Supplementary Information

Tandem indium(III)-catalyzed cycloisomerization and intermolecular hydrofunctionalization of 1,6-enynes

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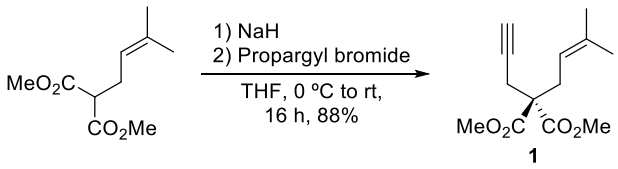
1. General methods

All reactions were carried out in flame-dried glassware, under argon atmosphere, using standard gas-tight syringes, cannulae and septa. Reaction temperatures refer to external bath temperatures. All the heating reactions were heated in an oil bath or an aluminium heating block. Low temperature reactions were carried out into an Cryocool-Inmersion Cooler C-100 II from Neslab. Toluene was distilled from sodium/benzophenone. THF and dichloromethane were dried via MBraun MB-SPS 800 Solvent Purification System. All purchased reagents were used without further purification unless otherwise noted. Indium(III) iodide (99.998%) was used under argon in a glove box Inert Pure Lab^{He}. Completion of the reactions and reaction times were estimated by thin-layer chromatography (TLC) using pre-coated silica gel foils (Alugram® Xtra SIL G/UV254, 0.20 mm thick), UV light as the visualizing agent, and ethanolic phosphomolybdic acid as the developing agent. Flash column chromatography was performed using 230-400 mesh silica gel. ^{1}H NMR and ^{13}C NMR spectra were recorded at room temperature in $CDCl_3$ using a 300 and 400 MHz Bruker Advance spectrometer and calibrated to the solvent peak. DEPT data were used to assign carbon types. Chemical shifts are reported in ppm (δ) relative to the solvent $CDCl_3$ (δ_H 7.26 ppm and δ_C 77.1 ppm). The data of HRMS was obtained with a QSTAR Elite hybrid quadrupole time-of-flight (TOF) ESI mass spectrometer, operating in the positive ionization mode.

2. Synthesis and characterization of starting 1,6-enynes

Dimethyl 2-(3-methylbut-2-en-1-yl)-2-(prop-2-yn-1-yl) malonate (1).[1]

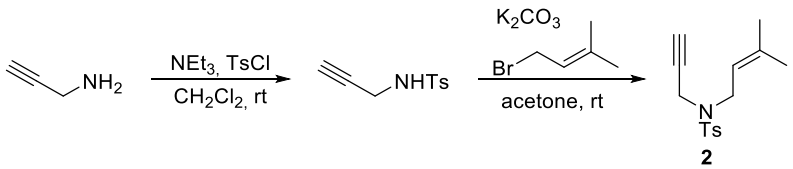


1

A suspension of NaH (580 mg, 24.2 mmol, 95%) in THF (70 mL) was cooled to 0 ºC and dimethyl 2-(3-methylbut-2-en-1-yl) malonate[2] (4.40 g, 21.9 mmol) in THF (10 mL) was dropwise added. Upon complete addition, propargyl bromide (80% sol in toluene, 3.60 mL, 24.2 mmol) was added dropwise and reaction mixture was stirred at rt for 16 h. The reaction mixture was poured into a mixture of H_2O (30 mL) and EtOAc (30 mL). After separation of the layers, the aqueous phase was extracted with EtOAc (2 × 30 mL) and the combined organic layer was dried with anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. After purification by column chromatography (5% EtOAc/hexane) **1** (4.5 g, 88%) was obtained as a colourless oil.

R_f = 0.22 (10% EtOAc/hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.90 (t, *J* = 7.8 Hz, 1H), 3.73 (s, 6H), 2.80-2.76 (m, 4H), 2.00 (t, *J* = 2.7 Hz, 1H), 1.70 (s, 3H), 1.65 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5 (2×C), 137.0 (C), 117.0 (CH), 79.3 (C), 71.2 (CH), 57.2 (C), 52.7 (2×CH_3), 30.8 (CH_2), 26.1 (CH_3), 22.5 (CH_2), 17.9 (CH_3).

4-Methyl-*N*-(3-methylbut-2-en-1-yl)-*N*-(prop-2-yn-1-yl)benzenesulfonamide (2).[3]



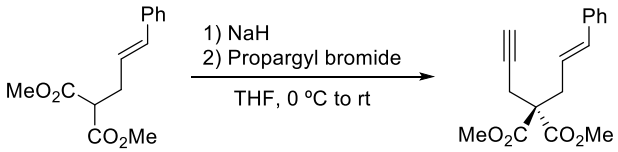
2

To a stirred solution of propargylamine (1.16 mL, 18.16mmol) in CH_2Cl_2 (25 mL), TsCl (3.15 g, 16.50 mmol) and NEt_3 (5.73 mL, 41.25 mmol) were sequentially added and the resulting mixture was stirred overnight at rt. The reaction mixture was then extracted with CH_2Cl_2 (2 × 20 mL), and the combined organic layer was washed with saturated aqueous NaCl (20 mL), dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure to afford, after purification by column chromatography (15-30% EtOAc/hexane) 4-methyl-*N*-(prop-2-yn-1-yl)-benzenesulfonamide (2.76 g, 82%) as a white solid.

K_2CO_3 (1.34 g, 9.70 mmol), 1-bromo-3-methylbut-2-ene (1.12 mL, 9.7 mmol) were sequentially added to a stirred solution of 4-methyl-*N*-(prop-2-yn-1-yl)-benzenesulfonamide (1.01 g, 4.85 mmol) in acetone (8 mL) and the resulting mixture was stirred at rt for 24 h. After completion, K_2CO_3 was removed by filtration in vacuum and the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl ether (80 mL), washed with saturated aqueous NaCl (40 mL), dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure to afford, after purification by column chromatography (5% EtOAc/hexane) **2** (1.23 g, 91%) as a colourless oil.

R_f = 0.45 (20% EtOAc/hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.3 Hz, 2H), 7.26 (d, *J* = 8.1 Hz, 2H), 5.07 (t, *J* = 7.3 Hz, 1H), 4.04 (d, *J* = 2.5 Hz, 2H), 3.79 (d, *J* = 7.3 Hz, 2H), 2.39 (s, 3H), 1.98 (t, *J* = 2.5 Hz, 1H), 1.70 (s, 3H), 1.64 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.4 (C), 139.0 (C), 136.2 (C), 129.4 (2×CH), 127.8 (2×CH), 117.9 (CH), 77.1 (C), 73.4 (CH), 43.9 (CH_2), 35.4 (CH_2), 25.9 (CH_3), 21.5 (CH_3), 17.8 (CH_3).

Dimethyl 2-cinnamyl-2-(prop-2-yn-1-yl)malonate (*E*)-4.[4]

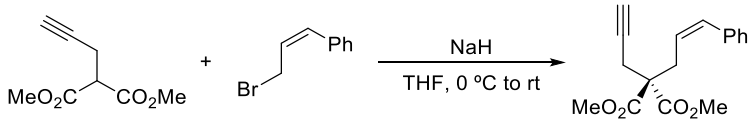


(*E*)-**4**

A suspension of NaH (86 mg, 3.21 mmol, 95% dry) in dry THF (10 mL) was cooled to 0 ºC and a solution of (*E*)-dimethyl 2-cinnamylmalonate[5] (725 mg, 2.92 mmol) in dry THF (6 mL) was added dropwise. After stirring at that temperature for 1h, propargyl bromide (0.360 mL, 3.21 mmol) was added dropwise and the reaction mixture was allowed to warm to rt overnight. The resulting mixture was diluted with H_2O (20 mL) and the aqueous phase was extracted with EtOAc (2 x 15 mL). The combined organic extracts were washed with saturated aqueous NaCl (15 mL), dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure to afford, after purification by column chromatography (10% EtOAc/hexane) (*E*)-**4** (0.712 g, 71%) as a pale yellow oil.

R_f = 0.39 (10% EtOAc/hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29-7.14 (m, 5H), 6.47 (d, *J* = 15.7 Hz, 1H), 5.95 (dt, *J* = 15.7, 7.7 Hz, 1H), 3.71 (s, 6H), 2.91 (dd, *J* = 7.6, 1.3 Hz, 2H), 2.80 (d, *J* = 2.7 Hz, 2H), 2.01 (t, *J* = 2.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.2 (2×C), 137.0 (C), 134.7 (CH), 128.5 (2×CH), 127.6 (CH), 126.3 (2×CH), 123.1 (CH), 78.8 (C), 71.7 (C), 57.2 (CH), 52.9 (2×CH_3), 35.9 (CH_2), 22.9 (CH_2).

Dimethyl (*Z*)-2-(3-phenylallyl)-2-(prop-2-yn-1-yl)malonate ((*Z*)-4).



(*E*)-**4**

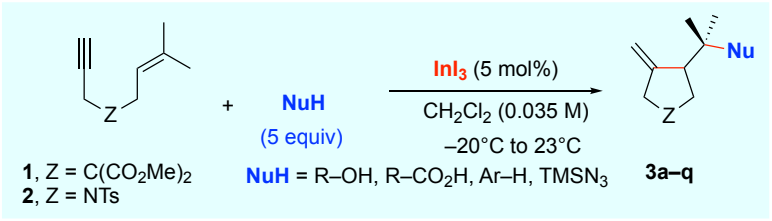
A suspension of NaH (131 mg, 4.74 mmol, 90% dry) in dry THF (14 mL) was cooled to 0 ºC and dimethyl propargylmalonate (672 mg, 3.95 mmol) was added dropwise. After stirring at that temperature for 1h, a solution of (*Z*)-cinammyl bromide (0.933 g, 4.74 mmol) in dry THF (6 mL) was added dropwise and the reaction mixture was allowed to warm to rt overnight. The resulting mixture was diluted with H_2O (20 mL) and the aqueous phase was extracted with ethyl ether (2 x 15 mL). The combined organic extracts were washed with saturated aqueous NaCl (15 mL), dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure to afford, after purification by column chromatography (3-10% EtOAc/hexane) (*Z*)-**4** (0.931 g, 82%) as a yellow oil.

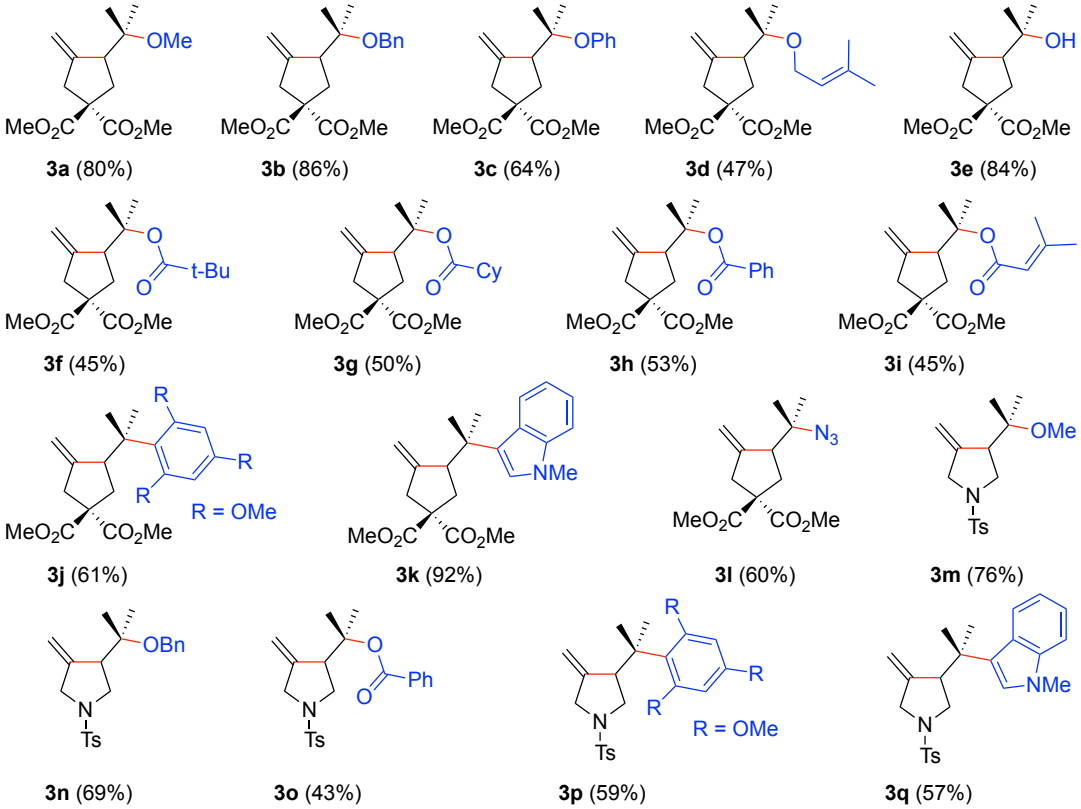
R_f = 0.39 (20% EtOAc/hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36-7.19 (m, 5H), 6.60 (d, *J* = 11.7 Hz, 1H), 5.48 (dt, *J* = 11.7, 7.5 Hz, 1H), 3.67 (s, 6H), 3.13 (dd, *J* = 7.5, 1.8 Hz, 2H), 2.83 (d, *J* = 2.7 Hz, 2H), 1.87 (t, *J* = 2.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.2 (2×C), 136.8 (C), 133.1 (CH), 128.8 (2×CH), 128.2 (2×CH), 126.9 (CH), 124.7 (CH), 78.5 (C), 71.8 (CH), 57.0 (C), 52.8 (2×CH_3), 30.7(CH_2), 22.9 (CH_2). HRMS (ESI) m/z calcd for $C_{17}H_{18}O_4Na$ $[M+Na]^+$ 309.1103; found 309.1109.

3. General procedure for tandem indium(III)-catalyzed cycloisomerization and intermolecular hydrofunctionalization of 1,6-enynes

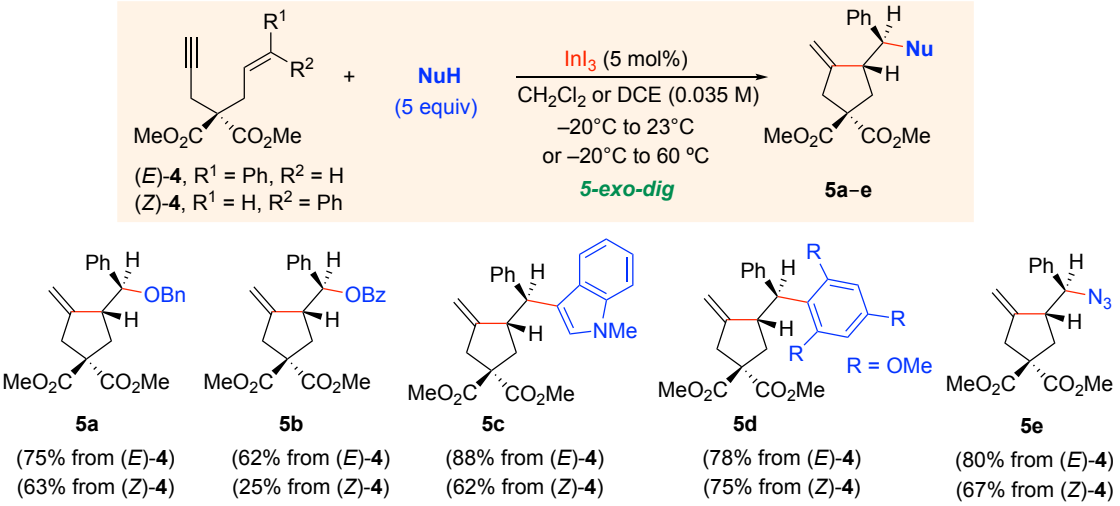
In a capped vial filled with argon and equipped with a magnetic stir bar, InI_3 (5 mol%) was placed and the corresponding solvent (2 mL) was added. The suspension was cooled down to –20 ºC and a solution of 1,6-enyne (1 equiv.) and the nucleophile (5 equiv.) in dichloromethane or dichloroethane, adjusting the volume until the final concentration of the reaction mixture was ~0.035 M, was added dropwise. The resulting mixture was left warming at rt or heated (40-60 ºC) until the starting material was consumed (TLC and/or GC-MS). The solvent was evaporated in vacuum and the residue was purified by column chromatography (EtOAc/hexane) to afford the corresponding product (Schemes 1 and 2).

Scheme 1. Tandem indium-catalyzed cyclizations and intermolecular additions to 1,6-enynes **1** and **2**.





Scheme 2. Tandem indium(III)-catalyzed 1,6-enyne cyclizations and intermolecular additions to 1,6-enynes (*E*)-**4** and (*Z*)-**4**.



4. Synthesis and characterization data for reaction products

Dimethyl 3-(2-methoxypropan-2-yl)-4-methylenecyclopentane-1,1-dicarboxylate (3a).[6]

Following the general procedure, the reaction of 1,6-enyne **1** (50 mg, 0.21 mmol) and MeOH (40 µL, 1.05 mmol) with InI_3 (5.2 mg, 0.01 mmol) in CH_2Cl_2 (6.6 mL) was stirred at rt for 21 h. After purification by column chromatography (2-10% EtOAc/hexane) **3a** (43 mg, 80%) was obtained as a colourless oil.

R_f = 0.26 (10% EtOAc/hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.03 (br s, 1H), 4.97 (br s, 1H), 3.72 (s, 3H), 3.71 (s, 3H), 3.18 (s, 3H), 2.95-2.78 (m, 3H), 2.55 (ddd, *J* = 13.5, 8.3, 1.7 Hz, 1H), 2.00 (dd, *J* = 13.7, 9.3 Hz, 1H), 1.17 (s, 3H), 1.11 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1 (C), 172.0 (C), 148.2 (C), 110.6 (CH_2), 76.8 (C), 58.6 (C), 52.7 (2×CH_3), 49.1 (CH), 49.0 (CH_3), 43.4 (CH_2), 36.0 (CH_2), 22.6 (CH_3), 22.2 (CH_3).

1a:[7] R_f = 0.22 (10% EtOAc/hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.72 (s, 1H), 5.39 (s, 1H), 3.73 (s, 6H), 3.19 (s, 2H), 3.05 (s, 2H), 1.82 (s, 3H), 1.78 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6 (2×C), 138.8 (C), 135.7 (CH), 124.4 (CH), 120.7 (CH), 59.3 (C), 52.8 (2×CH_3), 43.3 (CH_2), 40.3 (CH_2), 27.3 (CH_3), 19.8 (CH_3). HRMS (ESI) m/z calcd for $C_{13}H_{18}O_4Na$ $[M+Na]^+$ 261.1103; found 261.1098.

Dimethyl 3-(2-(benzyloxy)propan-2-yl)-4-methylenecyclopentane-1,1-dicarboxylate (3b).[8]

Following the general procedure, the reaction of 1,6-enyne **1** (50 mg, 0.21 mmol) and benzyl alcohol (11 µL, 1.05 mmol) with InI_3 (5.2 mg, 0.01 mmol) in CH_2Cl_2 (6.6 mL) was stirred at rt for 4 h. After purification by column chromatography (5% EtOAc/hexane) **3b** (63 mg, 86%) was obtained as a colourless oil. R_f = 0.29 (10% EtOAc/hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (d, *J* = 4.3 Hz, 4H), 7.29-7.21 (m, 1H), 5.05 (m, 2H), 4.46 (s, 2H), 3.73 (s, 3H), 3.72 (s, 3H), 2.89-2.84 (m, 3H), 2.61 (ddd, *J* = 13.7, 8.9, 2.0 Hz, 1H), 2.11 (dd, *J* = 13.7, 9.4 Hz, 1H), 1.30 (s, 3H), 1.24 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1 (C), 172.0 (C), 148.2 (C), 139.6 (C), 128.3 (2×CH), 127.2 (2×CH), 127.1 (CH), 110.8 (CH_2), 77.5 (C), 63.5 (CH_2), 58.6 (C), 52.8 (CH_3), 52.7 (CH_3), 50.0 (CH), 43.5 (CH_2), 36.1 (CH_2), 23.3 (CH_3), 22.7 (CH_3).

Dimethyl 3-methylene-4-(2-phenoxypropan-2-yl)cyclopentane-1,1-dicarboxylate (3c).

Following the general procedure, the reaction of 1,6-enyne **1** (50 mg, 0.21 mmol) and phenol (94 mg, 1.05 mmol) with InI_3 (5.2 mg, 0.01 mmol) in CH_2Cl_2 (6.6 mL) was stirred at rt for 19 h. After purification by column chromatography (2-10% EtOAc/hexane) **3c** (45 mg, 64%) as a light pink oil.

R_f = 0.52 (10% EtOAc/hexane). IR (ATR) ν_{max} = 2953, 1734 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.29-7.20 (m, 2H), 7.09-7.02 (m, 1H), 6.97 (d, *J* = 7.0 Hz, 2H), 5.15 (d, *J* = 6.1 Hz, 2H), 3.74 (s, 3H), 3.73 (s, 3H), 3.06-2.85 (m, 3H), 2.70 (ddd, *J* = 13.8, 8.5, 1.6 Hz, 1H), 2.23 (dd, *J* = 13.1, 9.0 Hz, 1H), 1.27 (s, 3H), 1.26 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1 (C), 172.0 (C), 155.0 (C), 148.2 (C), 129.0 (2×CH), 124.1 (2×CH), 123.4 (CH), 111.4 (CH_2), 82.2 (C), 58.7 (C), 52.8 (2×CH_3), 51.9 (CH), 43.5 (CH_2), 36.3 (CH_2), 24.7 (CH_3), 23.5 (CH_3). HRMS (ESI) m/z calcd for $C_{19}H_{24}O_5Na$ $[M+Na]^+$ 355.1521; found 355.1508.

Dimethyl 3-(2-((3-methylbut-2-en-1-yl)oxy)propan-2-yl)-4-methylenecyclopentane-1,1-dicarboxylate (3d).

Following the general procedure, the reaction of 1,6-enyne **1** (50 mg, 0.21 mmol) and 3-methylbut-2-en-1-ol (11 µL, 1.05 mmol) with InI_3 (5.2 mg, 0.01 mmol) in CH_2Cl_2 (6.6 mL) was stirred at rt for 19 h. After purification by column chromatography (5-10% EtOAc/hexane) **3d** (32 mg, 47%) was obtained as a colourless oil.

R_f = 0.23 (10% EtOAc/hexane). IR (ATR) ν_{max} = 2921, 1735 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 5.27 (t, *J* = 6.7 Hz, 1H), 5.02 (m, 2H), 3.89 (t, *J* = 5.6 Hz, 2H), 3.73 (s, 3H), 3.72 (s, 3H), 2.94-2.82 (m, 3H), 2.60-2.50 (m, 1H), 2.01 (dd, *J* = 13.2, *J* = 9.6 Hz, 1H), 1.72 (s, 3H), 1.65 (s, 3H), 1.23 (s, 3H), 1.15 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1 (C), 172.0 (C), 148.2 (C), 135.4 (C), 122.0 (CH), 110.5 (CH_2), 76.8 (C), 58.6 (C), 58.1 (CH_2), 52.8 (CH_3), 52.7 (CH_3), 49.1 (CH), 43.4 (CH_2), 36.1 (CH_2), 25.9 (CH_3), 23.4 (CH_3), 22.8 (CH_3), 18.1 (CH_3). HRMS (ESI) m/z calcd for $C_{18}H_{28}O_5Na$ $[M+Na]^+$ 347.1834; found 347.1831.

Dimethyl 3-(2-hydroxypropan-2-yl)-4-methylenecyclopentane-1,1-dicarboxylate (3e).[6]

Following the general procedure, the reaction of 1,6-enyne **1** (50 mg, 0.21 mmol) and H_2O (20 µL, 1.05 mmol) with InI_3 (5.2 mg, 0.01 mmol) in CH_2Cl_2 (6.6 mL) was stirred at rt for 20 h. After purification by column chromatography (20-30% EtOAc/hexane) **3e** (45 mg, 84%) was obtained as a colourless oil.

R_f = 0.28 (30% EtOAc/hexane). ^1H NMR (300 MHz, $CDCl_3$) δ 5.10 (br s, 1H), 5.02 (br s, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 2.87 (s, 2H), 2.72-2.58 (m, 2H), 2.05-1.95 (m, 1H), 1,61 (br s, 1H), 1.24 (s, 3H), 1.19 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9 (C), 171.9 (C), 148.5 (C), 111.3 (CH), 72.6 (C), 58.8 (C), 52.8 (2×CH_3), 52.6 (CH), 43.5 (CH_2), 36.2 (CH_2), 28.1 (CH_3), 26.1 (CH_3).

Dimethyl 3-methylene-4-(2-(pivaloyloxy)propan-2-yl)cyclopentane-1,1-dicarboxylate (3f).

Following the general procedure, the reaction of 1,6-enyne **1** (50 mg, 0.21 mmol) and pivalic acid (107 mg, 1.05 mmol) with InI_3 (5.2 mg, 0.01 mmol) in CH_2Cl_2 (6.6 mL) was stirred at rt for 1 h. After purification by column chromatography (5% EtOAc/hexane) **3f** (32 mg, 45%) was obtained as a light yellow oil.

R_f = 0.41 (10% EtOAc/hexane). IR (ATR) ν_{max} = 2923, 1737 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 5.09 (s, 1H), 4.98 (s, 1H), 3.74 (s, 3H), 3.73 (s, 3H), 3.10 (t, *J* = 8.9 Hz, 1H), 2.90 (s, 2H), 2.63 (dd, *J* = 13.7, 8.3 Hz, 1H), 2.03 (dd, *J* = 14,5, 9.3 Hz, 1H), 1.51 (s, 3H), 1.46 (s, 3H), 1.15 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.7 (C), 171.9 (C), 171.7 (C), 147.5 (C), 111.5 (CH_2), 83.4 (C), 58.6 (C), 52.8 (2×CH_3), 50.8 (CH), 43.7 (CH_2), 39.5 (C), 35.8 (CH_2), 27.2 (3×CH_3), 23.5 (CH_3), 23.2 (CH_3). HRMS (ESI) m/z calcd for $C_{18}H_{28}O_6Na$ $[M+Na]^+$ 363.1784; found 363.1779.

Dimethyl 3-(2-((cyclohexanecarbonyl)oxy)propan-2-yl)-4-methylenecyclopentane-1,1-dicarboxylate (3g).

Following the general procedure, the reaction of 1,6-enyne **1** (50 mg, 0.21 mmol) and cyclohexanecarboxylic acid (130 µL, 1.05 mmol) with InI_3 (5.2 mg, 0.01 mmol) in CH_2Cl_2 (6.6 mL) was stirred at rt for 2 h. After purification by column chromatography (5% EtOAc/hexane) **3g** (38 mg, 50%) was obtained as a light yellow oil.

R_f = 0.35 (10% EtOAc/hexane). IR (ATR) ν_{max} = 2927, 1736, 1713 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 5.07 (s, 1H), 4.96 (s, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 3.14 (t, *J* = 9.5 Hz, 1H), 2.88 (s, 2H), 2.60 (dd, *J* = 13.8, 8.8 Hz, 1H), 2.18 (tt, *J* = 11.0, 3.6 Hz, 1H), 2.02 (dd, *J* = 14.2, 9.3 Hz, 1H), 1.90-1.80 (m, 2H), 1.78-1.67 (m, 2H), 1.50 (s, 3H), 1.44 (s, 3H), 1.42-1.14 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.4 (C), 171.9 (C), 171.7 (C), 147.5 (C), 111.4 (CH_2), 83.4 (C), 77.2 (C), 58.5 (C), 52.8 (2×CH_3), 50.5 (CH), 44.3 (CH), 43.7 (CH_2), 35.7 (CH_2), 29.0 (2×CH_2), 25.8 (CH_2), 25.5 (CH_2), 23.6 (CH_3), 23.1 (CH_3). HRMS (ESI) m/z calcd for $C_{20}H_{30}O_6Na$ $[M+Na]^+$ 389.1940; found 389.1932.

Dimethyl 3-(2-(benzoyloxy)propan-2-yl)-4-methylenecyclopentane-1,1-dicarboxylate (3h).

Following the general procedure, the reaction of 1,6-enyne **1** (50 mg, 0.21 mmol) and benzoic acid (128 mg, 1.05 mmol) with InI_3 (5.2 mg, 0.01 mmol) in CH_2Cl_2 (6.6 mL) was stirred at rt for 10 h. After purification by column chromatography (5% EtOAc/hexane) **3h** (40 mg, 53%) was obtained as a light yellow oil.

R_f = 0.27 (5% EtOAc/hexane). IR (ATR) ν_{max} = 2923, 1733 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.00-7.95 (m, 2H), 7.53 (tt, *J* = 7.3, 1.7 Hz, 1H), 7.43 (t, *J* = 7.4 Hz, 2H), 5.11 (s, 1H), 5.04 (s, 1H), 3.74 (s, 3H), 3.73 (s, 3H), 3.37 (t, *J* = 9.2 Hz, 1H), 2.95 (s, 2H), 2.71 (dd, *J* = 13.9, 8.8 Hz, 1H), 2.11 (dd, *J* = 13.5, 9.7 Hz, 1H), 1.65 (s, 3H), 1.61 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8 (C), 171.7 (C), 165.6 (C), 147.3 (C), 132.6 (CH), 131.7 (C), 129.5 (2×CH), 128.3 (2×CH), 111.6 (CH_2), 84.9 (C), 58.5 (C), 52.9 (CH_3), 52.8 (CH_3), 50.4 (CH), 43.8 (CH_2), 36.0 (CH_2), 23.7 (CH_3), 23.2 (CH_3). HRMS (ESI) m/z calcd for $C_{20}H_{24}O_6Na$ $[M+Na]^+$ 383.1471; found 383.1461.

Dimethyl 3-(2-((3-methylbut-2-enoyl)oxy)propan-2-yl)-4-methylenecyclopentane-1,1-dicarboxylate (3i).

Following the general procedure, the reaction of 1,6-enyne **1** (50 mg, 0.21 mmol) and 3-methylbut-2-enoic acid (105 mg, 1.05 mmol) with InI_3 (5.2 mg, 0.01 mmol) in CH_2Cl_2 (6.6 mL) was stirred at rt for 2h. After purification by column chromatography (5-20% EtOAc/hexane) **3i** (32 mg, 45%) was obtained as a light yellow oil.

R_f = 0.37 (20% EtOAc/hexane). IR (ATR) ν_{max} = 2954, 1735, 1713 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 5.58 (t, *J* = 1.3 Hz, 1H), 5.07 (s, 1H), 4.97 (s, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 3.22 (t, *J* = 9.3 Hz, 1H), 2.88 (s, 2H), 2.61 (dd, *J* = 13.9, 8.5 Hz, 1H), 2.12 (d, *J* = 1.1 Hz, 3H), 2.02 (dd, *J* = 13.7, 9.3 Hz, 1H), 1.85 (d, *J* = 1.1 Hz, 3H), 1.51 (s, 3H), 1.48 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9 (C), 171.7 (C), 166.0 (C), 155.7 (C), 147.6 (C), 117.4 (CH), 111.2 (CH_2), 83.1 (C), 58.5 (C), 52.8 (2×CH_3), 50.3 (CH), 43.7 (CH_2), 35.8 (CH_2), 27.4 (CH_3), 23.9 (CH_3), 23.2 (CH_3), 20.0 (CH_3). HRMS (ESI) m/z calcd for $C_{18}H_{26}O_6Na$ $[M+Na]^+$ 361.1627; found 361.1619.

Dimethyl 3-methylene-4-(2-(2,4,6-trimethoxyphenyl)propan-2-yl)cyclopentane-1,1-dicarboxylate (3j).

