SUPPORTING INFORMATION

Enantioselective Synthesis of α-Amino Esters through Petasis Borono-Mannich Multicomponent Reaction of Potassium Trifluroborate Salts

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1. General Considerations

■ ***Reactions & Reagents***

All commercial reagents and solvents were used as received without further purification. The reaction does not require anhydrous without anaerobic and is carried out using standard Schlenk techniques. Analytical grade reagents such as toluene ($PhCH_3$), trifluorotoluene ($PhCF_3$), tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), methyl tert-butyl ether (MTBE). Reaction materials various types of amines and aldehydes, such as *p*-methoxyaniline, *m*-methoxyaniline, dibenzylamine, 2-bromo-4-methoxyaniline, and ethyl glyoxylate, benzaldehyde, furfural were obtained from Energy Chemical (https://www.energy-chemical.com) and J&K Chemical (http://www.jkchemical.com) and used without further purification.

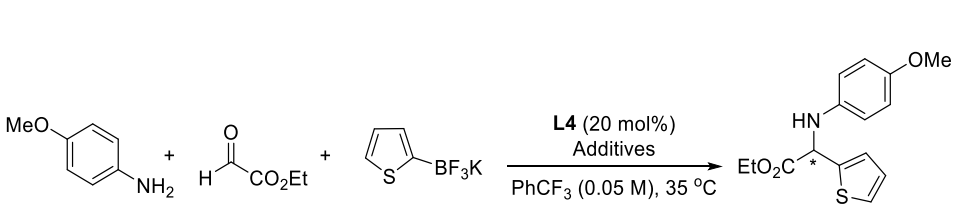
■ ***Chromatography***

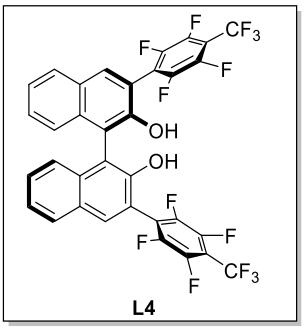
Analytical thin layer chromatography (TLC) was carried out on silica-coated aluminium plates (silicagel 60 F254 Huang Hai) and visualized under UV light (254 nm)

■ ***Analytical Instrumentation***

Melting points were determined using a Büchi B-540 capillary melting point apparatus. NMR data including ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded on Bruker 400 MHz or 600 MHz. All of the ^{13}C NMR spectra were broad band proton-decoupled. ^{1}H NMR Chemical shifts were reported in ppm relative to residual signals of the solvents ($CDCl_3$: 7.26 ppm; $(CD_3)_2SO$: 2.50 ppm). ^{13}C NMR chemical shifts were reported in ppm relative to the solvent ($CDCl_3$:77.16 ppm; $(CD_3)_2SO$: 39.52 ppm). Hexafluorobenzene (δ = -164.9 ppm) was employed as an external standard in 19F NMR spectra. Coupling constants J are given in Hertz (Hz). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet or as a combination of them. High-resolution mass spectra (HRMS) were recorded on an Agilent 6210 TOF LC/MS using ESI as ion source. Optical rotations were determined using an AUTOPOL V automatic polarimeter. Enantioselectivities were determined by HPLC analysis using Agilent 1100 HPLC equipped with Daicel Chiralpak IA, IB, IC, IF, IG and AS-H column.

2. Complete Data for Reaction Optimization





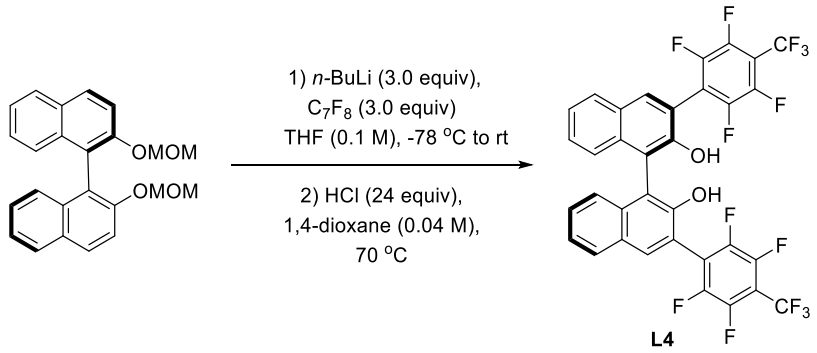
Entry	1b:2 (equiv)	Additive	1b:3a (equiv)	Temp. (°C)	yield (%)[b]	*ee* (%)[c]
1	1:1.2	4 Å MS (65 mg), LiBr (3.0 equiv)	1:2	35	51	64
2	1:1.2	4 Å MS (250 mg), LiBr (3.0 equiv)	1:2	35	47	45
3	1:1.2	4 Å MS (125 mg), LiBr (3.0 equiv)	1:2.5	35	44	62
4	1:1.2	4 Å MS (125 mg), LiBr (3.0 equiv)	1:3	35	61	61
5	1:1.2	4 Å MS (125 mg), LiBr (3.0 equiv)	1:4	35	51	65
6	1:1.5	4 Å MS (125 mg), LiBr (3.0 equiv)	1:2	35	50	65
7	1:2	4 Å MS (125 mg), LiBr 3.0 equiv)	1:2	35	52	66
8	1:1.2	4 Å MS (125 mg), LiBr (2.0 equiv)	1:2	35	44	67
9	1:1.2	4 Å MS (125 mg), LiBr (4.0 equiv)	1:2	35	53	67
10	1:1.2	4 Å MS (125 mg), LiBr (3.0 equiv)	1:2	50	47	54
11	1:1.2	4 Å MS (125 mg), LiBr (3.0 equiv)	1:2	70	55	52
12	1:1.2	4 Å MS (125 mg), LiBr (3.0 equiv)	1:2	35	37	46
13	1:1.2	4 Å MS (125 mg), LiBr (3.0 equiv)	1:2	35	48	36
14	1:1.2	4 Å MS (125 mg), LiBr (3.0 equiv), TFA (1.0 equiv)	1:2	35	49	12
15	1:1.2	4 Å MS (125 mg), LiBr (3.0 equiv), CSA (1.0 equiv)	1:2	35	33	31
16	1:1.2	4 Å MS (125 mg), LiBr (3.0 equiv), TsOH (1.0 equiv)	1:2	35	41	40

[a] General reaction conditions: **1b** (0.1 mmol), 35 °C, 4 Å MS (125 mg).

[b] Determined by integration of ^{1}H NMR signals relative to triphenylmethane as an internal standard.

[c] Ratio determined by HPLC with chiral Daicel Chiralpak IG column.

3. Synthesis of the BINOL Catalyst

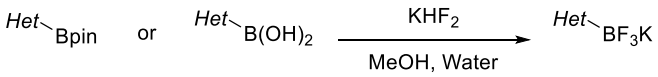


To a flame-dried flask equipped with a magnetic stirbar was added 2,2'-bis(methoxymethoxy)-1,1'-binaphthalene[1] (1.1058 g, 2.96 mmol, 1.0 equiv) and THF (24 mL). The reaction mixture was then cooled down to 0 °C followed by the addition of 2.5 M *n*-BuLi (3.6 mL, 8.88 mmol, 3.0 equiv) and allowed to stir at the same temperature in 2 hours. The reaction temperature was futher decreased to -78 °C and perfluorotoluene (2.9 mL, 20.72 mmol, 7.0 equiv) was added dropwise via syringe. The reaction mixture was then warmed up to room temperature and stirred at this temperature for 12 h. After completion, the reaction was quenched with saturated aq. NH_4Cl (5 mL), extracted with Et_2O (3 × 10 mL), and wash with brine (10 mL). After the removal of solvents via rotary evaporation, the reaction mixture was purified by column chromatography on silica gel using 2-5% Ethyl Acetate in *n*-Hexane as eluent. The product was obtained as white solid in 87% yield. The product (2.0605 g, 2.6 mmol) was dissolved in1,4-dioxane (1.0 mL, 0.04 M). To this solution was added saturated HCl (24.0 equiv) at 70 °C for 12 h. The resulting solution was diluted with water (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with water (10 mL) and saturated aq. $NaHCO_3$ (10 mL) and dried over Na_2SO_4. After evaporation of the solvents, the residue was purified by flash column chromatography on silica gel (*n*-Hexane/Et_2O = 100/1) to afford **L4** in 90% yield. The spectra data is in agreement with literature reported value[2].

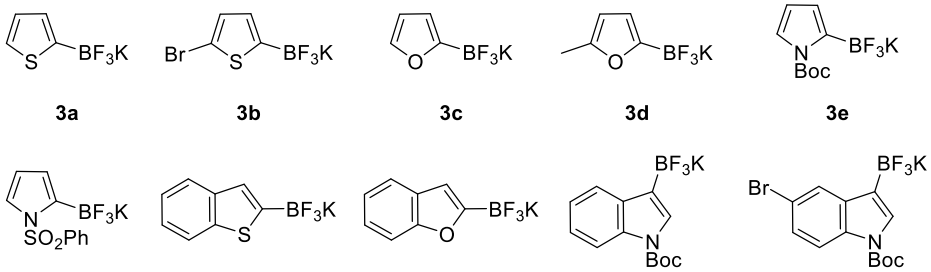
4. Synthesis of Heterocyclic Potassium Trifluoroboric

[1] (a) M. Moliterno, R. Cari, A. Puglisi and M. Bella, *Angew. Chem. Int. Ed.*, 2016, **55**, 6525. (b) J.-Z. Wang, J. Zhou, C. Xu, H. Sun, L. Kürti and Q.-L. Xu, *J. Am. Chem. Soc.*, 2016, **138**, 5202. (c) S. Narute, R. F. Parnes, T. Dean and P. Doron, *J. Am. Chem. Soc.*, 2016, **138** , 16553.
[2] J.-L. Shih, T. S. Nguyen and J. A. May, *Angew. Chem. Int. Ed.*, 2015, **54**, 9931.

4.1 General Procedure A for the Synthesis of Potassium Trifluoroborates

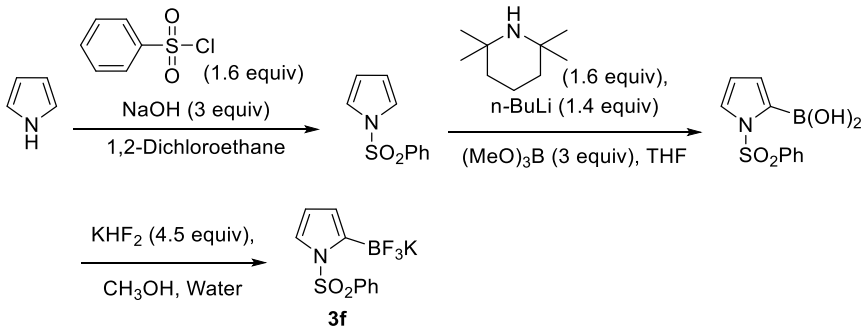


To a solution of the Boric acid or pinacolborane (3.0 mmol, 1.0 equiv) in methanol (10 mL) and water (10 mL) was added potassium hydrogen fluoride (9.0 mmol, 3.0 equiv). The mixture was stirred at room temperature for 3 h. Then it was concentrated in vacuum and the resulting solid was extracted with acetone (3 × 5 mL). The combined acetone extracts were filtered and concentrated in vacuum. The residue was dispersed with Et_2O (10 mL) and the resulting suspension was filtered to afford the potassium trifluoroborates as white solids.



The title compound **3a**[3], **3b**[3], **3c**[3], **3d**[3], **3e**[3], **3h**[4], **3i**[5] were prepared according to those reported in the literature. **3c** were purchased from Alfa Aesa.

4.2 General Procedure B for the Synthesis of 3f



NaOH (3.4 g, 84 mmol) were combined in 1,2-Dichloroethane (25 mL) and stirred at 0 °C for completely dissolved. Pyrrole (2 mL, 15.4 mmol) is added dropwise. Subsequently, benzenesulfonyl chloride (4 mL, 33 mmol) was added dropwise. The reaction was stirred at 0 °C for 12 h. The reaction was quenched with water (10 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried over Na_2SO_4,

[3] J.-L. Shih, T. S. Nguyen and J. A. May, *Angew. Chem. Int. Ed.*, 2015, **54**, 9931.
[4] P. Kassis, V. Bénéteau, J.-Y. Mérour and S. Routier, *Synthesis*, 2009, **2009**, 2447.
[5] Y. Zhang and M. G. Banwell, *J. Org. Chem.*, 2017, **82**, 9328.

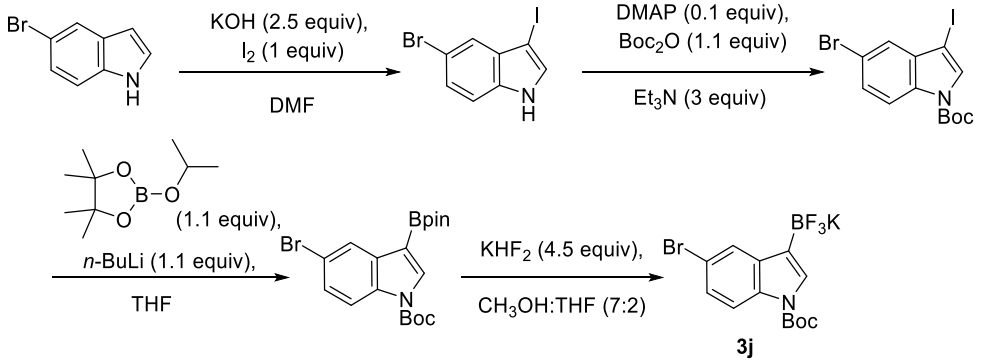
filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (petroleum ether/ EtOAc = 50/1) to give the product as white solid in 60% yield.

The 2,2,6,6-tetramethylpiperidine (3 mL, 16.5 mmol) were combined in THF (20 mL). The reaction was cooled to -78 °C and *n*-BuLi (2.5 M in *n*-Hexane, 8.4 mL, 21 mmol) was added dropwise over 20 min. The reaction was stirred at –78 °C for 1 h. The product obtained in the fiest step (3 g, 15 mmol) in THF (5 mL) was added dropwise over 10 min. Then $(MeO)_3B$ (5 mL, 45 mmol) is added dropwise. The reaction was stirred at –78 °C for 3 h, then The temperature slowly rises to room temperature and to react overnight. The reaction was quenched with HCl (0.5 M in water, 20mL) and r. otary evaporation to remove THF. The product was separated and extracted with Et_2O (3 × 15 mL). The combined organic phases were dried over Na_2SO_4, filtered, concentrated *in vacuo* and used without purification for the next stage[6].

Following the procedure reported, a magnetically stirred mixture of the product obtained in the second step (3.7 g, 15 mmol) in methanol (30 mL) was treated dropwise with a solution of KHF_2 (5.3 g, 67.5 mmol) in water (20 mL) at 0 °C, and the ensuing white suspension was stirred at room temperature for 12 h then concentrated under reduced pressure. The residue thus obtained was re-dissolved in 50% methanol/water (50 mL), and all the volatile materials were again removed under reduced pressure. The resulting solid was extracted with acetone (3 x 10 mL). The combined acetone extracts were filtered and concentrated in vacuum. The residue was dispersed with Et_2O (10 mL) and the resulting suspension was filtered to afford the **3h** as white solid in 65% yield within 3 steps.

[6] M. David, W. Stuart, Haynes and G. L. Challis, *J. Am. Chem. Soc*., 2015, **137**, 7889.

4.3 General Procedure C for the Synthesis of 3j



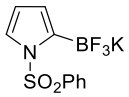
Indole (3 g, 15.4 mmol) and KOH (3 g, 46.2 mmol) were combined in DMF (30 mL) and stirred at 0 ºC for 1 h. The reaction was cooled to 0 °C and I_2 (4 g, 15.6 mmol) in DMF (15 mL) was added dropwise over 10 min. The reaction was stirred at 0 °C for 12 h. The reaction was diluted with 5% aq. $Na_2S_2O_3$ (10 mL) and CH_2Cl_2 (20 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with 5% $Na_2S_2O_3$ aqueous solution (100 mL), dried over Na_2SO_4, filtered, concentrated *in vacuo* and used without purification for the next stage.

The crude product was dissolved in CH_2Cl_2 (30 mL). Et_3N (6.4 mL, 46.2 mmol) and DMAP (188 mg, 1.54 mmol) and Boc_2O (3.9 mL, 17 mmol) were added in one portion and the reaction was stirred at room temperature for 2 h. The reaction mixture was diluted with 5% $Na_2S_2O_3$ aqueous solution (50 mL) and CH_2Cl_2 (20 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by flash column chromatography (petroleum ether/ EtOAc = 20/1) to give the indole as white solid in 70% yield.

Under argon atomsphere, *tert*-butyl 3-iodo-1H-indole-1-carboxylate (5.7 g, 13.6 mmol) was dissolved in anhydrous THF (30 mL) and cooled to –78 °C. *n*-BuLi (2.5 M in *n*-Hexane, 6.0 mL, 14.9 mmol) was added dropwise over 10 min. The reaction was stirred at –78 °C for 1 h, then isopropoxypinacol boronate (3.1 mL, 14.9 mmol) was added dropwise over 15 min. The reaction mixture was kept at –78 °C for an additional hour, then the cooling bath was removed and the reaction mixture was stirred at room temperature for 30 min. The reaction was diluted with saturated aq. KH_2PO_4 (10 mL) and extracted with Et_2O (3 × 20 mL). The combined organic phases were washed with water (20 mL) and brine (20 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude product was used without purification for the next stage.

Following the procedure reported, a magnetically stirred mixture of 3-Bpin-N-Boc-indole (6 g, 14.2 mmol) in 70% methanol/THF (40 mL) was treated dropwise with a solution of KHF_2 (6.6 g, 85 mmol) in water (20 mL) at 0 °C, and the ensuing white suspension was stirred at room temperature for 12 h then concentrated under reduced pressure. The residue thus obtained was re-dissolved in 50% methanol/water (50 mL), and all the volatile materials were again removed under reduced pressure. The resulting solid was extracted with acetone (3 x 10 mL). The combined acetone extracts were filtered and concentrated in vacuum. The residue was dispersed with Et_2O (10 mL) and the resulting suspension was filtered to afford the **3j** as white solid in 21% yield within 4 steps.

1-(phenylsulfonyl)-2-(trifluoro-l4-boranyl)-1H-pyrrole, potassium salt (3f)



The title compound was prepared according to the General Procedure **B** as white solid in 65% yield within 3 steps.

mp: 202.1-203.2 °C

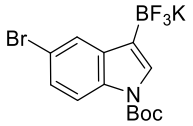
^{1}H NMR (400 MHz, DMSO-d_6): δ 7.89 (d, *J* = 7.7 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.52 (d, *J* = 7.7 Hz, 2H), 7.18 (s, 1H), 6.10 (s, 2H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 140.9, 133.5, 129.3, 127.4, 123.1, 118.7, 112.3 ppm.

^{19}F NMR (376 MHz, DMSO): δ -162.63.

HRMS (ESI) *m/z* calcd. for $C_{10}H_8BF_3NO_2S$ $[M-K]^-$: 274.0326; found 274.0323.

***Tert*-butyl 5-bromo-3-(trifluoro-λ^4-boranyl)-1*H*-indole-1-carboxylate, potassium salt (3j)**



The title compound was prepared according to the General Procedure **C** as white solid in 21% yield within 4 steps.

mp: 167.5-169.8 °C

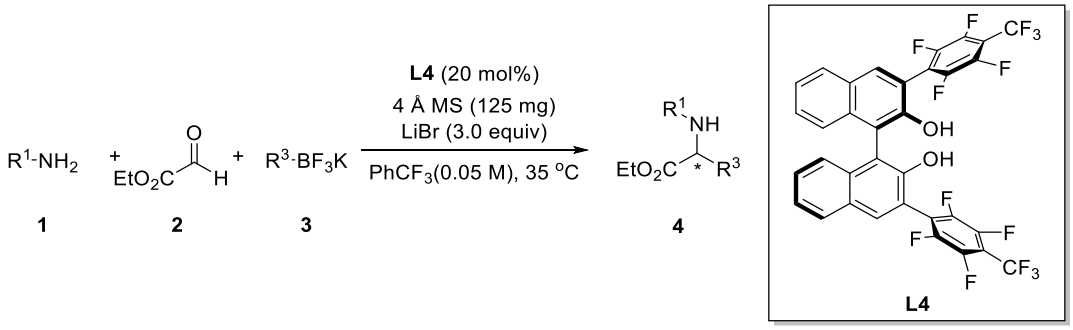
^{1}H NMR (400 MHz, DMSO) δ 7.90 (d, *J* = 8.0 Hz, 1H), 7.74 (s, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 7.21 (s, 1H), 1.61 (s, 9H).

