Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

A Simple Removable Aliphatic Nitrile (2-Cyano-2,2-Di-Isobutyl Acetic Acid) Template for Remote *meta*-Selective C−H Functionalization

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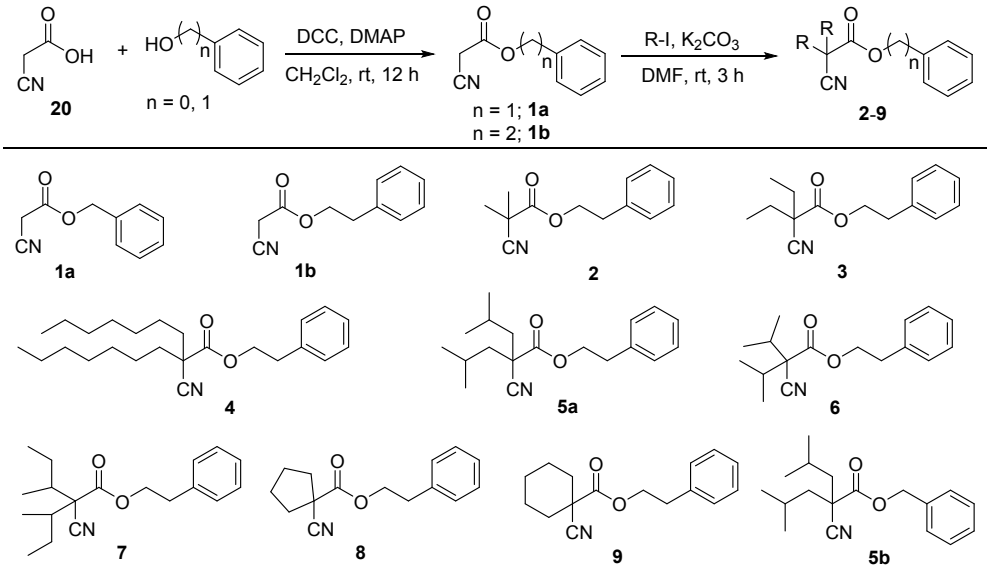
1. GENERAL INFORMATION:

IR spectra were recorded on a Bruker Tensor 37 (FTIR) spectrophotometer. ^{1}H NMR spectra were recorded on Bruker Avance 400 (400 MHz) spectrometer at 295 K in $CDCl_3$; chemical shifts (δ ppm) and coupling constants (Hz) are reported in standard fashion with reference to internal standard tetramethylsilane (TMS) (δ_H = 0.00 ppm). $^{13}C\{^{1}H\}$ NMR spectra were recorded on Bruker Avance 400 (100 MHz) spectrometer at RT in $CDCl_3$; chemical shifts (δ ppm) are reported relative to $CHCl_3$ [δ_C = 77.00 ppm (central line of the triplet)]. In the ^{1}H-NMR, the following abbreviations were used throughout: s = singlet, d = doublet, t = triplet, q = quartet, qui = quintet, sept = septet, dd = doublet of doublets, m = multiplet and br. s = broad singlet. The assignment of signals was confirmed by ^{1}H, $^{13}C\{^{1}H\}$, and DEPT spectra. High-resolution mass spectra (HR-MS) were recorded on an Agilent 6538 UHD Q-TOF electron spray ionization (ESI) mode and atmospheric pressure chemical ionization (APCI) modes. Unless otherwise stated, all small-scale reactions were carried out by using a Schlenk tube. Reactions were monitored by TLC on silica gel using a combination of hexane and ethyl acetate as eluents. Solvents were distilled prior to use; petroleum ether with a boiling range of 60 to 80 °C was used. $Pd(OAc)_2$, Ac-Gly-OH, AgOAc and 1,1,1,3,3,3-Hexafluoro-2-propanol (HFIP) were purchased from Sigma-Aldrich and used as received. Olefin coupling partners, DCC, DMF, DCM, K_2CO_3, LiOH and HCl were purchased from Sigma-Aldrich/TCI/local sources and used as received. Acme's silica gel (60–120 mesh) was used for column chromatography (approximately 20 g per one gram of crude material).

2. EXPERIMENTAL SECTION

2.1. Synthesis of substrates with different templates (1-9)

Table S1. Substrates with Different Templates



General Procedure:

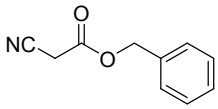
To a stirred solution of alcohol (3 mmol) and cyanoacetic acid **20** (3.6 mmol) in dry CH_2Cl_2 (20 mL) was added DCC (3.6 mmol) and DMAP (0.36 mmol) and under nitrogen at room temperature. After stirring for 12 h, the precipitate was filtered and washed with CH_2Cl_2. The filtrate was concentrated under vacuum and the crude product was purified by flash column chromatography using hexanes/EtOAc as the eluent to yield the ester **1**.

To a stirred soulition of cyanoester **1** (2 mmol) and potassium carbonate (4 mmol) in DMF (20 mL) was added alkyl iodide (4.8 mmol) slowly by a syringe at 0 ^oC. The resulting mixture was stirred at room temperature for 3 h. The reaction mixture was quenched by addition of water (15 mL), extracted with methyl *tert*-butyl ether (3 x 15 mL), and dried over anhydrous $MgSO_4$. Evaporation of the solvent under vacuum and pudification by flash column chromotagraphy hexanes/EtOAc as the eluent furnished pure dialkylated products (**2-7**).

To a stirred soulition of cyanoester **1** (2 mmol) and potassium carbonate (4 mmol) in DMF (20 mL) was added alkyl iodide (2.4 mmol) slowly by a syringe at 0 ^oC. The resulting mixture was stirred at room temperature for 3 h. The reaction mixture was quenched by addition of water (15 mL), extracted with methyl *tert*-butyl ether (3 x 15 mL), and dried over anhydrous $MgSO_4$. Evaporation of the solvent under vacuum and pudification by flash column chromotagraphy hexanes/EtOAc as the eluent furnished pure dialkylated products (**8**, **9**).

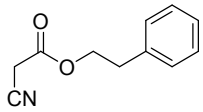
Spectral data of compounds:

Benzyl 2-cyanoacetate (**1a**):



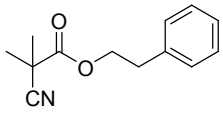
Yield: 76% (399 mg). Physical aspect: colourless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–30 (m, 5H), 5.22 (s, 2H), 3.47 (s, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.8, 134.3, 128.8, 128.7 (2C), 128.5 (2C), 112.8, 68.4, 24.7 ppm. HRMS (ESI) calculated $[M+NH_4]^+$ for $C_{10}H_{13}N_2O_2$: 193.0972, found: 193.0977.

Phenethyl 2-cyanoacetate (**1b**):



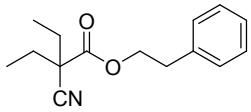
Yield: 81% (459 mg). Physical aspect: colourless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.30 (m, 2H), 7.28–7.20 (m, 3H), 4.41 (t, J = 7.0 Hz, 2H), 3.41 (s, 2H), 2.99 (t, J = 7.0 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.78, 136.80, 128.85 (2C), 128.61 (2C), 126.84, 112.88, 67.17, 34.72, 24.61 ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{11}H_{12}NO_2$: 190.0863, found: 190.0867.

Phenethyl 2-cyano-2-methylpropanoate (**2**):



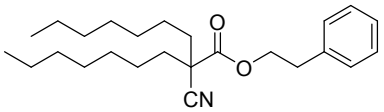
Yield: 93% (404 mg). Physical aspect: colourless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.17 (m, 5H), 4.41 (t, J = 6.9 Hz, 2H), 3.00 (t, J = 6.9 Hz, 2H), 1.54 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.5, 136.9, 128.9 (2C), 128.5 (2C), 126.8, 120.6, 66.9, 38.6, 34.8, 24.7 (2C) ppm. HRMS (ESI) calculated $[M+NH_4]^+$ for $C_{13}H_{19}N_2O_2$: 235.1441, found: 235.1444.

Phenethyl 2-cyano-2-ethylbutanoate (**3**):



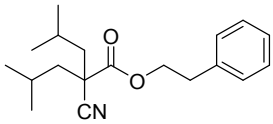
Yield: 92% (451 mg). Physical aspect: colourless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.17 (m, 5H), 4.42 (t, J = 6.9 Hz, 2H), 3.00 (t, J = 6.9 Hz, 2H), 1.94–1.73 (m, 4H), 0.96 (t, J = 7.4 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.0, 137.0, 128.9 (2C), 128.5 (2C), 126.7, 119.0, 66.7, 51.6, 34.9, 30.4 (2C), 9.6 (2C) ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{15}H_{20}NO_2$: 246.1489, found: 246.1493.

Phenethyl 2-cyano-2-heptylnonanoate (**4**):



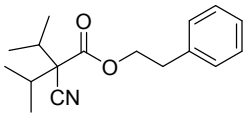
Yield: 87% (670 mg). Physical aspect: colourless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.18 (m, 5H), 4.41 (t, J = 6.8 Hz, 2H), 3.00 (t, J = 6.8 Hz, 2H), 1.84–1.64 (m, 4H), 1.53–1.40 (m, 2H), 1.30–1.15 (m, 18H), 0.88 (t, J = 7.0 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.26, 137.08, 128.92 (2C), 128.53 (2C), 126.75, 119.34, 66.68, 50.06, 37.47 (2C), 34.86, 31.61 (2C), 29.15 (2C), 28.81 (2C), 25.31 (2C), 22.52 (2C), 13.97 (2C) ppm. HRMS (ESI) calculated $[M+NH_4]^+$ for $C_{25}H_{43}N_2O_2$: 403.3319, found: 403.3321.

Phenethyl 2-cyano-2-isobutyl-4-methylpentanoate (**5a**):



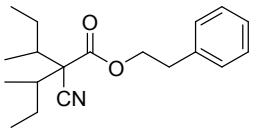
Yield: 94% (566 mg). Physical aspect: colourless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.19 (m, 5H), 4.38 (t, J = 6.9 Hz, 2H), 3.01 (t, J = 6.8 Hz, 2H), 1.82–1.60 (m, 6H), 0.98 (d, J = 6.5 Hz, 6H), 0.78 (d, J = 6.4 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.90, 137.11, 128.97 (2C), 128.56 (2C), 126.77, 119.52, 66.91, 47.77, 47.37 (2C), 34.73, 25.94 (2C), 23.31 (2C), 22.47 (2C) ppm. HRMS (ESI) calculated $[M+NH_4]^+$ for $C_{19}H_{31}N_2O_2$: 319.2380, found: 319.2384.

Phenethyl 2-cyano-2-isopropyl-3-methylbutanoate (**6**):



Yield: 81% (442 mg). Physical aspect: colourless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.20 (m, 5H), 4.40 (t, J = 6.9 Hz, 2H), 3.01 (t, J = 6.9 Hz, 2H), 2.32–2.19 (m, 2H), 1.03 (d, J = 6.8 Hz, 6H), 0.95 (d, J = 6.7 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.84, 137.09, 128.97 (2C), 128.53 (2C), 126.72, 118.53, 66.40, 59.98, 34.88, 32.30 (2C), 18.22 (2C), 17.64 (2C) ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{17}H_{24}NO_2$: 274.1802, found: 274.1806.

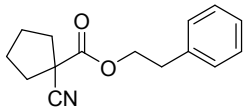
Phenethyl 2-(sec-butyl)-2-cyano-3-methylpentanoate (**7**):



Yield: 77% (463 mg). Physical aspect: colourless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.20 (m, 5H), 4.42–4.34 (m, 2H), 3.00 (t, J = 6.8 Hz, 2H), 2.04–1.87 (m, 2H), 1.77–1.63 (m, 1H), 1.45–1.29 (m,

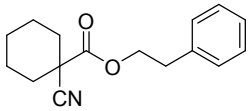
1H), 1.28–1.12 (m, 2H), 1.01–0.98 (m, 3H), 0.94–0.85 (m, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.12, 168.05, 137.11, 137.09, 128.95, 128.94, 128.47, 126.66, 118.98, 118.80, 77.32, 77.00, 76.68, 66.35, 66.33, 60.33, 59.91, 59.64, 39.25, 38.59, 38.52, 38.15, 34.82, 34.80, 25.39, 25.29, 24.67, 24.43, 14.28, 13.63, 13.54, 12.75, 12.09, 12.07, 11.98, 11.91 ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{19}H_{28}NO_2$: 302.2115, found: 302.2119.

Phenethyl 1-cyanocyclopentane-1-carboxylate (**8**):



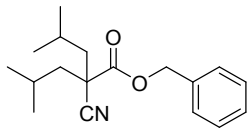
Yield: 84% (243 mg). Physical aspect: colourless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.20 (m, 5H), 4.40 (t, J = 6.9 Hz, 2H), 2.99 (t, J = 6.9 Hz, 2H), 2.24–2.11 (m, 4H), 1.88–1.77 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.40, 136.95, 128.86 (2C), 128.43 (2C), 126.64, 120.76, 66.76, 47.41, 37.54 (2C), 34.75, 24.97 (2C) ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{15}H_{18}NO_2$: 244.1332, found: 244.1335.

Phenethyl 1-cyanocyclohexane-1-carboxylate (**9**):



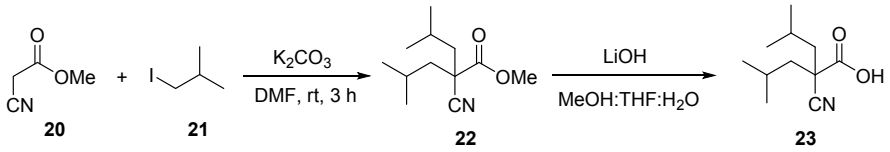
Yield: 86% (442 mg). Physical aspect: colourless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.18 (m, 5H), 4.39 (t, J = 6.9 Hz, 2H), 2.98 (t, J = 6.9 Hz, 2H), 2.01 (d, J = 13.2 Hz, 2H), 1.76–1.59 (m, 7H), 1.29–1.15 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.02, 136.91, 128.81 (2C), 128.37 (2C), 126.58, 118.91, 66.57, 45.20, 34.69, 32.65 (2C), 24.40, 22.01 (2C) ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{16}H_{20}NO_2$: 258.1489, found: 258.1491.

Benzyl 2-cyano-2-isobutyl-4-methylpentanoate (**5b**):

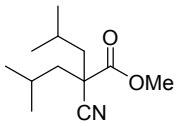


Yield: 93% (534 mg). Physical aspect: colourless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49–7.28 (m, 5H), 5.22 (s, 2H), 1.89–1.74 (m, 4H), 1.71–1.62 (m, 2H), 1.00 (d, J = 6.5 Hz, 6H), 0.81 (d, J = 6.4 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.71, 134.42, 128.63, 128.58 (2C), 128.53 (2C), 119.48, 68.04, 47.75, 47.39 (2C), 25.91 (2C), 23.27 (2C), 22.47 (2C) ppm. HRMS (ESI) calculated $[M+NH_4]^+$ for $C_{18}H_{29}N_2O_2$: 305.2224, found: 305.2227.

2.2. Multi-gram scale synthesis of aliphatic template (23):

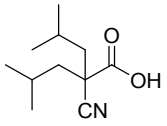


*Synthesis of methyl 2-cyano-2-isobutyl-4-methylpentanoate (**22**):*



To a stirred soulition of methyl cyanoacetate **20** (19.8 g, 200 mmol) and potassium carbonate (55.2 g, 400 mmol) in DMF (300 mL) was added alkyl iodide **21** (88.32 g, 480 mmol) slowly by a syringe at 0 ^{o}C. The resulting mixture was stirred at room temperature for 5 h. The reaction mixture was quenched by addition of water (200 mL), extracted with methyl *tert*-butyl ether (3 x 200 mL), and dried over anhydrous $MgSO_4$. Evaporation of the solvent under vacuum furnished dialkylated product **22** as colourless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.76 (s, 3H), 1.87–1.75 (m, 4H), 1.68–1.61 (m, 2H), 0.99 (d, J = 6.2 Hz, 6H), 0.83 (d, J = 6.1 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.43, 119.53, 53.05, 47.61, 47.39 (2C), 25.95 (2C), 23.33 (2C), 22.32 (2C) ppm. HRMS (ESI) calculated $[M+NH_4]^+$ for $C_{12}H_{25}N_2O_2$: 229.1911, found: 229.1910.

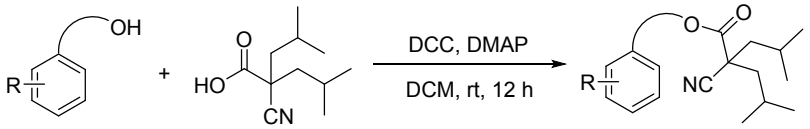
*Synthesis of 2-cyano-2-isobutyl-4-methylpentanoic acid (**23**):*



To a stirred solution of the above dialkylated ester **22** in MeOH/THF/H_2O (1.5:1:0.5) (500 mL) was added LiOH·H_2O (25.2 g, 600 mol) at room temperature and stirred the reaction mixture for 24 h at the same temperature. The organic solvents were removed under reduced pressure, and the resulting residue was diluted with H_2O and Et_2O. After removing the organic layer, the aqueous phase was acidified with 2M HCl to reach the pH=1, then extracted with EtOAc for three times. Organic exctracts were dried over Na_2SO_4, concentrated under rotavap to get the desired product **23** (37.4 g, 92% yield over two steps) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.29 (brs, 1H), 1.97–1.85 (m, 4H), 1.79–1.71 (m, 2H), 1.06 (d, J = 6.5 Hz, 6H), 0.94 (d, J = 6.4 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.23, 118.86, 48.00, 47.19 (2C), 26.07 (2C), 23.36 (2C), 22.47 (2C) ppm. HRMS (ESI) calculated $[M+NH_4]^+$ for $C_{11}H_{23}N_2O_2$: 215.1754, found: 215.1757.

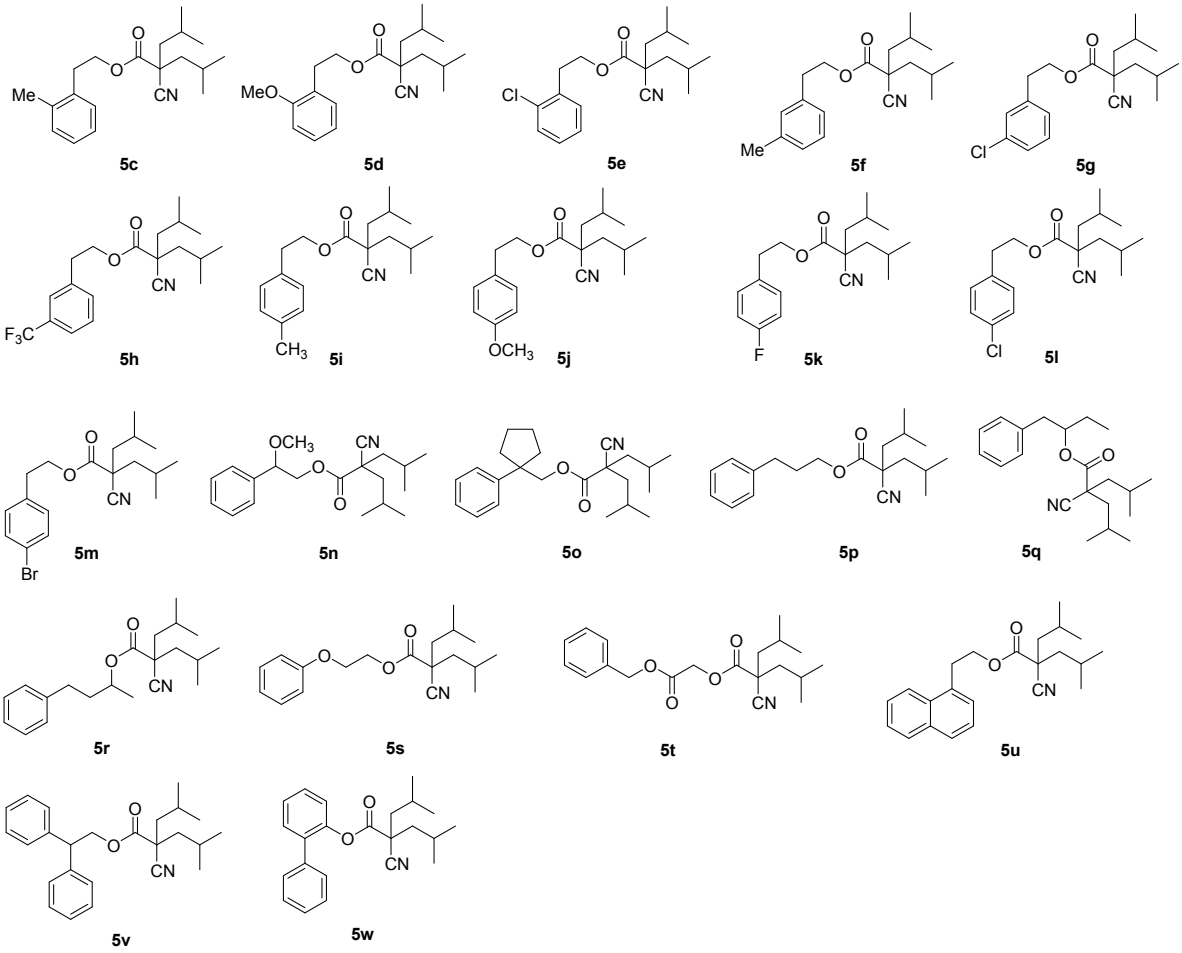
2.3. Synthesis of starting materials:

General procedure for preparation of starting materials:

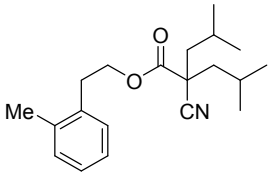


To a stirred solution of alcohol (0.5 mmol) and acid template (0.55 mmol) in dry CH_2Cl_2 (5 mL) was added DCC (0.6 mmol) and DMAP (0.055 mmol) and under nitrogen at room temperature. After stirring for 12 h, the precipitate was filtered and washed with CH_2Cl_2. The filtrate was concentrated under vacuum and the crude product was purified by flash column chromatography using hexanes/EtOAc as the eluent to yield the corresponding ester template. The following substrates were prepared according to the above general procedure.

Table S2. Diffirent starting materials.

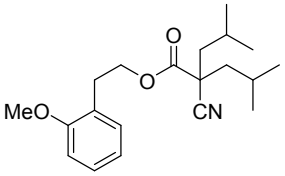


2-Methylphenethyl 2-cyano-2-isobutyl-4-methylpentanoate (**5c**):



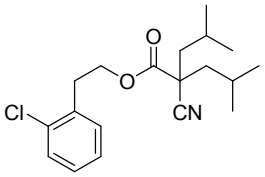
Yield: 85% (134 mg). Physical aspect: colourless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.2–7.11 (m, 4H), 4.34 (t, J = 7.2 Hz, 2H), 3.02 (t, J = 7.2 Hz, 2H), 2.36 (s, 3H), 1.84–1.72 (m, 4H), 1.69–1.60 (m, 2H), 0.99 (d, J = 6.4 Hz, 6H), 0.79 (d, J = 6.3 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.97, 136.27, 134.97, 130.34, 129.60, 126.90, 126.10, 119.49, 66.05, 47.69, 47.31(2C), 31.75, 25.90 (2C), 23.28 (2C), 22.35 (2C), 19.30 ppm. HRMS (ESI) calculated $[M+NH_4]^+$ for $C_{20}H_{33}N_2O_2$: 333.2537, found: 333.2536.

2-Methoxyphenethyl 2-cyano-2-isobutyl-4-methylpentanoate (**5d**):



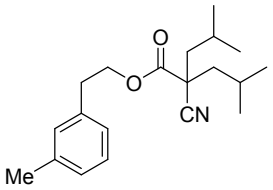
Yield: 79% (131 mg). Physical aspect: colourless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24–7.19 (m, 2H), 6.89 (td, J = 7.4, 1.0 Hz, 1H), 6.84 (d, J = 8.1 Hz, 1H), 4.36 (t, J = 6.9 Hz, 2H), 3.81 (s, 3H), 3.02 (t, J = 6.9 Hz, 2H), 1.81–1.73 (m, 4H), 1.66–1.59 (m, 2H), 0.98 (d, J = 6.4 Hz, 6H), 0.78 (d, J = 6.3 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.82, 157.43, 130.90, 128.05, 125.11, 120.35, 119.52, 110.11, 65.71, 55.09, 47.72, 47.22 (2C), 29.52, 25.84 (2C), 23.26 (2C), 22.30 (2C) ppm. HRMS (ESI) calculated $[M+NH_4]^+$ for $C_{20}H_{33}N_2O_3$: 349.2486, found: 349.2483.

2-Chlorophenethyl 2-cyano-2-isobutyl-4-methylpentanoate (**5e**):



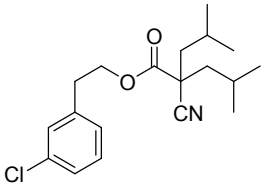
Yield: 95% (159 mg). Physical aspect: colourless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.29 (m, 2H), 7.24–7.16 (m, 2H), 4.40 (t, J = 6.7 Hz, 2H), 3.17 (t, J = 6.7 Hz, 2H), 1.82–1.72 (m, 4H), 1.67–1.60 (m, 2H), 0.97 (d, J = 6.5 Hz, 6H), 0.77 (d, J = 6.4 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.87, 134.71, 134.03, 131.57, 129.57, 128.38, 126.93, 119.48, 65.23, 47.74, 47.33 (2C), 32.41, 25.94 (2C), 23.32 (2C), 22.34 (2C) ppm. HRMS (ESI) calculated $[M+NH_4]^+$ for $C_{19}H_{30}ClN_2O_2$: 353.1990, found: 353.1994.

3-Methylphenethyl 2-cyano-2-isobutyl-4-methylpentanoate (**5f**):



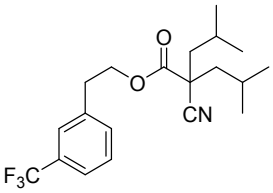
Yield: 82% (129 mg). Physical aspect: colourless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20 (t, J = 7.5 Hz, 1H), 7.11–7.01 (m, 3H), 4.36 (t, J = 6.9 Hz, 2H), 2.97 (t, J = 6.9 Hz, 2H), 2.33 (s, 3H), 1.83–1.72 (m, 4H), 1.68–1.59 (m, 2H), 0.98 (d, J = 6.5 Hz, 6H), 0.78 (d, J = 6.3 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.92, 138.15, 136.97, 129.80, 128.44, 127.47, 125.93, 119.57, 66.99, 47.71, 47.35 (2C), 34.60, 25.94 (2C), 23.30 (2C), 22.41 (2C), 21.28 ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{20}H_{30}NO_2$: 316.2271, found: 316.2273.

3-Chlorophenethyl 2-cyano-2-isobutyl-4-methylpentanoate (**5g**):



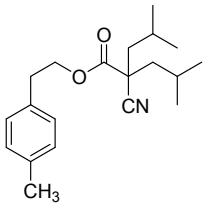
Yield: 93% (156 mg). Physical aspect: colourless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.21 (m, 3H), 7.19–7.13 (m, 1H), 4.37 (t, J = 6.7 Hz, 2H), 3.00 (t, J = 6.7 Hz, 2H), 1.82–1.72 (m, 4H), 1.69–1.61 (m, 2H), 0.98 (d, J = 6.5 Hz, 6H), 0.78 (d, J = 6.3 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.86, 139.17, 134.30, 129.82, 129.04, 127.23, 126.99, 119.42, 66.41, 47.67, 47.32 (2C), 34.28, 25.94 (2C), 23.26 (2C), 22.38 (2C) ppm. HRMS (ESI) calculated $[M+NH_4]^+$ for $C_{19}H_{30}ClN_2O_2$: 353.1990, found: 353.1995.

3-(Trifluoromethyl)phenethyl 2-cyano-2-isobutyl-4-methylpentanoate (**5h**):



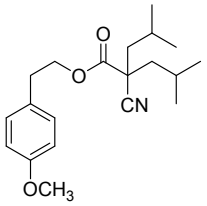
Yield: 82% (151 mg). Physical aspect: colourless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56–7.38 (m, 4H), 4.40 (t, J = 6.6 Hz, 2H), 3.09 (t, J = 6.6 Hz, 2H), 1.81–1.70 (m, 4H), 1.68–1.60 (m, 2H), 0.96 (d, J = 6.4 Hz, 6H), 0.75 (d, J = 6.3 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.89, 138.18, 132.57, 130.94 (q, $J_{C\text{-}F}$ = 31.8 Hz) 129.06, 125.57 (q, $J_{C\text{-}F}$ = 3.7 Hz), 124.01 (q, $J_{C\text{-}F}$ = 270.7 Hz), 123.71 (q, $J_{C\text{-}F}$ = 3.7 Hz), 119.36, 66.36, 47.66, 47.32 (2C), 34.42, 25.92 (2C), 23.22 (2C), 22.31 (2C) ppm. HRMS (ESI) calculated $[M+NH_4]^+$ for $C_{20}H_{30}F_3N_2O_2$: 387.2254, found: 387.2260.

4-Methylphenethyl 2-cyano-2-isobutyl-4-methylpentanoate (**5i**):



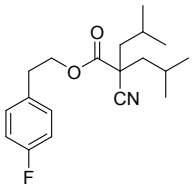
Yield: 83% (131 mg). Physical aspect: colourless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19 –7.07 (m, 4H), 4.35 (t, J = 6.9 Hz, 2H), 2.97 (t, J = 6.9 Hz, 2H), 2.32 (s, 3H), 1.82–1.72 (m, 4H), 1.67–1.59 (m, 2H), 0.98 (d, J = 6.5 Hz, 6H), 0.79 (d, J = 6.4 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.91, 136.28, 133.93, 129.22 (2C), 128.84 (2C), 119.58, 67.04, 47.73, 47.34 (2C), 34.27, 25.93 (2C), 23.29 (2C), 22.45 (2C), 20.97 ppm. HRMS (ESI) calculated $[M+NH_4]^+$ for $C_{20}H_{33}N_2O_2$: 333.2537, found: 333.2534.

4-methoxyphenethyl 2-cyano-2-isobutyl-4-methylpentanoate (**5j**)



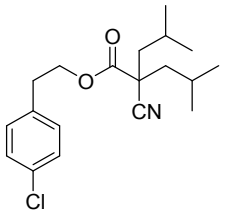
Yield: 73% (121 mg). Physical aspect: colourless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22–7.13 (m, 2H), 6.88–6.82 (m, 2H), 4.33 (t, J = 6.9 Hz, 2H), 3.78 (s, 3H), 2.95 (t, J = 6.9 Hz, 2H), 1.83–1.74 (m, 4H), 1.68–1.62 (m, 2H), 0.98 (d, J = 6.5 Hz, 6H), 0.79 (d, J = 6.3 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.90, 158.45, 129.95 (2C), 129.07, 119.57, 113.94 (2C), 67.12, 55.21, 47.68, 47.33 (2C), 33.80, 25.92 (2C), 23.28 (2C), 22.42 (2C). HRMS (ESI) calculated $[M+NH_4]^+$ for $C_{20}H_{33}N_2O_3$: 349.2486, found: 349.2496.

4-Fluorophenethyl 2-cyano-2-isobutyl-4-methylpentanoate (**5k**):



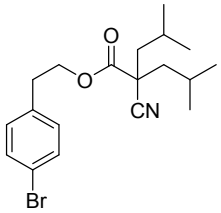
Yield: 88% (140 mg). Physical aspect: colourless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.18 (m, 2H), 7.00 (t, J = 8.7 Hz, 2H), 4.35 (t, J = 6.7 Hz, 2H), 2.99 (t, J = 6.7 Hz, 2H), 1.82–1.71 (m, 4H), 1.68–1.61 (m, 2H), 0.98 (d, J = 6.4 Hz, 6H), 0.77 (d, J = 6.3 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.86, 161.79 (d, $J_{C\text{-}F}$ = 243.3 Hz), 132.83 (d, $J_{C\text{-}F}$ = 3.3 Hz), 130.47 (2C, d, $J_{C\text{-}F}$ = 7.9 Hz), 119.45, 115.30 (2C, d, $J_{C\text{-}F}$ = 21.1 Hz), 66.81, 47.61, 47.32 (2C), 33.84, 25.90 (2C), 23.23 (2C), 22.35 (2C) ppm. HRMS (ESI) calculated $[M+Na]^+$ for $C_{19}H_{26}FNNaO_2$: 342.1840, found: 342.1859.

4-Chlorophenethyl 2-cyano-2-isobutyl-4-methylpentanoate (**5l**):



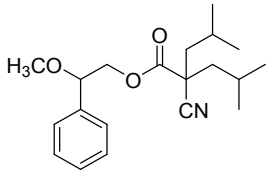
Yield: 92% (154 mg). Physical aspect: colourless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.26 (m, 2H), 7.23–7.18 (m, 2H), 4.35 (t, J = 6.6 Hz, 2H), 2.99 (t, J = 6.6 Hz, 2H), 1.81–1.69 (m, 4H), 1.67–1.61 (m, 2H), 0.98 (d, J = 6.5 Hz, 6H), 0.77 (d, J = 6.3 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.85, 135.60, 132.63, 130.35 (2C), 128.64 (2C), 119.44, 66.56, 47.59, 47.33 (2C), 34.01, 25.91 (2C), 23.24 (2C), 22.38 (2C) ppm. HRMS (ESI) calculated $[M+Na]^+$ for $C_{19}H_{26}ClNNaO_2$: 358.1544, found: 358.1548.

4-Bromophenethyl 2-cyano-2-isobutyl-4-methylpentanoate (**5m**):



Yield: 84% (159 mg). Physical aspect: colourless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.39 (m, 2H), 7.18–7.11 (m, 2H), 4.35 (t, J = 6.6 Hz, 2H), 2.96 (t, J = 6.6 Hz, 2H), 1.80–1.70 (m, 4H), 1.66–1.60 (m, 2H), 0.97 (d, J = 6.5 Hz, 6H), 0.77 (d, J = 6.4 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.67, 136.07, 131.47 (2C), 130.65 (2C), 120.53, 119.29, 66.34, 47.49, 47.19 (2C), 33.95, 25.79 (2C), 23.14 (2C), 22.30 (2C) ppm. HRMS (ESI) calculated $[M+NH_4]^+$ for $C_{19}H_{30}{}^{79}BrN_2O_2$: 397.1485, found: 397.1492; $C_{19}H_{30}{}^{81}BrN_2O_2$: 399.1465, found: 399.1474.

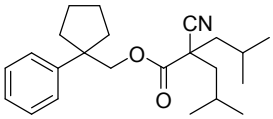
2-Methoxy-2-phenylethyl 2-cyano-2-isobutyl-4-methylpentanoate (**5n**):



Yield: 82% (136 mg). Physical aspect: colourless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.31 (m, 5H), 4.49 (dd, J = 7.9, 4.0 Hz, 1H), 4.36 (dd, J = 11.4, 7.9 Hz, 1H), 4.20 (dd, J = 11.4, 4.0 Hz, 1H), 3.28 (s, 3H), 1.88–1.76 (m, 4H), 1.70–1.63 (m, 2H), 1.03 (d, J = 6.4 Hz, 3H), 1.00 (d, J = 6.5 Hz, 3H), 0.86 (d, J = 6.2 Hz, 3H), 0.81 (d, J = 6.4 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.72, 137.40, 128.62

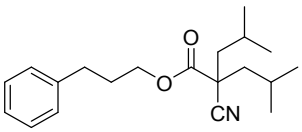
(2C), 128.45, 126.97 (2C), 119.51, 81.01, 69.19, 56.87, 47.74, 47.35 (2C), 25.91, 25.89, 23.25, 23.21, 22.55, 22.39 ppm. HRMS (ESI) calculated $[M+NH_4]^+$ for $C_{20}H_{33}N_2O_3$: 349.2486, found: 349.2491.

(1-Phenylcyclopentyl)methyl 2-cyano-2-isobutyl-4-methylpentanoate (**5o**):



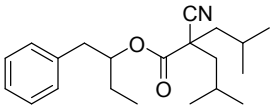
Yield: 87% (154 mg). Physical aspect: colourless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.32 (m, 2H), 7.32–7.24 (m, 2H), 7.21–7.14 (m, 1H), 4.08 (s, 2H), 2.16–1.92 (m, 4H), 1.80–1.71 (m, 4H), 1.71–1.52 (m, 6H), 0.90 (d, J = 6.4 Hz, 6H), 0.64 (d, J = 6.3 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.59, 145.61, 127.92 (2C), 126.99 (2C), 126.08, 119.14, 72.95, 50.36, 47.64, 47.13 (2C), 34.57 (2C), 25.70 (2C), 23.30 (2C), 23.08 (2C), 21.97 (2C) ppm. HRMS (ESI) calculated $[M+NH_4]^+$ for $C_{23}H_{37}N_2O_2$: 373.2850, found: 373.2851.

3-Phenylpropyl 2-cyano-2-isobutyl-4-methylpentanoate (**5p**):



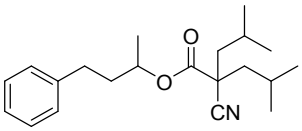
Yield: 90% (142 mg). Physical aspect: colourless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.25 (m, 2H), 7.22–7.17 (m, 3H), 4.18 (t, J = 6.5 Hz, 2H), 2.77–2.71 (m, 2H), 2.07–1.97 (m, 2H), 1.93–1.81 (m, 4H), 1.72–1.64 (m, 2H), 1.05 (d, J = 6.3 Hz, 6H), 0.89 (d, J = 6.2 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.80, 140.52, 128.39 (2C), 128.29 (2C), 126.04, 119.51, 65.52, 47.58, 47.29 (2C), 31.84, 29.75, 25.93 (2C), 23.23 (2C), 22.50 (2C) ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{20}H_{30}NO_2$: 316.2271, found: 316.2274.

1-Phenylbutan-2-yl 2-cyano-2-isobutyl-4-methylpentanoate (**5q**):



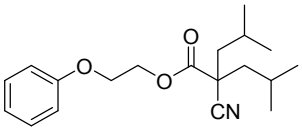
Yield: 84% (138 mg). Physical aspect: colourless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.19 (m, 5H), 5.04 (dq, J = 7.5, 5.9 Hz, 1H), 2.98 (dd, J = 13.8, 7.7 Hz, 1H), 2.86 (dd, J = 13.8, 5.9 Hz, 1H), 1.82–1.55 (m, 8H), 1.04–0.97 (m, 6H), 0.94 (d, J = 6.4 Hz, 3H), 0.85 (d, J = 6.3 Hz, 3H), 0.71 (d, J = 6.5 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.52, 137.06, 129.43 (2C), 128.45 (2C), 126.60, 119.72, 79.38, 47.62, 47.07, 46.96, 39.30, 26.03, 25.93, 25.74, 23.32, 23.16, 22.92, 22.89, 9.31 ppm. HRMS (ESI) calculated $[M+NH_4]^+$ for $C_{21}H_{35}N_2O_2$: 347.2693, found: 347.2695.

4-Phenylbutan-2-yl 2-cyano-2-isobutyl-4-methylpentanoate (**5r**):



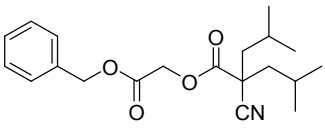
Yield: 85% (140 mg). Physical aspect: colourless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.24 (m, 2H), 7.24–7.14 (m, 3H), 5.01 (dq, J = 12.5, 6.3 Hz, 1H), 2.78–2.61 (m, 2H), 2.05–1.99 (m, 1H), 1.95–1.80 (m, 5H), 1.72–1.62 (m, 2H), 1.33 (d, J = 6.3 Hz, 3H), 1.07 (dd, J = 6.4, 4.1 Hz, 6H), 0.92 (dd, J = 6.3, 1.1 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.43, 141.06, 128.48 (2C), 128.24 (2C), 126.06, 119.77, 73.65, 47.67, 47.42, 47.23, 37.28, 31.48, 26.05, 25.99, 23.27, 23.16, 22.96, 22.92, 19.44 ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{21}H_{32}NO_2$: 330.2428, found: 330.2429.

2-Phenoxyethyl 2-cyano-2-isobutyl-4-methylpentanoate (**5s**):



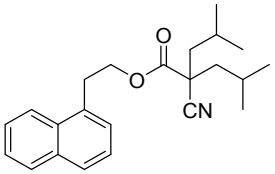
Yield: 86% (136 mg). Physical aspect: colourless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.25 (m, 2H), 6.97 (t, J = 7.4 Hz, 1H), 6.88 (dd, J = 8.7, 0.9 Hz, 2H), 4.54 (t, J = 4.8 Hz, 2H), 4.23 (t, J = 4.8 Hz, 2H), 1.91–1.82 (m, 4H), 1.72–1.65 (m, 2H), 1.02 (d, J = 6.3 Hz, 6H), 0.88 (d, J = 6.2 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.89, 158.14, 129.48 (2C), 121.24, 119.42, 114.45 (2C), 65.01, 64.48, 47.83, 47.36 (2C), 25.96 (2C), 23.22 (2C), 22.51 (2C) ppm. HRMS (ESI) calculated $[M+NH_4]^+$ for $C_{19}H_{31}N_2O_3$: 335.2329, found: 335.2331.

2-(benzyloxy)-2-oxoethyl 2-cyano-2-isobutyl-4-methylpentanoate (**5t**):



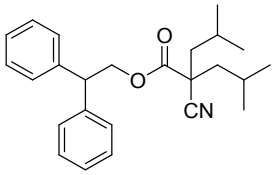
Yield: 80% (138 mg). Physical aspect: colourless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.31 (m, 5H), 5.21 (s, 2H), 4.75 (s, 2H), 1.95–1.86 (m, 4H), 1.75–1.67 (m, 2H), 1.04 (d, J = 6.4 Hz, 6H), 0.89 (d, J = 6.3 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.50, 166.43, 134.74, 128.65 (3C), 128.46 (2C), 119.27, 67.34, 61.83, 47.47, 47.03 (2C), 25.83 (2C), 23.23 (2C), 22.86 (2C) ppm. HRMS (ESI) calculated $[M+NH_4]^+$ for $C_{20}H_{31}N_2O_4$: 363.2278, found: 363.2276.

2-(Naphthalen-1-yl)ethyl 2-cyano-2-isobutyl-4-methylpentanoate (**5u**):



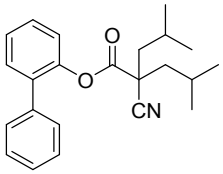
Yield: 86% (151 mg). Physical aspect: colourless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 7.7 Hz, 1H), 7.80–7.74 (m, 1H), 7.59–7.54 (m, 1H), 7.52–7.47 (m, 1H), 7.43 (d, J = 0.8 Hz, 1H), 7.42 (s, 1H), 4.50 (t, J = 7.2 Hz, 2H), 3.49 (t, J = 7.2 Hz, 2H), 1.81– 1.71 (m, 4H), 1.66–1.59 (m, 2H), 0.97 (d, J = 6.3 Hz, 6H), 0.75 (d, J = 6.2 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.02, 133.87, 132.85, 131.84, 128.84, 127.67, 127.38, 126.33, 125.68, 125.48, 123.36, 119.55, 66.43, 47.78, 47.28 (2C), 31.68, 25.92 (2C), 23.30 (2C), 22.38 (2C) ppm. HRMS (ESI) calculated $[M+NH_4]^+$ for $C_{23}H_{33}N_2O_2$: 369.2537, found: 369.2540.

2,2-Diphenylethyl 2-cyano-2-isobutyl-4-methylpentanoate (**5v**):



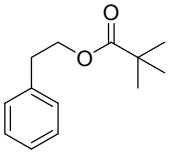
Yield: 81% (153 mg). Physical aspect: colourless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.20 (m, 10H), 4.71 (d, J = 7.5 Hz, 2H), 4.45 (t, J = 7.5 Hz, 1H), 1.73–1.60 (m, 4H), 1.59–1.53 (m, 2H), 0.89 (d, J = 6.3 Hz, 6H), 0.69 (d, J = 6.3 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.76, 140.37 (2C), 128.61 (4C), 128.12 (4C), 126.97 (2C), 119.35, 68.73, 49.52, 47.69, 47.19 (2C), 25.83 (2C), 23.08 (2C), 22.42 (2C) ppm. HRMS (ESI) calculated $[M+NH_4]^+$ for $C_{25}H_{35}N_2O_2$: 395.2693, found: 395.2700.

[1,1'-Biphenyl]-2-yl 2-cyano-2-isobutyl-4-methylpentanoate (**5w**):



Yield: 77% (134 mg). Physical aspect: colourless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49–7.32 (m, 8H), 7.21–7.15 (m, 1H), 1.70–1.55 (m, 6H), 0.94 (d, J = 6.3 Hz, 6H), 0.75 (d, J = 6.4 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.32, 147.18, 136.80, 134.90, 131.30, 129.50 (2C), 128.42, 128.38 (2C), 127.70, 126.80, 122.10, 119.21, 47.56, 46.65 (2C), 25.84 (2C), 23.33 (2C), 22.94 (2C) ppm. HRMS (ESI) calculated $[M+NH_4]^+$ for $C_{23}H_{31}N_2O_2$: 367.2380, found: 367.2386.

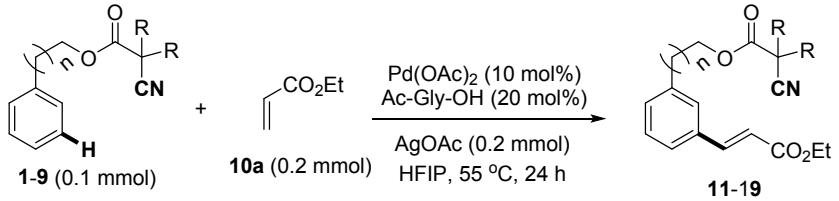
Phenethyl pivalate (**27**):



Yield: 90% (93 mg). Physical aspect: colourless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.25 (m, 2H), 7.25–7.17 (m, 3H), 4.27 (t, J = 6.9 Hz, 2H), 2.93 (t, J = 6.9 Hz, 2H), 1.16 (s, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.42, 137.96, 128.92 (2C), 128.36 (2C), 126.42, 64.78, 38.65, 35.11, 27.11 (3C) ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{13}H_{19}O_2$: 207.1380, found: 207.1385.

2.4. Tuning of templates and optimization studies

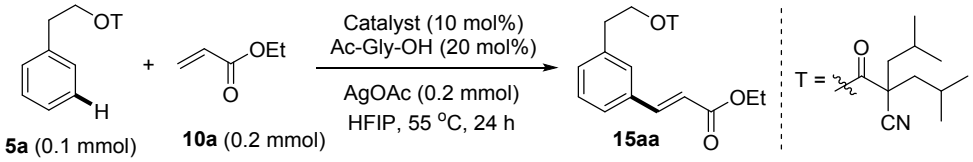
2.4.1 Screening of Template:



Entry	Substrate	R	n	Product	Yield (%)[a] mono:di	Selectivity (*m*:others)[b]
1	**1a**	H	0	**11a**	-	-
2	**1b**	H	0	**11b**	Trace	-
3	**2**	CH_3	1	**12**	63:13	92:08
4	**3**	CH_2CH_3	1	**13**	64:13	92:08
5	**4**	$(CH_2)_6CH_3$	1	**14**	12:0	91:09
6	**5a**	$CH_2CH(CH_3)_2$	1	**15a**	77:12	96:04
7	**6**	$CH(CH_3)_2$	1	**16**	59:10	94:06
8	**7**	$CH_2(CH_3)C_2H_5$	1	**17**	46:08	92:08
9	**8**	$(CH_2)_4$	1	**18**	72:18	92:08
10	**9**	$(CH_2)_5$	1	**19**	74:19	91:09
11	**5b**	$CH_2CH(CH_3)_2$	0	**15b**	Trace	-

[a]Yields were determined by crude ^{1}H NMR analysis using CH_2Br_2 as the internal standard. [b]Selectivity was determined by ^{1}H NMR analysis.

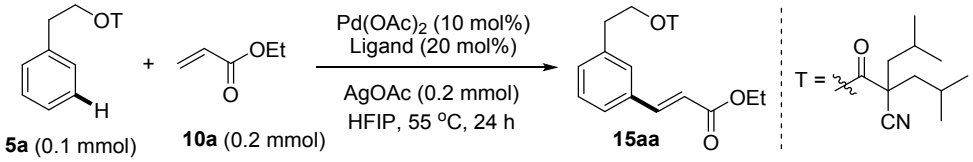
2.4.2. Screening of Catalyst:



Entry	Catalyst	Yield (%)[a] mono:di	Selectivity (*m*:others)[b]
1	No Catalyst	-	-
2	$Pd(OAc)_2$	77:12	96:04
3	$PdCl_2$	57:11	91:09
4	$PdCl_2(CH_3CN)_2$	52:10	90:10
5	$PdCl_2$(nbd)	49:05	92:08
6	$Pd(PPh_3)_4$	51:07	89:11

[a]Yields were determined by crude ^{1}H NMR analysis using CH_2Br_2 as the internal standard. [b]Selectivity was determined by ^{1}H NMR analysis.

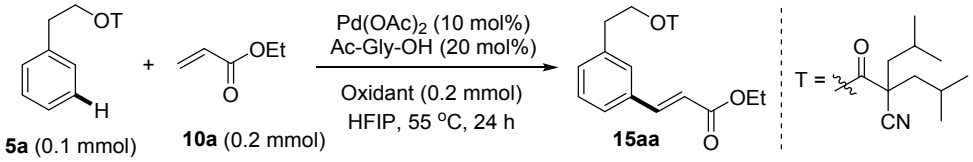
2.4.3 Screening of Ligand:



Entry	Ligand	Yield (%)[a] mono:di	Selectivity (*m*:others)[b]
1	No ligand	19:0	88:12
2	*N*-Boc-Gly-OH	04:0	-
3	*N*-Ac-Gly-OH	77:12	96:04
4	*N*-Ac-Leu-OH	57:08	96:04
5	*N*-Boc-Val-OH	18:03	90:10
6	*N*-Boc-Ala-OH	Trace	-
7	Glycine	0	-

[a]Yields were determined by crude ^{1}H NMR analysis using CH_2Br_2 as the internal standard. [b]Selectivity was determined by ^{1}H NMR analysis.

2.4.4 Screening of Oxidant:

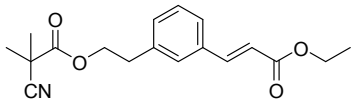


Entry	Oxidant	Yield (%)[a] mono:di	Selectivity (*m*:others)[b]
1	No oxidant	09:0	76:23
2	AgOAc	77:12	96:4
3	Ag_2CO_3	54:07	92:08
4	AgOTf	08:0	-
5	AgTFA	08:0	-
6	$K_2S_2O_8$	18:0	86:14
7	Oxone	Trace	-

[a]Yields were determined by crude ^{1}H NMR analysis using CH_2Br_2 as the internal standard. [b]Selectivity was determined by ^{1}H NMR analysis.

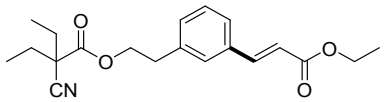
Spectral data:

Ethyl (*E*)-3-(3-(2-((2-cyano-2-methylpropanoyl)oxy)ethyl)phenyl)acrylate (**12**):



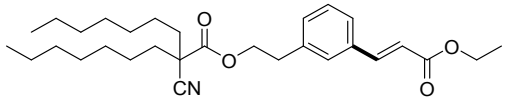
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, J = 16.0 Hz, 1H), 7.50–7.38 (m, 2H), 7.35 (t, J = 7.5 Hz, 1H), 7.29–7.26 (m, 1H), 6.45 (d, J = 16.0 Hz, 1H), 4.42 (t, J = 6.8 Hz, 2H), 4.27 (q, J = 7.1 Hz, 2H), 3.03 (t, J = 6.8 Hz, 2H), 1.54 (s, 6H), 1.34 (t, J = 7.1 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.46, 166.87, 144.16, 137.74, 134.82, 130.85, 129.14, 128.57, 126.56, 120.54, 118.61, 66.62, 60.49, 38.55, 34.68, 24.70 (2C), 14.27 ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{18}H_{22}NO_4$: 316.1543, found: 316.1542.

(*E*)-3-(3-Ethoxy-3-oxoprop-1-en-1-yl)phenethyl 2-cyano-2-ethylbutanoate (**13**):



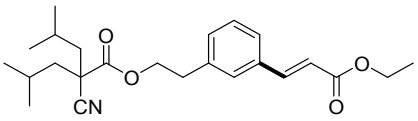
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (d, J = 16.0 Hz, 1H), 7.45–7.37 (m, 2H), 7.34 (t, J = 7.8 Hz, 1H), 7.28 (d, J = 7.5 Hz, 1H), 6.46 (d, J = 16.1 Hz, 1H), 4.43 (t, J = 6.7 Hz, 2H), 4.26 (q, J = 7.1 Hz, 2H), 3.03 (t, J = 6.7 Hz, 2H), 1.92–1.83 (m, 2H), 1.83–1.74 (m, 2H), 1.34 (t, J = 7.1 Hz, 3H), 0.95 (t, J = 7.4 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.85, 166.78, 144.09, 137.77, 134.70, 130.78, 129.05, 128.48, 126.47, 118.84, 118.48, 66.32, 60.38, 51.53, 34.63, 30.34 (2C), 14.20, 9.57 (2C) ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{20}H_{26}NO_4$: 344.1856, found: 344.1853.

(*E*)-3-(3-Ethoxy-3-oxoprop-1-en-1-yl)phenethyl 2-cyano-2-heptylnonanoate (**14**):



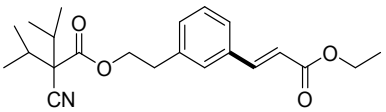
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (d, J = 16.0 Hz, 1H), 7.42–7.39 (m, 2H), 7.34 (t, J = 7.8 Hz, 1H), 7.28 (d, J = 7.5 Hz, 1H), 6.45 (d, J = 16.0 Hz, 1H), 4.42 (t, J = 6.7 Hz, 2H), 4.27 (q, J = 7.1 Hz, 2H), 3.03 (t, J = 6.7 Hz, 2H), 1.84–1.76 (m, 2H), 1.73–1.65 (m, 2H), 1.34 (t, J = 7.1 Hz, 3H), 1.30–1.10 (m, 20H), 0.87 (t, J = 7.0 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.30, 166.87, 144.20, 137.91, 134.83, 130.89, 129.13, 128.62, 126.54, 119.34, 118.61, 66.40, 60.48, 50.05, 37.51 (2C), 34.69, 31.63 (2C), 29.16 (2C), 28.85 (2C), 25.34 (2C), 22.55 (2C), 14.29, 14.02 (2C) ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{30}H_{46}NO_4$: 484.3421, found: 484.3413.

(*E*)-3-(3-Ethoxy-3-oxoprop-1-en-1-yl)phenethyl 2-cyano-2-isobutyl-4-methylpentanoate (**15aa**):



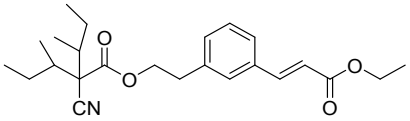
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, J = 16.0 Hz, 1H), 7.41 (d, J = 9.1 Hz, 2H), 7.34 (t, J = 7.4 Hz, 1H), 7.30 (d, J = 7.5 Hz, 1H), 6.46 (d, J = 16.0 Hz, 1H), 4.39 (t, J = 6.7 Hz, 2H), 4.26 (q, J = 7.1 Hz, 2H), 3.04 (t, J = 6.7 Hz, 2H), 1.81–1.71 (m, 4H), 1.67–1.60 (m, 2H), 1.34 (t, J = 7.1 Hz, 3H), 0.96 (d, J = 6.4 Hz, 6H), 0.76 (d, J = 6.3 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.86, 166.84, 144.16, 137.90, 134.81, 130.89, 129.11, 128.52, 126.52, 119.44, 118.57, 66.59, 60.43, 47.64, 47.31 (2C), 34.49, 25.91 (2C), 23.25 (2C), 22.38 (2C), 14.25 ppm. HRMS (ESI) calculated $[M+NH_4]^+$ for $C_{24}H_{37}N_2O_4$: 417.2748, found: 417.2745.

(*E*)-3-(3-Ethoxy-3-oxoprop-1-en-1-yl)phenethyl 2-cyano-2-isopropyl-3-methylbutanoate (**16**):



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (d, J = 16.0 Hz, 1H), 7.50–7.37 (m, 2H), 7.34 (t, J = 7.4 Hz, 1H), 7.29 (d, J = 7.5 Hz, 1H), 6.46 (d, J = 16.0 Hz, 1H), 4.41 (t, J = 6.8 Hz, 2H), 4.27 (q, J = 7.1 Hz, 2H), 3.03 (t, J = 6.7 Hz, 2H), 2.30–2.20 (m, 2H), 1.34 (t, J = 7.1 Hz, 3H), 1.02 (d, J = 6.8 Hz, 6H), 0.94 (d, J = 6.7 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.78, 166.89, 144.20, 137.91, 134.75, 130.89, 129.10, 128.56, 126.53, 118.51, 118.46, 66.07, 60.44, 59.91, 34.67, 32.27 (2C), 18.18 (2C), 17.59 (2C), 14.26 ppm. HRMS (ESI) calculated $[M+NH_4]^+$ for $C_{22}H_{33}N_2O_4$: 389.2435, found: 389.2435.

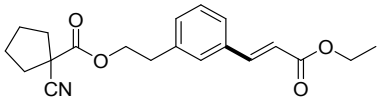
(*E*)-3-(3-Ethoxy-3-oxoprop-1-en-1-yl)phenethyl 2-(sec-butyl)-2-cyano-3-methylpentanoate (**17**):



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, J = 16.0 Hz, 1H), 7.41 (d, J = 8.8 Hz, 2H), 7.34 (t, J = 7.4 Hz, 1H), 7.31–7.22 (m, 2H), 6.46 (d, J = 16.0 Hz, 1H), 4.40 (t, J = 6.2 Hz, 2H), 4.27 (q, J = 7.1 Hz, 2H), 3.02 (t, J = 6.7 Hz, 2H), 2.04–1.88 (m, 2H), 1.74–1.63 (m, 1H), 1.34 (t, J = 7.1 Hz, 3H), 1.28–1.13 (m, 2H), 0.99 (t, J = 6.9 Hz, 3H), 0.94–0.84 (m, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$):δ = 168.08, 166.90, 144.22, 138.01, 134.84, 130.92, 129.11, 128.60, 126.52, 118.96, 118.61, 66.06, 60.46, 59.93, 39.30, 38.65, 38.60, 38.24, 34.70, 34.68, 25.46, 25.36, 24.74, 24.50, 14.33, 14.28, 13.68, 13.59, 12.81, 12.11, 12.09, 12.00, 11.94 ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{24}H_{34}NO_4$: 400.2482, found: 400.2479.

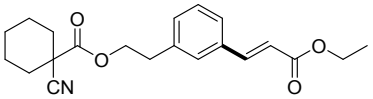
.

.(*E*)-3-(3-Ethoxy-3-oxoprop-1-en-1-yl)phenethyl 1-cyanocyclopentane-1-carboxylate (**18**):



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, J = 16.0 Hz, 1H), 7.46–7.38 (m, 2H), 7.34 (t, J = 7.5 Hz, 1H), 7.29–7.26 (m, 1H), 6.45 (d, J = 16.0 Hz, 1H), 4.42 (t, J = 6.8 Hz, 2H), 4.27 (q, J = 7.1 Hz, 2H), 3.02 (t, J = 6.8 Hz, 2H), 2.26–2.12 (m, 4H), 1.90–1.78 (m, 4H), 1.34 (t, J = 7.1 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.50, 166.86, 144.17, 137.83, 134.79, 130.85, 129.11, 128.56, 126.53, 120.78, 118.57, 66.56, 60.46, 47.46, 37.66 (2C), 34.70, 25.06 (2C), 14.26 ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{20}H_{24}NO_4$: 342.1700, found: 342.1709.

(*E*)-3-(3-Ethoxy-3-oxoprop-1-en-1-yl)phenethyl 1-cyanocyclohexane-1-carboxylate (**19**):



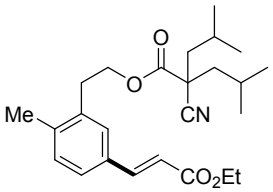
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, J = 16.0 Hz, 1H), 7.42–7.39 (m, 2H), 7.34 (t, J = 7.4 Hz, 1H), 7.30–7.25 (m, 1H), 6.45 (d, J = 16.0 Hz, 1H), 4.41 (t, J = 6.8 Hz, 2H), 4.27 (q, J = 7.1 Hz, 2H), 3.02 (t, J = 6.8 Hz, 2H), 2.05–2.00 (m, 2H), 1.78–1.64 (m, 7H), 1.34 (t, J = 7.1 Hz, 3H), 1.28–1.25 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.16, 166.85, 144.18, 137.83, 134.77, 130.84, 129.11, 128.55, 126.55, 119.00, 118.55, 66.41, 60.45, 45.34, 34.69, 32.83 (2C), 24.51, 22.12 (2C), 14.25 ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{21}H_{26}NO_4$: 356.1856, found: 356.1860.

2.5. General procedure for template-assisted *meta*-selective C–H olefination

2.5.1. General procedure for mono *meta*-selective C–H olefination

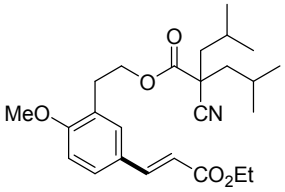
An oven dried 10 mL glass vial equipped with a magnetic stir-bar was charged with substrate (0.2 mmol), olefin (0.4 mmol), $Pd(OAc)_2$ (10 mol %), Ac-Gly-OH (20 mol%), AgOAc (0.4 mmol), and hexafluoroisopropanol (HFIP) (2 mL), then the resulting mixture was heated in a 55 °C oil bath with rapid stirring for 24 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and filtered through a short pad of celite. Evaporation of the solvent(s) under reduced pressure and purification of the residue by silica gel column chromatography using petroleum ether/ethyl acetate as the eluent provided the desired *meta*-olefinated product.

(*E*)-5-(3-Ethoxy-3-oxoprop-1-en-1-yl)-2-methylphenethyl 2-cyano-2-isobutyl-4-methylpentanoate (**15ca**):



GP was carried out with comound **5c** (63 mg, 0.2 mmol), ethyl acrylate **10a** (40 mg, 0.4 mmol), $Pd(OAc)_2$ (5 mg, 10 mol %), Ac-Gly-OH (5 mg, 20 mol%), AgOAc (67 mg, 0.4 mmol) in HFIP (2 mL) at 55 °C for 24 h. Purification of the crude mixture by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 85:15) furnished the *meta*-olefinated product **15ca** (69 mg, 83%, *m*:others = 94:6) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (d, J = 16.0 Hz, 1H), 7.36 (s, 1H), 7.32 (dd, J = 7.8, 1.7 Hz, 1H), 7.19 (d, J = 7.9 Hz, 1H), 6.42 (d, J = 16.0 Hz, 1H), 4.36 (t, J = 7.1 Hz, 2H), 4.26 (q, J = 7.1 Hz, 2H), 3.05 (t, J = 7.1 Hz, 2H), 2.39 (s, 3H), 1.83–1.71 (m, 4H), 1.68–1.60 (m, 2H), 1.33 (t, J = 7.1 Hz, 3H), 0.97 (d, J = 6.5 Hz, 6H), 0.78 (d, J = 6.3 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.05, 167.08, 144.19, 139.12, 135.80, 132.57, 131.04, 129.32, 126.59, 119.49, 117.60, 65.86, 60.41, 47.70, 47.36 (2C), 31.70, 25.97 (2C), 23.32 (2C), 22.39 (2C), 19.45, 14.31 ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{25}H_{36}NO_4$: 414.2639, found: 414.2643.

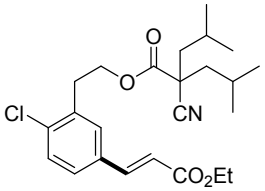
(*E*)-5-(3-Ethoxy-3-oxoprop-1-en-1-yl)-2-methoxyphenethyl 2-cyano-2-isobutyl-4-methylpentanoate (**15da**):



GP was carried out with comound **5d** (66 mg, 0.2 mmol), ethyl acrylate **10a** (40 mg, 0.4 mmol), $Pd(OAc)_2$ (5 mg, 10 mol %), Ac-Gly-OH (5 mg, 20 mol%), AgOAc (67 mg, 0.4 mmol) in HFIP (2 mL) at

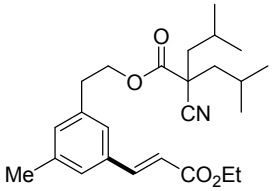
55 °C for 24 h. Purification of the crude mixture by silica gel column chromatography (petroleum ether/ethyl acetate, 80:20) furnished the *meta*-olefinated product **15da** (81 mg, 95%, *m*:others = 98:2) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, J = 16.0 Hz, 1H), 7.46–7.34 (m, 2H), 6.86 (d, J = 9.1 Hz, 1H), 6.33 (d, J = 15.9 Hz, 1H), 4.37 (t, J = 6.8 Hz, 2H), 4.25 (q, J = 7.1 Hz, 2H), 3.87 (s, 3H), 3.04 (t, J = 6.8 Hz, 2H), 1.81–1.70 (m, 4H), 1.66–1.59 (m, 2H), 1.33 (t, J = 7.1 Hz, 3H), 0.97 (d, J = 6.4 Hz, 6H), 0.78 (d, J = 6.3 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.93, 167.26, 159.31, 144.02, 130.45, 128.85, 127.06, 125.99, 119.54, 116.04, 110.48, 65.47, 60.27, 55.51, 47.79, 47.28 (2C), 29.55, 25.93 (2C), 23.34 (2C), 22.41 (2C), 14.31 ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{25}H_{36}NO_5$: 430.2588, found: 430.2588.

(*E*)-2-Chloro-5-(3-ethoxy-3-oxoprop-1-en-1-yl)phenethyl 2-cyano-2-isobutyl-4-methylpentanoate (**15ea**):



GP was carried out with comound **5e** (67 mg, 0.2 mmol), ethyl acrylate **10a** (40 mg, 0.4 mmol), $Pd(OAc)_2$ (5 mg, 10 mol %), Ac-Gly-OH (5 mg, 20 mol%), AgOAc (67 mg, 0.4 mmol) in HFIP (2 mL) at 55 °C for 24 h. Purification of the crude mixture by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 85:15) furnished the *meta*-olefinated product **15ea** (68 mg, 79%, *m*:others = 87:13) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, J = 16.0 Hz, 1H), 7.50 (d, J = 1.8 Hz, 1H), 7.41–7.34 (m, 2H), 6.45 (d, J = 16.0 Hz, 1H), 4.41 (t, J = 6.7 Hz, 2H), 4.25 (q, J = 7.1 Hz, 2H), 3.18 (t, J = 6.7 Hz, 2H), 1.81–1.72 (m, 4H), 1.68–1.62 (m, 2H), 1.33 (t, J = 7.1 Hz, 3H), 0.96 (d, J = 6.4 Hz, 6H), 0.77 (d, J = 6.3 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.88, 166.65, 142.79, 135.83, 135.46, 133.54, 130.92, 130.16, 127.70, 119.42, 119.36, 64.96, 60.58, 47.74, 47.32 (2C), 32.41, 25.96 (2C), 23.33 (2C), 22.38 (2C), 14.27 ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{24}H_{33}ClNO_4$: 434.2093, found: 434.2097.

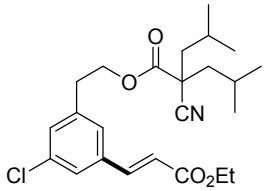
(*E*)-3-(3-Ethoxy-3-oxoprop-1-en-1-yl)-5-methylphenethyl 2-cyano-2-isobutyl-4-methylpentanoate (**15fa**):



GP was carried out with comound **5f** (63 mg, 0.2 mmol), ethyl acrylate **10a** (40 mg, 0.4 mmol), $Pd(OAc)_2$ (5 mg, 10 mol %), Ac-Gly-OH (5 mg, 20 mol%), AgOAc (67 mg, 0.4 mmol) in HFIP (2 mL) at 55 °C for

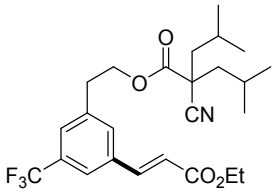
24 h. Purification of the crude mixture by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 85:15) furnished the *meta*-olefinated product **15fa** (66 mg, 80%, *m*:others = 94:6) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (d, J = 16.0 Hz, 1H), 7.22 (s, 2H), 7.13 (s, 1H), 6.44 (d, J = 16.0 Hz, 1H), 4.37 (t, J = 6.7 Hz, 2H), 4.26 (q, J = 7.1 Hz, 2H), 3.00 (t, J = 6.7 Hz, 2H), 2.35 (s, 3H), 1.82–1.70 (m, 4H), 1.68–1.61 (m, 2H), 1.33 (t, J = 7.1 Hz, 3H), 0.97 (d, J = 6.4 Hz, 6H), 0.77 (d, J = 6.3 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.90, 166.95, 144.39, 138.86, 137.77, 134.77, 131.88, 127.24, 125.71, 119.50, 118.32, 66.68, 60.41, 47.67, 47.34 (2C), 34.42, 25.94 (2C), 23.28 (2C), 22.40 (2C), 21.14, 14.28 ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{25}H_{36}NO_4$: 414.2639, found: 414.2640.

(*E*)-3-Chloro-5-(3-ethoxy-3-oxoprop-1-en-1-yl)phenethyl 2-cyano-2-isobutyl-4-methylpentanoate (**15ga**):



GP was carried out with comound **5g** (67 mg, 0.2 mmol), ethyl acrylate **10a** (40 mg, 0.4 mmol), $Pd(OAc)_2$ (5 mg, 10 mol %), Ac-Gly-OH (5 mg, 20 mol%), AgOAc (67 mg, 0.4 mmol) in HFIP (2 mL) at 55 °C for 24 h. Purification of the crude mixture by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 85:15) furnished the *meta*-olefinated product **15ga** (61 mg, 71%, *m*:others = 93:7) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 (d, J = 16.0 Hz, 1H), 7.40 (d, J = 1.4 Hz, 1H), 7.33–7.26 (m, 2H), 6.46 (d, J = 16.0 Hz, 1H), 4.38 (t, J = 6.6 Hz, 2H), 4.27 (q, J = 7.1 Hz, 2H), 3.02 (t, J = 6.6 Hz, 2H), 1.82–1.71 (m, 4H), 1.69–1.62 (m, 2H), 1.33 (t, J = 7.1 Hz, 3H), 0.97 (d, J = 6.4 Hz, 6H), 0.78 (d, J = 6.3 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.85, 166.42, 142.57, 139.80, 136.52, 135.00, 130.51, 126.90, 126.23, 120.10, 119.37, 66.14, 60.62, 47.63, 47.32 (2C), 34.20, 25.95 (2C), 23.26 (2C), 22.39 (2C), 14.23 ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{24}H_{33}ClNO_4$: 434.2093, found: 434.2101.

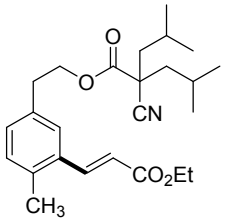
(*E*)-3-(3-Ethoxy-3-oxoprop-1-en-1-yl)-5-(trifluoromethyl)phenethyl 2-cyano-2-isobutyl-4-methylpentanoate (**15ha**):



GP was carried out with comound **5h** (74 mg, 0.2 mmol), ethyl acrylate **10a** (40 mg, 0.4 mmol), $Pd(OAc)_2$ (5 mg, 10 mol %), Ac-Gly-OH (5 mg, 20 mol%), AgOAc (67 mg, 0.4 mmol) in HFIP (2 mL) at

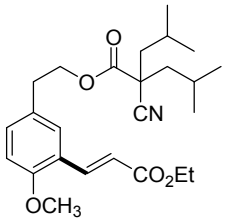
55 °C for 24 h. Purification of the crude mixture by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 85:15) furnished the *meta*-olefinated product **15ha** (54 mg, 58%, *m*:others = 100:0) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (d, J = 16.2 Hz, 1H), 7.66 (s, 1H), 7.63 (s, 1H), 7.54 (s, 1H), 6.54 (d, J = 16.0 Hz, 1H), 4.41 (t, J = 6.5 Hz, 2H), 4.28 (q, J = 7.1 Hz, 2H), 3.12 (t, J = 6.5 Hz, 2H), 1.82–1.70 (m, 4H), 1.68–1.61 (m, 2H), 1.34 (t, J = 7.1 Hz, 3H), 0.96 (d, J = 6.4 Hz, 6H), 0.75 (d, J = 6.3 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.91, 166.35, 142.37, 139.18, 135.78, 131.83 (q, $J_{C\text{-}F}$ = 32.4 Hz), 131.77, 126.99 (q, $J_{C\text{-}F}$ = 3.5 Hz), 123.63 (q, $J_{C\text{-}F}$ = 271 Hz), 123.17 (q, $J_{C\text{-}F}$ = 3.6 Hz), 120.68, 119.34, 66.11, 60.75, 47.64, 47.34 (2C), 34.37, 25.96 (2C), 23.26 (2C), 22.35 (2C), 14.25 ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{25}H_{33}F_3NO_4$: 468.2356, found: 468.2361.

(*E*)-3-(3-Ethoxy-3-oxoprop-1-en-1-yl)-4-methylphenethyl 2-cyano-2-isobutyl-4-methylpentanoate (**15ia**):



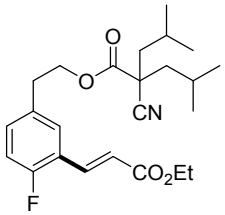
GP was carried out with comound **5i** (63 mg, 0.2 mmol), ethyl acrylate **10a** (40 mg, 0.4 mmol), $Pd(OAc)_2$ (5 mg, 10 mol %), Ac-Gly-OH (5 mg, 20 mol%), AgOAc (67 mg, 0.4 mmol) in HFIP (2 mL) at 55 °C for 24 h. Purification of the crude mixture by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 85:15) furnished the *meta*-olefinated product **15ia** (64 mg, 77%, *m*:others = 95:5) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, J = 15.9 Hz, 1H), 7.43 (s, 1H), 7.21–7.12 (m, 2H), 6.39 (d, J = 15.9 Hz, 1H), 4.37 (t, J = 6.8 Hz, 2H), 4.27 (q, J = 7.1 Hz, 2H), 3.00 (t, J = 6.8 Hz, 2H), 2.41 (s, 3H), 1.81–1.71 (m, 4H), 1.67–1.61 (m, 2H), 1.34 (t, J = 7.1 Hz, 3H), 0.97 (d, J = 6.4 Hz, 6H), 0.77 (d, J = 6.3 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.90, 166.98, 141.94, 136.11, 135.12 (2C), 133.63, 131.04, 130.60, 126.85, 119.56, 66.72, 60.45, 47.69, 47.34 (2C), 34.24, 25.94 (2C), 23.28 (2C), 22.45 (2C), 19.33, 14.29 ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{25}H_{36}NO_4$: 414.2639, found: 414.2644.

(*E*)-3-(3-Ethoxy-3-oxoprop-1-en-1-yl)-4-methoxyphenethyl 2-cyano-2-isobutyl-4-methylpentanoate (**15ja**):



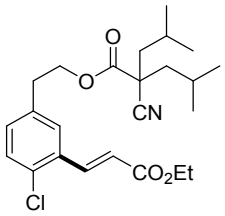
GP was carried out with comound **5j** (66 mg, 0.2 mmol), ethyl acrylate **10a** (40 mg, 0.4 mmol), $Pd(OAc)_2$ (5 mg, 10 mol %), Ac-Gly-OH (5 mg, 20 mol%), AgOAc (67 mg, 0.4 mmol) in HFIP (2 mL) at 55 °C for 24 h. Purification of the crude mixture by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 80:20) furnished the *meta*-olefinated product **15ja** (72 mg, 84%, *m*:others = 100:0) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (d, J = 16.2 Hz, 1H), 7.38 (d, J = 2.1 Hz, 1H), 7.26 (dd, J = 7.9, 2.7 Hz, 1H), 6.87 (d, J = 8.5 Hz, 1H), 6.54 (d, J = 16.2 Hz, 1H), 4.35 (t, J = 6.8 Hz, 2H), 4.26 (q, J = 7.1 Hz, 2H), 3.87 (s, 3H), 2.97 (t, J = 6.7 Hz, 2H), 1.82–1.71 (m, 4H), 1.67–1.61 (m, 2H), 1.33 (t, J = 7.1 Hz, 3H), 0.97 (d, J = 6.5 Hz, 6H), 0.78 (d, J = 6.3 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.90, 167.38, 157.28, 139.63, 131.97, 129.24 (2C), 123.51, 119.53, 119.05, 111.34, 66.85, 60.29, 55.57, 47.67, 47.34 (2C), 33.76, 25.94 (2C), 23.29 (2C), 22.43 (2C), 14.32 ppm. HRMS (ESI) calculated $[M+NH_4]^+$ for $C_{25}H_{39}N_2O_5$: 447.2853, found: 447.2861.

(*E*)-3-(3-Ethoxy-3-oxoprop-1-en-1-yl)-4-fluorophenethyl 2-cyano-2-isobutyl-4-methylpentanoate (**15ka**):



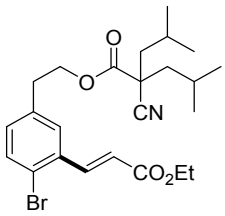
GP was carried out with comound **5k** (64 mg, 0.2 mmol), ethyl acrylate **10a** (40 mg, 0.4 mmol), $Pd(OAc)_2$ (5 mg, 10 mol %), Ac-Gly-OH (5 mg, 20 mol%), AgOAc (67 mg, 0.4 mmol) in HFIP (2 mL) at 55 °C for 24 h. Purification of the crude mixture by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 85:15) furnished the *meta*-olefinated product **15ka** (61 mg, 73%, *m*:others = 95:5) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, J = 16.2 Hz, 1H), 7.43 (dd, J = 6.9, 2.2 Hz, 1H), 7.31–7.23 (m, 1H), 7.06 (dd, J = 10.3, 8.5 Hz, 1H), 6.56 (d, J = 16.2 Hz, 1H), 4.36 (t, J = 6.6 Hz, 2H), 4.27 (q, J = 7.1 Hz, 2H), 3.01 (t, J = 6.6 Hz, 2H), 1.81–1.70 (m, 4H), 1.66–1.61 (m, 2H), 1.34 (t, J = 7.1 Hz, 3H), 0.97 (d, J = 6.5 Hz, 6H), 0.77 (d, J = 6.4 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.91, 166.71, 160.36 (d, $J_{C\text{-}F}$ = 251.7 Hz), 136.81 (d, $J_{C\text{-}F}$ = 2.3 Hz), 133.45 (d, $J_{C\text{-}F}$ = 3.6 Hz), 132.21 (d, $J_{C\text{-}F}$ = 8.6 Hz), 129.40 (d, $J_{C\text{-}F}$ = 3.1 Hz), 122.58 (d, $J_{C\text{-}F}$ = 12.2 Hz), 121.21 (d, $J_{C\text{-}F}$ = 6.7 Hz), 119.47, 116.33 (d, $J_{C\text{-}F}$ = 22.1 Hz), 66.57, 60.59, 47.62, 47.38 (2C), 33.89, 25.97 (2C), 23.29 (2C), 22.42 (2C), 14.27 ppm. HRMS (ESI) calculated $[M+NH_4]^+$ for $C_{24}H_{36}FN_2O_4$: 435.2654, found: 435.2663.

(*E*)-4-Chloro-3-(3-ethoxy-3-oxoprop-1-en-1-yl)phenethyl 2-cyano-2-isobutyl-4-methylpentanoate (**15la**):



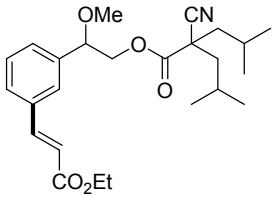
GP was carried out with comound **5l** (67 mg, 0.2 mmol), ethyl acrylate **10a** (40 mg, 0.4 mmol), $Pd(OAc)_2$ (5 mg, 10 mol %), Ac-Gly-OH (5 mg, 20 mol%), AgOAc (67 mg, 0.4 mmol) in HFIP (2 mL) at 55 °C for 24 h. Purification of the crude mixture by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 85:15) furnished the *meta*-olefinated product **15la** (60 mg, 69%, *m*:others = 98:2) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (d, J = 16.1 Hz, 1H), 7.52 (d, J = 2.1 Hz, 1H), 7.37 (d, J = 8.2 Hz, 1H), 7.24 (dd, J = 8.2, 2.1 Hz, 1H), 6.48 (d, J = 16.0 Hz, 1H), 4.37 (t, J = 6.6 Hz, 2H), 4.28 (q, J = 7.1 Hz, 2H), 3.02 (t, J = 6.6 Hz, 2H), 1.80–1.69 (m, 4H), 1.66–1.61 (m, 2H), 1.34 (t, J = 7.1 Hz, 3H), 0.97 (d, J = 6.4 Hz, 6H), 0.76 (d, J = 6.3 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.90, 166.43, 139.98, 136.37, 133.42, 132.85, 131.70, 130.28, 128.09, 121.23, 119.45, 66.35, 60.67, 47.59, 47.36 (2C), 34.08, 25.96 (2C), 23.27 (2C), 22.41 (2C), 14.27 ppm. HRMS (ESI) calculated $[M+NH_4]^+$ for $C_{24}H_{36}ClN_2O_4$: 451.2358, found: 451.2365.

