Palladium-Catalyzed Stitching of 1,3-C(sp^3)–H bonds with Dihaloarenes: Short Synthesis of (±)-Echinolactone D.

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Supporting Information

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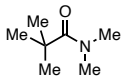
General Information.

Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. Anhydrous solvents were obtained from the solvent purification system produced by *JC* Meyer Solvent Systems. Analytical thin-layer chromatography (TLC) was performed on Merck Millipore precoated (0.25 mm thickness) silica gel plates with F254 fluorescent indicator. TLC plates were visualized by exposure to ultraviolet light (UV) and/or submersion in aqueous potassium permanganate solution ($KMnO_4$), followed by brief heating on a hot plate (120 °C, 10–15 s). Flash-column chromatography was performed employing silica gel (32-63 μm particle size) supplied by Dynamic Adsorbents. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on Bruker DRX-600 instrument (600 MHz). Chemical shifts are expressed in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CHCl_3$, δ 7.26). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances, b = broad, app = apparent), coupling constant, *J*, in Hertz (Hz) AND integration. Proton-decoupled carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded on Bruker DRX-600 instrument (150 MHz). Chemical shifts are expressed in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent ($CDCl_3$, δ 77.2). High-resolution mass spectra (HRMS) were recorded on an Agilent Mass spectrometer using ESI-TOF (electrospray ionization-time of flight).

Substrate Structures.

Pivalamide Substrates:



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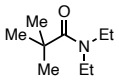

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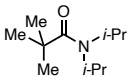

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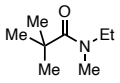

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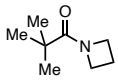

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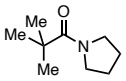

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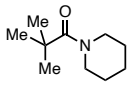

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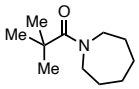

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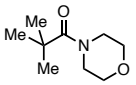

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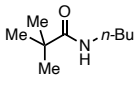

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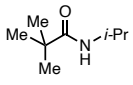

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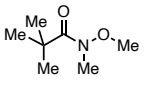

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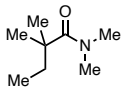

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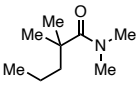

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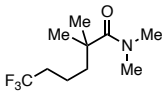

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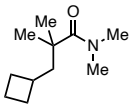

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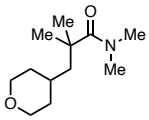

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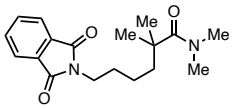

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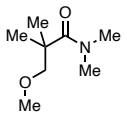

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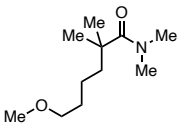

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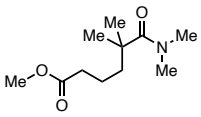

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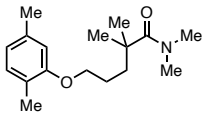

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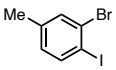
1-bromo-2-iodoarene Substrates:

8



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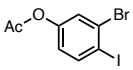

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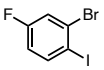

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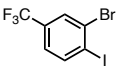

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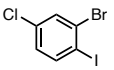

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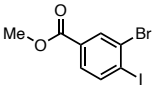

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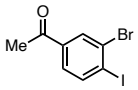

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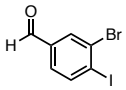

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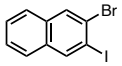
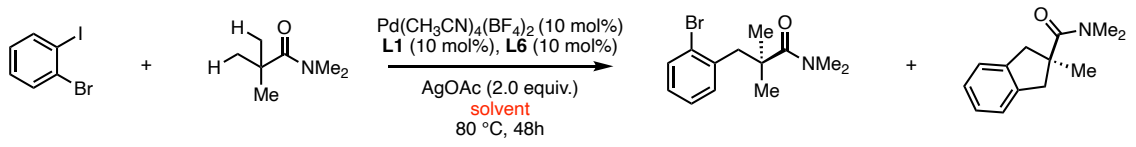


16s

Experimental Section.

Reaction Optimization Tables.

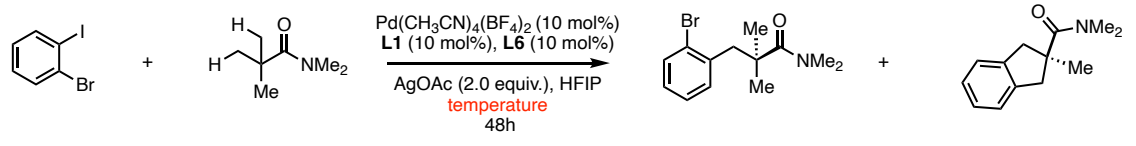
Table S1. Solvent Investigation.[a,b]



entry	solvent	**10** (%)	**13** (%)
1.	HFIP	3	64
2.	DCE	0	0
3.	TFE	15	14
4.	DMF	0	0
5.	Dioxane	0	0

[a]Conditions: **8** (0.15 mmol), **9** (0.10 mmol), $Pd(CH_3CN)_4(BF_4)_2$ (10 mol%), **L1** (10 mol%), **L6** (10 mol%), AgOAc (2.0 equiv), solvent (0.5 mL), 80 °C, 48h. [b]Yields were determined by ^1H NMR analysis of an unpurified product mixture using CH_2Br_2 as an internal standard.

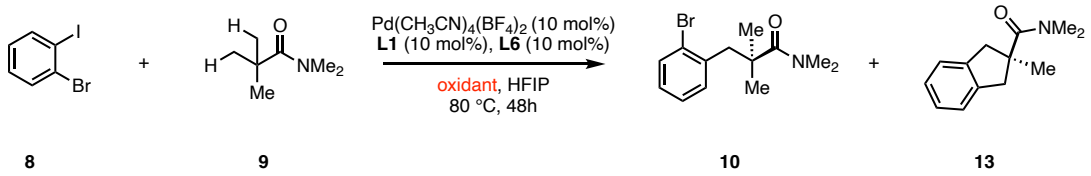
Table S2. Temperature Investigation.[a,b]



entry	temperature	**10** (%)	**13** (%)
1.	70 °C	14	51
2.	80 °C	3	64
3.	90 °C	5	50
4.	100 °C	0	43

[a]Conditions: **8** (0.15 mmol), **9** (0.10 mmol), $Pd(CH_3CN)_4(BF_4)_2$ (10 mol%), **L1** (10 mol%), **L6** (10 mol%), AgOAc (2.0 equiv), HFIP (0.5 mL), temperature (°C), 48h. [b]Yields were determined by ^1H NMR analysis of an unpurified product mixture using CH_2Br_2 as an internal standard.

Table S3. Oxidant Investigation.[a,b]

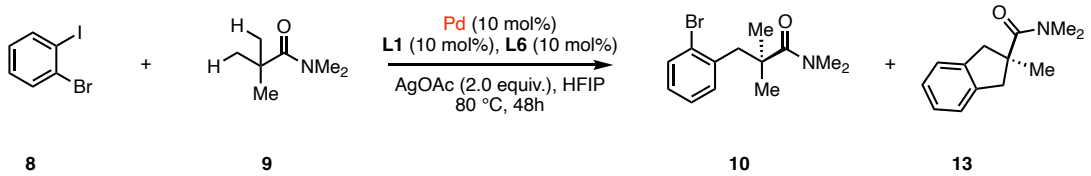


8 9 10 13

entry	oxidant	**10** (%)	**13** (%)
1.	none	10	0
2.	AgOAc (1.0 equiv)	5	42
3.	AgOAc (2.0 equiv)	3	64
4.	AgTFA (2.0 equiv)	12	40
5.	Ag_2O (2.0 equiv)	0	0
6.	Ag_2CO_3 (2.0 equiv)	20	18

[a]Conditions: **8** (0.15 mmol), **9** (0.10 mmol), $Pd(CH_3CN)_4(BF_4)_2$ (10 mol%), **L1** (10 mol%), **L6** (10 mol%), oxidant, HFIP (0.5 mL), 80°C, 48h. [b]Yields were determined by ^1H NMR analysis of an unpurified product mixture using CH_2Br_2 as an internal standard.

Table S4. Palladium Source Investigation.[a,b]

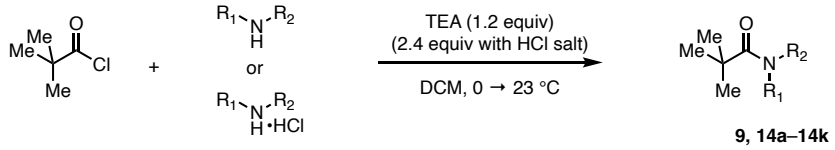


8 9 10 13

entry	Pd	**10** (%)	**13** (%)
1.	$Pd(OAc)_2$	9	51
2.	$Pd(TFA)_2$	11	49
3.	$Pd(PhCN)_2Cl_2$	14	45
4.	$Pd(CH_3CN)_4(BF_4)_2$	3	64
5.	PdI_2	26	36

[a]Conditions: **8** (0.15 mmol), **9** (0.10 mmol), Pd (10 mol%), **L1** (10 mol%), **L6** (10 mol%), AgOAc (2.0 equiv), HFIP (0.5 mL), 80°C, 48h. [b]Yields were determined by ^1H NMR analysis of an unpurified product mixture using CH_2Br_2 as an internal standard.

General Procedure A: Preparation of Substrates 9, 14a–14k.



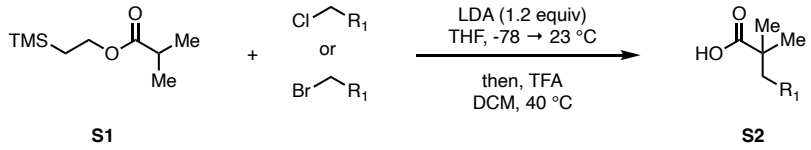
9, 14a–14k

Triethylamine (1.20 equiv or 2.40 equiv with HCl salts) was added in to a solution of pivaloyl chloride (1 equiv) in dichloromethane (0.15 M) at 23 °C. The reaction vessel was then placed in an ice bath and allowed to cool to 0 °C over 20 min. The corresponding amine (1.10 equiv) was added dropwise via a syringe pump over 30 min to the reaction mixture. Upon completion of the addition, the ice bath was removed and the reaction mixture was allowed to warm to 23 °C over 1 h. The reaction mixture was allowed to stir at 23 °C for 8 h. The product mixture was diluted sequentially with dichloromethane and saturated aqueous ammonium chloride solution. The diluted product mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with dichloromethane. The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution. The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by a flash-column chromatography (eluting with 10% ethyl acetate–hexanes) to provide the corresponding amide substrates **9, 14a–14k**.

The spectroscopic data for the corresponding amide substrates **9, 14a–14k** prepared according to this general procedure matched the previously reported ^{1}H NMR data.[1,2,3,4]

General Procedure B: Preparation of Substrates 17a–17j.

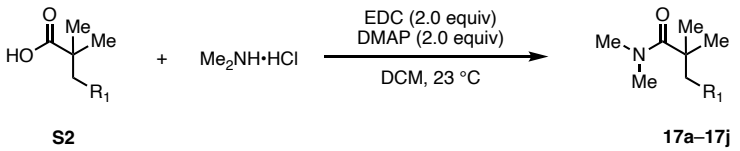
*Synthesis of the carboxylic acid **S2**:*



S1 **S2**

A solution of n-butyllithium in hexanes (2.50 M, 1.20 equiv) was added dropwise via syringe over 30 min to a solution of diisopropylamine (1.25 equiv) in tetrahydrofuran (0.20 M) at –78 °C. The resulting solution was stirred for 45 min at –78 °C. A solution of the ester **S1** (1 equiv) in tetrahydrofuran was then added dropwise via syringe over 15 min at –78 °C. Upon completion of the addition, the reaction mixture was stirred for 1 hour at –78 °C. The corresponding alkyl chloride or alkyl bromide (1.30 equiv) was then added dropwise via syringe at –78 °C. The reaction mixture was allowed to slowly warm to 23 °C overnight. The warmed product mixture was diluted sequentially with water, ethyl acetate and saturated aqueous ammonium chloride solution. The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate. The organic layers were combined, and the combined organic layers were washed with saturated aqueous sodium chloride solution. The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was subsequently dissolved in dichloromethane (0.20 M) at 23 °C. Trifluoroacetic acid (6.50 equiv) was subsequently added to the solution at 23 °C. The reaction mixture was then placed in an oil bath that had been preheated to 40 °C. The reaction mixture was stirred at 40 °C for 15 hours. The product mixture was allowed to cool to 23 °C over 30 min. The cooled product mixture was concentrated and the residue obtained was diluted sequentially with ethyl acetate, water, and 1.0 M hydrochloric acid solution until the pH < 4. The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate. The organic layers were combined, and the combined organic layers were washed with saturated aqueous sodium chloride solution. The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained containing the carboxylic acid **S2** was used in the following step without further purification.

*Synthesis of the gem-dimethyl amide substrates **17a–17j**:*



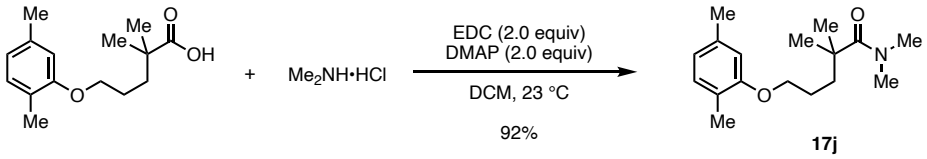
S2 **17a–17j**

(4-Dimethylamino)pyridine (DMAP, 2.00 equiv), dimethylamine hydrochloride (1.50 equiv), and EDC (2.00 equiv) were added in sequence to a solution of the carboxylic acid **S2** (1 equiv) in dichloromethane (0.20 M) at 23 °C. The reaction mixture was stirred for at 23 °C for 12 h. The product mixture was then diluted sequentially with dichloromethane, water, and saturated aqueous

ammonium chloride solution. The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with dichloromethane. The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution. The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 20% ethyl acetate–hexanes initially) to provide the *gem*-dimethyl amide substrates **17a–17j**.

The spectroscopic data for the corresponding *gem*-dimethyl amide substrates **17c–17f** and **17i** prepared according to this general procedure B matched the previously reported ^{1}H NMR data.[2,3,5]

*Synthesis of the gem-dimethyl amide Gemfibrozil analogue **17j**:*



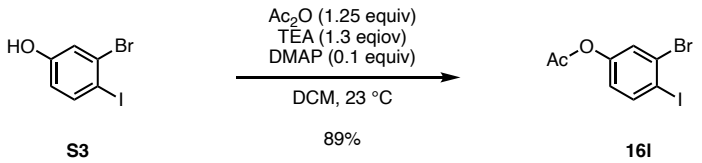
(4-Dimethylamino)pyridine (DMAP, 489 mg, 4.00 mmol, 2.00 equiv), dimethylamine hydrochloride (246 mg, 3.0 mmol, 1.5 equiv), and EDC (620 mg, 4.00 mmol, 2.00 equiv) were added in sequence to a solution of the carboxylic acid Gemfibrozil (500 mg, 2.00 mmol, 1 equiv) in dichloromethane (10.0 mL) at 23 °C. The reaction mixture was stirred for at 23 °C for 12 h. The product mixture was then diluted sequentially with dichloromethane (20 mL), water (10 mL), and saturated aqueous ammonium chloride solution (20 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (2 x 20 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 20% ethyl acetate–hexanes) to provide the *gem*-dimethyl amid Gemfibrozil analogue **17j** (colorless oil, 510 mg, 92%).

The spectroscopic data for the amide **17j** matched the previously reported ^{1}H NMR data.[6]

General Procedure C: Preparation of Substrates 8, 16k–16s.

Substrates **8, 16k** and **16m**–**16s** were obtained from commercial sources.

*Synthesis of the 4-bromo-3-iodophenyl acetate **16l**:*

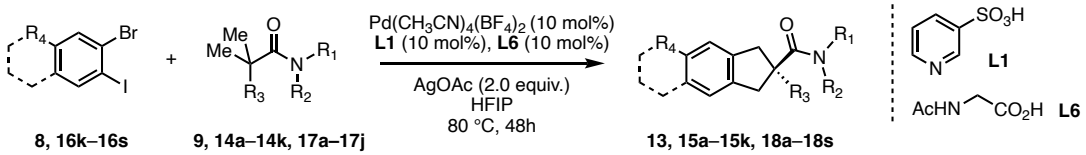


S3 **16l**

(4-Dimethylamino)pyridine (DMAP, 12.0 mg, 0.10 mmol, 0.10 equiv), triethylamine (0.180 mL, 1.30 mmol, 1.30 equiv), and acetic anhydride (0.12 mL, 1.25 mmol, 1.25 equiv) were added in sequence to a solution of 4-bromo-3-iodophenol (**S3**, 300 mg, 1.0 mmol, 1 equiv) in dichloromethane (6.0 mL) at 23 °C. The reaction mixture was stirred for at 23 °C for 12 h. The product mixture was then diluted sequentially with dichloromethane (10 mL), water (5 mL), and saturated aqueous ammonium chloride solution (5 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (2 x 10 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 10% ethyl acetate–hexanes) to provide the 4-bromo-3-iodophenyl acetate **16l** (colorless oil, 303 mg, 89%).

R_f = 0.20 (10% ethyl acetate–hexane). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.74 – 7.54 (m, 2H), 7.01 (dd, J = 8.7, 2.7 Hz, 1H), 2.31 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 168.77, 149.39, 133.32, 132.78, 126.55, 123.06, 100.79, 20.99. HRMS-CI (m/z): $[M + H]^+$ calcd for $C_8H_7BrIO_2$, 340.8674; found, 340.8686.

General Procedure D: Stitching of Native Amides and 1-bromo-2-iododarenes.



A screw-capped 16 x 125 mm culture tube was sequentially charged under air with $Pd(CH_3CN)_4(BF_4)_2$ (4.44 mg, 10.0 μmol, 0.10 equiv), ligand (**L1**) (1.58 mg, 10.0 μmol, 0.10 equiv), ligand (**L6**) (1.17 mg, 10.0 μmol, 0.10 equiv), silver acetate (33.2 mg, 0.20 mmol, 2.00 equiv), the 1-bromo-2-iododarene **8, 16k**–**16s** (0.15 mmol, 1.50 equiv), the *gem*-dimethyl amide **9, 14a**–**14k** or **17a**–**17j** (0.10 mmol, 1 equiv) and HFIP (0.5 mL) at 23 °C. The reaction vessel was sealed, and the mixture was allowed to stir for 10 min at 23 °C. The reaction vessel was then placed into a heat block that had been preheated to 80 °C. The reaction mixture was allowed to stir for 48 hours at 80 °C. After being allowed to cool to room temperature, the product mixture was diluted with DCM and filtered through a pad of Celite. The filtrate was concentrated and the residue obtained was purified by flash-column, preparative thin-layer chromatography, or preparative HPLC chromatography to provide the desired benzo-fused products **13**, **15a**–**15k**, or **18a**–**18s**.

Deviations from general procedure:

i) For substrates **14i**–**j**, **17f**, **17i**, **17n**, **17r**–**s** the palladium and ligand loading was increased to $Pd(CH_3CN)_4(BF_4)_2$ (8.88 mg, 20.0 μmol, 0.20 equiv), ligand (**L1**) (3.16 mg, 20.0 μmol, 0.20 equiv), ligand (**L6**) (2.34 mg, 20.0 μmol, 0.20 equiv).

ii) For substrate **14h** the palladium, ligand loading, and reaction time was increased to $Pd(CH_3CN)_4(BF_4)_2$ (8.88 mg, 20.0 μmol, 0.20 equiv), ligand (**L1**) (3.16 mg, 20.0 μmol, 0.20 equiv), ligand (**L6**) (2.34 mg, 20.0 μmol, 0.20 equiv), and 72h.

iii) For substrates **16r, 17e**, and **17j** the palladium source was changed and the ligand loading was increased to $Pd(OAc)_2$ (4.49 mg, 20.0 μmol, 0.20 equiv), ligand (**L1**) (3.16 mg, 20.0 μmol, 0.20 equiv), ligand (**L6**) (2.34 mg, 20.0 μmol, 0.20 equiv).

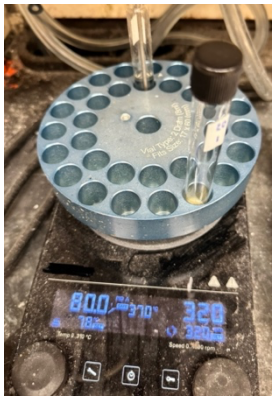
Graphical Representation For General Procedure.

