Supporting Information

Highly Enantioselective Michael Additions of Indole to Benzylidene Malonate using simple Bis(oxazoline) ligands: Importance of Metal/Ligand Ratios

Ramesh Rasappan, Markus Hager, Anja Gissibl, Oliver Reiser*.

Institut für Organische Chemie, Universität Regensburg, Universitätsstr. 31, 93053 Regensburg, Germany.

Table of Contents

General Information:

Reactions were carried out in Schlenk tube under nitrogen atmosphere, unless otherwise stated. EtOH was dried by distillation over Mg and stored over molecular sieves 3Å. Diethylbezylidene malonates were synthesized by classical Aldol reaction conditions and the crude products were distilled to obtain the pure product. 5-methoxyindole was purchased from Aldrich and used directly without further purification. Silica gel 60 (Merck, 0.063-0.200 mm) was used for the column purification, TLC analysis was done on silica gel 60 F_{254} (Merck) coated on aluminium sheets. ^{1}H (300 MHz) and ^{13}C (75.5 MHz) NMR spectrum were recorded on a Bruker Avance 300 Spectrometer in $CDCl_3$ with $CHCl_3$ (7.27 ppm for ^{1}H, 77 ppm for ^{13}C) as a standard. Mass spectrometry (Finnigan ThermoQuest TSQ 7000) was done by the Central Analytical Laboratory (Universität Regensburg). Optical rotations were measured on a Perkin Elmer 241 Polarimeter.

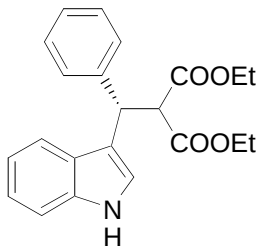
Stereochemical Assignment:

The absolute configurations of Michael addition adducts were assigned by comparison of their optical rotations with literature values. The absolute configurations of *p*-methylphenyl and *o*-bromo phenyl Michael adducts were assigned by an analogy.

General Procedure: Catalytic asymmetric Michael additions

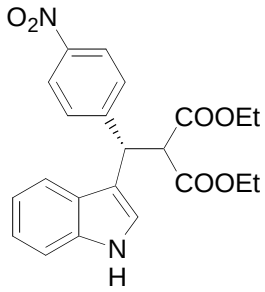
To a Schlenk tube ligand **2b** (12.0mg, 0.05mmol) and $Cu(OTf)_2$ (18.1mg, 0.05mmol) were added under air atmosphere. Ethanol (2 mL) was added and the mixture was stirred for 1h at room temperature (20-25°C). To the resulting blue-green solution malonate (1mmol, 1.0 eq.) in EtOH (2 mL) was added and stirring was continued for 20 min before the indole (1.2mmol, 1.2 eq.) was added. After stirring for 8h at room temperature, the red colored solution was concentrated under reduced pressure. The crude product purified by column chromatography (performed with hexanes/DCM 1:1, followed by DCM).

(S)–Ethyl 2–ethoxycarbonyl–3–(3–indolyl)–3–phenyl propanoate



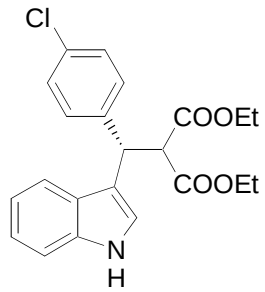
Prepared according to the general procedure and purified by column chromatography (performed with hexanes/DCM 1:1, followed by DCM) to obtain the pure product as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93-1.06 (m, 6 H), 3.93-4.06 (m, 4 H), 4.30 (d, *J* = 11.8 Hz, 1 H), 5.09 (d, *J* = 11.8 Hz, 1 H), 7.00-7.07 (m, 1 H), 7.09-7.31 (m, 6 H), 7.37 (d, *J* = 7.4 Hz, 2 H), 7.56 (d, *J* = 8.0 Hz, 1 H), 8.07 (brs, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.1, 167.9, 141.4, 136.2, 128.4, 128.2, 126.8, 126.7, 122.3, 120.9, 119.5, 119.4, 117.0, 111.0, 61.5, 61.4, 58.4, 42.9, 13.8, 13.8; MS (CI): m/z (%) = 383 (MNH_4^+, 89), 366 (MH^+, 3), 206 (100), 178 (5); mp 174-176°C; HPLC analysis (Chiralcel OD/OD-H, 10% iPrOH/n-hexane, 0.5 mL/min, 254 nm; t_r (minor) = 26.67 min, t_r (major) = 31.40 min); >99 % *ee*; $[\alpha]_D^{25}$ = + 65.4 (20mg/2 mL CH_2Cl_2).

(S)–Ethyl 2–ethoxycarbonyl–3–(3–indolyl)–3–(p-nitrophenyl) propanoate



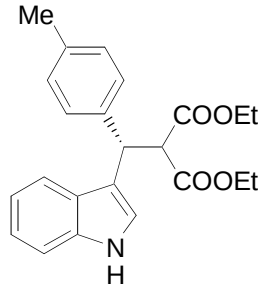
Prepared according to the general procedure and purified by column chromatography (performed with hexanes/DCM 1:1, followed by DCM) to obtain the pure product as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.01 (t, *J* = 7.1 Hz, 3 H), 1.07 (t, *J* = 7.1 Hz, 3 H), 3.97-4.08 (m, 4 H), 4.32 (d, *J* = 11.8 Hz, 1 H), 5.20 (d, *J* = 11.5 Hz, 1 H), 7.05 (m, 1 H), 7.16 (m, 1 H), 7.21 (d, *J* = 2.5 Hz, 1 H), 7.32 (d, *J* = 8.2 Hz, 1 H), 7.47 (d, *J* = 8.0 Hz, 1 H), 7.55 (m, 2 H), 8.10 (m, 2 H), 8.15 (brs, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.5, 167.4, 149.3, 146.7, 136.2, 129.2, 126.3, 123.7, 122.7, 121.3, 119.9, 118.9, 115.4, 111.3, 61.8, 57.7, 42.5, 13.9, 13.8; MS (CI): m/z (%) = 428 (MNH_4^+, 100), 410 (2), 398 (7), 251 (25), 221 (22), 178 (11); mp 105-107°C; HPLC analysis (Chiralcel AS, 15% iPrOH/n-hexane, 0.5 mL/min, 254 nm; t_r (major) = 29.13 min, t_r (minor) = 39.83 min); >80 % *ee*; $[\alpha]_D^{25}$ = + 6.9 (20mg/2 mL CH_2Cl_2).

(S)–Ethyl 2–ethoxycarbonyl–3–(3–indolyl)–3–(p-chlorophenyl) propanoate



Prepared according to the general procedure and purified by column chromatography (performed with hexanes/DCM 1:1, followed by DCM) to obtain the pure product as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00 (t, *J* = 7.1 Hz, 3 H), 1.05 (t, *J* = 7.1 Hz, 3 H), 3.96-4.06 (m, 4 H), 4.24 (d, *J* = 11.8 Hz, 1 H), 5.06 (d, *J* = 11.8 Hz, 1 H), 7.00-7.07 (m, 1 H), 7.10-7.23 (m, 4 H), 7.27-7.34 (m, 3 H), 7.49 (d, *J* = 8.2 Hz, 1 H), 8.05 (brs, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.9, 167.8, 140.1, 136.3, 132.5, 129.6, 128.5, 126.5, 122.4, 121.0, 119.7, 119.2, 116.4, 111.1, 61.6, 58.2, 42.3, 13.9, 13.8; MS (CI): m/z (%) = 417 (MNH_4^+, 100), 399 (3), 242 (30), 240 (67), 206 (2), 178 (8); mp 157-158°C; HPLC analysis (Chiralcel OD/OD-H, 15% iPrOH/n-hexane, 0.5 mL/min, 254 nm; t_r (minor) = 9.75 min, t_r (major) = 17.66 min); >98 % *ee*; $[\alpha]_D^{25}$ = + 48.2 (20mg/2 mL CH_2Cl_2).

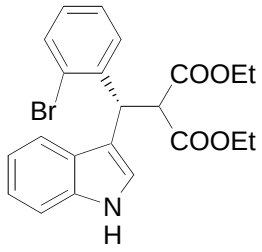
(S)–Ethyl 2–ethoxycarbonyl–3–(3–indolyl)–3–(p-methylphenyl) propanoate



Prepared according to the general procedure and purified by column chromatography (performed with hexanes/DCM 1:1, followed by DCM) to obtain the pure product as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.98 (t, *J* = 7.1 Hz, 3 H), 1.04 (t, *J* = 7.1 Hz, 3 H), 2.24 (s, 3 H), 3.94-4.05 (m, 4 H), 4.27 (d, *J* = 11.8 Hz, 1 H), 5.04 (d, *J* = 11.8 Hz, 1 H), 6.99-7.06 (m, 3 H), 7.08-7.18 (m, 2 H), 7.22-7.31 (m, 3 H), 7.55 (d, *J* = 8.0 Hz, 1 H), 7.99 (brs, 1

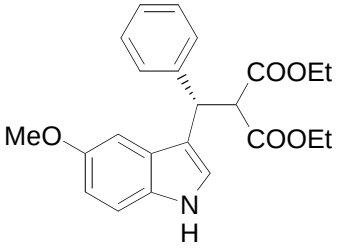
H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.1, 167.9, 138.4, 136.2, 136.2, 129.0, 128.0, 126.7, 122.2, 120.8, 119.5, 119.5, 117.3, 110.9, 61.4, 61.4, 58.4, 42.4, 21.0, 13.8, 13.8; MS (CI): m/z (%) = 397 (MNH_4^+, 73), 379 (2), 220 (100), 178 (7); mp 140-142°C; HPLC analysis (Chiralcel OD/OD-H, 10% iPrOH/n-hexane, 0.5 mL/min, 254 nm; t_r (major) = 22.12 min, t_r (minor) = 25.47 min); >94 % *ee*; $[\alpha]_D^{25}$ = + 26.7 (10mg/2 mL CH_2Cl_2).

