

Supporting information for:

CuO/SiO₂ as simple, effective and recoverable catalyst for alkylation of indole derivatives with diazocompounds

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General information

Unless otherwise stated, all the reactions were carried out under an atmosphere of dry nitrogen or argon using oven-dried (120°C) glassware. Dichloromethane, dichloroethane and acetonitrile were distilled from calcium hydride. THF was distilled from sodium and benzophenone.

Analytical TLC was performed on ready-made plates coated with silica gel on aluminium (Merck 60 F₂₅₄). Products were visualized by ultraviolet light and treatment either with *p*-anisaldehyde or phosphomolybdic acid stain followed by gentle heating or with iodine stain. Flash chromatography was performed using Merck silica gel 60 (230-400 mesh).

NMR spectra were recorded on a Bruker AV-400 spectrometer as solutions in deuteriochloroform (CDCl₃), unless otherwise indicated. ¹H and ¹³C chemical shifts are reported in parts per million (ppm) downfield to tetramethylsilane using the residual solvent signal as internal standard. Proton (¹H) NMR information is given in the following format: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant(s) (*J*) in Hertz (Hz), number of protons. The prefix *app* is occasionally applied when the true signal multiplicity was unresolved and br indicates the signal in question broadened.

All melting points were recorded on Büchi apparatus with samples crystallized from hexane and are reported uncorrected. High-resolution mass spectra (HRMS) were recorded at the MS service of CEQMA (Centro de Química y Materiales de Aragón) in a Bruker Microtof-Q spectrometer by electrospray ionization (ESI).

1*H*-Indole (**1b**), 2-methyl-1*H*-indole (**1h**), 1,2-dimethyl-1*H*-indole (**1i**), 1*H*-pyrrole (**5a**) *tert*-butyl diazoacetate (**2f**) and dimethyl diazomalonate (**2g**) were commercially available and they were used as received.

Part 1: Preparation of the catalysts and starting materials

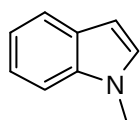
Preparation of the catalysts CuO/SiO₂, CuO_x/SiO₂-Al₂O₃, CuO/TiO₂

Catalysts were prepared by the chemisorptions-hydrolysis method.¹ Three different supports were used: Silica gel (surface area: 300 m²/g, pore volume: 1.70 ml/g, mean pore radius: 114 Å), SiO₂-AlO₃ (13% alumina, surface area: 485 m²/g, pore volume: 0.79 ml/g, mean pore radius: 33 Å) and TiO₂ (Degussa P-25 80% anatase, 20% rutile, surface area: 50 m²/g).

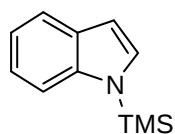
The powder was added to a [Cu(NH₃)₄]²⁺ solution prepared by dropping aqueous NH₃ to a Cu(NO₃)₂·3H₂O solution until pH 9 had been reached. After 20 min under stirring, the slurry, held in an ice bath at 273 K, was diluted with water. The solid was separated by filtration, washed with water, dried overnight at 383 K, and calcined in air at 673 K.

Preparation of N-alkyl indole derivatives

To an ice-bath cooled suspension of washed NaH (1.2 equiv.) in THF was added dropwise the corresponding indole derivative (1 equiv.) at 0°C. The resulting mixture was stirred at 0°C for 30 min. and at room temperature for additional 30 min. After cooling to 0 °C, haloalkane (1.2-3 equiv.) was added and the solution was stirred at room temperature for 24h. Then a saturated aqueous solution of NH₄Cl was added and the product was extracted with AcOEt. The combined organic phases were washed by water and brine, and dried over MgSO₄. The product was then purified by flash chromatography.

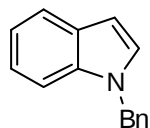


1-Methyl-1H-indole (1a). Chemical yield: 90%, colorless oil, *R_f* (Hex/AcOEt 9/1) 0.57; ¹H NMR: 7.64-7.68 (m, 1H), 7.33-7.37 (m, 1H), 7.22-7.27 (m, 1H), 7.11-7.16 (m, 1H), 7.07 (d, *J* = 3Hz, 1H), 6.50-6.52 (m, 1H), 3.81 (s, 1H); ¹³C NMR: 136.6, 128.7, 128.4, 121.4, 120.8, 119.2, 109.1, 100.8, 32.8. The analysis data obtained are in agreement with the literature values.²

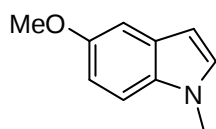


1-(Trimethylsilyl)-1H-indole (1c). Chemical yield: 75%, colorless oil, *R_f* (Hex/AcOEt 9/1) 0.78; ¹H NMR: 7.73-7.77 (m, 1H), 7.58-7.61 (m, 1H), 7.20-

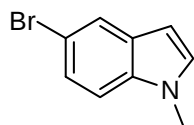
7.31 (m, 3H), 6.69 (dd, $J = 0.9, 3.1$ Hz, 1H), 0.64 (s, 9H); ^{13}C NMR: 140.1, 131.5, 129.8, 121.4, 120.8, 119.8, 112.9, 104.5, -0.1. The analysis data obtained are in agreement with the literature values.³



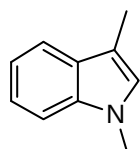
1-Benzyl-1H-indole (1d). Chemical yield: 65%, white solid, m.p. = 44-45°C; R_f (Hex/AcOEt 9/1) 0.60; ^1H NMR: 7.66 (d, $J = 7.7$ Hz, 1H), 7.27-7.33 (m, 3H), 7.16-7.21 (m, 1H), 7.10-7.15 (m, 3H), 6.57 (s, 2H), 5.34 (s, 2H); ^{13}C NMR: 137.5, 136.3, 128.7, 128.2, 127.6, 126.7, 121.7, 121.0, 119.50, 119.49, 109.7, 101.7, 50.0. The analysis data obtained are in agreement with the literature values.⁴



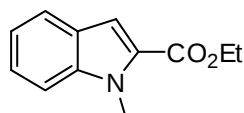
5-Methoxy-1-methyl-1H-indole (1f). Chemical yield: 50%, white solid, m.p. = 95-96°C (hexane), R_f (Hex/AcOEt 9/1) 0.42; ^1H NMR: 7.22 (d, $J = 8.3$ Hz, 1H), 7.10 (d, $J = 2.4$, 1H), 7.02 (d, $J = 3.0$ Hz, 1H), 6.89 (dd, $J = 2.5, 8.5$ Hz, 1H), 6.40 (dd, $J = 0.7, 3.0$ Hz, 1H), 3.86 (s, 3H), 3.77 (s, 3H); ^{13}C NMR: 154.0, 132.1, 129.3, 128.7, 111.8, 109.9, 102.5, 100.4, 55.9, 33.0. The analysis data obtained are in agreement with the literature values.⁵



5-Bromo-1-methyl-1H-indole (1g). Chemical yield: 87%, white oily solid, R_f (Hex/AcOEt 9/1) 0.42; ^1H NMR: 7.54-7.56 (m, 1H), 7.30 (dd, $J = 1.9, 8.7$ Hz, 1H), 7.19 (d, $J = 8.7$ Hz, 1H), 7.05 (d, $J = 3$ Hz, 1H), 6.42 (dd, $J = 0.8, 3.1$ Hz, 1H), 3.77 (s, 3H); ^{13}C NMR: 135.3, 130.1, 129.9, 124.2, 123.2, 112.6, 110.6, 100.5, 32.9. The analysis data obtained are in agreement with the literature values.⁴



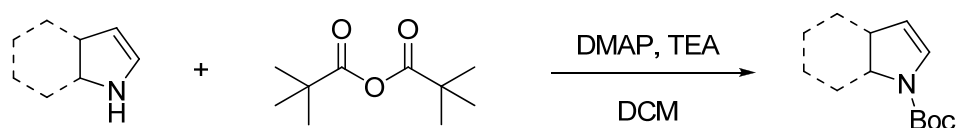
1,3-Dimethyl-1H-indole (1j). Chemical yield: 88%, colorless oil, R_f (Hex/AcOEt 9/1) 0.67; ^1H NMR: 7.57 (*app* dt, $J = 8.0, 1.0$ Hz, 1H), 7.28 (*app* dt, $J = 8.0, 1.0$ Hz, 1H), 7.22 (ddd, $J = 1.1, 6.8, 8.0$ Hz, 1H), 7.11 (ddd, $J = 1.1, 6.8, 8.0$ Hz, 1H), 6.82 (d, $J = 0.9$ Hz, 1H), 3.74 (s, 3H), 2.33 (d, $J = 0.9$ Hz, 3H); ^{13}C NMR: 136.9, 128.6, 126.5, 121.3, 118.9, 118.4, 110.0, 108.9, 32.4, 9.4. The analysis data obtained are in agreement with the literature values.⁴



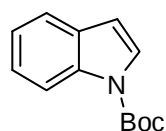
Ethyl 1-methyl-1H-indole-2-carboxylate (1k). Chemical yield: 83%, white solid, m.p. = 58-59°C (hexane), R_f (Hexane/Et₂O) 0.44; ^1H NMR:

7.68 (dt, $J = 8.0, 0.9$ Hz, 1H), 7.38-7.41 (m, 1H), 7.36 (dd, $J = 1.1, 6.5$ Hz, 1H), 7.30-7.32 (m, 1H), 7.12-7.17 (m, 1H), 4.28 (q, $J = 7.1$ Hz, 2H), 4.09 (s, 3H), 1.41 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR: 162.2, 139.6, 128.0, 125.9, 124.9, 122.5, 120.5, 110.2, 110.1, 60.5, 31.6, 14.4. The analysis data obtained are in agreement with the literature values.⁶

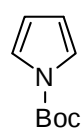
Preparation of *tert*-butyl 1*H*-indole-1-carboxylate (1e) and *tert*-butyl 1*H*-pyrrole-1-carboxylate (5b).



To a stirred solution of N-heterocycle (4.27 mmol) in DCM (50 mL) was successively added DMAP (52 mg, 0.427 mmol), triethylamine (560 mg, 0.768 mL, 5.55 mmol) and Boc₂O (1.211 mg, 5.55 mmol). The resulting solution was stirred at room temperature for 24 h. Then, aqueous solution of NH₄Cl (30 mL) was added and the organic phase was separated. The aqueous phase was extracted with EtOAc (3 × 30 mL), the combined organic phases were washed with water (30 mL) and brine (30 mL) and dried over MgSO₄. Flash chromatography (hexane/Et₂O 95/5) affords the desired compounds.



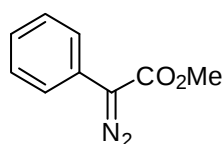
***tert*-Butyl 1*H*-indole-1-carboxylate (1e):** colorless oil (920 mg, 100% yield). R_f (Hexane/Et₂O 9/1) 0.66; ^1H NMR: 8.16 (d, $J = 8.0$ Hz, 1H), 7.61 (d, $J = 3.7$ Hz, 1H), 7.55-7.59 (m, 1H), 7.29-7.35 (m, 1H), 7.23 (td, $J = 7.5, 1.1$ Hz, 1H), 6.58 (dd, $J = 0.7, 3.7$ Hz, 1H) 1.69 (s, 9H); ^{13}C NMR: 149.8, 135.1, 130.5, 125.9, 124.2, 122.6, 120.9, 115.1, 107.2, 83.6, 28.2. The analysis data obtained are in agreement with the literature values.⁷



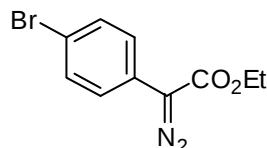
***tert*-Butyl 1*H*-pyrrole-1-carboxylate (5b):** colorless oil (800 mg, 64%); R_f (Hexane/Et₂O 9/1) 0.71; ^1H NMR: 7.22-7.25 (m, 2H), 6.20-6.23 (m, 2H), 1.60 (s, 9H); ^{13}C NMR: 148.9, 119.9, 111.8, 83.5, 28.0. The analysis data obtained are in agreement with the literature values.⁸

Preparation of phenyldiazoacetates.

To a stirred solution of methyl phenylacetate (3.0 g, 20.0 mmol) and *p*-acetamidobenzenesulfonyl azide (5.76 g, 24 mmol) in dry acetonitrile (40 mL) was added dropwise solution of DBU (3.73 mL) in dry acetonitrile (10 mL) at 0°C. The mixture was stirred overnight and the solvent was removed in vacuum. Solid residues were dissolved in dichloromethane and the solution was washed with saturated aqueous solution of NH₄Cl, water and brine. After drying with MgSO₄ and concentration in vacuum, a short chromatography column (hexane/AcOEt 95/5) affords the titled compound as an orange oil (2.8 g, 80% yield).

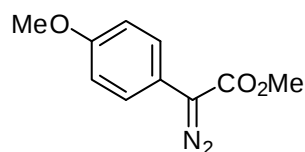


Methyl phenyldiazoacetate (2a). Chemical yield: 80%, orange oil, *R_f* (Hexane/Et₂O 9/1) 0.51; ¹H NMR: 7.46-7.50 (m, 2H), 7.36-7.40 (m, 2H), 7.16-7.21 (m, 1H), 3.87 (s, 3H); ¹³C NMR: 166.0, 129.4, 126.3, 126.0, 124.4, 52.4 (C=N₂ missing). The analysis data obtained are in agreement with the literature values.⁹



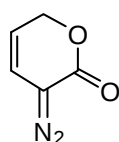
Reaction performed with ethyl 2-(4-bromophenyl) acetate affords **ethyl diazo(4-bromophenyl)acetate (2b)** (eluent hexane/Et₂O 90/10).

Chemical yield: 90%, orange solid, *R_f* (Hex/AcOEt 9/1) 0.60; m.p. = 54-55°C (hexane); ¹H NMR: 7.49 (dt, *J* = 8.9, 2.3 Hz, 2H), 7.36 (dt, *J* = 8.9, 2.3 Hz, 2H), 4.33 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H); ¹³C NMR: 164.8, 132.0, 125.3, 124.8, 119.2, 61.1, 14.5 (C=N₂ missing). The analysis data obtained are in agreement with the literature values.¹⁰



Reaction performed with methyl 2-(4-methoxyphenyl)acetate affords **methyl diazo(4-methoxyphenyl)acetate (2c)** (eluent hexane/AcOEt 95/5).

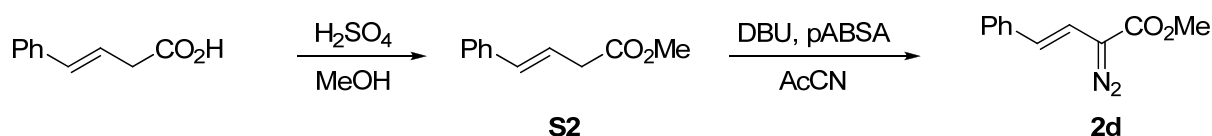
Chemical yield: 71%, orange solid, *R_f* (Hex/AcOEt 9/1) 0.50; m.p. < 40°C (hexane), ¹H NMR: 7.38 (app d, *J* = 9.1 Hz, 2H), 6.94 (app d, *J* = 9.1 Hz, 2H), 3.85 (s, 3H), 3.81 (s, 3H); ¹³C NMR: 166.1, 158.1, 128.9, 116.8, 114.6, 55.3, 51.9 (C=N₂ missing). The analysis data obtained are in agreement with the literature values.⁹



Reaction performed with 5,6-dihydro-2*H*-pyran-2-one affords **3-diazo-3,6-dihydro-2*H*-pyran-2-one (2e)** (eluent hexane/AcOEt 2/1).

Chemical yield: 63%, orange solid, m.p. = 59-60°C (hexane); *R_f* (Hexane/iPrOH 8/2) 0.37; ¹H NMR: 6.20 (dt, *J* = 10.0, 1.8 Hz, 1H), 5.38 (td, *J* = 3.3, 10.0 Hz, 1H), 4.99 (dd, *J* = 3.3, 1.8 Hz, 2H); ¹³C NMR: 164.0, 113.7, 113.1, 69.8 (C=N₂ missing). The analysis data obtained are in agreement with the literature values.¹¹

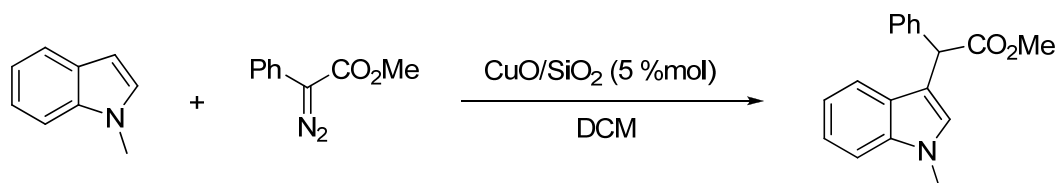
Preparation of (*E*)-methyl 2-diazo-4-phenylbut-3-enoate (2d)



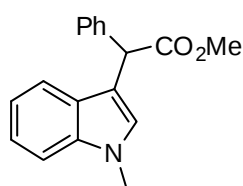
(*E*)-Methyl 4-phenylbut-3-enoate S2. Concentrated H₂SO₄ (0.2 mL) was added to the solution of *trans*-styryl acetic acid (500 mg, 3.1 mmol) in 10 mL methanol and the reaction mixture was heated under reflux overnight. Reaction mixture was diluted with 30 mL ethyl acetate, and washed once with 10 mL saturated NaHCO₃. Organic layer was washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The colorless oil was directly used in the next step without further purification. ¹H NMR: 7.35-7.39 (m, 2H), 7.28-7.34 (m, 2H), 7.20-7.25 (m, 1H), 6.46-6.52 (m, 1H), 6.29 (dt, *J* = 15.9, 7.1 Hz, 1H), 3.72 (s, 3H).

(*E*)-Methyl 2-diazo-4-phenylbut-3-enoate (2d). To a stirred solution of crude (*E*)-methyl 4-phenylbut-3-enoate and *p*-acetamidobenzenesulfonyl azide (889 mg, 3.7 mmol) in dry acetonitrile (20 mL) was added dropwise solution of DBU (0.553 mL) in dry acetonitrile (5 mL) at 0°C. The mixture was stirred overnight and the solvent was removed in vacuum. Solid residues were dissolved in dichloromethane and the solution was washed with saturated aqueous solution of NH₄Cl, water and brine. After drying with MgSO₄ and concentration in vacuum, a short column of chromatography (hexane/AcOEt 95/5) affords the titled compound as an orange oil (370 mg, 53% over two steps). ¹H NMR: 7.29-7.39 (m, 4H), 7.17-7.21 (m, 1H), 6.48 (d, *J* = 16.3 Hz, 1H), 6.20 (d, *J* = 16.3 Hz, 1H), 3.66 (s, 3H). The analysis data obtained are in agreement with the literature values.¹²

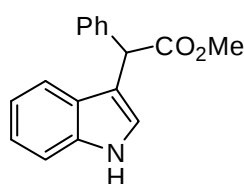
Part 2: Cu-catalyzed insertion in indole derivatives



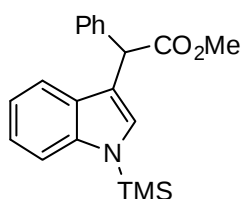
Typical conditions for the carbene insertion in indole derivatives. A solution of indole derivative (0.75 mmol.) in DCM (3 mL) was added to a dried powder of CuO/SiO₂ (copper content 4% wt, 5 mol%). To the resulting suspension was added a solution of diazo compound (0.5 mmol.) in DCM (2 mL) in 2 hours with a syringe pump. The reaction was stirred at room temperature for 15 hours. Then, concentration and direct purification with flash chromatography affords the desired product.



Methyl 2-(1-methyl-1H-indol-3-yl)-2-phenylacetate (3a). Chemical yield: 89%; colorless oil; *R_f* (Hex/AcOEt 80/20) 0.44; ¹H NMR: 7.41-7.47 (m, 3H), 7.19-7.35 (m, 5H), 7.04-7.10 (m, 2H), 5.27 (s, 1H), 3.76 (s, 3H), 3.75 (s, 3H); ¹³C NMR: 173.6, 138.8, 137.1, 128.7, 128.5, 128.0, 127.3, 127.1, 122.0, 119.4, 119.1, 112.2, 109.5, 52.4, 48.9, 32.9; HRMS (ESI-MS) *m/z*: [M+H]⁺, calcd for C₁₈H₁₈NO₂⁺, 280.1332, found 280.1328.

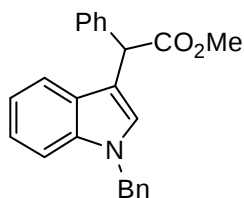


Methyl 2-(1H-indol-3-yl)-2-phenylacetate (3b). Chemical yield: 75%; colorless oil; *R_f* (Hex/AcOEt 80/20) 0.26; ¹H NMR: 8.13 (s, 1H), 7.41-7.49 (m, 3H), 7.30-7.36 (m, 3H), 7.25-7.30 (m, 1H), 7.15-7.21 (m, 2H), 7.05-7.11 (m, 1H), 5.29 (s, 1H), 3.76 (s, 3H); ¹³C NMR: 173.6, 138.6, 136.4, 128.7, 128.5, 127.4, 126.7, 123.4, 122.4, 119.9, 119.1, 113.8, 111.4, 52.4, 49.0; HRMS (ESI-MS) *m/z*: [M+Na]⁺, calcd for C₁₇H₁₅NO₂Na⁺, 288.0995, found 288.0990.

