Electronic Supplementary Material (ESI) for ChemComm.

Supporting Information

Organic Photocatalysis for the Radical Couplings of Boronic Acid Derivatives in Batch and Flow

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1 General information

1.1 General experimental and analytical methods

General methods: All reactions, unless otherwise noted, were performed magnetically stirred under Ar atmosphere using standard Schlenk techniques. Reagents were purchased from different commercial sources and used without further purification. The removal of solvent under reduced pressure was carried out on a standard rotary evaporator.

Solvents: Degassed solvents were degassed by purging with Ar for at least 20 min. Solvents for flash column chromatography and crystallisations were distilled under reduced pressure. *Iso*-hexane mentioned as petrol ether (PE) consist of the boiling fractions between 40 and 50°C.

Chromatography: Analytical thin-layer chromatography (TLC) was carried out on pre-coated glass plates (silica gel 60 F_{254}) from Merck. Compound spots were visualised under ultraviolet (UV) light (254 nm or 365 nm for fluorescent compounds), ceric ammonium molybdate (CAM), ninhydrin or $KMnO_4$ stain solutions. For flash column chromatography silica gel 60 from Merck, with a particle size between 40 and 63 µm, was used. Crudes were often loaded onto columns using dry loading technique with ISOLUTE® HM-N.

NMR spectroscopy: ^{1}H-NMR spectra were recorded on a Bruker Avance DRX-600 spectrometer at 600 MHz and are reported as follows: chemical shift δ in ppm (multiplicity, coupling constants *J* in Hz, number of protons, assignment). The multiplicity and shape of the ^{1}H signals are designated by the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septet, m = multiplet, br = broad, or combinations thereof. These chemical shifts δ are reported to the nearest 0.01 ppm with the residual solvent peak as the internal reference ($CDCl_3$ = 7.26 ppm, methanol-d_4 = 3.31 ppm, water-d^2 = 4.79 ppm). ^{13}C-NMR spectra were recorded on the same spectrometer at 150 MHz with ^{1}H decoupling. All ^{13}C resonances are reported to the nearest 0.1 ppm with the central resonance of the solvent peak as the internal reference ($CDCl_3$ = 77.16 ppm, methanol-d_4 = 49.00 ppm). The ^{13}C signal of the carbon bonded to boron was not observed in some cases due to quadrupolar relaxation. ^{11}B-NMR NMR

spectra were recorded on a Bruker DRX-600 spectrometer at 193 MHz with ^{1}H decoupling. All chemical shifts δ are reported to the nearest 0.1 ppm with $BF_3{\cdot}OEt_2$ as the external standard ($BF_3{\cdot}OEt_2$ = 0.0 ppm). Spectra are assigned using ^{1}H-COSY, ^{13}C-DEPT-135, HSQC and HMBC where appropriate to facilitate structural determination. The numbering of the proton and carbon atoms does not match the IUPAC nomenclature. Diastereotopic protons in the ^{1}H-NMR spectra are referenced with a and b, nomenclature is arbitrarily and does not correspond to the spin system.

Infrared spectroscopy: Infrared spectra were recorded neat on a Perkin-Elmer Spectrum One FT-IR spectrometer using Universal ATR sampling measuring unit. Selected peaks are reported in wavenumbers (cm^{-1}) of absorption.

High-resolution mass spectrometry (HRMS) was performed using a Waters Micromass LCT Premier™ spectrometer using time of flight (TOF) mass detection and positive ESI ionization method. Unless otherwise stated, reported mass correspond to the parent molecular ion associated with a proton $[M+H]^+$ or a sodium cation $[M+Na]^+$ (^{23}Na isotope). All *m/z* values are reported to four decimal places and within ± 5 ppm of the calculated value.

Melting points (m.p.) were recorded on a Stanford Research Systems OptiMelt Automated Melting Point System calibrated against vanillin (m.p. 83°C), phenacetin (m.p. 136°C) and caffeine (m.p. 237°C).

1.2 Photochemical experiments

Batch photochemical experiments were performed magnetically stirred in 5 mL glass test tubes, sealed with a rubber septum. The tubes were externally irradiated with blue light either using a coiled commercial LED strip (Ledxon, 14.4 W at 470 nm) or a LED torch (Thorlabs, 253 mW at 470 nm). To maintain a constant reaction temperature of 30°C, the setup was cooled by a constant air flow from a clip fan (**Figure S1**).

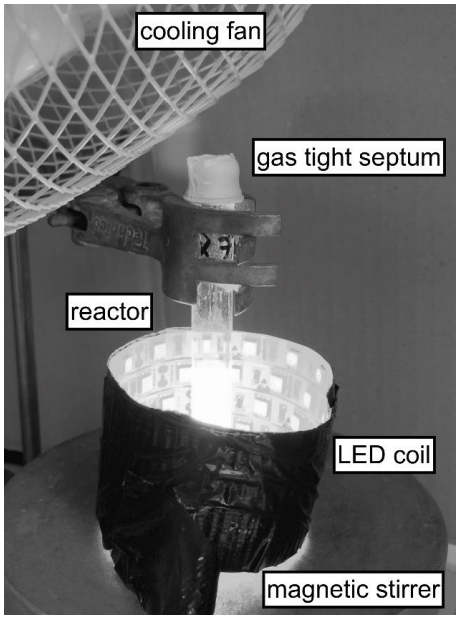


Figure S1 – Typical batch photoreactor setup.

Continuous flow photochemical experiments:

Reactions using the UV-150 (Vapourtec) photoreactor were performed using a Vapourtec E-series unit equipped with a UV-150 module with blue LEDs (17 W at 420 nm). The pumps used on this equipment are peristaltic pumps (V3) allowing to deliver accurate flow rates between 100 µL/min and 10 mL/min. The reactor coil (10 mL) is made of FEP tubing with thin walls (outer diameter: 1.6 mm, inner diameter: 1.3 mm).

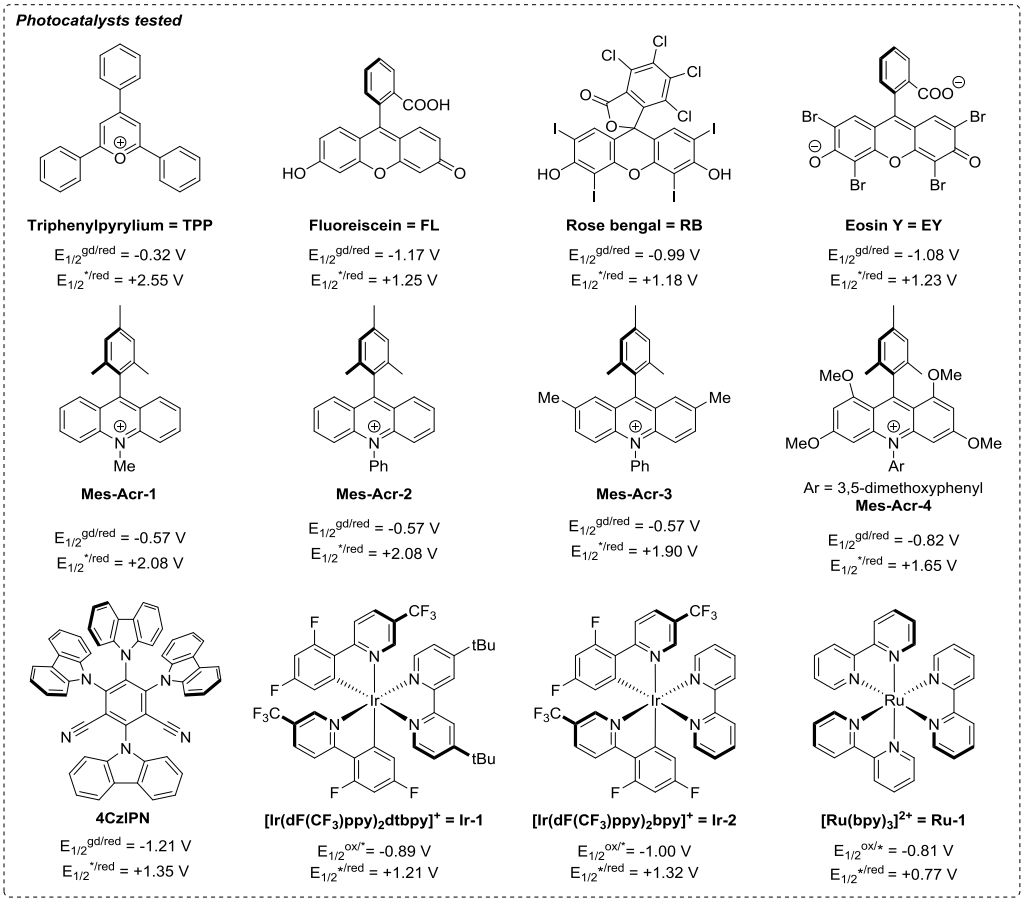
Reactions using the Photosyn (Uniqsis) photoreactor were performed using a prototype unit (2 LED arrays of 350 W that produce 420 W at 450 nm) system with liquid cooling. The pump used on this equipment was a peristaltic pump (SF-10). The reactor coils used were made of PFA and the volumes were 5 mL (outer diameter: 1.59 mm, inner diameter: 1.0 mm) or 50 mL (outer diameter: 3.2 mm, inner diameter: 2.4 mm).

NMR following experiments were carried out by adapting the mentioned batch procedures **GP(n)** to a 0.05 mmol scale, employing the corresponding deuterated solvents

and 1,3,5-trimethoxybenzene as internal standard. After being prepared in a separate vial, the reaction mixture was transferred in an NMR tube under argon. An initial ^{1}H-NMR measurement (time zero) was made before the tube was irradiated. Irradiation times were accurately measured by the use of a stopwatch. Integrating the product and starting material peaks against the internal standard gave access to conversions and yields over time.

2 Organic photocatalyst selection

Table S1 – Photocatalysts investigated



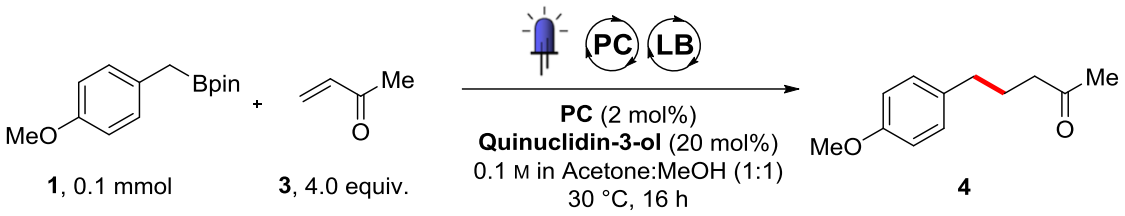
2.1 Photocatalyst optimisation

2.1.1 With boronic ester model substrate

Optimisation protocol: A 5 mL glass vial equipped with a magnetic stir bar was charged with 2-(4-methoxybenzyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**1**, 25 mg, 0.10 mmol), the desired photoredox catalyst (2.0 µmol, 2 mol%) and quinuclidin-3-ol as Lewis base catalyst (2.5 mg, 0.02 mmol, 20 mol%). The vial was then sealed with a rubber septum and evacuated/backfilled with argon three times. Methyl vinyl ketone (33 µL, 0.4 mmol, 4.0 equiv.) was then added followed by 1.0 mL of a degassed acetone/methanol (1:1) mixture to lead a clear yellow transparent 0.1 M solution. This solution was then stirred while irradiated with a commercial blue LED strip (Ledxon, 14.4 W, 470 nm) for

24 hours, the temperature was maintained at 30°C using a desktop fan. After 24 h of irradiation the mixture was concentrated and dried *in vacuo*. Dibromomethane (10 µL, exact mass measured on balance) was added to the dry crude mixture as internal standard to determine the NMR yield in **4**.

Table S2 – Photocatalyst screening with boronic ester **1**.



1, 0.1 mmol **3**, 4.0 equiv. **4**

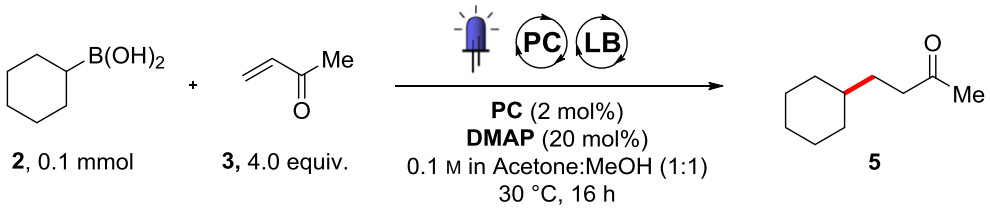
Entry	PC	Yield[a]	Comment
1	**Ir-1**	**82%**	
2	**Ir-2**	**86%**	
3	Ru-1	31%	
4	DCA	0%	Photobleached
5	TPP	0%	Photobleached
6	FL	11%	Photobleached
7	**RB**	**74%**	
8[b]	EY	15%	Photobleached
9	Mes-Acr-1	67%	
10	Mes-Acr-2	58%	Photobleached
11	Mes-Acr-3	62%	
12	**Mes-Acr-4**	**83%**	
13	4CzIPN	52%	

[a]Yield in **4** determined by ^{1}H-NMR analysis of crude reaction mixture using CH_2Br_2 as an internal standard.
[b]Green LEDs were used instead (14 W @540 nm).

2.2 With boronic acid model substrate

Optimisation protocol: A 5 mL glass vial equipped with a magnetic stir bar was charged with cyclohexylboronic acid (**2**, 12.8 mg, 0.10 mmol), the desired photoredox catalyst (2.0 µmol, 2 mol%) and DMAP as Lewis base catalyst (2.4 mg, 0.02 mmol, 20 mol%). The vial was then sealed with a rubber septum and evacuated/backfilled with argon three times. Methyl vinyl ketone (33 µL, 0.4 mmol, 4.0 equiv.) was then added followed by 1.0 mL of a degassed acetone/methanol (1:1) mixture to lead a clear yellow transparent 0.1 M solution. This solution was then stirred while irradiated with a commercial blue LED strip (Ledxon, 14.4 W, 470 nm) for 24 hours, the temperature was maintained at 30°C using a desktop fan. After 24 h of irradiation the mixture was concentrated and dried *in vacuo*. Dibromomethane (10 µL, exact mass measured on balance) was added to the dry crude mixture as internal standard to determine the NMR yield in **5**.

Table S3 –Photocatalyst screening with boronic acid **2**.



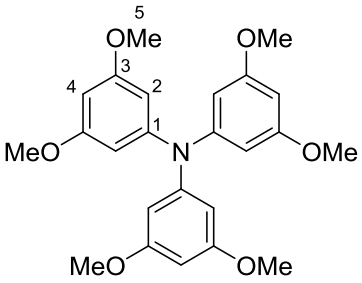
2, 0.1 mmol **3**, 4.0 equiv. **5**

Entry	PC	Yield[a]
1	**Ir-1**	**89%**
2	**Ir-2**	**90%**
3	Ru-1	26%
4	RB	59%
5	Mes-Acr-1	15%
6	Mes-Acr-3	36%
7	**Mes-Acr-4**	**95%**
8	**4CzIPN**	**83%**

[a]Yield in **5** determined by ^{1}H-NMR analysis of crude reaction mixture using CH_2Br_2 as an internal standard.

2.3 Synthetic procedures for non-commercial available organic photocatalysts

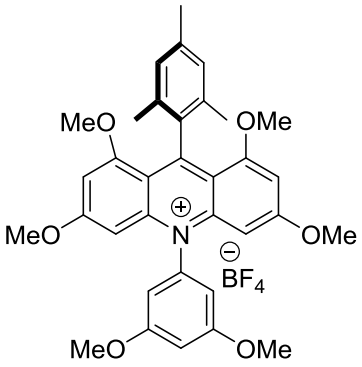
Tris(3,5-dimethoxyphenyl)amine



In a 250 mL two-necked round-bottom flask equipped with a magnetic stir bar were placed 3,5-dimethoxyaniline (1.75 g, 11.4 mmol, 1.0 equiv.), 1-bromo-3,5-dimethoxybenzene (4.96 g, 22.8 mmol, 2.0 equiv.), and chloro[(tri-*tert*-butylphosphine)-2-(2-aminobiphenyl)]palladium(II) (168.8 mg, 0.34 mmol, 3.0 mol%). The headspace was purged with argon and the solid content dissolved with THF (40 mL). A 2.0 M solution of sodium *tert*-butoxide in THF (23 mL, 46 mmol, 4.0 equiv.) was then added in one portion under argon, and the reaction mixture was heated to 70°C. After 24 h, the reaction mixture was cooled down to room temperature. The THF solution was filtered through a pad of celite® and concentrated *in vacuo*. Residue was dissolved with 100 mL of water and 50 mL of MTBE. Layers were separated and aqueous layer extracted with MTBE (3 x 50 mL). Combined organic layers were washed with brine and dried over $MgSO_4$. Further removal of the solvent *in vacuo* resulted in tris(3,5-dimethoxyphenyl)amine (4.80 g, 11.3 mmol) as a brown amorphous solid in 99% yield.

^{1}H-NMR (600 MHz, $CDCl_3$) δ 6.26 (d, *J* = 2.3 Hz, 6H, H_2), 6.17 (t, *J* = 2.3 Hz, 3H, H_4), 3.71 (s, 12H, H_5). **^{13}C-NMR (151 MHz, $CDCl_3$)** δ 161.1 (C_3), 149.1 (C_1), 103.1 (C_2), 95.5 (C_4), 55.3 (C_5). **HRMS for $[C_{24}H_{28}NO_6]^+$** calculated 426.1911 found 426.1916. **R_f** (1:1 EtOAc/PE) = 0.38. Spectroscopic data were consistent with literature values.[1]

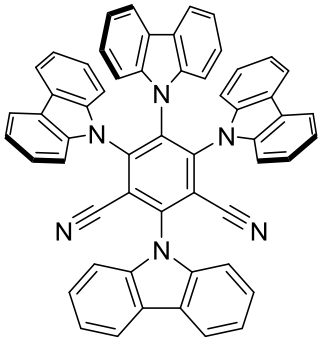
10-(3,5-Dimethoxyphenyl)-9-mesityl-1,3,6,8-tetramethoxyacridin-10-ium tetrafluoroborate (Mes-Acr-4)



In a 250 mL round-bottom flask equipped with a magnetic stir bar were placed tris(3,5-dimethoxyphenyl)amine (4.80 g, 11.3 mmol, 1.0 equiv.) and 2,4,6-trimethlbenzoyl chloride (4.0 mL, 24 mmol, 2.1 equiv.) followed by chlorobenzene (60 mL). Triflic acid (950 µL, 11.3 mmol, 1.0 equiv.) was then added slowly and the mixture heated to 90°C. After 24 h the reaction mixture was cooled to room temperature and washed with aqueous 0.2 M $NaBF_4$ solution (3 × 30 mL) and water (2 × 60 mL). To the organic layer was then dried over $MgSO_4$ and concentrated *in vacuo* and cold MTBE (200 mL) was added slowly until a precipitate started to form. An additional 400 mL of MTBE was added slowly and the mixture was stirred at 0°C for 2 h. The orange precipitate was then filtered-off and the solid was washed with cold MTBE (200 mL). This brown-orange solid was then purified by column chromatography (CH_2Cl_2) to afford **Mes-Acr-4** (3.75 g, 6.77 mmol) as a bright orange solid in 60% yield.

^{1}H-NMR (600 MHz, $CDCl_3$) δ 6.91 (s, 2H), 6.83 (t, *J* = 2.2 Hz, 1H), 6.63 (d, *J* = 2.1 Hz, 2H), 6.49 (d, *J* = 2.3 Hz, 2H), 6.19 (d, *J* = 2.3 Hz, 2H), 3.93 (s, 6H), 3.86 (s, 6H), 3.49 (s, 6H), 2.38 (s, 3H), 1.84 (s, 6H). **^{13}C-NMR (151 MHz, $CDCl_3$)** δ 168.22, 163.14, 162.22, 160.68, 144.76, 139.81, 136.43, 131.99, 127.03, 113.32, 105.56, 102.81, 97.62, 92.67, 57.04, 56.49, 56.21, 21.10, 20.16. **HRMS for $[C_{34}H_{37}NO_6{}^{11}BF_4]^+$** calculated 554.2537 found 554.2542. **R_f** (CH_2Cl_2) = 0.08. Spectroscopic data were consistent with literature values.[1]

2,4,5,6-Tetra(9*H*-carbazol-9-yl)isophthalonitrile (4CzIPN)



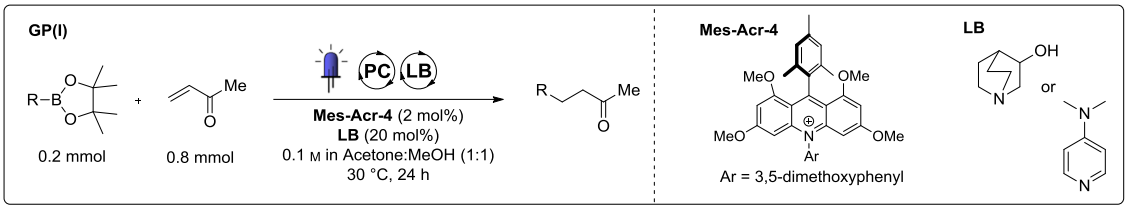
In a 250 mL round-bottom flask equipped with a magnetic stir bar was added carbazole (3.67 g, 21.9 mmol, 4.4 equiv.). The flask was sealed with a rubber septum and flushed with argon. THF (44 mL) was then added, and the solution was cooled to 0°C. The flask was then charged with a 1.0 M NaHMDS solution in THF (20.9 mL, 20.9 mmol, 4.2 equiv.). The resulting orange-brown solution was then allowed to warm to room temperature and stirred for 1 h. The flask was then charged with tetrafluoroisophthalonitrile (1.00 g, 5.0 mmol, 1.0 equiv.) and equipped with a reflux condenser. The solution was heated at 70°C under argon for 72 h. The brown mixture with yellow precipitate was then allowed to cool to room temperature and filtered. The resulting yellow solid was successively washed with Et_2O (200 mL) and cold $CHCl_3$ (300 mL). The yellow filtrate was then purified by column chromatography (50% CH_2Cl_2 in PE) to deliver **4CzIPN** (2.2 g, 2.76 mmol) as a bright yellow solid in 55% yield.

^{1}H-NMR (600 MHz, $CDCl_3$) δ 8.23 (d, *J* = 7.7 Hz, 2H), 7.75 – 7.68 (m, 8H), 7.53 (t, *J* = 7.2 Hz, 2H), 7.34 (d, *J* = 7.5 Hz, 2H), 7.25 – 7.21 (m, 4H), 7.13 – 7.06 (m, 8H), 6.83 (t, *J* = 8.0 Hz, 4H), 6.65 (t, *J* = 7.7 Hz, 2H). **^{13}C-NMR (151 MHz, $CDCl_3$)** δ 145.2, 144.6, 140.0, 138.2, 136.9, 134.7, 126.9, 125.8, 124.9, 124.7, 124.5, 123.8, 122.4, 121.9, 121.4, 121.0, 120.4, 119.6, 116.3, 111.6, 109.9, 109.5, 109.4. **HRMS for $[C_{56}H_{33}N_6]^+$** calculated 789.2761 found 789.2770. **R_f** (1:1 CH_2Cl_2/PE) = 0.19. Spectroscopic data were consistent with literature values.[2]

3 Organic photocatalyst performance assessment

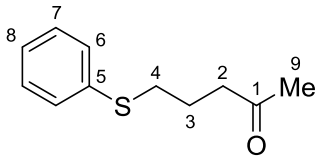
3.1 Synthetic procedures and characterisation for coupling products

3.1.1 Using boronic esters



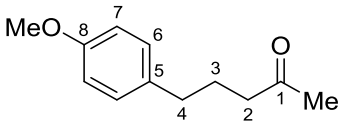
GP(I): A 5 mL glass vial equipped with a magnetic stir bar was charged with the desired boronic ester (0.20 mmol, 1.0 equiv.), **Mes-Acr-4** (2.6 mg, 2 mol%) and the desired Lewis base catalyst (0.04 mmol, 20 mol%). The vial was then sealed with a rubber septum and evacuated/backfilled with argon three times. Methyl vinyl ketone (66 µL, 0.8 mmol, 4.0 equiv.) was then added followed by 2.0 mL of a degassed acetone/methanol (1:1) mixture to lead a clear yellow transparent 0.1 M solution. This solution was then stirred while irradiated with a commercial blue LED strip (Ledxon, 14.4 W, 450 nm) for 24 hours, the temperature was maintained at 30°C using a desktop fan. The content of the vial was then concentrated *in vacuo* and immobilised on ISOLUTE® HM-N for easy dry loading on flash column chromatography to yield the pure product.

5-(Phenylthio)pentan-2-one (9)



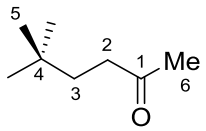
Obtained following **GP(I)** using quinuclidin-3-ol (5.0 mg, 40 µmol, 20 mol%) as Lewis base catalyst. Purification by column chromatography on silica gel (5% to 7% EtOAc in hexane) afforded product **9** (31 mg, 0.16 mmol) as a colourless oil in 80% yield. Repeating the same procedure with **Ir-2** instead of **Mes-Acr-4** afforded the same product in 91% yield. **^{1}H-NMR (600 MHz, $CDCl_3$)** δ 7.35 – 7.31 (m, 2H, H_6), 7.30 – 7.26 (m, 2H, H_7), 7.20 – 7.14 (m, 1H, H_8), 2.94 (t, *J* = 7.0 Hz, 2H, H_4), 2.60 (t, *J* = 7.0 Hz, 2H, H_2), 2.12 (s, 3H, H_9), 1.90 (p, *J* = 7.0 Hz, 2H, H_3). **^{13}C-NMR (151 MHz, $CDCl_3$)** δ 208.1 (C_1), 136.2 (C_5), 129.3 (C_6), 129.0 (C_7), 126.1 (C_8), 42.0 (C_2), 33.1 (C_4), 30.1 (C_9), 23.1 (C_3). **HRMS for $[C_{11}H_{15}OS]^+$** calculated 195.0844 found 195.0838. **R_f** (1:4 EtOAc/PE) = 0.43. Spectroscopic data were consistent with literature values.[3]

5-(4-Methoxyphenyl)pentan-2-one (4)



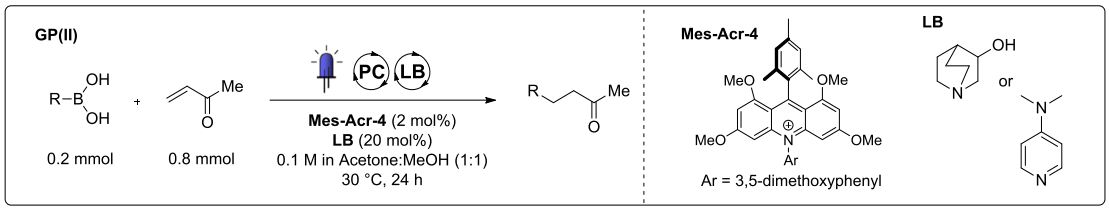
Obtained following **GP(I)** using quinuclidin-3-ol (5.0 mg, 40 µmol, 20 mol%) as Lewis base catalyst. Purification by column chromatography on silica gel (10% EtOAc in hexane) afforded product **4** (30 mg, 0.16 mmol) as colourless oil in 78% yield. Repeating the same procedure with **Ir-2** instead of **Mes-Acr-4** afforded the same product in 82% yield. **^{1}H-NMR (600 MHz, $CDCl_3$)** δ 7.08 (d, *J* = 8.6 Hz, 2H, H_6), 6.83 (d, *J* = 8.6 Hz, 2H, H_7), 3.79 (s, 3H, O*Me*), 2.56 (t, *J* = 7.5 Hz, 2H, H_4), 2.42 (t, *J* = 7.5 Hz, 2H, H_2), 2.11 (s, 3H, CO*Me*), 1.87 (p, *J* = 7.5 Hz, 2H, H_3).**^{13}C-NMR (151 MHz, $CDCl_3$)** *δ* 209.0 (C_1), 158.0 (C_8), 133.7 (C_5), 129.5 (C_6), 113.9 (C_7), 55.4 (O*Me*), 42.9 (C_2), 34.2 (C_4), 30.1 (CO*Me*), 25.6 (C_3). **HRMS for $[C_{12}H_{17}O_2]^+$** calculated 193.1223 found 193.1228. **R_f** (1:4 EtOAc/PE) = 0.38. Spectroscopic data were consistent with literature values.[4]

5,5-Dimethylhexan-2-one (10)



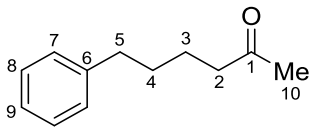
Obtained following **GP(I)** at 0.2 mmol scale using DMAP (4.8 mg, 40 µmol, 20 mol%) as Lewis base catalyst. Purification by column chromatography on silica gel (5% Et_2O in pentane) afforded product **10** (9 mg, 0.07 mmol) as a colourless oil in 35% yield. Repeating the same procedure with **Ir-2** instead of **Mes-Acr-4** afforded the same product in 45% yield. **^{1}H-NMR (600 MHz, $CDCl_3$)** δ 2.42 – 2.36 (m, 2H, H_3), 2.15 (s, 3H, H_6), 1.50 – 1.45 (m, 2H, H_2), 0.88 (s, 9H, H_5). **NMR (151 MHz, $CDCl_3$)** δ 209.8 (C_1), 39.7 (C_2), 37.5 (C_3), 30.1 (C_4), 30.0 (C_6), 29.3 (C_5). **HRMS for $[C_8H_{17}O]^+$** calculated 129.1274 found 129.1269. **R_f** (1:4 EtOAc/PE) = 0.66. Spectroscopic data were consistent with literature values.[5]

3.1.2 Using boronic acids



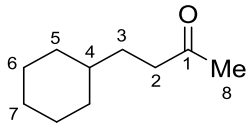
GP(II): A 5 mL glass vial equipped with a magnetic stir bar was charged with the desired boronic acid (0.20 mmol, 1.0 equiv.), **Mes-Acr-4** (2.6 mg, 2 mol%) and the desired Lewis base catalyst (0.04 mmol, 20 mol%). The vial was then sealed with a rubber septum and evacuated/backfilled with argon three times. Methyl vinyl ketone (66 µL, 0.8 mmol, 4.0 equiv.) was then added followed by 2.0 mL of a degassed acetone/methanol (1:1) mixture to lead a clear yellow transparent 0.1 M solution. This solution was then stirred while irradiated with a commercial blue LED strip (Ledxon, 14.4 W, 470 nm) for 24 hours, the temperature was maintained at 30°C using a desktop fan. The content of the vial was then concentrated *in vacuo* and immobilised on ISOLUTE® HM-N for easy dry loading on flash column chromatography to yield the pure product.

