	957.46460	23.31254	49.9763
2	17.370	MM	0.9179	958.37378	17.40067	50.0237

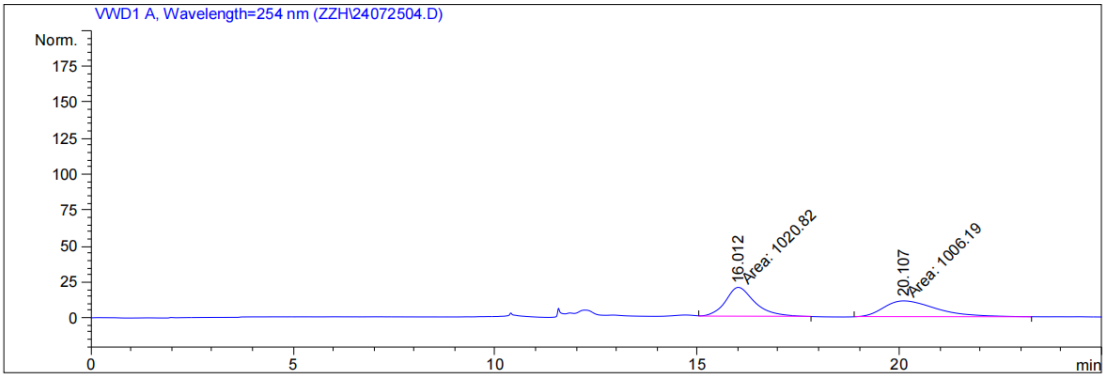


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	14.376	MM	0.4000	388.93243	16.20718	5.0625
2	15.494	MM	0.6378	7293.64893	190.60555	94.9375

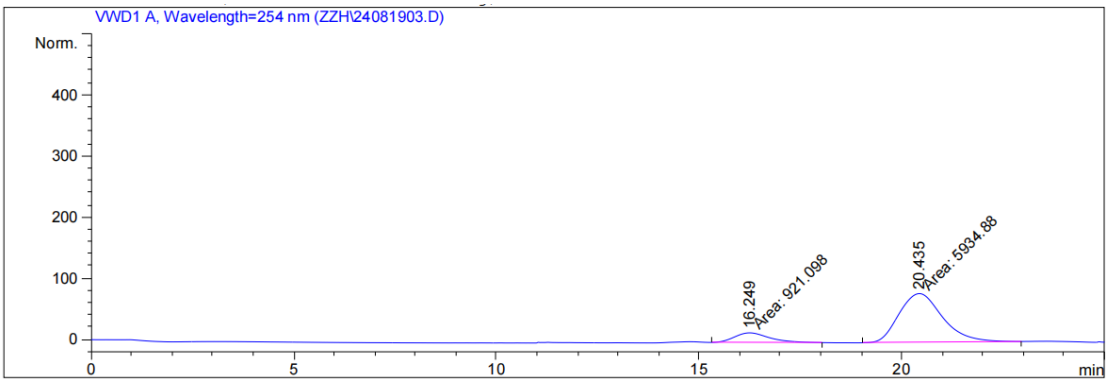


3ab

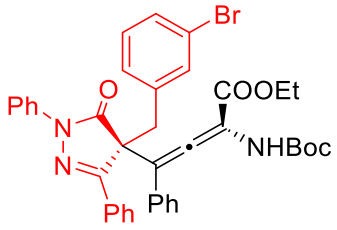
HPLC using an IE-H + ID-H column, n-hexane / ^{i}PrOH = 75/1, flow rate = 0.8 mL/min



Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	16.012	MM	0.8467	1020.82245	20.09473	50.3611
2	20.107	MM	1.5268	1006.18542	10.98349	49.6389

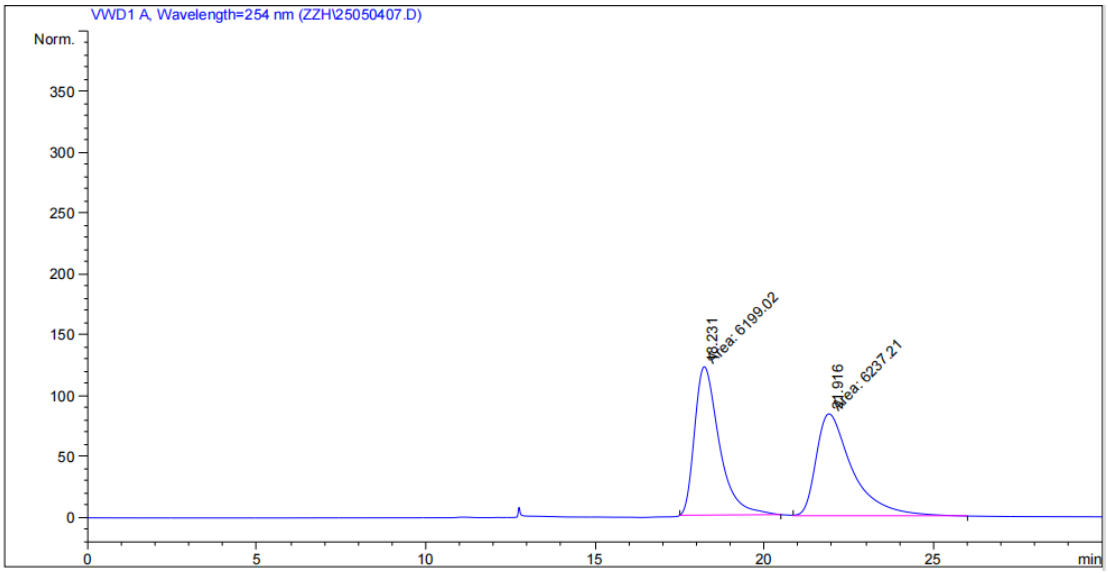


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	16.249	MM	0.9837	921.09827	15.60676	13.4350
2	20.435	MM	1.2435	5934.88379	79.54350	86.5650

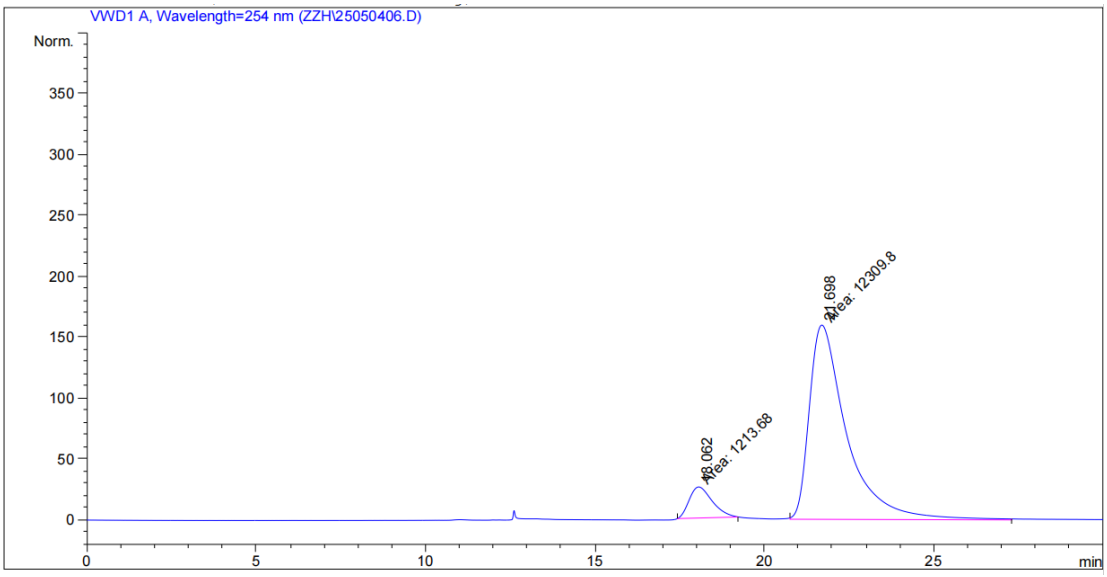


3ac

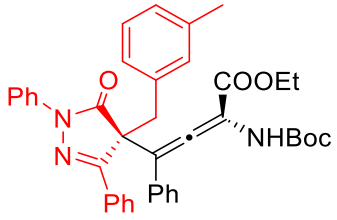
HPLC using an ID-H + IF-H column, n-hexane / ^{i}PrOH = 75/1, flow rate = 0.8 mL/min



Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	18.231	MM	0.8476	6199.01904	121.89616	49.8464
2	21.916	MM	1.2408	6237.21094	83.77977	50.1536

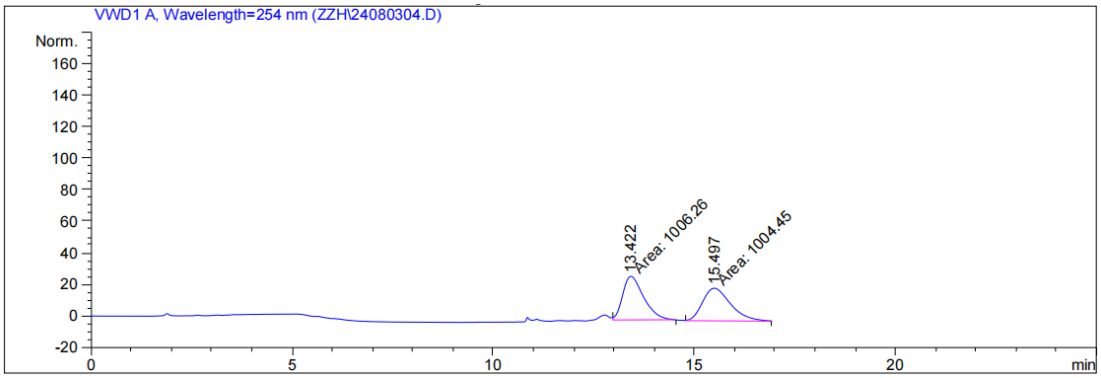


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	18.062	MM	0.7920	1213.67688	25.54013	8.9746
2	21.698	MM	1.2865	1.23098e4	159.46886	91.0254

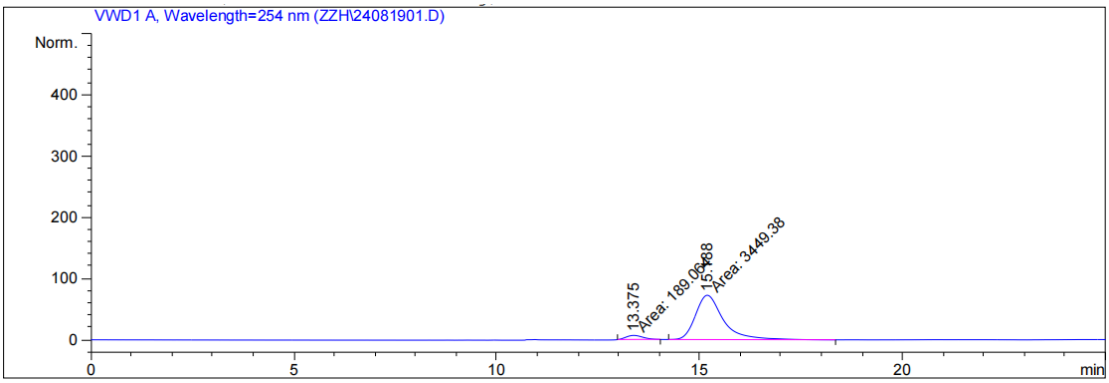


3ad

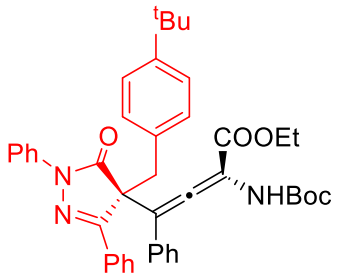
HPLC using an IF-H + IG-H column, n-hexane / ^{i}PrOH = 75/1, flow rate = 0.8 mL/min



Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	13.422	MM	0.6063	1006.26495	27.65995	50.0451
2	15.497	MM	0.8089	1004.45154	20.69582	49.9549

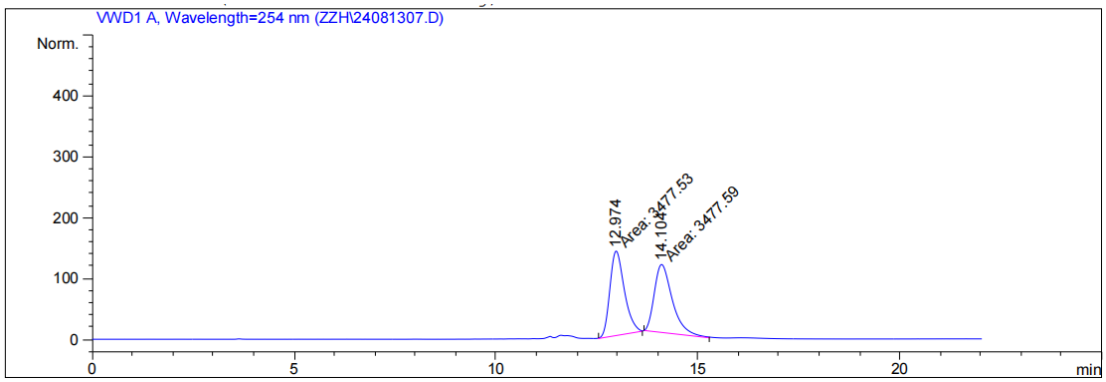


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	13.375	MM	0.4755	189.06381	6.62747	5.1963
2	15.188	MM	0.7941	3449.38281	72.39834	94.8037

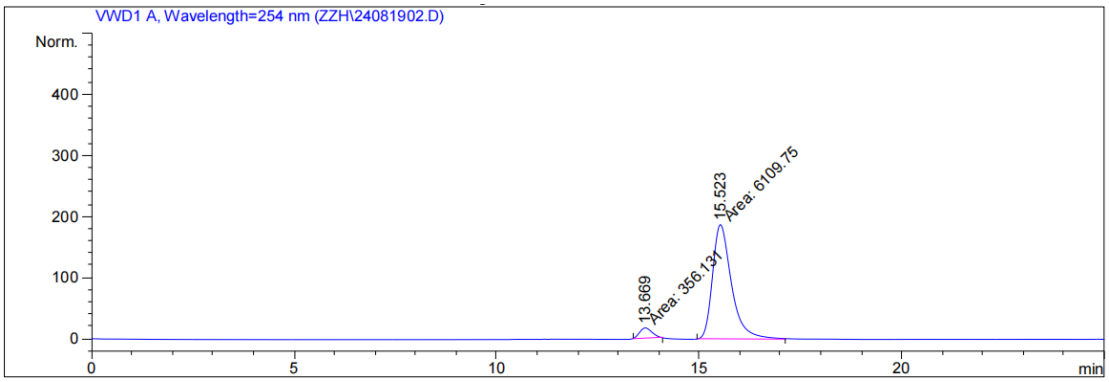


3ae

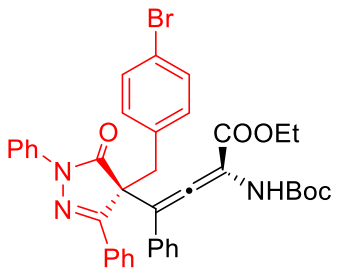
HPLC using an IF-H + IE-H column, n-hexane / ^{i}PrOH = 75/1, flow rate = 0.8 mL/min



Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	12.974	MM	0.4172	3477.53101	138.93565	49.9995
2	14.104	MM	0.5184	3477.59399	111.80254	50.0005

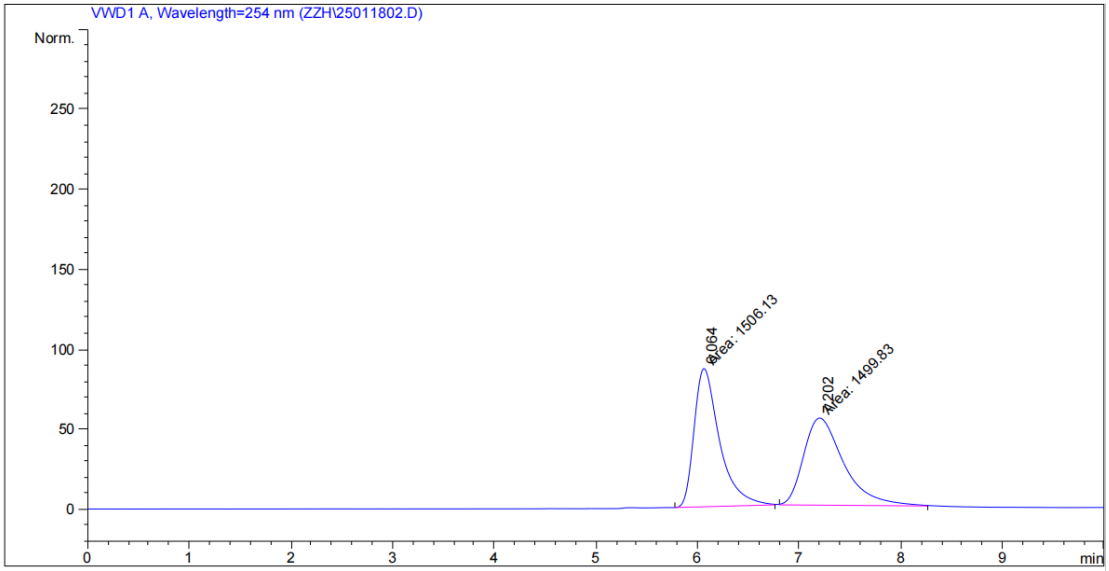


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	13.669	MM	0.3517	356.13141	16.87637	5.5079
2	15.523	MM	0.5443	6109.75391	187.08218	94.4921

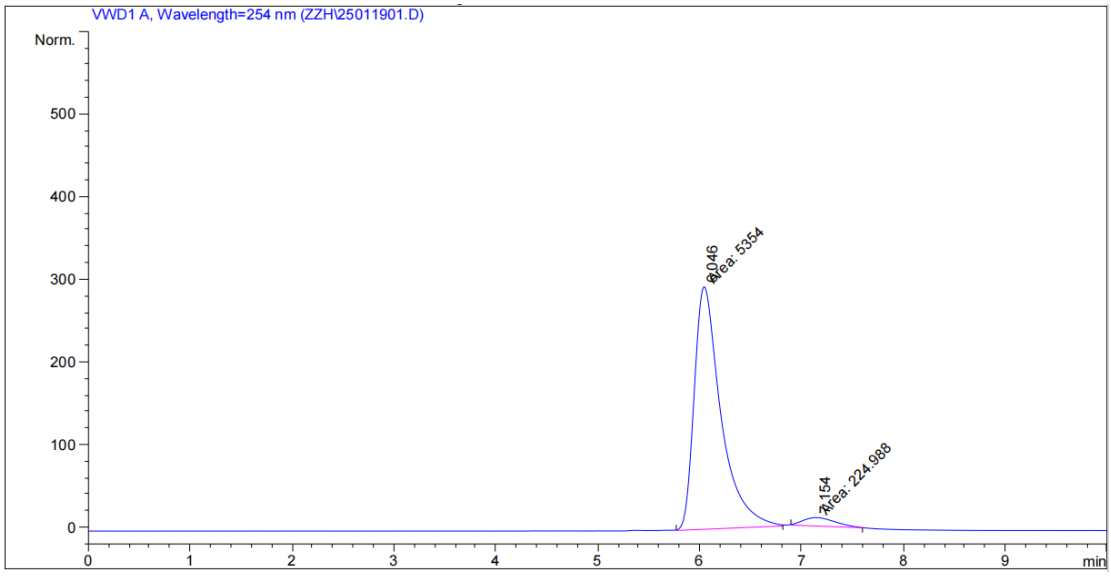


3af

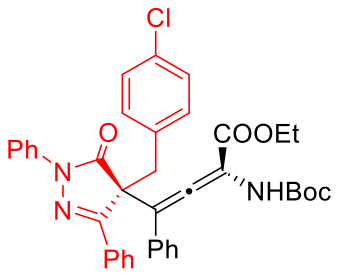
HPLC using an IC-H column, n-hexane / ^{i}PrOH = 75/1, flow rate = 0.8 mL/min



Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	6.064	MM	0.2904	1506.12659	86.44693	50.1047
2	7.202	MM	0.4584	1499.83167	54.52889	49.8953

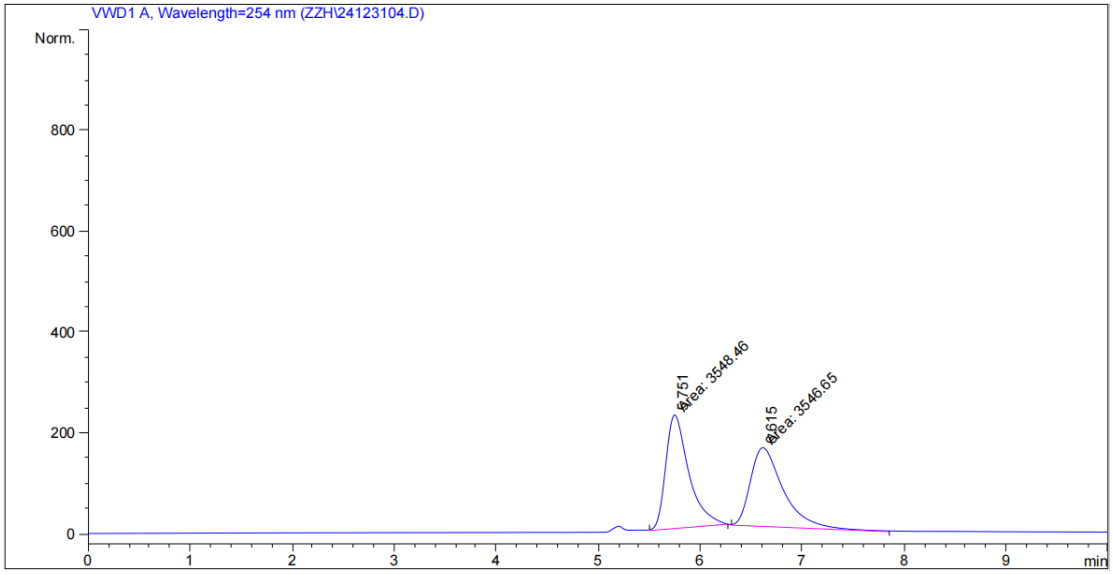


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	6.046	MM	0.3043	5354.00049	293.19586	95.9672
2	7.154	MM	0.3679	224.98814	10.19347	4.0328

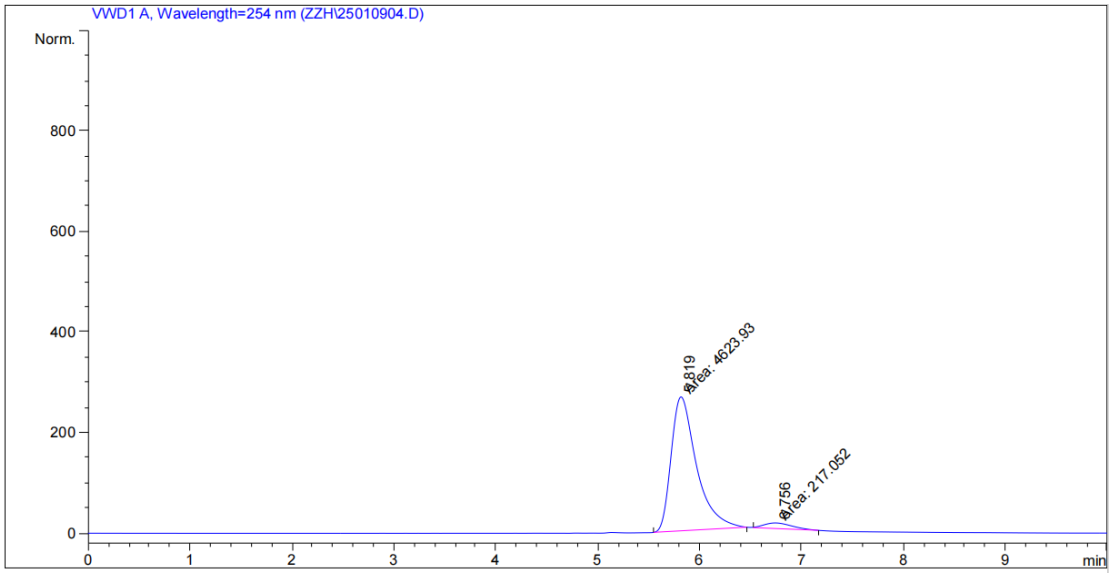


3ag

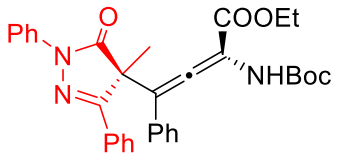
HPLC using an IC-H column, n-hexane / ^{i}PrOH = 75/1, flow rate = 0.8 mL/min



Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	5.751	MM	0.2625	3548.46045	225.29529	50.0128
2	6.615	MM	0.3780	3546.64502	156.36909	49.9872

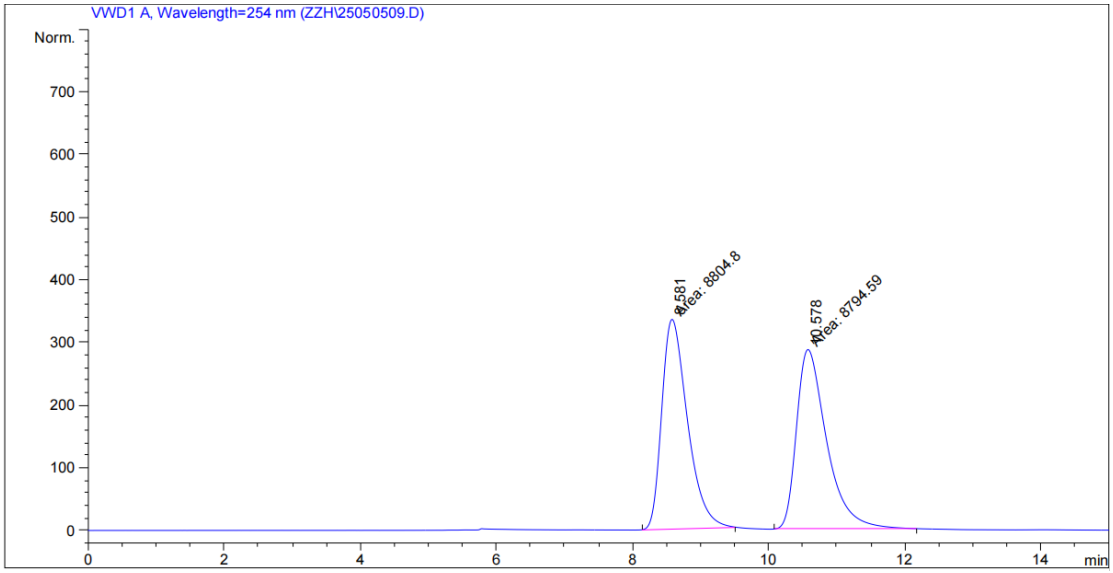


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	5.819	MM	0.2892	4623.92627	266.47314	95.5164
2	6.756	MM	0.3210	217.05194	11.26861	4.4836

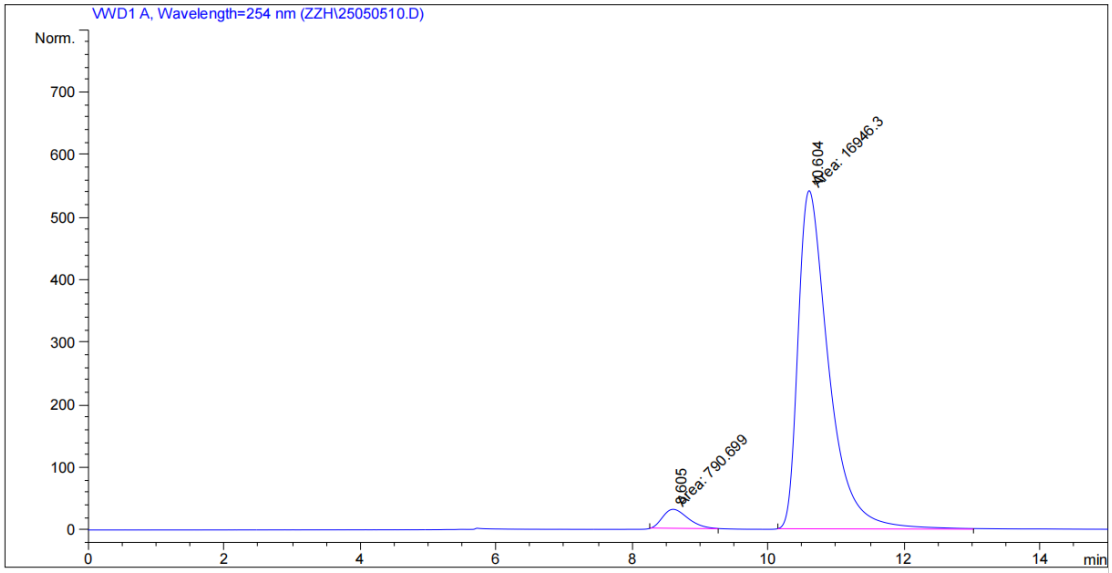


3ah

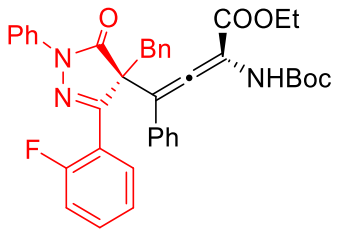
HPLC using an IE-H column, n-hexane / ^{i}PrOH = 75/1, flow rate = 0.8 mL/min



Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	8.581	MM	0.4382	8804.80176	334.91064	50.0290
2	10.578	MM	0.5126	8794.58887	285.95285	49.9710

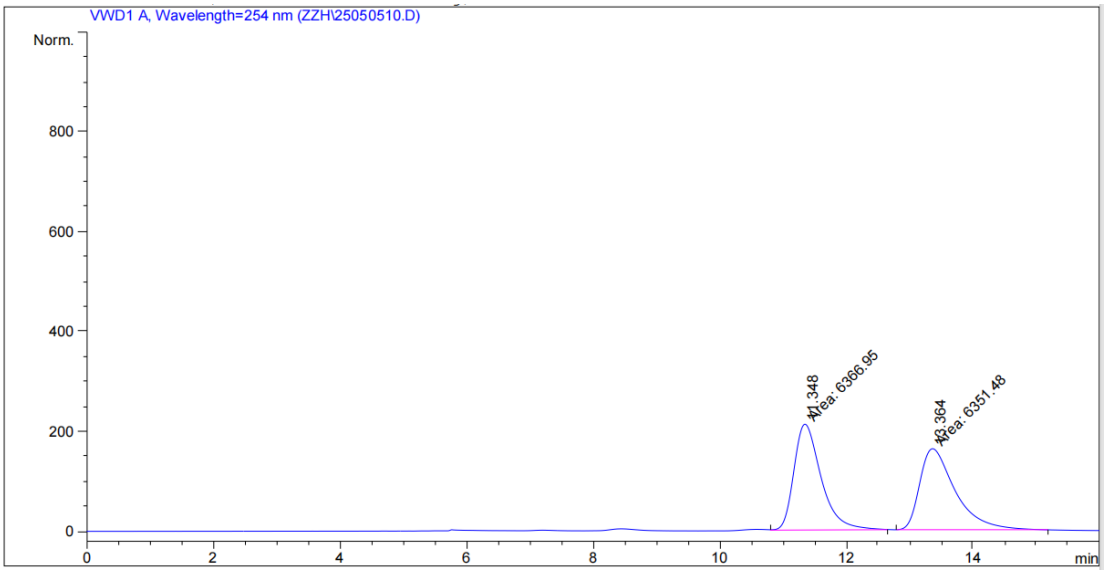


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	8.605	MM	0.4324	790.69946	30.47791	4.4579
2	10.604	MM	0.5224	1.69463e4	540.67267	95.5421

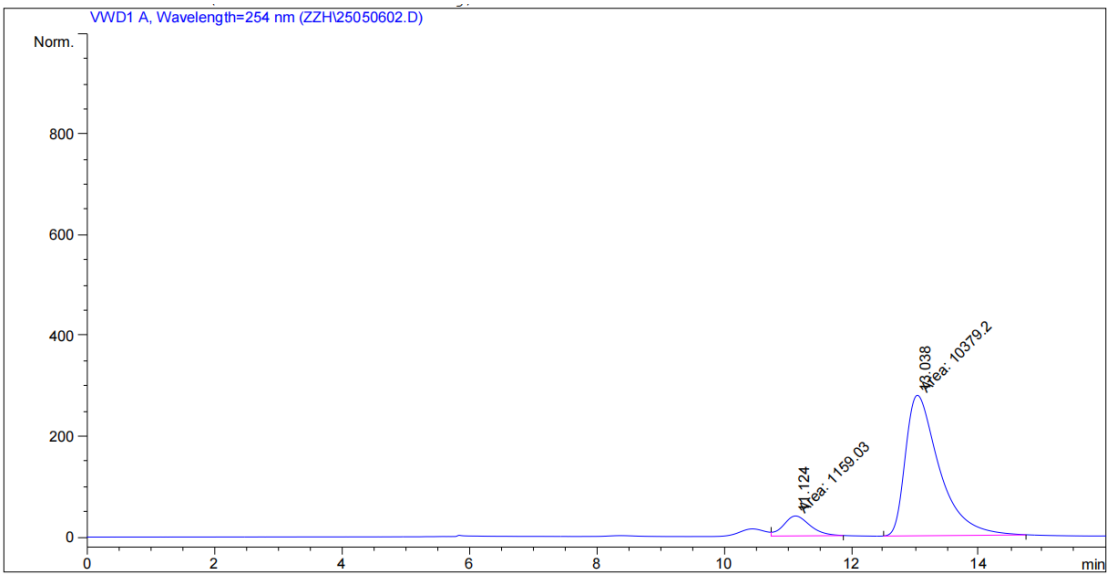


3ai

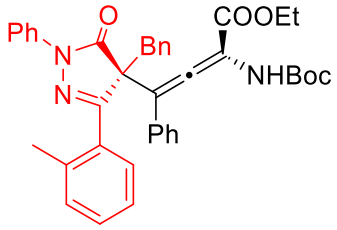
HPLC using an IE-H column, n-hexane / ^{i}PrOH = 75/1, flow rate = 0.8 mL/min



Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	11.348	MM	0.5004	6366.95166	212.06699	50.0608
2	13.364	MM	0.6518	6351.47754	162.41649	49.9392

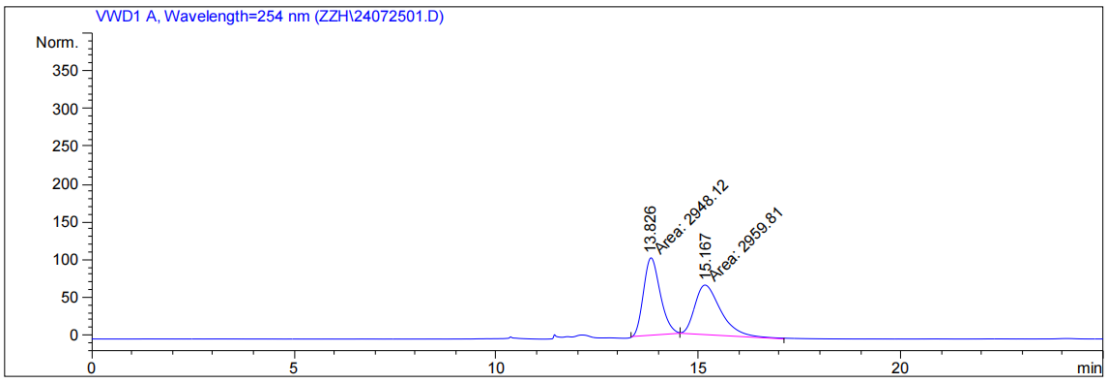


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	11.124	MM	0.4855	1159.03162	39.79158	10.0452
2	13.038	MM	0.6196	1.03792e4	279.18295	89.9548

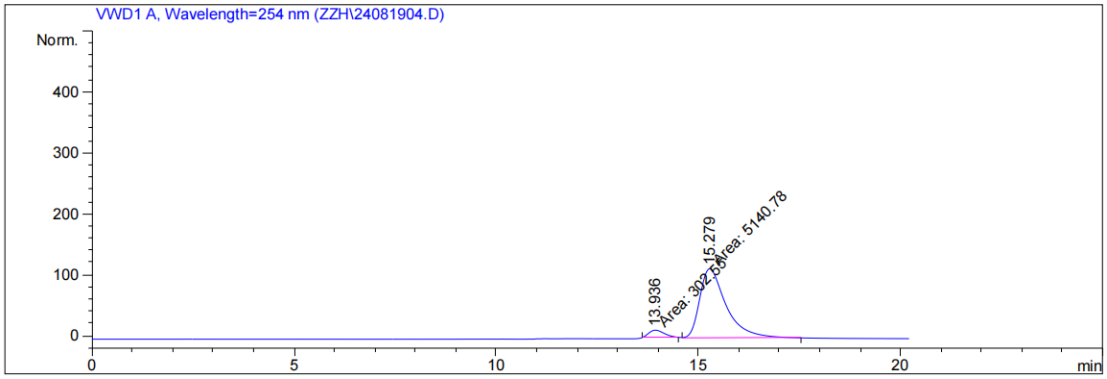


3aj

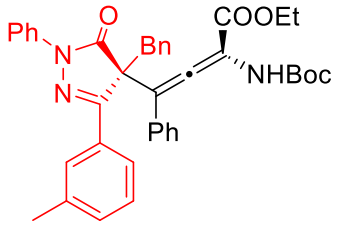
HPLC using an IE-H +ID-H column, n-hexane / ^{i}PrOH = 75/1, flow rate = 0.8 mL/min



Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	13.826	MM	0.4791	2948.12183	102.54867	49.9011
2	15.167	MM	0.7511	2959.80566	65.67534	50.0989

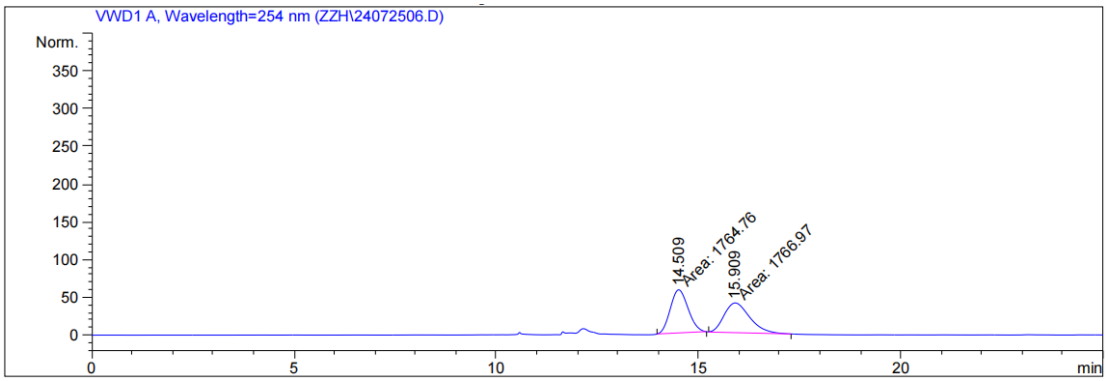


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	13.936	MM	0.4327	302.55029	11.65475	5.5582
2	15.279	MM	0.7555	5140.77734	113.40039	94.4418

