Synthesis of the 5/5-Spiroindimicin Alkaloids: Development of a General Synthetic Approach and Biological Investigations

Ankush Banerjee, Tiffany A. Brisco, Sneha Ray, Arani Datta, Xiaoyu Zhang, Zhen Zhang, Alexander A. Busse, Hanspeter Niederstrasser, Krissty Sumida, Bruce A. Posner, Dawn M. Wetzel, Margaret, A. Phillips, Myles W. Smith*

Department of Biochemistry, UT Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390, United States.

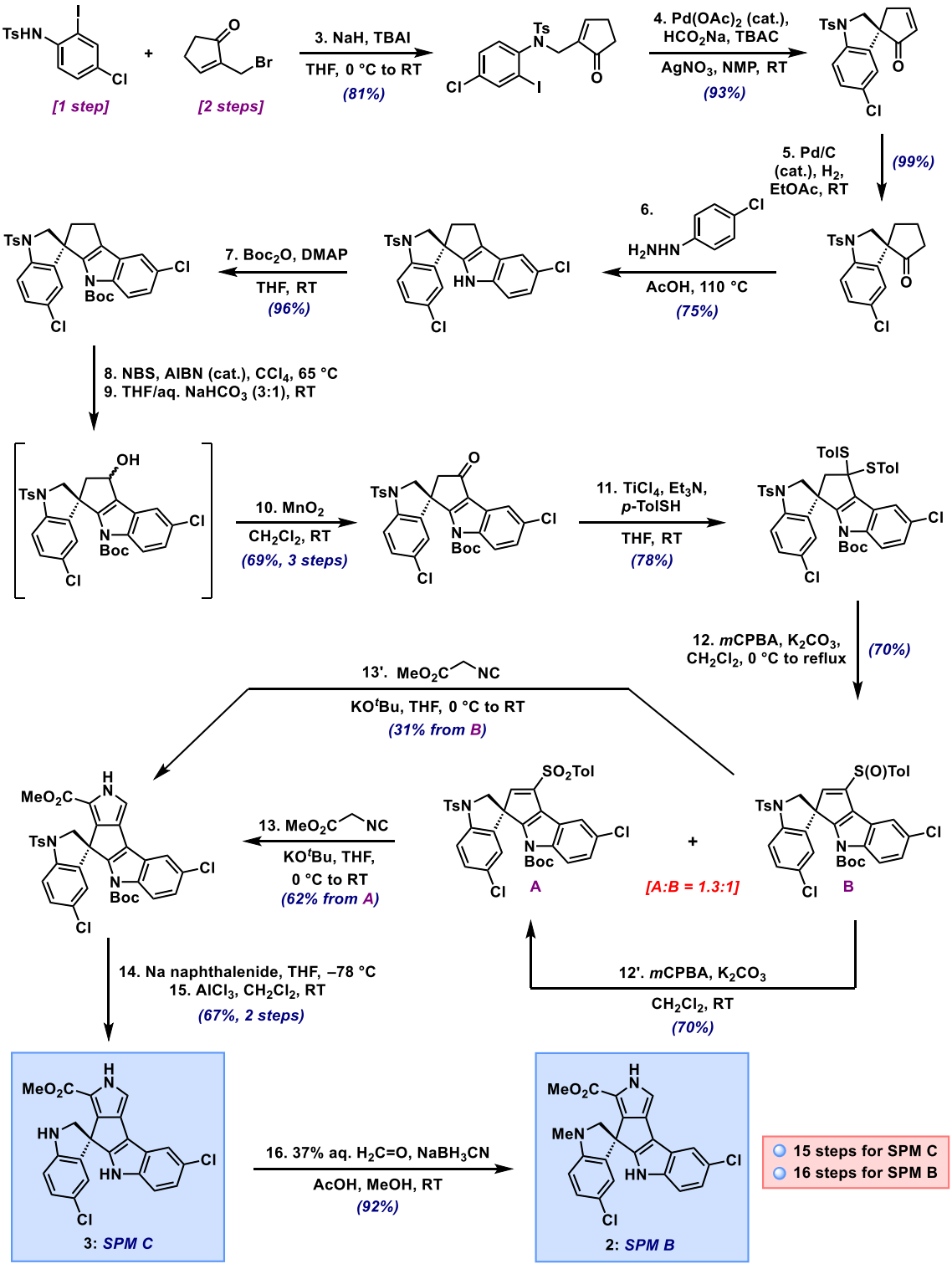
*myles.smith@utsouthwestern.edu

1. General Information

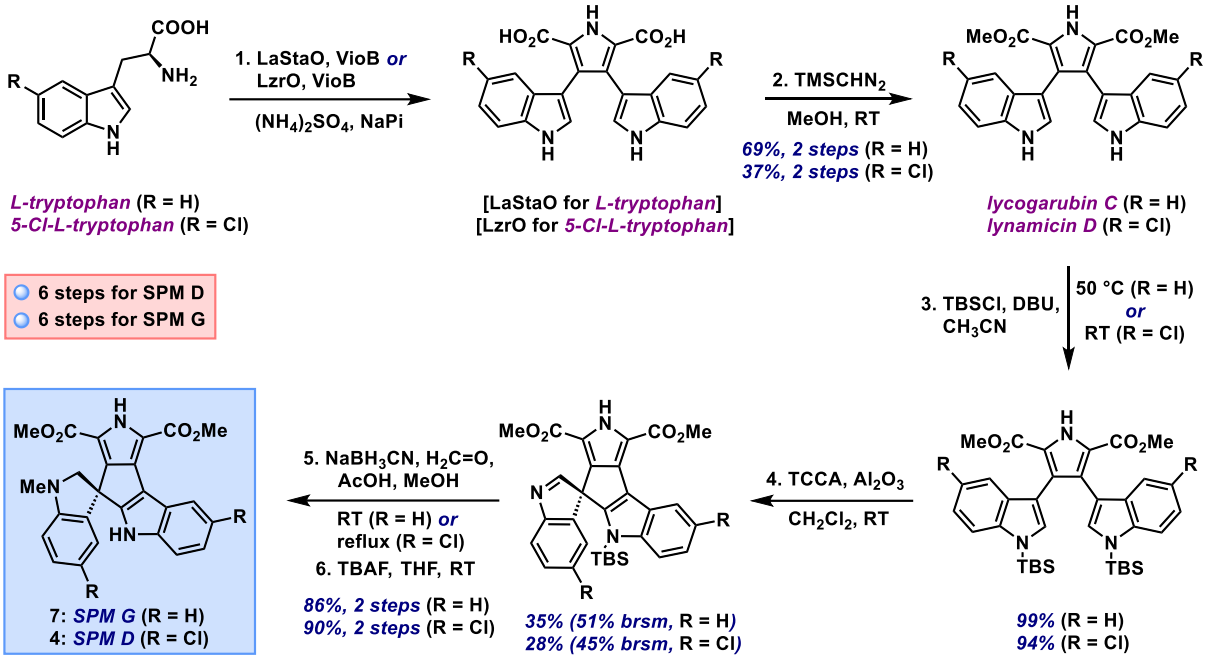
All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise stated. An oil bath was used as the heat source for reactions that require heating. Dry methylene chloride (CH_2Cl_2), tetrahydrofuran (THF), *N*,*N*-dimethylformamide (DMF), and toluene (PhMe) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns; 1,2-dichloroethane (DCE), methanol (MeOH) and acetonitrile (MeCN) were purchased in anhydrous form from Sigma–Aldrich or Acros and used as received; acetic acid (AcOH) and 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) were purchased from Oakwood and used as received. Yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60 F_{254}) using UV light and an aqueous solution of cerium ammonium sulfate and ammonium molybdate and heat as visualizing agents. Preparative TLC was carried out on 0.25 mm E. Merck silica gel plates (60 F_{254}). SiliCycle silica gel (60 Å, academic grade, particle size 40–63 μm) was used for flash column chromatography. NMR spectra were recorded on Varian MR400, Bruker AN400 and AN600 instruments and calibrated using residual undeuterated solvent as an internal reference (for $CDCl_3$, ^{1}H = δ 7.26 and ^{13}C = δ 77.16; for acetone-d_6, ^{1}H = δ 2.05 and ^{13}C = δ 29.84; for CD_3OD, ^{1}H = δ 3.31 and ^{13}C = δ 49.00; for DMSO-d_6, ^{1}H = δ 2.50 and ^{13}C = δ 39.52). The following abbreviations are used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, br = broad, app = apparent. High-resolution mass spectrometric data (ESI) were acquired on a SCIEX TripleTOF 6600 High Resolution Accurate Mass System (UT Southwestern Metabolomics Core Facility). Optical rotation data were recorded on a Rudolph Research Analytical Autopol® IV Polarimeter.

2. Synthetic Schemes for Sperry's and Xu's 5/5-Spiroindimicin Syntheses

Scheme S1: Sperry's synthesis of (±)-spiroindimicins B (**2**) and C (**3**)

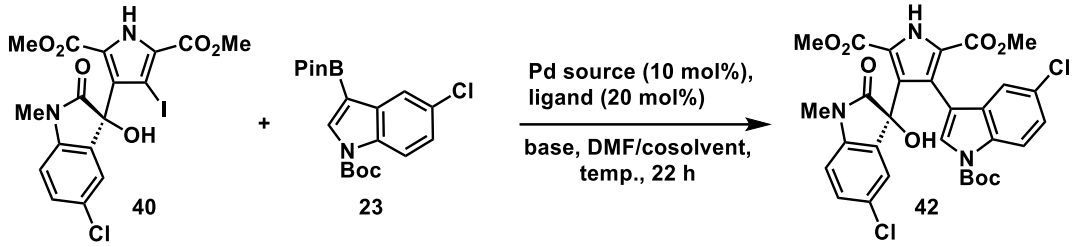


Scheme S2: Xu's synthesis of (±)-spiroindimicins D (**4**) and G (**7**)



3. Optimization of Key Cross-Coupling and Spirocyclization Steps

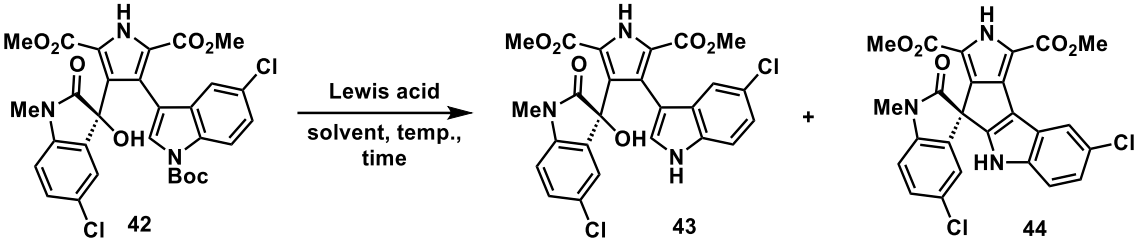
Table S1: Full optimization of Suzuki coupling towards SPM D (**4**)



Entry	ArBpin [equiv]	Catalyst/Ligand	Temp. [°C]	Base [equiv]	Solvent/Cosolvent	Yield [%][a]
1	**23** (1.8)	$Pd(PPh_3)_4$	80	K_3PO_4 (3.6)	dioxane/H_2O	ND
2	**23** (1.8)	$Pd(OAc)_2$/SPhos	80	K_3PO_4 (3.6)	dioxane/H_2O	ND
3	**23** (1.8)	$Pd(OAc)_2$/SPhos	75	K_2CO_3 (3.6)	THF/H_2O	ND
4	**23** (1.8)	$Pd(dppf)Cl_2$	23	Cs_2CO_3 (3.6)	DMF	ND
5	**23** (1.8)	$Pd(dppf)Cl_2$	40	Cs_2CO_3 (3.6)	DMF	5
6	**23** (1.8)	XPhos Pd G2	40	Cs_2CO_3 (3.6)	DMF/H_2O	ND
7	**23** (1.8)	PEPPSI-IPr	40	Cs_2CO_3 (3.6)	DMF/H_2O	ND
8	**23** (1.8)	$Pd_2(dba)_3$/SPhos	40	Cs_2CO_3 (3.6)	DMF/H_2O	8
9	**23** (1.8)	$Pd(OAc)_2$/SPhos	40	Cs_2CO_3 (3.6)	DMF/H_2O	26
10	**23** (1.8)	$Pd(OAc)_2$/SPhos	50	Cs_2CO_3 (3.6)	DMF/H_2O	15
11	**23** (1.8)	$Pd(OAc)_2$/DavePhos	40	Cs_2CO_3 (3.6)	DMF/H_2O	ND
12	**23** (1.8)	$Pd(OAc)_2$/CyJohnPhos	40	Cs_2CO_3 (3.6)	DMF/H_2O	ND
13	**23** (1.8)	SPhos Pd G4	40	Cs_2CO_3 (3.6)	DMF/H_2O	39
14	**23** (1.8)	SPhos Pd G4	40	Cs_2CO_3 (3.6)	DMF	11
15	**23** (1.8)	SPhos Pd G4	40	Cs_2CO_3 (3.6)	DMF/MeOH	ND
16	**23** (1.8)	SPhos Pd G4	40	K_3PO_4 (3.6)	DMF/ H_2O	51
17	**23** (1.8)	SPhos Pd G4	40	K_3PO_4 (3.6)	NMP/H_2O	ND
18	**23** (1.8)	SPhos Pd G4	40	K_3PO_4 (3.6)	DMA/H_2O	28
19	**23** (1.8)	SPhos Pd G4	40	K_3PO_4 (3.6)	DMF/ H_2O	52[b]
20	**23** (2.0)	SPhos Pd G4	40	K_3PO_4 (3.6)	DMF/ H_2O	72[c]
21	**23 (2.5)**	**SPhos Pd G4**	**40**	**K_3PO_4 (3.6)**	**DMF/H_2O**	**81** [d]

[a]Reactions were carried out using 0.04 mmol of **40**; ^1H NMR yield using CH_2Br_2 as internal standard; [b]Reaction was carried out on 0.27 mmol scale; [c]Reaction was carried out on 0.43 mmol scale; [d]Reaction was carried out on 0.82 mmol scale.

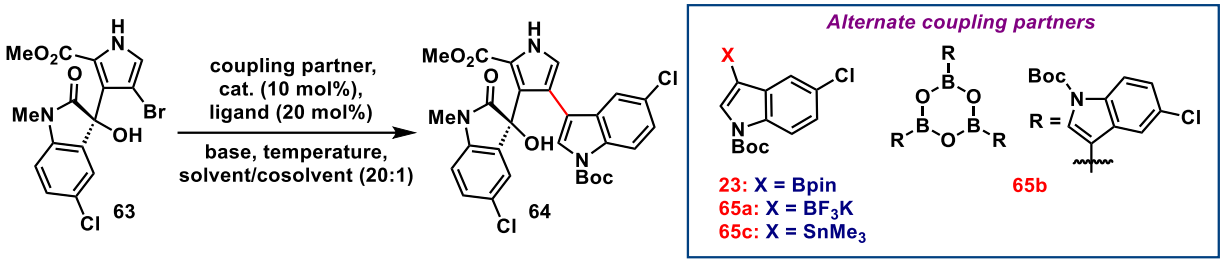
Table S2: Full optimization of spirocyclization step towards SPM D (**4**)



Entry	Lewis Acid [equiv]	Solvent	Temp [°C]	Time	Yield of 43 [%][a]	Yield of 44 [%][a]
1	$Sc(OTf)_3$ (1)	DCE	23	24 h	not determined	not determined
2	$Sc(OTf)_3$ (1)	DCE	70	30 min	11	31
3	$Yb(OTf)_3$ (1)	DCE	70	5 h	39	trace
4	–	DCM/TFA (4:1)	0–23	12 h	decomposed	not detected
5	$In(OTf)_3$ (1)	DCE	70	1 h	19	22
6	$Cu(OTf)_2$ (1)	DCE	70	1.5 h	not determined	29
7	$Cu(OTf)_2$ (1)	DCE	70	4 h	not detected	42
8	TMSOTf (1)	DCE	23	1 h	not determined	22
9	$Zn(OTf)_2$ (1)	DCE	70	12 h	not detected	not detected
10	$Ce(OTf)_3$ (1)	DCE	70	12 h	not detected	not detected
11	$Zn(OTf)_2$ (1)	DCE	85	24 h	83	11
12	$Ce(OTf)_3$ (1)	DCE	85	24 h	55	38
13	$Ce(OTf)_3$ (1)	DCE	85	48 h	45[b]	41[b]
14	BF_3•Et_2O (1)	DCE	23	24 h	9	trace
15	BF_3•Et_2O (1)	DCE	70	30 min	not detected	43
16	BF_3•Et_2O (0.2)	DCE	70	2 h	21	36
17	BF_3•Et_2O (0.2)	DCE	70	3 h	not detected	35
18	BF_3•Et_2O (1)	DCE	70	10 min	not detected	55
19	BF_3•Et_2O (1)	DCE	70	5 min	not detected	55
20	**BF_3•Et_2O (0.5)**	**DCE**	**70**	**20 min**	**not detected**	**58**
21	BF_3•Et_2O (1)	DCE	50	1.5 h	not determined	34
22	BF_3•Et_2O (0.2)	$PhCF_3$	70	10 min	12	25
23	BF_3•Et_2O (1)	THF	70	18 h	not detected	not detected
24	BF_3•Et_2O (1)	CH_3CN	70	20 min	36	8
25	BF_3•Et_2O (1)	toluene	70	5 min	53	38
26	BF_3•Et_2O (1)	toluene	70	12 min	23	52
27	BF_3•Et_2O (1)	toluene	70	24 min	12	54
28	BF_3•Et_2O (0.5)	PhMe/DCE (1:1)	70	24 min	not determined	43

[a]All reactions were carried out on 0.019 mmol scale; ^{1}H NMR yield using CH_2Br_2 as internal standard; [b]Isolated yield.

Table S3: Full optimization of Suzuki coupling towards SPM B (**2**)



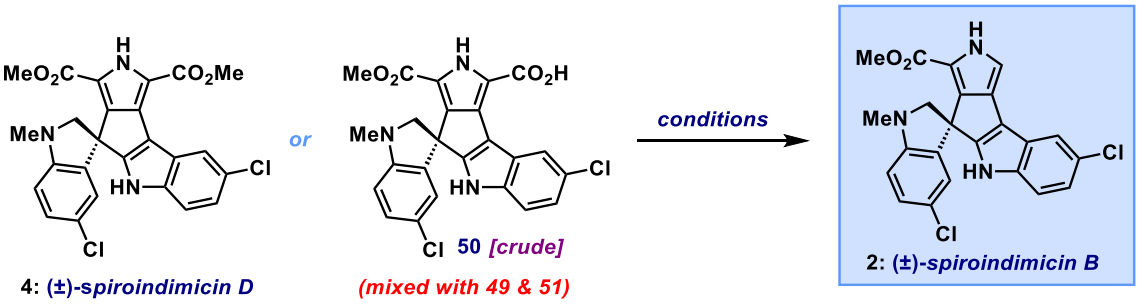
Entry	Partner [equiv]	Catalyst/ Ligand	Additive [equiv]	Temp [°C]	Time [h]	Base [equiv]	Solvent	Yield [%][a]
1	**23** (2.5)	SPhos Pd G4	-	50	24	K_3PO_4 (3.6)	DMF/H_2O	ND
2	**23** (2.5)	SPhos Pd G4	-	70	24	K_3PO_4 (3.6)	DMF/H_2O	7
3[b]	**23** (2.5)	SPhos Pd G4	-	80	24	K_3PO_4 (3.6)	DMF/H_2O	7
4	**23** (2.5)	SPhos Pd G4	-	110	6	K_3PO_4 (3.6)	DMF/H_2O	5
5	**23** (2.5)	SPhos Pd G4	-	70	24	Cs_2CO_3 (3.6)	DMF/H_2O	ND
6	**23** (2.5)	$Pd(OAc)_2$/SPhos	-	70	24	K_3PO_4 (3.6)	DMF/H_2O	ND
7	**23** (2.5)	(^{t}Bu)$_2$PMe Pd G4	-	70	24	K_3PO_4 (3.6)	DMF/H_2O	ND
8	**23** (2.5)	XPhos Pd G2	-	70	24	K_3PO_4 (3.6)	DMF/H_2O	ND
9	**23** (2.5)	PEPPSI-IPr	-	70	24	K_3PO_4 (3.6)	DMF/H_2O	ND
10	**23** (2.5)	$Pd(dppf)Cl_2$	-	70	24	K_3PO_4 (3.6)	DMF/H_2O	ND
11	**23** (2.5)	SPhos Pd G4 /SPhos (1:1)	-	70	24	K_3PO_4 (3.6)	DMF/H_2O	ND
12	**23** (2.5)	XPhos Pd G2/XPhos (1:1)	-	70	24	K_3PO_4 (3.6)	DMF/H_2O	ND
13	**23** (2.5)	SPhos Pd G4 /SPhos (1:1)	-	70	24	K_3PO_4 (3.6)	dioxane/H_2O	ND
14	**23** (2.5)	SPhos Pd G4	-	70	24	K_3PO_4 (3.6)	dioxane/H_2O	ND
15	**23** (2.5)	SPhos Pd G4	-	70	24	CsF (3.6)	DMF/H_2O	5
16	**23** (2.5)	SPhos Pd G4	-	70	24	KO^{t}Bu (3.6)	DMF	ND
17[c]	**65a** (2.5)	SPhos Pd G4	-	70–90	36	K_3PO_4 (3.6)	DMF/H_2O	ND
18[d]	**65c** (2.5)	$Pd(PPh_3)_4$	CuTC (1.5)	23–80	36	-	NMP	ND
19	**65b** (0.9)	SPhos Pd G4	-	70	24	K_3PO_4 (3.6)	DMF/H_2O	10
20	**65b** (0.9)	$Pd(OAc)_2$/RuPhos	-	70	24	K_3PO_4 (3.6)	DMF/H_2O	ND
21	**65b** (0.9)	SPhos Pd G4 /SPhos (1:1)	-	70	24	K_3PO_4 (3.6)	DMF/H_2O	ND
22	**23** (2.5)	$NiCl_2$(dppe)/dppe (1:1)	-	110	4	K_3PO_4 (3.6)	dioxane	decomposed
23	**65b** (0.9)	$NiCl_2$(dppp)	-	110	4	K_3PO_4 (3.6)	dioxane	decomposed
24	**23** (2.5)	SPhos Pd G4	CuCl (1.0)	70	24	K_3PO_4 (3.6)	DMF/H_2O	11

25	**23** (2.5)	$Pd(OAc)_2$/dppf	CuCl (1.0)	110	24	Cs_2CO_3 (3.6)	DMF	6
26	**23** (2.5)	SPhos Pd G4	CuCl (1.0)	70	24	K_3PO_4 (3.6)	DMF	13
27	**23** (2.5)	$Pd(dppf)Cl_2$/dppf (1:1)	CuCl (1.0)	70	24	K_3PO_4 (3.6)	DMF	ND
28	**23** (2.5)	SPhos Pd G4	CuCl (2.5)	70	24	K_3PO_4 (3.6)	DMF	22
29	**23** (2.5)	SPhos Pd G4	CuCl (0.5)	70	24	K_3PO_4 (3.6)	DMF	trace
30	**65b** (0.9)	SPhos Pd G4	CuCl (2.5)	70	24	K_3PO_4 (3.6)	DMF	11
31	**23** (2.5)	SPhos Pd G4	CuI(2.5)	70	24	K_3PO_4 (3.6)	DMF	6
32	**23** (2.5)	SPhos Pd G4	CuTc (2.5)	70	24	K_3PO_4 (3.6)	DMF	ND
33	**23** (2.5)	SPhos Pd G4	CuCl (2.5)	85	24	K_3PO_4 (3.6)	DMF	21
34	**23** (3.5)	SPhos Pd G4	CuCl (3.5)	70	24	K_3PO_4 (3.6)	DMF	34
35[e]	**23** (3.5)	SPhos Pd G4	CuCl (3.5)	70	48	K_3PO_4 (3.6)	DMF	24
36	**23 (5.0)**	**SPhos Pd G4**	**CuCl (5.0)**	**70**	**24**	**K_3PO_4 (5.0)**	**DMF**	**44**
37	**23** (5.0)	SPhos Pd G4 (15 mol %)	CuCl (5.0)	70	24	K_3PO_4 (5.0)	DMF	42
38	**23** (5.0)	SPhos Pd G4	CuCl (2.5)	70	24	K_3PO_4 (5.0)	DMF	29
39	**23** (2.5)	SPhos Pd G4	CuCl (5.0)	70	24	K_3PO_4 (3.6)	DMF	27
40	**23** (5.0)	SPhos Pd G4	CuCl (5.0)	70	24	K_3PO_4 (5.0)	DMF/H_2O (20:1)	27
41	**23** (5.0)	SPhos Pd G4	CuCl (5.0)	70	24	Cs_2CO_3 (5.0)	DMF	35

[a]Reactions were carried out using 0.035 mmol of **63**, ^{1}H NMR yield using CH_2Br_2 as internal standard; [b]Coupling partner **23** was added in a batchwise manner (initially 1.3 equiv **23** then another 1.2 equiv **23** after 6 h); [c]Reaction was carried out at 70 °C for 24 h, no product formation observed, so another 1.0 equiv coupling partner **65a** and 0.1 equiv. catalyst added and heated at 90 °C; [d]The temperature of the reaction was gradually increased from 23 to 80 °C as no product formation was observed; [e]Coupling partner **23** and CuCl was added in a batchwise manner (initially 2.5 equiv **23** and CuCl then another 1.0 equiv **23** and CuCl after 24 h).

4. Attempted Decarboxylations for the Synthesis of SPM B (2)

Table S4: Decarboxylation conditions attempted for the synthesis of SPM B (**2**)

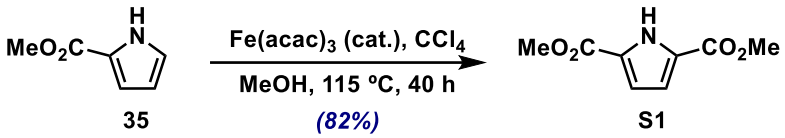


4: (±)-spiroindimicin D | 50 [crude] (mixed with 49 & 51) | 2: (±)-spiroindimicin B

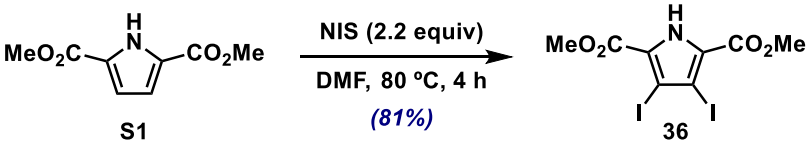
Entry	Starting Material	Conditions	Result
1	**50**	neat, 180 °C, 3 h	CM
2	**50**	TFA/CH_2Cl_2 (1:4), 0 to 85 °C, 20 h	NR
3	**50**	*p*-TsOH•H_2O, toluene, 85 °C, 16 h	CM
4	**50**	2 M HCl/THF (1:1), 50 to 65 °C, 16 h	NR
5	**50**	6 M HCl/1,4-dioxane (1:6), 95 °C, 16 h	NR
6	**50**	Cu_2O, 1,10-phenanthroline, NMP/quinoline (3:1), 170 °C, 0.5 h	CM
7	**50**	Cu powder, quinoline 180 °C, 1 h	CM
8	**50**	$Pd(TFA)_2$, TFA, DMF/DMSO (10:1), 80 °C, 12 h	CM
9	**50**	$Pd(OAc)_2$, dppb, Et_3SiH, Piv_2O, toluene, 160 °C, 6 h	CM
10	**50**	Ag_2CO_3, AcOH, DMSO, 110 to 130 °C	NR
11	**4**	KOH, ethylene glycol, 160 °C	CM
12	**4**	LiCl, H_2O, DMSO, reflux	CM

NR = No Reaction; CM = Complex Mixture

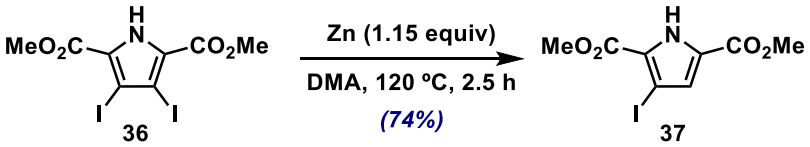
5. Experimental Procedures



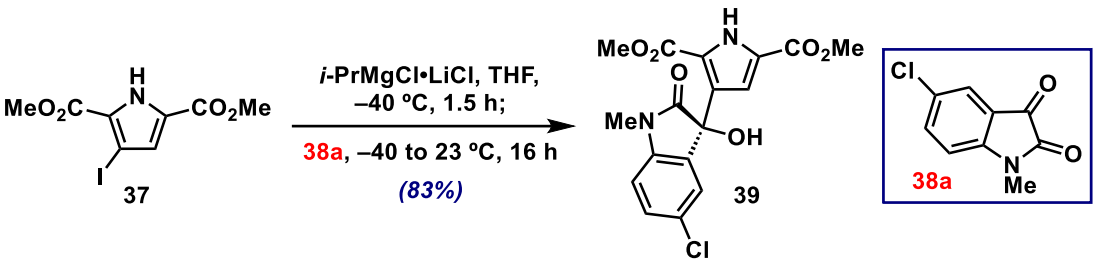
Dimethyl pyrrole-2,5-dicarboxylate (S1): A reaction flask was charged under argon with methyl 2-pyrrolecarboxylate (**35**, 5.45 g, 43.6 mmol, 1.0 equiv) and $Fe(acac)_3$ (927 mg, 2.62 mmol, 0.06 equiv), and CCl_4 (12 mL) and MeOH (66 mL) were added. The flask was sealed and heated for 40 h at 115 °C with continuous stirring. When the reaction was complete, the reaction was cooled to room temperature, and the flask was carefully opened (**CAUTION**: some pressure build-up is seen on large scale). The reaction mixture was filtered through a short pad of silica gel, rinsing with EtOAc (2 × 100 mL). The eluent was concentrated, and the residue chromatographed on silica gel (20–35% EtOAc/hexanes gradient) to give pure dimethyl pyrrole-2,5-dicarboxylate (**S1**) (6.55 g, 82%). ^{1}H NMR spectral data are in agreement with the literature.[3,4]



Dimethyl 3,4-diiodopyrrole-2,5-dicarboxylate (36): A 100 mL round-bottom flask containing diester **S1** (2.5 g, 13.7 mmol, 1.0 equiv) and a magnetic stir bar was evacuated under vacuum and backfilled with argon (× 3). DMF (30 mL) was added followed by NIS (6.8 g, 30 mmol, 2.2 equiv). The resulting reaction mixture was stirred at 80 °C for 4 h. After complete consumption of starting material, indicated by TLC, DMF was evaporated *in vacuo.* To this crude residue 30 mL EtOAc and 30 mL H_2O was added and stirred for 15 min. The product **36** was precipitated. It was filtered and washed with H_2O (40 mL) and dried under vacuum to obtain desired product **36** in 81% yield (4.8 g, pale yellow solid). ^{1}H NMR spectral data are in agreement with the literature.[4,5]

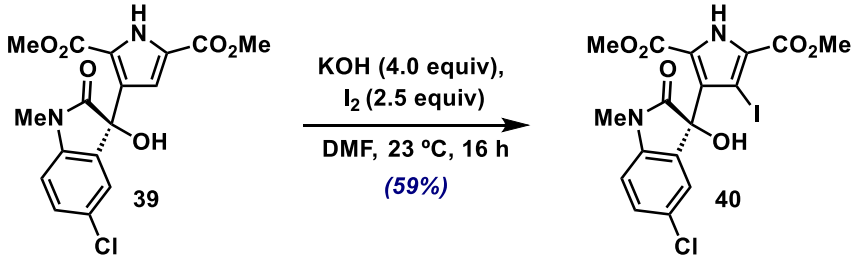


Dimethyl 3-iodo-1H-pyrrole-2,5-dicarboxylate (37): Iodine (11.7 mg, 0.046 mmol, 0.1 equiv) was added to zinc powder (34 mg, 0.53 mmol, 1.15 equiv) under an argon atmosphere and the ensuing mixture was stirred at room temperature for 2 min before being treated with DMA (0.3 mL). The resulting suspension was stirred for a further 2 min before compound **36** (200 mg, 0.46 mmol, 1.0 equiv) was added and the reaction heated at 120 °C for 2.5 h. After cooling to room temperature, the reaction mixture was treated with silica gel (1.2 g) and concentrated under reduced pressure. The free flowing solid thus obtained was chromatographed on silica gel (15–30% EtOAc/hexanes gradient) to give pure dimethyl 3-iodopyrrole-2,5-dicarboxylate (**37**) (104.7 mg, 74%, white solid). 1H NMR spectral data are in agreement with the literature.[4,5]



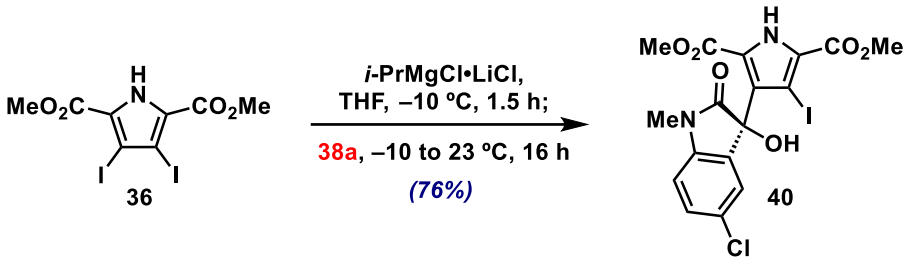
Grignard addition product 39: A 50 mL round-bottom flask containing iodide **37**[5] (531 mg, 1.72 mmol, 1.0 equiv) and a magnetic stir bar was evacuated under vacuum and backfilled with argon (× 3). THF (12 mL) was added and the reaction mixture was cooled to –40 °C. *i*-PrMgCl•LiCl (1.3 M in THF, 2.91 mL, 3.80 mmol, 2.2 equiv) was added dropwise and the resulting reaction mixture was stirred at –40 °C for 1.5 h. A solution of *N*-methyl 5-chloroisatin[6] (**38a**, 403 mg, 2.06 mmol, 1.2 equiv; azeotropically dried with PhMe × 2) in THF (8 mL) was added dropwise at the same temperature. The resulting reaction mixture was slowly warmed up to room temperature and stirred overnight (16 h). After complete consumption of starting material **37** (TLC), the reaction was quenched with saturated NH_4Cl solution (15 mL) and transferred to a separatory funnel, diluting with EtOAc (15 mL) and water (15 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 12 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude residue was purified by flash chromatography (silica gel, EtOAc/hexanes, 30–95%) to afford **39** (537 mg, 83%).

Physical Properties: Pale yellow solid;
R_f = 0.18 (silica gel, 50% EtOAc/hexanes);
Melting Point = 108–109 °C;
MS (ESI): calculated for $C_{17}H_{16}ClN_2O_6$ $[M + H]^+$ 379.0691, found 379.0691;
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.91 (br s, 1H), 7.35 – 7.30 (m, 2H), 7.03 (br s, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 6.35 (d, *J* = 1.6 Hz, 1H), 3.96 (s, 3H), 3.84 (s, 3H), 3.17 (s, 3H);
^{13}C NMR (101 MHz, $CDCl_3$): δ 176.0, 161.6, 160.3, 142.6, 132.3, 131.7, 130.1, 128.7, 125.6, 124.5, 122.7, 115.1, 109.6, 75.0, 53.0, 52.3, 26.6.



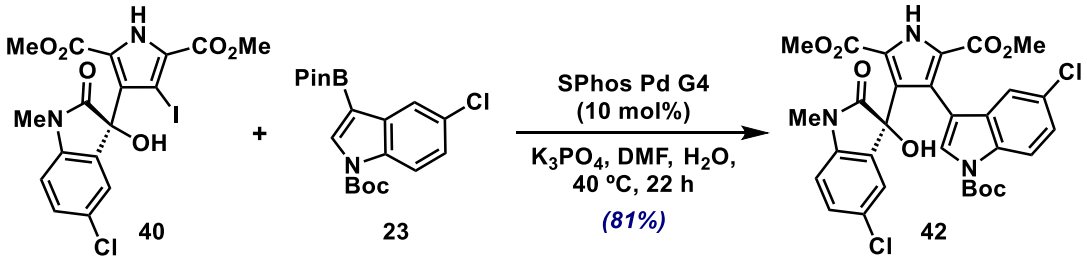
Synthesis of 39 from 40: A 100 mL round-bottom flask containing diester **39** (520 mg, 1.37 mmol, 1.0 equiv) and a magnetic stir bar was evacuated under vacuum and backfilled with argon (× 3). DMF (25 mL) was added followed by KOH (307 mg, 5.48 mmol, 4.0 equiv) and it was stirred for 10 min. To this stirring solution I_2 (869 mg, 3.42 mmol, 2.5 equiv) was added and the resulting reaction mixture was stirred at 23 °C for 16 h. After complete consumption of starting material, indicated by TLC, the reaction was quenched with saturated Na_2SO_3

solution (60 mL) and water (60 mL), transferred to a separatory funnel and diluting with EtOAc (60 mL). the aqueous layer was extracted with EtOAc (2 × 40 mL). The combined organic layers were washed with water (2 × 40 mL), brine (2 × 40 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford pure **40** (406 mg, 59%).



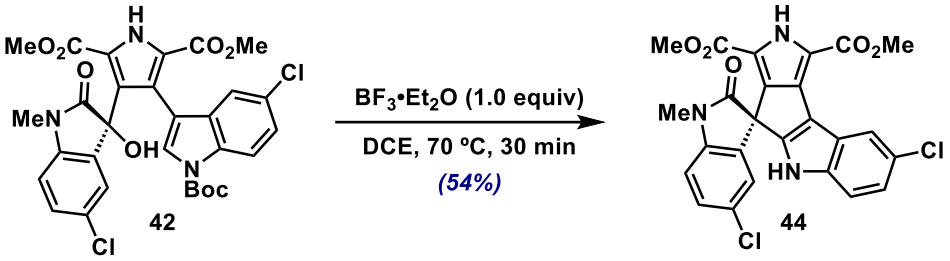
Iodinated Grignard addition product 40: A 100 mL round-bottom flask containing **36** (500 mg, 1.15 mmol, 1.0 equiv; azeotropically dried with PhMe × 2) and a magnetic stir bar was evacuated under vacuum and backfilled with argon (× 3). THF (16 mL) was added and the solution was cooled to –10 °C. *i*-PrMgCl•LiCl (1.3 M in THF, 1.95 mL, 2.53 mmol, 2.2 equiv) was added dropwise and the reaction was stirred at –10 °C for 1.5 h. Then, a solution of *N*-methyl 5-chloroisatin[6] (**38a**, 450 mg, 2.30 mmol, 2.0 equiv; azeotropically dried with PhMe × 2) in THF (15 mL) was added dropwise. The resulting reaction mixture was stirred at this temperature for 15 min, then the cooling bath was removed and the reaction stirred overnight at room temperature (16 h). After complete consumption of starting material **36** (TLC), the reaction was quenched with saturated NH_4Cl solution (20 mL) and transferred to a separatory funnel, diluting with EtOAc (15 mL) and water (15 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude residue was purified by flash chromatography (silica gel, EtOAc/hexanes, 30–100%) to afford **40** (439 mg, 76%). [**Note**: Upon scale-up with 1.0 g of **36**, 801 mg (69%) of **40** was obtained]

Physical Properties: Yellow solid;
R_f = 0.18 (silica gel, 50% EtOAc/hexanes);
Melting Point = 260–262 °C (decomposed);
MS (ESI): calculated for $C_{17}H_{15}ClIN_2O_6$ $[M + H]^+$ 504.9658, found 504.9656;
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.18 (br s, 1H), 7.93 (s, 1H), 7.33 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.11 (s, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 4.05 (s, 3H), 3.90 (s, 3H), 3.27 (s, 3H);
^{13}C NMR (151 MHz, $CDCl_3$): δ 174.0, 161.8, 159.3, 143.6, 134.5, 132.0, 130.2, 128.7, 126.4, 125.4, 124.1, 109.8, 76.5, 69.3, 53.9, 52.5, 26.8.



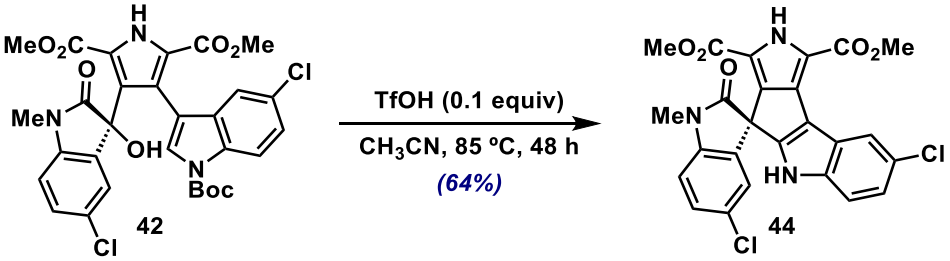
Suzuki coupling product 42: A solution of iodide **40** (416 mg, 0.82 mmol, 1.0 equiv) and indole boronate **23**[4] (778 mg, 2.06 mmol, 2.5 equiv) in DMF (30 mL) was degassed by argon sparge for 30 min. SPhos Pd G4 (64.0 mg, 0.082 mmol, 0.1 equiv) was added to the reaction mixture followed by a solution of K_3PO_4 (630 mg, 2.97 mmol, 3.6 equiv) in degassed water (1.5 mL). The resulting reaction mixture was heated at 40 °C for 22 h. After complete consumption of starting material **40** (TLC), the contents were transferred to a separatory funnel and diluted with EtOAc (30 mL) and cold water (50 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with cold water (× 3) then brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude residue was purified by flash chromatography (silica gel, EtOAc/hexanes, 30–80%) to afford a mixture of desired product **42** (dr = 1:1) along with the by-product pinacol. This mixture was redissolved in CH_2Cl_2 (50 mL) and transferred to a separatory funnel. The organic layer was washed with water (2 × 50 mL), brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford pure compound **42** (418 mg, 81%, dr = 1:1). [**Note**: These additional aqueous washes removed the pinacol. Upon scale-up with 800 mg of **40**, 752 mg (76%) of **42** was obtained]

Physical Properties: Yellow solid;
R_f = 0.20 (silica gel, 50% EtOAc/hexanes);
Melting Point = 142–144 °C;
MS (ESI): calculated for $C_{30}H_{28}Cl_2N_3O_8$ $[M + H]^+$ 628.1248, found 628.1257;
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.99 (br s, 2H), 8.07 (br s, 1H), 7.98 (br s, 2H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.19 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.16 (s, 2H), 7.13 (dd, *J* = 8.8, 2.0 Hz, 1H), 6.99 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.97 (d, *J* = 2.0 Hz, 1H), 6.91 (d, *J* = 2.0 Hz, 1H), 6.77 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.67 (br s, 1H), 6.57 (d, *J* = 1.2 Hz, 1H), 6.09 (d, *J* = 8.4 Hz, 1H), 6.06 (d, *J* = 8.0 Hz, 1H), 4.10 (s, 6H), 3.62 (s, 3H), 3.59 (s, 3H), 2.87 (s, 3H), 2.45 (s, 3H), 1.67 (s, 9H), 1.66 (s, 9H); [**Note**: For integration purposes, 1H corresponds to 1 proton of a given diastereomer in the inseparable 1:1 diastereomeric mixture]
^{13}C NMR (151 MHz, $CDCl_3$): δ 175.4, 174.7, 162.42, 162.40, 159.74, 159.71, 149.2, 148.9, 142.2, 141.5, 133.3, 132.80, 132.77, 132.63, 132.60, 132.5, 132.1, 131.8, 131.5, 129.1, 128.9, 128.7, 128.5, 127.9, 126.5, 126.2, 125.6, 124.9, 124.7, 124.6, 124.3, 124.2, 122.9, 122.5, 119.8, 119.7, 119.1, 119.0, 115.9, 115.7, 111.6, 111.2, 108.6, 108.2, 84.5, 84.3, 75.18, 75.16, 53.7 (two signals merged), 52.34, 52.32, 28.3, 28.2, 25.9, 25.6.



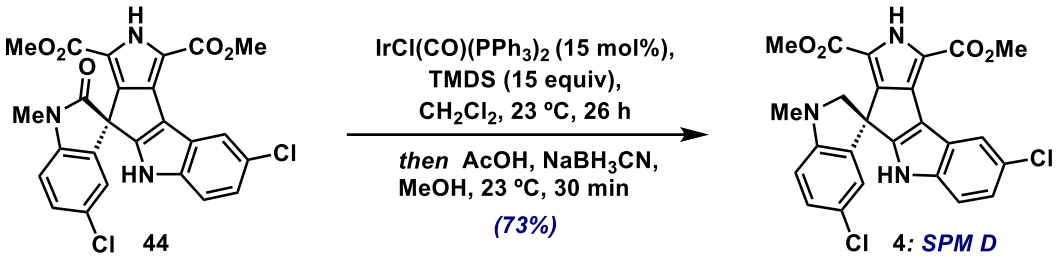
BF_3•Et_2O-mediated synthesis of spirocycle 44: A 25 mL round-bottom flask containing Suzuki product **42** (60 mg, 0.095 mmol, 1.0 equiv) and a magnetic stir bar was evacuated under vacuum and backfilled with argon (× 3). After that, 1,2-dichloroethane (DCE, 10 mL) was added followed by BF_3•Et_2O (12 µL, 0.095 mmol, 1.0 equiv) and the resulting mixture was heated at 70 °C for 30 min. After complete consumption of starting material **42** (TLC), the reaction was cooled to room temperature and quenched with Et_3N (0.13 mL, 0.95 mmol, 10 equiv) and saturated $NaHCO_3$ solution (5 mL). The contents were transferred to a separatory funnel and diluted with CH_2Cl_2 (15 mL) and water (15 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude residue was purified by flash chromatography (silica gel, EtOAc/hexanes, 60–80%) to afford **44** (26.5 mg, 54%). [**Note**: Upon scale-up with 150 mg of **42**, 55.2 mg of **44** (46%) was obtained]

Physical Properties: Pale yellow solid;
R_f = 0.18 (silica gel, 50% EtOAc/hexanes);
Melting Point = >260 °C;
MS (ESI): calculated for $C_{25}H_{18}Cl_2N_3O_5$ $[M + H]^+$ 510.0618, found 510.0620;
^{1}H NMR (600 MHz, Acetone-d_6): δ 10.92 (br s, 2H), 8.37 (d, *J* = 2.4 Hz, 1H), 7.41–7.39 (m, 1H), 7.38 (d, *J* = 8.7 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 1H), 7.15 (dd, *J* = 8.7, 2.1 Hz, 1H), 6.84 (d, *J* = 2.4 Hz, 1H), 4.02 (s, 3H), 3.51 (s, 3H), 3.36 (s, 3H);
^{13}C NMR (151 MHz, Acetone-d_6): δ 172.9, 161.2, 160.0, 152.0, 145.5, 140.1, 138.2, 134.2, 130.9, 129.7, 128.0, 126.5, 124.1, 123.4, 122.8, 121.2, 120.6, 116.8, 115.5, 114.6, 110.5, 55.7, 52.1, 51.8, 27.2.



Triflic acid-catalyzed synthesis of spirocycle 44: A 10 mL sealed tube containing Suzuki product **42** (27.9 mg, 0.0443 mmol, 1.0 equiv) and a magnetic stir bar was evacuated and backfilled with argon (× 3). CH_3CN (2 mL) was added followed by solution of triflic acid (TfOH) in CH_3CN (20 µL, 0.22 M, 0.00443 mmol, 0.1 equiv) and the resulting mixture was heated at 85 °C for 48 h. The reaction was then allowed to cool to room temperature and

quenched with saturated $NaHCO_3$ solution (10 mL). The contents were transferred to a separatory funnel and diluted with EtOAc (10 mL) and water (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude residue was purified by flash chromatography (silica gel, EtOAc/hexanes, 50–100%) to afford spirocycle **44** (14.5 mg, 64%), along with deBoc product **43** (4.3 mg, 18%).

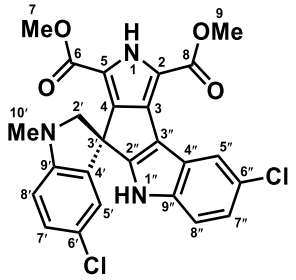


Spiroindimicin D (4)*:* A 10 mL round-bottom flask containing spirocyclic product **44** (9.0 mg, 0.0176 mmol, 1.0 equiv) and a magnetic stir bar was evacuated under vacuum and backfilled with argon (× 3). CH_2Cl_2 (1.2 mL) was added and the reaction mixture was degassed by argon sparge for 10 min. Vaska's complex ($IrCl(CO)(PPh_3)_2$, 1.4 mg, 0.0018 mmol, 0.1 equiv) was then added followed by dropwise addition of 1,1,3,3-tetramethyldisiloxane (TMDS, 32 µL, 0.176 mmol, 10.0 equiv). The resulting reaction mixture was stirred at room temperature for 5 h. A second batch of catalyst (0.7 mg, 0.0009 mmol, 0.05 equiv) and TMDS (16 µL, 0.09 mmol, 5.0 equiv) was added and the stirring was continued. After 26 h, MeOH (1 mL) was added to the reaction mixture and, when effervescence stopped, glacial AcOH (2 µL, 0.036 mmol, 2 equiv) was added followed by $NaBH_3CN$ (1.2 mg, 0.0176 mmol, 1.0 equiv). The reaction mixture was allowed to stir for 30 min then was quenched with 1 N NaOH (2 mL) and transferred to a separatory funnel, diluting with CH_2Cl_2 (5 mL) and water (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were washed with 1 N NaOH (2 × 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude residue was purified by PTLC (silica gel, 40% ethyl acetate in hexane) to afford spiroindimicin D (**4**, 6.4 mg, 73%).

Scaled-up Synthesis of SPM D (4): A 50 mL round-bottom flask containing spirocyclic product **44** (92.0 mg, 0.18 mmol, 1.0 equiv) and a magnetic stir bar was evacuated under vacuum and backfilled with argon (× 3). CH_2Cl_2 (12 mL) was added and the reaction mixture was degassed by argon sparge for 20 min. Vaska's complex ($IrCl(CO)(PPh_3)_2$, 14 mg, 0.018 mmol, 0.1 equiv) was then added followed by dropwise addition of 1,1,3,3-tetramethyldisiloxane (TMDS, 0.32 mL, 1.8 mmol, 10.0 equiv). The resulting reaction mixture was stirred at room temperature for 5 h. A second batch of catalyst (7 mg, 0.009 mmol, 0.05 equiv) and TMDS (0.16 mL, 0.9 mmol, 5.0 equiv) was added and the stirring was continued. After 26 h, a third batch of catalyst (7 mg, 0.009 mmol, 0.05 equiv) and TMDS (0.16 mL, 0.9 mmol, 5.0 equiv) was added and the stirring was continued for another 10 h. MeOH (10 mL) was added to the reaction mixture and, when effervescence stopped, glacial AcOH (12 µL,

0.216 mmol, 1.2 equiv) was added followed by $NaBH_3CN$ (12 mg, 0.18 mmol, 1.0 equiv). The reaction mixture was allowed to stir for 30 min then was quenched with 1 N NaOH (10 mL) and transferred to a separatory funnel, diluting with CH_2Cl_2 (15 mL) and water (15 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with 1 N NaOH (2 × 20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude residue was purified by flash chromatography (silica gel, EtOAc/hexanes, 10–35%) to afford spiroindimicin D (**4**, 54.6 mg, 61%).

Physical Properties: white solid;
R_f = 0.32 (silica gel, 35% EtOAc/hexanes);
Melting Point = 176–178 °C (decomposed);
MS (ESI): calculated for $C_{25}H_{20}Cl_2N_3O_4$ $[M + H]^+$ 496.0825, found 496.0826;
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.24 (br s, 1H), 8.56 (br s, 1H), 8.13 (s, 1H), 7.17 (d, *J* = 8.4 Hz, 1H), 7.11 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.07 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.56 (d, *J* = 8.4 Hz, 1H), 6.52 (d, *J* = 2.0 Hz, 1H), 4.09 (s, 3H), 4.06 (d, *J* = 8.8 Hz, 1H), 3.66 (s, 3H), 3.59 (d, *J* = 8.4 Hz, 1H), 2.86 (s, 3H);
^{13}C NMR (101 MHz, $CDCl_3$): δ 160.9, 159.9, 157.1, 152.1, 139.7, 138.3, 133.2, 132.6, 128.6, 126.6, 123.6, 123.0, 122.6, 122.4, 120.7, 119.9, 114.1, 113.1, 111.5, 109.2, 64.0, 52.2, 51.8, 51.6, 36.6.

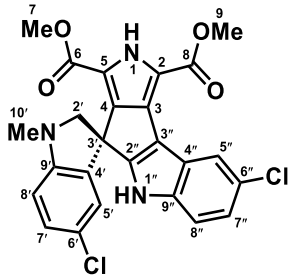


4*: spiroindimicin D*

Table S5: Comparison of ^{1}H NMR shifts (δ) of natural,[7] Xu's,[2] and our synthetic spiroindimicin D (**4**) in $CDCl_3$.

Position	**Natural 4** (500 MHz)	**Synthetic 4** ***(Xu)*** (400 MHz)	**Synthetic 4** ***(Smith)*** (400 MHz)
1	8.52 (s, 1H)	8.37 (br s, 1H)	8.56 (br s, 1H)
7*	4.09 (s, 3H)	4.10 (s, 3H)	4.09 (s, 3H)
9*	3.67 (s, 3H)	3.68 (s, 3H)	3.66 (s, 3H)
2′	4.07 (d, *J* = 8.5 Hz, 1H) 3.61 (d, *J* = 8.5 Hz, 1H)	4.08 (d, *J* = 8.7 Hz, 1H) 3.61 (d, *J* = 8.7 Hz, 1H)	4.06 (d, *J* = 8.8 Hz, 1H) 3.59 (d, *J* = 8.4 Hz, 1H)
5′	6.53 (s, 1H)	6.53 (d, *J* = 2.1 Hz, 1H)	6.52 (d, *J* = 2.0 Hz, 1H)
7′	7.09 (d, *J* = 8.0 Hz, 1H)	7.10 (dd, *J* = 8.0, 2.0 Hz, 1H)	7.07 (dd, *J* = 8.4, 2.4 Hz, 1H)
8′	6.61 (d, *J* = 8.0 Hz, 1H)	6.59 (d, *J* = 8.4 Hz, 1H)	6.56 (d, *J* = 8.4 Hz, 1H)
10′	2.89 (s, 3H)	2.90 (s, 3H)	2.86 (s, 3H)
1″	–	9.20 (br s, 1H)	9.24 (br s, 1H)
5″	8.12 (s, 1H)	8.14 (s, 1H)	8.13 (s, 1H)
7″	7.13 (dd, *J* = 8.5, 2.0 Hz, 1H)	7.13 (dd, *J* = 8.7, 2.1 Hz, 1H)	7.11 (dd, *J* = 8.8, 2.0 Hz, 1H)
8″	7.17 (d, *J* = 8.5 Hz, 1H)	7.19 (d, *J* = 8.7 Hz, 1H)	7.17 (d, *J* = 8.4 Hz, 1H)

*As described in the paper, we conducted 1D NOE experiments of SPM D (**4**) to validate the isolation group's assignment of each methyl ester unit, finding that these had been incorrectly assigned. Namely, the C-9 OMe signal should be at δ = 4.09 ppm and the C-7 OMe signal should be at δ = 3.67 ppm in the natural product.

