

Supporting Information

Nickel-Catalyzed Enantioselective Carbamoyl Iodination: A Surrogate for Carbamoyl Iodides

Austin D. Marchese,[†] Marco Wollenburg,^{†,‡} Bijan Mirabi,[†] Xavier Abel-Snape,[†] Andrew Whyte,[†] Frank Glorius,^{‡*} Mark Lautens^{†*}

[†]Department of Chemistry, Davenport Chemical Laboratories, University of Toronto, 80 St. George Street, Toronto, Ontario M5S 3H6, Canada

[‡]Organisch-Chemisches Institut, Westfälische Wilhelms-Universität Münster, Corrensstraße 40, 48149 Münster, Germany

Contents

General Considerations	2
Full Optimization	3
Mechanistic Studies	5
Unsuccessful Substrates	6
General Procedure 1	6
General Procedure 2	7
General Procedure 3	8
Starting Materials	9
Products	17
Total Synthesis of (-)-Esermethole and (-)-Phenserine	43
References	46

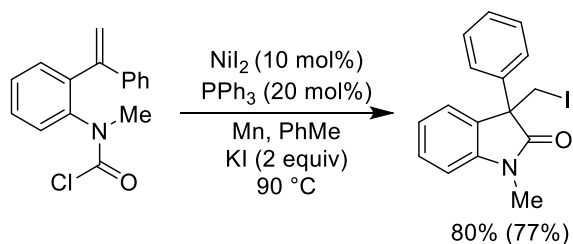
General Considerations

All reactions were performed in a dry environment under an inert atmosphere of argon unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) and visualized under UV light or by iodine staining. Flash column chromatography was performed with Silicycle 46-60 μm silica gel. Catalytic reactions were performed in 2-dram vials equipped with a Teflon cap. THF was distilled over sodium/benzophenone. Toluene and DCM were distilled over CaH_2 . 1,3,5-Trimethoxybenzene was dried over night under vacuum and stored in a desiccator.

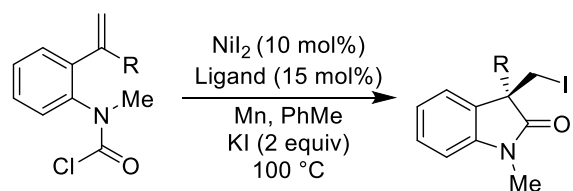
All reagents and organic building blocks were purchased from commercial suppliers (Sigma-Aldrich, Alfa Aesar, TCI, Combi-Blocks, Oakwood Chemical, AK Scientific) and used as received. NMR characterization data was collected at 296 K on a Varian Mercury 400 or an Agilent DD2 500 equipped with a 5mm Xses Cold Probe. Spectra were internally referenced to the residual solvent signal (^1H NMR: $\text{CDCl}_3 = 7.26$ ppm, ^{13}C NMR: $\text{CDCl}_3 = 77.0$ ppm). Data for ^1H NMR is reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant (Hz), integration. Coupling constants were rounded to the nearest 0.5 Hz. Infrared (IR) spectra were recorded on a PerkinElmer Spectrum 100 instrument equipped with a single-bounce diamond / ZnSe ATR accessory. Melting point ranges were determined on a Fisher-Johns Melting Point Apparatus and are reported uncorrected. High resolution mass spectra (HRMS) were obtained on a Micromass 70S-250 spectrometer (EI) or an ABI/Sciex QStar Mass Spectrometer (ESI) or a JEOL AccuTOF model JMS-T1000LC mass spectrometer equipped with and IONICS® Direct Analysis in Real Time (DART) ion source at Advanced Instrumentation for Molecular Structure (AIMS) in the Department of Chemistry at the University of Toronto. Chiral HPLC was performed on Agilent 1100 or 1200 Series operated by ChemStation LC 3D software.

Starting materials **1b**, **1c**, **1f** and **1i** previously synthesized according to Lautens.¹ Starting material **1t** was synthesized according to Tong,² as well as product **2t** was matched with the literature characterization data according to Tong.² Absolute configuration was determined by comparing HPLC traces of **3a** with Hiyama and coworkers³ as well as comparing HPLC and specific rotation of (–)-Esermethole and (–)-Phenserine. Configuration of all other compounds were assumed by analogy.

Full Optimization



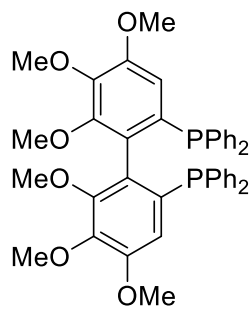
Entry	Variation from Standard	Yield
1	4 equiv KI instead of 2 equiv	72%
2	No Mn	<5%
3	No Ni	<5%
3	5 mol% NiI_2	51%
4	Zn instead of Mn	N.R.
5	Dioxane instead of Toluene	30%
6	$\text{P}(\text{O}i\text{Pr})_3$ instead of PPh_3	N.R.
7	NiBr_2	54%



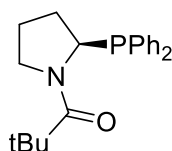
Entry	R =	Ligand	Yield	e.r
1	Ph	BINAP/BINAPO (90:10)	53%	63:37
2	Ph	MONOPhos	28%	55:45
3	Ph	Tol-BINAP	64%	65:35
4	Ph	MOP	10%	N. R.
5	Ph	DIOP	50%	52:48
6	Ph	Josiphos	20%	50:50
7	Ph	Modified-Garphos	46%	75:25
8	Ph	“Troost ligand”	N.R.	N. A
9	Ph	BDPP	83%	54:46
10	Ph	NMDPP	45%	50:50
11	Ph	Proline- PPh_2	70%	55:45
12	Ph	(S)- <i>s</i> BuPHOX	65%	60:40
13	Ph	(S)-BnPHOX	71%	50:50
14	Ph	(S)- <i>t</i> BuPHOX	83%	83:17
15	<i>i</i> Pr	(S)- <i>t</i> BuPHOX	91%	92:8
16	<i>i</i> Pr	BINAP	78%	67:23
17	<i>i</i> Pr	(S)- <i>t</i> BuPHOX, 85°C	91%	95:5
18	<i>i</i> Pr	(S)- <i>t</i> Bu-PHOX, 80°C	25%	95.5:4.5
19	<i>i</i> Pr	(S)- <i>t</i> BuPHOX, 85°C , 0.04 mmol ligand	91%	95:5
20	<i>i</i> Pr	(S)- <i>t</i> BuPHOX, 85°C , 0.022 mmol ligand	65%	N. A

21	iPr	1.8 equiv Mn	95%	N. R.
22	iPr	Dry Solvent, Dry KI, Prestir NiI ₂ , Mn, KI, (<i>S</i>)- <i>t</i> BuPHOX (15-20min)	Triplicate average 94% yield (87%)	95:5

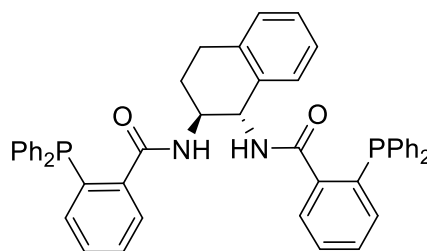
Note* we experienced reproducibility issues that we believe stem from 2 factors. 1) solvent and KI dryness and 2) an adverse reaction of the substrate with the NiI₂ and Mn in the solid phase. To circumvent this issue, we employed a 15-20 minute pre-stir of the NiI₂, Mn, ligand and KI (see general procedure 3).



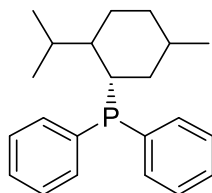
Modified-Garphos



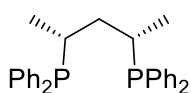
Proline-PPh₂



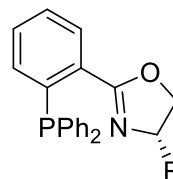
Modified Trost Ligand



NMDPP

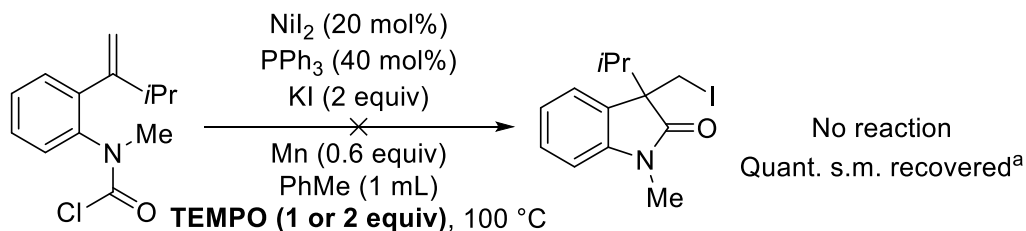
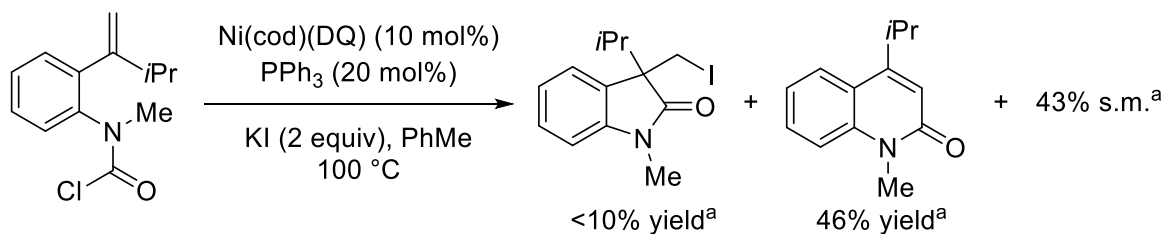
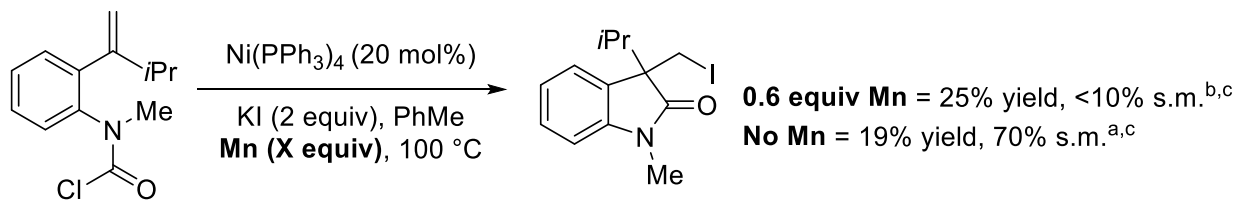
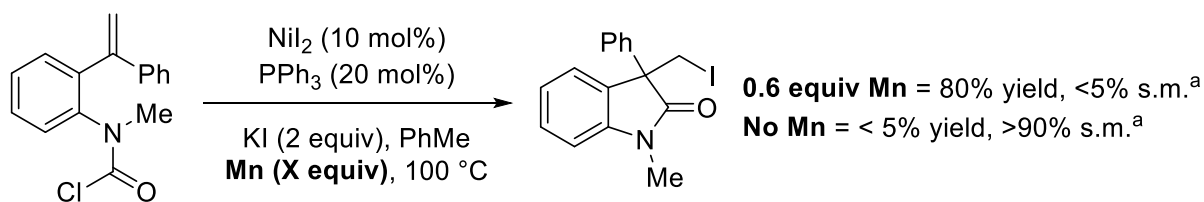


BDPP



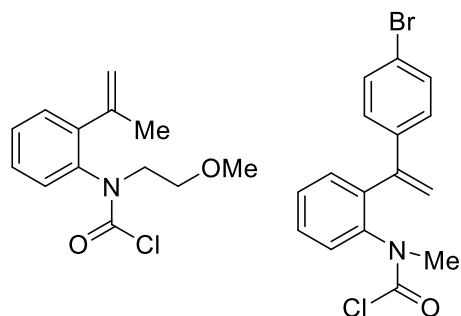
Phox

Mechanistic Studies

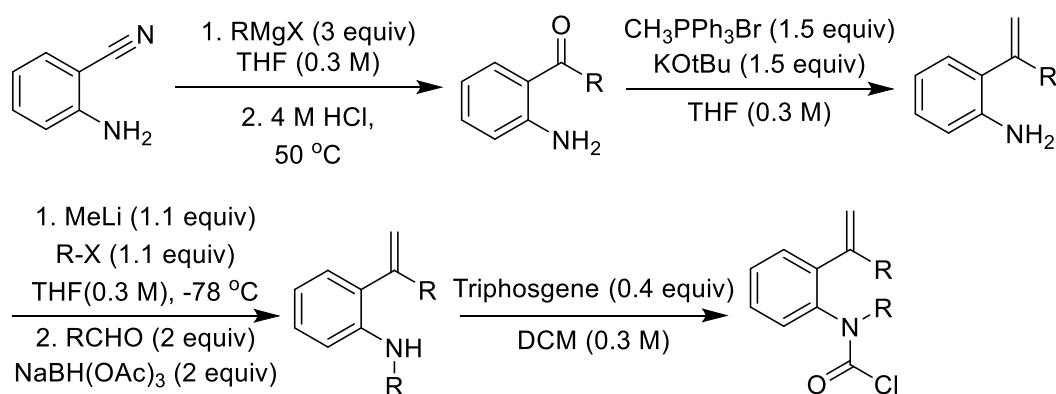


Reactions were run for 24 h on a 0.1 mmol scale (0.1 M). a) Yields were determined via NMR analysis with 1,3,5-trimethoxybenzene. b) Isolated yield. c) Reaction was set up in a glove box.

Unsuccessful Substrates



General Procedure 1



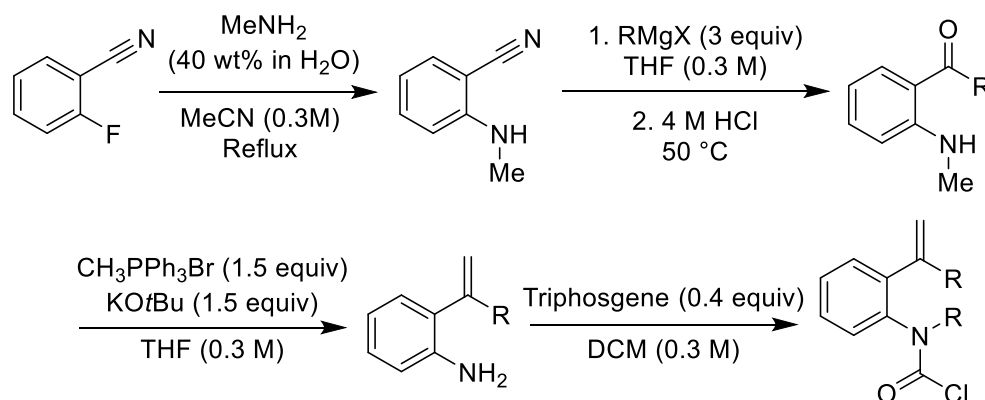
Synthesized according to Lautens.¹ The 2-aminobenzonitrile (typically 10 mmol) was stirred in THF (0.3 M) at 0 °C. Then the corresponding Grignard reagent (3.0 M, 3 equiv) was added slowly. The reaction was let stir at room temperature until completion, which was tracked by TLC. The reaction was cooled to room temperature and quenched slowly with 1M HCl. The imine hydrolysis was stirred at room temperature overnight. In some cases, the imine hydrolysis required refluxing 4M HCl in EtOH overnight to convert to the corresponding ketone. The acidic hydrolysis was run until imine was no longer visualized on TLC and the reaction was quenched with NaHCO₃. The reaction was diluted in EtOAc and washed twice with water. The organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The ketone was used with no further purification or purified with flash column chromatography if needed.

Potassium *tert*-butoxide (1.5 equiv) was added slowly to methyl triphenylphosphonium bromide (1.5 equiv) in THF (0.3 M) at 0 °C. The suspension turned yellow upon addition of the base. The suspension was warmed to room temperature and stirred for 30 minutes. The reaction was cooled to 0 °C and the 2-aminobenzophenone (typically 10 mmol) was added in THF (10 mL). The reaction was warmed to room temperature and stirred until consumption of starting material was observed by TLC (typically 4 h). Upon completion the reaction was diluted with 200 mL of pentane and filtered over a silica plug eluting with mixtures of ethyl acetate and pentane. The crude styrene was concentrated under reduced pressure and used with no further purification assuming full conversion.

- The 2-aminostyrene was dissolved in THF (0.3 M) and cooled to $-78\text{ }^{\circ}\text{C}$. Then methyllithium (1.2 equiv, 1.2 M in Et_2O) was added dropwise. The reaction was stirred for 1 h. Then the alkyl halide (1.1 equiv) was added and the reaction was warmed to room temperature and stirred overnight. The reaction was quenched with H_2O then diluted with ethyl acetate. The organic layer was separated, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give the methylated amine.
- The 2-aminostyrene was dissolved in ethyl acetate (0.25 M). The aldehyde (1.5 equiv) was added followed by trifluoroacetic acid (2 equiv). The reaction was stirred for 30 minutes then sodium triacetoxyborohydride (2 equiv) was added. The reduction was stirred for 2 h then quenched with 4 M NaOH. The reaction was diluted with ethyl acetate and washed twice with brine. The organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude was purified by flash column chromatography

The alkylated aniline could be used with no further purification assuming full conversion but was purified with flash column chromatography in cases where the conversion was poor. The methylated amine was dissolved in dichloromethane (0.3 M) and cooled to $0\text{ }^{\circ}\text{C}$. Then pyridine (2 equiv) was added followed by triphosgene (0.35 – 0.5 equiv). The reaction was warmed to room temperature and stirred until completion indicated by TLC. The reaction was quenched with 1M HCl and extracted twice with dichloromethane. The organic layers were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude starting materials were purified by flash column chromatography in ethyl acetate/pentane or dichloromethane/pentane mixtures.

