Divergent Enantioselective Synthesis of (Nor)illudalane Sesquiterpenes via Pd^0-Catalyzed Asymmetric $C(sp^3)$–H Activation

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General Informations

Techniques:

All reactions involving air-sensitive material were carried out in pre-dried glassware under an argon atmosphere by using Schlenk techniques employing double-line argon-vacuum lines and working in an argon-filled glove box. Analytical thin layer chromatography (TLC) was performed using pre-coated Merck silica gel 60 F254 plates (0.25 mm). Visualization of the developed chromatogram was performed by UV absorbance (254 nm) or TLC stains ($KMnO_4$ and Phosphomolybdic acid). Flash chromatography was performed using Silicycle SiliaFlash P60 (230-400 mesh) with the indicated solvent system, using gradients of increasing polarity in most cases.

Chemicals:

Anhydrous solvents were purchased from Acros Organics or Sigma-Aldrich. The solvents were degassed by three cycles of freeze-pump-thaw and storing in single-necked flasks equipped with a J-Young PTFE valve when necessary. Palladium complexes were purchased from Sigma-Aldrich or Strem. All other chemical reagents were purchased from Sigma-Aldrich, Acros Organics, Alfa Aesar Apollo scientific and Fluorochem and used as received without further purification unless otherwise stated.

Instrumentation:

GCMS analyses were performed with a Shimadzu QP2010SB GCMS apparatus on a Rtx®-5ms-Low-Bleed column lined with a mass (EI) detection system. HPLC analyses was performed using a Shimadzu Prominence system with SIL-20A auto sample, CTO-20AC column oven, LC-20AD pump system, DGU-20A3 degasser and SPD-M20A Diode Array or UV/VIS detector. The following chiral columns from Daicel Chemical Industries were used: OJ-H (Chiralcel®), IA (Chiralpak®) in 4.6 x 250 mm size. Melting points were obtained on a Büchi melting point M-565, and are uncorrected. IR spectra were recorded on an ATR Varian Scimitar 800 and are reported in reciprocal centimeters (cm^{-1}). Nuclear magnetic resonance spectra were recorded on a Bruker Advance 400 (400 MHz), Advance 500 (500 MHz) and Advance 600 (600 MHz) in deuterated chloroform (residual peaks ^{1}H δ 7.26 ppm, ^{13}C δ 77.16 ppm) unless otherwise noted. ^{19}F NMR spectra were referenced to external $CFCl_3$. Data are reported in parts per million (ppm) as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintuplet, sept = septuplet, m = multiplet and brs = broad singlet), coupling constant in Hz and integration. High resolution mass spectra were recorded by Dr. H. Nadig, Dr. M. Pfeffer and S. Mittelheisser (Department of Chemistry, University of Basel) on a Bruker maXis 4G QTOF ESI mass spectrometer. Optical rotations were measured on a Perkin Elmer 341 Polarimeter in a 1 mL micro cuvette (cell length 100mm) with NaD-Line (λ = 589 nm). The concentration (c) was given in g/100 mL.

Ligands preparation

For C_2 symetrical Herrmann-Kundig type NHCs:

L^7 was graciously furnished by Pr. E. P. Kündig, L^1 and L^8-L^{12} were prepared as reported.[1]

For C_2 symetrical and achiral IBiox-type NHCs:

L^2-L^3 and L^{13}-L^{15} were prepared as reported.[2]

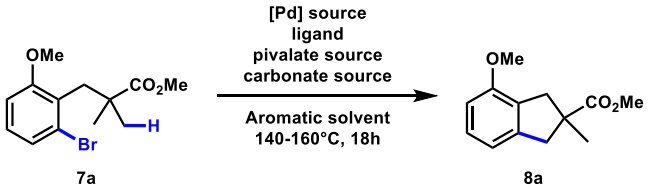
For Binepine ligand:

L^4 was previously prepared in our group.[3]

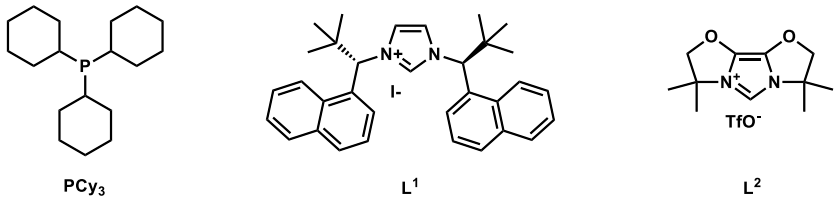
For TADDOL phosphoramidite/phosphonite ligands:

L^5-L^6 were previously prepared as reported.[4]

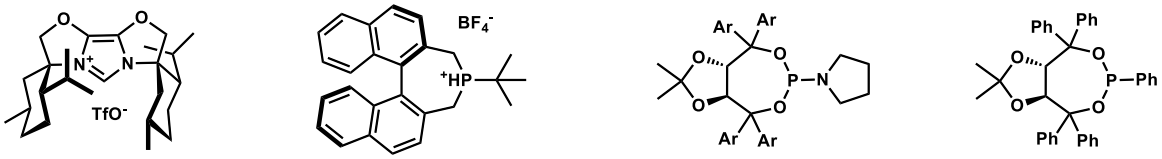
Optimisation Studies - preliminary screening



7a 8a



PCy_3 L^1 L^2



L^3 L^4 Ar = 3,5-$(CF_3)_2$Ph L^5 L^6

Condition	Ligand	Conversion (%)[a]	Ratio of 8a (%)[a]	e.r. (S):(R)[b]
A	PCy_3	100	90	/
B	L^2	100	95	/
B	L^3	100	93	56:44
C	L^4	92	60	49:51
B	L^1	100	100	66:34
D	L^5	68	28	51:49
D	L^6	61	14	49:51

Table S1. Optimisation Studies - preliminary screening. [a] Based on GC/MS analysis. [b] Determined by HPLC on a chiral stationary phase

Conditions:

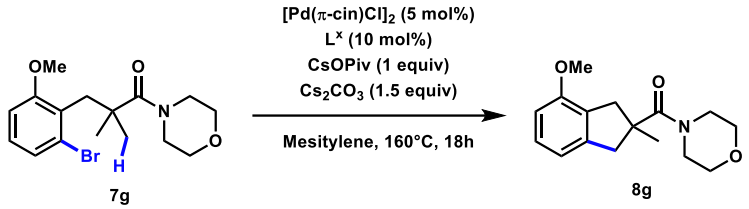
A: **7a** (0.2 mmol), Pd_2dba_3 (2.5 mol%), PCy_3 (10 mol%), PivOH (30 mol%) and K_2CO_3 (1.5 equiv) in xylenes (2 mL) at 140°C for 18h.

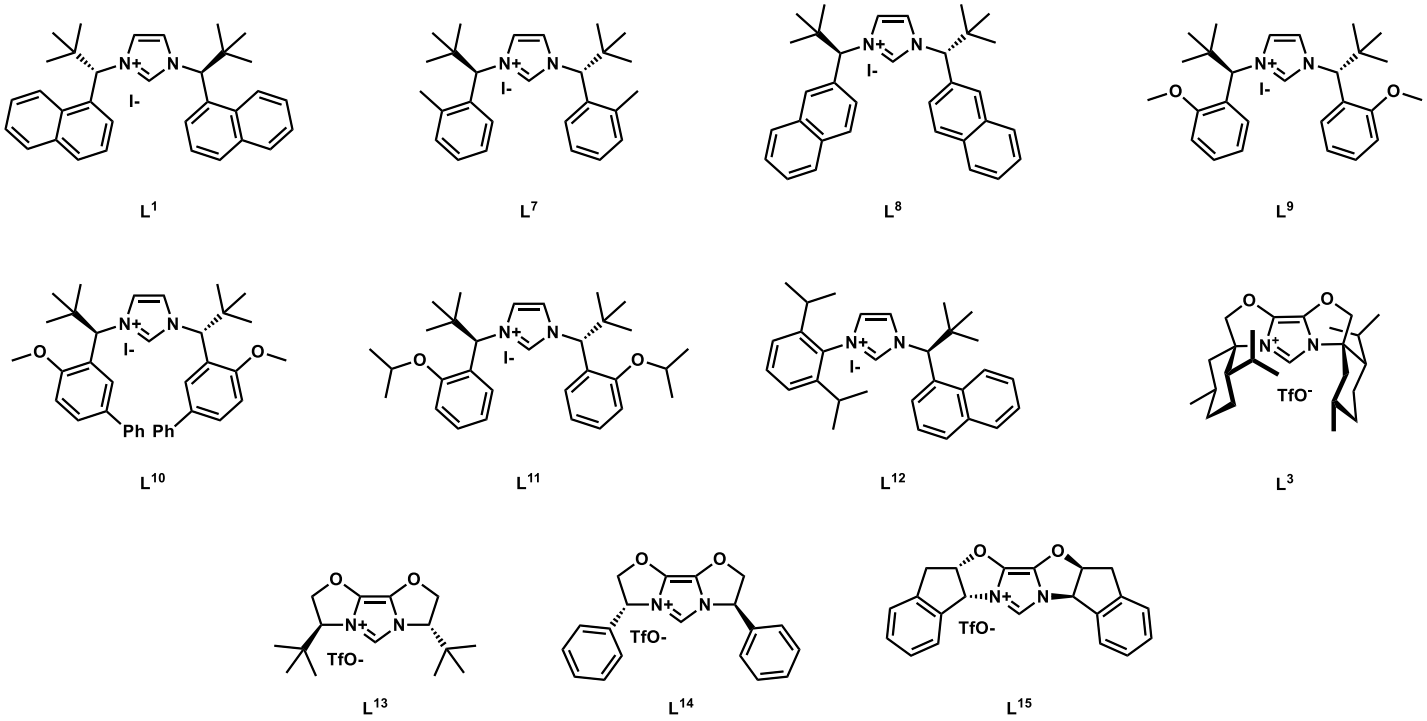
B: **7a** (0.2 mmol), $[Pd(\pi\text{-cin})Cl]_2$ (5 mol%), L^2 (10 mol%), CsOPiv (1 equiv), Cs_2CO_3 (1.5 equiv), in mesitylene (2 mL) at 160°C for 18h.

C: **7a** (0.2 mmol), Pd_2dba_3 (2.5 mol%), L^4 (10 mol%), PivOH (50 mol%) and Cs_2CO_3 (2 equiv) in xylenes (2 mL) at 140°C for 18h.

D: **7a** (0.2 mmol), $Pddba_2$ (10 mol%), L^5 (20 mol%), PivOH (50 mol%) and Cs_2CO_3 (2 equiv) in xylenes (2 mL) at 140°C for 18h.

Optimisation Studies - screening of chiral NHCs

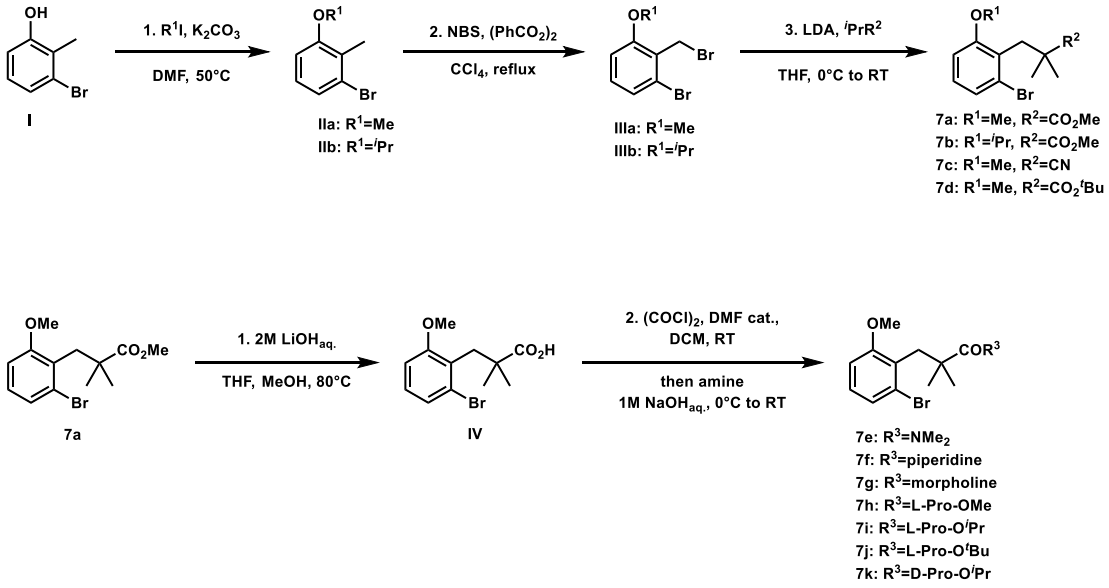




Condition	Ligand	Conversion (%)[a]	Ratio of 8g (%)[a]	e.r. (S):(R)[b]
B	L^1	100	100	80:20
B	L^7	100	100	20:80
B	L^8	100	92	26.5:73.5
B	L^9	100	100	17:83
B	L^{10}	100	100	19:81
B	L^{11}	80	76	22.5:77.5
B	L^{12}	42	22	66.5:33.5
B	L^3	100	100	66:34
B	L^{13}	100	100	27:73
B	L^{14}	40	11	62:38
B	L^{15}	90	56	61:39

Table S2. Optimisation studies - preliminary screening. [a] Based on GC/MS analysis. [b] Determined by HPLC on a chiral stationary phase

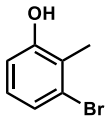
Experimental procedures - preparation of model substrates



Scheme S2: route for preparation of substrates.

3-bromo-2-methylphenol (I):

3-bromo-2-methylphenol is a commercially available compound from different providers but quite expensive, so we modified an existing procedure[5] to prepare large amount of this simple building block via a Sandmeyer Reaction. In a reactor equipped with a mechanical stirrer and a condenser, freshly distilated 3-bromo-2-methylaniline (70 g, 376 mmol) was added to an aqueous 1M solution of sulfuric acid (451 mL, 451 mmol) at 0° C under vigorous stirring (formation of a white suspension of anilinium). Then a saturated solution of sodium nitrite (31.1 g, 451 mmol) in water was added dropwise at -5°C. After stirring at -5° C for 20 min (most of the solid is dissolve at this point), concentrated sulfuric acid (14 mL, 258 mmol) was added and the solution was heated at 100°C for 1 h. The mixture was then diluted with water, extracted with Et_2O, dried and concentrated to yield a black slurry. The residue was purified by sublimation under vacuum (0.1 mbar), and the obtained orange solid was recrystallize with cyclohexane to yield **I** as a white crystalline solid (32 g, 171 mmol, 46 % yield).



Chemical Formula: C_7H_7BrO
Exact Mass: 185.9680
Molecular Weight: 187.0360

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.14 (dd, *J* = 8.0, 1.1 Hz, 1H), 6.92 (td, *J* = 8.0, 0.5 Hz, 1H), 6.71 (ddd, *J* = 8.0, 1.1, 0.5 Hz, 1H), 4.87 (s, 1H), 2.34 (s, 3H)
^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) 154.5, 127.6, 126.2, 125.1, 124.6, 114.2, 15.7
IR (neat)**:** ν (cm^{-1}) 3283, 1435, 1241, 998, 762
GCMS (EI): m/z for $C_7H_7{}^{79}BrO$ $[M]^{+\bullet}$: 186

Mp = 96-98°C
Rf = 0.25 in a 85:15 mixture of pentane and ethyl acetate

General procedure for preparation of 7a-7d:

O-alkylation:

3-bromo-2-methylphenol (**I**) was dissolved in DMF (2.5 mL per mmol) and K_2CO_3 (3 equiv) was added, the mixture was then stirred during 5 min at room temperature. After this period, alkyl iodide (MeI or ^{i}PrI, 5 equiv) was added in one portion and the reaction was stirred at 50°C during 2h. The reaction was then diluted with water, extracted with EtOAc and concentrated to yield the corresponding 2-bromo-6-alkyloxytoluene which was used in the next step without further purification.

Benzylic bromination:

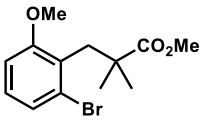
A solution of 2-bromo-6-alkyloxytoluene, N-bromosuccinimide (1.05 equiv) and benzoyl peroxide (4 mol%) in CCl_4 (2 mL per mmol) was heated to reflux and stirred overnight. The reaction mixture was then cooled to room temperature and filtered. The filtrate was diluted with DCM and washed successively with 2M NaOH, water and brine. The organic layer was dried over $MgS0_4$, filtered and concentrated under reduced pressure to give the corresponding benzyl bromide which was used in the next step without further purification.

Benzylation of alkyl isobutyrate:

A solution of LDA (1.05 equiv) in THF (2 mL per mmol) was prepared from diisopropylamine (1.05 equiv) and 2.5 M n-BuLi in hexane (1.05 equiv), stirred at 0°C during 15 min. To the LDA solution, isopropyl derivative (^{i}PrCO$_2$Me, ^{i}PrCO$_2$tBu or ^{i}PrCN, 1 equiv) was added dropwise at 0°C and the mixture was stirred at the same temperature for 45 min. Benzyl bromide (**IIIa** or **IIIb**, 1 equiv) in THF (1 mL per mmol) was added slowly to the solution always at 0°C. The mixture was stirred for 16 h with the ice bath warming to room temperature. Water was then add to the reaction at 0°C. The mixture was extracted three times with Et_2O, the combined organic layers were washed with brine. The organic layer was dried over $MgSO_4$, filtered and then concentrated under vacuum to give the corresponding crude material, which was purified by column chromatography (Cy/AcOEt: 95/5 to 90/10).

methyl 3-(2-bromo-6-methoxyphenyl)-2,2-dimethylpropanoate (7a):

From **IIIa** and ^{i}PrCO$_2$Me. Obtained as a colourless oil, which crystallize on standing (21.4 g, 71 mmol, 75% over three steps).



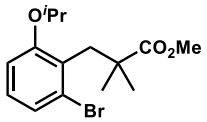
Chemical Formula: $C_{13}H_{17}BrO_3$
Exact Mass: 300.0361
Molecular Weight: 301.1800

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.16 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.04 (t, *J* = 8.1 Hz, 1H), 6.76 (dd, *J* = 8.1, 1.1 Hz, 1H), 3.74 (s, 3H), 3.67 (s, 3H), 3.18 (s, 2H), 1.21 (s, 6H)
^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) 178.3, 159.1, 128.4, 127.4, 127.3, 125.2, 109.3, 55.6, 51.8, 43.4, 39.3, 25.6
IR (neat)**:** ν (cm^{-1}) 2980, 1716, 1265, 1146, 1029, 771
HRMS (ESI): Calcd for $C_{13}H_{17}{}^{79}BrNaO_3$ $[M+Na]^+$: 323.0253, found 323.0251

Mp = 42-44°C
Rf = 0.22 in a 90:10 mixture of pentane and ethyl acetate

methyl 3-(2-bromo-6-isopropoxyphenyl)-2,2-dimethylpropanoate (7b):

From **IIIb** and ^{i}PrCO$_2$Me.Obtained as a colourless liquid (410 mg, 1.25 mmol, 71% over three steps).



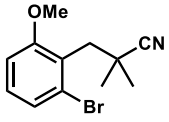
Chemical Formula: $C_{15}H_{21}BrO_3$
Exact Mass: 328.0674
Molecular Weight: 329.2340

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.12 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.00 (t, *J* = 8.0 Hz, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 4.50 (sept, *J* = 6.1 Hz, 1H), 3.66 (s, 3H), 3.18 (s, 3H), 1.32 (d, J = 6.1 Hz, 6H), 1.22 (s, 6H)
^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) 178.5, 157.6, 128.3, 128.2, 127.5, 124.8, 111.6, 70.7, 52.0, 43.8, 38.7, 25.8, 22.1
IR (neat)**:** ν (cm^{-1}) 2977, 1729, 1444, 1258, 1139, 962
HRMS (ESI): Calcd for $C_{15}H_{21}{}^{79}BrNaO_3$ $[M+Na]^+$: 351.0566, found 351.0566

Rf = 0.40 in a 90:10 mixture of pentane and ethyl acetate

3-(2-bromo-6-methoxyphenyl)-2,2-dimethylpropanenitrile (7c):

From **IIIa** and ^{i}PrCN. Obtained as a colourless liquid (494 mg, 1.84 mmol, 74% over three steps).



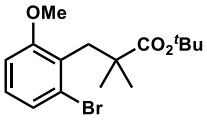
Chemical Formula: $C_{12}H_{14}BrNO$
Exact Mass: 267.0259
Molecular Weight: 268.1540

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.19 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.10 (t, *J* = 8.1 Hz, 1H), 6.84 (dd, *J* = 8.1, 1.1 Hz, 1H), 3.82 (s, 3H), 3.17 (s, 3H), 1.45 (s, 6H)
^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) 159.2, 129.3, 127.0, 125.4, 125.3, 125.3, 109.8, 55.6, 38.9, 33.9, 27.9
IR (neat)**:** ν (cm^{-1}) 2977, 1462, 1271, 1033, 774
HRMS (ESI): Calcd for $C_{12}H_{14}{}^{79}BrNaO$ $[M+Na]^+$: 290.0151, found 290.0149

Rf = 0.27 in a 90:10 mixture of pentane and ethyl acetate

tert-butyl 3-(2-bromo-6-methoxyphenyl)-2,2-dimethylpropanoate (7d):

From **IIIa** and ^{i}PrCO$_2{}^{t}$Bu. Obtained as a colourless liquid (856 mg, 2.49 mmol, 71% over three steps).



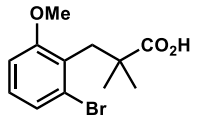
Chemical Formula: $C_{16}H_{23}BrO_3$
Exact Mass: 342.0831
Molecular Weight: 343.2610

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.16 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.03 (t, *J* = 8.1 Hz, 1H), 6.77 (dd, *J* = 8.1, 1.1 Hz, 1H), 3.75 (s, 3H), 3.19 (s, 2H), 1.44 (s, 9H), 1.13 (s, 6H)
^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) 177.6, 159.3, 128.2, 127.9, 127.5, 125.2, 109.4, 79.8, 55.5, 44.3, 37.8, 28.2, 25.7
IR (neat)**:** ν (cm^{-1}) 2975, 1720, 1461, 1261, 1135, 1035
HRMS (ESI): Calcd for $C_{16}H_{23}{}^{79}BrNaO_3$ $[M+Na]^+$: 365.0723, found 365.0725

Rf = 0.42 in a 90:10 mixture of pentane and ethyl acetate

3-(2-bromo-6-methoxyphenyl)-2,2-dimethylpropanoic acid (IV):

7a (12.3 g, 40.9 mmol) was dissolved in a mixture THF (70 mL), MeOH (70 mL) and 2M aqueous LiOH (70 ml). The reaction was then heat at 80°C for 6 hours. After cooling to room temperature, the organic solvents were removed under reduced pressure. The obtained aqueous solution was washed with diethyl ether, acidified to pH<0 and extracted three times with DCM. The combined organic layers were then dried over MgSO4, filtered and concentrated under reduced pressure to yield **IV** (10.7 g, 37.2 mmol, 91% yield) as a yellow solid.



Chemical Formula: $C_{12}H_{15}BrO_3$
Exact Mass: 286.0205
Molecular Weight: 287.1530

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.17 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.05 (t, *J* = 8.1 Hz, 1H), 6.77 (dd, *J* = 8.1, 1.1 Hz, 1H), 3.72 (s, 3H), 3.24 (s, 2H), 1.23 (s, 6H)
^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) 184.6, 159.1, 128.5, 127.3, 127.0, 125.2, 109.2, 55.0, 43.2, 39.3, 25.3
IR (neat)**:** ν (cm^{-1}) 2971, 1687, 1265, 1033, 764
HRMS (ESI): Calcd for $C_{12}H_{15}{}^{79}BrNaO_3$ $[M+Na]^+$: 309.0097, found 309.0094

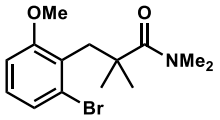
Mp = 122-124°C
Rf = 0.26 in a 70:30 mixture of pentane and ethyl acetate

General procedure for preparation of 7e-7k:

IV was dissolved in dry DCM (10 mL per mmol), then oxalyl chloride (1.1 equiv) was added, follow by few drops of DMF to initiate the reaction. After 1 hour of stirring at room temperature, the reaction was cooled to 0°C and the amine (free base or salt, 3 equiv) and aqueous 1M NaOH (10 equiv) were added in one portion. The mixture was vigorously stirred for 16 hours with the ice bath warming to room temperature. The organic layer was then separated, washed with 2M HCl, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Crude material was then purified by flash column chromatography to yield the corresponding pure amide.

3-(2-bromo-6-methoxyphenyl)-N,N,2,2-tetramethylpropanamide (7e):

From **IV** and $HNMe_2$•HCl. Obtained as a colourless oil, which crystallize on standing (240 mg, 0.764 mmol, 97%).



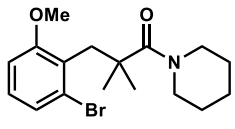
Chemical Formula: $C_{14}H_{20}BrNO_2$
Exact Mass: 313.0677
Molecular Weight: 314.2230

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.16 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.03 (t, *J* = 8.1 Hz, 1H), 6.77 (dd, *J* = 8.1, 1.1 Hz, 1H), 3.75 (s, 3H), 3.25 (s, 3H), 3.10 (brs, 6H), 1.26 (s, 6H)
^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) 177.4, 159.1, 128.4, 127.6, 127.2, 125.3, 109.3, 55.6, 43.8, 38.7, 37.7, 27.0
IR (neat)**:** ν (cm^{-1}) 2981, 2937, 1619, 1465, 1258, 1030, 776
HRMS (ESI): Calcd for $C_{14}H_{20}{}^{79}BrNNaO_2$ $[M+Na]^+$: 336.0570, found 336.0575

Mp = 62-64°C
Rf = 0.22 in a 50:50 mixture of pentane and ethyl acetate

3-(2-bromo-6-methoxyphenyl)-2,2-dimethyl-1-(piperidin-1-yl)propan-1-one (7f):

From **IV** and piperidine. Obtained as a colourless oil, which crystallize on standing (490 mg, 1.38 mmol, 99%).

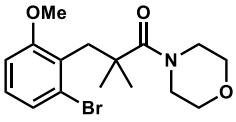


Chemical Formula: $C_{17}H_{24}BrNO_2$
Exact Mass: 353.0990
Molecular Weight: 354.2880

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.16 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.03 (t, *J* = 8.1 Hz, 1H), 6.77 (dd, *J* = 8.1, 1.1 Hz, 1H), 3.75 (s, 3H), 3.70-3.65 (m, 4H), 3.24 (s, 2H), 1.71-1.64 (m, 3H), 1.64-1.56 (m, 3H), 1.21 (s, 6H)
^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) 176.2, 159.2, 128.4, 127.8, 127.3, 125.3, 109.3, 55.6, 46.6, 43.7, 37.4, 27.0, 26.3, 25.0
IR (neat)**:** ν (cm^{-1}) 2935, 2854, 1611, 1415, 1265, 1028, 774
HRMS (ESI): Calcd for $C_{17}H_{24}{}^{79}BrNNaO$ $[M+Na]^+$: 376.0883, found 376.0883
Mp = 96-98°C
Rf = 0.25 in a 70:30 mixture of pentane and ethyl acetate

3-(2-bromo-6-methoxyphenyl)-2,2-dimethyl-1-morpholinopropan-1-one (7g):

From **IV** and morpholine. Obtained as a colourless oil, which crystallize on standing (480 mg, 1.35 mmol, 97%).

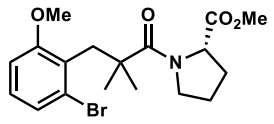


Chemical Formula: $C_{16}H_{22}BrNO_3$
Exact Mass: 355.0783
Molecular Weight: 356.2600

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.17 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.05 (t, *J* = 8.1 Hz, 1H), 6.78 (dd, *J* = 8.1, 1.1 Hz, 1H), 3.76 (s, 3H), 3.77-3.72 (m, 4H), 3.73-3.69 (m, 4H), 3.23 (s, 2H), 1.23 (s, 6H)
^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) 176.6, 159.0, 128.6, 127.4, 127.2, 125.4, 109.4, 67.1, 55.7, 46.2, 43.6, 37.5, 27.0
IR (neat)**:** ν (cm^{-1}) 2946, 2846, 1624, 1269, 1111, 1031, 775
HRMS (ESI): Calcd for $C_{16}H_{22}{}^{79}BrNNaO_3$ $[M+Na]^+$: 378.0675, found 378.0677
Mp = 86-88°C
Rf = 0.24 in a 50:50 mixture of pentane and ethyl acetate

methyl (3-(2-bromo-6-methoxyphenyl)-2,2-dimethylpropanoyl)-L-prolinate (7h):

From **IV** and H-L-Pro-OMe•HCl. Obtained as a wax (368 mg, 0.924 mmol, 89%).

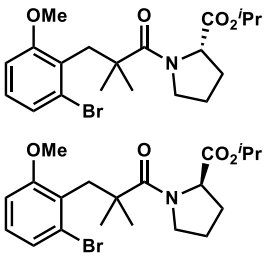


Chemical Formula: $C_{18}H_{24}BrNO_4$
Exact Mass: 397.0889
Molecular Weight: 398.2970

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.15 (d, *J* = 8.1 Hz, 1H), 7.03 (t, *J* = 8.1 Hz, 1H), 6.77 (d, *J* = 8.1 Hz, 1H), 4.54-4.46 (m, 1H), 3.84-3.67 (m, 2H), 3.74 (s, 3H), 3.71 (s, 3H), 3.25 (d, *J* = 13.5 Hz, 1H), 3.19 (d, *J* = 13.5 Hz, 1H), 2.20-2.09 (m, 1H), 2.09-2.00 (m, 1H), 1.94-1.79 (m, 2H), 1.29 (s, 3H), 1.18 (s, 3H)
^{13}C NMR (126 MHz, $CDCl_3$): 176.4, 173.6, 159.2, 128.4, 127.4, 127.2, 125.3, 109.4, 61.3, 55.5, 52.1, 48.5, 44.0, 36.9, 28.0, 26.4, 26.1, 25.4
IR (neat)**:** ν (cm^{-1}) 2948, 1743, 1622, 1397, 1159, 1031
HRMS (ESI): Calcd for $C_{18}H_{24}{}^{79}BrNNaO_4$ $[M+Na]^+$: 420.0781, found 420.0788
Rf = 0.24 in a 60:40 mixture of pentane and ethyl acetate
$[\alpha]_D^{20}$ = - 44.7° (c = 0.70, $CHCl_3$)

isopropyl (3-(2-bromo-6-methoxyphenyl)-2,2-dimethylpropanoyl)-L-prolinate (7i) and isopropyl (3-(2-bromo-6-methoxyphenyl)-2,2-dimethylpropanoyl)-D-prolinate (7k):

From **IV** and H-L-Pro-O^{i}Pr•HCl or H-D-Pro-O^{i}Pr•HCl respectively. Obtained as a colourless oil, which crystallize on standing, **7i** (698 mg, 1.64 mmol, 90%), **7k** (279 mg, 0.655 mmol, 93%).



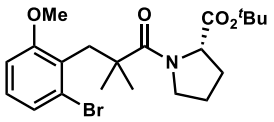
Chemical Formula: $C_{20}H_{28}BrNO_4$
Exact Mass: 425.1202
Molecular Weight: 426.3510

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.15 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.03 (t, *J* = 8.1 Hz, 1H), 6.77 (dd, *J* = 8.1, 1.1 Hz, 1H), 5.02 (sept, *J* = 6.2 Hz, 1H), 4.53-4.42 (m, 1H), 3.85-3.67 (m, 2H), 3.74 (s, 3H), 3.27 (d, *J* = 13.5 Hz, 1H), 3.19 (d, *J* = 13.5 Hz, 1H), 2.21-2.09 (m, 1H), 2.09-1.97 (m, 1H), 1.93- 1.76 (m, 2H), 1.31 (s, 3H), 1.25 (d, *J* = 6.2 Hz, 3H), 1.21 (d, *J* = 6.2 Hz, 3H), 1.19 (s, 3H)
^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) 176.6, 172.4, 159.2, 128.4, 127.3, 127.2, 125.3, 109.4, 68.2, 61.7, 55.5, 48.6, 44.1, 36.9, 28.0, 26.4, 26.1, 25.5, 21.9, 21.8
IR (neat)**:** ν (cm^{-1}) 2975, 1742, 1627, 1401, 1177, 1035, 781
HRMS (ESI): Calcd for $C_{20}H_{28}{}^{79}BrNNaO_4$ $[M+Na]^+$: 448.1094, found 448.1097

Mp = 88-90°C
Rf = 0.32 in a 60:40 mixture of pentane and ethyl acetate
For 6e $[\alpha]_D^{23}$ = - 23.7° (c = 1.05, $CHCl_3$)
For 6f $[\alpha]_D^{23}$ = + 22.8° (c = 0.50, $CHCl_3$)

tert-butyl (3-(2-bromo-6-methoxyphenyl)-2,2-dimethylpropanoyl)-L-prolinate (7j):

From **IV** and H-L-Pro-O^{t}Bu•HCl. Obtained as a wax (344 mg, 0.781 mmol, 89%).



Chemical Formula: $C_{21}H_{30}BrNO_4$
Exact Mass: 439.1358
Molecular Weight: 440.3780

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.16 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.03 (t, *J* = 8.1 Hz, 1H), 6.77 (dd, *J* = 8.1, 1.1 Hz, 1H), 4.44-4.35 (m, 1H), 3.75 (s, 3H), 3.81-3.67 (m, 2H), 3.26 (d, *J* = 13.5 Hz, 1H), 3.19 (d, *J* = 13.5 Hz, 1H), 2.20-2.08 (m, 1H), 2.08-1.96 (m, 1H), 1.91-1.75 (m, 2H), 1.45 (s, 9H), 1.30 (s, 3H), 1.19 (s, 3H)
^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) 176.0, 172.3, 159.2, 128.4, 127.5, 127.3, 125.3, 109.3, 80.7, 62.2, 55.5, 48.5, 44.0, 37.0, 28.1, 28.1, 26.4, 26.3, 25.5
IR (neat)**:** ν (cm^{-1}) 2974, 1736, 1623, 1365, 1148, 1033, 772
HRMS (ESI): Calcd for $C_{21}H_{30}{}^{79}BrNNaO_4$ $[M+Na]^+$: 462.1250, found 462.1253
Rf = 0.28 in a 70:30 mixture of pentane and ethyl acetate
$[\alpha]_D^{23}$ = - 34.6° (c = 2.40, $CHCl_3$)

Experimental procedures - C(sp^3)-H arylation with model substrates

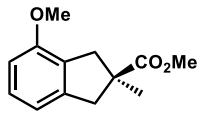
General procedure:

In an oven dry catalysis tube, substrate (0.2 mmol) was introduced. Then the tube was tranfer in glovebox and $[Pd(\pi\text{-cin})Cl]_2$ (5.2 mg, 10 µmol, 5 mol%), L^1 (11.8 mg, 20 µmol, 10 mol%), cesium pivalate (46.8 mg, 0.2 mmol, 1 equiv) and cesium carbonate (97.7 mg, 0.3 mmol, 1.5 equiv) were introduced and the tube was close with a septum. Outside of the glovebox, mesitylene (2 mL) was added. The reaction was stirred at room temperature for 10 min, then, under pressure of argon, the septum was rapidely exchange for a screw cap. The tube was then introduced in a 160°C preheated aluminium heating block and stirred at this temperature for 18 hours. After this period the reaction was coolded to room temperature, diluted with DCM (1 mL), filtered over a pad of celite (washed three times with 1 mL of DCM). The crude material was analyzed by GC-MS and then concentrated and purified by flash column chromatography to yield the corresponding indane product. Enantiomeric/diastereomeric ratio were then determined by HPLC using a chiral stationary phase.