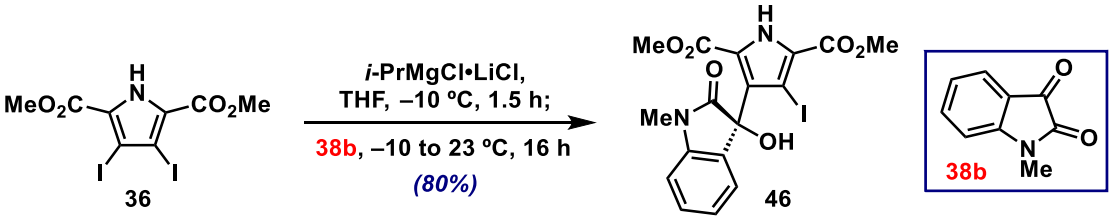


4: ***spiroindimicin D***

Table S6: Comparison of ^{13}C NMR shifts (δ) of natural,[7] Xu's,[2] and our synthetic spiroindimicin D (**4**) in $CDCl_3$.

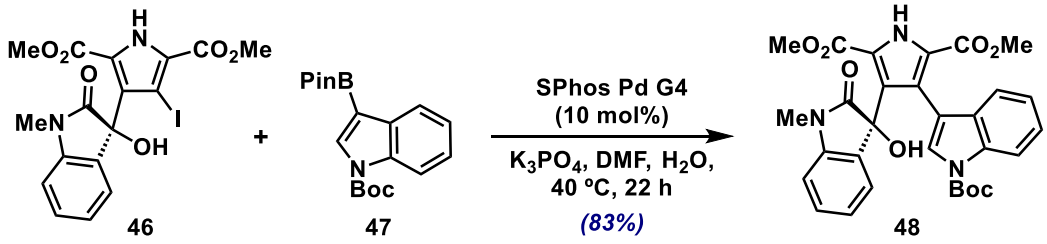
Position	**Natural 4** (126 MHz)[a]	**Synthetic 4** ***(Xu)*** (101 MHz)	**Synthetic 4** ***(Smith)*** (101 MHz)
2	114.0[b]	114.2[b]	114.1[b]
3	119.8	119.9	119.9
4	139.5	139.6	139.7
5	111.5[b]	111.6[b]	111.5[b]
6[c]	159.7	159.9	159.9
7[c]	51.7	51.8	51.8
8[c]	160.8	160.9	160.9
9[c]	52.0	52.2	52.2
2′	63.8	64.1	64.0
3′	51.5	51.7	51.6
4′	133.2	133.2	133.2
5′	122.9	123.0	123.0
6′	123.6	123.7	123.6
7′	128.5	128.7	128.6
8′	109.3	109.2	109.2
9′	151.9	152.2	152.1
10′	36.6	36.7	36.6
2″	156.8	157.1	157.1
3″	132.3	132.6	132.6
4″	122.5	122.7	122.6
5″	120.6	120.8	120.7
6″	126.4	126.7	126.6
7″	122.3	122.5	122.4
8″	112.9	113.0	113.1
9″	138.2	138.2	138.3

[a]Natural **4** referenced to $CDCl_3$ at δ 77.03. [b]Assignments may be interchangeable.[c]As described above, based on our NOE data, the assignments of C6 and C7 should be swapped with those of C8 and C9, respectively.



Grignard addition product 46: A 100 mL round-bottom flask containing **36** (500 mg, 1.15 mmol, 1.0 equiv; azeotropically dried with PhMe × 2) and a magnetic stir bar was evacuated under vacuum and backfilled with argon (× 3). THF (16 mL) was added and the solution was cooled to –10 °C. *i*-PrMgCl•LiCl (1.3 M in THF, 1.95 mL, 2.53 mmol, 2.2 equiv) was added dropwise and the reaction was stirred at –10 °C for 1.5 h. Then, a solution of *N*-methylisatin (**38b**, 370 mg, 2.30 mmol, 2.0 equiv; azeotropically dried with PhMe × 2) in THF (15 mL) was added dropwise. The resulting reaction mixture was stirred at this temperature for 15 min, then the cooling bath was removed and the reaction stirred overnight at room temperature (16 h). After complete consumption of starting material **36** (TLC), the reaction was quenched with saturated NH_4Cl solution (20 mL) and transferred to a separatory funnel, diluting with EtOAc (15 mL) and water (15 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude residue was purified by flash chromatography (silica gel, EtOAc/hexanes, 30–100%) to afford **46** (429 mg, 80%). Crystals of **46** suitable for X-ray analysis were obtained by slow evaporation from CH_2Cl_2. [**Note**: Upon scale-up with 3.5 g of **36**, 2.98 g of **46** (79%) was obtained]

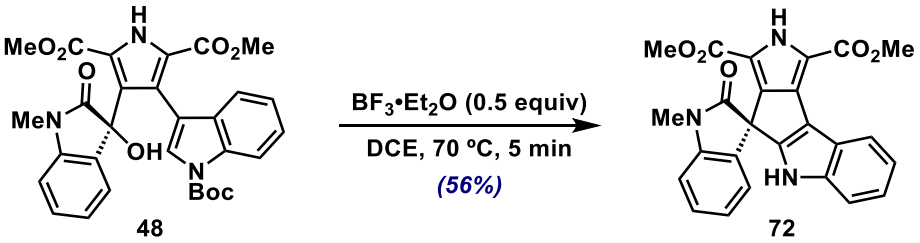
Physical Properties: Yellow solid;
R_f = 0.14 (silica gel, 40% EtOAc/hexanes);
MS (ESI): calculated for $C_{17}H_{16}IN_2O_6$ $[M + H]^+$ 471.0048, found 471.0050;
^{1}H NMR (600 MHz, $CDCl_3$): δ 10.28 (br s, 1H), 7.83 (br s, 1H), 7.35 (td, *J* = 7.7, 1.2 Hz, 1H), 7.13 (d, *J* = 7.2 Hz, 1H), 7.03 (td, *J* = 7.5, 1.1 Hz, 1H), 6.87 (d, *J* = 7.8 Hz, 1H), 4.03 (s, 3H), 3.88 (s, 3H), 3.28 (s, 3H);
^{13}C NMR (151 MHz, $CDCl_3$): δ 174.4, 161.8, 159.3, 145.0, 135.0, 130.5, 130.4, 126.3, 124.8, 124.1, 123.4, 108.8, 76.6, 69.4, 53.8, 52.4, 26.6.



Suzuki coupling product 48: A solution of iodide **46** (107 mg, 0.227 mmol, 1.0 equiv) and indole boronate **47**[4] (195 mg, 0.57 mmol, 2.5 equiv) in DMF (10 mL) was degassed by argon sparge for 30 min. SPhos Pd G4 (18.0 mg, 0.023 mmol, 0.1 equiv) was added to the reaction mixture followed by a solution of K_3PO_4 (174 mg, 0.82 mmol, 3.6 equiv) in degassed water

(0.5 mL). The resulting reaction mixture was heated at 40 °C for 22 h. After complete consumption of starting material **46** (TLC), the contents were transferred to a separatory funnel and diluted with EtOAc (12 mL) and cold water (25 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 12 mL). The combined organic layers were washed with cold water (× 3) then brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude residue was purified by flash chromatography (silica gel, EtOAc/hexanes, 30–80%) to afford a mixture of desired product **48** (dr = 1.4:1) along with the by-product pinacol. This mixture was redissolved in CH_2Cl_2 (25 mL) and transferred to a separatory funnel. The organic layer was washed with water (2 × 25 mL), brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford pure compound **48** (104.7 mg, 83%, dr = 1:0.72). [**Note**: These additional aqueous washes removed the pinacol. Upon scale-up with 1.95 g of **46**, 1.92 g of **48** (83%) was obtained]

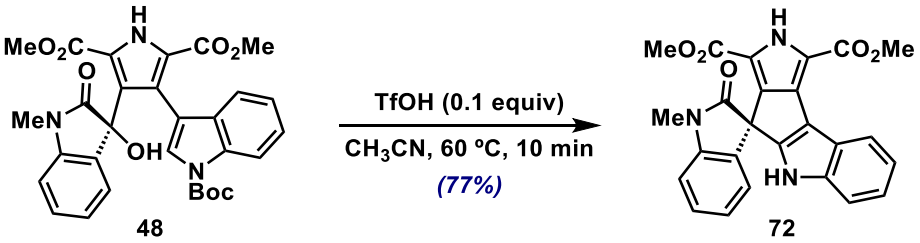
Physical Properties: Yellow solid;
R_f = 0.27 (silica gel, 40% EtOAc/hexanes);
MS (ESI): calculated for $C_{30}H_{30}N_3O_8$ $[M + H]^+$ 560.2027, found 560.2031;
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.03 (br s, $1H_{minor}$), 9.98 (br s, $1H_{major}$), 8.02 (d, *J* = 6.8 Hz, $1H_{major}$), 7.97−7.76 (m, 2H), 7.26–7.20 (m, 3H), 7.17−7.07 (m, $2H_{major}$ + $2H_{minor}$), 7.03 (d, *J* = 7.6 Hz, $1H_{major}$), 6.98 (td, *J* = 7.4, 0.7 Hz, $1H_{major}$), 6.90 (t, *J* = 7.6 Hz, $1H_{minor}$), 6.86 (d, *J* = 7.2 Hz, $1H_{minor}$), 6.73 (t, *J* = 7.4 Hz, $1H_{minor}$), 6.60 (d, *J* = 7.6 Hz, $1H_{minor}$), 6.37−6.29 (m, $1H_{major}$ + $1H_{minor}$), 6.25 (d, *J* = 7.6 Hz, $1H_{major}$), 6.19 (d, *J* = 8.0 Hz, $1H_{minor}$), 4.06 (s, $3H_{major}$ + $3H_{minor}$), 3.54 (s, $3H_{major}$), 3.52 (s, $3H_{minor}$), 2.94 (s, $3H_{minor}$), 2.24 (s, $3H_{major}$), 1.67 (s, $9H_{minor}$), 1.64 (s, $9H_{major}$) [**Note:** where possible, individual signals for the major and minor atropisomers are indicated];
^{13}C NMR (101 MHz, $CDCl_3$): δ 175.9, 174.6, 162.5, 162.4, 160.0, 149.5, 149.2, 143.5, 142.9, 134.4, 134.20, 134.19, 133.7, 133.6, 132.2, 130.8, 130.5, 130.3, 129.6, 128.9, 125.2, 124.7, 124.4, 124.3, 124.2, 124.1, 124.0, 122.7, 122.6, 122.54, 122.47, 122.3, 120.7, 120.5, 119.8, 119.6, 114.6, 114.5, 112.4, 111.6, 107.8, 107.2, 83.7, 83.4, 75.3, 75.2, 53.43, 53.41, 52.12, 52.08, 28.34, 28.29, 25.9, 25.2. [**Note:** two carbon signals missing due to signal overlap]



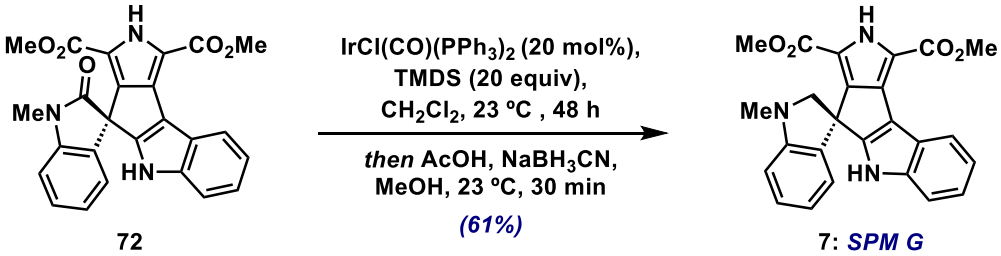
BF_3•Et_2O-mediated synthesis of spirocycle 72: A 50 mL round-bottom flask containing Suzuki product **48** (100 mg, 0.178 mmol, 1.0 equiv) and a magnetic stir bar was evacuated under vacuum and backfilled with argon (× 3). 1,2-dichloroethane (DCE, 15 mL) was added followed by BF_3•Et_2O (11 µL, 0.089 mmol, 0.5 equiv) and the resulting mixture was heated at 70 °C for 5 min. After complete consumption of starting material **48** (TLC), the reaction was cooled to room temperature and quenched with Et_3N (0.25 mL, 1.78 mmol, 10 equiv) and saturated $NaHCO_3$ solution (15 mL). The contents were transferred to a separatory funnel and

diluted with CH_2Cl_2 (25 mL) and water (15 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude residue was purified by flash chromatography (silica gel, EtOAc/hexanes, 50–65%) to afford **72** (44.3 mg, 56%). [**Note**: Upon scale-up with 600 mg of **48**, 271 mg of **72** (57%) was obtained]

Physical Properties: Yellow solid;
R_f = 0.19 (silica gel, 40% EtOAc/hexanes);
Melting Point = 192–194 °C;
MS (ESI): calculated for $C_{25}H_{20}N_3O_5$ $[M + H]^+$ 442.1397, found 442.1402;
^{1}H NMR (600 MHz, $CDCl_3$): δ 9.13 (br s, 1H), 8.24 (d, *J* = 7.2 Hz, 1H), 8.11 (br s, 1H), 7.34 (td, *J* = 7.8, 1.2 Hz, 1H), 7.26–7.22 (m, 2H), 7.19 (t, *J* = 8.1 Hz, 1H), 7.00 (d, *J* = 7.8 Hz, 1H), 6.95 (td, *J* = 7.2, 1.1 Hz, 1H), 6.78 (dd, *J* = 7.2, 1.1 Hz, 1H), 4.08 (s, 3H), 3.51 (s, 3H), 3.38 (s, 3H);
^{13}C NMR (151 MHz, $CDCl_3$): δ 173.5, 160.9, 159.6, 148.7, 145.2, 140.6, 137.8, 133.6, 129.3, 127.8, 123.8, 123.3, 122.7, 121.9, 121.3, 121.2, 119.2, 117.5, 114.5, 112.1, 108.2, 55.0, 52.1, 51.8, 27.2.

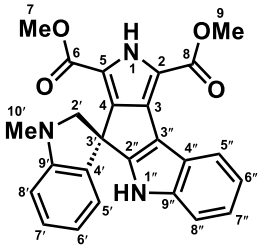


Triflic acid-catalyzed synthesis of spirocycle 72: A 50 mL round-bottom flask containing Suzuki product **48** (243 mg, 0.433 mmol, 1.0 equiv) and a magnetic stir bar was evacuated and backfilled with argon (× 3). CH_3CN (20 mL) was added followed by triflic acid (TfOH, 4 µL, 0.0433 mmol, 0.1 equiv) and the resulting mixture was heated at 60 °C for 10 min. After complete consumption of starting material **48** (TLC), the reaction was allow to cool to room temperature and quenched with saturated $NaHCO_3$ solution (20 mL). The contents were transferred to a separatory funnel and diluted with EtOAc (25 mL) and water (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude residue was purified by flash chromatography (silica gel, EtOAc/hexanes, 50–65%) to afford **72** (146 mg, 77%).



Spiroindimicin G (7): A 10 mL round-bottom flask containing spirocyclic product **72** (44.3 mg, 0.1 mmol, 1.0 equiv) and a magnetic stir bar was evacuated under vacuum and backfilled with argon (× 3). CH_2Cl_2 (7.0 mL) was added and the reaction mixture was degassed by argon sparge for 15 min. Vaska's complex ($IrCl(CO)(PPh_3)_2$, 7.8 mg, 0.01 mmol, 0.10 equiv) was then added followed by dropwise addition of 1,1,3,3-tetramethyldisiloxane (TMDS, 176 µL, 1.0 mmol, 10.0 equiv). The resulting reaction mixture was stirred at room temperature for 5 h. A second batch of catalyst (3.9 mg, 0.005 mmol, 0.05 equiv) and TMDS (88 µL, 0.5 mmol, 5.0 equiv) was added and the stirring was continued. A third batch of catalyst (3.9 mg, 0.005 mmol, 0.05 equiv) and TMDS (88 µL, 0.5 mmol, 5.0 equiv) were added after 30 h. After 48 h (total reaction time), MeOH (7 mL) was added to the reaction mixture and, when effervescence stopped, glacial AcOH (11 µL, 0.2 mmol, 2 equiv) was added followed by $NaBH_3CN$ (6.2 mg, 0.10 mmol, 1.0 equiv). The reaction mixture was allowed to stir for 30 min then was quenched with 1 N NaOH (10 mL) and transferred to a separatory funnel, diluting with CH_2Cl_2 (20 mL) and water (15 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with 1 N NaOH (2 × 20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude residue was purified by flash chromatography (silica gel, EtOAc/hexanes, 0–35%) to afford spiroindimicin G **7** (26.2 mg, 61%). [**Note**: Upon scale-up with 117 mg of **72**, 49 mg of **7** (44%) was obtained]

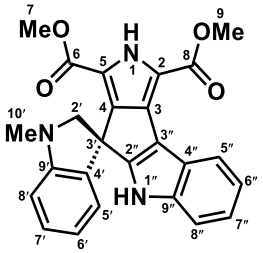
Physical Properties: White solid;
R_f = 0.42 (silica gel, 35% EtOAc/hexanes);
Melting Point = 140–141 °C;
MS (ESI): calculated for $C_{25}H_{22}N_3O_4$ $[M + H]^+$ 428.1605, found 428.1611;
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.15 (br s, 1H), 8.39 (br s, 1H), 8.18 (d, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 7.20 (td, *J* = 7.5, 1.2 Hz, 1H), 7.17−7.12 (m, 2H), 6.70 (d, *J* = 8.0 Hz, 1H), 6.60−6.55 (m, 2H), 4.09 (s, 3H), 4.04 (d, *J* = 8.8 Hz, 1H), 3.62 (s, 3H), 3.60 (d, *J* = 8.8 Hz, 1H), 2.92 (s, 3H);
^{13}C NMR (101 MHz, $CDCl_3$): δ 161.2, 160.2, 156.8, 153.6, 140.7, 140.0, 133.6, 131.5, 128.7, 122.8, 122.0, 121.9, 121.03, 120.96, 119.8, 118.9, 113.9, 112.1, 111.6, 108.3, 64.2, 52.0, 51.9, 51.6, 36.7.



7*: spiroindimicin G*

Table S7: Comparison of ^{1}H NMR shifts (δ) of natural,[8] Xu,[2] and our synthetic spiroindimicin G (**7**) in $CDCl_3$.

Position	**Natural 7** (500 MHz)	**Synthetic 7** ***(Xu)*** (400 MHz)	**Synthetic 7** ***(Smith)*** (400 MHz)
1	9.16 (s, 1H)	9.21 (br s, 1H)	9.15 (br s, 1H)
7	4.08 (s, 3H)	4.08 (s, 3H)	4.09 (s, 3H)
9	3.60 (s, 3H)	3.61 (s, 3H)	3.62 (s, 3H)
2′	4.01 (d, *J* = 8.7 Hz, 1H) 3.59 (d, *J* = 8.7 Hz, 1H)	4.03 (d, *J* = 8.8 Hz, 1H) 3.60 (d, *J* = 8.8 Hz, 1H)	4.04 (d, *J* = 8.8 Hz, 1H) 3.60 (d, *J* = 8.8 Hz, 1H)
5′	6.57	6.56 (m, 1H)	6.57−6.55 (m, 1 of 2H)
6′	6.58	6.57 (m, 1H)	6.60−6.58 (m, 1 of 2H)
7′	7.14 (dd, *J* = 7.9, 7.9 Hz, 1H)	7.15 (td, *J* = 7.5, 2.8 Hz, 1H)	7.15−7.12 (m, 1 of 2H)
8′	6.70 (d, *J* = 7.9 Hz, 1H)	6.69 (d, *J* = 7.9 Hz, 1H)	6.70 (d, *J* = 8.0 Hz, 1H)
10′	2.90 (s, 3H)	2.90 (s, 3H)	2.92 (s, 3H)
1″	8.58 (s, 1H)	8.39 (br s, 1H)	8.39 (br s, 1H)
5″	8.18 (d, *J* = 7.8 Hz, 1H)	8.19 (d, *J* = 7.8 Hz, 1H)	8.18 (d, *J* = 8.0 Hz, 1H)
6″	7.20 (dd, *J* = 7.8, 7.8 Hz, 1H)	7.20 (td, *J* = 7.5, 1.2 Hz, 1H)	7.20 (td, *J* = 7.5, 1.2 Hz, 1H)
7″	7.16 (dd, *J* = 7.8, 7.8 Hz, 1H)	7.17 (td, *J* = 7.2, 1,1 Hz, 1H)	7.17−7.15 (m, 1 of 2H)
8″	7.24 (d, *J* = 7.8 Hz, 1H)	7.24 (d, *J* = 8.0 Hz, 1H)	7.25 (d, *J* = 8.0 Hz, 1H)

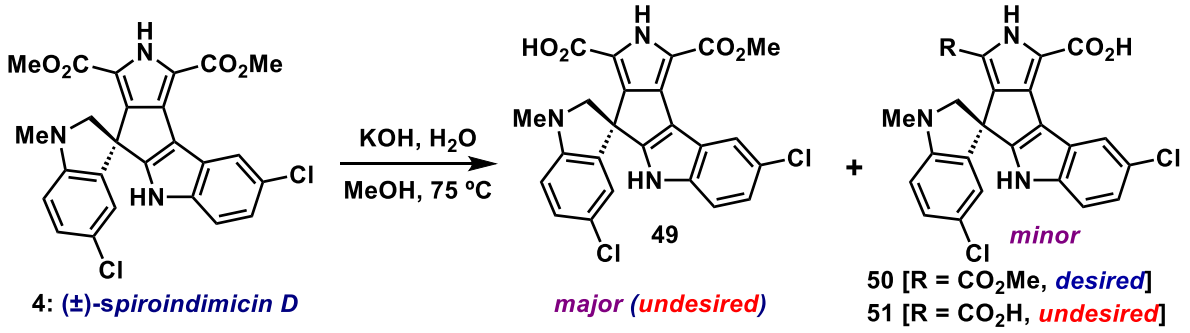


7*: spiroindimicin G*

Table S8: Comparison of ^{13}C NMR shifts (δ) of natural,[8] Xu,[2] and our synthetic spiroindimicin G (**7**) in $CDCl_3$

Position	**Natural 7** (126 MHz)	**Synthetic 7** ***(Xu)*** (101 MHz)	**Synthetic 7** ***(Smith)*** (101 MHz)
2	113.9[a]	113.9[a]	113.9[a]
3	133.6	133.6	133.6
4	140.8	140.8	140.7
5	119.8[a]	119.8[a]	119.8[a]
6	161.2	161.2	161.2
7	52.0	52.0	52.0
8	160.2	160.2	160.2
9	51.6	51.6	51.6
2′	64.1	64.2	64.2
3′	51.9	51.9	51.9
4′	131.6	131.5	131.5
5′	122.9	122.9	122.8
6′	119.0	118.9	118.9
7′	128.7	128.7	128.7
8′	108.4	108.3	108.3
9′	153.6	153.6	153.6
10′	36.7	36.7	36.7
2″	156.8	156.8	156.8
3″	111.6	111.6	111.6
4″	121.9	121.9	121.9
5″	120.9	120.9	120.96
6″	121.0	121.0	121.03
7″	122.0	122.0	122.0
8″	112.1	112.1	112.1
9″	140.0	140.0	140.0

[a]Assignments may be interchangeable.



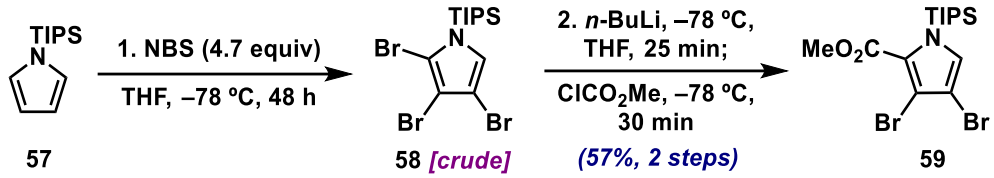
Attempted regioselective ester hydrolysis of SPM D (4): To a solution of SPM D (**4**) (9.6 mg, 0.019 mmol, 1.0 equiv) in MeOH/H_2O (4:1, 1.25 mL) at room temperature under argon was added KOH (1.1 mg, 0.019 mmol, 1.0 equiv). The mixture was heated to 75 °C and stirred for 12 h at this temperature. After complete consumption of **4**, the reaction mixture was allow to cool to room temperature and quenched with 1 N HCl (to pH = 4). The contents were transferred to a separatory funnel, diluting with CH_2Cl_2 (10 mL) and water (5 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The resulting crude residue (8.8 mg) was analysed by ^{1}H NMR, which showed a 4:1:0.4 mixture of **49**/**50**/**51**. The HRMS of this crude mixture further supported the formation of **49**, **50**, and **51**. [**Note:** NMR spectra of **49**, **50**, and **51** significantly broadened after silica gel purification, hence characterization was done at the crude stage]

MS (ESI): calculated for $C_{24}H_{18}Cl_2N_3O_4$ $[M + H]^+$ 482.0669, found 482.0674 [for **49** & **50**]; calculated for $C_{23}H_{16}Cl_2N_3O_4$ $[M + H]^+$ 468.0512, found 468.0515 [for **51**];

Crude ^{1}H NMR (600 MHz, Acetone-d_6) δ 11.80 (br s, $1H_{minor}$), 11.26 (br d, J = 4.7 Hz, $1H_{minor}$), 10.87–10.73 (br s, $1H_{major}$ + $2H_{minor}$), 10.53 (br s, $1H_{minor}$), 10.50 (br s, $1H_{major}$), 10.34 (br s, $1H_{minor}$), 8.37 (d, J = 2.1 Hz, $1H_{minor}$), 8.36 (d, J = 2.0 Hz, $1H_{minor}$), 8.34 (d, J = 2.0 Hz, $1H_{major}$), 7.40–7.36 (m, $1H_{major}$ + $2H_{minor}$), 7.10 (dd, J = 8.7, 2.1 Hz, $1H_{major}$ + $2H_{minor}$), 7.07 (dd, J = 8.4, 2.1 Hz, $1H_{major}$ + $2H_{minor}$), 6.71–6.66 (m, $1H_{major}$ + $2H_{minor}$), 6.52 (d, J = 2.1 Hz, $1H_{minor}$), 6.50 (d, J = 2.1 Hz, $1H_{major}$), 6.48 (d, J = 2.1 Hz, $1H_{minor}$), 4.26 (d, J = 8.6 Hz, $1H_{minor}$), 4.25 (d, J = 8.8 Hz, $1H_{major}$), 4.17 (d, J = 9.0 Hz, $1H_{minor}$), 4.01 (s, $3H_{major}$), 3.76 (d, J = 9.0 Hz, $1H_{minor}$), 3.74 (d, J = 8.7 Hz, $1H_{minor}$), 3.73 (d, J = 8.8 Hz, $1H_{major}$), 3.63 (s, $3H_{minor}$), 2.95 (s, $3H_{minor}$), 2.92 (s, $3H_{minor}$), 2.91 (s, $3H_{major}$).

Crude ^{13}C NMR (151 MHz, Acetone-d_6) δ 161.5, 161.30, 161.27, 160.70, 160.68, 160.5, 158.8, 158.7, 153.6, 153.5, 140.4, 140.0, 139.9, 139.7, 134.9, 134.5, 133.8, 128.95, 128.91, 126.24, 126.19, 126.17, 125.0, 124.9, 124.4, 124.2, 123.6, 123.51, 123.46, 123.1, 123.04, 123.02, 122.8, 122.5, 122.22, 122.19, 121.6, 121.3, 121.2, 114.8, 114.53, 114.48, 114.47, 114.46, 114.4, 113.5, 112.1, 111.9, 111.1, 111.0, 109.8, 109.4, 64.2, 64.1, 52.5, 52.4, 52.3, 52.0, 51.6, 36.1, 36.0. [**Note:** 10 carbon signals missing due to signal overlap or low abundance for **51**]

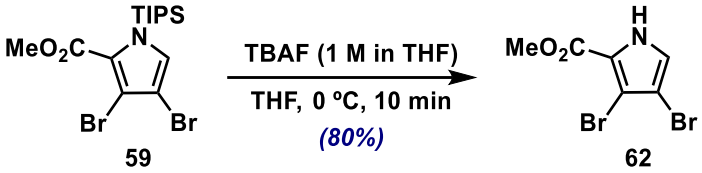
3-step synthesis of methyl 3,4-dibromopyrrole-2-carboxylate (62)



Methyl 3,4-dibromo-1-(triisopropylsilyl)pyrrole-2-carboxylate (59): A 100 mL round-bottom flask containing *N*-TIPS Pyrrole (**57**, 1.0 g, 4.47 mmol, 1.0 equiv) and a magnetic stir bar was evacuated under vacuum and backfilled with argon (× 3). THF (30 mL) was added and the reaction mixture was cooled to –78 °C. NBS (2.4 g, 13.4 mmol, 3.0 equiv) was added and the resulting reaction mixture was stirred at –78 °C overnight. The progress of the reaction was monitored by ^{1}H NMR and after 20 h NMR analysis of an aliquot indicated a mixture of mono-, di- and tri- (desired) brominated *N*-TIPS pyrroles. Another portion of NBS (477 mg, 2.68 mmol, 0.6 equiv) was added and the stirring continued. After 6 h, NMR analysis indicated the mixture of di- and tribrominated *N*-TIPS pyrroles (0.6:1 ratio), so another portion of NBS (477 mg, 2.68 mmol, 0.6 equiv) was added and stirring continued 16 h. After 16 h, NMR analysis showed a mixture of di- and tribrominated *N*-TIPS pyrrole derivatives in 1:4 ratio. A final portion of NBS (400 mg, 0.5 equiv) was added and stirring was continued until complete conversion of di- to tribrominated pyrrole by ^{1}H NMR (typically 4 h). To this crude residue hexane (40 mL) was added to precipitate the succinimide by-product. The suspension was filtered through neutral alumina and washed with hexane. The filtrate was concentrated *in vacuo* and then directly subjected to the next step without further purification.[9]

A 100 mL round-bottom flask containing crude tribrominated *N*-TIPS pyrrole **58** and a magnetic stir bar was evacuated under vacuum and backfilled with argon (× 3). THF (36 mL) was added and the solution was cooled to –78 °C. *n*-BuLi (2.5 M in hexane, 1.6 mL, 4.02 mmol, 0.9 equiv) was added dropwise and the reaction was stirred at –78 °C for 30 min. Then, methyl chloroformate (0.48 mL, 6.25 mmol, 1.4 equiv) was added dropwise and stirring was continued at –78 °C for 25 min. After complete consumption of starting material **58** (TLC), the reaction was quenched with saturated NH_4Cl solution (25 mL) and transferred to a separatory funnel, diluting with EtOAc (30 mL) and water (15 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude residue was purified by flash chromatography (silica gel, EtOAc/hexanes, 0–5%) to afford **59** (1.127 g, 57% over 2 steps).[10]

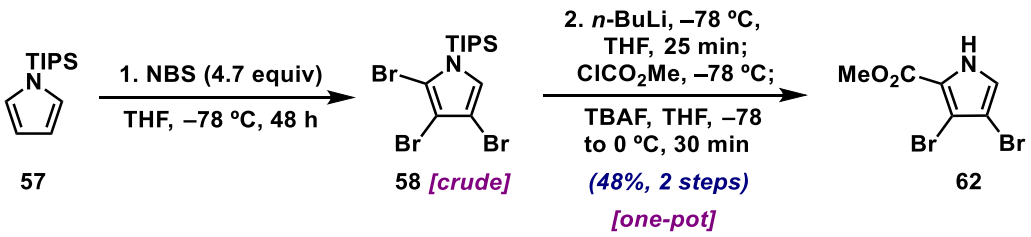
Physical Properties: Colorless sticky oil;
R_f = 0.17 (silica gel, hexanes);
MS (ESI): calculated for $C_{15}H_{26}Br_2NO_2Si$ $[M + H]^+$ 438.0094, found 438.0092;
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08 (s, 1H), 3.86 (s, 3H), 1.68 (hept, *J* = 7.6 Hz, 3H), 1.11 (d, *J* = 7.6 Hz, 18H);
^{13}C NMR (101 MHz, $CDCl_3$): δ 161.5, 130.8, 125.8, 109.9, 103.5, 51.7, 18.4, 13.6.



Methyl 3,4-dibromopyrrole-2-carboxylate (62): A 100 mL round-bottom flask containing **59** (1.0 g, 2.28 mmol, 1.0 equiv) and a magnetic stir bar was evacuated under vacuum and backfilled with argon (× 3). THF (30 mL) was added and the reaction mixture was cooled to 0 °C. TBAF (1 M in THF, 2.3 mL, 2.28 mmol, 1.0 equiv) was added dropwise and the resulting reaction mixture was stirred at 0 °C for 10 min. After complete consumption of starting material **59** (TLC), the reaction was quenched with saturated NH_4Cl solution (10 mL) and transferred to a separatory funnel, diluting with EtOAc (30 mL) and water (15 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude residue was purified by flash chromatography (silica gel, EtOAc/hexanes, 10–30%) to afford **62** (516 mg, 80%).

Physical Properties: White solid;
R_f = 0.40 (silica gel, 30% EtOAc/hexanes);
Melting Point = 129–131 °C;
MS (ESI): calculated for $C_6H_6Br_2NO_2$ $[M + H]^+$ 281.8760, found 281.8767;
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.44 (br s, 1H), 7.00 (d, *J* = 3.2 Hz, 1H), 3.91 (s, 3H);
^{13}C NMR (151 MHz, $CDCl_3$): δ 160.1, 122.4, 120.8, 106.2, 102.9, 52.2.

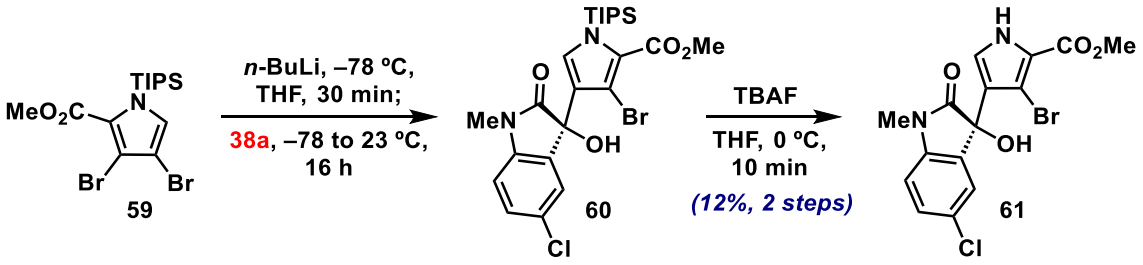
2-step synthesis of methyl 3,4-dibromopyrrole-2-carboxylate (62)



Tribrominated *N*-TIPS pyrrole **58** was synthesized by following the same procedure outlined above starting from *N*-TIPS pyrrole (**57**, 1.0 g, 4.47 mmol), and was subjected to the next step without further purification.

A 100 mL round-bottom flask containing crude tribrominated *N*-TIPS pyrrole **58** (previous step) and a magnetic stir bar was evacuated under vacuum and backfilled with argon (× 3). THF (36 mL) was added, and the solution was cooled to –78 °C. *n*-BuLi (2.5 M in hexane, 1.6 mL, 4.02 mmol, 0.9 equiv) was added dropwise and the reaction mixture was stirred at –78 °C for 30 min. Then, methyl chloroformate (0.48 mL, 6.25 mmol, 1.4 equiv) was added dropwise and stirring was continued at –78 °C for 25 min. After complete consumption of starting material **58** (TLC), TBAF (1 M in THF, 4.7 mL, 4.7 mmol, 1.05 equiv) was added dropwise. The flask was removed from the –78 °C bath and transferred to an ice-water bath.

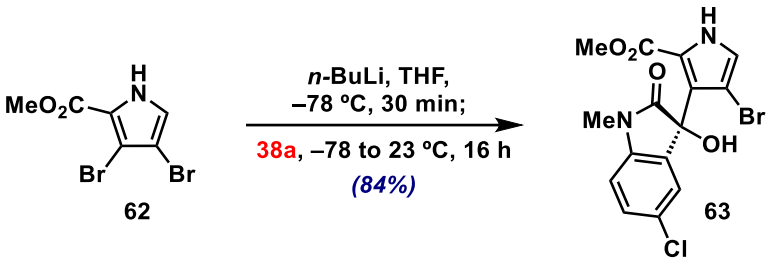
After complete consumption of **59** (TLC, 20 min), the reaction was quenched with saturated NH_4Cl solution (15 mL) and transferred to a separatory funnel, diluting with EtOAc (30 mL) and water (15 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude residue was purified by flash chromatography (silica gel, EtOAc/hexanes, 10–30%) to afford **62** (602 mg, 48% over 2 steps).



Addition product 61: A 25 mL round-bottom flask containing **59** (150 mg, 0.34 mmol, 1.0 equiv) and a magnetic stir bar was evacuated under vacuum and backfilled with argon (× 3). THF (5 mL) was added and the reaction mixture was cooled to –78 °C. *n*-BuLi (2.5 M in hexane, 0.14 mL, 0.34 mmol, 1.0 equiv) was added dropwise and the resulting reaction mixture was stirred at –78 °C for 30 min. Then, a solution of *N*-methyl 5-chloroisatin[4] (**38a**, 100 mg, 0.51 mmol, 1.5 equiv) in THF (5 mL) was added dropwise. The resulting reaction mixture was stirred at this temperature for 15 min, then the cooling bath was removed and the reaction stirred overnight at room temperature (16 h). After complete consumption of starting material **59** (TLC), the reaction was quenched with saturated NH_4Cl solution (15 mL) and transferred to a separatory funnel, diluting with EtOAc (15 mL) and water (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude residue was attempted to purify by flash chromatography (silica gel, EtOAc/hexanes, 0–30%) to afford yellow solid (27 mg) which is a mixture of **60** and unreacted *N*-methyl 5-chloroisatin. This material was carried into the next step without further purification.

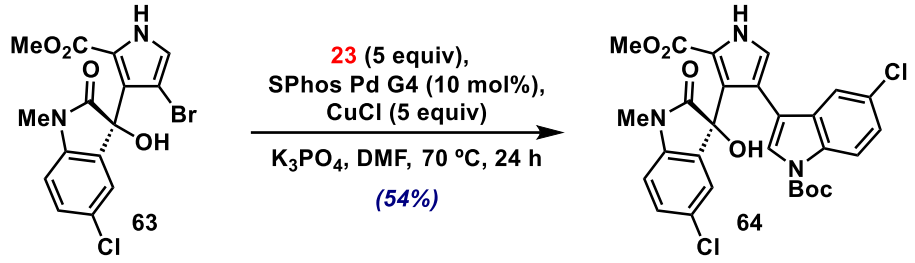
A 10 mL round-bottom flask containing 27 mg of mixture of solid from previous step and a magnetic stir bar was evacuated under vacuum and backfilled with argon (× 3). THF (2 mL) was added and the reaction mixture was cooled to 0 °C. TBAF (1 M in THF, 42 µL, 0.042 mmol) was added dropwise and the resulting reaction mixture was stirred at 0 °C for 10 min. After complete consumption of starting material (TLC), the reaction was quenched with saturated NH_4Cl solution (4 mL) and transferred to a separatory funnel, diluting with EtOAc (10 mL) and water (5 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude residue was purified by flash chromatography (silica gel, EtOAc/hexanes, 60–100%) to afford **61** (15.2 mg, 12%, over two steps). Crystals of **61** suitable for X-ray analysis were obtained by slow evaporation from EtOAc/hexanes.

Physical Properties: White solid;
R_f = 0.15 (silica gel, 50% EtOAc/hexanes);
MS (ESI): calculated for $C_{15}H_{13}BrClN_2O_4$ $[M + H]^+$ 398.9742, found 398.9743;
^{1}H NMR (600 MHz, Acetone-d_6): δ 11.33 (br s, 1H), 7.44 (s, 1H), 7.37 (dd, *J* = 8.1, 2.1 Hz, 1H), 7.12 (d, *J* = 2.4 Hz, 1H), 7.04 (d, *J* = 8.4 Hz, 1H), 5.65 (br s, 1H), 3.77 (s, 3H), 3.23 (s, 3H);
^{13}C NMR (151 MHz, Acetone-d_6): δ 175.6, 160.5, 144.5, 134.0, 130.3, 128.0, 126.6, 125.4, 123.3, 121.6, 110.6, 100.3, 75.2, 51.5, 26.5.



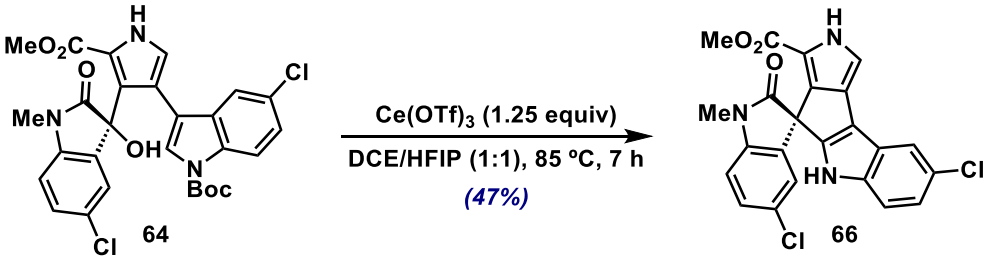
Addition product 63: A 100 mL round-bottom flask containing **62** (200 mg, 0.7 mmol, 1.0 equiv) and a magnetic stir bar was evacuated under vacuum and backfilled with argon (× 3). THF (12 mL) was added and the solution was cooled to –78 °C. *n*-BuLi (2.5 M in hexane, 0.56 mL, 1.41 mmol, 2.0 equiv) was added dropwise and the reaction mixture stirred at –78 °C for 30 min. Then, a solution of *N*-methyl 5-chloroisatin[6] (**38a**, 207 mg, 1.06 mmol, 1.5 equiv; azeotropically dried with PhMe × 2) in THF (15 mL) was added dropwise. The resulting reaction mixture was stirred at this temperature for 15 min, then the cooling bath was removed and the reaction stirred overnight at room temperature (16 h). After complete consumption of starting material **62** (TLC), the reaction was quenched with saturated NH_4Cl solution (20 mL) and transferred to a separatory funnel, diluting with EtOAc (15 mL) and water (15 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude residue was purified by flash chromatography (silica gel, EtOAc/hexanes, 30–65%) to afford **63** (238 mg, 84%). Crystals of **63** suitable for X-ray analysis were obtained by slow evaporation from EtOAc/hexanes. [**Note**: Upon scale-up with 381 mg **62**, 433 mg (81%) of **63** was obtained]

Physical Properties: Beige solid;
R_f = 0.19 (silica gel, 50% EtOAc/hexanes);
Melting Point = 244–246 °C (decomposed);
MS (ESI): calculated for $C_{15}H_{13}BrClN_2O_4$ $[M + H]^+$ 398.9742, found 398.9743;
^{1}H NMR (600 MHz, $CDCl_3$): δ 10.29 (br s, 1H), 8.52 (br s, 1H), 7.29 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.14 (d, *J* = 1.8 Hz, 1H), 6.79 (d, *J* = 8.3 Hz, 1H), 6.77 (d, *J* = 3.0 Hz, 1H), 3.95 (s, 3H), 3.26 (s, 3H);
^{13}C NMR (151 MHz, $CDCl_3$): δ 175.3, 162.6, 142.5, 133.0, 129.9, 129.0, 128.8, 125.1, 124.5, 120.2, 109.7, 96.8, 75.7, 53.3, 26.7.



Suzuki coupling product 64: A solution of bromide **63** (100 mg, 0.25 mmol, 1.0 equiv) and 3-indole boronate **23**[4] (472 mg, 1.25 mmol, 5 equiv) in DMF (10 mL) was degassed by argon sparge for 20 min. SPhos Pd G4 (20.0 mg, 0.025 mmol, 0.1 equiv) was added to the reaction mixture followed by CuCl (124 mg, 1.25 mmol, 5 equiv) and K_3PO_4 (266 mg, 1.25 mmol, 5 equiv). The resulting reaction mixture was heated at 70 °C for 24 h. After complete consumption of starting material **63** (TLC), the contents were transferred to a separatory funnel and diluted with EtOAc (20 mL) and cold water (50 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with cold water (× 3) then brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude residue was purified by flash chromatography (silica gel, EtOAc/hexanes, 10–50%) to afford a mixture of desired product **64** along with the by-product pinacol. This mixture of compounds was redissolved in CH_2Cl_2 (30 mL) and transferred to a separatory funnel. The organic layer was washed with water (2 × 30 mL), brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford pure compound **64** (76.2 mg, 54%). [**Note:** These additional aqueous washes removed the pinacol]

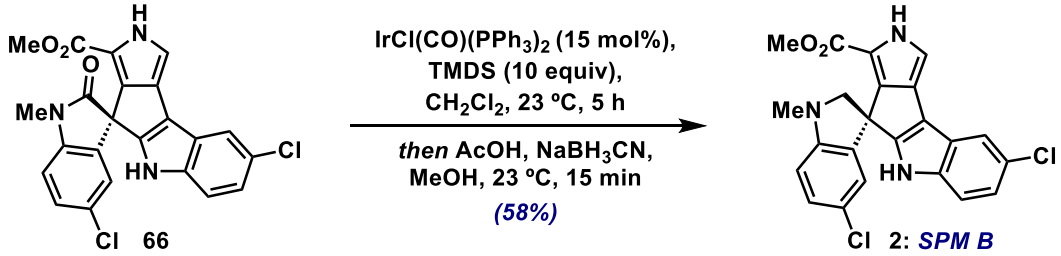
Physical Properties: Brown solid;
R_f = 0.33 (silica gel, 60% EtOAc/hexanes);
MS (ESI): calculated for $C_{28}H_{26}Cl_2N_3O_6$ $[M + H]^+$ 570.1193, found 570.1195;
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.60 (br s, 1H), 8.43 (br s, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.15 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.13 (d, *J* = 2.4 Hz, 1H), 6.95 (br s, 1H), 6.90 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.78 (d, *J* = 3.2 Hz, 1H), 6.70 (br s, 1H), 6.06 (d, *J* = 8.0 Hz, 1H) 4.02 (s, 3H), 2.62 (s, 3H), 1.65 (s, 9H);
^{13}C NMR (101 MHz, $CDCl_3$): δ 175.3, 163.0, 149.0, 142.0, 132.8, 132.7, 132.3, 129.1, 128.4, 128.0, 126.5, 125.5, 124.6, 123.8, 120.5, 119.1, 115.8, 115.4, 112.6, 108.5, 84.4, 75.3, 53.0, 28.3, 25.7. [**Note:** one aromatic carbon signal missing due to signal overlap]



Spirocyclized product 66: A 10 mL reaction vial containing Suzuki product **64** (11 mg, 0.019 mmol, 1.0 equiv) and a magnetic stir bar was evacuated under vacuum and backfilled with

argon (× 3). 1,2-dichloroethane (DCE, 0.8 mL) and HFIP (0.8 mL) were added followed by $Ce(OTf)_3$ (14.3 mg, 0.024 mmol, 1.25 equiv). The reaction vial was then sealed, and the resulting reaction mixture was heated at 85 °C for 7 h. After complete consumption of starting material **64** (TLC), the reaction was cooled to room temperature and quenched with saturated $NaHCO_3$ solution (4 mL). The contents were transferred to a separatory funnel and diluted with CH_2Cl_2 (10 mL) and water (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude residue was purified by PTLC (silica gel, 60% EtOAc/hexanes) to afford spirocycle **66** (4.1 mg, 47%). [**Note**: In a reaction with 64 mg **64**, 22.1 mg of **66** (44%) was obtained via flash chromatographic purification (silica gel, EtOAc/hexanes, 10–50%)]

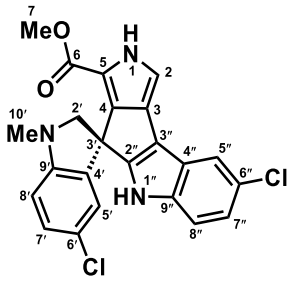
Physical Properties: Beige solid;
R_f = 0.18 (silica gel, 60% EtOAc/hexanes);
MS (ESI): calculated for $C_{23}H_{16}Cl_2N_3O_3$ $[M + H]^+$ 452.0563, found 452.0566;
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.73 (br s, 1H), 8.05 (br s, 1H), 7.67 (d, *J* = 2.4 Hz, 1H), 7.31 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 1H), 7.12 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.93 (d, *J* = 2.4 Hz, 1H), 6.91 (d, *J* = 8.4 Hz, 1H), 6.78 (d, *J* = 2.4 Hz, 1H), 3.49 (s, 3H), 3.37 (s, 3H);
^{13}C NMR (151 MHz, $CDCl_3$): δ 173.7, 159.9, 146.7, 143.7, 138.6, 130.2, 129.1, 128.6, 127.4, 126.5, 124.3, 122.6, 122.0, 119.4, 118.2, 116.4, 113.3, 110.0, 109.0, 55.2, 51.4, 27.3. [**Note:** one aromatic carbon signal missing due to signal overlap]



Spiroindimicin B (2): A 10 mL reaction vial containing spirocycle **66** (24.0 mg, 0.053 mmol, 1.0 equiv) and a magnetic stir bar was evacuated under vacuum and backfilled with argon (× 3). CH_2Cl_2 (2.4 mL) was added and the solution was degassed by argon sparge for 15 min. Vaska's complex ($IrCl(CO)(PPh_3)_2$, 6.3 mg, 0.0079 mmol, 0.15 equiv) was then added followed by dropwise addition of 1,1,3,3-tetramethyldisiloxane (TMDS, 94 µL, 0.53 mmol, 10.0 equiv). The reaction was stirred at room temperature for 5 h. MeOH (2.0 mL) was added to the reaction mixture and, when effervescence stopped, glacial AcOH (6 µL, 0.106 mmol, 2 equiv) was added followed by $NaBH_3CN$ (3.5 mg, 0.053 mmol, 1.0 equiv) and allowed to stir for 15 min. The reaction was quenched with 1 N NaOH (3 mL) and transferred to a separatory funnel, diluting with CH_2Cl_2 (10 mL) and water (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with 1 N NaOH (2 × 15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude residue was purified by flash chromatography (silica gel,

EtOAc/hexanes, 10–35%) to afford spiroindimicin B (**2**, 13.6 mg, 58%, 67% brsm) along with reovered **66** (3.1 mg).

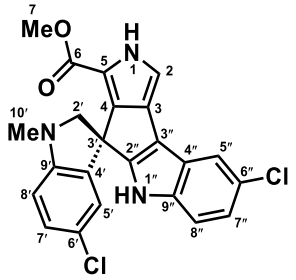
Physical Properties: White solid;
R_f = 0.34 (silica gel, 35% EtOAc/hexanes);
MS (ESI): calculated for $C_{23}H_{18}Cl_2N_3O_2$ $[M + H]^+$ 438.0771, found 438.0785;
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.73 (br s, 1H), 8.22 (br s, 1H), 7.63 (d, *J* = 2.4 Hz, 1H), 7.19 (d, *J* = 8.4 Hz, 1H), 7.10–7.08 (m, 1H), 7.08–7.06 (m, 1H), 6.92 (d, *J* = 3.0 Hz, 1H), 6.58 (d, *J* = 8.4 Hz, 1H), 6.54 (d, *J* = 2.4 Hz, 1H), 4.09 (d, *J* = 8.4 Hz, 1H), 3.63 (d, *J* = 8.4 Hz, 1H), 3.63 (s, 3H), 2.90 (s, 3H);
^{13}C NMR (151 MHz, $CDCl_3$): δ 160.6, 154.8, 152.2, 139.9, 137.9, 134.2, 128.3, 127.4, 126.1, 123.5, 123.1, 122.0, 121.8, 119.1, 116.9, 113.1, 112.2, 110.3, 108.9, 64.6, 52.0, 51.3, 36.7.



2*: spiroindimicin B*

Table S9: Comparison of ^{1}H NMR shifts (δ) of natural,[7] Sperry,[1] and our synthetic spiroindimicin B (**2**) in $CDCl_3$.

Position	**Natural 2** (500 MHz)	**Synthetic 2** ***(Sperry)*** (500 MHz)	**Synthetic 2** ***(Smith)*** (600 MHz)
1	8.88 (br s, 1H)	8.71 (br s, 1H)	8.73 (br s, 1H)
2	6.91(d, *J* = 3.0 Hz, 1H)	6.92 (d, *J* = 2.7 Hz, 1H)	6.92 (d, *J* = 3.0 Hz, 1H)
7	3.61 (s, 3H)	3.62 (s, 3H)	3.63 (s, 3H)
2′	3.64 (d, *J* = 8.5 Hz, 1H) 4.07 (d, *J* = 8.5 Hz, 1H)	3.63 (d, *J* = 8.6 Hz, 1H) 4.09 (d, *J* = 8.6 Hz, 1H)	3.63 (d, *J* = 8.4 Hz, 1H) 4.09 (d, *J* = 8.4 Hz, 1H)
5′	6.54 (d, *J* = 2.0 Hz, 1H)	6.54 (d, *J* = 2.1 Hz, 1H)	6.54 (d, *J* = 2.4 Hz, 1H)
7′	7.07 (dd, *J* = 8.5, 2.0 Hz, 1H)	7.09 (dd, *J* = 8.4, 2.3 Hz, 1H)	7.10–7.08 (m, 1H)
8′	6.57 (d, *J* = 8.5 Hz, 1H)	6.58 (d, *J* = 8.4 Hz, 1H)	6.58 (d, *J* = 8.4 Hz, 1H)
10′	2.88 (s, 3H)	2.90 (s, 3H)	2.90 (s, 3H)
1″	8.45 (br s, 1H)	8.18 (br s, 1H)	8.22 (br s, 1H)
5″	7.62 (d, *J* = 1.5 Hz, 1H)	7.62 (d, *J* = 2.2 Hz, 1H)	7.63 (d, *J* = 2.4 Hz, 1H)
7″	7.06 (dd, *J* = 9.0, 1.5 Hz, 1H)	7.08 (dd, *J* = 8.4, 2.3 Hz, 1H)	7.08–7.06 (m, 1H)
8″	7.15 (d, *J* = 9.0 Hz, 1H)	7.19 (d, *J* = 8.3 Hz, 1H)	7.19 (d, *J* = 8.4 Hz, 1H)

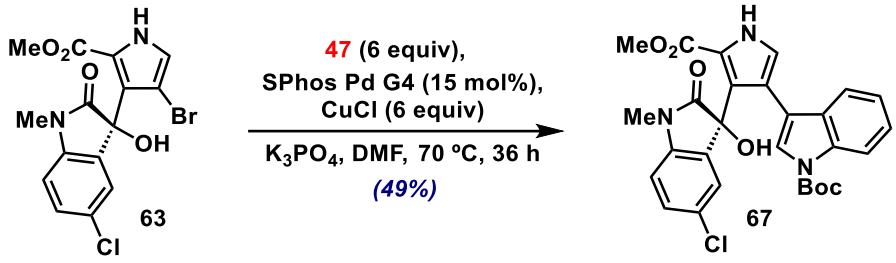


2*: spiroindimicin B*

Table S10: Comparison of ^{13}C NMR shifts (δ) of natural,[8] Sperry,[1] and our synthetic spiroindimicin B (**2**) in $CDCl_3$

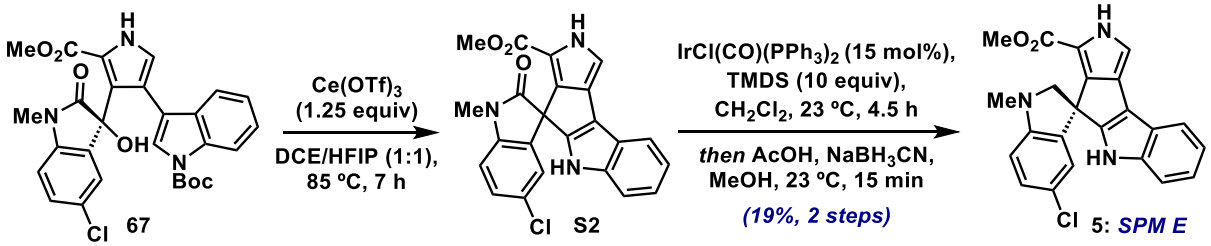
Position	**Natural 2**[a] (126 MHz)	**Synthetic 2** ***(Sperry)***[b] (126 MHz)	**Synthetic 2** ***(Smith)*** (151 MHz)
2	110.3	110.2	110.3
3	127.2	127.3	127.4
4	140.1	ND	139.9
5	116.7	116.8	116.9
6	160.5	160.4	160.6
7	51.1	51.1	51.3
2′	64.3	64.4	64.6
3′	51.8	51.8	52.0
4′	134.2	134.1	134.2
5′	123.1	123.0	123.1
6′	123.5	123.4	123.5
7′	128.2	128.2	128.3
8′	108.9	108.8	108.9
9′	151.9	152.0	152.2
10′	36.6	36.5	36.7
2″	154.5	154.6	154.8
3″	112.1	ND	112.2
4″	121.8	121.9	121.8
5″	118.9	118.9	119.1
6″	125.9	126.0	126.1
7″	121.5	121.6	121.8
8″	113.1	112.9	113.1
9″	137.8	137.7	137.9

ND = Not Detected. [a]Natural **2** referenced to $CDCl_3$ at δ 77.03. [b] Sperry's $CDCl_3$ referenced at δ 77.01.



