Supporting Information

Switchable N–H vs C3–H Carboxylation of Indoles using Dual-Function Reagents

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1. General Information

^{1}H (400 MHz), ^{13}C (100 MHz) and $^{19}F\{^{1}H\}$ (376 MHz) NMR measurements were carried out using either a Bruker AVII400 FT-NMR or AVIII HD 400 FT-NMR spectrometer at 298 K. For ^{13}C NMR spectra, all spectra were recorded with decoupling to ^{1}H unless otherwise noted. Chemical shifts in ^{1}H NMR spectra are reported in delta (δ) units, parts per million (ppm) relative to residual solvent peaks found at δ = 7.26 ppm ($CDCl_3$), δ = 2.50 ppm (DMSO-d_6) or δ = 4.79 ppm (D_2O). Chemical shifts in ^{13}C NMR spectra are reported in delta (δ) units, parts per million (ppm) relative to the residual solvent peaks found at δ = 77.0 ppm ($CDCl_3$) or δ = 39.5 ppm (DMSO-d_6). All *J* coupling constants were measured in Hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad.

High resolution electrospray ionisation (ESI) samples were analysed using a MaXis (Bruker Daltonics, Bremen, Germany) time of flight (TOF) mass spectrometer. Samples were introduced to the mass spectrometer via a Dionex Ultimate 3000 autosampler and uHPLC pump. High resolution electron ionisation (EI) mass spectrometry was carried out using a LECO HRT+ (LECO Corporation, St Joseph, Mi, USA) time-of-flight (TOF) mass spectrometer.

Analytical thin layer chromatography (TLC) was performed on Merck precoated analytical plates, 0.25-mm thick, silica gel 60 F254.

Flash chromatography was performed using Silica Gel high purity grade, pore size 60 Å, 230-400 mesh particle size, 40-60 μm particle size, purchased from Merck.

All reagents and solvents were bought from commercial suppliers and used without further purification unless otherwise noted. Anhydrous AcroSeal™ *N*,*N*-dimethylformamide (DMF) was purchased from Thermo Fisher Scientific Inc. and used without further purification. The concentration of *n*-BuLi in hexane was determined by titration prior to use.[1] The $^{13}CO_2$ used for the labelling experiments was purchased from Merck (364592-1L, packaged in a 450 mL carbon steel lecture bottle with brass CGA 110/180 valve and equipped with a stainless-steel control valve. Merck state that nominal gas pressures at 21 ºC are 20 PSIG).

Reactions were carried out as followed, unless otherwise stated:

- 0.25 mmol scale reactions with 0.2 M solvent concentration were carried out in 2.0-5.0 mL Biotage® vials **A**.
- 0.50 mmol scale reactions with 0.2 M solvent concentration were carried out in 2.0-5.0 mL Biotage® vials **A**.
- 0.50 mmol scale reactions with 0.05 M solvent concentration were carried out in 10-20 mL Biotage® vials **B**.
- 1.00 mmol scale reactions with 0.2 M solvent concentration were carried out in 10-20 mL Biotage® vials **B**.

In each case the Biotage® vials were heat-gunned under vacuum, purged with cycles of vacuum and N_2, and sealed using Biotage® crimper, **C**, and crimp cap, **D,** under a flow of N_2. Reactions were heated on a hot plate within aluminium block **E** or **F**.

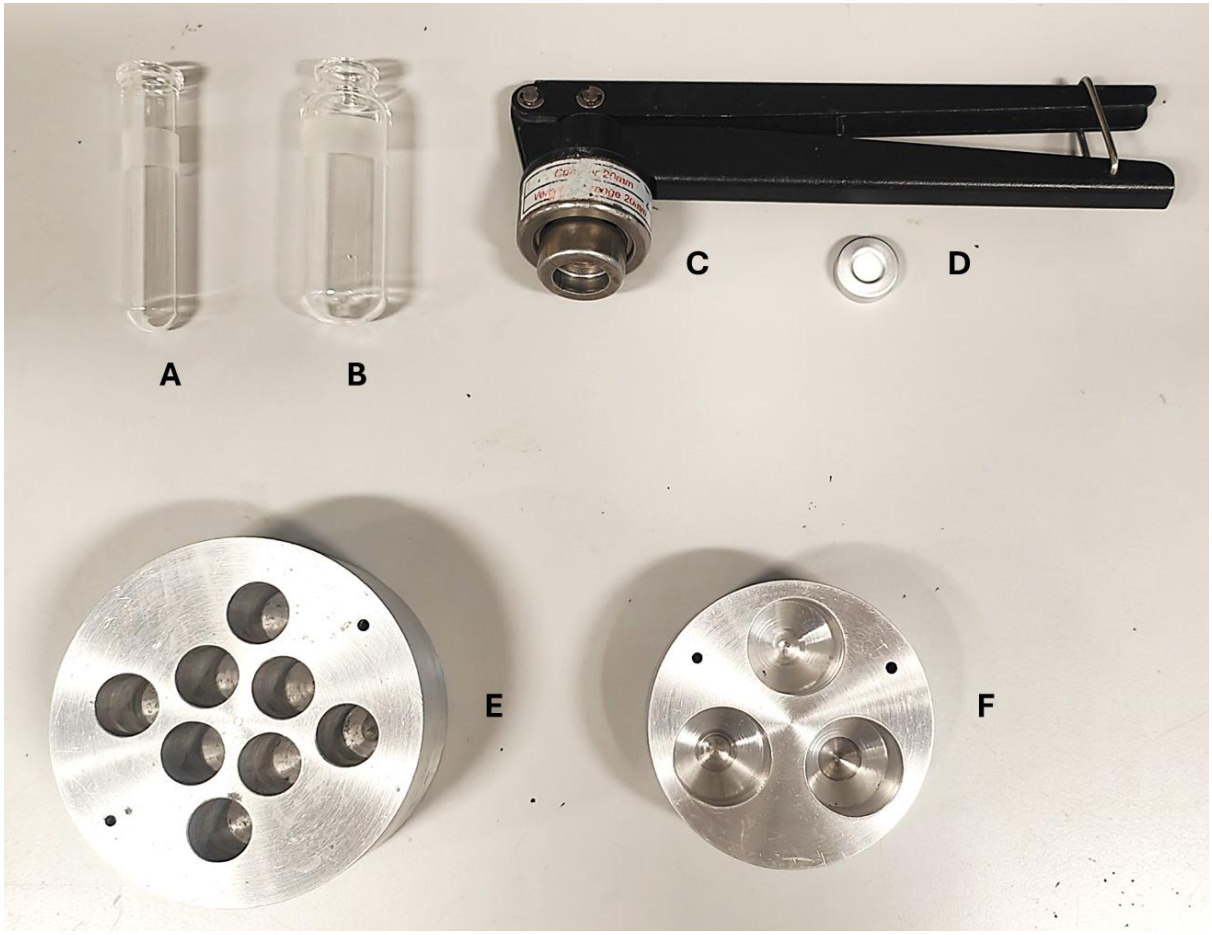
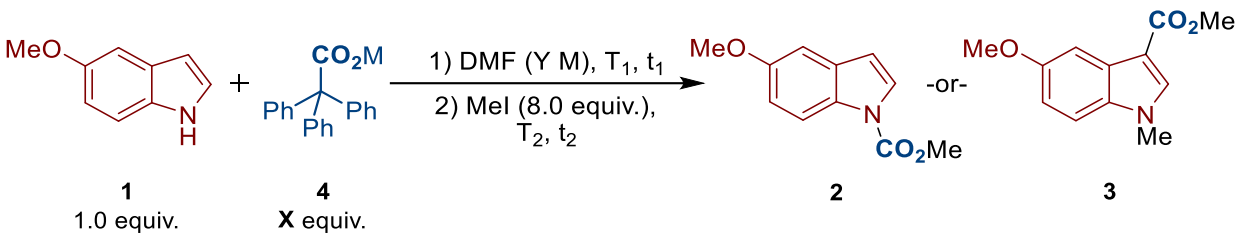


Figure 1: General equipment for carboxylation reactions, including: **A**, 2.0-5.0 mL Biotage® vials, **B**, 10-20 mL Biotage® vials, **C**, Biotage® crimper, **D**, crimp cap, and **E/F**, aluminium blocks.

2. Optimisation data

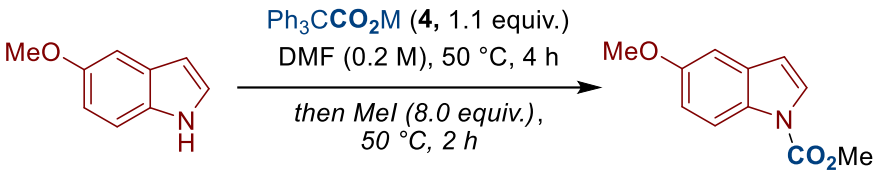
General Procedure for Optimisation



1 1.0 equiv. **4** **X** equiv. **2** **3**

Adapted from the works of Perry and co-workers[2] A Biotage® microwave vial, equipped with a magnetic stir bar and septum, was dried under vacuum with a heat gun. The vial was charged with the 5-methoxy indole (74 mg, 0.50 mmol, 1.00 equiv.), and Ph_3CCO_2**M** (**X** equiv.). The vial was purged through cycles of vacuum/N_2 gas. DMF (**Y** M) was then added, and the vial was firmly sealed using a Biotage® crimper and crimp cap under a flow of N_2 gas. The reaction mixture was left to stir at $\mathbf{T_1}$ °C for $\mathbf{t_1}$ hours. After this time, MeI (0.25 mL, 4.00 mmol, 8.00 equiv.) was added and reaction continued to stir at $\mathbf{T_2}$ °C for $\mathbf{t_2}$ hours. The reaction mixture was cooled to room temperature, quenched with sat. $NaHCO_3$ and extracted with Et_2O. The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The yield of the reaction was determined by quantitative ^1H NMR analysis of the crude mixture in $CDCl_3$ against an internal standard ($CHCl_2CHCl_2$).

Salt Screen (N–H carboxylation)



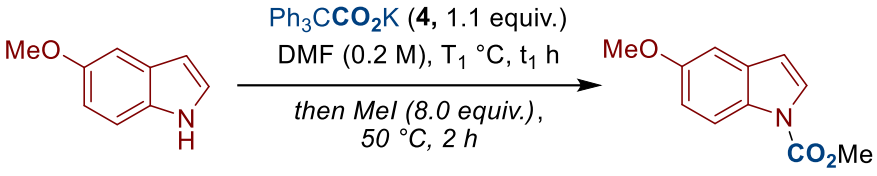
1a
1.0 equiv.

2a

Entry	M	1a (%)[a]	2a (%)[a]	Ph_3CH (%)[c]
1	Li	31	63	93
2	Na	17	71	82
3	K	3	93	97
4	Cs	4	88	88
5	Rb	22	75	97

[a] NMR yields using 1,1,2,2-tetrachloroethane as an internal standard.
[c] Mass recovery wrt reagent **4**.

Temperature Screen (N–H Carboxylation)



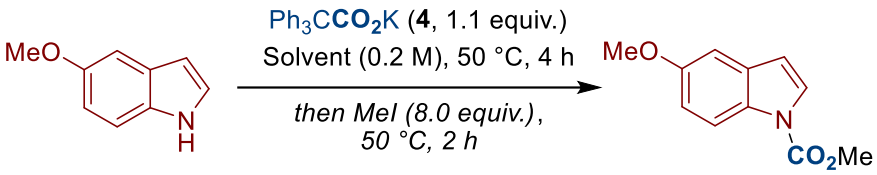
1a
1.0 equiv.

2a

Entry	T_1 / °C	t_1 / h	1a (%)[a]	2a (%)[a]	Ph_3CH (%)[c]
1	30	16	3	48	48
2	50	16	9	86	93
3	50	4	3	93	97
4	60	16	12	71	93

[a] NMR yields using 1,1,2,2-tetrachloroethane as an internal standard.
[c] Mass recovery wrt reagent **4**.

Solvent Screen (N–H carboxylation)



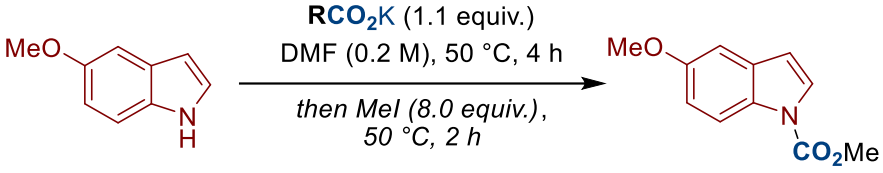
1a
1.0 equiv.

2a

Entry	Solvent	1a (%)[a]	2a (%)[a]	Ph_3CH (%)[c]
1	DMF	3	93	97
2	DMSO	5 (13)[b]	75	93
3	DMA	2 (2)[b]	93	95
4	THF	94 (2)[b]	0	0
5	PhMe	97	0	0

[a] NMR yields using 1,1,2,2-tetrachloroethane as an internal standard. [b] Mass balance recovered as 1-methylindole post-methylation). [c] Mass recovery wrt reagent **4**.

Dual Function Reagent Base Screen (N–H carboxylation)



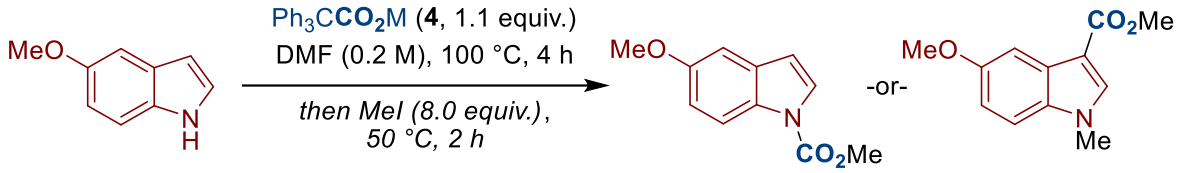
1a
1.0 equiv.

2a

Entry	R	1a (%)[a]	2a (%)[a]
1	Ph_3C	3	93
2	CH_2CO_2Et	78	3
3	CH_2CN	98	0

[a] NMR yields using 1,1,2,2-tetrachloroethane as an internal standard.

Salt Screen (C3–H carboxylation)



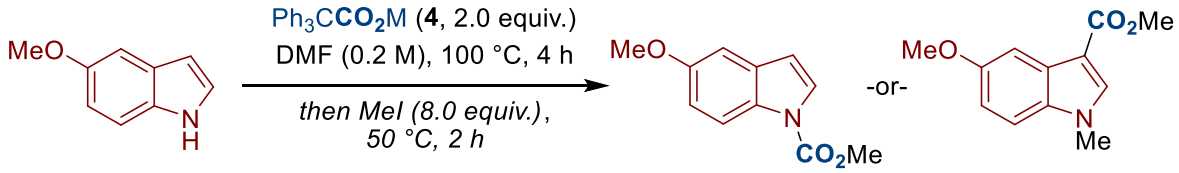
1a
1.0 equiv.

2a **3a**

Entry	M	1a (%)[a]	2a (%)[a]	3a (%)[a]	Ph_3CH (%)[c]
1	Li	22	25	16	99
2	Na	19	39	21	74
3	K	28	38	25	96
4	Cs	14	65	11	90
5	Rb	21	43	22	90

[a] NMR yields using 1,1,2,2-tetrachloroethane as an internal standard.
[c] Mass recovery wrt reagent **4**.

Secondary Salt Screen (C3–H carboxylation)



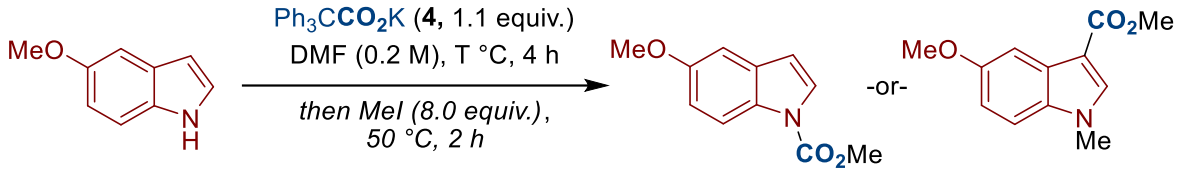
1a
1.0 equiv.

2a **3a**

Entry	M	1a (%)[a]	2a (%)[a]	3a (%)[a]	Ph_3CH (%)[c]
1	K	12	44	35	71 (18)[d]
2	Cs	5	20	33	96

[a] NMR yields using 1,1,2,2-tetrachloroethane as an internal standard.
[c] Mass recovery wrt reagent **4**. [d] Mass balance recovered as Ph_3CCO_2Me indicating no decarboxylation of reagent **4**.

Temperature Screen (C3–H Carboxylation)



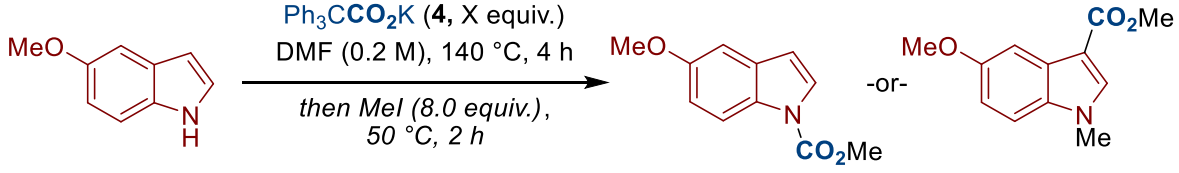
1a
1.0 equiv.

2a **3a**

Entry	T °C	1a (%)[a]	2a (%)[a]	3a (%)[a]	Ph_3CH (%)[c]
1	50	4	50	0	97
2	100	12	44	35	71(18)[d]
3	140	4	20	67	89

[a] NMR yields using 1,1,2,2-tetrachloroethane as an internal standard.
[c] Mass recovery wrt reagent **4**. [d] Mass balance recovered as Ph_3CCO_2Me indicating no decarboxylation of reagent **4**.

Equivalents Screen (C3–H Carboxylation)



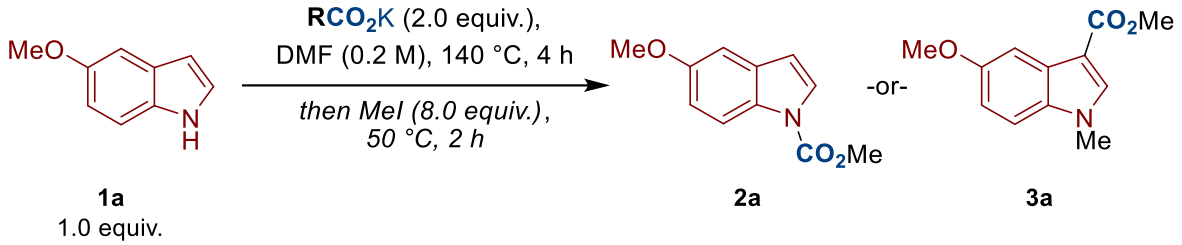
1a
1.0 equiv.

2a **3a**

Entry	X equiv.	1a (%)[a]	2a (%)[a]	3a (%)[a]	Ph_3CH (%)[c]
1	1.1	56	30	14	84
2	1.5	12	31	36	86
3	2.0	4	20	67	88
4	3.0	0	7	85	89

[a] NMR yields using 1,1,2,2-tetrachloroethane as an internal standard.
[c] Mass recovery wrt reagent **4**.

Dual Function Reagent Base Screen (C3–H carboxylation)



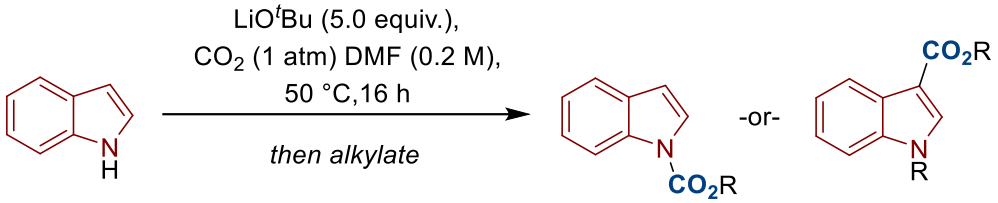
1a
1.0 equiv.

2a **3a**

Entry	R	1a (%)[a]	2a (%)[a]	3a (%)[a]
1	Ph_3C	4	20	67
2	CH_2CO_2Et	7	20	60
3	CH_2CN	18	46	34

[a] NMR yields using 1,1,2,2-tetrachloroethane as an internal standard.

Control reactions for switchable N–H vs C3–H carboxylation (N–H carboxylation)



1c
1.0 equiv.

2c **3c**

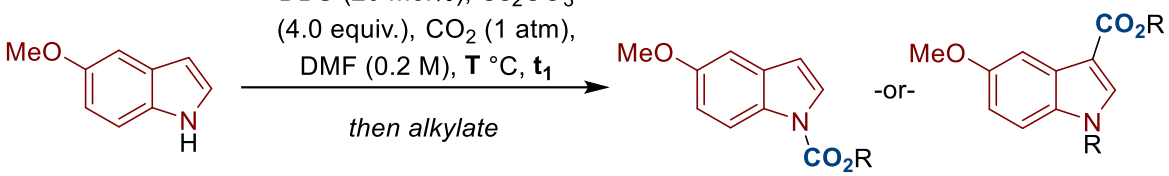
Adapted from the works of Kobayashi and co-workers[3] A Biotage® microwave vial, equipped with a magnetic stir bar and septum, was dried under vacuum with a heat gun. The vial was charged with the 5-methoxy indole (59 mg, 0.50 mmol, 1.00 equiv.), and LiO^{t}Bu (200 mg, 2.50 mmol, 5.00 equiv.). The vial was purged through cycles of vacuum/CO_2 gas. DMF (0.2 M) was then added. The vial was allowed to stir at 50 °C for 16 hours under an atmosphere of CO_2. After this time, MeI (0.25 mL, 4.00 mmol, 8.00 equiv.) was added and reaction continued to stir at 50 °C for 2 hours. The reaction mixture was cooled to room temperature, quenched with sat. $NaHCO_3$ and extracted with Et_2O. The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The

yield of the reaction was determined by quantitative ^{1}H NMR analysis of the crude mixture in $CDCl_3$ against an internal standard ($CHCl_2CHCl_2$).

Entry	1c (%)[a]	2c (%)[a]	3c (%)[a]
1	5	50	8

[a] NMR yields using 1,1,2,2-tetrachloroethane as an internal standard.

Control reactions for switchable N–H vs C3–H carboxylation (C3–H carboxylation)



1a
1.0 equiv.

2a **3a**

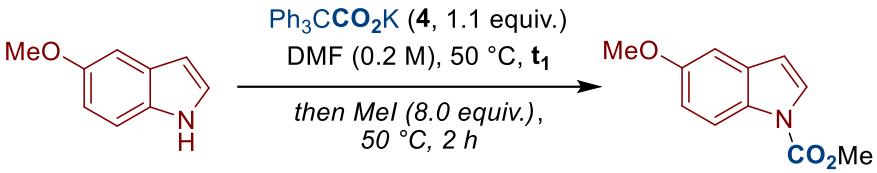
Adapted from the works of Hopmann and Repo and co-workers[4] A Biotage® microwave vial, equipped with a magnetic stir bar and septum, was dried under vacuum with a heat gun. The vial was charged with the 5-methoxy indole (74 mg, 0.50 mmol, 1.00 equiv.), and Cs_2CO_3 (651 mg, 2.00 mmol, 4.00 equiv.). The vial was purged through cycles of vacuum/CO_2 gas. DMF (0.2 M) was then added, followed quickly by the addition of DBU (15 µL, 0.10 mmol). The vial was allowed to stir at **T** °C for $\mathbf{t_1}$ hours under an atmosphere of CO_2. After this time, the appropriate alkyl halide (1.00 mmol, 2.00 equiv.) was added and reaction continued to stir at 50 °C for 16 hours. The reaction mixture was cooled to room temperature, quenched with sat. $NaHCO_3$ and extracted with Et_2O. The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The yield of the reaction was determined by quantitative ^{1}H NMR analysis of the crude mixture in $CDCl_3$ against an internal standard ($CHCl_2CHCl_2$).

Entry	T °C	t_1	1a (%)[a]	2a (%)[a]	3a (%)[a]
1	25	5 min	6	88[b]	n.d.
2	140	4 h	3	64[c]	8

[a] NMR yields using 1,1,2,2-tetrachloroethane as an internal standard.
[b] *R* = C_5H_{11}. [c] *R* = CH_3.

3. Mechanistic studies

Time variation (N–H Carboxylation)



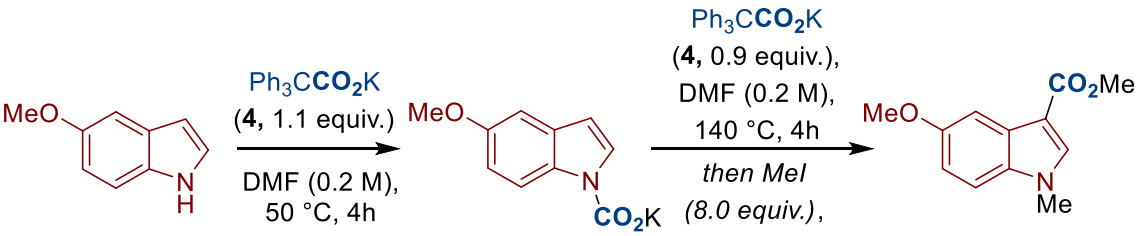
1a
1.0 equiv.

2a

Entry	t_1	1a (%)[a]	2a (%)[a]	Ph_3CH (%)[c]
1	1 min	72	18	17 (74)[d]
2	5 min	19	77	79 (10)[d]
3	15 min	4	86	89 (8)[d]
4	30 min	4	87	89 (6)[d]
5	1 h	3	91	93 (4)[d]
6	4 h	4	93	97 (0)[d]

[a] NMR yields using 1,1,2,2-tetrachloroethane as an internal standard. [c] Mass recovery wrt reagent **4**. [d] Mass balance recovered as Ph_3CCO_2Me indicating no decarboxylation of reagent **4**.

Reversibility investigation (N–H vs C3–H Carboxylation)



1a
1.0 equiv.

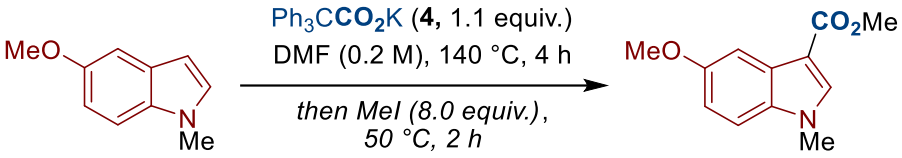
2a'

3a

Entry	1a (%)[a]	2a (%)[a]	3a (%)[a]	Ph_3CH (%)[c]
1	4	20	67	84 (11)[d]

[a] NMR yields using 1,1,2,2-tetrachloroethane as an internal standard. [c] Mass recovery wrt reagent **4**. [d] Mass balance recovered as Ph_3CCO_2Me indicating no decarboxylation of reagent **4**.

Control reaction (C3–H Carboxylation)



1a'
1.0 equiv.

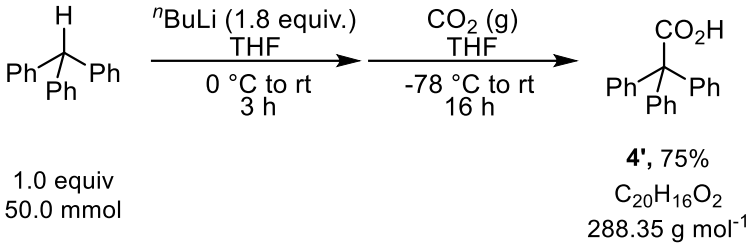
3a

Entry	1a' (%)[a]	3a (%)[a]	Ph_3CH (%)[c]
1	93	0	33 (60)[d]

[a] NMR yields using 1,1,2,2-tetrachloroethane as an internal standard.
[c] Mass recovery wrt reagent **4**. [d] Mass balance recovered as Ph_3CCO_2Me indicating no decarboxylation of reagent **4**.

4. Experimental procedures for preparation of carboxylate salts and associated characterization data

Synthesis of triphenyl acetic acid (4')



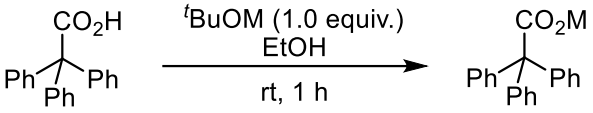
Adapted from the works of Perry and co-workers[2] A 1000 mL 3-neck flask was dried with a heat gun under *vacuo*. The flask was charged with triphenylmethane (12.2 g, 50.0 mmol, 1.00 equiv.) and placed under an inert atmosphere through cycles of N_2 gas and vacuum. Anhydrous THF (200 mL, 0.25 M) was added, and the solution was cooled to 0 °C using an ice bath. *n*-BuLi (36 mL, 90.0 mmol, 1.80 equiv., 2.5 M in hexane) was added dropwise, giving a deep red solution. Upon complete addition of the *n*-BuLi, the reaction mixture was warmed to room temperature and left to stir for 3 hours. A liquid N_2 bath was then used to solidify the reaction mixture, to then place under vacuum for 5 minutes. The flask was cut off from the vacuum and warmed to –78 °C in a dry ice/acetone bath to give a red solution (*caution*: upon thawing, N_2 gas is released from the reaction mixture creating a pressure build up. To prevent a large pressure build-up, thaw the reaction slowly. If necessary, keep the vacuum tap open at the beginning of the process to avoid pressure build-up, then close to avoid evaporating too much solvent). The flask was filled with CO_2 gas *via* balloon attached with a needle and the mixture was warmed to room temperature. The solution was left to stir at room temperature for 16 hours. Following this, the solution was quenched with H_2O (150 mL) and acidified to pH 1 using 1 M HCl. The organic phase was then extracted with EtOAc (3 x 150 mL), dried over Na_2SO_4 and the solvent was removed *in vacuo*, leaving 20 mL of solvent. The contents were then filtered under vacuum and washed with cold hexane. The product was dried under vacuum and obtained as a white solid (10.8 g, 37.5 mmol, 75%).

^{1}H NMR (400 MHz, DMSO-d_6, 298 K): δ (ppm) = 13.22 (1H, br s, CO_2**H**), 7.34-7.19 (9H, m, Ar**H**), 7.16-7.11 (6H, m, Ar**H**).

^{13}C NMR (101 MHz, DMSO-d_6, 298 K): δ (ppm) = 174.3 (**C**O_2H) 143.2 (**C**$_{Ar}$), 129.9 (**C**H$_{Ar}$), 127.6 (**C**H$_{Ar}$),126.6 (**C**H$_{Ar}$), 66.9 (Ph_3**C**).

All spectroscopic data is consistent with the reported values.[2]

General Procedure for the preparation of triphenyl acetate salts (4)

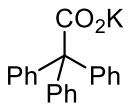


4'
1.0 equiv.

4

Adapted from the works of Perry and co-workers[2] A 250 mL RBF equipped with a stir bar was charged with Ph_3CCO_2H (1.00 equiv.) and EtOH (0.4 M). In a separate flask, MO*t*-Bu (1.00 equiv.) or M_2CO_3 (0.5 equiv.) was dissolved in EtOH (0.4 M). The MO*t*-Bu/M_2CO_3 solution was slowly added to the solution containing Ph_3CCO_2H and the MO*t*-Bu/M_2CO_3 flask was rinsed with small portions of EtOH to ensure all the MO*t*-Bu/M_2CO_3 was transferred. The resulting mixture was stirred at room temperature for 1 h. The solution was then concentrated under *vacuo* until ~25% of the solvent remained. The remaining mixture was cooled in an ice bath then filtered under *vacuo* and washed with cold Et_2O. The white solid obtained was then dried under *vacuo* overnight at 40 °C.