6-Phenylhexan-2-one (11)



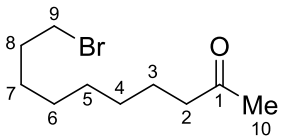
Obtained following **GP(II)** at 0.2 mmol scale using DMAP (4.8 mg, 40 µmol, 20 mol%) as Lewis base catalyst. Purification by column chromatography on silica gel (3% EtOAc in hexane) afforded product **11** (32 mg, 0.18 mmol) as colourless oil in 89% yield. Repeating the same procedure with **Ir-2** instead of **Mes-Acr-4** afforded the same product in 70% yield. **^{1}H-NMR (600 MHz, $CDCl_3$)** δ 7.31 – 7.26 (m, 2H, H_8), 7.21 – 7.16 (m, 3H, H_7 and H_9), 2.67 – 2.60 (m, 2H, H_5), 2.48 – 2.42 (m, 2H, H_2), 2.13 (s, 3H, H_{10}), 1.67 – 1.60 (m, 4H, H_2 and H_3). **^{13}C-NMR (151 MHz, $CDCl_3$)** δ 208.9 (C_1), 142.2 (C_6), 128.4 (C_7), 128.3 (C_8), 125.7 (C_9), 43.6 (C_2), 35.7 (C_5), 30.9 (C_{10}), 29.9 (C_4), 23.5 (C_3). **IR (ATR – neat)** $\tilde{\nu}$ (cm^{-1}) = 2989, 2922, 1712, 1454, 1356, 1159, 1031, 745, 699. **HRMS for $[C_{12}H_{17}NO]^+$** calculated 177.1279 found 177.1279. **R_f** (1:4 EtOAc/PE) = 0.43.

4-Cyclohexylbutan-2-one (5)



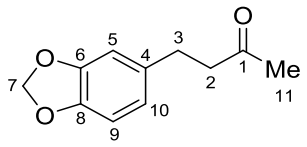
Obtained following **GP(II)** at 0.2 mmol scale using DMAP (4.8 mg, 40 µmol, 20 mol%) as Lewis base catalyst. Purification by column chromatography on silica gel (10% Et_2O in pentane) afforded product **5** (28 mg, 0.18 mmol) as colourless oil in 90% yield. Repeating the same procedure with **Ir-2** instead of **Mes-Acr-4** afforded the same product in 90% yield. **^{1}H-NMR (600 MHz, $CDCl_3$)** δ 2.43 (t, *J* = 7.8 Hz, 2H, H_2), 2.14 (s, 3H, H_8), 1.72 – 1.63 (m, 5H, H_{5a}, H_{6a} and H_{7a}), 1.50 – 1.43 (m, 2H, H_3), 1.26 – 1.08 (m, 4H, H_4, H_{6b} and H_{7b}), 0.93 – 0.84 (m, 2H, H_{5b}). **^{13}C-NMR (151 MHz, $CDCl_3$)** δ 209.6 (C_1), 41.4 (C_8), 37.2 (C_4), 33.1 (C_5), 31.2 (C_3), 29.8 (C_8), 26.5 (C_7), 26.2 (C_6). **HRMS for $[C_{10}H_{19}O]^+$** calculated 155.1430 found 155.1428. **R_f** (1:4 EtOAc/PE) = 0.51. Spectroscopic data were consistent with literature values.[6]

10-Bromodecan-2-one (12)



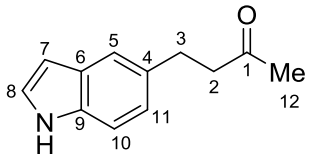
Obtained following **GP(II)** at 0.2 mmol scale using DMAP (4.8 mg, 40 µmol, 20 mol%) as Lewis base catalyst. Purification by column chromatography (5% EtOAc in hexane) afforded product **12** (26 mg, 0.11 mmol) as colourless oil in 55% yield. Repeating the same procedure with **Ir-2** instead of **Mes-Acr-4** afforded the same product in 71% yield. **^{1}H-NMR (600 MHz, $CDCl_3$)** δ 3.39 (t, *J* = 6.8 Hz, 2H, H_9), 2.41 (t, *J* = 7.4 Hz, 2H, H_2), 2.12 (s, 3H, H_{10}), 1.84 (p, *J* = 7.0 Hz, 2H, H_8), 1.60 – 1.49 (m, 2H, H_3), 1.44 – 1.38 (m, 2H, H_7), 1.34 – 1.26 (m, 6H, H_4, H_5 and H_6). **^{13}C-NMR (151 MHz, $CDCl_3$)** δ 209.2 (C_1), 43.7 (C_2), 34.0 (C_9), 32.7 (C_8), 29.9 (C_{10}), 29.2 (C_5), 29.0 (C_6), 28.5 (C_4), 28.1 (C_7), 23.7 (C_3). **HRMS for $[C_{10}H_{20}OBr]^+$** calculated 235.0698 found 235.0693. **R_f** (1:4 EtOAc/PE) = 0.44. Spectroscopic data were consistent with literature values.[7]

4-(Benzo[d][1,3]dioxol-5-yl)butan-2-one (13)



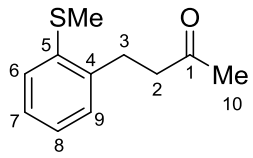
Obtained following **GP(II)** at 0.2 mmol scale using quinuclidin-3-ol (5.0 mg, 40 µmol, 20 mol%) as Lewis base catalyst. Purification by column chromatography on silica gel (5% EtOAc in hexane) afforded product **13** (27 mg, 0.14 mmol) as an amorphous solid in 70% yield. Repeating the same procedure with **Ir-2** instead of **Mes-Acr-4** afforded the same product in 46% yield. **^{1}H-NMR (600 MHz, CDCl$_3$)** δ 6.71 (d, *J* = 7.9 Hz, 1H, H_9), 6.66 (d, *J* = 1.7 Hz, 1H, H_5), 6.61 (dd, *J* = 8.0, 1.7 Hz, 1H, H_{10}), 5.90 (s, 2H, H_7), 2.80 (t, *J* = 7.6 Hz, 2H, H_3), 2.70 (t, *J* = 7.6 Hz, 2H, H_2), 2.12 (s, 3H, H_{11}). **^{13}C-NMR (151 MHz, CDCl$_3$)** δ 208.0 (C_1), 147.7 (C_6), 145.9 (C_8), 134.9 (C_4), 121.1 (C_{10}), 108.9 (C_5), 108.3 (C_9), 100.9 (C_7), 45.5 (C_2), 30.2 (C_3), 29.6 (C_{11}). **IR (ATR – neat)** $\tilde{\nu}$ (cm^{-1}) = 2921, 2897, 2782, 1713, 1504, 1489, 1443, 1360, 1245, 1187, 1159, 1096, 1035, 922, 803, 773. **HRMS for [C$_{11}$H$_{12}$O$_3$]$^+$** calculated 192.0786 found 192.0782. **R$_f$** (1:4 EtOAc/PE) = 0.27.

4-(1H-indol-5-yl)butan-2-one (14)



Obtained following **GP(II)** at 0.2 mmol scale using quinuclidin-3-ol (5.0 mg, 40 µmol, 20 mol%) as Lewis base catalyst. Purification by column chromatography on silica gel (15% EtOAc in hexane) afforded product **14** (19 mg, 0.10 mmol) as a colourless oil in 52% yield. Repeating the same procedure with **Ir-2** instead of **Mes-Acr-4** afforded the same product in 48% yield. **^{1}H-NMR (600 MHz, CDCl$_3$)** δ 8.18 (bs, 1H, N*H*), 7.45 (s, 1H, H_5), 7.31 (d, *J* = 8.3 Hz, 1H, H_{10}), 7.18 (t, *J* = 2.8 Hz, 1H, H_8), 7.03 (dd, *J* = 8.3, 1.7 Hz, 1H; H_{11}), 6.50 (ddd, *J* = 3.1, 2.0, 0.9 Hz, 1H, H_7), 3.01 (t, *J* = 7.7 Hz, 2H, H_3), 2.81 (t, *J* = 7.7 Hz, 2H, H_2), 2.15 (s, 3H, H_{12}). **^{13}C-NMR (151 MHz, CDCl$_3$)** δ 208.9 (C_1), 134.6 (C_9), 132.4 (C_4), 128.2 (C_6), 124.6 (C_8), 122.8 (C_{11}), 119.9 (C_5), 111.1 (C_{10}), 102.3 (C_7), 46.3 (C_2), 30.3 (C_{12}), 30.1 (C_3). **IR (ATR – neat)** $\tilde{\nu}$ (cm^{-1}) = 3675, 3400, 2996, 2972, 1707, 1479, 1413, 1362, 1221, 1161, 1066, 729. **HRMS for [C$_{12}$H$_{13}$NO]$^+$** calculated 187.0997 found 187.0992. **R$_f$** (2:3 EtOAc/PE) = 0.52.

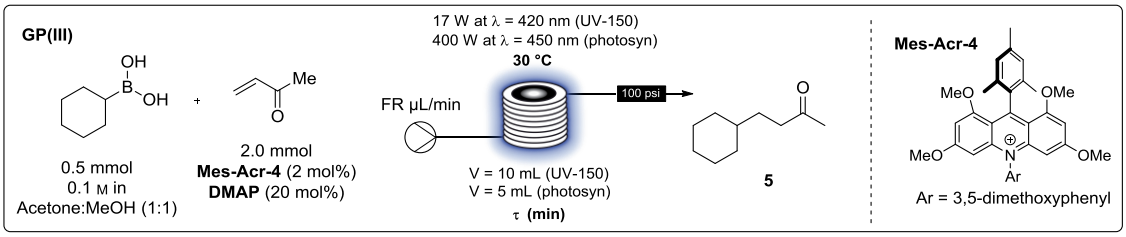
4-(2-(Methylthio)phenyl)butan-2-one (15)



Obtained following **GP(II)** at 0.2 mmol scale using quinuclidin-3-ol (5.0 mg, 40 µmol, 20 mol%) as Lewis base catalyst. Purification by column chromatography on silica gel (3% EtOAc in hexane) afforded product **15** (25 mg, 0.13 mmol) as a colourless oil in 65% yield. Repeating the same procedure with **Ir-2** instead of **Mes-Acr-4** afforded the same product in 60% yield. **^{1}H-NMR (600 MHz, CDCl$_3$)** δ 7.24 – 7.18 (m, 2H, H_6 and H_7), 7.15 (d, *J* = 8.0 Hz, 1H, H_9), 7.09 (ddd, *J* = 8.0, 6.0, 2.6 Hz, 1H; H_8), 2.99 (dd, *J* = 8.6, 6.9 Hz, 2H, H_3), 2.78 (dd, *J* = 8.5, 7.0 Hz, 2H, H_2), 2.47 (s, 3H, S*Me*), 2.16 (s, 3H, H_{10}). **^{13}C-NMR (151 MHz, CDCl$_3$)** δ 208.0 (C_1), 138.7 (C_5), 137.1 (C_4), 129.2 (C_9), 127.0 (C_6), 125.6 (C_7), 125.1 (C_8), 43.5 (C_2), 29.9 (C_3), 27.9 (C_{10}), 15.7 (S*Me*). **IR (ATR – neat)** $\tilde{\nu}$ (cm^{-1}) = 3060, 2921, 1715, 1590, 1471, 1439, 1358, 1286, 1159, 1068, 967, 957, 747. **HRMS for [$C_{11}H_{15}OS$]$^+$** calculated 195.0844 found 195.0838. **R_f** (1:4 EtOAc/PE) = 0.40.

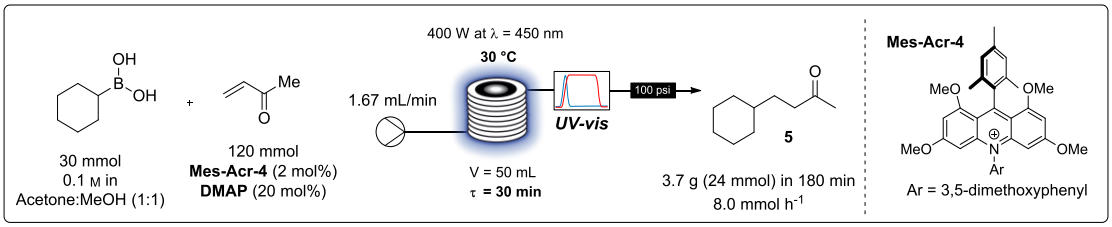
3.2 Continuous flow protocols

3.2.1 Optimisation protocol



GP(III): A 10 mL conical-shaped flask was charged with cyclohexyl boronic acid (64 mg, 0.50 mmol, 1.0 equiv.), **Mes-Acr-4** (5.5 mg, 0.01 mmol, 2 mol%) and DMAP (12 mg, 0.10 mmol, 20 mol%). The flask was then sealed with a rubber septum and evacuated/backfilled with argon three times. Methyl vinyl ketone (165 µL, 2.0 mmol, 4.0 equiv.) was then added followed by 5.0 mL of a degassed acetone/methanol (1:1) mixture to lead a clear yellow transparent 0.1 M solution. The clear solution was then pumped at the desired flow rate (FR) through the desired reactor held at 30°C. Once the reaction mixture has fully be taken up by the pump, the input was swapped to acetone:methanol (1:1) solvent to push the rest of the reaction mixture through the reactor. The totality of the reaction plug was collected in a round bottom flask and concentrated *in vacuo*. 1,3,5-trimethoxybenzene (30 mg, exact mass measured on balance) was added to the dry crude mixture as internal standard to determine the NMR yield of **5**.

3.2.2 Scale up experiment



Protocol: A 500 mL conical-shaped flask equipped with a magnetic stir bar was charged with cyclohexyl boronic acid (3.84 g, 30 mmol, 1.0 equiv.), **Mes-Acr-4** (384 mg, 0.6 mmol, 2 mol%) and DMAP (732 mg, 6.0 mmol, 20 mol%) as Lewis base catalyst. The flask was then sealed with a rubber septum and evacuated/backfilled with argon three times. Methyl vinyl ketone (6.0 mL, 120 mmol, 4.0 equiv.) was then added followed by 300 mL of a degassed acetone/methanol (1:1) mixture to lead a clear yellow transparent 0.1 M solution. The clear solution was then pumped at 1.66 mL/min through the Photosyn reactor (50 mL, i.d. = 2.4 mm) held at 30°C. Once the reaction mixture has fully be taken up by the pump, the input was swapped to acetone:methanol (1:1) solvent to push the rest of the reaction mixture through the reactor. The reaction plug monitored by UV-vis detection (Uniqsis Flow-UV), the totality of the plug was collected in a round bottom flask. The content of the flask was then concentrated *in vacuo* and immobilised on ISOLUTE® HM-N. This immobilised crude was filtered on a pad of silica gel with 5% Et_2O in PE (3 L) to yield the pure product **5** (3.72 g, 24.1 mmol) as a colourless oil in 81% yield.

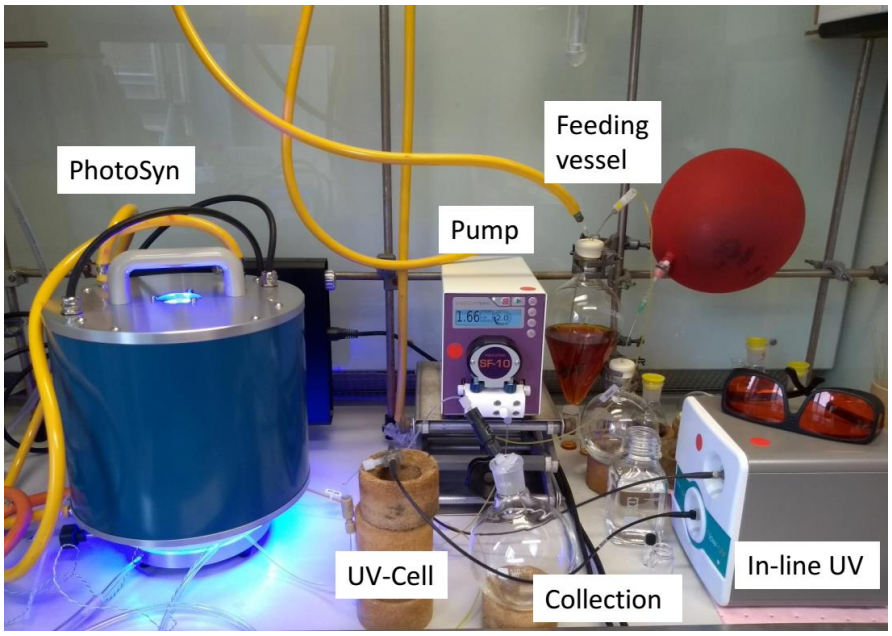
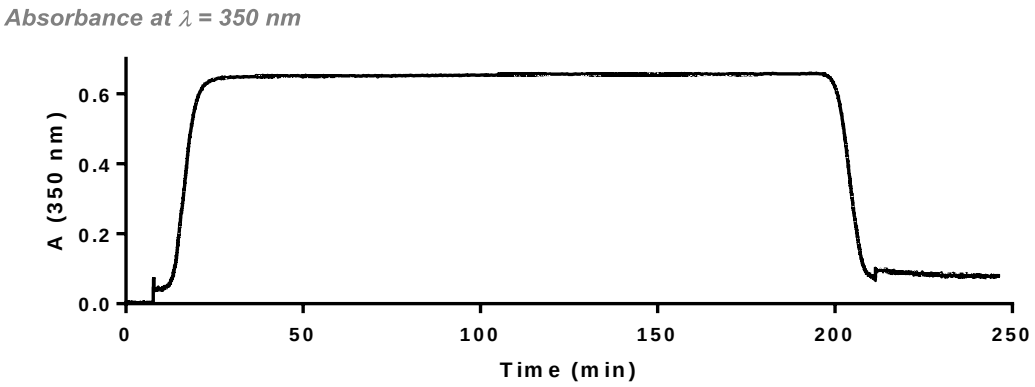


Figure S2 – Reaction setup.



Graph S1 – UV-vis inline detector trace for the 180 min run (absorbance at 350 nm).

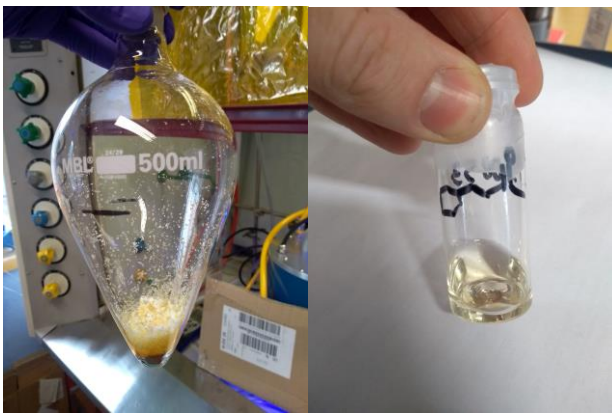
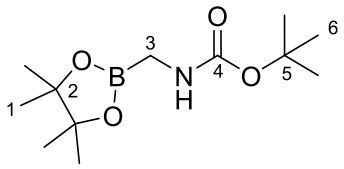


Figure S3 – Reagents before reaction (left) and pure product (right).

4 APIs synthesis

4.1 Synthetic procedures and characterisation for starting materials

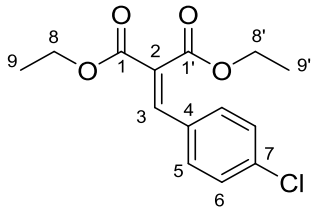
***Tert*-butyl ((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)carbamate**



A solution of NaHMDS (1 M in THF, 5.6 mL, 5.6 mmol, 1.0 equiv.) in THF (30 mL) was cooled to -78°C. 2-(chloromethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.98 g, 5.6 mmol, 1.0 equiv.) in THF (6 mL) was added dropwise and the reaction mixture was stirred at -78°C for 20 min, before it was allowed to warm to room temperature and stirred for additional 2 h. The reaction mixture was then cooled to 0°C before MeOH (0.44 mL, 11 mmol, 2.0 equiv.) was added, the mixture was then stirred at this temperature for 1 h. Boc_2O (1.5 mL, 6.7 mmol, 1.2 equiv.) was then added and the mixture was stirred at room temperature for 72 h. The solvent was evaporated and the crude mixture was loaded on oven dried silica. Column chromatography on oven-dried silica (20% Et_2O in PE) afforded the product (1.1 g, 4.3 mmol) as a colourless oil in 77% yield.

^{1}H-NMR (600 MHz, $CDCl_3$) δ 4.63 (s, 1H, *NH*), 2.77 (d, *J* = 4.4 Hz, 2H, H_3), 1.44 (s, 9H, H_6), 1.27 (s, 12H, H_1). **^{13}C-NMR (151 MHz, $CDCl_3$)** δ 157.1 (C_4), 84.2 (C_2), 79.2 (C_5), 28.6 (C_6), 24.9 (C_1). **^{11}B-NMR (193 MHz, $CDCl_3$)** δ 32.6. **IR (ATR – neat)** $\tilde{\nu}$ (cm^{-1}) = 3376, 2979, 1697, 1506, 1382, 1367, 1335, 1167, 1141, 968, 845, 780. **HRMS for $[C_{12}H_{24}O_4NBNa]^+$** calculated 280.1691 found 280.1686. **R_f** (1:1 EtOAc/PE) = 0.28.

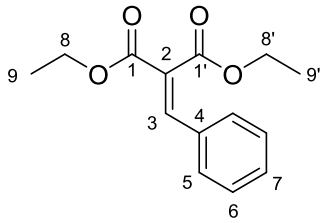
Diethyl 2-(4-chlorobenzylidene)malonate



4-Chlorobenzaldehyde (7.00 g, 50.0 mmol, 1.0 equiv.) was added to a solution of diethyl malonate (6.3 mL, 42.0 mmol, 0.8 equiv.) and piperidine (0.5 mL, 5.0 mmol, 0.1 equiv.) in toluene (25 mL). Glacial acetic acid (0.3 mL, 5.0 mmol, 0.1 equiv.) was added and the reaction mixture was heated to 160°C for 24 h with a Dean-Stark apparatus. The solvent was evaporated under reduced pressure and the orange residue was diluted with EtOAc (30 mL). The organic phase was washed with water (30 mL), aqueous 1 M HCl (30 mL), saturated aqueous $NaHCO_3$ (30 mL) and brine (30 mL). The organic phase was then dried over $MgSO_4$ and the solvents removed *in vacuo*. Column chromatography on silica gel (15% EtOAc in PE) afforded the product (4.10 g, 14.5 mmol) as a yellowish oil in 29% yield.

^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.69 (s, 1H, H_3), 7.41 (d, *J* = 8.6 Hz, 2H, H_5), 7.37 (d, *J* = 8.6 Hz, 2H, H_6), 4.35 (q, *J* = 7.1 Hz, 2H, H_8), 4.32 (q, *J* = 7.1 Hz, 2H, $H_{8'}$), 1.35 (t, *J* = 7.1 Hz, 3H, H_9), 1.31 (t, *J* = 7.1 Hz, 3H, $H_{9'}$). **^{13}C-NMR (151 MHz, $CDCl_3$)** δ 166.4 (C_1), 163.9 ($C_{1'}$), 140.6 (C_3), 136.6 (C_7), 131.4 (C_4), 130.7 (C_5), 129.1 (C_6), 126.9 (C_2), 61.8 (C_8), 61.8 ($C_{8'}$), 14.1 (C_9), 13.9 ($C_{9'}$). **HRMS for $[C_{14}H_{15}O_4ClNa]^+$** calculated 305.0551 found 305.0540. **R_f** (2:1 EtOAc/PE) = 0.50. Spectroscopic data were consistent with literature values.[8]

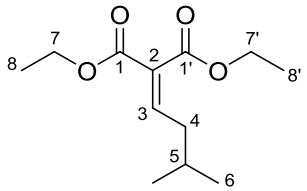
Diethyl 2-benzylidenemalonate



A solution of diethylmalonate (3.8 mL, 25 mmol, 1.0 equiv.), benzaldehyde (2.4 mL, 24 mmol, 1.0 equiv.), piperidine (0.40 mL, 4.0 mmol, 0.2 equiv.) and benzoic acid (0.32 g, 2.6 mmol, 0.1 equiv.) in toluene (25 mL) was heated to 130°C for 21 h with a Dean-Stark apparatus. The reaction mixture was then washed with water (25 mL), aqueous 1 M HCl (25 mL), saturated aqueous $NaHCO_3$ (25 mL) and brine (25 mL). The organic phase was then dried with $MgSO_4$ and the solvents were removed *in vacuo*. Column chromatography (0% to 5% EtOAc in hexane) afforded the product (5.4 g, 22 mmol) as a yellowish oil in 91% yield.

^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.74 (s, 1H, H_3), 7.45 (dd, *J* = 7.7, 2.0 Hz, 2H, H_5), 7.41 – 7.36 (m, 3H, H_6 and H_7), 4.34 (q, *J* = 7.1 Hz, 2H, H_8), 4.31 (q, *J* = 7.1 Hz, 2H, $H_{8'}$), 1.33 (t, *J* = 7.1 Hz, 3H, H_9), 1.28 (t, *J* = 7.1 Hz, 3H, $H_{9'}$). **^{13}C-NMR (151 MHz, $CDCl_3$)** δ 166.8 (C_1), 164.3 ($C_{1'}$), 142.3 (C_3), 133.1 (C_4), 130.7 (C_6), 129.6 (C_5), 128.9 (C_7), 126.5 (C_2), 61.8 (C_8 and $C_{8'}$), 14.3 (C_9), 14.0 ($C_{9'}$). **HRMS for $[C_{14}H_{15}O_4]^+$** calculated 247.0965 found 247.0978. **R_f** (1:4 EtOAc/PE) = 0.53. Spectroscopic data were consistent with literature values.[9]

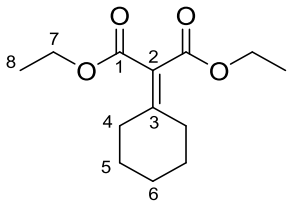
1,3-Diethyl 2- (3- methylbutylidene)propanedioate



A solution of diethyl malonate (7.6 mL, 50 mmol, 1.0 equiv.) and piperidine (0.5 mL, 5.0 mmol, 0.1 equiv.) in heptane (25 mL) was mixed with glacial acetic acid (0.3 mL, 5.0 mmol, 0.1 equiv.) and *iso*-valeraldehyde (5.3 mL, 50 mmol, 1.0 equiv.). The solution was heated to 160°C for 24 h using a Dean-Stark apparatus. Water (15 mL) and diethyl ether (15 mL) were then added and the phases separated. The organic phase was washed with saturated aqueous $NaHCO_3$ (15 mL), brine (15 mL), water (15 mL), and dried over $MgSO_4$.. Solvents were then removed *in vacuo*. Column chromatography on silica gel (5% EtOAc in PE) afforded the product (5.00 g, 21.9 mmol) as a colourless oil in 44% yield.