Suzuki coupling product 67: A solution of bromide **63** (50 mg, 0.125 mmol, 1.0 equiv) and indole boronate **47**[2] (257 mg, 0.75 mmol, 6 equiv) in DMF (5 mL) was degassed by argon sparge for 15 min. SPhos Pd G4 (14.7 mg, 0.0188 mmol, 0.15 equiv) was added to the reaction mixture followed by CuCl (74.3 mg, 0.75 mmol, 6 equiv) and K_3PO_4 (159 mg, 0.75 mmol, 6 equiv). The resulting mixture was heated at 70 °C for 36 h. After complete consumption of starting material **63** (TLC), the contents were transferred to a separatory funnel and diluted with EtOAc (20 mL) and cold water (40 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with cold water (× 3) and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude residue was purified by flash chromatography (silica gel, EtOAc/hexanes, 10–50%) to afford a mixture of desired product **67** along with the by-product pinacol. This mixture of compounds was redissolved in CH_2Cl_2 (20 mL) and transferred to a separatory funnel. The organic layer was washed with water (2 × 20 mL), brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford pure compound **67** (33.1 mg, 49%). [**Note:** These additional aqueous washes removed the pinacol]

Physical Properties: Beige solid;
R_f = 0.33 (silica gel, 60% EtOAc/hexanes);
MS (ESI): calculated for $C_{28}H_{27}ClN_3O_6$ $[M + H]^+$ 536.1583, found 536.1571;
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.41 (br s, 1H), 8.42 (br s, 1H), 8.01 (d, *J* = 8.0 Hz, 1H), 7.21 (t, *J* = 7.6 Hz, 1H), 7.14 (d, *J* = 2.0 Hz, 1H), 7.06 (t, *J* = 7.6 Hz, 1H), 6.89 (dd, *J* = 8.2, 1.4 Hz, 1H), 6.87–6.76 (m, 3H), 6.03 (d, *J* = 8.4 Hz, 1H), 4.03 (s, 3H), 2.50 (s, 3H), 1.66 (s, 9H);
^{13}C NMR (151 MHz, $CDCl_3$): δ 175.4, 162.9, 149.3, 142.1, 134.3, 133.1, 131.8, 131.1, 128.9, 128.0, 125.4, 125.2, 124.4, 123.7, 122.7, 120.4, 119.5, 116.5, 114.8, 112.9, 108.5, 83.8, 75.5, 53.0, 28.3, 25.6.

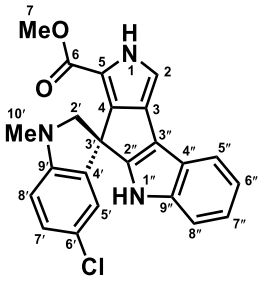


Spiroindimicin E (5): A reaction tube containing Suzuki product **67** (64 mg, 0.119 mmol, 1.0 equiv) and a magnetic stir bar was evacuated under vacuum and backfilled with argon (× 3). 1,2-dichloroethane (DCE, 5.0 mL) and HFIP (5.0 mL) were added followed by $Ce(OTf)_3$ (88

mg, 0.149 mmol, 1.25 equiv). The reaction tube was then sealed, and the resulting reaction mixture was heated at 85 °C for 7 h. After complete consumption of starting material **67** (TLC), the reaction was cooled to room temperature and quenched with saturated $NaHCO_3$ solution (15 mL). The contents were transferred to a separatory funnel and diluted with CH_2Cl_2 (20 mL) and water (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude residue was purified by two rounds of flash chromatography on silica gel: first, with EtOAc/hexanes, 25–60%, to afford desired product **S2** along with an inseparable impurity, then with 30% acetone/hexane to afford 19.6 mg of spirocyclic product **S2** containing a trace amount of an inseparable impurity. This material was directly subjected to the final reduction step.

A 10 mL reaction vial containing the so-obtained spirocyclic product **S2** and a magnetic stir bar was evacuated under vacuum and backfilled with argon (× 3). CH_2Cl_2 (1.8 mL) was added and the reaction mixture was degassed by argon sparge for 15 min. Vaska's complex ($IrCl(CO)(PPh_3)_2$, 5.3 mg, 0.0068 mmol) was then added followed by dropwise addition of 1,1,3,3-tetramethyldisiloxane (TMDS, 80 µL, 0.46 mmol). The resulting reaction mixture was stirred at room temperature for 4.5 h. MeOH (1.8 mL) was then added to the reaction mixture and, when effervescence stopped, glacial AcOH (6 µL, 0.09 mmol) was added followed by $NaBH_3CN$ (3.1 mg, 0.048 mmol) and allowed to stir for 15 min. The reaction was quenched with 1 N NaOH (3 mL) and transferred to a separatory funnel, diluting with CH_2Cl_2 (10 mL) and water (5 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with 1 N NaOH (2 × 15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude residue was purified by flash chromatography (silica gel, EtOAc/hexanes, 10–35%) to afford spiroindimicin E (**5**, 9.4 mg, 19% over two steps).

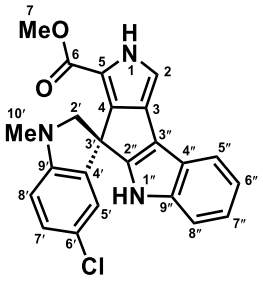
Physical Properties: White solid;
R_f = 0.39 (silica gel, 35% EtOAc/hexanes);
MS (ESI): calculated for $C_{23}H_{19}ClN_3O_2$ $[M + H]^+$ 404.1160, found 404.1168;
^{1}H NMR (400 MHz, CD_3OD): 7.61–7.57 (m, 1H), 7.30–7.26 (m, 1H), 7.06–7.01 (m, 3H), 6.95 (s, 1H), 6.64 (d, *J* = 8.4 Hz, 1H), 6.35 (d, *J* = 2.4 Hz, 1H), 4.09 (d, *J* = 8.8 Hz, 1H), 3.68 (d, *J* = 8.8 Hz, 1H), 3.58 (s, 3H), 2.94 (s, 3H);
^{13}C NMR (151 MHz, CD_3OD): 162.4, 155.1, 154.0, 143.2, 141.7, 136.4, 128.7, 123.5, 123.4, 122.2, 121.7, 120.6, 119.9, 117.3, 113.2, 113.1, 111.6, 109.5, 65.4, 53.1, 51.2, 36.3. [**Note:** one aromatic carbon signal missing due to signal overlap]
^{1}H NMR (600 MHz, DMSO-d_6): 11.4 (br d, *J* = 2.4 Hz, 1H), 11.27 (br s, 1H), 7.65–7.61 (m, 1H), 7.29–7.26 (m, 1H), 7.08 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.04 (d, *J* = 3.0 Hz, 1H), 7.04–7.00 (m, 2H), 6.71 (d, *J* = 8.4 Hz, 1H), 6.22 (d, *J* = 2.4 Hz, 1H), 4.02 (d, *J* = 9.0 Hz, 1H), 3.70 (d, *J* = 9.0 Hz, 1H), 3.52 (s, 3H), 2.91 (s, 3H);
^{13}C NMR (151 MHz, DMSO-d_6): 160.1, 153.7, 152.5, 141.8, 139.8, 134.9, 127.6, 126.4, 121.7, 120.4, 120.33, 120.31, 119.3, 119.0, 115.5, 112.6, 111.4, 111.2, 108.5, 63.3, 51.2, 50.7, 35.7.



5*: spiroindimicin E*

Table S11: Comparison of ^{1}H NMR shifts (δ) of natural,[11] and our synthetic spiroindimicin E (**5**) in CD_3OD.

Position	**Natural 5** (700 MHz)	**Synthetic 5** ***(Smith)*** (400 MHz)
1	–	–
2	6.95 (s, 1H)	6.95 (s, 1H)
7	3.58 (s, 3H)	3.58 (s, 3H)
2′	4.09 (d, *J* = 8.8 Hz, 1H) 3.69 (d, *J* = 8.8 Hz, 1H)	4.09 (d, *J* = 8.8 Hz, 1H) 3.68 (d, *J* = 8.8 Hz, 1H)
5′	6.34 (d, *J* = 2.0 Hz, 1H)	6.35 (d, *J* = 2.4 Hz, 1H)
7′	7.044 (d = 6.06 Hz, 1H)	7.06–7.01 (m, 1 of 3H)
8′	6.64 (d, *J* = 8.5 Hz, 1H)	6.64 (d, *J* = 8.4 Hz, 1H)
10′	2.95 (s, 3H)	2.94 (s, 3H)
1″	–	–
5″	7.28 (dd, *J* = 7.3, 0.7 Hz, 1H)	7.30–7.26 (m, 1H)
6″	7.03 (d, *J* = 1.72 Hz, 1H)	7.06–7.01 (m, 1 of 3H)
7″	7.045 (d, *J* = 0.81 Hz, 1H)	7.06–7.01 (m, 1 of 3H)
8″	7.58 (dd, *J* = 7.4, 0.7 Hz, 1H)	7.61–7.58 (m, 1H)



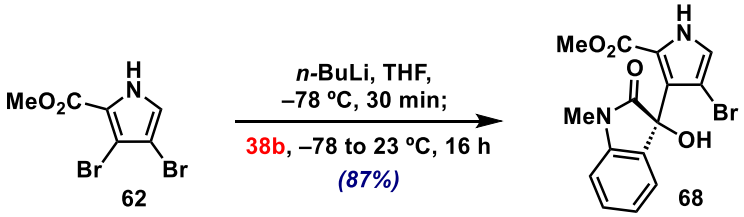
5*: spiroindimicin E*

Table S12: Comparison of ^{13}C NMR shifts (δ) of natural,[11] and our synthetic spiroindimicin E (**5**) in CD_3OD.

Position	**Natural 5** (175 MHz)	**Synthetic 5** ***(Smith)*** (151 MHz)	**Difference** ($\Delta = \delta_{natural} - \delta_{synthetic}$)
2	111.4	111.6	–0.2

3	125.7	ND	
4	142.9	143.2	–0.3
5	117.0	117.3	–0.3
6	162.3	162.4	–0.1
7	52.1	51.2	–0.9
2′	65.0	65.4	–0.4
3′	52.8	53.1	–0.3
4′	136.4	136.4	0
5′	123.7	123.5	+0.2
6′	123.1	123.4	–0.3
7′	128.1	128.7	–0.6
8′	109.7	109.5	+0.2
9′	153.7	155.1	**–1.4**
10′	36.2	36.3	–0.1
2″	152.3	154.0	**–1.7**
3″	118.4	113.2	**+5.2**
4″	122.0	122.2	–0.2
5″	113.5	113.1	+0.4
6″	121.0	121.7	–0.7
7″	120.5	120.6	–0.1
8″	119.7	119.9	–0.2
9″	141.7	141.7	0

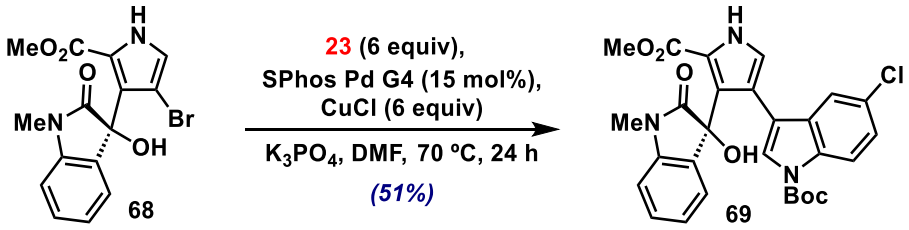
Note: The chemical shifts of a few carbons – most notably C-3″ – for our synthetic **5** deviate significantly from that reported by the isolation chemists. It is possible that this larger deviation could result from typographical error or due to the inadvertent selection of an impurity peak. Multiple attempts to contact the corresponding author to obtain the original NMR spectra for comparison (only tabulated NMR data are provided in the SI of their paper) received no response.



Methyl 4-bromo-3-(3-hydroxy-1-methyl-2-oxoindolin-3-yl)-1H-pyrrole-2-carboxylate (68): A 100 mL round-bottom flask containing **62** (243 mg, 0.86 mmol, 1.0 equiv) and a magnetic stir bar was evacuated under vacuum and backfilled with argon (× 3). THF (12 mL) was added and the resulting solution was cooled to –78 °C. *n*-BuLi (2.5 M in hexane, 0.7 mL, 1.72 mmol, 2.0 equiv) was added dropwise and the reaction was stirred at –78 °C for 30 min. Then, a solution of *N*-methylisatin (**38b**, 208 mg, 1.3 mmol, 1.5 equiv; azeotropically dried with PhMe × 2) in THF (15 mL) was added dropwise. The reaction mixture was stirred at this temperature for 15 min, then the cooling bath was removed and the reaction stirred overnight at room

temperature (16 h). After complete consumption of starting material **62** (TLC), the reaction was quenched with saturated NH_4Cl solution (20 mL) and transferred to a separatory funnel, diluting with EtOAc (15 mL) and water (15 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude residue was purified by flash chromatography (silica gel, EtOAc/hexanes, 40–85%) to afford **68** (272 mg, 87%).

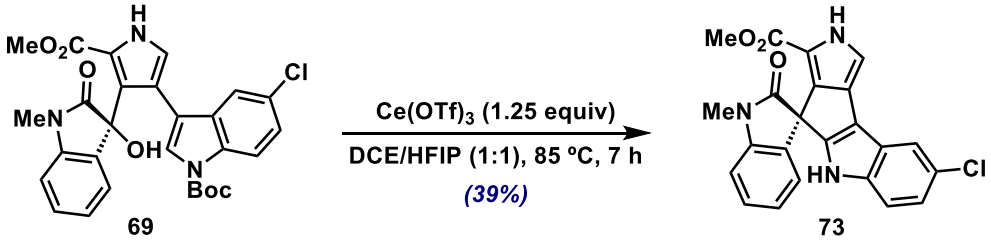
Physical Properties: Yellow solid;
R_f = 0.18 (silica gel, 50% EtOAc/hexanes);
Melting Point = 228–230 °C;
MS (ESI): calculated for $C_{15}H_{14}BrN_2O_4$ $[M + H]^+$ 365.0131, found 365.0134;
^{1}H NMR (600 MHz, $CDCl_3$): δ 10.07 (br s, 1H), 8.34 (br s, 1H), 7.32 (td, *J* = 7.8, 1.2 Hz, 1H), 7.19 (d, *J* = 7.2 Hz, 1H), 7.04 (td, *J* = 7.7, 1.0 Hz, 1H), 6.86 (d, *J* = 7.8 Hz, 1H), 6.78 (d, *J* = 3.0 Hz, 1H), 3.96 (s, 3H), 3.28 (s, 3H);
^{13}C NMR (151 MHz, $CDCl_3$): δ 175.6, 162.5, 144.0, 131.3, 130.00, 129.97, 124.7, 124.2, 123.5, 120.3, 108.7, 97.1, 75.8, 53.2, 26.6.



Suzuki coupling product 69: A solution of bromide **68** (64 mg, 0.175 mmol, 1.0 equiv) and indole boronate **23**[4] (396 mg, 1.05 mmol, 6 equiv) in DMF (8 mL) was degassed by argon sparge for 20 min. SPhos Pd G4 (21.0 mg, 0.026 mmol, 0.15 equiv) was added to the reaction mixture followed by CuCl (103 mg, 1.05 mmol, 6 equiv) and K_3PO_4 (223 mg, 1.05 mmol, 6 equiv). The resulting reaction mixture was heated at 70 °C for 24 h. After complete consumption of starting material **68** (TLC), the contents were transferred to a separatory funnel and diluted with EtOAc (20 mL) and cold water (50 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with cold water (× 3) and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude residue was purified by flash chromatography (silica gel, EtOAc/hexanes, 10–50%) to afford a mixture of desired product **69** along with the by-product pinacol. This mixture of compounds was redissolved in CH_2Cl_2 (20 mL) and transferred to a separatory funnel. The organic layer was washed with water (2 × 20 mL), brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford pure compound **69** (48.0 mg, 51%). [**Note**: These additional aqueous washes removed the pinacol]

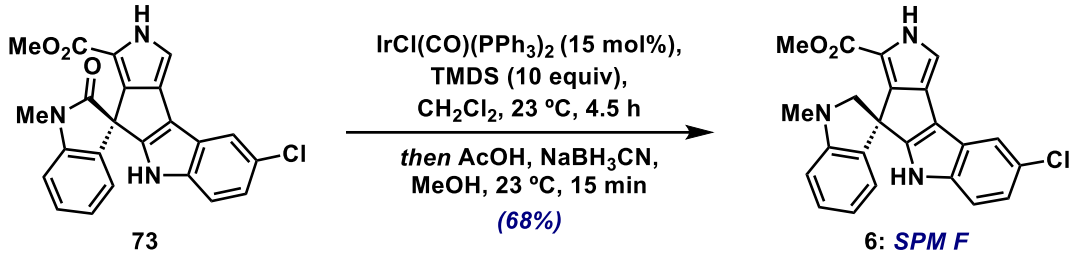
Physical Properties: Brown solid;
R_f = 0.34 (silica gel, 60% EtOAc/hexanes);
MS (ESI): calculated for $C_{28}H_{27}ClN_3O_6$ $[M + H]^+$ 536.1583, found 536.1587;

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.41 (br s, 1H), 8.22 (br s, 1H), 7.90 (br d, *J* = 8.4 Hz, 1H), 7.18 (d, *J* = 7.2 Hz, 1H), 7.14 (dd, *J* = 8.8, 2.0 Hz, 1H), 6.99 (t, *J* = 7.8 Hz, 1H), 6.89 (br s, 1H), 6.83–6.76 (m, 2H), 6.69 (br s, 1H), 6.21 (d, *J* = 7.6 Hz, 1H), 4.03 (s, 3H), 2.61 (s, 3H), 1.65 (s, 9H);
^{13}C NMR (151 MHz, $CDCl_3$): δ 175.5, 162.9, 149.1, 143.3, 132.8, 132.6, 132.5, 131.5, 129.5, 128.3, 126.6, 124.7, 124.4, 123.6, 122.6, 120.3, 119.2, 115.7, 115.6, 112.5, 107.8, 84.2, 75.3, 53.0, 28.3, 25.5.



***Spirocyclized Product 73*:** A reaction tube containing Suzuki coupling product **69** (68 mg, 0.127 mmol, 1.0 equiv) and a magnetic stir bar was evacuated under vacuum and backfilled with argon (× 3). 1,2-dichloroethane (DCE, 5.0 mL) and HFIP (5.0 mL) were added followed by $Ce(OTf)_3$ (93 mg, 0.159 mmol, 1.25 equiv). The reaction vial was then sealed, and the reaction was heated at 85 °C for 7 h. After complete consumption of starting material **69** (TLC), the reaction was cooled to room temperature and quenched with saturated $NaHCO_3$ solution (15 mL). The contents were transferred to a separatory funnel and diluted with CH_2Cl_2 (20 mL) and water (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude residue was purified by two rounds of flash chromatography on silica gel: first, with EtOAc/hexanes, 25–60%, to afford desired product **73** along with an inseparable impurity, then with 30% acetone/hexane to afford pure compound **73** (20.7 mg, 39%).

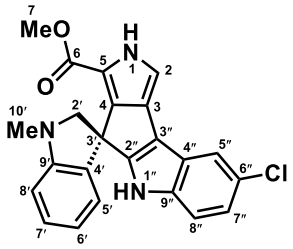
Physical Properties: Beige solid;
R_f = 0.19 (silica gel, 60% EtOAc/hexanes);
MS (ESI): calculated for $C_{23}H_{17}ClN_3O_3$ $[M + H]^+$ 418.0953, found 418.0953;
^{1}H NMR (600 MHz, DMSO-d_6): δ 11.59 (br s, 1H), 11.51 (br d, *J* = 2.4 Hz, 1H), 7.82 (d, *J* = 1.8 Hz, 1H), 7.34 (td, *J* = 7.8, 1.2 Hz, 1H), 7.27 (d, *J* = 8.8 Hz, 1H), 7.21 (d, *J* = 7.8 Hz, 1H), 7.16 (d, *J* = 2.4 Hz, 1H), 7.06 (dd, *J* = 8.7, 2.1 Hz, 1H), 6.90 (td, *J* = 7.5, 0.6 Hz, 1H), 6.64 (d, *J* = 6.8 Hz, 1H), 3.36 (s, 3H), 3.31 (s, 3H);
^{13}C NMR (151 MHz, DMSO-d_6): δ 173.4, 159.7, 149.2, 145.2, 138.2, 138.0, 128.8, 128.6, 126.7, 124.1, 122.6, 122.5, 121.2, 120.7, 118.3, 115.7, 115.2, 113.9, 112.1, 108.5, 54.8, 50.8, 26.7.



Spiroindimicin F (6): A 10 mL reaction vial containing spirocyclic product **73** (16.1 mg, 0.039 mmol, 1.0 equiv) and a magnetic stir bar was evacuated under vacuum and backfilled with argon (× 3). CH_2Cl_2 (1.8 mL) was added and the resulting solution was degassed by argon sparge for 15 min. Vaska's complex ($IrCl(CO)(PPh_3)_2$, 4.5 mg, 0.0058 mmol, 0.15 equiv) was then added followed by dropwise addition of 1,1,3,3-tetramethyldisiloxane (TMDS, 68 µL, 0.39 mmol, 10.0 equiv). The reaction was stirred at room temperature for 4.5 h. MeOH (1.8 mL) was added to the reaction mixture and, when effervescence stopped, glacial AcOH (5 µL, 0.078 mmol, 2.0 equiv) was added followed by $NaBH_3CN$ (2.5 mg, 0.039 mmol, 1.0 equiv) and allowed to stir for 15 min. The reaction was quenched with 1 N NaOH (3 mL) and transferred to a separatory funnel, diluting with CH_2Cl_2 (10 mL) and water (5 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with 1 N NaOH (2 × 15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude residue was purified by flash chromatography (silica gel, EtOAc/hexanes, 10–35%) to afford spiroindimicin F (**6**, 10.5 mg, 68%). Crystals of **6** suitable for X-ray analysis were obtained by slow evaporation from CH_2Cl_2/MeOH.

Physical Properties: White solid;
R_f = 0.40 (silica gel, 35% EtOAc/hexanes);
MS (ESI): calculated for $C_{23}H_{19}ClN_3O_2$ $[M + H]^+$ 404.1160, found 404.1162;
^{1}H NMR (600 MHz, DMSO-d_6): 11.41 (br s, 1H), 11.37 (br d, J = 2.4 Hz, 1H), 7.72 (d, J = 1.8 Hz, 1H), 7.25 (d, J = 9.0 Hz, 1H), 7.10 (d, J = 2.4 Hz, 1H), 7.07 (td, J = 7.5, 1.0 Hz, 1H), 7.00 (dd, J = 8.7, 2.1 Hz, 1H), 6.72 (d, J = 7.8 Hz, 1H), 6.45 (td, J = 7.4, 0.8 Hz, 1H), 6.34 (dd, J = 7.2, 1.2 Hz, 1H), 3.98 (d, J = 8.8 Hz, 1H), 3.65 (d, J = 9.0 Hz, 1H), 3.47 (s, 3H), 2.90 (s, 3H);
^{13}C NMR (151 MHz, DMSO-d_6): δ 160.1, 156.1, 153.6, 141.8, 138.2, 132.3, 128.0, 125.9, 123.8, 122.1, 121.2, 120.0, 118.1, 117.5, 115.5, 113.9, 111.6, 111.0, 107.7, 63.4, 51.7, 50.5, 36.0.

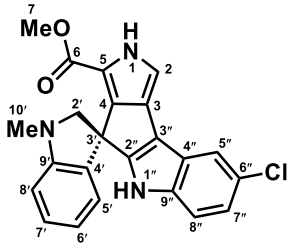
Note: In the isolation paper, the authors stated that the NMR data of **6** were acquired in CD_3OD, but we found that the NMR data of synthetic **6** only matched the natural material perfectly when measured in DMSO-d_6. This hypothesis is strengthened by the observation of the N–H signals in the ^{1}H NMR spectrum of natural **6**, which are typically not observed for these compounds in CD_3OD. We believe that the isolation chemists may have mistakenly listed the wrong NMR solvent for **6**; attempts to contact the corresponding author and obtain original copies of the NMR spectra were unsuccessful. The structure of synthetic SPM F was further confirmed by single crystal X-ray analysis.



6*: spiroindimicin F*

Table S13: Comparison of ^{1}H NMR shifts (δ) of natural,[11] and our synthetic spiroindimicin F (**6**) in DMSO-*d*$_6$.

Position	**Natural 6** (700 MHz)	**Synthetic 6** ***(Smith)*** (400 MHz)
1	11.35 (s, 1H)	11.37 (br d, *J* = 2.4 Hz, 1H)
2	7.09 (d, *J* = 2.7 Hz, 1H)	7.10 (d, *J* = 2.4 Hz, 1H)
7	3.47 (s, 3H)	3.47 (s, 3H)
2′	3.90 (d, 1H) 3.64 (d, 1H)	3.98 (d, *J* = 8.8 Hz, 1H) 3.65 (d, *J* = 9.0 Hz, 1H)
5′	6.33 (d, *J* = 7.3 Hz, 1H)	6.34 (dd, *J* = 7.2, 1.2 Hz, 1H)
6′	6.44 (t, *J* = 7.3 Hz, 1H)	6.45 (td, *J* = 7.4, 0.8 Hz, 1H)
7′	7.06 (d, *J* = 8.1, 1.2 Hz, 1H)	7.07 (td, *J* = 7.5, 1.0 Hz, 1H)
8′	6.71 (d, *J* = 8.0 Hz, 1H)	6.72 (d, *J* = 7.8 Hz, 1H)
10′	2.90 (s, 3H)	2.90 (s, 3H)
1″	11.40 (s, 1H)	11.41 (br s, 1H)
5″	7.72 (s, 1H)	7.72 (d, *J* = 1.8 Hz, 1H)
7″	6.99 (dd, *J* = 8.6, 2.04 Hz, 1H)	7.00 (dd, *J* = 8.7, 2.1 Hz, 1H)
8″	7.25 (d, *J* = 8.6 Hz, 1H)	7.25 (d, *J* = 9.0 Hz, 1H)



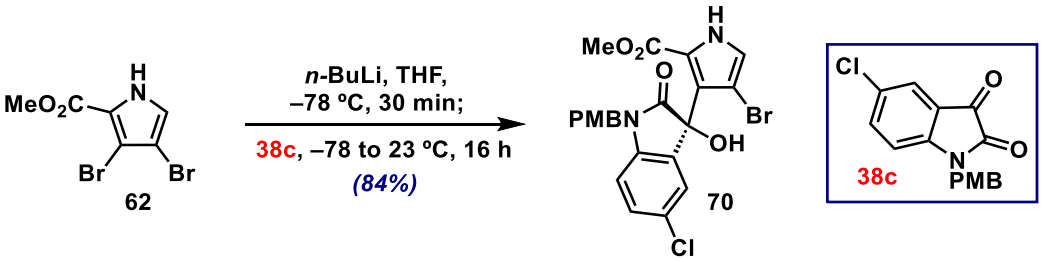
6*: spiroindimicin F*

Table S14: Comparison of ^{13}C NMR shifts (δ) of natural,[11] and our synthetic spiroindimicin F (**6**) in DMSO-*d*$_6$.

Position	**Natural 6** (175 MHz)	**Synthetic 6** ***(Smith)*** (151 MHz)	**Difference** ($\Delta = \delta_{natural} - \delta_{synthetic}$)
2	111.0	111.6	–0.6
3	125.5	125.9	–0.4

4	141.5	141.8	–0.3
5	115.2	115.5	–0.3
6	159.9	160.1	–0.2
7	50.1	50.5	–0.4
2′	63.1	63.4	–0.3
3′	51.4	51.7	–0.3
4′	132.2	132.3	–0.1
5′	121.6	121.2	+0.4
6′	117.1	117.5	–0.4
7′	127.6	128.0	–0.4
8′	107.2	107.7	–0.5
9′	153.3	153.6	–0.3
10′	35.7	36.0	–0.3
2″	155.7	156.1	–0.4
3″	110.6	111.0	+0.6
4″	120.8	120.0	+0.8
5″	117.7	118.1	–0.4
6″	123.1	122.1	**+1.0**
7″	119.7	113.9	**+5.8**
8″	123.5	123.8	–0.3
9″	138.0	138.2	–0.2

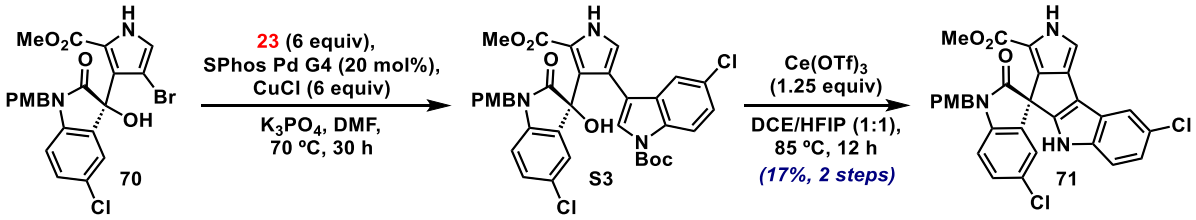
Note: The chemical shift of C-7″ for our synthetic **6** deviates significantly from that reported by the isolation chemists. It is possible that this could be a typographical error. As mentioned above, multiple attempts to contact the corresponding author to obtain the original NMR spectra received no response.



Methyl-4-bromo-3-(5-chloro-3-hydroxy-1-(4-methoxybenzyl)-2-oxoindolin-3-yl)-1H-pyrrole-2-carboxylate (70): A 100 mL round-bottom flask containing **62** (281 mg, 1.0 mmol, 1.0 equiv) and a magnetic stir bar was evacuated under vacuum and backfilled with argon (× 3). THF (15 mL) was added, and the resulting solution was cooled to –78 °C. *n*-BuLi (2.5 M in hexane, 0.8 mL, 2.0 mmol, 2.0 equiv) was added dropwise and the reaction was stirred at –78 °C for 30 min. Then, a solution of *N*-PMB-isatin[12] (**38c**, 453 mg, 1.5 mmol, 1.5 equiv; azeotropically dried with PhMe × 2) in THF (15 mL) was added dropwise. The reaction mixture was stirred at this temperature for 15 min, then the cooling bath was removed, and the reaction stirred overnight at room temperature (16 h). After complete consumption of starting material **62** (TLC), the reaction was quenched with saturated NH_4Cl solution (20 mL) and transferred

to a separatory funnel, diluting with EtOAc (20 mL) and water (20 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude residue was purified by flash chromatography (silica gel, EtOAc/hexanes, 10–50%) to afford **70** (425 mg, 84%).

Physical Properties: Beige solid;
R_f = 0.20 (silica gel, 50% EtOAc/hexanes);
MS (ESI): calculated for $C_{22}H_{19}BrClN_2O_5$ $[M + H]^+$ 505.0160, found 505.0167;
^{1}H NMR (600 MHz, $CDCl_3$): δ 10.12 (br s, 1H), 8.56 (s, 1H), 7.31 (d, *J* = 8.6 Hz, 2H), 7.18 (dd, *J* = 8.3, 2.4 Hz, 1H), 7.16 (d, *J* = 1.9 Hz, 1H), 6.86 (d, *J* = 8.7 Hz, 2H), 6.78 (d, *J* = 3.2 Hz, 1H), 6.69 (d, *J* = 8.3 Hz, 1H), 4.99 (d, *J* = 15.5 Hz, 1H), 4.77 (d, *J* = 15.5 Hz, 1H), 3.94 (s, 3H), 3.78 (s, 3H);
^{13}C NMR (151 MHz, $CDCl_3$): δ 175.5, 162.4, 159.3, 142.0, 132.9, 129.8, 129.1, 129.0, 128.8, 127.0, 125.4, 124.3, 120.5, 114.3, 110.8, 97.2, 75.7, 55.4, 53.3, 44.0.

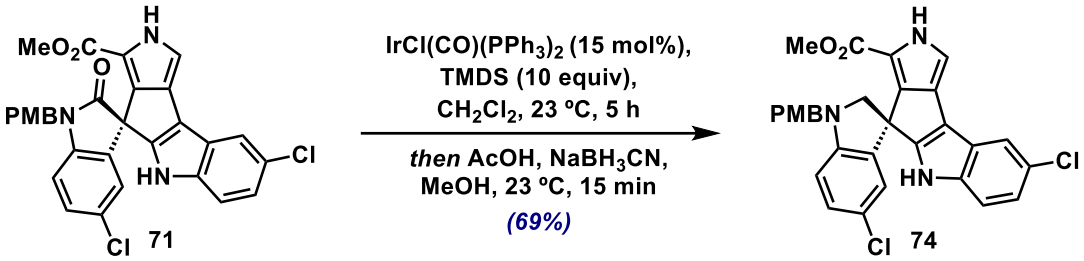


***Spirocyclized Product 71*:** A solution of bromide **70** (50 mg, 0.098 mmol, 1.0 equiv) and indole boronate **23**[4] (222 mg, 0.59 mmol, 6 equiv) in DMF (4 mL) was degassed by argon sparge for 20 min. SPhos Pd G4 (15.7 mg, 0.0196 mmol, 0.20 equiv) was added to the reaction mixture followed by CuCl (58 mg, 0.59 mmol, 6 equiv) and K_3PO_4 (125 mg, 0.59 mmol, 6 equiv). The resulting reaction mixture was heated at 70 °C for 30 h. After complete consumption of starting material **70** (TLC), the contents were transferred to a separatory funnel and diluted with EtOAc (15 mL) and cold water (20 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organic layers were washed with cold water (× 3) and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude residue was purified by flash chromatography (silica gel, EtOAc/hexanes, 10–40%) to afford a mixture of desired product **S3** along with the by-product pinacol and undesired impurities. This mixture of compounds was redissolved in CH_2Cl_2 (20 mL) and transferred to a separatory funnel. The organic layer was washed with water (2 × 20 mL), brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford 50 mg of **S3** along with a trace amount of an inseparable impurity. This material was directly subjected to the next spirocyclization step. [**Note**: These additional aqueous washes removed the pinacol]

A reaction tube containing the so-obtained Suzuki product **S3** and a magnetic stir bar was evacuated under vacuum and backfilled with argon (× 3). 1,2-dichloroethane (DCE, 4.0 mL) and HFIP (4.0 mL) were added followed by $Ce(OTf)_3$ (51 mg, 0.087 mmol, 1.25 equiv). The reaction vial was then sealed, and the reaction was heated at 85 °C for 12 h. After complete consumption of starting material **S3** (TLC), the reaction was cooled to room temperature and

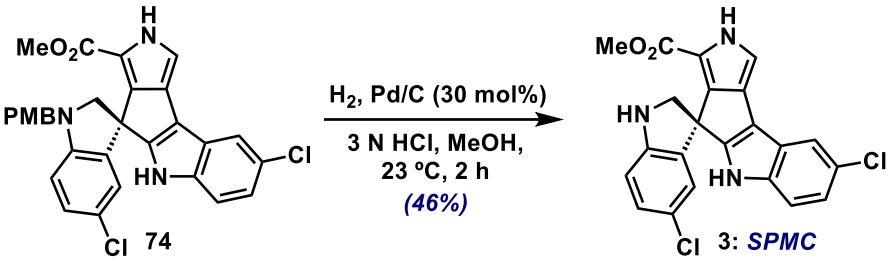
quenched with saturated $NaHCO_3$ solution (10 mL). The contents were transferred to a separatory funnel and diluted with CH_2Cl_2 (10 mL) and water (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude residue was purified by flash chromatography (silica gel, EtOAc/hexanes, 10–30%) to afford **71** (9.4 mg, 17%, 2 steps). [**Note:** Unlike other spirocyclization products mentioned above, the spirocyclized product **71** is less polar than the corresponding Suzuki product **S3**]

Physical Properties: Beige solid;
R_f = 0.21 (silica gel, 40% EtOAc/hexanes);
MS (ESI): calculated for $C_{30}H_{22}Cl_2N_3O_4$ $[M + H]^+$ 558.0982, found 558.0989;
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.75 (br s, 1H), 7.99 (br s, 1H), 7.69 (d, *J* = 1.8 Hz, 1H), 7.41 (d, *J* = 8.6 Hz, 2H), 7.20 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.18 (d, *J* = 8.4 Hz, 1H), 7.12 (dd, *J* = 8.4, 1.9 Hz, 1H), 6.95 (d, *J* = 2.4 Hz, 1H), 6.92–6.87 (m, 3H), 6.78 (d, *J* = 2.1 Hz, 1H), 4.96 (d, *J* = 15.1 Hz, 1H), 4.89 (d, *J* = 15.1 Hz, 1H), 3.80 (s, 3H), 3.18 (s, 3H);
^{13}C NMR (151 MHz, $CDCl_3$): δ 173.7, 159.6, 147.0, 142.9, 138.6, 130.3, 129.8, 128.9, 128.5, 127.9, 127.6, 126.5, 124.3, 122.6, 122.1, 119.4, 118.0, 116.6, 114.4, 113.3, 111.0, 109.8, 55.5, 55.3, 51.2, 44.6. [**Note:** two aromatic carbon signals missing due to signal overlap]



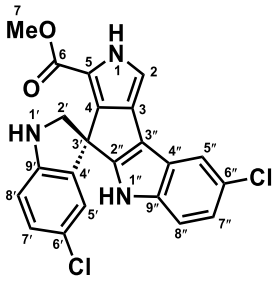
N-PMB Spiroindimicin C (74): A 10 mL reaction vial containing spirocyclic product **71** (28 mg, 0.05 mmol, 1.0 equiv) and a magnetic stir bar was evacuated under vacuum and backfilled with argon (× 3). CH_2Cl_2 (2.2 mL) was added and the resulting solution was degassed by argon sparge for 20 min. Vaska's complex ($IrCl(CO)(PPh_3)_2$, 6.0 mg, 0.0075 mmol, 0.15 equiv) was then added followed by dropwise addition of 1,1,3,3-tetramethyldisiloxane (TMDS, 89 µL, 0.5 mmol, 10.0 equiv). The reaction was stirred at room temperature for 5 h. MeOH (2.0 mL) was added to the reaction mixture and, when effervescence stopped, glacial AcOH (6 µL, 0.1 mmol, 2 equiv) was added followed by $NaBH_3CN$ (3.0 mg, 0.05 mmol, 1.0 equiv) and allowed to stir for 15 min. The reaction was quenched with 1 N NaOH (3 mL) and transferred to a separatory funnel, diluting with CH_2Cl_2 (10 mL) and water (5 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with 1 N NaOH (2 × 15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude residue was purified by flash chromatography (silica gel, EtOAc/hexanes, 10–30%) to afford PMB protected spiroindimicin C (**74**, 18.9 mg, 69%).

Physical Properties: Beige solid;
R_f = 0.45 (silica gel, 40% EtOAc/hexanes);
MS (ESI): calculated for $C_{30}H_{24}Cl_2N_3O_3$ $[M + H]^+$ 544.1189, found 544.1201;
^{1}H NMR (600 MHz, DMSO-d_6): δ 11.52 (br s, 1H), 11.43 (br d, *J* = 2.2 Hz, 1H), 7.74 (d, *J* = 1.9 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 1H), 7.11 (d, *J* = 2.4 Hz, 1H), 7.07 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.03 (dd, *J* = 8.6, 2.1 Hz, 1H), 6.92 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.4 Hz, 1H), 6.25 (d, *J* = 2.4 Hz, 1H), 4.57 (d, *J* = 14.7 Hz, 1H), 4.32 (d, *J* = 14.7 Hz, 1H), 4.04 (d, *J* = 9.1 Hz, 1H), 3.73 (s, 3H), 3.57 (d, *J* = 9.1 Hz, 1H), 3.42 (s, 3H);
^{13}C NMR (151 MHz, DMSO-d_6): δ 160.1, 158.5, 155.3, 151.4, 141.3, 138.2, 134.2, 129.5, 129.3, 127.6, 125.7, 124.0, 121.9, 121.1, 120.3, 120.1, 118.3, 115.6, 114.0, 113.8, 111.8, 111.3, 108.5, 61.2, 55.1, 51.7, 51.1, 50.7.



Spiroindimicin C (3): A 10 mL reaction vial containing *N*-PMB spiroindimicin C (**74**, 7 mg, 0.013 mmol, 1.0 equiv) and a magnetic stir bar was evacuated under vacuum and backfilled with argon (× 3). MeOH (1.2 mL) and freshly prepared 3 N aqueous HCl (0.12 mL) were added followed by Pd/C (10 wt%, 4.1 mg, 0. 0038 mmol, 0.3 equiv). H_2 was bubbled through the reaction mixture for 10 min, after which the reaction was stirred at 23 °C under a H_2 atmosphere (balloon) for 2 h. After complete consumption of starting material **74** (TLC), the reaction mixture was filtered through a Celite pad, washing with MeOH/EtOAc (1:3, 16 mL). The filtrate was quenched with saturated $NaHCO_3$ solution (10 mL) and transferred to a separatory funnel, diluting with EtOAc (5 mL) and water (5 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude residue was purified by flash chromatography (silica gel, EtOAc/hexanes, 30–70%) to afford spiroindimicin C (**3**, 2.5 mg, 46%).

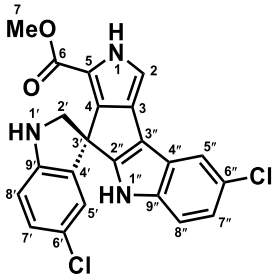
Physical Properties: white solid;
R_f = 0.23 (silica gel, 50% EtOAc/hexanes);
MS (ESI): calculated for $C_{22}H_{16}Cl_2N_3O_2$ $[M + H]^+$ 424.0614, found 424.0638;
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.70 (br s, 1H), 8.32 (br s, 1H), 7.63 (d, *J* = 1.9 Hz, 1H), 7.20 (d, *J* = 8.6 Hz, 1H), 7.09 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.03 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.91 (d, *J* = 2.6 Hz, 1H), 6.74 (d, *J* = 8.4 Hz, 1H), 6.57 (d, *J* = 2.1 Hz, 1H), 4.48 (d, *J* = 9.0 Hz, 1H), 4.08 (br s, 1H), 3.74 (d, *J* = 9.0 Hz, 1H), 3.67 (s, 3H);
^{13}C NMR (151 MHz, $CDCl_3$): δ 160.5, 154.8, 150.3, 140.9, 138.0, 133.4, 128.4, 127.2, 126.2, 124.3, 123.5, 122.0, 121.8, 119.1, 116.8, 113.2, 112.3, 111.3, 110.2, 56.7, 53.6, 51.5.



3*: spiroindimicin C*

Table S15: Comparison of ^{1}H NMR shifts (δ) of natural,[7] Sperry,[1] and our synthetic spiroindimicin C (**3**) in $CDCl_3$.

Position	**Natural 3** (500 MHz)	**Synthetic 3** ***(Sperry)*** (500 MHz)	**Synthetic 3** ***(Smith)*** (600 MHz)
1	8.88 (s, 1H)	8.70 (s, 1H)	8.70 (br s, 1H)
2	6.91(d, *J* = 2.5 Hz, 1H)	6.91 (d, *J* = 2.5 Hz, 1H)	6.91 (d, *J* = 2.6 Hz, 1H)
7	3.66 (s, 3H)	3.67 (s, 3H)	3.67 (s, 3H)
1′	–	–	4.08 (br s, 1H)
2′	3.76 (d, *J* = 9.0 Hz, 1H) 4.45 (d, *J* = 9.0 Hz, 1H)	3.73 (d, *J* = 9.0 Hz, 1H) 4.47 (d, *J* = 9.0 Hz, 1H)	3.74 (d, *J* = 9.0 Hz, 1H) 4.48 (d, *J* = 9.0 Hz, 1H)
5′	6.57 (d, *J* = 2.0 Hz, 1H)	6.57 (d, *J* = 2.0 Hz, 1H)	6.57 (d, *J* = 2.1 Hz, 1H)
7′	7.04 (dd, *J* = 8.5, 2.0 Hz, 1H)	7.03 (dd, *J* = 8.4, 2.1 Hz, 1H)	7.03 (dd, *J* = 8.4, 2.2 Hz, 1H)
8′	6.76 (d, *J* = 8.5 Hz, 1H)	6.73 (d, *J* = 8.4 Hz, 1H)	6.74 (d, *J* = 8.4 Hz, 1H)
1″	8.55 (s, 1H)	8.27 (s, 1H)	8.32 (br s, 1H)
5″	7.63 (d, *J* = 2.0 Hz, 1H)	7.62 (d, *J* = 2.0 Hz, 1H)	7.63 (d, *J* = 1.9 Hz, 1H)
7″	7.09 (dd, *J* = 8.8, 2.0 Hz, 1H)	7.09 (dd, *J* = 8.7, 2.1 Hz, 1H)	7.09 (dd, *J* = 8.6, 2.0 Hz, 1H)
8″	7.19 (d, *J* = 8.8 Hz, 1H)	7.19 (d, *J* = 8.7 Hz, 1H)	7.20 (d, *J* = 8.6 Hz, 1H)



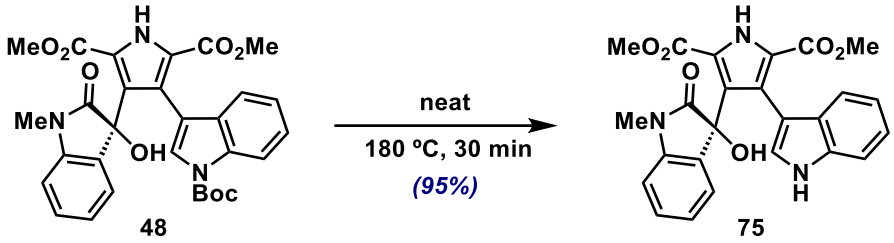
3*: spiroindimicin C*

Table S16: Comparison of ^{13}C NMR shifts (δ) of natural,[8] Sperry,[1] and our synthetic spiroindimicin C (**3**) in $CDCl_3$

Position	**Natural 3**[a] (126 MHz)	**Synthetic 3** ***(Sperry)***[b] (126 MHz)	**Synthetic 3** ***(Smith)*** (151 MHz)
2	110.1	110.0	110.2
3	127.0	127.0	127.2
4	141.0	140.8	140.9
5	116.7	116.7	116.8
6	160.4	160.3	160.5
7	51.4	51.3	51.5
2′	56.3	56.5	56.7
3′	53.3	53.3	53.6
4′	133.6	133.3	133.4
5′	123.4	123.4	123.5
6′	124.7	124.1	124.3
7′	128.3	128.2	128.4
8′	111.6	111.1	111.3
9′	149.7	150.2	150.3
2″	154.5	154.6	154.8
3″	112.3	112.2	112.3
4″	121.8	121.9	121.8
5″	118.9	119.0	119.1
6″	126.0	126.0	126.2
7″	121.6	121.6	121.8
8″	113.1	113.0	113.2
9″	137.8	137.9	138.0

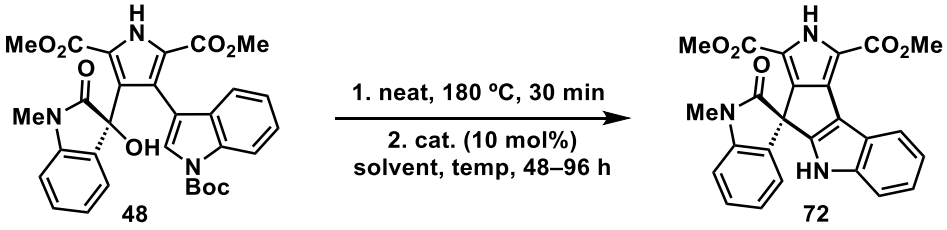
[a]Natural **3** referenced to $CDCl_3$ at δ 77.03. [b] Sperry's $CDCl_3$ referenced at δ 77.0.

6. Preliminary Studies Toward an Asymmetric Spirocyclization



DeBoc product 75: A 25 mL round-bottom flask containing Suzuki product **48** (205 mg, 0.366 mmol, 1.0 equiv) and a magnetic stir bar was evacuated under vacuum and backfilled with argon (× 3). It was heated neat at 180 °C for 30 min with slow stirring. The resulting crude residue was purified by flash chromatography (silica gel, EtOAc/hexanes, 50–100%) to afford **75** (dr = 1.4:1, 159 mg, 95%).

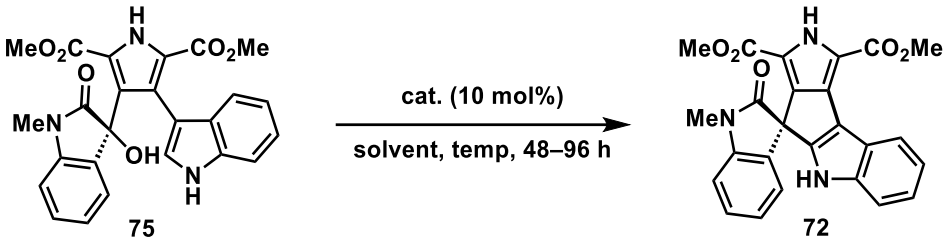
Physical Properties: Beige solid;
R_f = 0.13 (silica gel, 70% EtOAc/hexanes);
MS (ESI): calculated for $C_{25}H_{22}N_3O_6$ $[M + H]^+$ 460.1503, found 460.1491;
^{1}H NMR (600 MHz, $CDCl_3$): δ 9.97 (s, $1H_{major}$), 9.95 (s, $1H_{minor}$), 8.77 (s, $1H_{major}$), 8.08 (br s, $1H_{minor}$), 7.97 (br s, $1H_{minor}$), 7.72 (br s, $1H_{major}$), 7.22 (dd, J = 7.5, 0.9 Hz, $1H_{major}$), 7.21–7.16 (m, $1H_{major}$ + $2H_{minor}$), 7.13 (d, J = 7.8 Hz, $1H_{minor}$), 7.10–7.05 (m, $1H_{major}$ + $1H_{minor}$), 7.02 (ddd, J = 7.9, 7.0, 1.0 Hz, $1H_{minor}$), 6.98–6.93 (m, $2H_{major}$ + $1H_{minor}$), 6.91 (td, J = 7.5, 0.9 Hz, $1H_{minor}$), 6.82 (td, J = 7.5, 0.8 Hz, $1H_{major}$), 6.54 (t, J = 7.4 Hz, $1H_{major}$), 6.25 (d, J = 7.5 Hz, $1H_{minor}$), 6.10 (d, J = 6.8 Hz, $1H_{major}$), 6.06 (d, J = 7.7 Hz, $1H_{major}$), 5.90 (br s, $1H_{minor}$), 4.05 (s, $3H_{major}$), 4.01 (br s, $3H_{minor}$), 3.53 (s, $3H_{major}$), 3.52 (s, $3H_{minor}$), 2.35 (br s, $3H_{major}$), 2.23 (br s, $3H_{minor}$);
^{13}C NMR (151 MHz, $CDCl_3$): δ 174.8, 174.7, 162.9, 162.7, 160.5, 160.3, 143.7, 142.7, 135.1, 135.0, 134.7, 133.8, 132.5, 131.9, 129.3, 129.2, 127.9, 127.8, 125.8, 124.4, 124.2, 124.1, 124.0, 123.5, 123.0, 122.8, 122.5, 122.3, 122.1, 121.8, 121.4, 121.1, 119.7, 119.6, 119.3, 118.4, 110.6, 110.5, 108.6, 107.9, 106.6, 105.7, 75.5, 75.1, 53.3 (2 signals overlap), 52.04, 51.96, 25.30, 25.26.



General Procedure I: One-pot synthesis of 72 from 48 via chiral Brønsted acid catalysis

A 10 mL vial containing Suzuki product **48** (0.019 mmol, 1.0 equiv) and a magnetic stir bar was evacuated under vacuum and backfilled with argon (× 3). It was heated neat at 180 °C for 30 min with slow stirring. After cooling to room temperature, the residue containing deBoc product **75** was dissolved in solvent (1 mL) and a chiral Brønsted acid (**76a–c**, **76h–k** 0.0019 mmol, 0.1 equiv) was added. The reaction was stirred at various temperatures (see Table 5,

entry 1, 4–9). At the end of the reaction, the solution was concentrated *in vacuo* and the crude residue was purified by flash chromatography (silica gel, EtOAc/hexanes, 30–70%) to afford **72** containing a trace amount of an inseparable impurity.