(*E*)-4-Bromo-3-(3-ethoxy-3-oxoprop-1-en-1-yl)phenethyl 2-cyano-2-isobutyl-4-methylpentanoate (**15ma**):



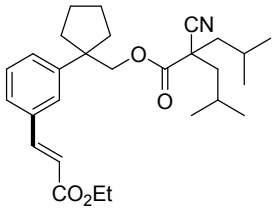
GP was carried out with comound **5m** (76 mg, 0.2 mmol), ethyl acrylate **10a** (40 mg, 0.4 mmol), $Pd(OAc)_2$ (5 mg, 10 mol %), Ac-Gly-OH (5 mg, 20 mol%), AgOAc (67 mg, 0.4 mmol) in HFIP (2 mL) at 55 °C for 24 h. Purification of the crude mixture by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 85:15) furnished the *meta*-olefinated product **15ma** (62 mg, 65%, *m*:others = 89:11) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, J = 16.0 Hz, 1H), 7.56 (d, J = 8.2 Hz, 1H), 7.51 (d, J = 2.1 Hz, 1H), 7.16 (dd, J = 8.2, 2.2 Hz, 1H), 6.44 (d, J = 15.9 Hz, 1H), 4.38 (t, J = 6.6 Hz, 2H), 4.28 (q, J = 7.1 Hz, 2H), 3.00 (t, J = 6.6 Hz, 2H), 1.80–1.70 (m, 4H), 1.66–1.60 (m, 2H), 1.35 (t, J = 7.1 Hz, 3H), 0.96 (d, J = 6.4 Hz, 6H), 0.76 (d, J = 6.3 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.88, 166.32, 142.50, 137.06, 134.69, 133.54, 131.89, 128.26, 123.57, 121.41, 119.44, 66.26, 60.67, 47.58, 47.35 (2C), 34.11, 25.95 (2C), 23.27 (2C), 22.42 (2C), 14.26 ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{24}H_{33}{}^{79}BrNO_4$: 478.1587, found: 478.1596; $C_{24}H_{33}{}^{81}BrNO_4$: 480.1567, found: 480.1579.

(*E*)-2-(3-(3-Ethoxy-3-oxoprop-1-en-1-yl)phenyl)-2-methoxyethyl 2-cyano-2-isobutyl-4-methylpentanoate (**15na**):



GP was carried out with comound **5n** (66 mg, 0.2 mmol), ethyl acrylate **10a** (40 mg, 0.4 mmol), $Pd(OAc)_2$ (5 mg, 10 mol %), Ac-Gly-OH (5 mg, 20 mol%), AgOAc (67 mg, 0.4 mmol) in HFIP (2 mL) at 55 °C for 24 h. Purification of the crude mixture by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 80:20) furnished the *meta*-olefinated product **15na** (62 mg, 73%, *m*:others = 98:2) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (d, J = 16.0 Hz, 1H), 7.54 (s, 1H), 7.50 (dt, J = 6.6, 2.1 Hz, 1H), 7.45–7.37 (m, 2H), 6.48 (d, J = 16.0 Hz, 1H), 4.51 (dd, J = 7.6, 4.1 Hz, 1H), 4.35 (dd, J = 11.4, 7.6 Hz, 1H), 4.27 (q, J = 7.1 Hz, 2H), 4.21 (dd, J = 11.4, 4.1 Hz, 1H), 3.30 (s, 3H), 1.87–1.74 (m, 4H), 1.71–1.63 (m, 2H), 1.34 (t, J = 7.1 Hz, 3H), 1.03 (d, J = 6.4 Hz, 3H), 0.99 (d, J = 6.5 Hz, 3H), 0.85 (d, J = 6.2 Hz, 3H), 0.80 (d, J = 6.4 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.77, 166.82, 143.96, 138.45, 135.01, 129.29, 128.86, 128.18, 126.39, 119.49, 118.98, 80.75, 69.05, 60.55, 57.12, 47.73, 47.40 (2C), 25.97, 25.95, 23.28, 23.25, 22.57, 22.42, 14.29 ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{25}H_{36}NO_5$: 430.2588, found: 430.2591.

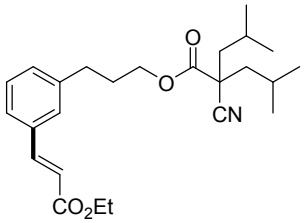
(*E*)-(1-(3-(3-Ethoxy-3-oxoprop-1-en-1-yl)phenyl)cyclopentyl)methyl 2-cyano-2-isobutyl-4-methylpentanoate (**15oa**):



GP was carried out with comound **5o** (71 mg, 0.2 mmol), ethyl acrylate **10a** (40 mg, 0.4 mmol), $Pd(OAc)_2$ (5 mg, 10 mol %), Ac-Gly-OH (5 mg, 20 mol%), AgOAc (67 mg, 0.4 mmol) in HFIP (2 mL) at 55 °C for 24 h. Purification of the crude mixture by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 85:15) furnished the *meta*-olefinated product **15oa** (63 mg, 69%, *m*:others = 100:0) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (d, J = 16.0 Hz, 1H), 7.51 (s, 1H), 7.43–7.31 (m, 3H), 6.46 (d, J = 16.0 Hz, 1H), 4.27 (q, J = 7.1 Hz, 2H), 4.08 (s, 2H), 2.14–2.07 (m, 2H), 2.07–1.98 (m, 2H), 1.81–1.75 (m, 4H), 1.69–1.53 (m, 6H) 1.34 (t, J = 7.1 Hz, 3H), 0.89 (d, J = 6.3 Hz, 6H), 0.62 (d, J = 6.2 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.82, 167.00, 146.66, 144.69, 134.34, 129.35, 128.73, 127.00, 125.92, 119.32, 118.29, 72.89, 60.47, 50.56, 47.75, 47.32 (2C), 34.75 (2C), 25.89 (2C),

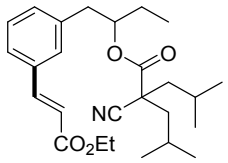
23.43 (2C), 23.24 (2C), 22.12 (2C), 14.30 ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{28}H_{40}NO_4$: 454.2952, found: 454.2960.

(*E*)-3-(3-(3-Ethoxy-3-oxoprop-1-en-1-yl)phenyl)propyl 2-cyano-2-isobutyl-4-methylpentanoate (**15pa**):



GP was carried out with comound **5p** (63 mg, 0.2 mmol), ethyl acrylate **10a** (40 mg, 0.4 mmol), $Pd(OAc)_2$ (5 mg, 10 mol %), Ac-Gly-OH (5 mg, 20 mol%), AgOAc (67 mg, 0.4 mmol) in HFIP (2 mL) at 55 °C for 24 h. Purification of the crude mixture by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 85:15) furnished the *meta*-olefinated product **15pa** (59 mg, 72%, *m*:others = 93:7) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (d, J = 16.0 Hz, 1H), 7.40–7.31 (m, 3H), 7.22 (d, J = 7.5 Hz, 1H), 6.44 (d, J = 16.0 Hz, 1H), 4.27 (q, J = 7.1 Hz, 2H), 4.20 (t, J = 6.4 Hz, 2H), 2.83–2.73 (m, 2H), 2.09–2.00 (m, 2H), 1.92–1.80 (m, 4H), 1.73–1.66 (m, 2H), 1.34 (t, J = 7.1 Hz, 3H), 1.06 (d, J = 6.4 Hz, 6H), 0.89 (d, J = 6.2 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.91, 166.91, 144.42, 141.32, 134.71, 130.33, 129.07, 128.06, 125.95, 119.59, 118.36, 65.42, 60.44, 47.63, 47.39 (2C), 31.77, 29.69, 26.03 (2C), 23.33(2C), 22.57 (2C), 14.28 ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{25}H_{36}NO_4$: 414.2639, found: 414.2638.

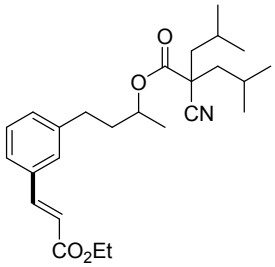
(*E*)-1-(3-(3-Ethoxy-3-oxoprop-1-en-1-yl)phenyl)butan-2-yl 2-cyano-2-isobutyl-4-methylpentanoate (**15qa**):



GP was carried out with comound **5q** (66 mg, 0.2 mmol), ethyl acrylate **10a** (40 mg, 0.4 mmol), $Pd(OAc)_2$ (5 mg, 10 mol %), Ac-Gly-OH (5 mg, 20 mol%), AgOAc (67 mg, 0.4 mmol) in HFIP (2 mL) at 55 °C for 24 h. Purification of the crude mixture by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 85:15) furnished the *meta*-olefinated product **15qa** (60 mg, 70%, *m*:others = 96:4) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (d, J = 16.0 Hz, 1H), 7.42–2.37 (m, 2H), 7.35–7.28 (m, 2H), 6.46 (d, J = 16.0 Hz, 1H), 5.07–5.01 (m, 1H), 4.26 (q, J = 7.1 Hz, 2H), 2.99 (dd, J = 13.9, 7.9 Hz, 1H), 2.89 (dd, J = 13.9, 5.6 Hz, 1H), 1.83–1.60 (m, 6H), 1.59–1.51 (m, 2H) 1.34 (t, J = 7.1 Hz, 3H), 1.05–0.98 (m, 6H), 0.91 (d, J = 6.2 Hz, 3H), 0.86 (d, J = 6.2 Hz, 3H), 0.67 (d, J = 6.2 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.54, 166.91, 144.26, 137.90, 134.75, 131.41, 129.06, 129.02,

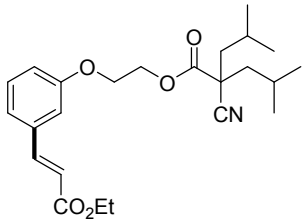
126.42, 119.69, 118.55, 79.14, 60.46, 47.60, 47.06, 47.01, 39.15, 26.14, 25.95, 25.78, 23.35, 23.17, 22.98, 22.83, 14.28, 9.33 ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{26}H_{38}NO_4$: 428.2795, found: 428.2800.

(*E*)-4-(3-(3-Ethoxy-3-oxoprop-1-en-1-yl)phenyl)butan-2-yl 2-cyano-2-isobutyl-4-methylpentanoate (**15ra**):



GP was carried out with comound **5r** (66 mg, 0.2 mmol), ethyl acrylate **10a** (40 mg, 0.4 mmol), $Pd(OAc)_2$ (5 mg, 10 mol %), Ac-Gly-OH (5 mg, 20 mol%), AgOAc (67 mg, 0.4 mmol) in HFIP (2 mL) at 55 °C for 24 h. Purification of the crude mixture by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 85:15) furnished the *meta*-olefinated product **15ra** (61 mg, 71%, *m*:others = 93:7) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (d, J = 16.0 Hz, 1H), 7.40–7.28 (m, 3H), 7.21 (d, J = 7.4 Hz, 1H), 6.43 (d, J = 16.0 Hz, 1H), 5.06–4.96 (m, 1H), 4.27 (q, J = 7.1 Hz, 2H), 2.77 (ddd, J = 14.0, 10.6, 5.7 Hz, 1H), 2.67 (ddd, J = 13.9, 10.4, 6.0 Hz, 1H), 2.10–2.00 (m, 1H), 1.93–1.83 (m, 5H), 1.71–1.66 (m, 2H), 1.34 (t, J = 7.0 Hz, 6H), 1.07 (dd, J = 6.3, 4.0 Hz, 6H), 0.92 (dd, J = 6.3, 1.6 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.43, 166.94, 144.47, 141.77, 134.71, 130.21, 129.06, 127.91, 125.88, 119.74, 118.33, 73.50, 60.45, 47.64, 47.43, 47.18, 37.14, 31.30, 26.06, 25.99, 23.29, 23.15, 22.94 (2C), 19.44, 14.28 ppm. HRMS (ESI) calculated $[M+Na]^+$ for $C_{26}H_{37}NNaO_4$: 450.2615, found: 450.2614.

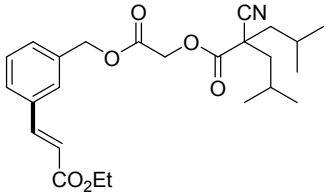
(*E*)-2-(3-(3-Ethoxy-3-oxoprop-1-en-1-yl)phenoxy)ethyl 2-cyano-2-isobutyl-4-methylpentanoate (**15sa**):



GP was carried out with comound **5s** (63 mg, 0.2 mmol), ethyl acrylate **10a** (40 mg, 0.4 mmol), $Pd(OAc)_2$ (5 mg, 10 mol %), Ac-Gly-OH (5 mg, 20 mol%), AgOAc (67 mg, 0.4 mmol) in HFIP (2 mL) at 55 °C for 24 h. Purification of the crude mixture by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 85:15) furnished the *meta*-olefinated product **15sa** (62 mg, 75%, *m*:others = 97:3) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (d, J = 16.0 Hz, 1H), 7.31 (t, J = 7.9 Hz, 1H), 7.15 (d, J = 7.6 Hz, 1H), 7.06–6.99 (m, 1H), 6.95–6.88 (m, 1H), 6.42 (d, J = 16.0 Hz, 1H), 4.58–4.52 (m, 2H), 4.30–4.23 (m, 4H), 1.91–1.82 (m, 4H), 1.74–1.66 (m, 2H), 1.34 (t, J = 7.1 Hz, 3H), 1.02 (d, J = 6.4 Hz,

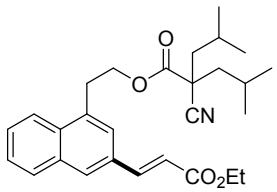
6H), 0.88 (d, J = 6.2 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.95, 166.84, 158.54, 144.19, 135.98, 130.01, 121.32, 119.41, 118.83, 116.49, 113.59, 65.28, 64.38, 60.55, 47.83, 47.43 (2C), 26.02 (2C), 23.27 (2C), 22.56 (2C), 14.29 ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{24}H_{34}NO_5$: 416.2431, found: 416.2434.

(*E*)-2-((3-(3-Ethoxy-3-oxoprop-1-en-1-yl)benzyl)oxy)-2-oxoethyl 2-cyano-2-isobutyl-4-methylpentanoate (**15ta**):



GP was carried out with comound **5t** (69 mg, 0.2 mmol), ethyl acrylate **10a** (40 mg, 0.4 mmol), $Pd(OAc)_2$ (5 mg, 10 mol %), Ac-Gly-OH (5 mg, 20 mol%), AgOAc (67 mg, 0.4 mmol) in HFIP (2 mL) at 55 °C for 24 h. Purification of the crude mixture by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 85:15) furnished the *meta*-olefinated product **15ta** (59 mg, 67%, *m*:others = 89:11) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, J = 16.0 Hz, 1H), 7.45 (dd, J = 4.1, 2.1 Hz, 2H), 7.37 (t, J = 7.8 Hz, 1H), 7.32 (dd, J = 5.2, 3.7 Hz, 1H), 6.45 (d, J = 16.0 Hz, 1H), 4.26 (q, J = 7.1 Hz, 2H), 4.14 (s, 2H), 3.71 (s, 2H), 1.83–1.74 (m, 2H), 1.48–1.39 (m, 4H), 1.34 (t, J = 7.1 Hz, 3H), 0.98 (d, J = 6.6 Hz, 6H), 0.95 (d, J = 6.6 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.35, 169.97, 166.81, 143.99, 134.93, 134.13, 131.16, 129.22, 128.91, 127.01, 122.01, 118.80, 66.84, 60.51, 43.65 (2C), 41.06, 39.15, 24.76 (2C), 23.96 (2C), 23.87 (2C), 14.28 ppm.

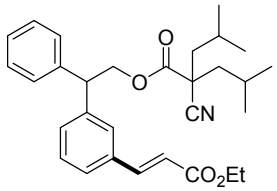
(*E*)-2-(3-(3-Ethoxy-3-oxoprop-1-en-1-yl)naphthalen-1-yl)ethyl 2-cyano-2-isobutyl-4-methylpentanoate (**15ua**):



GP was carried out with comound **5u** (70 mg, 0.2 mmol), ethyl acrylate **10a** (40 mg, 0.4 mmol), $Pd(OAc)_2$ (5 mg, 10 mol %), Ac-Gly-OH (5 mg, 20 mol%), AgOAc (67 mg, 0.4 mmol) in HFIP (2 mL) at 55 °C for 24 h. Purification of the crude mixture by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 85:15) furnished the *meta*-olefinated product **15ua** (69 mg, 77%, *m*:others = 98:2) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (s, 1H), 7.89 (d, J = 16.0 Hz, 1H), 7.86 (d, J = 8.8 Hz, 1H), 7.77–7.72 (m, 1H), 7.69 (dd, J = 8.5, 1.4 Hz, 1H), 7.50–7.40 (m, 2H), 6.58 (d, J = 16.0 Hz, 1H), 4.50 (t, J = 7.1 Hz, 2H), 4.30 (q, J = 7.1 Hz, 2H), 3.50 (t, J = 7.1 Hz, 2H), 1.79–1.72 (m,

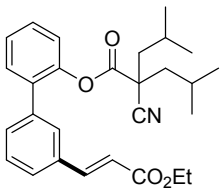
4H), 1.65–1.60 (m, 2H), 1.37 (t, J = 7.1 Hz, 3H), 0.96 (d, J = 6.3 Hz, 6H), 0.75 (d, J = 6.2 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.95, 166.91, 144.69, 134.67, 133.73, 132.33, 131.77, 129.66, 128.25, 127.50, 126.86, 125.45, 123.28, 119.47, 118.77, 66.28, 60.53, 47.77, 47.24 (2C), 31.49, 25.92 (2C), 23.29 (2C), 22.37 (2C), 14.33 ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{28}H_{36}NO_4$: 450.2639, found: 450.2648.

(*E*)-2-(3-(3-Ethoxy-3-oxoprop-1-en-1-yl)phenyl)-2-phenylethyl 2-cyano-2-isobutyl-4-methylpentanoate (**15va**):



GP was carried out with comound **5v** (75 mg, 0.2 mmol), ethyl acrylate **10a** (40 mg, 0.4 mmol), $Pd(OAc)_2$ (5 mg, 10 mol %), Ac-Gly-OH (5 mg, 20 mol%), AgOAc (67 mg, 0.4 mmol) in HFIP (2 mL) at 55 °C for 24 h. Purification of the crude mixture by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 85:15) furnished the *meta*-olefinated product **15va** (61 mg, 65%, *m*:others = 93:7) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (d, J = 16.0 Hz, 1H), 7.44–7.23 (m, 9H), 6.42 (d, J = 16.0 Hz, 1H), 4.78–4.66 (m, 2H), 4.47 (t, J = 7.5 Hz, 1H), 4.26 (q, J = 7.1 Hz, 2H), 1.73–1.66 (m, 2H), 1.63–1.53 (m, 4H), 1.33 (t, J = 7.1 Hz, 3H), 0.89 (t, J = 6.6 Hz, 6H), 0.69 (dd, J = 8.7, 6.4 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.82, 166.83, 144.19, 141.29, 139.85, 134.94, 130.13, 129.26, 128.82 (2C), 128.13 (2C), 127.89, 127.27, 126.65, 119.35, 118.69, 68.54, 60.51, 49.43, 47.70, 47.29 (2C), 25.91 (2C), 23.14, 23.10, 22.48, 22.47, 14.29 ppm. HRMS (ESI) calculated $[M+NH_4]^+$ for $C_{30}H_{41}N_2O_4$: 493.3061, found: 493.3064.

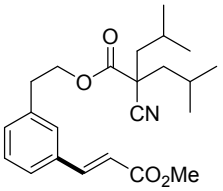
(*E*)-3'-(3-Ethoxy-3-oxoprop-1-en-1-yl)-[1,1'-biphenyl]-2-yl 2-cyano-2-isobutyl-4-methylpentanoate (**15wa**):



GP was carried out with comound **5w** (70 mg, 0.2 mmol), ethyl acrylate **10a** (40 mg, 0.4 mmol), $Pd(OAc)_2$ (5 mg, 10 mol %), Ac-Gly-OH (5 mg, 20 mol%), AgOAc (67 mg, 0.4 mmol) in HFIP (2 mL) at 55 °C for 24 h. Purification of the crude mixture by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 85:15) furnished the *meta*-olefinated product **15wa** (62 mg, 69%, *m*:others = 100:0) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73 (d, J = 16.0 Hz, 1H), 7.61 (s, 1H),

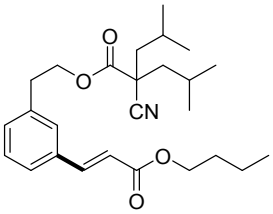
7.55–7.50 (m, 2H), 7.48–7.35 (m, 4H), 7.19 (dd, J = 8.2, 1.1 Hz, 1H), 6.50 (d, J = 16.0 Hz, 1H), 4.26 (q, J = 7.1 Hz, 2H), 1.72–1.55 (m, 6H), 1.33 (t, J = 7.1 Hz, 3H), 0.93 (d, J = 6.2 Hz, 6H), 0.74 (d, J = 6.3 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.25, 166.75, 147.11, 143.92, 137.56, 134.66, 134.04, 131.37, 131.12, 128.99, 128.87, 128.83, 127.25, 126.88, 122.16, 119.09, 118.93, 60.45, 47.47, 46.64 (2C), 25.83 (2C), 23.26 (2C), 22.90 (2C), 14.22 ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{28}H_{34}NO_4$: 448.2482, found: 448.2484.

(*E*)-3-(3-Methoxy-3-oxoprop-1-en-1-yl)phenethyl 2-cyano-2-isobutyl-4-methylpentanoate (**15ab**):



GP was carried out with comound **5a** (60 mg, 0.2 mmol), olefin **10b** (34 mg, 0.4 mmol), $Pd(OAc)_2$ (5 mg, 10 mol %), Ac-Gly-OH (5 mg, 20 mol%), AgOAc (67 mg, 0.4 mmol) in HFIP (2 mL) at 55 °C for 24 h. Purification of the crude mixture by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 85:15) furnished the *meta*-olefinated product **15ab** (54 mg, 71%, *m*:others = 95:5) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (d, J = 16.0 Hz, 1H), 7.44–7.39 (m, 2H), 7.35 (t, J = 7.4 Hz, 1H), 7.32–7.29 (m, 1H), 6.47 (d, J = 16.0 Hz, 1H), 4.39 (t, J = 6.7 Hz, 2H), 3.81 (s, 3H), 3.04 (t, J = 6.7 Hz, 2H), 1.81–1.70 (m, 4H), 1.65–1.61 (m, 2H), 0.96 (d, J = 6.5 Hz, 6H), 0.76 (d, J = 6.3 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.91, 167.36, 144.51, 137.97, 134.75, 130.99, 129.16, 128.59, 126.62, 119.49, 118.12, 66.63, 51.69, 47.66, 47.35 (2C), 34.52, 25.94 (2C), 23.28 (2C), 22.40 (2C) ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{23}H_{32}NO_4$: 386.2326, found: 386.2324.

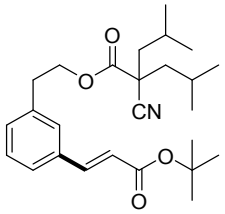
(*E*)-3-(3-Butoxy-3-oxoprop-1-en-1-yl)phenethyl 2-cyano-2-isobutyl-4-methylpentanoate (**15ac**):



GP was carried out with comound **5a** (60 mg, 0.2 mmol), olefin **10c** (51 mg, 0.4 mmol), $Pd(OAc)_2$ (5 mg, 10 mol %), Ac-Gly-OH (5 mg, 20 mol%), AgOAc (67 mg, 0.4 mmol) in HFIP (2 mL) at 55 °C for 24 h. Purification of the crude mixture by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 85:15) furnished the *meta*-olefinated product **15ac** (57 mg, 67%, *m*:others = 95:5) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (d, J = 16.0 Hz, 1H), 7.46–7.38 (m, 2H), 7.34 (t, J = 7.6 Hz, 1H), 7.32–7.28 (m, 1H), 6.46 (d, J = 16.0 Hz, 1H), 4.39 (t, J = 6.7 Hz, 2H), 4.21 (t, J = 6.7 Hz, 2H), 3.04

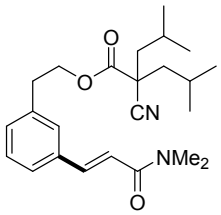
(t, J = 6.7 Hz, 2H), 1.81–1.61 (m, 9H), 1.49–1.39 (m, 2H), 1.00–0.94 (m, 8H), 0.76 (d, J = 6.3 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.92, 167.01, 144.17, 137.91, 134.86, 130.92, 129.14, 128.55, 126.57, 119.48, 118.61, 66.63, 64.42, 47.67, 47.35 (2C), 34.52, 30.74, 25.95 (2C), 23.28 (2C), 22.41 (2C), 19.17, 13.71 ppm. HRMS (ESI) calculated $[M+Na]^+$ for $C_{26}H_{37}NNaO_4$: 450.2615, found: 450.2621.

(*E*)-3-(3-(*tert*-Butoxy)-3-oxoprop-1-en-1-yl)phenethyl 2-cyano-2-isobutyl-4-methylpentanoate (**15ad**):



GP was carried out with comound **5a** (60 mg, 0.2 mmol), olefin **10d** (51 mg, 0.4 mmol), $Pd(OAc)_2$ (5 mg, 10 mol %), Ac-Gly-OH (5 mg, 20 mol%), AgOAc (67 mg, 0.4 mmol) in HFIP (2 mL) at 55 °C for 24 h. Purification of the crude mixture by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 85:15) furnished the *meta*-olefinated product **15ad** (56 mg, 66%, *m*:others = 95:5) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (d, J = 16.0 Hz, 1H), 7.39 (dd, J = 6.9, 1.2 Hz, 2H), 7.33 (t, J = 7.9 Hz, 1H), 7.28 (d, J = 8.1 Hz, 1H), 6.38 (d, J = 16.0 Hz, 1H), 4.38 (t, J = 6.8 Hz, 2H), 3.03 (t, J = 6.7 Hz, 2H), 1.81–1.70 (m, 4H), 1.67–1.61 (m, 2H), 1.53 (s, 9H), 0.97 (d, J = 6.5 Hz, 6H), 0.77 (d, J = 6.3 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.90, 166.18, 143.14, 137.81, 135.05, 130.67, 129.08, 128.40, 126.46, 120.52, 119.48, 80.48, 66.64, 47.69, 47.34 (2C), 34.53, 28.17 (3C), 25.95 (2C), 23.29 (2C), 22.42 (2C) ppm. HRMS (ESI) calculated $[M+Na]^+$ for $C_{26}H_{37}NNaO_4$: 450.2615, found: 450.2619.

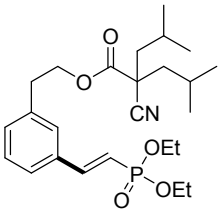
(*E*)-3-(3-(Dimethylamino)-3-oxoprop-1-en-1-yl)phenethyl 2-cyano-2-isobutyl-4-methylpentanoate (**15ae**):



GP was carried out with comound **5a** (60 mg, 0.2 mmol), olefin **10e** (40 mg, 0.4 mmol), $Pd(OAc)_2$ (5 mg, 10 mol %), Ac-Gly-OH (5 mg, 20 mol%), AgOAc (67 mg, 0.4 mmol) in HFIP (2 mL) at 55 °C for 24 h. Purification of the crude mixture by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 50:50) furnished the *meta*-olefinated product **15ae** (57 mg, 72%, *m*:others = 98:2) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, J = 15.5 Hz, 1H), 7.49 (s, 1H), 7.38 (d, J = 7.7 Hz, 1H), 7.32 (t, J = 7.5 Hz, 1H), 7.25 (d, J = 7.5 Hz, 1H), 6.96 (d, J = 15.5 Hz, 1H), 4.38 (t, J = 6.6 Hz, 2H), 3.19 (s, 3H), 3.07 (s, 3H), 3.04 (t, J = 6.6 Hz, 2H), 1.81–1.70 (m, 4H), 1.66–1.60 (m, 2H), 0.95 (d, J = 6.4 Hz,

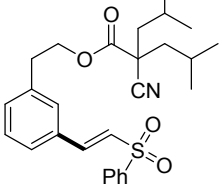
6H), 0.75 (d, J = 6.3 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.90, 166.64, 141.94, 137.82, 135.71, 130.11, 129.03, 127.85, 126.99, 119.56, 117.74, 66.81, 47.61, 47.35 (2C), 37.40, 35.91, 34.60, 25.93 (2C), 23.29 (2C), 22.34 (2C) ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{24}H_{35}N_2O_3$: 399.2642, found: 399.2649.

(*E*)-3-(2-(Diethoxyphosphoryl)vinyl)phenethyl 2-cyano-2-isobutyl-4-methylpentanoate (**15af**):



GP was carried out with comound **5a** (60 mg, 0.2 mmol), olefin **10f** (66 mg, 0.4 mmol), $Pd(OAc)_2$ (5 mg, 10 mol %), Ac-Gly-OH (5 mg, 20 mol%), AgOAc (67 mg, 0.4 mmol) in HFIP (2 mL) at 55 °C for 24 h. Purification of the crude mixture by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 45:55) furnished the *meta*-olefinated product **15af** (67 mg, 73%, *m*:others = 92:8) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49 (dd, J = 22.6, 17.5 Hz, 1H), 7.44–7.27 (m, 4H), 6.30 (t, J = 17.5 Hz, 1H), 4.38 (t, J = 6.7 Hz, 2H), 4.19–4.08 (m, 4H), 3.04 (t, J = 6.6 Hz, 2H), 1.81–1.72 (m, 4H), 1.66–1.61 (m, 2H), 1.36 (t, J = 7.1 Hz, 6H), 0.96 (d, J = 6.4 Hz, 6H), 0.76 (d, J = 6.3 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.92, 148.30 (d, $J_{C\text{-}P}$ = 6.4 Hz), 137.93, 135.26 (d, $J_{C\text{-}P}$ = 23.1 Hz), 130.89, 129.14, 128.09, 126.44, 119.49, 114.42 (d, $J_{C\text{-}P}$ = 189.7 Hz), 66.66, 61.85, 61.80, 47.64, 47.37 (2C), 34.54, 25.95 (2C), 23.29 (2C), 22.40 (2C), 16.41, 16.35 ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{25}H_{39}NO_5P$: 464.2560, found: 464.2567.

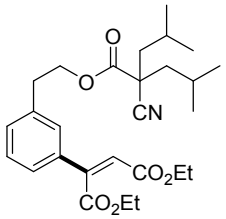
(*E*)-3-(2-(Phenylsulfonyl)vinyl)phenethyl 2-cyano-2-isobutyl-4-methylpentanoate (**15ag**):



GP was carried out with comound **5a** (60 mg, 0.2 mmol), olefin **10g** (67 mg, 0.4 mmol), $Pd(OAc)_2$ (5 mg, 10 mol %), Ac-Gly-OH (5 mg, 20 mol%), AgOAc (67 mg, 0.4 mmol) in HFIP (2 mL) at 55 °C for 24 h. Purification of the crude mixture by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 50:50) furnished the *meta*-olefinated product **15ag** (62 mg, 67%, *m*:others = 97:3) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98–7.89 (m, 2H), 7.67 (d, J = 15.5 Hz, 1H), 7.64–7.60 (m, 1H), 7.58–7.52 (m, 2H), 7.44 (s, 1H), 7.39–7.30 (m, 3H), 6.96 (d, J = 15.5 Hz, 1H), 4.35 (t, J = 6.5 Hz, 2H), 3.02 (t, J = 6.5 Hz, 2H), 1.79–1.65 (m, 4H), 1.64–1.59 (m, 2H), 0.93 (d, J = 6.4 Hz, 6H), 0.72 (d, J = 6.3

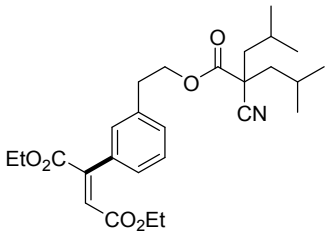
Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.89, 142.00, 140.76, 138.37, 133.30, 132.79, 131.85, 129.36, 129.27 (2C), 128.94, 127.82, 127.69 (2C), 127.42, 119.49, 66.56, 47.56, 47.35 (2C), 34.47, 25.93 (2C), 23.26 (2C), 22.36 (2C) ppm. HRMS (ESI) calculated $[M+Na]^+$ for $C_{27}H_{33}NNaO_4S$: 490.2023, found: 490.2031.

Diethyl 2-(3-(2-((2-cyano-2-isobutyl-4-methylpentanoyl)oxy)ethyl)phenyl)maleate (**15ah**):



GP was carried out with comound **5a** (60 mg, 0.2 mmol), olefin **10h** (69 mg, 0.4 mmol), $Pd(OAc)_2$ (5 mg, 10 mol %), Ac-Gly-OH (5 mg, 20 mol%), AgOAc (67 mg, 0.4 mmol) in HFIP (2 mL) at 55 °C for 24 h. Purification of the crude mixture by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 80:20) furnished the *meta*-olefinated product **15ah** (66 mg, 70%, *m*:others = 97:3) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.29 (m, 4H), 6.32 (s, 1H), 4.42 (q, J = 7.2 Hz, 2H), 4.38 (t, J = 6.8 Hz, 2H), 4.24 (q, J = 7.1 Hz, 2H), 3.04 (t, J = 6.8 Hz, 2H), 1.82–1.70 (m, 4H), 1.67–1.61 (m, 2H), 1.38 (t, J = 7.1 Hz, 3H), 1.32 (t, J = 7.1 Hz, 3H), 0.97 (d, J = 6.4 Hz, 6H), 0.76 (d, J = 6.3 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.86, 167.73, 164.81, 148.41, 138.09, 133.85, 131.23, 129.24, 127.03, 125.33, 119.46, 117.77, 66.51, 61.80, 60.90, 47.66, 47.33 (2C), 34.56, 25.93 (2C), 23.25 (2C), 22.37 (2C), 14.13, 13.97 ppm. HRMS (ESI) calculated $[M+Na]^+$ for $C_{27}H_{37}NNaO_6$: 494.2513, found: 494.2522.

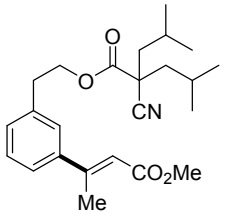
Diethyl 2-(3-(2-((2-cyano-2-isobutyl-4-methylpentanoyl)oxy)ethyl)phenyl)fumarate (**15ai**):



GP was carried out with comound **5a** (60 mg, 0.2 mmol), olefin **10i** (69 mg, 0.4 mmol), $Pd(OAc)_2$ (5 mg, 10 mol %), Ac-Gly-OH (5 mg, 20 mol%), AgOAc (67 mg, 0.4 mmol) in HFIP (2 mL) at 55 °C for 24 h. Purification of the crude mixture by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 80:20) furnished the *meta*-olefinated product **15ai** (64 mg, 68%, *m*:others = 97:3) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.26 (m, 2H), 7.17–7.09 (m, 2H), 6.99 (s, 1H), 4.37 (t, J = 7.3 Hz, 2H), 4.27 (q, J = 7.1 Hz, 2H), 4.05 (q, J = 7.1 Hz, 2H), 3.02 (t, J = 7.2 Hz, 2H), 1.86–1.76 (m,

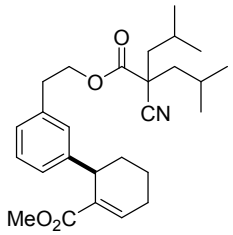
4H), 1.69–1.62 (m, 2H), 1.30 (t, J = 7.1 Hz, 3H), 1.09 (t, J = 7.1 Hz, 3H), 1.01 (d, J = 6.4 Hz, 6H), 0.83 (d, J = 6.3 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.91, 166.10, 165.21, 143.69, 136.32, 134.35, 129.34, 129.19, 128.94, 127.96, 127.52, 119.54, 66.79, 61.88, 60.78, 47.73, 47.35 (2C), 34.60, 25.97 (2C), 23.31 (2C), 22.47 (2C), 14.07, 13.82 ppm. HRMS (ESI) calculated $[M+Na]^+$ for $C_{27}H_{37}NNaO_6$: 494.2513, found: 494.2519.

(*E*)-3-(4-Methoxy-4-oxobut-2-en-2-yl)phenethyl 2-cyano-2-isobutyl-4-methylpentanoate (**15aj**):



GP was carried out with comound **5a** (60 mg, 0.2 mmol), olefin **10j** (40 mg, 0.4 mmol), $Pd(OAc)_2$ (5 mg, 10 mol %), Ac-Gly-OH (5 mg, 20 mol%), AgOAc (67 mg, 0.4 mmol) in HFIP (2 mL) at 55 °C for 24 h. Purification of the crude mixture by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 85:15) furnished the *meta*-olefinated product **15aj** (34 mg, 43%, *m*:others = 94:6) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.26 (m, 4H), 6.13 (d, J = 1.3 Hz, 1H), 4.39 (t, J = 6.8 Hz, 2H), 3.76 (s, 3H), 3.04 (t, J = 6.8 Hz, 2H), 2.57 (d, J = 1.2 Hz, 3H), 1.81–1.71 (m, 4H), 1.68–1.61 (m, 2H), 0.96 (d, J = 6.5 Hz, 6H), 0.77 (d, J = 6.3 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.93, 167.18, 155.63, 142.61, 137.50, 129.73, 128.79, 126.88, 124.87, 119.49, 116.87, 66.75, 51.11, 47.68, 47.37 (2C), 34.68, 25.96 (2C), 23.29 (2C), 22.41 (2C), 18.03 ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{24}H_{34}NO_4$: 400.2482, found: 400.2488.

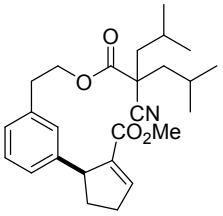
Methyl 3'-(2-((2-cyano-2-isobutyl-4-methylpentanoyl)oxy)ethyl)-1,4,5,6-tetrahydro-[1,1'-biphenyl]-2-carboxylate (**15ak**):



GP was carried out with comound **5a** (60 mg, 0.2 mmol), olefin **10k** (56 mg, 0.4 mmol), $Pd(OAc)_2$ (5 mg, 10 mol %), Ac-Gly-OH (5 mg, 20 mol%), AgOAc (67 mg, 0.4 mmol) in HFIP (2 mL) at 55 °C for 24 h. Purification of the crude mixture by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 85:15) furnished the *meta*-olefinated product **15ak** (62 mg, 71%, *m*:others = 100:0) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.24 (m, 1H), 7.21 (t, J = 7.6 Hz, 1H), 7.08 (d, J = 7.6 Hz, 1H), 7.03 (s, 1H), 7.00 (d, J = 7.7 Hz, 1H), 4.36 (t, J = 7.1 Hz, 2H), 3.92 (s, 1H), 3.59 (s, 3H), 2.98 (t, J =

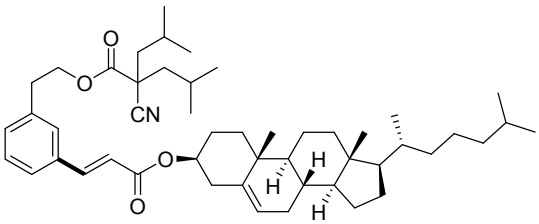
7.1 Hz, 2H), 2.40–2.18 (m, 2H), 1.97–1.86 (m, 1H), 1.85–1.70 (m, 5H), 1.69–1.60 (m, 2H), 1.55–1.44 (m, 2H), 0.98 (dd, J = 6.4, 3.6 Hz, 6H), 0.79 (dd, J = 6.2, 4.5 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.94, 167.48, 145.47, 141.71, 136.82, 131.72, 128.30, 128.23, 126.74, 126.18, 119.57, 67.04, 51.48, 47.75, 47.38 (2C), 39.42, 34.73, 31.34, 25.97 (2C), 25.85, 23.31 (2C), 22.43, 22.41, 16.93 ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{27}H_{38}NO_4$: 440.2795, found: 440.2799.

Methyl 5-(3-(2-((2-cyano-2-isobutyl-4-methylpentanoyl)oxy)ethyl)phenyl)cyclopent-1-ene-1-carboxylate (**15al**):



GP was carried out with comound **5a** (60 mg, 0.2 mmol), olefin **10l** (50 mg, 0.4 mmol), $Pd(OAc)_2$ (5 mg, 10 mol %), Ac-Gly-OH (5 mg, 20 mol%), AgOAc (67 mg, 0.4 mmol) in HFIP (2 mL) at 55 °C for 24 h. Purification of the crude mixture by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 85:15) furnished the *meta*-olefinated product **15al** (57 mg, 67%, *m*:others = 100:0) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (t, J = 7.5 Hz, 1H), 7.10–7.01 (m, 3H), 6.99 (dd, J = 4.1, 2.3 Hz, 1H), 4.36 (t, J = 7.0 Hz, 2H), 4.19–4.08 (m, 1H), 3.60 (s, 3H), 2.98 (t, J = 7.1 Hz, 2H), 2.78–2.60 (m, 1H), 2.60–2.44 (m, 2H), 1.94–1.85 (m, 1H), 1.83–1.73 (m, 4H), 1.68–1.61 (m, 2H), 0.98 (dd, J = 6.4, 1.1 Hz, 6H), 0.79 (dd, J = 6.3, 1.9 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.95, 165.12, 145.58, 145.03, 139.05, 137.08, 128.65, 127.65, 126.95, 125.36, 119.58, 67.04, 51.31, 49.99, 47.76, 47.40 (2C), 34.74, 34.09, 32.21, 25.99 (2C), 23.34 (2C), 22.45, 22.44 ppm. HRMS (ESI) calculated $[M+Na]^+$ for $C_{26}H_{35}NNaO_4$: 448.2458, found: 448.2460.

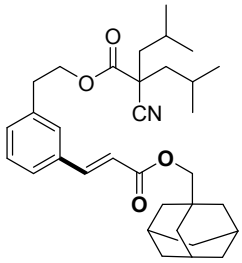
3-((*E*)-3-(((3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl)oxy)-3-oxoprop-1-en-1-yl)phenethyl 2-cyano-2-isobutyl-4-methylpentanoate (**15am**):



GP was carried out with comound **5a** (60 mg, 0.2 mmol), olefin **10m** (176 mg, 0.4 mmol), $Pd(OAc)_2$ (5 mg, 10 mol %), Ac-Gly-OH (5 mg, 20 mol%), AgOAc (67 mg, 0.4 mmol) in HFIP (2 mL) at 55 °C for 24 h. Purification of the crude mixture by silica gel column chromatography (petroleum ether/ethyl acetate,

100:0 to 85:15) furnished the *meta*-olefinated product **15am** (93 mg, 63%, *m*:others = 93:7) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, J = 16.0 Hz, 1H), 7.43–7.39 (m, 2H), 7.37–7.27 (m, 2H), 6.44 (d, J = 16.0 Hz, 1H), 5.41 (d, J = 3.8 Hz, 1H), 4.83–4.67 (m, 1H), 4.39 (t, J = 6.7 Hz, 2H), 3.03 (t, J = 6.9 Hz, 2H), 2.40 (d, J = 7.4 Hz, 2H), 2.05–1.86 (m, 4H), 1.85–1.71 (m, 5H), 1.70–1.61 (m, 3H), 1.57 (s, 3H), 1.55–1.44 (m, 4H), 1.39–1.25 (m, 4H), 1.22–1.09 (m, 6H), 1.05 (s, 3H), 1.04–1.00 (m, 2H), 0.97 (dd, J = 6.5, 4.0 Hz, 7H), 0.92 (d, J = 6.5 Hz, 3H), 0.87 (dd, J = 6.6, 1.8 Hz, 6H), 0.77 (d, J = 6.3 Hz, 6H), 0.69 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.93, 166.30, 144.04, 139.71, 137.90, 134.97, 130.88, 129.15, 128.54, 126.54, 122.71, 119.49, 119.08, 74.14, 66.63, 56.72, 56.17, 50.08, 47.72, 47.37 (2C), 42.34, 39.76, 39.53, 38.23, 37.04, 36.64, 36.20, 35.79, 34.56, 31.93, 31.90, 28.22, 28.01, 27.89, 25.97 (2C), 24.29, 23.83, 23.32 (2C), 22.80, 22.55, 22.46 (2C), 21.06, 19.34, 18.72, 11.86 ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{49}H_{74}NO_4$: 740.5612, found: 740.5572.

(*E*)-3-(3-(Adamantan-1-ylmethoxy)-3-oxoprop-1-en-1-yl)phenethyl 2-cyano-2-isobutyl-4-methylpentanoate (**15an**):

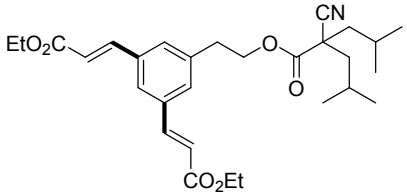


GP was carried out with comound **5a** (60 mg, 0.2 mmol), olefin **10n** (88 mg, 0.4 mmol), $Pd(OAc)_2$ (5 mg, 10 mol %), Ac-Gly-OH (5 mg, 20 mol%), AgOAc (67 mg, 0.4 mmol) in HFIP (2 mL) at 55 °C for 24 h. Purification of the crude mixture by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 85:15) furnished the *meta*-olefinated product **15an** (68 mg, 66%, *m*:others = 97:3) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, J = 16.0 Hz, 1H), 7.43 (d, J = 10.8 Hz, 2H), 7.35 (t, J = 7.5 Hz, 1H), 7.30 (d, J = 7.6 Hz, 1H), 6.49 (d, J = 16.0 Hz, 1H), 4.39 (t, J = 6.7 Hz, 2H), 3.82 (s, 2H), 3.04 (t, J = 6.7 Hz, 2H), 2.06–1.94 (m, 4H), 1.81–1.59 (m, 17H), 0.97 (d, J = 6.4 Hz, 6H), 0.77 (d, J = 6.3 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.93, 167.13, 144.10, 137.88, 134.87, 130.91, 129.13, 128.53, 126.61, 119.47, 118.66, 74.10, 66.65, 47.66, 47.35 (2C), 39.30 (3C), 36.96 (3C), 34.52, 33.35, 28.05 (3C), 25.95 (2C), 23.29 (2C), 22.41 (2C) ppm. HRMS (ESI) calculated $[M+NH_4]^+$ for $C_{33}H_{49}N_2O_4$: 537.3687, found: 537.3681.

2.5.2. General procedure for homo *meta*-selective bis-olefination:

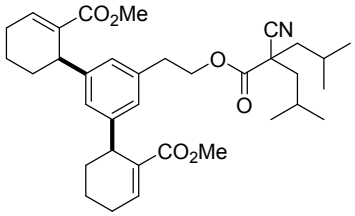
An oven dried 10 mL glass vial equipped with a magnetic stir-bar was charged with substrate (0.2 mmol), olefin (0.8 mmol), $Pd(OAc)_2$ (10 mol %), Ac-Gly-OH (20 mol%), AgOAc (0.8 mmol), and hexafluoroisopropanol (HFIP) (2 mL), then the resulting mixture was heated in a 55 °C oil bath with rapid stirring for 36 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and filtered through a short pad of celite. Evaporation of the solvent(s) under reduced pressure and purification of the residue by silica gel column chromatography using petroleum ether/ethyl acetate as the eluent provided the desired *meta*-olefinated product.

Diethyl 3,3'-(5-(2-((2-cyano-2-isobutyl-4-methylpentanoyl)oxy)ethyl)-1,3-phenylene)(2*E*,2'*E*)-diacrylate (**15aa$_{di}$**):



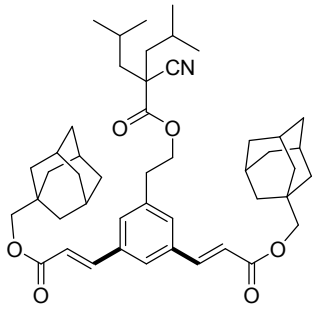
GP was carried out with comound **5a** (60 mg, 0.2 mmol), olefin **10a** (80 mg, 0.8 mmol), $Pd(OAc)_2$ (5 mg, 10 mol %), Ac-Gly-OH (5 mg, 20 mol%), AgOAc (134 mg, 0.8 mmol) in HFIP (2 mL) at 55 °C for 36 h. Purification of the crude mixture by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 75:25) furnished the *meta*-olefinated product **15aa$_{di}$** (72 mg, 73%, (*m*,*m'*):others = 95:5) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (d, J = 16.0 Hz, 2H), 7.54 (s, 1H), 7.46 (d, J = 1.3 Hz, 2H), 6.50 (d, J = 16.0 Hz, 2H), 4.40 (t, J = 6.6 Hz, 2H), 4.27 (q, J = 7.1 Hz, 4H), 3.07 (t, J = 6.6 Hz, 2H), 1.80–1.70 (m, 4H), 1.67–1.61 (m, 2H), 1.34 (t, J = 7.1 Hz, 6H), 0.96 (d, J = 6.4 Hz, 6H), 0.75 (d, J = 6.3 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.89, 166.61 (2C), 143.26 (2C), 138.74, 135.56 (2C), 129.96 (2C), 126.17, 119.62 (2C), 119.44, 66.35, 60.60 (2C), 47.61, 47.33 (2C), 34.40, 25.95 (2C), 23.27 (2C), 22.38 (2C), 14.26 (2C) ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{29}H_{40}NO_6$: 498.2850, found: 498.2854.

Dimethyl 5'-(2-((2-cyano-2-isobutyl-4-methylpentanoyl)oxy)ethyl)-1,1",4,4",5,5",6,6"-octahydro-[1,1':3',1"-terphenyl]-2,2"-dicarboxylate (**15ak$_{di}$**):



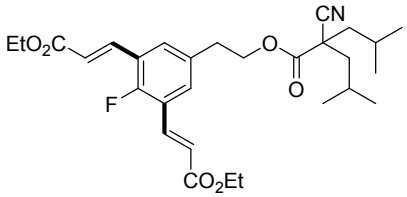
GP was carried out with comound **5a** (60 mg, 0.2 mmol), olefin **10k** (112 mg, 0.8 mmol), $Pd(OAc)_2$ (5 mg, 10 mol %), Ac-Gly-OH (5 mg, 20 mol%), AgOAc (134 mg, 0.8 mmol) in HFIP (2 mL) at 55 °C for 36 h. Purification of the crude mixture by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 75:25) furnished the *meta*-olefinated product **15ak$_{di}$** (91 mg, 79%, (*m*,*m'*):others = 100:0) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (s, 2H), 6.84 (dd, *J* = 4.2, 1.4 Hz, 2H), 6.74 (d, *J* = 6.6 Hz, 1H), 4.38–4.31 (m, 2H), 3.85 (d, *J* = 13.0 Hz, 2H), 3.57 (d, *J* = 1.1 Hz, 6H), 2.94 (t, *J* = 7.4 Hz, 2H), 2.37–2.17 (m, 4H), 1.91–1.78 (m, 6H), 1.73–1.64 (m, 4H), 1.52–1.41 (m, 4H), 1.02–0.97 (m, 6H), 0.84 –0.78 (m, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.97, 167.58, 167.55, 145.13, 145.01, 141.46, 141.44, 136.45, 136.36, 131.87, 126.05, 125.95, 125.74, 125.66, 119.57, 67.18, 51.38, 51.36, 47.73, 47.42, 39.43, 39.37, 34.73, 31.42, 31.32, 25.99, 25.83, 25.78, 23.32, 22.44, 22.42, 22.38, 17.13, 16.98 ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{35}H_{48}NO_6$: 578.3476, found: 578.3463.

Bis(((1s,3s)-adamantan-1-yl)methyl) 3,3'-(5-(2-((2-cyano-2-isobutyl-4-methylpentanoyl)oxy)ethyl)-1,3-phenylene)(2*E*,2'*E*)-diacrylate (**15an$_{di}$**):



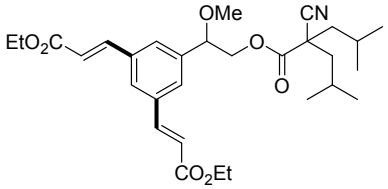
GP was carried out with comound **5a** (60 mg, 0.2 mmol), olefin **10n** (176 mg, 0.8 mmol), $Pd(OAc)_2$ (5 mg, 10 mol %), Ac-Gly-OH (5 mg, 20 mol%), AgOAc (134 mg, 0.8 mmol) in HFIP (2 mL) at 55 °C for 36 h. Purification of the crude mixture by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 80:20) furnished the *meta*-olefinated product **15an$_{di}$** (91 mg, 62%, (*m*,*m'*):others = 95:5) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 16.0 Hz, 2H), 7.58 (s, 1H), 7.47 (d, *J* = 1.3 Hz, 2H), 6.53 (d, *J* = 16.0 Hz, 2H), 4.41 (t, *J* = 6.6 Hz, 2H), 3.83 (s, 4H), 3.07 (t, *J* = 6.6 Hz, 2H), 2.06–1.95 (m, 8H), 1.79–1.59 (m, 28H), 0.97 (d, *J* = 6.4 Hz, 6H), 0.77 (d, *J* = 6.3 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.96, 166.86 (2C), 143.21 (2C), 138.70, 135.62 (2C), 130.06 (2C), 126.11, 119.72 (2C), 119.44, 74.24 (2C), 66.41, 47.64, 47.35 (2C), 39.31 (6C), 36.96 (6C), 34.43, 33.37 (2C), 28.06 (6C), 25.99 (2C), 23.31 (2C), 22.43 (2C) ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{47}H_{64}NO_6$: 738.4728, found: 738.4729.

Diethyl 3,3'-(5-(2-((2-cyano-2-isobutyl-4-methylpentanoyl)oxy)ethyl)-2-fluoro-1,3-phenylene)(2*E*,2'*E*)-diacrylate (**15ka$_{di}$**):



GP was carried out with comound **5k** (64 mg, 0.2 mmol), olefin **10a** (80 mg, 0.8 mmol), $Pd(OAc)_2$ (5 mg, 10 mol %), Ac-Gly-OH (5 mg, 20 mol%), AgOAc (134 mg, 0.8 mmol) in HFIP (2 mL) at 55 °C for 36 h. Purification of the crude mixture by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 75:25) furnished the *meta*-olefinated product **15ka$_{di}$** (38 mg, 37%, (*m*,*m'*):others = 94:6) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (d, J = 16.2 Hz, 2H), 7.48 (d, J = 6.5 Hz, 2H), 6.58 (d, J = 16.2 Hz, 2H), 4.38 (t, J = 6.5 Hz, 2H), 4.28 (q, J = 7.1 Hz, 4H), 3.03 (t, J = 6.5 Hz, 2H), 1.83–1.72 (m, 4H), 1.67–1.62 (m, 2H), 1.35 (t, J = 7.1 Hz, 6H), 0.96 (d, J = 6.4 Hz, 6H), 0.76 (d, J = 6.3 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.90, 166.47 (2C), 158.50 (d, $J_{C\text{-}F}$ = 258.8 Hz), 136.02 (2C, d, $J_{C\text{-}F}$ = 3.9 Hz) 133.69 (d, $J_{C\text{-}F}$ = 4.2 Hz) 130.61 (2C, d, $J_{C\text{-}F}$ = 3.4 Hz), 123.45 (2C, d, $J_{C\text{-}F}$ = 12.6 Hz), 121.96 (2C, d, $J_{C\text{-}F}$ = 6.1 Hz), 119.44, 66.32, 60.71 (2C), 47.55, 47.34 (2C), 33.90, 25.97 (2C), 23.27 (2C), 22.38 (2C), 14.25 (2C) ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{29}H_{39}FNO_6$: 516.2756, found: 516.2751.

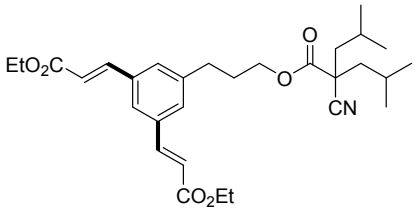
Diethyl 3,3'-(5-(2-((2-cyano-2-isobutyl-4-methylpentanoyl)oxy)-1-methoxyethyl)-1,3-phenylene)(2*E*,2'*E*)-diacrylate (**15na$_{di}$**):



GP was carried out with comound **5n** (66 mg, 0.2 mmol), olefin **10a** (80 mg, 0.8 mmol), $Pd(OAc)_2$ (5 mg, 10 mol %), Ac-Gly-OH (5 mg, 20 mol%), AgOAc (134 mg, 0.8 mmol) in HFIP (2 mL) at 55 °C for 36 h. Purification of the crude mixture by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 70:30) furnished the *meta*-olefinated product **15na$_{di}$** (80 mg, 76%, (*m*,*m'*):others = 97:3) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (d, J = 16.1 Hz, 2H), 7.61 (s, 1H), 7.56 (d, J = 1.4 Hz, 2H), 6.52 (d, J = 16.0 Hz, 2H), 4.53 (dd, J = 7.4, 4.1 Hz, 1H), 4.37–4.20 (m, 6H), 3.32 (s, 3H), 1.87–1.75 (m, 4H), 1.70–1.64 (m, 2H), 1.35 (t, J = 7.1 Hz, 6H), 1.02 (d, J = 6.4 Hz, 3H), 0.98 (d, J = 6.5 Hz, 3H), 0.85 (d, J = 6.2 Hz, 3H), 0.79 (d, J = 6.3 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.76, 166.52 (2C), 143.05 (2C), 139.43, 135.76 (2C), 127.70 (3C), 119.97 (2C), 119.41, 80.49, 68.87, 60.67

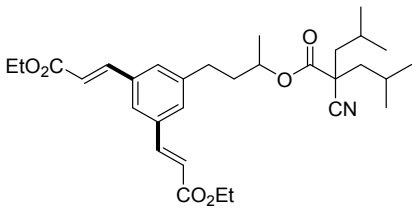
(2C), 57.30, 47.68, 47.39 (2C), 25.97, 25.95, 23.27, 23.25, 22.55, 22.40, 14.26 (2C) ppm. HRMS (ESI) calculated $[M+NH_4]^+$ for $C_{30}H_{45}N_2O_7$: 545.3221, found: 545.3210.

Diethyl 3,3'-(5-(3-((2-cyano-2-isobutyl-4-methylpentanoyl)oxy)propyl)-1,3-phenylene)(2*E*,2'*E*)-diacrylate (**15pa$_{di}$**):



GP was carried out with comound **5p** (63 mg, 0.2 mmol), olefin **10a** (80 mg, 0.8 mmol), $Pd(OAc)_2$ (5 mg, 10 mol %), Ac-Gly-OH (5 mg, 20 mol%), AgOAc (134 mg, 0.8 mmol) in HFIP (2 mL) at 55 °C for 36 h. Purification of the crude mixture by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 75:25) furnished the *meta*-olefinated product **15pa$_{di}$** (74 mg, 72%, (*m*,*m'*):others = 92:8) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 16.0 Hz, 2H), 7.52 (s, 1H), 7.38 (s, 2H), 6.47 (d, *J* = 16.0 Hz, 2H), 4.28 (q, *J* = 7.1 Hz, 4H), 4.20 (t, *J* = 6.4 Hz, 2H), 2.84–2.76 (m, 2H), 2.11–2.02 (m, 2H), 1.90–1.83 (m, 4H), 1.73–1.67 (m, 2H), 1.34 (t, *J* = 7.1 Hz, 6H), 1.06 (d, *J* = 6.3 Hz, 6H), 0.90 (d, *J* = 6.2 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.92, 166.66 (2C), 143.52 (2C), 142.07, 135.45 (2C), 129.52 (2C), 125.61, 119.60, 119.40 (2C), 65.25, 60.60 (2C), 47.62, 47.41 (2C), 31.68, 29.61, 26.06 (2C), 23.35 (2C), 22.58 (2C), 14.28 (2C) ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{30}H_{42}NO_6$: 512.3007, found: 512.3010.

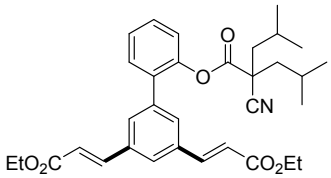
Diethyl 3,3'-(5-(3-((2-cyano-2-isobutyl-4-methylpentanoyl)oxy)butyl)-1,3-phenylene)(2*E*,2'*E*)-diacrylate (**15ra$_{di}$**):



GP was carried out with comound **5r** (66 mg, 0.2 mmol), olefin **10a** (80 mg, 0.8 mmol), $Pd(OAc)_2$ (5 mg, 10 mol %), Ac-Gly-OH (5 mg, 20 mol%), AgOAc (134 mg, 0.8 mmol) in HFIP (2 mL) at 55 °C for 36 h. Purification of the crude mixture by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 75:25) furnished the *meta*-olefinated product **15ra$_{di}$** (77 mg, 73%, (*m*,*m'*):others = 90:10) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 16.0 Hz, 2H), 7.51 (s, 1H), 7.36 (d, *J* = 1.1 Hz, 2H), 6.47 (d, *J* = 16.0 Hz, 2H), 5.01 (dq, *J* = 12.6, 6.3 Hz, 1H), 4.28 (q, *J* = 7.1 Hz, 4H), 2.84–2.75 (m, 1H), 2.73–2.65 (m, 1H), 2.08–2.01 (m, 1H), 1.95–1.81 (m, 5H), 1.73–1.66 (m, 2H), 1.38–1.31 (m,

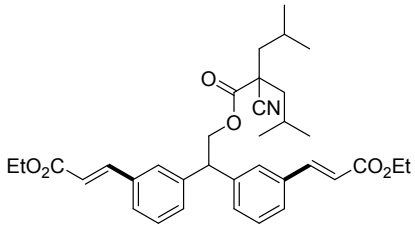
9H), 1.08 (dd, J = 6.3, 3.9 Hz, 6H), 0.93 (dd, J = 6.2, 2.0 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.46, 166.68 (2C), 143.56 (2C), 142.53, 135.43 (2C), 129.39 (2C), 125.52, 119.74, 119.35 (2C), 73.38, 60.61 (2C), 47.61, 47.46, 47.14, 37.06, 31.20, 26.10, 26.00, 23.31, 23.16, 22.98, 22.92, 19.47, 14.28 (2C) ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{31}H_{44}NO_6$: 526.3163, found: 526.3151.

Diethyl 3,3'-(2'-((2-cyano-2-isobutyl-4-methylpentanoyl)oxy)-[1,1'-biphenyl]-3,5-diyl)(2*E*,2'*E*)-diacrylate (**15wa$_{di}$**):



GP was carried out with comound **5w** (70 mg, 0.2 mmol), olefin **10a** (80 mg, 0.8 mmol), $Pd(OAc)_2$ (5 mg, 10 mol %), Ac-Gly-OH (5 mg, 20 mol%), AgOAc (134 mg, 0.8 mmol) in HFIP (2 mL) at 55 °C for 36 h. Purification of the crude mixture by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 75:25) furnished the *meta*-olefinated product **15wa$_{di}$** (86 mg, 79%, (*m*,*m'*):others = 97:3) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (d, J = 16.0 Hz, 2H), 7.65 (dd, J = 7.4, 1.3 Hz, 3H), 7.48–7.36 (m, 3H), 7.21 (d, J = 7.9 Hz, 1H), 6.54 (d, J = 16.0 Hz, 2H), 4.27 (q, J = 7.1 Hz, 4H), 1.71–1.65 (m, 2H), 1.63–1.54 (m, 4H), 1.34 (t, J = 7.1 Hz, 6H), 0.91 (d, J = 6.2 Hz, 6H), 0.73 (d, J = 6.3 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.29, 166.51 (2C), 147.14, 143.03 (2C), 138.42, 135.49 (2C), 133.41, 131.07, 130.26 (2C), 129.27, 127.02, 126.70, 122.28, 120.03 (2C), 119.06, 60.62 (2C), 47.49, 46.69 (2C), 25.89 (2C), 23.29 (2C), 22.96 (2C), 14.23 (2C) ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{33}H_{40}NO_6$: 546.2850, found: 546.2857.

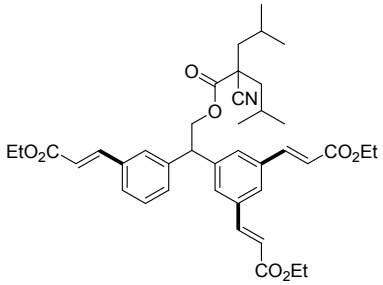
Diethyl 3,3'-((2-((2-cyano-2-isobutyl-4-methylpentanoyl)oxy)ethane-1,1-diyl)bis(3,1-phenylene))(2*E*,2'*E*)-diacrylate (**24**):



GP was carried out with comound **5v** (75 mg, 0.2 mmol), olefin **10a** (80 mg, 0.8 mmol), $Pd(OAc)_2$ (5 mg, 10 mol %), Ac-Gly-OH (5 mg, 20 mol%), AgOAc (134 mg, 0.8 mmol) in HFIP (2 mL) at 55 °C for 36 h. Purification of the crude mixture by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 75:25) furnished the *meta*-olefinated product **24** (67 mg, 59%, (*m*,*m'*):others = 88:12) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, J = 16.0 Hz, 2H), 7.47–7.39 (m, 4H), 7.37 (t, J = 7.6 Hz, 2H), 7.31 (d, J = 7.6 Hz, 2H), 6.43 (d, J = 16.0 Hz, 2H), 4.73 (d, J = 7.4 Hz, 2H), 4.50 (t, J =

7.3 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 4H), 1.74–1.65 (m, 2H), 1.64–1.54 (m, 4H), 1.33 (t, *J* = 7.1 Hz, 6H), 0.88 (d, *J* = 6.3 Hz, 6H), 0.68 (d, *J* = 6.4 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.80, 166.77 (2C), 144.02 (2C), 140.71 (2C), 135.07 (2C), 129.97 (2C), 129.39 (2C), 127.86 (2C), 126.81 (2C), 119.28, 118.85 (2C), 68.26, 60.52 (2C), 49.23, 47.61, 47.29 (2C), 25.91 (2C), 23.09 (2C), 22.45 (2C), 14.27 (2C) ppm. HRMS (ESI) calculated $[M+Na]^+$ for $C_{35}H_{43}NNaO_6$: 596.2983, found: 596.2988.

Diethyl 3,3'-(5-(2-((2-cyano-2-isobutyl-4-methylpentanoyl)oxy)-1-(3-((E)-3-ethoxy-3-oxoprop-1-en-1-yl)phenyl)ethyl)-1,3-phenylene)(2*E*,2'*E*)-diacrylate (**25**):

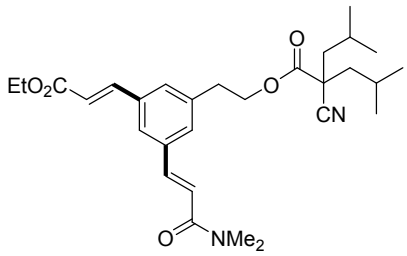


GP was carried out with comound **5v** (75 mg, 0.2 mmol), olefin **10a** (120 mg, 1.2 mmol), $Pd(OAc)_2$ (5 mg, 10 mol %), Ac-Gly-OH (5 mg, 20 mol%), AgOAc (200 mg, 1.2 mmol) in HFIP (2 mL) at 55 °C for 36 h. Purification of the crude mixture by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 60:40) furnished the tri *meta*-olefinated product **25** (41 mg, 31%, (*m*,*m'*,*m''*):others = 87:13) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (dd, *J* = 16.0, 2.1 Hz, 3H), 7.57 (s, 1H), 7.47–7.36 (m, 5H), 7.30 (d, *J* = 7.8 Hz, 1H), 6.46 (d, *J* = 16.0 Hz, 2H), 6.43 (d, *J* = 16.0 Hz, 1H), 4.74 (qd, *J* = 11.1, 7.4 Hz, 2H), 4.52 (t, *J* = 7.3 Hz, 1H), 4.29–4.23 (m, 6H), 1.74–1.67 (m, 2H), 1.64–1.55 (m, 4H), 1.34 (td, *J* = 7.1, 1.7 Hz, 9H), 0.88 (dd, *J* = 9.2, 4.5 Hz, 6H), 0.68 (dd, *J* = 9.2, 6.4 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.81, 166.74, 166.50 (2C), 143.88, 143.13 (2C), 141.62, 140.23, 135.81 (2C), 135.25, 129.86, 129.54, 129.19 (2C), 127.88, 126.98, 126.20, 119.90 (2C), 119.24, 119.06, 68.06, 60.67 (2C), 60.56, 49.12, 47.59, 47.32 (2C), 25.94 (2C), 23.12, 23.09, 22.47, 22.45, 14.28, 14.26 (2C) ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{40}H_{50}NO_8$: 672.3531, found: 672.3519.

2.5.3. General procedure for hetero *meta*-selective bis-olefination:

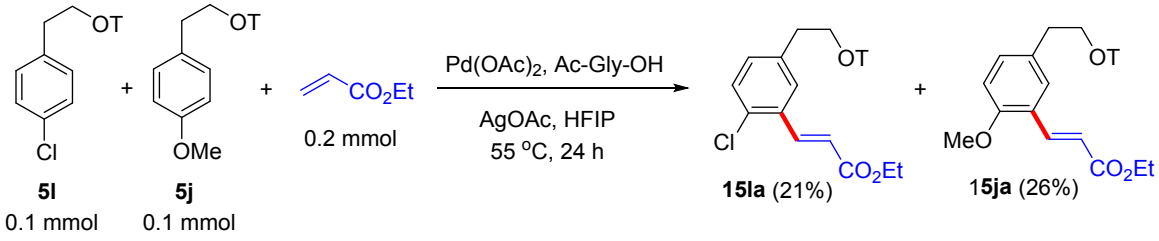
An oven dried 10 mL glass vial equipped with a magnetic stir-bar was charged with substrate (0.2 mmol), olefin (0.4 mmol), $Pd(OAc)_2$ (10 mol %), Ac-Gly-OH (20 mol%), AgOAc (0.4 mmol), and hexafluoroisopropanol (HFIP) (2 mL), then the resulting mixture was heated in a 55 °C oil bath with rapid stirring for 36 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and filtered through a short pad of celite. Evaporation of the solvent(s) under reduced pressure and purification of the residue by silica gel column chromatography using petroleum ether/ethyl acetate as the eluent provided the desired *meta*-olefinated product.

3-((*E*)-3-(Dimethylamino)-3-oxoprop-1-en-1-yl)-5-((E)-3-ethoxy-3-oxoprop-1-en-1-yl)phenethyl 2-cyano-2-isobutyl-4-methylpentanoate (**26**):



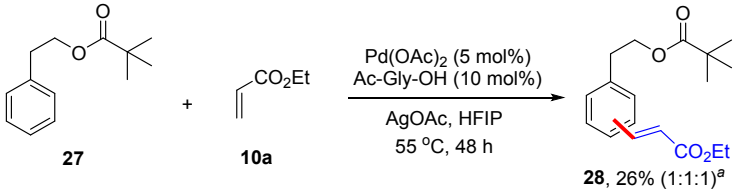
GP was carried out with comound **15aa** (80 mg, 0.2 mmol), olefin **10o** (79 mg, 0.4 mmol), $Pd(OAc)_2$ (5 mg, 10 mol %), Ac-Gly-OH (5 mg, 20 mol%), AgOAc (67 mg, 0.4 mmol) in HFIP (2 mL) at 55 °C for 36 h. Purification of the crude mixture by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 45:55) furnished the *meta*-olefinated product **26** (61 mg, 61%, (*m*,*m'*):others = 96:4) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, J = 16 Hz, 1H), 7.64 (d, J = 15.6 Hz, 1H), 7.51 (d, J = 1.3 Hz, 2H), 7.40 (s, 1H), 7.00 (d, J = 15.6 Hz, 1H), 6.48 (d, J = 16.0 Hz, 1H), 4.39 (t, J = 6.4 Hz, 2H), 4.27 (q, J = 7.1 Hz, 2H), 3.20 (s, 3H), 3.11–3.04 (m, 5H), 1.80–1.67 (m, 4H), 1.66–1.60 (m, 2H), 1.34 (t, J = 7.1 Hz, 3H), 0.95 (d, J = 6.4 Hz, 6H), 0.74 (d, J = 6.3 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.90, 166.69, 166.37, 143.52, 141.10, 138.68, 136.49, 135.46, 129.56, 129.27, 126.52, 119.55, 119.36, 118.81, 66.57, 60.60, 47.58, 47.38 (2C), 37.46, 35.97, 34.51, 25.97 (2C), 23.31 (2C), 22.35 (2C), 14.28 ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{29}H_{41}N_2O_5$: 497.3010, found: 497.3005.

2.6. Intermolecular competetion experiment:



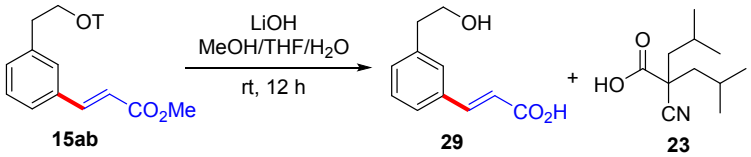
An oven dried 10 mL glass vial equipped with a magnetic stir-bar was charged with substrate **5l** (0.1 mmol), substrate **5j** (0.1 mmol), olefin (0.2 mmol), $Pd(OAc)_2$ (10 mol %), Ac-Gly-OH (20 mol%), AgOAc (0.2 mmol), and hexafluoroisopropanol (HFIP) (2 mL), then the resulting mixture was heated in a 55 °C oil bath with rapid stirring for 24 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and filtered through a short pad of celite. Evaporation of the solvent(s) under reduced pressure and purification of the residue by silica gel column chromatography using petroleum ether/ethyl acetate as the eluent provided the product **15la** (9 mg, 21%) and **15ja** (11 mg, 26%).

2.7. Control experiment:



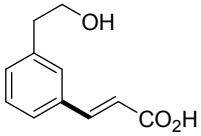
An oven dried 10 mL glass vial equipped with a magnetic stir-bar was charged with compound **27** (0.2 mmol), ethyl acrylate (0.4 mmol), $Pd(OAc)_2$ (10 mol %), Ac-Gly-OH (20 mol%), AgOAc (0.4 mmol), and hexafluoroisopropanol (HFIP) (2 mL), then the resulting mixture was heated in a 55 °C oil bath with rapid stirring for 48 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and filtered through a short pad of celite. Evaporation of the solvent(s) under reduced pressure and the crude products was submitted for ^{1}H NMR analyusis using CH_2Br_2 as external standard (**28**, yield 26% selectivity 1:1:1).

2.8. General procedures for cleavage of template



To the solution of compound **15ab** (60 mg, 0.15 mmol) in MeOH (1.2 mL), THF (0.6 mL), and H_2O (0.3 mL) was added $LiOH{\cdot}H_2O$ (38 mg, 0.90 mmol) at room temperature. The resulting mixture was stirred at room temperature for 24 h. The organic solvents were removed under reduced pressure, and the resulting residue was diluted with H_2O (15mL). The aqueous phase was acidified with 2M HCl (2 mL) and extracted with EtOAc (3 x 10 mL). The combined organic exctract was dried over Na_2SO_4, concentrated in rotavap and purified by flash column chromatography to get the diacid product **29** (27 mg, 94%) along with recovered template **23** (27 mg, 91% yield).

(*E*)-3-(3-(2-hydroxyethyl)phenyl)acrylic acid (**29**):



^{1}H NMR (400 MHz, $CDCl_3$+ DMSOd_6): δ = 7.68 (d, J = 16.2 Hz, 1H), 7.40 (s, 2H), 7.33 (t, J = 7.7 Hz, 1H), 7.26 (d, J = 7.5 Hz, 1H), 6.44 (d, J = 16.0 Hz, 1H), 4.79 (brs, 2H), 3.87 (t, J = 5.9 Hz, 2H), 2.89 (t, J = 6.4 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$ + DMSOd_6): δ = 169.05, 145.01, 139.48, 134.66, 130.89, 128.94, 128.68, 126.12, 118.47, 63.23, 38.93 ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{11}H_{13}O_3$: 193.0859, found: 193.0865.

3. DFT Computational Details:

***meta*-C−H activation by the mononuclear Pd complex:**

The carboxylate assisted concerted metalation deportation mechanism is the most predominant pathway for the C-H activation catalyzed by the palladium –carboxylate. First, the trimeric palladium acetate converted into monomer, ($Pd(OAc)_2$). The mechanism of the catalytic process was studied through three key steps: 1) activation of meta−CH bond, 2) Alkene insertion, and 3) β- hydride elimination. Figure S1 of supporting information (SI) shows the catalytic steps along with the complete free energy profile of the Pd monomeric mechanism. The first step is the *meta*-C−H bond activation of the substrate, this approach is based on the earlier reports.[1,2] First, the addition of the substrate to the palladium monomer forms a weakly coordinated nitrile group to the Pd center (**Int0a_a**) with energy of **18.21 kcal mol^{-1}.** The dihedral angle at the oxygen of the ether group of substrate helps in the bending of the aromatic ring towards the palladium center in **Int0_a**. The difference in values of free energy and enthalpy for this conversion are 16.21 and 8.71 kcal mol^{-1}, respectively, as compared to the trimeric palladium acetate. The natural charges on the Pd and *meta*-carbon atoms are 0.7022e and -0.1929e, respectively. The Pd−O bond of one of the acetate group breaks, and the hydrogen of the *meta*-carbon atom of the aromatic ring migrates to the oxygen of the acetate group by forming an intermediate, **Int1_a**. This intermediate has 9.01 kcal mol^{-1} higher energy than the reactants. In this conversion, the charge on Pd atom changes to 0.5293e. The WBI of Pd−C bond changes from the 0.0012 to 0.7377. The conversion from **Int0_a** to **Int1** occurs through the transition state (TS1_a). The TS1_a was verified by the intrinsic reaction curve (IRC) by connecting the reactant and product, which is shown in Figure S2 (A). The activation free energy of TS1_a is 29.11, and the activation enthalpy is 24.0 kcal mol^{-1}. The WBI of Pd–C and O—H bonds of acetate are 0.4299 and 0.3276, respectively. After the activation of C−H bond, the second step is the insertion of the alkene group near to palladium center after removal of the acetic acid. This step leads to the formation of the intermediate **Int2_a**. In this intermediate, both carbons of the alkene group are within same distance (2.15 Å) from the metal center, and WBI of Pd center with carbon atoms is nearly equal to 0.4. The Int3_a is obtained after the breaking of the Pd−C (aromatic ring) and formation of C−C bond with beta carbon of alkene. At the same time, the alpha carbon atom forms a bond with Pd center. The bond distance of Pd−C is the 2.06 and WBI of this bond is 0.7164. The natural charge on the metal center changes to 0.4929 from 0.4463. The conversion of the **Int2_a** to **Int3_a** happens through the formation of transition state, TS2_a. The corresponding IRC and the transition state are shown in **Figure S2**. During the formation of the transition state, the WBI of Pd−C (meta carbon) changes from 0.7192 to 0.4913, and at the same time, the C(meta)−C(β) changes from 0.017 to 0.4785. These WBI values give evidence of breaking Pd−C(meta) bond and forming the C−C bond. The required activation energy for the formation of this transition state

is 16.13 kcal mol^{-1}. The formation of **Int2_a** and **Int3_a** needs the free energies of 5.59 and -7.33 kcal mol^{-1}, respectively. The orientation of hydrogen atom on the β-carbon towards the Pd center facilitates the formation of an intermediate **Int4_a**. The distance between Pd and hydrogen is 3.57Å, and the WBI value for the Pd-H is 0.0039. These values suggest that the atoms are in the non-bonded state. The hydrogen atom is transferred to the metal center as the hydride from the intermediate **Int5_a**, where the Pd−H bond distance is 1.53 Å. This conversion from Int4_a to Int5_a occurs through the transition state TS3_a, which is shown in Figure S2. The activation free energy for the formation of TS3_a requires 16.65 kcal mol^{-1}, and the activation enthalpy is 6.79 kcal mol^{-1}. The formation of Int4_a and Int5_a requires the free energies of -2.50 and 9.50 kcal mol^{-1}, respectively. The conversion of the TS3_a to Int5_a, the charge on the Pd center changes from 0.3727e to 0.3613e and the WBI of the bond Pd−H changes to 0.7476 from 0.1459. The bond index for the Pd−C(α) in Int5_a was computed as 0.3378, and the WBI of Pd−N is 0.0091. By comparing overall three steps of the mechanism, we observe that the activation of the C−H bond is the rate determining step.