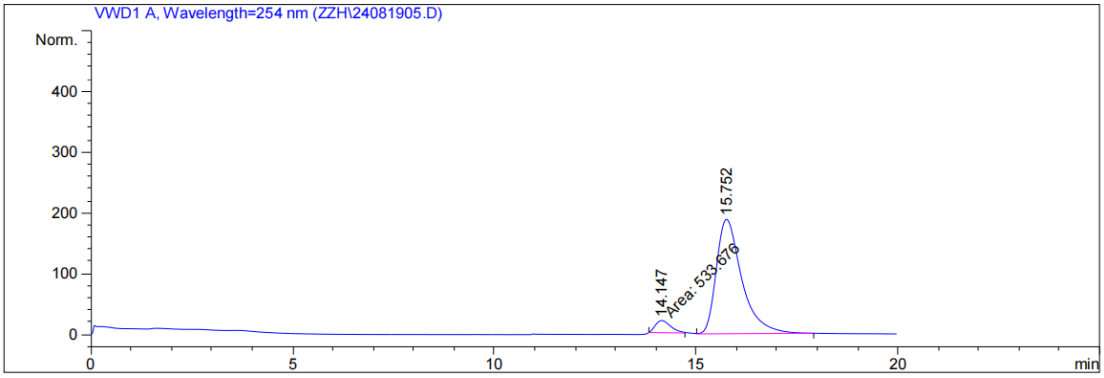


3ak

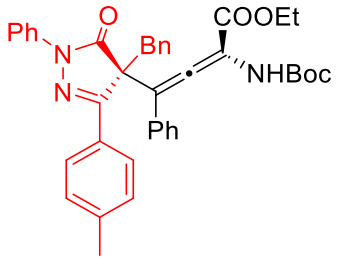
HPLC using an IE-H +IF-H column, n-hexane / ^{i}PrOH = 75/1, flow rate = 0.8 mL/min



Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	14.509	MM	0.5128	1764.76147	57.35728	49.9687
2	15.909	MM	0.7432	1766.97229	39.62490	50.0313

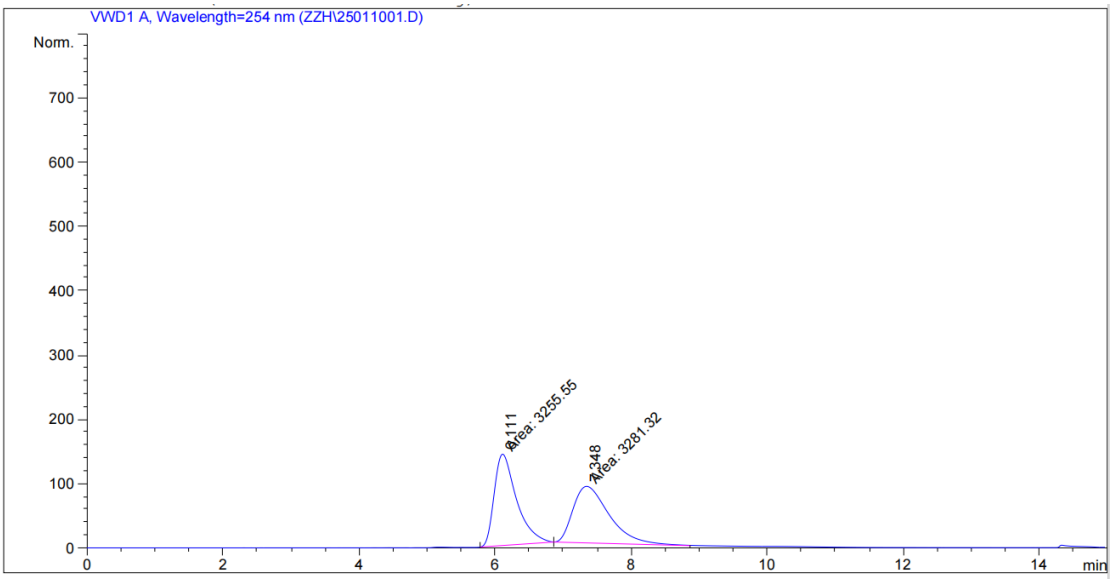


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	14.147	MM	0.4431	533.67639	20.07552	6.0398
2	15.752	VB	0.6679	8302.26172	188.61220	93.9602

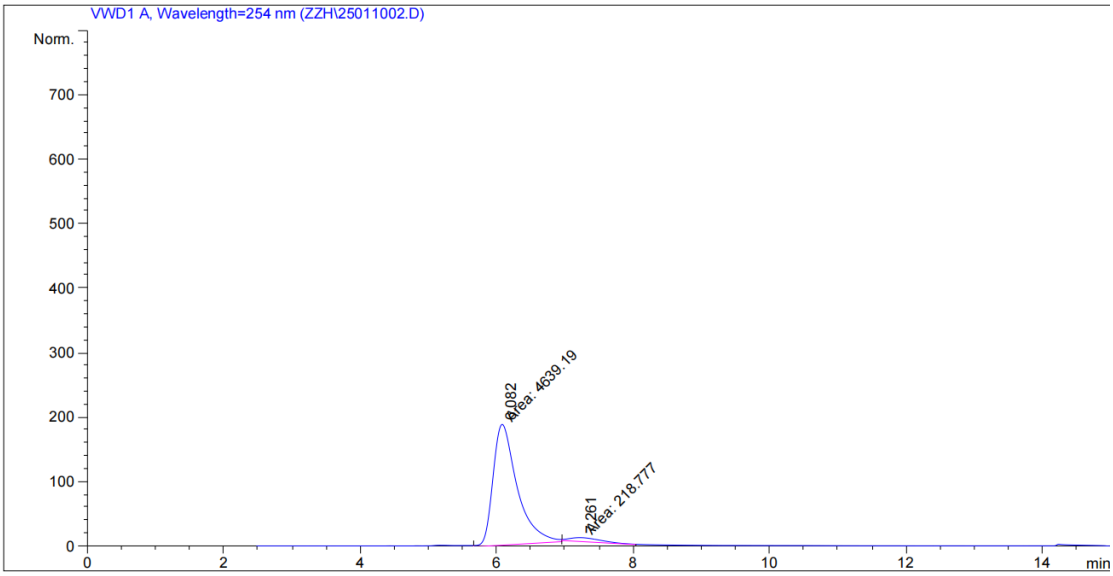


3al

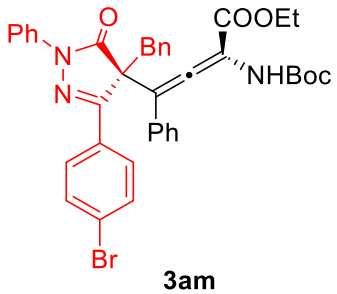
HPLC using an IE-H column, n-hexane / ^{i}PrOH = 75/1, flow rate = 0.8 mL/min



Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	6.111	MM	0.3816	3255.54517	142.17850	49.8028
2	7.348	MM	0.6208	3281.32349	88.09888	50.1972

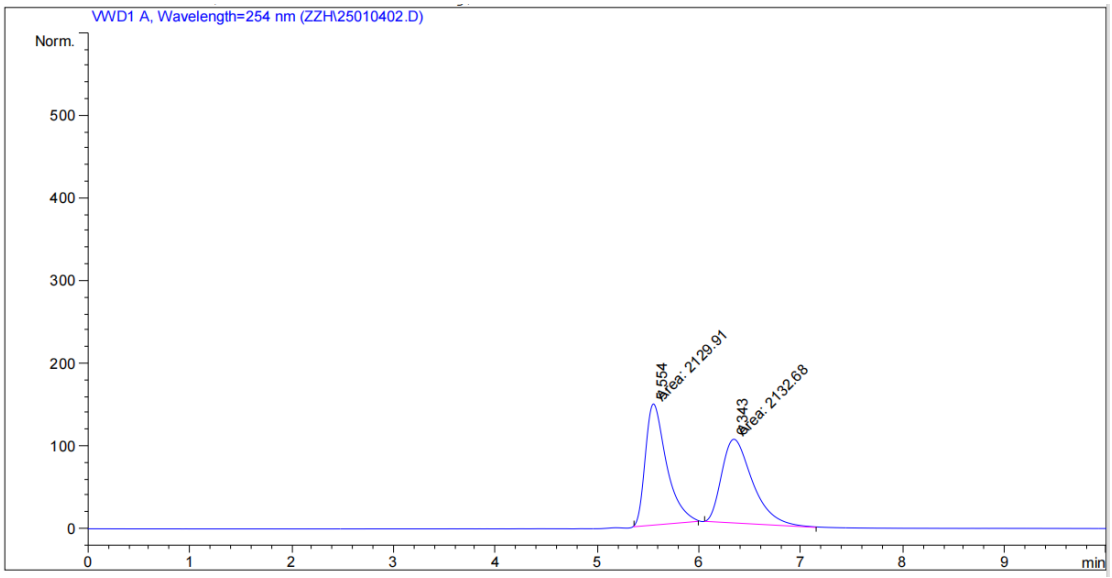


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	6.082	MM	0.4123	4639.18604	187.51526	95.4965
2	7.261	MM	0.5671	218.77727	6.42914	4.5035

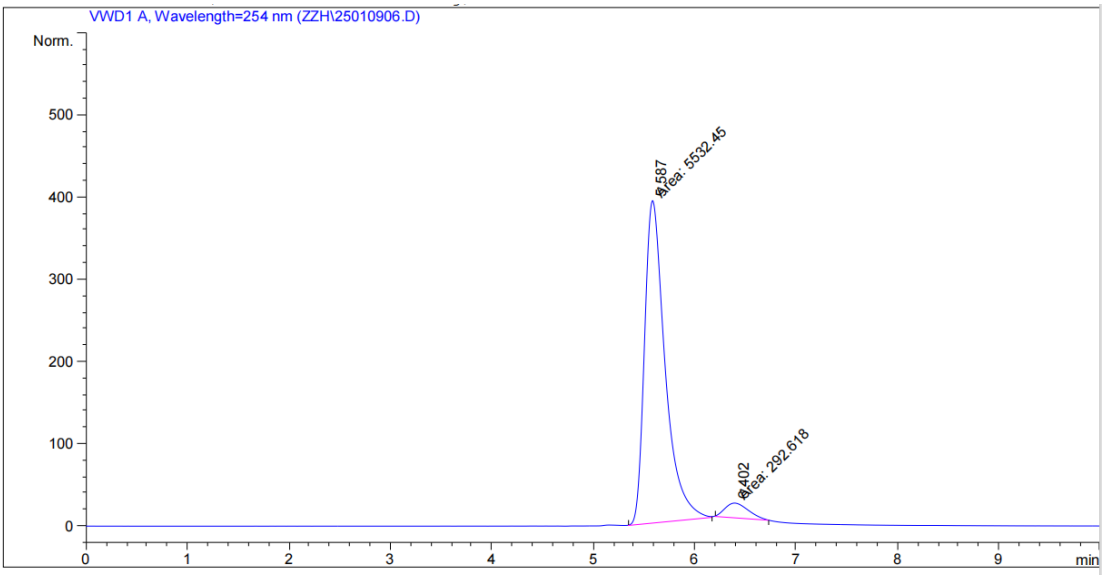


3am

HPLC using an IC-H column, n-hexane / ^{i}PrOH = 75/1, flow rate = 0.8 mL/min



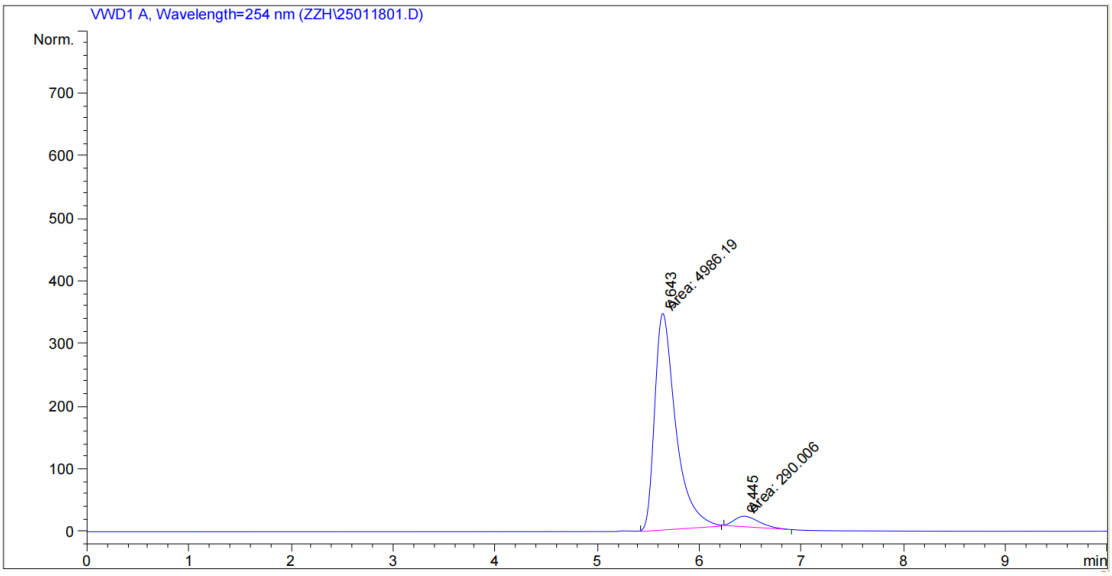
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	5.554	MM	0.2419	2129.91309	146.76863	49.9675
2	6.343	MM	0.3512	2132.68164	101.21317	50.0325



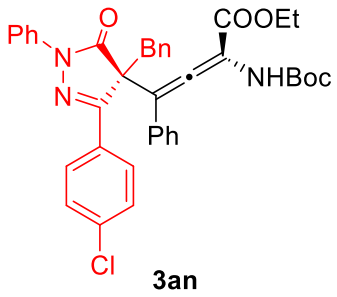
Gram-scale preparation of **3am**

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	5.587	MM	0.2352	5532.45166	392.08133	94.9766
2	6.402	MM	0.2697	292.61768	18.08373	5.0234

Gram-scale of **3am**

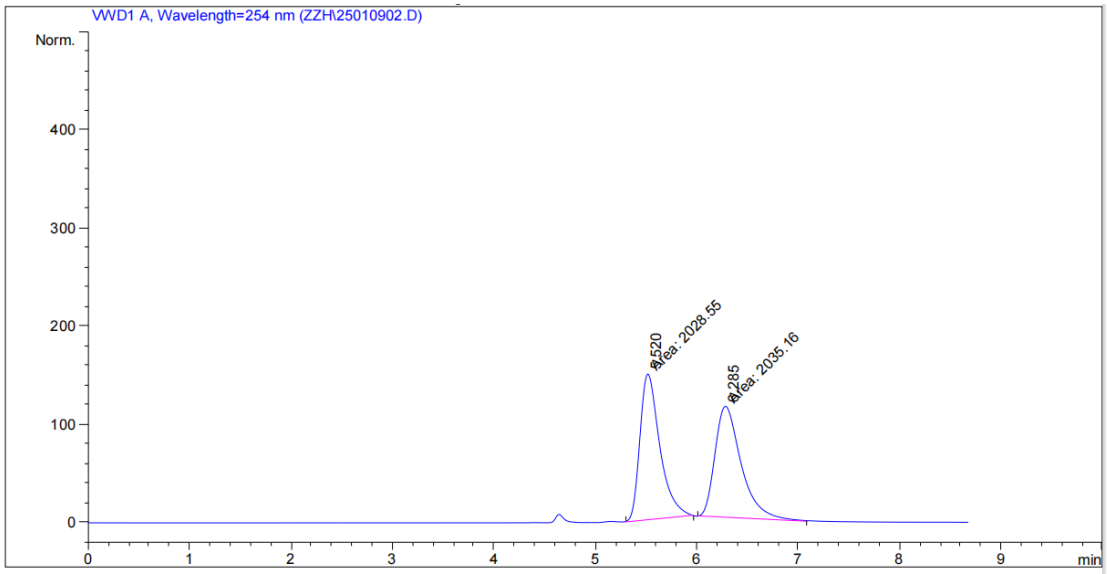


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	5.643	MM	0.2400	4986.18994	346.20059	94.5035
2	6.445	MM	0.2874	290.00589	16.81933	5.4965

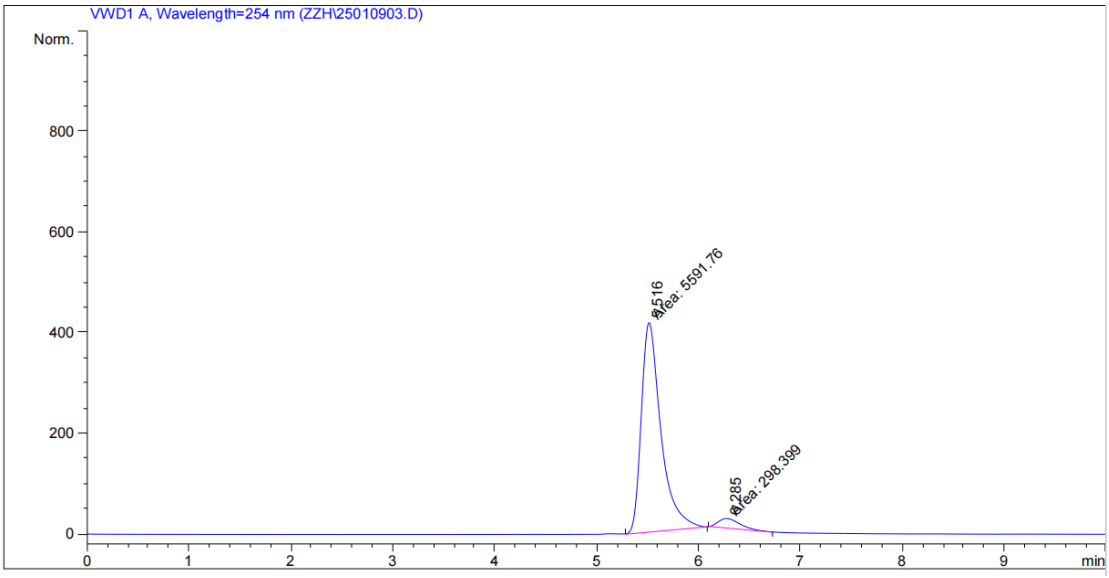


3an

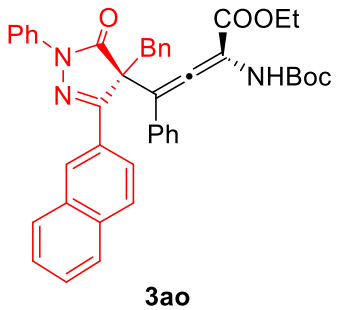
HPLC using an IC-H column, n-hexane / ^{i}PrOH = 75/1, flow rate = 0.8 mL/min



Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	5.520	MM	0.2278	2028.55347	148.41714	49.9187
2	6.285	MM	0.3004	2035.15796	112.93128	50.0813

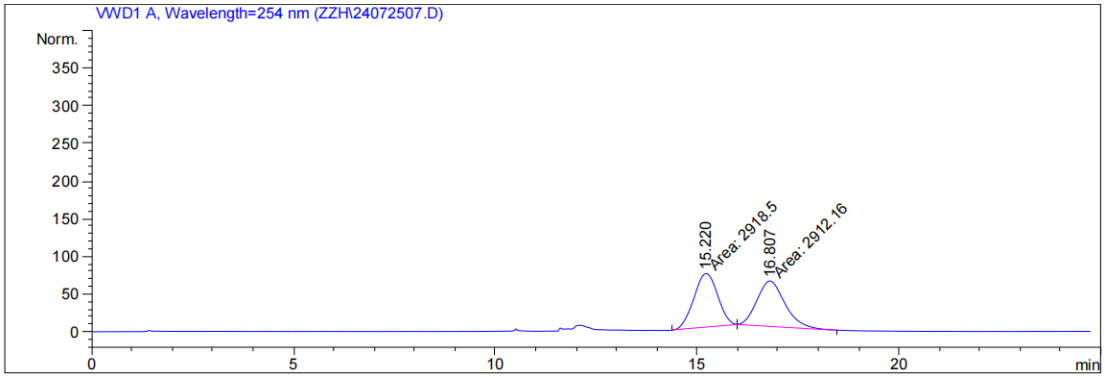


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	5.516	MM	0.2238	5591.75586	416.39645	94.9339
2	6.285	MM	0.2594	298.39938	19.17167	5.0661

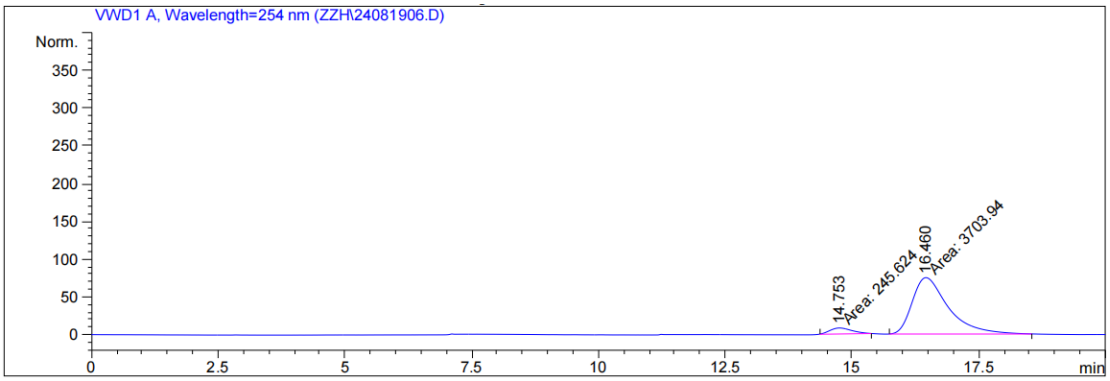


3ao

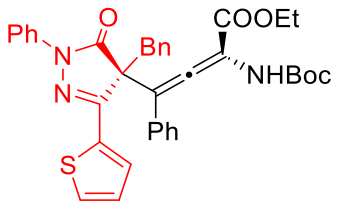
HPLC using an IE-H + IF-H column, n-hexane / ^{i}PrOH = 75/1, flow rate = 0.8 mL/min



Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	15.220	MM	0.6836	2918.49780	71.15408	50.0543
2	16.807	MM	0.8054	2912.16284	60.26203	49.9457

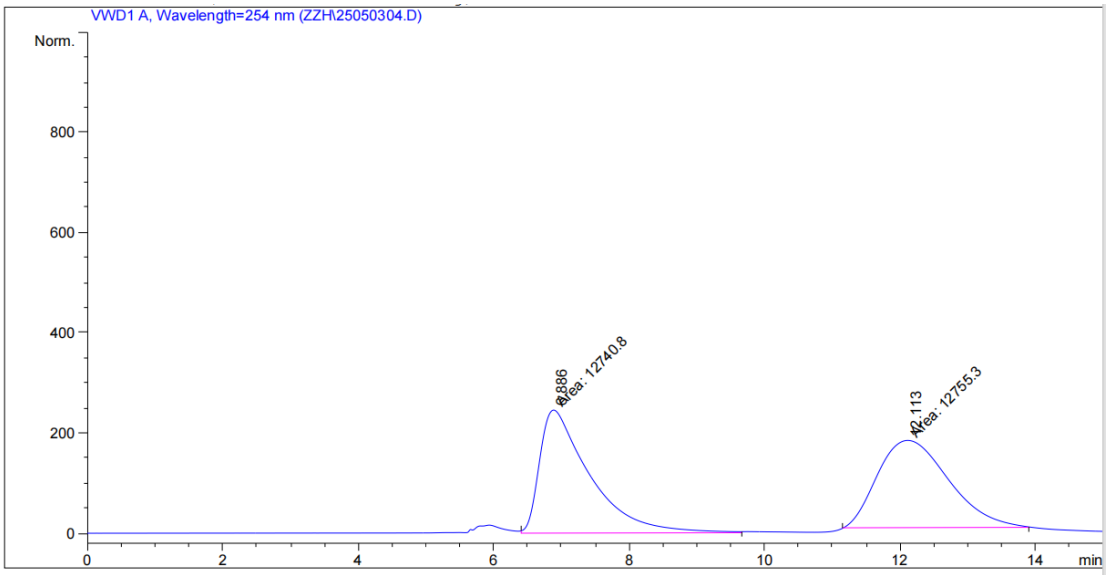


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	14.753	MM	0.5097	245.62442	8.03156	6.2190
2	16.460	MM	0.8269	3703.94043	74.65293	93.7810

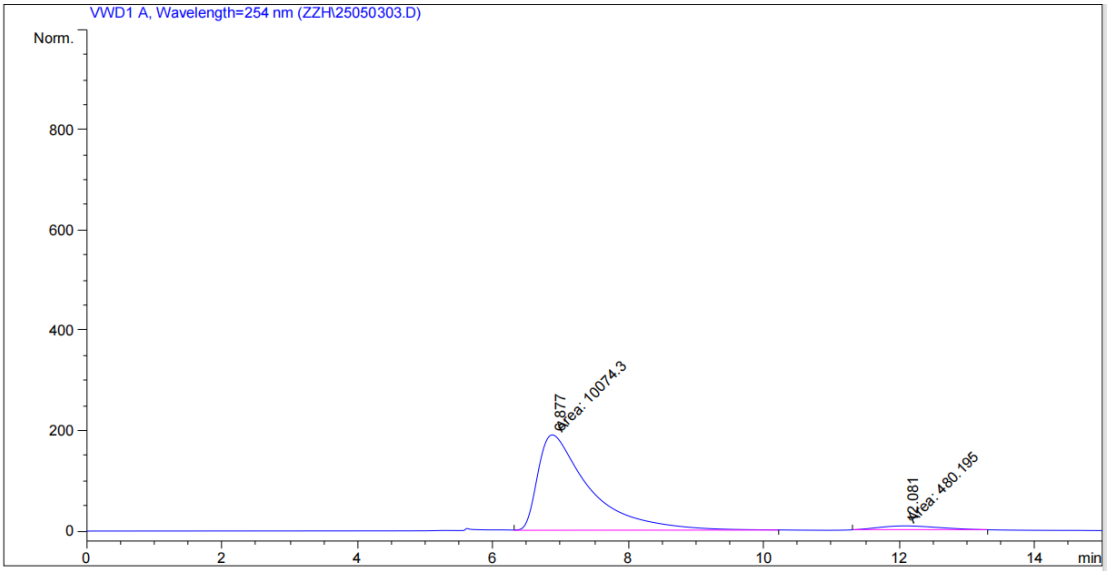


3ap

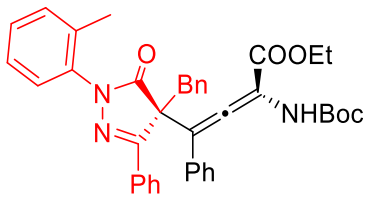
HPLC using an IC-H column, n-hexane / ^{i}PrOH = 75/1, flow rate = 0.8 mL/min



Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	6.886	MM	0.8636	1.27408e4	245.87285	49.9716
2	12.113	MM	1.2209	1.27553e4	174.12833	50.0284

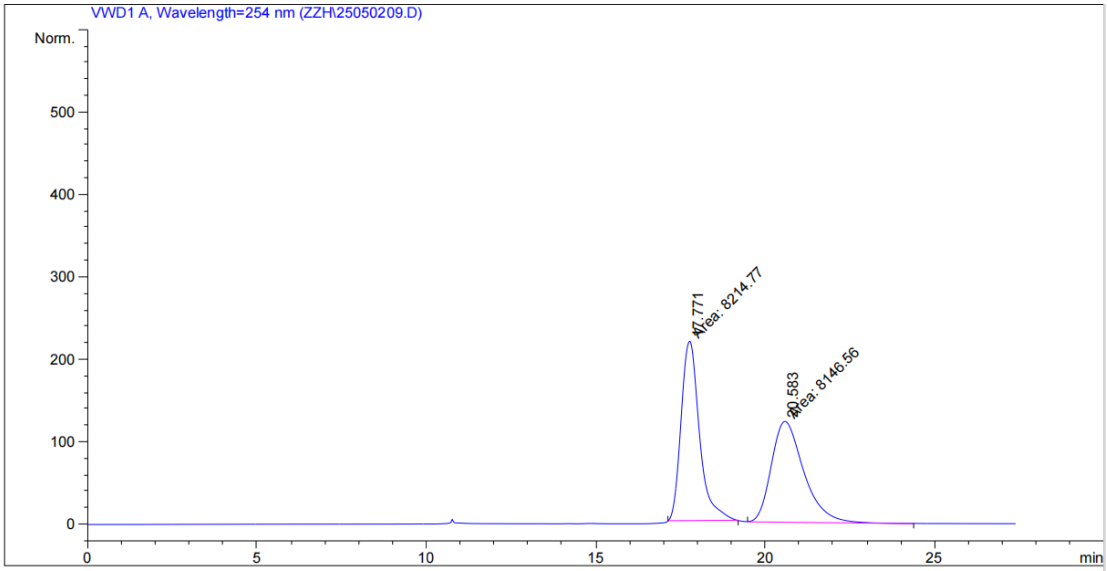


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	6.877	MM	0.8829	1.00743e4	190.18083	95.4503
2	12.081	MM	1.0335	480.19525	7.74382	4.5497

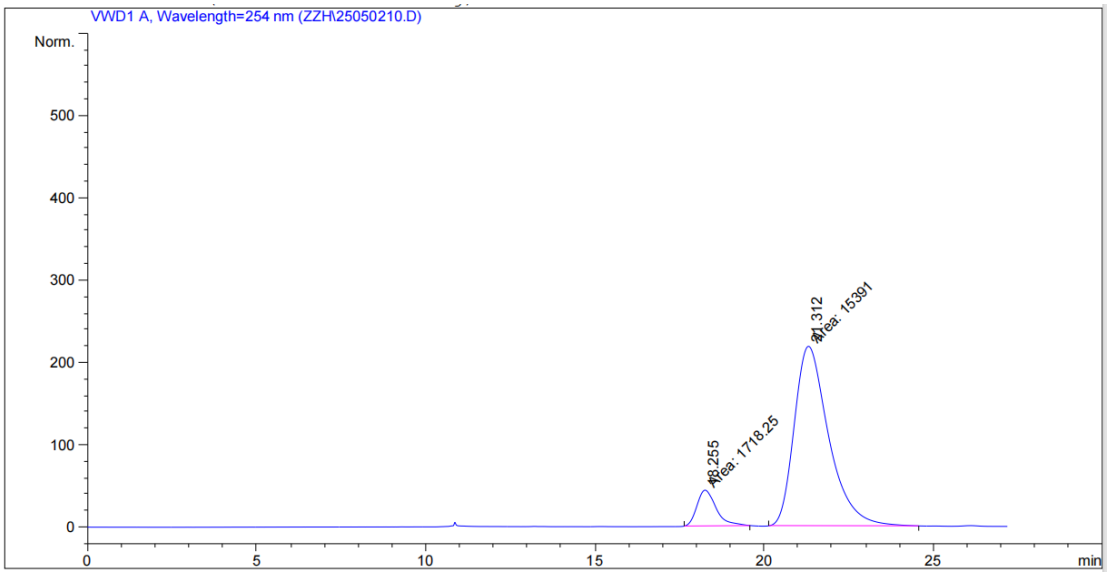


3aq

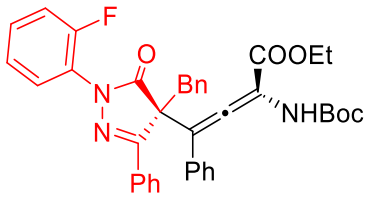
HPLC using an ID-H + IG-H column, n-hexane / ^{i}PrOH = 75/1, flow rate = 0.8 mL/min



Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	17.771	MM	0.6296	8214.76563	217.47247	50.2084
2	20.583	MM	1.1116	8146.56494	122.13978	49.7916

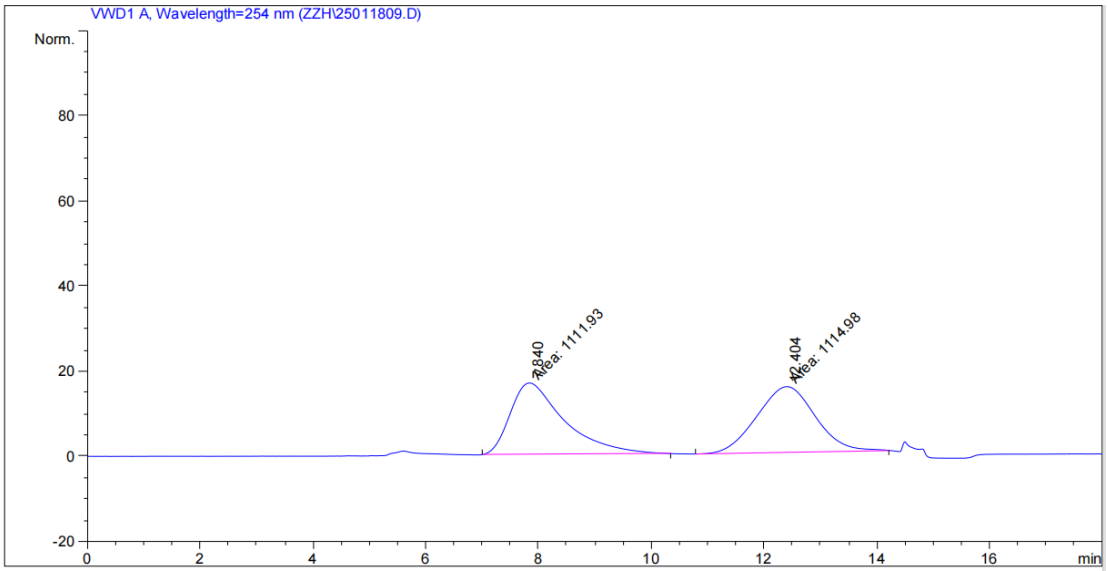


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	18.255	MM	0.6588	1718.25488	43.46891	10.0429
2	21.312	MM	1.1779	1.53910e4	217.76854	89.9571

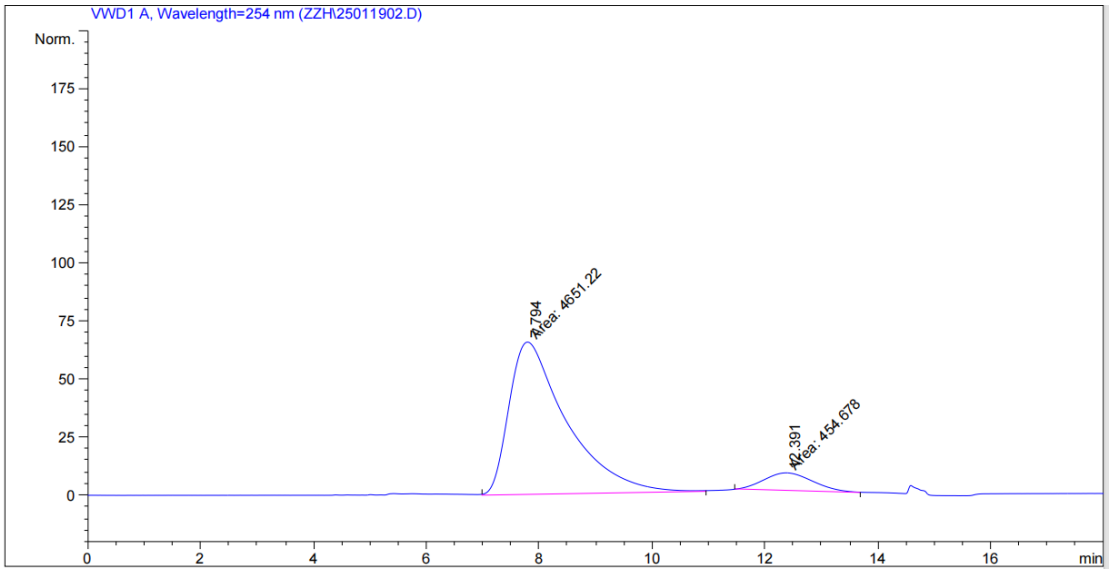


3ar

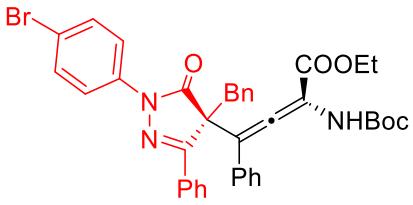
HPLC using an IC-H column, n-hexane / ^{i}PrOH = 75/1, flow rate = 0.8 mL/min



Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	7.840	MM	1.1065	1111.93469	16.74901	49.9317
2	12.404	MM	1.2018	1114.97791	15.46262	50.0683

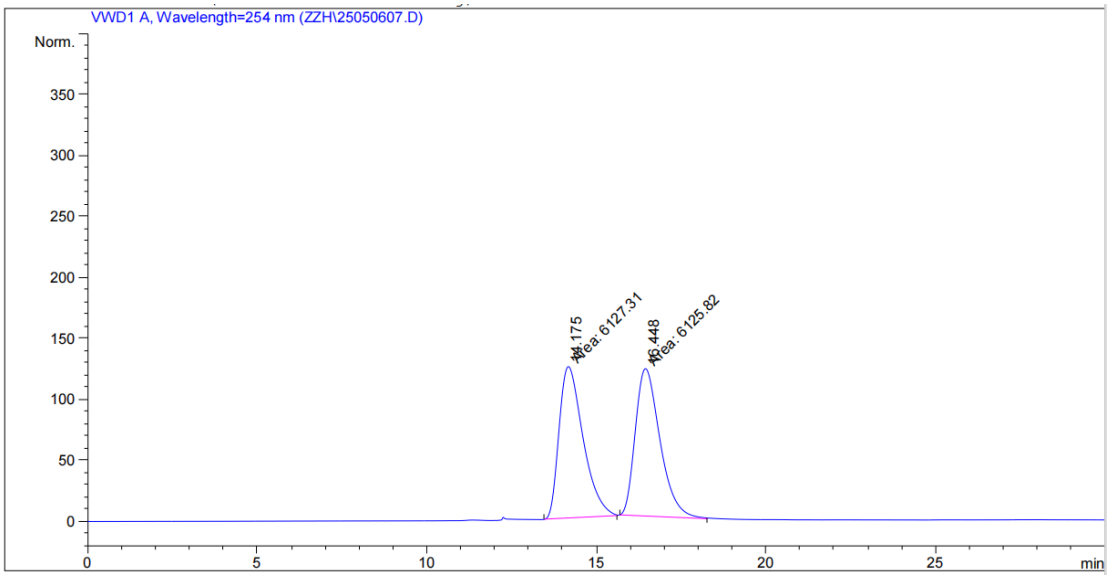


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	7.794	MM	1.1816	4651.22217	65.60494	91.0950
2	12.391	MM	0.9987	454.67841	7.58785	8.9050

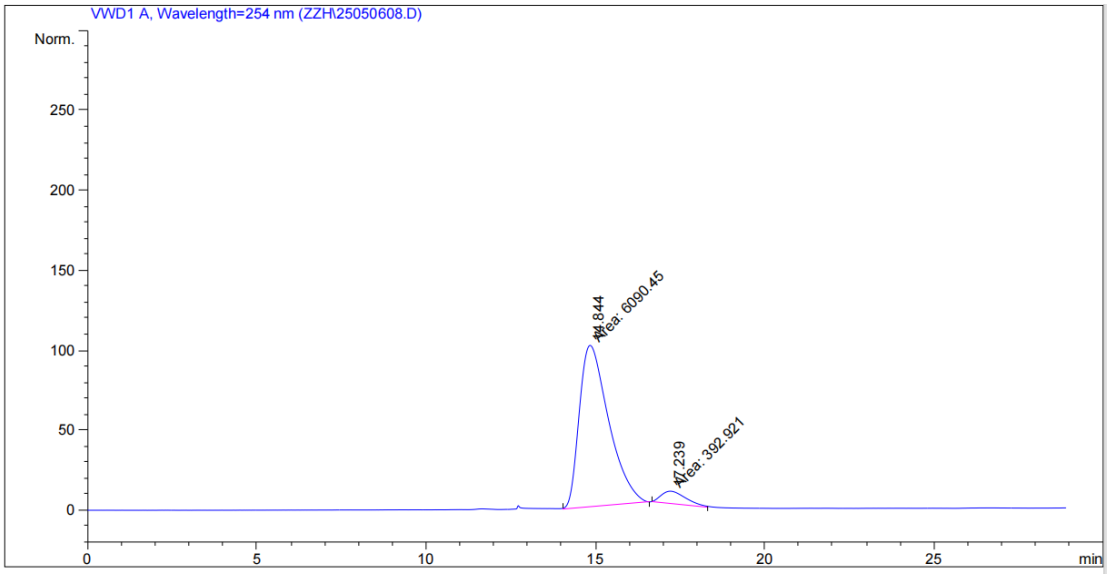


3as

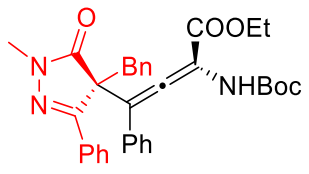
HPLC using an IC-H + IC-H column, n-hexane / ^{i}PrOH = 75/1, flow rate = 0.8 mL/min



Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	14.175	MM	0.8227	6127.31250	124.12262	50.0061
2	16.448	MM	0.8450	6125.82373	120.81930	49.9939

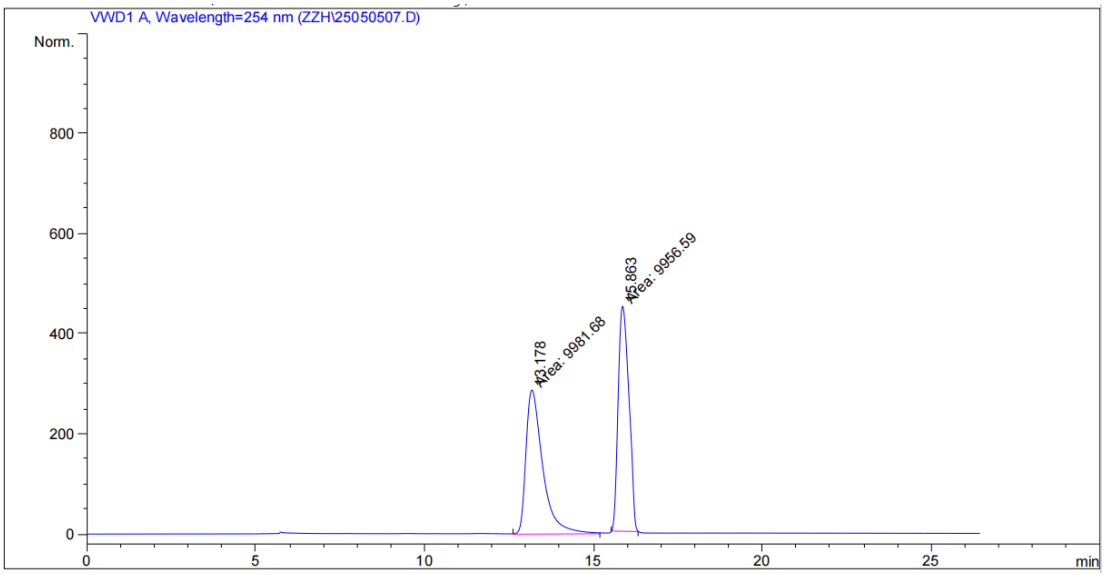


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	14.844	MM	1.0058	6090.45020	100.92268	93.9396
2	17.239	MM	0.8489	392.92062	7.71435	6.0604

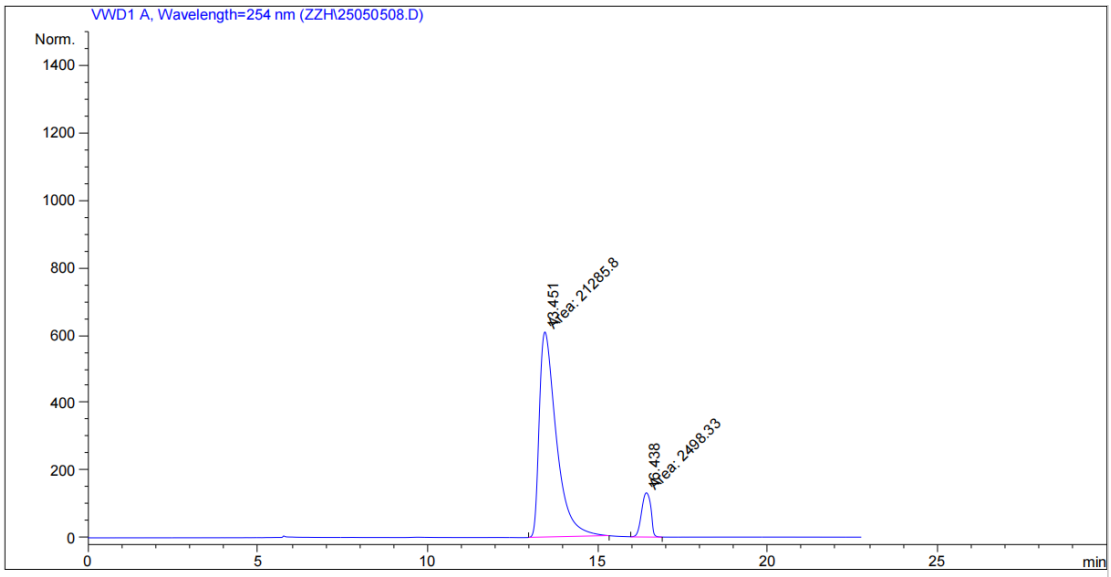


3at

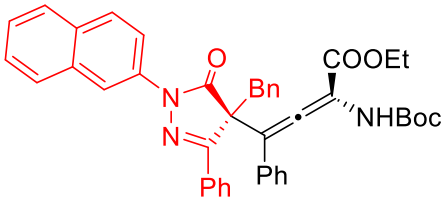
HPLC using an IE-H column, n-hexane / ^{i}PrOH = 75/1, flow rate = 0.8 mL/min



Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	13.178	MM	0.5780	9981.67578	287.84473	50.0629
2	15.863	MM	0.3693	9956.58691	449.37958	49.9371

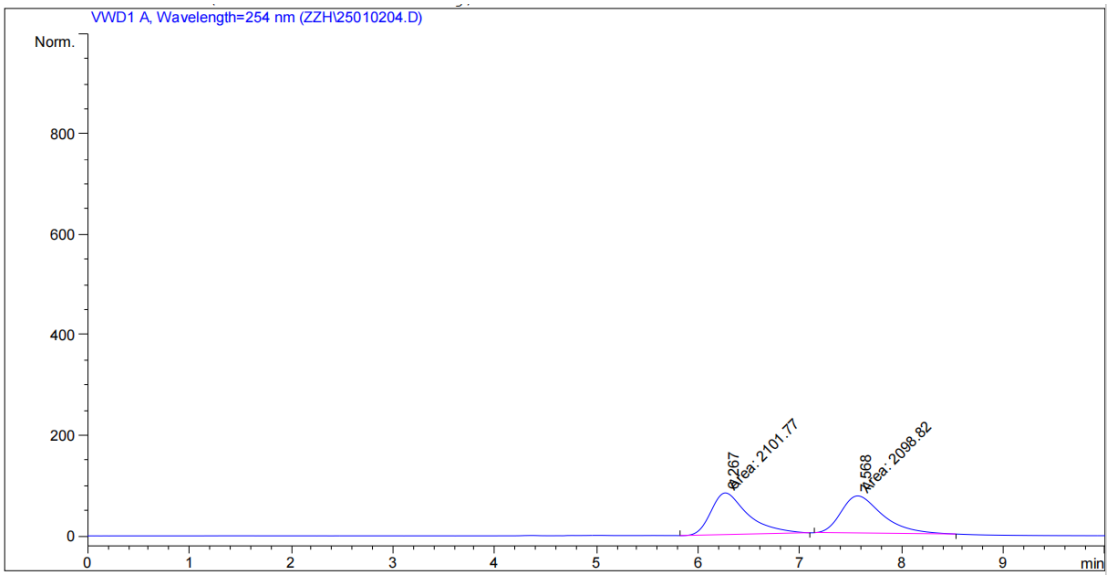


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	13.451	MM	0.5839	2.12858e4	607.58350	89.4958
2	16.438	MM	0.3177	2498.33301	131.06386	10.5042

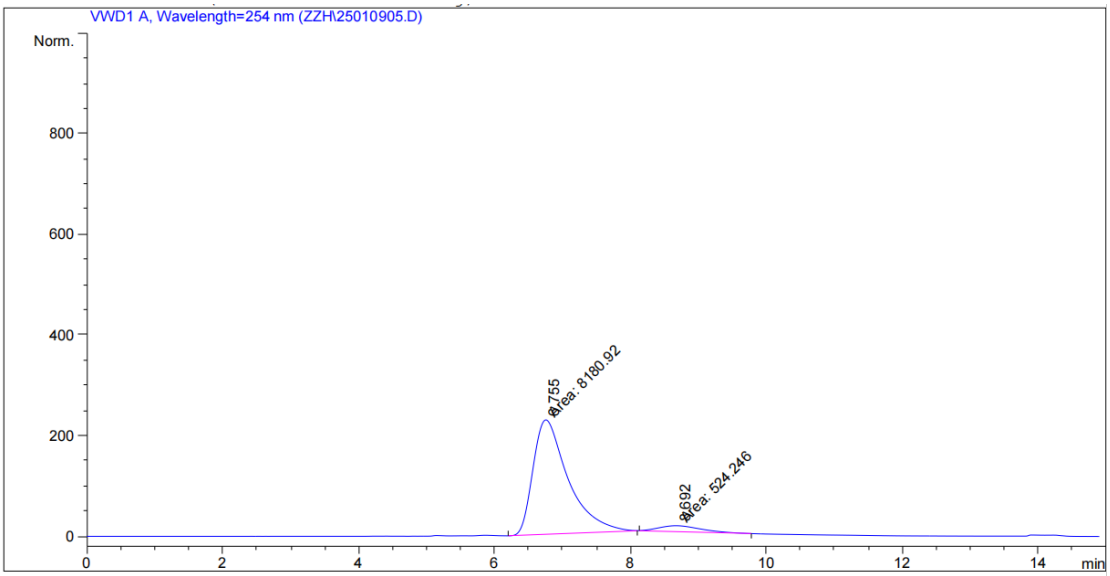


3au

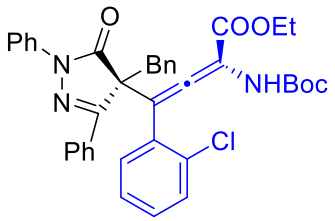
HPLC using an IC-H column, n-hexane / ^{i}PrOH = 75/1, flow rate = 0.8 mL/min



Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	6.267	MM	0.4212	2101.77002	83.15883	50.0352
2	7.568	MM	0.4730	2098.81689	73.96039	49.9648

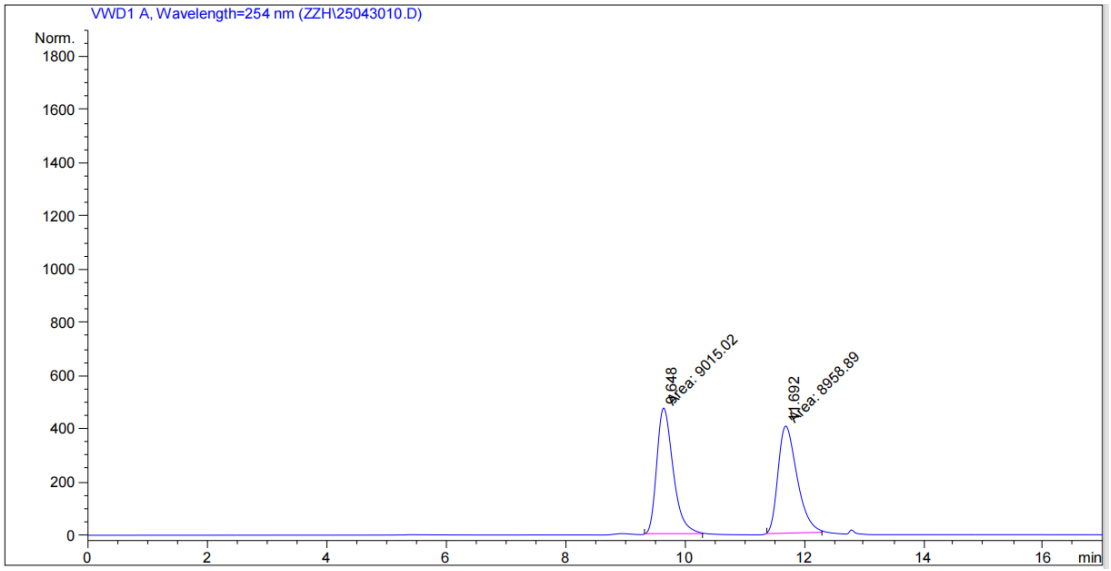


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	6.755	MM	0.5995	8180.92187	227.44434	93.9778
2	8.692	MM	0.7270	524.24561	12.01822	6.0222

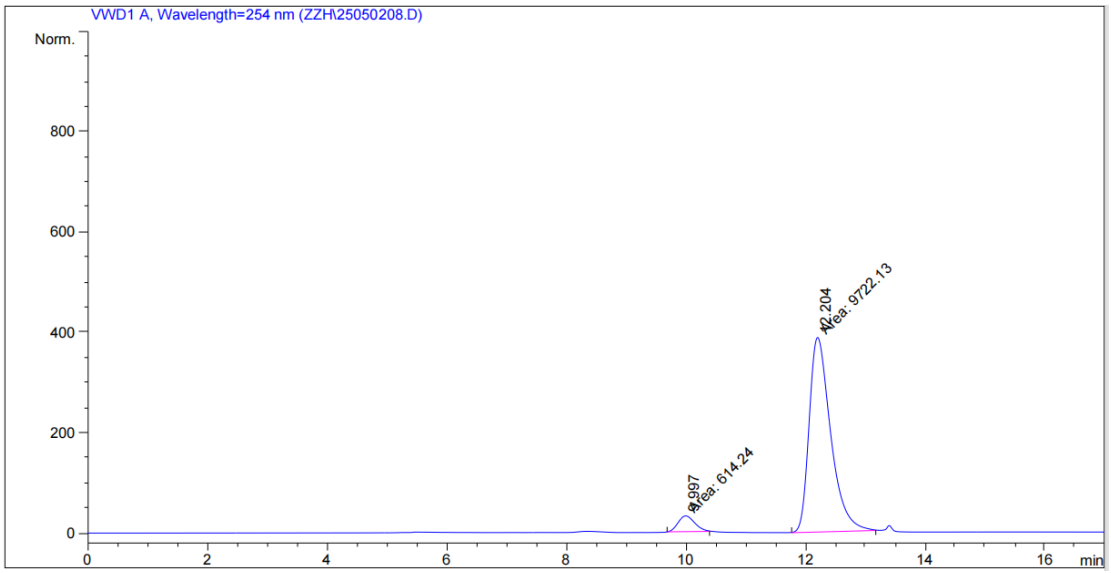


3ba

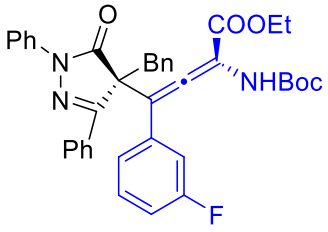
HPLC using an IE-H column, n-hexane / ^{i}PrOH = 75/1, flow rate = 0.8 mL/min



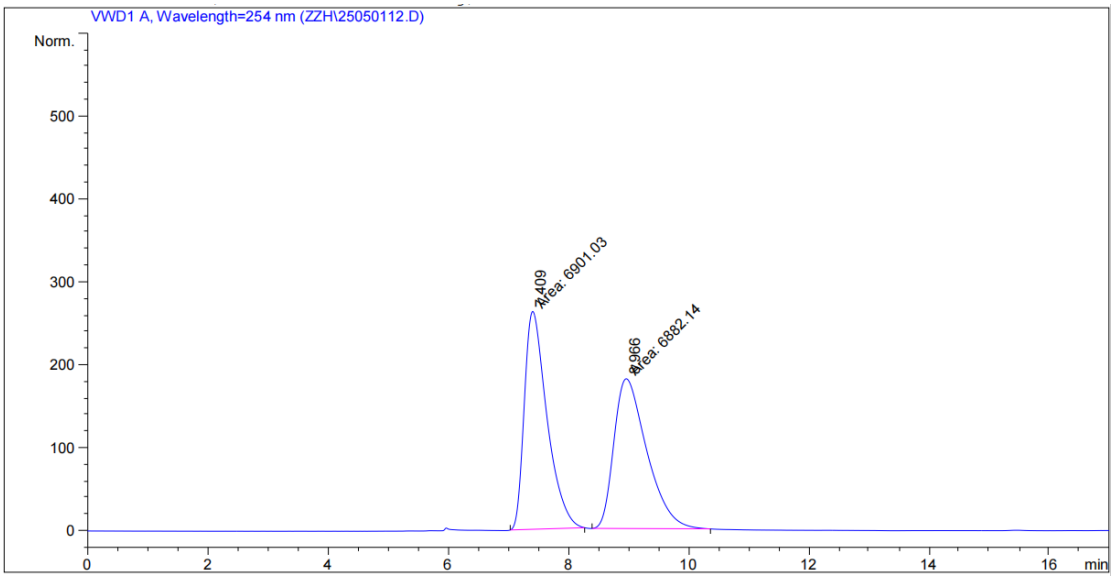
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	9.648	MM	0.3180	9015.01563	472.44955	50.1561
2	11.692	MM	0.3705	8958.89160	403.03043	49.8439



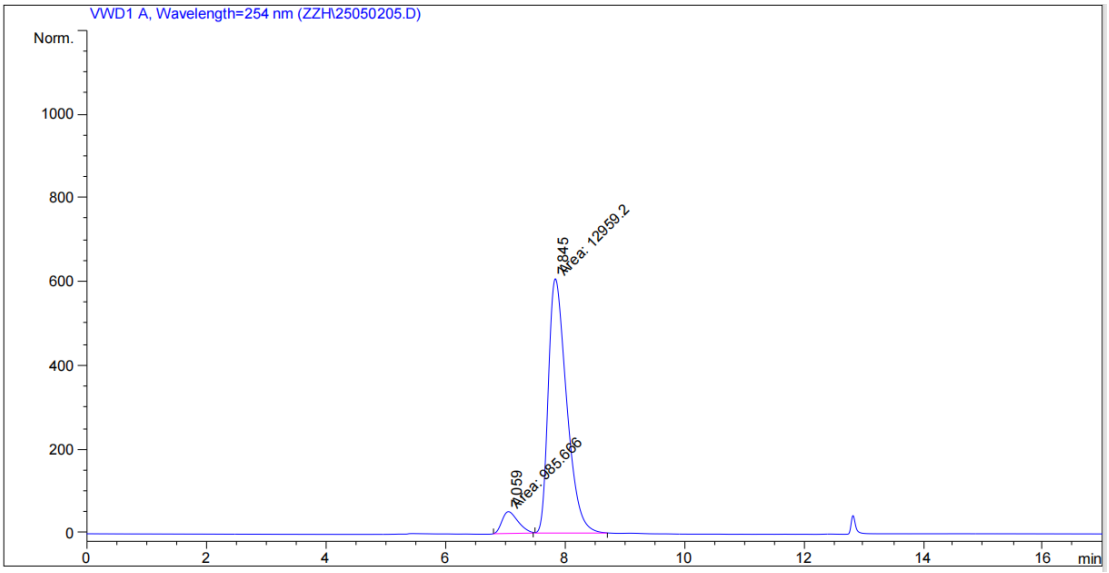
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	9.997	MM	0.3246	614.23993	31.54284	5.9425
2	12.204	MM	0.4178	9722.13477	387.80310	94.0575



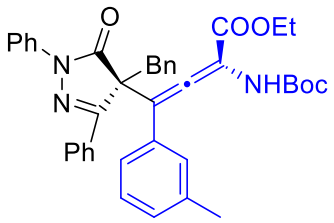
3ca



Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	7.409	MM	0.4379	6901.02734	262.66187	50.0685
2	8.966	MM	0.6351	6882.14307	180.61353	49.9315

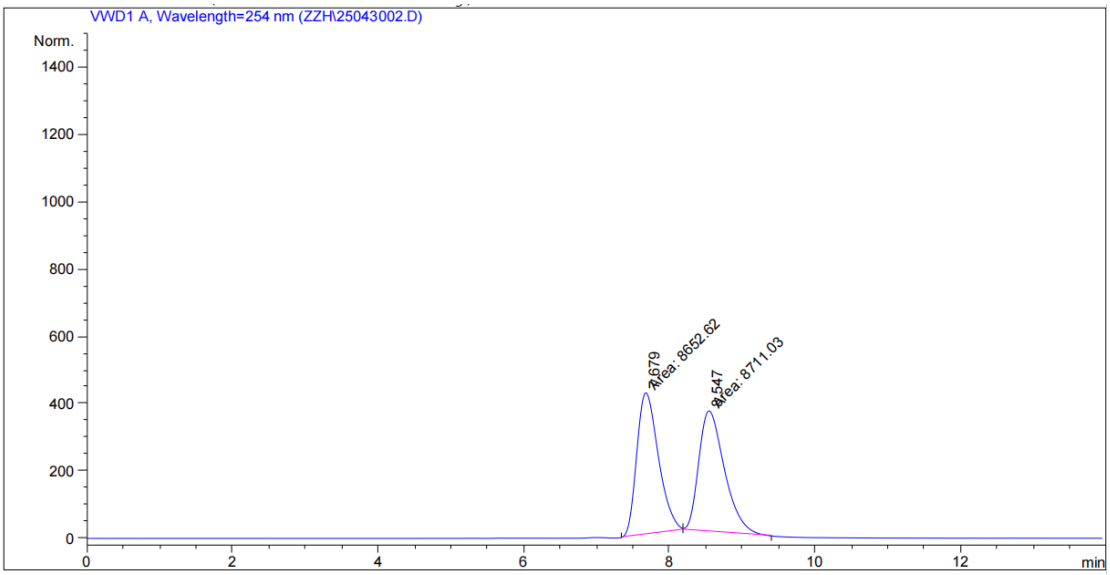


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	7.059	MM	0.3133	985.66602	52.44098	7.0683
2	7.845	MM	0.3558	1.29592e4	607.10730	92.9317

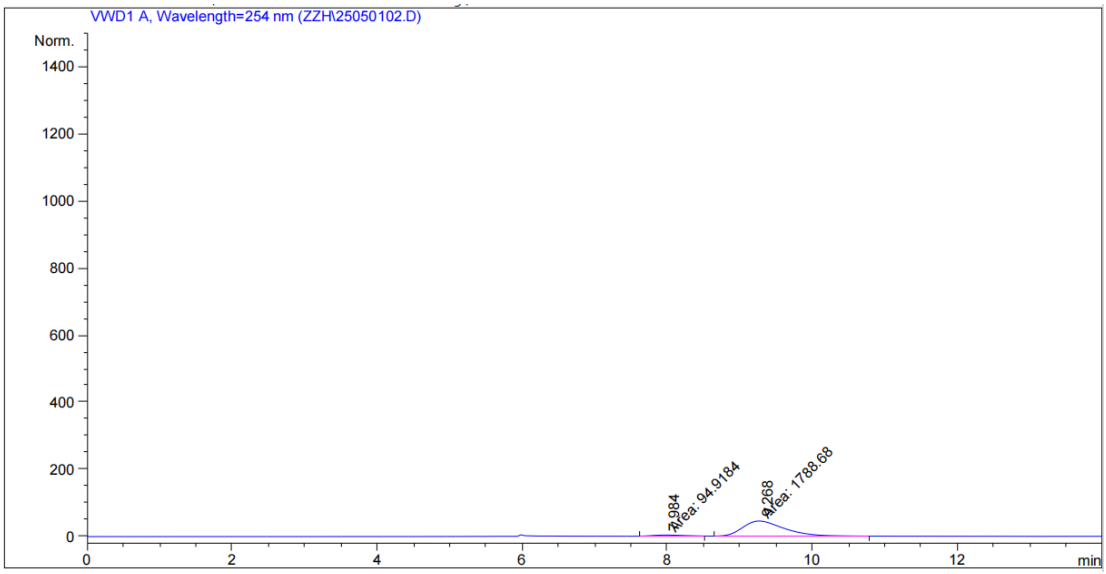


3da

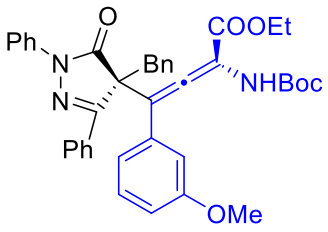
HPLC using an IE-H column, n-hexane / ^{i}PrOH = 75/1, flow rate = 0.8 mL/min



Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	7.679	MM	0.3442	8652.61621	419.00735	49.8318
2	8.547	MM	0.4071	8711.03418	356.64206	50.1682

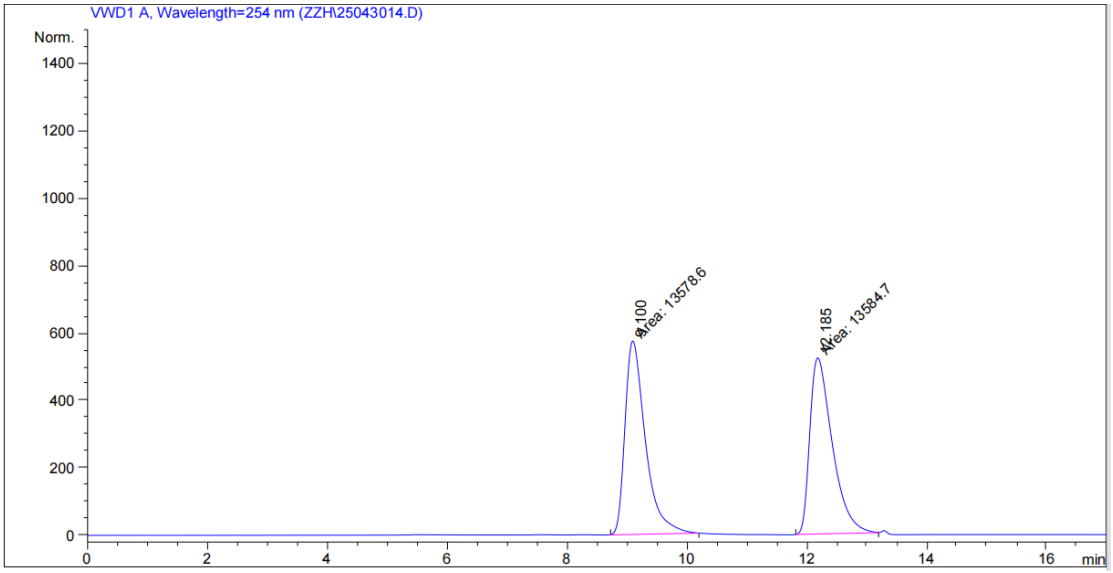


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	7.984	MM	0.4790	94.91843	3.30281	5.0392
2	9.268	MM	0.6647	1788.68286	44.85073	94.9608

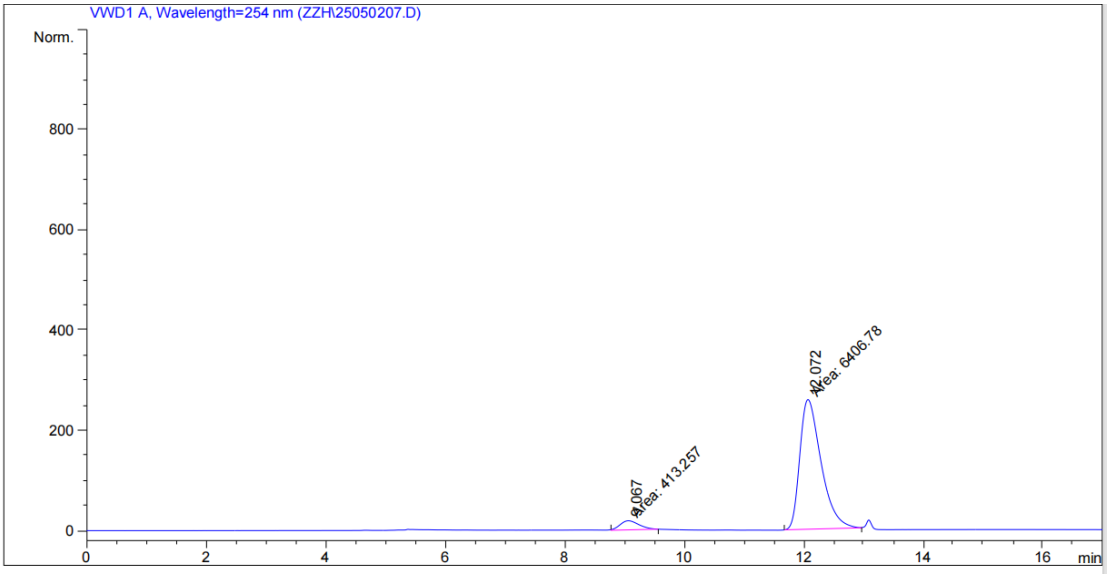


3ea

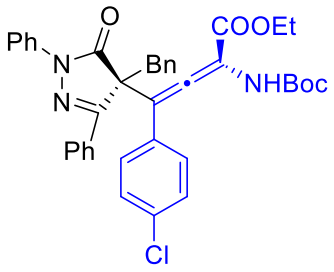
HPLC using an IE-H column, n-hexane / ^{i}PrOH = 75/1, flow rate = 0.8 mL/min



Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	9.100	MM	0.3945	1.35786e4	573.62183	49.9888
2	12.185	MM	0.4336	1.35847e4	522.12103	50.0112

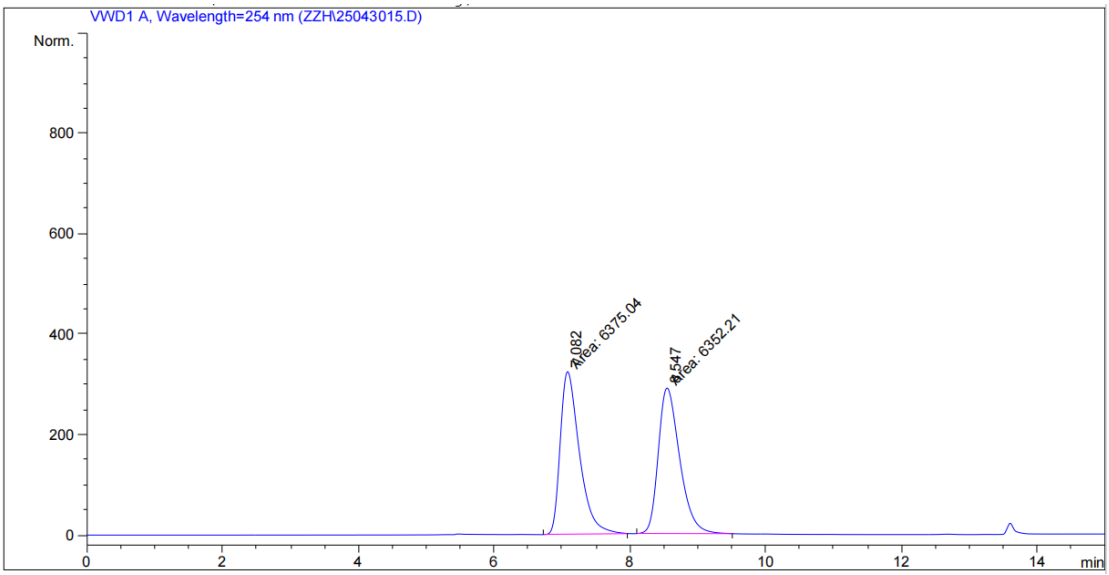


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	9.067	MM	0.3736	413.25677	18.43521	6.0595
2	12.072	MM	0.4129	6406.78076	258.58331	93.9405

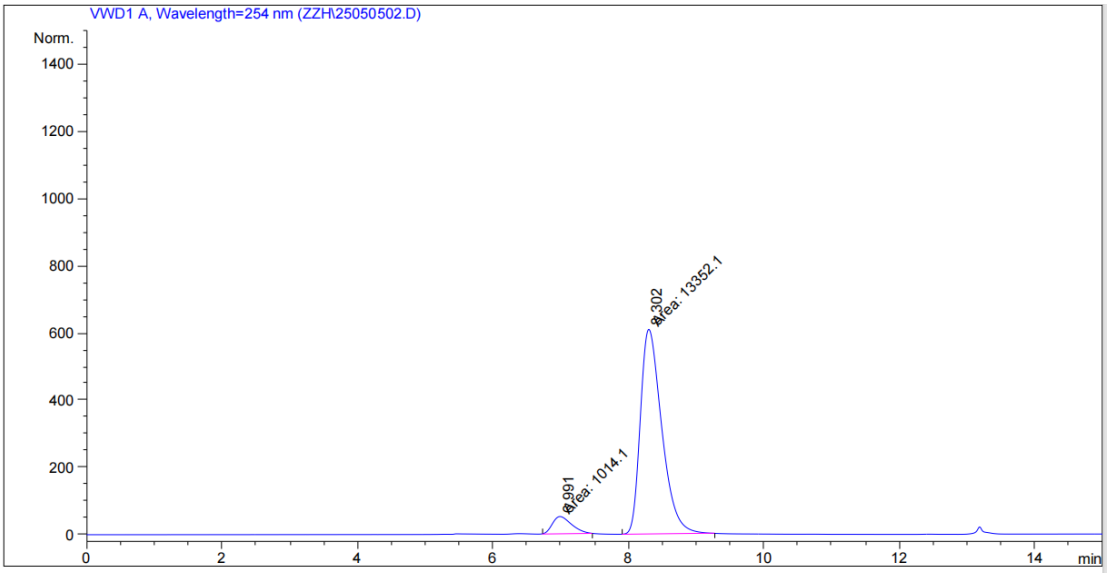


3fa

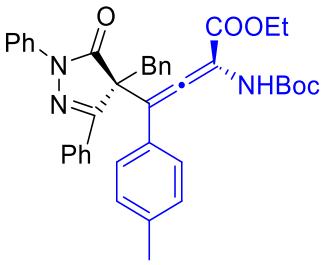
HPLC using an IE-H column, n-hexane / ^{i}PrOH = 75/1, flow rate = 0.8 mL/min



Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	7.082	MM	0.3282	6375.04395	323.78406	50.0897
2	8.547	MM	0.3653	6352.21094	289.78165	49.9103

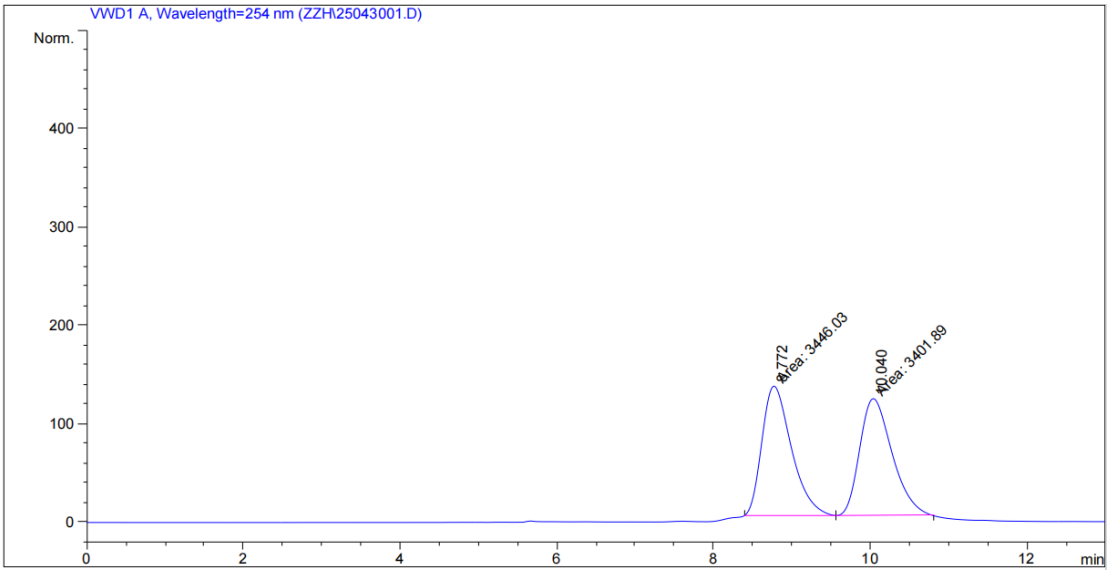


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	6.991	MM	0.3283	1014.09753	51.48822	7.0589
2	8.302	MM	0.3658	1.33521e4	608.32684	92.9411

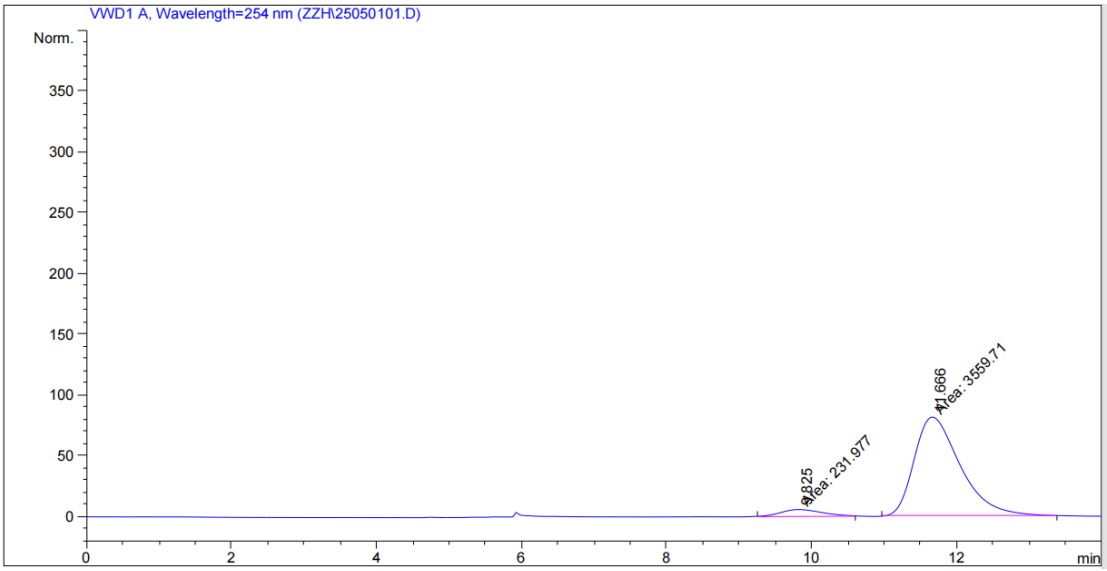


3ga

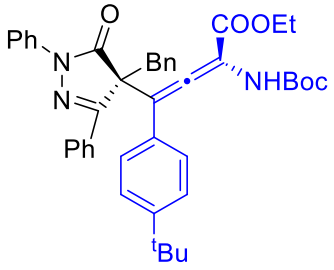
HPLC using an IE-H column, n-hexane / ^{i}PrOH = 75/1, flow rate = 0.8 mL/min



Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	8.772	MM	0.4370	3446.03174	131.42622	50.3223
2	10.040	MM	0.4784	3401.89355	118.52341	49.6777

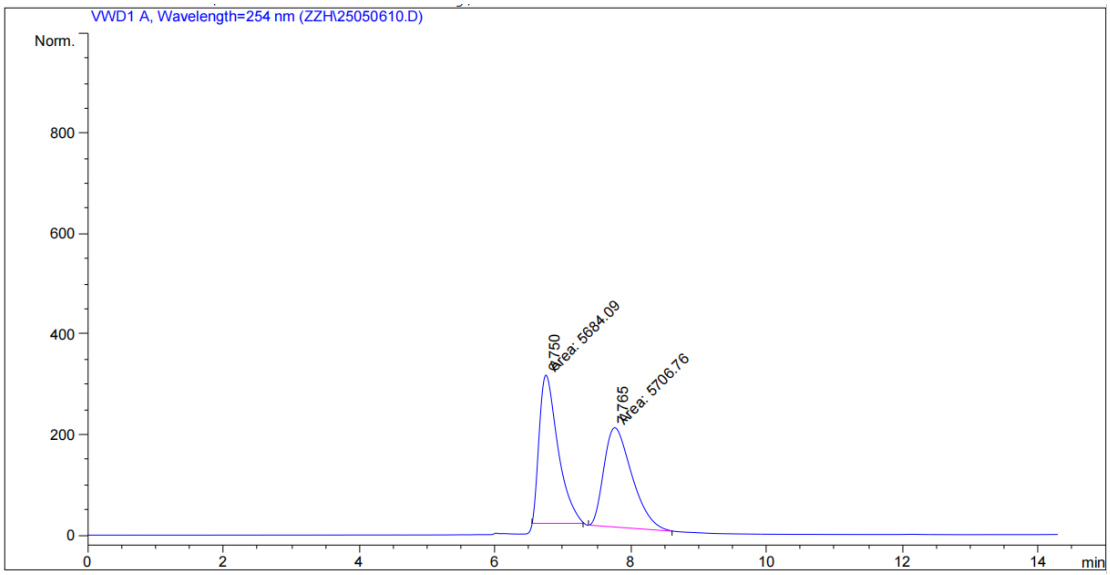


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	9.825	MM	0.6734	231.97688	5.74131	6.1180
2	11.666	MM	0.7333	3559.70874	80.90701	93.8820