Racemic materials were obtained following the same procedure, using L^2 as ligand.

methyl (S)-4-methoxy-2-methyl-2,3-dihydro-1H-indene-2-carboxylate (8a):

From **7a**. Obtained as a yellow liquid (40.5 mg, 0.184 mmol, 92%).



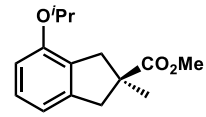
Chemical Formula: $C_{13}H_{16}O_3$
Exact Mass: 220.1099
Molecular Weight: 220.2680

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.15 (t, *J* = 7.8 Hz, 1H), 6.81 (d, *J* = 7.8 Hz, 1H), 6.68 (d, *J* = 7.8 Hz, 1H), 3.82 (s, 3H), 3.72 (s, 3H), 3.50 (d, *J* = 16.0 Hz, 1H), 3.39 (d, *J* = 16.4 Hz, 1H), 2.84 (d, *J* = 16.4 Hz, 1H), 2.82 (d, *J* = 16.0 Hz, 1H), 1.37 (s, 3H)
^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) 178.3, 156.3, 143.3, 128.9, 128.2, 117.1, 108.2, 55.3, 52.2, 49.4, 44.5, 41.0, 25.6
IR (neat)**:** ν (cm^{-1}) 2950, 1730, 1590, 1261, 1075, 766

HRMS (ESI): Calcd for $C_{13}H_{16}NaO_3$ $[M+Na]^+$: 243.0992, found 243.0990
Rf = 0.21 in a 95:5 mixture of pentane and ethyl acetate
HPLC separation: Chiralcel® OJ-H; 99:1 (n-heptane/i-PrOH), 0.8 ml.min^{-1}, 204 nm, tr(major) = 16.4 min, tr(major) = 18.1 min, 66:34 e.r.

methyl (S)-4-isopropoxy-2-methyl-2,3-dihydro-1H-indene-2-carboxylate (8b):

From **7b**. Obtained as a yellow liquid (46.2 mg, 0.186 mmol, 93%).

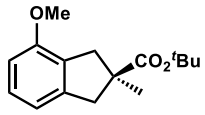


Chemical Formula: $C_{15}H_{20}O_3$
Exact Mass: 248.1412
Molecular Weight: 248.3220

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) δ 7.11 (t, *J* = 7.8 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 6.69 (d, *J* = 7.8 Hz, 1H), 4.51 (sept, *J* = 6.1 Hz, 1H), 3.72 (s, 3H), 3.50 (d, *J* = 16.0 Hz, 1H), 3.37 (d, *J* = 16.3 Hz, 1H), 2.85 (d, *J* = 16.3 Hz, 1H), 2.81 (d, *J* = 16.0 Hz, 1H), 1.36z (s, 3H), 1.33 (d, *J* = 6.1 Hz, 3H), 1.32 (d, *J* = 6.1 Hz, 3H)
^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) 178.4, 154.8, 143.4, 130.4, 128.0, 117.0, 111.5, 70.4, 52.2, 49.3, 44.5, 41.2, 25.6, 22.4, 22.4
IR (neat)**:** ν (cm^{-1}) 2976, 1732, 1477, 1259, 1111, 766
HRMS (ESI): Calcd for $C_{15}H_{20}NaO_3$ $[M+Na]^+$: 271.1305, found 271.1305
Rf = 0.26 in a 95:5 mixture of pentane and ethyl acetate
HPLC separation: Chiralcel® OJ-H; 99:1 (n-heptane/i-PrOH), 0.8 ml.min^{-1}, 221 nm, tr(major) = 7.5 min, tr(minor) = 8.8 min, 71:29 e.r.

tert-butyl (S)-4-methoxy-2-methyl-2,3-dihydro-1H-indene-2-carboxylate (8d):

From **7d**. Obtained as a yellow oil mixed with significant amount of protodebrominated byproduct (12.6 mg, 0.048 mmol, 24%). NMR data are given from the racemate.

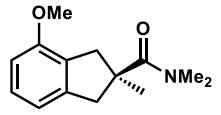


Chemical Formula: $C_{16}H_{22}O_3$
Exact Mass: 262.1569
Molecular Weight: 262.3490

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.14 (t, *J* = 7.8 Hz, 1H), 6.81 (d, *J* = 7.8 Hz, 1H), 6.68 (d, *J* = 7.8 Hz, 1H), 3.82 (s, 3H), 3.46 (d, *J* = 16.0 Hz, 1H), 3.32 (d, *J* = 16.3 Hz, 1H), 2.80 (d, *J* = 16.3 Hz, 1H), 2.76 (d, *J* = 16.0 Hz, 1H), 1.46 (s, 9H), 1.32 (s, 3H)
^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) 177.0, 156.3, 143.6, 129.1, 128.1, 117.2, 108.1, 80.3, 77.4, 77.2, 76.9, 55.3, 50.1, 44.3, 41.0, 28.2, 25.6
IR (neat)**:** ν (cm^{-1}) 2974, 1721, 1260, 1112, 1076, 767
HRMS (ESI): Calcd for $C_{16}H_{22}NaO_3$ $[M+Na]^+$: 285.1461, found 285.1463
Rf = 0.32 in a 95:5 mixture of pentane and ethyl acetate
HPLC separation: Chiralcel OJ-H; 99.5:0.5 (n-heptane/i-PrOH), 0.8 ml.min^{-1}, 220 nm, tr(major) = 7.3 min, tr(minor) = 8.3 min, 58:42 e.r.

(S)-4-methoxy-N,N,2-trimethyl-2,3-dihydro-1H-indene-2-carboxamide (8e):

From **7e**. Obtained as a wax (44.3 mg, 0.19 mmol, 95%).

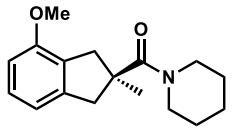


Chemical Formula: $C_{14}H_{19}NO_2$
Exact Mass: 233.1416
Molecular Weight: 233.3110

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.16 (t, *J* = 7.8 Hz, 1H), 6.82 (d, *J* = 7.8 Hz, 1H), 6.68 (d, *J* = 7.8 Hz, 1H), 3.82 (s, 3H), 3.61 (d, *J* = 16.5 Hz, 1H), 3.35 (d, *J* = 16.5 Hz, 1H), 3.02 (brs, 6H), 2.95 (d, *J* = 16.5 Hz, 1H), 2.88 (d, *J* = 16.5 Hz, 1H), 1.36 (s, 3H)
^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) 176.9, 156.3, 143.1, 128.6, 128.3, 117.2, 108.0, 55.2, 49.5, 45.9, 41.7, 37.9, 26.5
IR (neat)**:** ν (cm^{-1}) 2935, 1620, 1263, 1075, 766
HRMS (ESI): Calcd for $C_{14}H_{19}NNaO_2$ $[M+Na]^+$: 256.1308, found 256.1309
Rf = 0.25 in a 50:50 mixture of pentane and ethyl acetate
HPLC separation: Chiralcel® OJ-H; 95:5 (n-heptane/i-PrOH), 1.0 ml.min^{-1}, 204 nm, tr(minor) = 16.7 min, tr(major) = 18.5 min, 82:18 e.r.

(S)-(4-methoxy-2-methyl-2,3-dihydro-1H-inden-2-yl)(piperidin-1-yl)methanone (8f):

From **7f**. Obtained as a wax (51.9 mg, 0.19 mmol, 95%).

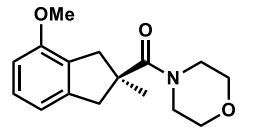


Chemical Formula: $C_{17}H_{23}NO_2$
Exact Mass: 273.1729
Molecular Weight: 273.3760

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.15 (t, *J* = 7.8 Hz, 1H), 6.82 (d, *J* = 7.8 Hz, 1H), 6.68 (d, *J* = 7.8 Hz, 1H), 3.82 (s, 3H), 3.62 (d, *J* = 16.5 Hz, 1H), 3.59-3.44 (m, 4H), 3.35 (d, *J* = 16.5 Hz, 1H), 2.93 (d, *J* = 16.5 Hz, 1H), 2.87 (d, *J* = 16.5 Hz, 1H), 1.70-1.61 (m, 2H), 1.61-1.53 (m, 4H), 1.35 (s, 3H)
^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) 175.5, 156.3, 143.1, 128.6, 128.2, 117.2, 108.0, 55.2, 49.6, 46.1, 46.0, 41.8, 27.1, 26.2, 24.8
IR (neat)**:** ν (cm^{-1}) 2932, 2853, 1623, 1420, 1258, 1076, 1013, 764
HRMS (ESI): Calcd for $C_{17}H_{23}NNaO_2$ $[M+Na]^+$: 296.1621, found 296.1621
Rf = 0.26 in a 75:25 mixture of pentane and ethyl acetate
HPLC separation: Chiralpak® IA; 95:5 (n-heptane/i-PrOH), 1.0 ml.min^{-1}, 205 nm, tr(major) = 10.6 min, tr(minor) = 11.7 min, 85:15 e.r.

(S)-(4-methoxy-2-methyl-2,3-dihydro-1H-inden-2-yl)(morpholino)methanone (8g):

From **7g**. Obtained as a wax (52.3 mg, 0.19 mmol, 95%).

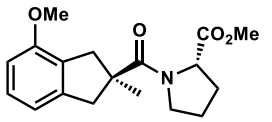


Chemical Formula: $C_{16}H_{21}NO_3$
Exact Mass: 275.1521
Molecular Weight: 275.3480

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.17 (t, *J* = 7.8 Hz, 1H), 6.82 (d, *J* = 7.5 Hz, 1H), 6.69 (d, *J* = 8.1 Hz, 1H), 3.82 (s, 3H), 3.70-3.66 (m, 4H), 3.64-3.56 (m, 4H), 3.60 (d, *J* = 16.5 Hz, 1H), 3.33 (d, *J* = 16.5 Hz, 1H), 2.93 (d, *J* = 16.5 Hz, 1H), 2.88 (d, *J* = 16.5 Hz, 1H), 1.36 (s, 3H)
^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) 175.9, 156.3, 142.7, 128.5, 128.2, 117.2, 108.1, 67.0, 55.2, 49.2, 46.0, 45.4, 41.8, 27.2
IR (neat)**:** ν (cm^{-1}) 2961, 2926, 2852, 1626, 1416, 1264, 1113, 765
HRMS (ESI): Calcd for $C_{16}H_{21}NNaO_3$ $[M+Na]^+$: 298.1414, found 298.1417
Rf = 0.25 in a 50:50 mixture of pentane and ethyl acetate
HPLC separation: Chiralpak® IA; 95:5 (n-heptane/i-PrOH), 1.0 ml.min^{-1}, 205 nm, tr(major) = 14.5 min, tr(minor) = 15.6 min, 82:18 e.r.

methyl ((S)-4-methoxy-2-methyl-2,3-dihydro-1H-indene-2-carbonyl)-L-prolinate (8h):

From **7h**. Obtained as a wax (52.1 mg, 0.164 mmol, 82%).

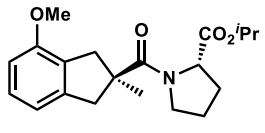


Chemical Formula: $C_{18}H_{23}NO_4$
Exact Mass: 317.1627
Molecular Weight: 317.3850

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.15 (t, *J* = 7.8 Hz, 1H), 6.82 (d, *J* = 7.8 Hz, 1H), 6.68 (d, *J* = 7.8 Hz, 1H), 4.54 (dd, *J* = 8.5, 4.8 Hz, 1H), 3.82 (s, 3H), 3.72 (s, 3H), 3.77-3.63 (m, 2H), 3.61 (d, *J* = 16.2 Hz, 1H), 3.38 (d, *J* = 16.4 Hz, 1H), 2.94 (d, *J* = 16.4 Hz, 1H), 2.87 (d, *J* = 16.2 Hz, 1H), 2.22-2.13 (m, 1H), 2.12- 2.04 (m, 1H), 2.01- 1.86 (m, 2H), 1.36 (s, 3H)
^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) 176.1, 173.4, 156.4, 143.1, 128.6, 128.2, 117.2, 108.1, 60.6, 55.3, 52.2, 49.6, 47.8, 44.8, 40.7, 28.3, 25.9, 25.4
IR (neat)**:** ν (cm^{-1}) 2953, 1743, 1623, 1401, 1264, 1173, 1075, 766
HRMS (ESI): Calcd for $C_{18}H_{23}NNaO_4$ $[M+Na]^+$: 340.1519, found 340.1520
Rf = 0.25 in a 60:40 mixture of pentane and ethyl acetate
HPLC separation: with L^2 Chiralpak® IA; 95:5 (n-heptane/i-PrOH), 1.0 ml.min^{-1}, 205 nm, tr(major) = 22.2 min, tr(minor) = 25.8 min, 64:36 e.r.
With L^1 Chiralpak® IA; 95:5 (n-heptane/i-PrOH), 1.0 ml.min^{-1}, 205 nm, tr(major) = 22.2 min, tr(minor) = 25.9 min, 83:17 e.r.

isopropyl ((S)-4-methoxy-2-methyl-2,3-dihydro-1H-indene-2-carbonyl)-L-prolinate (8i):

From **7i**. Obtained as a wax (56.7 mg, 0.164 mmol, 82%).



Chemical Formula: $C_{20}H_{27}NO_4$
Exact Mass: 345.1940
Molecular Weight: 345.4390

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.15 (t, *J* = 7.8 Hz, 1H), 6.81 (d, *J* = 7.8 Hz, 1H), 6.68 (d, *J* = 7.8 Hz, 1H), 5.03 (hept, *J* = 6.2 Hz, 1H), 4.49 (dd, *J* = 8.6, 4.8 Hz, 1H), 3.81 (s, 3H), 3.76-3.60 (m, 2H), 3.60 (d, *J* = 16.2 Hz, 1H), 3.39 (d, *J* = 16.4 Hz, 1H), 2.94 (d, *J* = 16.4 Hz, 1H), 2.86 (d, *J* = 16.2 Hz, 1H), 2.21-2.11 (m, 1H), 2.12-2.00 (m, 1H), 1.99-1.83 (m, 2H), 1.35 (s, 3H), 1.26 (d, *J* = 6.2 Hz, 3H), 1.19 (d, *J* = 6.2 Hz, 3H)

^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) 175.9, 172.3, 156.4, 143.2, 128.6, 128.2, 117.2, 108.1, 68.3, 61.0, 55.3, 49.7, 47.8, 44.7, 40.7, 28.3, 25.9, 25.4, 21.9, 21.8

IR (neat)**:** ν (cm^{-1}) 2977, 1735, 1625, 1401, 1264, 1185, 1107, 1076, 767

HRMS (ESI): Calcd for $C_{20}H_{27}NNaO_4$ $[M+Na]^+$: 368.1832, found 368.1834

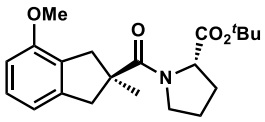
Rf = 0.27 in a 70:30 mixture of pentane and ethyl acetate

HPLC separation: with L^2 Chiralpak® IA; 95:5 (n-heptane/i-PrOH), 1.0 $ml.min^{-1}$, 205 nm, tr(major) = 14.8 min, tr(minor) = 18.3 min, 66:34 e.r.

With L^1 Chiralpak® IA; 95:5 (n-heptane/i-PrOH), 1.0 $ml.min^{-1}$, 205 nm, tr(major) = 14.8 min, tr(minor) = 18.3 min, 87:13 e.r.

tert-butyl ((S)-4-methoxy-2-methyl-2,3-dihydro-1H-indene-2-carbonyl)-L-prolinate (8j):

From **7j**. Obtained as a wax (60.4 mg, 0.168 mmol, 84%).



Chemical Formula: $C_{21}H_{29}NO_4$
Exact Mass: 359.2097
Molecular Weight: 359.4660

Description of major diastereoisomer:

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.14 (t, *J* = 7.8 Hz, 1H), 6.81 (d, *J* = 7.8 Hz, 1H), 6.67 (d, *J* = 7.8 Hz, 1H), 4.42 (dd, *J* = 8.5, 4.8 Hz, 1H), 3.81 (s, 3H), 3.75-3.56 (m, 2H), 3.61 (d, *J* = 16.3 Hz, 1H), 3.38 (d, *J* = 16.4 Hz, 1H), 2.94 (d, *J* = 16.4 Hz, 1H), 2.86 (d, *J* = 16.3 Hz, 1H), 2.19-2.09 (m, 1H), 2.11-1.98 (m, 1H), 1.96-1.82 (m, 2H), 1.44 (s, 9H), 1.35 (s, 3H)

^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) 175.7, 172.0, 156.4, 143.2, 128.7, 128.1, 117.2, 108.1, 80.9, 61.5, 55.3, 49.7, 47.7, 44.8, 40.7, 28.3, 28.1, 25.9, 25.4

IR (neat)**:** ν (cm^{-1}) 2973, 1735, 1625, 1151, 1076, 766

HRMS (ESI): Calcd for $C_{21}H_{29}NNaO_4$ $[M+Na]^+$: 382.1989, found 382.1988

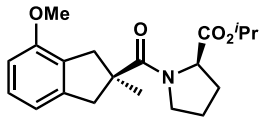
Rf = 0.33 in a 70:30 mixture of pentane and ethyl acetate

HPLC separation: with L^2 Chiralpak® IA; 95:5 (n-heptane/i-PrOH), 1.0 $ml.min^{-1}$, 205 nm, tr(major) = 11.0 min, tr(minor) = 14.6 min, 62:38 e.r.

With L^1 Chiralpak® IA; 95:5 (n-heptane/i-PrOH), 1.0 $ml.min^{-1}$, 205 nm, tr(major) = 10.8 min, tr(minor) = 14.6 min, 83:17 e.r.

isopropyl ((S)-4-methoxy-2-methyl-2,3-dihydro-1H-indene-2-carbonyl)-D-prolinate (8k):

From **7k**. Obtained as a wax (56.0 mg, 0.162 mmol, 81%).



Chemical Formula: $C_{20}H_{27}NO_4$
Exact Mass: 345.1940
Molecular Weight: 345.4390

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.15 (t, *J* = 7.8 Hz, 1H), 6.82 (d, *J* = 7.8 Hz, 1H), 6.68 (d, *J* = 7.8 Hz, 1H), 5.04 (hept, *J* = 6.2 Hz, 1H), 4.49 (dd, *J* = 8.6, 4.8 Hz, 1H), 3.81 (s, 3H), 3.76-3.60 (m, 2H), 3.61 (d, *J* = 16.2 Hz, 1H), 3.33 (d, *J* = 16.4 Hz, 1H), 2.95 (d, *J* = 16.4 Hz, 1H), 2.86 (d, *J* = 16.2 Hz, 1H), 2.21-2.11 (m, 1H), 2.12-2.00 (m, 1H), 1.99-1.83 (m, 2H), 1.37 (s, 3H), 1.26 (d, *J* = 6.2 Hz, 3H), 1.21 (d, *J* = 6.2 Hz, 3H)

^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) 175.9, 172.2, 156.3, 143.2, 128.5, 128.2, 117.2, 108.0, 68.3, 60.9, 55.2, 49.9, 47.8, 45.0, 40.3, 28.3, 25.8, 25.1, 21.9, 21.8

IR (neat)**:** ν (cm^{-1}) 2977, 1735, 1625, 1401, 1264, 1185, 1107, 1076, 767

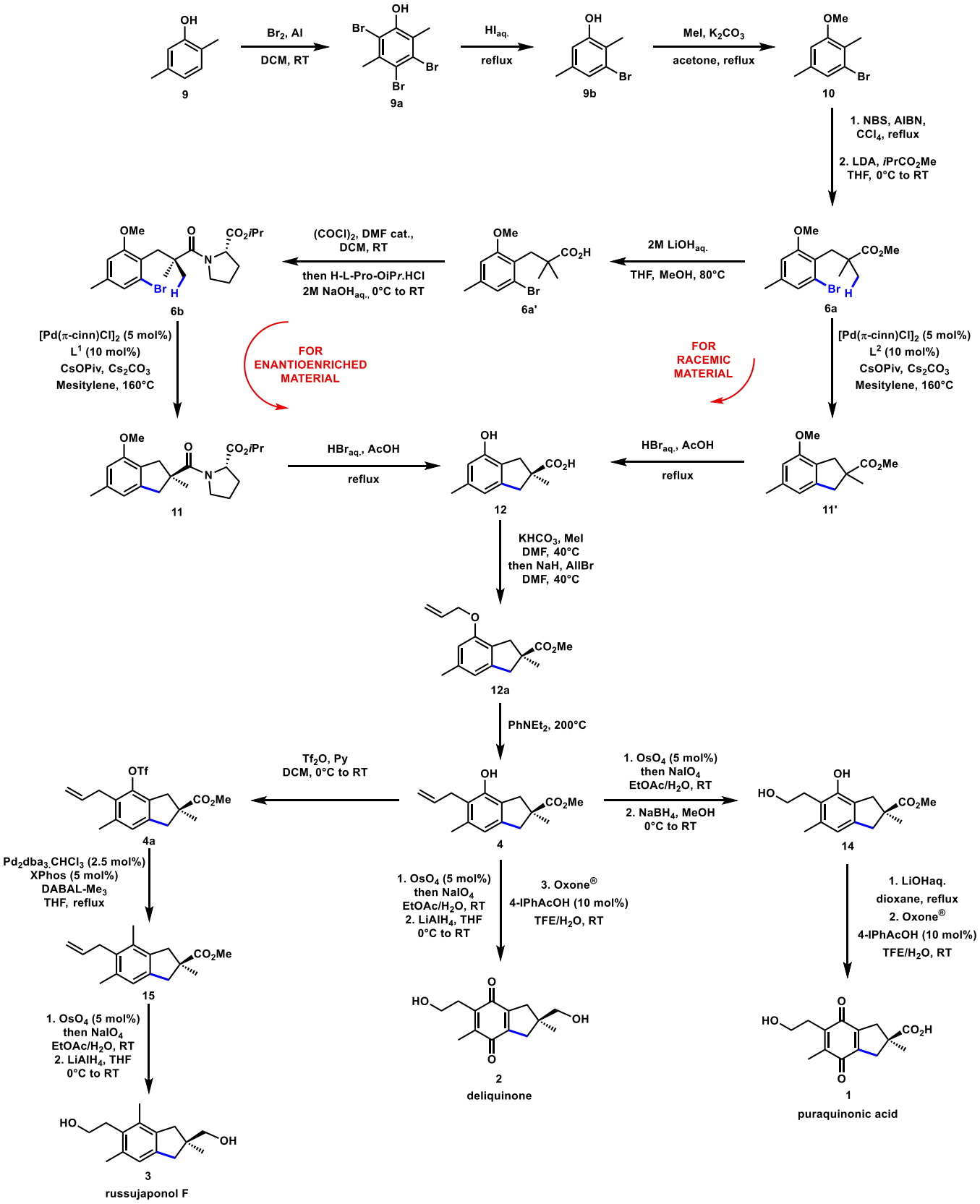
HRMS (ESI): Calcd for $C_{20}H_{27}NNaO_4$ $[M+Na]^+$: 368.1836, found 368.1834

Rf = 0.27 in a 70:30 mixture of pentane and ethyl acetate

HPLC separation: with L^2 Chiralpak® IA; 95:5 (n-heptane/i-PrOH), 1.0 $ml.min^{-1}$, 205 nm, tr(minor) = 14.6 min, tr(major) = 16.0 min, 36:64 e.r.

With L^1 Chiralpak® IA; 95:5 (n-heptane/i-PrOH), 1.0 $ml.min^{-1}$, 205 nm, tr(major) = 14.6 min, tr(minor) = 16.6 min, 63:37 e.r.

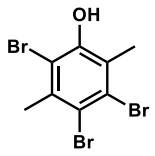
Experimental procedures - synthesis of russujaponol F, deliquinone and puraquinonic acid



Scheme S2: Route for synthesis of racemic and enantioenriched russujaponol F, deliquinone and puraquinonic acid.

2,4,5-tribromo-3,6-dimethylphenol (9a):

A modification of the procedure of Gould[6] was used. Aluminium (4.01 g, 0.15 mol, 0.45 equiv) was cautiously added in small portions to bromine (100 mL, 1.94 mol, 5.8 equiv) cooled to 0°C, and the mixture was stirred for 20 min. A solution of 2,5-dimethylphenol (**9**) (40.3 g, 330 mmol) in DCM (200 mL) was added over 2 h, and the mixture was stirred for additional 2 h at 0°C (Caution! a copius amount of HBr is evolved in this reaction which can be trapped by a water trap connected to an aqueous sodium carbonate scrubber). The reaction was then diluted at 0°C with DCM (200 mL) and water (200 mL). Then 5% aqueous $NaHSO_3$ was added until the colour of bromine disappear. The phases were separated and the aqueous layer was extracted twice with DCM, the combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure to yield 2,4,5-tribromo-3,6-dimethylphenol (115 g, 320 mmol) as a white solid which was used in the next step without futher purification. Spectroscopic data are consistent with those previously reported.[6]

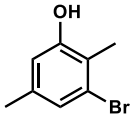


Chemical Formula: $C_8H_7Br_3O$
Exact Mass: 355.8047
Molecular Weight: 358.8550

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 5.83 (s, 1H), 2.66 (s, 3H), 2.47 (s, 3H)
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 149.9, 136.2, 128.2, 125.3, 118.4, 112.7, 26.5, 19.1
IR (neat)**:** ν (cm^{-1}) 3491, 1365, 1444, 1032, 654
HRMS (ESI): Calcd for $C_8H_6{}^{79}Br_3O$ $[M-H]^-$: 354.7974, found 354.7976
Mp = 179-182°C
Rf = 0.39 in a 90:10 mixture of pentane and ethyl acetate

3-bromo-2,5-dimethylphenol (9b):

A modification of the procedure of Gould[6] was used. A suspension of the **9a** (115 g, 320 mmol) in aqueous HI (57%, 250 mL) was heated at reflux under argon for 16 h and cooled. TBME (500 mL) was added, and at 0°C under stirring, $NaHSO_3$ (40%, 900 mL) was added dropwise. The layers were separated and the aqueous layer was extracted twice with TBME (300 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield **9b** (54.7 g, 272 mmol) nearly pure as a light brown solid which was used in the next step without futher purification. Spectroscopic data are consistent with those previously reported.[6]

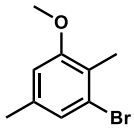


Chemical Formula: C_8H_9BrO
Exact Mass: 199.9837
Molecular Weight: 201.0630

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.98 (s, 1H), 6.54 (s, 1H), 4.73 (s, 1H), 2.29 (s, 3H), 2.24 (s, 3H)
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 154.1, 137.8, 125.8, 125.7, 121.3, 115.1, 20.78, 15.3
IR (neat)**:** ν (cm^{-1}) 3306, 2921, 1399, 1272, 1124, 1007, 814
HRMS (ESI): Calcd for $C_8H_8{}^{79}BrO$ $[M-H]^-$: 198.9764, found 198.9765
Mp = 85-88°C
Rf = 0.29 in a 85:15 mixture of pentane and ethyl acetate

1-bromo-3-methoxy-2,5-dimethylbenzene (10):

9b (54.4 g, 271 mmol) was dissolved in acetone (500 mL), then potassium carbonate (56.0 g, 405 mmol, 1.5 equiv) and methyl iodide (51.0 mL, 115 g, 810 mmol, 3.0 equiv) were added. The resulting dark brown mixture was stirred under reflux for 24h, during this period, after 12h, another equivalent of methyl iodide (16.0 mL, 270 mmol, 1.0 equiv) was added. The dark brown suspension was concentrated carefully under reduced pressure. The residue was diluted with diethyl ether (700 mL) and water (500 mL) and the layers were separated. The aqueous phase was extracted twice with diethyl ether (200 mL). The combined organic phases were washed twice with water (200 mL), then with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was obtained as a brown liquid which was distilled under reduced pressure to give **10** as a colorless liquid (53.47 g, 249 mmol, 76% over 3 steps). Spectroscopic data are consistent with those previously reported.[6]

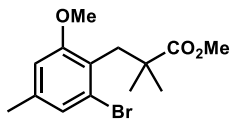


Chemical Formula: $C_9H_{11}BrO$
Exact Mass: 213.9993
Molecular Weight: 215.0900

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.00 (s, 1H), 6.59 (s, 1H), 3.81 (s, 3H), 2.30 (s, 3H), 2.27 (s, 3H)
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 158.2, 137.4, 125.6, 125.0, 123.8, 110.4, 55.9, 21.3, 15.4
IR (neat)**:** ν (cm^{-1}) 2925, 1264, 1144, 1046, 828
GCMS (EI): m/z for $C_9H_{11}{}^{79}BrO$ $[M]^{+\bullet}$: 214
Bp = 54-59°C at 0.1 mbar
Rf = 0.53 in a 95:5 mixture of pentane and ethyl acetate

methyl 3-(2-bromo-6-methoxy-4-methylphenyl)-2,2-dimethylpropanoate (6a):

10 (3.50 g, 16.3 mmol) was disolved in tetrachloromethane (20mL) and N-bromosuccinimide (3.77 g, 21.2 mmol, 1.32 equiv) was added followed by AIBN (321 mg, 1.86 mmol, 12 mol%). The resulting light yellow suspension was stirred under refluxed overnight. The reaction mixture was cooled in an ice bath, filtered and washed with a minimal amount of cold DCM. The filtrate was concentrated under reduced pressure to give an orange oil which was used without futher purification.
A solution of LDA (25.3 mmol, 1.55 equiv) in THF (25 mL) was prepared from freshly distillated diisopropylamine (25.3 mmol, 1.55 equiv) and 2.5 M (titrated) *n*-BuLi in hexane (10.1 mL, 25.3 mmol, 1.55 equiv), mixed for 15 min at 0°C. To the LDA solution, methyl isobutyrate (24.5 mmol, 1.5 equiv) was added dropwise at 0°C and the mixture was stirred at 0°C for 45 min. Freshly prepared crude 3-Bromo-2- bromomethyl-5-methyl-methoxybenzene from the previous step was diluted in THF (16 mL) and added slowly to the LDA solution at 0°C. The mixture was slowly warmed to room temperature and stirred for 16 h. The reaction was quenched at 0°C with water (30 mL). The mixture was extracted three times with diethyl ether (30 mL), the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and then concentrated in vacuo to give the crude ester. The crude materail was purified by flash column chromatography to yield **6a** as a colorless oil, which crystallize on standing (3.85 g, 12.2 mmol, 75% yield).



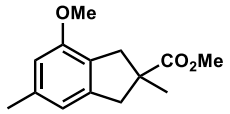
Chemical Formula: $C_{14}H_{19}BrO_3$
Exact Mass: 314.0518
Molecular Weight: 315.2070

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.00 (s, 1H), 6.57 (s, 1H), 3.72 (s, 3H), 3.66 (s, 3H), 3.13 (s, 2H), 2.29 (s, 3H), 1.20 (s, 6H)
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 178.4, 158.8, 138.6, 126.9, 125.6, 124.2, 110.4, 55.5, 51.8, 43.4, 39.0, 25.6, 21.3
IR (neat)**:** ν (cm^{-1}) 2968, 1719, 1266, 1148, 1042, 822
HRMS (ESI): Calcd for $C_{14}H_{20}{}^{79}BrNaO_3$ $[M+Na]^+$: 337.0410, found 337.0413

Mp = 63-65°C
Rf = 0.26 in a 90:10 mixture of pentane and ethyl acetate

methyl 4-methoxy-2,6-dimethyl-2,3-dihydro-1H-indene-2-carboxylate (11'):

In an oven dry catalysis tube, **6a** (506 mg, 1.15 mmol) was introduced. Then the tube was tranfer in glovebox and $[Pd(\pi\text{-cin})Cl]_2$ (29.8 mg, 57.5 µmol, 5 mol%), L^2 (67.7 mg, 115 µmol, 10 mol%), cesium pivalate (269 mg, 1.15 mmol, 1 equiv) and cesium carbonate (562 mg, 1.72 mmol, 1.5 equiv) were introduced and the tube was close with a septum. Outside of the glovebox, mesitylene (6 mL) was added. The reaction was stirred at room temperature for 10 min, then, under pressure of argon, the septum was rapidely exchange for a screw cap. The tube was then introduced in a 160°C preheated aluminium heating block and stirred at this temperature for 18 hours. After this period the reaction was coolded to room temperature, diluted with DCM (6 mL), filtered over a pad of celite (washed three times with 6 mL of DCM). The crude material was analyzed by GC-MS, then concentrated and purified by flash column chromatography to yield **11'** as a yellow liquid (361 mg, 1.00 mmol, 87%).



Chemical Formula: $C_{14}H_{18}O_3$
Exact Mass: 234.1256
Molecular Weight: 234.2950

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 6.64 (s, 1H), 6.50 (s, 1H), 3.80 (s, 7H), 3.71 (s, 6H), 3.45 (d, *J* = 16.0 Hz, 3H), 3.33 (d, *J* = 16.1 Hz, 3H), 2.79 (d, *J* = 16.1 Hz, 3H), 2.76 (d, *J* = 16.0 Hz, 3H), 2.33 (s, 8H), 1.36 (s, 6H)

^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) 178.4, 156.0, 143.3, 138.3, 125.9, 117.7, 109.4, 77.4, 77.2, 76.9, 55.3, 52.2, 49.5, 44.4, 40.8, 25.6, 21.8

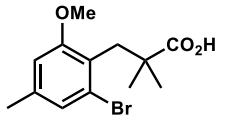
IR (neat)**:** ν (cm^{-1}) 2950, 2843, 1730, 1593, 1461, 1317, 1199, 1111, 1083, 829

HRMS (ESI): Calcd for $C_{14}H_{18}NaO_3$ $[M+Na]^+$: 257.1154, found 257.1148

Rf = 0.38 in a 95:5 mixture of pentane and ethyl acetate

3-(2-bromo-6-methoxy-4-methylphenyl)-2,2-dimethylpropanoic acid (6a'):

6a (3.5 g, 11.1 mmol) was dissolved in a mixture THF (20 mL), MeOH (20 mL) and 2M aqueous LiOH (20 ml). The reaction was then heat at 80°C for 6 hours. After cooling to room temperature, the organic solvents were removed under reduced pressure. The obtained aqueous solution was washed with diethyl ether, acidified to pH<0 and extracted three times with DCM. The combined organic layers were then dry over $MgSO_4$, filtered and concentrated under reduced pressure to yield **6a'** as a yellow solid, which was engaged in the next step without further purifications.