(S)–Ethyl 2–ethoxycarbonyl–3–(3–indolyl)–3–(o-bromophenyl) propanoate



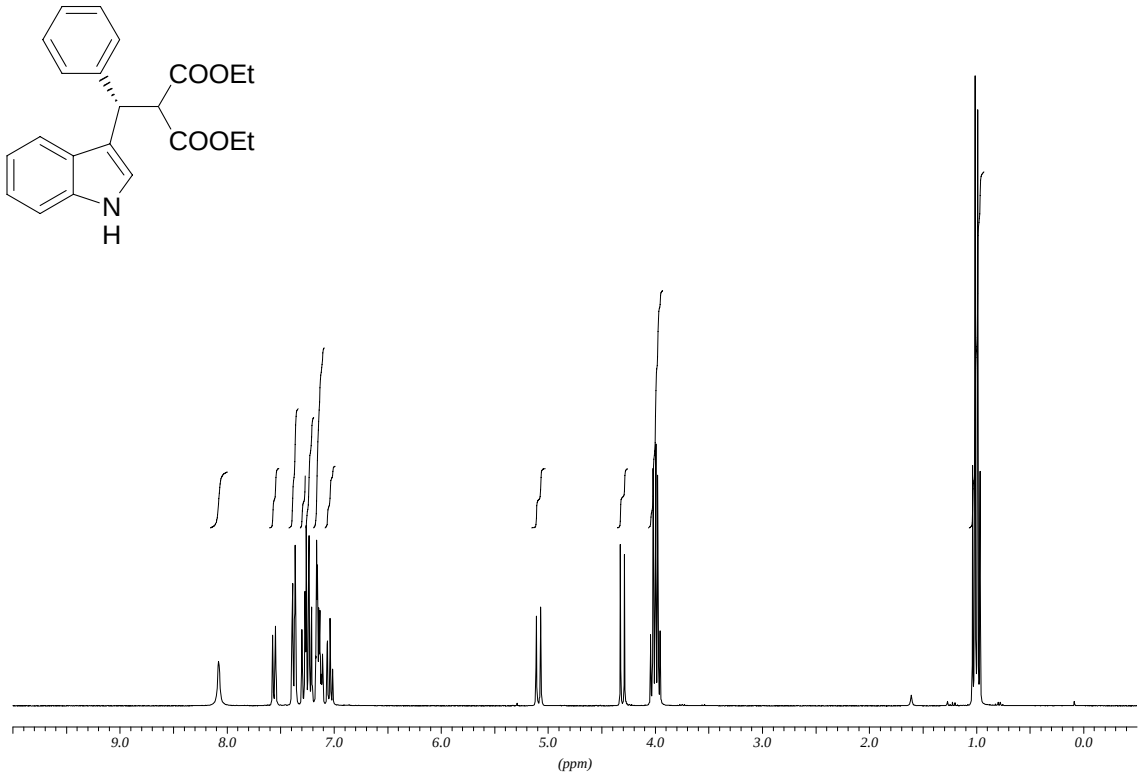
Prepared according to the general procedure and purified by column chromatography (performed with hexanes/DCM 1:1, followed by DCM) to obtain the pure product as a brown gummy solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.1 Hz, 3 H), 1.03 (t, *J* = 7.1 Hz, 3 H), 3.92-4.07 (m, 4 H), 4.37 (d, *J* = 11.5 Hz, 1 H), 5.64 (d, *J* = 11.5 Hz, 1 H), 6.97-7.31 (m, 5 H), 7.41 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.53 (dd, *J* = 8.0, 1.4 Hz, 1 H), 7.72 (d, *J* = 7.7 Hz, 1 H), 8.08 (brs, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.0, 167.7, 140.8, 136.1, 133.2, 129.1, 128.2, 127.6, 126.7, 124.9, 122.3, 122.2, 119.7, 115.6, 111.2, 61.6, 58.0, 41.8, 41.4, 14.1, 13.8, 13.7; MS (CI): m/z (%) = 461 (MNH_4^+, 100), 444 (MH^+, 4), 284 (58), 206 (3), 178 (12); HPLC analysis (Chiralcel OD/OD-H, 10% iPrOH/n-hexane, 0.5 mL/min, 254 nm; t_r (minor) = 24.30 min, t_r (major) = 37.42 min); >85 % *ee*; $[\alpha]_D^{25}$ = + 48.5 (20mg/2 mL CH_2Cl_2).

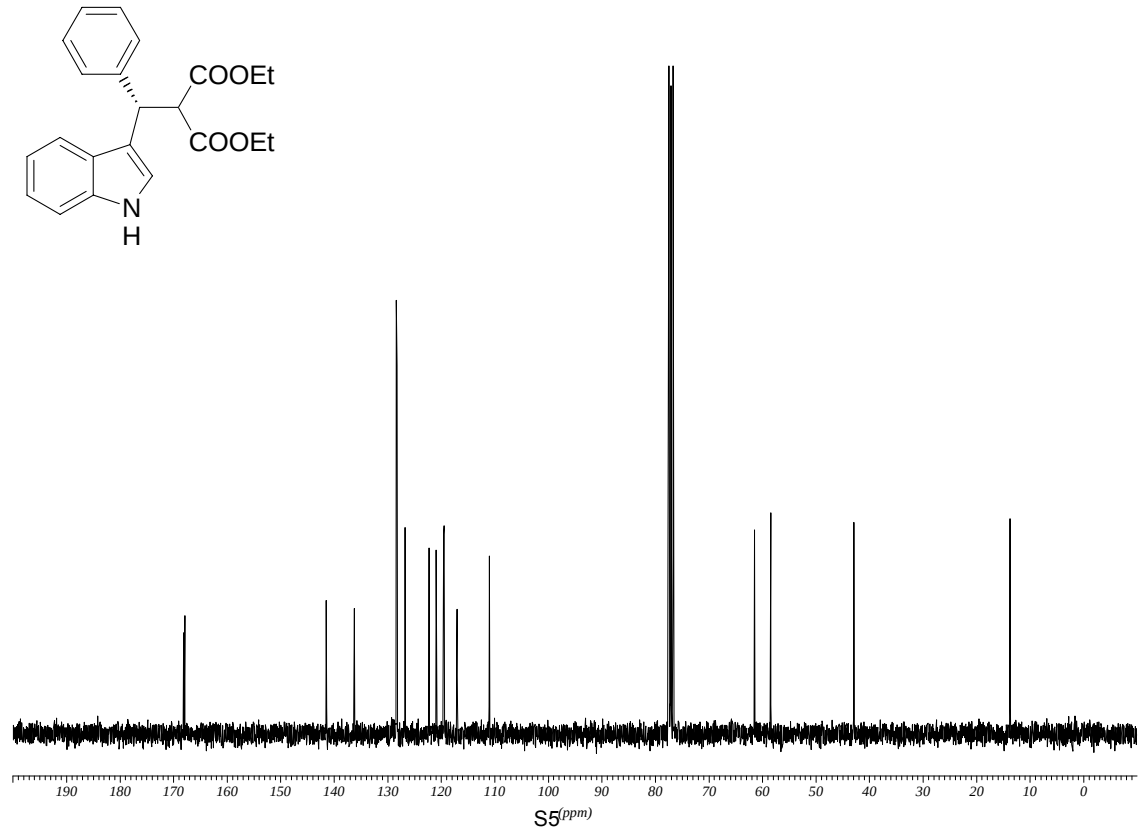
(S)–Ethyl 2–ethoxycarbonyl–3–[3–(5-methoxyindolyl)]–3–phenyl propanoate