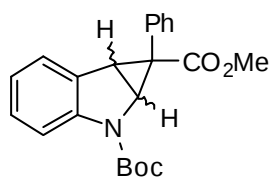


Methyl 2-(1-(trimethylsilyl)-1H-indol-3-yl)-2-phenylacetate (3c). Chemical yield : 47%; colorless oil; *R_f* (Hex/AcOEt 80/20) 0.63; ¹H NMR:

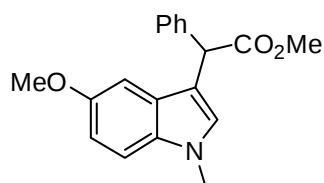
7.42-7.50 (m, 4H), 7.30-7.35 (m, 2H), 7.25-7.29 (m, 1H), 7.16-7.21 (m, 2H), 7.08-7.12 (m, 1H), 5.28 (s, 1H), 3.77 (s, 3H), 0.56 (s, 9H); ^{13}C NMR: 173.5, 140.7, 138.6, 130.3, 128.7, 128.6, 128.5, 127.3, 121.6, 119.9, 119.4, 115.2, 113.1, 52.3, 49.1, 0.1; HRMS (ESI-MS) m/z : $[\text{M}+\text{H}]^+$, calcd for $\text{C}_{20}\text{H}_{24}\text{NO}_2\text{Si}^+$, 338.1571; found 338.1574.



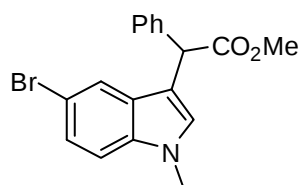
Methyl 2-(1-benzyl-1H-indol-3-yl)-2-phenylacetate (3d). Chemical yield: 83%; white crystals; m.p. = 111-113°C (hexane); R_f (Hex/AcOEt 80/20) 0.42; ^1H NMR: 7.44-7.50 (m, 3H), 7.20-7.35 (m, 8H), 7.13-7.17 (m, 1H), 7.05-7.12 (m, 3H), 5.38 (s, 1H), 5.35 (s, 2H), 3.82 (s, 3H); ^{13}C NMR: 173.5, 138.7, 137.5, 136.8, 128.8, 128.6, 128.5, 127.6, 127.5, 127.4, 127.3, 126.7, 122.1, 119.6, 119.3, 112.7, 110.0, 52.4, 50.2, 49.0; HRMS (ESI-MS) m/z : $[\text{M}+\text{H}]^+$, calcd for $\text{C}_{24}\text{H}_{22}\text{NO}_2^+$, 356.1645; found 356.1646.



1-tert-Butyl 2-methyl 2-phenyl-1a,2a-dihydrocyclopropa[b]indole-1,2-dicarboxylate (3e) (isolated as a mixture of *endo* and *exo* diastereomers in 1:1 ratio). Chemical yield: 86%; colorless solid; m.p. = 131-133°C (hexane); R_f (Hex/AcOEt 80/20) 0.45; ^1H NMR: 7.35-7.47 (m, 3H), 6.85-7.14 (m, 15H), 4.98 (d, J = 6.9 Hz, 1H), 4.87 (d, J = 6.8 Hz, 1H), 3.70-3.90 (m, 2H), 3.67 (s, 3H), 3.65 (s, 3H), 1.66 (s, 9H), 1.60 (s, 9H); ^{13}C NMR: 173.7, 173.4, 152.9, 151.7, 142.5, 141.4, 132.4, 132.1, 130.5, 130.4, 129.3, 128.4, 127.9, 127.7, 127.3, 127.2, 125.6, 125.2, 122.4, 122.3, 114.7, 114.5, 82.7, 81.9, 52.8, 52.7, 50.7, 50.6, 35.5, 34.7, 32.2, 31.9, 28.5, 28.4; HRMS (ESI-MS) m/z : $[\text{2M}+\text{Na}]^+$, calcd for $\text{C}_{44}\text{H}_{46}\text{N}_2\text{O}_8\text{Na}^+$, 753.3146; found 753.3133.

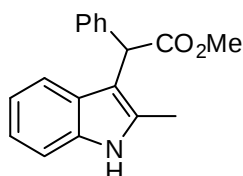


Methyl 2-(5-methoxy-1-methyl-1H-indol-3-yl)-2-phenylacetate (3f). Chemical yield: 79%; pale yellow oil; R_f (Hex/AcOEt 80/20) 0.33; ^1H NMR: (7.36-7.40 (m, 2H), 7.23-7.29 (m, 2H), 7.17-7.29 (m, 2H), 7.08-7.12 (m, 1H), 6.95 (s, 1H), 6.80-6.85 (m, 2H), 5.11 (s, 1H), 3.65 (s, 3H), 3.62 (s, 3H), 3.54 (s, 3H); ^{13}C NMR: 173.5, 154.0, 138.7, 132.5, 128.6, 128.5, 128.4, 127.4, 127.2, 112.0, 111.5, 110.2, 101.1, 55.9, 52.3, 48.9, 32.9; HRMS (ESI-MS) m/z : $[\text{M}+\text{Na}]^+$, calcd for $\text{C}_{19}\text{H}_{19}\text{NO}_3\text{Na}^+$, 332.1257; found 332.1242.



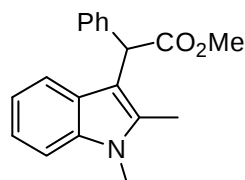
Methyl 2-(5-bromo-1-methyl-1H-indol-3-yl)-2-phenylacetate (3g).

Chemical yield: 83%; colorless oil; R_f (Hex/AcOEt 80/20) 0.33; ^1H NMR: 7.57 (dd, $J = 0.4, 1.8$ Hz, 1H), 7.39-7.43 (m, 2H), 7.25-7.36 (m, 4H), 7.15 (dd, $J = 0.4, 8.7$ Hz, 1H), 7.07 (s, 1H), 5.19 (s, 1H), 3.76 (s, 3H), 3.73 (s, 3H); ^{13}C NMR: 173.3, 138.4, 135.8, 129.2, 128.74, 128.69, 128.3, 127.5, 124.8, 121.6, 112.8, 111.8, 111.0, 52.5, 48.6, 33.0; HRMS (ESI-MS) m/z : $[\text{M}+\text{Na}]^+$, calcd for $\text{C}_{18}\text{H}_{17}\text{BrNO}_2\text{Na}^+$, 380.0257, found, 380.0250.



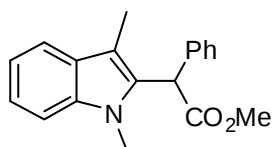
Methyl 2-(2-methyl-1H-indol-3-yl)-2-phenylacetate (3h).

Chemical yield: 70%; orange solid; m.p. = 161-162°C (hexane); R_f (Hex/AcOEt 80/20) 0.22; ^1H NMR: 7.92 (*br s*, 1H), 7.47 (d, $J = 8.0$ Hz, 1H), 7.35-7.45 (m, 1H), 7.27-7.30 (m, 4H), 7.21-7.27 (m, 1H), 7.11 (*app dt*, $J = 1.1, 7.1$ Hz, 1H), 7.04 (ddd, $J = 1.1, 7.1, 8.0$ Hz, 1H), 5.29 (s, 1H), 3.74 (s, 3H), 2.35 (s, 3H); ^{13}C NMR: 173.8, 138.7, 135.2, 133.1, 128.41, 128.39, 127.8, 126.9, 121.3, 119.7, 119.4, 110.4, 108.5, 52.3, 48.1, 12.2; HRMS (ESI-MS) m/z : $[\text{M}+\text{H}]^+$, calcd for $\text{C}_{18}\text{H}_{18}\text{NO}_2^+$, 280.1132, 280.1136.



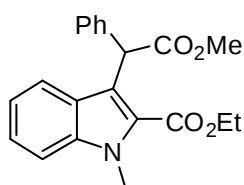
Methyl 2-(1,2-dimethyl-1H-indol-3-yl)-2-phenylacetate (3i).

Chemical yield: 90%; colorless solid; m.p. = 97-99°C (hexane); R_f (Hex/AcOEt 80/20) 0.55; ^1H NMR: 7.47-7.51 (m, 1H), 7.27-7.30 (m, 4H), 7.20-7.25 (m, 1H), 7.16 (ddd, $J = 1.1, 7.0, 8.1$ Hz, 1H), 7.04 (ddd, $J = 1.1, 7.0, 8.1$ Hz, 1H), 5.33 (s, 1H), 3.73 (s, 3H), 3.68 (s, 3H), 2.37 (s, 3H); ^{13}C NMR: 173.9, 139.0, 136.8, 134.9, 128.4, 126.9, 126.8, 120.9, 119.4, 119.3, 108.8, 107.9, 52.3, 48.3, 29.7, 10.8; HRMS (ESI-MS) m/z : $[\text{M}+\text{Na}]^+$, calcd for $\text{C}_{19}\text{H}_{18}\text{NO}_2\text{Na}^+$, 316.1308, found 316.1308.

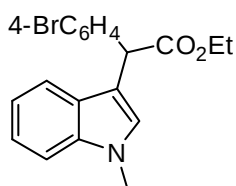


Methyl 2-(1,3-dimethyl-1H-indol-2-yl)-2-phenylacetate (3j).

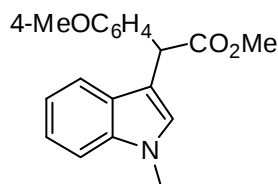
Chemical yield: 41%; pale yellow oil; R_f (Hex/AcOEt 80/20) 0.55; ^1H NMR: 7.59-7.63 (m, 1H), 7.22-7.36 (m, 5H), 7.13-7.20 (m, 3H), 5.51 (s, 1H), 3.82 (s, 3H), 3.53 (s, 3H), 2.33 (s, 3H); ^{13}C NMR: 172.0, 137.2, 136.6, 131.6, 128.7, 128.3, 127.3, 121.9, 119.0, 118.8, 109.8, 109.1, 52.6, 47.9, 30.9, 9.1; HRMS (ESI-MS) m/z : $[\text{M}+\text{Na}]^+$, calcd for $\text{C}_{19}\text{H}_{18}\text{NO}_2\text{Na}^+$, 316.1308, found 316.1295.



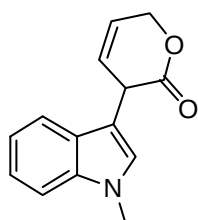
Ethyl 3-[(methoxycarbonyl)(phenyl)methyl]-1-methyl-1H-indole-2-carboxylate (3k). Chemical yield : 50%; pale yellow oil; R_f (Hex/AcOEt 80/20) 0.34; $^1\text{H NMR}$: 7.46-7.49 (m, 1H), 7.36-7.40 (m, 1H), 7.22-7.35 (m, 6H), 7.04-7.09 (m, 1H), 6.16 (s, 1H), 4.36-4.46 (m, 2H), 4.03 (s, 3H), 3.73 (s, 3H), 1.39 (t, $J = 7.1$ Hz, 3H); $^{13}\text{C NMR}$: 173.5, 162.4, 138.9, 138.7, 128.8, 128.4, 127.0, 126.1, 125.8, 125.2, 122.3, 120.7, 119.9, 110.4, 61.1, 52.4, 48.6, 32.5, 14.4; **HRMS** (ESI-MS) m/z : $[\text{M}+\text{Na}]^+$, calcd for $\text{C}_{21}\text{H}_{21}\text{NO}_4\text{Na}^+$, 374.1363; found 374.1376.



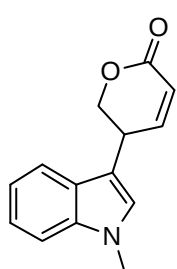
Ethyl 2-(4-bromophenyl)-2-(1-methyl-1H-indol-3-yl)acetate (4b). Chemical yield : 79%; colorless oil; R_f (Hex/AcOEt 80/20) 0.33; $^1\text{H NMR}$: 7.37-7.41 (m, 3H), 7.24-7.29 (m, 3H), 7.16-7.21 (m, 1H), 7.01-7.06 (m, 2H), 5.10 (s, 1H), 4.12 (m, 2H), 3.66 (s, 3H), 1.17 (t, $J = 7.1$ Hz, 3H); $^{13}\text{C NMR}$: 172.7, 138.1, 137.2, 131.7, 130.3, 127.9, 127.0, 122.1, 121.3, 119.4, 119.1, 111.7, 109.5, 61.4, 48.5, 32.9, 14.3; **HRMS** (ESI-MS) m/z : $[\text{M}+\text{Na}]^+$, calcd for $\text{C}_{20}\text{H}_{18}\text{BrNO}_2\text{Na}^+$, 294.0413; found 294.0405.



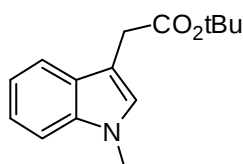
Methyl 2-(4-methoxyphenyl)-2-(1-methyl-1H-indol-3-yl)acetate (4c). Chemical yield : 85%; pale yellow oil; R_f (Hex/AcOEt 80/20) 0.33; $^1\text{H NMR}$: 7.44-7.48 (m, 1H), 7.35-7.39 (m, 2H), 7.26-7.33 (m, 1H), 7.21-7.26 (m, 1H), 7.06-7.11 (m, 1H), 7.06 (s, 1H), 6.86-7.89 (m, 2H), 5.24 (s, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 3.76 (s, 3H); $^{13}\text{C NMR}$: 173.9, 158.8, 137.2, 130.9, 129.5, 127.9, 127.1, 121.9, 119.3, 119.2, 114.0, 112.5, 109.4, 55.3, 52.3, 48.1, 32.9; **HRMS** (ESI-MS) m/z : $[\text{M}+\text{Na}]^+$, calcd for $\text{C}_{19}\text{H}_{19}\text{NO}_3\text{Na}^+$, 332.1257; found 332.1256.



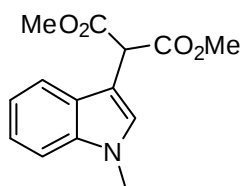
3,6-dihydro-3-(1-methyl-1H-indol-3-yl)-pyran-2-one (4ea). Chemical yield : 27%; brown oil; R_f (Hex/iPrOH 80/20) 0.47; $^1\text{H NMR}$: 7.72-7.75 (m, 1H), 7.23-7.32 (m, 2H), 7.14-7.18 (m, 1H), 6.97 (s, 1H), 5.96-6.06 (m, 2H), 4.96 (m, 1H), 4.86 (m, 1H), 4.49 (m, 1H), 3.65 (s, 3H); $^{13}\text{C NMR}$: 169.9, 137.5, 127.3, 126.9, 126.7, 122.4, 122.2, 119.6, 109.8, 109.5, 68.8, 38.5, 32.9; **HRMS** (ESI-MS) m/z : $[\text{M}+\text{K}]^+$, calcd for $\text{C}_{14}\text{H}_{13}\text{NO}_2\text{K}^+$, 266.0578, found 266.0575.



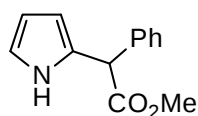
5,6-dihydro-5-(1-methyl-1H-indol-3-yl)pyran-2-one (4eb). Chemical yield : 11%; brown oil; R_f (Hex/iPrOH 80/20) 0.34; $^1\text{H NMR}$: 7.55-7.58 (m, 1H), 7.33-7.36 (m, 1H), 7.27-7.30 (m, 1H), 7.14-7.19 (m, 1H), 7.07-7.12 (m, 1H), 6.93 (s, 1H), 6.16 (dd, $J = 2.1, 9.7$ Hz, 1H), 4.56 (ddd, $J = 1.0, 5.2, 11.0$ Hz, 1H), 4.41 (ddd, $J = 0.7, 7.9, 11.0$ Hz, 1H), 4.06 (m, 1H), 3.78 (s, 3H); $^{13}\text{C NMR}$: 164.0, 149.7, 127.2, 126.6, 122.4, 120.8, 119.7, 118.5, 110.1, 109.9, 71.4, 33.0, 32.1; **HRMS** (ESI-MS) m/z : $[\text{M}+\text{H}]^+$, calcd for $\text{C}_{14}\text{H}_{14}\text{NO}_2^+$, 228.1019, found 228.1016.



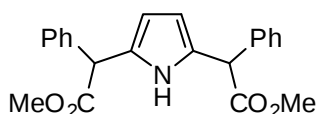
tert-Butyl 2-(1-methyl-1H-indol-3-yl)acetate (4f). Chemical yield : 39%; colorless oil; R_f (Hex/AcOEt 80/20) 0.39; $^1\text{H NMR}$: 7.61-7.64 (m, 1H), 7.29-7.32 (m, 1H), 7.21-7.26 (m, 1 H), 7.11-7.16 (m, 1H), 6.95 (s, 1H), 3.66 (s, 3H), 3.59 (s, 2H), 1.38 (s, 9H); $^{13}\text{C NMR}$: 171.6, 137.0, 127.9, 127.7, 121.7, 119.2, 119.1, 109.3, 107.6, 80.7, 32.8, 32.6, 28.2; **HRMS** (ESI-MS) m/z : $[\text{M}+\text{Na}]^+$, calcd for $\text{C}_{15}\text{H}_{19}\text{NO}_2\text{Na}^+$, 268.1308; found 268.1307.



Dimethyl 2-(1-methyl-1H-indol-3-yl)malonate (4g). Chemical yield : 85%; white solid; m.p. = 167-168°C (hexane); R_f (Hex/AcOEt 80/20) 0.20; $^1\text{H NMR}$: 7.60-7.65 (m, 1H), 7.22-7.33 (m, 3H), 7.15 (ddd, $J = 1.1, 7.0, 8.0$ Hz, 1H), 4.97 (s, 1H), 3.79 (s, 3H), 3.76 (s, 6H); $^{13}\text{C NMR}$: 169.2, 136.9, 128.7, 127.1, 122.1, 119.8, 119.1, 109.6, 105.7, 52.9, 49.3, 33.0; **HRMS** (ESI-MS) m/z : $[\text{M}+\text{Na}]^+$, calcd for $\text{C}_{14}\text{H}_{15}\text{NO}_4\text{Na}^+$, 284.0893, found 284.0892.

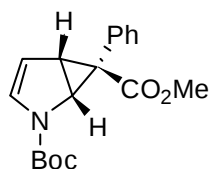


Methyl 2-phenyl-2-(1H-pyrrol-2-yl)acetate (6a). Chemical yield : 69%; brown oil; R_f (Hex/AcOEt 80/20) 0.37; $^1\text{H NMR}$: 8.82 (br s, 1H), 7.25-7.35 (m, 5H), 6.76-6.79 (m, 1H), 6.17 (dt, $J = 3.3, 2.7$ Hz, 1H), 6.04-6.07 (m, 1H), 5.09 (s, 1H), 3.76 (s, 3H); $^{13}\text{C NMR}$: 172.9, 138.4, 128.8, 127.9, 127.5, 127.4, 118.0, 108.4, 107.8, 52.5, 50.1; **HRMS** (ESI-MS) m/z : $[\text{M}+\text{Na}]^+$, calcd for $\text{C}_{13}\text{H}_{13}\text{NO}_2\text{Na}^+$, 238.0838, found 238.0840.



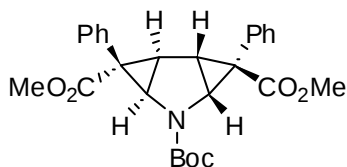
Dimethyl 2,2'-(1H-pyrrole-2,5-diyl)bis(2-phenylacetate) (7a). Chemical yield : 14%; brown oil; R_f (Hex/AcOEt 80/20) 0.26; $^1\text{H NMR}$: 9.12-9.21 (m, 1H), 7.15-7.27 (m, 10H), 5.87 (d, $J = 2.7$ Hz, 1H), 5.84 (d, $J = 2.7$ Hz, 1H),

4.951 (s, 1H), 4.945 (s, 1H), 3.668 (s, 3H), 3.666 (s, 3H); ^{13}C NMR: 172.7, 138.3, 138.2, 128.8, 128.1, 128.0, 127.83, 127.79, 127.63, 127.62, 108.04, 107.99, 52.6, 50.42, 50.39; HRMS (ESI-MS) m/z : $[\text{M}+\text{Na}]^+$, calcd for $\text{C}_{22}\text{H}_{21}\text{NO}_4\text{Na}^+$, 386.1363, found 386.1359.