Potassium 2,2,2-triphenyl acetate (4-K)



4-K, 97%
$C_{20}H_{15}KO_2$
326.44 g mol^{-1}

Potassium 2,2,2-triphenyl acetate was obtained as a white solid at 97% (14.3 g, 43.7 mmol) from Ph_3CCO_2H (13.0 g, 45.0 mmol, 1.00 equiv.), ^{t}BuOK (5.15 g, 45.0 mmol, 1.00 equiv.) and EtOH (225 mL, 0.2 M), following **General Procedure** f**or the preparation of triphenyl acetate salts**.

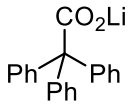
^{1}H NMR (400 MHz, D_2O, 298 K): δ (ppm) = 7.28-7.16 (15H, *m*, Ar**H**).

^{13}C NMR (101 MHz, D_2O, 298 K): δ (ppm) = 180.3 (**C**O_2K), 145.5 (**C**$_{Ar}$), 130.3 (**C**H$_{Ar}$), 127.7 (**C**H$_{Ar}$), 126.2 (**C**H$_{Ar}$), 70.3 (Ph_3**C**).

Elemental Analysis: Calcd. For $C_{20}H_{15}KO_2$: C, 73.59; H, 4.63. Found: C, 73.70; H, 4.68

All spectroscopic data is consistent with the reported values.[2]

Lithium 2,2,2-triphenyl acetate (4-Li)



4-Li, 81%
$C_{20}H_{15}LiO_2$
294.28 g mol^{-1}

Lithium 2,2,2-triphenyl acetate was obtained as a white solid at 81% (188 mg, 0.64 mmol) from Ph_3CCO_2H (228 mg, 0.79 mmol, 1.00 equiv.), ^{t}BuOLi (63 mg, 0.79 mmol, 1.00 equiv.) and EtOH (3.0 mL, 0.2 M), following **General Procedure** f**or the preparation of triphenyl acetate salts**.

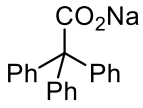
^{1}H NMR (400 MHz, D_2O, 298 K): δ (ppm) = 7.35-7.25 (15H, *m*, Ar**H**).

^{13}C NMR (101 MHz, D_2O, 298 K): δ (ppm) = 180.3 (**C**O_2Li), 145.5 (**C**$_{Ar}$), 130.3 (**C**H$_{Ar}$), 127.7 (**C**H$_{Ar}$), 126.2 (**C**H$_{Ar}$), 70.3 (Ph_3**C**).

Elemental Analysis: Calcd. For $C_{20}H_{15}LiO_2$: C, 81.63; H, 5.14. Found C, 79.52; H, 5.12.

All spectroscopic data is consistent with the reported values.[2]

Sodium 2,2,2-triphenyl acetate (4-Na)



4-Na, 96%
$C_{20}H_{15}NaO_2$
310.33 g mol^{-1}

Sodium 2,2,2-triphenyl acetate was obtained as a white solid at 96% (1.49 g, 4.80 mmol) from Ph_3CCO_2H (1.44 g, 5.00 mmol, 1.00 equiv.), ^{t}BuONa (481 mg, 5.00 mmol,

1.00 equiv.) and EtOH (25 mL, 0.2 M), following **General Procedure** f**or the preparation of triphenyl acetate salts**.

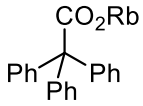
^{1}H NMR (400 MHz, D_2O, 298 K): δ (ppm) = 7.35-7.26 (15H, *m*, Ar**H**).

^{13}C NMR (101 MHz, D_2O, 298 K): δ (ppm) = 180.3 (**C**O_2Na), 145.5 (**C**$_{Ar}$), 130.3 (**C**H$_{Ar}$), 127.7 (**C**H$_{Ar}$), 126.2 (**C**H$_{Ar}$), 70.3 (Ph_3**C**).

Elemental Analysis: Calcd. For $C_{20}H_{15}NaO_2$: C, 77.41; H, 4.87. Found: C, 76.11; H, 5.07.

All spectroscopic data is consistent with the reported values.[2]

Rubidium 2,2,2-triphenyl acetate (4-Rb)



4-Rb, 74%
$C_{20}H_{15}RbO_2$
372.81 g mol^{-1}

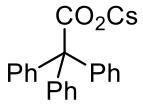
Rubidium 2,2,2-triphenyl acetate was obtained as a white solid at 74% (2.77 g, 7.40 mmol) from Ph_3CCO_2H (2.88 g, 10.0 mmol, 1.00 equiv.), Rb_2CO_3 (1.16 g, 5.00 mmol, 0.50 equiv.) and EtOH (50 mL, 0.2 M), following **General Procedure** f**or the preparation of triphenyl acetate salts**.

^{1}H NMR (400 MHz, D_2O, 298 K): δ (ppm) = 7.36-7.26 (15H, *m*, Ar**H**).

^{13}C NMR (101 MHz, D_2O, 298 K): δ (ppm) = 180.3 (**C**O_2Rb), 145.5 (**C**$_{Ar}$), 130.3 (**C**H$_{Ar}$), 127.7 (**C**H$_{Ar}$), 126.2 (**C**H$_{Ar}$), 70.3 (Ph_3**C**).

Elemental Analysis: Calcd. For $C_{20}H_{15}RbO_2$: C, 64.44; H, 4.06. Found C, 64.07; H, 4.19.

Cesium 2,2,2-triphenyl acetate (4-Cs)



4-Cs, 96%
$C_{20}H_{15}CsO_2$
420.24 g mol^{-1}

Cesium 2,2,2-triphenyl acetate was obtained as a white solid at 96% (2.02 g, 4.81 mmol) from Ph_3CCO_2H (1.44 g, 5.0 mmol, 1.00 equiv.), Cs_2CO_3 (815 mg, 2.50 mmol, 0.50 equiv.) and MeOH (25 mL, 0.2 M), following **General Procedure** f**or the preparation of triphenyl acetate salts**.

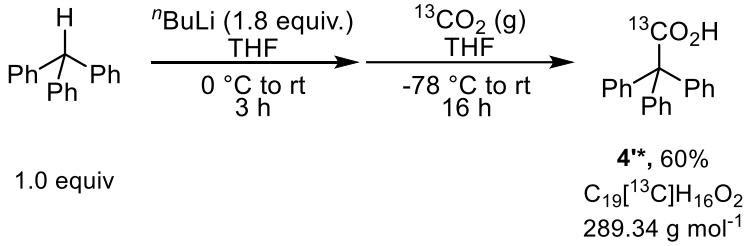
^{1}H NMR (500 MHz, D_2O, 298 K): δ (ppm) = 7.35-7.26 (15H, *m*, Ar**H**).

^{13}C NMR (126 MHz, D_2O, 298 K): δ (ppm) = 180.3 (**C**O_2Cs), 145.5 (**C**$_{Ar}$), 130.3 (**C**H$_{Ar}$), 127.7 (**C**H$_{Ar}$), 126.2 (**C**H$_{Ar}$), 70.3 (Ph_3**C**).

Elemental Analysis: Calcd. For $C_{20}H_{15}CsO_2$: C, 57.16; H, 3.60. Found C, 57.02; H, 3.57.

All spectroscopic data is consistent with the reported values.[2]

Synthesis of ^{13}C labelled triphenyl acetic acid (4'*)



Adapted from the works of Perry and co-workers[2] A 500 mL 3-neck RBF was equipped with a stir bar and dried with a heat gun under *vacuo*. The flask was charged with triphenylmethane (5.38 g, 22.0 mmol, 1.00 equiv.) and placed under an inert atmosphere through cycles of N_2 gas and vacuum. THF (110 mL, 0.20 M) was added, and the solution was cooled to 0 °C. *n*-BuLi (13.8 mL, 26.4 mmol, 1.20 equiv., 1.91 M in hexane) was added dropwise to form a red solution. Upon complete addition of *n*-BuLi, the solution was warmed to room temperature and stirred for 3 h. The mixture was solidified in a liquid N_2 bath, then placed under vacuum for 5 min. The tap to the vacuum was closed and the mixture was warmed to –78 °C in a dry ice/acetone bath to give a red solution. The flask was filled with $^{13}CO_2$ gas *via* connection to a $^{13}CO_2$ cannister (364592-1L purchased from Merck. One litre of CO_2 gas is approximately 45 mmol, 2.05 equiv. Packaged in a 450 mL carbon steel lecture bottle with brass CGA 110/180 valve and equipped with a stainless-steel control valve. Merck state that nominal gas pressures at 21 ºC are 20 psig. *Note: open the control valve carefully to*

avoid over pressure). The mixture was warmed to room temperature and stirred overnight. The valves between the $^{13}CO_2$ cannister and the reaction vessel were kept open overnight. The product mixture was quenched with 55 mL H_2O and acidified to pH 1 with 2 M HCl. The organic phase was then extracted with EtOAc (3 × 80 mL), dried over Na_2SO_4 and concentrated under *vacuo* until ~10% solvent remained. The contents were then filtered under *vacuo* and washed with ice-cold EtOAc. One portion was purified by filtration and another by column chromatography in 0-50% EtOAc in Hexane (Rf = 0.26 (hexane:EtOAc, 1:1)). Drying *in vacuo* afforded the product as a white solid at 60% (3.83 g, 13.2 mmol).

^{1}H NMR (**400 MHz, DMSO-d_6):** δ (ppm) 13.23 (br.s, 1H, CO_2**H**), 7.33-7.29 (m, 6H, Ar**H**), 7.27-7.23 (m, 3H, Ar**H**), 7.14- 7.12 (m, 6H, Ar**H**).

^{13}C NMR (**101 MHz, DMSO-d_6):** δ (ppm) 174.3 (**^{13}C**O_2H), 143.3 (d, *J* = 1.5 Hz. **C**$_{Ar}$), 129.9 (d, *J* = 2.2 Hz, **C**H$_{Ar}$), 127.7 (**C**H$_{Ar}$), 126.7 (**C**H$_{Ar}$), 67.0 (d, *J* = 53.3 Hz, Ar$_3$**C**).

% ^{13}C incorporation: Found to be >99% by quantitative ^{13}C NMR.

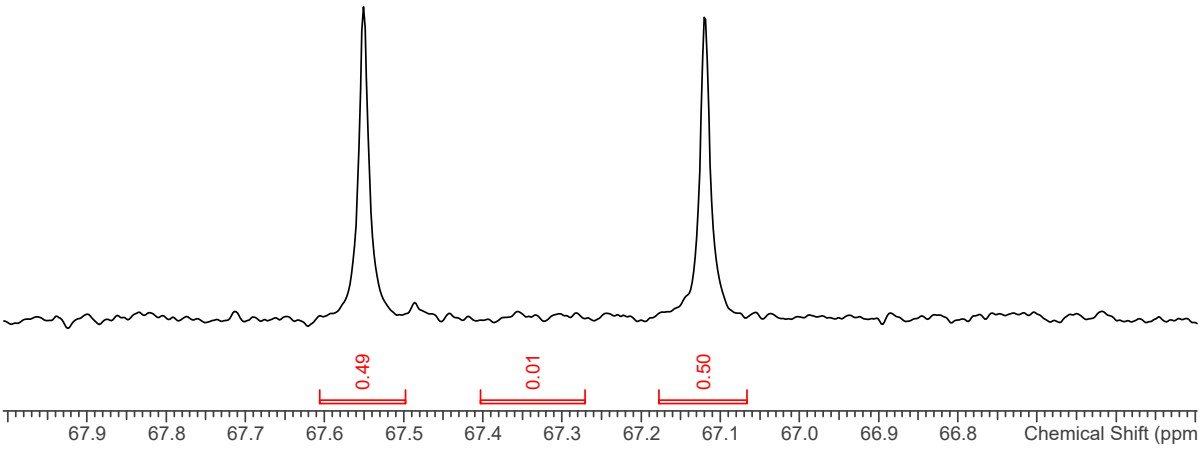
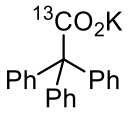


Figure 2: ^{13}C incorporation for $Ph_3C^{13}CO_2H$.

All spectroscopic data is consistent with the reported values.[2]

Figure 3: General setup for the preparation of $Ph_3C^{13}CO_2H$.

^{13}C labelled potassium 2,2,2-triphenyl acetate (4*-K)



4*-K, 83%
$C_{19}[^{13}C]H_{15}KO_2$
327.44 g mol^{-1}

^{13}C labelled potassium 2,2,2-triphenyl acetate was obtained as a white solid at 83% (1.38 g, 4.20 mmol) from $Ph_3C^{13}CO_2H$ (1.45 g, 5.00 mmol, 1.00 equiv.), ^{t}BuOK (561 mg, 5.00 mmol, 1.00 equiv.) and EtOH (25 mL, 0.2 M). following **General Procedure for the preparation of triphenyl acetate salts**.

^{1}H NMR (400 MHz, D_2O, 298 K): δ (ppm) = 7.35-27 (15H, *m*, Ar**H**).

^{13}C NMR (101 MHz, D_2O, 298 K): δ (ppm) = 180.3 (^{13}**C**O_2K), 145.5 (d, *J* = 1.5 Hz, **C**$_{Ar}$), 130.3 (d, *J* = 1.5 Hz, **C**H$_{Ar}$), 127.7 (**C**H$_{Ar}$), 126.2 (**C**H$_{Ar}$), 70.3 (d, *J* = 49.2 Hz, Ph_3**C**).

% ^{13}C incorporation: Found to be >99% by quantitative ^{13}C NMR.

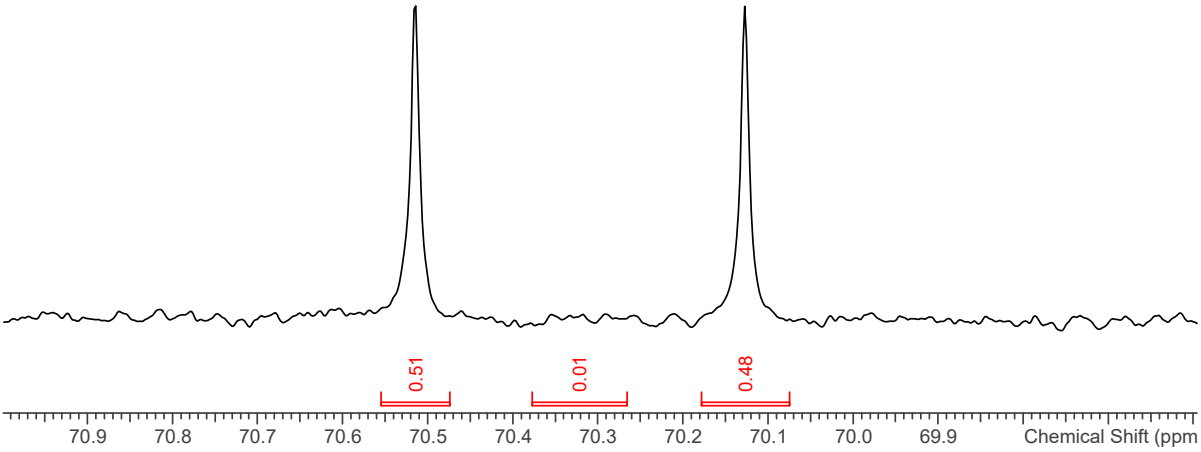
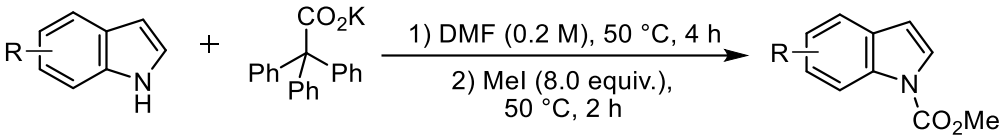


Figure 4: ^{13}C incorporation for $Ph_3C^{13}CO_2K$.

All spectroscopic data is consistent with the reported values.[2]

5. General Experimental procedures for carboxylation

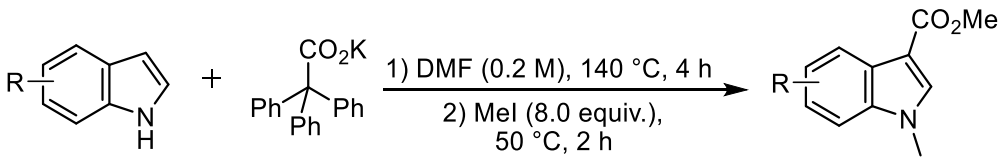
General Procedure 1 (N–H carboxylation of indoles):



1 1.0 equiv. **4** 1.1 equiv **2**

A Biotage® microwave vial, equipped with a magnetic stir bar and septum, was dried under vacuum with a heat gun. The vial was charged with the appropriate indole (1.00 equiv.) and Ph_3CCO_2K (359 mg, 1.00 mmol, 1.10 equiv.). The vial was purged through cycles of vacuum/N_2 gas. DMF (5.0 mL, 0.2 M) was then added, and the vial was firmly sealed using a Biotage® crimper and crimp cap under a flow of N_2 gas. The reaction mixture was left to stir at 50 °C for 4 hours. After this time, MeI (0.50 mL, 8.00 mmol 8.00 equiv.) was added and the reaction stirred at 50 °C for 2 hours. The reaction mixture was cooled to room temperature, quenched with sat. $NaHCO_3$ and extracted with Et_2O. The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified using silica gel column chromatography.

General Procedure 2 (C3–H carboxylation of indoles):

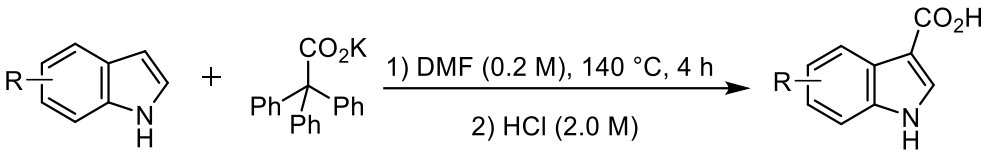


1 1.0 equiv. **4** 2.0 equiv **3**

A Biotage® microwave vial, equipped with a magnetic stir bar and septum, was dried under vacuum via a heat gun. The vial was charged with the appropriate indole (1.00 equiv.) and Ph_3CCO_2K (326 mg, 1.00 mmol, 2.00 equiv.). The vial was purged through cycles of vacuum/N_2 gas. DMF (2.5 mL, 0.2 M) was then added, and the vial was firmly sealed using a Biotage® crimper and crimp cap under a flow of N_2 gas. The reaction mixture was left to stir at 140 °C for 4 hours. After this time, the reaction was cooled to room temperature and MeI (0.25 mL, 4.00 mmol, 8.00 equiv.) was added. The reaction was then stirred at 50 °C for 2 hours. The reaction mixture was cooled to room temperature, quenched with sat. $NaHCO_3$ and extracted with Et_2O. The organic phase

was dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified using silica gel column chromatography.

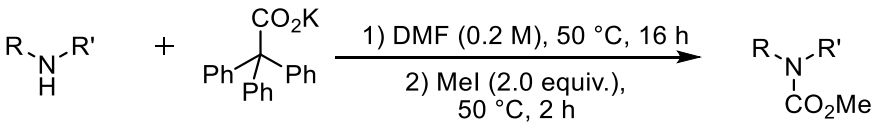
General Procedure 3 (C3–H carboxylation and acidification of indoles)



1 1.0 equiv. **4** 2.0 equiv **3'**

A Biotage® microwave vial, equipped with a magnetic stir bar and septum, was dried under vacuum via a heat gun. The vial was charged with the appropriate indole (1.00 equiv.) and Ph_3CCO_2K (326 mg, 1.00 mmol, 2.00 equiv.). The vial was purged through cycles of vacuum/N_2 gas. DMF (2.5 mL, 0.2 M) was then added, and the vial was firmly sealed using a Biotage® crimper and crimp cap under a flow of N_2 gas. The reaction mixture was left to stir at 140 °C for 4 hours. After this time, the reaction was cooled to room temperature and hexane (5 mL) was added with rapid stirring. The reaction was filtered and washed with hexane (3 x 5 mL) and Et_2O (2.5 mL). The resulting salt was dried under vacuum overnight at 40°C. The product was dissolved in H_2O (10 mL) and acidified to pH 1 with aqueous HCl (2.0 M). The organic phase was extracted with EtOAc (3 x 10 mL), washed with H_2O (10 mL) and brine (10 mL), and dried over Na_2SO_4. Concentration and drying *in vacuo* then afforded the desired carboxylic acid.

General Procedure 4 (N–H carboxylation of amines)



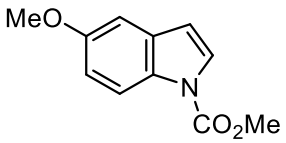
11 1.0 equiv. **4** 1.1 equiv **12**

A Biotage® microwave vial, equipped with a magnetic stir bar and septum, was dried under vacuum via a heat gun. The vial was charged with the appropriate amine (1.00 equiv.), and Ph_3CCO_2K (359 mg, 1.00 mmol, 1.10 equiv.). The vial was purged through cycles of vacuum/N_2 gas. DMF (5.0 mL, 0.2 M) was then added, and the vial was firmly sealed using a Biotage® crimper and crimp cap under a flow of N_2 gas. The reaction mixture was left to stir at 50 °C for 16 hours. After this time, MeI (0.13 mL, 2.00 mmol

2.00 equiv.) was added and the reaction stirred at 50 °C for 2 hours. The reaction mixture was cooled to room temperature, quenched with sat. $NaHCO_3$ and extracted with Et_2O. The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified using silica gel column chromatography.

6. Experimental procedures for N–H carboxylation of indoles and associated characterization data (2a-l)

Methyl 5-methoxy-1H-indole-1-carboxylate (2a):



2a, 87%
$C_{11}H_{11}NO_3$
205.07 g mol^{-1}

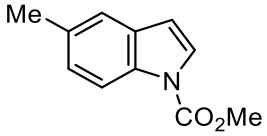
Methyl 5-methoxy-1H-indole-1-carboxylate was obtained as a pale-yellow solid at 87% (179 mg, 0.87 mmol) from 5-methoxy-1H-indole (147 mg, 1.00 mmol) following **procedure 1**. Purification by silica gel column chromatography in 0-40% Et_2O in hexane. Rf = 0.40 (Hexane:Et_2O, 70:30).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ (ppm) = 8.06 (1H, *br* d, *J* = 8.3 Hz, Ar**H**), 7.57 (1H, d, *J* = 3.5 Hz, Ar**H**), 7.04 (1H, d, *J* = 2.6 Hz, Ar**H**), 6.95 (1H, dd, *J* = 9.0, 2.5 Hz, Ar**H**), 6.53 (1H, dd, *J* = 3.7, 0.7 Hz, Ar**H**), 4.03 (3H, s, $CO_2C\mathbf{H_3}$), 3.85 (3H, s, $OC\mathbf{H_3}$)

^{13}C NMR (101 MHz, $CDCl_3$, 298 K): δ (ppm) = 156.1 (**C**O_2Me), 151.4 (**C**$_{Ar}$), 131.3 (**C**$_{Ar}$), 129.9 (**C**$_{Ar}$), 126.1 (**C**H$_{Ar}$), 115.8 (**C**H$_{Ar}$), 113.2 (**C**H$_{Ar}$), 108.0 (**C**H$_{Ar}$), 103.6 (**C**H$_{Ar}$), 55.6 ($CO_2\mathbf{C}H_3$), 53.7 ($O\mathbf{C}H_3$).

All spectroscopic data is consistent with the reported values.[5]

Methyl-5-methyl-1H-indole-1-carboxylate (2b):



2b, 70%
$C_{11}H_{11}NO_2$
189.08 g mol^{-1}

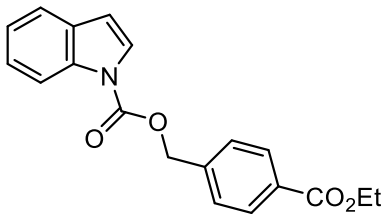
Methyl 5-methyl-1H-indole-1-carboxylate was obtained as a pale-yellow solid at 70% (132 mg, 0.70 mmol) from 5-methyl-1H-indole (131 mg, 1.00 mmol) following **procedure 1**. Purification by silica gel column chromatography in 0-20% Et_2O in hexane. Rf = 0.54 (Hexane:Et_2O, 80:20).

^{1}H NMR (400 MHz, DMSO-d_6, 298 K): δ (ppm) = 7.97 (1H, d, *J* = 8.4 Hz, Ar**H**), 7.65 (1H, d, *J* = 3.7 Hz, Ar**H**), 7.42-7.40 (1H, m, Ar**H**), 7.15 (1H, dd, *J* = 8.4, 1.7 Hz, Ar**H**), 6.66 (1H, dd, *J* = 3.7, 0.7 Hz, Ar**H**), 3.98 (3H, s, $CO_2C\mathbf{H_3}$), 2.39 (3H, s, $C\mathbf{H_3}$).

^{13}C NMR (101 MHz, DMSO-d_6, 298 K): δ (ppm) = 150.9 (**C**O_2Me), 132.8 (**C**$_{Ar}$),131.9 (**C**$_{Ar}$), 130.3 (**C**$_{Ar}$), 125.8 (**C**H$_{Ar}$), 125.6 (**C**H$_{Ar}$), 120.9 (**C**H$_{Ar}$), 114.2 (**C**H$_{Ar}$), 107.8 (**C**H$_{Ar}$), 54.0 ($CO_2\mathbf{C}H_3$), 20.9 (**C**H$_3$).

All spectroscopic data is consistent with the reported values.[5]

4-(ethoxycarbonyl)benzyl-1H-indole-1-carboxylate (2c):



2c, 77%
$C_{19}H_{17}NO_4$
323.35 g mol^{-1}

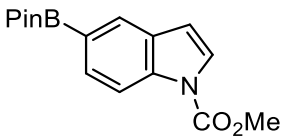
4-(ethoxycarbonyl)benzyl-1H-indole-1-carboxylate was obtained as a white solid at 77% (125 mg, 0.39 mmol) from indole (59 mg, 0.50 mmol) and Ph_3CCO_2K (180 mg, 0.55 mmol) in DMF (2.5 mL, 0.2 M) following a modified **procedure 1**. Alkylation was conducted using ethyl-4-(bromomethyl)benzoate (243 mg, 1.00 mmol). Purification by silica gel column chromatography in 0-25% EtOAc in hexane. Rf = 0.13 (hexane:EtOAc, 99:1).

^{1}H NMR (400 MHz, DMSO-d_6, 298 K): δ (ppm) = 8.09 (1H, d, *J* = 7.8 Hz, Ar**H**), 8.03-7.99 (2H, m, Ar**H**), 7.77 (1H, d, *J* = 3.7 Hz, Ar**H**), 7.70-7.63 (3H, m, Ar**H**), 7.34 (1 H, td, *J* = 7.8, 1.3 Hz, Ar**H**), 7.26 (1H, td, *J* = 7.5, 1.0 Hz, Ar**H**), 6.77 (1H, dd, *J* = 3.8, 0.6 Hz, Ar**H**), 5.56 (2H, s, $CO_2C\mathbf{H_2}$Ar), 4.32 (2H, q, *J* = 7.1 Hz, $CO_2C\mathbf{H_2}CH_3$), 1.32 (3H, t, *J* = 7.1 Hz, $CO_2CH_2C\mathbf{H_3}$).

^{13}C NMR (101 MHz, DMSO-d_6, 298 K): δ (ppm) = 165.4 (**C**O_2Et), 150.1 (**C**O_2Me), 140.7 (**C**$_{Ar}$), 134.6 (**C**$_{Ar}$), 130.2 (**C**$_{Ar}$), 129.8 (**C**$_{Ar}$), 129.4 (**C**H$_{Ar}$), 128.0 (**C**H$_{Ar}$), 125.8 (**C**H$_{Ar}$), 124.5 (**C**H$_{Ar}$), 123.1 (**C**H$_{Ar}$), 121.2 (**C**H$_{Ar}$), 114.6 (**C**H$_{Ar}$), 108.4 (**C**H$_{Ar}$), 67.6 ($CO_2\mathbf{C}H_2$Ar), 60.8 ($CO_2\mathbf{C}H_2CH_3$), 14.1 ($CO_2CH_2\mathbf{C}H_3$).

HRMS (EI): Found *m/z* 323.1154, $[M]^+$; calculated for $[C_{19}H_{17}NO_4]^+$: 323.1152.

Methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole-1-carboxylate (2d):



2d, 52%
$C_{16}H_{20}BNO_4$
301.15 g mol^{-1}

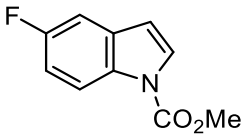
Methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole-1-carboxylate was obtained as a white solid at 52% (157 mg, 0.52 mmol) from 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (243 mg, 1.00 mmol) following **procedure 1**. Purification by silica gel column chromatography in 0-20% Et_2O in hexane, followed by recrystallization in hexane. Rf = 0.30 (Hexane: Et_2O, 80:20).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ (ppm) = 8.16 (1H, br d, *J* = 7.6 Hz, Ar**H**), 8.07 (1H, t, *J* = 0.9 Hz, Ar**H**), 7.78 (1H, dd, *J* = 8.3, 1.0 Hz, Ar**H**), 7.59 (1H, d, *J* = 3.7 Hz, Ar**H**), 6.61 (1H, dd, *J* = 3.7, 0.7 Hz, Ar**H**), 4.05 (3H, s, $CO_2C\mathbf{H_3}$), 1.37 (12H, s, $C\mathbf{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$, 298 K): δ (ppm) = 151.5 (**C**O_2Me), 144.6 (**C**$_{Ar}$), 137.3 (**C**$_{Ar}$), 130.8 (**C**H$_{Ar}$), 130.1 (**C**$_{Ar}$), 128.3 (**C**H$_{Ar}$), 125.5 (**C**H$_{Ar}$), 114.4 (**C**H$_{Ar}$), 108.4 (**C**H$_{Ar}$), 83.7 (O**C**$(CH_3)_2$C), 53.8 (CO_2**C**H_3), 24.9 (**C**H_3).

All spectroscopic data is consistent with the reported values.[6]

Methyl-5-fluoro-1H-indole-1-carboxylate (2e):



2e, 69%
$C_{10}H_8NO_2F$
193.18 g mol^{-1}

Methyl 5-fluoro-1H-indole-1-carboxylate was obtained as a white solid at 69% (68 mg, 0.35 mmol) from 5-fluoro-1H-indole (68 mg, 0.50 mmol) and Ph_3CCO_2K (180 mg, 0.55 mmol) in DMF (2.5 mL, 0.2 M) following **procedure 1**. Alkylation was conducted using MeI (0.25 mL, 4.00 mmol). Purification by silica gel column chromatography in 0-10% EtOAc in hexane. Rf = 0.30 (Hexane:EtOAc, 95:5).

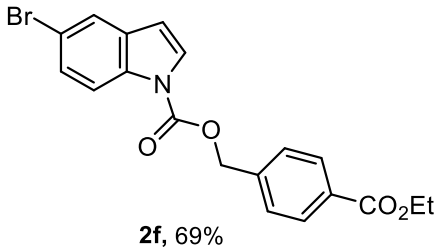
^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ (ppm) = 8.12 (1H, br s, Ar**H**), 7.63 (1H, d, *J* = 3.7 Hz, Ar**H**), 7.22 (1H, dd, *J* = 8.8, 2.2 Hz, Ar**H**), 7.06 (1H, tdd, *J* = 9.2, 2.4, 0.4 Hz, Ar**H**), 6.55 (1H, dd, *J* = 3.7, 0.7 Hz, Ar**H**), 4.04 (3H, s, $CO_2C\mathbf{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$, 298 K): δ (ppm) = 159.4 (d, *J* = 237.0 Hz, $\mathbf{C}F_{Ar}$), 151.3 ($\mathbf{C}O_2Me$), 131.3 (d, *J* = 9.6 Hz, $\mathbf{C}_{Ar}$), 129.4 ($\mathbf{C}H_{Ar}$), 127.0 ($\mathbf{C}_{Ar}$), 116.0 (d, *J* = 9.6 Hz, $\mathbf{C}H_{Ar}$), 112.2 (d, *J* = 25.0 Hz, $\mathbf{C}H_{Ar}$), 107.8 (d, *J* = 3.7 Hz, $\mathbf{C}H_{Ar}$), 106.5 (d, *J* = 25.0 Hz, $\mathbf{C}H_{Ar}$), 53.9 ($CO_2\mathbf{C}H_3$).