General Procedure II: Synthesis of 72 from 75 via chiral Brønsted acid catalysis

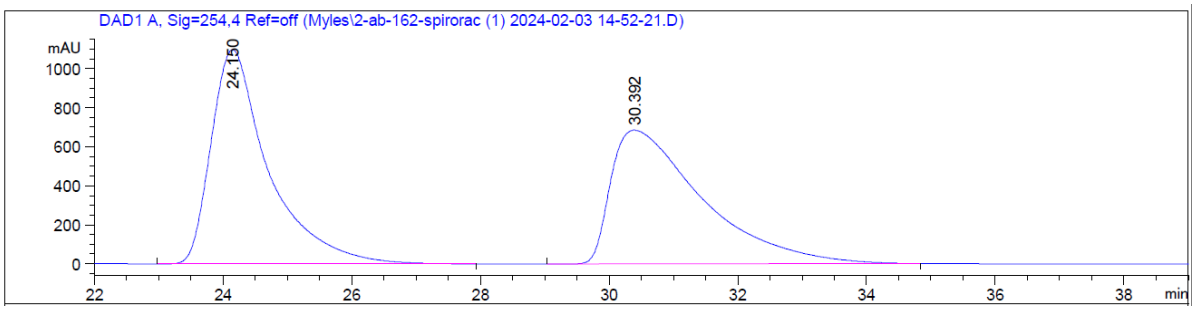
A 10 mL vial containing **75** (0.019 mmol, 1.0 equiv) and a magnetic stir bar was evacuated under vacuum and backfilled with argon (× 3). Solvent (1 mL) was added followed by chiral Brønsted acid (**76d–g**, **76k–p** 0.0019 mmol, 0.1 equiv). The reaction was stirred at various temperatures (see Table 5, entry 2, 3, 10–24). At the end of the reaction, the solution was concentrated *in vacuo* and the crude residue was purified by flash chromatography (silica gel, EtOAc/hexanes, 30–70%) to afford **72**.

Synthesis of spirocyclic product 72 by using catalyst 76k: The reaction was performed according to *General Procedure II* using 25.2 mg (0.055 mmol, 1.0 equiv) of **75** and 4.9 mg (0.0055 mmol, 0.1 equiv) of catalyst **76k** in DCE at 60 °C. After 40 h, the spirocyclic product **72** (6.2 mg) was isolated in 26% yield. The enantiopurity of **72** was determined to be 34% ee by HPLC (AD-H, hexane/*i*-PrOH = 90/10, 1.0 mL/min, 254 nm t_{major} = 25.89 min and t_{minor} = 33.39 min.

Optical Rotation $[\alpha]^{25}_{D}$ = +0.91 (c = 0.439, MeOH; 34% ee).

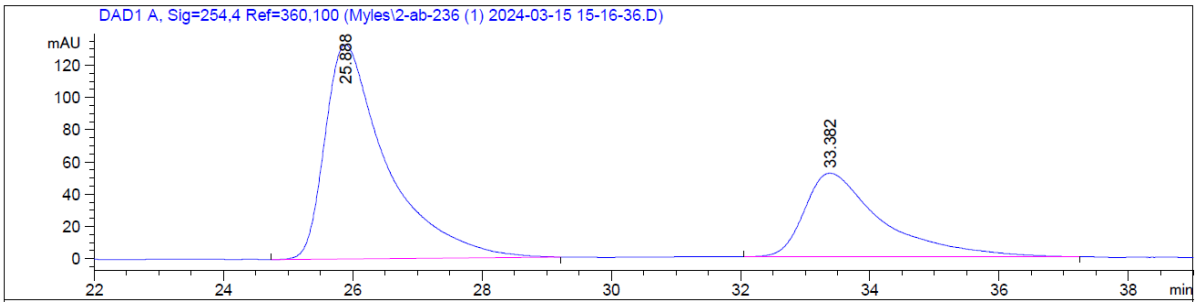
HPLC Traces for (±)-72 and Enantioenriched 72

(±)-72 (AD-H, hexane/*i*-PrOH = 90/10, 1.0 mL/min):



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.150	BB	0.9076	6.78865e4	1097.61304	50.1698
2	30.392	BB	1.4663	6.74270e4	685.07770	49.8302
Totals :				1.35314e5	1782.69073	

Enantioenriched 72 (AD-H, hexane/*i*-PrOH = 90/10, 1.0 mL/min):



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.888	BB	0.9563	8793.42969	132.84219	67.2270
2	33.382	BB	1.1591	4286.76709	51.71145	32.7730
Totals :				1.30802e4	184.55364	

7. Details for Single Crystal X-ray Analyses of 46, 61, 63, and 6

X-ray Experimental for $C_{17}H_{15}N_2O_6I$ (46): Crystals grew as clusters of colorless intergrown, prisms by slow evaporation from CH_2Cl_2. The data crystal was cut from a larger cluster of crystals and had approximate dimensions; 0.18 x 0.13 x 0.10 mm. The data were collected on a Rigaku Oxford Diffraction HyPix6000E Synergy diffractometer using a μ-focus Cu Kα radiation source (λ = 1.5418Å) with collimating mirror monochromators. A total of 5308 frames of data were collected using ω-scans with a scan range of 0.5° and a counting time of 4.5 seconds per frame for frames collected with a detector offset of +/- 48.1° and 20 seconds per frame with frames collected with a detector offset of +/- 105.1°. The data were collected at 100 K using an Oxford Cryostream low temperature device. Details of crystal data, data collection and structure refinement are listed in Table S16. Data collection, unit cell refinement and data reduction were performed using Rigaku Oxford Diffraction's CrysAlisPro V 1.171.42.88a.[13] The structure was solved by direct methods using SHELXT[14] and refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for the non-H atoms using SHELXL-2018/3.[15] Structure analysis was aided by use of the programs PLATON[16] and OLEX2.[17] The hydrogen atoms on the carbon atoms were calculated in ideal positions with isotropic displacement parameters set to 1.2xUeq of the attached atom (1.5xUeq for methyl hydrogen atoms). The hydrogen atoms on the hydroxyl group oxygen atoms, O5 and O11, and

the pyrrole nitrogen atoms, N1 and N3, were observed in a ΔF map and refined with isotropic displacement parameters.

The function, $\Sigma w(|F_O|^2 - |F_C|^2)^2$, was minimized, where $w = 1/[(\sigma(F_O))^2 + (0.0895*P)^2 + (5.9843*P)]$ and $P = (|F_O|^2 + 2|F_C|^2)/3$. $R_w(F^2)$ refined to 0.144, with R(F) equal to 0.0530 and a goodness of fit, S, = 1.04. Definitions used for calculating R(F), $R_w(F^2)$ and the goodness of fit, S, are given below.[18] The data were checked for secondary extinction effects but no correction was necessary. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1992).[19] All figures were generated using SHELXTL/PC.[20] Tables of positional and thermal parameters, bond lengths and angles, torsion angles and figures are found elsewhere.

Table S17. Crystal data and structure refinement for 46.

Empirical formula	C17 H15 I N2 O6	
Formula weight	470.21	
Temperature	100.00(11) K	
Wavelength	1.54184 Å	
Crystal system	triclinic	
Space group	P -1	
Unit cell dimensions	a = 10.8128(4) Å	α= 96.120(4)°.
	b = 11.8787(6) Å	β= 91.980(3)°.
	c = 13.9111(5) Å	γ = 96.465(4)°.
Volume	1763.32(13) Å^3	
Z	4	
Density (calculated)	1.771 Mg/m^3	
Absorption coefficient	14.611 mm^{-1}	
F(000)	928	
Crystal size	0.18 x 0.13 x 0.1 mm^3	
Theta range for data collection	3.199 to 77.890°.	
Index ranges	-13<=h<=13, -14<=k<=15, -14<=l<=17	
Reflections collected	28722	
Independent reflections	7208 [R(int) = 0.0765]	
Completeness to theta = 67.684°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00 and 0.508	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7208 / 4 / 491	
Goodness-of-fit on F^2	1.041	
Final R indices [I>2sigma(I)]	R1 = 0.0530, wR2 = 0.1424	
R indices (all data)	R1 = 0.0540, wR2 = 0.1437	

Extinction coefficient	n/a
Largest diff. peak and hole	2.519 and -1.428 e.Å^{-3}

Figure S1. View of molecule 1 in **46** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level.

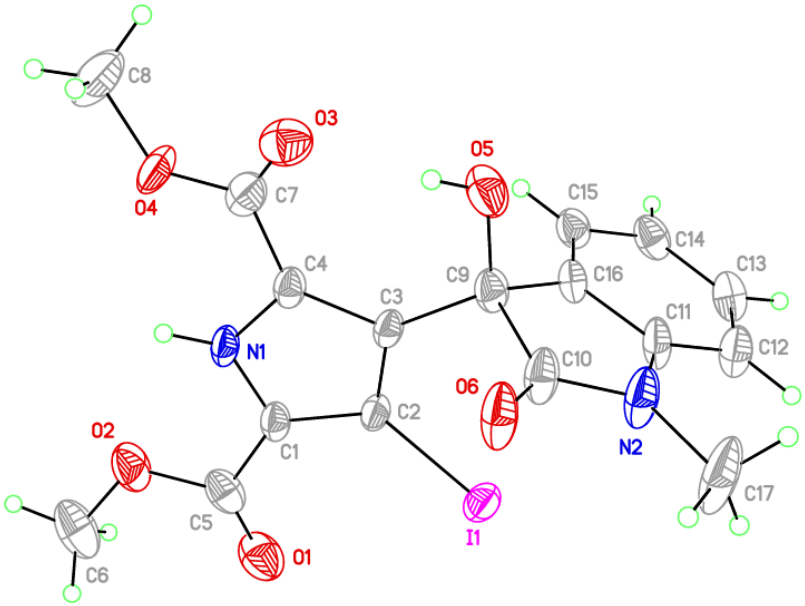
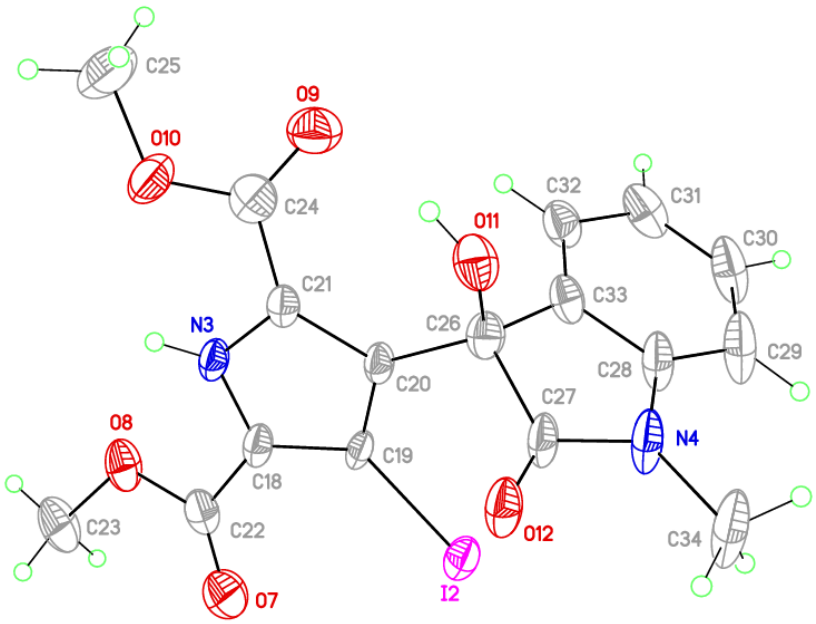


Figure S2. View of molecule 2 in **46** showing the atom labelling scheme. Displacement ellipsoids are scaled to the 50% probability level.



X-ray Experimental for $C_{15}H_{12}N_2O_4ClBr$ (61): Crystals grew as clusters of colorless prisms by slow evaporation from EtOAc/hexanes. The data crystal was cut from a cluster of crystals and had approximate dimensions; 0.31 x 0.24 x 0.14 mm. The data were collected on an Agilent Technologies SuperNova Dual Source diffractometer using a μ-focus Cu Kα radiation source (λ = 1.5418Å) with collimating mirror monochromators. A total of 5502 frames of data were collected using ω-scans with a scan range of 0.5° and a counting time of 4.5 seconds per frame for frames collected with a detector offset of +/- 47.1° and 18 seconds per frame with frames collected with a detector offset of 107.8°. The data were collected at 100 K using an Oxford Cryostream low temperature device. Details of crystal data, data collection and structure refinement are listed in Table S17. Data collection, unit cell refinement and data reduction were performed using Rigaku Oxford Diffraction's CrysAlisPro V 1.171.42.88a.[13] The structure was solved by direct methods using SHELXT[14] and refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for the non-H atoms using SHELXL-2018/3.[15] Structure analysis was aided by use of the programs PLATON[16] and OLEX2.[17] The hydrogen atoms on the carbon atoms were calculated in ideal positions with isotropic displacement parameters set to 1.2xUeq of the attached atom (1.5xUeq for methyl hydrogen atoms).

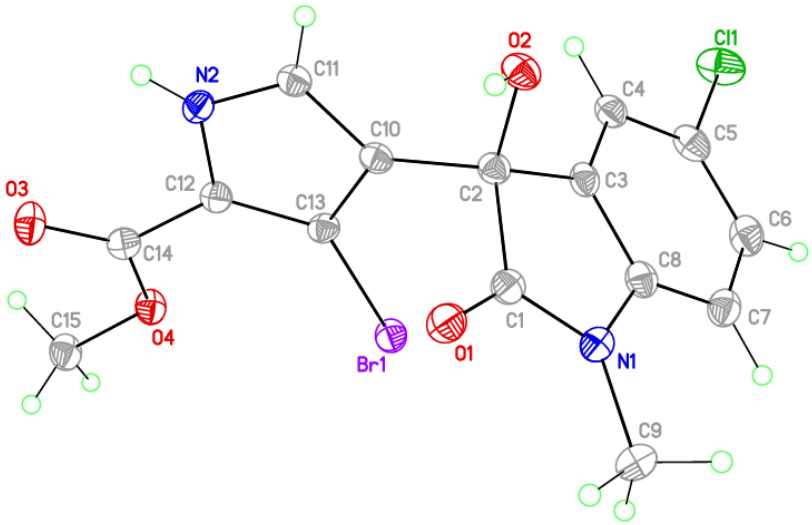
The function, $\Sigma w(|F_O|^2 - |F_C|^2)^2$, was minimized, where $w = 1/[(\sigma(F_O))^2 + (0.0323*P)^2 + (0.8078*P)]$ and $P = (|F_O|^2 + 2|F_C|^2)/3$. $R_w(F^2)$ refined to 0.0620, with R(F) equal to 0.0237 and a goodness of fit, S, = 1.06. Definitions used for calculating R(F), $R_w(F^2)$ and the goodness of fit, S, are given below.[18] The data were checked for secondary extinction effects but no correction was necessary. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1992).[19] All figures were generated using SHELXTL/PC.[20] Tables of positional and thermal parameters, bond lengths and angles, torsion angles and figures are found elsewhere.

Table S18. Crystal data and structure refinement for 61.

Empirical formula	C15 H12 Br Cl N2 O4	
Formula weight	399.63	
Temperature	100.02(14) K	
Wavelength	1.54184 Å	
Crystal system	triclinic	
Space group	P -1	
Unit cell dimensions	a = 9.1305(3) Å	α= 73.634(4)°.
	b = 9.5099(3) Å	β= 81.798(3)°.
	c = 9.6003(4) Å	γ = 72.598(3)°.
Volume	761.66(5) $Å^3$	
Z	2	
Density (calculated)	1.742 Mg/m^3	
Absorption coefficient	5.503 mm^{-1}	
F(000)	400	

Crystal size	0.309 x 0.242 x 0.143 mm^3
Theta range for data collection	4.811 to 76.971°.
Index ranges	-11<=h<=11, -11<=k<=9, -12<=l<=11
Reflections collected	12747
Independent reflections	3097 [R(int) = 0.0193]
Completeness to theta = 67.684°	98.8 %
Absorption correction	Gaussian and multi-scan
Max. and min. transmission	1.00 and 0.568
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3097 / 0 / 218
Goodness-of-fit on F^2	1.058
Final R indices [I>2sigma(I)]	R1 = 0.0237, wR2 = 0.0620
R indices (all data)	R1 = 0.0237, wR2 = 0.0620
Extinction coefficient	n/a
Largest diff. peak and hole	0.411 and -0.446 $e.Å^{-3}$

Figure S3. View of **61** showing the atom labelling scheme. Displacement ellipsoids are scaled to the 50% probability level.



X-ray Experimental for $C_{15}H_{12}N_2O_4ClBr$ (62): Crystals grew as clusters of colorless prisms by slow evaporation from EtOAc/hexanes. The data crystal was cut from a larger crystal and had approximate dimensions; 0.32 x 0.20 x 0.14 mm. The data were collected on an Agilent Technologies SuperNova Dual Source diffractometer using a μ-focus Cu Kα radiation source (λ = 1.5418Å) with collimating mirror monochromators. A total of 4298 frames of data were collected using ω-scans with a scan range of 0.5° and a counting time of 6 seconds per frame for frames collected with a detector offset of +/- 48.8° and 24 seconds per frame with frames

collected with a detector offset of 107.8°. The data were collected at 100 K using an Oxford Cryostream low temperature device. Details of crystal data, data collection and structure refinement are listed in Table S18. Data collection, unit cell refinement and data reduction were performed using Rigaku Oxford Diffraction's CrysAlisPro V 1.171.41.123a.[13] The structure was solved by direct methods using SHELXT[14] and refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for the non-H atoms using SHELXL-2018/3.[15] Structure analysis was aided by use of the programs PLATON[16] and OLEX2.[17] The hydrogen atoms on the carbon atoms were calculated in ideal positions with isotropic displacement parameters set to 1.2xUeq of the attached atom (1.5xUeq for methyl hydrogen atoms). The hydrogen atoms on O2 and N2 were observed in a ΔF map and refined with isotropic displacement parameters.

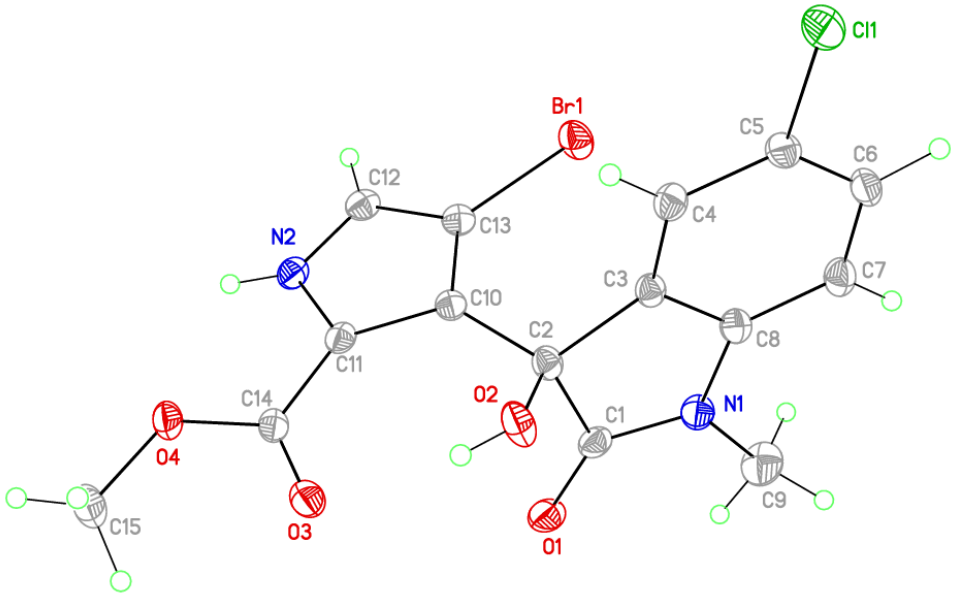
The function, $\Sigma w(|F_O|^2 - |F_C|^2)^2$, was minimized, where $w = 1/[(\sigma(F_O))^2 + (0.0426*P)^2 + (1.4442*P)]$ and $P = (|F_O|^2 + 2|F_C|^2)/3$. $R_w(F^2)$ refined to 0.0758, with R(F) equal to 0.0276 and a goodness of fit, S, = 1.10. Definitions used for calculating R(F), $R_w(F^2)$ and the goodness of fit, S, are given below.[18] The data were checked for secondary extinction effects but no correction was necessary. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1992).[19] All figures were generated using SHELXTL/PC.[20] Tables of positional and thermal parameters, bond lengths and angles, torsion angles and figures are found elsewhere.

Table S19. Crystal data and structure refinement for 62.

Empirical formula	C15 H12 Br Cl N2 O4	
Formula weight	399.63	
Temperature	100.1(4) K	
Wavelength	1.54184 Å	
Crystal system	monoclinic	
Space group	P 1 21/c 1	
Unit cell dimensions	a = 13.45120(10) Å	α= 90°.
	b = 8.02230(10) Å	β= 104.1410(10)°.
	c = 14.9534(2) Å	γ = 90°.
Volume	1564.72(3) $Å^3$	
Z	4	
Density (calculated)	1.696 Mg/m^3	
Absorption coefficient	5.358 mm^{-1}	
F(000)	800	
Crystal size	0.322 x 0.205 x 0.143 mm^3	
Theta range for data collection	3.388 to 77.235°.	
Index ranges	-15<=h<=16, -10<=k<=10, -18<=l<=15	
Reflections collected	21679	

Independent reflections	3240 [R(int) = 0.0336]
Completeness to theta = 67.684°	99.9 %
Absorption correction	Gaussian and multi-scan
Max. and min. transmission	0.973 and 0.299
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3240 / 0 / 218
Goodness-of-fit on F^2	1.099
Final R indices [I>2sigma(I)]	R1 = 0.0276, wR2 = 0.0758
R indices (all data)	R1 = 0.0276, wR2 = 0.0758
Extinction coefficient	n/a
Largest diff. peak and hole	0.728 and -0.481 e.Å^{-3}

Figure S4. View of **62** showing the atom labelling scheme. Displacement ellipsoids are scaled to the 50% probability level.



X-ray Experimental for $C_{23}H_{18}N_3O_2Cl$ (6): Crystals grew as clusters of colorless prisms by slow evaporation from CH_2Cl_2/MeOH. The data crystal was cut from a cluster of crystals and had approximate dimensions; 0.22 x 0.17 x 0.11 mm. The data were collected on an Agilent Technologies SuperNova Dual Source diffractometer using a μ-focus Cu Kα radiation source (λ = 1.5418Å) with collimating mirror monochromators. A total of 3974 frames of data were collected using ω-scans with a scan range of 0.5° and a counting time of 6.5 seconds per frame for frames collected with a detector offset of +/- 47.2° and 26 seconds per frame with frames collected with a detector offset of 107.8°. The data were collected at 100 K using an Oxford Cryostream low temperature device. Details of crystal data, data collection and structure refinement are listed in Table S19. Data collection, unit cell refinement and data reduction were

performed using Rigaku Oxford Diffraction's CrysAlisPro V 1.171.42.88a.[13] The structure was solved by direct methods using SHELXT[14] and refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for the non-H atoms using SHELXL-2018/3.[15] Structure analysis was aided by use of the programs PLATON[16] and OLEX2.[17] The hydrogen atoms on the carbon atoms were calculated in ideal positions with isotropic displacement parameters set to 1.2xUeq of the attached atom (1.5xUeq for methyl hydrogen atoms). The hydrogen atoms on N1 and N2 were observed in a ΔF map and refined with isotropic displacement parameters.

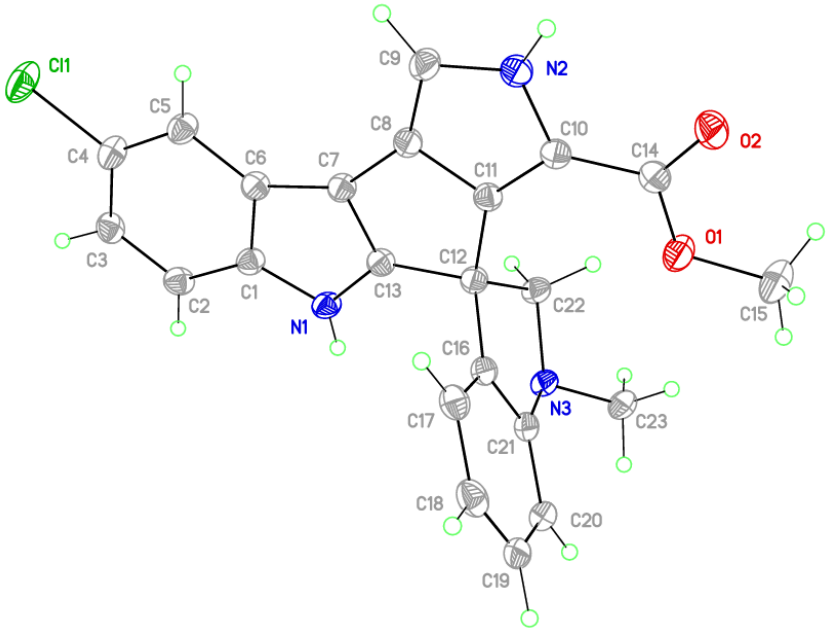
The function, $\Sigma w(|F_O|^2 - |F_C|^2)^2$, was minimized, where $w = 1/[(\sigma(F_O))^2 + (0.0459*P)^2 + (1.0147*P)]$ and $P = (|F_O|^2 + 2|F_C|^2)/3$. $R_w(F^2)$ refined to 0.0895, with R(F) equal to 0.0343 and a goodness of fit, S, = 1.04. Definitions used for calculating R(F), $R_w(F^2)$ and the goodness of fit, S, are given below.[18] The data were checked for secondary extinction effects but no correction was necessary. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1992).[19] All figures were generated using SHELXTL/PC.[20] Tables of positional and thermal parameters, bond lengths and angles, torsion angles and figures are found elsewhere.

Table S20. Crystal data and structure refinement for 6.

Empirical formula	C23 H18 Cl N3 O2	
Formula weight	403.85	
Temperature	100.01(12) K	
Wavelength	1.54184 Å	
Crystal system	monoclinic	
Space group	P 1 21/n 1	
Unit cell dimensions	a = 10.26480(10) Å	α= 90°.
	b = 14.87010(10) Å	β= 97.8740(10)°.
	c = 12.73740(10) Å	γ = 90°.
Volume	1925.89(3) $Å^3$	
Z	4	
Density (calculated)	1.393 Mg/m^3	
Absorption coefficient	1.962 mm^{-1}	
F(000)	840	
Crystal size	0.22 x 0.171 x 0.11 mm^3	
Theta range for data collection	4.596 to 76.999°.	
Index ranges	-12<=h<=12, -18<=k<=18, -14<=l<=16	
Reflections collected	25979	
Independent reflections	3983 [R(int) = 0.0151]	
Completeness to theta = 67.684°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.84846	
Refinement method	Full-matrix least-squares on F^2	

Data / restraints / parameters	3983 / 0 / 272
Goodness-of-fit on F^2	1.036
Final R indices [I>2sigma(I)]	R1 = 0.0343, wR2 = 0.0894
R indices (all data)	R1 = 0.0345, wR2 = 0.0895
Extinction coefficient	n/a
Largest diff. peak and hole	0.431 and -0.267 e.Å^{-3}

Figure S5. View of **6** showing the heteroatom labelling scheme. Displacement ellipsoids are scaled to the 30% probability level.



8. Experimental Details for Biological Assays

T. brucei cell viability assay

These assays were carried out as previously reported,[4] with the inclusion of paclitaxel as a positive control.

P. falciparum growth inhibition assays

These assays were carried out as previously reported.[4]

Concentration–response assays in *Leishmania amazonensis*

Stocks of compounds and the reference drug paclitaxel (Sigma) were made in DMSO at 10 mM and stored at –20 °C. Maximum DMSO concentration in assays was 0.2% v/v.

L. amazonensis promastigotes (strain IFLA/BR/67/PH8, from Norma W. Andrews, University of Maryland, College Park, MD) were maintained as described previously.[21] They were converted to *L. amazonensis* amastigotes by growing them axenically at 32 °C and pH 4.5 in M199 media (Invitrogen) supplemented with 20% heat-inactivated FBS (Invitrogen), 0.25% glucose, 0.1% hemin (25 mg/mL in 50% triethanolamine), 10 mM adenine, 5 mM L glutamine, 1% penicillin−streptomycin, 0.5% trypticase, and 40 mM sodium succinate.[22,23] For compound testing, 6–9 day old axenic amastigotes were used. Compounds were dry spotted onto white 96-well plates (Corning 3903) using an Echo 655 acoustic liquid dispenser (Beckman Coulter). Axenic amastigotes were then added (200 μL, 1×10^6 cells/mL) and plates incubated at 32 °C for 72 h.[21] DMSO at 0.1% (no drug) served as a neutral control (100% survival), and 5 μM SW389119 was a inhibitory control (0% survival). Antiparasitic activity was measured using a CellTiter-Glo® Luminescent Cell Viability Assay (Promega)[14] on a Perkin Elmer EnVision plate reader following the manufacturer's protocol. EC_{50} values were determined using Genedata Screener v19.[21,24,25]

All experiments were performed as 3 technical replicates, using only internal wells to decrease evaporation-related edge effects; at least 3 biological repeats were independently conducted.[21] The mean EC_{50} values ± SE shown were calculated from each biological replicate.[21]

HepG2 cytotoxicity assay

HepG2 cells (ATCC® HB-8065™) were cultured in ATCC complete Eagle's Minimum Essential Medium supplemented with 10% fetal bovine serum (R&D Systems, Minneapolis, MN, USA), 2 mM L-glutamine, and 1% Penicillin/Streptomycin. The cells were maintained until ≈ 90 % confluency at 37 °C under a humidified atmosphere and 5% CO_2 before resuspending or plating. For cytotoxicity assay, 60 μL of the cells were dispensed at 1.5×10^4 cells/mL in white 384 well plates (Greiner Bio-One 781098) using a BioTek MultiFlo Washer Dispenser (Agilent). Plated cells were then incubated overnight at 37 °C/5% CO_2. Compounds were then added using an Echo 655 acoustic liquid dispenser (Beckman Coulter) from 10 mM DMSO stocks and normalized to a final 0.5% DMSO concentration. 10 μM Brefeldin A (Cayman Chemical, #11861) was used as a positive kill control. After 96 hours of growth at 37 °C/5% CO_2, the plates were equilibrated at room temperature for 5 min before addition of 10 μL CellTiter-Glo(Promega) diluted by half with 1X PBS/0.1% Triton X-100 to each well using a Biomek i7 liquid handler (Beckman Coulter). Plates were then shaken for 5 minutes at

room temperature. Luminescence was read on a PerkinElmer EnVision plate reader. CC50 values were determined using Genedata Screener v19.

All experiments were performed as 3 technical replicates and 3 biological repeats were independently conducted.[21] The mean CC_{50} values ± SE shown were calculated from each biological replicate.[2]

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18. $R_W(F^2) = \{\Sigma w(|F_o|^2 - |F_c|^2)^2/\Sigma w(|F_o|)^4\}^{1/2}$ where w is the weight given each reflection. $R(F) = \Sigma(|F_o| - |F_c|)/\Sigma|F_o|\}$ for reflections with $F_o > 4(\sigma(F_o))$. $S = [\Sigma w(|F_o|^2 - |F_c|^2)^2/(n - p)]^{1/2}$, where n is the number of reflections and p is the number of refined parameters.
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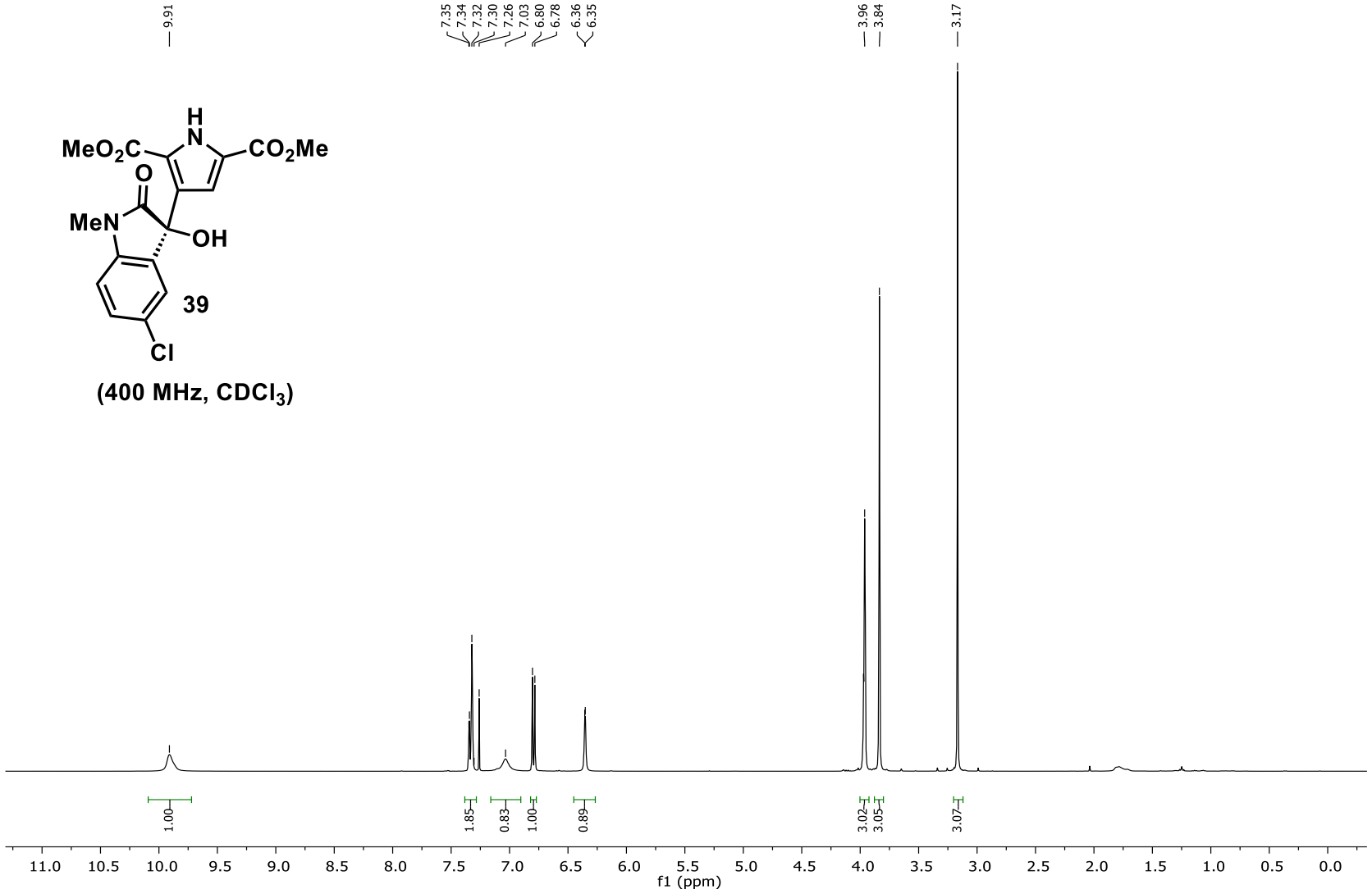
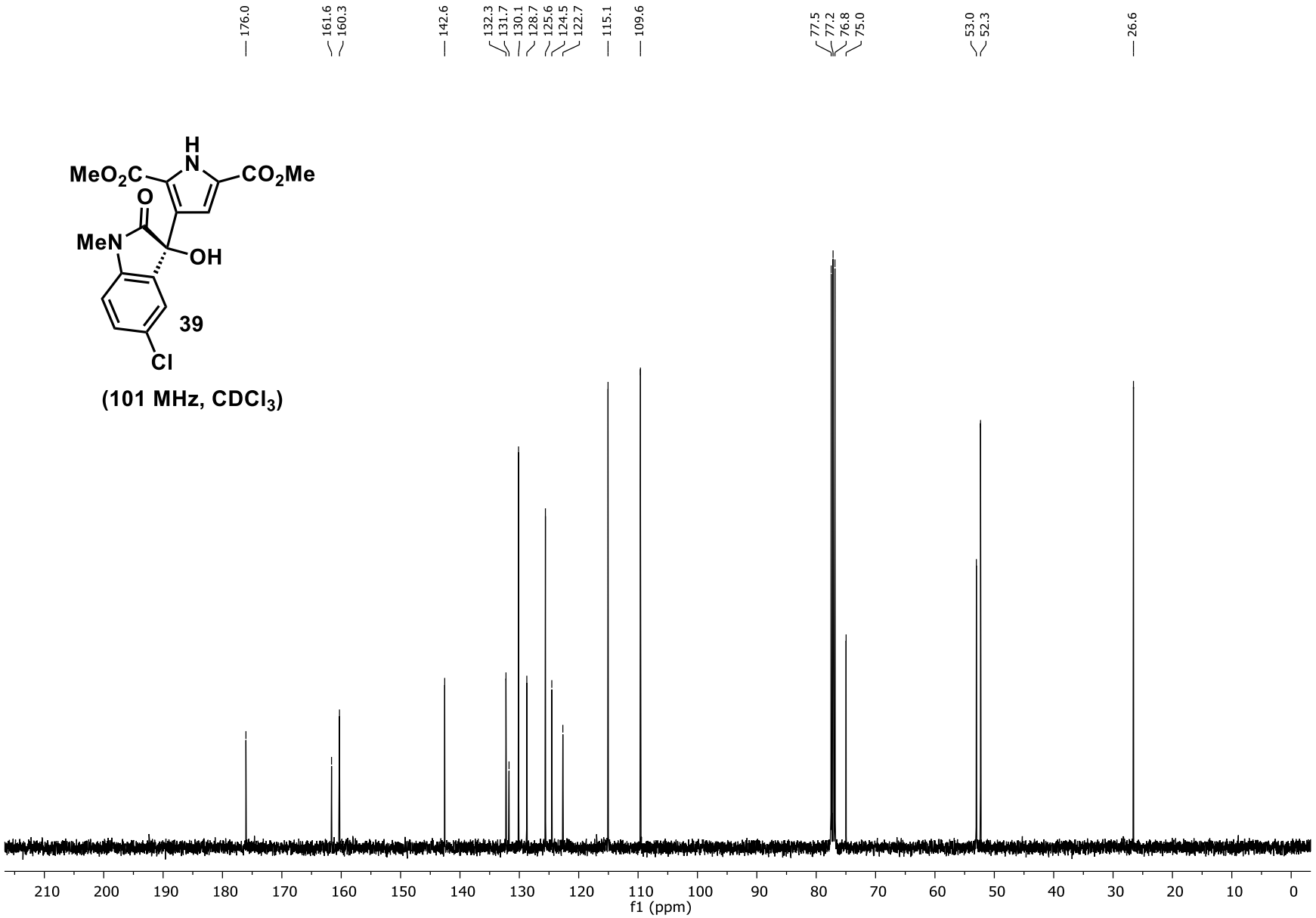
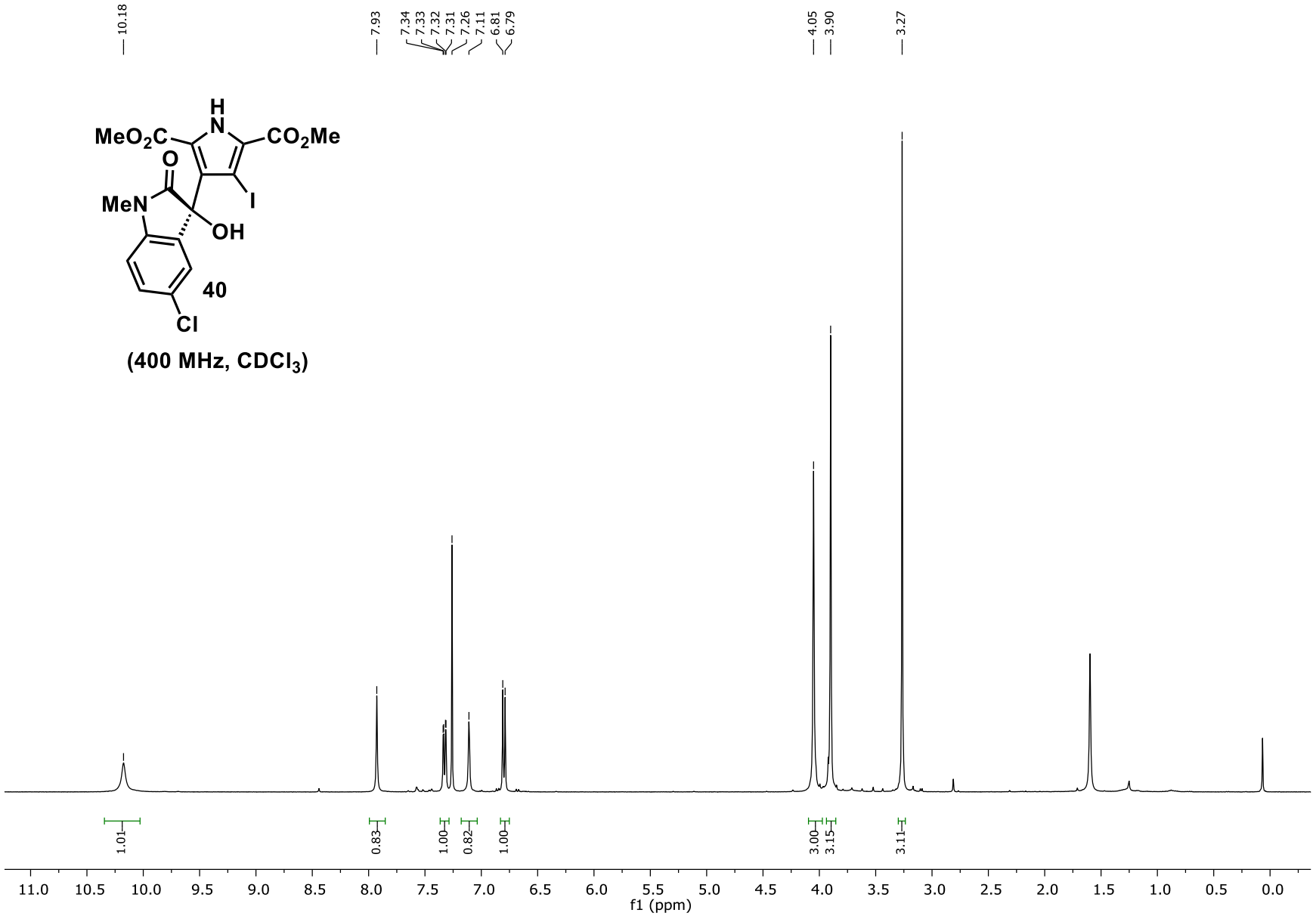
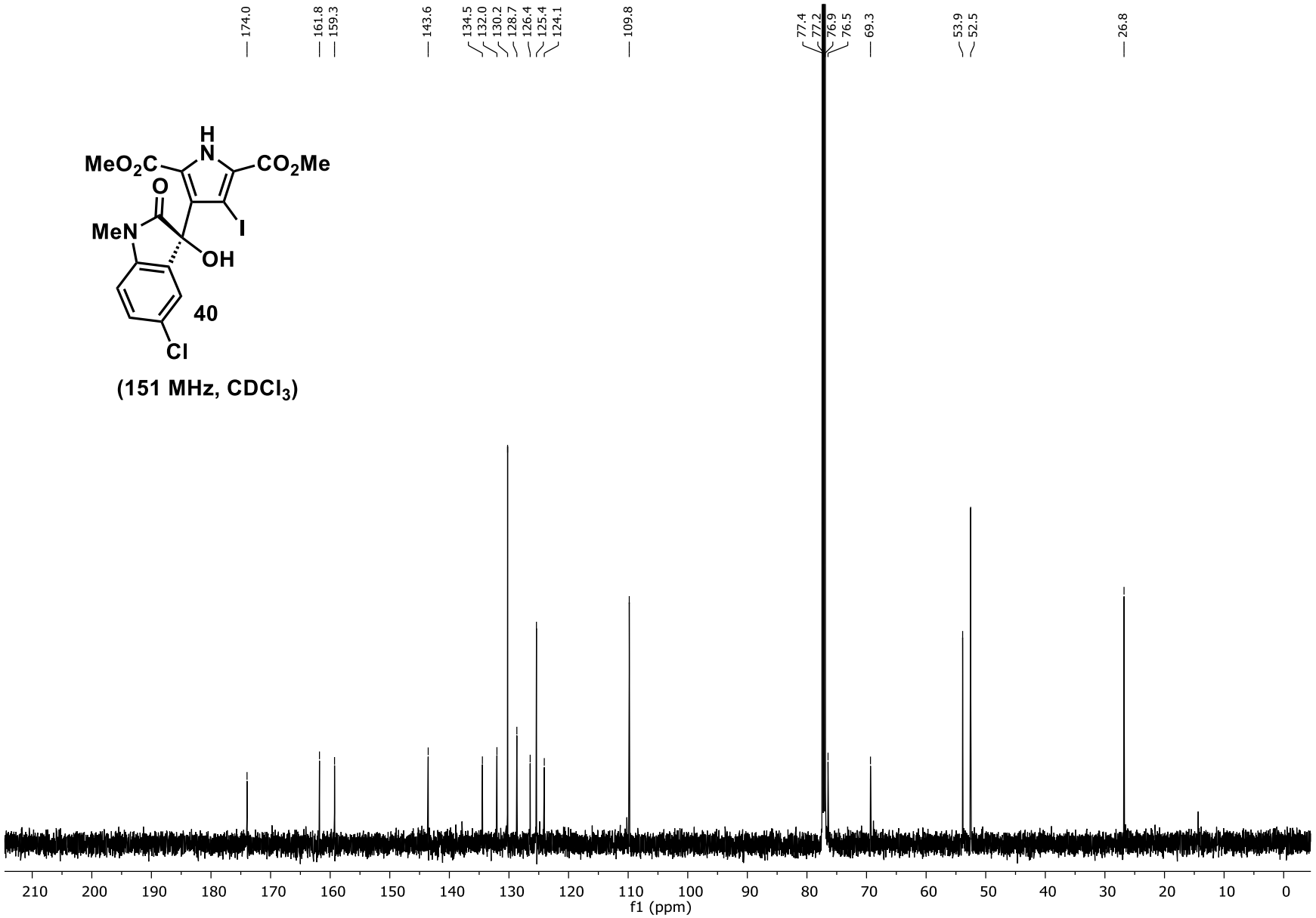
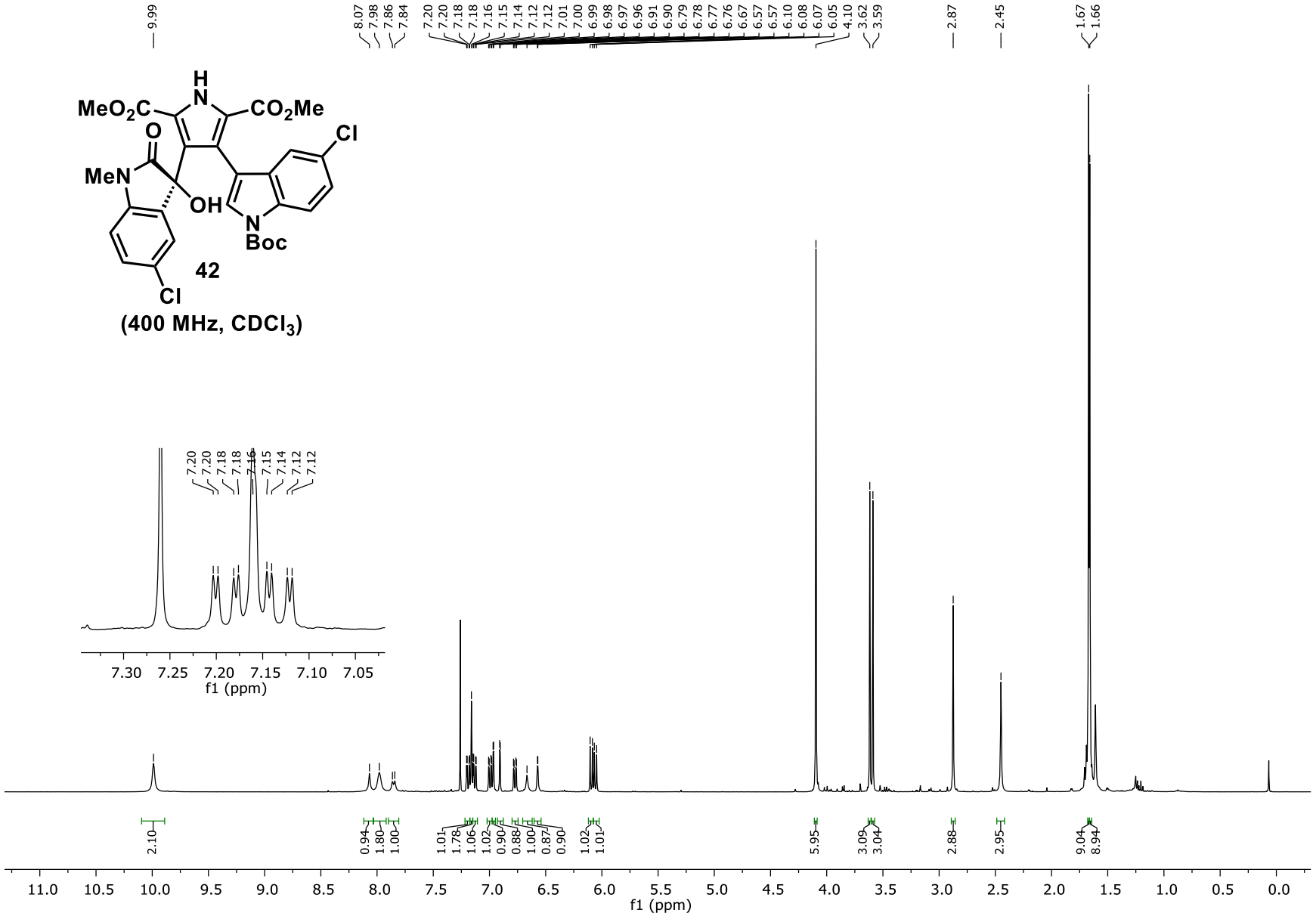
10. NMR Spectra

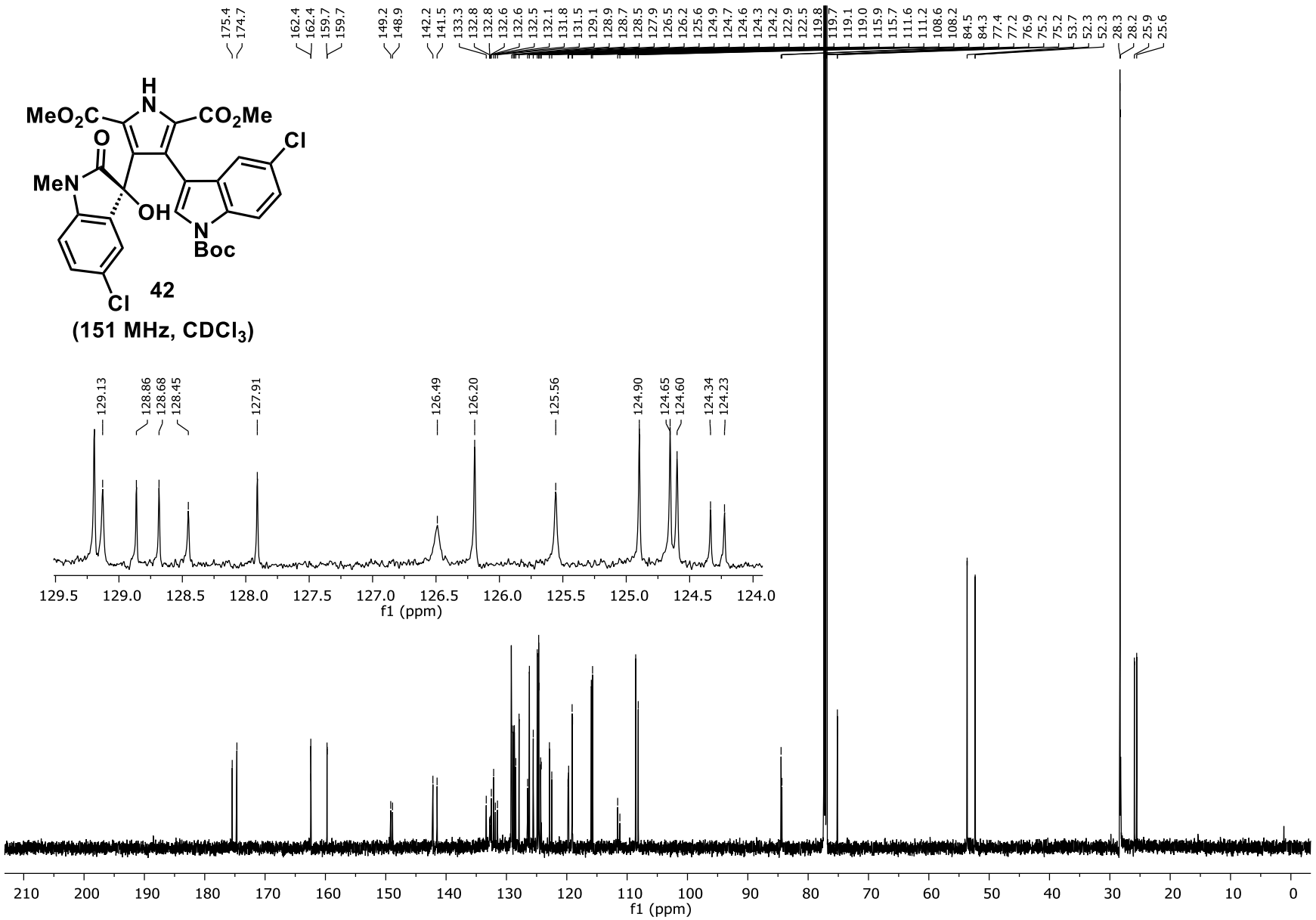


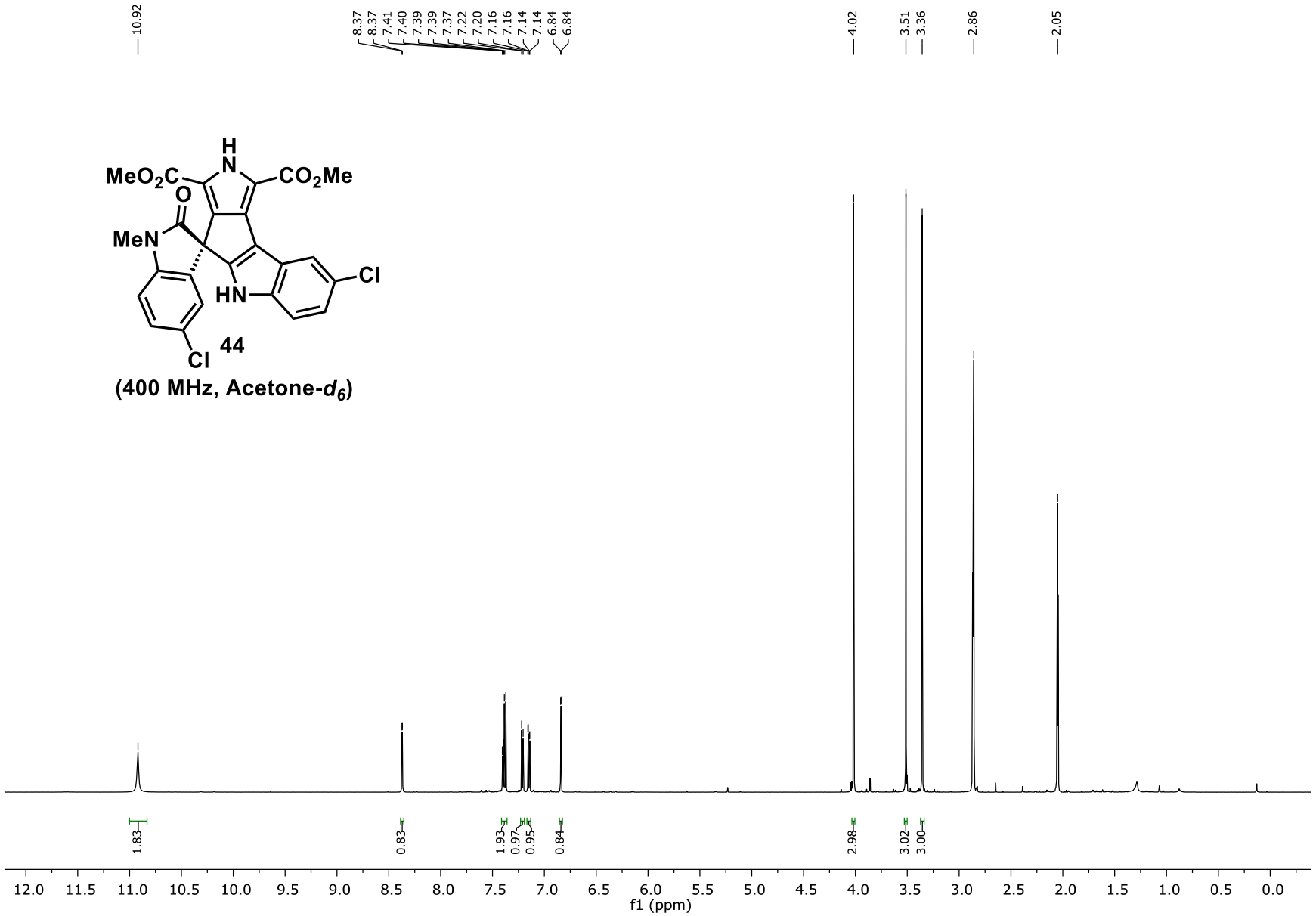

176.0
161.6
160.3
142.6
132.3
131.7
130.1
128.7
125.6
124.5
122.7
115.1
109.6
77.5
77.2
76.8
75.0
53.0
52.3
26.6
MeO2C
CO2Me
H
N
O
MeN
OH
39
Cl
(101 MHz, CDCl3)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