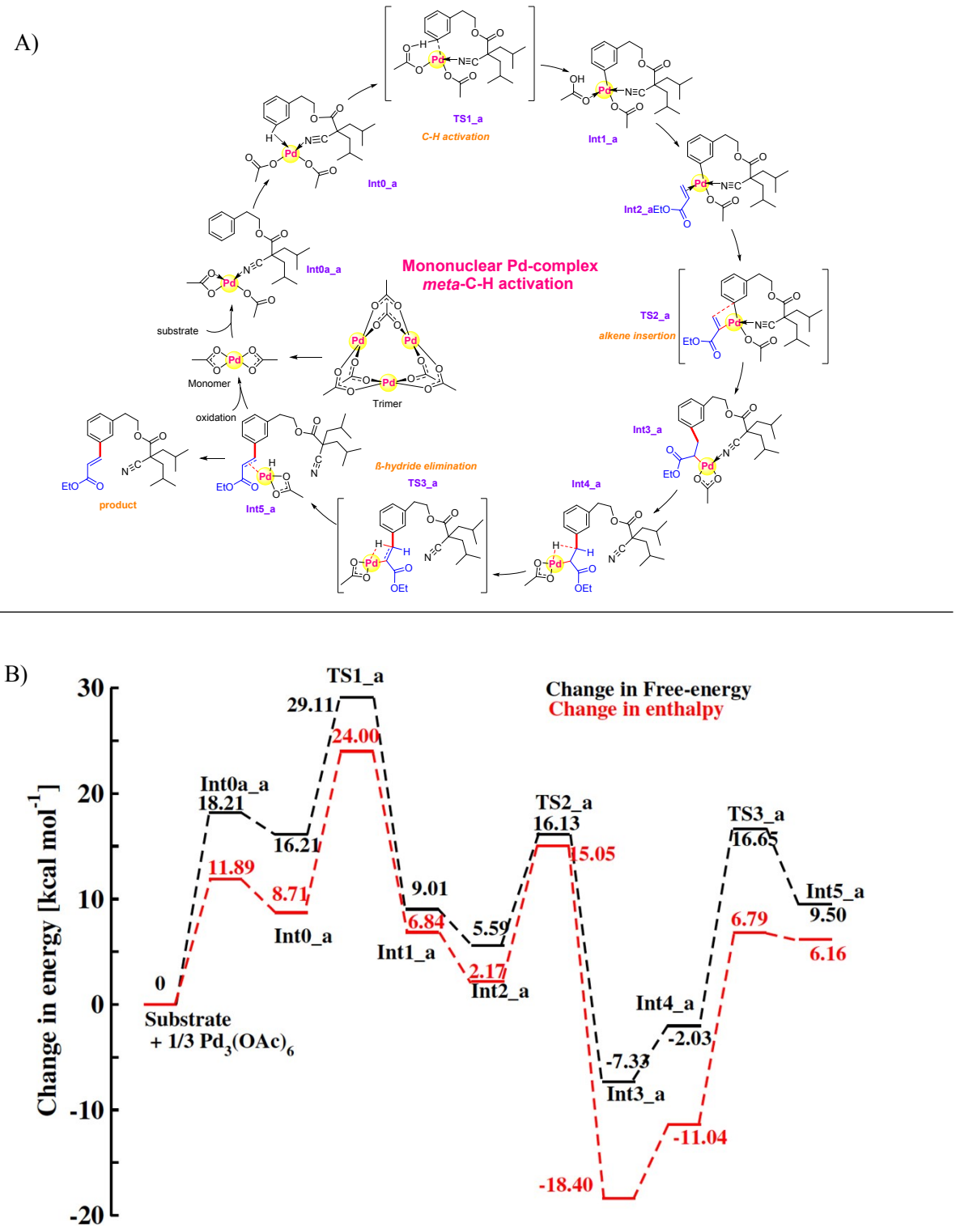


Figure S1. A) Detailed mechanism of *meta* C—H activation catalyzed by the $Pd_3(OAc)_6$. B) The energy profile computed at the B3LYP/ LANL2DZ+f (Pd, Ag)/6-31G(d) (for other), M06/SDD (for metal atoms)/6-311++G(d,p).

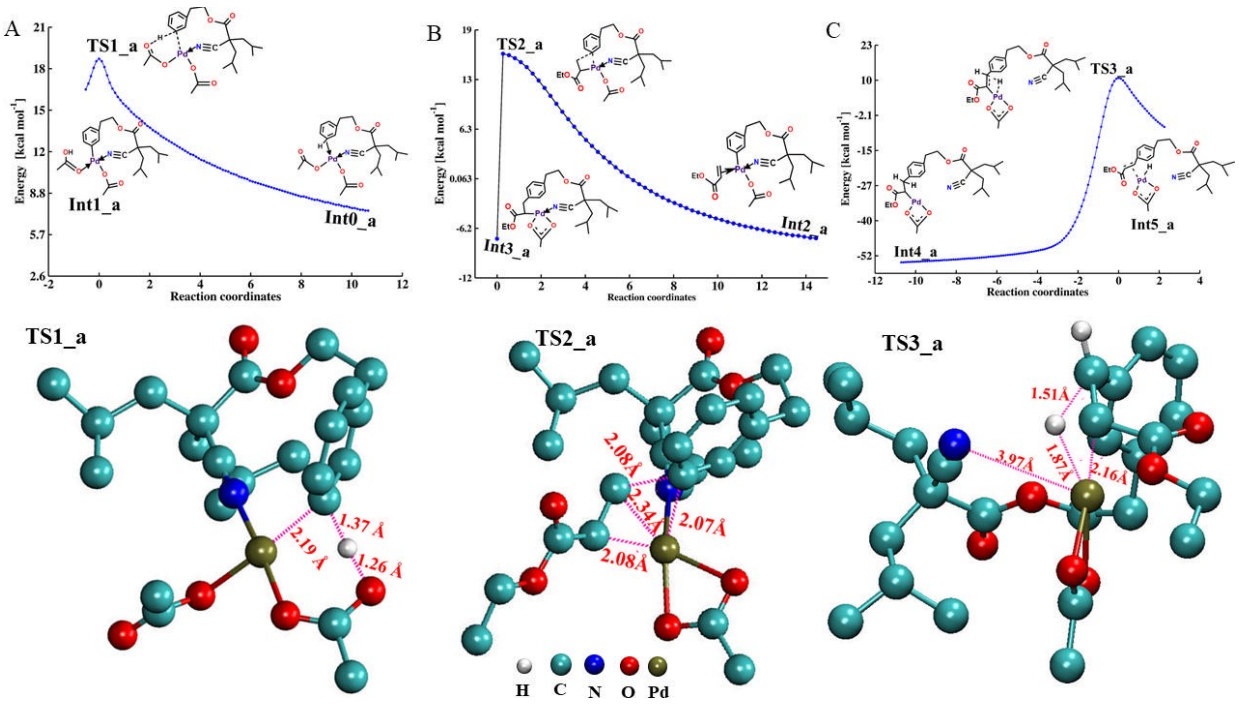


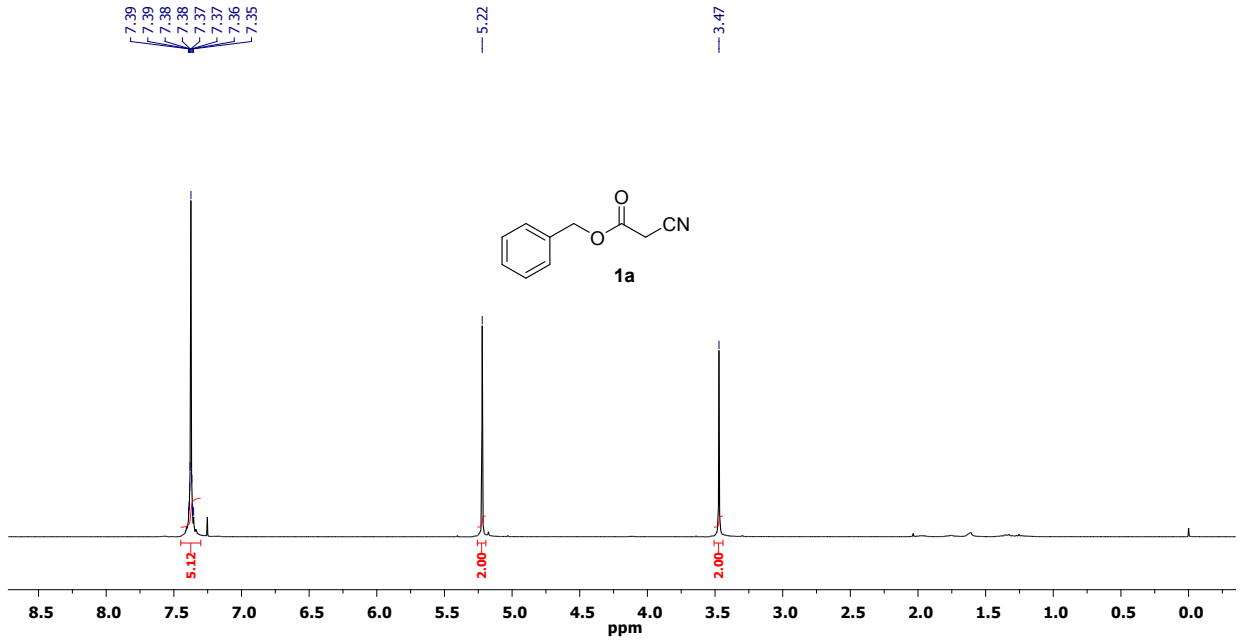
Figure S2. The A, B and C represents the Intrinsic Reaction Curves (IRCs) for the meta C—H activation, Alkene Insertion and β-Hydride elimination respectively. The corresponding transition states are shown in the same order (Hydrogen atoms are omitted for the Clarity of the structure).

References:

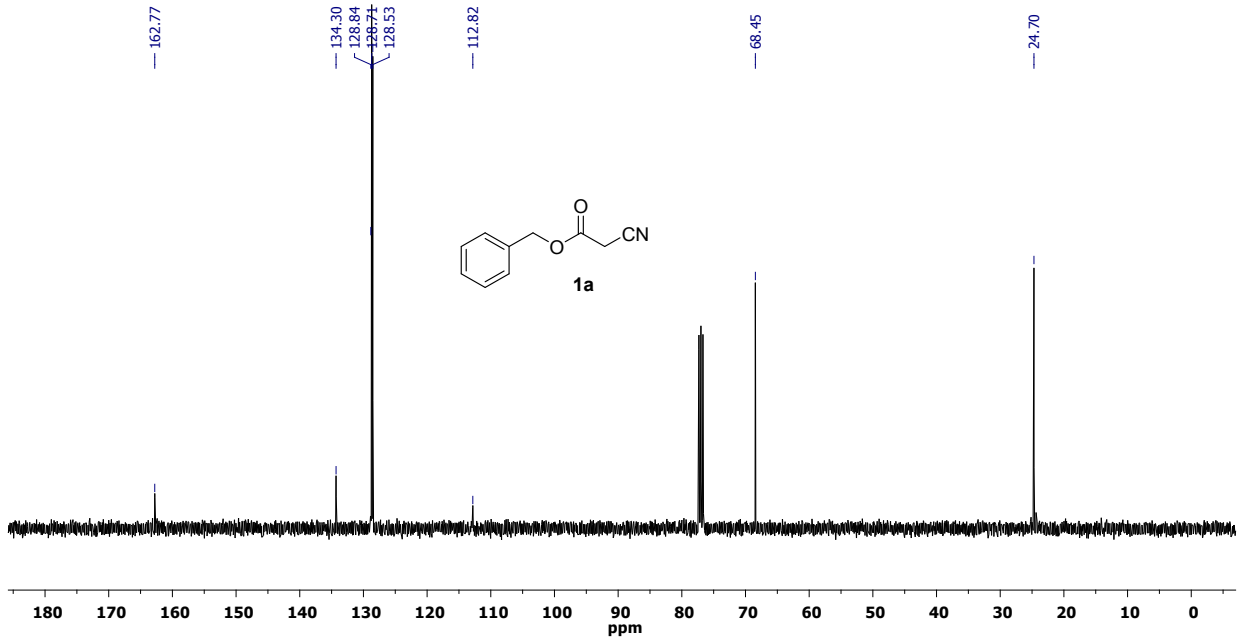
1) Dutta, U.; Modak, A.; Bhaskararao, B.; Bera, M.; Bag, S.; Mondal, A.; Lupton, D. W.; Sunoj, R. B.; Maiti, D. Catalytic Arene Meta-C–H Functionalization Exploiting a Quinoline-Based Template. *ACS Catal.* **2017**, *7*, 3162–3168.

2) Yang, Y.-F.; Cheng, G.-J.; Liu, P.; Leow, D.; Sun, T.-Y.; Chen, P.; Zhang, X.; Yu, J.-Q.; Wu, Y.-D.; Houk, K. N. Palladium-Catalyzed Meta-Selective C–H Bond Activation with a Nitrile-Containing Template: Computational Study on Mechanism and Origins of Selectivity. *J. Am. Chem. Soc.* **2014**, *136*, 344–355.

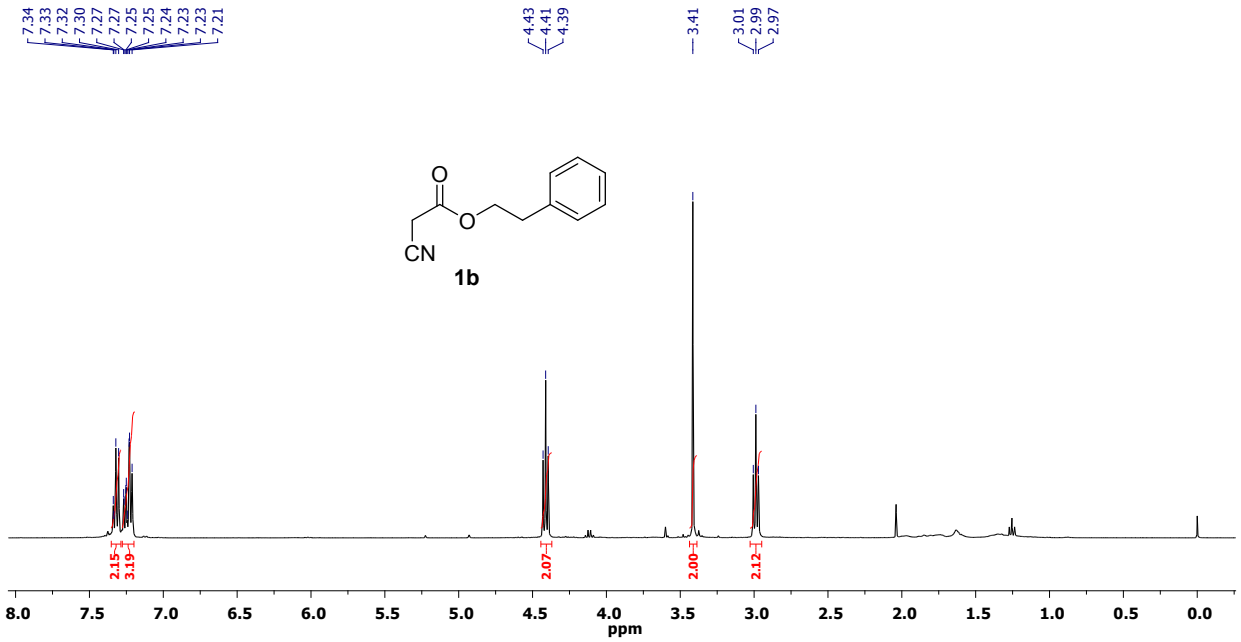
^{1}H NMR, ^{13}C NMR Spectra:



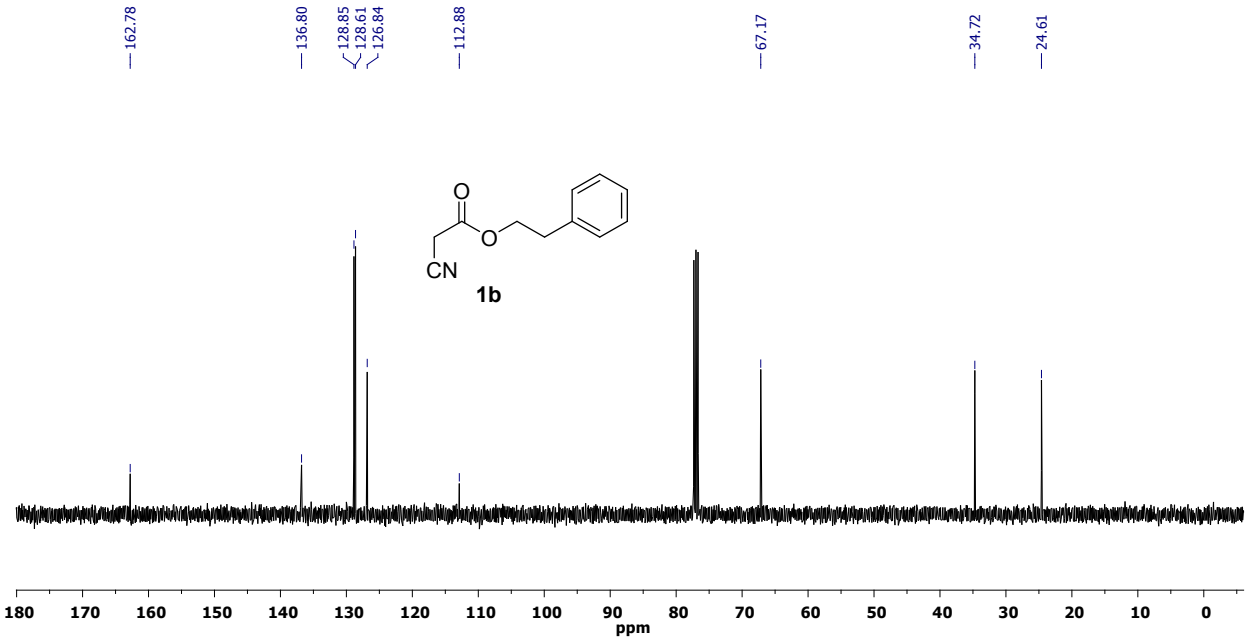
^{1}H-NMR (400 MHz) spectrum of **1a** in $CDCl_3$



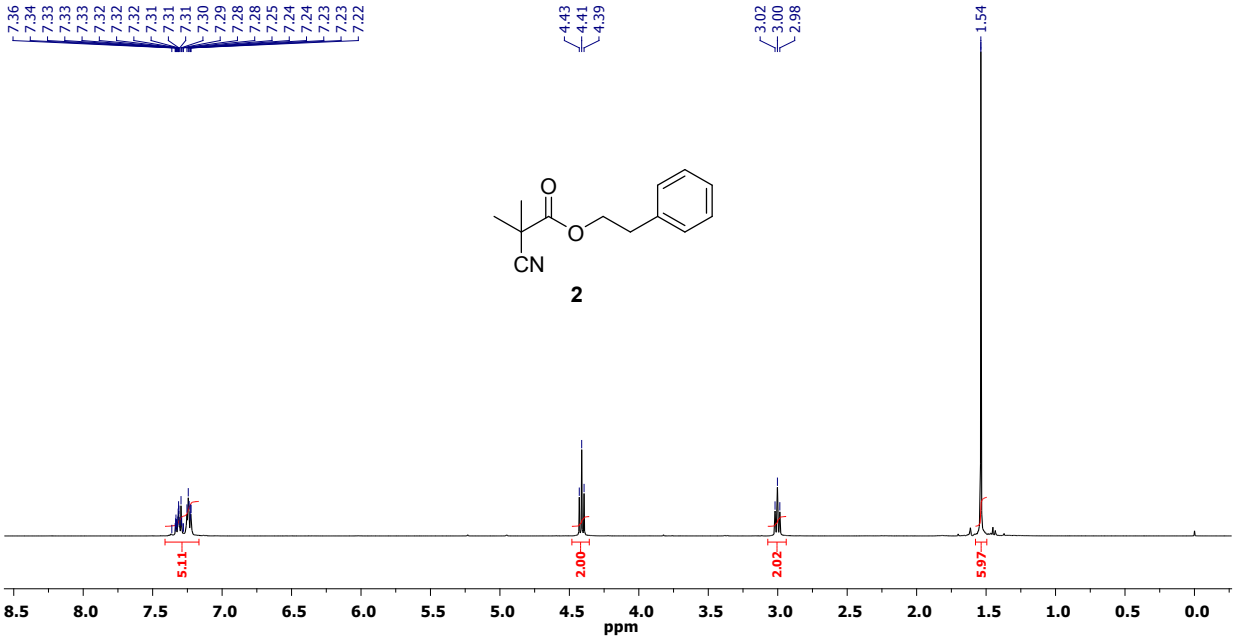
^{13}C-NMR (100 MHz) spectrum of **1a** in $CDCl_3$



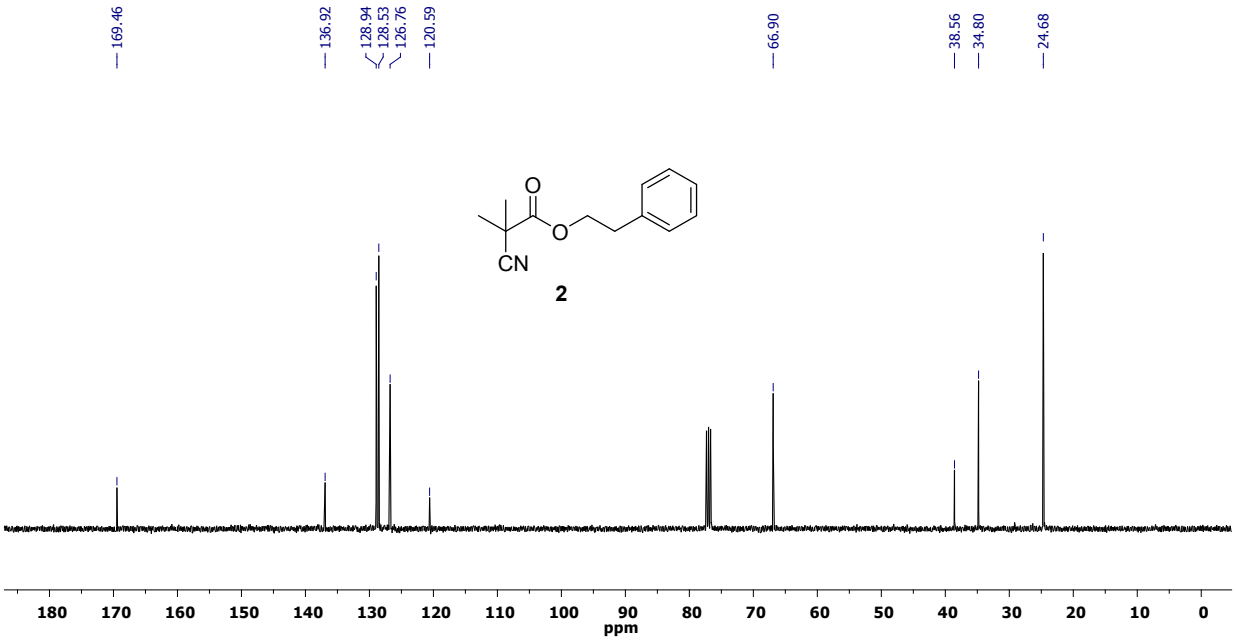
^{1}H-NMR (400 MHz) spectrum of **1b** in $CDCl_3$



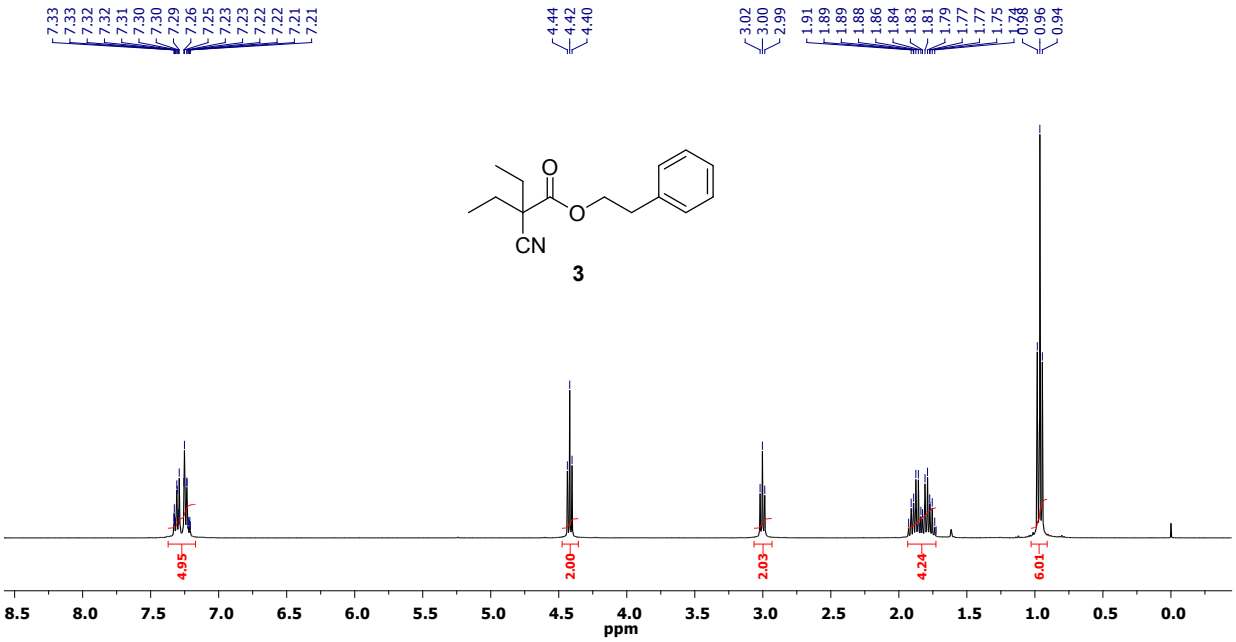
^{13}C-NMR (100 MHz) spectrum of **1b** in $CDCl_3$



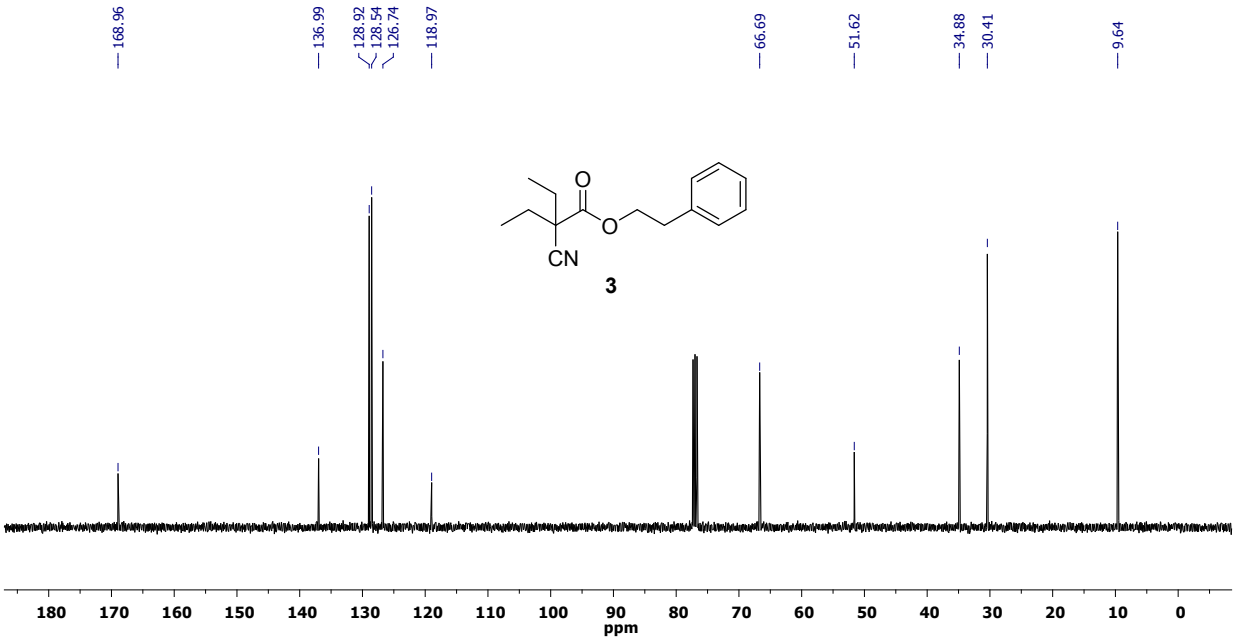
^{1}H-NMR (400 MHz) spectrum of **2** in $CDCl_3$



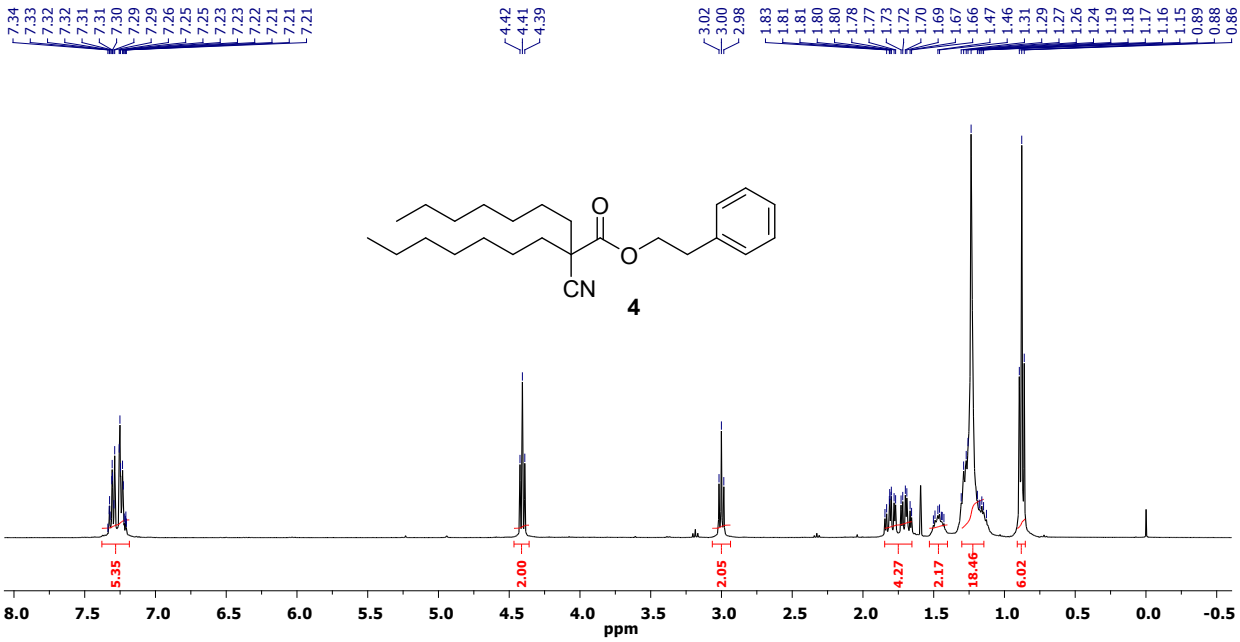
^{13}C-NMR (100 MHz) spectrum of **2** in $CDCl_3$



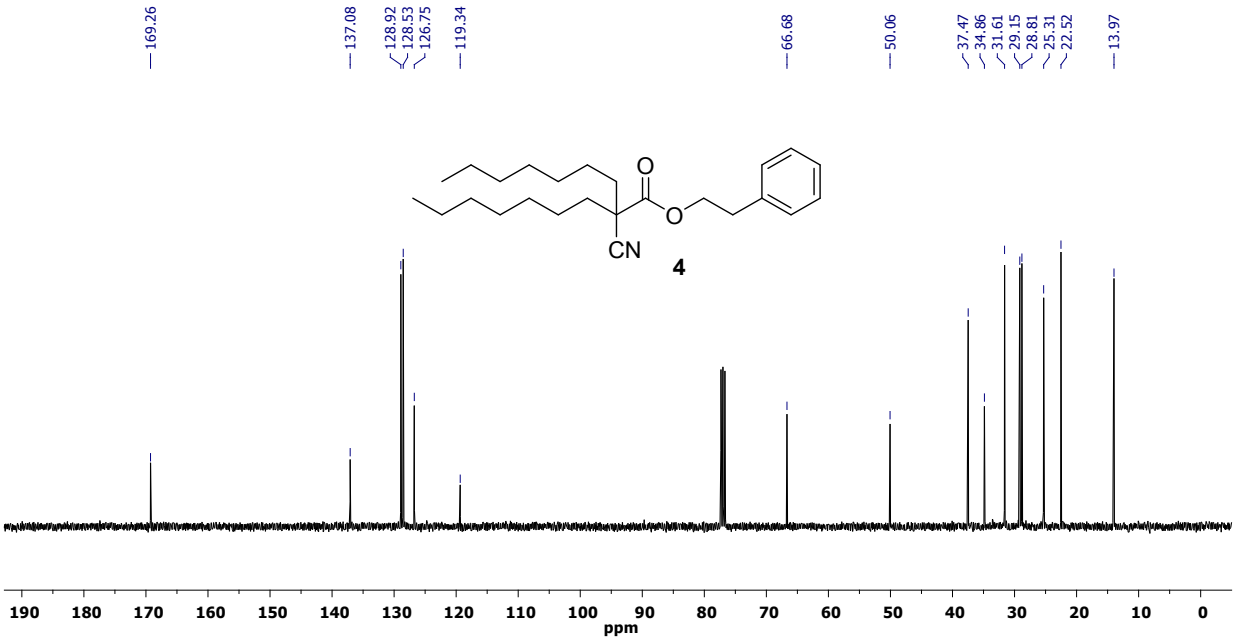
^{1}H-NMR (400 MHz) spectrum of **3** in $CDCl_3$



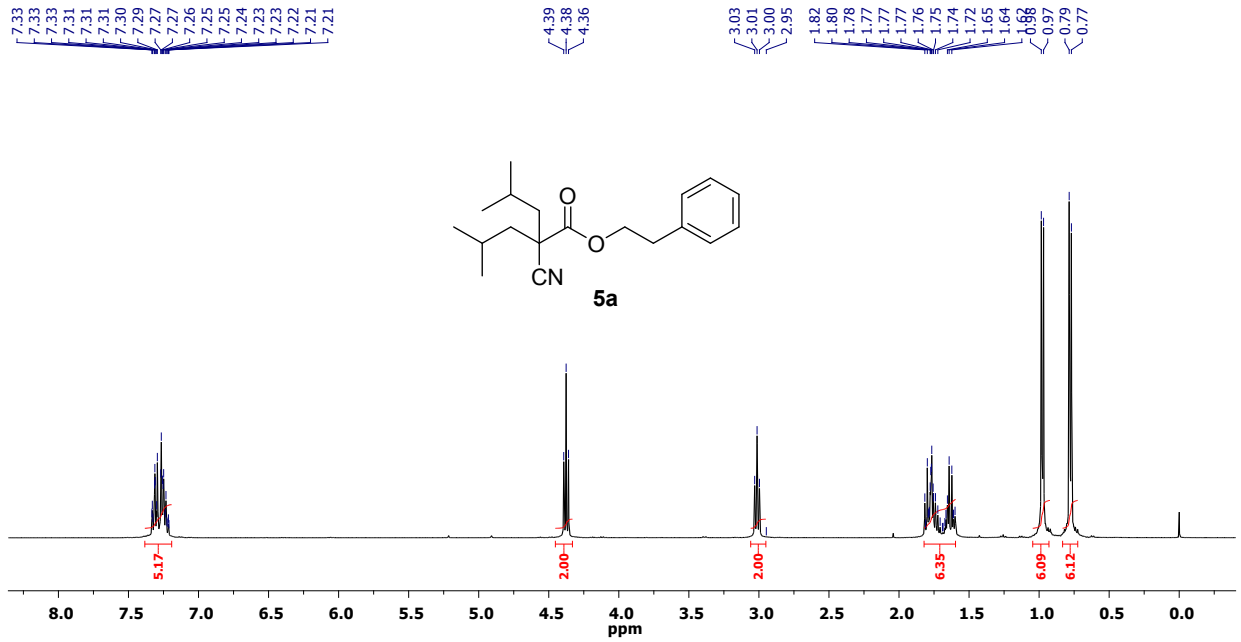
^{13}C-NMR (100 MHz) spectrum of **3** in $CDCl_3$



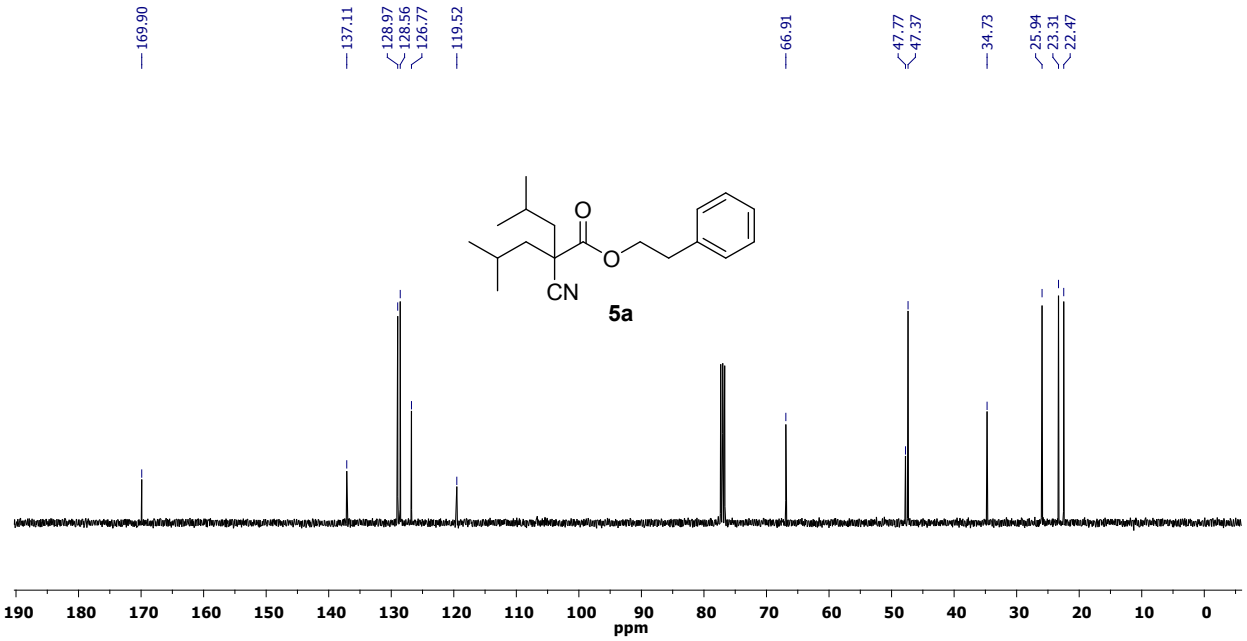
^{1}H-NMR (400 MHz) spectrum of **4** in $CDCl_3$



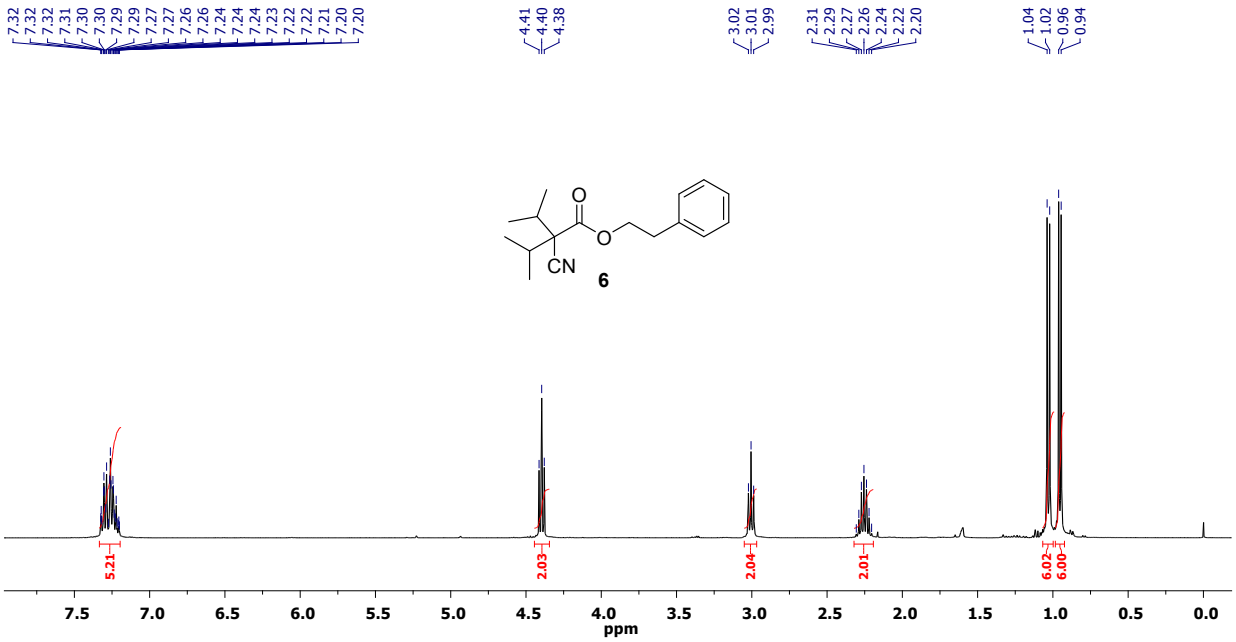
^{13}C-NMR (100 MHz) spectrum of **4** in $CDCl_3$



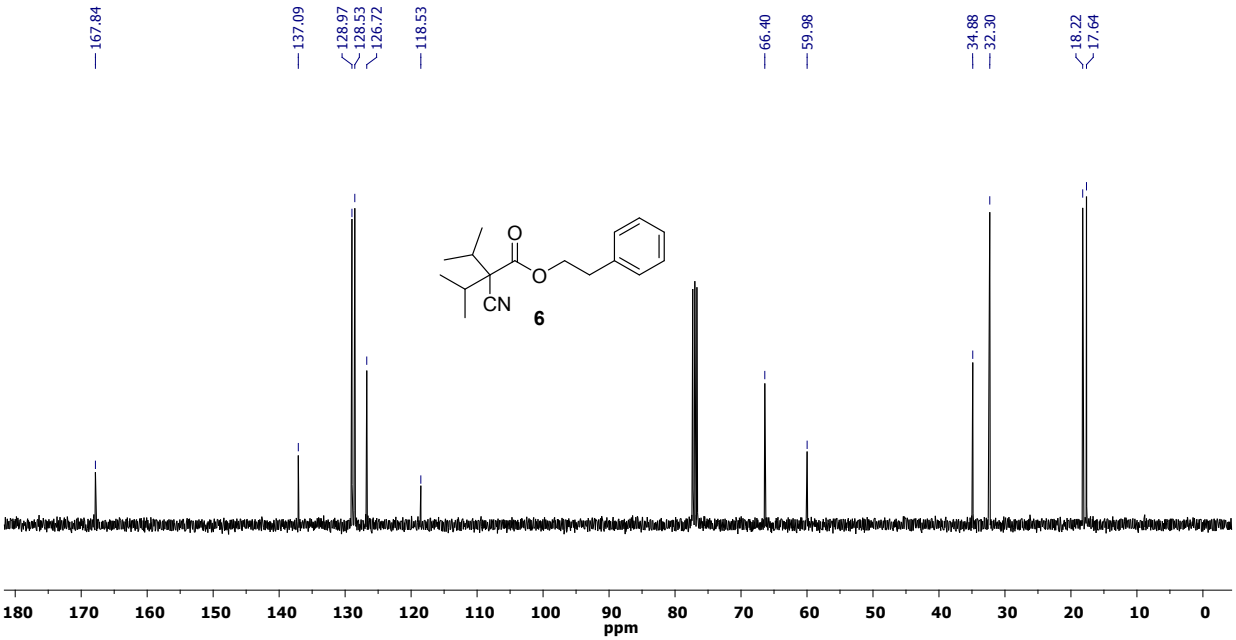
^{1}H-NMR (400 MHz) spectrum of **5a** in $CDCl_3$



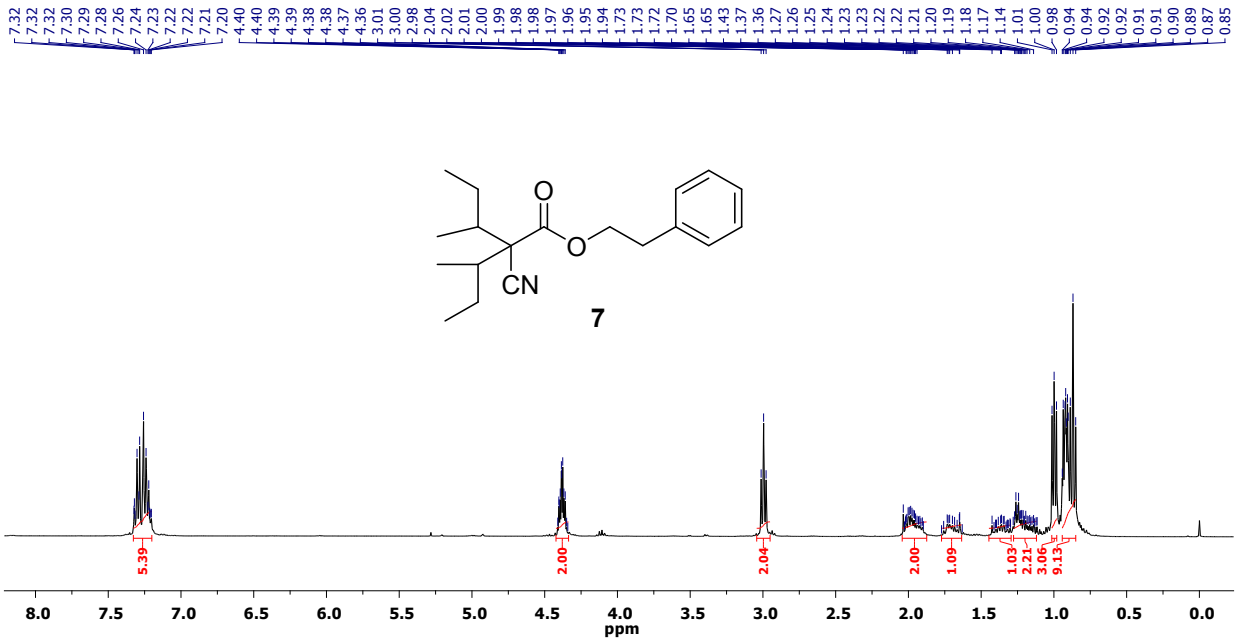
^{13}C-NMR (100 MHz) spectrum of **5a** in $CDCl_3$



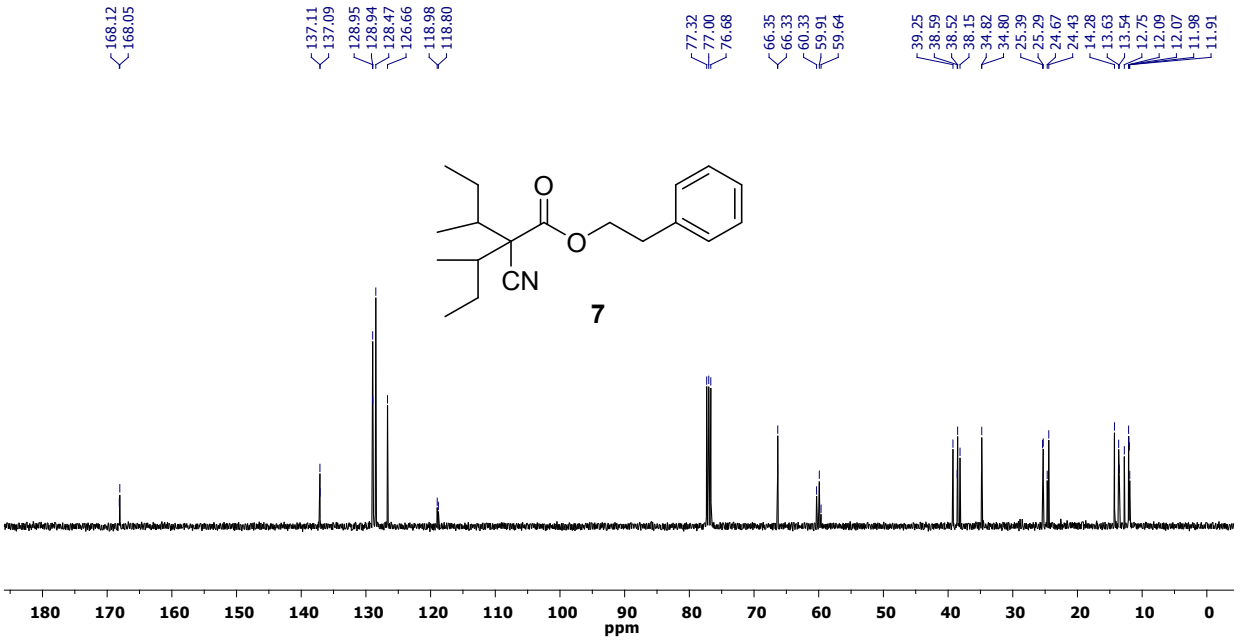
^{1}H-NMR (400 MHz) spectrum of **6** in $CDCl_3$



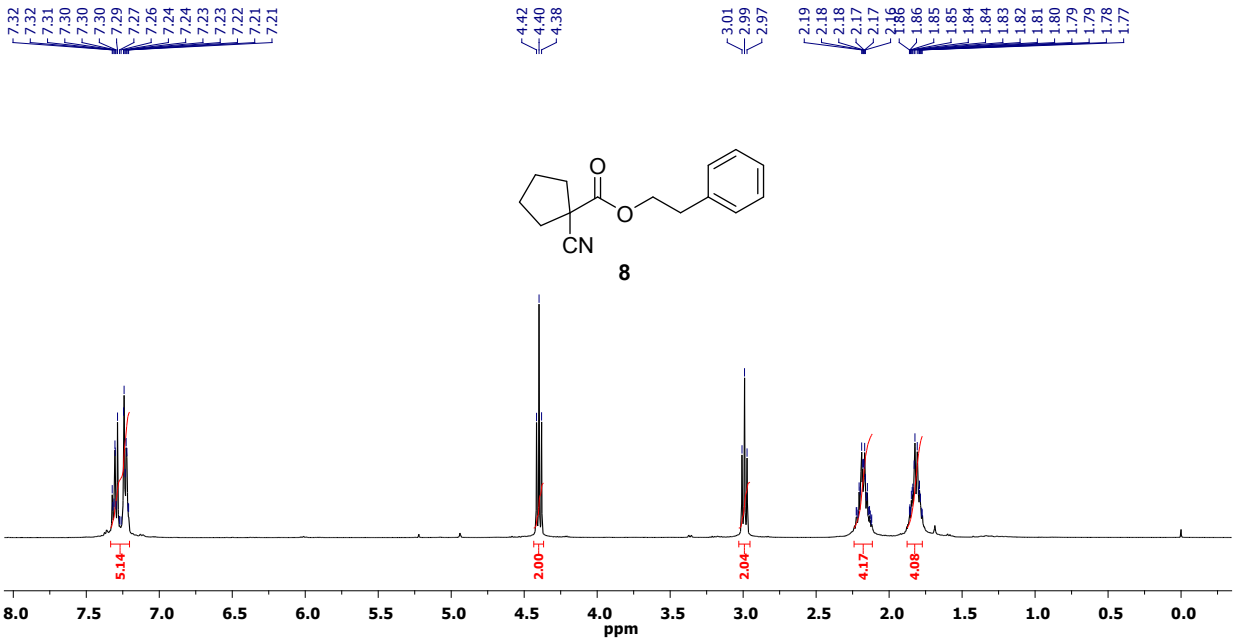
^{13}C-NMR (100 MHz) spectrum of **6** in $CDCl_3$



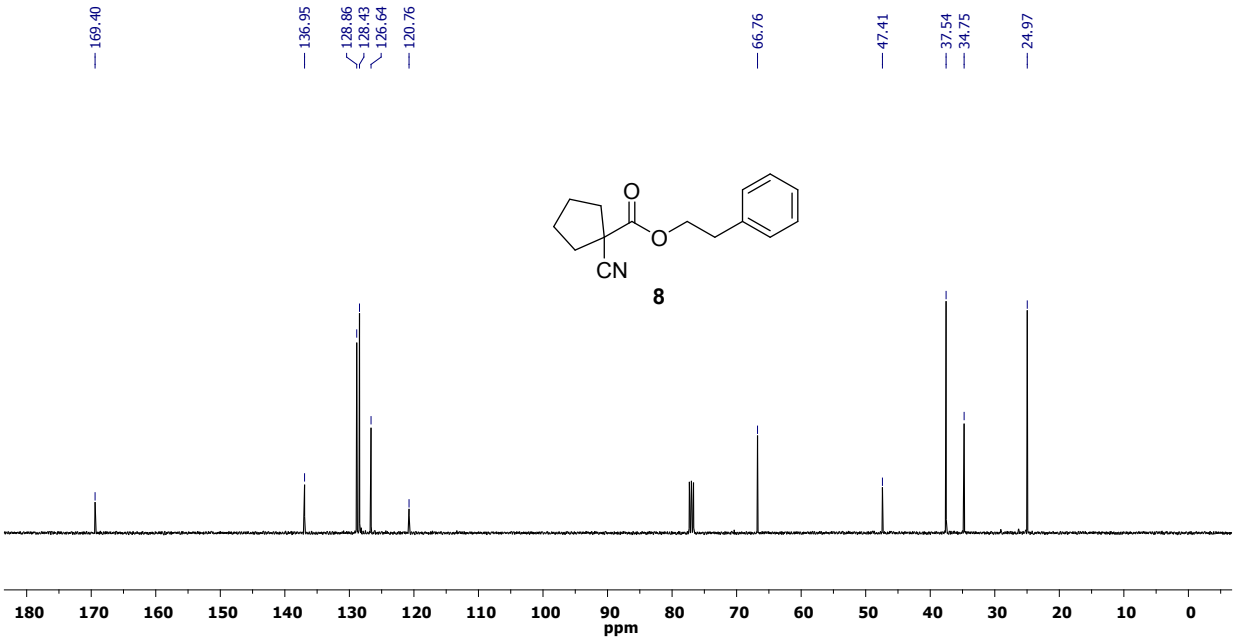
^{1}H-NMR (400 MHz) spectrum of **7** in $CDCl_3$



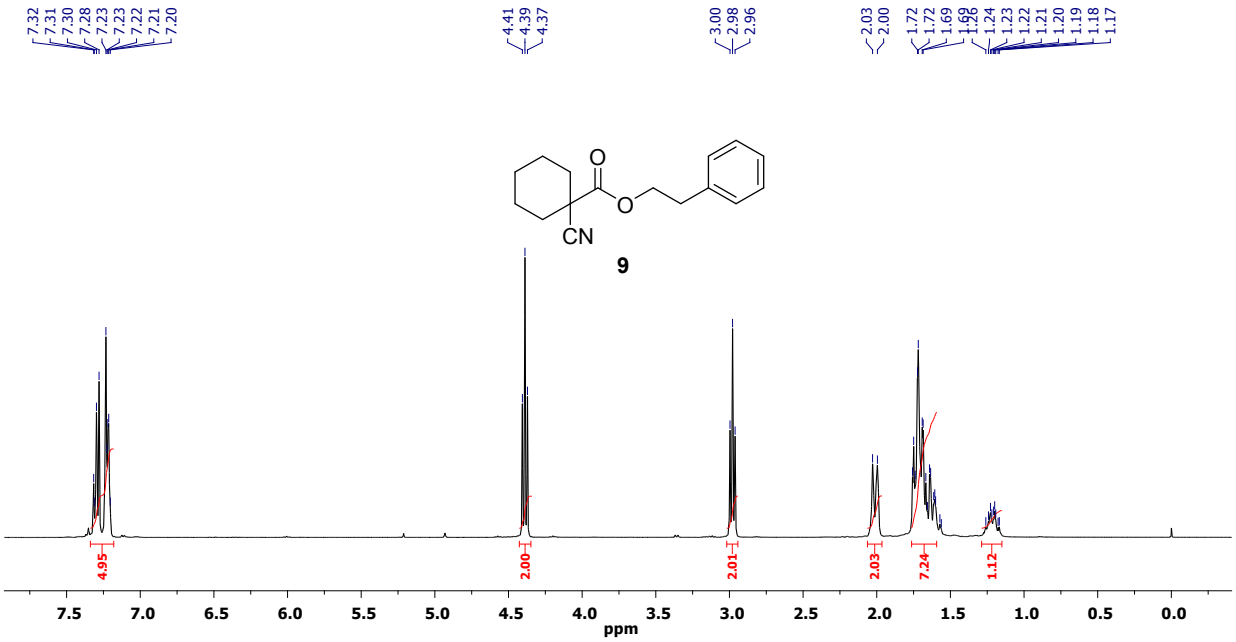
^{13}C-NMR (100 MHz) spectrum of **7** in $CDCl_3$



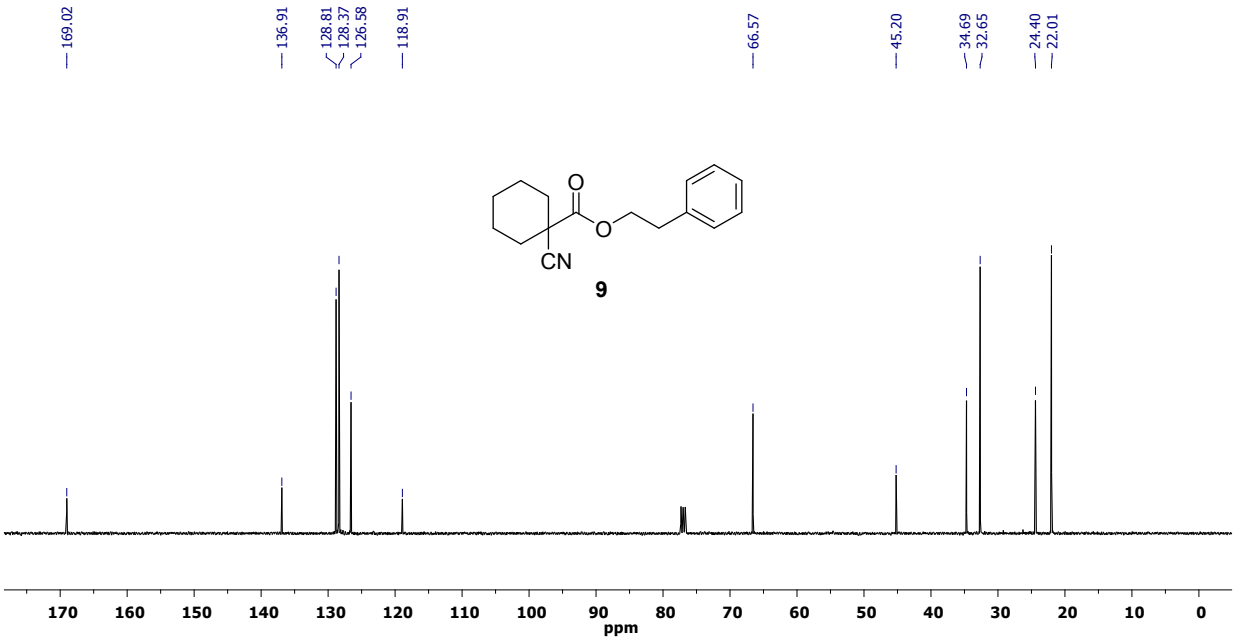
^{1}H-NMR (400 MHz) spectrum of **8** in $CDCl_3$



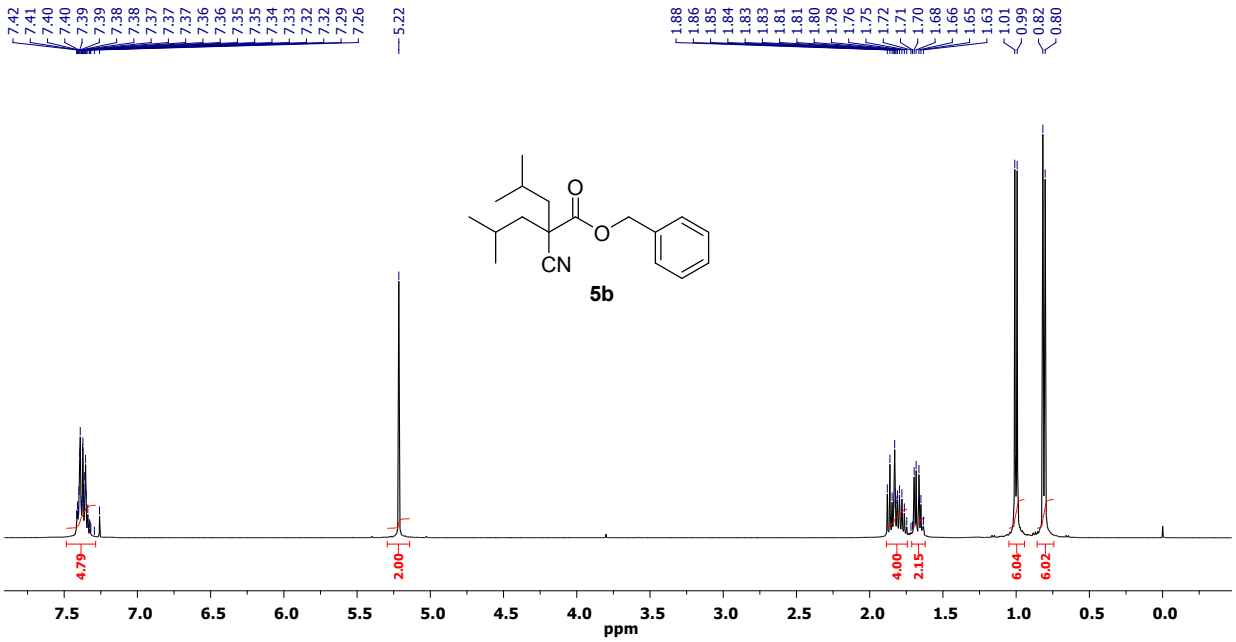
^{13}C-NMR (100 MHz) spectrum of **8** in $CDCl_3$



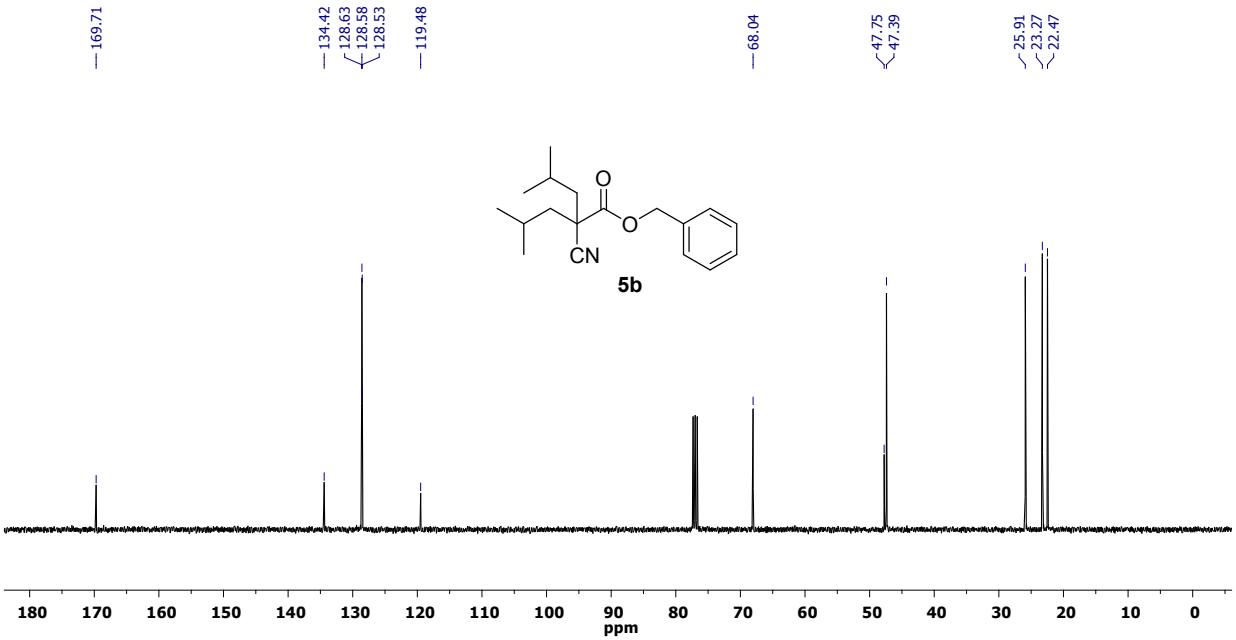
^{1}H-NMR (400 MHz) spectrum of **9** in $CDCl_3$



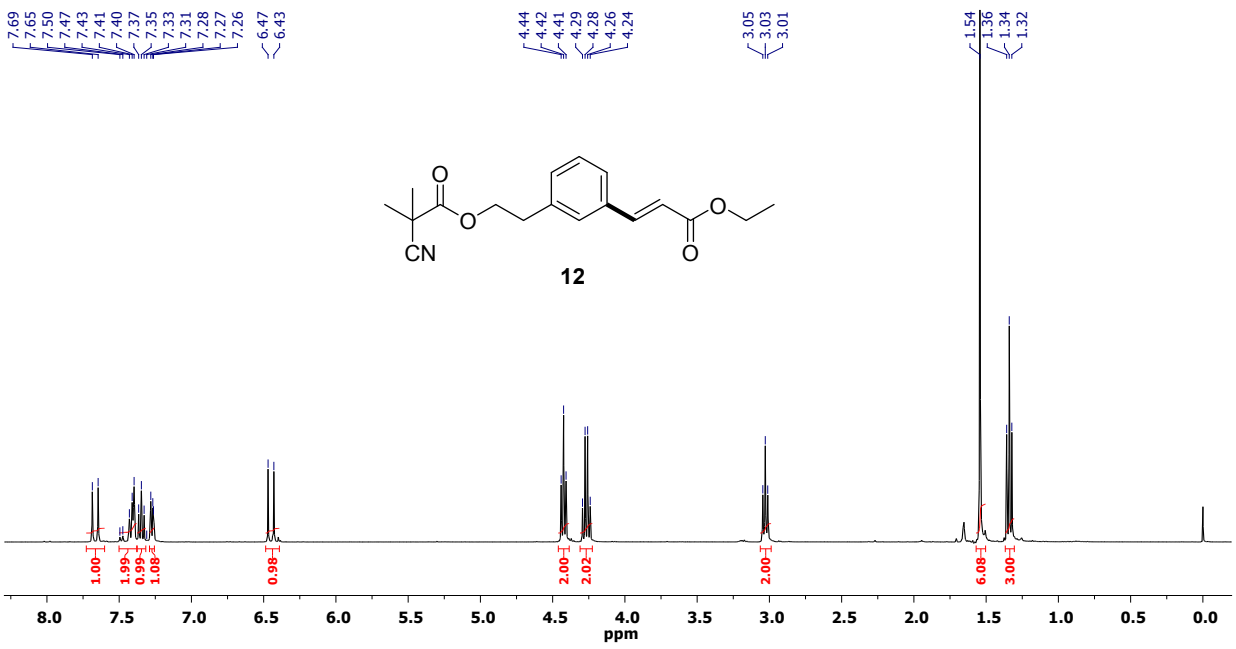
^{13}C-NMR (100 MHz) spectrum of **9** in $CDCl_3$



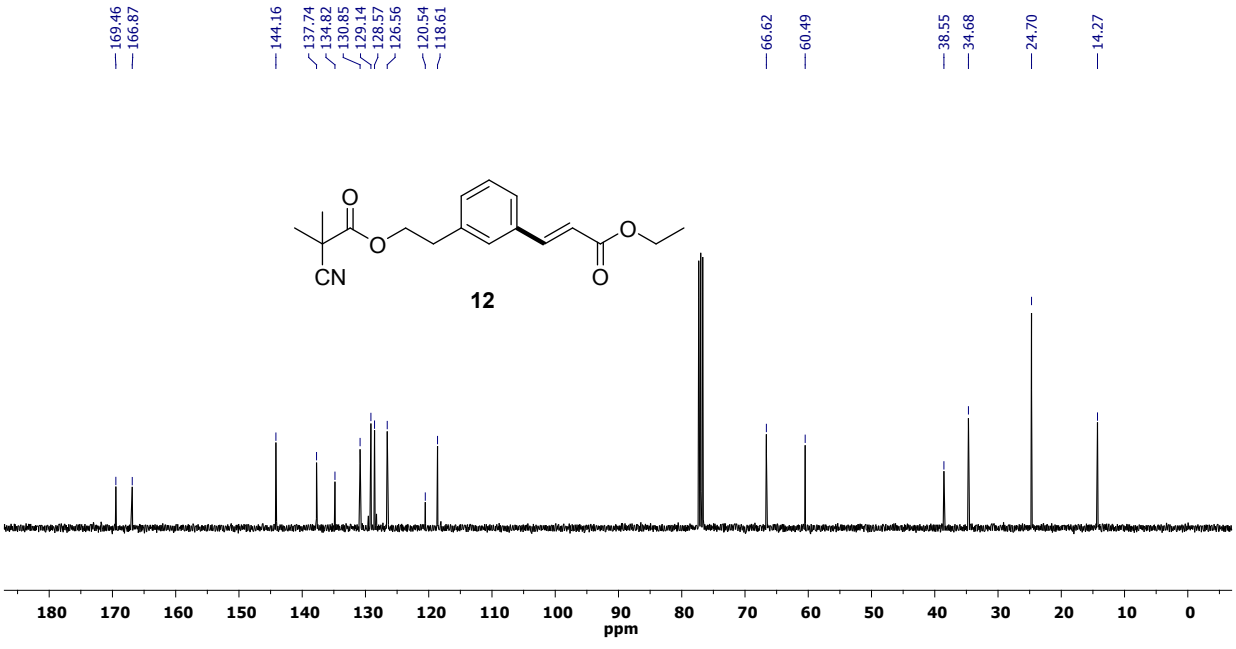
^{1}H-NMR (400 MHz) spectrum of **5b** in $CDCl_3$



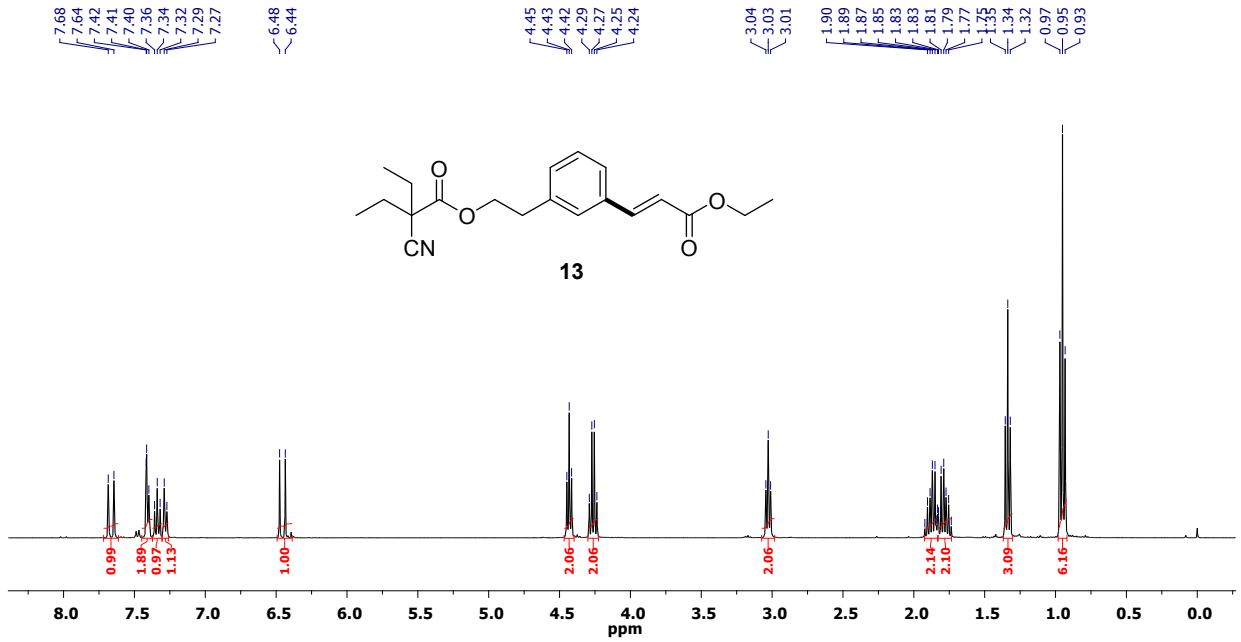
^{13}C-NMR (100 MHz) spectrum of **5b** in $CDCl_3$



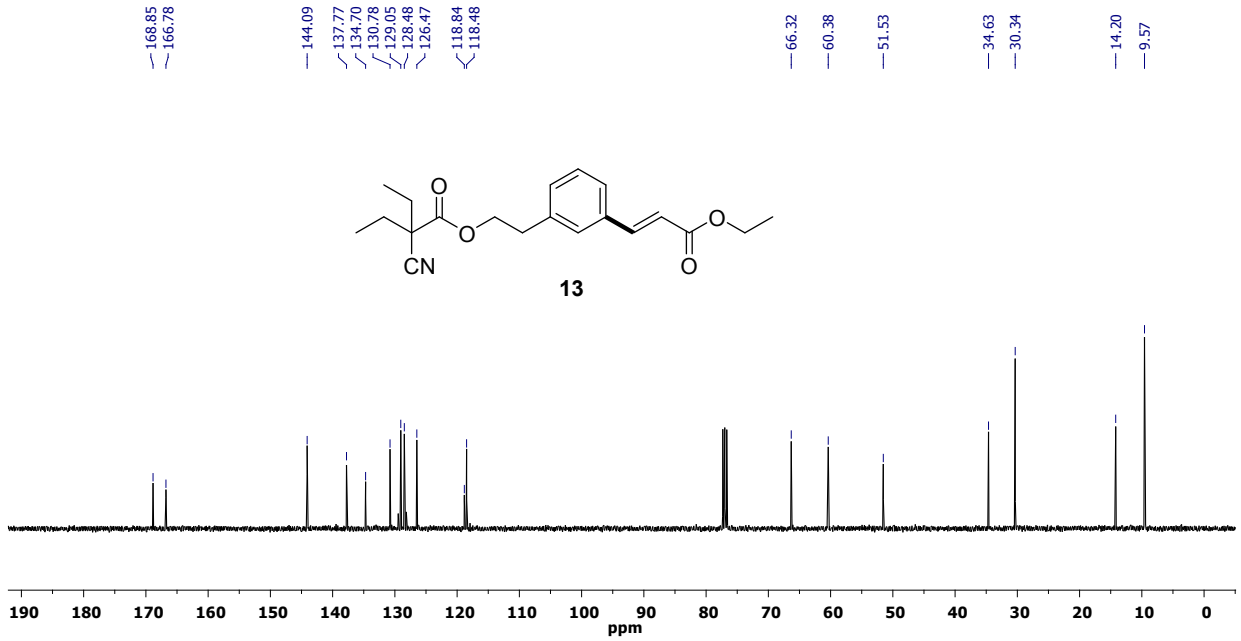
^{1}H-NMR (400 MHz) spectrum of **12** in $CDCl_3$



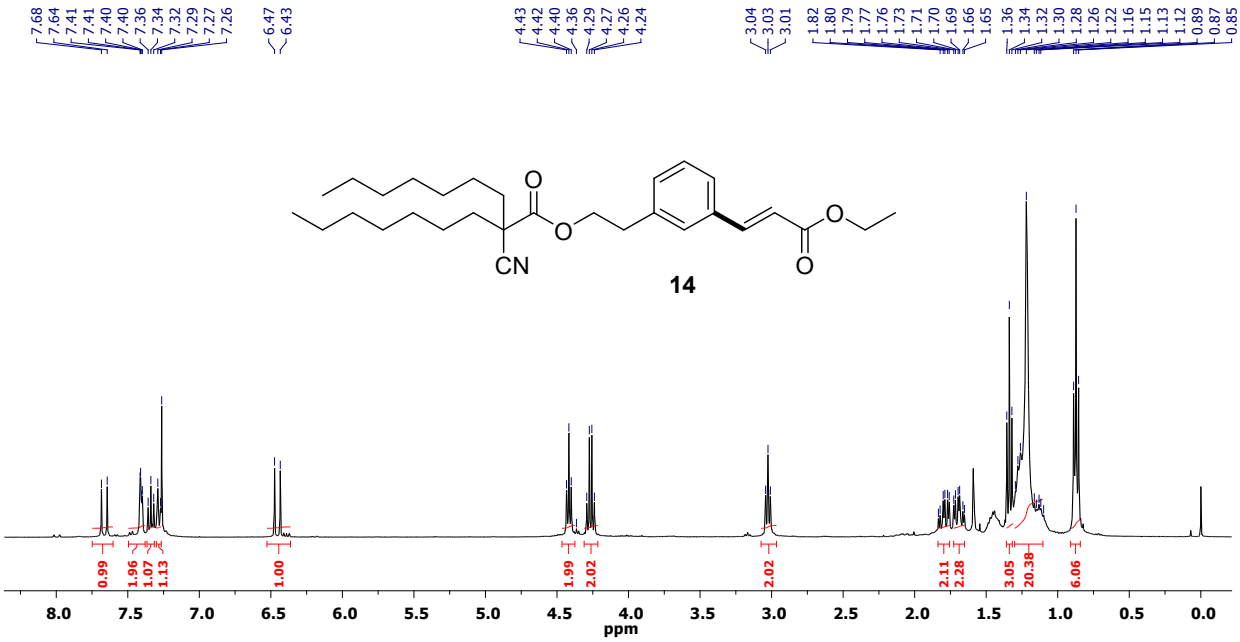
^{13}C-NMR (100 MHz) spectrum of **12** in $CDCl_3$



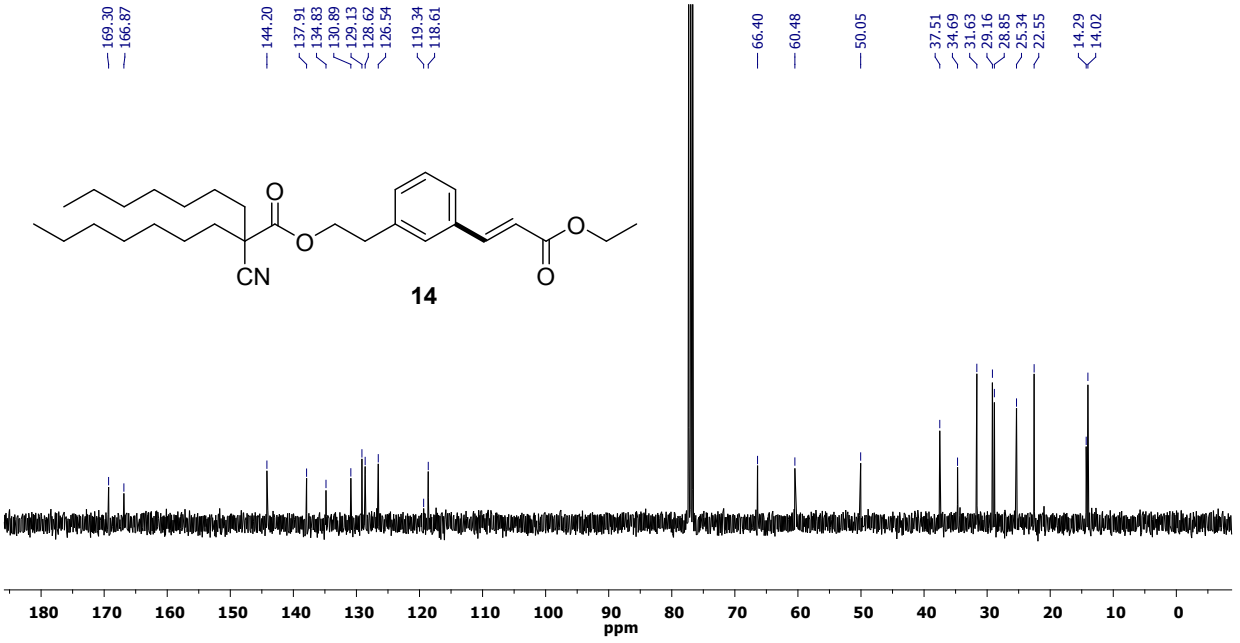
^{1}H-NMR (400 MHz) spectrum of **13** in $CDCl_3$



