Electronic Supplementary Information

Dehydration *in Water*. Solid-Supported Lipases as Green Catalysts for Esterification

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1. General Information

A solution of 2 wt % surfactant/H_2O was prepared by dissolving the surfactant in degassed HPLC grade water and was stored under argon. TPGS-750-M was obtained from (PHT International, although it is also available from Sigma-Aldrich (catalog #733857). Novozym 435 was purchased from Strem Chemicals Inc. (06-3122). A suspension of CalB was purchased from Sigma-Aldrich (cat. No. L3170). Palatase 20000L (originating from *Rhizomucor miehei*) was purchased from Strem Chemicals Inc. (cat. no. 06-3118). Lipozyme ® RM was purchased from Strem Chemicals Inc. (cat. no. 06-3120). Amano Lipase PS was purchased from Sigma-Aldrich (cat. no. 534641). Lipase from Candida rugosa was purchased from Sigma (cat. no. L1754). Lipase from *Rhizopus niveus* was purchased from Sigma (cat. no. 62310). Lewatit Vp OC 1600 was a kind donation from Anthem Biosciences. All commercially available reagents were purchased from Sigma-Aldrich, Combi-Blocks, Ambeed Inc., Acros Organics, BLD Pharma, Fischer Scientific, or ChemScene. All commercial reagents were used without further purification. Thin layer chromatography (TLC) was done using Silica Gel 60 F254 plates (Merck, 0.25 mm thick). The developed TLC plate was analyzed by a UV lamp (254 nm). The plates were further analyzed with the use of bromocresol green stain or basic potassium permanganate stain and developed with a heat gun. All commercially available reagents were used without further purification. Flash chromatography was performed using Silicycle Silicaflash® P60 unbonded grade silica. ^{1}H, ^{13}C, and ^{19}F NMR were recorded at 25 °C on either an Agilent Technologies 400 MHz, a Bruker Avance III HD 400 MHz, or a Agilent Technologies 500 MHz, a Bruker Avance III HD 400 MHz spectrometer in $CDCl_3$ with residual $CHCl_3$ (^{1}H = 7.26 ppm, ^{13}C = 77.16 ppm) as internal standard. Chemical shifts are reported in parts per million (ppm, or Hz). The data presented will be reported as follows: chemical shift, multiplicity (s = singlet, bs = broad singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quartet, quin = quintet, m = multiplet), coupling constant (if applicable), and integration. High-resolution mass analyses (HRMS) were recorded on a Waters GCT Premier GC TOF (EI-HRMS) or a Shimadzu LCMS-9030 UHPLC-QTOF (ESI-HRMS).

Preparation of Aqueous Media

Preparation of Aqueous Surfactant Solution

2 wt % TPGS-750-M, as a wax, was added to a vial and then dissolved in deionized water to the desired mass (*i.e.,* 2 g of wax and 98 g of water).

Preparation of the Buffer Solutions

Aqueous 1 M stock solutions of potassium phosphate monobasic (A) and potassium phosphate dibasic (B) were prepared. A pH = 7 phosphate buffer solution was then prepared by S3 mixing 38.5 mL of solution A with 61.5 mL of solution B. The pH was controlled and adjusted, if needed, with a 1 M solution of NaOH or HCl. The buffer solution was diluted with deionized water. 2 wt % of TPGS-750-M, as a wax, was dissolved and used as media of the reaction.

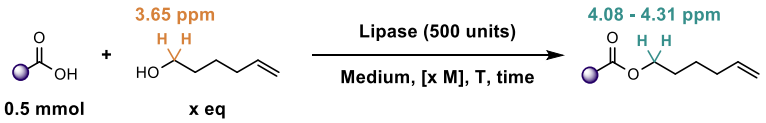
2. Optimization Studies

General Information

In general, quantitative (q) ^{1}H NMR analysis of the reaction between a carboxylic acid and 5-hexen-1-ol was foundto be the most efficient method of yield optimization. 1,3,5-Trimethoxybenzene was used as internal standard for NMR, and reaction tracking by TLC was enabled by visualization with potassium permanganate stain to oxidize the terminal alkene of the alcohol. Consumption of acid could be followed by staining with bromocresol green.

General Procedure for Optimizations

A general procedure for optimization studies is as follows:



A 1-dram glass vial was charged with carboxylic acid (0.5 mmol, 1 equiv), alcohol (x equivalents), enzyme and magnetic stir bar. The aqueous reaction medium was then added to the desired concentration and the vial capped and set into an aluminum heating block on magnetic stirrer set to the desired temperature. The reaction was tracked by extracting an aliquot and TLC analysis as above. Upon completion, water was added to make the total aqueous volume of 1 mL (if necessary) and 1 mL of extraction solvent (2-MeTHF, MTBE, toluene, or DCM) was added to the vial. The capped vial was then centrifuged and the organic layer transferred into a vial containing internal standard (28.0 mg 1,3,5-trimethoxybenzene per 0.5 mmol of acid). The extraction was repeated until the organic layer no longer showed material via TLC analysis (typically 3 x 1 mL extraction was adequate). The organic layer was dried under vacuum and analyzed by q^{1}H NMR.

For esters of 5-hexen-1-ol, the conversion can be followed by quantifying the integration of the methylene protons alpha- to the alcohol oxygen. The resonance of these protons moves from a triplet centered at 3.65 ppm to a triplet centered between 4.08 and 4.31 ppm. At 100% conversion, this triplet integrates to 2H relative to the internal standard singlet at 3.75 ppm integrating to 3H.

Results on the effect on yield from the variation of the following parameters can be found: in the following figures in the main text of this manuscript:

- enzyme type: Figure 3
- alcohol equivalents: Figure 5a
- reaction medium: Figure 4
- buffer concentration: Figure 5c

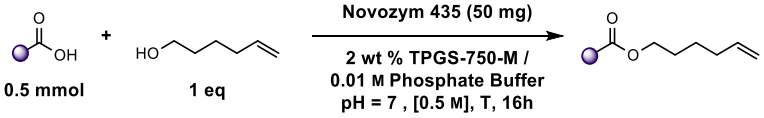
A general procedure for the hydrolysis study was performed as follows:

A 1-dram glass vial was charged with carboxylic acid methyl ester (0.5 mmol, 1 equiv), and alcohol (x equiv) if required, enzyme (50 mg) and magnetic stir bar. Aqueous reaction medium was then added to the desired concentration and the vial capped and set into an aluminum heating block on magnetic stirrer set

to the desired temperature. The reaction was tracked by extracting an aliquot and TLC analysis as above. Upon completion, water was added to make the total aqueous volume of 1 mL (if necessary) and 1 mL of extraction solvent (2-MeTHF, MTBE, toluene or DCM) was added to the vial. The capped vial was then centrifuged and the organic layer transferred into a vial containing internal standard (28.0 mg of 1,3,5-trimethoxybenzene per 0.5 mmol of acid). The extraction was repeated until the organic layer no longer showed material via TLC analysis (typically 3 x 1 mL extraction was adequate). The organic layer was dried under vacuum and analyzed by q^{1}H NMR.

Additional Optimizations

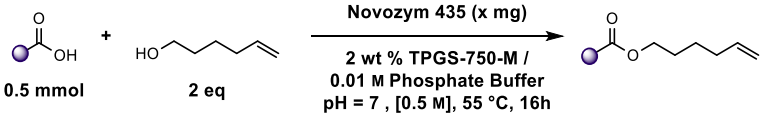
Effect of reaction temperature on yield of esterification:



A 1-dram glass vial was charged with phenylpropionic acid (75 mg, 0.5 mmol, 1 equiv), alcohol (50.1 mg, 1 equiv, 60.0 µL), Novozym 435 (500 units, 100 mg) and magnetic stir bar. 1 mL of 2 wt % TPGS-750-M/0.01 M phosphate buffer (pH = 7) was then added and the vial capped and set into an aluminum heating block on magnetic stirrer set to the desired temperature. The reaction was tracked by extracting an aliquot and TLC analysis as above. Upon completion, water was added to make the total aqueous volume of 1 mL (if necessary) and 1 mL of extraction solvent (2Me-THF, MTBE, toluene or DCM) was added to the vial. The capped vial was then centrifuged to separate the layers and the organic layer transferred into a vial containing internal standard (28.0 mg of 1,3,5-trimethoxybenzene per 0.5 mmol of acid). The extraction was repeated until the organic layer no longer showed material via TLC analysis (typically 3 x 1 mL extraction was adequate). The organic layer was dried under vacuum and analyzed by q^{1}H NMR.

Block Temperature	^{1}H NMR Yield
35 °C	47%
45 °C	54%
55 °C	62%
65 °C	55%
75 °C	trace

Effect of enzyme loading on yield of esterification:

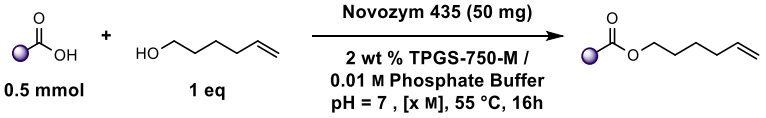


A 1-dram glass vial was charged with phenylpropionic acid (75 mg, 0.5 mmol, 1 equiv), alcohol (100.2 mg, 2 equiuv, 120.0 µL), Novozym 435 (to desired loading) and magnetic stir bar. 1 mL of 2 wt % TPGS-750-M/0.01 M phosphate buffer (pH = 7) was then added and the vial capped and set into an aluminum heating block on magnetic stirrer set to 55 °C. The reaction was tracked by extracting an aliquot and TLC analysis as above. Upon completion, water was added to make the total aqueous volume of 1 mL (if necessary) and 1 mL of extraction solvent (2Me-THF, MTBE, toluene or DCM) was added to the vial. The capped vial

was then centrifuged to separate the layers and the organic layer transferred into a vial containing internal standard (28.0 mg of 1,3,5-trimethoxybenzene per 0.5 mmol of acid). The extraction was repeated until the organic layer no longer showed material via TLC analysis (typically 3 x 1 mL extraction was adequate). The organic layer was dried under vacuum and analyzed by q^{1}H NMR.

Loading (units/mg)	^{1}H NMR Yield
500u /100 mg	85%
250u / 50 mg	84%
125u / 25 mg	61%

Effect of concentration on yield of esterification:



A 1-dram glass vial was charged with phenylpropionic acid (75 mg, 0.5 mmol, 1 equiv), alcohol (100.2 mg, 2 equiv, 120.0 µL), Novozym 435 (500 units, 100 mg) and magnetic stir bar. Water was then added to the desired concentration and the vial capped and set into an aluminum heating block on magnetic stirrer set to the desired temperature. The reaction was tracked by extracting an aliquot and TLC analysis as above. Upon completion, water was added to make the total aqueous volume of 1mL (if necessary) and 1 mL of extraction solvent (2-Me-THF, MTBE, toluene or DCM) was added to the vial. The capped vial was then centrifuged to separate the layers and the organic layer transferred into a vial containing internal standard (28.0 mg of 1,3,5-trimethoxybenzene per 0.5 mmol of acid). The extraction was repeated until the organic layer no longer showed material via TLC analysis (typically 3 x 1 mL extraction was adequate). The organic layer was dried under vacuum and analyzed by q^{1}H NMR spectroscopy.

Concentration	^{1}H NMR Yield
1 M	85%
0.5 M	83%
0.25 M	78%
0.1 M	65%

3. General Procedures

General Procedure A – General Alcohols

A 1-dram vial equipped with Teflon-coated magnetic stir bar was charged with carboxylic acid (0.5 mmol, 1 equiv), alcohol (1.0 mmol, 2 equiv) and Novozym 435 (50 mg). 500 µL of deionized (DI) water or an aqueous 2 wt % solution of TPGS-750-M (described in section 1) was added. The vial was capped and then set to stir (~30 s) before being centrifuged briefly (~30 s) on a bench centrifuge if material was found: to be adhering to the walls of the vial. The vial was then set to react for 12 h in an aluminum heating block preheated to 55 °C. Upon completion, the reaction was removed from heating and stirring before being allowed to cool to rt and then extracted with 3 x 1 mL of an appropriate extraction solvent (typically 2-Me THF, MTBE, toluene, or DCM). The crude extracts were concentrated under vacuum onto silica gel and then purified by column chromatography.

General Procedure B – Water Soluble Alcohols

A 1-dram vial equipped with a Teflon-coated magnetic stir bar was charged with carboxylic acid (0.5 mmol, 1 equiv), and Novozym 435 (50 mg). 500 µL of deionized (DI) water or an aqueous 2 wt % solution of TPGS-750-M (described in section 1) was added, followed by the alcohol (5.0 mmol, 10 equiv). The vial was capped and then set to stir (~30s) before being centrifuged briefly (~30s) on a bench centrifuge if material was found to be adhering to the walls of the vial. The vial was then set to react for 12 h in an aluminum heating block preheated to 55 °C. Upon completion, the reaction was removed from heating and stirring before being allowed to cool to rt and then extracted with 3 x 1 mL of an appropriate extraction solvent (typically 2-MeTHF, MTBE, toluene, or DCM). The crude extracts were concentrated under vacuum onto silica gel and then purified by column chromatography.

Note: For methanol and ethanol, the rate of stirring has a great effect on the extent of conversion. Rates of stirring were set to no higher than 700 rpm as greater stir rates resulted in mechanical degradation of the beads and dramatic reductions in yield.

4. Green Metrics Calculations

Complete E-Factors for recycling study

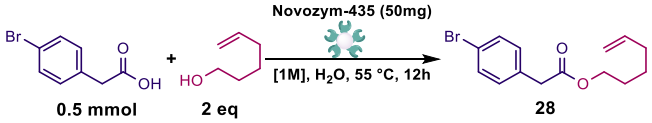
Complete E-Factors represent the ratio of total mass of material input (including starting materials) over mass of product outputs given by the following equation.

$$\frac{\sum \text{Mass of Starting Materials} + \text{Mass of Catalyst} + \text{Mass of Solvent} - \text{Mass Product}}{\text{Mass of Product}}$$

Or more specifically in our case for esterification:

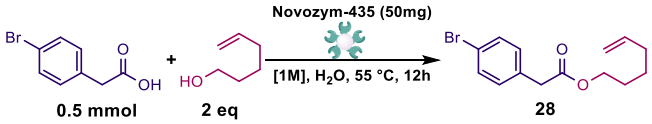
$$\frac{\text{Mass of Acid} + \text{Mass of Alcohol} + \text{Mass of Catalyst} + \text{Mass of Water} - \text{Mass of Product}}{\text{Mass of Product}}$$

Example calculations – Initial reaction



$$\text{cEF} = \frac{107.5\ \text{mg} + 100.16\ \text{mg} + 50\ \text{mg} + 500\ \text{mg} - 125.6\ \text{mg}}{125.6\ \text{mg}} = 4.67$$

Example calculations – First recycle



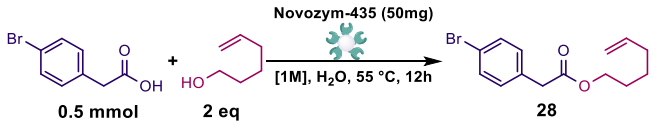
$$\text{cEF} = \frac{107.5\ \text{mg} + 100.16\ \text{mg} - 121.4}{121.4\ \text{mg}} = 0.72$$

Process Mass Intensity for recycling study

Reaction was carried out according to general procedure A and extracted with 3 x 1mL of 2-MeTHF (ρ = 0.854 mg/mL). Each reaction was purified over a short plug of silica in glass pipette using 3 mL of 10% EtOAc (ρ = 0.902 mg/mL) in hexanes (0.661 mg/mL) to elute.

$$\frac{\sum \text{Mass (Starting Materials} + \text{ Catalyst} + \text{ Solvent} + \text{ Extraction Solvent} + \text{Purification Solvent)}}{\text{Mass of Product}}$$

Example calculation: Initial Reaction



$$\frac{\sum \text{Mass of Starting Material} + \text{Mass of Catalyst} + \text{Mass of Water} + \text{ Mass 3mL 2meTHF} + \text{Mass 0.15mL Ethyl Acetate} + \text{Mass 2.85mL Hexanes}}{\text{Mass of Product}}$$

$$\frac{\sum 107.5\text{ mg}+100.12\text{ mg}+50\text{ mg}+500\text{mg}+2562\text{mg}+135.3\text{ mg}+4311.6\text{mg}}{125.6\text{ mg}} = 42.5$$

5. Recycling Study

Initial Reaction:

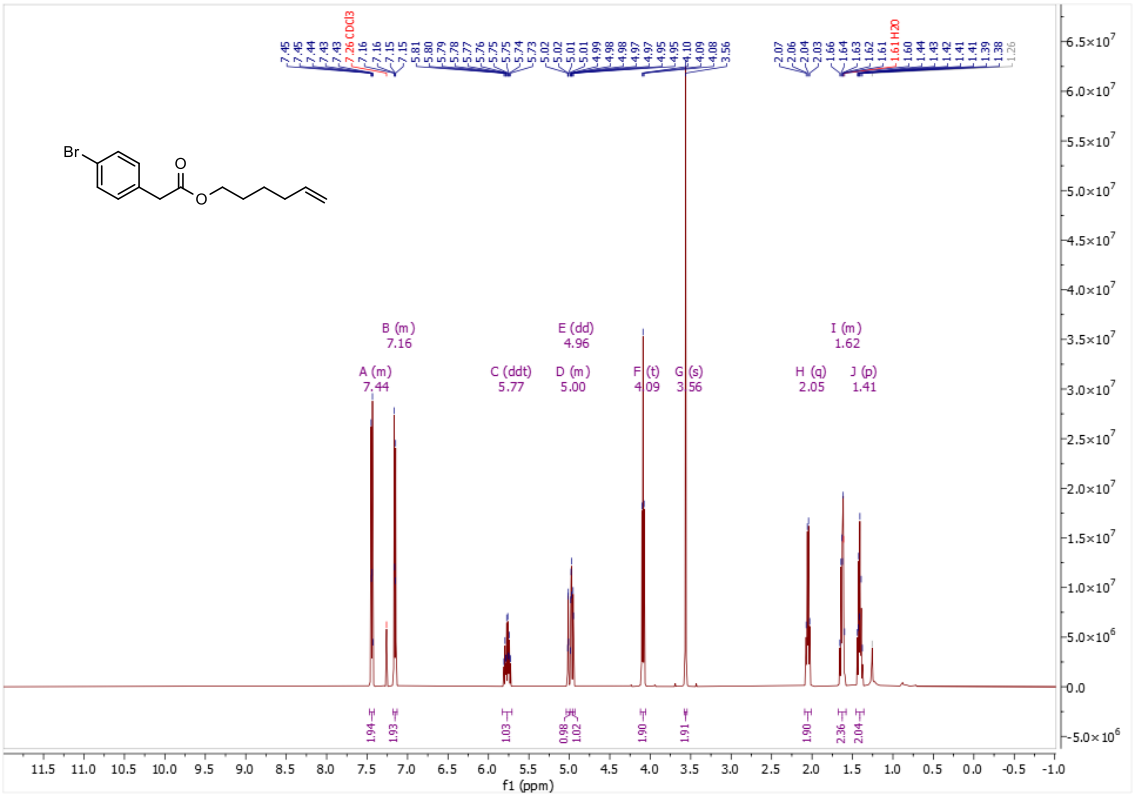
A 1-dram vial equipped with Teflon-coated magnetic stir bar was charged with 4-bromo phenylacetic acid (107.5 mg, 0.5 mmol, 1 equiv), 5-hexen-1-ol (100.16 mg, 1.0 mmol, 2 equiv) and Novozym 435 (50 mg). 500 µL of deionized (DI) water was added. The vial was capped and then set to stir for 12 h in an aluminum heating block preheated to 55 °C. Upon completion, the reaction was removed from heating and stirring before being allowed to cool to rt and then extracted with 3 x 1 mL of 2-MeTHF. The crude extracts were concentrated under vacuum onto silica gel and then purified by elution with 3 mL of 5% EtOAc/hexanes over a short (~4 cm) plug of silica in a glass pipette plugged with cotton.

1st and 2nd Recycles:

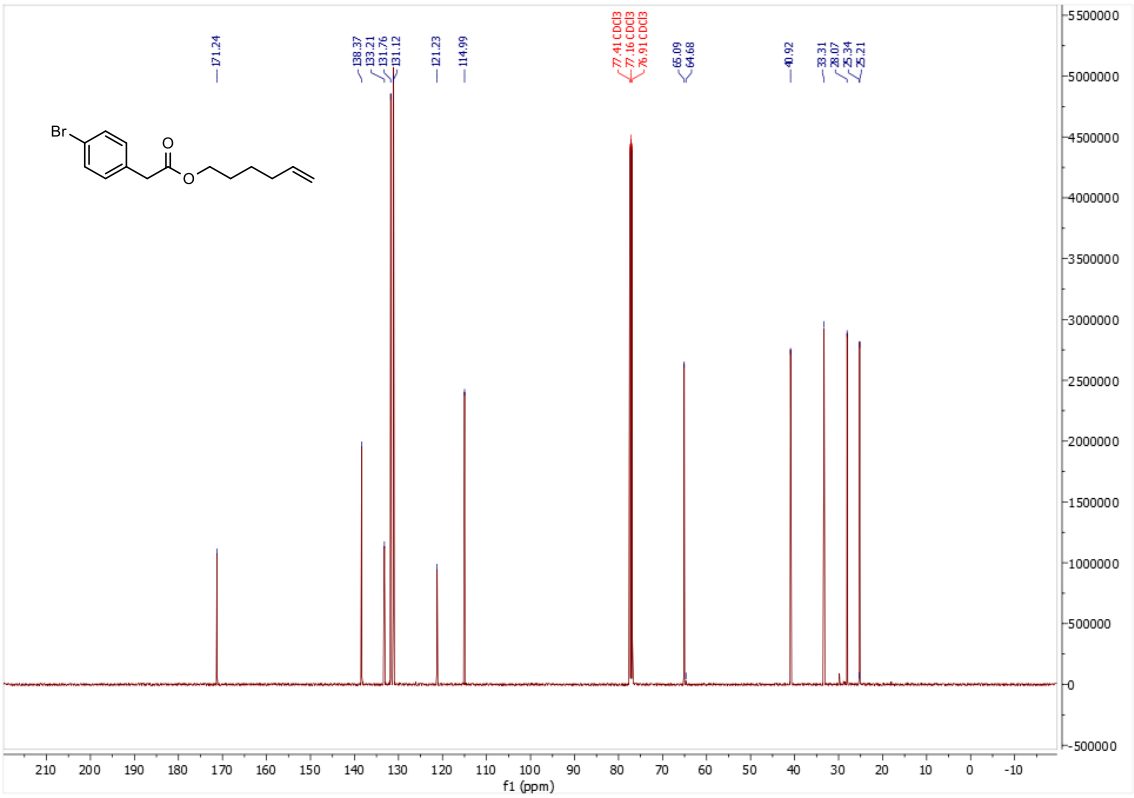
To the aqueous medium containing Novozym-435, 4-bromo phenylacetic acid (107.5 mg, 0.5 mmol, 1 equiv) and 5-hexen-1-ol (100.16 mg, 1.0 mmol, 2 equiv) were added. The vial was capped and then set to stir for 12 h in an aluminum heating block preheated to 55 °C. Upon completion, the reaction was removed from heating and stirring before being allowed to cool to rt and then extracted with 3 x 1 mL of 2-MeTHF. The crude extracts were concentrated under vacuum onto silica gel and then purified by elution with 3 mL of 5% EtOAc/hexanes over a short (~4 cm) plug of silica in a glass pipette plugged with cotton.

Characterization data for hex-5-en-1-yl 2-(4-bromophenyl)acetate **28**

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 – 7.41 (m, 2H), 7.18 – 7.13 (m, 2H), 5.77 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.04 – 4.96 (m, 1H), 4.96 (dd, *J* = 10.5, 2.0 Hz, 1H), 4.09 (t, *J* = 6.6 Hz, 2H), 3.56 (s, 2H), 2.05 (q, *J* = 7.2 Hz, 2H), 1.67 – 1.58 (m, 2H), 1.41 (p, *J* = 7.6 Hz, 2H). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 171.24, 138.37, 133.21, 131.76, 131.12, 121.23, 114.99, 77.41, 77.16, 76.91, 65.09, 64.68, 40.92, 33.31, 28.07, 25.34, 25.21.



^{1}H NMR of hex-5-en-1-yl 2-(4-bromophenyl)acetate (**28**).



^{13}C NMR of hex-5-en-1-yl 2-(4-bromophenyl)acetate (**28**).

6. Immobilization of Enzymes

To compare with their lyophilized or glycerol stock forms, the lipases from *R. miehie, B. cepacia, C. Rugosa,* and *R. niveus* were immobilized onto Lewatit 1600 VPOC according to the modified procedure from Tecelao, *et. al.* below. Immobilized lipases from *C. antarctica A* and *R. oryzae* were received as a kind gift from Anthem Biosciences Pvt. Ltd.

The immobilization procedure was modified from *Biochemical Engineering Journal*, 2012, **67**, 104-110.

Llyophilized enzymes (250 mg) were first suspended in 1 mL 0.05 M potassium phosphate buffer pH = 7.4. For glycerol stocks of enzymes, 1mL was used.

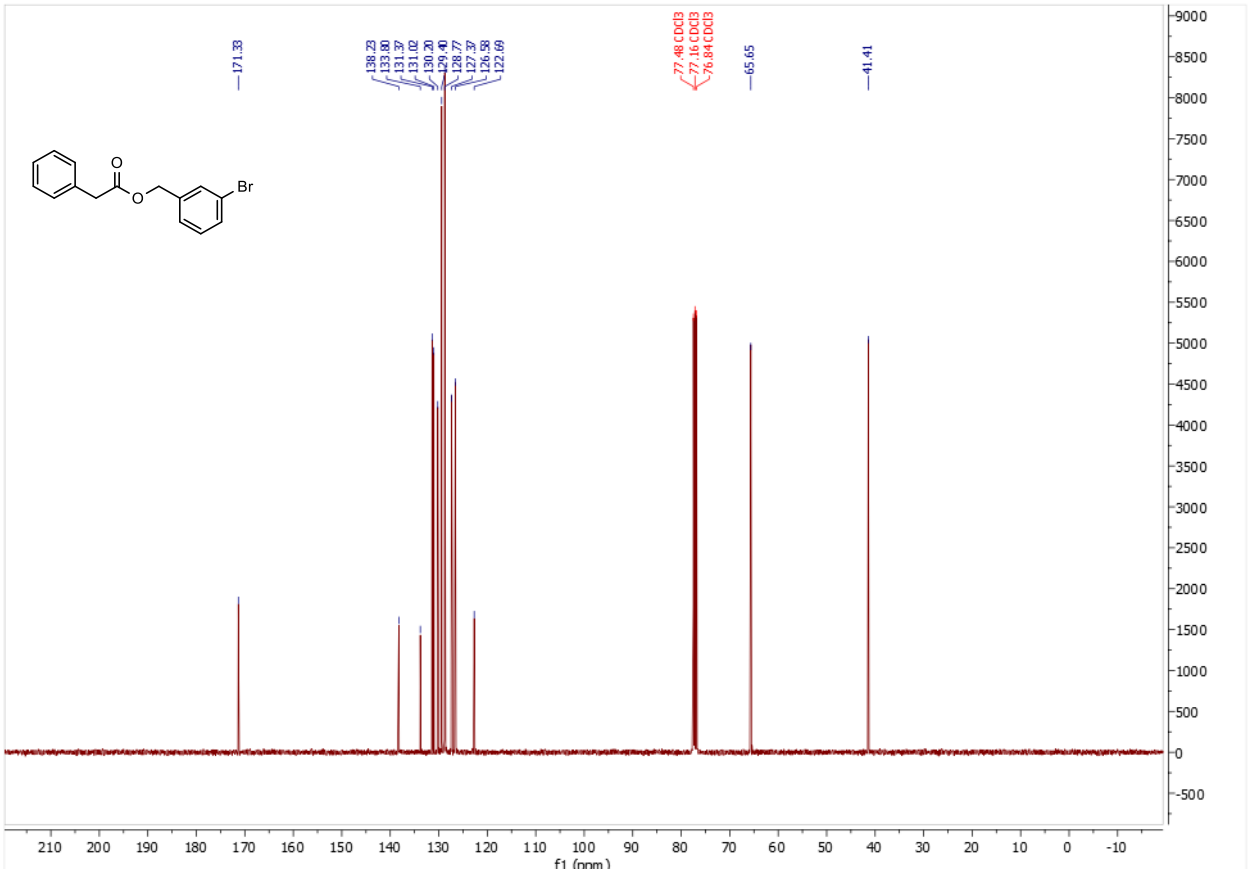
1 mL of enzyme solution was diluted with 1 mL of 0.05 M potassium phosphate buffer pH = 7.4 to which was added 500 mg of Lewatit VP OC 1600. This suspension was then shaken on an orbital shaker at rt overnight. The liquid was removed from the beads by micropipette and 5 mL of 0.05 M potassium phosphate buffer pH = 7.4 containing 2.5% glutaraldehyde was added and shaken on orbital shaker for 2h. The beads were then separated by vacuum filtration and stored in the fridge until use.

7. Characterization of Compounds

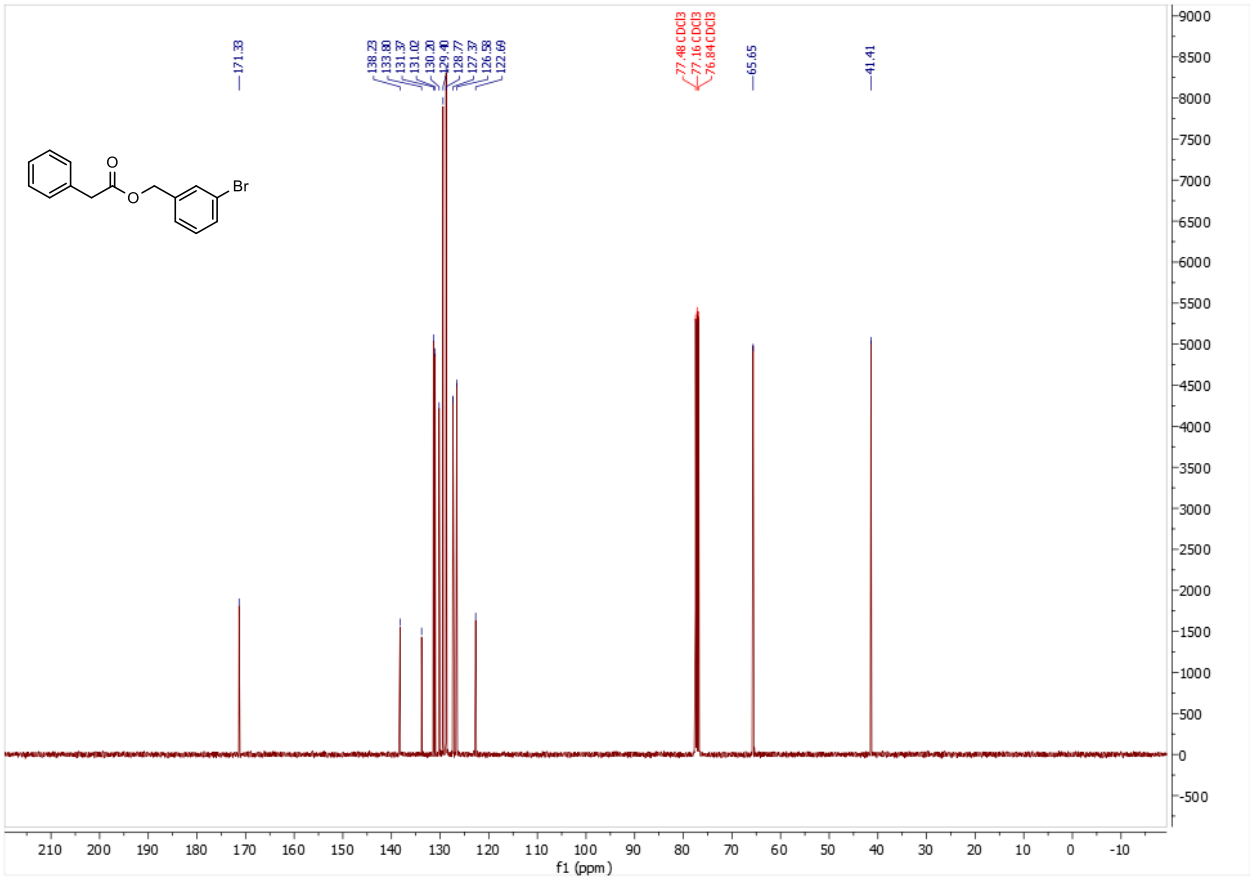
1. 3-Bromobenzyl 2-phenylacetate

General procedure A to yield **1** (140.4 mg, 92%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (q, *J* = 2.4 Hz, 2H), 7.40 – 7.26 (m, 5H), 7.26 – 7.16 (m, 2H), 5.10 (s, 2H), 3.69 (s, 2H). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 171.33, 138.23, 133.80, 131.37, 131.02, 130.20, 129.40, 128.77, 127.37, 126.58, 122.69, 65.65, 41.41. **Chemical Formula**: HRMS (EI) *m/z*: [M]+ calcd. for $C_{15}H_{13}BrO_2$: 304.0099; found: 304.0112 (4.3 ppm).



^{1}H NMR of 3-bromobenzyl 2-phenylacetate (**1**).