^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.01 (t, *J* = 8.0 Hz, 1H, H_3), 4.30 (q, *J* = 7.1 Hz, 2H, H_7), 4.23 (q, *J* = 7.1 Hz, 2H, $H_{7'}$), 2.20 – 2.16 (m, 2H, H_4), 1.86 – 1.76 (m, 1H, H_5), 1.32 (t, *J* = 7.1 Hz, 3H, H_8), 1.29 (t, *J* = 7.1 Hz, 3H, $H_{8'}$), 0.93 (d, *J* = 6.7 Hz, 6H, H_6). **^{13}C-NMR (151 MHz, $CDCl_3$)** δ 165.7 (C_1), 164.0 ($C_{1'}$), 148.3 (C_3), 129.3 (C_2), 61.2 (C_7), 61.1 ($C_{7'}$), 38.5 (C_4), 28.2 (C_5), 22.4 (C_6), 14.2 (C_8), 14.1 ($C_{8'}$). **HRMS for $[C_{12}H_{21}O_4]^+$** calculated 229.1434 found 229.1437. **R_f** (1:4 EtOAc/PE) = 0.58. Spectroscopic data were consistent with literature values.[10]

Diethyl 2-cyclohexylidenemalonate

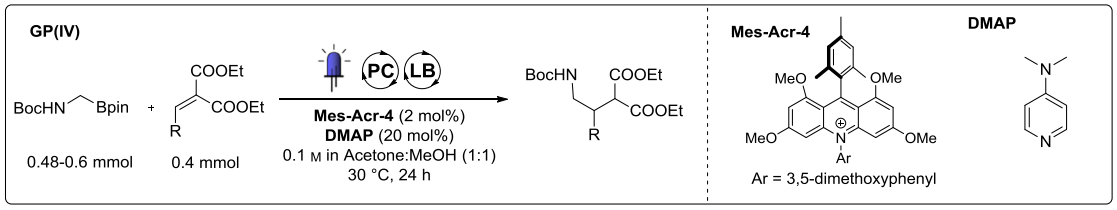


A mixture of THF (18 mL) and CH_2Cl_2 (56 mL) was cooled to 0°C and $TiCl_4$ (5.3 mL, 48 mmol, 1.9 equiv.) was added dropwise. Diethylmalonate (3.8 mL, 25 mmol, 1.0 equiv.) and cyclohexanone (2.7 mL, 29 mmol, 1.2 equiv.) were then added portionwise. The slurry was diluted by the addition of CH_2Cl_2 (30 mL), allowed to warm to room temperature and stirred for 18 h. The reaction mixture was washed with water (2 x 40 mL), the organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography on silica gel (0% to 5% EtOAc in hexane) afforded the product (3.2 g, 14 mmol) as a yellowish oil in 54% yield.

^{1}H-NMR (600 MHz, $CDCl_3$) δ 4.22 (q, *J* = 7.1 Hz, 4H, H_7), 2.59 – 2.43 (m, 4H, H_4), 1.75 – 1.65 (m, 4H, H_5), 1.65 – 1.53 (m, 2H, H_6), 1.28 (t, *J* = 7.1 Hz, 6H, H_8). **^{13}C-NMR (151 MHz, $CDCl_3$)** δ 165.9 (C_1), 161.7 (C_3), 121.9 (C_2), 61.0 (C_7), 32.7 (C_4), 28.3 (C_5), 26.2 (C_6), 14.2 (C_8). **HRMS for $[C_{13}H_{20}O_4Na]^+$** calculated 263.1259 found 263.1245. **R_f** (1:4 EtOAc/PE) = 0.63. Spectroscopic data were consistent with literature values.[11]

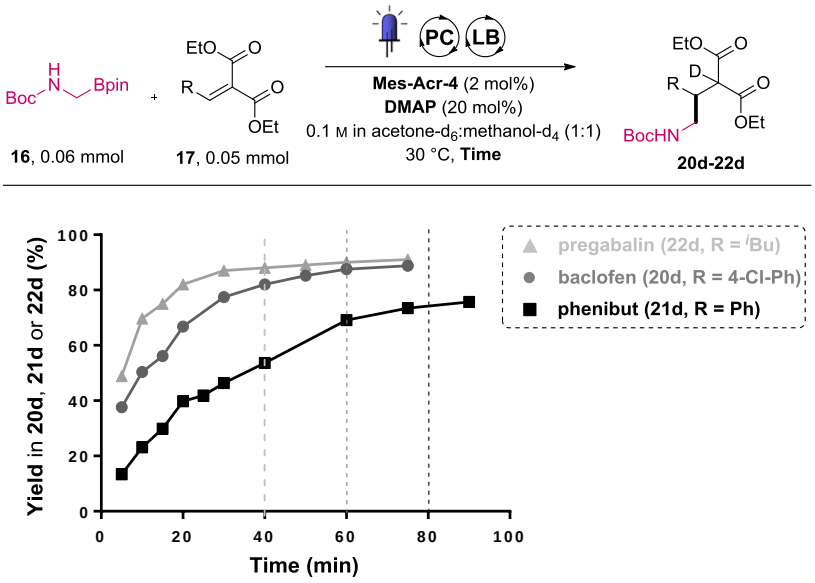
4.2 Synthetic procedures and characterisation for γ-amino butyric acid analogues

4.2.1 Batch protocol

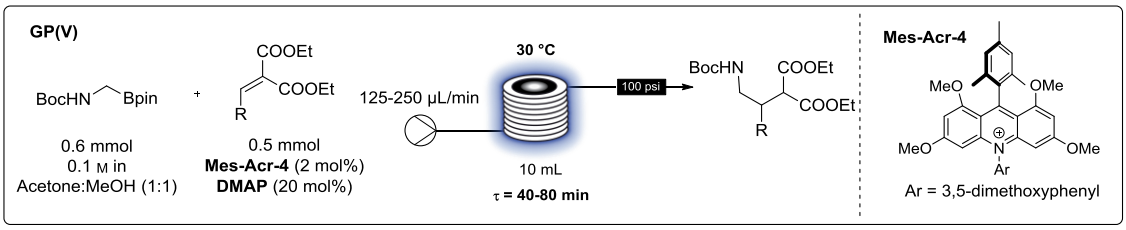


GP(IV): A 10 mL glass test tube equipped with a magnetic stirrer was charged with the desired alkene (0.4 mmol, 1.0 equiv.), *tert*-butyl((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)carbamate (0.48–0.60 mmol, 1.2–1.5 equiv.), the photoredox catalyst **Mes-Acr-4** (4.4 mg, 2.0 mol%) and DMAP (9.6 mg, 80 µmol, 20 mol%) as Lewis base catalyst. The test tube was then capped, evacuated and backfilled with argon three times before 4.0 mL of a degassed acetone/methanol (1:1) mixture was added to obtain a clear yellow transparent 0.1 M solution. This solution was then stirred while irradiated with a commercial blue LED strip (Ledxon, 14.4 W, 470 nm) for 24 hours, the temperature was maintained at 30°C using a desktop fan. The content of the vial was then concentrated *in vacuo* and purified by flash column chromatography to yield the pure product.

4.2.2 Flow protocol

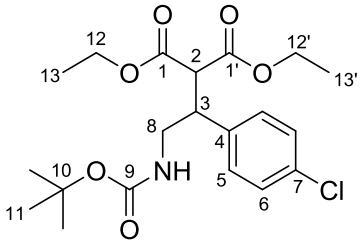


Graph S2 – Reaction following for drugs compounds precursors.



GP(V): A 10 mL conical-shaped flask was charged with the desired alkene (0.5 mmol, 1.0 equiv.), *tert*-butyl((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)carbamate (0.15 g, 0.60 mmol, 1.2 equiv.), the photoredox catalyst **Mes-Acr-4** (5.5 mg, 2.0 mol%) and DMAP (12 mg, 100 µmol, 20 mol%) as Lewis base catalyst. The flask was then capped, evacuated and backfilled with argon three times before 5.0 mL of a degassed acetone/methanol (1:1) mixture was added to obtain a clear yellow transparent 0.1 M solution. The clear solution was then pumped at 125 to 250 µL/min through a Vapourtec UV-150 photochemical reactor (10 mL reactor coil, FEP tubing, τ = 40 to 80 min) held at 30°C. Once the reaction mixture has fully be taken up by the pump, the input was swapped to acetone:methanol (1:1) solvent to push the rest of the reaction mixture through the reactor. When the reaction plug was exiting the output stream (yellow colour), the totality of the plug was collected in a vial wrapped in aluminium foil and concentrated *in vacuo* before being purified by flash column chromatography to yield the pure product.

Diethyl 2-(2-((tert-butoxycarbonyl)amino)-1-(4-chlorophenyl)ethyl)malonate (20)

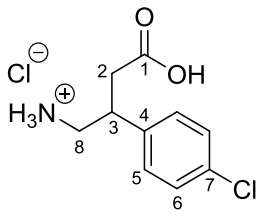


Obtained in batch following **GP(IV)** using diethyl 2-(4-chlorobenzylidene) malonate (0.11 g, 0.40 mmol) as olefin and *tert*-butyl ((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)carbamate (0.12 g, 0.48 mmol, 1.2 equiv.). Purification by column chromatography on silica gel (7% to 10% EtOAc and 1% Et_3N in hexane) afforded product **20** (0.11 g, 0.28 mmol) as a white solid in 70% yield.

Also obtained in flow following **GP(V)** using diethyl 2-(4-chlorobenzylidene) malonate (0.14 g, 0.50 mmol) and 60 min residence time. Purification by column chromatography on silica gel (7% to 10% EtOAc and 1% Et_3N in hexane) afforded product **20** (0.13 g, 0.35 mmol) as a white solid in 69% yield.

^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.3 Hz, 2H, H_5), 7.16 (d, *J* = 8.3 Hz, 2H, H_6), 4.52 –4.37 (m, 1H, N*H*), 4.23 (q, *J* = 7.1 Hz, 2H, H_{12}), 3.97 – 3.88 (m, 2H, $H_{12'}$), 3.66 (d, *J* = 10.3 Hz, 1H, H_2), 3.62 – 3.54 (m, 1H, H_3), 3.49 (m, 1H, H_{8a}), 3.37 (m, 1H, H_{8b}), 1.36 (s, 9H, H_{11}), 1.27 (t, *J* = 7.1 Hz, 3H, H_{13}), 0.99 (t, *J* = 7.1 Hz, 3H, $H_{13'}$). **^{13}C-NMR (151 MHz, $CDCl_3$)** δ 168.3 (C_1), 167.7 ($C_{1'}$), 155.8 (C_9), 137.8 (C_4), 133.6 (C_7), 130.1 (C_6), 129.0 (C_5), 79.8 (C_{10}), 62.2 (C_{12}), 61.8 ($C_{12'}$), 55.8 (C_2), 45.2 (C_3), 44.1 (C_8), 28.6 (C_{11}), 14.4 (C_{13}), 14.1 ($C_{13'}$). **HRMS for $[C_{20}H_{28}NO_6ClNa]^+$** calculated 436.1497 found 436.1483. **R_f** (1:1 Et_2O:PE) = 0.45. **M.p.** = 105–106°C. Spectroscopic data were consistent with literature values.[8]

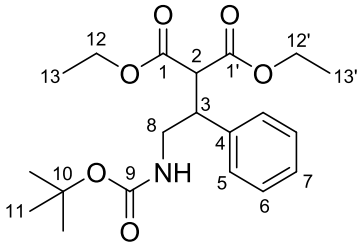
(±)-Baclofen·HCl



diethyl 2-(2-((*tert*-butoxycarbonyl)amino)-1-(4-chlorophenyl)ethyl)malonate (**20**, 0.11 g, 0.28 mmol.) was dissolved in aqueous 6 M HCl (3.0 mL) and heated to 120°C for 24 h in a sealed vial. The solvent was removed under reduced pressure, the residue was dissolved in water (6.0 mL) and washed with Et_2O (2 x 8 mL). Removal of the solvent *in vacuo* afforded the amino acid hydrochloride (67 mg, 0.27 mmol) as white crystals in 97% yield.

^{1}H-NMR (600 MHz, D_2O) δ 7.47 (d, *J* = 8.5 Hz, 2H, H_5), 7.36 (d, *J* = 8.5 Hz, 2H, H_6), 3.48 (m, 1H, H_3), 3.40 (dd, *J* = 12.9, 5.0 Hz, 1H, H_{8a}), 3.27 (dd, *J* = 12.9, 10.6 Hz, 1H, H_{8b}), 2.90 (dd, *J* = 16.0, 5.8 Hz, 1H, H_{2a}), 2.80 (dd, *J* = 16.0, 9.4 Hz, 1H, H_{2b}). **^{13}C-NMR (151 MHz, D_2O)** δ 173.9 (C_1), 136.8 (C_4), 133.4 (C_7), 129.4 (C_6), 129.2 (C_5), 43.5 (C_8), 39.4 (C_3), 38.1 (C_2). **HRMS for $[C_{10}H_{13}NO_2Cl]^+$** calculated 214.0629 found 214.0629. **M.p.** 195–198°C. Spectroscopic data were consistent with literature values.[12]

Diethyl 2-(2-((tert-butoxycarbonyl)amino)-1-phenylethyl)malonate (21)

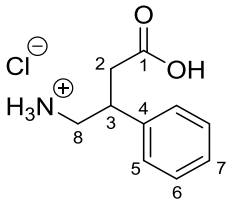


Obtained in batch following **GP(IV)** using diethyl 2-benzylidenemalonate (0.10 g, 0.41 mmol) as olefin and *tert*-butyl((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)carbamate (0.12 g, 0.48 mmol, 1.2 equiv.). Purification by column chromatography on silica gel (5% to 10% EtOAc and 1% Et_3N in hexane) afforded product **21** (0.12 g, 0.32 mmol) as an amorphous white solid in 78% yield.

Also obtained in flow following **GP(V)** using diethyl 2-benzylidenemalonate (0.12 g, 0.50 mmol) as olefin and 80 min residence time. Purification by column chromatography on silica gel (5% to 10% EtOAc and 1% Et_3N in hexane) afforded product **21** (0.14 g, 0.37 mmol) as an amorphous white solid in 74% yield.

^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H, H_6), 7.25 – 7.18 (m, 3H, H_6, H_7), 4.42 (s, 1H, N*H*), 4.24 (q, *J* = 7.2 Hz, 2H, H_{12}), 3.96 – 3.85 (m, 2H, $H_{12'}$), 3.70 (d, *J* = 10.4 Hz, 1H, H_2), 3.64 – 3.58 (m, 1H, H_3), 3.53 (dt, *J* = 13.0, 6.2 Hz, 1H, H_{8a}), 3.45 – 3.34 (m, 1H, H_{8b}), 1.37 (s, 9H, H_{11}), 1.28 (t, *J* = 7.2 Hz, 3H, H_{13}), 0.95 (t, *J* = 7.1 Hz, 3H, $H_{13'}$). **^{13}C-NMR (151 MHz, $CDCl_3$)** δ 168.3 (C_1), 167.6 ($C_{1'}$), 155.7 (C_9), 139.0 (C_4), 128.7 (C_6), 128.5 (C_5), 127.6 (C_7), 79.4 (C_{10}), 61.9 (C_{12}), 61.5 ($C_{12'}$), 55.9 (C_2), 45.5 (C_3), 44.1 (C_8), 28.4 (C_{11}), 14.2 (C_{13}), 13.8 ($C_{13'}$). **HRMS for $[C_{20}H_{29}NO_6Na]^+$** calculated 402.1887 found 402.1875. **R_f** (1:1 Et_2O:PE) = 0.45. Spectroscopic data were consistent with literature values.[8]

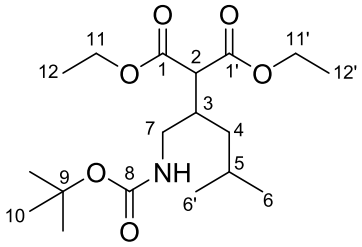
(±)-Phenibut·HCl



diethyl 2-(2-((tert-butoxycarbonyl)amino)-1-phenylethyl)malonate (**21**, 0.12 g, 0.32 mmol) was dissolved in aqueous 6 M HCl (3.0 mL) and heated to 120°C for 1 h. A small amount of active charcoal was added, and the mixture was heated to 120°C for 20 min. The mixture was allowed to cool to room temperature and filtered. Removal of the solvent *in vacuo* afforded the amino acid hydrochloride (61 mg, 0.28 mmol) as colourless crystals in 88% yield.

^{1}H-NMR (600 MHz, D_2O) δ 7.47 (t, *J* = 7.6 Hz, 2H, H_6), 7.40 (d, *J* = 7.6 Hz, 3H, H_5 and H_7), 3.50 – 3.37 (m, 2H, H_7, H_{8a}), 3.33 – 3.23 (m, 1H, H_{8b}), 2.92 – 2.86 (m, 1H, H_{2a}), 2.80 (dd, *J* = 16.1, 8.8 Hz, 1H, H_{2b}). **^{13}C-NMR (151 MHz, D_2O)** δ 175.5 (C_1), 138.3 (C_4), 129.3 (C_6), 128.3 (C_7), 127.8 (C_5), 43.8 (C_8), 39.9 (C_3), 38.2 (C_2). **HRMS for $[C_{10}H_{14}NO_2]^+$** calculated 180.1019 found 180.1021. **M.p.** 185–188°C. Spectroscopic data were consistent with literature values.[12]

Diethyl 2-(1-((tert-butoxycarbonyl)amino)-4-methylpentan-2-yl)malonate (22)

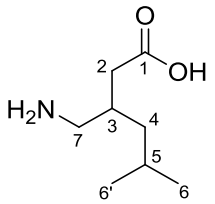


Obtained in batch following **GP(IV)** using diethyl 2-(3-methylbutylidene)malonate (91 mg, 0.40 mmol) as olefin and *tert*-butyl ((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)carbamate (0.12 g, 0.48 mmol, 1.2 equiv.). Purification by column chromatography on silica gel (0% to 7% EtOAc and 1% Et_3N in hexane) afforded product **22** (0.12 g, 0.34 mmol) as a colourless oil in 86% yield.

Also obtained in flow following **GP(V)** using diethyl 2-(3-methylbutylidene)malonate (0.11 g, 0.40 mmol) as olefin and 40 min residence time. Purification by column chromatography on silica gel (0% to 7% EtOAc and 1% Et_3N in hexane) afforded product **22** (0.15 g, 0.42 mmol) as a colourless oil in 85% yield.

^{1}H-NMR (600 MHz, $CDCl_3$) δ 4.82 (t, *J* = 6.5 Hz, 1H, N*H*), 4.27 – 4.14 (m, 4H, H_4, H_{11} and $H_{11'}$), 3.38 (d, *J* = 6.6 Hz, 1H, H_2), 3.26 (dt, *J* = 14.3, 5.4 Hz, 1H, H_{7a}), 3.18 (dt, *J* = 14.3, 6.8 Hz, 1H, H_{7b}), 2.40 (m, 1H, H_3), 1.68 (m, 1H, H_5) 1.41 (s, 9H, H_{10}), 1.29 – 1.21 (m, 7H, H_{4a}, H_{12} and $H_{12'}$), 1.11 (ddd, *J* = 13.8, 8.6, 5.2 Hz, 1H, H_{4b}), 0.95 – 0.81 (m, 6H, H_6 and $H_{6'}$). **^{13}C-NMR (151 MHz, $CDCl_3$)** δ 169.1 (C_1 and $C_{1'}$), 156.0 (C_8), 79.2 (C_9), 61.5 (C_{11} and $C_{11'}$), 54.3 (C_2), 41.7 (C_7), 39.3 (C_4), 37.0 (C_3), 28.5 (C_{10}), 25.4 (C_5), 23.4 (C_6), 22.1 ($C_{6'}$), 14.2 (C_{12} and $C_{12'}$). **HRMS for $[C_{18}H_{33}NO_6Na]^+$** calculated 382.2200 found 382.2188. **R_f** (1:1 Et_2O:PE) = 0.58. Spectroscopic data were consistent with literature values.[13]

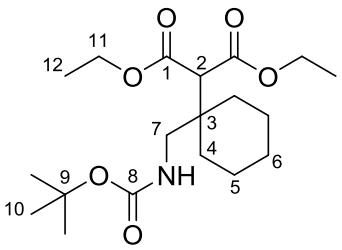
(±)-Pregabalin



diethyl 2-(1-((*tert*-butoxycarbonyl)amino)-4-methylpentan-2-yl)malonate (**22**, 89 mg, 0.24 mmol) was dissolved in aqueous 6 M HCl (3.0 mL) and heated to 125°C for 24 h. Removal of the solvent *in vacuo* at 60°C for 2 h afforded the amino acid hydrochloride (65 mg, 0.33 mmol) as a sticky residue in 94% yield. For the preparation of crystalline material, which was used for characterization, a sample of the hydrochloride was dissolved in water, neutralised with aqueous 1 M NaOH to pH 7 and recrystallised from a mixture of *iso*-PrOH (30%) in H_2O to afford colourless crystals of pregabalin as the free amino acid.

^{1}H-NMR (600 MHz, D_2O) δ 2.99 (m, 2H, H_{7a} and H_{7b}), 2.38 – 2.29 (m, 1H, H_{4a}), 2.24 (m, 1H, H_{4b}), 2.21 – 2.13 (m, 1H, H_3), 1.72 – 1.56 (m, 1H, H_5), 1.23 (t, J = 7.2 Hz, 2H, H_2), 1.02 – 0.82 (m, 6H, H_6 and $H_{6'}$). **^{13}C-NMR (151 MHz, D_2O)** δ 181.1 (C_1), 43.7 (C_7), 40.7 (C_4), 40.6 (C_2), 31.7 (C_3), 24.4 (C_5), 22.0 (C_6), 21.5 ($C_{6'}$). **HRMS for $[C_8H_{18}NO_2]^+$** calculated 160.1332 found 160.1334. **M.p.** 167–168°C. Spectroscopic data were consistent with literature values.[13]

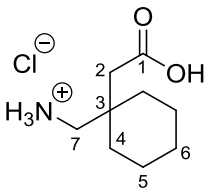
Diethyl 2-(1-((tert-butoxycarbonyl)amino)cyclohexyl)malonate (23)



Obtained in batch following **GP(IV)** with 48 h irradiation using diethyl 2-cyclohexylidenemalonate (96 mg, 0.40 mmol) as olefin and *tert*-butyl ((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)carbamate (0.15 g, 0.60 mmol, 1.5 equiv.). Purification by column chromatography on silica gel (5% to 10% EtOAc in hexane) afforded product **23** (82 mg, 0.22 mmol) as a colourless oil in 55% yield.

^{1}H-NMR (600 MHz, $CDCl_3$) δ 5.36 (t, *J* = 6.6 Hz, 1H, N*H*), 4.22 – 4.15 (m, 4H, H_{11}), 3.52 (s, 1H, H_2), 3.37 (d, *J* = 6.6 Hz, 2H, H_7), 1.63 – 1.44 (m, 9H, H_4, H_5 and H_{6a}), 1.42 (s, 9H, H_{10}), 1.37 – 1.29 (m, 1H, H_{6b}), 1.27 (t, *J* = 7.1 Hz, 6H, H_{12}). **^{13}C-NMR (151 MHz, $CDCl_3$)** δ 168.7 (C_1), 156.5 (C_8), 79.0 (C_9), 61.4 (C_{11}), 57.5 (C_2), 44.4 (C_7), 40.9 (C_3), 32.2 (C_4), 28.5 (C_{10}), 25.7 (C_6), 21.4 (C_5), 14.2 (C_{12}). **IR (ATR – neat)** $\tilde{\nu}$ (cm^{-1}) = 3420, 1752, 1716, 1511, 1454, 1366, 1240, 1095, 1031, 758. **HRMS for $[C_{19}H_{33}NO_6Na]^+$** calculated 394.2200 found 394.2188. **R_f** (1:1 Et_2O:PE) = 0.56.

Gabapentin·HCl



diethyl 2-(1-((tert-butoxycarbonyl)amino)cyclohexyl)malonate (**23**, 82 mg, 0.22 mmol) was dissolved in aqueous 6 M HCl (3.0 mL) and heated to 120°C for 24 h. The solvent was removed under reduced pressure, the residue was dissolved in water (6.0 mL) and washed with Et_2O (2 x 8 mL). Removal of the solvent *in vacuo* afforded the amino acid hydrochloride (41 mg, 0.20 mmol) as white crystals in 91% yield.

^{1}H-NMR (600 MHz, D_2O) δ 3.12 (s, 2H, H_7), 2.55 (s, 2H, H_2), 1.56 – 1.34 (m, 10H, H_4, H_5 and H_6). **^{13}C-NMR (151 MHz, D_2O)** δ 176.1 (C_1), 46.6 (C_7), 38.8 (C_2), 34.6 (C_3), 32.8 (C_4), 25.0 (C_6), 20.5 (C_5). **HRMS for $[C_9H_{18}NO_2]^+$** calculated 172.1332 found 172.1334. **M.p.** 116–118°C. Spectroscopic data were consistent with literature values.[14]

5 References

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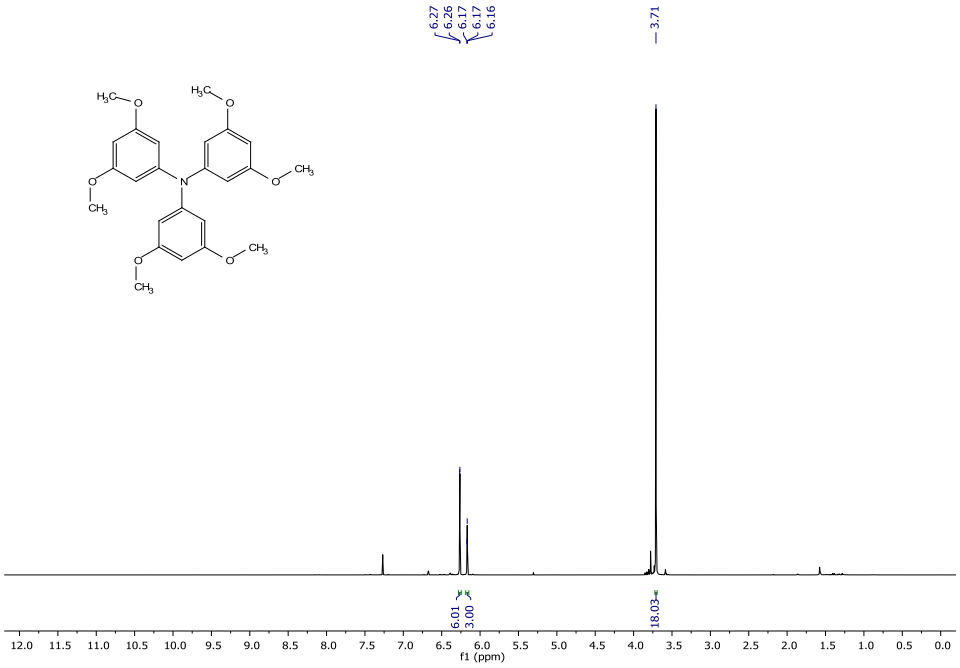
6 NMR spectra

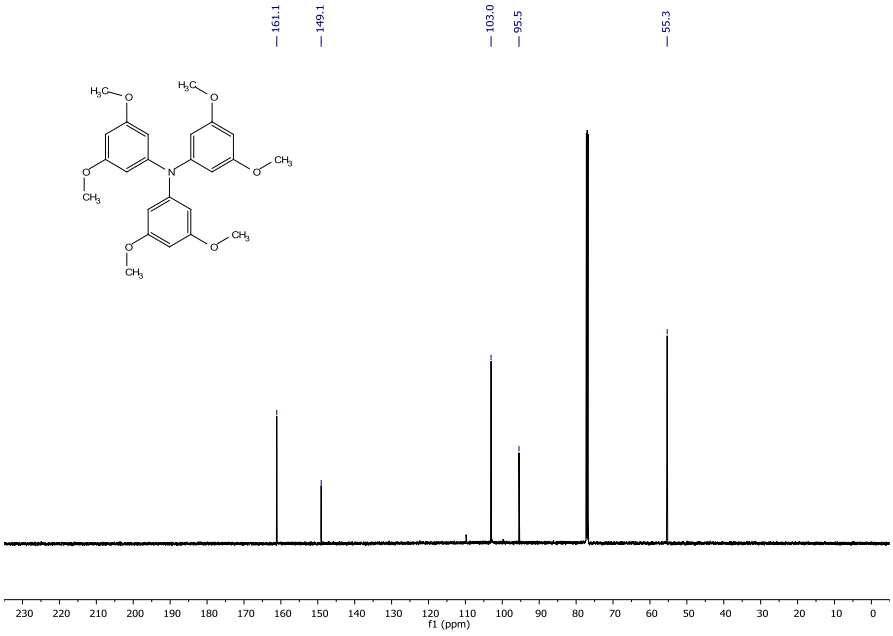
6.1 Organic dyes spectra

Tris(3,5-dimethoxyphenyl)amine

^{1}H-NMR (600 MHz, $CDCl_3$)