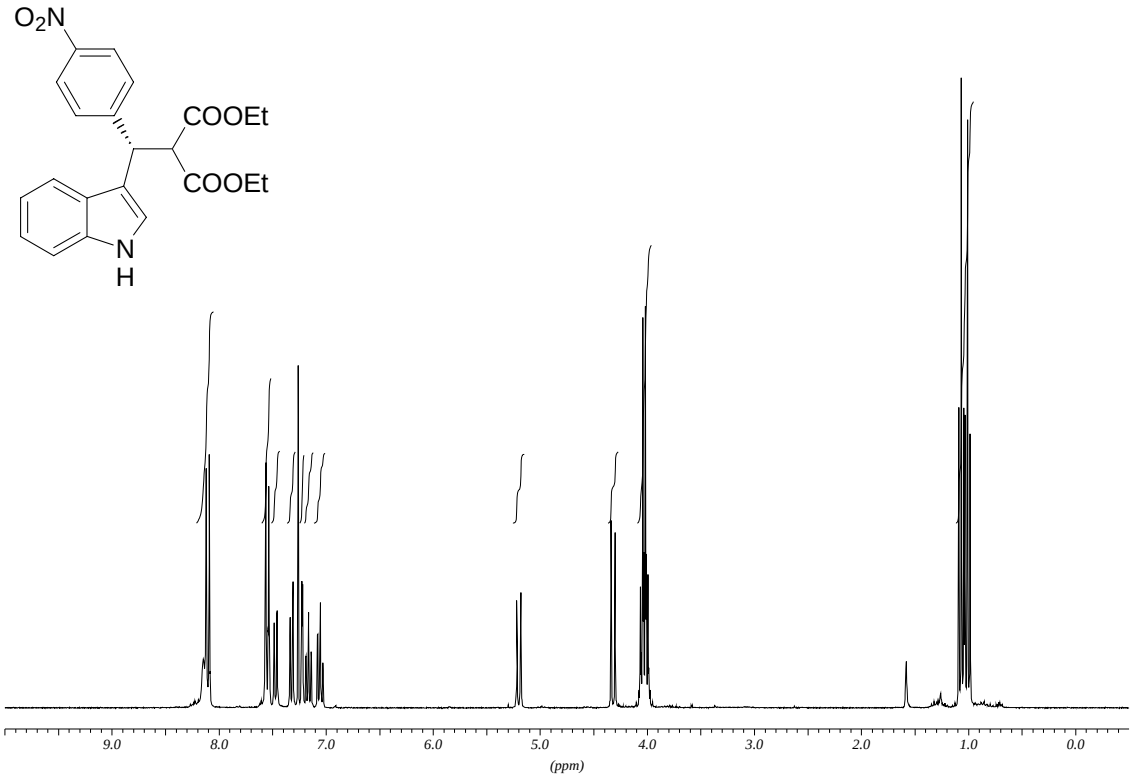
Prepared according to the general procedure and purified by column chromatography (performed with hexanes/DCM 1:1, followed by DCM) to obtain the pure product as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.97-1.04 (m, 6 H), 3.78 (s, 3 H), 3.93-4.07 (m, 4 H), 4.26 (d, *J* = 11.8 Hz, 1 H), 5.02 (d, *J* = 11.8 Hz, 1 H), 6.78 (dd, *J* = 8.8, 2.5 Hz, 1 H), 6.96 (d, *J* = 2.2 Hz, 1 H), 7.10-7.25 (m, 5 H), 7.33-7.40 (m, 1 H), 7.92 (brs, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.1, 167.9, 154.0, 141.4, 131.3, 128.4, 128.2, 127.2, 126.8, 121.6, 116.8, 112.5, 111.6, 101.3, 61.5, 61.4, 58.4, 55.8, 42.9, 13.8; MS (CI): m/z (%) = 413 (MNH_4^+, 71), 396 (MH^+, 3), 236 (100), 178 (13); mp 146-148°C; HPLC analysis (Chiralcel OD/OD-H, 10% iPrOH/n-hexane, 0.5 mL/min, 254 nm; t_r (minor) = 31.91 min, t_r (major) = 39.78 min); >89 % *ee*; $[\alpha]_D^{25}$ = + 11.3 (20mg/2 mL CH_2Cl_2).

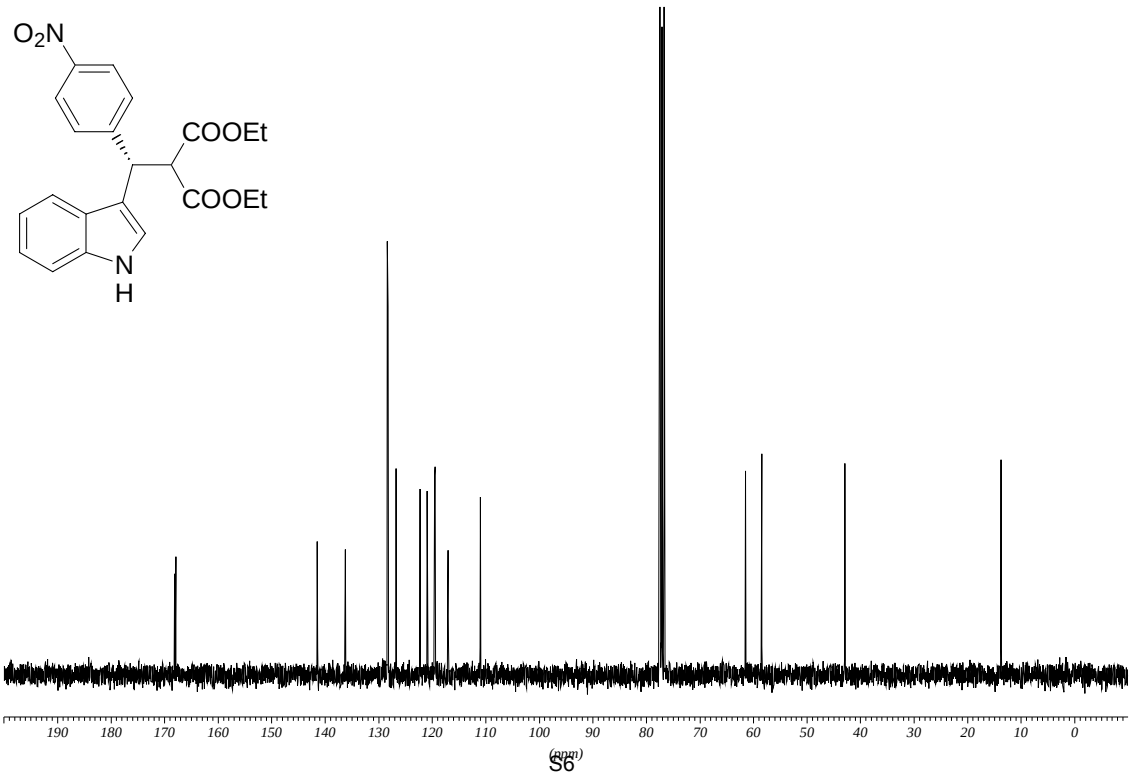
(S)–Ethyl 2–ethoxycarbonyl–3–(3–indolyl)–3–phenyl propanoate