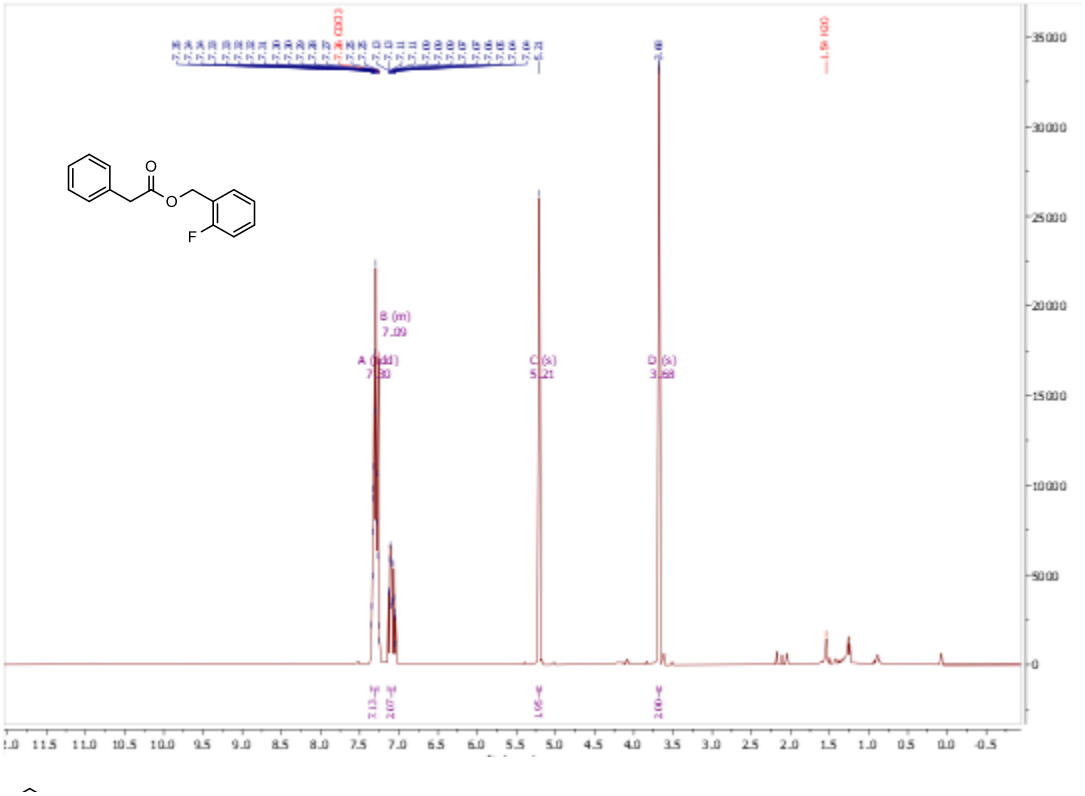


^{13}C NMR of 3-bromobenzyl 2-phenylacetate (**1**).

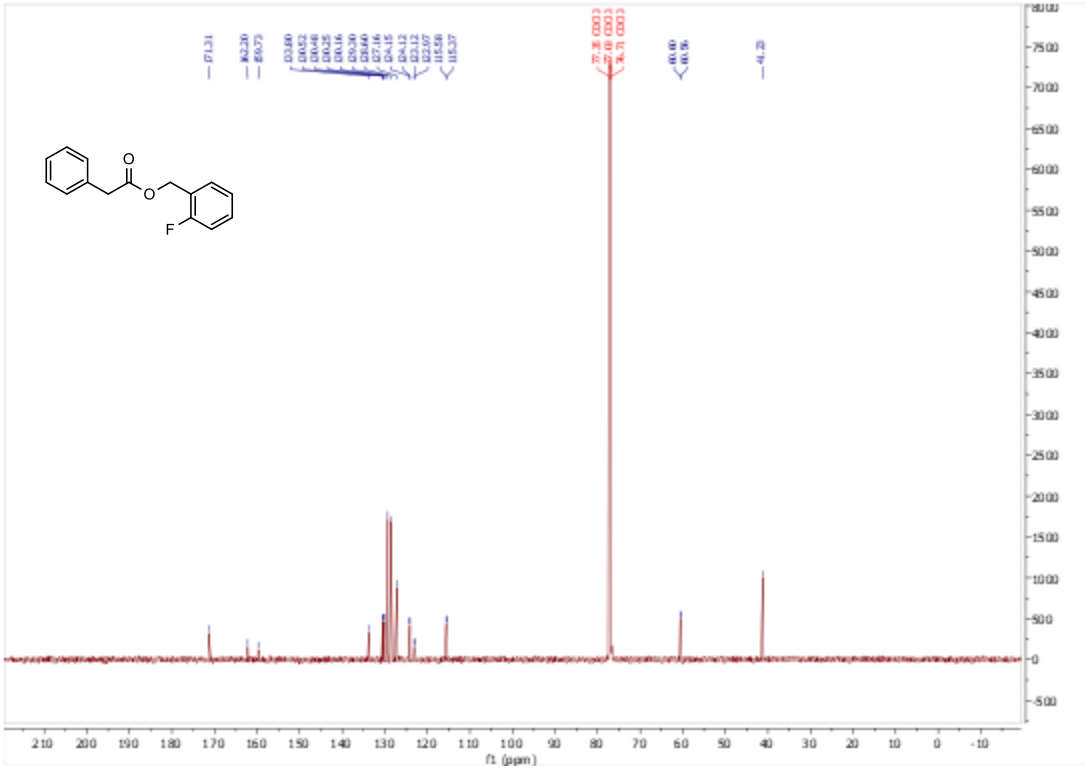
2. 2-Fluorobenzyl 2-phenylacetate

General procedure A with TPGS-750-M to yield **2** (20.8 mg, 17% yield).

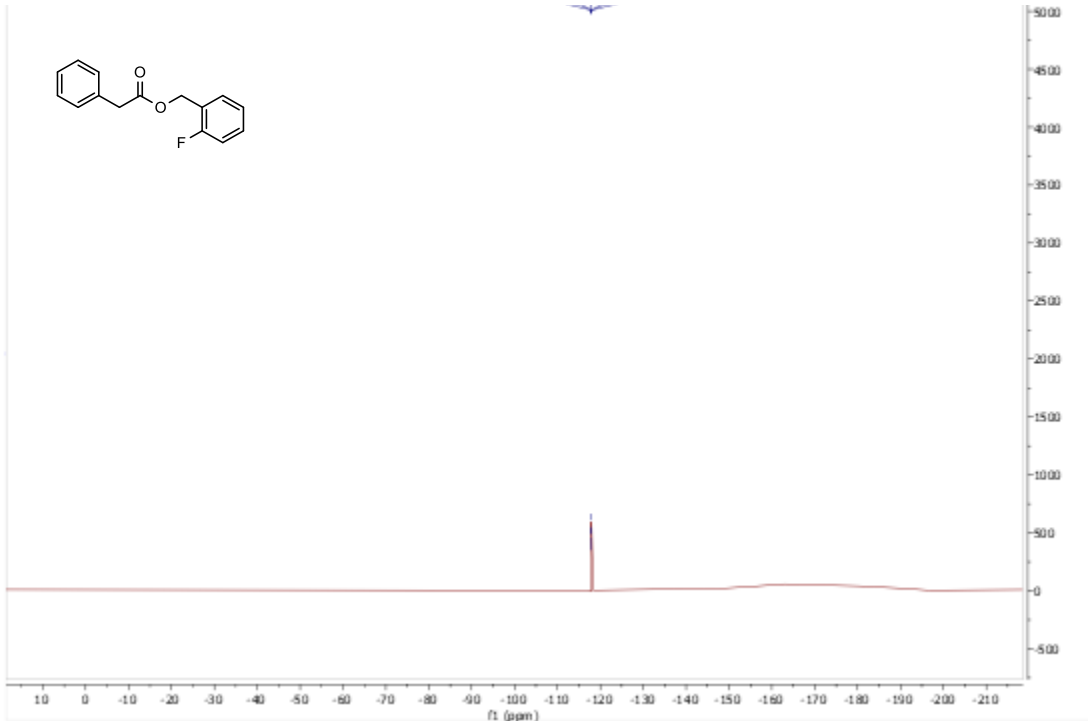
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (tdd, *J* = 10.7, 6.6, 4.0 Hz, 7H), 7.14 – 7.04 (m, 2H), 5.21 (s, 2H), 3.68 (s, 2H). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 171.31, 162.20, 159.73, 133.80, 130.52, 130.48, 130.25, 130.16, 129.30, 128.60, 127.16, 124.15, 124.12, 123.12, 122.97, 115.58, 115.37, 60.60, 60.56, 41.23. **^{19}F NMR (376 MHz, $CDCl_3$) δ** -117.93 (dt, *J* = 12.3, 6.1 Hz). **Chemical Formula**: HRMS (ESI) *m/z*: [M+Na]+ calcd. for $NaC_{15}H_{13}FO_2$: 267.0798; found: 267.0802 (1.5 ppm).



^{1}H NMR of 2-fluorobenzyl 2-phenylacetate (**2**).



^{13}C NMR of 2-fluorobenzyl 2-phenylacetate (**2**).

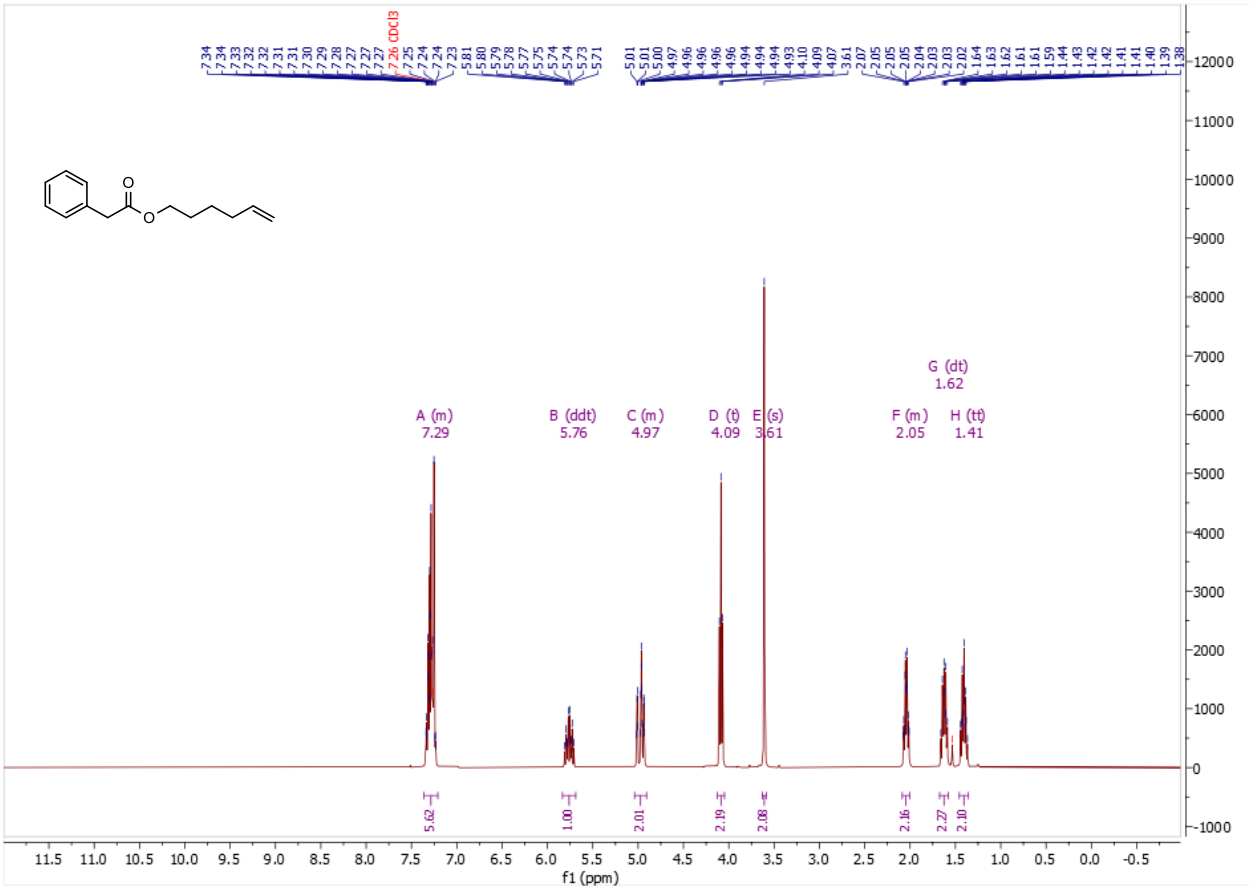


^{19}F NMR of 2-fluorobenzyl 2-phenylacetate (**2**).

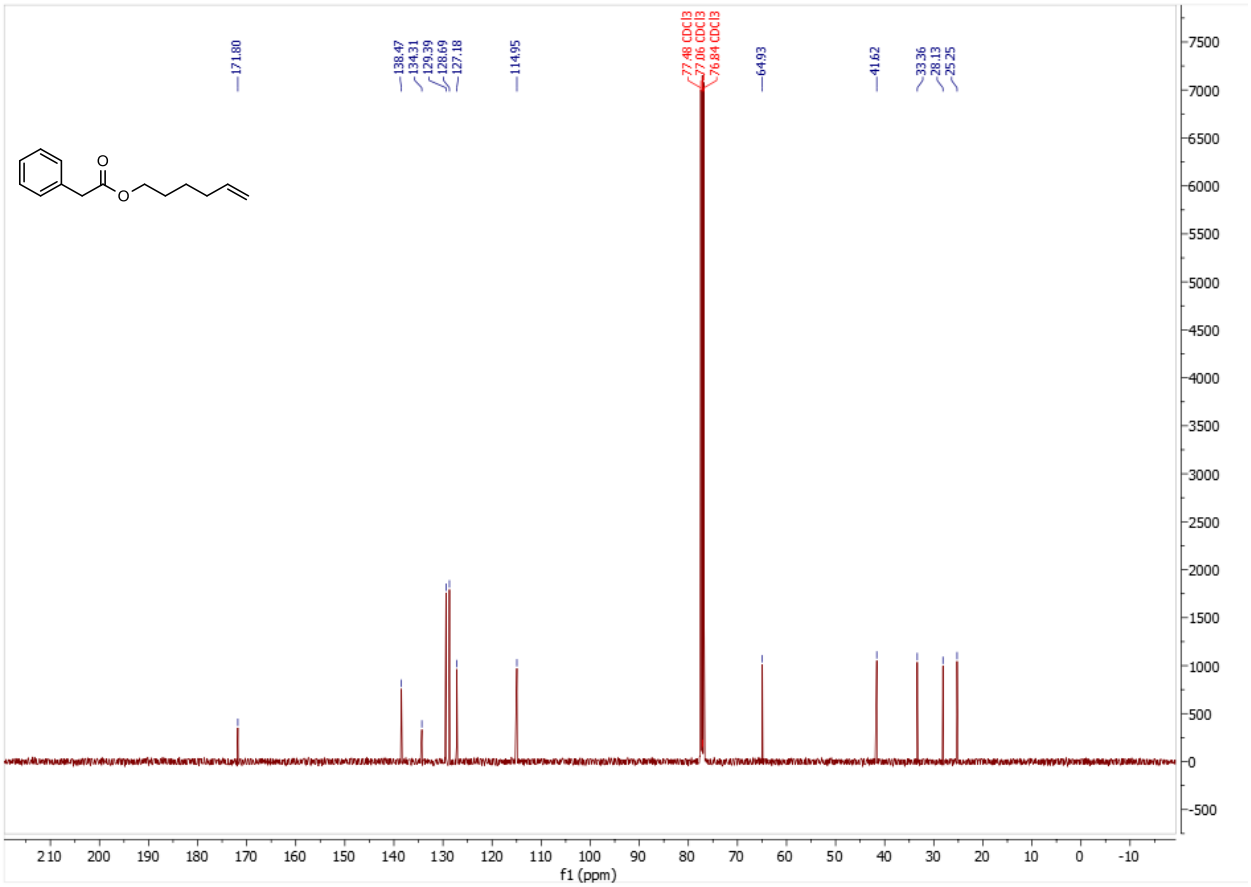
3. Hex-5-en-1-yl 2-phenylacetate

General procedure A with to yield **3** (93.9 mg, 86% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.21 (m, 6H), 5.76 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.04 – 4.91 (m, 2H), 4.09 (t, *J* = 6.6 Hz, 2H), 3.61 (s, 2H), 2.09 – 2.00 (m, 2H), 1.62 (dt, *J* = 14.9, 6.8 Hz, 2H), 1.41 (tt, *J* = 10.1, 6.4 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 171.80, 138.47, 134.31, 129.39, 128.69, 127.18, 114.95, 64.93, 41.62, 33.36, 28.13, 25.25. **Chemical Formula**: HRMS (ESI) *m/z*: [M+Na]+ calcd. for $NaC_{14}H_{18}O_2$: 241.1205; found: 241.1207 (0.80 ppm).



^{1}H NMR of hex-5-en-1-yl 2-phenylacetate (**3**).

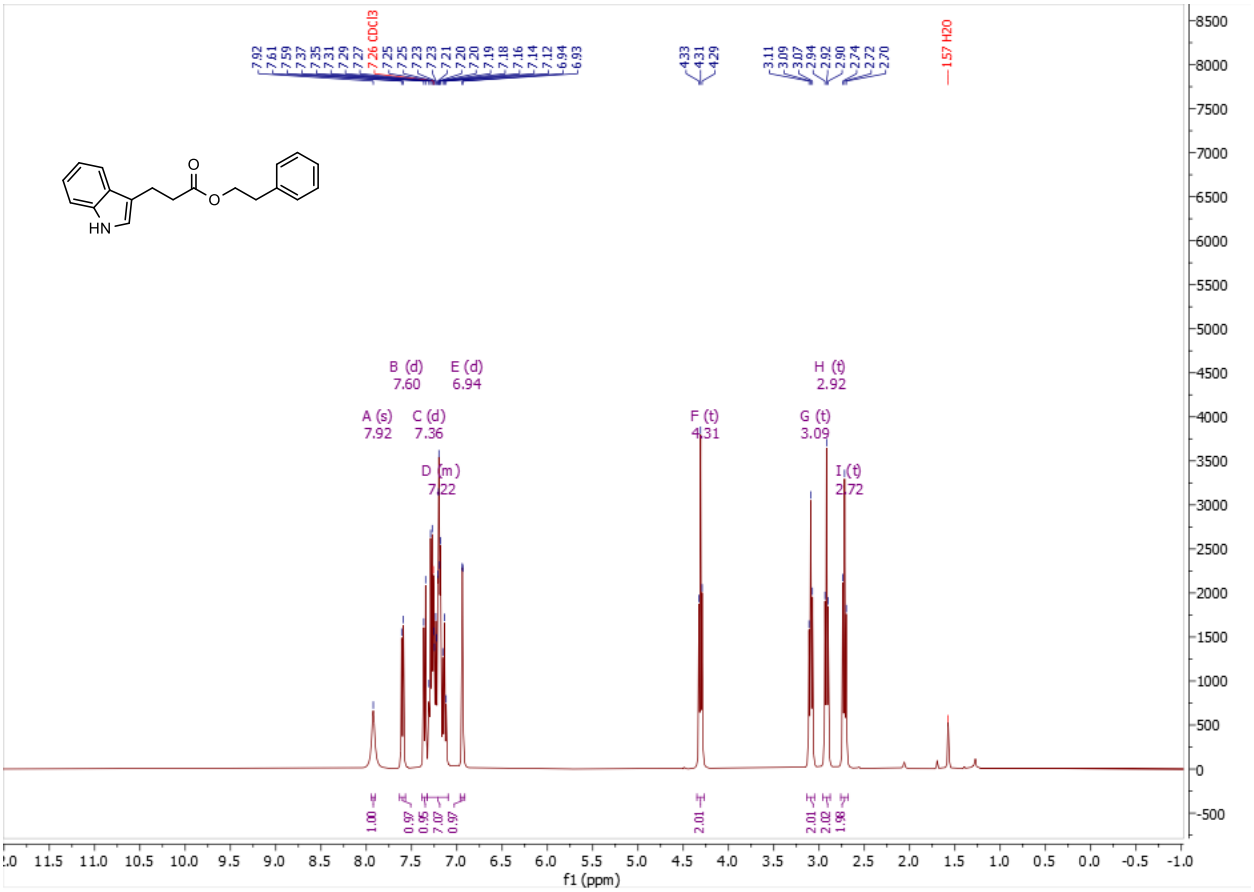


^{13}C NMR of hex-5-en-1-yl 2-phenylacetate (**3**).

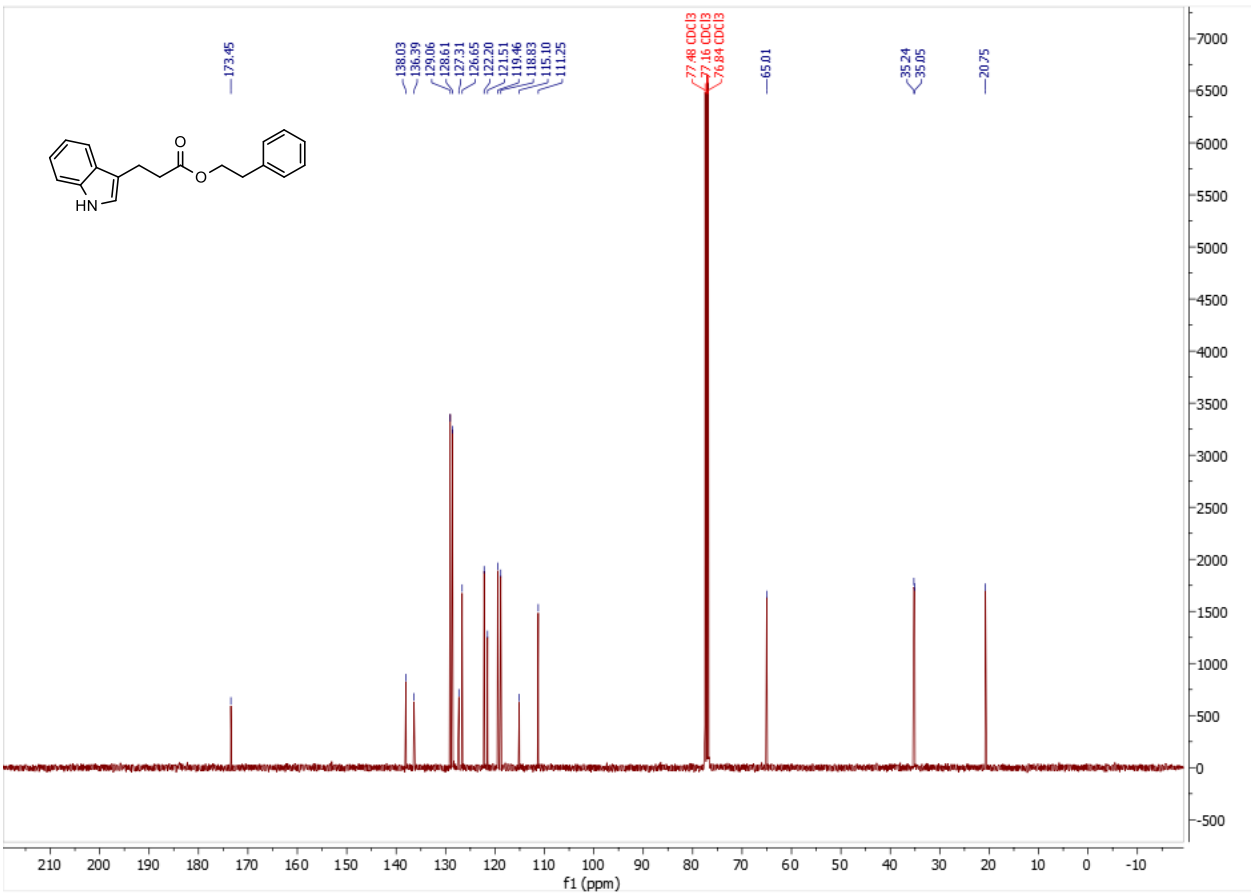
4. Phenethyl 3-(1H-indol-3-yl)propanoate

General procedure A to yield **4** (39.2 mg, 44% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.33 – 7.10 (m, 7H), 6.94 (d, *J* = 2.3 Hz, 1H), 4.31 (t, *J* = 7.0 Hz, 2H), 3.09 (t, *J* = 7.6 Hz, 2H), 2.92 (t, *J* = 7.0 Hz, 2H), 2.72 (t, *J* = 7.6 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 173.45, 138.03, 136.39, 129.06, 128.61, 127.31, 126.65, 122.20, 121.51, 119.46, 118.83, 115.10, 111.25, 65.01, 35.24, 35.05, 20.75. **Chemical Formula**: HRMS (ESI) *m/z*: [M+Na]+ calcd. for $NaC_{19}H_{19}NO_2$: 316.1314 ; found: 316.1315 (0.30 ppm).



^{1}H NMR of phenethyl 3-(1H-indol-3-yl)propanoate (**4**).

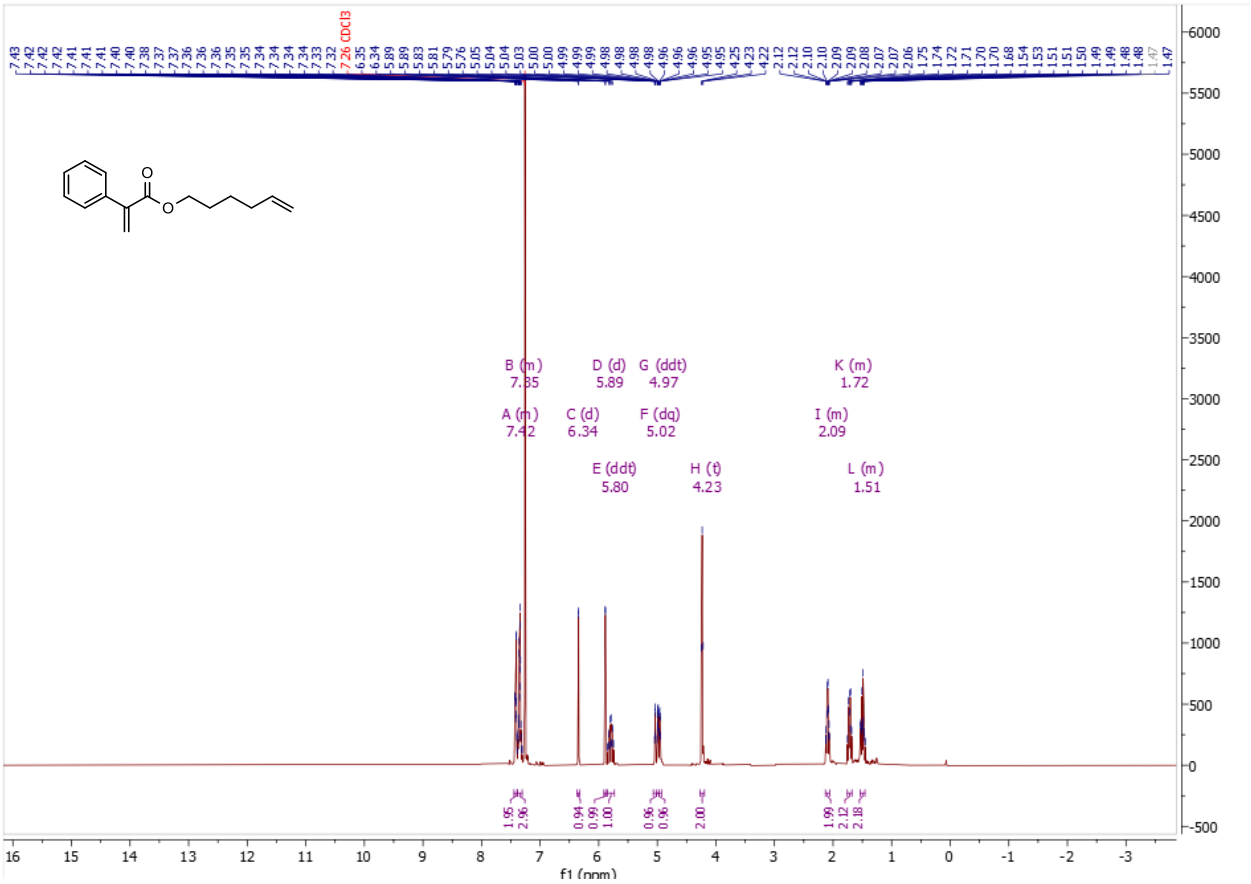


^{13}C NMR of phenethyl 3-(1H-indol-3-yl)propanoate (**4**).

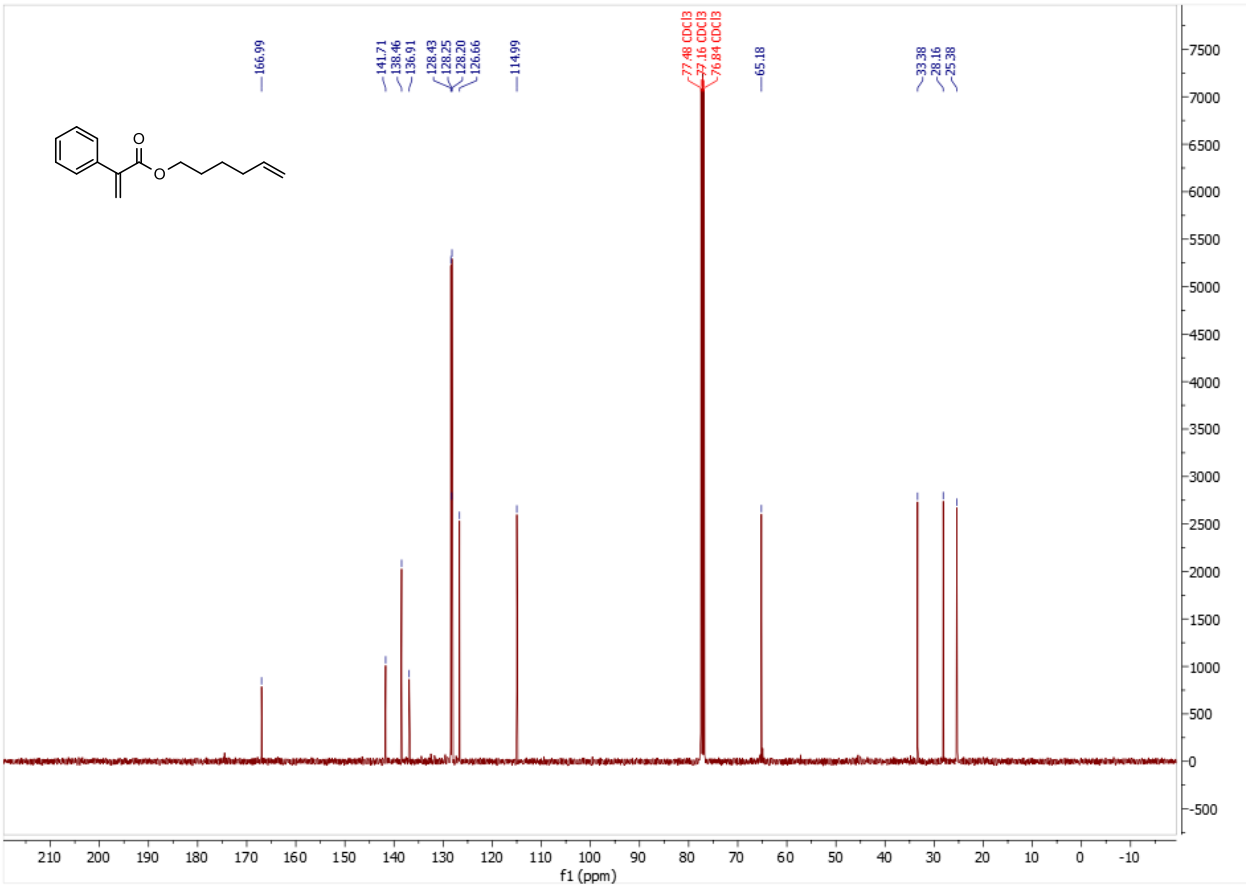
5. Hex-5-en-1-yl 2-phenylacrylate

General procedure A to yield **5** (67.9 mg, 59% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.39 (m, 2H), 7.39 – 7.31 (m, 3H), 6.34 (d, *J* = 1.3 Hz, 1H), 5.89 (d, *J* = 1.3 Hz, 1H), 5.80 (ddt, *J* = 16.9, 10.1, 6.6 Hz, 1H), 5.02 (dq, *J* = 17.1, 1.7 Hz, 1H), 4.97 (ddt, *J* = 10.2, 2.2, 1.3 Hz, 1H), 4.23 (t, *J* = 6.6 Hz, 2H), 2.13 – 2.06 (m, 2H), 1.76 – 1.68 (m, 2H), 1.54 – 1.46 (m, 2H). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 166.99, 141.71, 138.46, 136.91, 128.43, 128.25, 128.20, 126.66, 114.99, 65.18, 33.38, 28.16, 25.38. **Chemical Formula**: HRMS (ESI) *m/z*: [2M+Na]+ calcd. for $NaC_{30}H_{36}O_4$: 483.2511; found: 483.2513 (0.40 ppm).



^{1}H NMR of hex-5-en-1-yl 2-phenylacrylate (**5**).

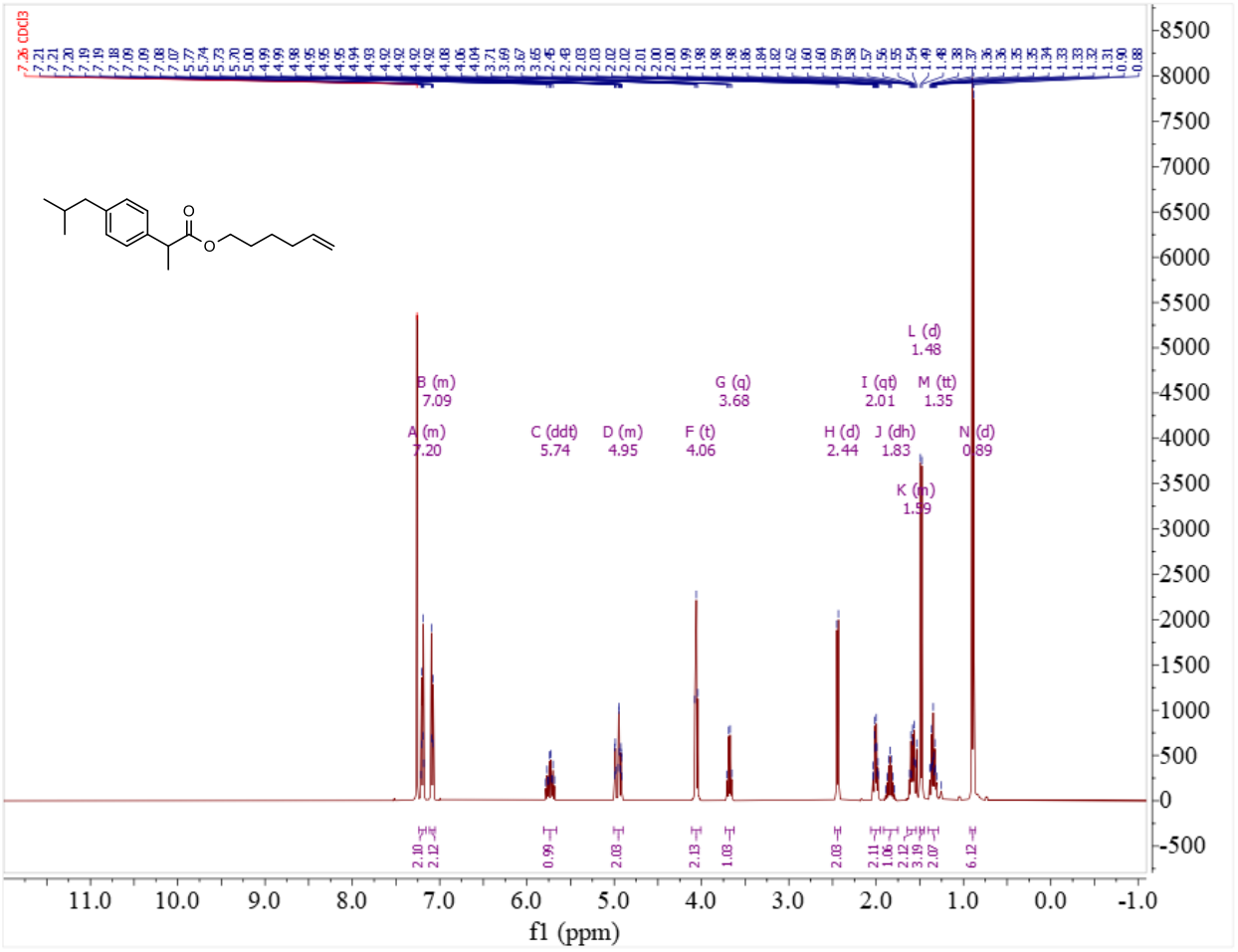


^{13}C NMR of hex-5-en-1-yl 2-phenylacrylate (**5**).