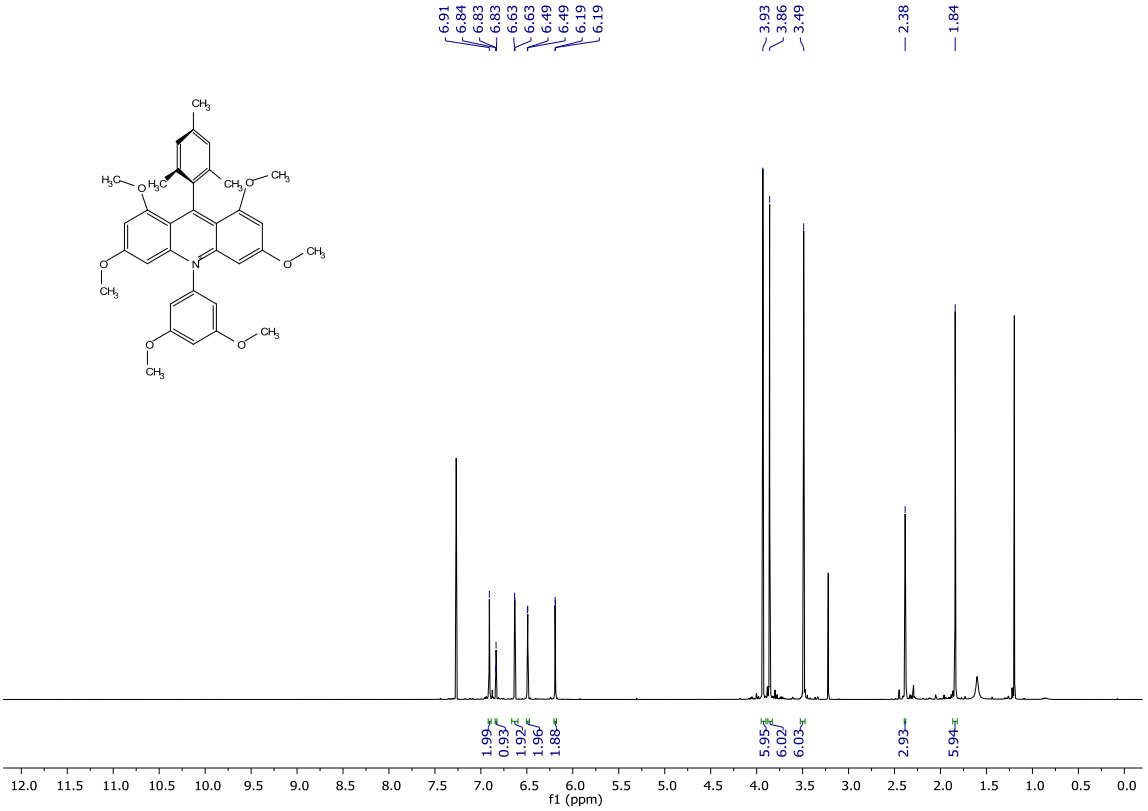


^{13}C-NMR (151 MHz, $CDCl_3$)

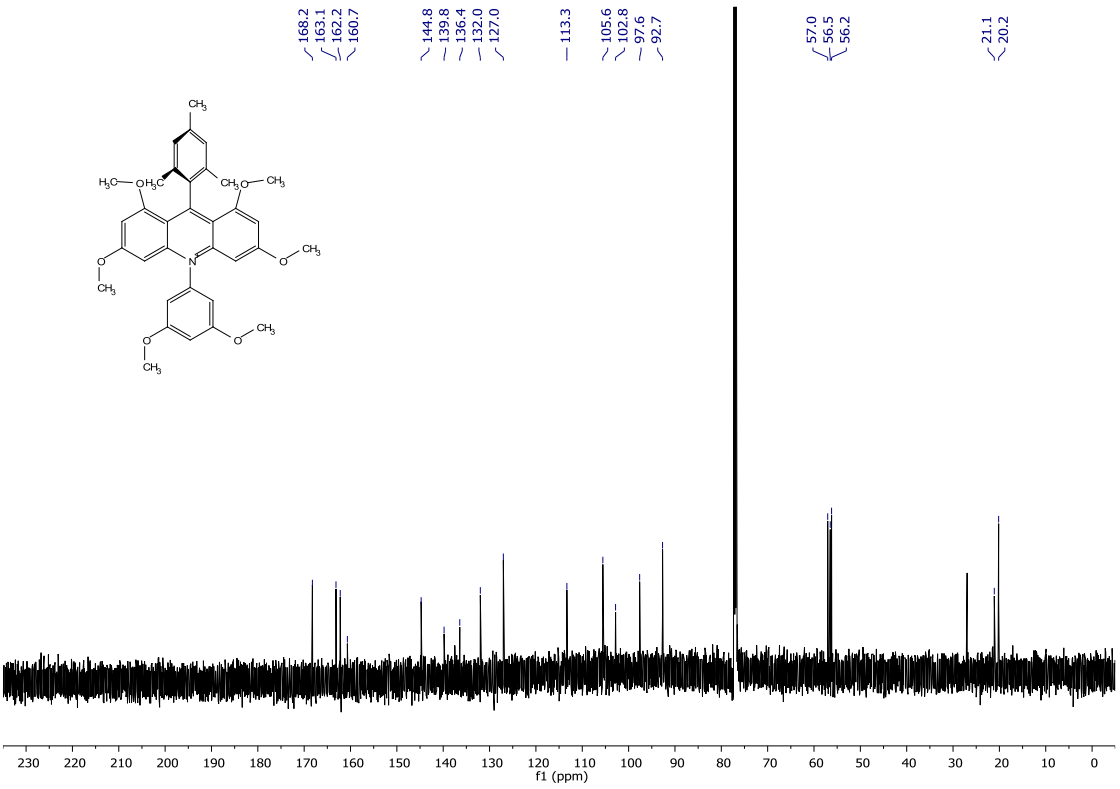


10-(3,5-Dimethoxyphenyl)-9-mesityl-1,3,6,8-tetramethoxyacridin-10-ium tetrafluoroborate (Mes-Acr-4)

^{1}H-NMR (600 MHz, $CDCl_3$)

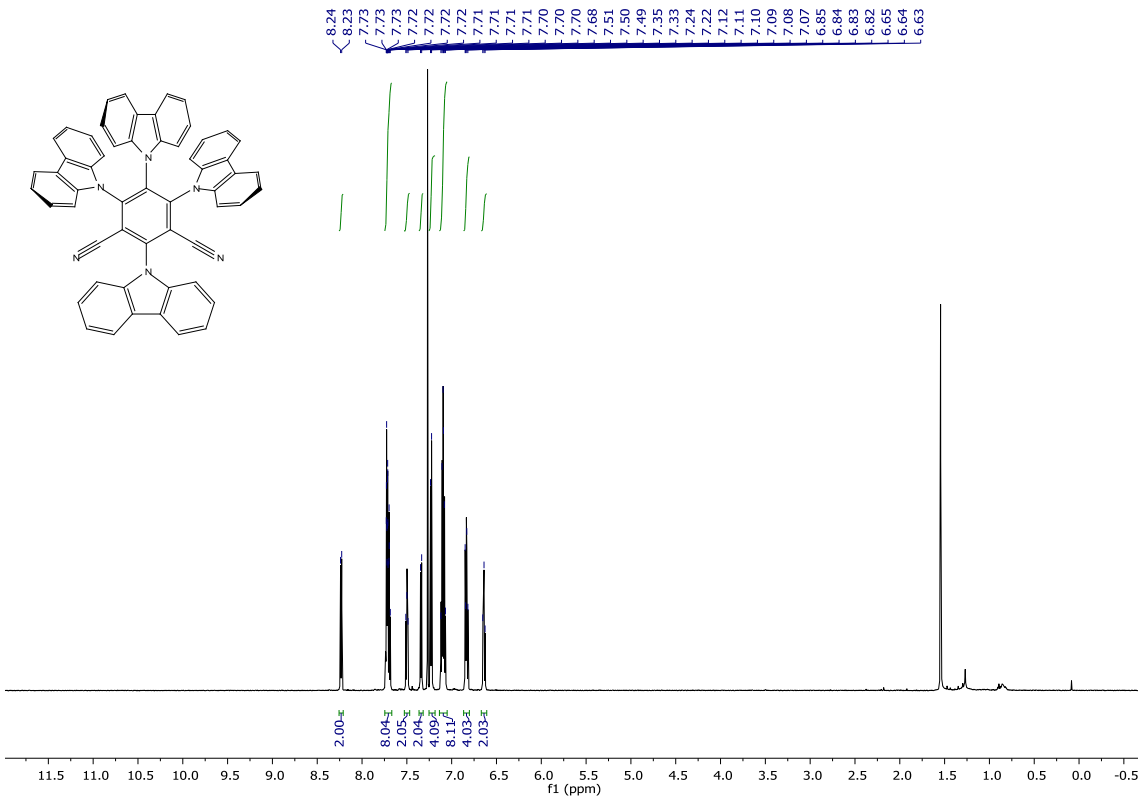


^{13}C-NMR (151 MHz, $CDCl_3$)

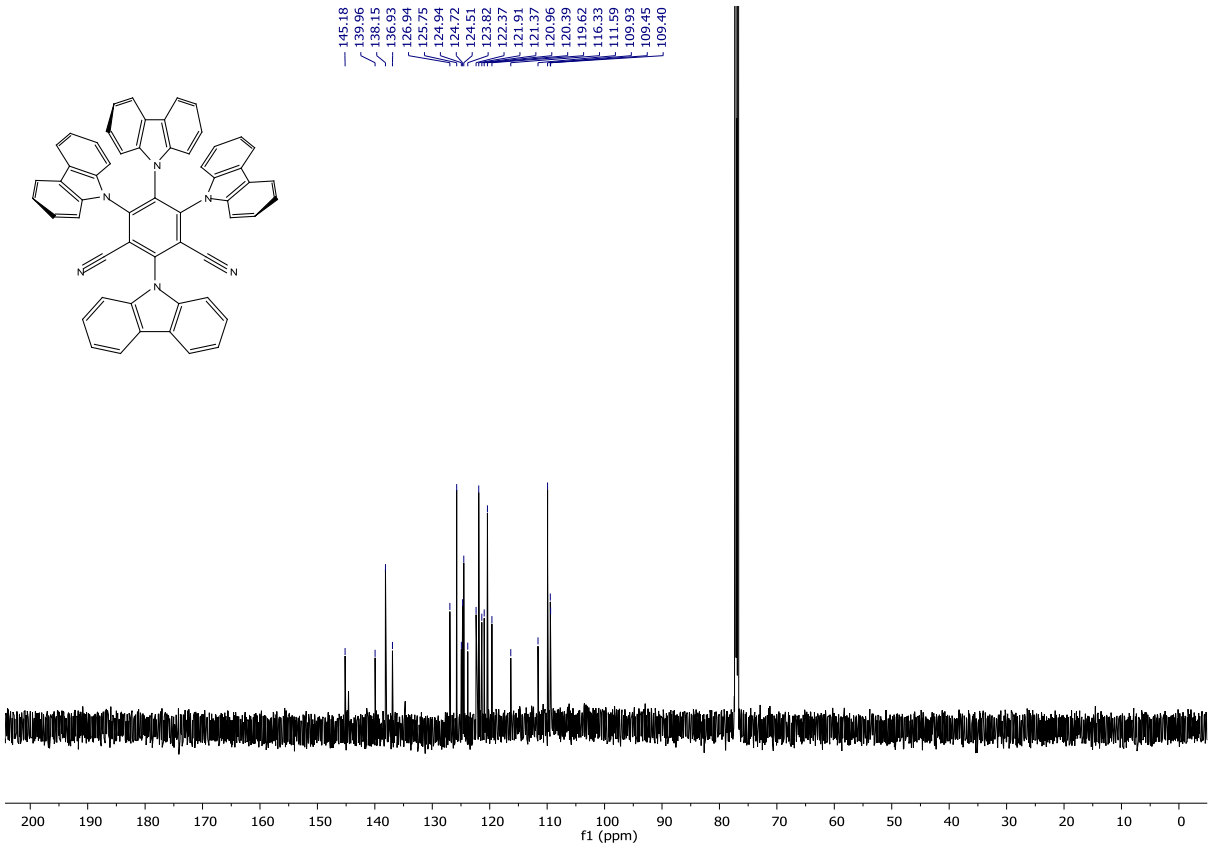


2,4,5,6-Tetra(9*H*-carbazol-9-yl)isophthalonitrile (4CzIPN)

^{1}H-NMR (600 MHz, $CDCl_3$)



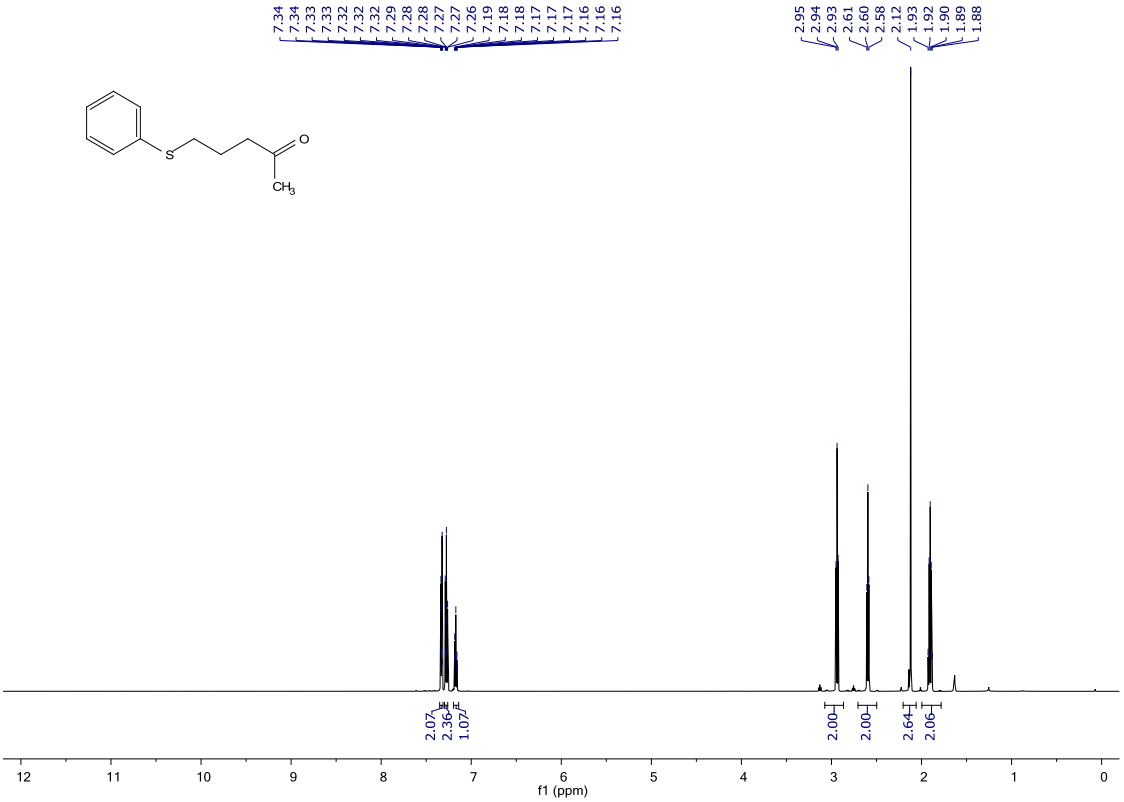
^{13}C-NMR (151 MHz, $CDCl_3$)



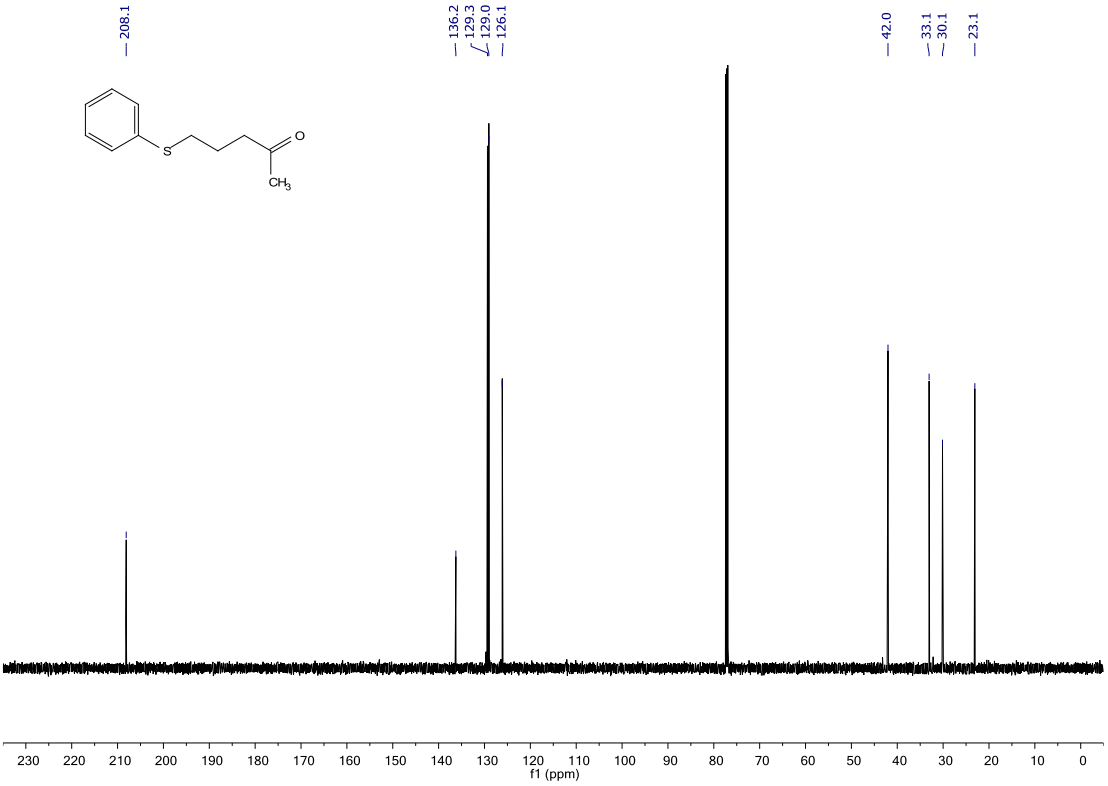
6.2 Coupling products spectra

5-(Phenylthio)pentan-2-one (9)

^{1}H-NMR (600 MHz, $CDCl_3$)

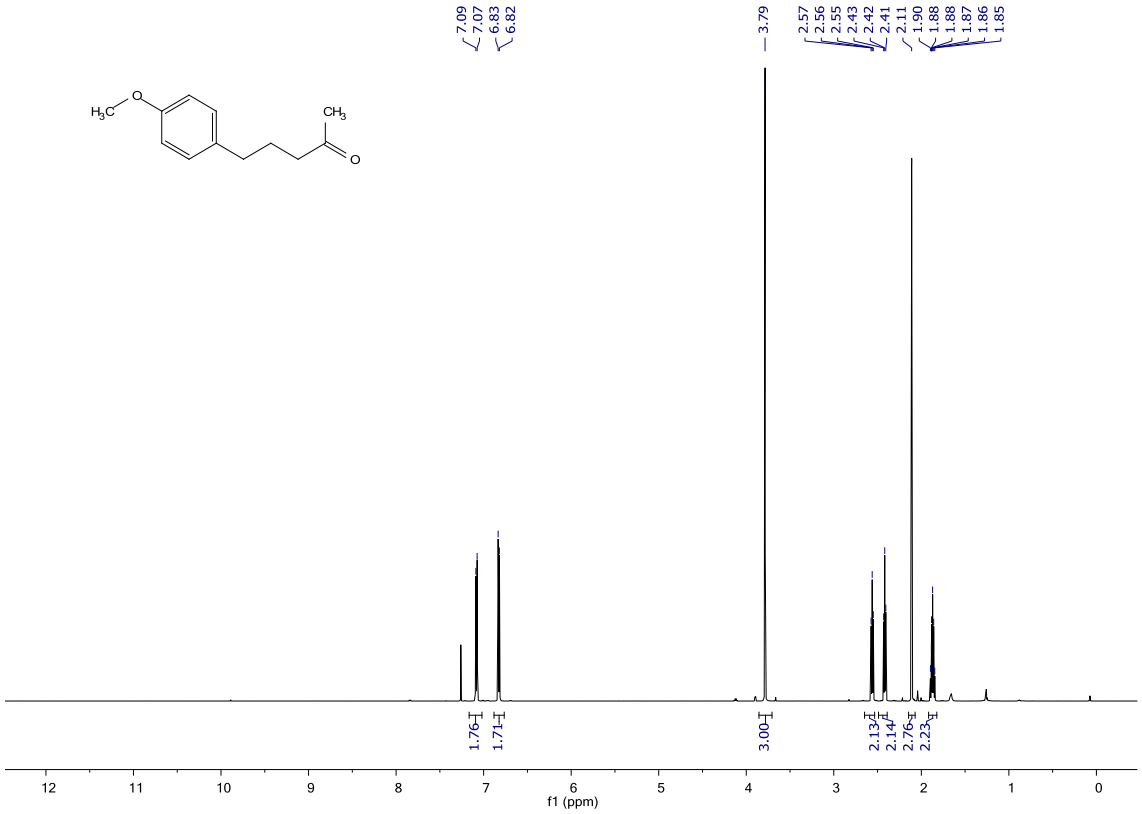


^{13}C-NMR (151 MHz, $CDCl_3$)

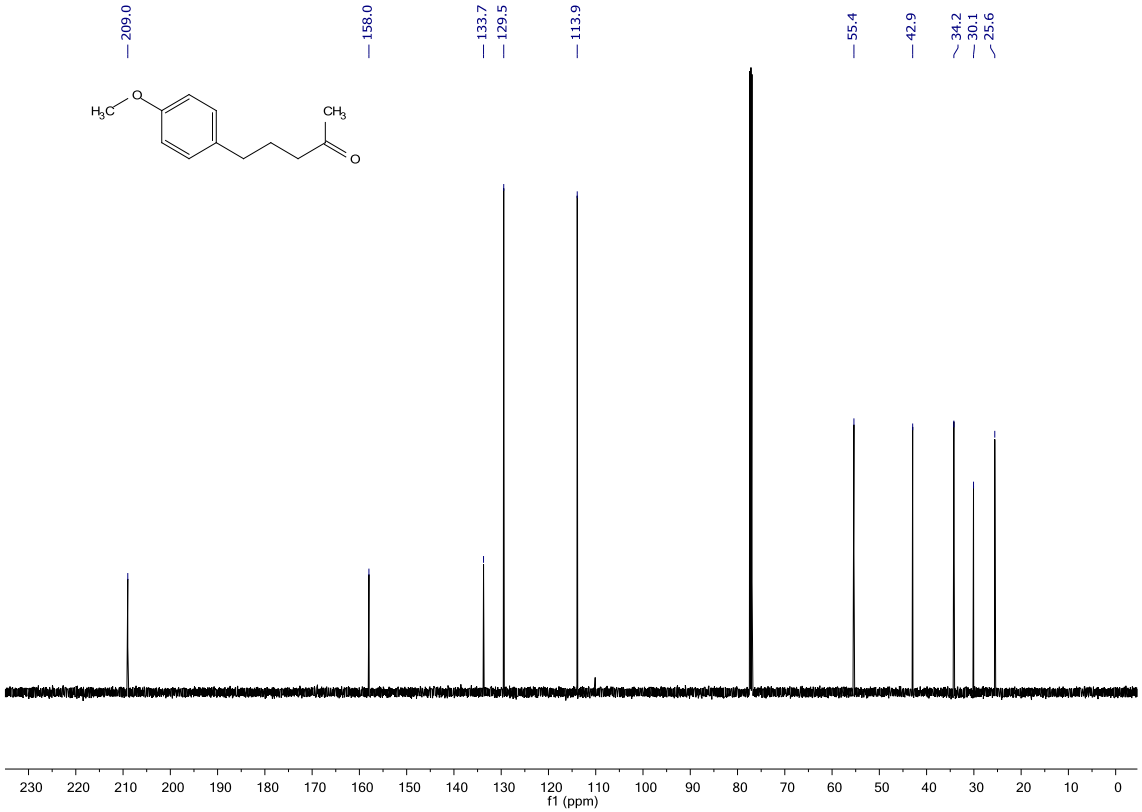


5-(4-Methoxyphenyl)pentan-2-one (4)

^{1}H-NMR (600 MHz, $CDCl_3$)

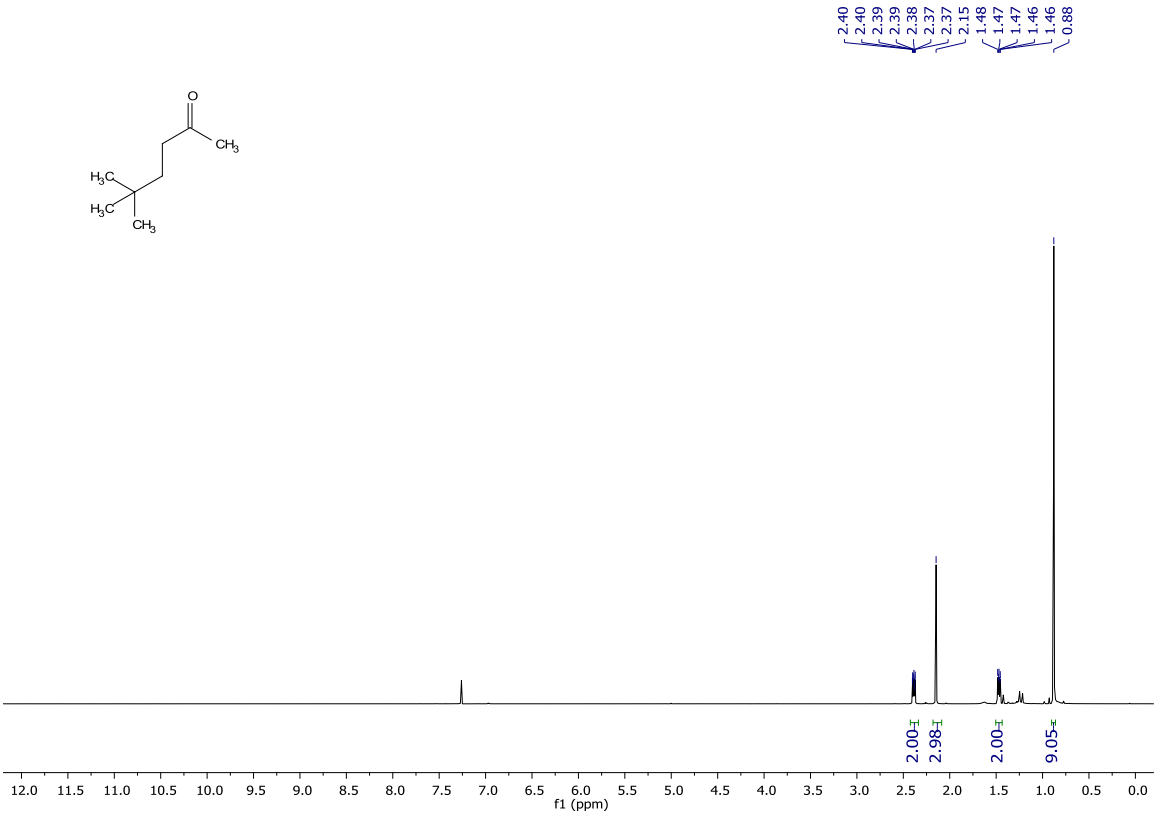


^{13}C-NMR (151 MHz, $CDCl_3$)

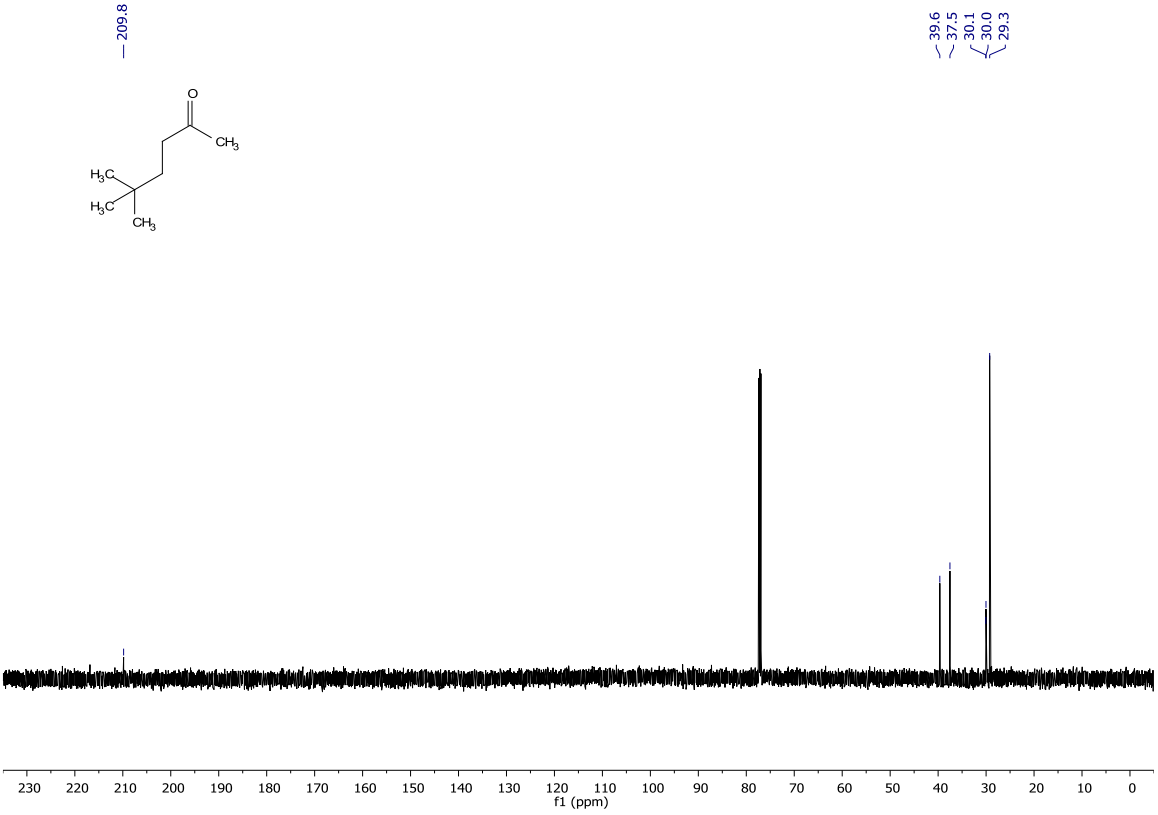


5,5-Dimethylhexan-2-one (10)

^{1}H-NMR (600 MHz, $CDCl_3$)