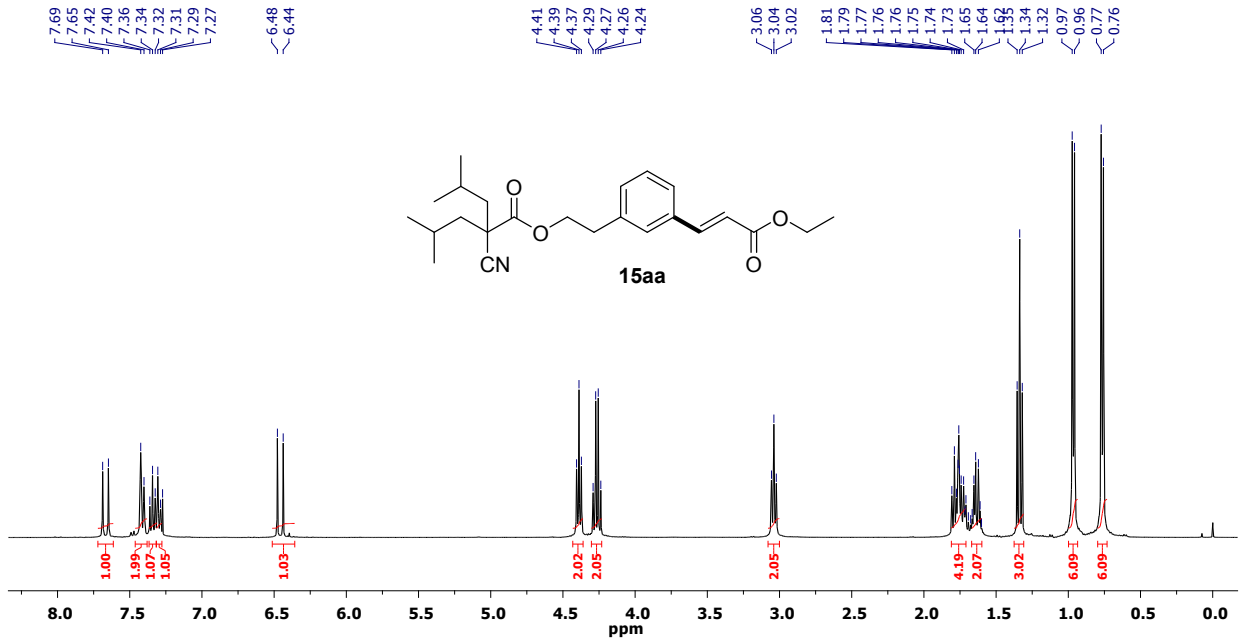
^{13}C-NMR (100 MHz) spectrum of **13** in $CDCl_3$



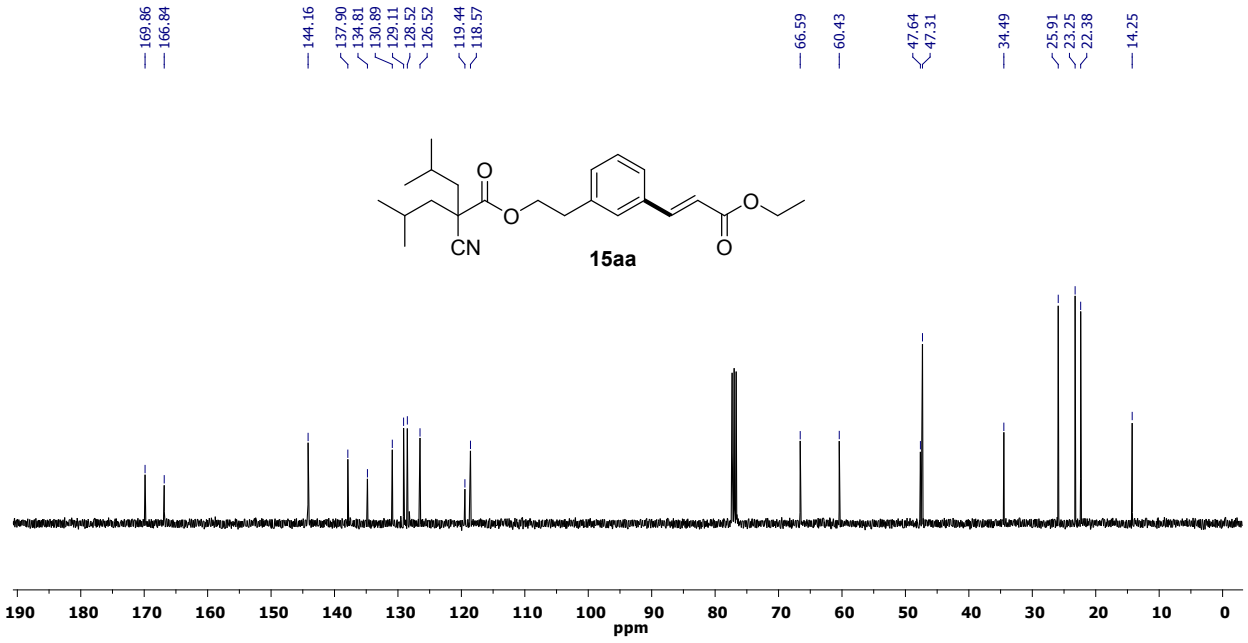
^{1}H-NMR (400 MHz) spectrum of **14** in $CDCl_3$



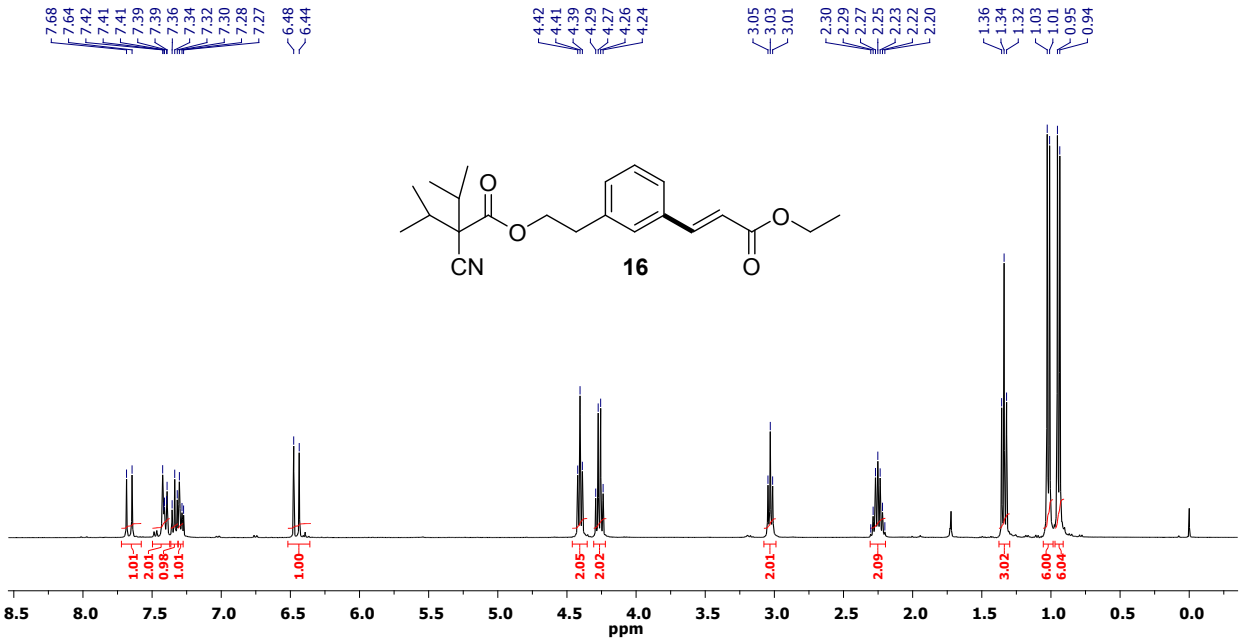
^{13}C-NMR (100 MHz) spectrum of **14** in $CDCl_3$



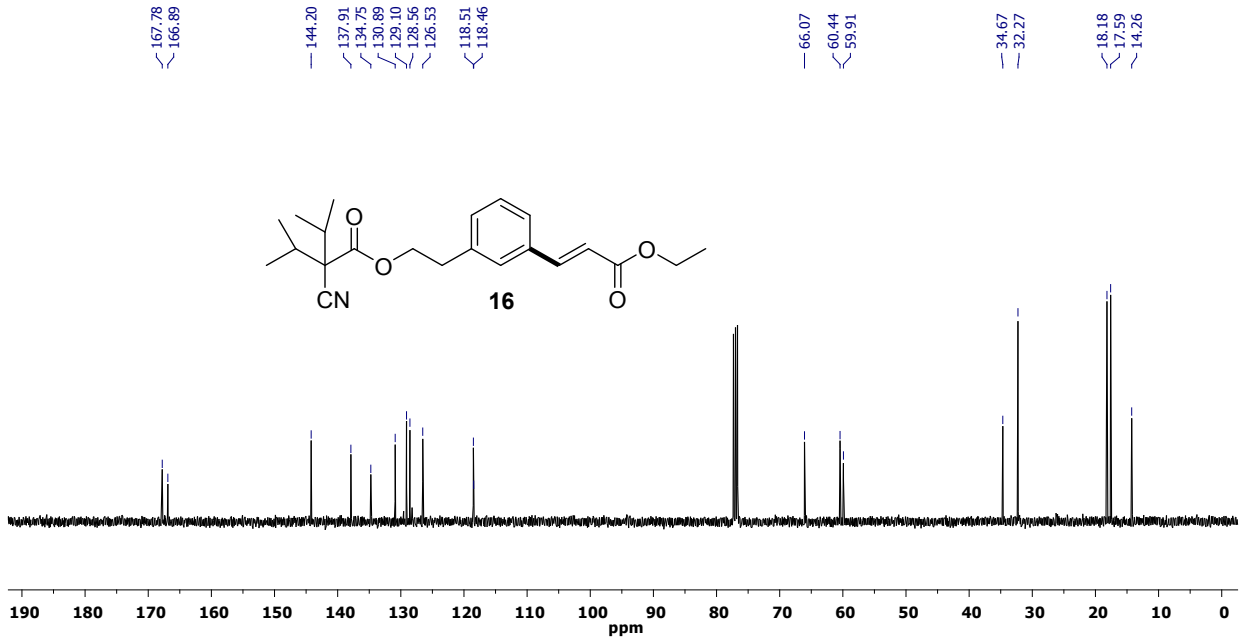
^{1}H-NMR (400 MHz) spectrum of **15aa** in $CDCl_3$



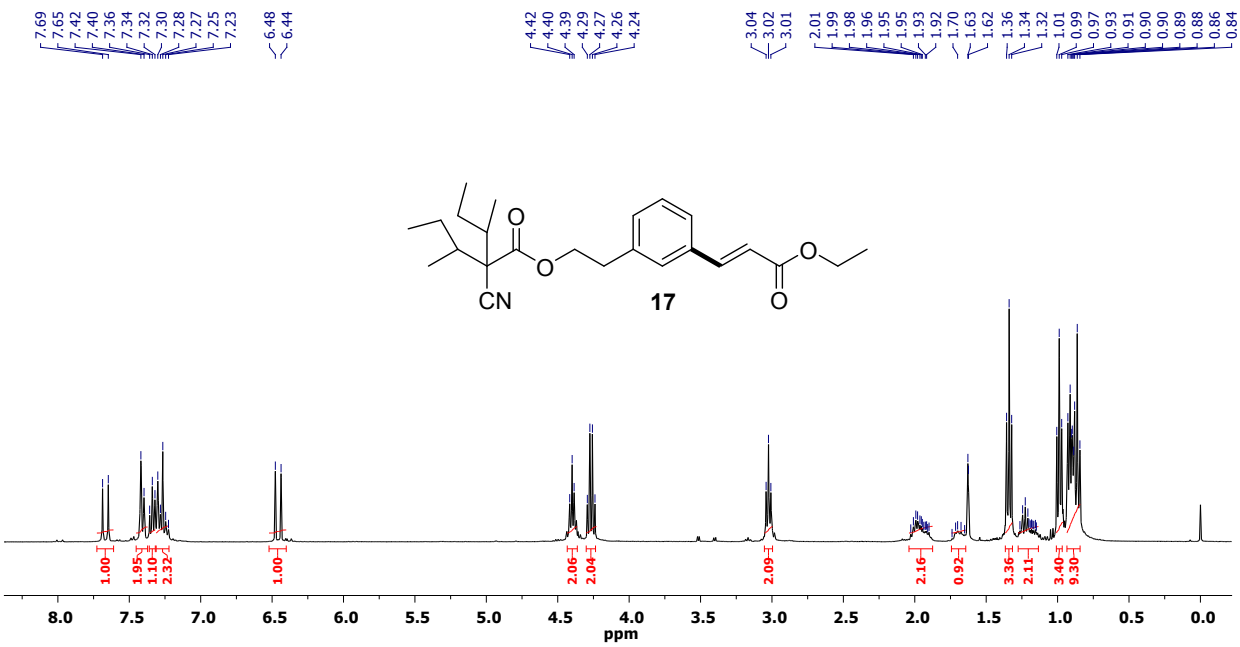
^{13}C-NMR (100 MHz) spectrum of **15aa** in $CDCl_3$



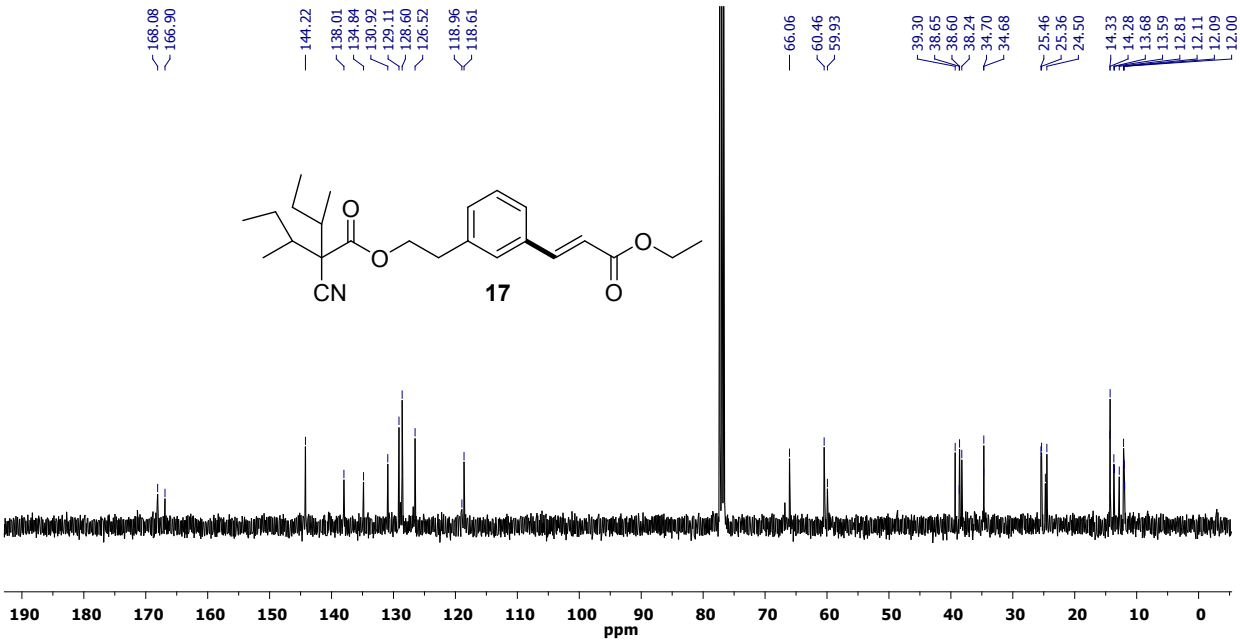
^{1}H-NMR (400 MHz) spectrum of **16** in $CDCl_3$



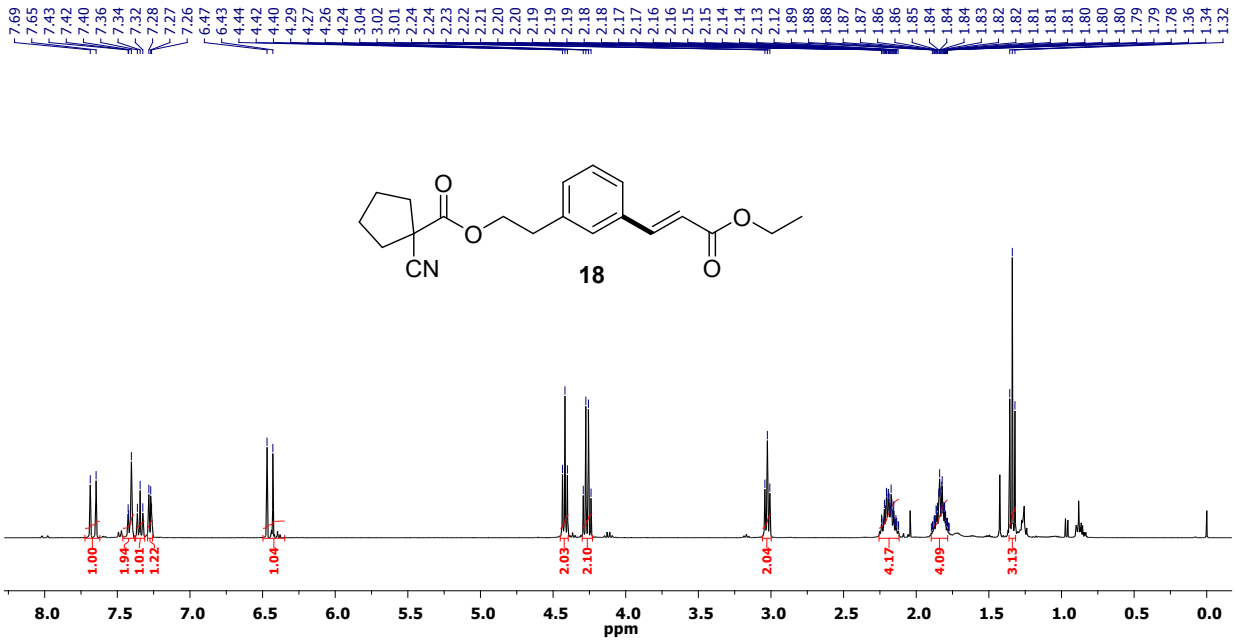
^{13}C-NMR (100 MHz) spectrum of **16** in $CDCl_3$



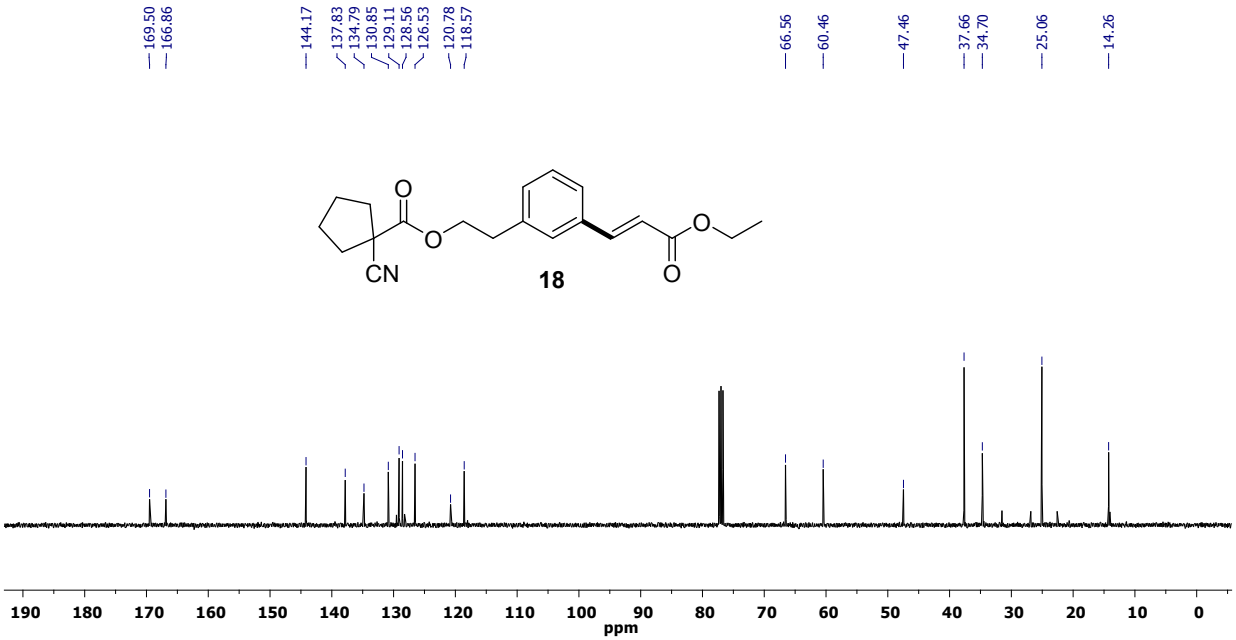
^{1}H-NMR (400 MHz) spectrum of **17** in $CDCl_3$



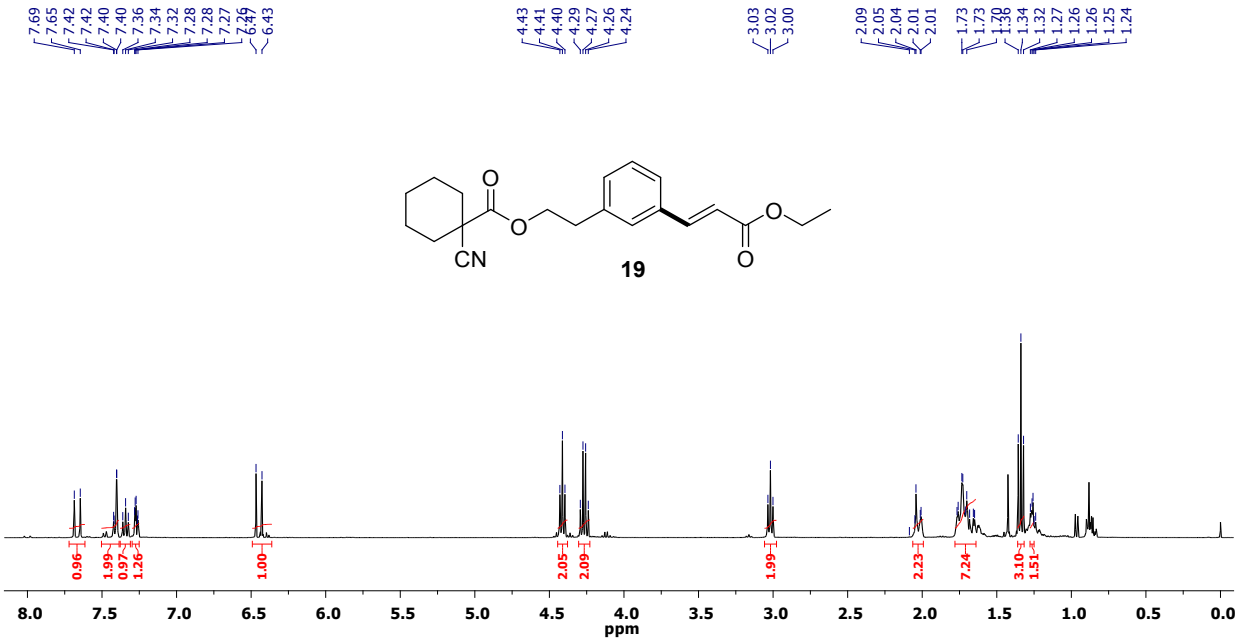
^{13}C-NMR (100 MHz) spectrum of **17** in $CDCl_3$



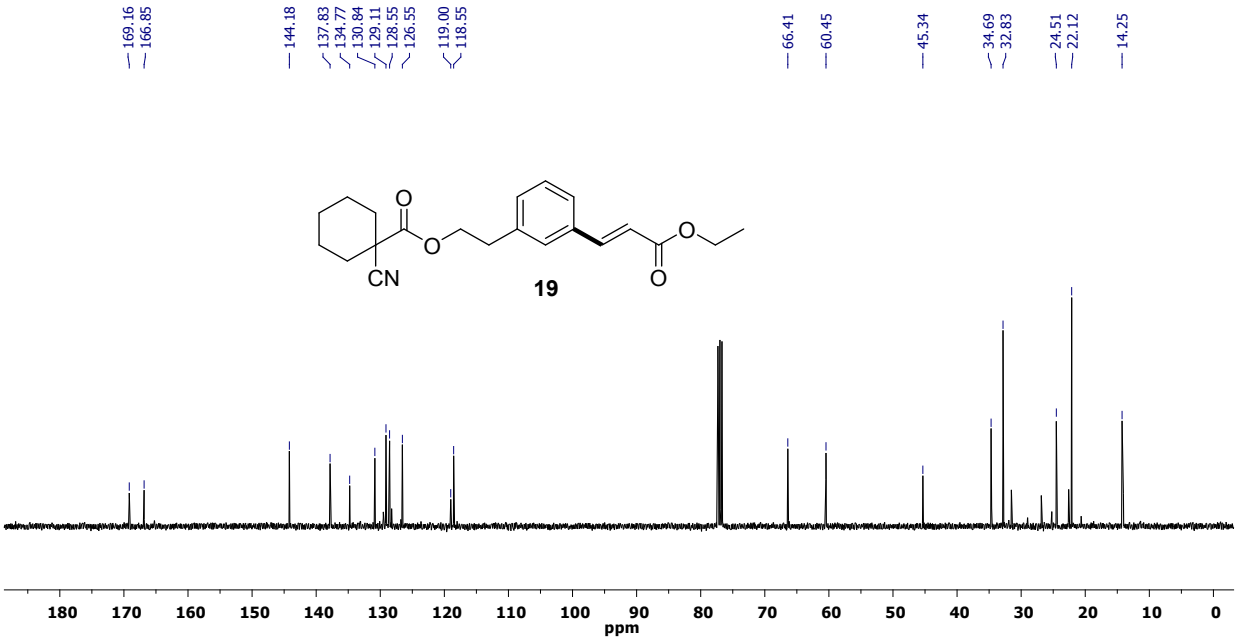
^{1}H-NMR (400 MHz) spectrum of **18** in $CDCl_3$



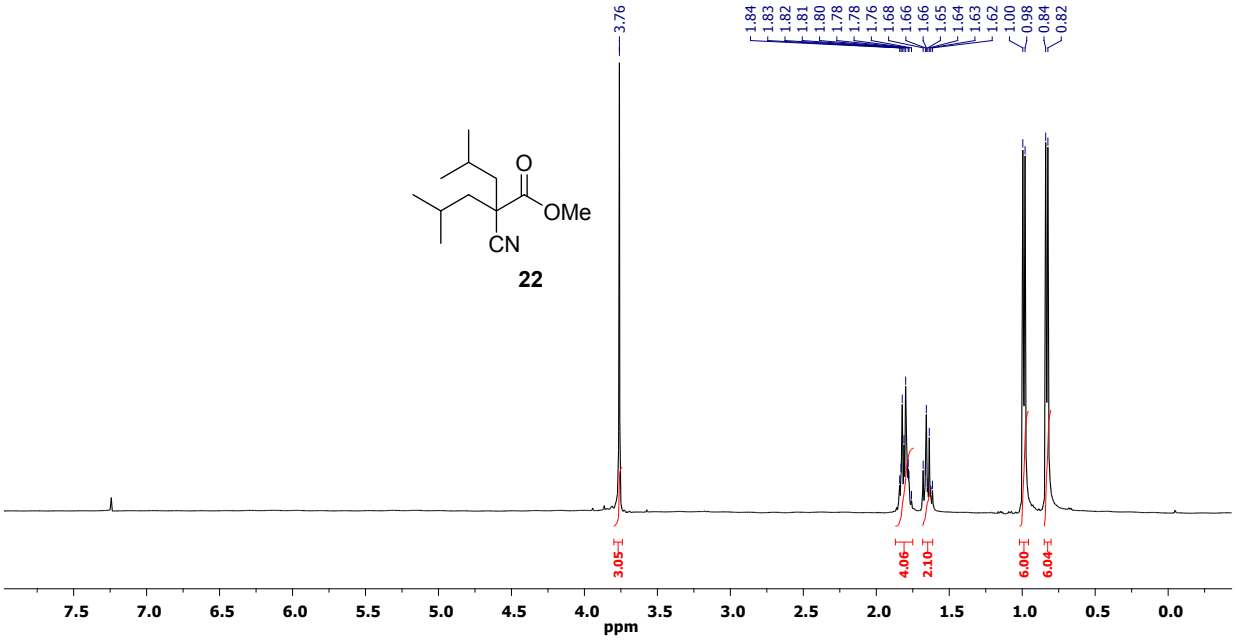
^{13}C-NMR (100 MHz) spectrum of **18** in $CDCl_3$



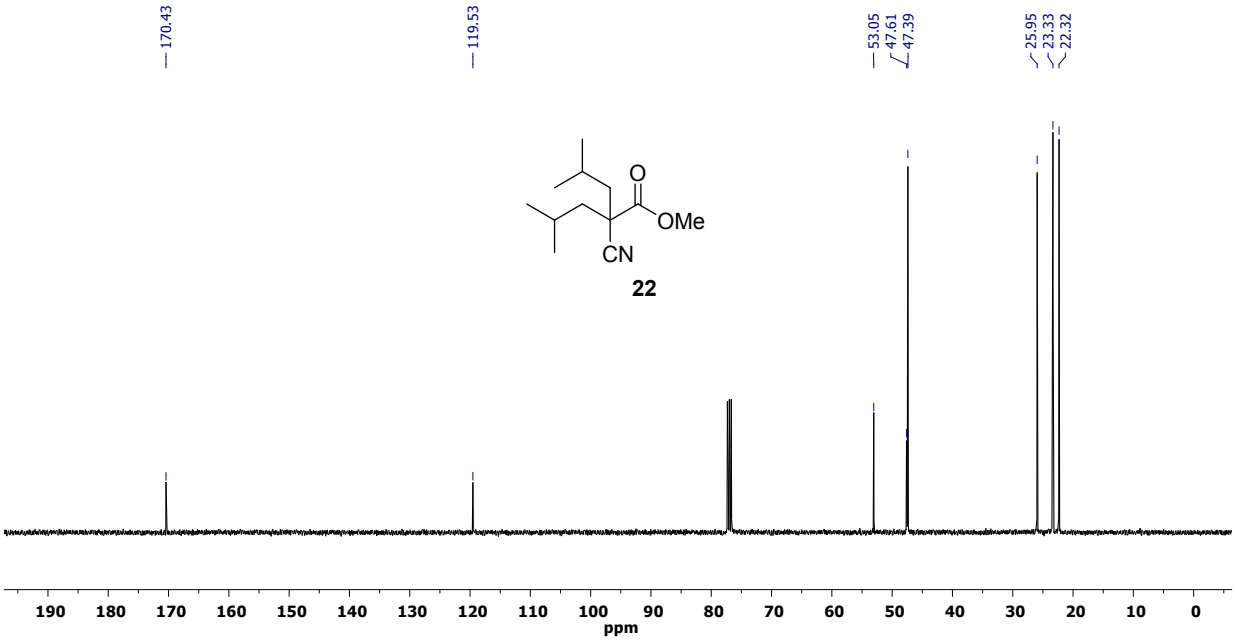
^{1}H-NMR (400 MHz) spectrum of **19** in $CDCl_3$



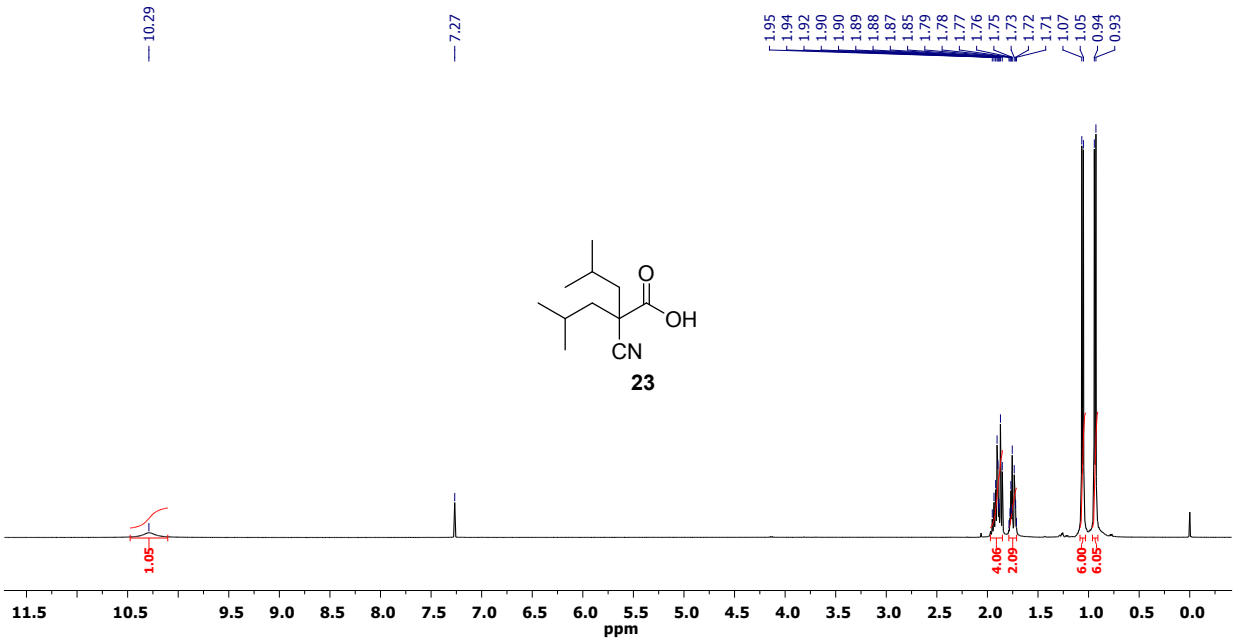
^{13}C-NMR (100 MHz) spectrum of **19** in $CDCl_3$



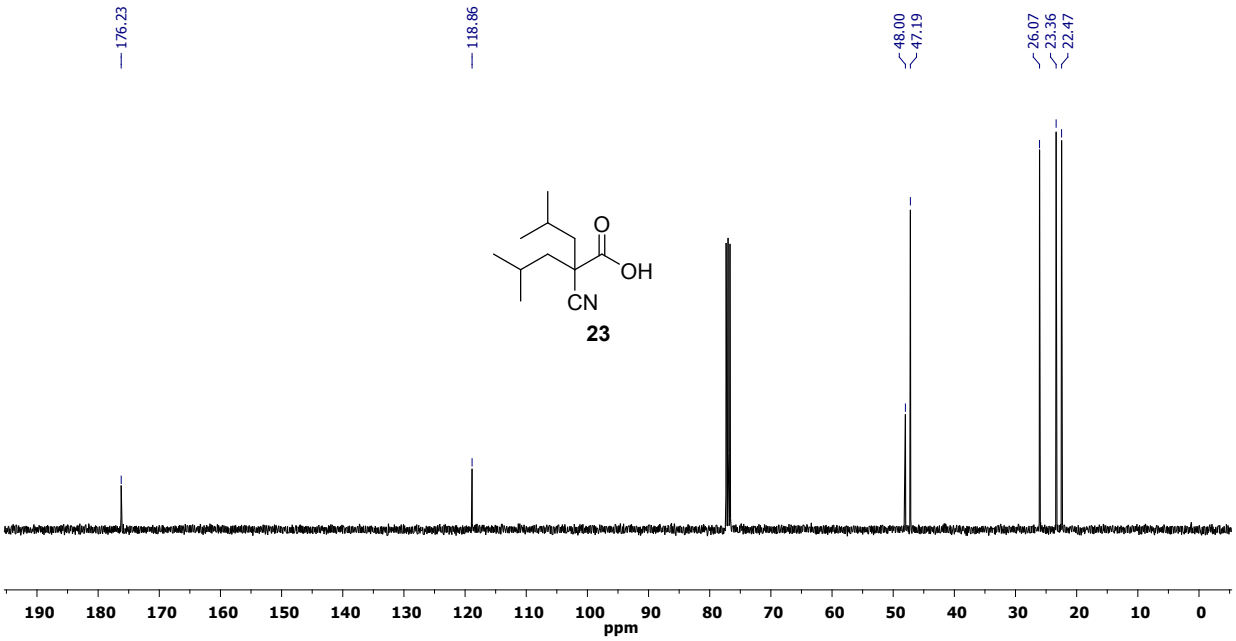
^{1}H-NMR (400 MHz) spectrum of **22** in $CDCl_3$



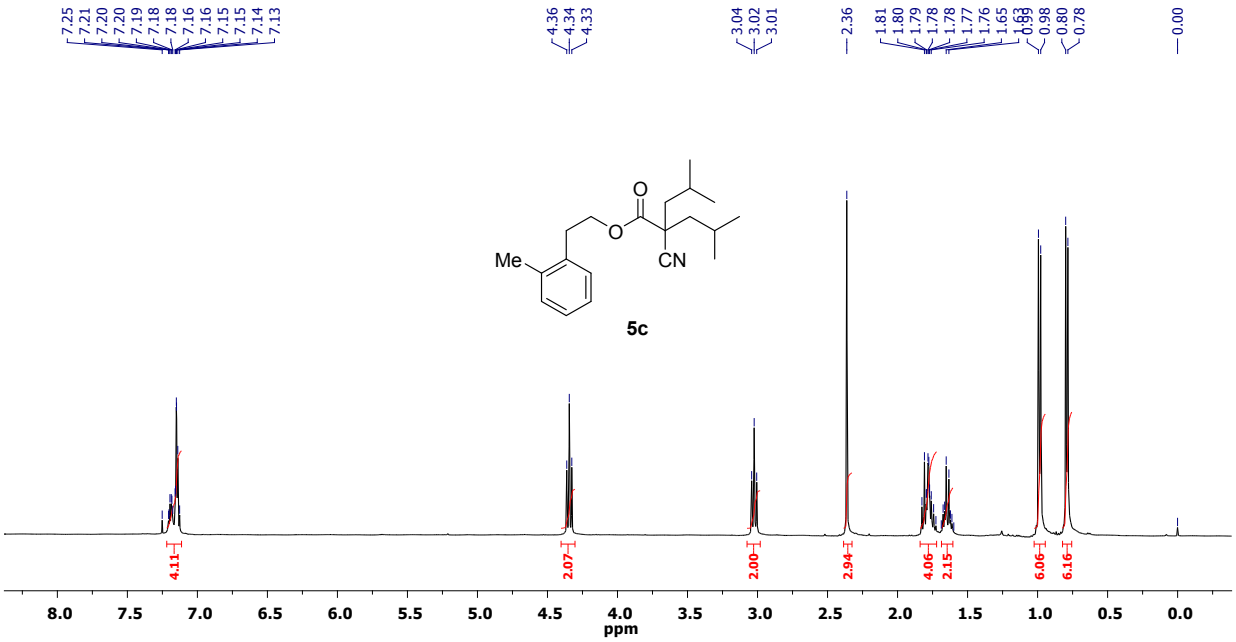
^{13}C-NMR (100 MHz) spectrum of **22** in $CDCl_3$



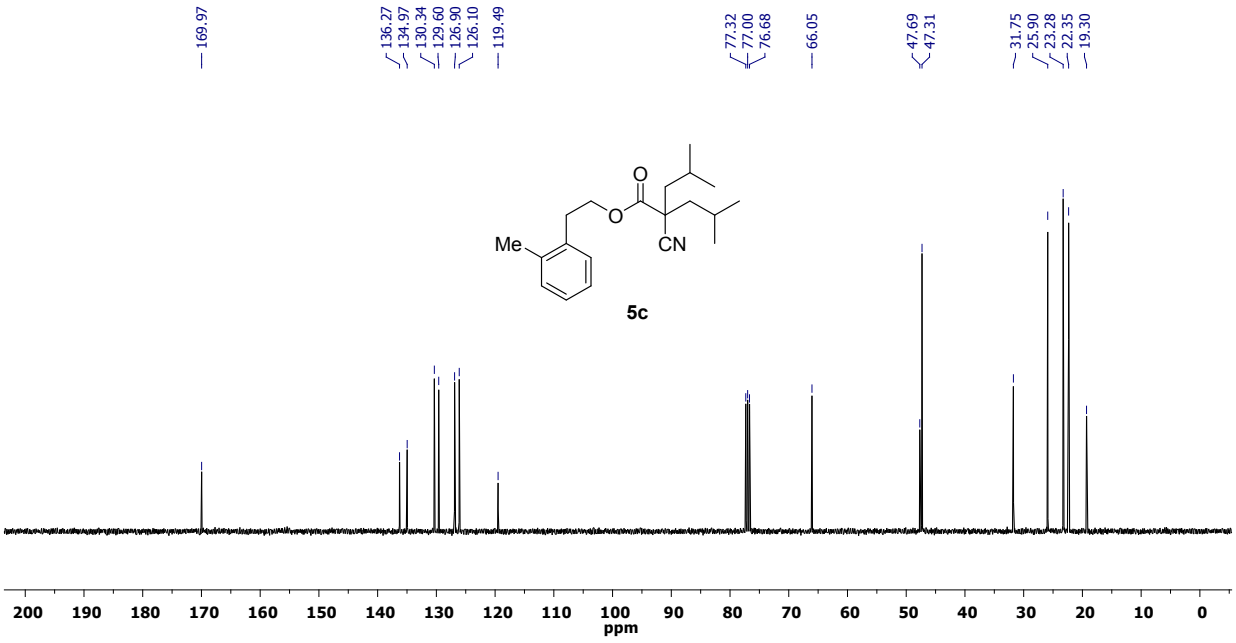
^{1}H-NMR (400 MHz) spectrum of **23** in $CDCl_3$



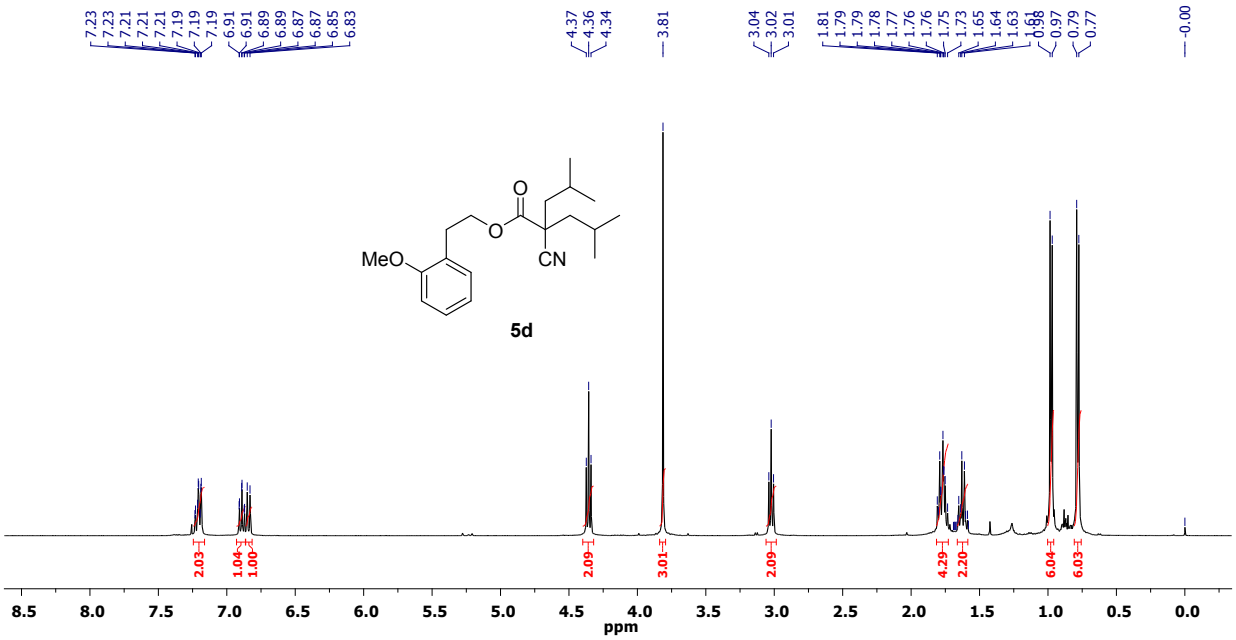
^{13}C-NMR (100 MHz) spectrum of **23** in $CDCl_3$



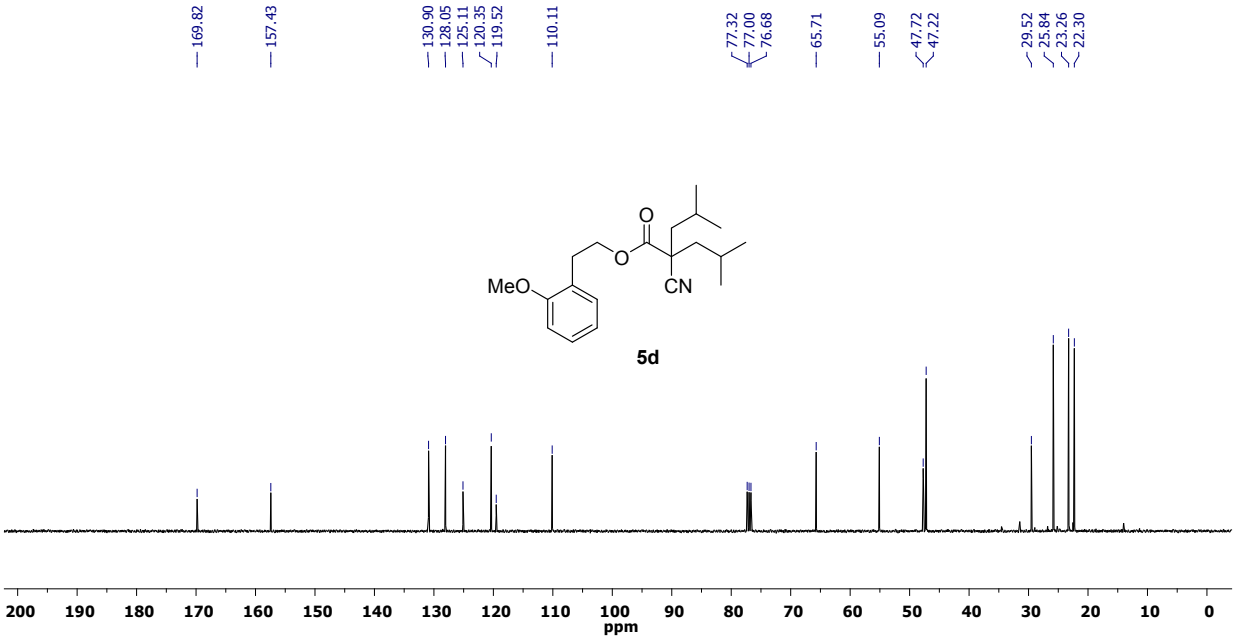
^{1}H-NMR (400 MHz) spectrum of **5c** in $CDCl_3$



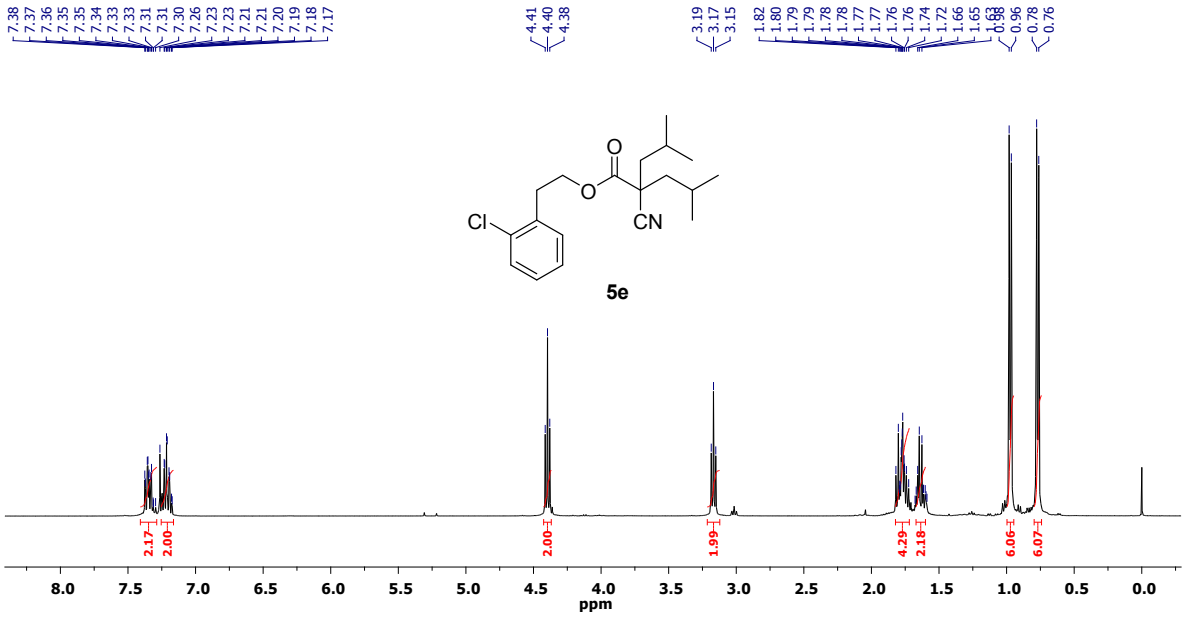
^{13}C-NMR (100 MHz) spectrum of **5c** in $CDCl_3$



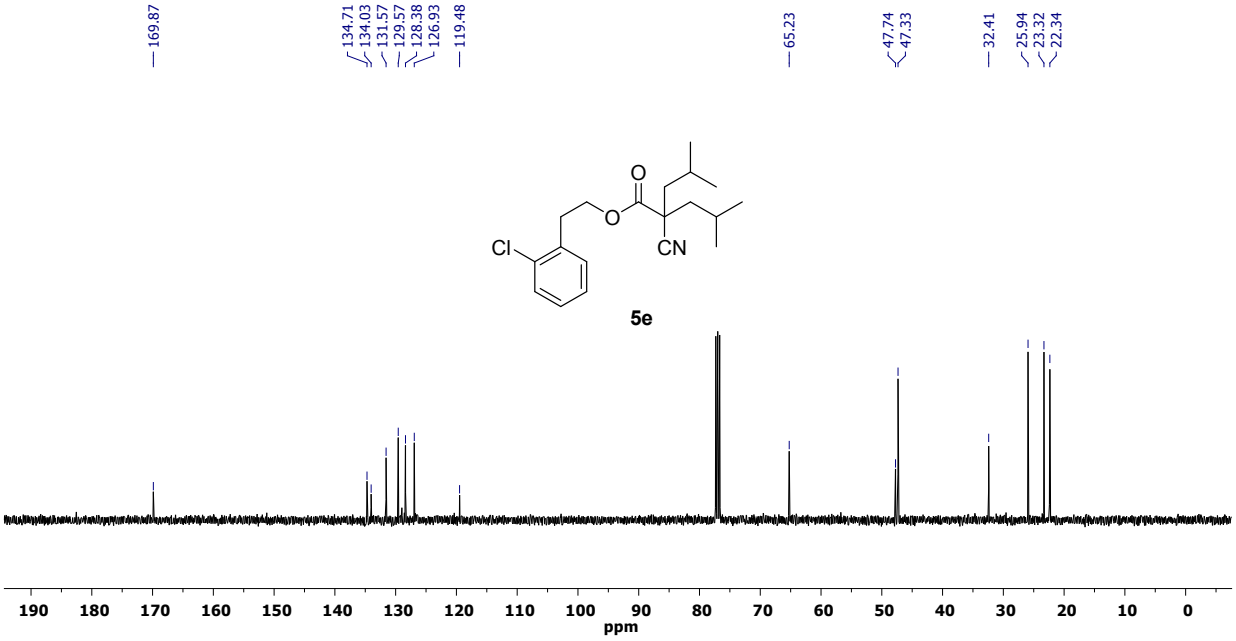
^{1}H-NMR (400 MHz) spectrum of **5d** in $CDCl_3$



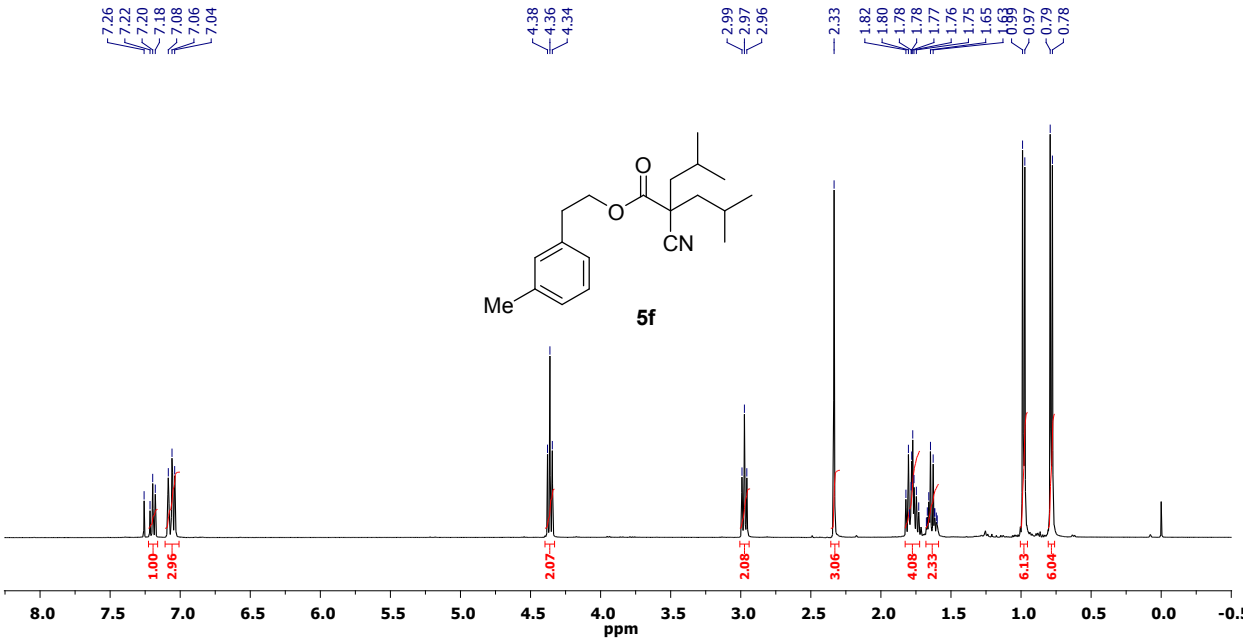
^{13}C-NMR (100 MHz) spectrum of **5d** in $CDCl_3$



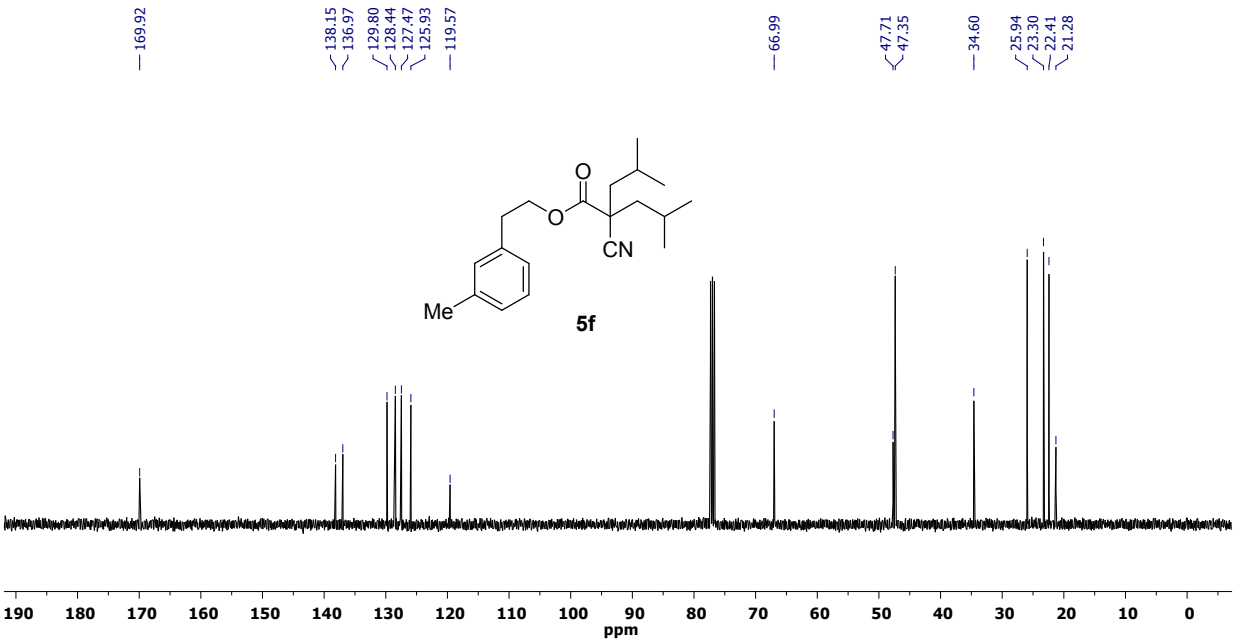
^{1}H-NMR (400 MHz) spectrum of **5e** in $CDCl_3$



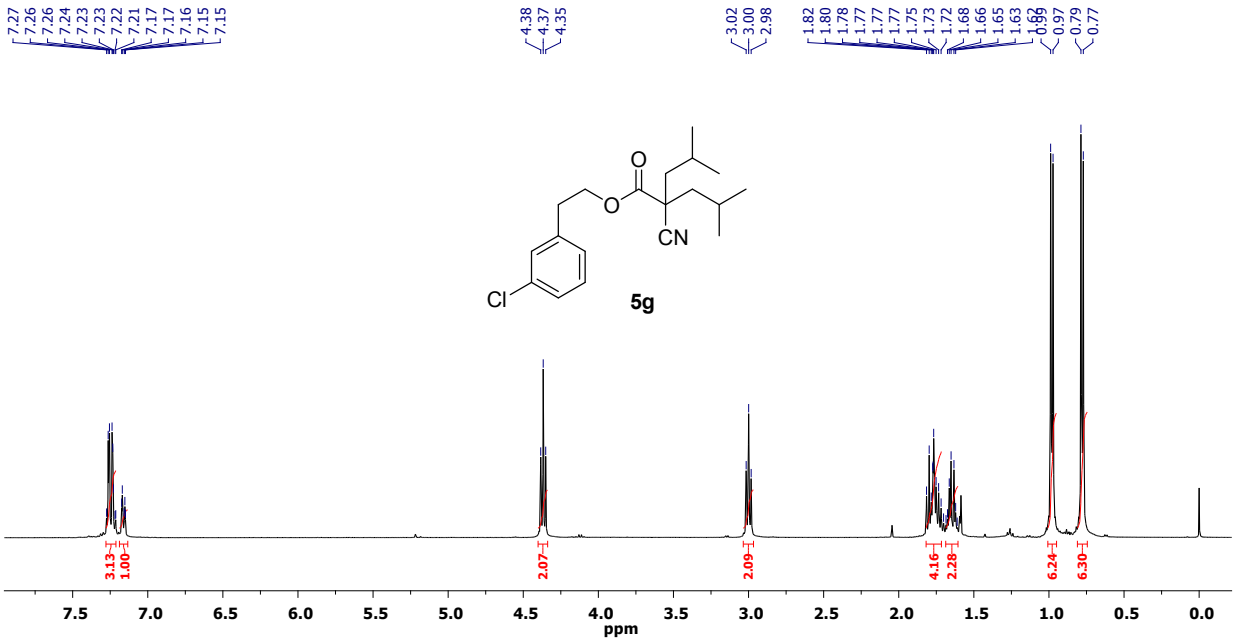
^{13}C-NMR (100 MHz) spectrum of **5e** in $CDCl_3$



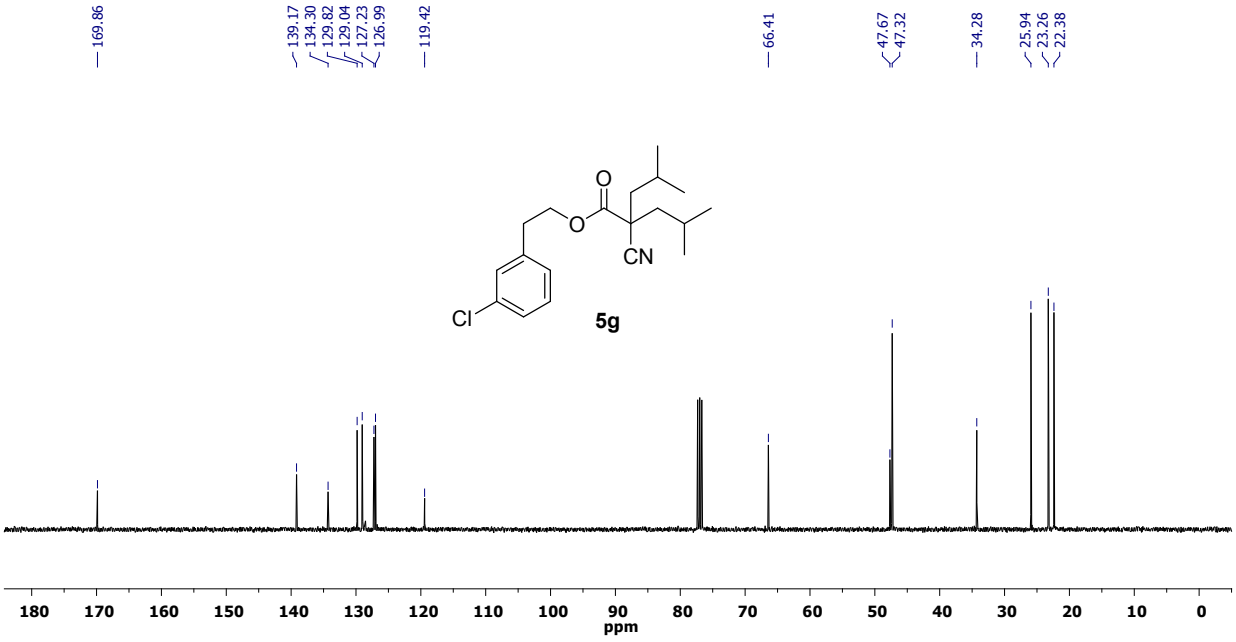
^{1}H-NMR (400 MHz) spectrum of **5f** in $CDCl_3$



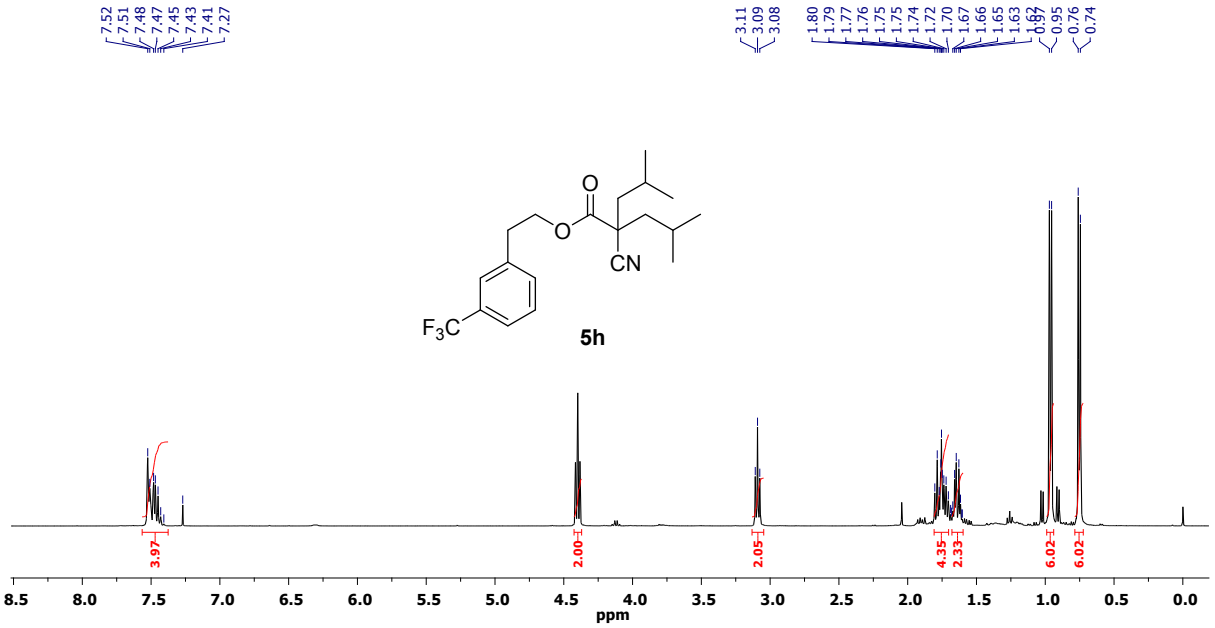
^{13}C-NMR (100 MHz) spectrum of **5f** in $CDCl_3$



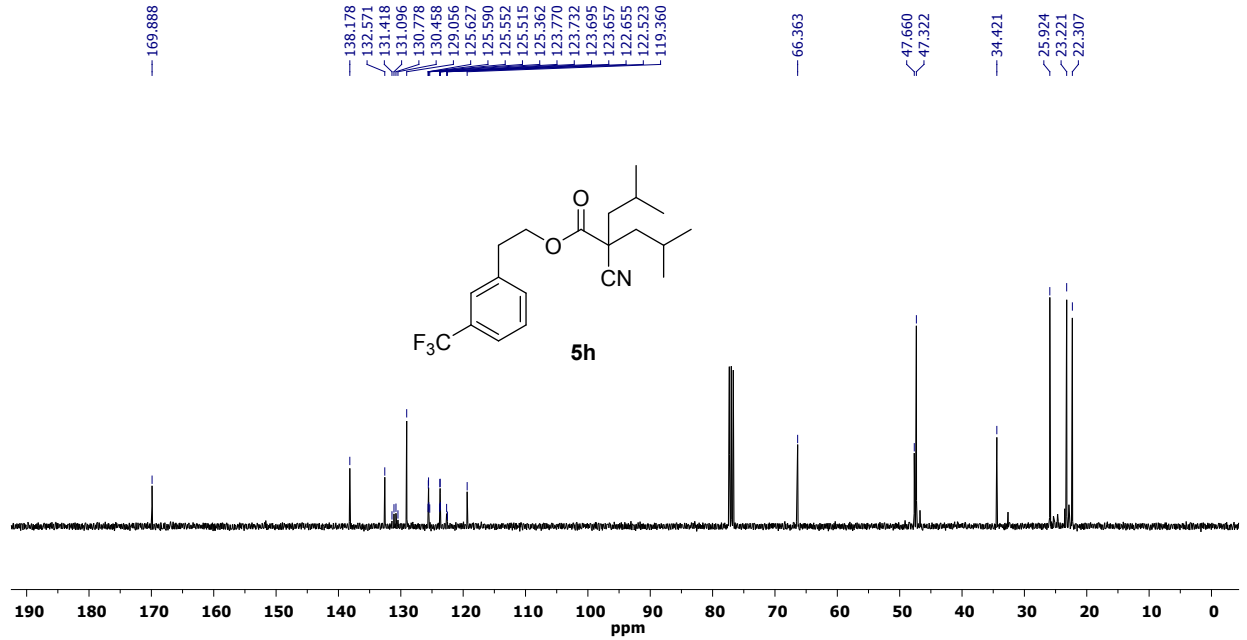
^{1}H-NMR (400 MHz) spectrum of **5g** in $CDCl_3$



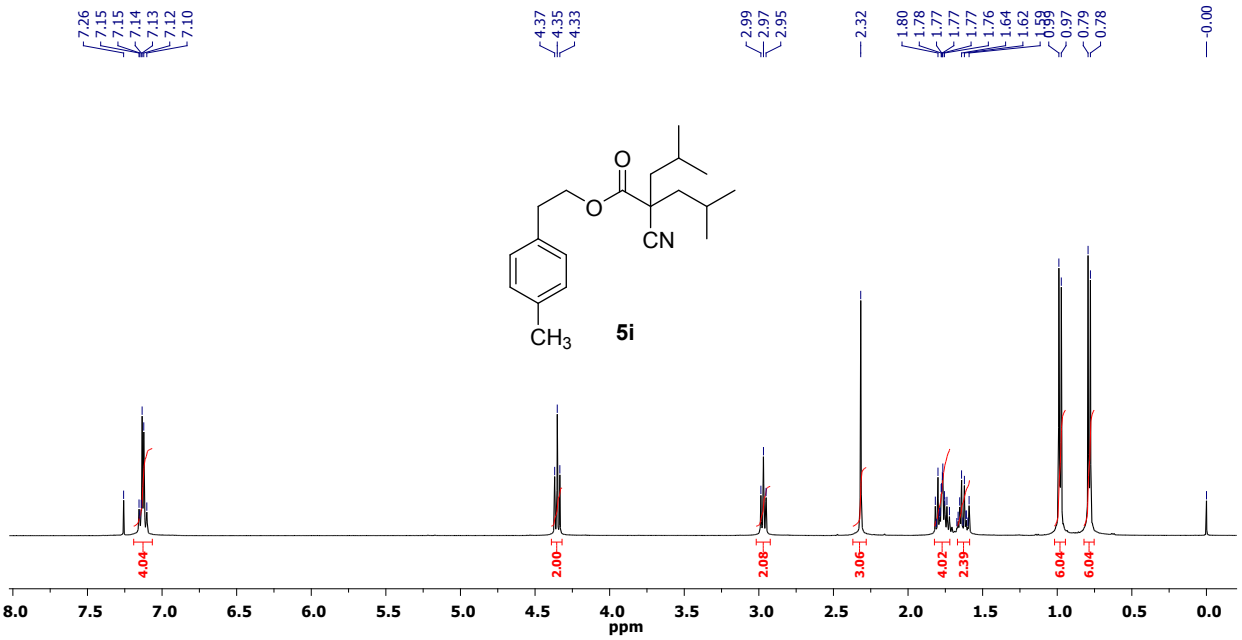
^{13}C-NMR (100 MHz) spectrum of **5g** in $CDCl_3$



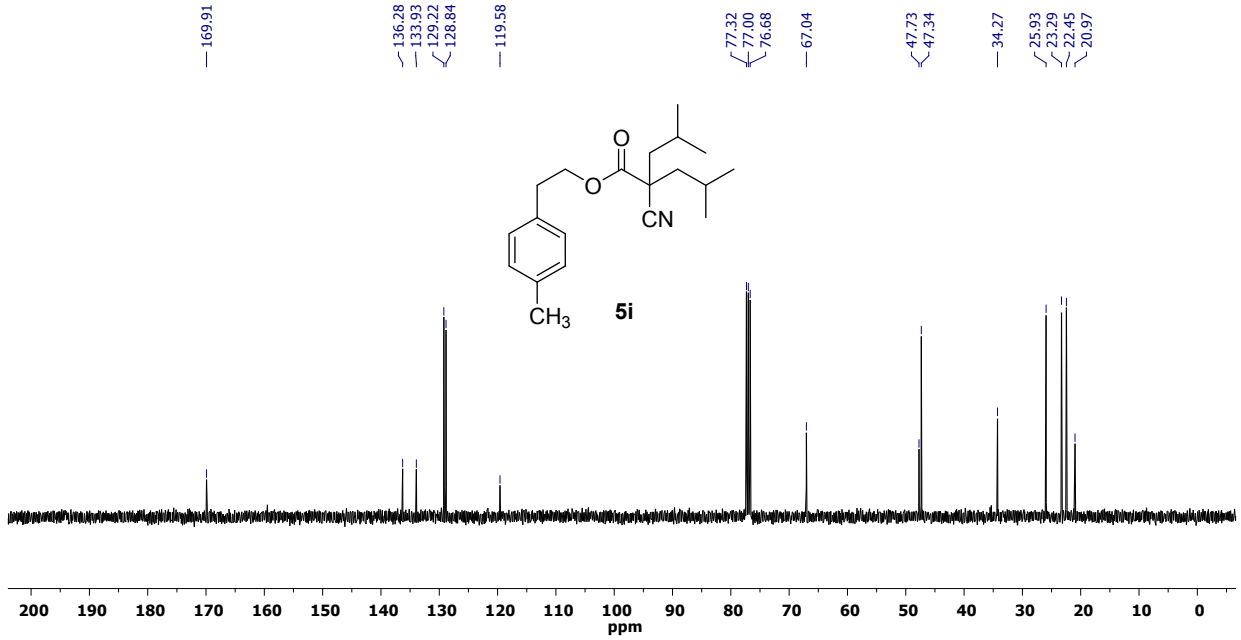
^{1}H-NMR (400 MHz) spectrum of **5h** in $CDCl_3$



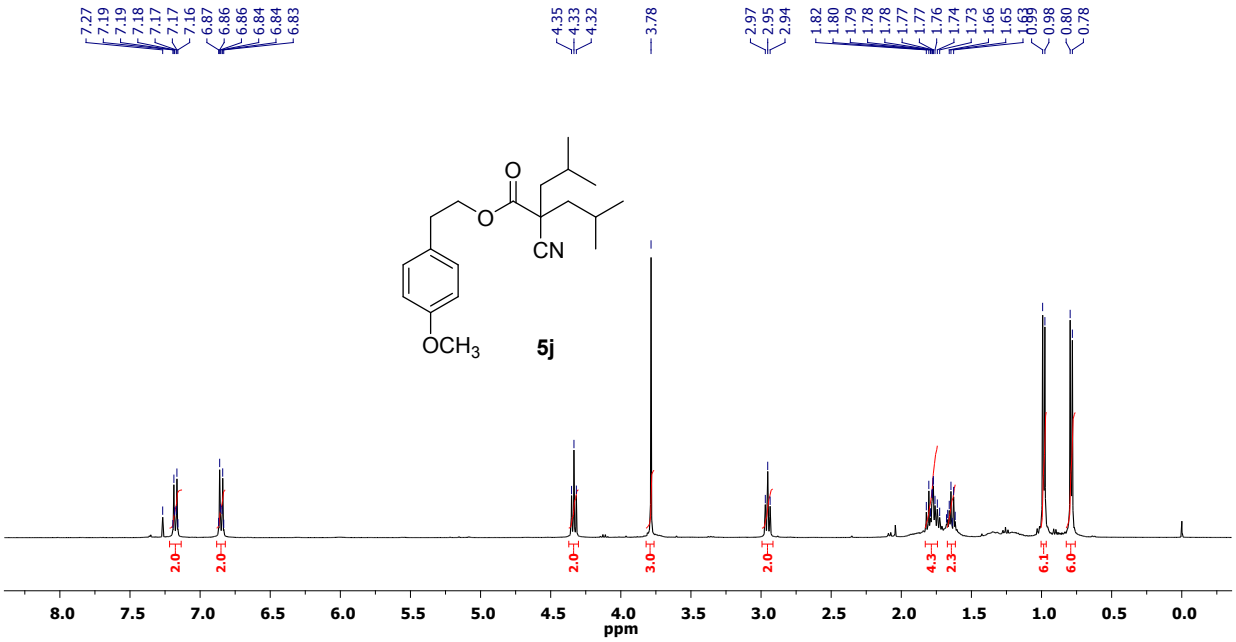
^{13}C-NMR (100 MHz) spectrum of **5h** in $CDCl_3$



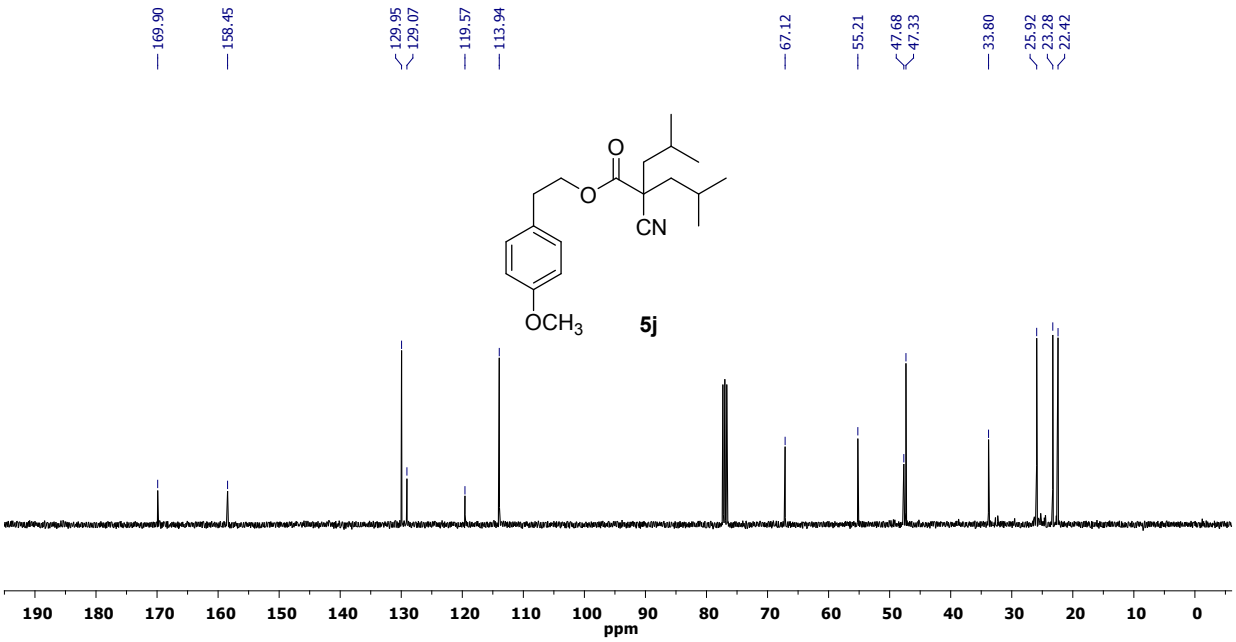
^{1}H-NMR (400 MHz) spectrum of **5i** in $CDCl_3$



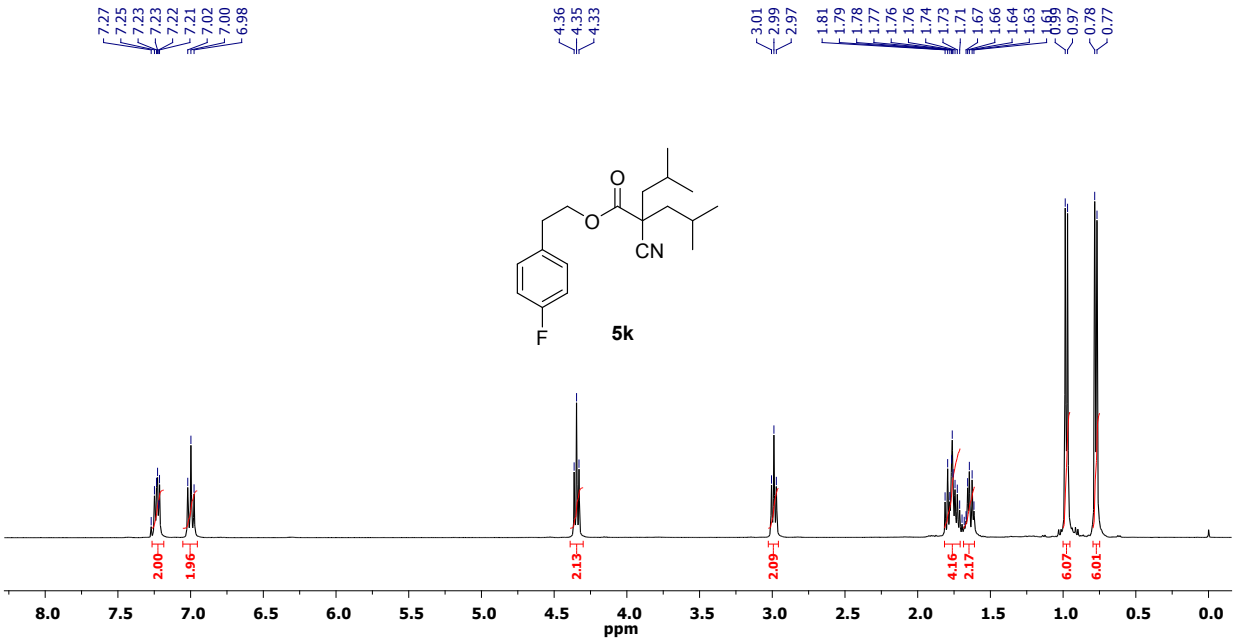
^{13}C-NMR (100 MHz) spectrum of **5i** in $CDCl_3$