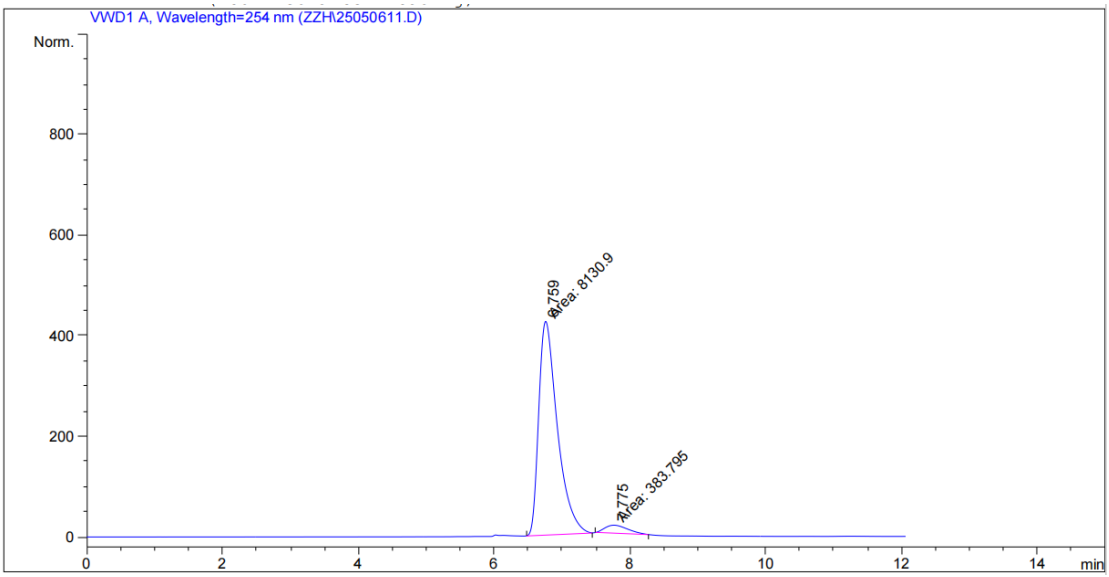


3ha

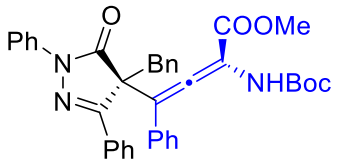
HPLC using an IE-H column, n-hexane / ^{i}PrOH = 75/1, flow rate = 0.8 mL/min



Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	6.750	MM	0.3209	5684.08594	295.25189	49.9005
2	7.765	MM	0.4802	5706.75635	198.08862	50.0995

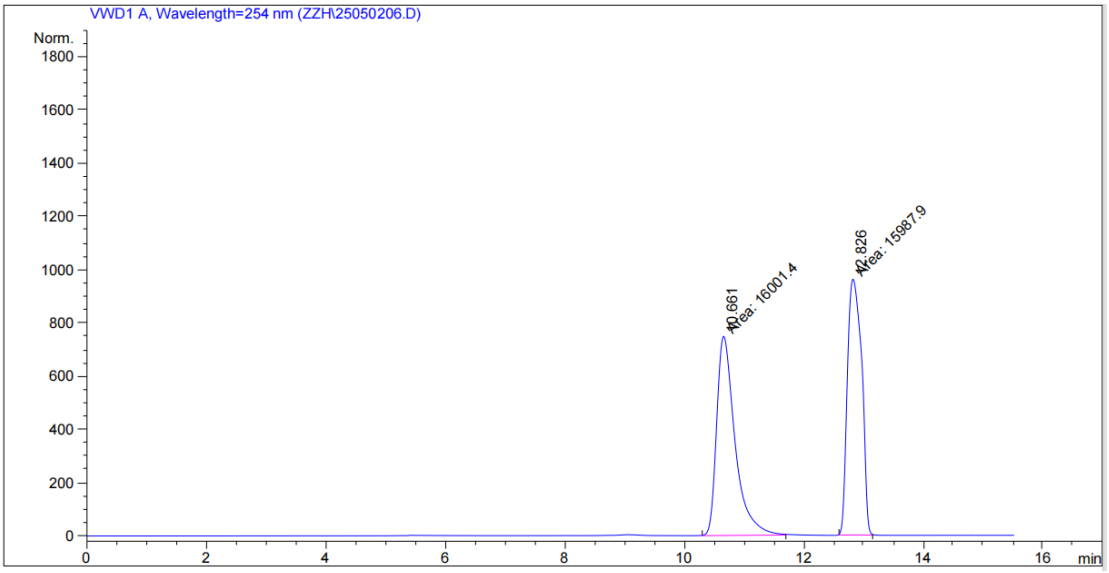


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	6.759	MM	0.3188	8130.89746	425.08722	95.4926
2	7.775	MM	0.3981	383.79514	16.06600	4.5074

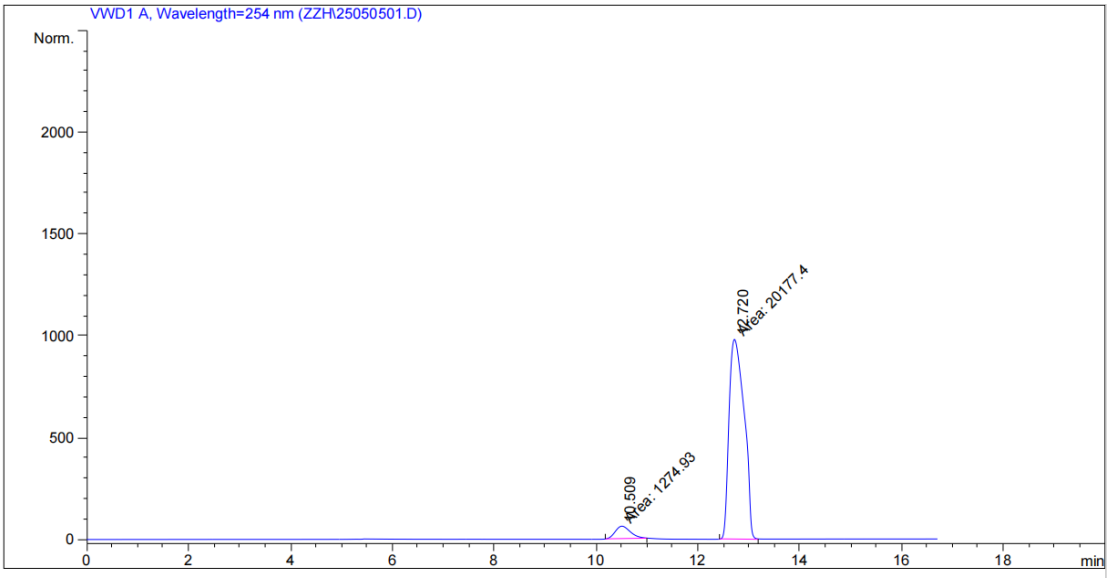


3ia

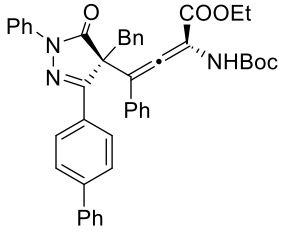
HPLC using an IE-H column, n-hexane / ^{i}PrOH = 75/1, flow rate = 0.8 mL/min



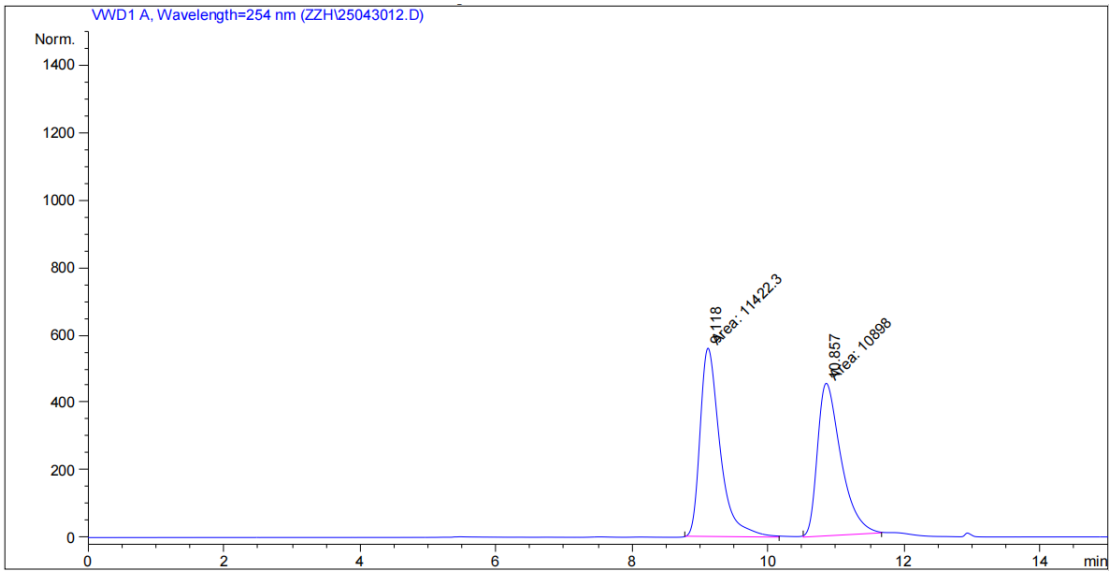
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	10.661	MM	0.3564	1.60014e4	748.26276	50.0211
2	12.826	MM	0.2773	1.59879e4	960.92285	49.9789



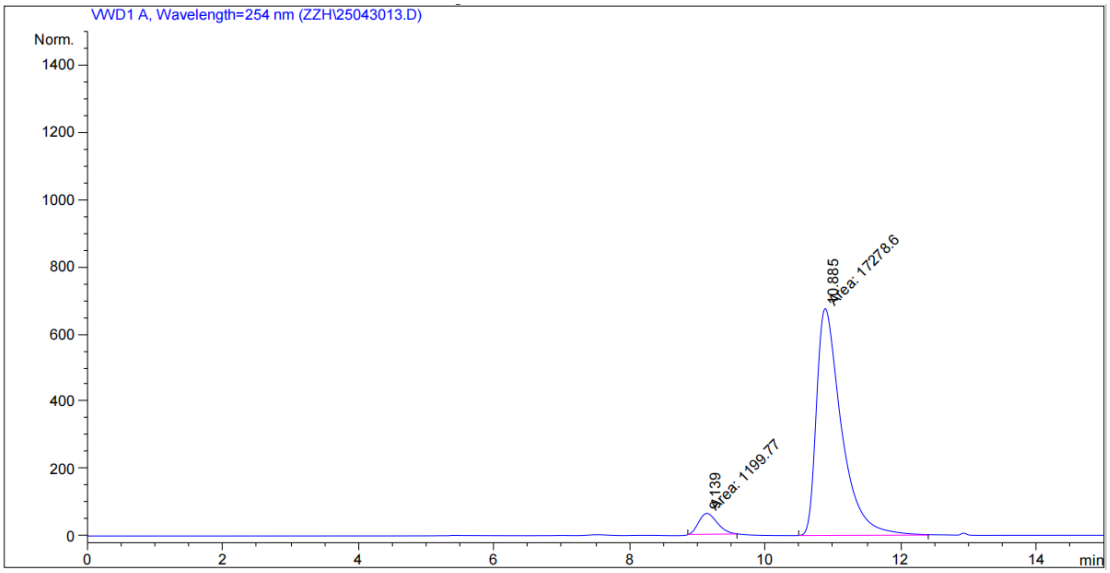
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	10.509	MM	0.3463	1274.92944	61.35424	5.9431
2	12.720	MM	0.3430	2.01774e4	980.49896	94.0569



HPLC using an IE-H column, n-hexane / ^{i}PrOH = 75/1, flow rate = 0.8 mL/min

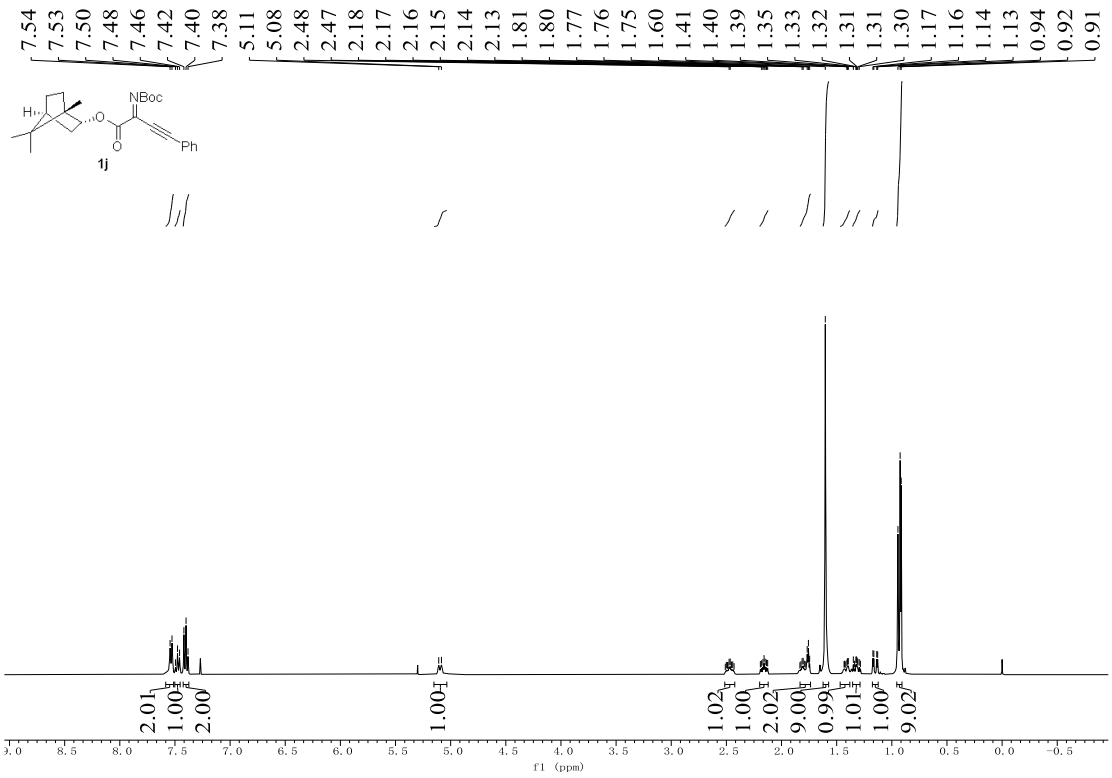


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	9.118	MM	0.3412	1.14223e4	557.90918	51.1744
2	10.857	MM	0.4020	1.08980e4	451.84204	48.8256



Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	9.139	MM	0.3203	1199.76843	62.43250	6.4928
2	10.885	MM	0.4271	1.72786e4	674.21155	93.5072

6. NMR Analysis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7.42
7.40
7.38
5.11
5.08
2.48
2.47
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2.17
2.16
2.15
2.14
2.13
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1.41
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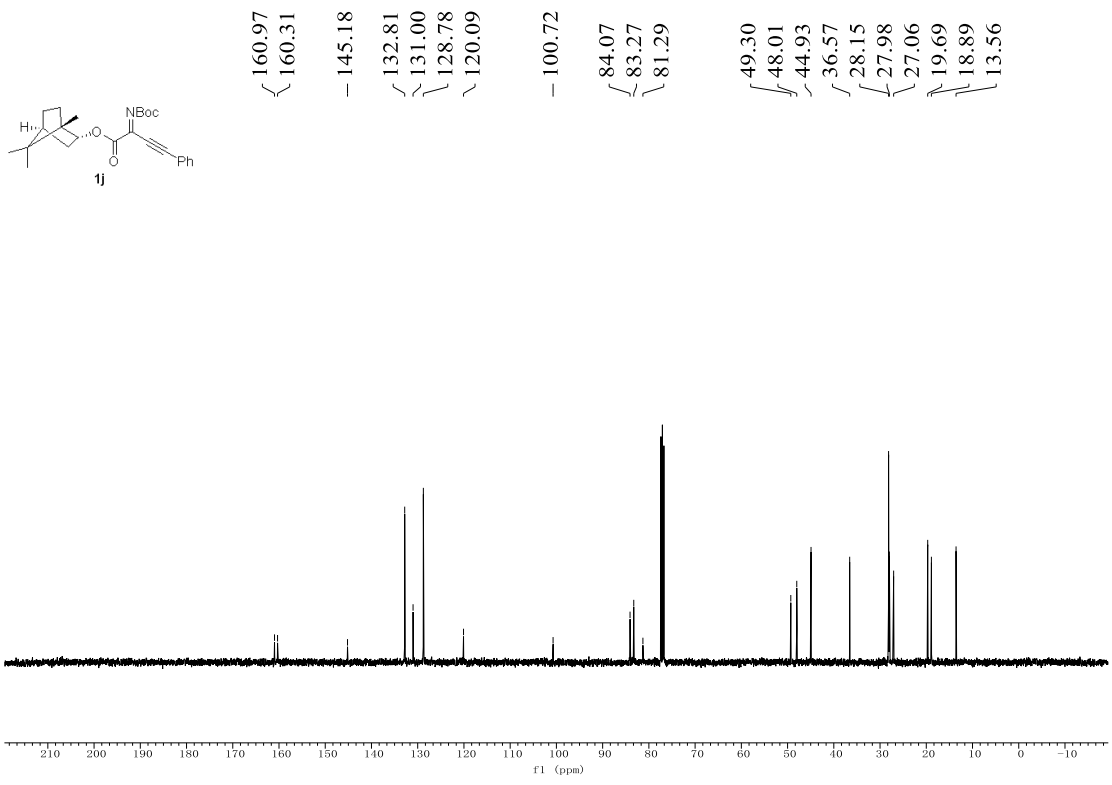
1.35
1.33
1.32
1.31
1.31
1.30
1.17
1.16
1.14
1.13
0.94
0.92
0.91
NBoc
Ph
1j
2.01
1.00
2.00
1.00
1.02
1.00
2.02
9.00
0.99
1.01
1.00
9.02
f1 (ppm)


160.97
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131.00
128.78
120.09
100.72
84.07
83.27
81.29
49.30
48.01
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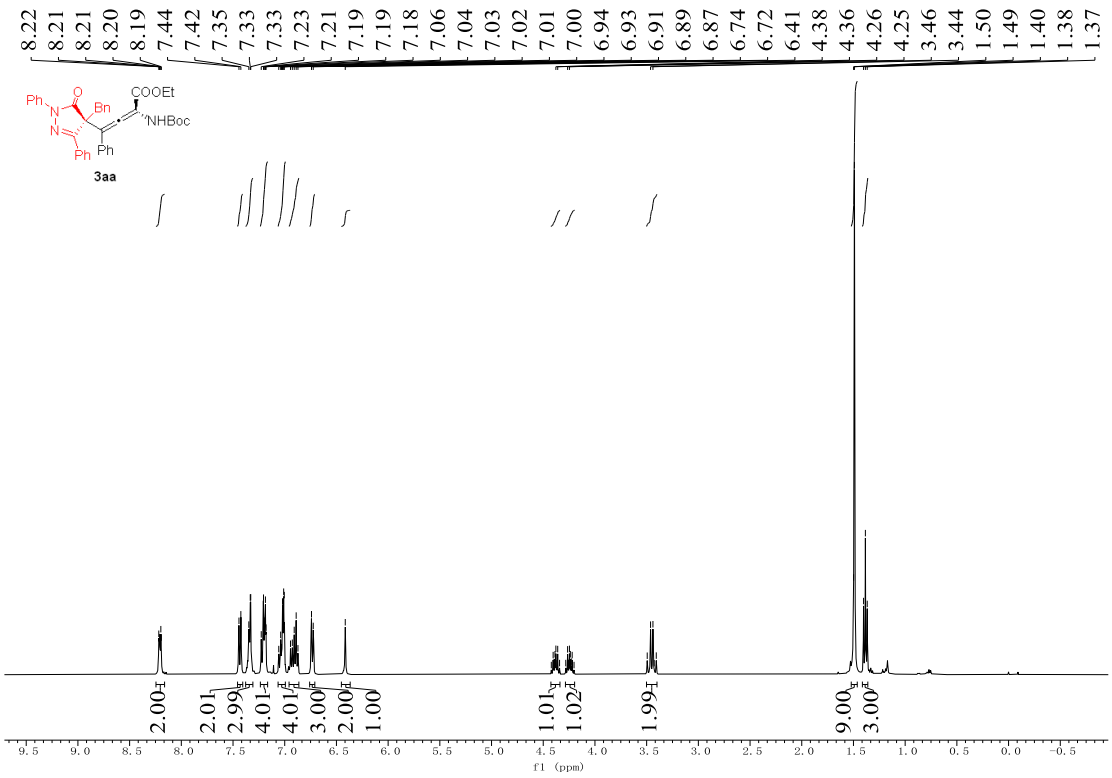
18.89
13.56
NBoc
Ph
1j
f1 (ppm)