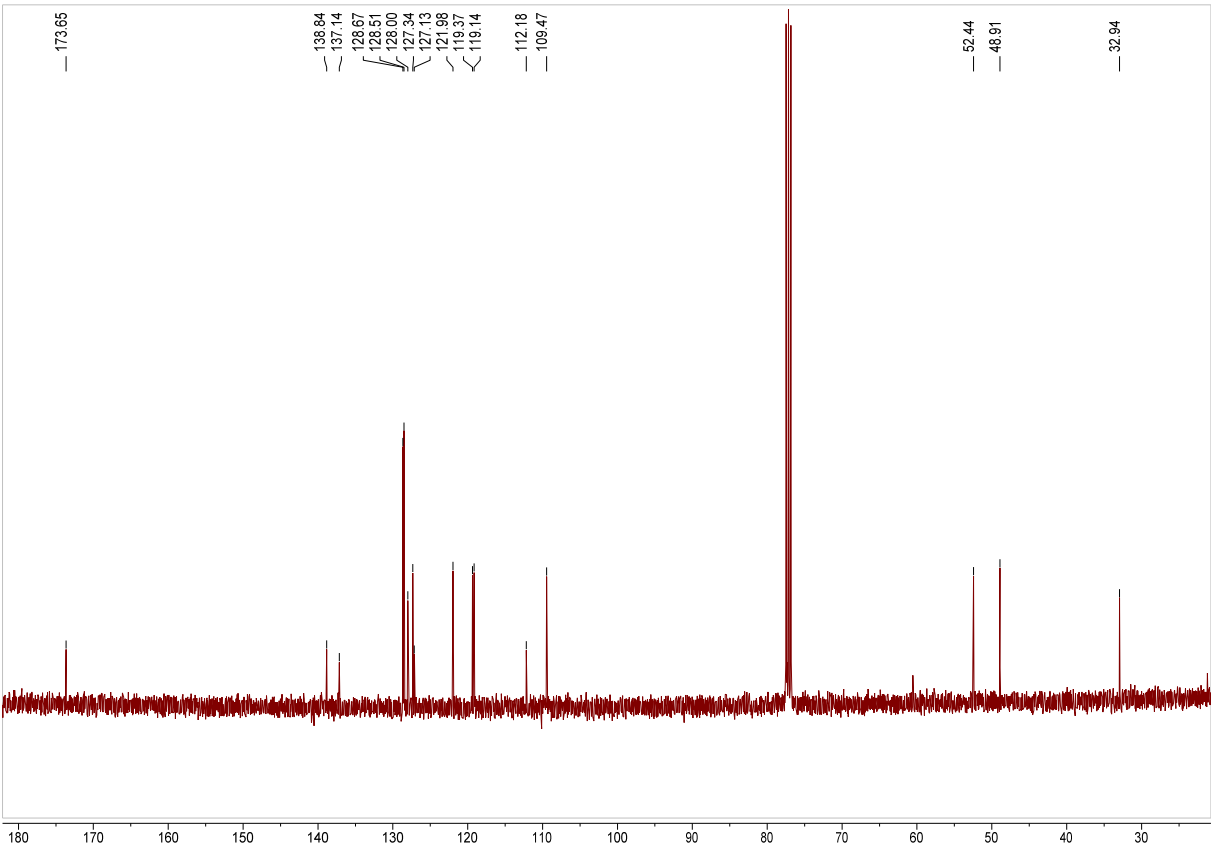
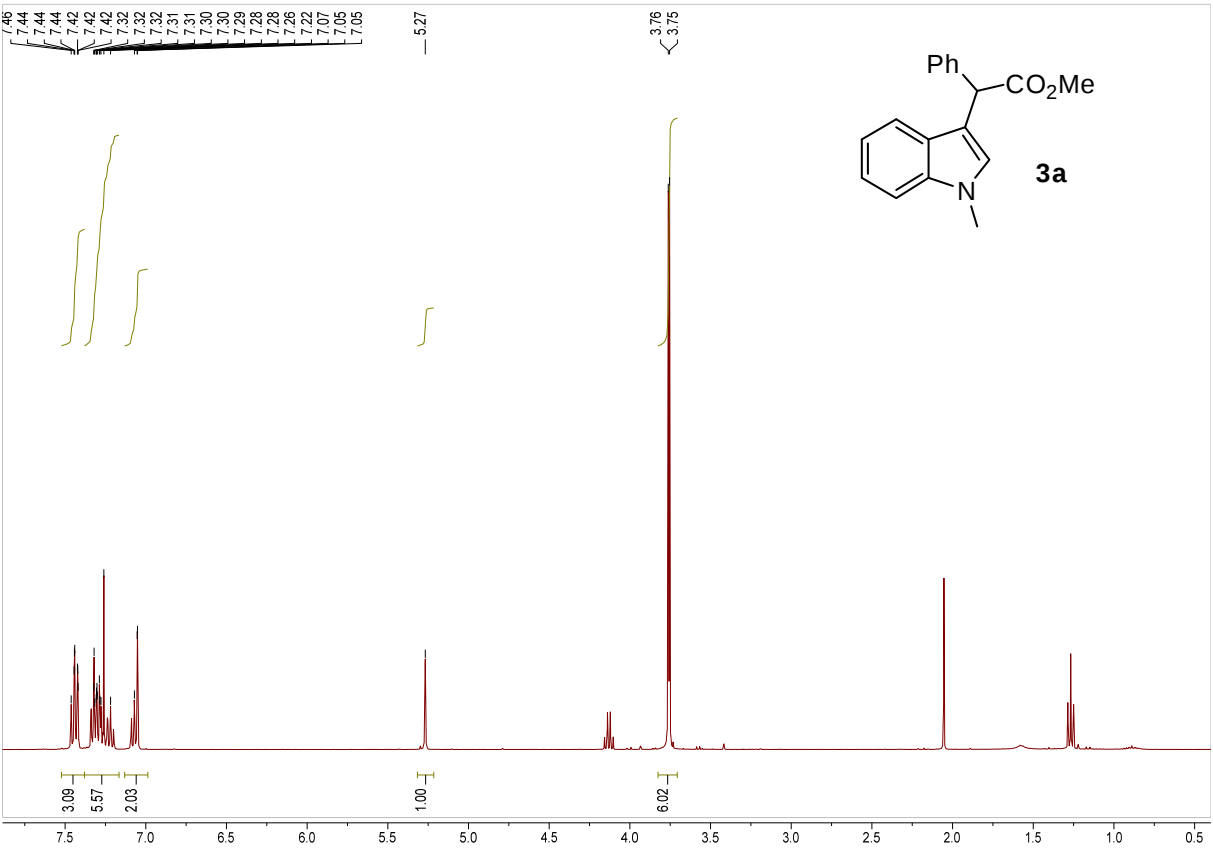
(1R*,5R*,6S*)-2-tert-Butyl 6-methyl 6-phenyl-2-azabicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate (6b). Isolated as a mixture of 2 rotamers in a 3/2 ratio. Chemical yield : 34%; white solid; m.p. = 122-123°C (hexane); R_f

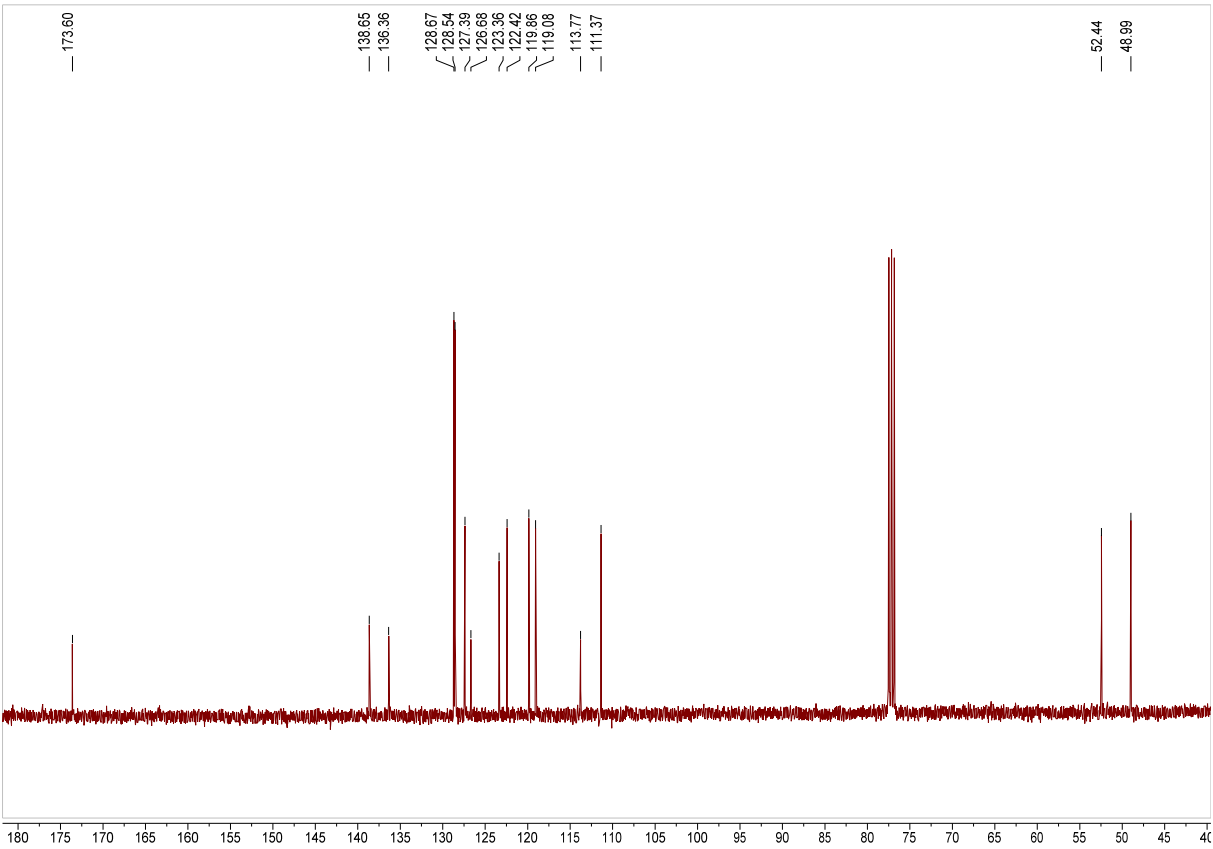
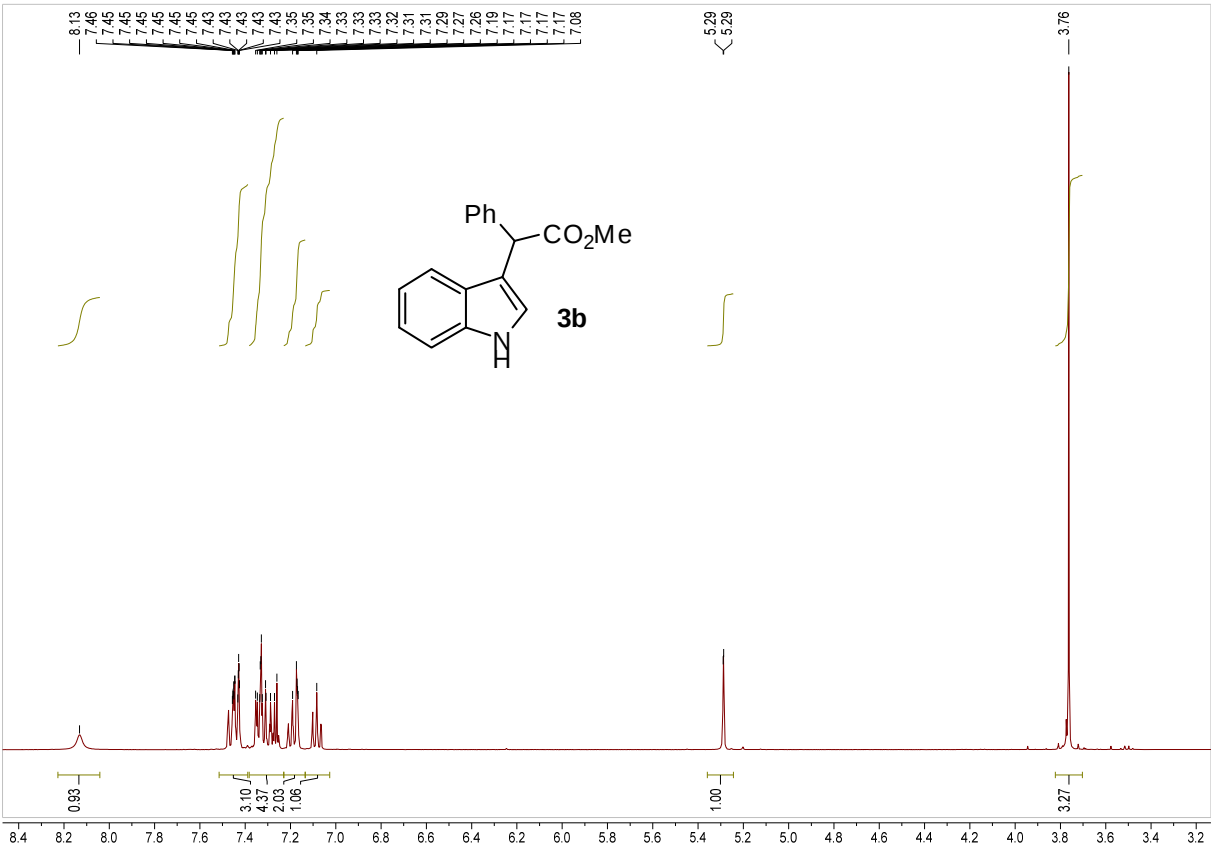
(Hex/AcOEt 80/20) 0.43; ^1H NMR: *major rotamer* 7.22-7.29 (m, 3H), 7.07-7.15 (2H), 5.90 (d, J = 3.9 Hz, 1H), 5.05 (dd, J = 2.7, 4.0 Hz, 1H), 4.62 (d, J = 6.5 Hz, 1H), 3.53 (s, 3H), 3.25 (m, 1H), 1.38 (s, 9H); *partial minor rotamer* 6.06 (d, J = 3.9 Hz, 1H), 5.12 (dd, J = 2.7, 4.1 Hz, 1H), 4.52 (d, J = 6.7 Hz, 1H), 3.56 (s, 3H), 1.52 (s, 9H); ^{13}C NMR: *major rotamer* 173.9, 151.5, 132.8, 131.2, 130.5, 127.7, 127.2, 107.4, 81.7, 52.6, 49.4, 38.4, 29.8, 28.3; *minor rotamer* 174.2, 151.3, 132.4, 131.0, 130.8, 127.8, 127.3, 107.4, 82.0, 52.7, 49.5, 39.7, 29.4, 28.5; HRMS (ESI-MS) m/z : $[\text{M}+\text{Na}]^+$, calcd for $\text{C}_{18}\text{H}_{21}\text{NO}_4\text{Na}^+$, 338.1363, found 338.1368.

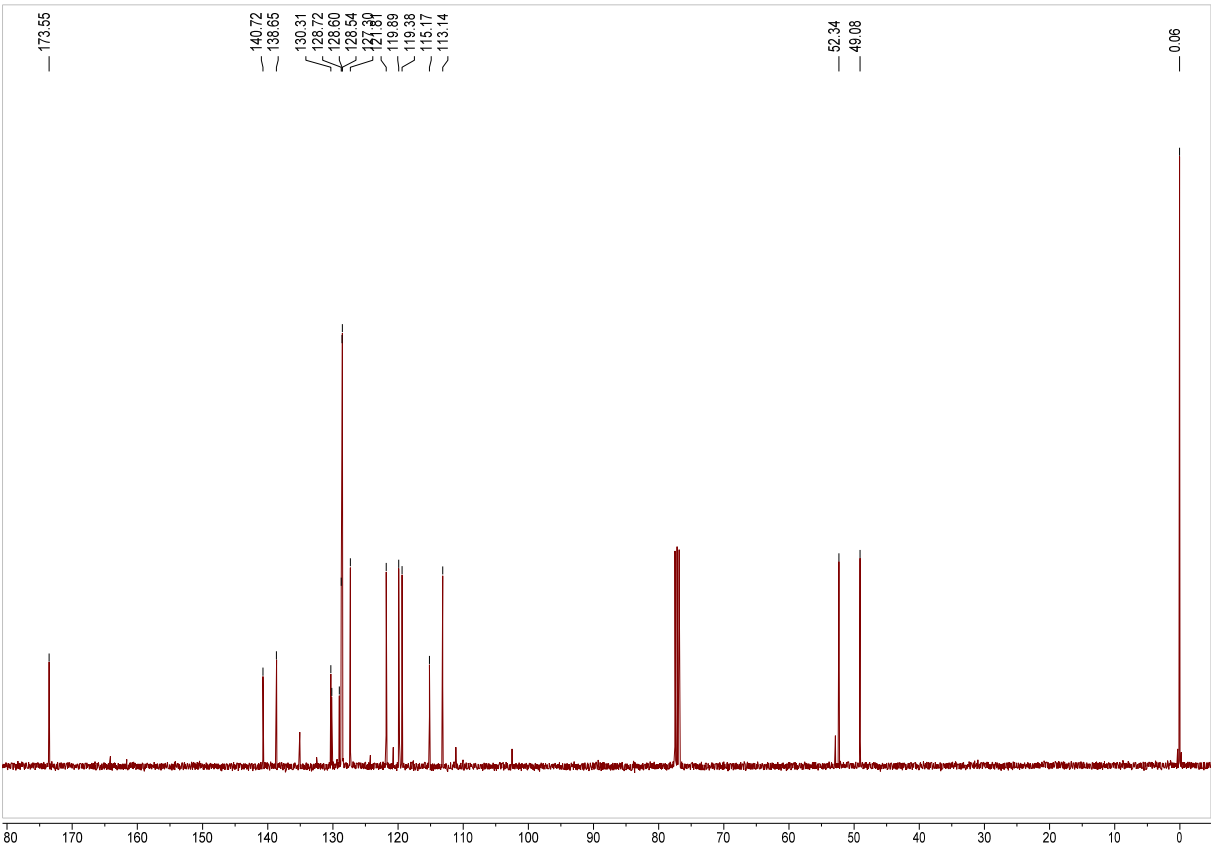
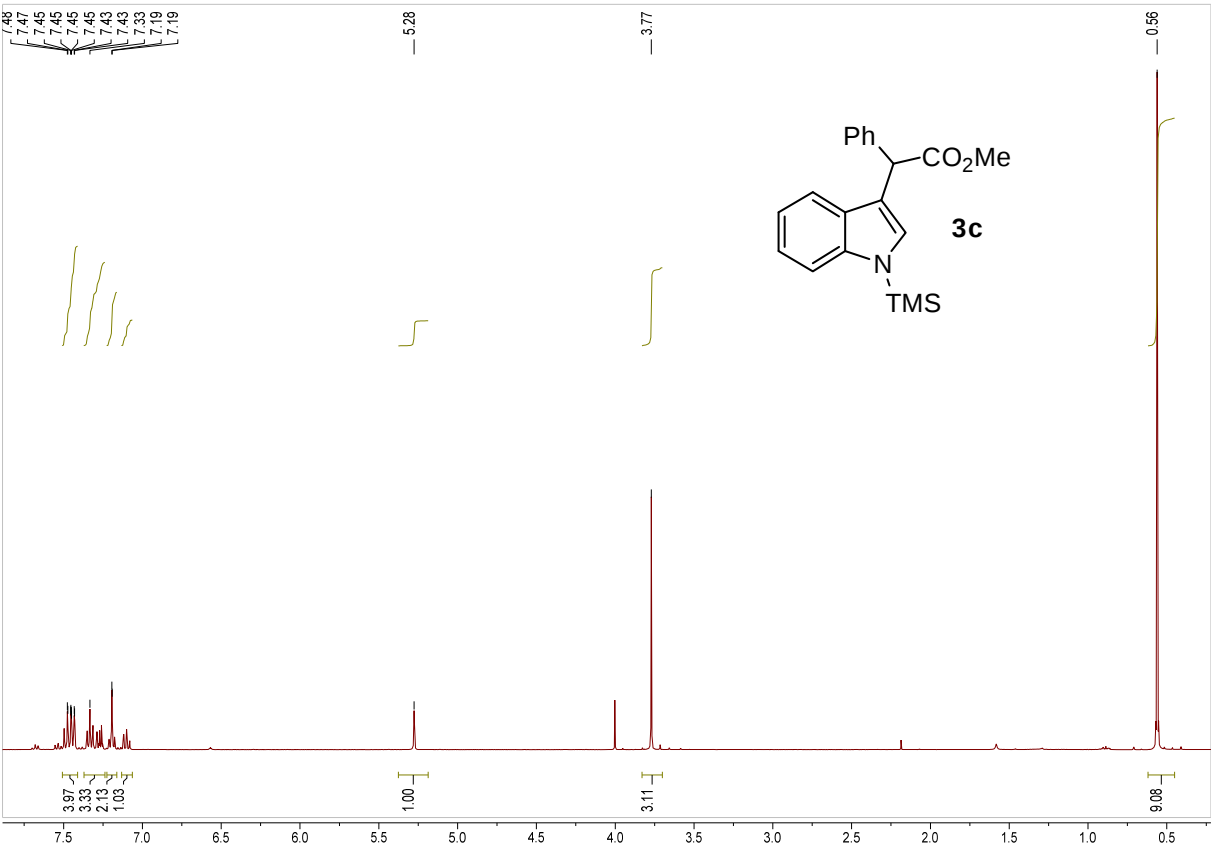