Depicted reaction represents stitching of 1-bromo-2-iodobenzene (**8**) and *N,N*-dimethylpivalamide (**9**) to provide bicycle **13**:

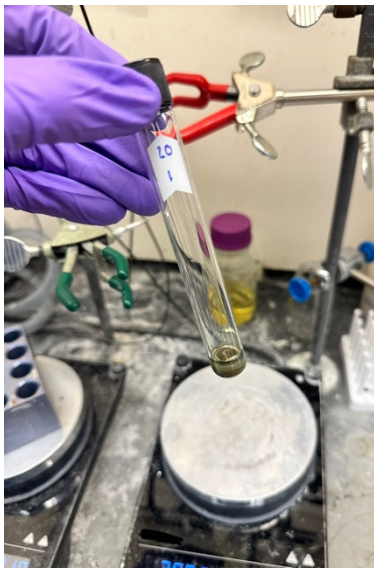
Reagents used:

Combined reagents:

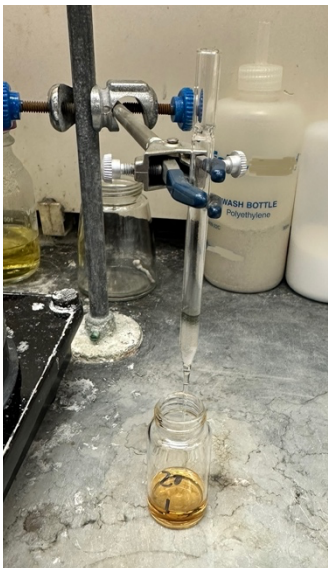
Reaction in progress:



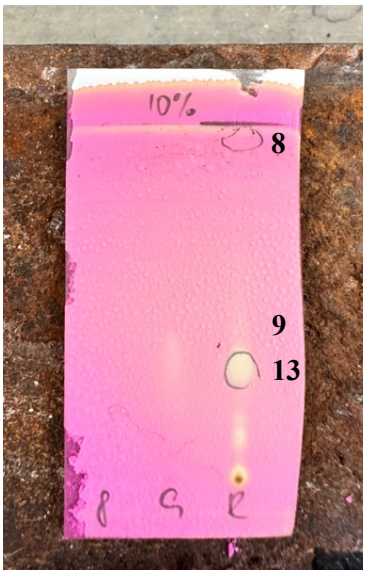
Appearance after 48 hours:



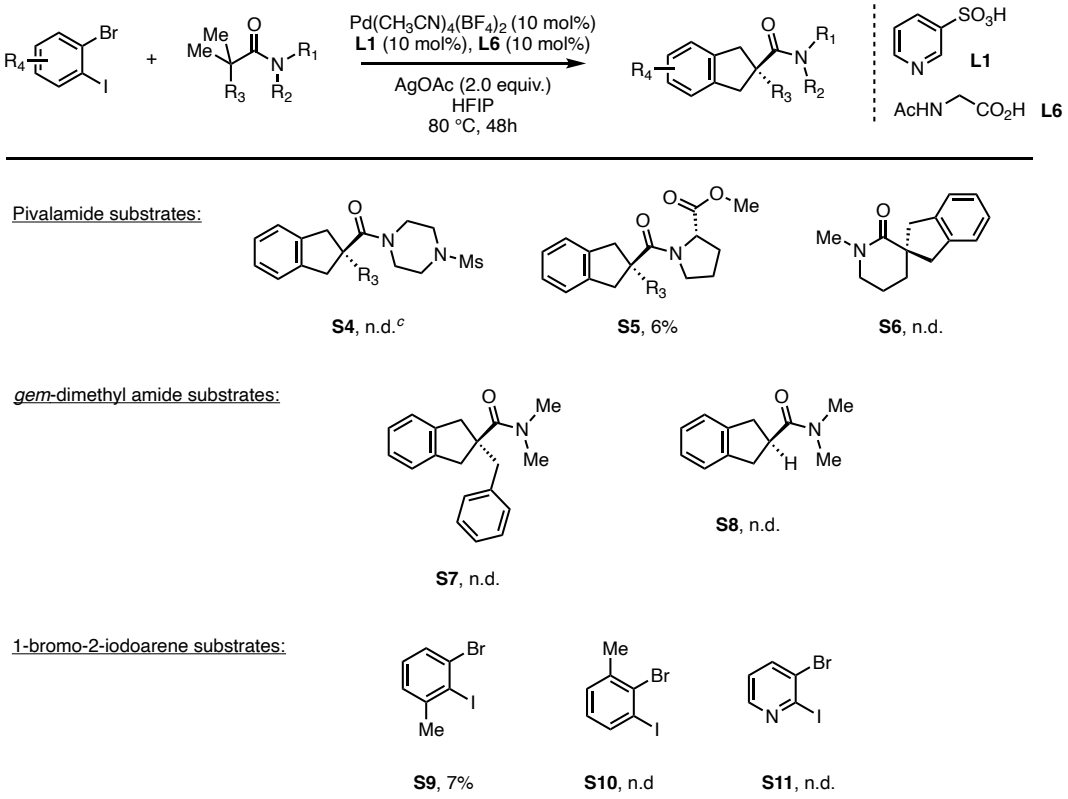
Filtration through Celite:



TLC (10% EtOAc–DCM):



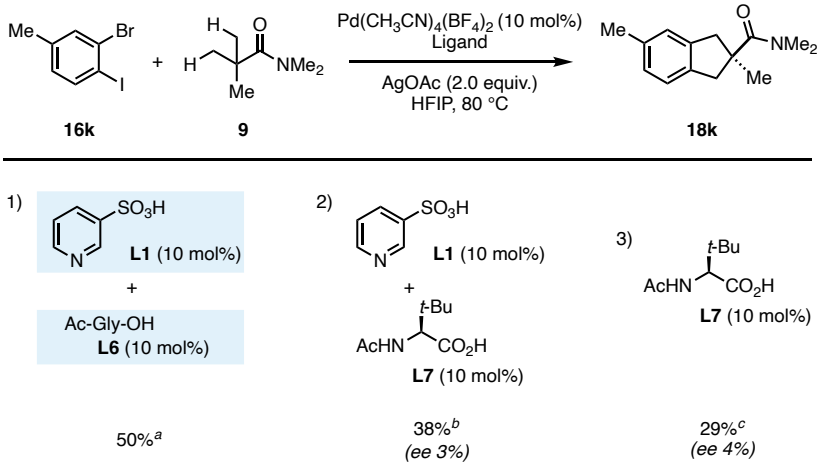
List of Unsuccessful Substrates.[a,b,c]



[a]Conditions: 1-bromo-2-iododarene (0.15 mmol), amide (0.10 mmol), $Pd(CH_3CN)_4(BF_4)_2$ (10 mol%), **L1** (10 mol%), **L6** (10 mol%), AgOAc (2.0 equiv), HFIP (0.5 mL), 80 °C, 48h. [b]Yields were determined by ^1H NMR analysis of an unpurified product mixture using CH_2Br_2 as an internal standard. [c]None detected.

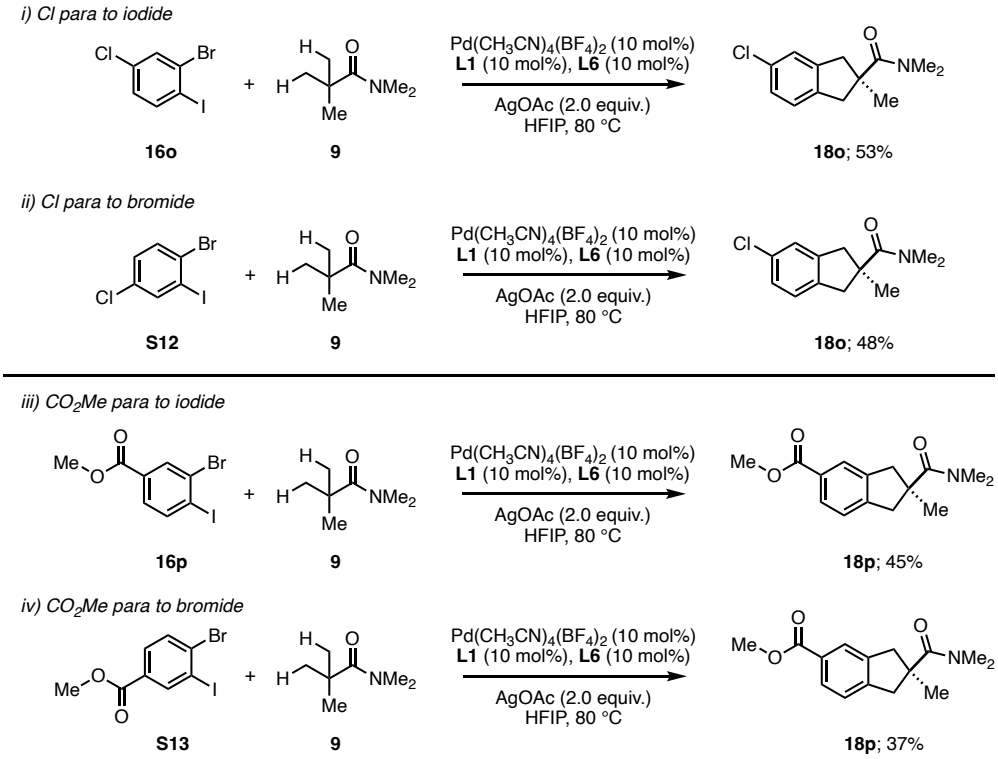
Examination of Enantioselectivity.[a,b,c]

Table S5. Investigation of enantioselectivity with chiral **L7**.



Conditions: [a]**16k** (0.15 mmol), **9** (0.10 mmol), Pd(CH3CN)4(BF4)2 (10 mol%), **L1** (10 mol%), **L6** (10 mol%), AgOAc (2.0 equiv), HFIP (0.5 mL), 80 °C, 48h. [b]**L1** (10 mol%), **L7** (10 mol%). [c]**L7** (10 mol%).

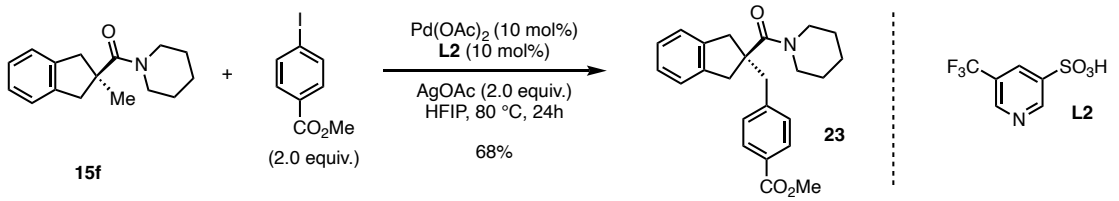
Investigation of the para substituent effect. [a,b]



[a]Conditions: 1-bromo-2-iododarene (0.15 mmol), **9** (0.10 mmol), $Pd(CH_3CN)_4(BF_4)_2$ (10 mol%), **L1** (10 mol%), **L6** (10 mol%), AgOAc (2.0 equiv), HFIP (0.5 mL), 80 °C, 48h. [b]Yields were determined by ^1H NMR of an unpurified product mixture using CH_2Br_2.

Synthetic Procedure for Preparation of 23 and 24.

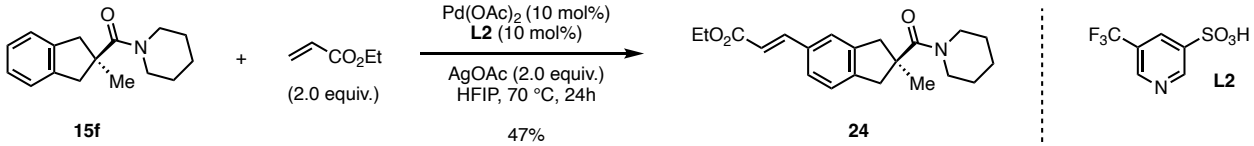
*Synthesis of the C2 arylated product **23**:*



A screw-capped culture tube was sequentially charged with $Pd(OAc)_2$ (2.20 mg, 10.0 μmol, 0.10 equiv), ligand (**L2**) (2.26 mg, 10.0 μmol, 0.10 equiv), silver acetate (36.7 mg, 0.2 mmol, 2.00 equiv), bicycle **15f** (24.3 mg, 0.10 mmol, 1 equiv), methyl 4-iodobenzoate (52.3 mg, 0.20 mmol, 2.00 equiv) and HFIP (0.50 mL) at 23 °C. The reaction vessel was sealed, and the mixture was allowed to stir for 10 min at 23 °C. The reaction vessel was then placed into a heat block that had been preheated to 80 °C. The reaction mixture was allowed to stir for 24 hours at 80 °C. After being allowed to cool to room temperature, the product mixture was diluted with DCM and filtered through a pad of Celite. The filtrate was concentrated and the residue obtained was purified by flash-column chromatography (eluting with 20% ethyl acetate–hexanes) to provide the C2 arylated product **23** (colorless oil, 25.6 mg, 68%).

R_f = 0.20 (20% ethyl acetate–hexane). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.94 (d, J = 8.2 Hz, 2H), 7.25 – 7.18 (m, 4H), 7.16 (d, J = 8.0 Hz, 2H), 3.92 (s, 3H), 3.60 – 3.43 (m, 6H), 3.12 (d, J = 16.1 Hz, 2H), 3.01 (s, 2H), 1.67 (q, J = 6.0 Hz, 2H), 1.62 – 1.54 (m, 4H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 173.73, 167.02, 143.23, 140.72, 130.06, 129.42, 128.53, 126.72, 124.57, 55.83, 52.04, 43.44, 43.06, 26.13, 24.64. HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{24}H_{28}NO_3$, 378.2069; found, 378.2075.

*Synthesis of the C5 olefinated product **24**:*



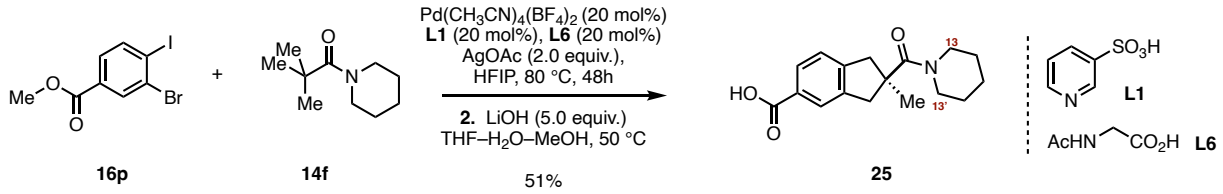
A screw-capped culture tube was sequentially charged with $Pd(OAc)_2$ (2.20 mg, 10.0 μmol, 0.10 equiv), ligand (**L2**) (2.26 mg, 10.0 μmol, 0.10 equiv), silver acetate (36.7 mg, 0.20 mmol, 2.00 equiv), bicycle **15f** (24.3 mg, 0.10 mmol, 1 equiv), ethyl acrylate (21.3 μL, 0.20 mmol, 2.00 equiv) and HFIP (0.5 mL) at 23 °C. The reaction vessel was sealed, and the mixture was allowed to stir for 10 min at 23 °C. The reaction vessel was then placed into a heat block that had been preheated to 70 °C. The reaction mixture was allowed to stir for 24 hours at 80 °C. After being allowed to cool to room temperature, the product mixture was diluted with DCM and filtered through a pad of Celite. The filtrate was concentrated and the residue obtained was purified by flash-column

chromatography (eluting with 25% ethyl acetate–hexanes) to provide the C5 olefinated product **24** (colorless oil, 16.0 mg, 47%).

R_f = 0.30 (20% ethyl acetate–hexane). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.69 (d, *J* = 16.0 Hz, 1H), 7.39 (s, 1H), 7.35 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.23 (d, *J* = 7.7 Hz, 1H), 6.41 (d, *J* = 16.0 Hz, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 3.70 – 3.49 (m, 6H), 2.94 (dd, *J* = 16.6, 3.0 Hz, 2H), 1.69 (q, *J* = 6.4 Hz, 2H), 1.64 – 1.57 (m, 4H), 1.38 (s, 3H), 1.36 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 174.97, 167.23, 144.88, 143.99, 141.95, 133.19, 127.11, 125.14, 124.11, 117.22, 60.43, 50.24, 45.21, 44.88, 26.21, 26.19, 24.69, 14.35. HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{21}H_{28}NO_3$, 342.2069; found, 342.2075.

Synthesis of Echinolactone D (29).

*Synthesis of the carboxylic acid **25** dual Pd-stitching:*



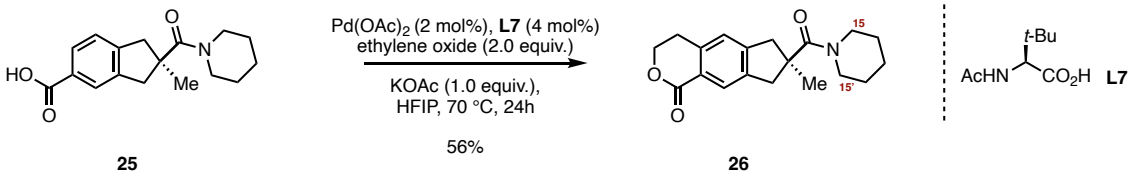
A screw-capped culture tube was sequentially charged with $Pd(CH_3CN)_4(BF_4)_2$ (311 mg, 0.70 mmol, 0.20 equiv), ligand (**L1**) (111.2 mg, 0.70 mmol, 0.20 equiv), ligand (**L6**) (81.9 mg, 0.70 mmol, 0.20 equiv), silver acetate (1.16 g, 7.00 mmol, 2.00 equiv), the methyl 3-bromo-4-iodobenzoate **16p** (1.78 g, 5.25 mmol, 1.50 equiv), the pivalamide **14f** (0.62 mL, 3.50 mmol, 1 equiv) and HFIP (17.5 mL) at 23 °C. The reaction vessel was sealed, and the mixture was allowed to stir for 10 min at 23 °C. The reaction vessel was then placed into a heat block that had been preheated to 80 °C. The reaction mixture was allowed to stir for 48 hours at 80 °C. After being allowed to cool to room temperature, the product mixture was diluted with DCM and filtered through a pad of Celite. The filtrate was concentrated and the residue obtained was used directly in the subsequent step.

Lithium hydroxide (419 mg, 17.5 mmol, 5.00 equiv) was added to a solution of the residue obtained in the previous step (nominally, 3.50 mmol, 1 equiv) dissolved in tetrahydrofuran (12 mL), water (12 mL), and methanol (12 mL) at 23 °C. The reaction mixture was then placed in an oil bath that had been preheated to 50 °C. The reaction mixture was stirred at 50 °C for 6 hours. The product mixture was allowed to cool to 23 °C over 30 min. The cooled product mixture was concentrated under reduced pressure and the residue obtained was diluted sequentially with dichloromethane (60 mL), water (60 mL), and 1.0 M hydrochloric acid solution (30 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (2 x 60 mL). The organic layers were combined, and the combined organic layers were washed with saturated aqueous sodium chloride solution. The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 50% ethyl acetate–hexanes) to provide the carboxylic acid **25** (yellow oil, 512 mg, 51%).

R_f = 0.30 (50% ethyl acetate–hexane). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.96 (t, *J* = 3.4 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 1H), 3.77 – 3.48 (m, 6H), 3.00 (dd, *J* = 16.5, 13.2 Hz, 2H), 1.70 (q, *J* = 6.1 Hz, 2H), 1.62 (p, *J* = 5.8 Hz, 4H), 1.39 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 174.86, 171.25, 147.81, 141.54, 129.09, 127.89, 126.55, 124.73, 77.23, 77.02, 76.81, 50.39, 45.45, 44.64, 26.17, 26.07, 24.67. HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{17}H_{22}NO_3$, 288.1600; found, 288.1611.

Note: Owing to extensive line broadening the carbon signal for C13/C13' was not observed in the ^{13}C NMR spectrum.

*Synthesis of the lactone **26** via ortho alkylation:*

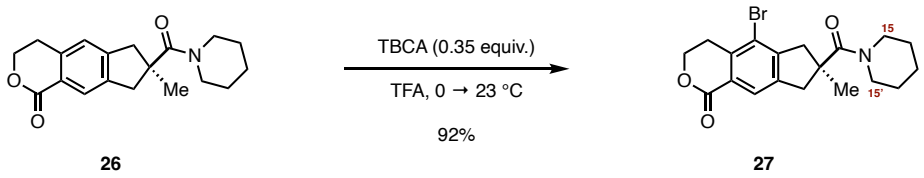


A screw-capped culture tube was sequentially charged with $Pd(OAc)_2$ (3.12 mg, 13.9 μmol, 0.02 equiv), ligand (**L7**) (4.82 mg, 27.8 μmol, 0.04 equiv), potassium acetate (68.3 mg, 0.696 mmol, 1.00 equiv), the carboxylic acid **25** (200 mg, 0.696 mmol, 1 equiv), HFIP (1.75 mL), and ethylene oxide (2.5 M in THF, 0.55 mL, 1.39 mmol, 2.00 equiv) at 23 °C. The reaction vessel was sealed, and the mixture was allowed to stir for 10 min at 23 °C. The reaction vessel was then placed into a heat block that had been preheated to 80 °C. The reaction mixture was allowed to stir for 24 hours at 70 °C. After being allowed to cool to room temperature, the product mixture was diluted with DCM and filtered through a pad of Celite. The filtrate was concentrated and the residue obtained was purified by flash-column chromatography (eluting with 40% ethyl acetate–hexanes) to provide the lactone **26** (yellow oil, 122 mg, 56%).

R_f = 0.20 (40% ethyl acetate–hexane). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.94 (s, 1H), 7.12 (s, 1H), 4.53 (t, *J* = 6.0 Hz, 2H), 3.73 (d, *J* = 17.1 Hz, 1H), 3.65 – 3.46 (m, 5H), 3.10 – 2.96 (m, 3H), 2.93 (d, *J* = 17.1 Hz, 1H), 1.70 (q, *J* = 6.1 Hz, 2H), 1.62 (p, *J* = 5.5 Hz, 4H), 1.38 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 174.60, 165.56, 148.19, 140.86, 138.39, 126.61, 123.85, 123.38, 67.26, 50.45, 45.68, 44.12, 28.04, 26.15, 25.88, 24.65. HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{19}H_{24}NO_3$, 314.1756; found, 314.1767.