8.22
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8.21
8.20
8.19
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7.35
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7.33
7.23
7.21
7.19
7.19
7.18
7.06
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7.03
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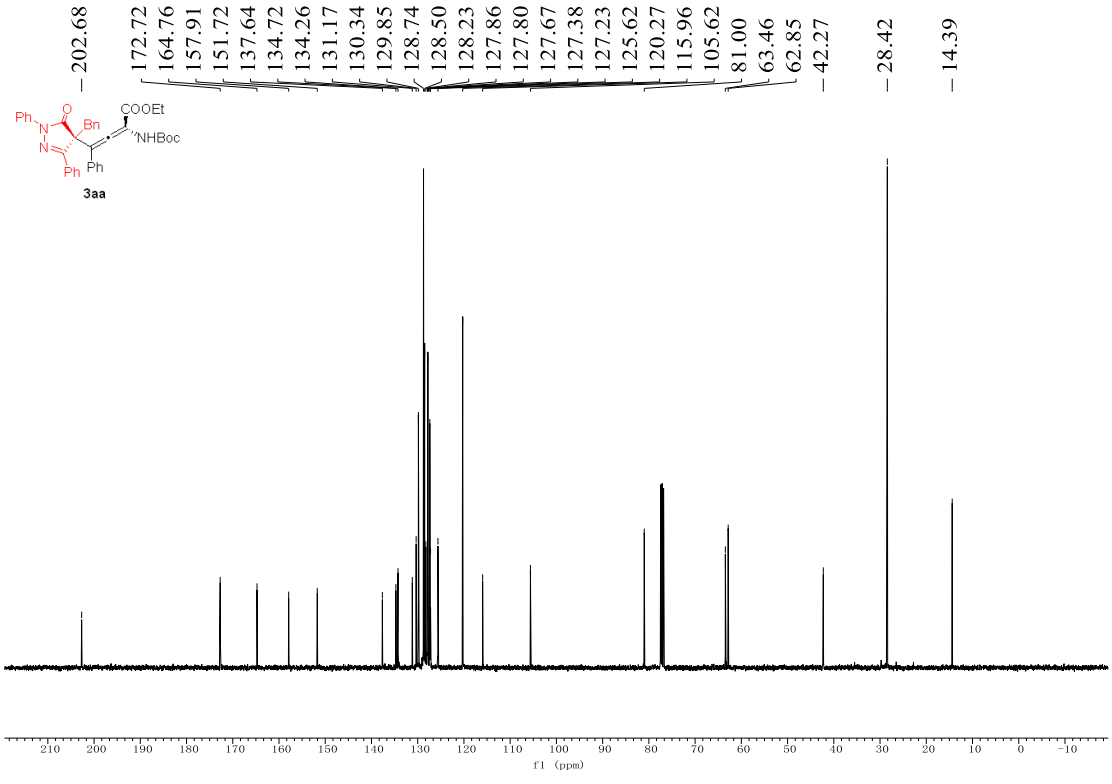
7.01
7.00
6.94
6.93
6.91
6.89
6.87
6.74
6.72
6.41
4.38
4.36
4.26
4.25
3.46
3.44
1.50
1.49
1.40
1.38
1.37
Ph
O
Bn
COOEt
N
NHBoc
Ph
Ph
3aa
2.00
2.01
2.99
4.01
4.01
3.00
2.00
1.00
1.01
1.02
1.99
9.00
3.00
f1 (ppm)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128.50
128.23
127.86
127.80
127.67
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127.23
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120.27
115.96
105.62
81.00
63.46
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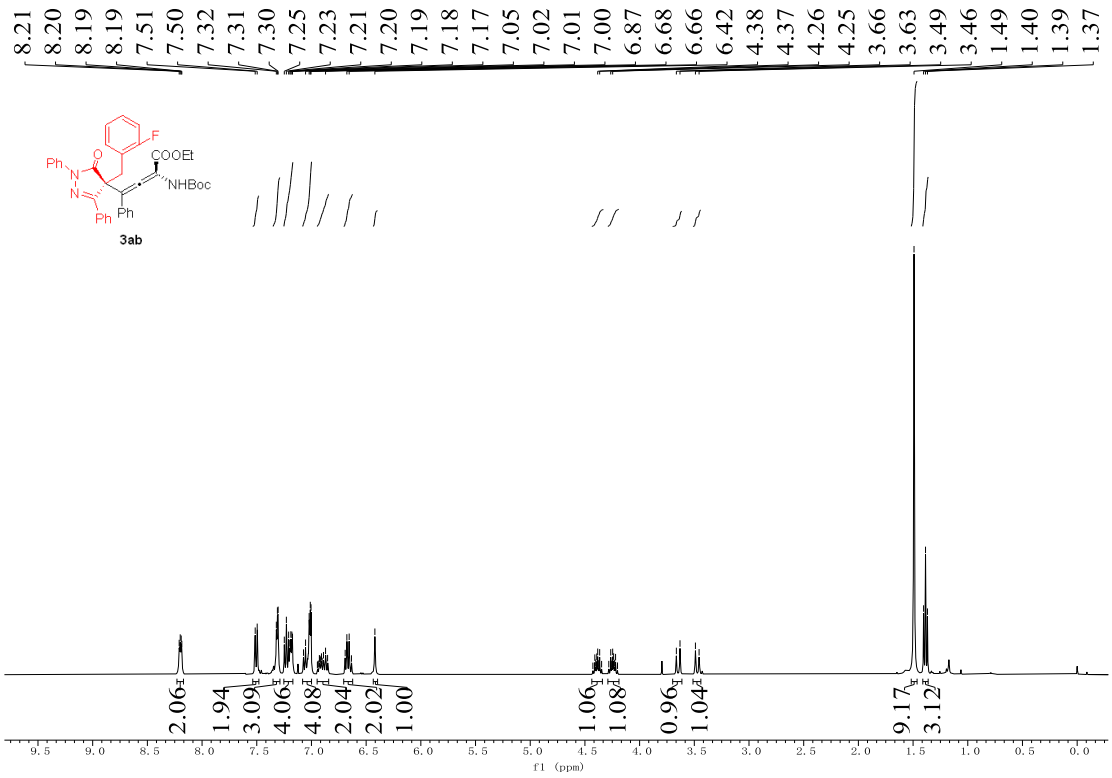
O
Bn
COOEt
N
NHBoc
Ph
Ph
3aa
f1 (ppm)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7.02
7.01
7.00
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6.66
6.42
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4.37
4.26
4.25
3.66
3.63
3.49
3.46
1.49
1.40
1.39
1.37
F
COOEt
NHBoc
Ph
O
N
N
Ph
Ph
3ab
2.06
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3.09
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2.02
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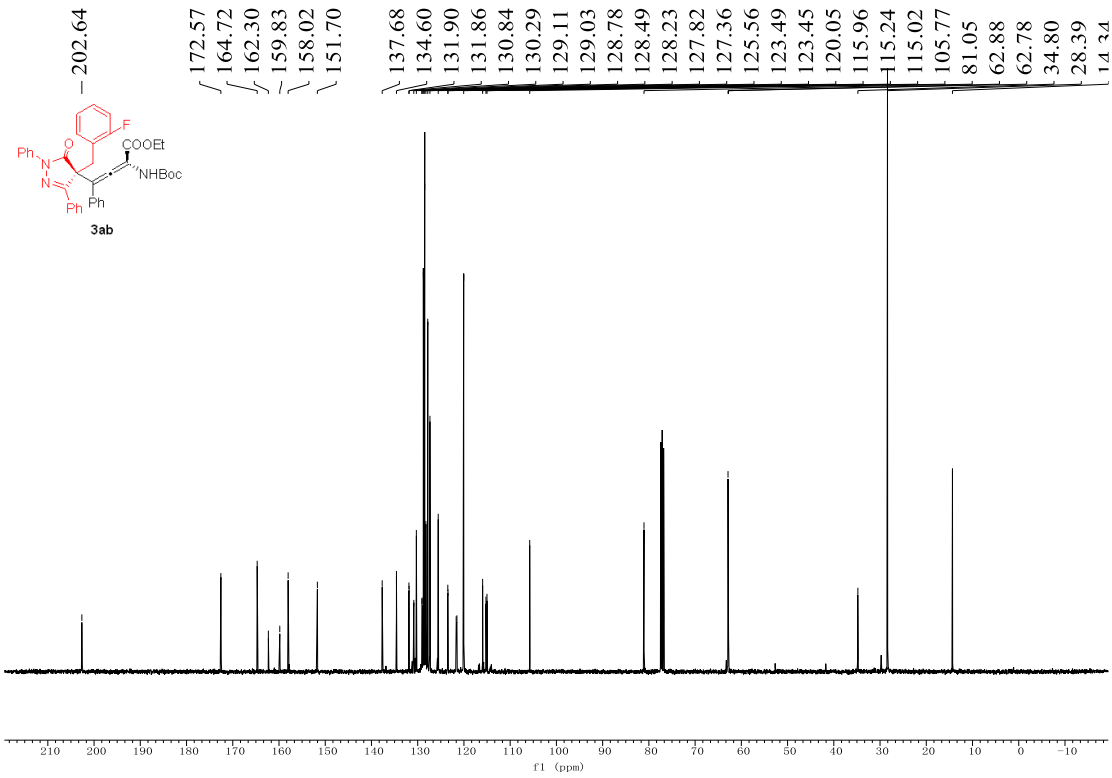
f1 (ppm)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129.03
128.78
128.49
128.23
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127.36
125.56
123.49
123.45
120.05
115.96
115.24
115.02
105.77
81.05
62.88
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14.34
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NHBoc
Ph
O
N
Ph
Ph
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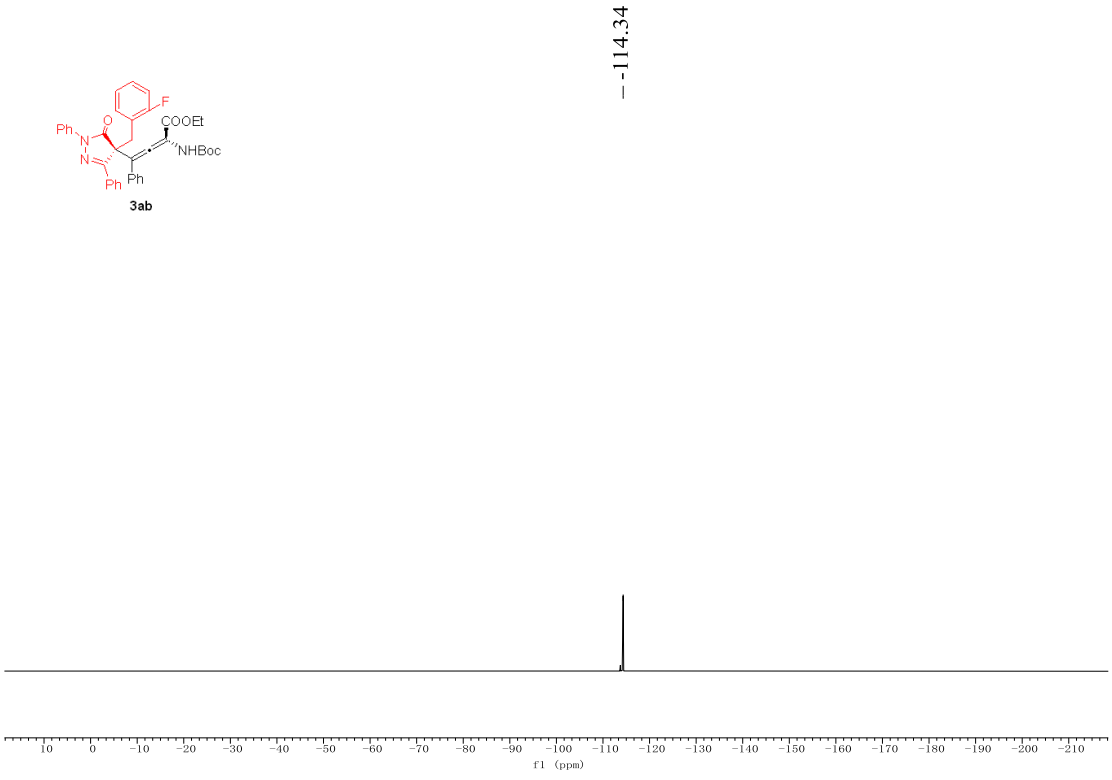
f1 (ppm)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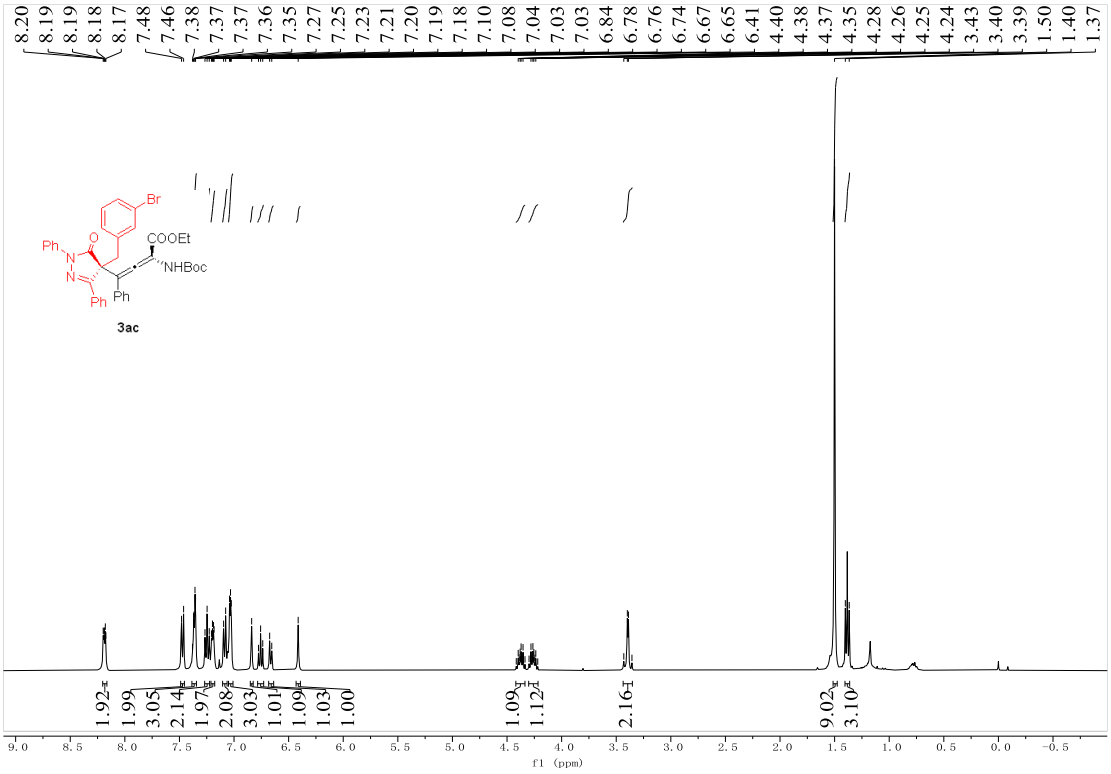
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Br
COOEt
NHBoc
Ph
Ph
Ph
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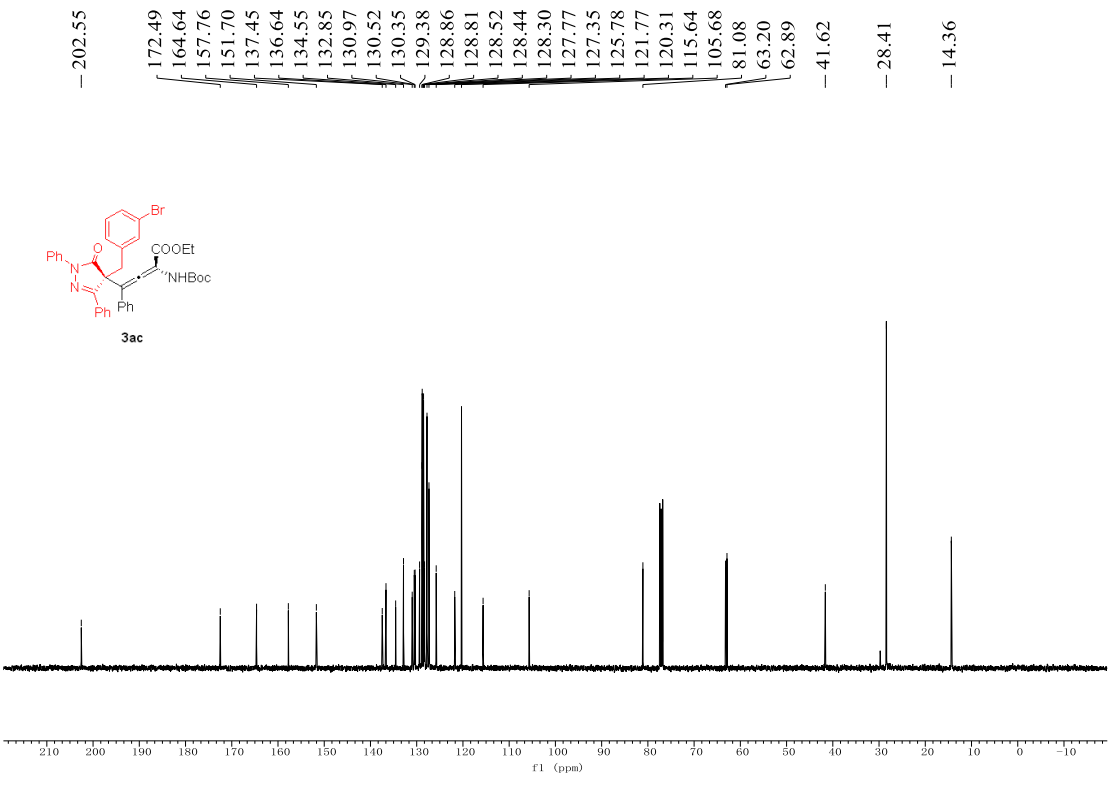
1.92 1.99 3.05 2.14 1.97 2.08 3.03 1.01 1.09 1.03 1.00 1.09 1.12 2.16 9.02 3.10
f1 (ppm)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28.41
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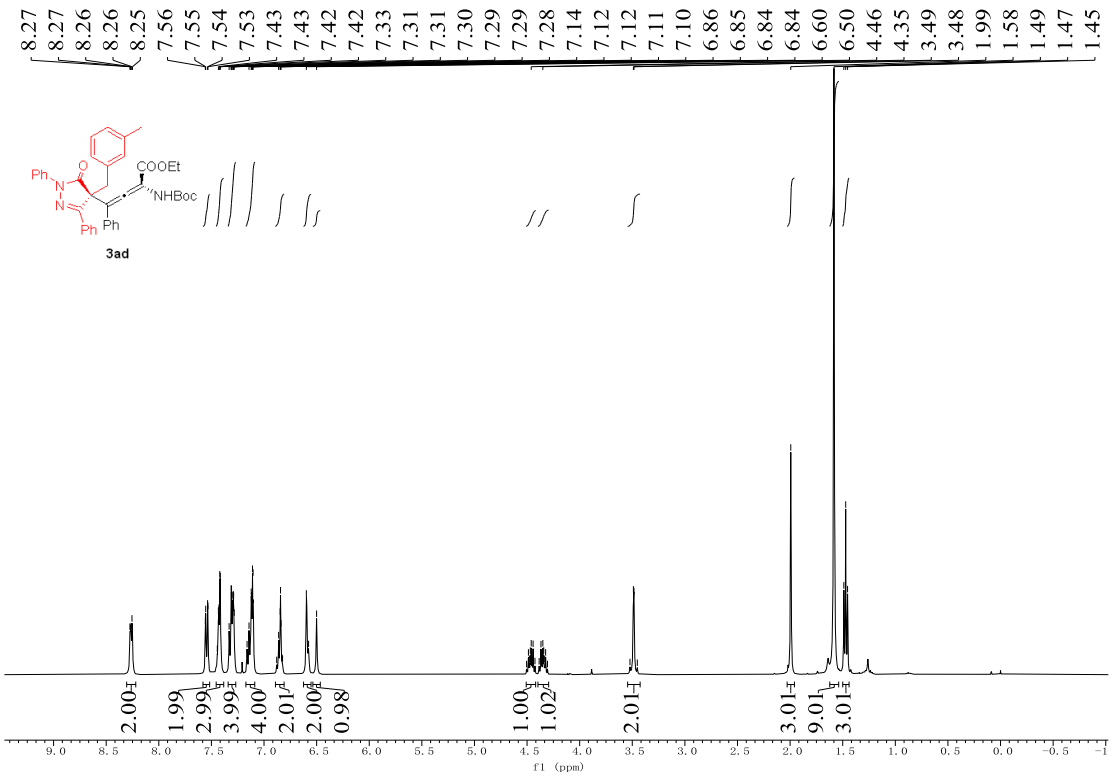
COOEt
NHBoc
Ph
Ph
Ph
3ac
f1 (ppm)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Ph
N
O
COOEt
NHBoc
Ph
Ph
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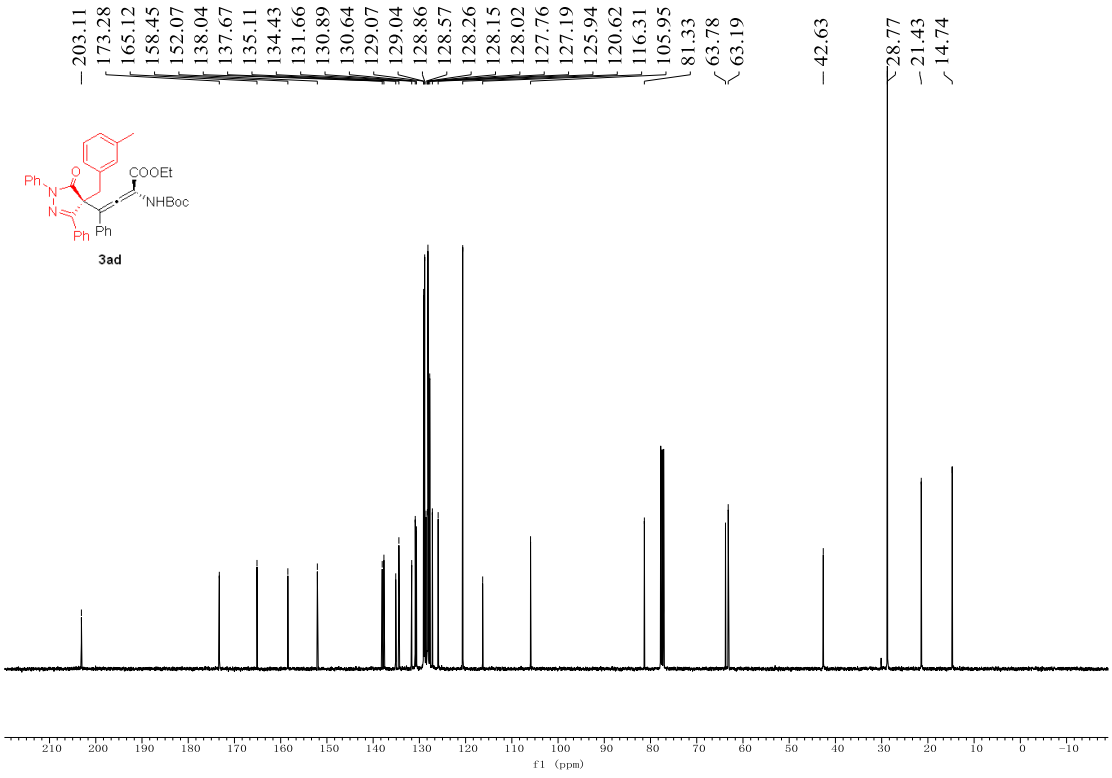
f1 (ppm)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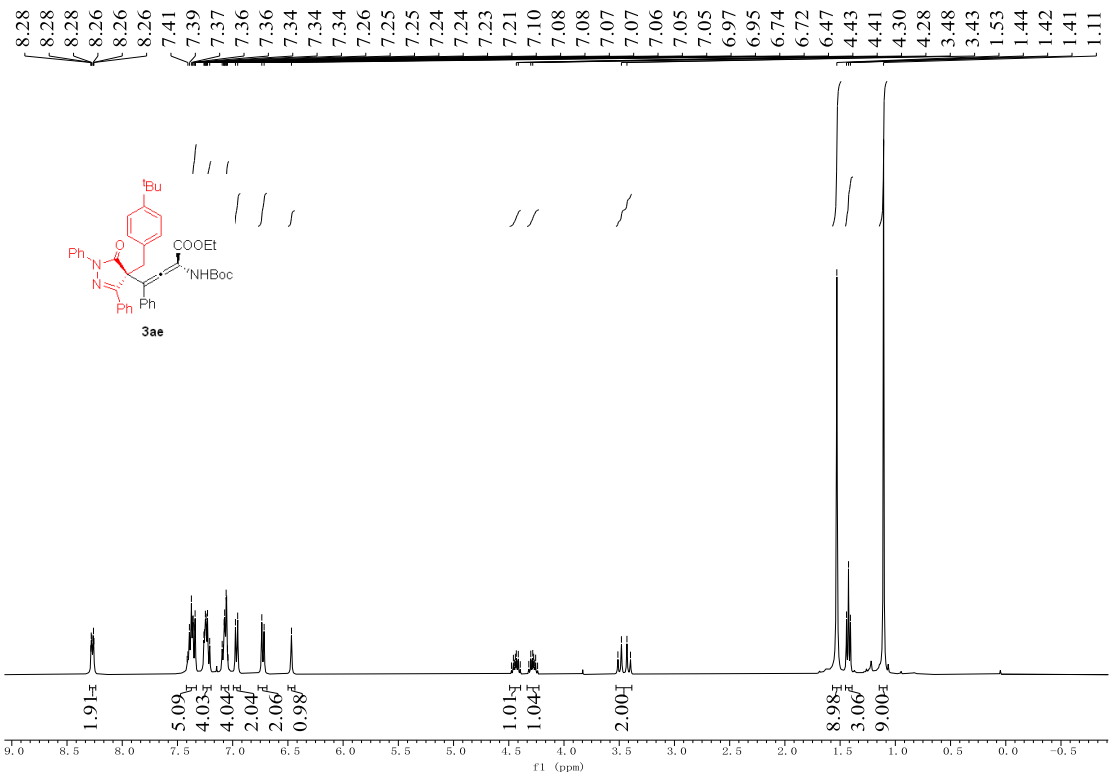
Ph
N
O
COOEt
NHBoc
Ph
Ph
3ad
f1 (ppm)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tBu
COOEt
NHBoc
Ph
Ph
Ph
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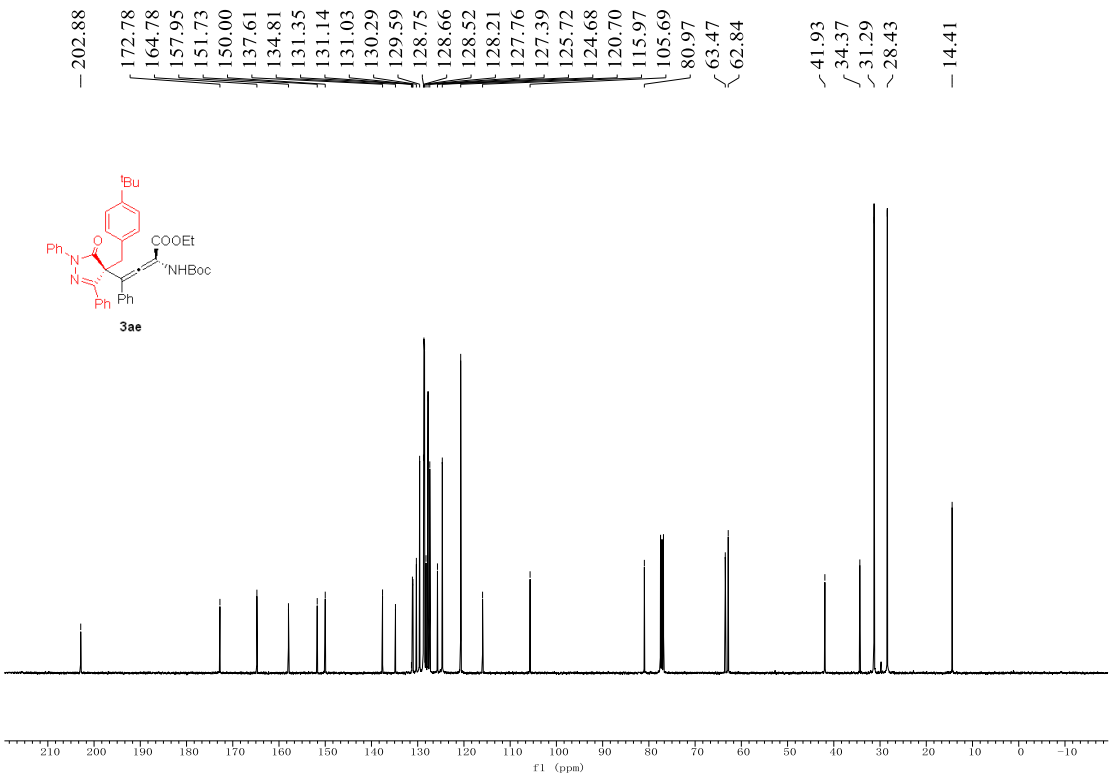
1.91 5.09 4.03 4.04 2.04 2.06 0.98 1.01 1.04 2.00 8.98 3.06 9.00
f1 (ppm)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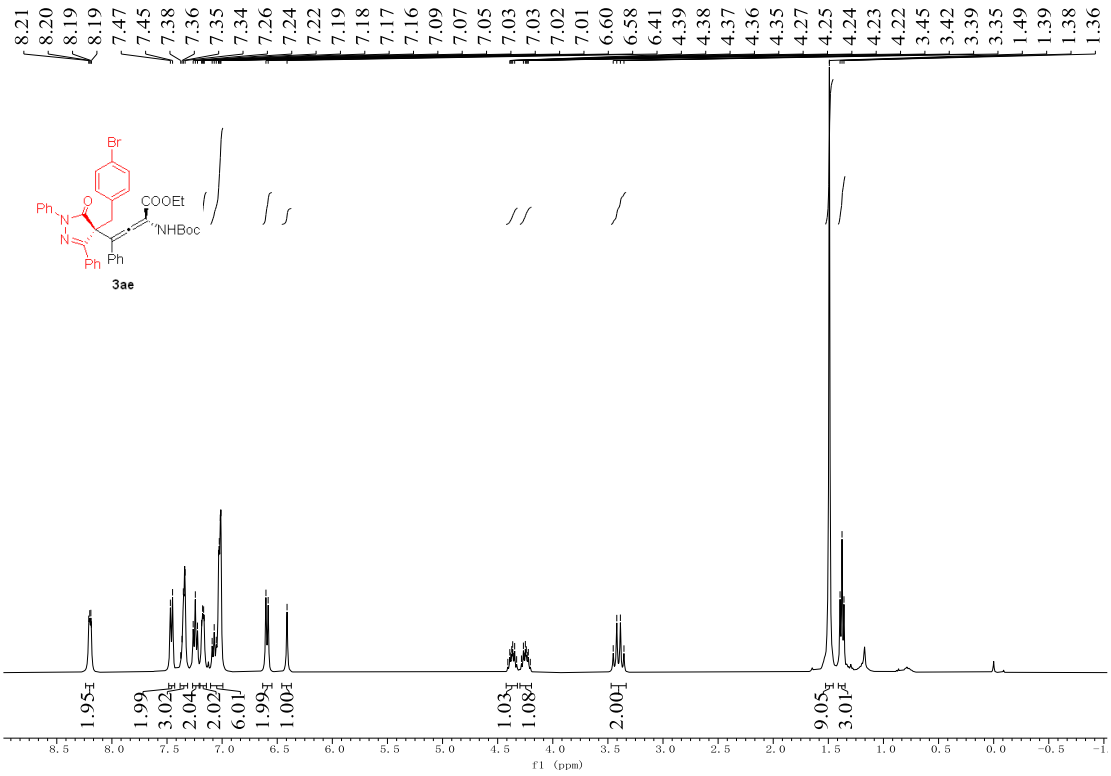
tBu
COOEt
NHBoc
Ph
Ph
Ph
3ae
f1 (ppm)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7.03
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7.01
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4.24
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4.22
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1.49
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1.38
1.36
Br
Ph
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COOEt
NHBoc
Ph
Ph
3ae
1.95
1.99
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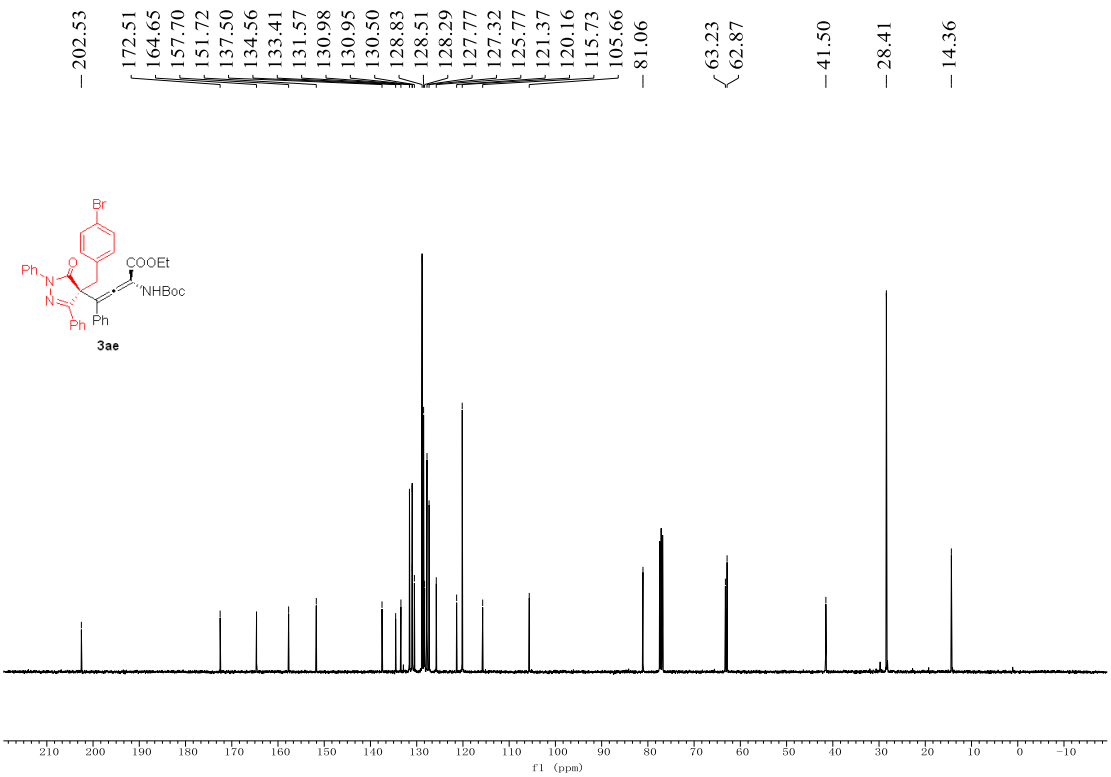
6.01
1.99
1.00
1.03
1.08
2.00
9.05
3.01
f1 (ppm)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127.32
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121.37
120.16
115.73
105.66
81.06
63.23
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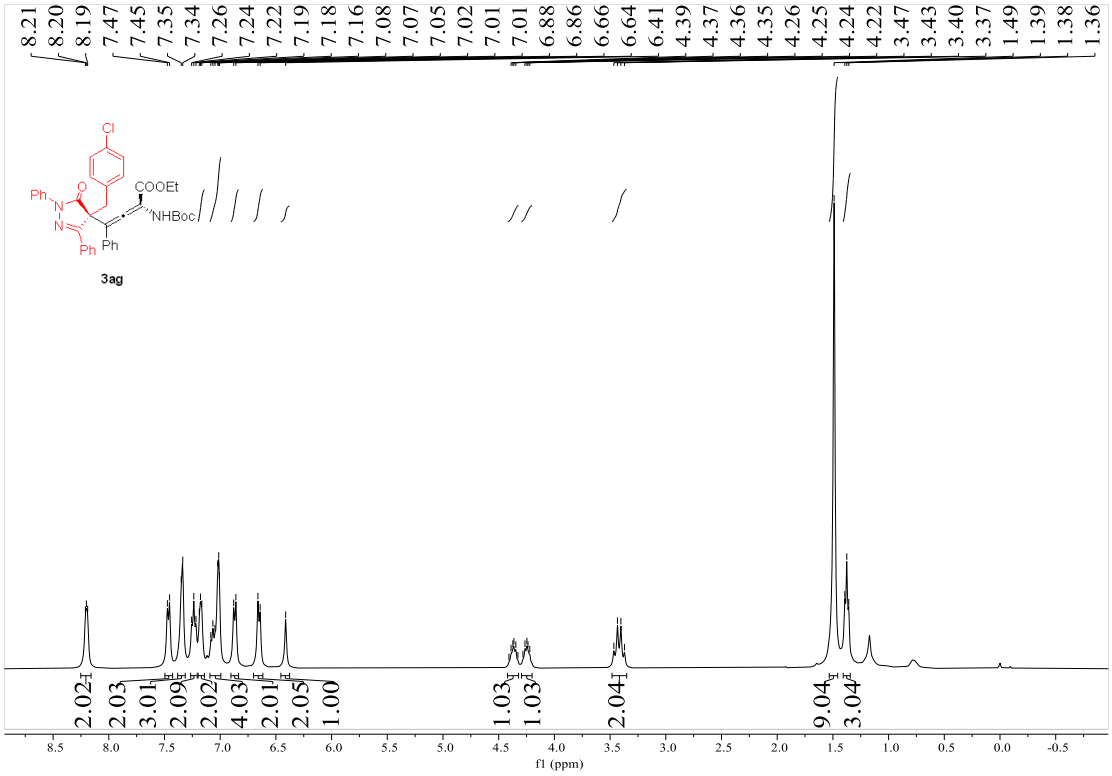
14.36
Br
Ph
O
N
N
COOEt
NHBoc
Ph
Ph
3ae
f1 (ppm)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Cl
Ph
O
N
N
COOEt
NHBoc
Ph
Ph
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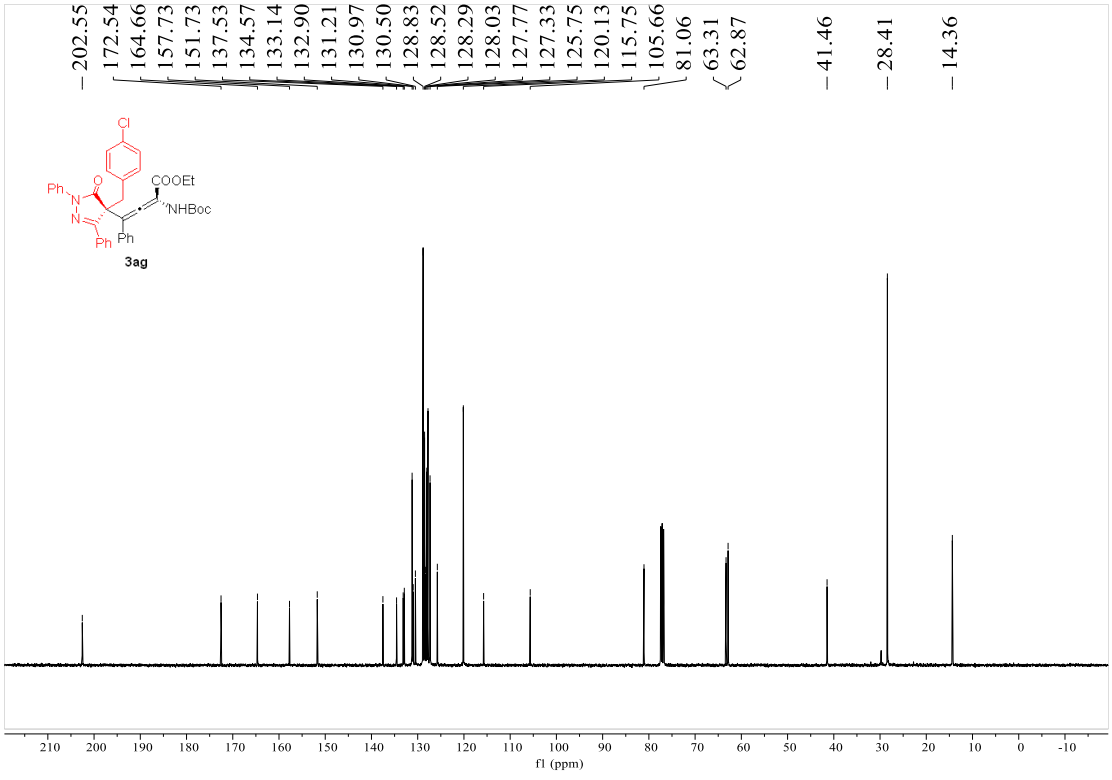
2.02 2.03 3.01 2.09 2.02 4.03 2.01 2.05 1.00 1.03 1.03 2.04 9.04 3.04
f1 (ppm)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Cl
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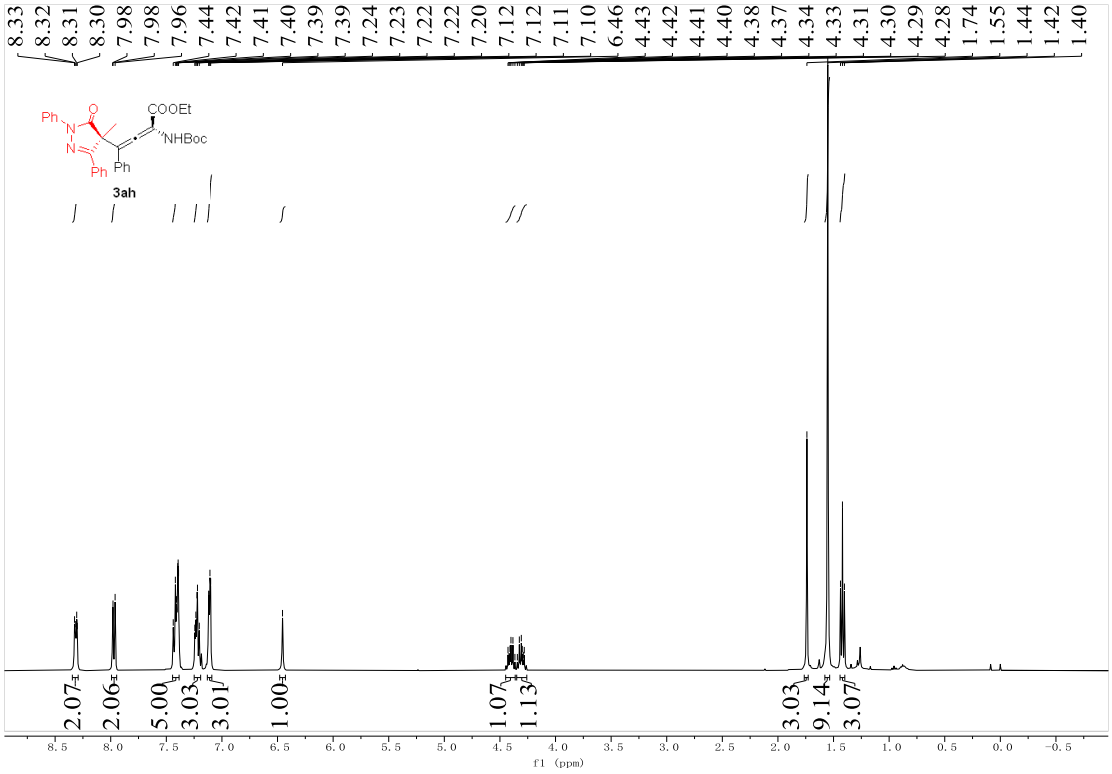
COOEt
NHBoc
Ph
Ph
3ag
f1 (ppm)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7.24
7.23
7.22
7.22
7.20
7.12
7.12
7.11
7.10
6.46
4.43
4.42
4.41
4.40
4.38
4.37
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4.30
4.29
4.28
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1.55
1.44
1.42
1.40
COOEt
NHBoc
Ph
Ph
Ph
3ah
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1.00
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3.03
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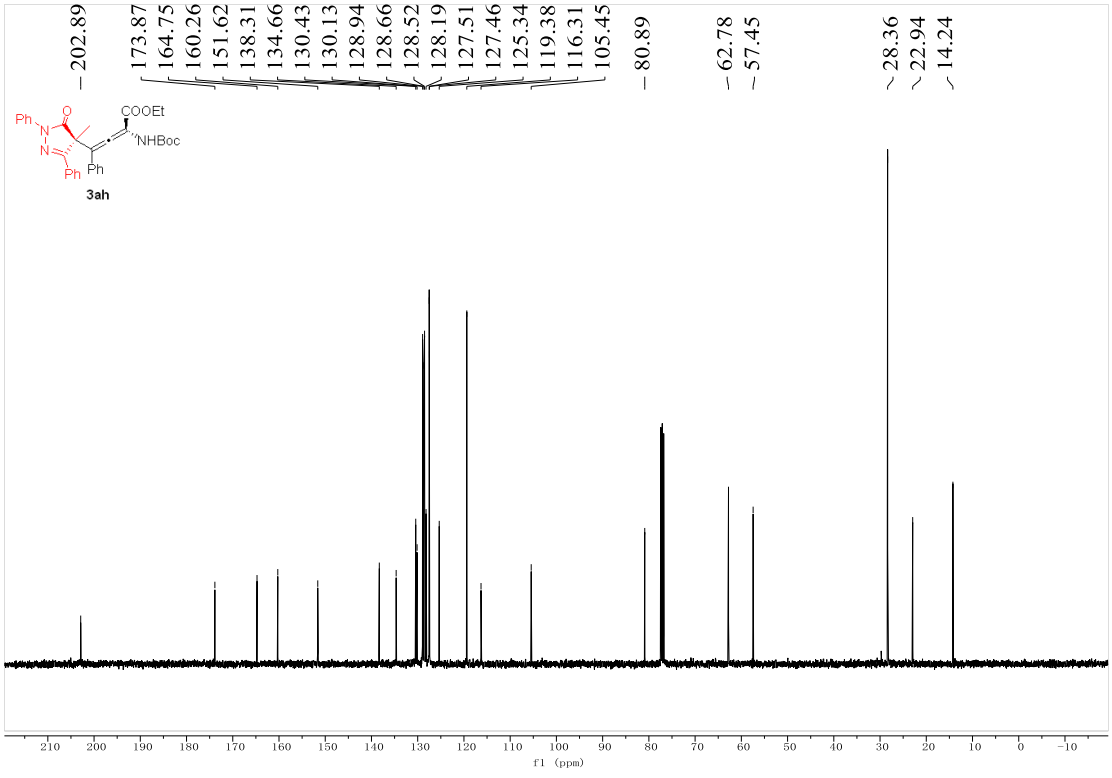
3.07
f1 (ppm)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127.51
127.46
125.34
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116.31
105.45
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28.36
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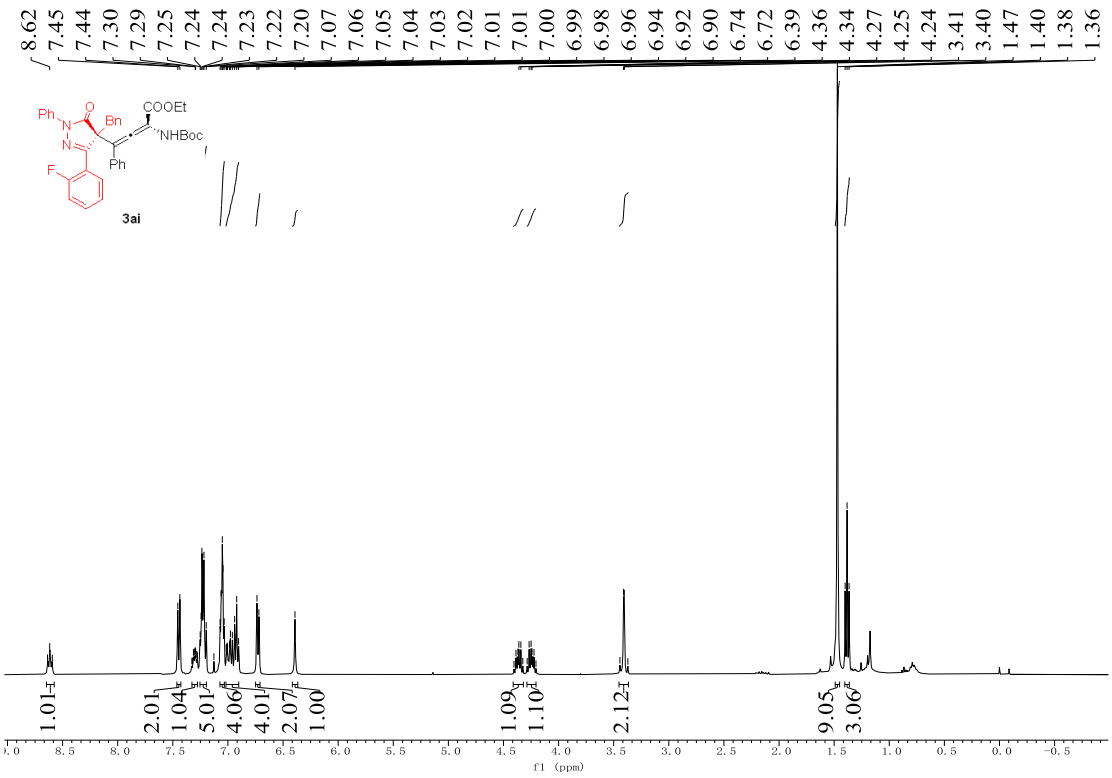
COOEt
NHBoc
Ph
Ph
Ph
3ah
f1 (ppm)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7.02
7.01
7.01
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6.98
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6.94
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6.39
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4.27
4.25
4.24
3.41
3.40
1.47
1.40
1.38
1.36
Ph
N
N
O
Bn
COOEt
NHBoc
Ph
F
3ai
1.01
2.01
1.04
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1.00
1.09
1.10
2.12
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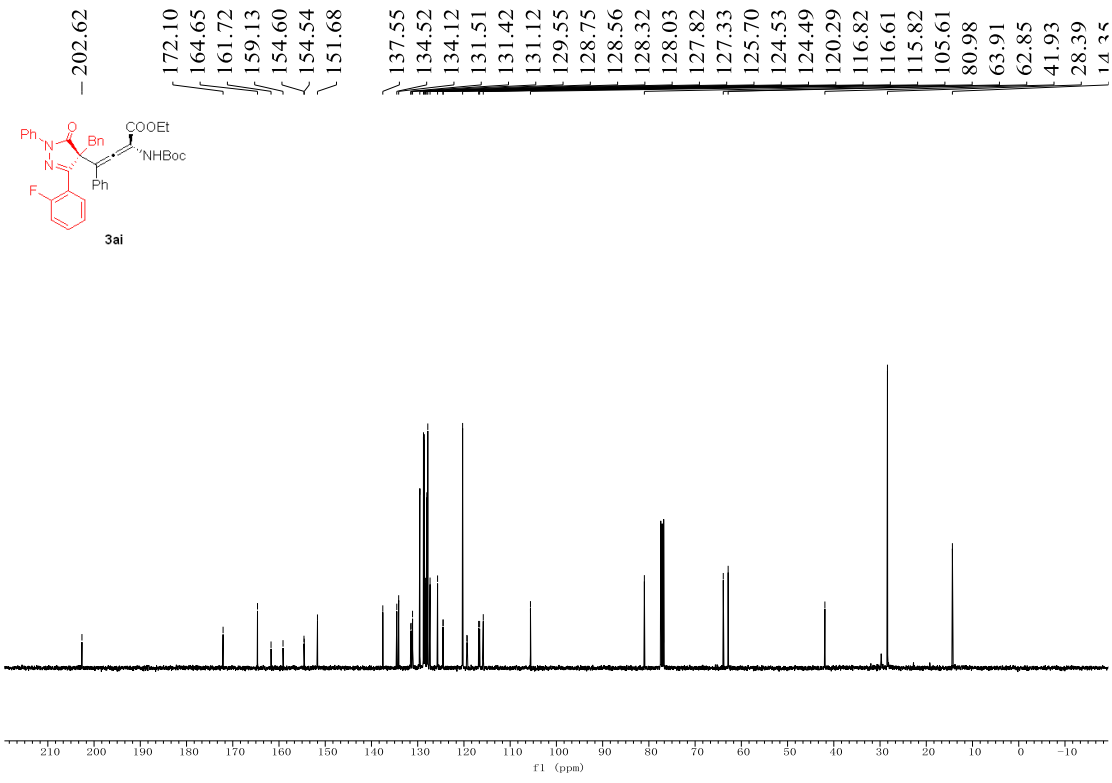
3.06
f1 (ppm)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131.12
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128.75
128.56
128.32
128.03
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127.33
125.70
124.53
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120.29
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116.61
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N
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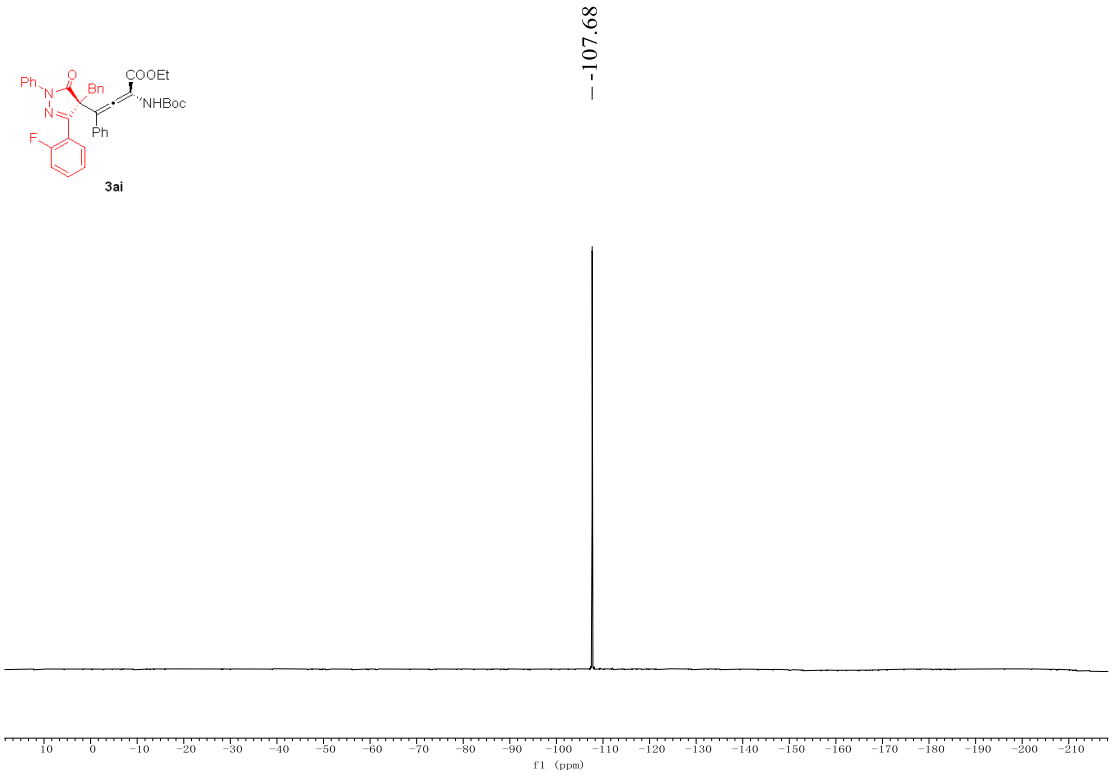
Bn
COOEt
NHBoc
Ph
F
3ai
f1 (ppm)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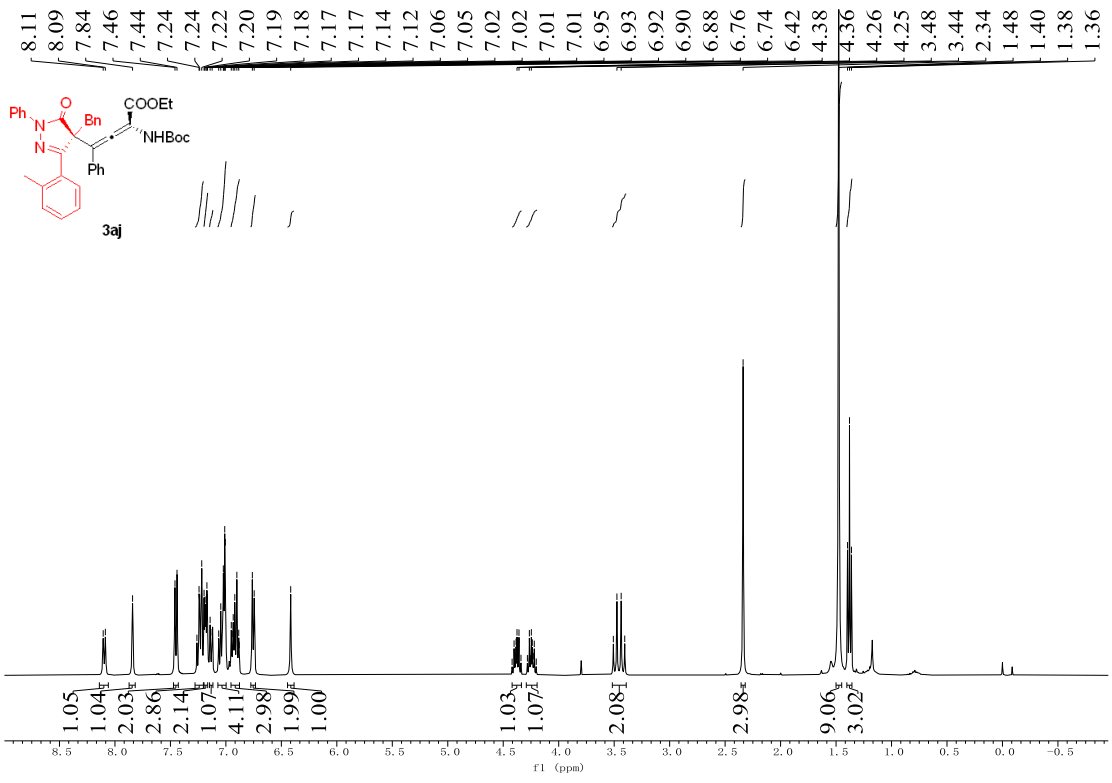
3ai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1.05
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1.07
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1.07
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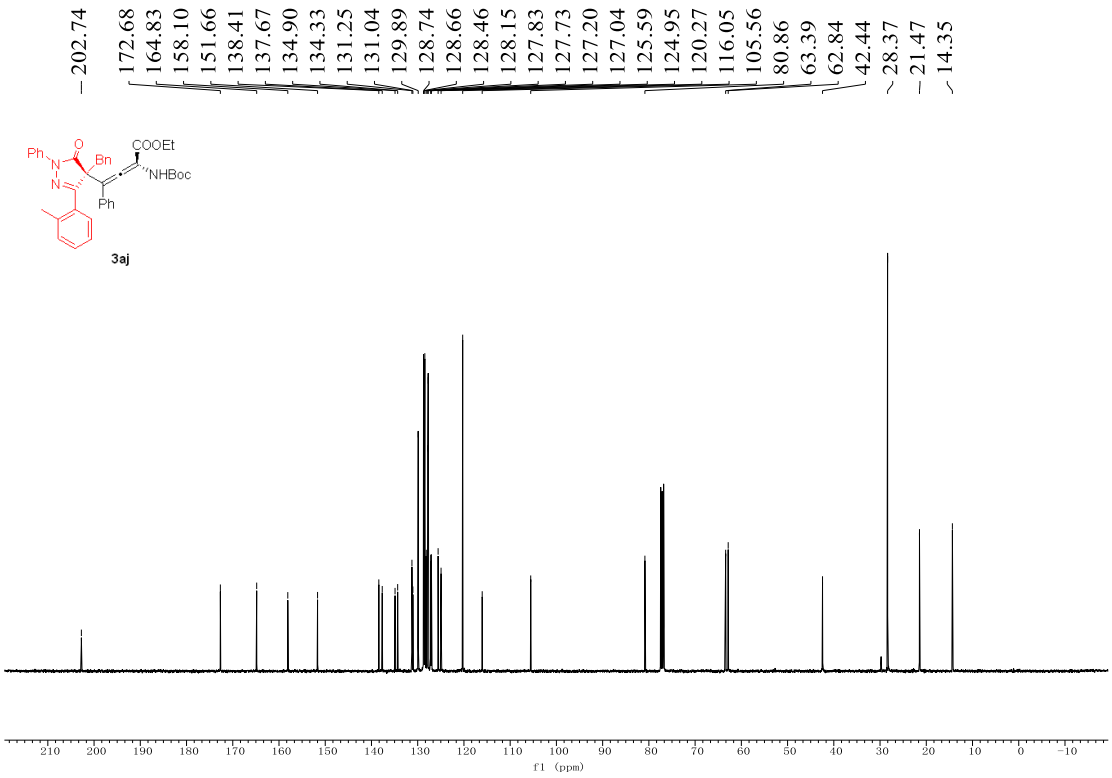
9.06
3.02
f1 (ppm)