^{13}C NMR (101 MHz, DMSO) δ 149.3, 137.6, 134.5, 127.6, 127.6, 125.1, 124.9, 115.8, 114.1, 82.8, 27.8 ppm.

^{19}F NMR (376 MHz, DMSO) δ -137.65.

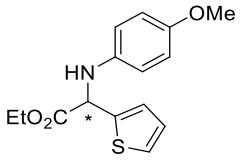
HRMS (ESI) *m/z* calcd. for $C_{15}H_{12}N_3O_3$ [M-K]$^-$: 362.0175; found 362.0189.

5. Asymmetric Petasis borono-Mannich reaction



To a 25 mL vial equipped with a stir bar was added 4 Å powdered molecular sieves (125 mg). The amine **1** (0.1 mmol, 1.0 equiv), ethyl glyoxylate **2a** (0.12 mmol, 1.2 equiv), **L4** (0.02 mmol， 0.2 equiv), potassium heteroaryl trifluoroborate salt **3** (0.2 mmol, 2.0 equiv), LiBr (0.3 mmol, 3.0 equiv) were then added. Ordinary $PhCF_3$ (2 mL, 0.05 M) was added. The reaction was heated to 35 ºC and monitored by TLC analysis. After the reaction is complete, the solution was filtered through a short celite pad. The combined organic layer was concentrated under reduced pressure and purified via flash column chromatography on silica gel to afford the corresponding products **4**.

ethyl 2-((4-methoxyphenyl)amino)-2-(thiophen-2-yl)acetate (4a)



The product was purified via flash column chromatography (*n*-Hexane/EtOAc = 30:1) to afford the yellow oil in 50% yield at 0.1 mmol scale.

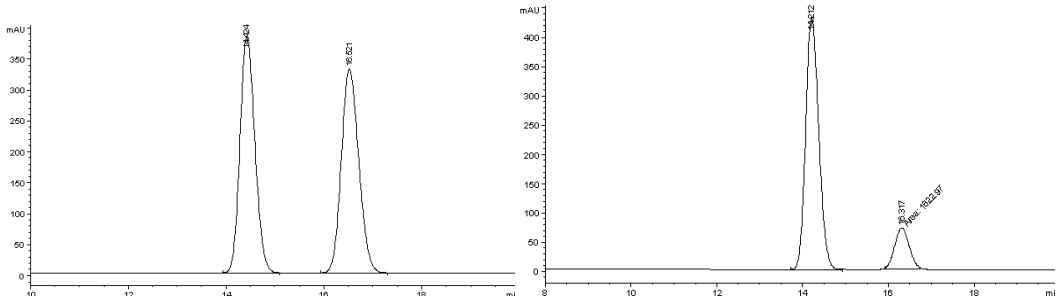
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.14 – 7.10 (m, 1H), 6.96 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.74 (d, *J* = 8.9 Hz, 2H), 6.61 (d, *J* = 8.9 Hz, 2H), 5.26 (s, 1H), 4.33 – 4.14 (m, 2H), 3.70 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.2, 153.0, 141.7, 140.1, 127.1, 125.6, 125.5, 115.3, 114.9, 62.1, 58.0, 55.7, 14.1 ppm.

HRMS (ESI) *m/z* calcd. for $C_{15}H_{18}NO_3S$ [M+H]$^+$: 292.1102; found 292.1104.

$[\alpha]_D^{20}$ = -5.0 (*c* 1.0, $CHCl_3$)

Enantiomeric excess was determined by chiral HPLC analysis using a Daicel Chiralpak IG column, *ee* = 70% (*n*-Hexane/ethanol = 70/30, flow rate 1 mL/min, λ = 210 nm, T = 20 °C, t_r (major) = 14.212 min, t_r (minor) = 16.317 min).



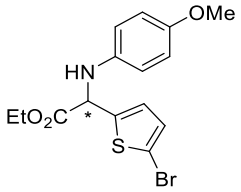
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.424	BB	0.3328	8146.77539	382.03665	49.9493
2	16.521	BB	0.3857	8163.31787	328.75235	50.0507
Totals :				1.63101e4	710.78900	

Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.212	BB	0.3319	9175.89355	431.81451	84.9709
2	16.317	MM	0.3880	1622.96667	69.70890	15.0291
Totals :				1.07989e4	501.52341	

ethyl 2-(5-bromothiophen-2-yl)-2-((4-methoxyphenyl)amino)acetate (4b)



The product was purified via flash column chromatography (*n*-Hexane/EtOAc = 30:1) to afford the yellow oil in 54% yield at 0.1 mmol scale.

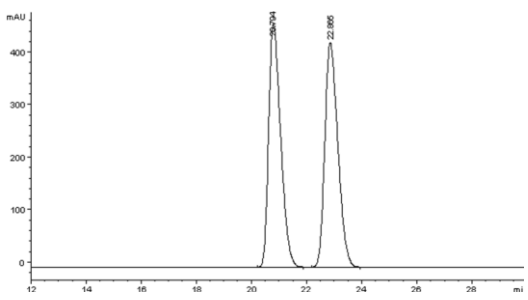
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.95 – 6.86 (m, 2H), 6.76 (d, *J* = 8.9 Hz, 2H), 6.61 (d, *J* = 8.9 Hz, 2H), 5.14 (s, 1H), 4.31 – 4.17 (m, 2H), 3.73 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H).

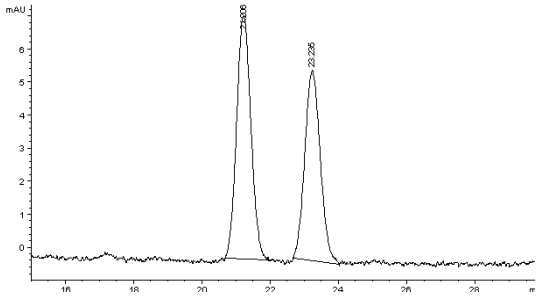
^{13}C NMR (101 MHz, $CDCl_3$): δ 170.5, 153.3, 143.6, 139.7, 130.1, 125.9, 115.4, 115.0, 112.3, 62.5, 58.3, 55.8, 14.2 ppm.

HRMS (ESI) *m/z* calcd. for $C_{15}H_{17}BrNO_3S$ $[M+H]^+$: 370.0107; found 370.0091.

$[\alpha]_D^{20}$ = -1.4 (*c* 1.0, $CHCl_3$)

Enantiomeric excess was determined by chiral HPLC analysis using a Daicel Chiralpak IG column, *ee* = 8% (*n*-Hexane/ethanol = 80/20, flow rate 0.8 mL/min, λ = 254 nm, T = 20 °C, t_r (major) = 21.206 min, t_r (minor) = 23.235 min).





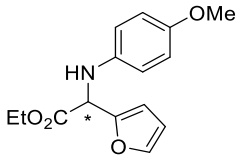
Signal 1: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.794	BB	0.4689	1.40475e4	464.44052	49.9638
2	22.865	BB	0.5100	1.40678e4	427.46362	50.0362
Totals :				2.81153e4	891.90414	

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.206	BB	0.3797	215.10541	7.34334	54.1332
2	23.235	BP	0.4084	182.25763	5.77218	45.8668
Totals :				397.36304	13.11553	

ethyl 2-(furan-2-yl)-2-((4-methoxyphenyl)amino)acetate (4c)



The product was purified via flash column chromatography (*n*-Hexane/EtOAc = 30:1) to afford the yellow oil in 69% yield at 0.1 mmol scale.

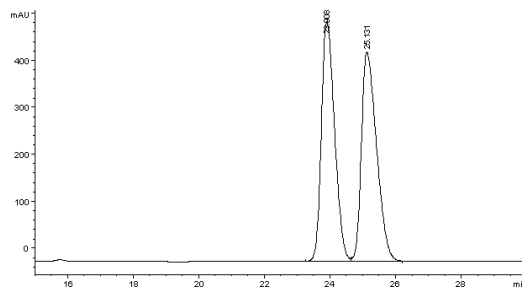
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (dd, *J* = 1.8, 0.9 Hz, 1H), 6.83 – 6.70 (m, 2H), 6.69 – 6.59 (m, 2H), 6.40 – 6.26 (m, 2H), 5.13 (s, 1H), 4.29 – 4.13 (m, 2H), 3.73 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 3H).

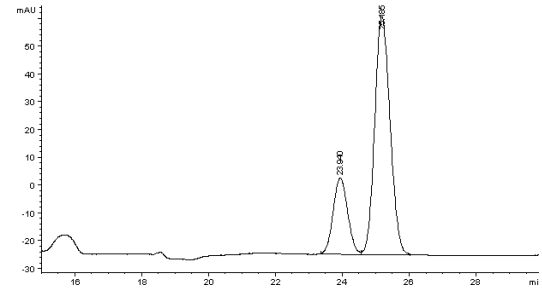
^{13}C NMR (101 MHz, $CDCl_3$): δ 170.3, 153.1, 150.5, 142.8, 140.0, 115.5, 114.9, 110.7, 108.2, 62.1, 56.4, 55.8, 14.2 ppm.

HRMS (ESI) *m/z* calcd. for $C_{15}H_{17}NNaO_4$ $[M+Na]^+$: 298.1050; found 298.1060.

$[\alpha]_D^{20}$ = -37.6 (*c* 1.0, $CHCl_3$)

Enantiomeric excess was determined by chiral HPLC analysis using a Daicel Chiralpak IF column, *ee* = 52% (*n*-Hexane/ethanol = 95/5, flow rate 0.7 mL/min, λ = 210 nm, T = 20 °C, t_r (major) = 25.185 min, t_r (minor) = 23.940 min).





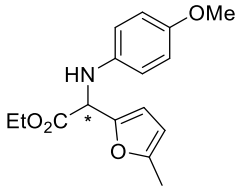
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.908	BV	0.4299	1.42669e4	510.73370	49.9575
2	25.131	VB	0.4947	1.42911e4	444.96167	50.0425
Totals :				2.85580e4	955.69537	

Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.940	BV	0.4519	826.51495	27.40252	23.2115
2	25.185	VB	0.4951	2734.28027	85.50409	76.7885
Totals :				3560.79523	112.90661	

ethyl 2-((4-methoxyphenyl)amino)-2-(5-methylfuran-2-yl)acetate (4d)



The product was purified via flash column chromatography (*n*-Hexane/EtOAc = 30:1) to afford the yellow oil in 52% yield at 0.1 mmol scale.

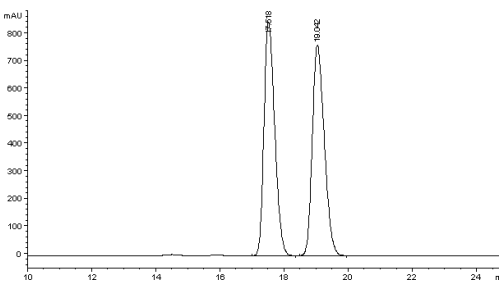
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.82 – 6.69 (m, 2H), 6.68 – 6.59 (m, 2H), 6.22 (d, *J* = 3.1 Hz, 1H), 5.91 (m, 1H), 5.06 (s, 1H), 4.34 – 4.06 (m, 2H), 3.72 (s, 3H), 2.27 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.6, 153.0, 152.6, 148.4, 140.2, 115.5, 114.9, 109.0, 106.6, 61.9, 56.5, 55.7, 14.2, 13.7 ppm.

HRMS (ESI) *m/z* calcd. for $C_{16}H_{20}NO_4$ $[M+H]^+$: 290.1387; found 290.1385.

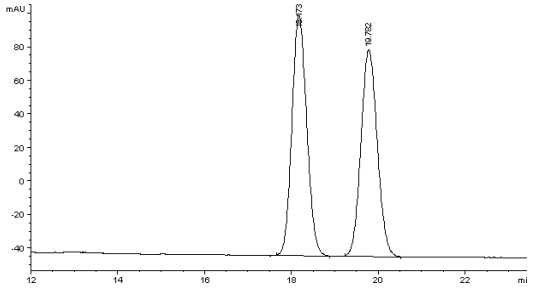
$[\alpha]_D^{20}$ = -1.8 (*c* 1.0, $CHCl_3$)

Enantiomeric excess was determined by chiral HPLC analysis using a Daicel Chiralpak IG column, *ee* = 3% (*n*-Hexane/ethanol = 80/20, flow rate 0.8 mL/min, λ = 210 nm, T = 20 °C, t_r (major) = 18.173 min, t_r (minor) = 19.782 min).



Signal 1: DAD1 C, Sig=210,8 Ref=360,100

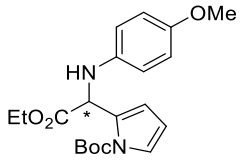
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.518	BB	0.3640	1.97711e4	847.97491	49.8930
2	19.042	BB	0.4035	1.98559e4	763.18927	50.1070
Totals :				3.96270e4	1611.16418	



Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.173	BB	0.3712	3404.46704	143.30035	51.4155
2	19.782	BB	0.4004	3217.01855	123.28986	48.5845
Totals :				6621.48560	266.59022	

tert-butyl-2-(2-ethoxy-1-((4-methoxyphenyl)amino)-2-oxoethyl)-1H-pyrrole-1-carboxylate (4e)



The product was purified via flash column chromatography (*n*-Hexane/EtOAc = 30:1) to afford the yellow oil in 60% yield at 0.1 mmol scale.

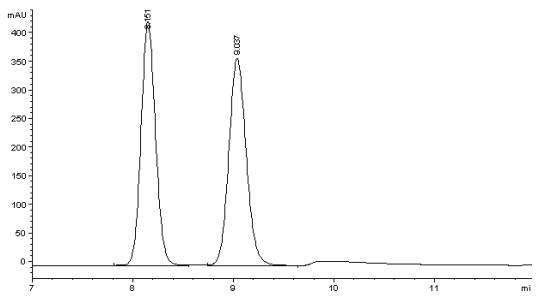
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 – 7.18 (m, 1H), 6.78 – 6.71 (m, 2H), 6.71 – 6.63 (m, 2H), 6.28 (dd, *J* = 3.5, 1.8 Hz, 1H), 6.09 (t, *J* = 3.4 Hz, 1H), 5.67 (s, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.72 (s, 3H), 1.58 (s, 9H), 1.26 – 1.17 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.4, 152.8, 149.4, 140.7, 131.1, 122.6, 115.7, 114.8, 114.2, 110.2, 84.3, 77.4, 61.7, 56.1, 55.7, 28.1, 14.3 ppm.

HRMS (ESI) *m/z* calcd. for $C_{20}H_{27}N_2O_5$ $[M+H]^+$: 375.1914; found 375.1903.

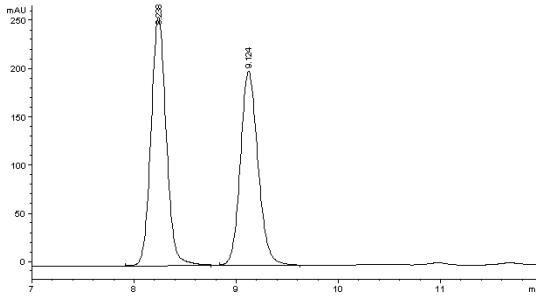
$[\alpha]_D^{20}$ = -11.6 (*c* 1.0, $CHCl_3$)

Enantiomeric excess was determined by chiral HPLC analysis using a Daicel Chiralpak IF column, *ee* = 5% (*n*-Hexane/ethanol = 80/20, flow rate 0.8 mL/min, λ = 210 nm, T = 20 °C, t_r (major) = 8.238 min, t_r (minor) = 9.124 min).



Signal 1: DAD1 C, Sig=210,8 Ref=360,100

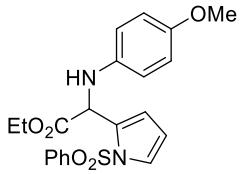
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.151	BB	0.1582	4329.51318	427.24313	49.7980
2	9.037	BB	0.1843	4364.64453	363.03137	50.2020
Totals :				8694.15771	790.27451	



Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.238	BB	0.1593	2682.54907	258.00803	52.6626
2	9.124	BB	0.1857	2411.28760	201.34644	47.3374
Totals :				5093.83667	459.35446	

ethyl 2-((4-methoxyphenyl)amino)-2-(1-(phenylsulfonyl)-1H-pyrrol-2-yl)acetate (4f)



The product was purified via flash column chromatography (*n*-Hexane/EtOAc = 20:1) to afford the yellow oil in 54% yield at 0.1 mmol scale.

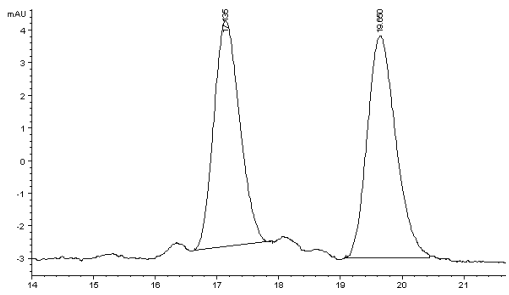
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (dd, *J* = 8.6, 1.3 Hz, 2H), 7.56 – 7.50 (m, 1H), 7.40 – 7.34 (m, 3H), 6.78 – 6.72 (m, 2H), 6.55 (d, *J* = 8.9 Hz, 2H), 6.29 – 6.24 (m, 2H), 5.71 (s, 1H), 4.14 (m, *J* = 7.1, 3.2 Hz, 2H), 3.75 (s, 3H), 1.19 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.6, 153.2, 140.1, 139.3, 133.8, 131.2, 129.1, 127.4, 124.4, 115.7, 114.8, 114.6, 111.6, 61.8, 55.8, 54.4, 14.2 ppm.

HRMS (ESI) *m/z* calcd. for $C_{21}H_{22}N_2NaO_5S$ $[M+Na]^+$: 437.1142; found 437.1132.

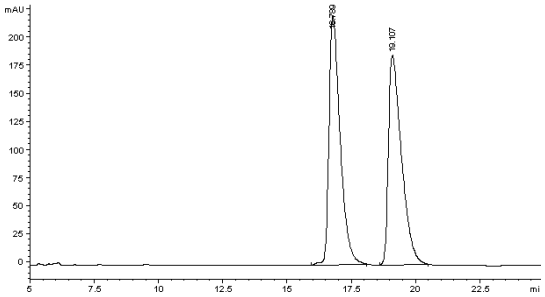
$[\alpha]_D^{20}$ = -2.2 (*c* 1.0, $CHCl_3$)

Enantiomeric excess was determined by chiral HPLC analysis using a Daicel Chiralpak IF column, *ee* = 0% (*n*-Hexane/ethanol = 90/10, flow rate 1 mL/min, λ = 254 nm, T = 20 °C, t_r (major) = 16.789 min, t_r (minor) = 19.107 min).



Signal 1: DAD1 B, Sig=254,16 Ref=360,100

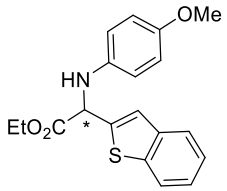
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.135	PP	0.3953	201.47104	6.92648	47.8159
2	19.650	BB	0.4524	219.87608	6.81508	52.1841
Totals :				421.34712	13.74156	



Signal 1: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.789	BB	0.4546	6693.90137	221.47264	50.3963
2	19.107	BB	0.5178	6588.61133	186.67503	49.6037
Totals :				1.32825e4	408.14767	

ethyl 2-(benzo[b]thiophen-2-yl)-2-((4-methoxyphenyl)amino)acetate (4g)



The product was purified via flash column chromatography (*n*-Hexane/EtOAc = 30:1) to afford the yellow oil in 15% yield at 0.1 mmol scale.