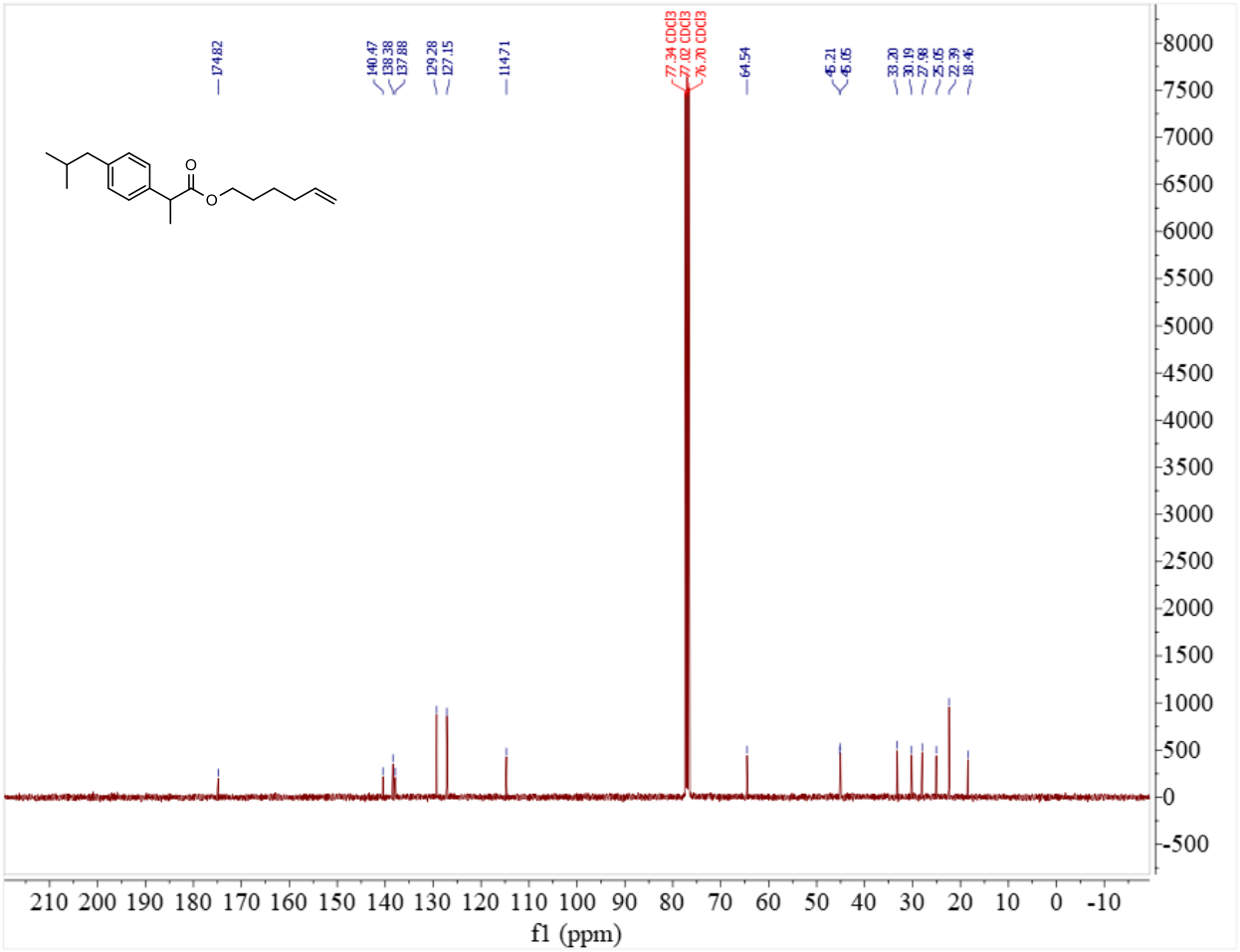
6. Hex-5-en-1-yl 2-(4-isobutylphenyl)propanoate

General procedure A to yield **6** (142.8 mg, 99% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.16 (m, 2H), 7.12 – 7.05 (m, 2H), 5.74 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.00 – 4.90 (m, 2H), 4.06 (t, *J* = 6.6 Hz, 2H), 3.68 (q, *J* = 7.1 Hz, 1H), 2.44 (d, *J* = 7.2 Hz, 2H), 2.01 (qt, *J* = 7.1, 1.4 Hz, 2H), 1.83 (dh, *J* = 13.3, 6.6 Hz, 1H), 1.64 – 1.54 (m, 2H), 1.48 (d, *J* = 7.2 Hz, 3H), 1.35 (tt, *J* = 9.9, 6.4 Hz, 2H), 0.89 (d, *J* = 6.7 Hz, 6H). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 174.82, 140.47, 138.38, 137.88, 129.28, 127.15, 114.71, 64.54, 45.21, 45.05, 33.20, 30.19, 27.98, 25.05, 22.39, 18.46. Spectral data are in agreement with data in *Org. Lett.* 2021, **23**, 2994–2999.



^{1}H NMR of hex-5-en-1-yl 2-(4-isobutylphenyl)propanoate (**4**).

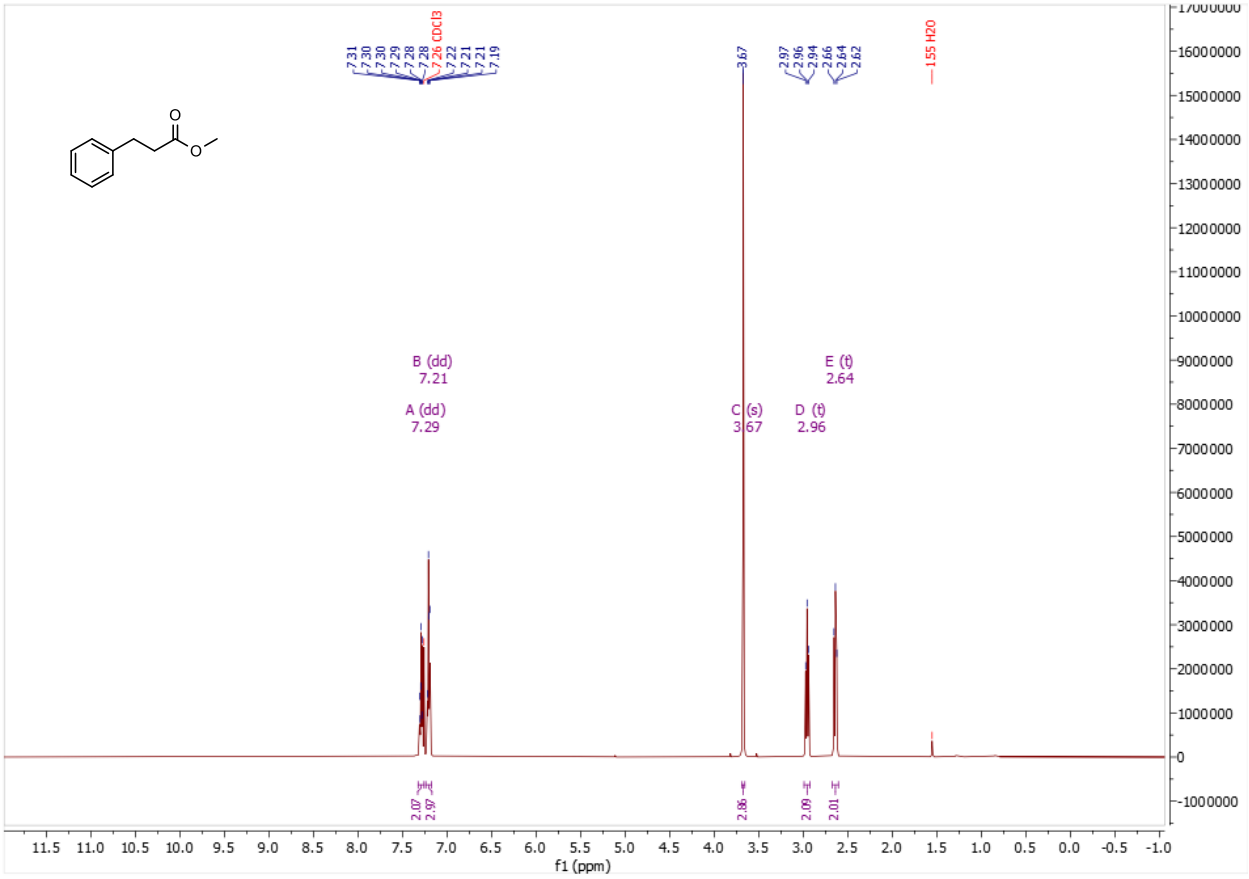


^{13}C NMR of hex-5-en-1-yl 2-(4-isobutylphenyl)propanoate (**4**).

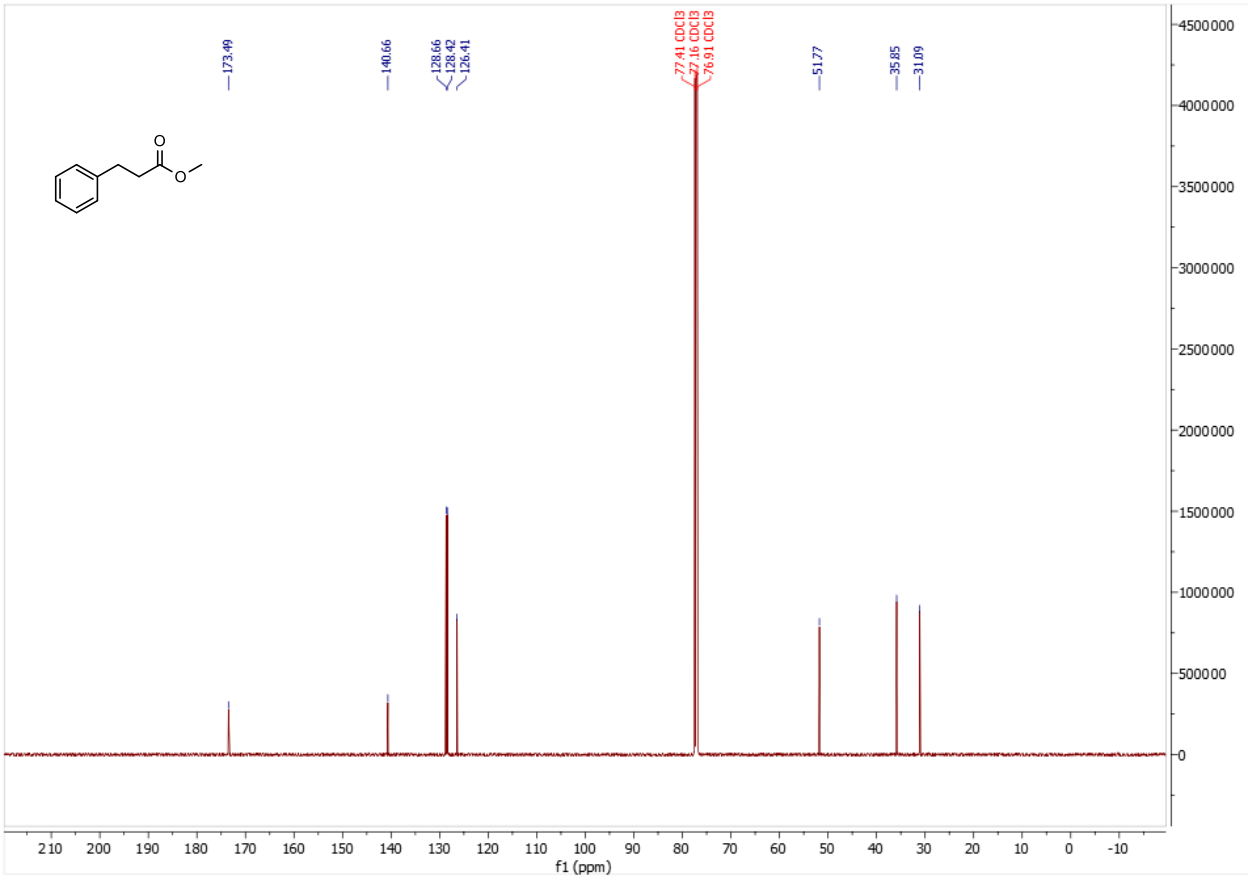
7. Methyl 3-phenylpropanoate

General procedure B to yield **7** (50.9 mg, 62% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (dd, *J* = 8.8, 6.5 Hz, 2H), 7.21 (dd, *J* = 7.8, 5.8 Hz, 3H), 3.67 (s, 3H), 2.96 (t, *J* = 7.9 Hz, 2H), 2.64 (t, *J* = 7.9 Hz, 2H). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 173.49, 140.66, 128.66, 128.42, 126.41, 51.77, 35.85, 31.09. Spectral data are in agreement with data in *J. Am. Chem. Soc.* 2023, **145**, 15680–15687.



^{1}H NMR of methyl 3-phenylpropanoate (**7**).

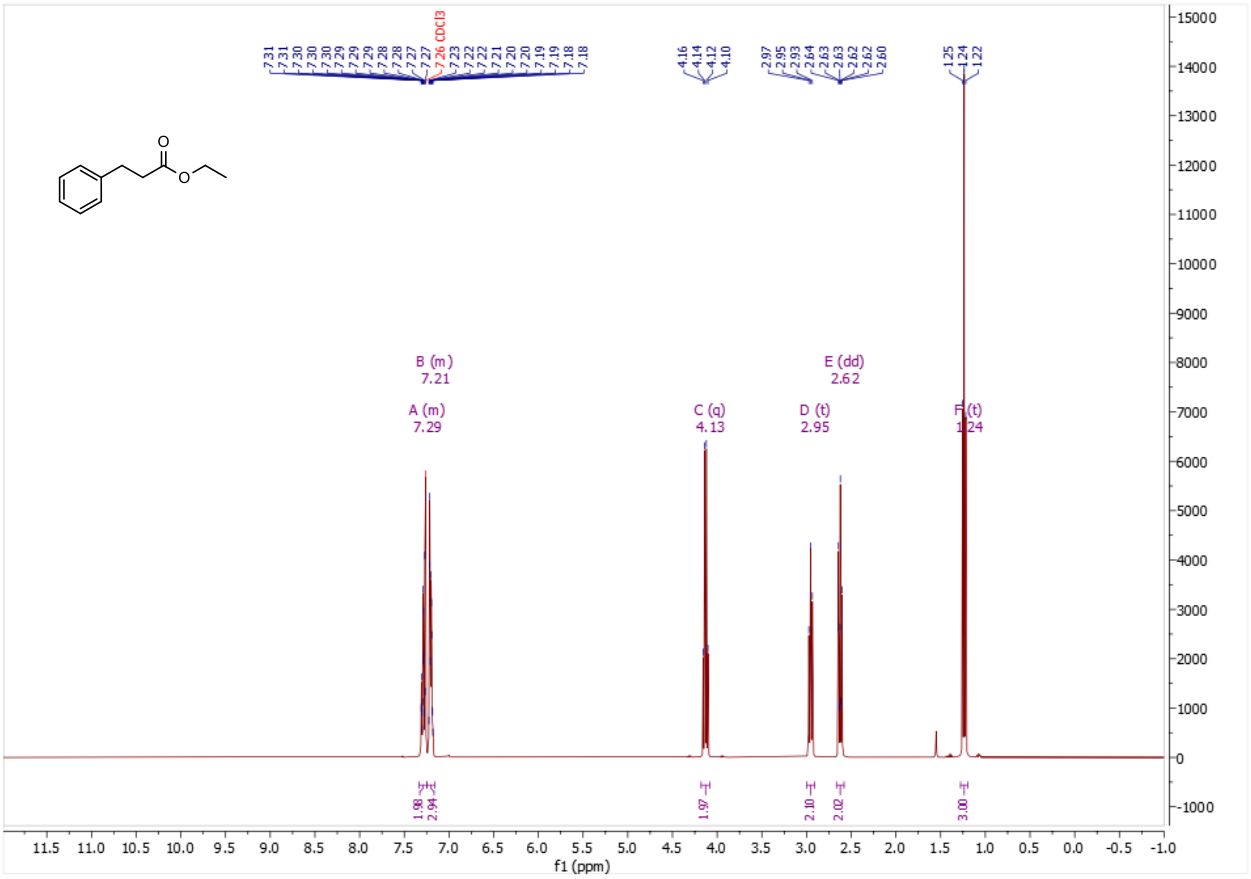


^{13}C NMR of methyl 3-phenylpropanoate (**7**).

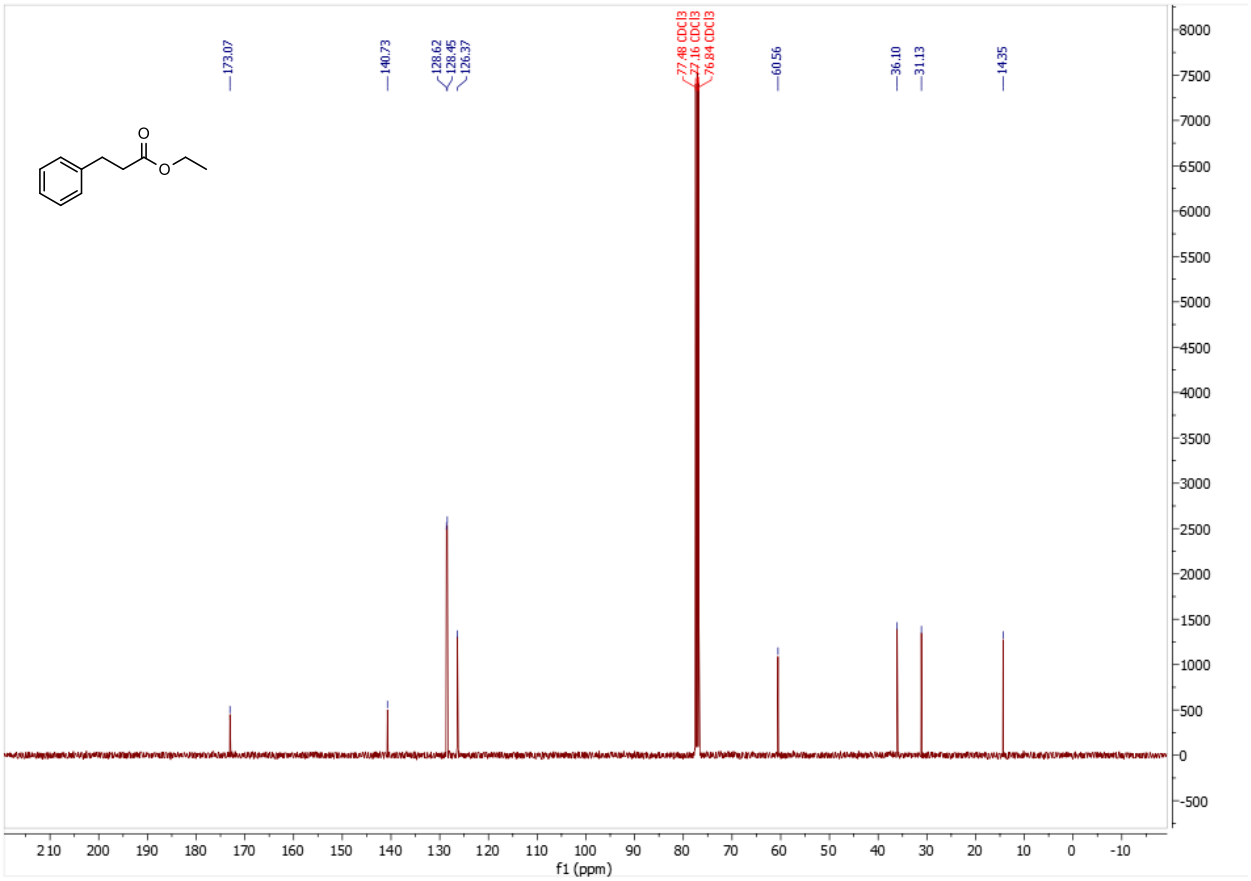
8. Ethyl 3-phenylpropanoate

General procedure B to yield **8** (74.9 mg, 84% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.24 (m, 2H), 7.25 – 7.16 (m, 3H), 4.13 (q, *J* = 7.1 Hz, 2H), 2.95 (t, *J* = 7.9 Hz, 2H), 2.62 (dd, *J* = 8.5, 7.2 Hz, 2H), 1.24 (t, *J* = 7.1 Hz, 3H).**^{13}C NMR (101 MHz, $CDCl_3$) δ** 173.07, 140.73, 128.62, 128.45, 126.37, 60.56, 36.10, 31.13, 14.35. Spectral data are in agreement with data in *J. Am. Chem. Soc.* 2023, **145**, 15680–15687.



^{1}H NMR of ethyl 3-phenylpropanoate (**8**).

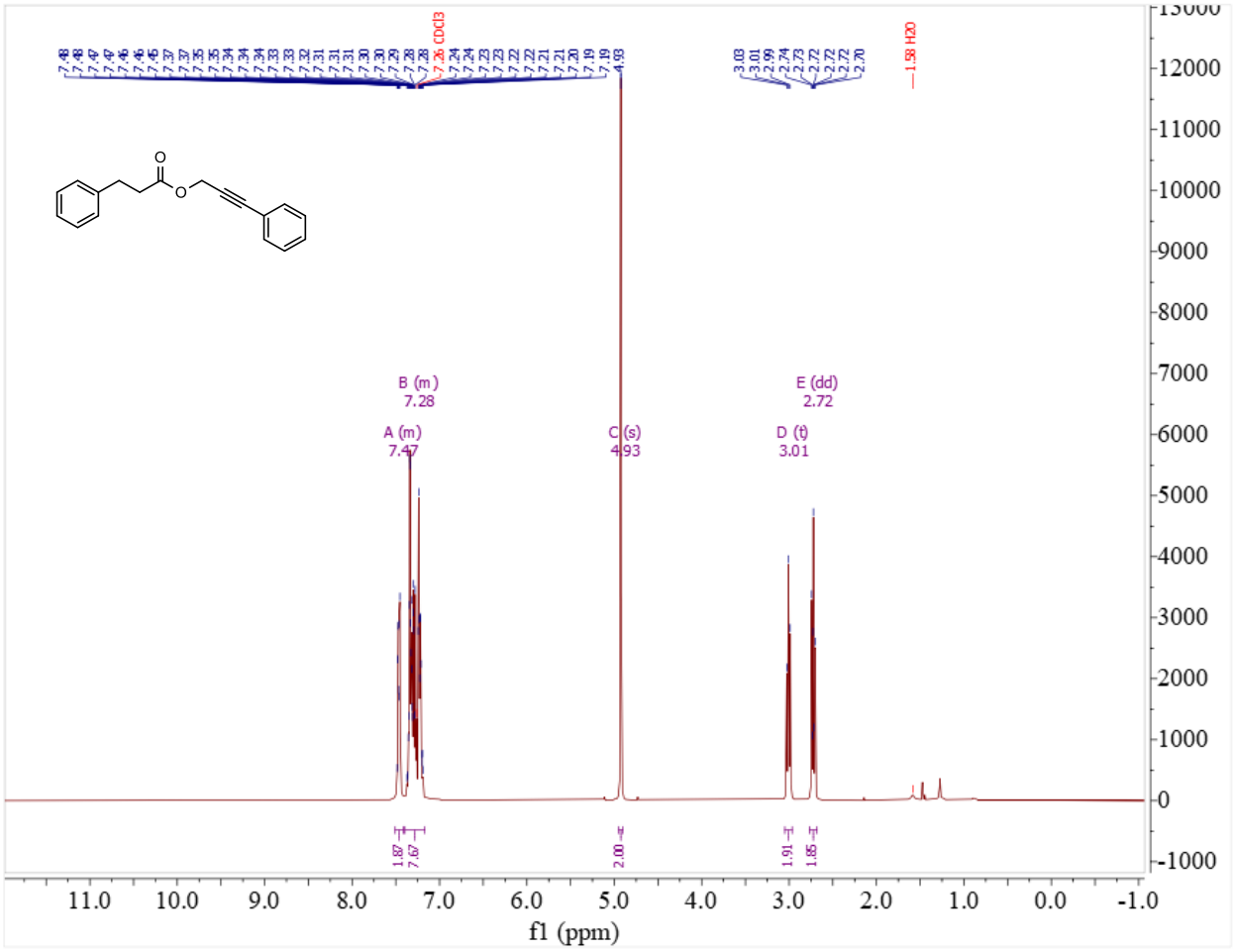


^{13}C NMR of ethyl 3-phenylpropanoate (**8**).

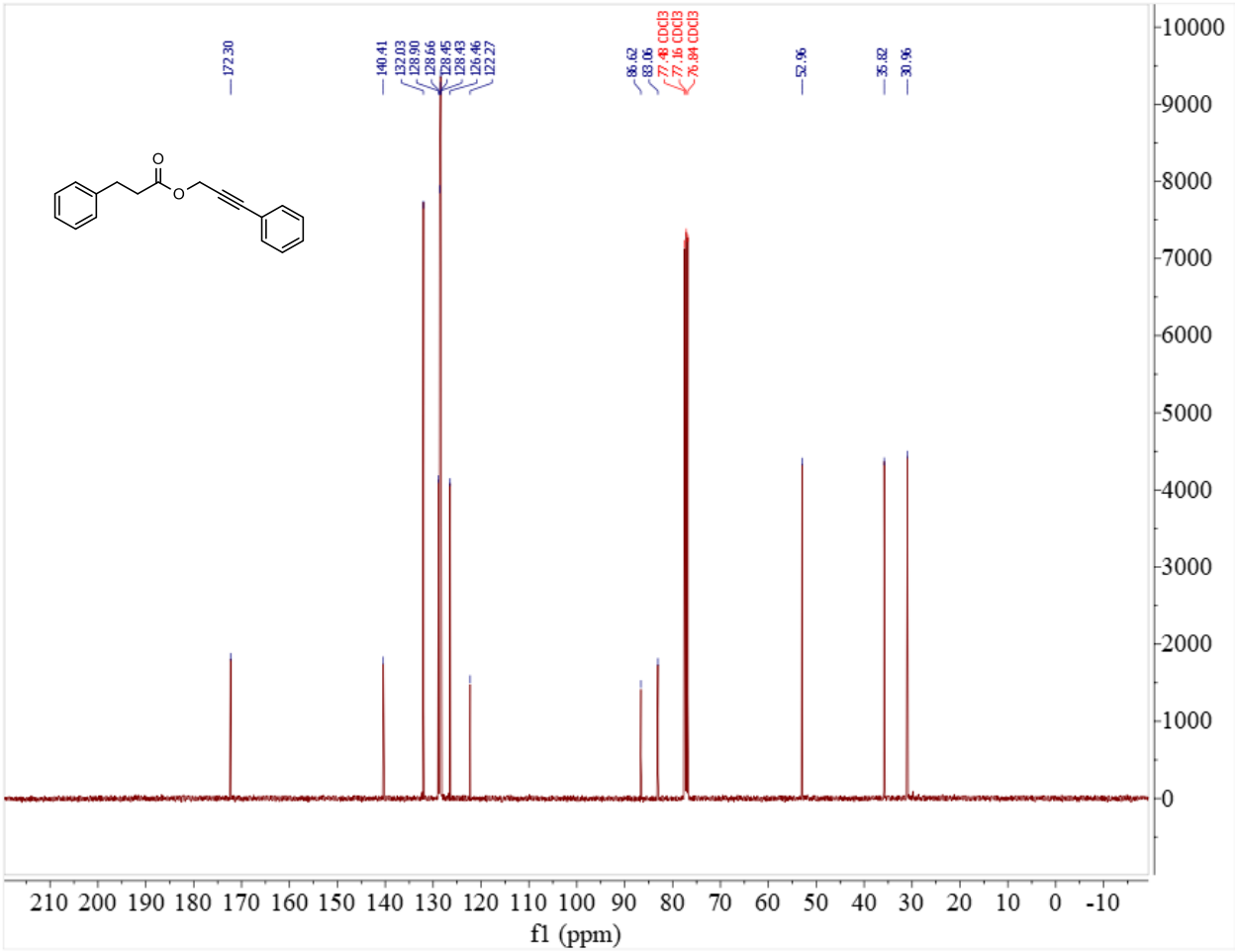
9. 3-Phenylprop-2-yn-1-yl 3-phenylpropanoate

General procedure A to yield **9** (58.2 mg, 44% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.41 (m, 2H), 7.39 – 7.17 (m, 8H), 4.93 (s, 2H), 3.01 (t, *J* = 7.8 Hz, 2H), 2.72 (dd, *J* = 8.4, 7.2 Hz, 2H).**^{13}C NMR (101 MHz, $CDCl_3$) δ** 172.30, 140.41, 132.03, 128.90, 128.66, 128.45, 128.43, 126.46, 122.27, 86.62, 83.06, 52.96, 35.82, 30.96. Spectral data are in agreement with data in *Synlett,* 2023, **34**, 2508-2514.



^{1}H NMR of 3-phenylprop-2-yn-1-yl 3-phenylpropanoate (**9**).

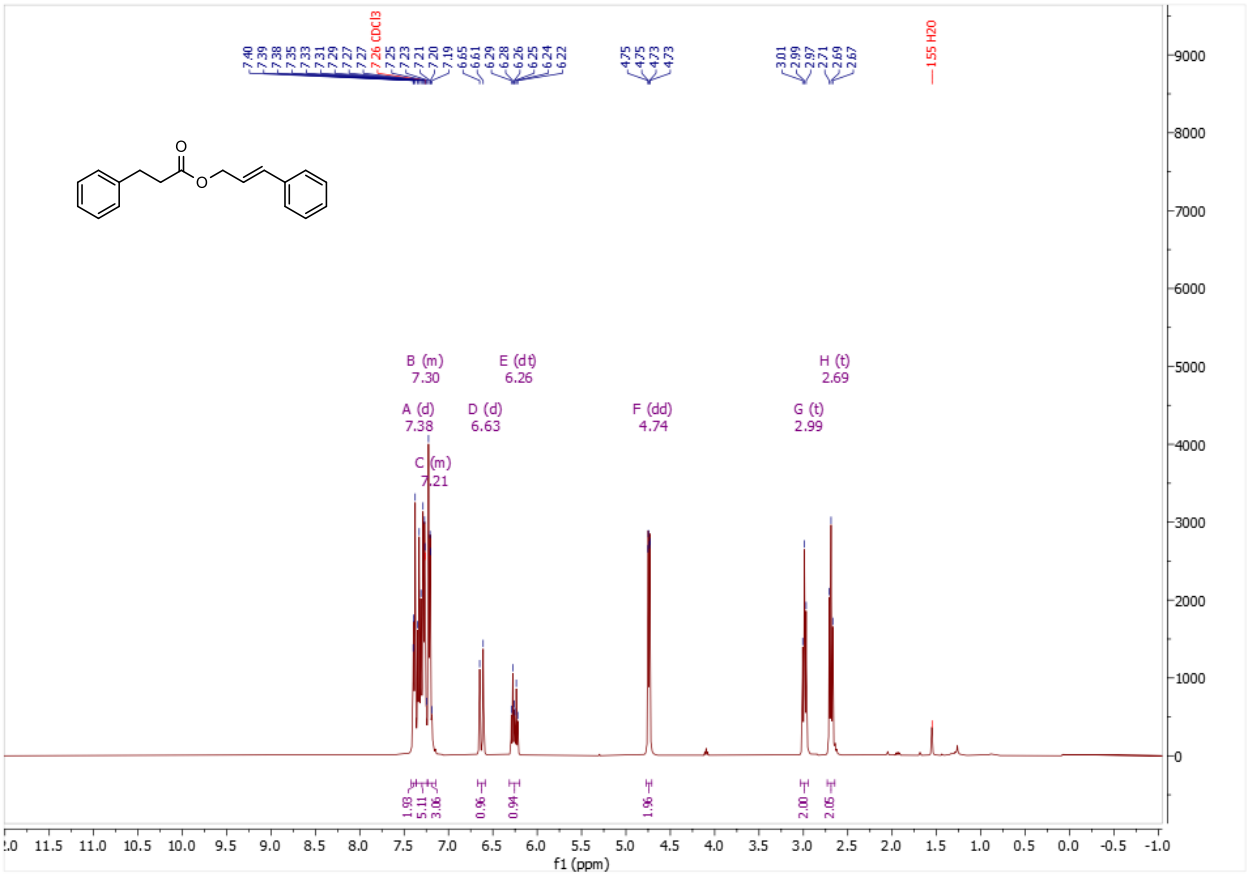


^{13}C NMR of 3-phenylprop-2-yn-1-yl 3-phenylpropanoate (**9**).