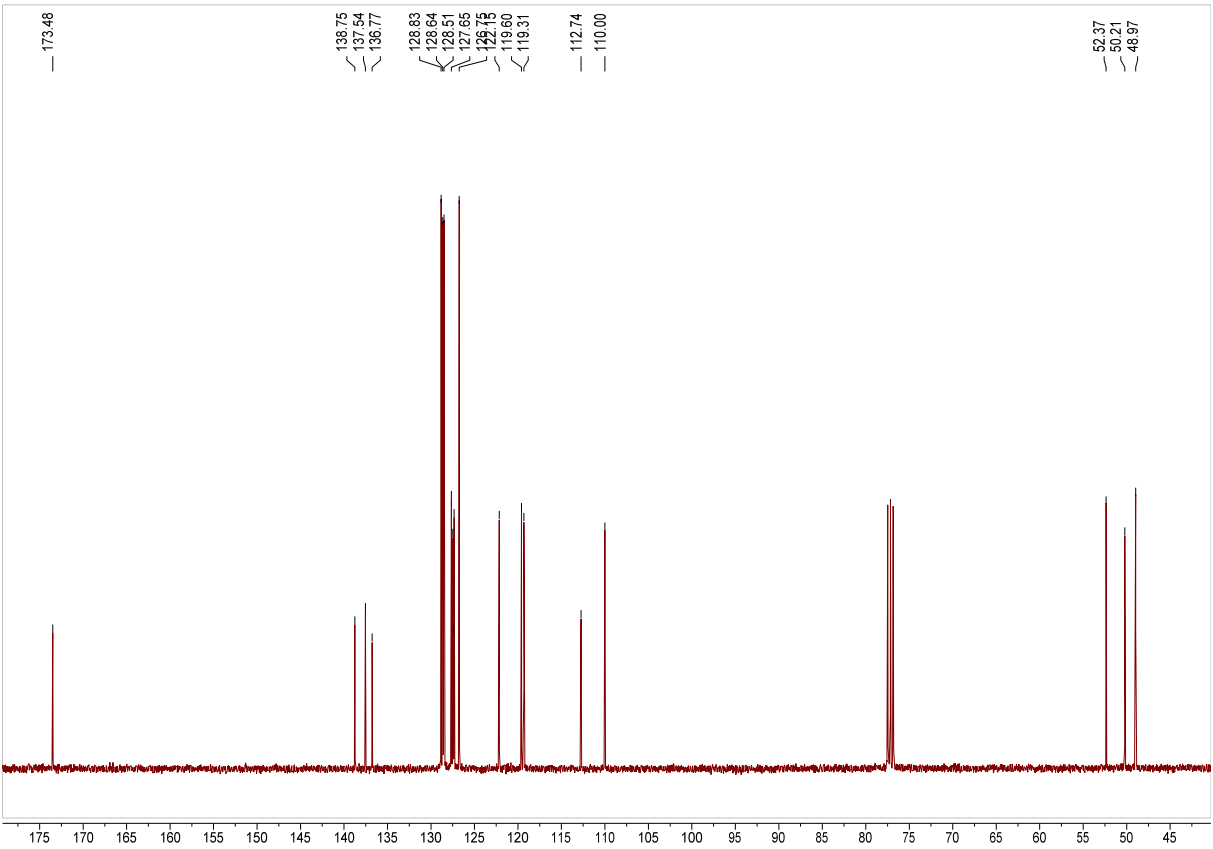
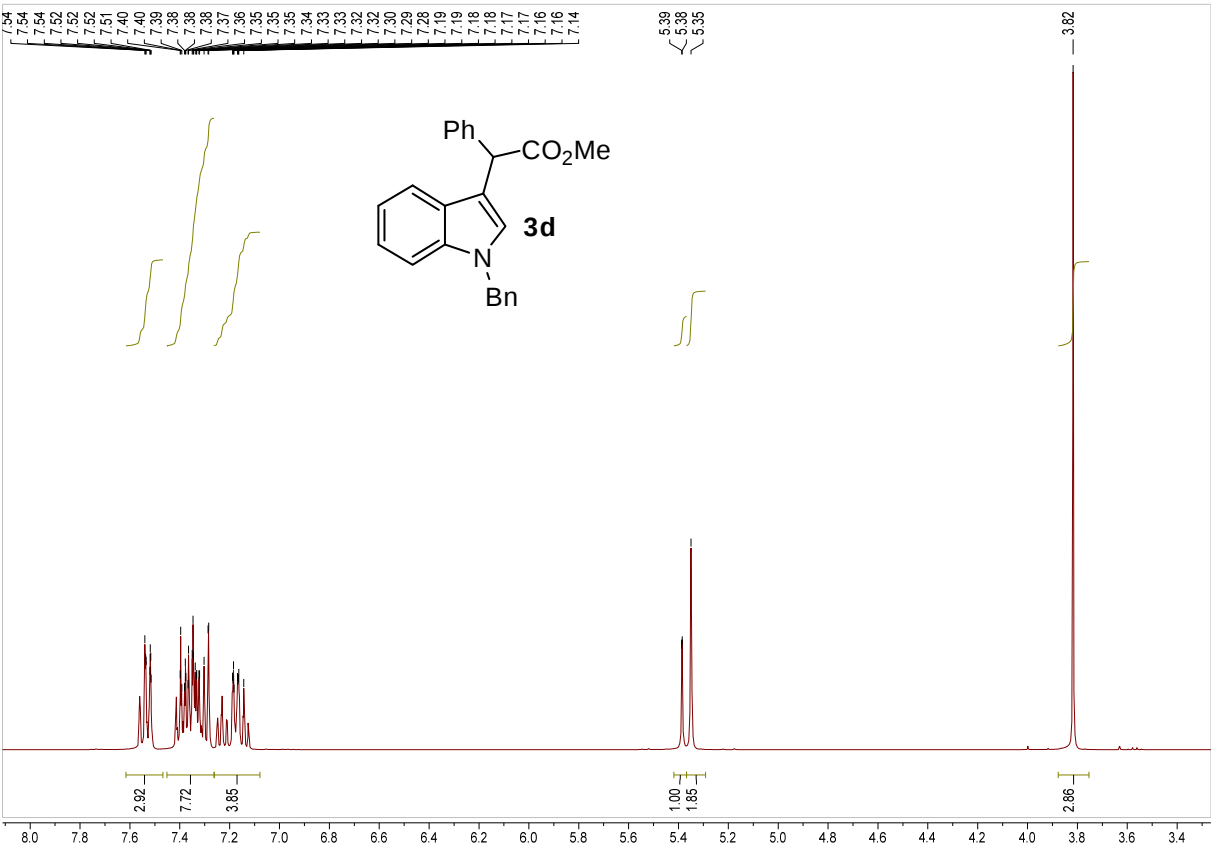
(1R*,3R*,4S*,5R*,6R*,7S*)-2-tert-Butyl 4,7-dimethyl 4,7-phenyl-2-azatricyclo[4.1.0.0^{3,5}]heptane-2,4,7-tricarboxylate (7b). Chemical yield : 56%; white solid; m.p. = 200-201°C

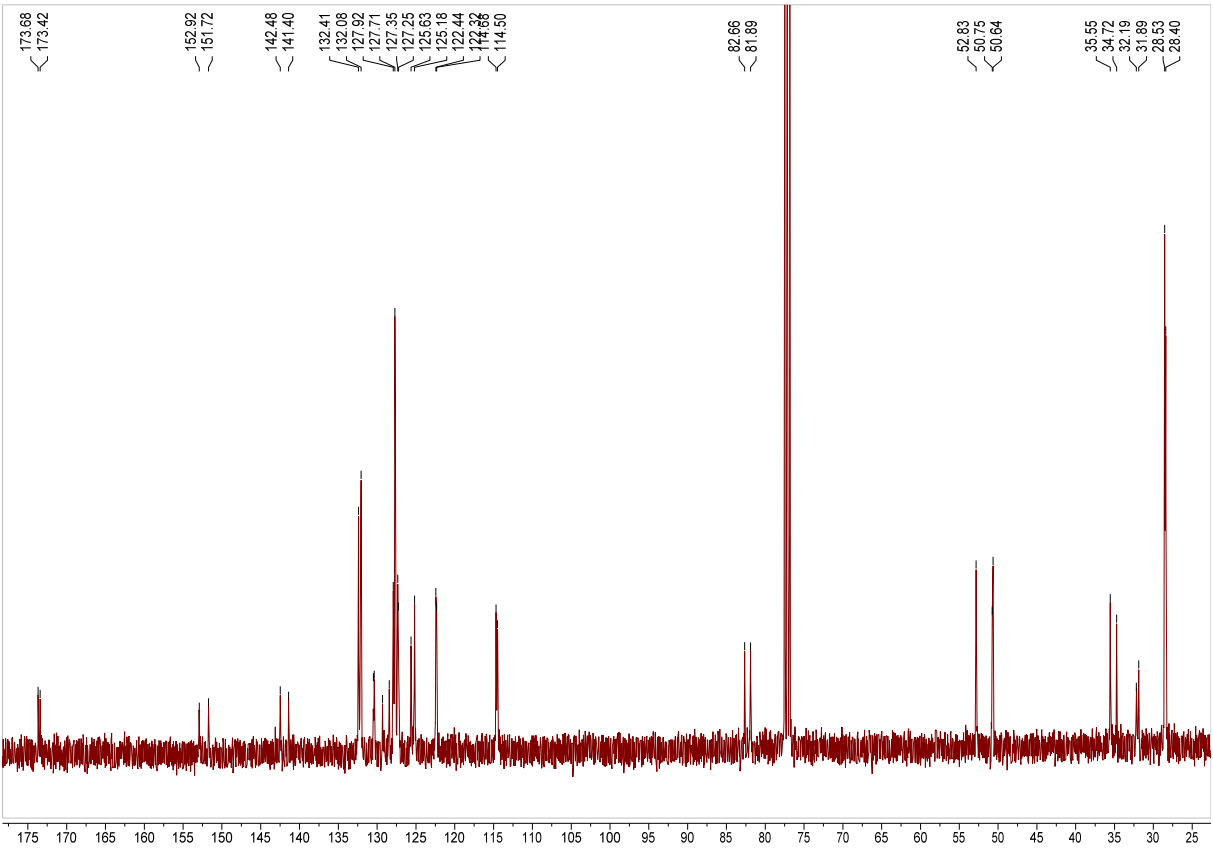
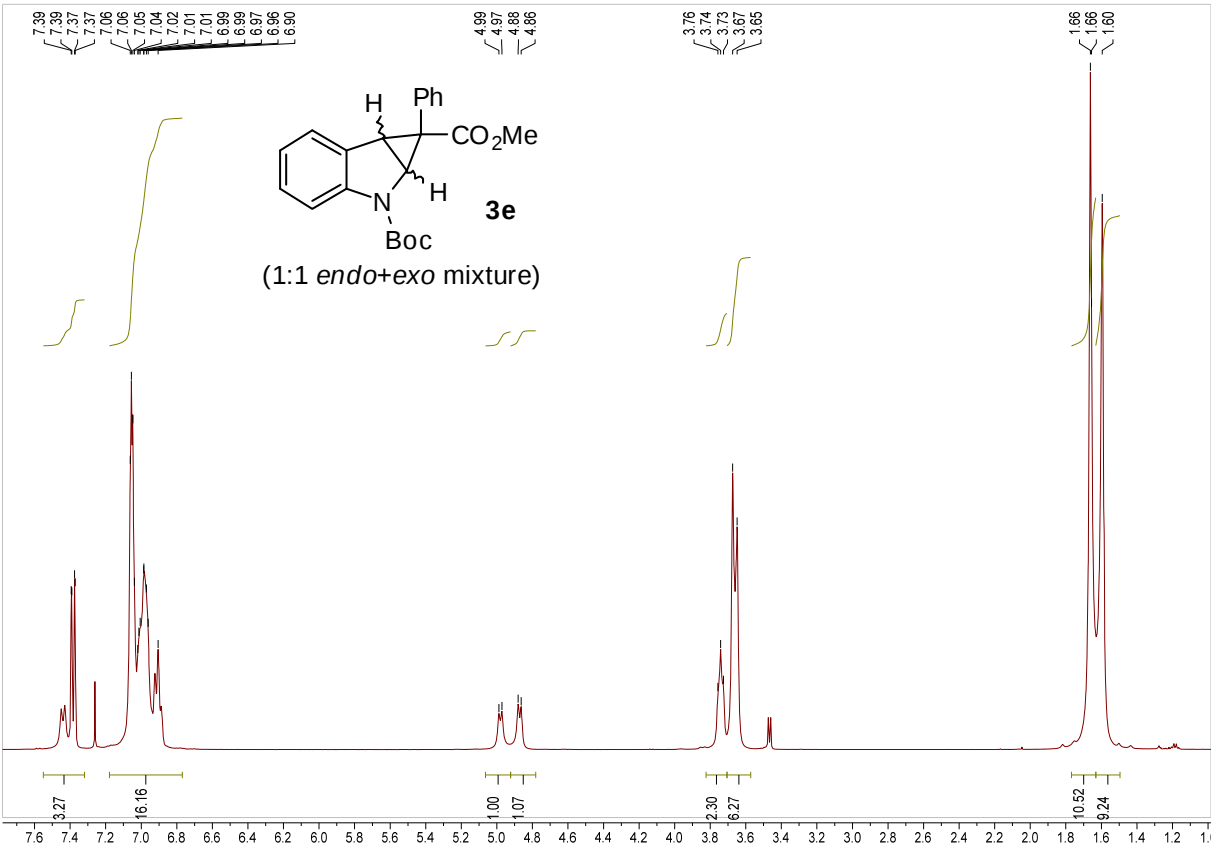
(hexane); R_f (Hex/AcOEt 80/20) 0.25; ^1H NMR: 7.22-7.42 (m, 10H), 3.53 (m, 3H), 3.50 (m, 3H), 3.03 (*app* d, J = 6.5 Hz, 1H), 2.93 (*app* d, J = 6.5 Hz, 1H), 2.62 (d, J = 6.5 Hz, 1H), 2.59 (d, J = 6.5 Hz, 1H), 1.51 (s, 9H); ^{13}C NMR: 172.0, 171.7, 154.6, 132.0, 131.9, 131.5, 128.8, 128.6, 127.94, 127.85, 81.1, 52.8, 52.6, 48.03, 47.99, 37.7, 37.5, 33.4, 32.1, 28.5; HRMS (ESI-MS) m/z : $[\text{M}+\text{Na}]^+$, calcd for $\text{C}_{27}\text{H}_{29}\text{NO}_6\text{Na}^+$, 486.1887, found 486.1895.

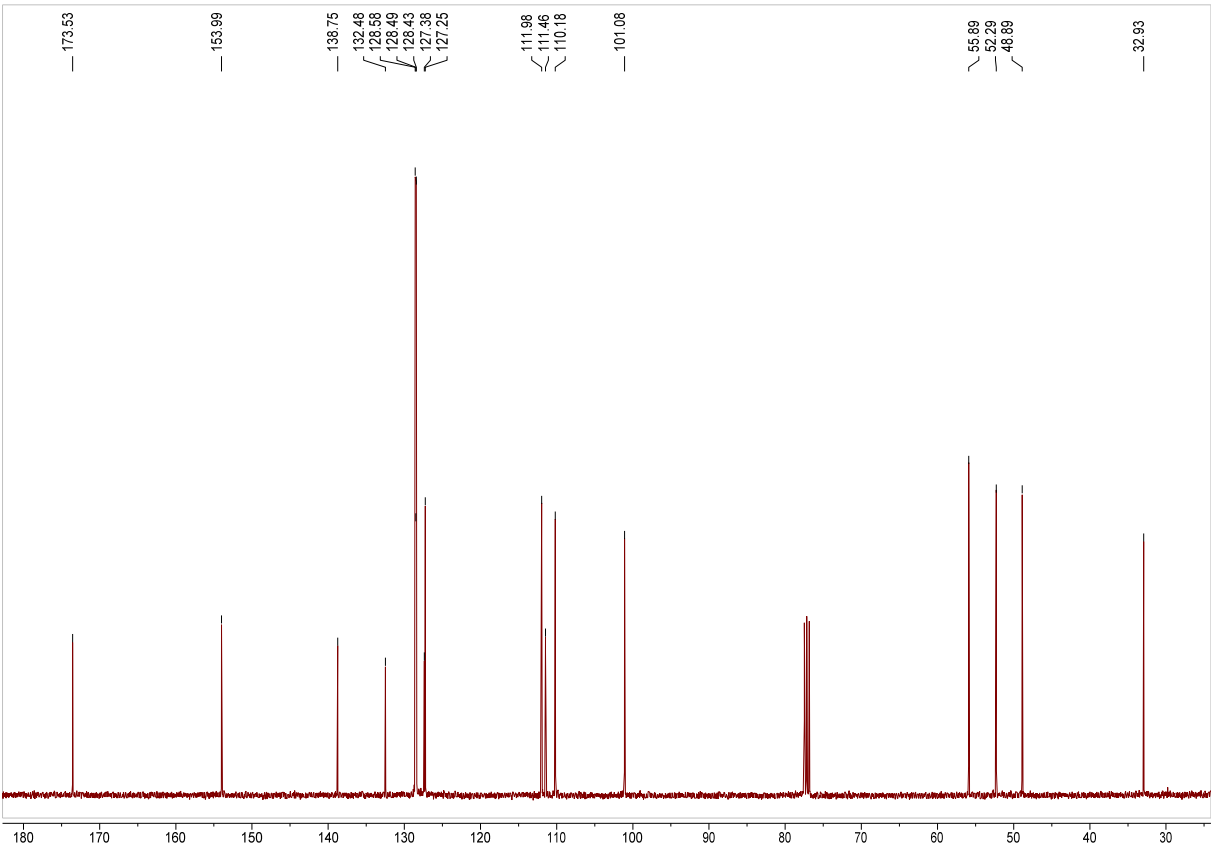
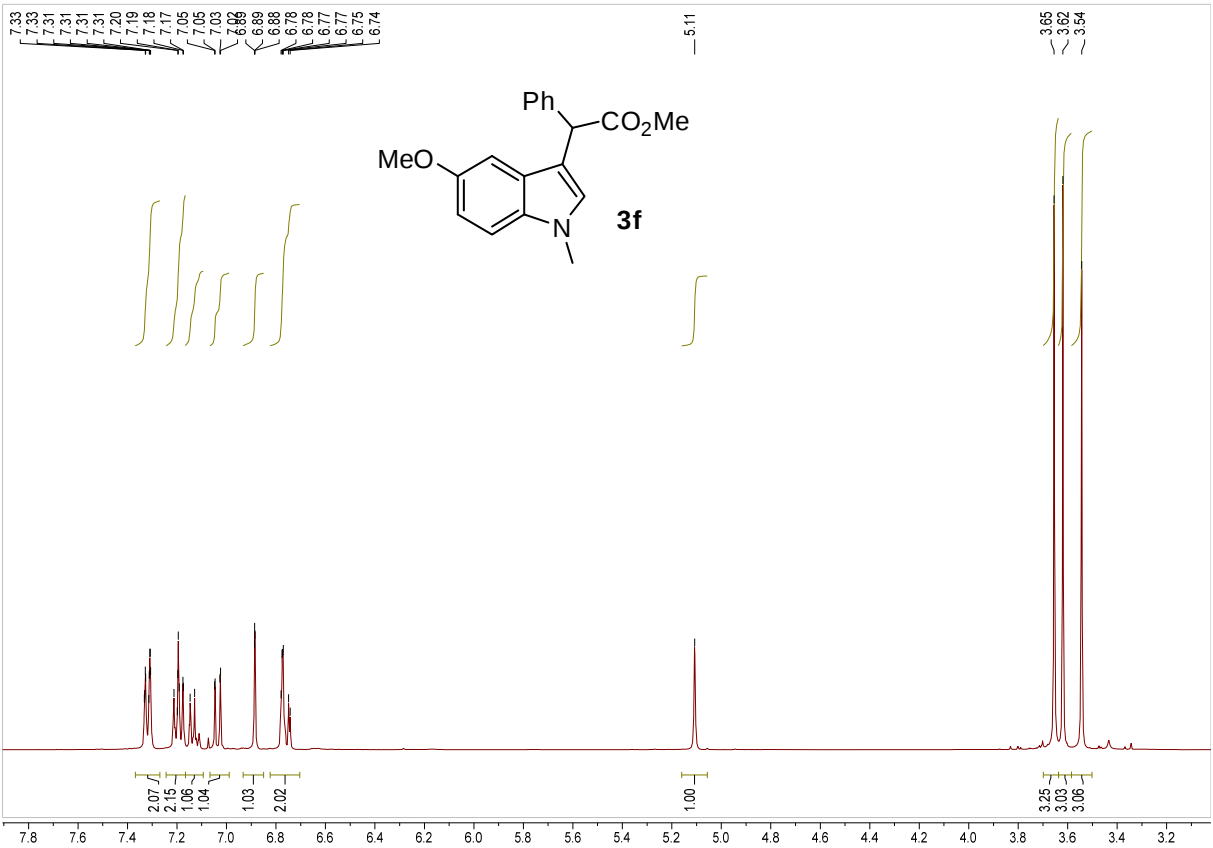