Chemical Formula: $C_{13}H_{17}BrO_3$
Exact Mass: 300.0361
Molecular Weight: 301.1800

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.01 (s, 1H), 6.57 (s, 1H), 3.69 (s, 3H), 3.19 (s, 2H), 2.29 (s, 3H), 1.22 (s, 6H).

^{13}C NMR (63 MHz, $CDCl_3$): δ (ppm) 184.9, 158.8, 138.7, 126.9, 125.6, 123.8, 110.4, 54.9, 43.2, 39.1, 25.2, 21.3

IR (neat)**:** ν (cm^{-1}) 2974, 2939, 1691, 1271, 1159, 1045, 830

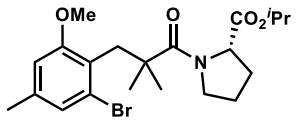
HRMS (ESI): Calcd for $C_{13}H_{17}{}^{79}BrNaO_3$ $[M+Na]^+$: 323.0253, found 323.0259

Mp = 100-103°C

Rf = 0.30 in a 70:30 mixture of pentane and ethyl acetate

isopropyl (3-(2-bromo-6-methoxy-4-methylphenyl)-2,2-dimethylpropanoyl)-L-prolinate (6b):

6a' was dissolved in dry DCM (110 mL), and then oxalyl chloride (1.1 equiv) was added, follow by few drops of DMF to initiate the reaction. After 1 hour of stirring at room temperature, the reaction was cooled to 0°C and H-L-Pro-O^{i}Pr•HCl (6.45 g, 33.3 mmol, 3 equiv) and 1M aqueous NaOH (110 mL, 110 mmol, 10 equiv) were added in one portion. The mixture was vigorously stirred for 16 hours with the ice bath warming to room temperature. The organic layer was then separated, washed with 2M HCl, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Crude material was then purified by flash column chromatography to yield **6b** as a colourless wax, which crystallize on standing (4.25 g, 9.66 mmol, 87%).



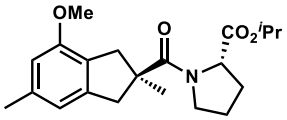
Chemical Formula: $C_{21}H_{30}BrNO_4$
Exact Mass: 439.1358
Molecular Weight: 440.3780

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 6.99 (s, 1H), 6.58 (s, 1H), 5.02 (sept, *J* = 6.3 Hz, 1H), 4.51-4.42 (m, 1H), 3.87-3.67 (m, 2H), 3.73 (s, 3H), 3.21 (d, *J* = 13.6 Hz, 1H), 3.13 (d, *J* = 13.6 Hz, 1H), 2.28 (s, 3H), 2.20-2.09 (m, 1H), 2.09-1.97 (m, 1H), 1.95-1.76 (m, 2H), 1.29 (s, 3H), 1.25 (d, *J* = 6.3 Hz, 3H), 1.21 (d, *J* = 6.3 Hz, 3H), 1.17 (s, 3H)
^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) 176.4, 172.5, 158.9, 138.6, 126.9, 125.7, 124.2, 110.5, 68.1, 61.6, 55.5, 48.5, 44.1, 36.5, 28.0, 26.4, 26.0, 25.4, 21.9, 21.8, 21.2

IR (neat)**:** ν (cm^{-1}) 2977, 2932, 1741, 1615, 1400, 1161, 1040, 833
HRMS (ESI): Calcd for $C_{21}H_{30}{}^{79}BrNNaO_4$ $[M+Na]^+$: 462.1250, found 462.1257
Mp = 75-79°C
Rf = 0.24 in a 70:30 mixture of pentane and ethyl acetate
$[\alpha]_D^{23}$ = - 39.4° (c = 1.00, $CHCl_3$)

isopropyl ((S)-4-methoxy-2,6-dimethyl-2,3-dihydro-1H-indene-2-carbonyl)-L-prolinate (11):

In an oven dry catalysis tube, **6b** (506 mg, 1.15 mmol) was introduced. Then the tube was tranfer in glovebox and $[Pd(\pi\text{-cin})Cl]_2$ (29.8 mg, 57.5 µmol, 5 mol%), L^1 (67.7 mg, 115 µmol, 10 mol%), cesium pivalate (269 mg, 1.15 mmol, 1 equiv) and cesium carbonate (562 mg, 1.72 mmol, 1.5 equiv) were introduced and the tube was close with a septum. Outside of the glovebox, mesitilene (6 mL) was added. The reaction was stirred at room temperature for 10 min, then, under pressure of argon, the septum was rapidely exchange for a screw cap. The tube was then introduced in a 160°C preheated aluminium heating block and stirred at this temperature for 18 hours. After this period the reaction was coolded to room temperature, diluted with DCM (6 mL), filtered over a pad of celite (washed three times with 6 mL of DCM). The crude material was analyzed by GC-MS, then concentrated and purified by flash column chromatography to yield **11** as a wax (361 mg, 1.00 mmol, 87%).



Chemical Formula: $C_{21}H_{29}NO_4$
Exact Mass: 359.2097
Molecular Weight: 359.4660

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 6.64 (s, 1H), 6.50 (s, 1H), 5.02 (sept, *J* = 6.2 Hz, 1H), 4.48 (dd, *J* = 8.6, 4.8 Hz, 1H), 3.79 (s, 3H), 3.78-3.59 (m, 2H), 3.56 (d, *J* = 16.3 Hz, 1H), 3.33 (d, *J* = 16.2 Hz, 1H), 2.89 (d, *J* = 16.2 Hz, 1H), 2.80 (d, *J* = 16.3 Hz, 1H), 2.33 (s, 3H), 2.21-2.10 (m, 1H), 2.09-2.00 (m, 1H), 1.97-1.81 (m, 2H), 1.34 (s, 3H), 1.25 (d, *J* = 6.2 Hz, 3H), 1.19 (d, *J* = 6.2 Hz, 3H)

^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) 175.9, 172.2, 156.1, 143.1, 138.2, 125.6, 117.7, 109.2, 68.2, 60.9, 55.2, 49.7, 47.7, 44.7, 40.4, 28.3, 25.9, 25.4, 21.9, 21.8, 21.8

IR (neat)**:** ν (cm^{-1}) 2976, 1736, 1626, 1400, 1185, 1108, 1085, 830

HRMS (ESI): Calcd for $C_{21}H_{29}NNaO_4$ $[M+Na]^+$: 382.1989, found 382.1994

Rf = 0.29 in a 70:30 mixture of pentane and ethyl acetate

HPLC separation: with L^2 Chiralpak® IA; 95:5 (n-heptane/i-PrOH), 1.0 $ml.min^{-1}$, 205 nm, tr(major) = 12.8 min, tr(minor) = 22.2 min, 66:34 e.r.

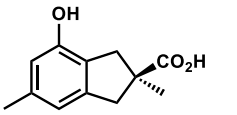
With L^1 Chiralpak® IA; 95:5 (n-heptane/i-PrOH), 1.0 $ml.min^{-1}$, 205 nm, tr(major) = 12.8 min, tr(minor) = 21.7 min, 85:15 e.r.

(S)-4-hydroxy-2,6-dimethyl-2,3-dihydro-1H-indene-2-carboxylic acid (12):

To **11** (931 mg, 2.59 mmol) was added glacial acetic acid (8 mL) and 48% aqueous hydrobromic acid (40 mL). The reaction mixture was refluxed for 2 hours. After this period, the reaction was diluted with water (50 mL) and extracted with DCM (3 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Two portions of toluene (10 mL) were added and evaporated to remove the last traces of AcOH. The crude material was purified by flash chromatography using cyclohexane/EtOAc (6:4) affording **12** (491 mg, 2.38 mmol, 92%) as a light yellow solid.

Then the product was enantioenriched by recrystallization as follow: the purified product was solubilized under heating in a mixture of $CHCl_3$ and cyclohexane (3:1) (proportion 40 mg/mL). The solution was then stored at room temperature for 4 days for crystallization. After separation, nearly racemic crystals (187 mg, 0.908 mmol, 35%) and concentrated enantioenriched mother liquor (304 mg, 1.47 mmol, 57%) were engaged in the next step to measure the enantiomeric ratio by HPLC using a chiral stationary phase.

Racemic material was prepared using the same procedure from racemic **11'** (890 mg, 3.80 mmol), glacial acetic acid (12 mL) and 48% aqueous hydrobromic acid (58 mL) to yield racemic **12** (682 mg, 3.31 mmol, 87%).



Chemical Formula: $C_{12}H_{14}O_3$
Exact Mass: 206.0943
Molecular Weight: 206.2410

^{1}H NMR (500 MHz, DMSO-d6): δ (ppm) 12.24 (bs, 1H), 9.03 (bs, 1H), 6.45 (s, 1H), 6.39 (s, 1H), 3.27 (d, *J* = 16.3 Hz, 1H), 3.16 (d, *J* = 16.3 Hz, 1H), 2.60 (d, *J* = 16.3 Hz, 1H), 2.63 (d, *J* = 16.3 Hz, 1H), 2.16 (s, 3H), 1.25 (s, 3H)

^{13}C NMR (126 MHz, DMSO-d6): δ (ppm) 178.7, 153.3, 143.2, 136.9, 123.9, 116.0, 113.7, 48.8, 43.8, 40.2, 25.1, 21.0

IR (neat)**:** ν (cm^{-1}) 3282, 2924, 1696, 1306, 1121, 835

HRMS (ESI): Calcd for $C_{12}H_{14}NaO_3$ $[M+Na]^+$: 229.0835, found 229.0838

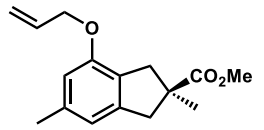
Mp = 160-163°C

Rf = 0.25 in a 60:40 mixture of pentane and ethyl acetate

$[\alpha]_D^{20}$ = + 6.9° (c = 0.57, $CHCl_3$)

methyl (S)-4-(allyloxy)-2,6-dimethyl-2,3-dihydro-1H-indene-2-carboxylate (12a):

12 (304 mg, 1.47 mmol) was dissolved in DMF (12 mL) and $KHCO_3$ (442 g, 4.41 mmol, 3 equiv) was added. The suspension was stirred for 10 minutes at room temperature, and then iodomethane (0.28 mL, 4.41 mmol, 3 equiv) was added. The mixture was stirred at 40°C until total consumption of starting material (approximatively 3 hours). To remove the excess of iodomethane, the reaction was heated to 65°C under a flow of argon for 15 min. After this period, the temperature was lowered to 40°C then NaH (106 mg, 4.41 mmol, 3 equiv) and allyl bromide (0.40 mL, 4.41 mmol, 3 equiv.) were added successively carefully. The reaction mixture was stirred for 30 min and then cooled with an ice bath, and then water (30 mL) was added. The reaction was extracted three times with DCM (15 mL); the combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography using cyclohexane/EtOAc (9:1) leading to **12a** as a light yellow oil (315 mg, 1.21 mmol, 82%).
Racemic material was prepared using the same procedure from racemic **12** (650 mg, 3.15 mmol), $KHCO_3$ (947 mg, 9.45 mmol, 3 equiv), iodomethane (0.59 mL, 9.45 mmol, 3 equiv), NaH (227 mg, 9.45 mmol, 3 equiv) and allyl bromide (0.82 mL, 9.45 mmol, 3 equiv) to yield racemic **12a** (730 mg, 2.80 mmol, 89%).

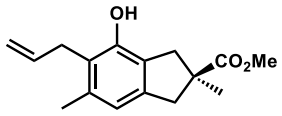


Chemical Formula: $C_{16}H_{20}O_3$
Exact Mass: 260.1412
Molecular Weight: 260.3330

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 6.65 (s, 1H), 6.50 (s, 1H), 6.06 (ddt, *J* = 17.2, 10.5, 5.1 Hz, 1H), 5.42 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.27 (dq, *J* = 10.5, 1.6 Hz, 1H), 4.53 (dt, *J* = 5.1, 1.6 Hz, 2H), 3.72 (s, 3H), 3.47 (d, *J* = 16.1 Hz, 1H), 3.37 (d, *J* = 16.1 Hz, 1H), 2.84 (d, *J* = 16.1 Hz, 1H), 2.77 (d, *J* = 16.1 Hz, 1H), 2.32 (s, 3H), 1.37 (s, 3H)
^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) 178.3, 155.1, 143.3, 138.1, 133.7, 126.3, 117.9, 117.1, 110.6, 68.7, 52.2, 49.5, 44.4, 40.8, 25.6, 21.8
IR (neat)**:** ν (cm^{-1}) 2926, 1730, 1591, 1315, 1112, 1073, 829
HRMS (ESI): Calcd for $C_{16}H_{20}NaO_3$ $[M+Na]^+$: 283.1305, found 283.1307
Rf = 0.25 in a 95:5 mixture of pentane and ethyl acetate
$[\alpha]_D^{23}$ = + 5.2° (c = 1.00, $CHCl_3$)
HPLC separation: Chiralpak® IA; 99:1 (n-heptane/i-PrOH), 1.0 ml.min^{-1}, 208 nm, tr(major) = 5.0 min, tr(minor) = 6.1 min, 96:4 e.r.

methyl (S)-5-allyl-4-hydroxy-2,6-dimethyl-2,3-dihydro-1H-indene-2-carboxylate (4):

A sealed tube charged with **12a** (204 mg, 0.784 mmol) and diethylaniline (3 mL) was heated under stirring at 200°C for 24 h. After this period, the reaction was poured into 1M HCl (30 mL) and extracted three times with DCM (30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography using cyclohexane/EtOAc (9:1) leading to **4** (163 mg, 0.626 mmol, 80%) as a yellow oil which solidified on standing.
Racemic material was prepared using the same procedure from racemic **12a** (700 mg, 2.69 mmol) to yield racemic **4** (616 mg, 2.37 mmol, 88%).



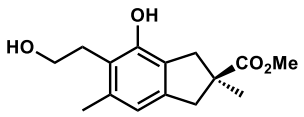
Chemical Formula: $C_{16}H_{20}O_3$
Exact Mass: 260.1412
Molecular Weight: 260.3330

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 6.65 (s, 1H), 5.95 (ddt, *J* = 17.1, 10.2, 5.9 Hz, 1H), 5.07 (dq, *J* = 10.2, 1.8 Hz, 1H), 5.05 (dq, *J* = 17.1, 1.8 Hz, 1H), 4.79 (s, 1H), 3.72 (s, 3H), 3.44 (d, *J* = 16.0 Hz, 1H), 3.40 (dt, *J* = 5.9, 1.8 Hz, 2H), 3.37 (d, *J* = 15.6 Hz, 1H), 2.77 (d, *J* = 16.0 Hz, 1H), 2.76 (d, *J* = 15.6 Hz, 1H), 2.26 (s, 3H), 1.38 (s, 3H)
^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) 178.2, 150.6, 1401.0, 136.8, 136.0, 124.6, 121.6, 118.9, 115.5, 52.3, 49.8, 44.3, 40.3, 30.8, 25.6, 20.0

IR (neat)**:** ν (cm^{-1}) 3464, 2929, 1712, 1195, 1113, 909
HRMS (ESI): Calcd for $C_{16}H_{20}NaO_3$ $[M+Na]^+$: 283.1305, found 283.1308
Mp = 65-67°C
Rf = 0.25 in a 85:15 mixture of pentane and ethyl acetate
$[\alpha]_D^{23}$ = + 10.8° (c = 1.00, $CHCl_3$)
HPLC separation: Chiralpak® IA; 97:3 (n-heptane/i-PrOH), 1.0 $ml.min^{-1}$, 208 nm, tr(minor) = 14.6 min, tr(major) = 16.8 min, 96:4 e.r.

methyl (S)- 4-hydroxy-5-(2-hydroxyethyl)-2,6-dimethyl-2,3-dihydro-1H-indene-2-carboxylate (14):

In a round bottom flask containing a stirred biphasic solution of **4** (102 mg, 0.392 mmol) in EtOAc (10 mL) and water (5 mL) was added OsO_4 (5.0 mg, 19.6 μmol, 5 mol%). After 5 minutes, $NaIO_4$ (210 mg, 0.98 mmol, 2.5 equiv) was added in two portions separated by 5 min. The solution was vigorously stirred for 3 h at room temperature. The layers were separated and the aqueous phase was extracted twice with ethyl acetate (6 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was diluted in MeOH (10 mL) and cooled to 0°C. After this, $NaBH_4$ (44.5 mg, 1.18 mmol, 3 equiv) was added and the reaction was allowed to reach room temperature. After 30 min, H_2O was added and the reaction was extracted three times with ethyl acetate (6 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography using cyclohexane/EtOAc (6:4) leading to **14** (78 mg, 0.295 mmol, 75%) as a light yellow oil.
Racemic material was prepared using the same procedure from racemic **4** (257 mg, 0.987 mmol), OsO_4 (12.5 mg, 49.4 μmol, 5 mol%), $NaIO_4$ (528 mg, 2.47 mmol, 2.5 equiv) and $NaBH_4$ (112 mg, 2.96 mmol, 3 equiv) to yield racemic **14** (195 mg, 0.737 mmol, 75%).

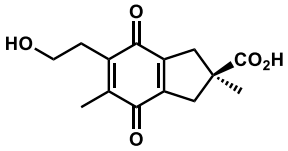


Chemical Formula: $C_{15}H_{20}O_4$
Exact Mass: 264.1362
Molecular Weight: 264.3210

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 6.63 (s, 1H), 3.95 – 3.86 (m, 2H), 3.71 (s, 3H), 3.42 (d, *J* = 16.0 Hz, 1H), 3.37 (d, *J* = 16.0 Hz, 1H), 2.88 (dd, *J* = 6.4, 4.6 Hz, 2H), 2.82 (d, *J* = 16.0 Hz, 1H), 2.75 (d, *J* = 16.0 Hz, 1H), 2.24 (s, 3H), 1.36 (s, 3H)
^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) 178.6, 151.9, 141.3, 136.1, 126.2, 123.1, 118.7, 64.0, 52.2, 49.6, 44.3, 40.9, 29.4, 25.6, 20.3
IR (neat)**:** ν (cm^{-1}) 3313, 2924, 1722, 1188, 1110, 905
HRMS (ESI): Calcd for $C_{15}H_{20}NaO_4$ $[M+Na]^+$: 287.1254, found 287.1256
Rf= 0.26 in a 70:30 mixture of pentane and ethyl acetate
$[\alpha]_D^{23}$ = + 1.5° (c = 1.00, $CHCl_3$)

(S)-(+)-puraquinonic acid (1):

Following a procedure of Yakura.[7] In a round bottom flask equipped with a condenser, **14** (66 mg, 0.25 mmol) and LiOH (157 mg, 3.75 mmol, 15 equiv) in 1,4-dioxane/H_2O (1:1, 6 mL) were refluxed for 1.5 h. After this period, the mixture was acidified with 1M HCl and extracted three times with EtOAc (15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was diluted in a mixture of 2,2,2-trifluoroethanol/H_2O (1:2, 3 mL). Then Oxone® (305 mg, 0.992 mmol, 4 equiv) and 4-iodophenoxyacetic acid (7.0 mg, 24.8 μmol, 10 mol%) were added at room temperature. The reaction mixture was stirred until total consumption of starting material (approximatively 1 hour) then EtOAc and water were added (5 mL each). The layers were separated and the aqueous layer was extracted with EtOAc, The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography using DCM/MeOH (93:7) leading to (S)-(+)-puraquinonic acid (**1**) (54.0 mg, 0.204 mmol, 82% over two steps) as a yellow oil.
Racemic material was prepared using the same procedure from racemic **14** (29.2 mg, 0.110 mmol), LiOH (39.7 mg, 1.66 mmol, 15 equiv), Oxone® (135.8 mg, 0.442 mmol, 4 equiv) and 4-iodophenoxyacetic acid (3.1 mg, 11.0 μmol, 10 mol%) to yield racemic puraquinonic acid (**1**) (25.1 mg, 0.095 mmol, 86%).



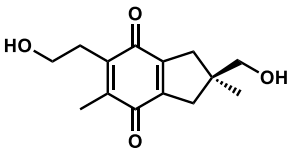
Chemical Formula: $C_{14}H_{16}O_5$
Exact Mass: 264.0998
Molecular Weight: 264.2770

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 3.76 (t, *J* = 6.4 Hz, 2H), 3.41-3.34 (m, 2H), 2.79 (t, *J* = 6.4 Hz, 2H), 2.77-2.71 (m, 2H), 2.07 (s, 3H), 1.42 (s, 3H)
^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) 186.4, 185.9, 181.7, 145.9, 145.5, 143.0, 141.5, 61.6, 47.1, 42.5, 42.4, 30.0, 25.8, 12.4
Spectroscopic data are consistent with those previously reported for synthetic material.[8]

IR (neat)**:** ν (cm^{-1}) 3394, 2925, 1706, 1221, 1172, 1103, 914
HRMS (ESI): Calcd for $C_{14}H_{16}NaO_5$ $[M+Na]^+$: 287.0890, found 287.0891
Rf = 0.12 in a 95:5 mixture of DCM and methanol
$[\alpha]_D^{23}$ = + 1.4° (c = 0.50, $CHCl_3$)
Reported value for the natural material (R): $[\alpha]_D^{22}$ = - 2.2° (c = 0.55, $CHCl_3$)[8]

(S)-(+)-deliquinone (2):

In a round bottom flask containing a stirred biphasic solution of **4** (114 mg, 0.438 mmol) in EtOAc (14 mL) and water (7 mL) was added OsO_4 (5.57 mg, 21.9 μmol, 5 mol%). After 5 minutes, $NaIO_4$ (234 mg, 1.10 mmol, 2.5 equiv) was added in two portions separated by 5 min. The solution was vigorously stirred for 3 h at room temperature. The layers were separated and the aqueous layer was extracted twice with EtOAc (8 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was diluted in dry THF (10 mL) and cooled to 0°C. After this, $LiAlH_4$ (49.9 mg, 1.31 mmol, 3 equiv) was added and the reaction was allowed to reach room temperature. After 1 h, H_2O was added and the reaction was extracted three times with ethyl acetate (8 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Then Following a procedure of Yakura.[7] The crude material was diluted in a mixture of 2,2,2-trifluoroethanol/H_2O (1:2, 9 mL). Then Oxone® (541 mg, 1.76 mmol, 4 equiv) and 4-iodophenoxyacetic acid (12.2 mg, 44.0 μmol, 10 mol%) were added at room temperature. The reaction mixture was stirred until total consumption of the starting material (approximatively 1 hour) then EtOAc and water were added (10 mL each). The layers were separated and the aqueous layer was extracted with EtOAc, The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography using DCM/MeOH (93:7) leading to (S)-(+)-deliquinone (**2**) (62.7 mg, 0.276 mmol, 62% over two steps) as a yellow oil.
Racemic material was prepared using the same procedure from racemic **4** (220 mg, 0.845 mmol), OsO_4 (11.1 mg, 43.7 μmol, 5 mol%), $NaIO_4$ (450 mg, 2.10 mmol, 2.5 equiv), $LiAlH_4$ (98.0 mg, 2.58 mmol, 3 equiv), Oxone® (1,04 g, 3.38 mmol, 4 equiv) and 4-iodophenoxyacetic acid (22.1 mg, 84.5 μmol, 10 mol%) to yield racemic deliquinone (**2**) (153 mg, 0.647 mmol, 76%).



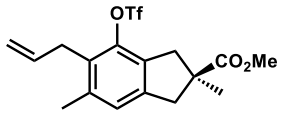
Chemical Formula: $C_{14}H_{18}O_4$
Exact Mass: 250.1205
Molecular Weight: 250.2940

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 3.74 (t, *J* = 6.5 Hz, 2H), 3.49 (s, 2H), 2.87-2.80 (m, 2H), 2.78 (t, *J* = 6.5 Hz, 2H), 2.53-2.47 (m, 2H), 2.06 (s, 3H), 1.75 (brs, 1H), 1.69 (brs, 1H), 1.16 (s, 3H)
^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) 187.0, 186.4, 147.2, 146.8, 142.8, 141.4, 70.2, 61.7, 43.0, 40.8, 40.7, 30.1, 25.0, 12.3
Spectroscopic data are consistent with those previously reported for natural material.[9]
IR (neat)**:** ν (cm^{-1}) 3395, 2925, 1644, 1249, 1033

HRMS (ESI): Calcd for $C_{14}H_{18}NaO_4$ $[M+Na]^+$: 273.1097, found 273.1095
Rf = 0.28 in a 95:5 mixture of DCM and methanol
$[\alpha]_D^{23}$ = + 0.9° (c = 1.00, $CHCl_3$)
Reported value for the natural material (R): $[\alpha]_D^{22}$ = - 0.5° (c = 0.6, $CHCl_3$)[9]

methyl (S)-5-allyl-2,6-dimethyl-4-(((trifluoromethyl)sulfonyl)oxy)-2,3-dihydro-1H-indene-2-carboxylate (4a):

To a solution of **4** (58.1 mg, 0.223 mmol) in DCM (1.2 mL), pyridine (54 µL, 0.669 mmol, 3 equiv) and trifluoromethanesulfonic anhydride (41 µL, 0.245 mmol, 1.1 equiv) were added. The reaction mixture was stirred a room temperature during 6 hours. The reaction was then concentrated and purified by flash column chromatographie to yield **4a** (80.9 mg, 0.206 mmol, 93%) as a colourless liquid.
Racemic material was prepared using the same procedure from racemic **4** (50 mg, 0.192 mmol), pyridine (47 µL, 0.576 mmol, 3 equiv) and trifluoromethanesulfonic anhydride (36 µL, 0.211 mmol, 1.1 equiv) to yield racemic **4a** (87.1 mg, 0.167 mmol, 87%).

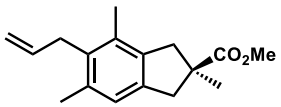


Chemical Formula: $C_{17}H_{19}F_3O_5S$
Exact Mass: 392.0905
Molecular Weight: 392.3892

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.03 (s, 1H), 5.83 (ddt, *J* = 17.1, 10.1, 5.8 Hz, 1H), 5.04 (dq, *J* = 10.1, 1.7 Hz, 1H), 4.89 (dq, *J* = 17.1, 1.7 Hz, 1H), 3.72 (s, 3H), 3.54 (d, *J* = 16.3 Hz, 1H), 3.49 (d, *J* = 16.1 Hz, 1H), 3.45 (dt, *J* = 5.8, 1.7 Hz, 2H), 2.95 (d, *J* = 16.3 Hz, 1H), 2.82 (d, *J* = 16.1 Hz, 1H), 2.30 (s, 2H), 1.37 (s, 3H)
^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) 177.3, 144.3, 142.9, 139.0, 134.4, 132.0, 129.2, 126.7, 118.7 (q, *J* = 319.8 Hz), 116.0, 52.4, 50.1, 44.1, 41.9, 31.2, 25.0, 19.9
^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -73.8
IR (neat)**:** ν (cm^{-1}) 2955, 1735, 1405, 1206, 1137, 817
HRMS (ESI): Calcd for $C_{17}H_{19}F_3NaO_5S$ $[M+Na]^+$: 415.0798, found 415.0795
Rf = 0.25 in a 95:5 mixture of pentane and ethyl acetate
$[\alpha]_D^{23}$ = + 4.0° (c = 1.09, $CHCl_3$)

methyl (S)-5-allyl-2,4,6-trimethyl-2,3-dihydro-1H-indene-2-carboxylate (15):

Following a procedure of Woodward.[10] In an oven dry catalysis tube, **4a** (80 mg, 0.204 mmol) was introduced. Then the tube was tranfer in glovebox and [Pd_2dba_3•$CHCl_3$] (5.3 mg, 5.1 µmol, 2.5 mol%) and Xphos (5.0 mg, 10.2 µmol, 5 mol%) were introduced and the tube was close with a septum. Outside of the glovebox, THF (2.5 mL) and DABAL-Me_3 (41.8 mg, 0.163 mmol, 0.8 equiv, as a solution in 0.8 mL of THF) were added. The septum was rapidely exchange for a screw cap. The tube was then introduced in a 75°C preheated aluminium heating block and stirred at this temperature for 4 hours. After this period the reaction was coolded to room temperature and quenched with 2M HCl (2 mL) and extracted three times with diethyl ether (3 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography to yield **15** as a colourless liquid (51.7 mg, 0.200 mmol, 98%).
Racemic material was prepared using the same procedure from racemic **4a** (50.2 mg, 0.128 mmol), [Pd_2dba_3•$CHCl_3$] (3.3 mg, 3.2 µmol, 2.5 mol%), Xphos (3.2 mg, 6.4 µmol, 5 mol%) and DABAL-Me_3 (26.3 mg, 0.102 mmol, 0.8 equiv) to yield racemic **15** (32.4 mg, 0.167 mmol, 98%).



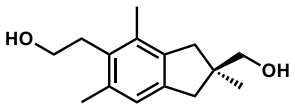
Chemical Formula: $C_{17}H_{22}O_2$
Exact Mass: 258.1620
Molecular Weight: 258.3610

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 6.88 (s, 1H), 5.88 (ddt, *J* = 17.1, 10.1, 5.7 Hz, 1H), 4.99 (dq, *J* = 10.1, 1.8 Hz, 1H), 4.88 (dq, *J* = 17.1, 1.8 Hz, 1H), 3.72 (s, 3H), 3.46 (d, J = 15.9 Hz, 1H), 3.40 (d, *J* = 15.9 Hz, 1H), 3.38 (dt, *J* = 5.7, 1.8 Hz, 3H), 2.79 (d, *J* = 15.9 Hz, 1H), 2.78 (d, *J* = 15.9 Hz, 1H), 2.27 (s, 3H), 2.18 (s, 3H), 1.37 (s, 3H)
^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) 178.5, 138.8, 138.3, 135.8, 135.3, 134.3, 132.7, 124.0, 114.9, 52.2, 49.1, 44.3, 43.7, 33.7, 25.8, 20.3, 16.0

IR (neat)**:** ν (cm^{-1}) 2931, 1732, 1208, 1112, 911
HRMS (ESI): Calcd for $C_{17}H_{22}NaO_2$ $[M+Na]^+$: 281.1512, found 281.1508
Rf = 0.33 in a 95:5 mixture of pentane and ethyl acetate
$[\alpha]_D^{23}$ = + 9.4° (c = 1.05, $CHCl_3$)

(S)-(+)-russujaponol F (3):

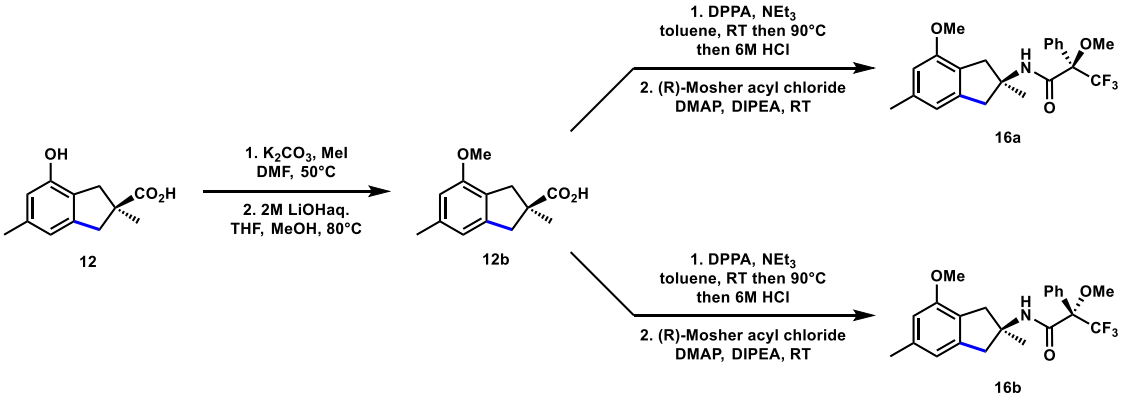
In a round bottom flask containing a stirred biphasic solution of **15** (51.7 mg, 0.200 mmol) in EtOAc (4 mL) and water (2 mL) was added OsO_4 (2.5 mg, 10.0 μmol, 5 mol%). After 5 minutes, $NaIO_4$ (107 mg, 0.500 mmol, 2.5 equiv) was added in two portions separated by 5 min. The solution was vigorously stirred for 3 h at room temperature. The layers were separated and the aqueous layer was extracted twice with EtOAc (5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was diluted in dry THF (5 mL) and cooled to 0°C. After this, $LiAlH_4$ (22.8 mg, 0.600 mmol, 3 equiv) was added and the reaction was allowed to reach room temperature overnight. After this period, H_2O was added and the reaction was extracted three times with ethyl acetate (5 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography to yield (S)-(+)-russujaponol F (**3**) as a colourless oil (39.8 mg, 0.170 mmol, 85%).
Racemic material was prepared using the same procedure from racemic **15** (20.5mg, 0.079 mmol), OsO_4 (1.0 mg, 4.0 μmol, 5 mol%), $NaIO_4$ (42.5 mg, 0.199 mmol, 2.5 equiv) and $LiAlH_4$ (9.1 mg, 0.238 mmol, 3 equiv) to yield racemic russujaponol F (**3**) (16.2 mg, 0.069 mmol, 87%).