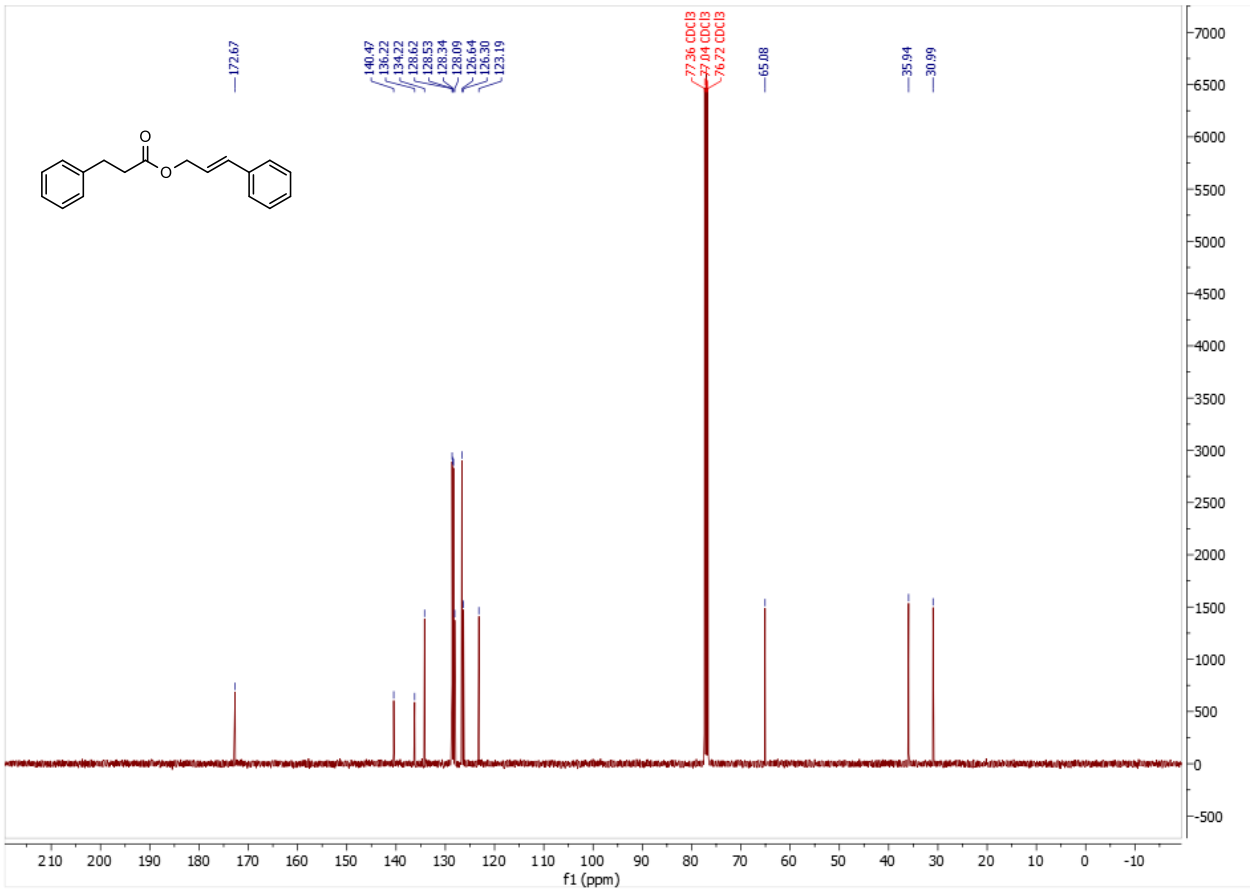
10. Cinnamyl 3-phenylpropanoate

General procedure A to yield **10** (113.2 mg, 85% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.1 Hz, 2H), 7.36 – 7.24 (m, 5H), 7.24 – 7.15 (m, 3H), 6.63 (d, *J* = 15.9 Hz, 1H), 6.26 (dt, *J* = 15.9, 6.4 Hz, 1H), 4.74 (dd, *J* = 6.5, 1.4 Hz, 2H), 2.99 (t, *J* = 7.8 Hz, 2H), 2.69 (t, *J* = 7.8 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 172.67, 140.47, 136.22, 134.22, 128.62, 128.53, 128.34, 128.09, 126.64, 126.30, 123.19, 65.08, 35.94, 30.99. Spectral data are in agreement with data in *J. Am. Chem. Soc.* 2023, **145**, 15680–15687.



^{1}H NMR of cinnamyl 3-phenylpropanoate (**10**).

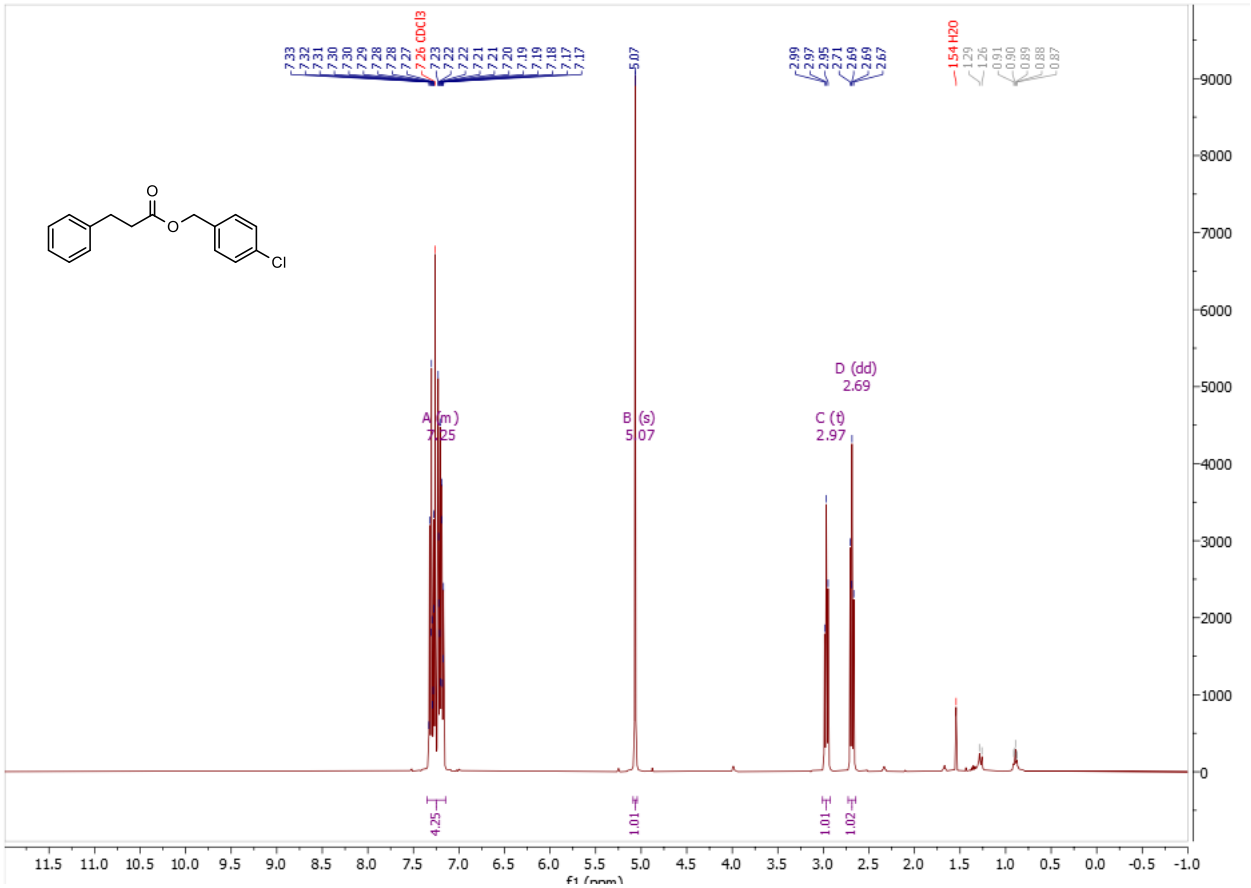


^{13}C NMR of cinnamyl 3-phenylpropanoate (**10**).

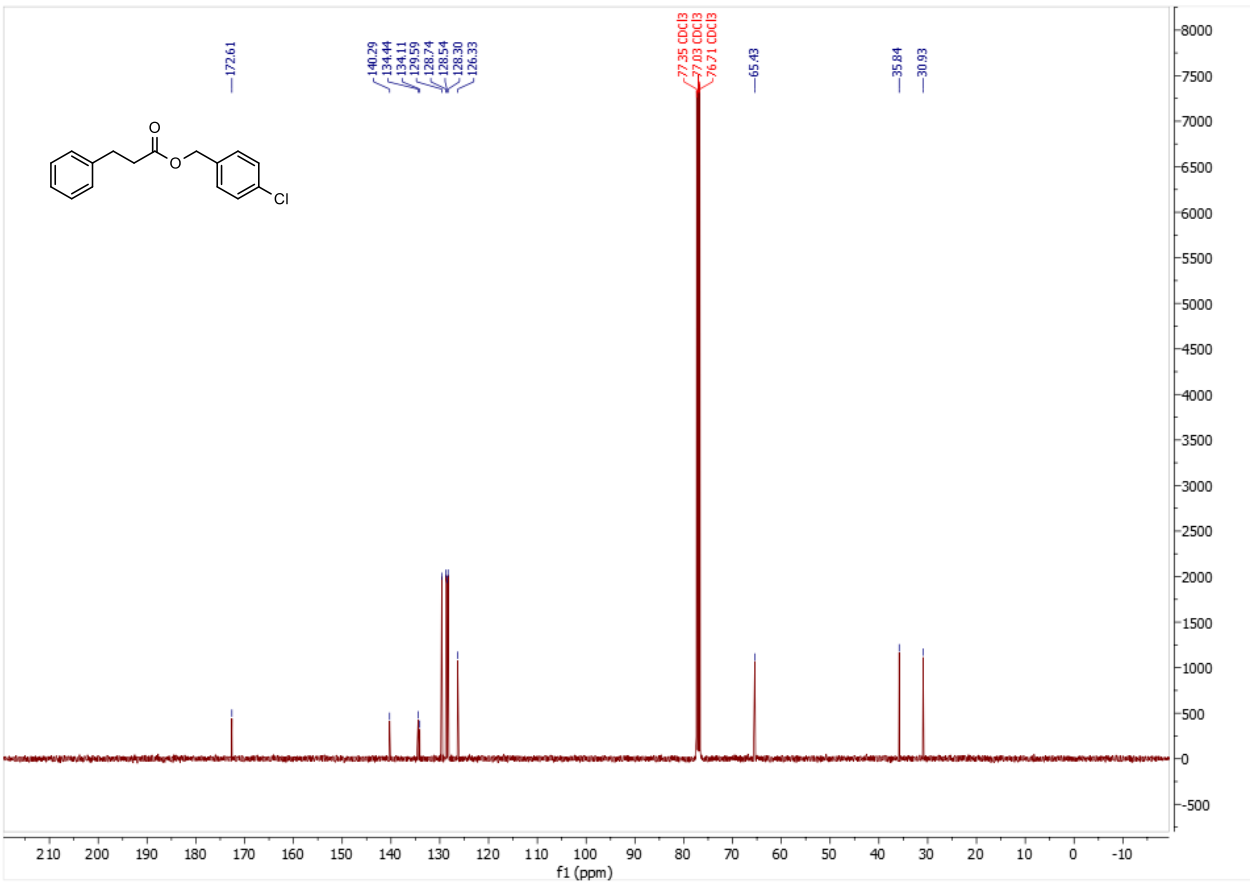
11. 4-Chlorobenzyl 3-phenylpropanoate

General procedure A using TPGS-750-M to yield **11** (92 mg, 67% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.15 (m, 4H), 5.07 (s, 1H), 2.97 (t, *J* = 7.7 Hz, 1H), 2.69 (dd, *J* = 8.3, 7.2 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 172.61, 140.29, 134.44, 134.11, 129.59, 128.74, 128.54, 128.30, 126.33, 65.43, 35.84, 30.93. Spectral data are in agreement with data in *Chem. Sci.,* 2022,**13**, 1440-1445.



^{1}H NMR of 4-chlorobenzyl 3-phenylpropanoate (**11**).

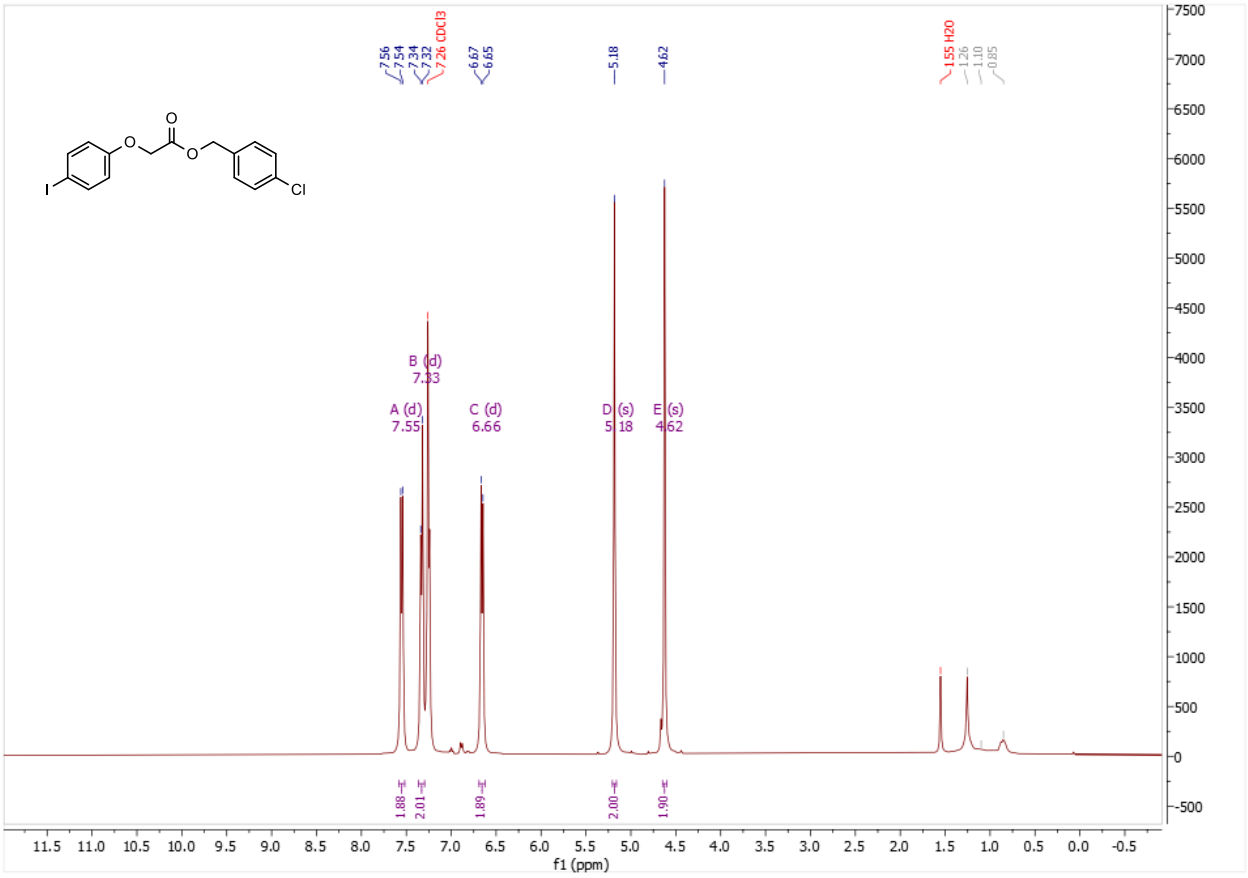


^{13}C NMR of 4-chlorobenzyl 3-phenylpropanoate (**11**).

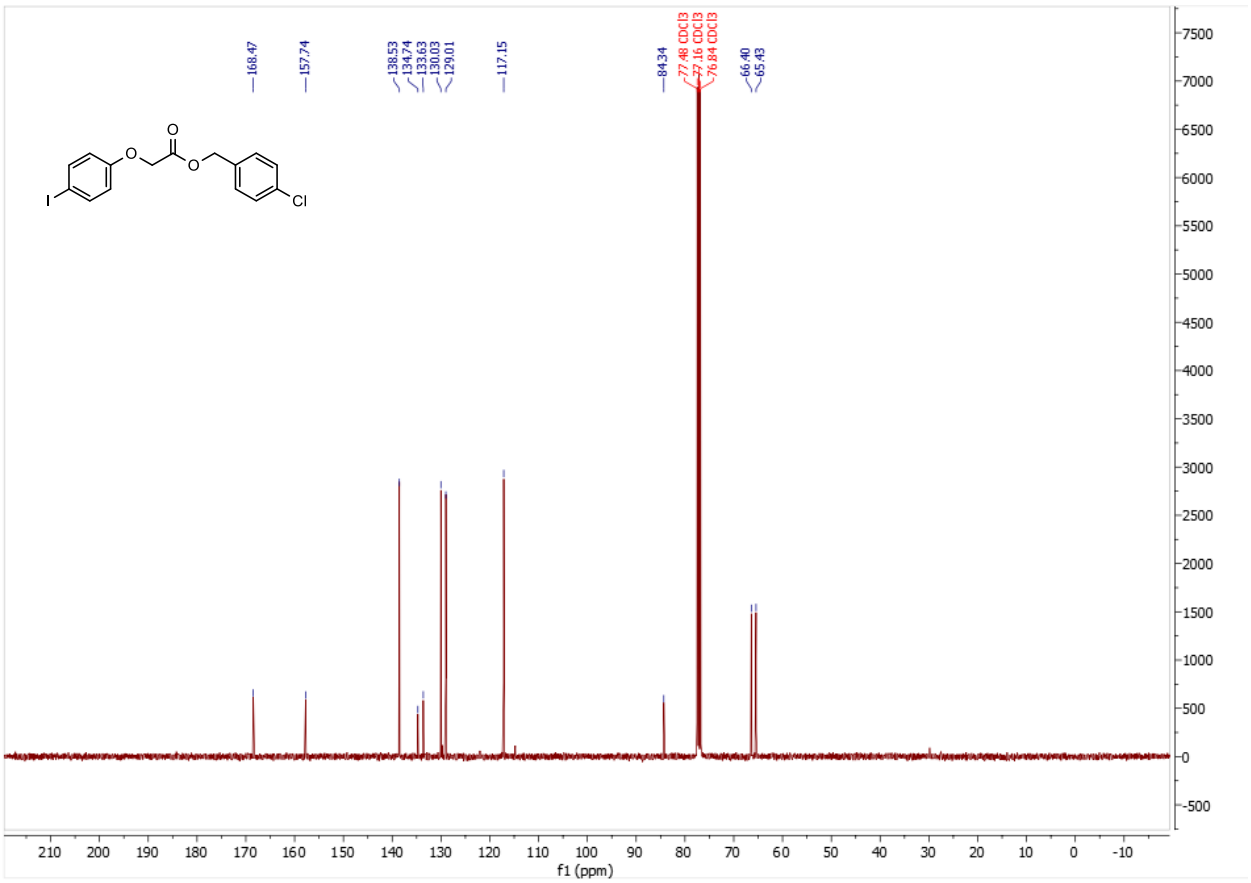
12. 4-Chlorobenzyl 2-(4-iodophenoxy)acetate

General procedure A to yield **12** (38.2 mg, 19% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 6.66 (d, *J* = 8.3 Hz, 2H), 5.18 (s, 2H), 4.62 (s, 2H). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 168.47, 157.74, 138.53, 134.74, 133.63, 130.03, 129.01, 117.15, 84.34, 66.40, 65.43. **Chemical Formula**: HRMS (EI) *m/z*: [M]+ calcd. for $C_{15}H_{12}ClIO_3$: 401.9520; found: 401.9521 (0.20 ppm).



^{1}H NMR of 4-chlorobenzyl 2-(4-iodophenoxy)acetate (**12**).

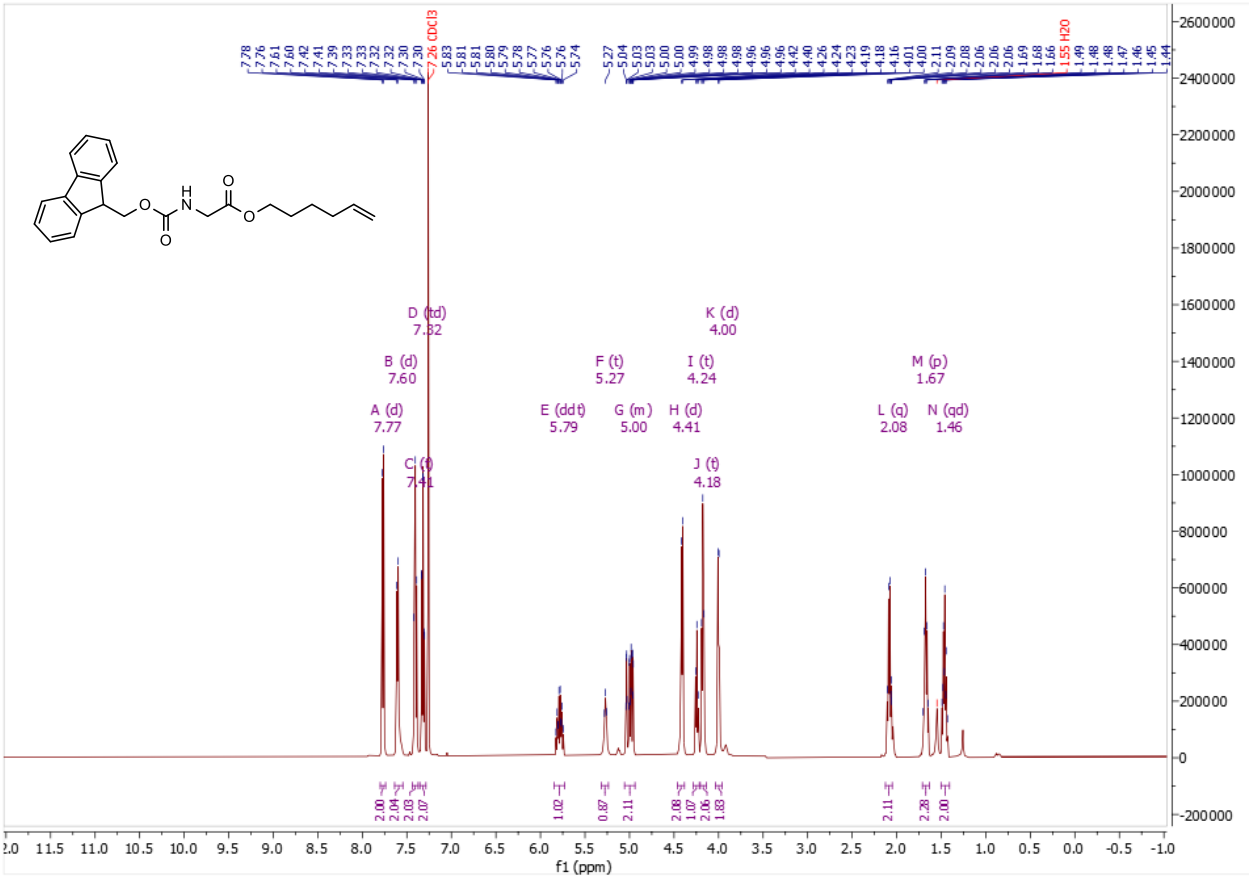


^{13}C NMR of 4-chlorobenzyl 2-(4-iodophenoxy)acetate (**12**).

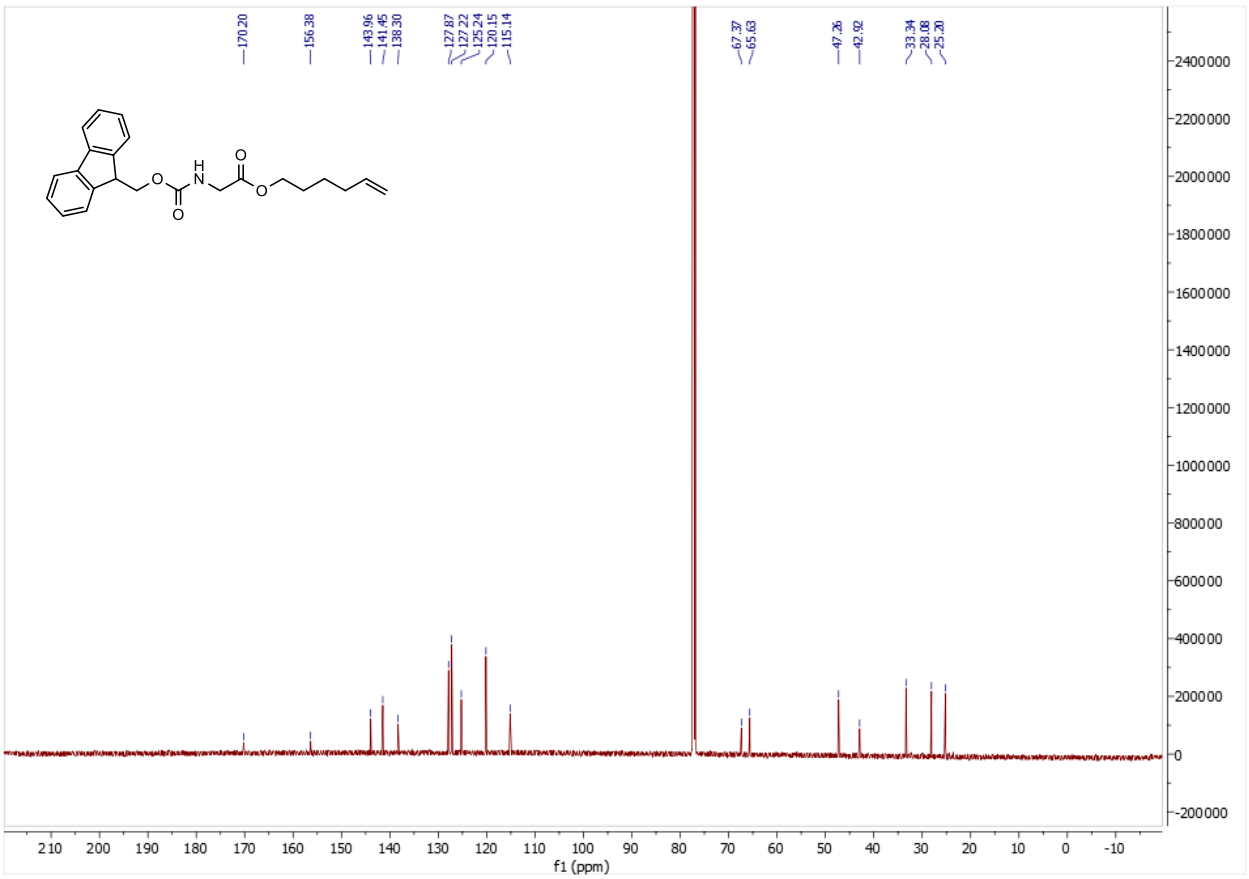
13. Hex-5-en-1-yl (*N*-Fmoc)glycinate

General procedure A using TPGS-750-M to yield **13** (39.2 mg, 44% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.5 Hz, 2H), 7.60 (d, *J* = 7.5 Hz, 2H), 7.41 (t, *J* = 7.4 Hz, 2H), 7.32 (td, *J* = 7.4, 1.1 Hz, 2H), 5.79 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.27 (t, *J* = 5.4 Hz, 1H), 5.06 – 4.94 (m, 2H), 4.41 (d, *J* = 7.2 Hz, 2H), 4.24 (t, *J* = 7.1 Hz, 1H), 4.18 (t, *J* = 6.7 Hz, 2H), 4.00 (d, *J* = 5.5 Hz, 2H), 2.08 (q, *J* = 7.2 Hz, 2H), 1.67 (p, *J* = 6.9 Hz, 2H), 1.46 (qd, *J* = 8.8, 6.3 Hz, 2H). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 170.20, 156.38, 143.96, 141.45, 138.30, 127.87, 127.22, 125.24, 120.15, 115.14, 67.37, 65.63, 47.26, 42.92, 33.34, 28.08, 25.20. Spectral data are in agreement with data in *Chem. Eur. J.,* 2007, **13**, 2358.



^{1}H NMR of phenethyl hex-5-en-1-yl (*N*-Fmoc)glycinate (**13**).

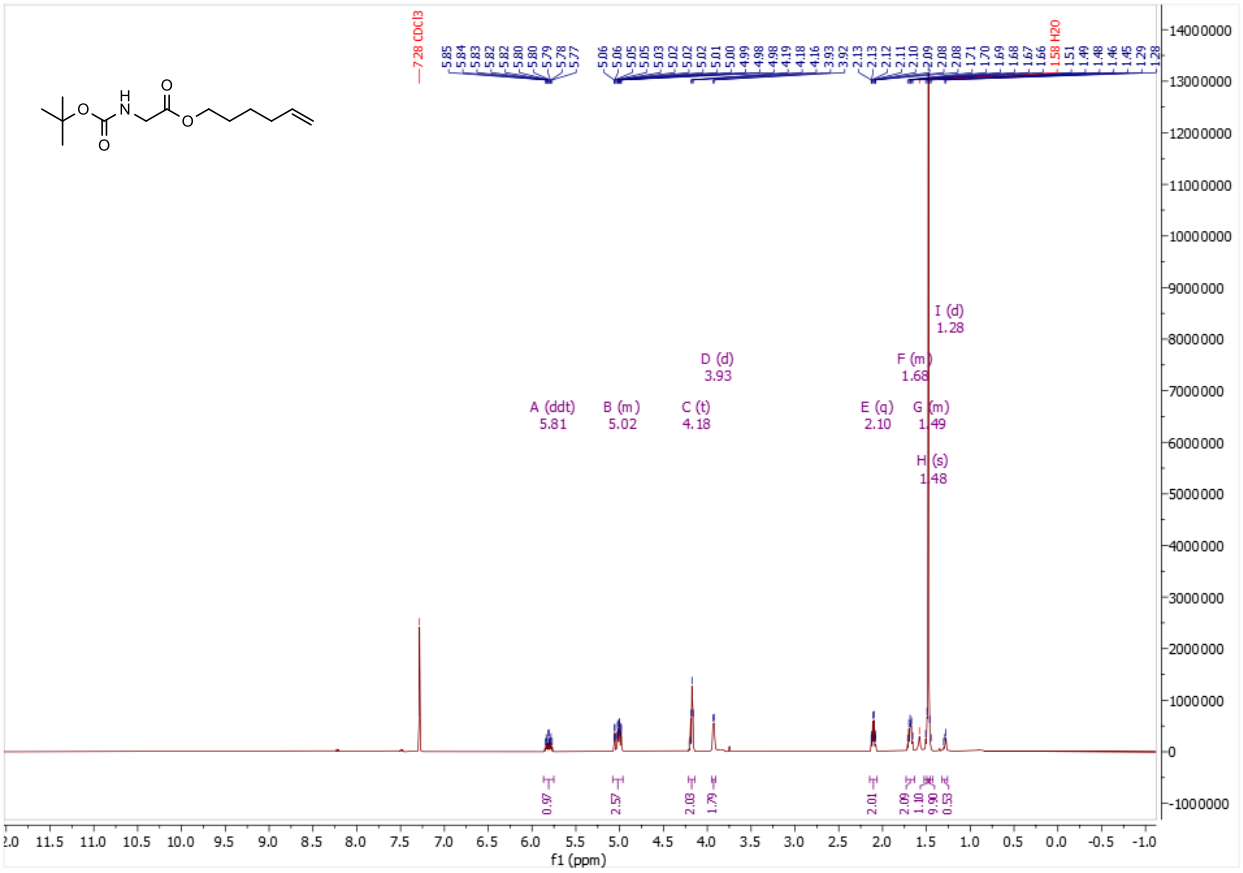


^{13}C NMR of hex-5-en-1-yl (*N*-Fmoc)glycinate (**13**).

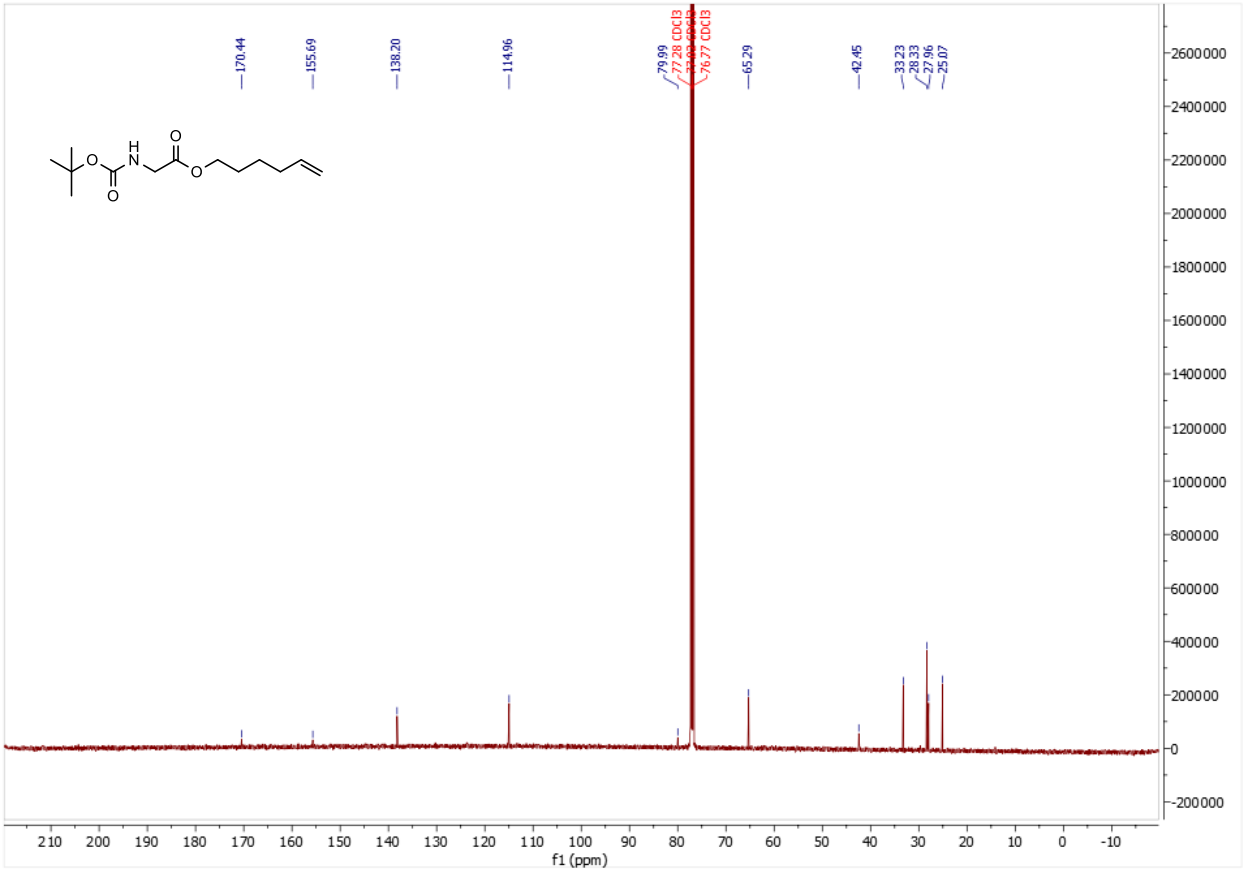
14. Hex-5-en-1-yl (*N*-Boc)glycinate

Modified general procedure A using 4 equivalents of 5-hexen-1-ol to yield **14** (69.5 mg, 54% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 (ddt, *J* = 16.9, 10.1, 6.6 Hz, 1H), 5.08 – 4.96 (m, 3H), 4.18 (t, *J* = 6.7 Hz, 2H), 3.93 (d, *J* = 5.6 Hz, 2H), 2.10 (q, *J* = 7.1 Hz, 2H), 1.73 – 1.64 (m, 2H), 1.53 – 1.43 (m, 1H), 1.48 (s, 10H), 1.28 (d, *J* = 5.7 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 170.44, 155.69, 138.20, 114.96, 79.99, 65.29, 42.45, 33.23, 28.33, 27.96, 25.07. **Chemical Formula**: HRMS (ESI) *m/z*: [M+Na]+ calcd. for $NaC_{13}H_{23}NO_4$: 280.1525; found: 280.1523 (0.70 ppm).