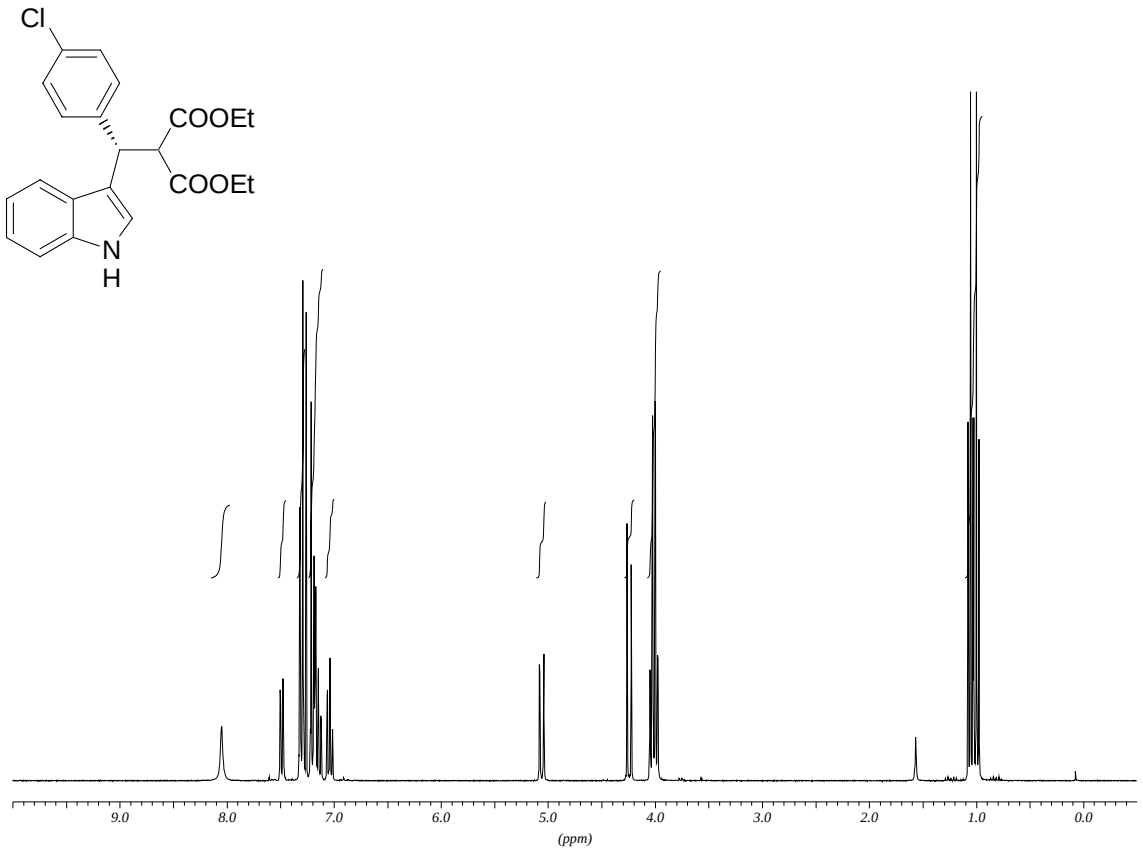


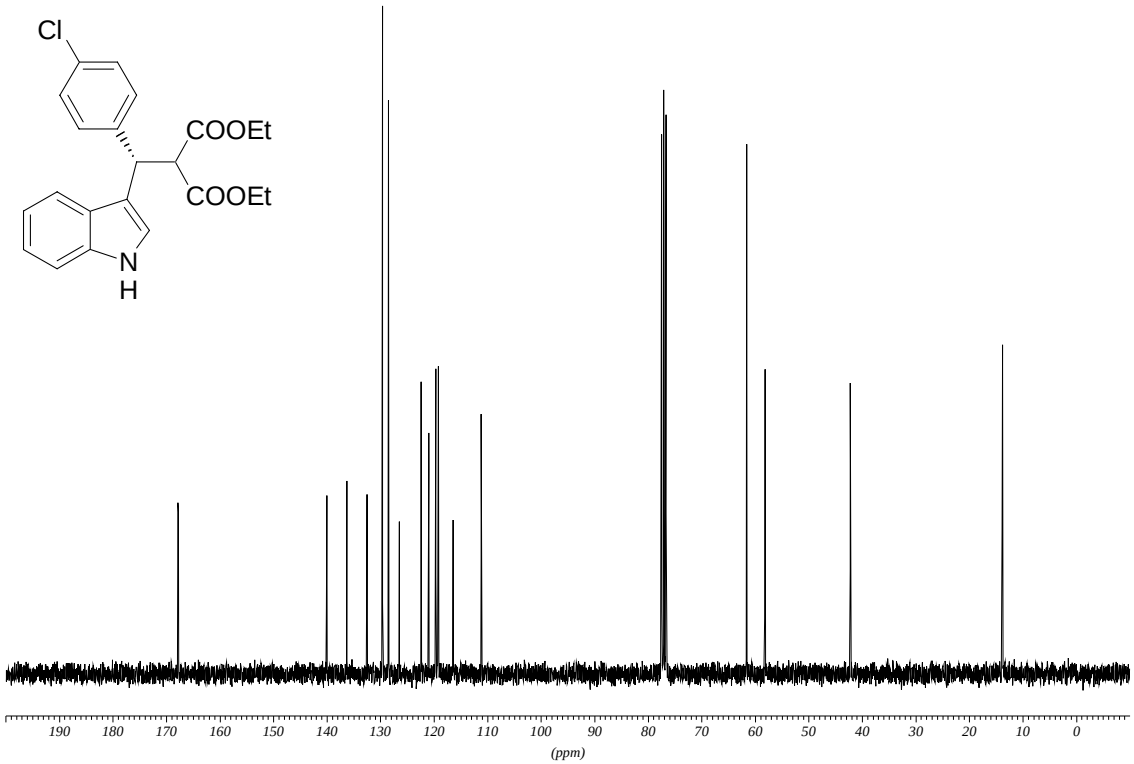
(S)–Ethyl 2–ethoxycarbonyl–3–(3–indolyl)–3–(p-nitrophenyl) propanoate



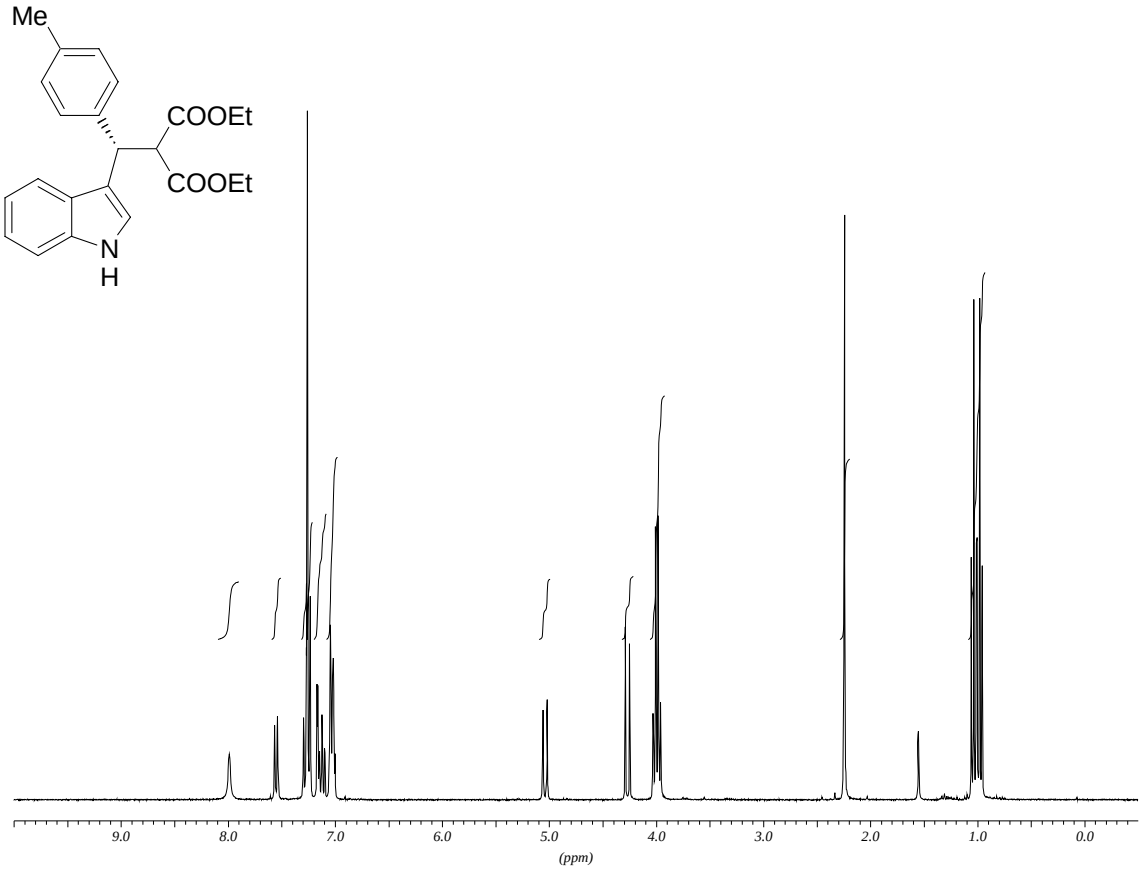


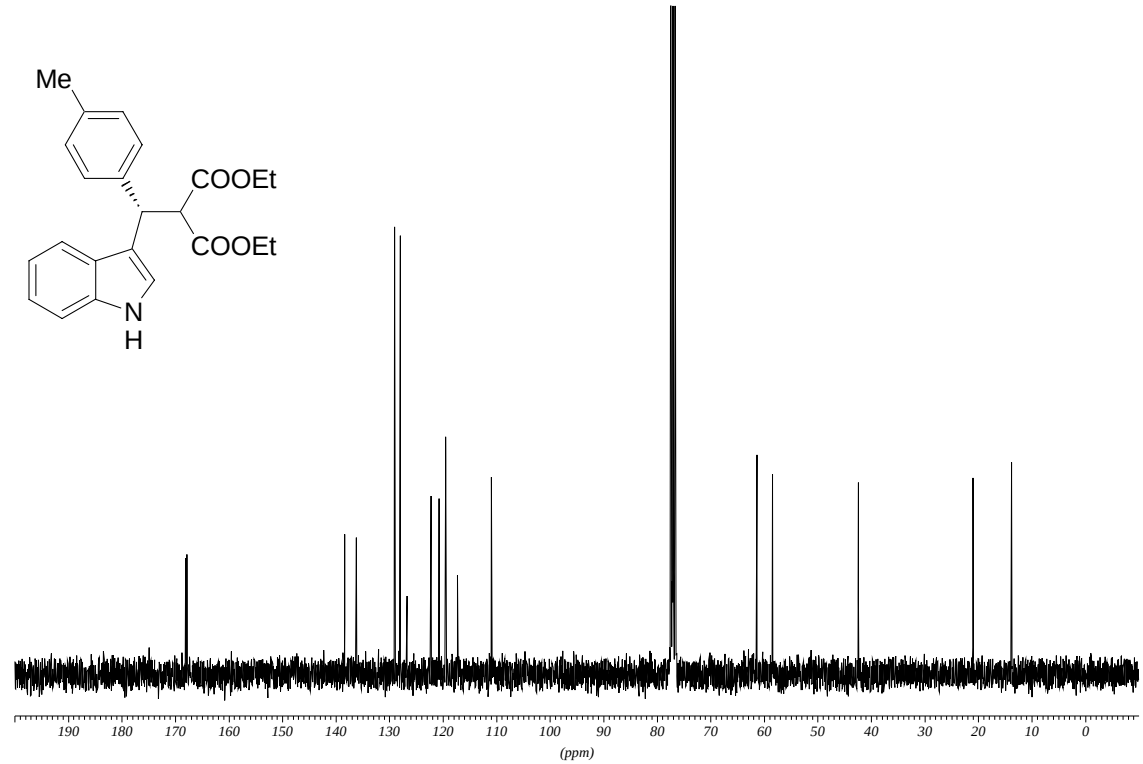
(S)–Ethyl 2–ethoxycarbonyl–3–(3–indolyl)–3–(p-chlorophenyl) propanoate