General Procedure 2



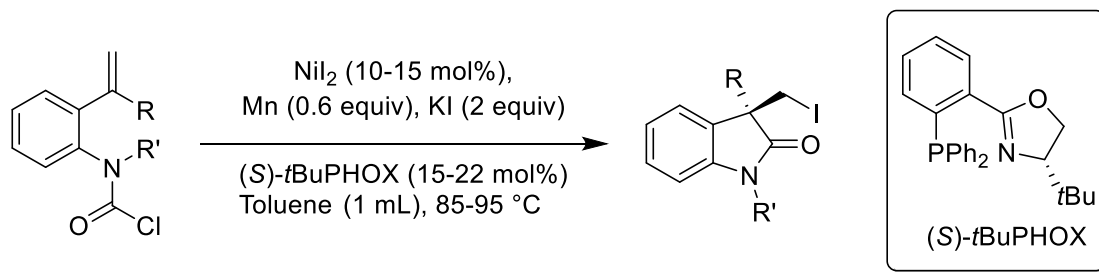
The 2-aminobenzonitrile (typically 10 mmol) was stirred in THF (0.3 M) at $0\text{ }^{\circ}\text{C}$. Then the corresponding Grignard reagent (3.0 M, 3 equiv) was added slowly. The reaction was let stir at room temperature until completion, which was tracked by TLC. The reaction was cooled to room temperature and quenched slowly with 1M HCl. The imine hydrolysis was stirred at room temperature overnight. In some cases, the imine hydrolysis required refluxing 4M HCl in EtOH overnight to convert to the corresponding ketone. The acidic hydrolysis was run until imine was no longer visualized on TLC and the reaction was quenched with NaHCO_3 . The reaction was diluted in ethyl acetate and washed twice with water. The organic layer was dried over magnesium

sulfate, filtered, and concentrated under reduced pressure. The ketone was used with no further purification or purified with flash column chromatography if needed.

Potassium *tert*-butoxide (1.5 equiv) was added slowly to methyl triphenylphosphonium bromide (1.5 equiv) in THF (0.3 M) at 0 °C. The suspension turned yellow upon addition of the base. The suspension was warmed to room temperature and stirred for 30 minutes. The reaction was cooled to 0 °C and the 2-aminobenzophenone (typically 10 mmol) was added in THF (10 mL). The reaction was warmed to room temperature and stirred until consumption of starting material was observed by TLC (typically 4 h). Upon completion the reaction was diluted with 200 mL of pentane and filtered over a silica plug eluting with mixtures of ethyl acetate and pentane. The crude styrene was concentrated under reduced pressure and used with no further purification assuming full conversion.

The alkylated aniline could be used with no further purification assuming full conversion but was purified with flash column chromatography in cases where the conversion was poor. The methylated amine was dissolved in dichloromethane (0.3 M) and cooled to 0 °C. Then pyridine (2 equiv) was added followed by triphosgene (0.35 – 0.5 equiv). The reaction was warmed to room temperature and stirred until completion indicated by TLC. The reaction was quenched with 1M HCl and extracted twice with dichloromethane. The organic layers were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude starting materials were purified by flash column chromatography in ethyl acetate/pentane or dichloromethane/pentane mixtures.

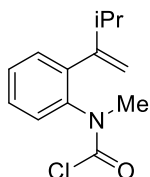
General Procedure 3



Reactions were run in 2-dram vials with magnetic stir bars that were both dried in an oven overnight. Of note, it was found to be very important that the reaction conditions are kept as anhydrous as possible; toluene was freshly distilled (less than 3 hours) and KI was dried under vacuum overnight. Upon the removal of the vial and stir bar from the oven, the vial was fit with a septum and an argon balloon delivering a generous flow of argon. After allowing the vial to cool, the vessel was charged with NiI_2 (10 mol%), Mn (0.6 equiv), $(S)\text{-tBuPhox}$ (15 mol%) and dry KI (2 equiv). The septum was replaced with a septum cap and the vial was again allowed to purge with argon for 5 minutes. 0.5 mL of freshly distilled toluene was added to the vial, and the contents were stirred for 15-20 minutes at room temperature. Substrate was weighed into a separate oven dried 2-dram vial that was also under a flow of argon. The substrate was dissolved in the remaining 0.5 mL of toluene and added to the vial. The vial was sealed with Teflon tape and put in an oil

bath of 85 or 95 °C. For substrates that proved difficult (ie. did not give full conversion using the above conditions), the same procedure was repeated using NiI₂ (15 mol%), Mn (0.6 equiv), (*S*)-*t*BuPhox (15 mol%) and dry KI (2equiv) for 36 h at 85 °C.

Starting Materials



methyl(2-(3-methylbut-1-en-2-yl)phenyl)carbamate hydrochloride

1a was synthesized by **General Procedure 1a** on a 10 mmol scale. Isolated by flash column chromatography using 20:1 Pentane:EtOAc yielding a white solid (Yield: 32%, 3.15 mmol, 747 mg).

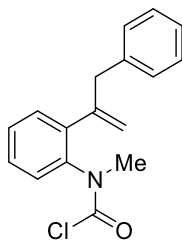
¹H NMR (500 MHz, Chloroform-*d*) δ 1.01 (d, *J* = 6.9 Hz, 3H), 1.17 (d, *J* = 6.7 Hz, 3H), 2.28 – 2.94 (m, 1H), 3.24 (s, 3H), 5.05 (t, *J* = 1.0 Hz, 1H), 5.25 (t, *J* = 1.4 Hz, 1H), 7.16 – 7.21 (m, 1H), 7.21 – 7.25 (m, 1H), 7.28 – 7.41 (m, 1H).

¹³C NMR (126 MHz, Chloroform-*d*) δ 21.4, 22.6, 33.0, 39.9, 113.4, 128.2, 128.7, 129.0, 130.8, 140.2, 141.5, 149.6, 153.8.

IR (thin film, cm⁻¹): 3050, 2964, 1734, 1493, 1358, 1272, 1235, 1087, 908, 858, 769, 664.

HRMS (DART): Calc. for C₁₃H₁₇NOCl 238.0993, found 238.0993.

m.p. 30-32 °C



methyl(2-(3-phenylprop-1-en-2-yl)phenyl)carbamate hydrochloride

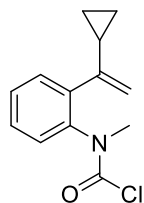
1d was synthesized by **General Procedure 1a** on a 7 mmol scale. Isolated by flash column chromatography using 20:1 Pentane:EtOAc yielding a thick yellow oil (Yield: 21%, 1.44 mmol, 412 mg).

^1H NMR (500 MHz, Chloroform-*d*) δ 3.15 (d, J = 1.0 Hz, 3H), 3.54 – 3.88 (m, 2H), 5.15 (p, J = 1.3 Hz, 2H), 7.07 – 7.24 (m, 5H), 7.27 – 7.49 (m, 4H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 40.0, 43.4, 117.6, 126.5, 128.4, 128.7, 128.9, 129.4, 129.5, 130.3, 138.4, 140.4, 140.4, 146.1, 149.5.

IR (thin film, cm^{-1}): 3029, 1732, 1599, 1490, 1354, 1196, 1070, 908, 852, 765, 700.

HRMS (DART): Calc. for $\text{C}_{17}\text{H}_{17}\text{NOCl}$ 286.0993, found 286.0994.



(2-(1-cyclopropylvinyl)phenyl)(methyl)carbamate

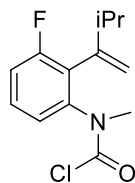
1e was synthesized by **General Procedure 1a** on a 10 mmol scale at 85 °C. Isolated by flash column chromatography using 20:1 Pentane:EtOAc yielding an amorphous yellow solid (Yield: 30%, 3.01 mmol, 697 mg).

^1H NMR (400 MHz, Chloroform-*d*) δ 0.48 – 0.69 (m, 2H), 0.70 – 1.15 (m, 2H), 1.32 – 1.62 (m, 1H), 3.28 (s, 3H), 4.96 (d, J = 0.9 Hz, 1H), 5.01 (t, J = 1.0 Hz, 1H), 7.17 – 7.24 (m, 1H), 7.30 – 7.42 (m, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 7.8, 9.1, 16.2, 39.9, 111.4, 127.4, 128.4, 128.8, 128.9, 130.2, 140.2, 141.6, 148.6.

IR (thin film, cm^{-1}): 3081, 3001, 1719, 1491, 1362, 906, 891, 707, 675.

HRMS (DART): Calc. for $\text{C}_{13}\text{H}_{15}\text{NOCl}$ 236.0837, found 236.0834.



(3-fluoro-2-(3-methylbut-1-en-2-yl)phenyl)(methyl)carbamate

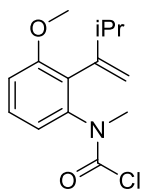
1g was synthesized by **General Procedure 1a** on a 5mmol scale. Isolated by flash column chromatography using 20:1 Pentane:EtOAc yielding a yellow oil (Yield: 34%, 1.69 mmol, 430 mg).

^1H NMR (500 MHz, Chloroform-*d*) δ 1.05 (dd, J = 6.9, 1.0 Hz, 3H), 1.18 (d, J = 6.7 Hz, 3H), 2.43 – 2.64 (m, 1H), 3.25 (s, 3H), 5.10 (s, 1H), 5.43 (s, 2H), 7.02 (d, J = 7.9 Hz, 1H), 7.13 (td, J = 8.5, 1.1 Hz, 1H), 7.30 (td, J = 8.2, 5.9 Hz, 1H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 21.1, 22.1, 33.2, 40.2, 115.7, 116.2 (d, J = 23.7 Hz), 124.7 (d, J = 3.4 Hz), 128.7 (d, J = 9.6 Hz), 130.1 (d, J = 19.1 Hz), 142.0 (d, J = 5.2 Hz), 146.4, 149.4, 160.1 (d, J = 246.5 Hz).

IR (thin film, cm^{-1}): 2974, 2878, 1736, 1609, 1463, 1348, 1258, 1054, 918, 812, 753.

HRMS (DART): Calc. for $\text{C}_{13}\text{H}_{16}\text{NOFCI}$ 256.0899, found 256.0892.



(3-methoxy-2-(3-methylbut-1-en-2-yl)phenyl)(methyl)carbamate

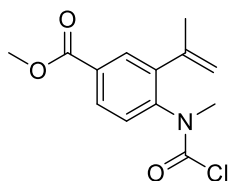
1h was synthesized by **General Procedure 2** on a 5 mmol scale. Isolated by flash column chromatography using 20:1 Pentane:EtOAc yielding a white solid (Yield: 10%, 0.47 mmol, 125.0mg).

^1H NMR (400 MHz, Chloroform-*d*) δ 1.06 (d, J = 6.9 Hz, 3H), 1.20 (d, J = 6.9 Hz, 3H), 2.46 – 2.80 (m, 1H), 3.27 (s, 3H), 3.84 (s, 3H), 5.40 (s, 2H), 6.85 (dd, J = 8.0, 1.0 Hz, 1H), 6.97 (dd, J = 8.3, 1.0 Hz, 1H), 7.31 (t, J = 8.1 Hz, 1H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 22.3, 33.3, 55.8, 55.9, 111.0, 111.1, 114.2, 120.9, 128.4, 128.7, 141.6, 150.0, 157.8.

IR (thin film, cm^{-1}): 2971, 2876, 1738, 1582, 1472, 1267, 1077, 910, 815, 751.

HRMS (DART): Calc. for $\text{C}_{14}\text{H}_{19}\text{NO}_2\text{Cl}$ 268.1100, found 268.1106.



methyl 4-((chlorocarbonyl)(methyl)amino)-3-(prop-1-en-2-yl)benzoate

1j was synthesized according to Lautens¹ on a 5mmol scale. To a 250 mL round bottom flask under argon was added Pd(dppf)Cl₂ (0.05 equiv), potassium isopropenyltrifluoroborate (2 equiv), potassium carbonate (2 equiv). The aryl bromide (5 mmol) was added in a 9:1 PhMe:H₂O mixture (0.5 M) and was refluxed for 12 h. The reaction was filtered through a celite pad and then diluted with EtOAc and washed with water twice. The organic layer was dried and purified with flash

column chromatography pentane → 10% EtOAc/pentane. From the α -amino styrene, **General Procedure 1a** was followed. Isolated by flash column chromatography using 20:1 Pentane:EtOAc yielding a white solid (Yield: 54%, 2.70 mmol, 717 mg).

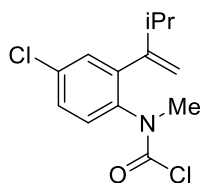
^1H NMR (400 MHz, Chloroform-*d*) δ 2.11 (dd, $J = 1.6, 0.9$ Hz, 3H), 3.26 (s, 3H), 3.93 (s, 3H), 5.08 (dd, $J = 1.5, 0.9$ Hz, 1H), 5.26 – 5.36 (m, 1H), 7.27 (d, $J = 8.9$ Hz, 1H), 7.94 – 8.04 (m, 2H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 23.2, 39.7, 52.4, 117.7, 127.7, 129.2, 129.4, 130.6, 131.2, 141.5, 141.6, 143.8, 148.9, 166.0.

IR (thin film, cm^{-1}): 3074, 2956, 1726, 1609, 1491, 1442, 1248, 1115, 928, 910, 876, 751.

HRMS (DART): Calc. for $\text{C}_{14}\text{H}_{19}\text{NOCl}$ 268.0735, found 268.0732.

m.p.: 55-57 °C



(4-chloro-2-(3-methylbut-1-en-2-yl)phenyl)(methyl)carbamate

1k was synthesized by **General Procedure 1a** on a 5 mmol scale. Isolated by flash column chromatography using 10:1 Pentane:EtOAc yielding a white solid (Yield: 48%, 2.38 mmol, 635 mg).

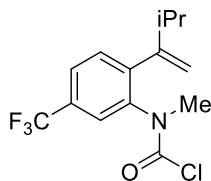
^1H NMR (500 MHz, Chloroform-*d*) δ 1.02 (d, $J = 6.9$ Hz, 3H), 1.17 (d, $J = 6.8$ Hz, 3H), 2.44 – 2.70 (m, 1H), 3.21 (s, 3H), 5.07 (s, 1H), 5.28 (t, $J = 1.2$ Hz, 1H), 7.13 (d, $J = 8.4$ Hz, 1H), 7.23 (d, $J = 2.5$ Hz, 1H), 7.30 (dd, $J = 8.4, 2.5$ Hz, 1H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 21.3, 22.5, 32.8, 39.8, 114.3, 128.3, 130.4, 130.7, 134.4, 138.7, 143.2, 149.4, 152.8.

IR (thin film, cm^{-1}): 2970, 2874, 1732, 1483, 1348, 1265, 1100, 1040, 915, 842, 736, 667.

HRMS (DART): Calc. for $\text{C}_{13}\text{H}_{16}\text{NOCl}_2$ 272.0603, found 272.0602.

m.p.: 50-52 °C



methyl(2-(3-methylbut-1-en-2-yl)-5-(trifluoromethyl)phenyl)carbamic chloride

1l was synthesized by **General Procedure 2** on a 5 mmol scale. Isolated by flash column chromatography using 20:1 Pentane:EtOAc yielding a white solid (Yield: 29%, 1.43 mmol, 437 mg).

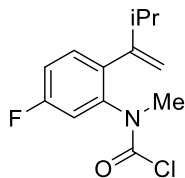
^1H NMR (500 MHz, Chloroform-*d*) δ 1.02 (d, $J = 6.9$ Hz, 3H), 1.18 (d, $J = 6.7$ Hz, 3H), 3.26 (s, 3H), 5.09 (s, 1H), 5.33 (s, 1H), 7.37 (dt, $J = 8.0, 0.7$ Hz, 1H), 7.48 (dt, $J = 2.0, 0.6$ Hz, 1H), 7.58 – 7.64 (m, 1H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 21.3, 22.5, 32.8, 39.8, 114.6, 123.3 (q, $J = 272.3$ Hz), 125.5 (q, $J = 3.6$ Hz), 126.4 (q, $J = 3.8$ Hz), 131.3, 131.6, 140.5, 145.4, 149.2, 152.8.

IR (thin film, cm^{-1}): 3053, 2964, 1740, 1429, 1311, 1130, 1083, 885, 849, 664.

HRMS (DART) ($\text{M} + \text{NH}_4$): Calc. for $\text{C}_{14}\text{H}_{19}\text{N}_2\text{OF}_3\text{Cl}$ 323.1132, found 323.1140.

m.p.: 35-37 $^\circ\text{C}$



(5-fluoro-2-(3-methylbut-1-en-2-yl)phenyl)(methyl)carbamic chloride

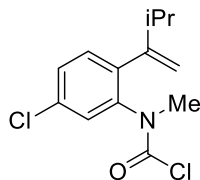
1m was synthesized according to **General Procedure 1a** on a 5 mmol scale. Isolated by flash column chromatography using 20:1 Pentane:EtOAc yielding a yellow oil (Yield: 28%, 1.40 mmol, 357 mg).

^1H NMR (500 MHz, Chloroform-*d*) δ 1.00 (d, $J = 6.9$ Hz, 3H), 1.16 (d, $J = 6.7$ Hz, 3H), 2.40 – 2.63 (m, 1H), 3.23 (s, 2H), 5.03 (s, 1H), 5.26 (s, 0H), 6.93 (dd, $J = 8.9, 2.6$ Hz, 1H), 7.07 (ddd, $J = 8.6, 7.9, 2.6$ Hz, 1H), 7.20 (dd, $J = 8.6, 6.2$ Hz, 1H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 21.3, 22.5, 33.0, 39.7, 113.9, 115.9 (d, $J = 20.5$ Hz), 116.2 (d, $J = 22.3$ Hz), 132.0 (d, $J = 8.6$ Hz), 137.7 (d, $J = 3.7$ Hz), 141.0 (d, $J = 9.5$ Hz), 149.3, 152.9, 161.6 (d, $J = 248.6$ Hz).

IR (thin film, cm^{-1}): 2964, 1734, 1599, 1498, 1351, 1278, 1196, 1070, 918, 819.

HRMS (DART): Calc. for $\text{C}_{13}\text{H}_{16}\text{NOFCl}$ 256.0899, found 256.0894.



(5-chloro-2-(3-methylbut-1-en-2-yl)phenyl)(methyl)carbamic chloride

1n was synthesized by **General Procedure 1a** on a 3.5 mmol scale. Isolated by flash column chromatography using 20:1 Pentane:EtOAc yielding a white solid (Yield: 48%, 1.67 mmol, 452 mg).