Note: Owing to extensive line broadening the carbon signal for C15/C15' was not observed in the ^{13}C NMR spectrum.

*Synthesis of the bromide **27** via electrophilic bromination:*



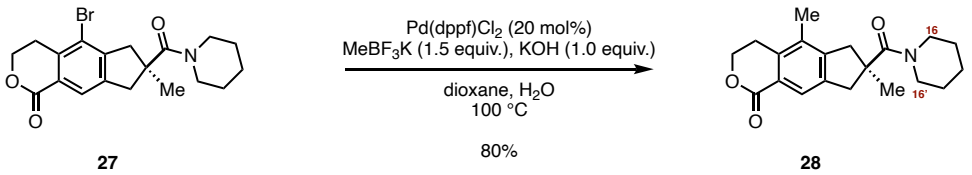
26 **27**

1,3,5-tribromo-1,3,5-triazine-2,4,6-trione (TBCA, 40.8 mg, 0.11 mmol, 0.35 equiv) was added to a solution of the lactone **26** (100 mg, 0.319 mmol, 1 equiv) in trifluoracetic acid (3.20 mL) at 0 °C. The reaction mixture was allowed to slowly warm to 23 °C over 1 hour and stirred at 23 °C for 3h. The product mixture was then diluted sequentially with dichloromethane (25 mL), water (10 mL), and saturated aqueous sodium bicarbonate solution (20 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (2 x 20 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 40% ethyl acetate–hexanes) to provide the bromide **27** (amorphous solid, 115 mg, 92%).

R_f = 0.30 (50% ethyl acetate–hexane). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.93 (s, 1H), 4.54 (t, J = 6.1 Hz, 2H), 3.71 (dd, J = 17.2, 3.7 Hz, 2H), 3.58 (s, 4H), 3.21 – 3.02 (m, 4H), 1.71 (q, J = 5.0 Hz, 2H), 1.63 (p, J = 5.6 Hz, 4H), 1.42 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 174.10, 164.68, 148.49, 141.73, 137.85, 125.83, 125.56, 120.14, 66.66, 49.49, 47.60, 45.55, 28.06, 26.24, 26.12, 24.62. HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{19}H_{23}BrNO_3$, 392.0861; found, 392.0869.

Note: Owing to extensive line broadening the carbon signal for C15/C15' was not observed in the ^{13}C NMR spectrum.

*Synthesis of the cross-coupled methylated product **28**:*



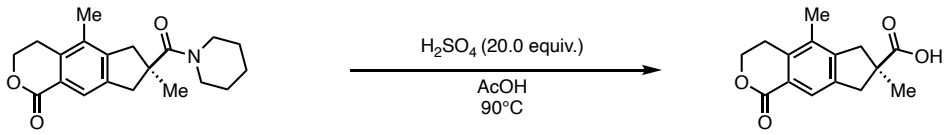
27 **28**

A screw-capped culture tube was sequentially charged with $Pd(dppf)Cl_2$ (22.4 mg, 30.6 μmol, 0.20 equiv), potassium methyltrifluoroborate (28.0 mg, 0.230 mmol, 1.5 equiv), potassium hydroxide (8.5 mg, 0.153mmol, 1.0 equiv), the bromide **27** (60.0 mg, 0.153 mmol, 1 equiv), dioxane (2.6 mL), and water (0.5 mL) at 23 °C. The reaction vessel was sealed, and the mixture was allowed to stir for 10 min at 23 °C. The reaction vessel was then placed into a heat block that had been preheated to 100 °C. The reaction mixture was allowed to stir for 48 hours at 70 °C. After being allowed to cool to room temperature, the product mixture was diluted with DCM and filtered through a pad of Celite. The filtrate was then diluted sequentially with ethyl acetate (10 mL), water (5 mL), and saturated aqueous ammonium chloride solution (10 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (2 x 15 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 50% ethyl acetate–hexanes) to provide the cross-coupled product **28** (colorless oil, 40 mg, 80%).

R_f = 0.20 (50% ethyl acetate–hexane). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.84 (s, 1H), 4.52 (t, *J* = 6.0 Hz, 2H), 3.69 (d, *J* = 17.2 Hz, 1H), 3.63 – 3.41 (m, 5H), 3.03 (d, *J* = 16.2 Hz, 1H), 2.98 (t, *J* = 6.1 Hz, 2H), 2.91 (d, *J* = 17.1 Hz, 1H), 2.24 (s, 3H), 1.70 (q, *J* = 6.0 Hz, 2H), 1.62 (q, *J* = 5.6 Hz, 4H), 1.39 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 174.78, 166.06, 146.94, 139.88, 136.67, 130.90, 124.20, 124.07, 66.72, 49.70, 45.31, 44.53, 26.44, 26.12, 25.09, 24.66, 15.27. HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{20}H_{26}NO_3$, 328.1913; found, 328.1919.

Note: Owing to extensive line broadening the carbon signal for C16/C16' was not observed in the ^{13}C NMR spectrum.

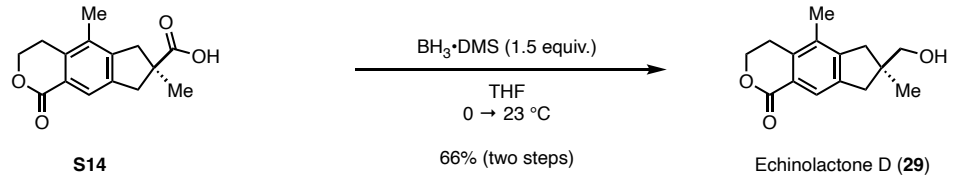
*Synthesis of the carboxylic acid **S14** via hydrolysis of the amide moiety:*



28 **S14**

Sulfuric acid (6.0 M, 0.30 mL, 1.83 mmol, 20.0 equiv) was added to a solution of the lactone **28** (30 mg, 92.0 μmol, 1 equiv) in acetic acid (1.00 mL) at 23 °C. The reaction vessel was sealed, and the sealed reaction vessel was then placed into a heat block that had been preheated to 90 °C. The reaction mixture was allowed to stir for 4 hours at 70 °C. After being allowed to cool to room temperature, the product mixture was sequentially diluted with dichloromethane (20 mL), water (20 mL), and 1.0 M hydrochloric acid solution (10 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (2 x 15 mL). The organic layers were combined, and the combined organic layers were washed with saturated aqueous sodium chloride solution. The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used directly in the subsequent step without further purification.

*Synthesis of echinolactone D (**29**):*



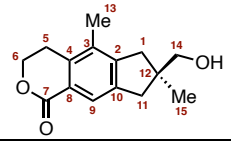
Borane dimethyl sulfide complex (2.0 M in THF, 69.0 µL, 0.137 mmol, 1.50 equiv) was added dropwise via a syringe at 0 °C to a solution of the residue obtained in the previous step (nominally, 0.092 mmol, 1 equiv) in tetrahydrofuran (0.90 mL). The reaction mixture was then allowed to slowly warm up to 23 °C over 1 hour. The product mixture was then diluted sequentially with ethyl acetate (5 mL), water (2.5 mL), and saturated aqueous ammonium chloride solution (2.5 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 40% ethyl acetate–hexanes) to provide echinolactone D (**29**) (colorless oil, 14.8 mg, 66% over two steps).

R_f = 0.30 (50% ethyl acetate–hexane). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.80 (s, 1H), 4.48 (t, J = 6.0 Hz, 2H), 3.54 (s, 2H), 2.99 – 2.88 (m, 4H), 2.71 (d, J = 15.9 Hz, 1H), 2.64 (d, J = 16.8 Hz, 1H), 2.19 (s, 3H), 1.18 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 166.15, 148.42, 141.49, 136.34, 130.93, 124.27, 123.76, 70.35, 66.72, 44.47, 42.60, 42.23, 25.08, 24.17, 15.28. HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{15}H_{19}O_3$, 247.1334; found, 247.1343.

The spectroscopic data for echinolactone D (**29**) matched the reported ^{1}H NMR data and ^{13}C NMR by Shiono and co-workers (see Table S6 and S7).[7]

Comparison of ^{1}H and ^{13}C NMR Data of Synthetic and Isolated Echinolactone D (29).

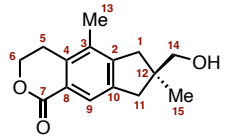
Table S6. Comparison of ^{1}H NMR data for synthetic and isolated echinolactone D (**29**).



position	synthetic (±)-**29** [600 MHz, $CDCl_3$]	isolated (+)-**29**[7] [100 MHz, $CDCl_3$]
	^{1}H [δ H (ppm), mult., *J* (Hz)]	^{1}H [δ H (ppm), mult., *J* (Hz)]
H-1	2.64 (1H, d, 16.8)	2.64 (1H, d, 16.6)
	2.99 – 2.88 (1H, m)*	2.96 (1H, d, 16.6)*
H-5	2.99 – 2.88 (2H, m)*	2.94 (2H, t, 5.9)
H-6	4.48 (2H, t, 6.0)	4.48 (2H, t, 5.9)
H-9	7.80 (1H, s)	7.80 (1H, s)
H-11	2.71 (1H, d, 15.9)	2.71 (1H, d, 16.6)
	2.99 – 2.88 (1H, m)*	2.96 (1H, d, 16.6)*
H-13	2.19 (3H, s)	2.19 (3H, s)
H-14	3.54 (2H, s)	3.53 (2H, s)
H-15	1.18 (3H, s)	1.18 (3H, s)

Note: *Signal overlap.

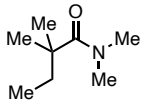
Table S7. Comparison of ^{13}C NMR data for synthetic and isolated echinolactone D (**29**).



position	synthetic (±)-**29** [151 MHz, $CDCl_3$]	isolated (+)-**29**[7] [25 MHz, $CDCl_3$]	Chemical Shift Difference
	^{13}C [δ (ppm)]	^{13}C [δ (ppm)]	[ppm]
1	42.2	42.2	0
2	148.4	148.4	0
3	130.9	130.9	0
4	136.3	136.3	0
5	25.1	25.1	0
6	66.7	66.7	0
7	166.2	166.1	0.1
8	123.8	123.7	0.1
9	124.3	124.2	0.1
10	141.5	141.5	0
11	42.6	42.6	0
12	44.5	44.4	0.1
13	15.3	15.2	0.1
14	70.4	70.3	0.1
15	24.2	24.1	0.1

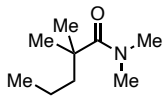
Characterization of Substrates and Products.

Substrates:



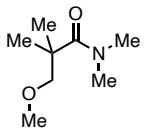
17a

N,*N*,2,2-tetramethylbutanamide (**17a**). R_f = 0.20 (30% ethyl acetate–hexanes). Prepared according to general procedure B: ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.04 (s, 6H), 1.66 (q, *J* = 7.5 Hz, 2H), 1.25 (s, 3H), 0.87 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 176.78, 42.92, 38.13, 33.14, 26.45, 9.39. HRMS-CI (m/z): $[M + H]^+$ calcd for $C_8H_{18}NO$, 144.1388; found, 144.1384.



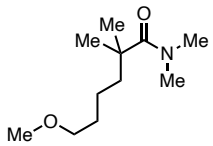
17b

N,*N*,2,2-tetramethylpentanamide (**17b**). R_f = 0.20 (30% ethyl acetate–hexanes). Prepared according to general procedure B: ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.04 (s, 6H), 1.63 – 1.55 (m, 2H), 1.30 – 1.26 (m, 8H), 0.92 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 176.90, 43.09, 42.64, 38.15, 26.98, 18.32, 14.70. HRMS-CI (m/z): $[M + H]^+$ calcd for $C_9H_{20}NO$, 158.1545; found, 158.1548.



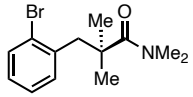
17g

3-methoxy-*N*,*N*,2,2-tetramethylpropanamide (**17g**). R_f = 0.25 (30% ethyl acetate–dichloromethane). Prepared according to general procedure B: ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.46 (s, 2H), 3.37 (s, 3H), 3.04 (s, 6H), 1.30 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 175.89, 80.40, 59.27, 43.18, 38.09, 23.23. HRMS-CI (m/z): $[M + H]^+$ calcd for $C_8H_{18}NO_2$, 160.1338; found, 160.1339.



5-methoxy-*N*,*N*,2,2-tetramethylpentanamide (**17h**). R_f = 0.35 (50% ethyl acetate–dichloromethane). Prepared according to general procedure B: ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.38 (t, *J* = 6.6 Hz, 2H), 3.34 (s, 3H), 3.05 (s, 6H), 1.67 – 1.63 (m, 2H), 1.57 (dq, *J* = 7.8, 6.6 Hz, 2H), 1.33 (dddd, *J* = 12.2, 9.5, 7.8, 5.1 Hz, 2H), 1.28 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 176.78, 72.69, 58.59, 42.55, 40.66, 38.19, 30.25, 26.86, 21.75. HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{11}H_{24}NO_2$, 202.1807; found, 202.1800.

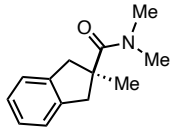
Intermediate:



10

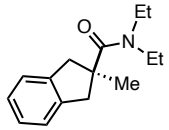
3-(2-bromophenyl)-*N*,*N*,2,2-tetramethylpropanamide (**10**). R_f = 0.50 (10% ethyl acetate–dichloromethane) ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.56 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.23 (td, *J* = 7.4, 1.3 Hz, 1H), 7.19 (dd, *J* = 7.7, 1.9 Hz, 1H), 7.08 (ddd, *J* = 8.0, 7.1, 1.9 Hz, 1H), 3.20 (s, 2H), 3.08 (s, 6H), 1.34 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 176.48, 137.94, 133.00, 131.66, 128.01, 127.11, 125.96, 44.10, 44.00, 38.69, 26.54. HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{13}H_{19}BrNO$, 284.0650; found, 284.0655.

Products:



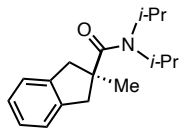
13

N,*N*,2-trimethyl-2,3-dihydro-1*H*-indene-2-carboxamide (**13**). R_f = 0.30 (10% ethyl acetate–dichloromethane). Prepared according to general procedure D and was obtained as a colorless oil (13.0 mg, 64%): ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.22 (dt, *J* = 4.5, 3.5 Hz, 2H), 7.19 (dt, *J* = 5.1, 3.6 Hz, 2H), 3.59 (d, *J* = 16.0 Hz, 2H), 3.06 (s, 6H), 2.97 – 2.92 (m, 2H), 1.38 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 176.85, 141.0, 126.59, 124.77, 49.68, 45.12, 37.77, 28.86. HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{13}H_{18}NO$, 204.1388; found, 204.1395.



15a

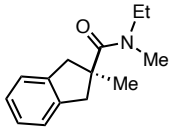
N,*N*-diethyl-2-methyl-2,3-dihydro-1*H*-indene-2-carboxamide (**15a**). R_f = 0.30 (10% ethyl acetate–dichloromethane). Prepared according to general procedure D and was obtained as a colorless oil (15.7 mg, 68%): ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.24 – 7.20 (m, 2H), 7.21 – 7.16 (m, 2H), 3.58 (d, *J* = 16.0 Hz, 2H), 3.42 (s, 3H), 2.92 (d, *J* = 15.6 Hz, 3H), 1.36 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 176.10, 141.03, 126.52, 124.71, 50.30, 45.11, 41.60, 40.68, 26.07, 14.30, 12.65. HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{15}H_{22}NO$, 232.1701; found, 232.1711.



15b

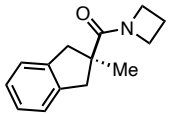
N,*N*-diisopropyl-2-methyl-2,3-dihydro-1*H*-indene-2-carboxamide (**15b**). R_f = 0.35 (10% ethyl acetate–dichloromethane). Prepared according to general procedure D and was obtained as a colorless oil (14.5 mg, 56%): ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.24 – 7.20 (m, 2H), 7.20 – 7.16 (m, 2H), 4.16 (p, *J* = 6.4 Hz, 1H), 3.58 (d, *J* = 16.0 Hz, 2H), 3.36 (p, *J* = 6.7 Hz, 1H), 2.90 (d, *J* = 16.0

Hz, 2H), 1.45 (d, J = 6.7 Hz, 6H), 1.35 (s, 3H), 1.25 (d, J = 6.6 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 175.68, 141.01, 126.47, 124.66, 51.18, 48.19, 46.54, 44.94, 25.91, 20.70. HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{17}H_{26}NO$, 260.2014; found, 260.2023.



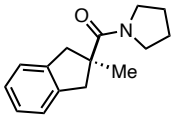
15c

N-ethyl-*N*,2-dimethyl-2,3-dihydro-1*H*-indene-2-carboxamide (**15c**). R_f = 0.30 (10% ethyl acetate–dichloromethane). Prepared according to general procedure D and was obtained as a colorless oil (12.8 mg, 59%): ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.25 – 7.21 (m, 2H), 7.22 – 7.14 (m, 2H), 3.58 (d, J = 16.0 Hz, 2H), 3.46 (q, J = 7.1 Hz, 2H), 3.03 (s, 3H), 2.93 (d, J = 16.8 Hz, 2H), 1.37 (s, 3H), 1.19 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 176.33, 141.01, 126.56, 124.74, 49.96, 45.11, 44.23, 25.89, 13.81, 12.01. HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{14}H_{20}NO$, 218.1545; found, 218.1553.



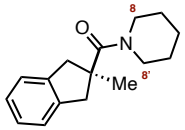
15d

azetidin-1-yl(2-methyl-2,3-dihydro-1*H*-inden-2-yl)methanone (**15d**). R_f = 0.20 (15% ethyl acetate–dichloromethane). Prepared according to general procedure D and was obtained as an amorphous solid (11.6 mg, 54%): ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.22 (dd, J = 5.3, 3.4 Hz, 2H), 7.17 (dd, J = 5.7, 3.0 Hz, 2H), 4.23 (s, 4H), 3.47 (d, J = 15.5 Hz, 2H), 2.82 (d, J = 15.4 Hz, 2H), 2.32 (tt, J = 8.6, 7.2 Hz, 2H), 1.31 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 176.88, 141.07, 126.47, 124.74, 51.96, 49.24, 43.41, 24.53, 15.86. HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{14}H_{18}NO$, 216.1388; found, 216.1395.



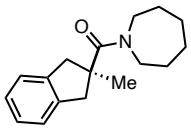
15e

(2-methyl-2,3-dihydro-1*H*-inden-2-yl)(pyrrolidin-1-yl)methanone (**15e**). R_f = 0.25 (20% ethyl acetate–dichloromethane). Prepared according to general procedure D and was obtained as a amorphous solid (13.2 mg, 58%): ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.22 (dd, J = 5.3, 3.4 Hz, 2H), 7.18 (dd, J = 5.6, 3.2 Hz, 2H), 3.75 – 3.44 (m, 6H), 2.92 (d, J = 15.8 Hz, 2H), 1.98 (s, 2H), 1.87 (s, 2H), 1.35 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 175.60, 141.13, 126.47, 124.76, 50.40, 47.68, 47.11, 44.21, 27.04, 24.67, 23.39. HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{15}H_{20}NO$, 230.1545; found, 230.1554.



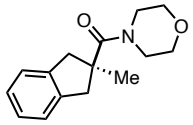
15f

(2-methyl-2,3-dihydro-1*H*-inden-2-yl)(piperidin-1-yl)methanone (**15f**). R_f = 0.30 (20% ethyl acetate–dichloromethane). Prepared according to general procedure D and was obtained as an amorphous solid (14.5 mg, 60%): ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.24 – 7.21 (m, 2H), 7.20 – 7.17 (m, 2H), 3.68 – 3.45 (m, 6H), 2.93 (d, *J* = 16.1 Hz, 2H), 1.74 – 1.65 (m, 2H), 1.64 – 1.55 (m, 4H), 1.38 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 175.40, 141.02, 126.56, 124.73, 49.81, 45.26, 26.42, 26.18, 24.72. HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{16}H_{22}NO$, 244.1701; found, 244.170. Note: Owing to extensive line broadening the carbon signal for C8/C8' was not observed in the ^{13}C NMR spectrum.



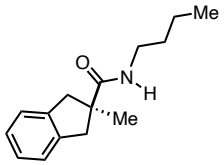
15g

azepan-1-yl(2-methyl-2,3-dihydro-1*H*-inden-2-yl)methanone (**15g**). R_f = 0.20 (20% ethyl acetate–dichloromethane). Prepared according to general procedure D and was obtained as an amorphous solid (14.4 mg, 56%): ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.24 – 7.20 (m, 2H), 7.18 (dd, *J* = 5.6, 3.2 Hz, 2H), 3.71 – 3.48 (m, 6H), 2.92 (d, *J* = 16.0 Hz, 2H), 1.79 (s, 4H), 1.62 (q, *J* = 3.0 Hz, 4H), 1.38 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 176.27, 141.03, 126.50, 124.70, 50.49, 47.91, 45.19, 30.06, 28.41, 26.89, 26.07, 25.81. HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{17}H_{23}NO$, 258.1858; found, 258.1867.