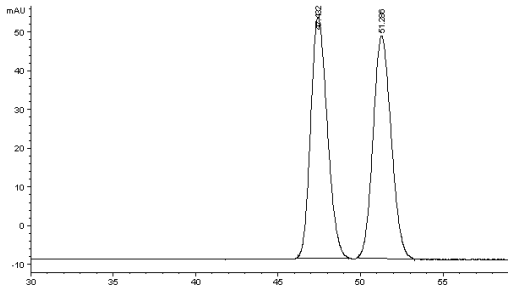
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 – 7.66 (m, 1H), 7.39 (d, *J* = 0.9 Hz, 1H), 7.31 (m, 1H), 6.77 – 6.71 (m, 2H), 6.69 – 6.62 (m, 2H), 5.32 (d, *J* = 1.0 Hz, 2H), 4.50 – 4.01 (m, 3H), 3.71 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.7, 153.1, 142.8, 139.8, 139.7, 124.5, 124.5, 123.7, 122.5, 122.5, 115.4, 115.0, 62.5, 58.6, 55.8, 14.2, 1.2 ppm.

HRMS (ESI) *m/z* calcd. for $C_{19}H_{20}NO_3S$ $[M+H]^+$: 342.1158; found 342.1154.

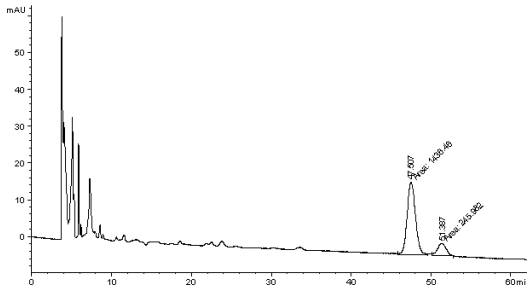
$[\alpha]_D^{20}$ = -3.4 (*c* 1.0, $CHCl_3$)

Enantiomeric excess was determined by chiral HPLC analysis using a Daicel Chiralpak IG column, *ee* = 71% (*n*-Hexane/ethanol = 80/20, flow rate 0.8 mL/min, λ = 210 nm, T = 20 °C, t_r (major) = 47.504 min, t_r (minor) = 51.387 min).



Signal 1: DAD1 C, Sig=210,8 Ref=360,100

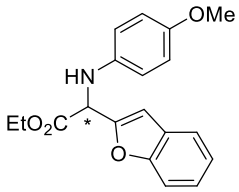
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	47.432	BB	0.9347	4354.21777	62.20268	49.9138
2	51.286	BB	0.9936	4369.25879	57.43264	50.0862
Totals :				8723.47656	119.63531	



Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	47.504	BB	0.8394	1332.29187	19.25233	85.6517
2	51.387	MM	1.1687	223.18504	3.18287	14.3483
Totals :				1555.47691	22.43520	

ethyl 2-((4-methoxyphenyl)amino)-2-(5-methylfuran-2-yl)acetate (4h)



The product was purified via flash column chromatography (*n*-Hexane/EtOAc = 30:1) to afford the yellow oil in 52% yield at 0.1 mmol scale.

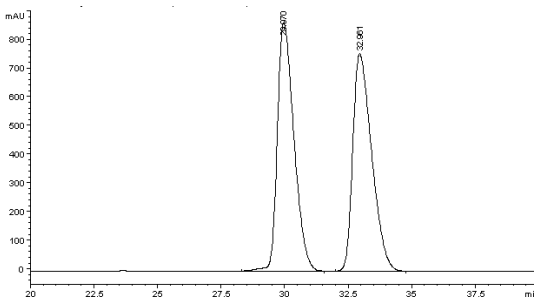
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (ddt, *J* = 17.3, 8.1, 0.8 Hz, 2H), 7.29 (dd, *J* = 7.2, 1.3 Hz, 1H), 7.21 (td, *J* = 7.5, 1.1 Hz, 1H), 6.78 – 6.73 (m, 3H), 6.68 (d, *J* = 9.0 Hz, 2H), 5.25 (s, 1H), 4.38 – 4.15 (m, 2H), 3.72 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H).

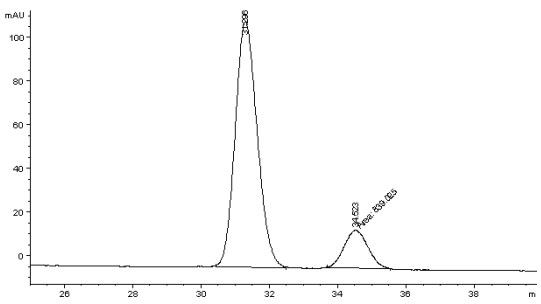
^{13}C NMR (101 MHz, $CDCl_3$): δ 169.8, 155.1, 153.3, 153.2, 139.5, 128.1, 124.6, 123.1, 121.3, 115.7, 114.9, 111.6, 105.3, 62.5, 56.9, 55.8, 29.8, 14.2 ppm.

HRMS (ESI) *m/z* calcd. for $C_{19}H_{19}NNaO_4$ $[M+Na]^+$: 348.1206; found 348.1198.

$[\alpha]_D^{20}$ = -15.6 (*c* 1.0, $CHCl_3$)

Enantiomeric excess was determined by chiral HPLC analysis using a Daicel Chiralpak IG column, *ee* = 71% (*n*-Hexane/ethanol = 80/20, flow rate 0.8 mL/min, λ = 210 nm, T = 20 °C, t_r (major) = 31.296 min, t_r (minor) = 34.523 min).





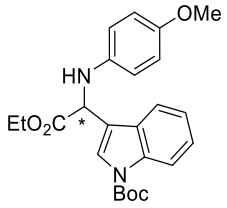
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.970	BB	0.6819	3.94948e4	866.26978	50.1949
2	32.961	BB	0.7630	3.91881e4	758.21582	49.8051
Totals :				7.86828e4	1624.48560	

Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	31.296	BB	0.6751	5048.79150	112.16405	85.7498
2	34.523	MM	0.8126	839.02521	17.20786	14.2502
Totals :				5887.81671	129.37192	

tert-butyl 3-(2-ethoxy-1-((4-methoxyphenyl)amino)-2-oxoethyl)-1H-indole-1-carboxylate (4i)



The product was purified via flash column chromatography (*n*-Hexane/EtOAc = 20:1) to afford the yellow oil in 80% yield at 0.1 mmol scale.

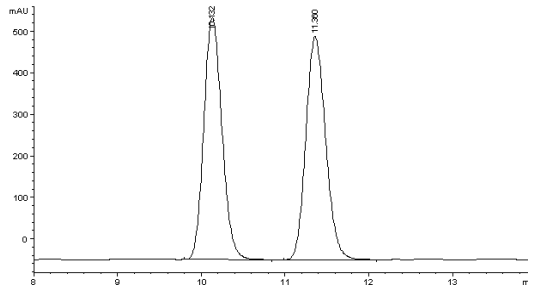
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, *J* = 8.3 Hz, 1H), 7.77 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.64 (s, 1H), 7.36 – 7.31 (m, 1H), 7.29 – 7.26 (m, 1H), 6.78 – 6.71 (m, 2H), 6.66 – 6.59 (m, 2H), 5.26 (s, 1H), 4.20 (ddq, *J* = 43.9, 10.7, 7.1 Hz, 2H), 3.72 (s, 3H), 1.65 (s, 9H), 1.21 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.1, 152.8, 140.6, 136.4, 132.9, 128.7, 128.1, 126.8, 125.5, 121.5, 115.2, 115.0, 114.5, 61.9, 60.0, 55.9, 55.6, 29.8, 14.3 ppm.

HRMS (ESI) *m/z* calcd. for $C_{24}H_{28}N_2O_5$ $[M+H]^+$: 425.2071; found 425.2056.

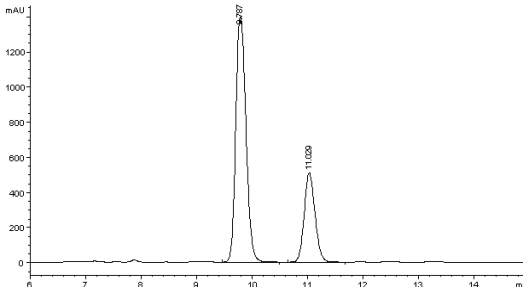
$[\alpha]_D^{20}$ = -17.2 (*c* 1.0, $CHCl_3$)

Enantiomeric excess was determined by chiral HPLC analysis using a Daicel Chiralpak IB column, *ee* = 44% (*n*-Hexane/ethanol = 95/5, flow rate 1 mL/min, λ = 210 nm, T = 20 °C, t_r (major) = 9.787 min, t_r (minor) = 11.029 min).



Signal 1: DAD1 C, Sig=210,8 Ref=360,100

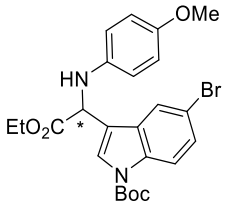
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.132	BP	0.2355	8782.79883	583.92041	49.8275
2	11.360	BB	0.2558	8843.60742	537.94012	50.1725
Totals :				1.76264e4	1121.86053	



Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.787	PB	0.2032	1.78714e4	1396.99585	71.9779
2	11.029	BB	0.2092	6957.57959	510.01678	28.0221
Totals :				2.48289e4	1907.01263	

tert-butyl-5-bromo-3-(2-ethoxy-1-((4-methoxyphenyl)amino)-2-oxoethyl)-1H-indole-1-carboxylate (4j)



The product was purified via flash column chromatography (*n*-Hexane/EtOAc = 20:1) to afford the white solid in 55% yield at 0.1 mmol scale.

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.07 (d, *J* = 2.0 Hz, 1H), 7.99 (d, *J* = 8.8 Hz, 1H), 7.89 (s, 1H), 7.50 (dd, *J* = 8.9, 2.0 Hz, 1H), 6.72 (s, 3H), 6.06 (d, *J* = 8.9 Hz, 1H), 5.54 – 5.46 (m, 1H), 4.20 – 4.02 (m, 2H), 3.34 (s, 3H), 1.63 (s, 9H), 1.12 (t, *J* = 7.1 Hz, 3H).

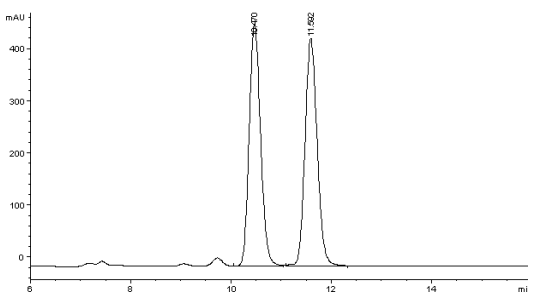
^{13}C NMR (101 MHz, DMSO-d_6): δ 172.1, 152.0, 149.1, 141.6, 134.1, 130.8, 127.7, 126.4, 123.4, 117.4, 117.1, 115.8, 114.9, 114.8, 85.1, 61.5, 55.7, 53.7, 28.1, 14.5 ppm.

HRMS (ESI) *m/z* calcd. for $C_{24}H_{28}BrN_2O_5$ $[M+H]^+$: 503.1176; found 503.1155.

MP:102.5-104.6 °C

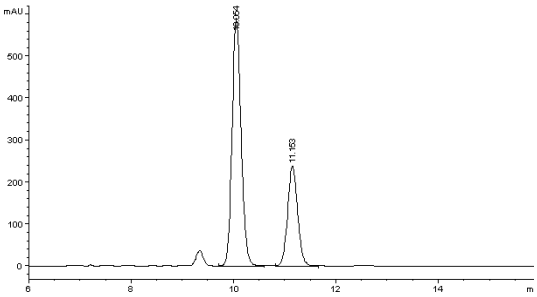
$[\alpha]_D^{20}$ = -6.8 (*c* 1.0, $CHCl_3$)

Enantiomeric excess was determined by chiral HPLC analysis using a Daicel Chiralpak IB column, *ee* = 38% (*n*-Hexane/ethanol = 95/5, flow rate 0.8 mL/min, λ = 230 nm, T = 20 °C, t_r (major) = 10.045 min, t_r (minor) = 11.153 min).



Signal 1: DAD1 D, Sig=230,16 Ref=360,100

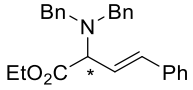
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.470	VB	0.2431	7286.79639	464.40128	49.8180
2	11.592	BB	0.2623	7340.03271	436.33588	50.1820
Totals :				1.46268e4	900.73715	



Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.054	BB	0.1901	7300.15283	590.95898	69.1579
2	11.153	BB	0.2117	3255.62134	237.85124	30.8421
Totals :				1.05558e4	828.81023	

ethyl (*E*)-2-(dibenzylamino)-4-phenylbut-3-enoate (4k)



The product was purified via flash column chromatography (*n*-Hexane/EtOAc = 30:1) to afford the colorless oil in 65% yield at 0.1 mmol scale.

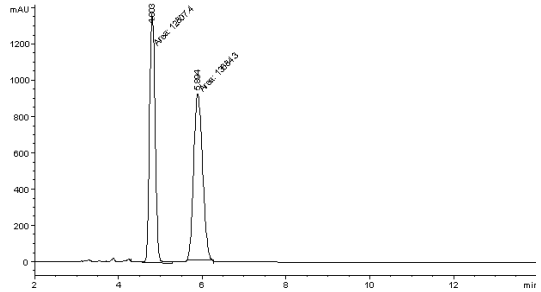
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 – 7.39 (m, 4H), 7.42 – 7.34 (m, 2H), 7.31 (td, *J* = 7.4, 3.1 Hz, 6H), 7.23 (ddd, *J* = 7.4, 5.6, 1.4 Hz, 3H), 6.57 (dd, *J* = 16.1, 1.2 Hz, 1H), 6.37 (dd, *J* = 16.1, 7.0 Hz, 1H), 4.33 – 4.17 (m, 2H), 4.10 (dd, *J* = 7.1, 1.3 Hz, 1H), 3.90 – 3.69 (m, 4H), 1.33 (t, *J* = 7.1 Hz, 3H).

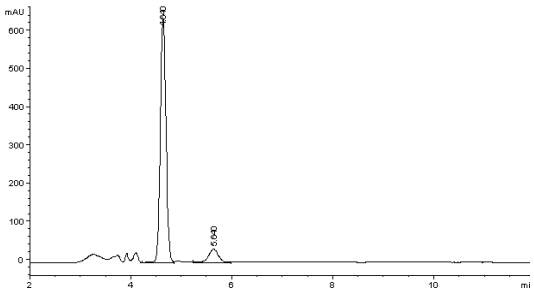
^{13}C NMR (101 MHz, $CDCl_3$): δ 172.1, 139.7, 136.7, 134.3, 128.8, 128.7, 128.4, 128.0, 127.1, 126.7, 124.6, 64.0, 60.8, 54.8, 14.6 ppm.

HRMS (ESI) *m/z* calcd. for $C_{26}H_{28}NO_2$ $[M+H]^+$: 386.2115; found 386.2129.

$[\alpha]_D^{20}$ = -68.6 (*c* 1.0, $CHCl_3$)

Enantiomeric excess was determined by chiral HPLC analysis using a Daicel Chiralpak IG column, *ee* = 82% (*n*-Hexane/ethanol = 70/30, flow rate 1 mL/min, λ = 210 nm, T = 20 °C, t_r (major) = 4.640 min, t_r (minor) = 5.640 min).





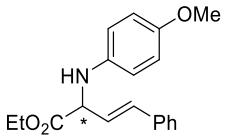
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.803	MM	0.1571	1.28074e4	1359.03162	48.3449
2	5.894	MM	0.2484	1.36843e4	918.00415	51.6551
Totals :				2.64917e4	2277.03577	

Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.640	VV	0.1230	4993.89014	639.90143	90.9349
2	5.640	BV	0.2119	497.82816	35.43938	9.0651
Totals :				5491.71829	675.34081	

ethyl (*E*)-2-((4-methoxyphenyl)amino)-4-phenylbut-3-enoate (4l)



The product was purified via flash column chromatography (*n*-Hexane/EtOAc = 30:1) to afford the yellow oil in 60% yield at 0.1 mmol scale.

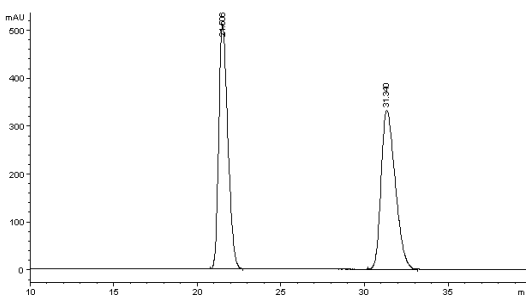
^{1}H NMR (400 MHz, $CDCl_3$): 7.40 – 7.35 (m, 2H), 7.34 – 7.28 (m, 2H), 6.82 – 6.74 (m, 3H), 6.64 (d, *J* = 8.9 Hz, 2H), 6.29 (dd, *J* = 15.9, 5.9 Hz, 1H), 4.65 (dd, *J* = 5.9, 1.5 Hz, 1H), 4.24 (p, *J* = 7.2 Hz, 2H), 3.73 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H).

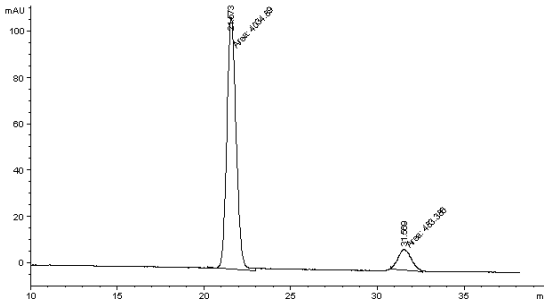
^{13}C NMR (101 MHz, $CDCl_3$): δ 172.1, 152.8, 140.6, 136.4, 132.9, 128.7, 128.1, 126.8, 125.5, 115.2, 115.0, 61.9, 60.0, 55.9, 14.3 ppm.

HRMS (ESI) *m/z* calcd. for $C_{19}H_{22}NO_3$ $[M+H]^+$: 312.1594; found 312.1604.

$[\alpha]_D^{20}$ = -14.8 (*c* 1.0, $CHCl_3$)

Enantiomeric excess was determined by chiral HPLC analysis using a Daicel Chiralpak IG column, *ee* = 80% (*n*-Hexane/ethanol = 70/30, flow rate 1 mL/min, λ = 210 nm, T = 20 °C, t_r (major) = 21.573 min, t_r (minor) = 31.569 min).





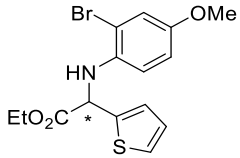
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.506	BB	0.5765	1.92909e4	510.94183	49.7503
2	31.340	BB	0.8778	1.94845e4	332.41995	50.2497
Totals :				3.87754e4	843.36179	

Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.573	MM	0.6197	4034.88989	108.51465	89.3015
2	31.569	MM	0.9030	483.38638	8.92198	10.6985
Totals :				4518.27628	117.43663	

ethyl 2-((2-bromo-4-methoxyphenyl)amino)-2-(thiophen-2-yl)acetate (4m)



The product was purified via flash column chromatography (*n*-Hexane/EtOAc = 30:1) to afford the yellow oil in 82% yield at 0.1 mmol scale.

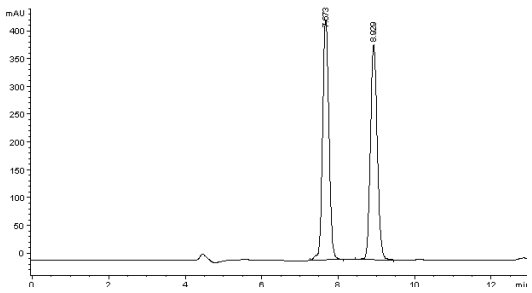
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.14 (dt, *J* = 3.5, 0.9 Hz, 1H), 7.07 (d, *J* = 2.8 Hz, 1H), 6.97 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.69 (dd, *J* = 8.9, 2.8 Hz, 1H), 6.49 (d, *J* = 8.9 Hz, 1H), 5.28 (s, 1H), 4.33 – 4.14 (m, 2H), 3.69 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.5, 152.5, 141.1, 137.4, 127.2, 125.8, 125.7, 118.5, 114.4, 113.4, 110.9, 62.3, 57.7, 55.9, 14.1 ppm.

HRMS (ESI) *m/z* calcd. for $C_{15}H_{16}BrNNaO_3S$ $[M+Na]^+$: 391.9926; found 391.9910.