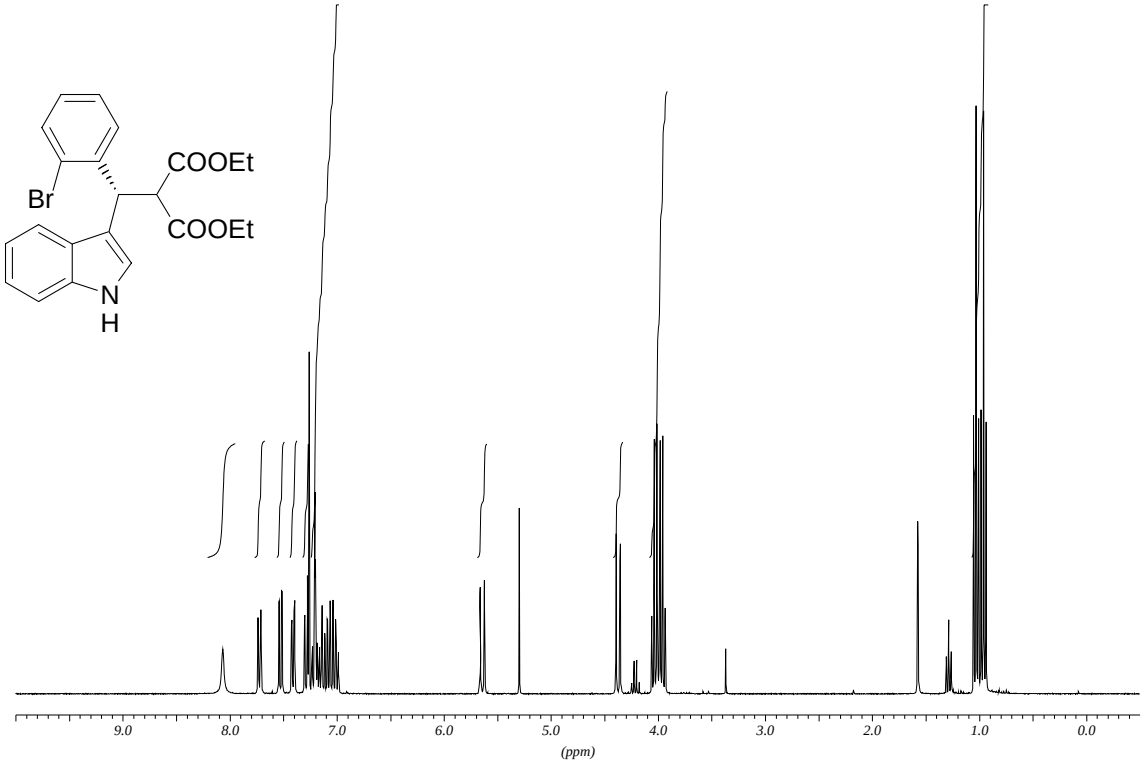


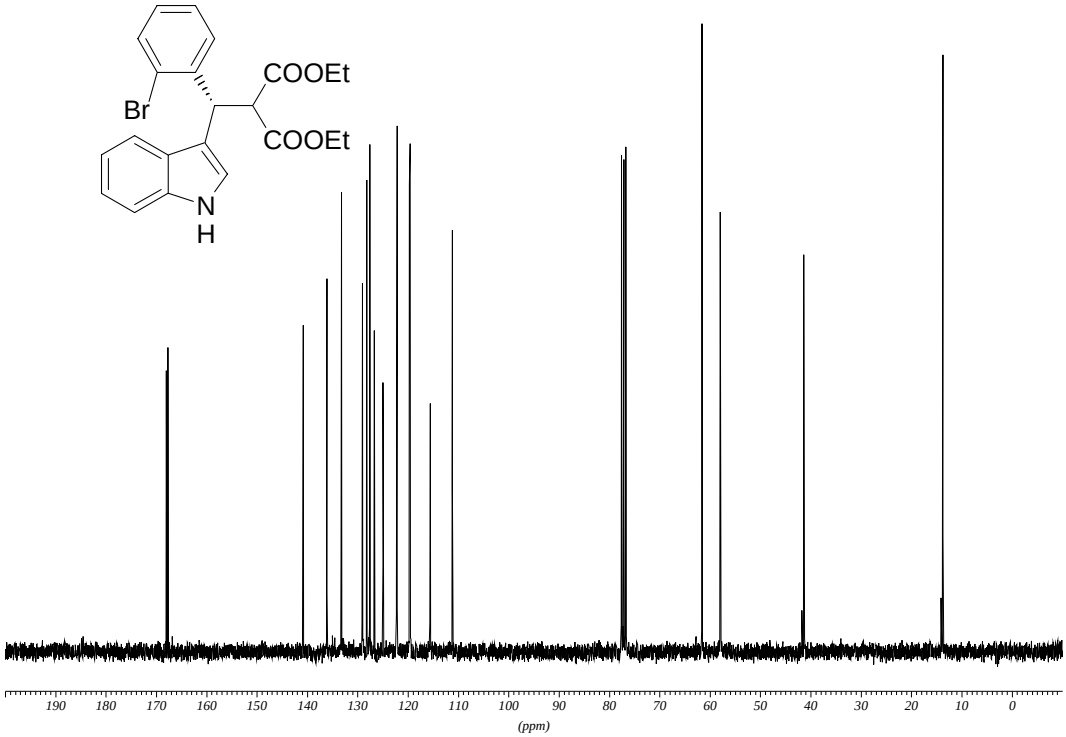
(S)–Ethyl 2–ethoxycarbonyl–3–(3–indolyl)–3–(p-methylphenyl) propanoate



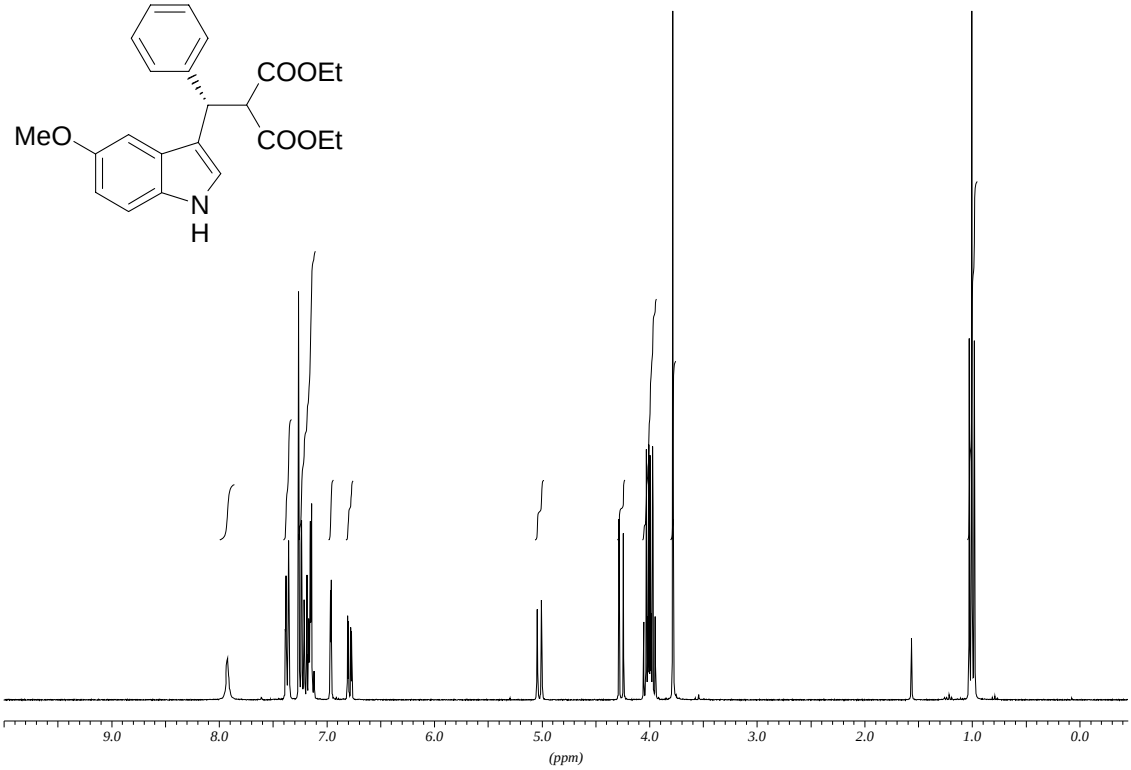


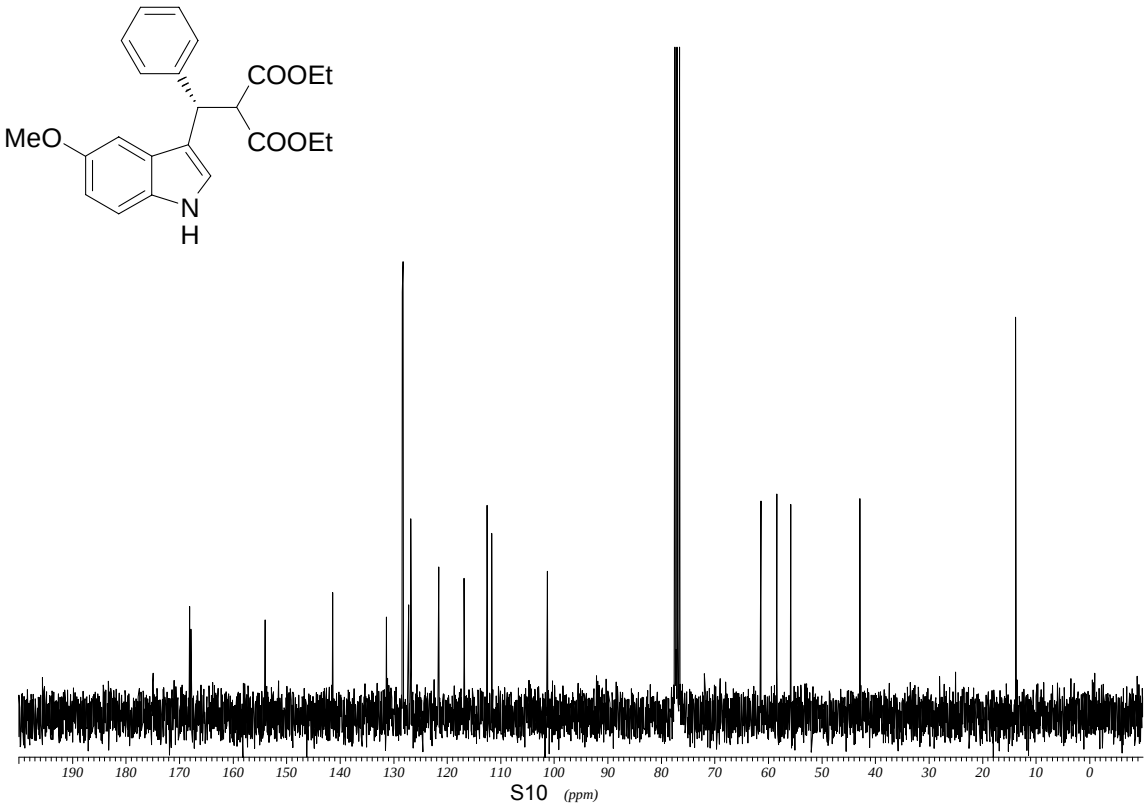
(S)–Ethyl 2–ethoxycarbonyl–3–(3–indolyl)–3–(o-bromophenyl) propanoate