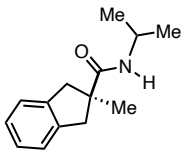
15h

(2-methyl-2,3-dihydro-1*H*-inden-2-yl)(morpholino)methanone (**15h**). R_f = 0.30 (20% ethyl acetate–dichloromethane). Prepared according to general procedure D and was obtained as a colorless oil (11.7 mg, 48%): ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.25 – 7.15 (m, 4H), 3.72 (t, *J* = 4.8 Hz, 4H), 3.64 (s, 4H), 3.58 (d, *J* = 16.2 Hz, 2H), 2.94 (d, *J* = 16.1 Hz, 2H), 1.39 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 175.81, 140.61, 126.77, 124.80, 66.89, 49.41, 45.22, 26.56. HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{15}H_{20}NO_2$, 246.1494; found, 246.1505. Note: Owing to extensive line broadening, one carbon signal was not observed in the ^{13}C NMR spectrum.



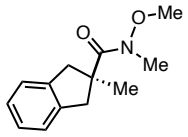
15i

N-butyl-2-methyl-2,3-dihydro-1*H*-indene-2-carboxamide (**15i**). R_f = 0.30 (20% ethyl acetate–hexane). Prepared according to general procedure D and was obtained as an amorphous solid (6.70 mg, 29%): ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.22 (dt, *J* = 4.7, 3.5 Hz, 2H), 7.19 (dt, *J* = 5.1, 3.6 Hz, 2H), 5.57 (s, 1H), 3.42 (d, *J* = 15.6 Hz, 2H), 3.29 (td, *J* = 7.1, 5.6 Hz, 2H), 2.84 (d, *J* = 15.5 Hz, 2H), 1.53 – 1.45 (m, 2H), 1.37 (s, 3H), 1.36 – 1.28 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 177.41, 141.48, 126.65, 124.79, 50.12, 44.35, 39.40, 31.71, 25.50, 20.03, 13.77. HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{15}H_{22}NO$, 232.1701; found, 232.1710.



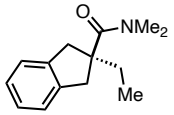
15j

N-isopropyl-2-methyl-2,3-dihydro-1*H*-indene-2-carboxamide (**15j**). R_f = 0.20 (20% ethyl acetate–hexane). Prepared according to general procedure D and was obtained as an amorphous solid (7.10 mg, 33%): ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.24 – 7.20 (m, 2H), 7.20 – 7.16 (m, 2H), 5.36 (s, 1H), 4.20 – 4.06 (m, 1H), 3.41 (d, *J* = 15.5 Hz, 2H), 2.82 (dd, J = 15.4, 1.8 Hz, 2H), 1.35 (s, 3H), 1.16 (d, *J* = 6.5 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 176.63, 141.44, 126.62, 124.78, 50.00, 44.26, 41.38, 25.55, 22.78. HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{14}H_{20}NO$, 218.1545; found, 218.1552.



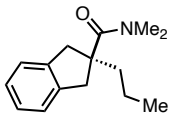
15k

N-methoxy-*N*,2-dimethyl-2,3-dihydro-1*H*-indene-2-carboxamide (**15k**). R_f = 0.20 (20% ethyl acetate–hexane). Prepared according to general procedure D and was obtained as a colorless oil (4.16 mg, 19%): ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.25 – 7.20 (m, 2H), 7.21 – 7.15 (m, 2H), 3.76 (s, 3H), 3.49 (d, *J* = 15.9 Hz, 2H), 3.27 (s, 3H), 2.99 – 2.87 (m, 2H), 1.35 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 178.54, 141.22, 126.37, 124.72, 60.74, 50.40, 43.81, 33.50, 24.48. HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{13}H_{18}NO_2$, 220.1338; found, 220.1345.



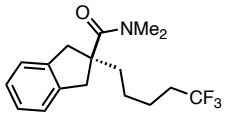
18a

2-ethyl-*N*,*N*-dimethyl-2,3-dihydro-1*H*-indene-2-carboxamide (**18a**). R_f = 0.20 (10% ethyl acetate–dichloromethane). Prepared according to general procedure D and was obtained as an amorphous solid (12.8 mg, 59%): ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.22 – 7.18 (m, 2H), 7.18 – 7.15 (m, 2H), 3.60 (d, *J* = 16.2 Hz, 2H), 3.17 – 2.89 (m, 8H), 1.76 (q, *J* = 7.4 Hz, 2H), 0.88 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 175.69, 141.31, 126.43, 124.37, 54.69, 42.96, 37.77, 30.99, 9.43. HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{14}H_{20}NO$, 218.1545; found, 218.1552.



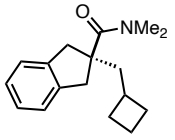
18b

N,*N*-dimethyl-2-propyl-2,3-dihydro-1*H*-indene-2-carboxamide (**18b**). R_f = 0.20 (10% ethyl acetate–dichloromethane). Prepared according to general procedure D and was obtained as an amorphous solid (14.1 mg, 61%): ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.21 – 7.18 (m, 2H), 7.18 – 7.14 (m, 2H), 3.61 (d, *J* = 16.1 Hz, 2H), 3.25 – 2.81 (m, 8H), 1.81 – 1.63 (m, 2H), 1.37 – 1.24 (m, 2H), 0.88 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 175.87, 141.31, 126.43, 124.36, 54.38, 43.41, 40.83, 37.78, 18.32, 14.53. HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{15}H_{22}NO$, 232.1701; found, 232.1711.



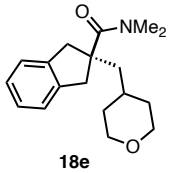
18c

N,*N*-dimethyl-2-(5,5,5-trifluoropentyl)-2,3-dihydro-1*H*-indene-2-carboxamide (**18c**). R_f = 0.30 (15% ethyl acetate–dichloromethane). Prepared according to general procedure D and was obtained as an amorphous solid (14.7 mg, 47%): ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.23 – 7.10 (m, 4H), 3.60 (d, *J* = 16.2 Hz, 2H), 3.18 – 2.95 (m, 8H), 2.14 – 1.97 (m, 2H), 1.80 – 1.69 (m, 2H), 1.51 (p, *J* = 7.8 Hz, 2H), 1.42 – 1.32 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 175.48, 140.95, 129.81, 127.98, 126.62, 126.15, 124.45, 53.99, 43.34, 38.03, 37.78, 33.86, 33.67, 33.48, 33.29, 24.19, 22.31. ^{19}F NMR (376 MHz, $CDCl_3$): δ –69.15. HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{17}H_{23}F_3NO$, 314.1732; found, 314.1741.



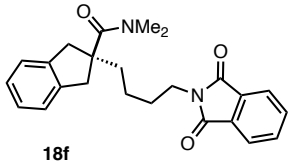
18d

2-(cyclobutylmethyl)-*N*,*N*-dimethyl-2,3-dihydro-1*H*-indene-2-carboxamide (**18d**). R_f = 0.30 (10% ethyl acetate–dichloromethane). Prepared according to general procedure D and was obtained as an amorphous solid (11.3 mg, 44%): ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.20 – 7.17 (m, 2H), 7.17 – 7.14 (m, 2H), 3.55 (d, *J* = 15.9 Hz, 2H), 3.01 (d, *J* = 15.9 Hz, 8H), 2.41 (dddd, *J* = 16.3, 14.4, 9.1, 7.2 Hz, 1H), 2.08 – 1.92 (m, 2H), 1.88 – 1.75 (m, 3H), 1.69 (qd, *J* = 8.5, 3.6 Hz, 1H), 1.62 – 1.50 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 175.71, 141.26, 126.39, 124.37, 54.20, 45.34, 43.43, 32.90, 29.84, 19.00. HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{17}H_{24}NO$, 258.1858; found, 258.1867.



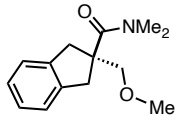
18e

N,*N*-dimethyl-2-((tetrahydro-2*H*-pyran-4-yl)methyl)-2,3-dihydro-1*H*-indene-2-carboxamide (**18e**). R_f = 0.35 (20% ethyl acetate–dichloromethane). Prepared according to general procedure D and was obtained as a colorless oil (11.3 mg, 40%): ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.20 – 7.11 (m, 4H), 3.86 (dd, *J* = 11.8, 4.3 Hz, 2H), 3.62 (d, *J* = 16.0 Hz, 2H), 3.35 (td, *J* = 11.8, 2.1 Hz, 2H), 3.22 – 2.87 (m, 8H), 1.67 (s, 3H), 1.56 – 1.44 (m, 2H), 1.24 (qd, *J* = 12.0, 4.5 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 175.76, 140.91, 126.53, 124.43, 67.99, 54.00, 45.21, 43.99, 38.00, 34.12, 31.87. HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{18}H_{26}NO_2$, 288.1964; found, 288.1974.



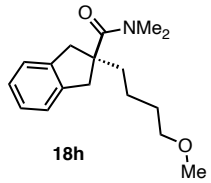
18f

2-(4-(1,3-dioxoisoindolin-2-yl)butyl)-*N*,*N*-dimethyl-2,3-dihydro-1*H*-indene-2-carboxamide (**18f**). R_f = 0.35 (10% ethyl acetate–dichloromethane). Prepared according to general procedure D and was obtained as an amorphous solid (18.3 mg, 47%): ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.84 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.72 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.23 – 7.17 (m, 2H), 7.17 – 7.12 (m, 2H), 3.80 – 3.48 (m, 4H), 3.03 (d, *J* = 16.2 Hz, 8H), 1.81 – 1.68 (m, 2H), 1.67 – 1.58 (m, 2H), 1.40 – 1.30 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 175.55, 168.34, 141.09, 133.88, 132.13, 126.50, 124.39, 123.18, 54.19, 43.29, 37.76, 37.61, 28.88, 22.18. HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{24}H_{27}N_2O_3$, 391.2022; found, 391.2028.



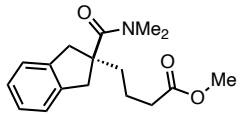
18g

2-(methoxymethyl)-*N*,*N*-dimethyl-2,3-dihydro-1*H*-indene-2-carboxamide (**18g**). R_f = 0.30 (30% ethyl acetate–dichloromethane). Prepared according to general procedure D and was obtained as a colorless oil (7.90 mg, 34%): ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.18 (ddt, *J* = 15.7, 5.1, 3.3 Hz, 4H), 3.47 (s, 2H), 3.40 (d, *J* = 16.5 Hz, 2H), 3.30 (s, 3H), 3.22 – 3.13 (m, 2H), 3.02 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 175.50, 141.05, 126.67, 124.69, 77.85, 59.20, 54.13, 40.76, 37.76. HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{14}H_{20}NO_2$, 234.1494; found, 234.1502.



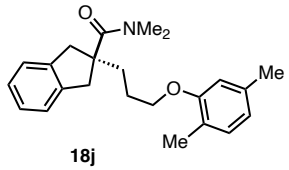
18h

2-(4-methoxybutyl)-*N*,*N*-dimethyl-2,3-dihydro-1*H*-indene-2-carboxamide (**18h**). R_f = 0.40 (50% ethyl acetate–dichloromethane). Prepared according to general procedure D and was obtained as an amorphous solid (14.3 mg, 52%): ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.23 – 7.13 (m, 4H), 3.61 (d, *J* = 16.1 Hz, 2H), 3.33 (t, *J* = 6.6 Hz, 2H), 3.31 (s, 3H), 3.19 – 2.99 (m, 8H), 1.75 – 1.69 (m, 2H), 1.52 (p, *J* = 6.9 Hz, 2H), 1.37 – 1.31 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 175.69, 141.19, 126.47, 124.42, 72.57, 58.59, 54.26, 43.37, 38.28, 37.77, 30.10, 21.74. HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{17}H_{26}NO_2$, 276.1964; found, 276.1960.



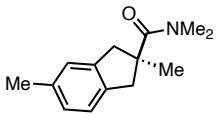
18i

methyl 4-(2-(dimethylcarbamoyl)-2,3-dihydro-1*H*-inden-2-yl)butanoate (**18i**). R_f = 0.30 (10% ethyl acetate–dichloromethane). Prepared according to general procedure D and was obtained as an amorphous solid (12.1 mg, 42%): ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.20 (dt, *J* = 6.2, 3.5 Hz, 2H), 7.17 (dt, *J* = 5.1, 3.5 Hz, 2H), 3.65 (s, 3H), 3.61 (d, *J* = 16.2 Hz, 2H), 3.05 (t, *J* = 18.3 Hz, 2H), 2.28 (t, *J* = 7.1 Hz, 2H), 1.81 – 1.71 (m, 2H), 1.67 – 1.57 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 175.41, 173.71, 141.05, 126.56, 124.43, 54.00, 51.51, 43.29, 37.76, 34.06, 20.49. HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{17}H_{24}NO_3$, 290.1756; found, 290.1766.



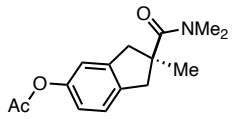
18j

2-(3-(2,5-dimethylphenoxy)propyl)-*N*,*N*-dimethyl-2,3-dihydro-1*H*-indene-2-carboxamide (**18j**). R_f = 0.30 (20% ethyl acetate–hexane). Prepared according to general procedure D and was obtained as an amorphous solid (11.5 mg, 33%): ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.24 – 7.19 (m, 2H), 7.19 – 7.16 (m, 2H), 7.00 (d, *J* = 7.5 Hz, 1H), 6.66 (d, *J* = 7.4 Hz, 1H), 6.58 (s, 1H), 3.91 (t, *J* = 5.9 Hz, 2H), 3.66 (d, *J* = 16.2 Hz, 2H), 3.07 (d, *J* = 16.2 Hz, 8H), 2.30 (s, 3H), 2.14 (s, 3H), 1.99 – 1.90 (m, 2H), 1.80 (dq, *J* = 11.9, 5.9 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 175.53, 156.78, 141.08, 136.50, 130.28, 126.55, 124.45, 123.34, 120.68, 111.84, 67.46, 54.03, 43.37, 37.77, 34.73, 25.24, 21.40, 15.80. HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{23}H_{30}NO_2$, 352.2277; found, 352.2288.



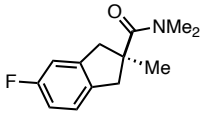
18k

(*S*)-*N*,*N*,2,5-tetramethyl-2,3-dihydro-1*H*-indene-2-carboxamide (**18k**). R_f = 0.30 (10% ethyl acetate–dichloromethane). Prepared according to general procedure D and was obtained as an amorphous solid (10.8 mg, 50%): ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.11 (d, *J* = 7.6 Hz, 1H), 7.05 (s, 1H), 7.01 (d, *J* = 7.6 Hz, 1H), 3.53 (dd, *J* = 19.3, 16.1 Hz, 2H), 3.05 (s, 6H), 2.89 (dd, *J* = 16.1, 6.0 Hz, 2H), 2.35 (s, 3H), 1.37 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 176.95, 141.15, 137.91, 136.23, 127.43, 125.42, 124.49, 49.76, 45.12, 44.72, 25.97, 21.29. HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{14}H_{20}NO$, 218.1545; found, 218.1553.



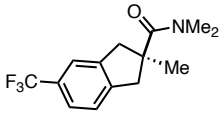
18l

(*S*)-2-(dimethylcarbamoyl)-2-methyl-2,3-dihydro-1*H*-inden-5-yl acetate (**18l**). R_f = 0.20 (20% ethyl acetate–dichloromethane). Prepared according to general procedure D and was obtained as a colorless oil (11.5 mg, 44%): ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.20 (d, *J* = 8.1 Hz, 1H), 6.94 (d, *J* = 2.2 Hz, 1H), 6.89 (dd, *J* = 8.2, 2.2 Hz, 1H), 3.57 (dd, *J* = 30.0, 16.2 Hz, 2H), 3.06 (s, 7H), 2.92 (dd, *J* = 16.2, 4.7 Hz, 2H), 2.31 (s, 3H), 1.39 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 176.48, 169.79, 149.65, 142.46, 138.46, 125.32, 119.80, 117.90, 50.32, 45.06, 44.43, 37.76, 25.72, 21.13. HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{15}H_{20}NO_3$, 262.1443; found, 262.1452.



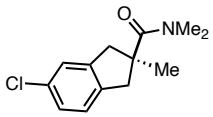
18m

(*S*)-5-fluoro-*N*,*N*,2-trimethyl-2,3-dihydro-1*H*-indene-2-carboxamide (**18m**). R_f = 0.30 (15% ethyl acetate–dichloromethane). Prepared according to general procedure D and was obtained as an amorphous solid (11.0 mg, 50%): ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.14 (dd, *J* = 8.3, 5.2 Hz, 1H), 6.94 – 6.80 (m, 2H), 3.55 (dd, *J* = 47.0, 16.2 Hz, 2H), 3.06 (s, 6H), 2.90 (dd, *J* = 16.2, 6.6 Hz, 2H), 1.38 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 176.44, 163.05, 161.43, 143.11, 143.04, 136.29, 136.27, 125.65, 125.59, 113.61, 113.46, 111.72, 111.57, 50.51, 45.19, 44.17, 25.66. ^{19}F NMR (376 MHz, $CDCl_3$): δ –119.79. HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{13}H_{17}FNO$, 222.1294; found, 222.1303.



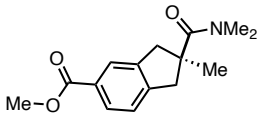
18n

(*S*)-*N*,*N*,2-trimethyl-5-(trifluoromethyl)-2,3-dihydro-1*H*-indene-2-carboxamide (**18n**). R_f = 0.30 (15% ethyl acetate–dichloromethane). Prepared according to general procedure D and was obtained as an amorphous solid (14.1 mg, 52%): ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.47 (s, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 7.8 Hz, 1H), 3.64 (t, *J* = 15.5 Hz, 2H), 3.08 (s, 7H), 2.99 (dd, *J* = 16.5, 6.3 Hz, 2H), 1.39 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 176.10, 145.17, 141.73, 129.43, 129.22, 129.01, 128.80, 127.15, 125.35, 124.93, 123.85, 123.83, 123.80, 123.77, 123.55, 121.75, 121.62, 121.60, 121.58, 121.55, 50.27, 44.92, 44.67, 37.78, 25.41. ^{19}F NMR (376 MHz, $CDCl_3$): δ –64.65. HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{14}H_{17}F_3NO$, 272.1262; found, 272.1270.



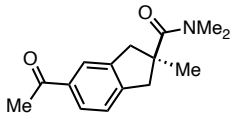
18o

(*S*)-5-chloro-*N*,*N*,2-trimethyl-2,3-dihydro-1*H*-indene-2-carboxamide (**18o**). R_f = 0.30 (15% ethyl acetate–dichloromethane). Prepared according to general procedure D and was obtained as an amorphous solid (12.6 mg, 53%): ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.21 – 7.19 (m, 1H), 7.17 – 7.10 (m, 2H), 3.55 (dd, *J* = 26.9, 16.3 Hz, 2H), 3.08 – 3.04 (m, 6H), 2.90 (dd, *J* = 16.3, 4.6 Hz, 2H), 1.38 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 176.32, 143.01, 139.43, 132.23, 126.79, 125.81, 124.90, 50.32, 44.92, 44.43, 37.83, 25.58. HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{13}H_{17}ClNO$, 238.0999; found, 238.1004.



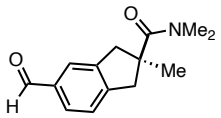
18p

methyl (*S*)-2-(dimethylcarbamoyl)-2-methyl-2,3-dihydro-1*H*-indene-5-carboxylate (**18p**). R_f = 0.30 (20% ethyl acetate–dichloromethane). Prepared according to general procedure D and was obtained as an amorphous solid (11.7 mg, 45%): ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.89 (d, *J* = 9.1 Hz, 2H), 7.28 (t, *J* = 3.9 Hz, 1H), 3.92 (s, 3H), 3.62 (dd, *J* = 31.4, 16.5 Hz, 2H), 3.15 – 2.91 (m, 8H), 1.38 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 176.30, 167.33, 146.73, 141.36, 128.85, 128.43, 125.96, 124.63, 52.02, 50.24, 45.21, 44.59, 37.82, 25.52. HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{15}H_{20}NO_3$, 262.1443; found, 262.1454.



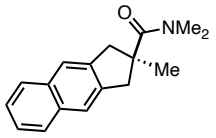
18q

(*S*)-5-acetyl-*N*,*N*,2-trimethyl-2,3-dihydro-1*H*-indene-2-carboxamide (**18q**). R_f = 0.30 (15% ethyl acetate–dichloromethane). Prepared according to general procedure D and was obtained as an amorphous solid (11.3 mg, 46%): ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.87 – 7.75 (m, 2H), 7.30 (d, *J* = 7.8 Hz, 1H), 3.63 (dd, *J* = 27.9, 16.5 Hz, 2H), 3.12 – 3.04 (m, 6H), 2.99 (dd, *J* = 16.5, 12.6 Hz, 2H), 2.61 (s, 3H), 1.39 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 198.05, 176.24, 147.02, 141.63, 136.26, 127.43, 124.74, 124.68, 50.29, 45.20, 44.60, 37.82, 26.71, 25.48. HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{15}H_{20}NO_2$, 246.1494; found, 246.1502.