^{13}F NMR (400 MHz, $CDCl_3$, 298 K): –120.77 ppm

All spectroscopic data is consistent with the reported values.[5]

4-(ethoxycarbonyl)benzyl-5-bromo-1H-indole-1-carboxylate (2f):



2f, 69%
$C_{19}H_{16}NO_4Br$
401.03 g mol^{-1}

4-(ethoxycarbonyl)benzyl-5-bromo-1H-indole-1-carboxylate was obtained as a light pink solid at 69% (140 mg, 0.35 mmol) from 5-bromo-1H-indole (98 mg, 0.50 mmol) and Ph_3CCO_2K (180 mg, 0.55 mmol) in DMF (2.5 mL, 0.2 M) following a modified **procedure 1**. Alkylation was conducted using ethyl-4-(bromomethyl)benzoate (243 mg, 1.00 mmol). Purification by silica gel column chromatography in 0-25% EtOAc in hexane. Rf = 0.17 (Hexane:EtOAc, 90:10).

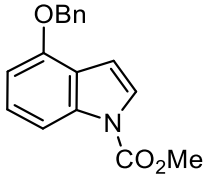
^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ (ppm) = 8.12-8.07 (2H, m, Ar**H**), 8.07-8.00 (1H, m, Ar**H**), 7.70 (1H, d, *J* = 1.7 Hz, Ar**H**), 7.62 (1H, d, *J* = 3.8 Hz, Ar**H**), 7.56-7.50 (2H, m, Ar**H**), 7.41 (1H, dd, *J* = 8.8, 1.7 Hz, Ar**H**), 6.55 (1H, dd, *J* = 3.7, 0.7 Hz, Ar**H**), 5.49 (2H, s, $CO_2C\mathbf{H_2}Ar$), 4.39 (2H, q, *J* = 7.2 Hz, $CO_2C\mathbf{H_2}CH_3$), 1.40 (3H, t, *J* = 7.2 Hz, $CO_2CH_2C\mathbf{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$, 298 K): δ (ppm) = (1 x $\mathbf{C}_{Ar}$ missing), 166.1 ($\mathbf{C}O_2Et$), 150.4 ($\mathbf{C}O_2CH_2Ar$), 139.6 ($\mathbf{C}_{Ar}$), 134.0 ($\mathbf{C}_{Ar}$), 132.2 ($\mathbf{C}_{Ar}$), 130.9 ($\mathbf{C}_{Ar}$), 130.1 ($\mathbf{C}H_{Ar}$), 128.0

(**C**H_{Ar}), 127.5 (**C**H_{Ar}), 126.5 (**C**H_{Ar}), 123.8 (**C**H_{Ar}), 116.5 (**C**H_{Ar}), 107.7 (**C**H_{Ar}), 68.2 (CO_2**C**H_2Ar), 61.2 (CO_2**C**H_2CH_3), 14.3 (CO_2CH_2**C**H_3).

HRMS (EI): Found *m/z* 163.0753, $[M–C_9H_5BrNO_2]^+$; calculated for $[C_{10}H_{11}O_2]^+$: 163.0754.

Methyl 4-(benzyloxy)-1H-indole-1-carboxylate (2h):



2h, 83%
$C_{17}H_{15}NO_3$
281.11 g mol^{-1}

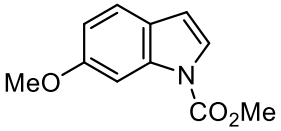
Methyl 4-(benzyloxy)-1H-indole-1-carboxylate was obtained as a white solid at 83% (233 mg, 0.83 mmol) from 4-(benzyloxy)-1H-indole (223 mg, 1.00 mmol) following **procedure 1**. Purification by silica gel column chromatography in 0-5% EtOAc in hexane. Rf = 0.31 (Hexane:EtOAc, 95:5).

^{1}H NMR (400 MHz, DMSO-d_6, 298 K): δ (ppm) = 7.71 (1H, d, *J* = 8.3 Hz, Ar**H**), 7.60 (1H, d, *J* = 3.7 Hz, Ar**H**), 7.52-7.48 (2H, m, Ar**H**), 7.43-7.37 (2H, m, Ar**H**), 7.35-7.30 (1H, m, Ar**H**), 7.25 (1H, t, *J* = 8.1 Hz, Ar**H**), 6.89 (1H, d, *J* = 7.7 Hz, Ar**H**), 6.76 (1H, dd, *J* = 3.8, 0.7 Hz, Ar**H**), 5.25 (2H, s, OC**H$_2$**), 3.98 (3H, s, CO_2C**H$_3$**).

^{13}C NMR (101 MHz, DMSO-d_6, 298 K): δ (ppm) = 151.6 (**C**O_2Me), 150.9 (**C**$_{Ar}$), 137.1 (**C**$_{Ar}$), 135.9 (**C**$_{Ar}$), 128.4 (**C**H_{Ar}), 127.8 (**C**H_{Ar}), 127.4 (**C**H_{Ar}), 125.5 (**C**H_{Ar}), 124.4 (**C**H_{Ar}), 120.3 (**C**$_{Ar}$), 107.8 (**C**H_{Ar}), 105.2 (**C**H_{Ar}), 104.8 (**C**H_{Ar}), 69.3 (**C**H_2), 54.1 (CO_2**C**H_3).

HRMS (ESI+) m/z = $[C_{17}H_{15}NO_3Na]^+$; Calculated: 304.0944. Observed: 304.0940 [M + Na]$^+$.

Methyl-6-methoxy-1H-indole-1-carboxylate (2i):



2i, 93%
$C_{11}H_{11}NO_3$
205.21 g mol^{-1}

Methyl 6-methoxy-1H-indole-1-carboxylate was obtained as a yellow oil at 93% (95 mg, 0.47 mmol) from 6-methoxy-1H-indole (74 mg, 0.5 mmol) and Ph_3CCO_2K (180 mg, 0.55 mmol) in DMF (2.5 mL, 0.2 M) following a modified **procedure 1**. Alkylation was conducted using MeI (0.25 mL, 4.00 mmol). Purification by silica gel column chromatography in 0-25% EtOAc in hexane. Rf = 0.23 (Hexane:EtOAc, 95:5).

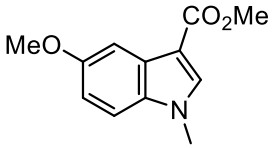
^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ (ppm) = 7.79 (1H, br s, Ar**H**), 7.48 (1H, d, *J* = 3.8 Hz, Ar**H**), 7.45-7.41 (1H, m, Ar**H**), 6.90 (1H, dd, *J* = 8.6, 2.3 Hz, Ar**H**), 6.52 (1 H, dd, *J* = 3.8, 0.7 Hz, Ar**H**), 4.03 (3H, s, $CO_2C\mathbf{H_3}$), 3.89 (3H, s, $OC\mathbf{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$, 298 K): δ (ppm) = 158.0 (**C**O_2Me), 151.6 (**C**$_{Ar}$), 136.3 (**C**$_{Ar}$), 134.1 (**C**$_{Ar}$), 124.2 (**C**H$_{Ar}$), 121.4 (**C**H$_{Ar}$), 112.2 (**C**H$_{Ar}$), 108.0 (**C**H$_{Ar}$), 99.4 (**C**H$_{Ar}$), 55.7 ($CO_2\mathbf{C}H_3$), 53.7 ($O\mathbf{C}H_3$).

HRMS (EI): Found *m/z* 205.0733, $[M]^+$; calculated for $[C_{11}H_{11}NO_3]^+$: 205.0733.

7. Experimental procedures for C3–H carboxylation of indoles and associated characterization data (3a-l)

Methyl 5-methoxy-1-methyl-1H-indole-3-carboxylate (3a)



3a, 66%
$C_{12}H_{13}NO_3$
219.09 g mol^{-1}

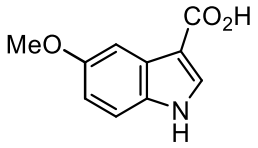
Methyl 5-methoxy-1-methyl-1H-indole-3-carboxylate was obtained as a white solid at 66% (72 mg, 0.33 mmol) from 5-methoxyindole (74 mg, 0.50 mmol) following **procedure 2**. Purification by silica gel column chromatography in 0-20% Et_2O in hexane. Rf = 0.35 (Hexane:Et_2O, 80:20).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ (ppm) = 7.71 (1H, s, Ar**H**), 7.65 (1H, d, *J* = 2.3 Hz, Ar**H**), 7.23 (1H, d, *J* = 8.9 Hz, Ar**H**), 6.94 (1H, dd, *J* = 8.9, 2.5 Hz, Ar**H**), 3.90 (3H, s, $CO_2C\mathbf{H_3}$), 3.90 (3H, s, $OC\mathbf{H_3}$), 3.80 (3H, s, $NC\mathbf{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$, 298 K): δ (ppm) = 165.5 ($\mathbf{C}O_2CH_3$), 155.9 ($\mathbf{C}_{Ar}$), 135.1 ($\mathbf{C}H_{Ar}$), 132.3 ($\mathbf{C}_{Ar}$), 127.5 ($\mathbf{C}_{Ar}$), 113.3 ($\mathbf{C}H_{Ar}$), 110.6 ($\mathbf{C}H_{Ar}$), 106.3 ($\mathbf{C}_{Ar}$), 102.9 ($\mathbf{C}H_{Ar}$), 55.8 ($CO_2\mathbf{C}H_3$), 50.9 ($O\mathbf{C}H_3$), 33.6 ($N\mathbf{C}H_3$).

All spectroscopic data is consistent with the reported values.[7]

5-methoxy-1H-indole-3-carboxylic acid (3a')



3a', 65%
$C_{10}H_9NO_3$
191.19 g mol^{-1}

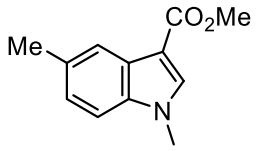
5-methoxy-1H-indole-3-carboxylic acid was obtained as a pale-yellow solid at 65% (62 mg, 0.33 mmol) from 5-methoxyindole (74 mg, 0.50 mmol) following **procedure 3**.

^{1}H NMR (400 MHz, DMSO-d_6, 298 K): δ (ppm) = 11.86 (1H, br s, CO_2**H**), 11.69 (1H, s, N**H**), 7.95-7.92 (1H, m, Ar**H**), 7.51-7.48 (1H, m, Ar**H**), 7.38-7.34 (1H, m, Ar**H**), 6.83-6.80 (1H, m, Ar**H**), 3.76 (3H, s, CO_2C**H_3**).

^{13}C NMR (101 MHz, DMSO-d_6, 298 K): δ (ppm) = 166.5 (**C**O_2H), 155.3 (**C**$_{Ar}$), 132.9 (**C**H$_{Ar}$), 131.8 (**C**$_{Ar}$), 127.2 (**C**$_{Ar}$), 113.4 (**C**H$_{Ar}$), 112.7 (**C**H$_{Ar}$), 107.5 (**C**$_{Ar}$), 102.6 (**C**H$_{Ar}$), 55.7 (O**C**H_3).

All spectroscopic data is consistent with the reported values.[8]

Methyl 5-methyl-1-methyl-1H-indole-3-carboxylate (3b)



3b, 71%
$C_{12}H_{13}NO_2$
203.24 g mol^{-1}

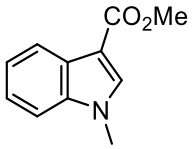
Methyl 5-methyl-1-methyl-1H-indole-3-carboxylate was obtained as an orange solid at 71% (72 mg, 0.36 mmol) from 5-methyl indole (66 mg, 0.50 mmol) following **procedure 2**. Purification by silica gel column chromatography in 0-50% EtOAc in hexane. Rf = 0.23 (Hexane: EtOAc, 90:10).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ (ppm) = 7.98-7.96 (1H, m, Ar**H**), 7.73 (1H, s, Ar**H**), 7.23 (1H, d, *J* = 8.3 Hz, Ar**H**), 7.12 (1H, dd, *J* = 8.3, 1.7 Hz, Ar**H**), 3.91 (3H, s, CO_2C**H_3**), 3.79 (3H, s, NC**H_3**), 2.50 (3H, s, C**H_3**).

^{13}C NMR (101 MHz, $CDCl_3$, 298 K): δ (ppm) = 165.6 (**C**O_2CH_3), 135.6 (**C**$_{Ar}$), 135.1 (**C**H$_{Ar}$), 131.4 (**C**$_{Ar}$), 126.8 (**C**$_{Ar}$), 124.3 (**C**H$_{Ar}$), 121.3 (**C**H$_{Ar}$), 109.4 (**C**H$_{Ar}$), 106.3 (**C**$_{Ar}$), 50.9 (CO_2**C**H_3), 33.4 (N**C**H_3), 21.5 (**C**H_3).

All spectroscopic data is consistent with the reported values.[9]

Methyl 1-methyl-1H-indole-3-carboxylate (3c)



3c, 73%
$C_{11}H_{11}NO_2$
189.08 g mol^{-1}

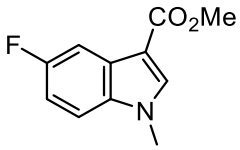
Methyl 1-methyl-1H-indole-3-carboxylate was obtained as a yellow solid at 73% (70 mg, 0.37 mmol) from indole (59 mg, 0.50 mmol) following **procedure 2**. Purification by silica gel column chromatography in 0-25% EtOAc in hexane. Rf = 0.23 (Hexane:EtOAc, 80:20).

^{1}H NMR (400 MHz, DMSO-d_6, 298 K): δ (ppm) = 8.12 (1H, s, Ar**H**), 8.02-7.98 (1H, m, Ar**H**), 7.54 (1H, d, *J* = 7.9 Hz, Ar**H**), 7.29-7.21 (2H, m, Ar**H**), 3.86 (3H, s, $CO_2C\mathbf{H_3}$), 3.80 (3H, s, $NC\mathbf{H_3}$).

^{13}C NMR (101 MHz, DMSO-d_6, 298 K): δ (ppm) = 164.4 ($\mathbf{C}O_2CH_3$), 136.9 ($\mathbf{C}_{Ar}$), 136.2 ($\mathbf{C}H_{Ar}$), 126.0 ($\mathbf{C}_{Ar}$), 122.4 ($\mathbf{C}H_{Ar}$), 121.5 ($\mathbf{C}H_{Ar}$), 120.5 ($\mathbf{C}H_{Ar}$), 110.8 ($\mathbf{C}H_{Ar}$), 105.1 ($\mathbf{C}_{Ar}$), 50.6 ($CO_2\mathbf{C}H_3$), 33.0 ($N\mathbf{C}H_3$).

All spectroscopic data is consistent with the reported values.[10]

Methyl 5-fluoro-1-methyl-1H-indole-3-carboxylate (3e)



3e, 89%
$C_{11}H_{10}FNO_2$
207.20 g mol^{-1}

Methyl 5-fluoro-1-methyl-1H-indole-3-carboxylate was obtained as a yellow solid at 89% (93 mg, 0.45 mmol) from 5-fluoro-1H-indole (68 mg, 0.50 mmol), following **procedure 2**. Purification by silica gel column chromatography in 5-50% EtOAc in hexane. Rf = 0.19 (Hexane:EtOAc, 75:25).

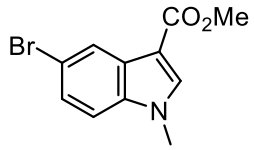
^{1}H NMR (400 MHz, DMSO-d_6, 298 K): δ (ppm) = 8.19 (1H, d, *J* = 1.5 Hz, Ar**H**), 7.66 (1H, dd, *J* = 9.8, 2.6 Hz, Ar**H**), 7.60-7.56 (1H, m, Ar**H**), 7.14 (1H, td, *J* = 9.2, 2.6 Hz, Ar**H**), 3.86 (3H, s, $CO_2C\mathbf{H_3}$), 3.80 (3H, s, $N\mathbf{C}H_3$).

^{13}C NMR (101 MHz, DMSO-d_6, 298 K): δ (ppm) = 164.2 ($\mathbf{C}O_2CH_3$), 158.5 (d, *J* = 234.8 Hz, $\mathbf{C}_{Ar}$), 137.6 ($\mathbf{C}H_{Ar}$), 133.7 ($\mathbf{C}_{Ar}$), 126.6 (d, *J* = 11.0 Hz, $\mathbf{C}_{Ar}$), 112.3 (d, *J* = 11.0 Hz, $\mathbf{C}H_{Ar}$), 110.6 (d, *J* = 26.4 Hz, $\mathbf{C}H_{Ar}$), 105.4 (d, *J* = 26.4 Hz, $\mathbf{C}H_{Ar}$), 105.2 (d, *J* = 4.4 Hz, $\mathbf{C}_{Ar}$), 50.6 ($CO_2\mathbf{C}H_3$), 33.4 ($N\mathbf{C}H_3$).

^{19}F NMR (376 MHz, DMSO-d_6, 298 K): δ (ppm) = –121.96.

All spectroscopic data is consistent with the reported values.[7]

Methyl 5-bromo-1-methyl-1H-indole-3-carboxylate (3f)



3f, 63%
$C_{11}H_{10}BrNO_2$
266.99 g mol^{-1}

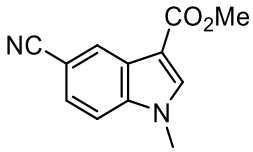
Methyl 5-bromo-1-methyl-1H-indole-3-carboxylate was obtained as a yellow solid at 63% (85 mg, 0.32 mmol) from 5-bromo-1H-indole (98 mg, 0.50 mmol) following **procedure 2**. Purification by silica gel column chromatography in 5-100% EtOAc in hexane. Rf = 0.31 (Hexane:EtOAc, 50:50).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ (ppm) = 8.28 (1H, d, *J* = 1.5 Hz, Ar**H**), 7.73 (1H, s, Ar**H**), 7.35 (1H, dd, *J* = 8.6, 1.8 Hz, Ar**H**), 7.17 (1H, d, *J* = 8.2 Hz, Ar**H**), 3.90 (3H, s, $CO_2C\mathbf{H_3}$), 3.78 (3H, s, $NC\mathbf{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$, 298 K): δ (ppm) = 165.0 ($\mathbf{C}O_2CH_3$), 135.9 ($\mathbf{C}H_{Ar}$), 129.4 ($\mathbf{C}_{Ar}$), 128.1 ($\mathbf{C}_{Ar}$), 125.8 ($\mathbf{C}H_{Ar}$), 124.3 ($\mathbf{C}H_{Ar}$), 115.6 ($\mathbf{C}_{Ar}$), 111.2 ($\mathbf{C}H_{Ar}$), 106.7 ($\mathbf{C}_{Ar}$), 51.1 ($CO_2\mathbf{C}H_3$), 33.6 ($N\mathbf{C}H_3$).

All spectroscopic data is consistent with the reported values.[7]

Methyl 5-cyano-1-methyl-1H-indole-3-carboxylate (3g)



3g, 75%
$C_{12}H_{10}N_2O_2$
214.22 g mol^{-1}

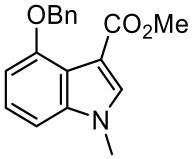
Methyl 5-cyano-1-methyl-1H-indole-3-carboxylate was obtained as a light pink solid at 75% (81 mg, 0.38 mmol) from 5-cyano-1H-indole (71 mg, 0.50 mmol) following **procedure 2**. Purification by silica gel column chromatography in 10-100% EtOAc in hexane. Rf = 0.26 (Hexane:EtOAc, 50:50).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ (ppm) = 8.52 (1H, d, *J* = 2.3 Hz, Ar**H**), 7.88 (1H, s, Ar**H**), 7.52 (1H, dd, *J* = 8.6, 1.6 Hz, Ar**H**), 7.41 (1H, dd, *J* = 8.6, 0.7 Hz, Ar**H**), 3.93 (3H, s, $CO_2C\mathbf{H_3}$), 3.88 (3H, s, $NC\mathbf{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$, 298 K): δ (ppm) = 164.5 ($\mathbf{C}O_2CH_3$), 138.6 ($\mathbf{C}_{Ar}$), 137.0 ($\mathbf{C}H_{Ar}$), 127.4 ($\mathbf{C}H_{Ar}$), 126.2 ($\mathbf{C}_{Ar}$), 125.8 ($\mathbf{C}H_{Ar}$), 120.2 ($C_{Ar}\mathbf{C}N$), 110.8 ($\mathbf{C}H_{Ar}$), 108.1 ($\mathbf{C}_{Ar}$), 105.3 ($\mathbf{C}_{Ar}$), 51.4 ($CO_2\mathbf{C}H_3$), 33.7 ($N\mathbf{C}H_3$).

HRMS (ESI+) m/z = $[C_{12}H_{11}N_2O_2]^+$; Calculated: 215.0815. Observed: 215.0810 [M + H]$^+$.

Methyl 4-(benzyloxy)-1-methyl-1H-indole-3-carboxylate (3h)



3h, 38%
$C_{18}H_{17}NO_3$
295.34 g mol^{-1}

Methyl 4-(benzyloxy)-1-methyl-1H-indole-3-carboxylate was obtained as a yellow oil at 38% (56 mg, 0.19 mmol) from 4-(benzyloxy)-1H-indole (112 mg, 0.50 mmol)

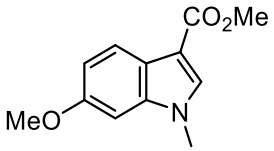
following **procedure 2**. Purification by silica gel column chromatography in 0-25% EtOAc in hexane. Rf = 0.16 (Hexane:EtOAc, 90:10).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ (ppm) = 7.74 (1H, s, Ar**H**), 7.64-7.53 (2H, m, Ar**H**), 7.43-7.36 (2H, m, 2 x Ar**H**), 7.34-7.28 (1H, m, Ar**H**), 7.20 (1H, t, *J* = 8.1 Hz, Ar**H**), 6.97 (1H, dd, *J* = 8.2, 0.7 Hz, Ar**H**), 6.78-6.73 (1H, m, Ar**H**), 5.25 (2H, s, OC**H$_2$**), 3.79 (3H, s, CO_2C**H$_3$**), 3.71 (3H, s, NC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$, 298 K): δ (ppm) = 165.1 (**C**O_2CH_3), 153.2 (**C**$_{Ar}$), 139.4 (**C**$_{Ar}$), 137.5 (**C**$_{Ar}$), 135.3 (**C**H$_{Ar}$), 128.3 (**C**H$_{Ar}$), 127.6 (**C**H$_{Ar}$), 127.5 (**C**H$_{Ar}$), 123.7 (**C**H$_{Ar}$), 116.1 (**C**$_{Ar}$), 107.6 (**C**$_{Ar}$), 104.5 (**C**H$_{Ar}$), 103.3 (**C**H$_{Ar}$), 70.7 (O**C**H$_2$), 51.1 (CO_2**C**H$_3$), 33.6 (N**C**H$_3$)

HRMS (ESI+) m/z = $[C_{18}H_{18}NO_3]^+$; Calculated: 296.1281. Observed: 296.1276 [M + H]$^+$. $C_{17}H_{14}NO_2$.

Methyl 6-methoxy-1-methyl-1H-indole-3-carboxylate (3i)



3i, 85%
$C_{12}H_{13}NO_3$
219.24 g mol^{-1}

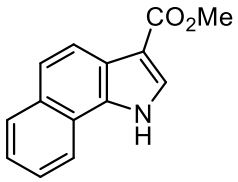
Methyl 6-methoxy-1-methyl-1H-indole-3-carboxylate was obtained as a beige solid at 85% (94 mg, 0.43 mmol) from 6-methoxy-1H-indole (74 mg, 0.50 mmol) following **procedure 2**. Purification by silica gel column chromatography in 25-100% EtOAc in hexane. Rf = 0.19 (Hexane:EtOAc, 75:25).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ (ppm) = 8.03 (1H, d, *J* = 8.8 Hz, Ar**H**), 7.67 (1H, s, Ar**H**), 6.93 (1H, dd, *J* = 8.7, 2.3 Hz, Ar**H**), 6.78 (1H, d, *J* = 2.1 Hz, Ar**H**), 3.89 (3H, s, CO_2C**H$_3$**), 3.89 (3H, s, OC**H$_3$**), 3.77 (3H, s, **N**CH_3).

^{13}C NMR (101 MHz, $CDCl_3$, 298 K): δ (ppm) = 165.5 (**C**O_2CH_3), 156.9 (**C**$_{Ar}$), 137.9 (**C**H$_{Ar}$), 134.2 (**C**$_{Ar}$), 122.3 (**C**H$_{Ar}$), 120.7 (**C**$_{Ar}$), 111.4 (**C**H$_{Ar}$), 106.9 (**C**$_{Ar}$), 93.3 (**C**H$_{Ar}$), 55.7 (CO_2**C**H$_3$), 50.9 (O**C**H$_3$), 33.4 (N**C**H$_3$).

HRMS (ESI+) m/z = $[C_{12}H_{14}NO_3]^+$; Calculated: 220.0968. Observed: 220.0967 [M + H]$^+$.

Methyl-1H-benzo[g]indole-3-carboxylate (3j):



3j, 85%
$C_{14}H_{11}NO_2$
225.25 g mol^{-1}

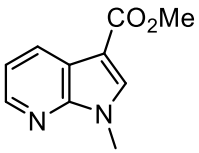
Methyl 1H-benzo*[g]*indole-3-carboxylate was obtained as a brown solid at 85% (97 mg, 0.43 mmol) from 1H-benzo[*g*]indole (84 mg, 0.50 mmol) and Ph_3CCO_2K (181 mg, 0.56 mmol) in DMF (2.5 mL, 0.2 M) following a modified **procedure 1**. Alkylation was conducted using MeI (0.25 mL, 4.00 mmol). Purification by silica gel column chromatography in 0-30% EtOAc in hexane. Rf = 0.24 (Hexane:EtOAc, 75:25).

^{1}H NMR (400 MHz, DMSO-d$_6$, 298 K): δ (ppm) = 12.82 (1H, br s, N**H**), 8.43 (1H, d, *J* = 8.3 Hz, Ar**H**), 8.21-8.07 (2H, m, Ar**H**), 7.98 (1H, d, *J* = 8.2 Hz, Ar**H**), 7.65 (1H, d, *J* = 8.8 Hz, Ar**H**), 7.63-7.55 (1H, m, Ar**H**), 7.52-7.45 (1H, m, Ar**H**), 3.85 (3H, s, $CO_2C\mathbf{H_3}$).

^{13}C NMR (101 MHz, DMSO-d$_6$, 298 K): δ (ppm) = 164.9 ($\mathbf{C}O_2CH_3$), 131.2 ($\mathbf{C}_{Ar}$), 130.0 ($\mathbf{C}_{Ar}$), 130.0 ($\mathbf{C}H_{Ar}$), 128.4 ($\mathbf{C}H_{Ar}$), 126.0 ($\mathbf{C}H_{Ar}$), 124.5 ($\mathbf{C}H_{Ar}$), 122.0 ($\mathbf{C}H_{Ar}$), 122.0 ($\mathbf{C}_{Ar}$), 121.9 ($\mathbf{C}H_{Ar}$), 120.7 ($\mathbf{C}H_{Ar}$), 120.1 ($\mathbf{C}_{Ar}$), 108.2 ($\mathbf{C}_{Ar}$), 50.8 ($CO_2\mathbf{C}H_3$).

All spectroscopic data is consistent with the reported values.[11]

Methyl 1-methyl-1H-pyrrolo[2,3-b]pyridine-3-carboxylate (3k)



3k, 70%
$C_{10}H_{10}N_2O_2$
160.20 g mol^{-1}

Methyl 1-methyl-1H-pyrrolo[2,3-*b*]pyridine-3-carboxylate was obtained as a white solid at 70% (56 mg, 0.35 mmol) from 7-azaindole (59 mg, 0.50 mmol) following a

modified **procedure 2**. Alkylation was conducted using MeI (0.13 mL, 2.00 mmol) Purification by silica gel column chromatography in 10-100% EtOAc in hexane. Rf = 0.41 (Hexane:EtOAc, 75:25).

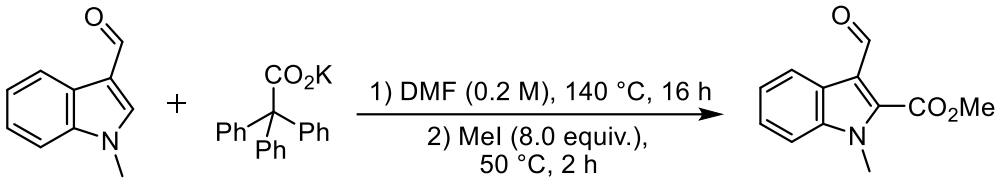
^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ (ppm) = 8.43-8.38 (2H, m, Ar**H**), 7.91 (1H, s, Ar**H**), 7.22 (1H, dd, *J* = 7.9, 4.8 Hz, Ar**H**), 3.93 (3H, s, $CO_2C\mathbf{H_3}$), 3.91 (3H, s, $NC\mathbf{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$, 298 K): δ (ppm) = 164.9 ($\mathbf{C}O_2CH_3$), 148.0 ($\mathbf{C}_{Ar}$), 144.1 ($\mathbf{C}H_{Ar}$), 135.0 ($\mathbf{C}H_{Ar}$), 129.9 ($\mathbf{C}H_{Ar}$), 119.0 ($\mathbf{C}_{Ar}$), 117.9 ($\mathbf{C}H_{Ar}$), 105.5 ($\mathbf{C}_{Ar}$), 51.2 ($CO_2\mathbf{C}H_3$), 31.8 ($N\mathbf{C}H_3$).

All spectroscopic data is consistent with the reported values.[12]

8. Experimental procedure for C2–H carboxylation of indole 7 and associated characterization data (8)

Methyl 3-formyl-1-methyl-1H-indole-2-carboxylate (8)



7
1.0 equiv.

4
1.1 equiv.

8, 70%
$C_{12}H_{11}NO_3$
217.22 g mol^{-1}

A Biotage® microwave vial, equipped with a magnetic stir bar and septum, was dried under vacuum via a heat gun. The vial was charged with 1-methyl-1H-indole-3-carbaldehyde (80 mg, 0.50 mmol) and Ph_3CCO_2K (180 mg, 0.55 mmol). The vial was purged through cycles of vacuum/N_2 gas. DMF (2.50 mL, 0.2 M) was then added, and the vial was firmly sealed using a Biotage® crimper and crimp cap under flow of N_2 gas. The reaction mixture was left to stir at 140 °C for 16 hours. After this time, the reaction was cooled and MeI (8.0 equiv.) was added. The reaction was then stirred at 50 °C for 2 hours. The reaction mixture was cooled to room temperature, quenched with sat. $NaHCO_3$ and extracted with Et_2O. The crude was purified using silica gel column chromatography in 0-60% Et_2O in hexane to obtain **methyl 3-formyl-1-methyl-1H-indole-2-carboxylate**, **8**, as an orange solid at 70% (76 mg, 0.35 mmol). Rf = 0.33 (Hexane:Et_2O, 50:50).