Chemical Formula: $C_{15}H_{22}O_2$
Exact Mass: 234.1620
Molecular Weight: 234.3390

^{1}H NMR (400 MHz, C_5D_5N): δ (ppm) 6.90 (s, 1H), 5.76 (bs, 2H), 3.99 (t, *J* = 7.6 Hz, 2H), 3.75 (s, 2H), 3.18 (d, *J* = 15.9 Hz, 1H), 3.15 (t, *J* = 7.6 Hz, 2H), 3.09 (d, *J* = 15.8 Hz, 1H), 2.71 (d, *J* = 15.8 Hz, 1H), 2.60 (d, *J* = 15.9 Hz, 1H), 2.37 (s, 3H), 2.24 (s, 3H), 1.35 (s, 3H)
^{13}C NMR (126 MHz, C_5D_5N): δ (ppm) 140.9, 140.7, 135.3, 134.1, 133.3, 125.0, 70.3, 62.0, 45.4, 43.9, 43.1, 34.5, 25.6, 20.9, 16.5
Spectroscopic data are consistent with those previously reported for natural material.[11]
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.86 (s, 1H), 3.74 (t, *J* = 7.5 Hz, 2H), 3.52 (s, 2H), 2.95 (t, *J* = 7.5 Hz, 2H), 2.88 (d, *J* = 16.0 Hz, 1H), 2.84 (d, *J* = 16.0 Hz, 1H), 2.63 (d, *J* = 16.0 Hz, 1H), 2.59 (d, *J* = 16.0 Hz, 1H), 2.32 (s, 3H), 2.22 (s, 3H), 1.18 (s, 3H)
^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) 140.3, 139.8, 135.3, 133.2, 132.3, 124.4, 71.1, 62.1, 44.3, 43.1, 42.4, 32.9, 24.6, 20.5, 16.2
IR (neat)**:** ν (cm^{-1}) 3313, 2920, 2867, 1460, 1037
HRMS (ESI): Calcd for $C_{15}H_{22}NaO_2$ $[M+Na]^+$: 257.1512, found 257.1514
Rf = 0.23 in a 50:50 mixture of pentane and ethyl acetate
$[\alpha]_D^{23}$ = + 1.0° (c = 1.07, $CHCl_3$)
$[\alpha]_D^{20}$ = + 2.1° (c = 0.53, MeOH)
Reported value for the natural material (S): $[\alpha]_D^{25}$ = + 1.3° (c = 3.1, MeOH)[11]

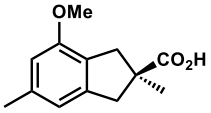
Determination of configuration – VCD and NOESY



Scheme S2: Route for synthesis of **12b**, **16a** and **16b**

(S)-4-methoxy-2,6-dimethyl-2,3-dihydro-1H-indene-2-carboxylic acid (12b):

12 (120 mg, 0.58 mmol) was dissolved in DMF (5 mL) and K_2CO_3 (401 mg, 2.9 mmol, 5 equiv) was added, the mixture was then stirred during 5 min at room temperature. After this period, methyl iodide (0.18 mL, 2.9 mmol, 5 equiv) was added in one portion and the reaction was stirred at 50°C during 2h. The reaction was then diluted with water, extracted with EtOAc and concentrated to yield **11'**, which was used in the next step without further purification. **11'** was dissolved in a mixture of THF (1.5 mL), MeOH (1.5 mL) and 2M aqueous LiOH (1.5 ml). The reaction was then heat at 80°C for 6 hours. After cooling to room temperature, the organic solvents were removed under reduced pressure. The obtained aqueous solution was washed with diethyl ether, acidified to pH<0 and extracted three times with DCM. The combined organic layers were then dry over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography to yield the corresponding pure **12b** (105 mg, 0.48 mmol, 82%) as a white solid.



Chemical Formula: $C_{13}H_{16}O_3$
Exact Mass: 220.1099
Molecular Weight: 220.2680

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 6.65 (s, 1H), 6.51 (s, 1H), 3.81 (s, 3H), 3.48 (d, *J* = 16.0 Hz, 1H), 3.39 (d, *J* = 16.1 Hz, 1H), 2.81 (d, *J* = 16.1 Hz, 1H), 2.79 (d, *J* = 16.0 Hz, 1H), 2.33 (s, 3H), 1.41 (s, 3H)
^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) 184.3, 156.0, 143.1, 138.4, 125.8, 117.7, 109.4, 55.3, 49.5, 44.2, 40.6, 25.3, 21.8
IR (neat)**:** ν (cm^{-1}) 2969, 2913, 2852, 1693, 1589, 1461, 1311, 1229, 1078, 825

HRMS (ESI): Calcd for $C_{13}H_{16}NaO_3$ $[M+Na]^+$: 243.0992, found 243.0993
Mp = 98-101°C
Rf = 0.26 in a 80:20 mixture of pentane and ethyl acetate
$[\alpha]_D^{20}$ = + 3.6° (c = 0.38, $CHCl_3$)

VCD experiments:

IR and vibrational circular dichroism (VCD) spectra were recorded on a Bruker PMA 50 accessory coupled to a Tensor 27 Fourier transform infrared spectrometer. A photoelastic modulator (Hinds PEM 90) set at l/4 retardation was used to modulate the handedness of the circular polarized light. Demodulation was performed by a lock-in amplifier (SR830 DSP). An optical low-pass filter (< 1800 cm^{-1}) in front of the photoelastic modulator was used to enhance the signal/noise ratio. A solution of 8 mg in 200 µl $CDCl_3$ of **12b** was prepared and measured in a transmission cell equipped with CaF_2 windows and a 200 mm spacer. The VCD spectrum of the pure solvent served as the reference and was subtracted from the VCD spectrum of the compound in order to eliminate artefacts. For both the sample and the reference, ca. 40'000 scans at 4 cm^{-1} resolution were averaged.

Calculations:

Density functional theory (DFT) as implemented in Gaussian09 was used to study the conformation and to calculate the corresponding IR and VCD spectra. The calculations were performed using the b3pw91 functional and a 6-31+G(d,p) basis set. The solvent was considered with a polarizable continuum model for chloroform, as implemented in Gaussian09, Revision C.01.[12] Prior to the calculation of the spectra all degrees of freedom were completely relaxed. IR and VCD spectra were constructed from calculated dipole and rotational strengths assuming Gaussian band shape with a half-width at half-maximum of 4 cm^{-1}. Frequencies were scaled by a factor of 0.97. To calculate the Boltzmann distribution of the different conformers a thermal free energy correction was applied.

Conformational search:

A systematic conformation search of **12b** was done. Conformational degrees of freedom are the orientation of the methyl group (methoxy), the orientation of the acid group and the five-membered ring, which is not planar. For the methoxy group only one conformation was considered because the other conformations are high up in energy and therefore not populated at room temperature. In total six conformers were found (Figure S1) differing in the orientation of the acid group and the conformation at the five-membered ring.

Assignment of absolute configuration:

As is evident from the comparison of the calculated VCD spectra of the individual conformers (Figure S4) the sign of many bands depends on the conformation. Therefore the calculated VCD spectrum depends on the Boltzmann weights and hence the relative free energy of the conformers, which is challenging to calculate accurately. However, there are some bands that have the same sign for all conformers (marked in Figures S4 and S5). Based on these bands and the overall shape of the VCD spectrum the absolute configuration can be assigned. The comparison between experiment and calculations show that the sample analysed has the same absolute configuration as the enantiomer considered in the calculations. Therefore we can assign the absolute configuration as the (S)-enantiomer.

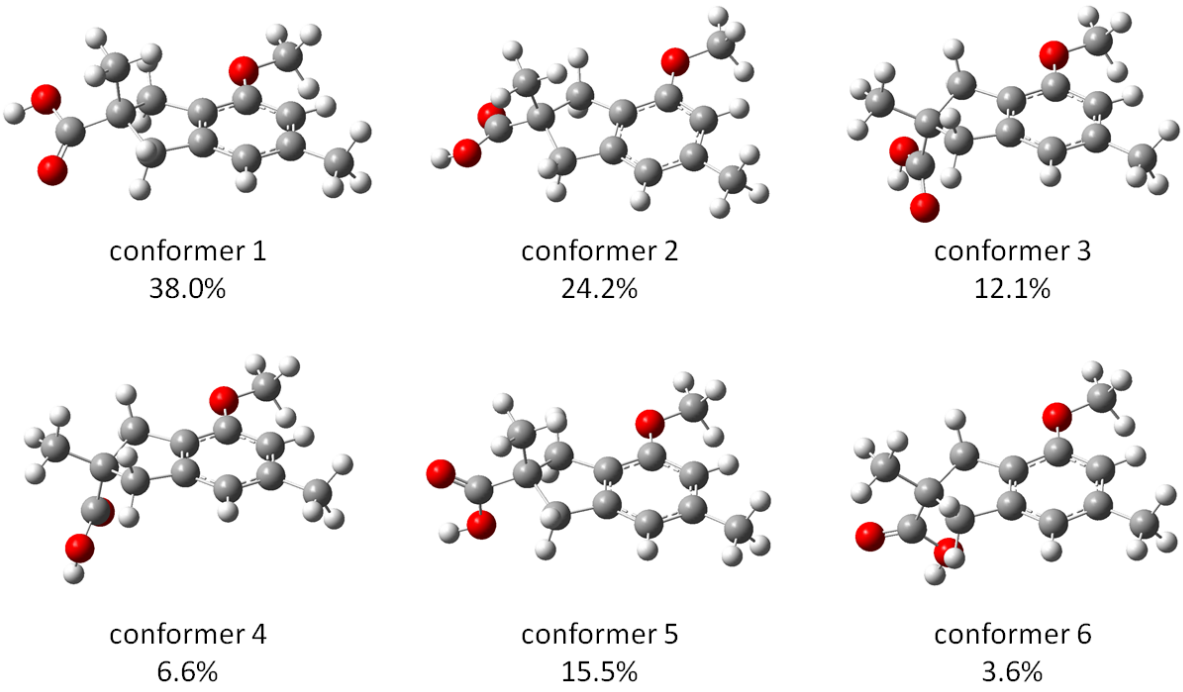


Figure S1: Six conformers of **12b** found by the systematic conformational search. The numbers show the fractions of the respective conformer according to a Boltzmann distribution at room temperature.

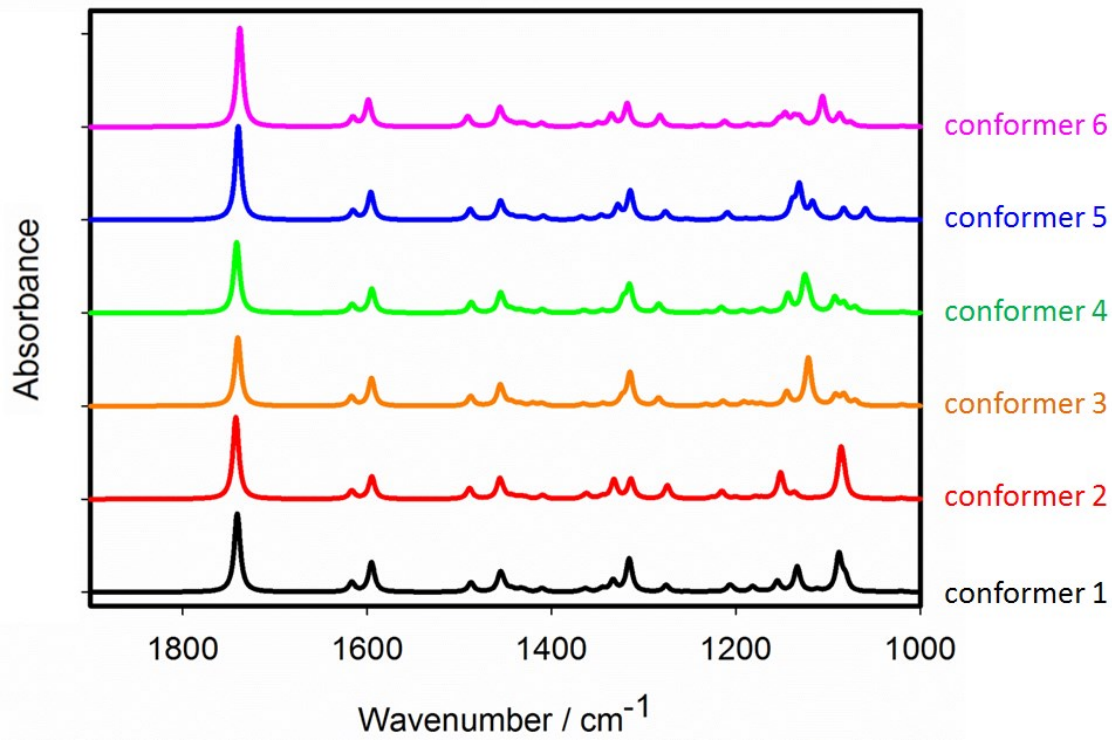


Figure S2: Calculated infrared spectra for the six conformers. Frequencies are scaled by 0.97.

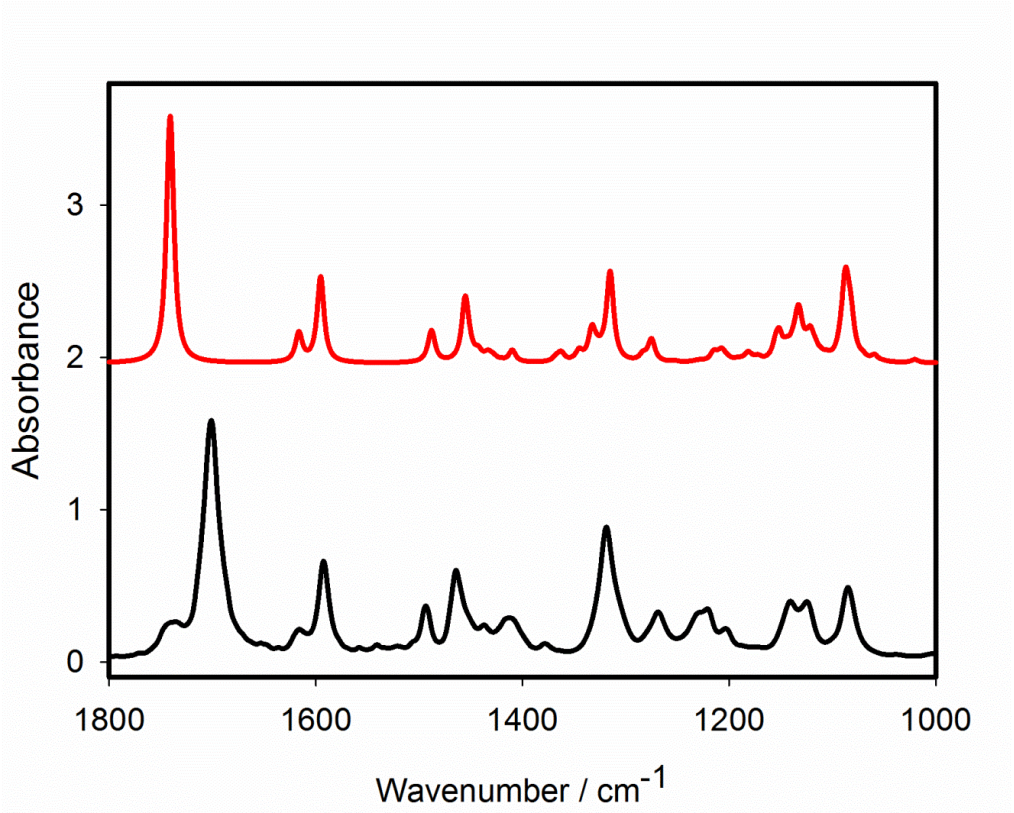


Figure S3: Comparison between experimental (black) and calculated (red) infrared spectra of **12b**. The calculated spectrum is the linear combination (Boltzmann weighted) of the spectra of the conformers. Frequencies are scaled by 0.97 for the calculated spectrum.

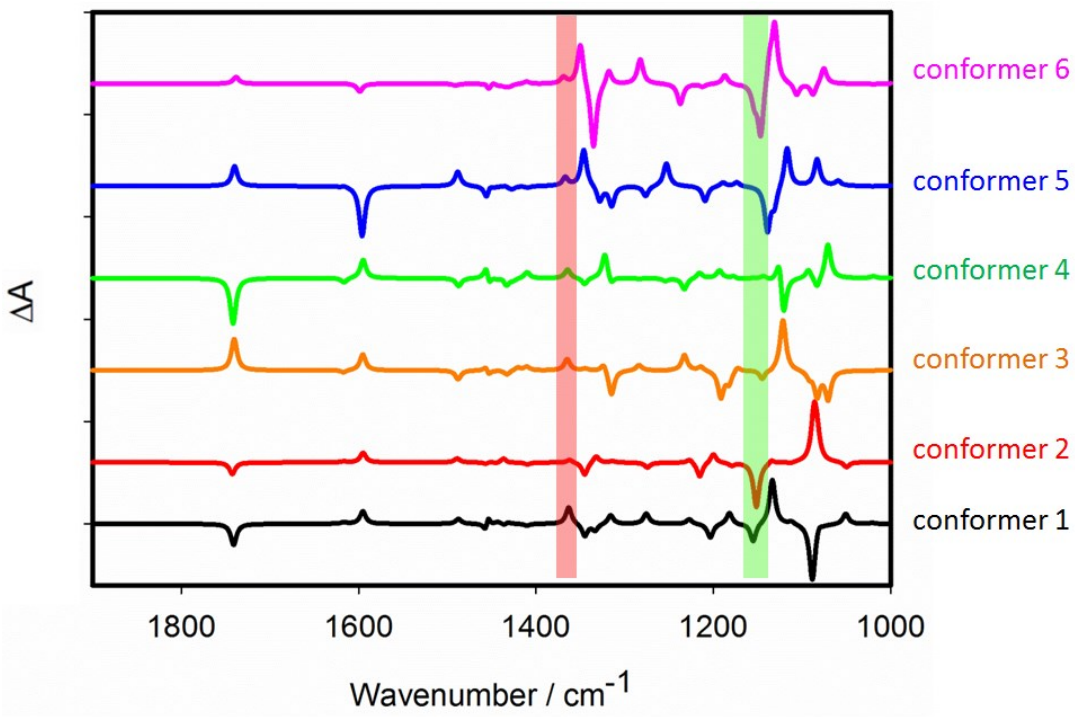


Figure S4: Calculated VCD spectra for the six conformers. Frequencies are scaled by 0.97. The green and red areas mark bands that show the same sign for all conformers. These bands are particularly meaningful for the assignment of the absolute configuration because the sign does not depend on distribution of conformers (Boltzmann factors).

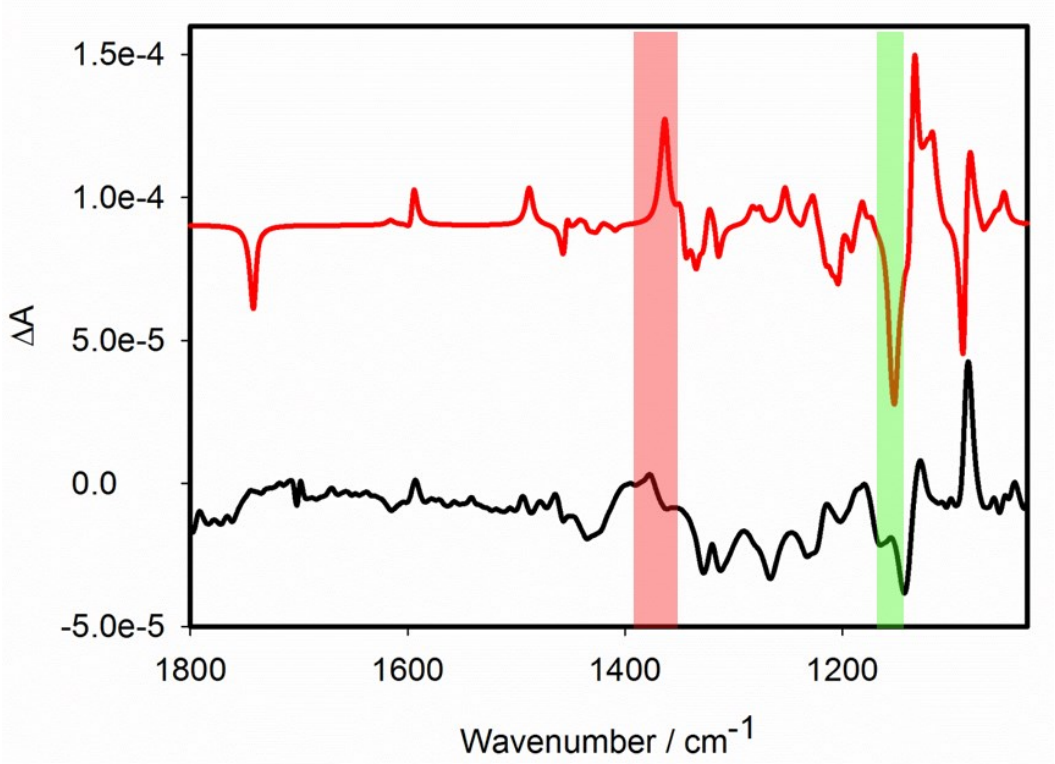
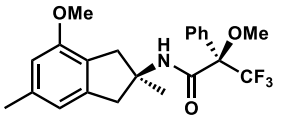


Figure S5: Comparison between experimental (black) and calculated (red) VCD spectra of **12b**. The calculated spectrum is the linear combination (Boltzmann weighted) of the spectra of the conformers. Frequencies are scaled by 0.97 for the calculated spectrum. The green and red areas mark bands that show the same sign for all conformers (see Figure S4).

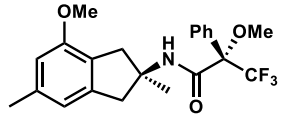
(R)-3,3,3-trifluoro-2-methoxy-N-((S)-4-methoxy-2,6-dimethyl-2,3-dihydro-1H-inden-2-yl)-2-phenylpropanamideacid (16a) and (S)-3,3,3-trifluoro-2-methoxy-N-((S)-4-methoxy-2,6-dimethyl-2,3-dihydro-1H-inden-2-yl)-2-phenylpropanamideacid (16b):

12b (100 mg, 0.46 mmol) was suspended in toluene (4.0 mL). Triethylamine (77 µL, 0.552 mmol, 1.2 equiv) was added, followed by the addition of diphenylphosphonic azide (103 µL, 0.46 mmol, 1 equiv). The mixture was stirred at room temperature for 2 hours. Then the mixture was heated at 90°C for 1 hour. The mixture was cooled down and poured into ice-cold 6M aqueous HCl (4 mL) and stirred overnight. The aqueous layer was collected, cooled down at 0°C, basified with 2M NaOH, and extracted three times with DCM (5 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the corresponding crude amine (60.1 mg, 0.314 mmol, 68%). After NMR analysis, the crude amine was considered enought pure to be engaged in the next step.
(R)- or (S)-Mosher acid (16.7 mg, 0.072 mmol, 1.1 equiv) was dissolved in dry DCM (0.85 mL), then oxalyl chloride (7 µL, 0.075 mmol, 1.15 equiv) was added, follow by one drops of a 10% solution of DMF in DCM to initiate the reaction. After 1 hour of stirring at room temperature, crude amine (12.4 mg, 0.065 mmol), NEt_3 (34 µL, 0.195 mmol, 3 equiv) and a crystal of DMAP were added. The mixture was stirred for 16 hours at room temperature. The reaction was then concentrated under reduced pressure and purified by flash column chromatography to yield the corresponding pure **16a** (15.6 mg, 0.038 mmol, 59%) and **16b** (18.9 mg, 0.046 mmol, 71%) amides as colourless wax.



Chemical Formula: $C_{22}H_{24}F_3NO_3$
Exact Mass: 407.1708
Molecular Weight: 407.4332

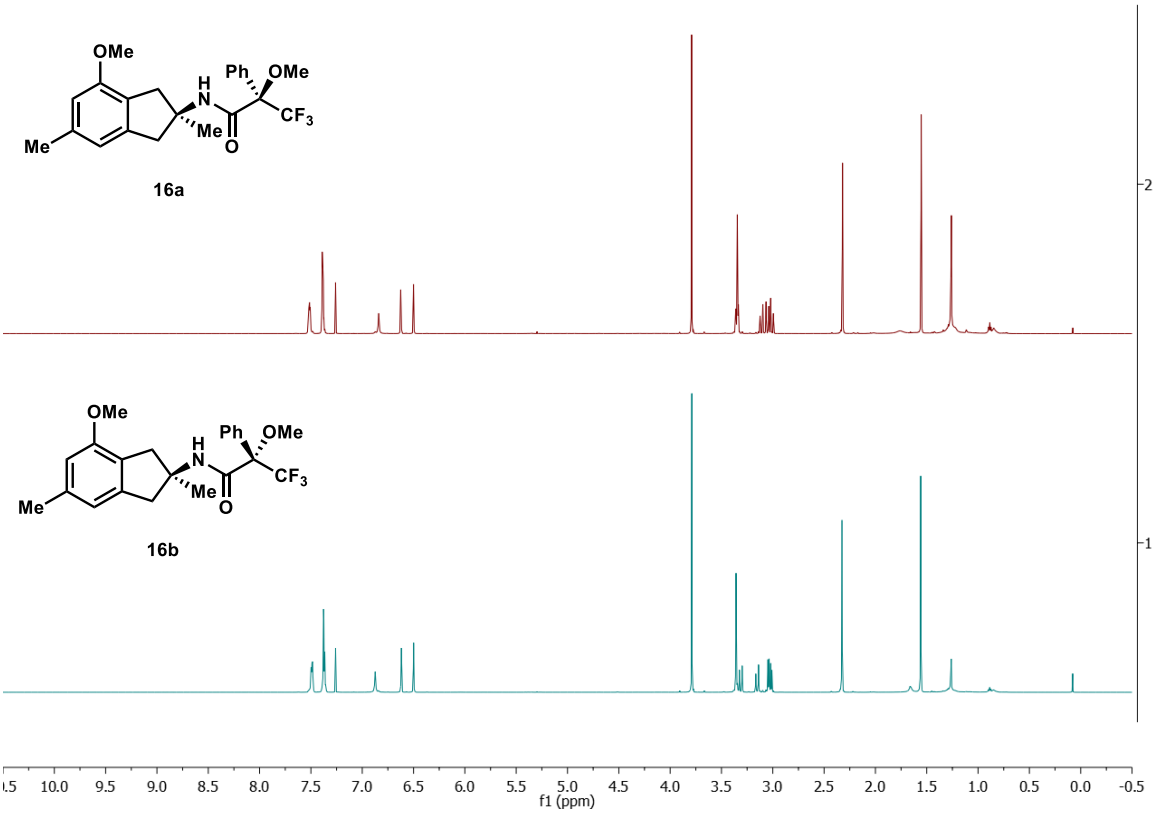
^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.54-7.49 (m, 2H), 7.41-7.36 (m, 3H), 6.84 (s, 1H), 6.63 (s, 1H), 6.50 (s, 1H), 3.79 (s, 3H), 3.35 (d, *J* = 16 Hz, 1H), 3.35-3.34 (m, 3H), 3.11 (d, *J* = 16.0 Hz, 1H), 3.05 (d, *J* = 16.0 Hz, 1H), 3.01 (d, *J* = 16.0 Hz, 1H), 2.32 (s, 3H), 1.55 (s, 3H)
^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) 165.9, 156.0, 143.0, 138.4, 133.1, 129.5, 128.6, 127.7, 125.1, 124.0 (q, *J* = 290.0 Hz), 117.8, 109.5, 84.1 (q, *J* = 25.8 Hz), 61.5, 55.3, 55.0, 46.3, 43.2, 29.9, 25.7, 21.9
^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -68.8
IR (neat)**:** ν (cm^{-1}) 3415, 2926, 2848, 1694, 1510, 1159, 1081, 833
HRMS (ESI): Calcd for $C_{22}H_{24}F_3NNaO_3$ $[M+Na]^+$: 430.1600, found 430.1601
Rf = 0.32 in a 90:10 mixture of pentane and ethyl acetate
$[\alpha]_D^{20}$ = + 24.2° (c = 0.13, $CHCl_3$)

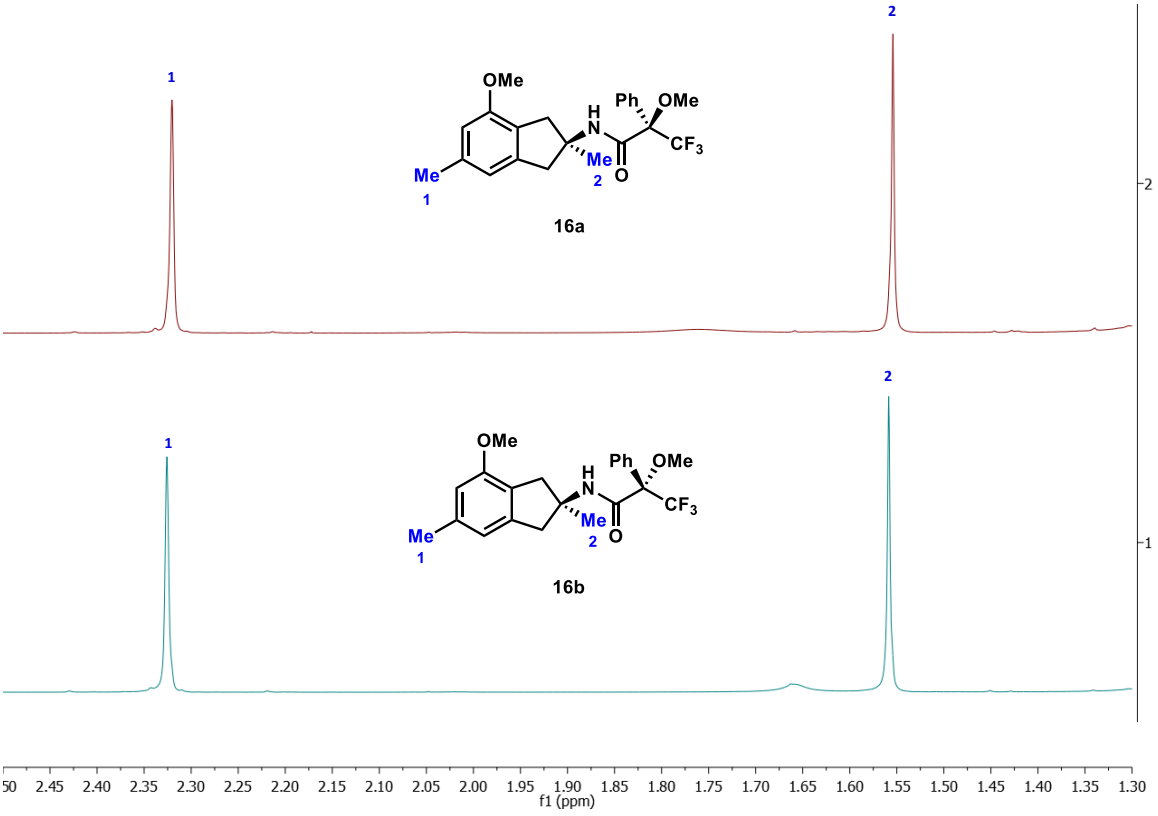


Chemical Formula: $C_{22}H_{24}F_3NO_3$
Exact Mass: 407.1708
Molecular Weight: 407.4332

^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.51-7.47 (m, 2H), 7.40-7.34 (m, 3H), 6.87 (s, 1H), 6.62 (s, 1H), 6.50 (s, 1H), 3.79 (s, 3H), 3.37-3.35 (m, 3H), 3.31 (d, *J* = 16.0 Hz, 1H), 3.15 (d, *J* = 16.0 Hz, 1H), 3.03 (d, *J* = 16.0 Hz, 1H), 3.02 (d, *J* = 16.0 Hz, 1H), 2.33 (s, 3H), 1.56 (s, 3H)
^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) 165.8, 156.0, 142.9, 138.4, 133.0, 129.5, 128.6, 127.8, 125.2, 124.0 (q, *J* = 289.9 Hz), 117.8, 109.5, 84.1 (q, *J* = 25.9 Hz), 61.4, 55.3, 55.0, 46.2, 43.2, 25.9, 21.8.
^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) δ -68.8
IR (neat)**:** ν (cm^{-1}) 3416, 2926, 2847, 1694, 1509, 1158, 1081, 833
HRMS (ESI): Calcd for $C_{22}H_{24}F_3NNaO_3$ $[M+Na]^+$: 430.1600, found 430.1600
Rf = 0.32 in a 90:10 mixture of pentane and ethyl acetate
$[\alpha]_D^{20}$ = + 9.4° (c = 0.18, $CHCl_3$)

NOESY NMR Analysis:


OMe
Ph
OMe
H
N
Me
O
CF3
Me
16a
OMe
Ph
OMe
H
N
Me
O
CF3
Me
16b
2
1
f1 (ppm)