^{1}H NMR of hex-5-en-1-yl (*N*-Boc)glycinate (**14**).

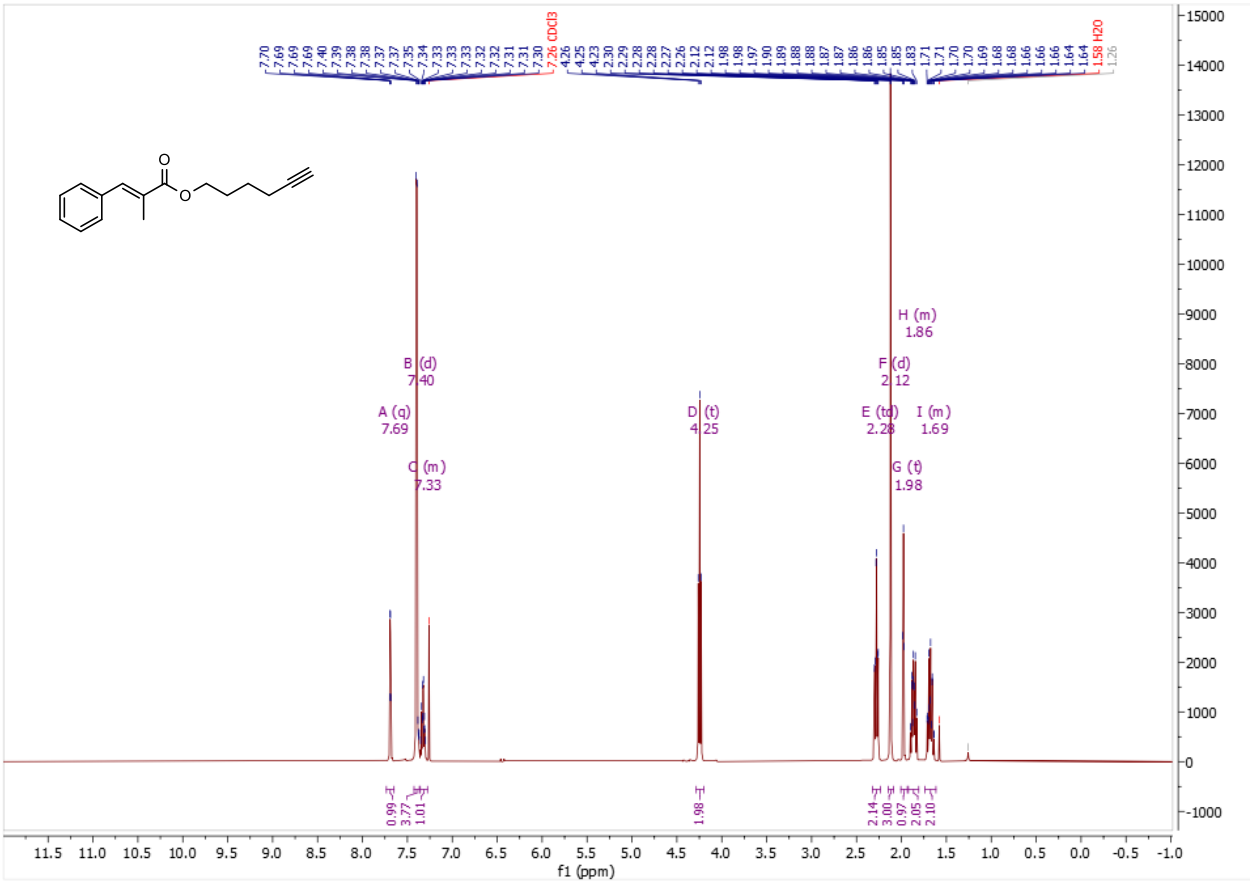


^{13}C NMR of hex-5-en-1-yl (*N*-Boc)glycinate (**14**).

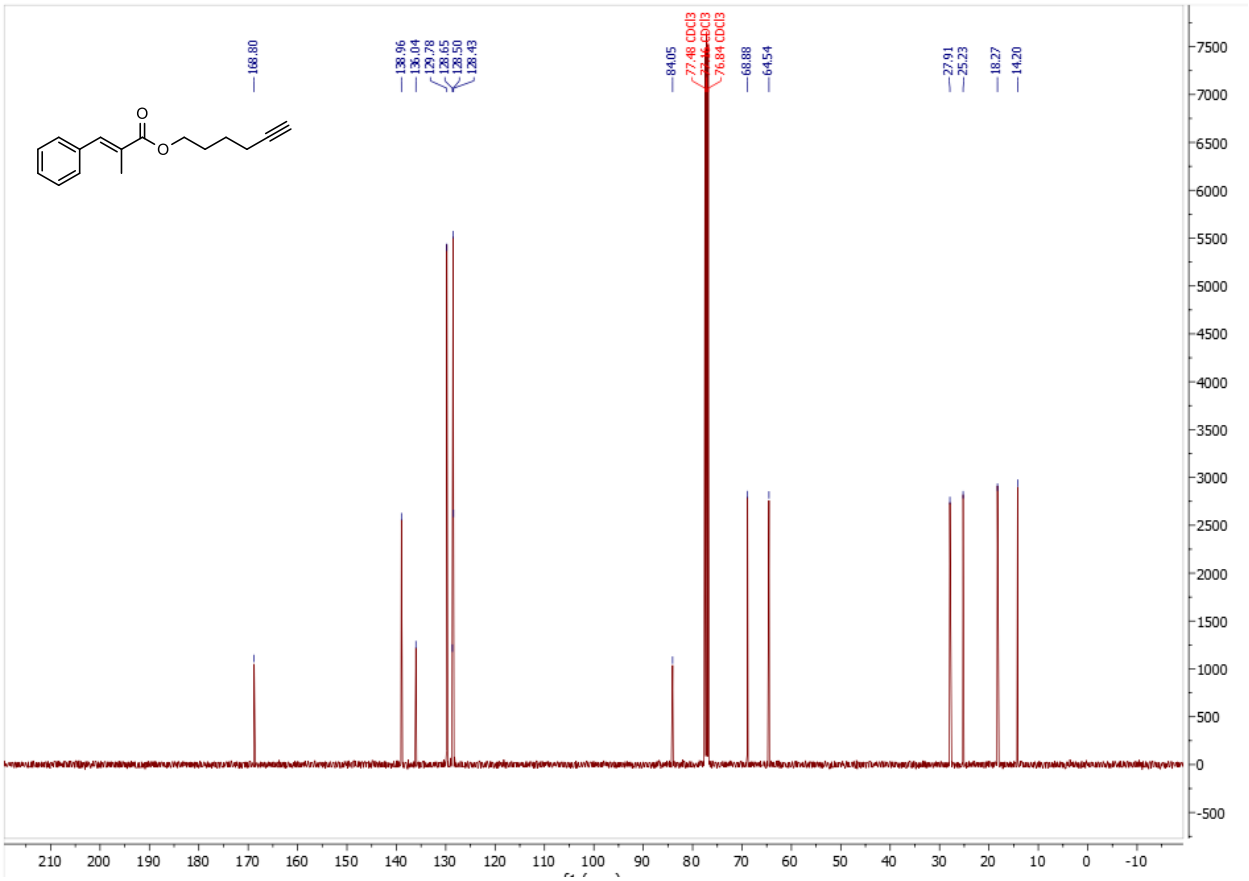
15. Hex-5-yn-1-yl (*E*)-2-methyl-3-phenylacrylate

General procedure A to yield **4** (42.35 mg, 30% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (q, *J* = 1.5 Hz, 1H), 7.40 (d, *J* = 4.4 Hz, 4H), 7.36 – 7.28 (m, 1H), 4.25 (t, *J* = 6.5 Hz, 2H), 2.28 (td, *J* = 7.1, 2.7 Hz, 2H), 2.12 (d, *J* = 1.5 Hz, 3H), 1.98 (t, *J* = 2.6 Hz, 1H), 1.92 – 1.81 (m, 2H), 1.74 – 1.62 (m, 2H). **^{13}C NMR (101 MHz, $CDCl_3$) δ** ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.80, 138.96, 136.04, 129.78, 128.65, 128.50, 128.43, 84.05, 68.88, 64.54, 27.91, 25.23, 18.27, 14.20. **Chemical Formula**: HRMS (EI) *m/z*: [M+H]+ calcd. for $C_{16}H_{19}O_2$: 243.1385; found: 243.1384 (0.40 ppm).



^{1}H NMR of hex-5-yn-1-yl (*E*)-2-methyl-3-phenylacrylate (**15**).

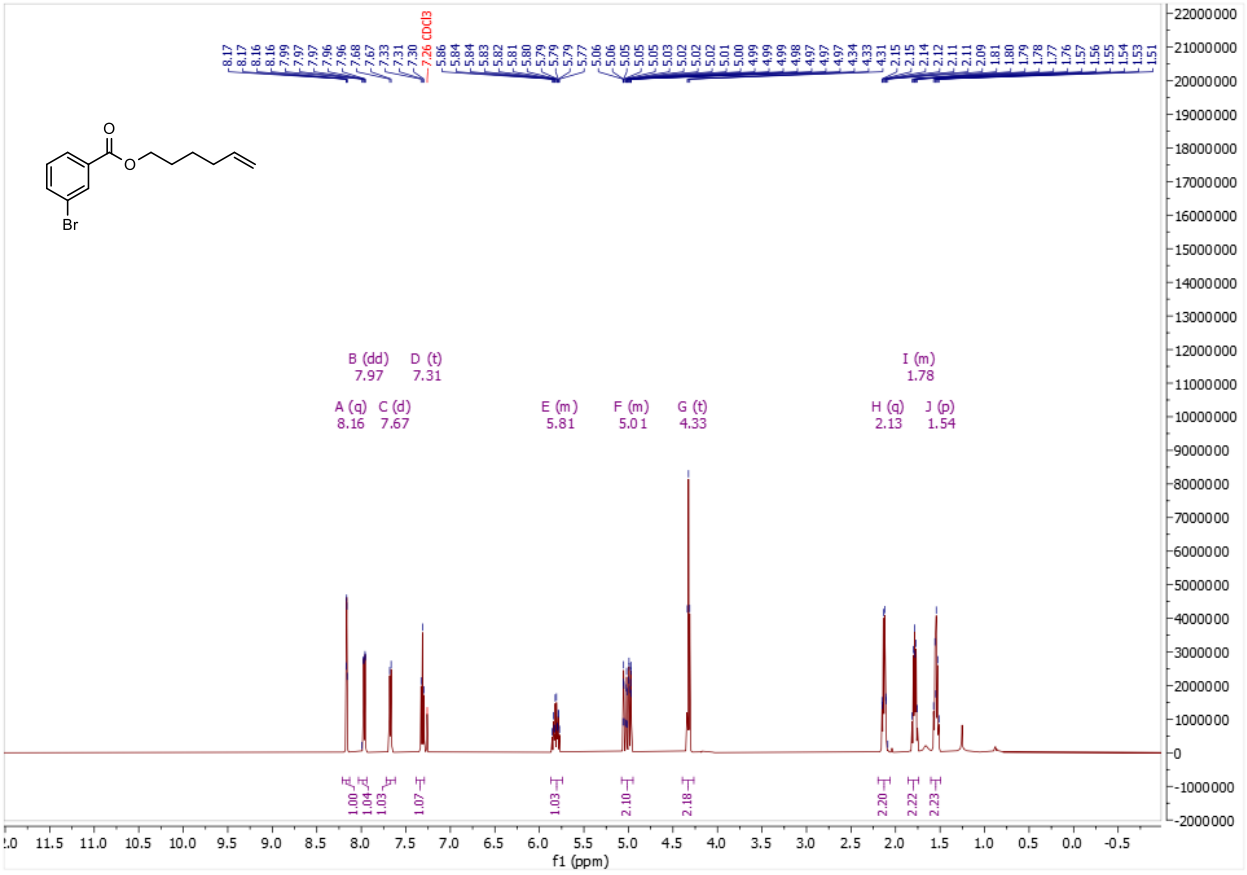


^{13}C NMR of hex-5-yn-1-yl (*E*)-2-methyl-3-phenylacrylate (**15**).

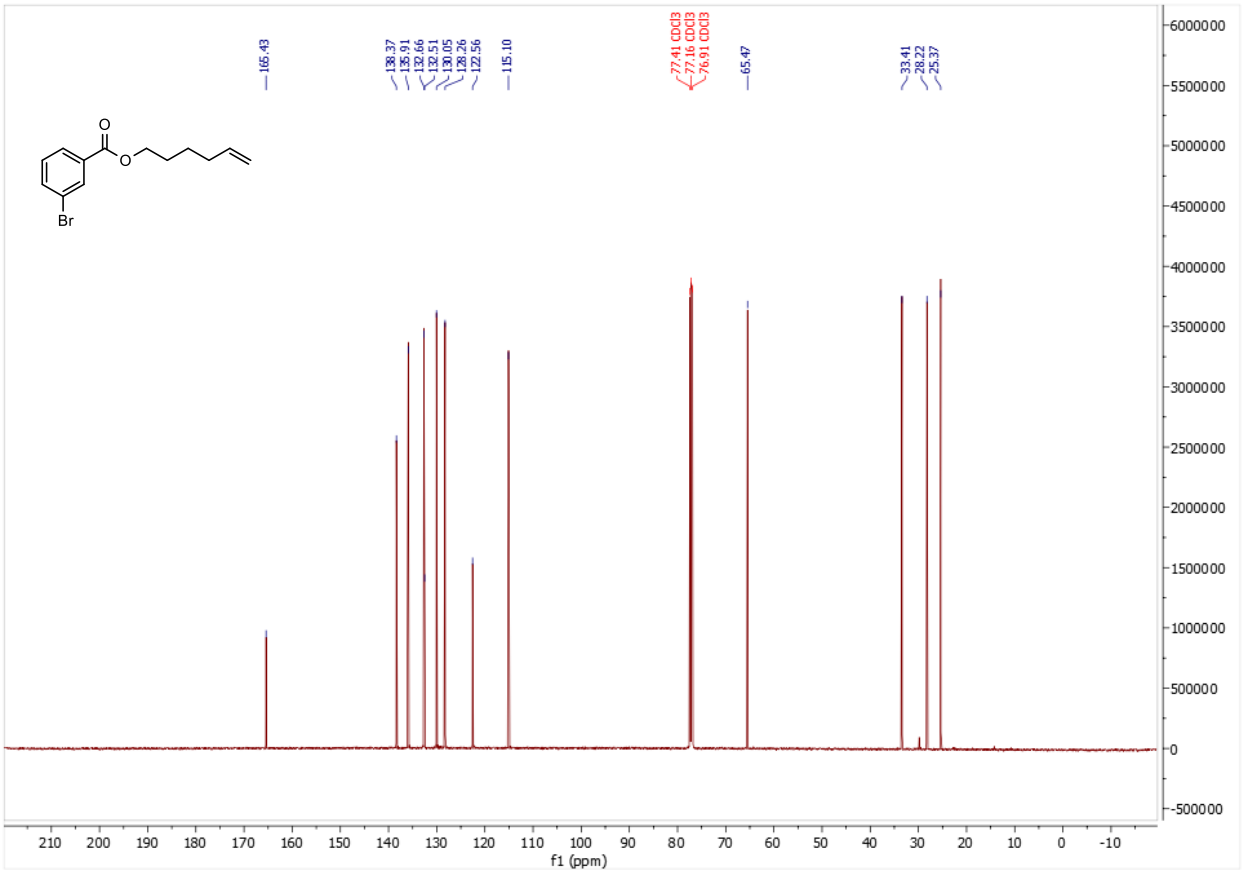
16. Hex-5-en-1-yl 3-bromobenzoate

General procedure A to yield **16** (127.4 mg, 90% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (q, *J* = 1.6 Hz, 1H), 7.97 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.67 (d, *J* = 7.9 Hz, 1H), 7.31 (t, *J* = 7.9 Hz, 1H), 5.87 – 5.74 (m, 1H), 5.08 – 4.95 (m, 2H), 4.33 (t, *J* = 6.7 Hz, 2H), 2.13 (q, *J* = 7.1 Hz, 2H), 1.86 – 1.74 (m, 2H), 1.54 (p, *J* = 7.5 Hz, 2H). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 165.43, 138.37, 135.91, 132.66, 132.51, 130.05, 128.26, 122.56, 115.10, 65.47, 33.41, 28.22, 25.37. **Chemical Formula**: HRMS (EI) *m/z*: [M]+ calcd. for $C_{13}H_{15}BrO_2$: 284.0236; found: 284.0224 (0.40 ppm).



^{1}H NMR of hex-5-en-1-yl 3-bromobenzoate (**16**).

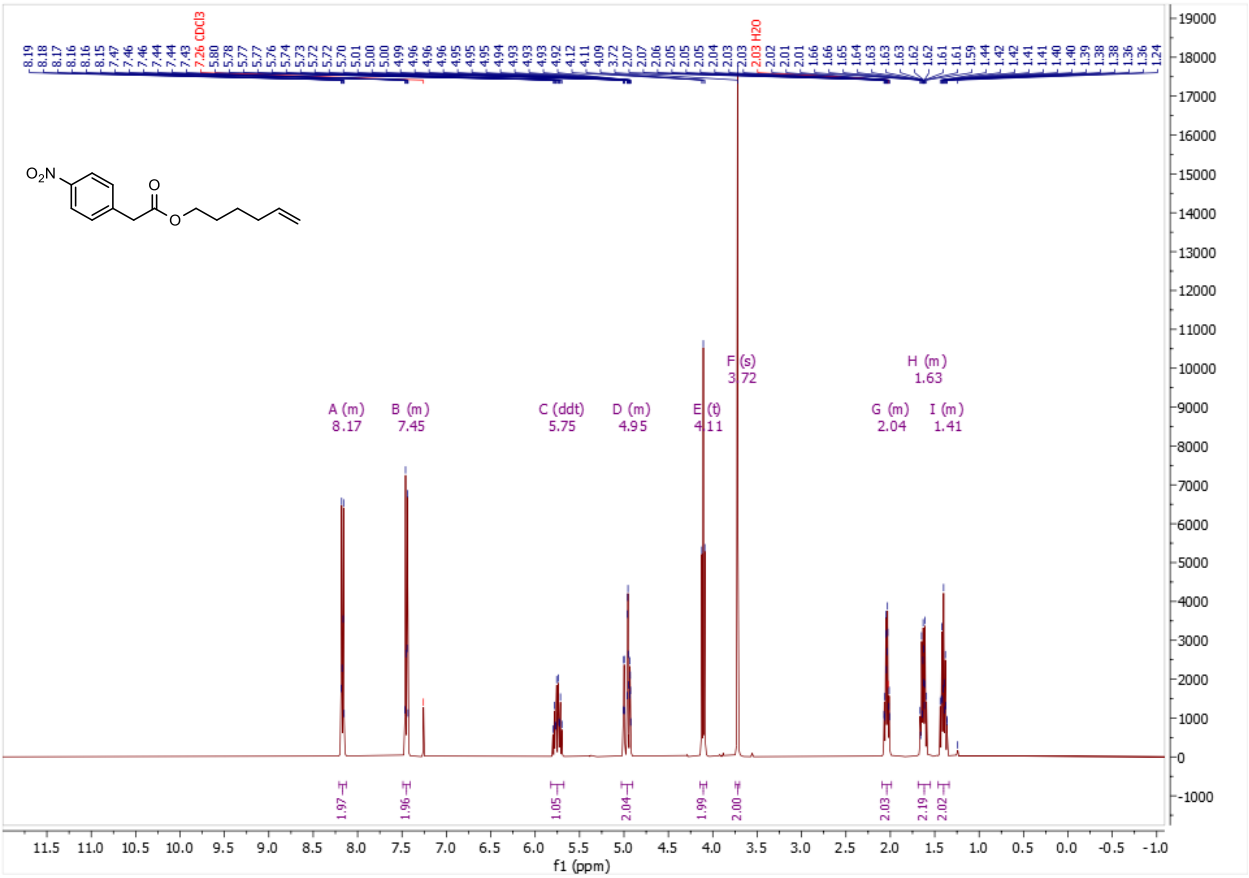


^{13}C NMR of hex-5-en-1-yl 3-bromobenzoate (**16**).

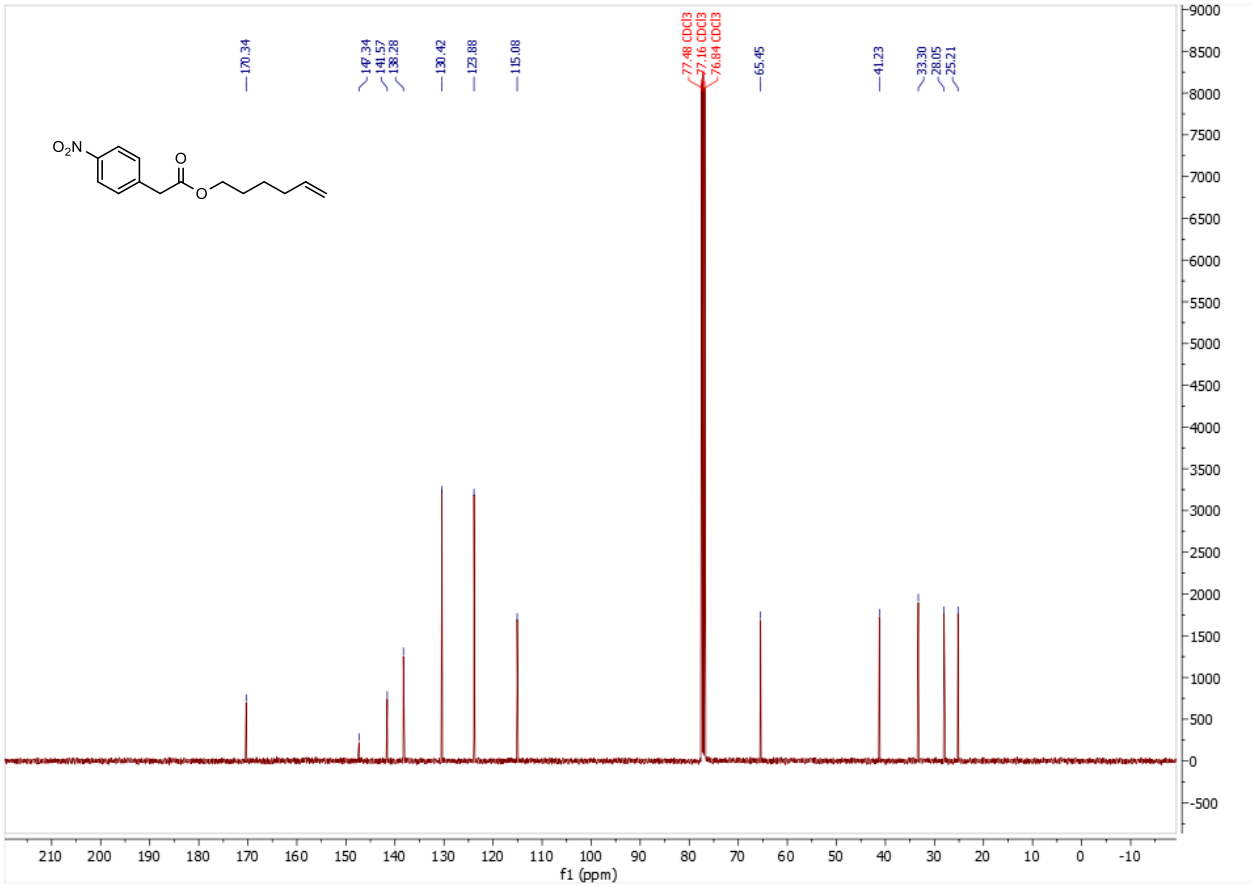
17. Hex-5-en-1-yl 2-(4-nitrophenyl)acetate

General procedure A to yield **7** (102.7 mg, 78% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 – 8.13 (m, 2H), 7.49 – 7.41 (m, 2H), 5.75 (ddt, *J* = 16.9, 10.1, 6.7 Hz, 1H), 5.03 – 4.90 (m, 2H), 4.11 (t, *J* = 6.6 Hz, 2H), 3.72 (s, 2H), 2.09 – 1.99 (m, 2H), 1.69 – 1.55 (m, 2H), 1.46 – 1.34 (m, 2H). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 173.45, 138.03, 136.39, 129.06, 128.61, 127.31, 126.65, 122.20, 121.51, 119.46, 118.83, 115.10, 111.25, 65.01, 35.24, 35.05, 20.75. **Chemical Formula**: HRMS (EI) *m/z*: [M]+ calcd. for $C_{14}H_{17}NO_4$: 263.1158; found: 263.971 (1.1 ppm).



^{1}H NMR of hex-5-en-1-yl 2-(4-nitrophenyl)acetate (**17**).

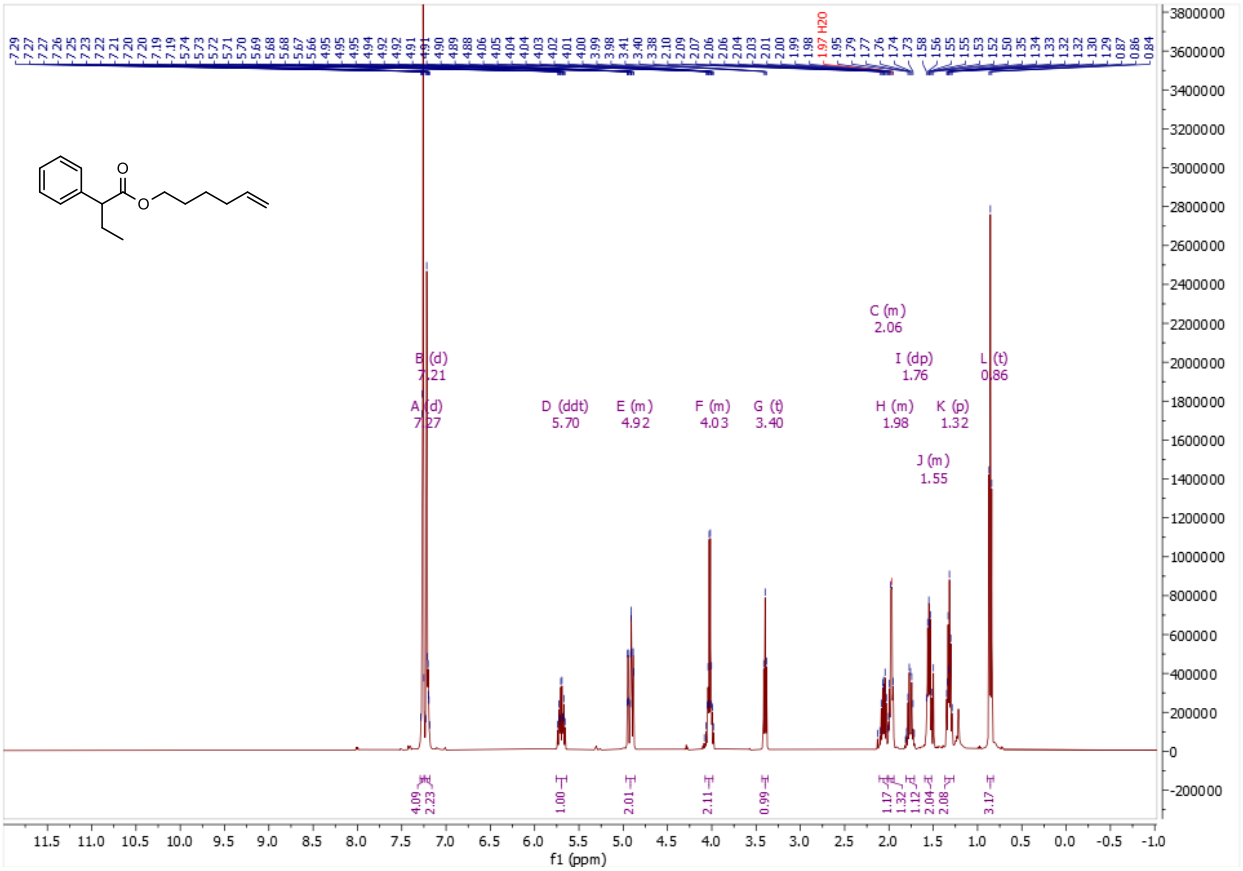


^{13}C NMR of hex-5-en-1-yl 2-(4-nitrophenyl)acetate (**17**).

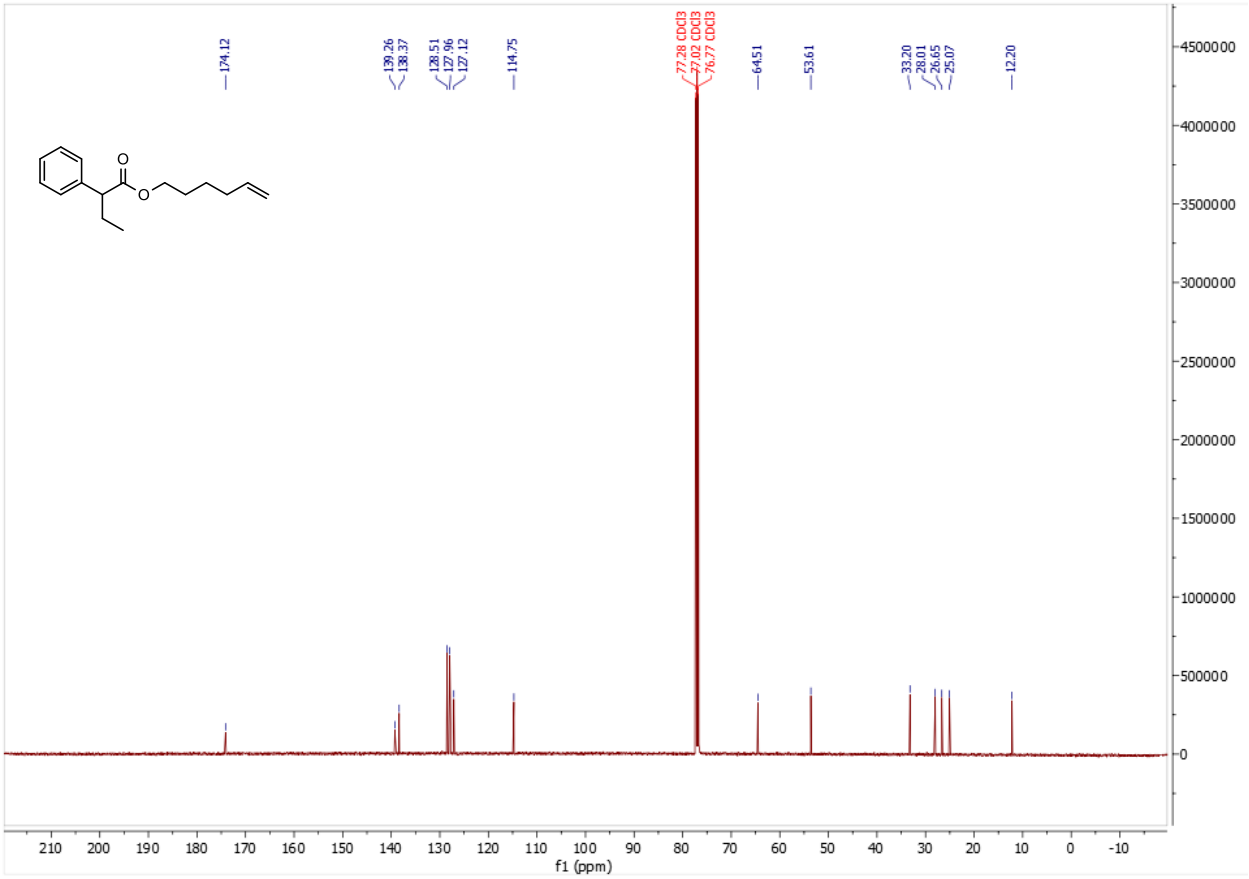
18. Hex-5-en-1-yl 2-phenylbutanoate

General procedure A to yield **18** (25.9 mg, 21% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, *J* = 5.1 Hz, 4H), 7.21 (d, *J* = 7.5 Hz, 2H), 5.70 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 4.97 – 4.87 (m, 2H), 4.07 – 3.99 (m, 2H), 3.40 (t, *J* = 7.7 Hz, 1H), 2.11 – 2.02 (m, 1H), 2.01 – 1.94 (m, 1H), 1.76 (dp, *J* = 14.6, 7.4 Hz, 1H), 1.60 – 1.52 (m, 2H), 1.32 (p, *J* = 7.6 Hz, 2H), 0.86 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 174.12, 139.26, 138.37, 128.51, 127.96, 127.12, 114.75, 64.51, 53.61, 33.20, 28.01, 26.65, 25.07, 12.20. **Chemical Formula**: HRMS (ESI) *m/z*: [M+Na]+ calcd. for $NaC_{16}H_{22}O_2$: 269.1518; found: 269.1519 (0.40 ppm).