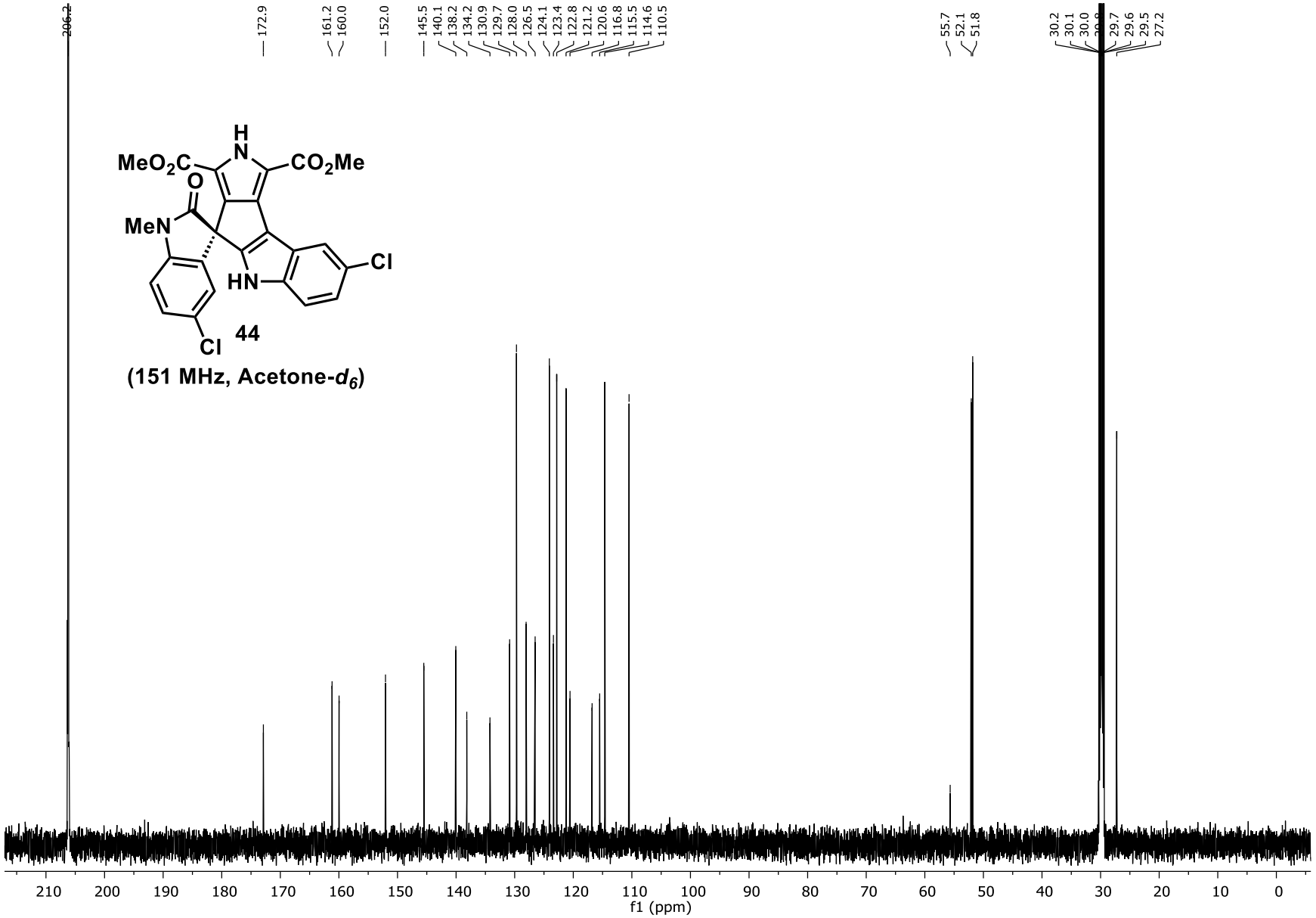

10.18
7.93
7.34
7.33
7.32
7.31
7.26
7.11
6.81
6.79
4.05
3.90
3.27
MeO2C
CO2Me
H
N
O
MeN
I
OH
40
Cl
(400 MHz, CDCl3)
1.01
0.83
1.00
0.82
1.00
3.00
3.15
3.11
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

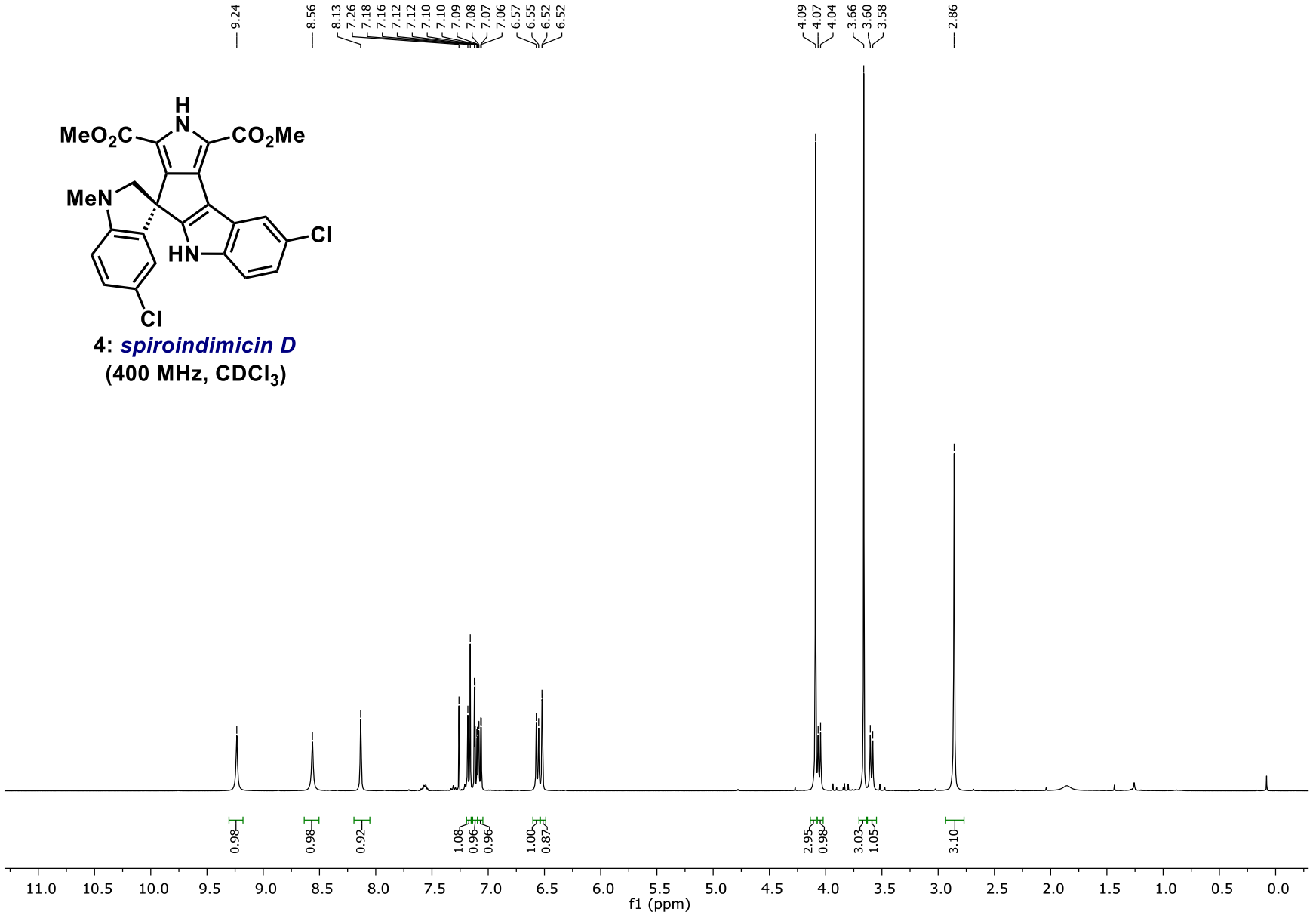

174.0
161.8
159.3
143.6
134.5
132.0
130.2
128.7
126.4
125.4
124.1
109.8
77.4
77.2
76.9
76.5
69.3
53.9
52.5
26.8
H
N
MeO2C
CO2Me
O
MeN
I
OH
40
Cl
(151 MHz, CDCl3)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


9.99
8.07
7.98
7.86
7.84
7.20
7.20
7.18
7.18
7.16
7.15
7.14
7.12
7.12
7.01
7.00
6.99
6.98
6.97
6.96
6.91
6.90
6.79
6.78
6.77
6.76
6.67
6.57
6.57
6.10
6.08
6.07
6.05
4.10
3.62
3.59
2.87
2.45
1.67
1.66
MeO2C
CO2Me
O
MeN
OH
N
Boc
Cl
Cl
42
(400 MHz, CDCl3)
f1 (ppm)
f1 (ppm)
2.10
0.94
1.80
1.00
1.01
1.78
1.06
1.02
0.90
0.88
1.00
0.87
0.90
1.02
1.01
5.95
3.09
3.04
2.88
2.95
9.04
8.94

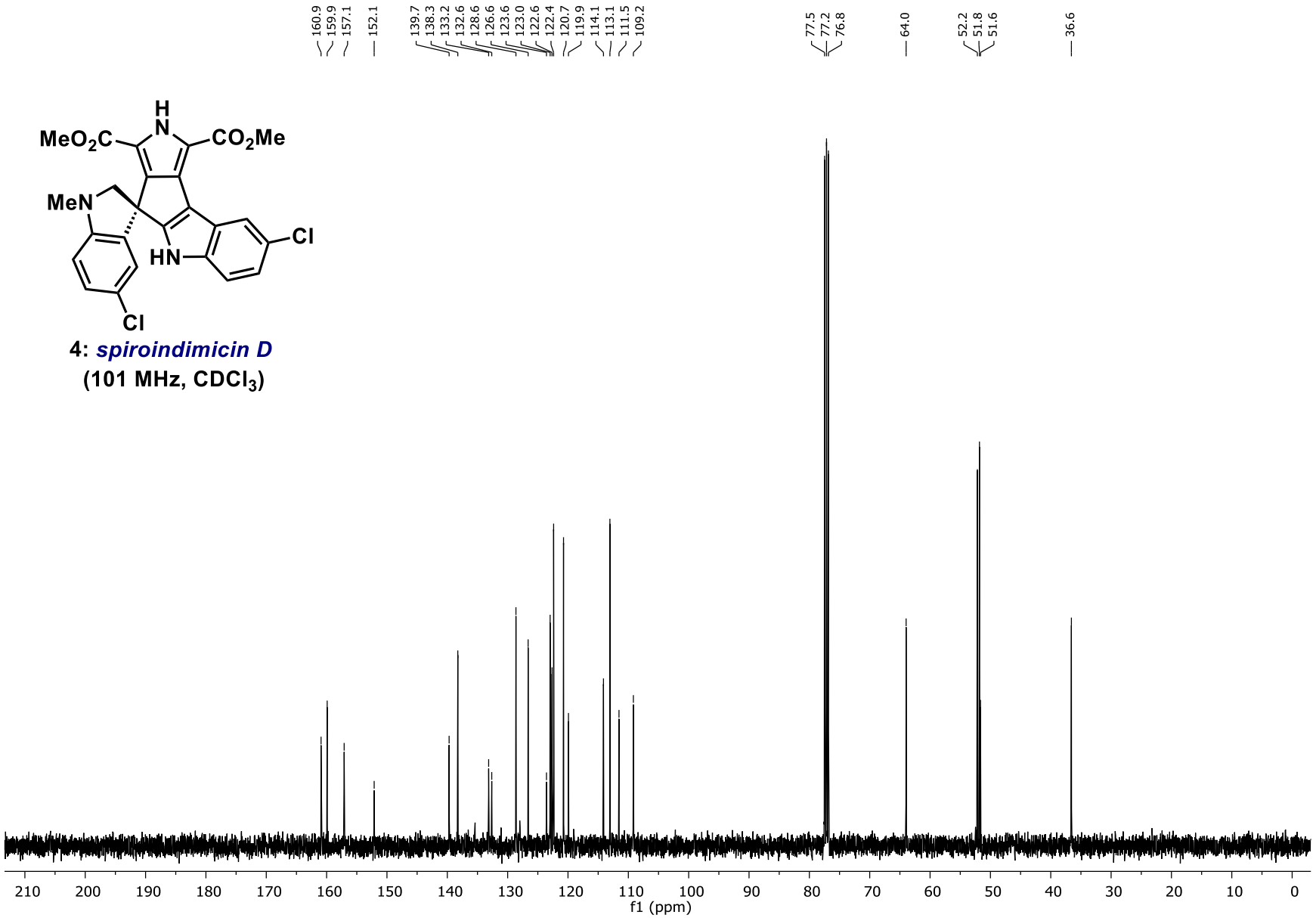

MeO2C
CO2Me
Cl
O
MeN
OH
N
Boc
Cl
42
(151 MHz, CDCl3)
f1 (ppm)
f1 (ppm)

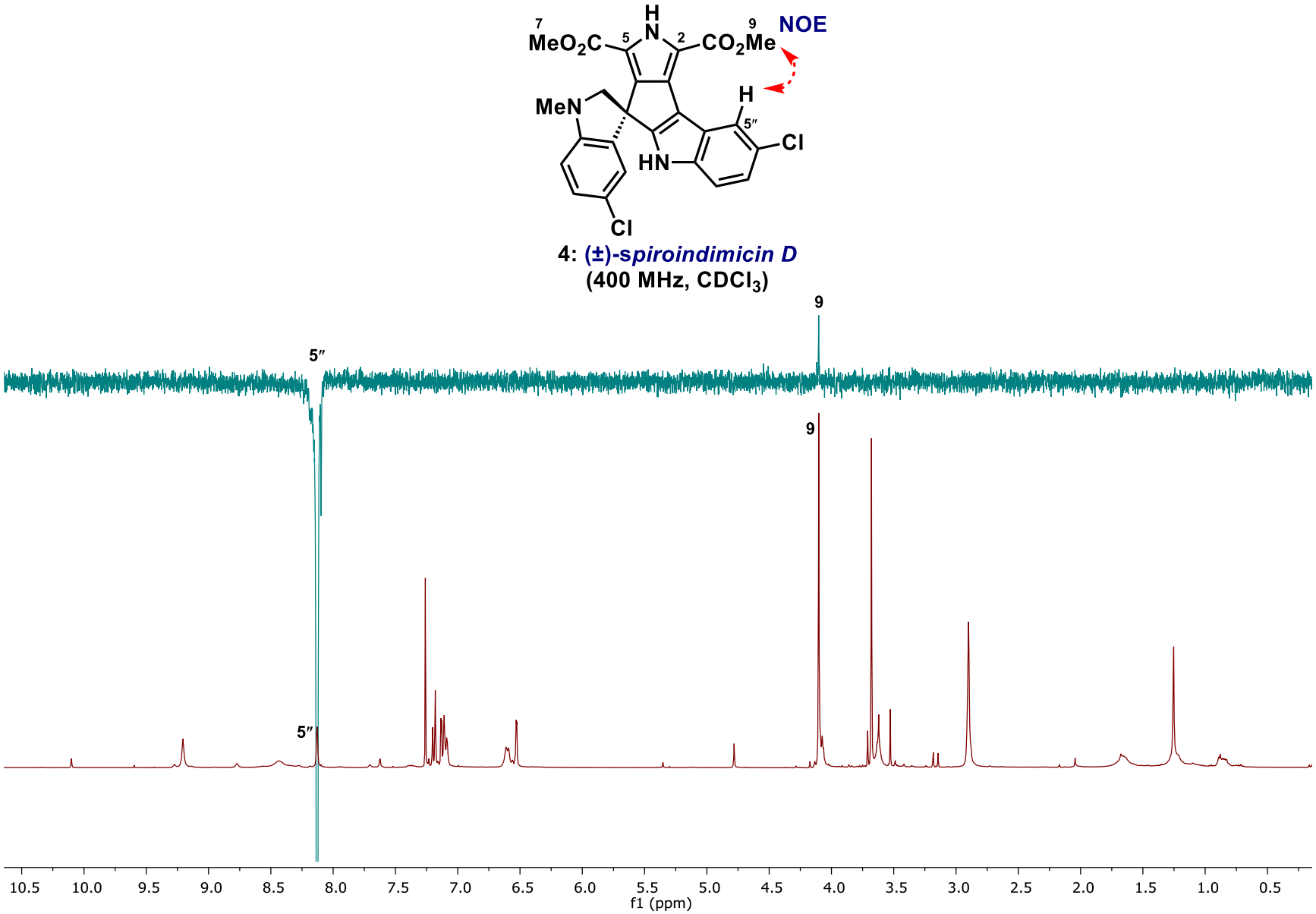

10.92
8.37
8.37
7.41
7.40
7.39
7.39
7.37
7.22
7.20
7.16
7.16
7.14
7.14
6.84
6.84
4.02
3.51
3.36
2.86
2.05
MeO2C
CO2Me
O
MeN
HN
Cl
Cl
44
(400 MHz, Acetone-d6)
1.83
0.83
1.93
0.97
0.95
0.84
2.98
3.02
3.00
f1 (ppm)

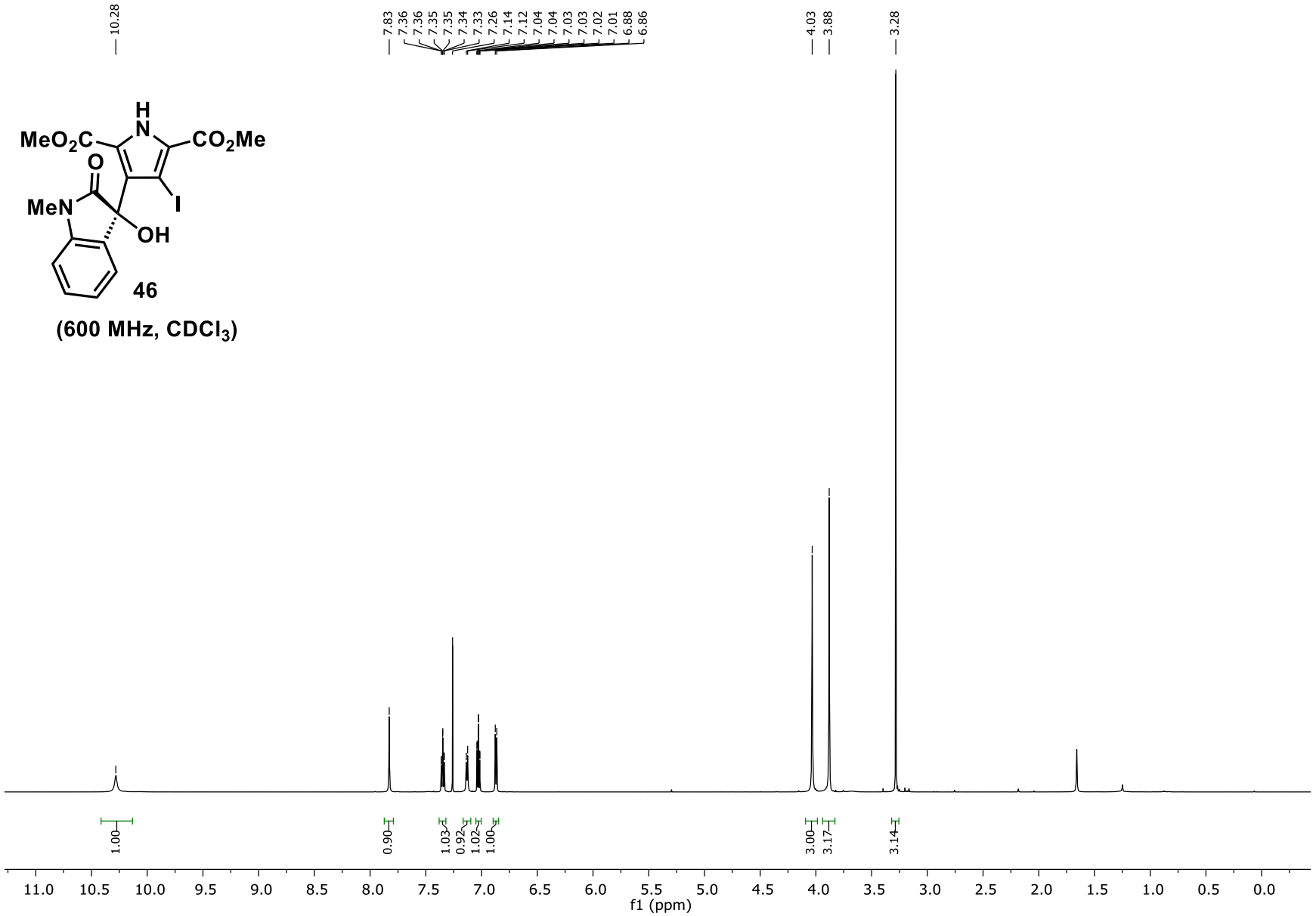

206.2
172.9
161.2
160.0
152.0
145.5
140.1
138.2
134.2
130.9
129.7
128.0
126.5
124.1
123.4
122.8
121.2
120.6
116.8
115.5
114.6
110.5
55.7
52.1
51.8
30.2
30.1
30.0
29.7
29.6
29.5
27.2
MeO2C
CO2Me
MeN
HN
Cl
Cl
44
(151 MHz, Acetone-d6)
f1 (ppm)

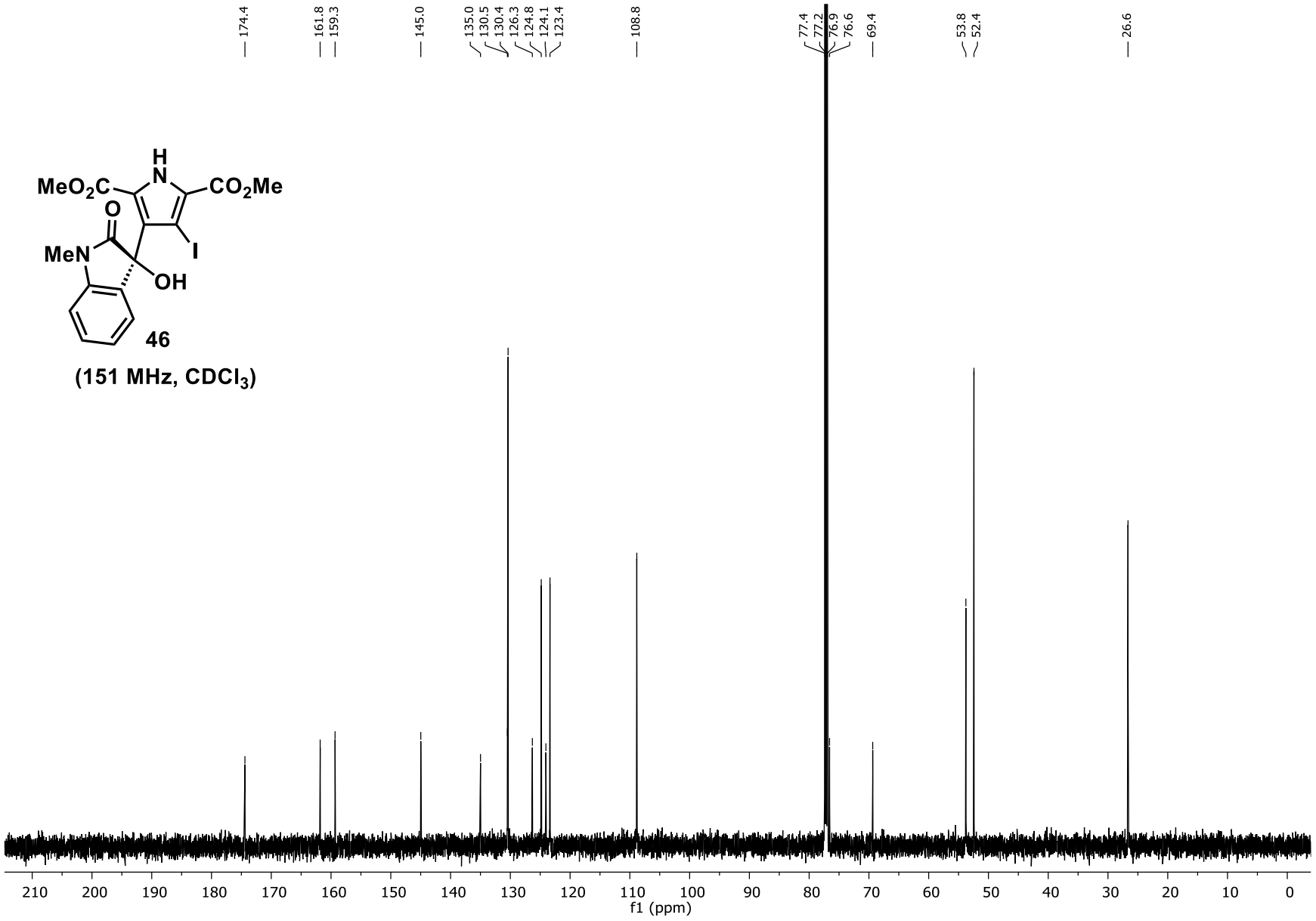


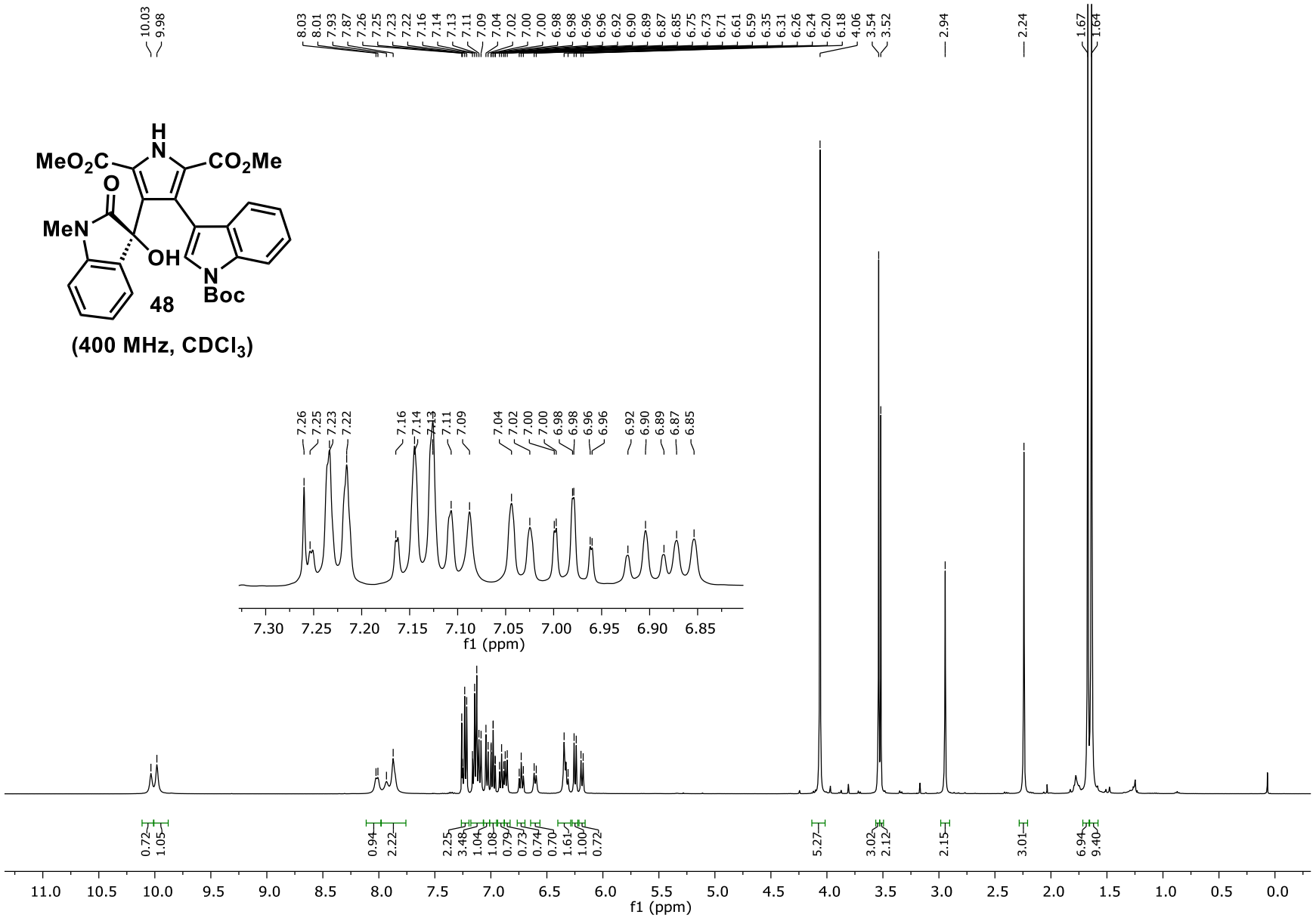
4: *spiroindimicin D*
(400 MHz, $CDCl_3$)

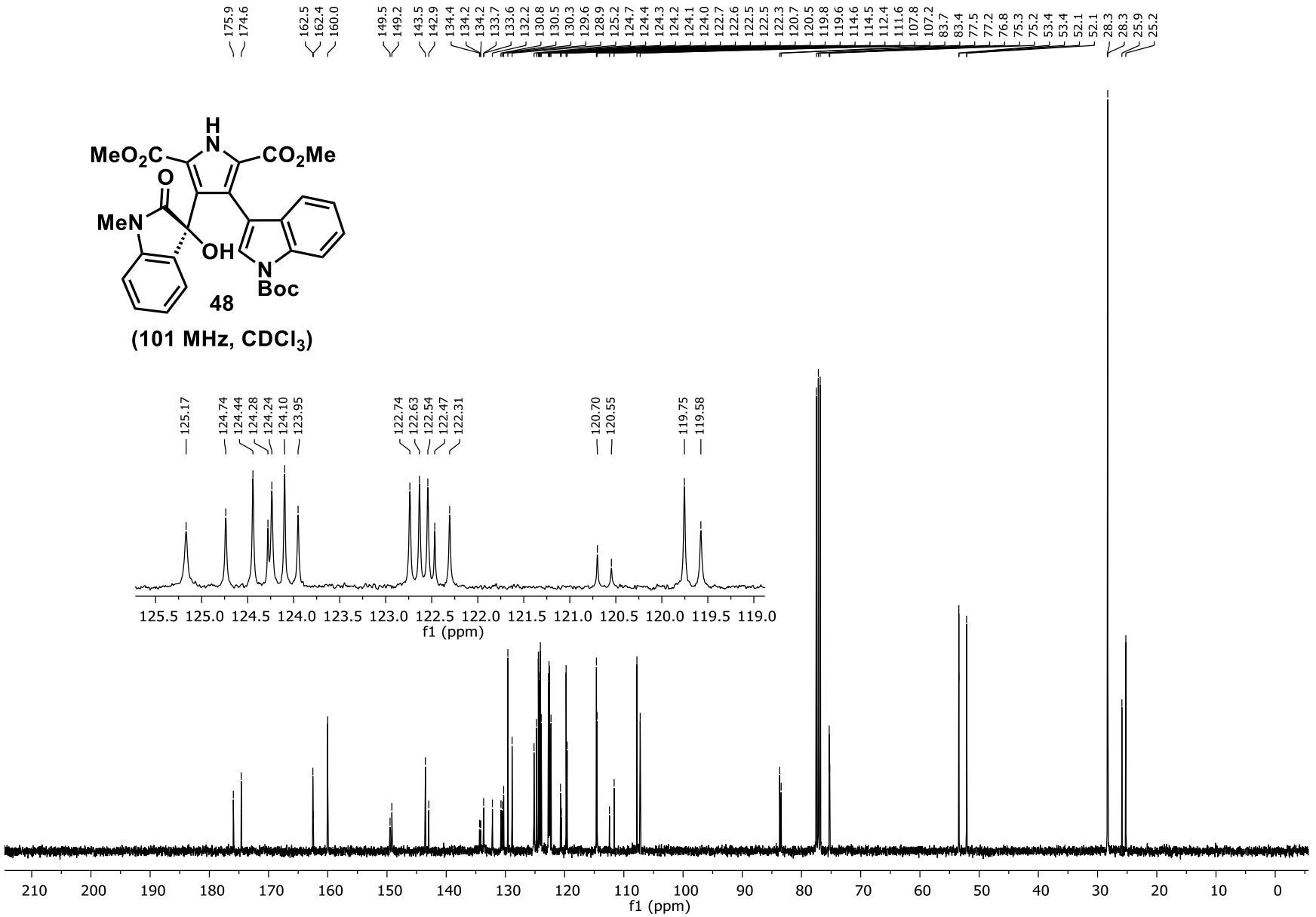

160.9
159.9
157.1
152.1
139.7
138.3
133.2
132.6
128.6
126.6
123.6
123.0
122.6
122.4
120.7
119.9
114.1
113.1
111.5
109.2
77.5
77.2
76.8
64.0
52.2
51.8
51.6
36.6
MeO2C
CO2Me
MeN
HN
Cl
Cl
4: spiroindimicin D
(101 MHz, CDCl3)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

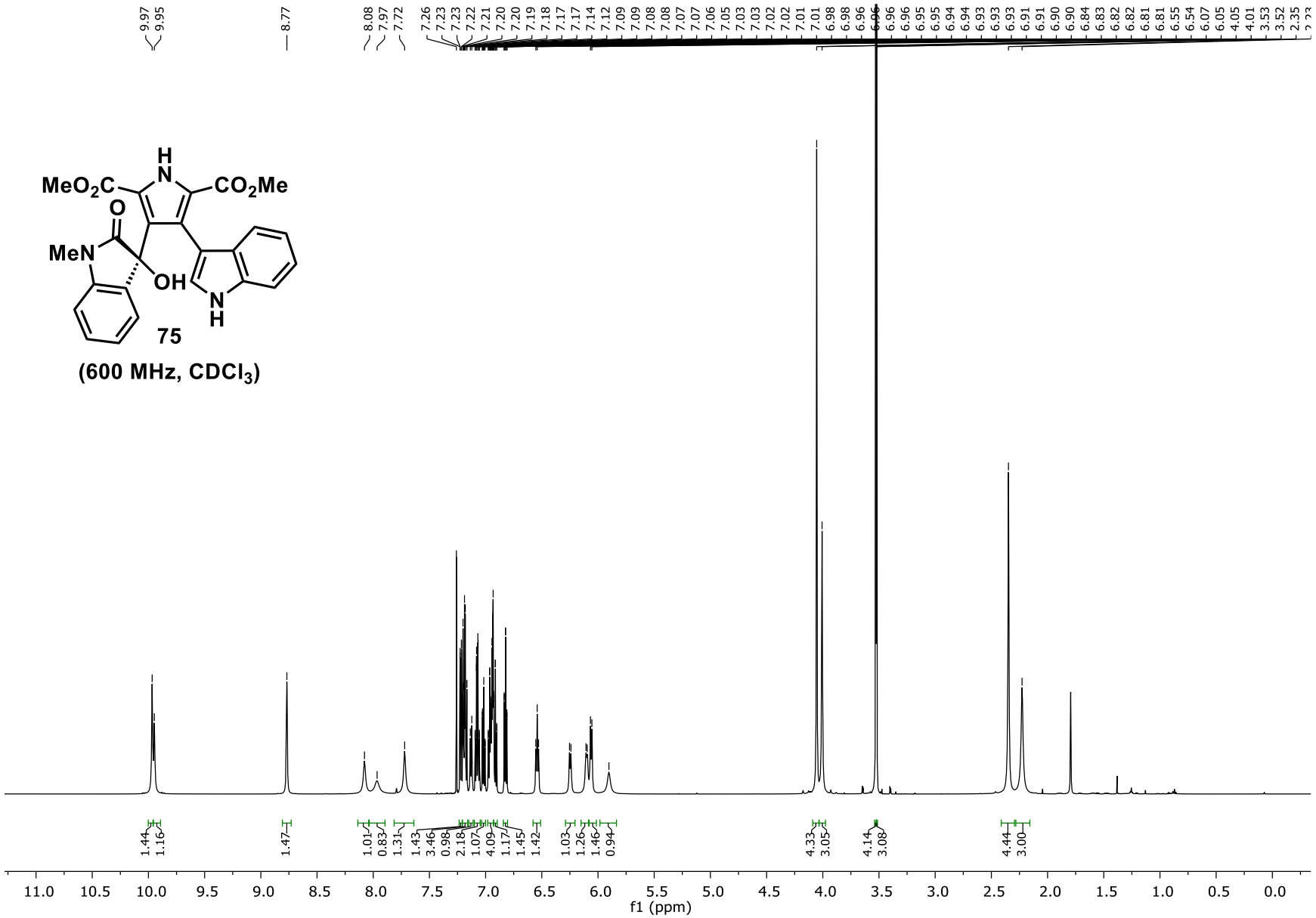

NOE
MeO2C
CO2Me
MeN
HN
Cl
Cl
H
4: (±)-spiroindimicin D
(400 MHz, CDCl3)
9
5″
9
5″
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

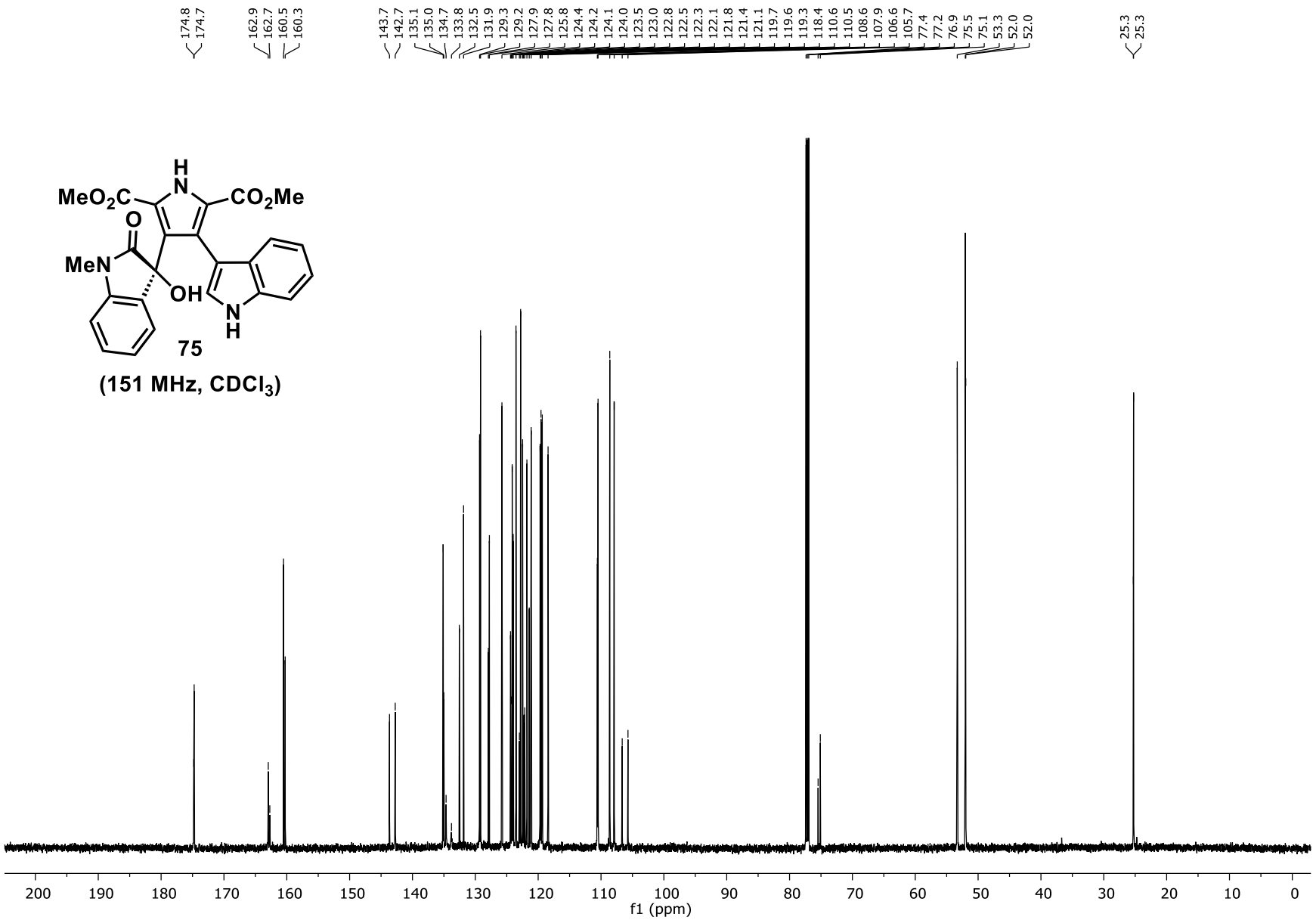

10.28
7.83
7.36
7.36
7.35
7.35
7.34
7.33
7.26
7.14
7.12
7.04
7.04
7.03
7.03
7.02
7.01
6.88
6.86
4.03
3.88
3.28
MeO2C
CO2Me
H
N
O
MeN
I
OH
46
(600 MHz, CDCl3)
1.00
0.90
1.03
0.92
1.02
1.00
3.00
3.17
3.14
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

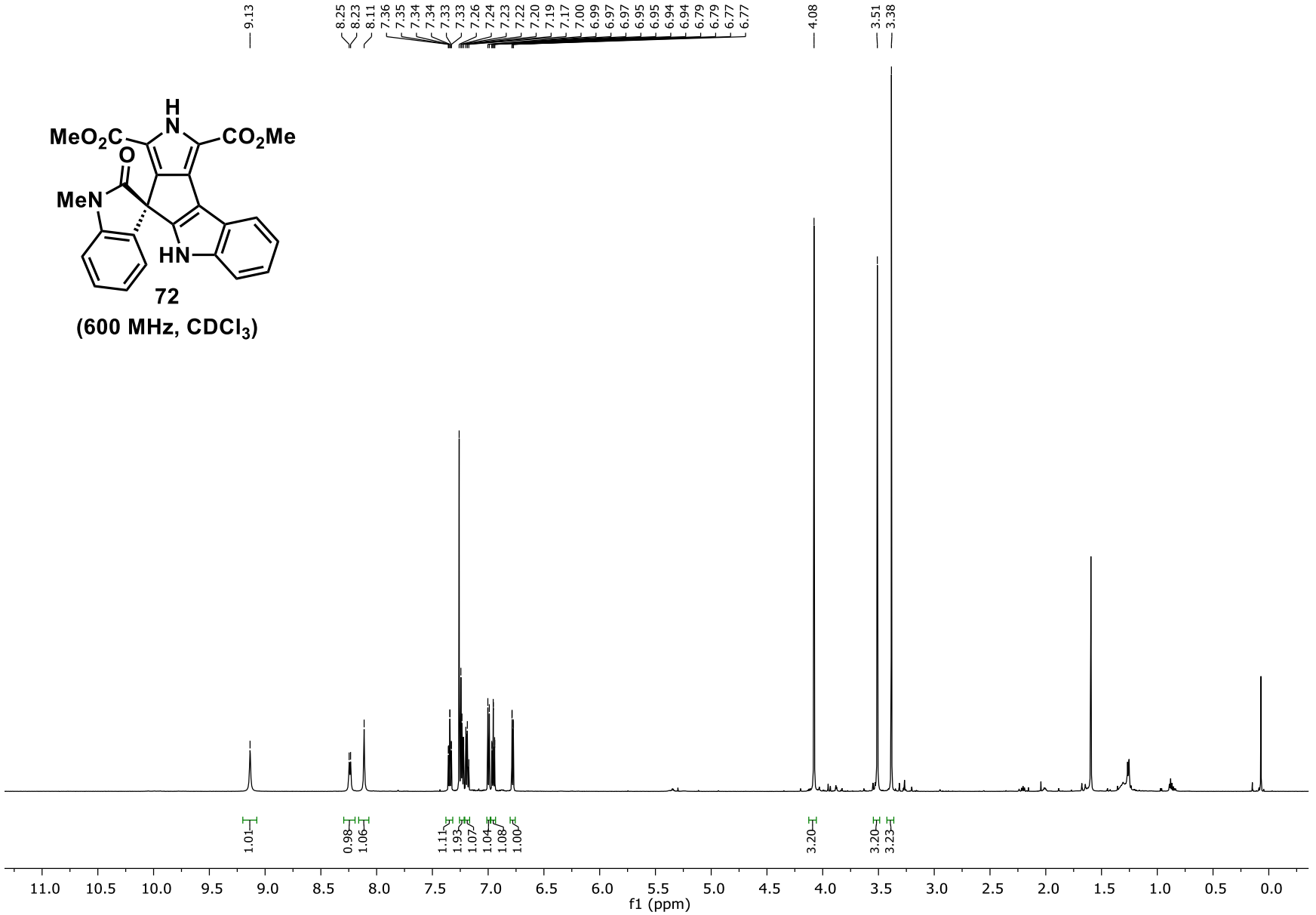

174.4
161.8
159.3
145.0
135.0
130.5
130.4
126.3
124.8
124.1
123.4
108.8
77.4
77.2
76.9
76.6
69.4
53.8
52.4
26.6
MeO2C
CO2Me
O
MeN
I
OH
46
(151 MHz, CDCl3)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

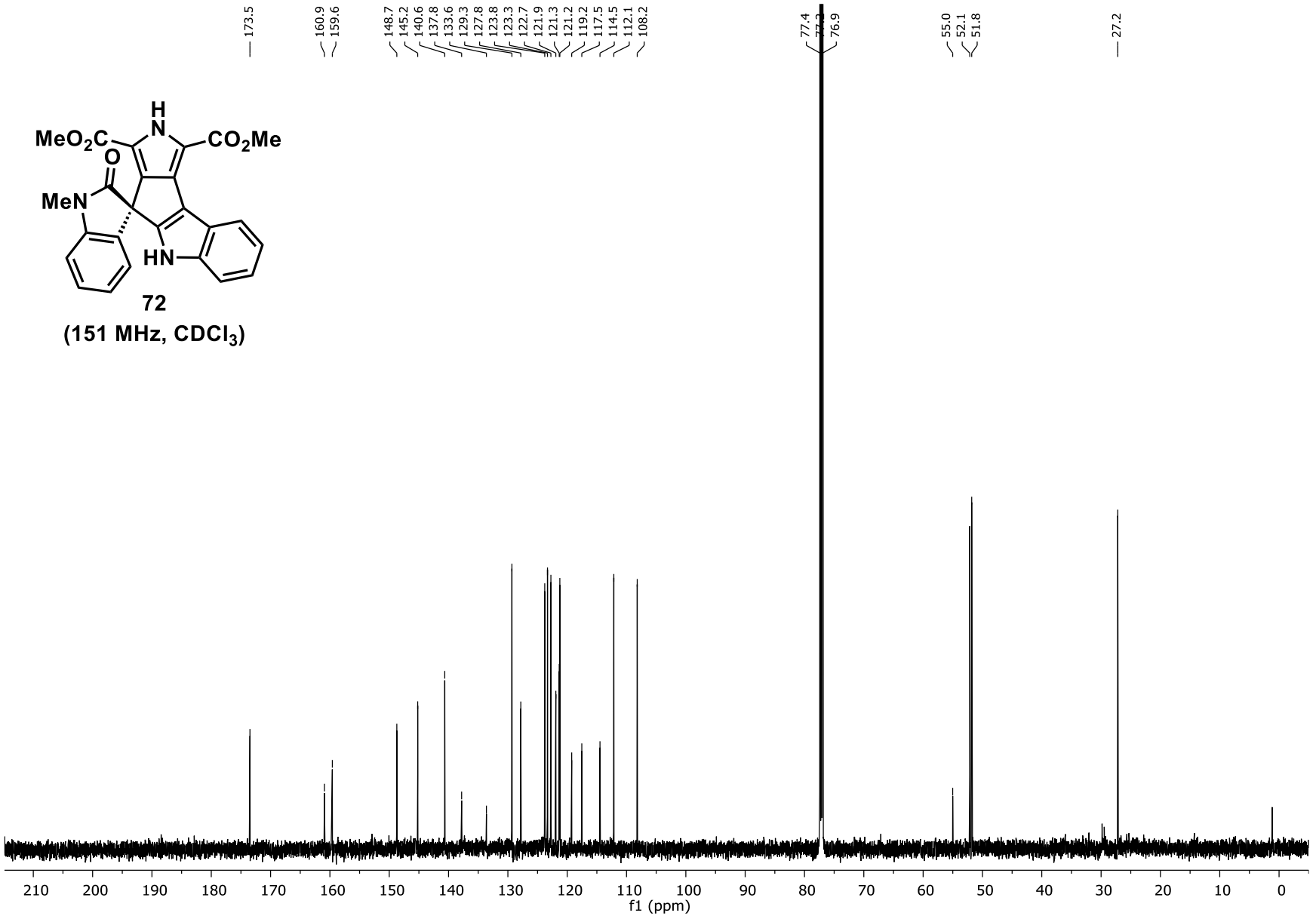

MeO2C
CO2Me
MeN
OH
N
Boc
48
(400 MHz, CDCl3)
f1 (ppm)

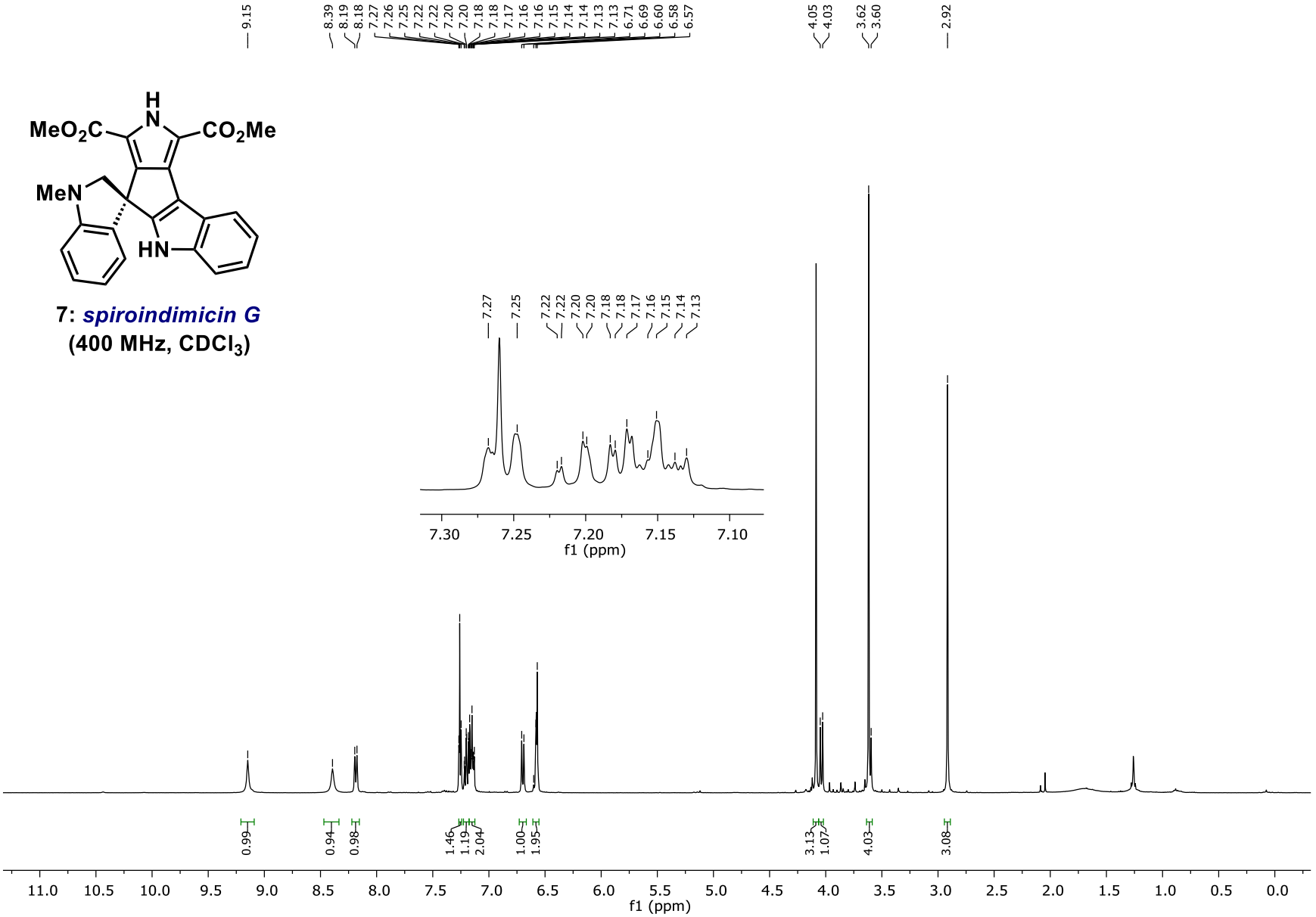

175.9
174.6
162.5
162.4
160.0
149.5
149.2
143.5
142.9
134.4
134.2
134.2
133.7
133.6
132.2
130.8
130.5
130.3
129.6
128.9
125.2
124.7
124.4
124.3
124.2
124.1
124.0
122.7
122.6
122.5
122.5
122.3
120.7
120.5
119.8
119.6
114.6
114.5
112.4
111.6
107.8
107.2
83.7
83.4
77.5
77.2
76.8
75.3
75.2
53.4
53.4
52.1
52.1
28.3
28.3
25.9
25.2
H
N
MeO2C
CO2Me
O
MeN
OH
N
Boc
48
(101 MHz, CDCl3)
125.17
124.74
124.44
124.28
124.24
124.10
123.95
122.74
122.63
122.54
122.47
122.31
120.70
120.55
119.75
119.58
125.5 125.0 124.5 124.0 123.5 123.0 122.5 122.0 121.5 121.0 120.5 120.0 119.5 119.0
f1 (ppm)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