1
2
OMe
Ph
OMe
H
N
Me
2
O
CF3
Me
1
16a
1
2
OMe
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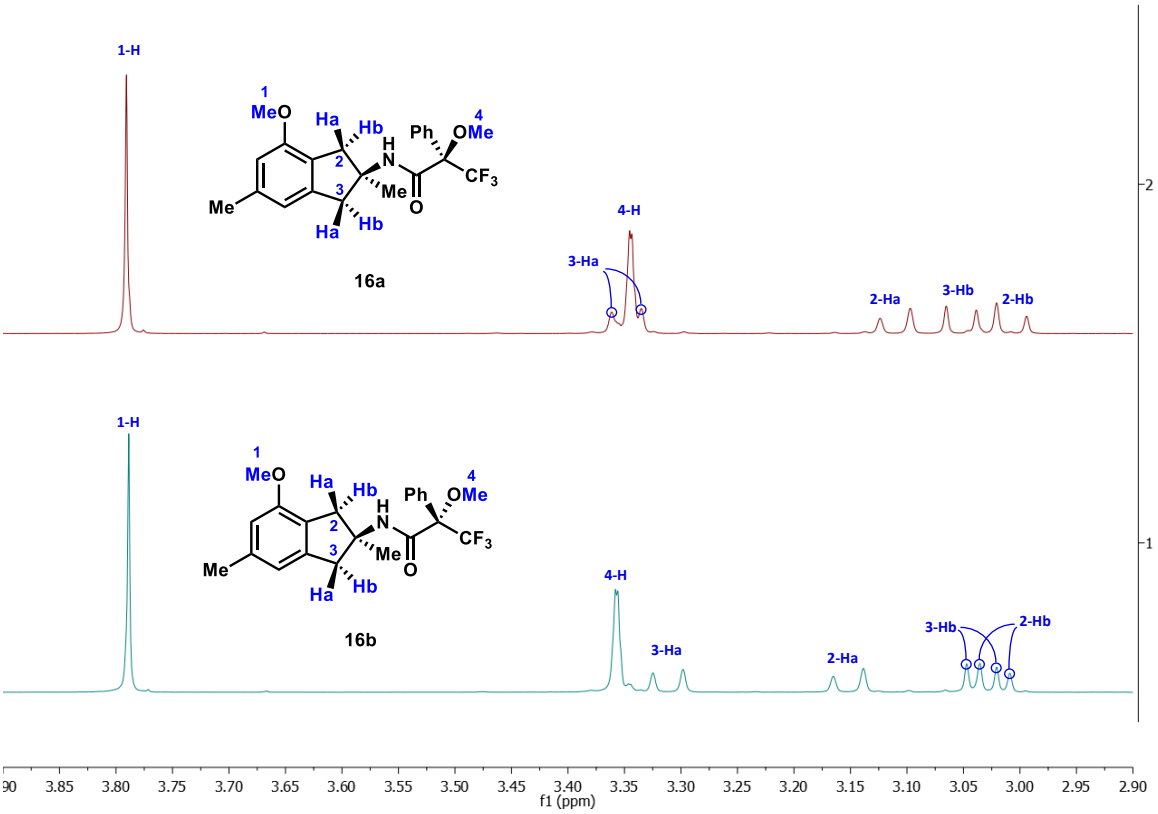
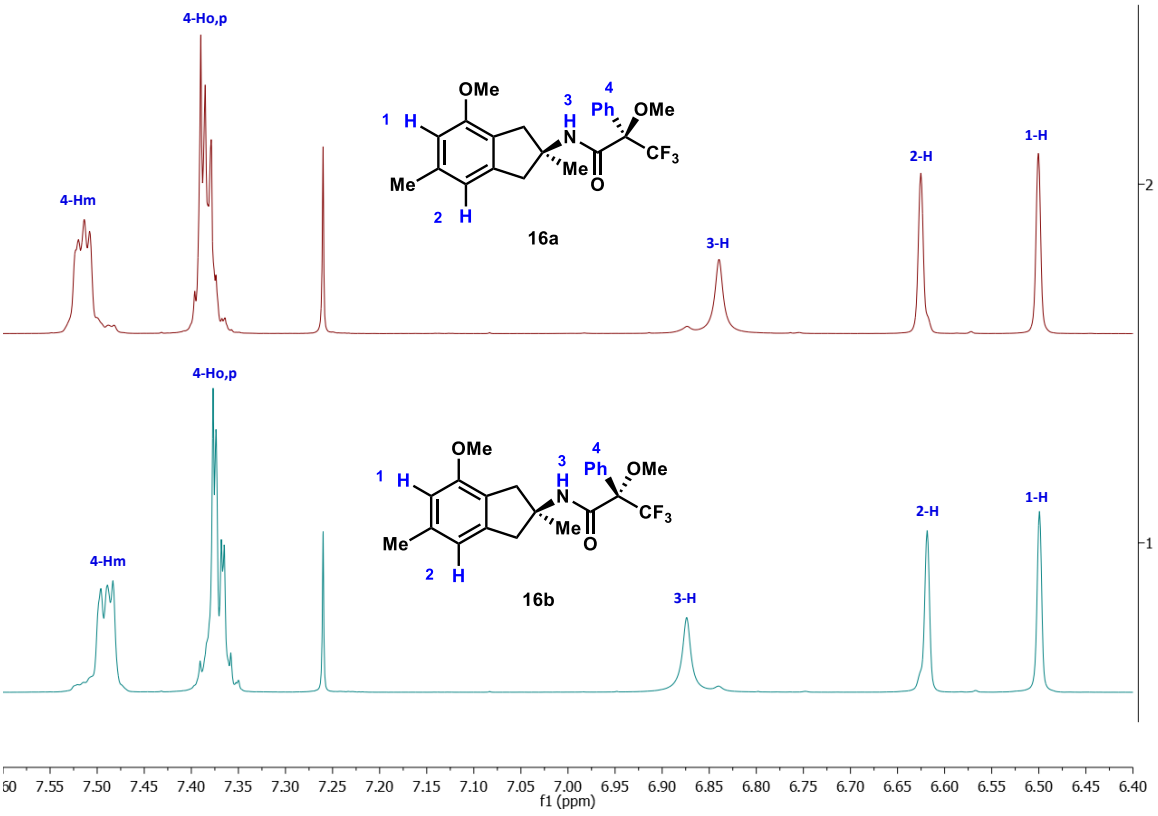
H
N
Me
2
O
CF3
Me
1
16b
2
1
f1 (ppm)


1-H
MeO
Ha
Hb
Ph
OMe
CF3
Me
Ha
Hb
16a
4-H
3-Ha
2-Ha
3-Hb
2-Hb
1-H
16b
4-H
3-Ha
2-Ha
3-Hb
2-Hb
f1 (ppm)


4-Ho,p
4-Hm
OMe
Ph
OMe
CF3
Me
16a
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2-H
1-H
4-Ho,p
4-Hm
16b
3-H
2-H
1-H
f1 (ppm)

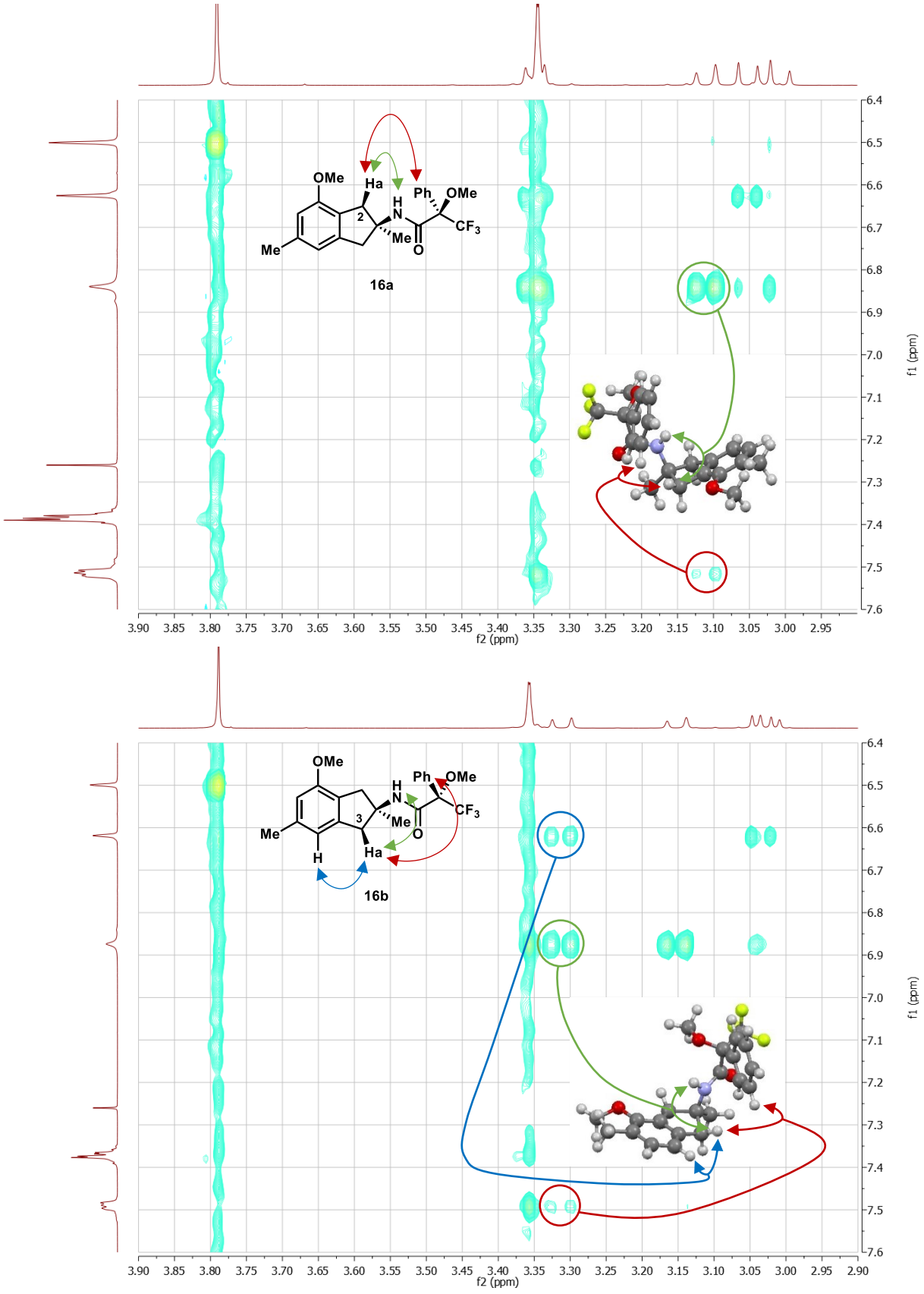

Figure S6: NOESY of Mosher amide

For **16a**, a correlation between the benzylic proton 2-Ha (identified by its correlation with the NH and the absence of correlation with the aromatic proton) and the meta proton of the phenyl group of the mosher amide part can be observed.
In the case of **16b**, a similar correlation can be observed between the benzylic proton 3-Ha (identified by its correlation with the NH and the aromatic proton) and the meta proton of the phenyl group of the mosher amide.
Precedent calculations on Mosher amides[13] indicate that the more stable conformer of such amides shows a synperiplanar relationship between the CF_3 and the carbonyl groups.
This indicates that the quaternary stereocenter constructed during the enantioselective C(sp^3)-H arylation step has the (S) configuration.

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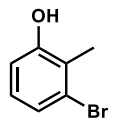
NMR Spectra and chromatograms

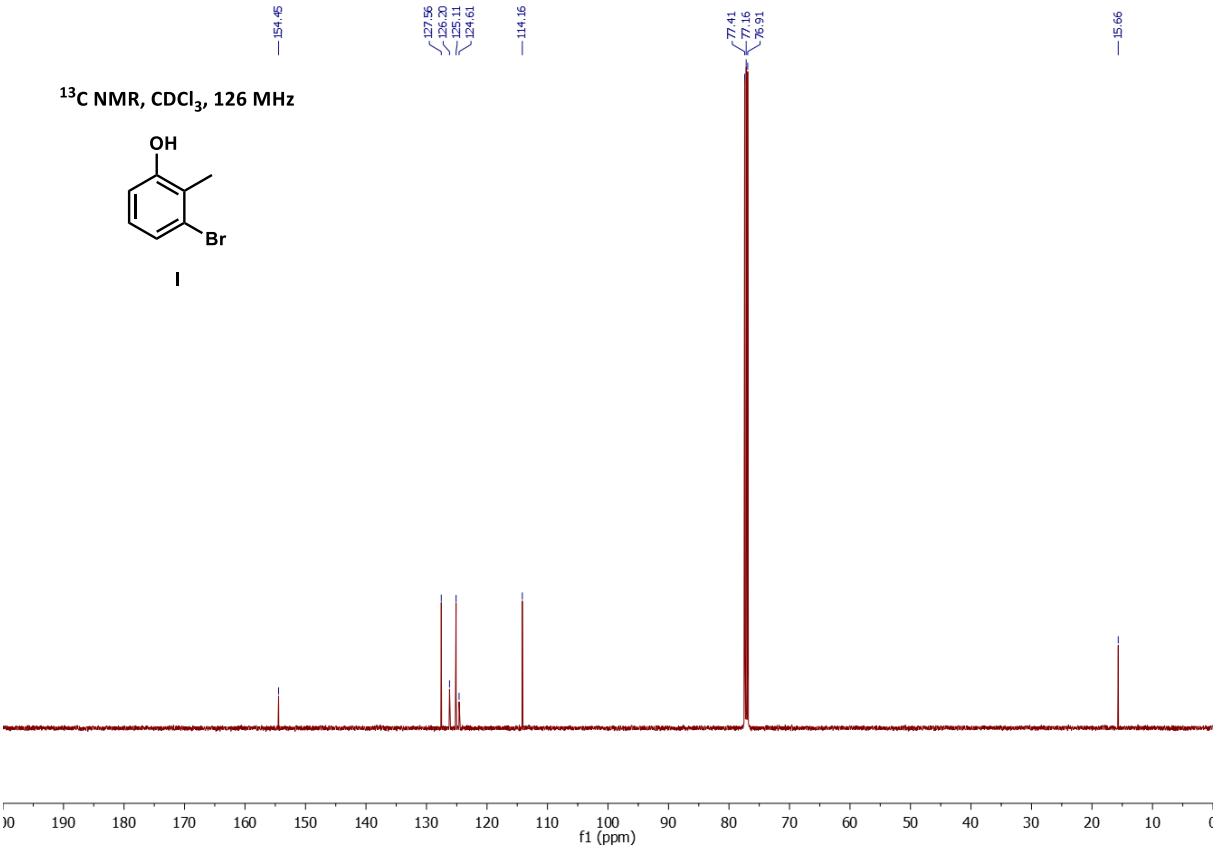
^{1}H NMR, $CDCl_3$, 500 MHz

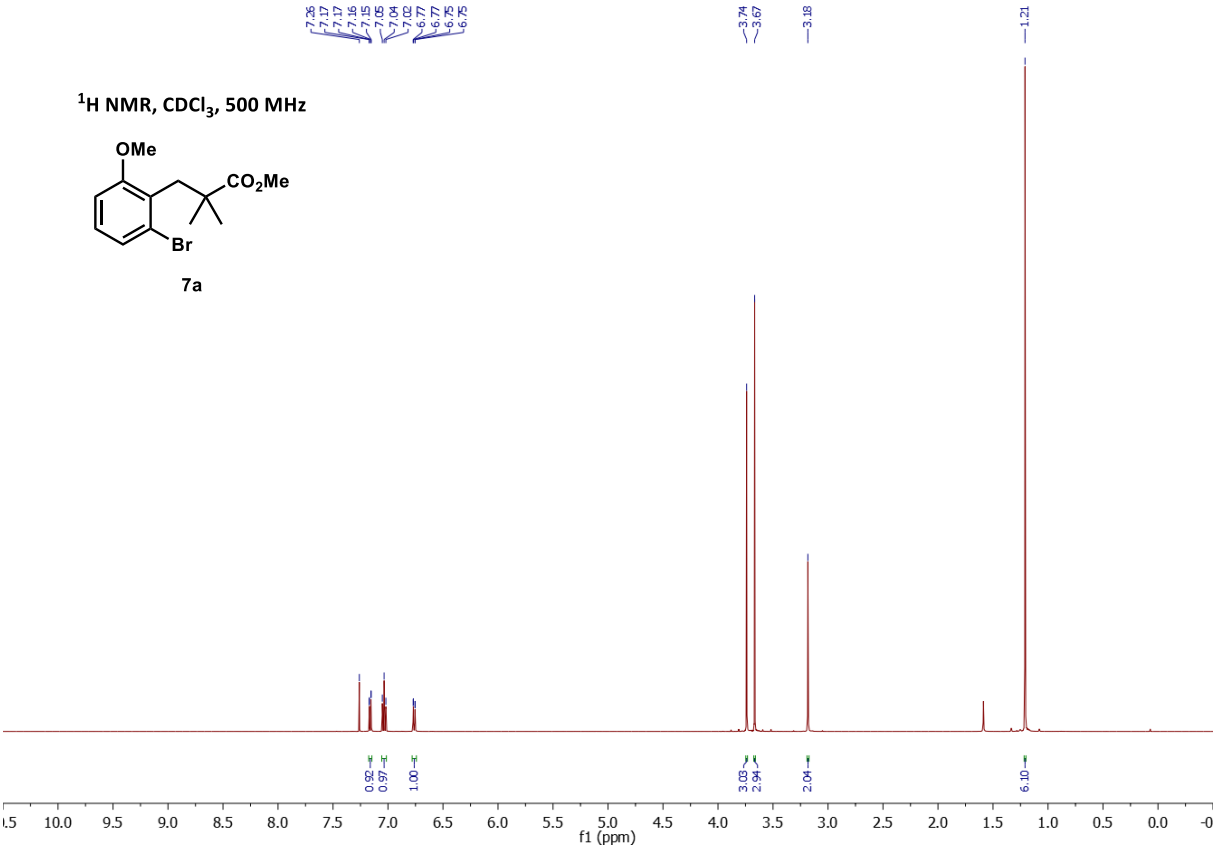


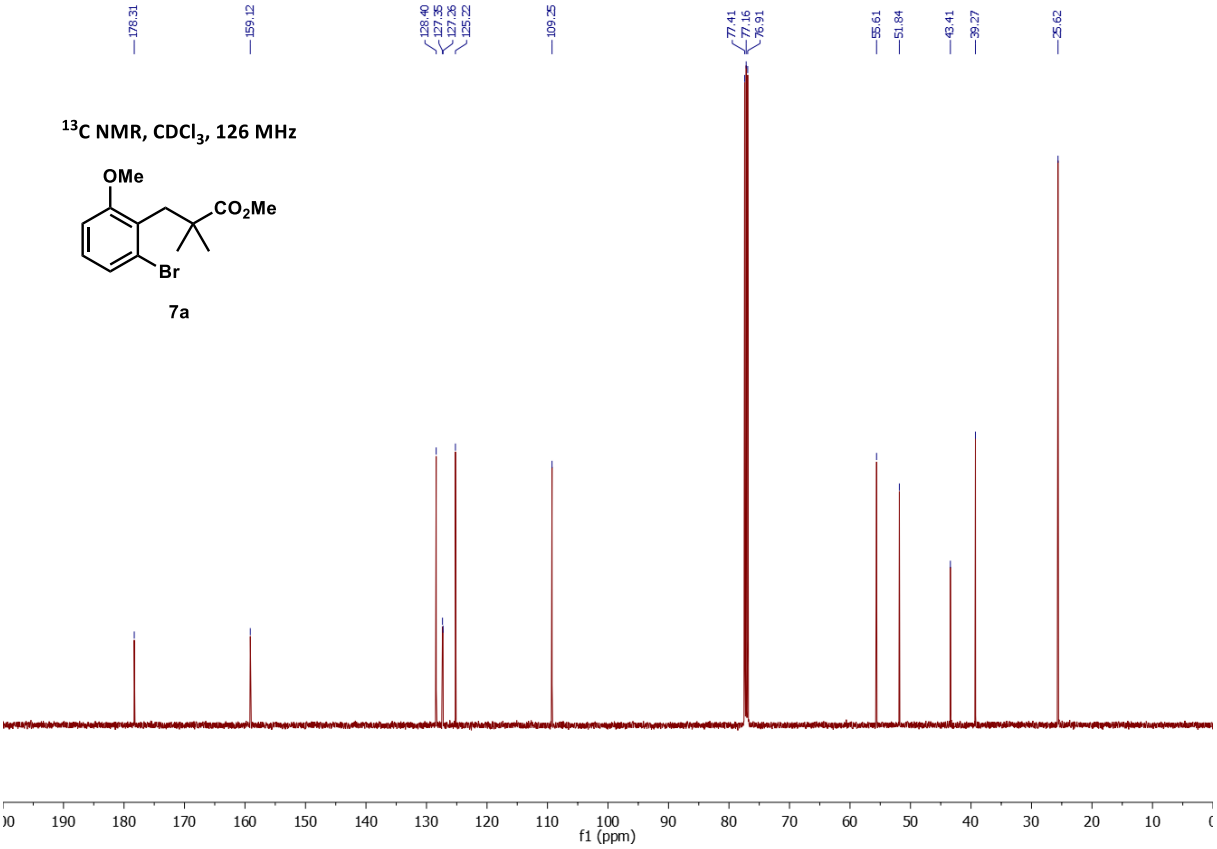
I

^{13}C NMR, $CDCl_3$, 126 MHz

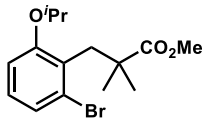
I




7.26
7.17
7.17
7.16
7.15
7.05
7.04
7.02
6.77
6.75
6.75
3.74
3.67
3.18
1.21
^{1}H NMR, CDCl$_3$, 500 MHz
OMe
CO$_2$Me
Br
7a
0.92
0.97
1.00
3.03
2.94
2.04
6.10
f1 (ppm)

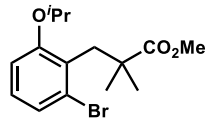

178.31
159.12
128.40
127.35
127.26
125.22
109.25
77.41
77.16
76.91
55.61
51.84
43.41
39.27
25.62
^{13}C NMR, CDCl$_3$, 126 MHz
OMe
CO$_2$Me
Br
7a
f1 (ppm)

^{1}H NMR, $CDCl_3$, 500 MHz



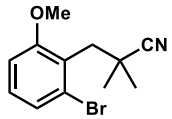
7b

^{13}C NMR, $CDCl_3$, 126 MHz



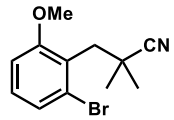
7b

^{1}H NMR, $CDCl_3$, 500 MHz



7c

^{13}C NMR, $CDCl_3$, 126 MHz



7c

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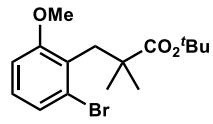
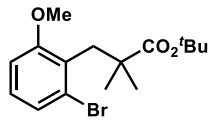


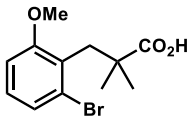
7d

^{13}C NMR, $CDCl_3$, 126 MHz



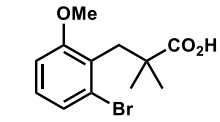
7d

^{1}H NMR, $CDCl_3$, 500 MHz



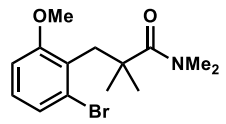
IV

^{13}C NMR, $CDCl_3$, 126 MHz



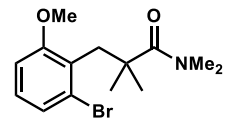
IV

^{1}H NMR, $CDCl_3$, 500 MHz



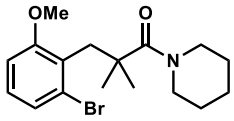
7e

^{13}C NMR, $CDCl_3$, 126 MHz



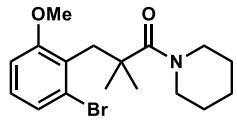
7e

^{1}H NMR, $CDCl_3$, 500 MHz



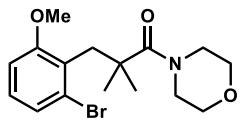
7f

^{13}C NMR, $CDCl_3$, 126 MHz



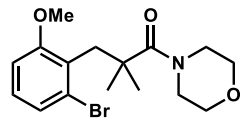
7f

^{1}H NMR, $CDCl_3$, 500 MHz

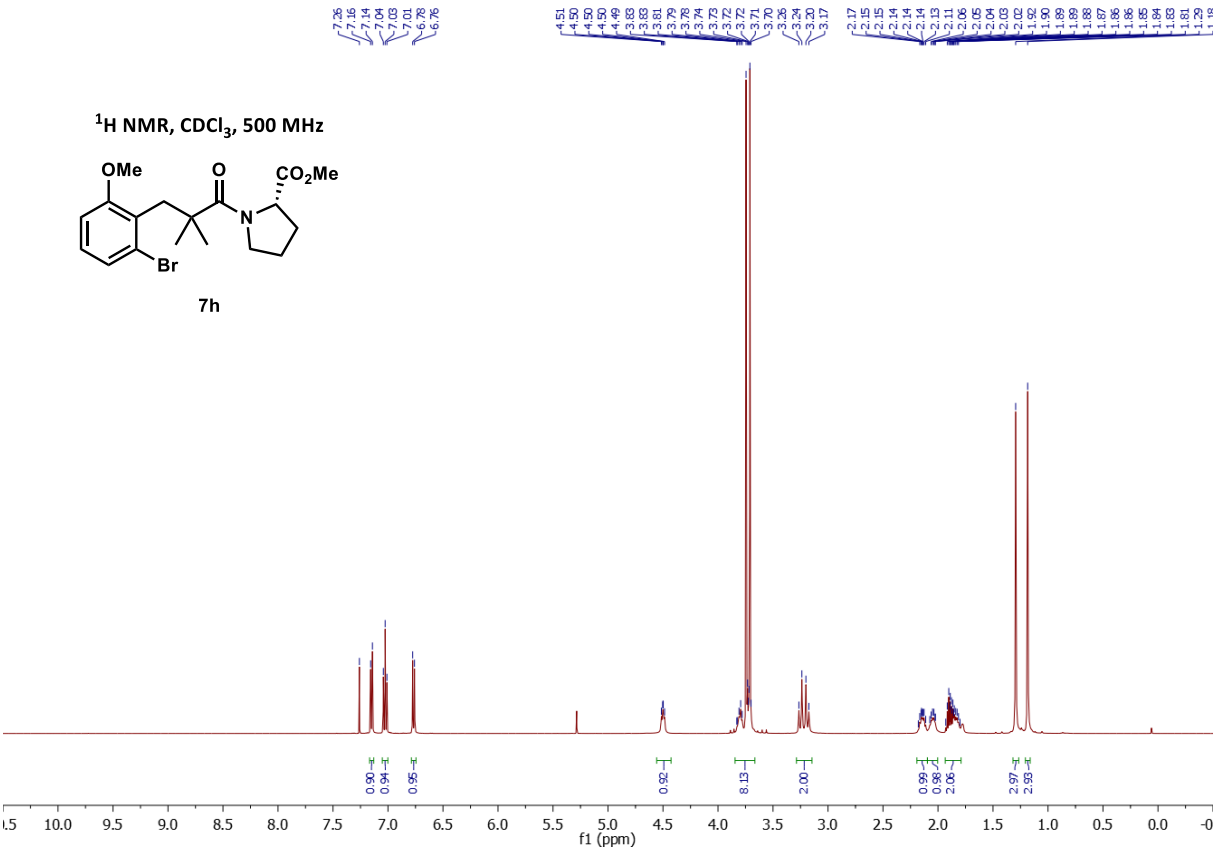


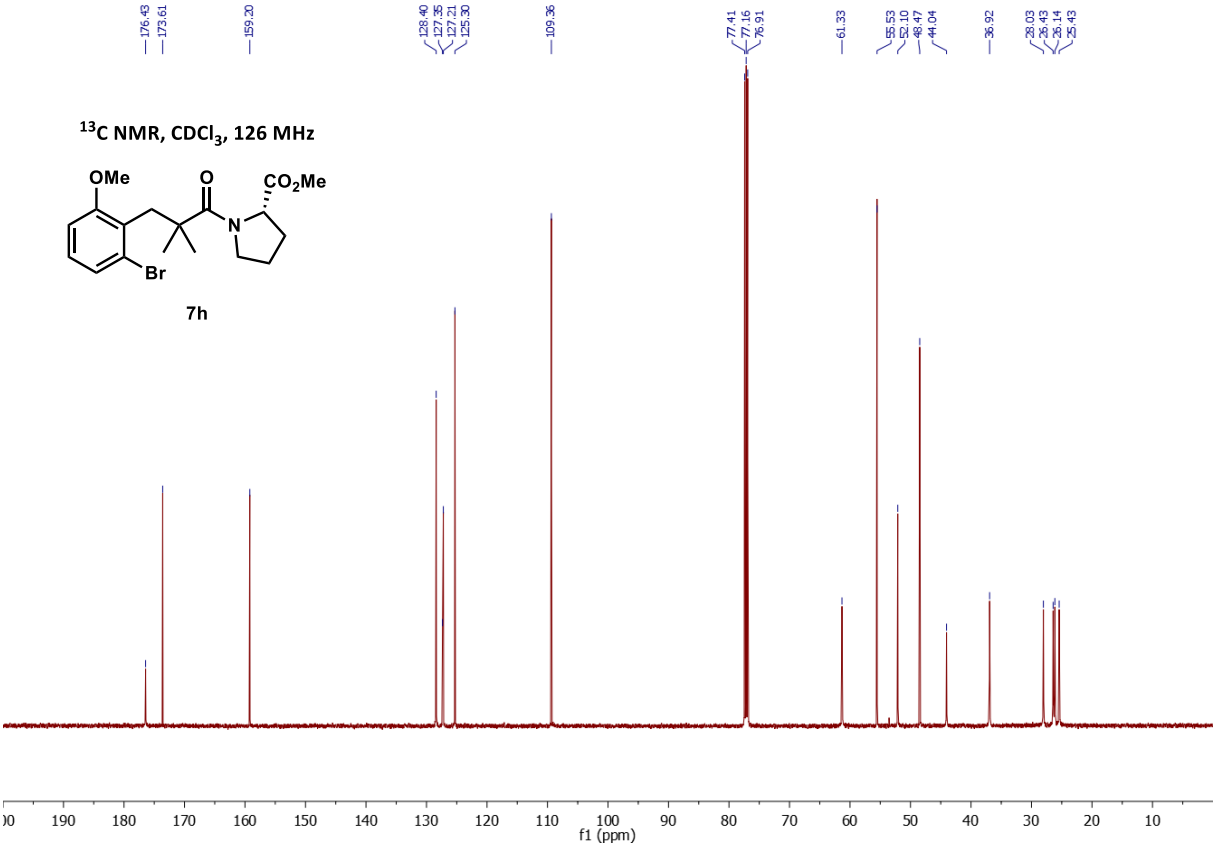
7g

^{13}C NMR, $CDCl_3$, 126 MHz

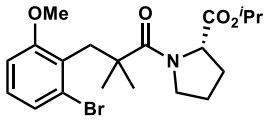


7g


^{1}H NMR, $CDCl_3$, 500 MHz
OMe
O
CO_2Me
N
Br
7h
f1 (ppm)

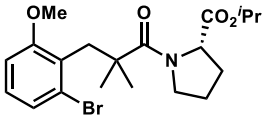

^{13}C NMR, $CDCl_3$, 126 MHz
OMe
O
CO_2Me
N
Br
7h
f1 (ppm)

^{1}H NMR, $CDCl_3$, 500 MHz



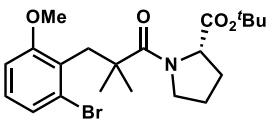
7i

^{13}C NMR, $CDCl_3$, 126 MHz



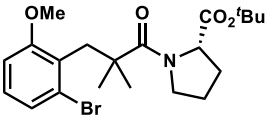
7i

^{1}H NMR, $CDCl_3$, 500 MHz



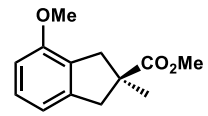
7j

^{13}C NMR, $CDCl_3$, 126 MHz



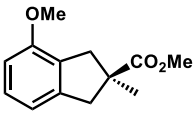
7j

^{1}H NMR, $CDCl_3$, 500 MHz



8a

^{13}C NMR, $CDCl_3$, 126 MHz



8a

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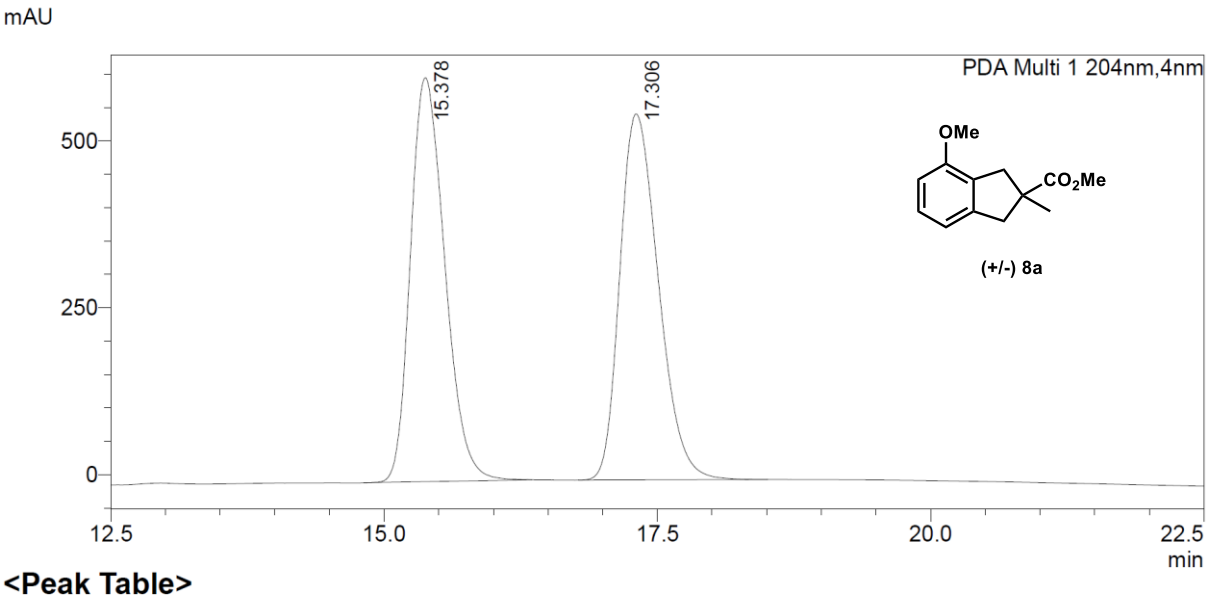

<Peak Table>

PDA Ch1 204nm

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Total		26732778	1153849	100.000

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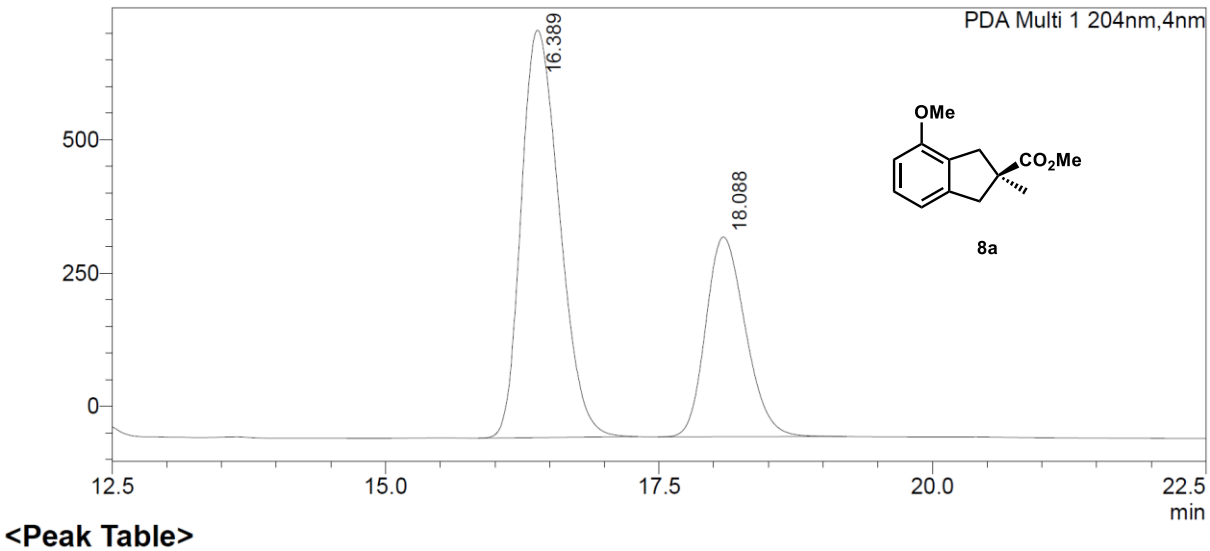

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PDA Ch1 204nm

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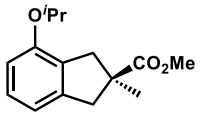
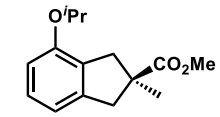
Total		28077896	1138819	100.000

