Titanium(IV)-Catalyzed Stereoselective Synthesis of Spirooxindole-1-pyrrolines

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Table of contents

I. General Information

The following abbreviations are used throughout: ethyl acetate (EtOAc), bis(oxazolinyl)pyridine (pybox), enantiomeric excess (*ee*), isopropanol (IPA), tetrahydrofuran (THF), Sodium tetrakis(3,5-trifluoromethyl)phenylborate (NaBArF), 2,6-Bis[(3a*R*,8a*S*)-3a,8a-dihydro-8H-indeno[1,2-d]oxazolin-2-yl]pyridine [(*R*,*S*)-indapybox].

Materials: Indole-2,3-dione (isatin) reagents were purchased from commercial sources. 5-Methoxy-2-(4-methoxyphenyl)oxazole was prepared according to literature procedure and was freshly purified before use.[1] Dry CH_2Cl_2, THF, and Et_2O solvents were dispensed from a solvent purification system that passes solvent through two columns of dry neutral alumina. Chloroform ($CHCl_3$) was purchased from EMD and is stabilized with 7.5% ethanol. 2,6-Bis[(3a*S*,8a*R*)-3a,8a-dihydro-8H-indeno[1,2-d]oxazolin-2-yl]pyridine [(*R*,*S*)-indapybox] was synthesized according to literature procedures.[2-4] Sodium tetrakis(3,5-trifluoromethyl)phenylborate (NaBArF) was synthesized according to literature procedure.[5] Scandium(III) chloride [$ScCl_3(THF)_3$] was prepared according to literature procedure,[2,6,7] while scandium(III) triflate [$Sc(OTf)_3$] was purchased from Strem Chemicals, Inc. or Sigma-Aldrich Co. LLC.

Synthesis, Purification and Analysis: All reactions were performed in oven-dried and argon-purged glassware (including 8- and 4-mL Fisher Scientific vials fitted with PTFE closure). Molecular sieves (4Å) < 50 μm were activated in a vacuum chamber by heating them with a heat gun for 15 min. All ^1H and ^{13}C spectra were recorded at ambient temperature at 600, 400 or 300 MHz and 150, 100, or 75 MHz, respectively, using a Bruker Avance 600 MHz NMR spectrometer, Varian VNMRS 600 (600 MHz), Varian Mercury 300 (300 MHz), MercuryPlus 300 (300 MHz), or Varian Inova 400 (400 MHz) spectrometers. The ^1H spectral data are reported as follows: chemical shift in parts per million downfield from tetramethylsilane on the δ scale, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; s, septet; m, multiplet; dd, doublet of doublets, and b, broadened), coupling constant (Hz), and integration. Carbon NMR chemical shifts are reported in ppm from tetramethylsilane with the solvent reference employed as the internal standard (deuterochloroform ($CDCl_3$) at 77.0 ppm). Infrared spectra were recorded neat on an ATI-FTIR spectrometer.

All HPLC analyses were performed on a Shimadzu LC-20AB system with a Daicel CHIRALPAK® AD-H column (4.6 x 250 mm, 5 μm), Daicel CHIRALPAK® AS-H column (4.6 x 250 mm, 5 μm), or Daicel CHIRALCEL® OD-H column (4.6 x 250 mm, 5 μm), each attached to a guard column, at a constant flow rate (isopropanol/hexanes isocratic system) using Shimadzu SPD-M20A photodiode array detector and 40 °C column oven temperature.

Compounds were analyzed for LRMS in the positive ion mode by an Applied Biosystems Qtrap (Foster City, CA). Source parameters were 5 kV spray voltage, with a curtain plate temperature of 275 °C and sheath gas setting of 15. Samples were analyzed via flow injection analysis by injecting 20 μL samples into a stream of 80% MeOH/20% aqueous solution of 0.1% formic acid, flowing at 200 μL per minute.

II. General Procedures

Synthesis of phosphonium ylide[8]

To a stirred solution of triphenylphosphine (1.15 equiv, 18.58 mmol, 4.86 g) in toluene (20 mL) was added ethyl bromoacetate (1 equiv, 16.16 mmol, 1.8 mL). The reaction was heated at 80 ˚C for 12 h. The cooled reaction mixture was concentrated *in vacuo* and dissolved in CH_2Cl_2 (100 mL) and added to a separatory funnel. To this was added an aqueous solution of KOH (2.0 g dissolved in 75 mL of H_2O), and the mixture was vigorously shaken and then let sit for 10 min. The organic layer was isolated, dried over Na_2SO_4, filtered and concentrated *in vacuo*.

Synthesis of acyl protected alkylidene oxindole[9,10]

In a 20 mL scintillation vial with a stir bar charged with 5-fluoroindoline-2,3-dione (1 equiv, 5.168 mmol, 0.86 g), in THF (0.65 M, 8 mL) was added phosphonium ylide (1.1 equiv, 5.7 mmol, 2.0 g). After 12 h the reaction was transferred to a 100 mL round bottom flask, concentrated *in vacuo*, and product was recrystallized from EtOH to afford N-H alkylidene product.

To a 250 mL round bottom flask equipped with a stir bar under inert atmosphere and charged with alkylidene (1 equiv, 8.1 mmol, 1.89 g) was added CH_2Cl_2 (0.1 M, 81 mL). Subsequently acetic anhydride (7 equiv, 56.7 mmol, 5.28 mL) and pyridine (1 equiv, 8.1 mmol, 0.65 mL) were added, followed immediately by *N,N*-dimethyl-aminopyridine (0.1 equiv, 0.81 mmol, 0.01 g). After the reaction was complete as judged by thin layer chromatography (3:7 EtOAc/hexanes) (generally done in about 45 min to 90 min), sat. aq. $NaHCO_3$ (80 mL) was added. The reaction was stirred until the evolution of gas ceased (generally about 2 h), and the organic layer was collected. The organic layer was washed 3 x 60 mL of sat. aq. $CuSO_4$, recollected and dried over Na_2SO_4, concentrated *in vacuo* and the product was recrystallized in EtOH. Filter sample through a pad of silica in 20% EtOAc/hexanes if recrystallization attempts yield a viscous oil. (Note: that aqueous $CuSO_4$ and $NaHCO_3$ react with each other exothermically and should not be mixed unless on a small scale.)

General procedure for Ti(IV)-catalyzed synthesis of spirooxindole-1-pyrrolines:

A solution of alkylidene oxindole (1.5 equiv, 0.15 mmol) and oxazole (1.0 equiv, 0.1 mmol) was prepared in dry CH_2Cl_2 (0.2 M) at 25 °C in a 4 mL oven dried scintillation vial fitted with a magnetic stir bar. To this homogeneous solution, a solution of $TiCl_4$ (0.2 equiv, 0.02 mmol, 1.0 M in CH_2Cl_2) was added and the reaction was sealed under argon atmosphere and stirred until completion as judged by TLC (10% EtOAc/CH_2Cl_2), which was < 1 h. Upon completion the reaction was diluted with 10 mL of CH_2Cl_2. The organic layer was washed with sat. sodium potassium tartrate (20 mL), brine (20 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Before purification the diastereomeric ratio (dr) was obtained using ^1H

NMR spectroscopy. The crude material was then purified by flash chromatography (gradient 100% DCM to 10% EtOAc/DCM) to yield the spiro-1-pyrroline product.

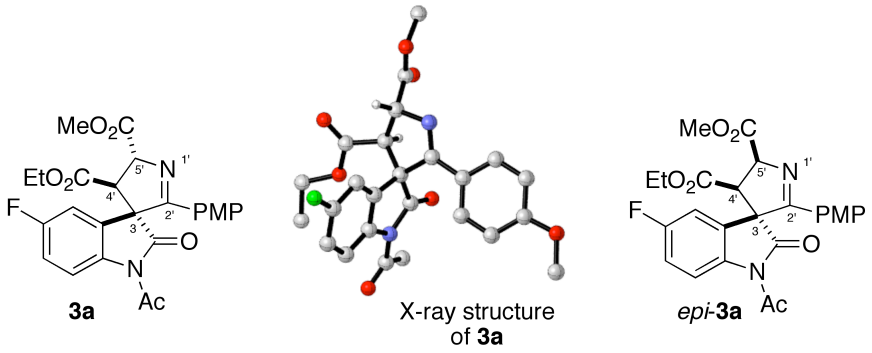
General procedure for Sc(III)-catalyzed synthesis of spirooxindole-1-pyrrolines:

To solution of $Sc(OTf)_3$ (0.2 equiv, 0.02 mmol) and dry CH_2Cl_2 (0.2 M) at 25 °C, in a 4 mL oven dried scintillation vial fitted with a magnetic stir bar, was added the alkylidene oxindole (1.5 equiv, 0.15 mmol) and oxazole (1.0 equiv, 0.1 mmol). The reaction was sealed under argon atmosphere and stirred until completion as judged by TLC (10% EtOAc/CH_2Cl_2), which was approximately 5 h. Upon completion the reaction was diluted with 10 mL of CH_2Cl_2. When judged to be complete, the reaction was concentrated in vacuo and the diastereomeric ratio was obtained using ^{1}H NMR spectroscopic analysis of the unpurified reaction mixture. The crude material was then purified by flash chromatography (gradient 100% DCM to 10% EtOAc/DCM) to yield the spiro-1-pyrroline product. Using 5 mol% catalyst loading is effective for high conversion, but it was observed that the rate of the reaction can be affected by the "age" and dryness of the $Sc(OTf)_3$ bottle.

General procedure for the Sc(III)-catalyzed enantioselective synthesis of spirooxindole-1-pyrrolines:

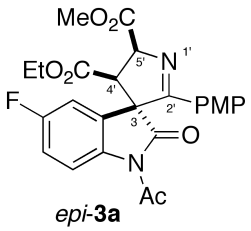
A 4 mL scintillation vial filled with 0.01 g of 4 Å molecular sieves and magnetic stir bar was dried under vacuum with a heat gun and then (*R*,*S*)-indapybox (0.11 equiv, 0.011 mmol 0.0044 g), NaBArF (0.1 equiv, 0.01 mmol, 0.0088 g), and $Sc(OTf)_3$ (0.2 equiv, 0.02 mmol, 0.010 g) were added, followed by $PhCH_3$ (0.5 mL). The mixture was allowed to stir at room temperature for 1-2 h to allow complexation of the ligand and metal. Then the alkylidene oxindole (1.5 equiv, 0.15 mmol) was added. After 5 min the oxazole (1.0 equiv, 0.1 mmol) was added. The reaction was then sealed under argon atmosphere and stirred until complete as judged by TLC (10% EtOAc/DCM), which was approximately 12 h. When judged to be complete, the reaction was concentrated in vacuo and the diastereomeric ratio was obtained using ^{1}H NMR analysis of the unpurified reaction mixture. A reversal in diastereoselectivity was observed when using the pybox ligand compared to conditions without a ligand. Next the mixture was purified by flash chromatography (gradient 100% DCM to 10% EtOAc/DCM) to yield the spirooxindole-1-pyrroline product. The enantioselectivity of the product was measured using HPLC with a chiral stationary phase, and compared to a racemic standard that was prepared using the Ti(IV)- or Sc(III)-catalyzed procedure without ligand.

III. Characterization Data

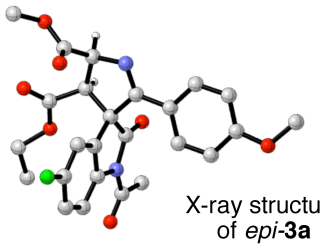


The stereochemistry for the major diastereomer **3a**, formed using $TiCl_4$ or $Sc(OTf)_3$ in the absence of ligand, was determined by X-ray crystallographic analysis to be the 3,4'-*trans*/4',5'-*trans* isomer (a racemic mixture of 3*S*,4'*R*,5'*R* and 3*R*,4'*S*,5'*S* notated 3*S**,4'*R**,5'*R**). The minor diastereomer (*epi*-**3a**) for this reaction was determined to be the 3,4'-*trans*/4',5'-*cis* isomer (3*S**,4'*R**,5'*S**) because this was identified as the major diasteromer using the Sc(III)-pybox conditions as confirmed using X-ray crystallography.