Following the general procedure, the reaction of 1,6-enyne **1** (50 mg, 0.21 mmol) and 1,3,5-timethoxybenzene (177 mg, 1.05 mmol) with InI_3 (5.2 mg, 0.01 mmol) in CH_2Cl_2 (6.6 mL) was stirred at rt for 19 h. After purification by column chromatography (5-20% EtOAc/hexane) **3j** (52 mg, 61%) was obtained as a light yellow oil.

R_f = 0.35 (20% EtOAc/hexane). IR (ATR) ν_{max} = 2953, 1731 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.12 (s, 2H), 4.93 (s, 1H), 4.64 (s, 1H), 3.79 (s, 3H), 3.75 (s, 6H), 3.68 (s, 6H), 2.96-2.86 (m, 2H), 2.79 (d, *J* = 15.1 Hz, 1H), 2.29 (ddd, *J* = 13.6, 8.6, 1.8 Hz, 1H), 1.89 (dd, *J* = 13.4, 9.5 Hz, 1H), 1.49 (s, 3H), 1.39 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3 (C), 172.2 (C), 160.6 (2×C), 158.8 (C), 150.2 (C), 117.4 (C), 109.3 (CH_2), 92.9 (2×CH_3), 58.7 (C), 56.0 (2×CH_3), 55.1 (CH), 52.6 (2×CH_3), 48.3 (CH_3), 44.5 (CH_2), 42.3 (C), 36.9 (CH_2), 27.5 (CH_3), 25.8 (CH_3). HRMS (ESI) m/z calcd for $C_{22}H_{30}O_7Na$ $[M+Na]^+$ 429.1889; found 429.1886.

Dimethyl 3-(2-(1-methyl-1*H*-indol-2-yl)propan-2-yl)-4-methylenecyclopentane-1,1-dicarboxylate (3k).[9]

Following the general procedure, the reaction of 1,6-enyne **1** (50 mg, 0.21 mmol) and *N*-methylindole (130 µL, 1.05 mmol) with InI_3 (5.2 mg, 0.01 mmol) in CH_2Cl_2 (6.6 mL) was stirred at rt for 8 h. After purification by column chromatography (5% EtOAc/hexane) **3k** (71 mg, 92%) was obtained as a light yellow oil.

R_f = 0.25 (20% EtOAc/hexane). ^1H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.4 Hz, 1H), 7.32-7.26 (m, 1H), 7.22 (td, *J* = 7.7, 1.1 Hz, 1H), 7.09 (td, *J* = 7.6, 1.1 Hz, 1H), 6.79 (s, 1H), 4.96 (s, 1H), 4.52 (s, 1H), 3.74 (s, 3H), 3.69 (s, 6H), 3.47 (t, *J* = 8.6 Hz, 1H), 2.84 (br s, 2H), 2.42 (dd, *J* = 13.8, 8.7 Hz, 1H), 1.89 (dd, *J* = 13.8, 9.1 Hz, 1H), 1.47 (s, 3H), 1.37 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2 (C), 172.0 (C), 149.0 (C), 137.8 (C), 126.1 (C), 126.0 (CH), 123.0 (C), 121.3 (CH), 121.2 (CH), 118.5 (CH), 110.5 (CH_2), 109.3 (CH), 58.7 (C), 52.1 (CH_3), 52.61 (CH_3), 49.7 (CH), 44.2 (CH_2), 37.9 (C), 36.6 (CH_2), 32.6 (CH_3), 26.0 (CH_3), 24.7 (CH_3).

Dimethyl 3-(2-azidopropan-2-yl)-4-methylenecyclopentane-1,1-dicarboxylate (3l).

Following the general procedure, the reaction of 1,6-enyne **1** (50 mg, 0.21 mmol) and trimethylsilyl azide (140 µL, 1.05 mmol) with InI_3 (10.4 mg, 0.02 mmol) in CH_2Cl_2 (6.6 mL) was heated at 50 ºC for 12 h. After purification by column chromatography (5-10% EtOAc/hexane) **3l** (30 mg, 60%) was obtained as a light yellow oil.

R_f = 0.34 (10% EtOAc/hexane). IR (ATR) ν_{max} = 2922, 2099, 1733 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 5.12 (s, 1H), 5.04 (s, 1H), 3.74 (s, 3H), 3.72 (s, 3H), 2.95-2.80 (m, 2H), 2.73-2.58 (m, 2H), 1.98 (dd, *J* = 11.5, 7.3 Hz, 1H), 1.33 (s, 3H), 1.28 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7 (C), 171.6 (C), 147.0 (C), 112.1 (CH_2), 63.6 (C), 58.6 (C), 52.8 (2×CH_3), 50.5 (CH), 43.3 (CH_2), 36.0 (CH_2), 24.4 (CH_3), 23.4 (CH_3). HRMS (ESI) m/z calcd for $C_{13}H_{19}N_3O_4Na$ $[M+Na]^+$ 304.1273; found 304.1268.

3-(2-Methoxypropan-2-yl)-4-methylene-1-tosylpyrrolidine (3m).[10]

Following the general procedure, the reaction of 1,6-enyne **2** (50 mg, 0.18 mmol) and methanol (36 µL, 0.90 mmol) with InI_3 (4.5 mg, 0.009 mmol) in CH_2Cl_2 (5 mL) was heated at 40 °C for 24 h. After purification by column chromatography (7-10% EtOAc/hexane) **3m** (42.1 mg, 76%) was obtained as a colorless oil.

R_f = 0.24 (20% EtOAc/hexane). ^1H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 7.9 Hz, 2H), 5.02 (br q, *J* = 4, 2 Hz, 2H), 3.78-3.76 (m, 2H), 3.39 (dd, *J* = 10.1, 4.5 Hz, 1H), 3.27 (dd, *J* = 10.1, 8.0 Hz, 1H), 3.08 (s, 3H), 2.81-2.76 (m, 1H), 2.41 (s, 3H), 1.11 (s, 3H), 0.99 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.8 (C), 143.7 (C), 132.9 (C), 129.8 (2×CH), 128.0 (2×CH), 110.7 (CH_2), 76.3 (C), 53.5 (CH_2), 51.0 (CH_3), 49.8 (CH_2), 49.2 (CH_3), 22.4 (CH_3), 21.9 (CH_3), 21.7 (CH).

3-(2-(Benzyloxy)propan-2-yl)-4- methylene-1-tosylpyrrolidine (3n).

Following the general procedure, the reaction of 1,6-enyne **2** (50 mg, 0.180 mmol) and benzyl alcohol (93 μL, 0.901 mmol) with InI_3 (4.5 mg, 0.009 mmol) in CH_2Cl_2 (5 mL) was heated at 40 °C for 20 h. After purification by column chromatography (5-7% EtOAc/hexane) **3n** (30.2 mg, 69%) was obtained as a yellow oil.

R_f = 0.31 (20% EtOAc/hexane). IR (ATR) ν_{max} = 3063, 2974, 2863, 1650, 1365, 1150 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ ^1H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, *J* = 6.4 Hz, 2H), 7.24-7.17 (m, 7H), 5.01 (d, *J* = 12.5 Hz, 2H), 4.30 (q, *J* = 14.0 Hz, 2H), 3.73 (br s, 2H), 3.45 (dd, *J* =10.1, 4.4 Hz, 1H), 3.26 (dd, *J* = 10.1, 8.0 Hz, 1H), 2.34 (br s, 1H), 2.34 (s, 3H), 1.17 (s, 3H), 1.06 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.5 (C), 143.6 (C), 139.2 (C), 132.7 (C), 129.7 (2×CH), 128.3 (2×CH), 127.9 (2×CH), 127.3 (CH), 127.2 (2×CH), 111.0 (CH_2), 76.8 (C), 63.7 (CH_2), 53.4 (CH_2), 51.7 (CH), 49.8 (CH_2), 22.9 (CH_3), 22.3 (CH_3), 21.6 (CH_3). HRMS (ESI) m/z calcd for $C_{22}H_{27}NO_5SNa$ $[M+Na]^+$ 408.1609; found 408.1621.

2-(4-Methylene-1-tosylpyrrolidin-3-yl)propan-2-yl benzoate (3o).

Following the general procedure, the reaction of 1,6-enyne **2** (100 mg, 0.36 mmol) and benzoic acid (220 mg, 1.80 mmol) with InI_3 (8.9 mg, 0.018 mmol) in CH_2Cl_2 (10 mL) was heated at 40 °C for 20 h. After purification by column chromatography (5-8% EtOAc/hexane) **3o** (61.5 mg, 43%) was obtained as a colourless oil.

R_f = 0.31 (20% EtOAc/hexane). IR (ATR) ν_{max} = 2922, 2863, 1821, 1717 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.0 Hz, 2H), 7.70 (d, *J* = 8.3 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.32 (d, *J* = 7.9 Hz, 2H), 5.09-5.06 (m, 2H), 3.94 (d, *J* = 13.8 Hz, 1H), 3.76 (d, *J* = 13.8 Hz, 1H), 3.57-3.49 (m, 2H), 3.29 (dd, *J* = 9.6, 7.5 Hz, 1H), 2.42 (s, 3H), 1.61 (s, 3H), 1.53 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6 (C), 143.8 (C), 143.7 (C), 132.8 (CH), 132.5 (C), 131.3 (C), 129.7 (2×CH), 129.4 (2×CH), 128.4 (2×CH), 127.8 (2×CH), 111.7 (CH_2), 84.0 (C), 53.1 (CH_2), 50.7 (CH_3), 49.8 (CH_2), 23.9 (CH), 23.6 (CH_3), 21.6 (CH_3). HRMS (ESI) m/z calcd for $C_{22}H_{25}NO_4SNa$ $[M+Na]^+$ 422.1402; found 422.1411.

3-Methylene-1-tosyl-4-(2-(2,4,6-trimethoxyphenyl)propan-2-yl)pyrrolidine (3p).

Following the general procedure, the reaction of 1,6-enyne **2** (75 mg, 0.27 mmol) and 1,3,5-timethoxybenzene (227 mg, 1.35 mmol) with InI_3 (6.7 mg, 0.014 mmol) in CH_2Cl_2 (8 mL) was heated at 40 °C for 20 h. After purification by column chromatography (7-10% EtOAc/hexane) **3p** (71.2 mg, 59%) was obtained as a colorless oil.

R_f =0.19 (20% EtOAc/hexane). IR (ATR) ν_{max} = 3060, 2975, 2865, 1656, 1370 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 7.7 Hz, 2H), 6.11 (s, 2H), 4.92 (d, *J* = 2.0 Hz, 1H), 4.72 (d, *J* = 2.0 Hz, 1H), 3.79 (s, 3H), 3.72-3.70 (m, 3H), 3.70 (s, 6H), 3.15 (d, *J* = 7.0 Hz, 2H), 2.42 (s, 3H), 1.41 (s, 3H), 1.28 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.5 (2×C), 159.1 (C), 146.4 (C), 143.2 (C), 133.0 (C), 129.5 (2×CH), 127.9 (2×CH), 116.1 (C), 109.4 (CH_2), 92.7 (2×CH), 55.8 (2×CH_3), 55.1 (CH_3), 54.4 (CH_2), 51.5 (CH_2), 49.3 (CH_3), 42.5 (C), 27.3 (CH), 26.3 (CH_3), 21.5 (CH_3). HRMS (ESI) m/z calcd for $C_{24}H_{31}NO_5SNa$ $[M+Na]^+$ 468.1821; found 468.1815.

1-Methyl-3-(2-(4-methylene-1-tosylpyrrolidin-3-yl)propan-2-yl)-1*H*-indole (3q).

Following the general procedure, the reaction of 1,6-enyne **2** (50 mg, 0.180 mmol) and *N*-methyl indol (113 μL, 0.901 mmol) with InI_3 (4.5 mg, 0.009 mmol) in CH_2Cl_2 (5 mL) was heated at 40 °C for 20 h. After purification by column chromatography (5-7% EtOAc/hexane) **3q** (41.8 mg, 57%) was obtained as a yellow oil.

R_f = 0.31 (20% EtOAc/hexane). IR (ATR) ν_{max} = 3050, 2970, 2862, 1650 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.63-7.59 (m, 2H), 7.29-7.22 (m, 5H), 7.08-7.03 (m, 1H), 6.80 (s, 1H), 4.98 (br s, 1H), 4.78 (br s, 1H), 3.96-3.89 (m, 1H), 3.71 (s, 3H), 3.70-3.67 (m, 1H), 3.39-3.36 (m, 1H), 3.26 (dd, *J* = 10.1, 3.2 Hz, 1H), 2.95 (dd, *J* = 10.2, 7.9 Hz, 1H), 2.42 (s, 3H), 1.31 (s, 3H), 1.26 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.3 (C), 143.5 (C), 137.9 (C), 132.7 (C), 129.6 (2×CH), 127.8 (2×CH), 126.4 (CH), 125.6 (C), 122.1 (C), 121.3 (CH), 120.9 (CH), 118.5 (CH), 110.6 (CH_2), 109.6 (CH), 53.7 (CH_2), 51.10 (CH_3), 51.05 (CH_2), 38.1 (C), 32.7 (CH), 26.4 (CH_3), 24.2 (CH_3), 21.6 (CH_3). HRMS (ESI) m/z calcd for $C_{24}H_{28}N_2O_2SNa$ $[M+Na]^+$ 431.1769; found 431.1771.

Dimethyl (*R)-3-((*S**)-benzyloxy)(phenyl)methyl)-4-methylenecyclopentane-1,1-dicarboxylate (5a).**

Following the general procedure, the reaction of 1,6-enyne (*E*)-**4** (83 mg, 0.29 mmol) and benzyl alcohol (0.150 mL, 1.453 mmol) with InI_3 (7.2 mg, 0.017 mmol) in CH_2Cl_2 (9 mL) was heated at 40°C for 20 h. After purification by column chromatography (10% EtOAc/hexane) **5a** (82 mg, 75%) was obtained as a colourless oil. Following the general procedure, the reaction of 1,6-enyne (*Z*)-**4** (50 mg, 0.175 mmol) and benzyl alcohol (0.091 mL, 0.875 mmol) with InI_3 (4.4 mg, 0.0088 mmol) in DCE (5 mL) was heated at 60°C for 20 h. After purification by column chromatography (10% EtOAc/hexane) **5a** (43 mg, 63%) was obtained as a colourless oil.

R_f = 0.10 (10% EtOAc/hexane). IR (ATR) ν_{max} = 2951, 1730, 1494, 1452 cm^{-1}. ^1H-NMR (300 MHz, $CDCl_3$): δ 7.31-7.17 (m, 10H), 4.83 (br s, 1H), 4.38 (d, *J* = 11.8 Hz, 1H), 4.36 (s, 1H), 4.31 (d, *J* = 5.9 Hz, 1H), 4.17 (d, *J* = 11.8 Hz, 1H), 3.63 (s, 3H), 3.60 (s, 3H), 2.94-2.69 (m, 3H), 2.46-2-29 (m, 2H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 172.2 (C), 172.1(C), 148.23 (C), 140.70 (C), 138.43 (C), 128.3 (2×CH), 128.2 (2×CH), 127.73 (CH), 127.70 (2×CH), 127.47 (CH), 127.44 (2×CH), 108.8 (CH_2), 83.35 (CH), 70.8 (CH_2), 58.7 (C), 52.75 (CH_3), 52.73 (CH_3), 49.4 (CH), 42.2 (CH_2), 35.52 (CH_2). HRMS (ESI) m/z calcd for $C_{24}H_{26}O_5Na$ $[M+Na]^+$ 417.1677; found 417.1665.

Dimethyl (*R)-3-((*S**)-benzoyloxy)(phenyl)methyl)-4-methylenecyclopentane-1,1-dicarboxylate (5b).**

Following the general procedure, the reaction of 1,6-enyne (*E*)-**4** (76 mg, 0.26 mmol) and benzoic acid (161 mg, 1.32 mmol) with InI_3 (6.5 mg, 0.013 mmol) in CH_2Cl_2 (12 mL) was heated at 40 °C for 20 h. After purification by column chromatography (10% EtOAc/hexane) **5b** (67 mg, 62%) was obtained as a colourless oil**.**

Following the general procedure, the reaction of 1,6-enyne (*Z*)-**4** (75 mg, 0.26 mmol) and benzoic acid (160 mg, 1.31 mmol) with InI_3 (12.9 mg, 0.026 mmol, 10 mol%) in CH_2Cl_2 (5 mL) was heated at 40 °C for 20 h. After purification by column chromatography (10% EtOAc/hexane) **5b** (30 mg, 25%) was obtained as a colourless oil**.**

R_f = 0.10 (10% EtOAc/hexane). IR (ATR) ν_{max} = 2952, 1721, 1432 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.12 (d, *J* = 8.5 Hz, 2H), 7.61-7.17 (m, 8H), 6.17 (d, *J* = 5.7 Hz, 1H), 5.03 (br s, 1H), 4.75 (br s, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 3.39-2.39 (m, 1H), 3.00 (s, 2H), 2.59 (dd, *J* = 7.6 Hz, 1H), 2.38 (dd, *J* = 9.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.9 (C), 171.8 (C), 165.5 (C), 146.8 (C), 139.2 (C), 133.1 (CH), 130.1 (CH), 129.72 (2×CH), 129.67 (CH), 128.51 (2×CH), 128.47 (2xCH), 128.0 (CH), 126.6 (2×CH), 109.8 (CH_2), 77.2 (CH), 58.5 (CH_3), 52.9 (CH_2), 47.8 (CH), 42.0 (CH_3), 35.6 (CH_2). HRMS (ESI) m/z calcd for $C_{24}H_{24}O_6Na$ $[M+Na]^+$ 431.1470; found 431.1460.

Dimethyl (*S)-3-((*S**)-1-methyl-1*H*-indol-3-yl)(phenyl)methyl)-4-methylenecyclopentane-1,1-dicarboxylate (5c).[11]**

Following the general procedure, the reaction of 1,6-enyne (*E*)-**4** (50 mg, 0.175 mmol) and *N*-methylindole (0.110 mL, 0.875 mmol) with InI_3 (4.3 mg, 0.009 mmol) in CH_2Cl_2 (5 mL) was heated at 40 °C for 20 h. After purification by column chromatography (10% EtOAc/hexane) **5c** (64 mg, 88%) was obtained as a colorless oil. Following the general procedure, the reaction of 1,6-enyne (*Z*)-**4** (50 mg, 0.175 mmol) and *N*-methylindole (0.110 mL, 0.875 mmol) with InI_3 (4.3 mg, 0.009 mmol) in DCE (5 mL) was heated at 60 °C for 18 h. After purification by column chromatography (10% EtOAc/hexane) **5c** (45.6 mg, 62%) was obtained as a colourless oil**.**

R_f = 0.10 (10% EtOAc/hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53 (d, *J* = 8.2 Hz, 1H), 7.32 (d, *J* = 7.5 Hz, 2H), 7.26-7.03 (m, 6H), 7.00 (s, 1H), 4.77 (s, 1H), 4.17-4.06 (m, 2H), 3.75 (s, 3H), 3.72 (s, 3H), 3.63 (s, 3H), 3.54-3.48 (m, 1H), 3.11 (d, *J* = 16.2 Hz, 1H), 2.89-2.84 (m, 1H), 2.74 (dd, *J* = 13.6, 8.1 Hz, 1H), 1.93 (dd, *J* = 13.7, 8.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.3 (C), 172.1 (C), 148.9 (C), 144.6 (C), 136.9 (C), 128.5 (2×CH), 128.1 (2×CH), 127.6 (CH), 126.2 (CH), 126.0 (CH), 121.6 (CH), 119.4 (CH), 118.9 (CH), 117.2 (CH), 110.1 (CH_2), 109.1 (CH), 58.4 (C), 52.8 (CH_3), 52.7 (CH_3), 48.1 (CH), 46.8 (CH), 41.8 (CH_2), 40.0 (CH_2), 32.8 (CH_3).

Dimethyl (*S)-3-methylene-4-((*S**)-phenyl(2,4,6-trimethoxyphenyl)methyl)cyclopentane-1,1-dicarboxylate (5d).[11]**

Following the general procedure, the reaction of 1,6-enyne (*E*)-**4** (50 mg, 0.178 mmol) and 1,3,5-timethoxybenzene (147.2 mg, 0.875 mmol) with InI_3 (4.4 mg, 0.009 mmol) in CH_2Cl_2 (5 mL) was heated at 40 °C for 20 h. After purification by column chromatography (10% EtOAc/hexane) **5d** (62 mg, 78%) was obtained as a colorless oil.

Following the general procedure, the reaction of 1,6-enyne (*Z*)-**4** (50 mg, 0.175 mmol) and 1,3,5-timethoxybenzene (147.2 mg, 0.875 mmol) with InI_3 (4.4 mg, 0.009 mmol) in DCE (5 mL) was heated at 60 °C for 16 h. After purification by column chromatography (10% EtOAc/hexane) **5d** (60 mg, 75%) was obtained as a colourless oil**.**

R_f = 0.10 (10% EtOAc/hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45 (d, *J* = 7.6 Hz, 2H), 7.18 (t, *J* = 7.2 Hz, 2H), 7.09 (t, *J* = 7.3 Hz, 1H), 6.07 (s, 2H), 4.72 (br s, 1H), 4.48 (d, *J* = 11.0 Hz,1H), 4.24 (br s, 1H), 3.81-4.03 (m, 1H), 3.81 (s, 6H) 3.76 (s, 3H), 3.74 (s, 3H), 3.66 (s, 3H), 3.03 (d, *J* = 17.4 Hz, 2H) 2.35 (dd, *J* = 7.0, 1.2 Hz, 1H), 1.64 (dd, *J* = 12.3, 10.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.5 (C), 172.4 (C), 159.5 (2xC), 158.7 (C), 151.4 (C), 144.6 (C), 128.2 (2×CH), 127.7 (2×CH), 125.5 (CH), 113.6 (2×CH), 108.1 (CH_2), 90.9 (CH), 57.7 (CH_3), 55.6 (CH_3), 55.2 (CH_3), 53.5 (C), 52.7 (CH_3), 52.6 (CH_3), 44.2 (CH), 43.0 (CH), 41.7 (CH_2), 40.0 (CH_2).

Dimethyl (*R)-3-((*S**)-azido(phenyl)methyl)-4-methylenecyclopentane-1,1-dicarboxylate (5e).**

Following the general procedure, the reaction of 1,6-enyne (*E*)-**4** (50 mg, 0.175 mmol) and trimethylsilyl azide (0.17 mL, 0.88 mmol) with InI_3 (8.7 mg, 0.018 mmol) in CH_2Cl_2 (5 mL) was heated at 50 °C for 40 h. After purification by column chromatography (5% EtOAc/hexane) **5e** (46 mg, 80%) was obtained as a colourless oil. Following the general procedure, the reaction of 1,6-enyne (*Z*)-**4** (50 mg, 0.175 mmol) and trimethylsilyl azide (0.17 mL, 0.88 mmol) with InI_3 (8.7 mg, 0.018 mmol) in DCE (5 mL) was heated at 50°C for 40 h. After

purification by column chromatography (10% EtOAc/hexane) **5e** (39 mg, 67%) was obtained as a colourless oil.

R_f = 0.48 (20% EtOAc/hexane). IR (ATR) ν_{max} = 2991, 2098, 1731, 1452, 1434 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.30 (m, 5H), 5.04 (q, *J* = 2.2 Hz, 1H), 4.68-4.66 (m, 2H), 3.74 (s, 3H), 3.69 (s, 3H), 3.05-2.96 (m, 3H), 2.44 (dd, *J* = 13.4, 7.8 Hz, 1H), 2.22 (dd, *J* = 13.4, 9.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8 (C), 171.7 (C), 147.7 (C), 138.5 (C), 128.7 (2×CH), 128.2 (CH), 127.1 (2×CH), 109.7 (CH_2), 68.9 (CH), 58.4 (C), 52.8 (2×CH_3), 48.0 (CH), 41.9 (CH_2), 35.6 (CH_2). HRMS (ESI) m/z calcd for $C_{17}H_{19}N_3O_4Na$ $[M+Na]^+$ 352.1273; found 352.1269.

Dimethyl (*Z*)-3-(2-methoxypropan-2-yl)-4-(methylene-d)cyclopentane-1,1-dicarboxylate ((*Z*)-3a-d_1).

Following the general procedure, the reaction of 1,6-enyne **1**-*d_1* (50 mg, 0.20 mmol), prepared from enyne **2** by metalation with *n*-BuLi in THF at –78 ºC followed by addition of D_2O in 77% yield with 91% D incorporation, and MeOH (40 µL, 1.00 mmol) with InI_3 (5.0 mg, 0.01 mmol) in CH_2Cl_2 (6 mL) was stirred at rt for 20 h. After purification by column chromatography (3-10% EtOAc/hexane) (*Z*)-**3a-d_1** (35 mg, 65%, 91% D) was obtained as a colourless oil. R_f = 0.26 (10% EtOAc/hexane). ^1H NMR (300 MHz, $CDCl_3$) δ 5.03 (br s, 1H), 3.72 (s, 3H), 3.71 (s, 3H), 3.18 (s, 3H), 2.95-2.78 (m, 3H), 2.55 (ddd, *J* = 13.5, 8.3, 1.7 Hz, 1H), 2.00 (dd, *J* = 13.7, 9.3 Hz, 1H), 1.17 (s, 3H), 1.11 (s, 3H). The ^1H NMR spectra of (*Z*)-**3a-d_1** showed deuteration (91% D) at the exocyclic alkenyl *Z*-hydrogen (4.97 ppm). R_f = 0.26 (10% EtOAc/hexane). IR (ATR) ν_{max} = 2953, 1731 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.03 (br s, 1H), 3.73 (s, 3H), 3.71 (s, 3H), 3.18 (s, 3H), 2.88-2.80 (m, 3H), 2.54 (ddd, *J* = 13.5, 10.0, 1.7 Hz, 1H), 2.0 (dd, *J* = 13.5, 6.7 Hz, 1H), 1.17 (s, 3H), 1.11 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1 (C), 172.0 (C), 148.1 (C), 110.3 (CH_2), 76.7 (C), 58.6 (C), 52.8 (2×CH_3), 49.1 (CH), 49.0 (CH_3), 43.4 (CH_2), 36.0 (CH_2), 22.6 (CH_3), 22.2 (CH_3). HRMS (ESI) m/z calcd for $C_{14}H_{21}DO_5Na$ $[M+Na]^+$ 294.1428; found 294.1423.

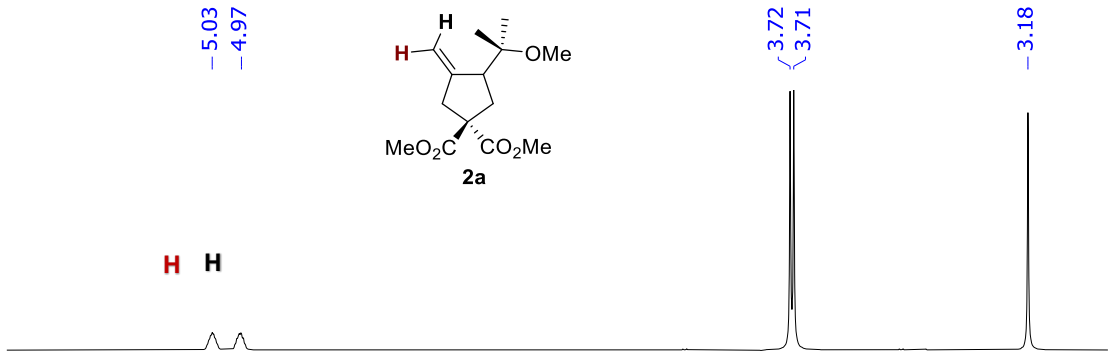
Dimethyl (*E*)-3-(2-(methoxy-d_3)propan-2-yl)-4-methylenecyclopentane-1,1-dicarboxylate ((*E*)-3a-d_4).[12]

Following the general procedure, the reaction of 1,6-enyne **1** (50 mg, 0.21 mmol) and MeOH-d_4 (43 µL, 1.05 mmol) with InI_3 (5.2 mg, 0.01 mmol) in CH_2Cl_2 (6 mL) was stirred at rt for 20 h. After purification by column chromatography (3-5% EtOAc/hexane) (*E*)-**3a-d_4** (42.7 mg, 74%, 75% D) was obtained as a colourless oil. R_f = 0.26 (10% EtOAc/hexane). ^1H NMR (300 MHz, $CDCl_3$) δ 4.97 (br s, 1H), 3.72 (s, 3H), 3.71 (s, 3H), 2.95-2.78 (m, 3H), 2.55 (ddd, *J* = 13.5, 8.3, 1.7 Hz, 1H), 2.00 (dd, *J* = 13.7, 9.3 Hz, 1H), 1.17 (s, 3H), 1.11 (s, 3H). The ^1H NMR spectra of (*E*)-**3a-d_4** showed deuteration (75% D) at the exocyclic alkenyl *E*-hydrogen (5.03 ppm) and the signal at 3.18 (3H) was absent in the spectrum.

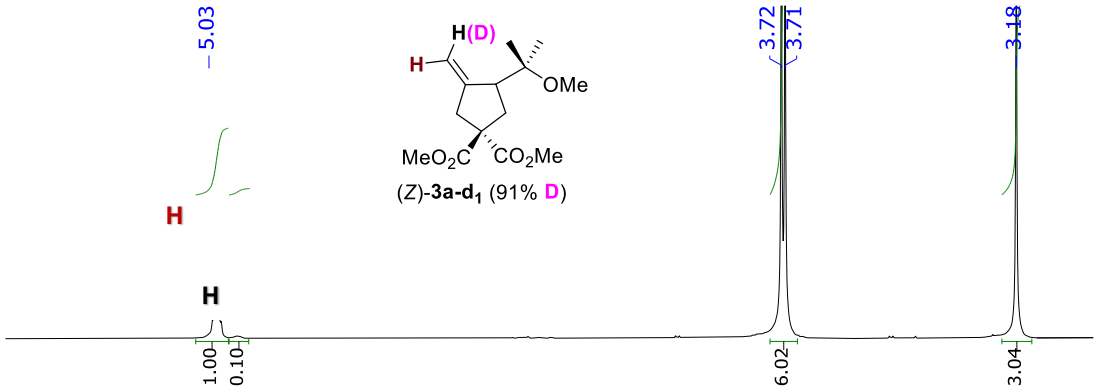
^1H NMR (300 MHz, $CDCl_3$): δ 4.97 (br s, 1H), 3.72 (s, 3H), 3.71 (s, 3H), 2.88-2.80 (m, 3H), 2.54 (ddd, *J* = 13.5, 8.5, 1.8 Hz, 1H), 2.0 (dd, *J* = 13.5, 4.1 Hz, 1H), 1.17 (s, 3H), 1.11 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1 (C), 172.0 (C), 148.1 (C), 110.6 (CH_2), 76.7 (C), 58.6 (C), 52.7 (2×CH_3), 49.1 (CH), 43.3 (CH_2), 36.0 (CH_2), 22.6 (CH_3), 22.2 (CH_3).