18r

(*S*)-5-formyl-*N*,*N*,2-trimethyl-2,3-dihydro-1*H*-indene-2-carboxamide (**18r**). R_f = 0.20 (20% ethyl acetate–dichloromethane). Prepared according to general procedure D and was obtained as an amorphous solid (8.78 mg, 38%): ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.96 (s, 1H), 7.72 (s, 1H), 7.69 (d, *J* = 7.7 Hz, 1H), 7.36 (d, *J* = 7.7 Hz, 1H), 3.64 (dd, *J* = 40.1, 16.6 Hz, 2H), 3.17 – 2.88 (m, 8H), 1.37 (s, 3H). ^{13}C NMR (151 MHz, CDCl3): δ 192.12, 176.08, 148.81, 142.15, 135.73, 129.44, 125.60, 125.24, 50.39, 45.36, 44.37, 37.87, 25.38. HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{14}H_{18}NO_2$, 232.1338; found, 232.1346.



18s

N,*N*,2-trimethyl-2,3-dihydro-1*H*-cyclopenta[*b*]naphthalene-2-carboxamide (**18s**). R_f = 0.30 (10% ethyl acetate–dichloromethane). Prepared according to general procedure D and was obtained as an amorphous solid (10.6 mg, 42%): ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.79 (dd, *J* = 6.2, 3.3 Hz, 2H), 7.68 (s, 2H), 7.42 (dd, *J* = 6.2, 3.2 Hz, 2H), 3.71 (dd, *J* = 16.3, 1.6 Hz, 2H), 3.12 (d, *J* = 16.1 Hz, 8H), 1.40 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 176.64, 140.37, 133.14, 127.46, 125.07, 122.82, 50.59, 44.55, 37.86, 24.93. HRMS-CI (m/z): $[M + H]^+$ calcd for $C_{17}H_{20}NO$, 254.1545; found, 254.1553.

Crystallographic Analysis of 15f, 18m, and 27.

Crystallographic Analysis for amide 15f.

The single crystal X-ray diffraction studies were carried out on a Bruker D8-Venture 3-circle diffractometer equipped with a Photon3 detector and Mo Kα radiation (λ = 0.7107 Å). Crystals of the subject compound were used as received. A 0.18 x 0.16 x 0.11 mm piece of a crystal was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using ω scans. Crystal-to-detector distance was 50 mm and exposure time was 10 seconds per frame using a scan width of 0.70°. Data collection was 99.5 % complete to 25.242° in θ. A total of 15560 reflections were collected covering the indices, −31<=h<=31, −7<=k<=7, −23<=l<=23. 2760 reflections were found to be symmetry independent, with a Rint of 0.0861. Indexing and unit cell refinement indicated a C-centered, Monoclinic lattice. The space group was found to be C2/c. The data were integrated using the Bruker SAINT Software program and scaled using the SADABS software program. Solution by direct methods (SHELXT) produced a complete phasing model consistent with the proposed structure. All nonhydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All carbon bonded hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014. Crystallographic data are summarized in Table S5. CCDC deposition number 2242697 contains the supplementary crystallography data for this paper.

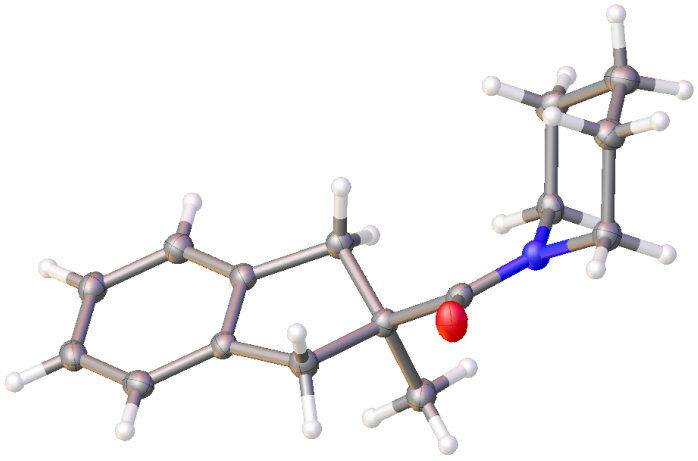


Figure S1. The crystal structure of amide **15f**.

Table S5. Crystallographic data and structure refinement of the amide **15f**:

Identification code	yu195_0m_a	
Empirical formula	C16 H21 N O	
Formula weight	243.34	
Temperature	100 K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C 1 2/c 1	
Unit cell dimensions	a = 25.263(6) Å	α = 90°.
	b = 6.0646(8) Å	β = 111.613(10)°.
	c = 18.877(3) Å	γ = 90°.
Volume	2688.8(9) $Å^3$	
Z	8	
Density (calculated)	1.202 Mg/m^3	
Absorption coefficient	0.074 mm^{-1}	
F(000)	1056	
Crystal size	0.18 x 0.16 x 0.11 mm^3	
Theta range for data collection	3.372 to 26.436°.	
Index ranges	-31<=h<=31, -7<=k<=7, -23<=l<=23	
Reflections collected	15560	
Independent reflections	2760 [R(int) = 0.0861]	
Completeness to theta = 25.242°	99.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.4908 and 0.4327	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2760 / 0 / 164	
Goodness-of-fit on F^2	1.015	
Final R indices [I>2sigma(I)]	R1 = 0.0461, wR2 = 0.1052	
R indices (all data)	R1 = 0.0771, wR2 = 0.1215	
Largest diff. peak and hole	0.367 and -0.184 $e.Å^{-3}$	

Crystallographic Analysis for amide 18m.

The single crystal X-ray diffraction studies were carried out on a Bruker D8-Venture 3-circle diffractometer equipped with a Photon3 detector and Mo Kα radiation (λ = 0.7107 Å). Crystals of the subject compound were used as received. A 0.18 x 0.06 x 0.06 mm piece of a crystal was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using ω scans. Crystal-to-detector distance was 50 mm and exposure time was 60 or 120 seconds per frame using a scan width of 0.70°. Data collection was 99.5 % complete to 25.242° in θ. A total of 6806 reflections were collected covering the indices, −7<=h<=7, −11<=k<=11, −13<=l<=14. 2347 reflections were found to be symmetry independent, with a Rint of 0.0591. Indexing and unit cell refinement indicated a Triclinic lattice. The space group was found to be P-1. The data were integrated using the Bruker SAINT Software program and scaled using the SADABS software program. Solution by direct methods (SHELXT) produced a complete phasing model consistent with the proposed structure. All nonhydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All carbon bonded hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014. Crystallographic data are summarized in Table S6. CCDC deposition number 2242698 contains the supplementary crystallography data for this paper.

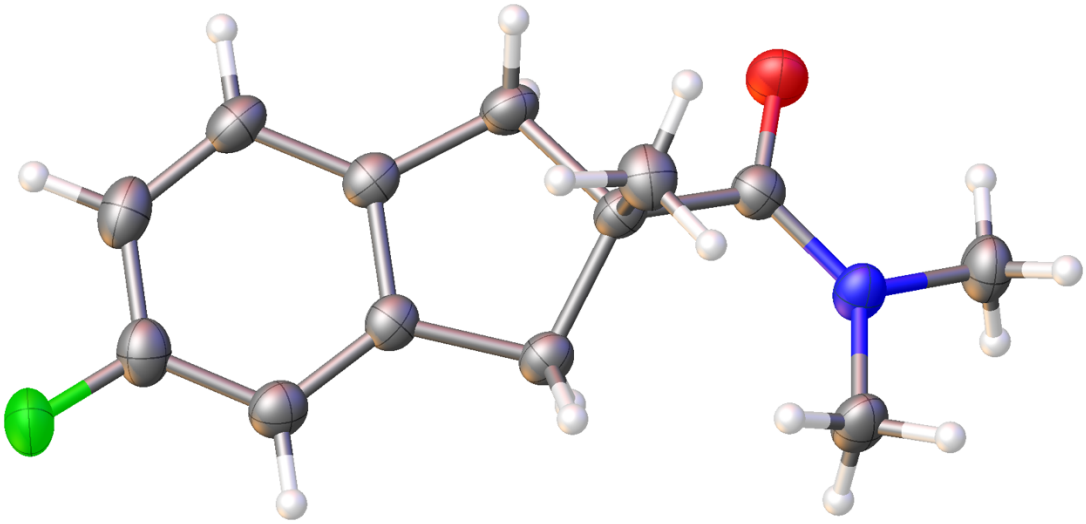


Figure S2. The crystal structure of amide **18m**.

Table S6. Crystallographic data and structure refinement of the amide **18m**:

Identification code	yu196_0m_a	
Empirical formula	C13 H16 F N O	
Formula weight	221.27	
Temperature	100 K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 5.9910(13) Å	α = 102.764(7)°.
	b = 9.2837(18) Å	β = 98.455(7)°.
	c = 11.199(2) Å	γ = 105.615(7)°.
Volume	570.8(2) $Å^3$	
Z	2	
Density (calculated)	1.287 Mg/m^3	
Absorption coefficient	0.092 mm^{-1}	
F(000)	236	
Crystal size	0.18 x 0.06 x 0.06 mm^3	
Theta range for data collection	2.605 to 26.499°.	
Index ranges	-7<=h<=7, -11<=k<=11, -13<=l<=14	
Reflections collected	6806	
Independent reflections	2347 [R(int) = 0.0591]	
Completeness to theta = 25.242°	99.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.4908 and 0.3777	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2347 / 0 / 158	
Goodness-of-fit on F^2	1.009	
Final R indices [I>2sigma(I)]	R1 = 0.0509, wR2 = 0.1212	
R indices (all data)	R1 = 0.0906, wR2 = 0.1395	
Largest diff. peak and hole	0.256 and -0.224 $e.Å^{-3}$	

Crystallographic Analysis for amide 27.

The single crystal X-ray diffraction studies were carried out on a Bruker APEX II Ultra diffractometer equipped with Mo Kα radiation (λ = 0.71073). Crystals of the subject compound were used as received (grown from Acetone / Ether vapor diffusion). A 0.200 x 0.040 x 0.030 mm crystal was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using K and ω scans. Crystal-to-detector distance was 45 mm using exposure time 1.0 s with a scan width of 0.65°. Data collection was 100.0% complete to 25.242° in θ. A total of 22529 reflections were collected covering the indices, -18<=h<=18, -15<=k<=15, -12<=l<=12. 3570 reflections were found to be symmetry independent, with a R_{int} of 0.0616. Indexing and unit cell refinement indicated a Primitive Monoclinic lattice. The space group was found to be $P2_1/c$. The data were integrated using the Bruker SAINT Software program and scaled using the SADABS software program. Solution by direct methods (SHELXT) produced a complete phasing model consistent with the proposed structure. All nonhydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All carbon bonded hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014. Crystallographic data are summarized in Table S7. CCDC deposition number 2255198 contains the supplementary crystallography data for this paper.

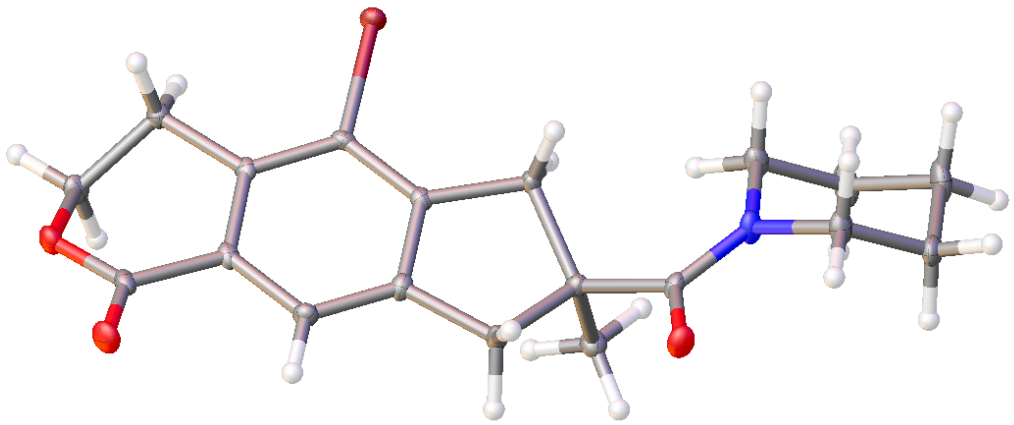


Figure S3. The crystal structure of amide **27.**

Table S7. Crystallographic data and structure refinement of the amide **27**:

Identification code	Yu229	
Empirical formula	C19 H22 Br N O3	
Formula weight	392.28	
Temperature	100.15 K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 1 21/c 1	
Unit cell dimensions	a = 14.8342(16) Å	α = 90°.
	b = 12.2694(14) Å	β = 109.049(4)°.
	c = 9.7645(14) Å	γ = 90°.
Volume	1679.9(4) $Å^3$	
Z	4	
Density (calculated)	1.551 Mg/m^3	
Absorption coefficient	2.464 mm^{-1}	
F(000)	808	
Crystal size	0.2 x 0.04 x 0.03 mm^3	
Crystal color, habit	colorless plank	
Theta range for data collection	1.452 to 26.718°.	
Index ranges	-18<=h<=18, -15<=k<=15, -12<=l<=12	
Reflections collected	22529	
Independent reflections	3570 [R(int) = 0.0616]	
Completeness to theta = 25.242°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.4875 and 0.4129	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3570 / 0 / 219	
Goodness-of-fit on F^2	1.063	
Final R indices [I>2sigma(I)]	R1 = 0.0258, wR2 = 0.0663	
R indices (all data)	R1 = 0.0272, wR2 = 0.0674	
Largest diff. peak and hole	0.426 and -0.472 $e.Å^{-3}$	

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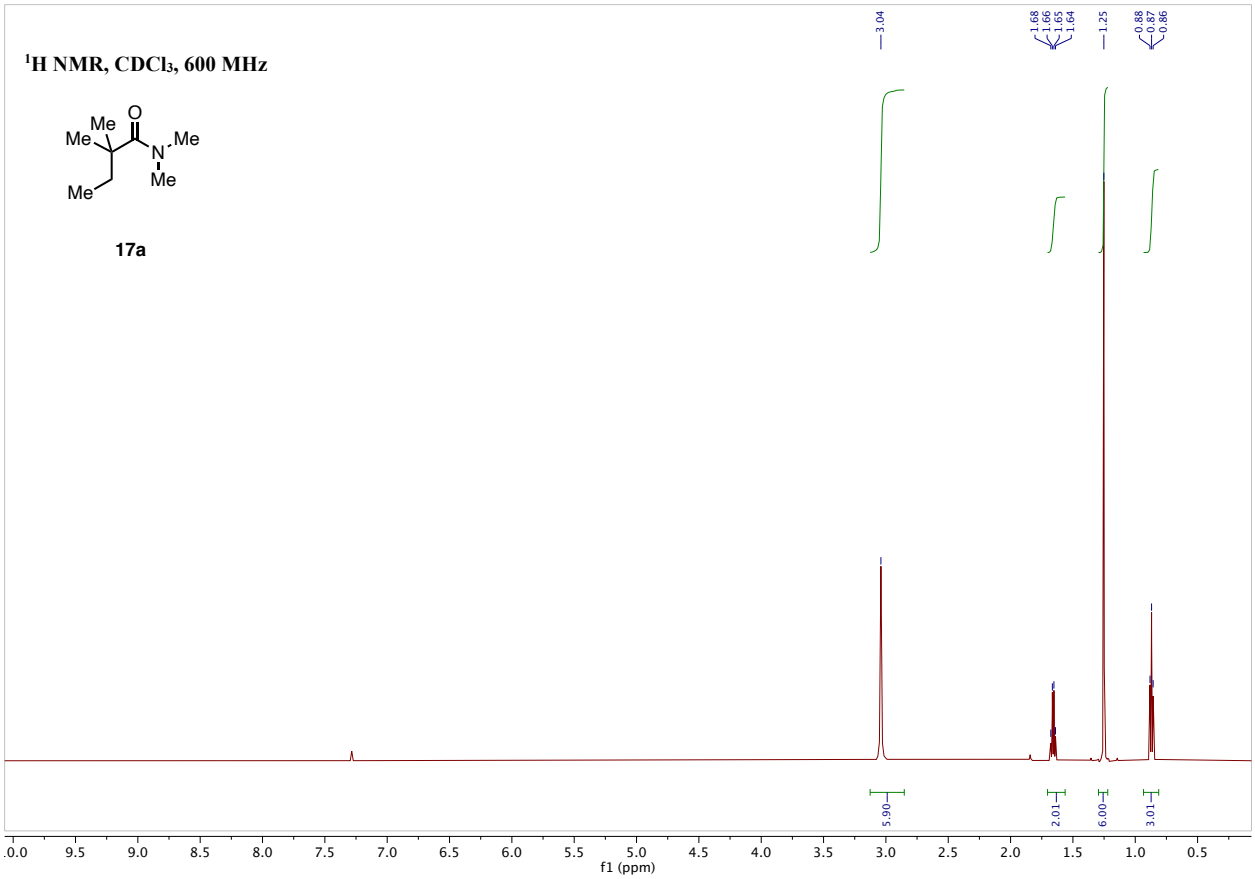
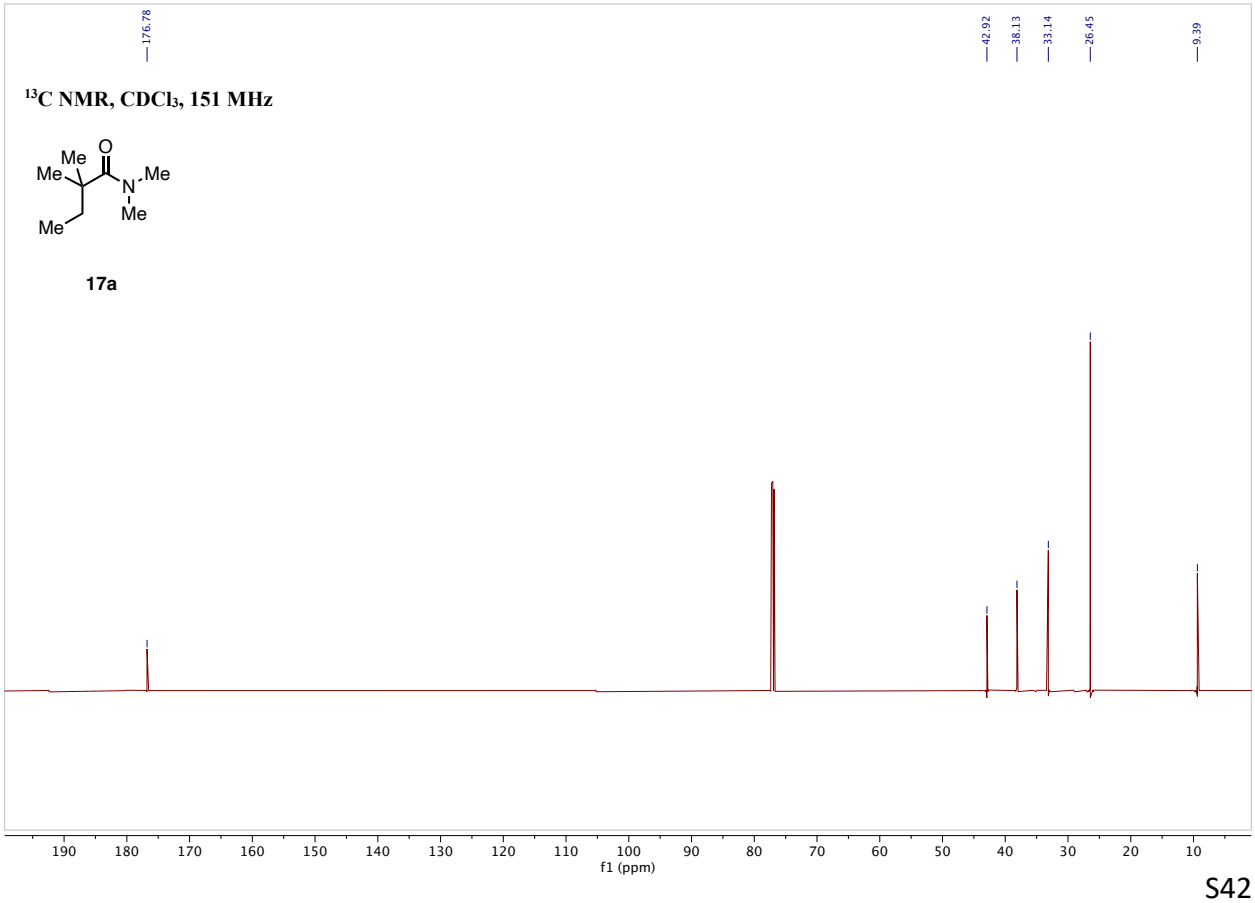
Catalogue of ^{1}H NMR and ^{13}C NMR Spectra.