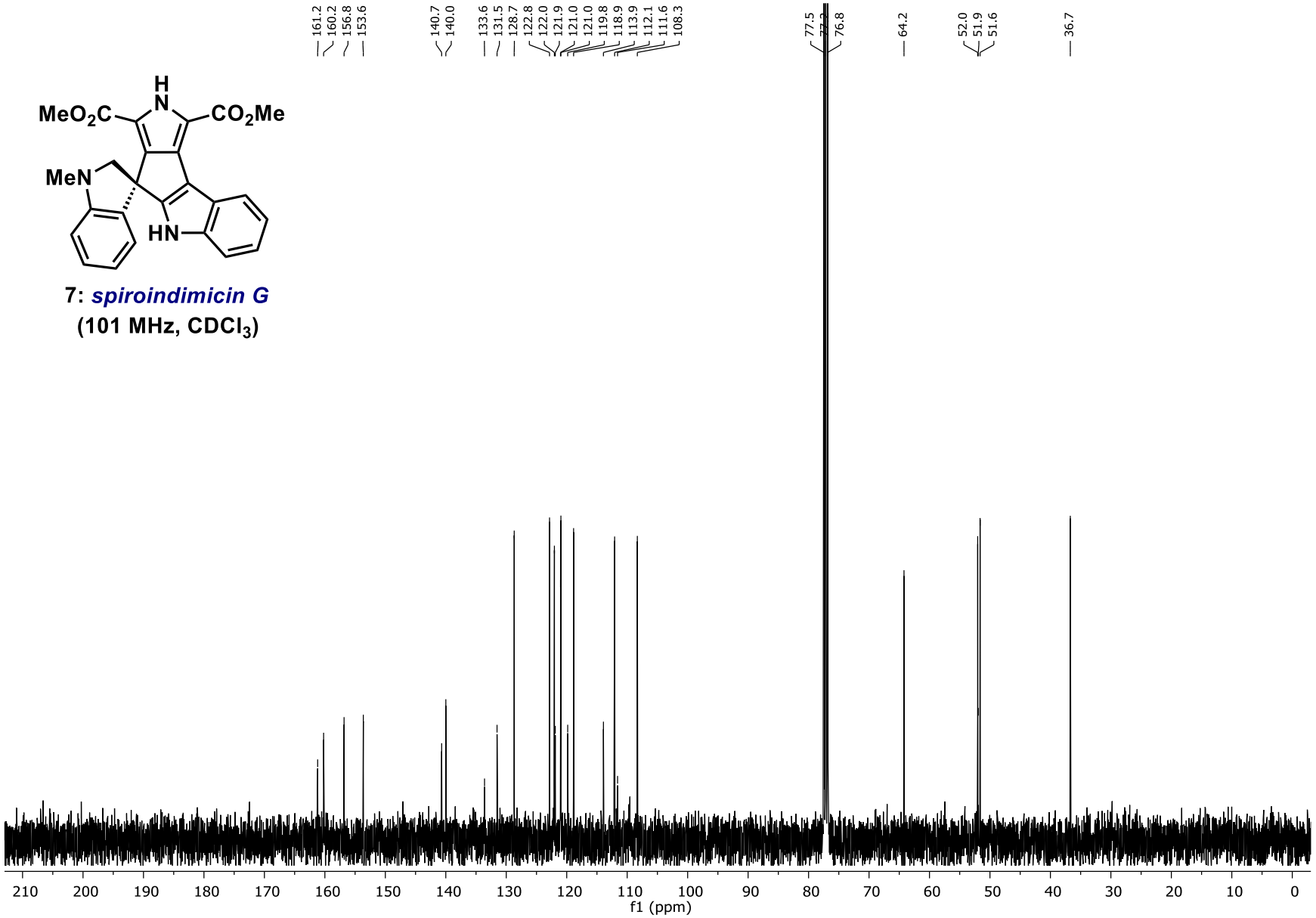

MeO2C
CO2Me
MeN
OH
75
(600 MHz, CDCl3)
f1 (ppm)


174.8
174.7
162.9
162.7
160.5
160.3
143.7
142.7
135.1
135.0
134.7
133.8
132.5
131.9
129.3
129.2
127.9
127.8
125.8
124.4
124.2
124.1
124.0
123.5
123.0
122.8
122.5
122.3
122.1
121.8
121.4
121.1
119.7
119.6
119.3
118.4
110.6
110.5
108.6
107.9
106.6
105.7
77.4
77.2
76.9
75.5
75.1
53.3
52.0
52.0
25.3
25.3
MeO2C
CO2Me
O
MeN
OH
H
N
N
H
75
(151 MHz, CDCl3)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

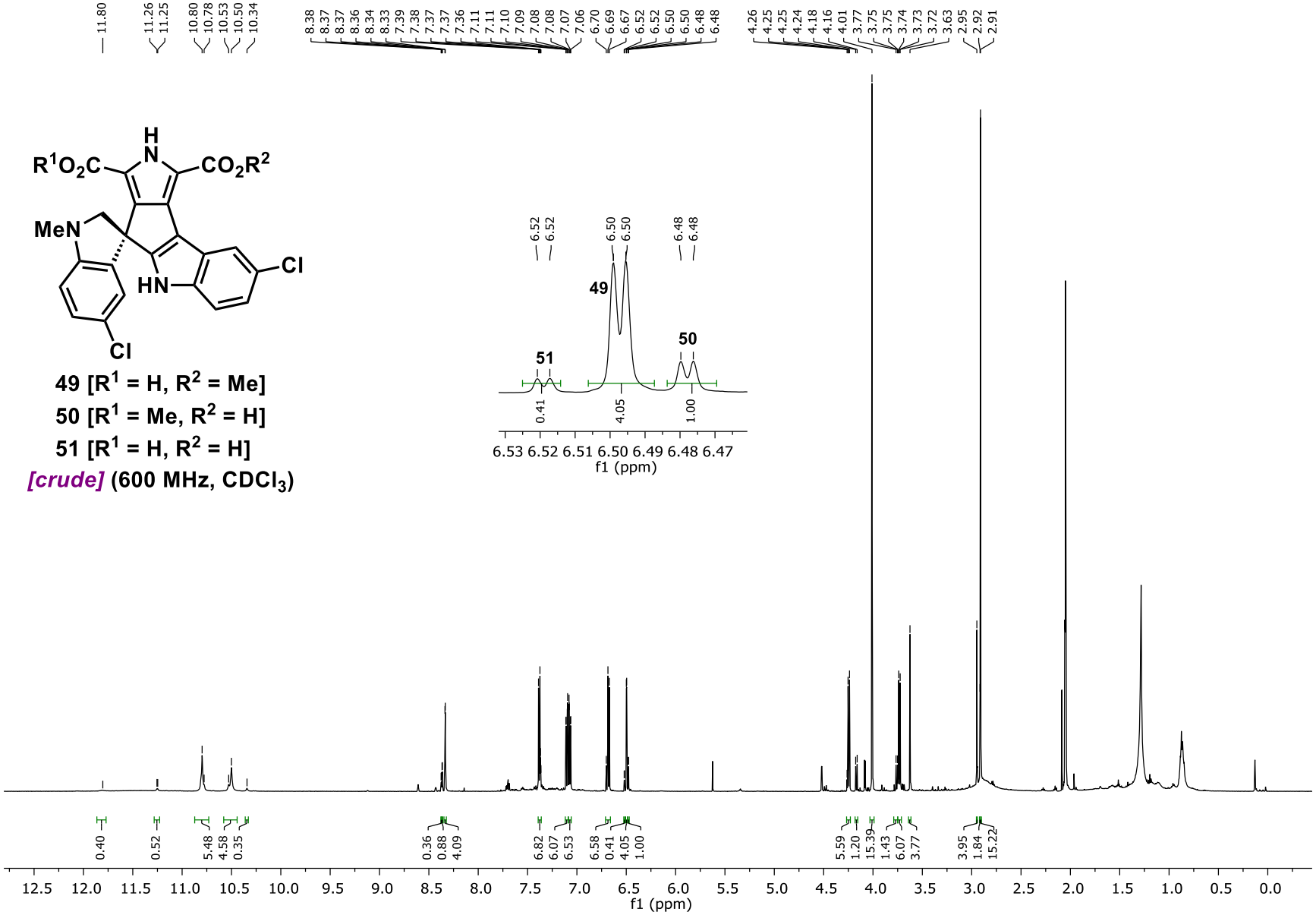

9.13
8.25
8.23
8.11
7.36
7.35
7.34
7.34
7.33
7.33
7.26
7.24
7.23
7.22
7.20
7.19
7.17
7.00
6.99
6.97
6.97
6.95
6.95
6.94
6.94
6.79
6.79
6.77
6.77
4.08
3.51
3.38
MeO2C
CO2Me
O
MeN
H
N
HN
72
(600 MHz, CDCl3)
1.01
0.98
1.06
1.11
1.93
1.07
1.04
1.08
1.00
3.20
3.20
3.23
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

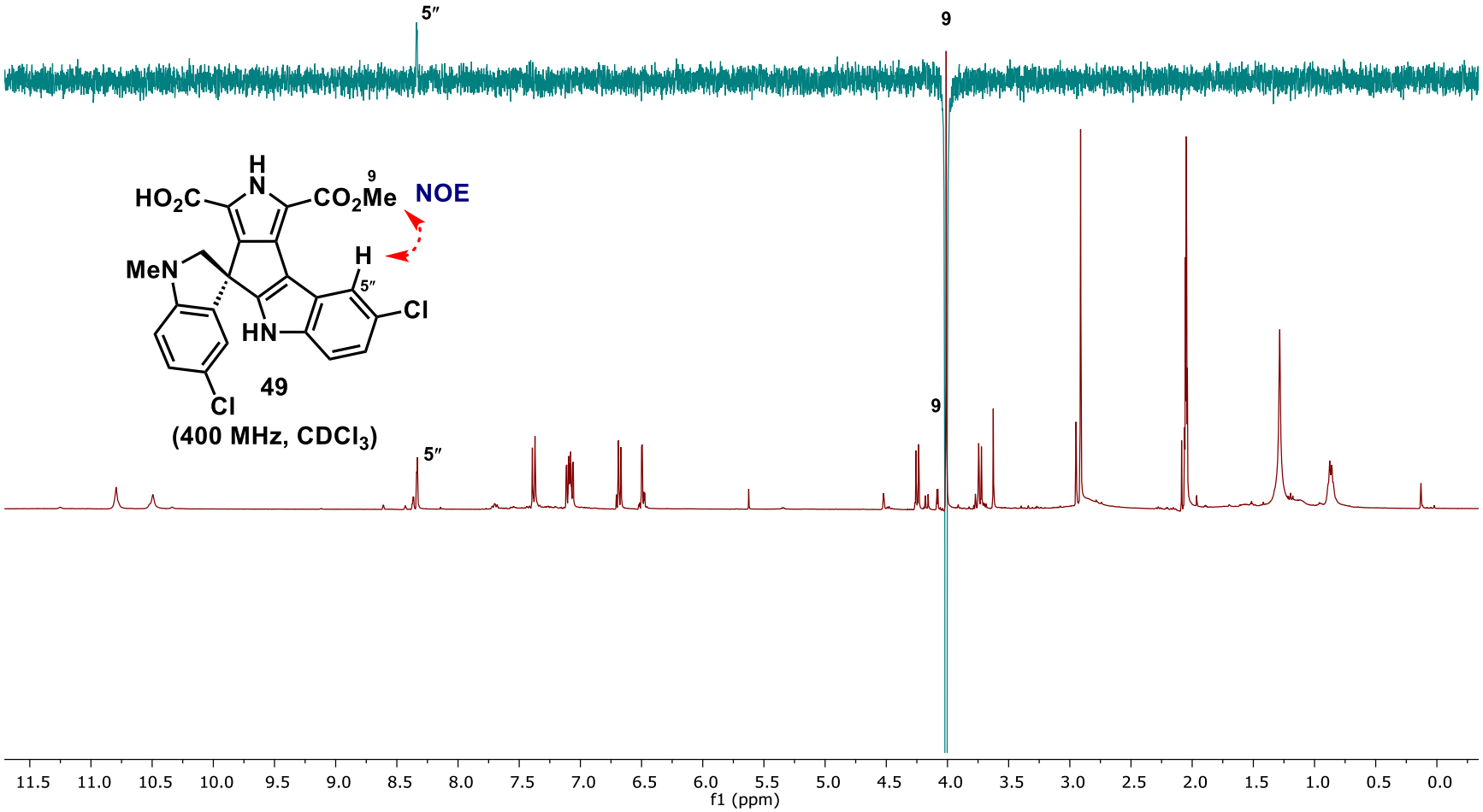

173.5
160.9
159.6
148.7
145.2
140.6
137.8
133.6
129.3
127.8
123.8
123.3
122.7
121.9
121.3
121.2
119.2
117.5
114.5
112.1
108.2
77.4
76.9
55.0
52.1
51.8
27.2
MeO2C
CO2Me
O
MeN
H
N
HN
72
(151 MHz, CDCl3)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

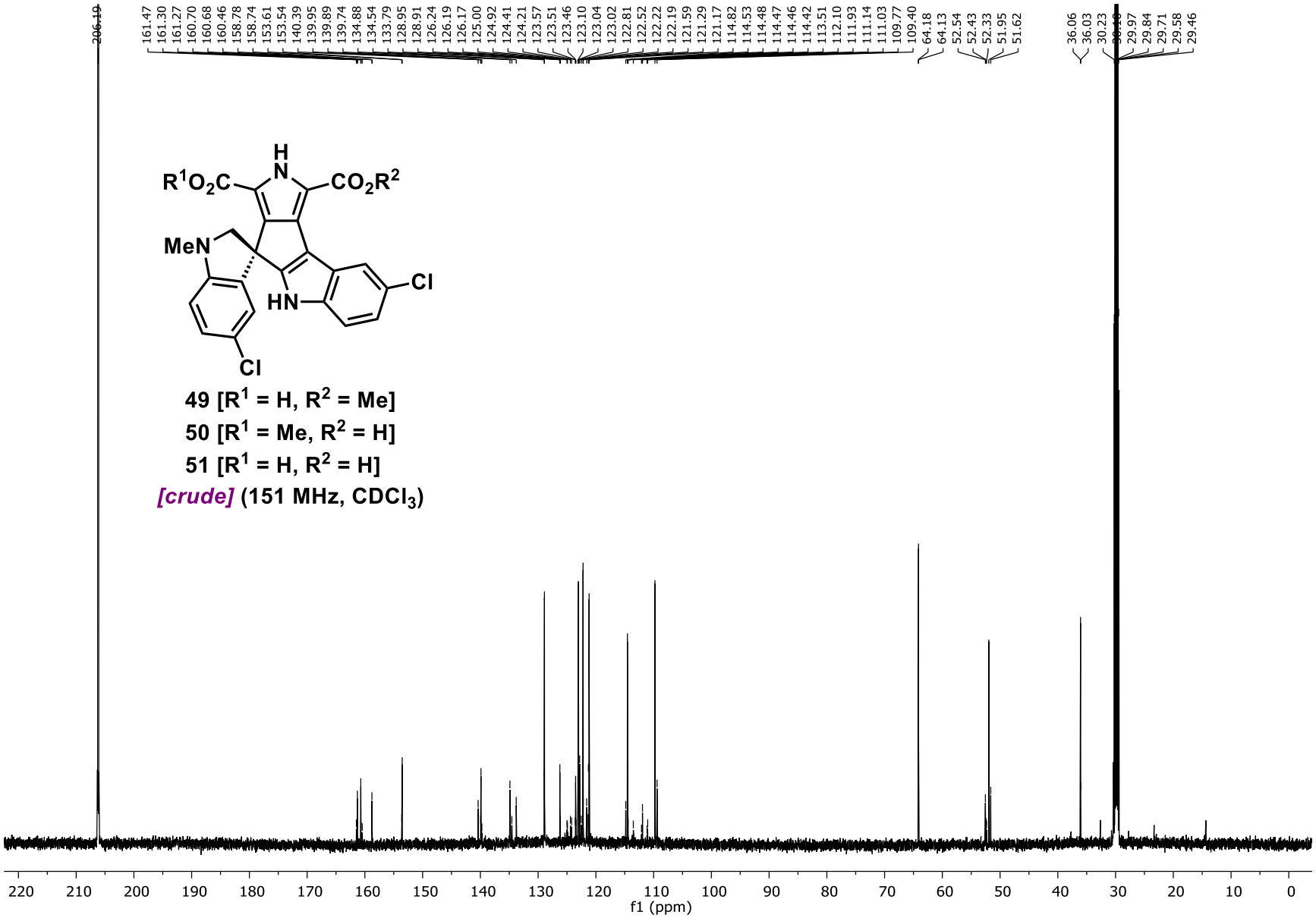

9.15
8.39
8.19
8.18
7.27
7.26
7.25
7.22
7.22
7.20
7.20
7.18
7.18
7.17
7.16
7.16
7.15
7.14
7.14
7.13
6.71
6.69
6.60
6.58
6.57
4.05
4.03
3.62
3.60
2.92
MeO2C
CO2Me
MeN
HN
H
N
7: spiroindimicin G
(400 MHz, CDCl3)
7.27
7.25
7.22
7.22
7.20
7.20
7.18
7.18
7.17
7.16
7.15
7.14
7.13
7.30
7.25
7.20
7.15
7.10
f1 (ppm)
0.99
0.94
0.98
1.46
1.19
2.04
1.00
1.95
3.13
1.07
4.03
3.08
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

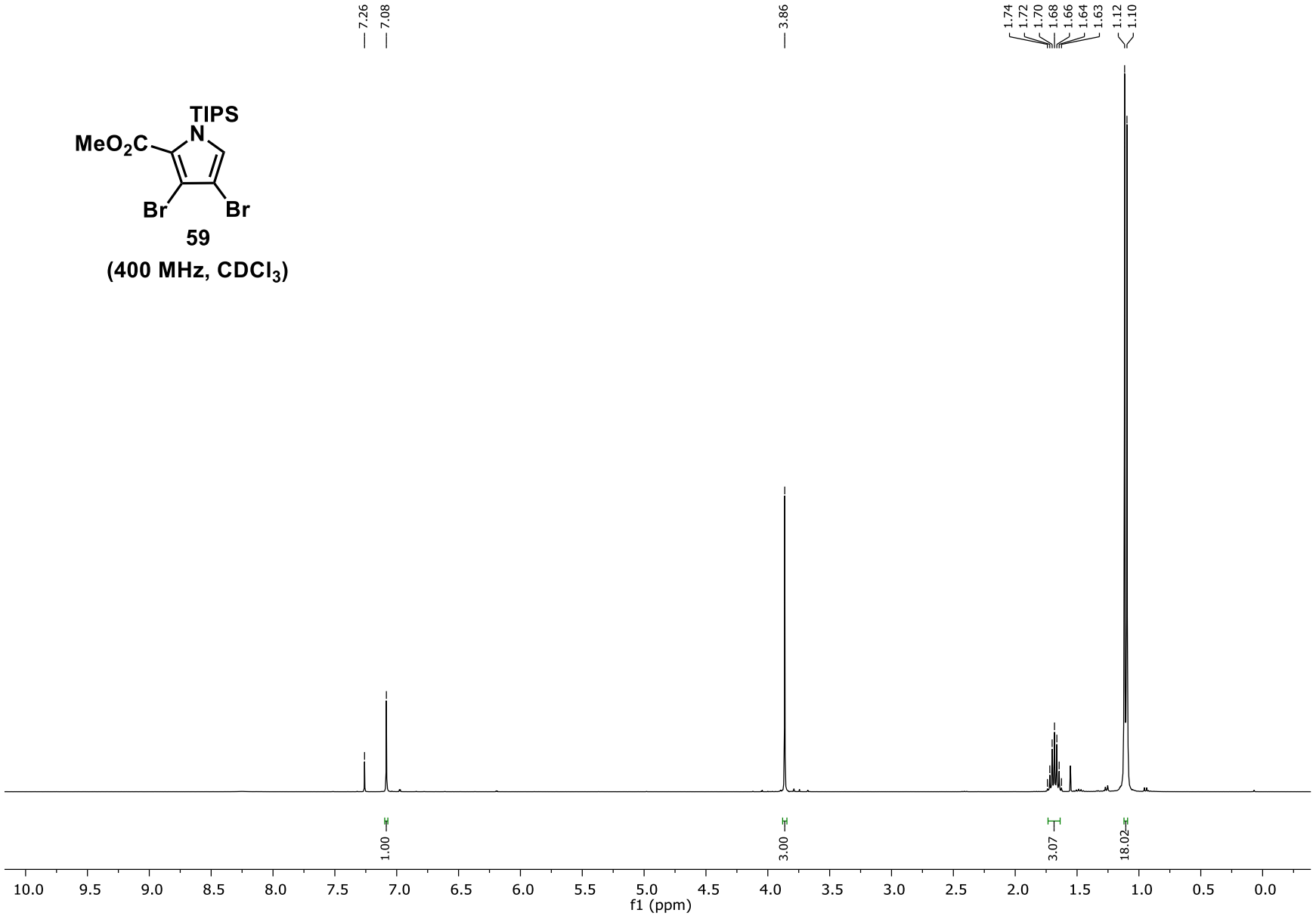


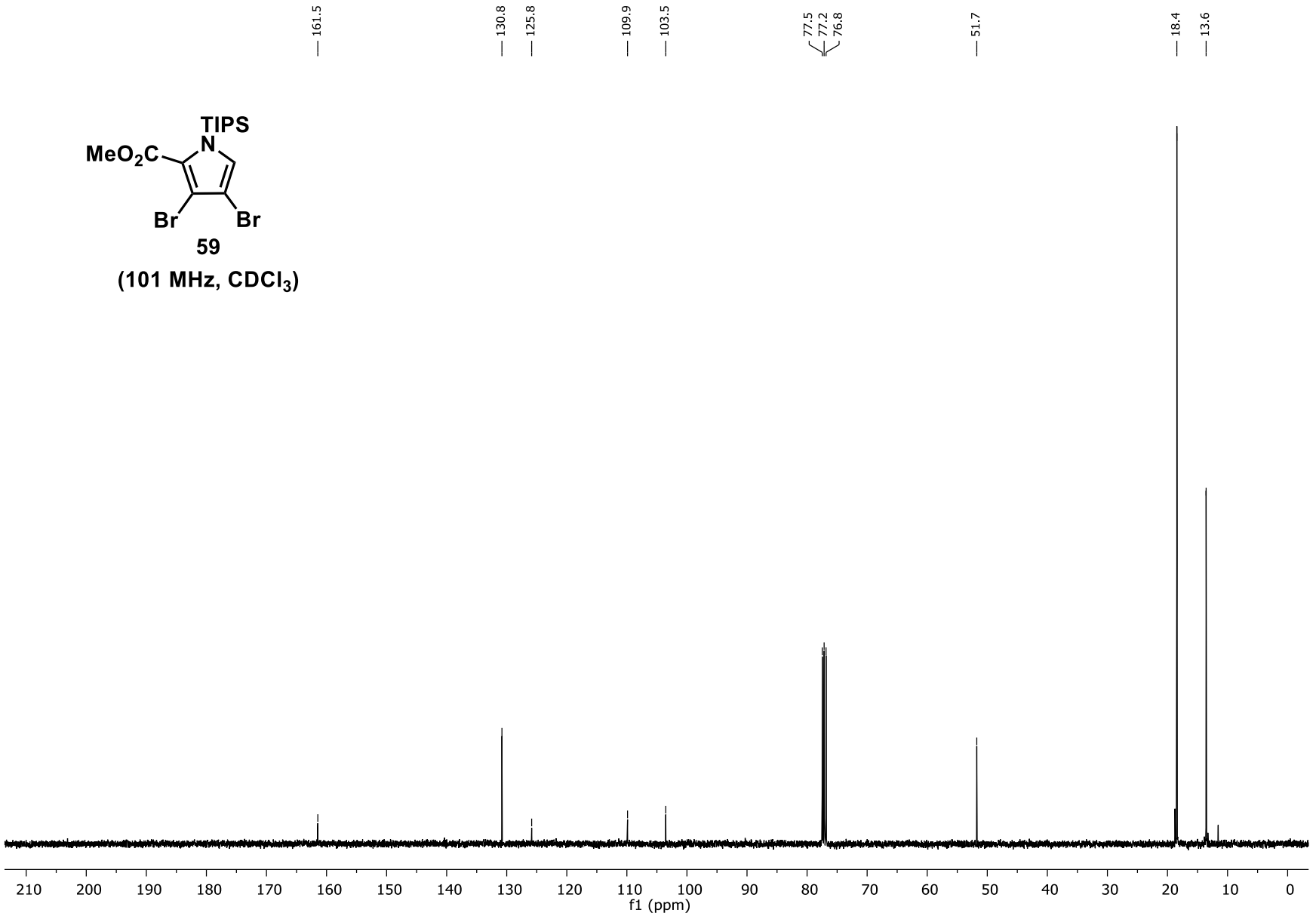
7: *spiroindimicin G*
(101 MHz, $CDCl_3$)

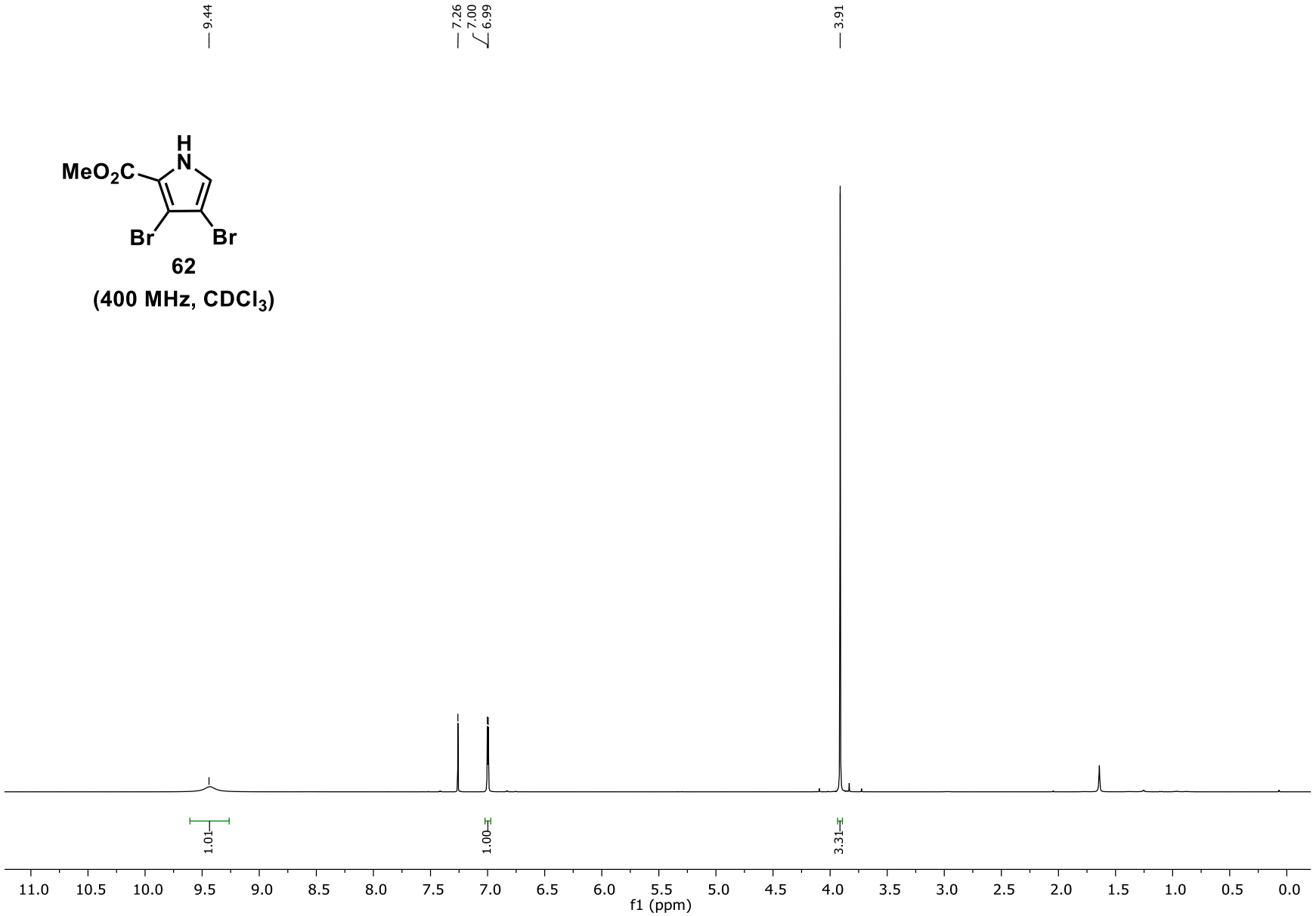

49 [R1 = H, R2 = Me]
50 [R1 = Me, R2 = H]
51 [R1 = H, R2 = H]
[crude] (600 MHz, CDCl3)
f1 (ppm)

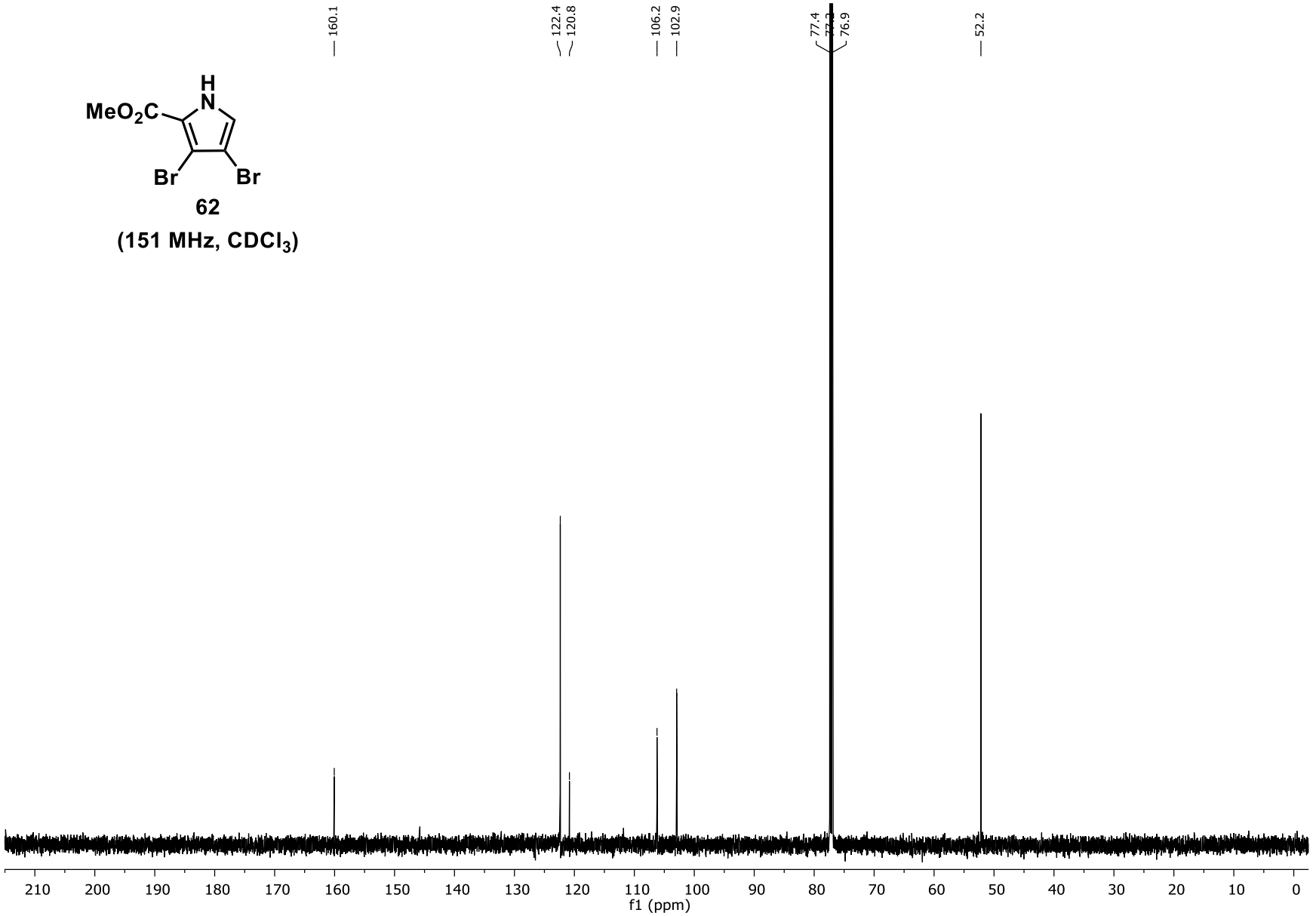

5″
9
HO2C
H
N
CO2Me
9
NOE
MeN
H
5″
Cl
HN
Cl
49
(400 MHz, CDCl3)
5″
9
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

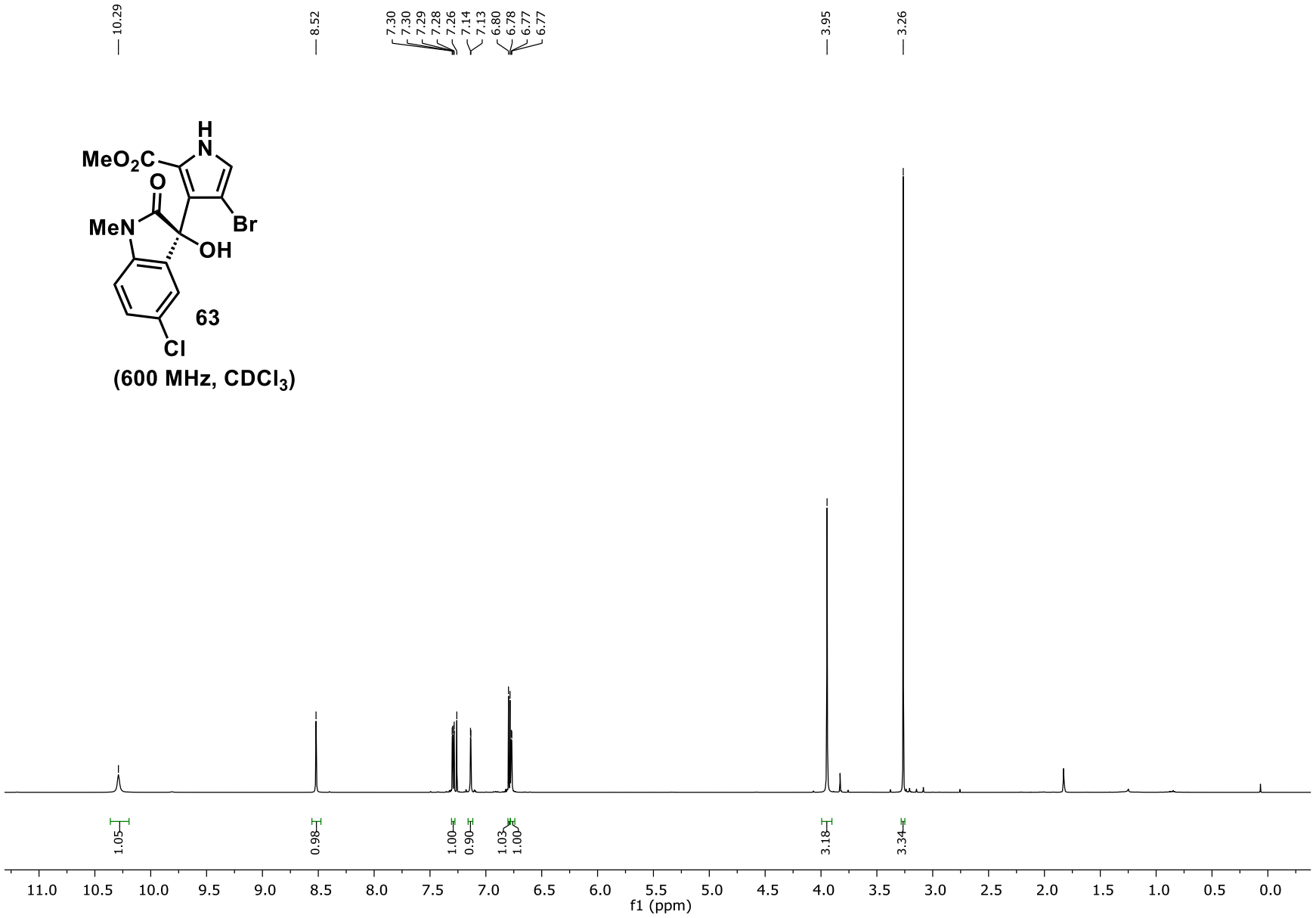

206.10
161.47
161.30
161.27
160.70
160.68
160.46
158.78
158.74
153.61
153.54
140.39
139.95
139.89
139.74
134.88
134.54
133.79
128.95
128.91
126.24
126.19
126.17
125.00
124.92
124.41
124.21
123.57
123.51
123.46
123.10
123.04
123.02
122.81
122.52
122.22
122.19
121.59
121.29
121.17
114.82
114.53
114.48
114.47
114.46
114.42
113.51
112.10
111.93
111.14
111.03
109.77
109.40
64.18
64.13
52.54
52.43
52.33
51.95
51.62
36.06
36.03
30.23
29.97
29.84
29.71
29.58
29.46
H
N
R1O2C
CO2R2
MeN
HN
Cl
Cl
49 [R1 = H, R2 = Me]
50 [R1 = Me, R2 = H]
51 [R1 = H, R2 = H]
[crude] (151 MHz, CDCl3)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

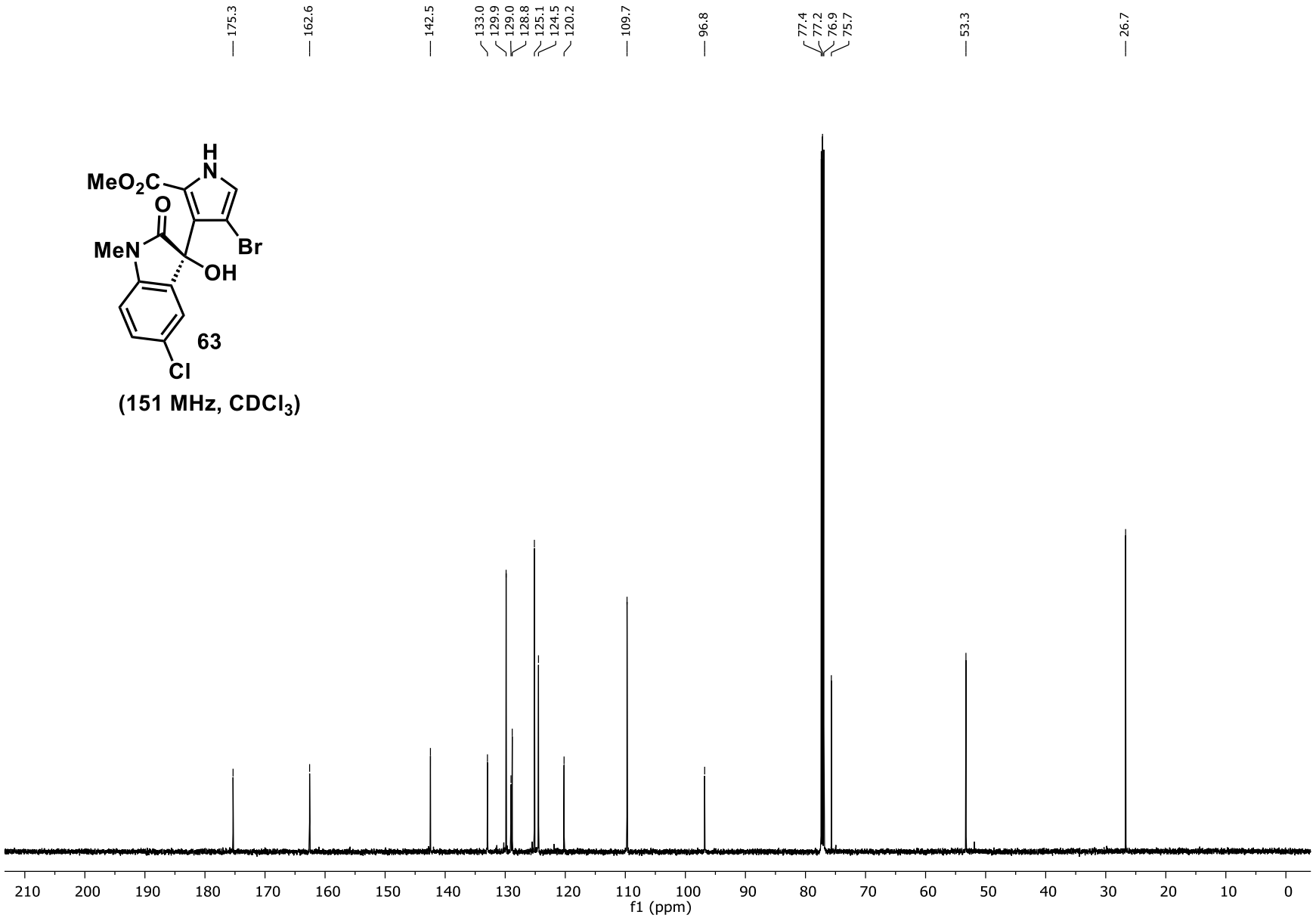

7.26
7.08
3.86
1.74
1.72
1.70
1.68
1.66
1.64
1.63
1.12
1.10
TIPS
N
MeO2C
Br
Br
59
(400 MHz, CDCl3)
1.00
3.00
3.07
18.02
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

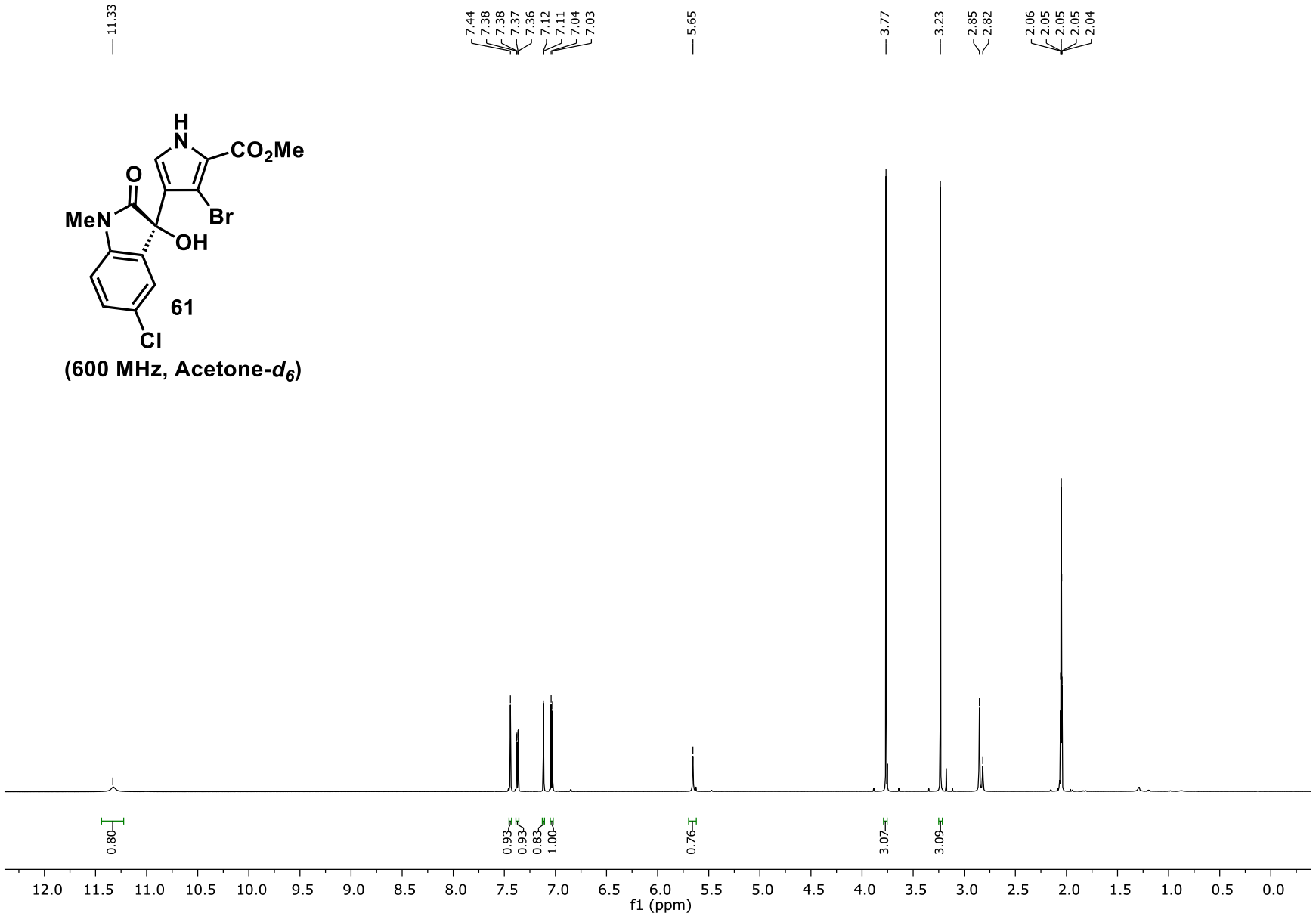

161.5
130.8
125.8
109.9
103.5
77.5
77.2
76.8
51.7
18.4
13.6
TIPS
N
MeO2C
Br
Br
59
(101 MHz, CDCl3)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

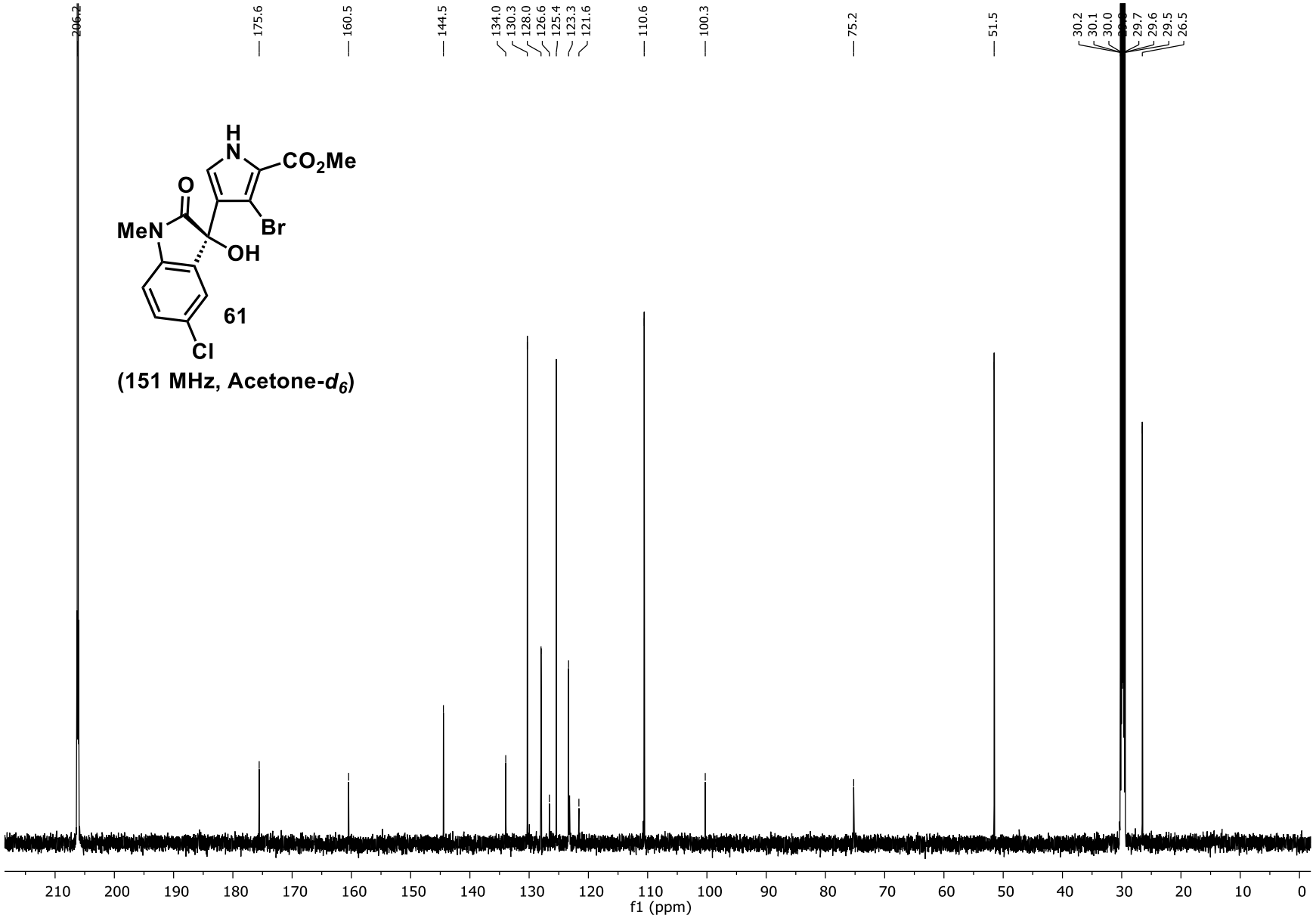

9.44
7.26
7.00
6.99
3.91
H
N
MeO2C
Br
Br
62
(400 MHz, CDCl3)
1.01
1.00
3.31
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

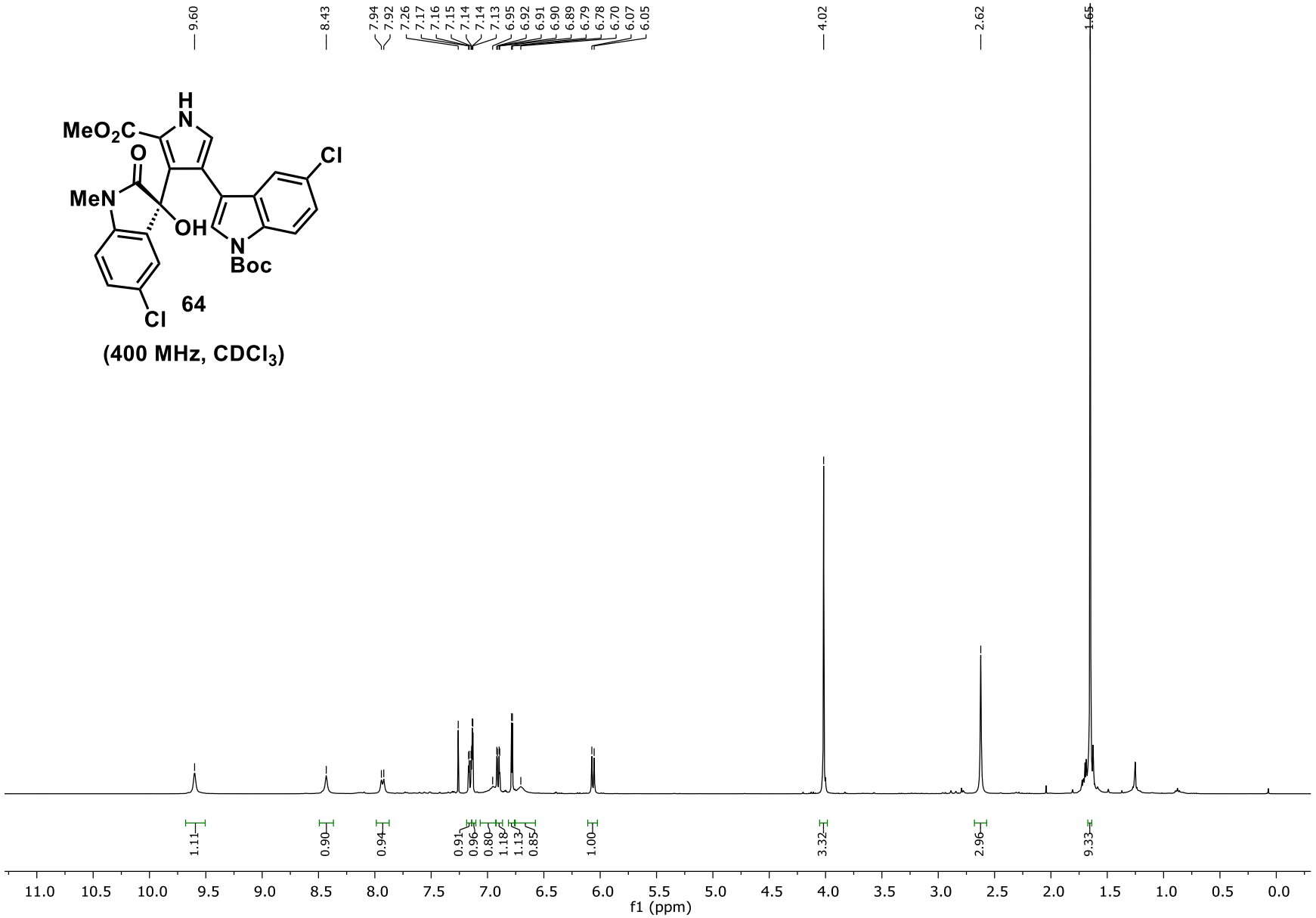

160.1
122.4
120.8
106.2
102.9
77.4
76.9
52.2
H
N
MeO2C
Br
Br
62
(151 MHz, CDCl3)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