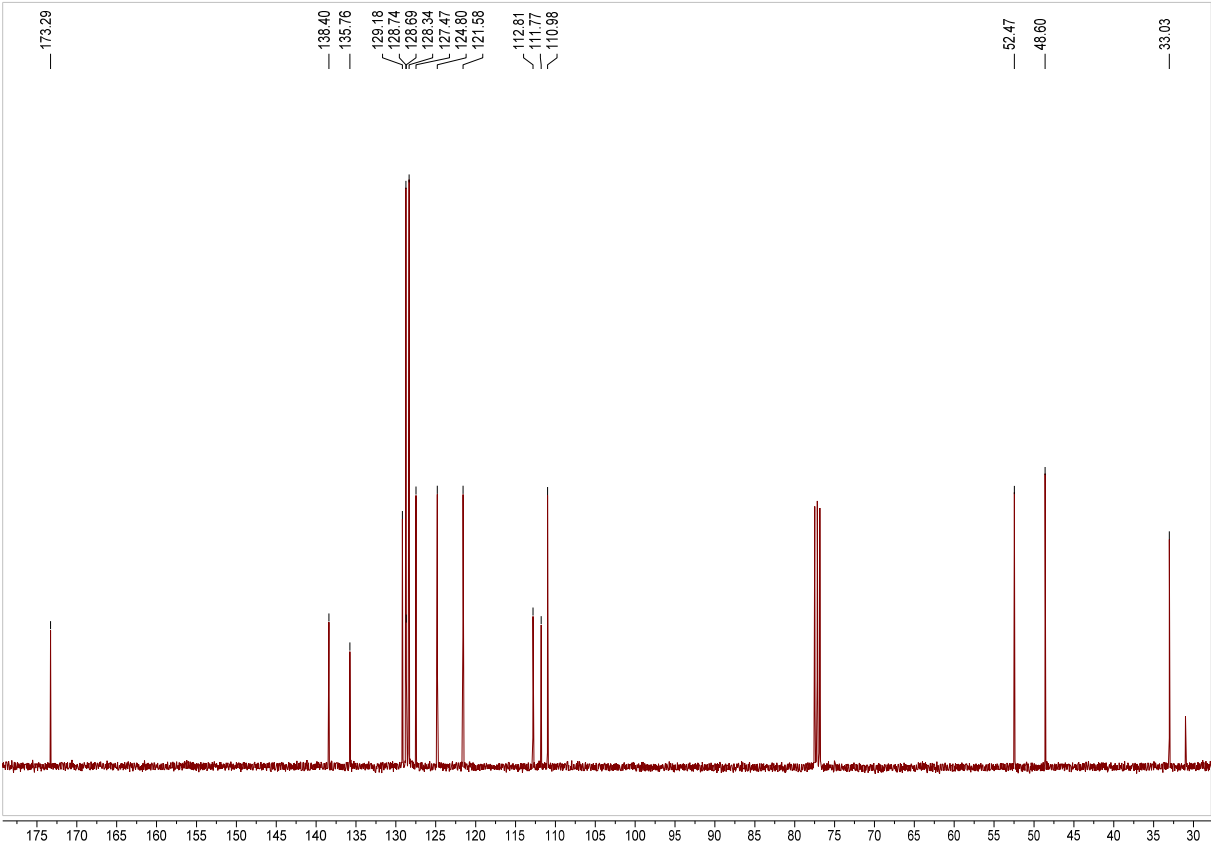
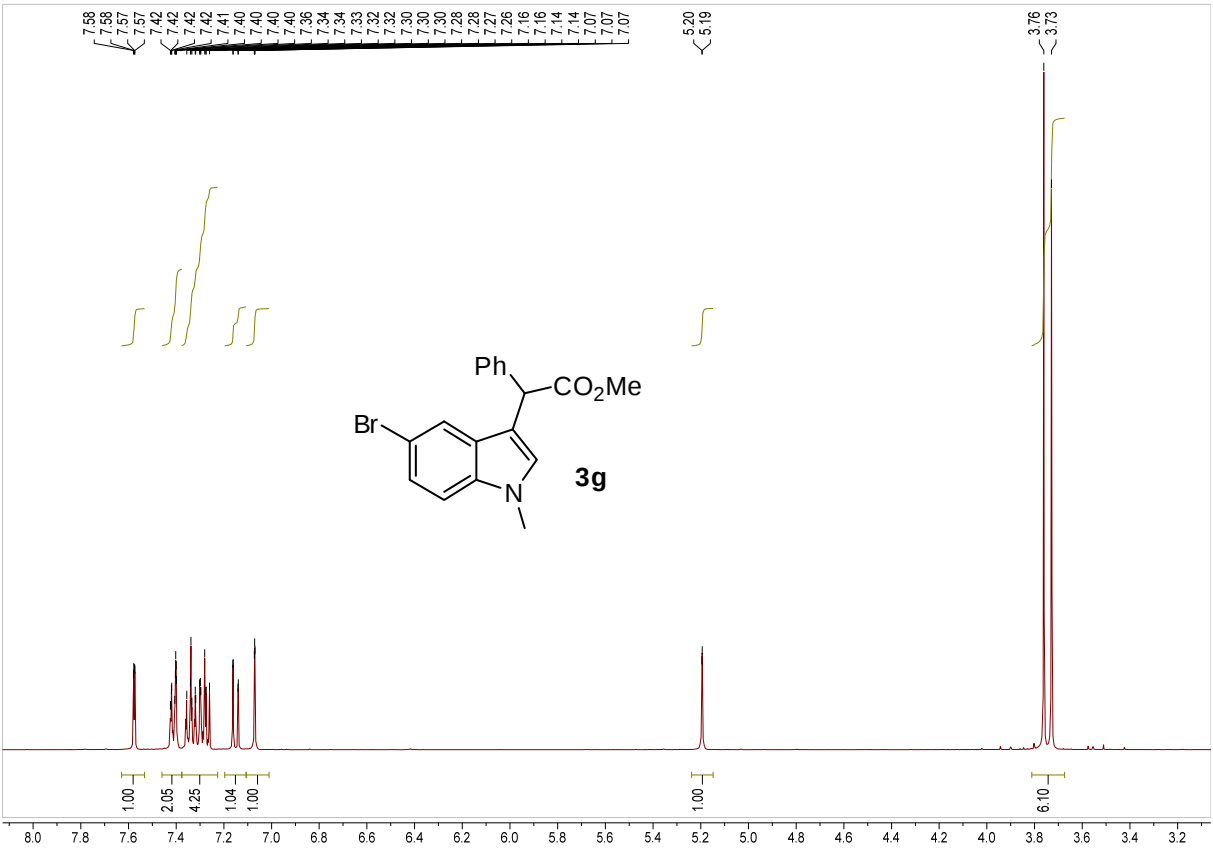