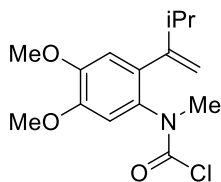
^1H NMR (500 MHz, Chloroform-*d*) δ 1.00 (d, $J = 6.9$ Hz, 3H), 1.16 (d, $J = 6.7$ Hz, 3H), 2.33 – 2.68 (m, 1H), 3.23 (s, 3H), 5.04 (s, 1H), 5.26 (s, 1H), 7.17 (d, $J = 8.3$ Hz, 1H), 7.21 (d, $J = 2.2$ Hz, 1H), 7.33 (dd, $J = 8.3, 2.2$ Hz, 1H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 21.3, 22.5, 32.9, 39.8, 114.1, 129.0, 129.2, 131.9, 133.2, 140.1, 141.0, 149.3, 152.8.

IR (thin film, cm^{-1}): 3068, 2964, 1734, 1493, 1358, 1272, 1235, 1087, 908, 858, 769, 664.

HRMS (DART): Calc. for $\text{C}_{13}\text{H}_{16}\text{NOCl}_2$ 272.0603, found 272.0600.

m.p.: 29-31 $^{\circ}\text{C}$



(4,5-dimethoxy-2-(3-methylbut-1-en-2-yl)phenyl)(methyl)carbamic chloride

1o was synthesized by **General Procedure 1a** on a 2.70 mmol scale. Isolated by flash column chromatography using 4:1 Pentane:EtOAc yielding a white/green solid (Yield: 68%, 2.06 mmol, 614 mg).

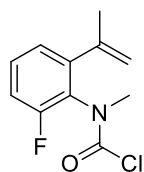
^1H NMR (500 MHz, Chloroform-*d*) δ 1.01 (d, $J = 6.8$ Hz, 3H), 1.16 (d, $J = 6.7$ Hz, 3H), 2.21 – 2.74 (m, 1H), 3.22 (s, 3H), 3.88 (s, 3H), 3.89 (s, 3H), 5.03 (s, 1H), 5.21 (s, 1H), 6.65 (s, 1H), 6.66 (s, 1H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 21.4, 22.6, 33.1, 40.0, 56.0, 56.2, 111.7, 112.6, 113.2, 132.6, 133.9, 148.3, 148.8, 150.0, 153.5.

IR (thin film, cm^{-1}): 3010, 2967, 1738, 1602, 1510, 1463, 1371, 1217, 1027, 934, 849, 779, 664.

HRMS (DART): Calc. for $\text{C}_{12}\text{H}_{24}\text{NO}_2\text{Cl}$ 298.1209, found 298.1211.

m.p.: 76-79 $^{\circ}\text{C}$



(2-fluoro-6-(prop-1-en-2-yl)phenyl)(methyl)carbamic chloride

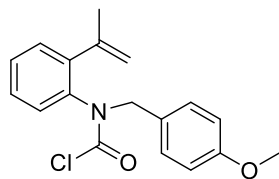
1p was synthesized according to Lautens¹ on a 5 mmol scale. To a 250 mL rb flask under argon was added Pd(dppf)Cl₂ (0.05 equiv), potassium isopropenyltrifluoroborate (2 equiv), potassium carbonate (2 equiv). The aryl bromide (5 mmol) was added in a 9:1 PhMe:H₂O mixture (0.5 M) and was refluxed for 12 h. The reaction was filtered through a celite pad and then diluted with EtOAc and washed with water twice. The organic layer was dried and purified with flash column chromatography pentane → 10% EtOAc/pentane. From the α -amino styrene, **General Procedure 1a** was followed. Isolated by flash column chromatography using 20:1 Pentane:EtOAc yielding a yellow oil (Yield: 18%, 0.89 mmol, 202 mg).

¹H NMR (400 MHz, Chloroform-*d*) δ 1.84 – 2.33 (m, 3H), 3.24 (s, 3H), 4.98 – 5.16 (m, 1H), 5.29 (s, 1H), 7.04 – 7.14 (m, 2H), 7.34 (td, *J* = 8.2, 5.5 Hz, 1H).

¹³C NMR (126 MHz, Chloroform-*d*) δ 23.3, 39.1 (d, *J* = 1.3 Hz), 115.0, 115.2, 116.6, 117.5, 124.8 (d, *J* = 3.5 Hz), 130.0 (d, *J* = 8.8 Hz), 141.3, 143.7, 158.3 (d, *J* = 250.3 Hz).

IR (thin film, cm⁻¹): 3067, 2948, 1741, 1575, 1468, 1350, 1240, 1115, 971, 849, 800, 754, 663, 591.

HRMS (DART): Calc. for C₁₁H₁₂NOFCI 228.0586, found 228.0586.



(4-methoxybenzyl)(2-(prop-1-en-2-yl)phenyl)carbamic chloride

1q was synthesized by **General Procedure 1b** on a 3.5 mmol scale. Isolated by flash column chromatography using 10:1 Pentane:EtOAc yielding a white solid (Yield: 38%, 1.33 mmol, 414 mg).

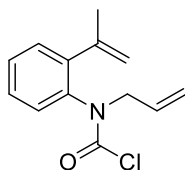
¹H NMR (500 MHz, Chloroform-*d*) δ 2.15 (s, 3H), 3.79 (s, 3H), 4.03 (d, *J* = 14.2 Hz, 1H), 5.13 (dd, *J* = 1.7, 0.9 Hz, 1H), 5.25 – 5.54 (m, 2H), 6.68 (d, *J* = 7.9 Hz, 1H), 6.79 (d, *J* = 8.7 Hz, 2H), 7.07 (d, *J* = 8.7 Hz, 2H), 7.11 – 7.20 (m, 1H), 7.32 (d, *J* = 4.0 Hz, 2H).

¹³C NMR (126 MHz, Chloroform-*d*) δ 23.4, 55.1, 55.2, 113.8, 117.1, 127.6, 128.8, 129.7, 130.7, 131.0, 138.0, 141.1, 142.6, 150.0, 159.4.

IR (thin film, cm^{-1}): 3067, 2911, 1734, 1609, 1510, 1447, 1374, 1245, 1176, 1037, 954, 852, 763, 604.

HRMS (DART): Calc. for $\text{C}_{18}\text{H}_{19}\text{NO}_2\text{Cl}$ 316.1100, found 316.1103.

m.p.: 56-58 $^{\circ}\text{C}$



allyl(2-(prop-1-en-2-yl)phenyl)carbamate

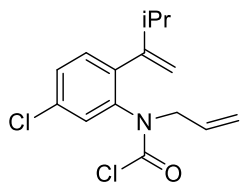
1r was synthesized by **General Procedure 1a** on a 4.5 mmol scale. Isolated by flash column chromatography using 20:1 Pentane:EtOAc yielding a yellow oil (Yield: 62%, 2.82 mmol, 665 mg).

^1H NMR (400 MHz, Chloroform-*d*) δ 2.11 (dd, $J = 1.5, 0.9$ Hz, 3H), 3.67 (ddt, $J = 14.7, 7.5, 1.1$ Hz, 1H), 4.68 (ddt, $J = 14.7, 5.6, 1.4$ Hz, 1H), 4.93 – 5.59 (m, 4H), 5.87 (dddd, $J = 17.4, 10.1, 7.5, 5.6$ Hz, 1H), 7.09 – 7.16 (m, 1H), 7.21 – 7.46 (m, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 23.4, 55.0, 117.1, 119.6, 127.8, 128.9, 129.8, 130.4, 131.0, 138.4, 141.3, 142.4, 149.4.

IR (thin film, cm^{-1}): 3081, 2990, 1734, 1491, 1377, 1221, 914, 770, 660.

HRMS (DART): Calc. for $\text{C}_{13}\text{H}_{15}\text{NOCl}$ 236.0837, found 236.0842.



allyl(5-chloro-2-(3-methylbut-1-en-2-yl)phenyl)carbamate

1s was synthesized by **General Procedure 1a** on a 3.5 mmol scale. Isolated by flash column chromatography using 20:1 Pentane:EtOAc yielding a yellow oil (Yield: 70%, 2.46 mmol, 734 mg).

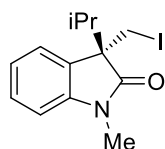
^1H NMR (500 MHz, Chloroform-*d*) δ 0.99 (d, $J = 6.9$ Hz, 3H), 1.18 (d, $J = 6.7$ Hz, 3H), 2.46 – 2.74 (m, 1H), 3.65 (ddt, $J = 14.7, 7.6, 1.0$ Hz, 1H), 4.64 (dd, $J = 14.7, 5.6$ Hz, 1H), 5.03 (s, 1H), 5.13 (dd, $J = 17.1, 1.4$ Hz, 1H), 5.21 (dd, $J = 10.1, 1.1$ Hz, 1H), 5.27 (t, $J = 1.3$ Hz, 1H), 5.84 (dddd, $J = 17.1, 10.1, 7.6, 5.6$ Hz, 1H), 7.07 – 7.21 (m, 2H), 7.33 (dd, $J = 8.3, 2.2$ Hz, 1H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 21.2, 22.6, 32.8, 54.6, 114.1, 120.1, 129.0, 130.6, 130.7, 131.9, 132.9, 139.2, 140.2, 149.1, 153.2.

IR (thin film, cm^{-1}): 3089, 2971, 1738, 1593, 1483, 1358, 1210, 1104, 914, 827, 690.

HRMS (DART): Calc. for $\text{C}_{15}\text{H}_{18}\text{NOCl}_2$ 298.0760, found 298.0755.

Products

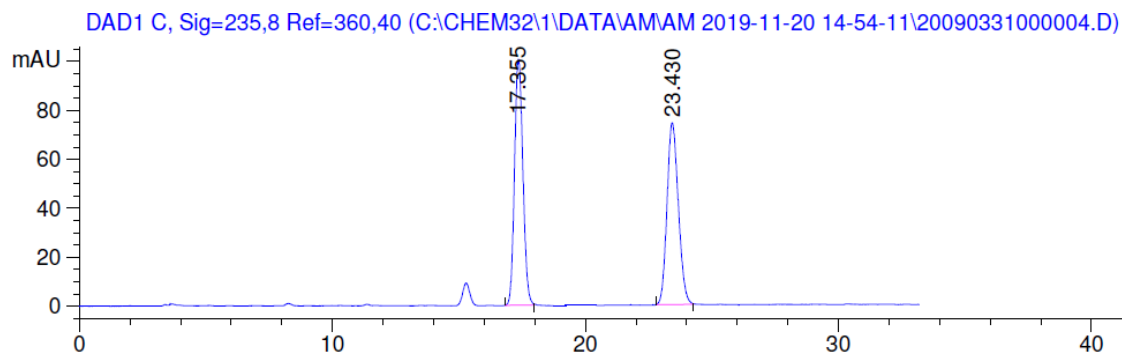


(S)-3-(iodomethyl)-3-isopropyl-1-methylindolin-2-one

2a was synthesized by **General Procedure 2** on a 0.2 mmol scale at 85 °C. Isolated by flash column chromatography using 4:1 Pentane:EtOAc yielding a white solid (Yield: 87%, 0.174 mmol, 57.3 mg). Enantiomeric purity was determined by HPLC analysis in comparison with racemic material $T_R = 17.36$ (minor) $T_R = 23.40$ (major) (95:5 e.r; Chiralcel IC column, 2.5% iPrOH in hexanes 1.0 mL/min, 235 nm). **m.p.**: 82-84 °C. Characterization was consistent with the literature for the racemic variant.³

^1H NMR (500 MHz, Chloroform-*d*) δ 0.82 (d, $J = 6.7$ Hz, 3H), 0.98 (d, $J = 6.9$ Hz, 3H), 2.28 (p, $J = 6.8$ Hz, 1H), 3.23 (s, 3H), 3.58 (d, $J = 1.3$ Hz, 2H), 6.86 (dt, $J = 7.7, 0.8$ Hz, 1H), 7.10 (td, $J = 7.5, 1.0$ Hz, 1H), 7.22 (ddd, $J = 7.4, 1.3, 0.6$ Hz, 1H), 7.34 (td, $J = 7.7, 1.3$ Hz, 1H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 9.6, 17.4, 18.2, 26.0, 35.4, 56.5, 108.0, 122.4, 123.5, 128.6, 130.1, 144.3, 177.6.

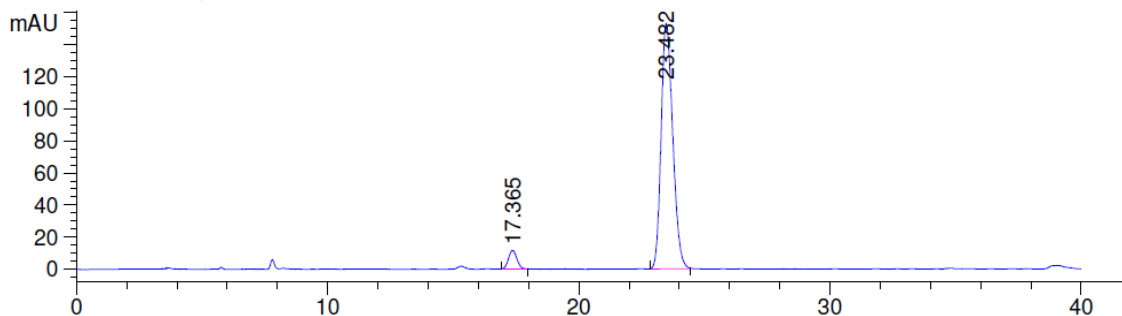


Signal 3: DAD1 C, Sig=235,8 Ref=360,40

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.355	BB	0.3588	2308.90674	100.59415	49.9502
2	23.430	BB	0.4680	2313.51050	74.36470	50.0498

Totals : 4622.41724 174.95885

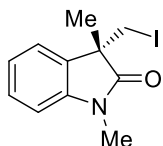
DAD1 C, Sig=235,8 Ref=360,40 (C:\CHEM32\1\DATA\AMAM 2019-11-20 19-49-50\20090331000003.D)



Signal 3: DAD1 C, Sig=235,8 Ref=360,40

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.365	BB	0.3117	267.09622	11.55278	5.1542
2	23.482	BB	0.4920	4914.96191	152.90491	94.8458

Totals : 5182.05814 164.45769



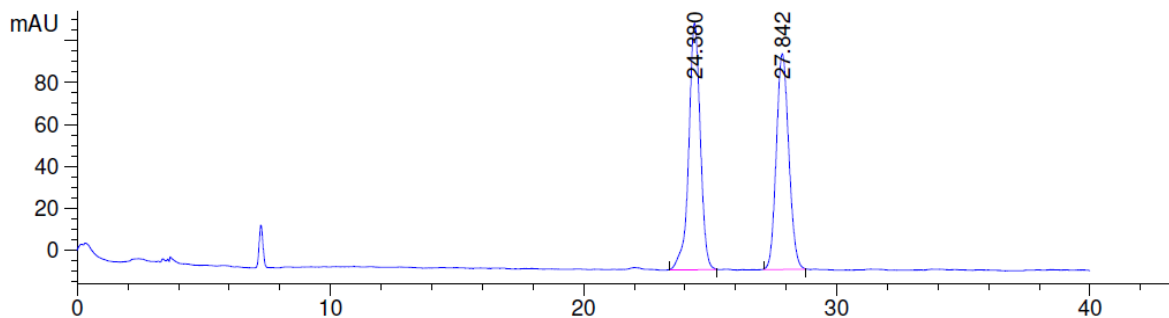
(S)-3-(iodomethyl)-1,3-dimethylindolin-2-one

2b was synthesized by **General Procedure 2** on a 0.2 mmol scale at 85 °C. Isolated by flash column chromatography using 4:1 Pentane:EtOAc yielding a white solid (Yield: 72%, 0.144 mmol, 43.3 mg). Enantiomeric purity was determined by HPLC analysis in comparison with racemic material $T_R = 23.34$ (minor) $T_R = 26.68$ (major) (97:3 e.r; Chiralcel IC column, 2.5% iPrOH in hexanes 1.0 mL/min, 235 nm). **m.p.**: 55-57 °C. Characterization was consistent with the literature for the racemic variant.³

¹H NMR (500 MHz, Chloroform-*d*) δ 1.52 (s, 3H), 3.24 (s, 3H), 3.43 (d, $J = 9.8$ Hz, 1H), 3.52 (d, $J = 9.8$ Hz, 1H), 6.88 (d, $J = 7.7$ Hz, 1H), 7.11 (td, $J = 7.5, 1.0$ Hz, 1H), 7.27 (ddd, $J = 7.4, 1.3, 0.6$ Hz, 1H), 7.34 (td, $J = 7.7, 1.3$ Hz, 1H).

¹³C NMR (126 MHz, Chloroform-*d*) δ 10.8, 23.0, 26.3, 48.6, 108.3, 122.6, 122.7, 128.7, 132.6, 143.2, 177.9.