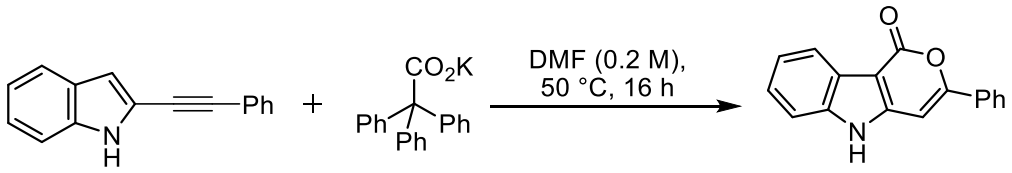
^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ (ppm) = 10.58 (1H, s, C(O)**H**), 8.51 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.47-7.41 (2H, m, Ar**H**), 7.39-7.33 (1H, m, Ar**H**), 4.08 (3H, s, $CO_2C\mathbf{H_3}$), 4.05 (3H, s, $NC\mathbf{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$, 298 K): δ (ppm) = 188.3 (**C**(O)H), 161.5 ($\mathbf{C}O_2CH_3$), 138.3 ($\mathbf{C}_{Ar}$), 133.2 ($\mathbf{C}_{Ar}$), 126.3 ($\mathbf{C}H_{Ar}$), 124.6 ($\mathbf{C}_{Ar}$), 124.1 ($\mathbf{C}H_{Ar}$), 123.8 ($\mathbf{C}H_{Ar}$), 120.0 ($\mathbf{C}_{Ar}$), 110.3 ($\mathbf{C}H_{Ar}$), 52.7 ($CO_2\mathbf{C}H_3$), 32.4 ($N\mathbf{C}H_3$).

All spectroscopic data is consistent with reported values.[13]

9. Experimental procedures for carboxylation of alkynyl indole and associated characterization data (10)

3-phenylpyrano[4,3-b]indol-1(5H)-one (10)



9
1.0 equiv.

4
1.1 equiv.

10, 67%
$C_{17}H_{11}NO_2$
261.28 g mol^{-1}

A Biotage® microwave vial, equipped with a magnetic stir bar and septum, was dried under vacuum via a heat gun. The vial was charged with 2-(phenylethynyl)-1H-indole (109 mg, 0.50 mmol) and Ph_3CCO_2K (180 mg, 0.55 mmol). The vial was purged through cycles of vacuum/N_2 gas. DMF (2.50 mL, 0.2 M) was then added, and the vial was firmly sealed using a Biotage® crimper and crimp cap under flow of N_2 gas. The reaction mixture was left to stir at 50 °C for 16 hours. After this time, the reaction was quenched with H_2O (10 mL) and extracted with Et_2O (3 x 10 mL). The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The crude was dissolved in hexane (20 mL), allowing the desired product to precipitate out. The mixture was filtered, and the residue was washed with hexane and Et_2O. Drying *in vacuo* then afforded **3-phenylpyrano[4,3-b]indol-1(5H)-one, 10,** at 67% (86 mg, 0.33 mmol).

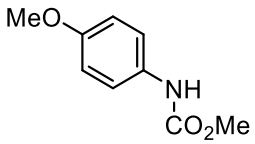
^{1}H NMR (400 MHz, DMSO-d_6, 298 K): δ (ppm) = 12.38 (1H, br s, N**H**), 8.02-7.94 (3H, m, Ar**H**), 7.61-7.49 (4H, m, Ar**H**), 7.45 (1H, s, Ar**H**), 7.41-7.27 (2H, m, Ar**H**).

^{13}C NMR (101 MHz, DMSO-d_6, 298 K): δ (ppm) = 158.8 (**C**O_2), 157.5 (**C**$_{Ar}$), 146.1 (**C**$_{Ar}$), 138.4 (**C**$_{Ar}$), 132.4 (**C**$_{Ar}$), 130.8 (**C**H$_{Ar}$), 129.6 (**C**H$_{Ar}$), 125.8 (**C**H$_{Ar}$), 125.0 (**C**H$_{Ar}$), 124.1 (**C**$_{Ar}$), 122.6 (**C**H$_{Ar}$), 120.3 (**C**H$_{Ar}$), 112.8 (**C**H$_{Ar}$), 99.7 (**C**$_{Ar}$), 94.2 (**C**H$_{Ar}$).

All spectroscopic data is consistent with reported values.[14]

10. Experimental procedures for N–H carboxylation of amines and associated characterization data (12a-h)

Methyl (4-methoxyphenyl) carbamate (12a)



12a, 85%
$C_9H_{11}NO_3$
181.07 g mol^{-1}

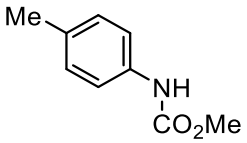
Methyl (4-methoxyphenyl) carbamate was obtained as a pale-yellow solid at 85% (154 mg, 0.85 mmol) from 4-methoxy aniline (123 mg, 1.00 mmol) following **procedure 4**. Purification by silica gel column chromatography in 0-100% CH_2Cl_2 in hexane. Rf = 0.49 (CH_2Cl_2).

^{1}H NMR (400 MHz, DMSO-d_6, 298 K): δ (ppm) = 9.40 (1H, *br* s, N**H**), 7.34 (2H, br d, *J* = 8.6 Hz, Ar**H**), 6.85 (2H, d, *J* = 8.9 Hz, Ar**H**), 3.70 (3H, s, $CO_2C\mathbf{H_3}$), 3.63 (3H, s, $OC\mathbf{H_3}$).

^{13}C NMR (101 MHz, DMSO-d_6, 298 K): δ (ppm) = 154.8 (**C**O_2Me), 154.1 (**C**$_{Ar}$), 132.2 (**C**$_{Ar}$), 119.8 (**C**H$_{Ar}$),113.9 (**C**H$_{Ar}$), 55.1 ($CO_2\mathbf{C}H_3$), 51.5 ($O\mathbf{C}H_3$).

All spectroscopic data is consistent with the reported values.[15]

Methyl (4-methylphenyl) carbamate (12b)



12b, 62%
$C_9H_{11}NO_2$
165.08 g mol^{-1}

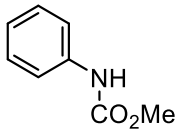
Methyl (4-methylphenyl) carbamate was obtained as a pale-yellow solid at 62% (51 mg, 0.31 mmol) from 4-methyl aniline (54 mg, 0.50 mmol) following **procedure 4** with a slight modification. Purification by silica gel column chromatography in 0-100% CH_2Cl_2 in Hexane. Rf = 0.50 (CH_2Cl_2).

^{1}H NMR (400 MHz, DMSO-d_6, 298 K): δ (ppm) = 9.49 (1H, *br* s, N**H**), 7.32 (2H, d, *J* = 8.3 Hz, Ar**H**), 7.06 (2H, d, *J* = 8.1 Hz, Ar**H**), 3.64 (3H, s, $CO_2C\mathbf{H_3}$), 2.22 (3H, s, $C\mathbf{H_3}$).

^{13}C NMR (101 MHz, DMSO-d_6, 298 K): δ (ppm) = 154.0 (**C**O_2Me), 136.6 (**C**$_{Ar}$), 131.2 (**C**H$_{Ar}$), 129.1 (**C**H$_{Ar}$), 118.2 (**C**$_{Ar}$), 51.5 ($CO_2\mathbf{C}H_3$), 20.3 (**C**H_3).

All spectroscopic data is consistent with that of previous reports.[15]

Methyl phenyl carbamate (12c)



12c, 69%
$C_8H_9NO_2$
151.06 g mol^{-1}

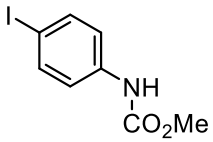
Methyl phenyl carbamate was obtained as a yellow oil at 69% (104 mg, 0.69 mmol), from aniline (93 mg, 1.00 mmol) following **procedure 4.** Purification by silica gel column chromatography in 0-50% CH_2Cl_2 in hexane. Rf = 0.29 (Hexane:CH_2Cl_2, 50:50).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ (ppm) = 7.40-7.35 (2H, m, Ar**H**), 7.34-7.28 (2H, m, Ar**H**), 7.12-7.02 (1H, m, Ar**H**), 6.61 (1H, *br* s, N**H**), 3.78 (3H, s, $CO_2C\mathbf{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$, 298 K): δ (ppm) = 154.0 (**C**O_2Me), 137.8 (**C**$_{Ar}$). 129.1 (**C**H$_{Ar}$), 123.5 (**C**H$_{Ar}$), 118.7 (**C**H$_{Ar}$), 52.3 ($CO_2\mathbf{C}H_3$).

All spectroscopic data is consistent with the reported values.[16]

Methyl (4-iodophenyl) carbamate (12d)



12d, 61%
$C_8H_8INO_2$
276.96 g mol^{-1}

Methyl (4-iodophenyl) carbamate was obtained as a yellow solid at 61% (169 mg, 0.61 mmol) from 4-iodo aniline (219 mg, 1.00 mmol) following **procedure 4**.

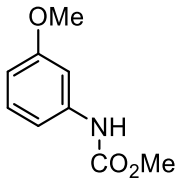
Purification by silica gel column chromatography in 0-100% CH_2Cl_2 in hexane. Rf = 0.41 (CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ (ppm) = 7.62-7.57 (2H, m, Ar**H**), 7.17 (2H, d, *J* = 8.7 Hz, Ar**H**), 6.65 (1H, *br* s, N**H**), 3.77 (3H, s, $CO_2C\mathbf{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$, 298 K): δ (ppm) = 153.8 (**C**O_2Me), 137.9 (**C**H_{Ar}), 137.7 (**C**$_{Ar}$), 120.5 (**C**H_{Ar}), 86.3 (**C**$_{Ar}$), 52.5 ($CO_2\mathbf{C}H_3$).

All spectroscopic data is consistent with the reported values.[17]

Methyl (3-methoxyphenyl) carbamate (12e)



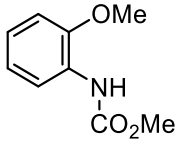
12e, 50%
$C_9H_{11}NO_3$
181.07 g mol^{-1}

Methyl (3-methoxyphenyl) carbamate was obtained as a yellow oil at 50% (91 mg, 0.50 mmol) from m-anisidine (123 mg, 1.00 mmol) following **procedure 4**. Purification by silica gel column chromatography in 10-100% CH_2Cl_2 in hexane. Rf = 0.24 (CH_2Cl_2). **^{1}H NMR (400 MHz, $CDCl_3$, 298 K):** δ (ppm) = 7.23-7.16 (1H, m, Ar**H**), 7.12 (1H, br s, Ar**H**), 6.89-6.82 (1H, m, Ar**H**), 6.69 (1H, br s, N**H**), 6.64-6.58 (1H, m, Ar**H**), 3.79 (3H, s, $CO_2C\mathbf{H_3}$), 3.77 (3H, s, $OC\mathbf{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$, 298 K): δ (ppm) = 160.3 (**C**O_2Me), 153.9 (**C**$_{Ar}$), 139.1 (**C**$_{Ar}$), 129.7 (**C**H_{Ar}), 110.9 (**C**H_{Ar}), 109.2 (**C**H_{Ar}), 104.4 (**C**H_{Ar}), 55.2 ($CO_2\mathbf{C}H_3$), 52.3 ($O\mathbf{C}H_3$).

All spectroscopic data is consistent with the reported values.[16]

Methyl (2-methoxyphenyl) carbamate (12f)



12f, 60%
$C_9H_{11}NO_3$
181.07 g mol^{-1}

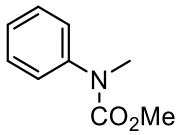
Methyl (2-methoxyphenyl) carbamate was obtained as a pale-yellow oil at 60% (109 mg, 0.60 mmol) from o-anisidine (123 mg, 1.00 mmol) following **procedure 4**. Purification by silica gel column chromatography in 0-50% Et_2O in hexane. Rf = 0.35 (Hexane:Et_2O, 80:20).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ (ppm) = 8.14-7.95 (1H, m, Ar**H**), 7.24 (1H, br s, N**H**), 7.02-6.94 (2H, m, Ar**H**), 6.84-6.79 (1H, m, Ar**H**), 3.81 (3H, s, $CO_2C\mathbf{H_3}$), 3.74 (3H, s, $OC\mathbf{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$, 298 K): δ (ppm) = 153.9 ($\mathbf{C}O_2Me$), 147.5 ($\mathbf{C}_{Ar}$), 127.5 ($\mathbf{C}_{Ar}$), 122.7 ($\mathbf{C}H_{Ar}$), 121.0 ($\mathbf{C}H_{Ar}$), 118.1 ($\mathbf{C}H_{Ar}$), 109.9 ($\mathbf{C}H_{Ar}$), 55.5 ($CO_2\mathbf{C}H_3$), 52.1 ($O\mathbf{C}H_3$).

All spectroscopic data is consistent with the reported values.[16]

Methyl methyl(phenyl) carbamate (12g)



12g: 83%
$C_9H_{11}NO_2$
165.08 g mol^{-1}

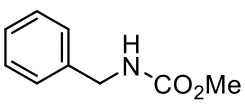
Methyl methyl(phenyl) carbamate was obtained as a yellow oil at 83% (137 mg, 0.83 mmol) from N-methylaniline (107 mg, 1.00 mmol) following **procedure 4**. Purification by silica gel column chromatography in 10-100% CH_2Cl_2 in hexane. Rf = 0.29 (CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ (ppm) = 7.40-7.30 (2H, m, Ar**H**), 7.25-7.19 (3H, m, Ar**H**), 3.71 (3H, s, $CO_2C\mathbf{H_3}$), 3.30 (3H, s, $NC\mathbf{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$, 298 K): δ (ppm) = 156.2 ($\mathbf{C}O_2Me$), 143.2 ($\mathbf{C}_{Ar}$), 128.9 ($\mathbf{C}H_{Ar}$), 126.2 ($\mathbf{C}H_{Ar}$), 125.8 ($\mathbf{C}H_{Ar}$), 52.9 ($CO_2\mathbf{C}H_3$), 37.8 ($N\mathbf{C}H_3$).

All spectroscopic data is consistent with the reported values.[18]

Methyl benzyl carbamate (12h)



12h, 45%
$C_9H_{11}NO_2$
165.08 g mol^{-1}

Methyl benzyl carbamate was obtained as a light-brown solid at 45% (74 mg, 0.45 mmol) from benzylamine (107 mg, 1.00 mmol) in DMF (20.0 mL, 0.05 M) following a modified **procedure 4**. Purification by silica gel column chromatography in 0-100% CH_2Cl_2 in hexane. Rf = 0.30 (CH_2Cl_2).

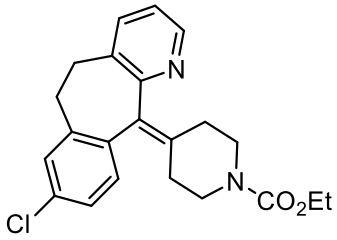
^{1}H NMR (400 MHz, DMSO-d$_6$, 298 K): δ (ppm) = 7.67 (1H, br s, N**H**), 7.34-7.29 (2H, m, Ar**H**), 7.26-7.20 (3H, m, Ar**H**), 4.18 (2H, d, *J* = 6.2 Hz, C**H**$_2$NH), 3.54 (3H, s, CO_2C**H**$_3$).

^{13}C NMR (101 MHz, DMSO-d$_6$, 298 K): δ (ppm) = 157.4 (**C**O_2Me), 140.3 (**C**$_{Ar}$), 128.7 (**C**H$_{Ar}$), 127.5 (**C**H$_{Ar}$), 127.2 (**C**H$_{Ar}$), 51.9 (CO_2**C**H$_3$), 44.3 (**C**H$_2$NH).

All spectroscopic data is consistent with the reported values.[15]

11. Experimental procedures for carboxylation of biologically relevant molecules and associated characterization data

Loratadine (14a)



14a, 50%
$C_{22}H_{23}ClN_2O_2$
382.14 g mol^{-1}

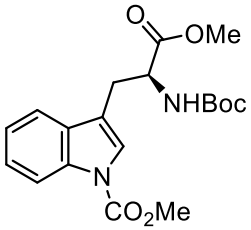
Loratadine was obtained as a white solid at 50% (191 mg, 0.50 mmol) from 8-chloro-11-(piperidin-4-ylidene)-6,11-dihydro-*5H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine (311 mg, 1.00 mmol) and Ph_3CCO_2K (359 mg, 1.10 mmol) in DMF (5.0 mL, 0.2 M) following a modified **procedure 4**. Alkylation was conducted using EtI (0.16 mL, 2.00 mmol). Purification by silica gel column chromatography in 25-100% EtOAc in hexane. Rf = 0.41 (EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ (ppm) = 8.40 (1H, dd, *J* = 4.8, 1.7 Hz, Ar**H**), 7.44 (1H, dd, *J* = 7.7, 1.7 Hz, Ar**H**), 7.17-7.08 (4H, m, Ar**H**), 4.13 (2H, q, *J* = 7.1 Hz, $CO_2C\mathbf{H_2}CH_3$), 3.81 (2H, *br* s, NC**H**H), 3.43-3.30 (2H, m, NCH**H**), 3.18-3.09 (2H, m, C**H**H), 2.89-2.76 (2H, m, CH**H**), 2.52-2.27 (4H, m, $C\mathbf{H_2}$), 1.25 (3H, t, *J* = 7.1 Hz, $CO_2CH_2C\mathbf{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$, 298 K): δ (ppm) = (1 x **C**H_{Ar} missing), 156.9 (**C**O_2Et), 155.5 (**C**$_{Ar}$), 146.5 (**C**H_{Ar}), 139.5 (R_2C=**C**), 137.6 ((C_{Ar})$_2$**C**=C), 134.0 (**C**$_{Ar}$), 133.4 (**C**$_{Ar}$), 132.9 (**C**$_{Ar}$), 130.5 (**C**H_{Ar}), 129.0 (**C**H_{Ar}), 126.2 (**C**H_{Ar}), 122.3 (**C**H_{Ar}), 61.3 ($CO_2\mathbf{C}H_2CH_3$), 44.8 (N**C**H_2), 31.7 ((C_{Ar})$_2$C=C(**C**H_2)), 31.4 ((C_{Ar})$_2$C=C(**C**H_2)), 30.7 (**C**H_2), 30.5 (**C**H_2), 14.7 ($CO_2CH_2\mathbf{C}H_3$).

All spectroscopic data is consistent with the reported values.[19]

Methyl (S)-3-(2-((boc)amino)-3-methoxy-3-oxopropyl)-1H-indole -1-carboxylate (14b)



14b, 79%
$C_{19}H_{24}N_2O_6$
376.16 g mol^{-1}

Methyl (S)-3-(2-((boc)amino)-3-methoxy-3-oxopropyl)-1H-indole-1-carboxylate was obtained as a white solid at 79% (297 mg, 0.79 mmol) from *N*-Boc-L-tryptophan methyl ester (318 mg, 1.00 mmol) following a modified **procedure 1**. Alkylation was conducted using MeI (0.13 mL, 2.00 mmol). Purification by silica gel column chromatography in 10-50% Et_2O in hexane. Rf = 0.20 (Hexane: Et_2O, 50:50).

^{1}H NMR (400 MHz, DMSO-d$_6$, 298 K): δ (ppm) = 8.08 (1H, d, *J* = 8.2 Hz, Ar**H**), 7.59 (1H, d, *J* = 7.7 Hz, N**H**Boc), 7.57-7.54 (1H, m, Ar**H**), 7.38-7.32 (2H, m, Ar**H**), 7.32-7.25 (1H, m, Ar**H**), 4.28 (1H, ddd, *J* = 9.8, 8.3, 4.8 Hz, C**H**), 3.98 (3H, s, $CO_2C\mathbf{H_3}$), 3.63 (3H, s, $CO_2C\mathbf{H_3}$), 3.17-3.08 (1H, m, C**H**H), 3.06-2.92(1H, m, CH**H**), 1.32 (9H, s, $OC(C\mathbf{H_3})_3$).

^{13}C NMR (101 MHz, DMSO-d$_6$, 298 K): δ (ppm) = 172.9 ($N\mathbf{C}O_2{}^t$Bu), 155.9 ($\mathbf{C}O_2$Me), 151.2 ($\mathbf{C}O_2$Me), 135.2 ($\mathbf{C}_{Ar}$), 130.5 ($\mathbf{C}_{Ar}$), 125.0 ($\mathbf{C}H_{Ar}$), 124.0 ($\mathbf{C}_{Ar}$), 123.3 ($\mathbf{C}H_{Ar}$), 119.5 ($\mathbf{C}H_{Ar}$), 117.5 ($\mathbf{C}H_{Ar}$), 115.1 ($\mathbf{C}H_{Ar}$), 78.8 ($\mathbf{C}$(NHBoc)H), 54.5 ($CO_2\mathbf{C}H_3$), 54.5 ($CO_2\mathbf{C}H_3$), 52.4 ($O\mathbf{C}(CH_3)_3$), 28.5 ($OC(\mathbf{C}H_3)_3$), 26.6 ($C\mathbf{H_2}$).

All spectroscopic data is consistent with the reported values.[20]

Retention of enantiomeric excess observed:

[α]$_D$ = 46.3 (589 nm, $CHCl_3$)

ee = 99%

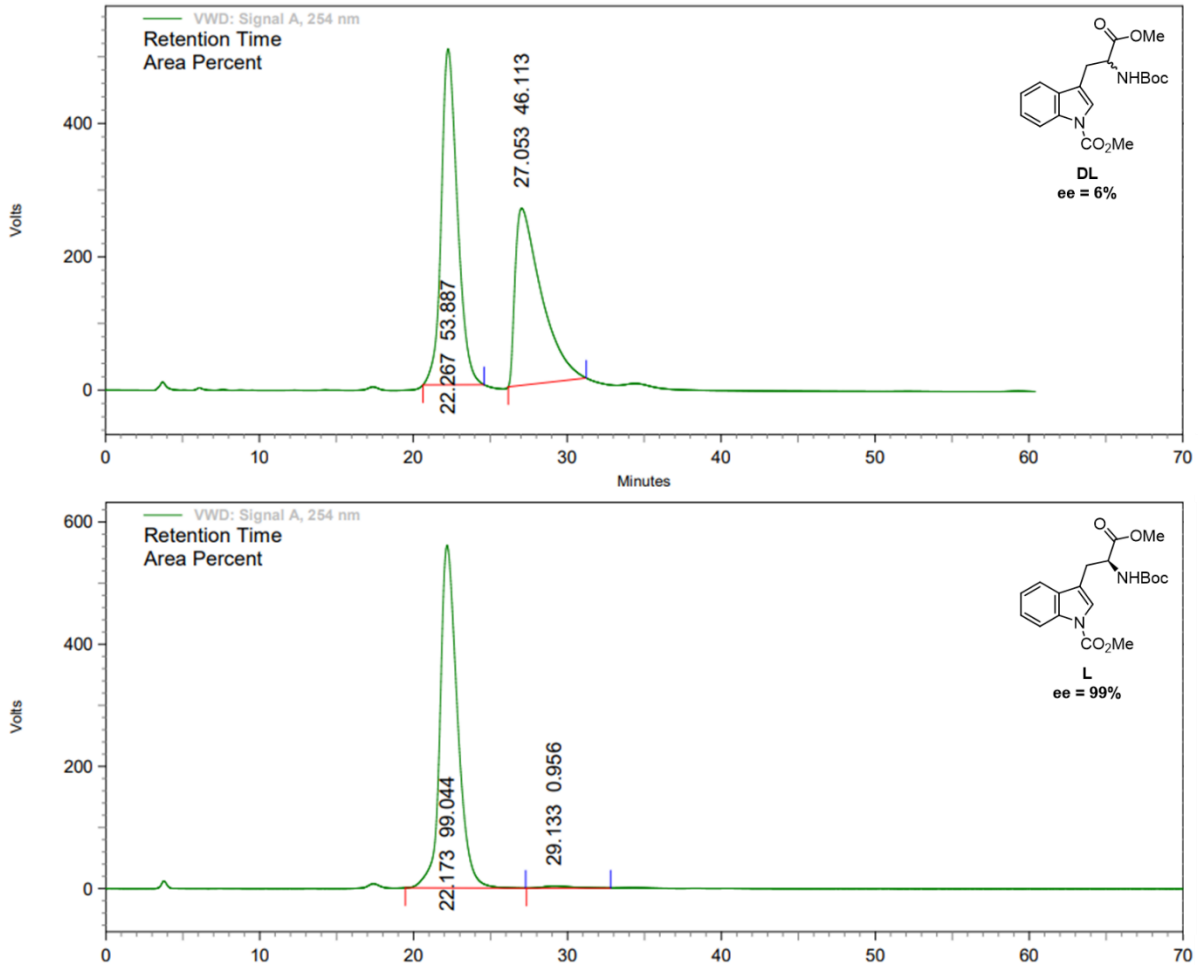
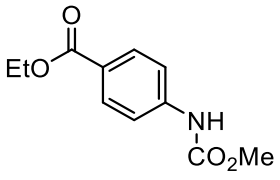


Figure 5: HPLC showing er for racemic methyl 3-(2-((boc)amino)-3-methoxy-3-oxopropyl)-1H-indole-1-carboxylate (top) and methyl (S)-3-(2-((boc)amino)-3-methoxy-3-oxopropyl)-1H-indole-1-carboxylate (bottom). *Column Conditions: OZ-H CHIRALCELL®, 5 µm, 4.6 mm ϕ x 250 mm (length) (Daicel corporation); 95:5 (hexane:isopropanol); 254 nm, 1 mL min^{-1}.*

Ethyl 4-((methoxycarbonyl)amino)benzoate (14c)



14c, 80%
$C_{11}H_{13}NO_4$
223.08 g mol^{-1}

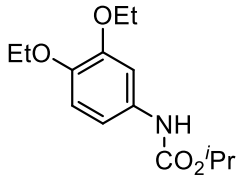
Ethyl 4-((methoxycarbonyl)amino)benzoate was obtained as a yellow solid at 80% (178 mg, 0.80 mmol) from benzocaine (165 mg, 1.00 mmol) following **procedure 4**. Purification by silica gel column chromatography in 0-25% EtOAc in hexane. Rf = 0.35 (Hexane:EtOAc, 75:25).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ (ppm) = 8.01-7.98 (2H, m, Ar**H**), 7.46 (2H, d, *J* = 8.8 Hz, Ar**H**), 6.96 (1H, br s, N**H**), 4.35 (2H, q, *J* = 7.2 Hz, $CO_2C\mathbf{H_2}CH_3$), 3.79 (3H, s, $CO_2C\mathbf{H_3}$), 1.38 (3H, t, *J* = 7.2 Hz, $CO_2CH_2C\mathbf{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$, 298 K): δ (ppm) = 166.2 ($\mathbf{C}O_2Et$), 153.6 ($\mathbf{C}O_2Me$), 142.1 ($\mathbf{C}_{Ar}$), 130.9 ($\mathbf{C}H_{Ar}$), 125.2 ($\mathbf{C}_{Ar}$), 117.5 ($\mathbf{C}H_{Ar}$), 60.8 ($CO_2\mathbf{C}H_2CH_3$), 52.6 ($CO_2\mathbf{C}H_3$), 14.4 ($CO_2CH_2\mathbf{C}H_3$).

All spectroscopic data is consistent with the reported values.[16]

Diethofencarb (14d):



14d, 93%
$C_{14}H_{21}NO_4$
267.33 g mol^{-1}

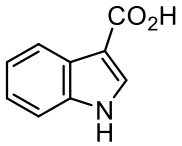
A 2.0-5.0 mL Biotage® microwave vial, equipped with a magnetic stir bar and septum, was dried under vacuum via a heat gun. The vial was charged with 3,4-diethoxy aniline (45 mg, 0.25 mmol), and Ph_3CCO_2K (163 mg, 0.50 mmol). The vial was purged through cycles of vacuum/N_2 gas. DMF (1.25 mL, 0.2 M) was then added, and the vial was firmly sealed using a Biotage® crimper and crimp cap under flow of N_2 gas. The reaction mixture was left to stir at 50 °C for 4 hours. After this time, 2-bromopropane (0.09 mL, 1.00 mmol) was added and the reaction continued to stir at 40 °C for 16 hours. The reaction mixture was cooled to room temperature, quenched with sat. $NaHCO_3$ (10 mL) and extracted with Et_2O (3 x 10 mL). The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified using silica gel column chromatography in 0-50% EtOAc in hexane to obtain the desired **diethofencarb, 14d,** as a pink solid at 93% (61 mg, 0.23 mmol). Rf = 0.57 (Hexane:EtOAc, 75:25).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ (ppm) = 7.17 (1H, br s, Ar**H**), 6.82-6.78 (1H, m, Ar**H**), 6.73-6.68 (1H, m, Ar**H**), 6.45 (1H, br s, N**H**), 4.99 (1H, spt. *J* = 6.3 Hz, $CO_2C\mathbf{H}(CH_3)_2$), 4.12-4.01 (4H, m, $OC\mathbf{H_2}CH_3$), 1.43 (3H, t, *J* = 7.0 Hz, $OCH_2C\mathbf{H_3}$), 1.41 (3H, t, *J* = 7.0 Hz, $OCH_2C\mathbf{H_3}$), 1.28 (6H, d, *J* = 6.3 Hz, $CO_2CH(C\mathbf{H_3})_2$).

^{13}C NMR (101 MHz, $CDCl_3$, 298 K): δ (ppm) = 153.4 ($\mathbf{C}O_2{}^iPr$), 149.1 ($\mathbf{C}_{Ar}$), 144.6 ($\mathbf{C}_{Ar}$), 131.9 ($\mathbf{C}_{Ar}$), 114.4 ($\mathbf{C}H_{Ar}$), 110.5 ($\mathbf{C}H_{Ar}$), 105.5 ($\mathbf{C}H_{Ar}$), 68.1 ($CO_2\mathbf{C}H(CH_3)_2$), 65.1 ($O\mathbf{C}H_2CH_3$), 64.4 ($O\mathbf{C}H_2CH_3$), 22.1 ($CO_2CH(\mathbf{C}H_3)_2$), 14.9 ($OCH_2\mathbf{C}H_3$), 14.7 ($OCH_2\mathbf{C}H_3$).

All spectroscopic data is consistent with the reported values.[21]

Indole-3-carboxylic acid (15)



15, 73%
$C_9H_7NO_2$
161.16 g mol^{-1}

Indole-3-carboxyllic acid was obtained as a pale pink solid at 73% (61 mg, 0.38 mmol) from indole (59 mg, 0.50 mmol) following **procedure 3**.

^{1}H NMR (400 MHz, DMSO-d_6, 298 K): δ (ppm) = 11.80 (1H, br s, N**H**), 8.03-7.97 (2H, m, Ar**H**), 7.48-7.43 (1H, m, Ar**H**), 7.20-7.11 (2H, m, Ar**H**).

^{13}C NMR (101 MHz, DMSO-d_6, 298 K): δ (ppm) = 166.4 ($\mathbf{C}O_2H$), 136.9 ($\mathbf{C}_{Ar}$), 132.7 ($\mathbf{C}H_{Ar}$), 126.5 ($\mathbf{C}_{Ar}$), 122.6 ($\mathbf{C}H_{Ar}$), 121.4 ($\mathbf{C}H_{Ar}$), 121.0 ($\mathbf{C}H_{Ar}$), 112.6 ($\mathbf{C}H_{Ar}$), 107.9 ($\mathbf{C}_{Ar}$).