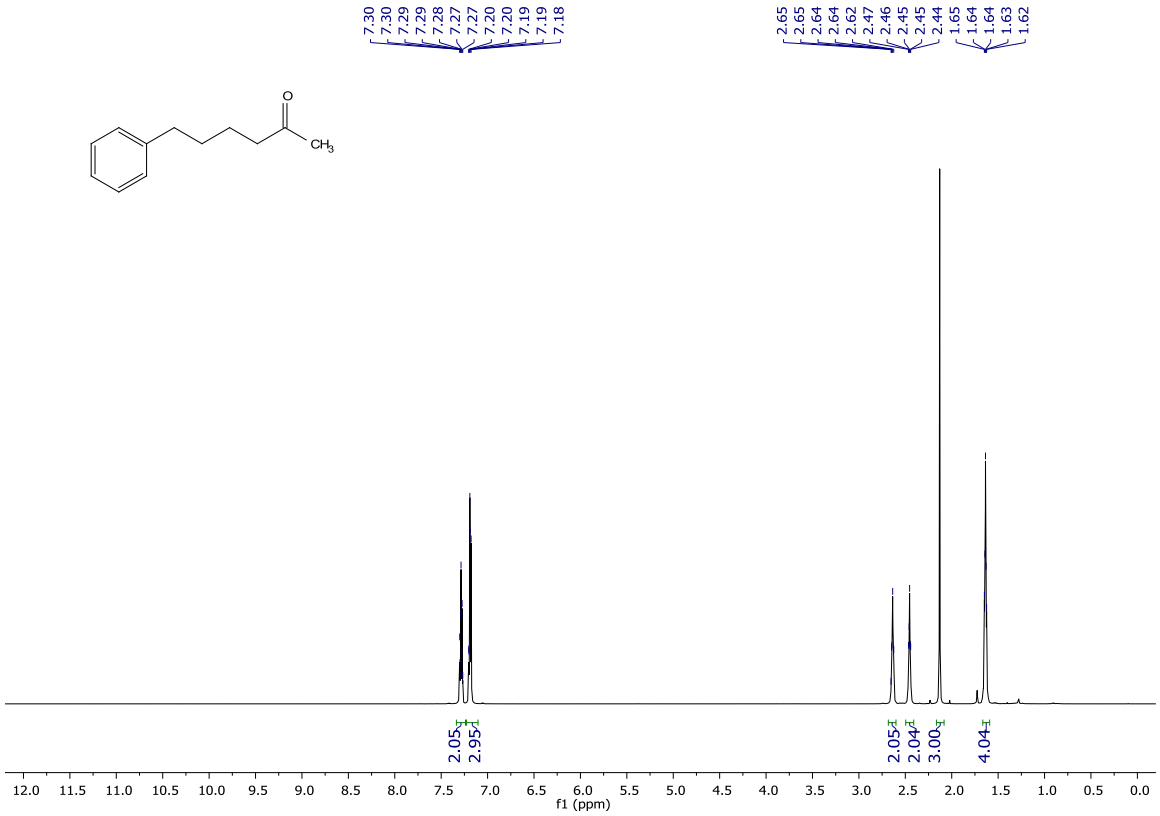


^{13}C-NMR (151 MHz, $CDCl_3$)

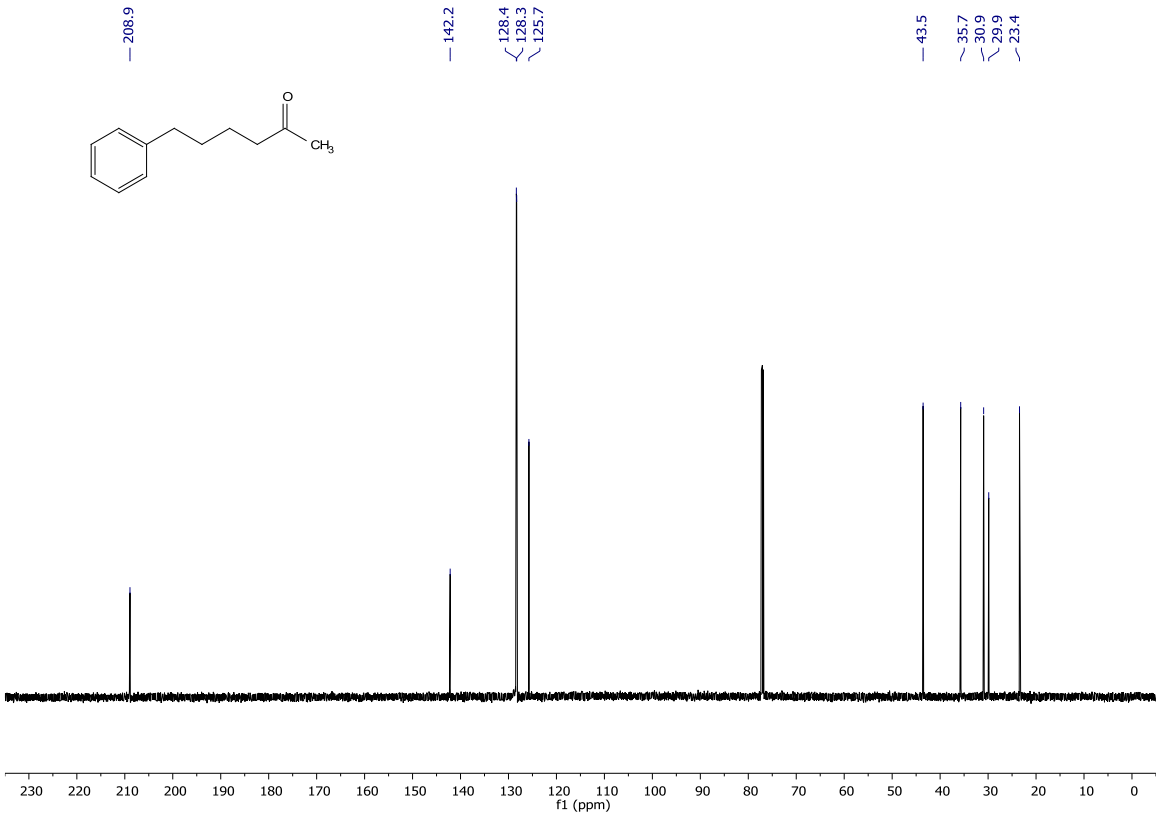


6-Phenylhexan-2-one (11)

^{1}H-NMR (600 MHz, $CDCl_3$)

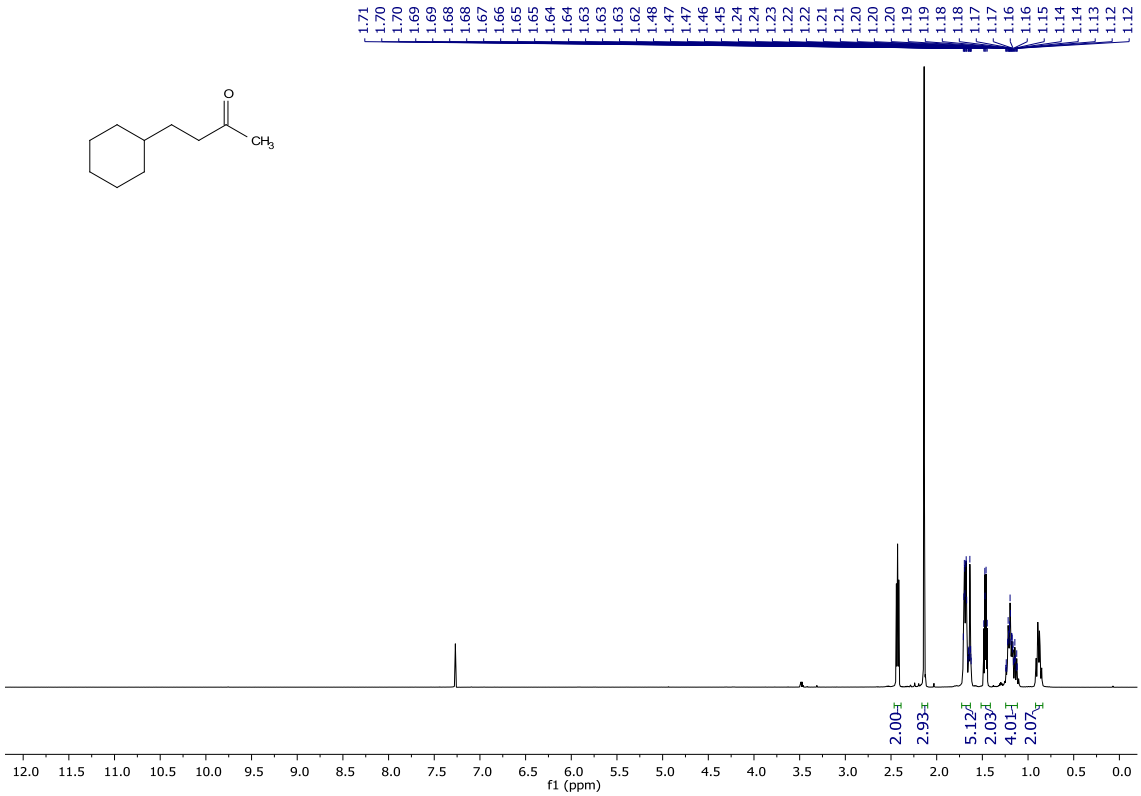


^{13}C-NMR (151 MHz, $CDCl_3$)

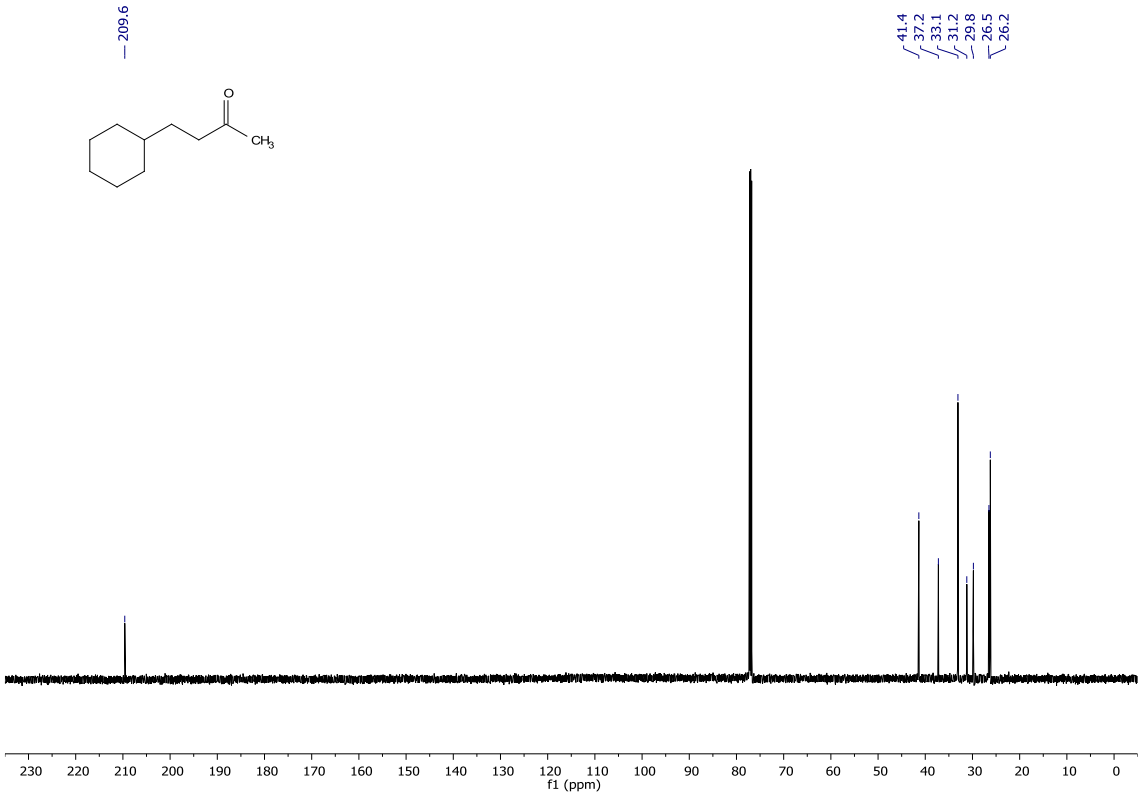


4-Cyclohexylbutan-2-one (5)

^{1}H-NMR (600 MHz, $CDCl_3$)

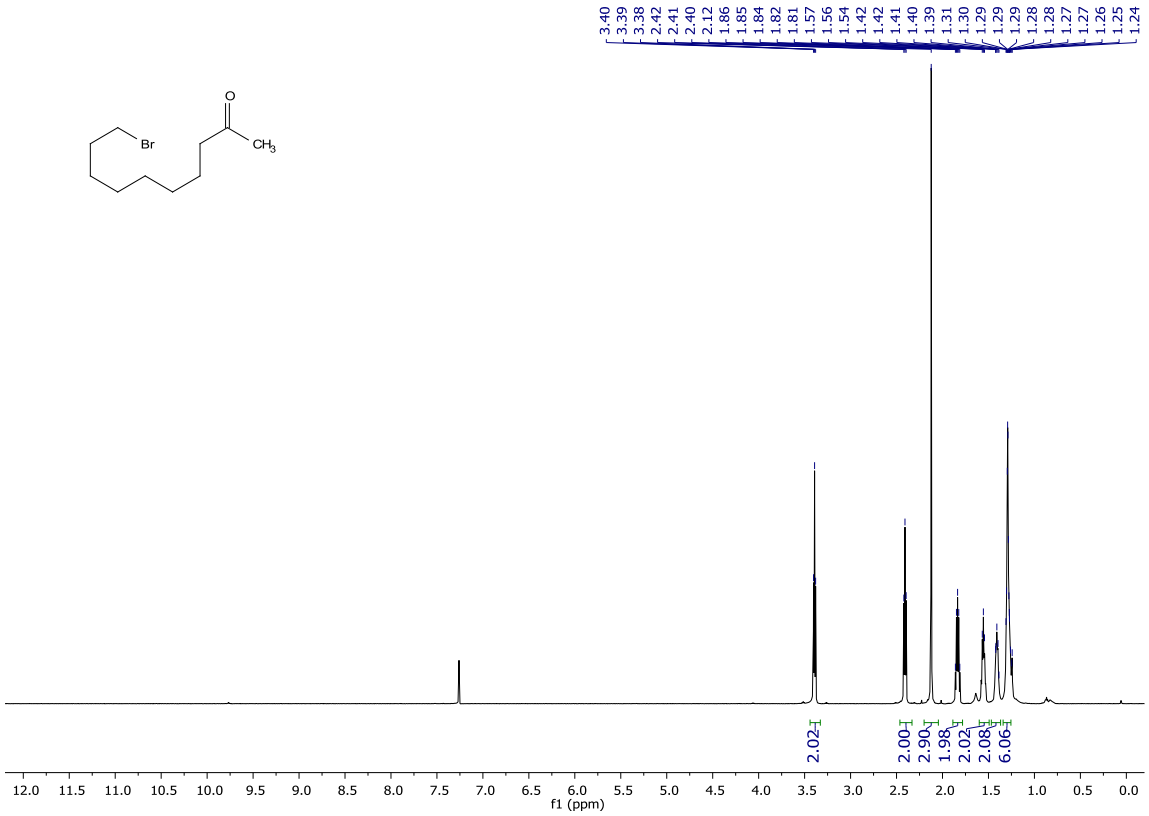


^{13}C-NMR (151 MHz, $CDCl_3$)

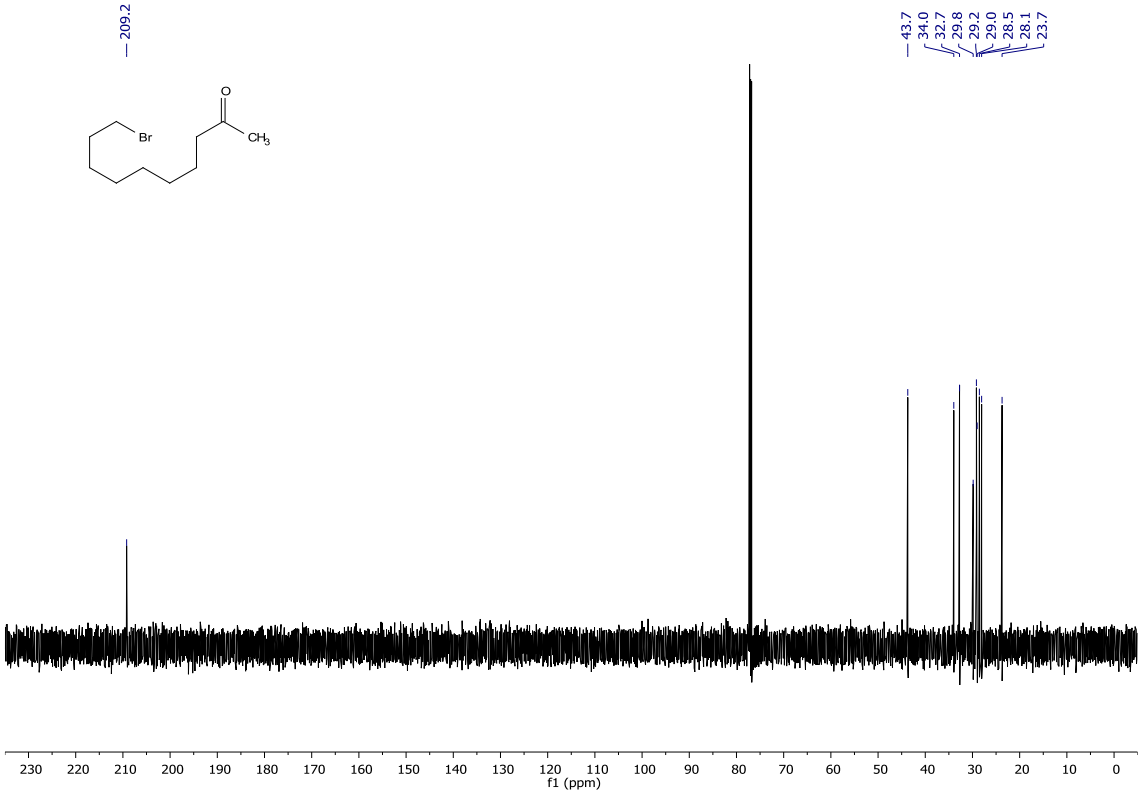


10-Bromodecan-2-one (12)

^{1}H-NMR (600 MHz, $CDCl_3$)

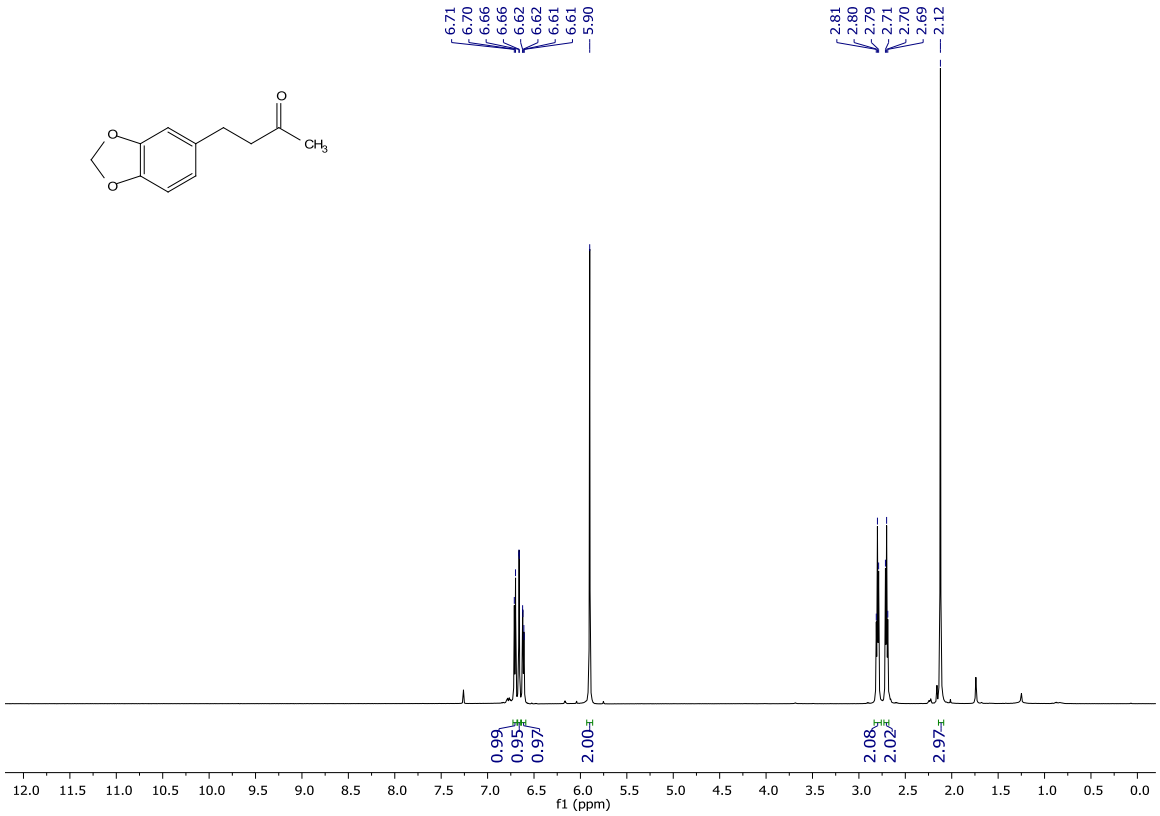


^{13}C-NMR (151 MHz, $CDCl_3$)

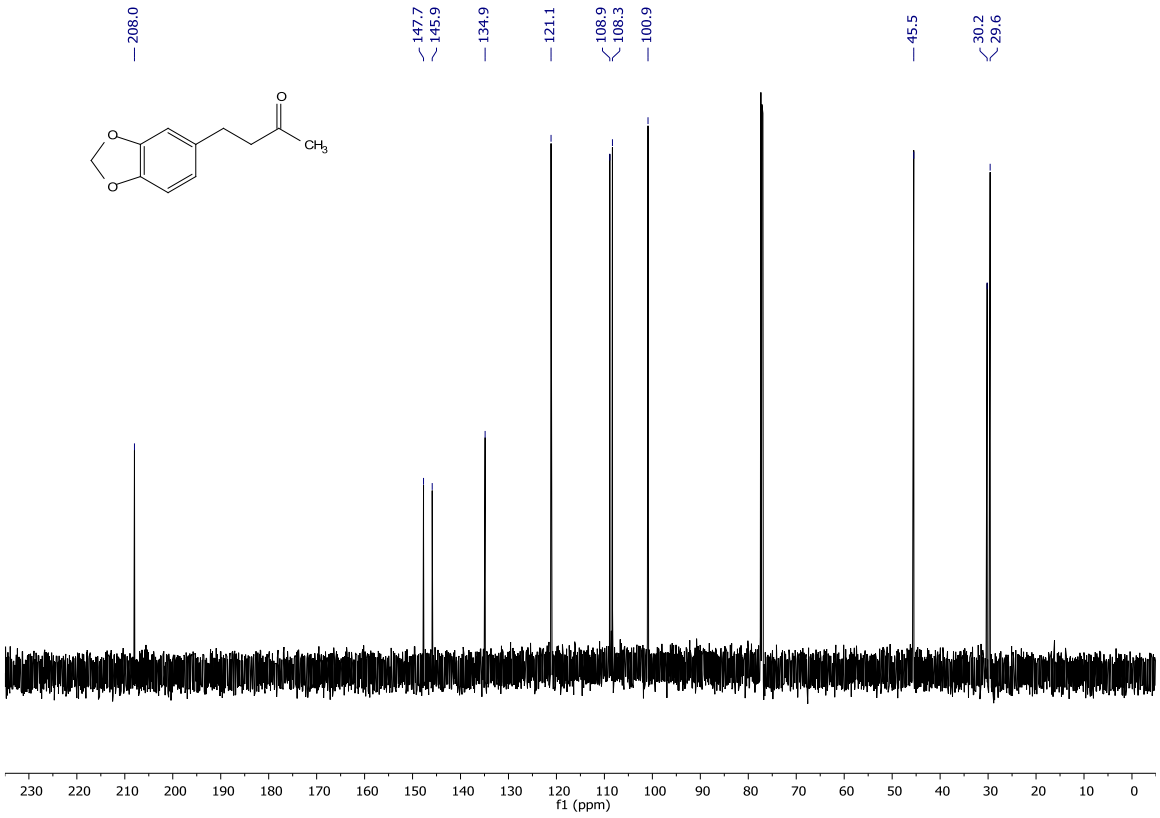


4-(Benzo[d][1,3]dioxol-5-yl)butan-2-one (13)

^{1}H-NMR (600 MHz, $CDCl_3$)

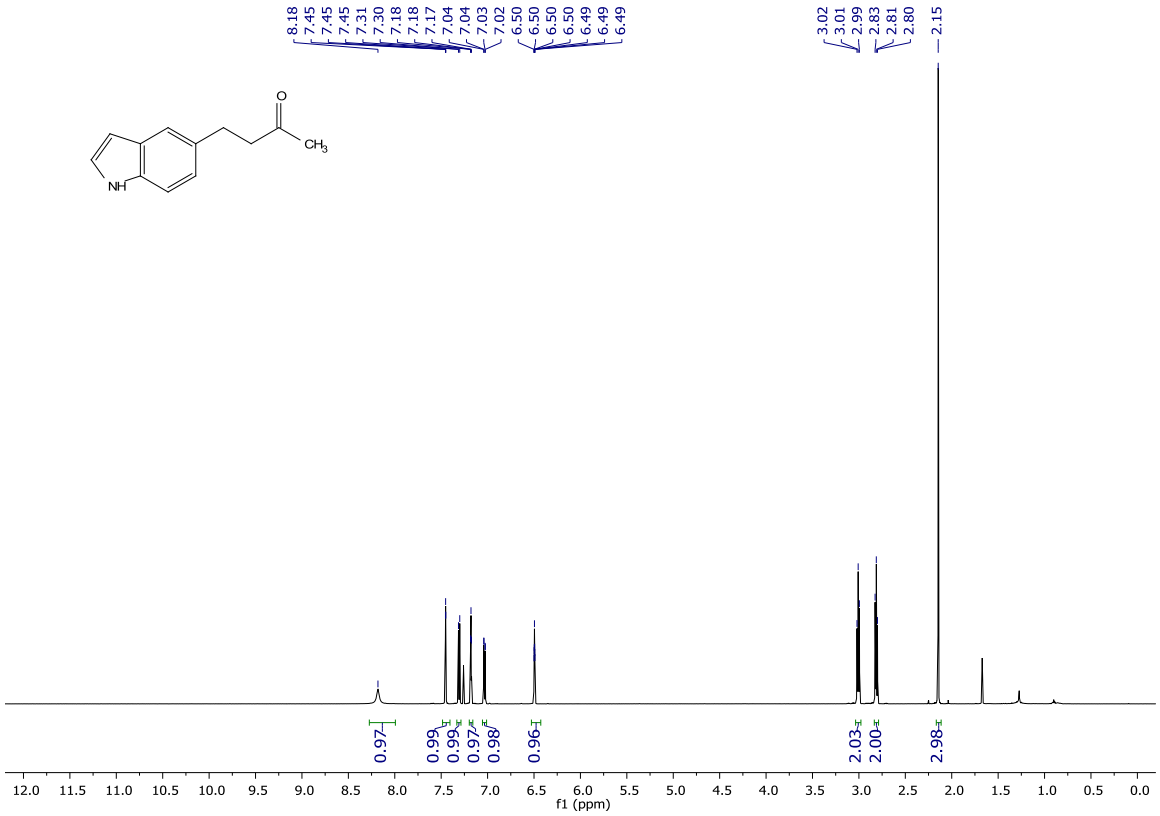


^{13}C-NMR (151 MHz, $CDCl_3$)

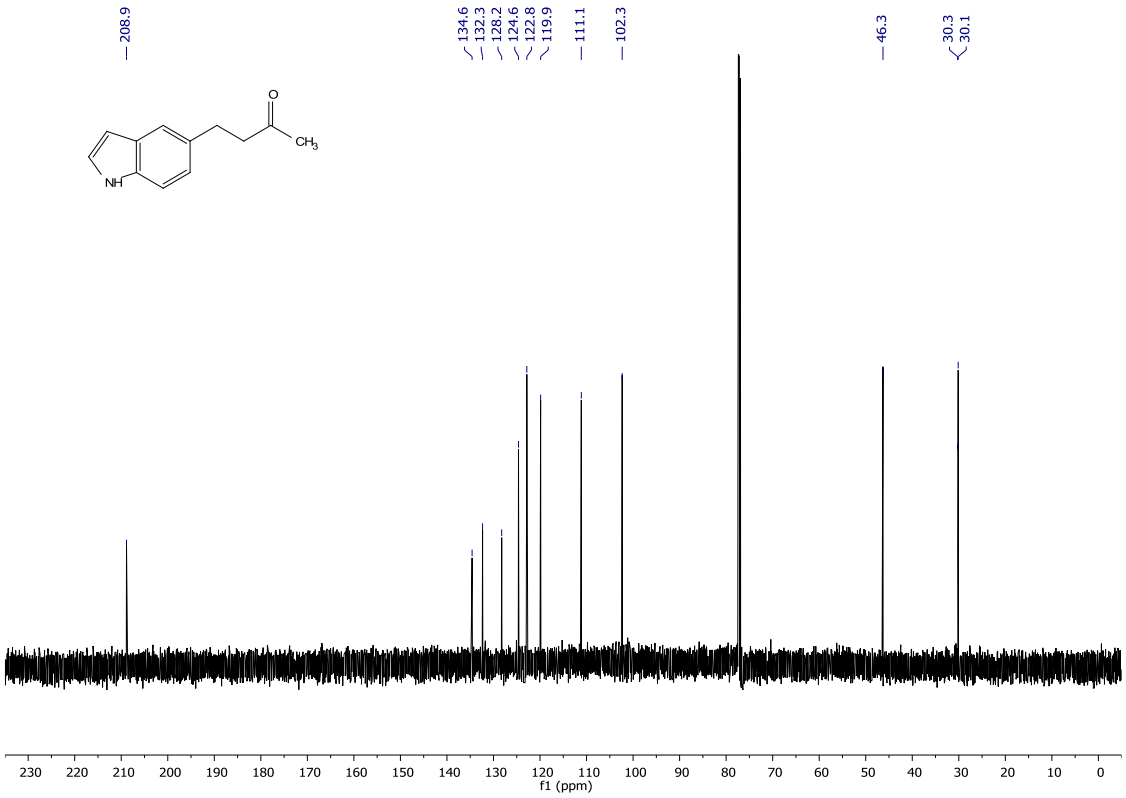


4-(1H-Indol-5-yl)butan-2-one (14)