^{1}H NMR of hex-5-en-1-yl 2-phenylbutanoate (**18**).

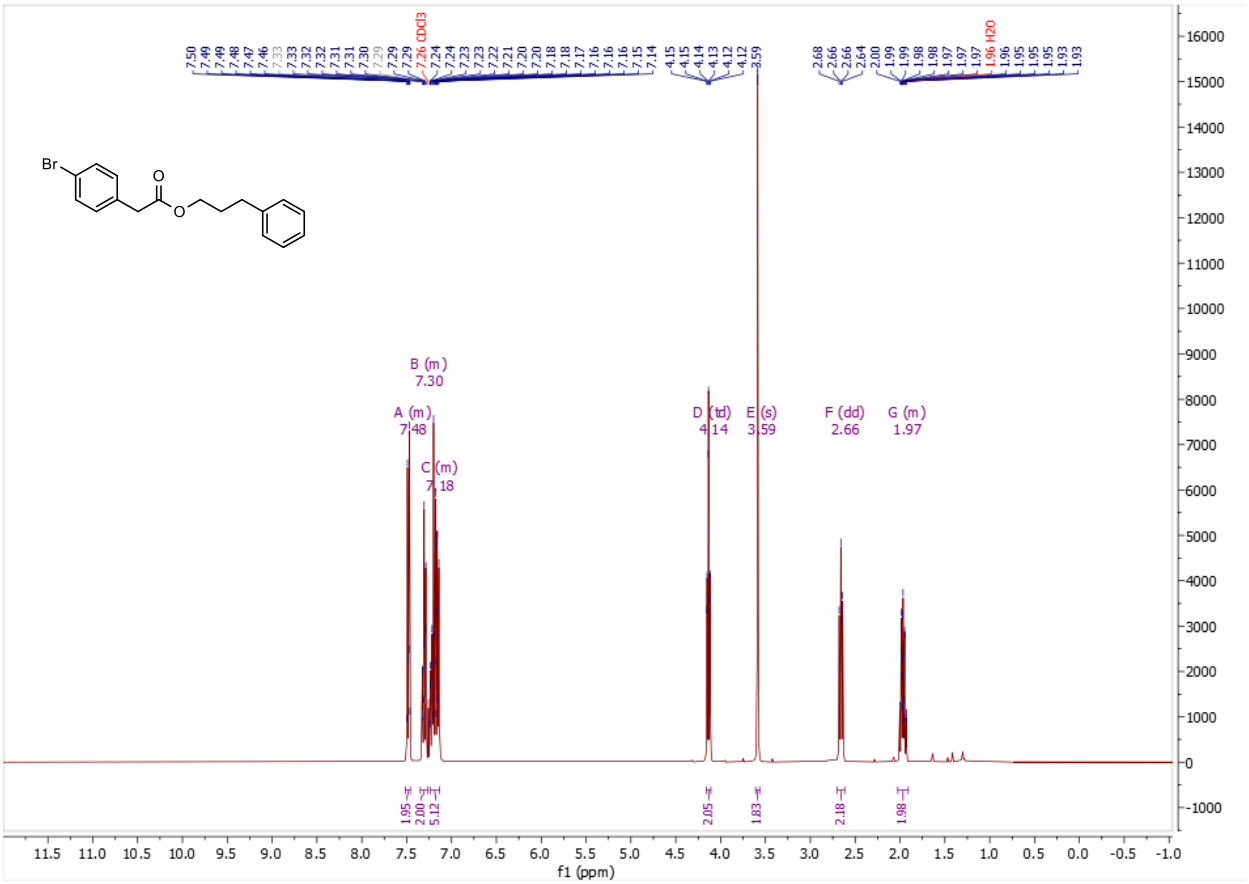


^{13}C NMR of hex-5-en-1-yl 2-phenylbutanoate (**18**).

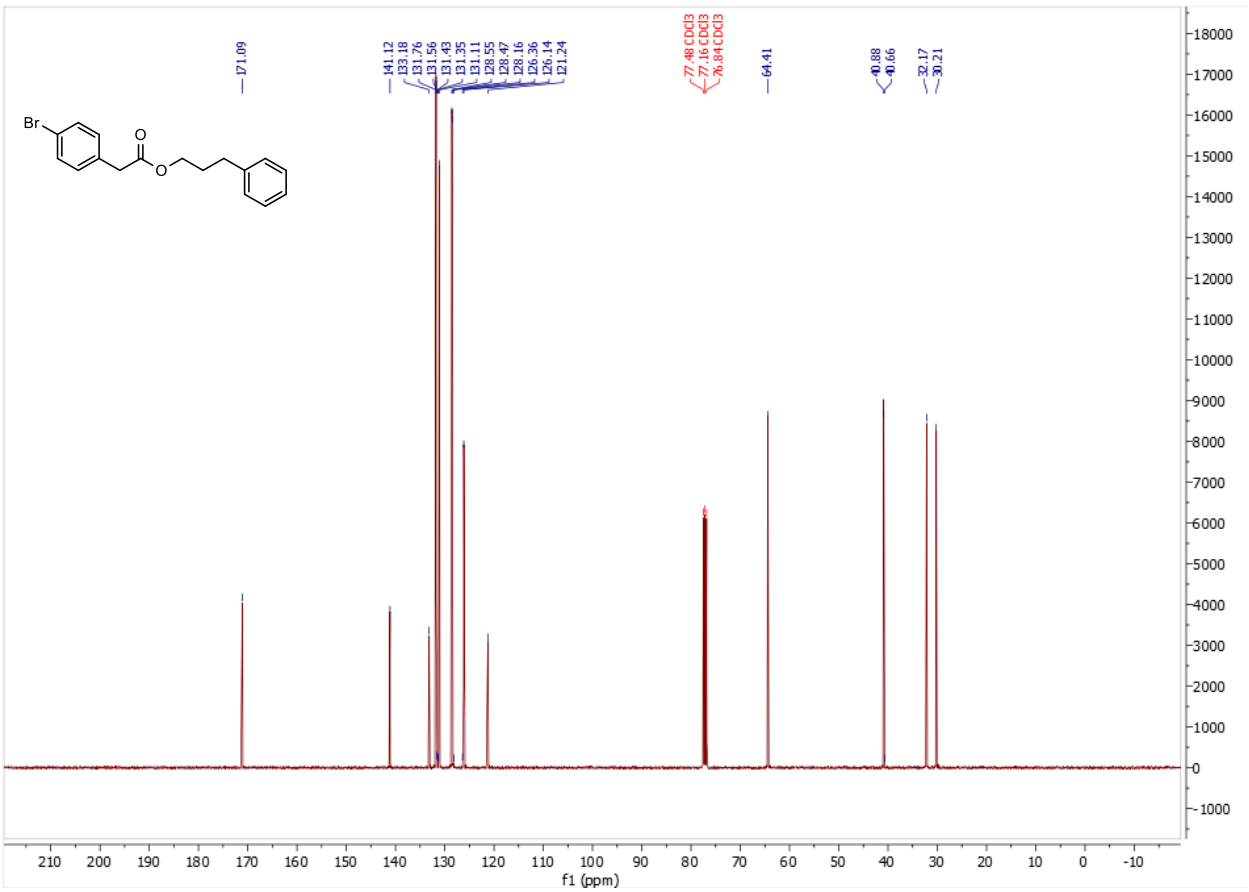
19. 3-Phenylpropyl 2-(4-bromophenyl)acetate

General procedure A to yield **19** (138.2 mg, 83% yield).

^{1}H NMR (400 MHz, $CDCl_3$) 7.51 – 7.46 (m, 2H), 7.35 – 7.27 (m, 2H), 7.23 – 7.14 (m, 5H), 4.14 (td, *J* = 6.5, 0.8 Hz, 2H), 3.59 (s, 2H), 2.66 (dd, *J* = 8.6, 6.8 Hz, 2H), 2.02 – 1.91 (m, 2H). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 171.09, 141.12, 133.18, 131.76, 131.56, 131.43, 131.35, 131.11, 128.55, 128.47, 128.16, 126.36, 126.14, 121.24, 64.41, 40.88, 40.66, 32.17, 30.21. **Chemical Formula**: HRMS (ESI) *m/z*: [M+Na]+ calcd. for $NaC_{17}H_{17}BrO_2$: 355.0310; found: 355.0312 (0.60 ppm).



^{1}H NMR of 3-phenylpropyl 2-(4-bromophenyl)acetate (**19**).

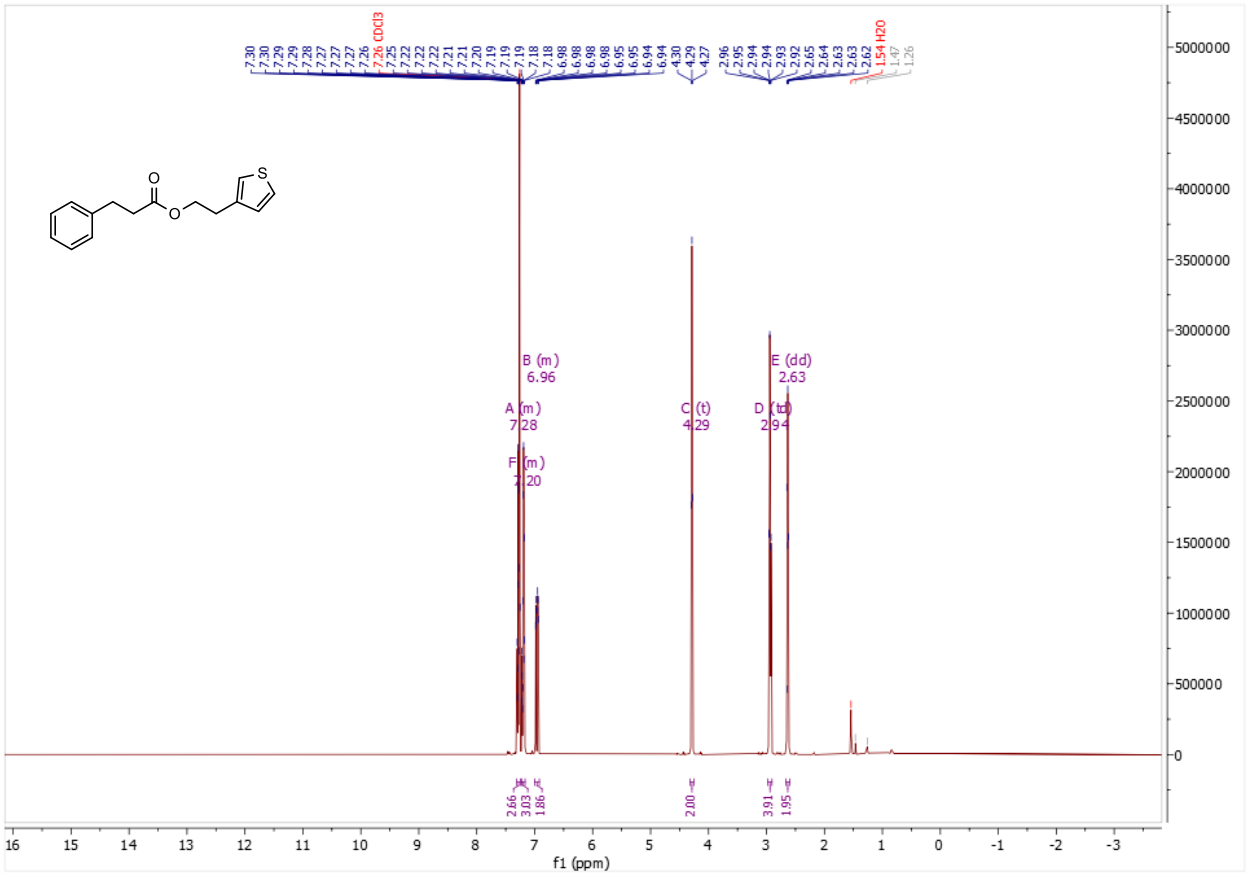


^{13}C NMR of 3-phenylpropyl 2-(4-bromophenyl)acetate (**19**).

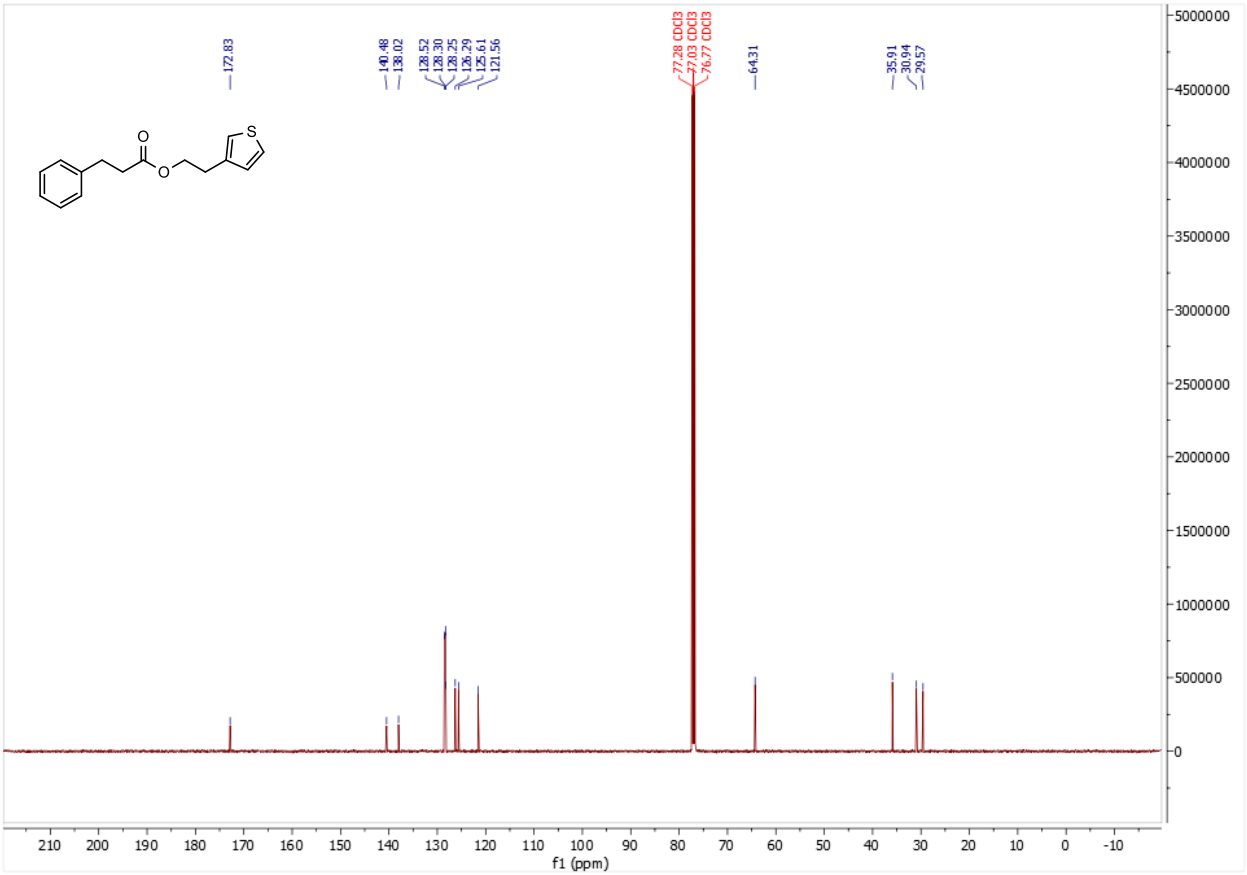
20. 2-(Thiophen-3-yl)ethyl 3-phenylpropanoate

General procedure A to yield **20** (113.1 mg, 87% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.25 (m, 3H), 7.23 – 7.17 (m, 3H), 7.00 – 6.92 (m, 2H), 4.29 (t, *J* = 6.9 Hz, 2H), 2.94 (td, *J* = 7.5, 2.7 Hz, 4H), 2.63 (dd, *J* = 8.3, 7.3 Hz, 2H). **^{13}C NMR (126 MHz, $CDCl_3$) δ** ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.83, 140.48, 138.02, 128.52, 128.30, 128.25, 126.29, 125.61, 121.56, 64.31, 35.91, 30.94, 29.57. **Chemical Formula**: HRMS (ESI) *m/z*: [M+Na]+ calcd. for $NaC_{15}H_{16}O_2S$: 283.0769; found: 283.0771 (0.70 ppm).



^{1}H NMR of 2-(thiophen-3-yl)ethyl 3-phenylpropanoate (**20**).

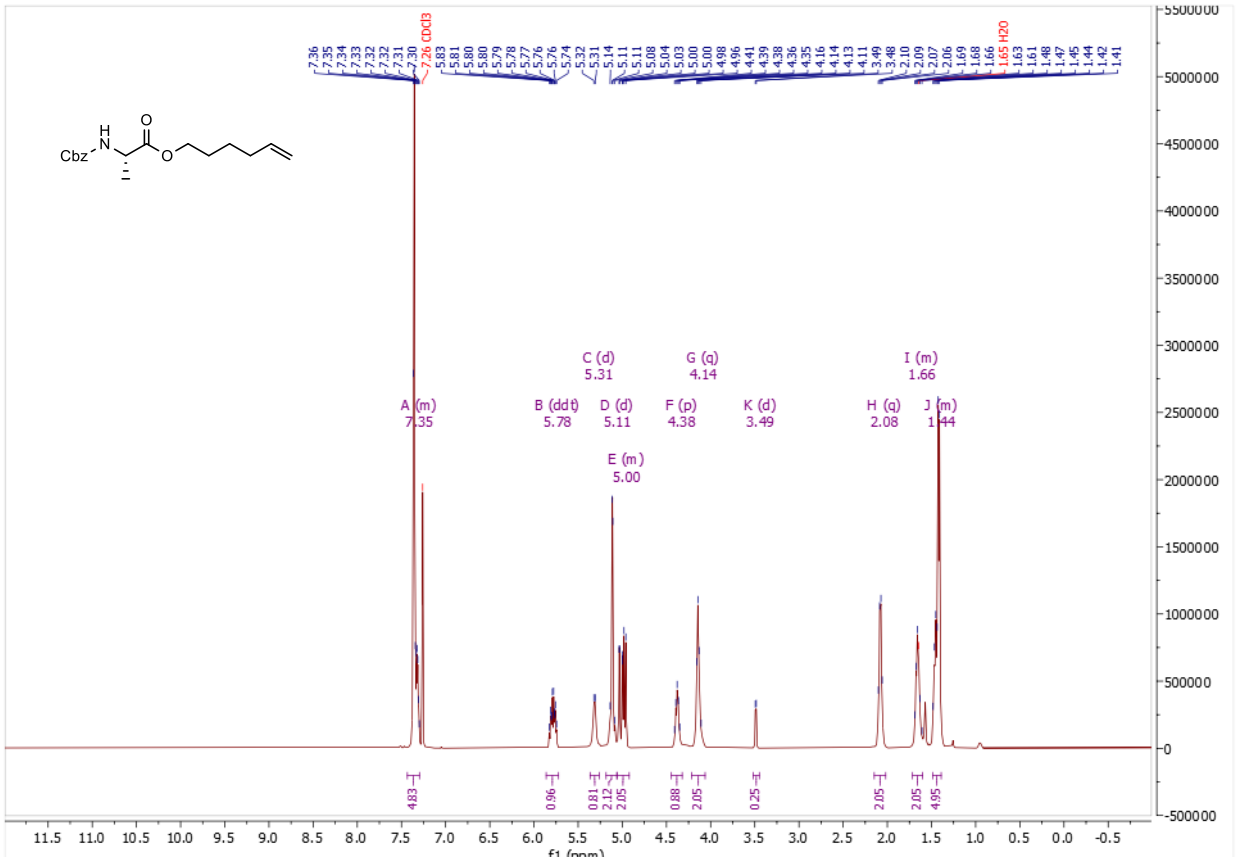


^{13}C NMR of phenethyl 2-(thiophen-3-yl)ethyl 3-phenylpropanoate (**20**).

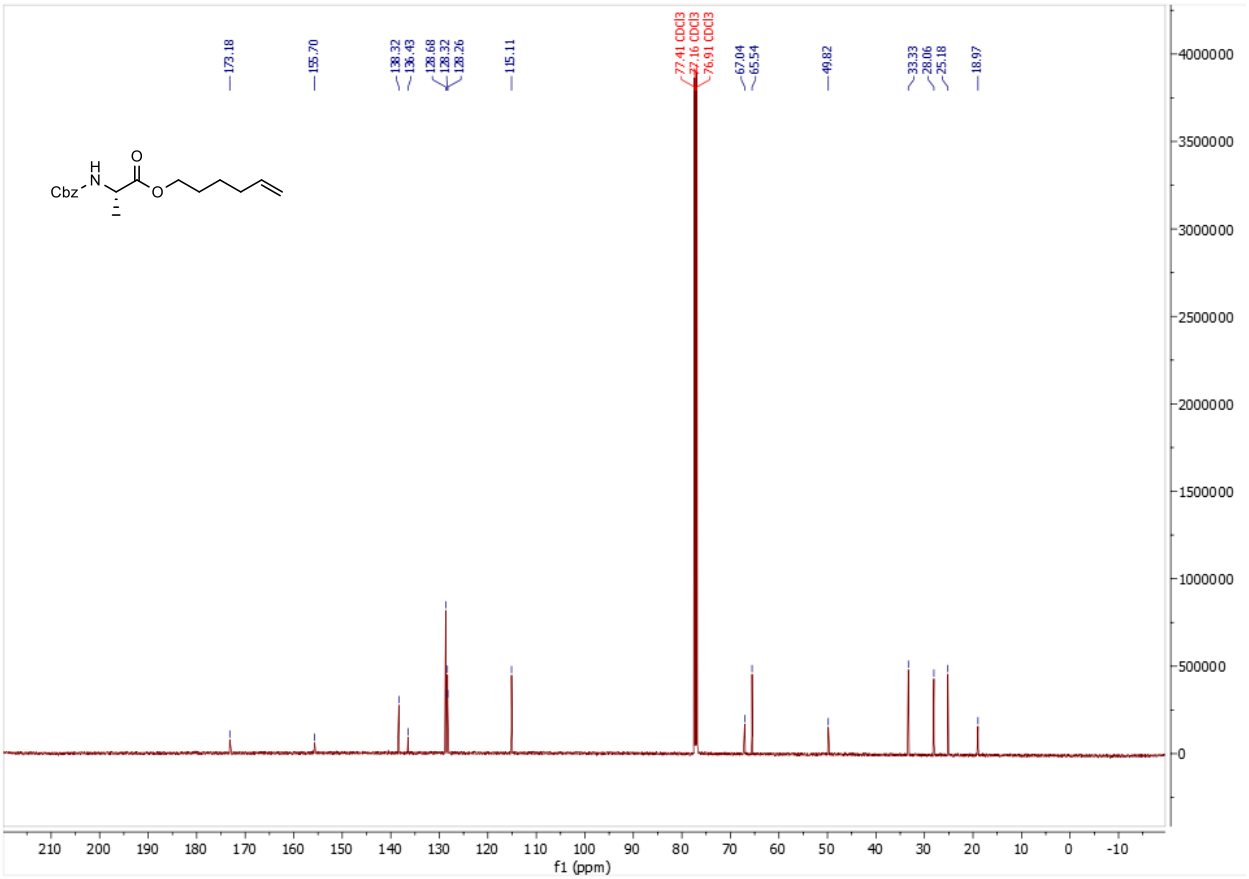
21. Hex-5-en-1-yl ((benzyloxy)carbonyl)-L-alaninate

General procedure A using 4 equivalents of the alcohol to yield **21** (76.3 mg, 50% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.30 (m, 5H), 5.78 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.31 (d, *J* = 7.6 Hz, 1H), 5.11 (d, *J* = 2.7 Hz, 2H), 5.06 – 4.92 (m, 2H), 4.38 (p, *J* = 7.3 Hz, 1H), 4.14 (q, *J* = 9.2 Hz, 2H), 3.49 (d, *J* = 5.5 Hz, 0H), 2.08 (q, *J* = 7.2 Hz, 2H), 1.71 – 1.60 (m, 2H), 1.49 – 1.39 (m, 5H). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 173.18, 155.70, 138.32, 136.43, 128.68, 128.32, 128.26, 115.11, 67.04, 65.54, 49.82, 33.33, 28.06, 25.18, 18.97. **Chemical Formula**: HRMS (ESI) *m/z*: [M+Na]+ calcd. for $NaC_{17}H_{23}NO_4$: 328.1525; found: 328.1530 (1.5 ppm).



^{1}H NMR of hex-5-en-1-yl ((benzyloxy)carbonyl)-L-alaninate (**21**).

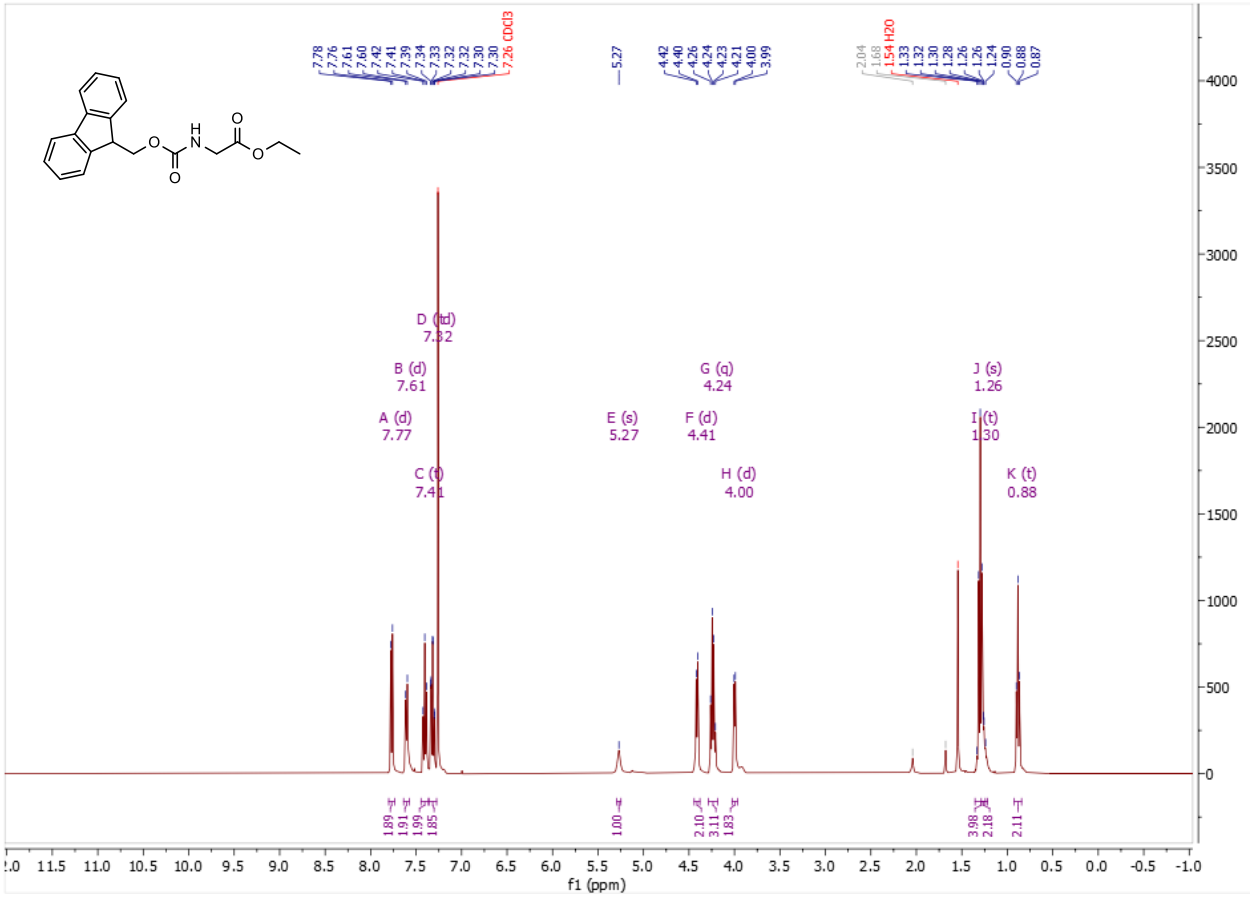


^{13}C NMR of hex-5-en-1-yl ((benzyloxy)carbonyl)-L-alaninate (**21**).

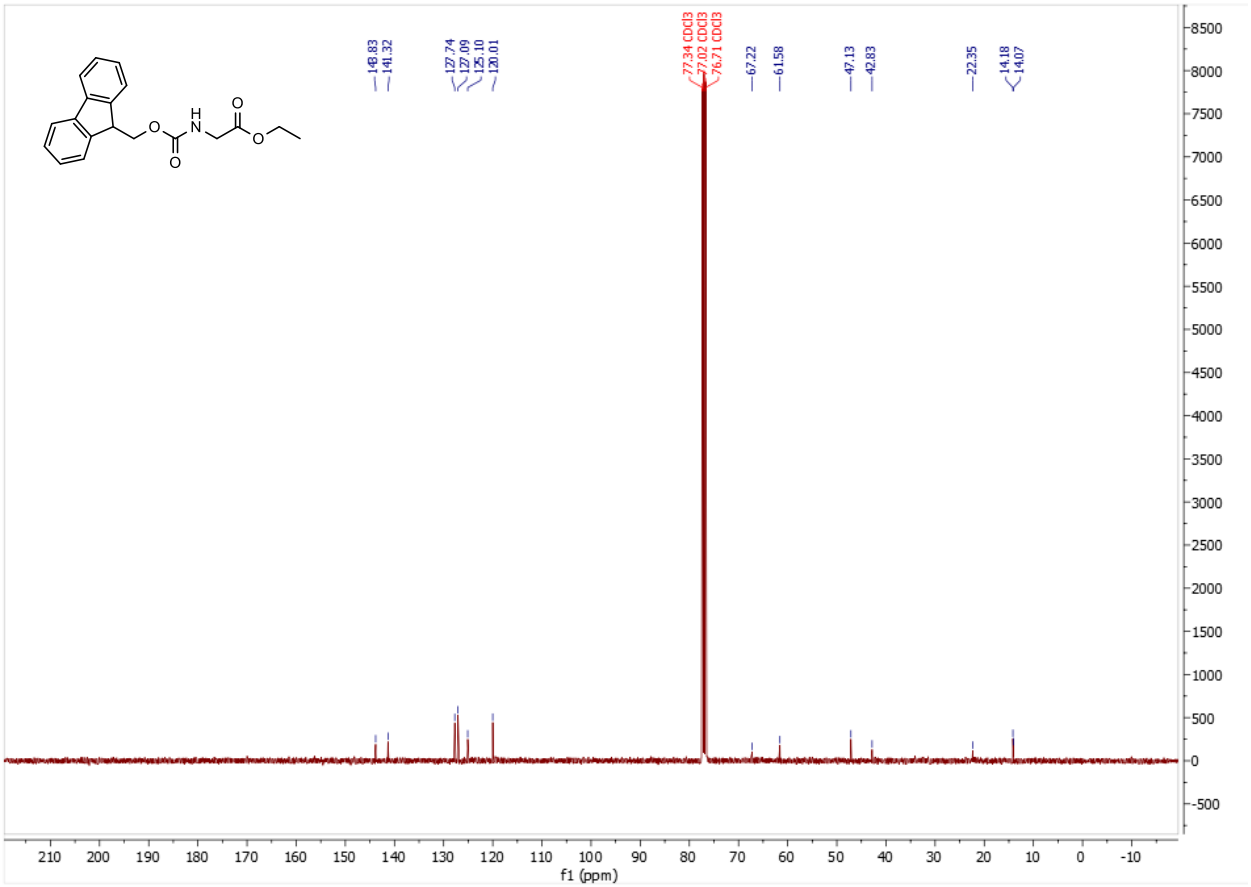
22. Ethyl (*N*-Fmoc)glycinate

General procedure B with TPGS-750-M to yield **22** (52 mg, 32% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.5 Hz, 2H), 7.61 (d, *J* = 7.5 Hz, 2H), 7.41 (t, *J* = 7.4 Hz, 2H), 7.32 (td, *J* = 7.5, 1.2 Hz, 2H), 5.27 (s, 1H), 4.41 (d, *J* = 7.1 Hz, 2H), 4.24 (q, *J* = 7.2 Hz, 3H), 4.00 (d, *J* = 5.5 Hz, 2H), 1.30 (t, *J* = 7.2 Hz, 4H), 1.26 (s, 2H), 0.88 (t, *J* = 7.0 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 143.83, 141.32, 127.74, 127.09, 125.10, 120.01, 67.22, 61.58, 47.13, 42.83, 22.35, 14.18, 14.07. **Chemical Formula**: HRMS (ESI) *m/z*: [M+Na]+ calcd. for $NaC_{19}H_{19}NO_4$: 348.1212; found: 348.1218 (1.7 ppm).



^{1}H NMR of ethyl (*N*-Fmoc)glycinate (**22**).