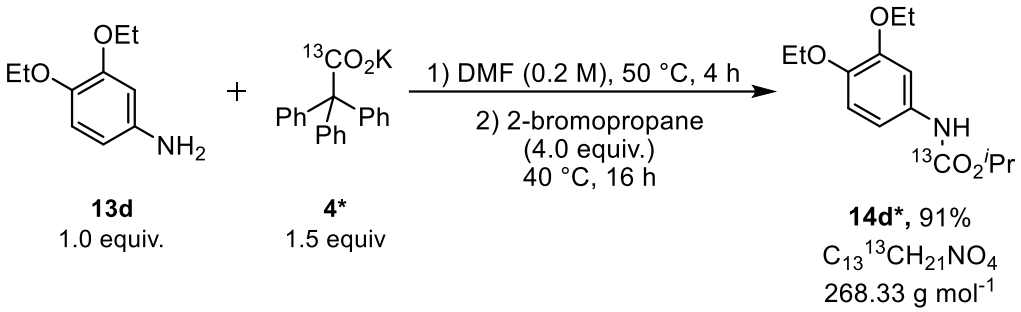
All spectroscopic data is consistent with reported values.[3]

12. Experimental procedures for ^{13}C labelled carboxylation and associated characterization data

The experimental procedures and characterization data in this section relate to the isotope labelling studies that were performed in this study. Both the non-labelled and labelled compounds were prepared in all cases for completeness. The ^{13}C incorporation was determined by quantitative ^{13}C NMR or by the comparison of mass spectral patterns through the following method:

- Relative abundance of ^{13}C = number of carbons × 0.011
- Observed abundance of ^{12}C is obtained from the mass signal intensities at M (m/z)
- Observed abundance of ^{13}C is obtained from the mass signal intensities at M+1 (m/z).
- Corrected abundance of ^{13}C = Observed abundance of ^{13}C – (Observed abundance of ^{12}C × Relative abundance of ^{13}C)
- %^{13}C incorporation = Corrected abundance of ^{13}C / (Corrected abundance of ^{13}C + Observed abundance of ^{12}C).

Diethofencarb (14d*):



13d
1.0 equiv.

4*
1.5 equiv

14d*, 91%
$C_{13}{}^{13}CH_{21}NO_4$
268.33 g mol^{-1}

A 2.0-5.0 mL Biotage® microwave vial, equipped with a magnetic stir bar and septum, was dried under vacuum via a heat gun. The vial was charged with 3,4-diethoxy aniline (45 mg, 0.25 mmol), and $Ph_3C^{13}CO_2K$ (124 mg, 0.38 mmol). The vial was purged through cycles of vacuum/N_2 gas. DMF (1.25 mL, 0.2 M) was then added, and the vial was firmly sealed using a Biotage® crimper and crimp cap under flow of N_2 gas. The reaction mixture was left to stir at 50 °C for 4 hours. After this time, 2-bromopropane (0.09 mL, 1.00 mmol) was added and the reaction continued to stir at 40 °C for 16 hours. The reaction mixture was cooled to room temperature, quenched with sat.

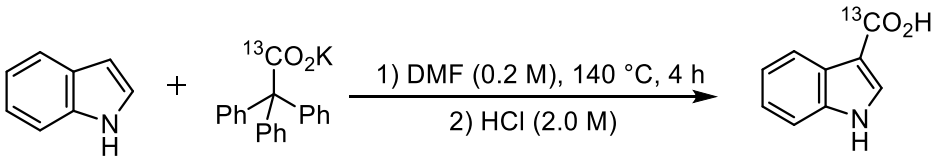
$NaHCO_3$ (10 mL) and extracted with Et_2O (3 x 10 mL). The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The crude was purified using silica gel column chromatography in 0-50% EtOAc in hexane to obtained the desired, ^{13}C labelled **diethofencarb** as a pink solid at 91% (62 mg, 0.23 mmol). Rf = 0.57 (Hexane:EtOAc, 75:25).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ (ppm) = 7.17 (1H, br s, Ar**H**), 6.82-6.78 (1H, m, Ar**H**), 6.73-6.68 (1H, m, Ar**H**), 6.45 (1H, br s, N**H**), 4.99 (1H, spt. *J* = 6.3 Hz, $^{13}CO_2C\mathbf{H}(CH_3)_2$), 4.12-4.01 (4H, app. m, $OC\mathbf{H_2}CH_3$), 1.43 (3H, t, *J* = 7.0 Hz, $OCH_2C\mathbf{H_3}$), 1.41 (3H, t, *J* = 7.0 Hz, $OCH_2C\mathbf{H_3}$), 1.28 (6H, d, *J* = 6.3 Hz, $^{13}CO_2CH(C\mathbf{H_3})_2$).

^{13}C NMR (101 MHz, $CDCl_3$, 298 K): δ (ppm) = 153.5 ($^{13}\mathbf{C}O_2{}^{i}Pr$), 149.2 ($\mathbf{C}_{Ar}$), 144.7 ($\mathbf{C}_{Ar}$), 131.9 ($\mathbf{C}_{Ar}$), 114.4 ($\mathbf{C}H_{Ar}$), 110.7 ($\mathbf{C}H_{Ar}$), 105.6 ($\mathbf{C}H_{Ar}$), 68.6 ($^{13}CO_2\mathbf{C}H(CH_3)_2$), 65.1 ($O\mathbf{C}H_2CH_3$), 64.5 ($O\mathbf{C}H_2CH_3$), 22.1 ($^{13}CO_2CH(\mathbf{C}H_3)_2$), 14.8 ($OCH_2\mathbf{C}H_3$), 14.7 ($OCH_2\mathbf{C}H_3$).

% ^{13}C incorporation: Found to be 97% by quantitative mass spectrometry.

Indole-3-carboxyllic acid (15*)



1c
1.0 equiv.

4*
2.0 equiv

15*, 70%
$C_9H_7NO_2$
162.16 g mol^{-1}

A Biotage® microwave vial, equipped with a magnetic stir bar and septum, was dried under vacuum via a heat gun. The vial was charged with indole (29 mg, 0.25 mmol) and $Ph_3C^{13}CO_2K$ (163 mg, 0.50 mmol). The vial was purged through cycles of vacuum/N_2 gas. DMF (1.25 mL, 0.2 M) was then added, and the vial was firmly sealed using a Biotage® crimper and crimp cap under flow of N_2 gas. The reaction mixture was left to stir at 140 °C for 4 hours. After this time, the reaction was cooled to room temperature and hexane (5 mL) was added with rapid stirring. The reaction was filtered and washed with hexane (3 x 5 mL) and Et_2O (2.5 mL). The resulting salt was dried under vacuum overnight at 40°C. The product was dissolved in H_2O (10 mL) and acidified to pH 1 with aqueous HCl (2.0 M). The organic phase was extracted with

EtOAc (3 x 10 mL), washed with H_2O (10 mL) and brine (10 mL), and dried over Na_2SO_4. Concentration and drying *in vacuo* then afforded the desired, labelled carboxylic acid **15*** at 70% (29 mg, 0.18 mmol).

^{1}H NMR (400 MHz, DMSO-d$_6$, 298 K): δ (ppm) = 11.80 (1H, br s, N**H**), 8.03-7.96 (2H, m, Ar**H**), 7.50-7.41 (1H, m, Ar**H**), 7.22-7.11 (2H, m, Ar**H**).

^{13}C NMR (101 MHz, DMSO-d$_6$, 298 K): δ (ppm) = 165.9 (^{13}**C**O$_2$H), 136.4 (d, *J* = 4.4 Hz, **C**$_{Ar}$), 132.3 (d, *J* = 5.9 Hz, **C**H$_{Ar}$), 126.0 (d, *J* = 4.4 Hz, **C**$_{Ar}$), 122.1 (**C**H$_{Ar}$), 121.0 (**C**H$_{Ar}$), 120.6 (**C**H$_{Ar}$), 112.2 (**C**H$_{Ar}$), 107.4 (d, *J* = 83.6 Hz, **C**$_{Ar}$).

% ^{13}C incorporation: Found to be 96% by quantitative ^{13}C NMR.

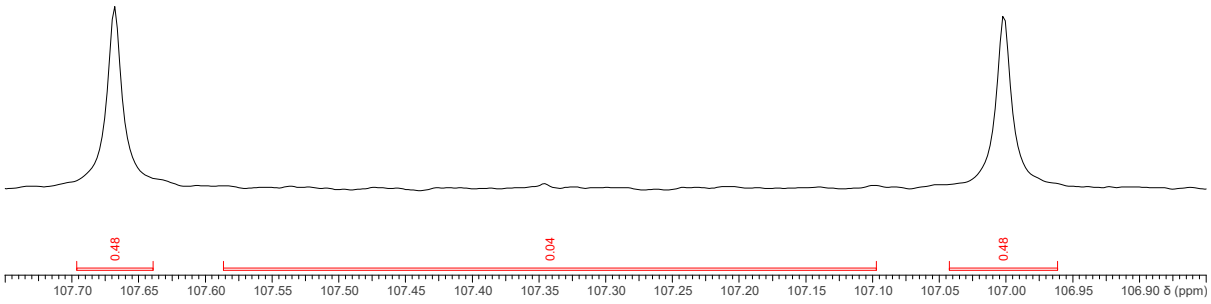


Figure 6: ^{13}C incorporation for **15***

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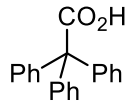
^{1}H NMR (400 MHz, DMSO-d_6, 298 K):

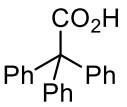
Triphenyl acetic acid



4'

^{13}C NMR (101 MHz, DMSO-d_6, 298 K):

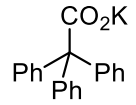
Triphenyl acetic acid



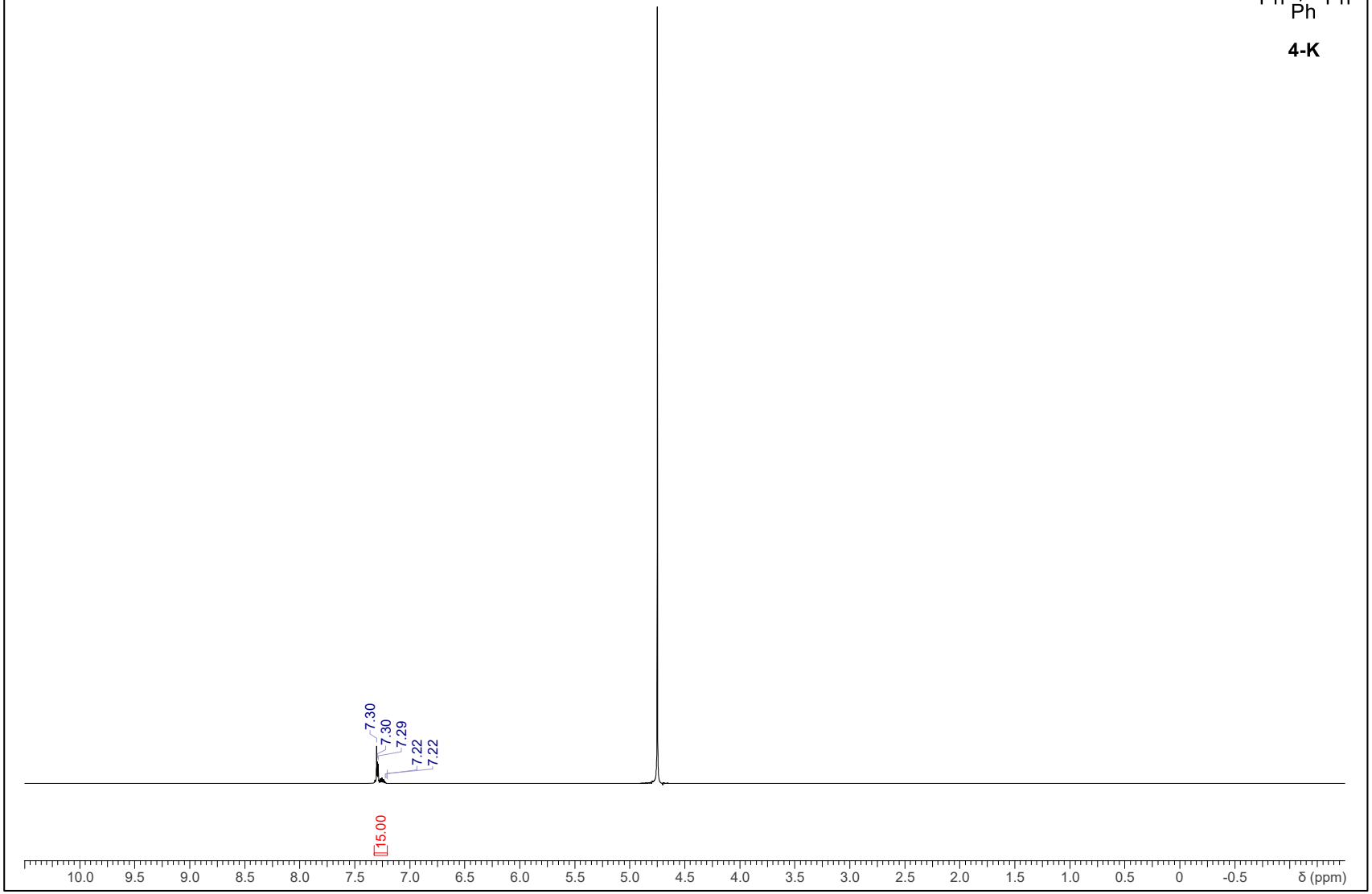
4'

^{1}H NMR (400 MHz, D_2O, 298 K):

Potassium triphenyl acetate

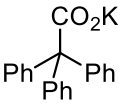


4-K



^{13}C NMR (101 MHz, D_2O, 298 K):

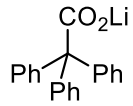
Potassium triphenyl acetate



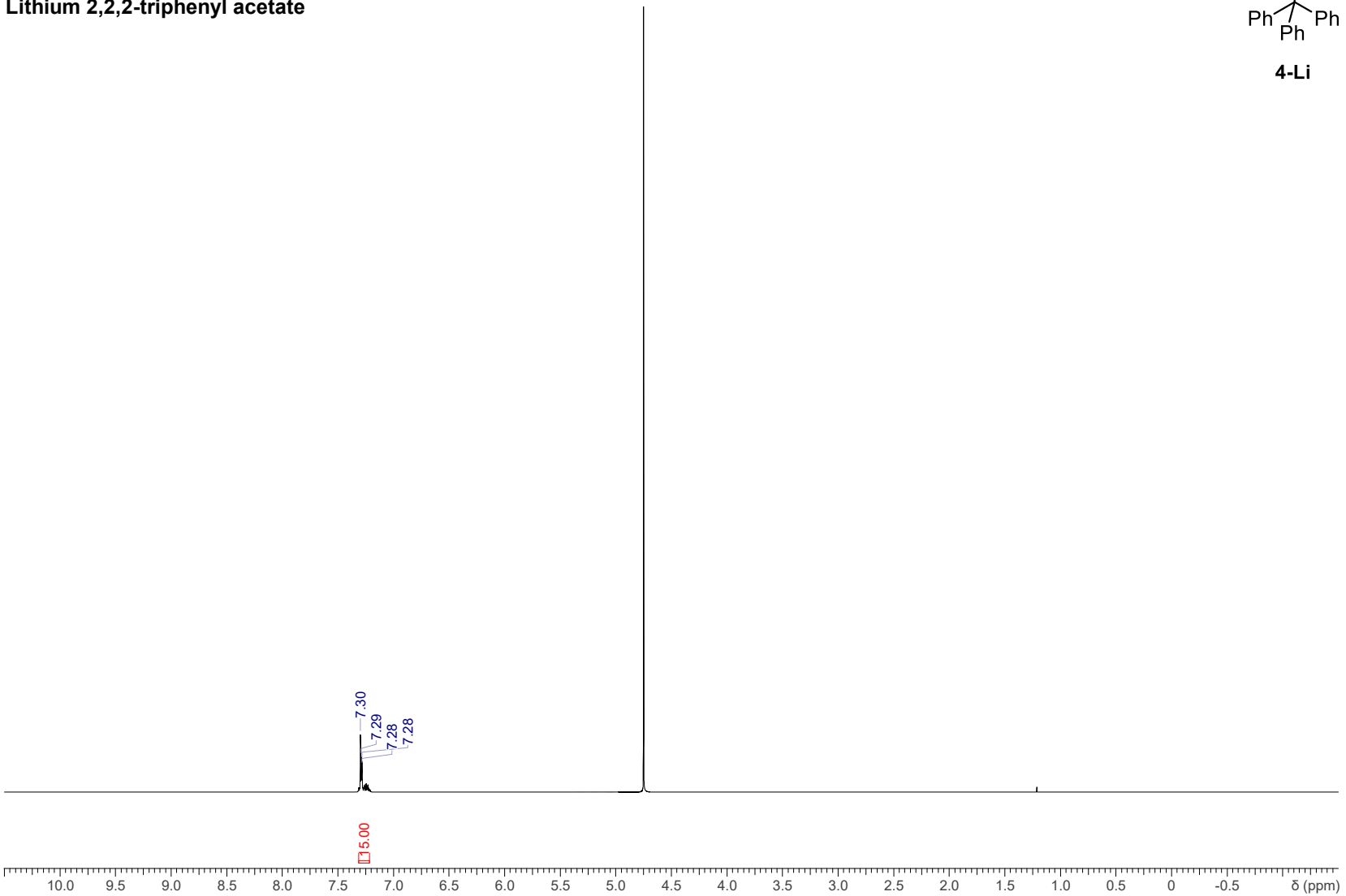
4-K

^{1}H NMR (400 MHz, D_2O, 298 K):

Lithium 2,2,2-triphenyl acetate

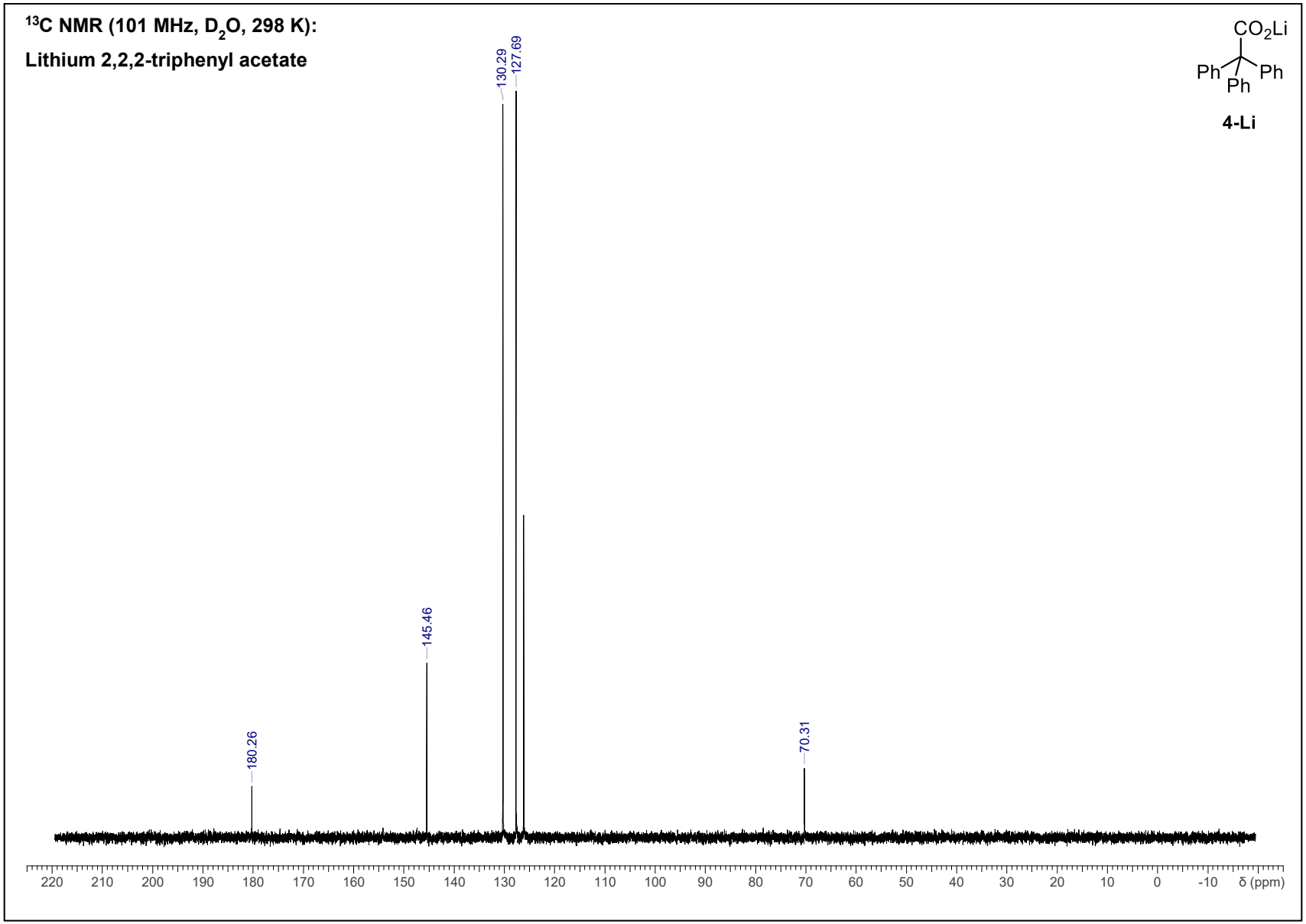


4-Li



^{13}C NMR (101 MHz, D_2O, 298 K):

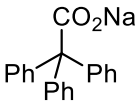
Lithium 2,2,2-triphenyl acetate



4-Li

^{1}H NMR (400 MHz, D_2O, 298 K):

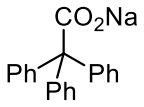
Sodium 2,2,2-triphenyl acetate



4-Na

^{13}C NMR (101 MHz, D_2O, 298 K):

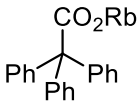
Sodium 2,2,2-triphenyl acetate



4-Na

^{1}H NMR (400 MHz, D_2O, 298 K):

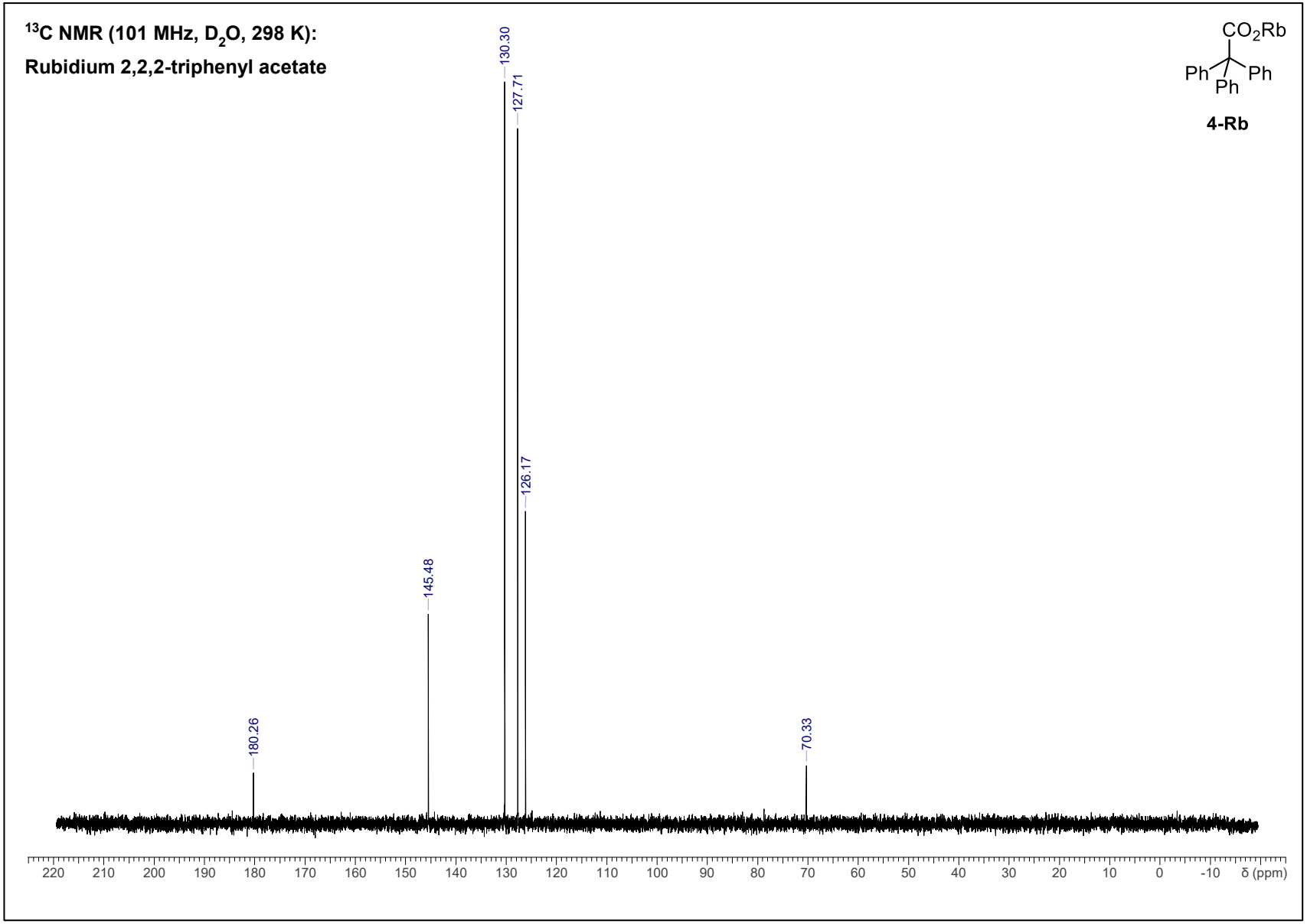
Rubidium 2,2,2-triphenyl acetate



4-Rb

^{13}C NMR (101 MHz, D_2O, 298 K):

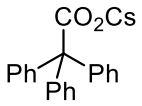
Rubidium 2,2,2-triphenyl acetate



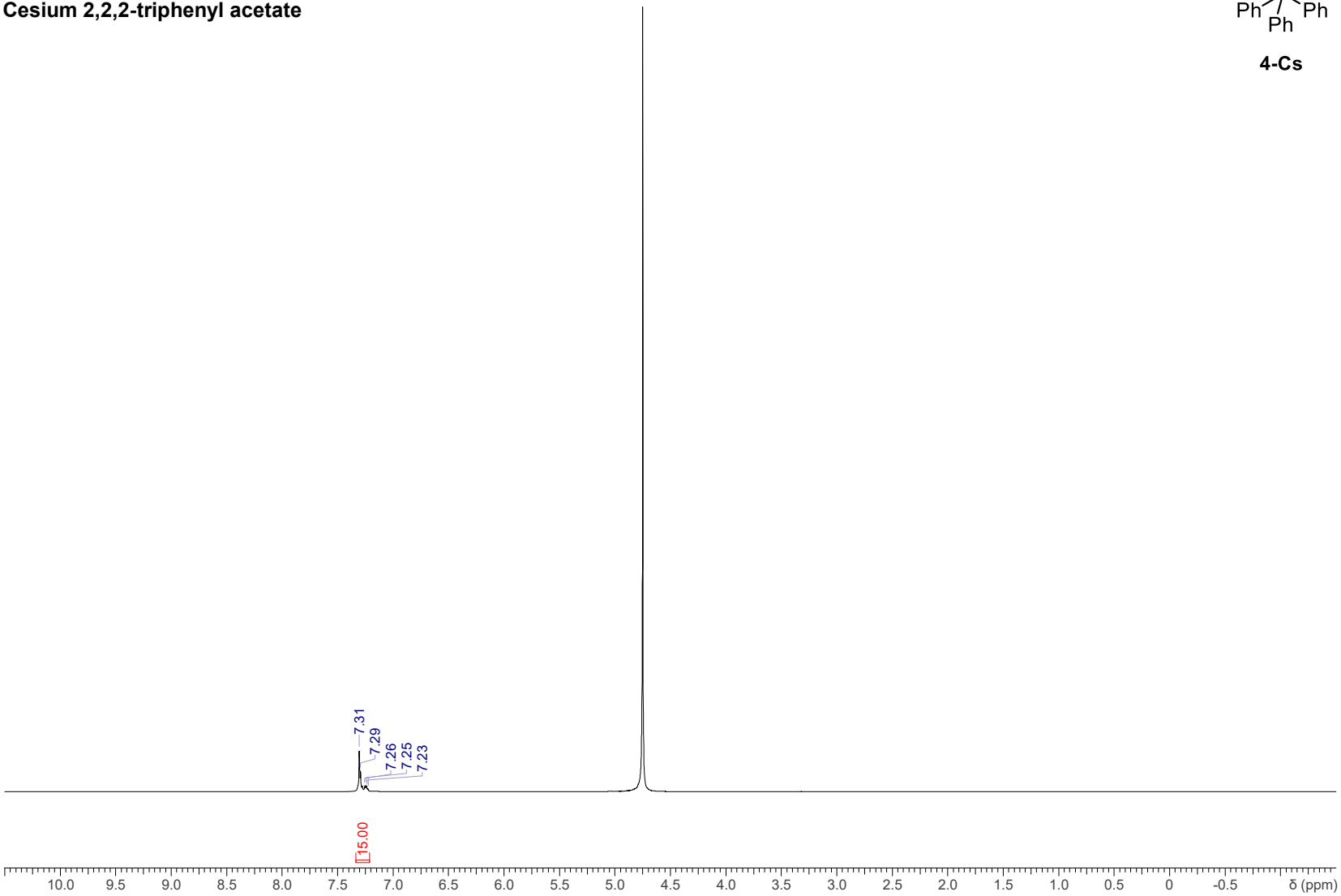
4-Rb

^{1}H NMR (400 MHz, D_2O, 298 K):

Cesium 2,2,2-triphenyl acetate

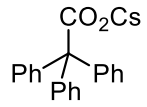


4-Cs



^{13}C NMR (101 MHz, D_2O, 298 K):

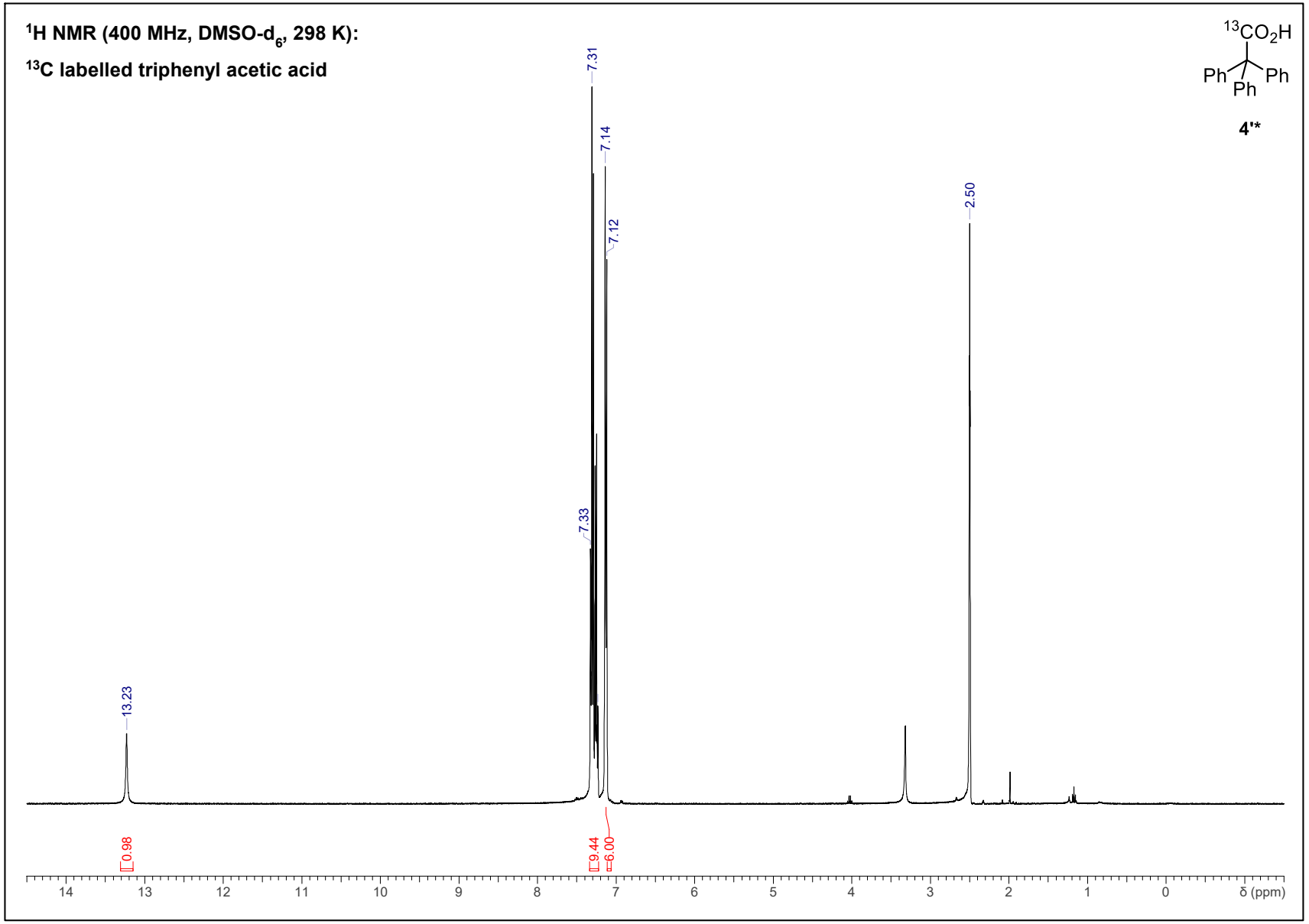
Cesium 2,2,2-triphenyl acetate



4-Cs

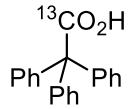
^{1}H NMR (400 MHz, DMSO-d$_6$, 298 K):