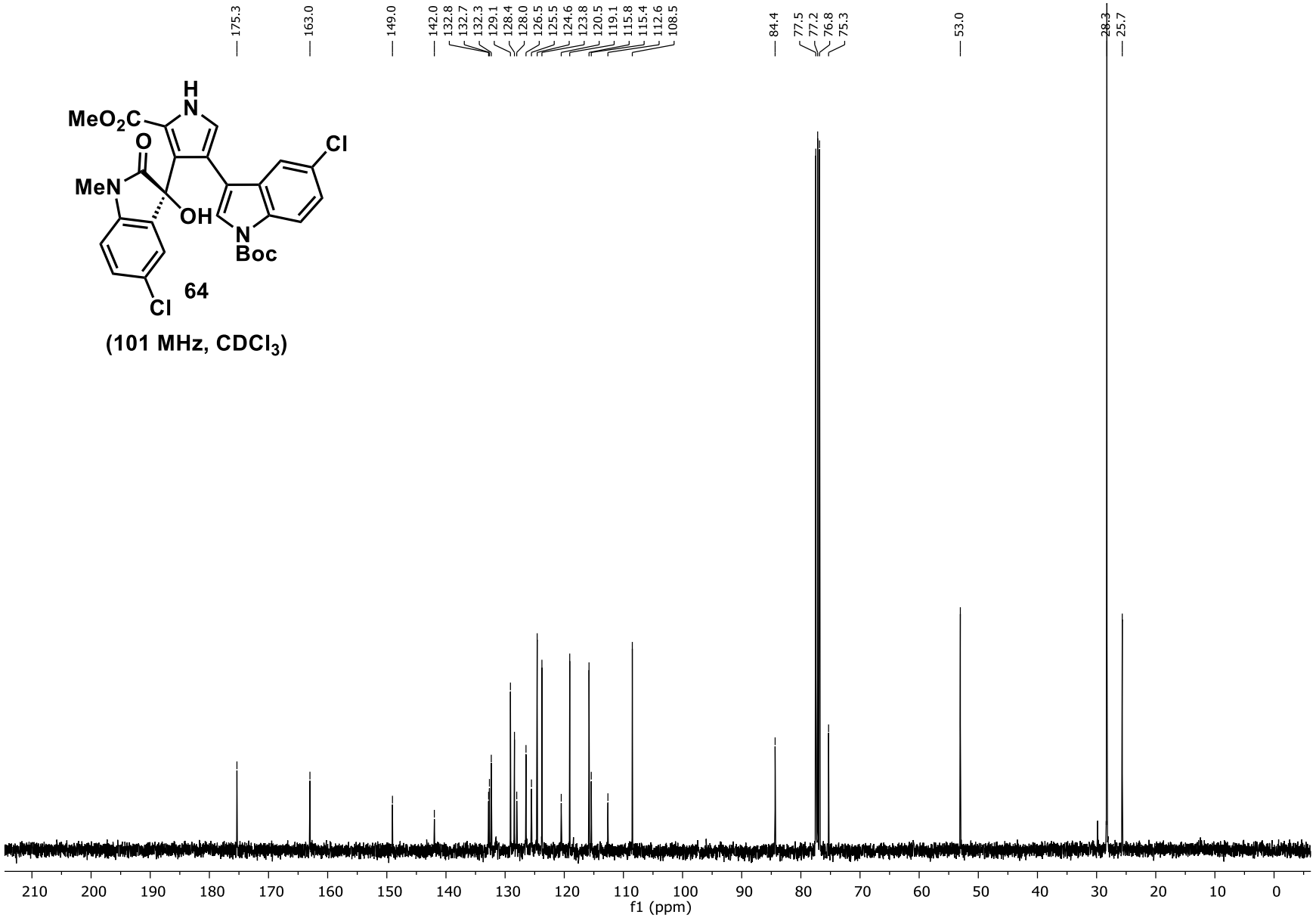

10.29
8.52
7.30
7.30
7.29
7.28
7.26
7.14
7.13
6.80
6.78
6.77
6.77
3.95
3.26
MeO2C
H
N
O
MeN
Br
OH
63
Cl
(600 MHz, CDCl3)
1.05
0.98
1.00
0.90
1.03
1.00
3.18
3.34
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

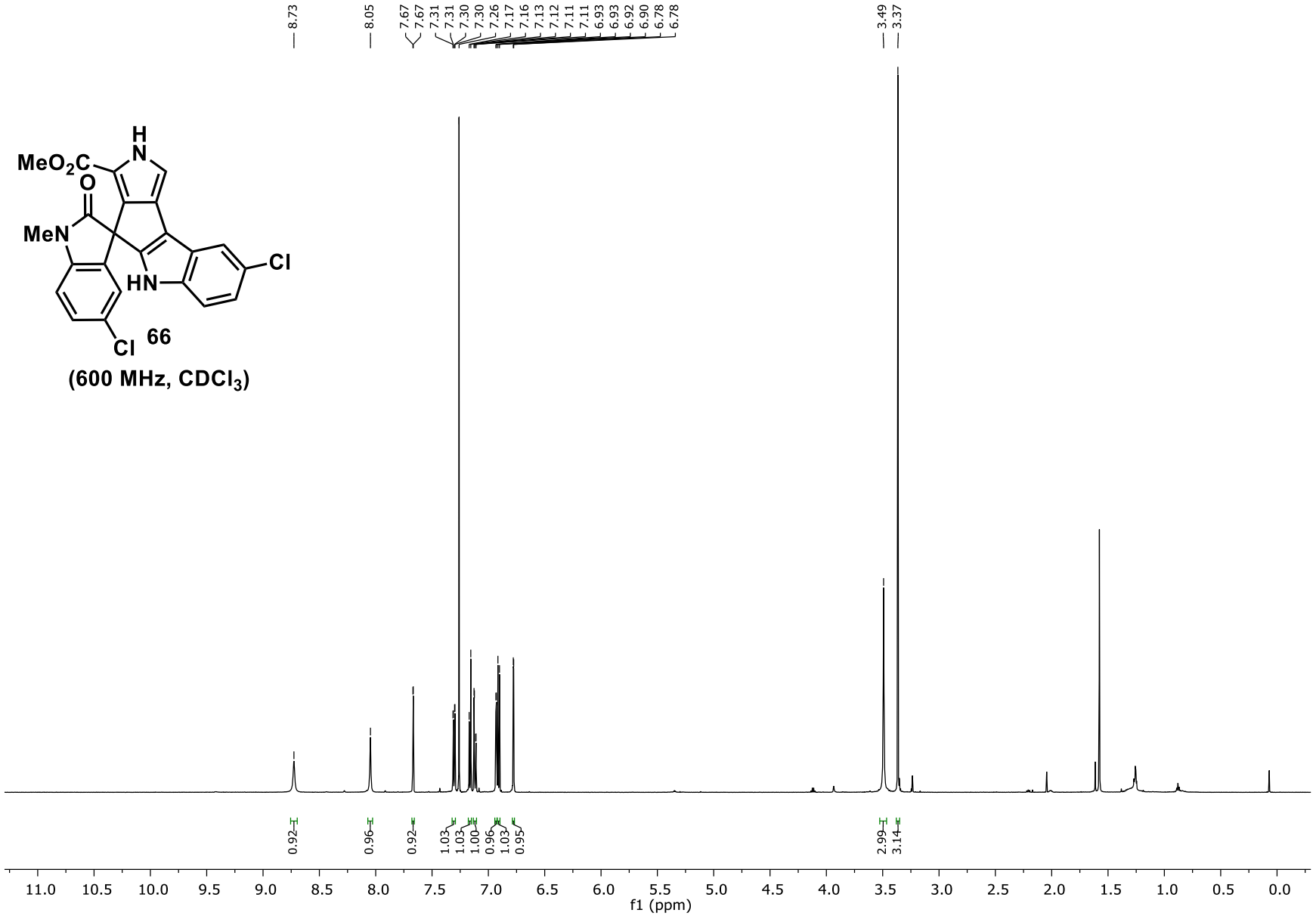

175.3
162.6
142.5
133.0
129.9
129.0
128.8
125.1
124.5
120.2
109.7
96.8
77.4
77.2
76.9
75.7
53.3
26.7
MeO2C
H
N
O
MeN
Br
OH
63
Cl
(151 MHz, CDCl3)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

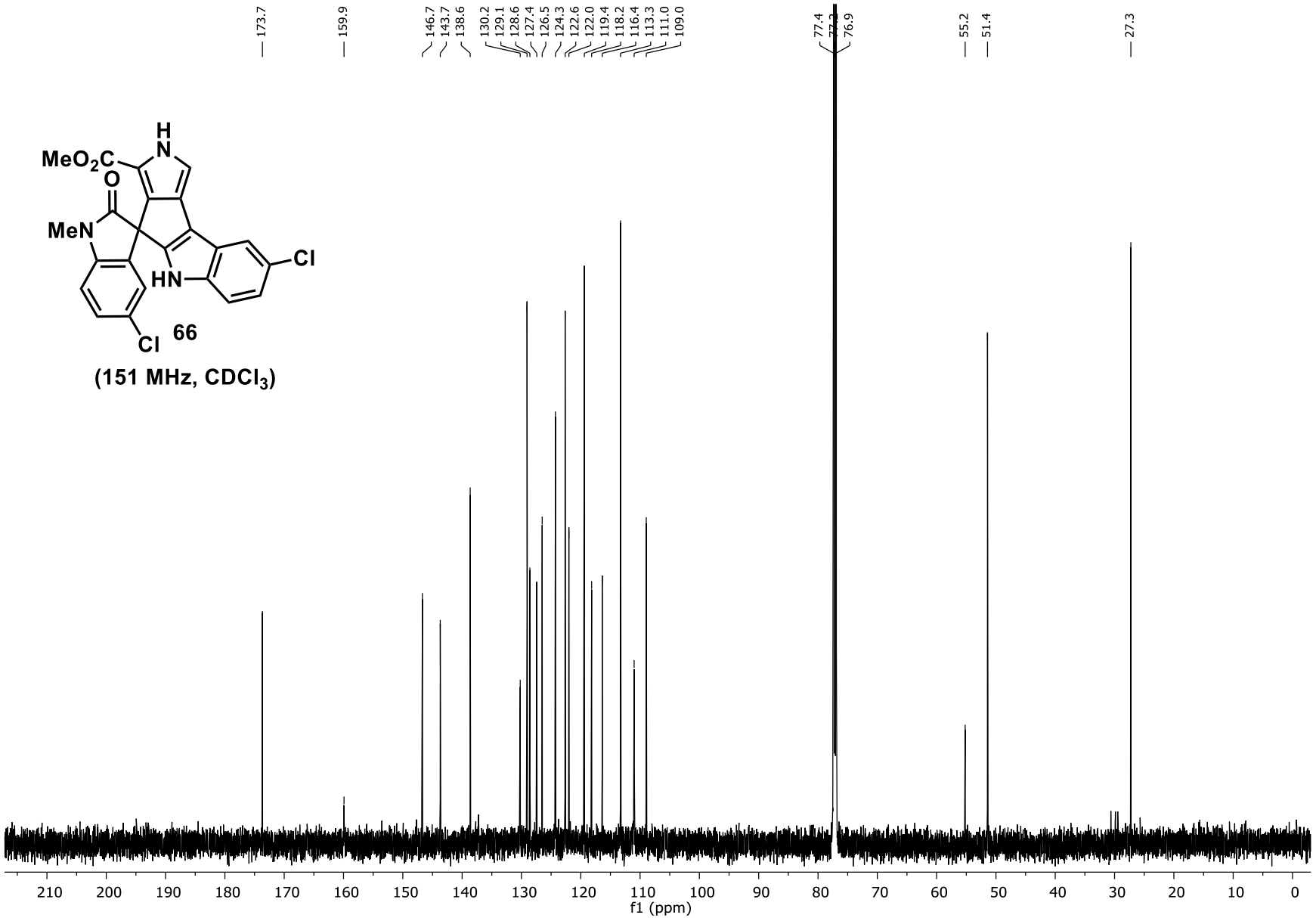

11.33
7.44
7.38
7.38
7.37
7.36
7.12
7.11
7.04
7.03
5.65
3.77
3.23
2.85
2.82
2.06
2.05
2.05
2.05
2.04
H
N
CO2Me
O
MeN
Br
OH
61
Cl
(600 MHz, Acetone-d6)
0.80
0.93
0.93
0.83
1.00
0.76
3.07
3.09
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

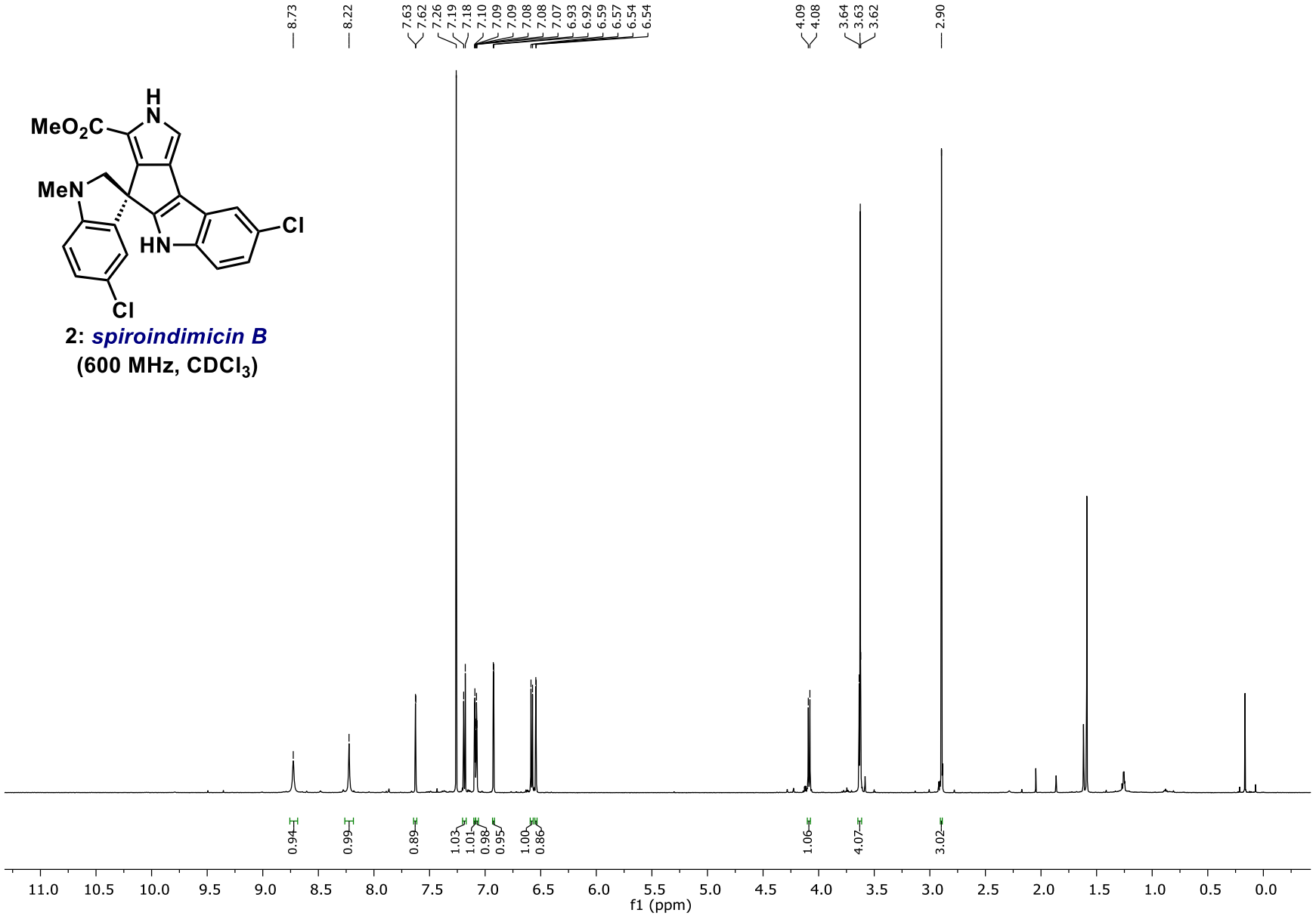

206.2
175.6
160.5
144.5
134.0
130.3
128.0
126.6
125.4
123.3
121.6
110.6
100.3
75.2
51.5
30.2
30.1
30.0
29.7
29.6
29.5
26.5
H
N
CO2Me
O
MeN
Br
OH
61
Cl
(151 MHz, Acetone-d6)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

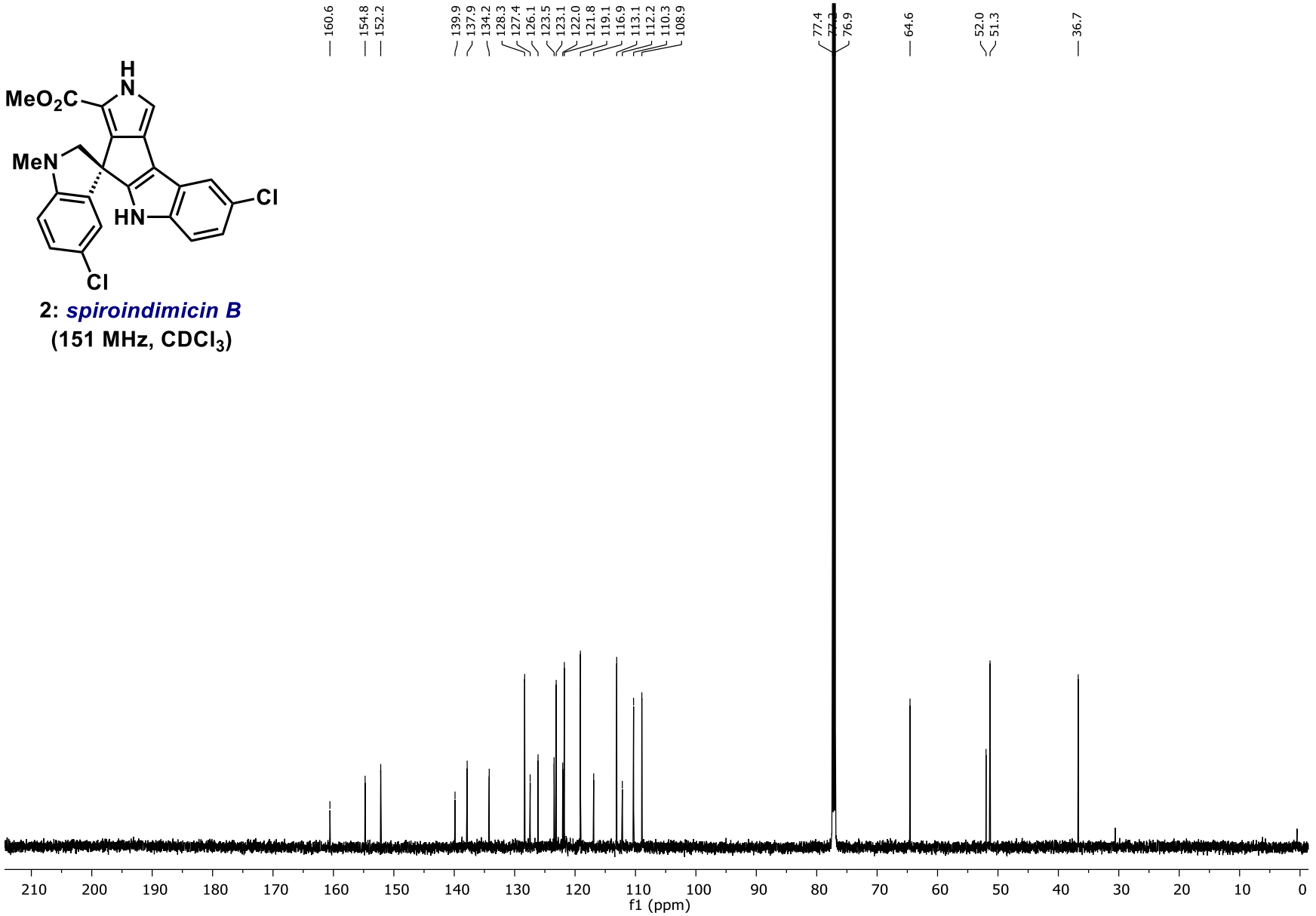

9.60
8.43
7.94
7.92
7.26
7.17
7.16
7.15
7.14
7.14
7.13
6.95
6.92
6.91
6.90
6.89
6.79
6.78
6.70
6.07
6.05
4.02
2.62
1.65
MeO2C
H
N
O
MeN
OH
N
Boc
Cl
Cl
64
(400 MHz, CDCl3)
1.11
0.90
0.94
0.91
0.96
0.80
1.18
1.13
0.85
1.00
3.32
2.96
9.33
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


175.3
163.0
149.0
142.0
132.8
132.7
132.3
129.1
128.4
128.0
126.5
125.5
124.6
123.8
120.5
119.1
115.8
115.4
112.6
108.5
84.4
77.5
77.2
76.8
75.3
53.0
28.3
25.7
MeO2C
H
N
O
MeN
OH
N
Boc
Cl
Cl
64
(101 MHz, CDCl3)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


8.73
8.05
7.67
7.67
7.31
7.31
7.30
7.30
7.26
7.17
7.16
7.13
7.12
7.11
7.11
6.93
6.92
6.90
6.78
6.78
3.49
3.37
MeO2C
O
MeN
H
N
HN
Cl
Cl
66
(600 MHz, CDCl3)
0.92
0.96
0.92
1.03
1.03
1.00
0.96
1.03
0.95
2.99
3.14
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

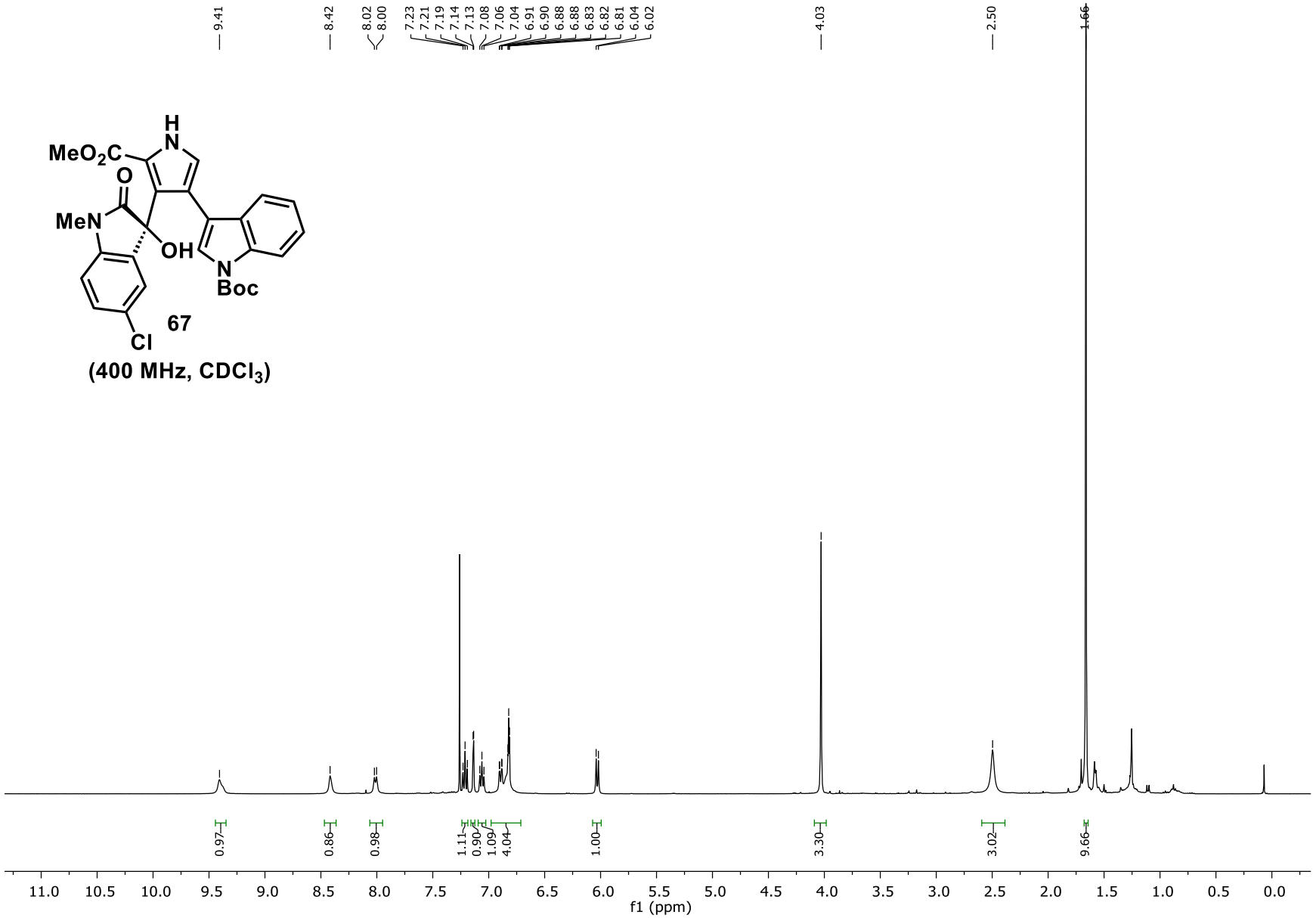

173.7
159.9
146.7
143.7
138.6
130.2
129.1
128.6
127.4
126.5
124.3
122.6
122.0
119.4
118.2
116.4
113.3
111.0
109.0
77.4
77.2
76.9
55.2
51.4
27.3
MeO2C
O
MeN
H
N
HN
Cl
Cl
66
(151 MHz, CDCl3)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

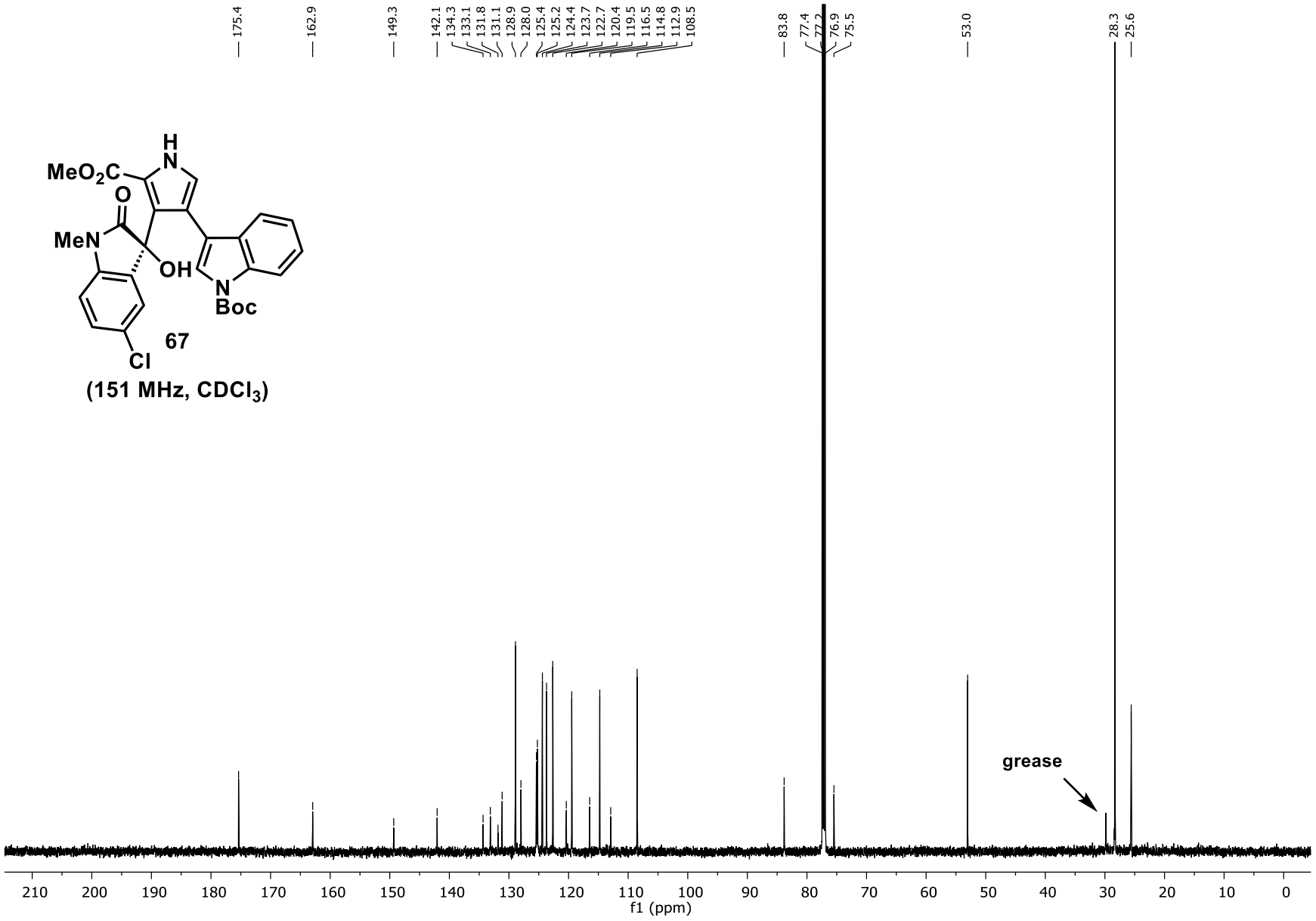

8.73
8.22
7.63
7.62
7.26
7.19
7.18
7.10
7.09
7.09
7.08
7.08
7.07
6.93
6.92
6.59
6.57
6.54
6.54
4.09
4.08
3.64
3.63
3.62
2.90
MeO2C
H
N
MeN
HN
Cl
Cl
2: spiroindimicin B
(600 MHz, CDCl3)
0.94
0.99
0.89
1.03
1.01
0.98
0.95
1.00
0.86
1.06
4.07
3.02
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



2: *spiroindimicin B*

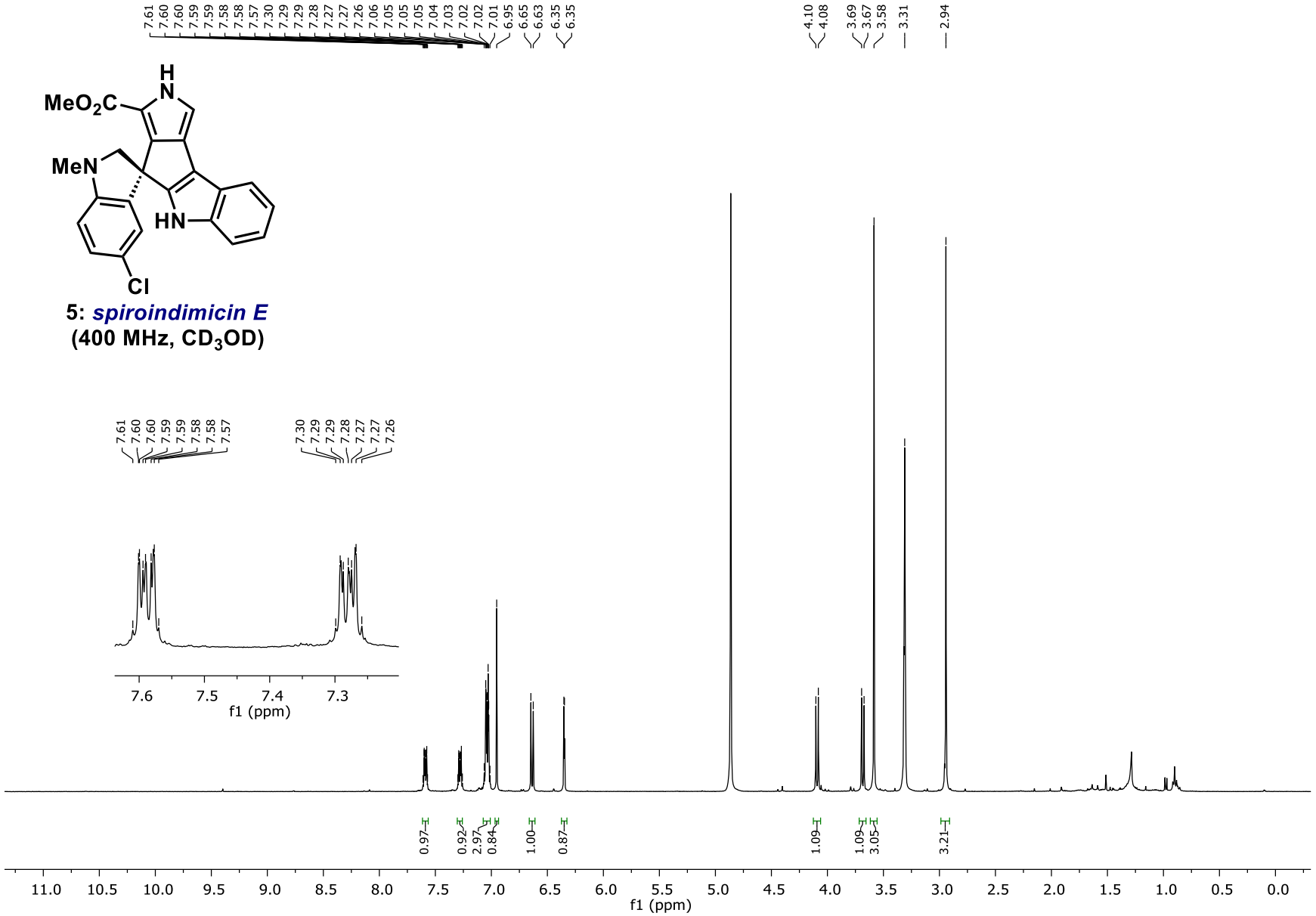
(151 MHz, $CDCl_3$)

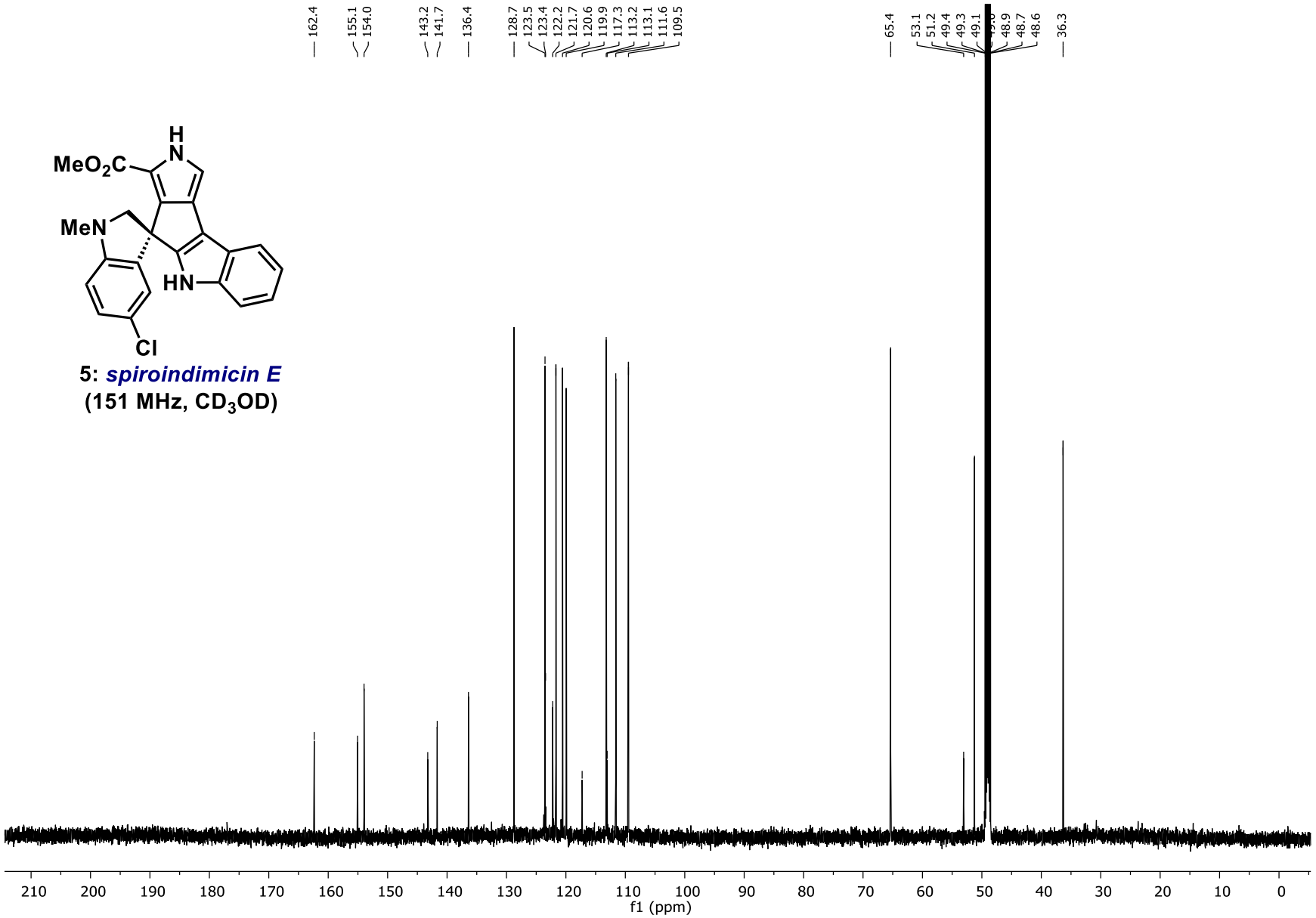

9.41
8.42
8.02
8.00
7.23
7.21
7.19
7.14
7.13
7.08
7.06
7.04
6.91
6.90
6.88
6.88
6.83
6.82
6.81
6.04
6.02
4.03
2.50
1.66
MeO2C
O
MeN
OH
H
N
N
Boc
Cl
67
(400 MHz, CDCl3)
0.97
0.86
0.98
1.11
0.90
1.09
4.04
1.00
3.30
3.02
9.66
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

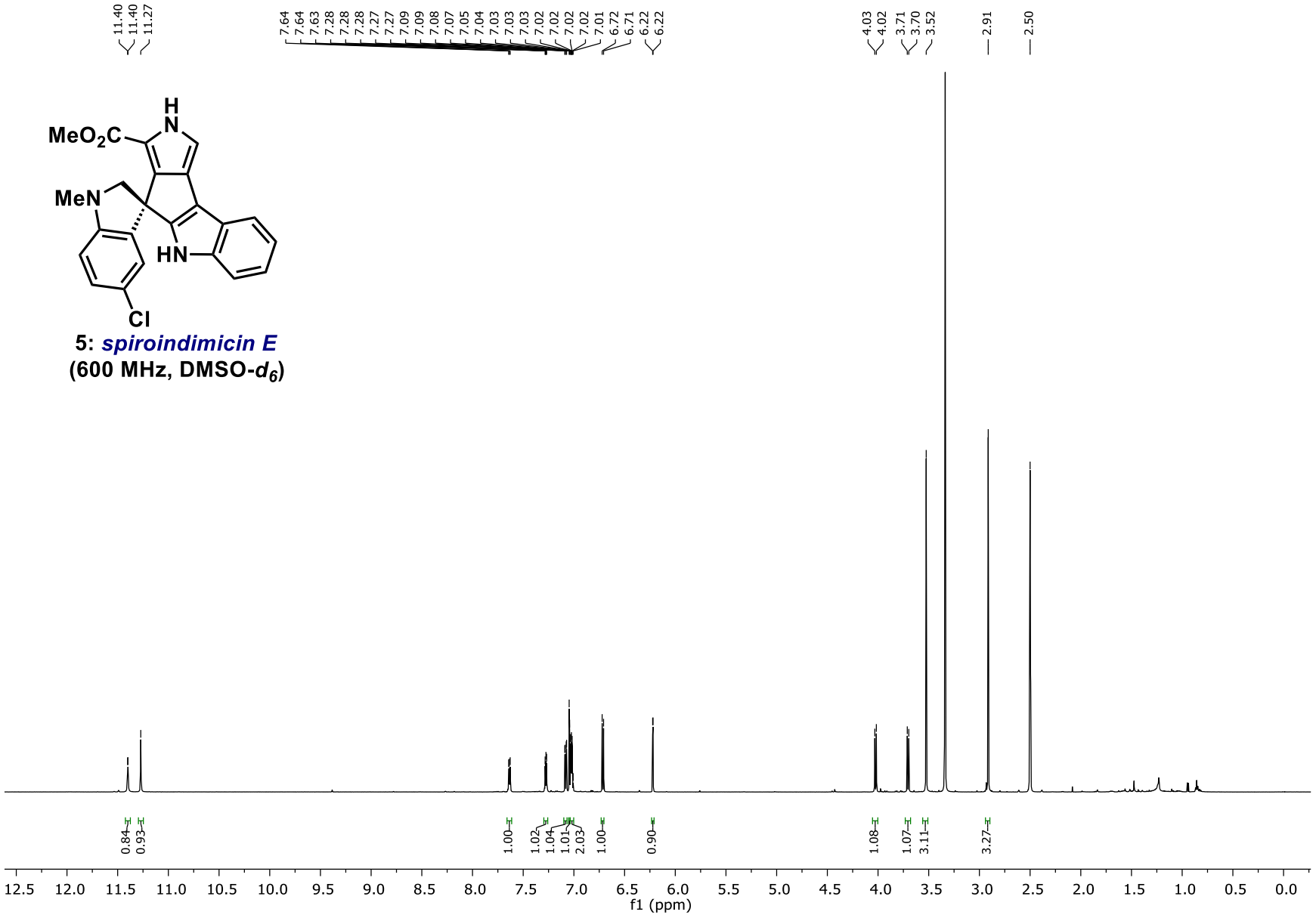


67

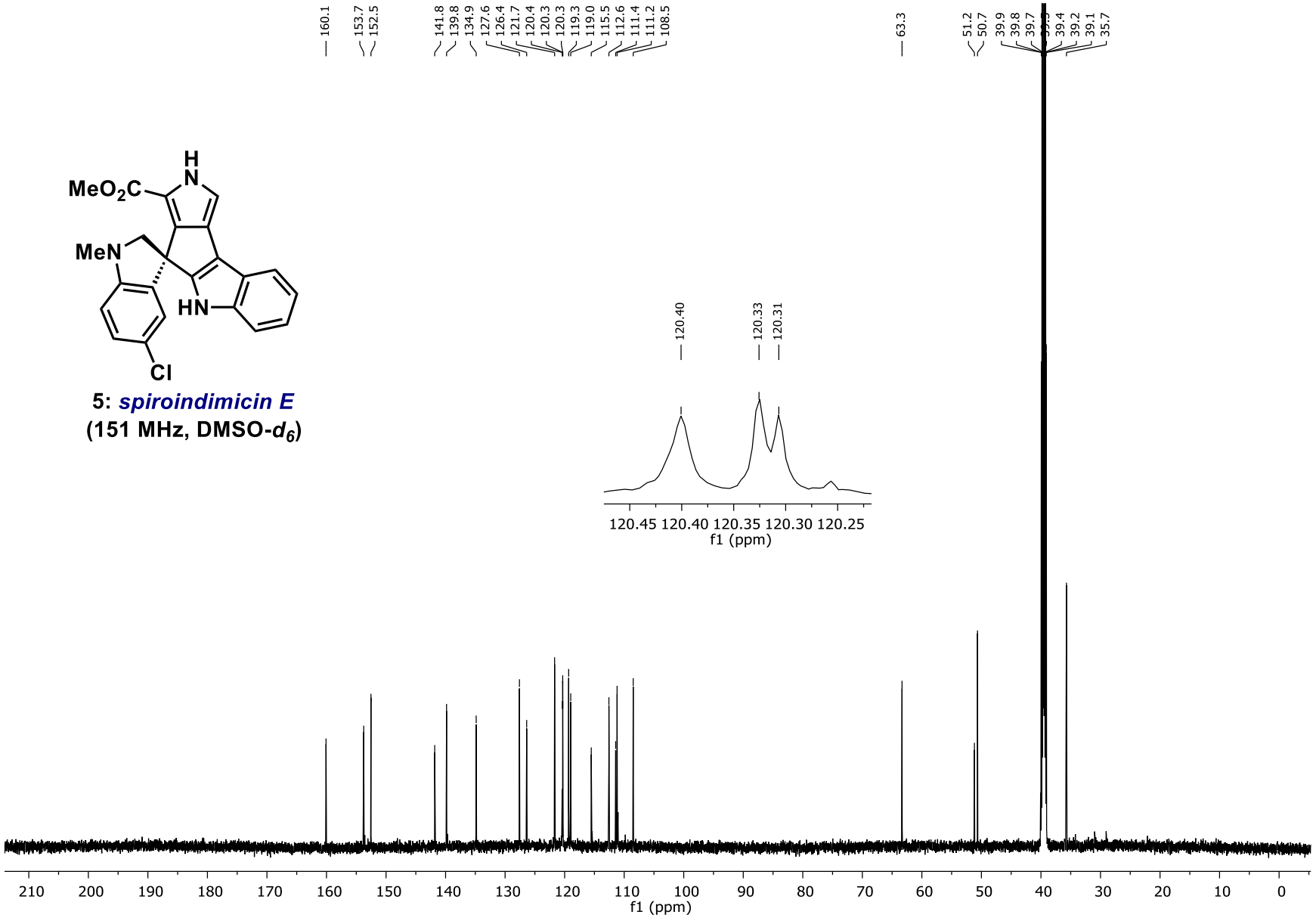
(151 MHz, $CDCl_3$)

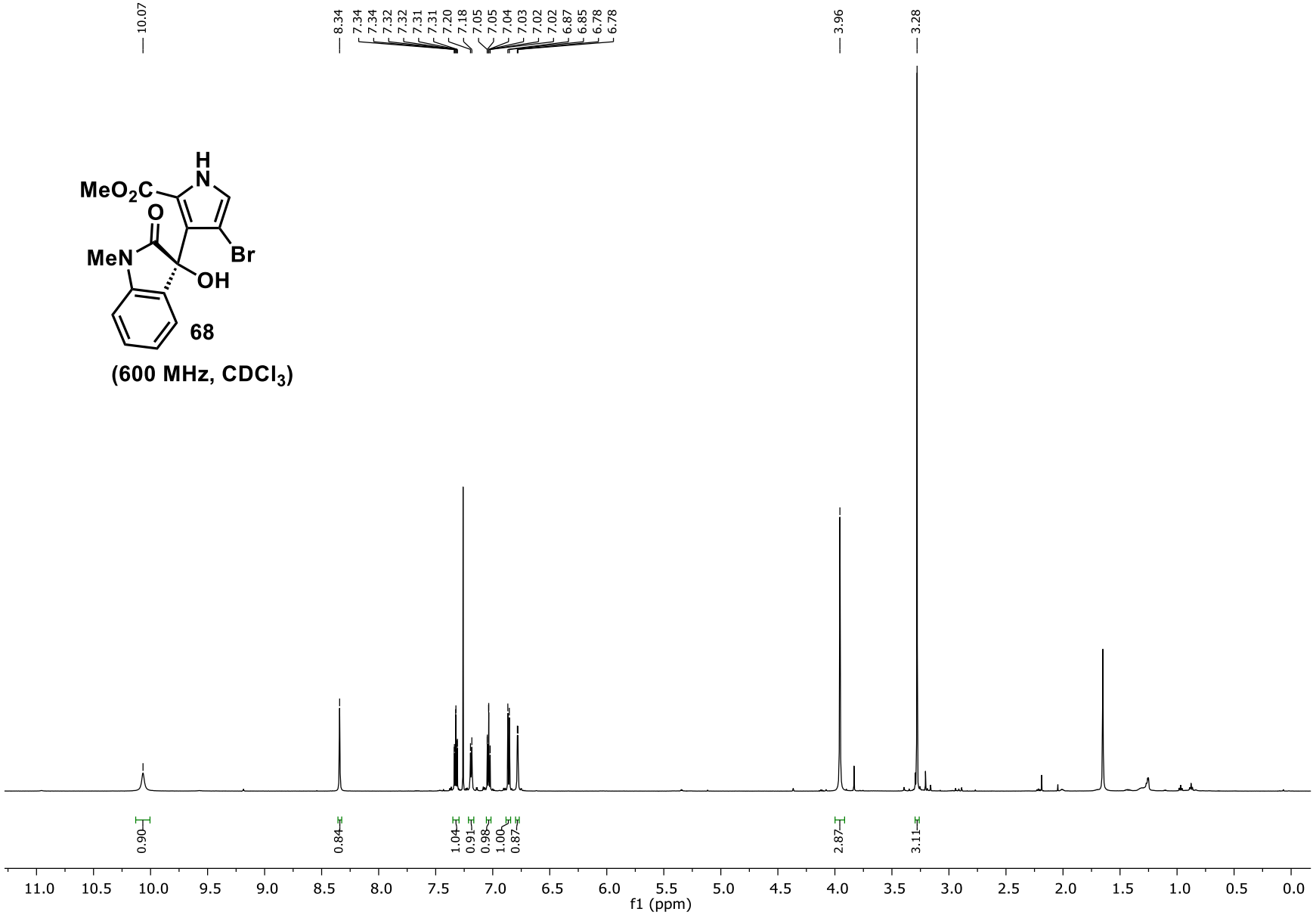

7.61 7.60 7.60 7.59 7.59 7.58 7.58 7.57 7.30 7.29 7.29 7.28 7.27 7.27 7.26 7.06 7.05 7.05 7.05 7.04 7.03 7.02 7.02 7.01 6.95 6.65 6.63 6.35 6.35
4.10 4.08 3.69 3.67 3.58 3.31 2.94
MeO2C
H
N
MeN
HN
Cl
5: spiroindimicin E
(400 MHz, CD3OD)
7.61 7.60 7.60 7.59 7.59 7.58 7.58 7.57
7.30 7.29 7.29 7.28 7.27 7.27 7.26
7.6 7.5 7.4 7.3
f1 (ppm)
0.97 0.92 2.97 0.84 1.00 0.87 1.09 1.09 3.05 3.21
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

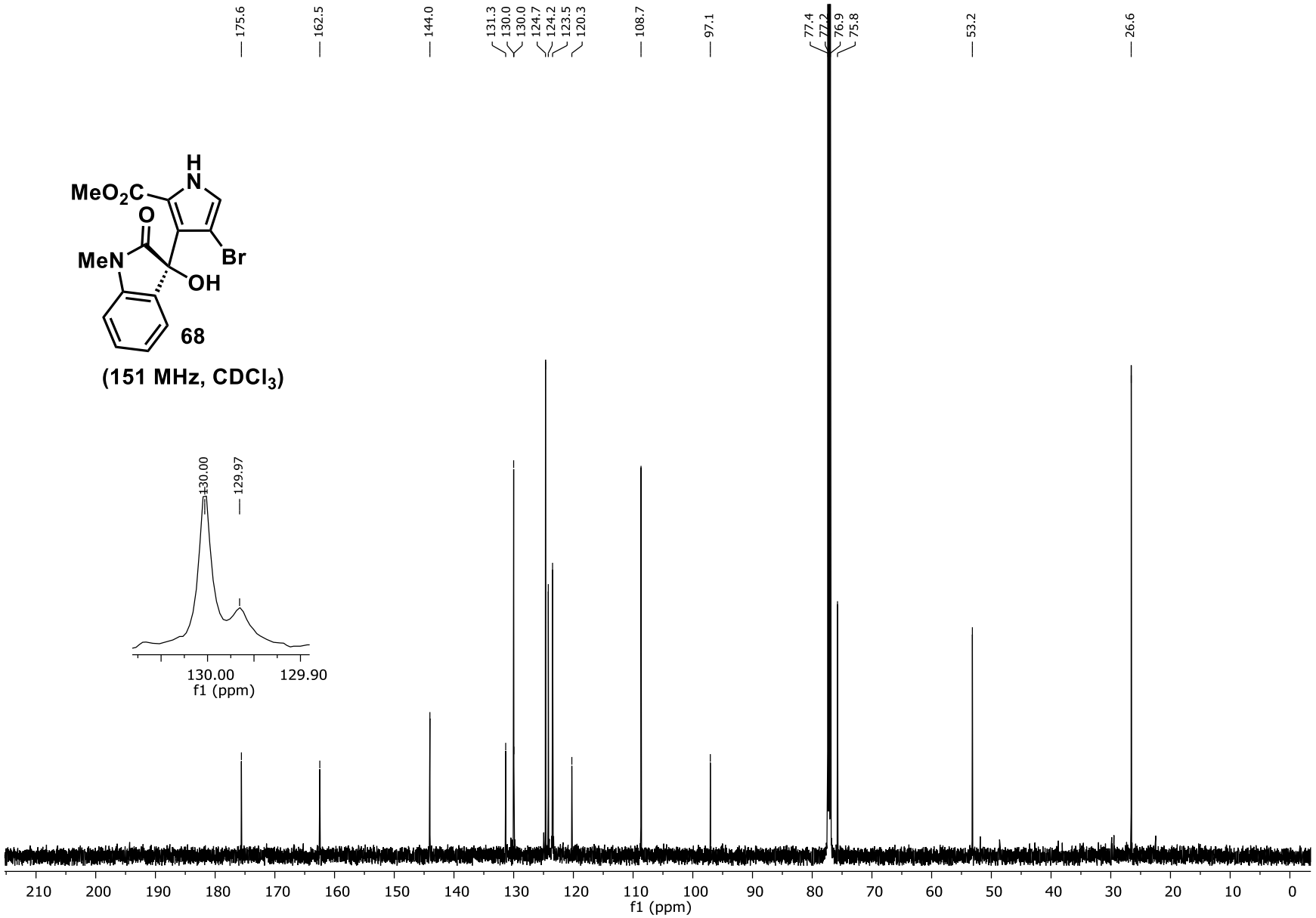

162.4
155.1
154.0
143.2
141.7
136.4
128.7
123.5
123.4
122.2
121.7
120.6
119.9
117.3
113.2
113.1
111.6
109.5
65.4
53.1
51.2
49.4
49.3
49.1
48.9
48.7
48.6
36.3
MeO2C
H
N
MeN
HN
Cl
5: spiroindimicin E
(151 MHz, CD3OD)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