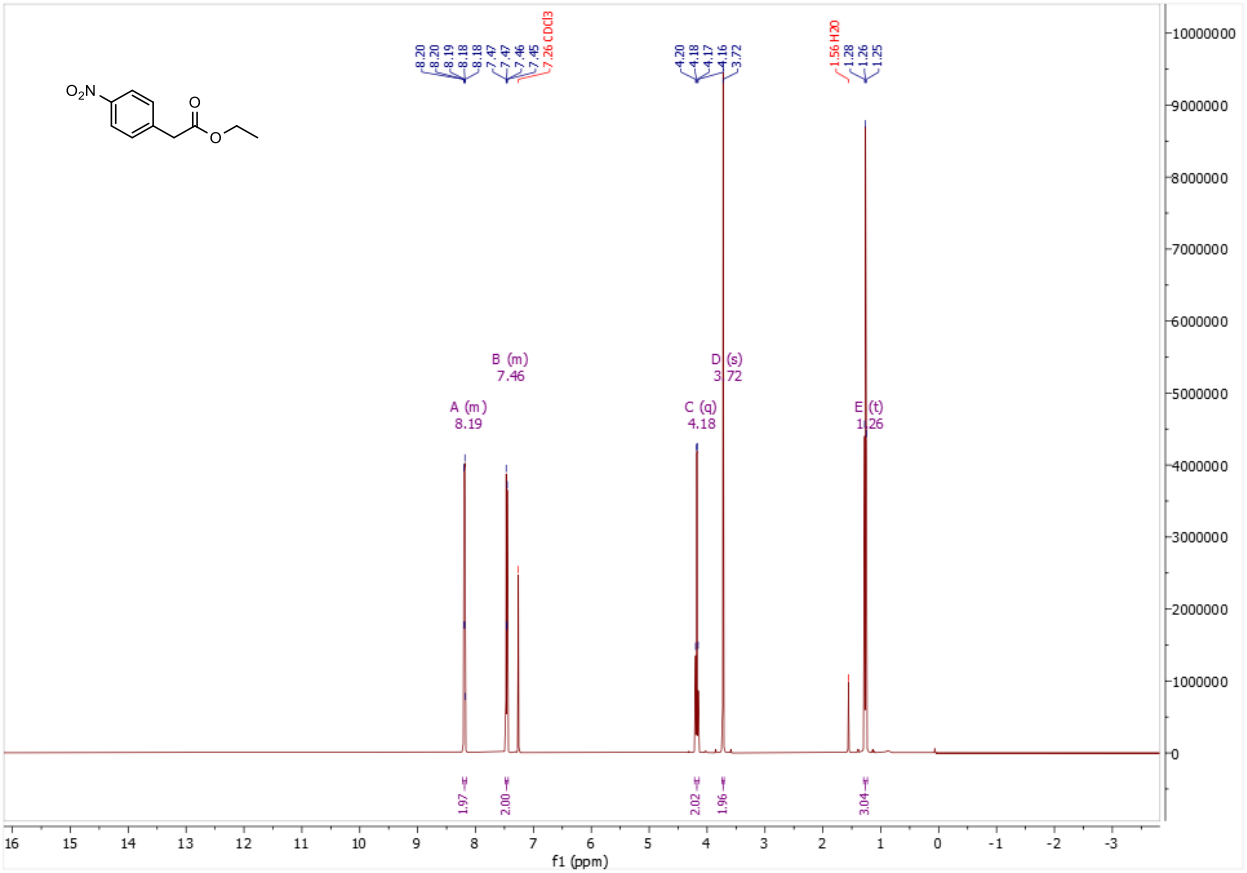


^{13}C NMR of ethyl (*N*-Fmoc)glycinate (**22**).

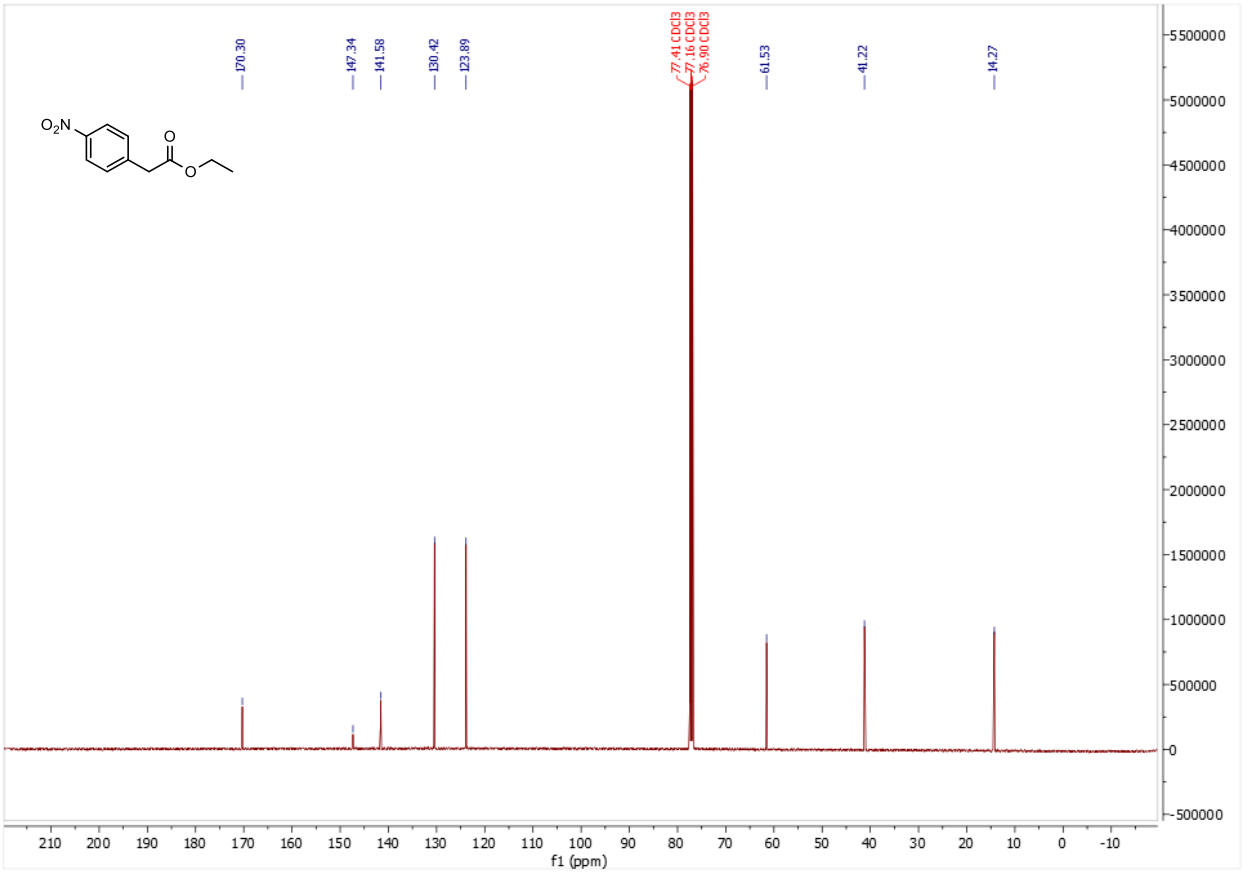
23. Ethyl 2-(4-nitrophenyl)acetate

General procedure A to yield **23** (49.2 mg, 47% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 – 8.16 (m, 2H), 7.49 – 7.44 (m, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.72 (s, 2H), 1.26 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 170.30, 147.34, 141.58, 130.42, 123.89, 77.41, 77.16, 76.90, 61.53, 41.22, 14.27. **Chemical Formula**: HRMS (EI) *m/z*: [M]+ calcd. for $C_{19}H_{19}NO_4$: 209.0688; found: 209.0682 (2.9 ppm).



^{1}H NMR of ethyl 2-(4-nitrophenyl)acetate (**23**).

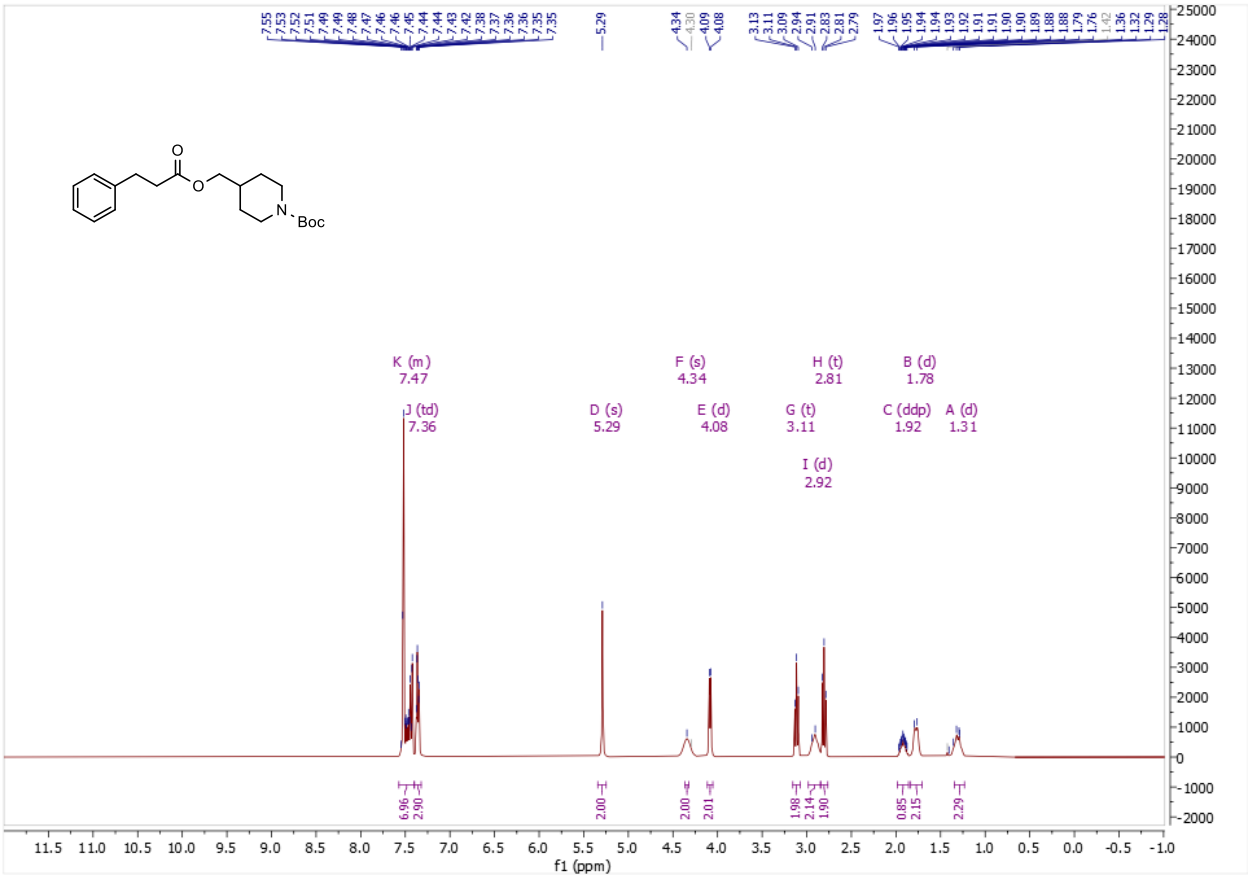


^{13}C NMR of ethyl 2-(4-nitrophenyl)acetate (**23**).

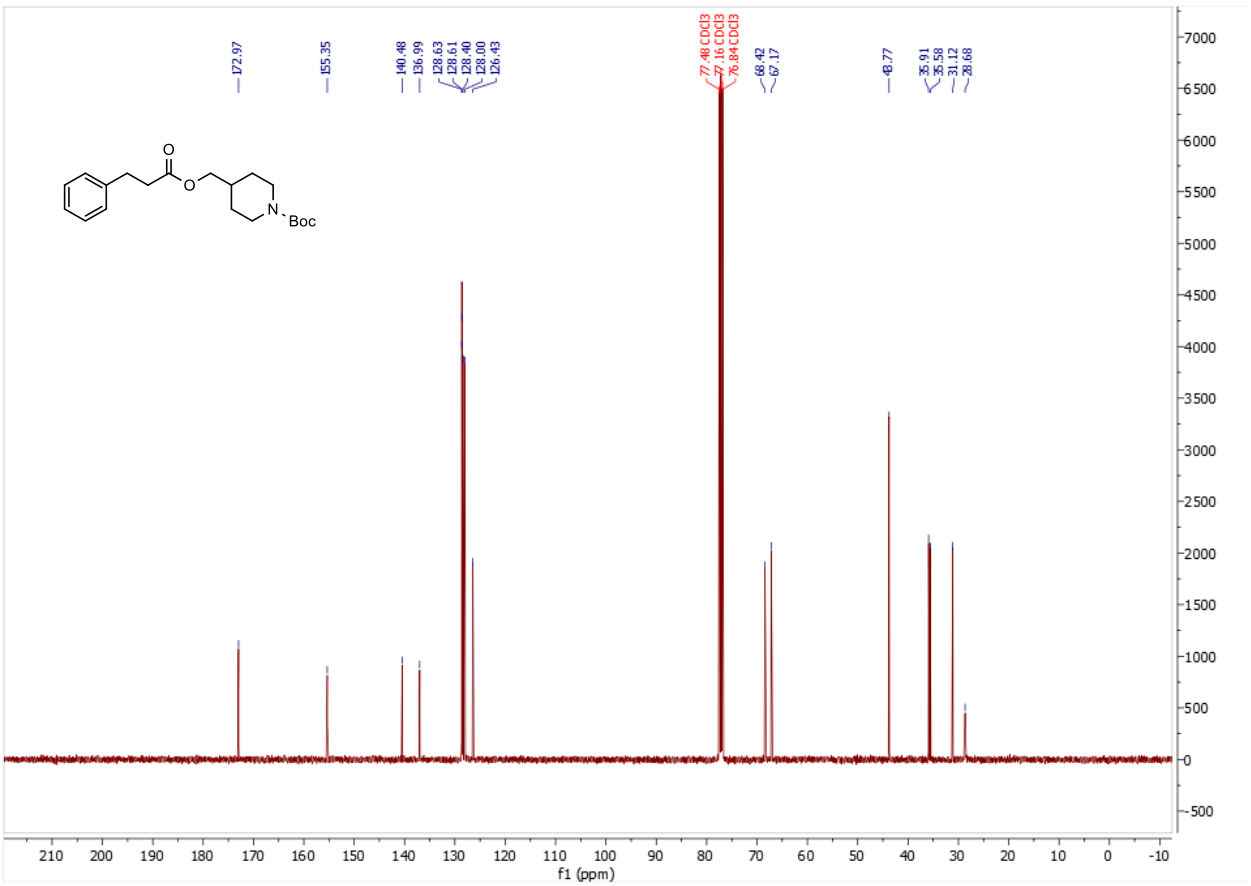
24. *t*-Butyl 4-(((3-phenylpropanoyl)oxy)methyl)piperidine-1-carboxylate

General procedure A to yield 2**4** (38.2 mg, 22% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.40 (m, 7H), 7.36 (td, *J* = 5.0, 2.6 Hz, 3H), 5.29 (s, 2H), 4.34 (s, 2H), 4.08 (d, *J* = 6.5 Hz, 2H), 3.11 (t, *J* = 7.7 Hz, 2H), 2.92 (d, *J* = 14.8 Hz, 2H), 2.81 (t, *J* = 7.7 Hz, 2H), 1.92 (ddp, *J* = 11.8, 8.0, 3.0 Hz, 1H), 1.78 (d, *J* = 12.0 Hz, 2H), 1.31 (d, *J* = 11.4 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 172.97, 155.35, 140.48, 136.99, 128.63, 128.61, 128.40, 128.00, 126.43, 77.48, 77.16, 76.84, 68.42, 67.17, 43.77, 35.91, 35.58, 31.12, 28.68. **Chemical Formula**: HRMS (ESI) *m/z*: [M+Na]+ calcd. for $NaC_{20}H_{29}NO_4$: 404.1838; found: 404.1838 (0.0 ppm).



^{1}H NMR of *t*-butyl 4-(((3-phenylpropanoyl)oxy)methyl)piperidine-1-carboxylate (2**4**).

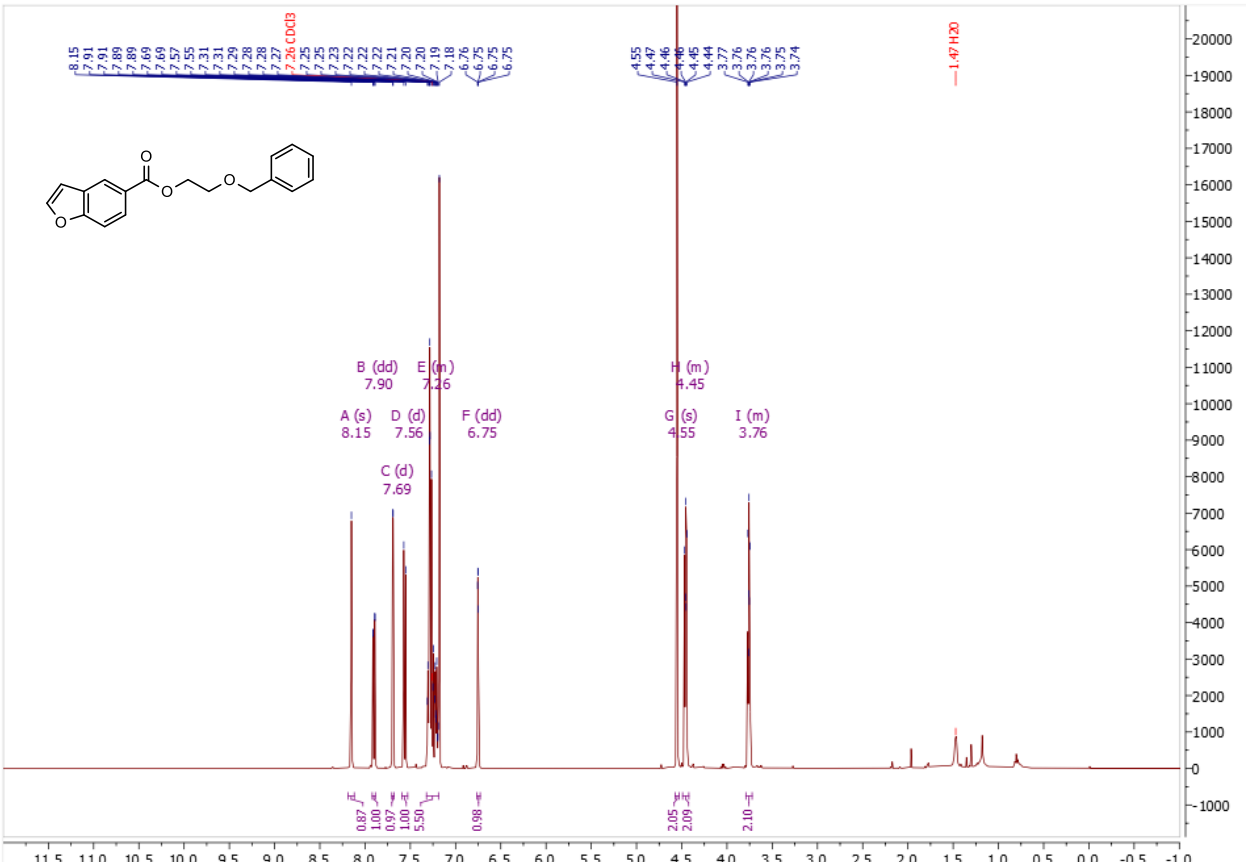


^{13}C NMR of *t*-butyl 4-(((3-phenylpropanoyl)oxy)methyl)piperidine-1-carboxylate (2**4**).

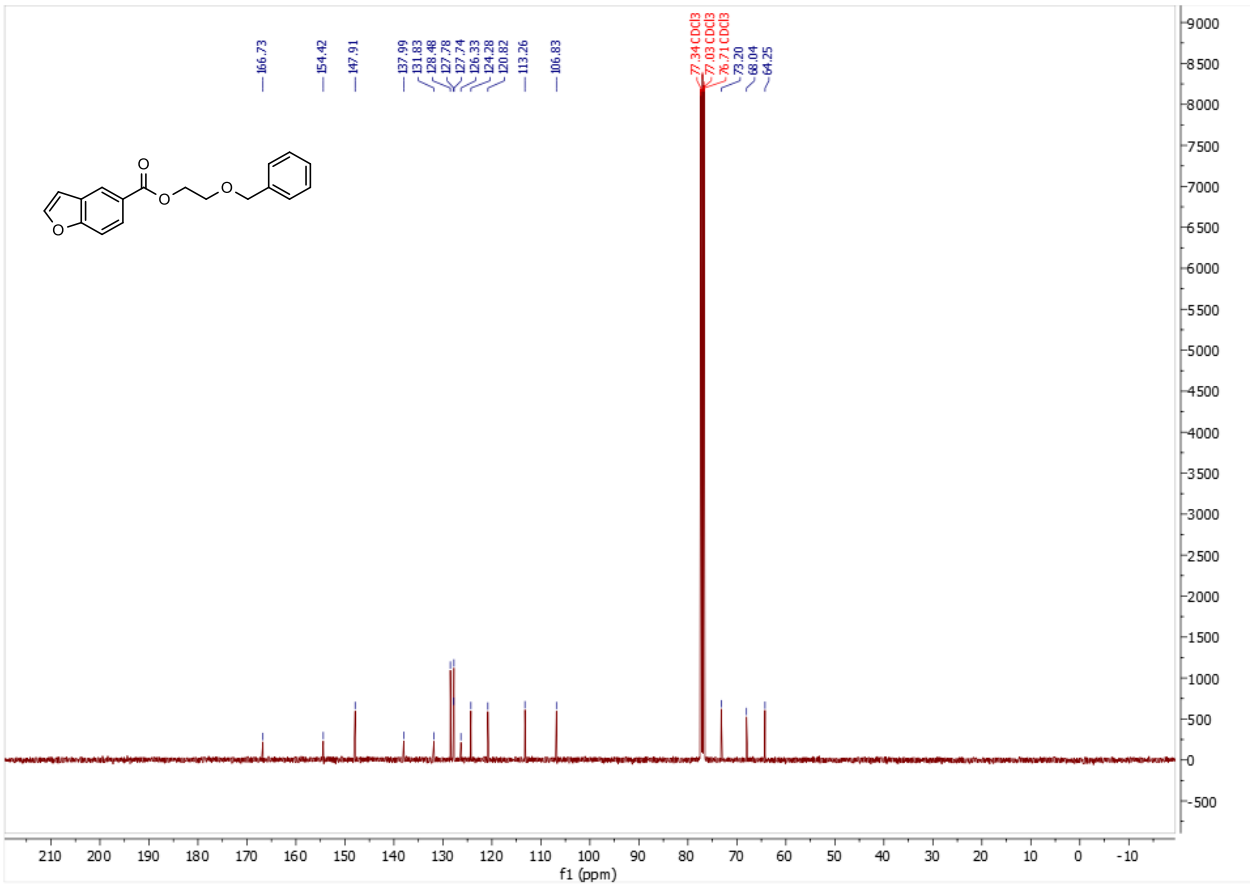
25. 2-(Benzyloxy)ethyl benzofuran-5-carboxylate

General procedure A using TPGS-750-M to yield **25** (23.7 mg, 16% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.98 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.77 (d, *J* = 2.2 Hz, 1H), 7.64 (d, *J* = 8.2 Hz, 1H), 7.40 – 7.27 (m, 5H), 6.83 (dd, *J* = 2.2, 1.0 Hz, 1H), 4.63 (s, 2H), 4.57 – 4.50 (m, 2H), 3.87 – 3.80 (m, 2H). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 166.73, 154.42, 147.91, 137.99, 131.83, 128.48, 127.78, 127.74, 126.33, 124.28, 120.82, 113.26, 106.83, 73.20, 68.04, 64.25. **Chemical Formula**: HRMS (EI) *m/z*: [M+Na]+ calcd. for $NaC_{18}H_{16}O_4$: 319.0947; found: 319.0947 (0.3 ppm).



^{1}H NMR of 2-(benzyloxy)ethyl benzofuran-5-carboxylate (**25**).

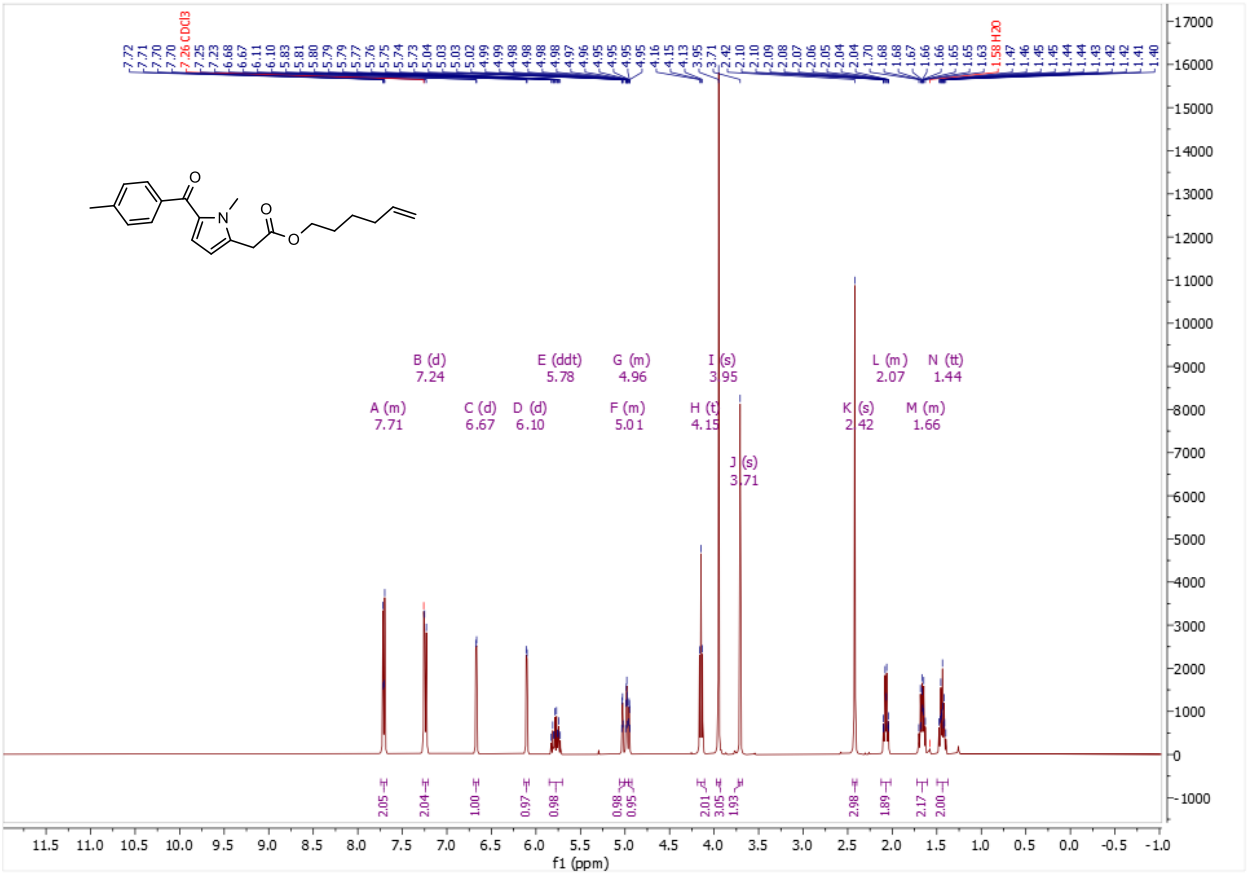


^{13}C NMR of 2-(benzyloxy)ethyl benzofuran-5-carboxylate (**25**).

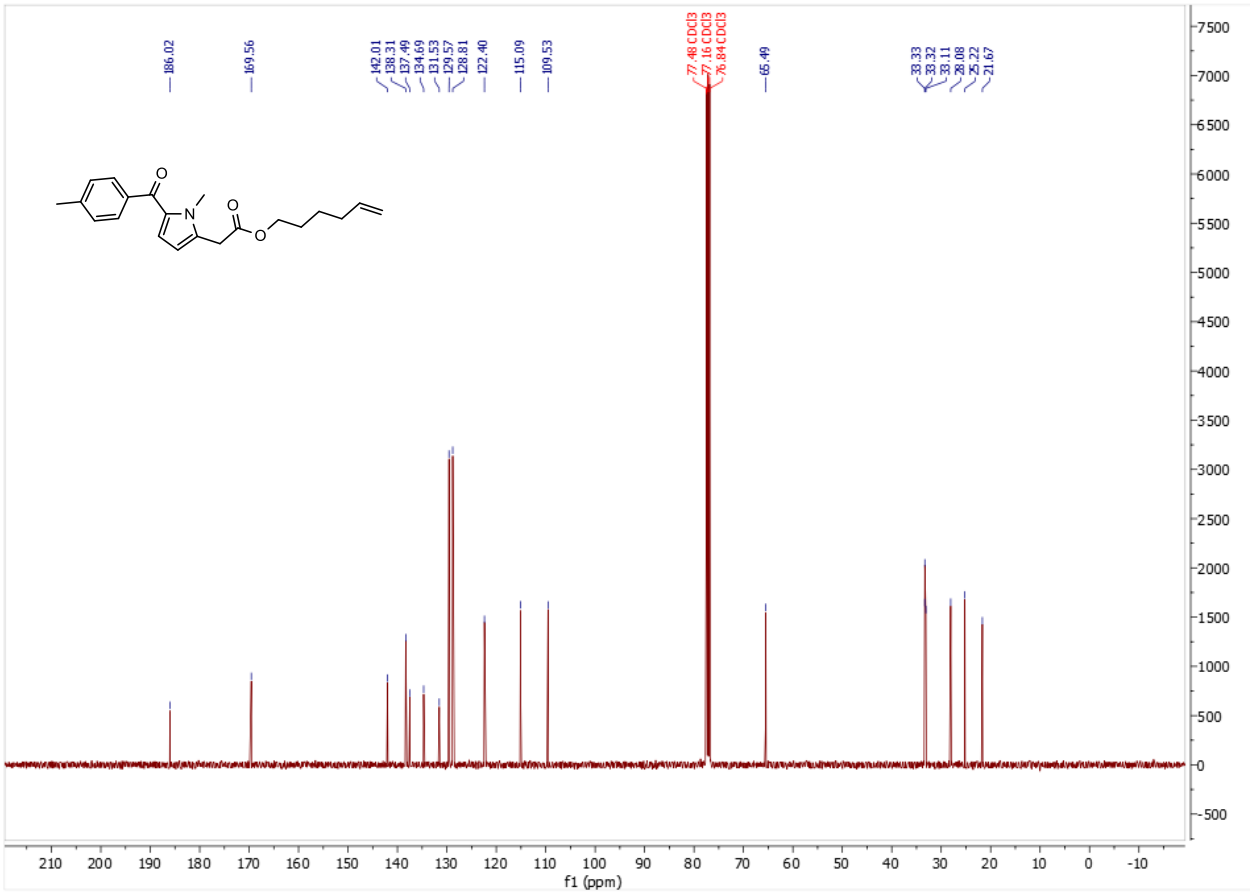
26. Hex-5-en-1-yl 2-(1-methyl-5-(4-methylbenzoyl)-1H-pyrrol-2-yl)acetate

A 1-dram vial equipped with Teflon-coated magnetic stir bar was charged with acid (Tolmetin) (0.5 mmol, 1 equiv) and 100 µL DMSO. This was heated vigorously with a heat gun until all material was dissolved. 5-hexen-1-ol (1.0 mmol, 2 equiv) and Novozym 435 (50 mg) were then added followed by 500 µL of aqueous 2 wt % solution of TPGS-750-M. The vial was capped and then set to stir (~30 s) before being centrifuged briefly (~30 s) on a bench centrifuge. Extraction and purification were then carried out according to General Procedure A to yield **26** (69.6 mg, 41% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.68 (m, 2H), 7.24 (d, *J* = 7.9 Hz, 2H), 6.67 (d, *J* = 4.0 Hz, 1H), 6.10 (d, *J* = 4.0 Hz, 1H), 5.78 (ddt, *J* = 16.9, 10.1, 6.6 Hz, 1H), 5.06 – 4.96 (m, 1H), 5.00 – 4.92 (m, 1H), 4.15 (t, *J* = 6.7 Hz, 2H), 3.95 (s, 3H), 3.71 (s, 2H), 2.42 (s, 3H), 2.12 – 2.02 (m, 2H), 1.72 – 1.61 (m, 2H), 1.44 (tt, *J* = 10.0, 6.4 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$) δ** 186.02, 169.56, 142.01, 138.31, 137.49, 134.69, 131.53, 129.57, 128.81, 122.40, 115.09, 109.53, 65.49, 33.33, 33.32, 33.11, 28.08, 25.22, 21.67. **Chemical Formula**: HRMS (EI) *m/z*: [M+H]+ calcd. for $C_{21}H_{25}NO_3$: 340.1912; found: 340.1912 (0.0 ppm).



^{1}H NMR of hex-5-en-1-yl 2-(1-methyl-5-(4-methylbenzoyl)-1H-pyrrol-2-yl)acetate (**26**).

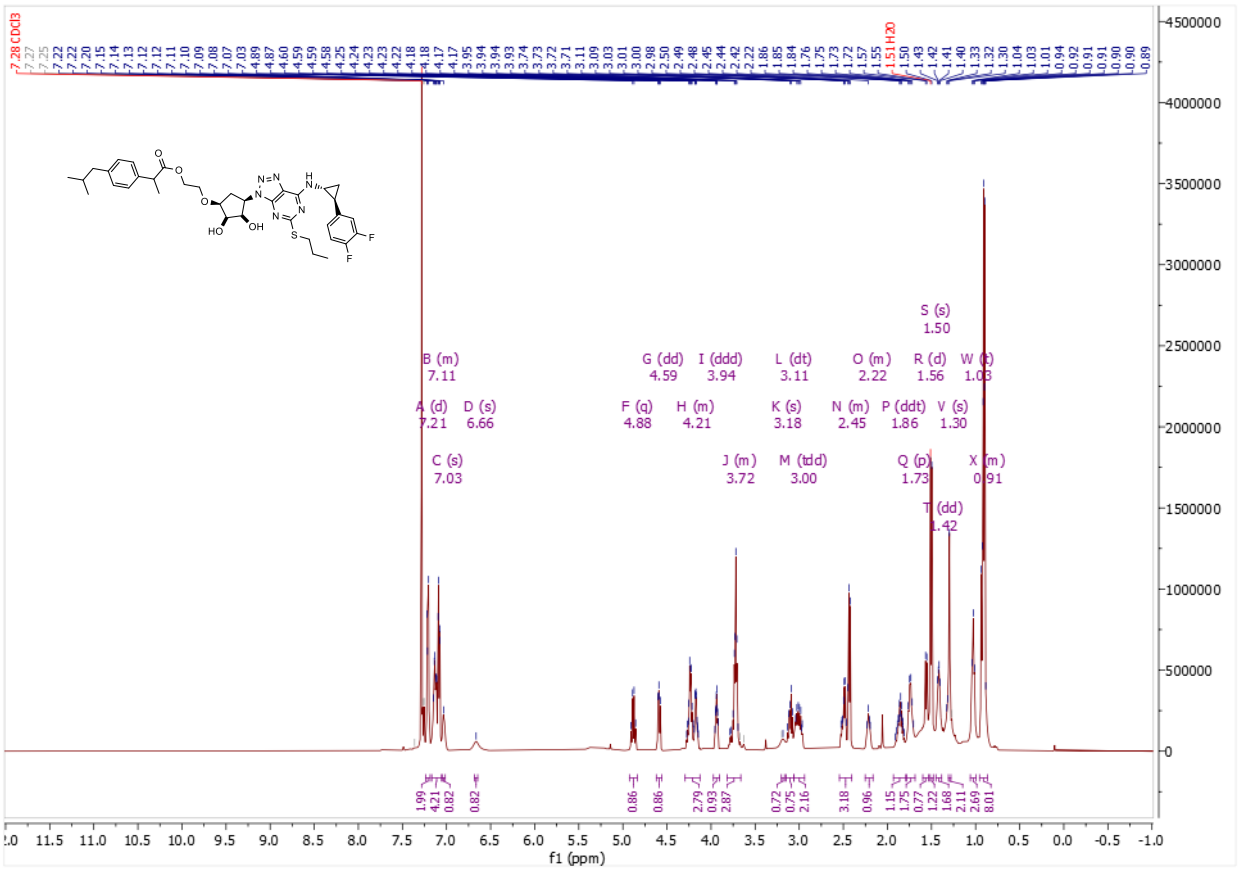


^{13}C NMR of hex-5-en-1-yl 2-(1-methyl-5-(4-methylbenzoyl)-1H-pyrrol-2-yl)acetate (**26**).