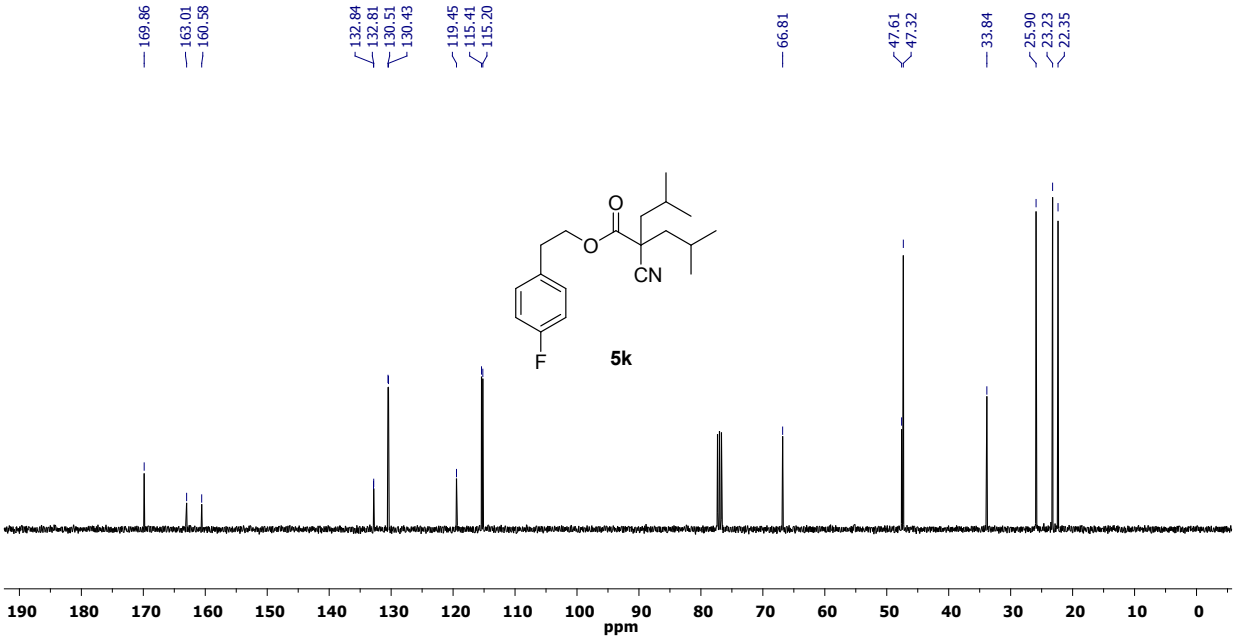
^{1}H-NMR (400 MHz) spectrum of **5j** in $CDCl_3$



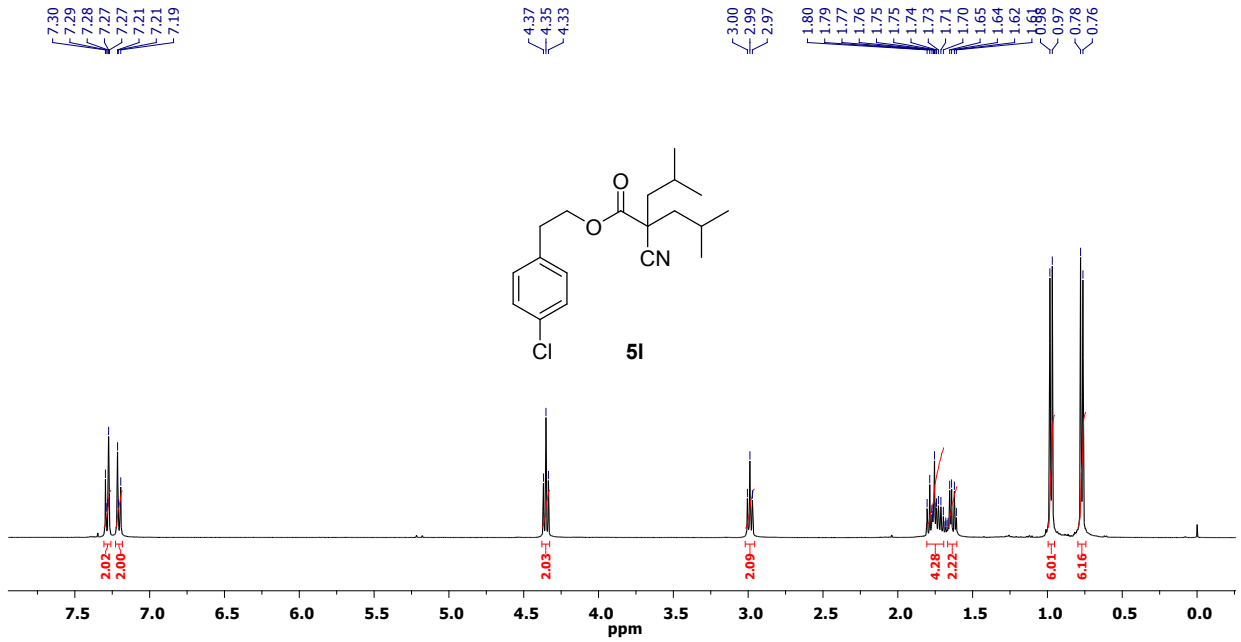
^{13}C-NMR (100 MHz) spectrum of **5j** in $CDCl_3$



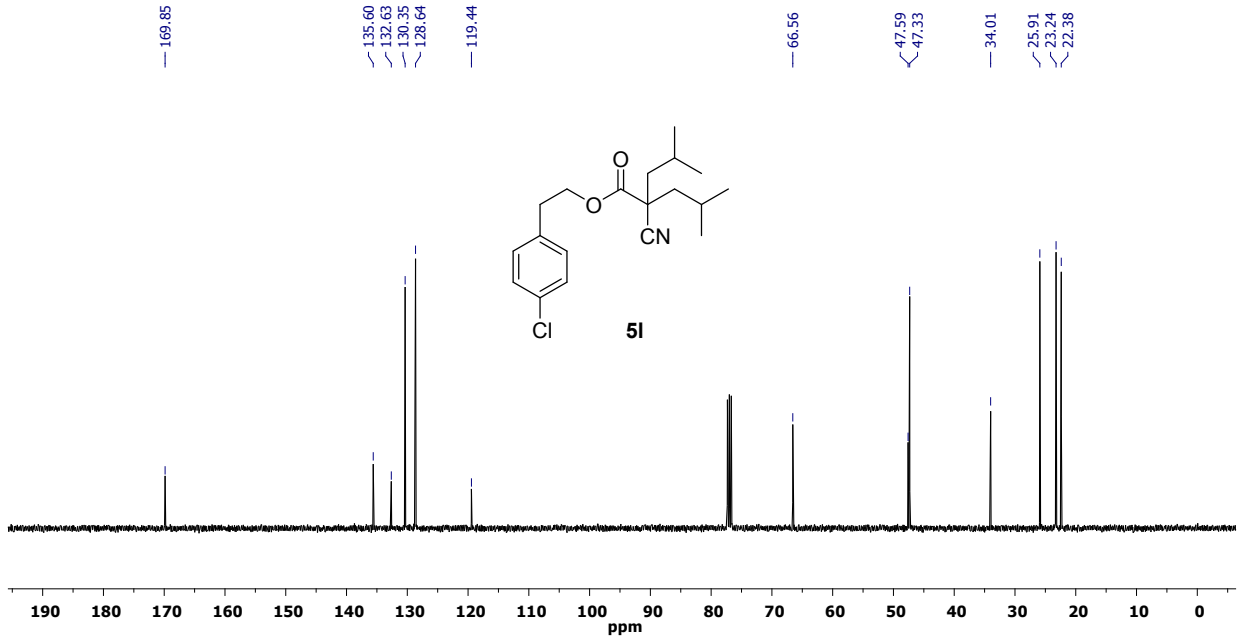
^{1}H-NMR (400 MHz) spectrum of **5k** in $CDCl_3$



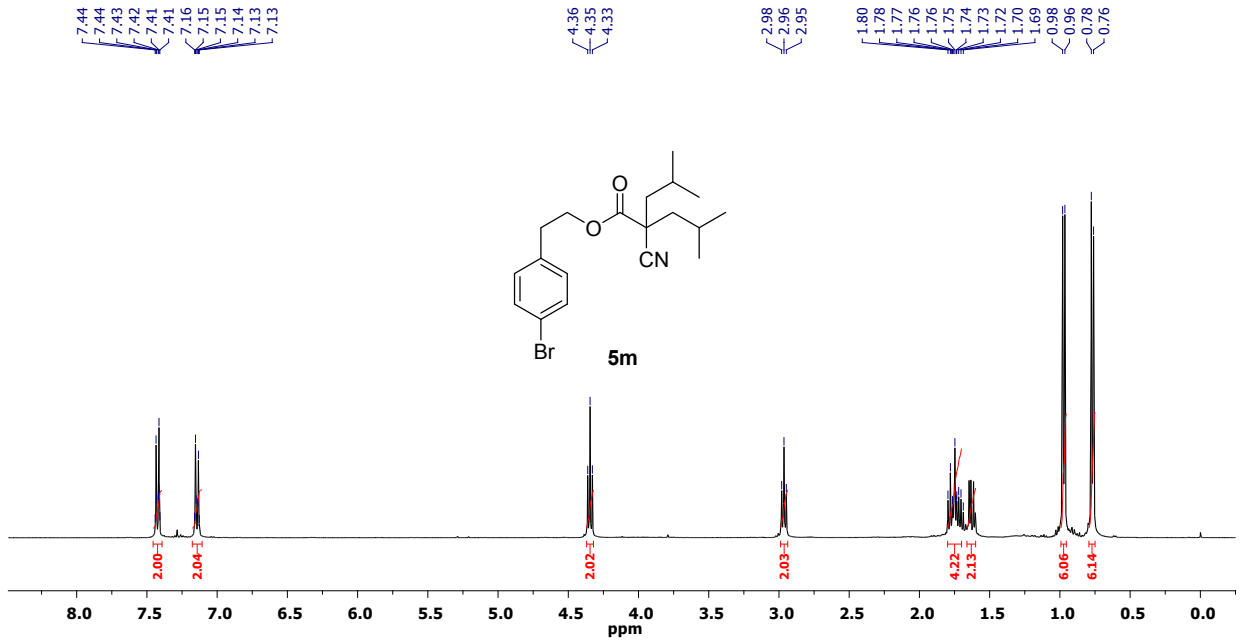
^{13}C-NMR (100 MHz) spectrum of **5k** in $CDCl_3$



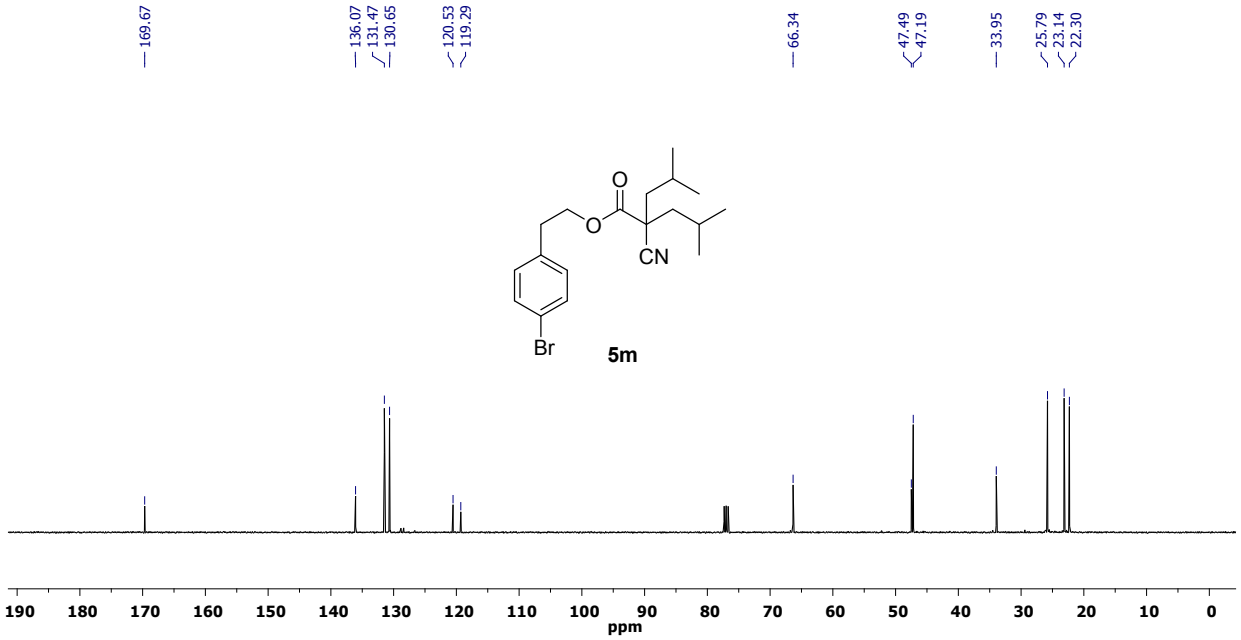
^{1}H-NMR (400 MHz) spectrum of **5l** in $CDCl_3$



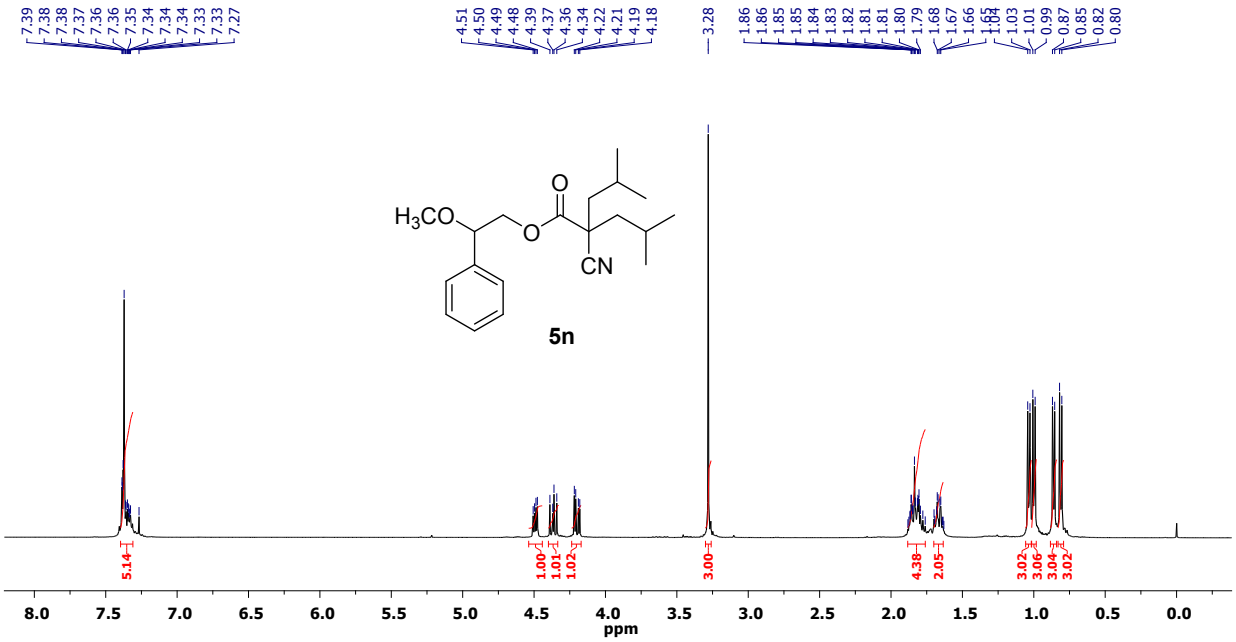
^{13}C-NMR (100 MHz) spectrum of **5l** in $CDCl_3$



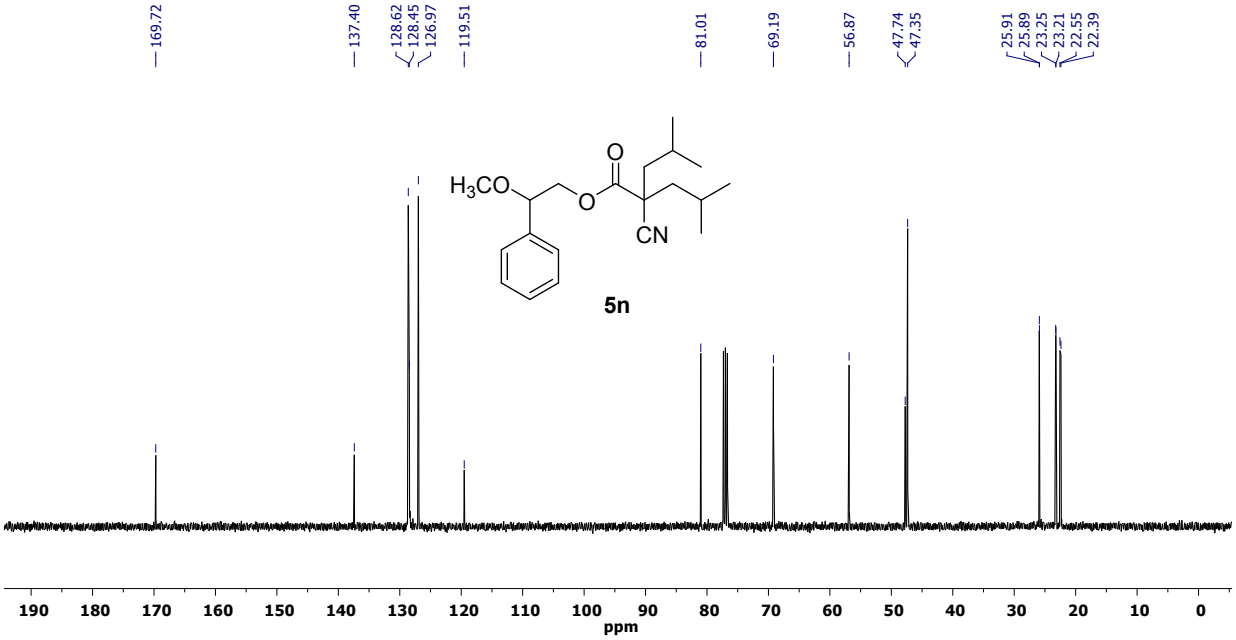
^{1}H-NMR (400 MHz) spectrum of **5m** in $CDCl_3$



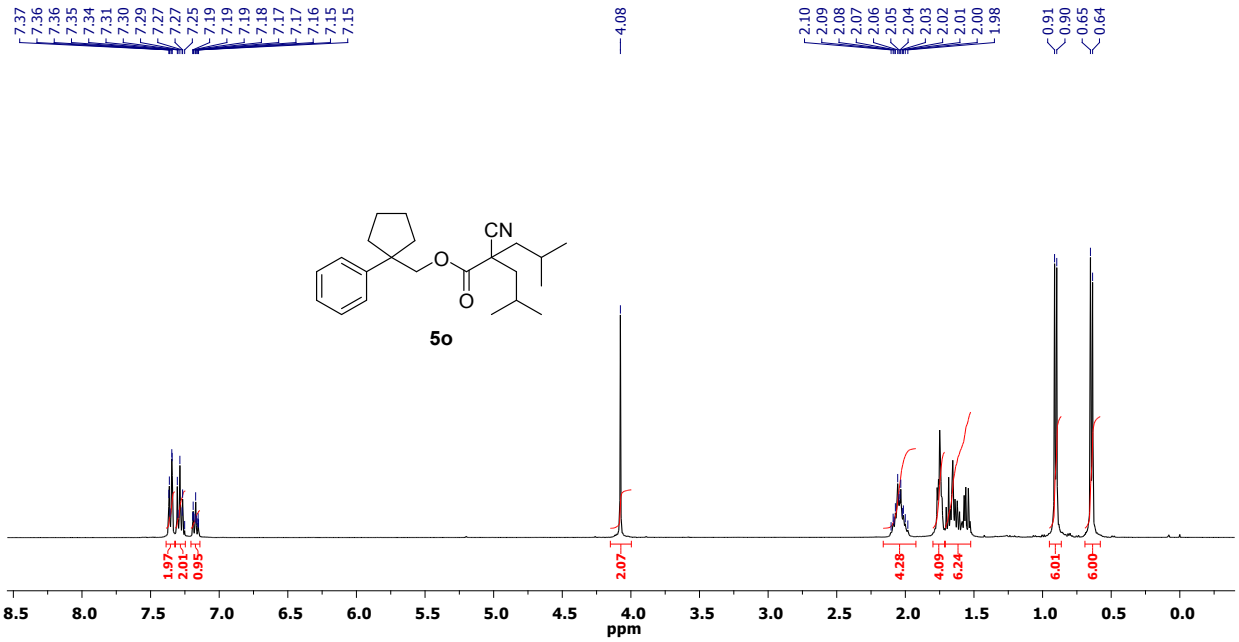
^{13}C-NMR (100 MHz) spectrum of **5m** in $CDCl_3$



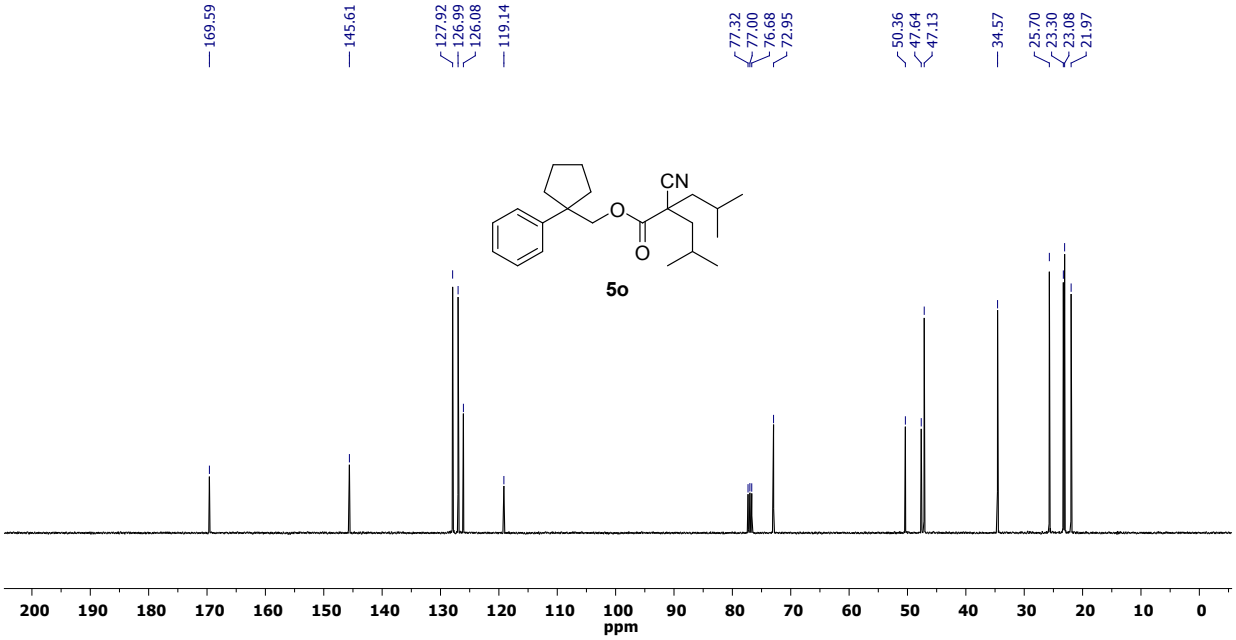
^{1}H-NMR (400 MHz) spectrum of **5n** in $CDCl_3$



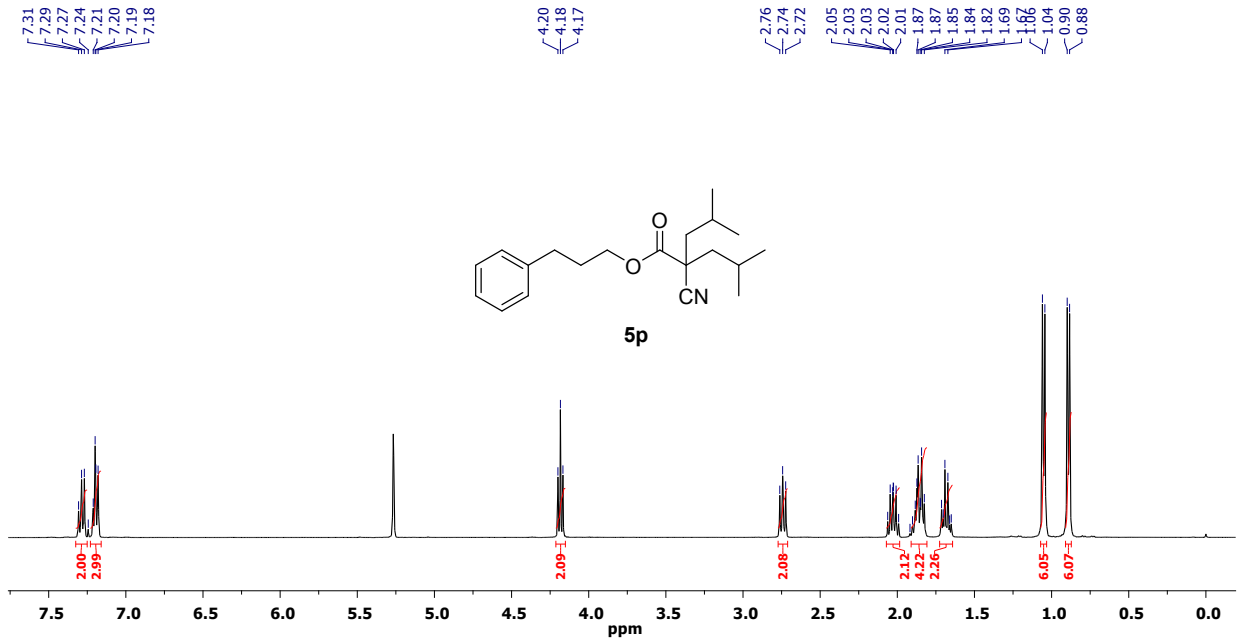
^{13}C-NMR (100 MHz) spectrum of **5n** in $CDCl_3$



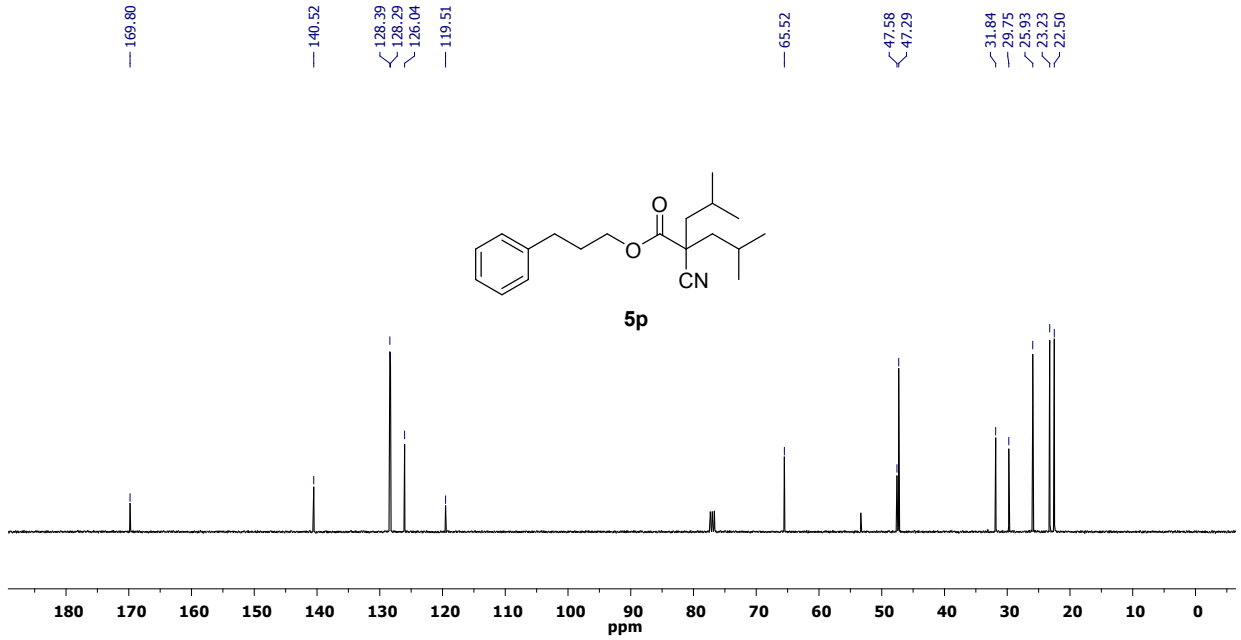
^{1}H-NMR (400 MHz) spectrum of **5o** in $CDCl_3$



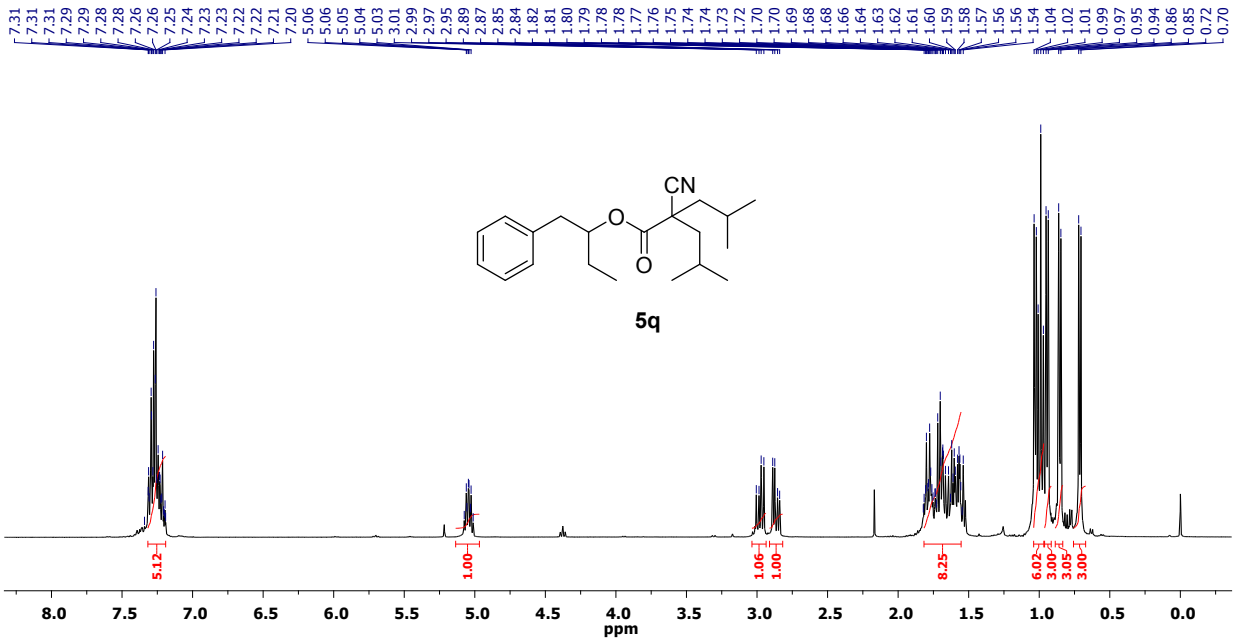
^{13}C-NMR (100 MHz) spectrum of **5o** in $CDCl_3$



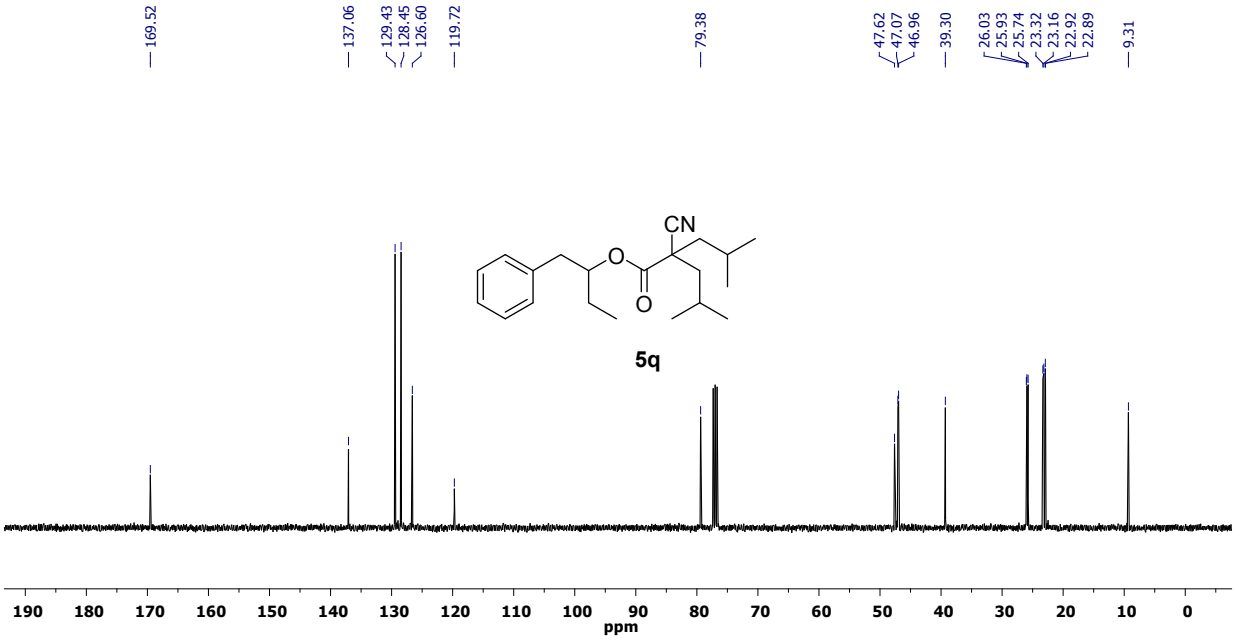
^{1}H-NMR (400 MHz) spectrum of **5p** in $CDCl_3$



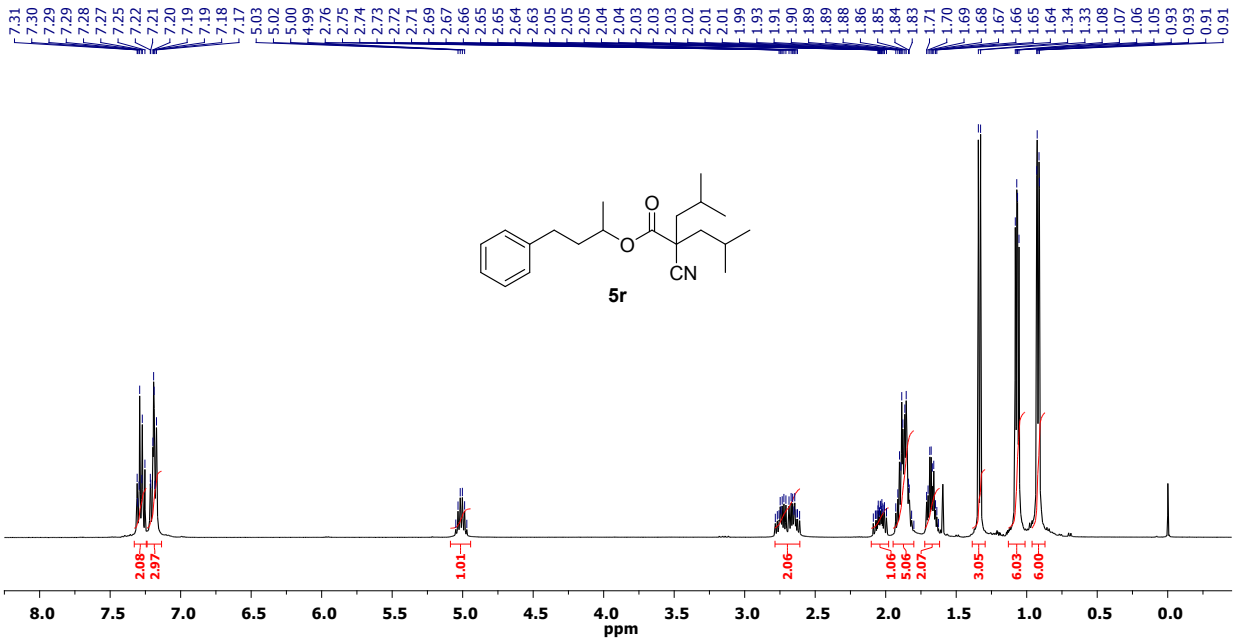
^{13}C-NMR (100 MHz) spectrum of **5p** in $CDCl_3$



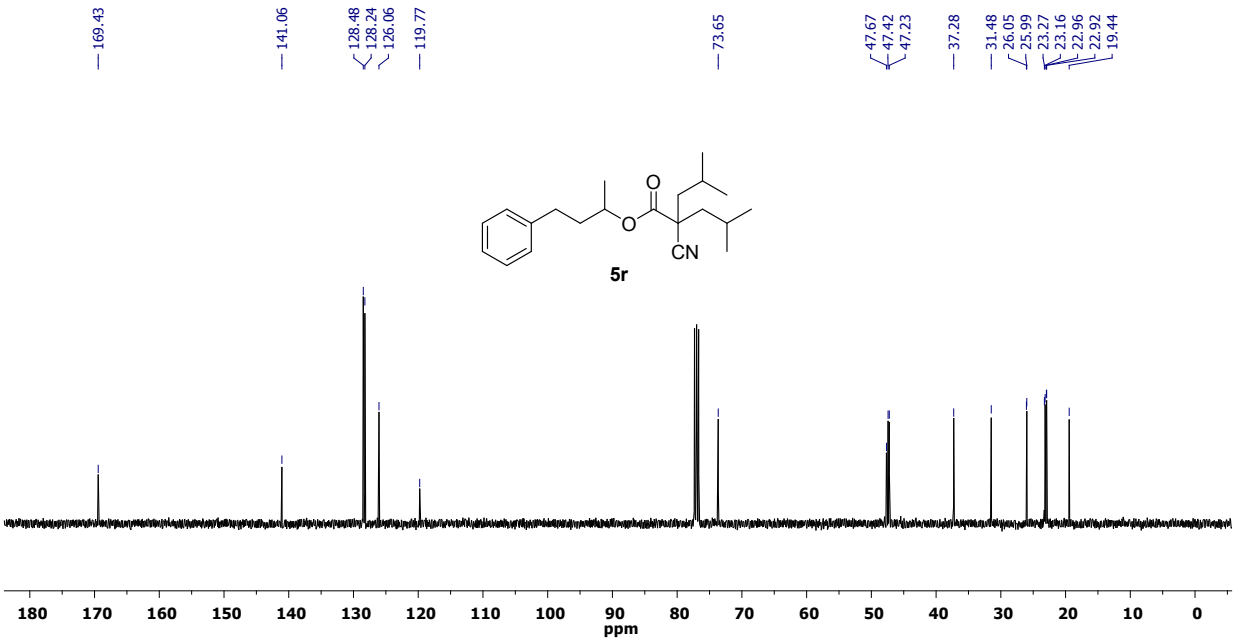
^{1}H-NMR (400 MHz) spectrum of **5q** in $CDCl_3$



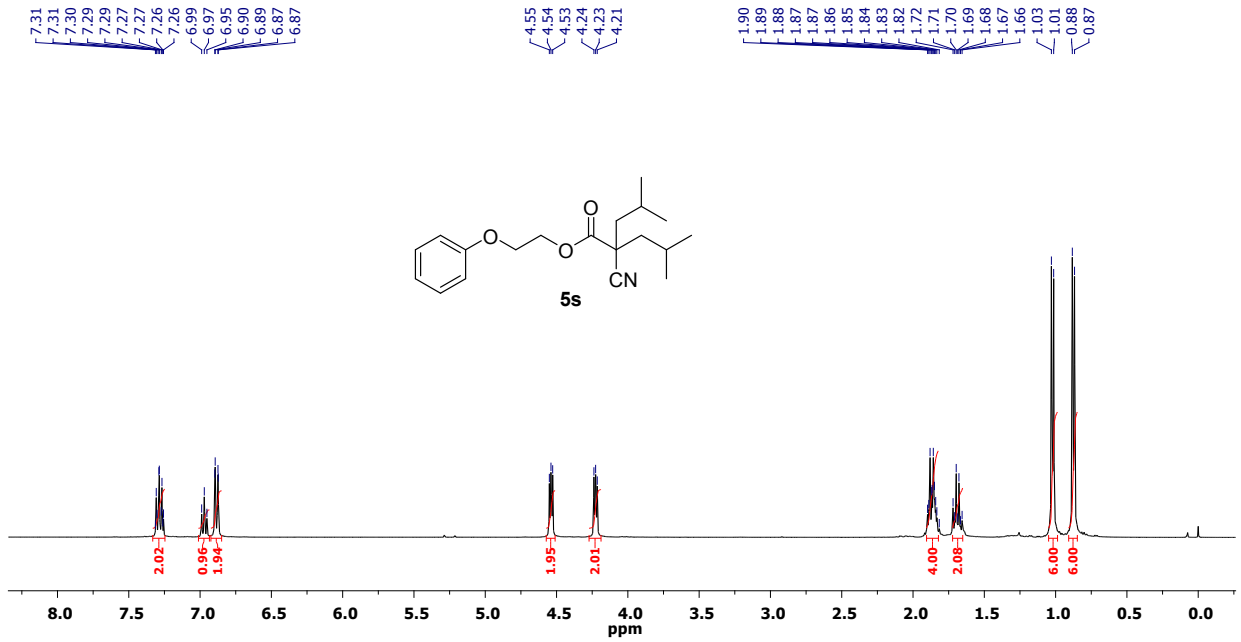
^{13}C-NMR (100 MHz) spectrum of **5q** in $CDCl_3$



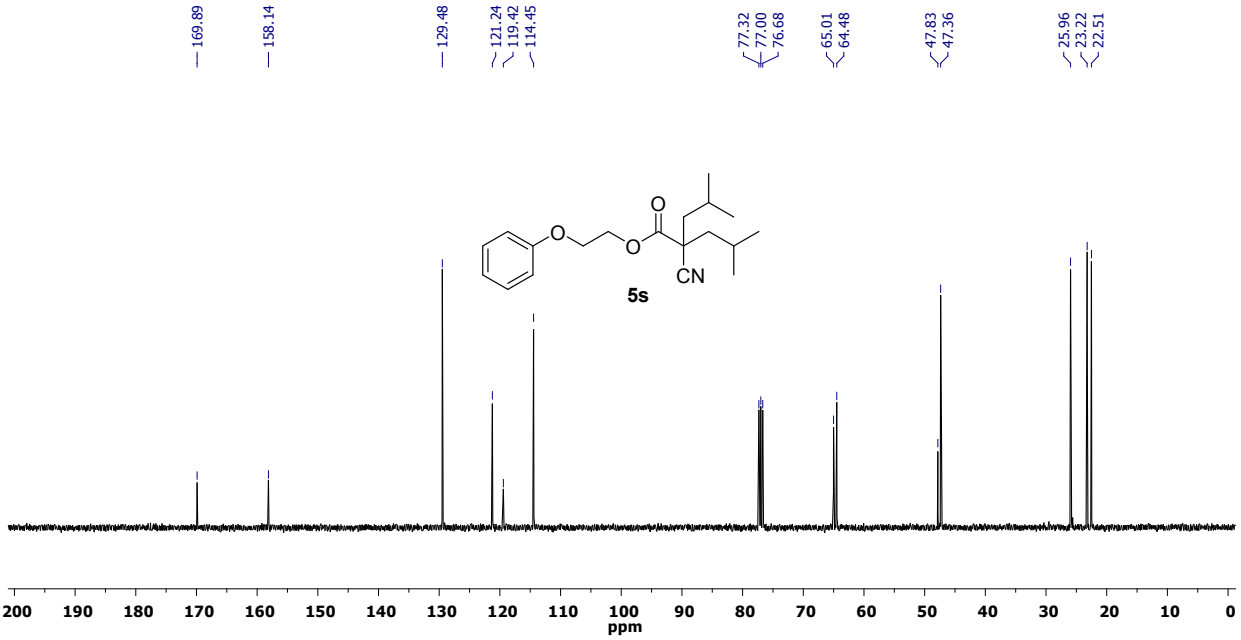
^{1}H-NMR (400 MHz) spectrum of **5r** in $CDCl_3$



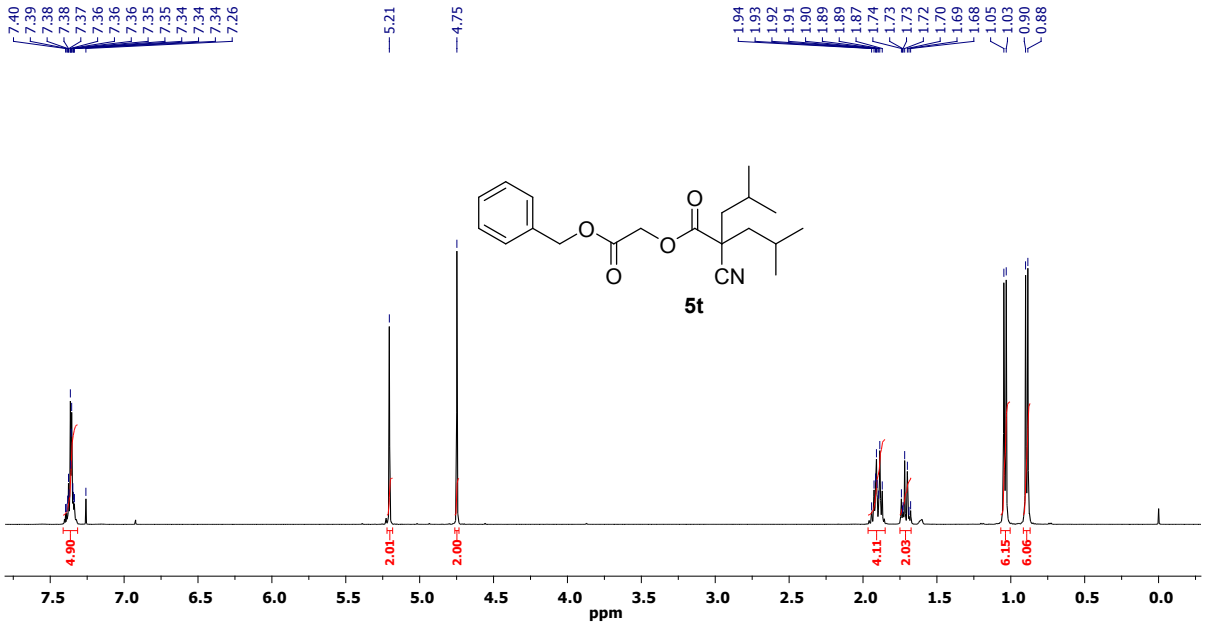
^{13}C-NMR (100 MHz) spectrum of **5r** in $CDCl_3$



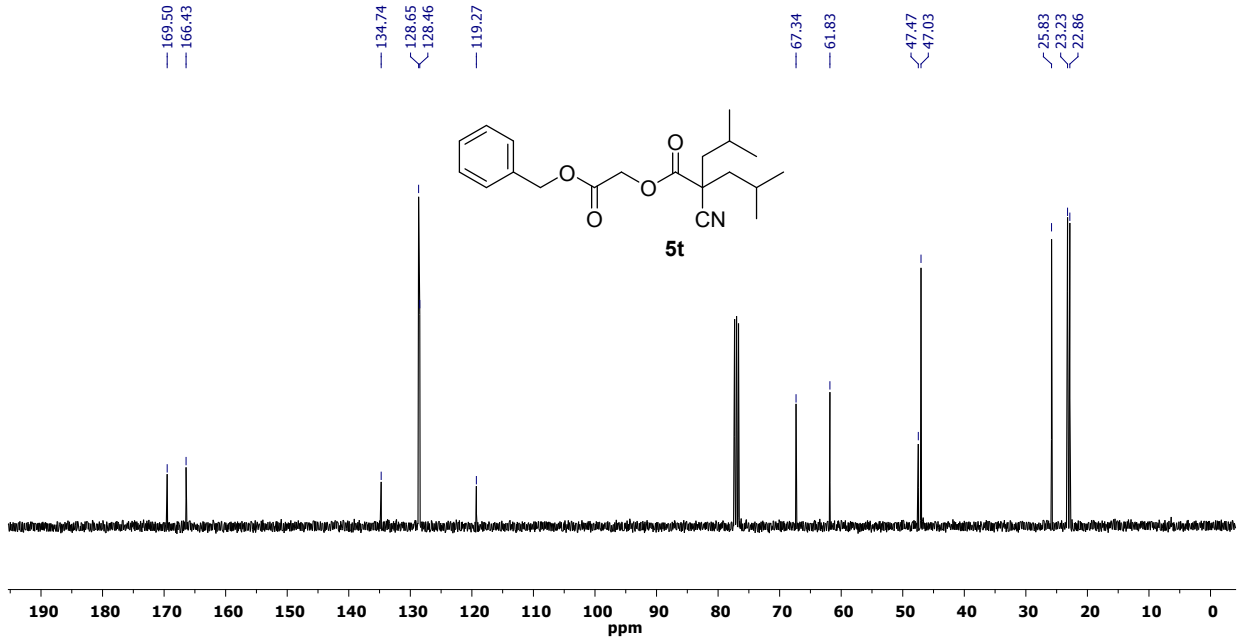
^{1}H-NMR (400 MHz) spectrum of **5s** in $CDCl_3$



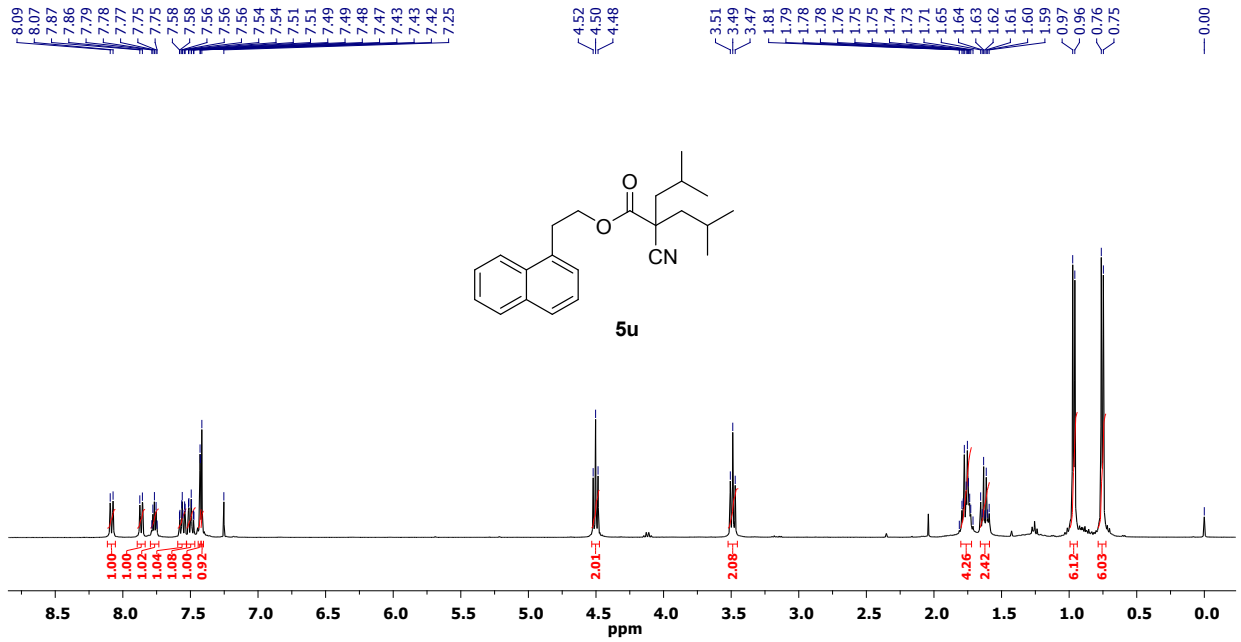
^{13}C-NMR (100 MHz) spectrum of **5s** in $CDCl_3$



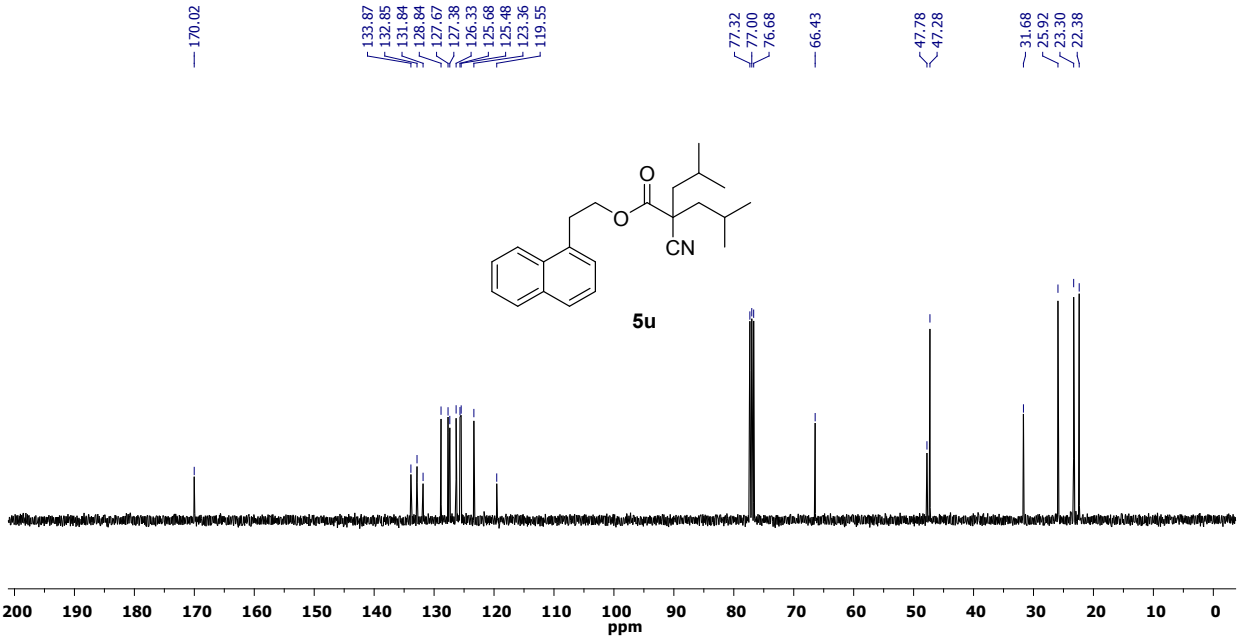
^{1}H-NMR (400 MHz) spectrum of **5t** in $CDCl_3$



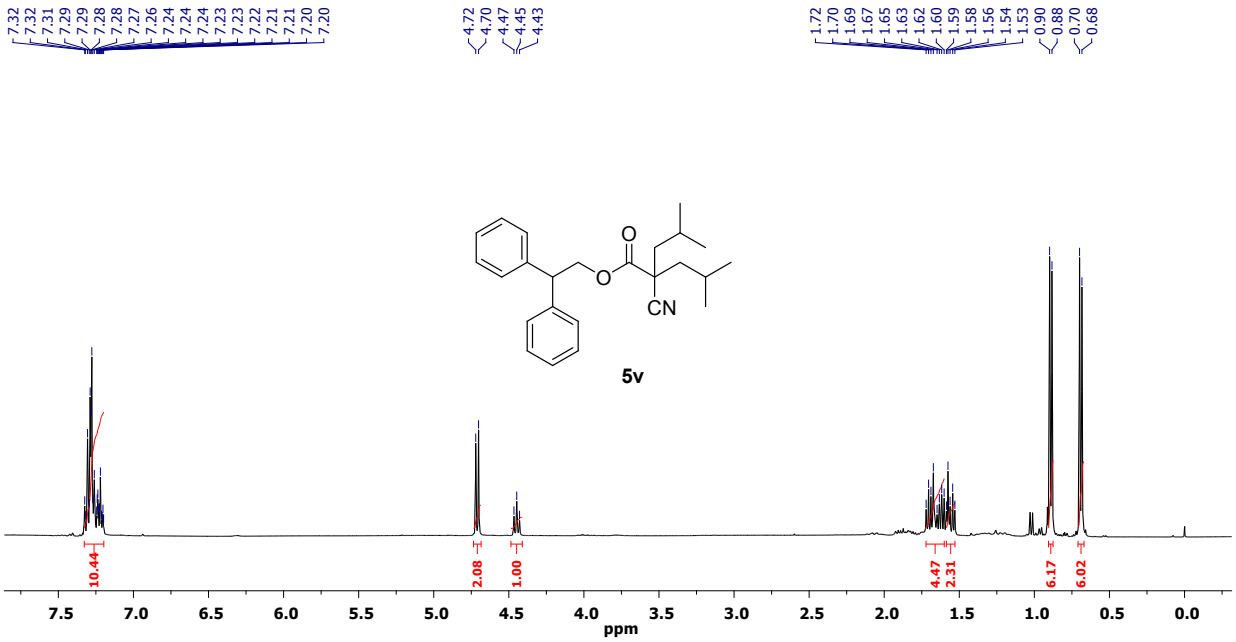
^{13}C-NMR (100 MHz) spectrum of **5t** in $CDCl_3$



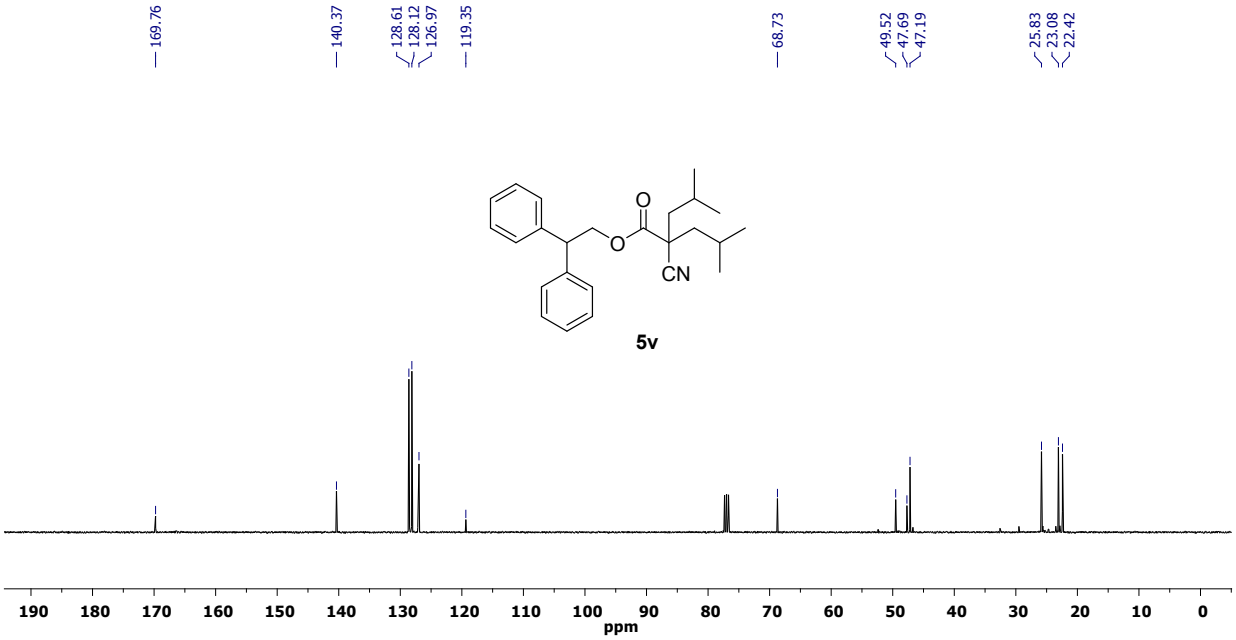
^{1}H-NMR (400 MHz) spectrum of **5u** in $CDCl_3$



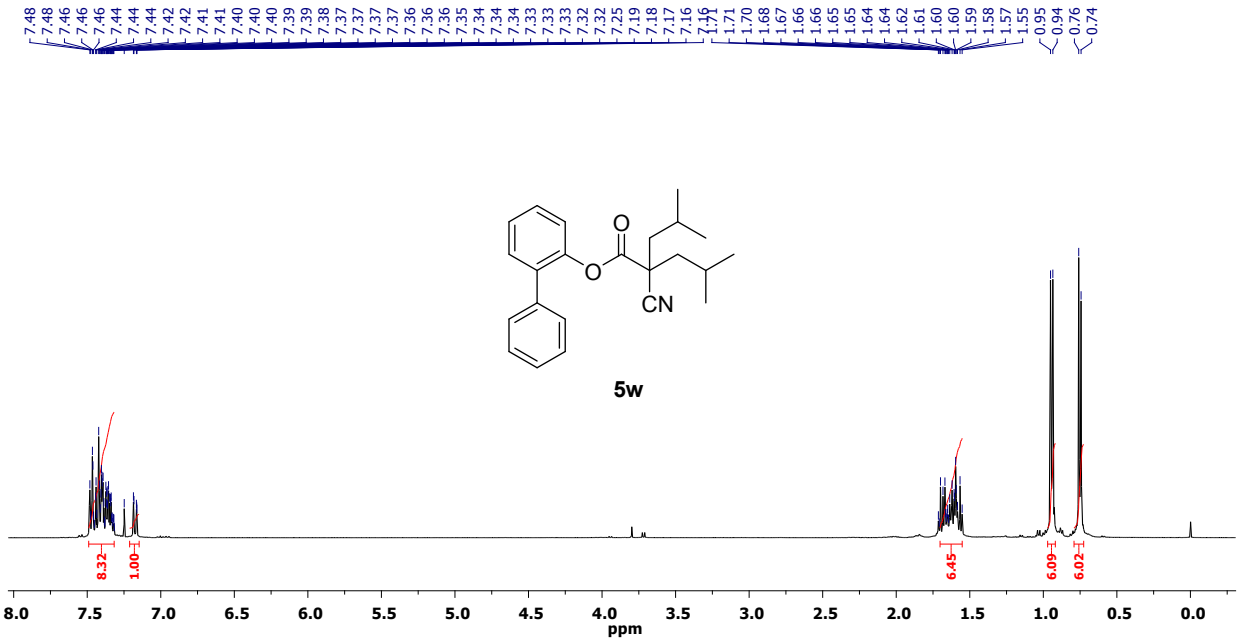
^{13}C-NMR (100 MHz) spectrum of **5u** in $CDCl_3$



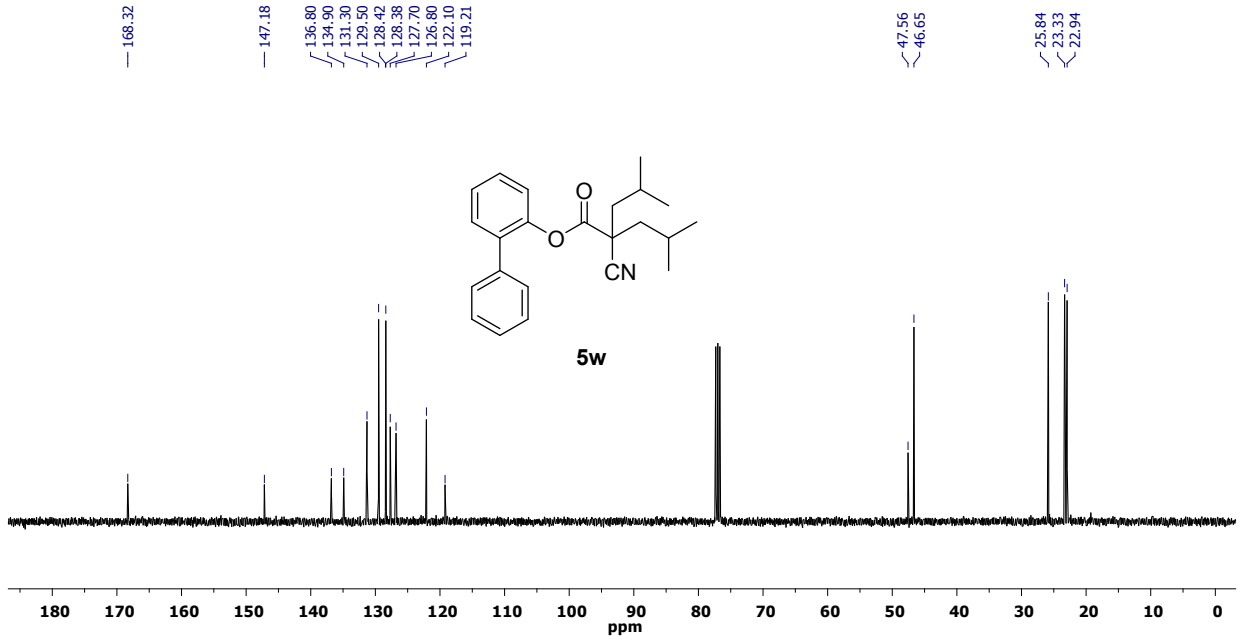
^{1}H-NMR (400 MHz) spectrum of **5v** in $CDCl_3$



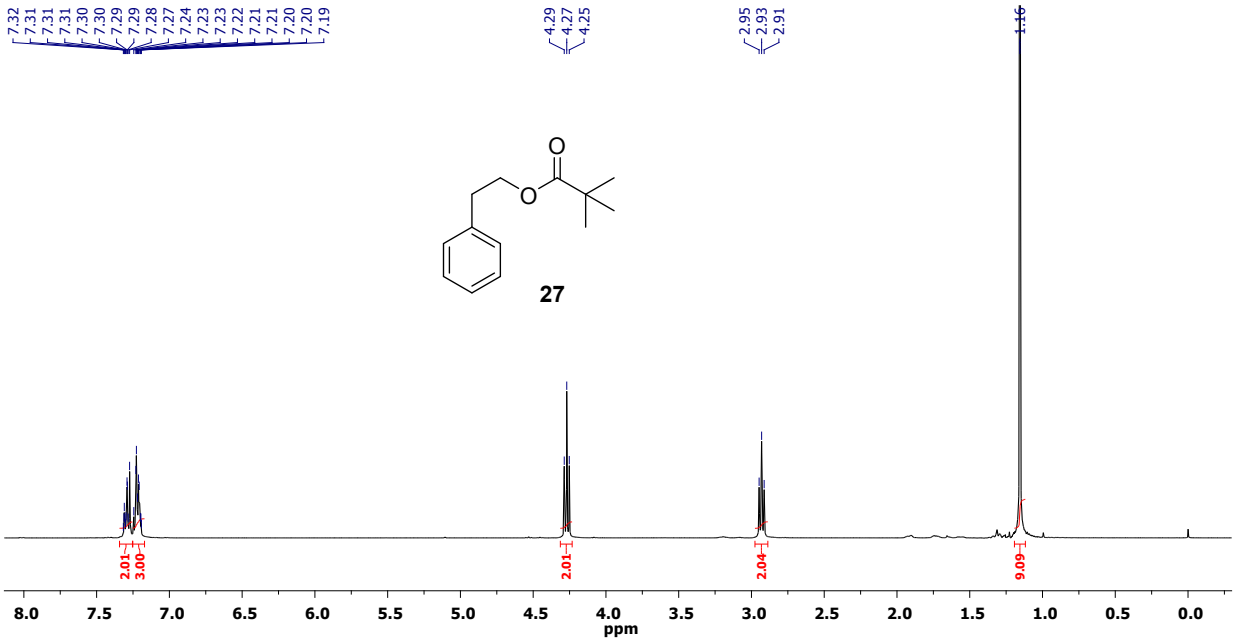
^{13}C-NMR (100 MHz) spectrum of **5v** in $CDCl_3$



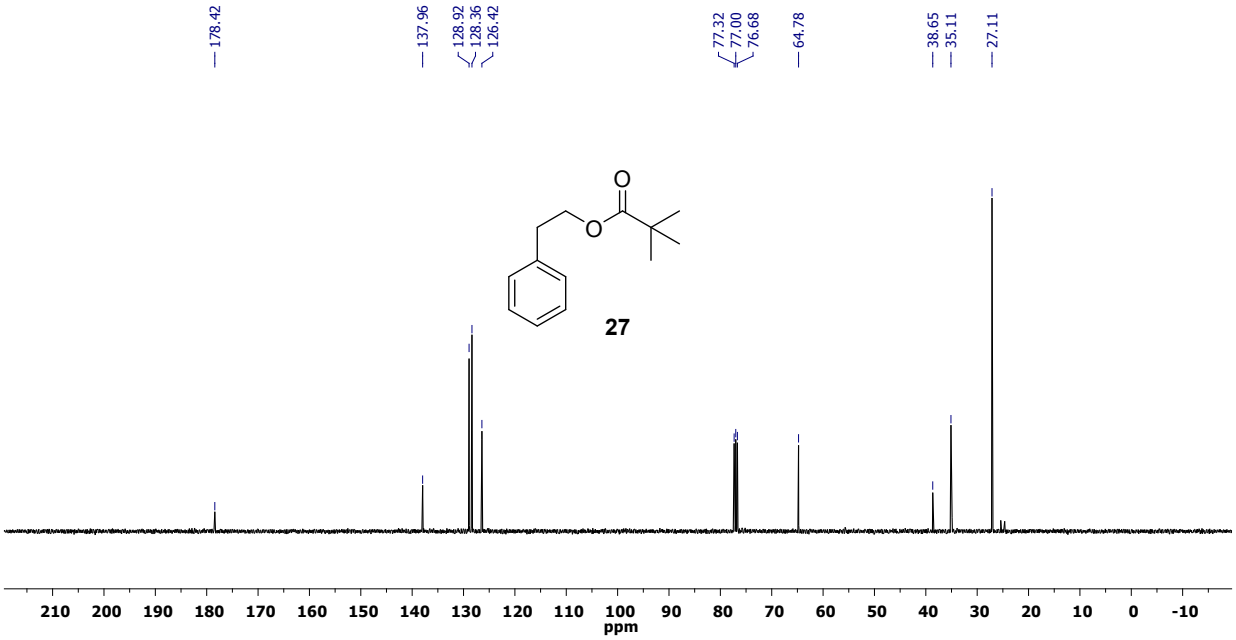
^{1}H-NMR (400 MHz) spectrum of **5w** in $CDCl_3$



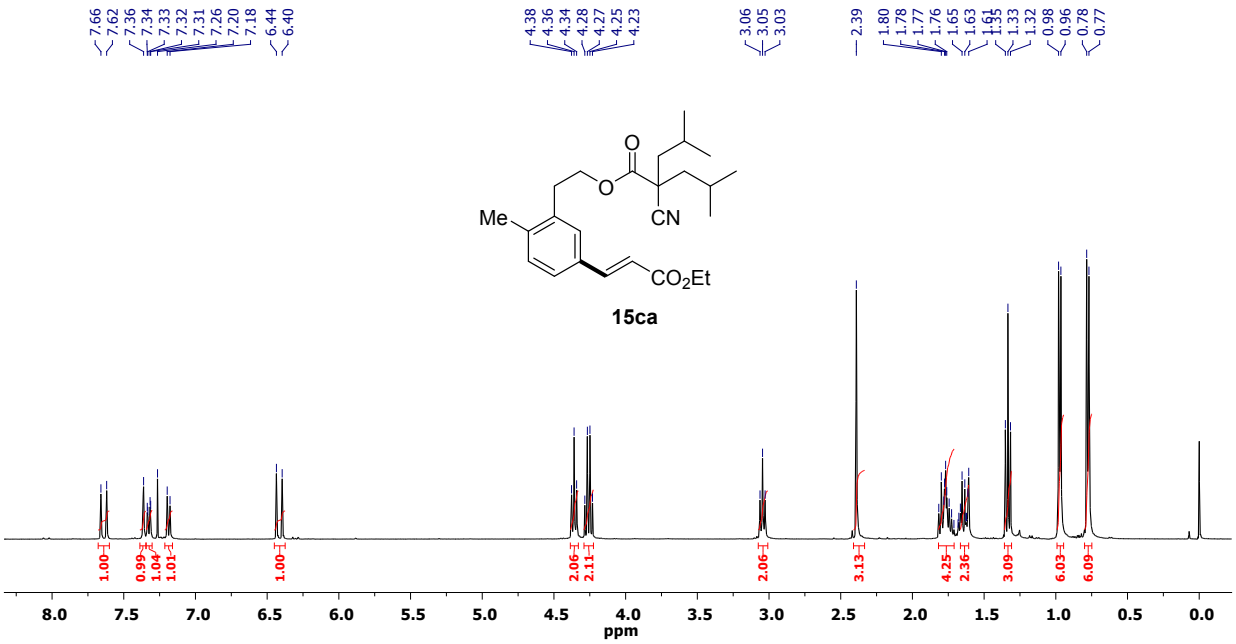
^{13}C-NMR (100 MHz) spectrum of **5w** in $CDCl_3$



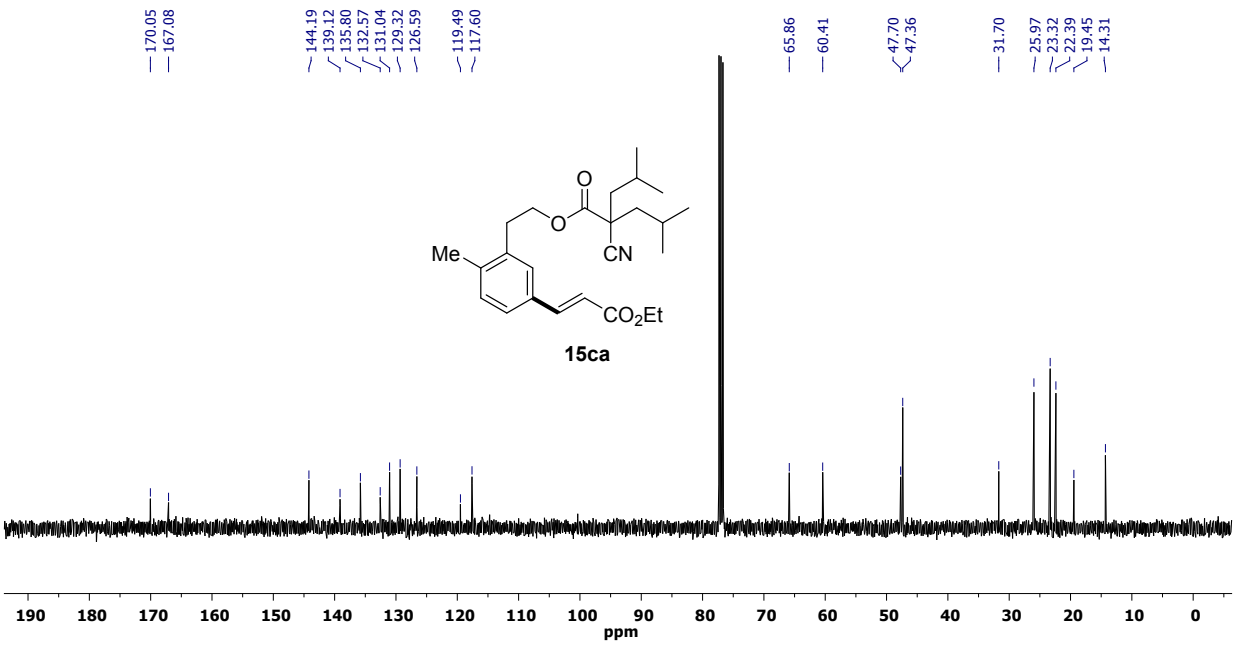
^{1}H-NMR (400 MHz) spectrum of **27** in $CDCl_3$



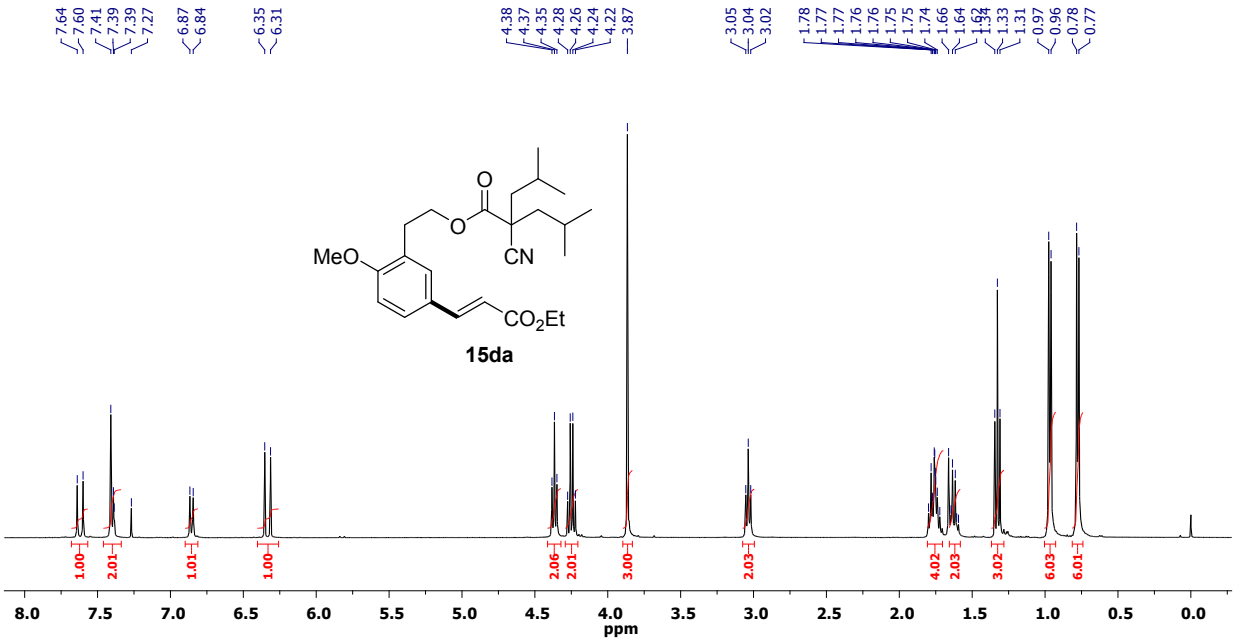
^{13}C-NMR (100 MHz) spectrum of **27** in $CDCl_3$



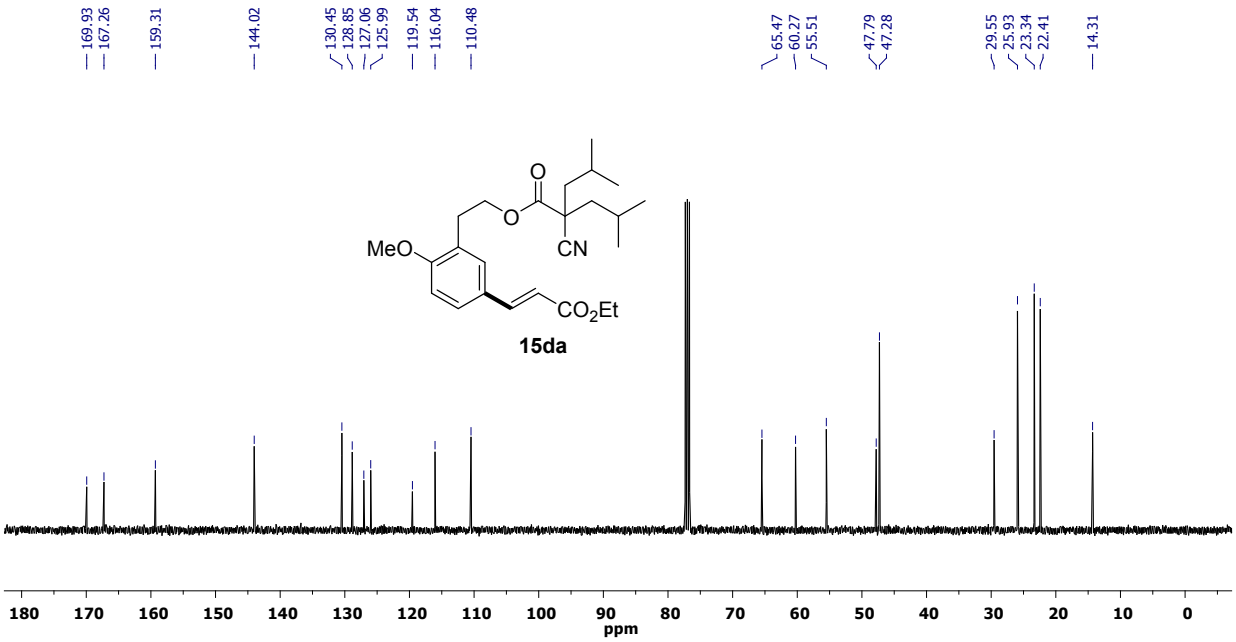
^{1}H-NMR (400 MHz) spectrum of **15ca** in $CDCl_3$