4'-ethyl 5'-methyl (3*S,4'*R**,5'*R**)-1-acetyl-5-fluoro-2'-(4-methoxyphenyl)-2-oxo-4',5'-dihydrospiro[indoline-3,3'-pyrrole]-4',5'-dicarboxylate (3a):** Synthesized according to the representative procedure for the titanium-catalyzed synthesis of spirooxindole-1-pyrrolines to afford the product as a white solid (43.2 mg, 90% yield, 91:9 dr). mp 65 – 68 ˚C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.33 (dd, J = 9.0, 4.6 Hz, 1H), 7.33 (d, J = 8.9 Hz, 2H), 7.10 (ddd, J = 8.9, 2.7 Hz, 1H), 6.76 (d, J = 9.0 Hz, 2H), 6.78-6.75 (m, 1H), 5.46 (d, J = 9.3 Hz, 1H), 4.38 (d, J = 9.2 Hz, 1H), 3.92 (s, 3H), 3.78 (q, J = 7.2 Hz, 2H), 3.76 (s, 3H), 2.72 (s, 3H), 0.81 (t, J = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.8, 170.7, 170.3, 168.9, 167.6, 162.4, 160.3 (d, J_{FC} = 247.5 Hz), 136.0 (d, J_{FCCCC} = 2.8 Hz), 129.5, 127.2 (d, J_{FCCC} = 8.0 Hz), 123.6, 118.7 (d, J_{FCCC} = 7.8 Hz), 116.9 (d, J_{FCC} = 22.5 Hz), 114.4, 111.5 (d, J_{FCC} = 24.8 Hz), 73.7, 67.4, 61.7, 58.3, 55.5, 53.3, 26.6, 13.6. IR (neat, selected peaks) 1751, 1728, 1605, 1255, 1171, 1014 cm^{-1}. LRMS calculated for $C_{25}H_{24}FN_2O_7$ $[M + H]^+$ 483.2, found 483.1. Recrystallization from DCM layered with hexanes and isopropyl alcohol afforded single crystals and the structure was confirmed by X-ray analysis.



epi-**3a**

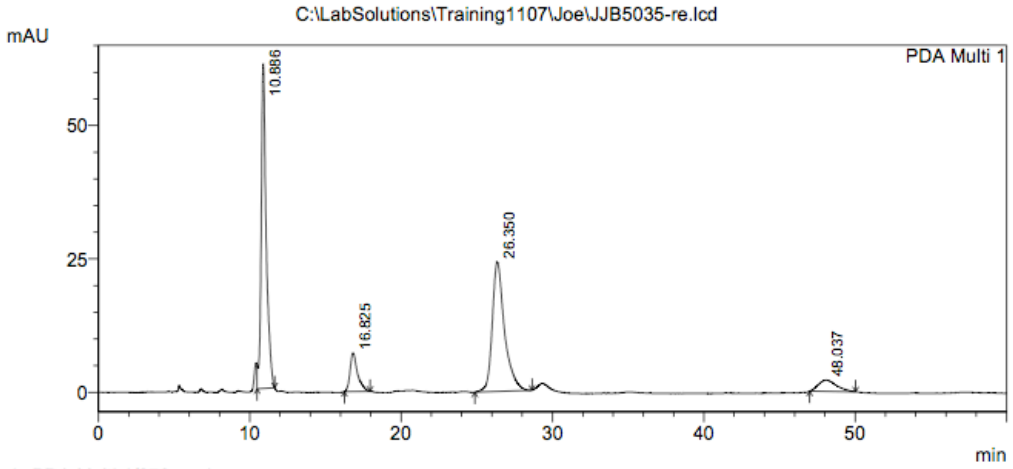


X-ray structure of *epi*-**3a**

The relative stereochemistry for *epi*-**3a**, formed using Sc-catalyzed conditions with the (*R*,*S*)-indapybox ligand was determined by X-ray crystallographic analysis to be the 3,4'-*trans*/4',5'-*cis* isomer. The absolute stereochemistry was assigned to be (3*S*,4'*R*,5'*S*) by analogy to the absolute configuration observed for products resulting from the addition of allylsilanes to alkylidene oxindoles using similar catalyst conditions.[11] (Note: the use of a chiral ligand promotes a reversal of diastereoselection relative to $TiCl_4$ or $Sc(OTf)_3$ conditions without ligand.)

4'-ethyl 5'-methyl (3*S*,4'*R*,5'*S*)-1-acetyl-5-fluoro-2'-(4-methoxyphenyl)-2-oxo-4',5'-dihydrospiro[indoline-3,3'-pyrrole]-4',5'-dicarboxylate (*epi*-3a): Synthesized according to the representative procedure for the Sc-catalyzed enantioselective synthesis of spirooxindole-1-pyrrolines to afford the product as a white foam (48.3 mg, 99% yield, 9:91 dr based on ^{1}H NMR, 86:14 er). $[\alpha]_D^{23.7}$ = + 53.8 (c = 1.82, $CHCl_3$ stabilized with 7.5% EtOH). Enantiomeric ratio was determined by HPLC with a Daicel CHIRALPAK® AD-H column (15% IPA/hexanes), 1.0 mL/min, t_R (major) = 49.8 min, t_R (minor) = 16.7 min, 86:14 er; . ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (dd, *J* = 9.0, 4.7 Hz, 1H), 7.63 (dd, *J* = 8.3, 2.8 Hz, 1H), 7.30 (d, *J* = 9.0 Hz, 2H), 7.10 (ddd, *J* = 8.8, 8.8, 2.8 Hz, 1H), 6.74 (d, *J* = 9.0 Hz, 2H), 5.40 (d, *J* = 9.2 Hz, 1H), 4.28 (d, *J* = 9.3 Hz, 1H), 3.90 (s, 3H), 3.79 – 3.73 (m, 2H), 3.75 (s, 3H), 2.69 (s, 3H), 0.79 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.1, 171.0, 170.5, 169.3, 167.1, 162.2, 160.5 (d, J_{FC} = 246.0 Hz), 136.2, 129.6, 128.1 (d, J_{FCCC} = 8.9 Hz), 123.9, 117.9 (d, J_{FCCC} = 7.8 Hz), 116.5 (d, J_{FCC} = 22.8 Hz), 114.3, 114.0 (d, J_{FCC} = 26.0 Hz), 73.4, 67.9, 61.5, 58.2, 55.4, 52.8, 26.6, 13.5. IR (neat, selected peaks) 1744, 1715, 1477, 1254, 1171, 1026, 653 cm^{-1}. LRMS calculated for $C_{25}H_{24}FN_2O_7$ $[M + H]^+$ 483.2, found 483.4.

Racemic standard mixture of **3a** (major) and *epi*-**3a** (minor):



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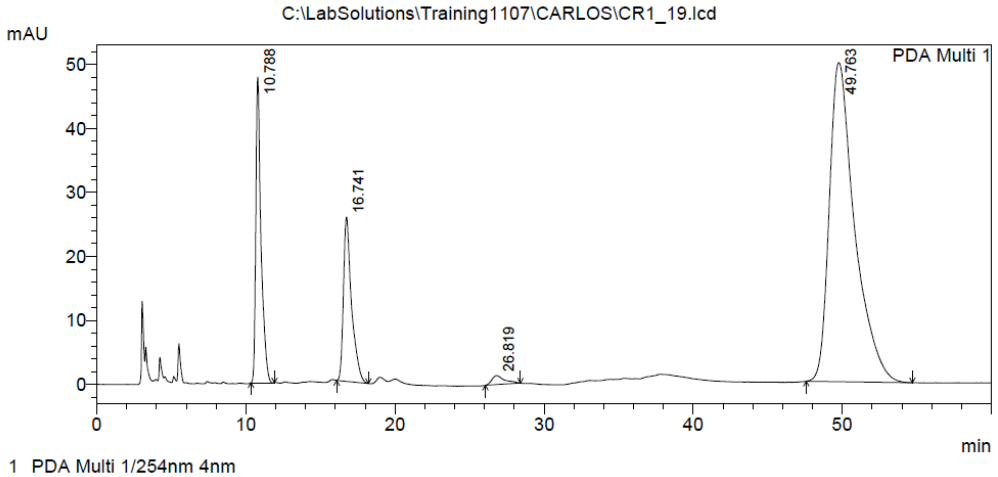
3	26.350	1367876	24298	42.904	25.706
4	48.037	176223	2112	5.527	2.234
Total		3188225	94524	100.000	100.000

Enantiomerically enriched *epi*-**3a** (86:14 er) [Peaks at 10.7 and 28.8 min correspond to **3a,** 94:6 er]:



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3	26.819	83912	1418	1.032	1.136
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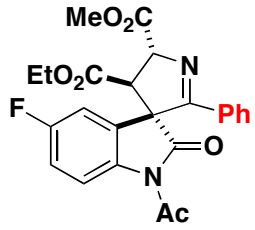
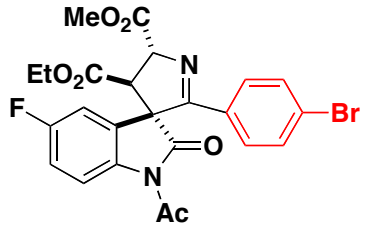
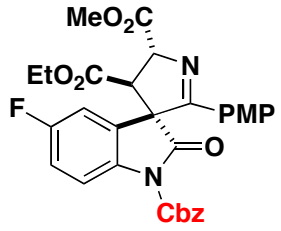
Total		8133381	124798	100.000	100.000



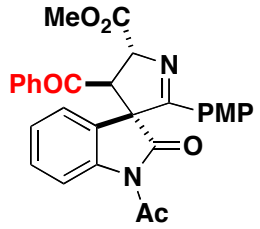
4'-ethyl 5'-methyl (3*S,4*R**,5*R**)-1-acetyl-5-fluoro-2-oxo-2'-phenyl-4',5'-dihydrospiro[indoline-3,3'-pyrrole]-4',5'-dicarboxylate (3b):** Synthesized according to the representative procedure for the titanium-catalyzed synthesis of spirooxindole-1-pyrrolines to afford the product as a white foam (43.8 mg, 75% yield, 90:10 dr). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.34 (dd, J = 9.0, 4.5 Hz, 1H), 7.41 – 7.34 (m, 3H), 7.28 – 7.24 (m, 2H), 7.11 (ddd, J = 8.7, 8.5, 2.7 Hz, 1H), 6.78 (dd, J = 7.2, 2.7 Hz, 1H), 5.50 (d, J = 9.3 Hz, 1H), 4.41 (d, J = 9.4 Hz, 1H), 3.93 (s, 3H), 3.79 (q, J = 7.0 Hz, 2H), 2.71 (d, J = 0.7 Hz, 3H), 0.81 (t, J = 7.1 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.6, 170.6, 170.1, 169.8, 167.5, 160.2 (d, J_{FC} = 247.6 Hz), 136.1 (d, J_{FCCCC} = 2.7 Hz), 131.9, 131.2, 129.0, 127.7, 126.9 (d, J_{FCCC} = 8.0 Hz), 118.8 (d, J_{FCCC} = 7.7 Hz), 117.1 (d, J_{FCC} = 22.5 Hz), 111.4 (d, J_{FCC} = 24.9 Hz), 73.9, 67.6, 61.8, 58.1, 53.3, 26.6, 13.6. IR (neat, selected peaks) 1753, 1732, 1477, 1371, 1275, 1173, 1014 cm^{-1}. LRMS calculated for $C_{24}H_{22}FN_2O_6$ $[M + H]^+$ 453.15, found 453.4.



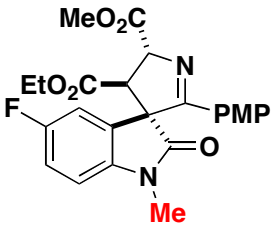
4'-ethyl 5'-methyl (3*S,4'*R**,5'*R**)-1-acetyl-2'-(4-bromophenyl)-5-fluoro-2-oxo-4',5'-dihydrospiro[indoline-3,3'-pyrrole]-4',5'-dicarboxylate (3c):** Synthesized according to the representative procedure for the titanium-catalyzed synthesis of spirooxindole-1-pyrrolines to afford the product as a white foam (46.8 mg, 85% yield, 86:14 dr , diastereoselectivity is the ratio of the major relative to the sum of minor diastereomers). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.34 (dd, J = 9.1, 4.5 Hz, 1H), 7.41 (d, J = 8.6 Hz, 2H), 7.23 (d, J = 8.6 Hz, 2H), 7.13 (ddd, J = 8.9, 8.8, 2.7 Hz, 1H), 6.78 (dd, J = 7.1, 2.7 Hz, 1H), 5.49 (d, J = 9.3 Hz, 1H), 4.40 (d, J = 9.3 Hz, 1H), 3.93 (s, 3H), 3.79 (q, J = 7.1 Hz, 2H), 2.71 (s, 3H), 0.80 (t, J = 7.1 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.4, 170.4, 169.8, 168.7, 167.3, 160.2 (d, J_{FC} = 248.0 Hz), 136.0 (d, J_{FCCCC} = 2.7 Hz), 132.3, 130.0, 129.1, 126.7, 126.5 (d, J_{FCCC} = 8.2 Hz), 118.9 (d, J_{FCCC} = 7.7 Hz), 117.2 (d, J_{FCC} = 22.4 Hz), 111.4 (d, J_{FCC} = 24.7 Hz), 73.9, 67.4, 61.8, 58.1, 53.3, 26.5, 13.5. IR (neat, selected peaks) 2029, 1753, 1709, 1477, 1259, 1169, 1009 cm^{-1}. LRMS calculated for $C_{24}H_{21}BrFN_2O_6$ $[M + H]^+$ 531.06, found 531.1.