^{1}H-NMR (600 MHz, $CDCl_3$)

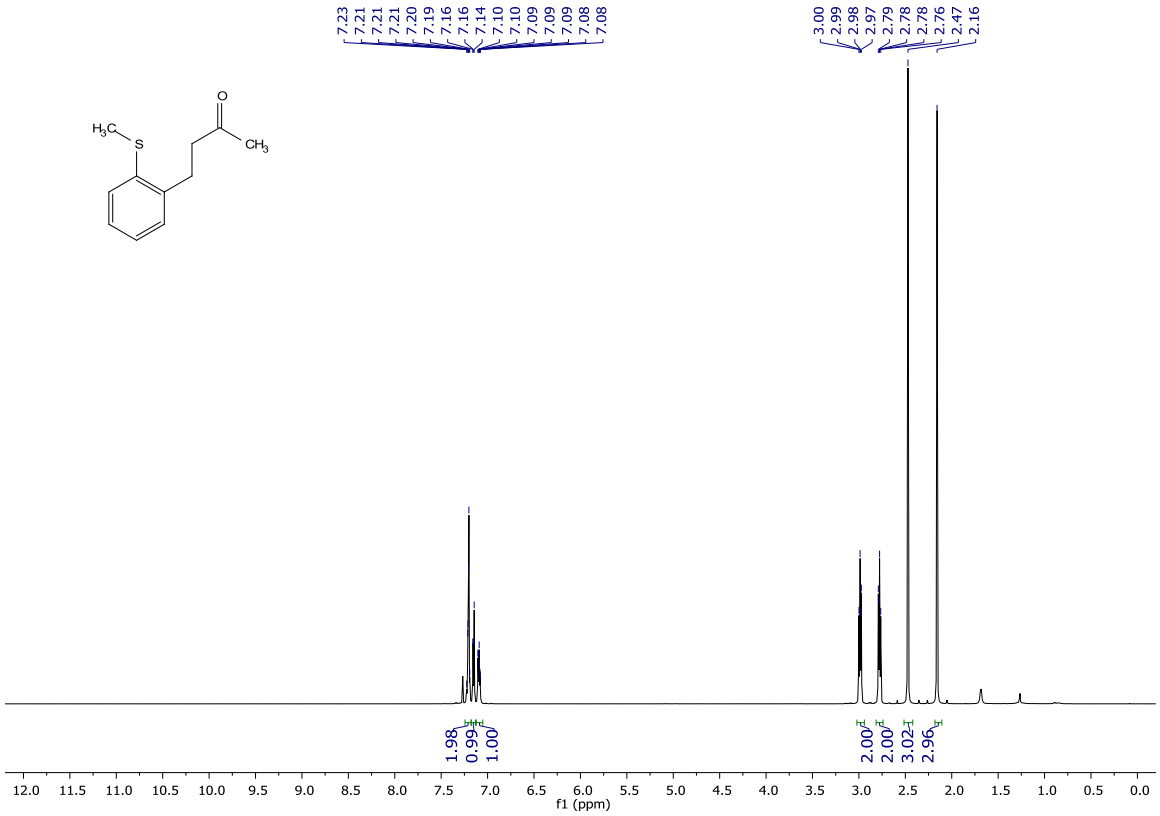


^{13}C-NMR (151 MHz, $CDCl_3$)

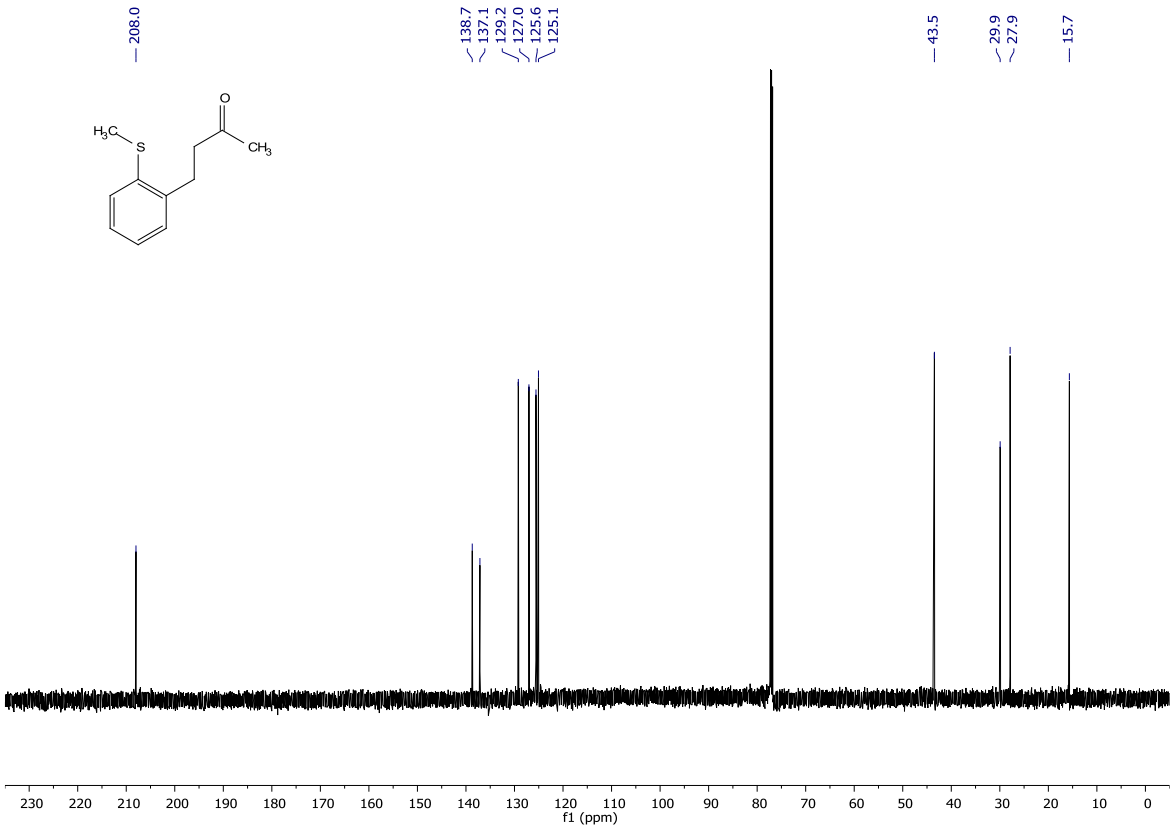


4-(2-(Methylthio)phenyl)butan-2-one (15)

^{1}H-NMR (600 MHz, $CDCl_3$)



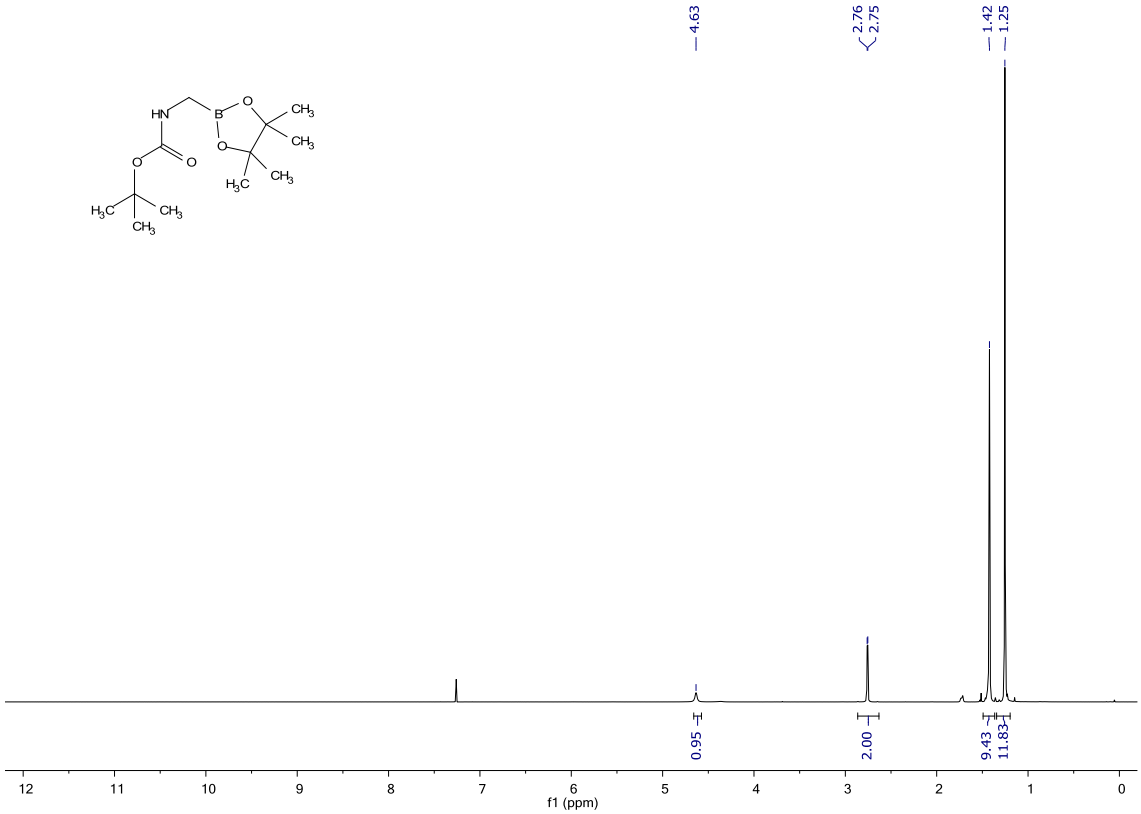
^{13}C-NMR (151 MHz, $CDCl_3$)



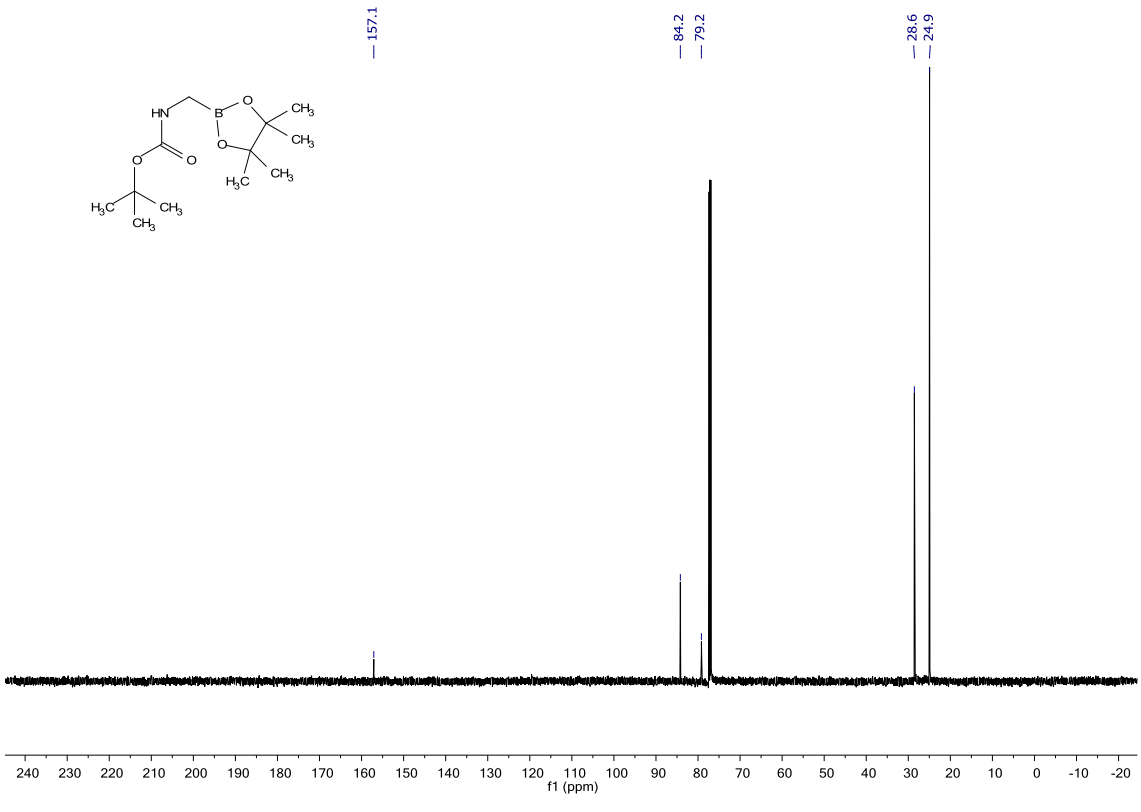
6.3 Starting materials spectra

Tert-butyl ((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)carbamate

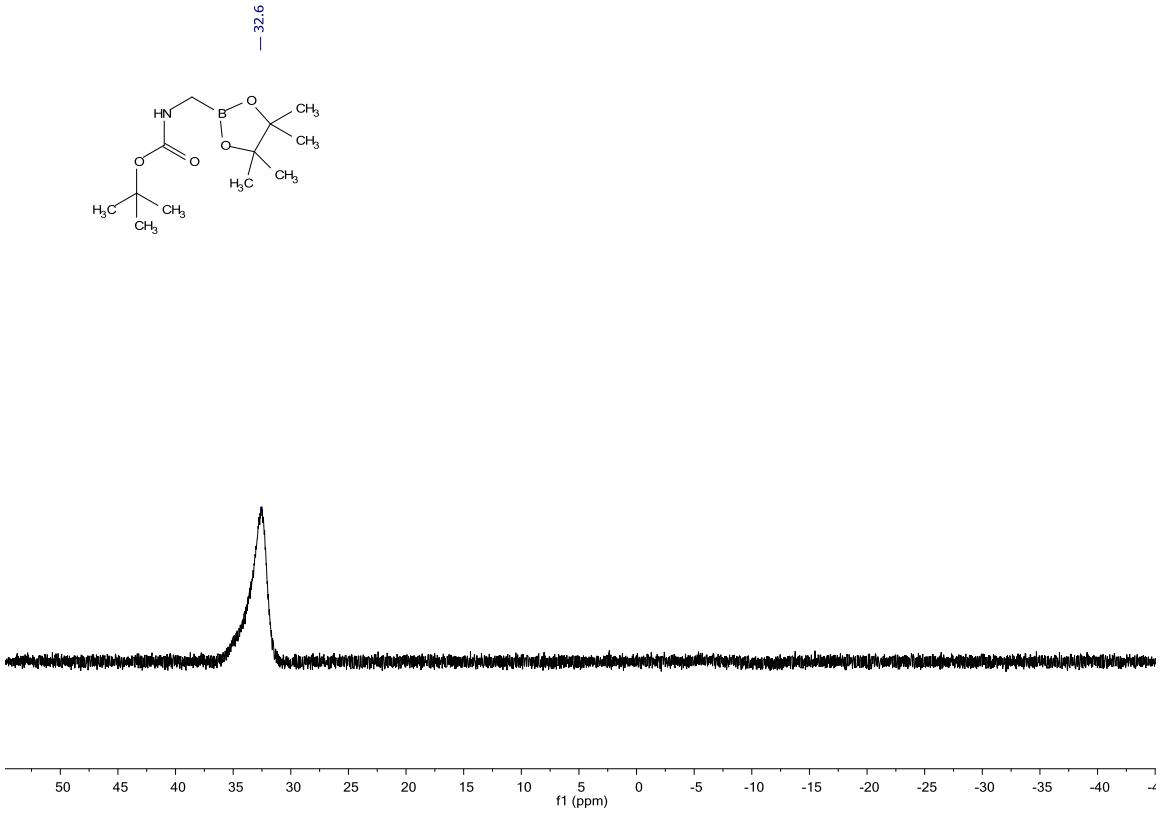
^{1}H-NMR (600 MHz, $CDCl_3$)



^{13}C-NMR (151 MHz, $CDCl_3$)

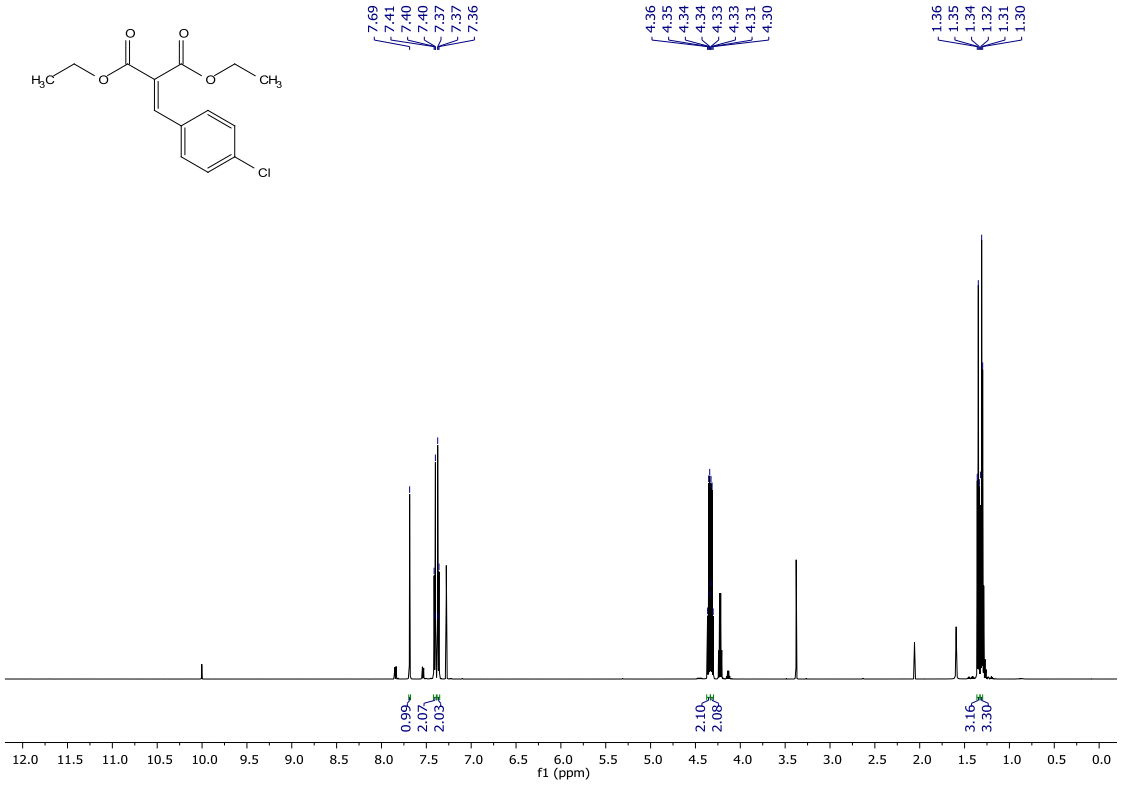


^{11}B-NMR (193 MHz, $CDCl_3$)

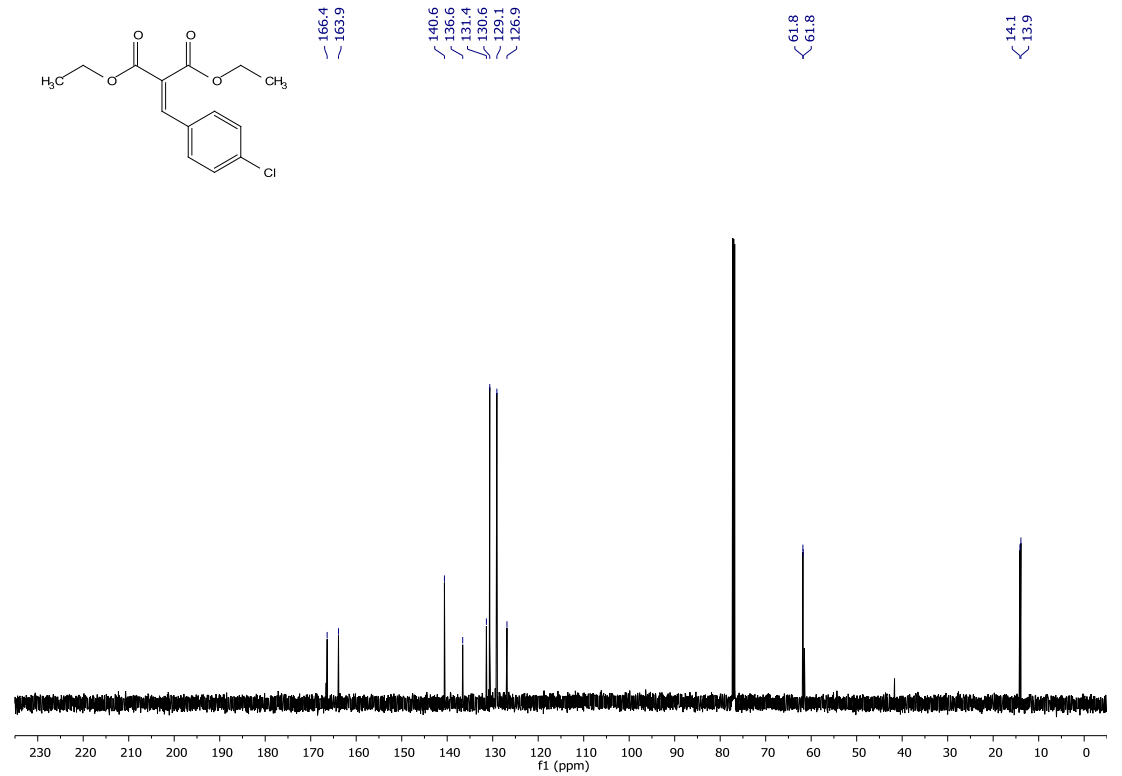


Diethyl 2-(4-chlorobenzylidene)malonate

^{1}H-NMR (600 MHz, $CDCl_3$)

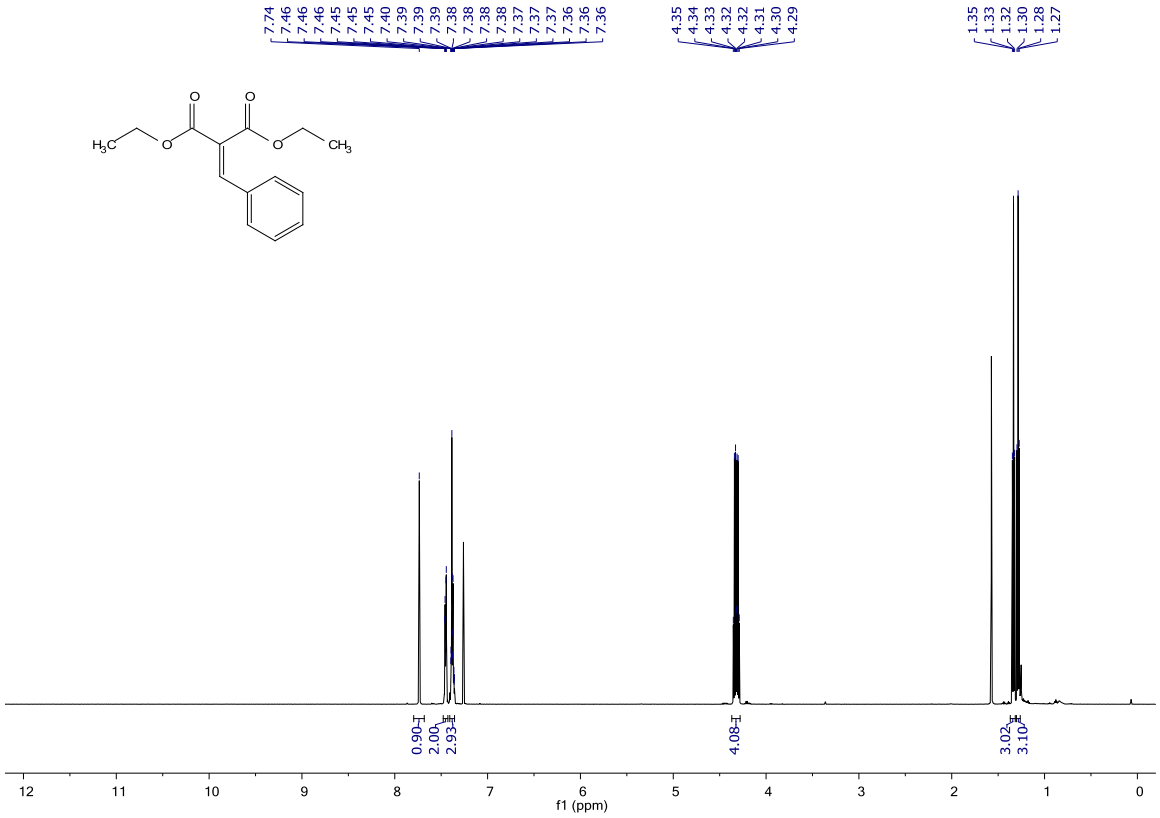


^{13}C-NMR (151 MHz, $CDCl_3$)

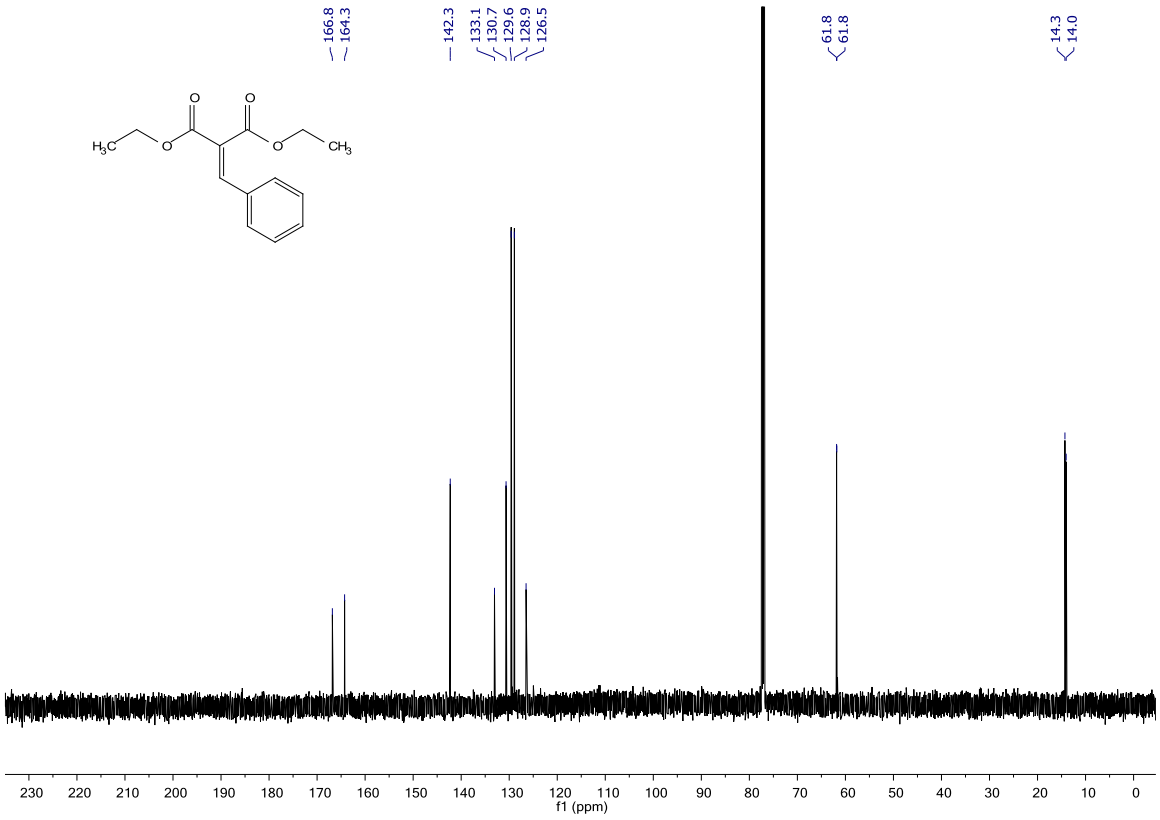


Diethyl 2-benzylidenemalonate

^{1}H-NMR (600 MHz, $CDCl_3$)