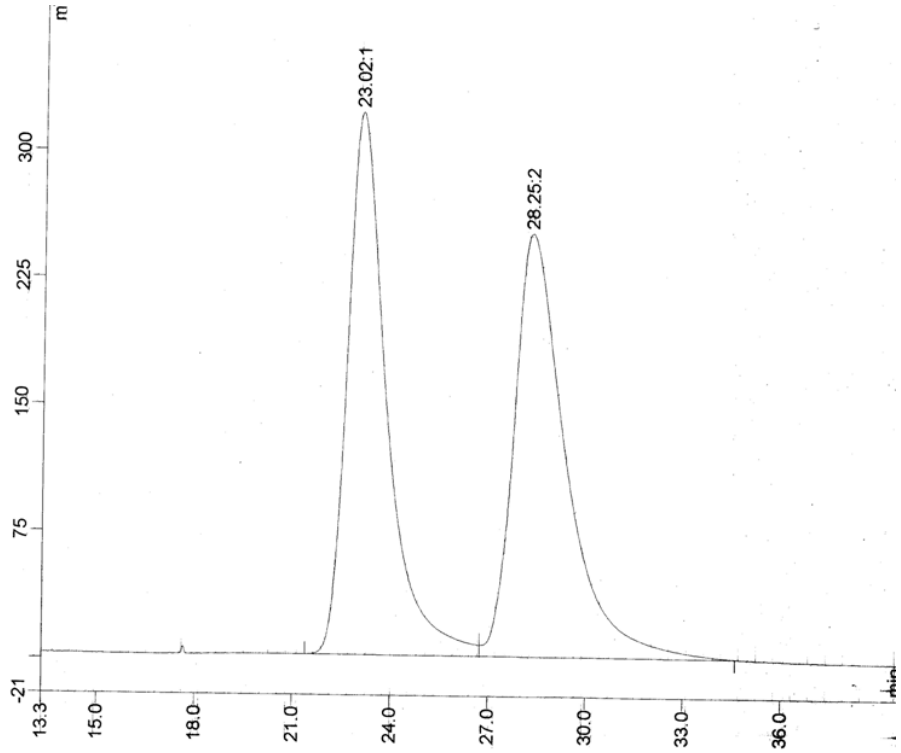


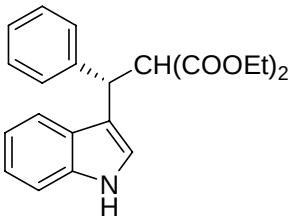


(S)–Ethyl 2–ethoxycarbonyl–3–[3–(5-methoxyindolyl)]–3–phenyl propanoate



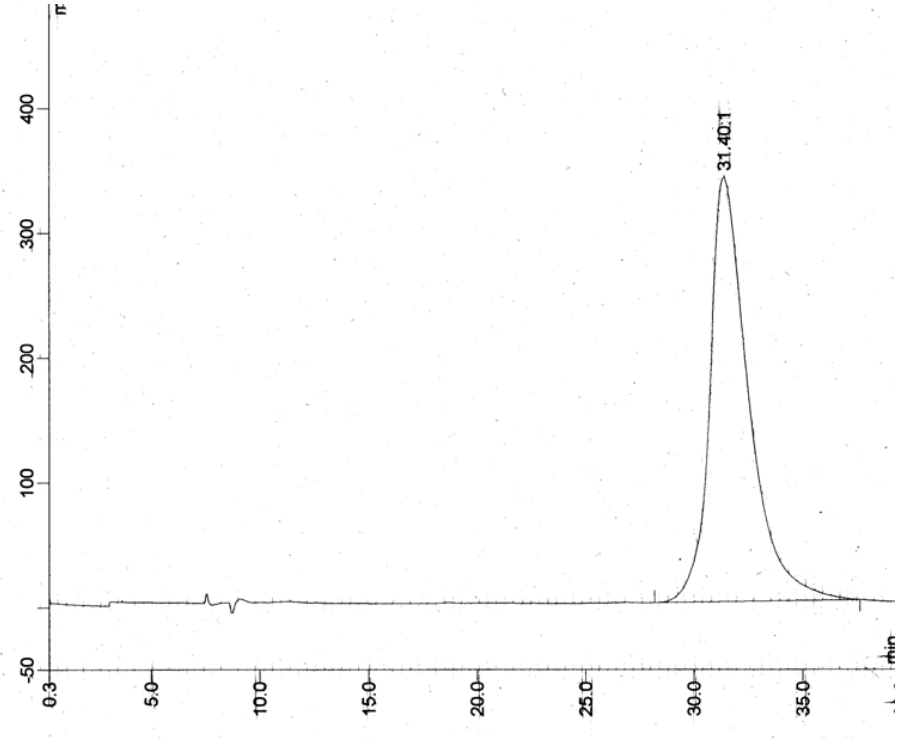


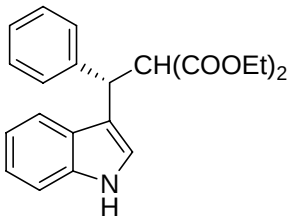




Area mV*min	Amount	Rel.Ar %
4.5010e+002	?	49.21
4.6451e+002	?	50.79

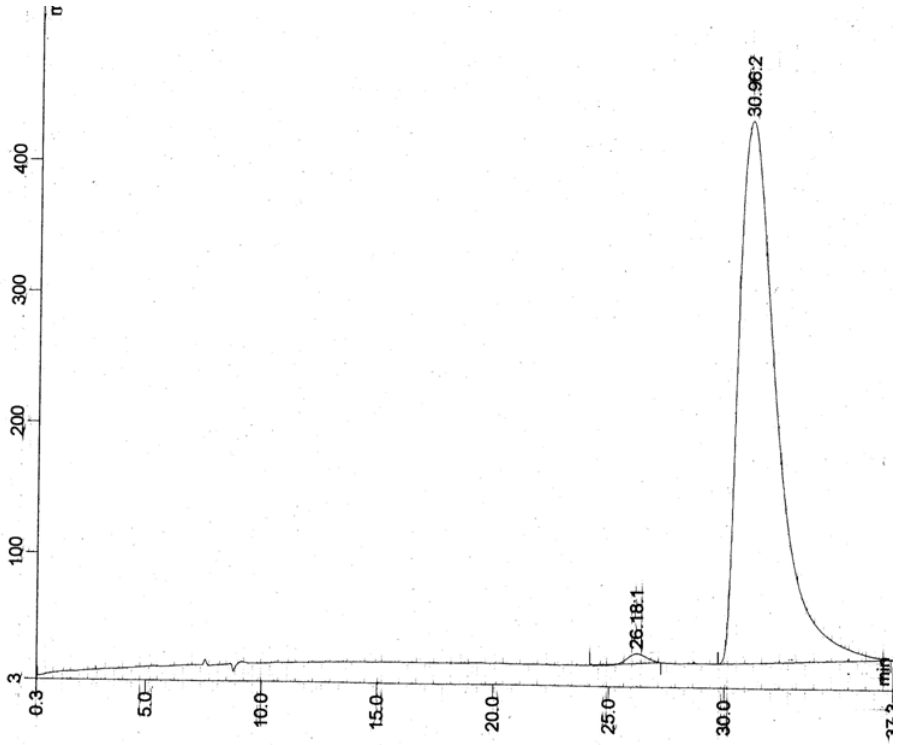
Racemic Control

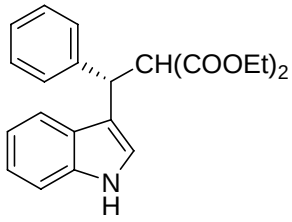




Area mV*min	Amount	Rel.Ar %
7.0741e+002	2.2789e+000	100.00

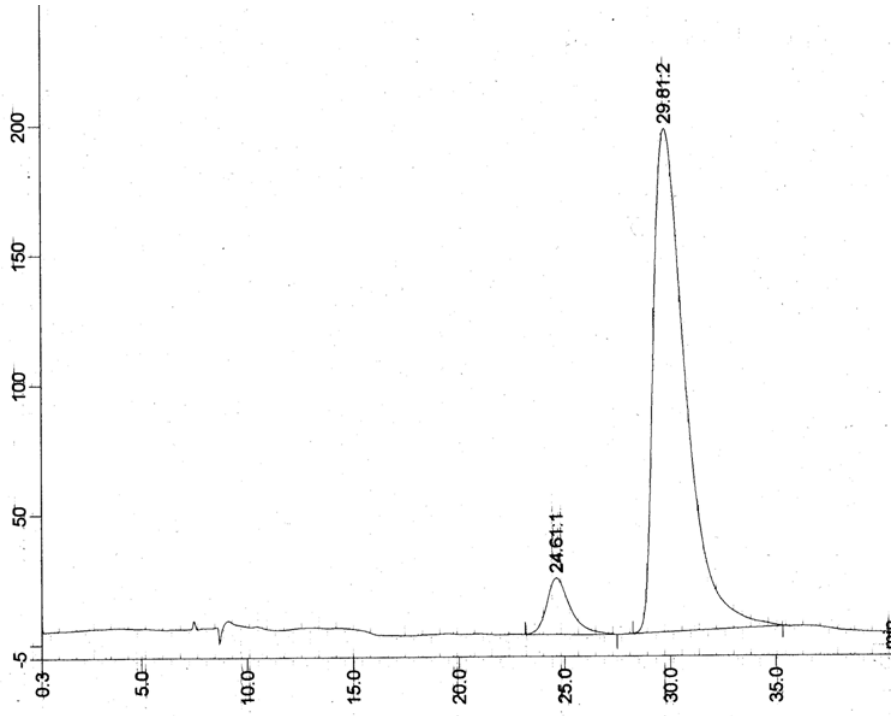
Table 1, Entry **13**
Cu/Ligand: 0.048/0.050