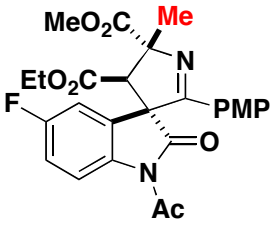
1-benzyl 4'-ethyl 5'-methyl (3*S,4'*R**,5'*R**)-5-fluoro-2'-(4-methoxyphenyl)-2-oxo-4',5'-dihydrospiro[indoline-3,3'-pyrrole]-1,4',5'-tricarboxylate (3d):** Synthesized according to the representative procedure for the titanium-catalyzed synthesis of spirooxindole-1-pyrrolines to afford the product as a white foam (52.0 mg, 90% yield, 90:10 dr, diastereoselectivity based on purified material and is the ratio of the major relative to the sum of minor diastereomers). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 9.0, 4.3 Hz, 1H), 7.50 (d, *J* = 6.8 Hz, 2H), 7.41 – 7.34 (m, 3H), 7.36 (d, *J* = 8.9 Hz, 2H), 7.08 (ddd, *J* = 8.8, 8.8, 2.7 Hz, 1H), 6.75 (dd, *J* = 7.2, 2.7 Hz, 1H), 6.72 (d, *J* = 9.0 Hz, 2H), 5.52 (d, *J* = 12.3 Hz, 1H), 5.48 (d, *J* = 12.3 Hz, 1H), 5.44 (d, *J* = 9.3 Hz, 1H), 4.41 (d, *J* = 9.3 Hz, 1H), 3.90 (s, 3H), 3.74 (s, 3H), 3.69-3.75 (m, 2H), 0.72 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.9, 170.2, 169.0, 167.6, 162.3, 160.1 (d, J_{FC} = 246.9 Hz), 150.6, 135.2 (d, J_{FCCCC} = 2.5 Hz), 134.7, 129.6, 128.8, 128.7, 128.1, 126.8 (d, J_{FCCC} = 8.1 Hz), 123.6, 117.2 (d, J_{FCCC} = 7.7 Hz), 116.9 (d, J_{FCC} = 22.8 Hz), 114.3, 111.6 (d, J_{FCC} = 24.9 Hz), 73.6, 69.2, 67.3, 61.6, 58.2, 55.4, 53.2, 13.4. IR (neat, selected peaks) 1772, 1730, 1483, 1255, 1225, 1153, 1020 cm^{-1}. LRMS calculated for $C_{31}H_{28}FN_2O_8$ $[M + H]^+$ 575.18, found 575.3.



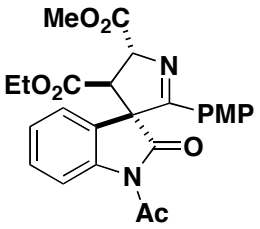
methyl (3*S,4'*R**,5'*R**)-1-acetyl-4'-benzoyl-2'-(4-methoxyphenyl)-2-oxo-4',5'-dihydrospiro[indoline-3,3'-pyrrole]-5'-carboxylate (3e):** Synthesized according to the representative procedure for the titanium-catalyzed synthesis of spirooxindole-1-pyrrolines to afford the product as a white foam (45.3 mg, 88% yield, >95:5 dr). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.3 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 1H), 7.34 – 7.32 (m, 2H), 7.28 (d, *J* = 9.0 Hz, 2H), 7.26 – 7.23 (m, 3H), 7.14 (t, *J* = 7.6 Hz, 1H), 6.98 (d, *J* = 7.5 Hz, 1H), 6.70 (d, *J* = 9.0 Hz, 2H), 5.92 (d, *J* = 8.6 Hz, 1H), 5.21 (d, *J* = 8.6 Hz, 1H), 3.91 (s, 3H), 3.73 (s, 3H), 2.56 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 195.9, 176.8, 170.9, 170.0, 167.9, 162.1, 139.0, 137.0, 133.6, 130.1, 129.5, 128.4, 127.5, 126.1, 125.0, 124.7, 124.1, 116.8, 114.3, 73.9, 68.3, 61.0, 55.4, 53.2, 26.6. IR (neat, selected peaks) 1745, 1699, 1604, 1250, 1169 cm^{-1}. LRMS calculated for $C_{29}H_{25}N_2O_6$ $[M + H]^+$ 497.17, found 497.3.



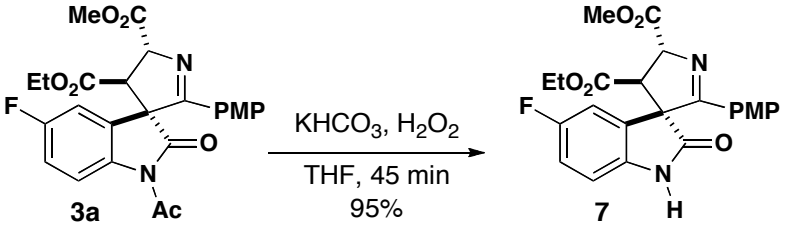
4'-ethyl 5'-methyl (3*S,4'*R**,5'*R**)-5-fluoro-2'-(4-methoxyphenyl)-1-methyl-2-oxo-4',5'-dihydrospiro[indoline-3,3'-pyrrole]-4',5'-dicarboxylate (3f)**: Synthesized according to the representative procedure for the titanium-catalyzed synthesis of spirooxindole-1-pyrrolines (100% conversion based on ^{1}H NMR spectroscopy, 38:30:18:14 mixture of diastereomers that were primarily inseparable). Peaks corresponding to the major diastereomer are as follows: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 (d, J = 8.9 Hz, 2H), 7.06 (ddd, J = 8.8, 8.8, 2.6 Hz, 1H), 6.88 (dd, J = 8.5, 4.0 Hz, 1H), 6.78 (dd, J = 7.4, 2.5 Hz, 1H), 6.72 (d, J = 9.0 Hz, 2H), 5.46 (d, J = 9.3 Hz, 1H), 4.35 (d, J = 9.3 Hz, 1H), 3.90 (s, 3H), 3.78 (dq, J = 10.6 Hz, J = 7.1 Hz 2H), 3.75 (s, 3H), 3.36 (s, 3H), 0.80 (t, J = 7.1 Hz, 3H). LRMS calculated for $C_{24}H_{24}FN_2O_6$ $[M + H]^+$ 455.16, found 455.2.



4'-ethyl 5'-methyl (3*S,4'*R**,5'*R**)-1-acetyl-5-fluoro-2'-(4-methoxyphenyl)-5'-methyl-2-oxo-4',5'-dihydrospiro[indoline-3,3'-pyrrole]-4',5'-dicarboxylate (3g):** Synthesized according to the representative procedure for the titanium-catalyzed synthesis of spirooxindole-1-pyrrolines to afford the product as a pale yellow foam (34.0 mg, 69% yield, 94:6 dr, diastereoselectivity based on purified material). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.37 (dd, J = 9.1, 4.7 Hz, 1H), 7.28 (d, J = 8.9 Hz, 2H), 7.12 (ddd, J = 8.7, 8.7, 2.7 Hz, 1H), 6.93 (dd, J = 7.8, 2.8 Hz, 1H), 6.73 (d, J = 8.9 Hz, 2H), 4.67 (s, 1H), 3.90 (s, 3H), 3.86 – 3.79 (m, 2H), 3.75 (s, 3H), 2.69 (s, 3H), 1.96 (s, 3H), 0.88 (t, J = 7.1 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.7, 173.1, 170.6, 166.9, 166.0, 162.2, 160.2 (d, J_{FC} = 246.3 Hz), 136.6 (d, J_{FCCCC} = 2.6 Hz), 129.6, 128.1 (d, J_{FCCC} = 8.0 Hz), 123.9, 118.5 (d, J_{FCCC} = 7.8 Hz), 116.6 (d, J_{FCC} = 22.4 Hz), 114.3, 112.6 (d, J_{FCC} = 25.2 Hz), 79.5, 68.1, 61.1, 60.0, 55.4, 53.4, 26.6, 23.4, 13.6. IR (neat, selected peaks) 1716, 1604, 1477, 1254, 1165, 1103 cm^{-1}. LRMS calculated for $C_{26}H_{26}FN_2O_7$ $[M + H]^+$ 497.17, found 497.2.

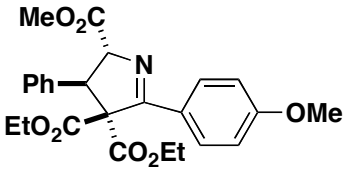


4'-ethyl 5'-methyl (3*S,4'*R**,5'*R**)-1-acetyl-2'-(4-methoxyphenyl)-2-oxo-4',5'-dihydrospiro[indoline-3,3'-pyrrole]-4',5'-dicarboxylate (3h):** Synthesized according to the representative procedure for the titanium-catalyzed synthesis of spirooxindole-1-pyrrolines to afford the product as a white foam (34.6 mg, 75% yield, 92:8 dr). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.33 (d, *J* = 8.2 Hz, 1H), 7.40 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.33 (d, *J* = 8.9 Hz, 2H), 7.16 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.05 (dd, *J* = 7.6, 1.2 Hz, 1H), 6.74 (d, *J* = 8.8 Hz, 2H), 5.50 (d, *J* = 9.3 Hz, 1H), 4.37 (d, *J* = 9.1 Hz, 1H), 3.92 (s, 3H), 3.75 (s, 3H), 3.74 – 3.70 (m, 1H), 2.73 (s, 3H), 0.75 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.2, 170.9, 170.5, 169.4, 167.8, 162.2, 139.9, 130.3, 129.5, 126.0, 125.3, 123.9, 123.7, 117.2, 114.3, 73.7, 67.5, 61.5, 58.3, 55.4, 53.2, 26.7, 13.5. IR (neat, selected peaks) 1747, 1711, 1604, 1252, 1171, 1014 cm^{-1}. LRMS calculated for $C_{25}H_{25}N_2O_7$ $[M + H]^+$ 465.17, found 465.3.

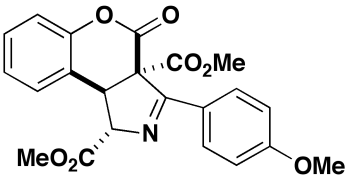


4'-ethyl 5'-methyl (3*S,4'*R**,5'*R**)-5-fluoro-2'-(4-methoxyphenyl)-2-oxo-4',5'-dihydrospiro[indoline-3,3'-pyrrole]-4',5'-dicarboxylate** (**7**): To a 0.2M solution of oxindole **3a** (400 mg, 0.8 mmol) in THF in a 20 mL scintillation vial fitted with a magnetic stir bar was added H_2O_2 (10 equiv, 16.0 mmol, 1.6 mL), $KHCO_3$ (2.0 equiv, 1.6 mmol, 160 mg). The mixture was stirred until complete as judged by TLC (10% EtOAc/CH_2Cl_2). The reaction was then diluted with ether (20 mL), brine (50 mL), and dried over $MgSO_4$ and purified using column chromatography with a gradient beginning with 100% CH_2Cl_2 ending with 10-15% EtOAc/CH_2Cl_2 to afford the product as a white solid (336 mg, 95% yield). mp 194 – 198 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.36 (s, 1H), 7.48 (d, *J* = 8.9 Hz, 2H), 6.98 (ddd, *J* = 8.7, 8.7, 2.5 Hz, 1H), 6.92 (dd, *J* = 8.6, 4.2 Hz, 1H), 6.75 (dd, *J* = 7.5, 2.5 Hz, 1H), 6.72 (d, *J* = 9.0 Hz, 2H), 5.49 (d, *J* = 9.2 Hz, 1H), 4.38 (d, *J* = 9.2 Hz, 1H), 3.92 (s, 3H), 3.84 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.78 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.72 (s, 3H), 0.78 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.1, 170.8, 169.3, 168.2, 162.3, 159.1 (d, J_{FC} = 243.3 Hz), 137.0, 129.5, 128.2 (d, J_{FCCC} = 7.9 Hz), 124.1, 116.6 (d, J_{FCC} = 23.5 Hz), 114.2, 112.5 (d, J_{FCC} = 25.2 Hz),

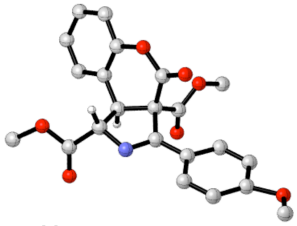
111.7, 73.9, 67.8, 61.5, 56.8, 55.4, 53.2, 13.6. IR (neat, selected peaks) 1736, 1714, 1606, 1485, 1261, 1174, 1022 cm^{-1}. LRMS calculated for $C_{23}H_{22}FN_2O_6$ $[M+H]^+$ 441.15, found 441.0.