5. ^{1}H NMR data of deuterated experiments

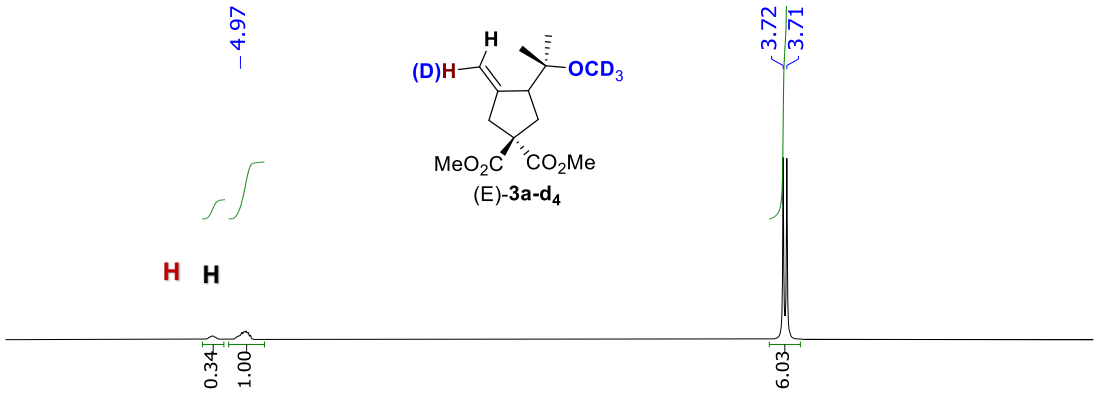
Reaction of 1,6-enyne **1** using MeOH as nucleophile.



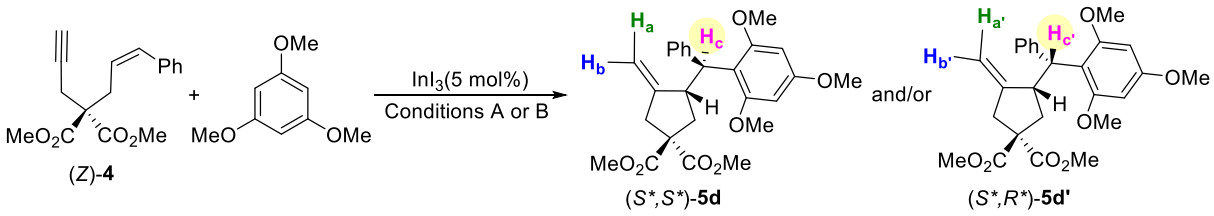
Reaction of 1,6-enyne **1-d$_1$** (91% **D**) using MeOH as nucleophile to afford (*Z*)-**3a-d$_1$** (91% **D**). The ^{1}H NMR spectra of (*Z*)-**3a-d$_1$** showed deuteration (91% D) at the exocyclic alkenyl *Z*-hydrogen (4.97 ppm).



Reaction of 1,6-enyne **1** using CD_3OD as nucleophile to afford (*E*)-**3a-d$_4$** (75% **D**). The ^{1}H NMR spectra of (*E*)-**3a-d$_4$** showed deuteration (75% **D**) at the exocyclic alkenyl *E*-hydrogen (5.03 ppm) and the signal at 3.18 (3H) was absent in the spectrum.

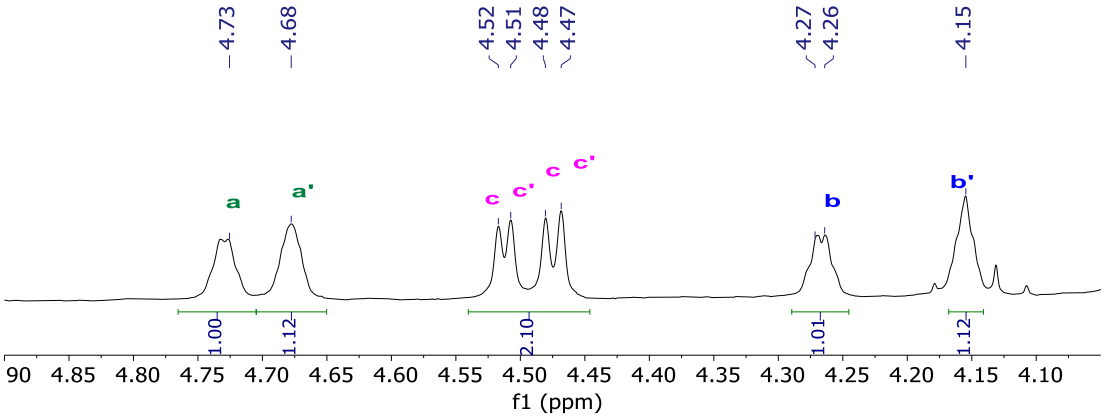


6. ^{1}H NMR spectra of the reaction of 1,6-enyne (*Z*)-4 with InI_3 (5 mol%) and 1,2,3-trimethoxibenzene at different temperatures



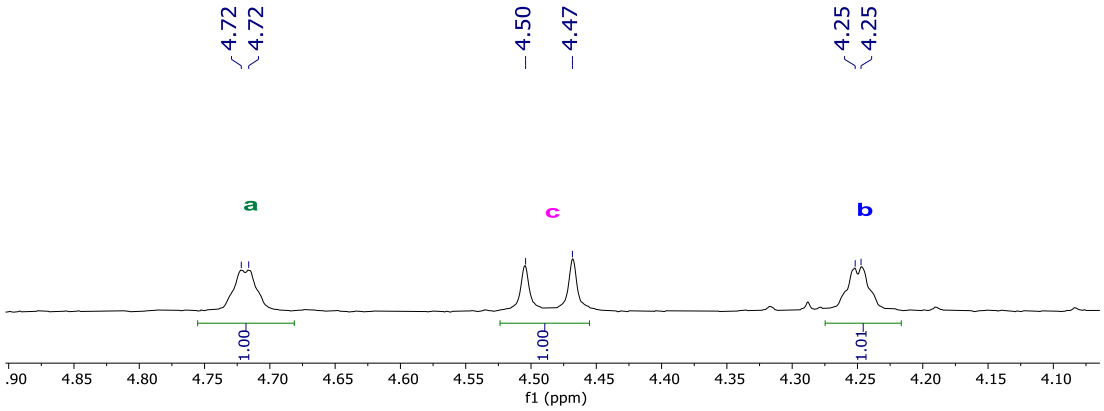
Conditions A: DCE (0.035 M), –20 ºC to 40 ºC, 22 h.

Broadening of the spectrum in the region of 4.1 to 4.8 ppm for (*S**,*S**)-**5d**/(*S**,*R**)-**5d'** with 1:1.12 ratio



Conditions B: DCE (0.035 M), –20 ºC to 60 ºC, 16 h.

Broadening of the spectrum in the region of 4.1 to 4.8 ppm for (*S**,*S**)-**5d**/(*S**,*R**)-**5d'** with 1:0 ratio



7. References

1 F. Schröder, C. Tugnym, E. Salanouve, H. Clavier, L. Giordano, D. Moraleda, Y. Gimbert, V. Mouriès-Mansuy, J.-P. Goddard, L. Fensterbank, Secondary Phosphine Oxide–Gold(I) Complexes and Their First Application in Catalysis, *Organometallics,* 2014, **33**, 4051−4056.

2 E. Nyfeler, P. Renaud, Decarboxylative Radical Azidation Using MPDOC and MMDOC Esters, *Org. Lett.,* 2008, **10**, 985–988.

3 T. Kataoka, H. Yoshimatsu, Y. Noda, T. Sato, H. Shimizu, M. Hori, Versatile Cyclisation Reactions Using Selenoboranes, *J. Chem. Soc. Perkin Trans. 1.,* 1987, 121−129.

4 L, Charruault, V. Michelet, R. Taras, S. Gladiali, J.-P. Genêt, Functionalized Carbo- and Heterocycles *via* Pt-Catalyzed Asymmetric Alkoxycyclization of 1,6-Enynes, *Chem. Commun*., 2004, 850–851.

5 J. W. Faller, Ruthenium Catalyzed Enyne Cycloisomerizations and Hydroxycyclizations with Skeletal Rearrangement, *J. Organomet. Chem*., 2006, **691**, 1912−1918.

6 M. Méndez, M. Paz Muñoz, A. M. Echavarren, Platinum-Catalyzed Alkoxy- and Hydroxycyclization of Enynes, *J. Am. Chem. Soc*., 2000, **122**, 11549−11550.

7 C. Nieto-Oberhuber, M. P. Muñoz, S. Lopez, E. Jiménez-Nuñez, C. Nevado, E. Herrero-Gómez, M. Raducan, A. M. Echavarren, Gold(I)-Catalyzed Cyclizations of 1,6-Enynes: Alkoxycyclizations and *exo*/*endo* Skeletal Rearrangements, *Chem. Eur. J.,* 2006, **12**, 1677−1693.

8 C. Tugny, N. Rio, M. Koohgard, N. Vanthuyne, D. Lesage, K. Bijouard, P. Zhang, J. Meijide Suárez, S. Roland, E. Derat, O. Bistri-Aslanoff, M. Sollogoub, L. Fensterbank, V. Mouriès-Mansuy, β-Cyclodextrin–NHC–Gold(I) Complex (β-ICyD)AuCl: A Chiral Nanoreactor for Enantioselective and Substrate-Selective Alkoxycyclization Reactions., *Adv. Synth. Catal.,* 2020, **10**, 5964−5972.

9 C. H. M. Amijs, C. Ferrer, A. M. Echavarren, Gold(I)-Catalysed Arylation of 1,6-Enynes: Different Site Reactivity of Cyclopropyl Gold Carbenes, *Chem. Commun*., 2007, 698−700.

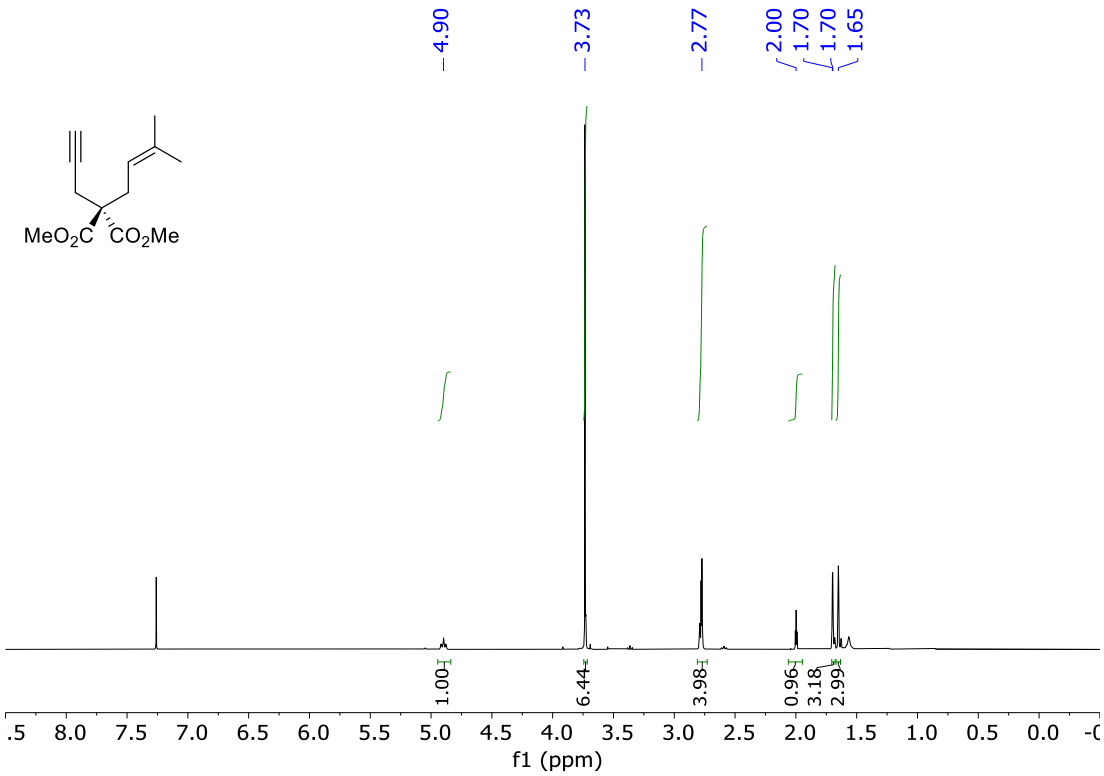
10 C. Nevado, L. Charruault, V. Michelet, C. Nieto-Oberhuber, M. P. Muñoz, M. Méndez, M.-N. Rager, J.-P. Genêt, A. M. Echavarren, On the Mechanism of Carbohydroxypalladation of Enynes. Additional Insights on the Cyclization of Enynes with Electrophilic Metal Complexes, *Eur. J. Org. Chem.,* 2003, 706−713.

11 P. Y. Toullec, E. Genin, L. Leseurre, J.-P. Genêt, V. Michelet, Room-Temperature Au^{I}-Catalyzed C–C Bond Formation through a Tandem Friedel–Crafts-Type Addition/Carbocyclization Reaction, *Angew. Chem., Int. Ed*., 2006, **45**, 7427−7430.

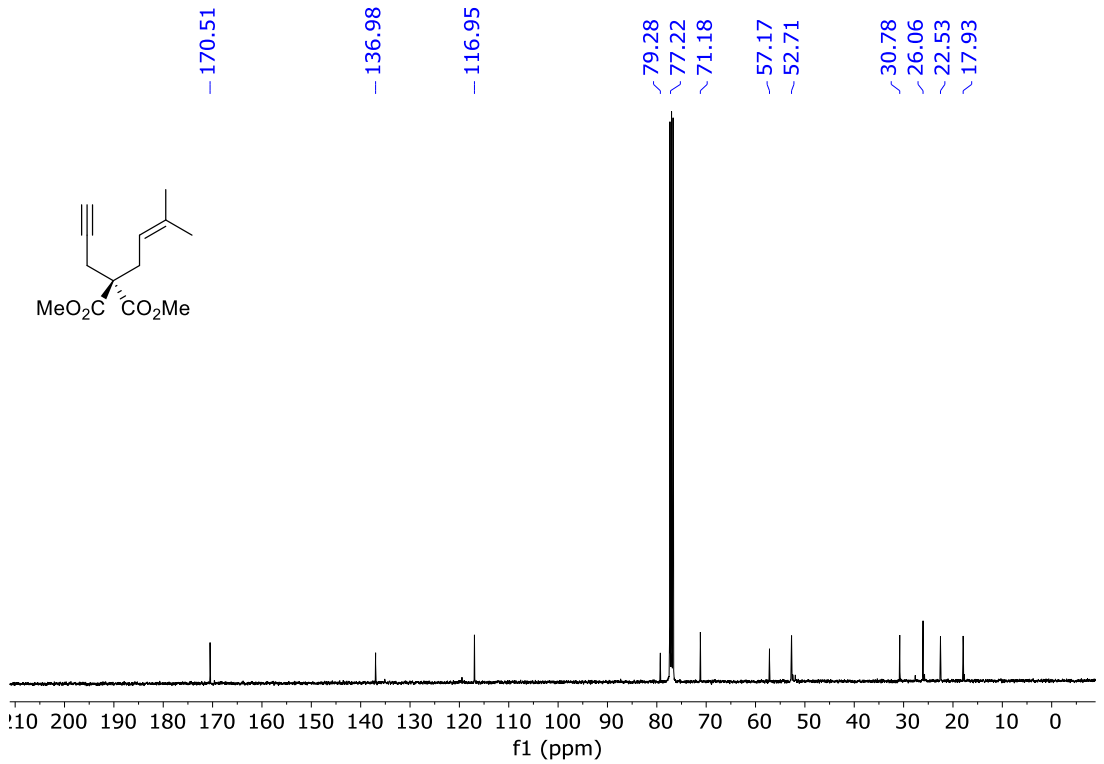
12 M. Méndez, M. P. Muñoz, C. Nevado, D. C. Cárdenas, A. M. Echavarren, Cyclizations of Enynes Catalyzed by $PtCl_2$ or Other Transition Metal Chlorides: Divergent Reaction Pathways, *J. Am. Chem. Soc*., 2001, **123**, 10511−10520.

8. ^{1}H NMR and ^{13}C NMR spectra for products

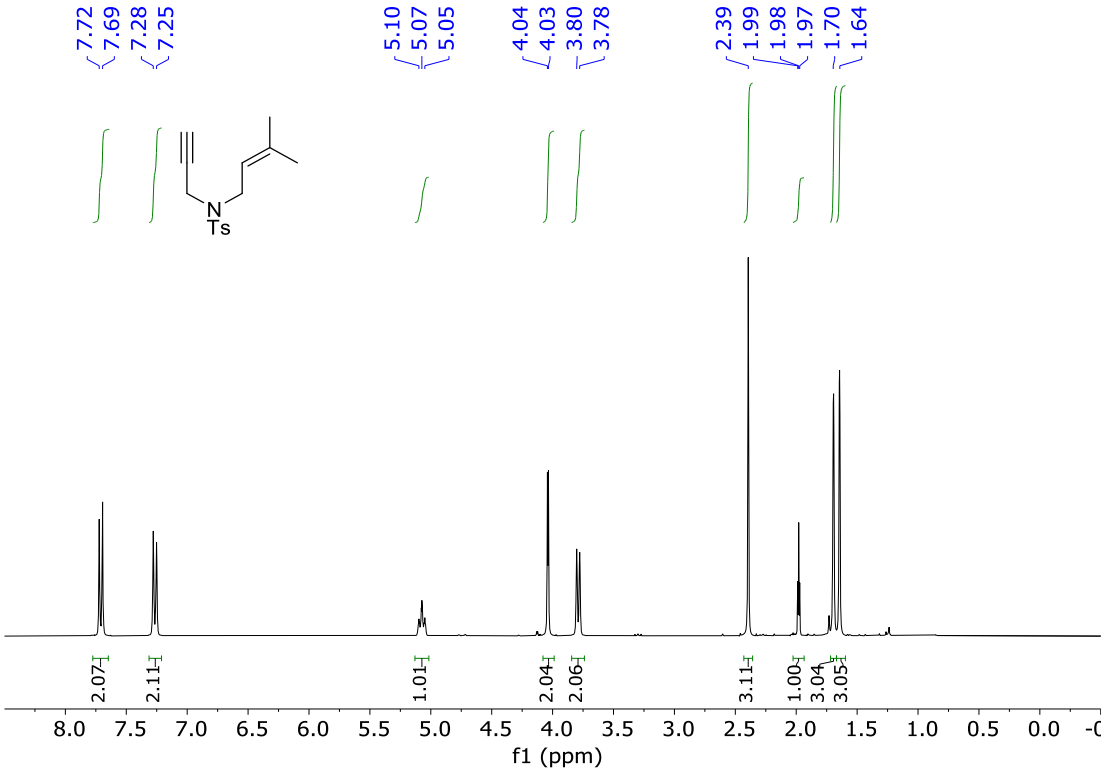
^{1}H NMR (400 MHz, $CDCl_3$, 300 K) spectrum of **1**



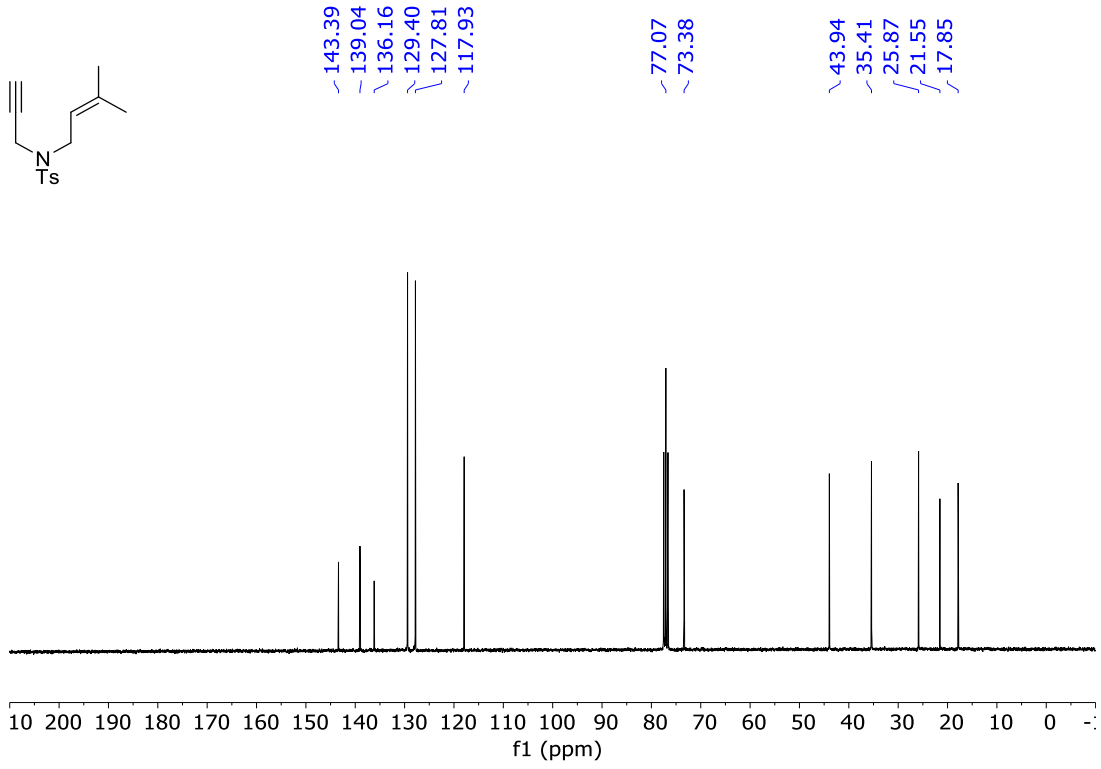
^{13}C NMR (100 MHz, $CDCl_3$, 300 K) spectrum of **1**



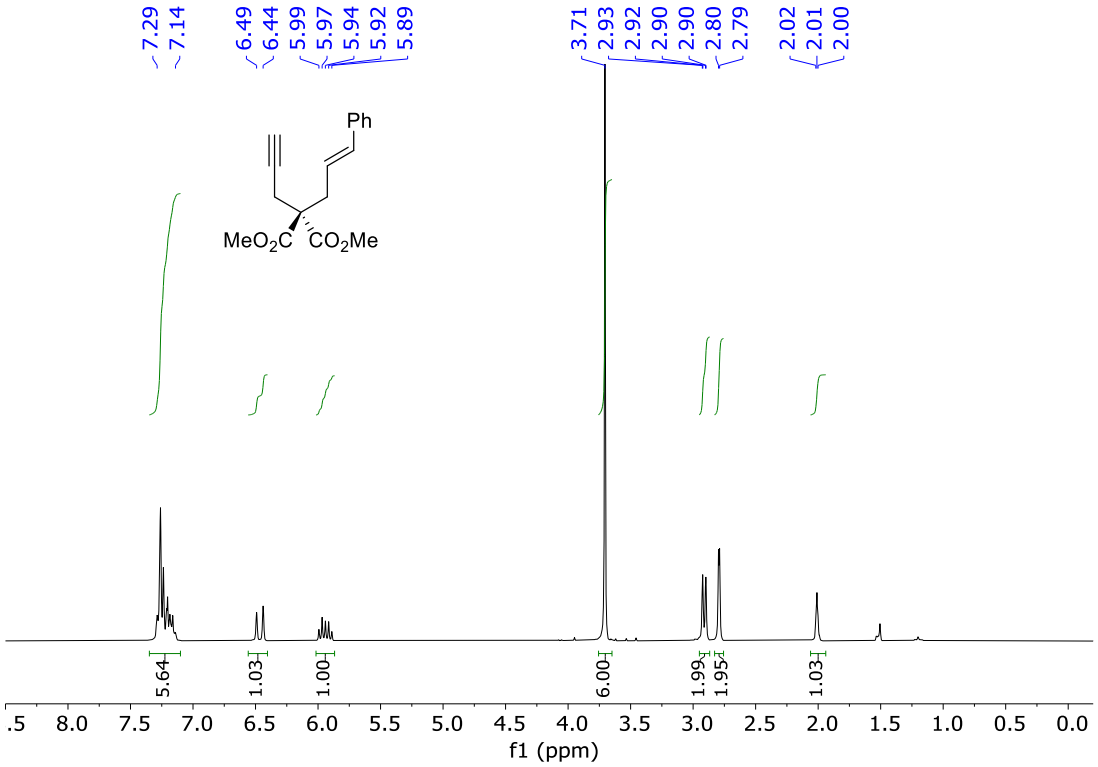
^{1}H NMR (300 MHz, $CDCl_3$, 300 K) spectrum of **2**



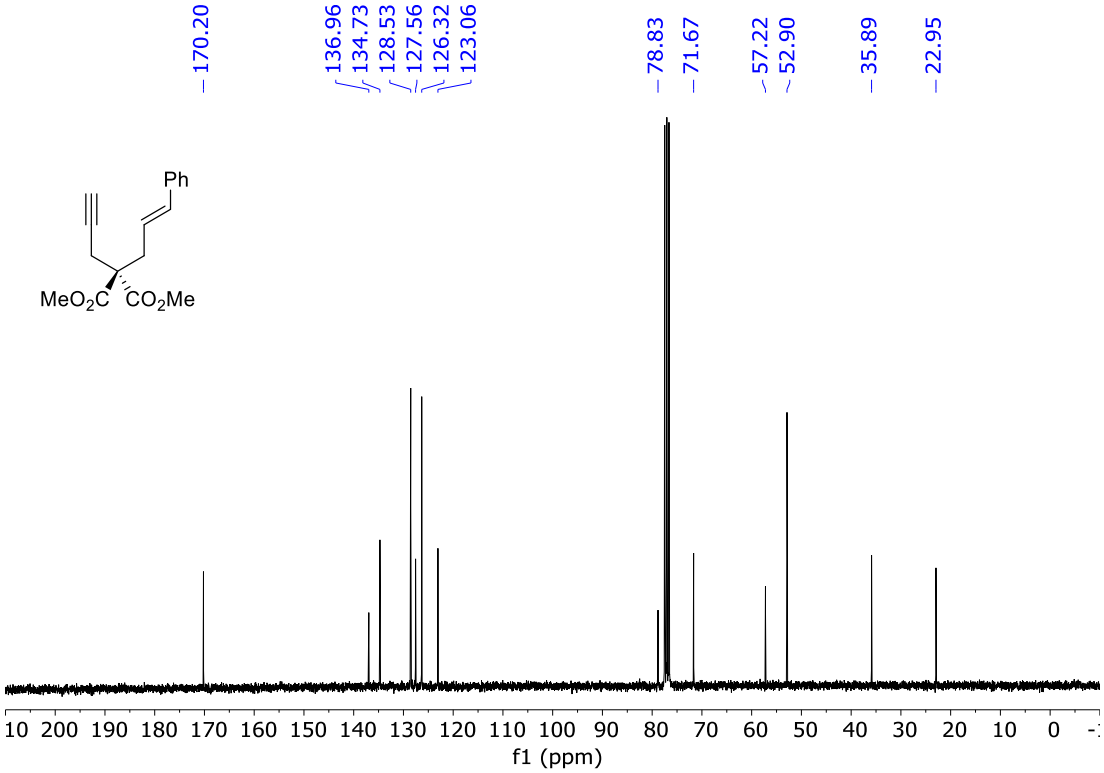
^{13}C NMR (75 MHz, $CDCl_3$, 300 K) spectrum of **2**



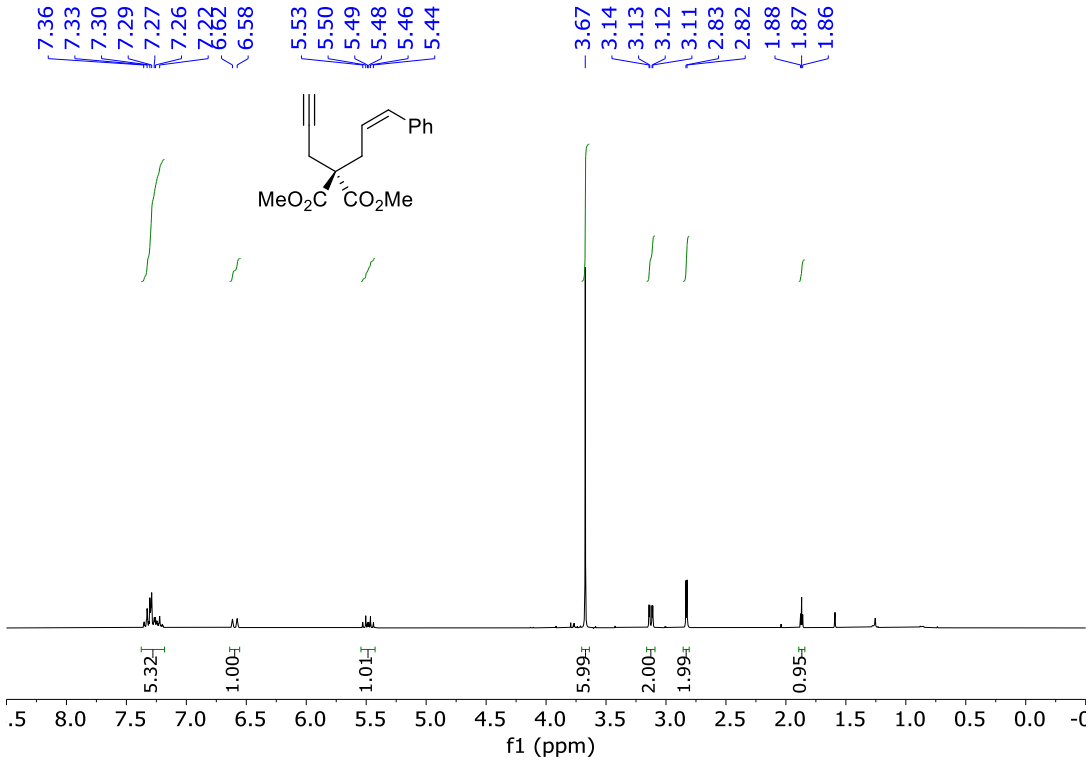
^{1}H NMR (300 MHz, $CDCl_3$, 300 K) spectrum of (*E*)-**4**



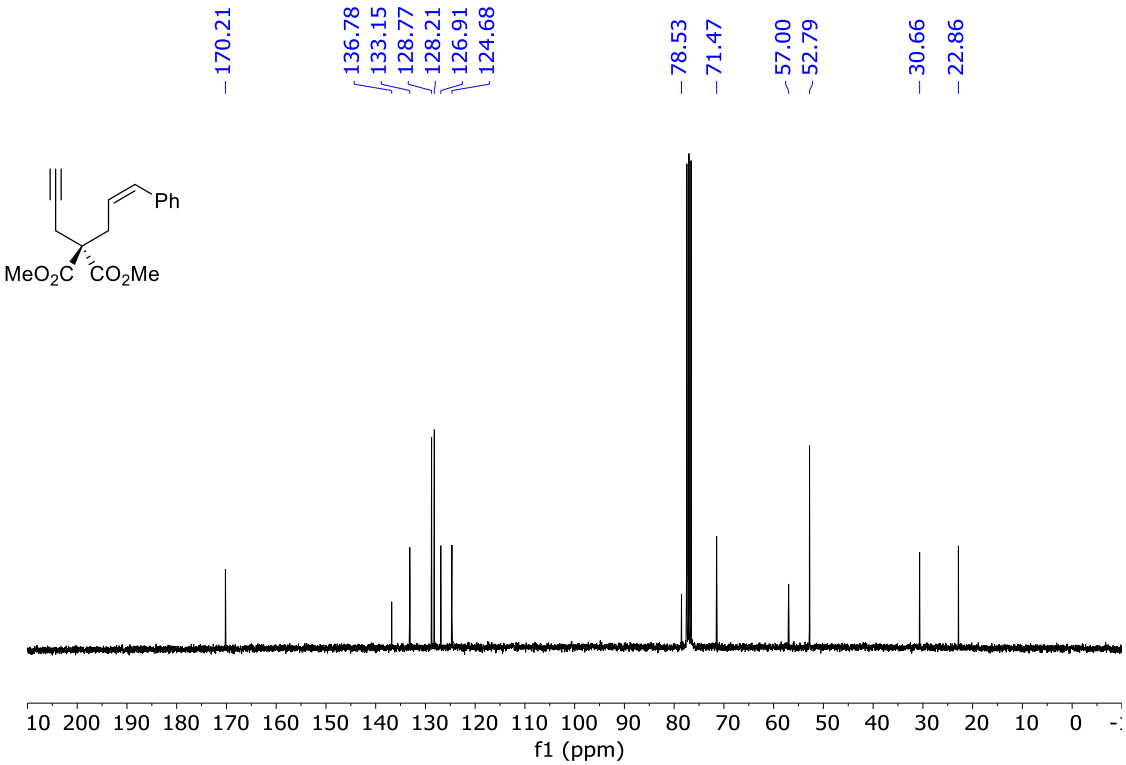
^{13}C NMR (75 MHz, $CDCl_3$, 300 K) spectrum of (*E*)-**4**