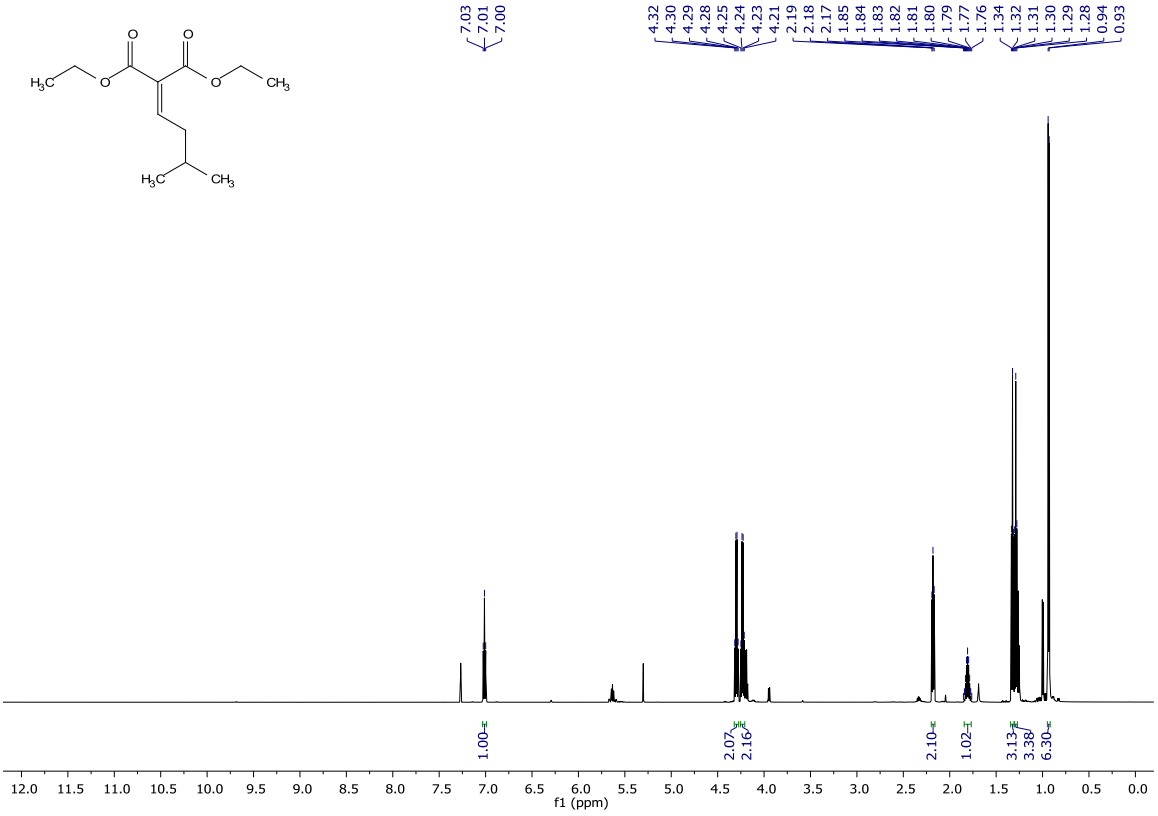


^{13}C-NMR (151 MHz, $CDCl_3$)

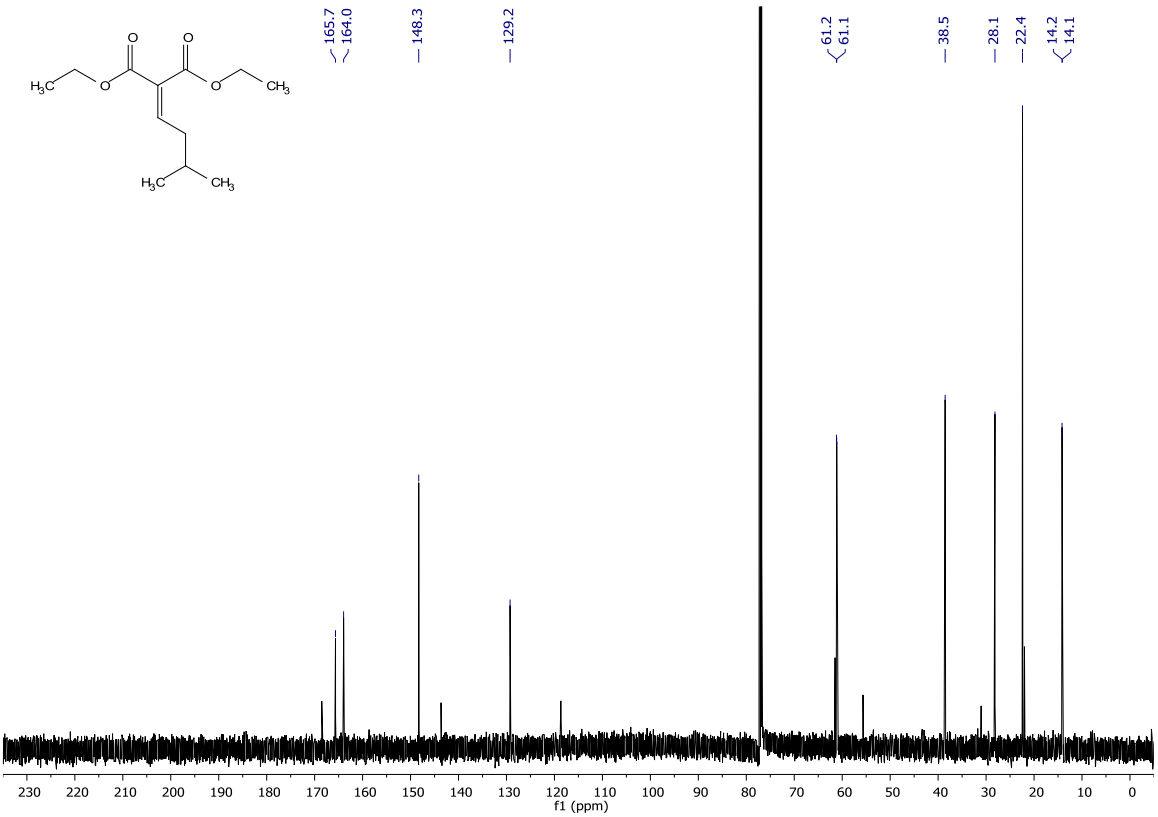


1,3-Diethyl 2-(3-methylbutylidene)propanedioate

^{1}H-NMR (600 MHz, $CDCl_3$)

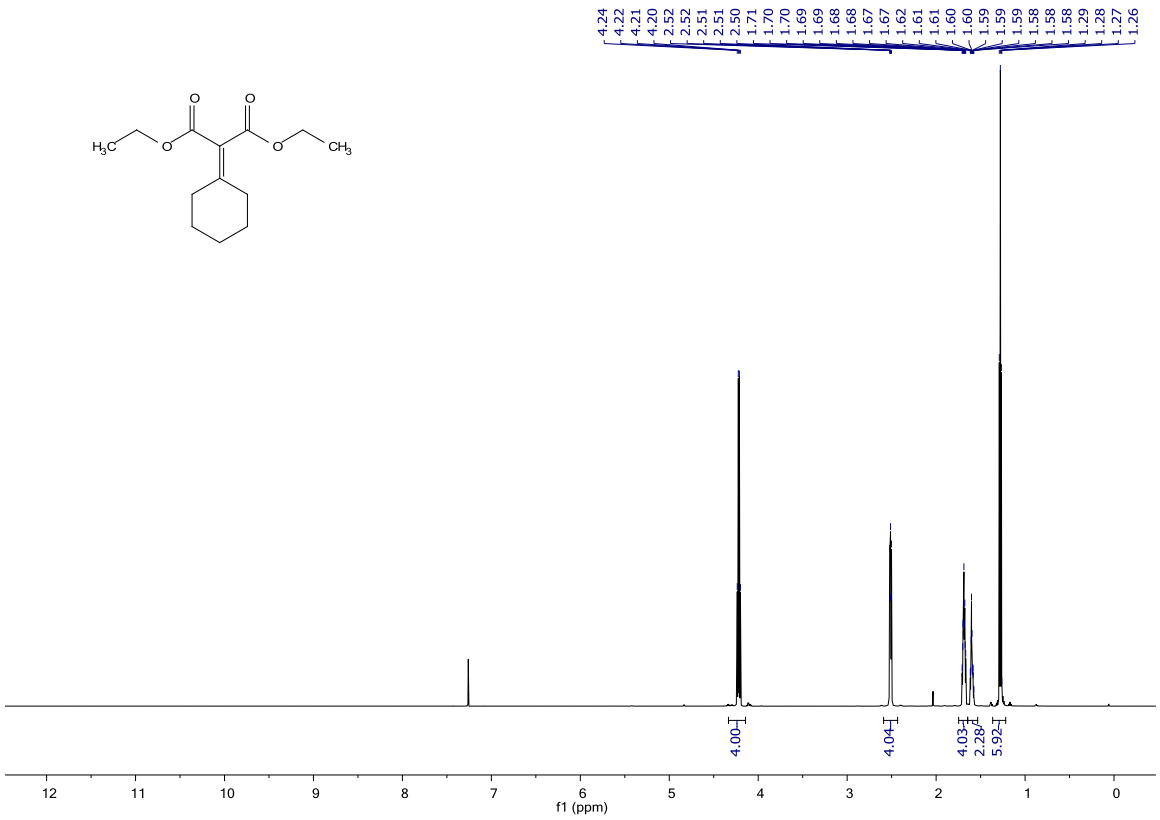


^{13}C-NMR (151 MHz, $CDCl_3$)

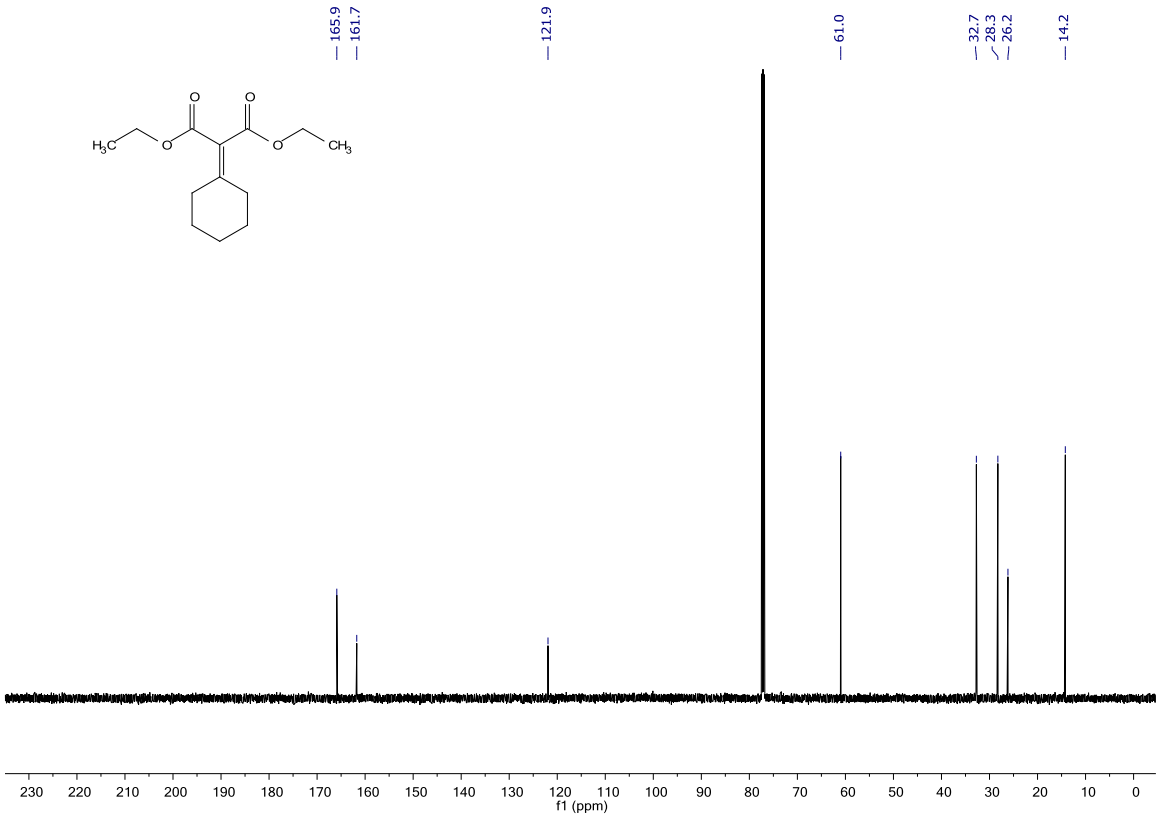


Diethyl 2-cyclohexylidenemalonate

^{1}H-NMR (600 MHz, $CDCl_3$)



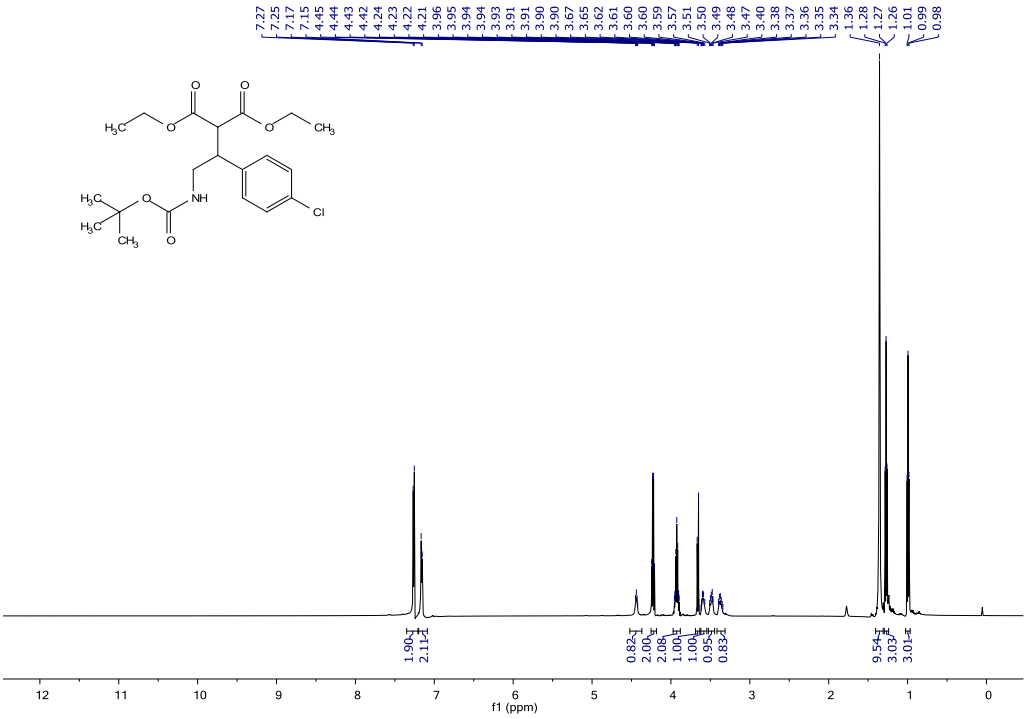
^{13}C-NMR (151 MHz, $CDCl_3$)



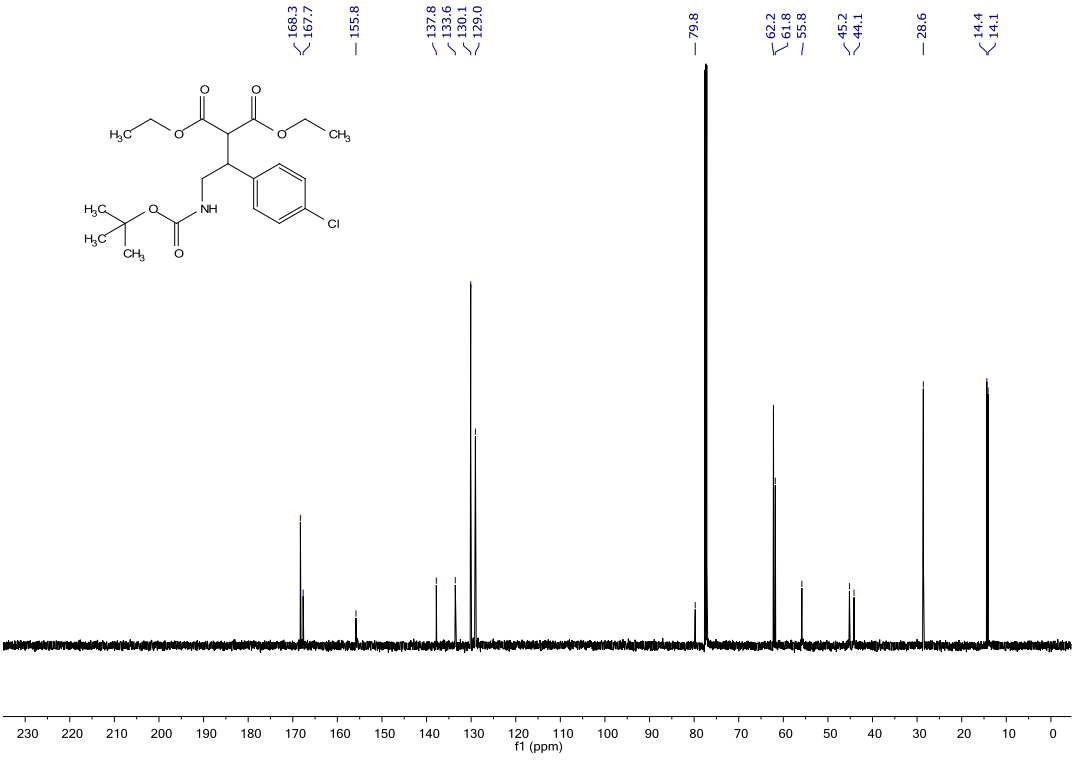
6.4 Coupling products and final APIs spectra

Diethyl 2-(2-((tert-butoxycarbonyl)amino)-1-(4-chlorophenyl)ethyl)malonate (20)

^{1}H-NMR (600 MHz, $CDCl_3$)

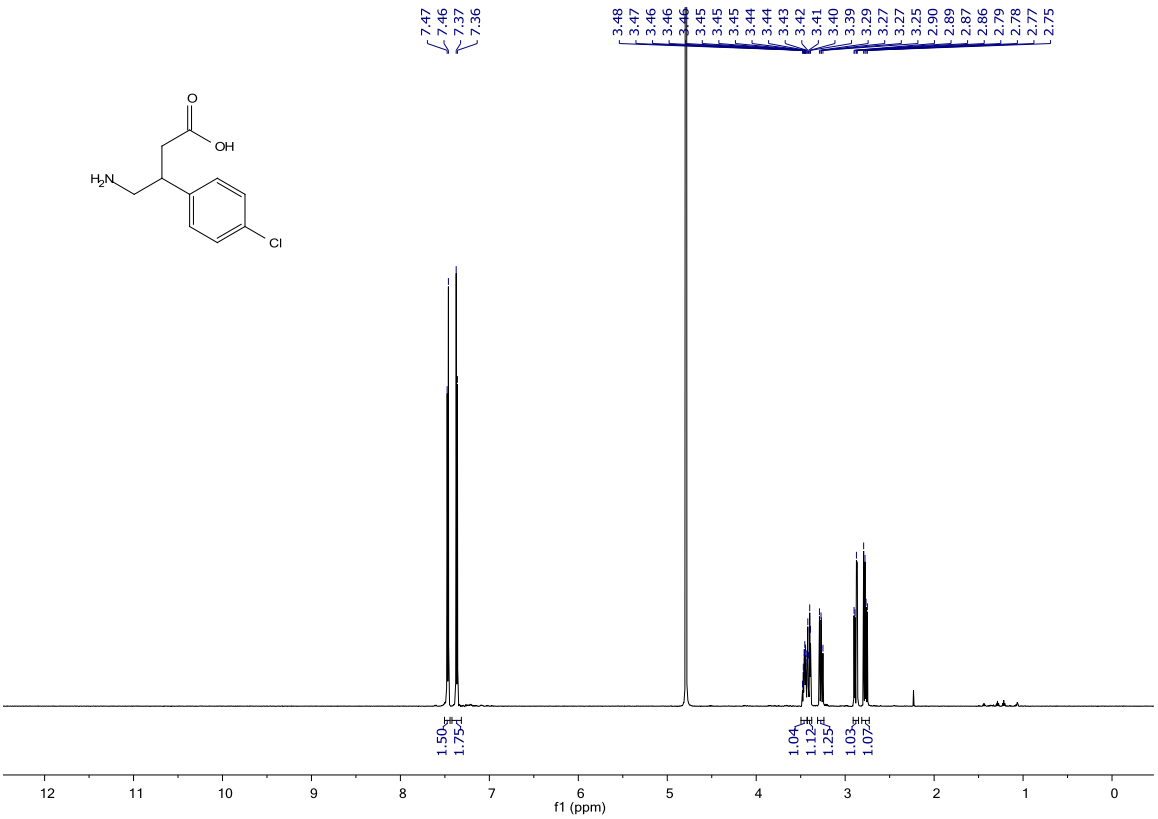


^{13}C-NMR (151 MHz, $CDCl_3$)

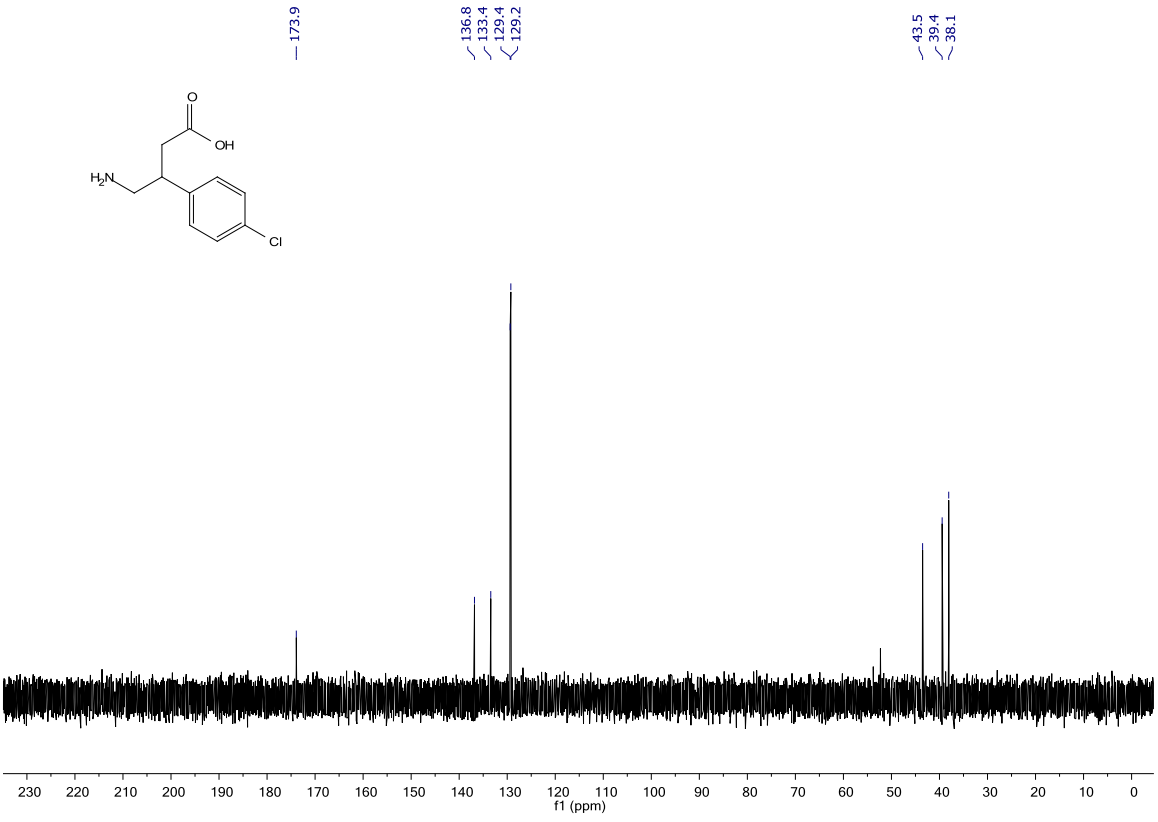


(±)-Baclofen·HCl

^{1}H-NMR (600 MHz, D_2O)

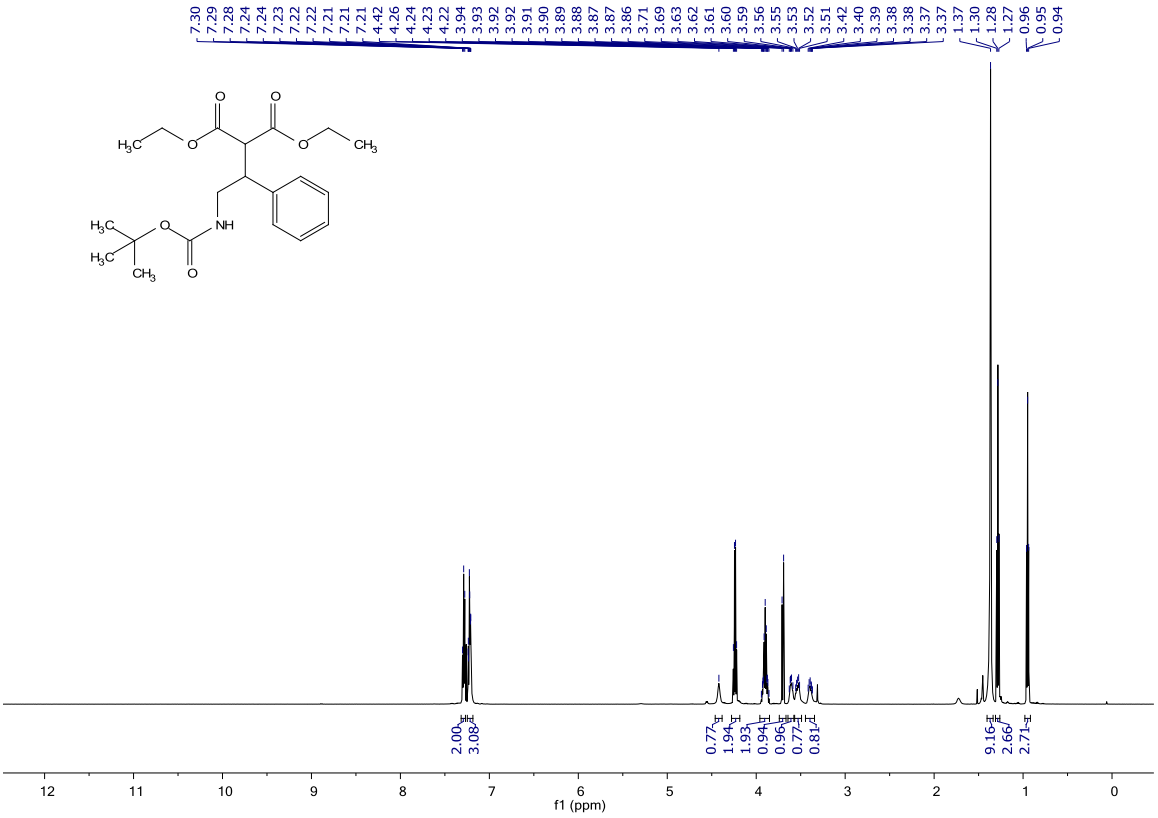


^{13}C-NMR (151 MHz, D_2O)

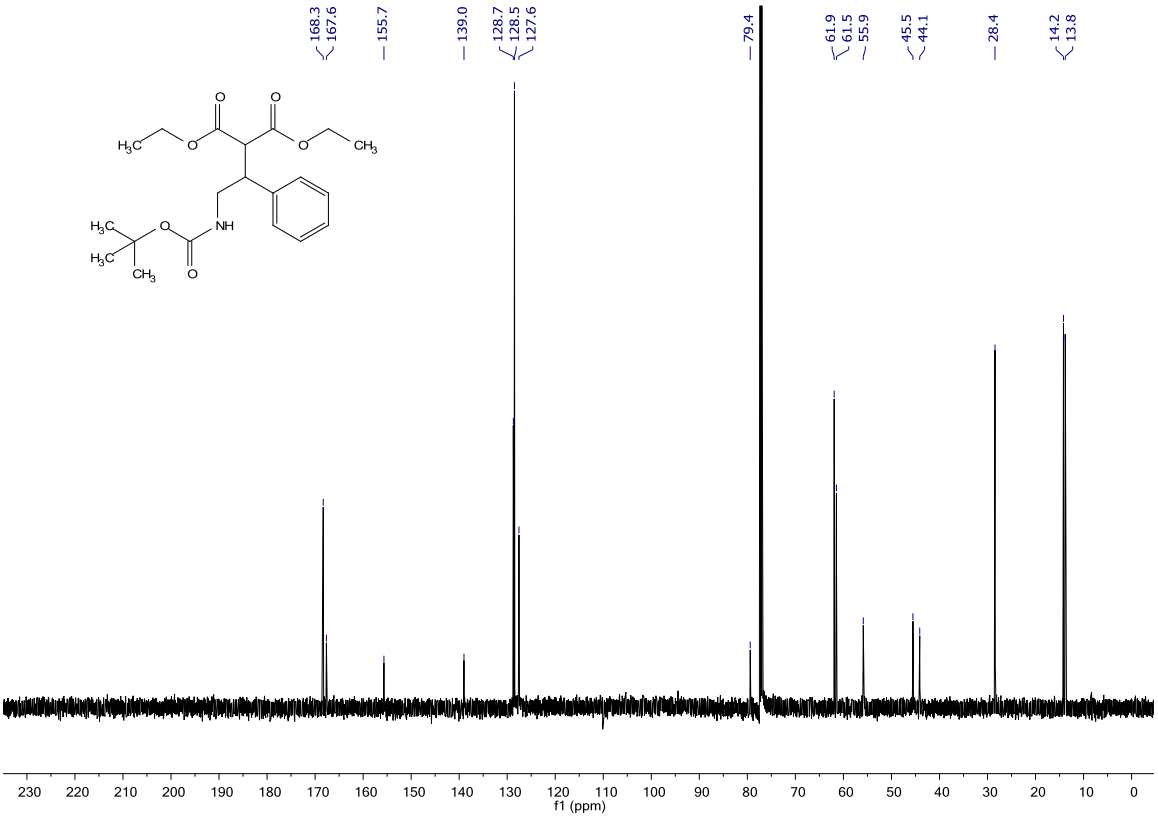


Diethyl 2-(2-((tert-butoxycarbonyl)amino)-1-phenylethyl)malonate (21)