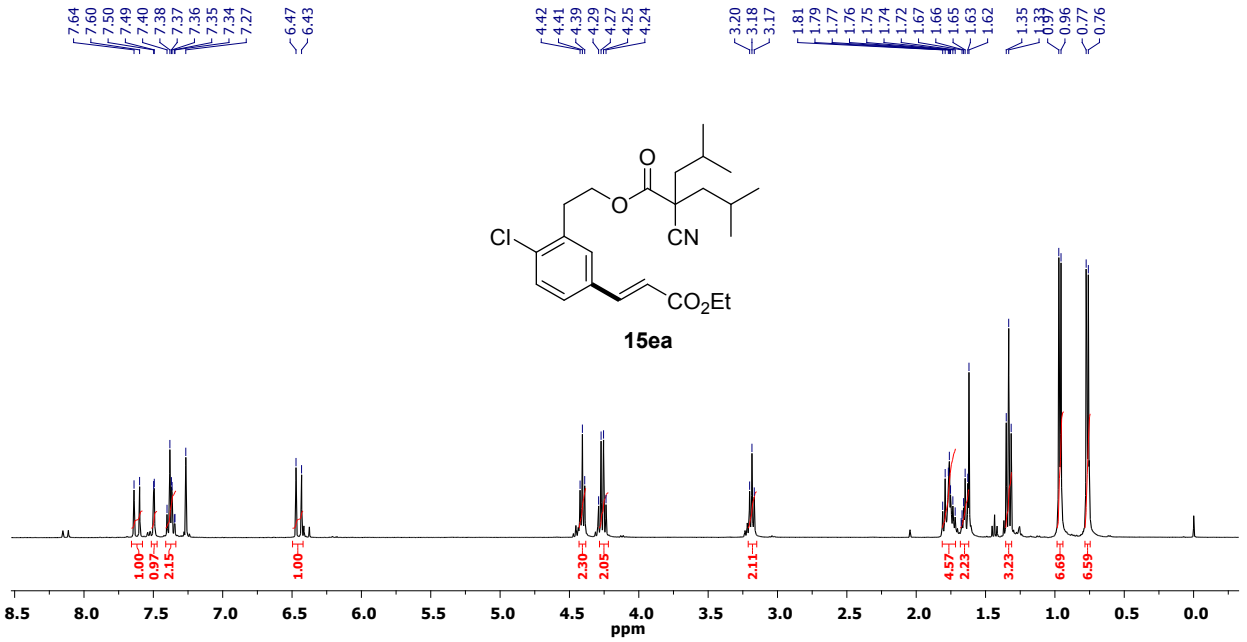
^{13}C-NMR (100 MHz) spectrum of **15ca** in $CDCl_3$



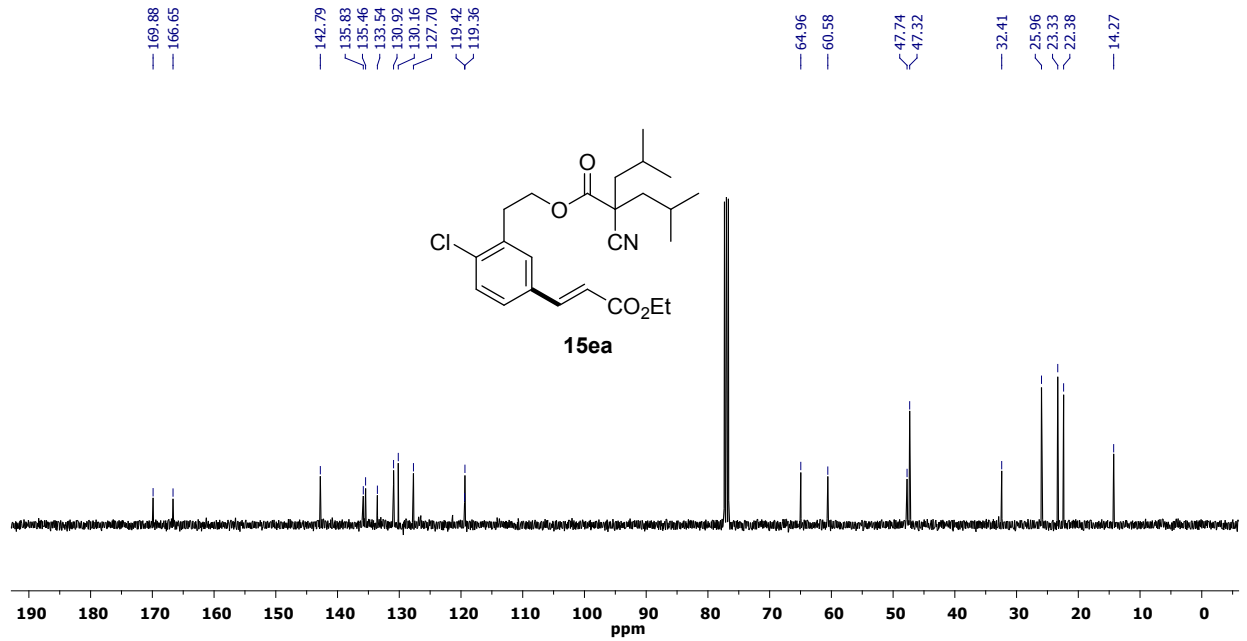
^{1}H-NMR (400 MHz) spectrum of **15da** in $CDCl_3$



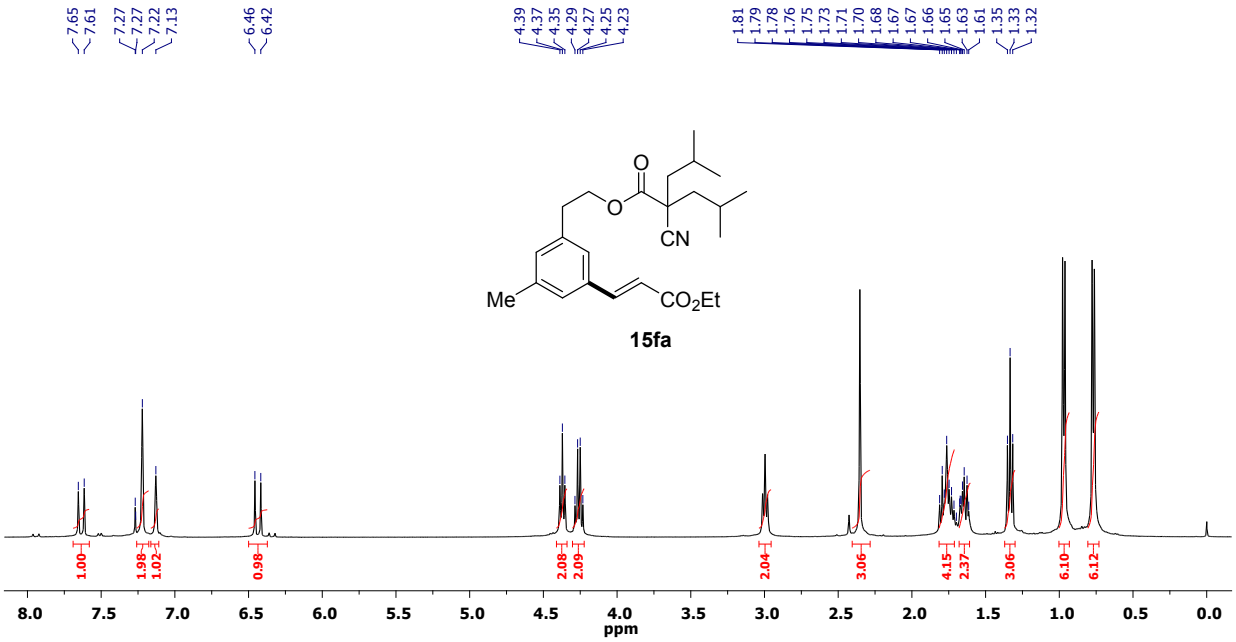
^{13}C-NMR (100 MHz) spectrum of **15da** in $CDCl_3$



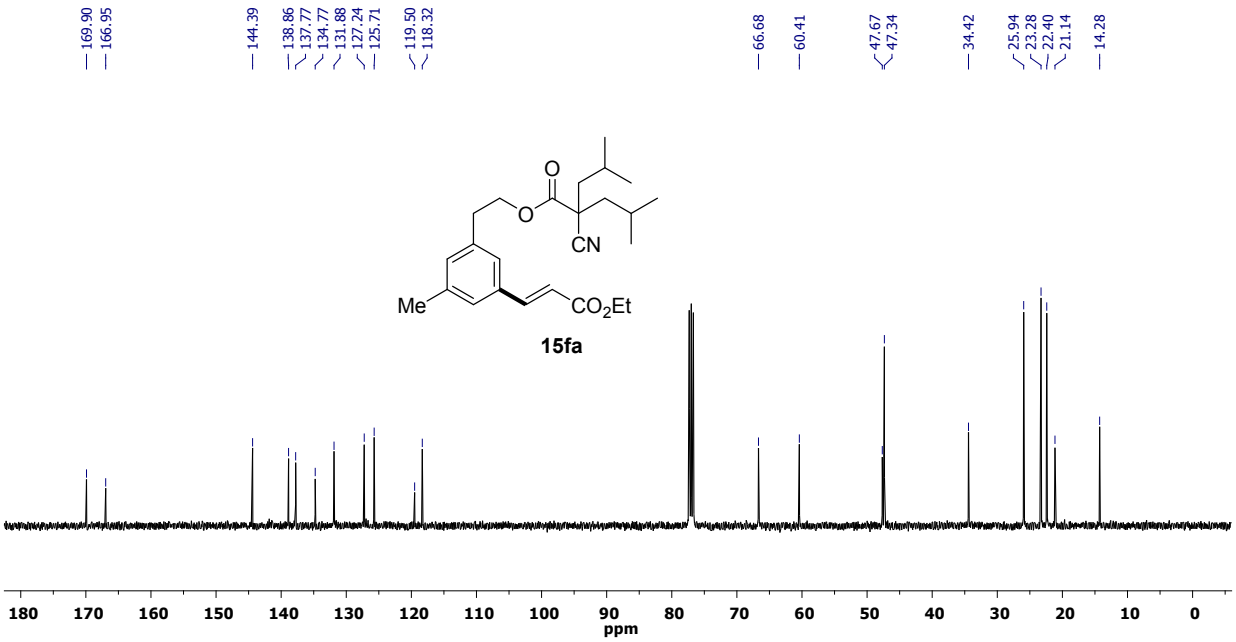
^{1}H-NMR (400 MHz) spectrum of **15ea** in $CDCl_3$



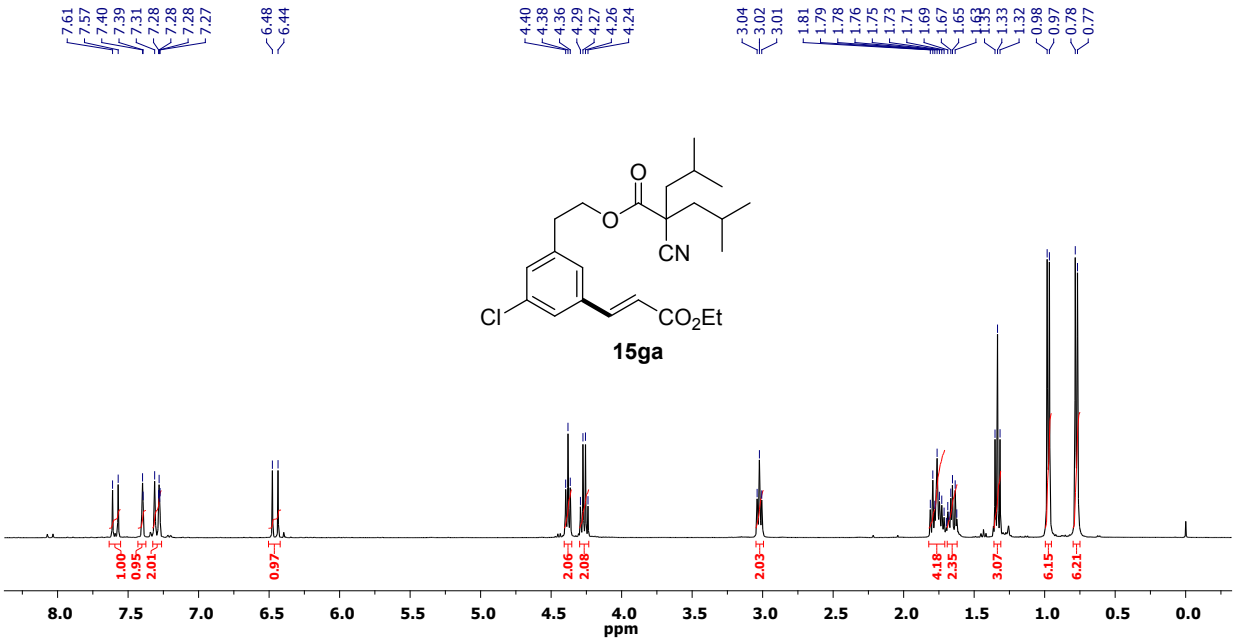
^{13}C-NMR (100 MHz) spectrum of **15ea** in $CDCl_3$



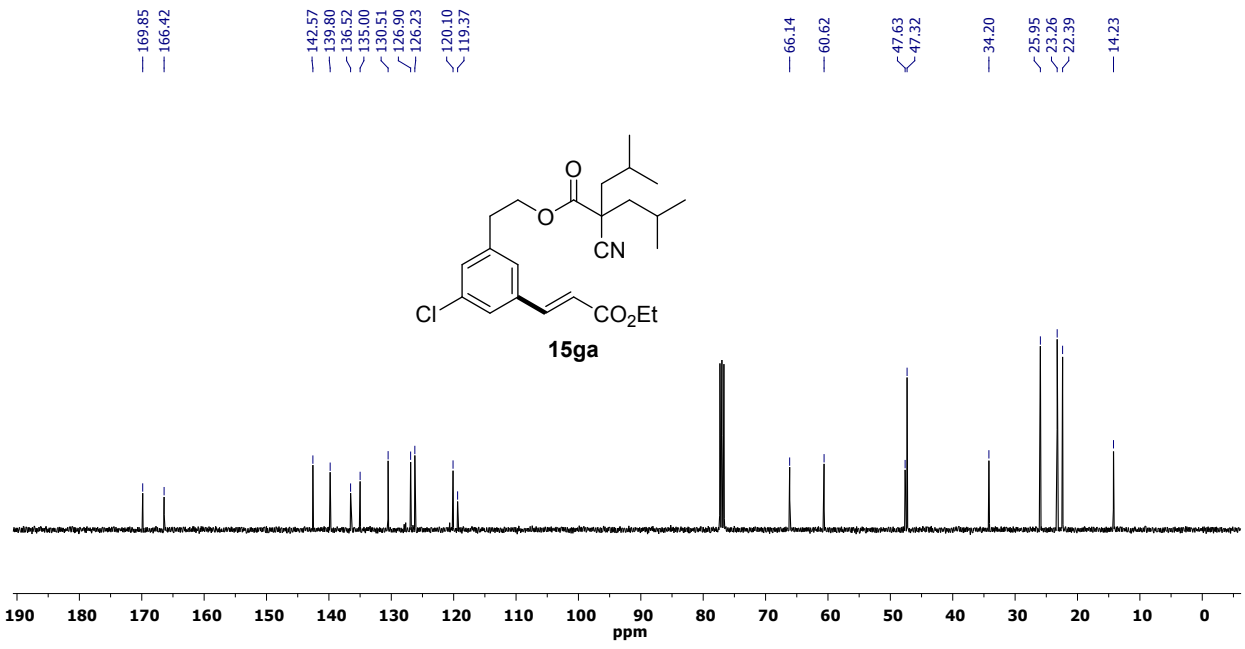
^{1}H-NMR (400 MHz) spectrum of **15fa** in $CDCl_3$



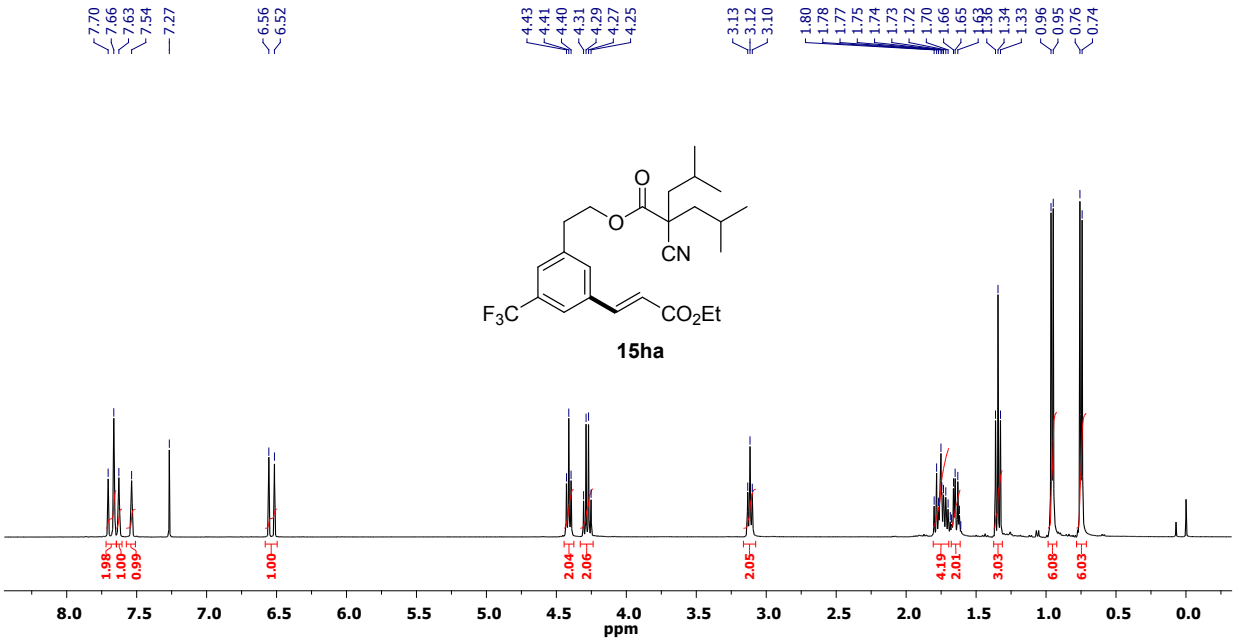
^{13}C-NMR (100 MHz) spectrum of **15fa** in $CDCl_3$



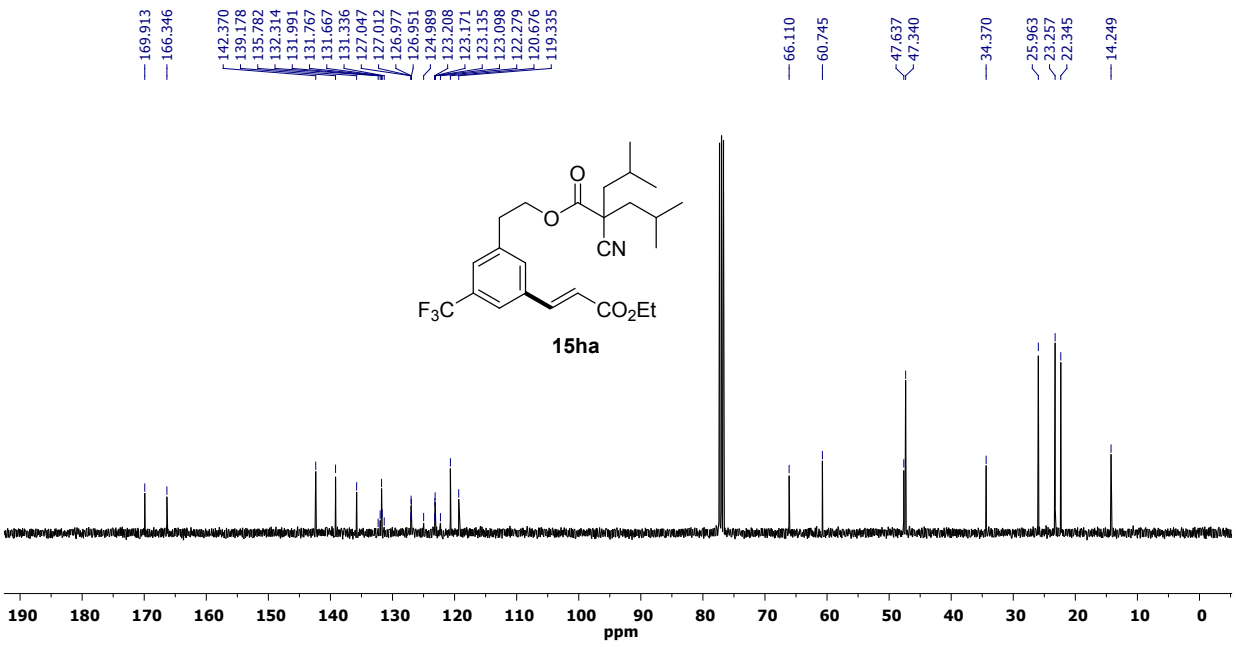
^{1}H-NMR (400 MHz) spectrum of **15ga** in $CDCl_3$



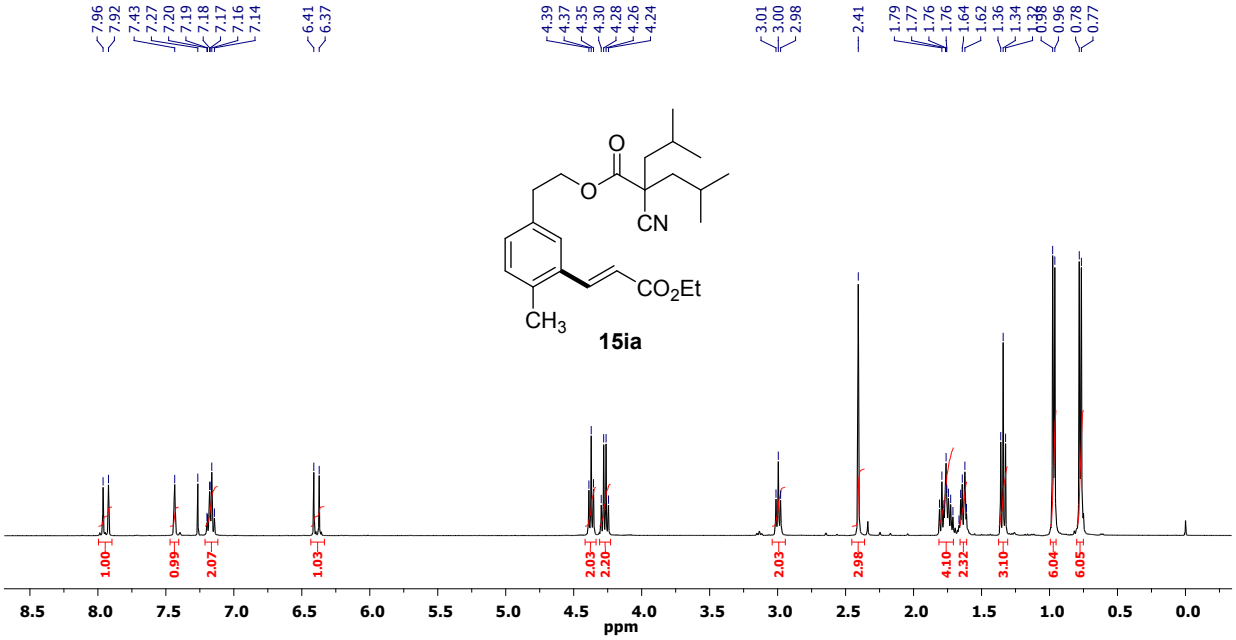
^{13}C-NMR (100 MHz) spectrum of **15ga** in $CDCl_3$



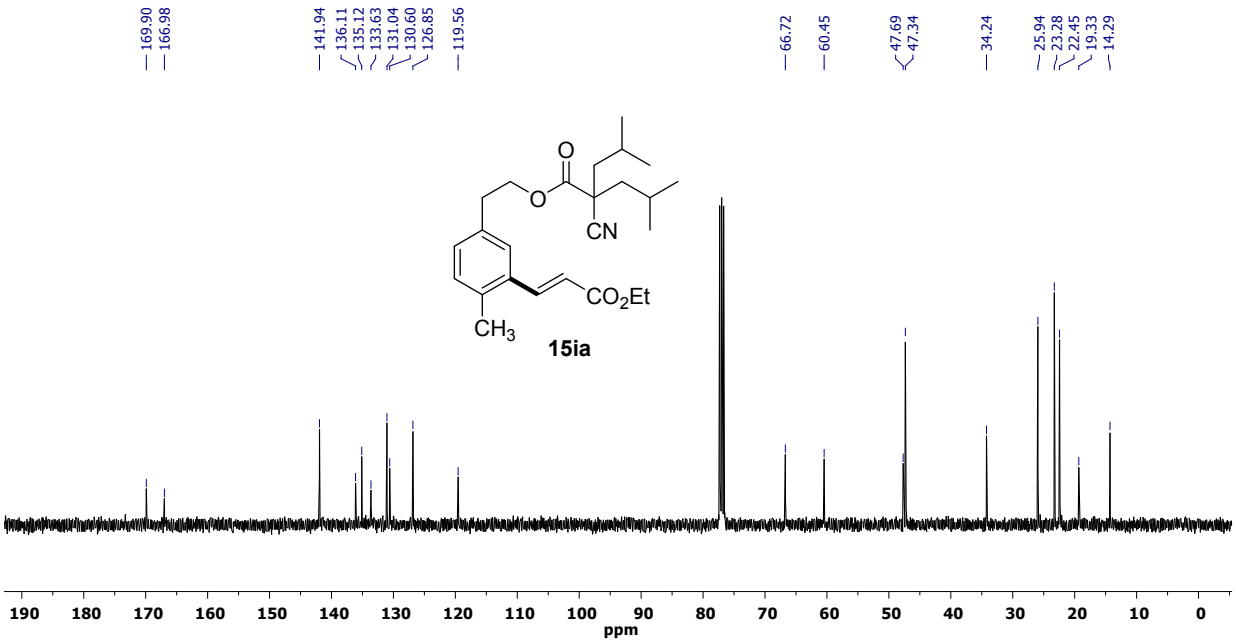
^{1}H-NMR (400 MHz) spectrum of **15ha** in $CDCl_3$



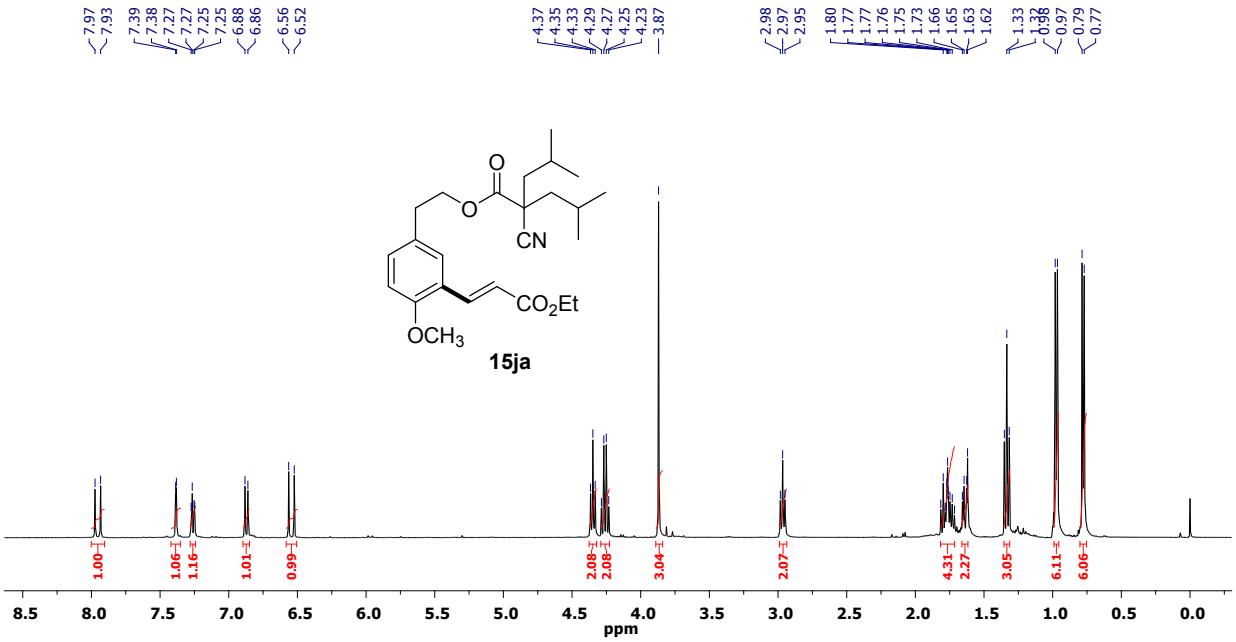
^{13}C-NMR (100 MHz) spectrum of **15ha** in $CDCl_3$



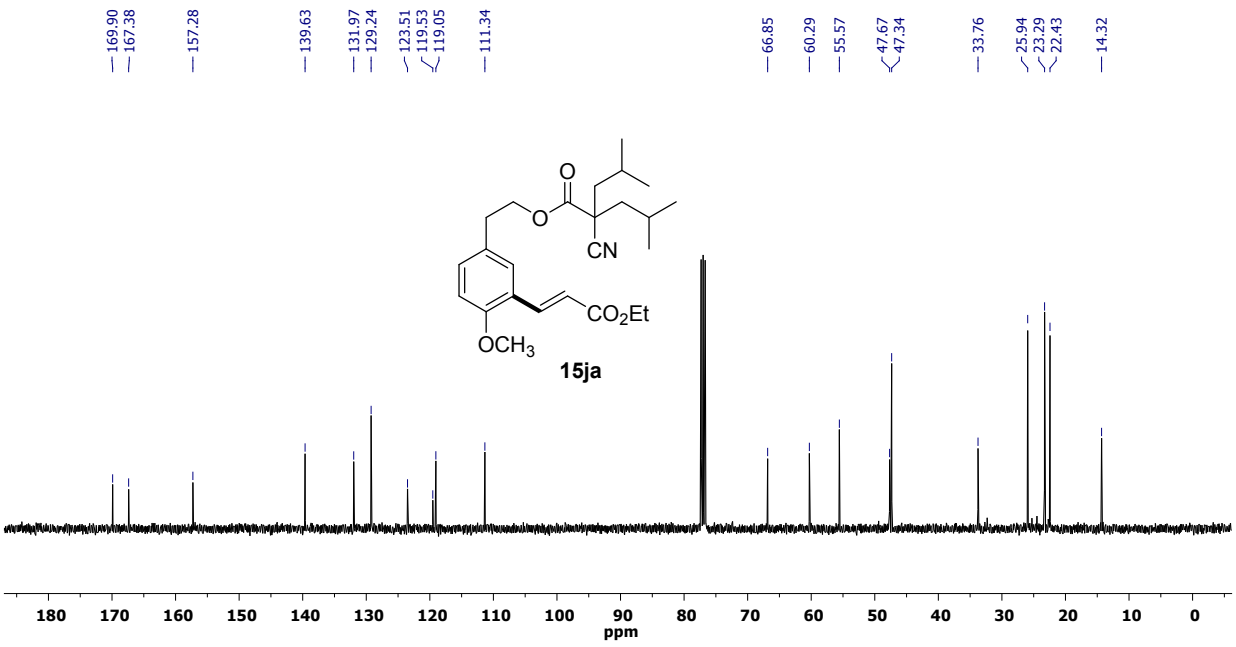
^{1}H-NMR (400 MHz) spectrum of **15ia** in $CDCl_3$



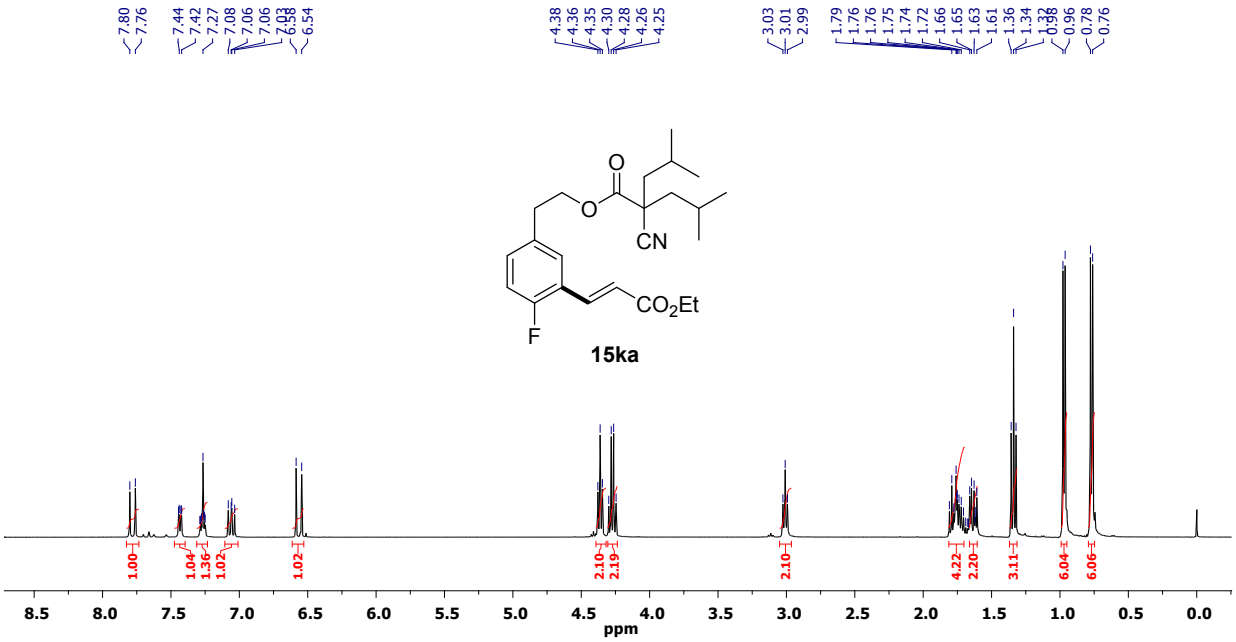
^{13}C-NMR (100 MHz) spectrum of **15ia** in $CDCl_3$



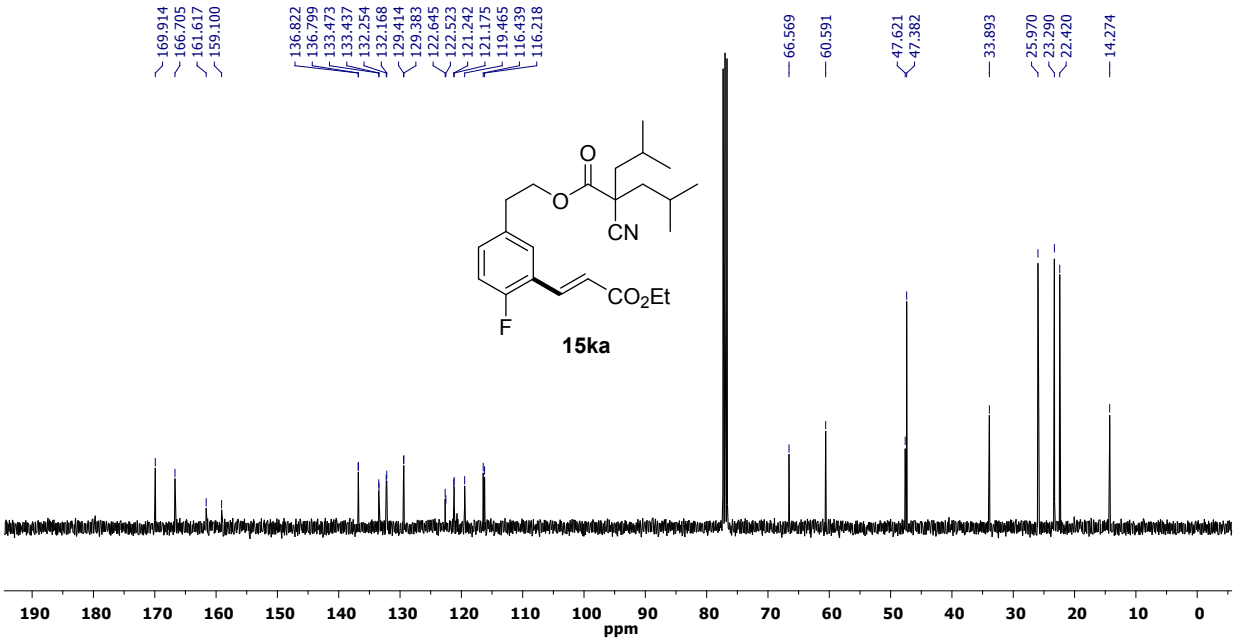
^{1}H-NMR (400 MHz) spectrum of **15ja** in $CDCl_3$



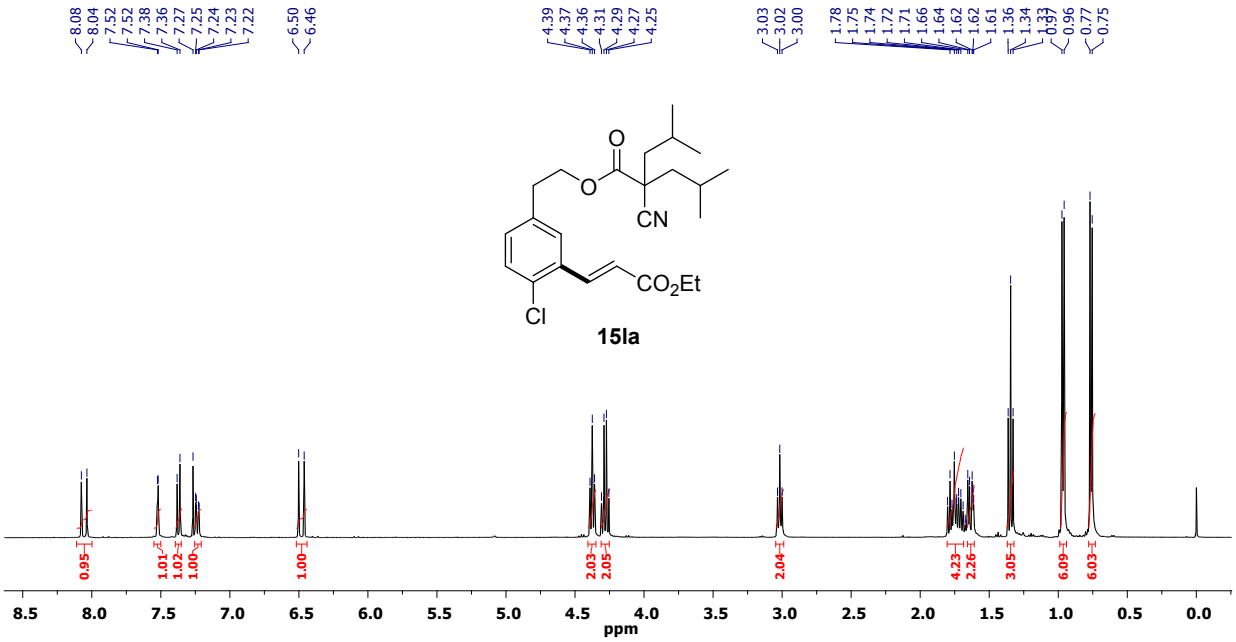
^{13}C-NMR (100 MHz) spectrum of **15ja** in $CDCl_3$



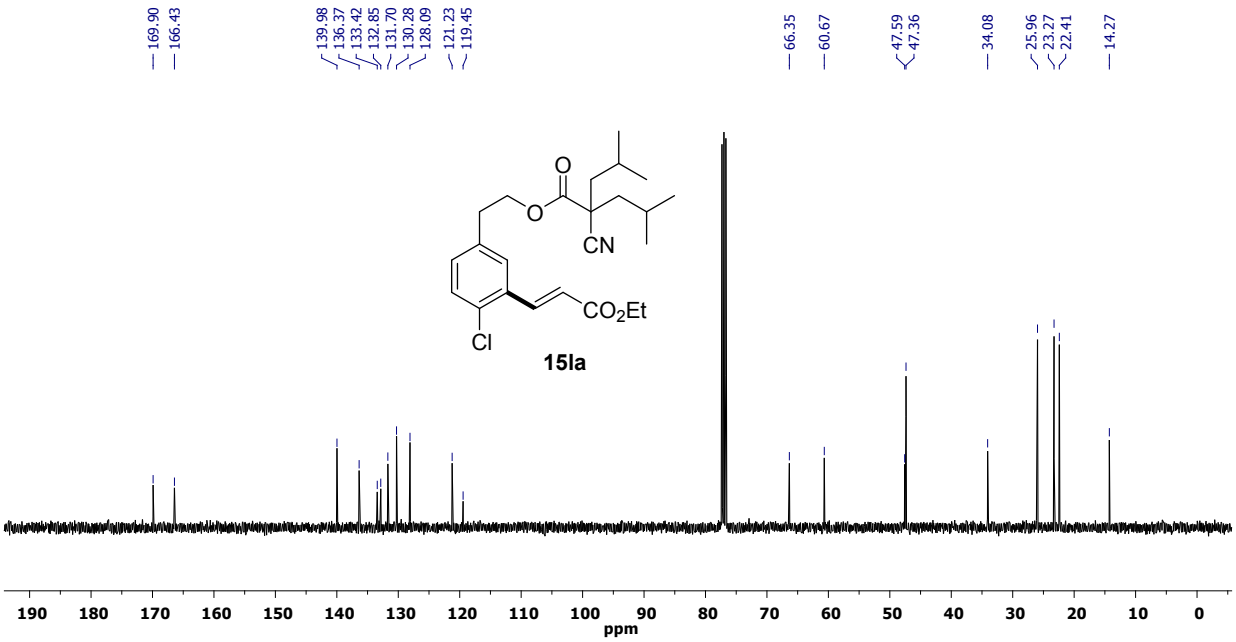
^{1}H-NMR (400 MHz) spectrum of **15ka** in $CDCl_3$



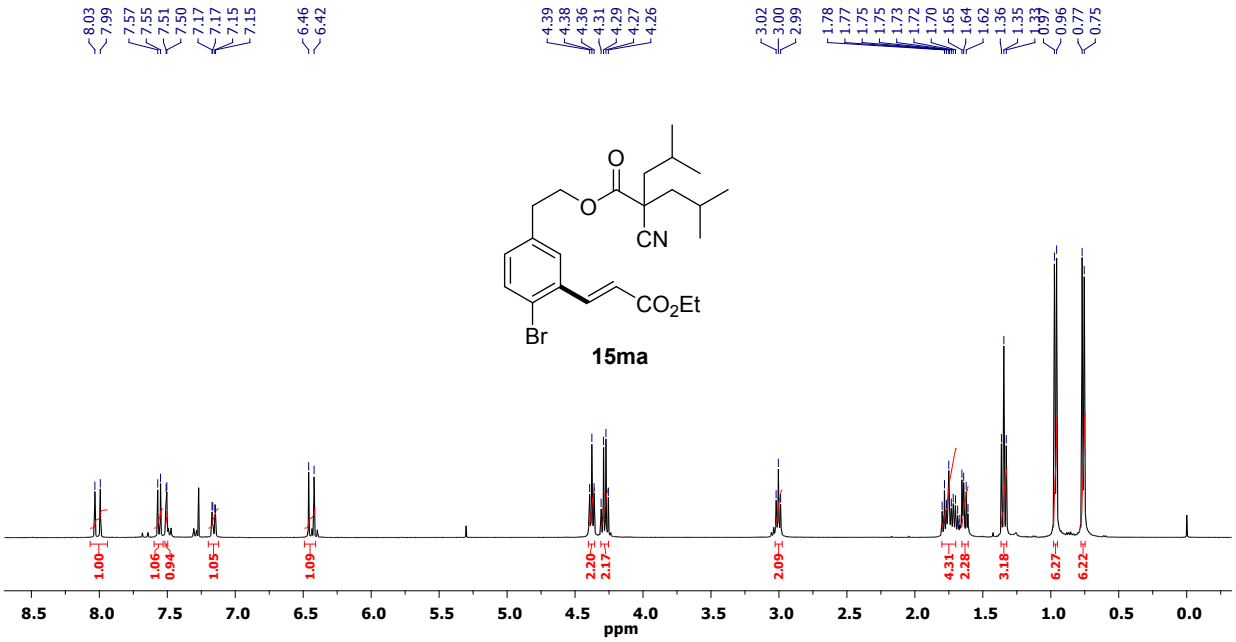
^{13}C-NMR (100 MHz) spectrum of **15ka** in $CDCl_3$



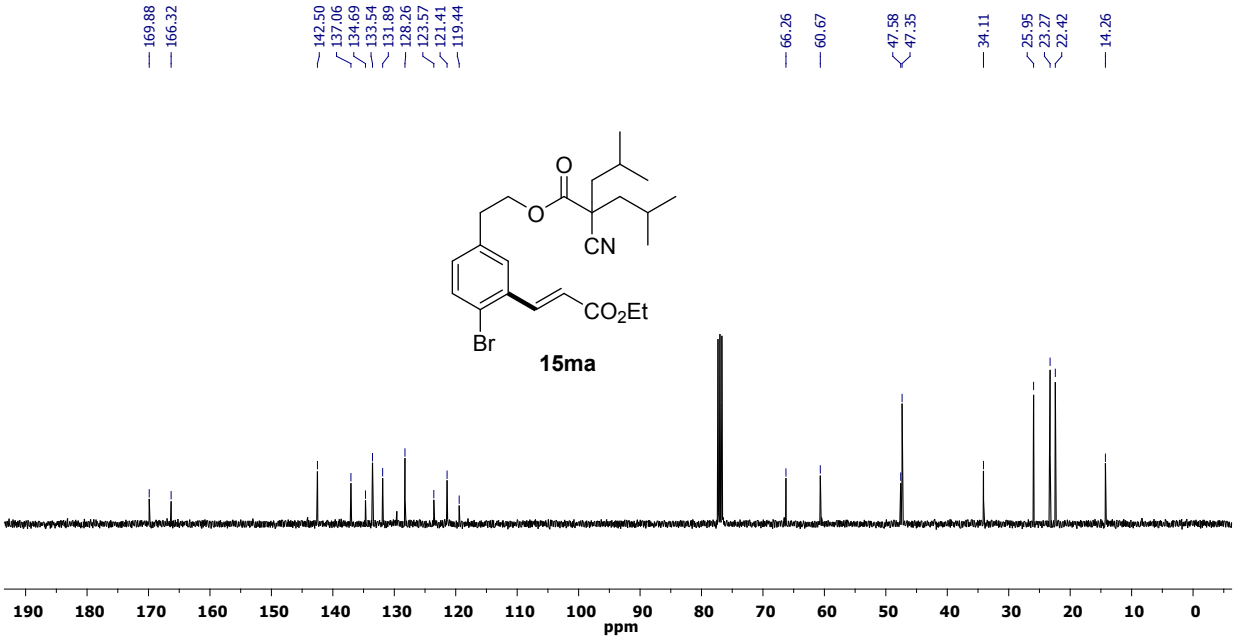
^{1}H-NMR (400 MHz) spectrum of **15la** in $CDCl_3$



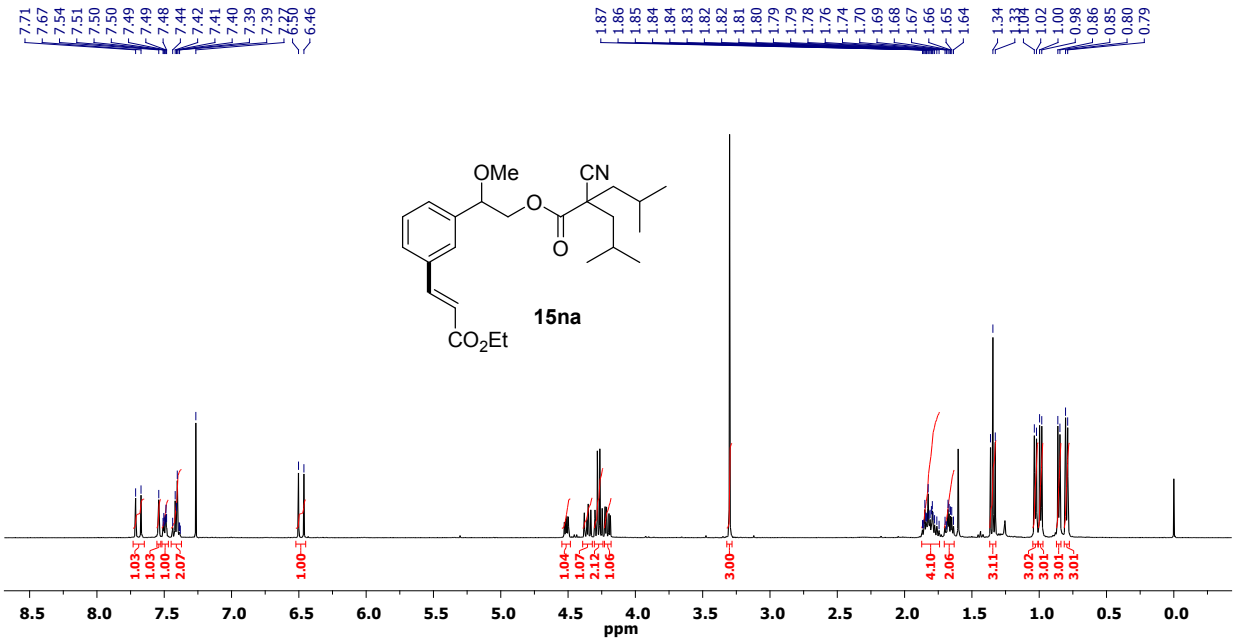
^{13}C-NMR (100 MHz) spectrum of **15la** in $CDCl_3$



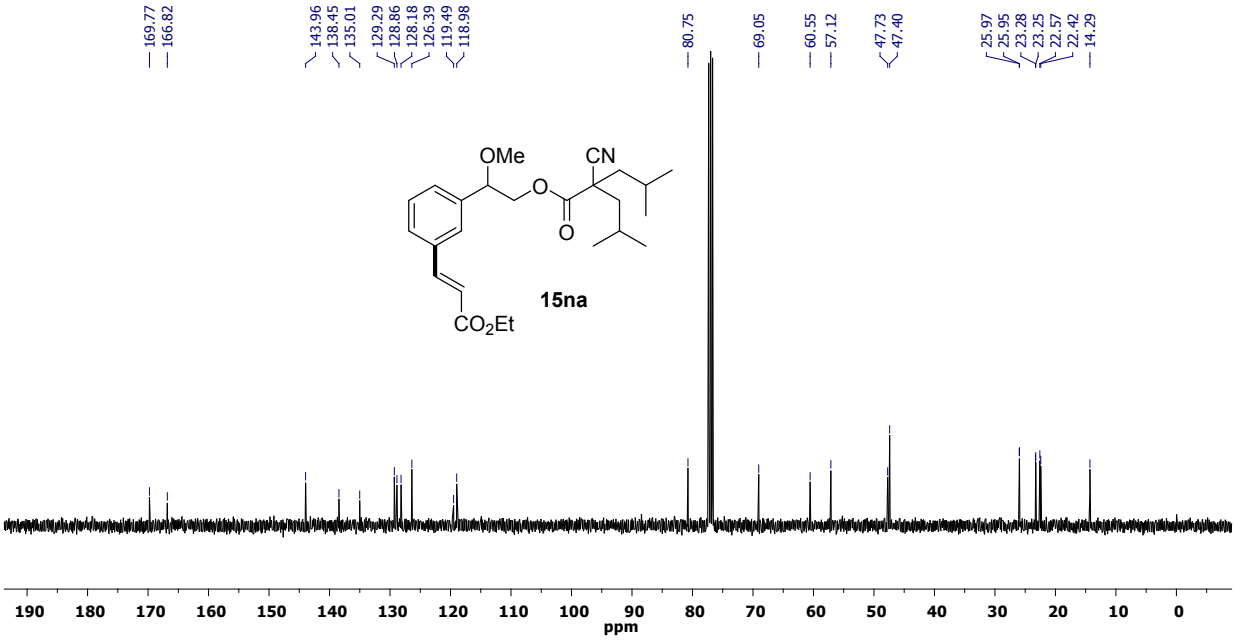
^{1}H-NMR (400 MHz) spectrum of **15ma** in $CDCl_3$



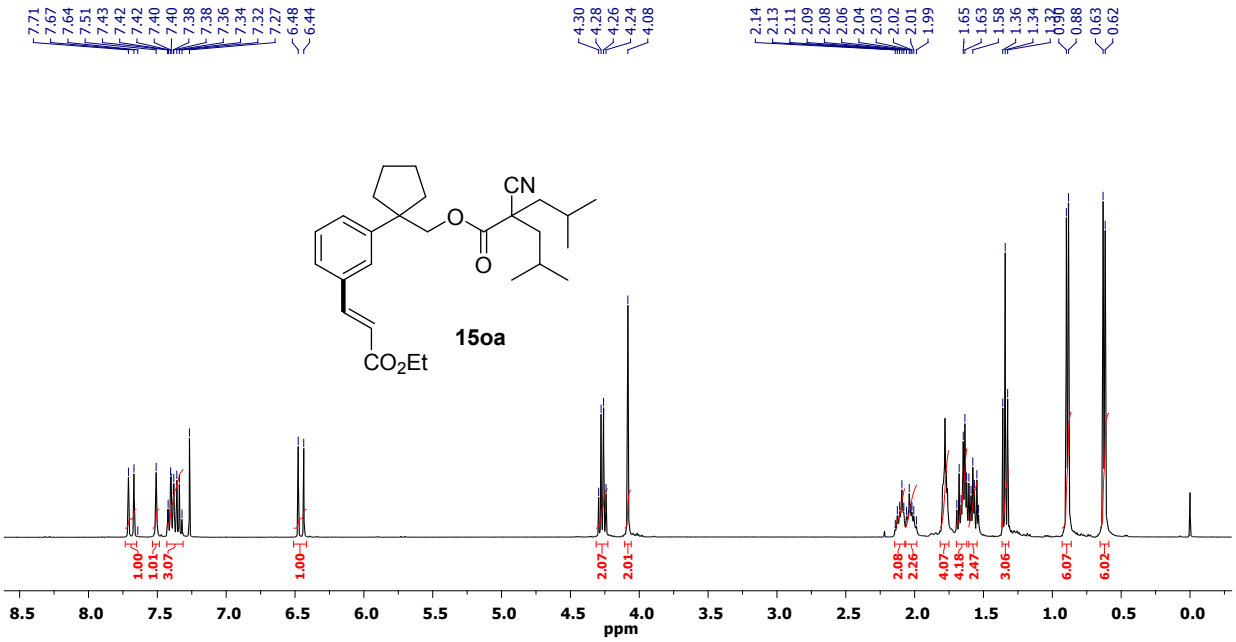
^{13}C-NMR (100 MHz) spectrum of **15ma** in $CDCl_3$



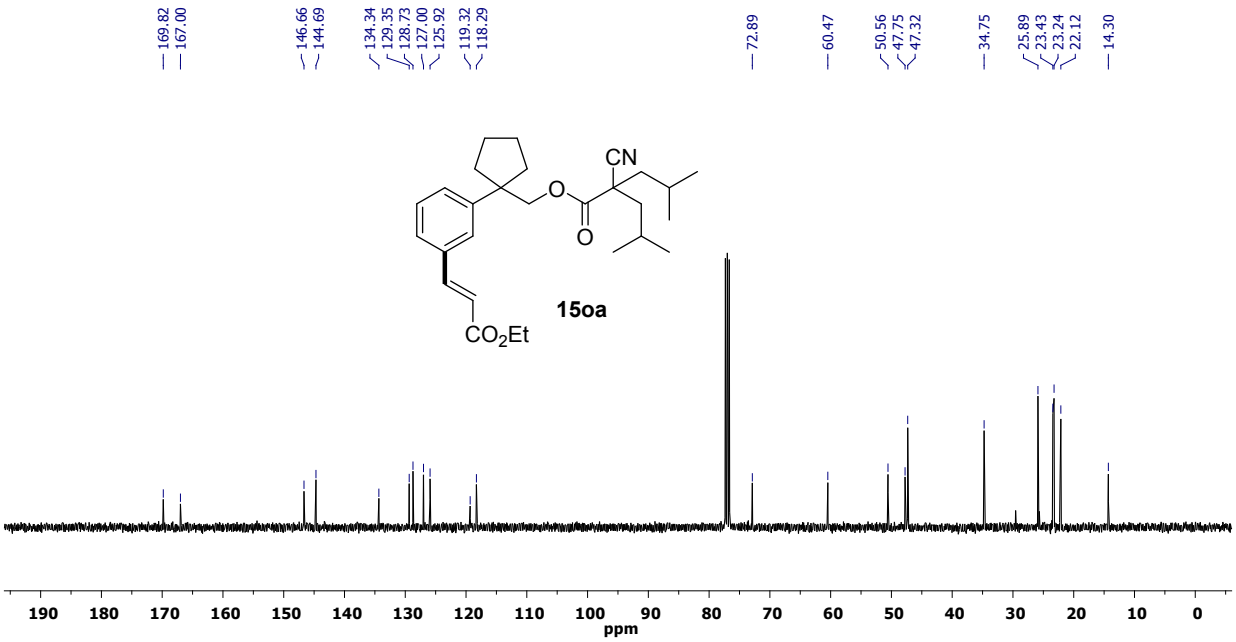
^{1}H-NMR (400 MHz) spectrum of **15na** in $CDCl_3$



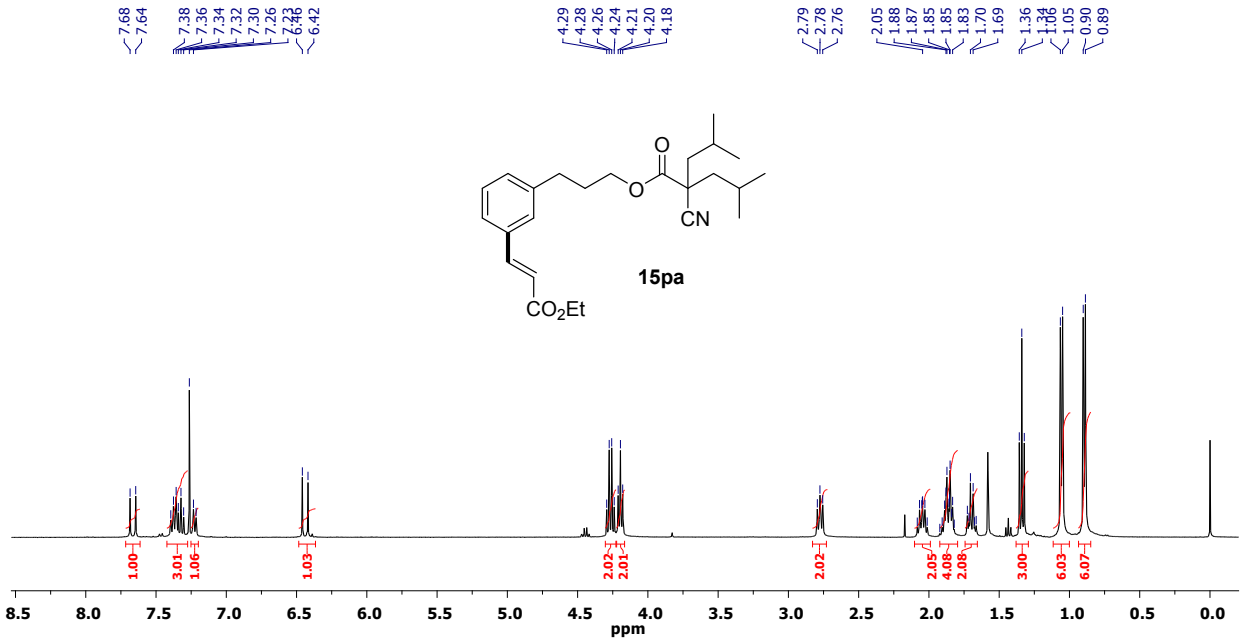
^{13}C-NMR (100 MHz) spectrum of **15na** in $CDCl_3$



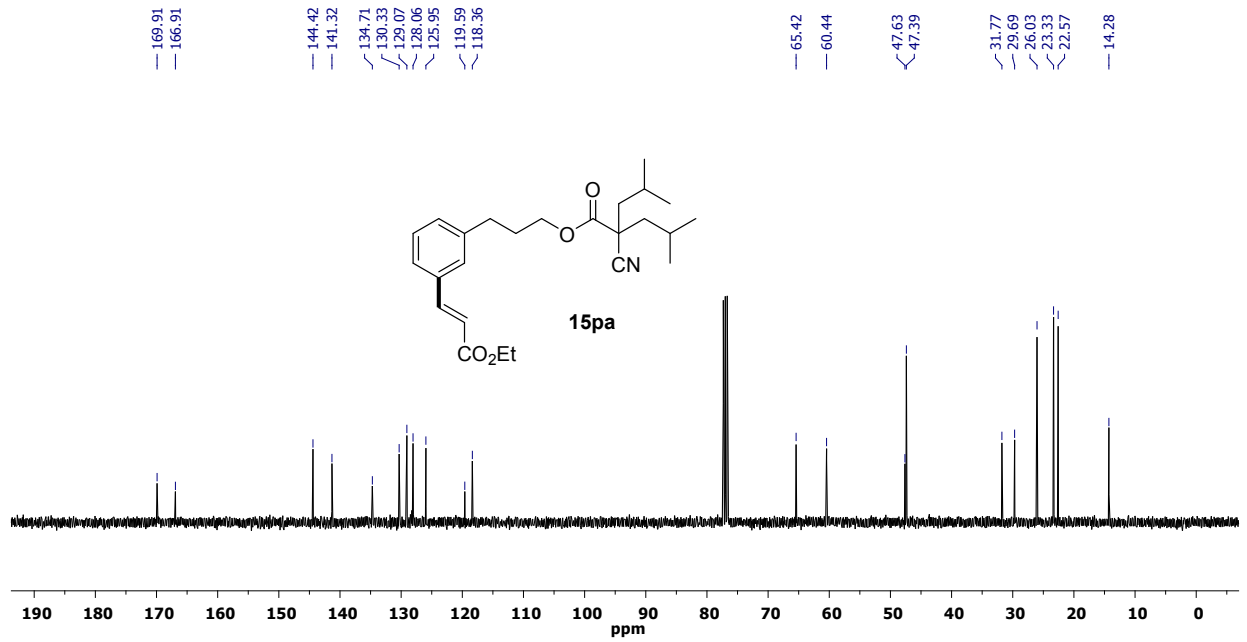
^{1}H-NMR (400 MHz) spectrum of **15oa** in $CDCl_3$



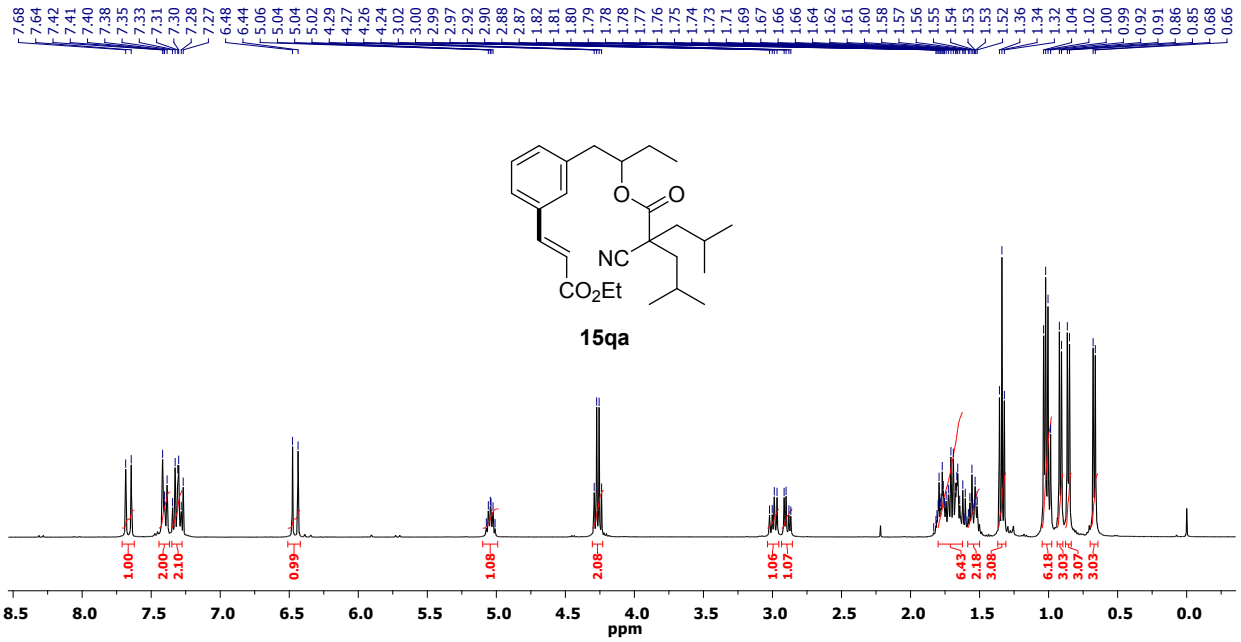
^{13}C-NMR (100 MHz) spectrum of **15oa** in $CDCl_3$



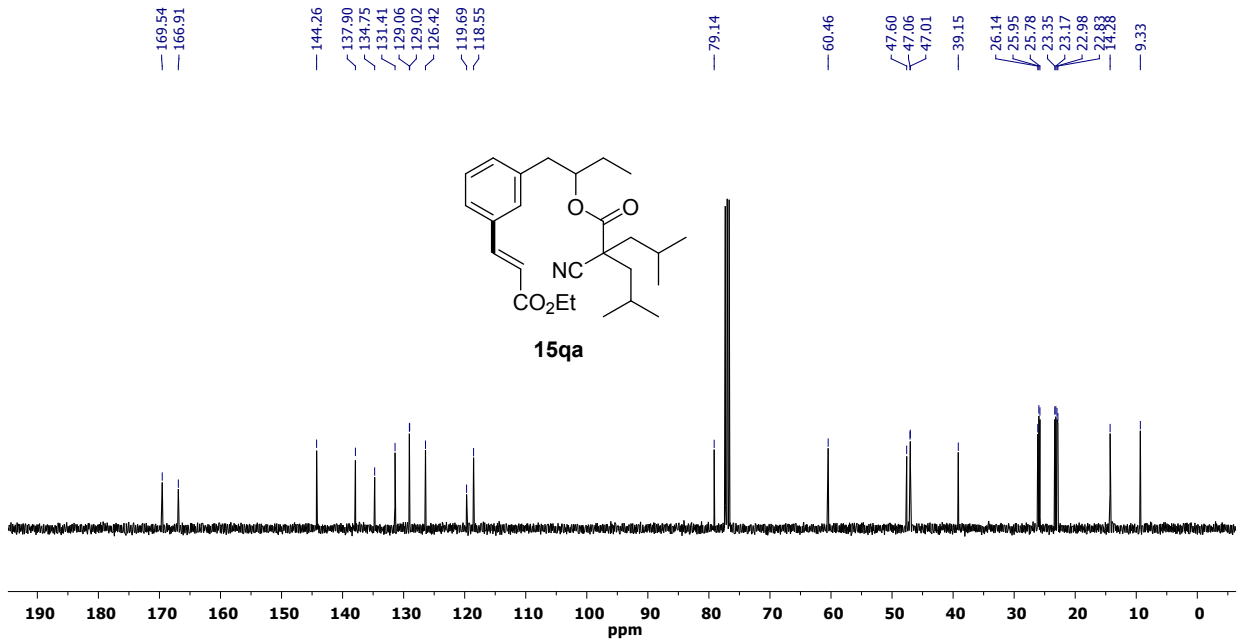
^{1}H-NMR (400 MHz) spectrum of **15pa** in $CDCl_3$



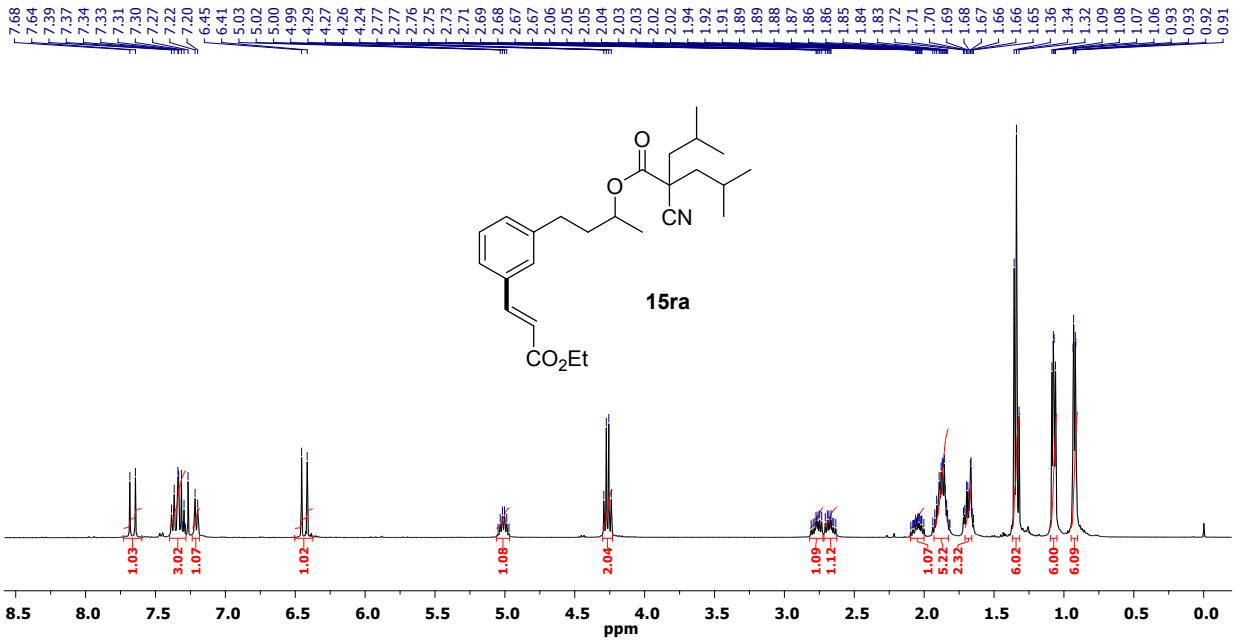
^{13}C-NMR (100 MHz) spectrum of **15pa** in $CDCl_3$



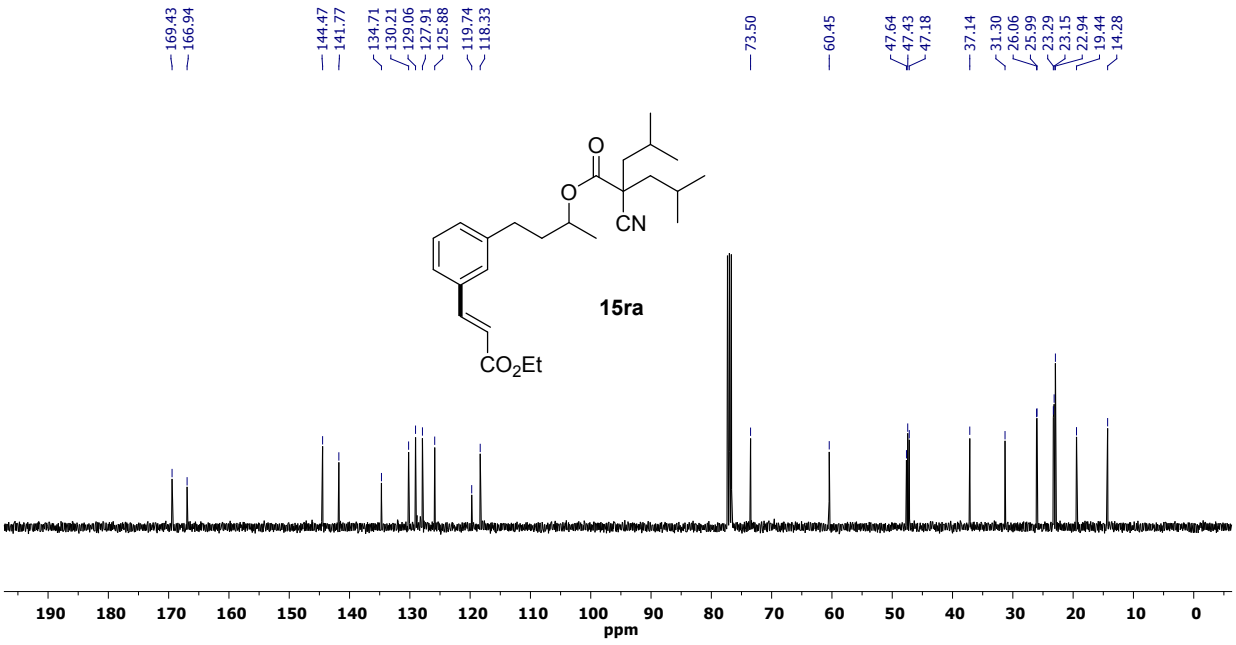
^{1}H-NMR (400 MHz) spectrum of **15qa** in $CDCl_3$



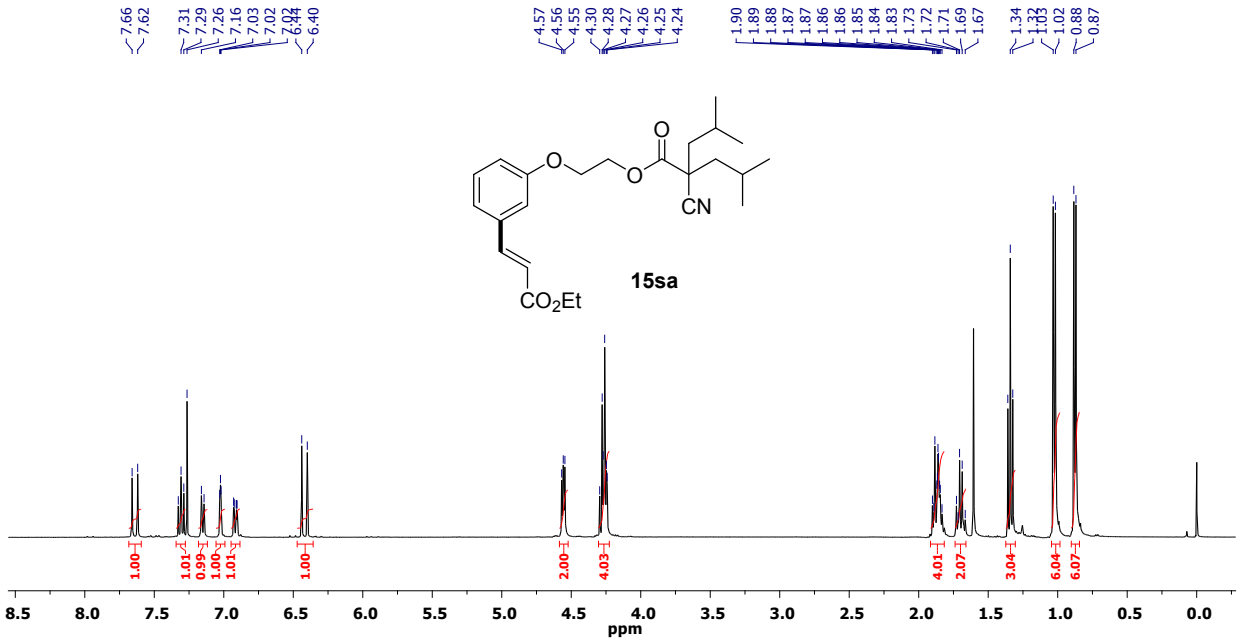
^{13}C-NMR (100 MHz) spectrum of **15qa** in $CDCl_3$



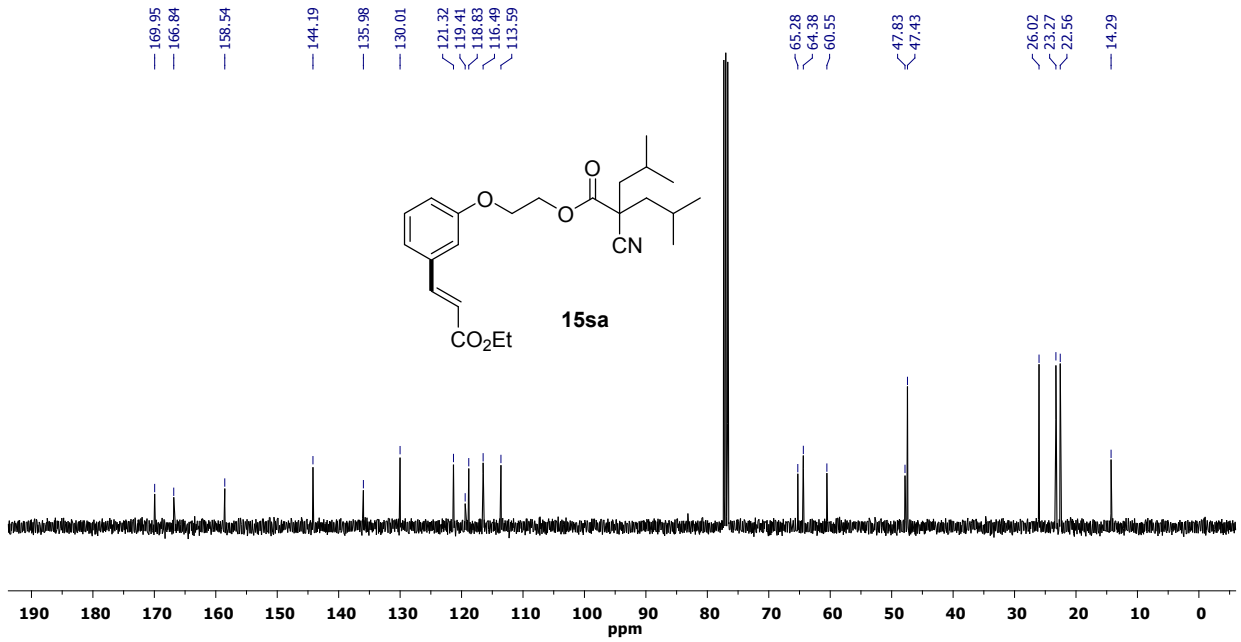
^{1}H-NMR (400 MHz) spectrum of **15ra** in $CDCl_3$



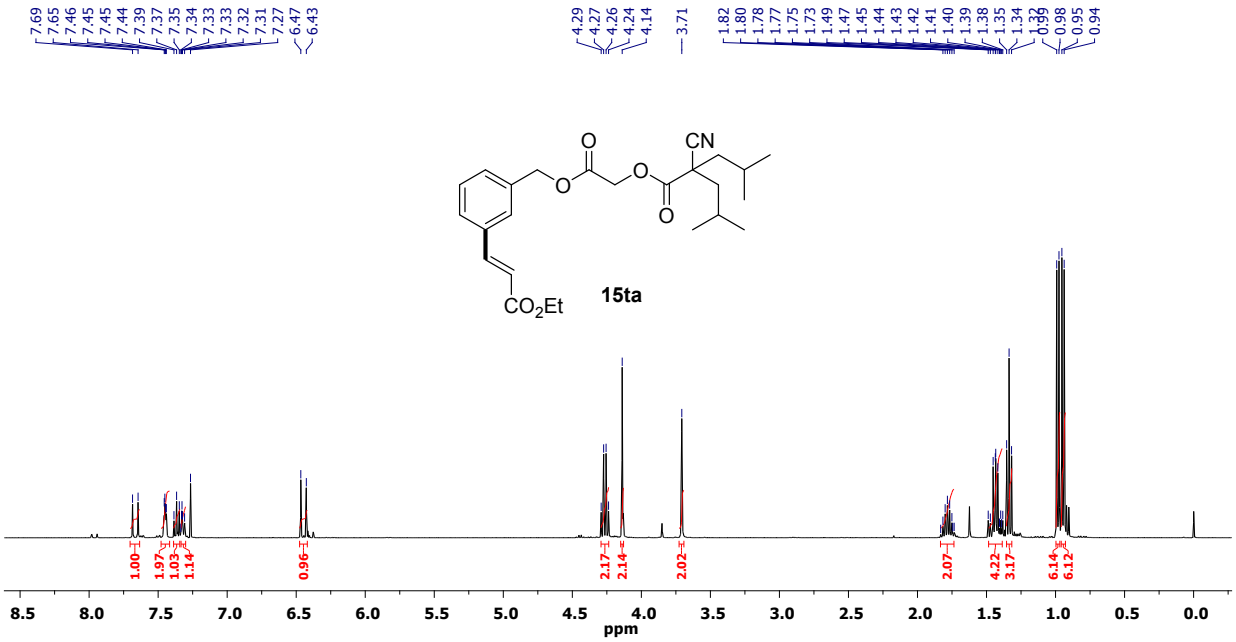
^{13}C-NMR (100 MHz) spectrum of **15ra** in $CDCl_3$