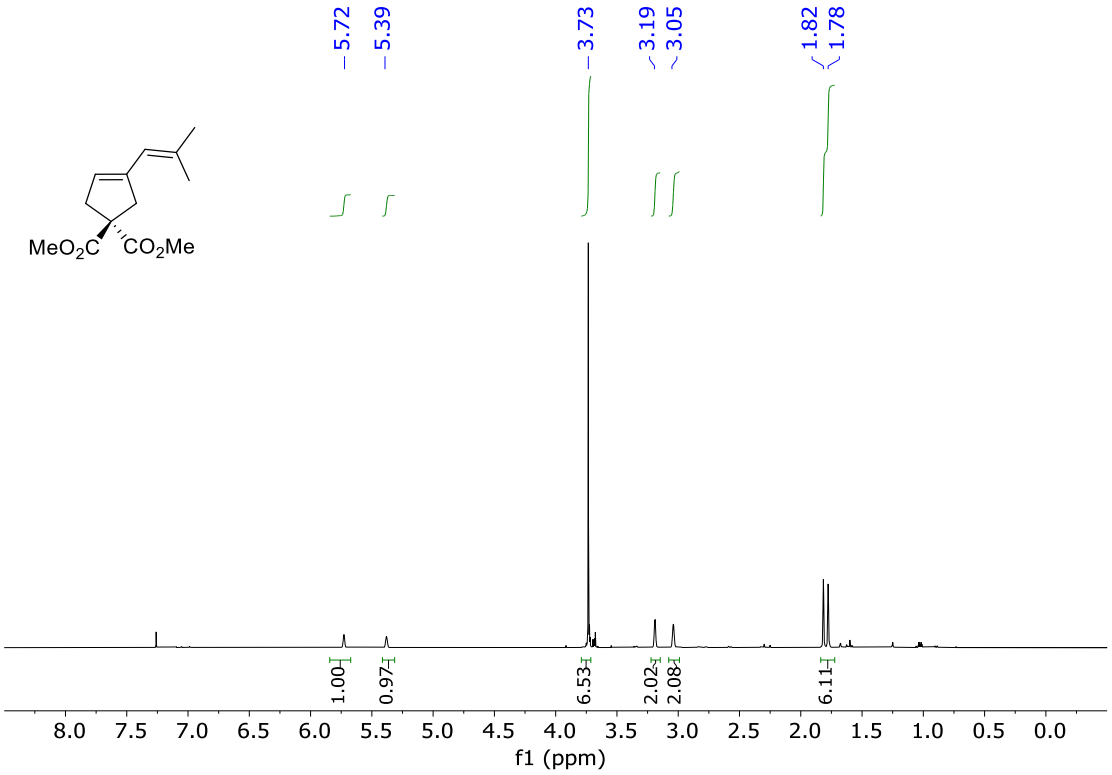
^{1}H NMR (300 MHz, $CDCl_3$, 300 K) spectrum of (*Z*)-**4**



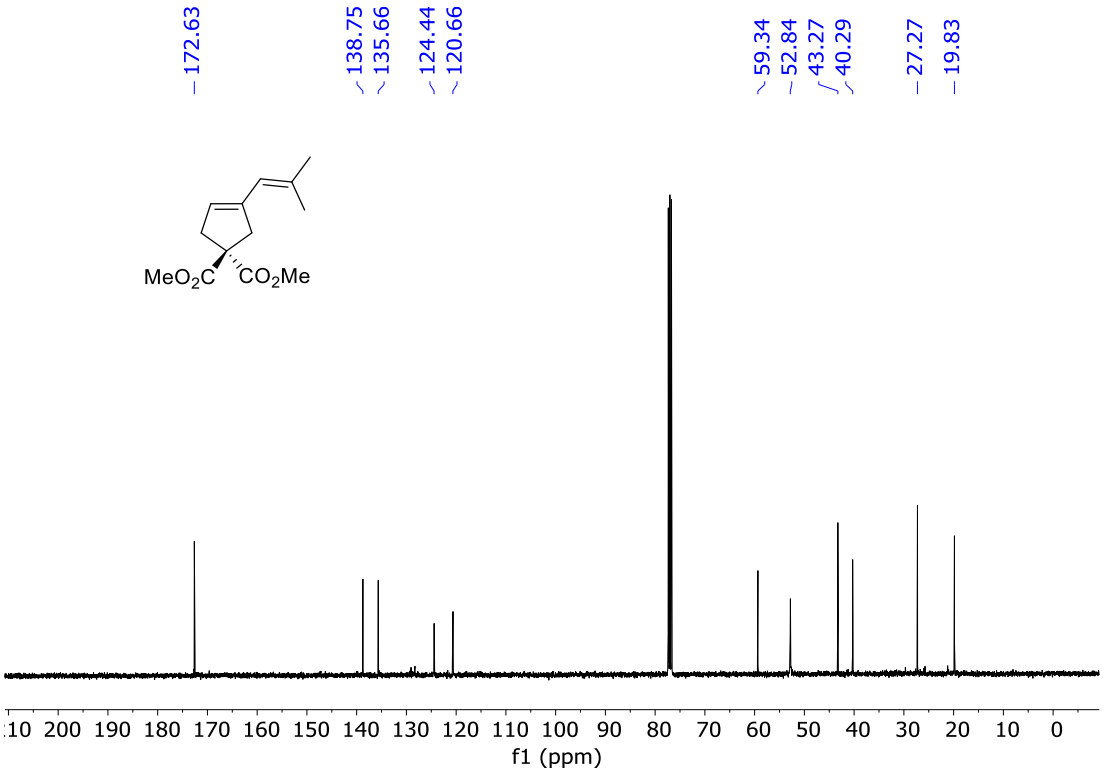
^{13}C NMR (75 MHz, $CDCl_3$, 300 K) spectrum of (*Z*)-**4**



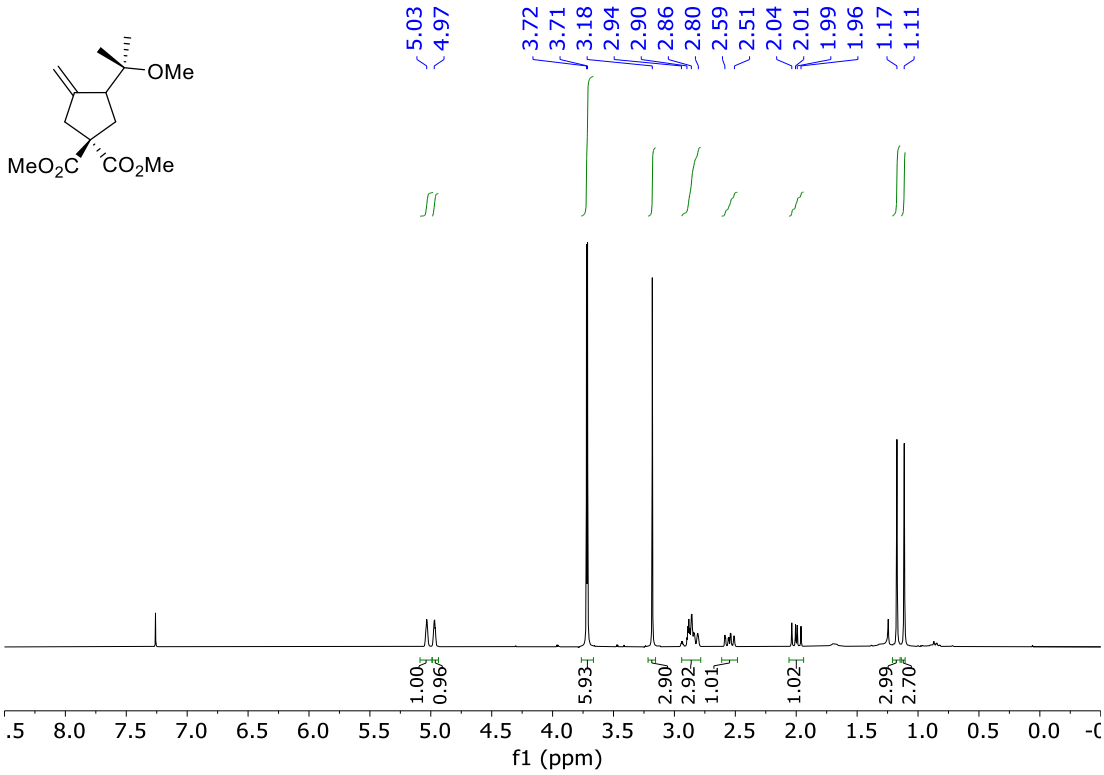
^{1}H NMR (400 MHz, $CDCl_3$, 300 K) spectrum of **1a**



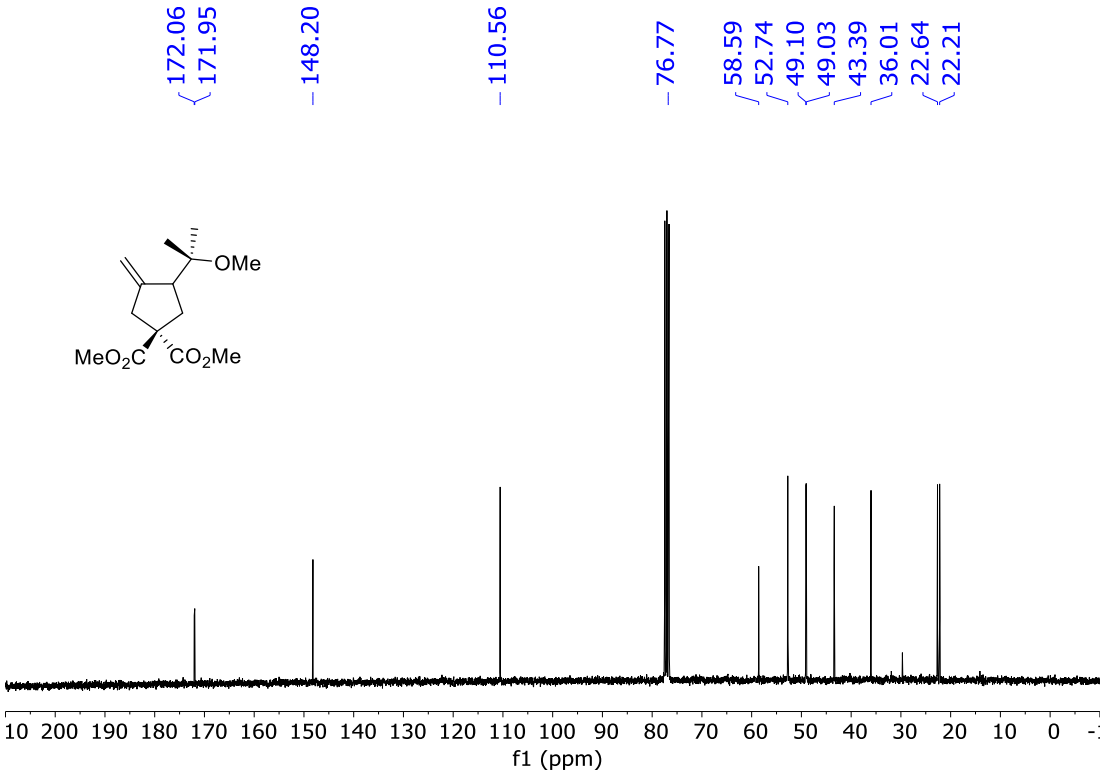
^{13}C NMR (100 MHz, $CDCl_3$, 300 K) spectrum of **1a**



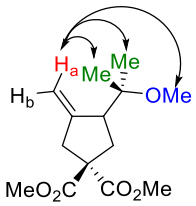
^{1}H NMR (300 MHz, $CDCl_3$, 300 K) spectrum of **3a**



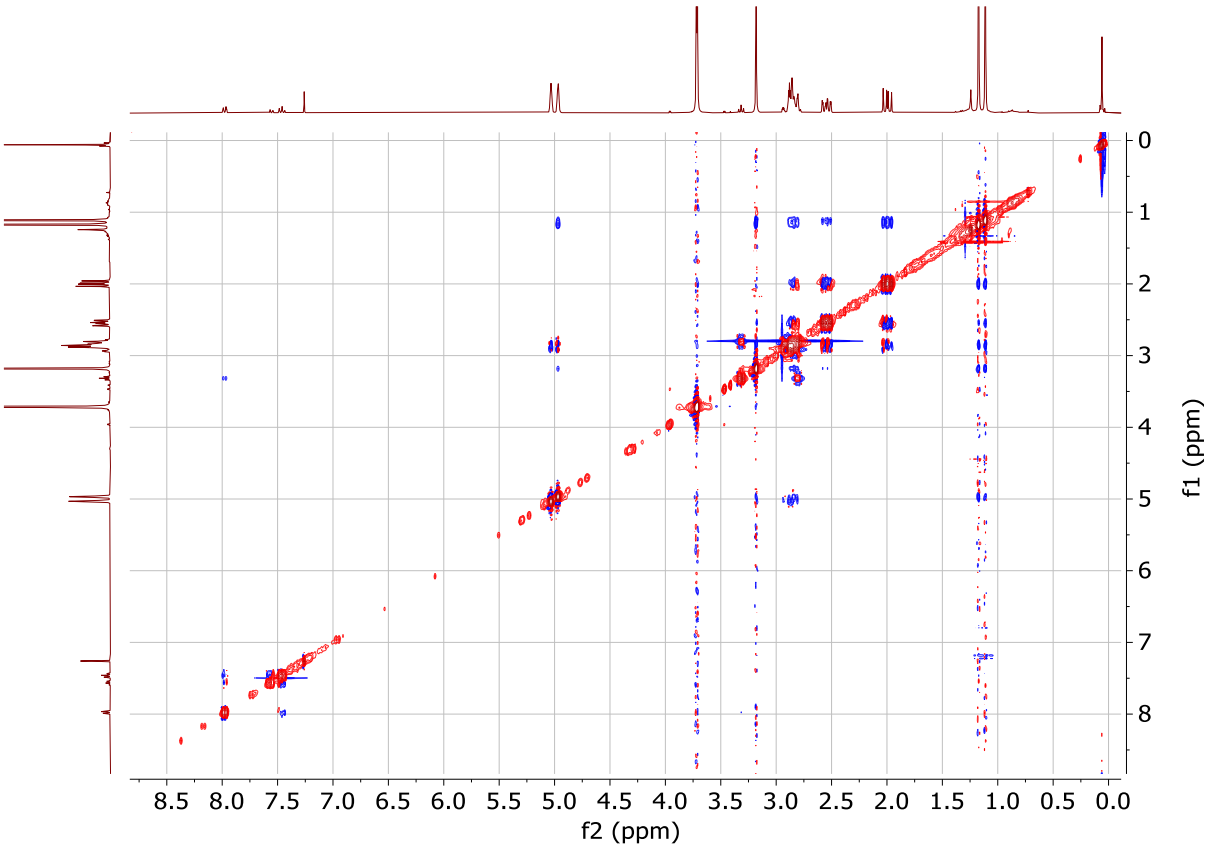
^{13}C NMR (75 MHz, $CDCl_3$, 300 K) spectrum of **3a**



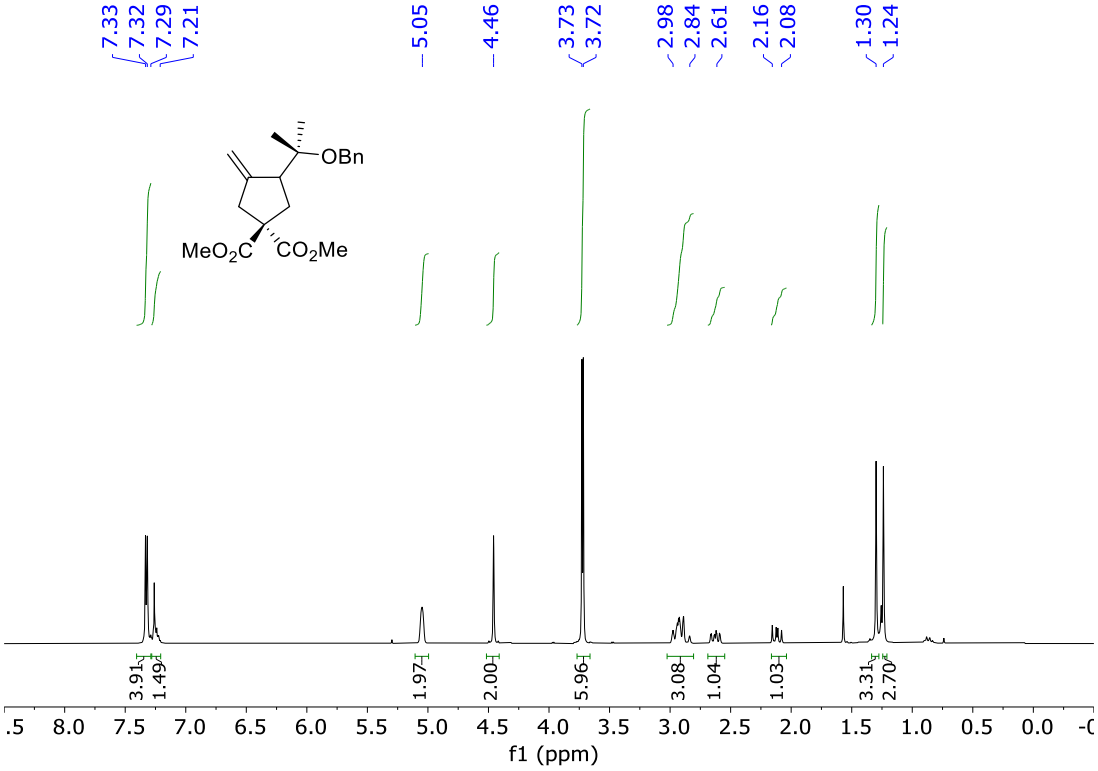
NOESY (300 MHz, $CDCl_3$, 300 K) spectrum of **3a**



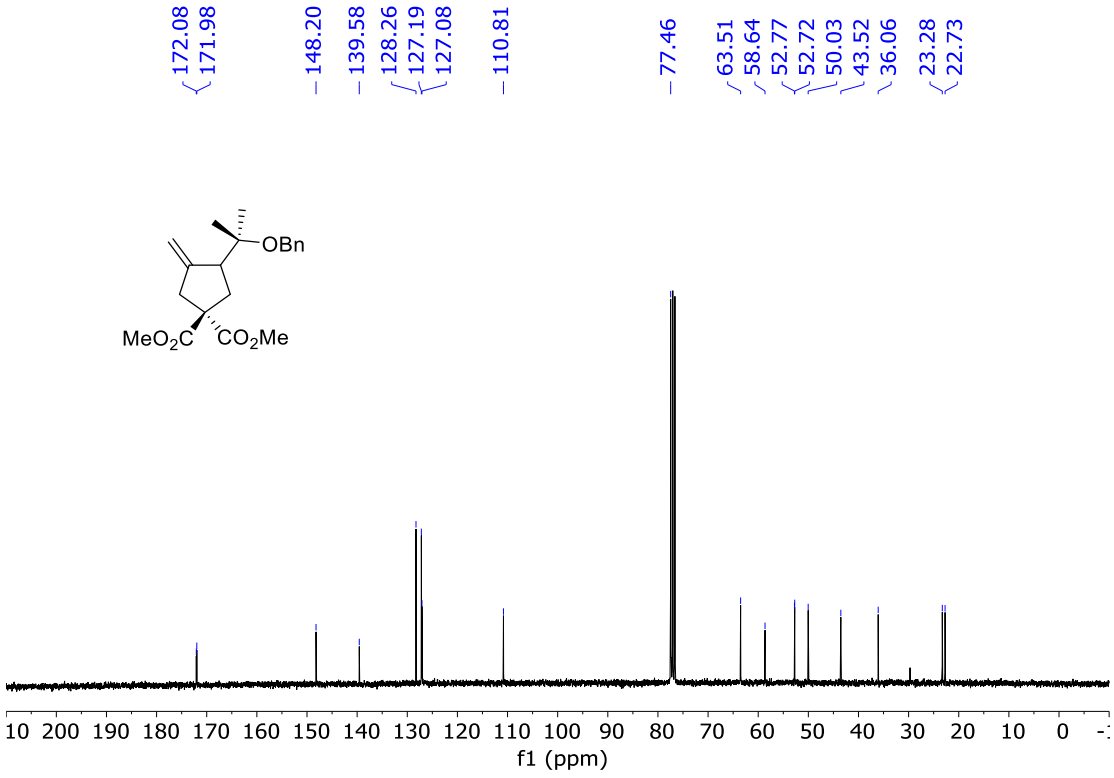
δ (Ha) = 4.97 ppm
δ (2 x Me) = 3.71 and 3.72 ppm
δ (OMe) = 3.18 ppm



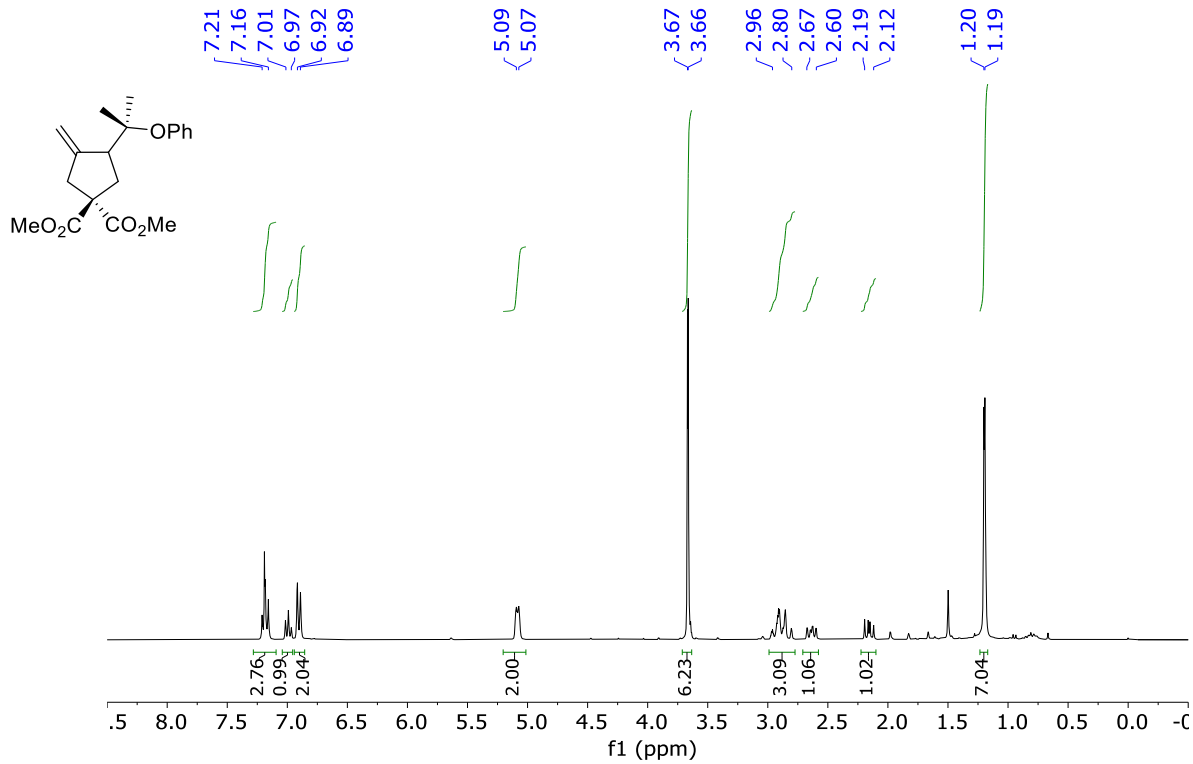
^{1}H NMR (300 MHz, $CDCl_3$, 300 K) spectrum of **3b**



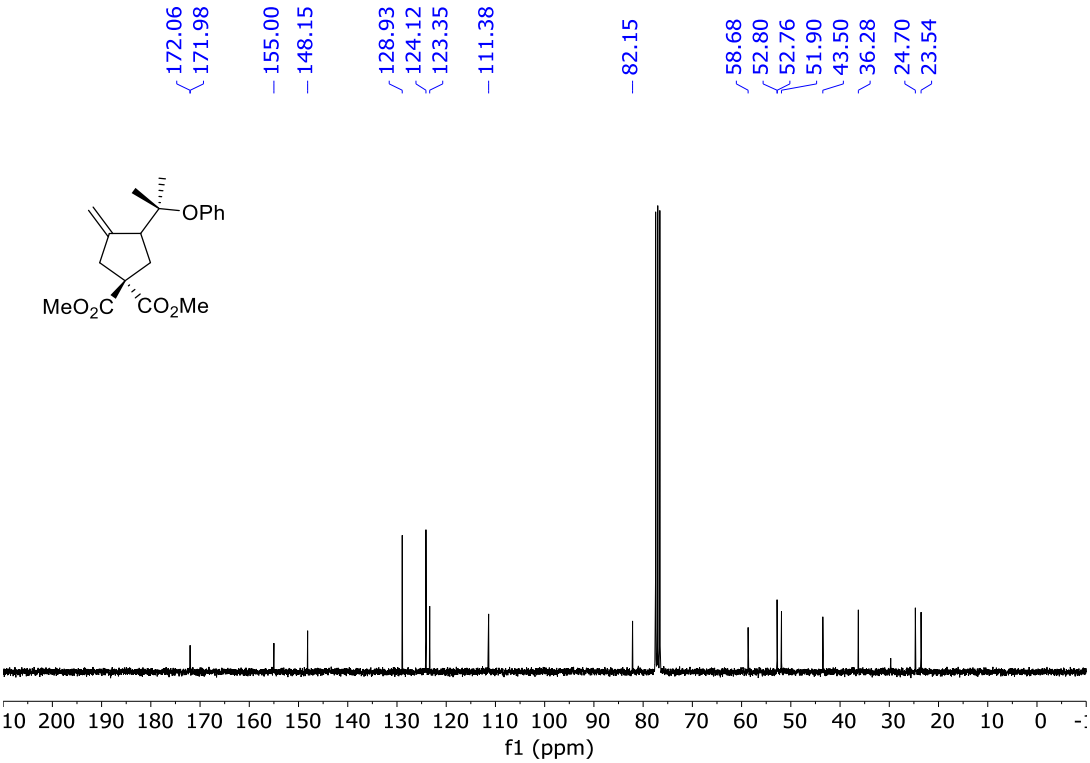
^{13}C NMR (75 MHz, $CDCl_3$, 300 K) spectrum of **3b**



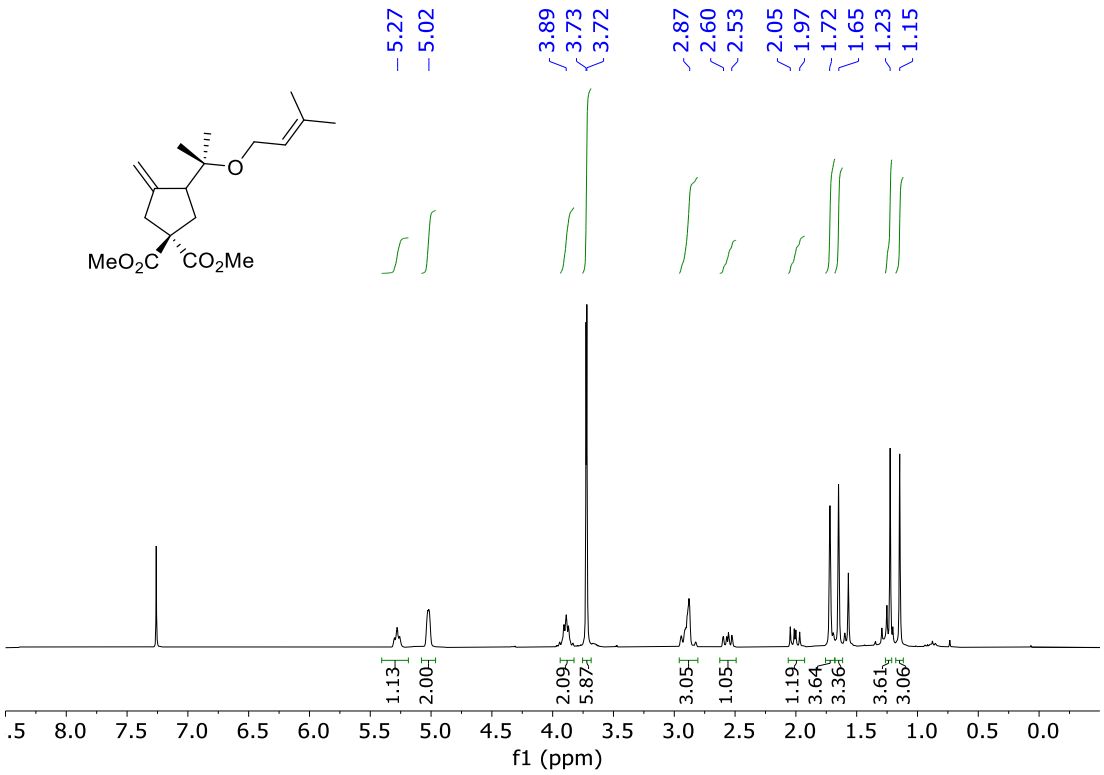
^{1}H NMR (300 MHz, $CDCl_3$, 300 K) spectrum of **3c**



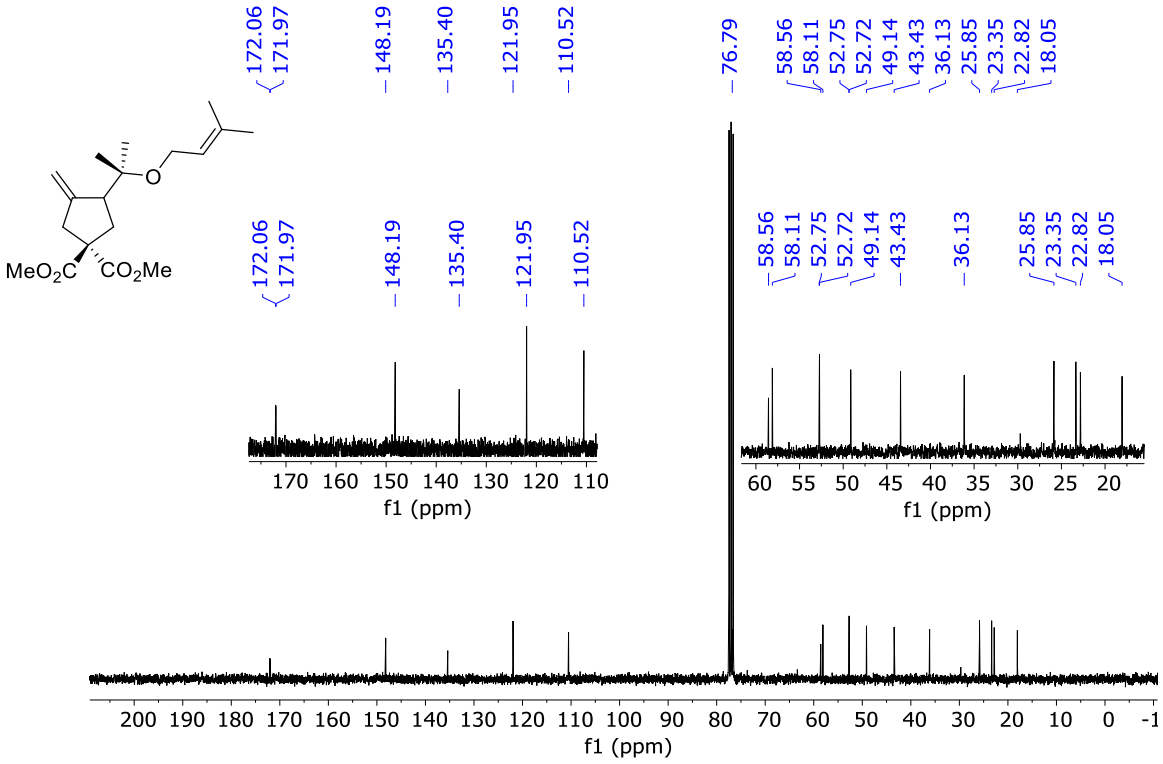
^{13}C NMR (75 MHz, $CDCl_3$, 300 K) spectrum of **3c**