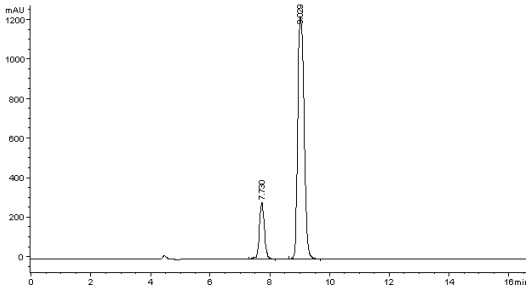
$[\alpha]_D^{20}$ = -4.8 (*c* 1.0, $CHCl_3$)

Enantiomeric excess was determined by chiral HPLC analysis using a Daicel Chiralpak IB column, *ee* = 69% (*n*-Hexane/ethanol = 95/5, flow rate 0.8 mL/min, λ = 210 nm, T = 20 °C, t_r (major) = 9.029 min, t_r (minor) = 7.730 min).



Signal 1: DAD1 B, Sig=254,16 Ref=360,100

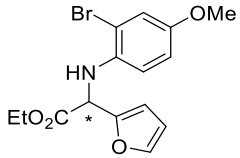
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.673	BB	0.1794	4945.45801	432.41245	50.8829
2	8.929	BB	0.1918	4773.83203	387.19693	49.1171
Totals :				9719.29004	819.60937	



Signal 1: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.730	BB	0.1794	3296.43848	284.09952	15.4313
2	9.029	VB	0.2381	1.80656e4	1224.75684	84.5687
Totals :				2.13621e4	1508.85635	

ethyl 2-((2-bromo-4-methoxyphenyl)amino)-2-(furan-2-yl)acetate (4n)



The product was purified via flash column chromatography (*n*-Hexane/EtOAc = 30:1) to afford the colorless oil in 82% yield at 0.1 mmol scale.

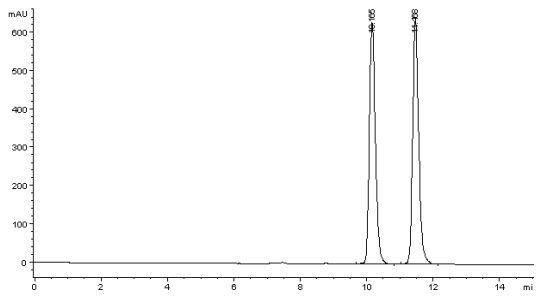
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (dd, *J* = 1.8, 0.9 Hz, 1H), 7.07 (d, *J* = 2.8 Hz, 1H), 6.73 (dd, *J* = 8.9, 2.8 Hz, 1H), 6.52 (d, *J* = 8.9 Hz, 1H), 6.40 – 6.30 (m, 2H), 5.16 (s, 1H), 4.32 – 4.18 (m, 2H), 3.71 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 169.7, 152.6, 150.0, 142.9, 137.4, 118.5, 114.4, 113.4, 111.0, 110.8, 108.3, 62.3, 56.1, 56.0, 14.2 ppm.

HRMS (ESI) *m/z* calcd. for $C_{15}H_{16}BrNNaO_4$ $[M+Na]^+$: 376.0155; found 376.0147.

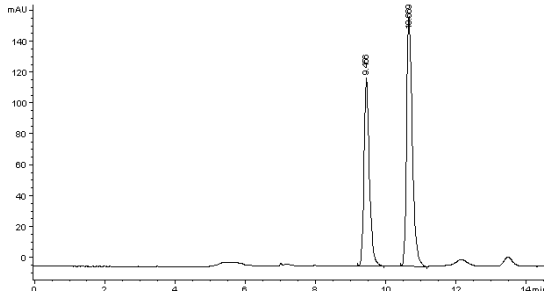
$[\alpha]_D^{20}$ = -8.0 (*c* 1.0, $CHCl_3$)

Enantiomeric excess was determined by chiral HPLC analysis using a Daicel Chiralpak AS-H column, *ee* = 17% (*n*-Hexane/ethanol = 90/10, flow rate 0.7 mL/min, λ = 210 nm, T = 20 °C, t_r (major) = 10.669 min, t_r (minor) = 9.456 min).



Signal 1: DAD1 B, Sig=254,16 Ref=360,100

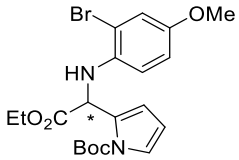
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.165	BP	0.1991	8068.90088	631.33661	50.1051
2	11.468	BB	0.1953	8035.04150	636.25348	49.8949
Totals :				1.61039e4	1267.59009	



Signal 1: DAD1 E, Sig=280,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.456	BB	0.1610	1307.00891	122.00075	41.5278
2	10.669	BP	0.1725	1840.30249	162.04771	58.4722
Totals :				3147.31140	284.04846	

tert-butyl-2-(1-((2-bromo-4-methoxyphenyl)amino)-2-ethoxy-2-oxoethyl)-1H-pyrrole-1-carboxylate (4o)



The product was purified via flash column chromatography (*n*-Hexane/EtOAc = 30:1) to afford the yellow oil in 54% yield at 0.1 mmol scale.

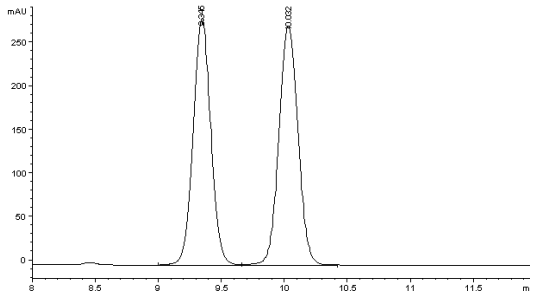
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (dd, *J* = 3.3, 1.8 Hz, 1H), 7.03 (d, *J* = 2.8 Hz, 1H), 6.74 (dd, *J* = 8.9, 2.7 Hz, 1H), 6.64 (d, *J* = 8.9 Hz, 1H), 6.28 (dd, *J* = 3.4, 1.8 Hz, 1H), 6.09 (t, *J* = 3.4 Hz, 1H), 5.71 (s, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.70 (s, 3H), 1.59 (s, 9H), 1.23 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.8, 152.3, 149.4, 138.1, 130.6, 122.7, 118.3, 117.6, 116.8, 115.2, 114.5, 114.4, 113.8, 110.9, 110.3, 84.5, 61.8, 56.0, 55.8, 28.1, 14.3 ppm.

HRMS (ESI) *m/z* calcd. for $C_{20}H_{25}BrN_2O_5$ $[M+H]^+$: 453.1009; found 453.1020.

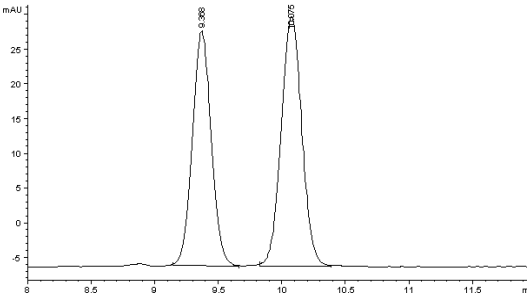
$[\alpha]_D^{20}$ = -4.0 (*c* 1.0, $CHCl_3$)

Enantiomeric excess was determined by chiral HPLC analysis using a Daicel Chiralpak IF column, *ee* = 7% (*n*-Hexane/ethanol = 95/5, flow rate 0.8 mL/min, λ = 254 nm, T = 20 °C, t_r (major) = 9.368 min, t_r (minor) = 10.075 min).



Signal 1: DAD1 B, Sig=254,16 Ref=360,100

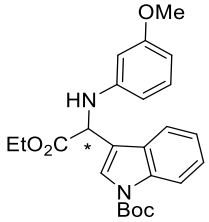
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.345	BV	0.1525	2782.70239	283.44800	49.1704
2	10.032	VB	0.1622	2876.59644	274.65588	50.8296
Totals :				5659.29883	558.10388	



Signal 1: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.368	BB	0.1613	351.36743	33.80398	46.5055
2	10.075	BB	0.1752	404.17285	35.94156	53.4945
Totals :				755.54028	69.74553	

tert-butyl 3-(2-ethoxy-1-((3-methoxyphenyl)amino)-2-oxoethyl)-1H-indole-1-carboxylate (4p)



The product was purified via flash column chromatography (*n*-Hexane/EtOAc = 30:1) to afford the yellow oil in 6% yield at 0.1 mmol scale.

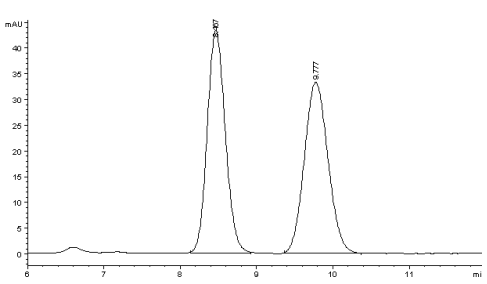
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, *J* = 8.2 Hz, 1H), 7.76 (d, *J* = 7.8 Hz, 1H), 7.34 (t, *J* = 7.8 Hz, 1H), 7.31 – 7.23 (m, 3H), 7.06 (t, *J* = 7.8 Hz, 1H), 6.29 (dd, *J* = 17.9, 8.2 Hz, 3H), 6.21 (s, 1H), 5.31 (s, 1H), 4.34 – 4.09 (m, 2H), 3.73 (d, *J* = 2.3 Hz, 3H), 1.65 (s, 9H), 1.24 – 1.20 (t, *J* = 7.1 Hz, 3H).

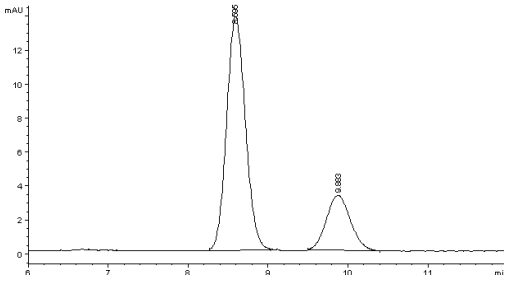
^{13}C NMR (101 MHz, $CDCl_3$): δ 171.8, 160.8, 149.6, 147.8, 130.2, 128.6, 124.9, 124.5, 122.9, 119.9, 117.4, 115.5, 106.5, 103.8, 99.7, 84.2, 77.4, 62.1, 55.2, 54.1, 29.9, 28.3, 22.9, 14.2 ppm.

HRMS (ESI) *m/z* calcd. for $C_{24}H_{28}N_2O_5$ $[M+H]^+$: 425.2071; found 425.2051.

$[\alpha]_D^{20}$ = -5.0 (*c* 1.0, $CHCl_3$)

Enantiomeric excess was determined by chiral HPLC analysis using a Daicel Chiralpak IG column, *ee* = 54% (*n*-Hexane/ethanol = 70/30, flow rate 1 mL/min, λ = 280 nm, T = 20 °C, t_r (major) = 8.595 min, t_r (minor) = 9.883 min).





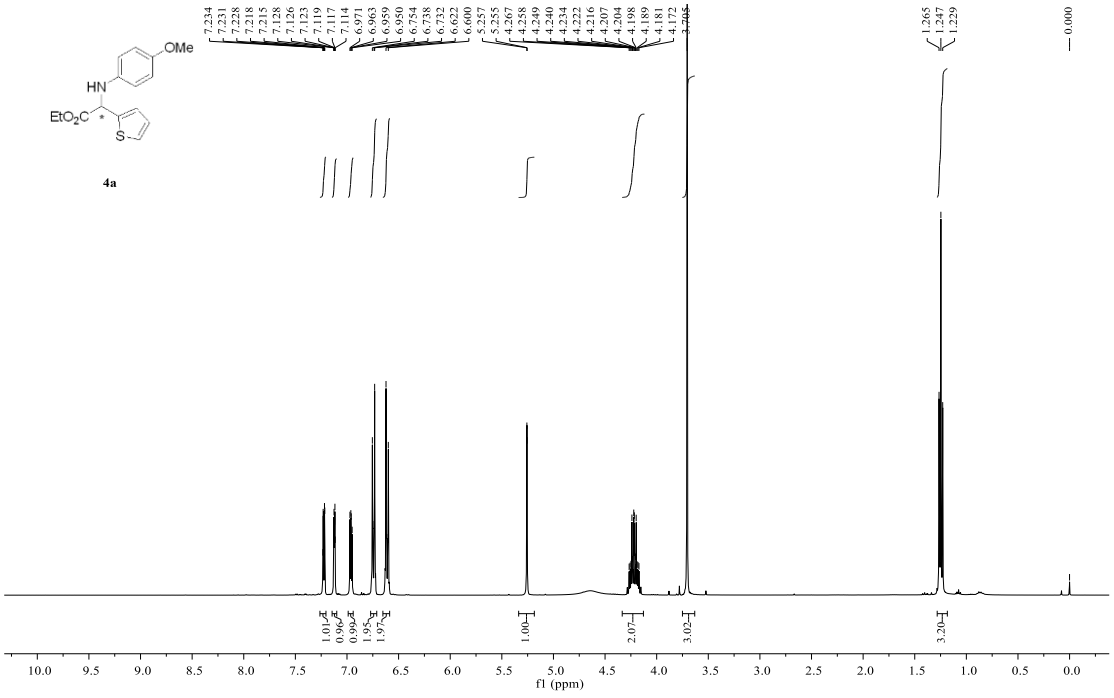
Signal 1: DAD1 E, Sig=280,16 Ref=360,100

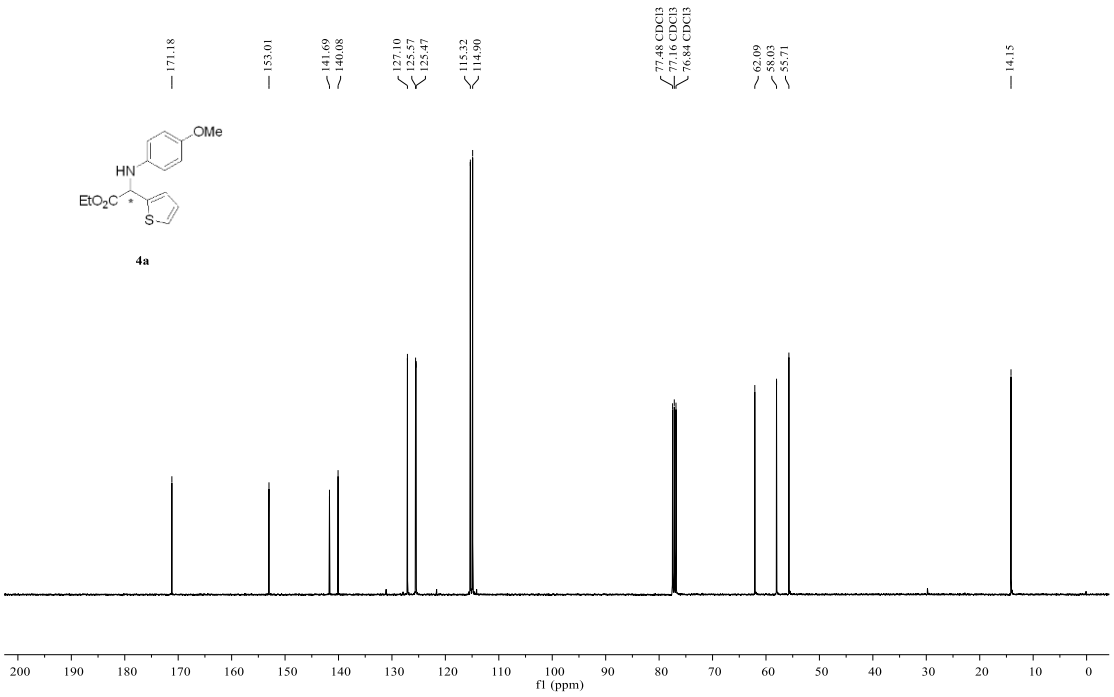
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.467	BB	0.2539	711.44336	43.24487	49.7653
2	9.777	BB	0.3356	718.15356	33.29865	50.2347
Totals :				1429.59692	76.54351	

Signal 1: DAD1 A, Sig=280,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.595	BB	0.2547	224.67871	13.74438	76.8035
2	9.883	PB	0.2753	67.85826	3.22796	23.1965
Totals :				292.53697	16.97235	

6. NMR Spectral for Characterization

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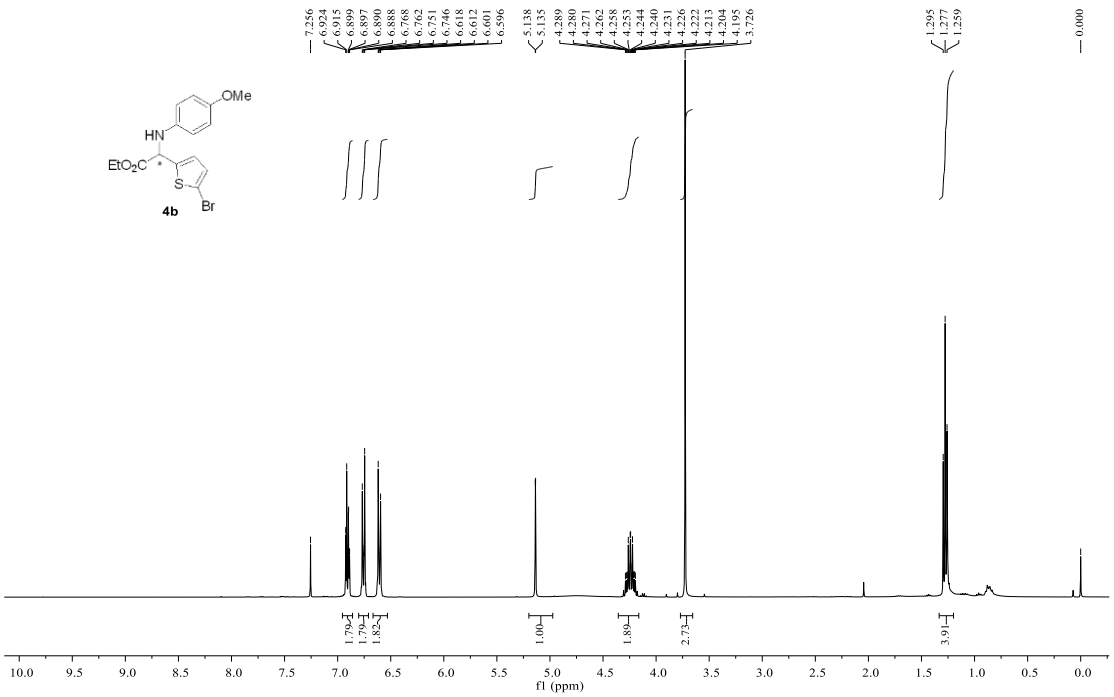
153.01
141.69
140.08
127.10
125.57
125.47
115.32
114.90
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
62.09
58.03
55.71
14.15
OMe
HN
EtO2C
S
4a
f1 (ppm)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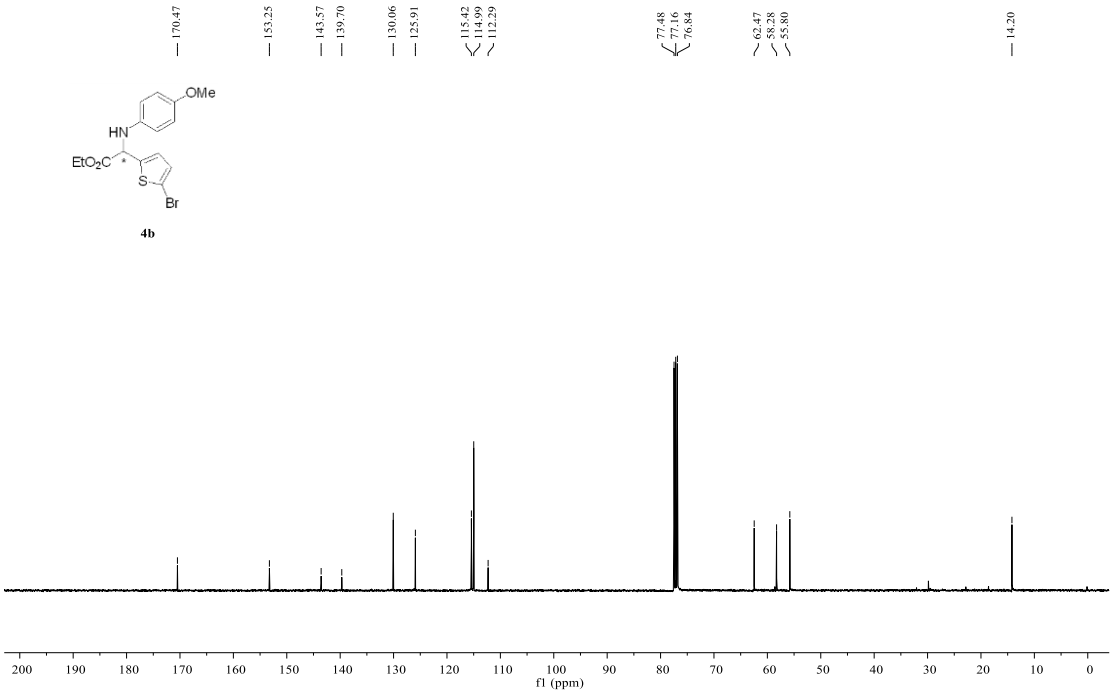
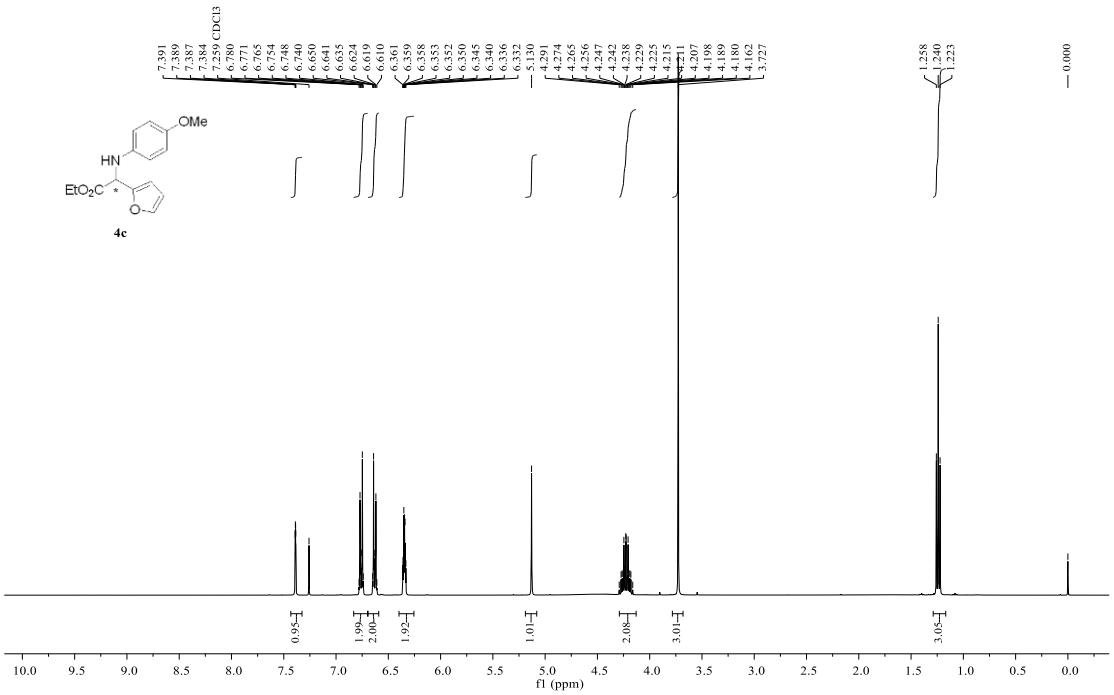
6.915
6.899
6.897
6.890
6.888
6.768
6.762
6.751
6.746
6.618
6.612
6.601
6.596
5.138
5.135
4.289
4.280
4.271
4.262
4.258
4.253
4.244
4.240
4.231
4.226
4.222
4.213
4.204
4.195
3.726
1.295
1.277
1.259
0.000
OMe
HN
EtO2C
S
Br
4b
1.79
1.79
1.82
1.00
1.89
2.73
3.91
f1 (ppm)