^{1}H NMR, $CDCl_3$, 500 MHz



8b

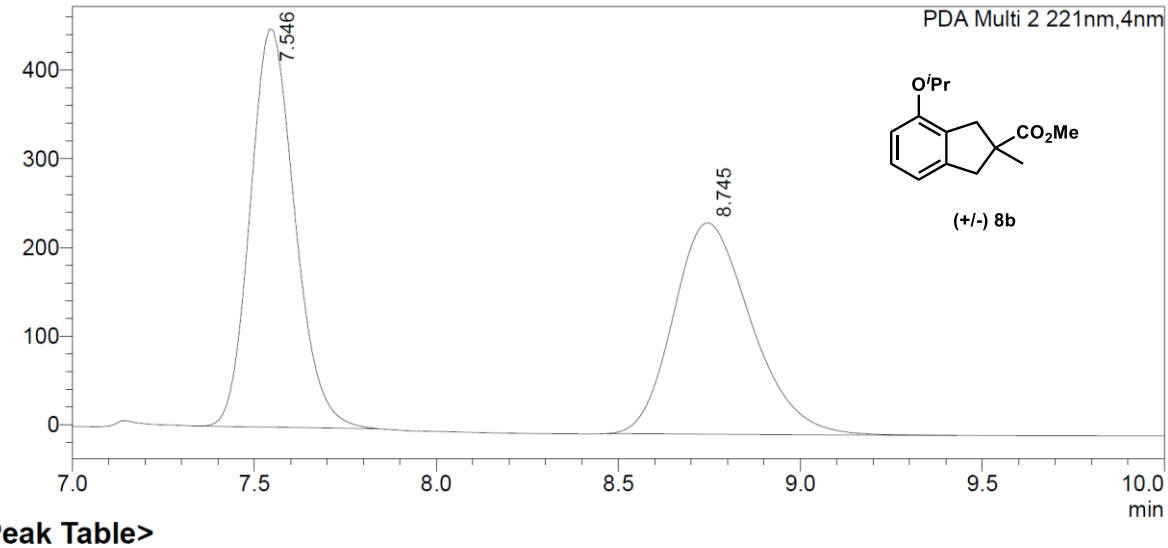
^{13}C NMR, $CDCl_3$, 126 MHz



8b

<Chromatogram>

mAU



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PDA Ch2 221nm

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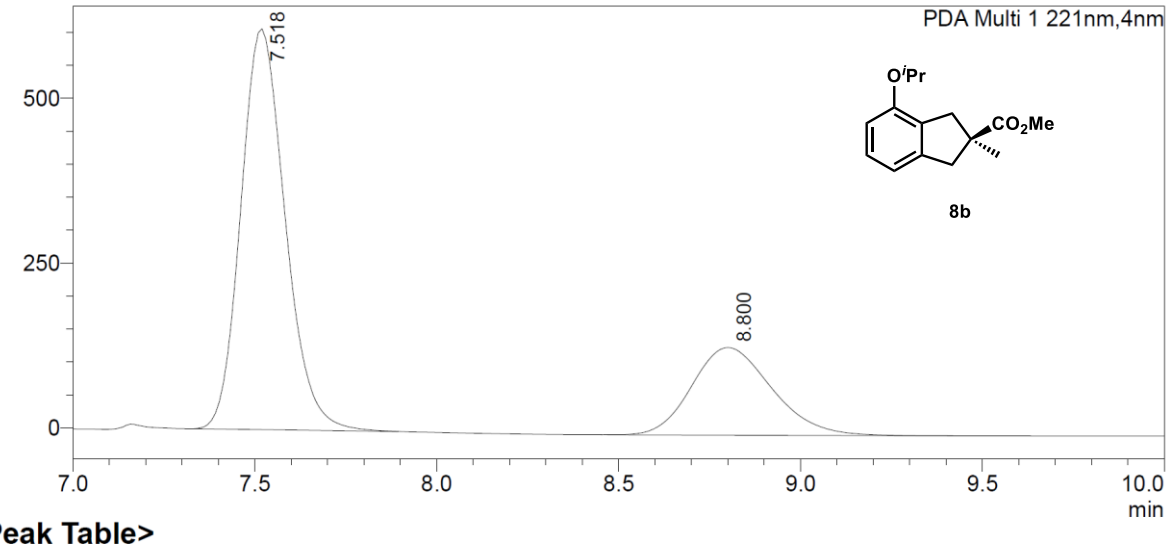

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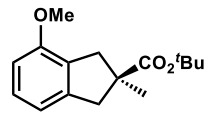
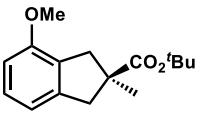
^{1}H NMR, $CDCl_3$, 500 MHz



8d

^{13}C NMR, $CDCl_3$, 126 MHz



8d

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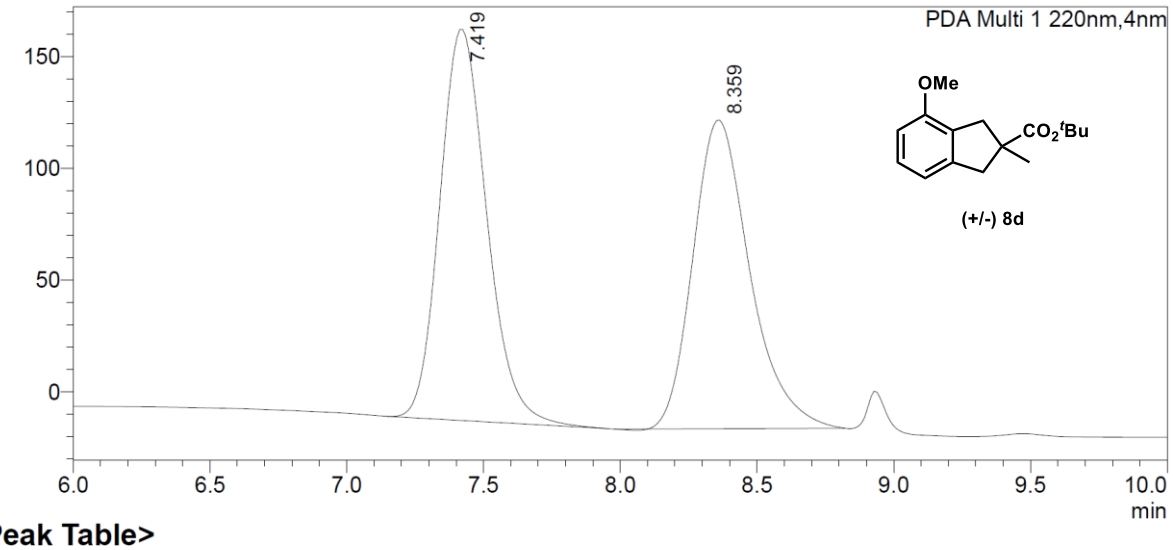

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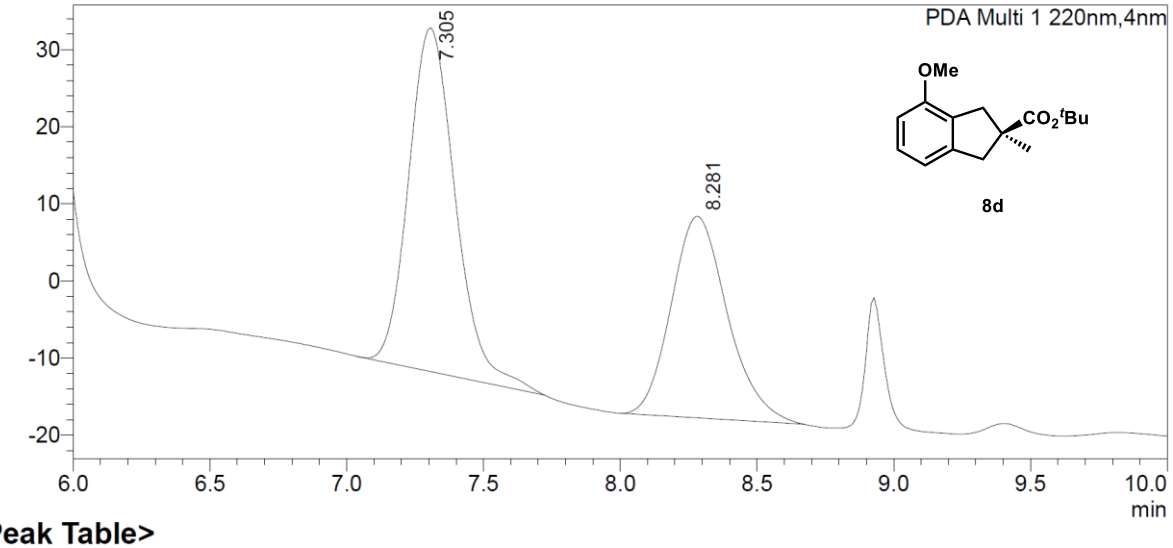
mAU



<Peak Table>

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Peak#	Ret. Time	Area	Height	Area%
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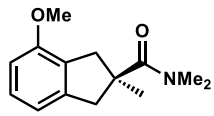
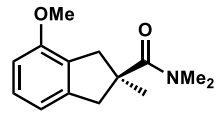
Total		901946	70741	100.000

^{1}H NMR, $CDCl_3$, 500 MHz



8e

^{13}C NMR, $CDCl_3$, 126 MHz



8e

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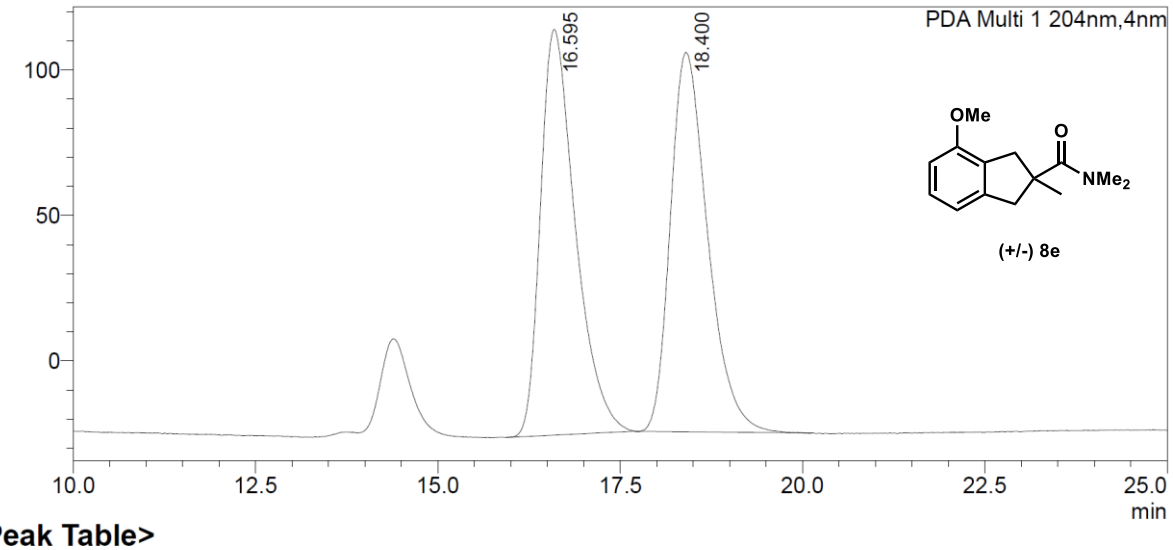

<Peak Table>

PDA Ch1 204nm

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<Chromatogram>

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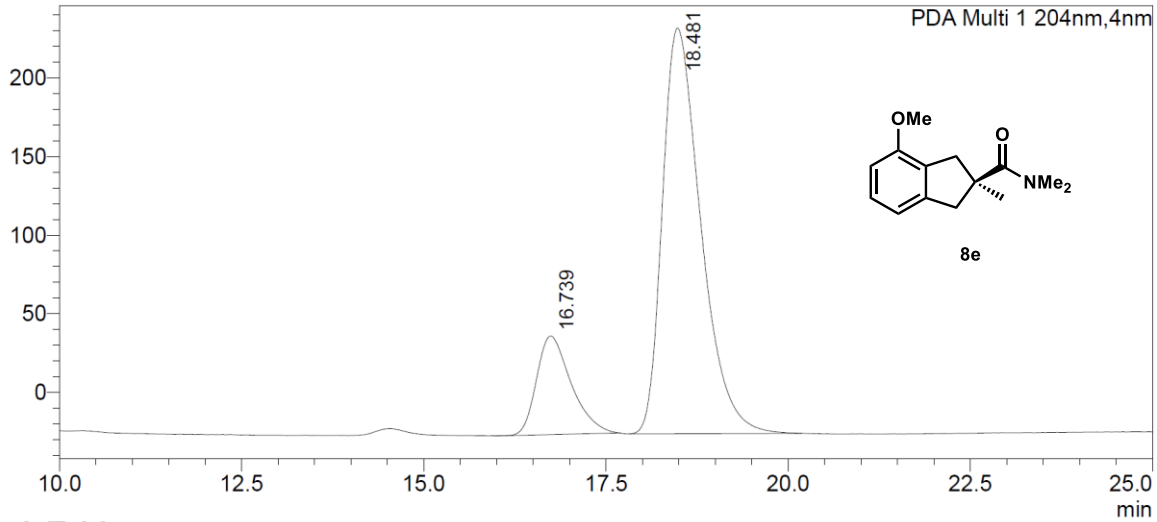

<Peak Table>

PDA Ch1 204nm

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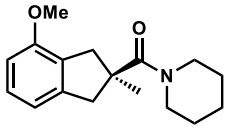
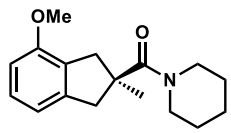
^{1}H NMR, $CDCl_3$, 500 MHz



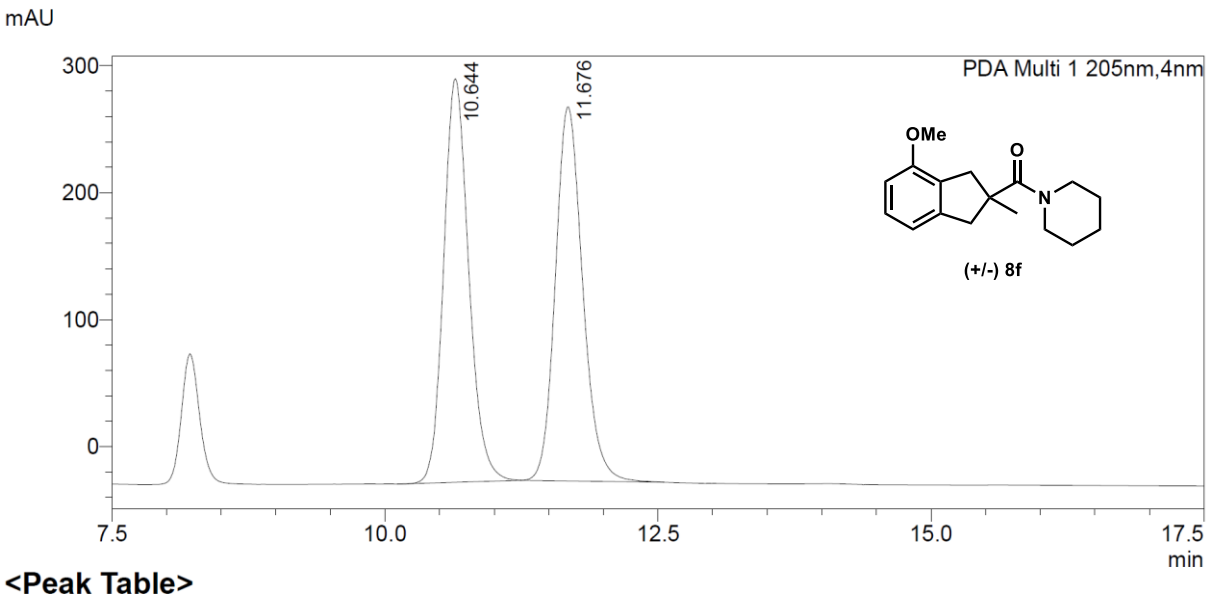
8f

^{13}C NMR, $CDCl_3$, 126 MHz



8f

<Chromatogram>

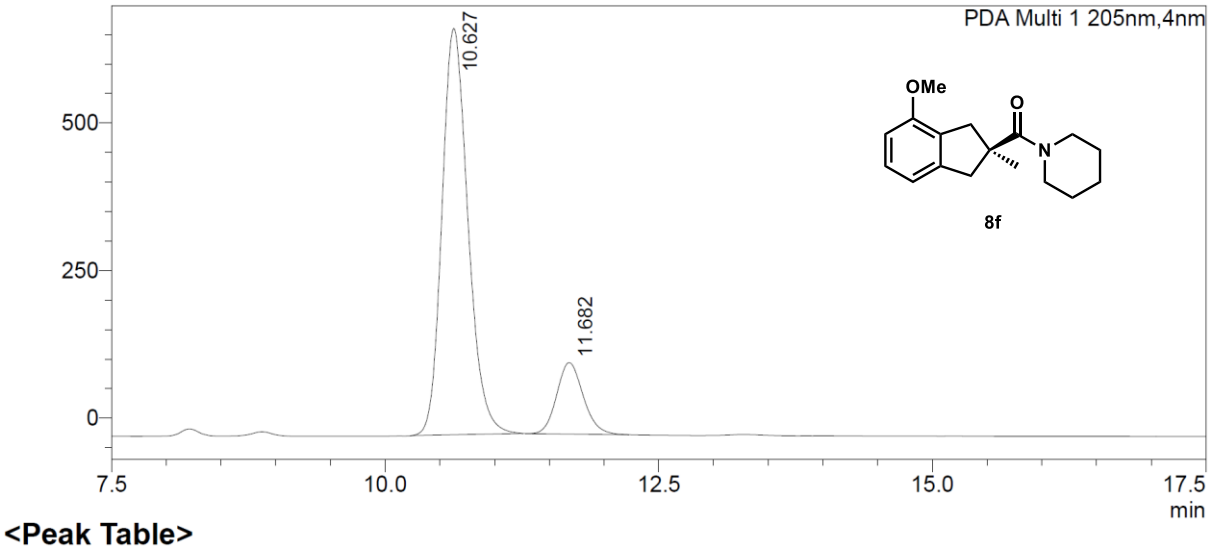


<Peak Table>

PDA Ch1 205nm

Peak#	Ret. Time	Area	Height	Area%
1	10.644	5075261	317900	49.733
2	11.676	5129706	294590	50.267
Total		10204967	612490	100.000

<Chromatogram>

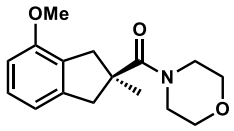


<Peak Table>

PDA Ch1 205nm

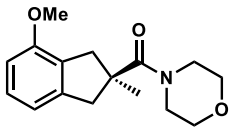
Peak#	Ret. Time	Area	Height	Area%
1	10.627	11395909	688748	84.796
2	11.682	2043259	121147	15.204
Total		13439168	809895	100.000

^{1}H NMR, $CDCl_3$, 500 MHz



8g

^{13}C NMR, $CDCl_3$, 126 MHz



8g

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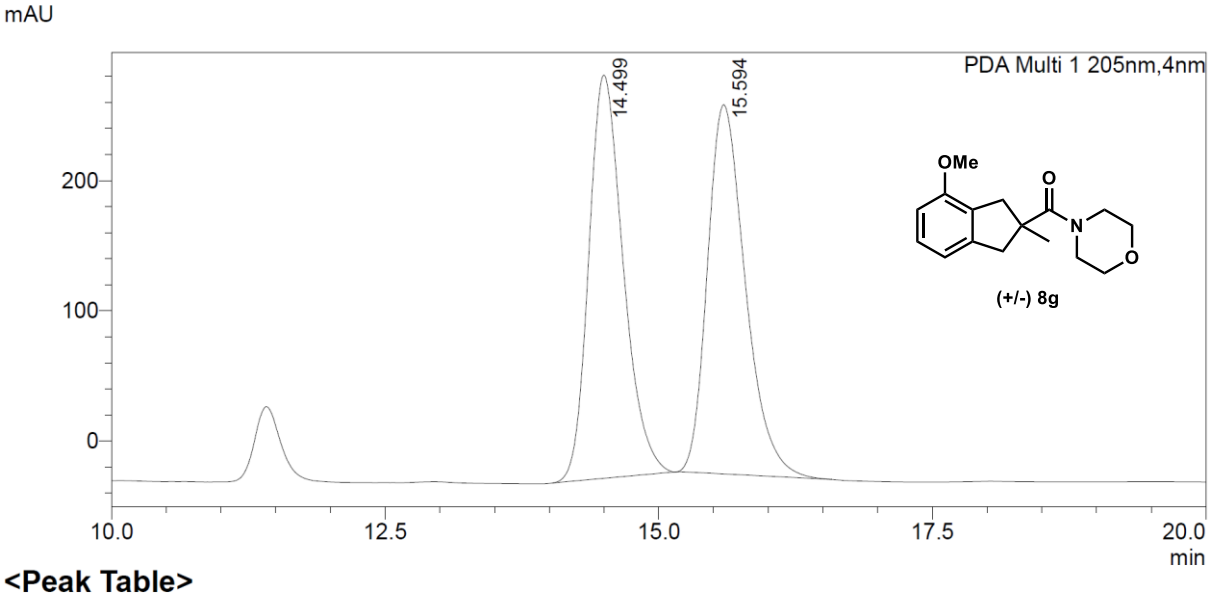
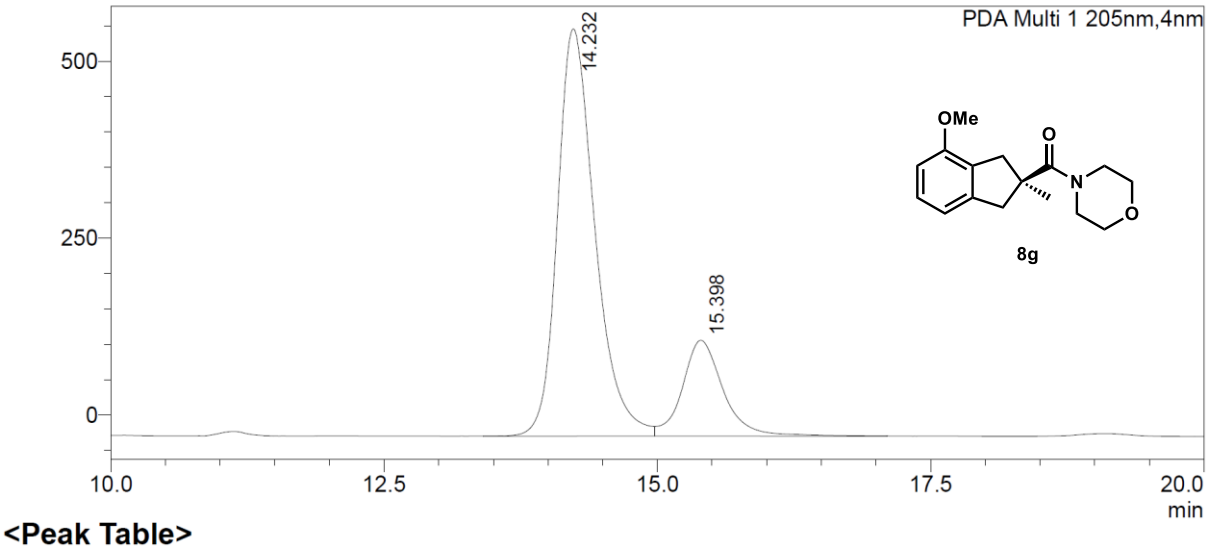


<Peak Table>

PDA Ch1 205nm

Peak#	Ret. Time	Area	Height	Area%
1	14.499	6779738	309557	49.841
2	15.594	6822886	283529	50.159
Total		13602624	593086	100.000

<Chromatogram>

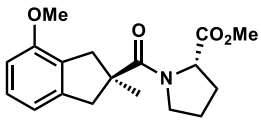


<Peak Table>

PDA Ch1 205nm

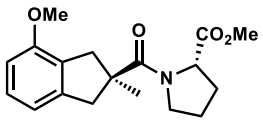
Peak#	Ret. Time	Area	Height	Area%
1	14.232	13766237	575649	79.675
2	15.398	3511859	135317	20.325
Total		17278096	710966	100.000

^{1}H NMR, $CDCl_3$, 500 MHz



8h

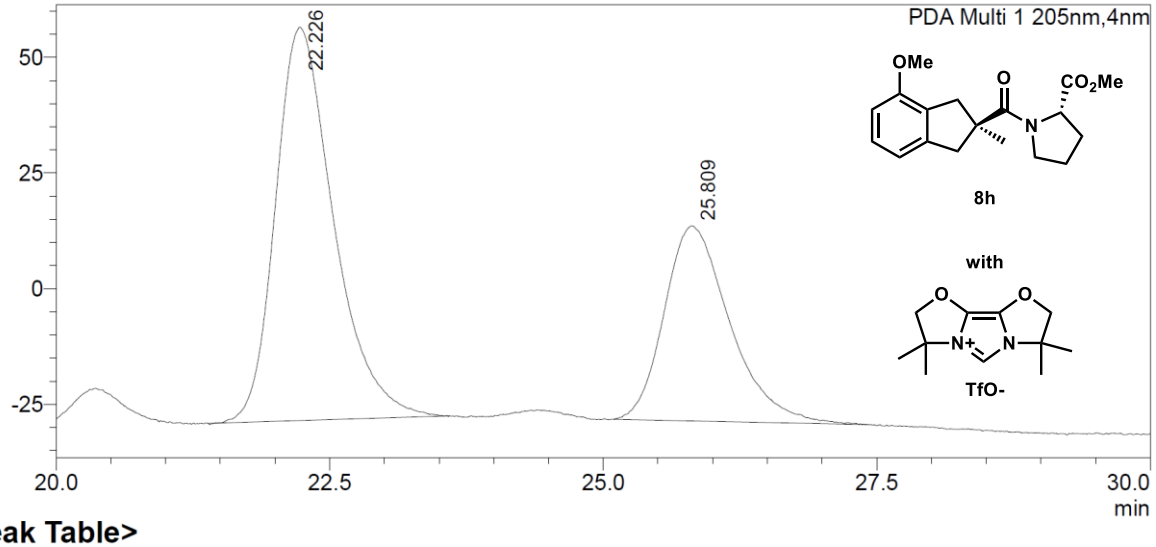
^{13}C NMR, $CDCl_3$, 126 MHz



8h

<Chromatogram>

mAU



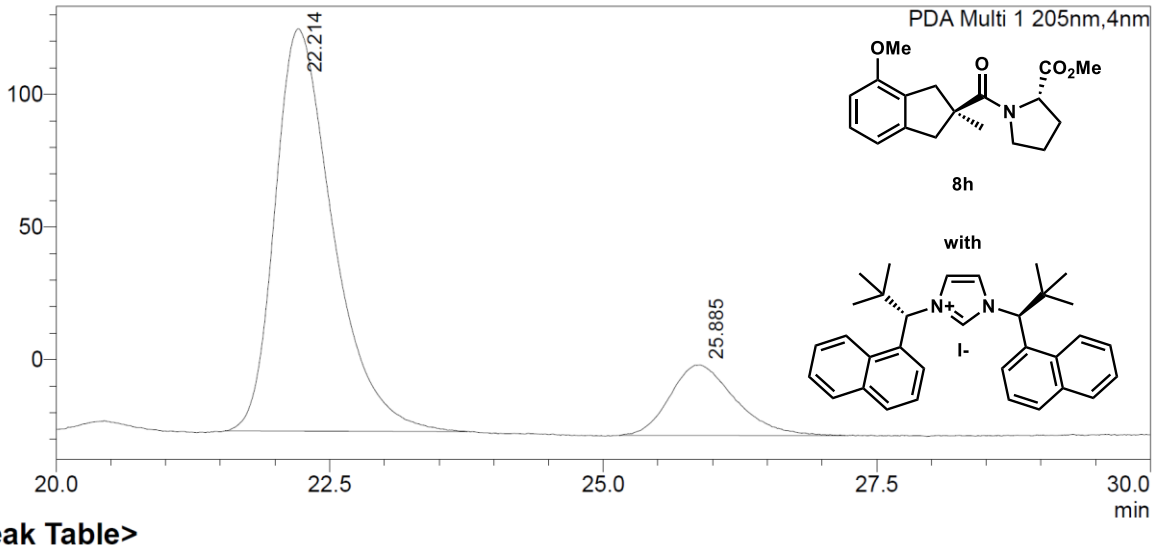
<Peak Table>

PDA Ch1 205nm

Peak#	Ret. Time	Area	Height	Area%
1	22.226	3144929	85062	64.131
2	25.809	1758950	42187	35.869
Total		4903879	127248	100.000

<Chromatogram>

mAU

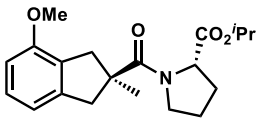


<Peak Table>

PDA Ch1 205nm

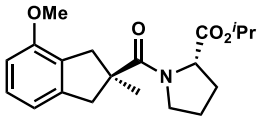
Peak#	Ret. Time	Area	Height	Area%
1	22.214	5609402	151676	83.579
2	25.885	1102089	26596	16.421
Total		6711492	178272	100.000

^{1}H NMR, $CDCl_3$, 500 MHz



8i

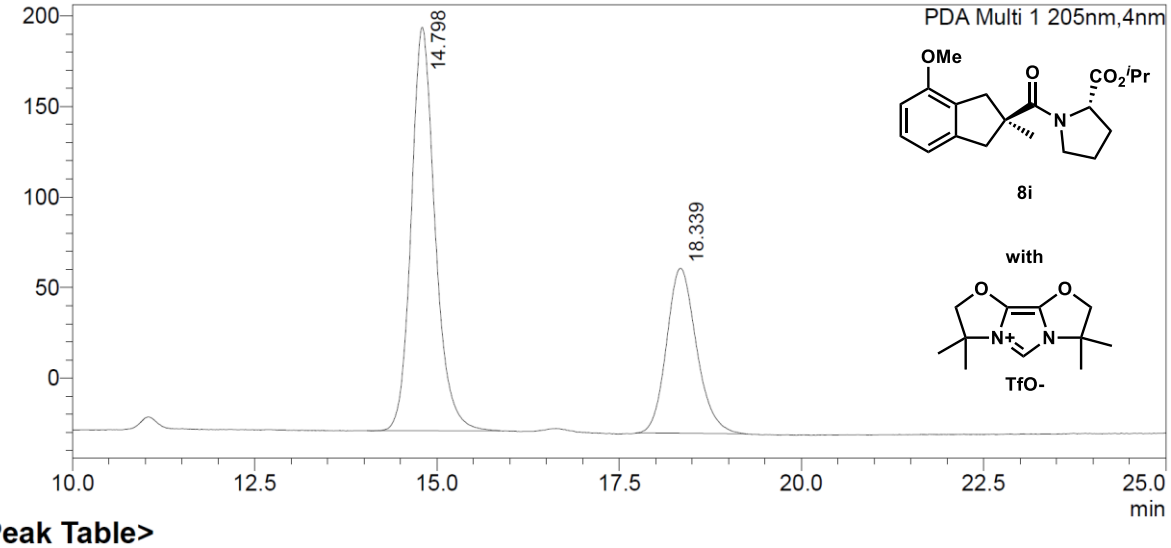
^{13}C NMR, $CDCl_3$, 126 MHz



8i

<Chromatogram>

mAU



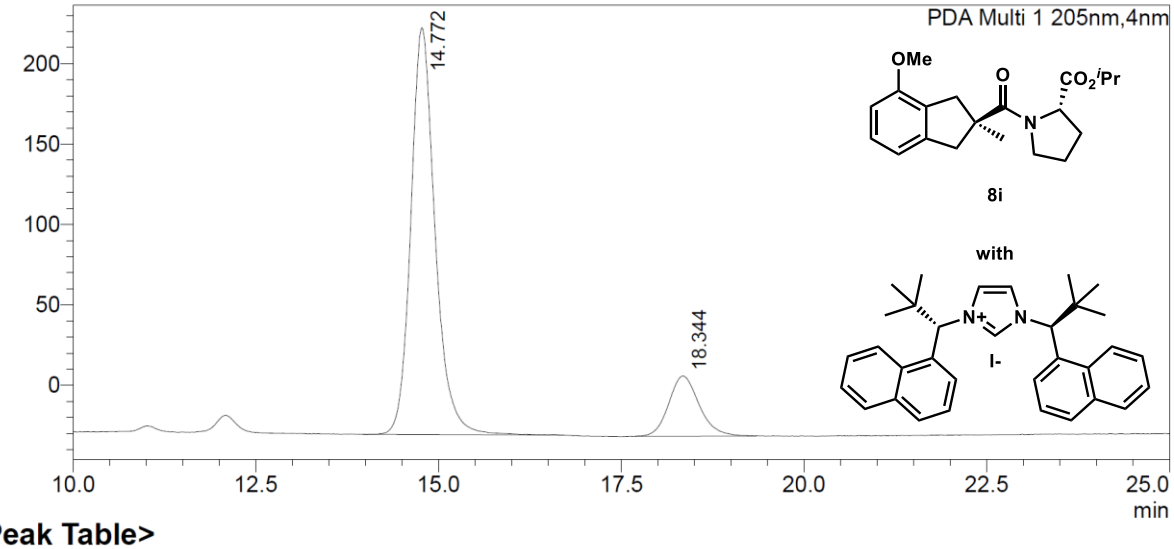
<Peak Table>

PDA Ch1 205nm

Peak#	Ret. Time	Area	Height	Area%
1	14.798	5076833	222836	66.051
2	18.339	2609355	91188	33.949
Total		7686187	314024	100.000

<Chromatogram>

mAU



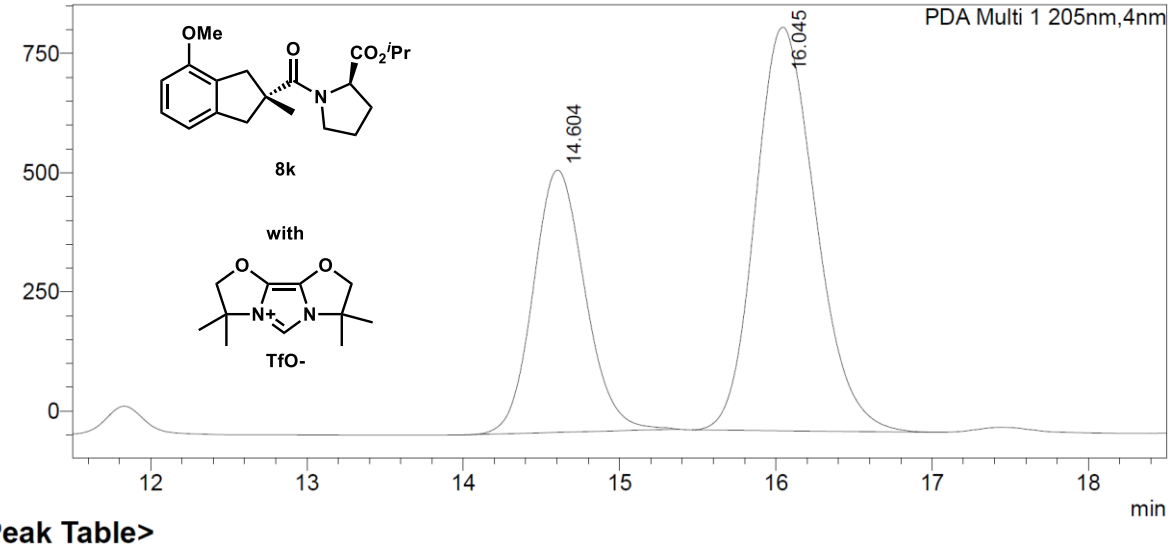
<Peak Table>

PDA Ch1 205nm

Peak#	Ret. Time	Area	Height	Area%
1	14.772	5842523	253013	87.058
2	18.344	868569	34187	12.942
Total		6711092	287200	100.000