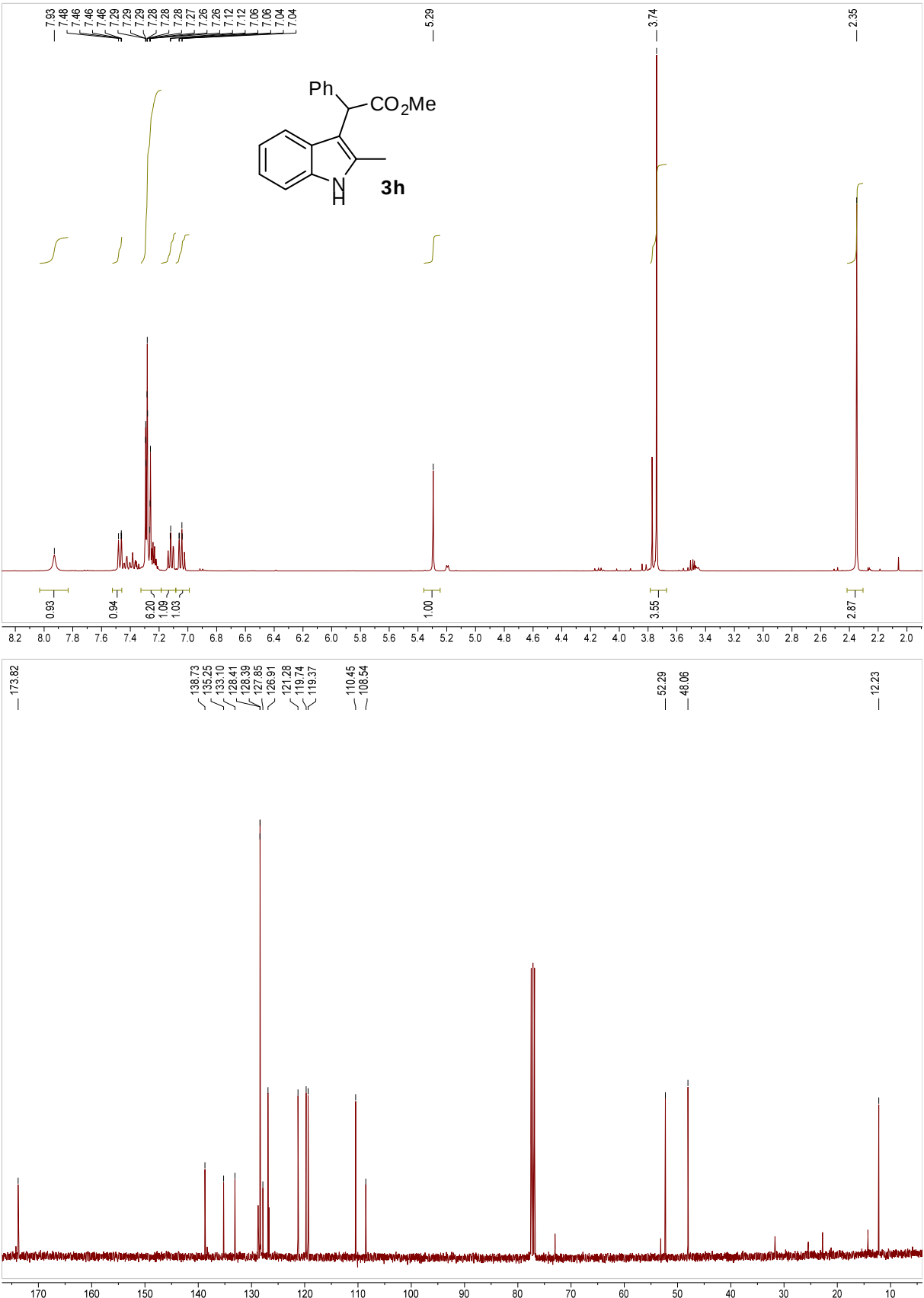


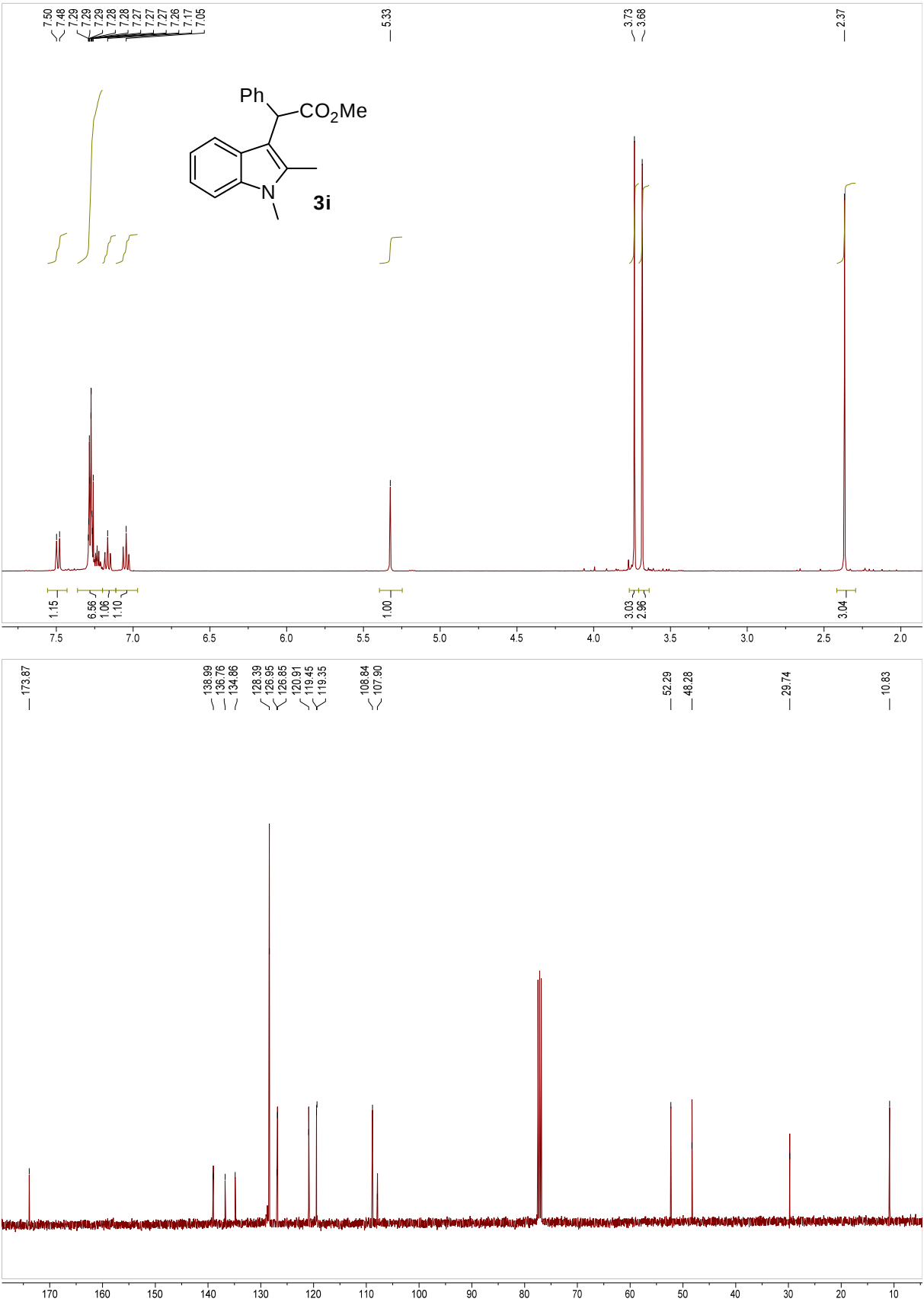


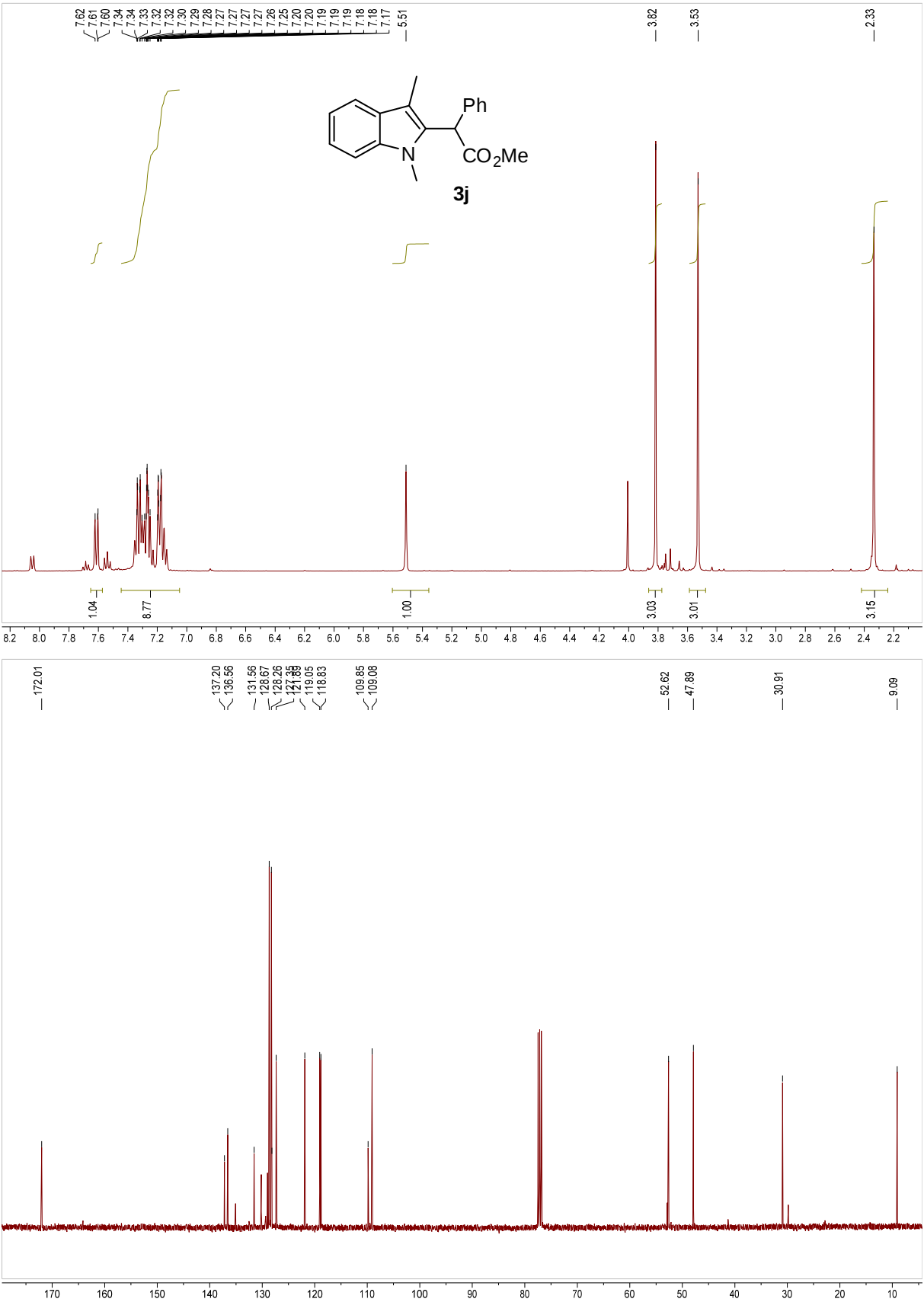


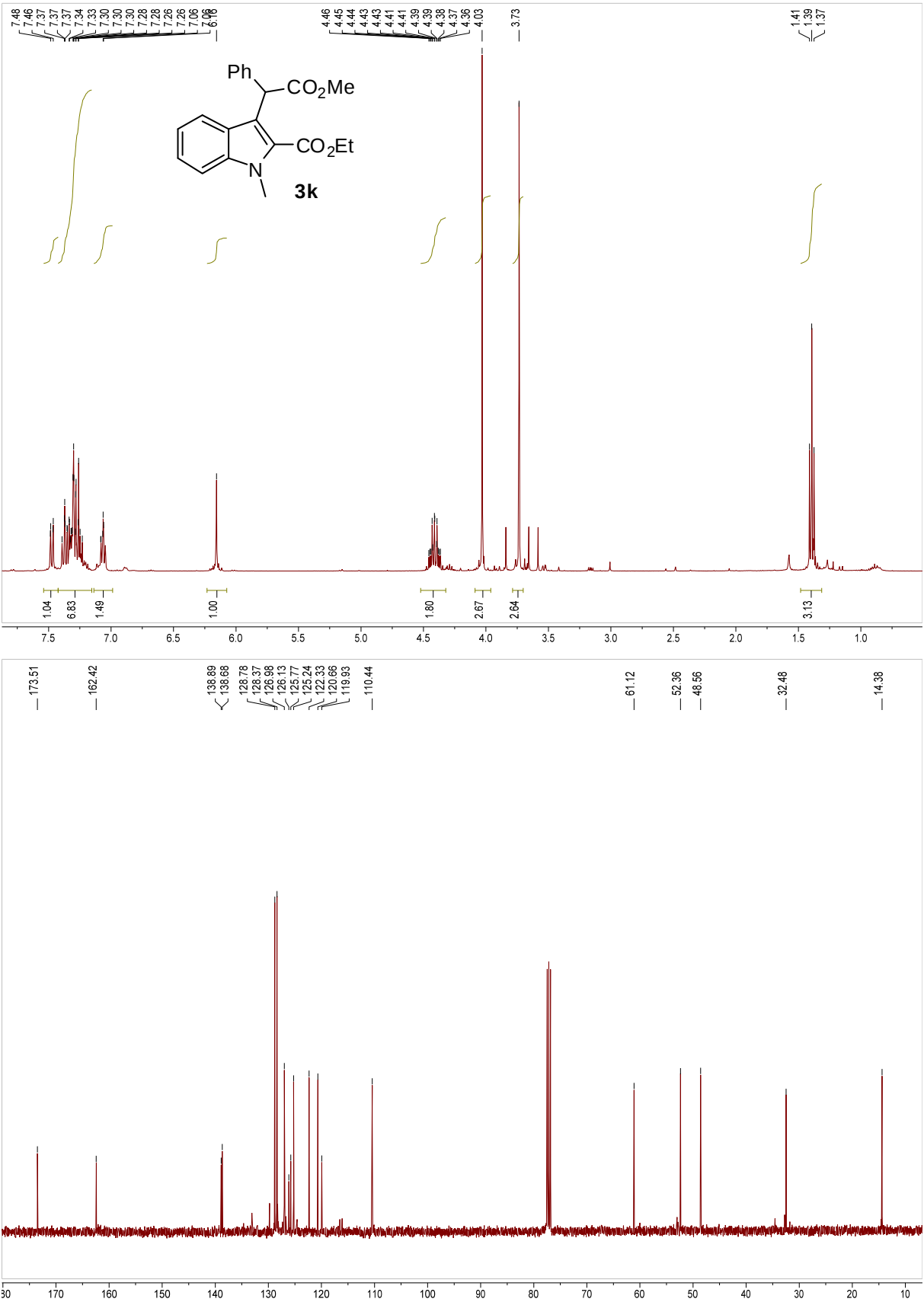


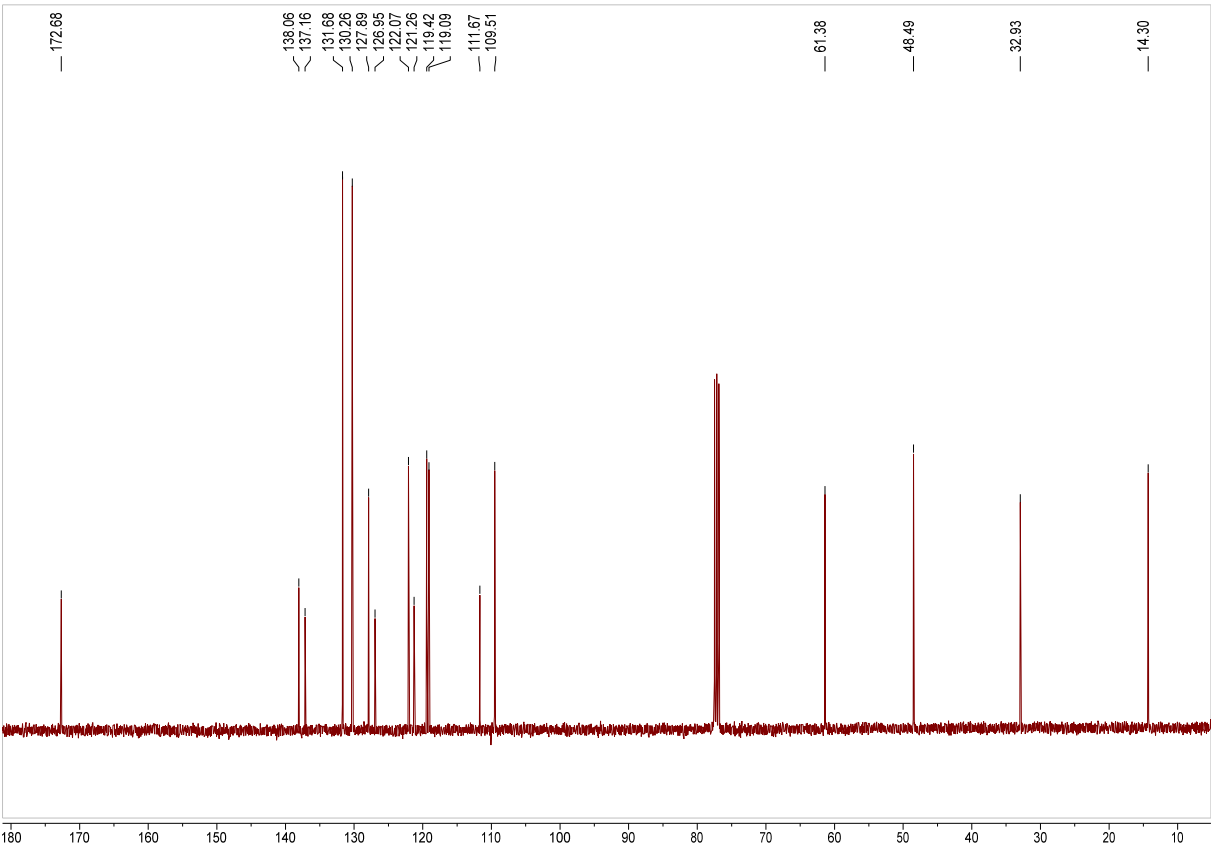
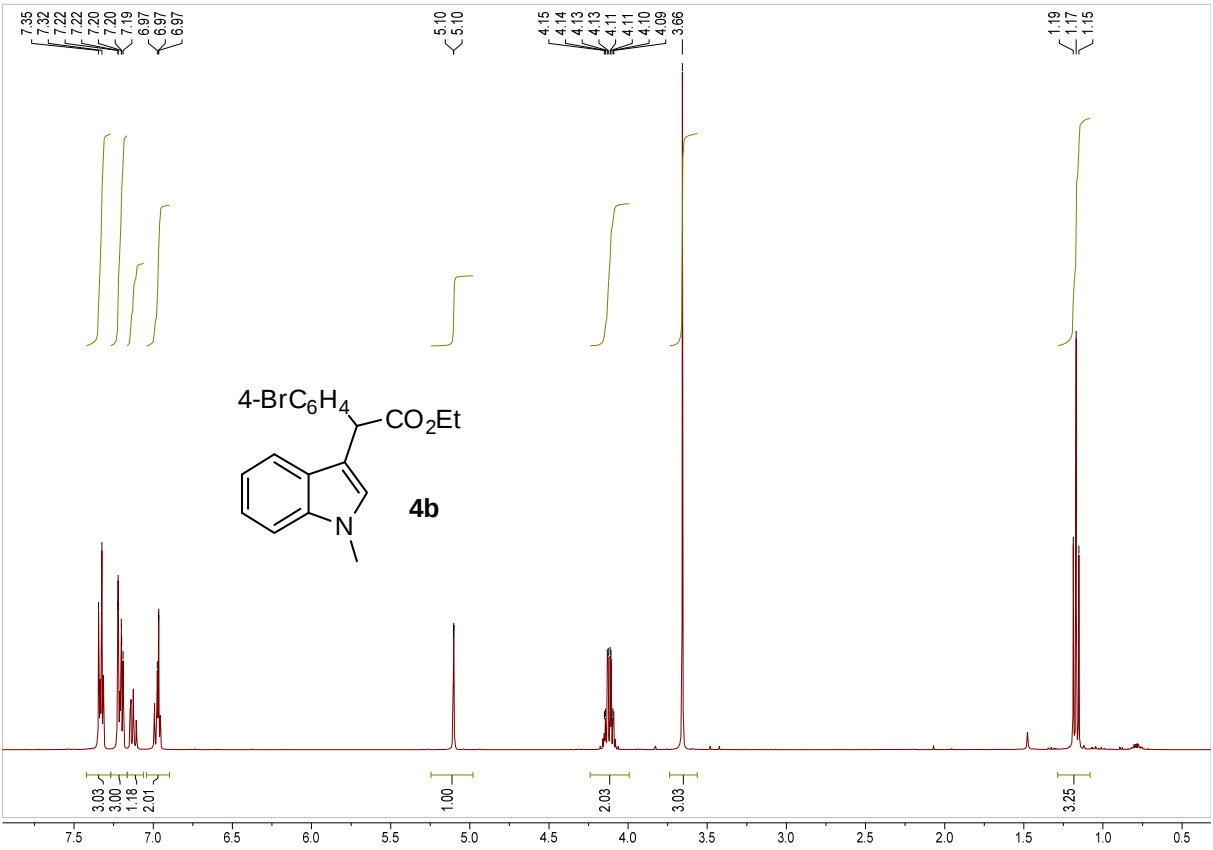


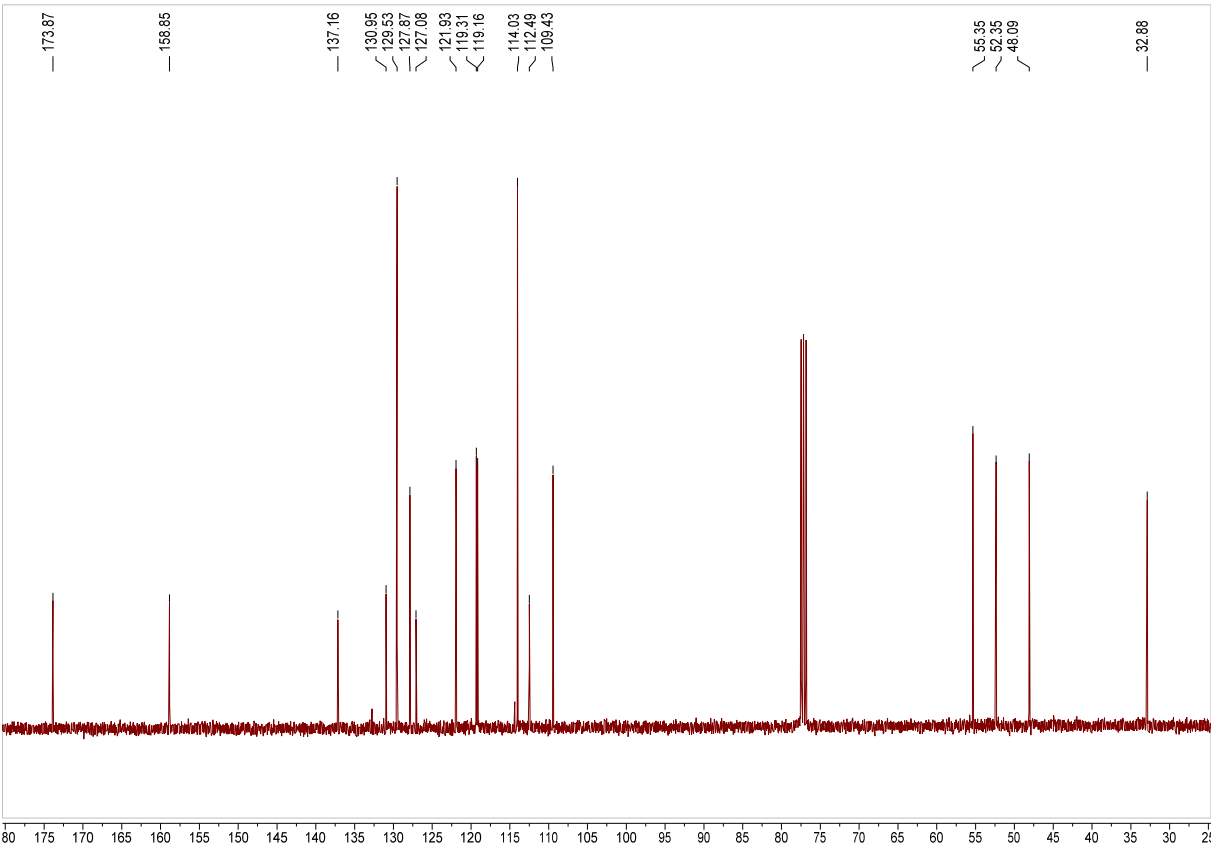
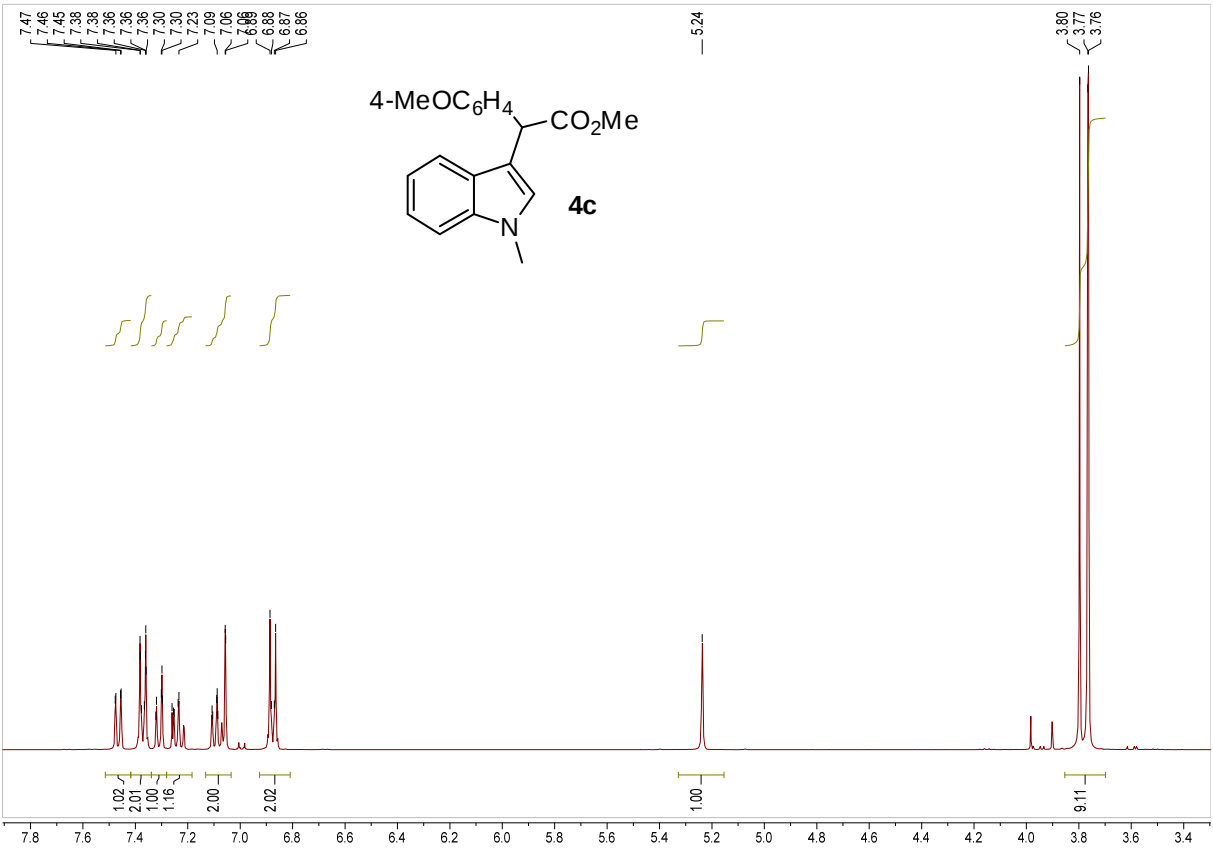


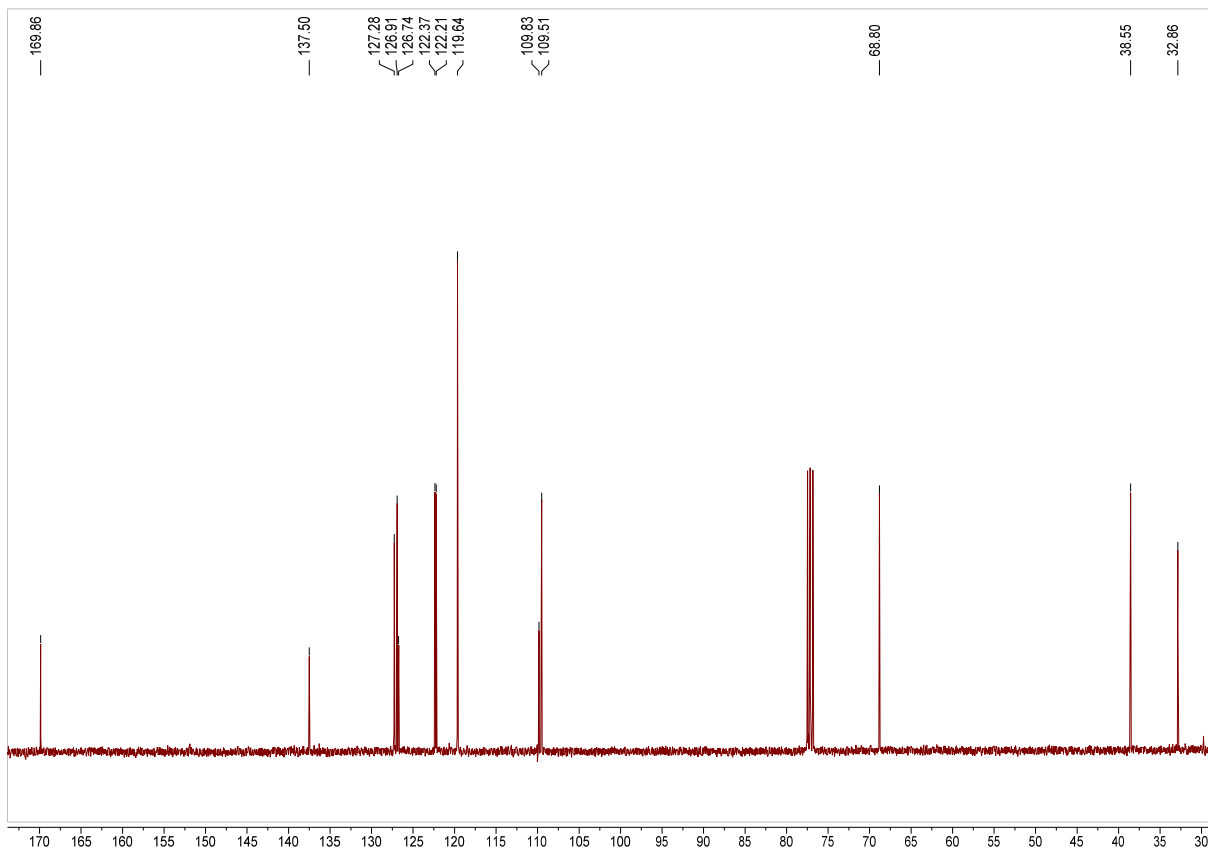
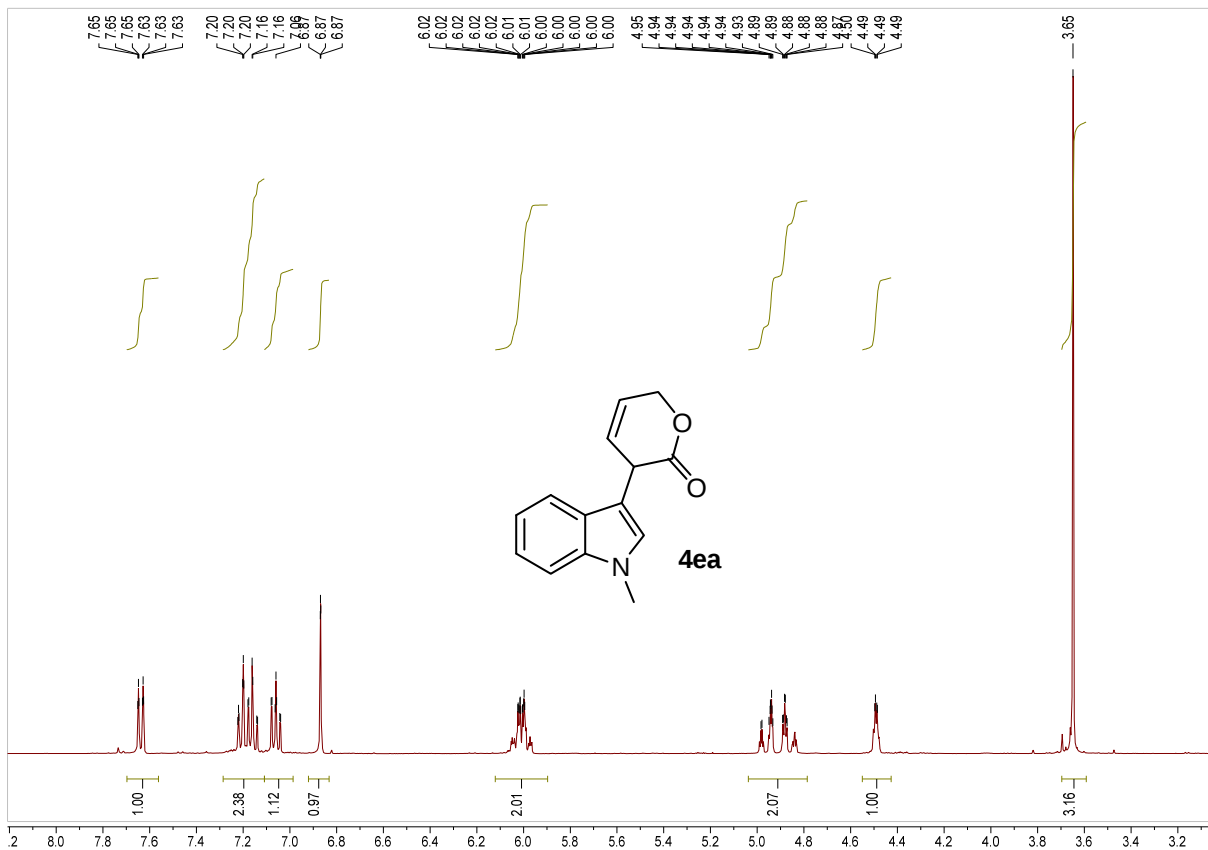


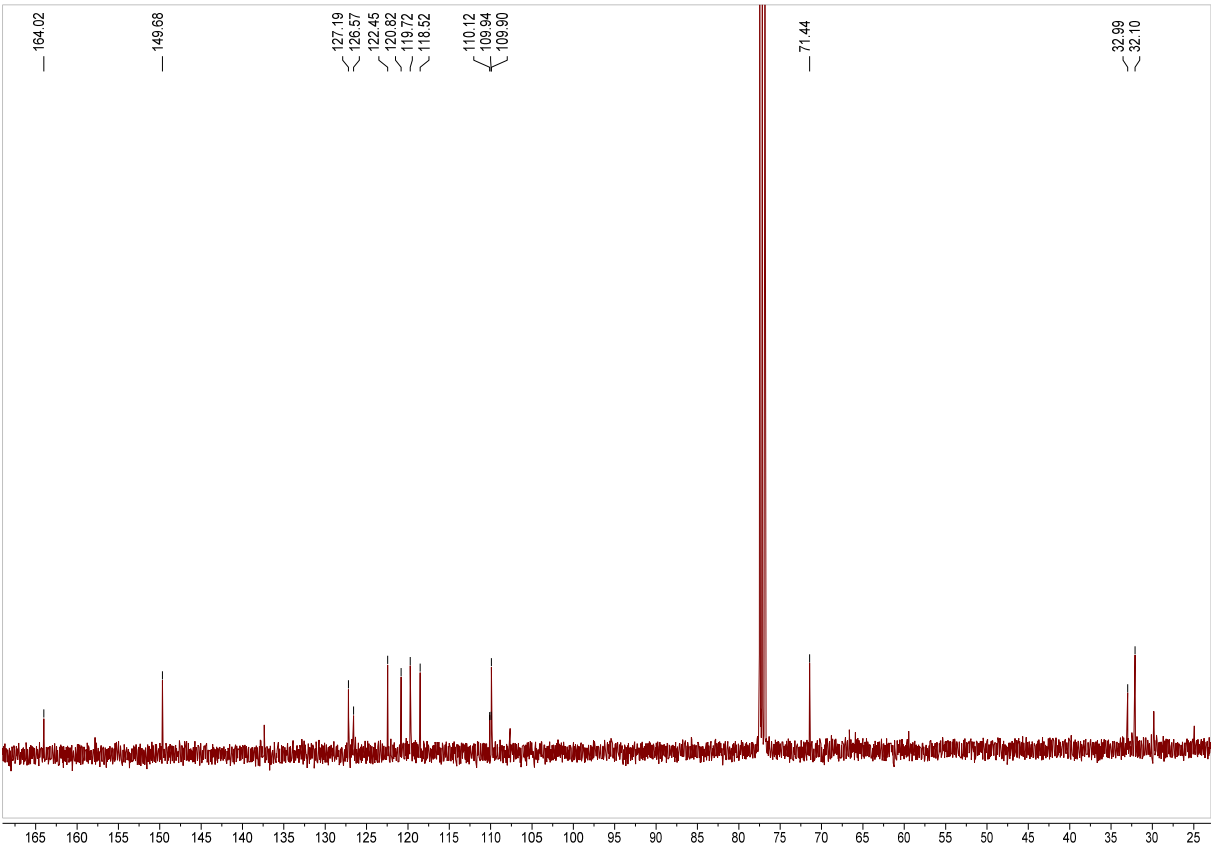
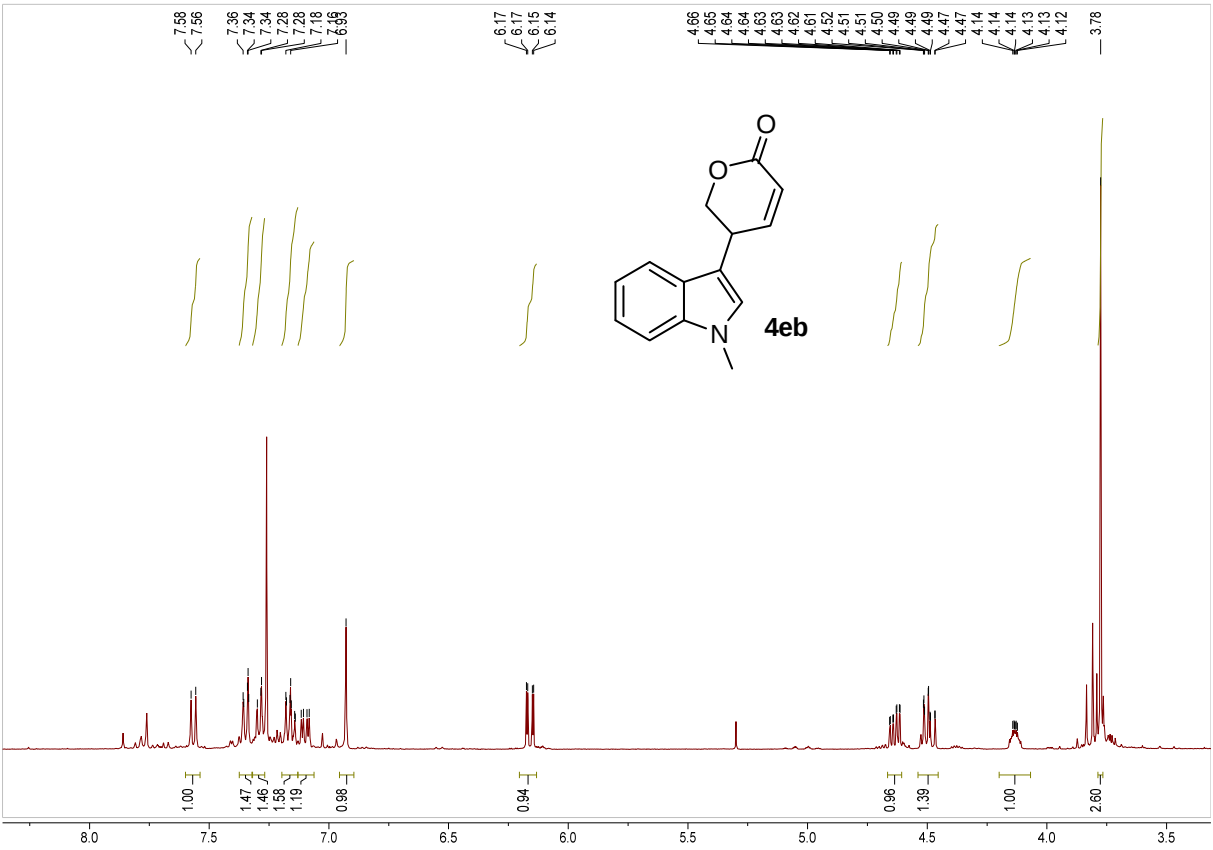