^{13}C labelled triphenyl acetic acid



^{13}C NMR (101 MHz, DMSO-d_6, 298 K):

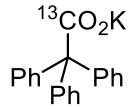
^{13}C labelled triphenyl acetic acid



4'*

^{1}H NMR (400 MHz, D_2O, 298 K):

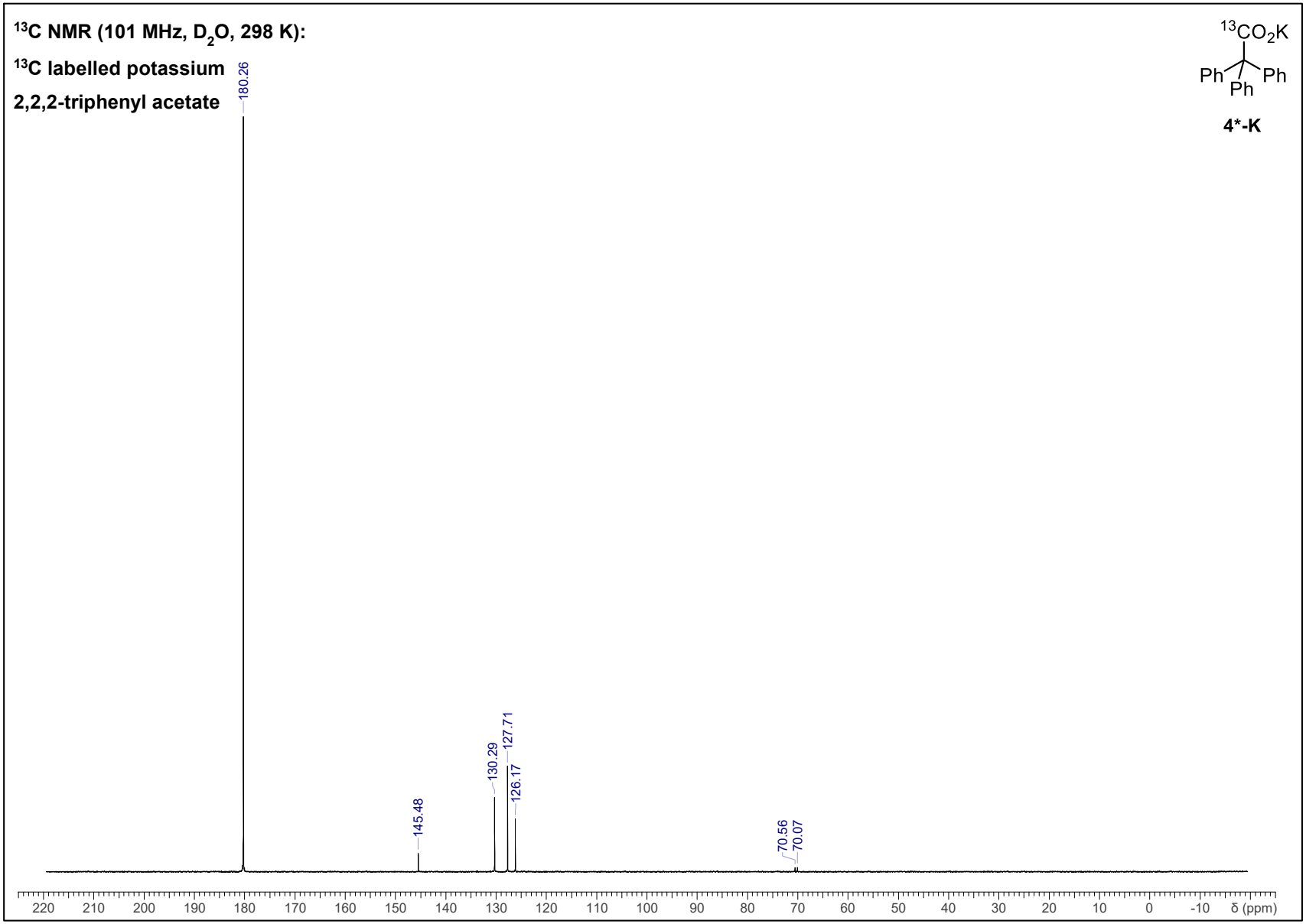
^{13}C labelled potassium 2,2,2-triphenyl acetate



4*-K

^{13}C NMR (101 MHz, D_2O, 298 K):

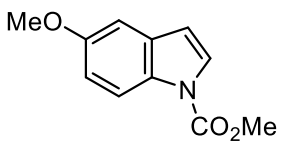
^{13}C labelled potassium 2,2,2-triphenyl acetate



4*-K

^{1}H NMR (400 MHz, $CDCl_3$, 298 K):

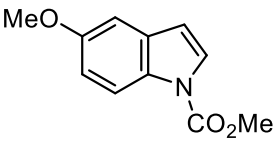
Methyl 5-methoxy-1H-indole-1-carboxylate



2a

^{13}C NMR (101 MHz, $CDCl_3$, 298 K):

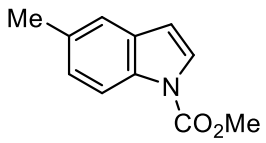
Methyl 5-methoxy-1H-indole-1-carboxylate



2a

^{1}H NMR (400 MHz, DMSO-d_6, 298 K):

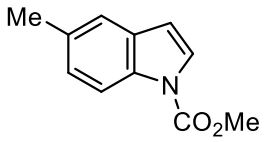
Methyl 5-methyl-1H-indole-1-carboxylate



2b

^{13}C NMR (101 MHz, DMSO-d_6, 298 K):

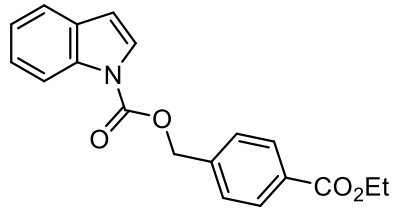
Methyl 5-methyl-1H-indole-1-carboxylate



2b

^{1}H NMR (400 MHz, DMSO-d_6, 298 K):

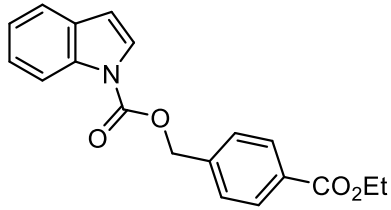
4-(ethoxycarbonyl)benzyl-1H-indole-1-carboxylate



2c

^{13}C NMR (101 MHz, DMSO-d_6, 298 K):

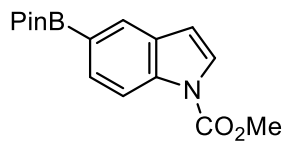
4-(ethoxycarbonyl)benzyl-1H-indole-1-carboxylate



2c

^{1}H NMR (400 MHz, $CDCl_3$, 298 K):

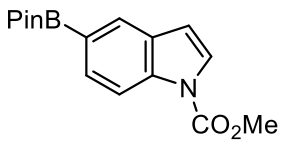
Methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaboronlan-2-yl)-1H-indole -1-carboxylate



2d

^{13}C NMR (101 MHz, $CDCl_3$, 298 K):

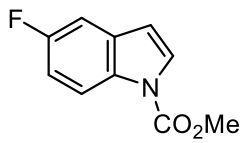
Methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole -1-carboxylate



2d

^{1}H NMR (400 MHz, $CDCl_3$, 298 K):

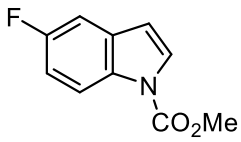
Methyl-5-fluoro-1H-indole-1-carboxylate



2e

^{13}C NMR (101 MHz, $CDCl_3$, 298 K):

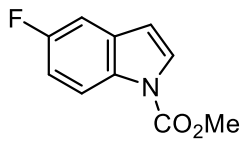
Methyl 5-fluoro-1H-indole-1-carboxylate



2e

^{19}F NMR (400 MHz, $CDCl_3$, 298 K):

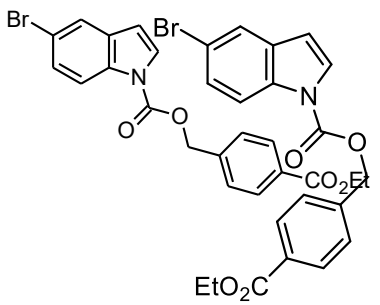
Methyl-5-fluoro-1H-indole-1-carboxylate



2e

^{1}H NMR (400 MHz, $CDCl_3$, 298 K):

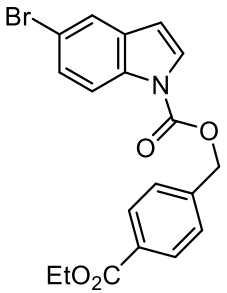
4-(ethoxycarbonyl)benzyl-5-bromo-1H-indole-1-carboxylate



2f

^{13}C NMR (101 MHz, $CDCl_3$, 298 K):

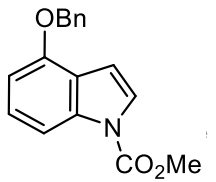
4-(ethoxycarbonyl)benzyl-5-bromo-1H-indole-1-carboxylate



2f

^{1}H NMR (400 MHz, DMSO-d_6, 298 K):

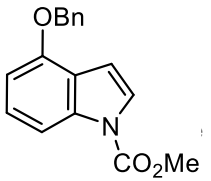
Methyl 4-(benzyloxy)-1H-indole-1-carboxylate



2h

^{13}C NMR (101 MHz, DMSO-d_6, 298 K):

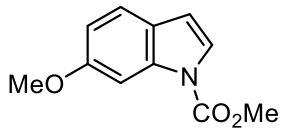
Methyl 4-(benzyloxy)-1H-indole-1-carboxylate



2h

^{1}H NMR (400 MHz, $CDCl_3$, 298 K):

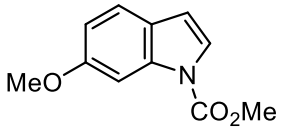
Methyl-6-methoxy-1H-indole-1-carboxylate



2i

^{13}C NMR (101 MHz, $CDCl_3$, 298 K):

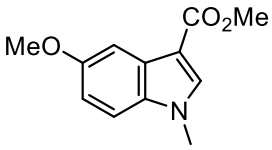
Methyl-6-methoxy-1H-indole-1-carboxylate



2i

^{1}H NMR (400 MHz, $CDCl_3$, 298 K):

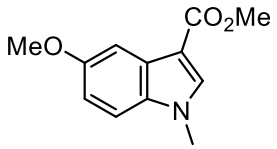
Methyl 5-methoxy-1-methyl-1H-indole-3-carboxylate



3a

^{13}C NMR (101 MHz, $CDCl_3$, 298 K):

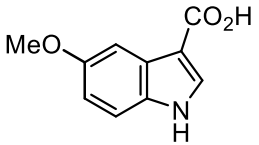
Methyl 5-methoxy-1-methyl-1H-indole-3-carboxylate



3a

^{1}H NMR (400 MHz, $CDCl_3$, 298 K):

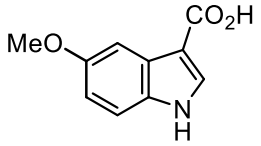
5-methoxy-1H-indole-3-carboxylic acid



3a'

^{13}C NMR (101 MHz, $CDCl_3$, 298 K):

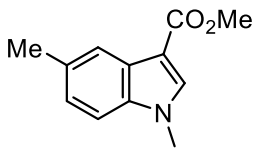
5-methoxy-1H-indole-3-carboxylic acid



3a'

^{1}H NMR (400 MHz, $CDCl_3$, 298 K):

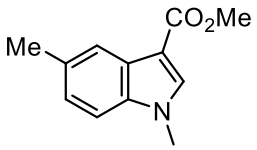
Methyl 5-methyl-1H-indole-3-carboxylate



3b

^{13}C NMR (101 MHz, $CDCl_3$, 298 K):

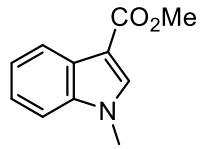
Methyl 5-methyl-1H-indole-3-carboxylate



3b

^{1}H NMR (400 MHz, DMSO-d_6, 298 K):

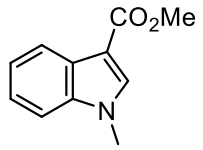
Methyl 1-methyl-1H-indole-3-carboxylate



3c

^{1}H NMR (400 MHz, DMSO-d_6, 298 K):

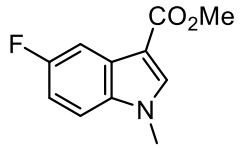
Methyl 1-methyl-1H-indole-3-carboxylate



3c

^{1}H NMR (400 MHz, DMSO-d_6, 298 K):

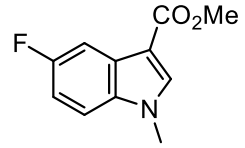
Methyl 5-fluoro-1-methyl-1H-indole-3-carboxylate



3e

^{13}C NMR (101 MHz, DMSO-d_6, 298 K):

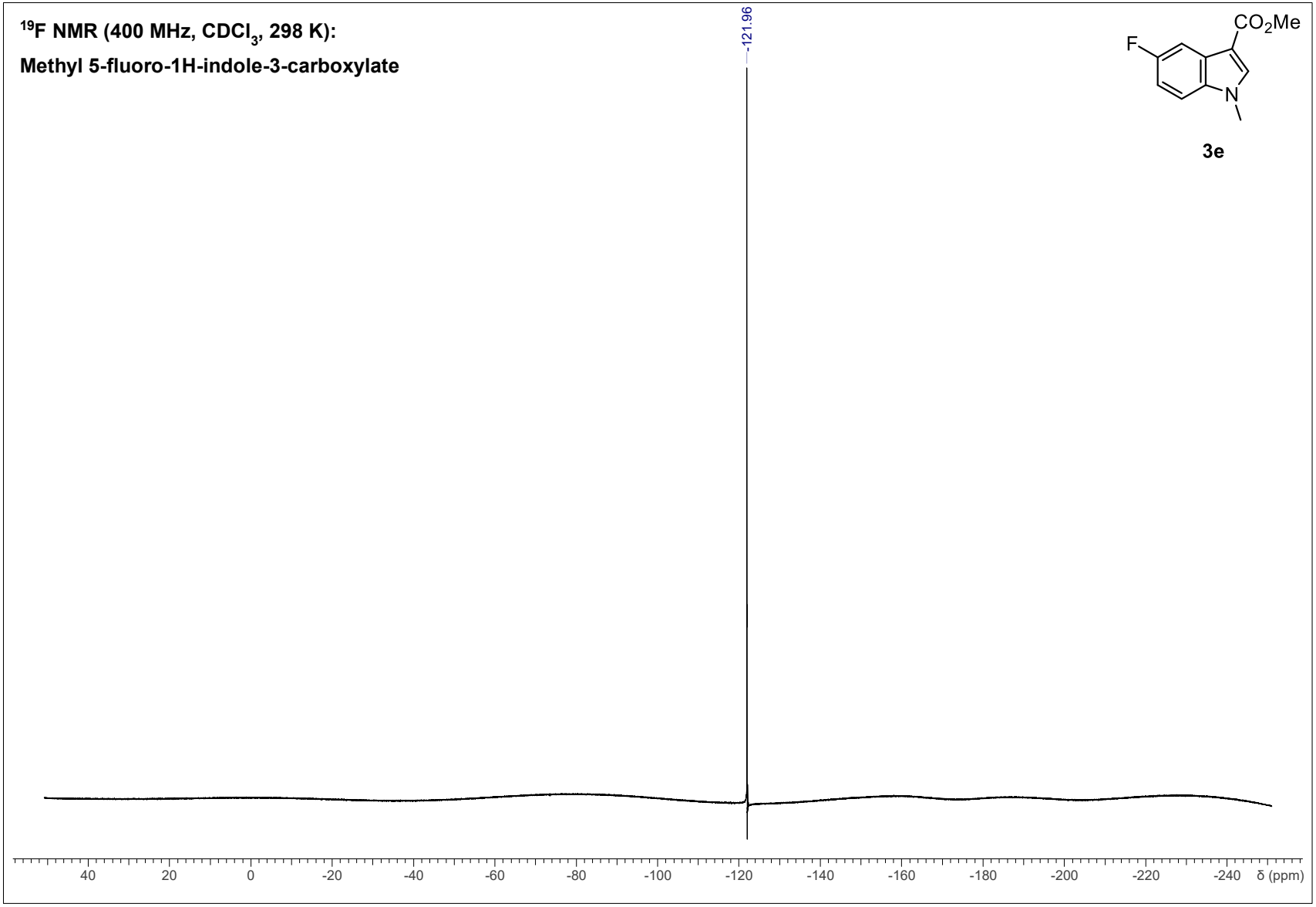
Methyl 5-fluoro-1-methyl-1H-indole-3-carboxylate



3e

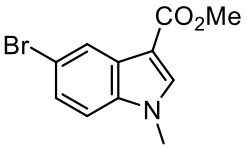
^{19}F NMR (400 MHz, $CDCl_3$, 298 K):

Methyl 5-fluoro-1H-indole-3-carboxylate



^{1}H NMR (400 MHz, $CDCl_3$, 298 K):

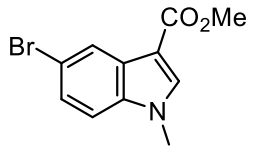
Methyl 5-bromo-1-methyl-1H-indole-3-carboxylate



3f

^{13}C NMR (101 MHz, $CDCl_3$, 298 K):

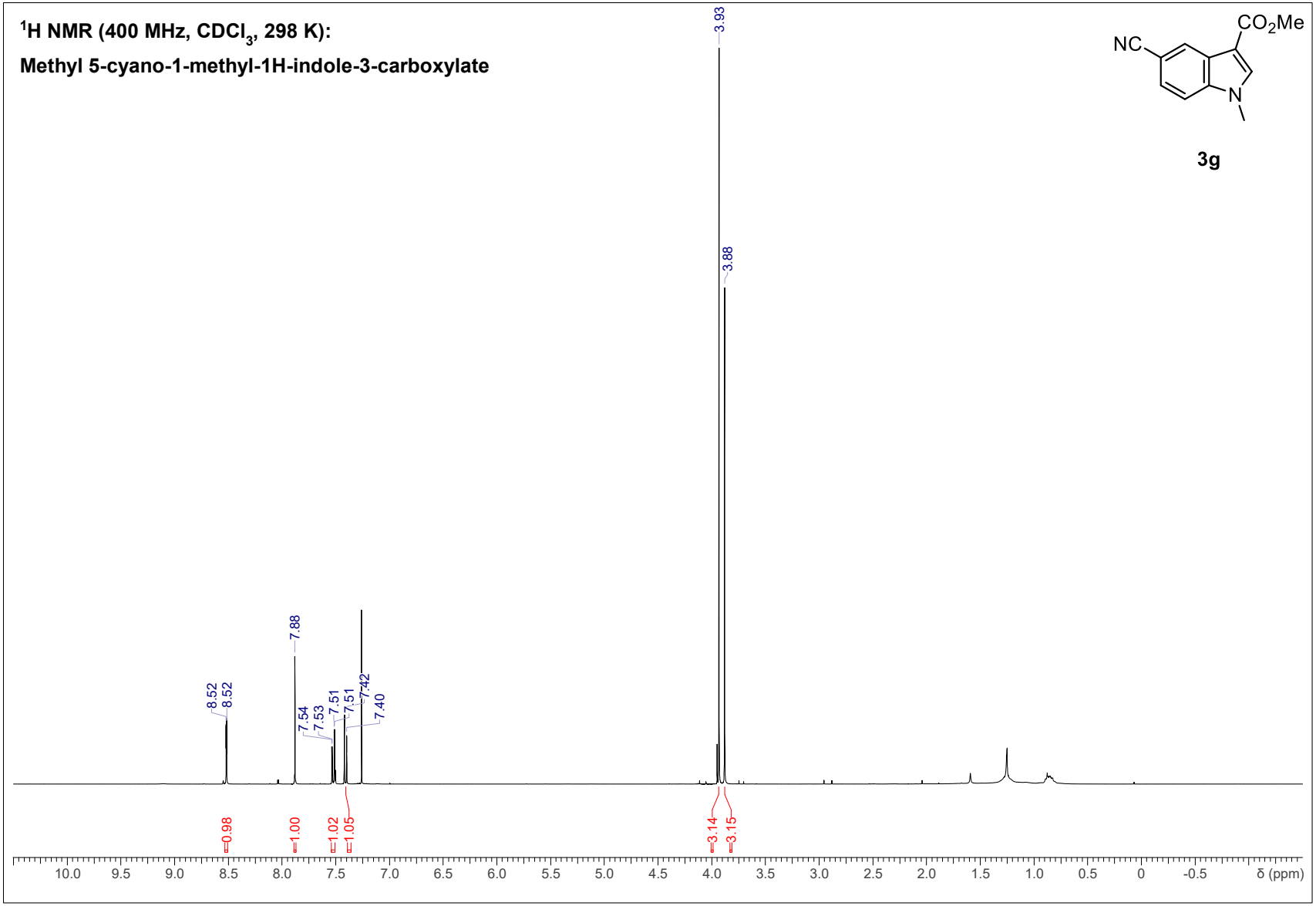
Methyl 5-bromo-1-methyl-1H-indole-3-carboxylate



3f

^{1}H NMR (400 MHz, $CDCl_3$, 298 K):

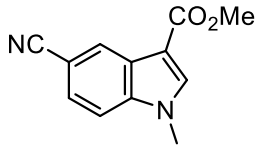
Methyl 5-cyano-1-methyl-1H-indole-3-carboxylate



3g

^{13}C NMR (101 MHz, $CDCl_3$, 298 K):

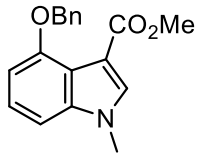
Methyl 5-cyano-1-methyl-1H-indole-3-carboxylate



3g

^{1}H NMR (400 MHz, $CDCl_3$, 298 K):

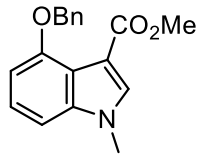
Methyl 4-(benzyoxy)-1-methyl-1H-indole-3-carboxylate



3h

^{13}C NMR (101 MHz, $CDCl_3$, 298 K):

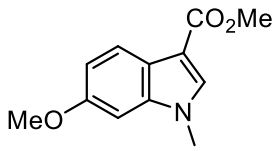
Methyl 4-(benzyoxy)-1-methyl-1H-indole-3-carboxylate



3h

^{1}H NMR (400 MHz, $CDCl_3$, 298 K):

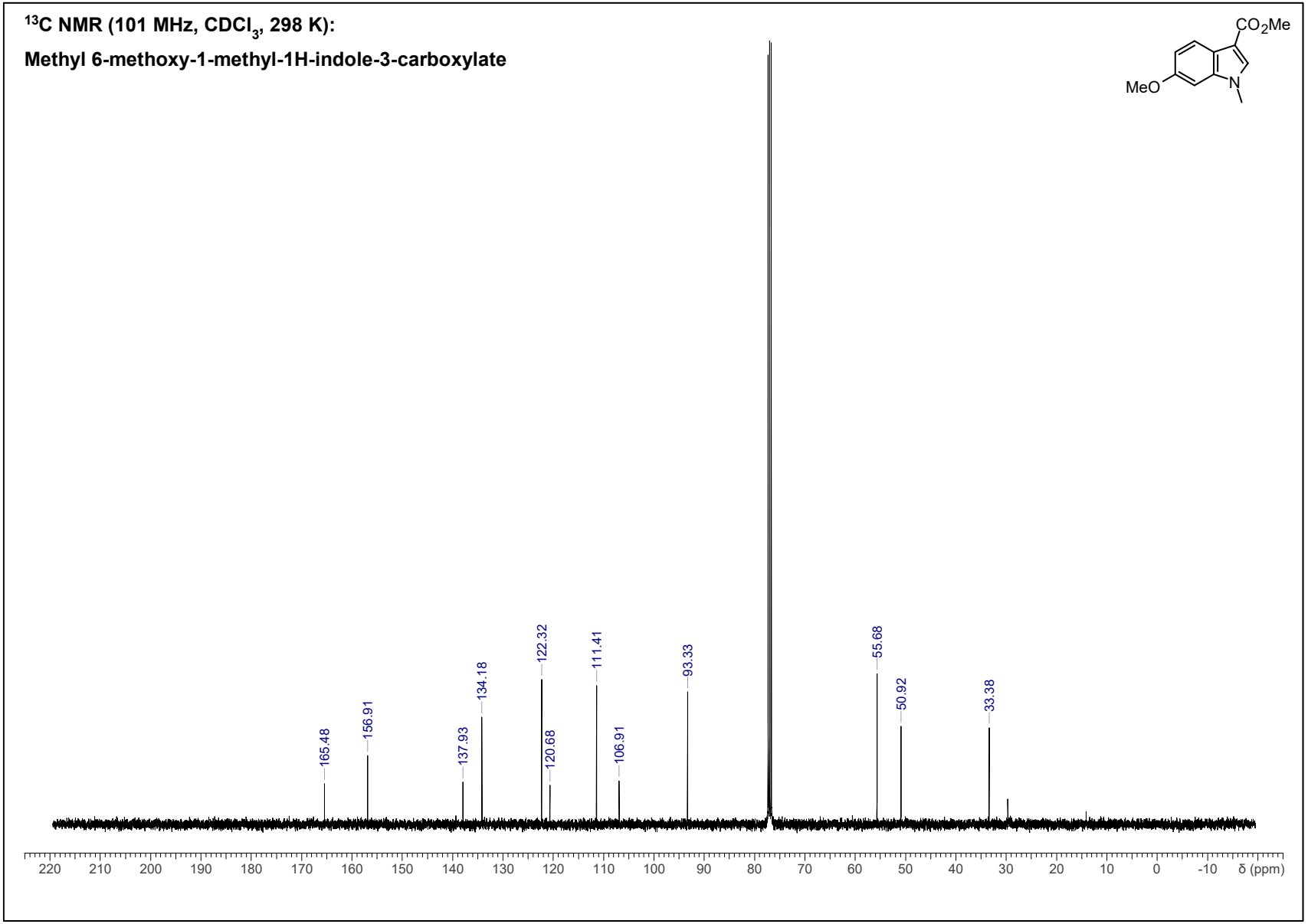
Methyl 6-methoxy-1-methyl-1H-indole-3-carboxylate



3i

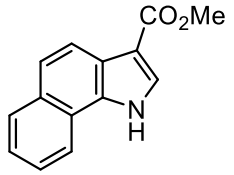
^{13}C NMR (101 MHz, $CDCl_3$, 298 K):

Methyl 6-methoxy-1-methyl-1H-indole-3-carboxylate



^{1}H NMR (400 MHz, DMSO-d_6, 298 K):

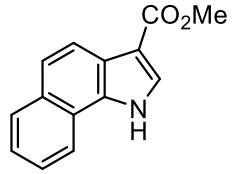
Methyl-1H-benzo[*g*]indole-3-carboxylate



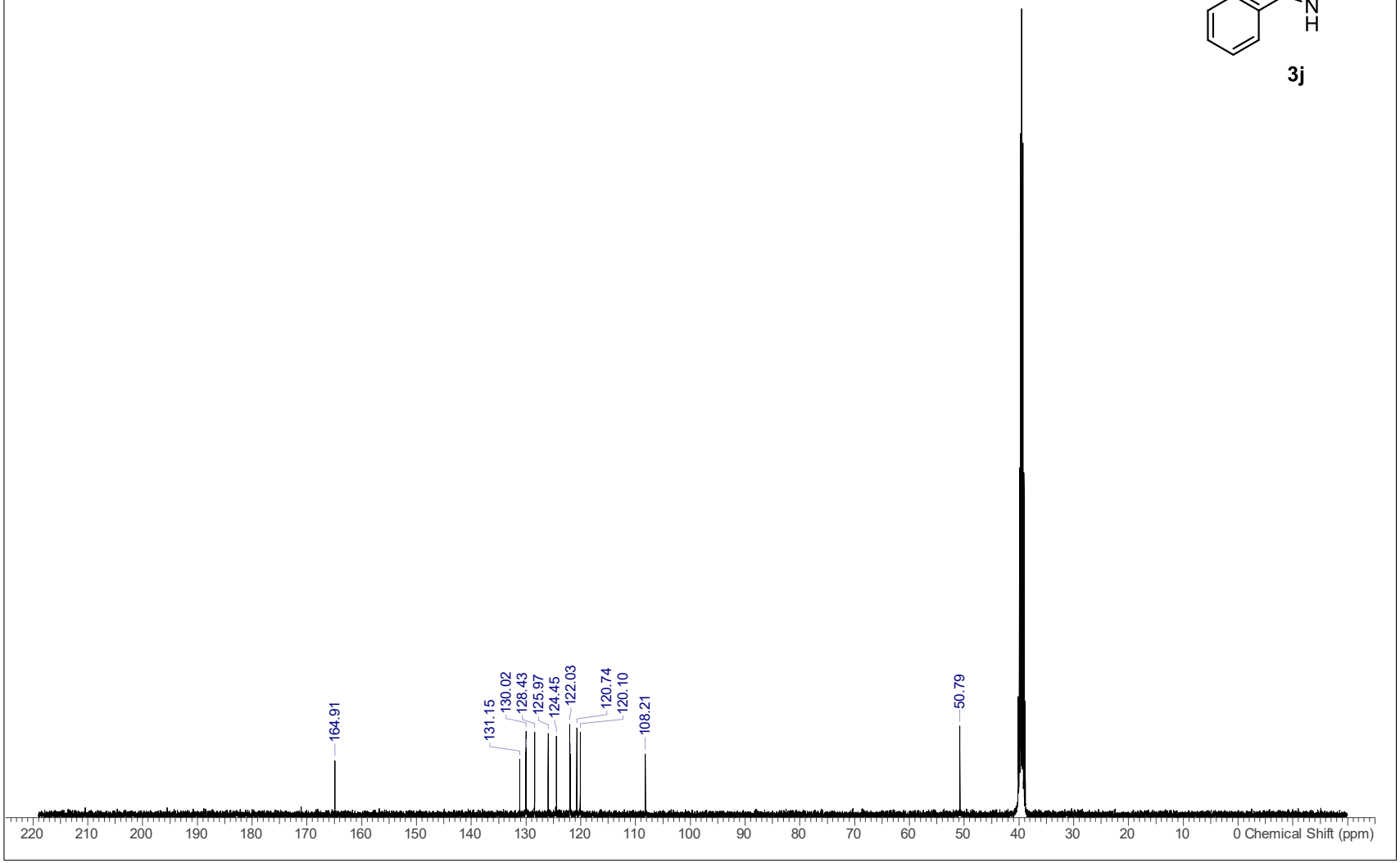
3j

^{13}C NMR (101 MHz, DMSO-d_6, 298 K):