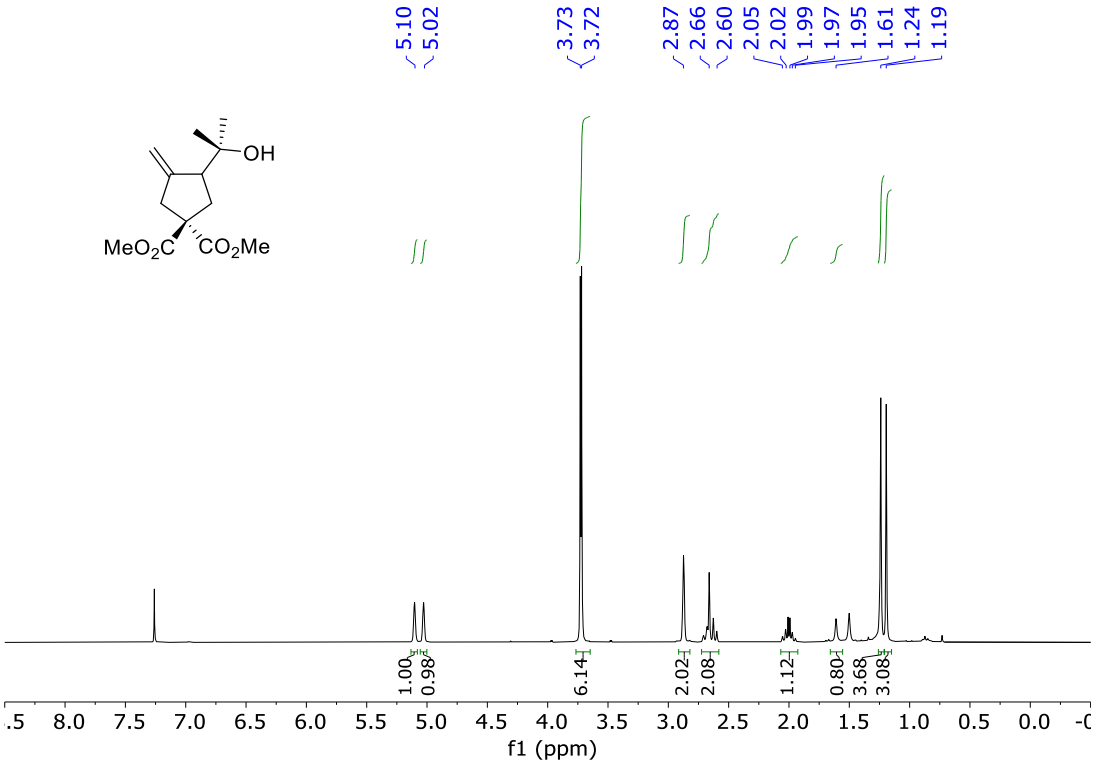
^{1}H NMR (300 MHz, $CDCl_3$, 300 K) spectrum of **3d**



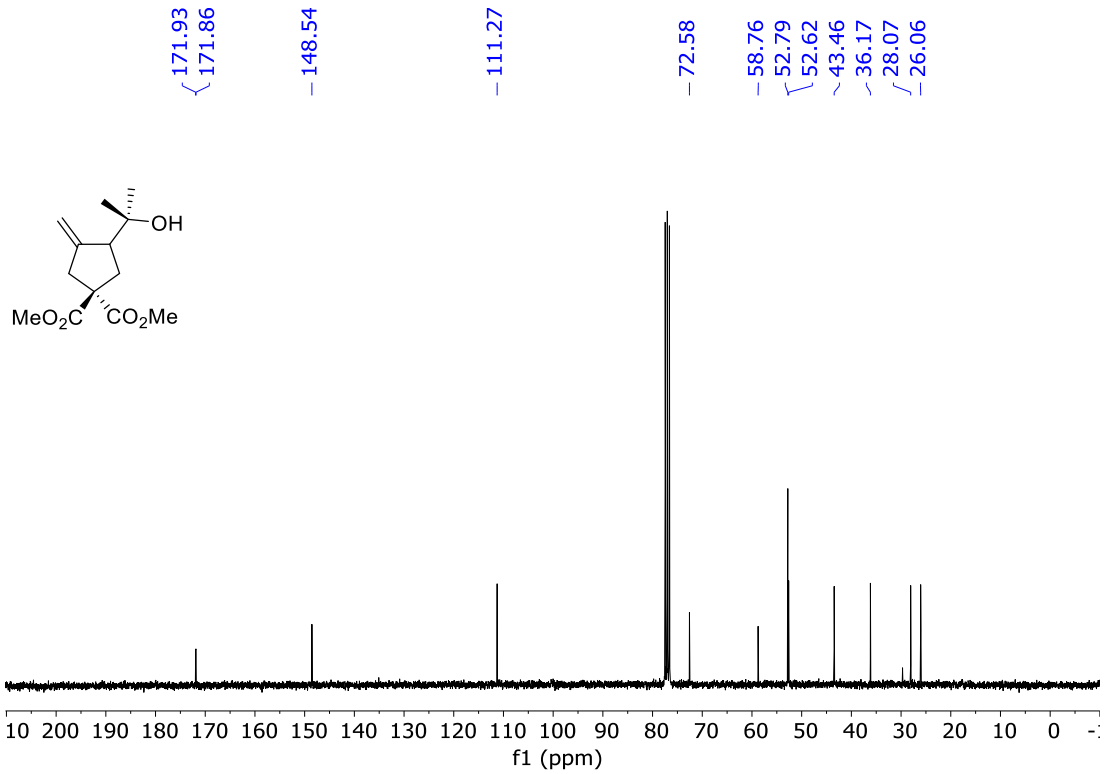
^{13}C NMR (75 MHz, $CDCl_3$, 300 K) spectrum of **3d**



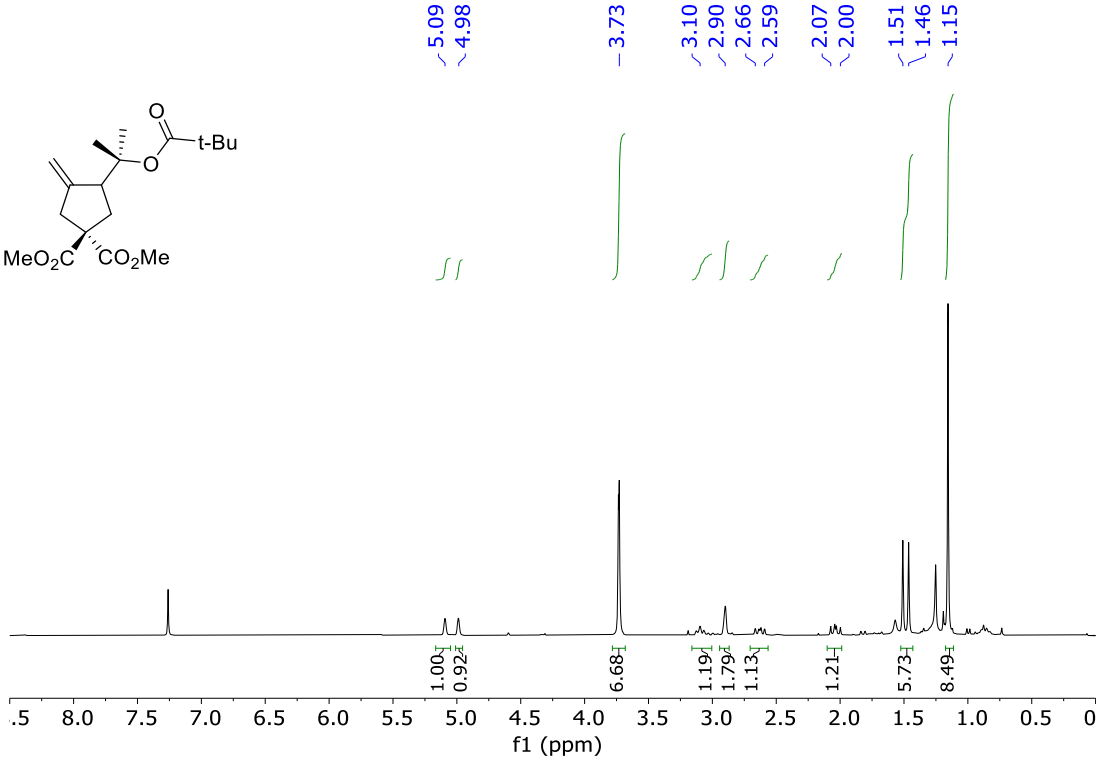
^{1}H NMR (300 MHz, $CDCl_3$, 300 K) spectrum of **3e**



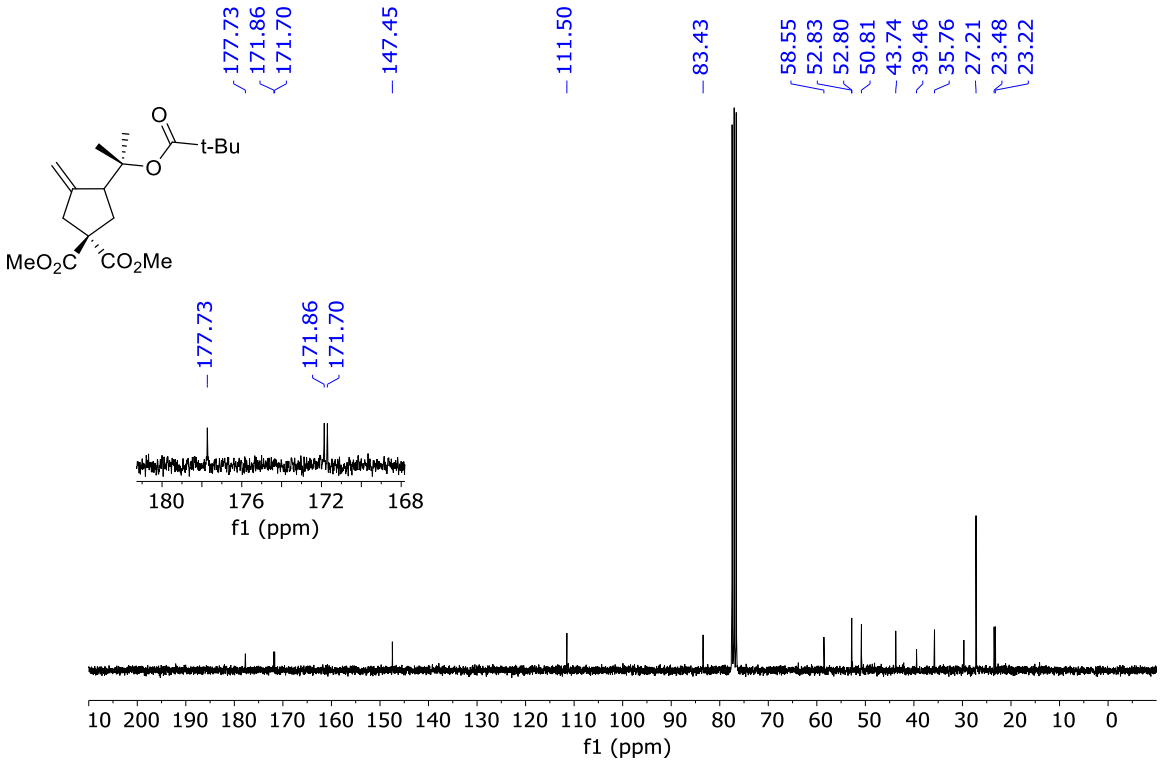
^{13}C NMR (75 MHz, $CDCl_3$, 300 K) spectrum of **3e**



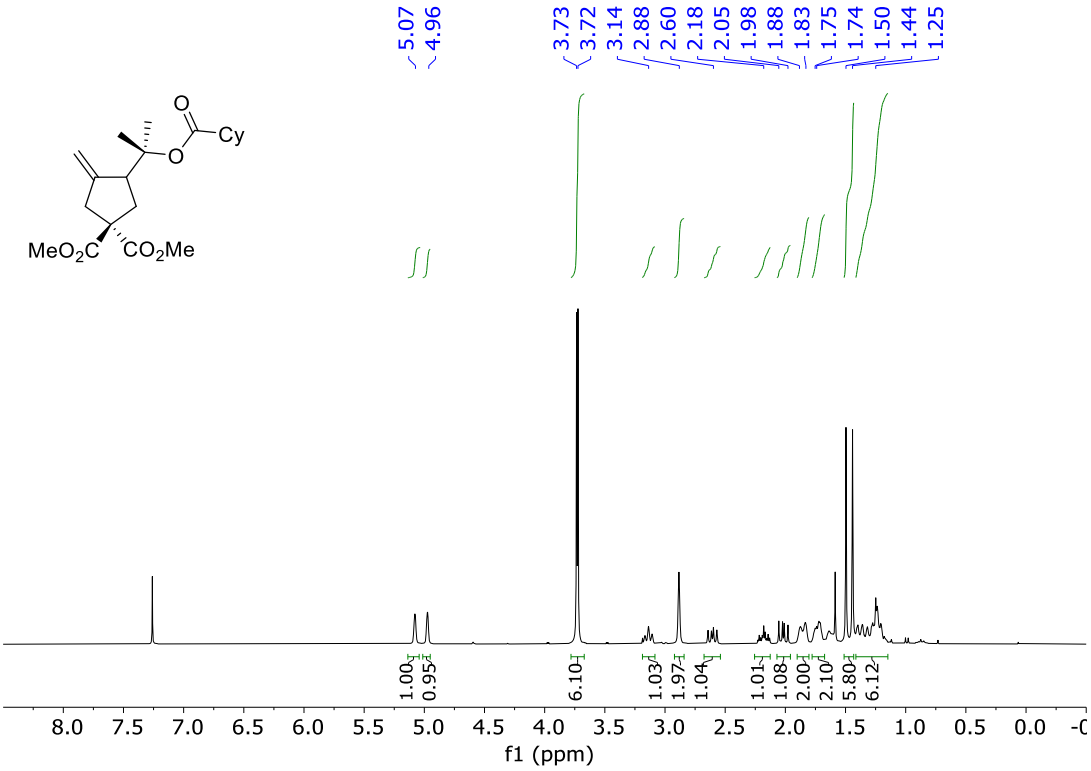
^{1}H NMR (300 MHz, $CDCl_3$, 300 K) spectrum of **3f**



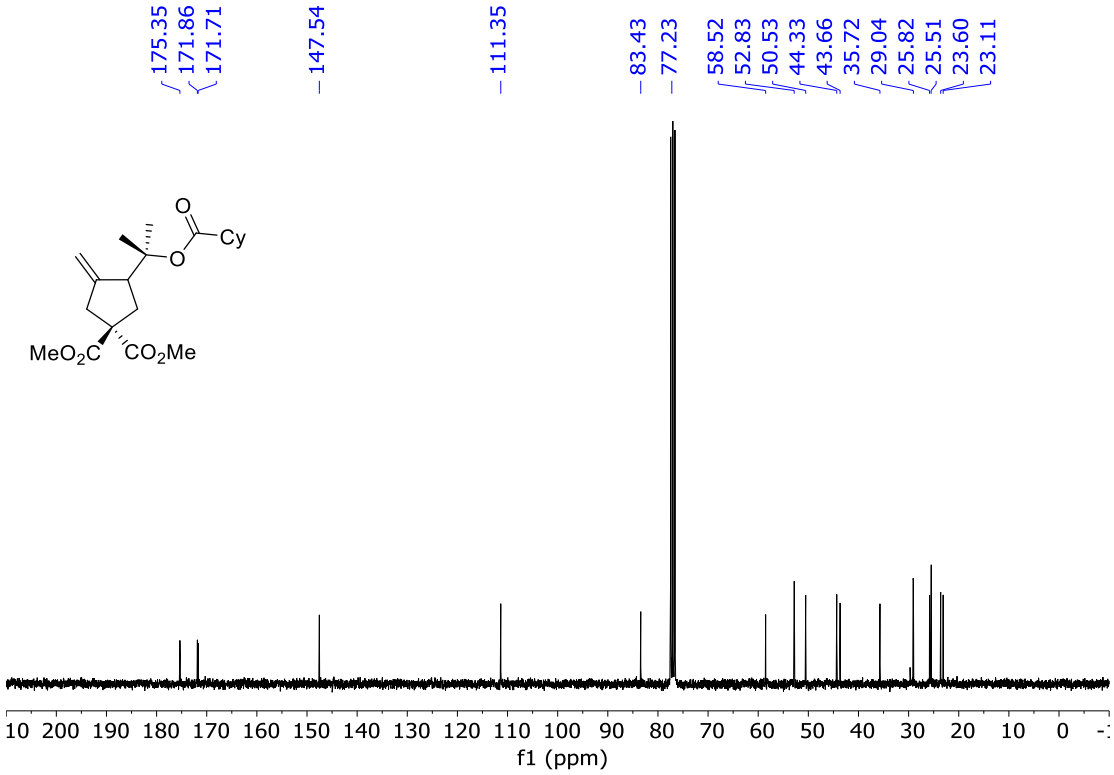
^{13}C NMR (75 MHz, $CDCl_3$, 300 K) spectrum of **3f**



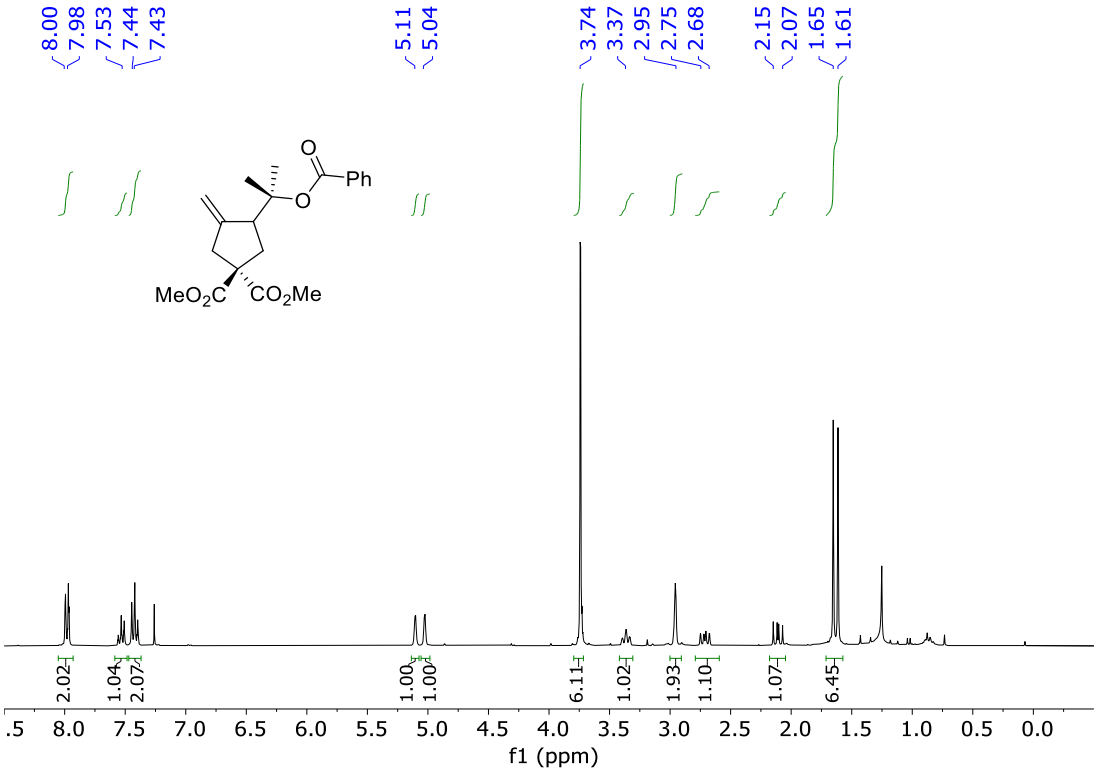
^{1}H NMR (300 MHz, $CDCl_3$, 300 K) spectrum of **3g**



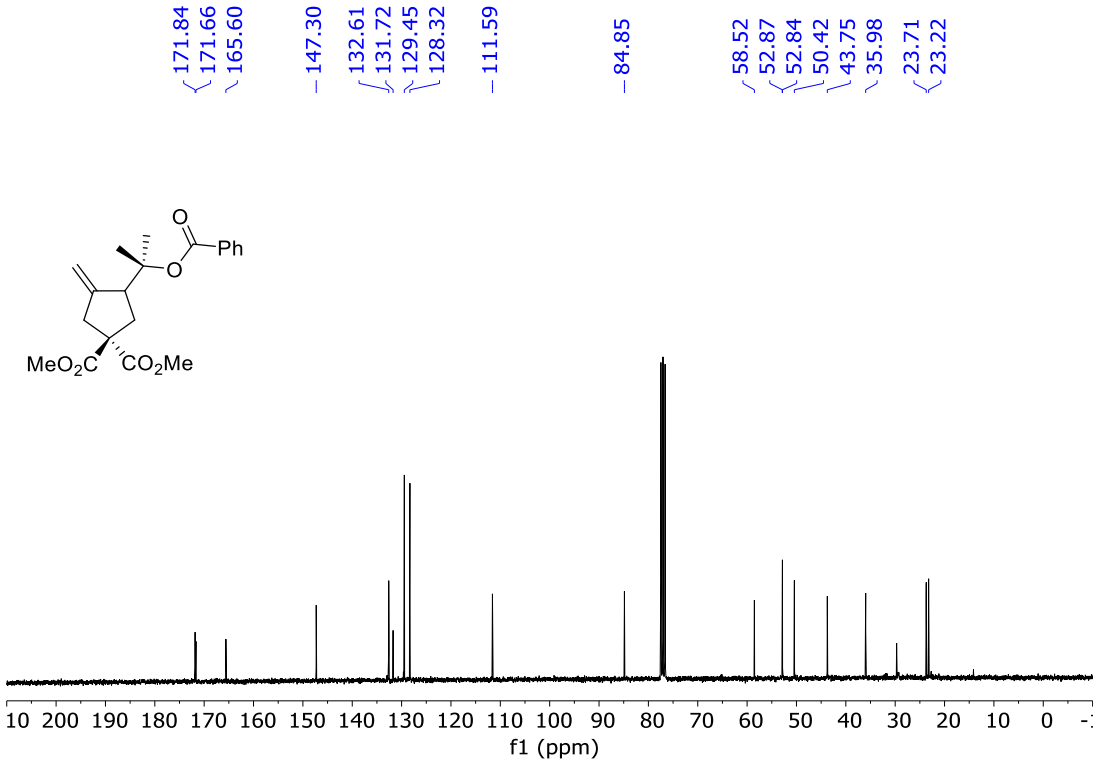
^{13}C NMR (75 MHz, $CDCl_3$, 300 K) spectrum of **3g**



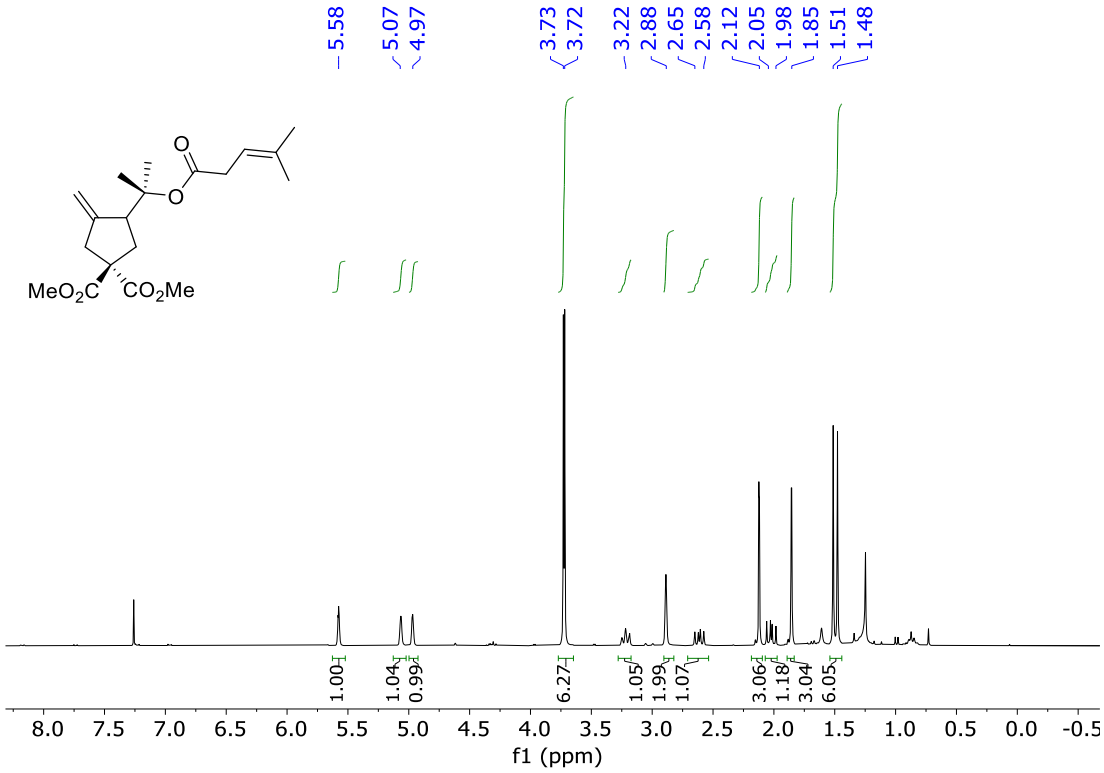
^{1}H NMR (300 MHz, $CDCl_3$, 300 K) spectrum of **3h**



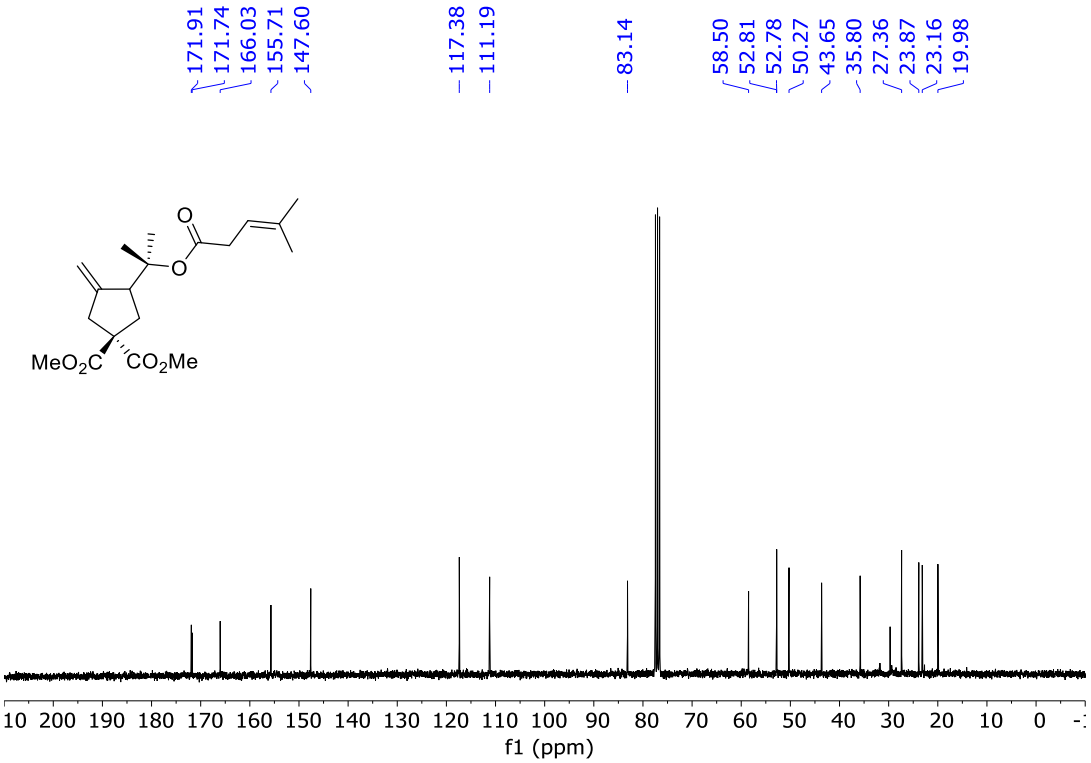
^{13}C NMR (75 MHz, $CDCl_3$, 300 K) spectrum of **3h**



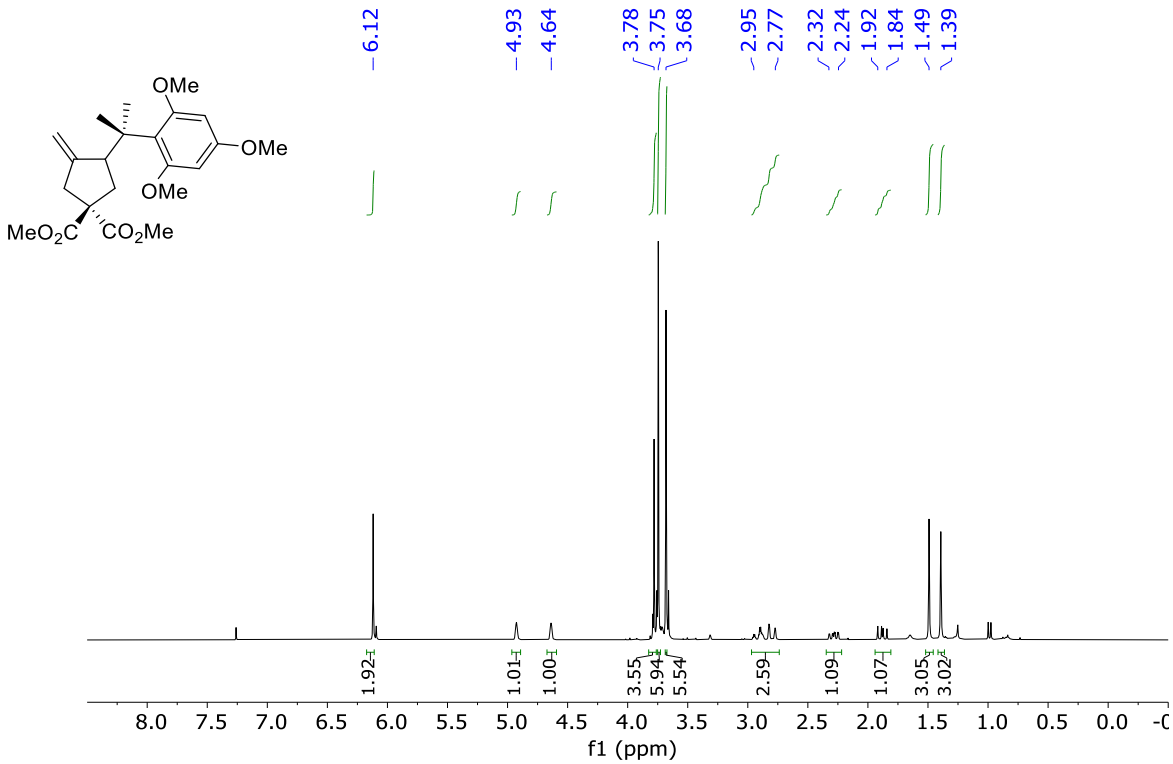
^{1}H NMR (300 MHz, $CDCl_3$, 300 K) spectrum of **3i**