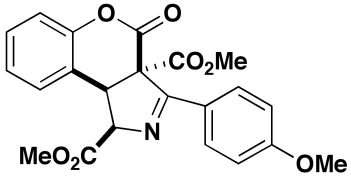
3,3-diethyl 5-methyl (4*R,5*R**)-2-(4-methoxyphenyl)-4-phenyl-4,5-dihydro-3H-pyrrole-3,3,5-tricarboxylate (9):** Synthesized according to the representative procedure for the titanium-catalyzed synthesis of spirooxindole-1-pyrrolines to afford the product as a yellow oil (55.5 mg, 99% yield, 73:27 dr). Representative peaks corresponding to the major diastereomer are as follows: ^{1}H NMR (600 MHz, $CDCl_3$, some peaks in the aromatic region (phenyl ring) not listed due to overlap with minor diastereomer) δ 8.10 (d, *J* = 9.0 Hz, 1H), 7.28 – 7.27 (m, 1H), 7.17 – 7.14 (m, 2H), 7.09 – 7.06 (m, 2H), 6.90 (d, *J* = 9.0 Hz, 1H), 5.48 (d, *J* = 7.2 Hz, 1H), 4.68 (d, *J* = 7.3 Hz, 1H), 4.28 (dq, *J* = 10.8, 7.1 Hz, 2H), 3.85 (s, 3H), 3.57 (d, *J* = 10.8, 7.1 Hz, 2H), 3.36 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.75 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.4, 168.4, 167.4, 166.2, 161.9, 136.1, 131.6, 131.0, 129.2, 127.9, 125.6, 113.2, 76.8, 76.0, 62.9, 61.5, 57.4, 55.4, 51.7, 14.0, 13.3. IR (neat, selected peaks) 1728, 1604, 1252, 1205, 1174, 1086, 1026, 841 cm^{-1}. LRMS calculated for $C_{25}H_{28}NO_7$ $[M + H]^+$ 454.19, found 454.3. The stereochemistry for the major isomer (4,5-*trans*) is drawn based on analogy to the spirooxindole-1-pyrroline stereochemistry.



11



X-ray structure **11**



epi-**11**
(minor)

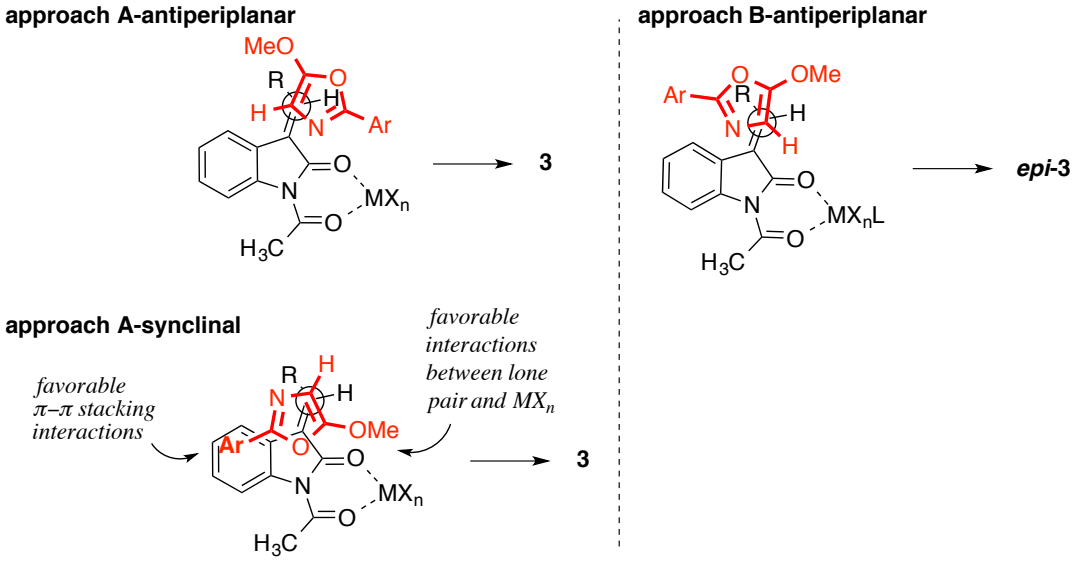
The relative stereochemistry (1*S**,3a*R**,9b*S**) for the major diastereomer of **11** was confirmed by X-ray crystallographic analysis. The stereochemistry for the minor diastereomer (*epi*-**11**) was assigned to be 1*R**,3a*R**,9b*S**.by analogy to the stereochemistry for the spirooxindole-1-pyrrolines.

Dimethyl (1*S,3a*R**,9b*S**)-3-(4-methoxyphenyl)-4-oxo-1,9b-dihydrochromeno[3,4-*c*]pyrrole-1,3a(4*H*)-dicarbox-ylate (11):** A solution of coumarin (1.0 equiv, 0.2 mmol) and oxazole (1.1 equiv, 0.22 mmol) was prepared in dry CH_2Cl_2 (0.2 M) at 25 °C in a 4 mL oven dried scintillation vial fitted with a magnetic stir bar. To this homogeneous solution, $TiCl_4$ (0.2 equiv, 0.04 mmol, 1.0 M in CH_2Cl_2) was added and the reaction was stirred for 45 min. Then the reaction was diluted with 10 mL of CH_2Cl_2. The organic layer was washed

with sat. sodium potassium tartrate (20 mL), brine (20 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Before purification the diastereomeric ratio (dr) was obtained using ^{1}H NMR spectroscopy. The crude material was then purified by flash chromatography (gradient 100% DCM to 1% EtOAc/DCM) to yield the pyrroline product (69.2 mg, 85% yield, 88:12 dr). Longer reaction times (e.g. 20h) were determined to increase the yield of the pyrroline and allowed the unreacted oxazoline to convert to a more polar by-product, making purification easier; however, these conditions led to a small erosion in the diastereoselectivity (74.6 mg, 91% yield, 80:20 dr). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 9.0 Hz, 2H), 7.44 – 7.32 (m, 2H), 7.21 – 7.15 (m, 2H), 6.93 (d, J = 9.0 Hz, 2H), 4.58 (d, J = 9.8 Hz, 1H), 4.45 (d, J = 9.8 Hz, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 3.70 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.3, 170.0, 168.2, 162.4, 161.7, 150.3, 131.3, 129.9, 129.8, 125.3, 124.4, 117.5, 117.3, 114.0, 77.5, 66.8, 55.5, 54.1, 53.1, 50.8; IR (neat, selected peaks) 2955, 1737, 1613, 1248, 1167, 1025, 837 cm^{-1}; LRMS calcd for $C_{22}H_{20}NO_7$ $[M + H]^+$ 410.12, found 410.2. Recrystallization from DCM layered with hexanes afforded single crystals and the structure was confirmed by X-ray analysis.

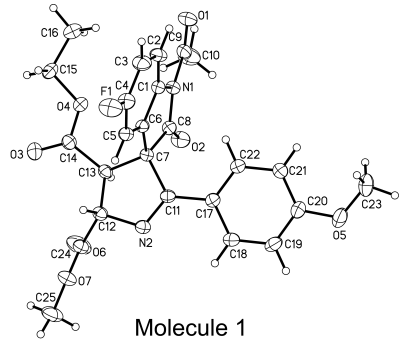
IV. Proposal for Reversal of Diastereoselectivity

In the absence of a large ligand such as (*R,S*)-indapybox, we propose that the oxazole can approach the prochiral alkylidene oxindole in either an antiperiplanar or synclinal orientation. Steric interactions between the aryl substituent of the oxazole and the β-position of the alkylidene oxindole are minimized in approach "A-antiperiplanar", giving rise to product **3** with *5R** stereochemistry. We propose that a synclinal orientation may occur if favorable π–π stacking and/or lone pair-MX_n interactions exist ("A-synclinal"). In the presence of the (*R,S*)-indapybox ligand, the oxazole is expected to approach from the *si*-face in an antiperiplanar orientation that minimize interactions between the aryl or methoxy group and the ligand framework, giving rise to product *epi*-**3** with opposite *5S** stereochemistry.



V. X-ray crystallographic Information

X-ray crystallographic Information for JJB4238 (**3a**)



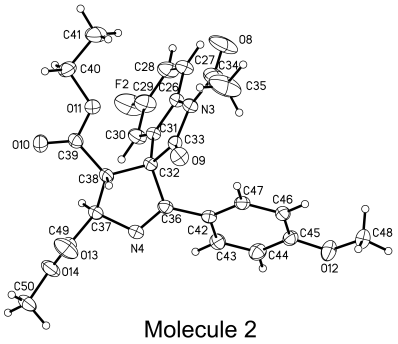


Figure S1. X-ray structure for JJB4238 (**3a**) with thermal displacement parameters at the 50% probability level for non-H atoms. There are two independent molecules in the asymmetric unit. The structure is centrosymmetric. In molecule 1, chirality is R, S, S for C7, C12, C13, respectively and in molecule 2, chirality is S, R, R, for C32, C37, C38, respectively

Table S1. Crystal data and structure refinement for JJB4238 (**3a**)

Identification code	sw03	
Empirical formula	$C_{25}H_{23}FN_2O_7$	
Formula weight	482.45	
Temperature	90(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C 2/c	
Unit cell dimensions	a = 31.188(9) Å	α= 90°.
	b = 10.623(3) Å	β= 100.167(3)°.
	c = 28.223(8) Å	γ = 90°.
Volume	9204(4) $Å^3$	
Z	16	
Density (calculated)	1.393 Mg/m^3	
Absorption coefficient	0.108 mm^{-1}	

F(000)	4032
Crystal size	1.193 x 1.139 x 0.963 mm^3
Crystal color and habit	colorless block
Diffractometer	Bruker SMART 1000
θrange for data collection	2.797 to 27.569°.
Index ranges	-40≤h≤40, -13≤k≤13, -36≤l≤36
Reflections collected	42994
Independent reflections	10567 [R(int) = 0.0295]
Observed reflections [I > 2σ(I)]	8509
Completeness to θ= 25.242°	99.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.746 and 0.657
Solution method	SHELXS-97 (Sheldrick, 2008)
Refinement method	SHELXL-2013 (Sheldrick, 2013)
Data / restraints / parameters	10567 / 0 / 639
Goodness-of-fit on F^2	1.058
Final R indices [I>2σ(I)]	R1 = 0.0413, wR2 = 0.1060
R indices (all data)	R1 = 0.0533, wR2 = 0.1114
Extinction coefficient	n/a
Largest diff. peak and hole	0.326 and -0.261 $e.Å^{-3}$

X-ray Crystallographic information for JJB5060 toluene solvate (*epi*-**3a**)

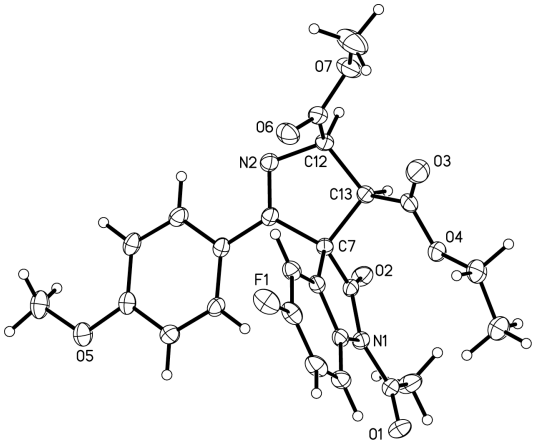
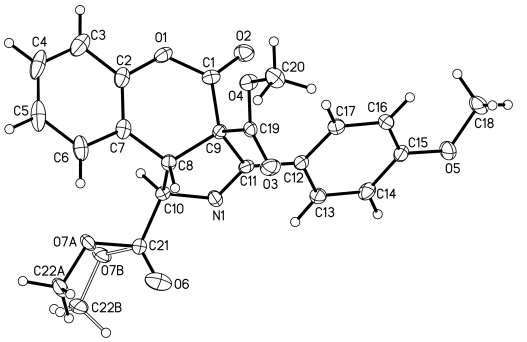


Figure S2. X-ray structure for JJB5060 toluene solvate (*epi*-**3a**) with thermal displacement parameters at the 50% probability level for non-H atoms.

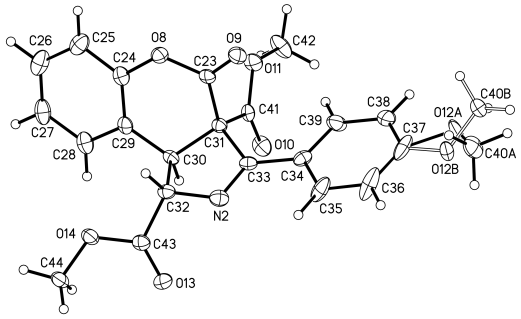
Table S2. Crystal data and structure refinement for JJB5060 toluene solvate. (*epi*-**3a**)

Identification code	mn2191	
Empirical formula	C32 H31 F N2 O7	
Formula weight	574.59	
Temperature	90(2) K	
Wavelength	1.54178 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 8.7859(2) Å	α= 81.6796(9)°.
	b = 12.7763(4) Å	β= 76.9516(8)°.
	c = 13.0960(3) Å	γ = 86.6732(8)°.
Volume	1416.52(6) $Å^3$	
Z	2	
Density (calculated)	1.347 Mg/m^3	
Absorption coefficient	0.829 mm^{-1}	
F(000)	604	
Crystal size	0.369 x 0.322 x 0.196 mm^3	
Crystal color and habit	colorless plate	
Diffractometer	Bruker Apex DUO	
Theta range for data collection	3.496 to 72.465°.	
Index ranges	-10<=h<=10, -14<=k<=15, -16<=l<=16	
Reflections collected	24676	
Independent reflections	5357 [R(int) = 0.0282]	
Observed reflections (I > 2sigma(I))	5191	
Completeness to theta = 67.679°	96.3 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.754 and 0.651	
Refinement method	SHELXL-2013 (Sheldrick, 2013)	
Data / restraints / parameters	5357 / 0 / 383	
Goodness-of-fit on F^2	1.020	
Final R indices [I>2sigma(I)]	R1 = 0.0463, wR2 = 0.1218	
R indices (all data)	R1 = 0.0472, wR2 = 0.1227	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.421 and -0.380 $e.Å^{-3}$	

X-ray Crystallographic Information for CR2-21 (**11**)



Molecule 1



Molecule 2

Figure S3. X-ray Structure for CR2-21 (**11**) with thermal displacement parameters at the 50% probability level for non-hydrogen atoms. Each of the two molecules in the asymmetric unit has minor disorder. In molecule1, the OMe group of the acetoxy group has 0.474(3)/0.526(3) disorder and in molecule2, the OMe group has 0.449(6)/0.551(6) disorder for A and B sets, respectively. In molecule 1, the chirality is R, S, R for C8, C9, C10, respectively. In molecule 2, the chirality is S, R, S for C30, C31, C32, respectively.