Methyl 1H-benzo[*g*]indole-3-carboxylate

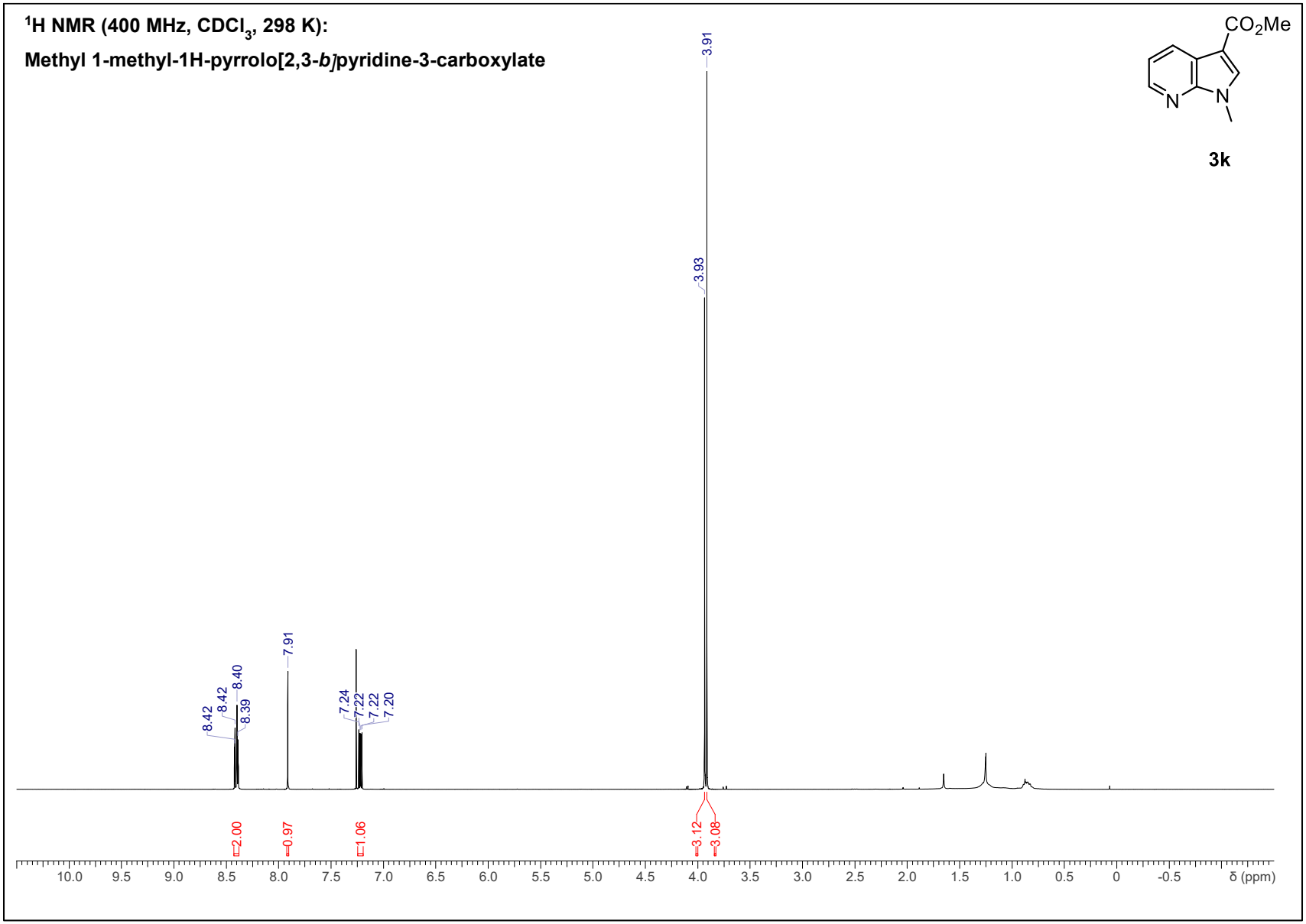


3j



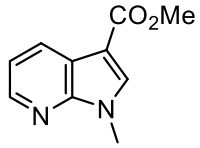
^{1}H NMR (400 MHz, $CDCl_3$, 298 K):

Methyl 1-methyl-1H-pyrrolo[2,3-*b*]pyridine-3-carboxylate



^{13}C NMR (101 MHz, $CDCl_3$, 298 K):

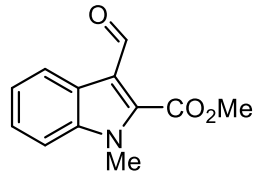
Methyl 1-methyl-1H-pyrrolo[2,3-*b*]pyridine-3-carboxylate



3k

^{1}H NMR (400 MHz, $CDCl_3$, 298 K):

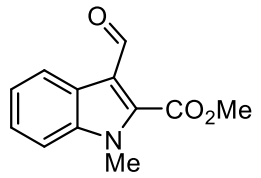
Methyl 3-formyl-1-methyl-1H-indole-2-carboxylate



8

^{13}C NMR (101 MHz, $CDCl_3$, 298 K):

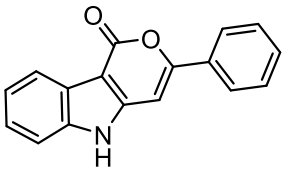
Methyl 3-formyl-1-methyl-1H-indole-2-carboxylate



8

^{1}H NMR (400 MHz, DMSO-d$_6$, 298 K):

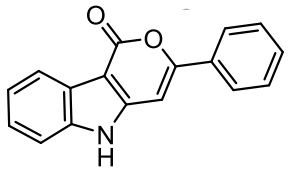
3-phenylpyrano[4,3-*b*]indol-1(5H)-one



10

^{13}C NMR (101 MHz, DMSO-d_6, 298 K):

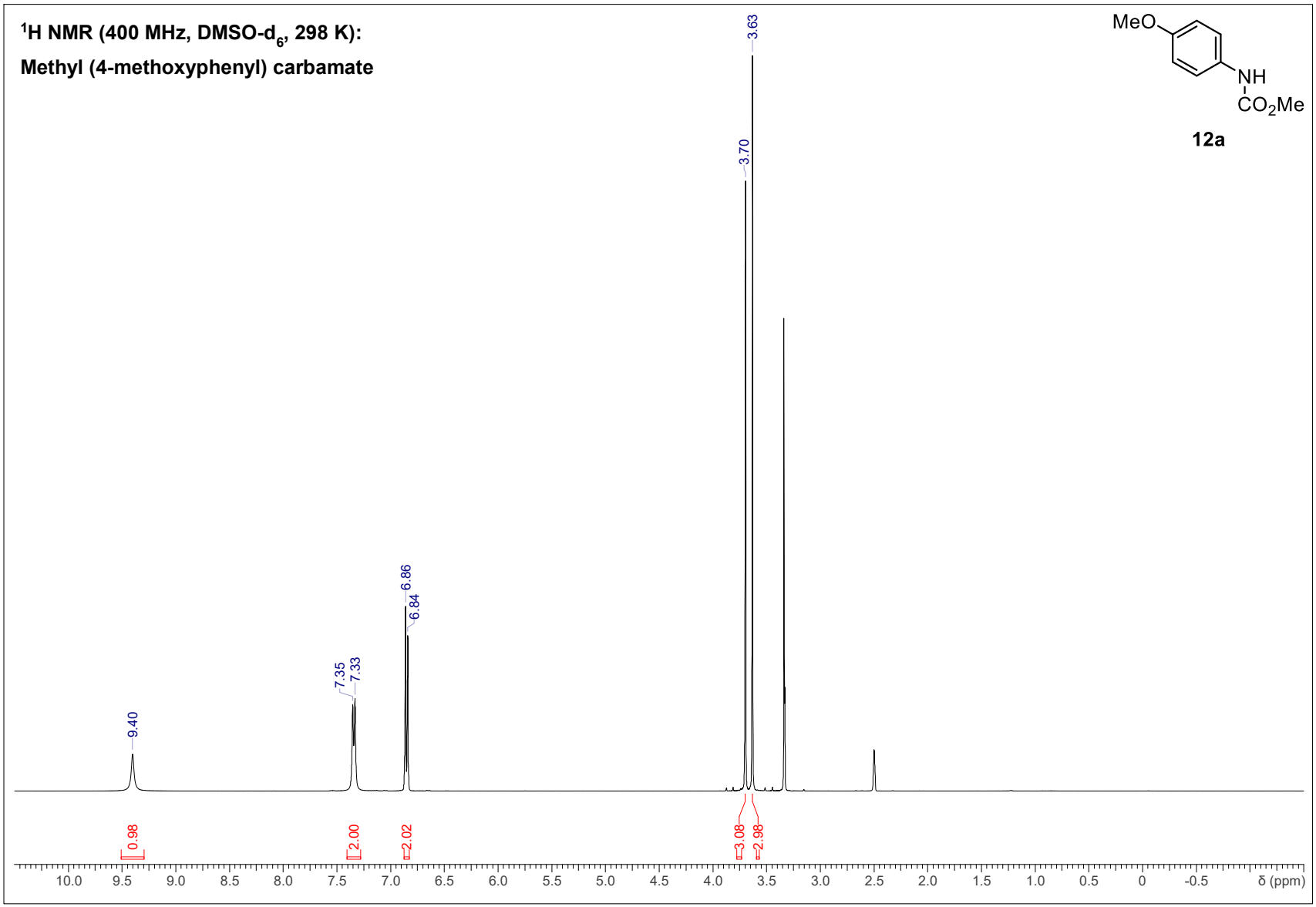
3-phenylpyrano[3,4-*b*]indol-1(5H)-one



10

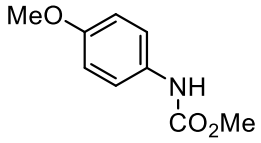
^{1}H NMR (400 MHz, DMSO-d_6, 298 K):

Methyl (4-methoxyphenyl) carbamate



^{13}C NMR (101 MHz, DMSO-d_6, 298 K):

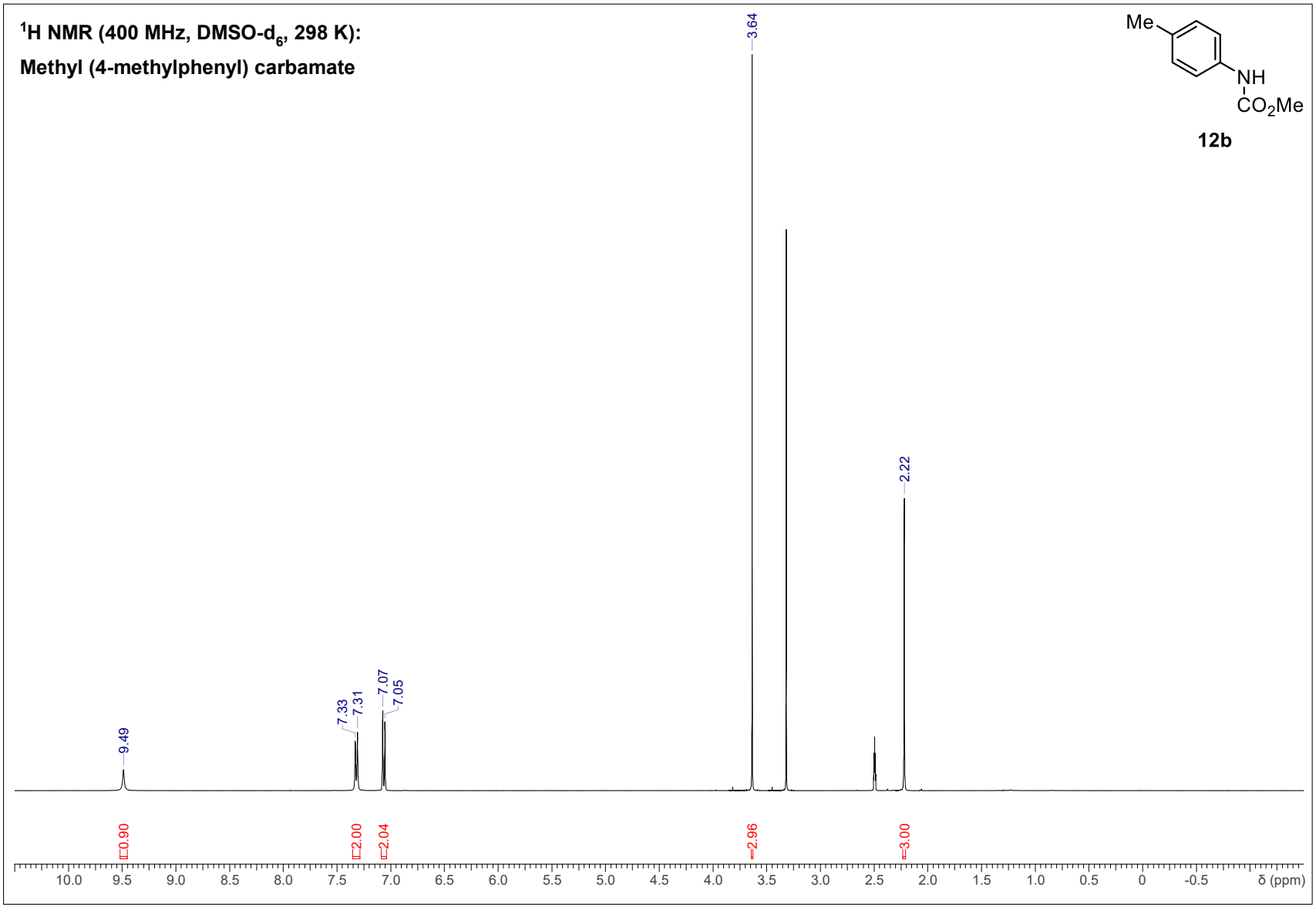
Methyl (4-methoxyphenyl) carbamate



12a

^{1}H NMR (400 MHz, DMSO-d_6, 298 K):

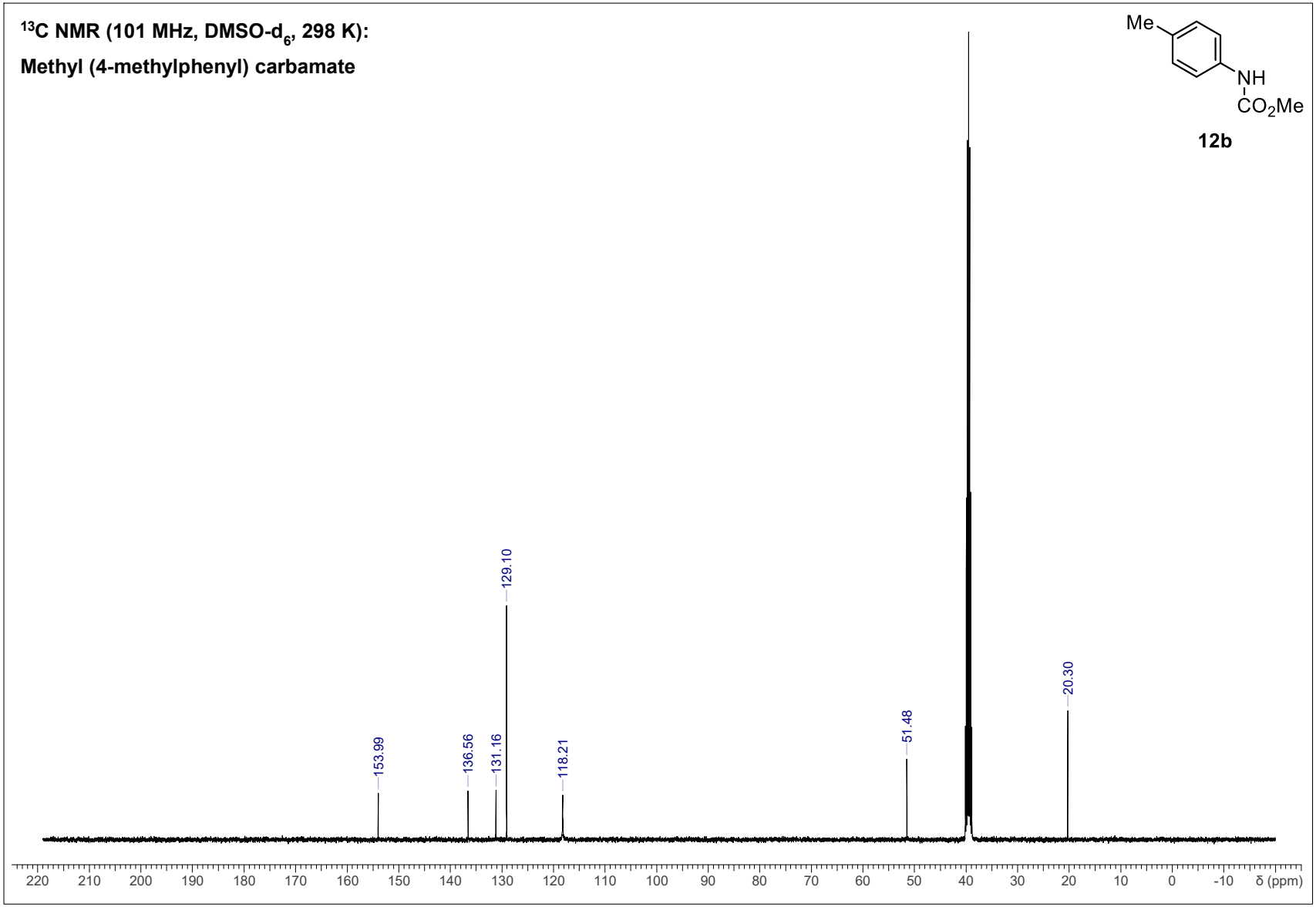
Methyl (4-methylphenyl) carbamate



12b

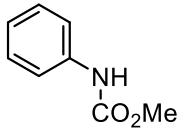
^{13}C NMR (101 MHz, DMSO-d_6, 298 K):

Methyl (4-methylphenyl) carbamate



^{1}H NMR (400 MHz, $CDCl_3$, 298 K):

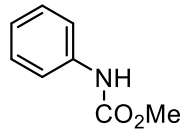
Methyl phenylcarbamate



12c

^{13}C NMR (101 MHz, $CDCl_3$, 298 K):

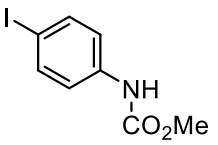
Methyl phenylcarbamate



12c

^{1}H NMR (400 MHz, $CDCl_3$, 298 K):

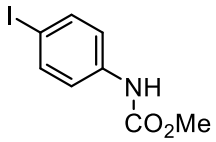
Methyl (4-iodophenyl)carbamate



12d

^{13}C NMR (101 MHz, $CDCl_3$, 298 K):

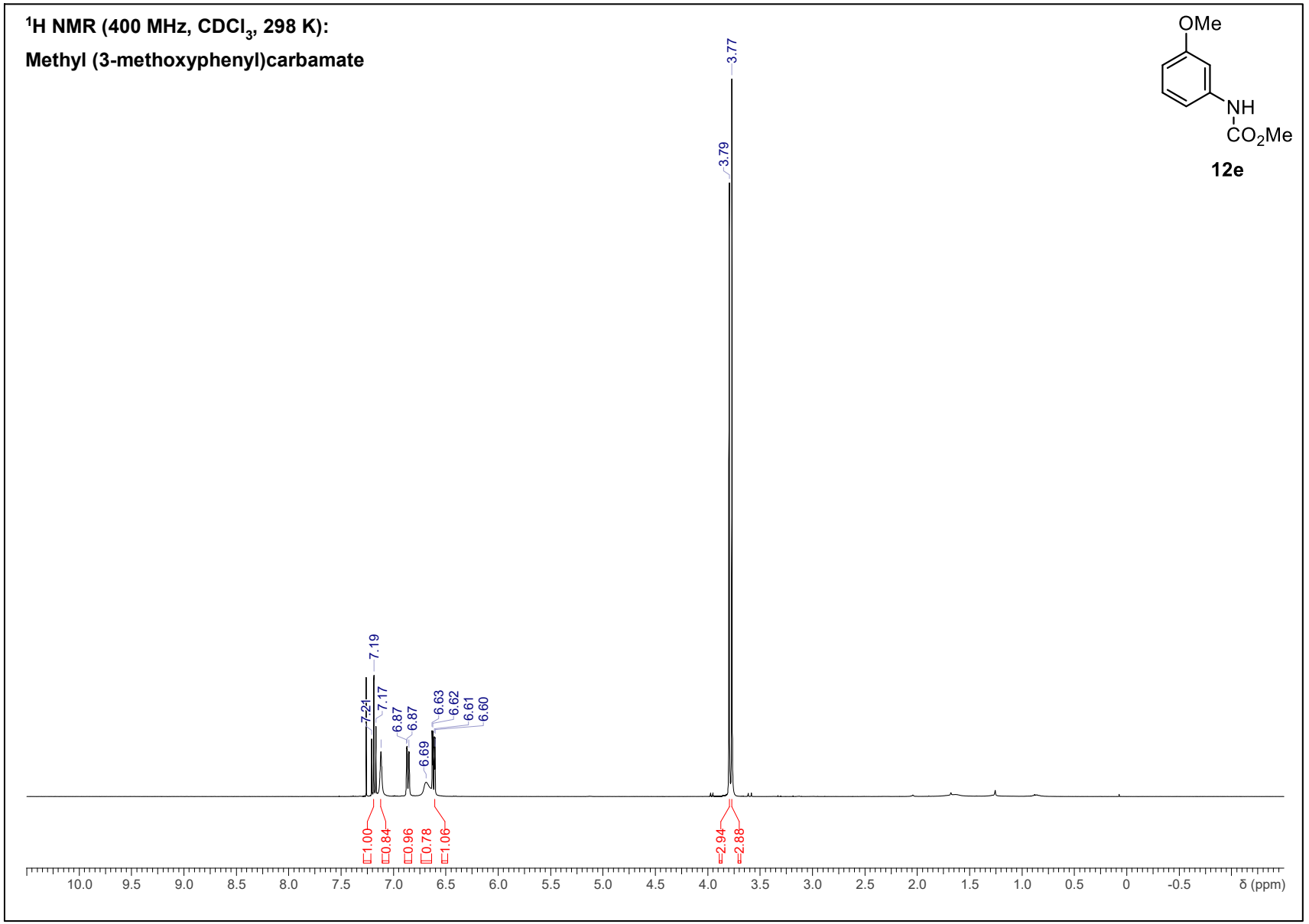
Methyl (4-iodophenyl) carbamate



12d

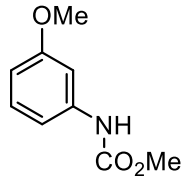
^{1}H NMR (400 MHz, $CDCl_3$, 298 K):

Methyl (3-methoxyphenyl)carbamate



^{13}C NMR (101 MHz, $CDCl_3$, 298 K):

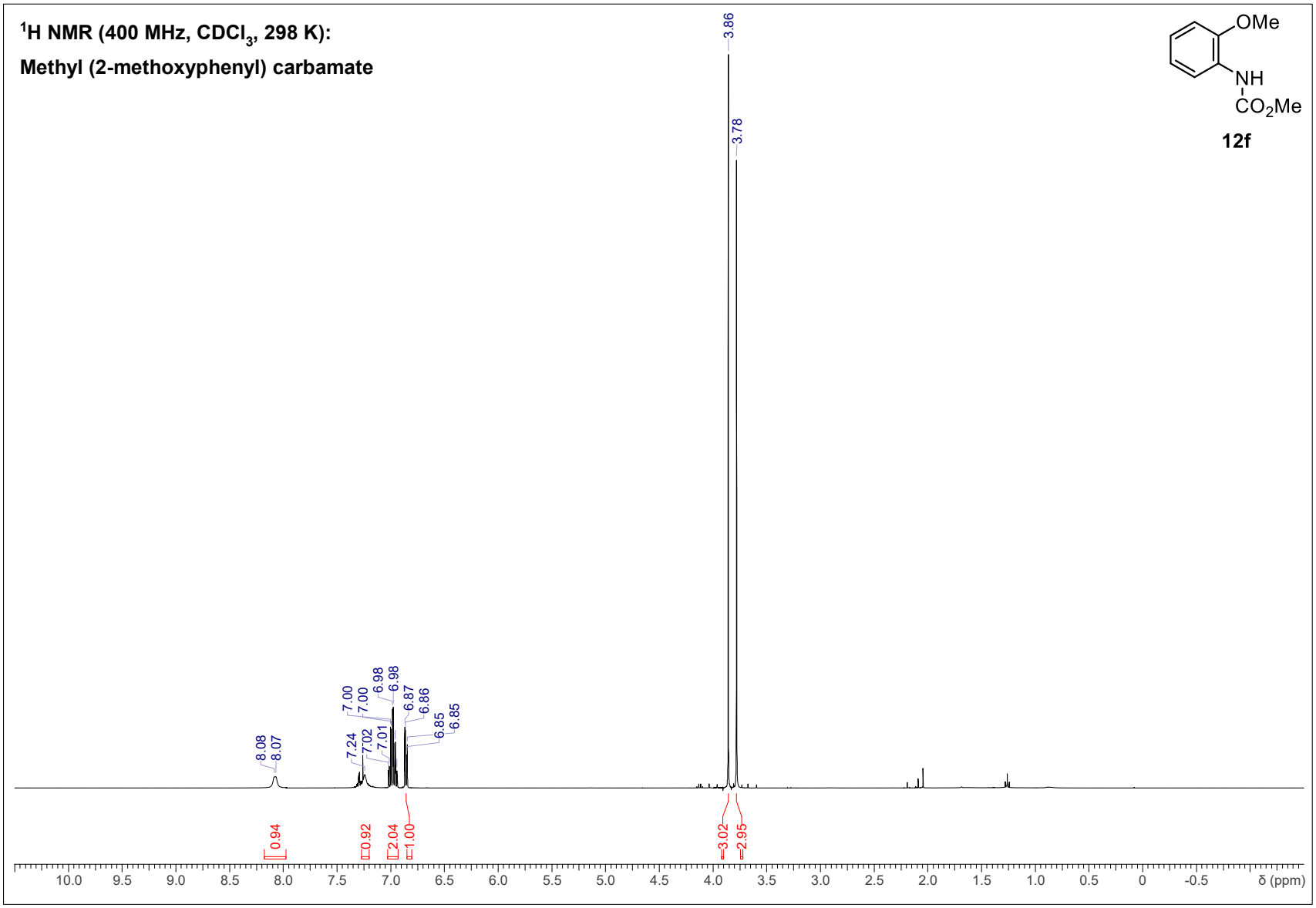
Methyl (3-methoxyphenyl)carbamate



12e

^{1}H NMR (400 MHz, $CDCl_3$, 298 K):

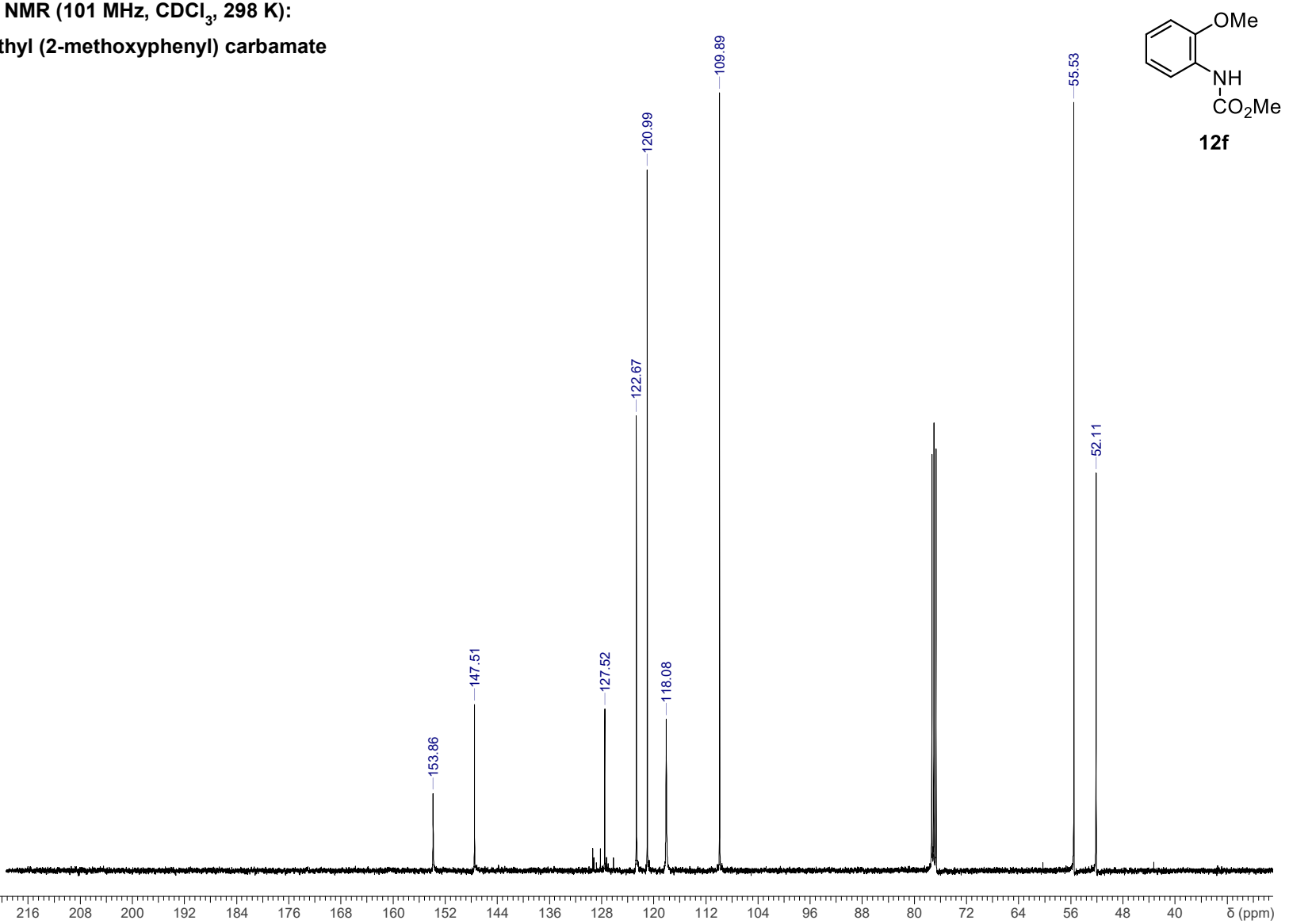
Methyl (2-methoxyphenyl) carbamate



12f

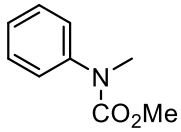
^{13}C NMR (101 MHz, $CDCl_3$, 298 K):

Methyl (2-methoxyphenyl) carbamate



^{1}H NMR (400 MHz, $CDCl_3$, 298 K):