^{1}H NMR, $CDCl_3$, 600 MHz

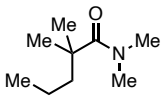
17a



^{13}C NMR, $CDCl_3$, 151 MHz

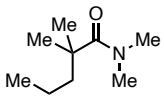
17a

^{1}H NMR, $CDCl_3$, 600 MHz



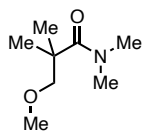
17b

^{13}C NMR, $CDCl_3$, 151 MHz



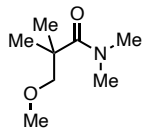
17b

^{1}H NMR, $CDCl_3$, 600 MHz



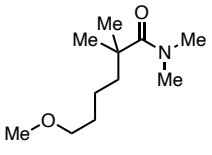
17g

^{13}C NMR, $CDCl_3$, 151 MHz

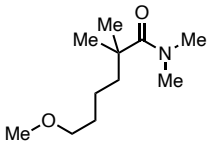


17g

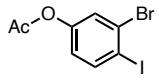
^{1}H NMR, $CDCl_3$, 600 MHz



^{13}C NMR, $CDCl_3$, 151 MHz

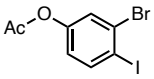


^{1}H NMR, $CDCl_3$, 600 MHz

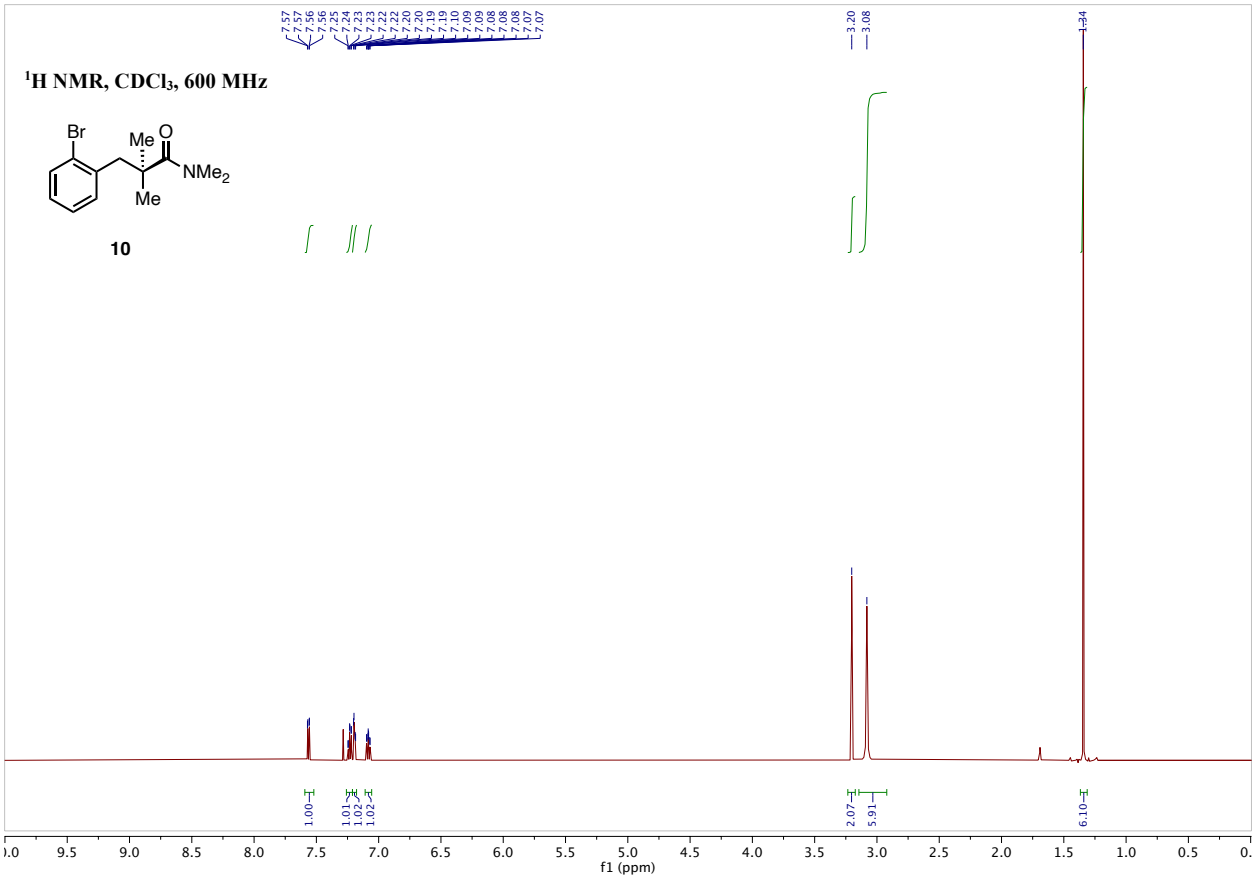


16l

^{13}C NMR, $CDCl_3$, 151 MHz

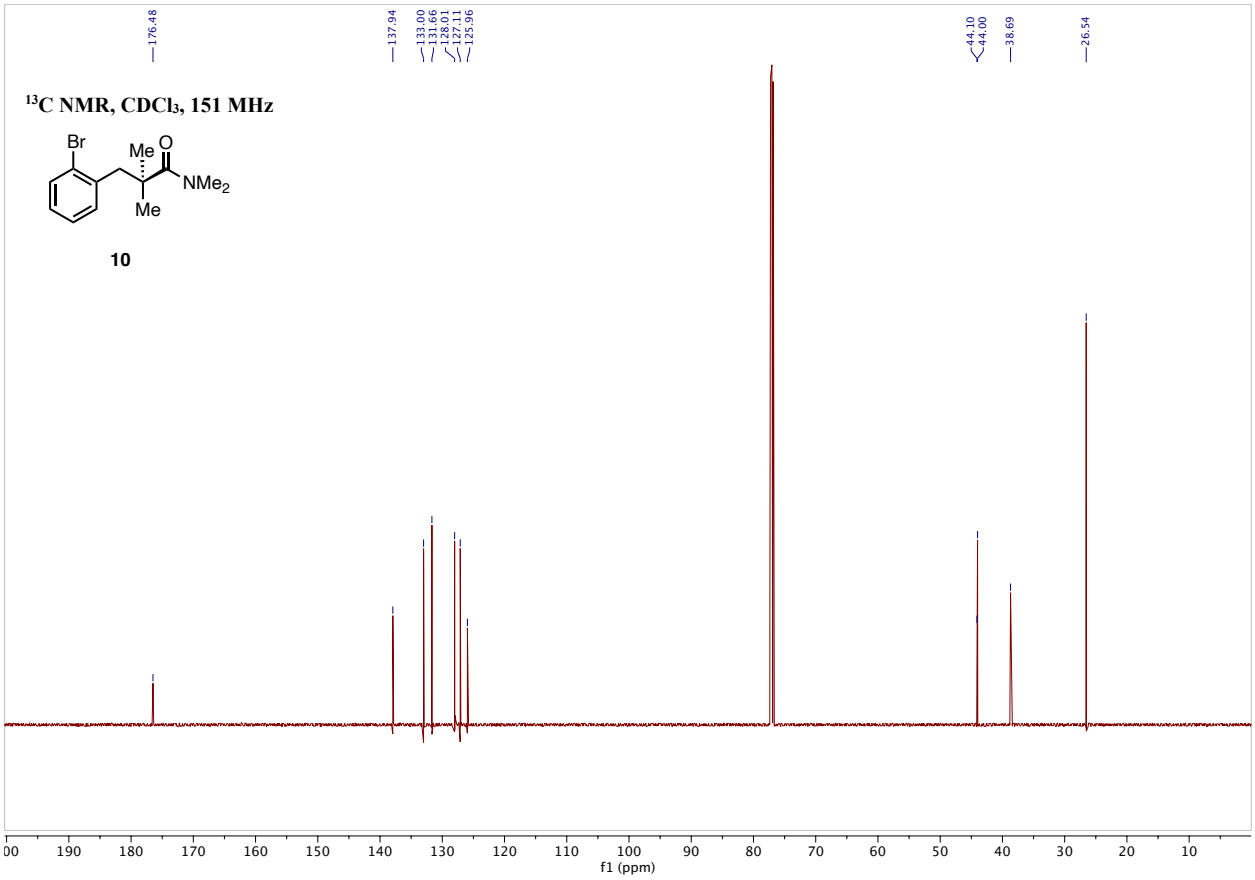


16l



^{1}H NMR, $CDCl_3$, 600 MHz

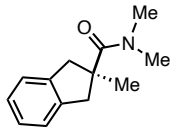
10



^{13}C NMR, $CDCl_3$, 151 MHz

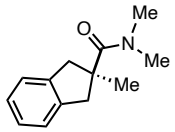
10

^{1}H NMR, $CDCl_3$, 600 MHz



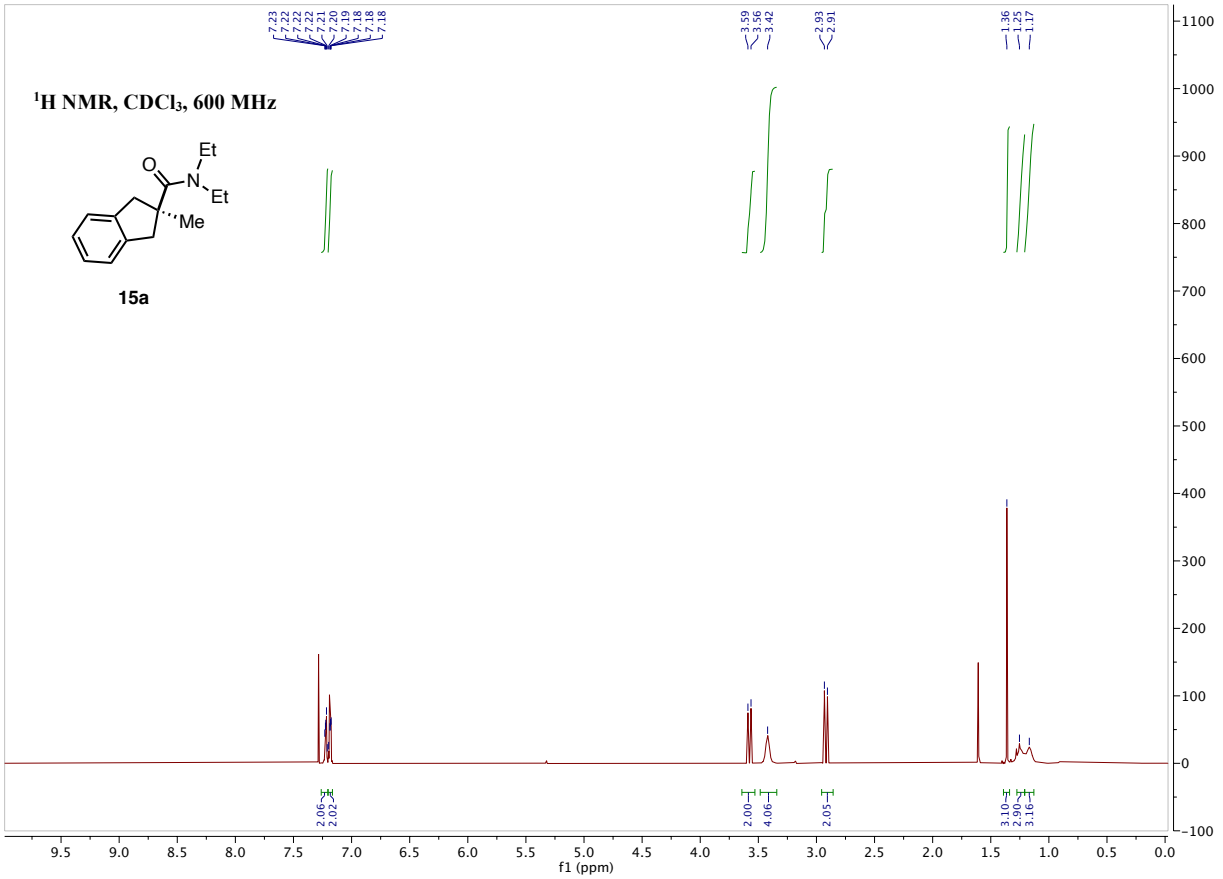
13

^{13}C NMR, $CDCl_3$, 151 MHz*



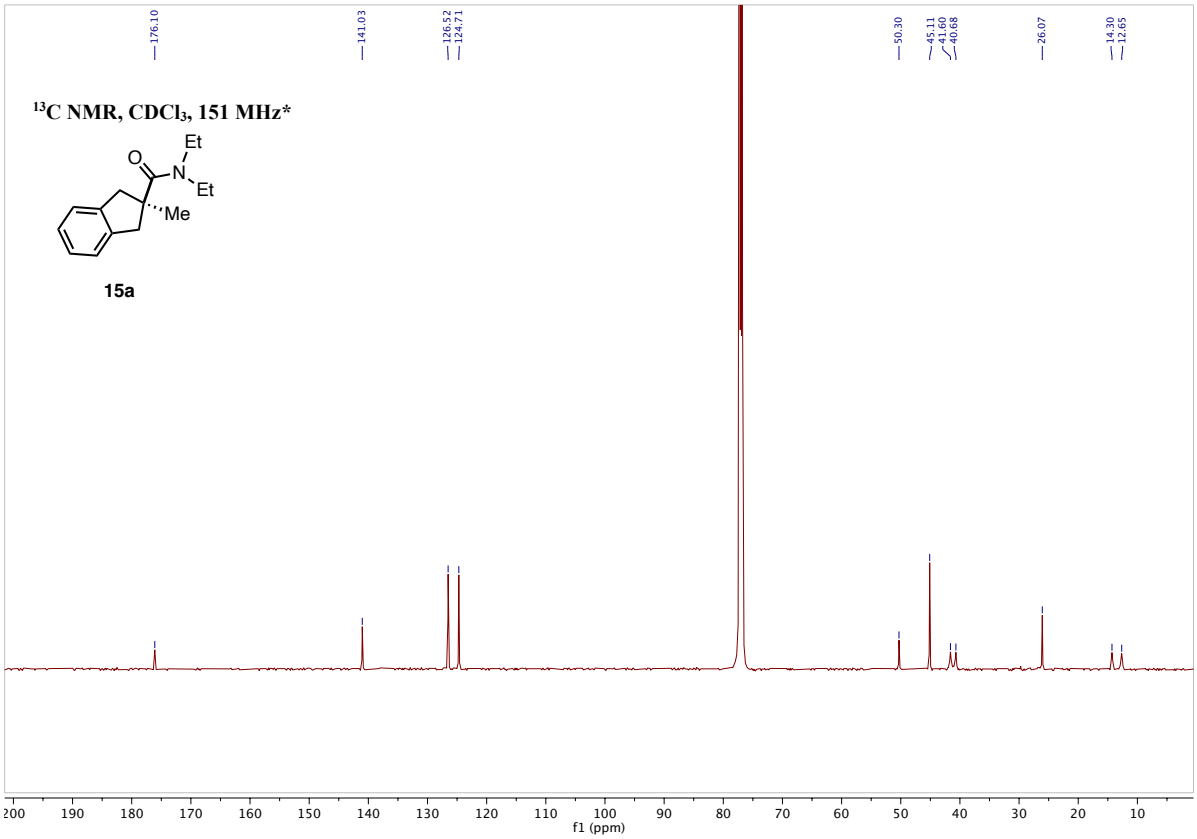
13

*Note: Apodization changed to 10.



^{1}H NMR, $CDCl_3$, 600 MHz

15a

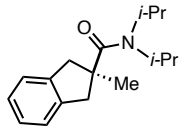


^{13}C NMR, $CDCl_3$, 151 MHz*

15a

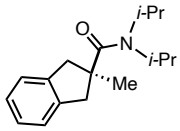
*Note: Apodization changed to 10.

^{1}H NMR, $CDCl_3$, 600 MHz



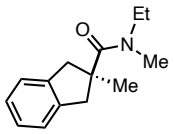
15b

^{13}C NMR, $CDCl_3$, 151 MHz



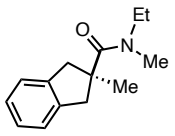
15b

^{1}H NMR, $CDCl_3$, 600 MHz



15c

^{13}C NMR, $CDCl_3$, 151 MHz

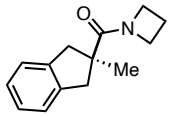


15c

Note: Extensive line broadening observed with **15c** in $CDCl_3$ at 23 °C.*

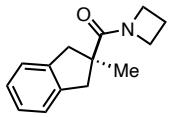
*Note: Apodization changed to 30.

^{1}H NMR, $CDCl_3$, 600 MHz



15d

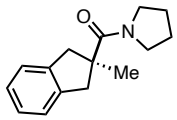
^{13}C NMR, $CDCl_3$, 151 MHz*



15d

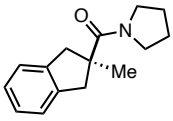
*Note: Apodization changed to 15.

^{1}H NMR, $CDCl_3$, 600 MHz



15e

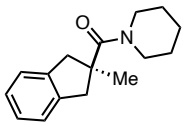
^{13}C NMR, $CDCl_3$, 151 MHz*



15e

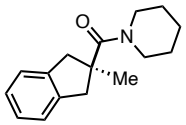
*Note: Apodization changed to 10.

^{1}H NMR, $CDCl_3$, 600 MHz



15f

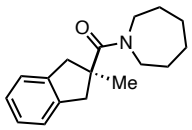
^{13}C NMR, $CDCl_3$, 151 MHz*



15f

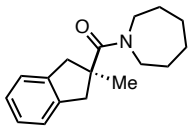
*Note: Apodization changed to 15.

^{1}H NMR, $CDCl_3$, 600 MHz



15g

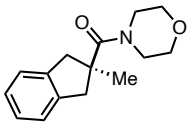
^{13}C NMR, $CDCl_3$, 151 MHz*



15g

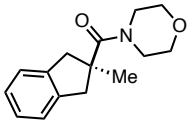
*Note: Apodization changed to 10.

^{1}H NMR, $CDCl_3$, 600 MHz



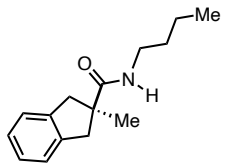
15h

^{13}C NMR, $CDCl_3$, 151 MHz



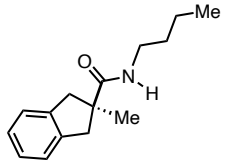
15h

^{1}H NMR, $CDCl_3$, 600 MHz



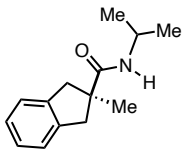
15i

^{13}C NMR, $CDCl_3$, 151 MHz



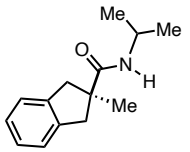
15i

^{1}H NMR, $CDCl_3$, 600 MHz



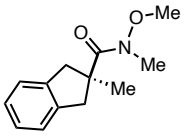
15j

^{13}C NMR, $CDCl_3$, 151 MHz



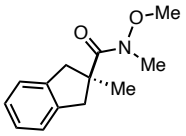
15j

^{1}H NMR, $CDCl_3$, 600 MHz



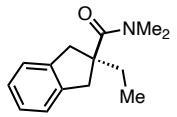
15k

^{13}C NMR, $CDCl_3$, 151 MHz



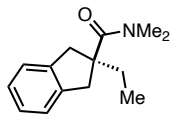
15k

^{1}H NMR, $CDCl_3$, 600 MHz



18a

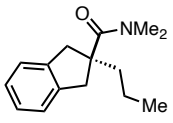
^{13}C NMR, $CDCl_3$, 151 MHz*



18a

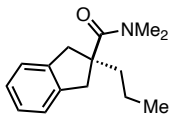
*Note: Apodization changed to 10.

^{1}H NMR, $CDCl_3$, 600 MHz



18b

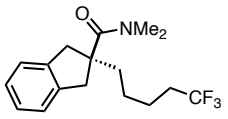
^{13}C NMR, $CDCl_3$, 151 MHz*



18b

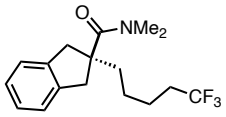
*Note: Apodization changed to 10.