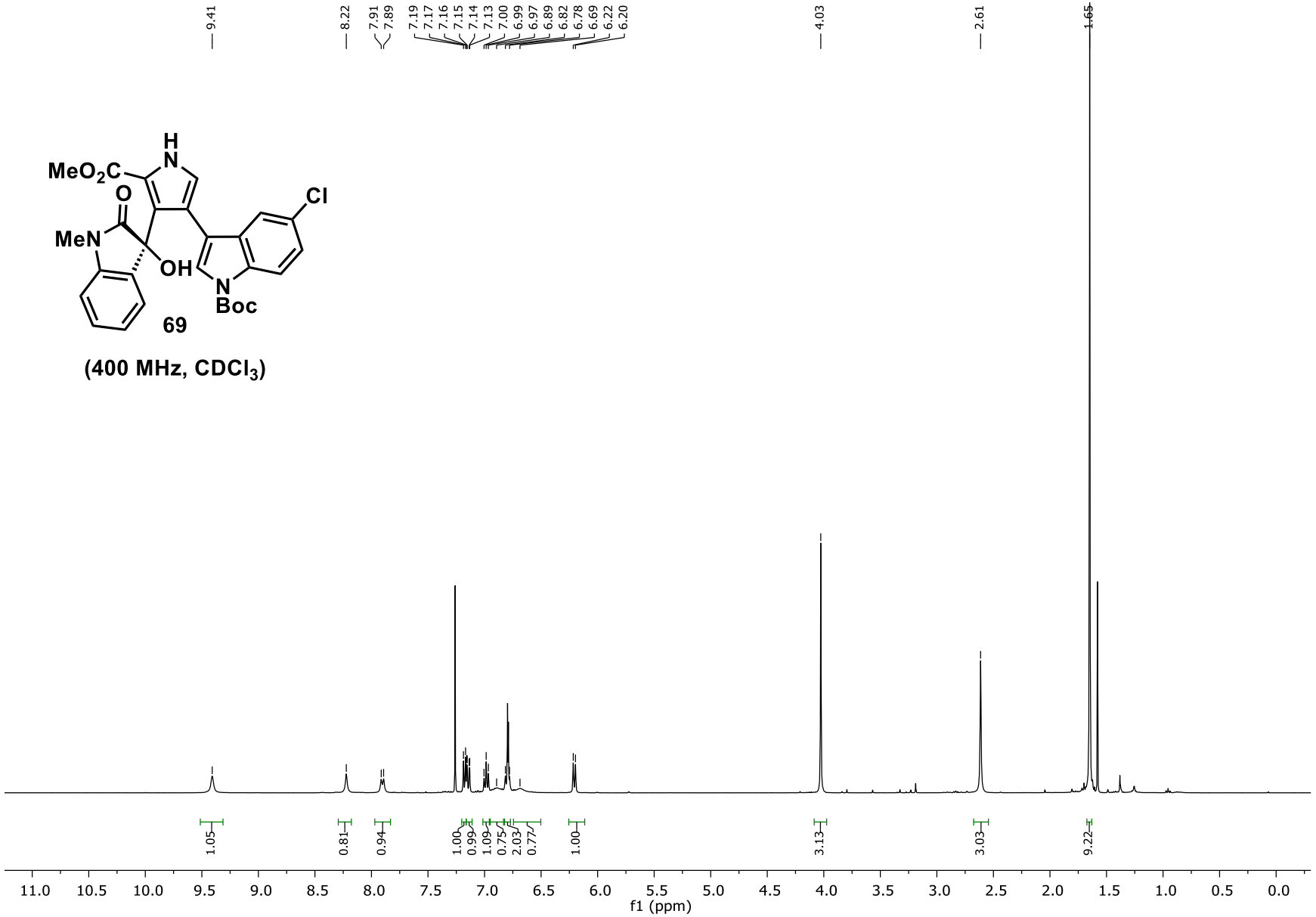


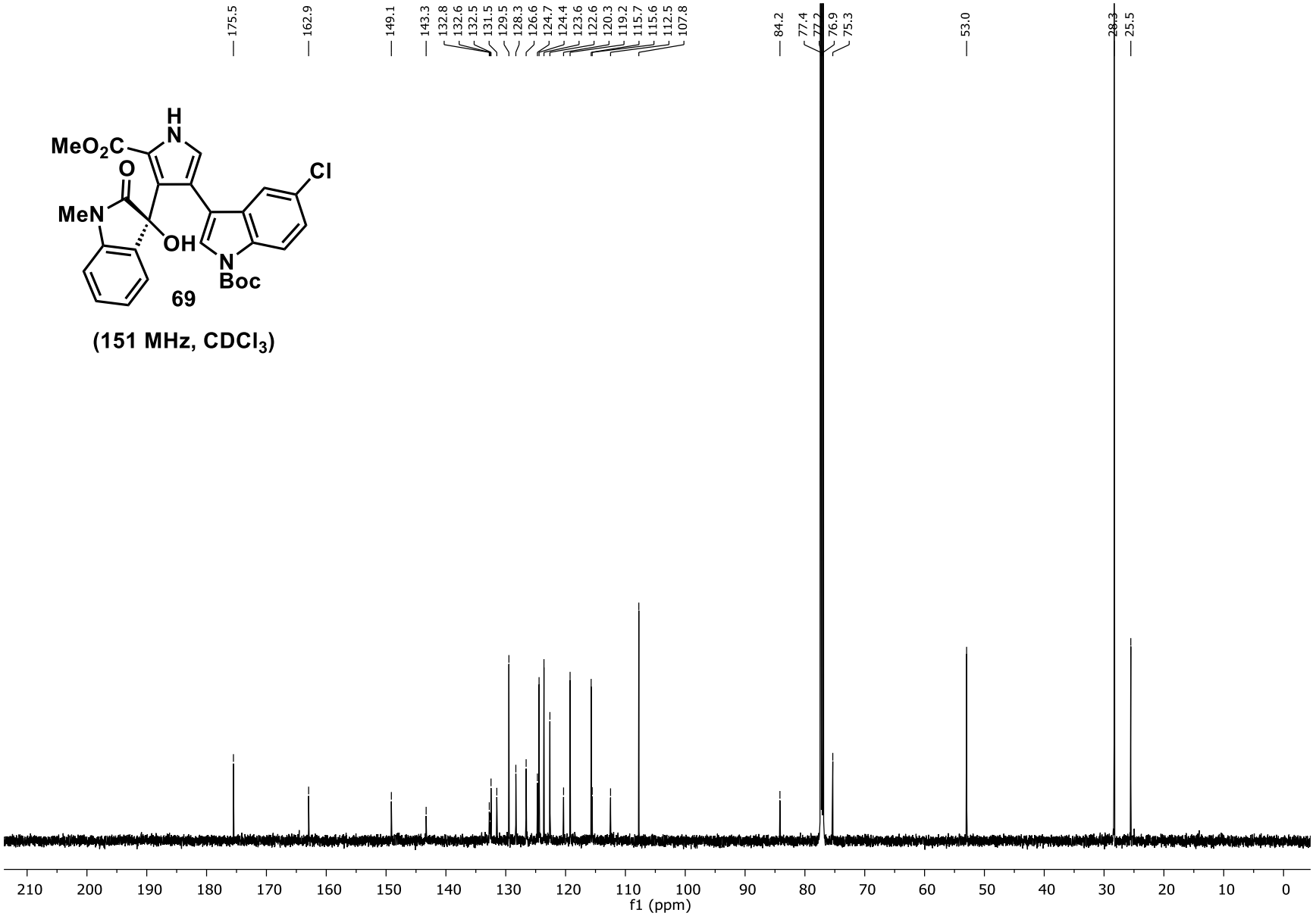
5: *spiroindimicin E*
(600 MHz, DMSO-d_6)

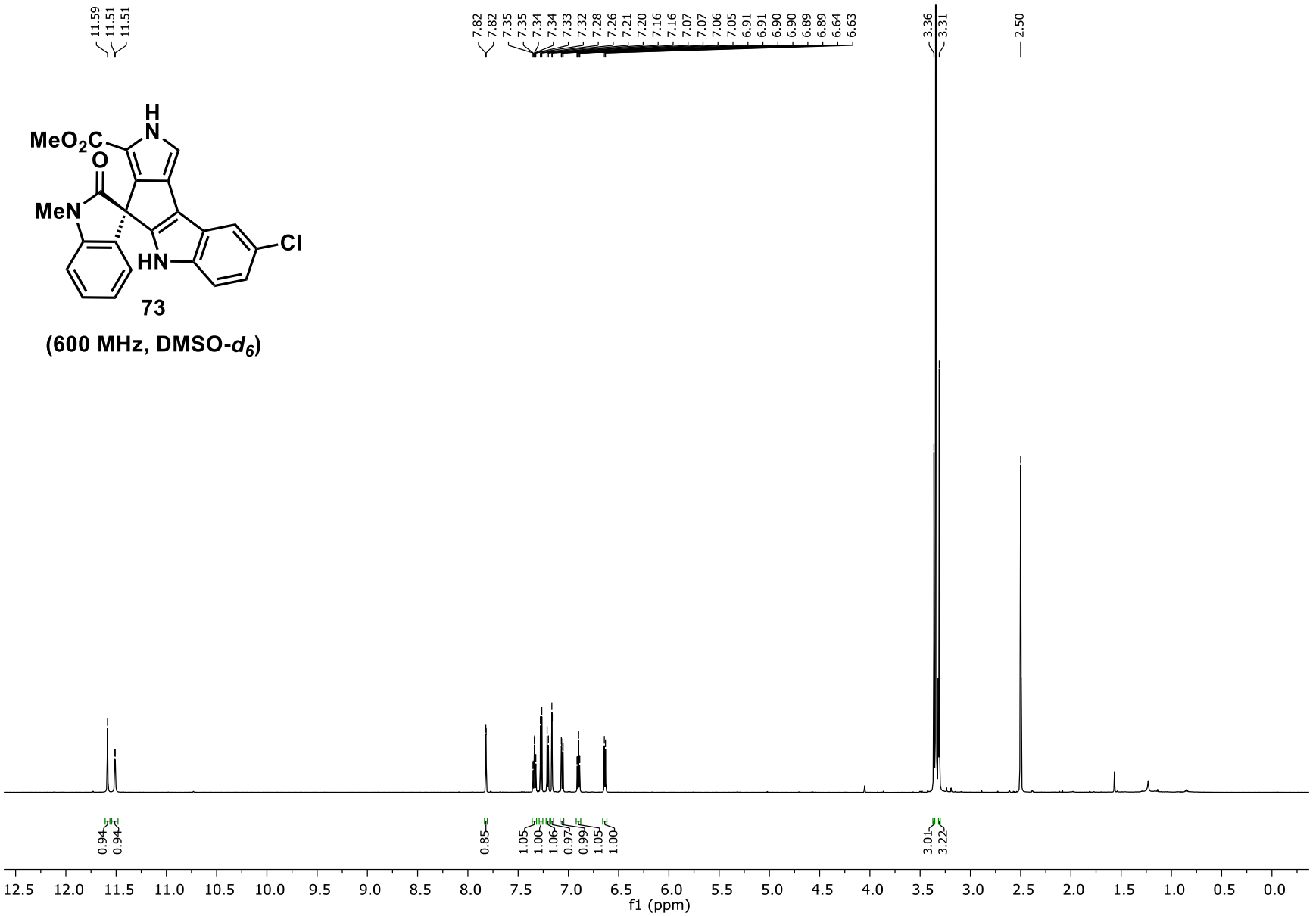

160.1
153.7
152.5
141.8
139.8
134.9
127.6
126.4
121.7
120.4
120.3
120.3
119.3
119.0
115.5
112.6
111.4
111.2
108.5
63.3
51.2
50.7
39.9
39.8
39.7
39.4
39.2
39.1
35.7
MeO2C
H
N
MeN
HN
Cl
5: spiroindimicin E
(151 MHz, DMSO-d6)
120.40
120.33
120.31
120.45 120.40 120.35 120.30 120.25
f1 (ppm)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

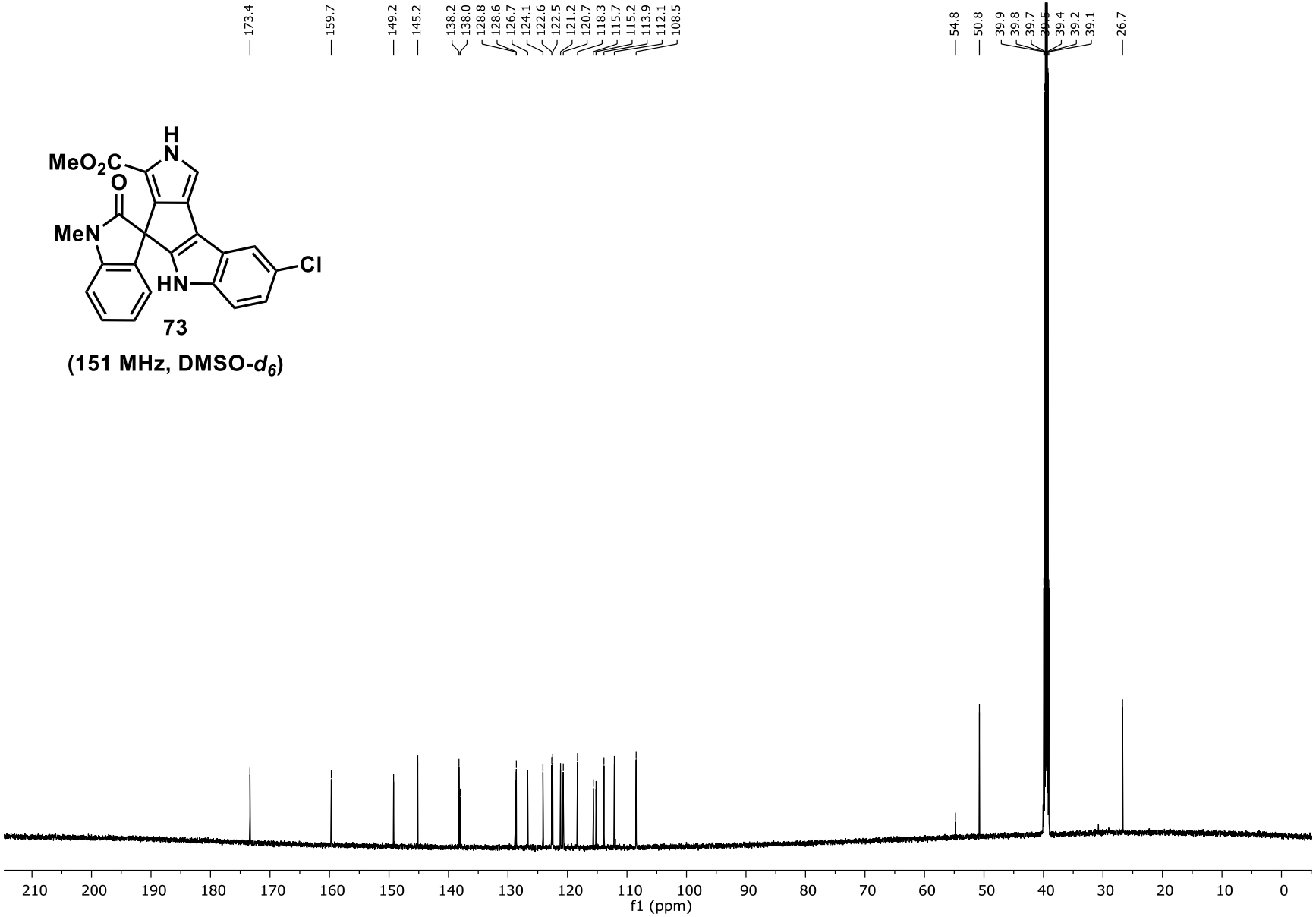

10.07
8.34
7.34
7.34
7.32
7.32
7.31
7.31
7.20
7.18
7.05
7.05
7.04
7.03
7.02
7.02
6.87
6.85
6.78
6.78
3.96
3.28
MeO2C
H
N
O
MeN
Br
OH
68
(600 MHz, CDCl3)
0.90
0.84
1.04
0.91
0.98
1.00
0.87
2.87
3.11
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

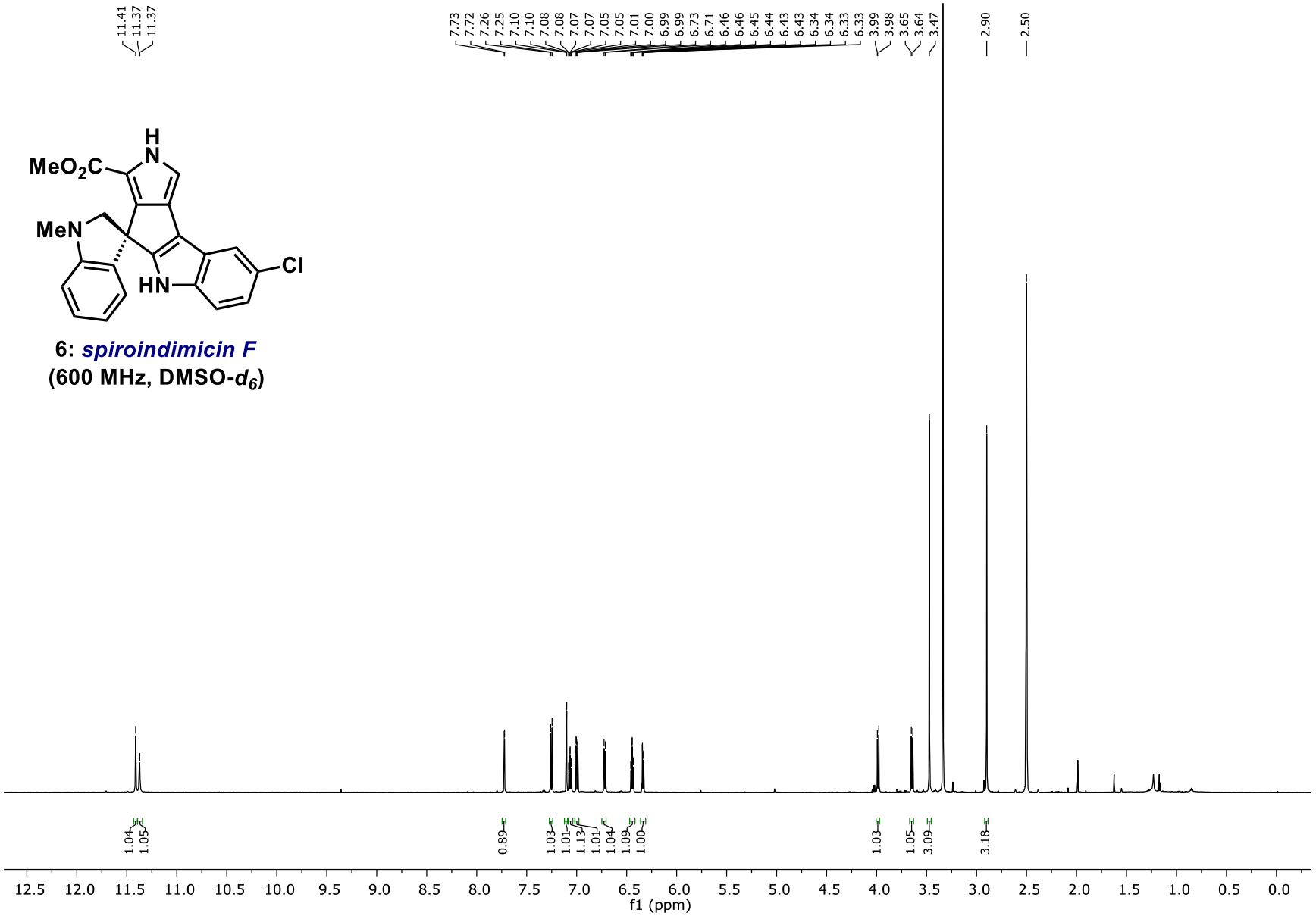

175.6
162.5
144.0
131.3
130.0
130.0
124.7
124.2
123.5
120.3
108.7
97.1
77.4
77.2
76.9
75.8
53.2
26.6
MeO2C
O
H
N
MeN
Br
OH
68
(151 MHz, CDCl3)
130.00
129.97
130.00
129.90
f1 (ppm)
f1 (ppm)


9.41
8.22
7.91
7.89
7.19
7.17
7.16
7.15
7.14
7.13
7.00
6.99
6.97
6.89
6.82
6.78
6.69
6.22
6.20
4.03
2.61
1.65
MeO2C
H
N
O
Cl
MeN
OH
N
Boc
69
(400 MHz, CDCl3)
1.05
0.81
0.94
1.00
0.99
1.09
0.75
2.03
0.77
1.00
3.13
3.03
9.22
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

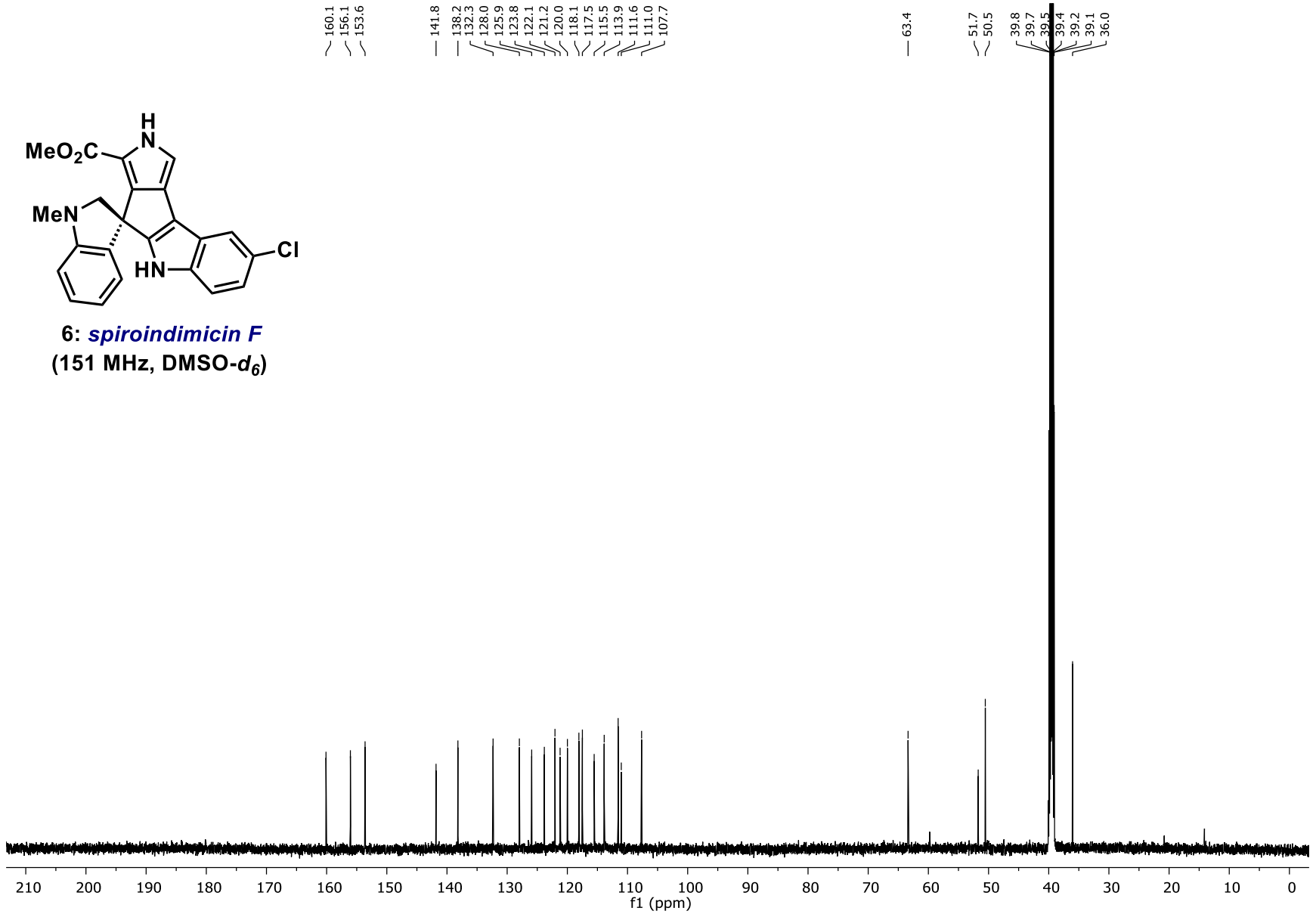

175.5
162.9
149.1
143.3
132.8
132.6
132.5
131.5
129.5
128.3
126.6
124.7
124.4
123.6
122.6
120.3
119.2
115.7
115.6
112.5
107.8
84.2
77.4
77.2
76.9
75.3
53.0
28.3
25.5
MeO2C
H
N
O
Cl
MeN
OH
N
Boc
69
(151 MHz, CDCl3)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


11.59
11.51
11.51
7.82
7.82
7.35
7.35
7.34
7.34
7.33
7.32
7.28
7.26
7.21
7.20
7.16
7.16
7.07
7.07
7.06
7.05
6.91
6.90
6.90
6.89
6.89
6.64
6.63
3.36
3.31
2.50
MeO2C
O
MeN
H
N
HN
Cl
73
(600 MHz, DMSO-d6)
0.94
0.94
0.85
1.05
1.00
1.06
0.97
0.99
1.05
1.00
3.01
3.22
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

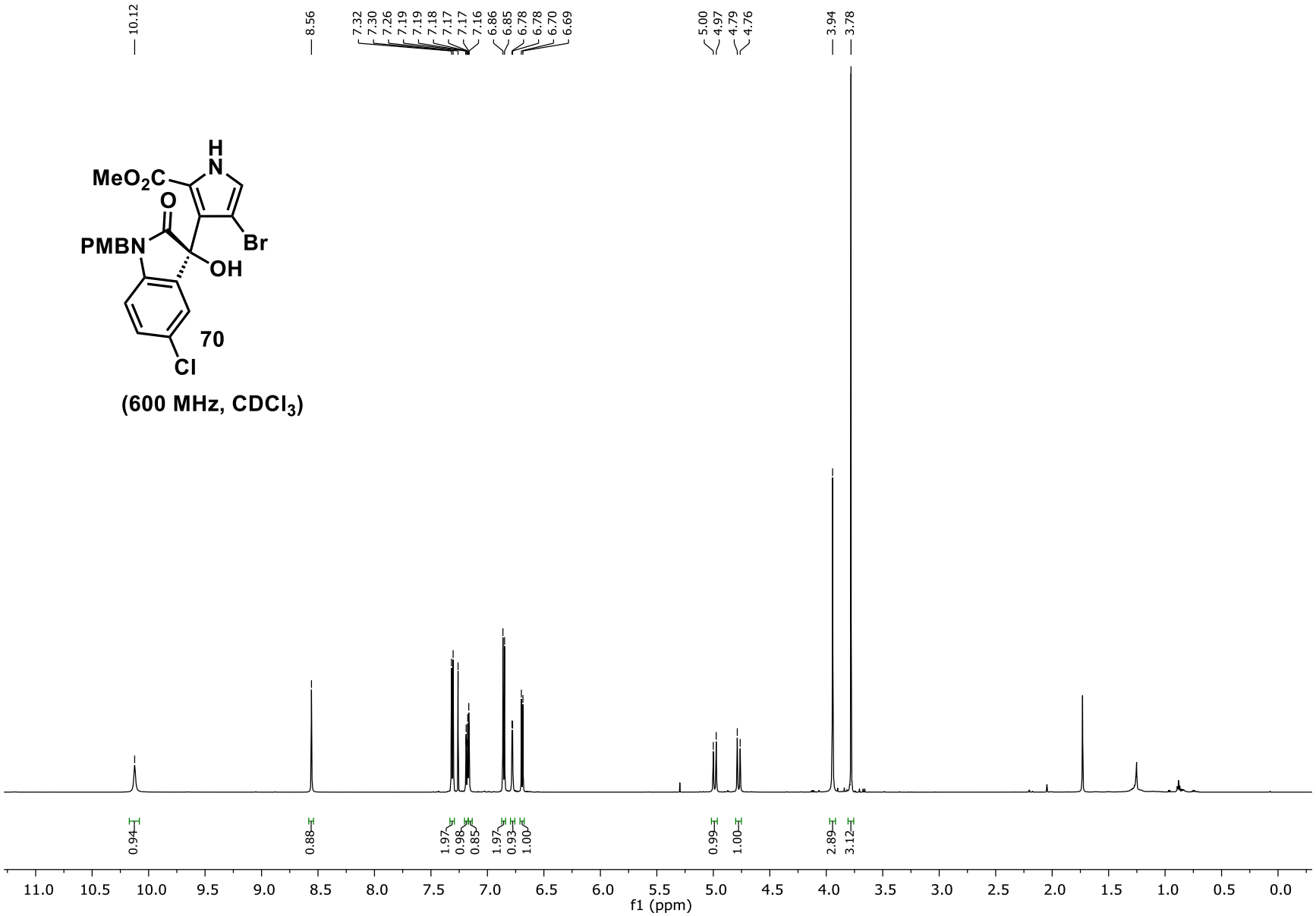

173.4
159.7
149.2
145.2
138.2
138.0
128.8
128.6
126.7
124.1
122.6
122.5
121.2
120.7
118.3
115.7
115.2
113.9
112.1
108.5
54.8
50.8
39.9
39.8
39.7
39.5
39.4
39.2
39.1
26.7
MeO2C
O
H
N
MeN
HN
Cl
73
(151 MHz, DMSO-d6)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

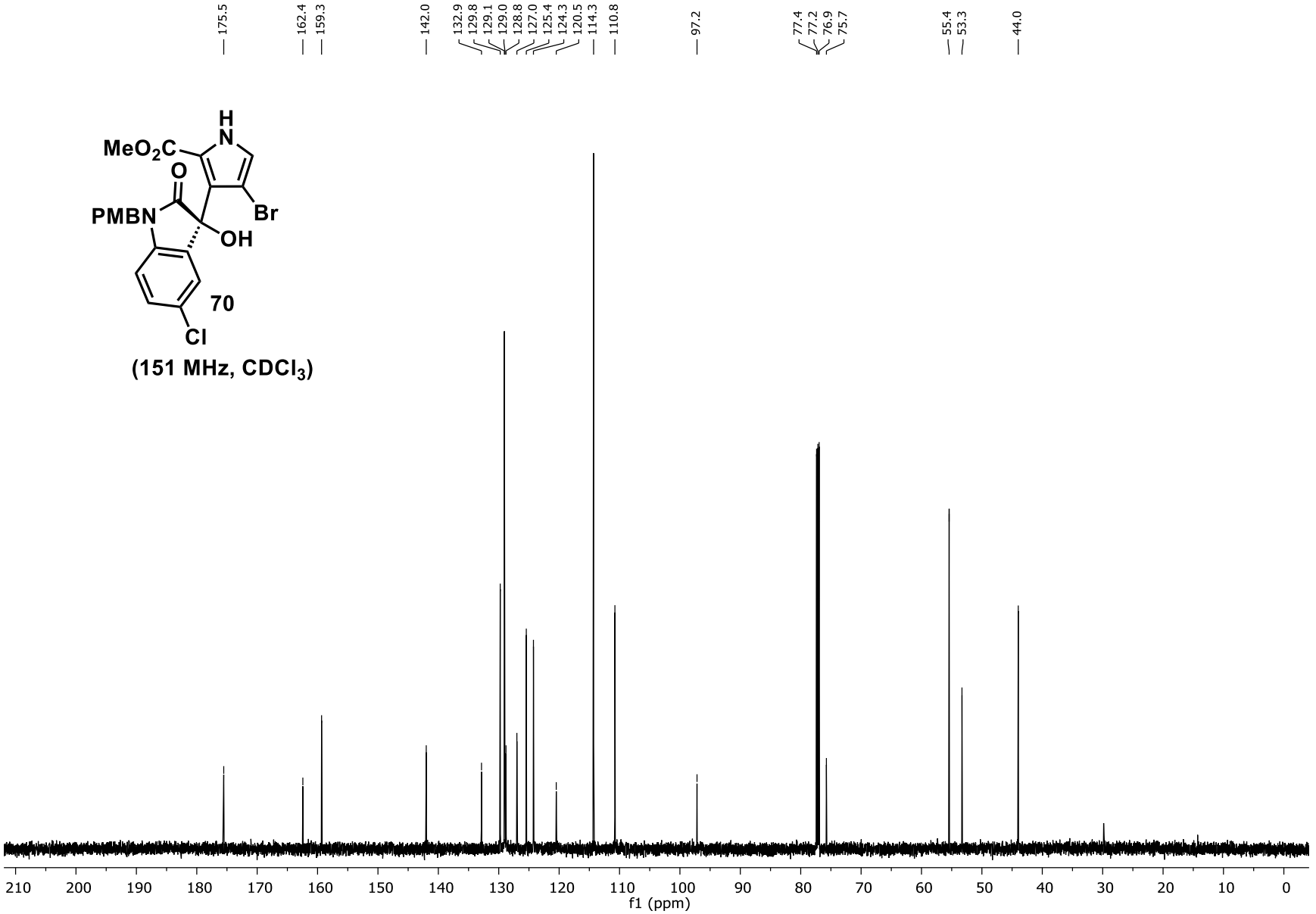


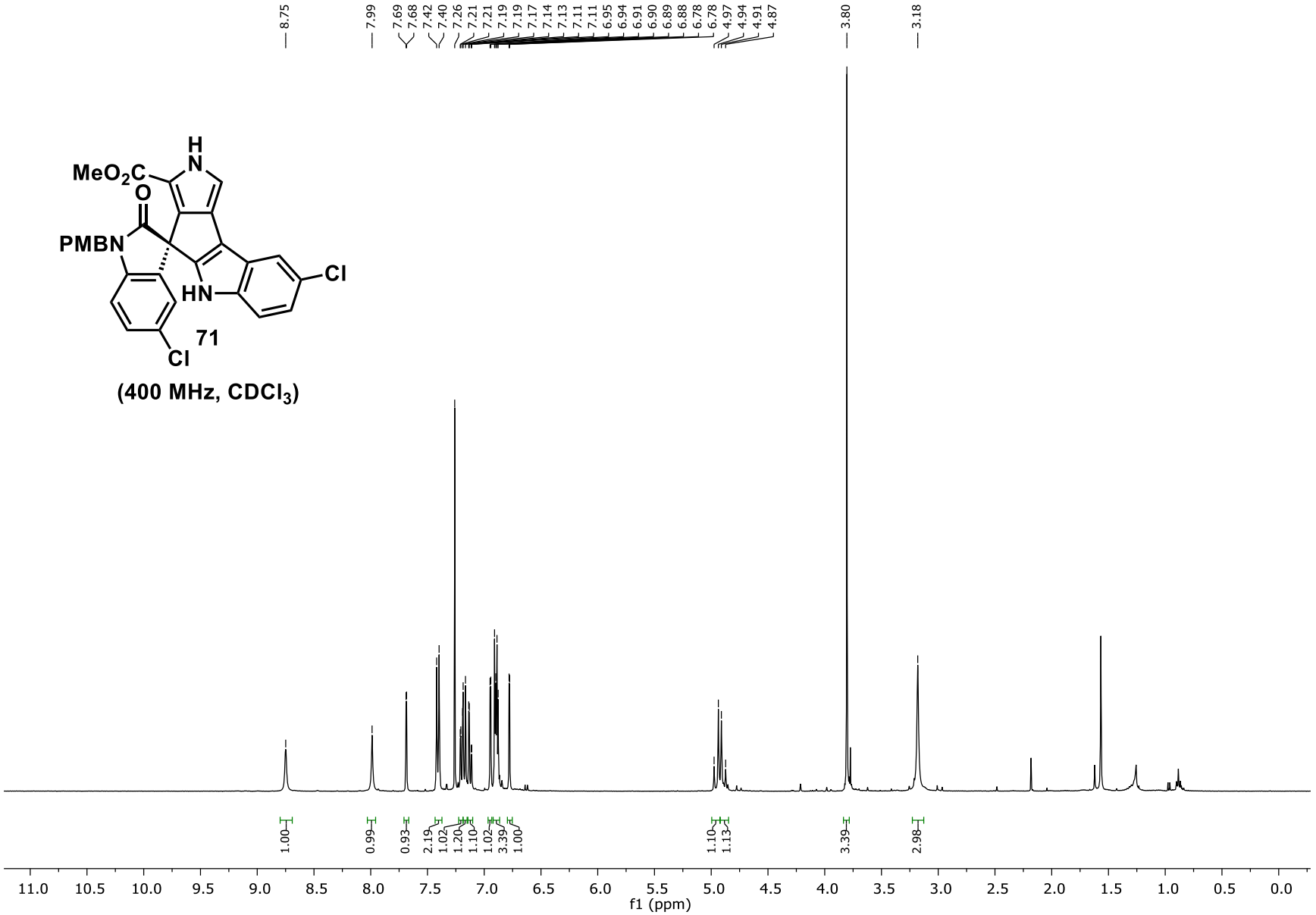
6: *spiroindimicin F*
(600 MHz, DMSO-d_6)

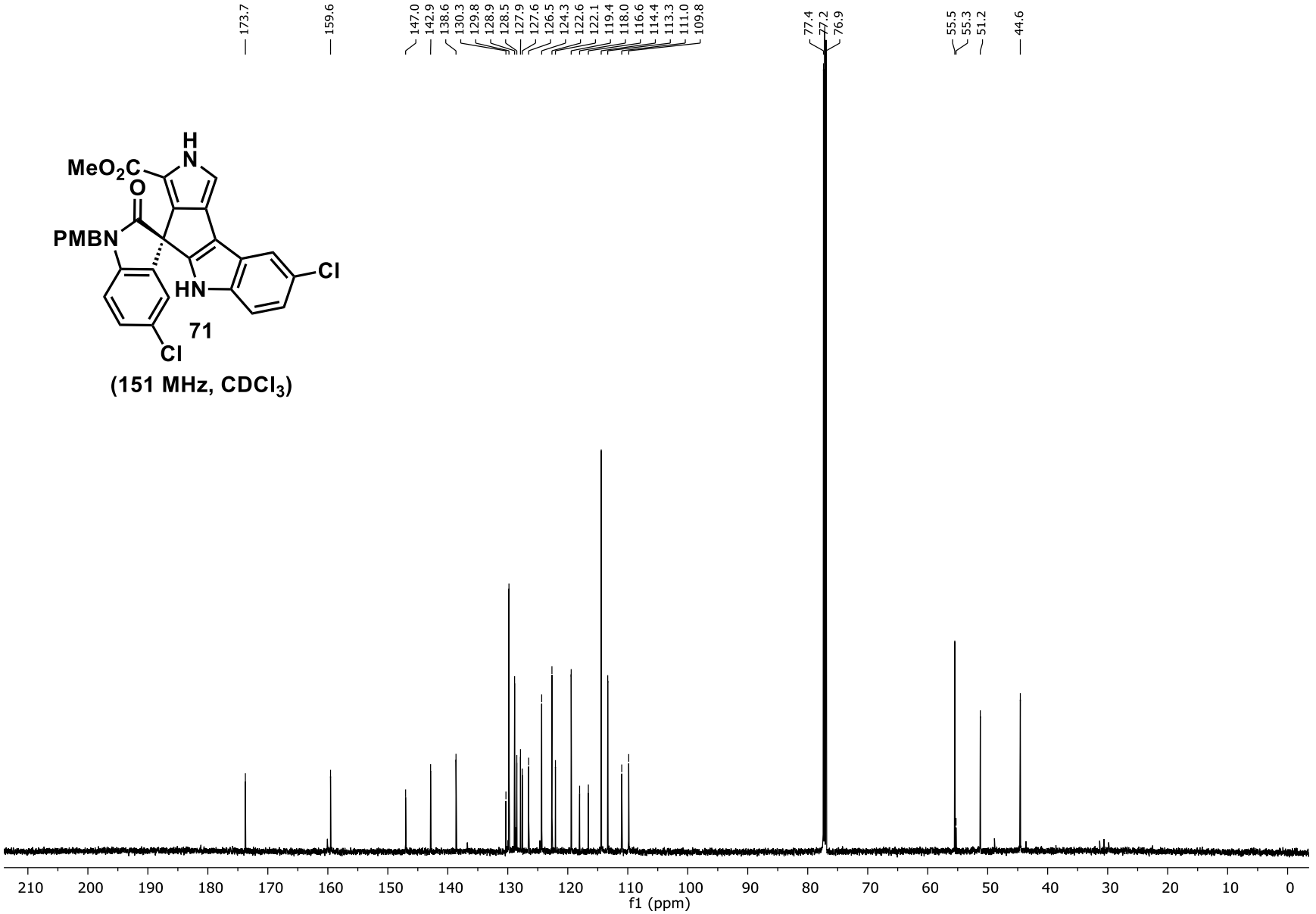


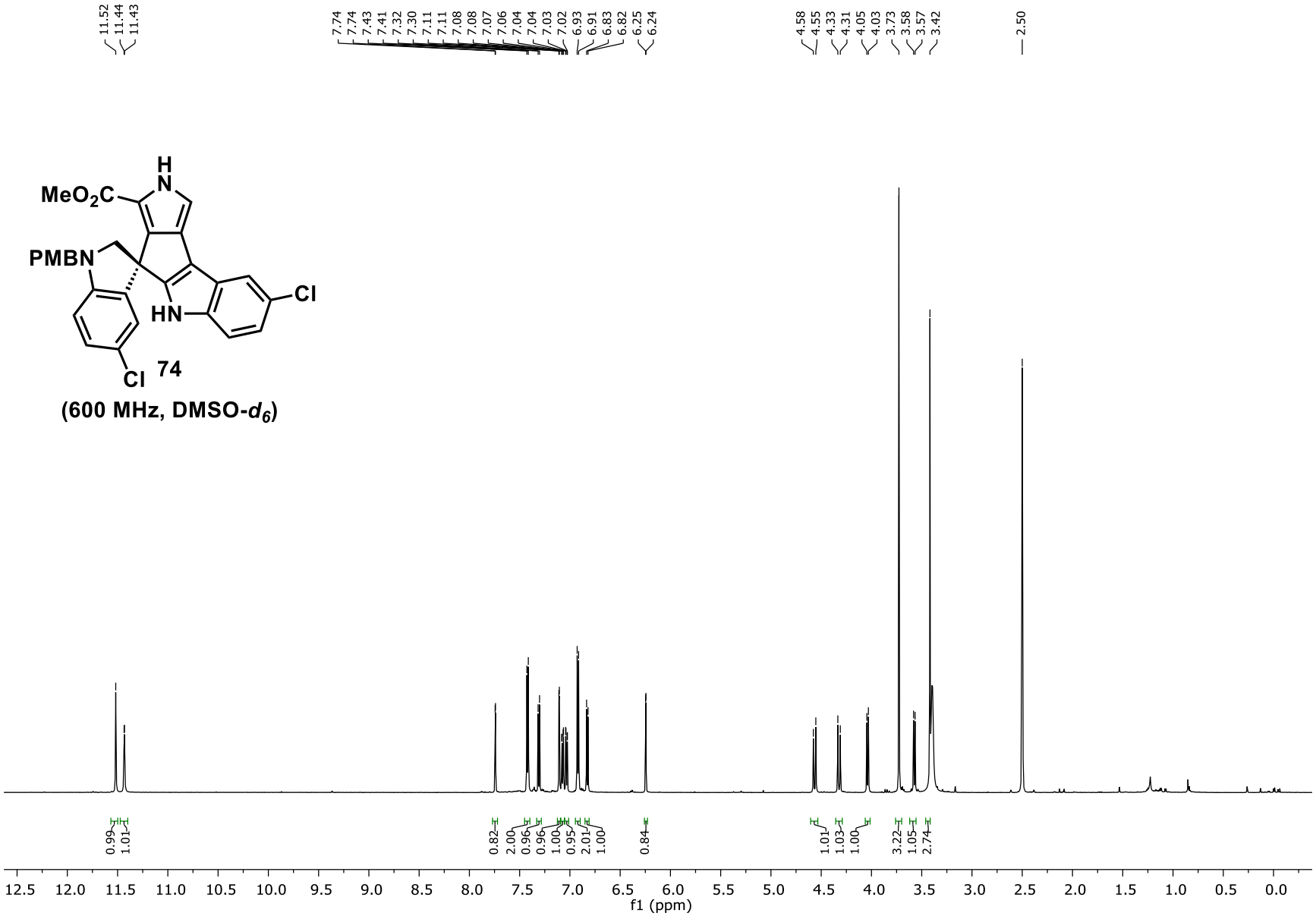
6: *spiroindimicin F*
(151 MHz, DMSO-d_6)

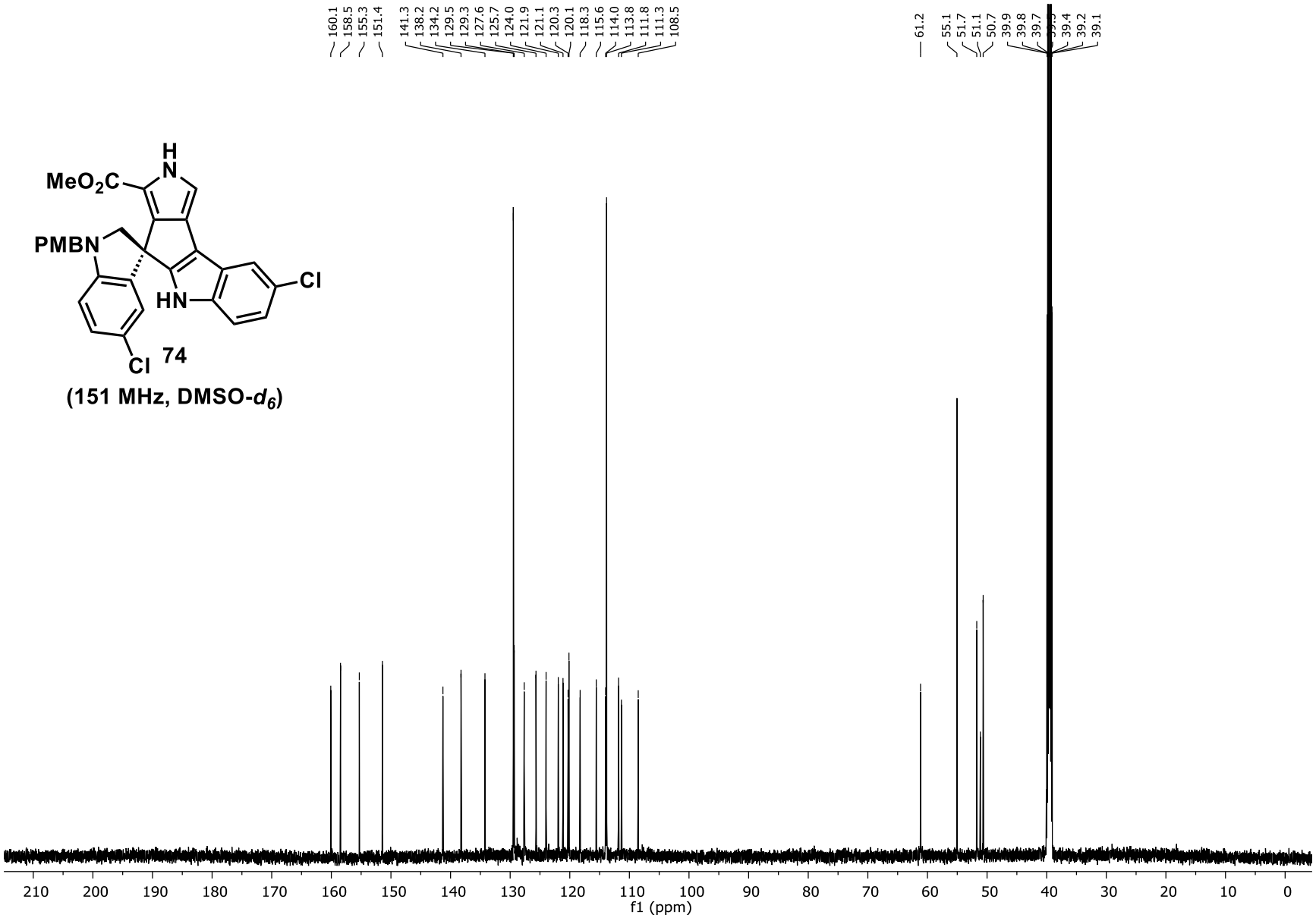

10.12
8.56
7.32
7.30
7.26
7.19
7.19
7.18
7.17
7.17
7.16
6.86
6.85
6.78
6.78
6.70
6.69
5.00
4.97
4.79
4.76
3.94
3.78
MeO2C
H
N
O
PMBN
Br
OH
70
Cl
(600 MHz, CDCl3)
0.94
0.88
1.97
0.98
0.85
1.97
0.93
1.00
0.99
1.00
2.89
3.12
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

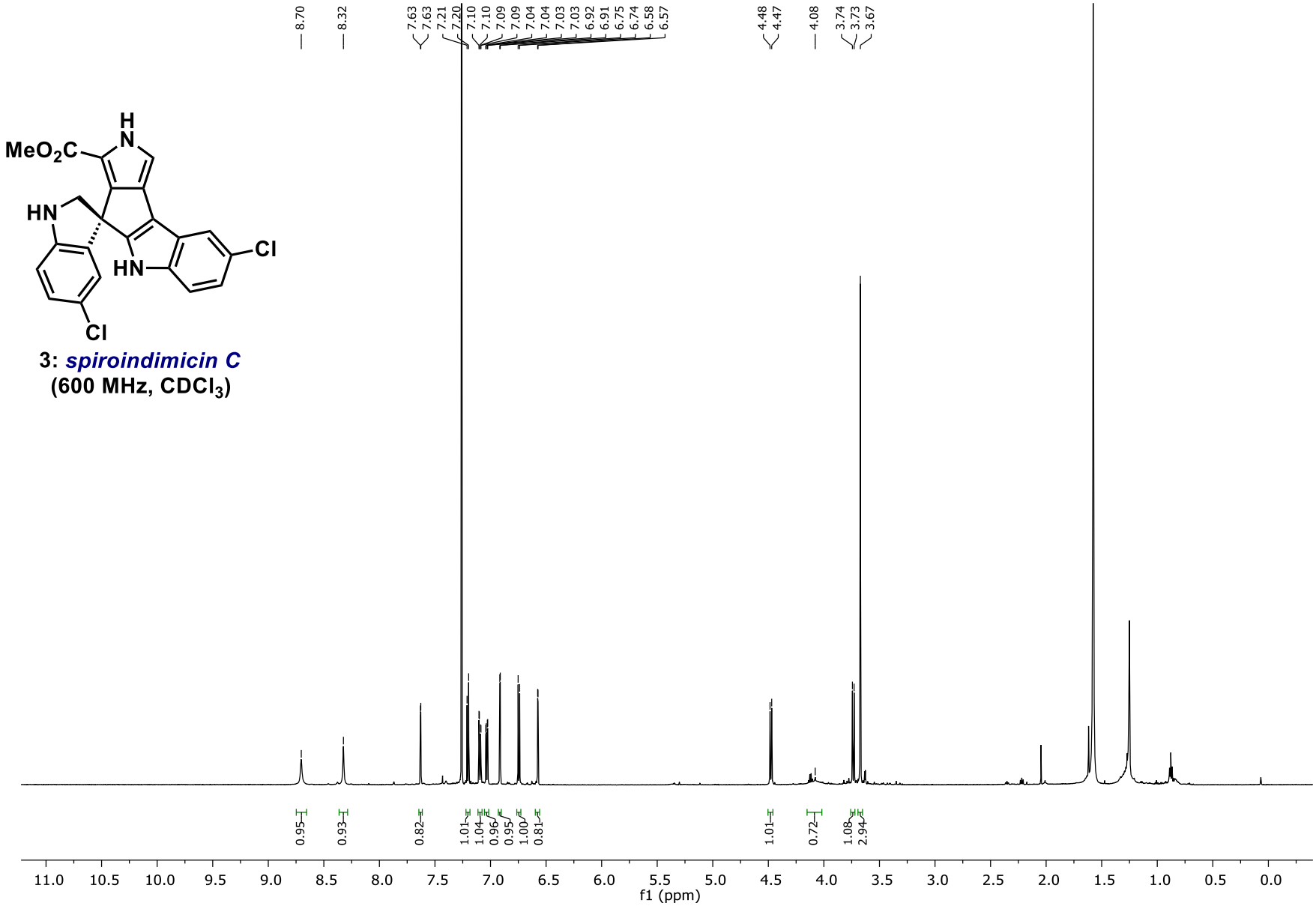

175.5
162.4
159.3
142.0
132.9
129.8
129.1
129.0
128.8
127.0
125.4
124.3
120.5
114.3
110.8
97.2
77.4
77.2
76.9
75.7
55.4
53.3
44.0
MeO2C
H
N
O
PMBN
Br
OH
70
Cl
(151 MHz, CDCl3)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


8.75
7.99
7.69
7.68
7.42
7.40
7.26
7.21
7.19
7.19
7.17
7.14
7.13
7.11
7.11
6.95
6.94
6.91
6.90
6.89
6.88
6.78
6.78
4.97
4.94
4.91
4.87
3.80
3.18
MeO2C
O
H
N
PMBN
HN
Cl
Cl
71
(400 MHz, CDCl3)
1.00
0.99
0.93
2.19
1.02
1.20
1.10
1.02
3.39
1.00
1.10
1.13
3.39
2.98
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

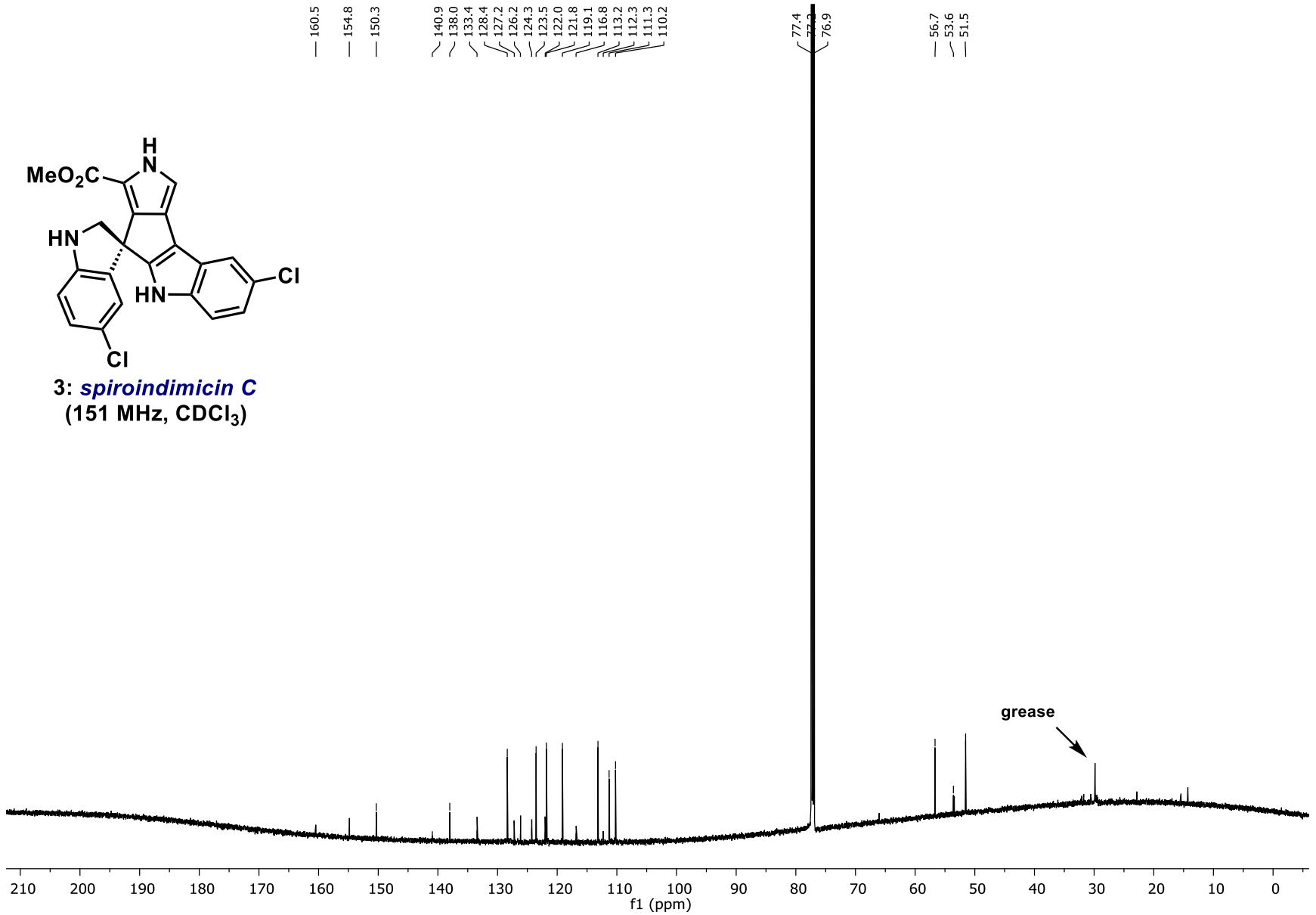

173.7
159.6
147.0
142.9
138.6
130.3
129.8
128.9
128.5
127.9
127.6
126.5
124.3
122.6
122.1
119.4
118.0
116.6
114.4
113.3
111.0
109.8
77.4
77.2
76.9
55.5
55.3
51.2
44.6
MeO2C
O
H
N
PMBN
HN
Cl
Cl
71
(151 MHz, CDCl3)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


11.52
11.44
11.43
7.74
7.74
7.43
7.41
7.32
7.30
7.11
7.11
7.08
7.08
7.07
7.06
7.04
7.04
7.03
7.02
6.93
6.91
6.83
6.82
6.25
6.24
4.58
4.55
4.33
4.31
4.05
4.03
3.73
3.58
3.57
3.42
2.50
H
N
MeO2C
PMBN
HN
Cl
Cl
74
(600 MHz, DMSO-d6)
0.99
1.01
0.82
2.00
0.96
0.96
1.00
0.95
2.01
1.00
0.84
1.01
1.03
1.00
3.22
1.05
2.74
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


160.1
158.5
155.3
151.4
141.3
138.2
134.2
129.5
129.3
127.6
125.7
124.0
121.9
121.1
120.3
120.1
118.3
115.6
114.0
113.8
111.8
111.3
108.5
61.2
55.1
51.7
51.1
50.7
39.9
39.8
39.7
39.4
39.2
39.1
MeO2C
H
N
PMBN
HN
Cl
Cl
74
(151 MHz, DMSO-d6)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



3: *spiroindimicin C*
(600 MHz, $CDCl_3$)



3: *spiroindimicin C*
(151 MHz, $CDCl_3$)