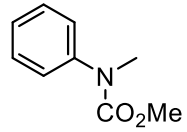
Methyl methyl(phenyl)carbamate



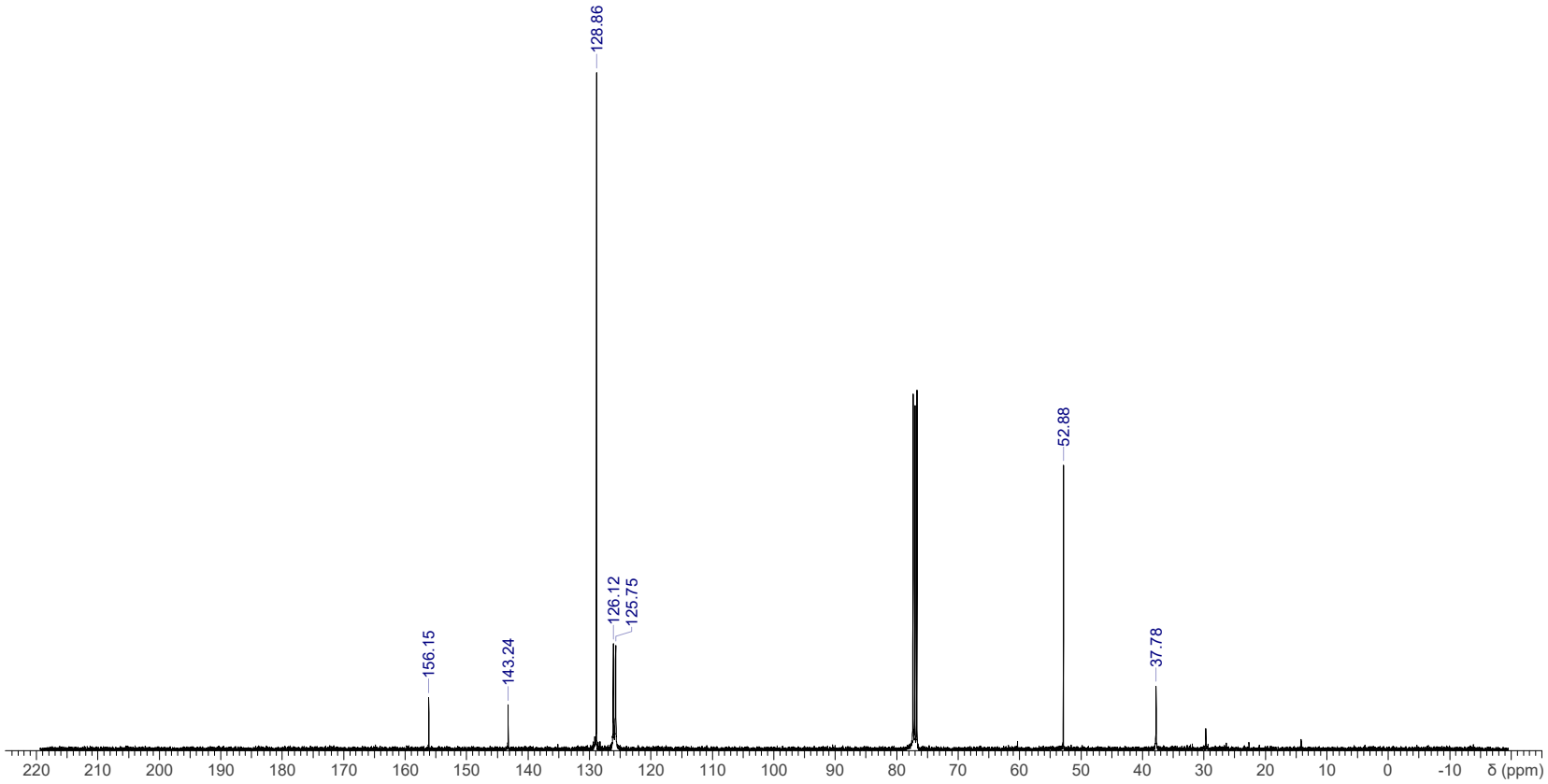
12g

^{13}C NMR (101 MHz, $CDCl_3$, 298 K):

Methyl methyl(phenyl)carbamate

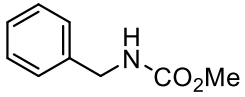


12g



^{1}H NMR (400 MHz, DMSO-d_6, 298 K):

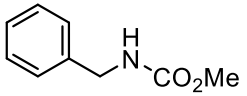
Methyl benzyl carbamate



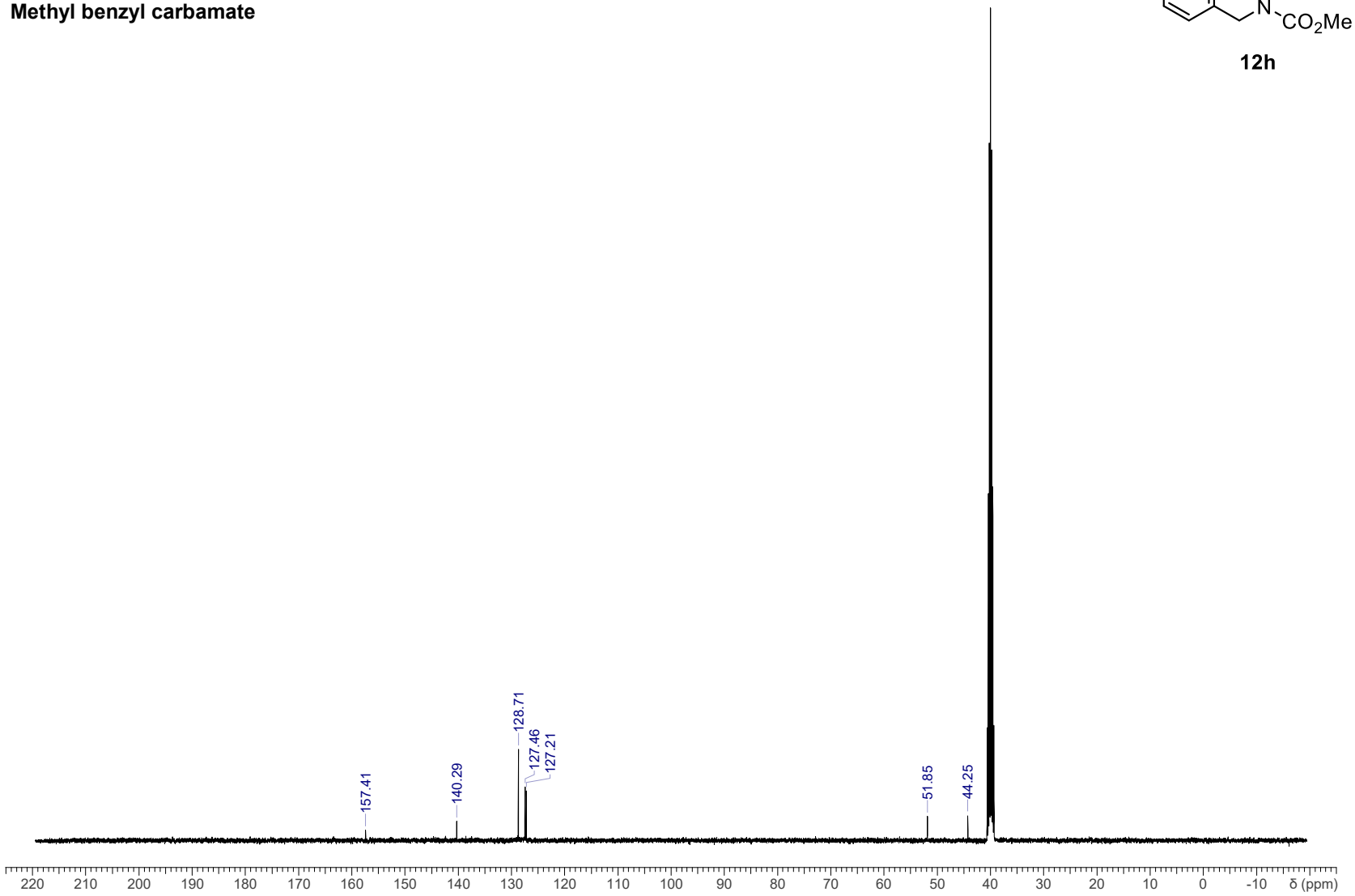
12h

^{13}C NMR (101 MHz, DMSO-d_6, 298 K):

Methyl benzyl carbamate

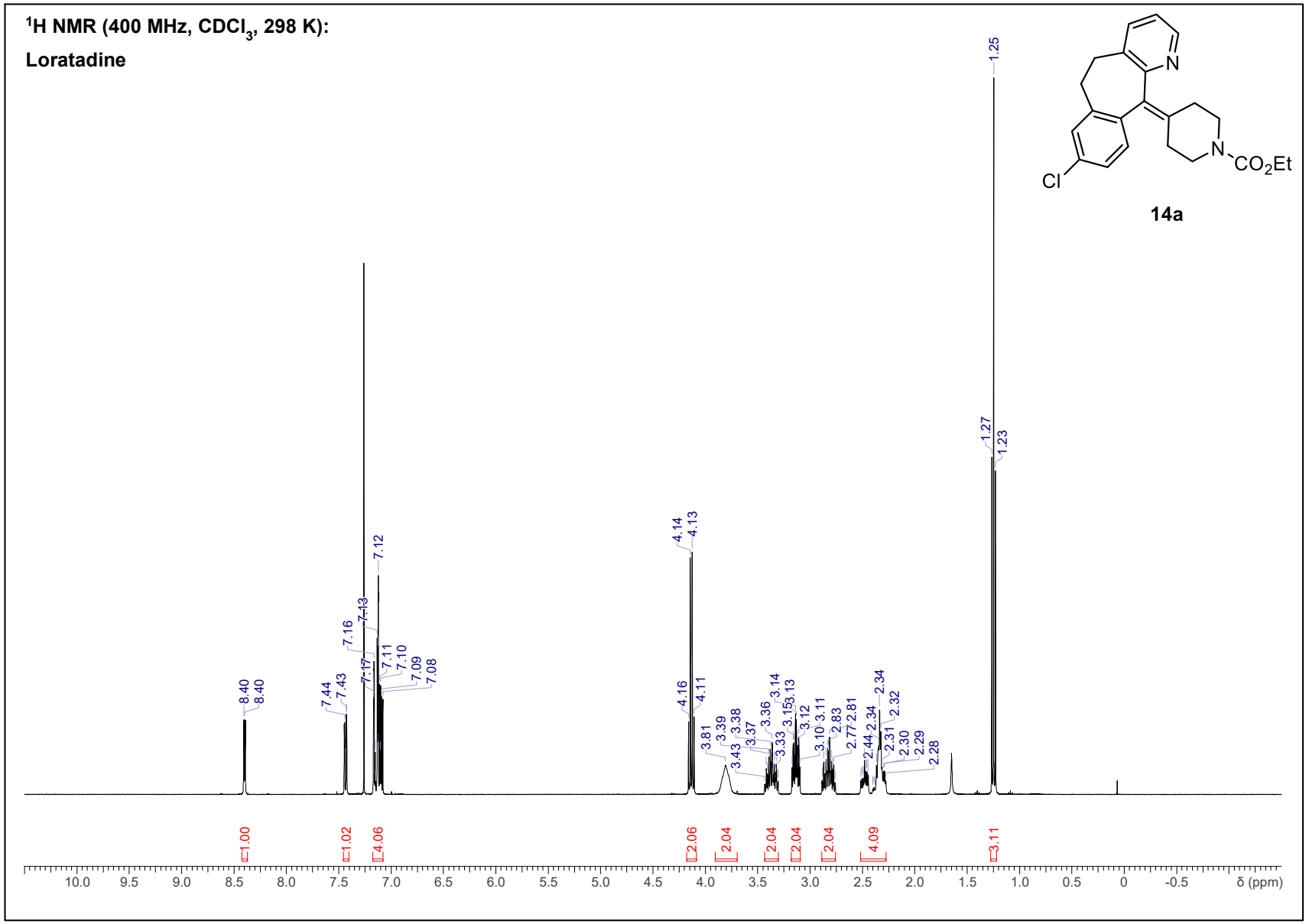


12h



^{1}H NMR (400 MHz, $CDCl_3$, 298 K):

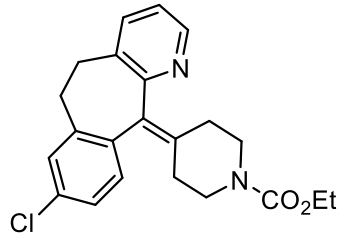
Loratadine



14a

^{13}C NMR (101 MHz, $CDCl_3$, 298 K):

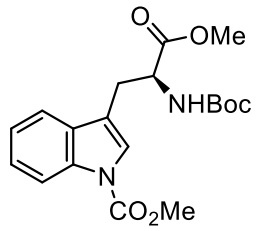
Loratadine



14a

^{1}H NMR (400 MHz, DMSO-d_6, 298 K):

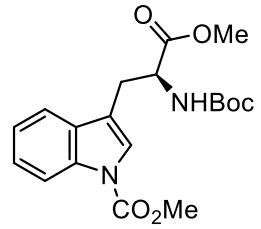
Methyl (S)-3-(2-((boc)amino)-3-methoxy-3-oxopropyl)-1H-indole-1-carboxylate



14b

^{13}C NMR (101 MHz, DMSO-d_6, 298 K):

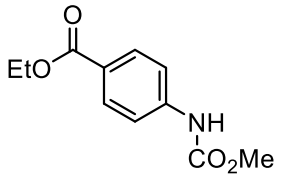
Methyl (S)-3-(2-((boc)amino)-3-methoxy-3-oxopropyl)-1H-indole-1-carboxylate



14b

^{1}H NMR (400 MHz, $CDCl_3$, 298 K):

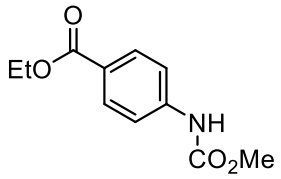
Ethyl-4(methoxycarbonyl)amino)benzoate



14c

^{13}C NMR (101 MHz, $CDCl_3$, 298 K):

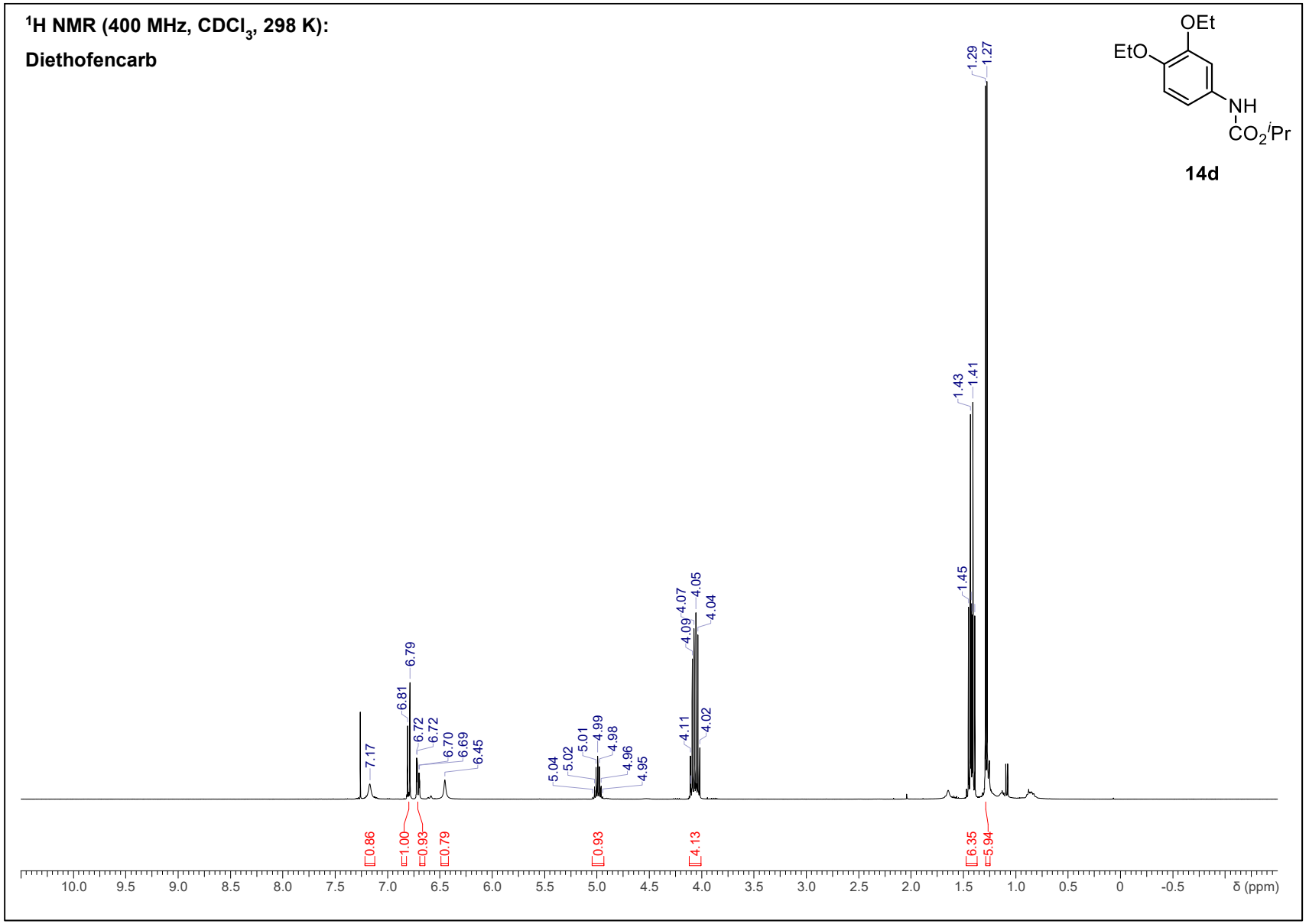
Ethyl-4(methoxycarbonyl)amino)benzoate



14c

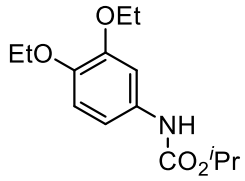
^{1}H NMR (400 MHz, $CDCl_3$, 298 K):

Diethofencarb



^{13}C NMR (101 MHz, $CDCl_3$, 298 K):

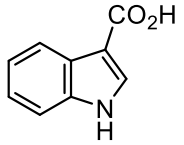
Diethofencarb



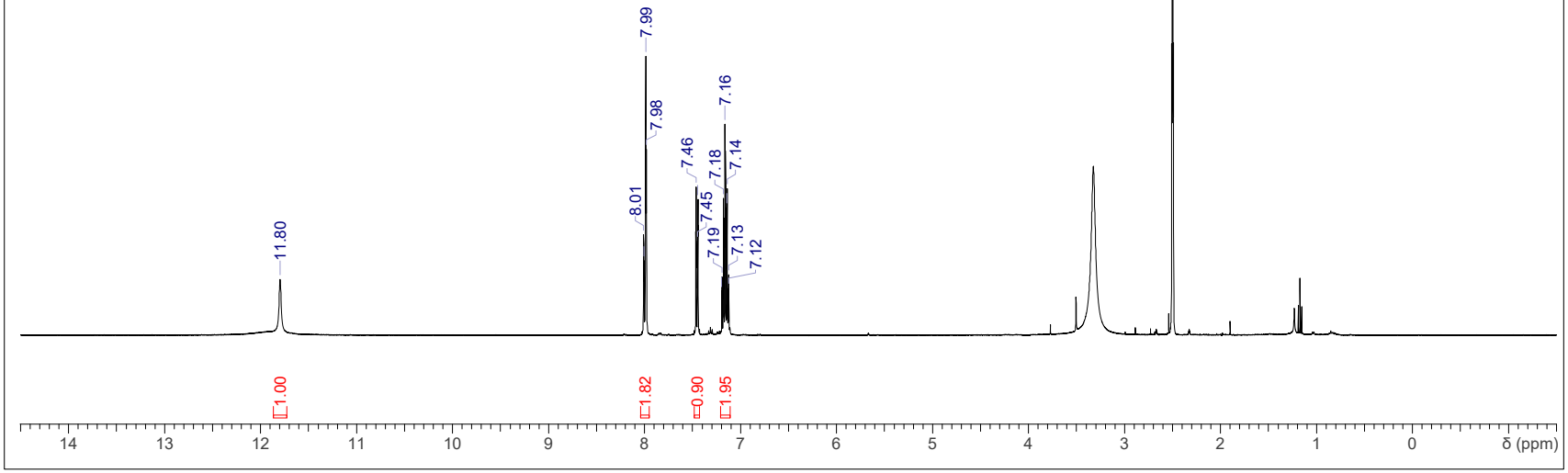
14d

^{1}H NMR (400 MHz, DMSO-d_6, 298 K):

Indole-3-carboxylic acid

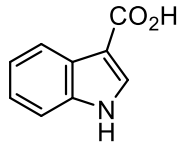


15



^{13}C NMR (101 MHz, DMSO-d_6, 298 K):

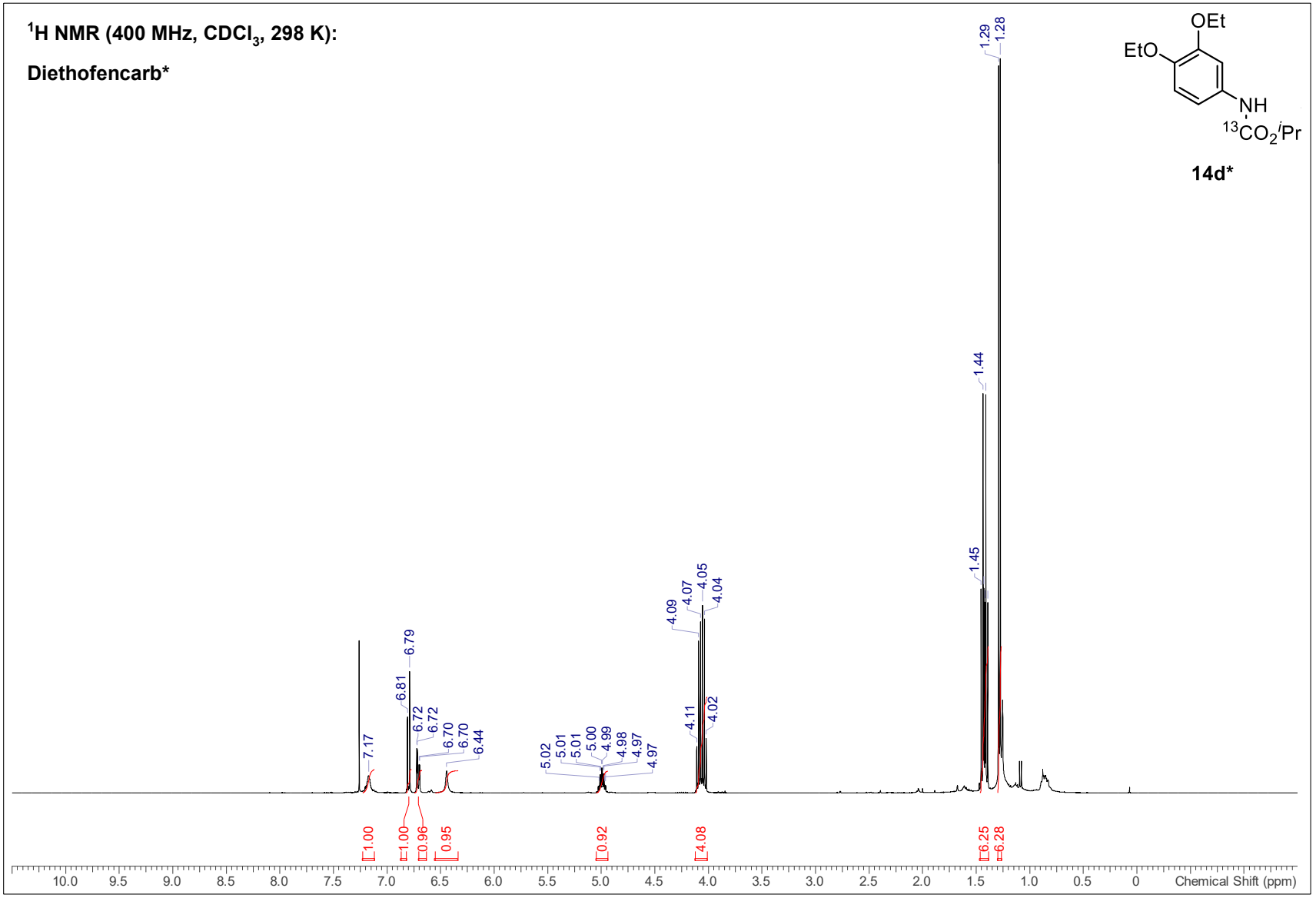
1H-Indole-3-carboxylic acid



15

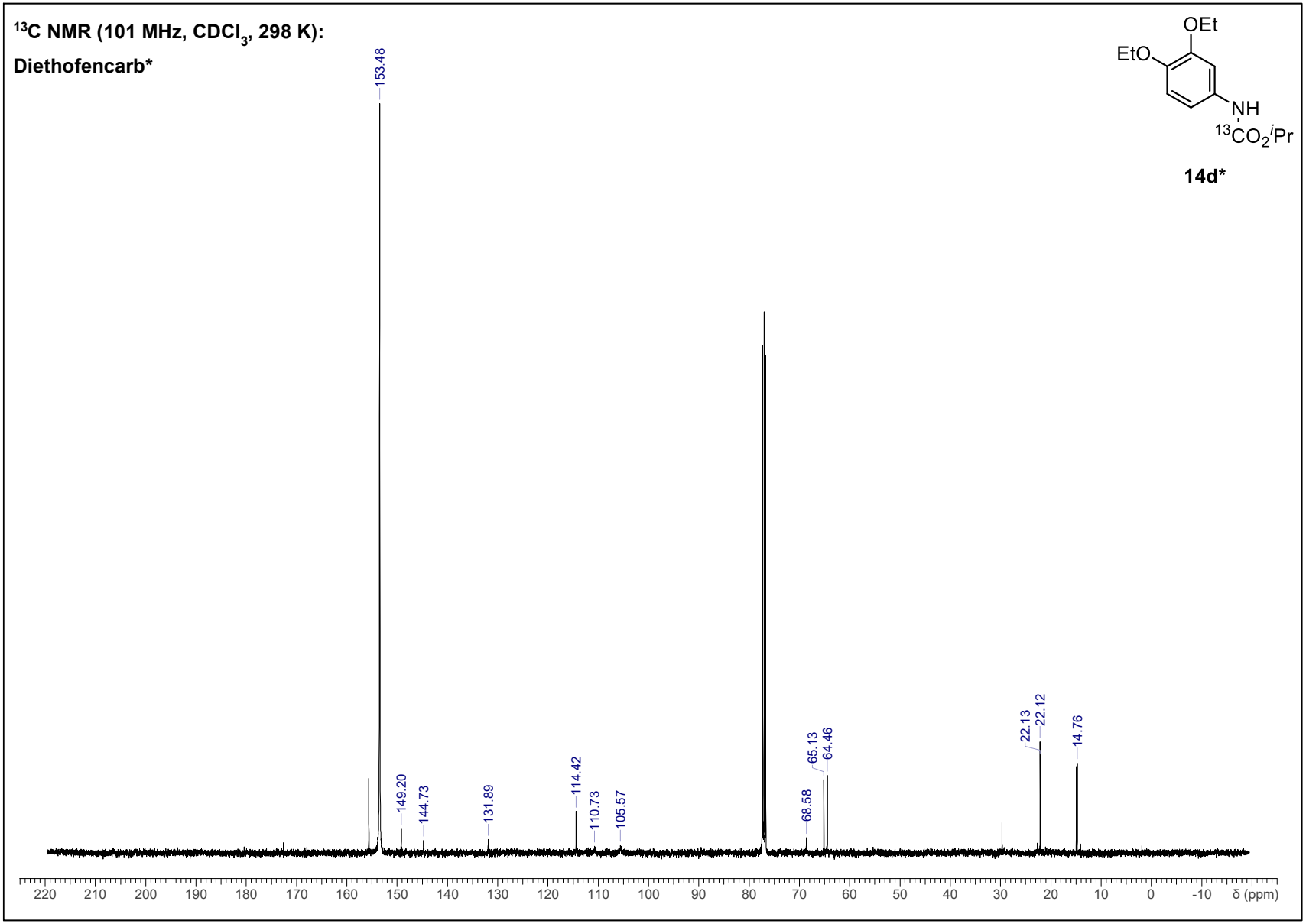
^{1}H NMR (400 MHz, $CDCl_3$, 298 K):

Diethofencarb*



^{13}C NMR (101 MHz, $CDCl_3$, 298 K):

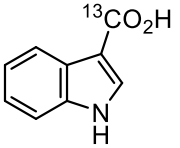
Diethofencarb*



14d*

^{1}H NMR (400 MHz, DMSO-d_6, 298 K):

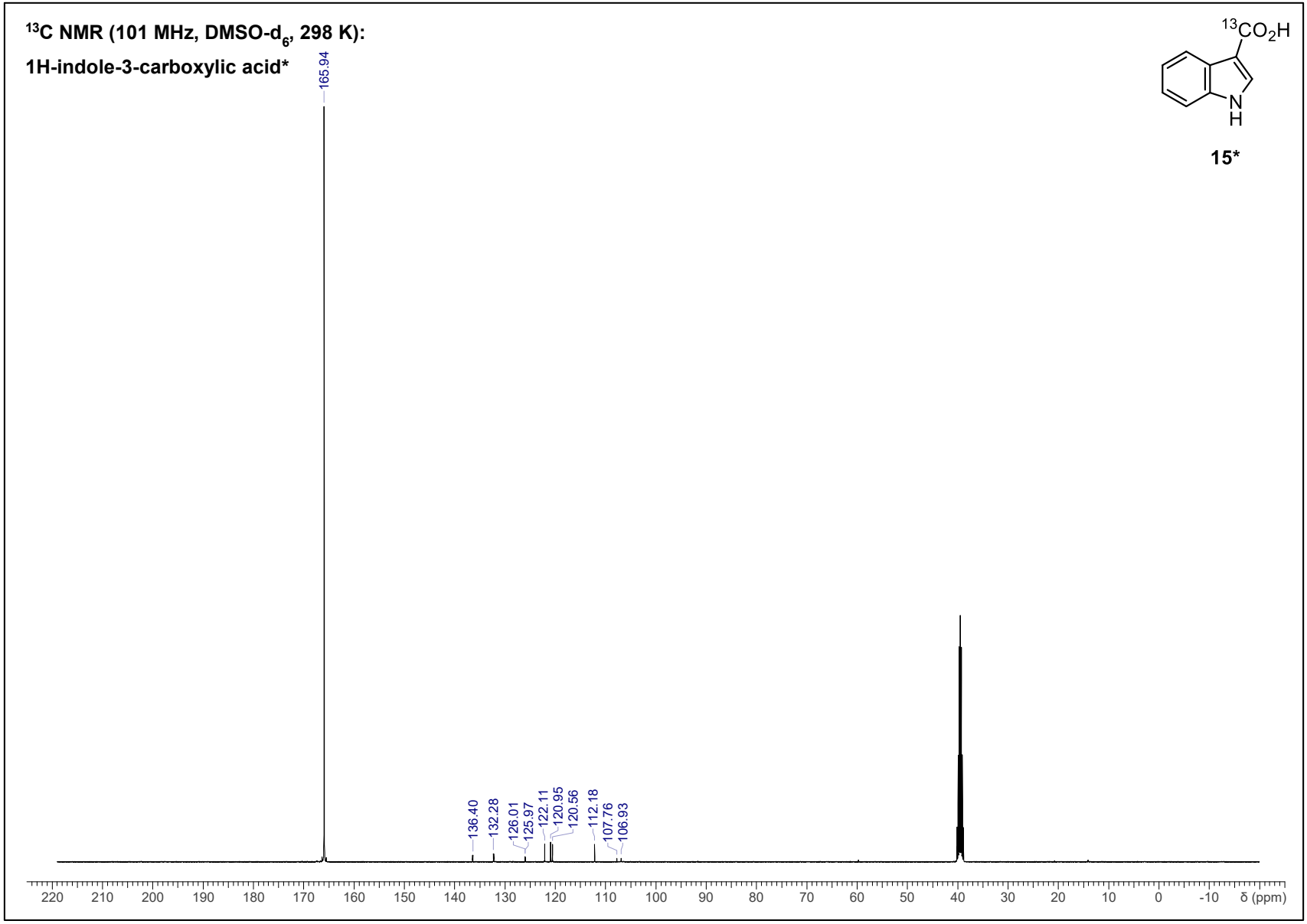
1H-indole-3-carboxylic acid*



15*

^{13}C NMR (101 MHz, DMSO-d_6, 298 K):

1H-indole-3-carboxylic acid*



15*