DAD1 B, Sig=220,2 Ref=360,40 (C:\CHEM32\1\DATA\AMAM 2019-11-27 22-55-42\20090331000003.D)

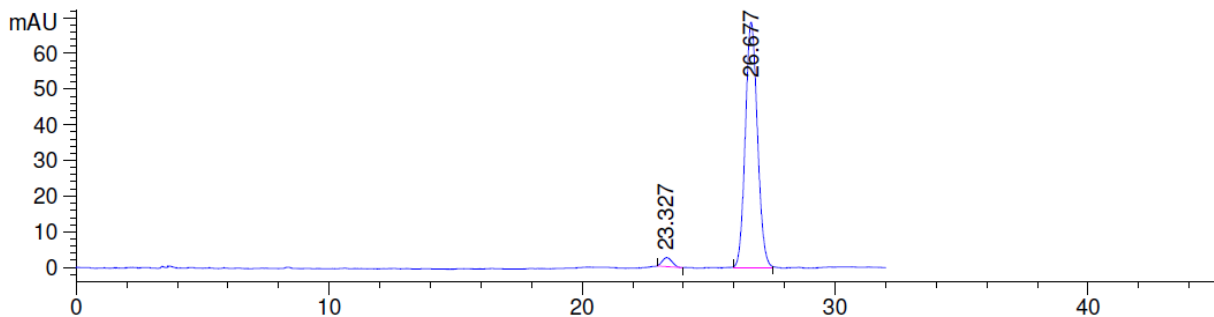


Signal 2: DAD1 B, Sig=220,2 Ref=360,40

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.380	BB	0.4879	3736.06006	117.83652	51.3776
2	27.842	BB	0.5320	3535.70435	103.11434	48.6224

Totals : 7271.76440 220.95086

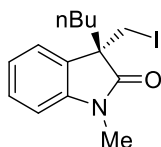
DAD1 C, Sig=235,8 Ref=360,40 (C:\CHEM32\1\DATA\AYEN\AM 2019-11-27 15-28-18\20090331000004.D)



Signal 3: DAD1 C, Sig=235,8 Ref=360,40

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.327	BB	0.3179	68.14662	2.55688	2.8954
2	26.677	BB	0.4959	2285.45239	68.74577	97.1046

Totals : 2353.59901 71.30265



(S)-3-butyl-3-(iodomethyl)-1-methylindolin-2-one

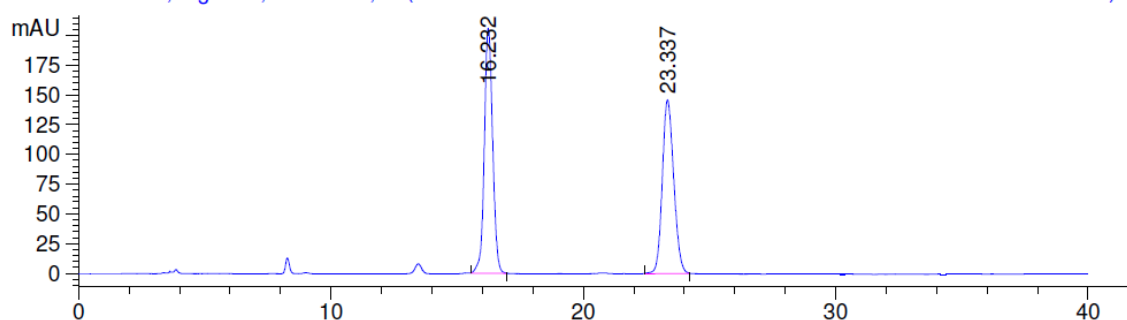
2c was synthesized by **General Procedure 2** on a 0.2 mmol scale at 85 °C. Isolated by flash column chromatography using 4:1 Pentane:EtOAc yielding a yellow oil (Yield: 90%, 0.180 mmol,

61.7 mg). Enantiomeric purity was determined by HPLC analysis in comparison with racemic material $T_R = 15.15$ (minor) $T_R = 21.67$ (major) (94:6 e.r; Chiralcel IC column, 2.5% iPrOH in hexanes 1.0 mL/min, 235 nm). Characterization was consistent with the literature for the racemic variant.³

^1H NMR (300 MHz, Chloroform-*d*) δ 0.76 (t, $J = 7.3$ Hz, 3H), 0.81 – 0.90 (m, 1H), 0.93 – 1.09 (m, 1H), 1.09 – 1.32 (m, 2H), 1.83 (tdd, $J = 12.9, 4.6, 1.3$ Hz, 1H), 1.96 (tdd, $J = 11.9, 4.7, 1.3$ Hz, 1H), 3.24 (s, 3H), 3.41 (d, $J = 8.4$ Hz, 1H), 3.52 (d, $J = 9.7$ Hz, 1H), 6.87 (d, $J = 7.9$ Hz, 1H), 7.12 (t, $J = 7.5$ Hz, 1H), 7.21 (d, $J = 6.1$ Hz, 1H), 7.34 (t, $J = 7.7$ Hz, 1H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 10.6, 13.7, 22.8, 26.2, 27.3, 37.2, 53.1, 108.1, 122.7, 122.7, 128.6, 131.1, 144.0, 177.5.

DAD1 C, Sig=235,8 Ref=360,40 (C:\CHEM32\1\DATA\AMAM 2019-11-29 17-34-32\20090331000003.D)

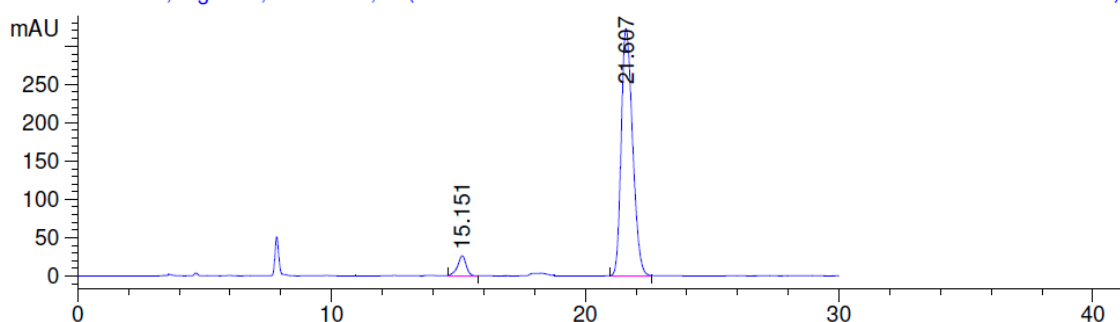


Signal 3: DAD1 C, Sig=235,8 Ref=360,40

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.232	BB	0.3519	4713.14990	206.00803	50.5833
2	23.337	BB	0.4869	4604.45215	146.03377	49.4167

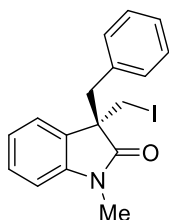
Totals : 9317.60205 352.04179

DAD1 C, Sig=235,8 Ref=360,40 (C:\CHEM32\1\DATA\AMAM 2019-12-01 15-48-37\20090331000005.D)



Signal 3: DAD1 C, Sig=235,8 Ref=360,40

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.151	BB	0.3536	610.76959	26.14274	5.7435
2	21.607	BB	0.4793	1.00233e4	322.78937	94.2565
Totals :				1.06341e4	348.93211	



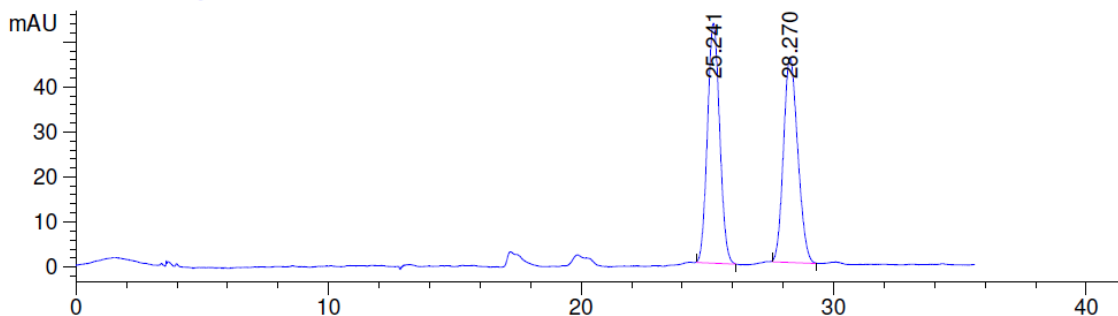
(S)-3-benzyl-3-(iodomethyl)-1-methylindolin-2-one

2d was synthesized by **General Procedure 2** on a 0.2 mmol scale at 85 °C for 36 h. Isolated by flash column chromatography using 4:1 Pentane:EtOAc yielding a white solid (Yield: 76%, 0.152 mmol, 57.3 mg). Enantiomeric purity was determined by HPLC analysis in comparison with racemic material $T_R = 24.35$ (minor) $T_R = 27.16$ (major) (96.5:3.5 e.r; Chiralcel IC column, 2.5% iPrOH in hexanes 1.0 mL/min, 235 nm). **m.p.**: 55-60 °C. Characterization was consistent with the literature for the racemic variant.³

¹H NMR (500 MHz, Chloroform-*d*) δ 3.00 (s, 3H), 3.16 (q, $J = 12.9$ Hz, 2H), 3.52 (d, $J = 9.8$ Hz, 1H), 3.69 (d, $J = 9.8$ Hz, 1H), 6.64 (d, $J = 7.8$ Hz, 1H), 6.84 (dd, $J = 7.9, 1.7$ Hz, 2H), 7.03 – 7.12 (m, 4H), 7.18 (ddd, $J = 7.4, 1.3, 0.6$ Hz, 1H), 7.26 (td, $J = 7.7, 1.3$ Hz, 1H).

¹³C NMR (126 MHz, Chloroform-*d*) δ 9.1, 26.0, 43.4, 54.6, 108.0, 122.3, 123.6, 126.8, 127.6, 128.7, 129.8, 130.0, 135.1, 143.7, 176.7.

DAD1 C, Sig=235,8 Ref=360,40 (C:\CHEM32\1\DATA\AMAM 2019-12-01 15-48-37\20090331000004.D)

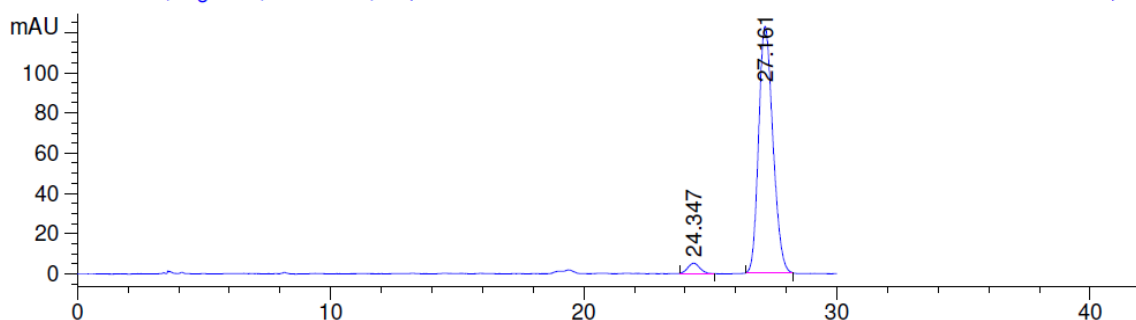


Signal 3: DAD1 C, Sig=235,8 Ref=360,40

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.241	BB	0.5071	1797.54041	53.34365	50.1578
2	28.270	BB	0.5340	1786.22986	45.50274	49.8422

Totals : 3583.77026 98.84639

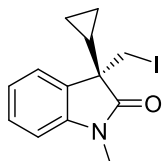
DAD1 C, Sig=235,8 Ref=360,40 (C:\CHEM32\1\DATA\AMAM 2019-12-01 15-48-37\20090331000006.D)



Signal 3: DAD1 C, Sig=235,8 Ref=360,40

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.347	BB	0.4052	170.55927	5.16574	3.4154
2	27.161	BB	0.6032	4823.20898	122.82138	96.5846

Totals : 4993.76825 127.98712



(S)-3-cyclopropyl-3-(iodomethyl)-1-methylindolin-2-one

2e was synthesized by **General Procedure 2** on a 0.2 mmol scale at 85 °C with 15 mol% catalyst for 36 h. Isolated by flash column chromatography using 5:1 Pentane:EtOAc yielding a white solid (Yield: 57%, 0.114 mmol, 37.2 mg). Enantiomeric purity was determined by HPLC analysis in comparison with racemic material T_R = 24.35 (minor) T_R = 28.64 (major) (94.5:5.5 e.r.; Chiralcel IC column, 2.5% iPrOH in hexanes 1.0 mL/min, 235 nm). **m.p.**: 95–98 °C

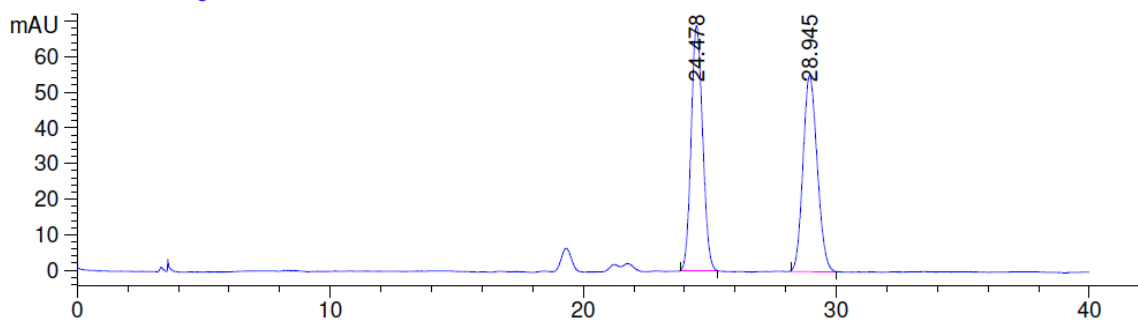
^1H NMR (400 MHz, Chloroform-*d*) δ -0.15 – 0.11 (m, 1H), 0.18 – 0.47 (m, 2H), 0.46 – 0.67 (m, 1H), 1.34 (tt, J = 8.1, 5.6 Hz, 1H), 3.22 (s, 3H), 3.51 (d, J = 9.8 Hz, 1H), 3.68 (d, J = 9.8 Hz, 1H), 6.85 (dt, J = 7.8, 0.8 Hz, 1H), 7.02 – 7.18 (m, 2H), 7.33 (td, J = 7.6, 1.5 Hz, 1H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 1.4, 1.9, 8.7, 16.7, 26.3, 52.9, 108.2, 122.3, 123.2, 128.9, 128.9, 144.1, 177.2.

IR (thin film, cm^{-1}): 3081, 2922, 1700, 1616, 1479, 1377, 1199, 1085, 1024, 884, 835, 762, 698, 595.

HRMS (DART): Calc. for $\text{C}_{13}\text{H}_{15}\text{INO}$ 328.0193, found 328.0190.

DAD1 D, Sig=254,8 Ref=360,40 (C:\CHEM32\1\DATA\AMAM 2020-01-13 22-39-55\20090331000003.D)

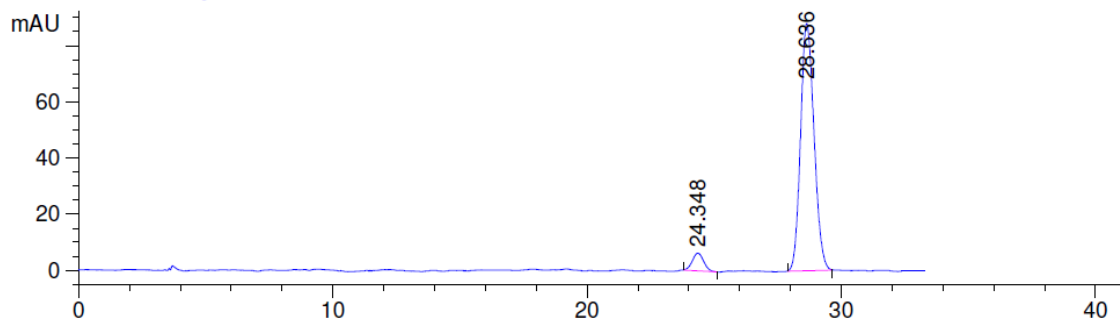


Signal 4: DAD1 D, Sig=254,8 Ref=360,40

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.478	BB	0.4784	2185.46338	69.02000	50.3189
2	28.945	BB	0.5777	2157.75952	55.11536	49.6811

Totals : 4343.22290 124.13536

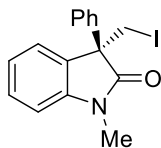
DAD1 C, Sig=235,8 Ref=360,40 (C:\CHEM32\1\DATA\AMAM 2020-01-14 15-06-43\20090331000003.D)



Signal 3: DAD1 C, Sig=235,8 Ref=360,40

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.348	BB	0.3729	197.82446	6.32413	5.7343
2	28.636	BB	0.5647	3251.99805	88.09261	94.2657

Totals : 3449.82251 94.41674

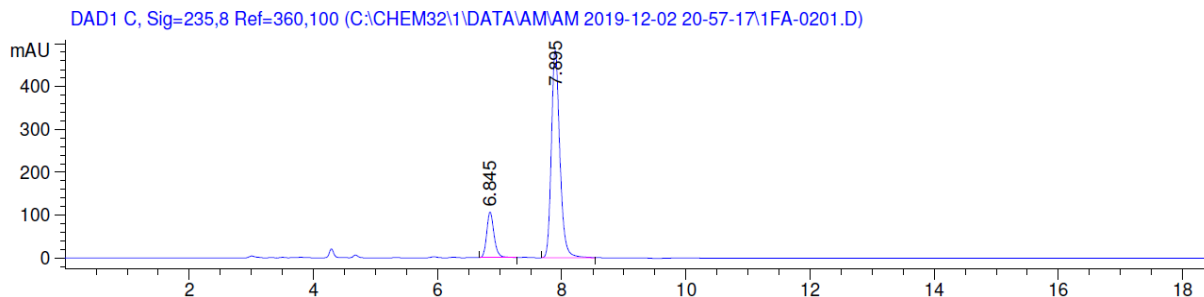


(S)-3-(iodomethyl)-1-methyl-3-phenylindolin-2-one

2f was synthesized by **General Procedure 2** on a 0.2 mmol scale at 95 °C. Isolated by flash column chromatography using 3:1 Pentane:EtOAc yielding a white solid (Yield: 74%, 0.148 mmol, 53.7 mg). Enantiomeric purity was determined by HPLC analysis in comparison with literature³ T_R = 6.85 (minor) T_R = 7.90 (major) (84:16 e.r; Chiralcel IA column, 10% iPrOH in hexanes 1.0 mL/min, 235 nm). **m.p.**: 140-143 °C. Characterization was consistent with the literature for the racemic variant.³

¹H NMR (500 MHz, Chloroform-*d*) δ 3.25 (s, 3H), 3.77 (d, J = 9.8 Hz, 1H), 4.04 (d, J = 9.8 Hz, 1H), 6.94 (d, J = 7.5 Hz, 1H), 7.20 (td, J = 7.5, 1.0 Hz, 1H), 7.28 – 7.35 (m, 3H), 7.36 – 7.49 (m, 4H).

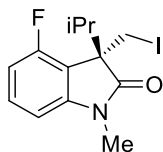
¹³C NMR (126 MHz, Chloroform-*d*) δ 10.5, 26.6, 56.6, 108.6, 122.8, 125.0, 127.1, 128.1, 128.8, 129.1, 130.8, 137.7, 144.0, 176.2.