Table S3. Crystal data and structure refinement for CR2-21 (**11**):

Identification code	mn2188	
Empirical formula	$C_{22}H_{19}NO_7$	
Formula weight	409.38	
Temperature	90(2) K	
Wavelength	0.71073 Å	
Crystal system	monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 17.736(3) Å	α= 90°.
	b = 12.166(2) Å	β= 91.250(3)°.
	c = 17.785(4) Å	γ = 90°.
Volume	3836.7(13) $Å^3$	
Z	8	
Density (calculated)	1.417 Mg/m^3	
Absorption coefficient	0.107 mm^{-1}	
F(000)	1712	
Crystal size	0.400 x 0.180 x 0.100 mm^3	
Crystal color and habit	colorless needle	
Diffractometer	Bruker SMART 1000	
Θ range for data collection	2.838 to 27.563°.	
Index ranges	-22≤h≤23, -15≤k≤15, -23≤l≤23	
Reflections collected	39895	
Independent reflections	8768 [R(int) = 0.0585]	
Observed reflections [I > 2σ(I)]	5977	
Completeness to θ= 25.242°	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.746 and 0.703	
Solution method	SHELXS-97 (Sheldrick, 2008)	
Refinement method	SHELXL-2013 (Sheldrick, 2013)	
Data / restraints / parameters	8768 / 0 / 587	
Goodness-of-fit on F^2	1.022	
Final R indices [I>2σ(I)]	R1 = 0.0573, wR2 = 0.1288	
R indices (all data)	R1 = 0.0937, wR2 = 0.1460	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.393 and -0.254 e.$Å^{-3}$	

VI. References

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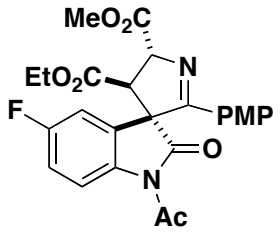
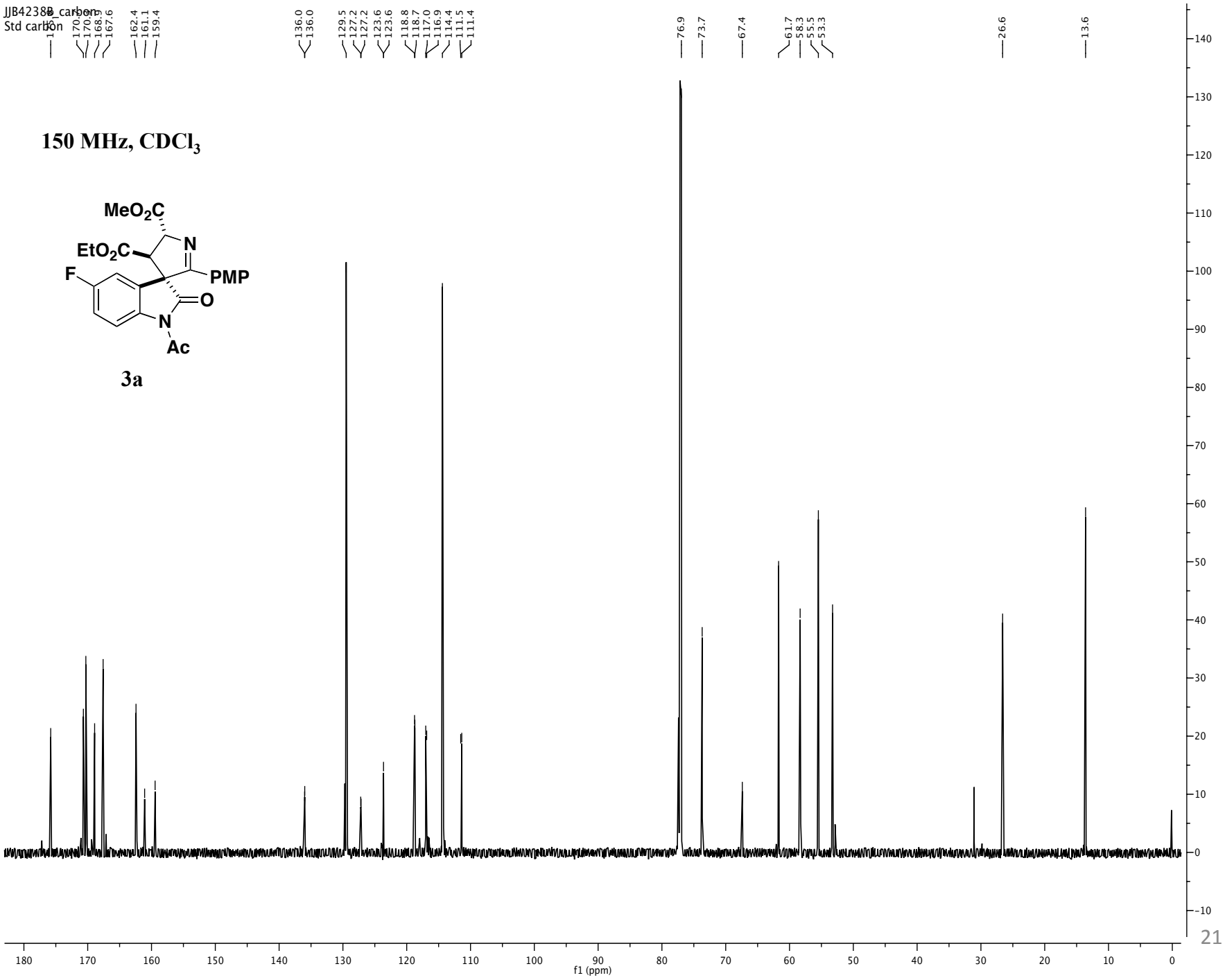
JJB5055_proton
Std proton

600 MHz, $CDCl_3$



3a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Std carbon
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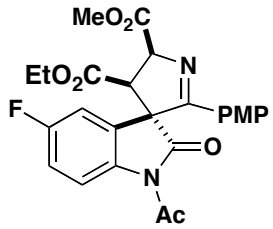
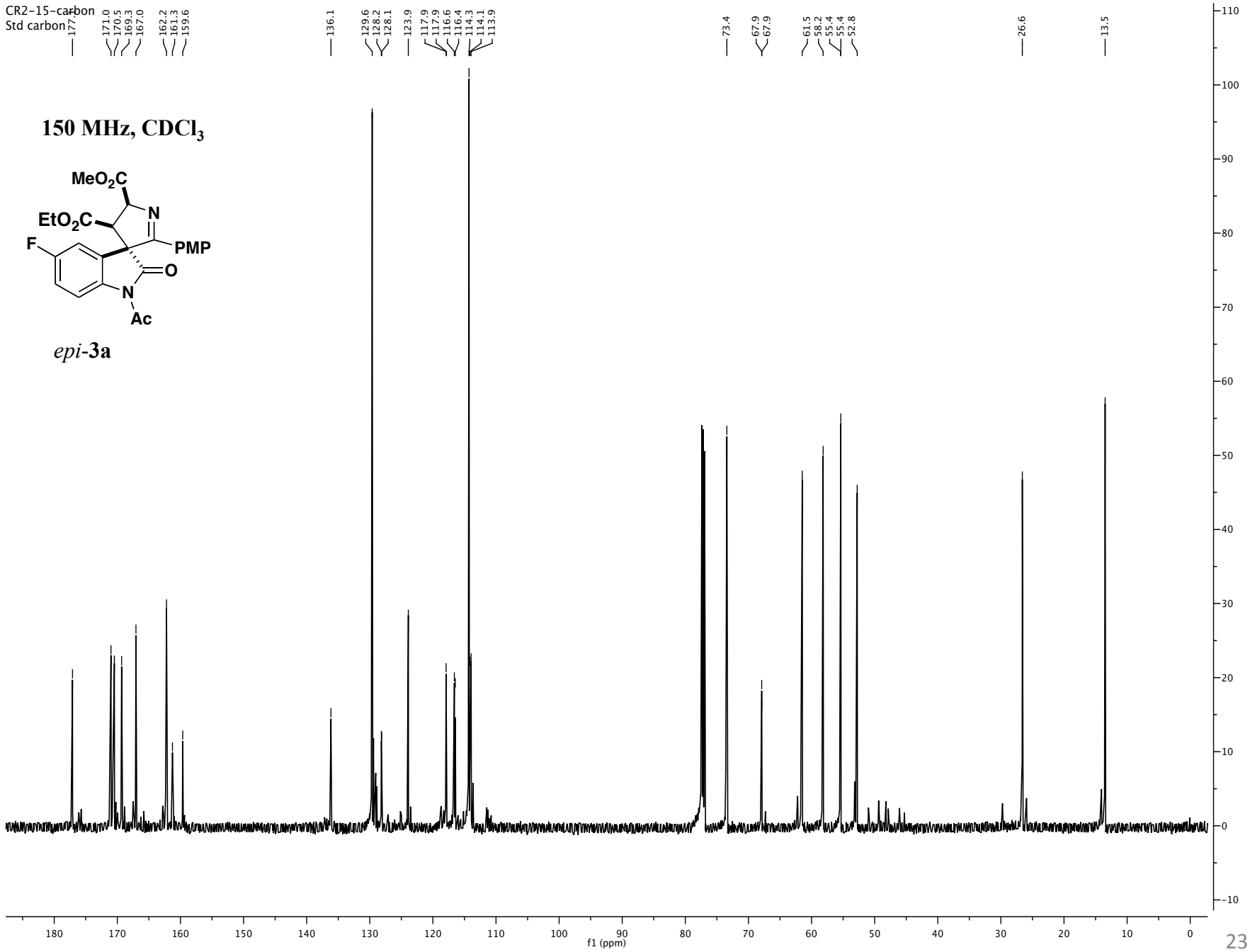
170.1
168.9
167.6
162.4
161.1
159.4
136.0
136.0
129.5
127.2
127.2
123.6
123.6
118.8
118.7
117.0
116.9
114.4
111.5
111.4
76.9
73.7
67.4
61.7
58.3
55.5
53.3
26.6
13.6
150 MHz, CDCl3
MeO2C
EtO2C
N
F
PMP
O
N
Ac
3a
f1 (ppm)

CR2-15pure_16SC
Std proton

400 MHz, $CDCl_3$

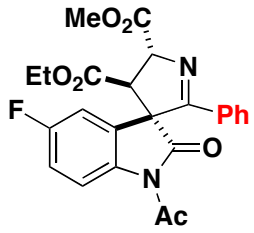


epi-**3a**


CR2-15-carbon
Std carbon
177.2
171.0
170.5
169.3
167.0
162.2
161.3
159.6
136.1
129.6
128.2
128.1
123.9
117.9
117.9
116.6
116.4
114.3
114.1
113.9
73.4
67.9
67.9
61.5
58.2
55.4
55.4
52.8
26.6
13.5
150 MHz, CDCl3
MeO2C
EtO2C
N
PMP
F
O
N
Ac
epi-3a
f1 (ppm)