3aj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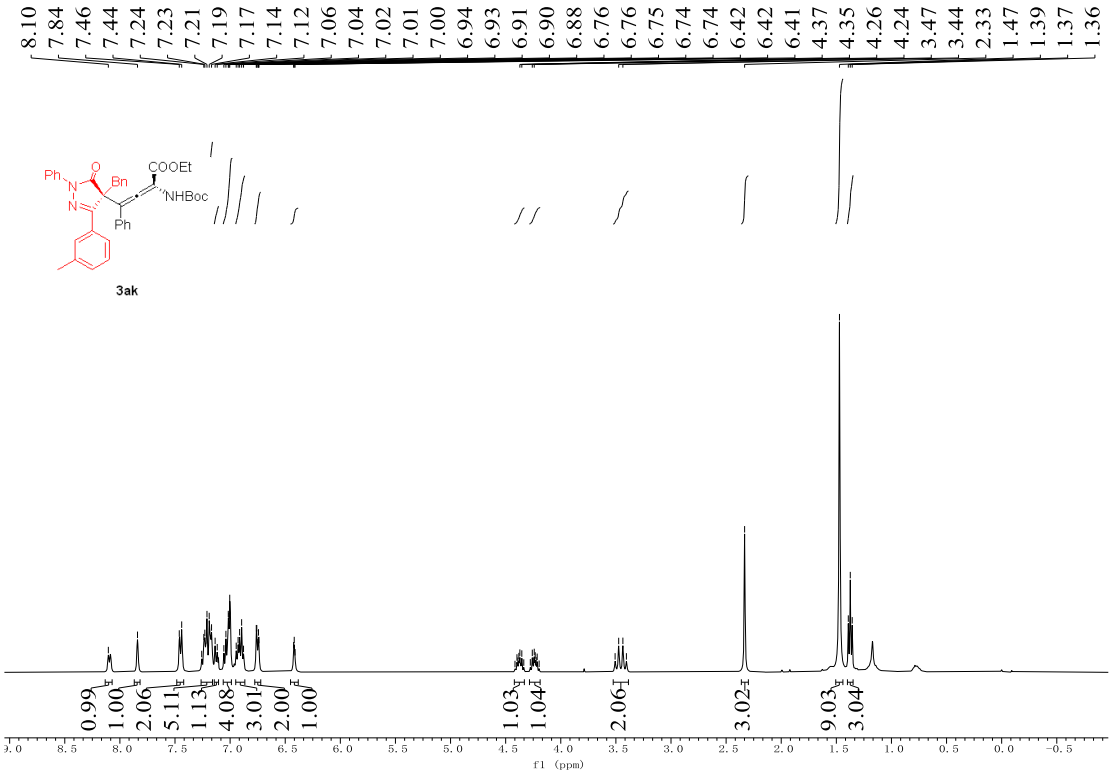
Bn
COOEt
NHBoc
Ph
3aj
f1 (ppm)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6.93
6.91
6.90
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6.74
6.42
6.42
6.41
4.37
4.35
4.26
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3.44
2.33
1.47
1.39
1.37
1.36
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N
O
Bn
COOEt
NHBoc
Ph
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5.11
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1.04
2.06
3.02
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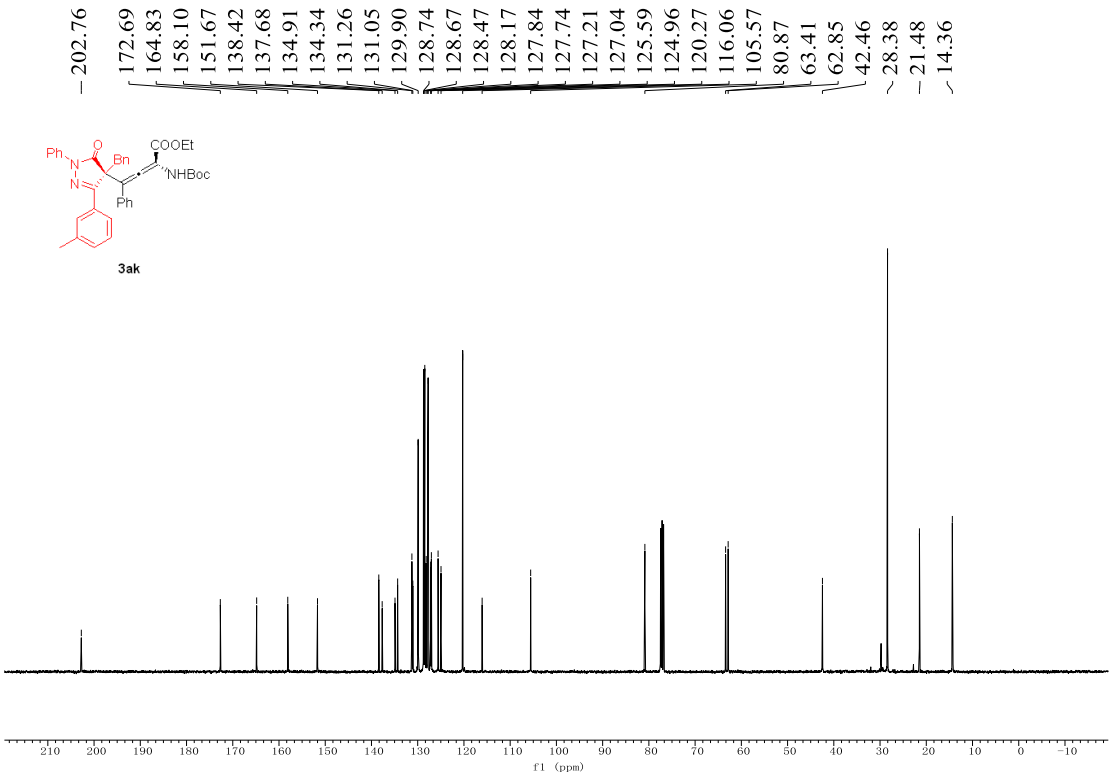
3.04
f1 (ppm)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128.74
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Bn
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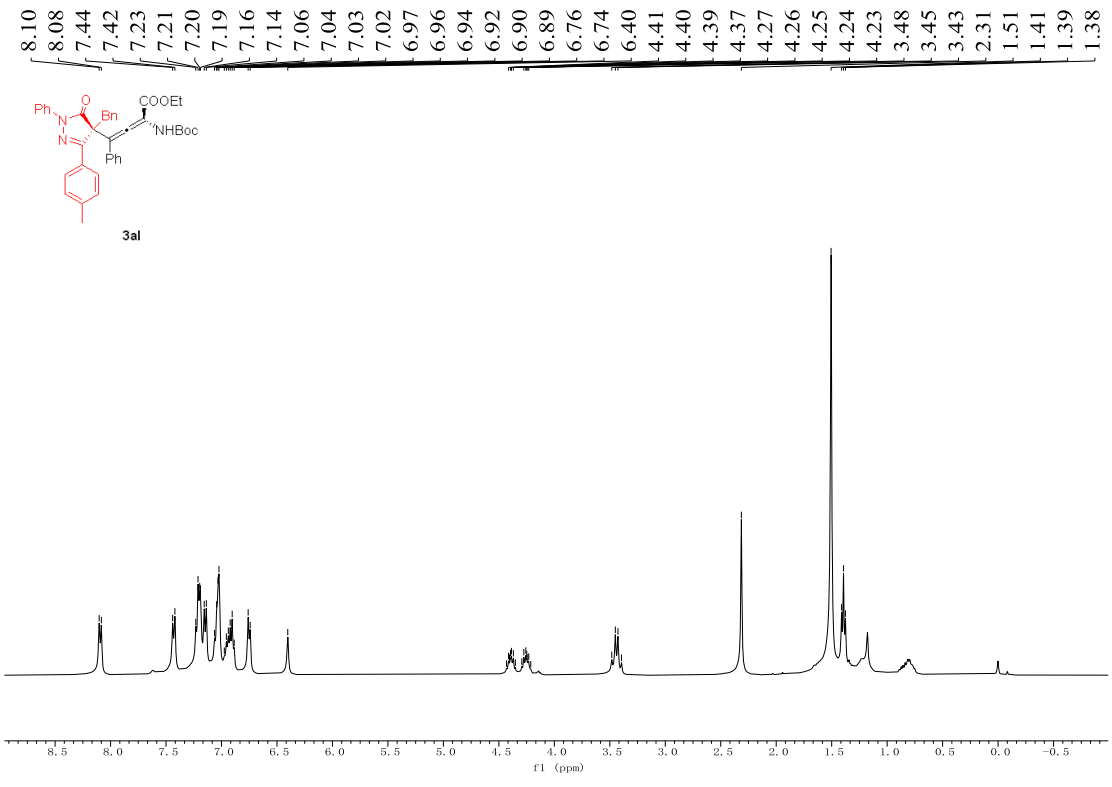
f1 (ppm)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COOEt
NHBoc
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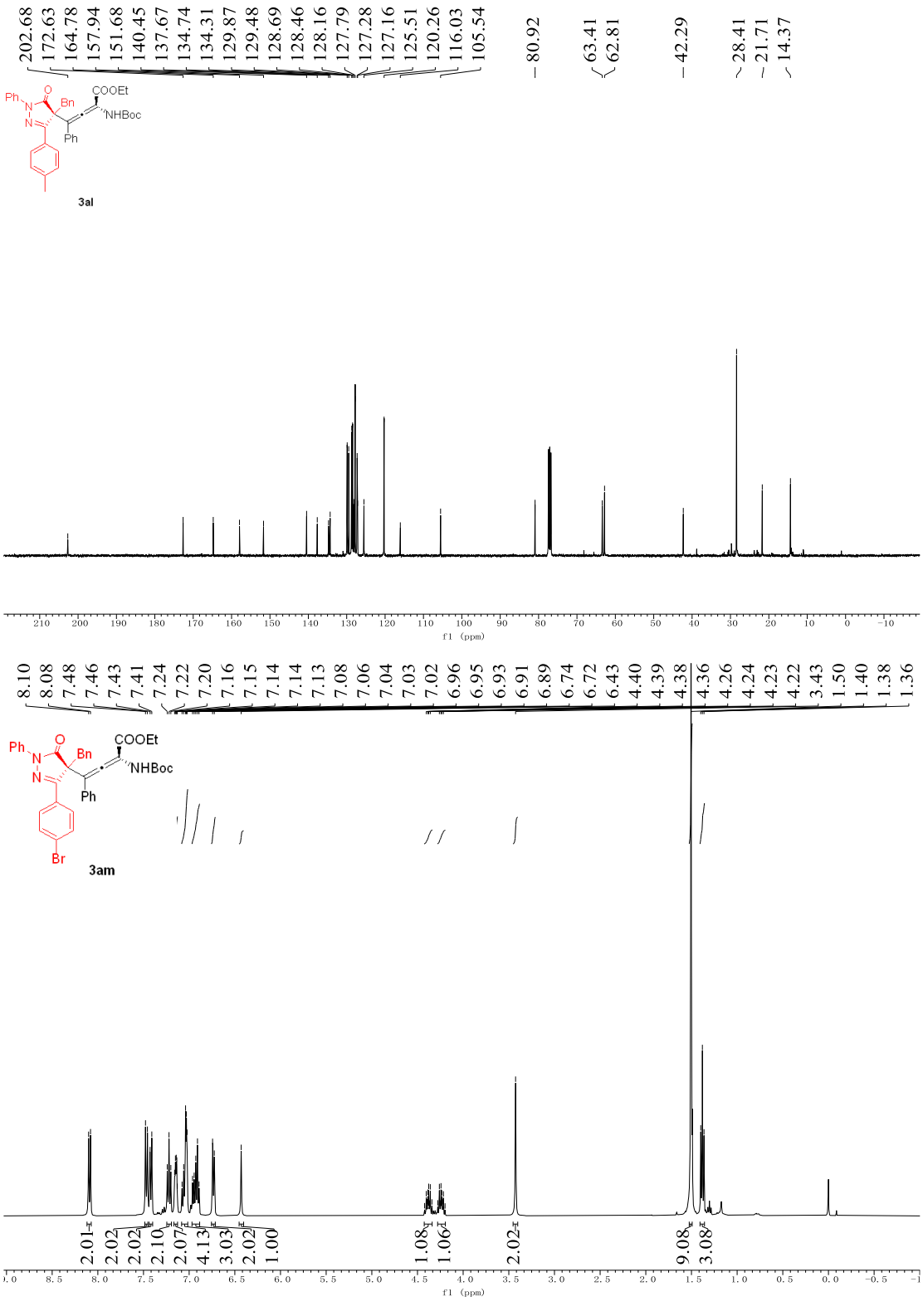
f1 (ppm)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NHBoc
Ph
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f1 (ppm)
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7.03
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6.91
6.89
6.74
6.72
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4.24
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4.22
3.43
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1.40
1.38
1.36
Ph
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O
Bn
COOEt
NHBoc
Ph
Br
3am
2.01
2.02
2.02
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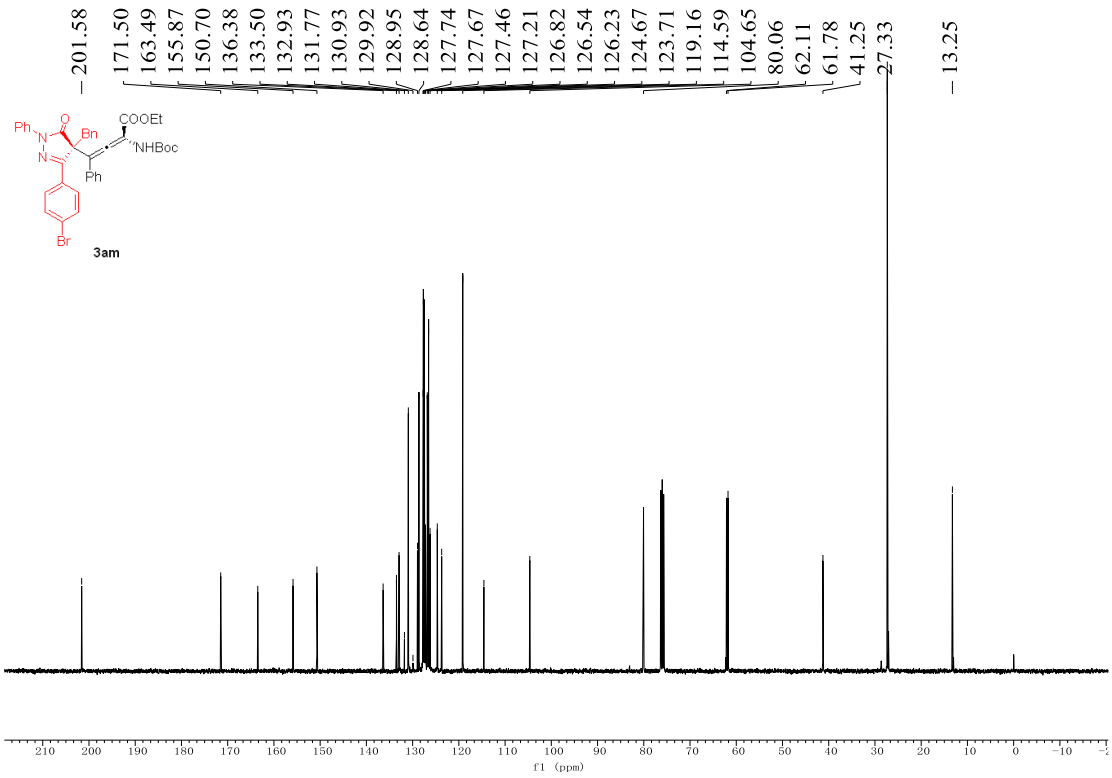
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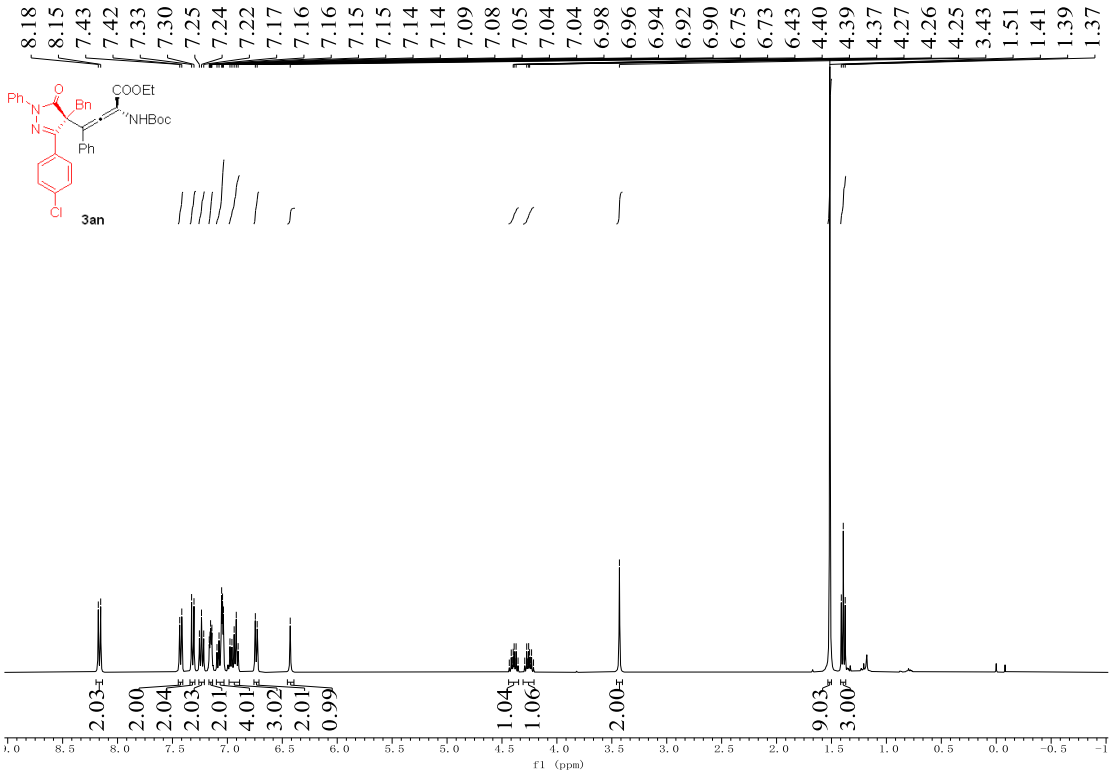
f1 (ppm)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4.27
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COOEt
NHBoc
Ph
Cl
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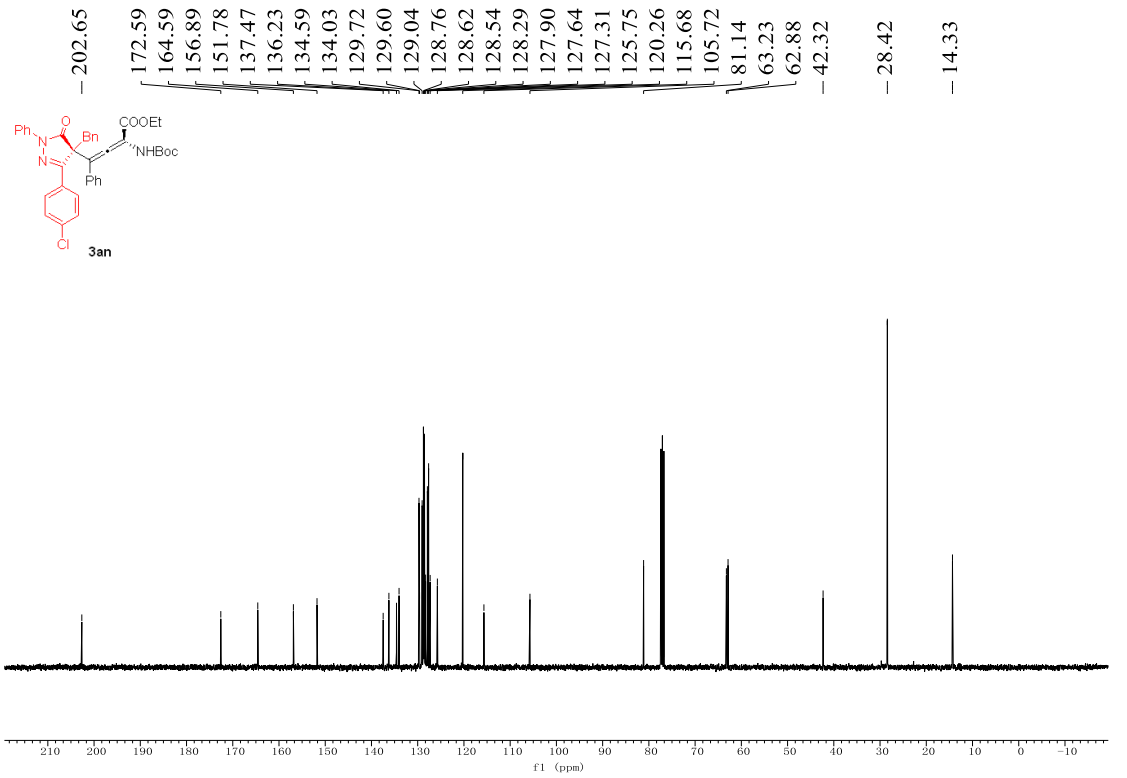
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63.23
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NHBoc
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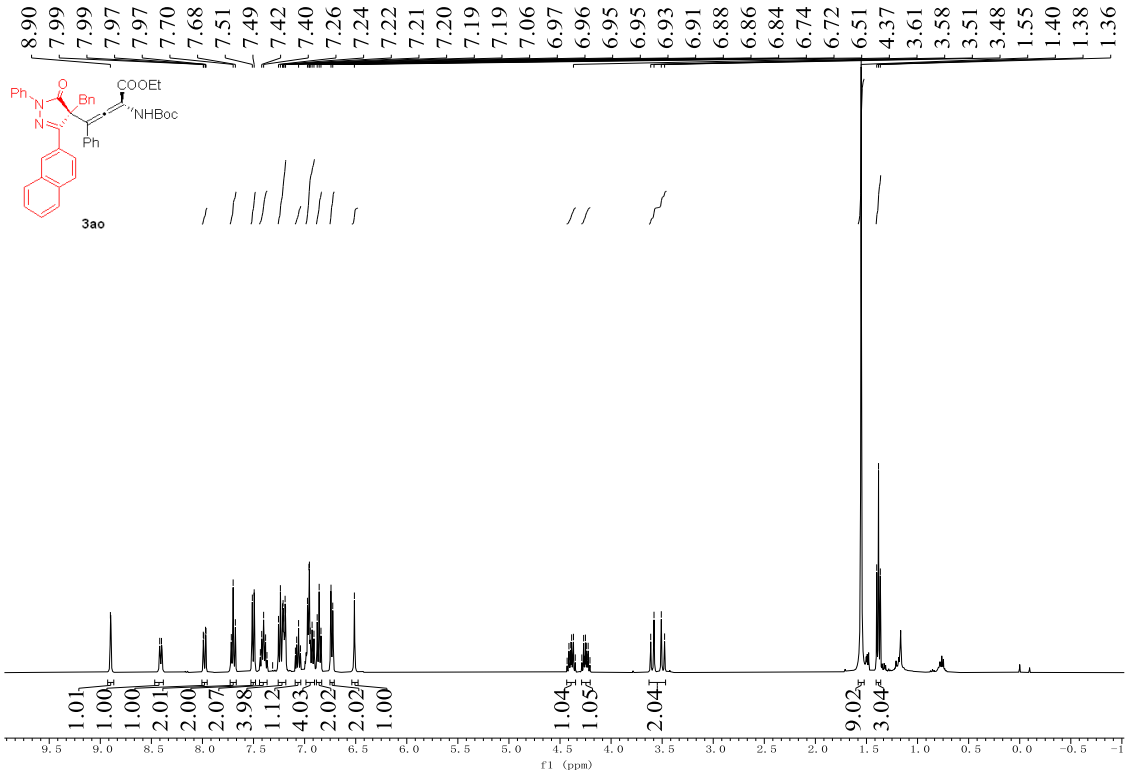
Cl
3an
f1 (ppm)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6.86
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1.36
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Ph
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1.00
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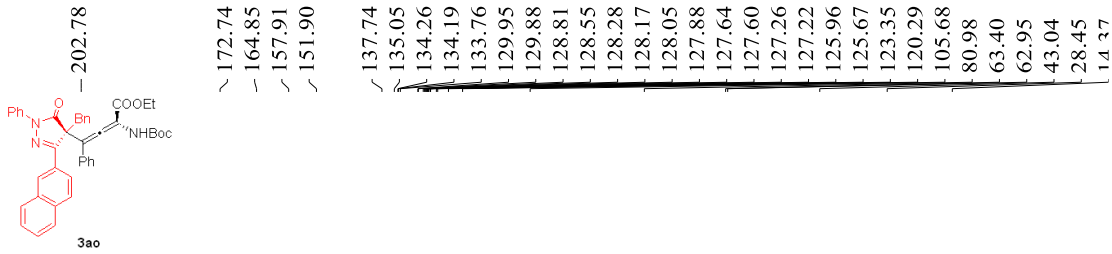
3.04
f1 (ppm)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Ph
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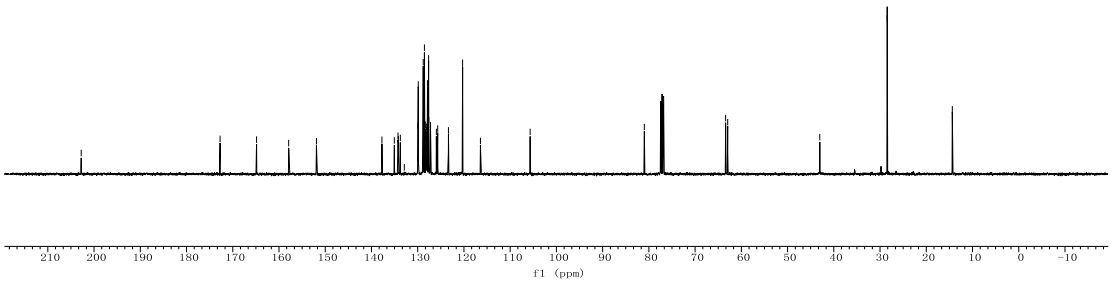
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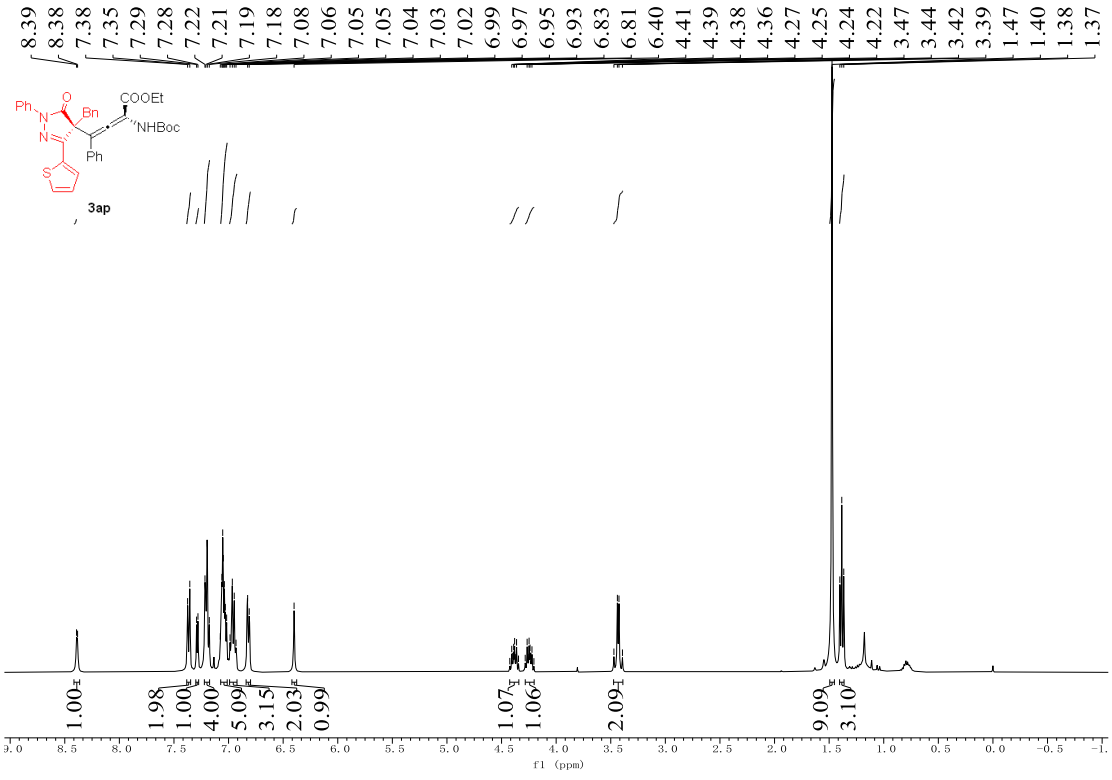
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4.36
4.27
4.25
4.24
4.22
3.47
3.44
3.42
3.39
1.47
1.40
1.38
1.37
Ph
O
N
N
Bn
COOEt
NHBoc
Ph
S
3ap
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1.98
1.00
4.00
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3.15
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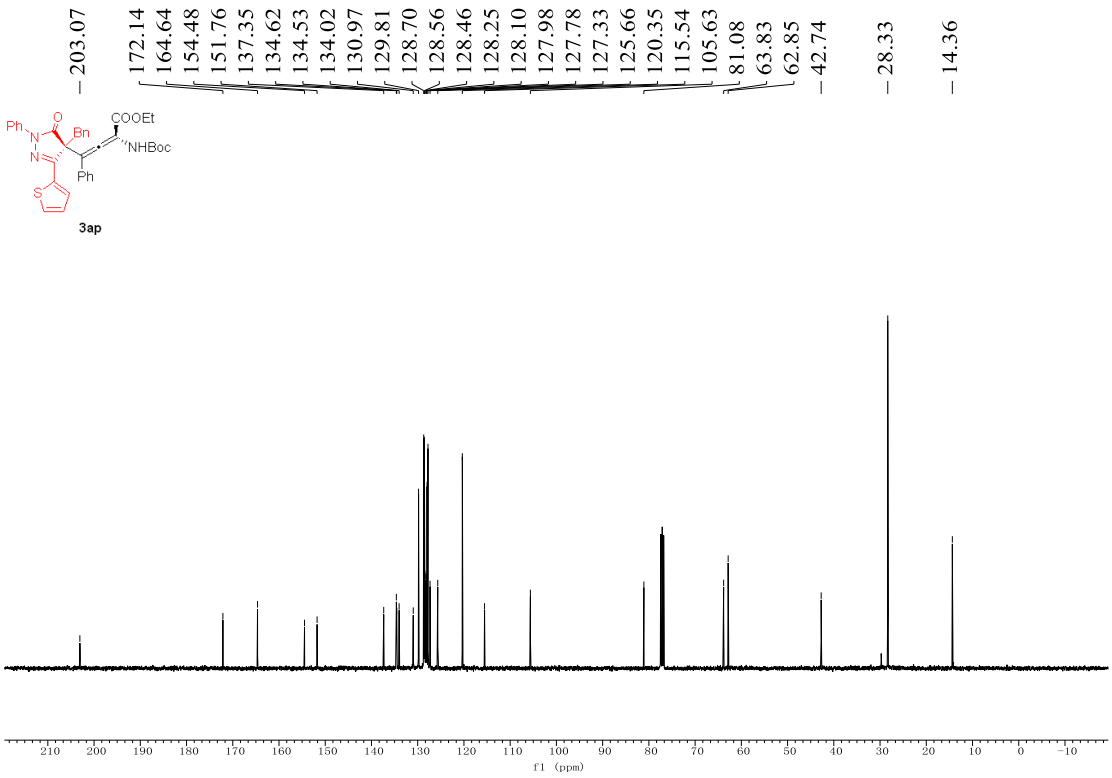
0.99
1.07
1.06
2.09
9.09
3.10
f1 (ppm)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127.78
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Ph
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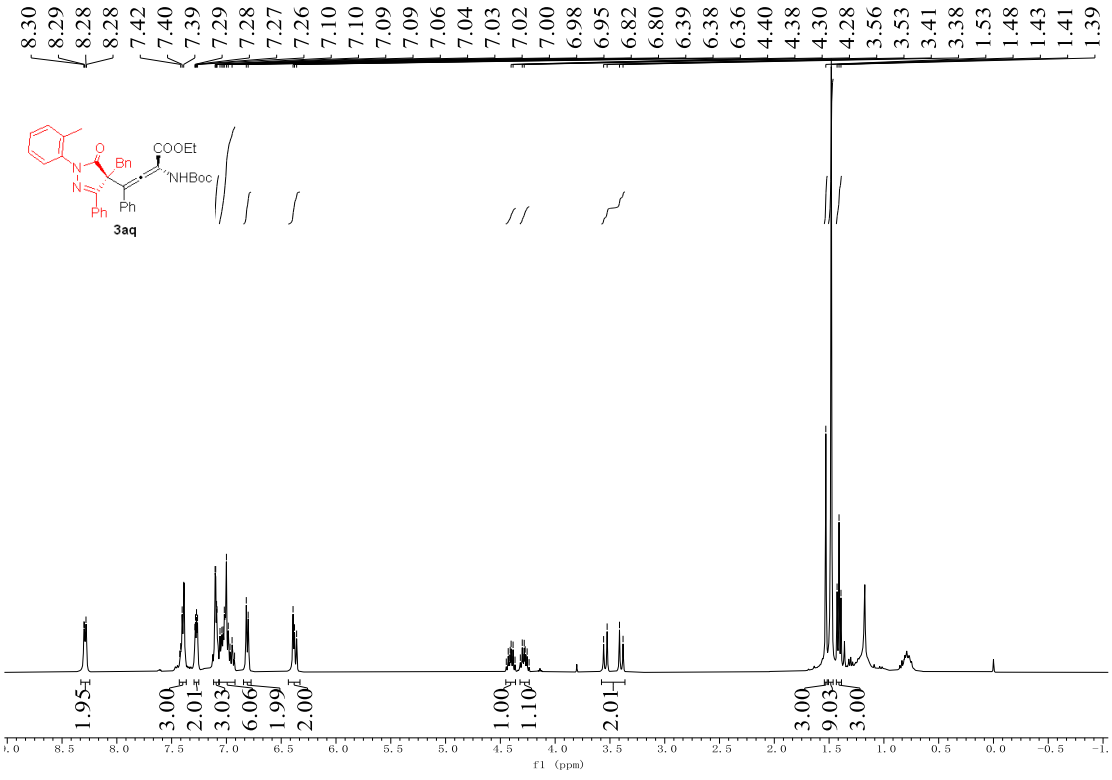
NHBoc
Ph
S
3ap
f1 (ppm)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7.06
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4.30
4.28
3.56
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3.41
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1.48
1.43
1.41
1.39
O
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N
Bn
COOEt
NHBoc
Ph
Ph
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1.00
1.10
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3.00
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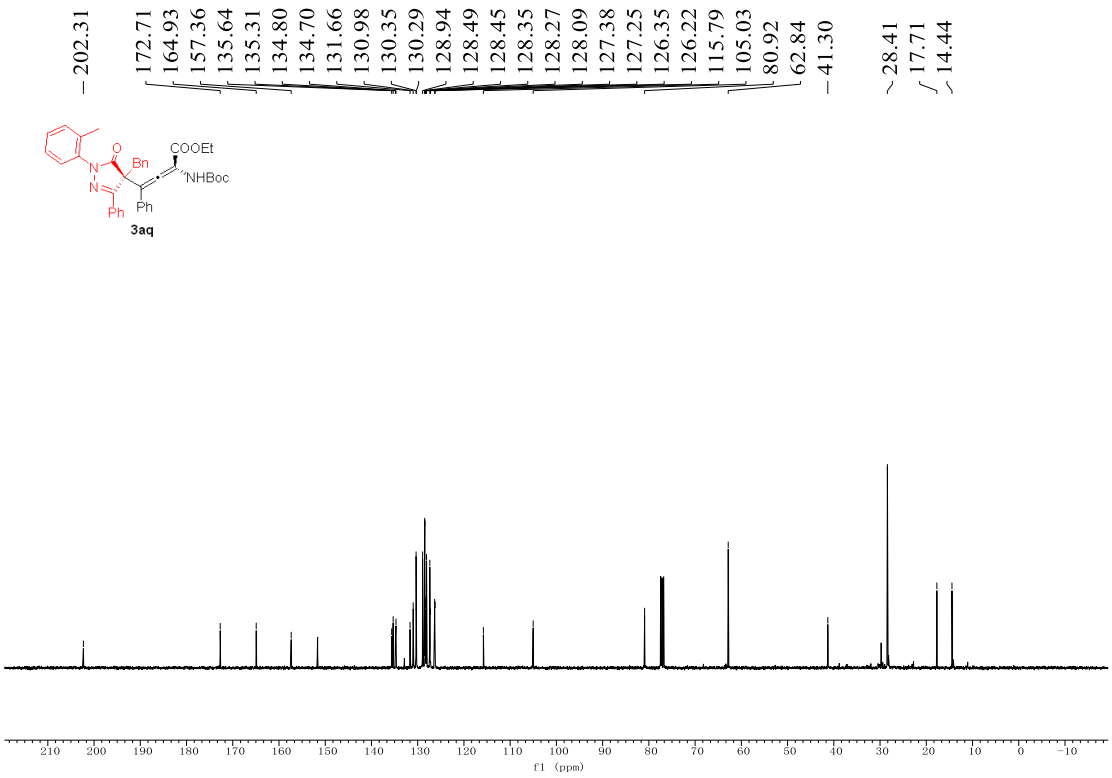
3.00
f1 (ppm)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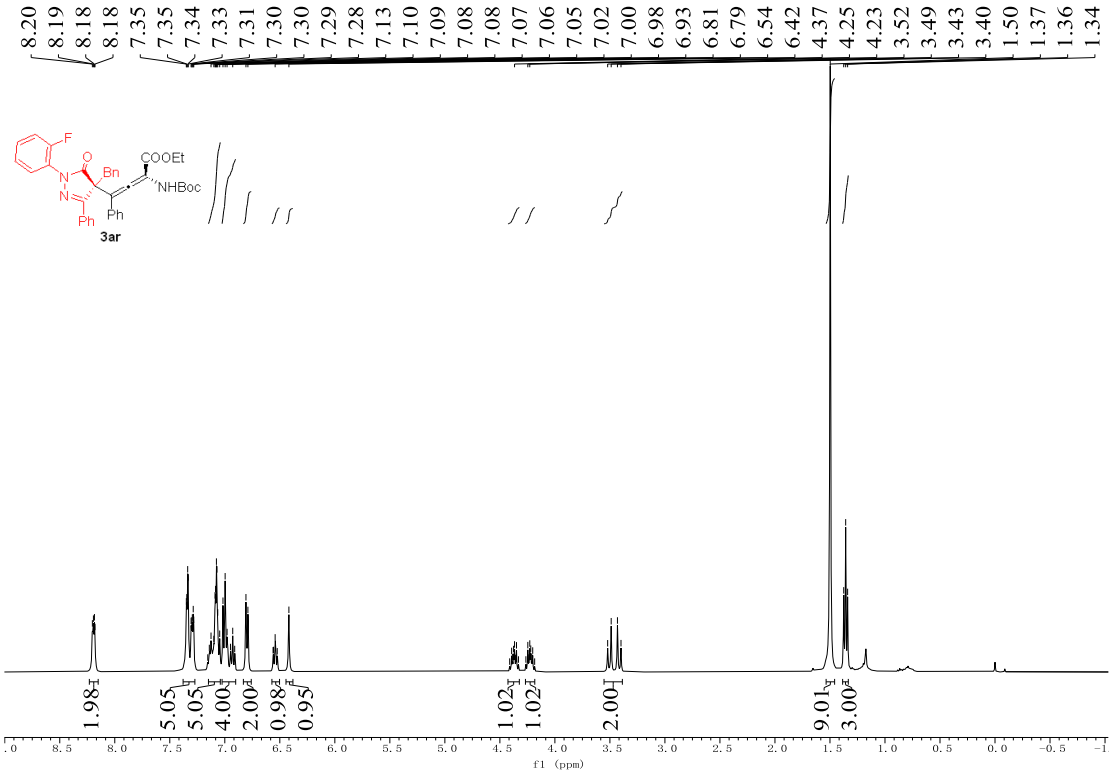