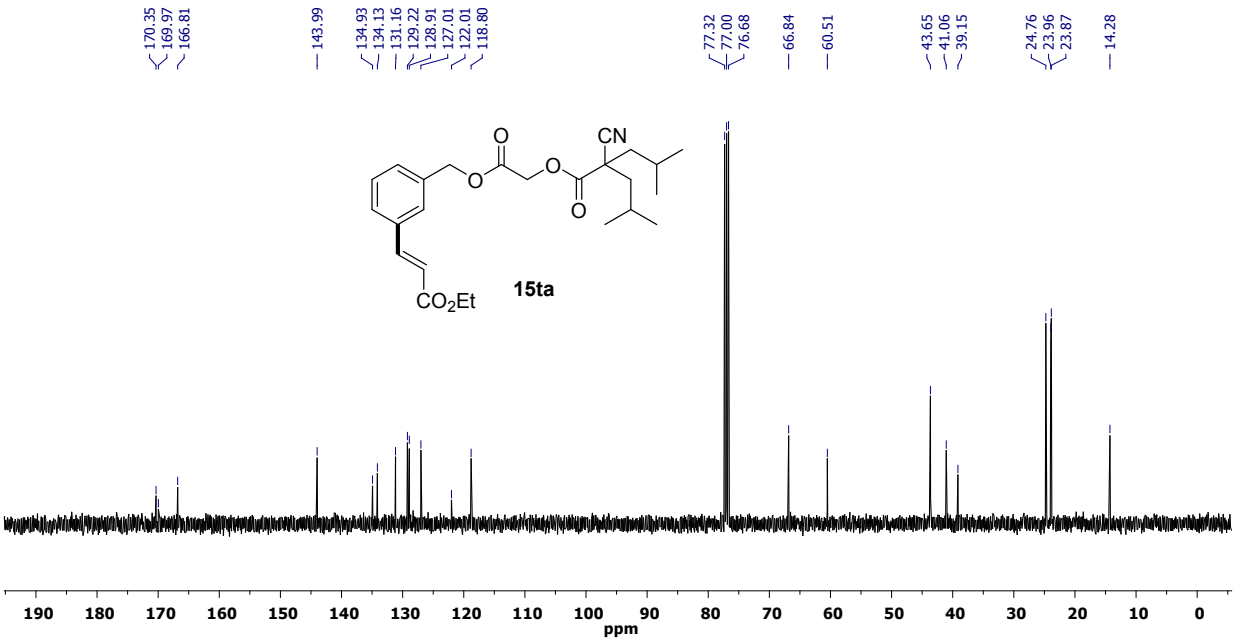
^{1}H-NMR (400 MHz) spectrum of **15sa** in $CDCl_3$



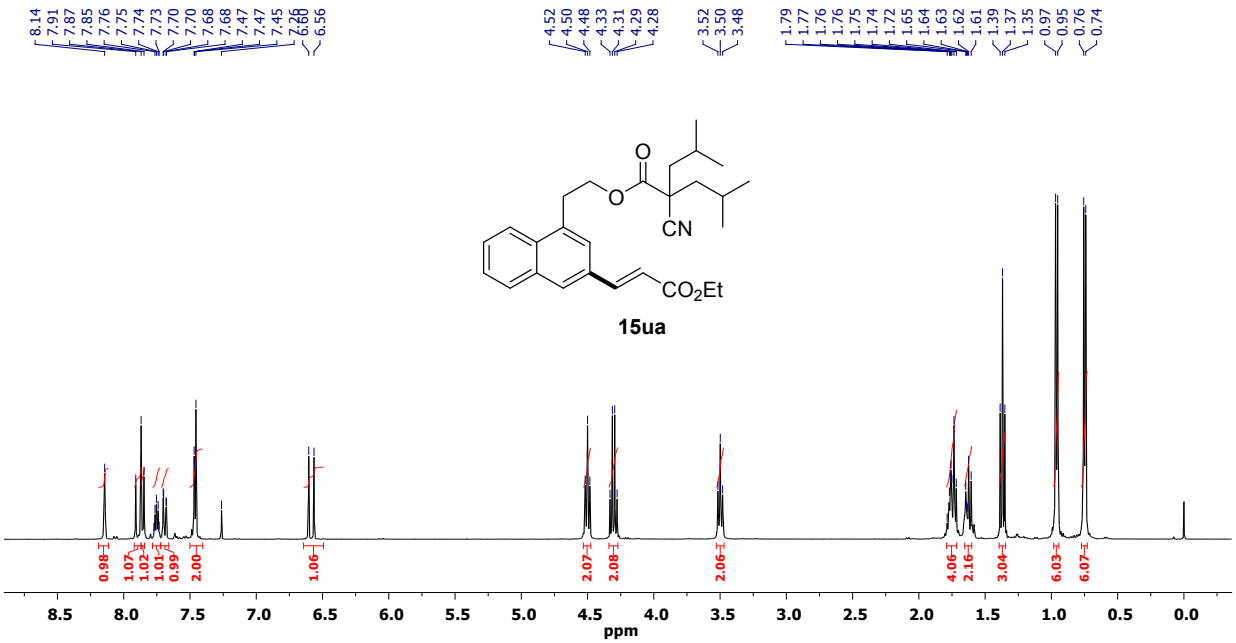
^{13}C-NMR (100 MHz) spectrum of **15sa** in $CDCl_3$



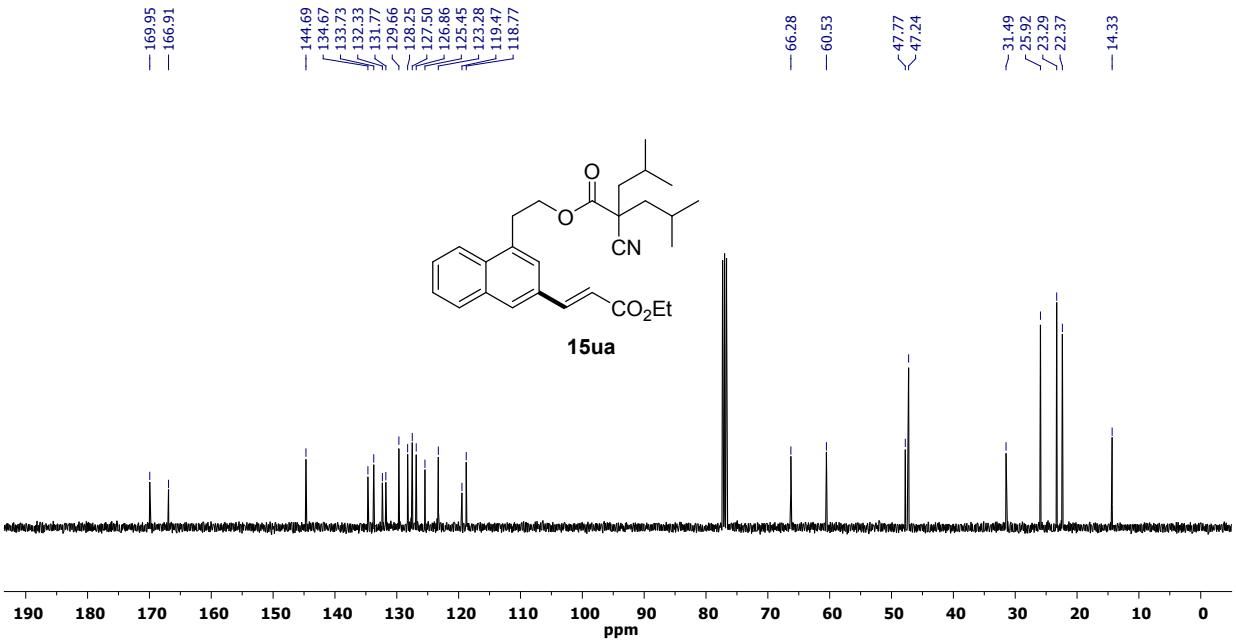
^{1}H-NMR (400 MHz) spectrum of **15ta** in $CDCl_3$



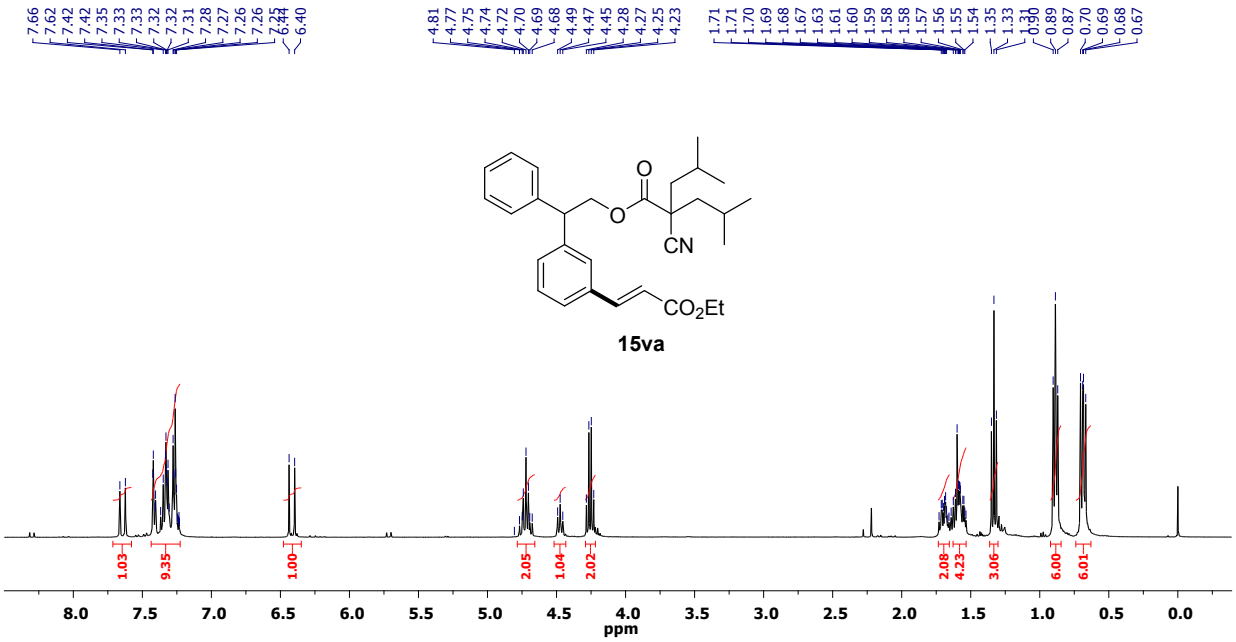
^{13}C-NMR (100 MHz) spectrum of **15ta** in $CDCl_3$



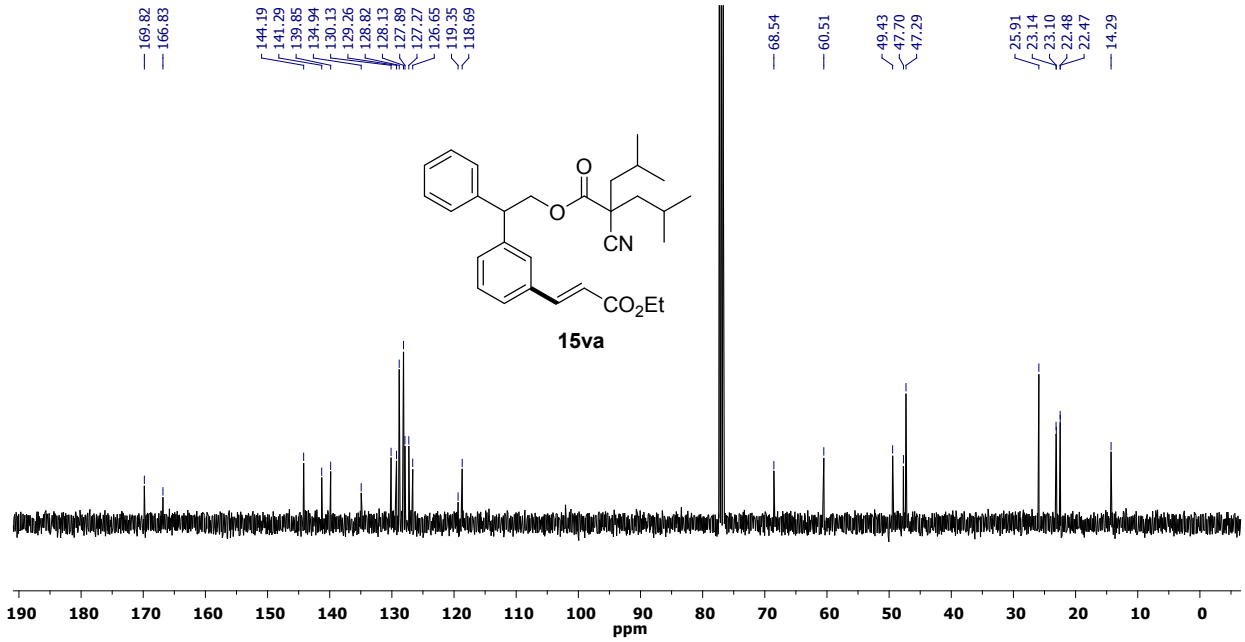
^{1}H-NMR (400 MHz) spectrum of **15ua** in $CDCl_3$



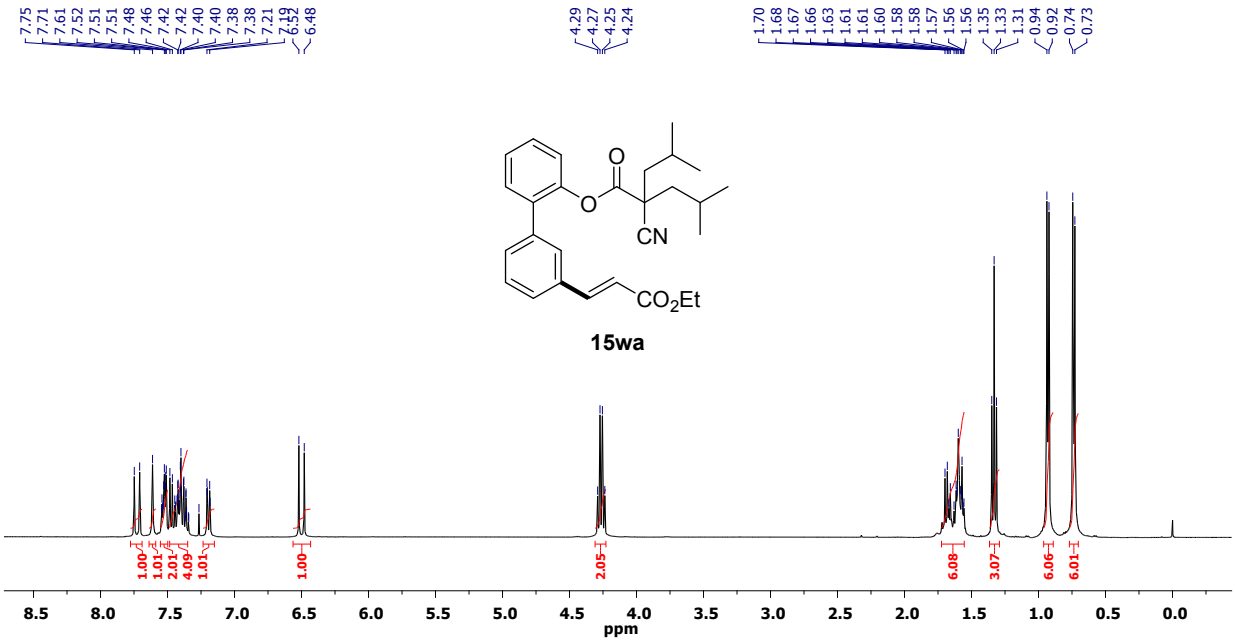
^{13}C-NMR (100 MHz) spectrum of **15ua** in $CDCl_3$



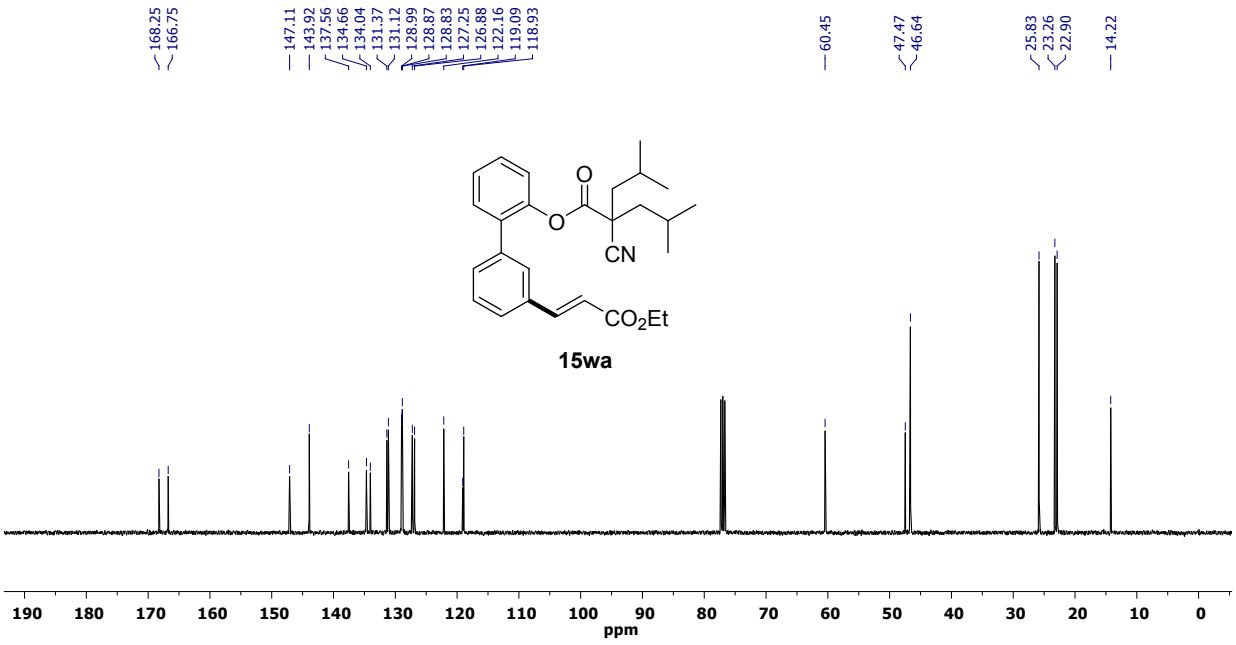
^{1}H-NMR (400 MHz) spectrum of **15va** in $CDCl_3$



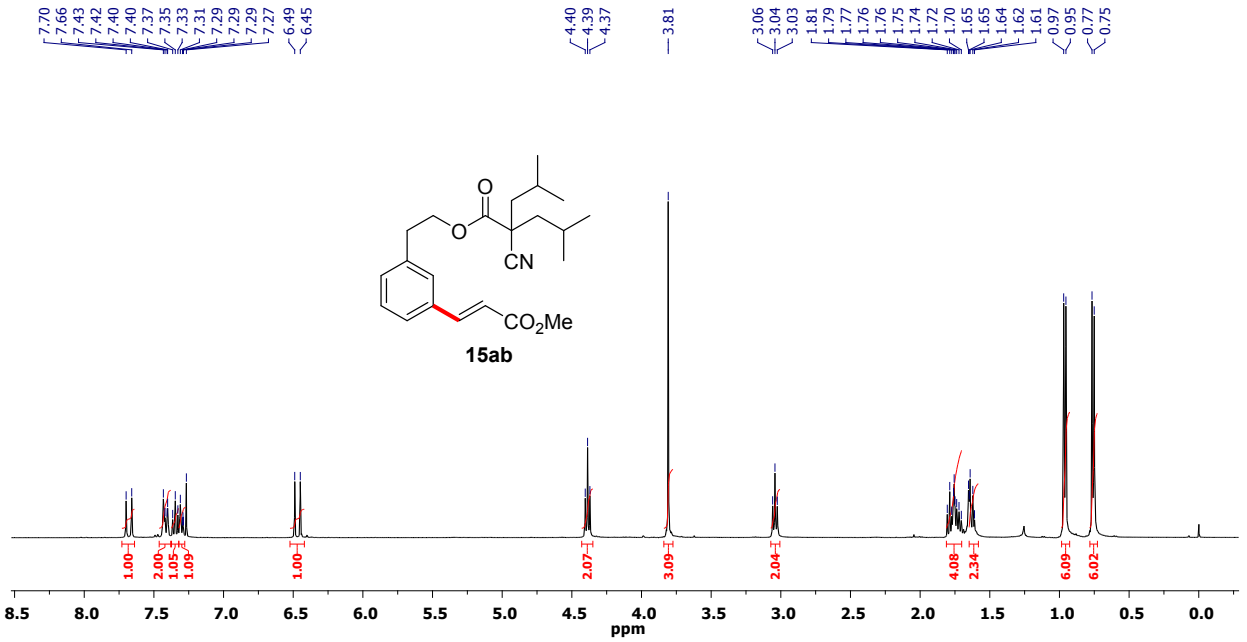
^{13}C-NMR (100 MHz) spectrum of **15va** in $CDCl_3$



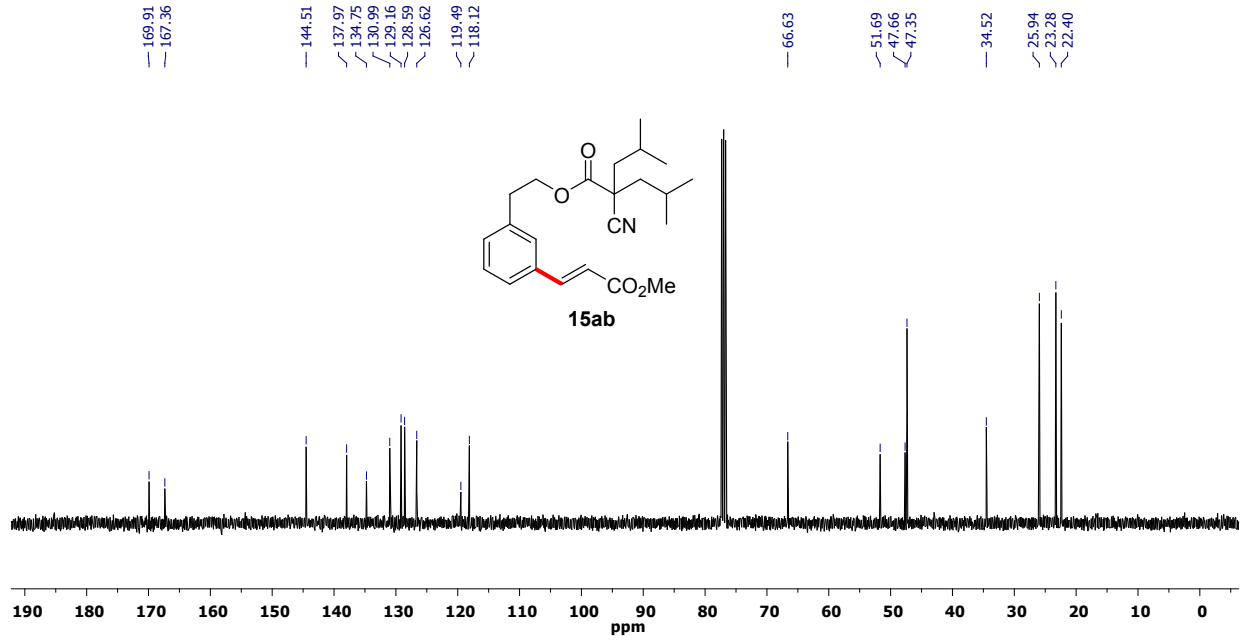
^{1}H-NMR (400 MHz) spectrum of **15wa** in $CDCl_3$



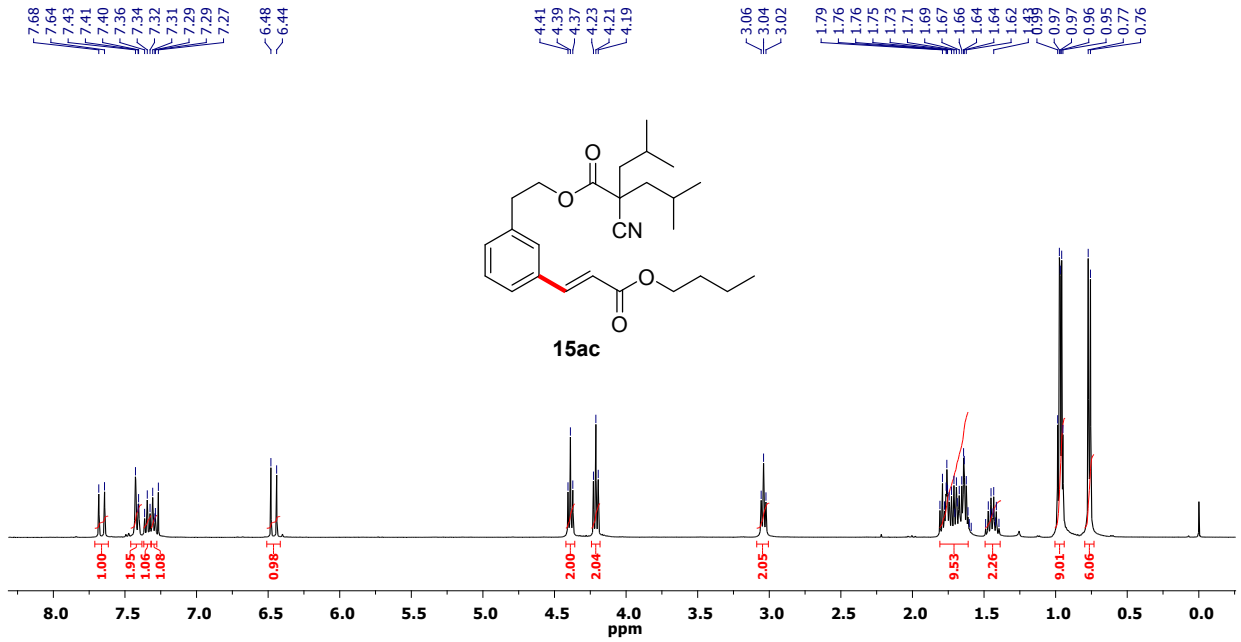
^{13}C-NMR (100 MHz) spectrum of **15wa** in $CDCl_3$



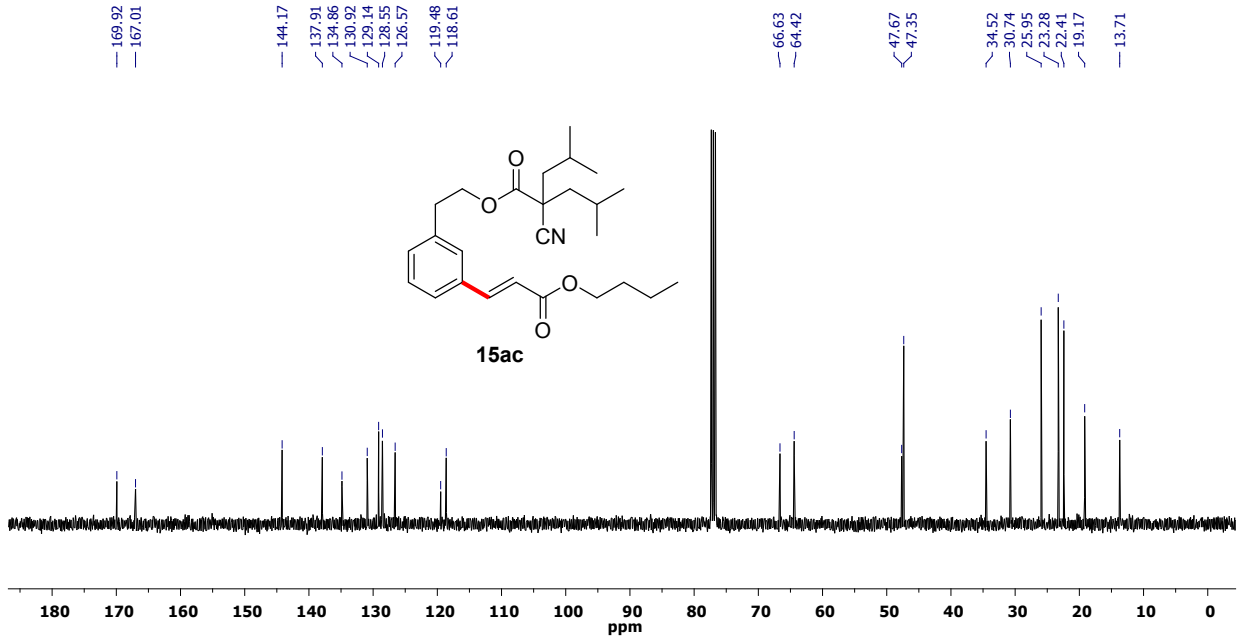
^{1}H-NMR (400 MHz) spectrum of **15ab** in $CDCl_3$



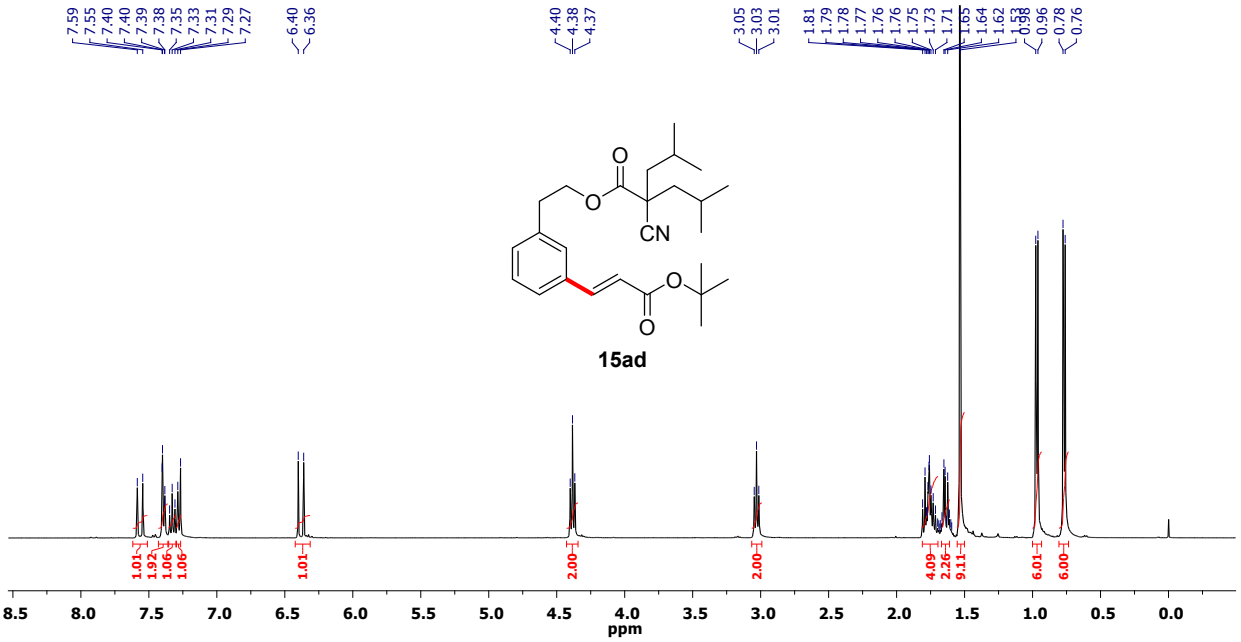
^{13}C-NMR (100 MHz) spectrum of **15ab** in $CDCl_3$



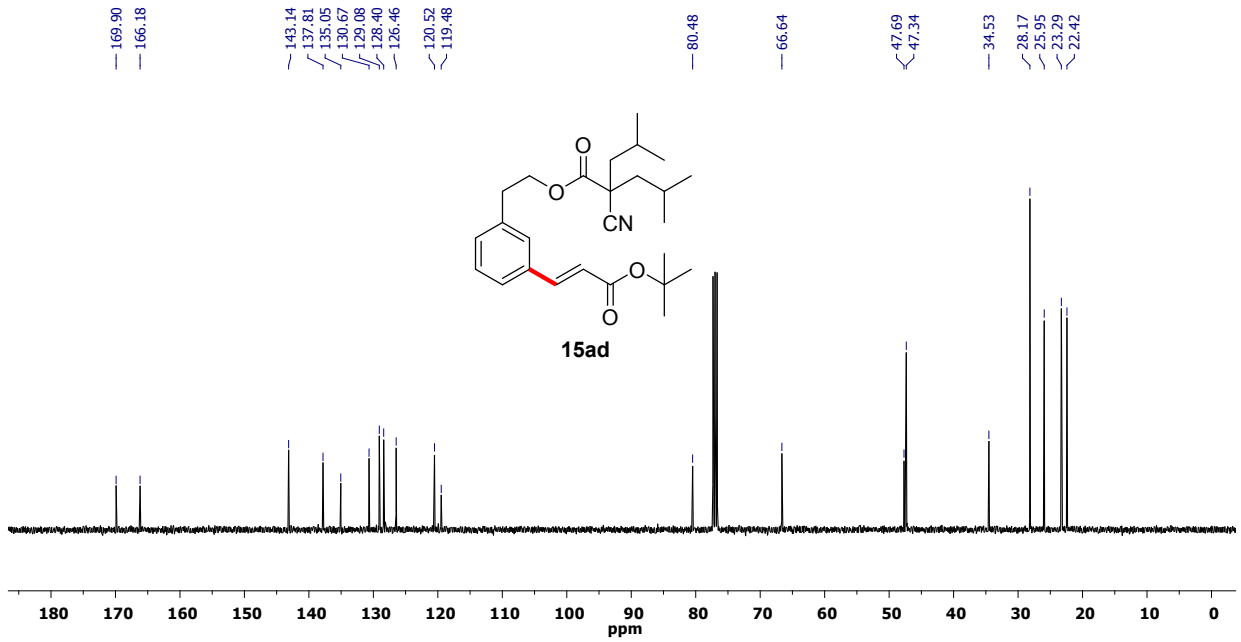
^{1}H-NMR (400 MHz) spectrum of **15ac** in $CDCl_3$



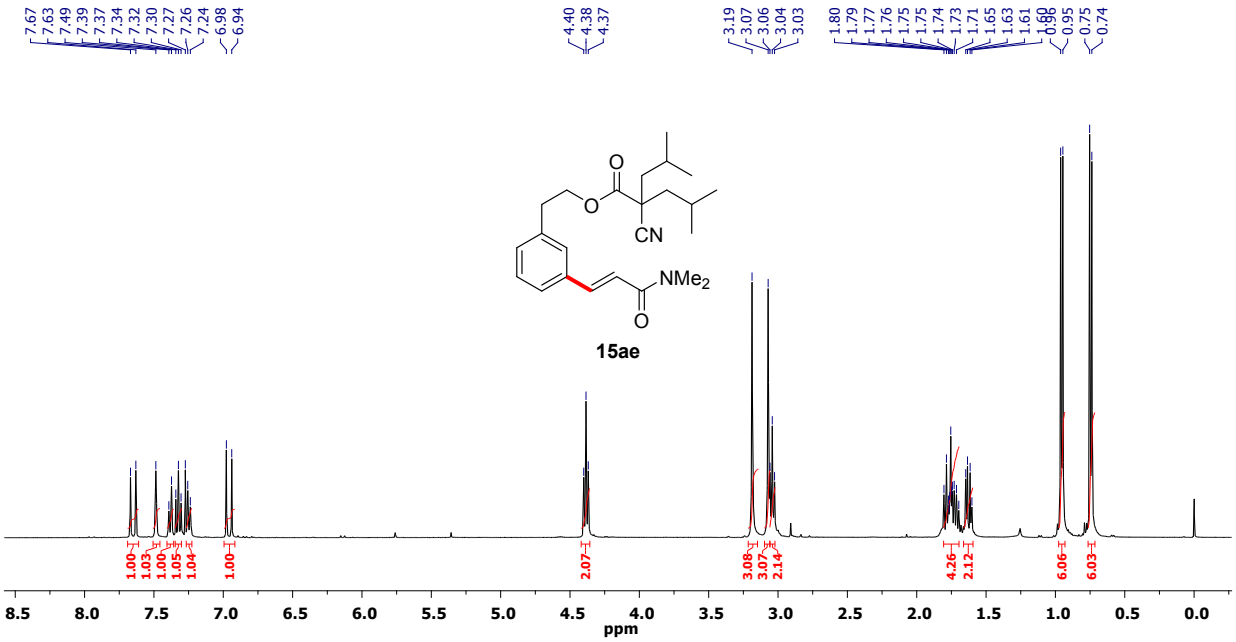
^{13}C-NMR (100 MHz) spectrum of **15ac** in $CDCl_3$



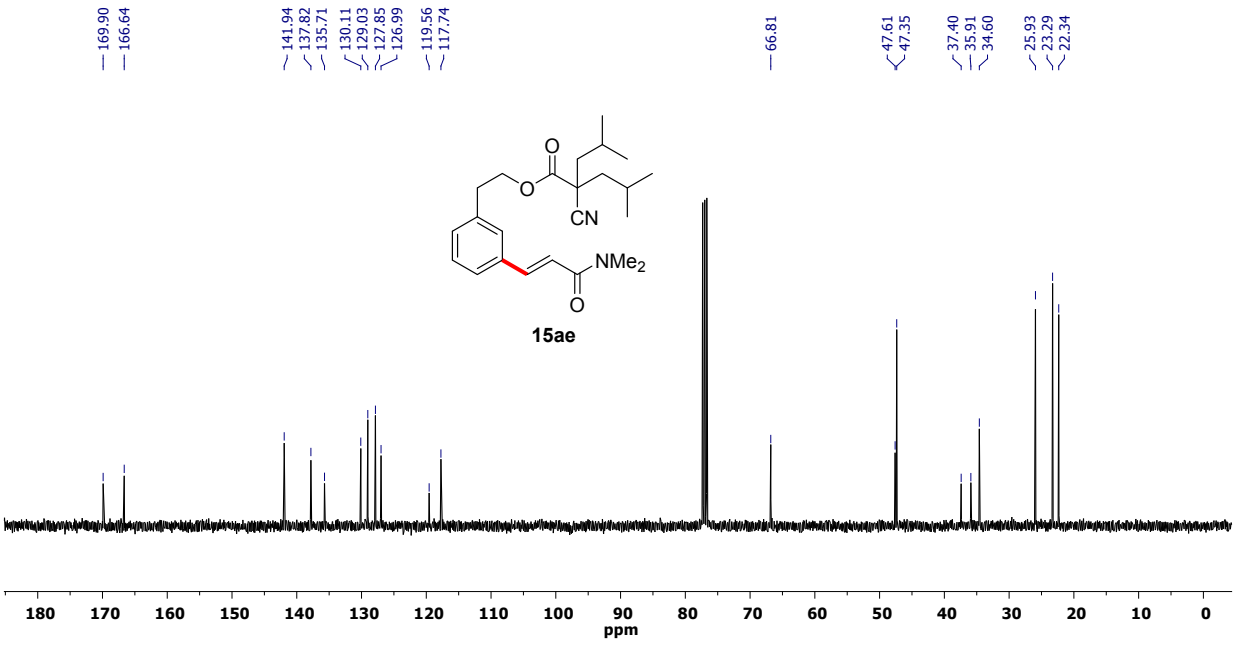
^{1}H-NMR (400 MHz) spectrum of **15ad** in $CDCl_3$



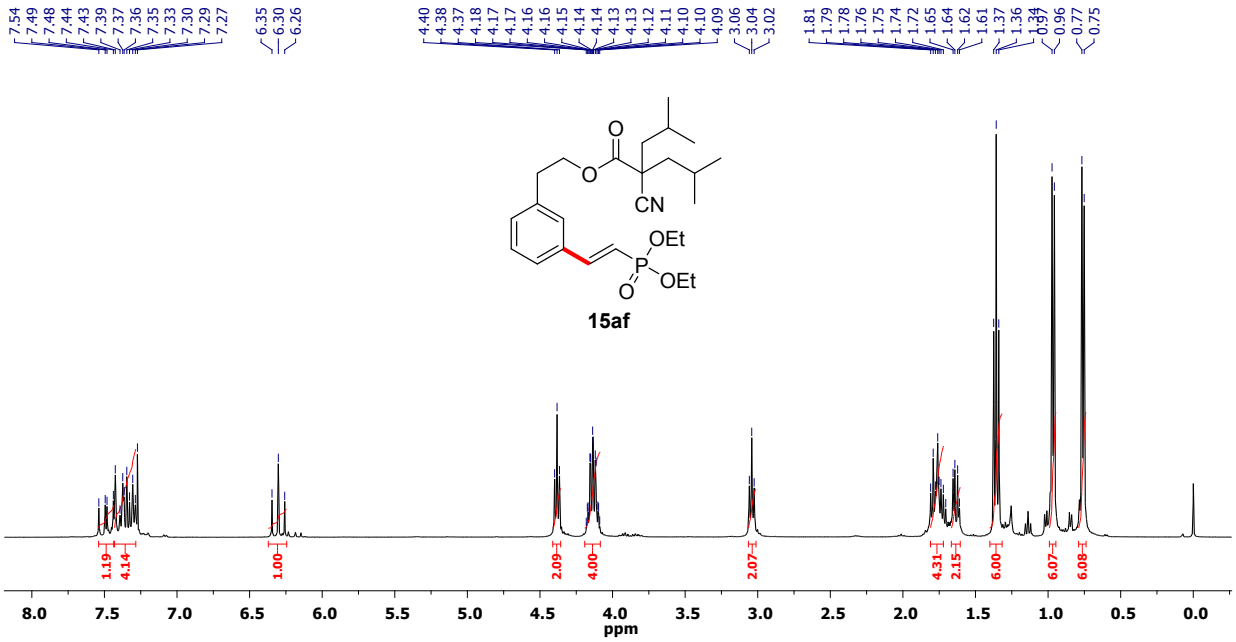
^{13}C-NMR (100 MHz) spectrum of **15ad** in $CDCl_3$



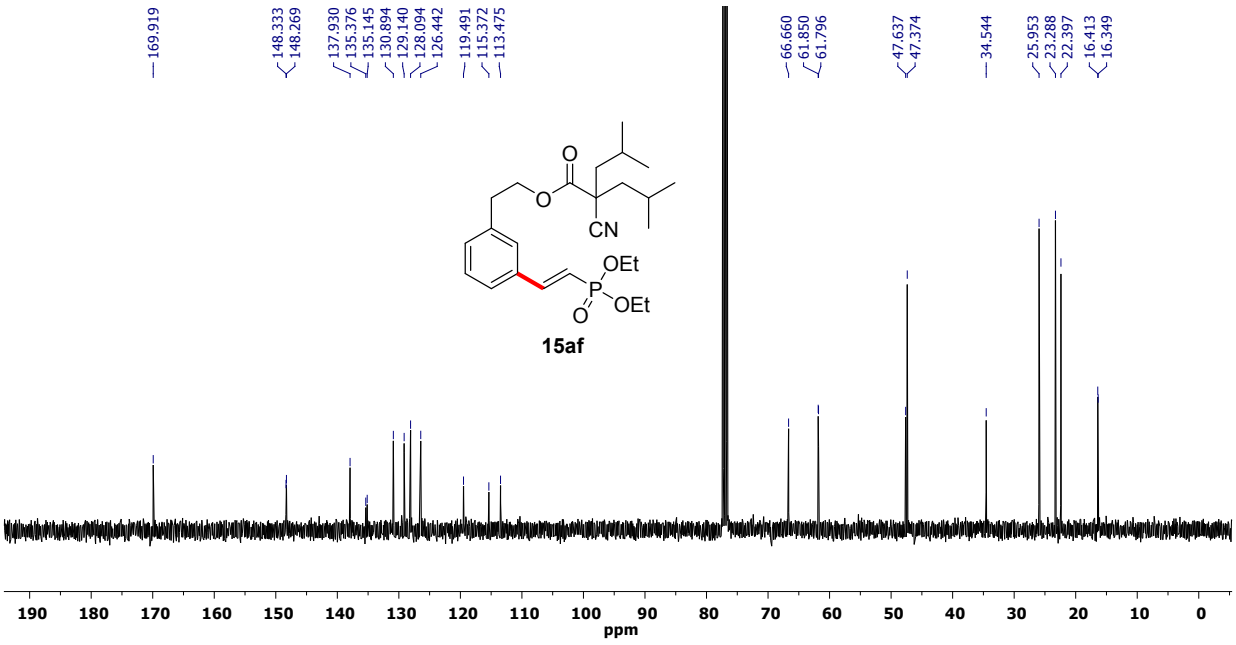
^{1}H-NMR (400 MHz) spectrum of **15ae** in $CDCl_3$



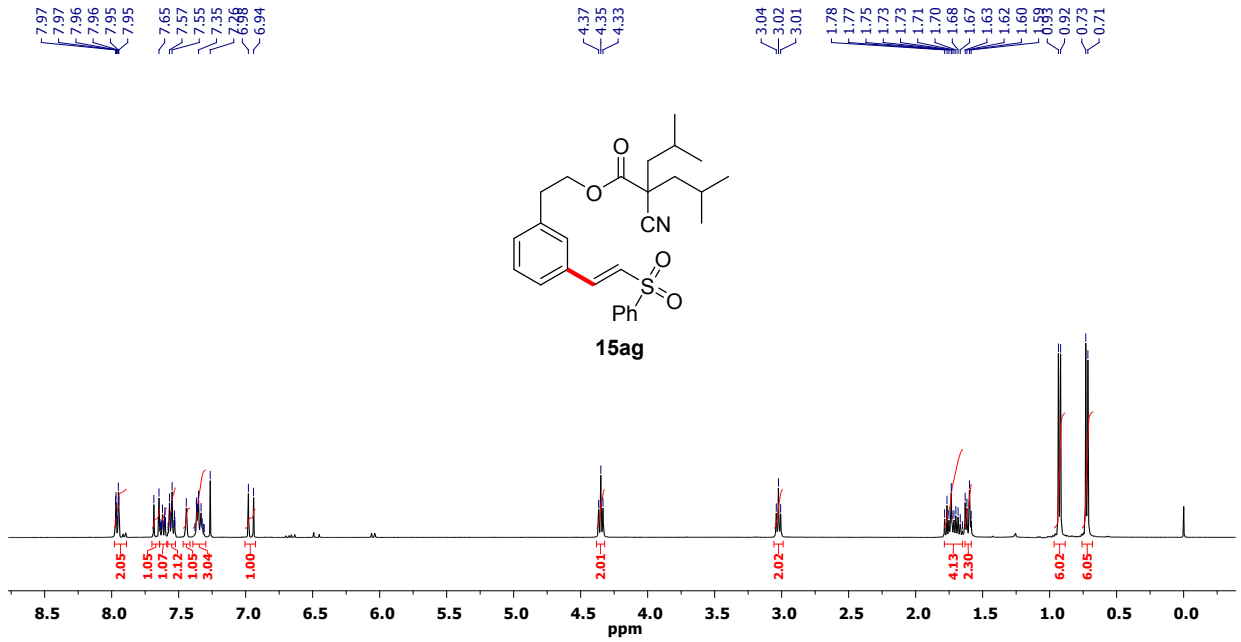
^{13}C-NMR (100 MHz) spectrum of **15ae** in $CDCl_3$



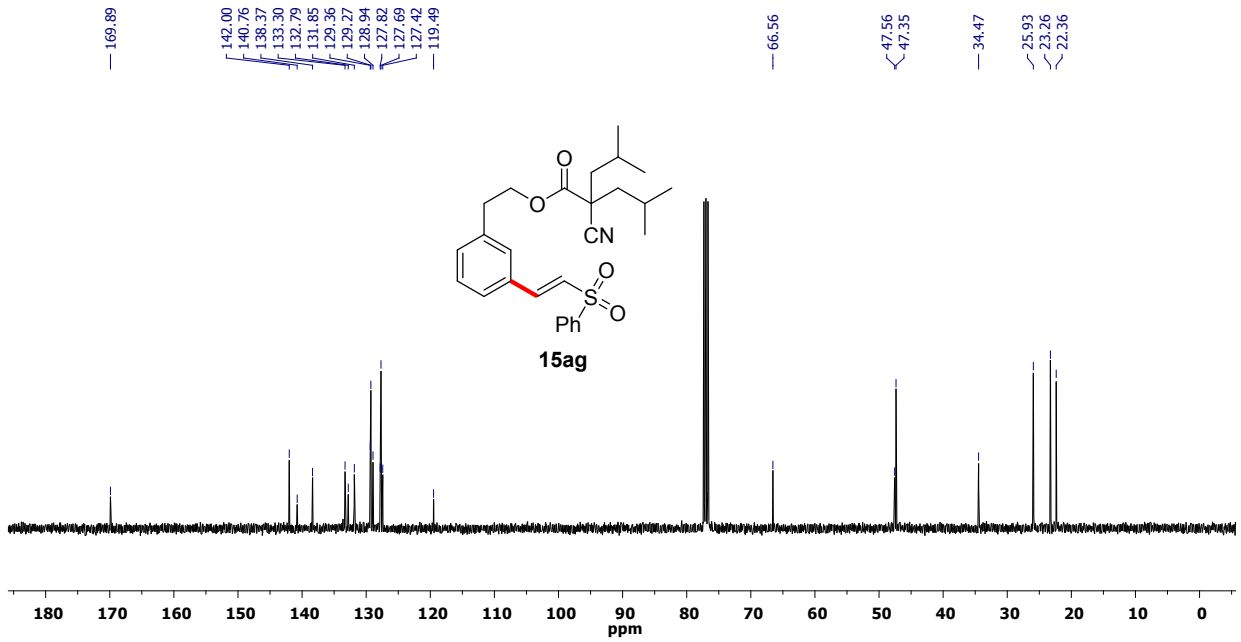
^{1}H-NMR (400 MHz) spectrum of **15af** in $CDCl_3$



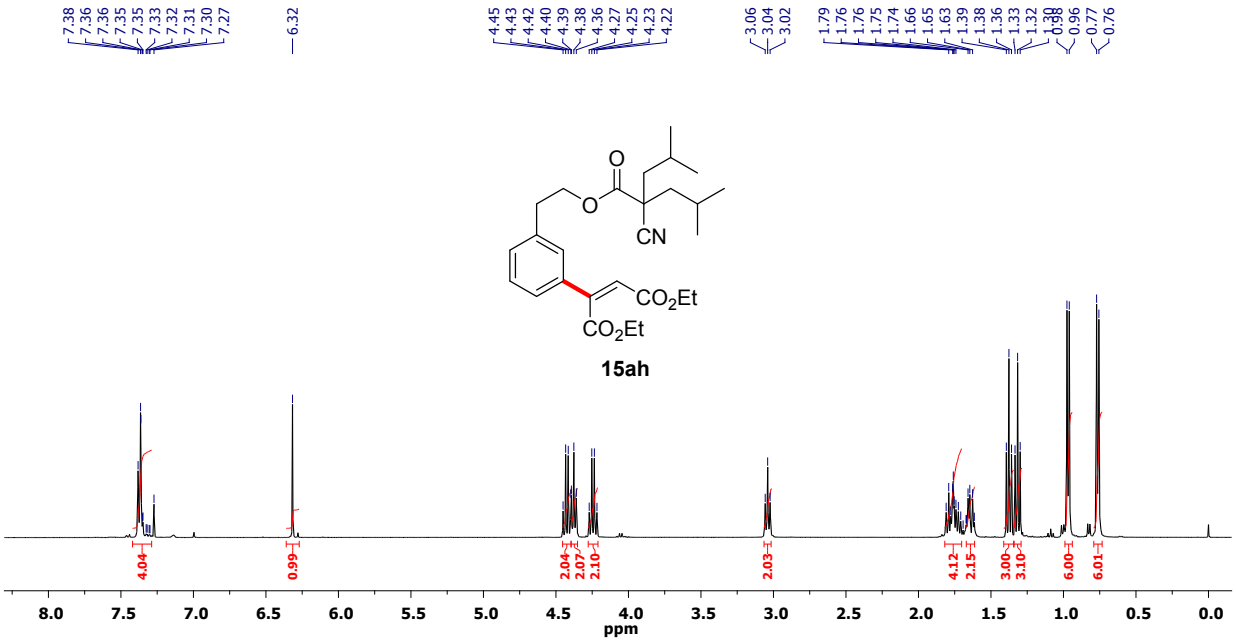
^{13}C-NMR (100 MHz) spectrum of **15af** in $CDCl_3$



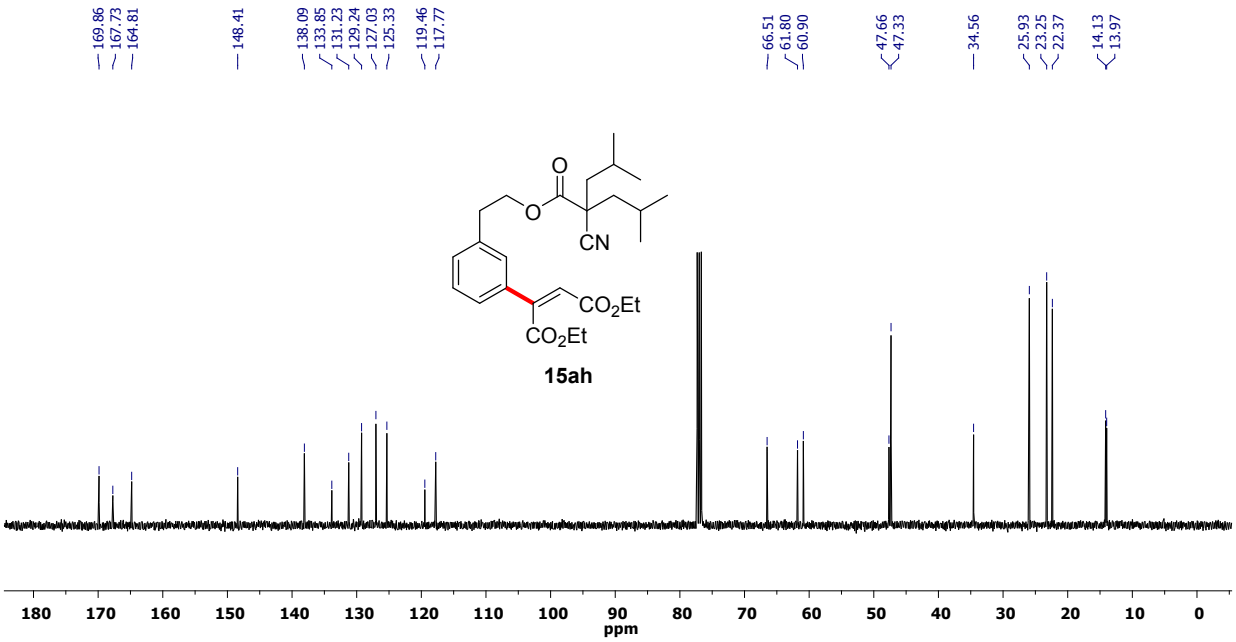
^{1}H-NMR (400 MHz) spectrum of **15ag** in $CDCl_3$



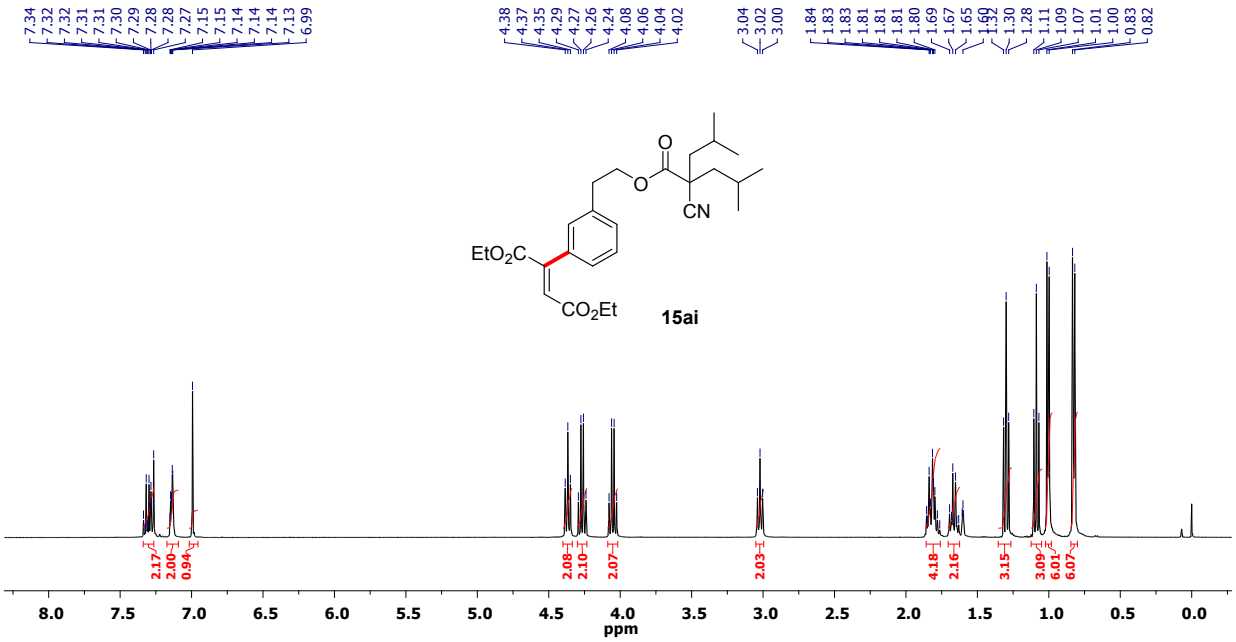
^{13}C-NMR (100 MHz) spectrum of **15ag** in $CDCl_3$



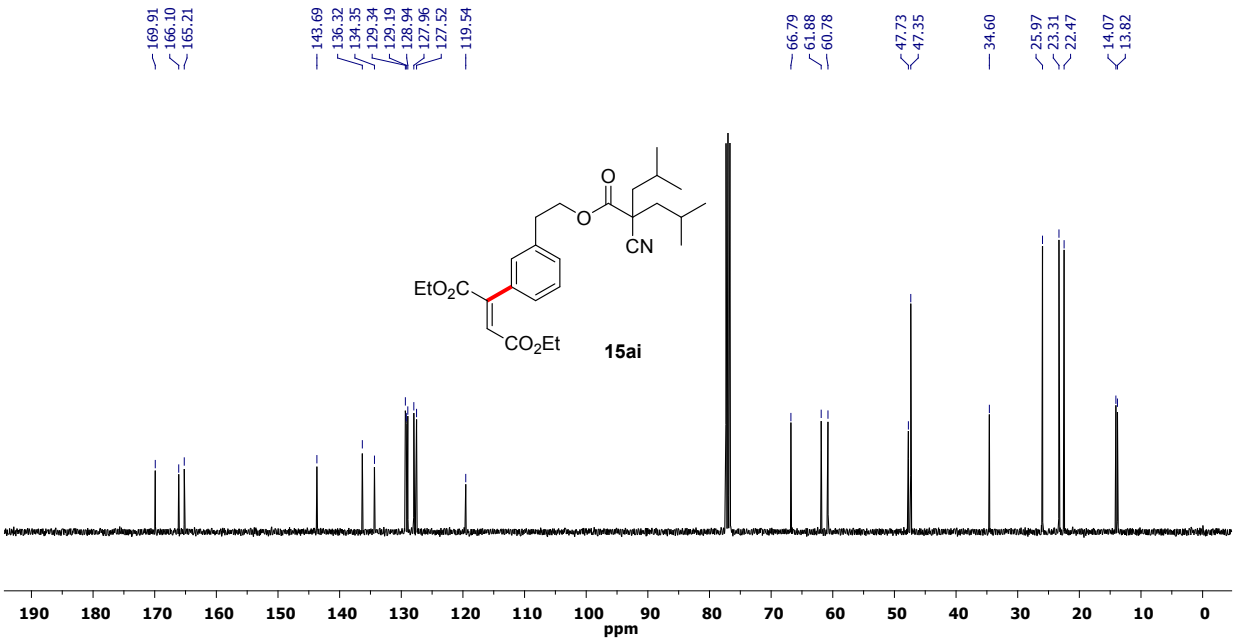
^{1}H-NMR (400 MHz) spectrum of **15ah** in $CDCl_3$



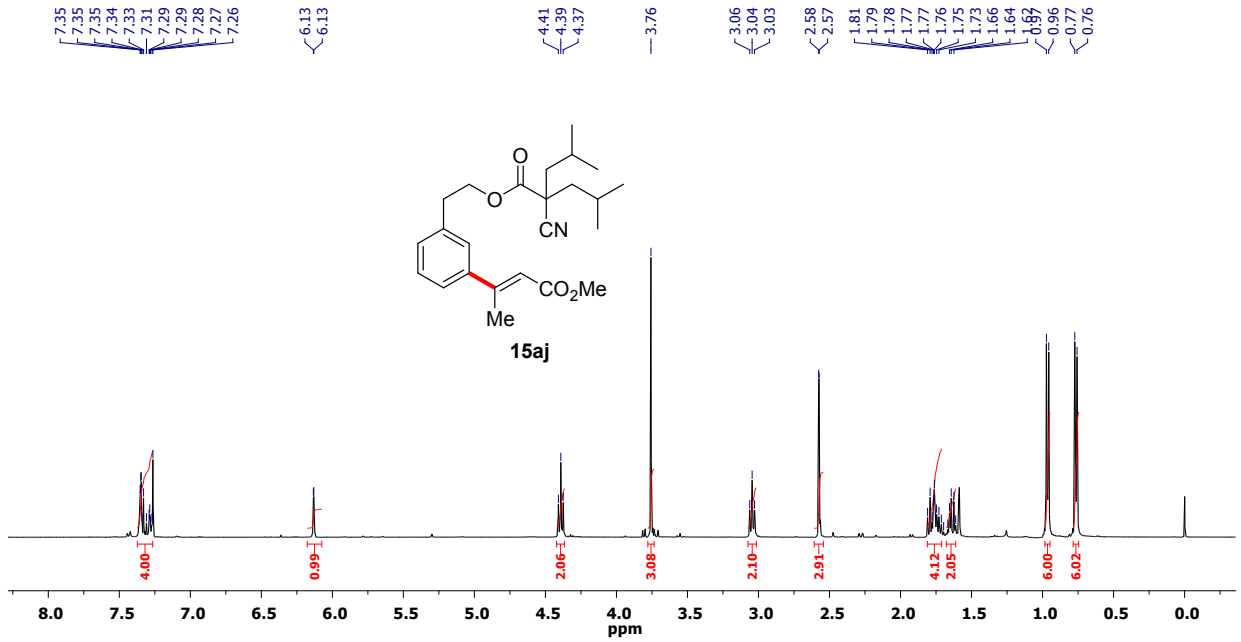
^{13}C-NMR (100 MHz) spectrum of **15ah** in $CDCl_3$



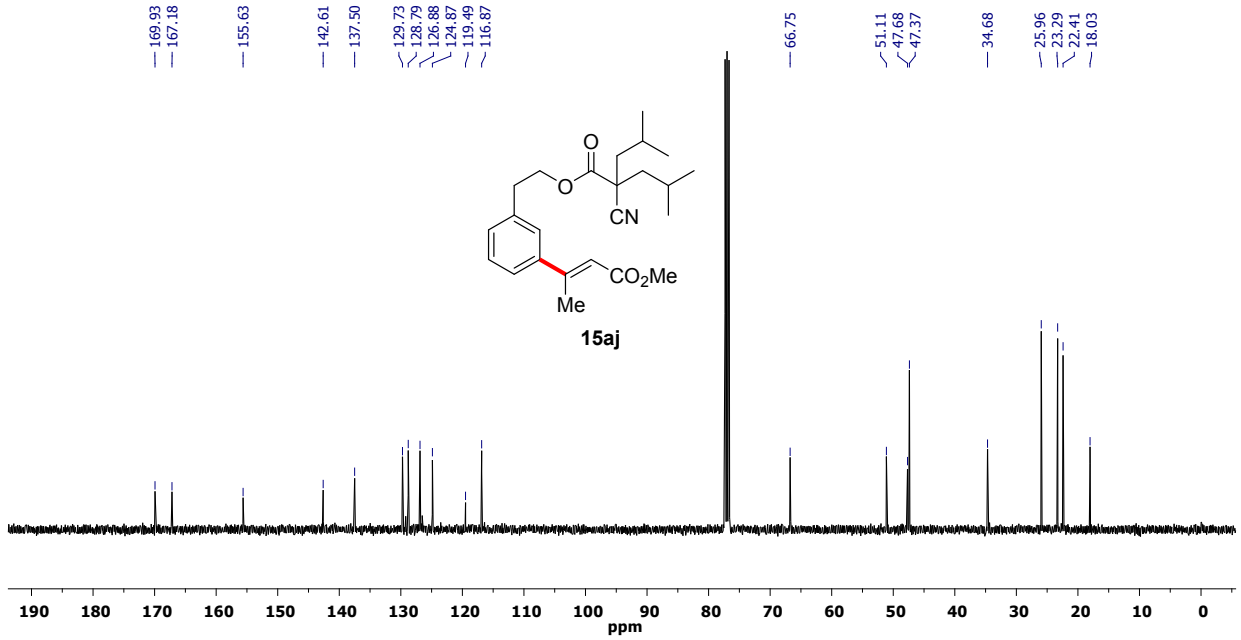
^{1}H-NMR (400 MHz) spectrum of **15ai** in $CDCl_3$



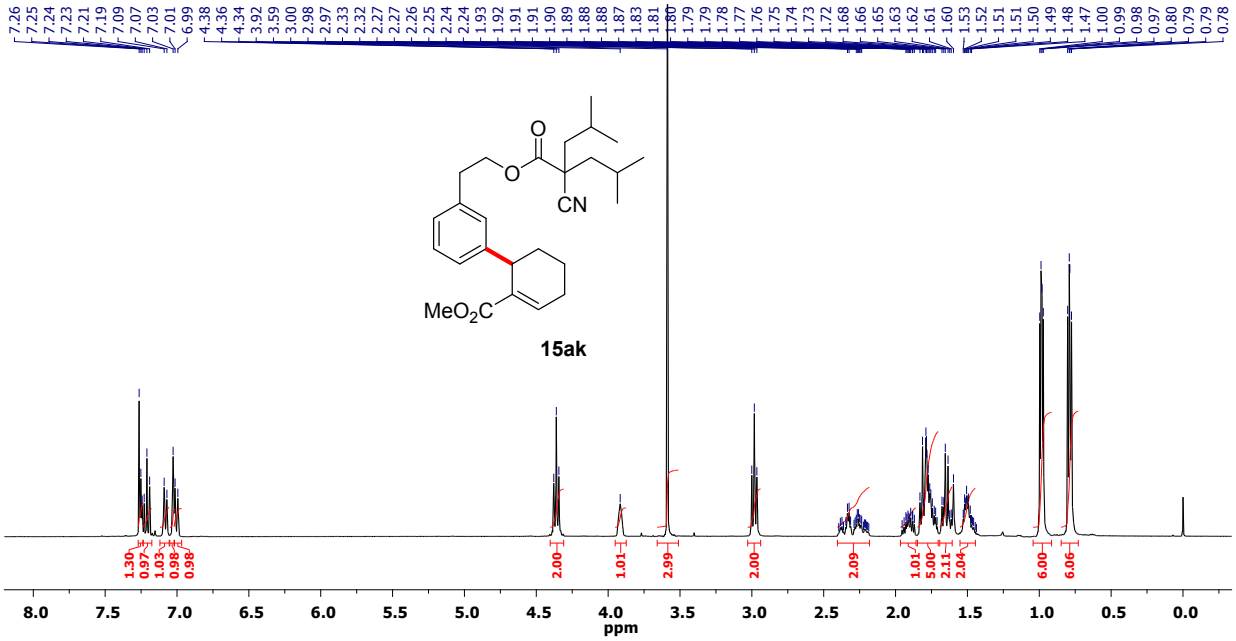
^{13}C-NMR (100 MHz) spectrum of **15ai** in $CDCl_3$



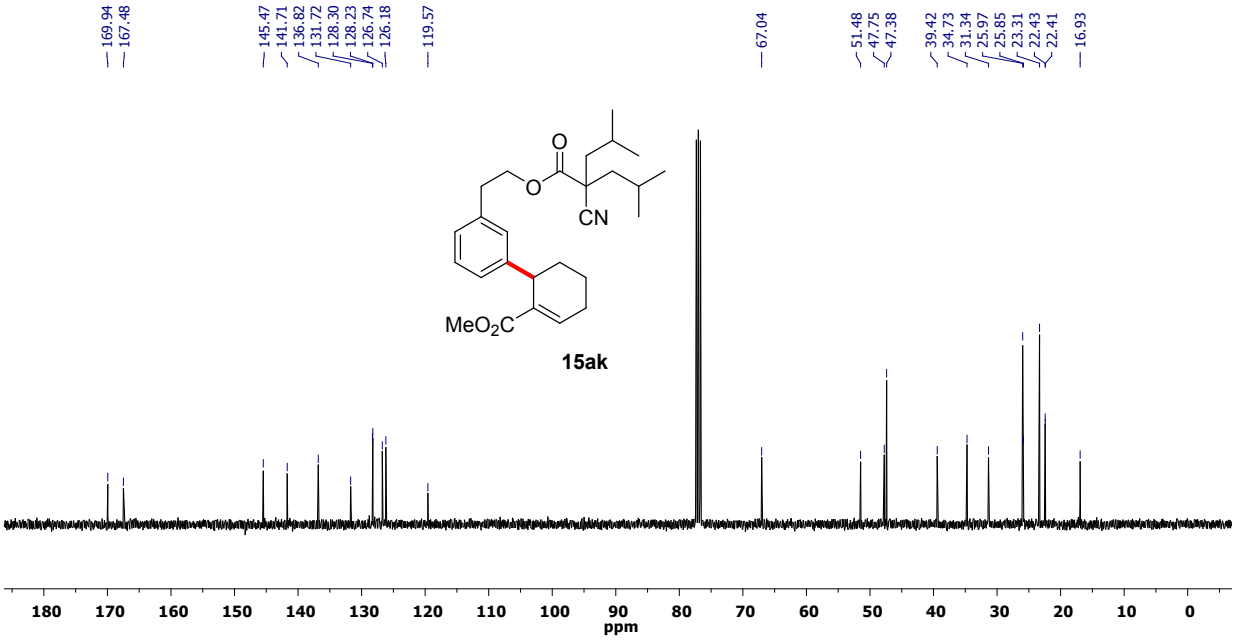
^{1}H-NMR (400 MHz) spectrum of **15aj** in $CDCl_3$



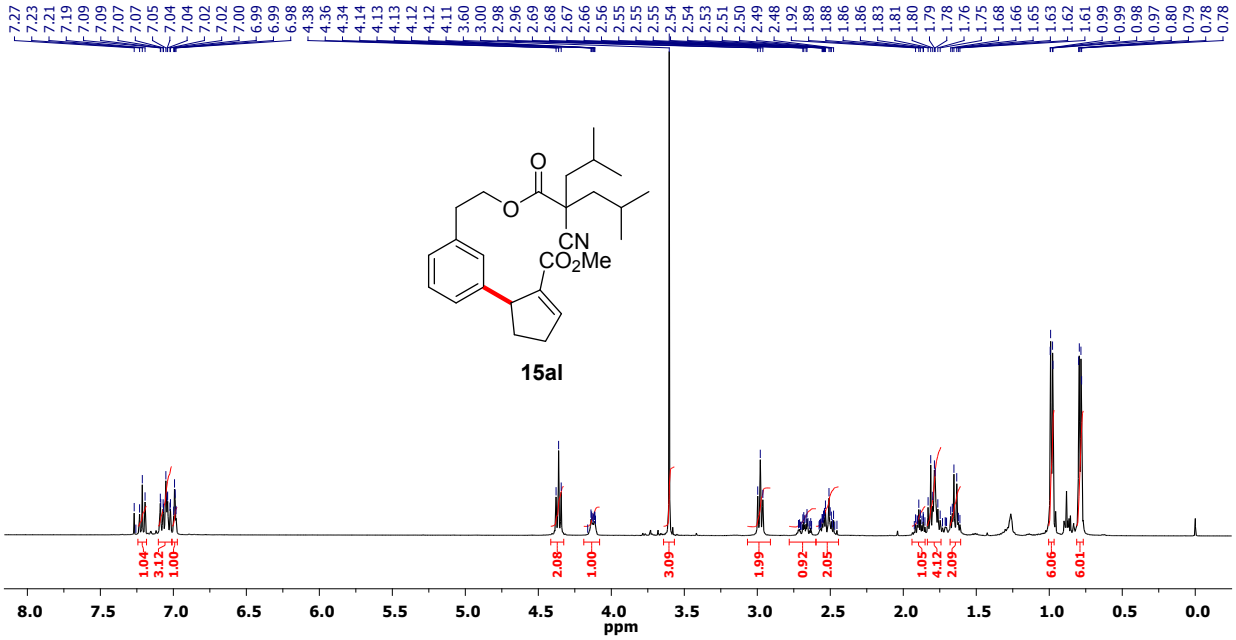
^{13}C-NMR (100 MHz) spectrum of **15aj** in $CDCl_3$



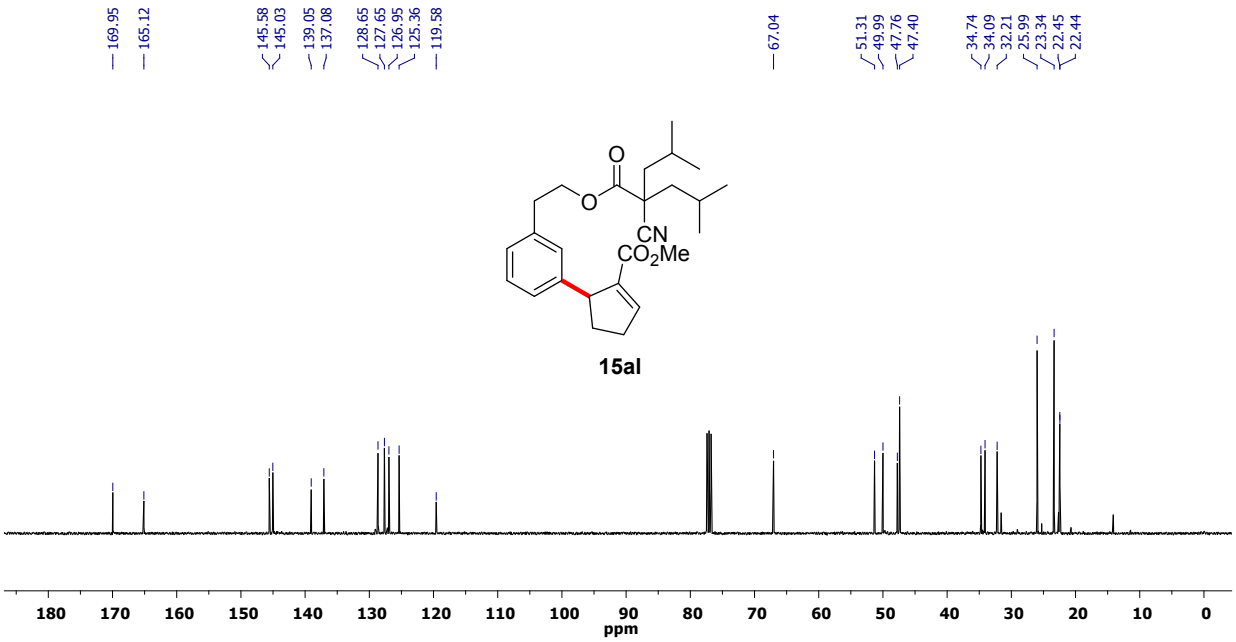
^{1}H-NMR (400 MHz) spectrum of **15ak** in $CDCl_3$



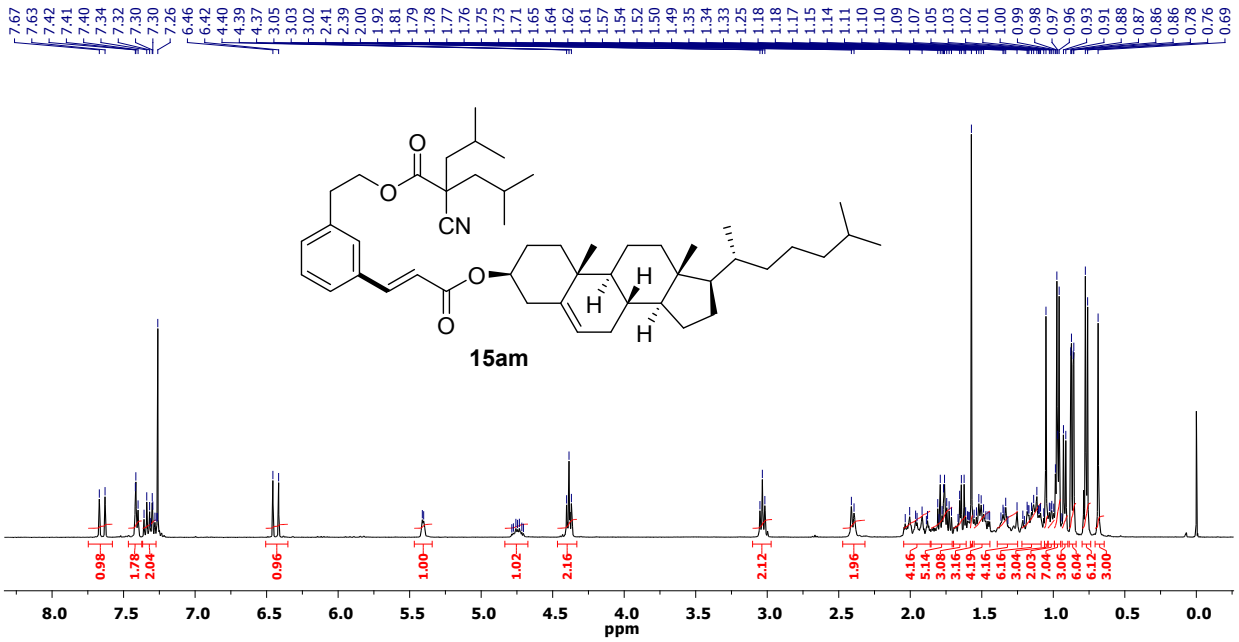
^{13}C-NMR (100 MHz) spectrum of **15ak** in $CDCl_3$



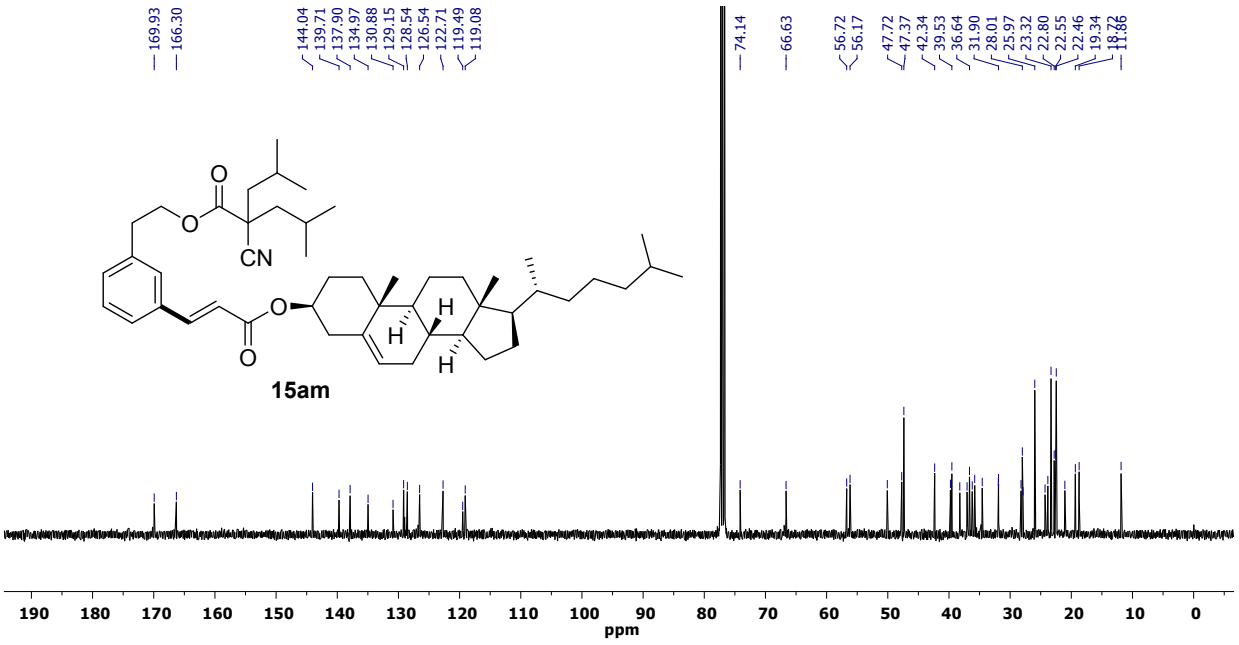
^{1}H-NMR (400 MHz) spectrum of **15al** in $CDCl_3$