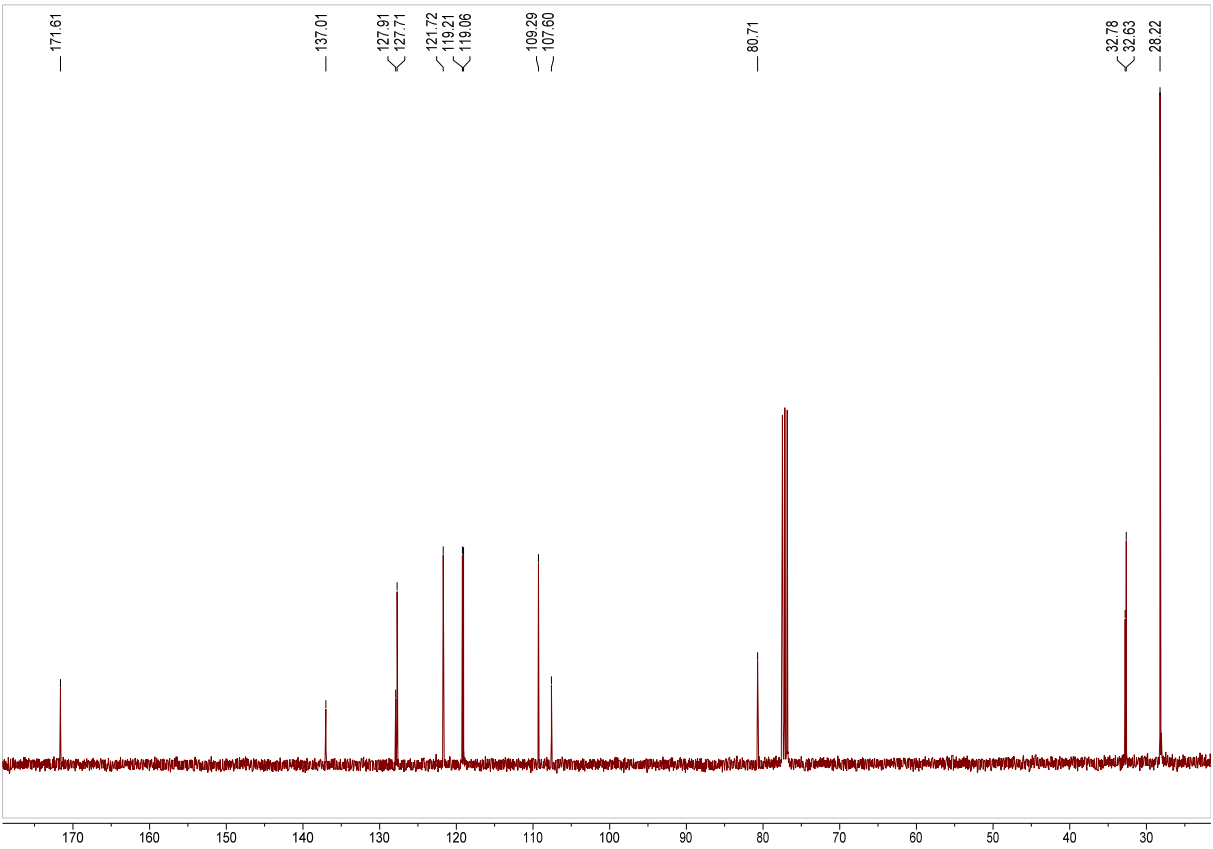
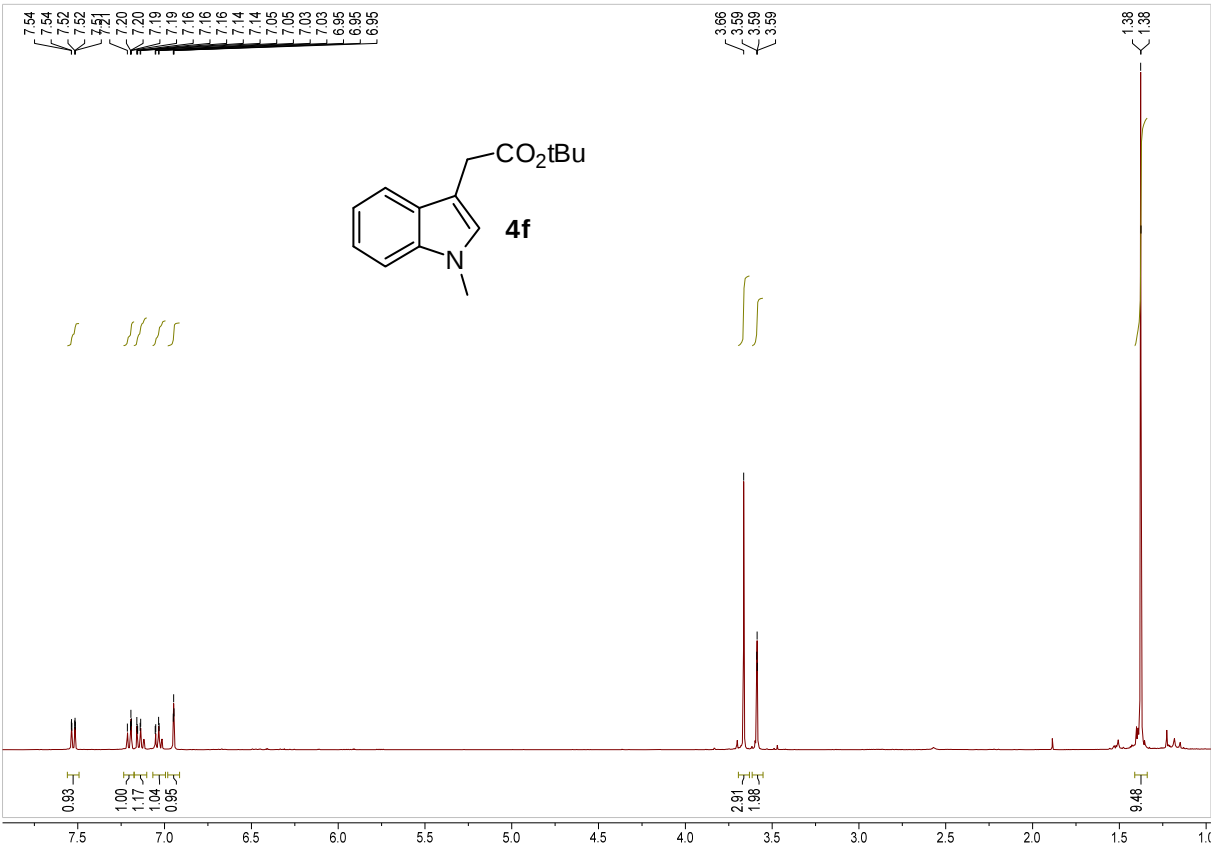


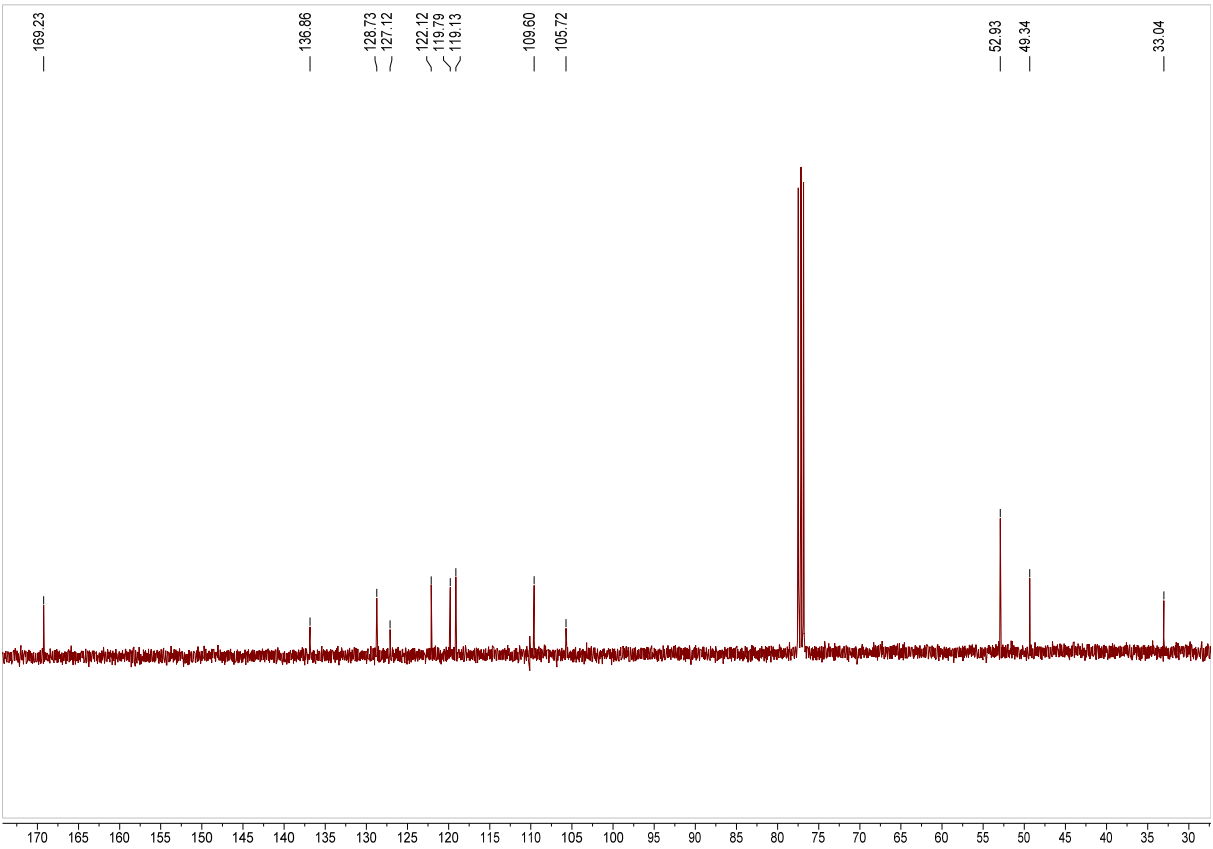
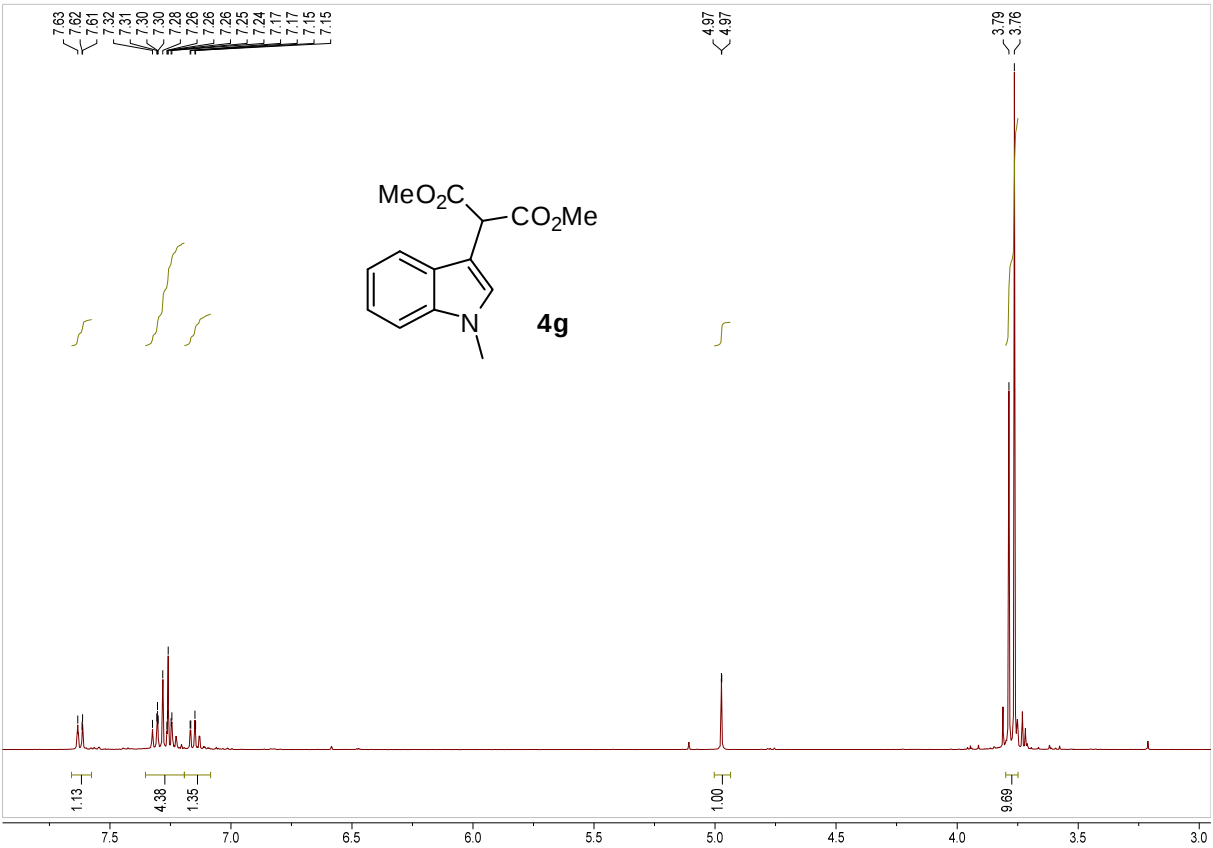


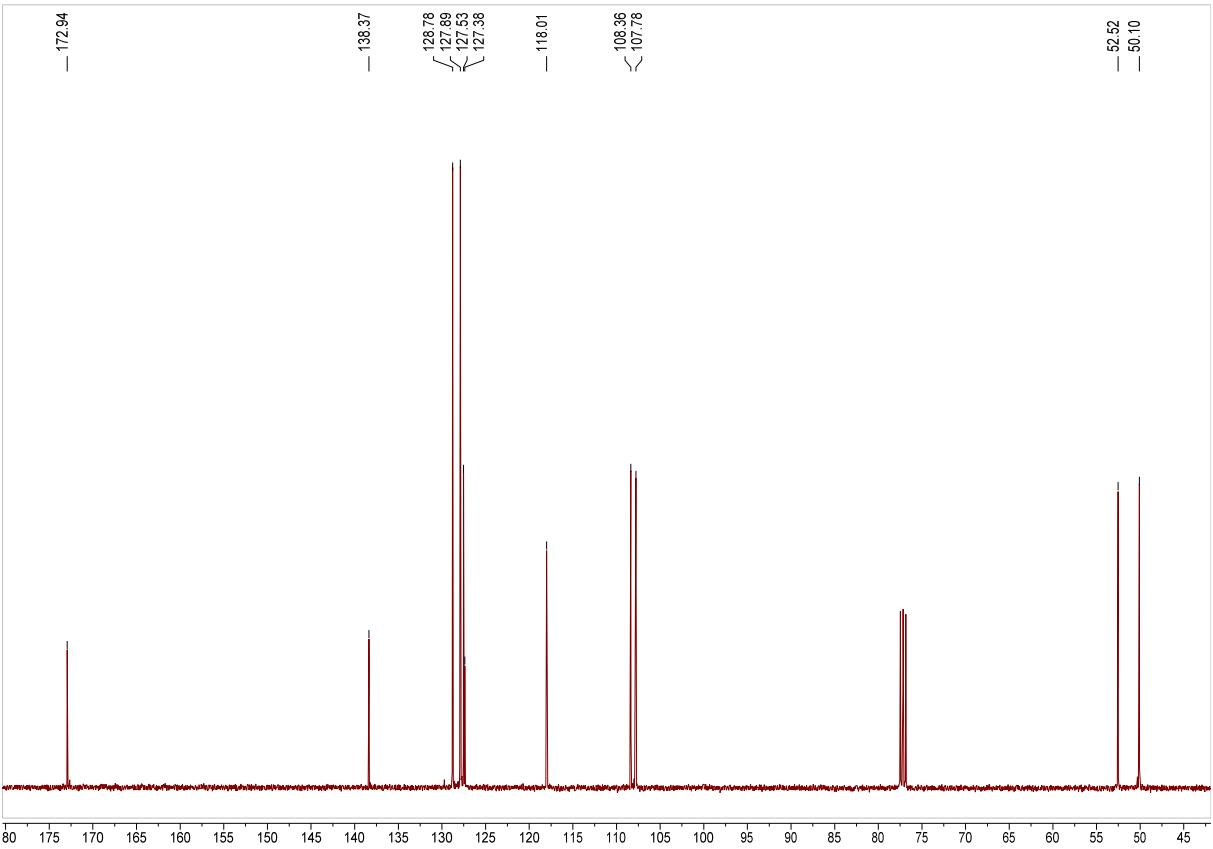
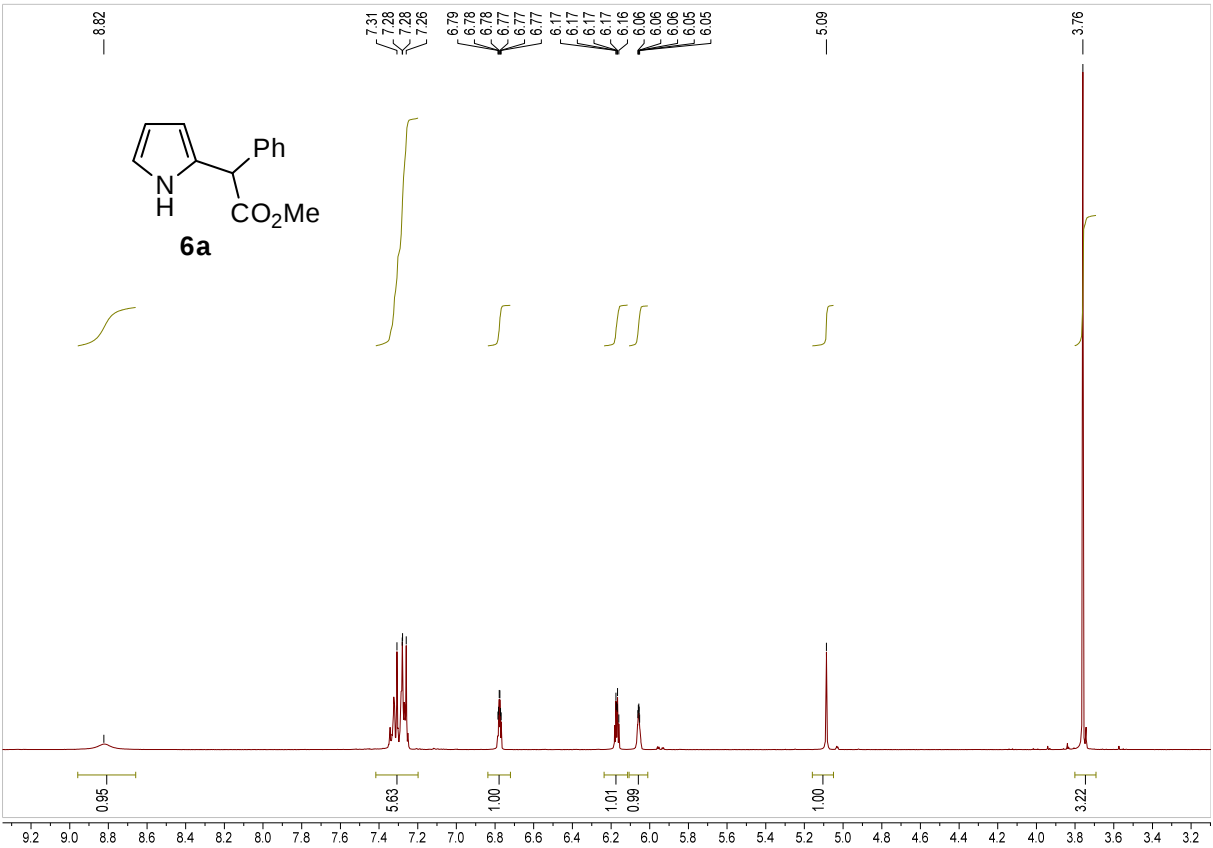