NHBoc
Bn
Ph
Ph
3aq
f1 (ppm)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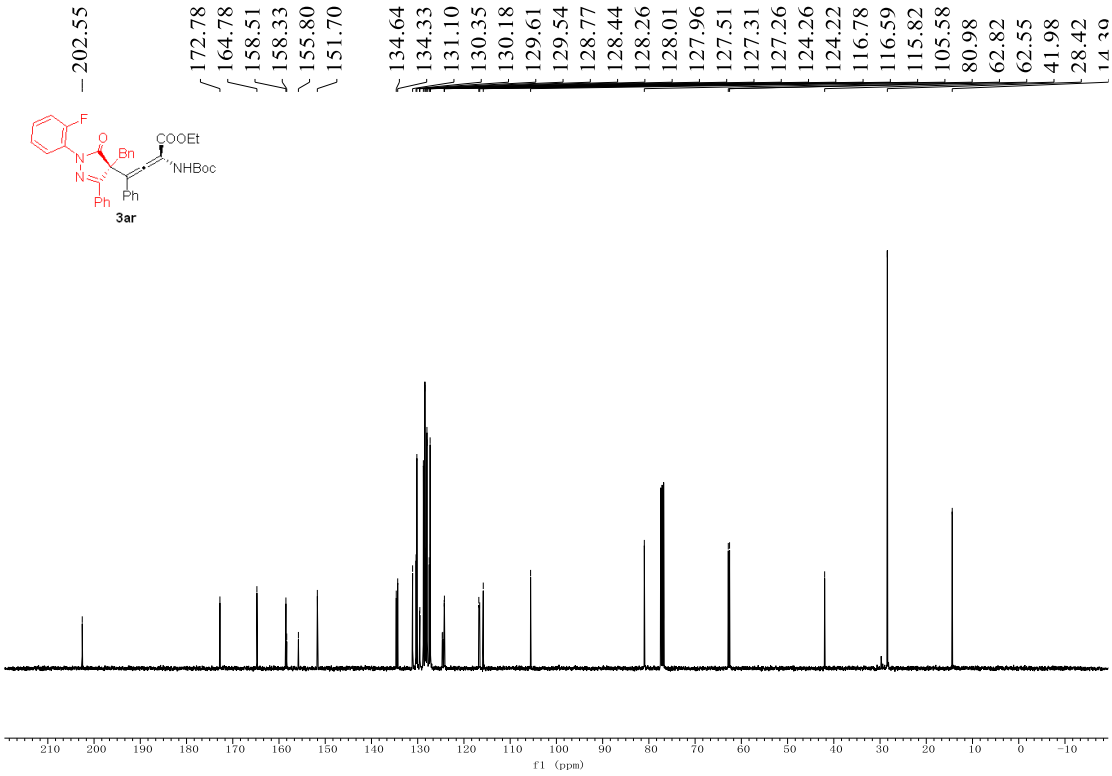
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124.22
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NHBoc
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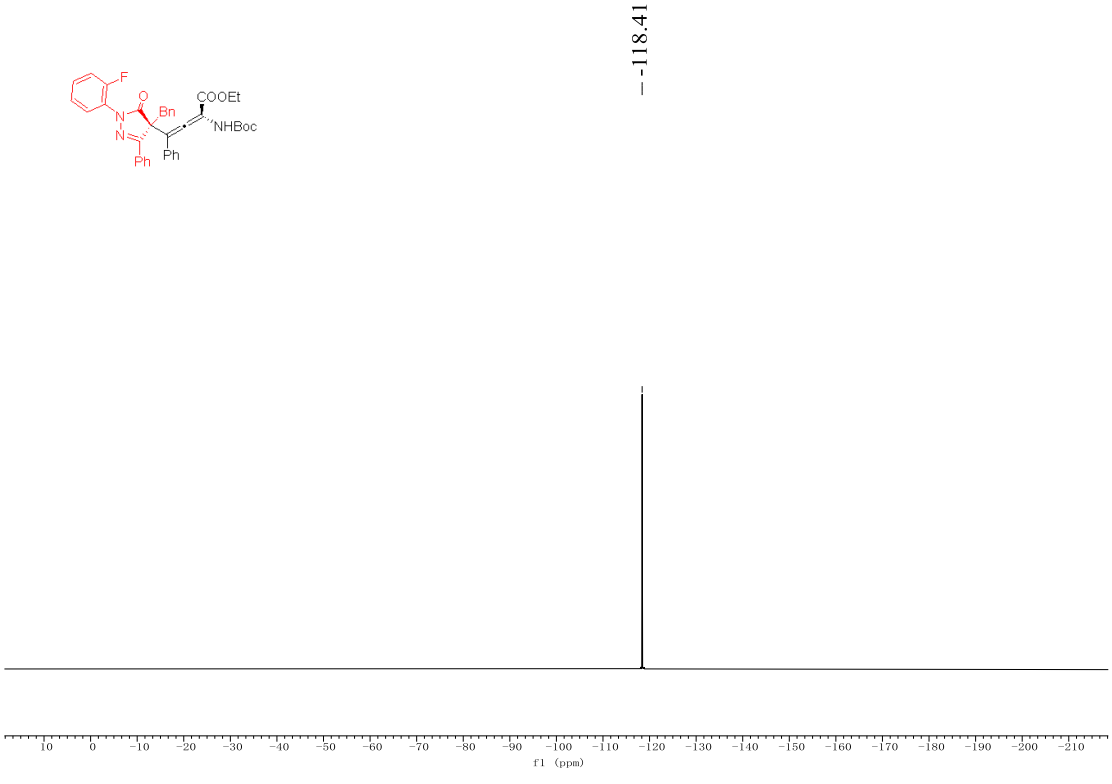
f1 (ppm)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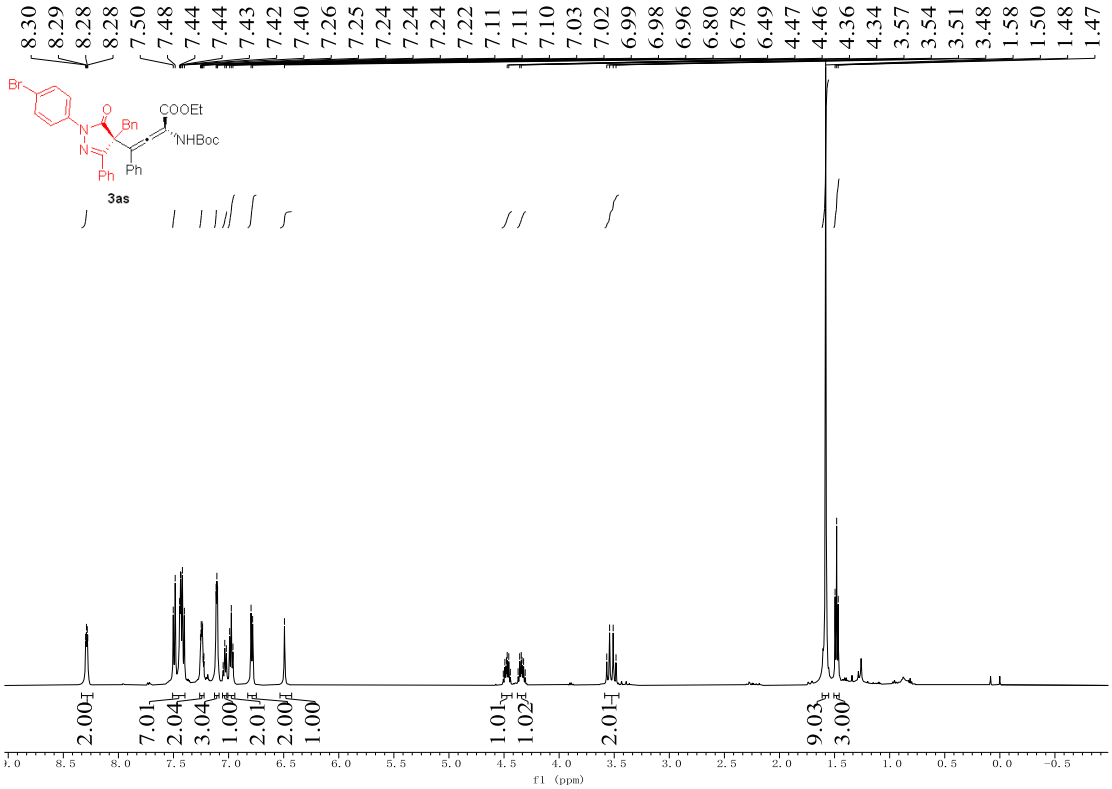
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N
Bn
COOEt
NHBoc
Ph
Ph
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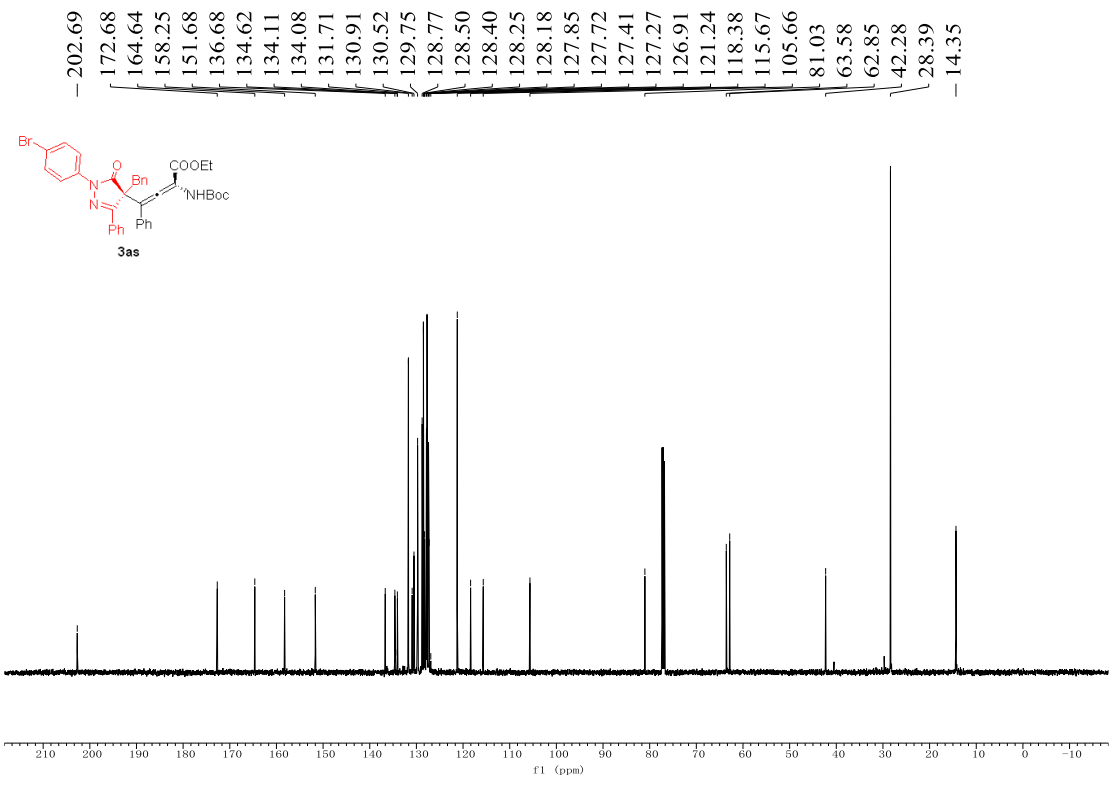
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NHBoc
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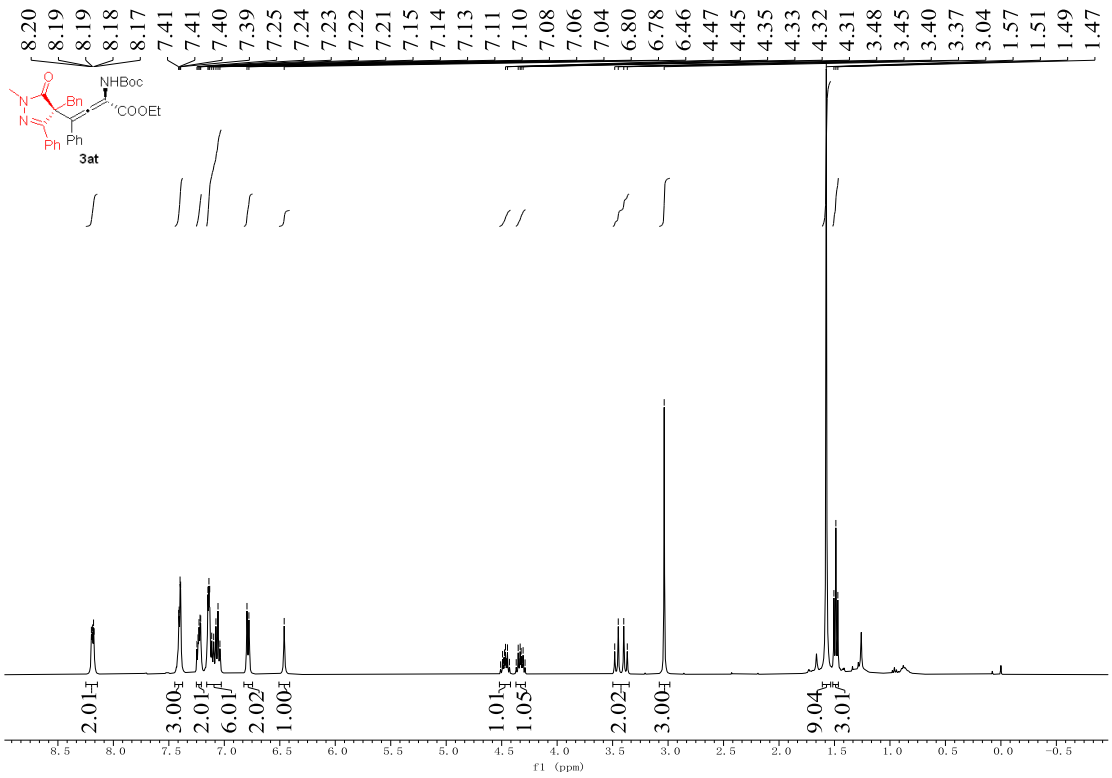
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COOEt
Bn
Ph
Ph
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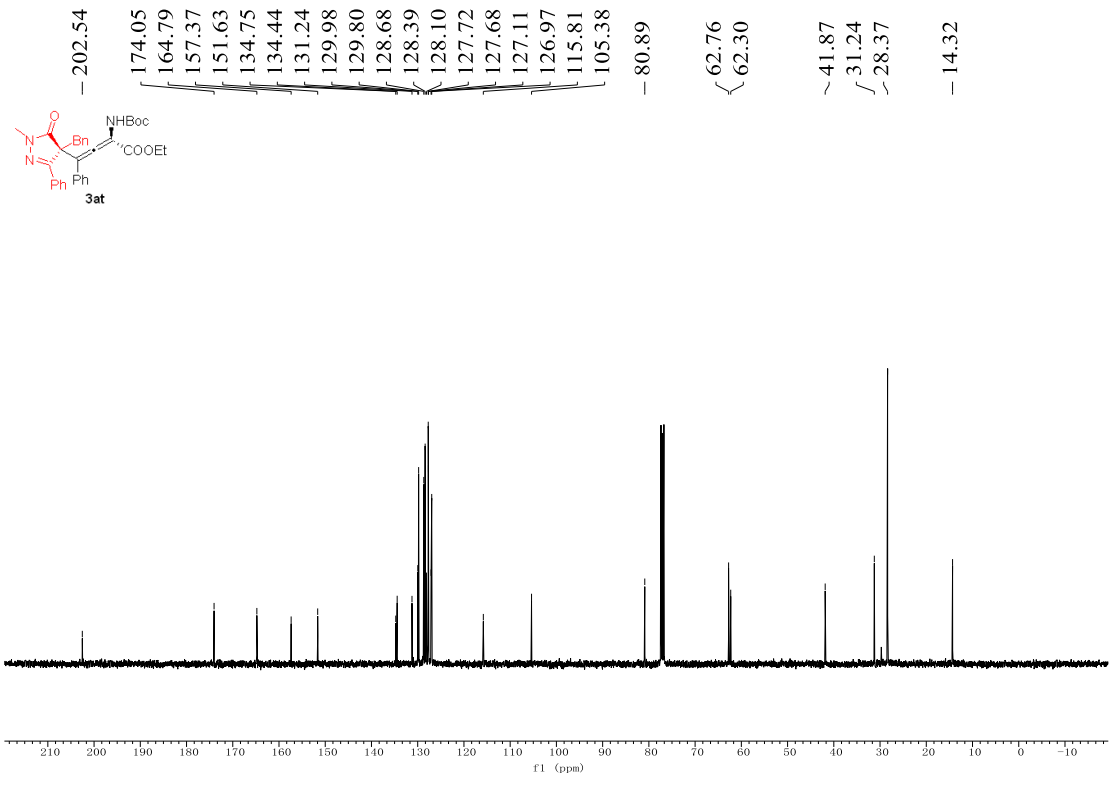
3.01
f1 (ppm)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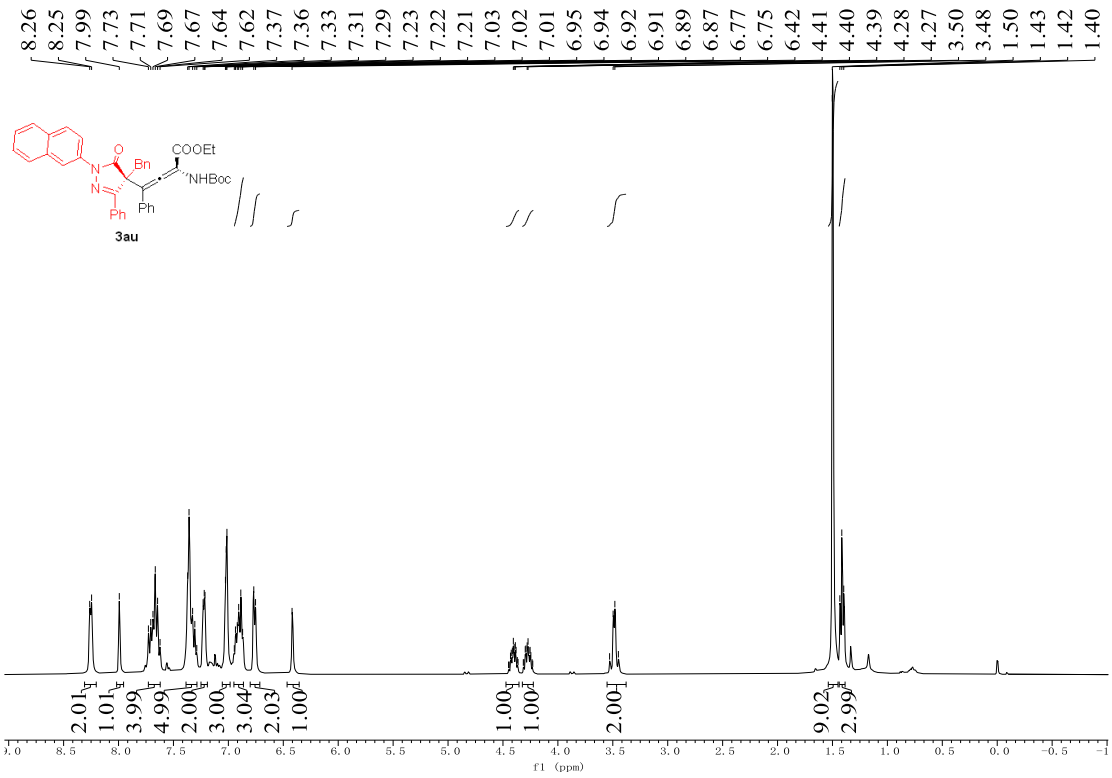
COOEt
Bn
Ph
Ph
3at
f1 (ppm)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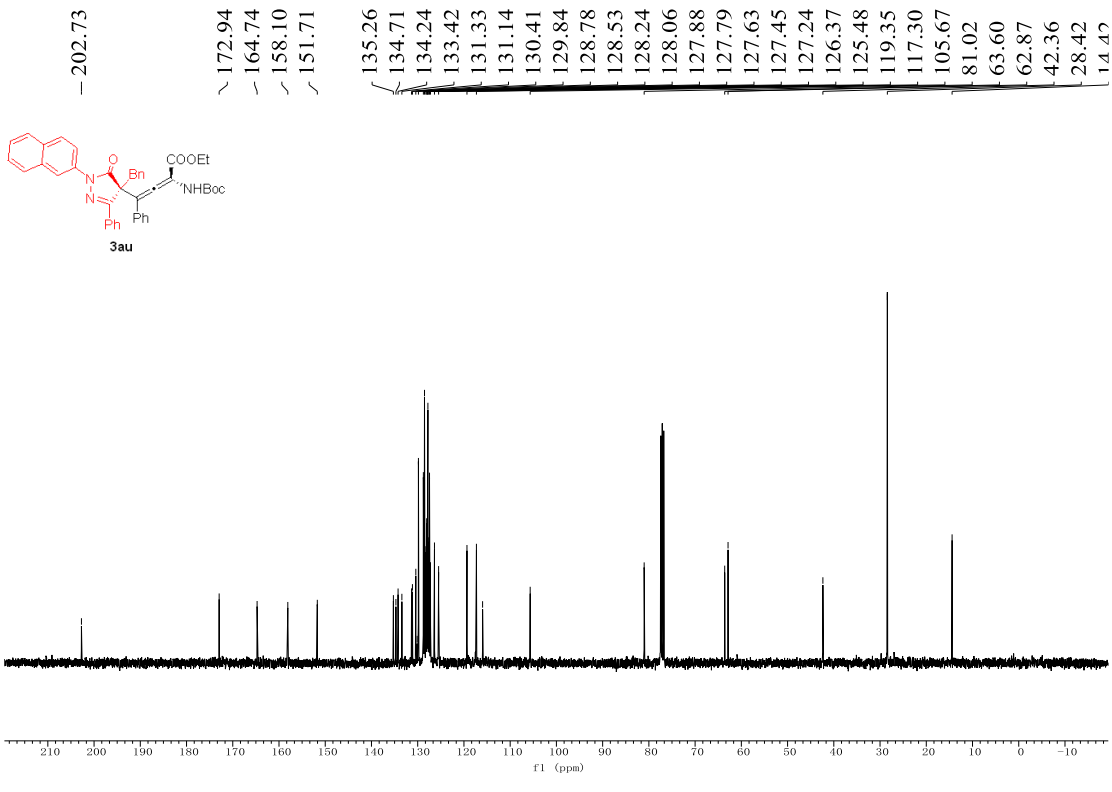
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Bn
NHBoc
Ph
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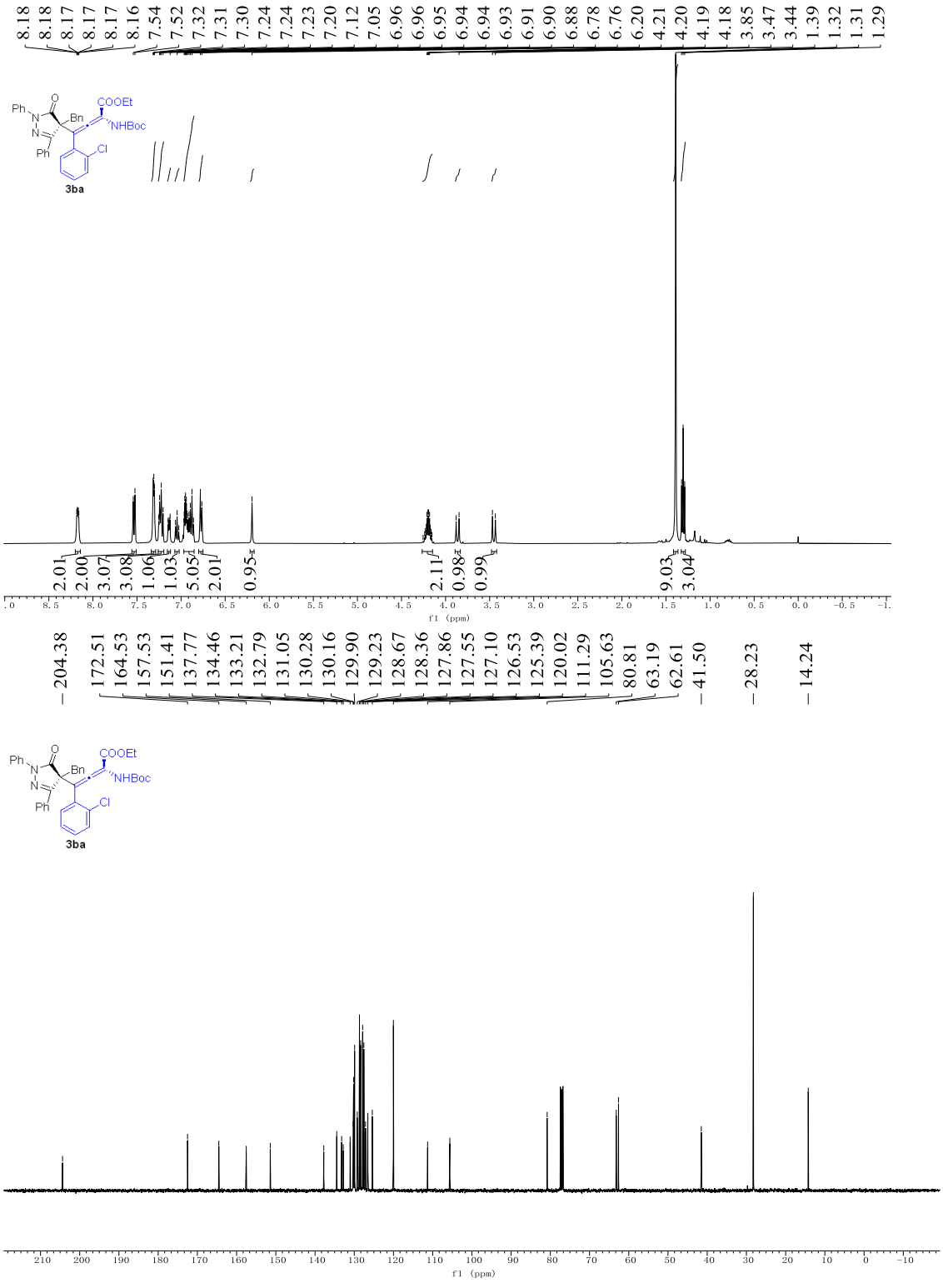
3au
f1 (ppm)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Ph
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O
Bn
COOEt
NHBoc
Ph
Cl
3ba
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f1 (ppm)
204.38 172.51 164.53 157.53 151.41 137.77 134.46 133.21 132.79 131.05 130.28 130.16 129.90 129.23 128.67 128.36 127.86 127.55 127.10 126.53 125.39 120.02 111.29 105.63 80.81 63.19 62.61 41.50 28.23 14.24
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NHBoc
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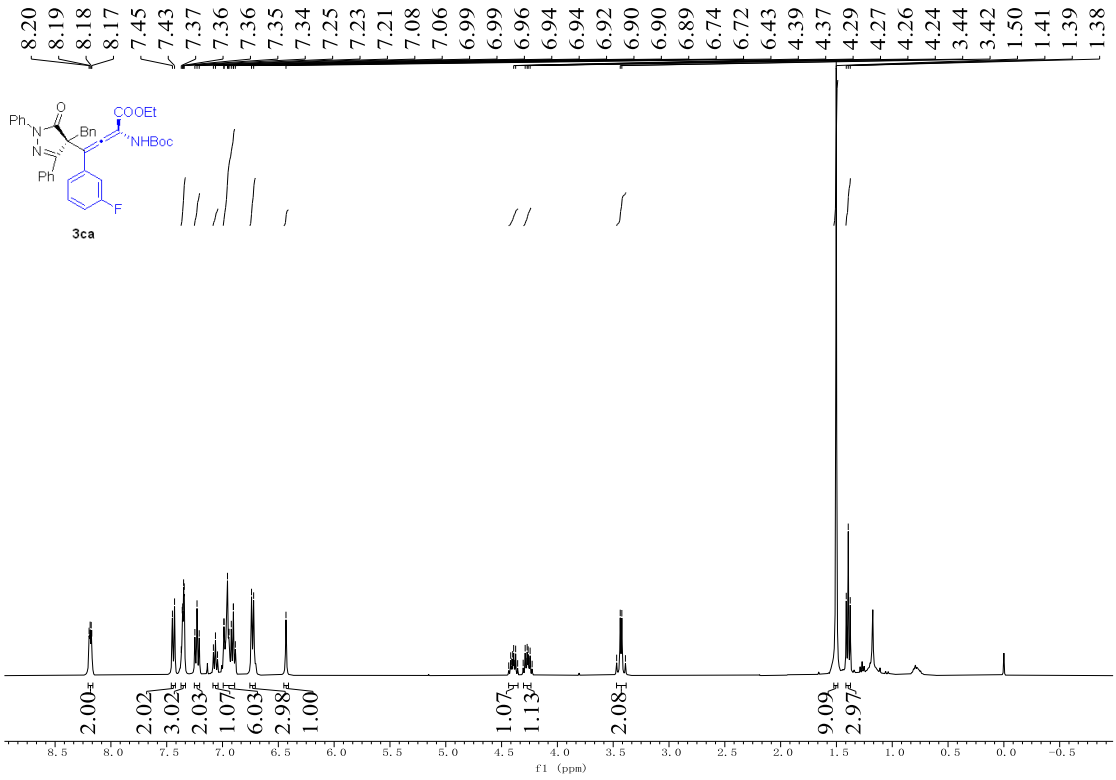
Cl
3ba
f1 (ppm)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Ph
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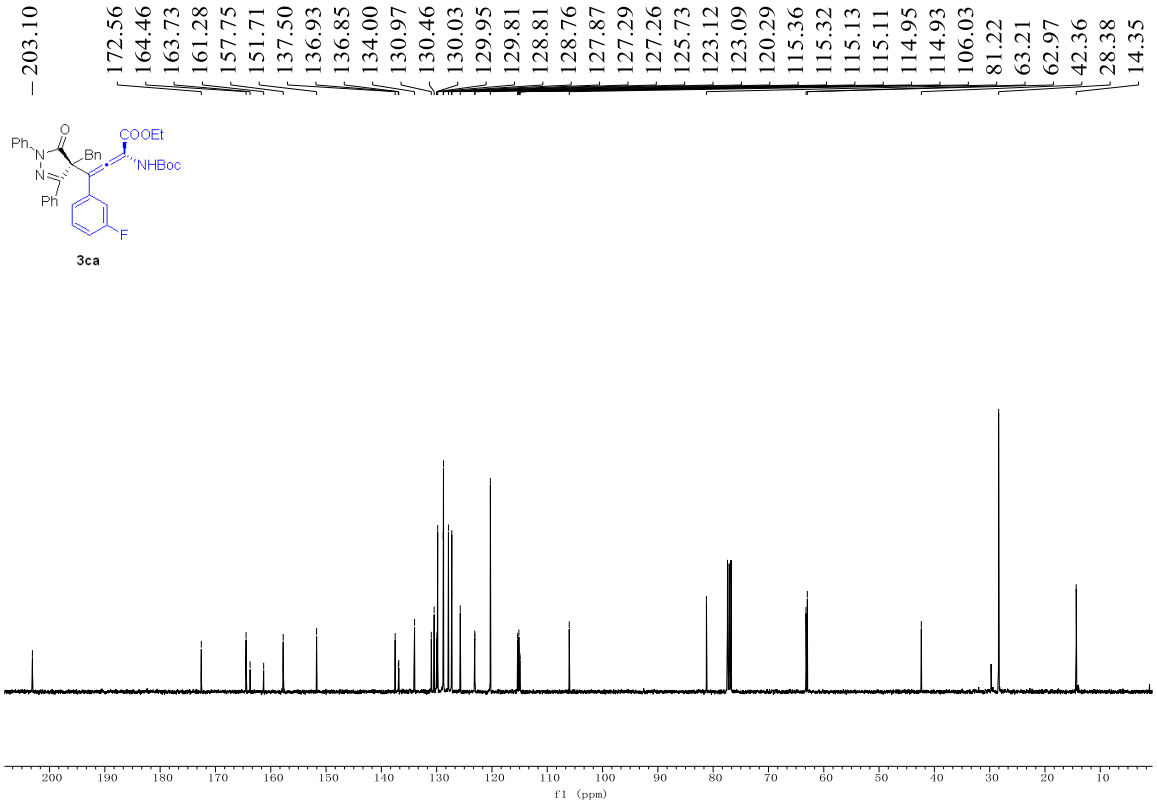
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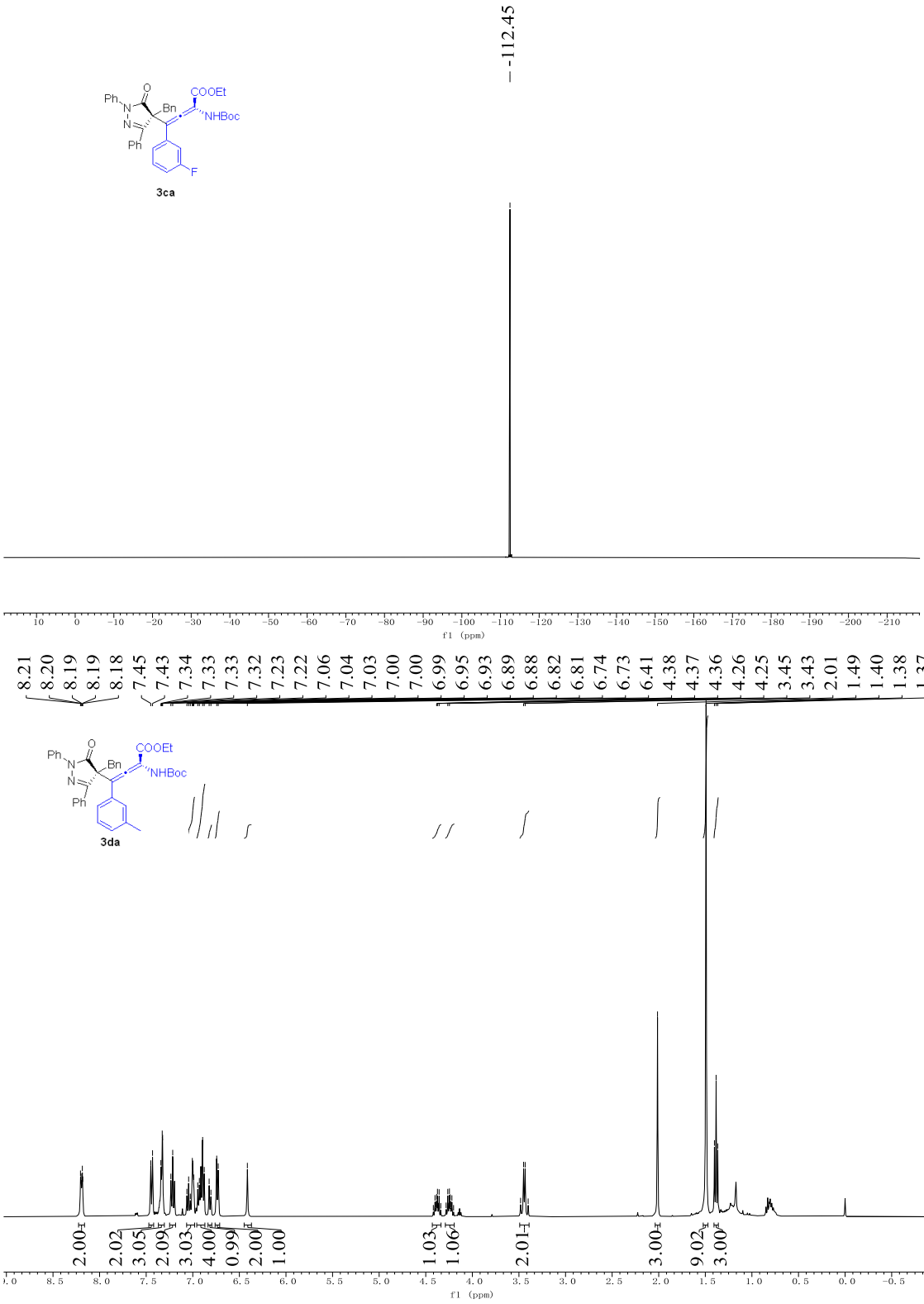
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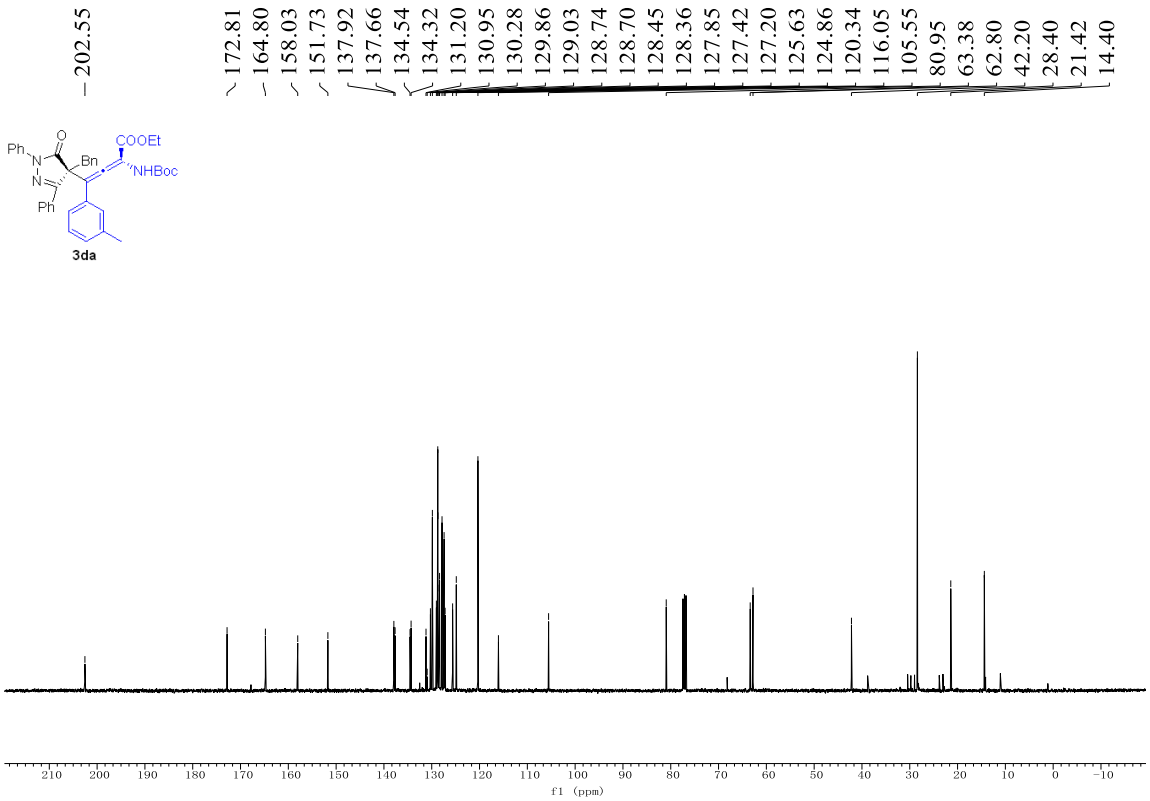
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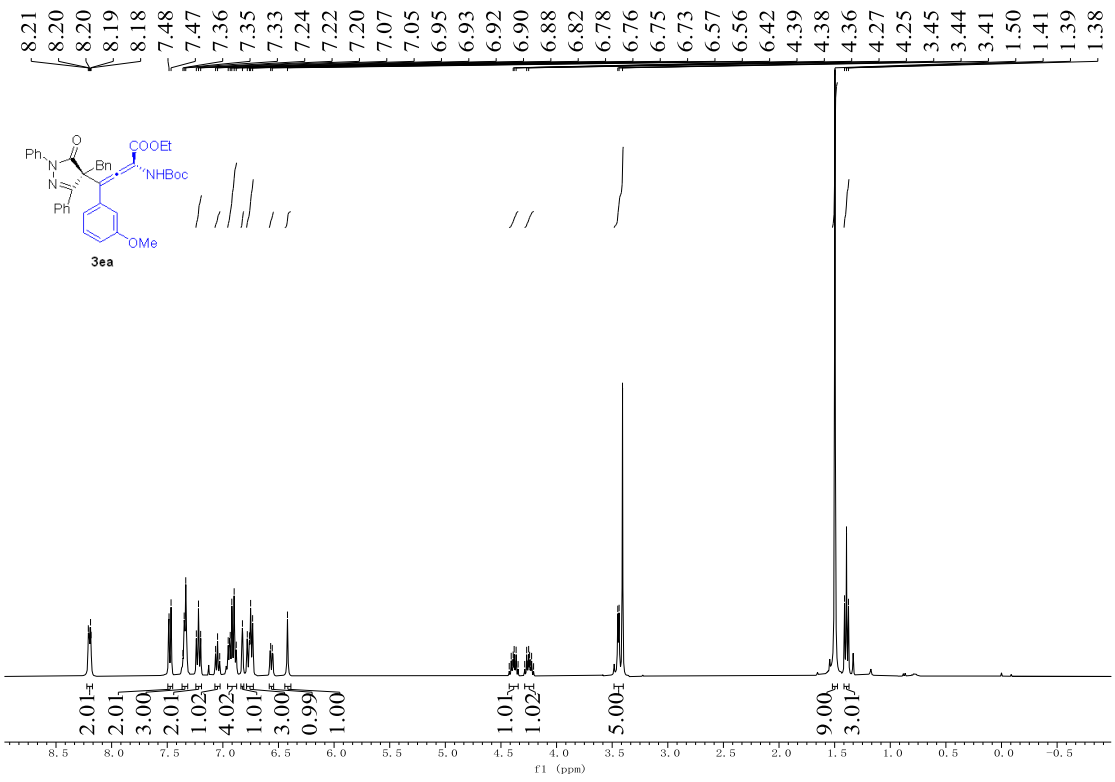
f1 (ppm)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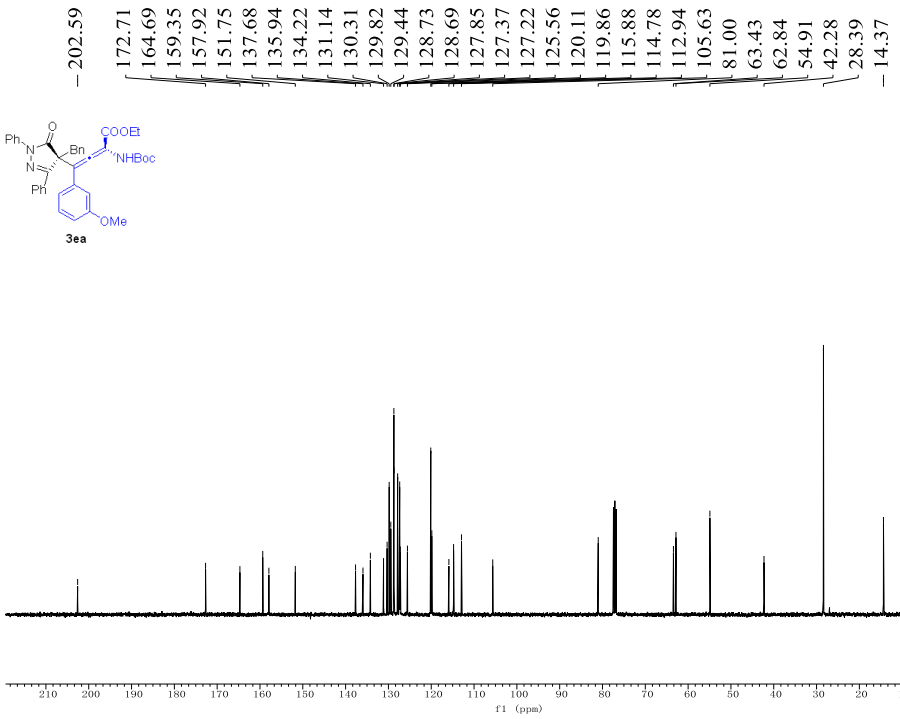
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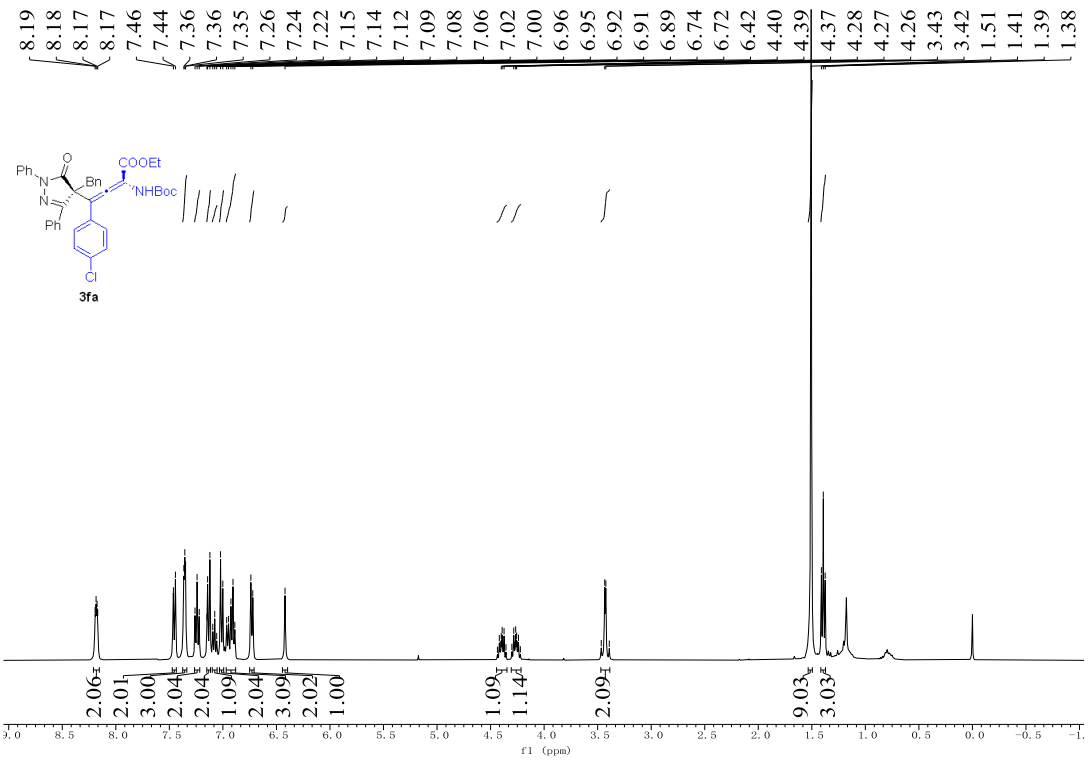
f1 (ppm)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Ph
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NHBoc
Cl
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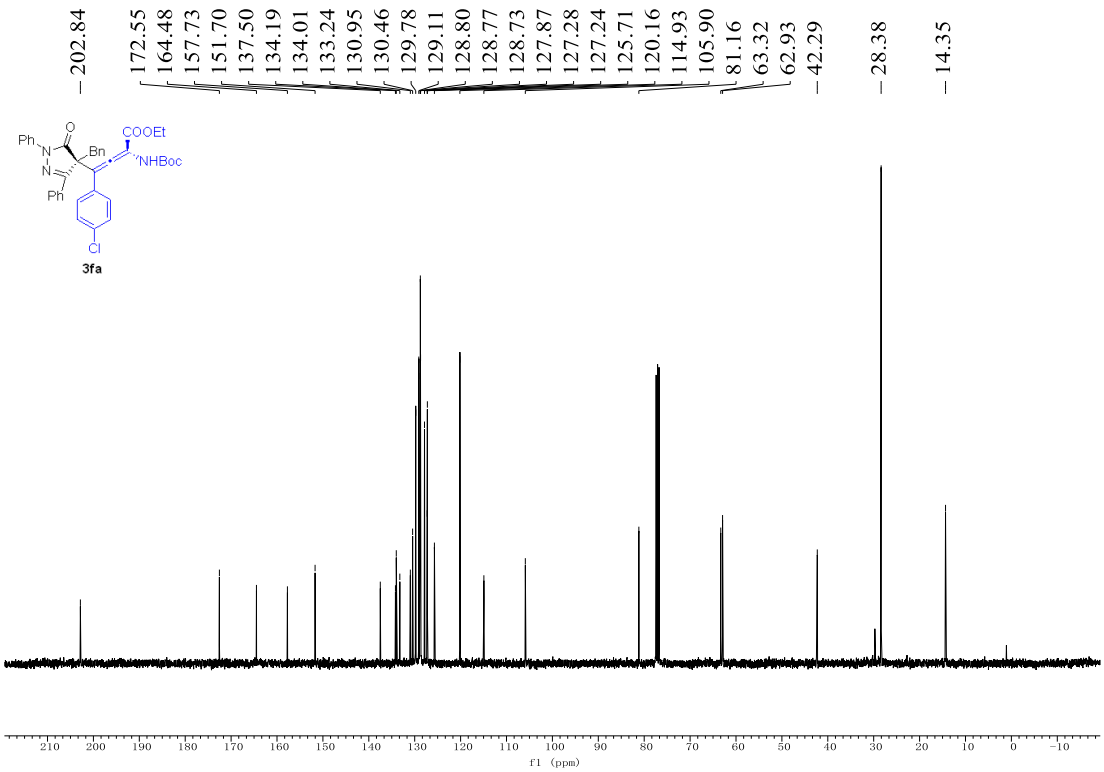
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COOEt
NHBoc
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Cl
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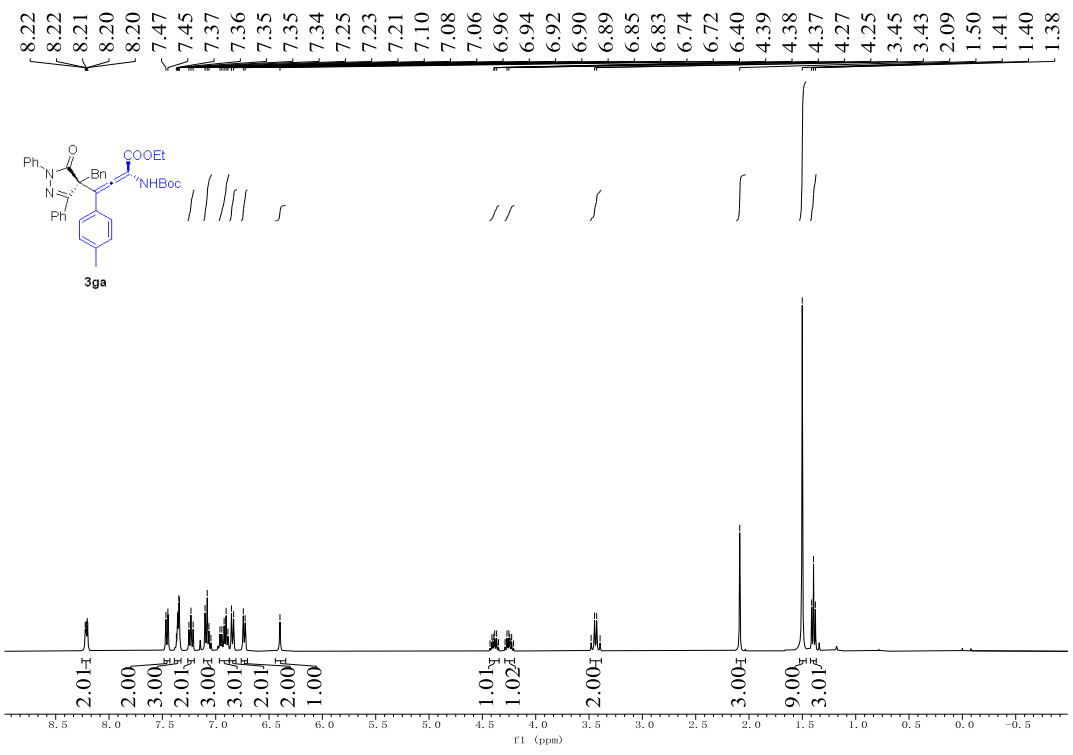
f1 (ppm)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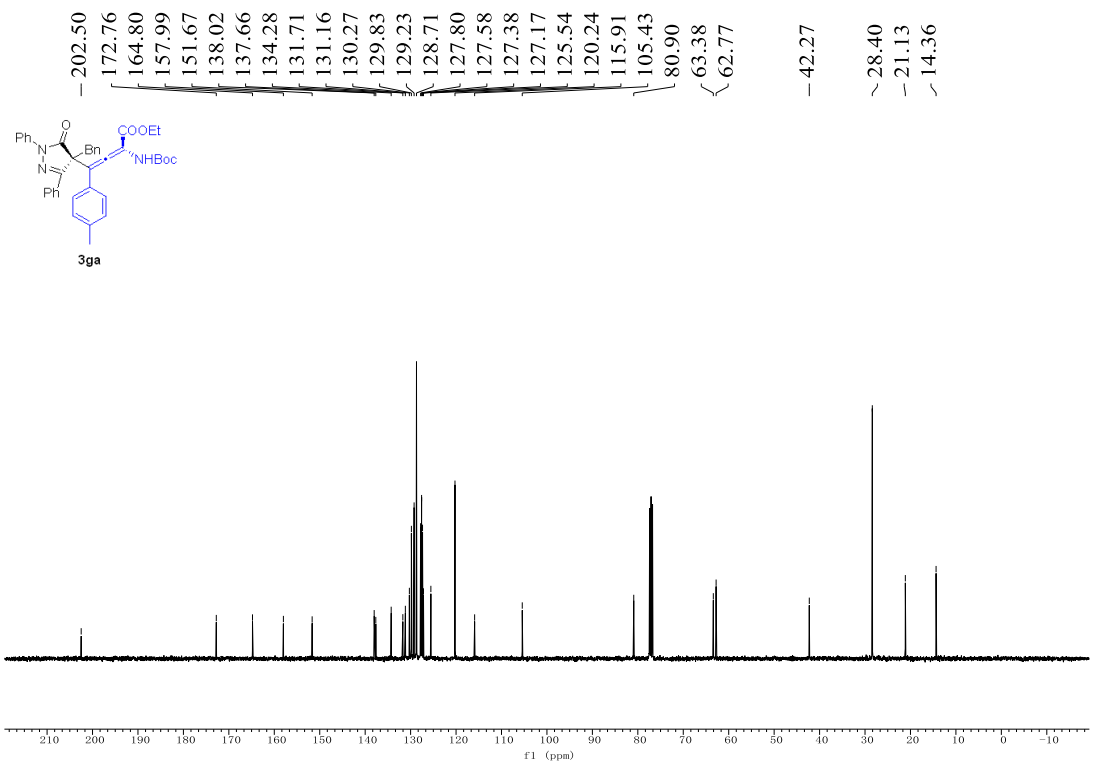
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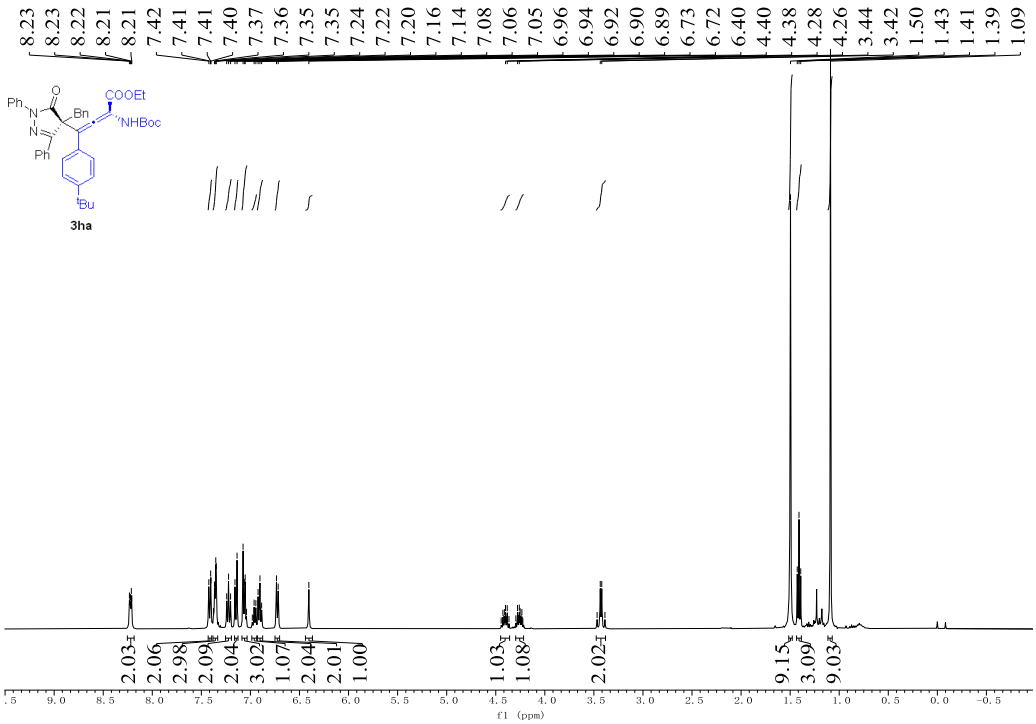
f1 (ppm)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4.26
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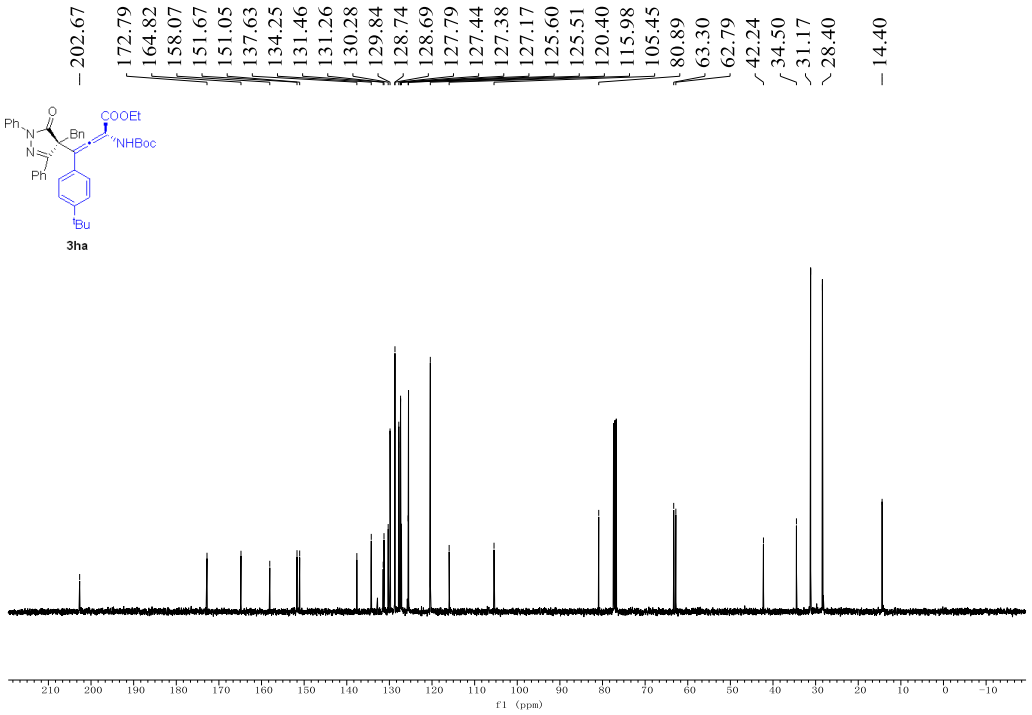
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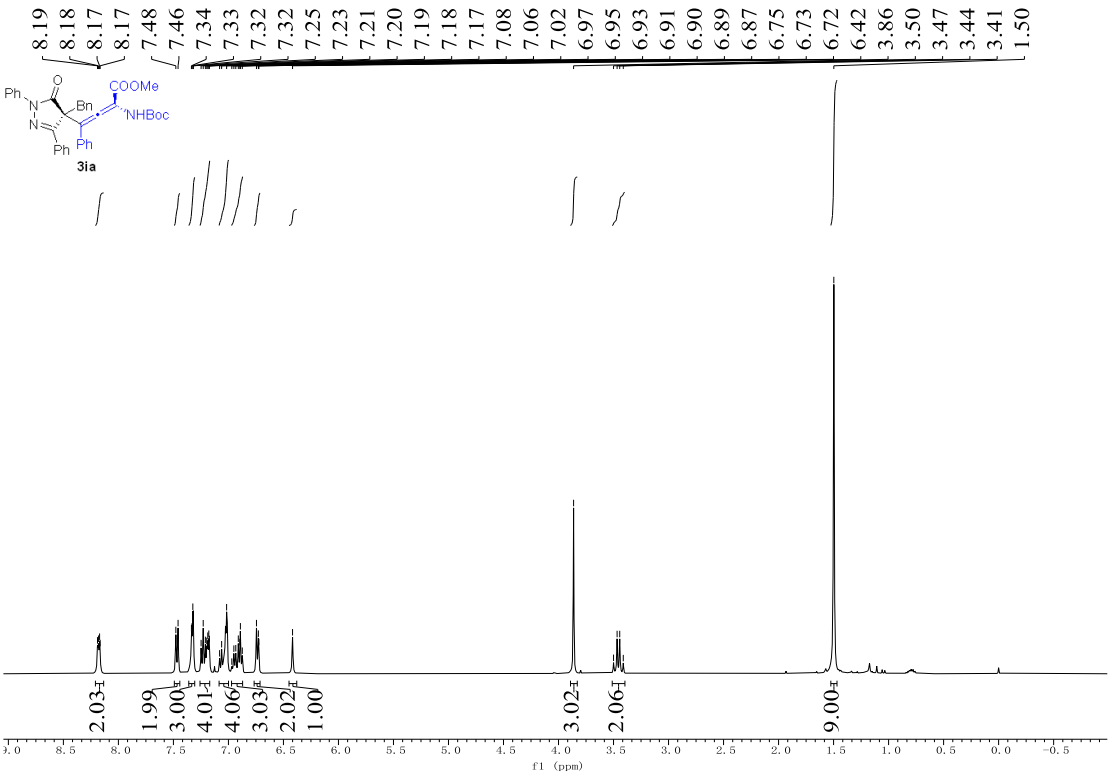
f1 (ppm)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Ph
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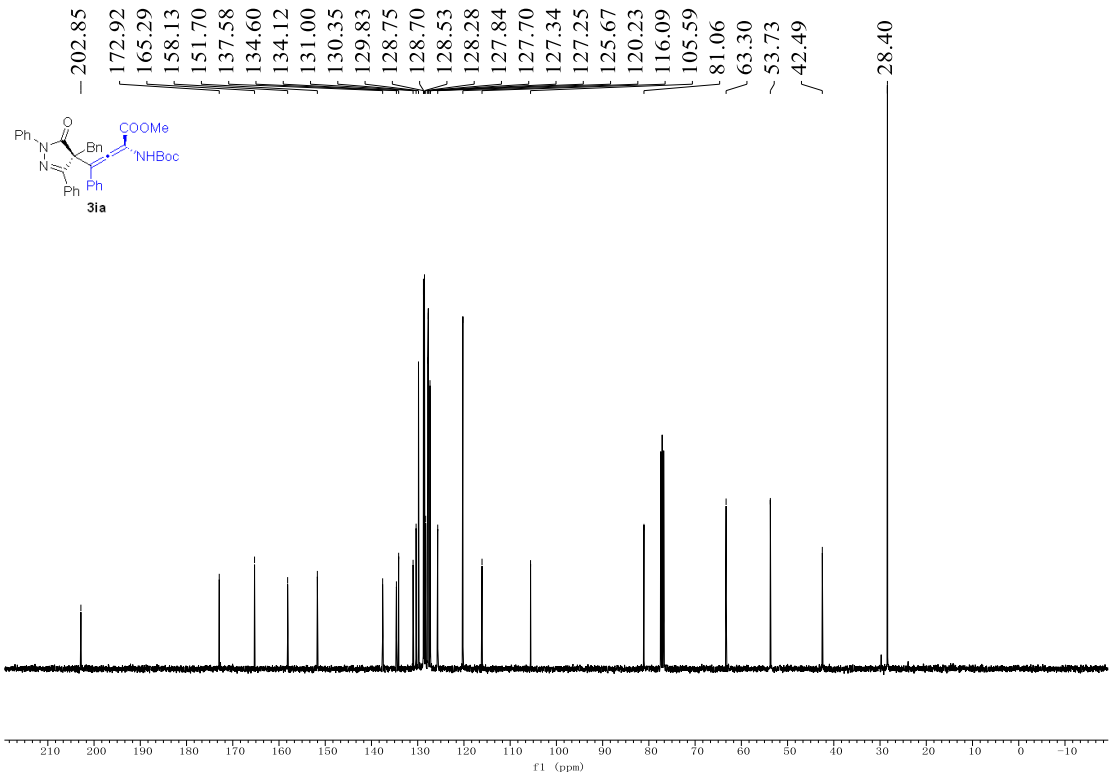
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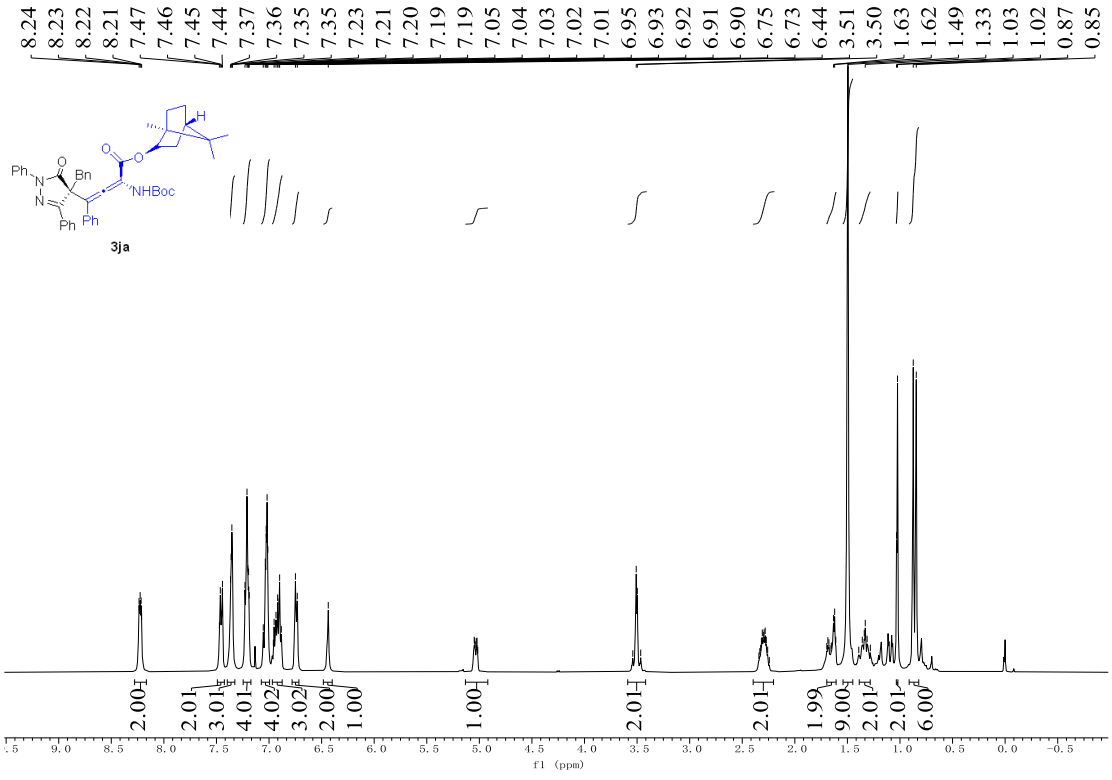
f1 (ppm)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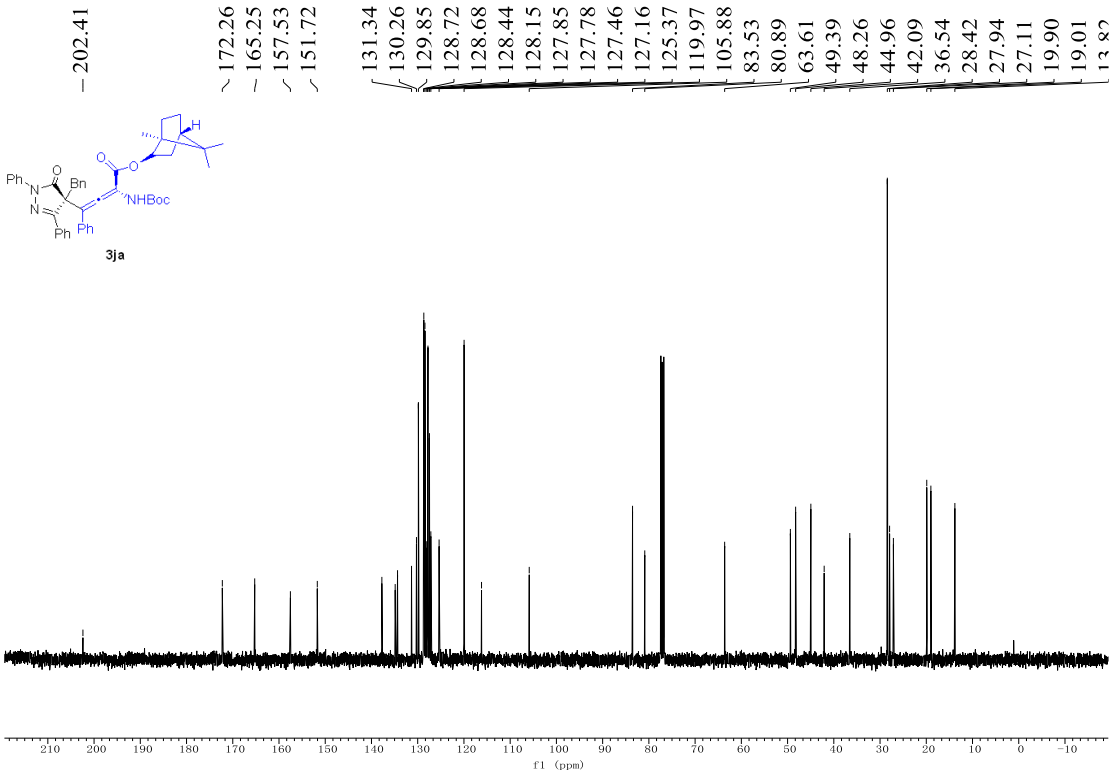
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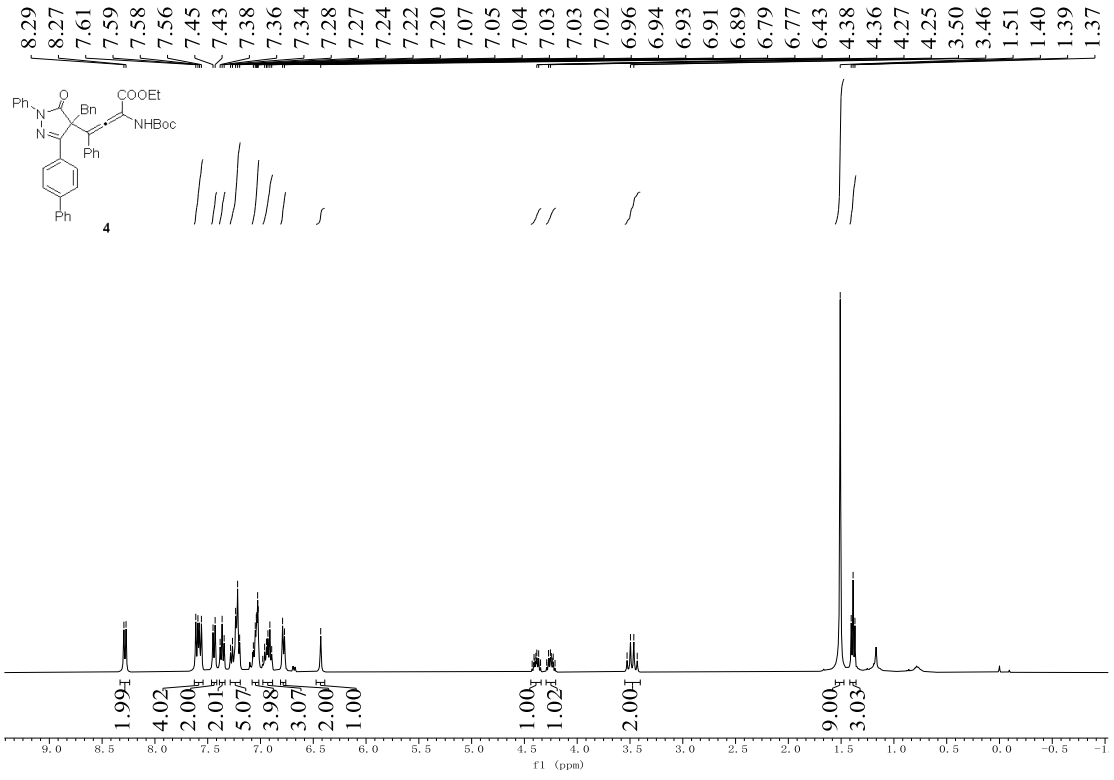
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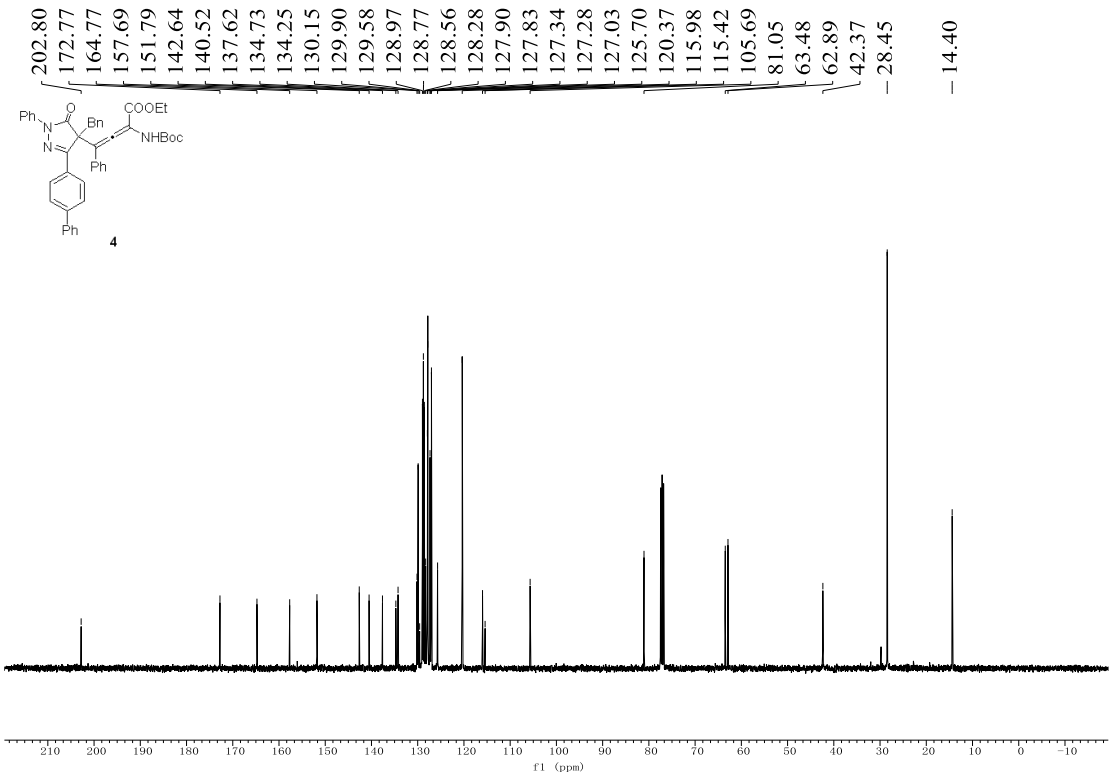
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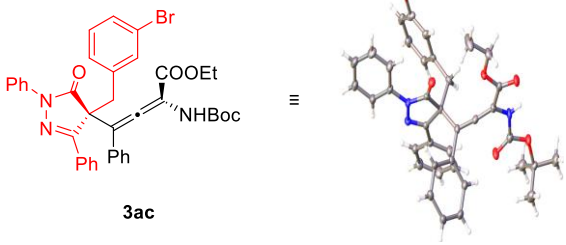
−10
f1 (ppm)