Signal 3: DAD1 C, Sig=235,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.845	BB	0.1270	886.45776	106.66335	16.1474
2	7.895	BB	0.1449	4603.31738	484.48285	83.8526

Totals : 5489.77515 591.14619



(S)-4-fluoro-3-(iodomethyl)-3-isopropyl-1-methylindolin-2-one

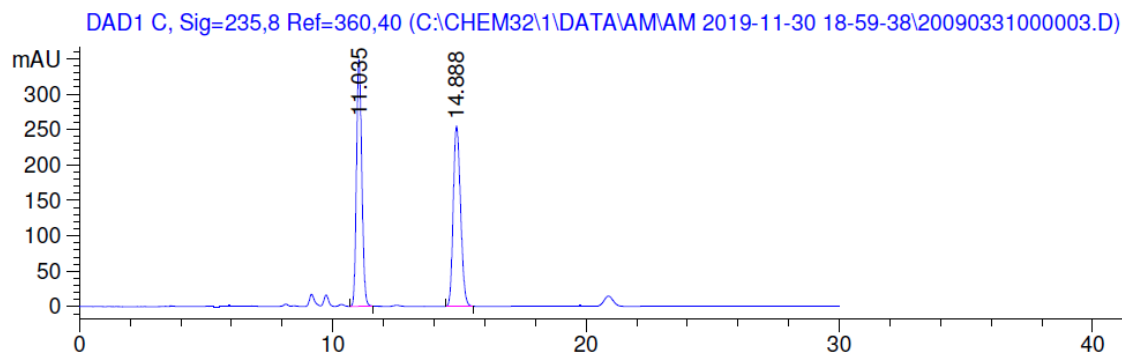
2g was synthesized by **General Procedure 2** on a 0.2 mmol scale at 85 °C. Isolated by flash column chromatography using 5:1 Pentane:EtOAc yielding a off-white foam (Yield: 85%, 0.170 mmol, 59.0 mg). Enantiomeric purity was determined by HPLC analysis in comparison with racemic material $T_R = 10.76$ (minor) $T_R = 14.69$ (major) (96.5:3.5 e.r; Chiralcel IC column, 2.5% iPrOH in hexanes 1.0 mL/min, 235 nm).

^1H NMR (500 MHz, Chloroform-*d*) δ 0.90 (d, $J = 6.7$ Hz, 3H), 0.98 (dd, $J = 7.0, 2.2$ Hz, 3H), 2.36 (pd, $J = 6.8, 1.9$ Hz, 1H), 3.21 (s, 3H), 3.67 (d, $J = 9.5$ Hz, 1H), 3.81 (d, $J = 9.5$ Hz, 1H), 6.66 (dd, $J = 7.8, 0.8$ Hz, 1H), 6.77 (ddd, $J = 9.4, 8.5, 0.8$ Hz, 1H), 7.30 (ddd, $J = 8.5, 7.8, 5.5$ Hz, 1H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 7.2 (d, $J = 1.4$ Hz), 18.1, 18.7 (d, $J = 4.1$ Hz), 26.4, 35.5, 58.4 (d, $J = 2.8$ Hz), 104.1 (d, $J = 3.0$ Hz), 110.3 (d, $J = 21.9$ Hz), 116.0 (d, $J = 20.0$ Hz), 130.4 (d, $J = 8.9$ Hz), 146.4 (d, $J = 9.9$ Hz), 158.9 (d, $J = 246.8$ Hz), 177.1.

IR (thin film, cm^{-1}): 2970, 2891, 1715, 1625, 1475, 1351, 1239, 1049, 789.

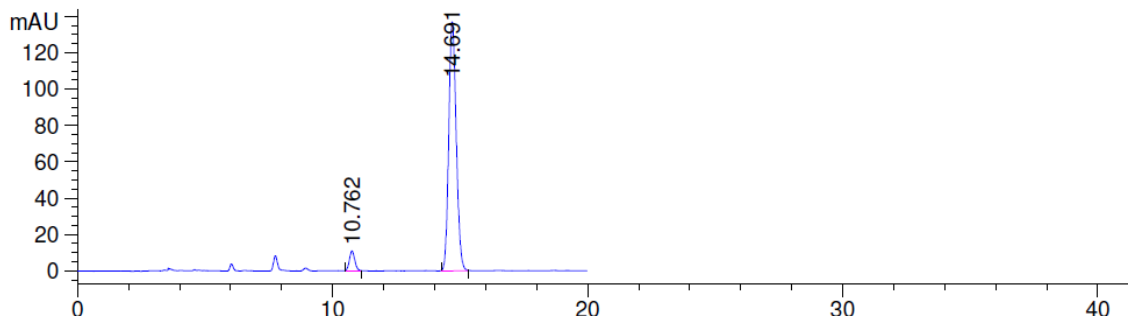
HRMS (DART): Calc. for $\text{C}_{13}\text{H}_{16}\text{FINO}$ 348.0255, found 348.0253.



Signal 3: DAD1 C, Sig=235,8 Ref=360,40

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.035	VB	0.2287	5093.43555	348.20837	49.9403
2	14.888	BB	0.3129	5105.61035	254.70448	50.0597
Totals :				1.01990e4	602.91286	

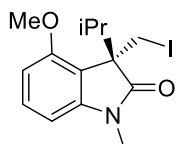
DAD1 C, Sig=235,8 Ref=360,40 (C:\CHEM32\1\DATA\AMAM 2019-11-30 22-32-41\20090331000004.D)



Signal 3: DAD1 C, Sig=235,8 Ref=360,40

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.762	BB	0.2248	159.42973	10.82757	5.3898
2	14.691	BB	0.3175	2798.54932	136.87343	94.6102

Totals : 2957.97905 147.70100



(S)-3-(iodomethyl)-3-isopropyl-4-methoxy-1-methylindolin-2-one

2h was synthesized by **General Procedure 2** on a 0.2 mmol scale at 85 °C with 15 mol% catalyst for 36 h. Isolated by flash column chromatography using 4:1 Pentane:EtOAc yielding a white solid (Yield: 70%, 0.140 mmol, 50.5 mg). Enantiomeric purity was determined by HPLC analysis in comparison with racemic material $T_R = 22.40$ (minor) $T_R = 24.03$ (major) (93:7 e.r; Chiralcel IC column, 2.5% iPrOH in hexanes 1.0 mL/min, 235 nm). **m.p.**: 72-75 °C

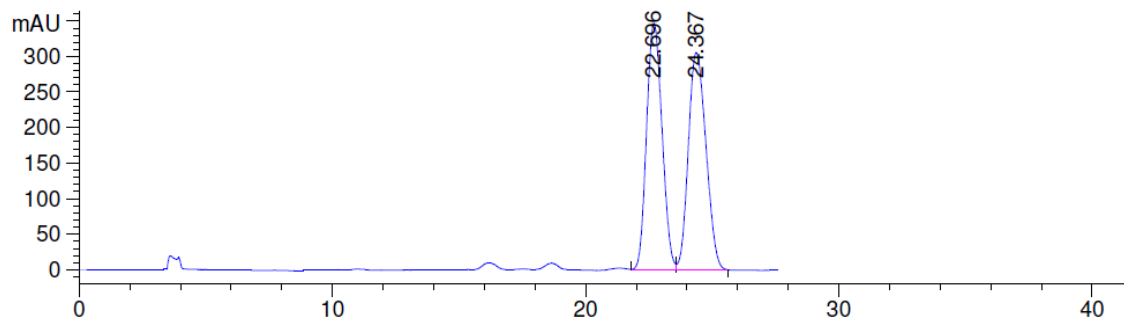
^1H NMR (400 MHz, Chloroform-*d*) δ 0.85 (d, $J = 6.9$ Hz, 3H), 1.01 (d, $J = 6.8$ Hz, 3H), 2.48 (p, $J = 6.9$ Hz, 1H), 3.19 (s, 3H), 3.74 (d, $J = 9.0$ Hz, 1H), 3.85 (s, 3H), 3.96 (d, $J = 9.0$ Hz, 1H), 6.50 (d, $J = 7.7$ Hz, 1H), 6.64 (d, $J = 8.5$ Hz, 1H), 7.28 (t, $J = 9.2$ Hz, 1H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 8.5, 17.3, 19.5, 26.2, 34.2, 55.4, 58.0, 101.3, 105.9, 117.2, 129.7, 145.5, 156.1, 177.5.

IR (thin film, cm^{-1}): 3096, 2960, 2884, 1707, 1605, 1472, 1358, 1263, 1070, 797, 766, 652, 599.

HRMS (DART): Calc. for $\text{C}_{14}\text{H}_{19}\text{INO}_2$ 360.0455, found 390.0451.

DAD1 C, Sig=235,8 Ref=360,40 (C:\CHEM32\1\DATA\AMAM 2020-01-12 17-54-34\20090331000003.D)

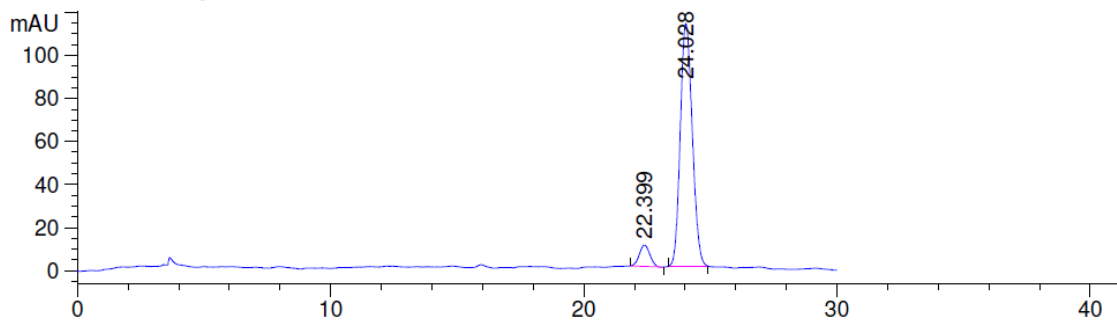


Signal 3: DAD1 C, Sig=235,8 Ref=360,40

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.696	VV	0.6566	1.47830e4	347.26700	49.9118
2	24.367	VB	0.7414	1.48353e4	306.13153	50.0882

Totals : 2.96183e4 653.39853

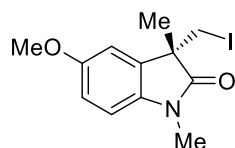
DAD1 C, Sig=235,8 Ref=360,40 (C:\CHEM32\1\DATA\AMAM 2020-01-12 17-54-34\20090331000005.D)



Signal 3: DAD1 C, Sig=235,8 Ref=360,40

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.399	BB	0.3536	284.69543	9.95696	7.0887
2	24.028	BB	0.5035	3731.48120	112.92599	92.9113

Totals : 4016.17664 122.88295



(S)-3-(iodomethyl)-5-methoxy-1,3-dimethylindolin-2-one

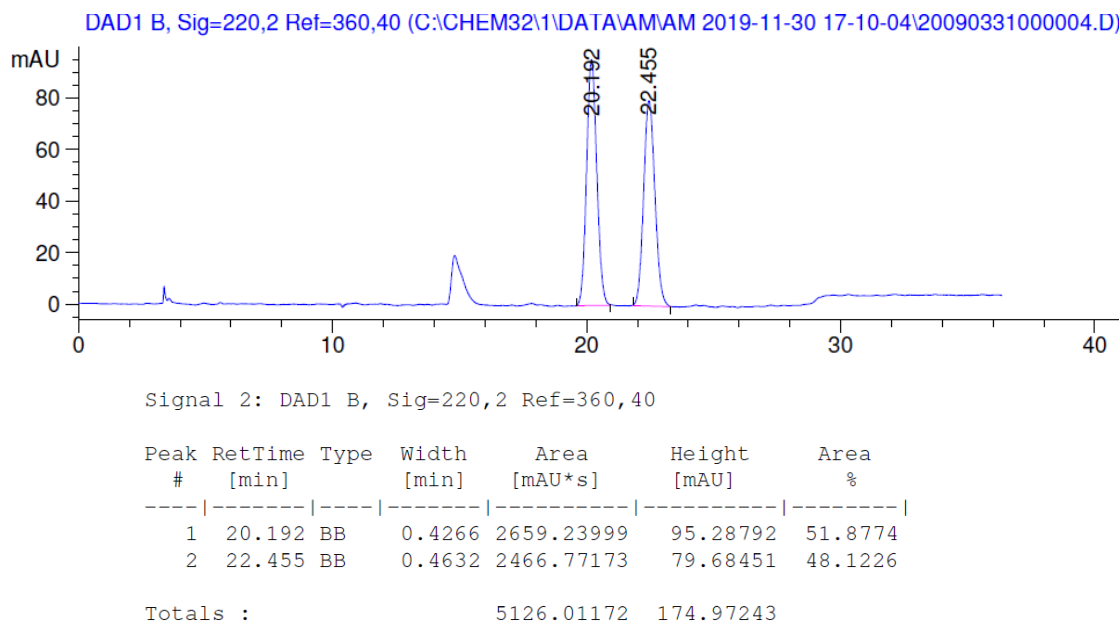
2i was synthesized by **General Procedure 2** on a 0.2 mmol scale at 85 °C with 15 mol% catalyst for 36 h. Isolated by flash column chromatography using 3:1 Pentane:EtOAc yielding a white solid (Yield: 62%, 0.124 mmol, 41.0 mg). Enantiomeric purity was determined by HPLC analysis in comparison with racemic material $T_R = 17.38$ (minor) $T_R = 19.22$ (major) (95.5:4.5 e.r; Chiralcel IC column, 5% iPrOH in hexanes 1.0 mL/min, 235 nm). **m.p.**: 103-106 °C

^1H NMR (500 MHz, Chloroform-*d*) δ 1.50 (s, 3H), 3.21 (s, 3H), 3.40 (d, $J = 9.8$ Hz, 1H), 3.50 (d, $J = 9.8$ Hz, 1H), 3.81 (s, 3H), 6.77 (d, $J = 8.4$ Hz, 1H), 6.85 (dd, $J = 8.4, 2.5$ Hz, 1H), 6.89 (d, $J = 2.4$ Hz, 1H).

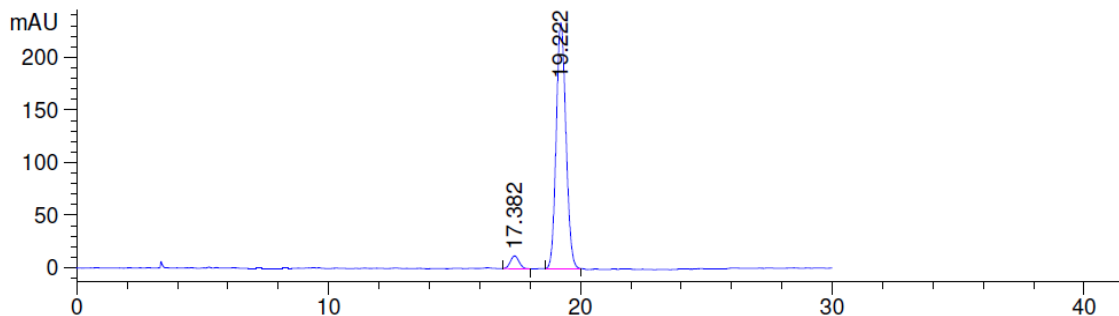
^{13}C NMR (126 MHz, Chloroform-*d*) δ 10.8, 23.0, 26.4, 48.9, 55.8, 108.5, 110.4, 112.6, 133.9, 136.7, 156.1, 177.5.

IR (thin film, cm^{-1}): 2956, 2831, 1705, 1605, 1500, 1434, 1358, 1291, 1225, 1123, 1030, 810.

HRMS (DART): Calc. for $\text{C}_{12}\text{H}_{15}\text{INO}_2$ 332.0142, found 332.013.



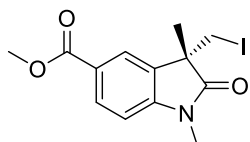
DAD1 B, Sig=220,2 Ref=360,40 (C:\CHEM32\1\DATA\AMAM 2019-11-30 17-10-04\20090331000005.D)



Signal 2: DAD1 B, Sig=220,2 Ref=360,40

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.382	BB	0.2889	292.50620	12.19014	4.4423
2	19.222	BB	0.4156	6292.03857	234.09091	95.5577

Totals : 6584.54477 246.28105



(S)-methyl 3-(iodomethyl)-1,3-dimethyl-2-oxindoline-5-carboxylate

2j was synthesized by **General Procedure 2** on a 0.2 mmol scale at 85 °C with 15 mol% catalyst for 36 h. Isolated by flash column chromatography using 3:1 Pentane:EtOAc yielding a white solid (Yield: 71%, 0.142 mmol, 55.7 mg). Enantiomeric purity was determined by HPLC analysis in comparison with racemic material $T_R = 21.50$ (minor) $T_R = 24.93$ (major) (97:3 e.r; Chiralcel IC column, 10% iPrOH in hexanes 1.0 mL/min, 235 nm). **m.p.**: 131-134 °C

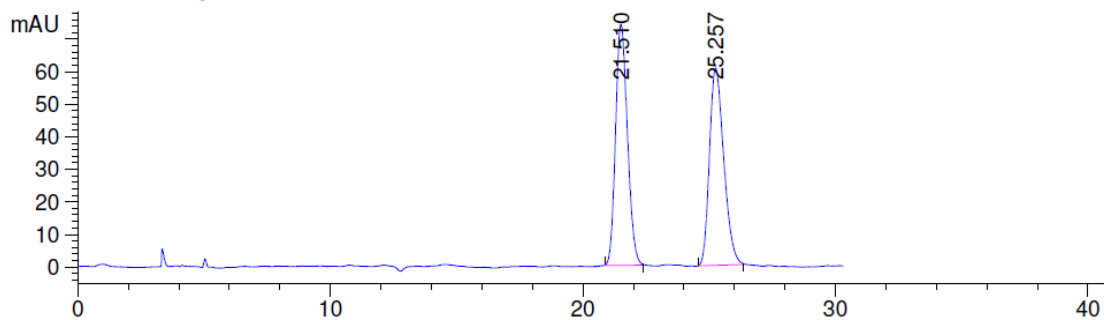
^1H NMR (400 MHz, Chloroform-*d*) δ 1.54 (s, 3H), 3.27 (s, 3H), 3.42 (d, $J = 9.9$ Hz, 1H), 3.54 (d, $J = 9.8$ Hz, 1H), 3.91 (s, 3H), 6.91 (dd, $J = 8.2, 0.5$ Hz, 1H), 7.91 (dd, $J = 1.7, 0.5$ Hz, 1H), 8.08 (dd, $J = 8.2, 1.7$ Hz, 1H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 9.7, 22.8, 26.5, 48.7, 52.1, 107.9, 123.9, 124.7, 131.4, 132.6, 147.3, 166.7, 178.3.