JJB5023_proton
Std proton

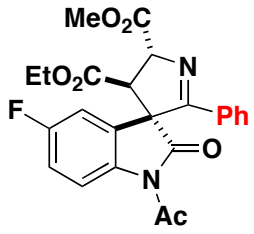
600 MHz, $CDCl_3$



3b

JJB5023_carbon
Std carbon

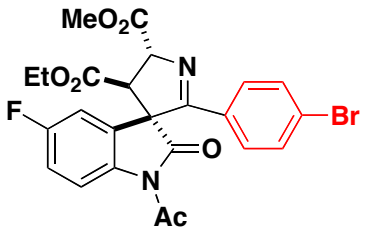
150 MHz, $CDCl_3$



3b

JJB5024_proton
Std proton

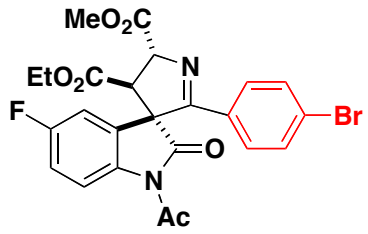
600 MHz, $CDCl_3$



3c

JJB5024_carbon
Std carbon

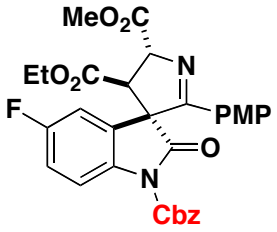
150 MHz, $CDCl_3$



3c

JJB5033_proton
Std proton

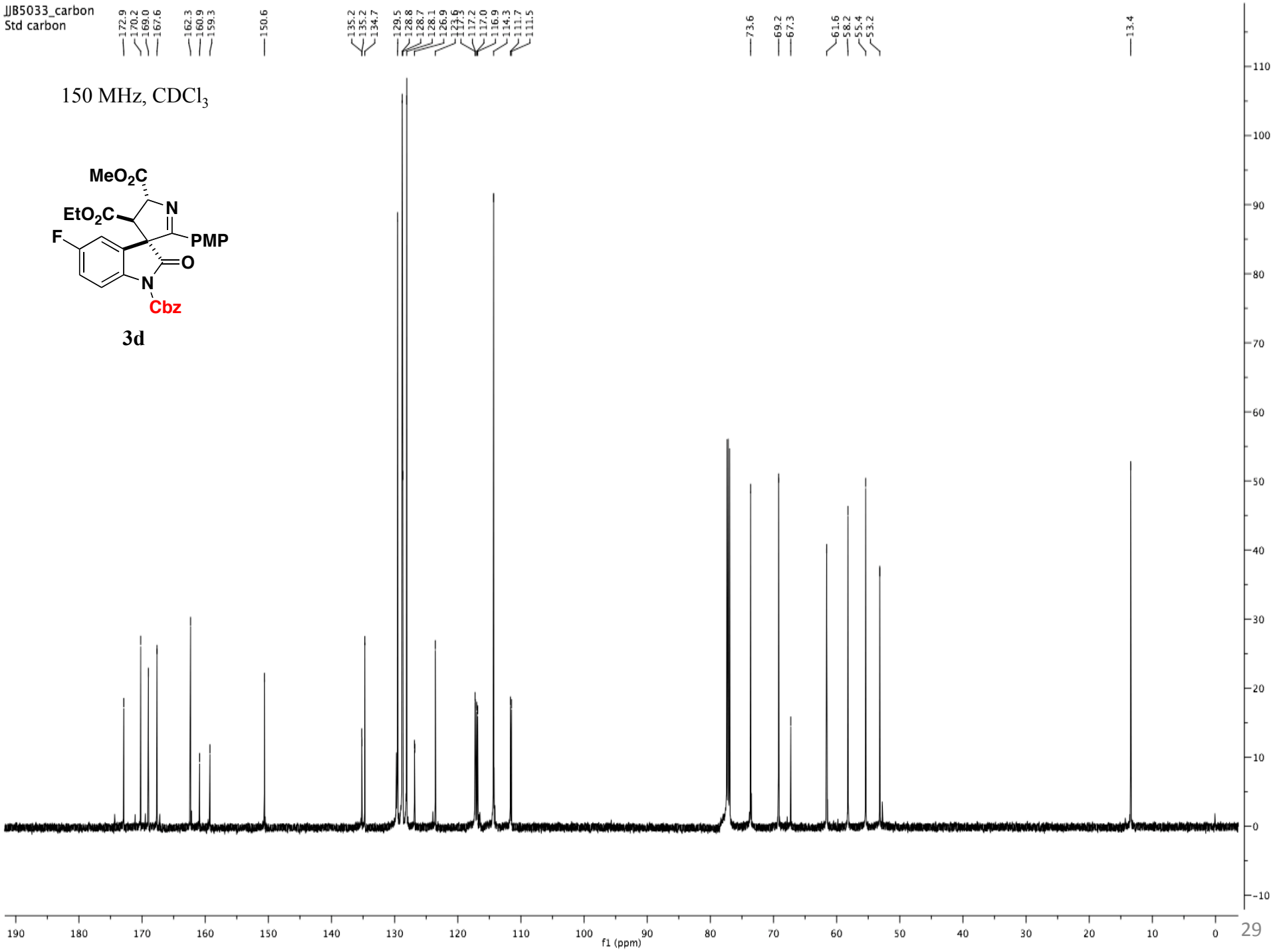
600 MHz, $CDCl_3$



3d

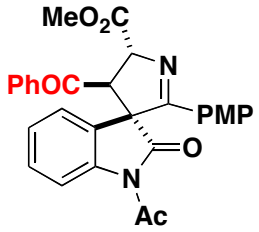
1.000 1.923 4.702 1.159 1.089 1.825 2.342 0.895 0.910 2.087 3.033 2.779

f1 (ppm)

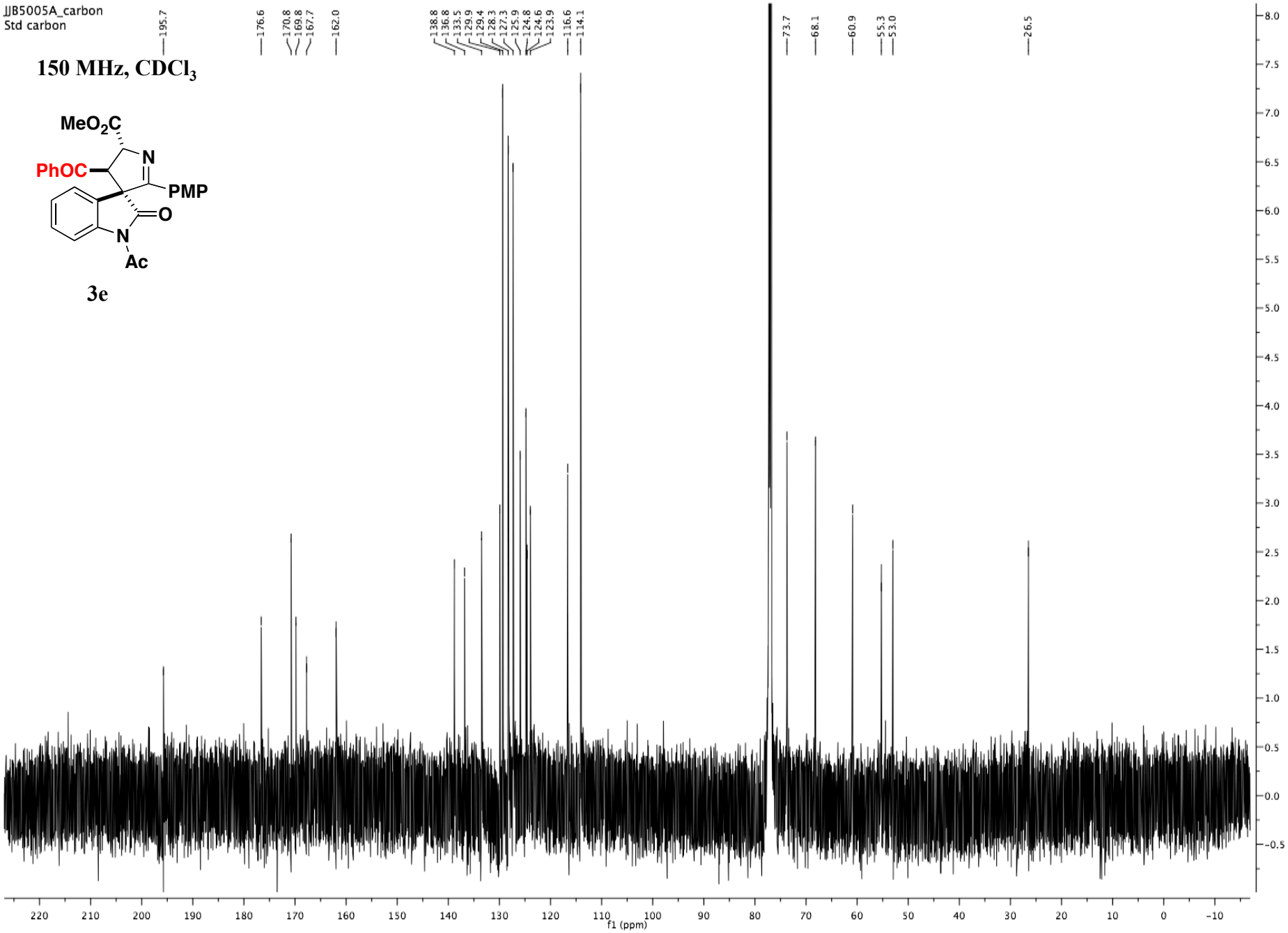

JJB5033_carbon
Std carbon
172.9
170.2
169.0
167.6
162.3
160.9
159.3
150.6
135.2
135.2
134.7
129.5
128.8
128.7
128.1
126.9
123.6
117.5
117.2
117.0
116.9
114.3
111.7
111.5
73.6
69.2
67.3
61.6
58.2
55.4
53.2
13.4
150 MHz, CDCl3
MeO2C
EtO2C
N
F
PMP
O
N
Cbz
3d
f1 (ppm)

JJB5005A_proton
Std proton

600 MHz, $CDCl_3$



3e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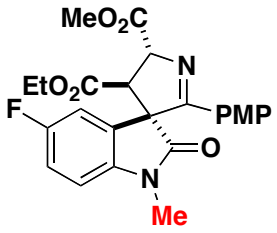
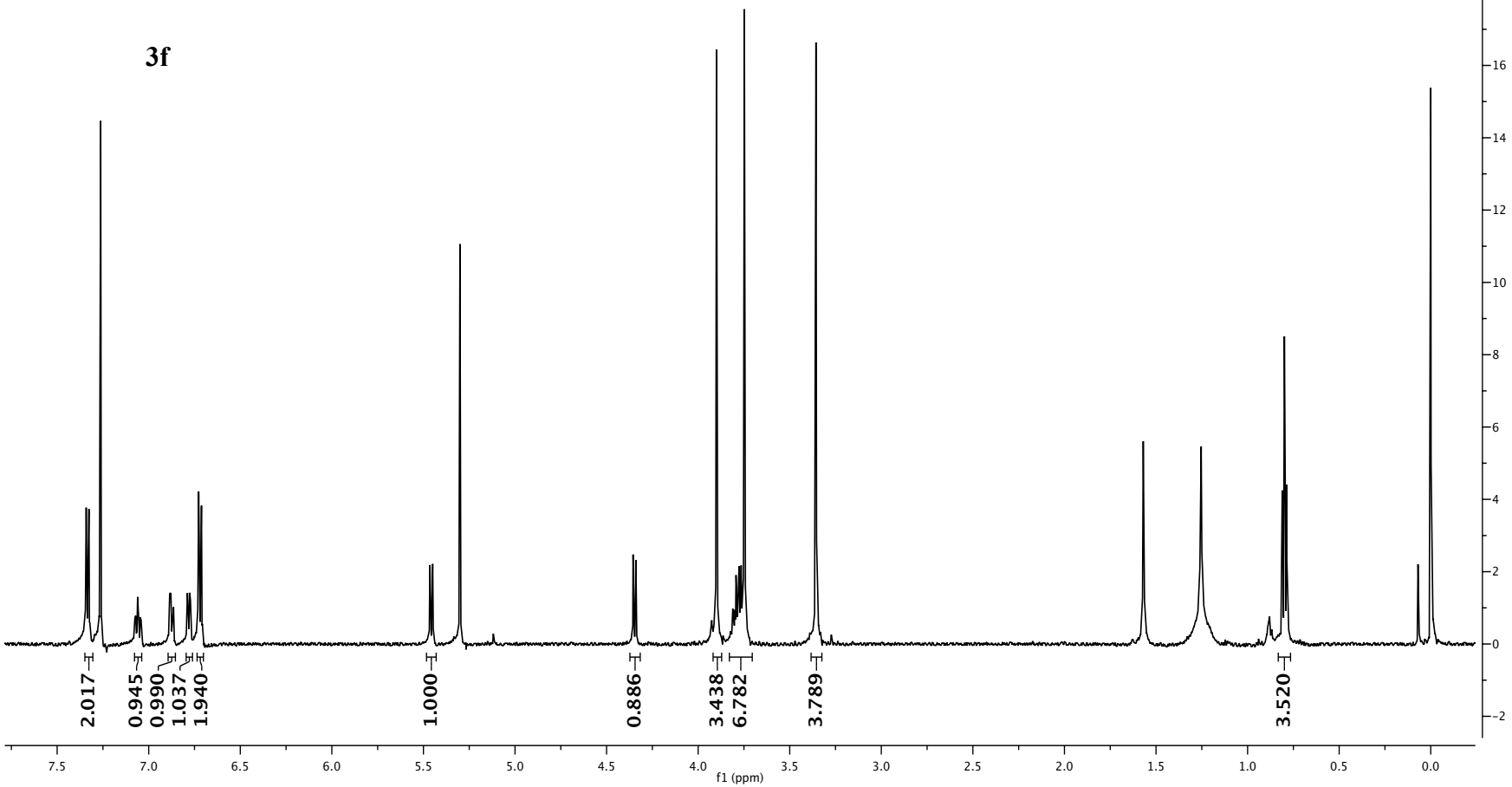
Std carbon
150 MHz, CDCl3
MeO2C
PhOC
N
PMP
O
N
Ac
3e
195.7
176.6
170.8
169.8
167.7
162.0
138.8
136.8
133.5
129.9
129.4
128.3
127.3
125.9
124.8
124.6
123.9
116.6
114.1
73.7
68.1
60.9
55.3
53.0
26.5
f1 (ppm)