170.47
153.25
143.57
139.70
130.06
125.91
115.42
114.99
112.29
77.48
77.16
76.84
62.47
58.28
55.80
14.20
OMe
HN
EtO2C
S
Br
4b
f1 (ppm)


7.391
7.389
7.387
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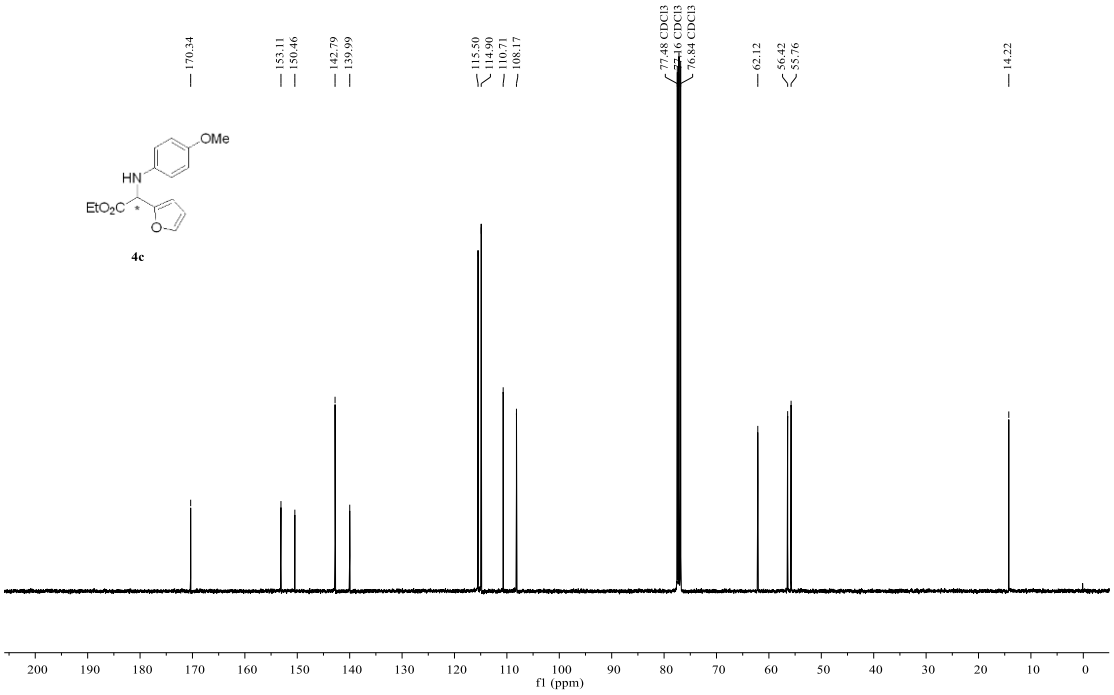
6.771
6.765
6.754
6.748
6.740
6.650
6.641
6.635
6.624
6.619
6.610
6.361
6.359
6.358
6.353
6.352
6.350
6.345
6.340
6.336
6.332
5.130
4.291
4.274
4.265
4.256
4.247
4.242
4.238
4.229
4.225
4.215
4.211
4.207
4.198
4.189
4.180
4.162
3.727
1.258
1.240
1.223
0.000
OMe
HN
EtO2C
O
4c
0.95
1.99
2.00
1.92
1.01
2.08
3.01
3.05
f1 (ppm)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139.99
115.50
114.90
110.71
108.17
77.48 CDCl3
77.16 CDCl3
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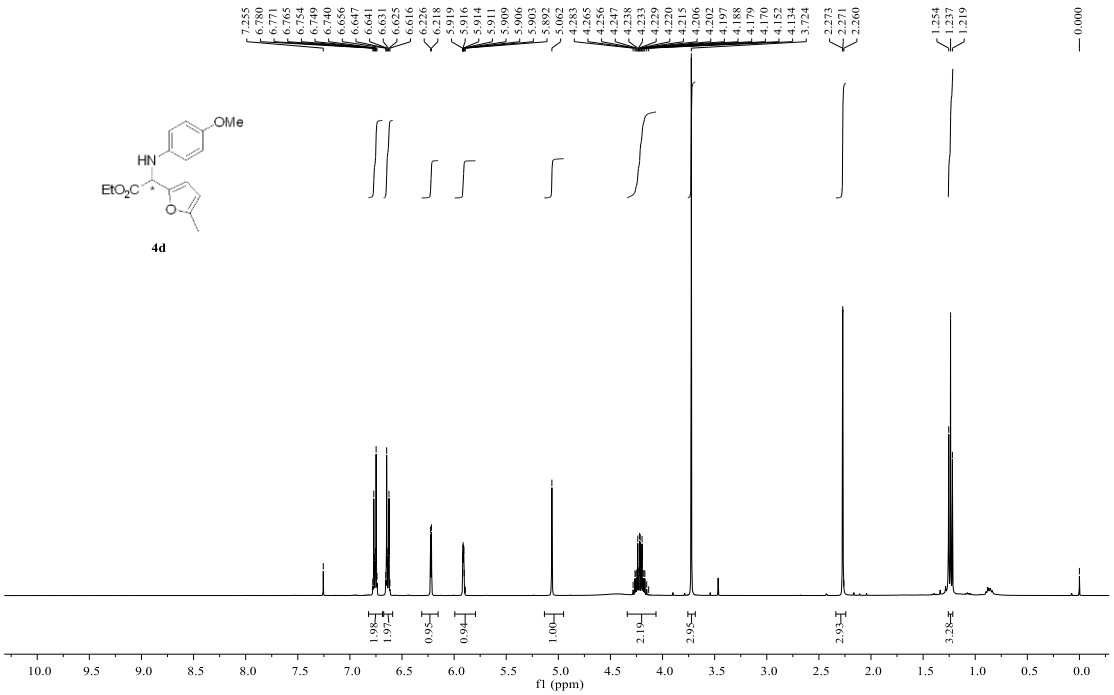
62.12
56.42
55.76
14.22
OMe
HN
EtO2C
O
4c
f1 (ppm)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6.740
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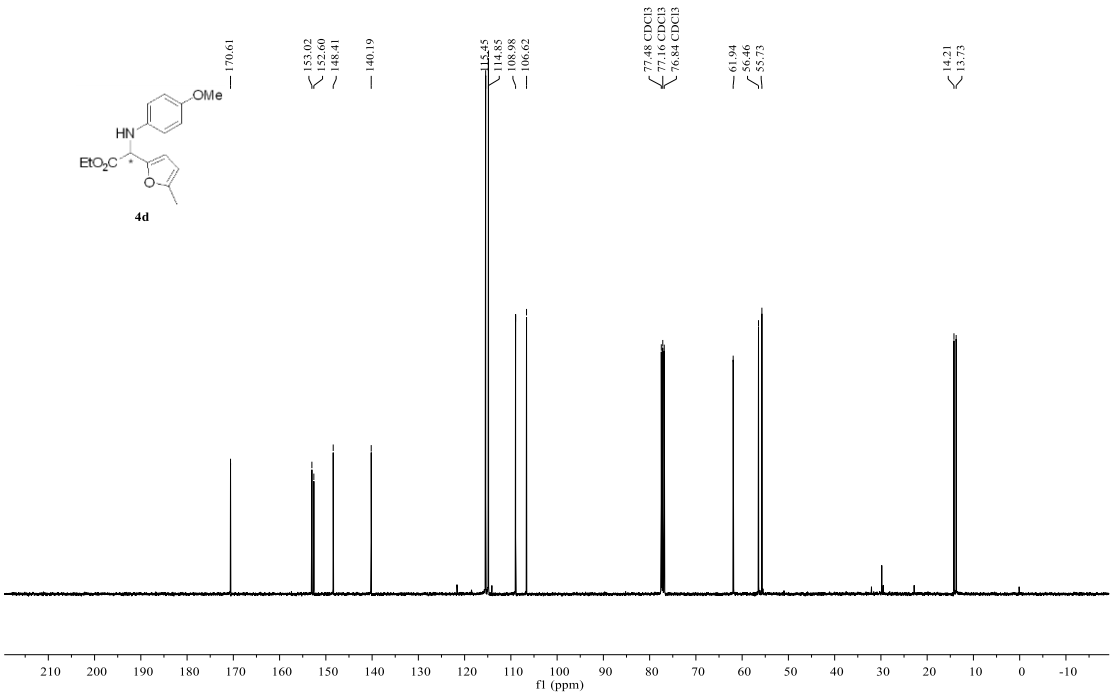
6.631
6.625
6.616
6.226
6.218
5.919
5.916
5.914
5.911
5.909
5.906
5.903
5.892
5.062
4.283
4.265
4.256
4.247
4.238
4.233
4.229
4.220
4.215
4.206
4.202
4.197
4.188
4.179
4.170
4.152
4.134
3.724
2.273
2.271
2.260
1.254
1.237
1.219
0.000
OMe
HN
EtO2C
O
4d
1.98
1.97
0.95
0.94
1.00
2.19
2.95
2.93
3.28
f1 (ppm)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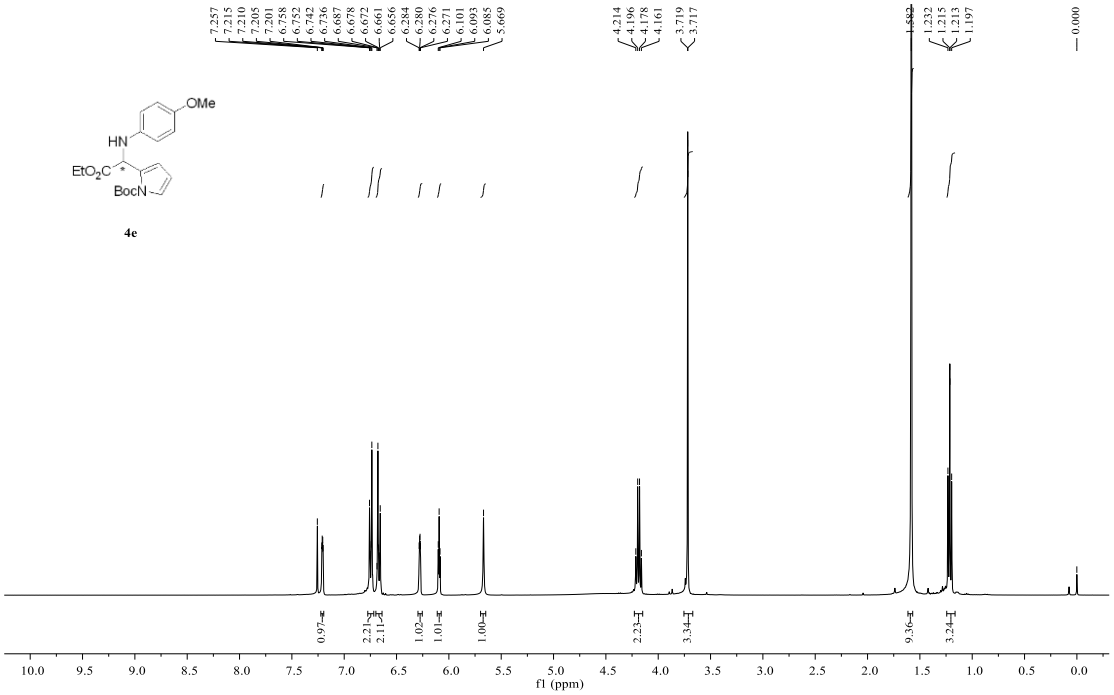
153.02
152.60
148.41
140.19
115.45
114.85
108.98
106.62
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
61.94
56.46
55.73
14.21
13.73
OMe
HN
EtO2C
O
4d
f1 (ppm)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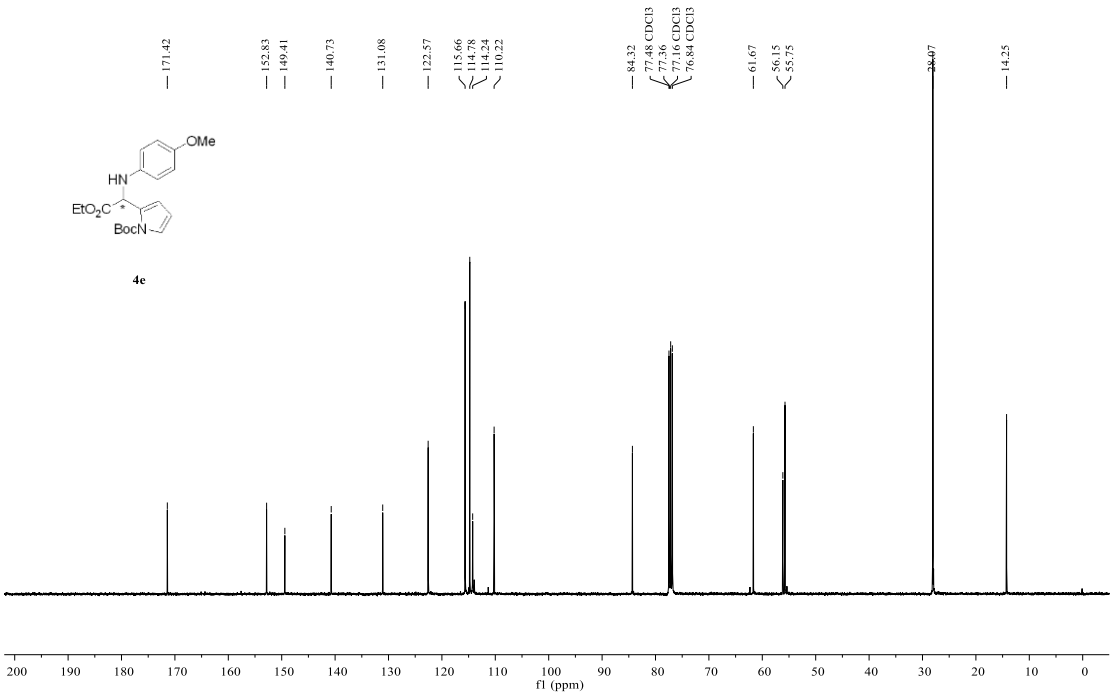
7.210
7.205
7.201
6.758
6.752
6.742
6.736
6.687
6.678
6.672
6.661
6.656
6.284
6.280
6.276
6.271
6.101
6.093
6.085
5.669
4.214
4.196
4.178
4.161
3.719
3.717
1.582
1.232
1.215
1.213
1.197
0.000
OMe
HN
EtO2C
BocN
4e
0.97
2.21
2.11
1.02
1.01
1.00
2.23
3.34
9.36
3.24
f1 (ppm)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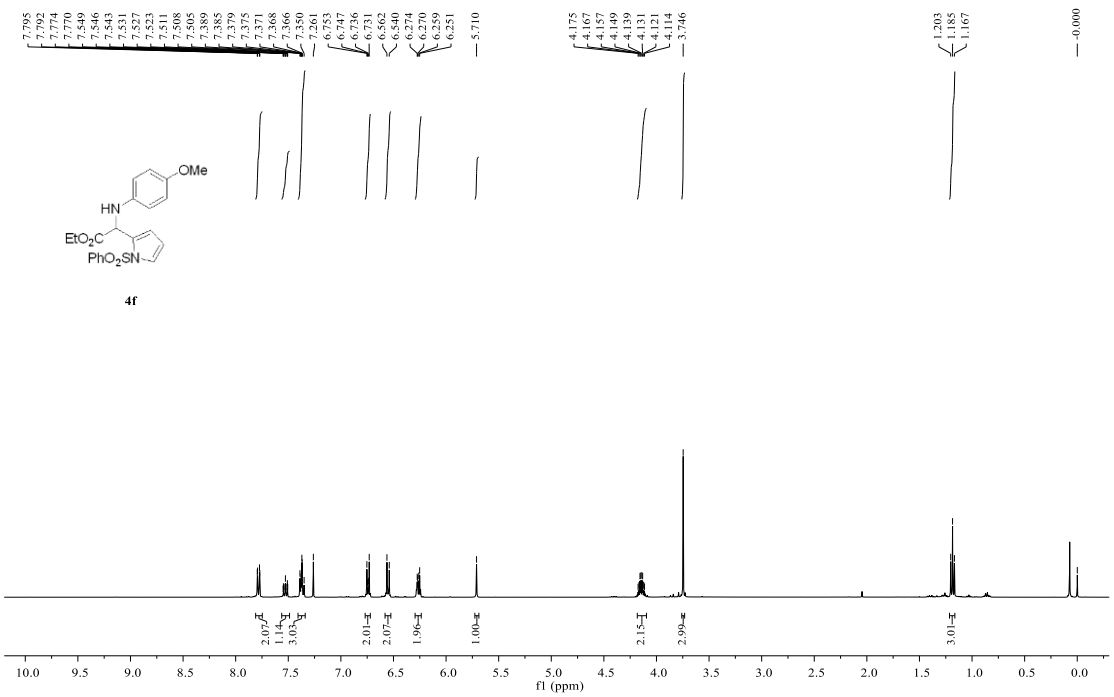
149.41
140.73
131.08
122.57
115.66
114.78
114.24
110.22
84.32
77.48 CDCl3
77.36
77.16 CDCl3
76.84 CDCl3
61.67
56.15
55.75
28.07
14.25
OMe
HN
EtO2C
BocN
4e
f1 (ppm)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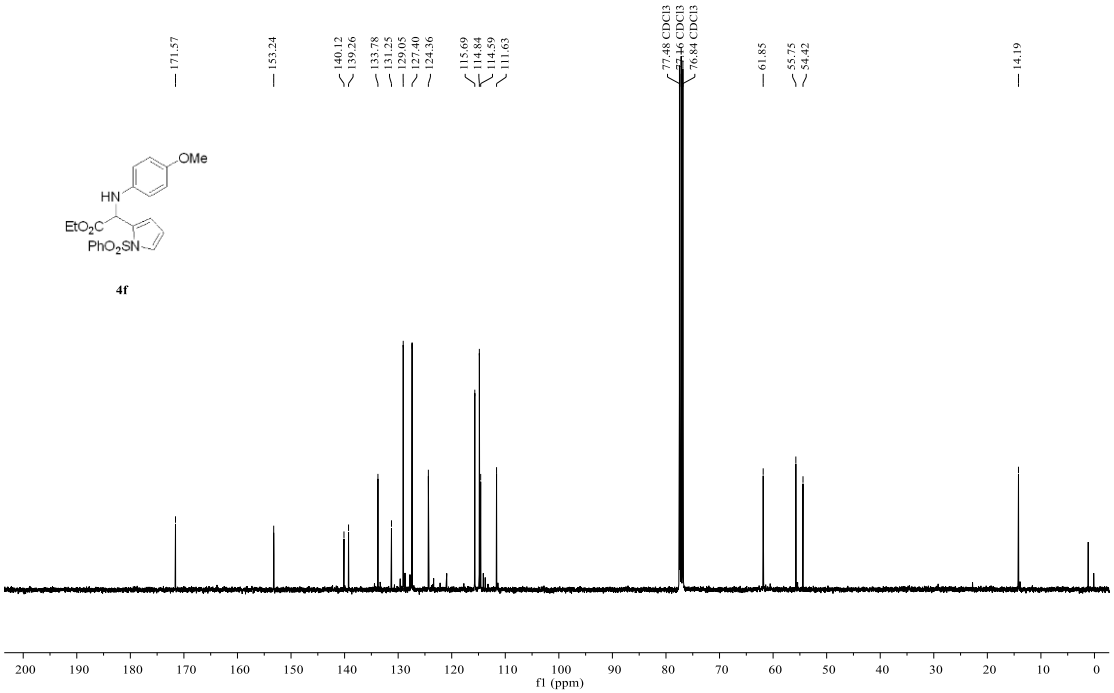
7.531
7.527
7.523
7.511
7.508
7.505
7.389
7.385
7.379
7.375
7.371
7.368
7.366
7.350
7.261
6.753
6.747
6.736
6.731
6.562
6.540
6.274
6.270
6.259
6.251
5.710
4.175
4.167
4.157
4.149
4.139
4.131
4.121
4.114
3.746
1.203
1.185
1.167
-0.000
OMe
HN
EtO2C
PhO2SN
4f
2.07
1.14
3.03
2.01
2.07
1.96
1.00
2.15
2.99
3.01
f1 (ppm)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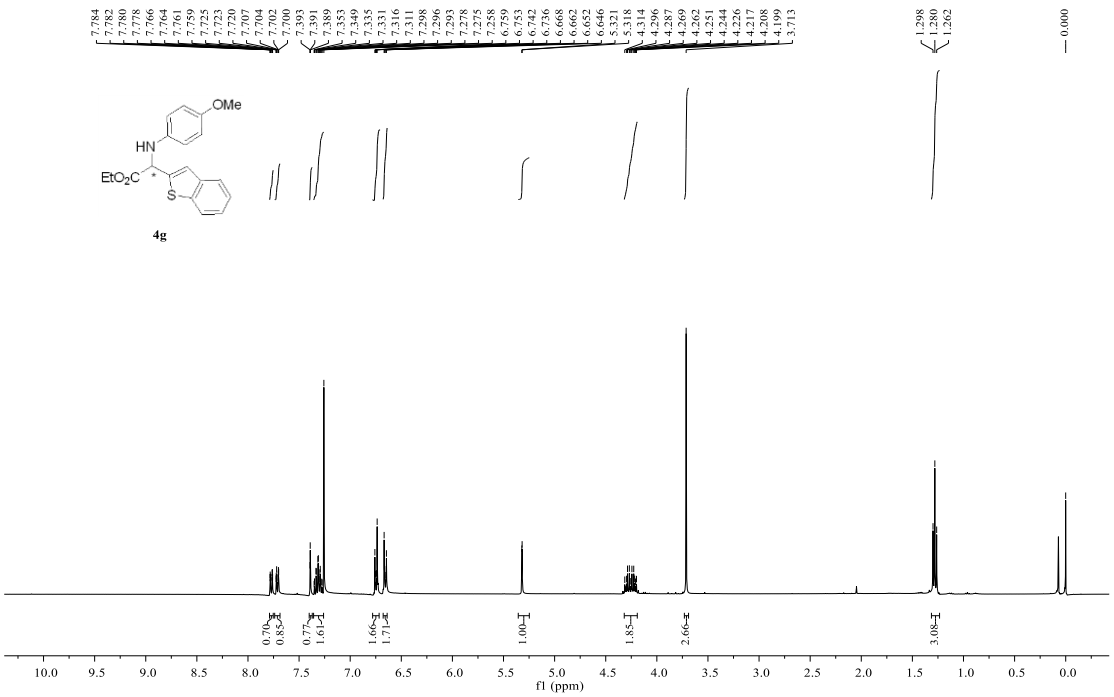
140.12
139.26
133.78
131.25
129.05
127.40
124.36
115.69
114.84
114.59
111.63
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
61.85
55.75
54.42
14.19
OMe
HN
EtO2C
PhO2SN
4f
f1 (ppm)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7.759
7.725
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7.720
7.707
7.704
7.702
7.700
7.393
7.391
7.389
7.353
7.349
7.335
7.331
7.316
7.311
7.298
7.296
7.293
7.278
7.275
7.258
6.759
6.753
6.742
6.736
6.668
6.662
6.652
6.646
5.321
5.318
4.314
4.296
4.287
4.269
4.262
4.251
4.244
4.226
4.217
4.208
4.199
3.713
1.298
1.280
1.262
0.000
OMe
HN
EtO2C
S