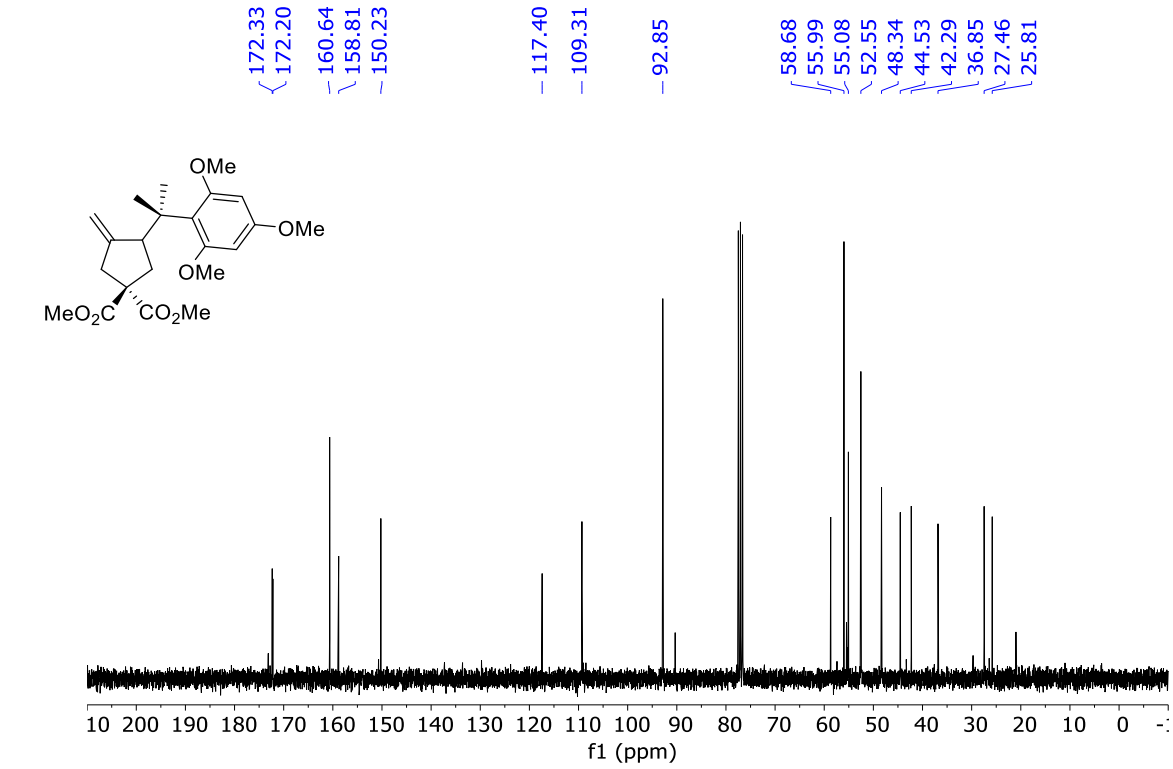
^{13}C NMR (75 MHz, $CDCl_3$, 300 K) spectrum of **3i**



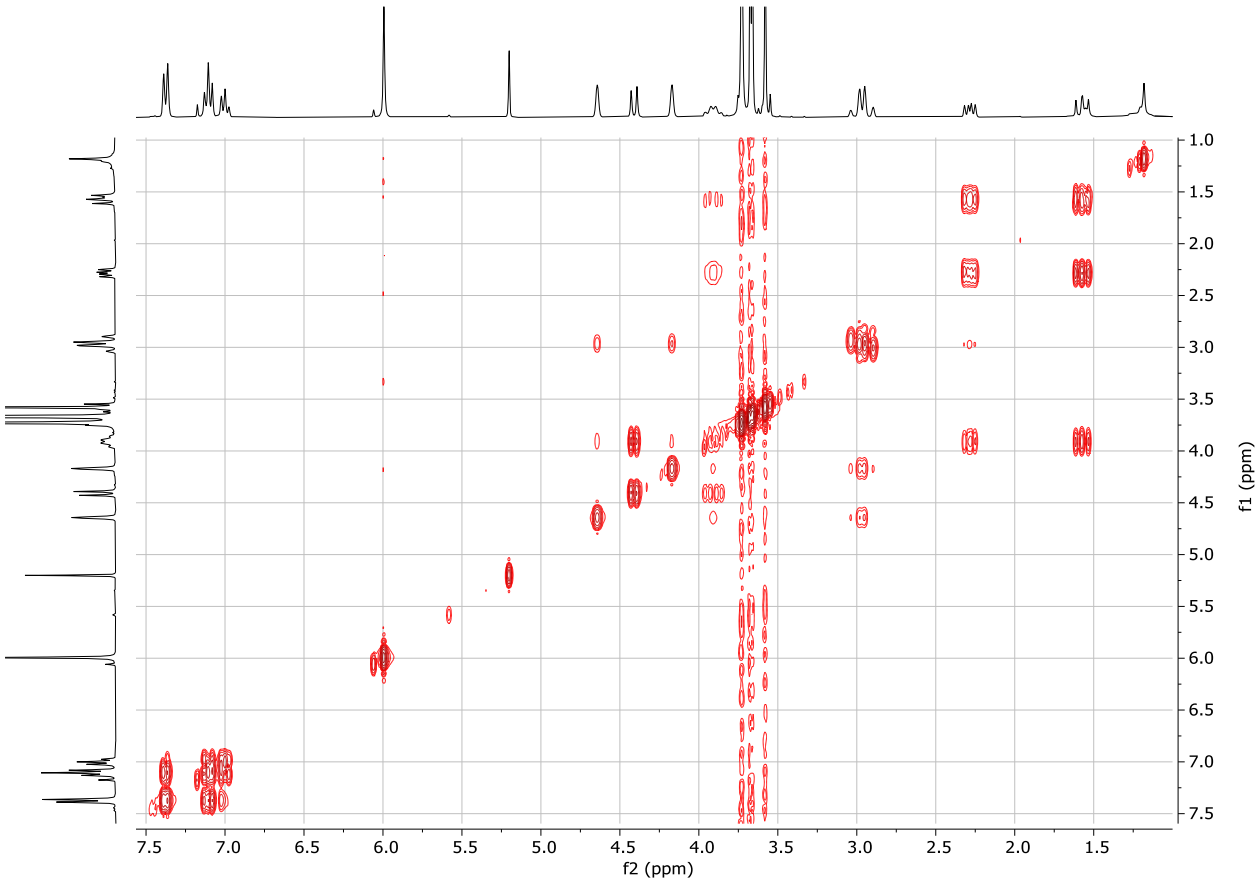
^{1}H NMR (300 MHz, $CDCl_3$, 300 K) spectrum of **3j**

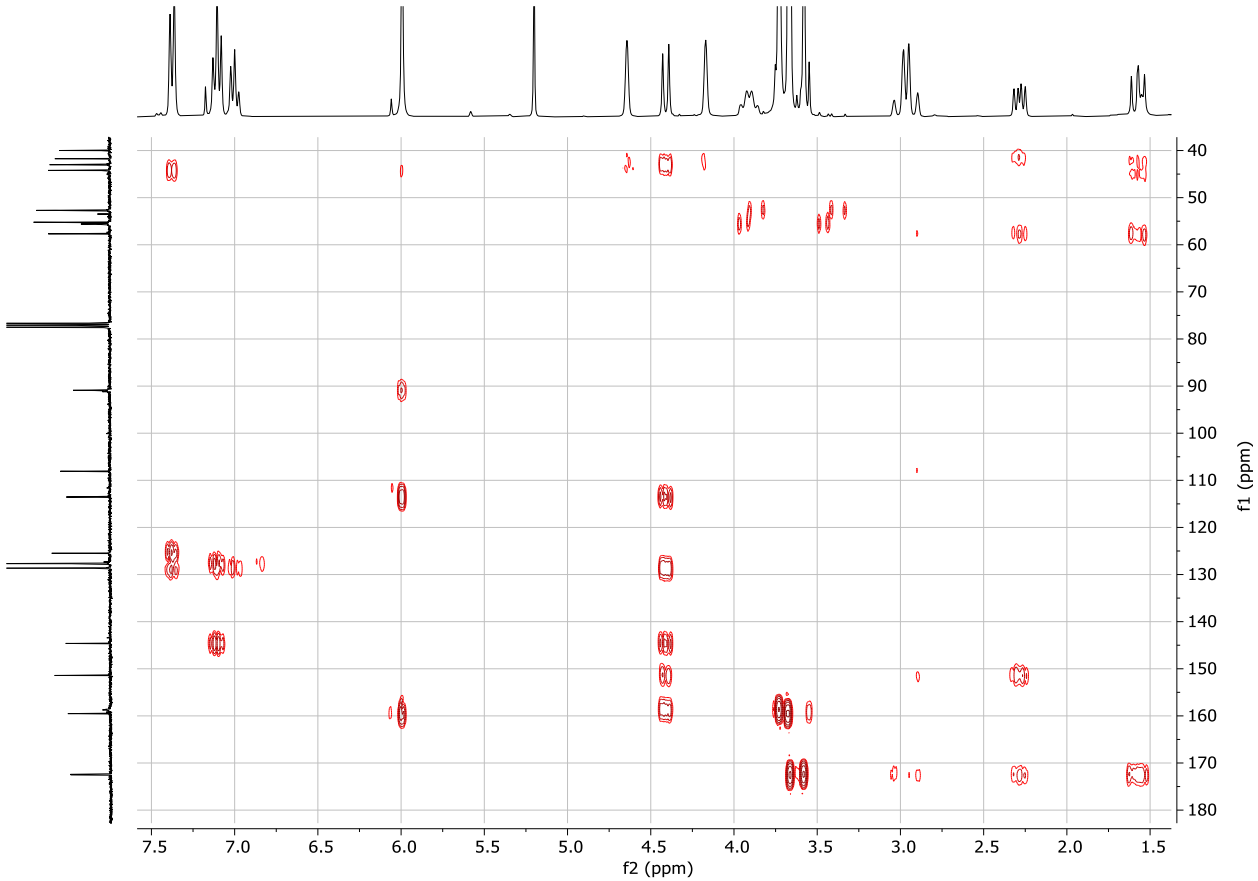


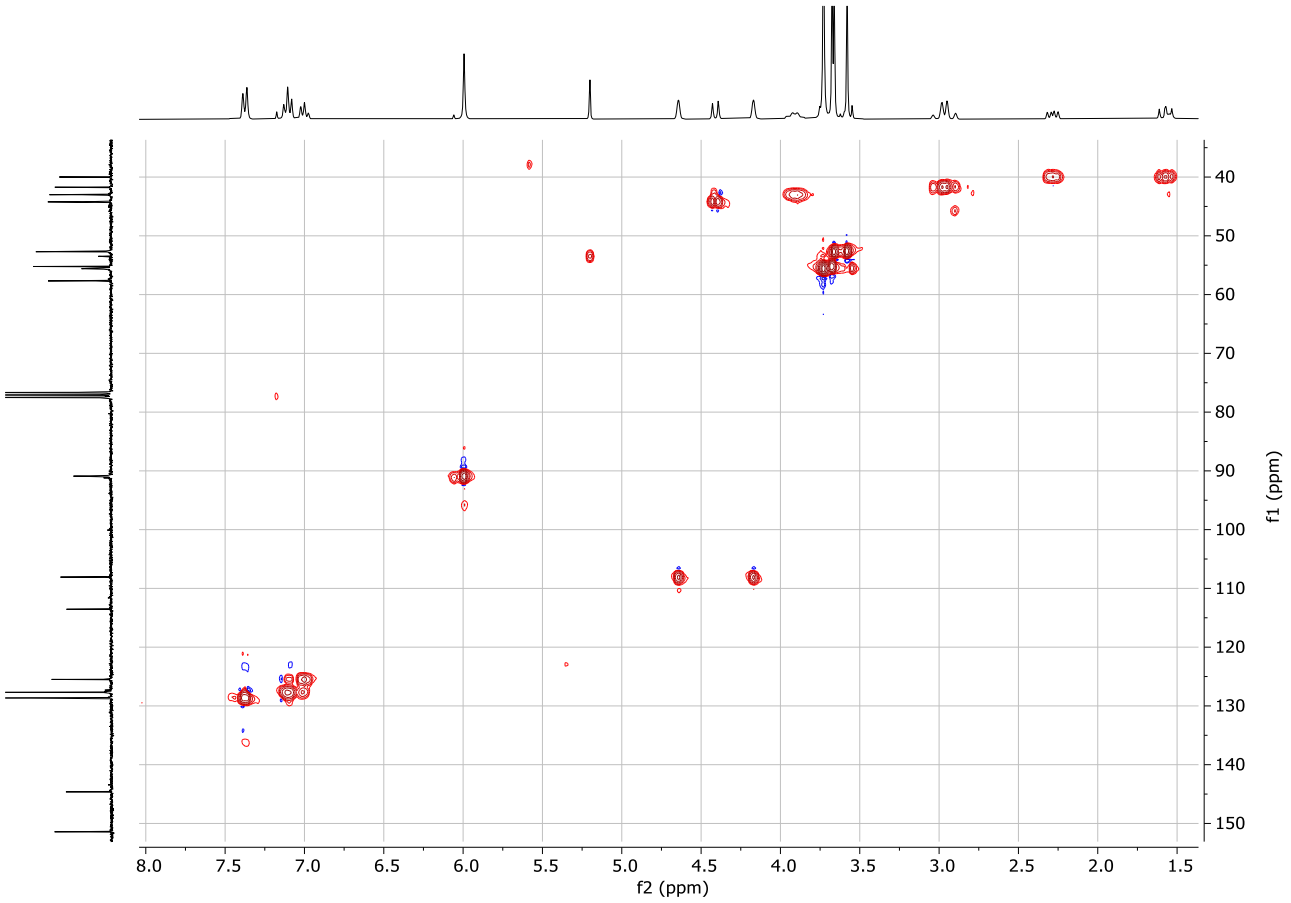
^{13}C NMR (75 MHz, $CDCl_3$, 300 K) spectrum of **3j**



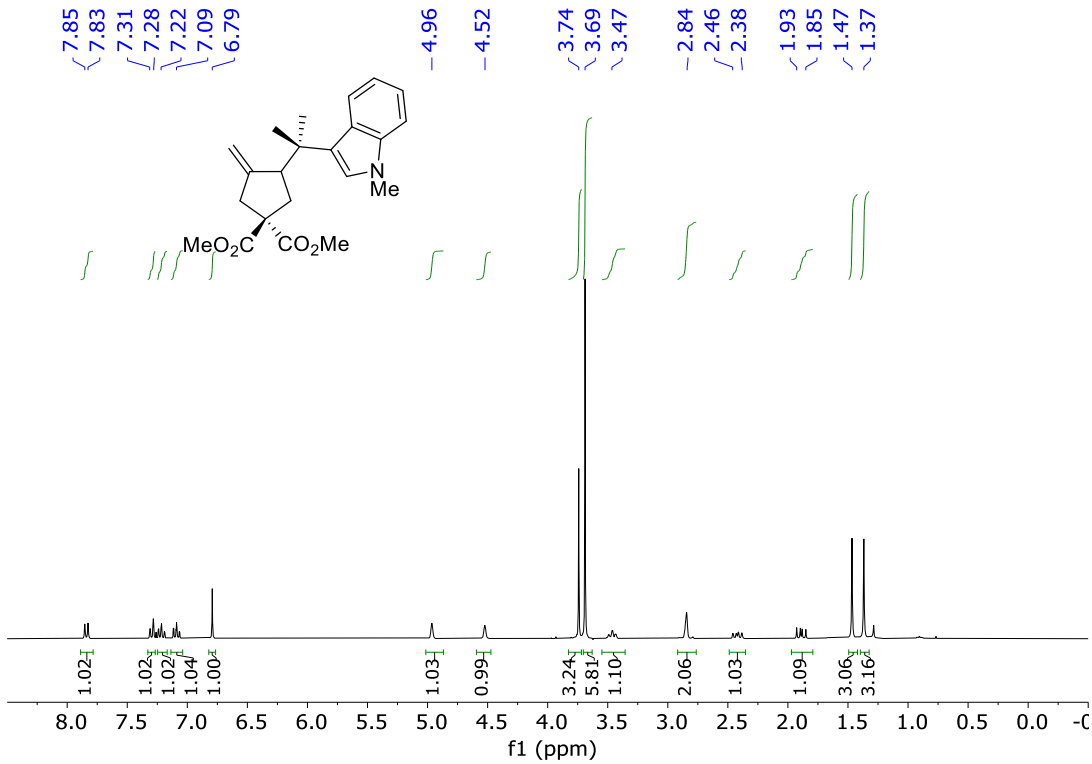
2D NMR (300 MHz, $CDCl_3$, 300 K) spectra of **3j**



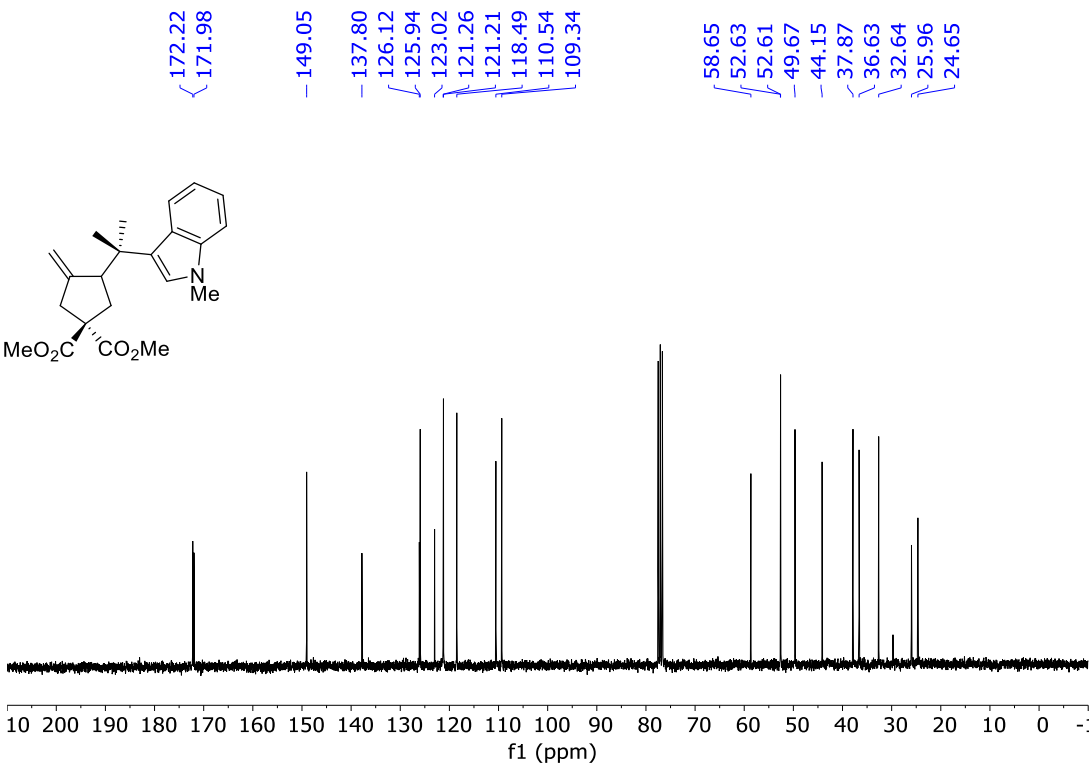



8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f2 (ppm)
40
50
60
70
80
90
100
110
120
130
140
150
f1 (ppm)

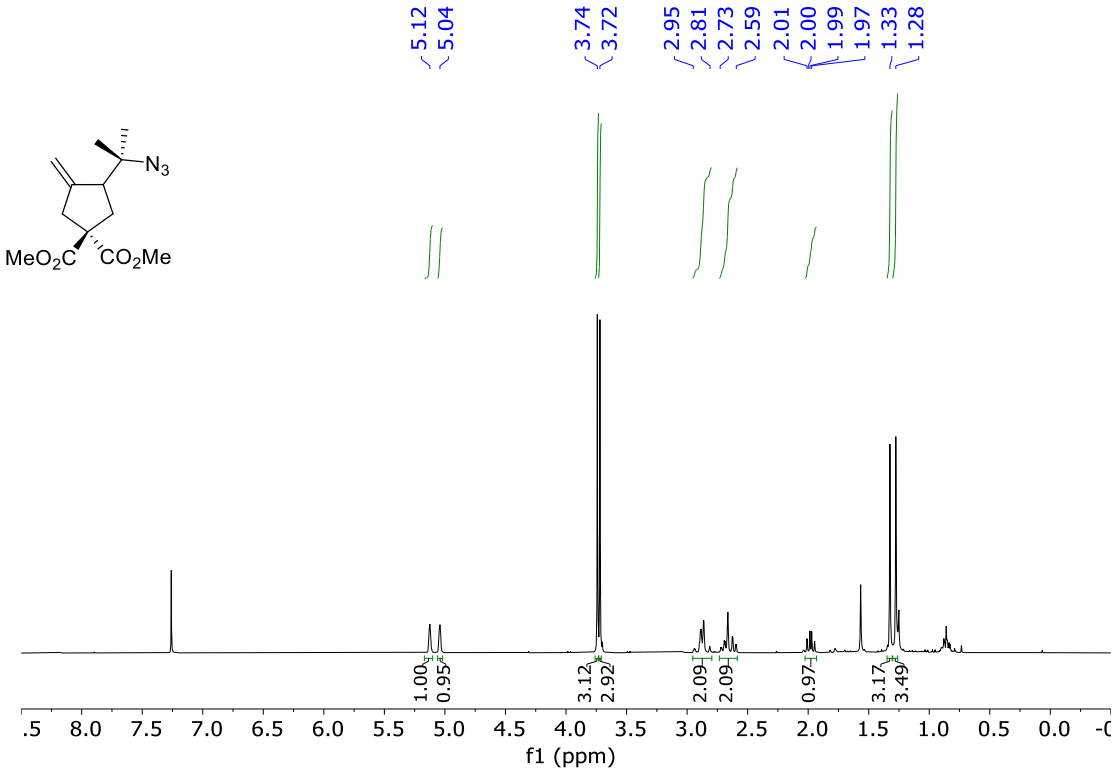
^{1}H NMR (300 MHz, $CDCl_3$, 300 K) spectrum of **3k**



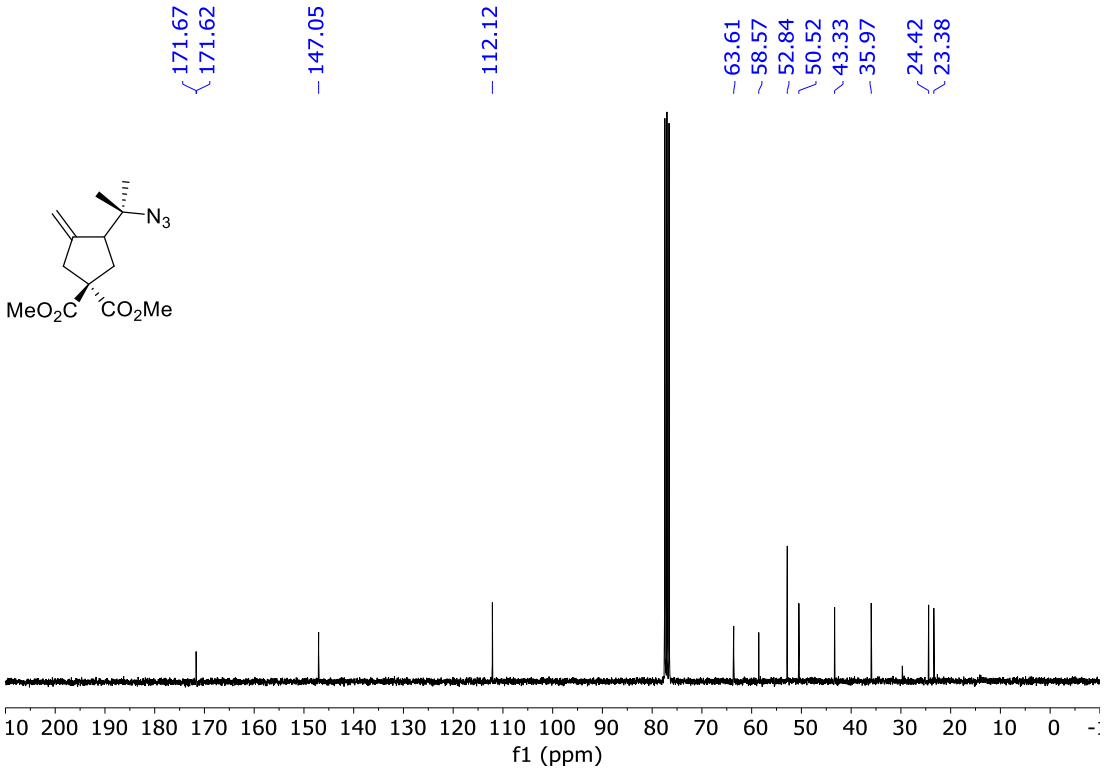
^{13}C NMR (75 MHz, $CDCl_3$, 300 K) spectrum of **3k**



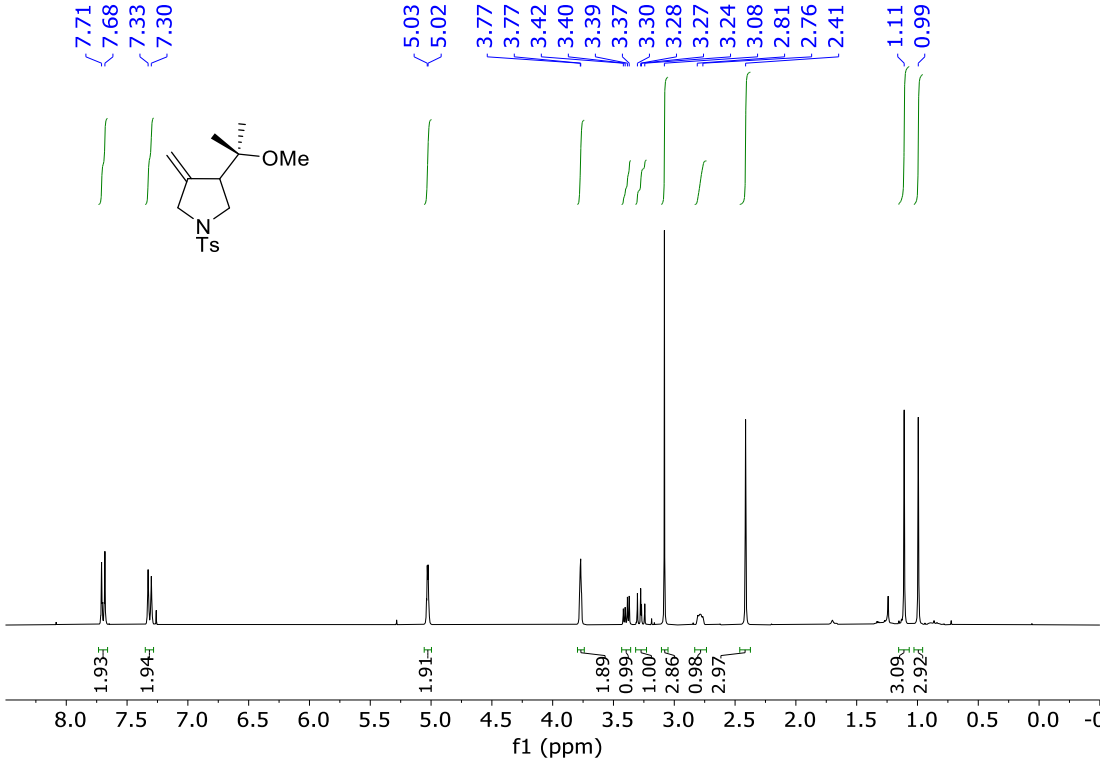
^{1}H NMR (300 MHz, $CDCl_3$, 300 K) spectrum of **3l**



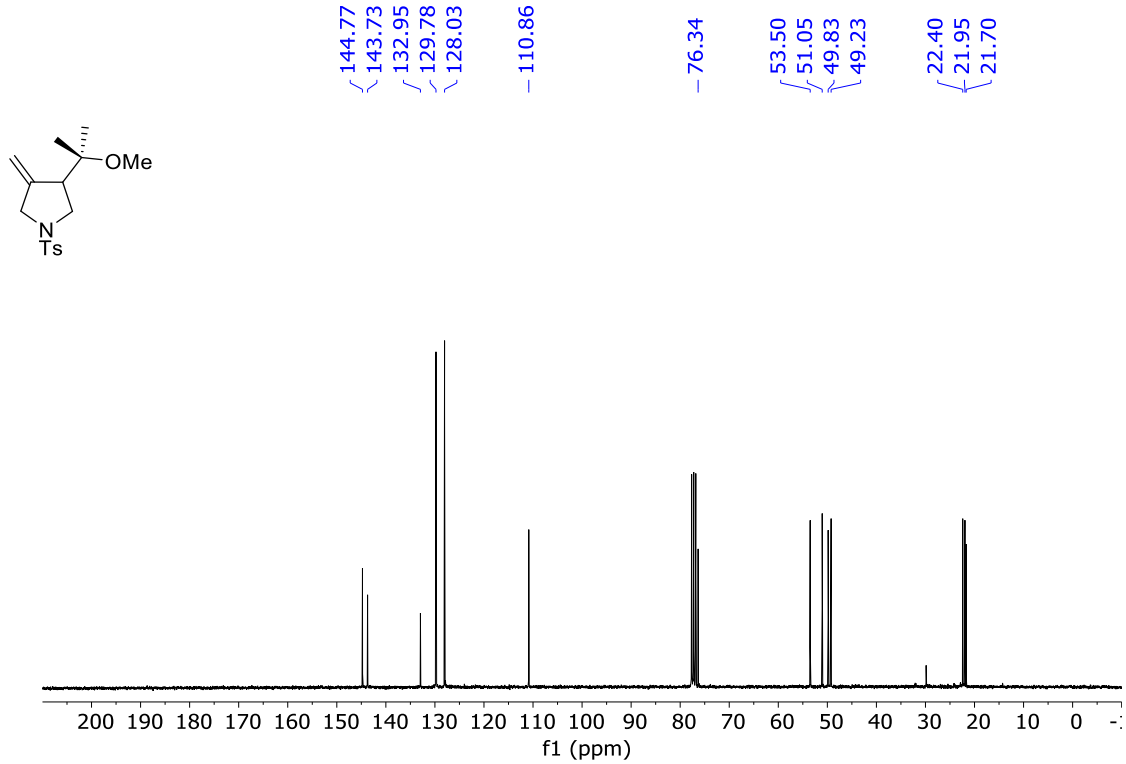
^{13}C NMR (75 MHz, $CDCl_3$, 300 K) spectrum of **3l**