JJB5015Major_proton
Std proton

600 MHz, $CDCl_3$

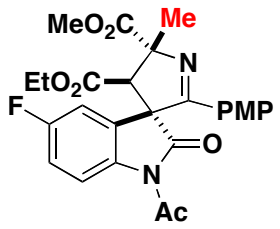


3f



JJB5021_Major_proton
JJB50214 low Rf minor

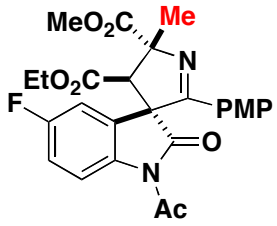
600 MHz, $CDCl_3$



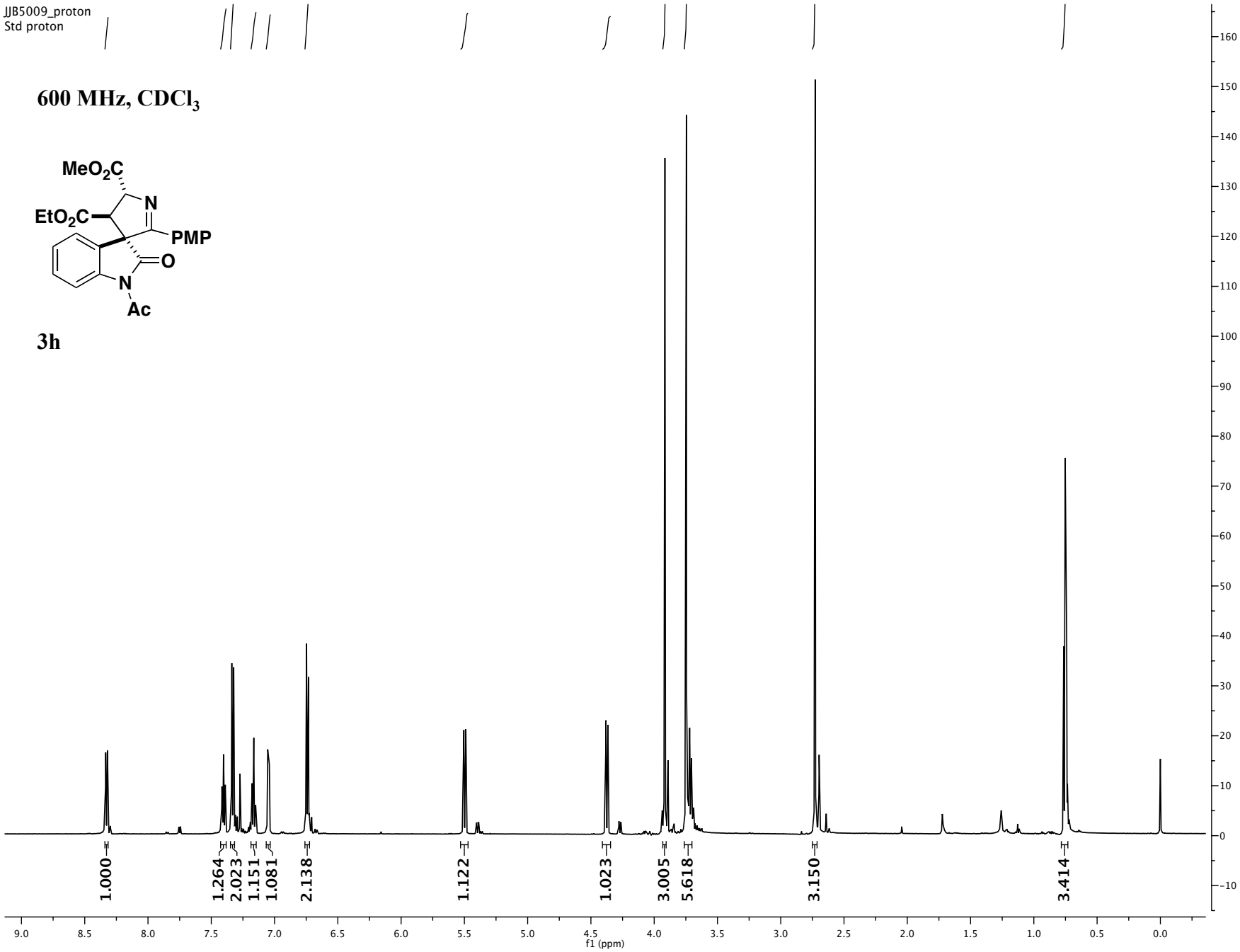
3g

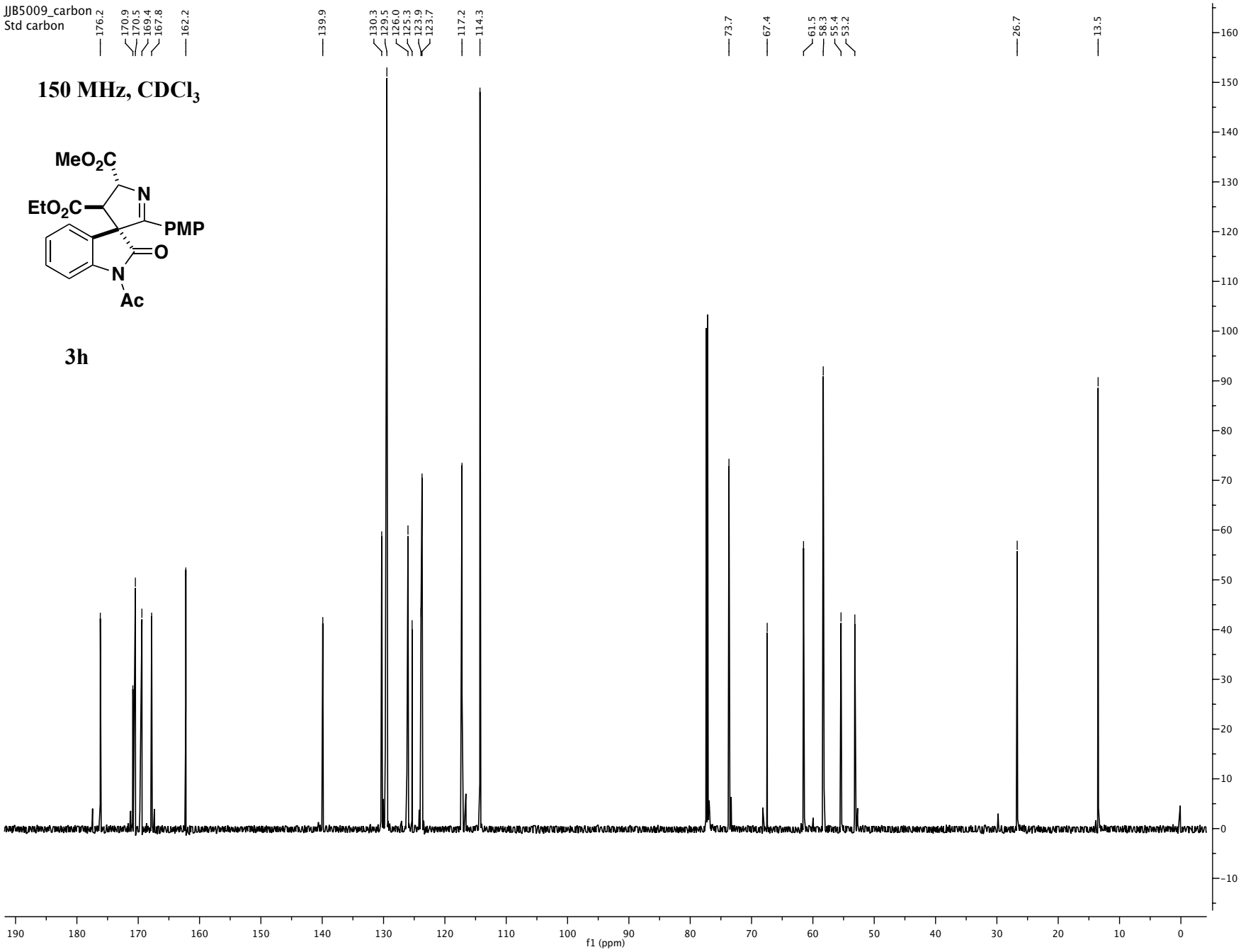
JJB5021_Major_carbon
Std carbon

150 MHz, $CDCl_3$



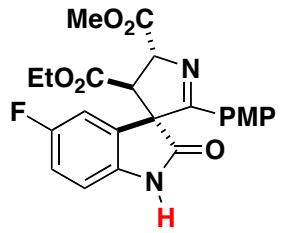
3g


JJB5009_proton
Std proton
600 MHz, CDCl3
MeO2C
EtO2C
N
PMP
O
N
Ac
3h
1.000
1.264
2.023
1.151
1.081
2.138
1.122
1.023
3.005
5.618
3.150
3.414
f1 (ppm)

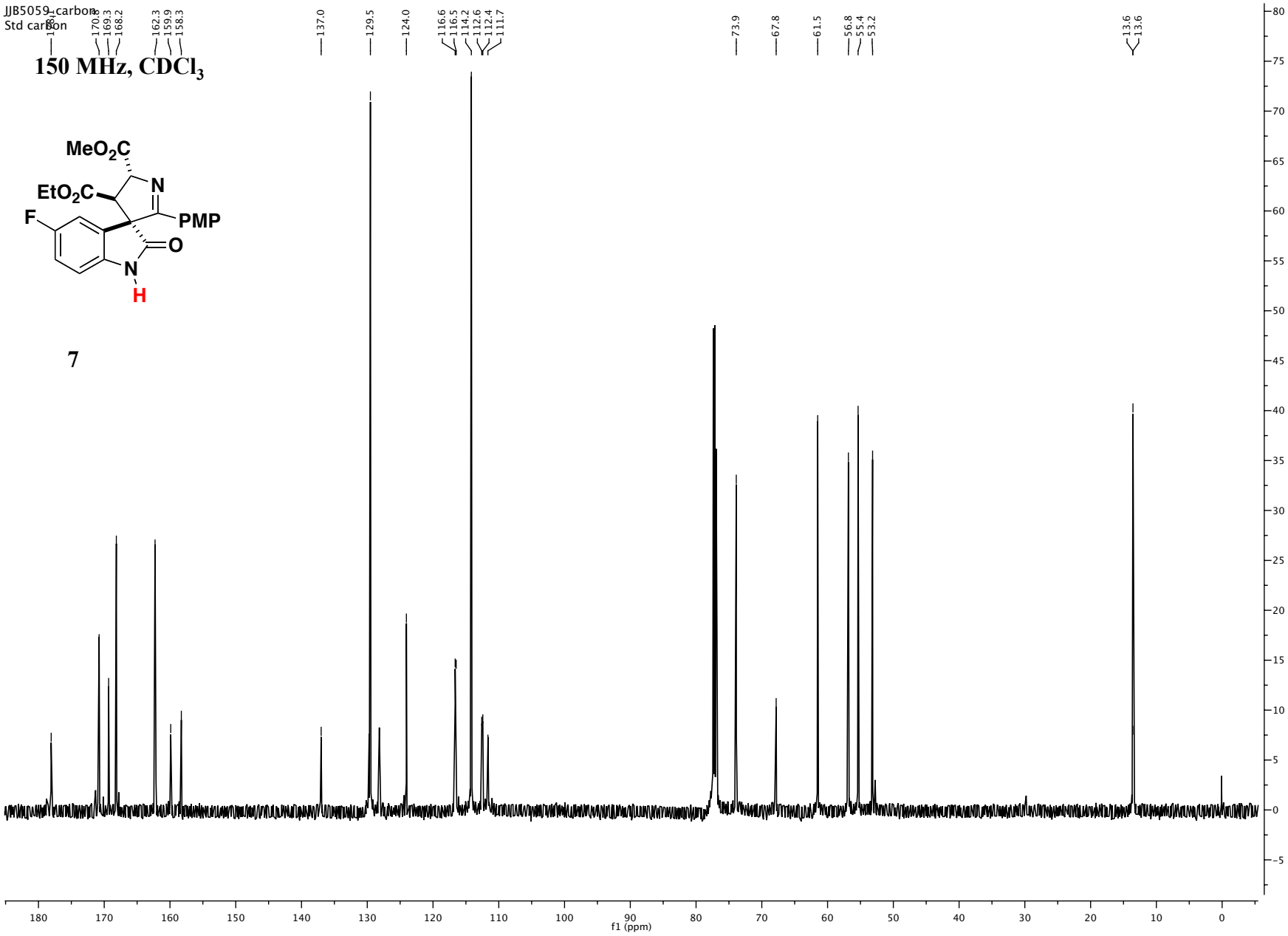

JJB5009_carbon
Std carbon
176.2
170.9
170.5
169.4
167.8
162.2
139.9
130.3
129.5
126.0
125.3
123.9
123.7
117.2
114.3
73.7
67.4
61.5
58.3
55.4
53.2
26.7
13.5
150 MHz, CDCl3
MeO2C
EtO2C
N
PMP
O
N
Ac
3h
f1 (ppm)