IR (thin film, cm^{-1}): 3020, 2952, 1715, 1624, 1457, 1354, 1297, 1251, 1104, 1013, 830, 772, 614, 578.

HRMS (DART): Calc. for $\text{C}_{13}\text{H}_{15}\text{INO}_3$ 360.0091, found 360.0093.

DAD1 C, Sig=235,8 Ref=360,40 (C:\CHEM32\1\DATA\AMAM 2020-01-14 20-40-26\20090331000003.D)

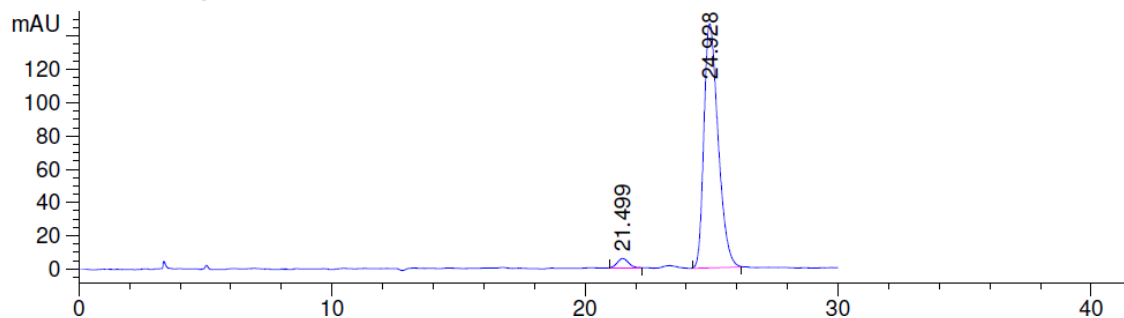


Signal 3: DAD1 C, Sig=235,8 Ref=360,40

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.510	BB	0.5054	2415.92236	74.09887	50.2928
2	25.257	BB	0.5927	2387.79395	60.60594	49.7072

Totals : 4803.71631 134.70481

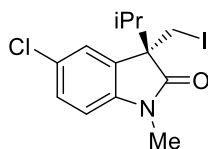
DAD1 C, Sig=235,8 Ref=360,40 (C:\CHEM32\1\DATA\AMAM 2020-01-14 20-40-26\20090331000004.D)



Signal 3: DAD1 C, Sig=235,8 Ref=360,40

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.499	BB	0.3657	168.36754	5.53783	2.8570
2	24.928	BB	0.5886	5724.75684	146.91437	97.1430

Totals : 5893.12437 152.45220



(S)-5-chloro-3-(iodomethyl)-3-isopropyl-1-methylindolin-2-one

2k was synthesized by **General Procedure 2** on a 0.2 mmol scale at 85 °C. Isolated by flash column chromatography using 4:1 Pentane:EtOAc yielding a white solid (Yield: 83%, 0.166

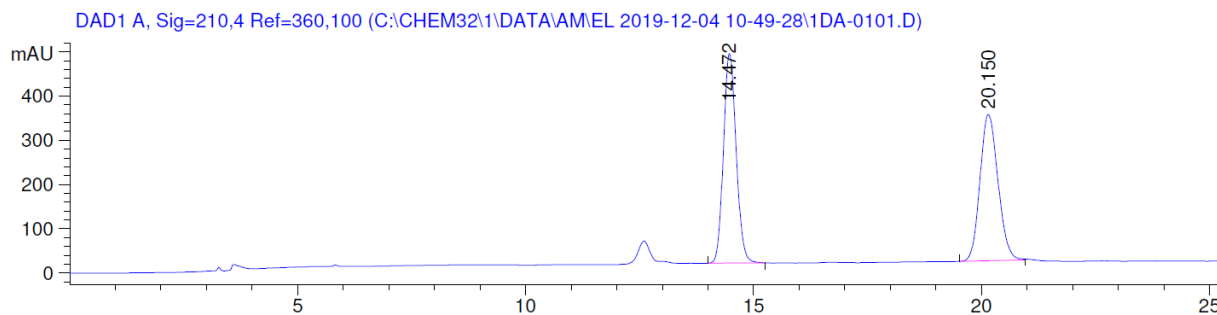
mmol, 60.3 mg). Enantiomeric purity was determined by HPLC analysis in comparison with racemic material $T_R = 14.41$ (minor) $T_R = 20.04$ (major) (96.5:3.5 e.r; Chiralcel IC column, 2.5% iPrOH in hexanes 1.0 mL/min, 235 nm). **m.p.**: 87-89 °C

^1H NMR (500 MHz, Chloroform-*d*) δ 0.83 (d, $J = 6.7$ Hz, 3H), 0.98 (d, $J = 6.9$ Hz, 3H), 2.26 (p, $J = 6.8$ Hz, 1H), 3.21 (s, 3H), 3.52 (d, $J = 9.7$ Hz, 1H), 3.56 (d, $J = 9.7$ Hz, 1H), 6.78 (d, $J = 8.3$ Hz, 1H), 7.20 (d, $J = 2.1$ Hz, 1H), 7.31 (dd, $J = 8.3, 2.1$ Hz, 1H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 8.7, 17.4, 18.1, 26.2, 35.5, 56.8, 108.9, 123.9, 127.8, 128.5, 131.8, 142.9, 177.1.

IR (thin film, cm^{-1}): 2970, 2898, 1711, 1625, 1470, 1348, 1235, 1040, 780, 766, 723.

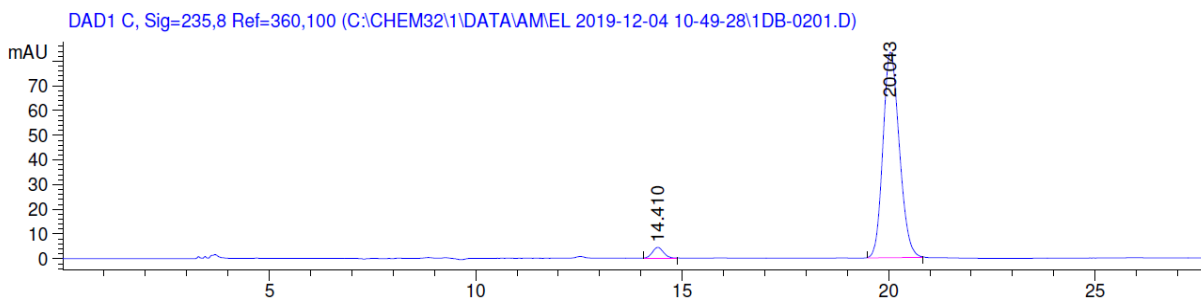
HRMS (DART): Calc. for $\text{C}_{13}\text{H}_{16}\text{ClINO}$ 363.9960, found 348.9958.



Signal 1: DAD1 A, Sig=210,4 Ref=360,100

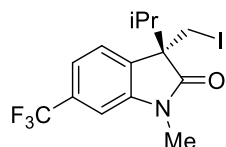
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.472	BB	0.3003	9183.58691	473.47446	50.2755
2	20.150	BB	0.4286	9082.94434	330.52921	49.7245

Totals : 1.82665e4 804.00366



Signal 3: DAD1 C, Sig=235,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.410	BB	0.2866	81.24783	4.33535	3.4062
2	20.043	BB	0.4290	2304.06274	83.22419	96.5938
Totals :				2385.31058	87.55954	



(S)-3-(iodomethyl)-3-isopropyl-1-methyl-6-(trifluoromethyl)indolin-2-one

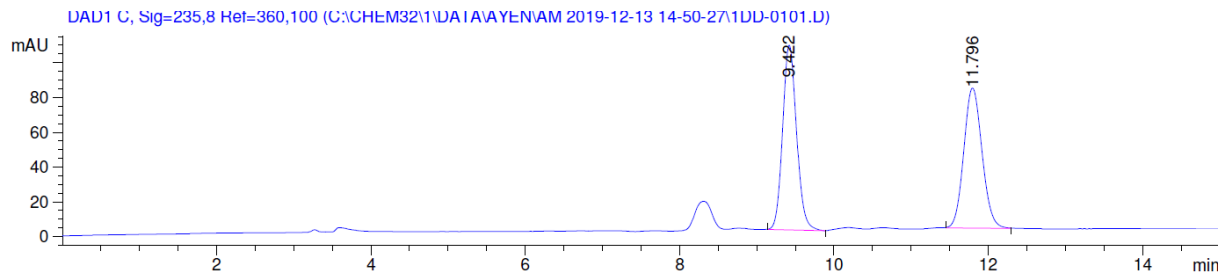
2l was synthesized by **General Procedure 2** on a 0.2 mmol scale at 85 °C. Isolated by flash column chromatography using 5:1 Pentane:EtOAc yielding a thick white oil (Yield: 51%, 0.102 mmol, 40.5 mg). Enantiomeric purity was determined by HPLC analysis in comparison with racemic material $T_R = 9.36$ (minor) $T_R = 11.71$ (major) (96:4 e.r; Chiralcel IC column, 2.5% iPrOH in hexanes 1.0 mL/min, 235 nm).

^1H NMR (600 MHz, Chloroform-*d*) δ 0.84 (d, $J = 6.8$ Hz, 3H), 0.98 (d, $J = 6.9$ Hz, 3H), 2.30 (pd, $J = 6.8, 1.0$ Hz, 1H), 3.26 (s, 3H), 3.56 (d, $J = 9.9$ Hz, 1H), 3.58 (d, $J = 9.8$ Hz, 1H), 7.06 (s, 1H), 7.32 (d, $J = 7.7$ Hz, 1H), 7.38 (d, $J = 8.7$ Hz, 1H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 8.2, 17.4, 18.0, 26.2, 35.6, 56.7, 104.7 (q, $J = 3.8$ Hz), 119.5 (q, $J = 4.1$ Hz), 123.6, 123.9 (q, $J = 272.4$ Hz), 131.1 (q, $J = 32.5$ Hz), 134.1 (d, $J = 1.4$ Hz), 144.9, 177.2.

IR (thin film, cm^{-1}): 2964, 2886, 1715, 1624, 1460, 1318, 1258, 1166, 1113, 1057, 977, 862, 664.

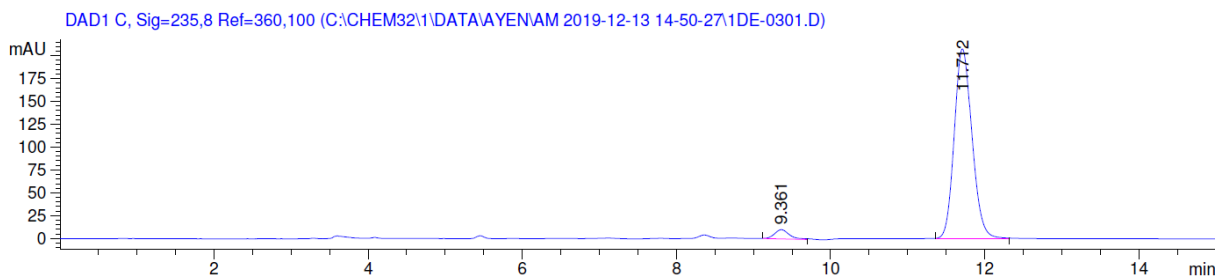
HRMS (DART): Calc. for $\text{C}_{14}\text{H}_{16}\text{F}_3\text{INO}$ 398.0223, found 398.0215.



Signal 3: DAD1 C, Sig=235,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.422	BB	0.1944	1333.24634	106.23284	50.2727
2	11.796	BB	0.2552	1318.78442	80.46143	49.7273

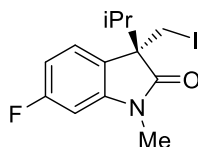
Totals : 2652.03076 186.69427



Signal 3: DAD1 C, Sig=235,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.361	BB	0.2013	135.44370	10.17294	3.9209
2	11.712	BB	0.2486	3318.95923	207.49199	96.0791

Totals : 3454.40292 217.66492



(S)-6-fluoro-3-(iodomethyl)-3-isopropyl-1-methylindolin-2-one

2m was synthesized by **General Procedure 2** on a 0.2 mmol scale at 85 °C. Isolated by flash column chromatography using 4:1 Pentane:EtOAc yielding a yellow oil (Yield: 69%, 0.138 mmol, 47.8 mg). Enantiomeric purity was determined by HPLC analysis in comparison with racemic material $T_R = 12.21$ (minor) $T_R = 15.94$ (major) (96.5:3.5 e.r; Chiralcel IC column, 2.5% iPrOH in hexanes 1.0 mL/min, 220 nm).

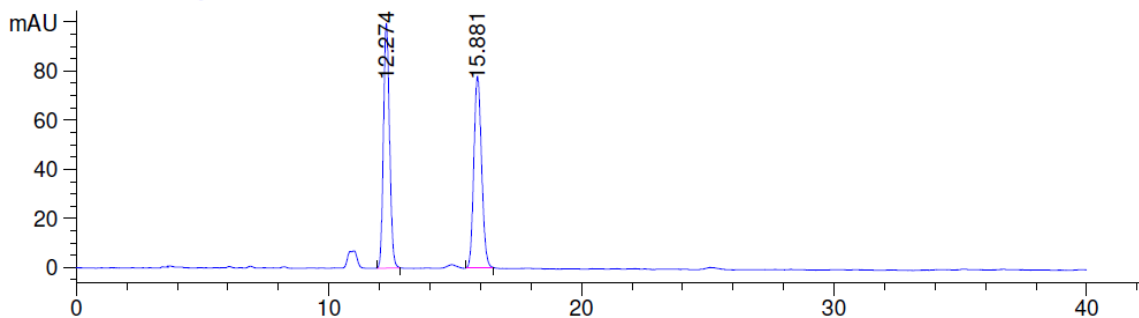
^1H NMR (400 MHz, Chloroform-*d*) δ 0.81 (d, $J = 6.7$ Hz, 3H), 0.97 (d, $J = 6.9$ Hz, 3H), 2.25 (p, $J = 6.8$ Hz, 1H), 3.20 (s, 3H), 3.47 – 3.65 (m, 2H), 6.60 (dd, $J = 8.8, 2.4$ Hz, 1H), 6.77 (ddd, $J = 9.4, 8.2, 2.3$ Hz, 1H), 7.14 (dd, $J = 8.2, 5.3$ Hz, 1H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 9.43, 17.31, 18.15, 26.17, 35.34, 56.28, 96.90 (d, $J = 27.5$ Hz), 108.48 (d, $J = 22.2$ Hz), 124.47 (d, $J = 9.5$ Hz), 125.31 (d, $J = 3.0$ Hz), 145.80 (d, $J = 11.4$ Hz), 163.30 (d, $J = 245.4$ Hz), 177.90.

IR (thin film, cm^{-1}): 2970, 2888, 1714, 1615, 1504, 1463, 1377, 1239, 1196, 1073, 987, 832.

HRMS (DART): Calc. for C₁₃H₁₆FINO 348.0255, found 348.0262.

DAD1 C, Sig=235,8 Ref=360,40 (C:\CHEM32\1\DATA\AYEN\AM 2019-11-28 18-12-53\20090331000003.D)

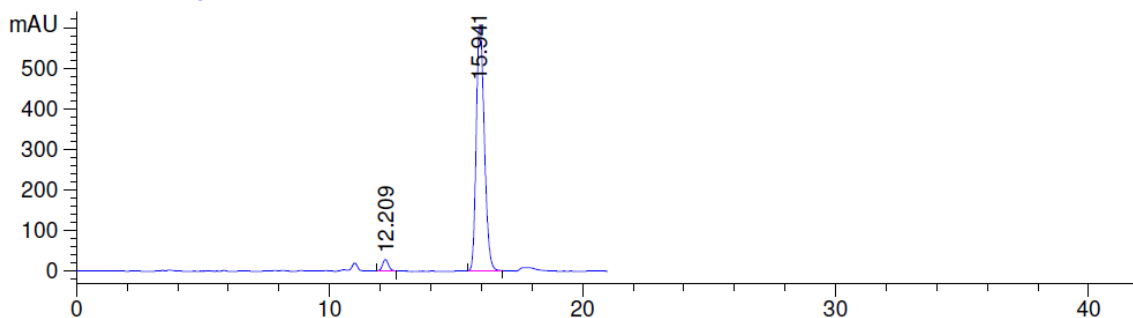


Signal 3: DAD1 C, Sig=235,8 Ref=360,40

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.274	BB	0.2603	1667.56592	99.60701	50.0368
2	15.881	BB	0.3307	1665.11084	78.09664	49.9632

Totals : 3332.67676 177.70365

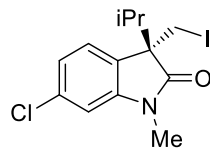
DAD1 B, Sig=220,2 Ref=360,40 (C:\CHEM32\1\DATA\AYEN\AM 2019-11-28 18-12-53\20090331000005.D)



Signal 2: DAD1 B, Sig=220,2 Ref=360,40

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.209	BB	0.2473	473.40231	28.72245	3.3886
2	15.941	BB	0.3442	1.34970e4	607.55310	96.6114

Totals : 1.39704e4 636.27555



(S)-6-chloro-3-(iodomethyl)-3-isopropyl-1-methylindolin-2-one

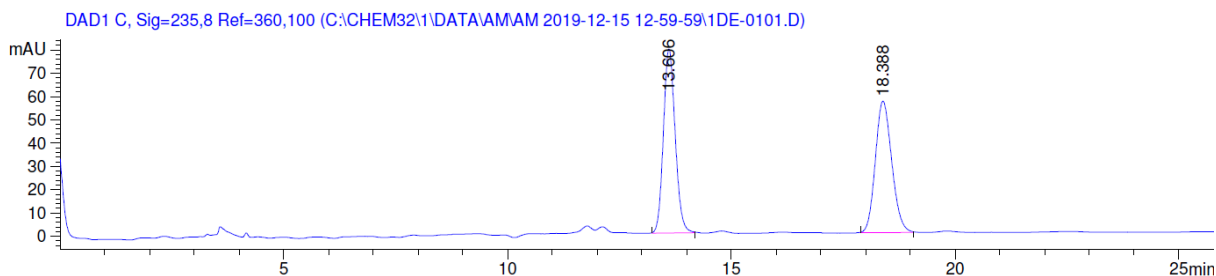
2n was synthesized by **General Procedure 2** on a 0.2 mmol scale at 85 °C. Isolated by flash column chromatography using 4:1 Pentane:EtOAc yielding a white solid (Yield: 65%, 0.130 mmol, 47.2 mg). Enantiomeric purity was determined by HPLC analysis in comparison with racemic material $T_R = 13.81$ (minor) $T_R = 18.31$ (major) (95:5 e.r; Chiralcel IC column, 2.5% iPrOH in hexanes 1.0 mL/min, 235 nm). **m.p.**: 87-89 °C

^1H NMR (500 MHz, Chloroform-*d*) δ 0.82 (d, $J = 6.8$ Hz, 3H), 0.97 (d, $J = 7.0$ Hz, 3H), 2.26 (p, $J = 6.8$ Hz, 1H), 3.21 (s, 3H), 3.53 (d, $J = 9.7$ Hz, 1H), 3.56 (d, $J = 9.7$ Hz, 1H), 6.86 (d, $J = 1.8$ Hz, 1H), 7.07 (dd, $J = 7.9, 1.8$ Hz, 1H), 7.13 (dd, $J = 7.9, 0.4$ Hz, 1H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 9.0, 17.3, 18.1, 26.2, 35.4, 56.4, 108.8, 122.3, 124.4, 128.4, 134.4, 145.5, 177.5.