<Chromatogram>

mAU



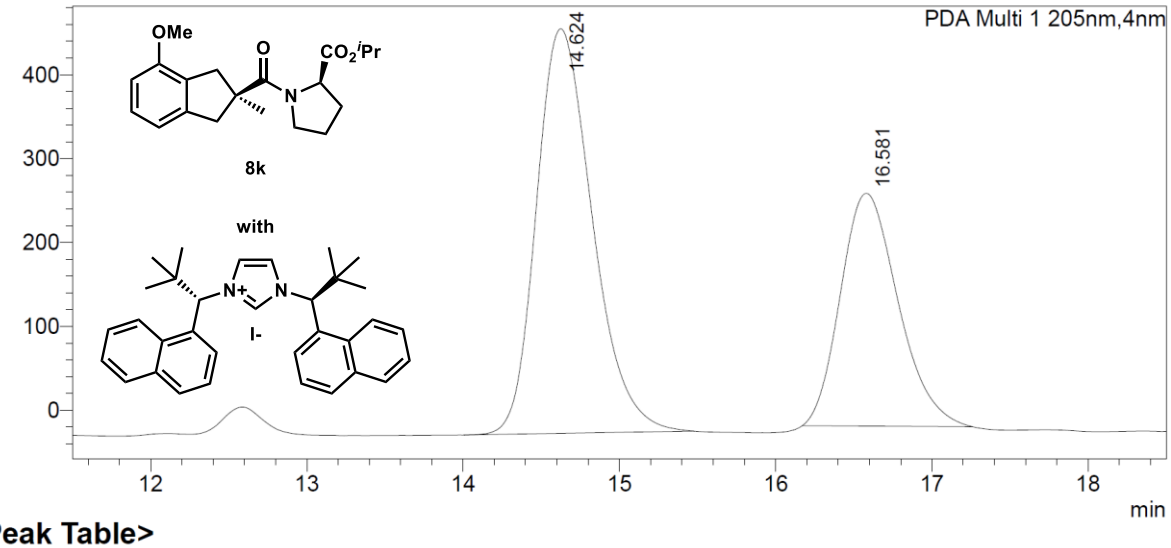
<Peak Table>

PDA Ch1 205nm

Peak#	Ret. Time	Area	Height	Area%
1	14.604	12689983	550521	35.815
2	16.045	22742276	846939	64.185
Total		35432258	1397460	100.000

<Chromatogram>

mAU

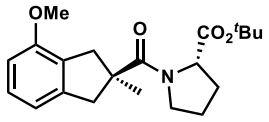


<Peak Table>

PDA Ch1 205nm

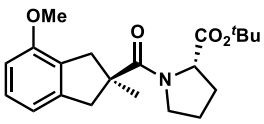
Peak#	Ret. Time	Area	Height	Area%
1	14.624	12018865	482571	62.798
2	16.581	7119918	277521	37.202
Total		19138783	760093	100.000

^{1}H NMR, $CDCl_3$, 500 MHz



8j

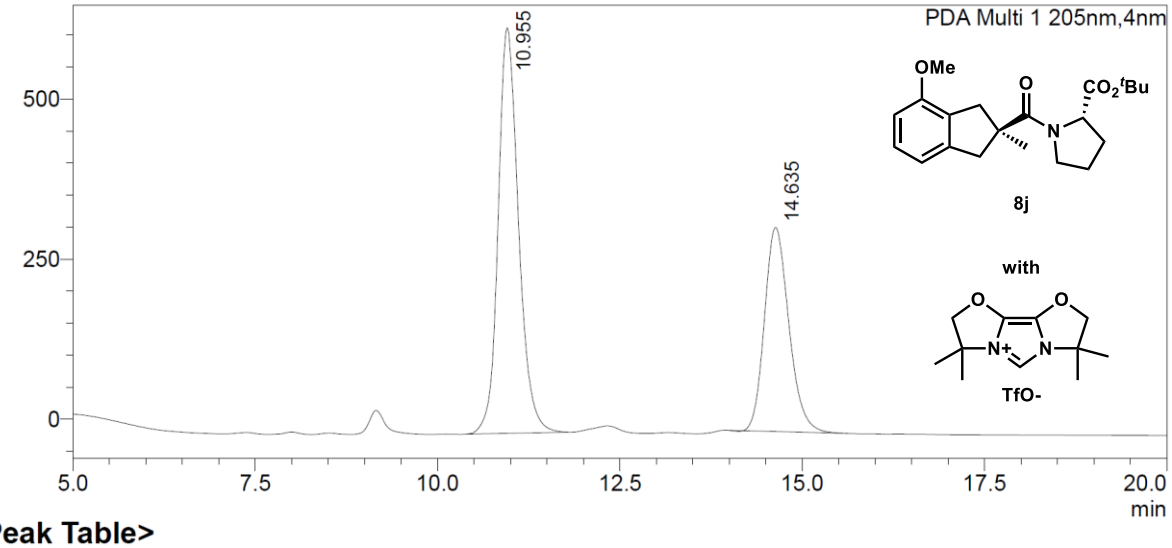
^{13}C NMR, $CDCl_3$, 126 MHz



8j

<Chromatogram>

mAU



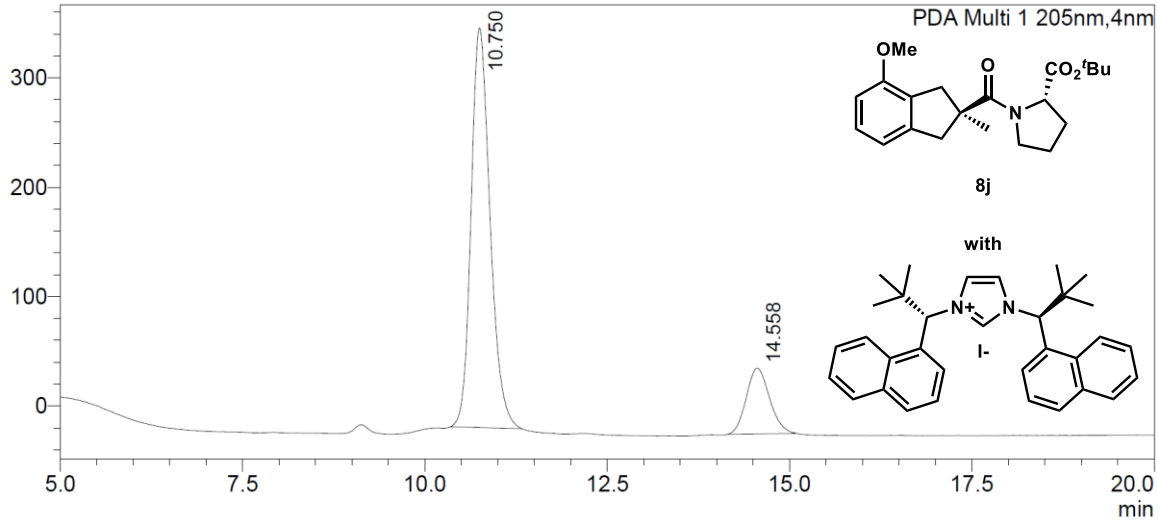
<Peak Table>

PDA Ch1 205nm

Peak#	Ret. Time	Area	Height	Area%
1	10.955	12332499	633593	62.397
2	14.635	7432194	319044	37.603
Total		19764693	952637	100.000

<Chromatogram>

mAU

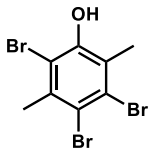


<Peak Table>

PDA Ch1 205nm

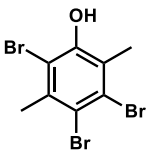
Peak#	Ret. Time	Area	Height	Area%
1	10.750	6616798	365456	83.192
2	14.558	1336847	60107	16.808
Total		7953645	425563	100.000

^{1}H NMR, $CDCl_3$, 400 MHz



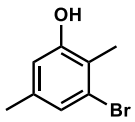
9a

^{13}C NMR, $CDCl_3$, 101 MHz



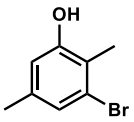
9a

^{1}H NMR, $CDCl_3$, 400 MHz



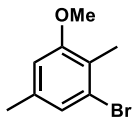
9b

^{13}C NMR, $CDCl_3$, 101 MHz



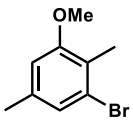
9b

^{1}H NMR, $CDCl_3$, 400 MHz



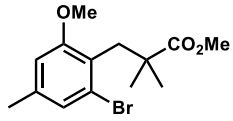
10

^{13}C NMR, $CDCl_3$, 101 MHz



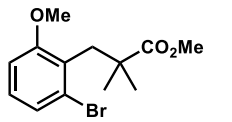
10

^{1}H NMR, $CDCl_3$, 400 MHz



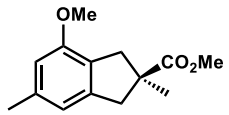
6a

^{13}C NMR, $CDCl_3$, 101 MHz



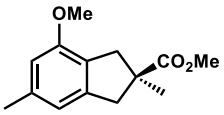
6a

1H NMR, $CDCl_3$, 500 MHz

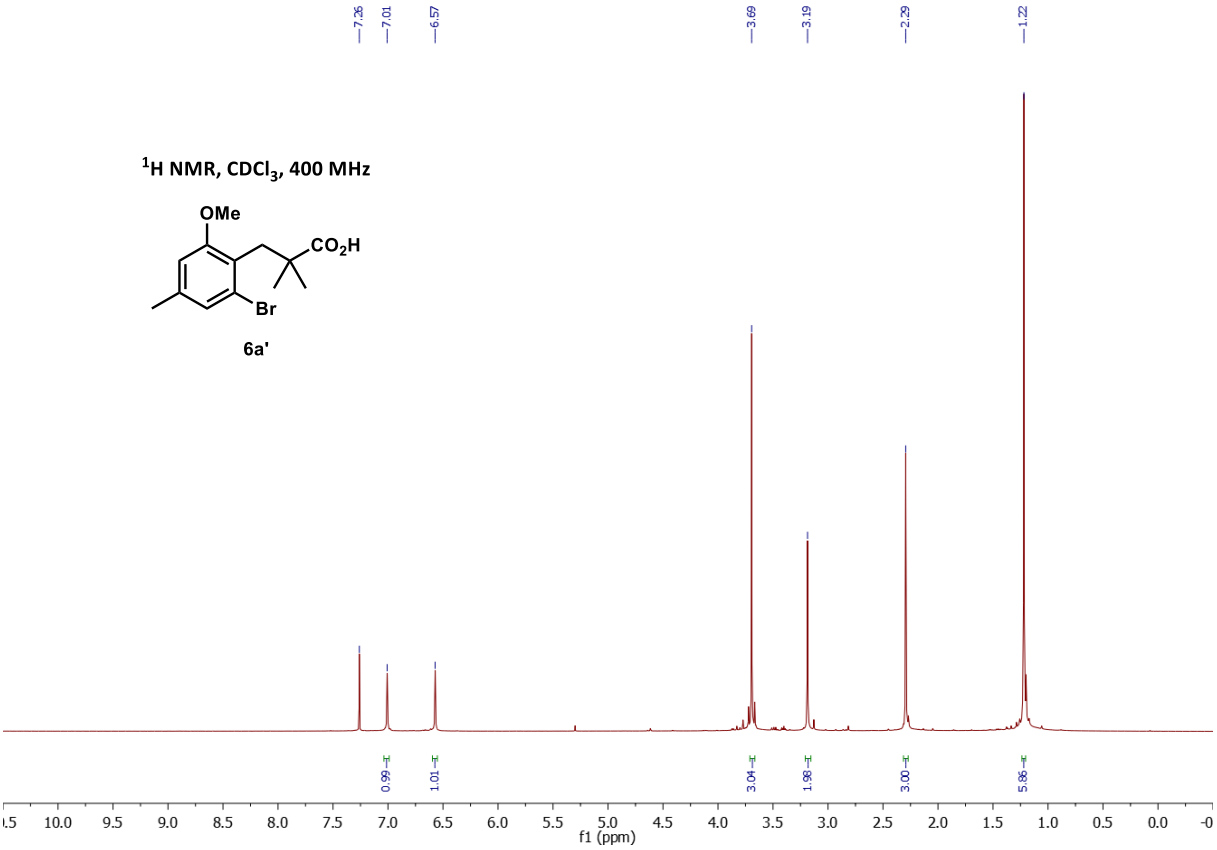


11'

^{13}C NMR, $CDCl_3$, 126 MHz

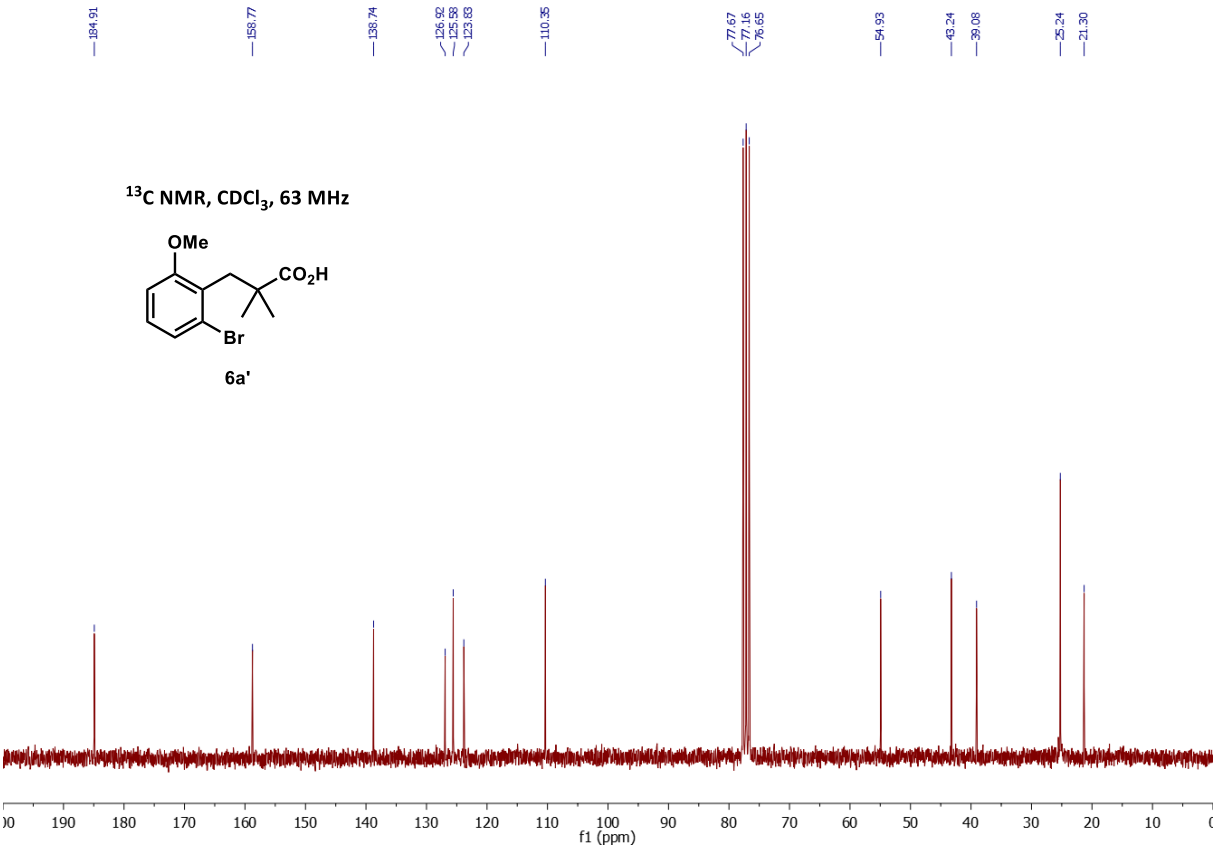


11'



^{1}H NMR, $CDCl_3$, 400 MHz

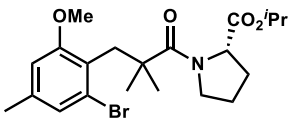
6a'



^{13}C NMR, $CDCl_3$, 63 MHz

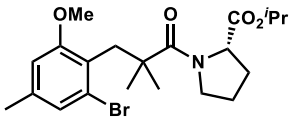
6a'

^{1}H NMR, $CDCl_3$, 500 MHz



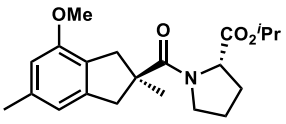
6b

^{13}C NMR, $CDCl_3$, 126 MHz



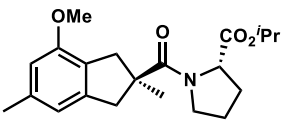
6b

^{1}H NMR, $CDCl_3$, 500 MHz



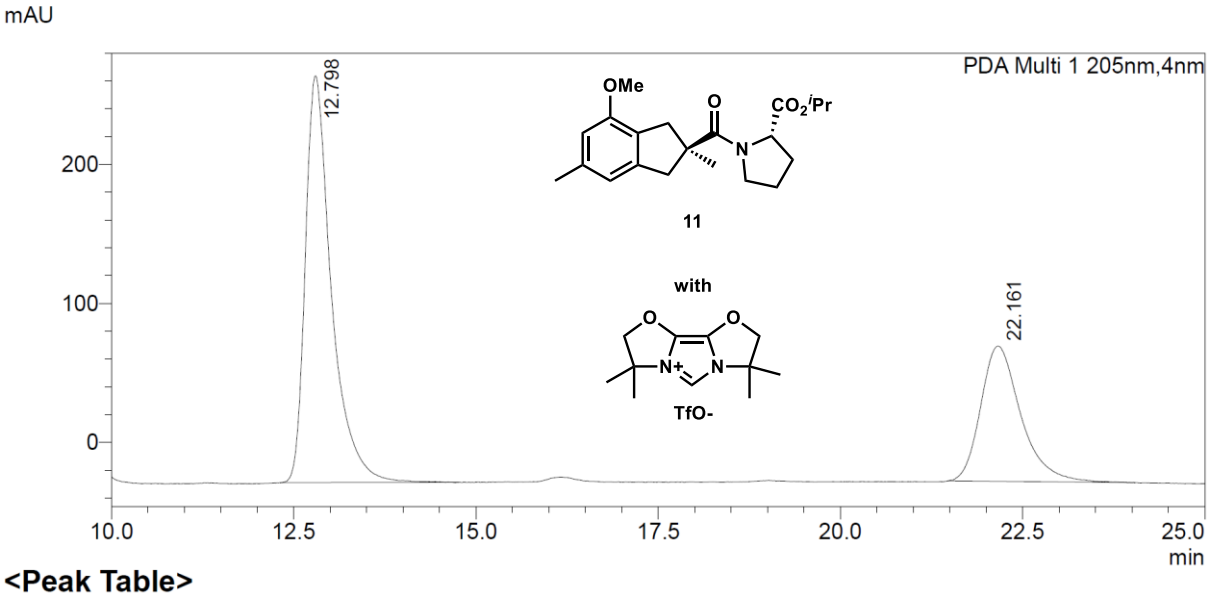
11

^{13}C NMR, $CDCl_3$, 126 MHz



11

<Chromatogram>

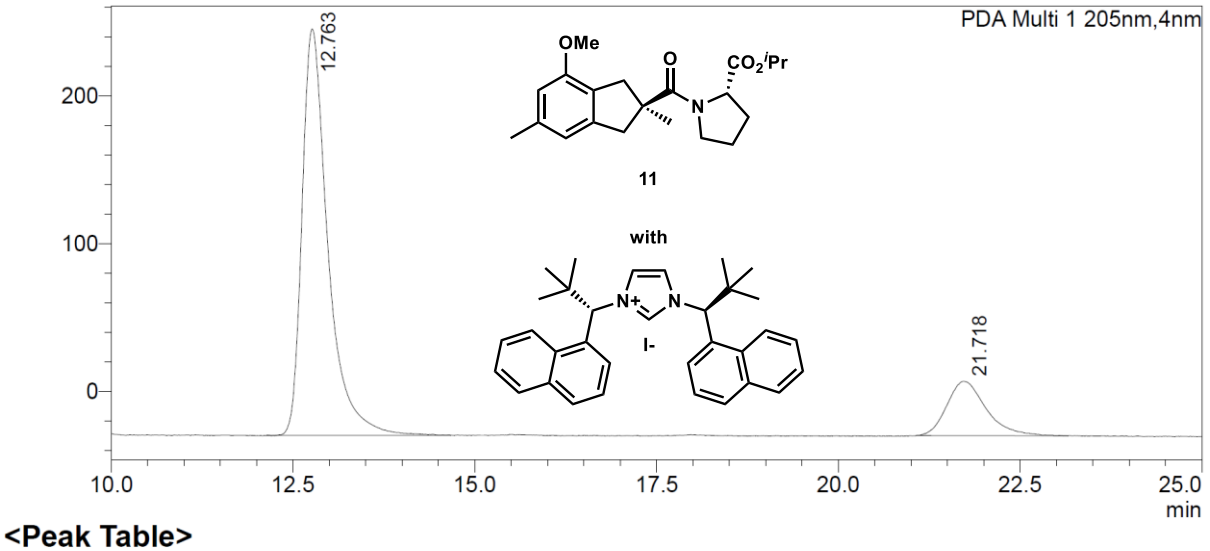


<Peak Table>

PDA Ch1 205nm

Peak#	Ret. Time	Area	Height	Area%
1	12.798	7298418	292502	66.186
2	22.161	3728758	97388	33.814
Total		11027177	389891	100.000

<Chromatogram>

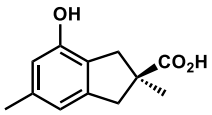


<Peak Table>

PDA Ch1 205nm

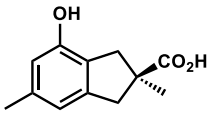
Peak#	Ret. Time	Area	Height	Area%
1	12.763	6790822	274912	85.107
2	21.718	1188296	34696	14.893
Total		7979119	309609	100.000

^{1}H NMR, DMSO-d6, 500 MHz



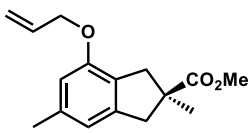
12

^{13}C NMR, DMSO-d6, 126 MHz



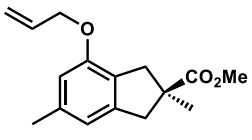
12

^{1}H NMR, $CDCl_3$, 500 MHz



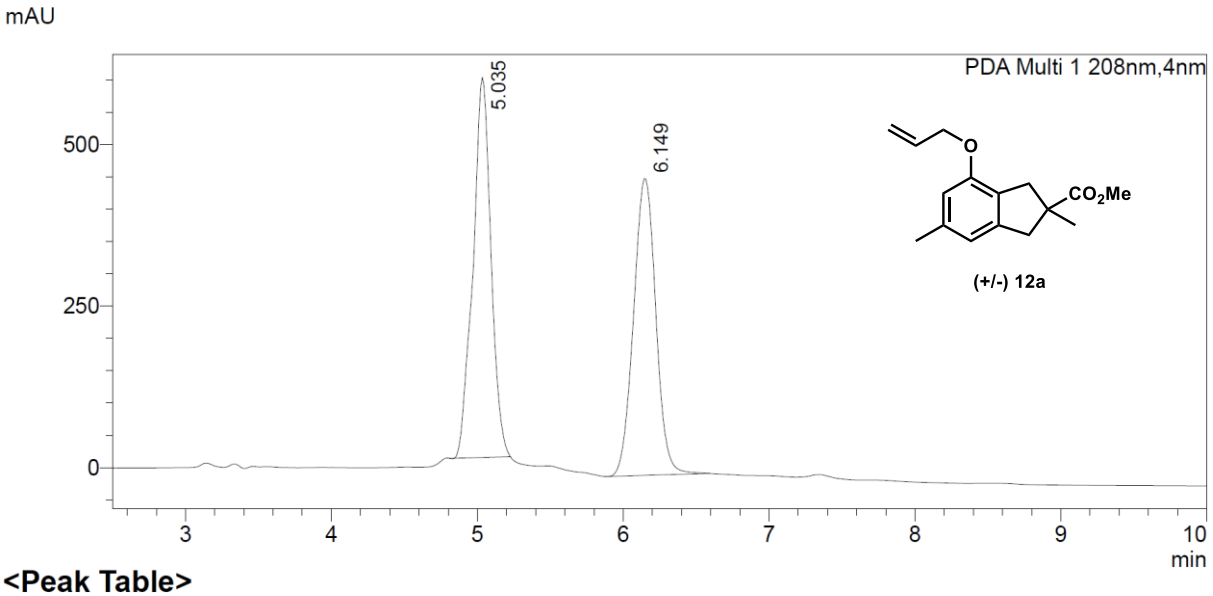
12a

^{13}C NMR, $CDCl_3$, 126 MHz



12a

<Chromatogram>

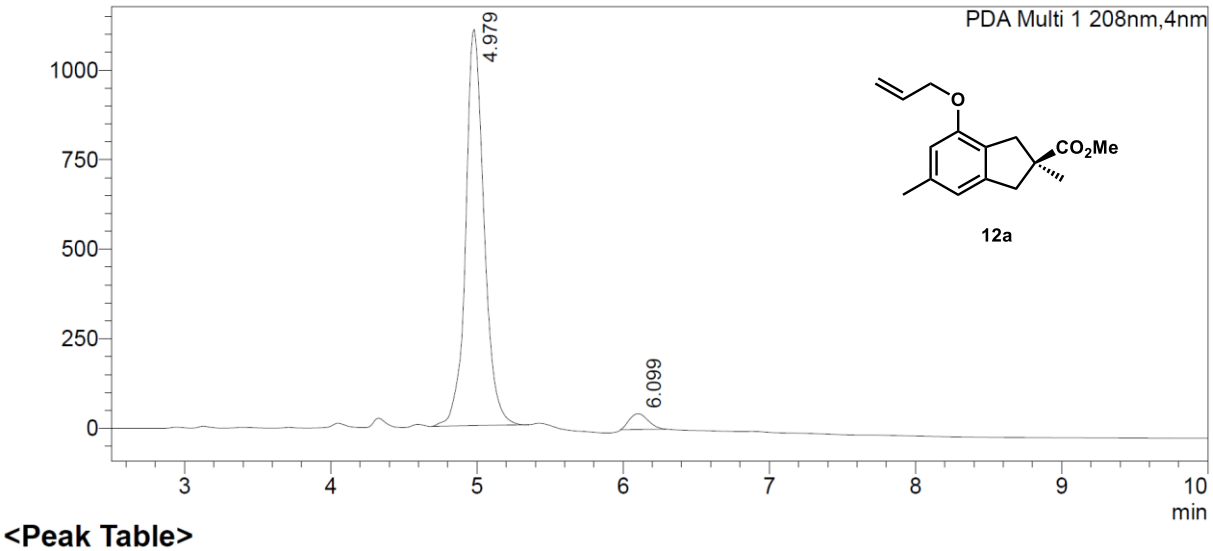


<Peak Table>

PDA Ch1 208nm

Peak#	Ret. Time	Area	Height	Area%
1	5.035	5058195	588405	50.908
2	6.149	4877789	459125	49.092
Total		9935984	1047530	100.000

<Chromatogram>

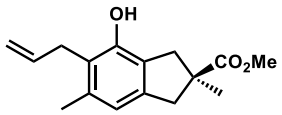


<Peak Table>

PDA Ch2 225nm

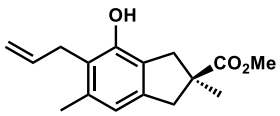
Peak#	Ret. Time	Area	Height	Area%
1	4.979	3389276	439702	95.732
2	6.097	151099	15414	4.268
Total		3540375	455117	100.000

^{1}H NMR, $CDCl_3$, 500 MHz



4

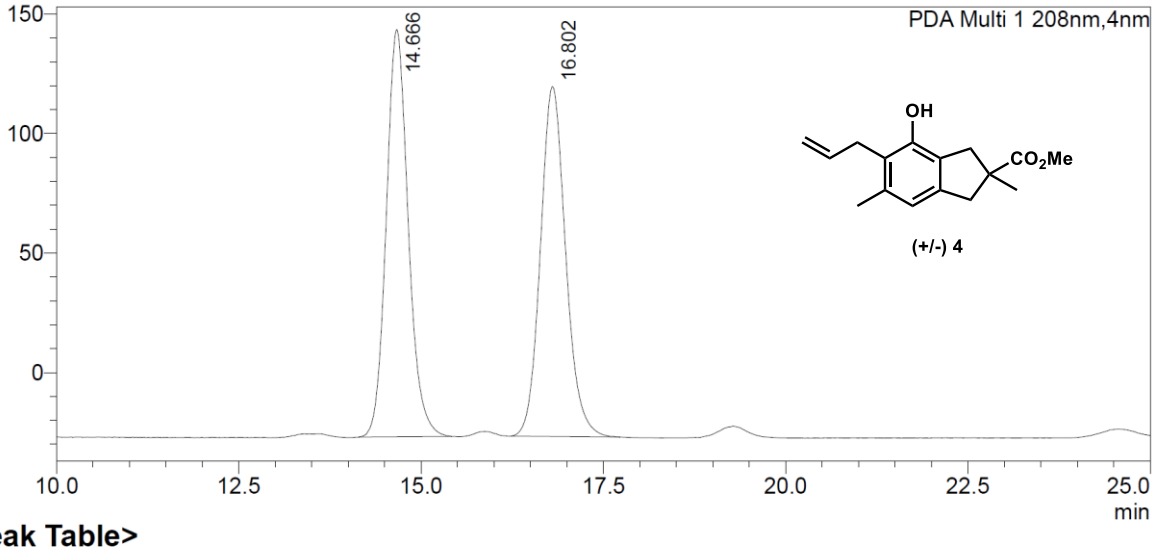
^{13}C NMR, $CDCl_3$, 126 MHz



4

<Chromatogram>

mAU



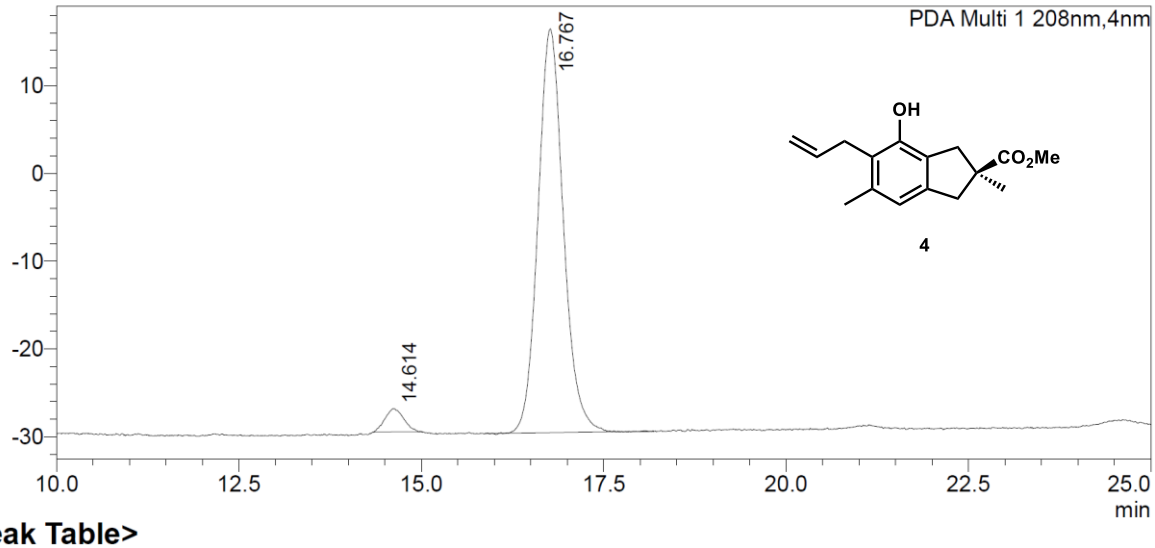
<Peak Table>

PDA Ch1 208nm

Peak#	Ret. Time	Area	Height	Area%
1	14.666	3577396	170451	50.347
2	16.802	3528036	146378	49.653
Total		7105432	316829	100.000

<Chromatogram>

mAU

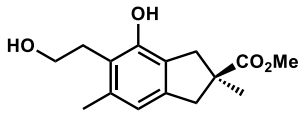


<Peak Table>

PDA Ch1 208nm

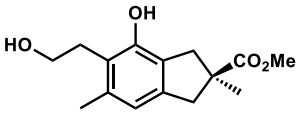
Peak#	Ret. Time	Area	Height	Area%
1	14.614	47308	2670	4.077
2	16.767	1113046	46025	95.923
Total		1160354	48696	100.000