^{1}H NMR, $CDCl_3$, 600 MHz



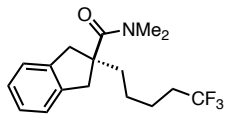
18c

^{13}C NMR, $CDCl_3$, 151 MHz



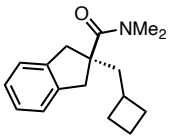
18c

^{19}F NMR, $CDCl_3$, 376 MHz



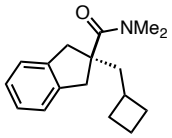
18c

^{1}H NMR, $CDCl_3$, 600 MHz



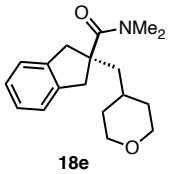
18d

^{13}C NMR, $CDCl_3$, 151 MHz



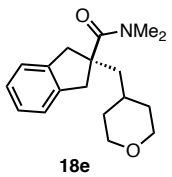
18d

^{1}H NMR, $CDCl_3$, 600 MHz



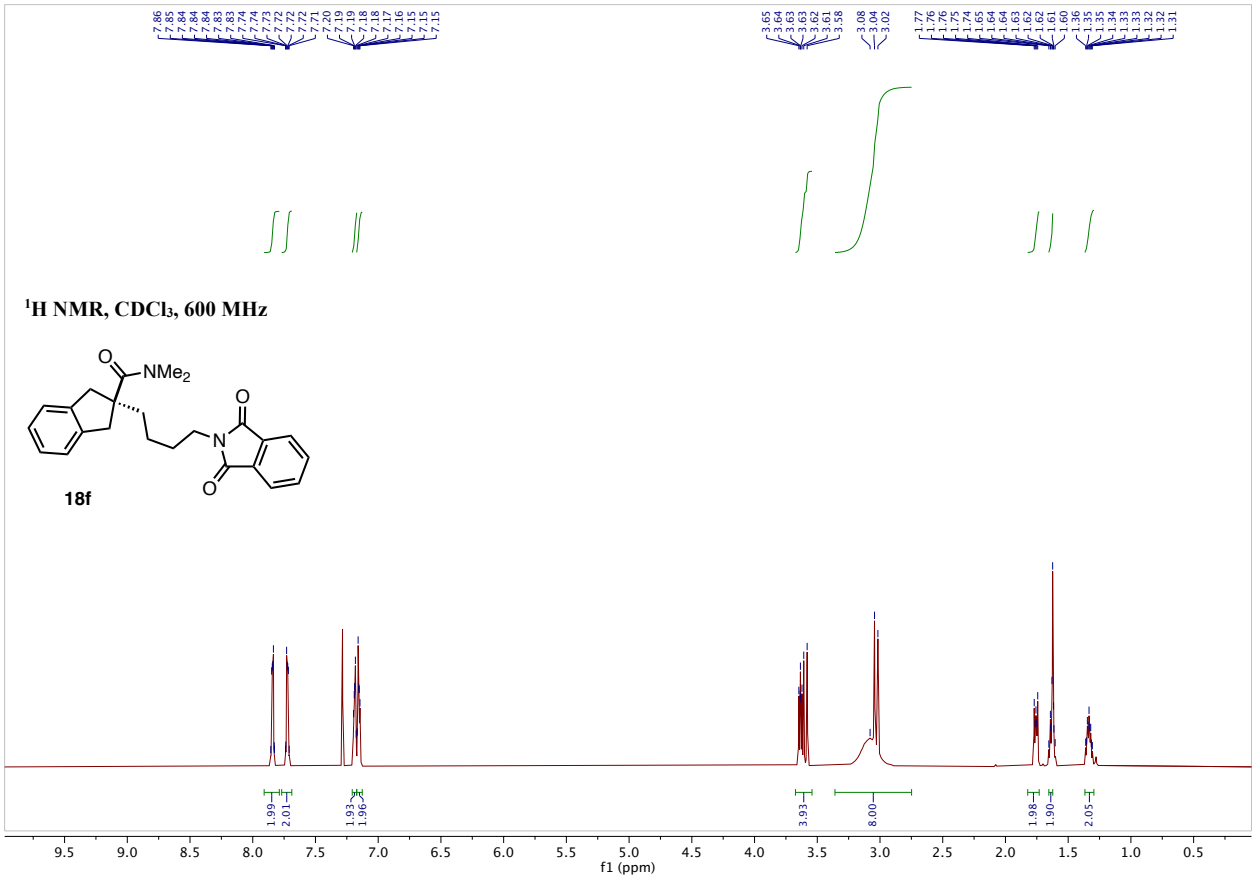
18e

^{13}C NMR, $CDCl_3$, 151 MHz



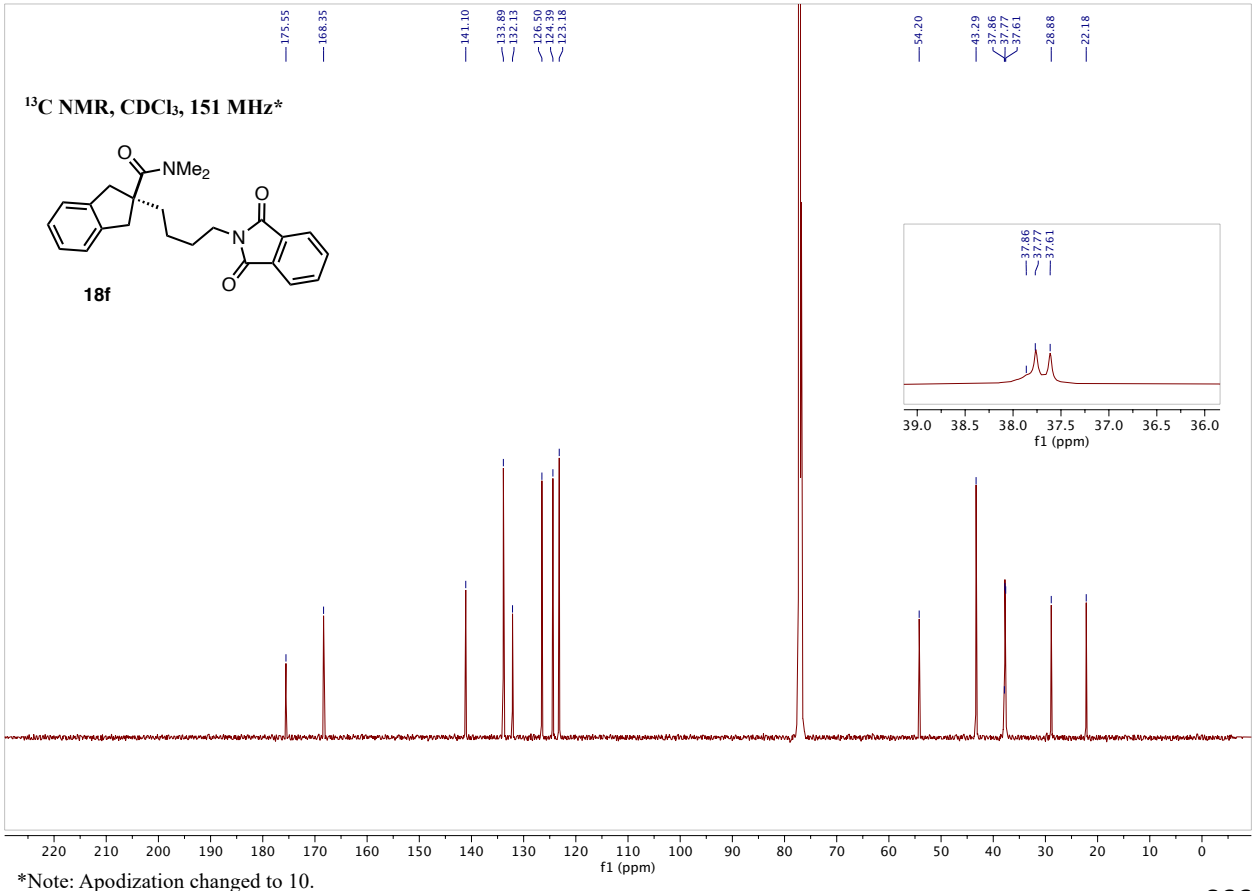
18e

*Note: Apodization changed to 5.



^{1}H NMR, $CDCl_3$, 600 MHz

18f

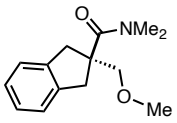


^{13}C NMR, $CDCl_3$, 151 MHz*

18f

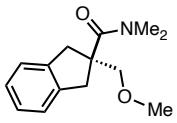
*Note: Apodization changed to 10.

^{1}H NMR, $CDCl_3$, 600 MHz

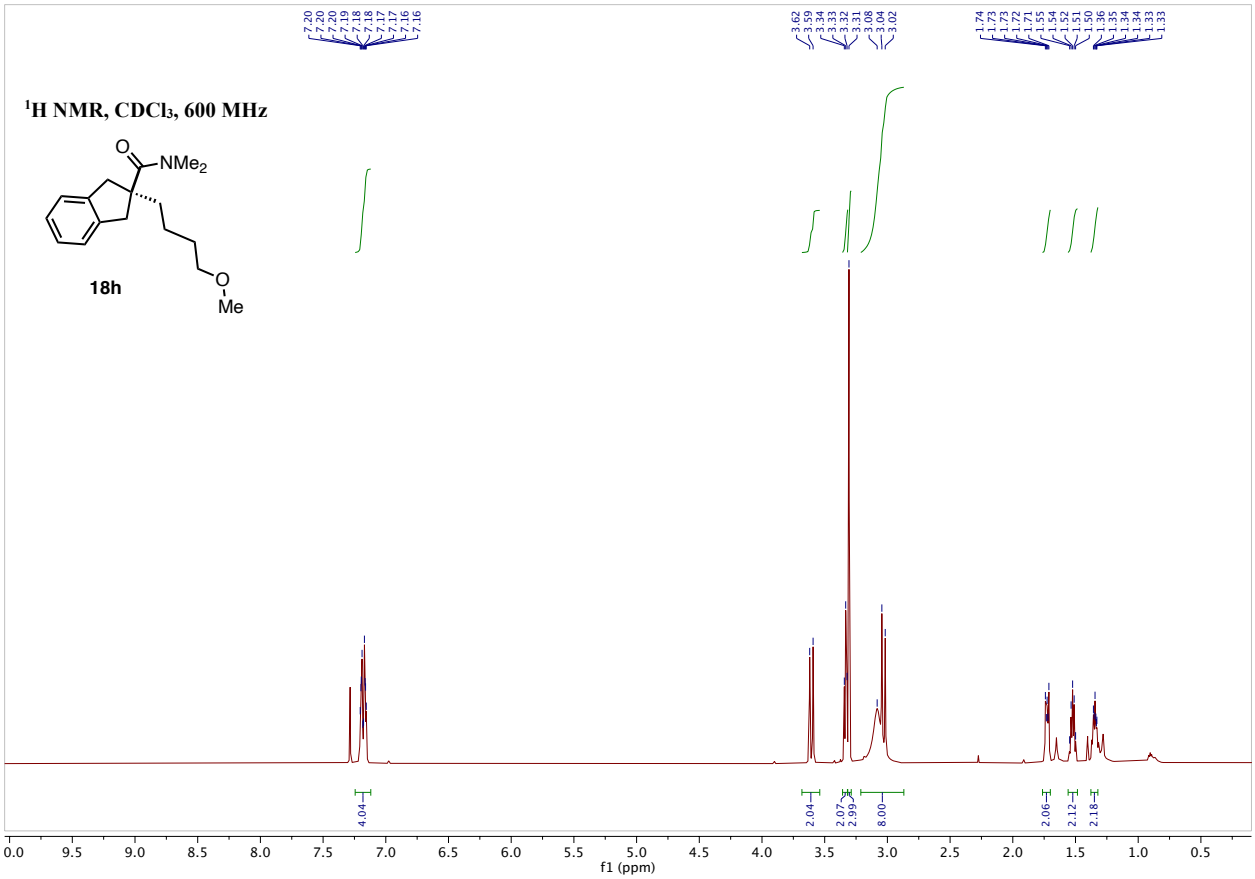


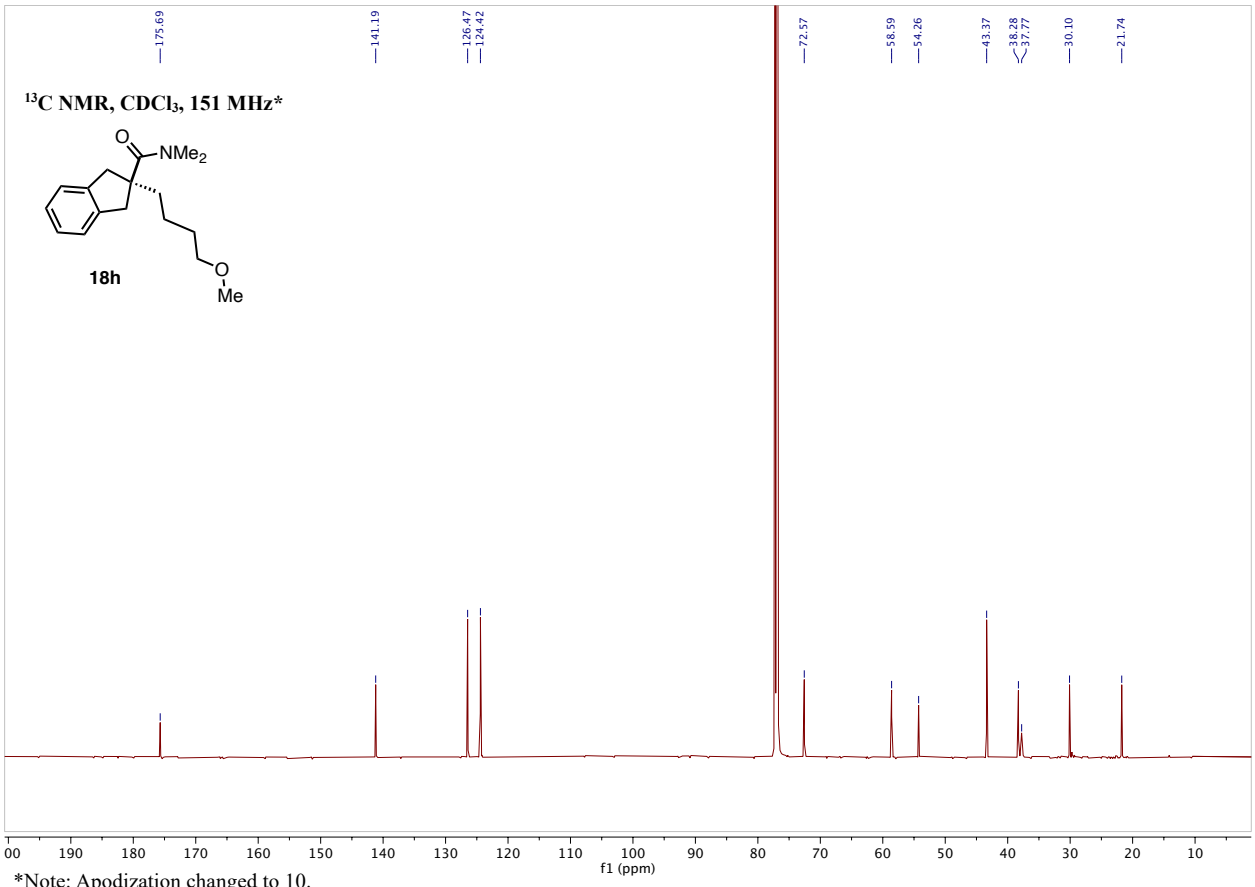
18g

^{13}C NMR, $CDCl_3$, 151 MHz



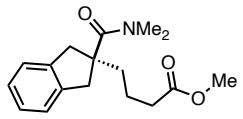
18g





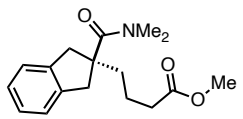
*Note: Apodization changed to 10.

^{1}H NMR, $CDCl_3$, 600 MHz



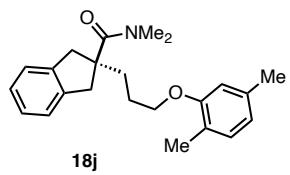
18i

^{13}C NMR, $CDCl_3$, 151 MHz



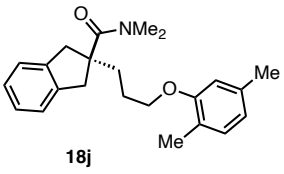
18i

^{1}H NMR, $CDCl_3$, 600 MHz



18j

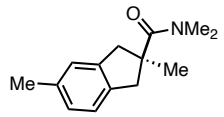
^{13}C NMR, $CDCl_3$, 151 MHz*



18j

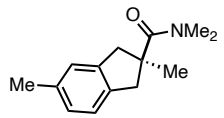
*Note: Apodization changed to 5.

^{1}H NMR, $CDCl_3$, 600 MHz



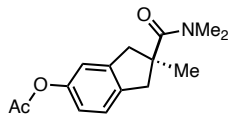
18k

^{13}C NMR, $CDCl_3$, 151 MHz



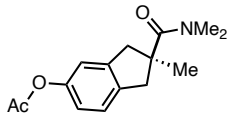
18k

^{1}H NMR, $CDCl_3$, 600 MHz



18l

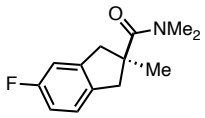
^{13}C NMR, $CDCl_3$, 151 MHz*



18l

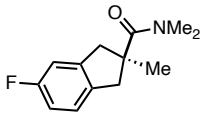
*Note: Apodization changed to 10.