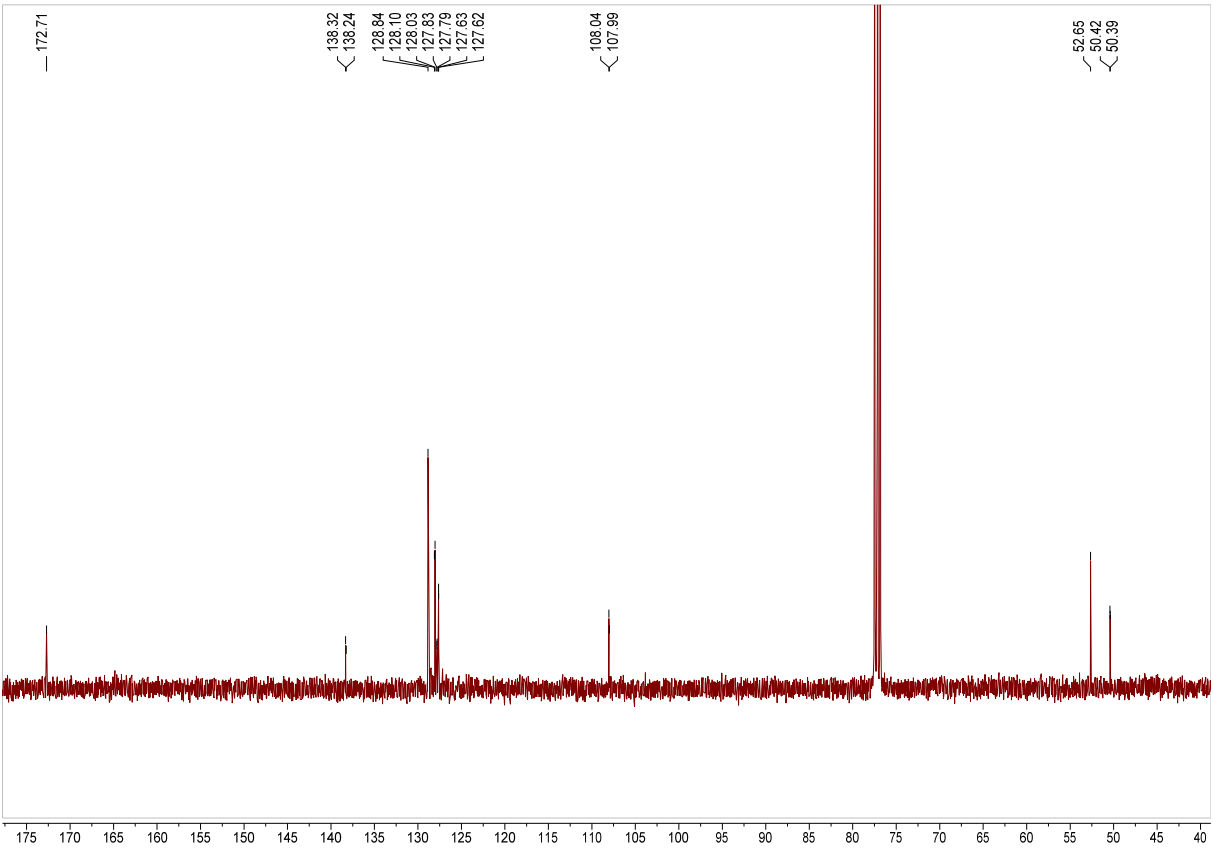
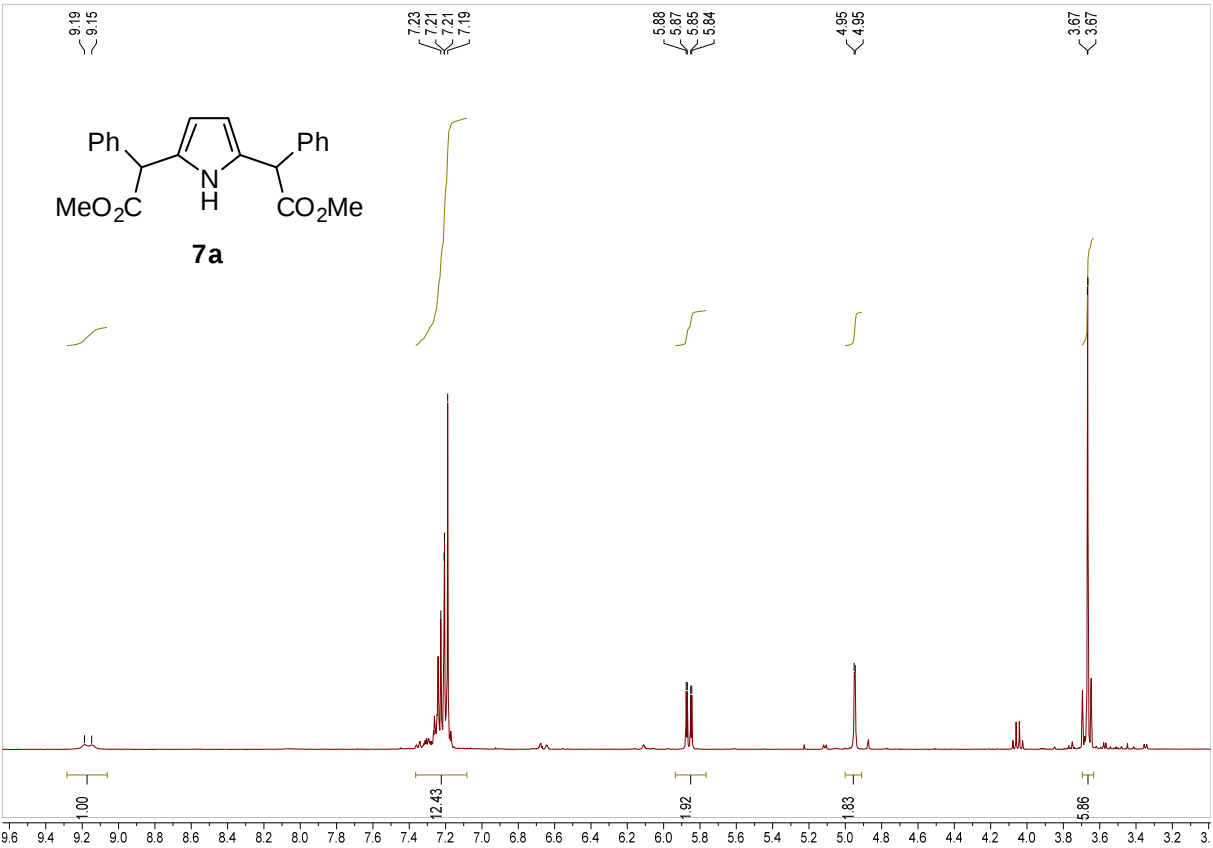


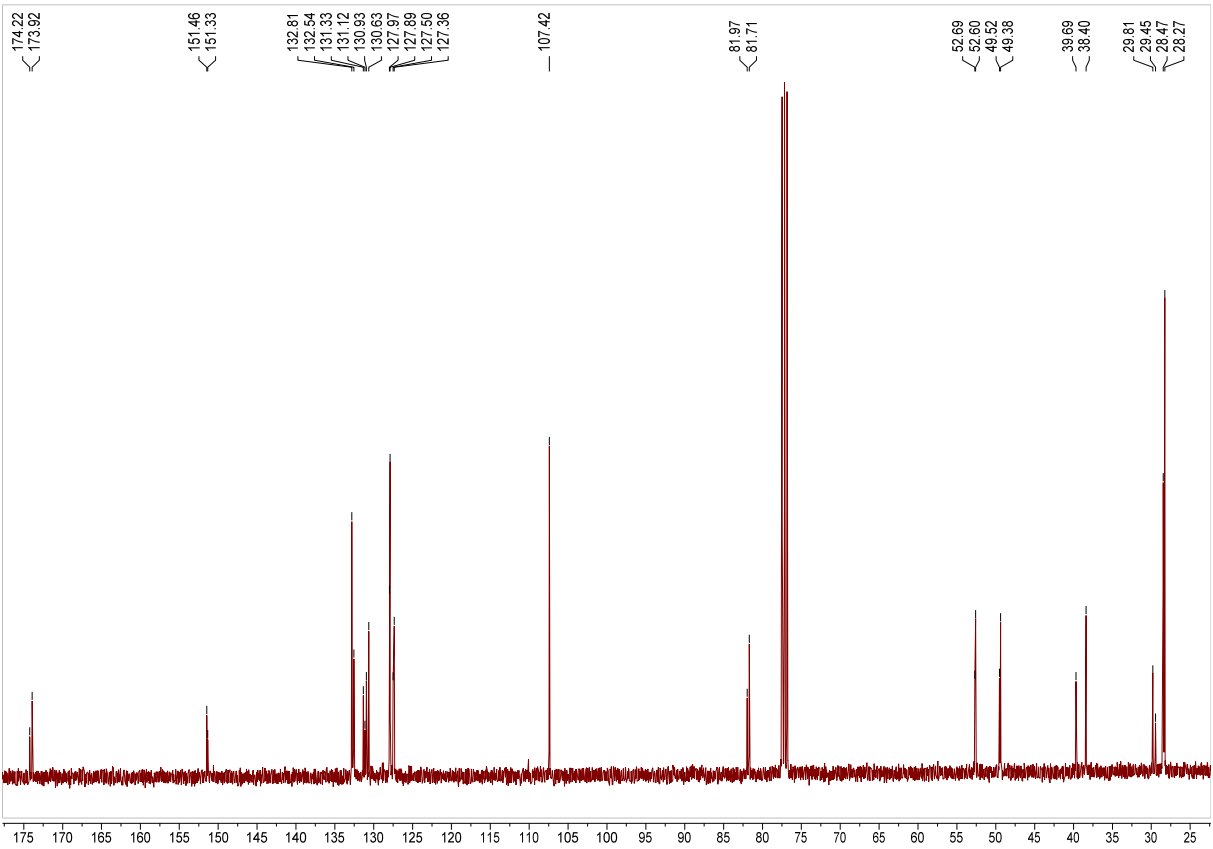
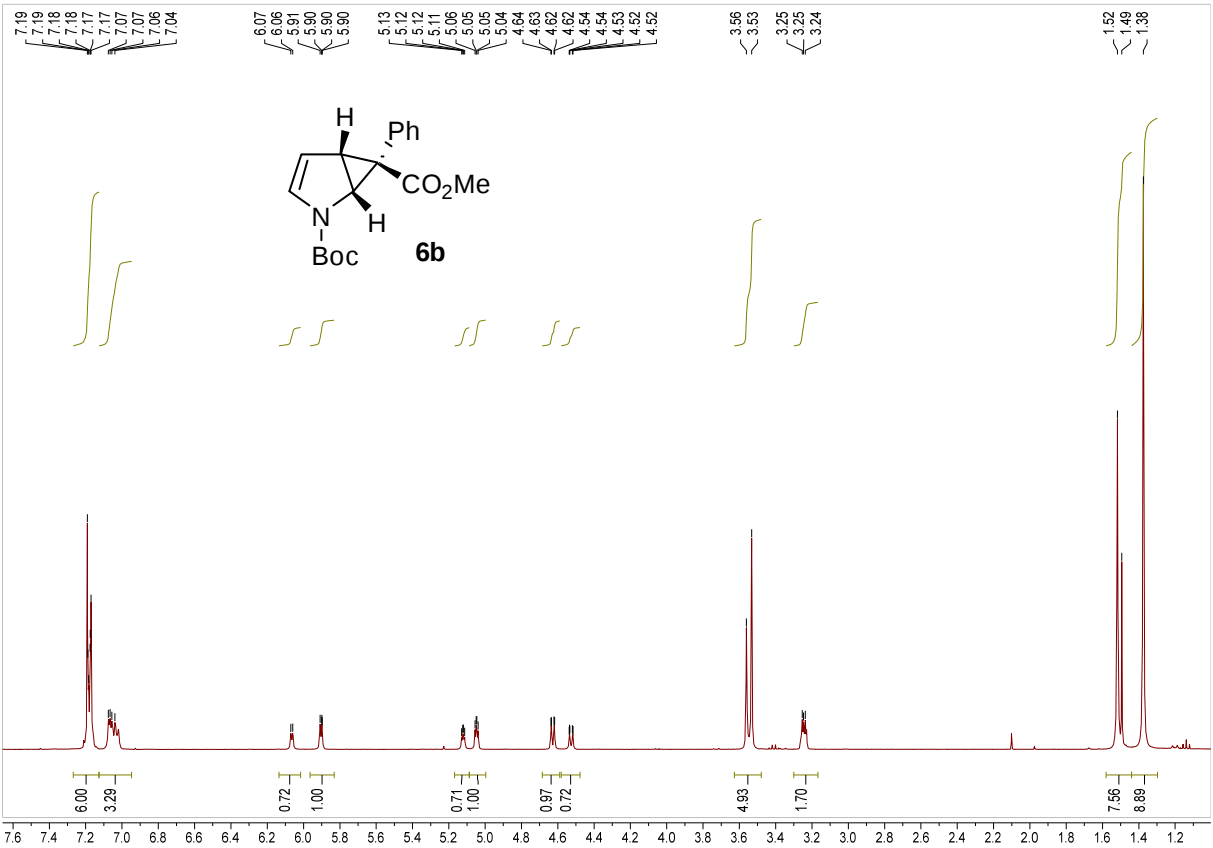


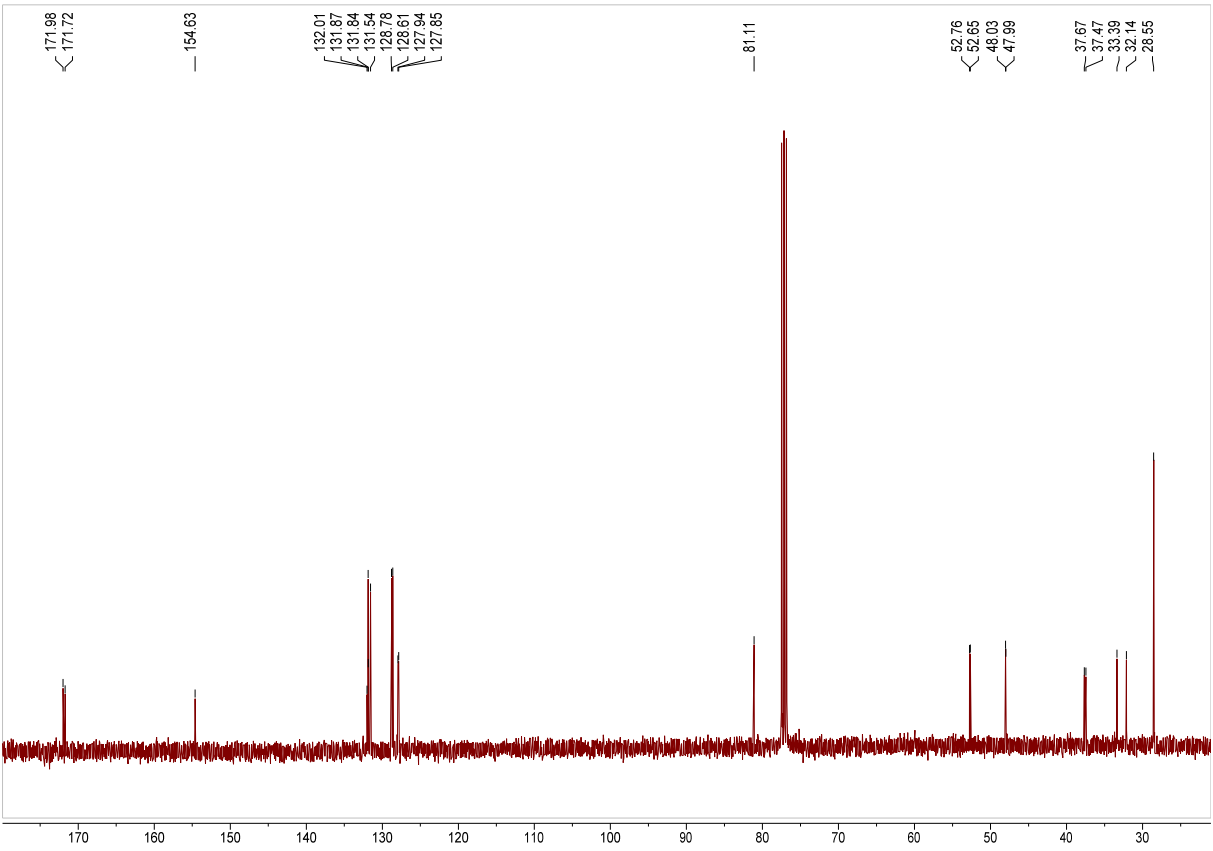
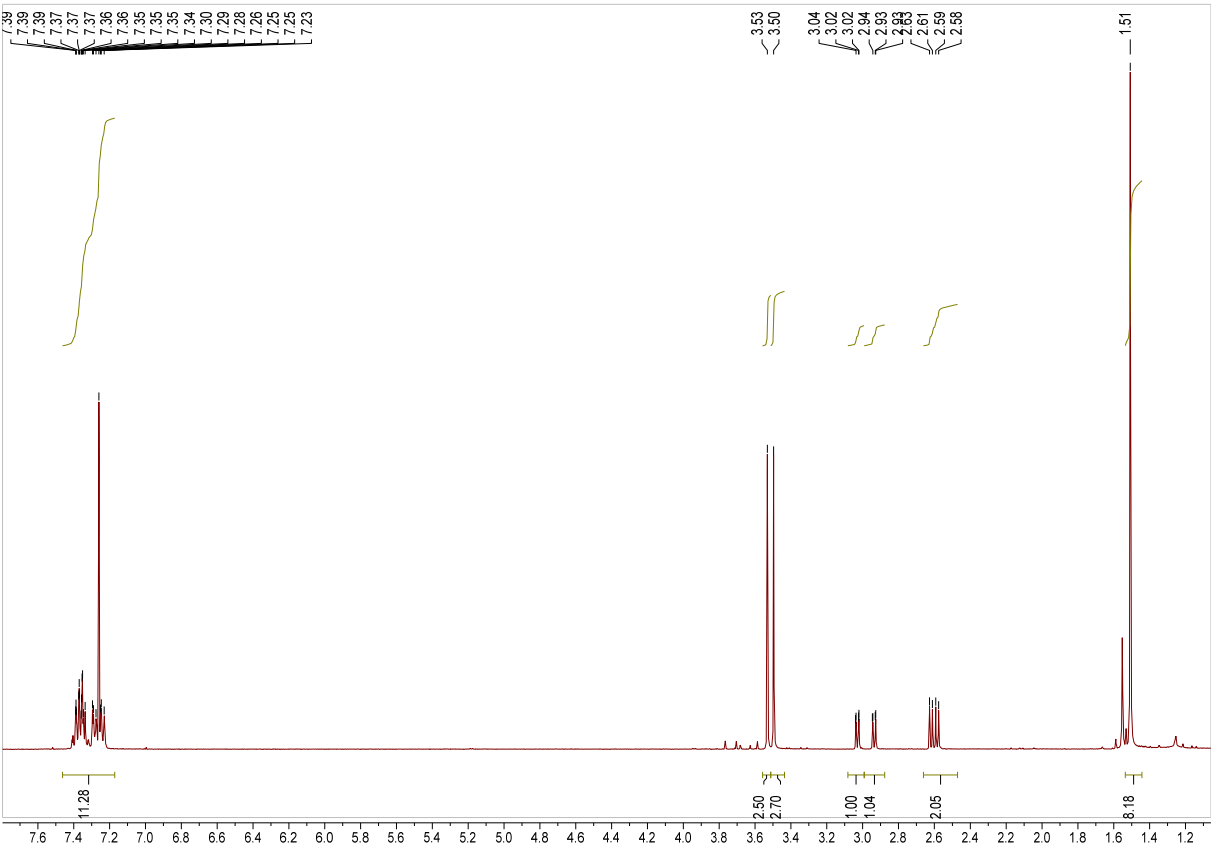












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