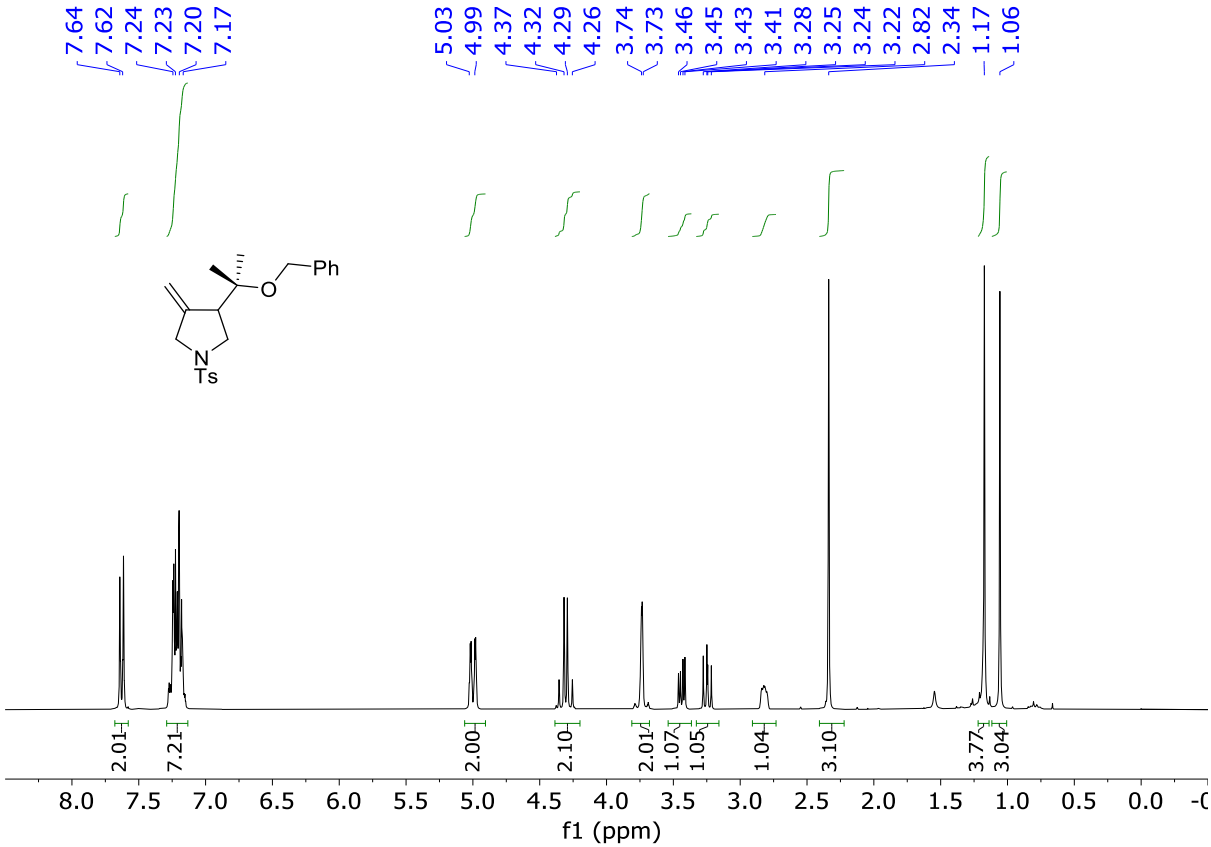
^{1}H NMR (300 MHz, $CDCl_3$, 300 K) spectrum of **3m**



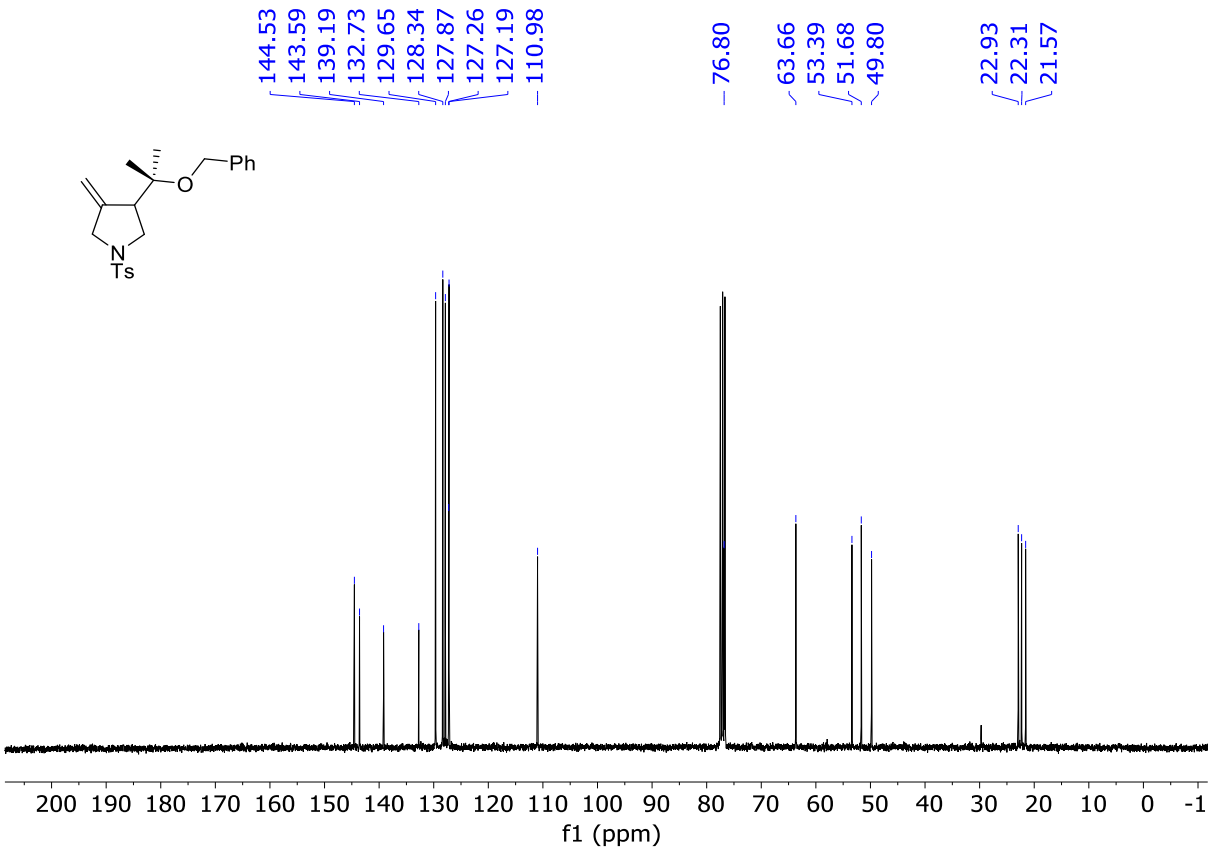
^{13}C NMR (75 MHz, $CDCl_3$, 300 K) spectrum of **3m**



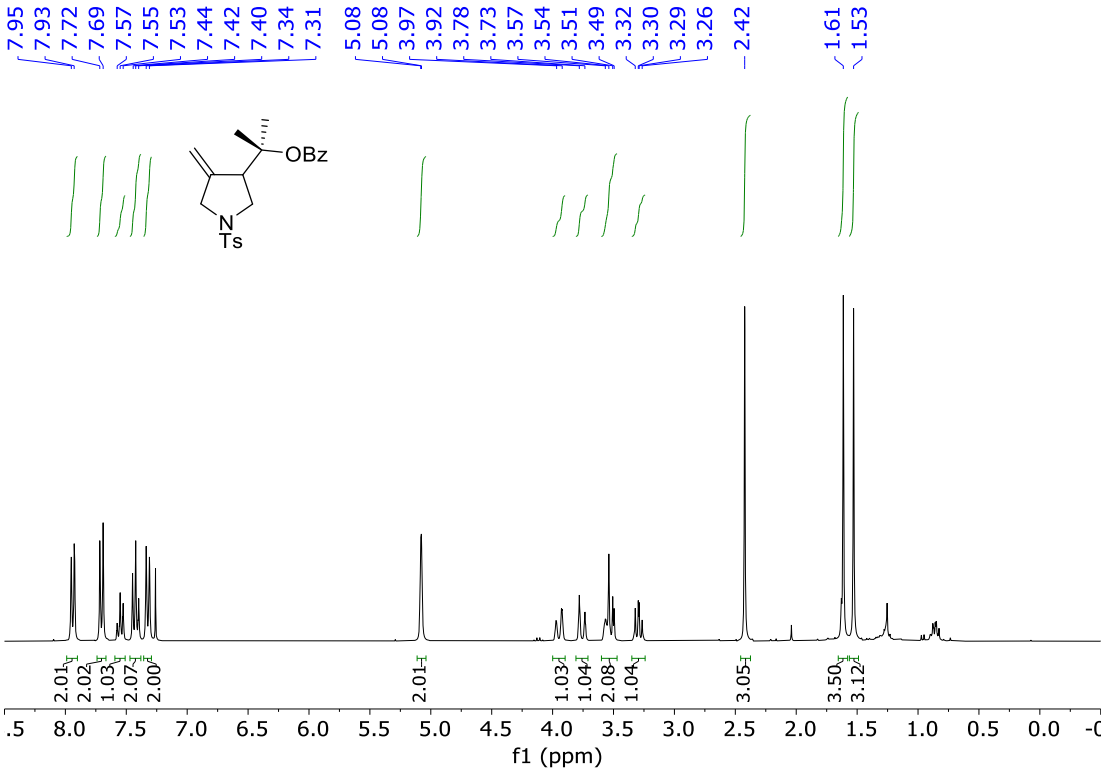
^{1}H NMR (300 MHz, $CDCl_3$, 300 K) spectrum of **3n**



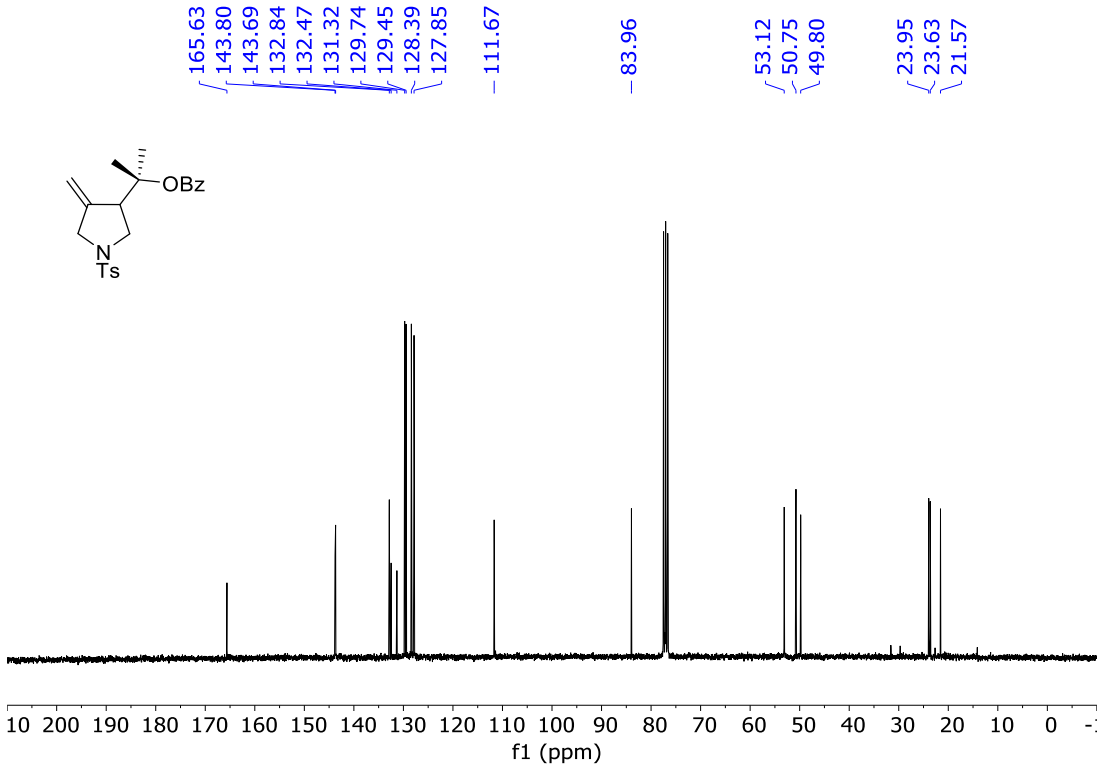
^{13}C NMR (75 MHz, $CDCl_3$, 300 K) spectrum of **3n**



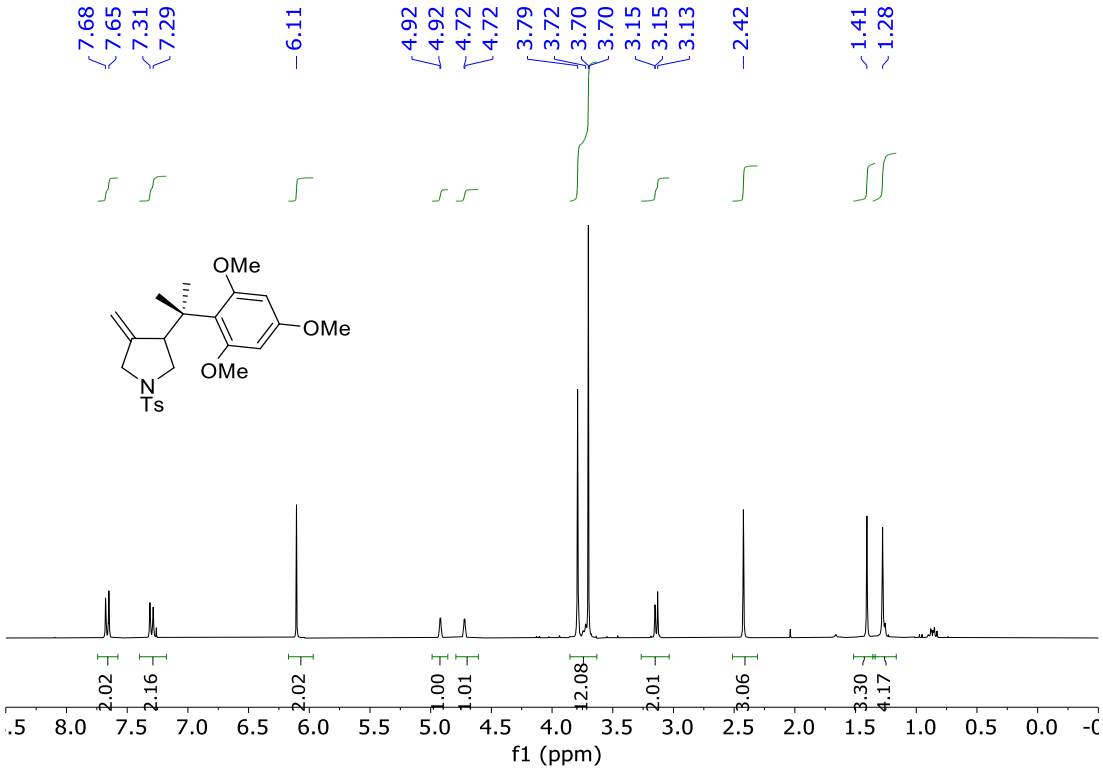
^{1}H NMR (300 MHz, $CDCl_3$, 300 K) spectrum of **3o**



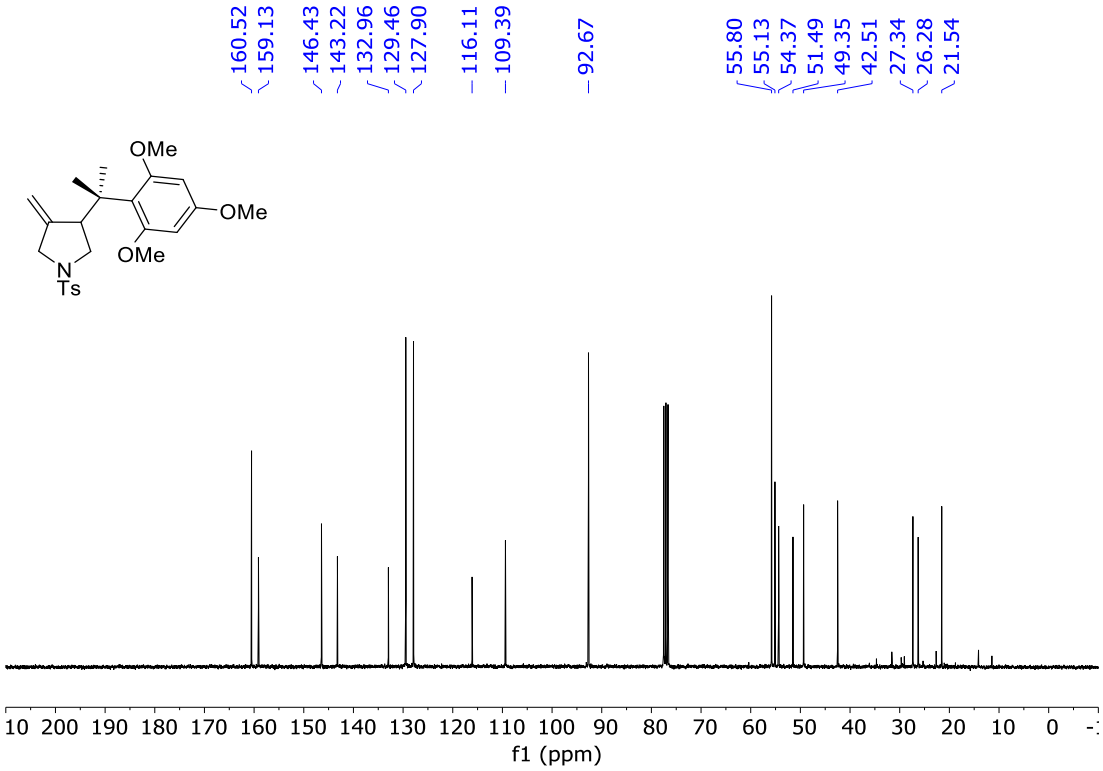
^{13}C NMR (75 MHz, $CDCl_3$, 300 K) spectrum of **3o**



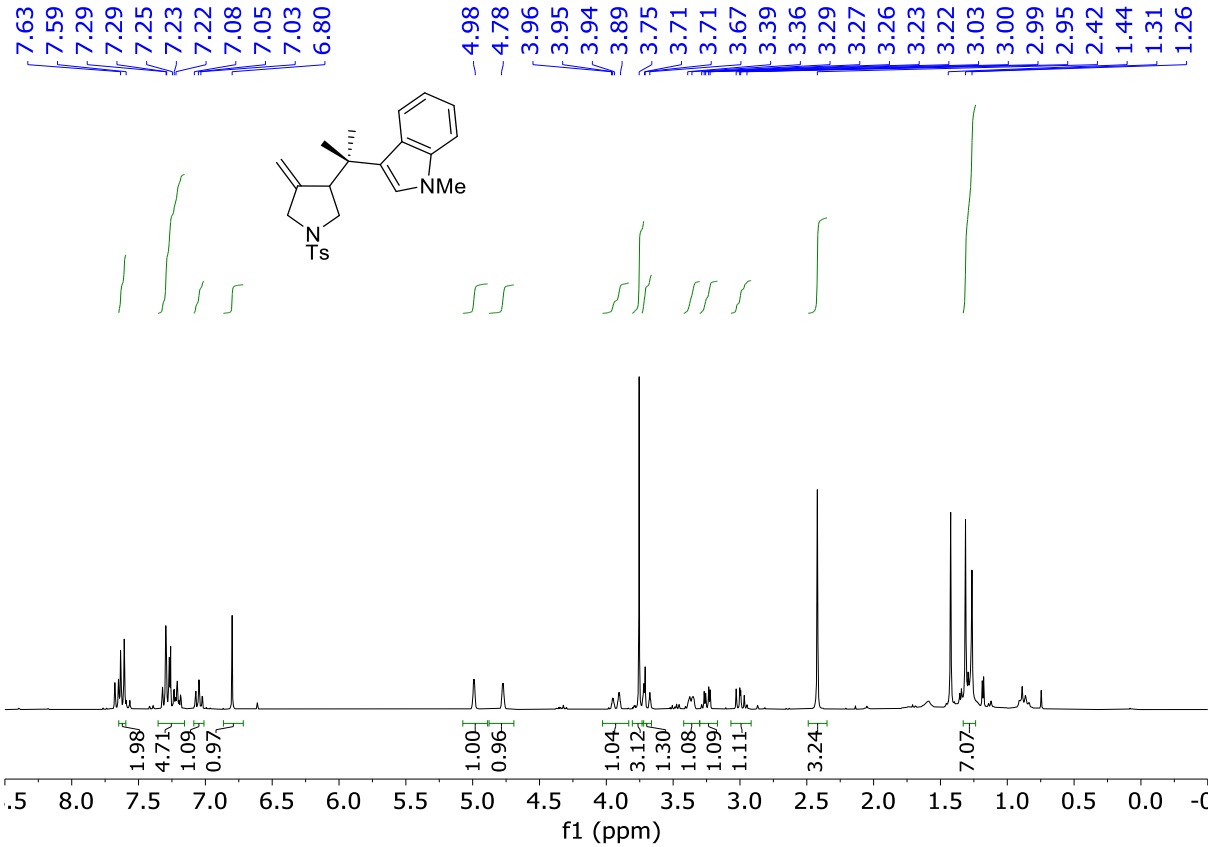
^{1}H NMR (300 MHz, $CDCl_3$, 300 K) spectrum of **3p**



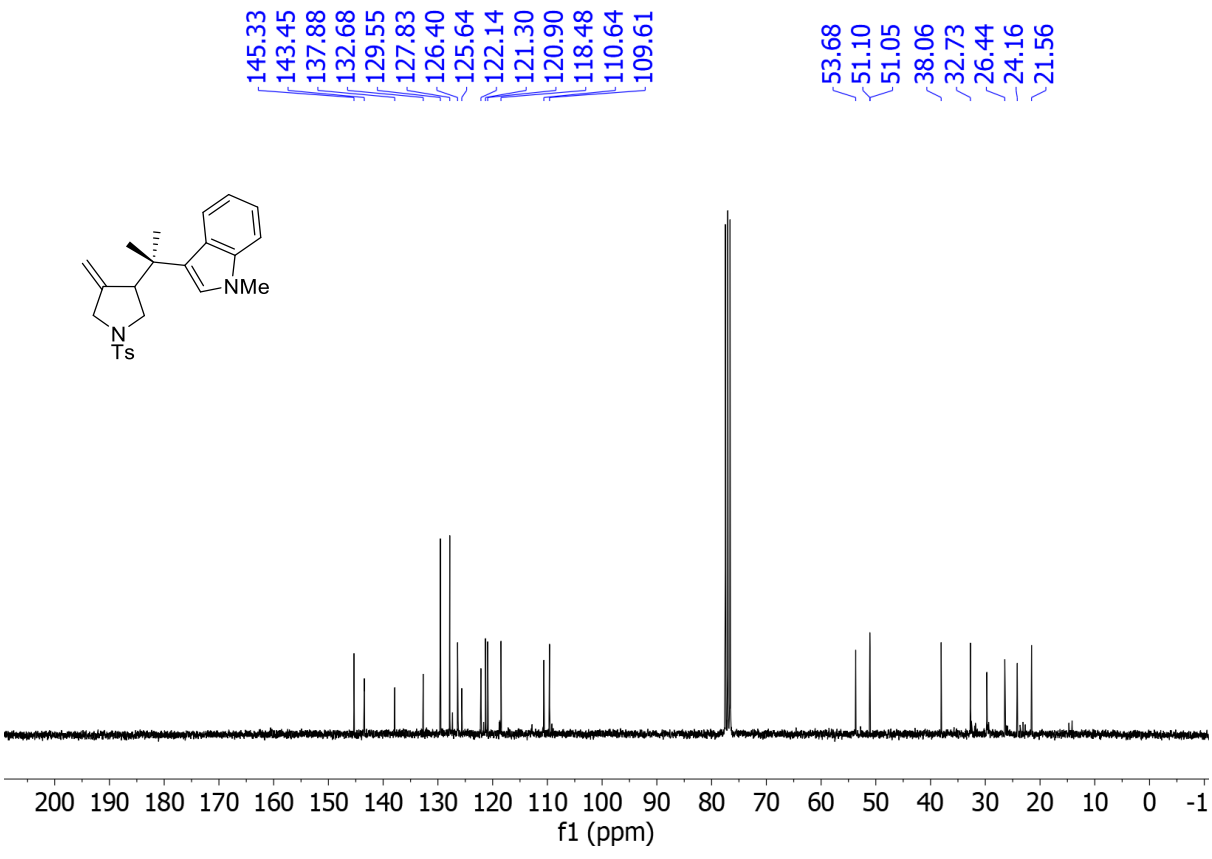
^{13}C NMR (75 MHz, $CDCl_3$, 300 K) spectrum of **3p**



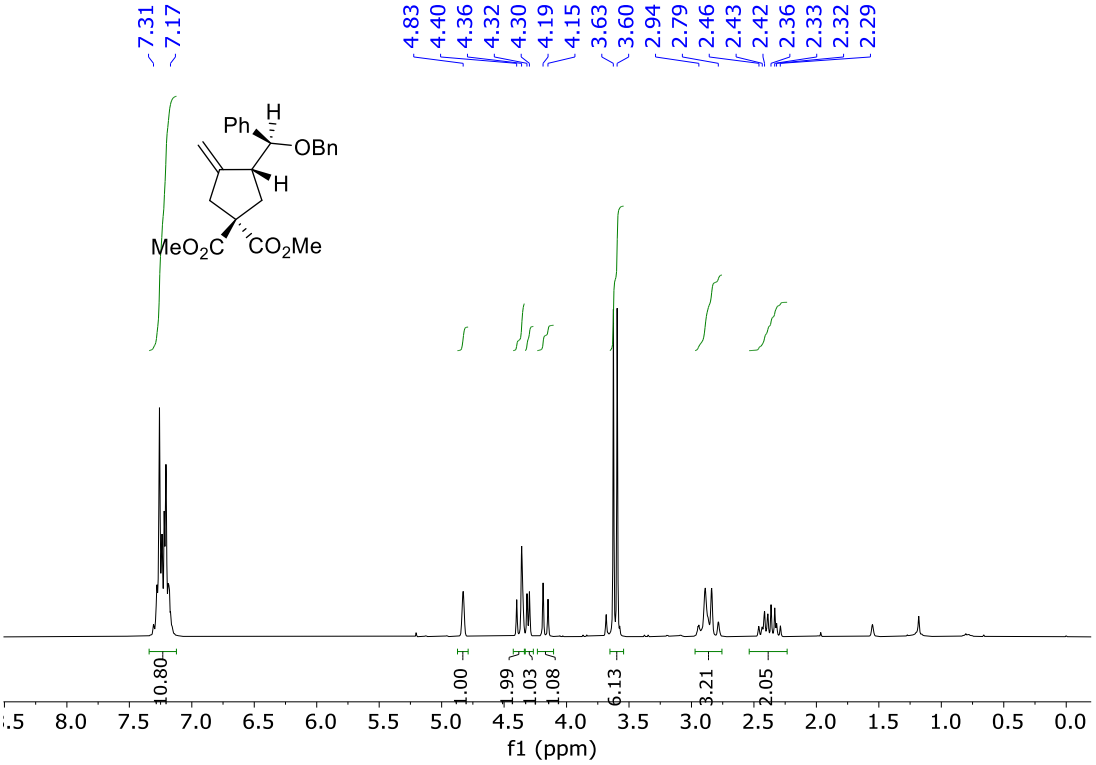
^{1}H NMR (300 MHz, $CDCl_3$, 300 K) spectrum of **3q**



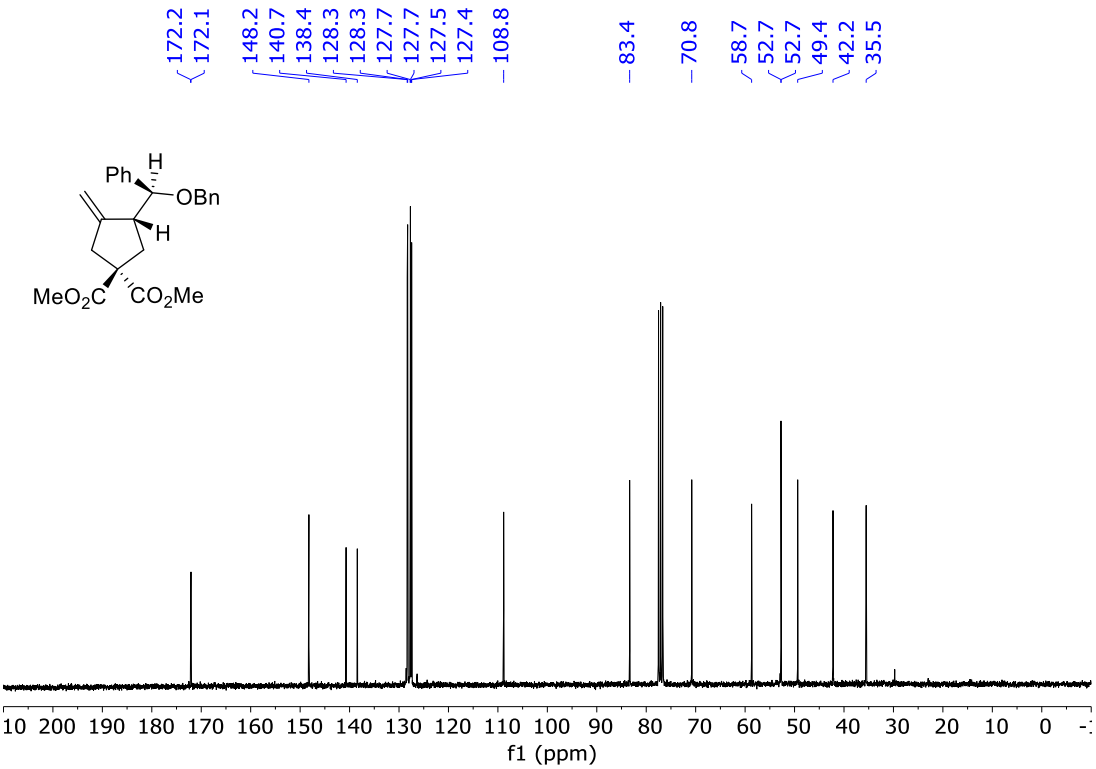
^{13}C NMR (75 MHz, $CDCl_3$, 300 K) spectrum of **3q**



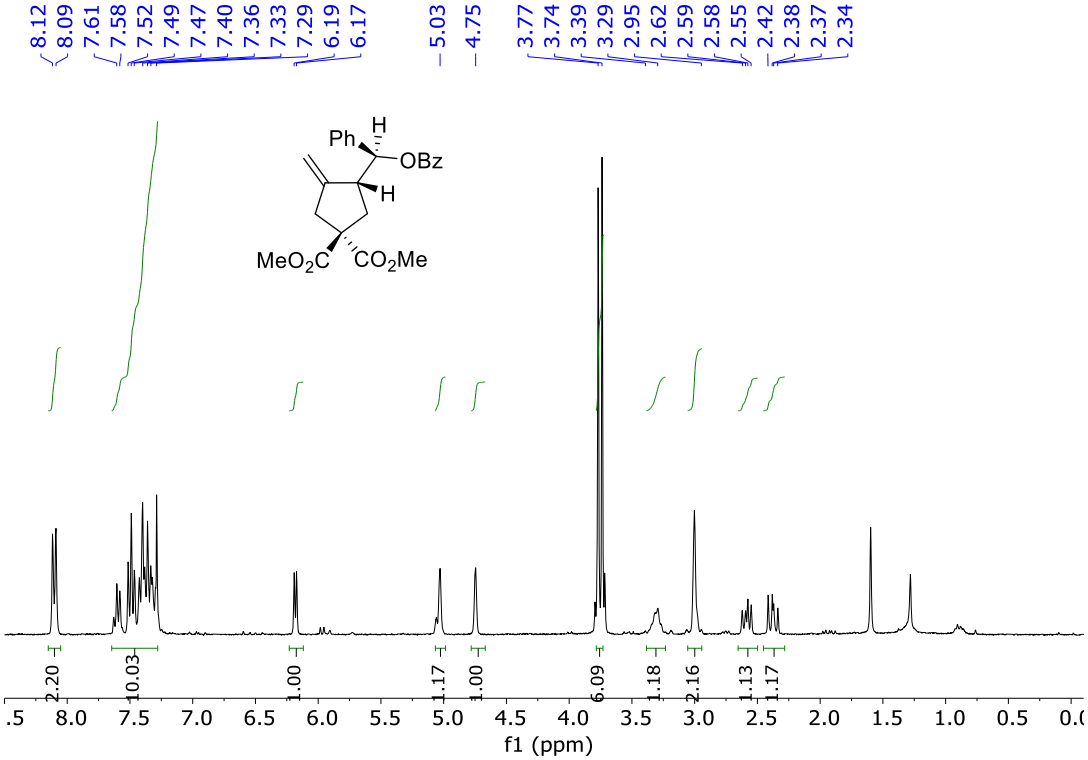
^{1}H NMR (300 MHz, $CDCl_3$, 300 K) spectrum of **5a**