4g
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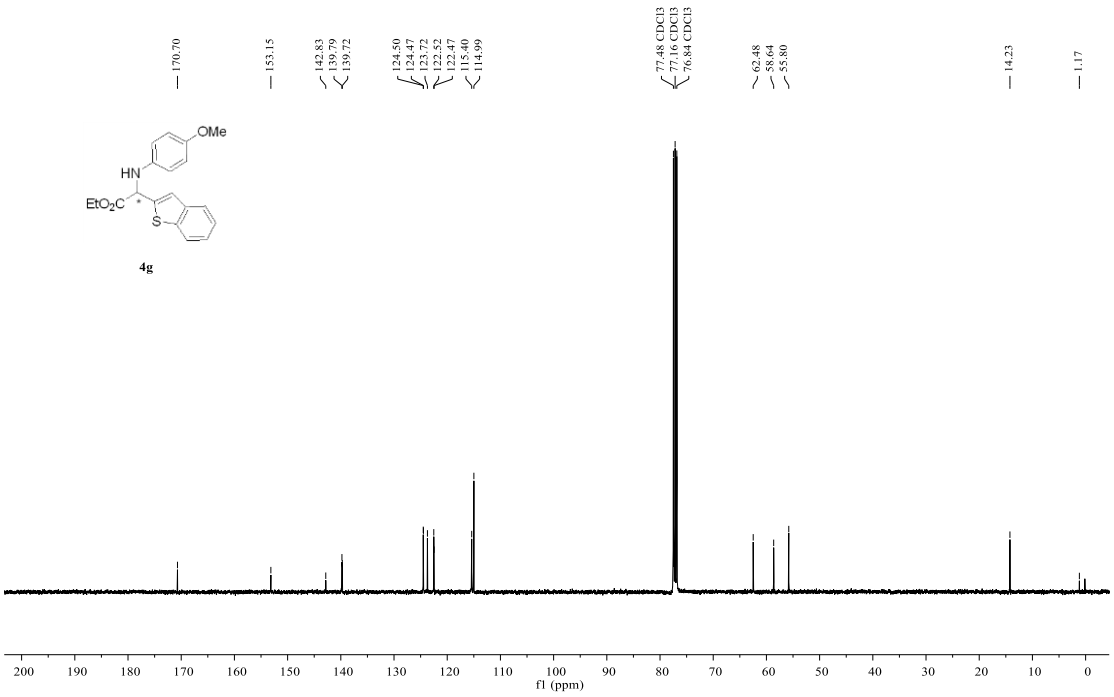
0.85
0.77
1.61
1.66
1.71
1.00
1.85
2.66
3.08
f1 (ppm)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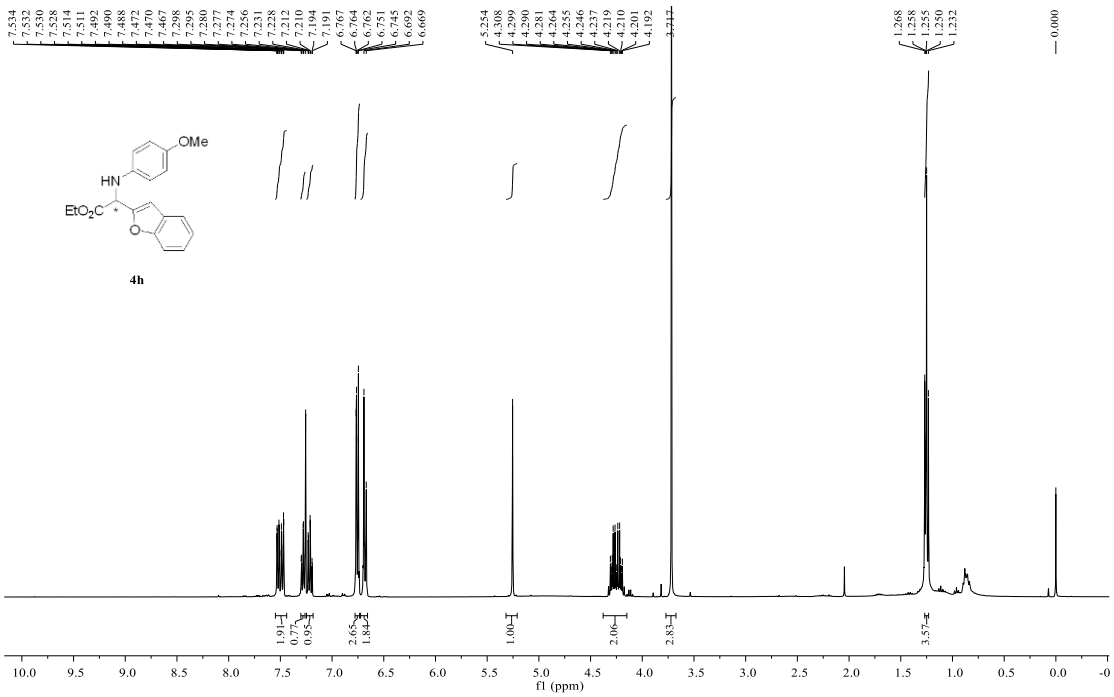
124.50
124.47
123.72
122.52
122.47
115.40
114.99
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
62.48
58.64
55.80
14.23
1.17
OMe
HN
EtO2C
S
4g
f1 (ppm)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7.530
7.528
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7.490
7.488
7.472
7.470
7.467
7.298
7.295
7.280
7.277
7.274
7.256
7.231
7.228
7.212
7.210
7.194
7.191
6.767
6.764
6.762
6.751
6.745
6.692
6.669
5.254
4.308
4.299
4.290
4.281
4.264
4.255
4.246
4.237
4.219
4.210
4.201
4.192
3.717
1.268
1.258
1.255
1.250
1.232
0.000
OMe
HN
EtO2C
O
4h
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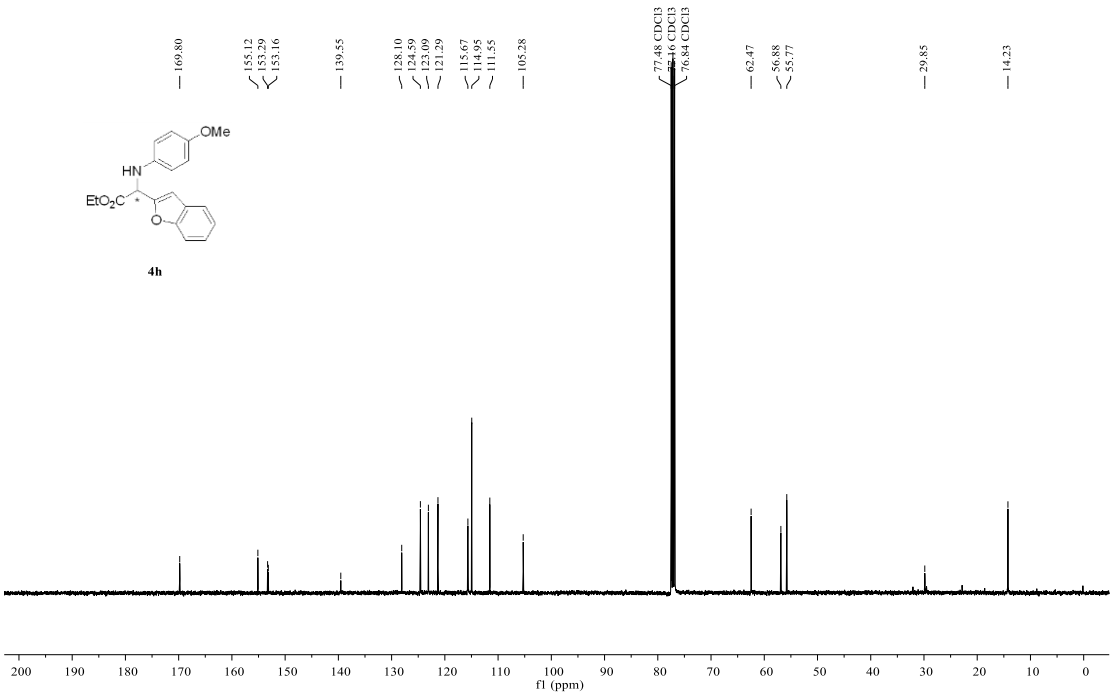
0.77
0.95
2.65
1.84
1.00
2.06
2.83
3.57
f1 (ppm)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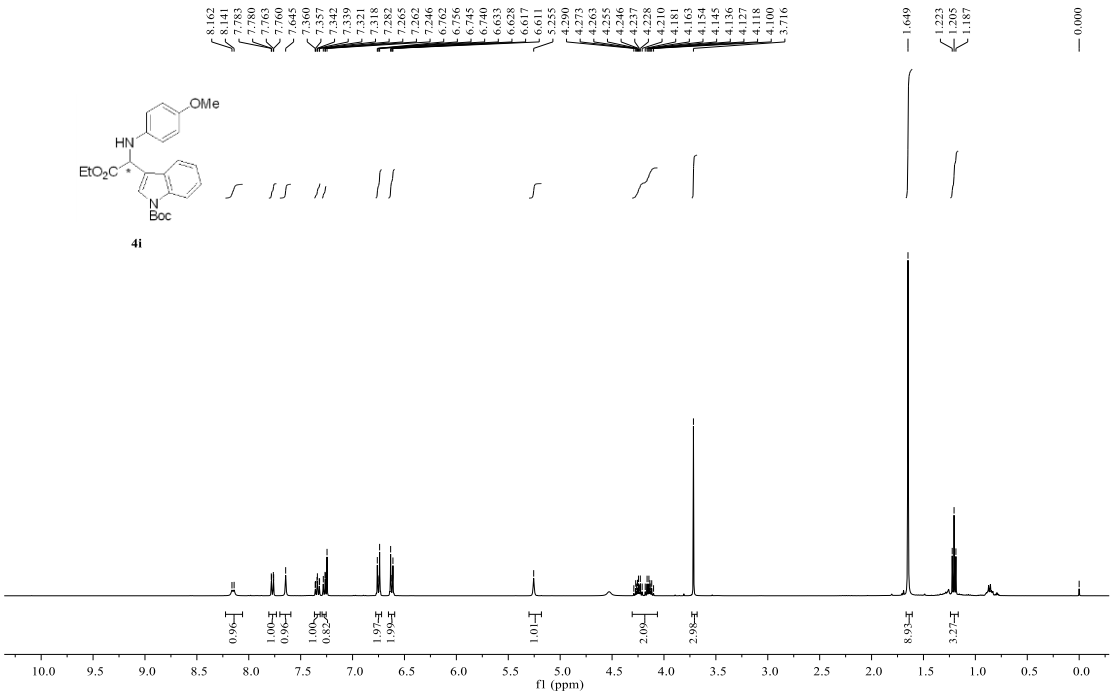
153.29
153.16
139.55
128.10
124.59
123.09
121.29
115.67
114.95
111.55
105.28
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
62.47
56.88
55.77
29.85
14.23
OMe
HN
EtO2C
O
4h
f1 (ppm)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7.760
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7.360
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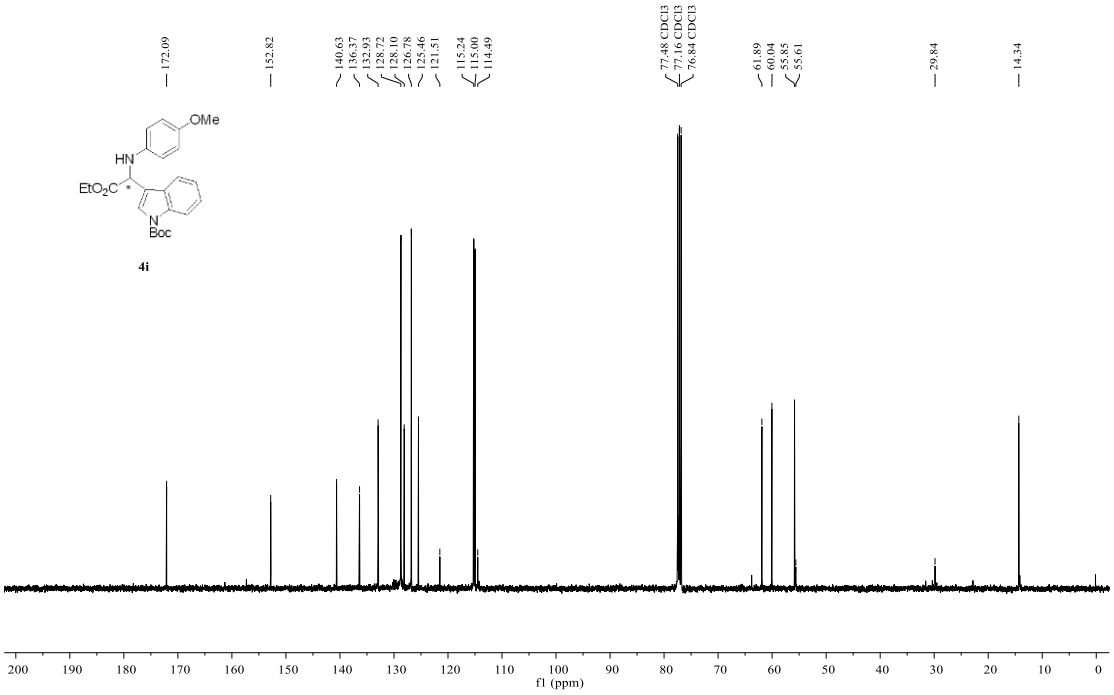
7.339
7.321
7.318
7.282
7.265
7.262
7.246
6.762
6.756
6.745
6.740
6.633
6.628
6.617
6.611
5.255
4.290
4.273
4.263
4.255
4.246
4.237
4.228
4.210
4.181
4.163
4.154
4.145
4.136
4.127
4.118
4.100
3.716
1.649
1.223
1.205
1.187
0.000
OMe
HN
EtO2C
N
Boc
4i
0.96
1.00
0.96
1.00
0.82
1.97
1.99
1.01
2.09
2.98
8.93
3.27
f1 (ppm)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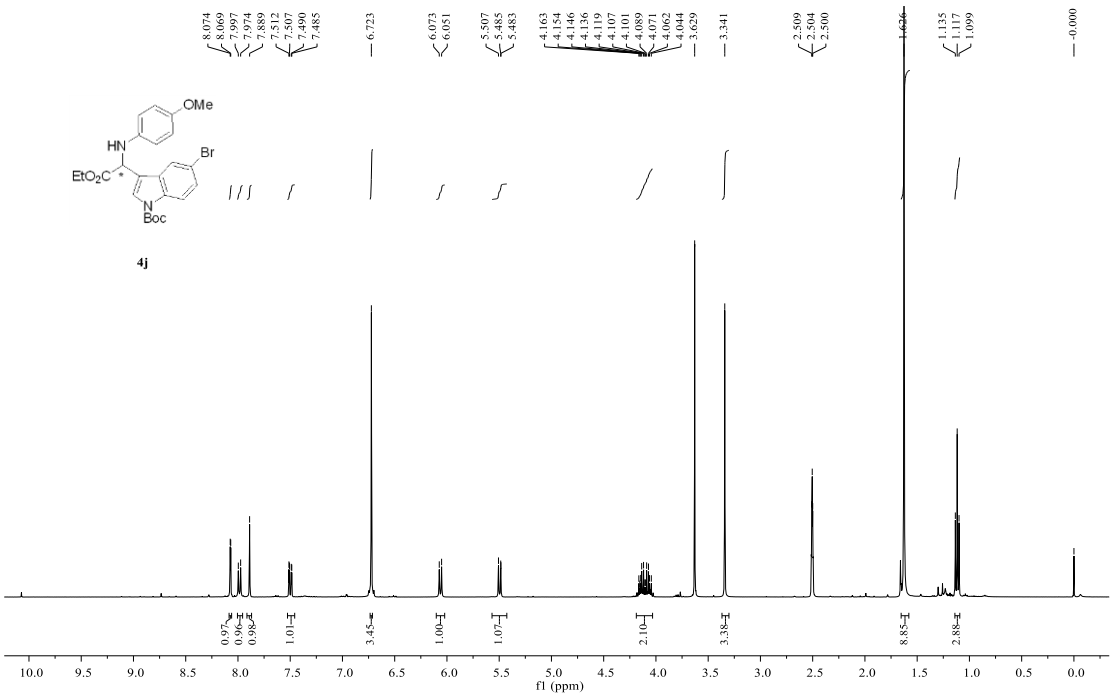
136.37
132.93
128.72
128.10
126.78
125.46
121.51
115.24
115.00
114.49
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
61.89
60.04
55.85
55.61
29.84
14.34
OMe
HN
EtO2C
N
Boc
4i
f1 (ppm)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7.974
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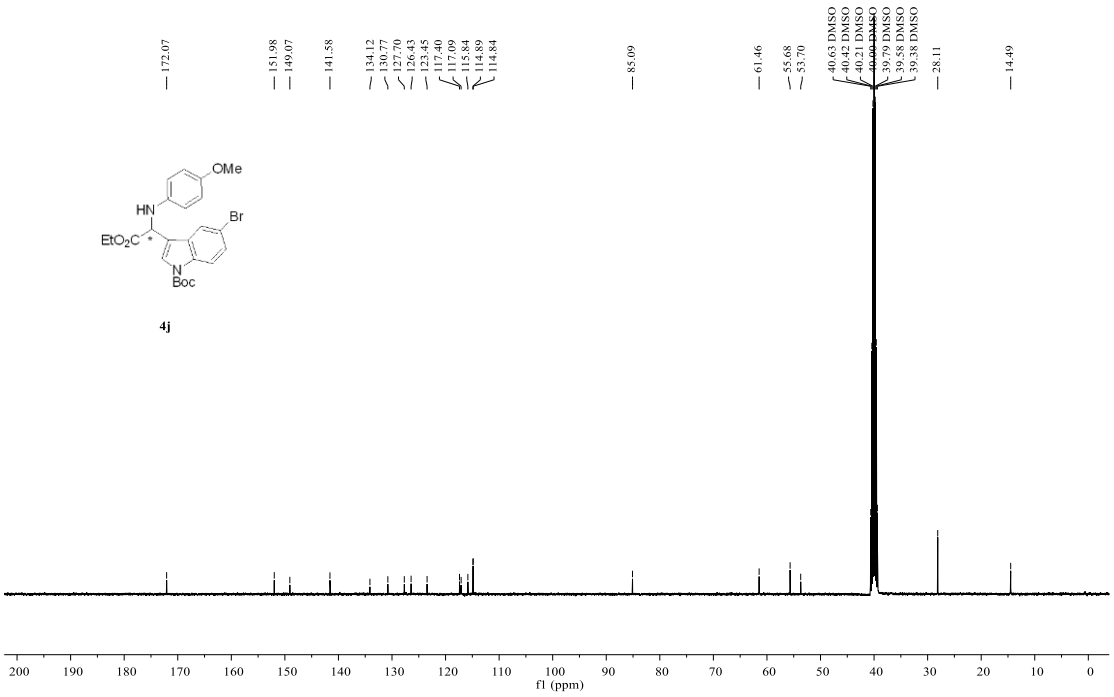
7.512
7.507
7.490
7.485
6.723
6.073
6.051
5.507
5.485
5.483
4.163
4.154
4.146
4.136
4.119
4.107
4.101
4.089
4.071
4.062
4.044
3.629
3.341
2.509
2.504
2.500
1.626
1.135
1.117
1.099
-0.000
OMe
HN
Br
EtO2C
N
Boc
4j
0.97
0.96
0.98
1.01
3.45
1.00
1.07
2.10
3.38
8.85
2.88
f1 (ppm)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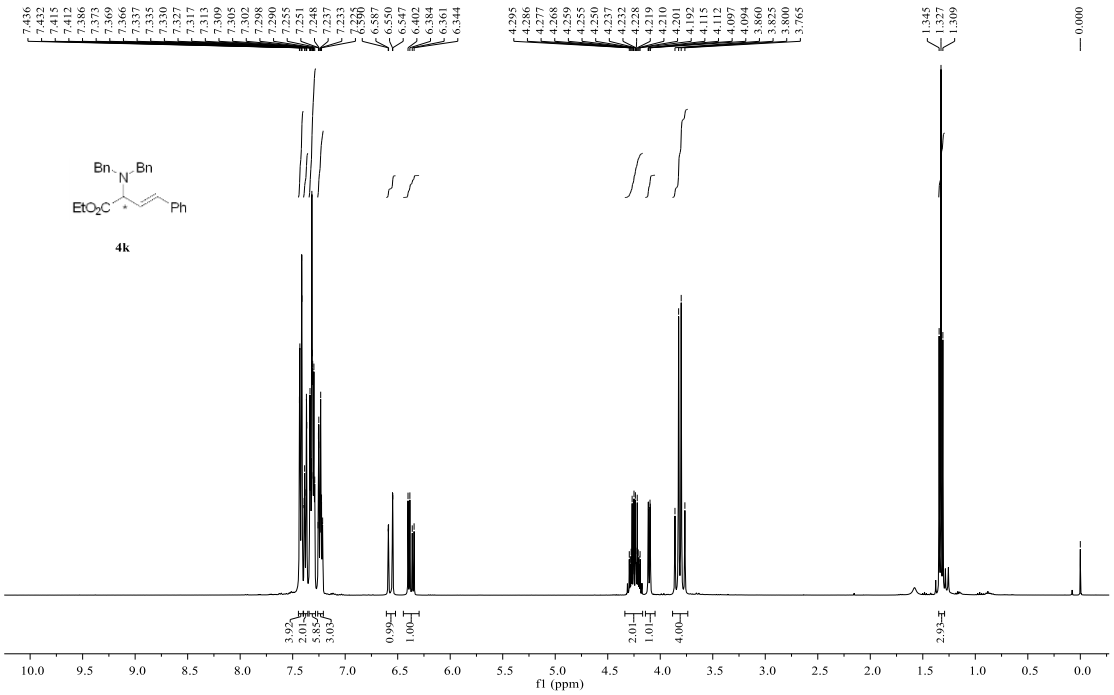
141.58
134.12
130.77
127.70
126.43
123.45
117.40
117.09
115.84
114.89
114.84
85.09
61.46
55.68
53.70
40.63 DMSO
40.42 DMSO
40.21 DMSO
39.79 DMSO
39.58 DMSO
39.38 DMSO
28.11
14.49
OMe
HN
Br
EtO2C
N
Boc
4j
f1 (ppm)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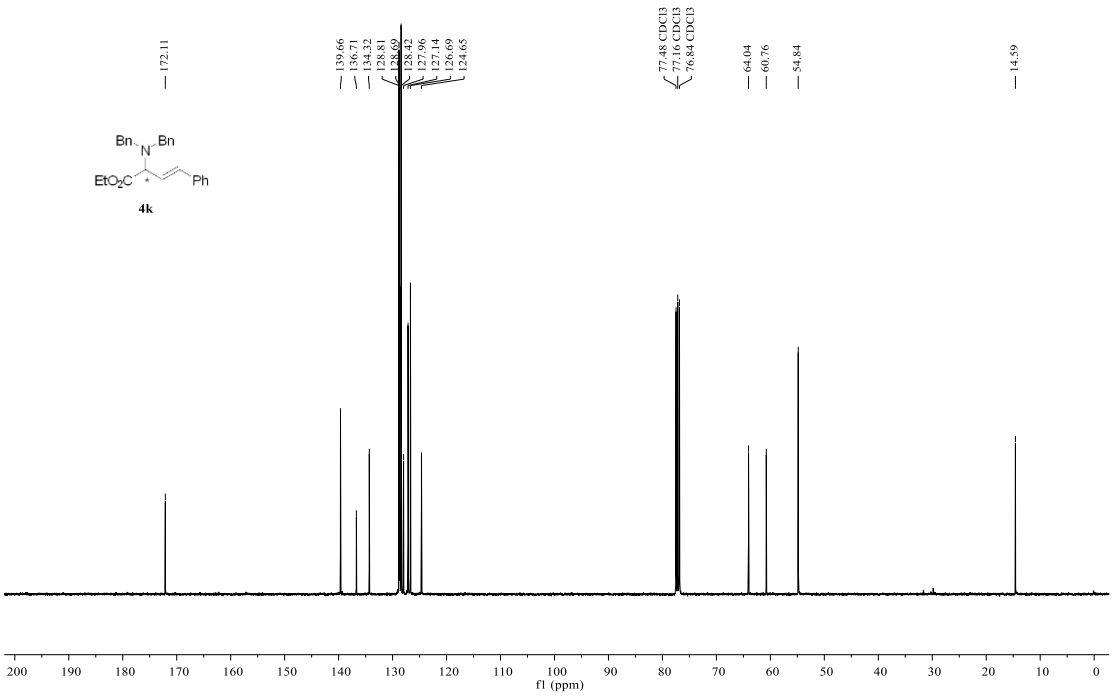
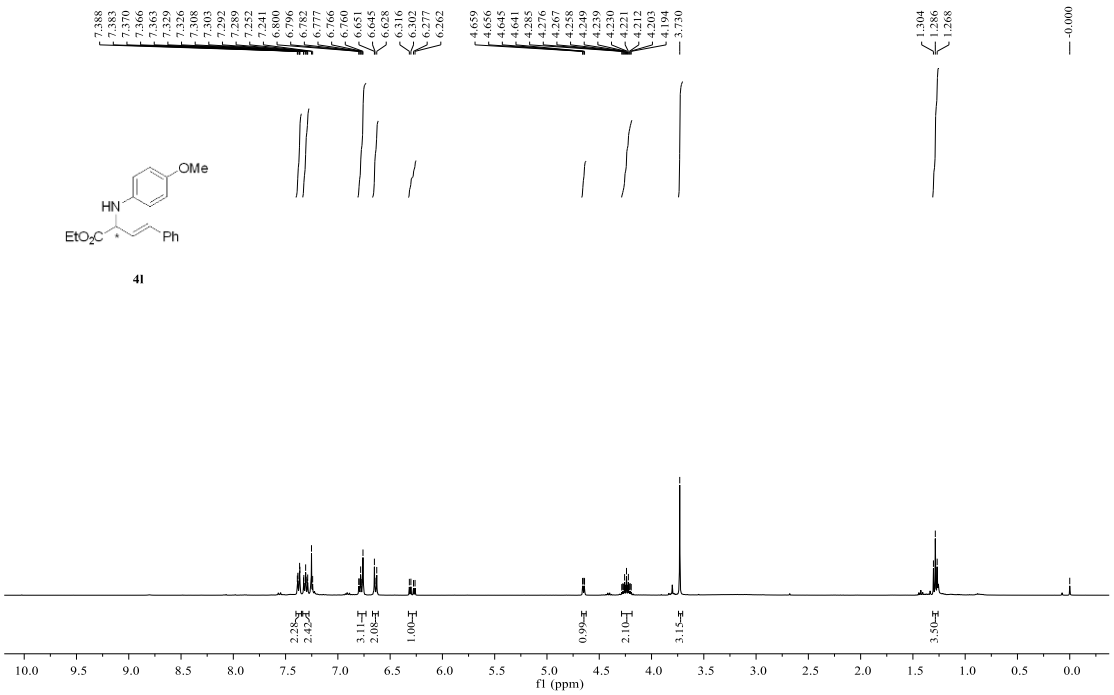
7.327
7.317
7.313
7.309
7.305
7.302
7.298
7.290
7.255
7.251
7.248
7.237
7.233
6.590
6.587
6.550
6.547
6.402
6.384
6.361
6.344
4.295
4.286
4.277
4.268
4.259
4.255
4.250
4.237
4.232
4.228
4.219
4.210
4.201
4.192
4.115
4.112
4.097
4.094
3.866
3.855
3.800
3.765
1.345
1.327
1.309
0.000
Bn
N
Bn
EtO2C
Ph
4k
3.92
2.01
5.85
3.03
0.99
1.00
2.01
1.01
4.00
2.93
f1 (ppm)