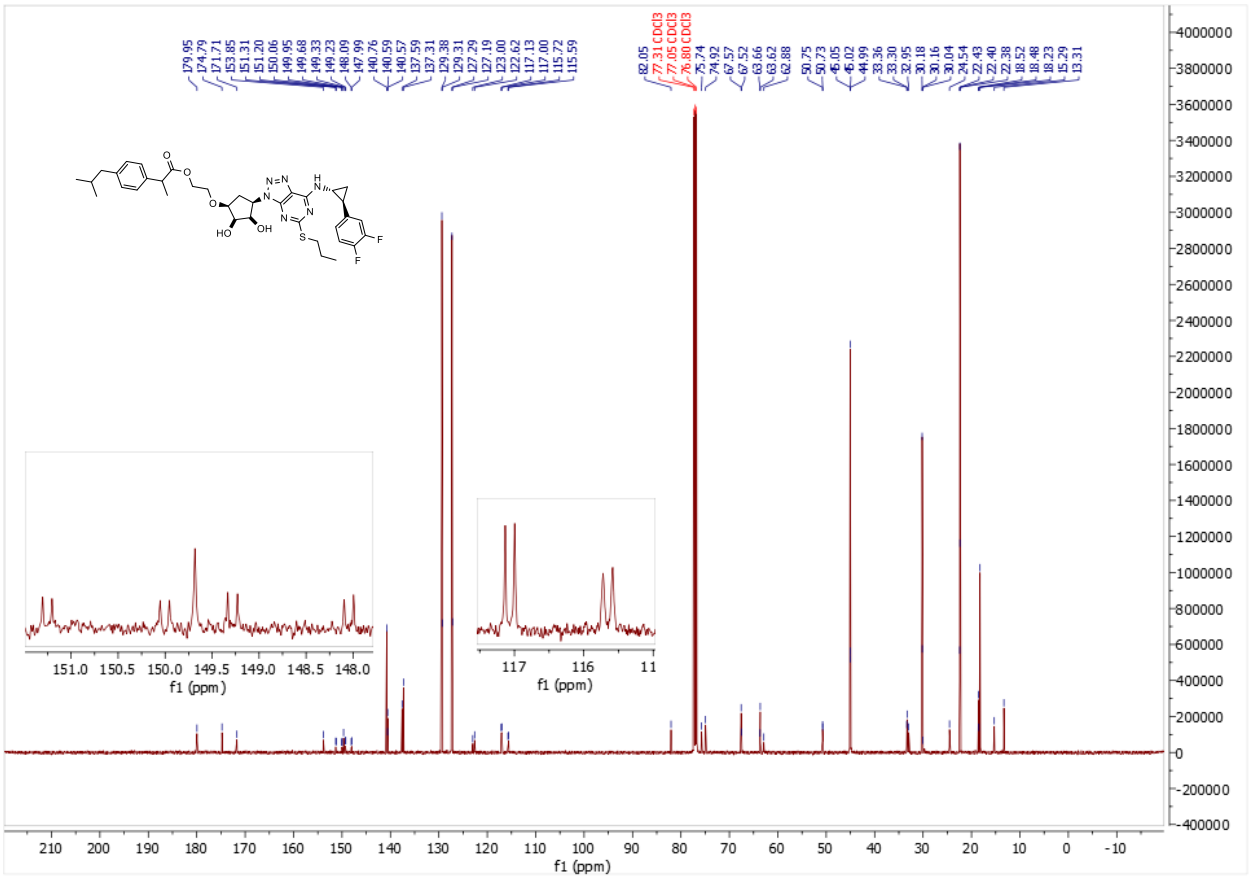
27. Ibuprofen-Ticagrelor Ester

A 1-dram vial equipped with Teflon-coated magnetic stir bar was charged with alcohol (Ticagrelor) (0.5 mmol, 1 equiv) and 100 µL DMSO. This was heated vigorously with a heat gun until all material was dissolved. Ibuprofen (1.0 mmol, 2 equiv) and Novozym 435 (50 mg) were then added followed by 500 µL of aqueous 2 wt % solution of TPGS-750-M. The vial was capped and then set to stir (~30s) before being centrifuged briefly (~30s) on a bench centrifuge. Extraction and purification were then carried out according to General Procedure A to yield **27** (167.1 mg, 47% yield).

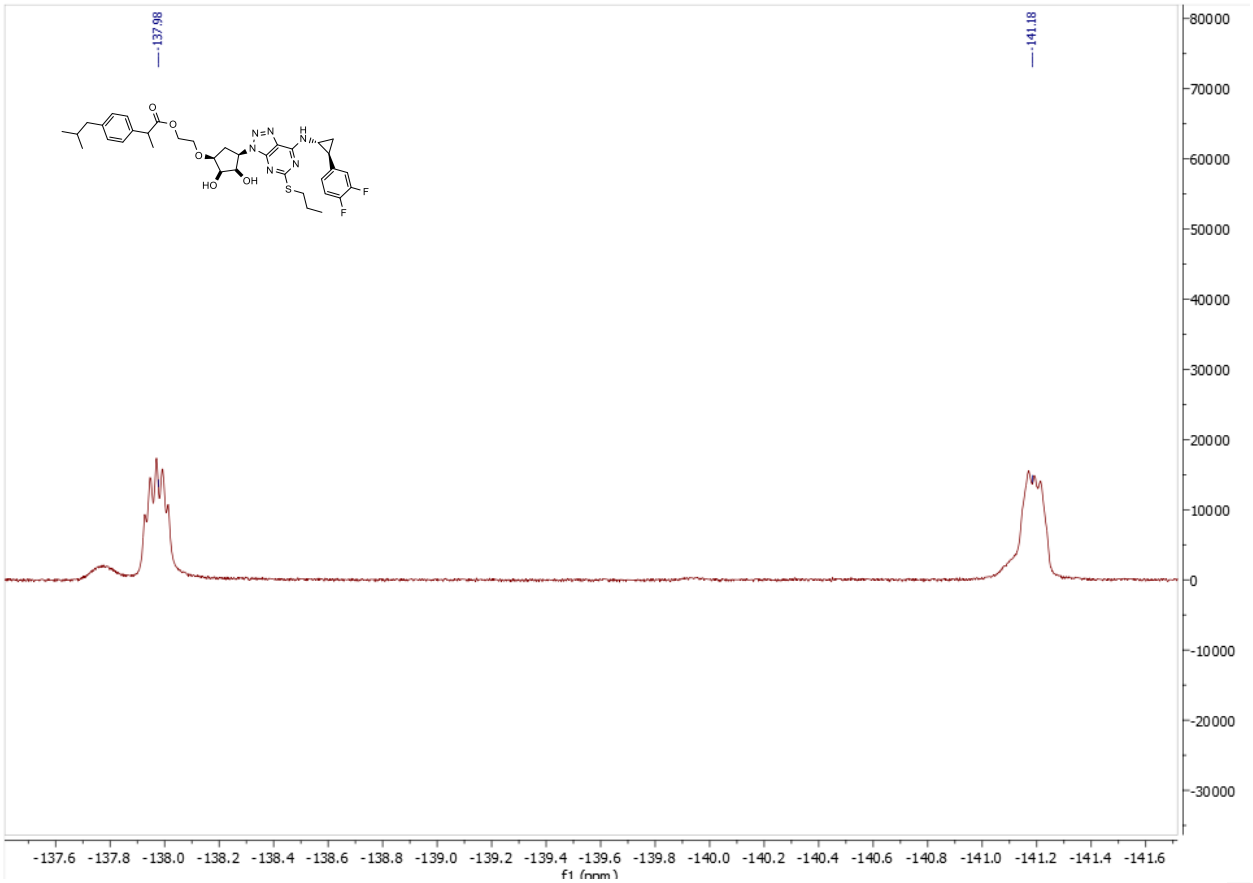
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.1 Hz, 2H), 7.17 – 7.06 (m, 4H), 7.03 (s, 1H), 6.66 (s, 1H), 4.88 (q, *J* = 8.7 Hz, 1H), 4.59 (dd, *J* = 7.8, 5.3 Hz, 1H), 4.29 – 4.13 (m, 3H), 3.94 (ddd, *J* = 7.5, 5.3, 2.3 Hz, 1H), 3.82 – 3.66 (m, 3H), 3.18 (s, 1H), 3.11 (dt, *J* = 14.1, 7.2 Hz, 1H), 3.00 (tdd, *J* = 12.5, 9.4, 5.6 Hz, 2H), 2.54 – 2.40 (m, 3H), 2.25 – 2.16 (m, 1H), 1.86 (ddt, *J* = 13.6, 9.7, 6.8 Hz, 1H), 1.73 (p, *J* = 7.4 Hz, 2H), 1.56 (d, *J* = 7.1 Hz, 1H), 1.50 (s, 1H), 1.42 (dd, *J* = 9.2, 5.3 Hz, 2H), 1.30 (s, 2H), 1.03 (t, *J* = 7.4 Hz, 3H), 0.96 – 0.87 (m, 8H). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 179.95, 174.79, 171.71, 153.85, 151.31, 151.20, 150.06, 149.95, 149.68, 149.33, 149.23, 148.09, 147.99, 140.76, 140.59, 140.57, 137.59, 137.31, 129.38, 129.31, 127.29, 127.19, 123.00, 122.62, 117.13, 117.00, 115.72, 115.59, 82.05, 75.74, 74.92, 67.57, 67.52, 63.66, 63.62, 62.88, 50.75, 50.73, 45.05, 45.02, 44.99, 33.36, 33.30, 32.95, 30.18, 30.16, 30.04, 24.54, 22.43, 22.40, 22.38, 18.52, 18.48, 18.23, 15.29, 13.31. **^{19}F NMR (471 MHz, $CDCl_3$) δ** -137.77, -137.97, -141.19. **Chemical Formula**: HRMS (ESI) *m/z*: [M+H]+ calcd. for $C_{35}H_{44}F_2N_6O_5S$ 711.3140, found: 711.3145 (0.7 ppm).



^{1}H NMR of Ibuprofen Ticagrelor ester (**27**).



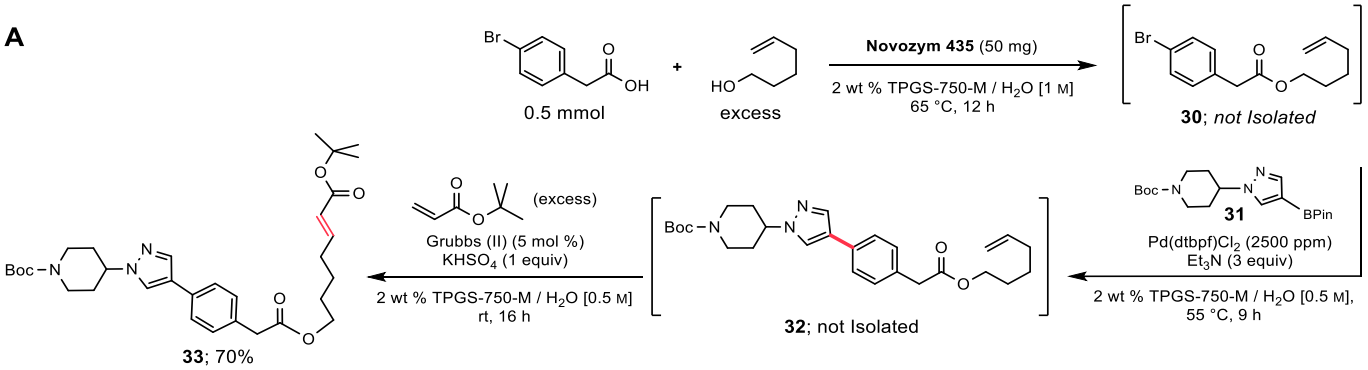
^{13}C NMR of Ibuprofen Ticagrelor ester (**27**).



^{19}F NMR of Ibuprofen Ticagrelor ester (**27**).

8. One-Pot Procedures

32. *t*-butyl (*E*)-4-(4-(4-(2-((7-(*t*-butoxy)-7-oxohept-5-en-1-yl)oxy)-2-oxoethyl)phenyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate



Esterification:

A 1-dram vial equipped with Teflon-coated magnetic stir bar was charged with 4-bromophenylacetic acid (57.0 mg, 0.25 mmol, 1 equiv), 5-hexen-1-ol (50.1 mg, 0.5 mmol, 2 equiv, 60.0 µL) and Novozym 435 (25 mg). 250 µL of aqueous 2 wt % solution of TPGS-750-M was added. The vial was capped and then set to stir (~30 s) before being centrifuged briefly (~30 s) on a bench centrifuge. The vial was then set to react for 14 h in an aluminum heating block preheated to 65 °C. The reaction was followed by TLC (eluting with 20% EtOAc/hexanes) and upon completion, the reaction was removed from heating and stirring before being allowed to cool to rt.

The reaction was then extracted with 3 x 1 mL of 2-MeTHF and the crude extracts were concentrated in a second 1-dram vial. The aqueous layer was then filtered over a short pad of Celite and the catalyst recovered. The aqueous filtrate was then added to the vial containing the crude concentrate and the volume made up to 0.5 mL with aqueous 2 wt % solution of TPGS-750-M.

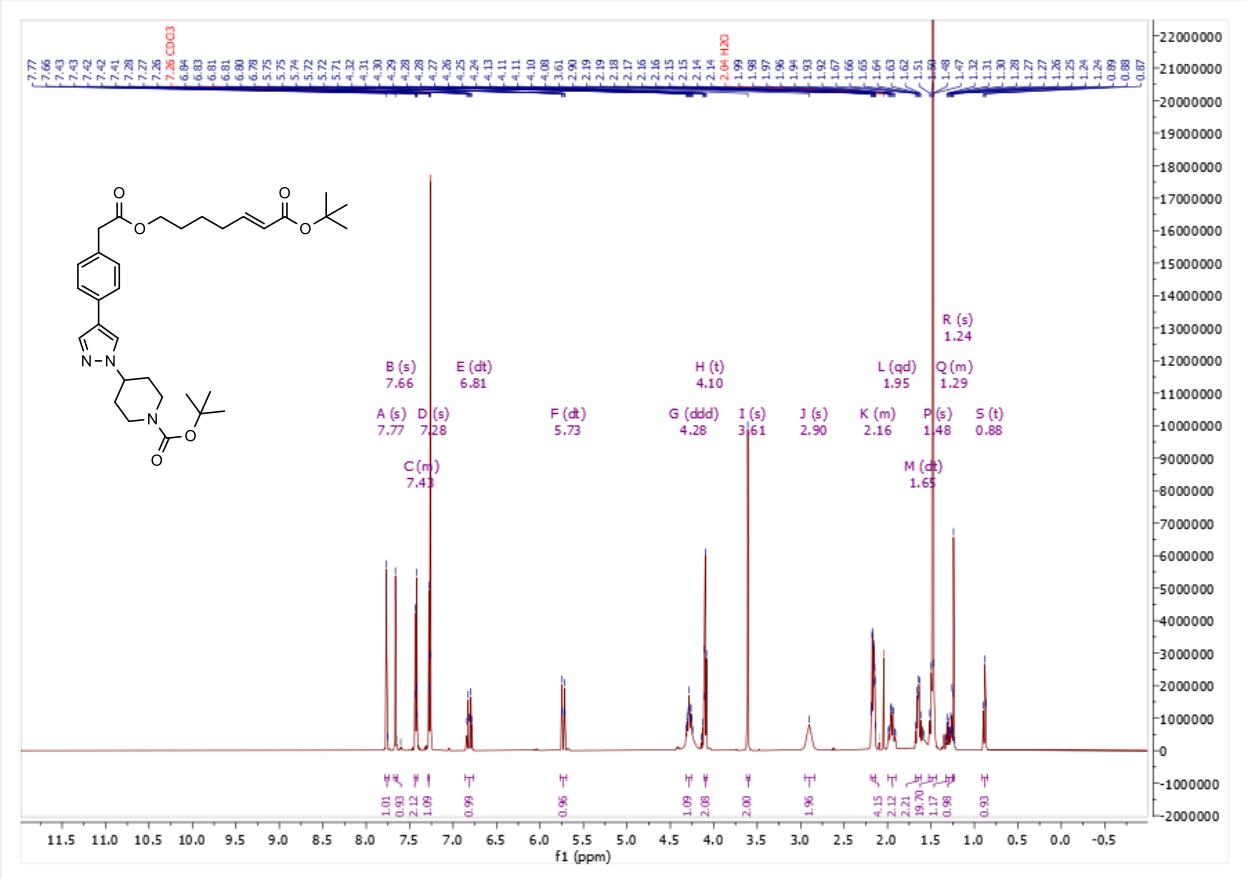
Suzuki Miyaura Coupling:

The vial containing the aqueous surfactant solution of crude extract was charged with a Teflon-coated magnetic stir bar and capped with a rubber septum. The aqueous solution was sparged vigorously with argon gas for 5 min to remove oxygen before the septum removed and *t*-butyl 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (117.9 mg, 0.3125 mmol, 1.25 equiv) was quickly added and the vial resealed with a rubber septum. The vial was evacuated and backfilled with argon 3x before triethylamine (75.9 mg, 0.75 mmol, 3 equiv, 105 µL) was added. The vial was returned to the aluminum heating block preheated to 55 °C and allowed to stir for 5 min. $Pd(dtbpf)Cl_2$ (0.41 mg, 0.000625 mmol, 0.0025 equiv) was then added via syringe to the reaction as a stock solution in DCM (0.41 mg/100 µL) through the septum. The reaction was left to proceed for 9 h and was followed by TLC (eluting with 20% EtOAc/hexanes).

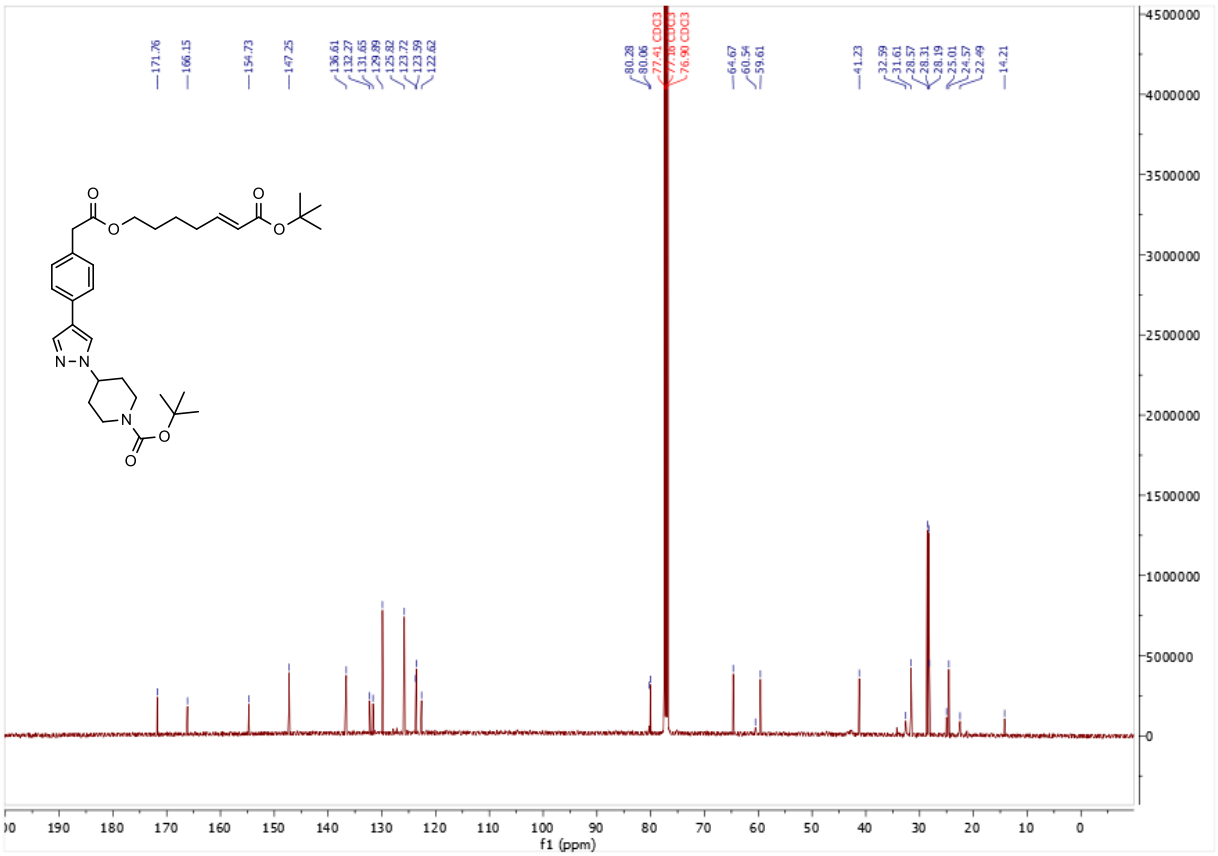
Olefin Metathesis:

Upon completion of the Suzuki Miyaura coupling, the vial was removed from heating and allowed to cool to rt. The septum was removed and $KHSO_4$ (34 mg, 0.25 mmol, 1 equiv) was added before the vial was re-sealed with the rubber septum. The vial was evacuated and backfilled with argon 3x before *t*-butyl acrylate (320 mg, 2.5 mmol, 10 equiv, 366 µL) was added via syringe through the septum followed by Grubbs II catalyst (8.5 mg, 0.01 mmol, 0.04 equiv) as a stock solution in DCM (8.5 mg / 100 µL). The reaction was left to stir for 16 h at rt before it was extracted 3x with EtOAc and the combined extracts filtered through a short plug of silica. The crude extracts were concentrated under vacuum and purified by silica gel chromatography eluting with a gradient of 5–30% EtOAc in hexanes. The product was concentrated under vacuum to yield a clear oil (99 mg, 70% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.66 (s, 1H), 7.44 – 7.41 (m, 2H), 7.28 (s, 1H), 6.81 (dt, *J* = 15.6, 6.9 Hz, 1H), 5.73 (dt, *J* = 15.6, 1.6 Hz, 1H), 4.28 (ddd, *J* = 11.6, 7.5, 4.0 Hz, 1H), 4.10 (t, *J* = 6.5 Hz, 2H), 3.61 (s, 2H), 2.90 (s, 2H), 2.19 – 2.14 (m, 4H), 1.95 (qd, *J* = 12.3, 4.4 Hz, 2H), 1.65 (dt, *J* = 15.0, 6.6 Hz, 2H), 1.48 (s, 20H), 1.33 – 1.25 (m, 1H), 1.24 (s, 1H), 0.88 (t, *J* = 7.1 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.76, 166.15, 154.73, 147.25, 136.61, 132.27, 131.65, 129.89, 125.82, 123.72, 123.59, 122.62, 80.28, 80.06, 64.67, 60.54, 59.61, 41.23, 32.59, 31.61, 28.57, 28.31, 28.19, 25.01, 24.57, 22.49, 14.21. **Chemical Formula**: HRMS (EI) *m/z*: [M+Na]+ calcd. for $C_{32}H_{45}N_3O_6$: 590.3208; found: 590.3221 (2.5 ppm).

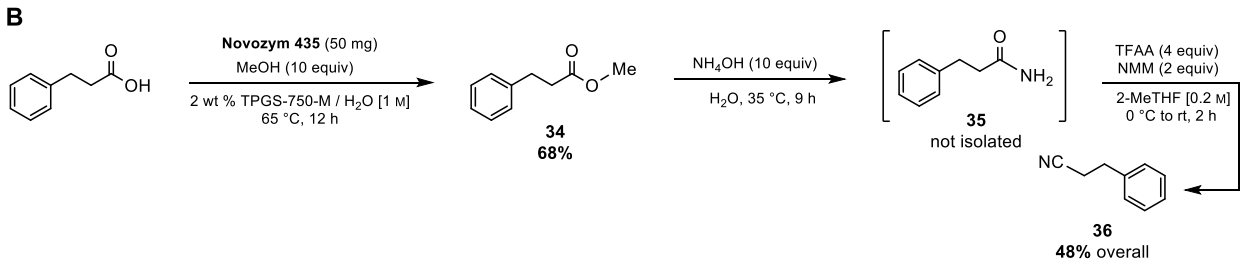


^{1}H NMR of *t*-butyl (*E*)-4-(4-(4-(2-((7-(*t*-butoxy)-7-oxohept-5-en-1-yl)oxy)-2-oxoethyl)phenyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (**32**)



^{13}C NMR of *t*-butyl (*E*)-4-(4-(4-(2-((7-(*t*-butoxy)-7-oxohept-5-en-1-yl)oxy)-2-oxoethyl)phenyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (**32**)

36. 3-phenylpropionitrile



Esterification

Esterification of phenylpropionic acid and methanol was performed according to general procedure B. The compound was isolated by column chromatography using 10% EtOAc in hexanes.

Amidation

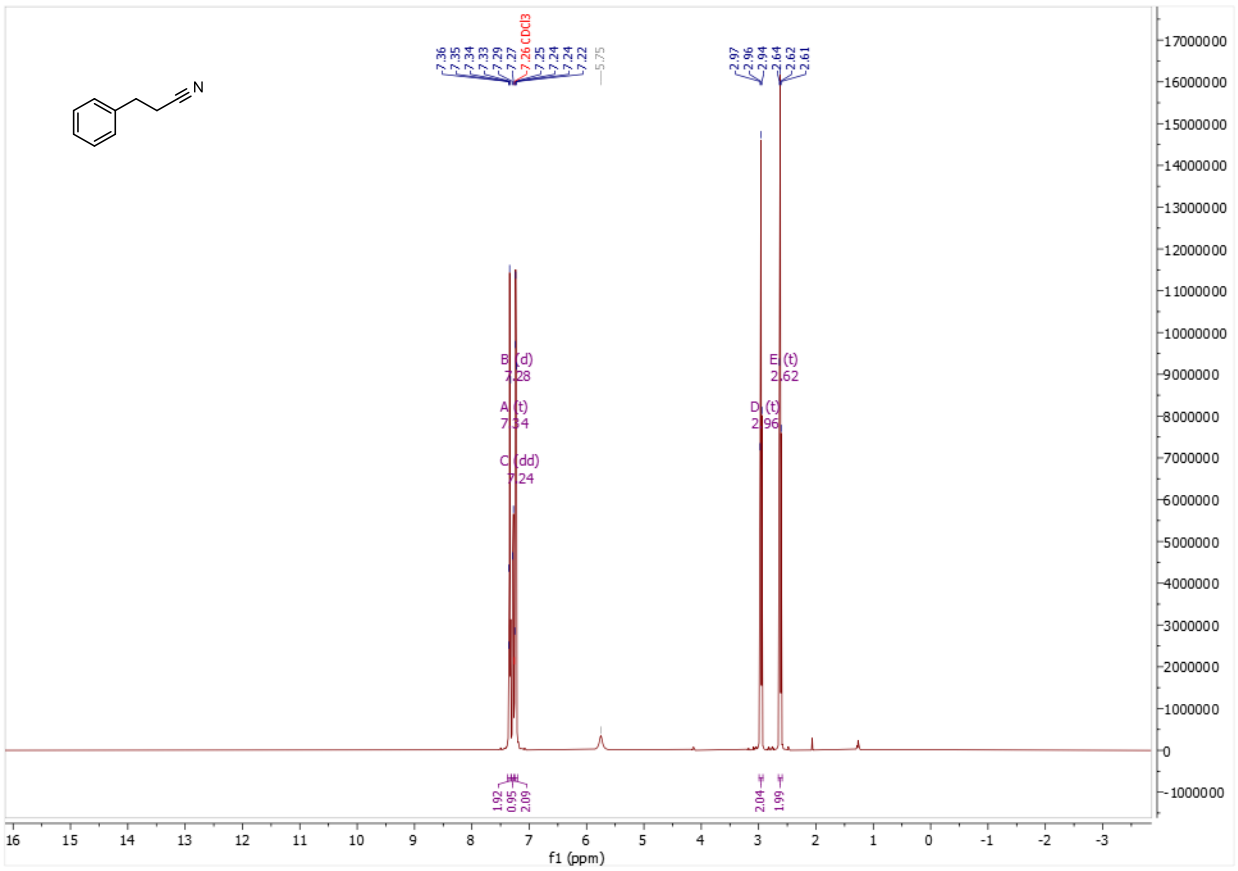
Pure ester **34** was concentrated into a 1-dram vial and the vial charged with a magnetic stirbar and 30% aqueous ammonium hydroxide (119 mg, 3.4 mmol, 1 equiv, 397 µL) and the reaction stirred for 9 h at 35 °C.

Dehydration

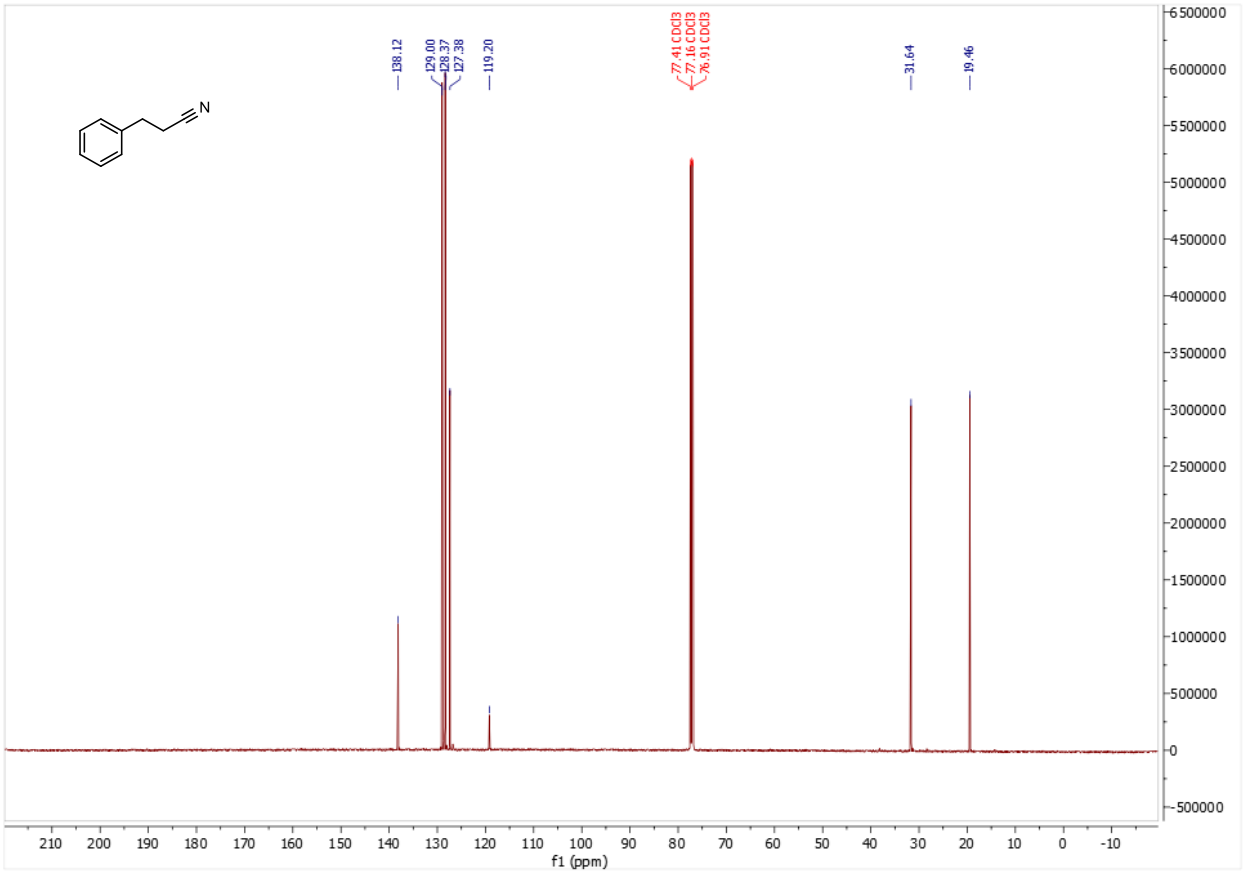
The reaction was neutralized with 1 M HCl solution and extracted 3x with EtOAc. The combined organic extracts were concentrated to give crude amide **35**. This amide was transferred to a 1-dram vial and azeotropically dried with toluene. The dry amide was dissolved in 2-MeTHF (0.57 mL) before being cooled on ice. To the cooled solution was added *N*-methylmorpholine (68.7 mg, 0.68 mmol, 2 equiv, 74.7 µL) followed by trifluoroacetic anhydride (285.6 mg, 1.36 mmol, 4 equiv, 190 µL). The reaction was stirred on ice for 10 min before being allowed to warm to rt and stirred over 2 h.

The product nitrile was extracted with EtOAc and purified by silica gel chromatography (5% EtOAc/hexanes) to yield **36** as a colorless oil (30.8 mg, 47% overall yield)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (t, *J* = 7.5 Hz, 2H), 7.28 (d, *J* = 7.2 Hz, 1H), 7.24 (dd, *J* = 8.0, 6.3 Hz, 2H), 2.96 (t, *J* = 7.5 Hz, 2H), 2.62 (t, *J* = 7.5 Hz, 2H). **^{13}C NMR (126 MHz, $CDCl_3$) δ** 138.12, 129.00, 128.37, 127.38, 119.20, 77.41, 77.16, 76.91, 31.64, 19.46. Spectral data are in agreement with data in *Organometallics*, 2022, **41**, 76.



^{1}H NMR of 3-phenylpropionitrile (**36**)



^{13}C NMR of 3-phenylpropionitrile (**36**)