IR (thin film, cm^{-1}): 2970, 2822, 1714, 1609, 1493, 1467, 1374, 1067, 981, 892.

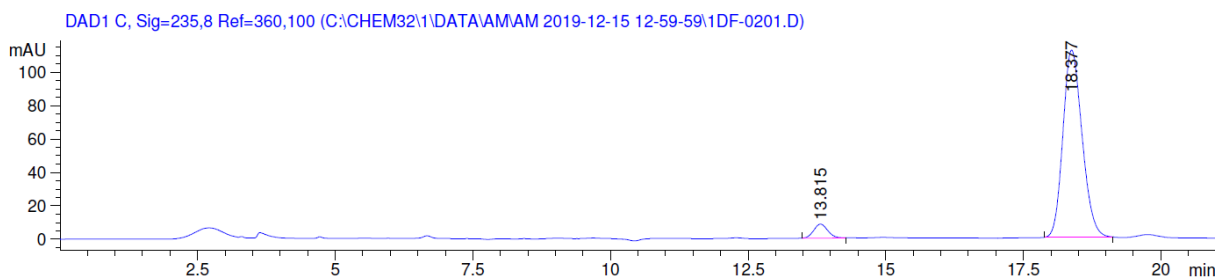
HRMS (DART): Calc. for $\text{C}_{13}\text{H}_{16}\text{ClINO}$ 363.9960, found 348.9962.



Signal 3: DAD1 C, Sig=235,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.606	BB	0.2809	1442.90063	79.06379	50.1027
2	18.388	BB	0.3949	1436.98669	56.46590	49.8973

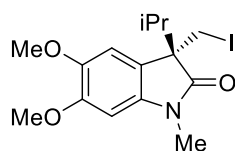
Totals : 2879.88733 135.52969



Signal 3: DAD1 C, Sig=235,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.815	BB	0.2754	149.05487	8.38423	5.1808
2	18.377	BB	0.3755	2728.01685	112.25558	94.8192

Totals : 2877.07172 120.63980



(S)-3-(iodomethyl)-3-isopropyl-5,6-dimethoxy-1-methylindolin-2-one

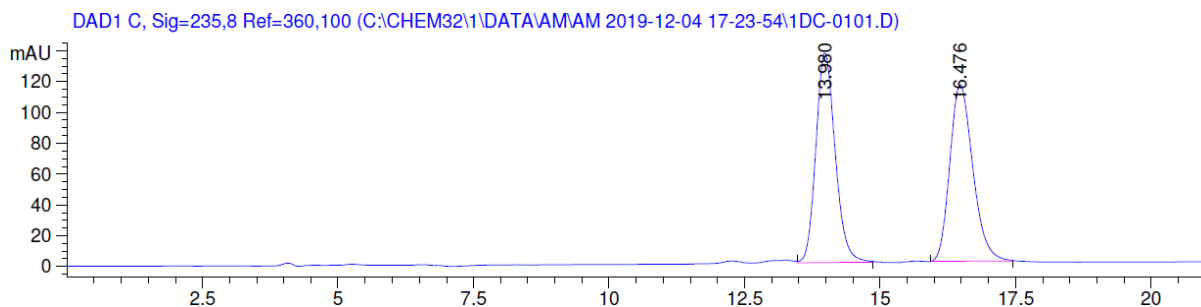
2o was synthesized by **General Procedure 2** on a 0.2 mmol scale at 85 °C. Isolated by flash column chromatography using 2:1 Pentane:EtOAc yielding a yellow oil (Yield: 57%, 0.114 mmol, 44.4 mg). Enantiomeric purity was determined by HPLC analysis in comparison with racemic material T_R = 13.85 (minor) T_R = 16.30 (major) (88:12 e.r; Chiralcel IC column, 10% iPrOH in hexanes 1.0 mL/min, 235 nm).

^1H NMR (500 MHz, Chloroform-*d*) δ 0.81 (d, J = 6.7 Hz, 3H), 0.94 (d, J = 6.9 Hz, 3H), 2.22 (p, J = 6.8 Hz, 1H), 3.20 (s, 3H), 3.53 (d, J = 2.0 Hz, 2H), 3.87 (s, 3H), 3.92 (s, 3H), 6.47 (s, 1H), 6.80 (s, 1H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 10.3, 17.4, 18.1, 26.1, 35.3, 56.2, 56.6, 57.0, 93.9, 108.8, 120.6, 138.2, 144.9, 149.8, 177.7.

IR (thin film, cm^{-1}): 2967, 2888, 1695, 1619, 1506, 1457, 1420, 1375, 1242, 1206, 1073, 908, 779, 726.

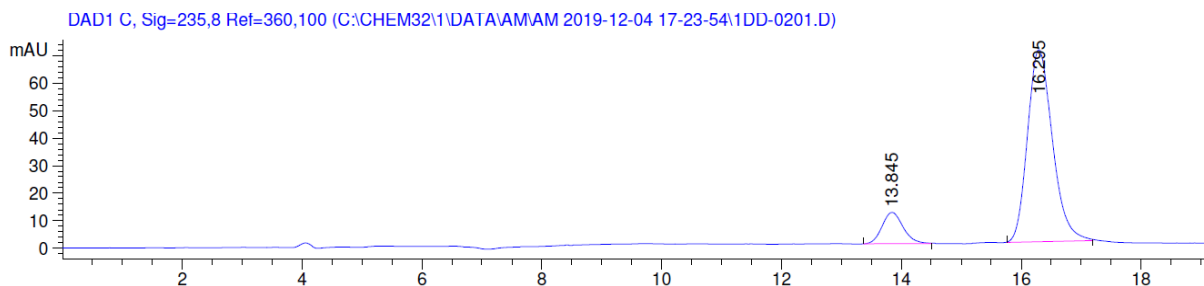
HRMS (DART): Calc. for $\text{C}_{13}\text{H}_{16}\text{ClINO}$ 390.0561, found 390.0568.



Signal 3: DAD1 C, Sig=235,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.980	VB	0.3833	3367.22681	135.78673	49.8709
2	16.476	BB	0.4568	3384.66113	114.51355	50.1291

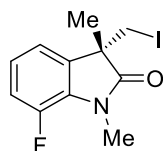
Totals : 6751.88794 250.30028



Signal 3: DAD1 C, Sig=235,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.845	BB	0.3844	277.79926	11.39544	12.0711
2	16.295	BB	0.4478	2023.56567	69.89079	87.9289

Totals : 2301.36493 81.28623



(S)-7-fluoro-3-(iodomethyl)-1,3-dimethylindolin-2-one

2p was synthesized by **General Procedure 2** on a 0.2 mmol scale at 85 °C with 15 mol % catalyst for 36 h. Isolated by flash column chromatography using 5:1 Pentane:EtOAc yielding a yellow oil (Yield: 76%, 0.152 mmol, 48.6mg). Enantiomeric purity was determined by HPLC analysis in

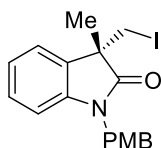
comparison with racemic material $T_R = 13.85$ (minor) $T_R = 16.30$ (major) (88:12 e.r; Chiralcel IC column, 10% iPrOH in hexanes 1.0 mL/min, 235 nm).

^1H NMR (400 MHz, Chloroform-*d*) δ 1.52 (s, 3H), 3.38 (d, $J = 9.8$ Hz, 1H), 3.45 (d, $J = 2.7$ Hz, 3H), 3.52 (d, $J = 9.8$ Hz, 1H), 6.96 – 7.15 (m, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 10.2, 23.1, 28.8 (d, $J = 5.7$ Hz), 49.0 (d, $J = 2.1$ Hz), 116.6 (d, $J = 19.3$ Hz), 118.4 (d, $J = 3.3$ Hz), 123.3 (d, $J = 6.4$ Hz), 129.8 (d, $J = 8.2$ Hz), 135.5 (d, $J = 3.2$ Hz), 147.9 (d, $J = 244.1$ Hz), 177.6.

IR (thin film, cm^{-1}): 2975, 2926, 1715, 1613, 1491, 1377, 1248, 1111, 1062, 781, 728, 568.

HRMS (DART): Calc. for $\text{C}_{11}\text{H}_{12}\text{NOFI}$ 319.9942, found 319.9942.



(S)-3-(iodomethyl)-1-(4-methoxybenzyl)-3-methylindolin-2-one

2q was synthesized by **General Procedure 2** on a 0.2 mmol scale at 85 °C. Isolated by flash column chromatography using 4:1 Pentane:EtOAc yielding a thick yellow oil (Yield: 90%, 0.180 mmol, 73.3 mg). Enantiomeric purity was determined by HPLC analysis in comparison with racemic material $T_R = 20.08$ (major) $T_R = 21.75$ (minor) (90:10 e.r; Chiralcel IC column, 5% iPrOH in hexanes 1.0 mL/min, 235 nm).

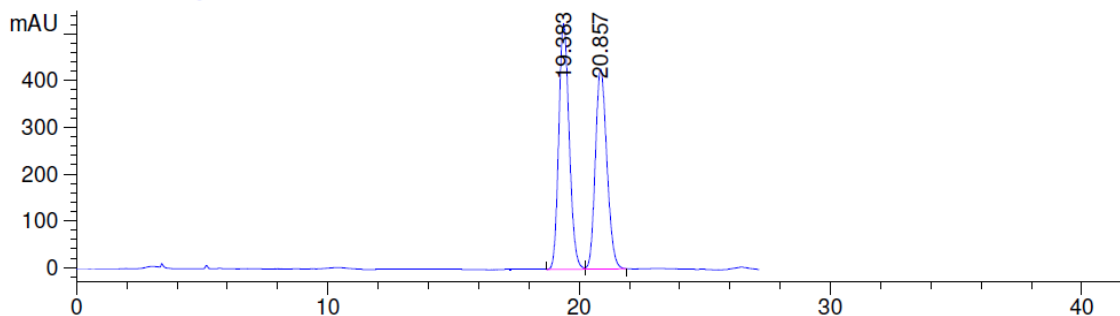
^1H NMR (500 MHz, Chloroform-*d*) δ 1.58 (s, 3H), 3.50 (d, $J = 9.8$ Hz, 1H), 3.62 (d, $J = 9.8$ Hz, 1H), 3.78 (s, 3H), 4.83 (d, $J = 15.4$ Hz, 1H), 4.98 (d, $J = 15.4$ Hz, 1H), 6.80 (dt, $J = 7.8, 0.7$ Hz, 1H), 6.86 (d, $J = 8.7$ Hz, 2H), 7.09 (td, $J = 7.5, 1.0$ Hz, 1H), 7.23 (td, $J = 7.7, 1.2$ Hz, 1H), 7.28 (dd, $J = 7.4, 1.2$ Hz, 1H), 7.33 (d, $J = 8.7$ Hz, 2H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 10.3, 23.5, 25.4, 43.5, 48.6, 55.2, 109.4, 114.1, 122.6, 127.7, 128.5, 128.9, 132.7, 142.3, 159.1, 178.0.

IR (thin film, cm^{-1}): 3040, 2831, 1715, 1613, 1513, 1489, 1467, 1348, 1252, 1173, 1027, 743.

HRMS (DART): Calc. for $\text{C}_{18}\text{H}_{19}\text{INO}_2$ 408.0455, found 408.0458.

DAD1 B, Sig=220,2 Ref=360,40 (C:\CHEM32\1\DATA\AMAM 2019-12-07 14-15-06\20090331000004.D)

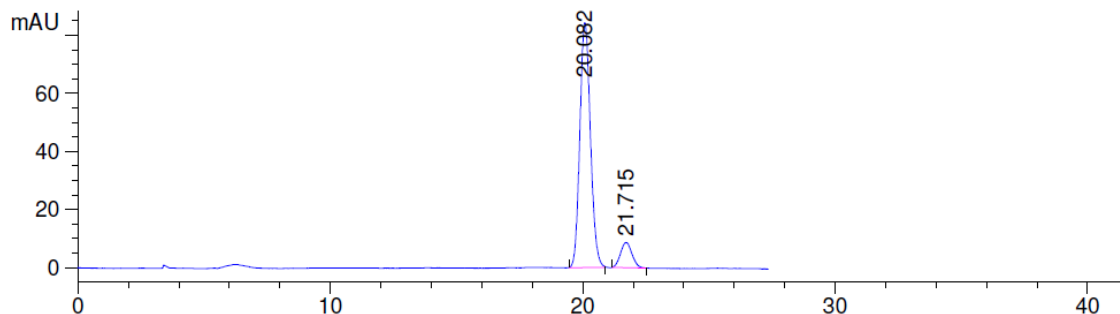


Signal 2: DAD1 B, Sig=220,2 Ref=360,40

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.383	BV	0.4495	1.51625e4	525.66803	52.6511
2	20.857	VB	0.4851	1.36355e4	427.57260	47.3489

Totals : 2.87980e4 953.24063

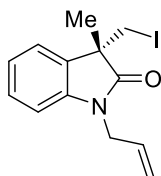
DAD1 D, Sig=254,8 Ref=360,40 (C:\CHEM32\1\DATA\AMAM 2019-12-07 14-15-06\20090331000005.D)



Signal 4: DAD1 D, Sig=254,8 Ref=360,40

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.082	BB	0.4392	2448.16846	84.21025	89.8478
2	21.715	BB	0.3860	276.62592	8.72347	10.1522

Totals : 2724.79437 92.93372



(S)-1-allyl-3-(iodomethyl)-3-methylindolin-2-one

2r was synthesized by **General Procedure 2** on a 0.2 mmol scale at 85 °C with 15 mol% catalyst for 36 h. Isolated by flash column chromatography using 5:1 Pentane:EtOAc yielding a white solid

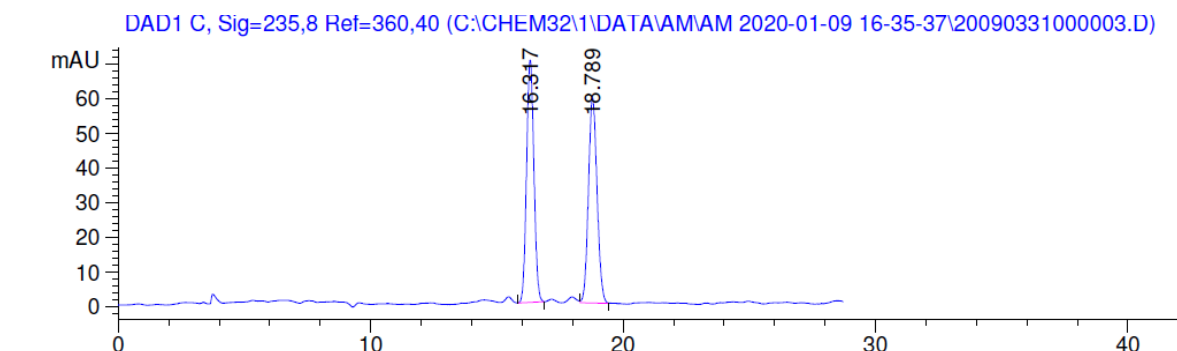
(Yield: 82%, 0.164 mmol, 53.5 mg). Enantiomeric purity was determined by HPLC analysis in comparison with racemic material $T_R = 15.98$ (minor) $T_R = 18.46$ (major) (93:7 e.r; Chiralcel IC column, 2.5% iPrOH in hexanes 1.0 mL/min, 235 nm). **m.p.**: 90-92 °C

^1H NMR (400 MHz, Chloroform-*d*) δ 1.54 (s, 3H), 3.44 (d, $J = 9.8$ Hz, 1H), 3.56 (d, $J = 9.8$ Hz, 1H), 4.29 (ddt, $J = 16.3, 5.5, 1.6$ Hz, 1H), 4.44 (ddt, $J = 16.3, 5.0, 1.8$ Hz, 1H), 5.23 (dd, $J = 10.3, 1.3$ Hz, 1H), 5.25 – 5.36 (m, 1H), 5.86 (ddt, $J = 17.2, 10.4, 5.3$ Hz, 1H), 6.87 (d, $J = 7.7$ Hz, 1H), 7.10 (td, $J = 7.5, 1.0$ Hz, 1H), 7.26 – 7.43 (m, 2H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 10.5, 23.3, 42.5, 48.6, 109.3, 117.7, 122.7, 128.5, 131.3, 132.6, 142.3, 177.6.

IR (thin film, cm^{-1}): 3017, 2929, 1703, 1612, 1488, 1358, 1186, 994, 923, 751, 641.

HRMS (DART): Calc. for $\text{C}_{13}\text{H}_{15}\text{INO}$ 328.0193, found 390.0196.