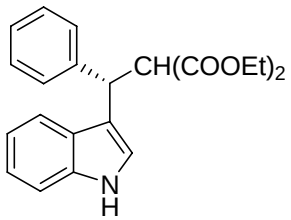




Area	Amount	Rel.Ar
mV*min		%
6.8129e+000	?	0.85
7.9039e+002	2.5463e+000	99.15

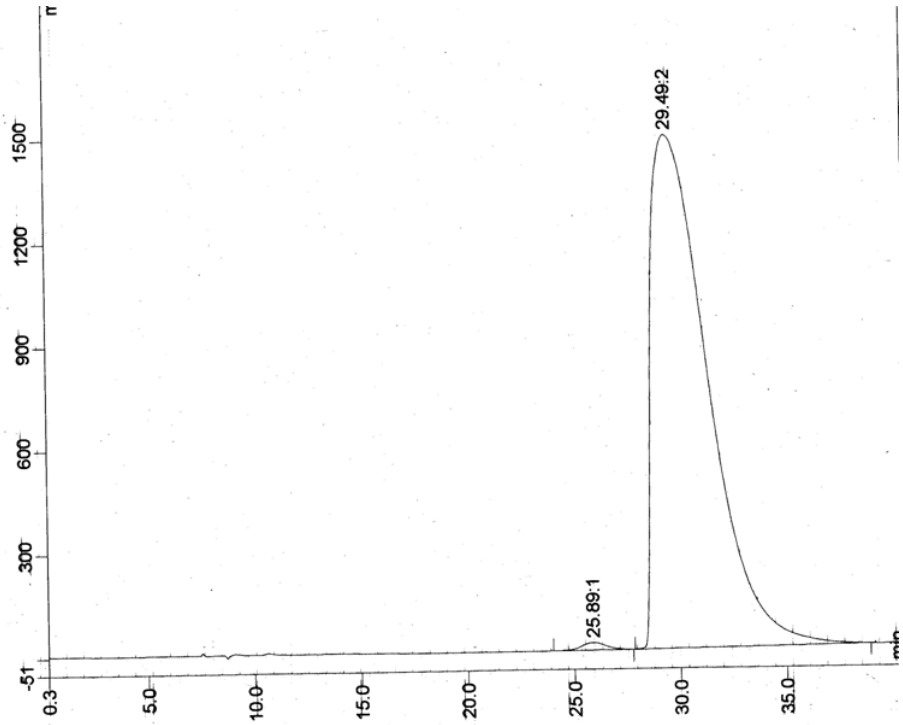
Entry **14**
Cu/Ligand: 0.050:0.050

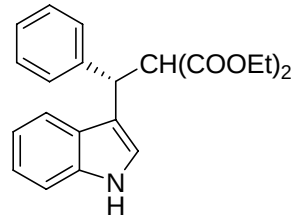




Area	Amount	Rel.Ar
mV*min		%
2.7914e+001	0.0000e+000	7.58
3.4011e+002	1.0957e+000	92.42

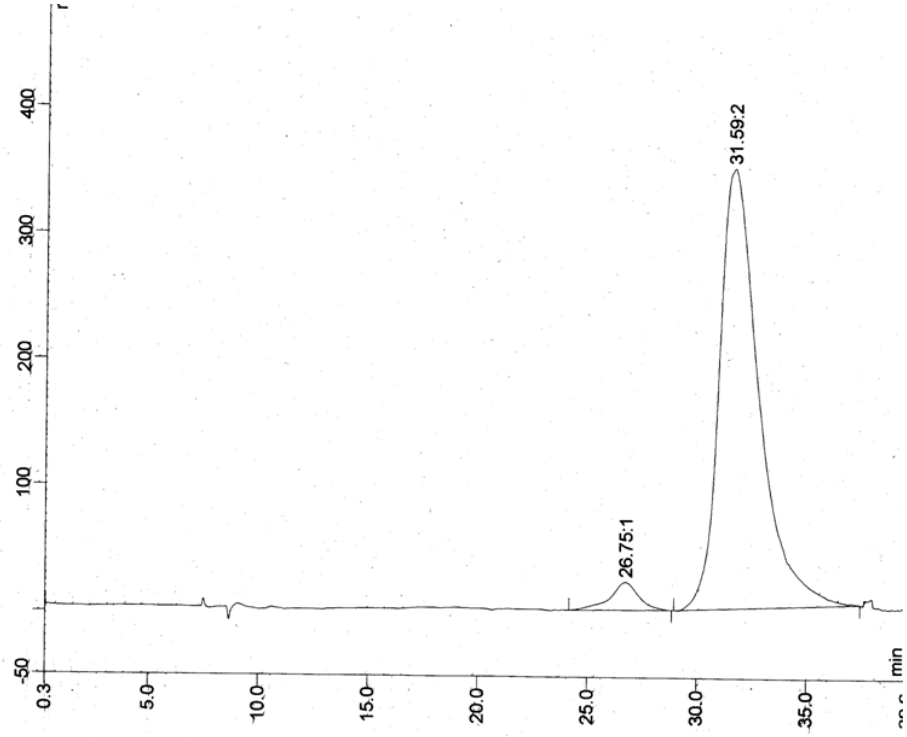
Entry **12**
Cu/Ligand: 0.045:0.050

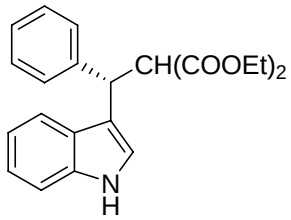




Area mV*min	Amount	Rel.Ar %
2.9611e+001	0.0000e+000	0.65
4.5335e+003	?	99.35

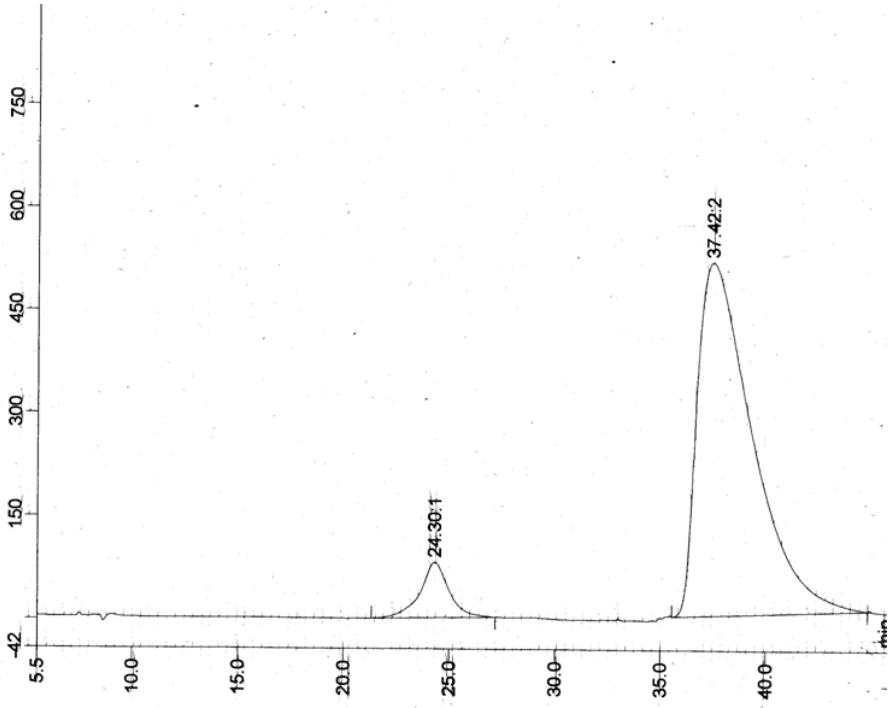
Entry **15**
Cu/Ligand: 0.055:0.050

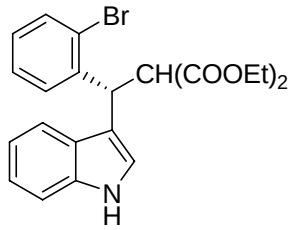




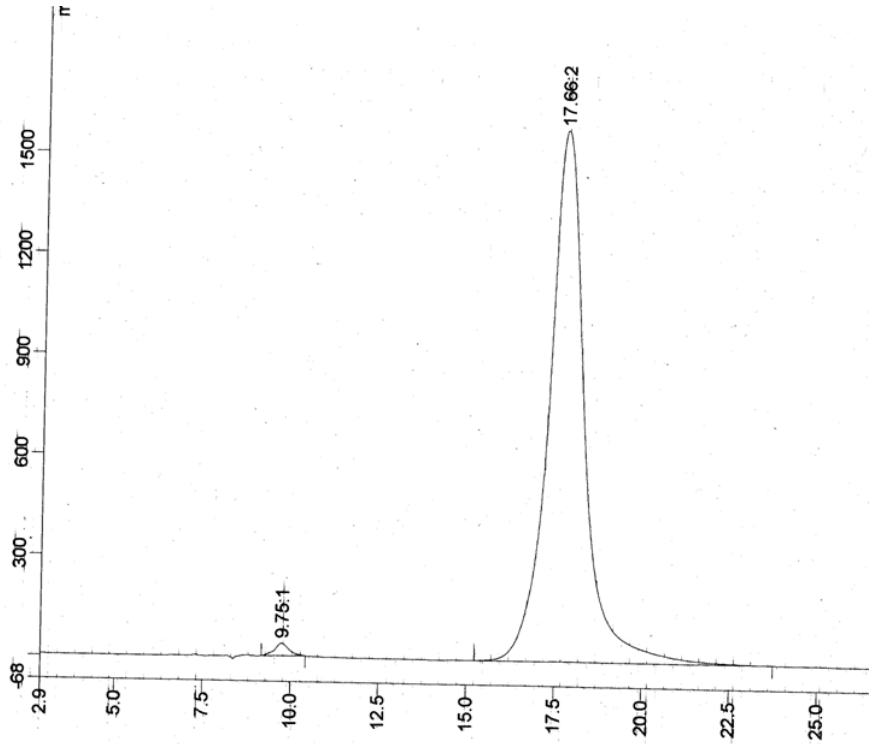
Area mV*min	Amount	Rel.Ar %
3.3876e+001	?	4.41
7.3420e+002	0.0000e+000	95.59