^{1}H-NMR (600 MHz, $CDCl_3$)

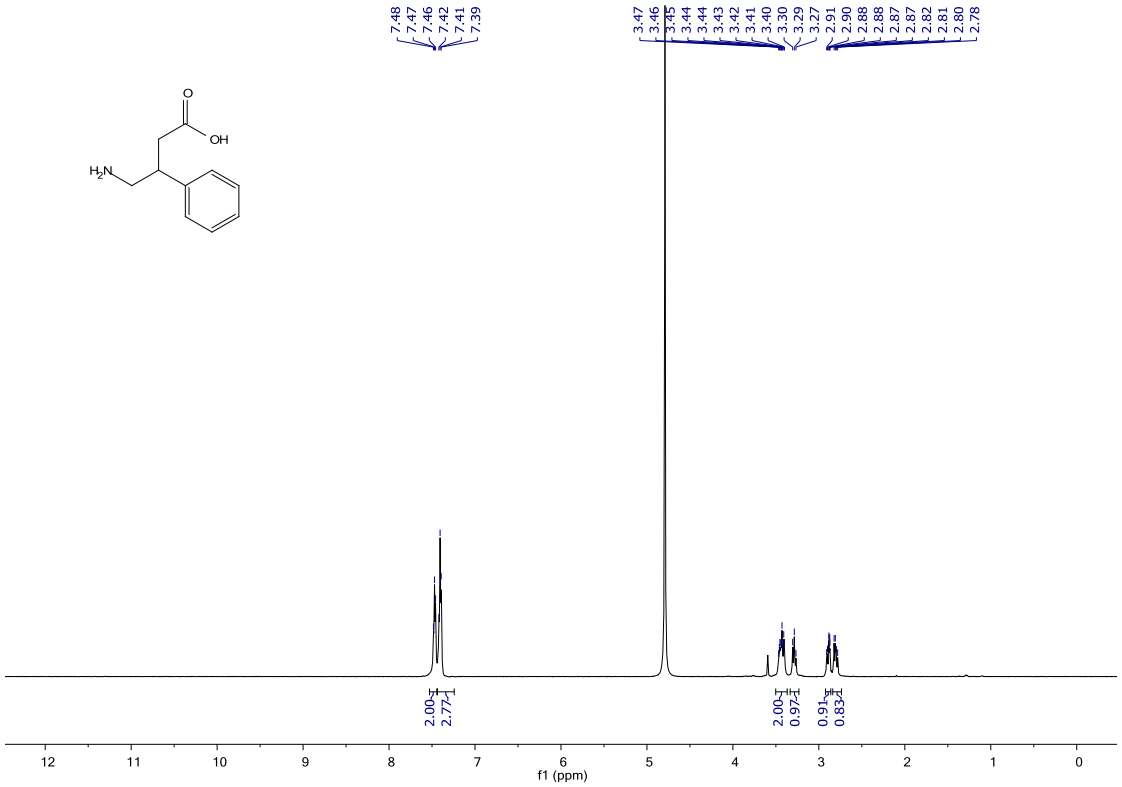


^{13}C-NMR (151 MHz, $CDCl_3$)

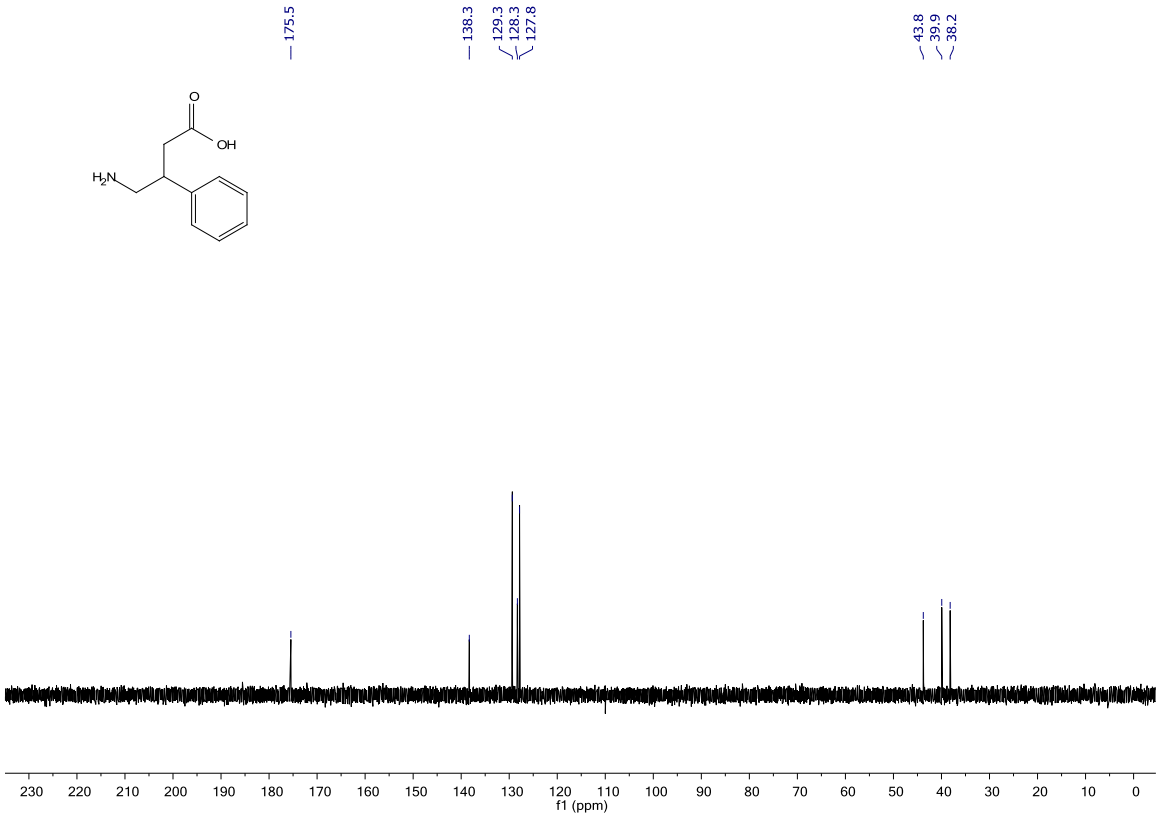


(±)-Phenibut·HCl

^{1}H-NMR (600 MHz, D_2O)

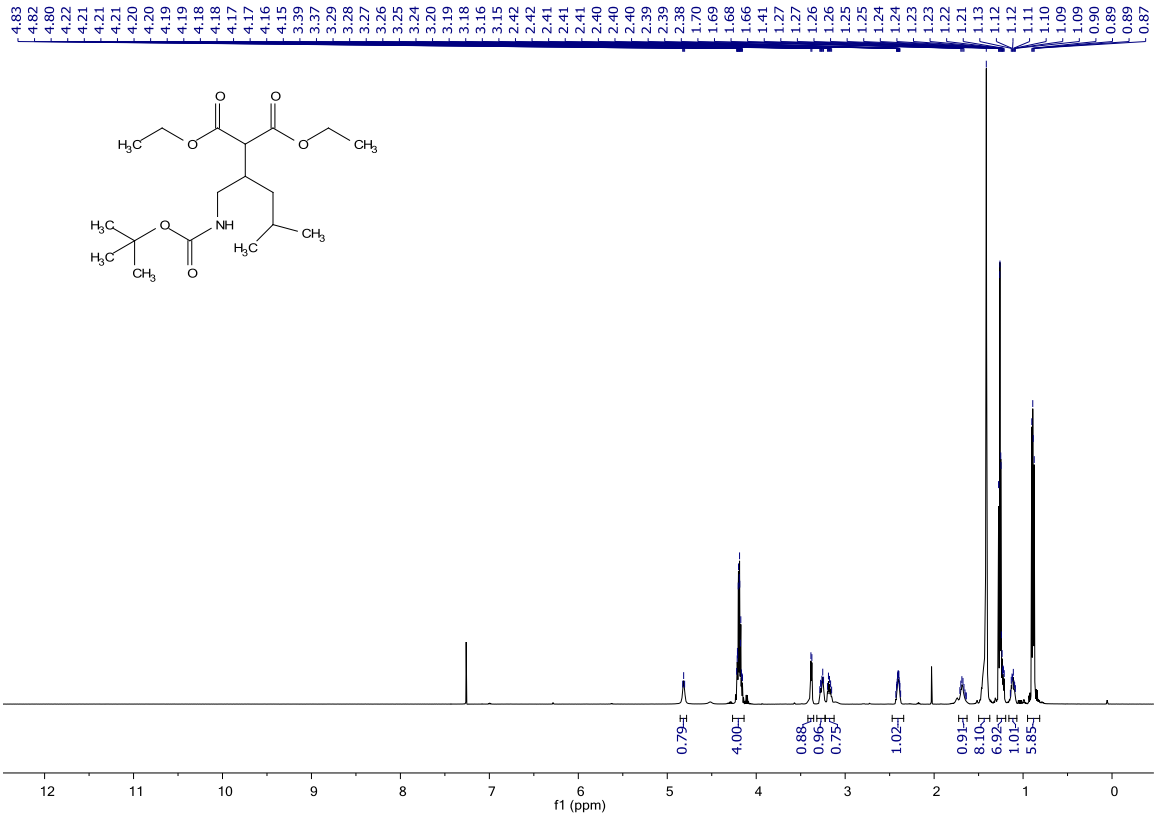


^{13}C-NMR (151 MHz, D_2O)

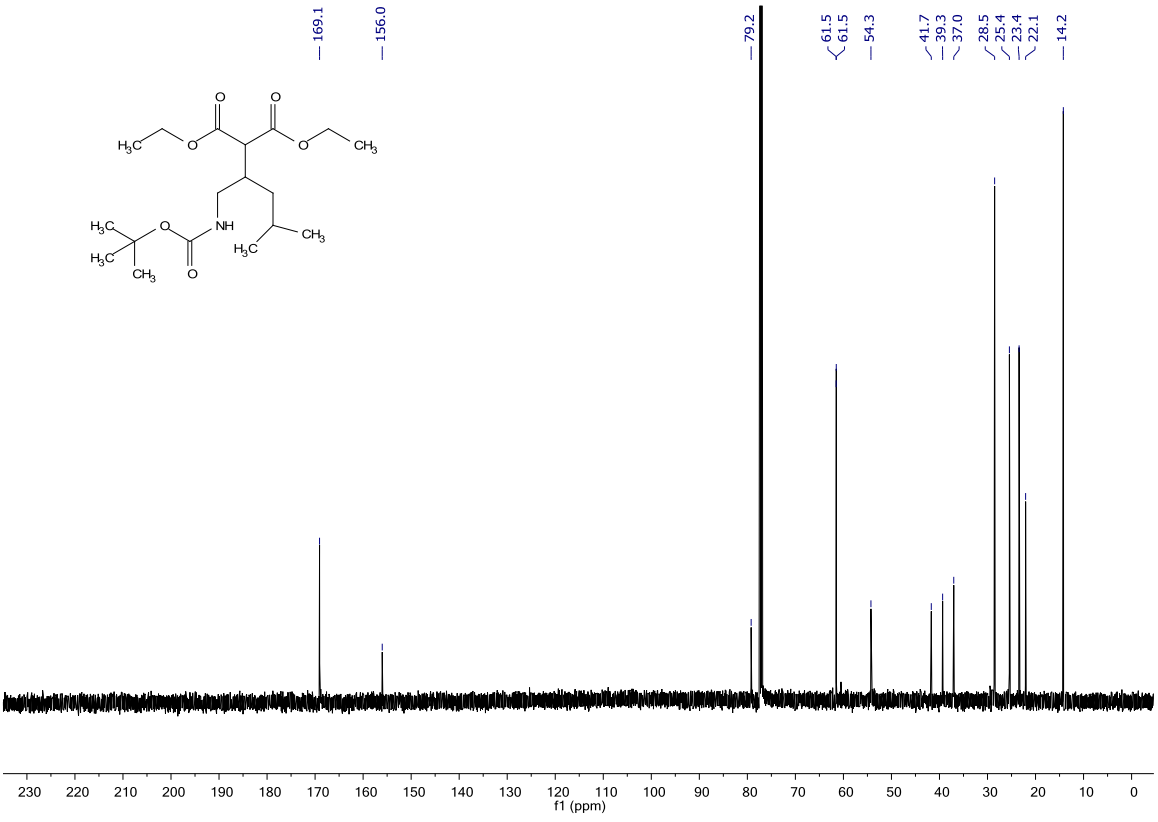


Diethyl 2-(1-((tert-butoxycarbonyl)amino)-4-methylpentan-2-yl)malonate (22)

^{1}H-NMR (600 MHz, $CDCl_3$)

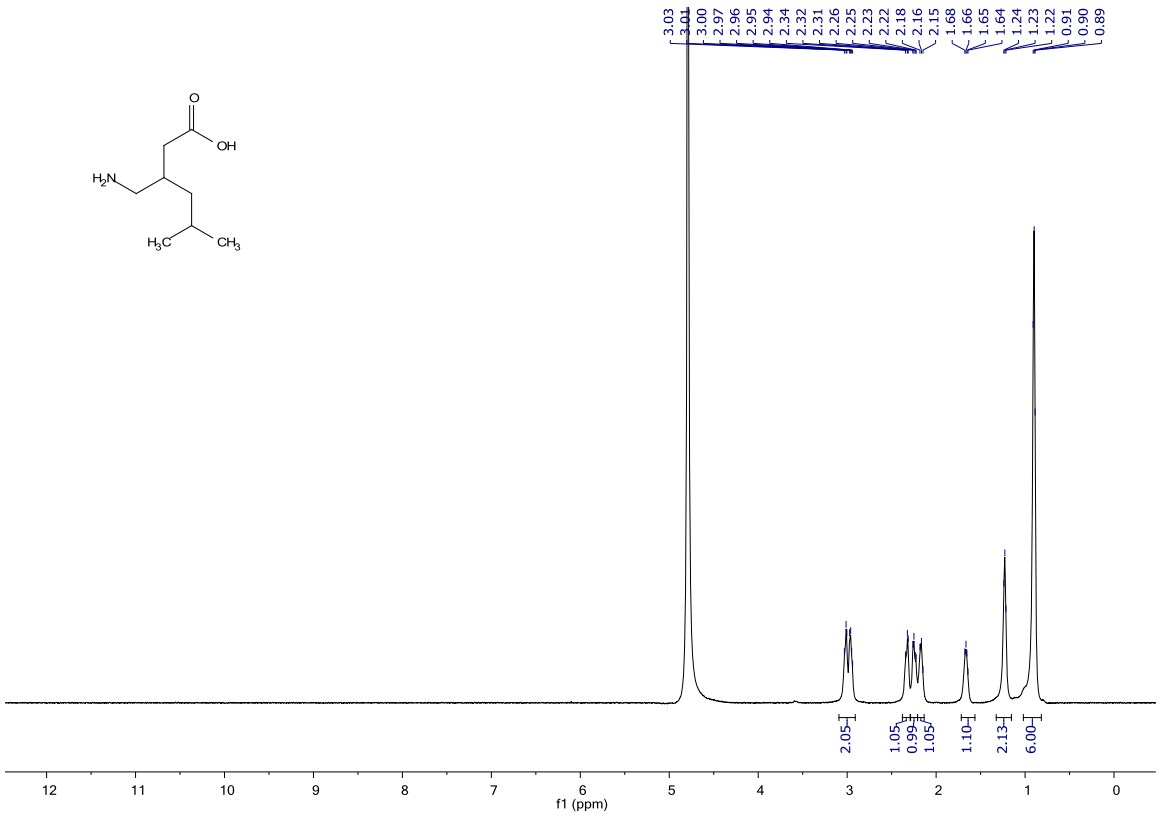


^{13}C-NMR (151 MHz, $CDCl_3$)

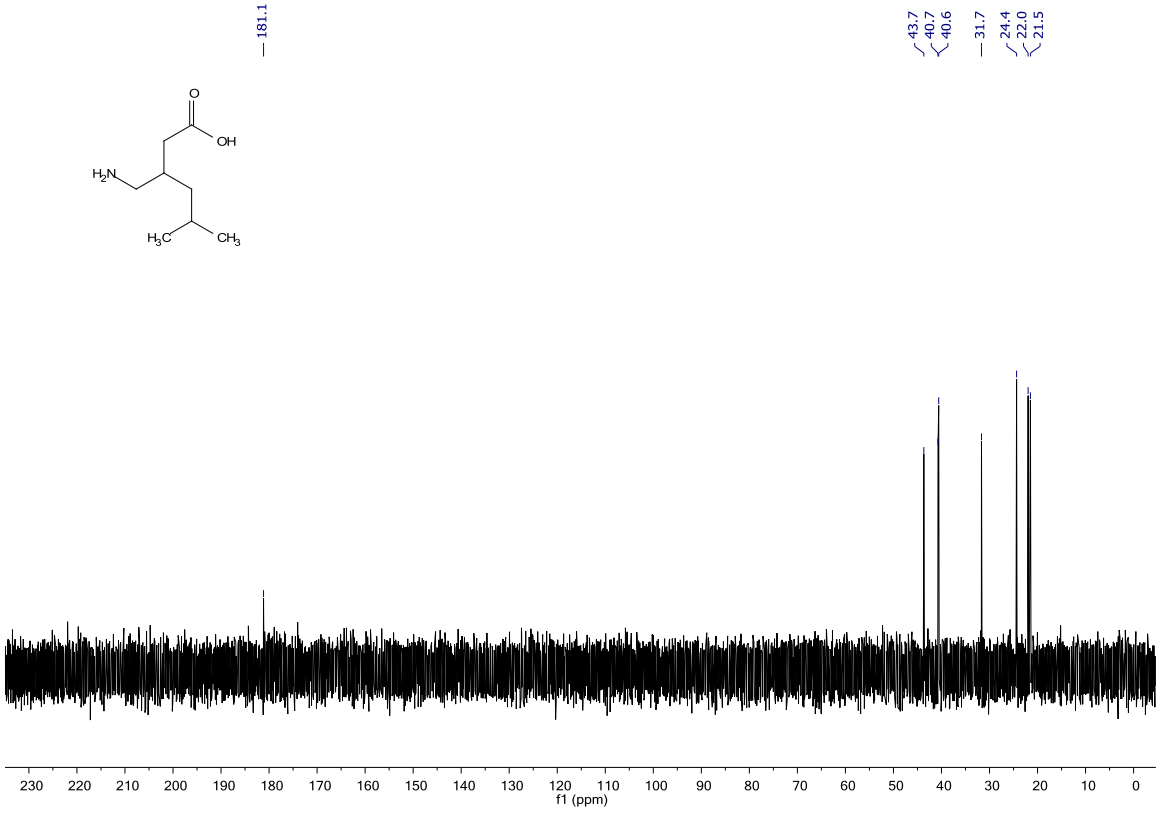


(±)-Pregabalin

^{1}H-NMR (600 MHz, D_2O)

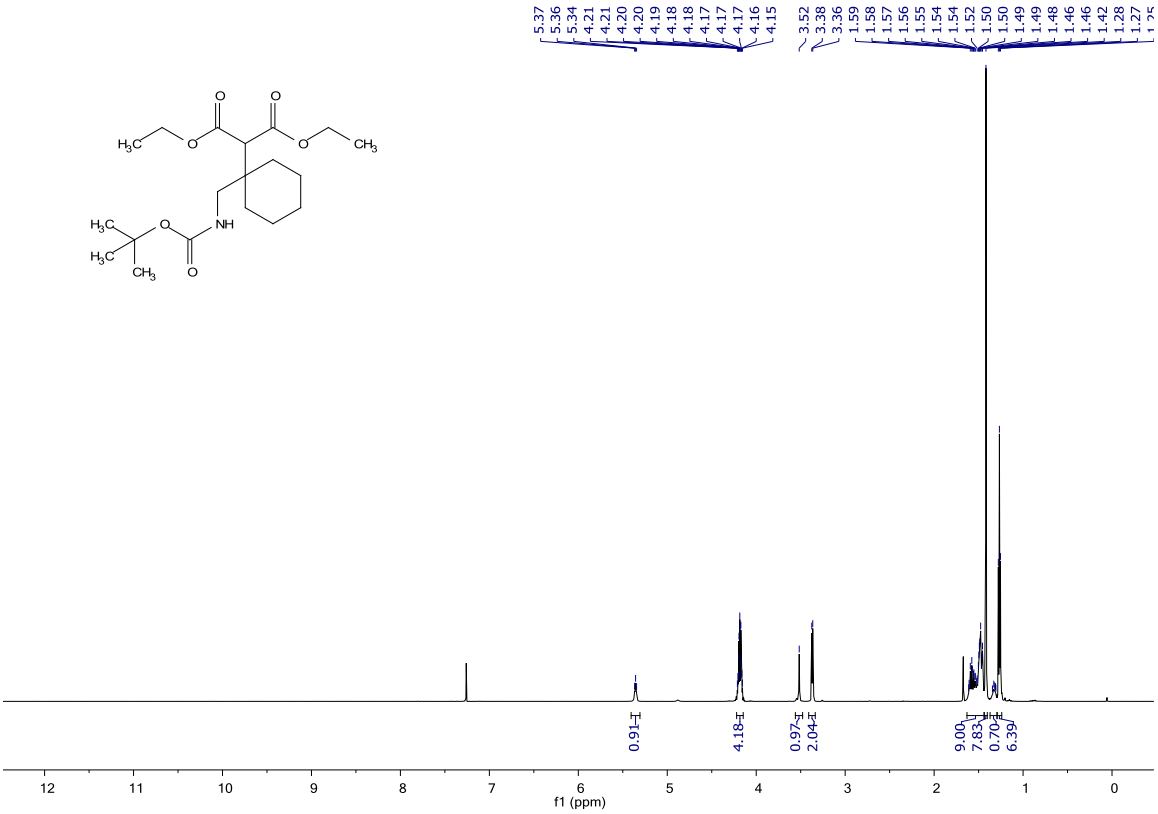


^{13}C-NMR (151 MHz, D_2O)

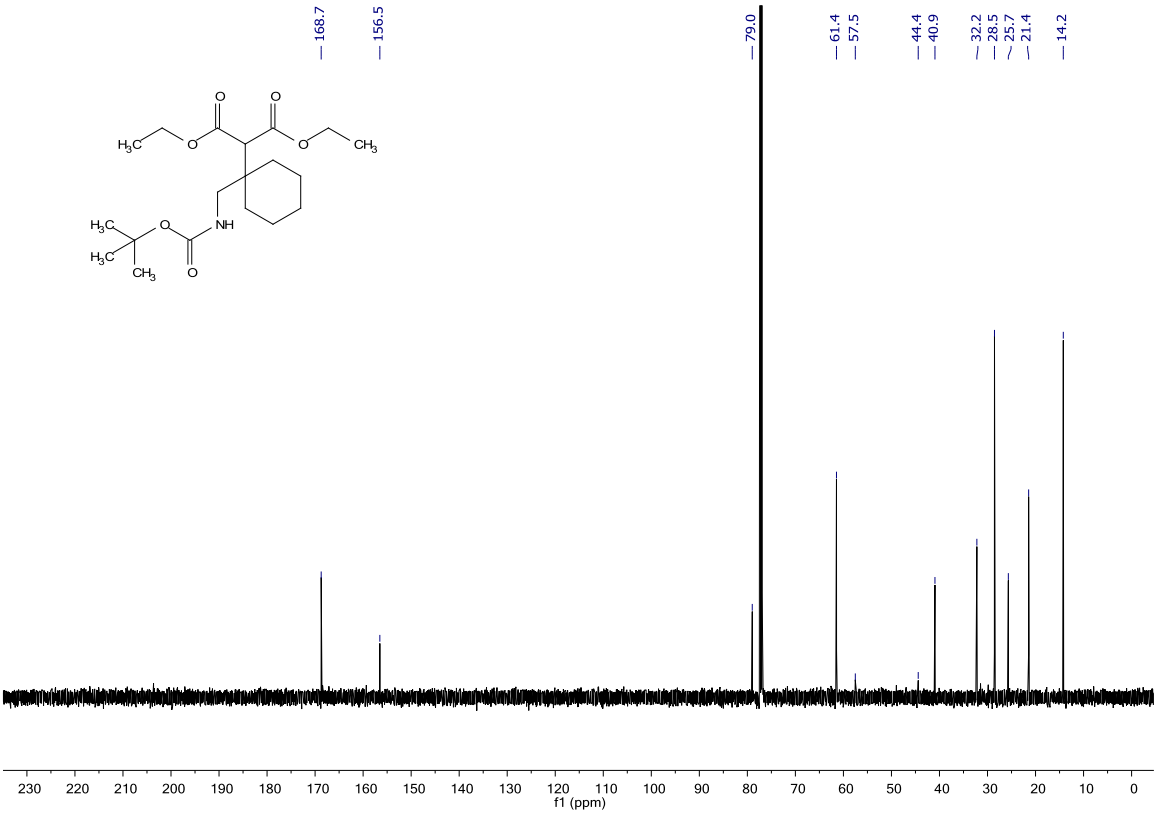


Diethyl 2-(1-((tert-butoxycarbonyl)amino)cyclohexyl)malonate (23)

^{1}H-NMR (600 MHz, $CDCl_3$)

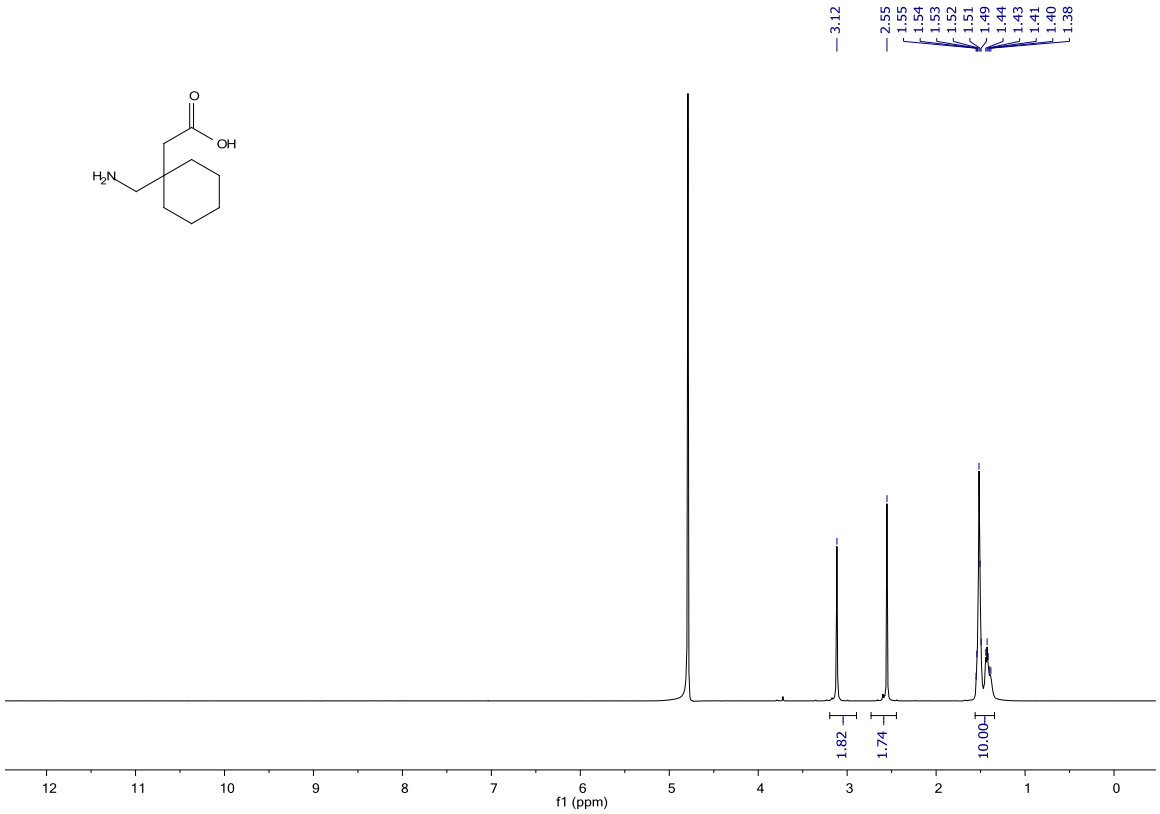


^{13}C-NMR (151 MHz, $CDCl_3$)



Gabapentin·HCl

^{1}H-NMR (600 MHz, D_2O)



^{13}C-NMR (151 MHz, D_2O)