7. X-ray crystal structure of 3ac



3ac ≡

CCDC 2527277

Table 1 Crystal data and structure refinement for 1.

Identification code	1
Empirical formula	$C_{39}H_{36}BrN_3O_5$
Formula weight	706.62
Temperature/K	120.00
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	9.3276(12)
b/Å	12.7751(17)
c/Å	29.524(4)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	3518.1(8)
Z	4
ρ_{calc}g/cm^3	1.334
μ/mm^{-1}	1.216
F(000)	1464.0
Crystal size/mm^3	0.2 × 0.2 × 0.18
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.216 to 51.468
Index ranges	-11 ⩽ h ⩽ 11, -15 ⩽ k ⩽ 15, -36 ⩽ l ⩽ 36
Reflections collected	77053
Independent reflections	6718 [R_{int} = 0.1205, R_{sigma} = 0.0583]
Data/restraints/parameters	6718/0/441
Goodness-of-fit on F^2	1.069
Final R indexes [I>=2σ (I)]	R_1 = 0.0383, wR_2 = 0.0677
Final R indexes [all data]	R_1 = 0.0554, wR_2 = 0.0753
Largest diff. peak/hole / e Å^{-3}	0.25/-0.33
Flack parameter	0.016(5)

8. Reference

1. (a) J. Yang, Z. Wang, Z. He, G. Li, L. Hong, W. Sun and R. Wang, *Angew. Chem. Int. Ed.*, 2019, **59**, 642-647; (b) X. Sheng, J. Zhang, H. Yang and G. Jiang, *Org. Lett.*, 2017, **19**, 2618-2621.
2. J.-Q. Chen, X. Luo, M. Chen, Y. Chen and J. Wu, *Org. Lett.*, 2023, **25**, 1978-1983.