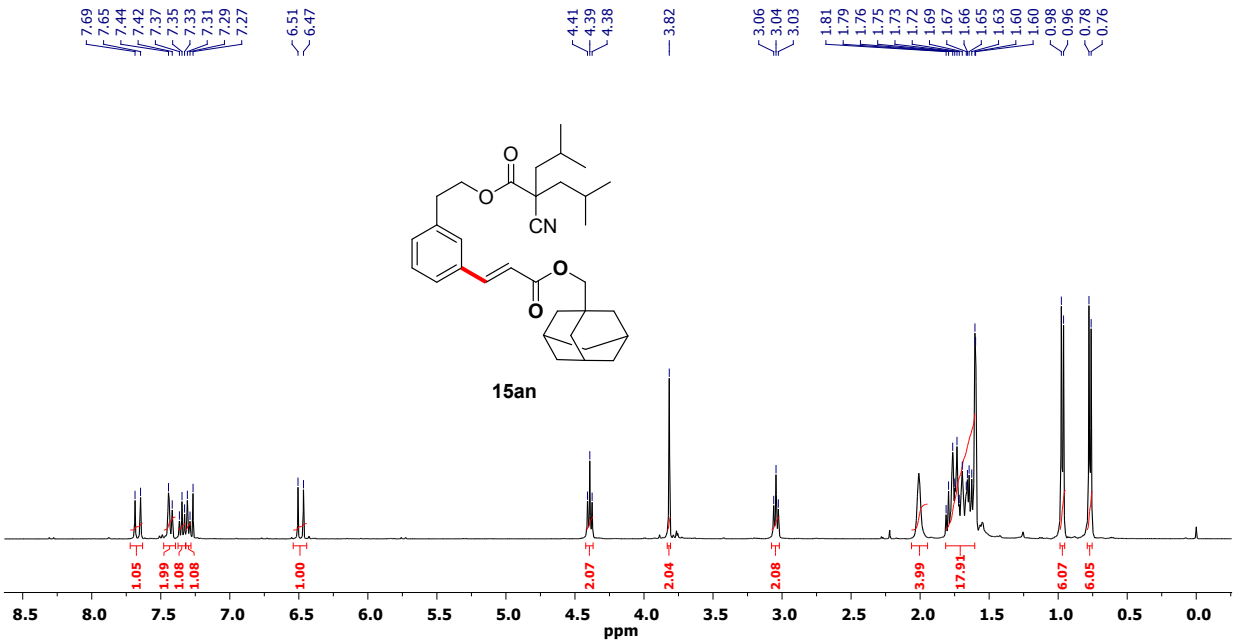
^{13}C-NMR (100 MHz) spectrum of **15al** in $CDCl_3$



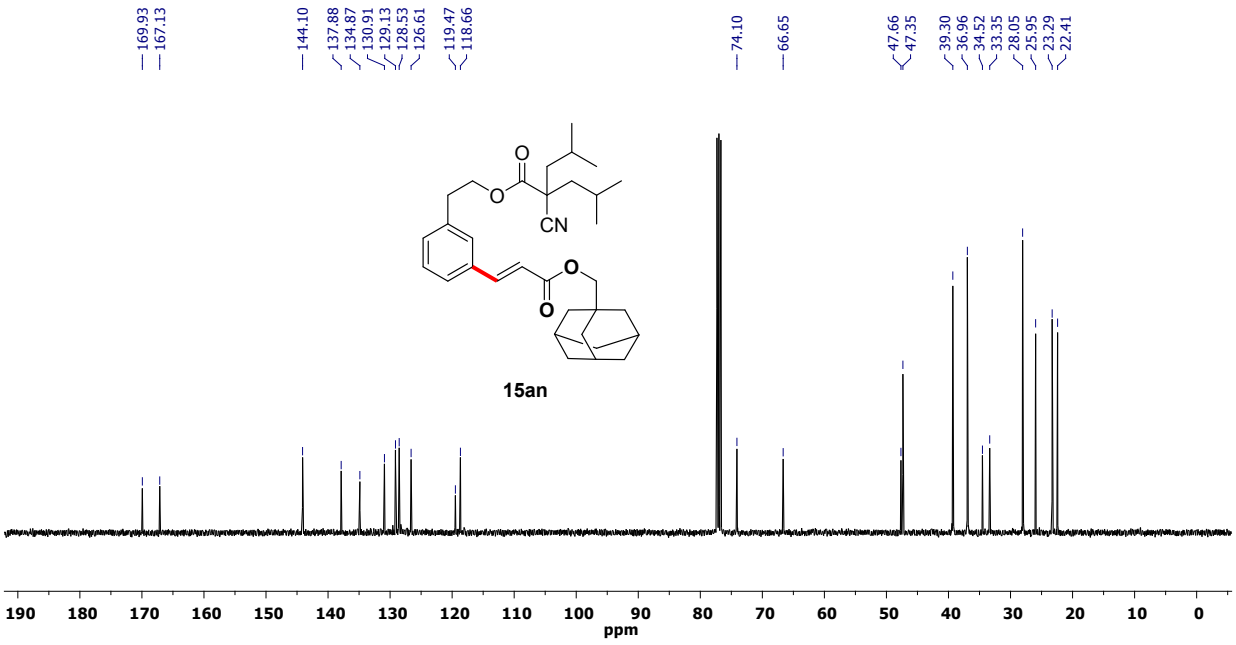
^{1}H-NMR (400 MHz) spectrum of **15am** in $CDCl_3$



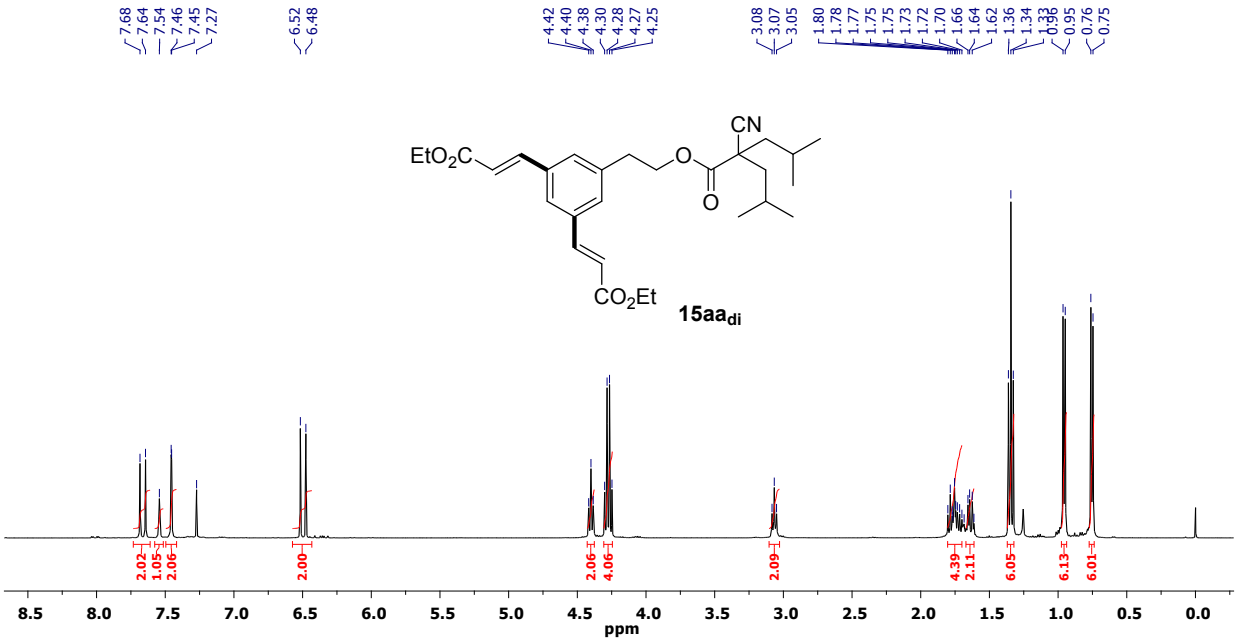
^{13}C-NMR (100 MHz) spectrum of **15am** in $CDCl_3$



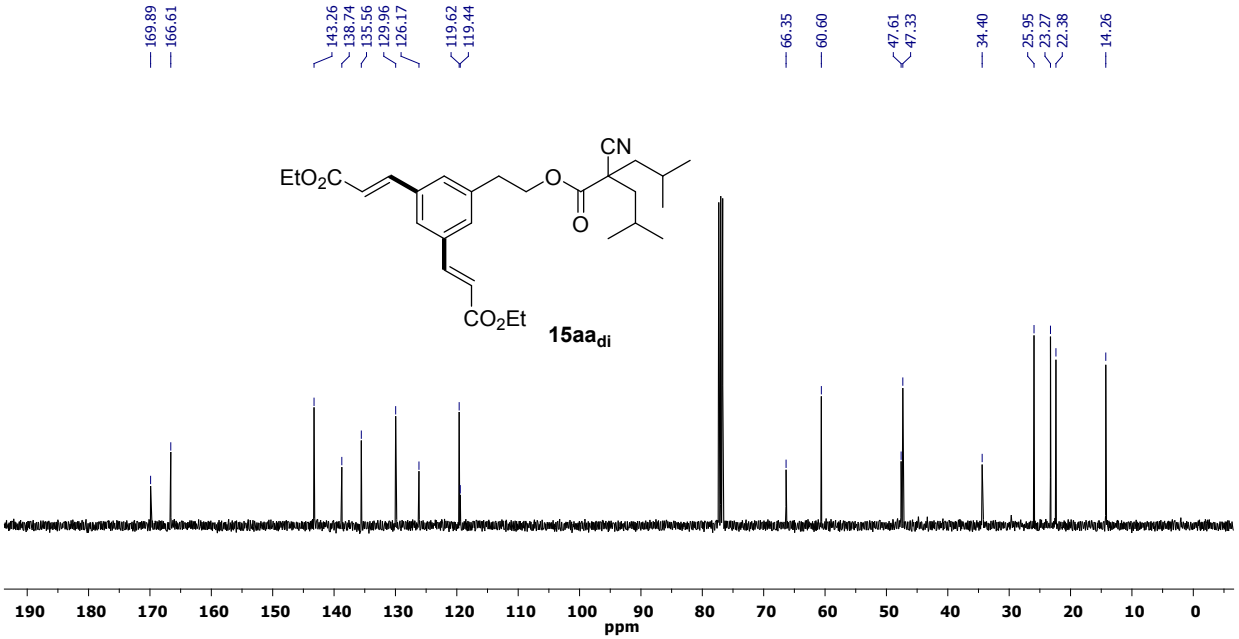
^{1}H-NMR (400 MHz) spectrum of **15an** in $CDCl_3$



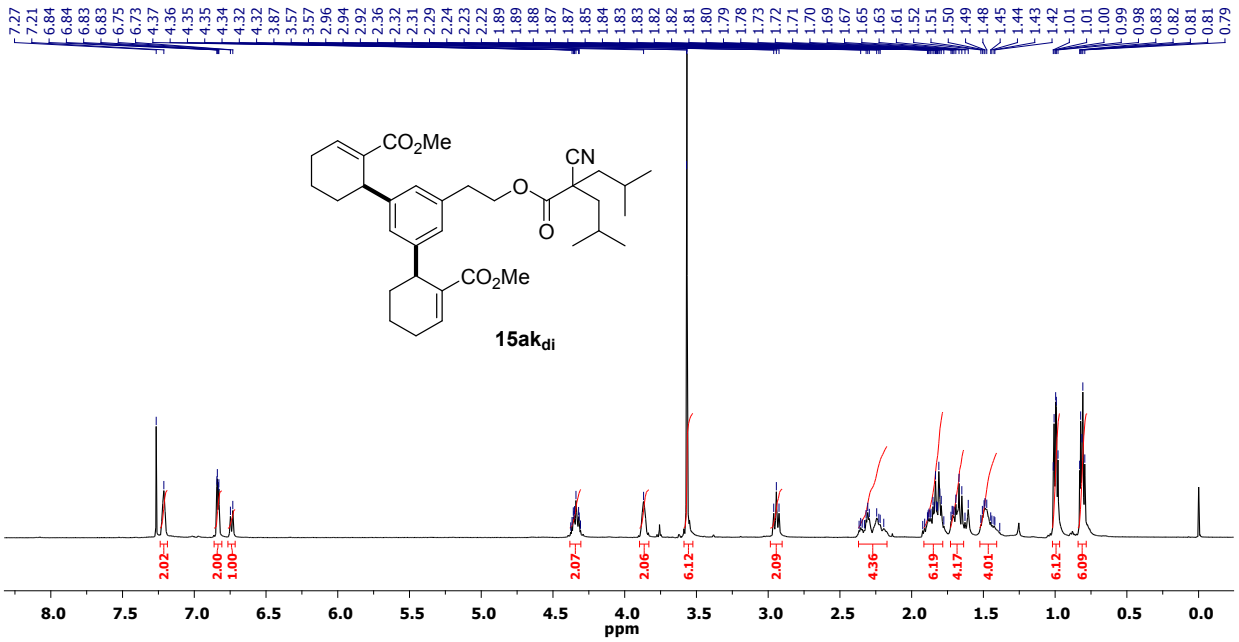
^{13}C-NMR (100 MHz) spectrum of **15an** in $CDCl_3$



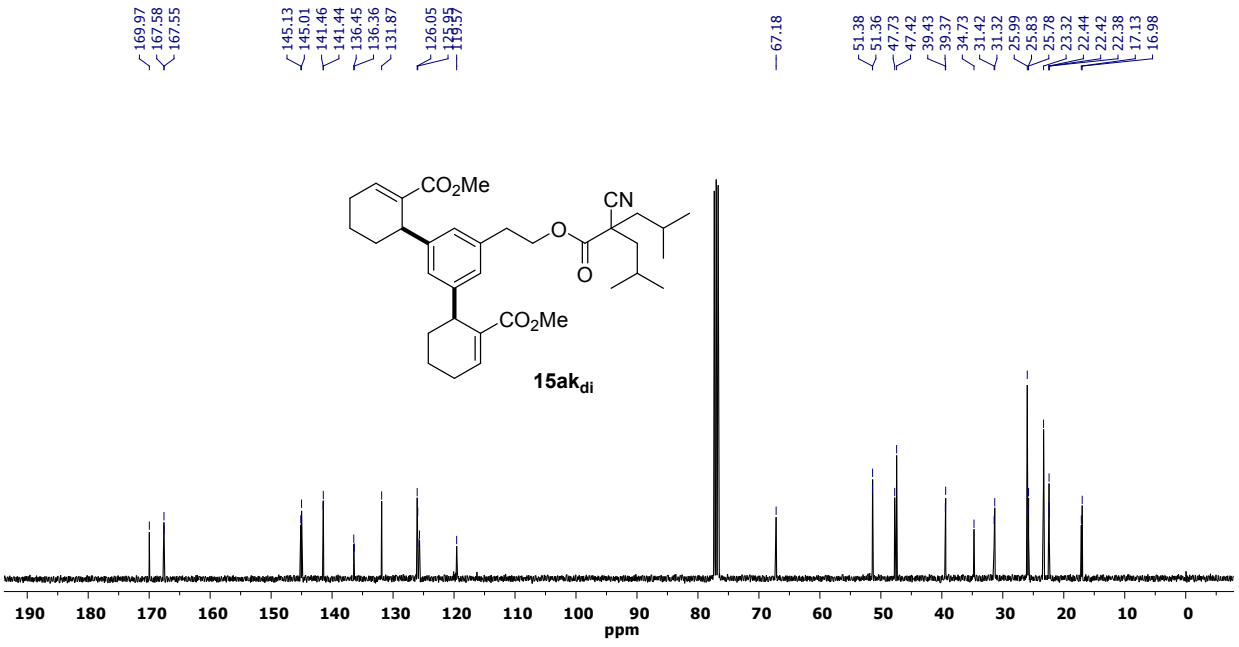
^{1}H-NMR (400 MHz) spectrum of **15aa$_{di}$** in $CDCl_3$



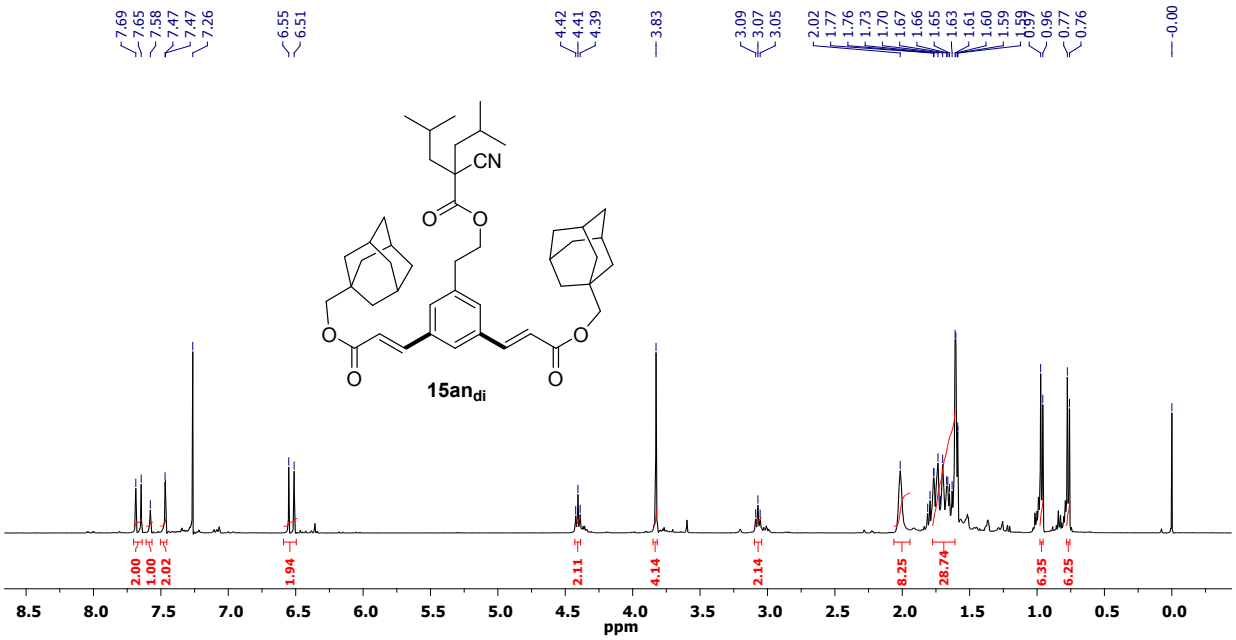
^{13}C-NMR (100 MHz) spectrum of **15aa$_{di}$** in $CDCl_3$



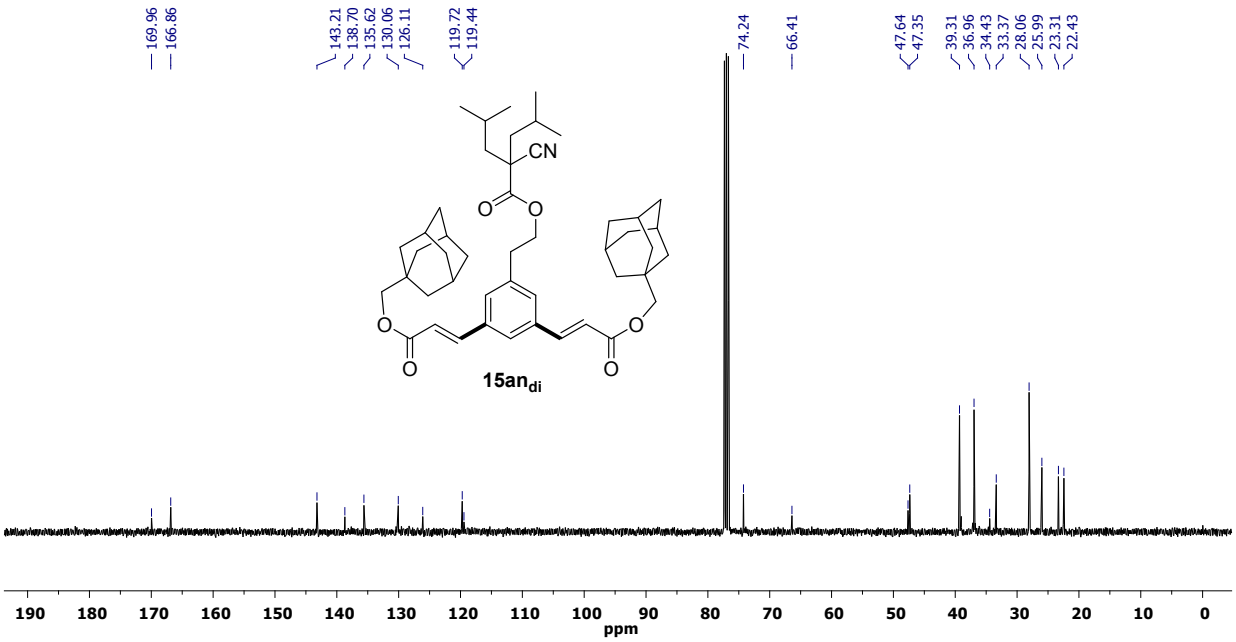
^{1}H-NMR (400 MHz) spectrum of **15ak$_{di}$** in $CDCl_3$



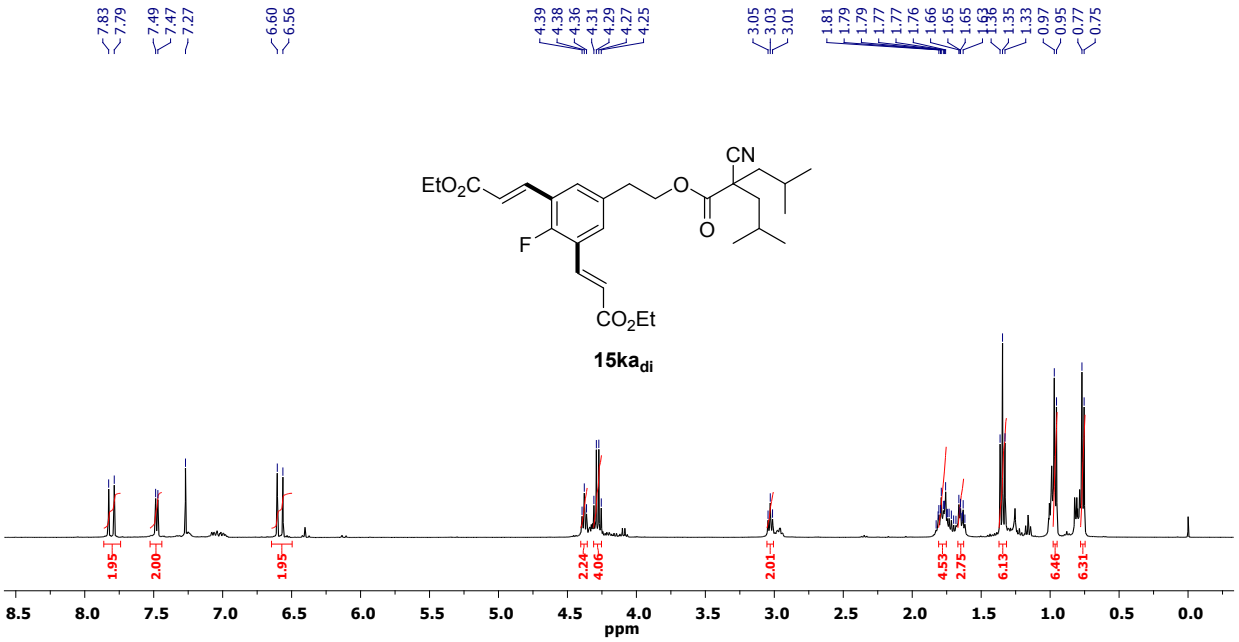
^{13}C-NMR (100 MHz) spectrum of **15ak$_{di}$** in $CDCl_3$



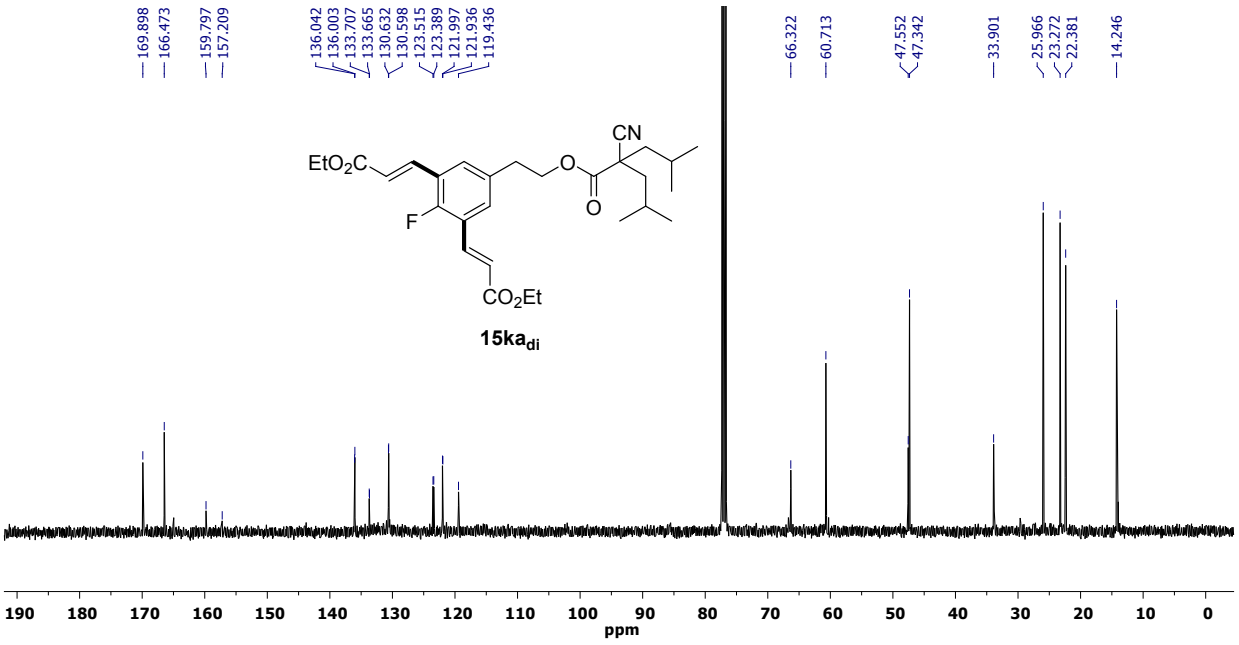
^{1}H-NMR (400 MHz) spectrum of **15an$_{di}$** in $CDCl_3$



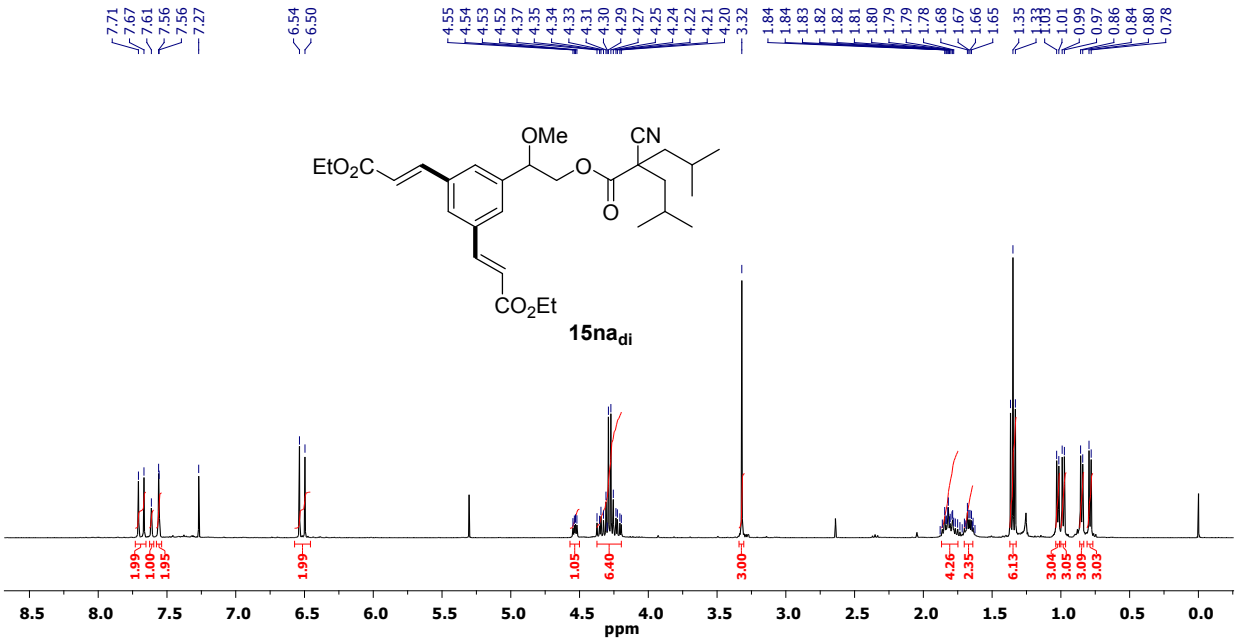
^{13}C-NMR (100 MHz) spectrum of **15an$_{di}$** in $CDCl_3$



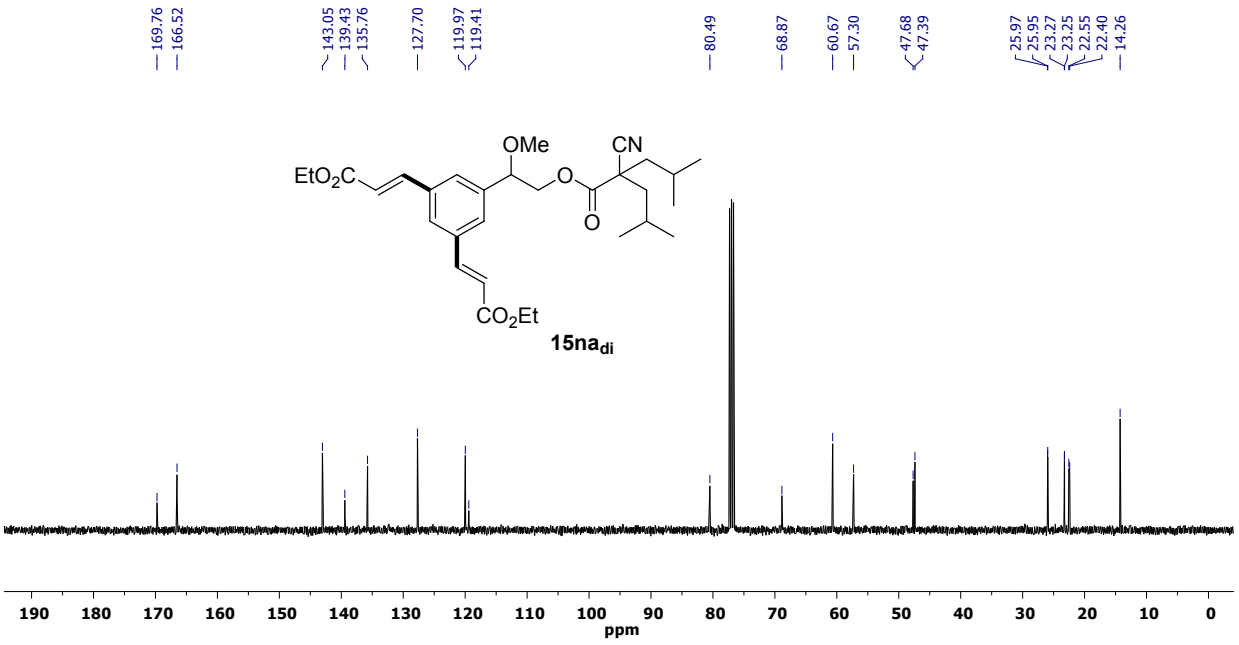
^{1}H-NMR (400 MHz) spectrum of **15ka$_{di}$** in $CDCl_3$



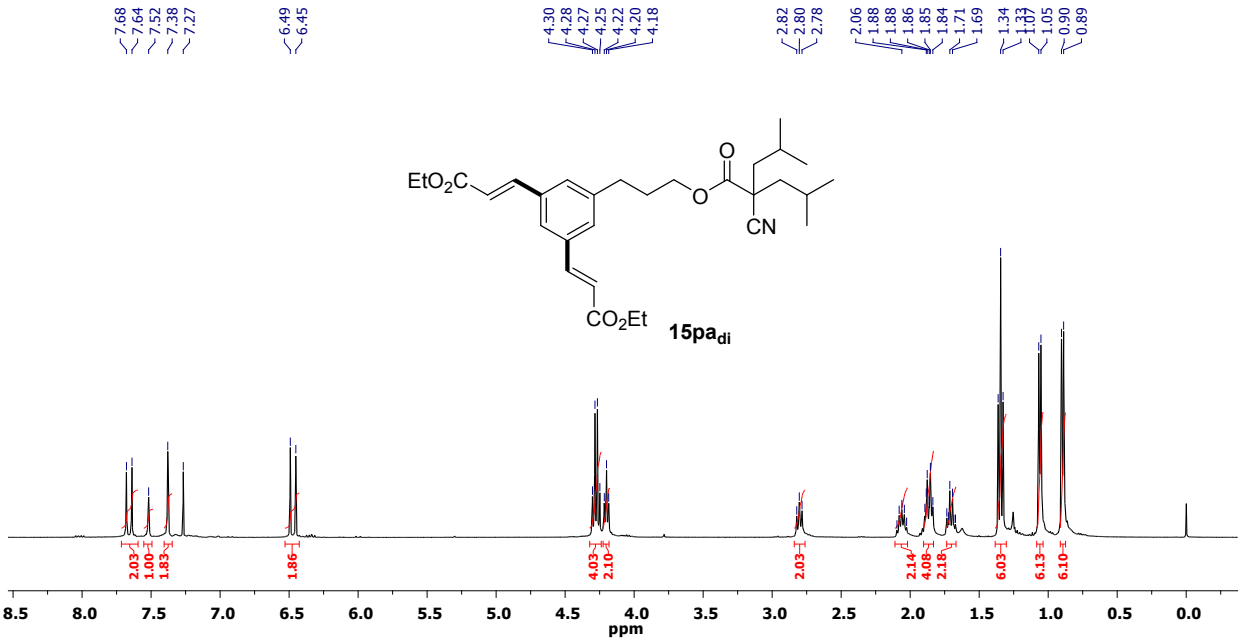
^{13}C-NMR (100 MHz) spectrum of **15ka$_{di}$** in $CDCl_3$



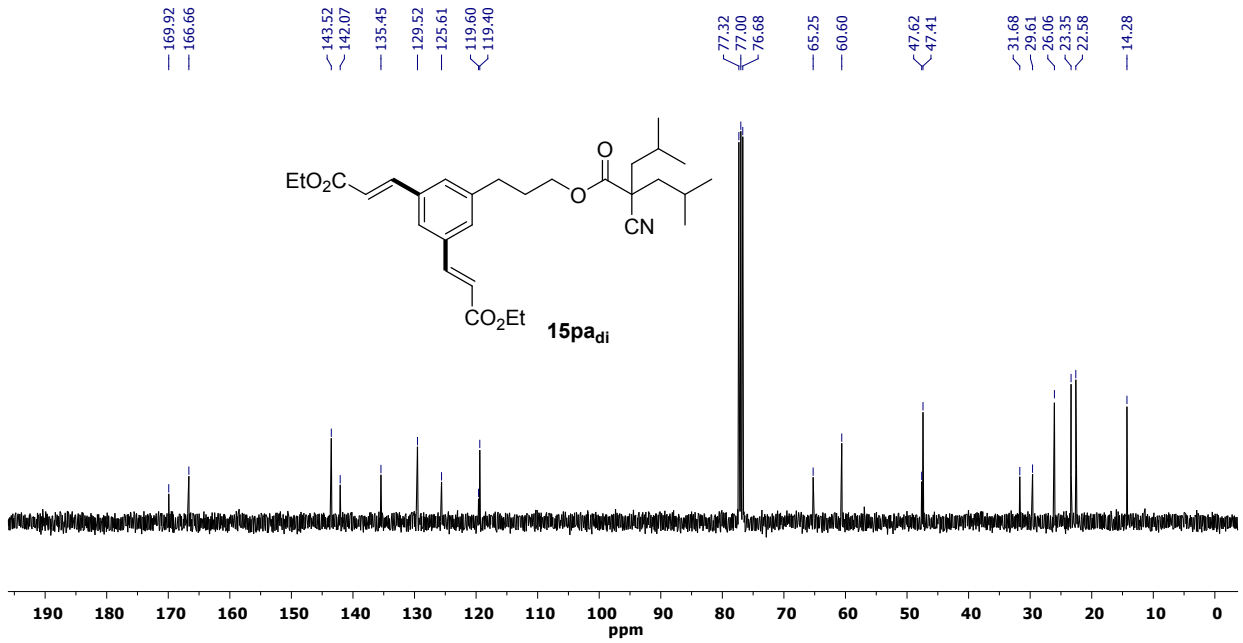
^{1}H-NMR (400 MHz) spectrum of **15na$_{di}$** in $CDCl_3$



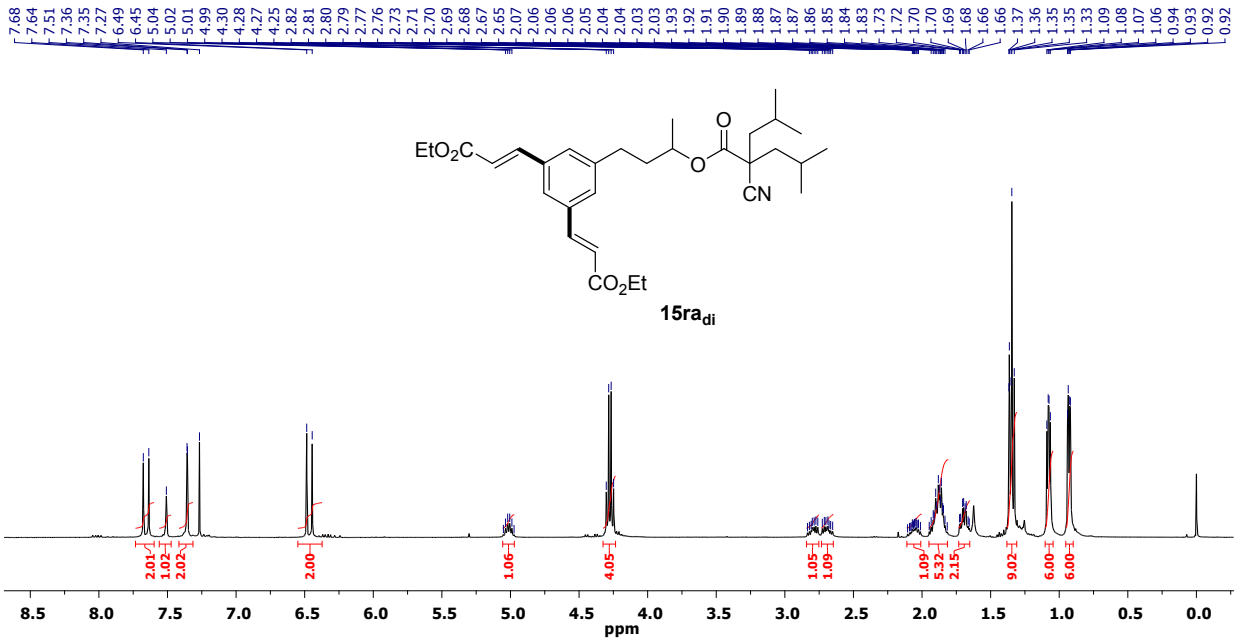
^{13}C-NMR (100 MHz) spectrum of **15na$_{di}$** in $CDCl_3$



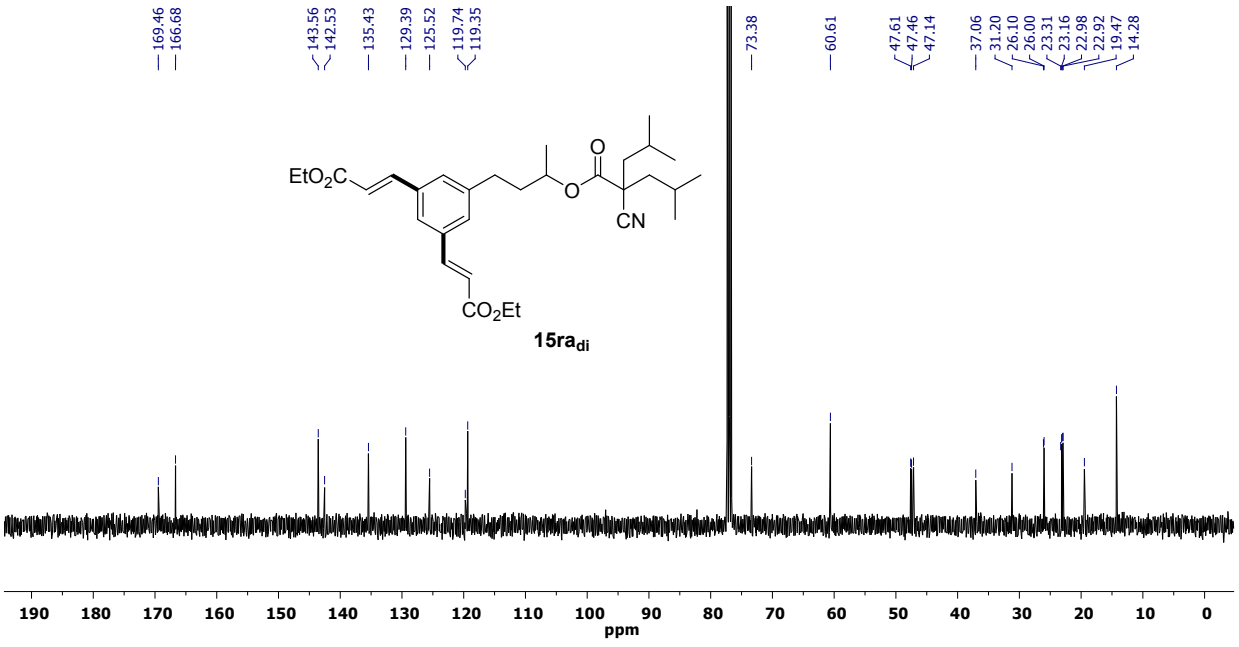
^{1}H-NMR (400 MHz) spectrum of **15pa$_{di}$** in $CDCl_3$



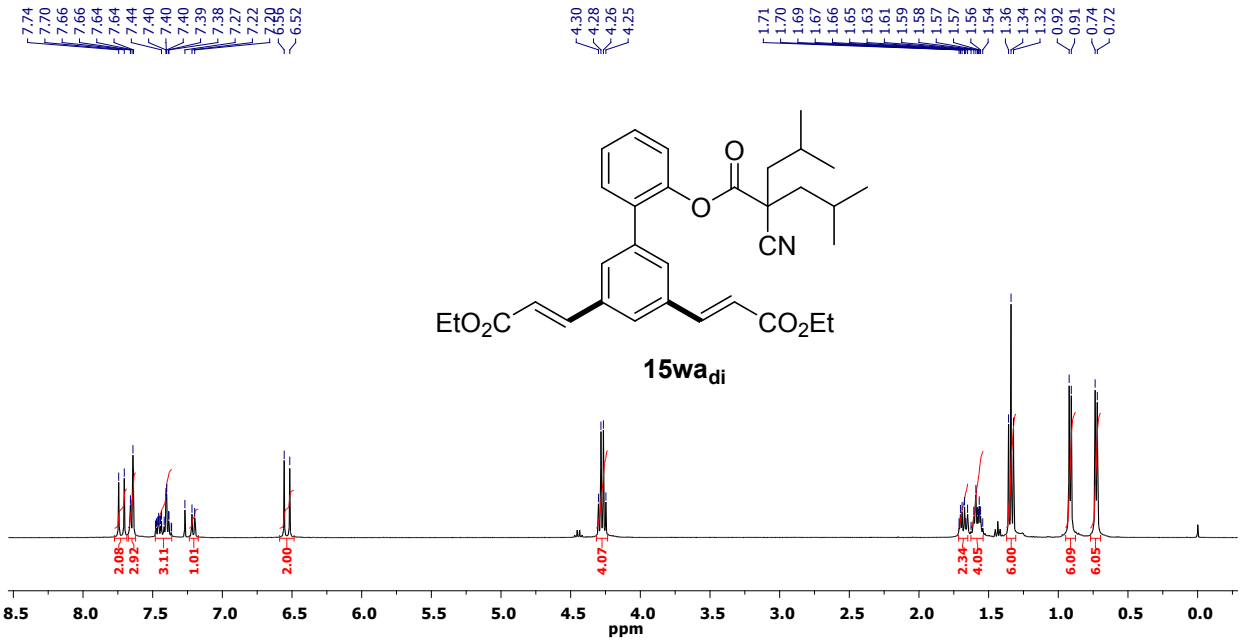
^{13}C-NMR (100 MHz) spectrum of **15pa$_{di}$** in $CDCl_3$



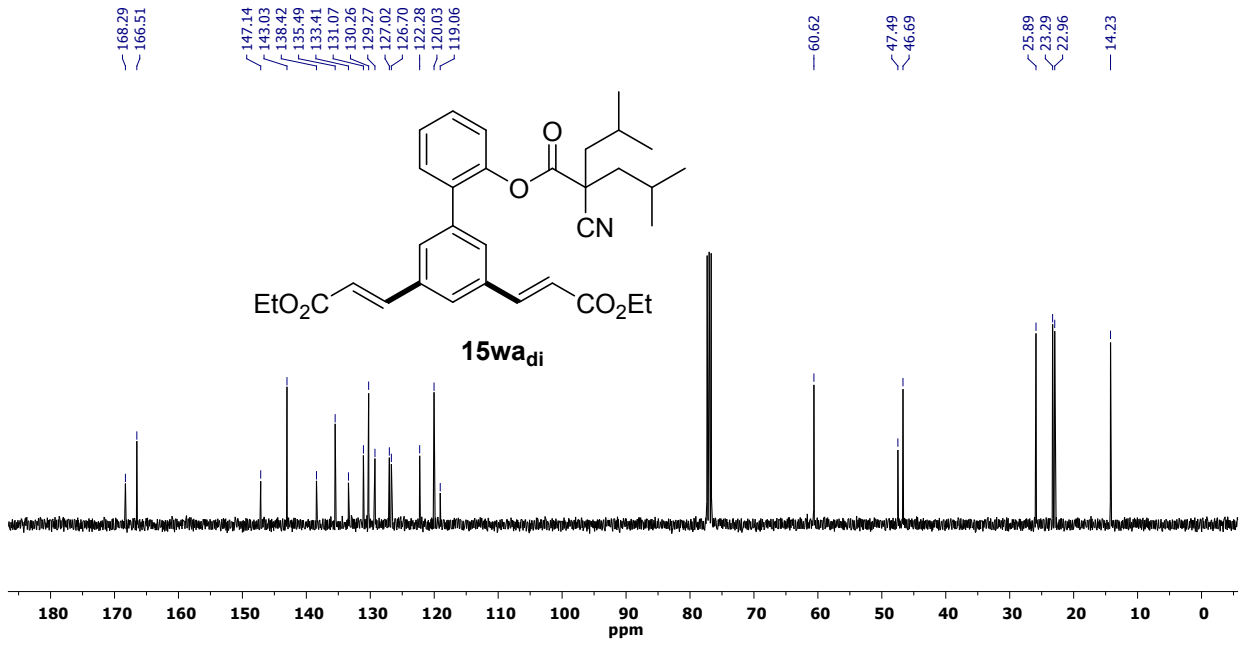
^{1}H-NMR (400 MHz) spectrum of **15ra$_{di}$** in $CDCl_3$



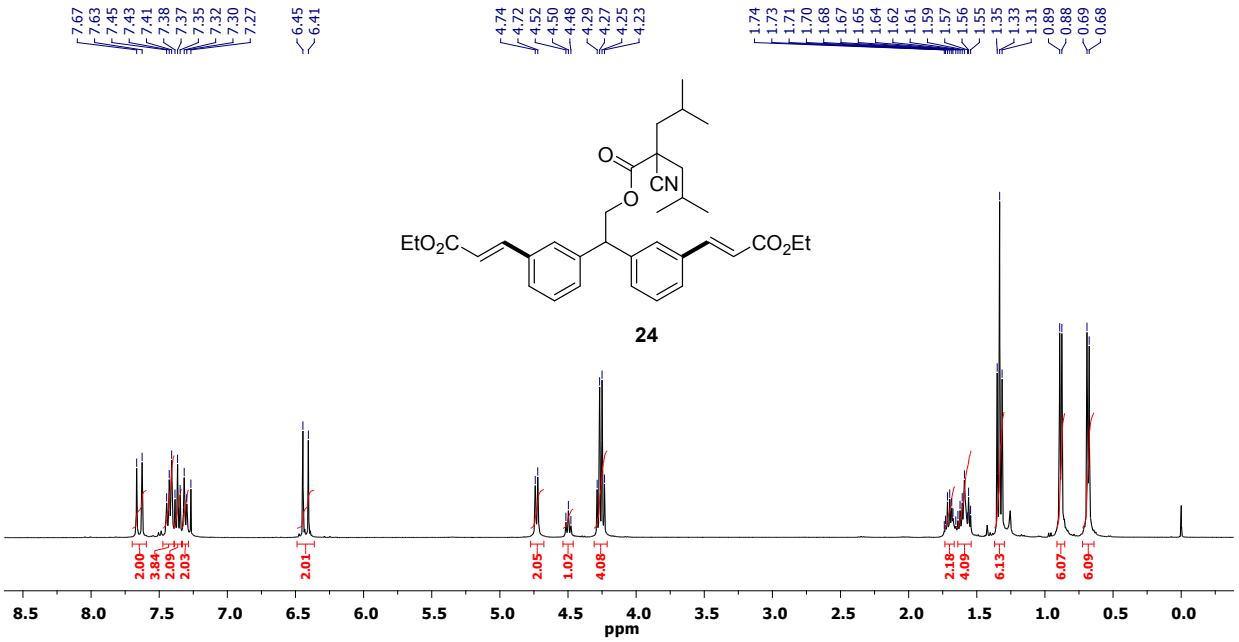
^{13}C-NMR (100 MHz) spectrum of **15ra$_{di}$** in $CDCl_3$



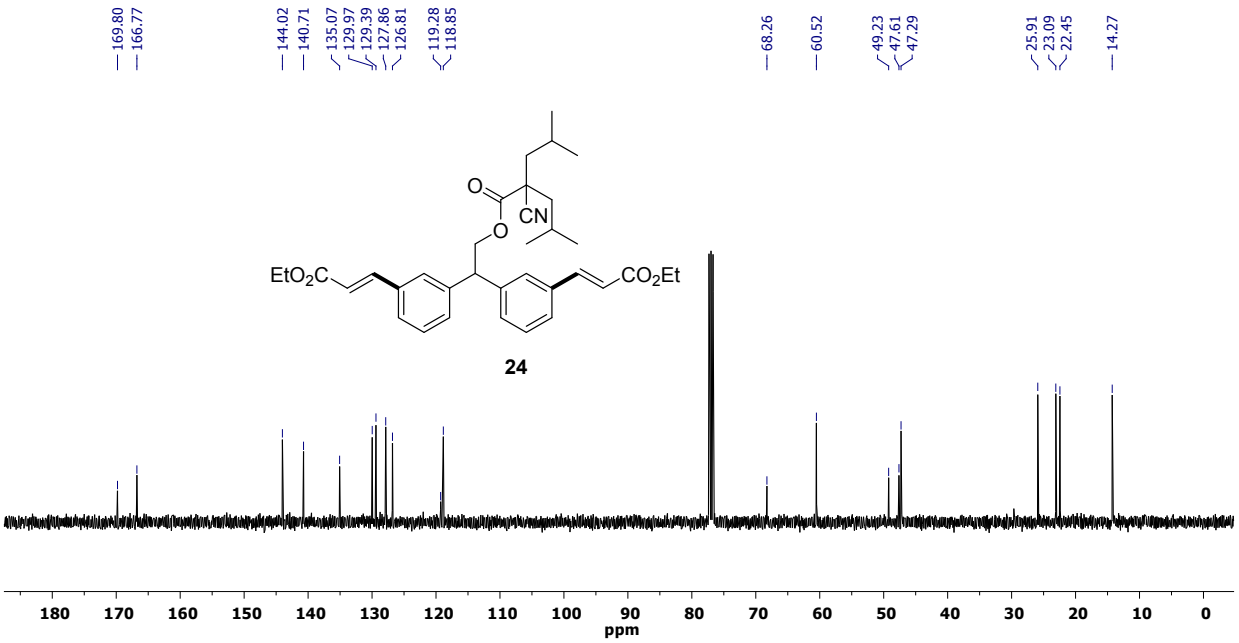
^{1}H-NMR (400 MHz) spectrum of **15wa$_{di}$** in $CDCl_3$



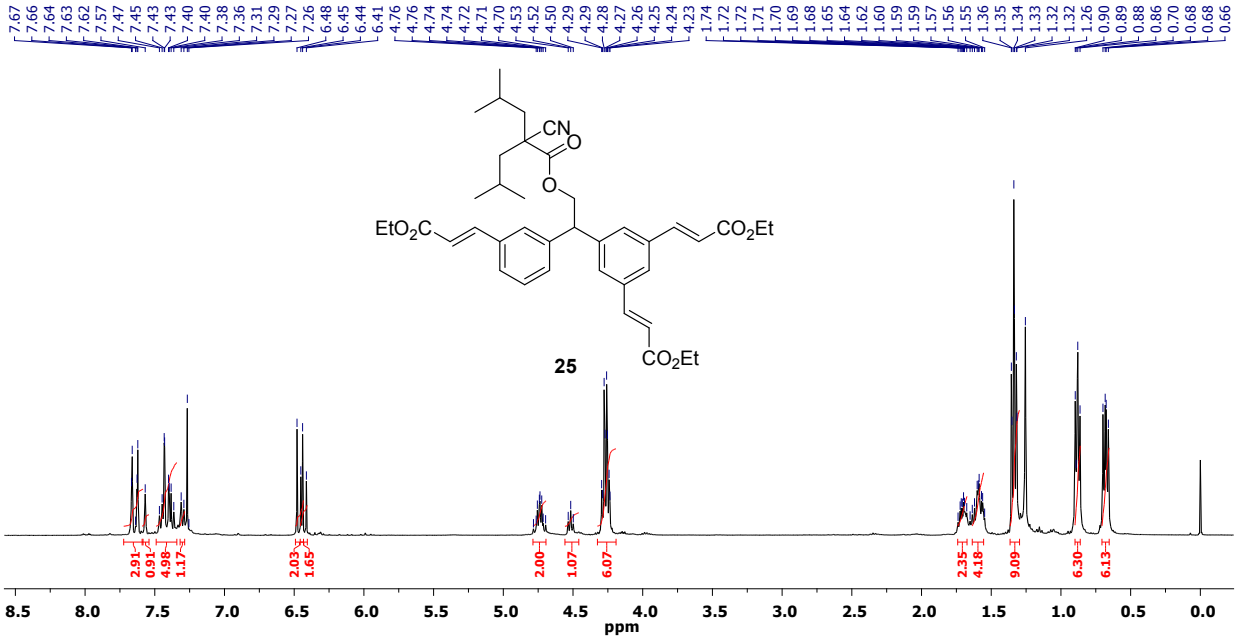
^{13}C-NMR (100 MHz) spectrum of **15wa$_{di}$** in $CDCl_3$



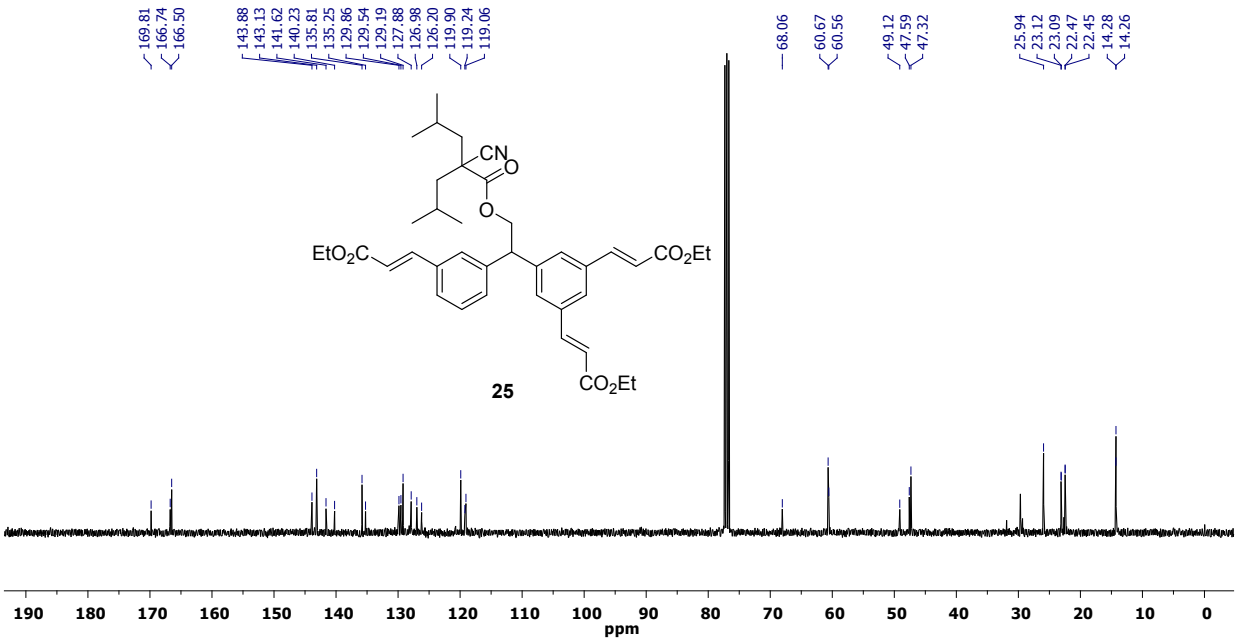
^{1}H-NMR (400 MHz) spectrum of **24** in $CDCl_3$



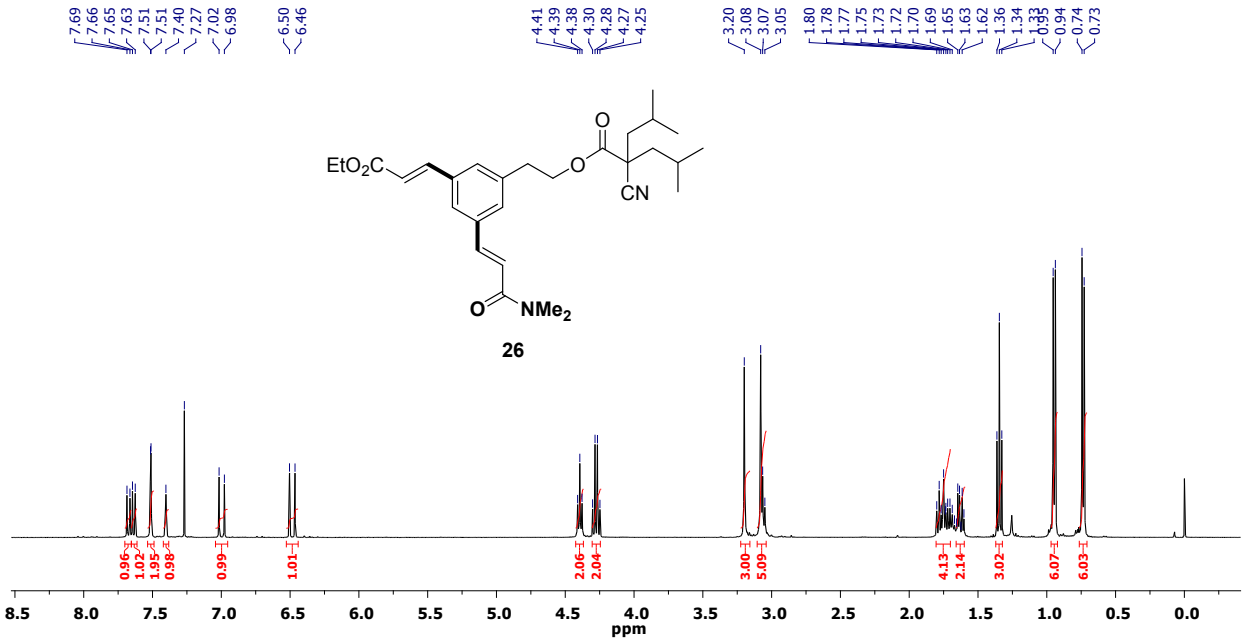
^{13}C-NMR (100 MHz) spectrum of **24** in $CDCl_3$



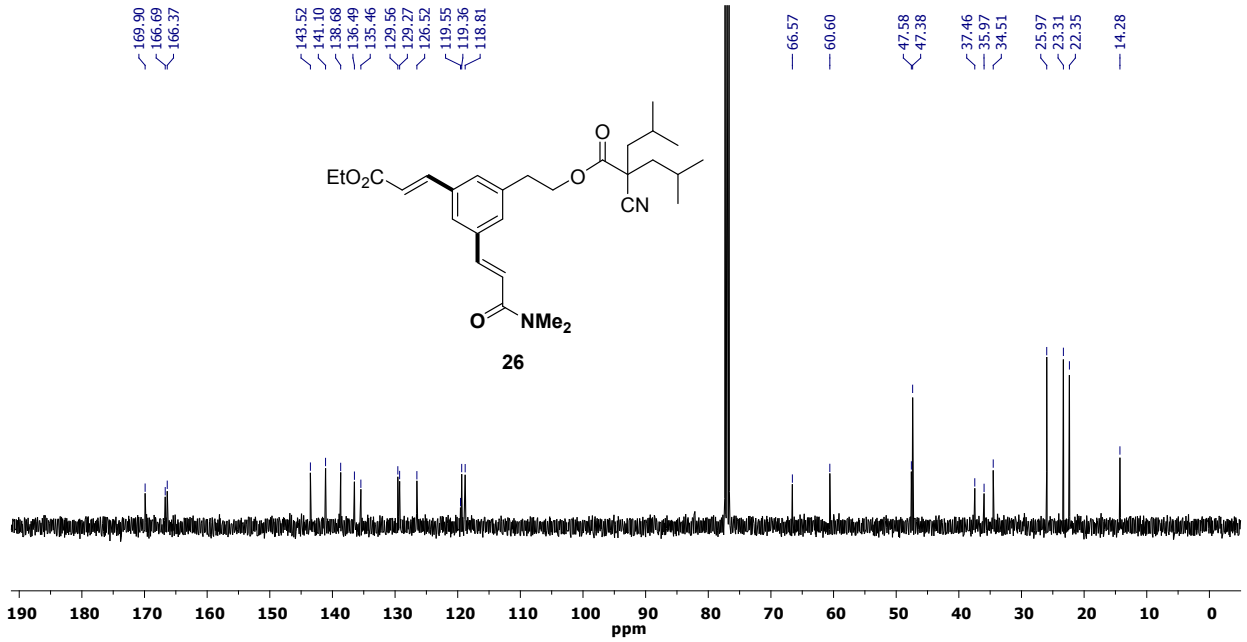
^{1}H-NMR (400 MHz) spectrum of **25** in $CDCl_3$



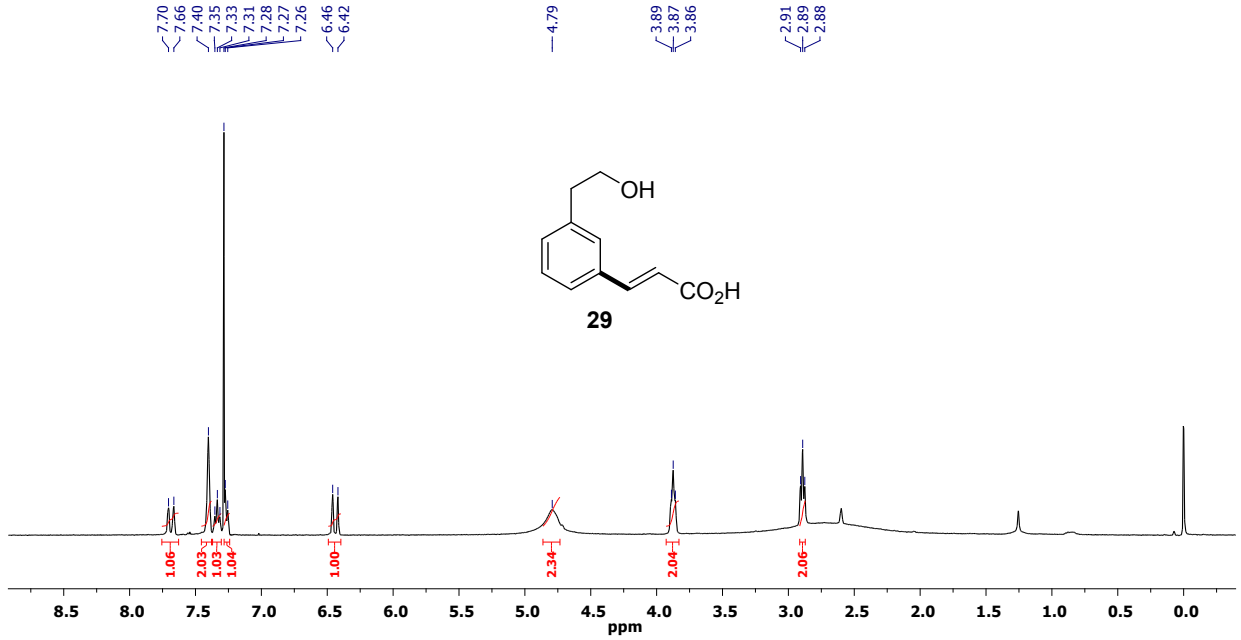
^{13}C-NMR (100 MHz) spectrum of **25** in $CDCl_3$



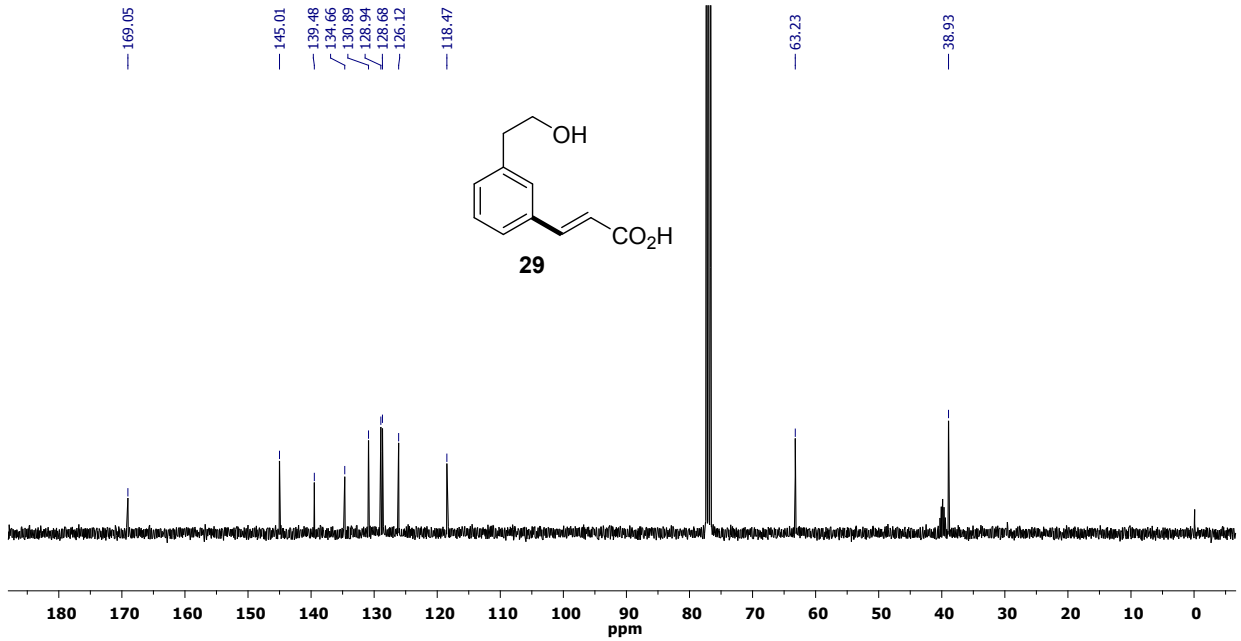
^{1}H-NMR (400 MHz) spectrum of **26** in $CDCl_3$



^{13}C-NMR (100 MHz) spectrum of **26** in $CDCl_3$



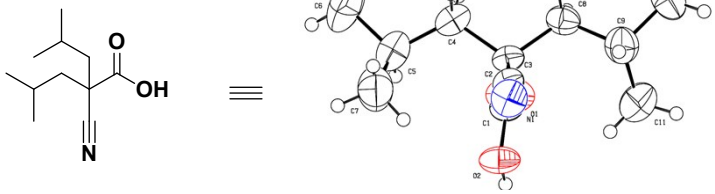
^{1}H-NMR (400 MHz) spectrum of **29** in $CDCl_3$+DMSOd_6



^{13}C-NMR (100 MHz) spectrum of **29** in $CDCl_3$+DMSOd_6

X-ray Diffraction Analysis of Compound 23 (Template):

Crystal of compound **23** was obtained by dissolving product in CH_2Cl_2 and allowing the solvent to slowly evaporate at room temperature. The crystal structure information for this compound has been deposited at the Cambridge Crystallographic Data Centre. **CCDC No. 1996777** contains the crystal structure information of this compound and can be obtained free of charge *via* http://www.ccdc.cam.ac.uk

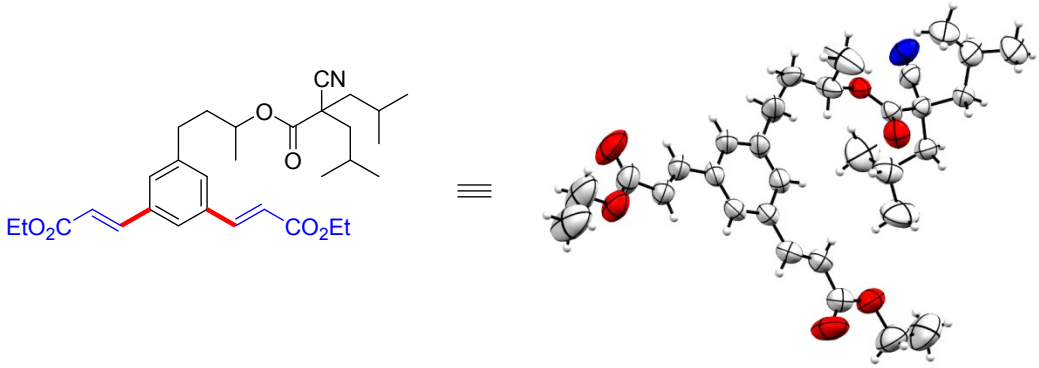


Crystal data and structure refinement:

Identification code	exp_9746
Empirical formula	$C_{8.8}H_{15.2}N_{0.8}O_{1.6}$
Formula weight	157.82
Temperature/K	298
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	6.4675(3)
b/Å	11.3902(5)
c/Å	16.6635(10)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1227.54(11)
Z	5
ρ_{calc}g/cm^3	1.067
μ/mm^{-1}	0.073
F(000)	432.0
Crystal size/mm^3	0.3 × 0.2 × 0.1
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.332 to 57.876
Index ranges	$-4 \le h \le 8$, $-13 \le k \le 14$, $-10 \le l \le 22$
Reflections collected	3643
Independent reflections	2588 [R_{int} = 0.0257, R_{sigma} = 0.0564]
Data/restraints/parameters	2588/0/132
Goodness-of-fit on F^2	1.289
Final R indexes [all data]	R_1 = 0.1051, wR_2 = 0.2449
Flack parameter	0.0(10)

X-ray Diffraction Analysis of Compound 15ra:

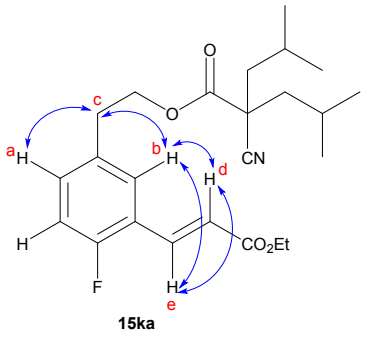
Crystal of compound **15ra** was obtained by dissolving product in CH_2Cl_2 and allowing the solvent to slowly evaporate at room temperature. The crystal structure information for this compound has been deposited at the Cambridge Crystallographic Data Centre. **CCDC No. 2042436** contains the crystal structure information of this compound and can be obtained free of charge *via* http://www.ccdc.cam.ac.uk



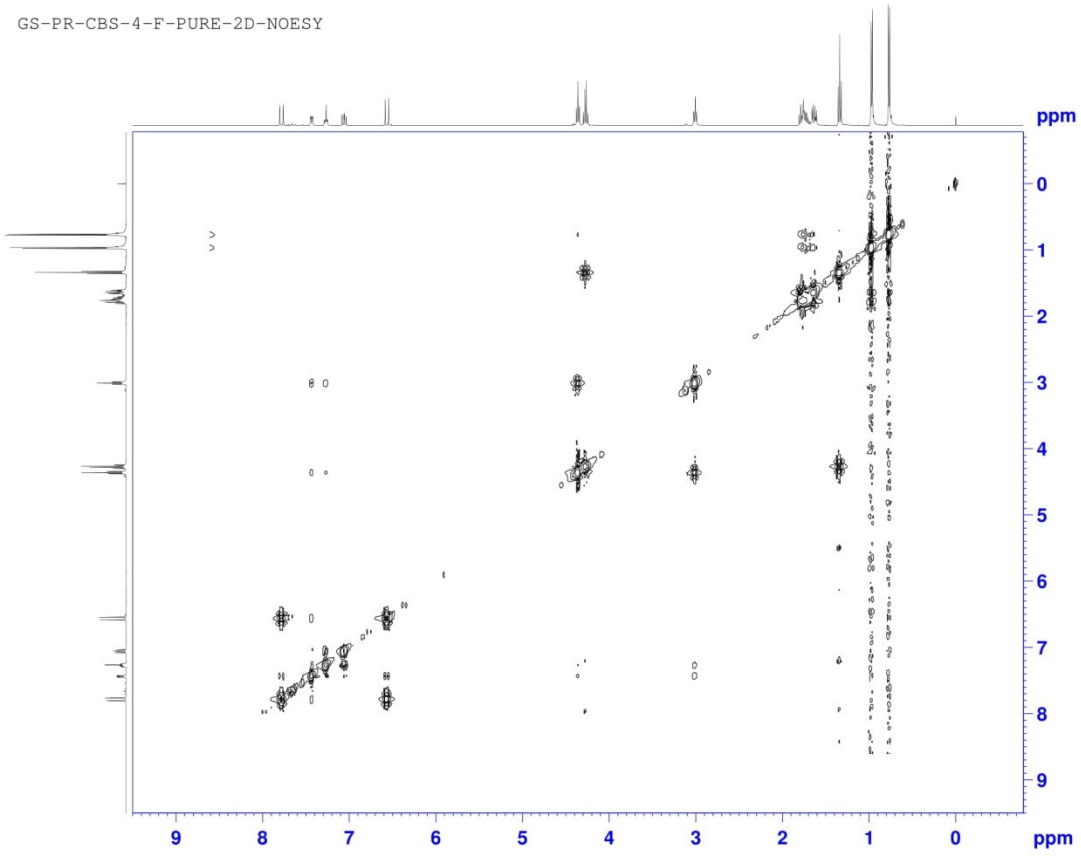
Crystal data and structure refinement:

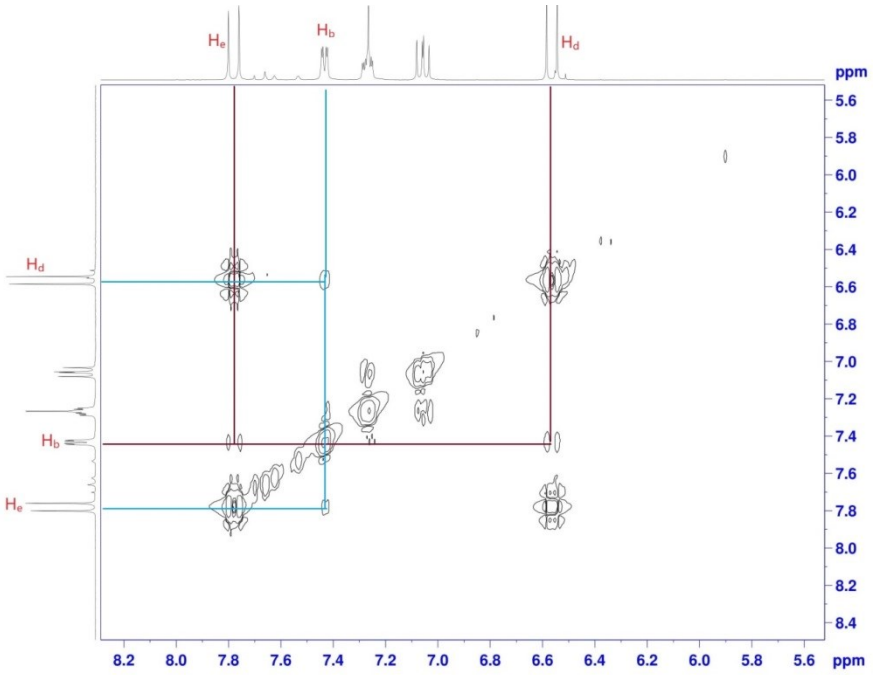
Identification code	mo_GSPRCBSCRY1_0ma
Empirical formula	$C_{31}H_{43}NO_6$
Formula weight	525.66
Temperature/K	273.15
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	7.6770(9)
b/Å	30.033(4)
c/Å	14.1867(18)
α/°	90
β/°	105.70
γ/°	90
Volume/Å^3	3148.9(7)
Z	4
ρ_{calc}g/cm^3	1.109
μ/mm^{-1}	0.076
F(000)	1136.0
Crystal size/mm^3	0.27 × 0.23 × 0.1
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.032 to 54.496
Goodness-of-fit on F^2	1.238
Final R indexes [all data]	R_1 = 0.1762, wR_2 = 0.3729
Largest diff. peak/hole / e Å^{-3}	0.57/-0.26

2D NOESY Spectra of compound **15ka**:



15ka

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6.6
6.8
7.0
7.2
7.4
7.6
7.8
8.0
8.2
8.4
8.2
8.0
7.8
7.6
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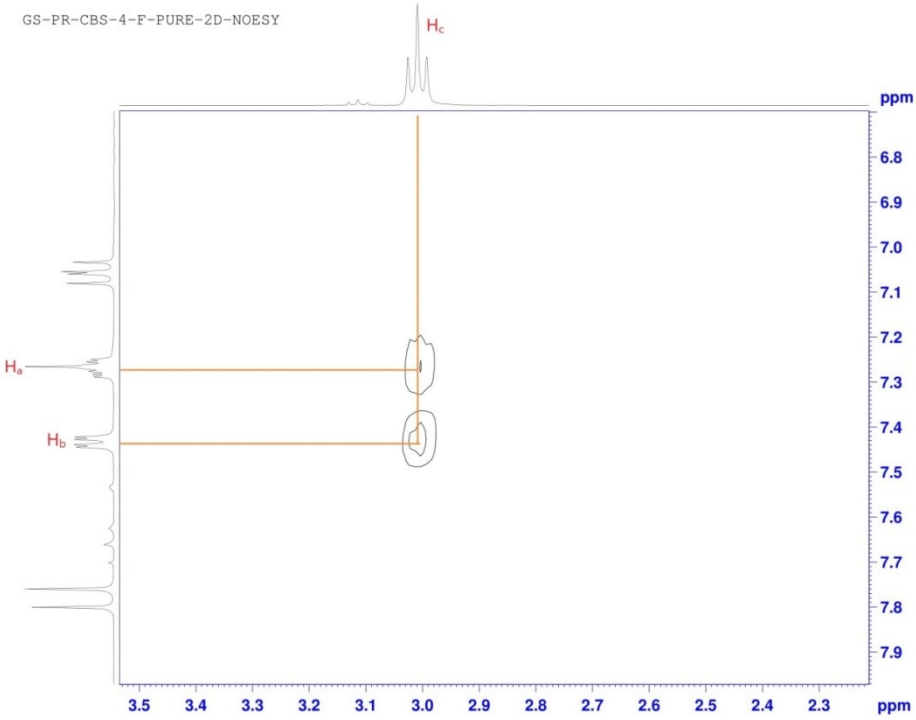
7.2
7.0
6.8
6.6
6.4
6.2
6.0
5.8
5.6
ppm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2.9
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2.6
2.5
2.4
2.3
ppm