172.11
139.66
136.71
134.32
128.81
128.60
128.42
127.96
127.14
126.69
124.65
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
64.04
60.76
54.84
14.59
Bn
N
Bn
EtO2C
Ph
4k
f1 (ppm)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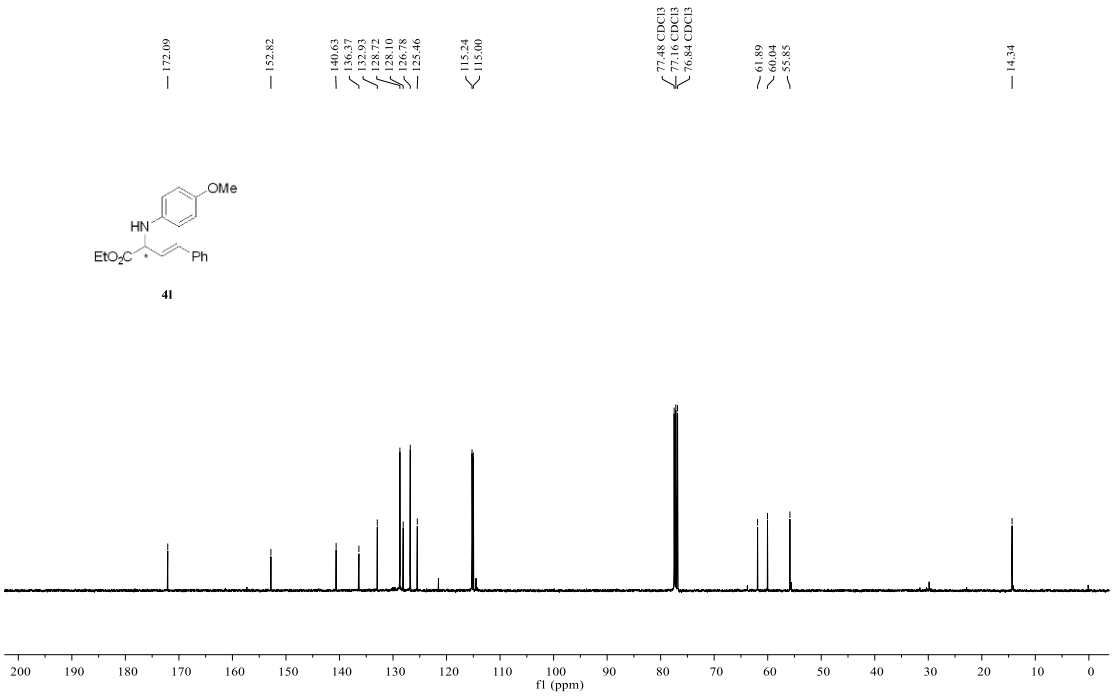
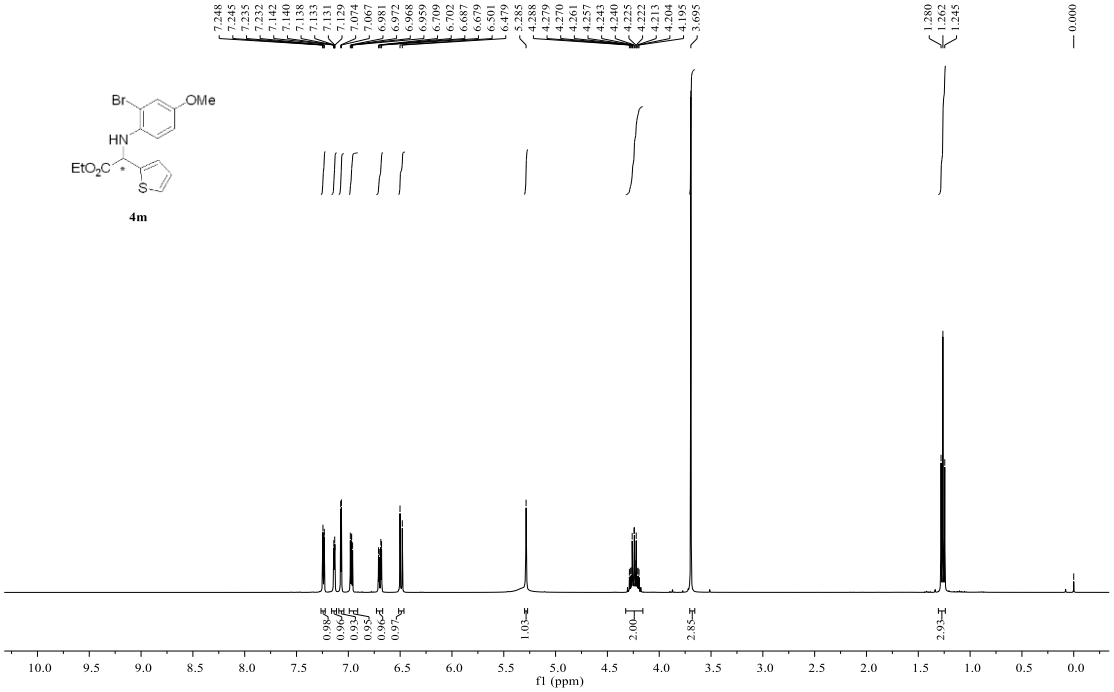
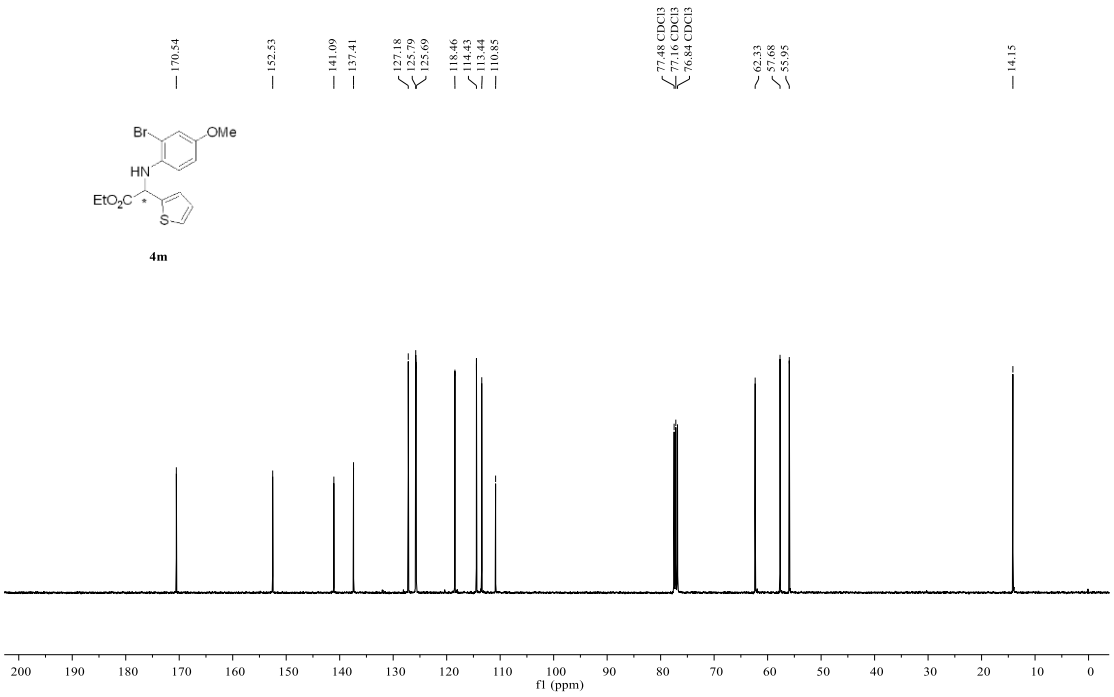
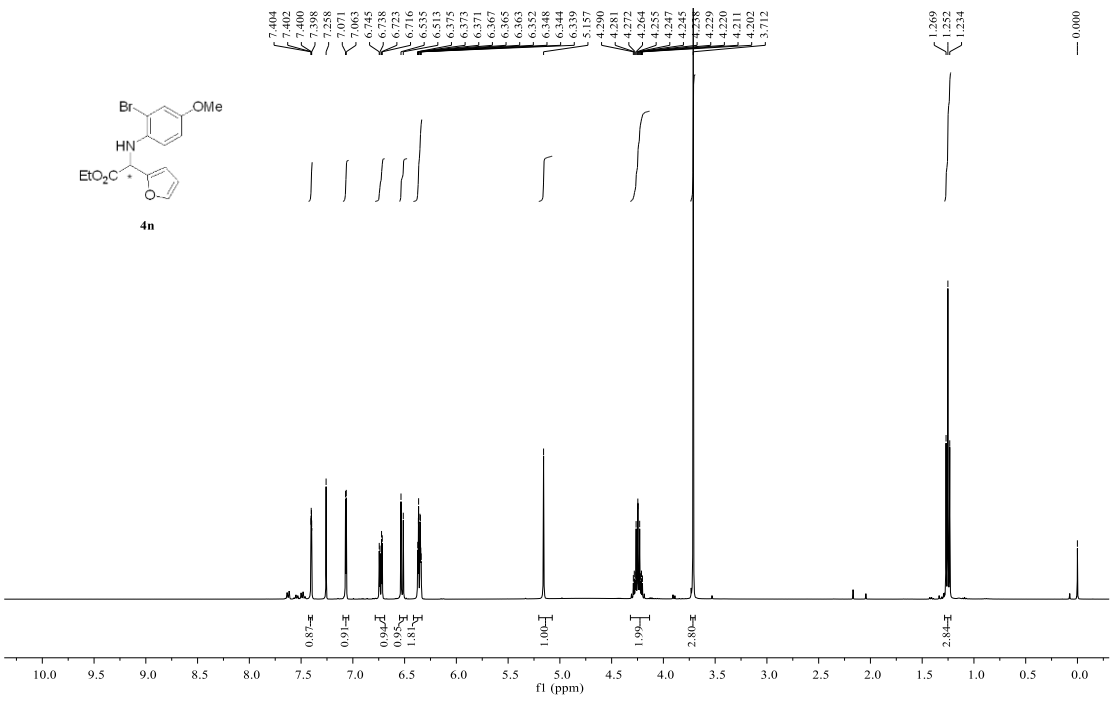
7.366
7.363
7.329
7.326
7.308
7.303
7.292
7.289
7.252
7.241
6.800
6.796
6.782
6.777
6.766
6.760
6.651
6.645
6.628
6.316
6.302
6.277
6.262
4.659
4.656
4.645
4.641
4.285
4.276
4.267
4.258
4.249
4.239
4.230
4.221
4.212
4.203
4.194
3.730
1.304
1.286
1.268
0.000
OMe
HN
EtO2C
Ph
4l
2.28
2.42
3.11
2.08
1.00
0.99
2.10
3.15
3.50
f1 (ppm)