^{1}H NMR, $CDCl_3$, 600 MHz



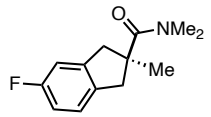
18m

^{13}C NMR, $CDCl_3$, 151 MHz



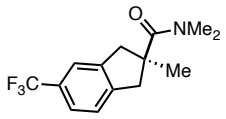
18m

^{19}F NMR, $CDCl_3$, 376 MHz



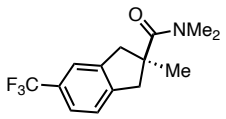
18m

^{1}H NMR, $CDCl_3$, 600 MHz



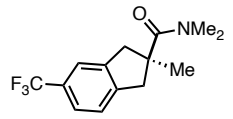
18n

^{13}C NMR, $CDCl_3$, 151 MHz



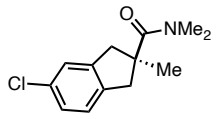
18n

^{19}F NMR, $CDCl_3$, 376 MHz



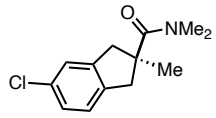
18n

^{1}H NMR, $CDCl_3$, 600 MHz



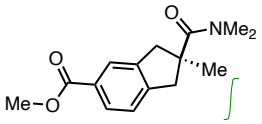
18o

^{13}C NMR, $CDCl_3$, 151 MHz



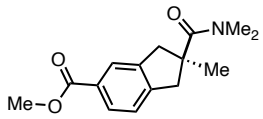
18o

^{1}H NMR, $CDCl_3$, 600 MHz

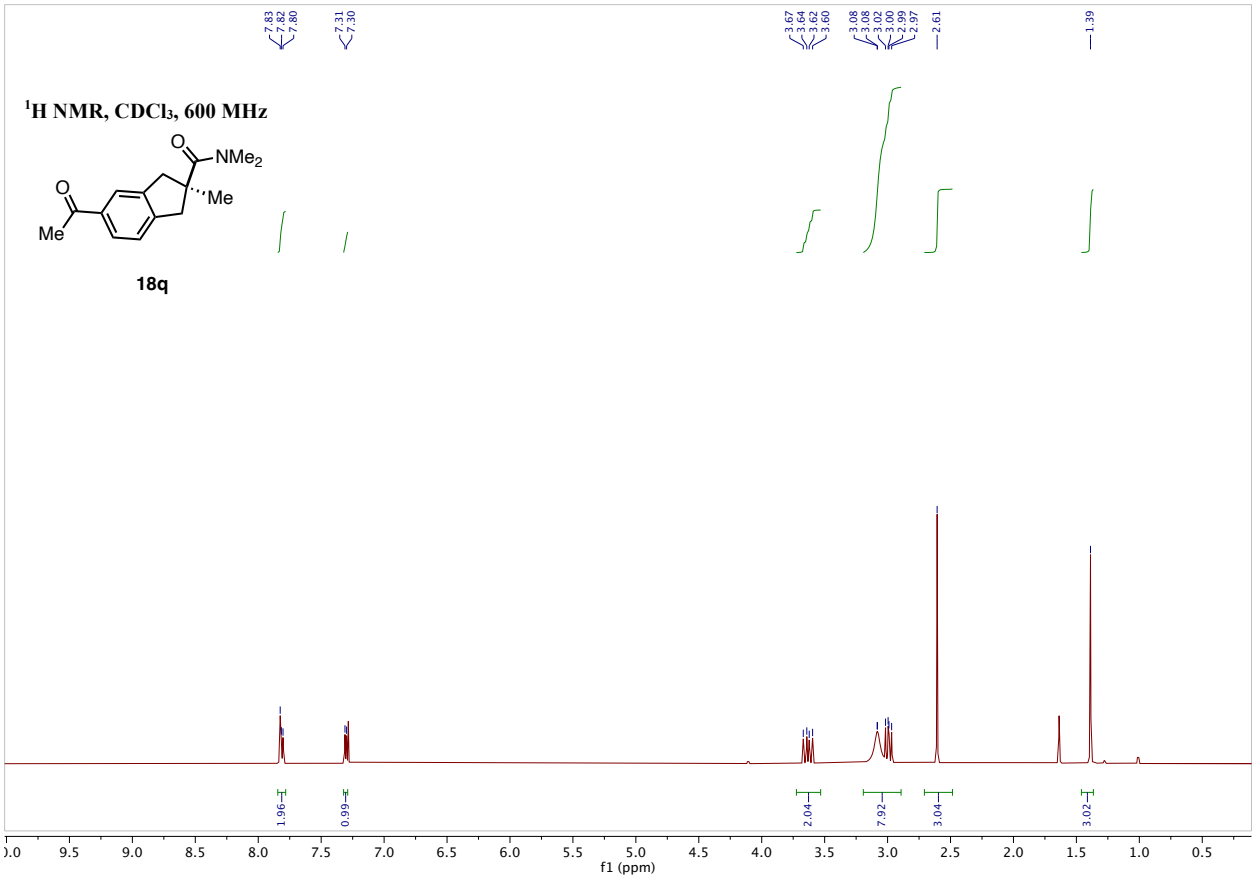


18p

^{13}C NMR, $CDCl_3$, 151 MHz

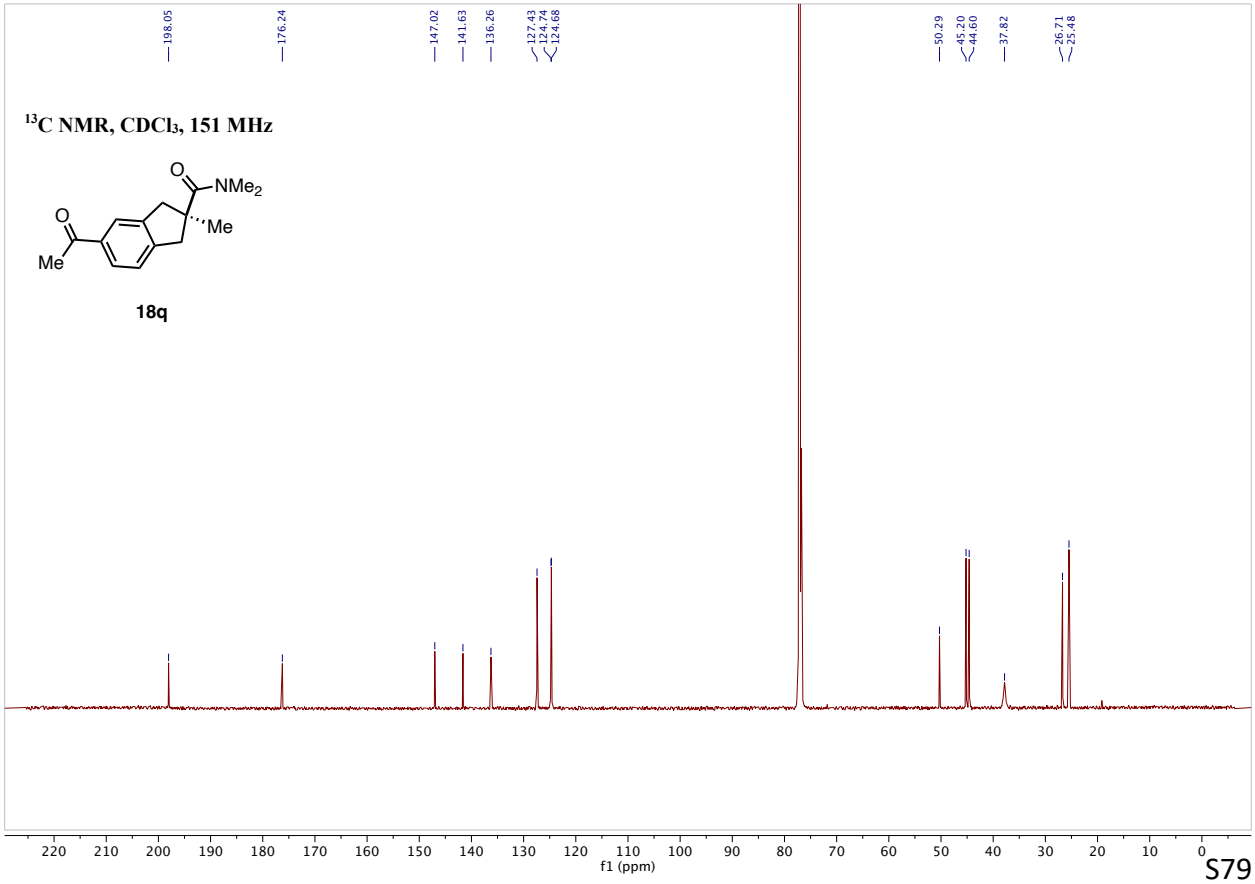


18p



^{1}H NMR, $CDCl_3$, 600 MHz

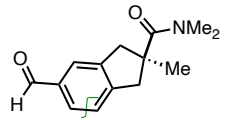
18q



^{13}C NMR, $CDCl_3$, 151 MHz

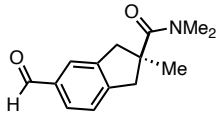
18q

^{1}H NMR, $CDCl_3$, 600 MHz



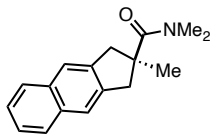
18r

^{13}C NMR, $CDCl_3$, 151 MHz



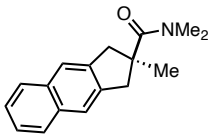
18r

^{1}H NMR, $CDCl_3$, 600 MHz

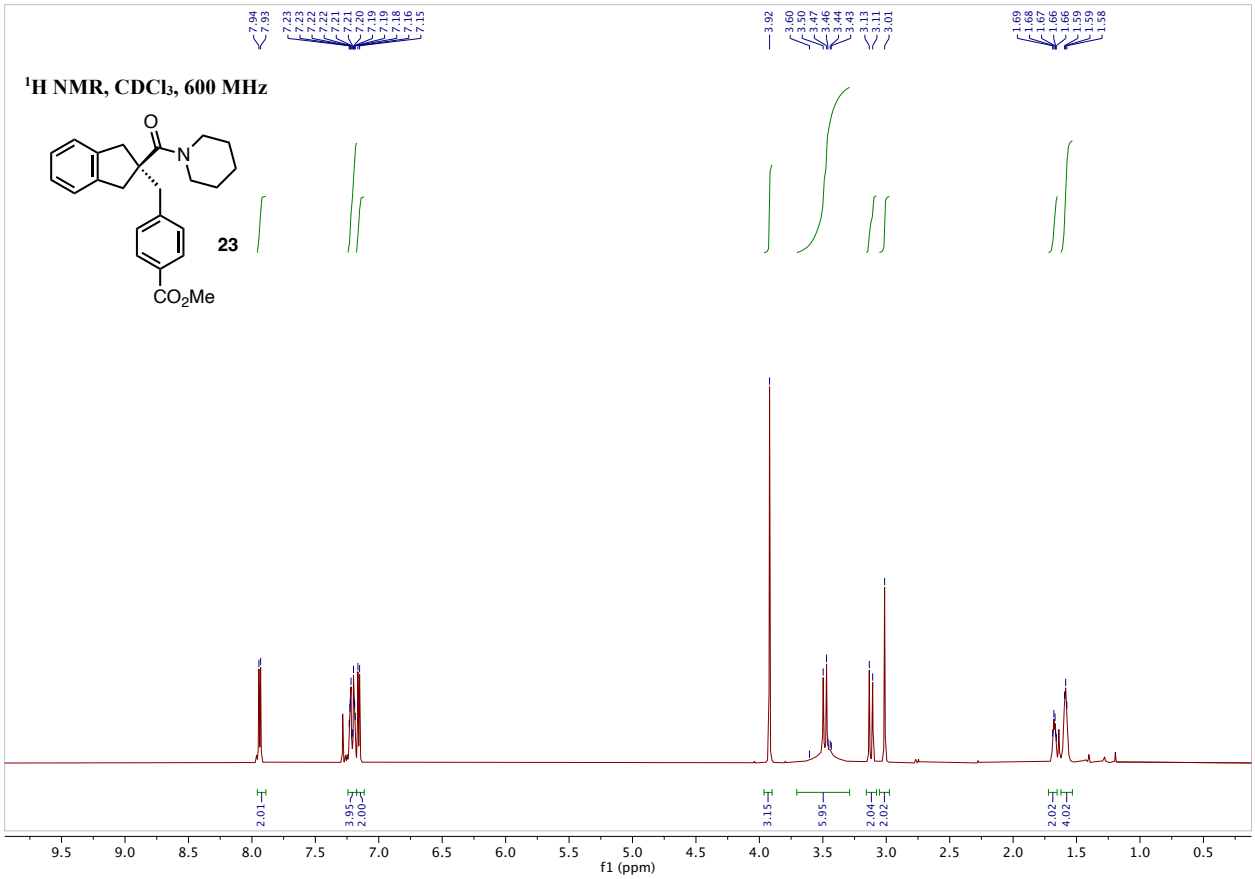


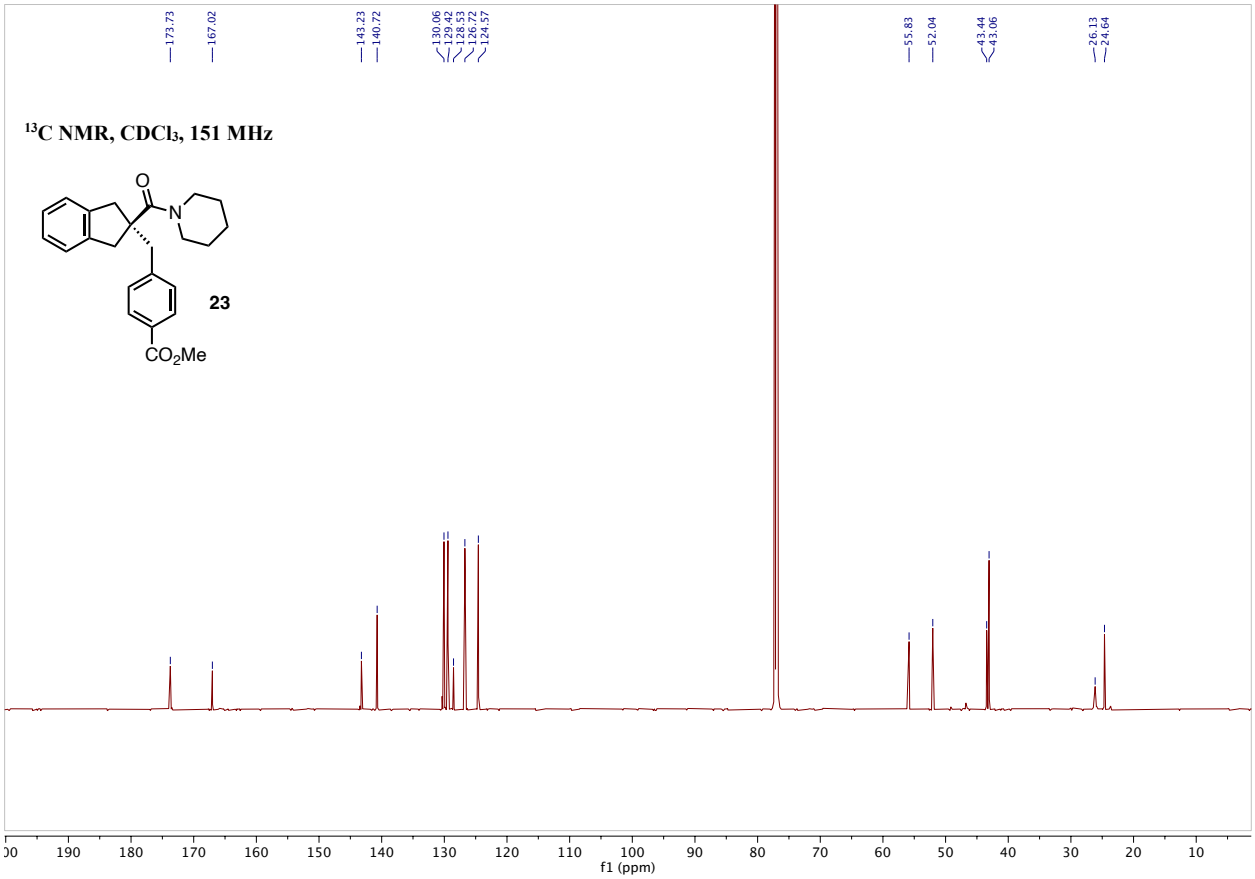
18s

^{13}C NMR, $CDCl_3$, 151 MHz

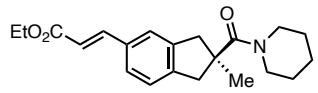


18s


7.94
7.93
7.23
7.23
7.22
7.22
7.21
7.21
7.20
7.19
7.19
7.18
7.16
7.15
3.92
3.60
3.50
3.47
3.46
3.44
3.43
3.13
3.11
3.01
1.69
1.68
1.67
1.66
1.66
1.59
1.59
1.58
1H NMR, CDCl3, 600 MHz
O
N
23
CO2Me
2.01
3.95
2.00
3.15
5.95
2.04
2.02
2.02
4.02
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

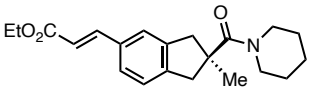

173.73
167.02
143.23
140.72
130.06
129.42
128.53
126.72
124.57
55.83
52.04
43.44
43.06
26.13
24.64
13C NMR, CDCl3, 151 MHz
O
N
23
CO2Me
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

^{1}H NMR, $CDCl_3$, 600 MHz

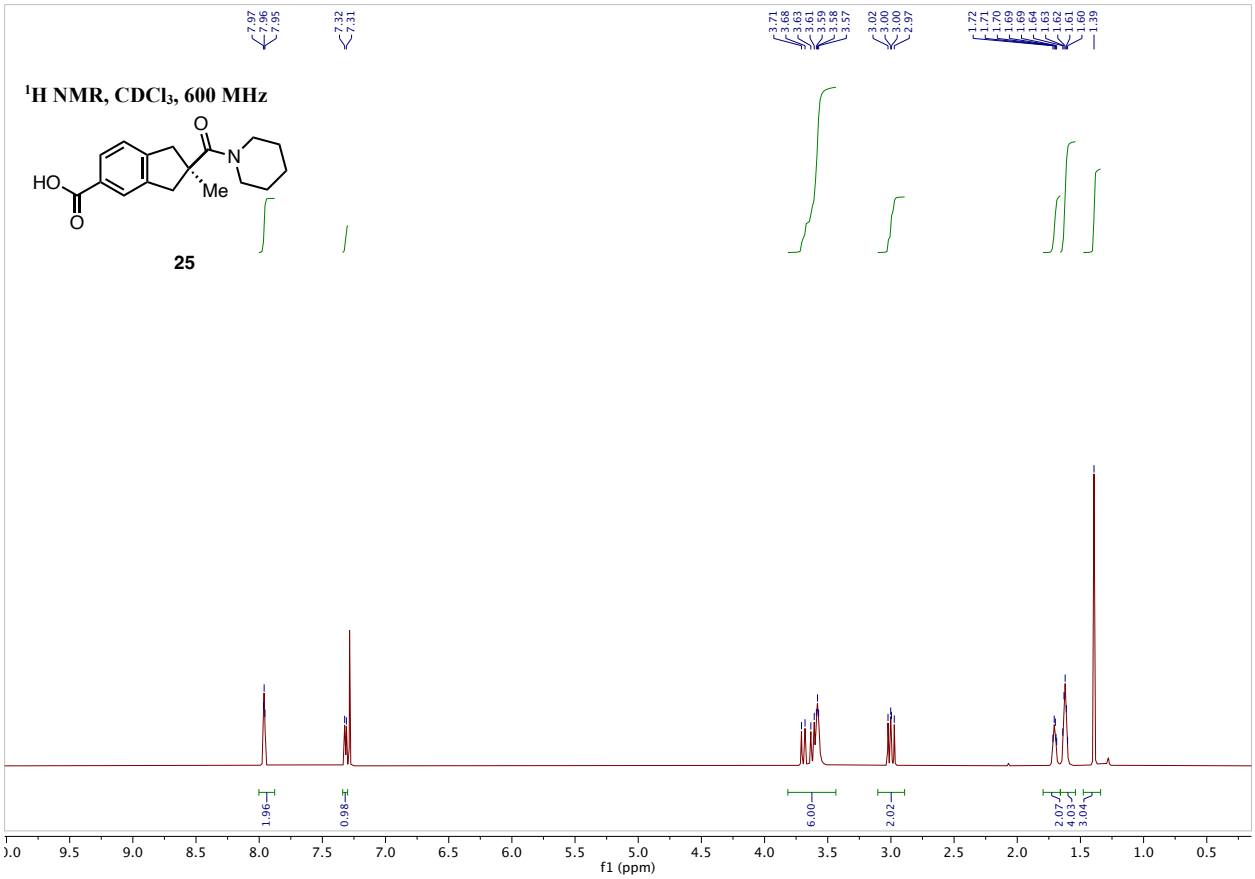


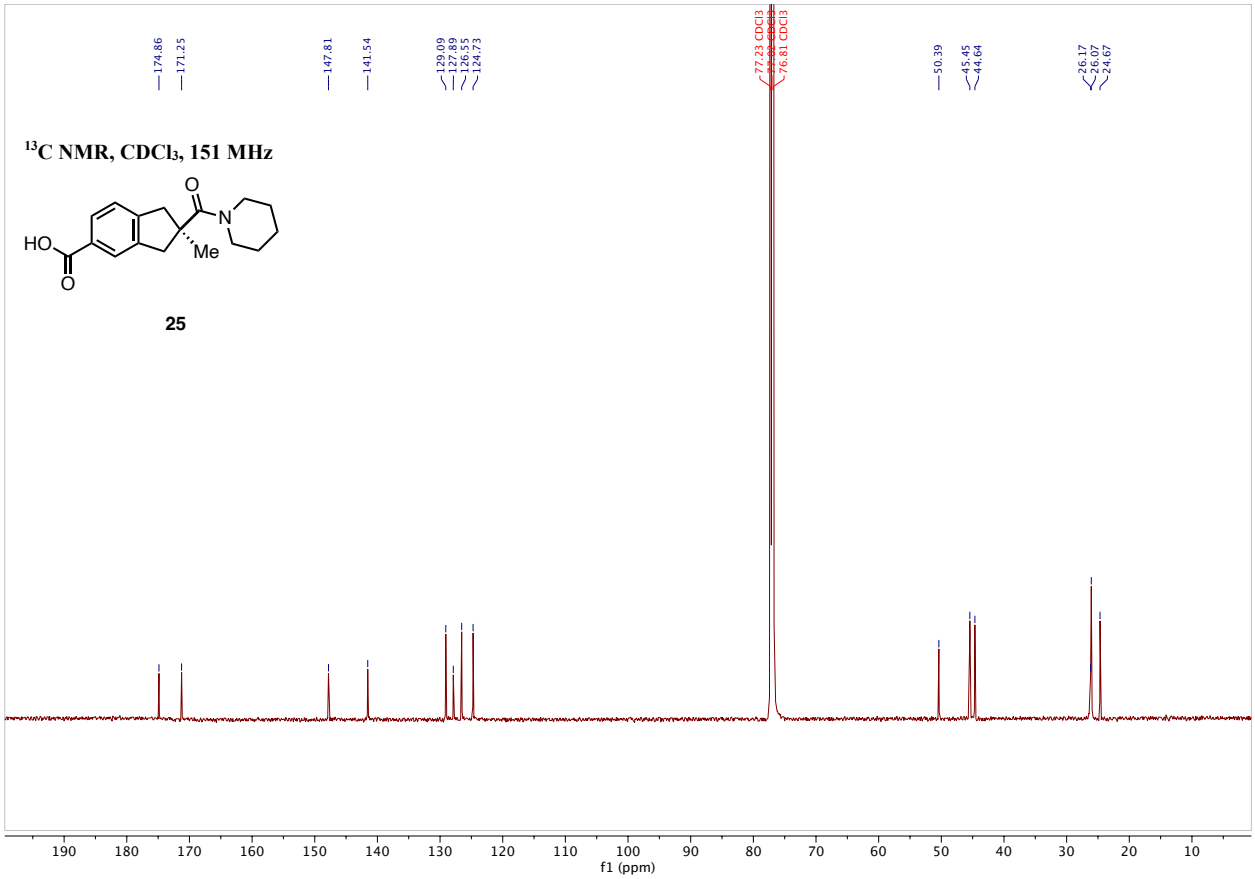
24

^{13}C NMR, $CDCl_3$, 151 MHz

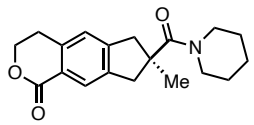


24


7.97
7.96
7.95
7.32
7.31
3.71
3.68
3.63
3.61
3.59
3.58
3.57
3.02
3.00
3.00
2.97
1.72
1.71
1.71
1.70
1.69
1.69
1.64
1.63
1.62
1.61
1.60
1.39
1H NMR, CDCl3, 600 MHz
HO
O
O
N
Me
25
1.96
0.98
6.00
2.02
2.07
4.03
3.04
f1 (ppm)

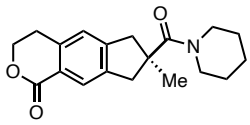

174.86
171.25
147.81
141.54
129.09
127.88
126.55
124.73
77.23 CDCl3
76.81 CDCl3
50.39
45.45
44.64
26.17
26.07
24.67
13C NMR, CDCl3, 151 MHz
HO
O
O
N
Me
25
f1 (ppm)

^{1}H NMR, $CDCl_3$, 600 MHz



26

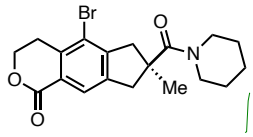
^{13}C NMR, $CDCl_3$, 151 MHz*



26

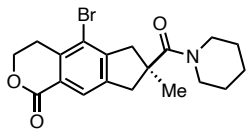
*Note: Apodization changed to 10.

^{1}H NMR, $CDCl_3$, 600 MHz



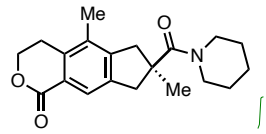
27

^{13}C NMR, $CDCl_3$, 151 MHz



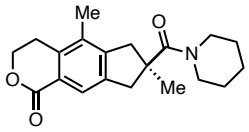
27

^{1}H NMR, $CDCl_3$, 600 MHz



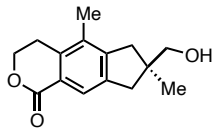
28

^{13}C NMR, $CDCl_3$, 151 MHz



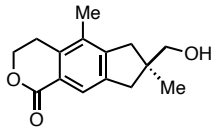
28

^{1}H NMR, $CDCl_3$, 600 MHz



Echinolactone D (**29**)

^{13}C NMR, $CDCl_3$, 151 MHz



Echinolactone D (**29**)