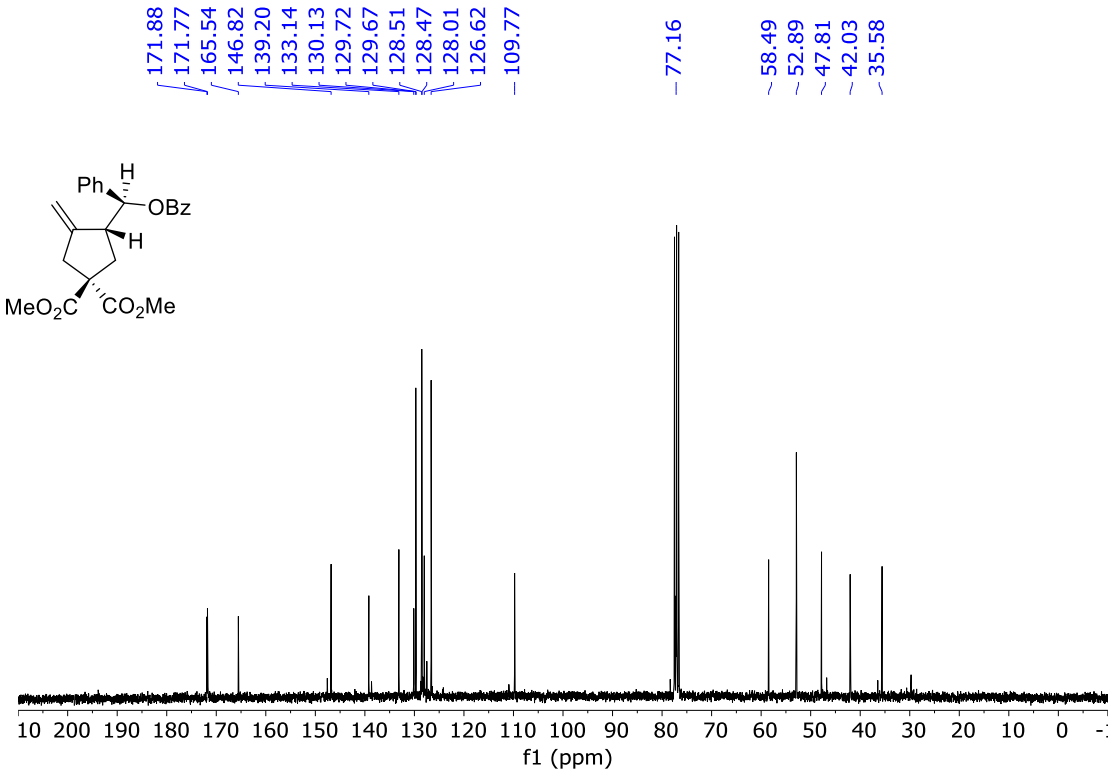
^{13}C NMR (75 MHz, $CDCl_3$, 300 K) spectrum of **5a**



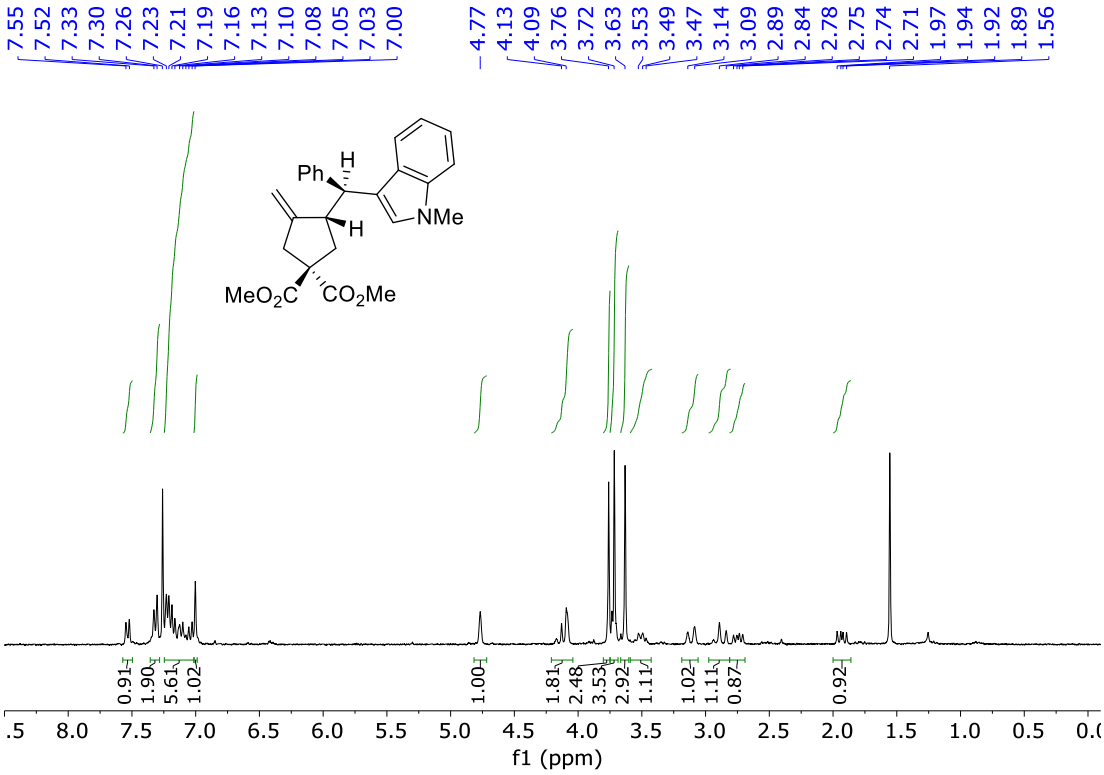
^{1}H NMR (300 MHz, $CDCl_3$, 300 K) spectrum of **5b**



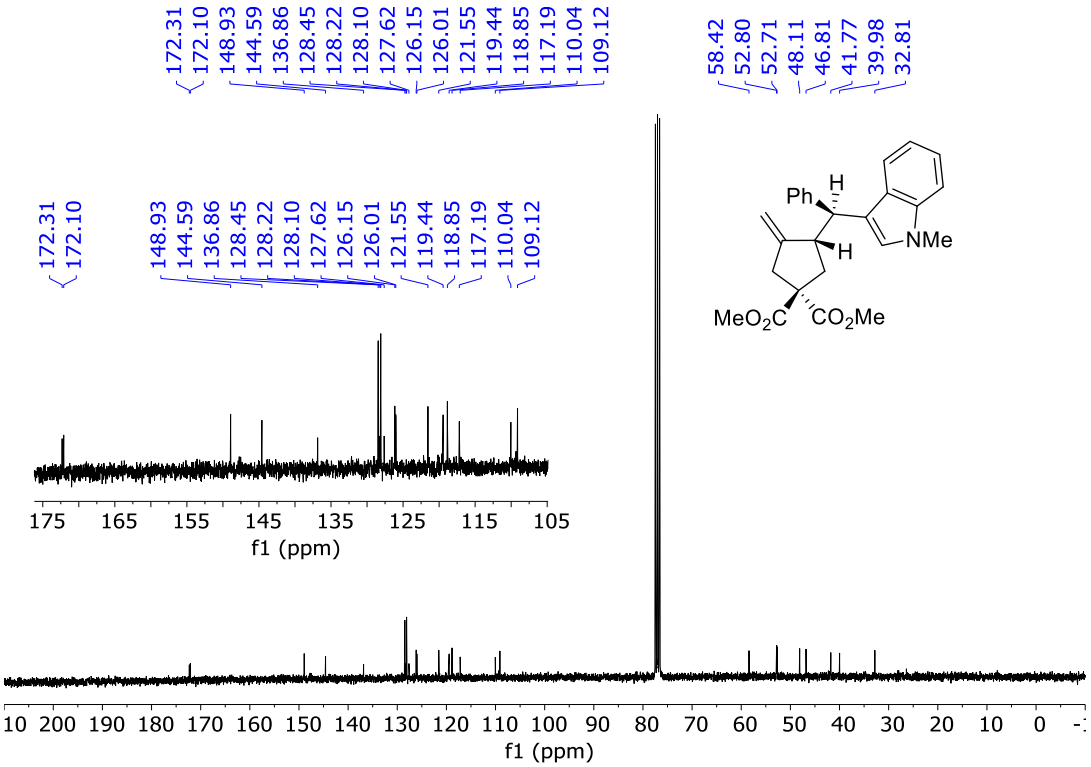
^{13}C NMR (75 MHz, $CDCl_3$, 300 K) spectrum of **5b**



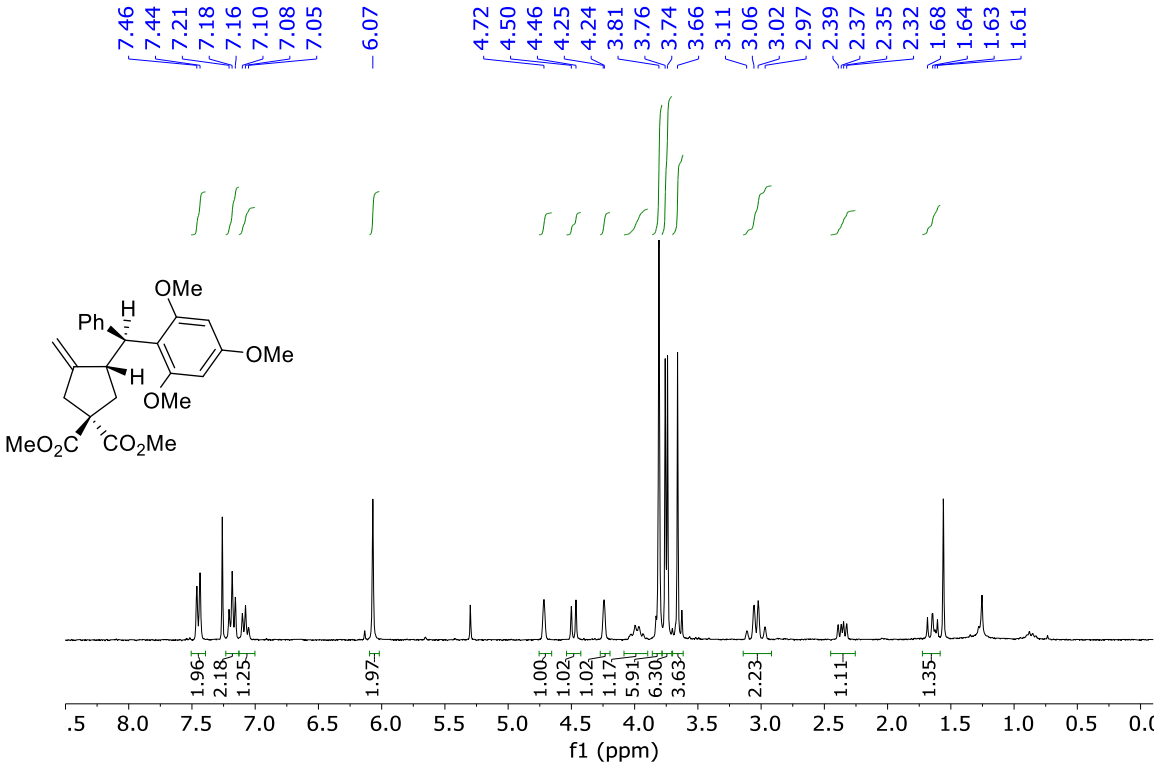
^{1}H NMR (300 MHz, $CDCl_3$, 300 K) spectrum of **5c**



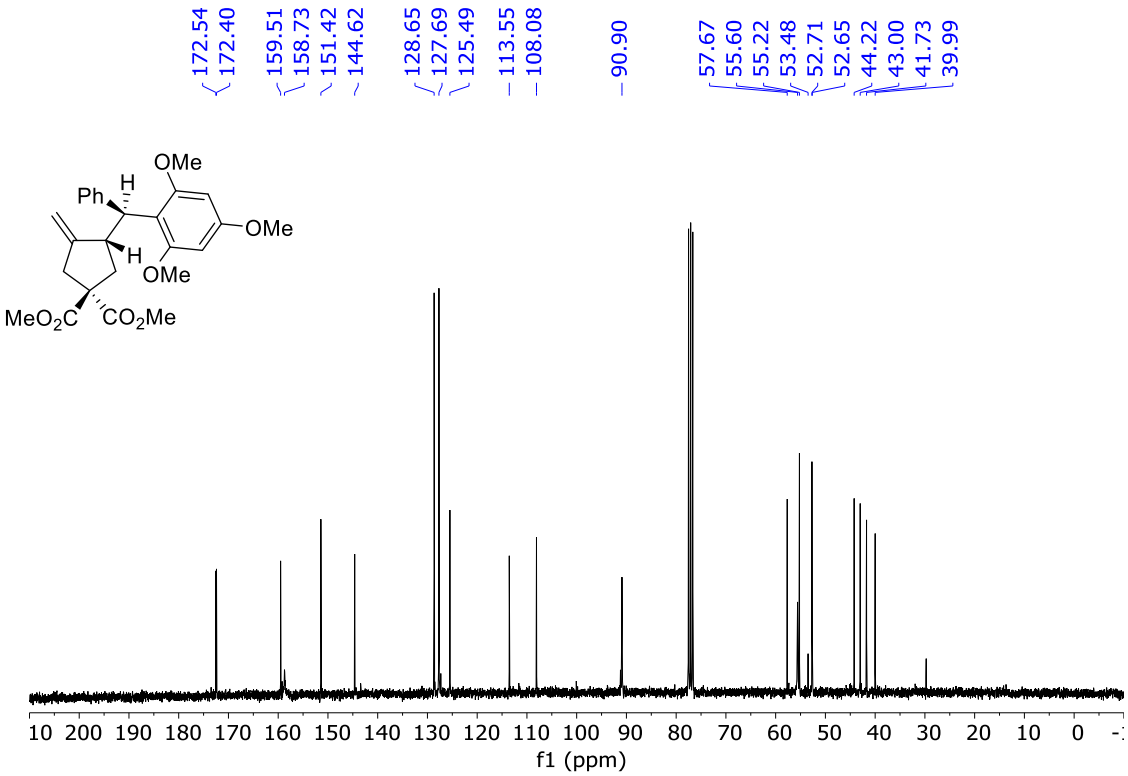
^{13}C NMR (75 MHz, $CDCl_3$, 300 K) spectrum of **5c**



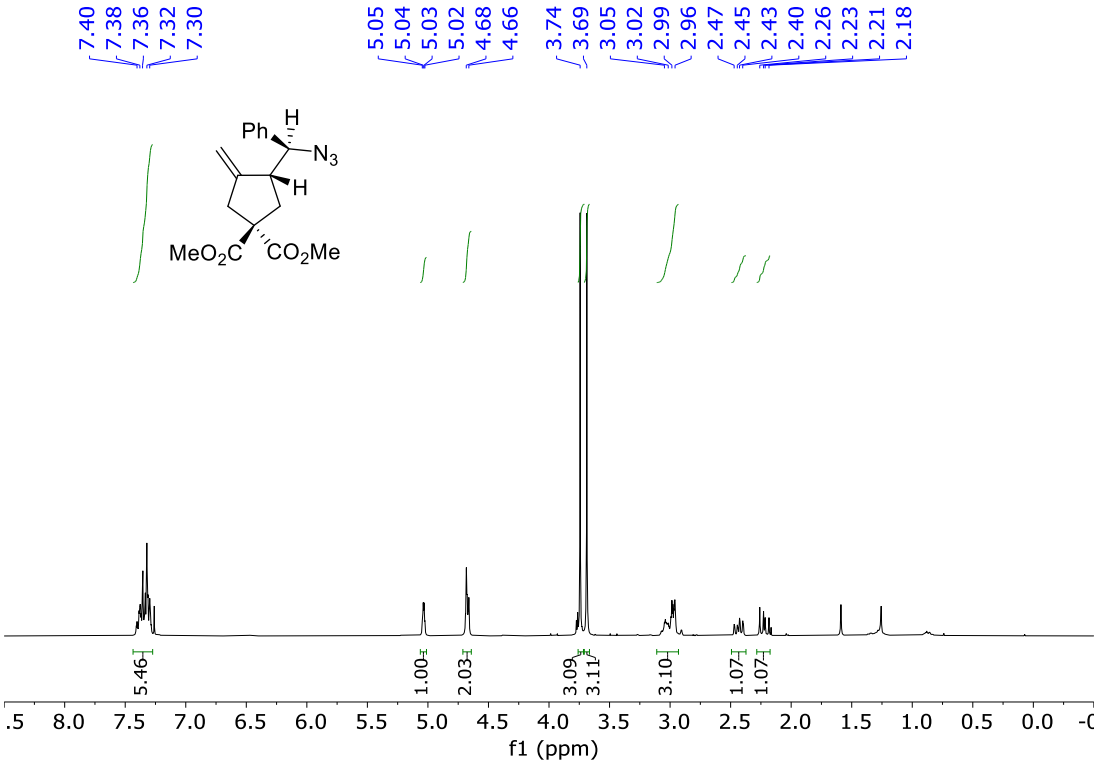
^{1}H NMR (300 MHz, $CDCl_3$, 300 K) spectrum of **5d**



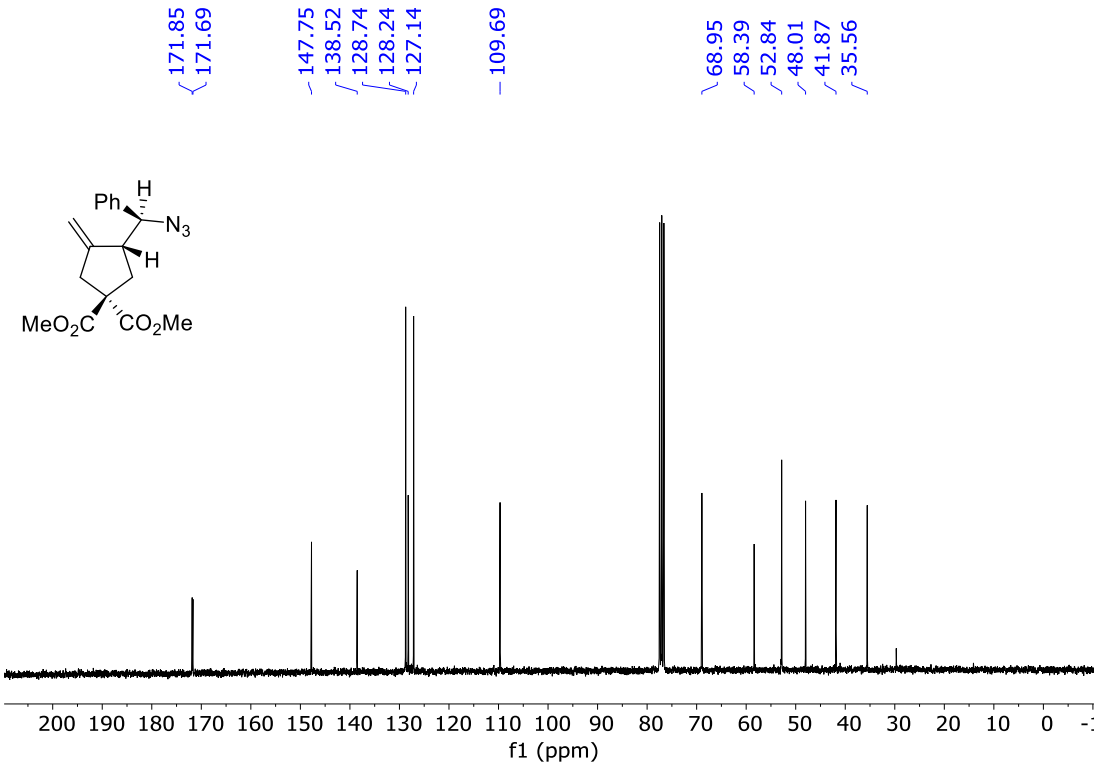
^{13}C NMR (75 MHz, $CDCl_3$, 300 K) spectrum of **5d**



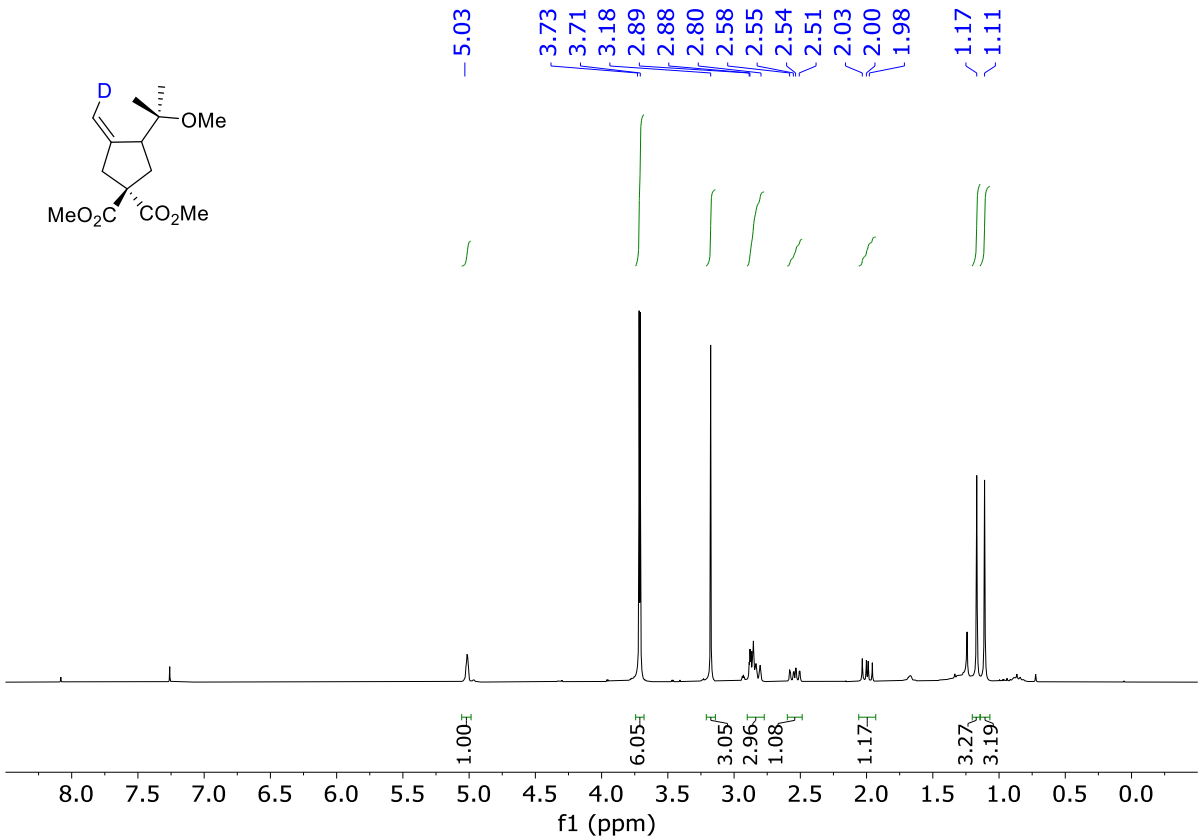
^{1}H NMR (300 MHz, $CDCl_3$, 300 K) spectrum of **5e**



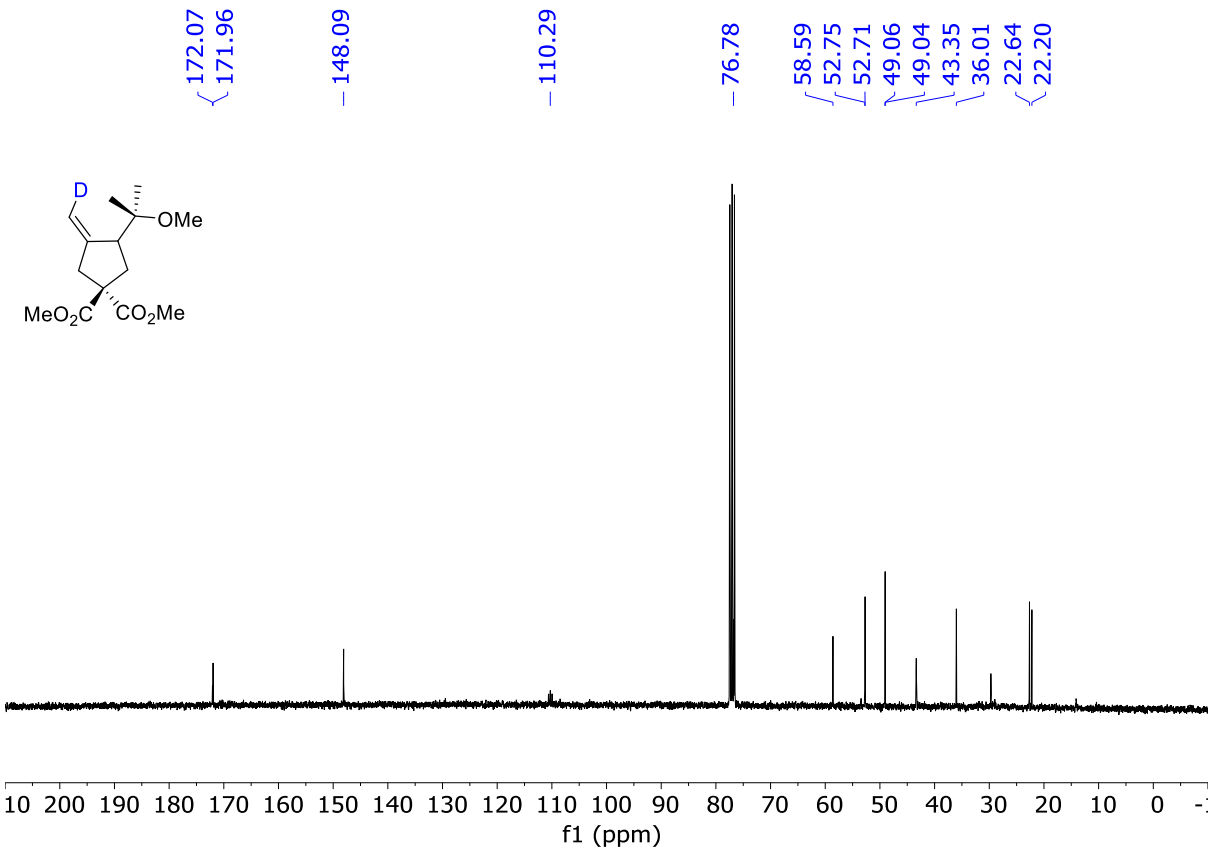
^{13}C NMR (75 MHz, $CDCl_3$, 300 K) spectrum of **5e**



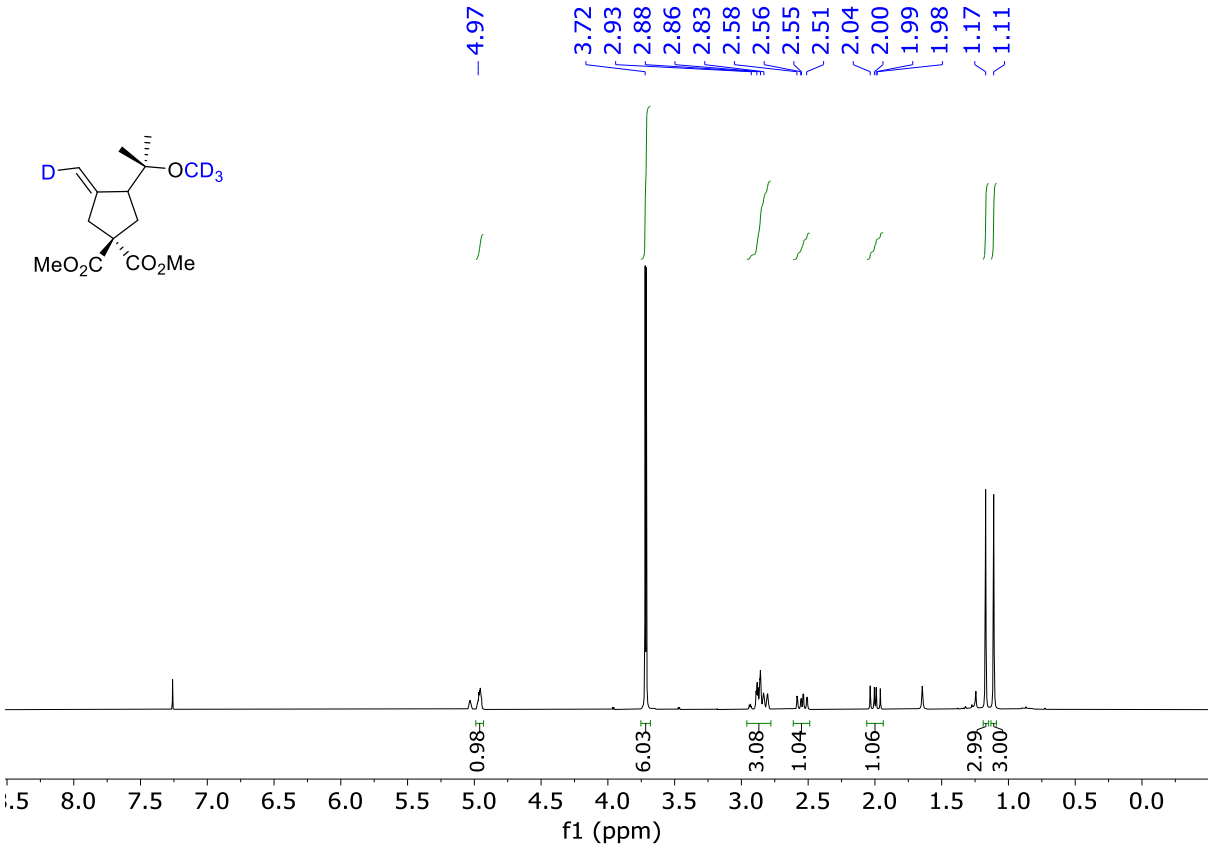
^{1}H NMR (300 MHz, $CDCl_3$, 300 K) spectrum of (*Z*)-**3a-d$_1$**



^{13}C NMR (75 MHz, $CDCl_3$, 300 K) spectrum of (*Z*)-**3a-d$_1$**



^{1}H NMR (300 MHz, $CDCl_3$, 300 K) spectrum of (*E*)-**3a-d$_4$**



^{13}C NMR (75 MHz, $CDCl_3$, 300 K) spectrum of (*E*)-**3a-d$_4$**