172.09
152.82
140.63
136.37
132.93
128.72
128.10
126.78
125.46
115.24
115.00
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
61.89
60.04
55.65
14.34
OMe
HN
EtO2C
Ph
4l
f1 (ppm)


7.248
7.245
7.235
7.232
7.142
7.140
7.138
7.133
7.131
7.129
7.074
7.067
6.981
6.972
6.968
6.959
6.709
6.702
6.687
6.679
6.501
6.479
5.285
4.288
4.279
4.270
4.261
4.257
4.243
4.240
4.225
4.222
4.213
4.204
4.195
3.695
1.280
1.262
1.245
0.000
Br
OMe
HN
EtO2C
S
4m
0.98
0.96
0.93
0.95
0.96
0.97
1.03
2.00
2.85
2.93
f1 (ppm)


170.54
152.53
141.09
137.41
127.18
125.79
125.69
118.46
114.43
113.44
110.85
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
62.33
57.68
55.95
14.15
Br
OMe
HN
EtO2C
S
4m
f1 (ppm)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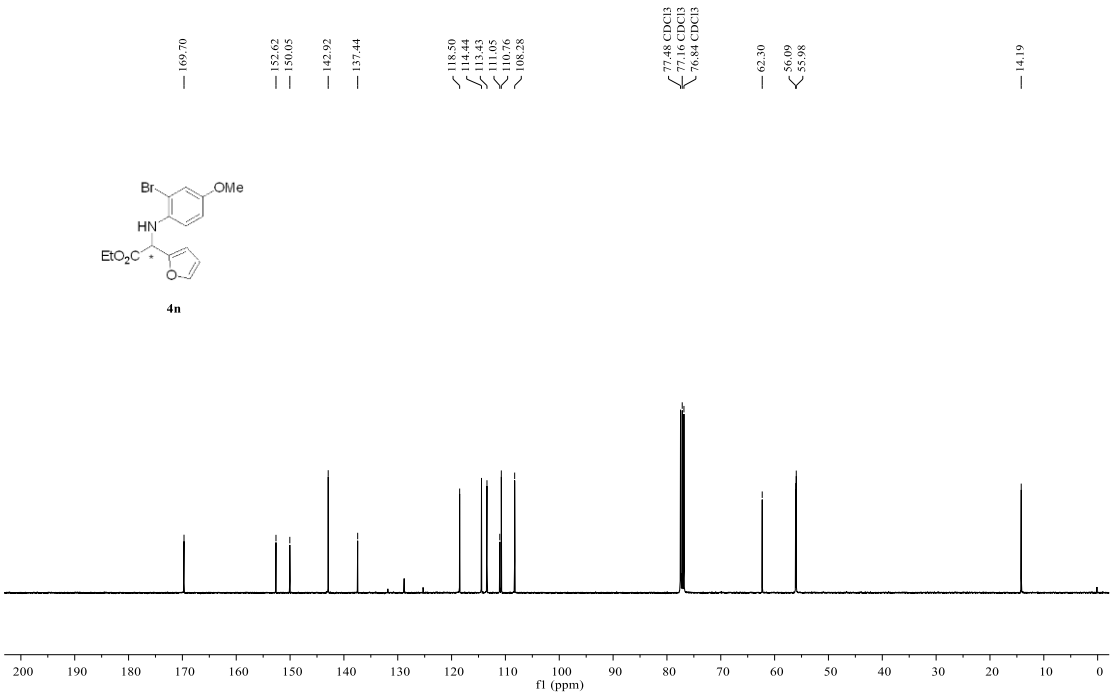
7.402
7.400
7.398
7.258
7.071
7.063
6.745
6.738
6.723
6.716
6.535
6.513
6.375
6.373
6.371
6.367
6.365
6.363
6.352
6.348
6.344
6.339
5.157
4.290
4.281
4.272
4.264
4.255
4.247
4.245
4.238
4.229
4.220
4.211
4.202
3.712
1.269
1.252
1.234
0.000
Br
OMe
HN
EtO2C
O
4n
0.87
0.91
0.94
0.95
1.81
1.00
1.99
2.80
2.84
f1 (ppm)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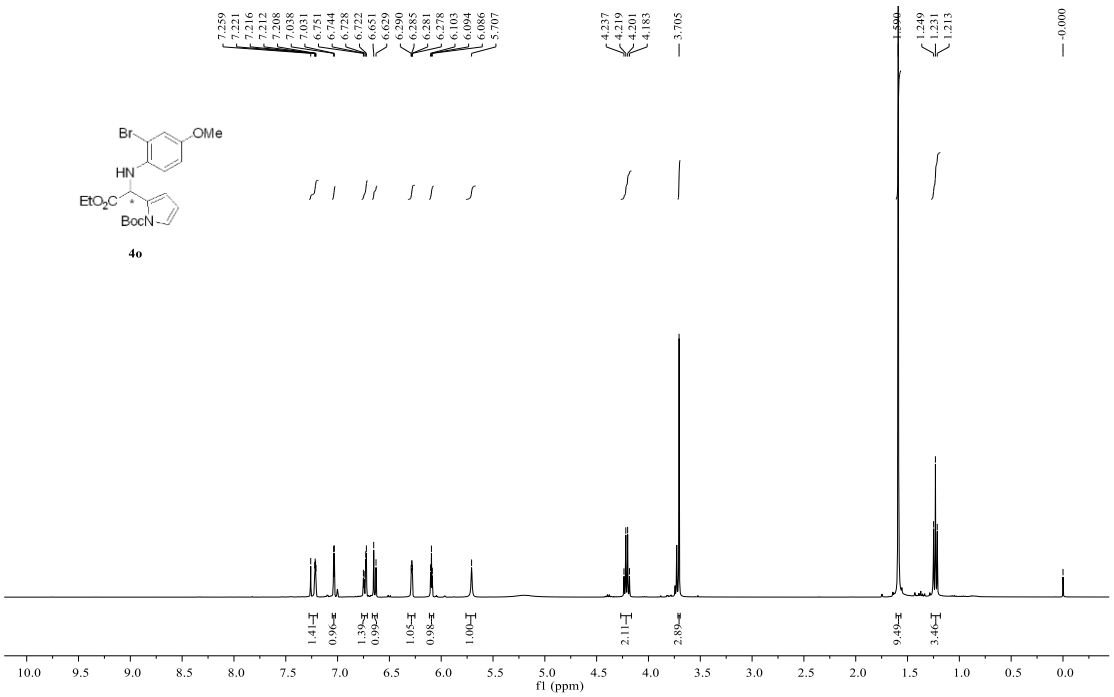
152.62
150.05
142.92
137.44
118.50
114.44
113.43
111.05
110.76
108.28
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
62.30
56.09
55.98
14.19
Br
OMe
HN
EtO2C
O
4n
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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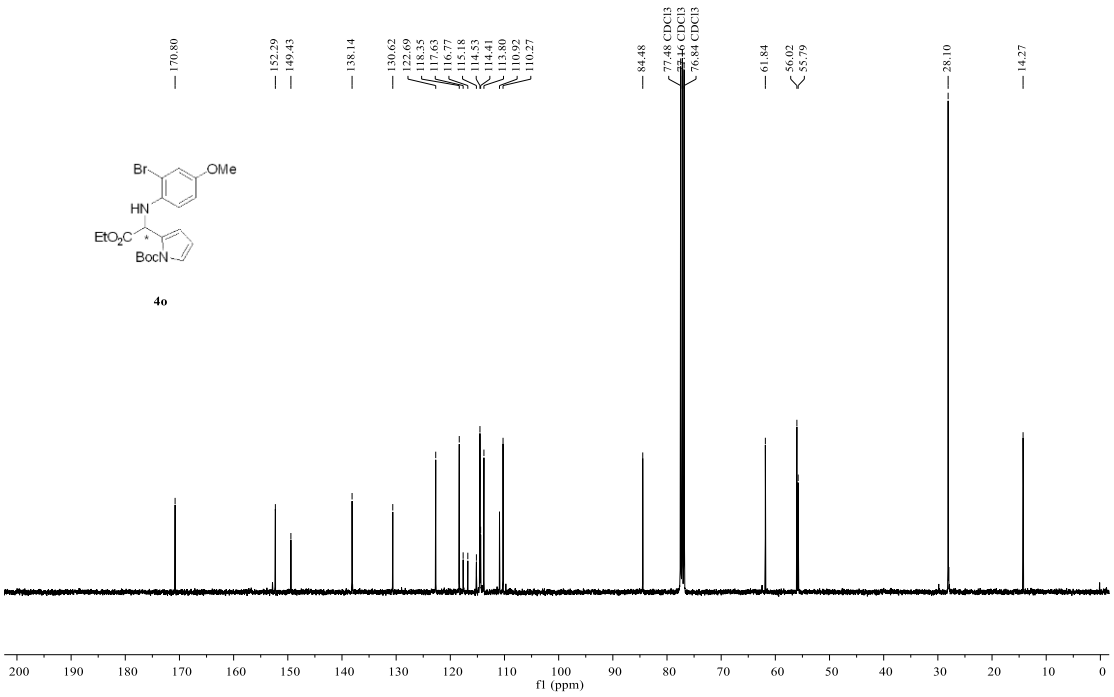
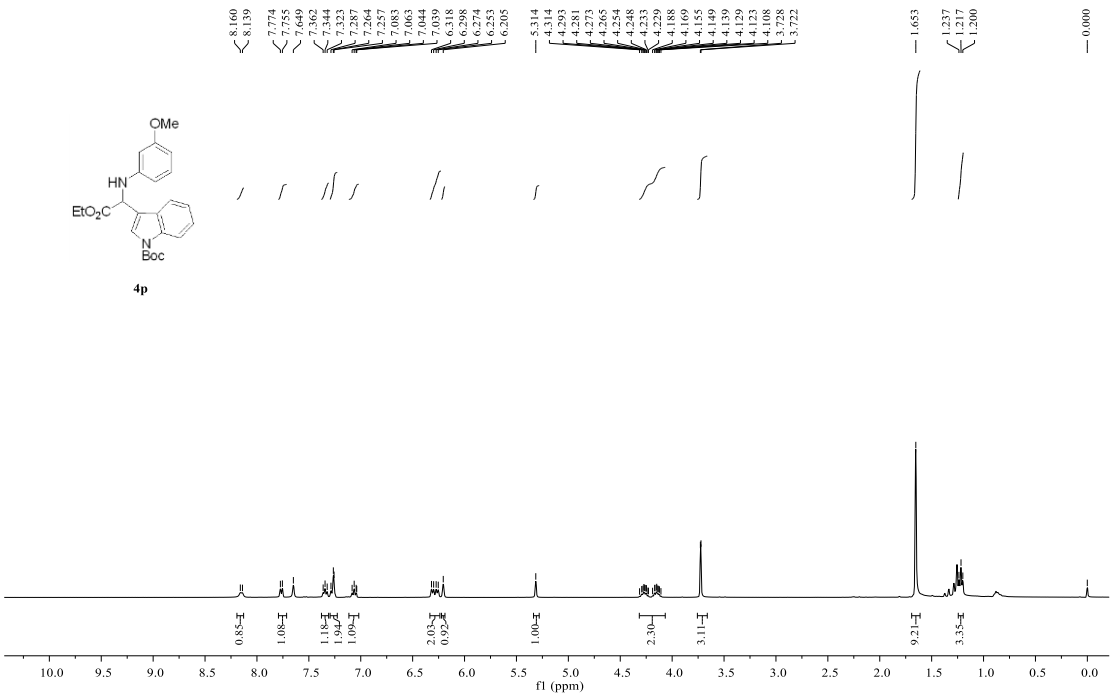
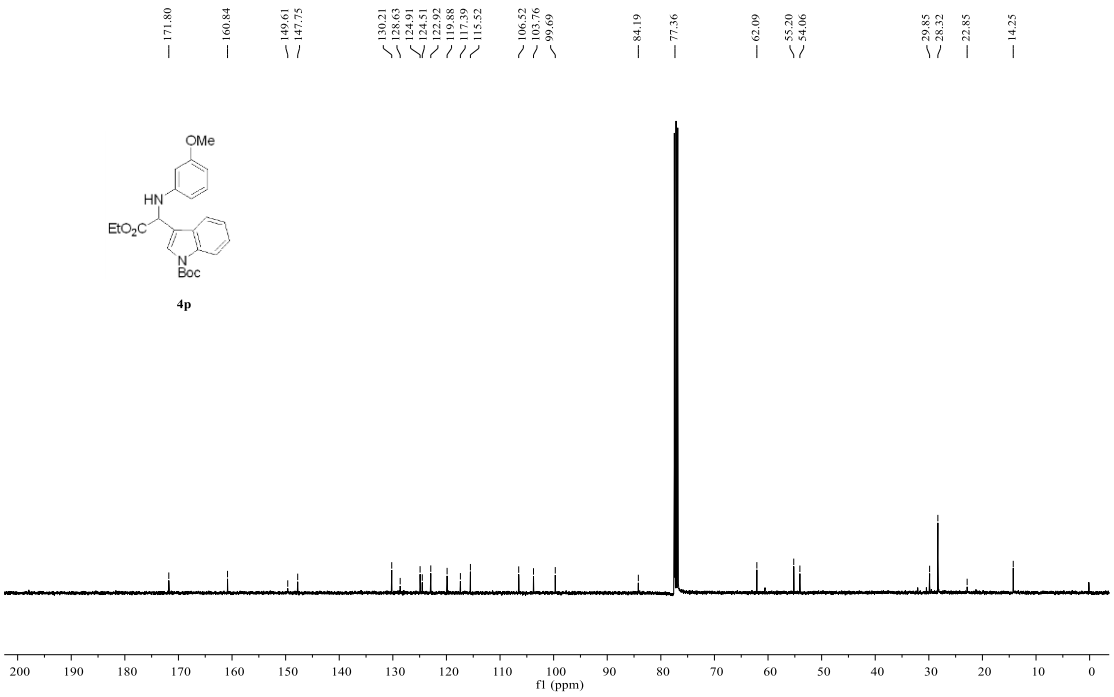
7.221
7.216
7.212
7.208
7.038
7.031
6.751
6.744
6.728
6.722
6.651
6.629
6.290
6.285
6.281
6.278
6.103
6.094
6.086
5.707
4.237
4.219
4.201
4.183
3.705
1.590
1.249
1.231
1.213
-0.000
Br
OMe
HN
EtO2C
BocN
4o
1.41
0.96
1.39
0.99
1.05
0.98
1.00
2.11
2.89
9.49
3.46
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


170.80
152.29
149.43
138.14
130.62
122.69
118.35
117.63
116.77
115.18
114.53
114.41
113.80
110.92
110.27
84.48
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
61.84
56.02
55.79
28.10
14.27
Br
OMe
HN
EtO2C
BocN
4o
f1 (ppm)


8.160
8.139
7.774
7.755
7.649
7.362
7.344
7.323
7.287
7.264
7.257
7.083
7.063
7.044
7.019
6.318
6.298
6.274
6.253
6.205
5.314
4.314
4.298
4.281
4.273
4.265
4.254
4.248
4.233
4.229
4.188
4.169
4.155
4.149
4.139
4.129
4.123
4.108
3.728
3.722
1.653
1.237
1.217
1.200
0.000
OMe
HN
EtO2C
N
Boc
4p
0.85
1.08
1.18
1.94
1.09
2.03
0.92
1.00
2.30
3.11
9.21
3.35
f1 (ppm)


171.80
160.84
149.61
147.75
130.21
128.63
124.91
124.51
122.92
119.88
117.39
115.52
106.52
103.76
99.69
84.19
77.36
62.09
55.20
54.06
29.85
28.32
22.85
14.25
OMe
HN
EtO2C
N
Boc
4p
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)