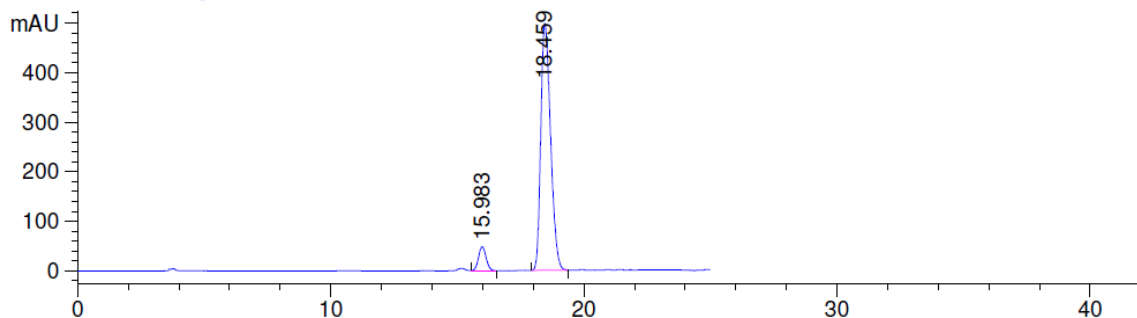


Signal 3: DAD1 C, Sig=235,8 Ref=360,40

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.317	VB	0.3160	1407.32349	69.87519	50.0394
2	18.789	VB	0.3672	1405.10815	59.13799	49.9606

Totals : 2812.43164 129.01318

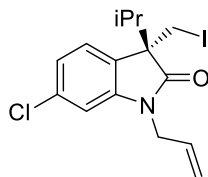
DAD1 C, Sig=235,8 Ref=360,40 (C:\CHEM32\1\DATA\AMAM 2020-01-09 16-35-37\20090331000004.D)



Signal 3: DAD1 C, Sig=235,8 Ref=360,40

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.983	VB	0.3222	1004.66187	48.59528	7.0294
2	18.459	BB	0.4176	1.32877e4	497.52325	92.9706

Totals : 1.42923e4 546.11854



(S)-1-allyl-6-chloro-3-(iodomethyl)-3-isopropylindolin-2-one

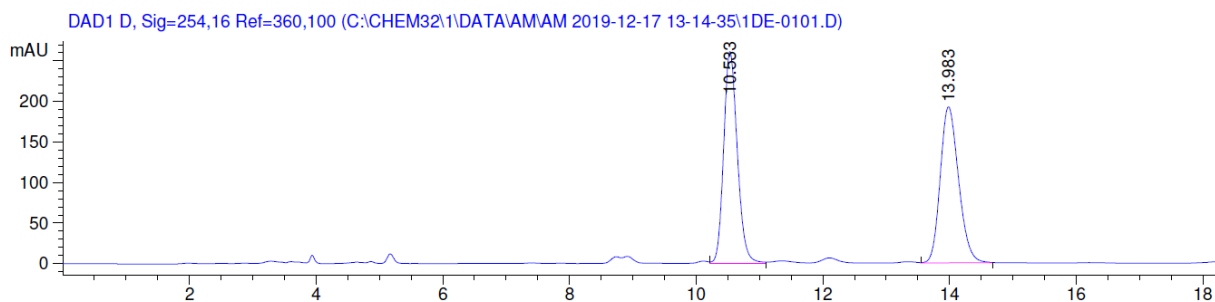
2s was synthesized by **General Procedure 2** on a 0.2 mmol scale at 85 °C with 15 mol% catalyst for 36 h. Isolated by flash column chromatography using 4:1 Pentane:EtOAc yielding a clear/yellow oil (Yield: 77%, 0.154 mmol, 59.9 mg). Enantiomeric purity was determined by HPLC analysis in comparison with racemic material $T_R = 10.71$ (minor) $T_R = 14.23$ (major) (91.5:8.5 e.r.; Chiralcel IC column, 2.5% iPrOH in hexanes 1.0 mL/min, 254 nm).

^1H NMR (600 MHz, Chloroform-*d*) δ 0.85 (d, $J = 6.7$ Hz, 3H), 0.98 (d, $J = 6.9$ Hz, 3H), 2.27 (p, $J = 6.8$ Hz, 1H), 3.57 (q, $J = 9.7$ Hz, 2H), 4.34 (qdt, $J = 16.4, 5.3, 1.7$ Hz, 2H), 5.26 (dd, $J = 10.3, 1.2$ Hz, 1H), 5.33 (dtd, $J = 17.2, 1.7, 0.9$ Hz, 1H), 5.82 (ddt, $J = 17.2, 10.6, 5.4$ Hz, 1H), 6.85 (d, $J = 1.9$ Hz, 1H), 7.07 (dd, $J = 8.0, 1.9$ Hz, 1H), 7.13 (d, $J = 7.9$ Hz, 1H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 8.9, 17.4, 18.1, 35.6, 42.5, 56.2, 109.7, 118.3, 122.3, 124.4, 128.5, 130.9, 134.3, 144.7, 177.2.

IR (thin film, cm^{-1}): 2970, 1714, 1605, 1490, 1443, 1374, 1192, 1077, 763.

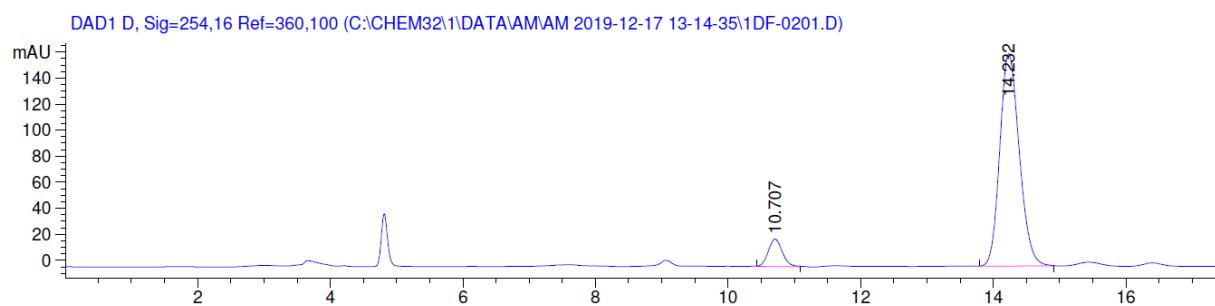
HRMS (DART): Calc. for $\text{C}_{15}\text{H}_{18}\text{ClINO}$ 390.0116, found 390.0116.



Signal 4: DAD1 D, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.533	VB	0.2305	3905.58569	261.18216	50.2520
2	13.983	VB	0.3104	3866.41699	192.45354	49.7480

Totals : 7772.00269 453.63570

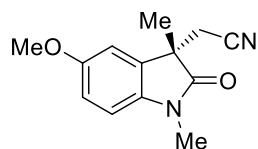


Signal 4: DAD1 D, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.707	BB	0.2253	309.87036	21.09917	8.5306
2	14.232	BB	0.3158	3322.58667	163.01064	91.4694

Totals : 3632.45703 184.10981

Total Synthesis of (-)-Esermethole and (-)-Phenserine

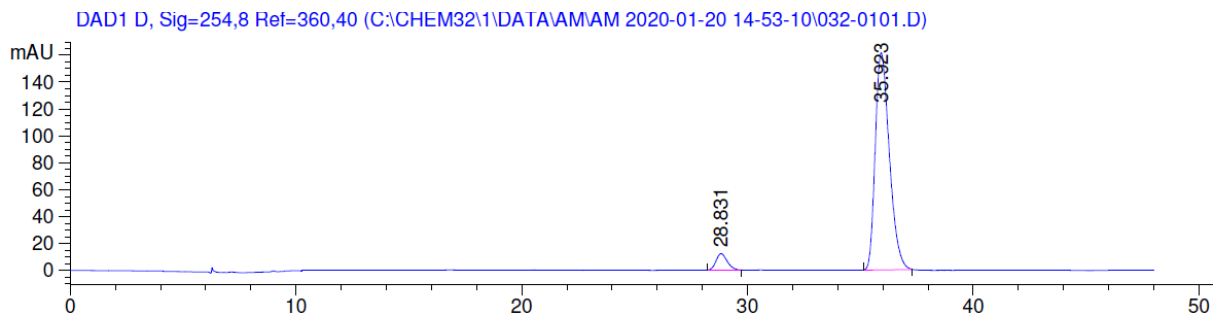


(S)-2-(5-methoxy-1,3-dimethyl-2-oxoindolin-3-yl)acetonitrile

3a: To a solution of **2l** (0.56mmol) in DMF (0.05 M) was added KCN (5 equiv). The reaction was heated to 85 °C and let stir overnight. The reaction was let cool and extracted 3x with EtOAc and water and then 5x with a saturated brine solution. The crude reaction mixture was purified via silica gel flash column chromatography eluting with 3:2 EtOAc:Pentanes affording a white oil. (103.7 mg, 0.45 mmol, 81%). Enantiomeric purity was determined by HPLC analysis according to Nakao and Hiyama.⁴ $T_R = 28.83$ (*R*) $T_R=35.92$ (*S*) (94.5:5.5 e.r; Chiralcel AD-H column, 5% iPrOH in hexanes 0.5 mL/min, 254nm). Characterization was consistent with the literature.⁴

¹H NMR (400 MHz, Chloroform-*d*) δ 1.50 (s, 3H), 2.56 (d, *J* = 16.6 Hz, 1H), 2.83 (d, *J* = 16.6 Hz, 1H), 3.21 (s, 3H), 3.80 (s, 3H), 6.80 (d, *J* = 8.5 Hz, 1H), 6.86 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.08 (d, *J* = 2.5 Hz, 1H).

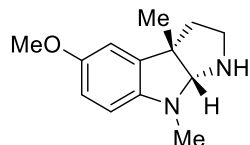
¹³C NMR (126 MHz, Chloroform-*d*) δ 22.2, 26.3, 26.6, 45.2, 55.9, 109.1, 110.5, 113.5, 116.6, 132.2, 136.0, 156.5, 177.1.



Signal 4: DAD1 D, Sig=254,8 Ref=360,40

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.831	BB	0.4212	419.86087	12.21082	5.6406
2	35.923	BB	0.6625	7023.69043	161.45108	94.3594

Totals : 7443.55130 173.66190

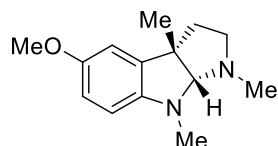


(3aS,8aR)-5-methoxy-3a,8-dimethyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole

Product **3b** was synthesized with a slight modification to the reported procedure by Hiyama and co-workers.⁴ To a solution of **3a** in THF (0.03 M) was added LiAlH₄ (4.0 equiv, 4.0 M in THF) dropwise with vigorous stirring. The reaction was let stir at room temp for 60 minutes and then subsequently refluxed at 67 °C for 30 minutes. The reaction was quenched with water and extracted 3 times with ethyl acetate, dried over MgSO₄ and dried *in vacuo*. The product was obtained with no further purification as a yellow/orange oil in a 94% yield. H¹ and C¹³ data was obtained on the unpurified material and was identical to the literature reported spectra.⁴

¹H NMR (500 MHz, Chloroform-*d*) δ 1.42 (s, 3H), 1.80 (ddt, *J* = 12.2, 9.8, 7.0 Hz, 1H), 2.01 (ddt, *J* = 12.1, 6.4, 3.2 Hz, 1H), 2.08 (br s, 1H), 2.79 (s, 3H), 2.81 – 2.97 (m, 1H), 3.07 (ddt, *J* = 10.2, 7.0, 3.5 Hz, 1H), 3.75 (s, 3H), 4.44 (s, 1H), 6.27 (dd, *J* = 8.3, 6.8 Hz, 1H), 6.62 – 6.66 (m, 1H), 6.66 – 6.71 (m, 1H).

¹³C NMR (126 MHz, Chloroform-*d*) δ 26.1, 33.2, 42.3, 46.2, 52.3, 56.1, 93.2, 105.7, 110.5, 111.9, 137.3, 145.6, 152.5.



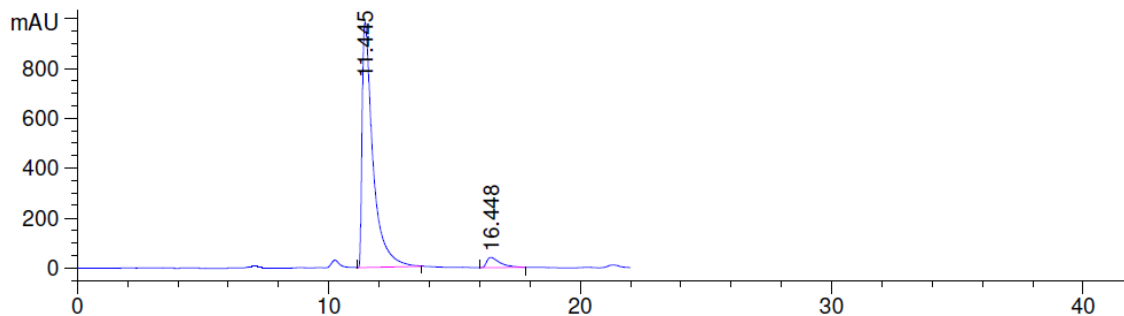
(-)-Esermethole

(-)-Esermethole was synthesized according to Hiyama.⁴ To a solution of **3c** and aqueous formaldehyde (5.0 equiv) in MeOH was added NaBH(OAc)₃ (5.0 equiv) at 0 °C. The reaction was allowed to warm to room temp and was stirred for 1.5 h. The product was extracted 3 times with DCM to afford (-)-Esermethole as a yellow/orange oil without further purification (73%, Enantiomeric purity was determined by HPLC analysis according to Nakao and Hiyama.³ T_R = 11.45 (*R*) T_R = 16.44 (95:5 e.r; Chiralcel OD-H column, 5% iPrOH in hexanes 0.5 mL/min, 254nm). [α]_D = -69.083 (c=0.0455, CH₂Cl₂).

¹H NMR (400 MHz, Chloroform-*d*) δ 1.43 (s, 3H), 1.95 (dd, *J* = 7.4, 5.4 Hz, 2H), 2.54 (s, 3H), 2.64 (dt, *J* = 9.1, 7.5 Hz, 1H), 2.72 (dt, *J* = 10.1, 5.3 Hz, 1H), 2.89 (s, 3H), 3.75 (s, 3H), 4.05 (s, 1H), 6.36 (dd, *J* = 8.2, 0.7 Hz, 1H), 6.54 – 6.74 (m, 2H).

¹³C NMR (126 MHz, Chloroform-*d*) δ 27.4, 38.0, 38.1, 40.8, 52.8, 53.2, 56.0, 98.3, 107.5, 109.8, 112.2, 138.2, 146.6, 153.0.

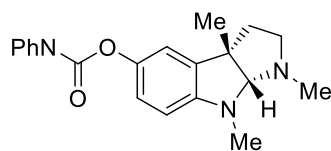
DAD1 D, Sig=254,8 Ref=360,40 (C:\CHEM32\1\DATA\AMAM 2020-01-21 22-42-45\20090331000003.D)



Signal 4: DAD1 D, Sig=254,8 Ref=360,40

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.445	BB	0.4298	2.93421e4	984.12885	95.1439
2	16.448	BB	0.5265	1497.60596	40.20959	4.8561

Totals : 3.08397e4 1024.33844



(-)-Phenserine

(-)-Phenserine was synthesized according to Brossi and Overmann.⁵ To a solution of (-)-Esermethole in DCM (0.1 M) was added BBr₃ (4.7 equiv) dropwise at room temperature. The reaction was let stir for 2 h. The crude reaction mixture as concentrated *in vacuo*, redissolved in methanol and stirred at room temperature for 10 minutes, which was then concentrated *in vacuo* again. The residue was subsequently dissolved in water, basified with sat. aqueous sodium bicarbonate. The aqueous layer was extracted with DCM 3 times, dried over MgSO₄ and concentrated *in vacuo* to afford a crude mixture of (-)-Eseroline. The crude reaction mixture was then dissolved in Et₂O (0.03 M) and Na⁰-metal was added. The reaction was stirred for 2 minutes, after which PhNCO was added (1.03 equiv). The reaction was let stir for 40 min, quenched with H₂O and extracted with ether. The organic layer was dried over MgSO₄ and concentrated *in vacuo*. The crude reaction mixture was purified via silica gel flash column chromatography (50:1 to 10:1 MeOH:DCM) affording an off-white foam (10% over 2 steps, 8.9 mg, 0.03mmol) [α]_D = -52.837 (c=0.027, CH₂Cl₂).

¹H NMR (400 MHz, Chloroform-*d*) δ 1.42 (s, 3H), 1.77 – 2.11 (m, 2H), 2.54 (s, 3H), 2.57 – 2.72 (m, 1H), 2.76 – 2.86 (m, 1H), 2.92 (s, 3H), 4.25 (s, 1H), 6.36 (d, *J* = 8.4 Hz, 1H), 6.80 (d, *J* = 2.4 Hz, 1H), 6.85 (dd, *J* = 8.4, 2.4 Hz, 2H), 7.01 – 7.12 (m, 1H), 7.29 (t, *J* = 7.9 Hz, 2H), 7.40 (d, *J* = 8.3 Hz, 2H).

¹³C NMR (126 MHz, Chloroform-*d*) δ 27.0, 37.1, 37.7, 40.3, 52.9, 53.1, 97.6, 106.9, 116.2, 118.6, 120.8, 123.7, 129.1, 137.2, 137.6, 142.9, 149.4, 152.4.

HRMS (DART): Calc. for C₂₀H₂₄N₃O₂ 338.1863, found 338.1868.

References

1. Whyte, A.; Burton, K. I.; Zhang, J.; Lautens, M. Enantioselective Intramolecular Copper-Catalyzed Borylacylation. *Angew. Chem. Int. Ed.* **2018**, *57*, 13927.
2. Chen, C.; Hu, J.; Su, J.; Tong, X. Synthesis of Substituted γ -Lactam via Pd(0)-Catalyzed Cyclization of Alkene-Tethered Carbamoyl Chloride. *Tet. Lett.* **2014**, *55*, 3229.
3. Yoon, H.; Marchese, A. D.; Lautens, M. Carboiodination Catalyzed by Nickel. *J. Am. Chem. Soc.* **2018**, *140*, 10950.
4. Nakao, Y.; Ebata, S.; Yada, A.; Hiyama, T.; Ikawa, M.; Ogoshi, S. Intramolecular Arylcyanation of Alkenes Catalyzed by Nickel/AlMe₂Cl. *J. Am. Chem. Soc.* **2008**, *130*, 12874.
5. (a) Huang, A.; Kodanko, J.; Overman, L. E. Asymmetric Synthesis of Pyrrolidinoindolines. Application for the Practical Total Synthesis of (–)-Phenserine. *J. Am. Chem. Soc.* **2004**, *126*, 14043. (b) Yu, Q.-S.; Brossi, A. Practical Synthesis of Unnatural (+)-Physostigmine and Carbamate Analogues. *Heterocycles* **1988**, *27*, 745.