^{1}H NMR, $CDCl_3$, 500 MHz



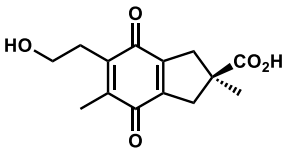
14

^{13}C NMR, $CDCl_3$, 126 MHz



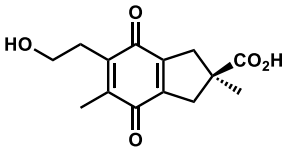
14

^{1}H NMR, $CDCl_3$, 500 MHz



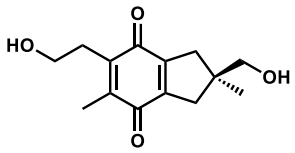
1

^{13}C NMR, $CDCl_3$, 126 MHz



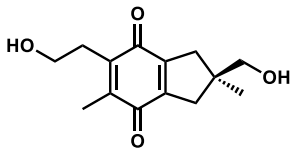
1

^{1}H NMR, $CDCl_3$, 500 MHz



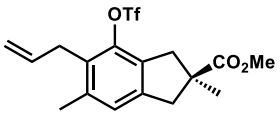
2

^{13}C NMR, $CDCl_3$, 126 MHz



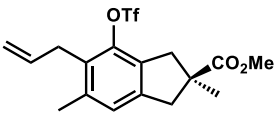
2

^{1}H NMR, $CDCl_3$, 500 MHz



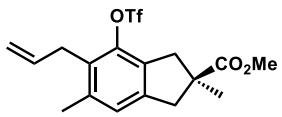
4a

^{13}C NMR, $CDCl_3$, 126 MHz



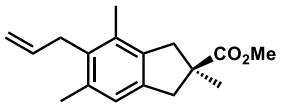
4a

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



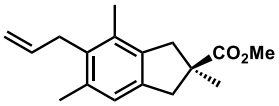
4a

^{1}H NMR, $CDCl_3$, 500 MHz

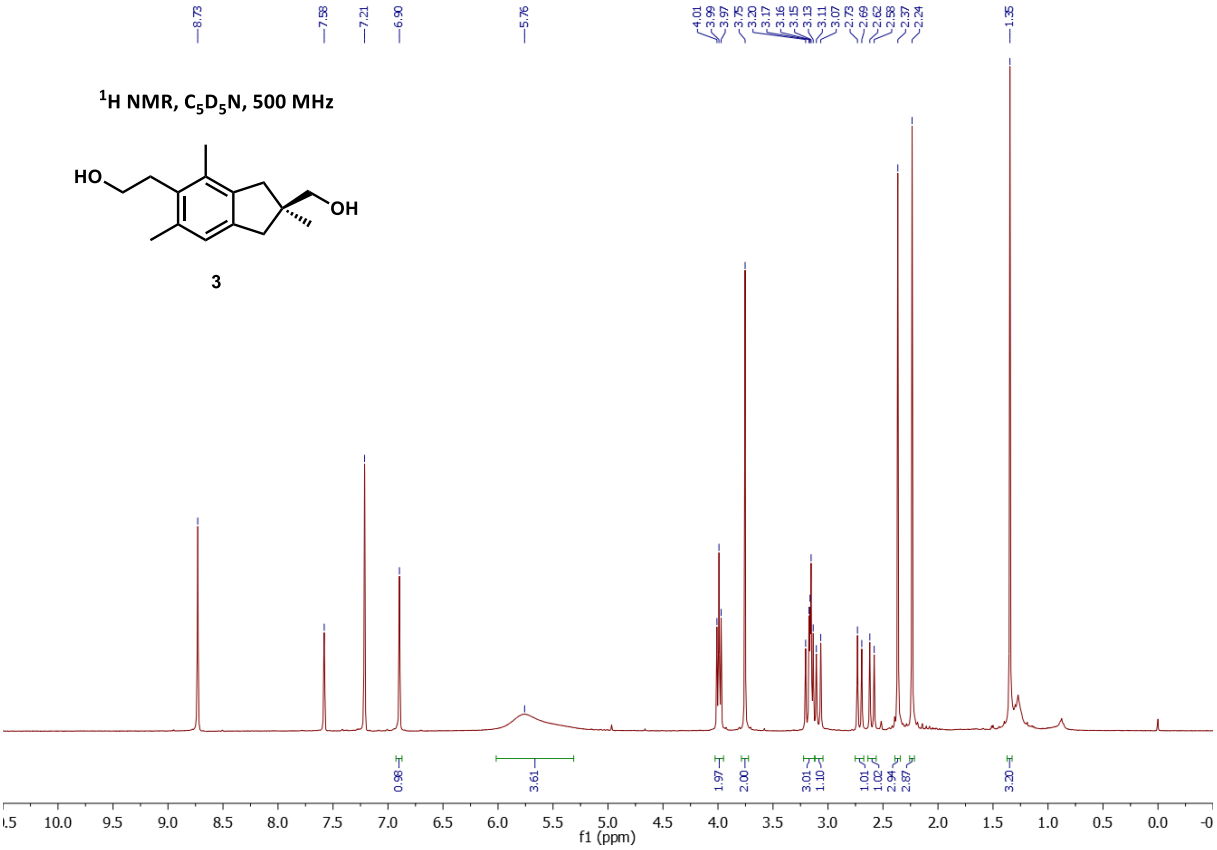


15

^{13}C NMR, $CDCl_3$, 126 MHz

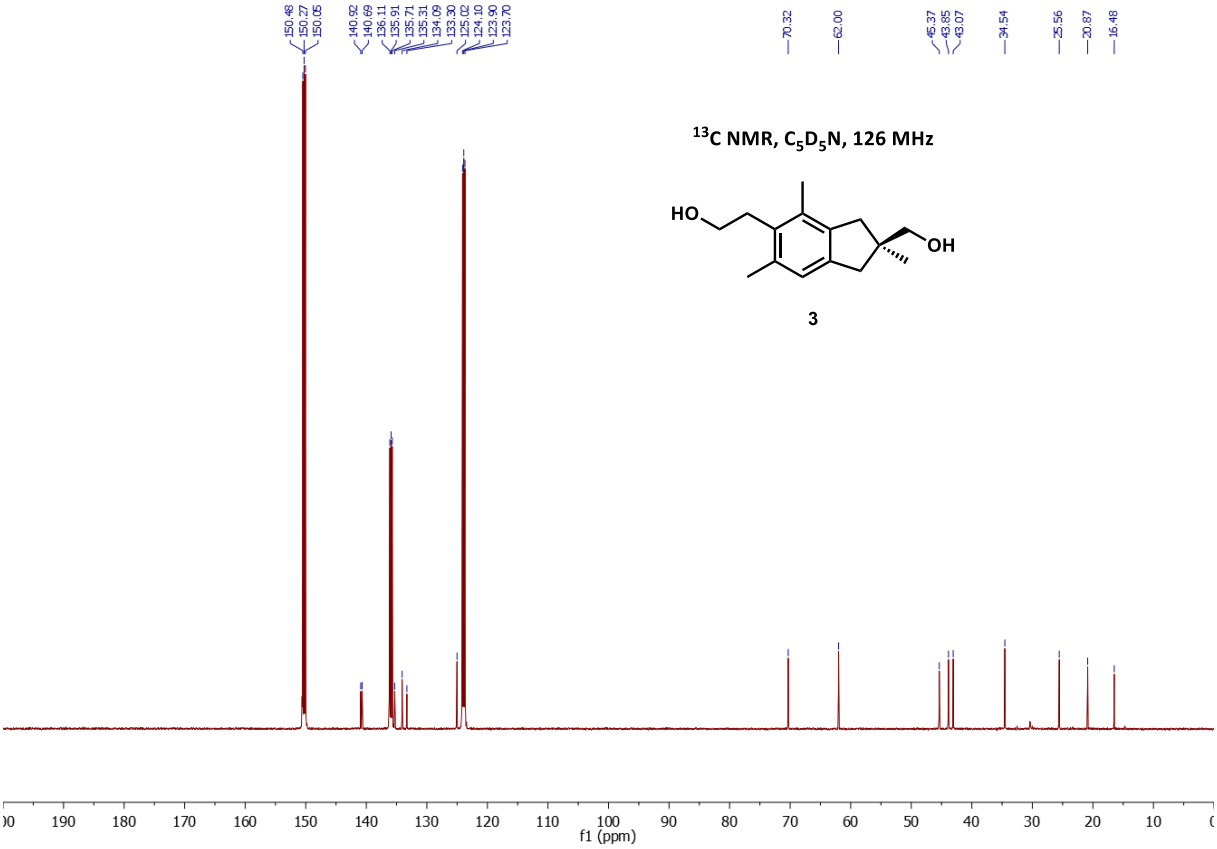


15



^{1}H NMR, C_5D_5N, 500 MHz

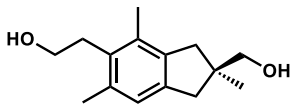
3



^{13}C NMR, C_5D_5N, 126 MHz

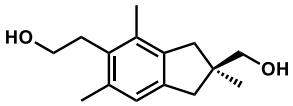
3

^{1}H NMR, $CDCl_3$, 500 MHz



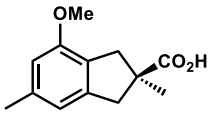
3

^{13}C NMR, $CDCl_3$, 126 MHz



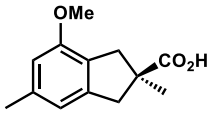
3

^{1}H NMR, $CDCl_3$, 500 MHz



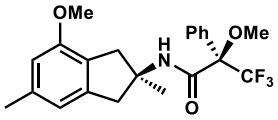
12b

^{13}C NMR, $CDCl_3$, 126 MHz



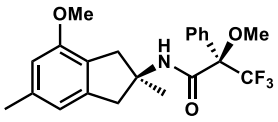
12b

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



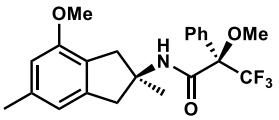
16a

^{13}C NMR, $CDCl_3$, 126 MHz

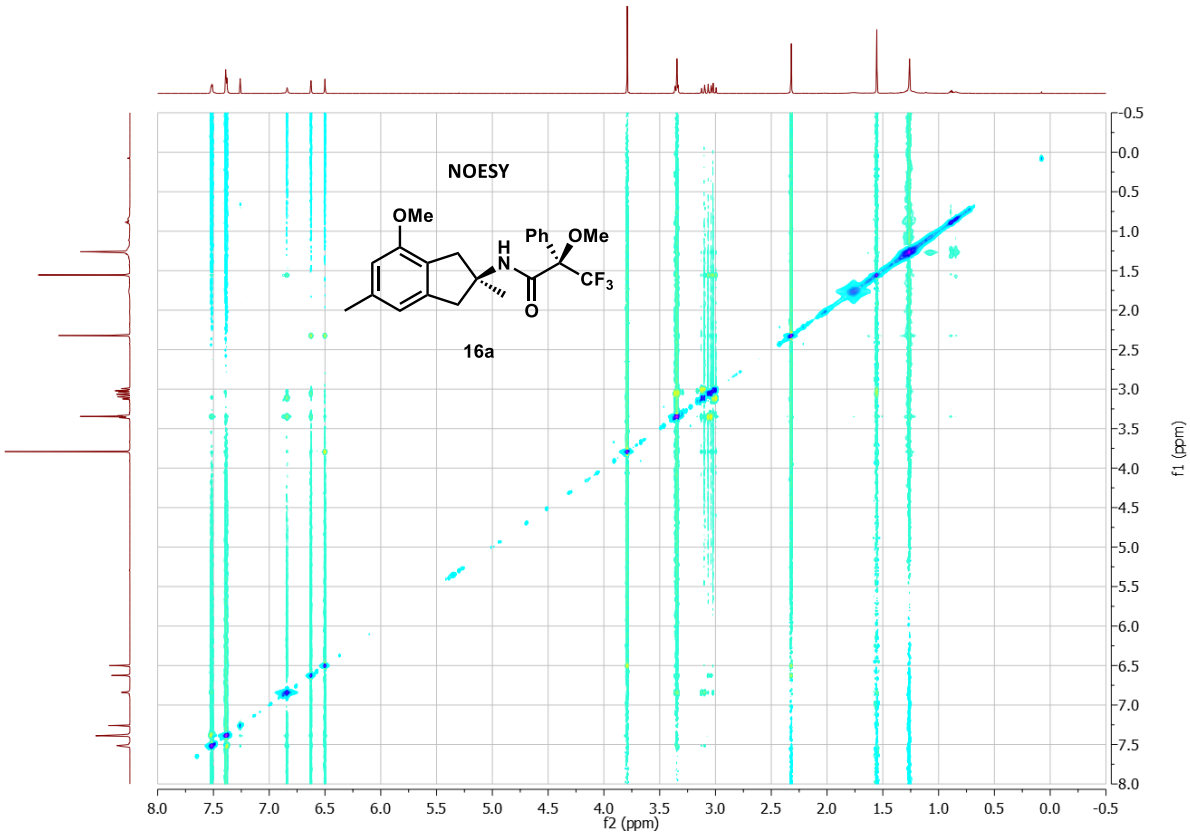


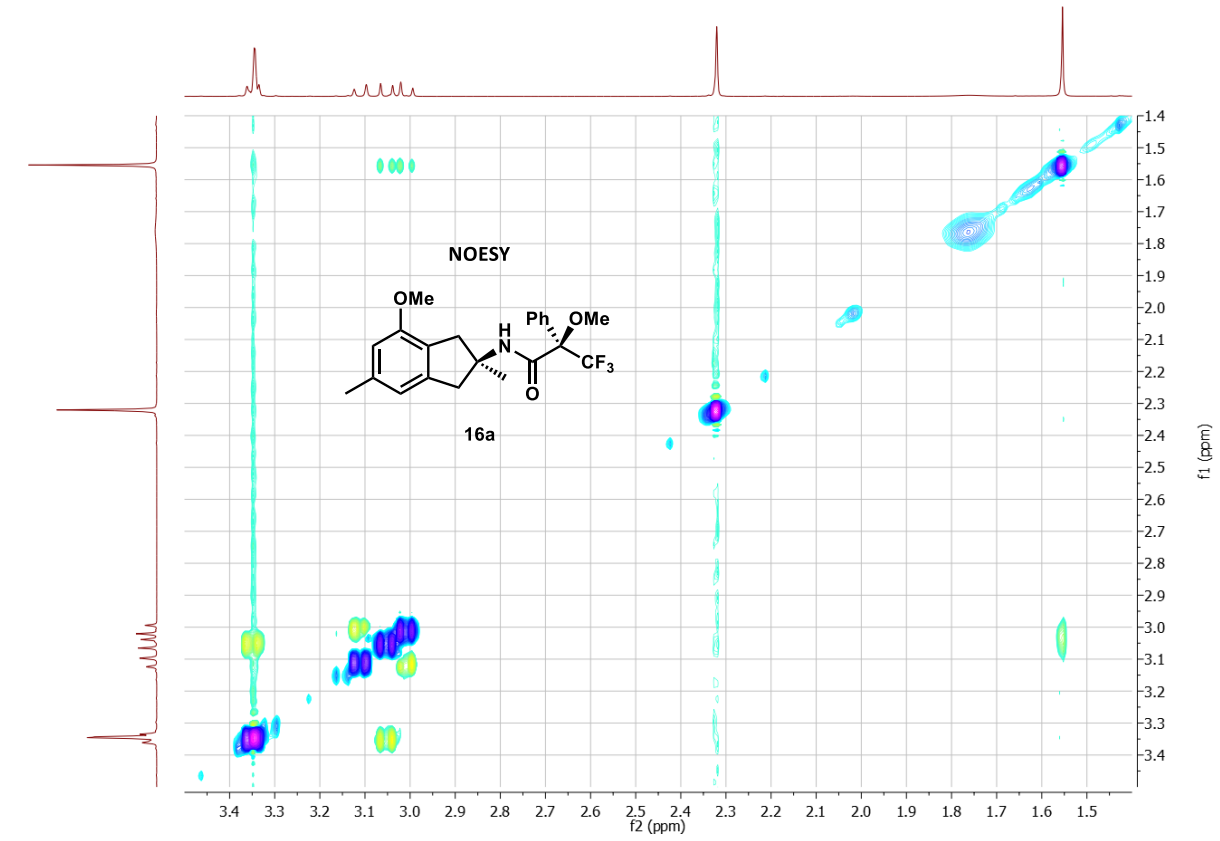
16a

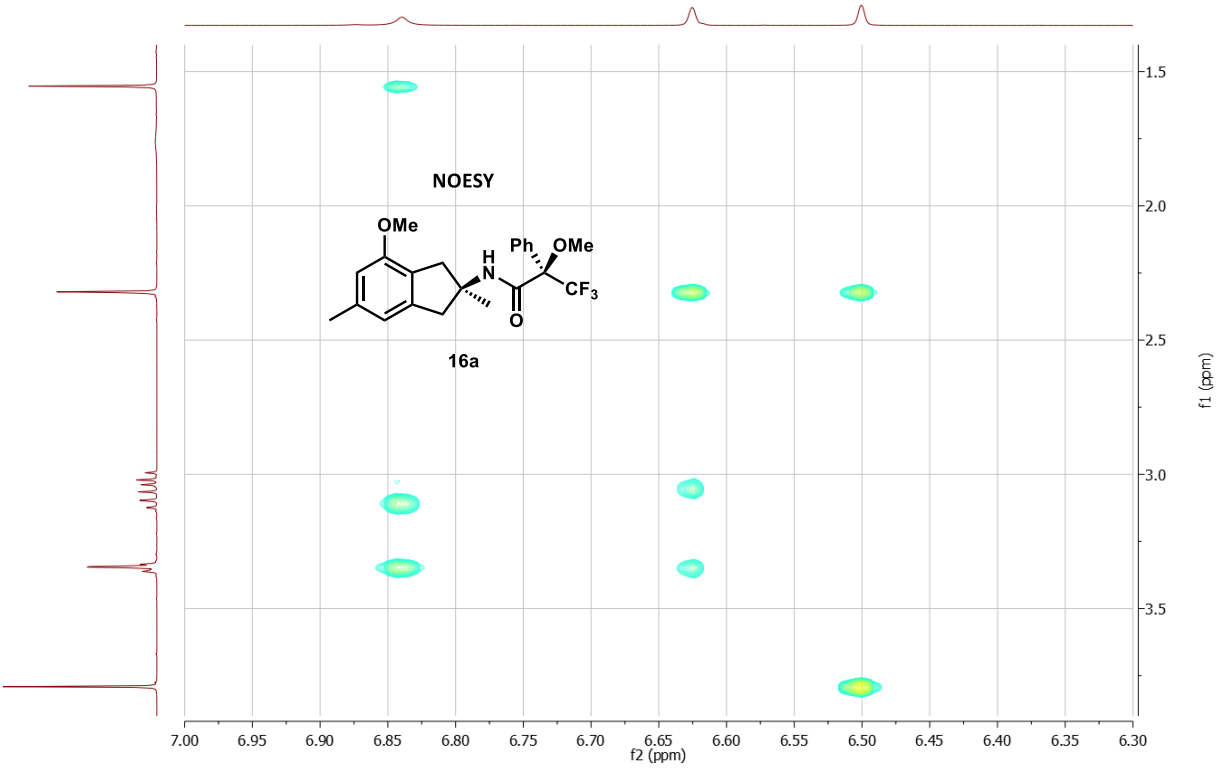
^{19}F NMR, $CDCl_3$, 376 MHz

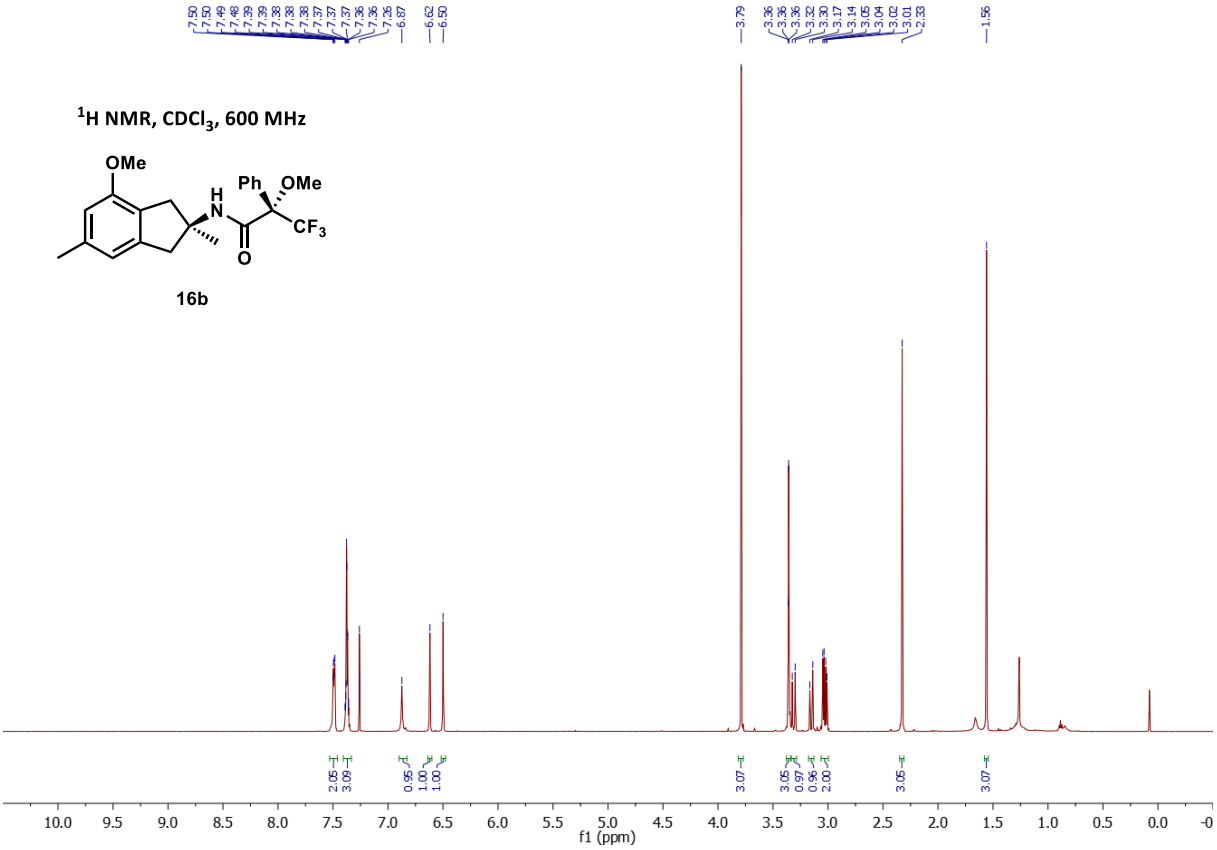


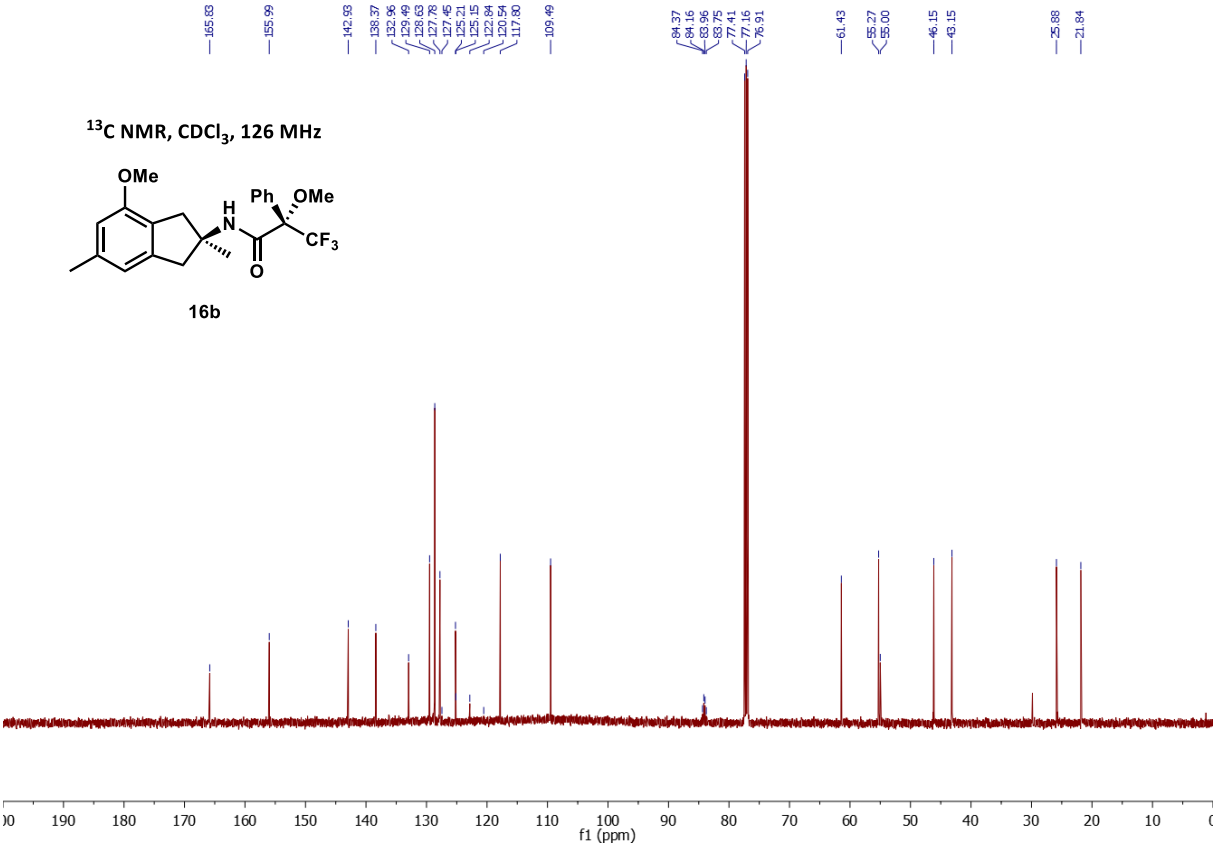
16a



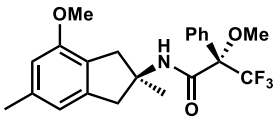

NOESY
OMe
Ph
OMe
H
N
CF3
O
16a
f2 (ppm)
f1 (ppm)


NOESY
OMe
Ph
OMe
H
N
CF3
O
16a
f2 (ppm)
f1 (ppm)

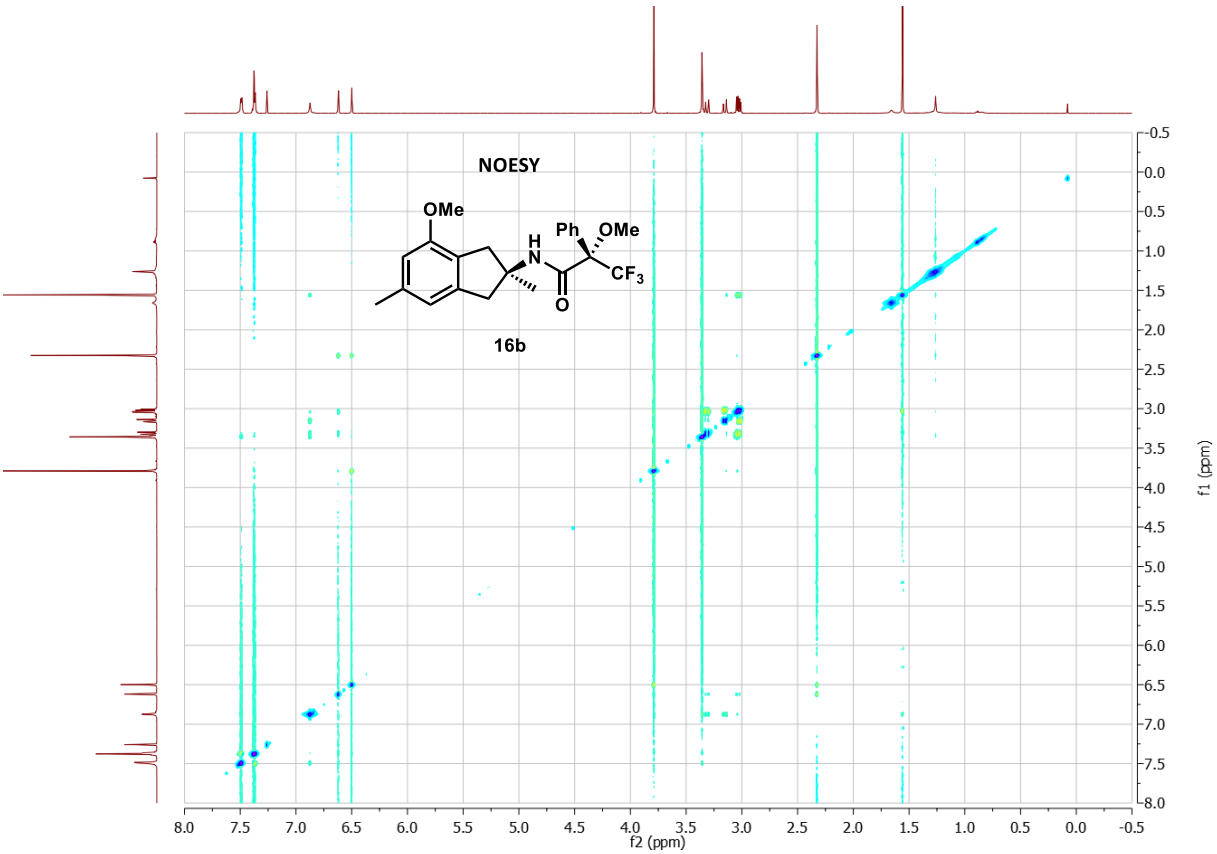

^{1}H NMR, $CDCl_3$, 600 MHz
OMe
Ph
OMe
H
N
CF3
O
16b
f1 (ppm)

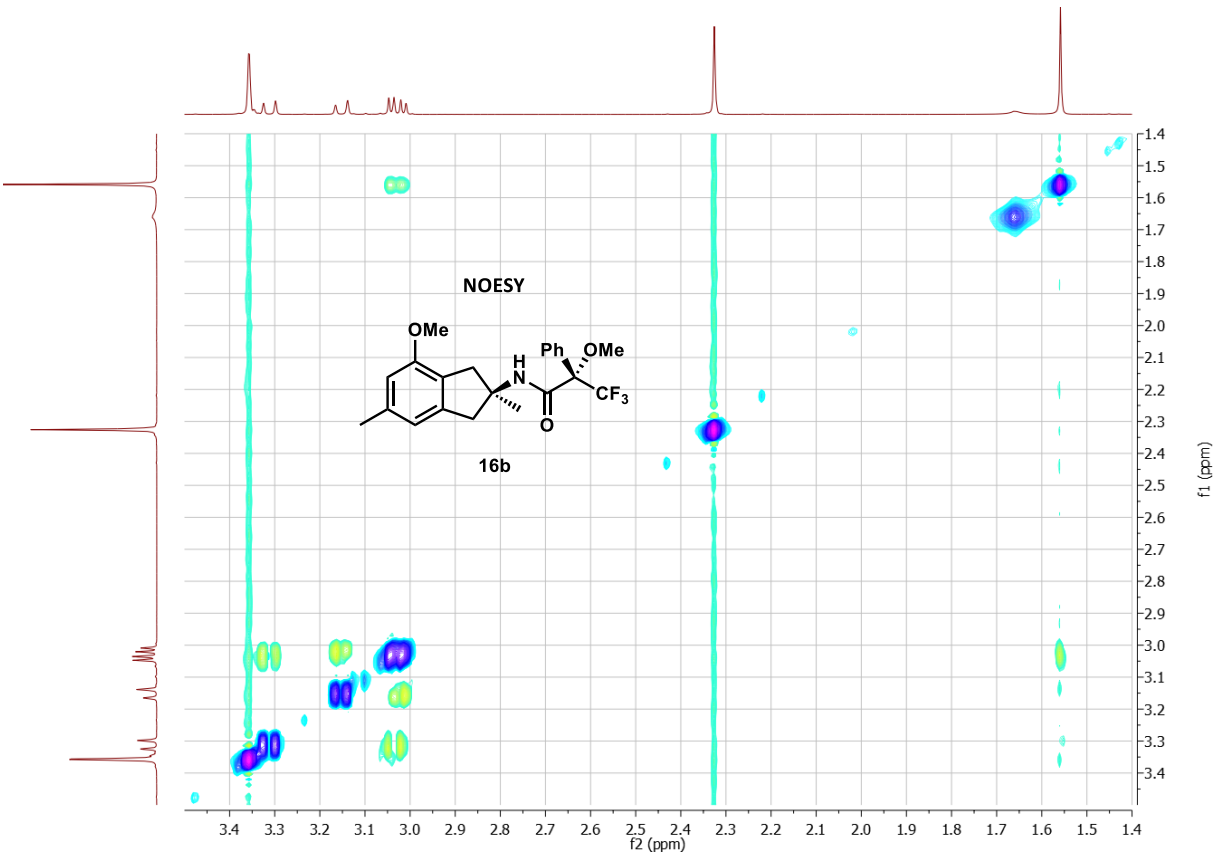

^{13}C NMR, $CDCl_3$, 126 MHz
OMe
Ph
OMe
H
N
CF3
O
16b
f1 (ppm)

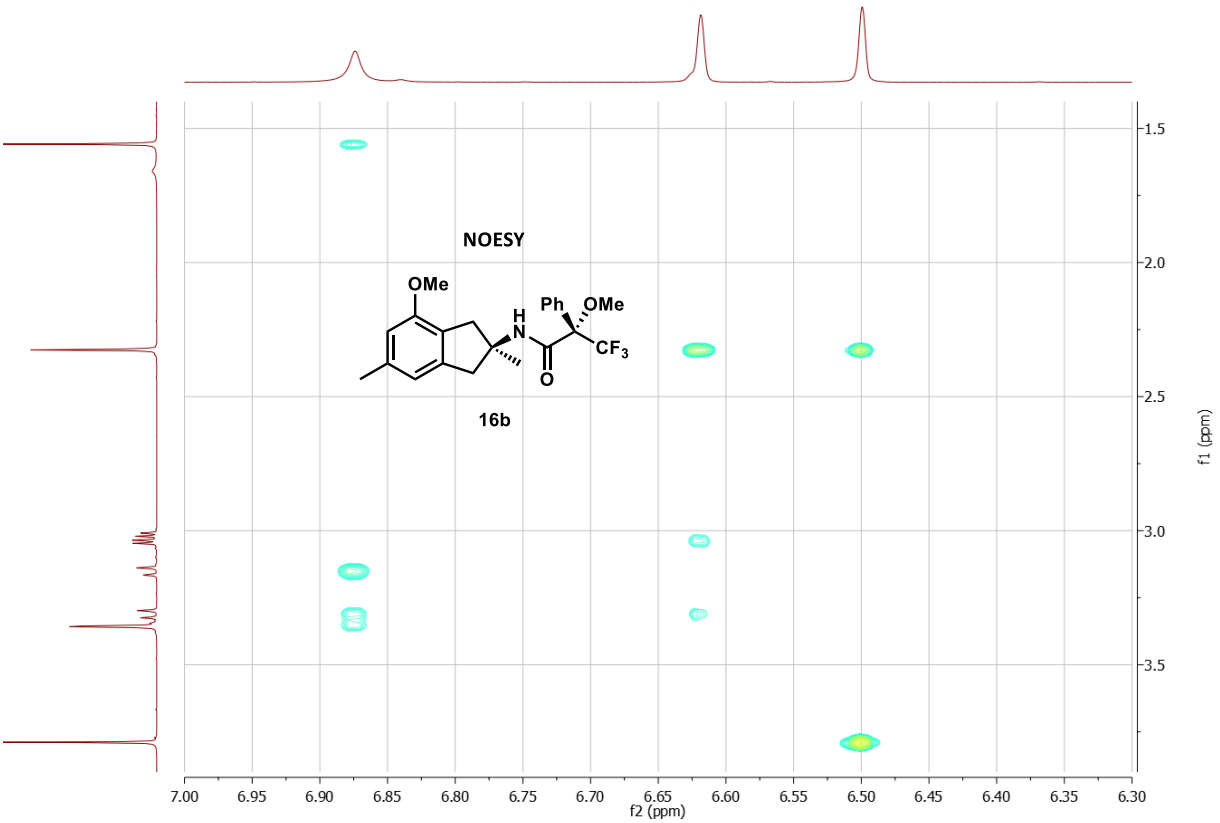
^{19}F NMR, $CDCl_3$, 376 MHz



16b




NOESY
OMe
Ph
OMe
H
N
CF3
O
16b
f1 (ppm)
f2 (ppm)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OMe
Ph
OMe
H
N
CF3
O
16b
f1 (ppm)
f2 (ppm)