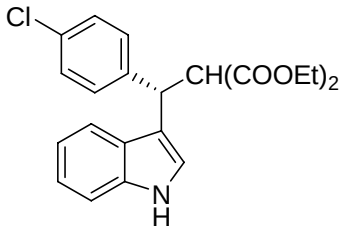
Entry **16**
Cu/Ligand: 0.065/0.050



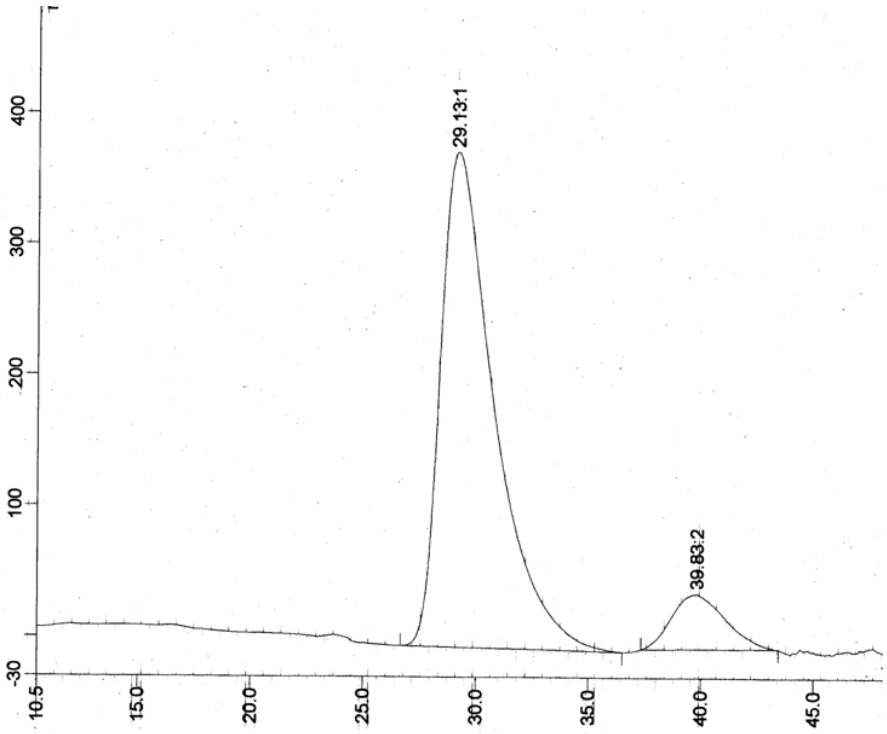


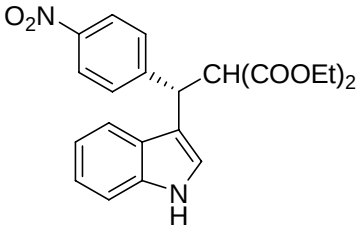
Area	Amount	Rel.Ar
mV*min		%
1.2769e+002	0.0000e+000	7.57
1.5592e+003	?	92.43



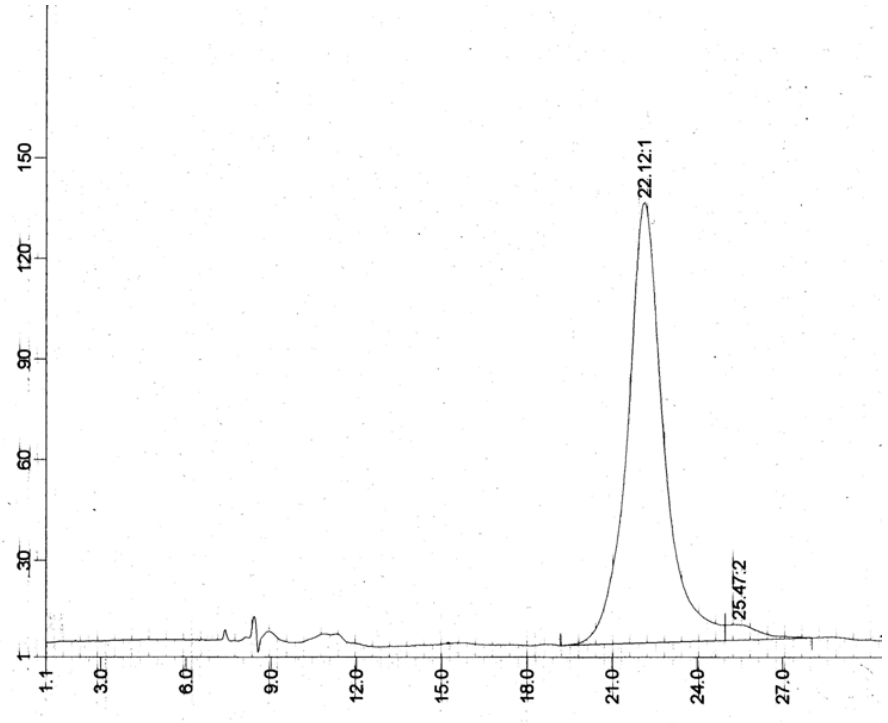


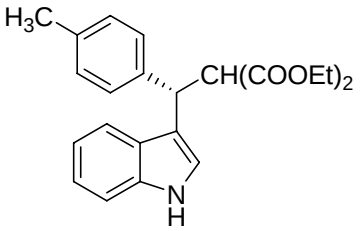
Area	Amount	Rel.Ar
mV*min		%
1.7144e+001	0.0000e+000	0.91
1.8718e+003	?	99.09



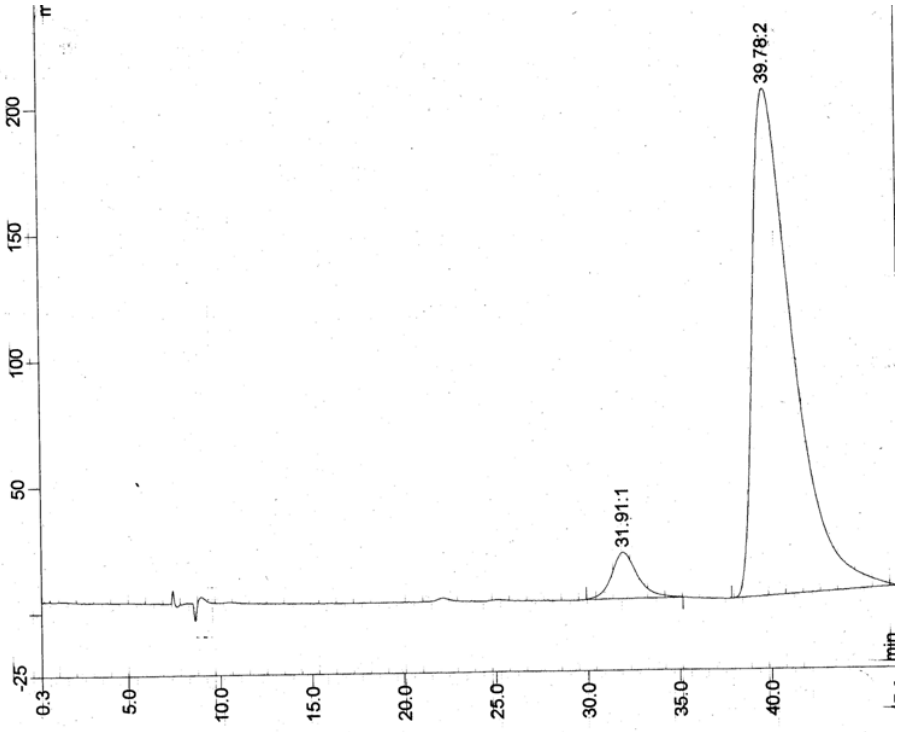


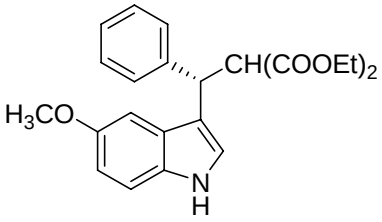
Area mV*min	Amount	Rel.Ar %
1.0486e+003	?	89.96
1.1707e+002	?	10.04





Area mV*min	Amount	Rel.Ar %
1.9423e+002	?	96.84
6.3299e+000	0.0000e+000	3.16





Area	Amount	Rel.Ar
mV*min		%
2.9905e+001	9.6340e-002	5.58
5.0576e+002	?	94.42