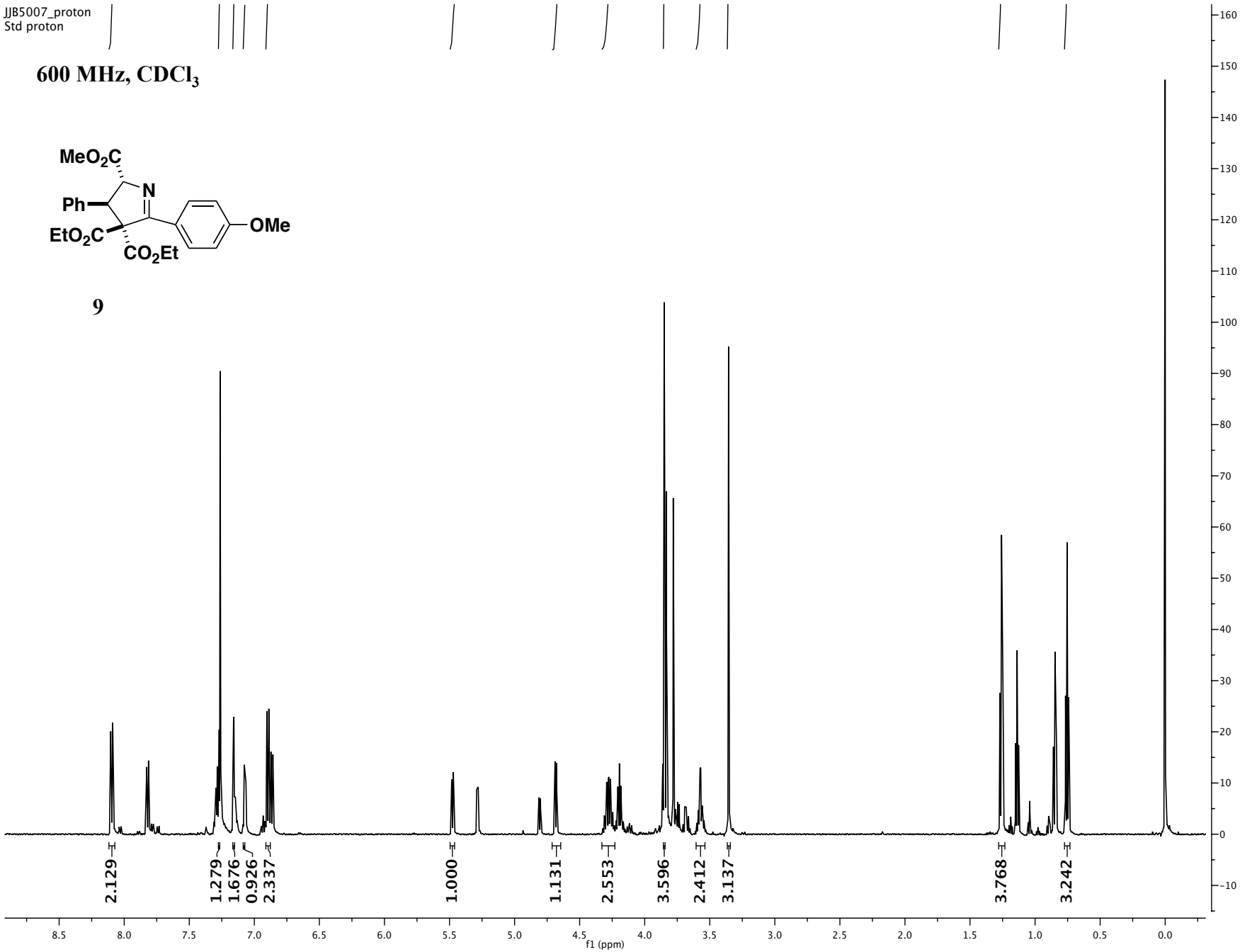
JJB5059_proton2
Std proton

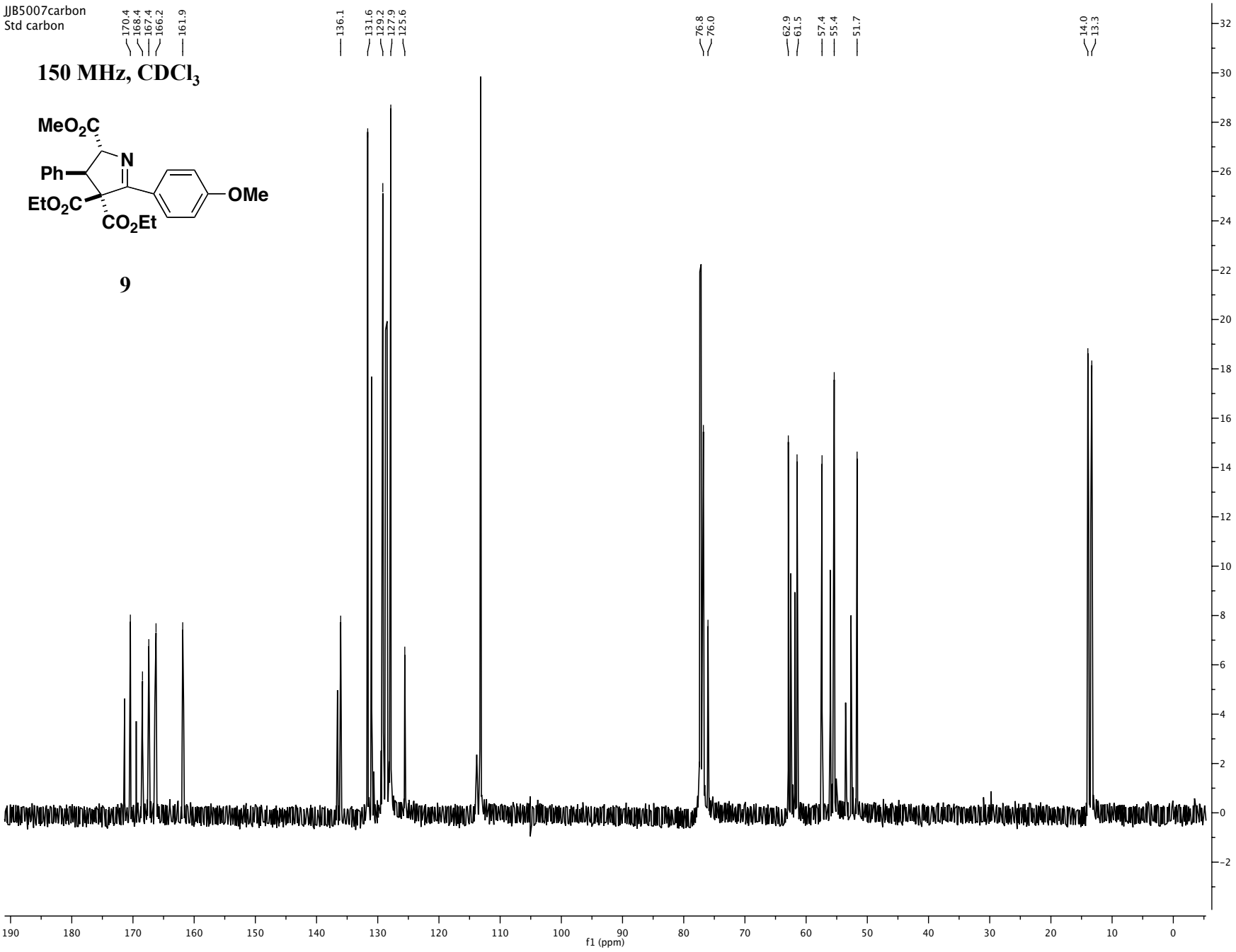
600 MHz, $CDCl_3$



7

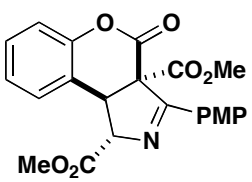

JJB5059-carbon
Std carbon
150 MHz, CDCl3
MeO2C
EtO2C
N
F
PMP
O
N
H
7
170.1
170.0
169.3
168.2
162.3
159.9
158.3
137.0
129.5
124.0
116.6
116.5
114.2
112.6
112.4
111.7
73.9
67.8
61.5
56.8
55.4
53.2
13.6
13.6
f1 (ppm)


JJB5007_proton
Std proton
600 MHz, CDCl3
MeO2C
N
Ph
EtO2C
CO2Et
OMe
9
2.129
1.279
1.676
0.926
2.337
1.000
1.131
2.553
3.596
2.412
3.137
3.768
3.242
f1 (ppm)


JJB5007carbon
Std carbon
170.4
168.4
167.4
166.2
161.9
136.1
131.6
129.2
127.9
125.6
76.8
76.0
62.9
61.5
57.4
55.4
51.7
14.0
13.3
150 MHz, CDCl3
MeO2C
Ph
EtO2C
CO2Et
N
OMe
9
f1 (ppm)

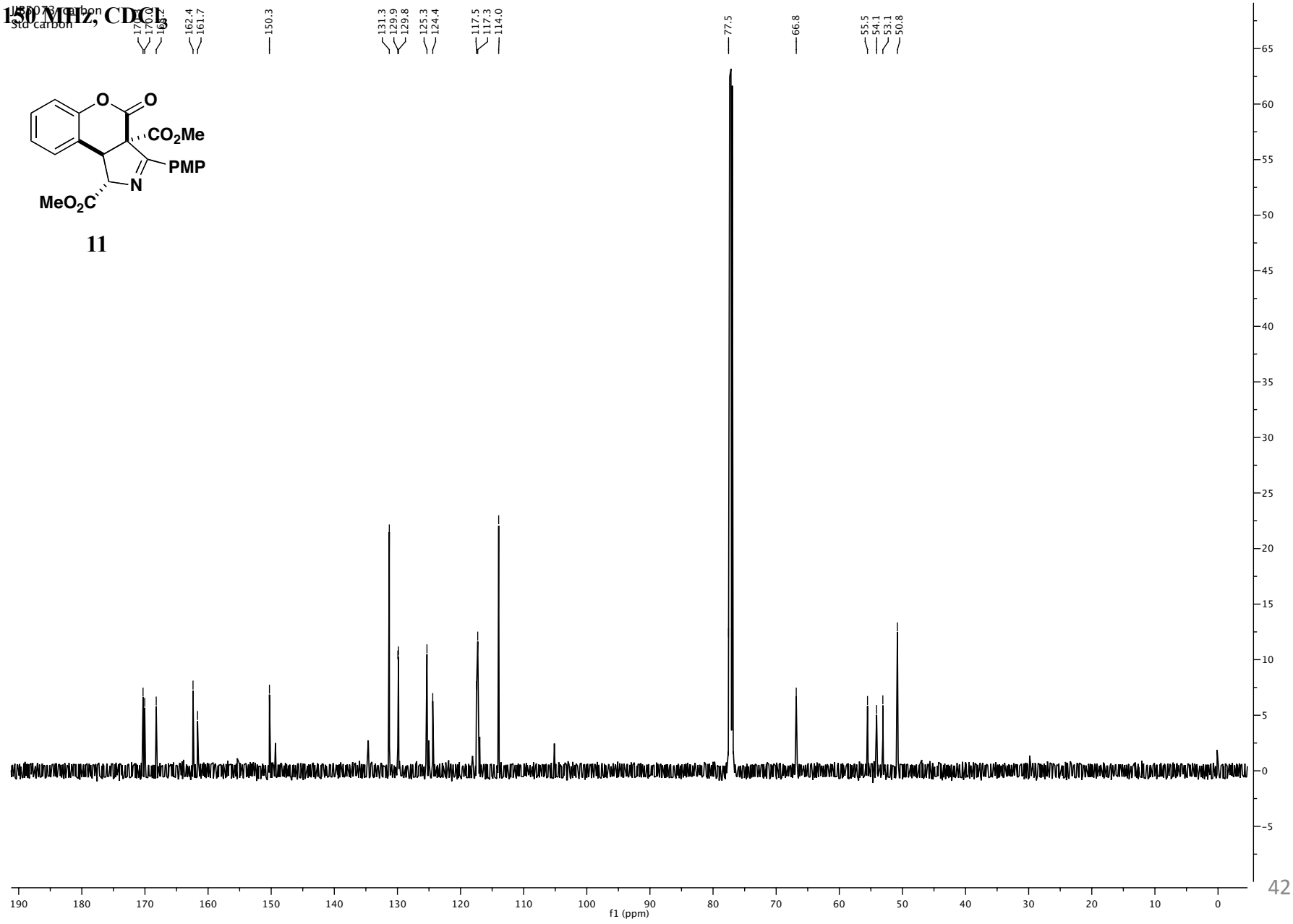
CR2-21pure_16SC
Std proton

400 MHz, $CDCl_3$



11

150 MHz, $CDCl_3$



11