Synthesis of (±)-*cis*-Clavicipitic Acid by a Rh(I)-Catalyzed Intramolecular Imine Reaction

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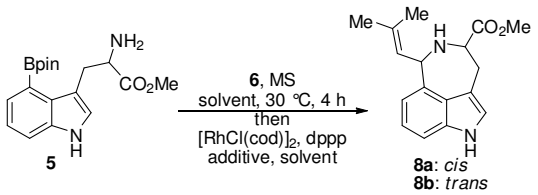
Abbreviations:
Pd_2dba_3 = Tris(dibenzylideneacetone)dipalladium(0); XPhos = 2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl; DME = Dimethoxyethane; cod = 1,5-Cyclooctadiene; TEA = triethylamine; dppp = 1,3-bis(diphenylphosphino)propane; DABCO = 1,4-diazabicyclo[2.2.2]octane; dppbenz = 1,2-Bis(diphenylphosphino)benzene; dppe = 1,2-bis(diphenylphosphino)etane; dppf = 1,1'-Bis(diphenylphosphino)ferrocene; Binap = (1,1′-Binaphthalene-2,2′-diyl)bis(diphenylphosphine); Josiphos (*R*,*S*)-PPF-Pcy_2 = (R)-1-[(S_P)-2-(Diphenylphosphino)ferrocenyl]ethyldicyclohexylphosphine; Josiphos (*R*,S)-cy_2PF-$PtBu_2$ = (R)-1-[(S_P)-2-(Dicyclohexylphosphino)ferrocenyl]ethyldi-*tert*-butylphosphine

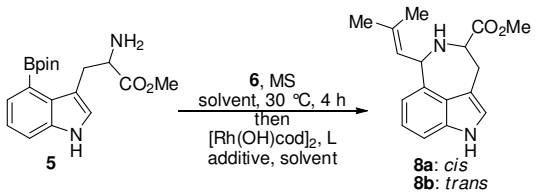
Table 1. Intramolecular Rh(I)-Catalyzed Hydroarylation of **5** and 3-methylbut-2-enal (**6**)



Entry[a]	Solvent	Additive (equiv)	Temp (°C)	Time (h)	Yield (%)[b]	dr (8a/8b)[c]
1	Dioxane	-	80	16	-	-
2	Dioxane	K_3PO_4 (0.2)	80	60	9	nd
3	Dioxane	KOH (0.7) in H_2O	80	60	18	nd
4	Dioxane	MeOH (3)	50	60	-	-
5	DME	CsF (3)	85	48	25	100/0
6	Toluene	TEA (2)	50	90	NR	-

[a]Reaction conditions: **5** (0.1 mmol), solvent (0.8 mL), molecular sieves 4 Å (100 mg), **6** (0.11 mmol), 30 °C, 4 h, then $[RhCl(cod)]_2$ (10 mol %), dppp (20 mol %), additive. [b] Yield of isolated product. [c]Determinated by analysis of the crude ^{1}H NMR with comparison to reported spectra. nd: not determined. NR: no reaction.

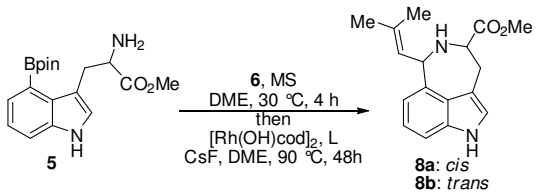
Table 2. Intramolecular Rh(I)-Catalyzed Hydroarylation of **5** and 3-methylbut-2-enal (**6**)



Entry[a]	Solvent	Additive (equiv)	Ligand	Temp (°C)	Time (h)	Yield (%)[b]	dr (8a/8b)[c]
1	Dioxane	-	-	80	60	-	-
2	DME	-	-	85	16	-	-
3	Dioxane	-	dppp	80	60	-	-
4	DME	K_3PO_4 (0.2)	dppp	85	48	7	-
5	DME	K_2CO_3 (2)	dppp	85	48	-	-
6	Dioxane	CsF (3)	dppp	90	60	33	100/0
7	DME	CsF (3)	dppp	85	48	41	100/0
8	DME	TEA (2)	dppp	85	48	-	-
9	DME	DABCO (2)	dppp	85	48	-	-
10	DME	CsF (3)	-	85	16	55	100/0
11	DME	KHF_2 (3)	-	85	60	-	-
12	DME	TBAF (3)	-	85	48	17	nd
13[d]	DME	CsF (3)	-	85	16	24	nd
14[e]	DME	CsF (3)	-	85	16	63	100/0
15[e]	DME	CsF (1)	-	85	16	22	nd

[a]Reaction conditions: **5** (0.1 mmol), solvent (0.8 mL), molecular sieves 4 Å (100 mg), **6** (0.11 mmol), 30 °C, 4h, then $[RhOH(cod)]_2$ (10 mol %), additive, ligand (20 mol %). [b]Yield of isolated product. [c]Determinated by analysis of the crude ^{1}H NMR with comparison to reported spectra. [d]The reaction was carried out with $[RhCl(C_2H_4)_2]_2$ (10 mol %). [e]After imine formation was diluted with DME (1.2 mL). nd: not determined.

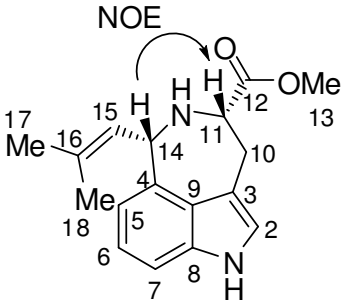
Table 3. Intramolecular Rh(I)-Catalyzed Hydroarylation of **5** and 3-methylbut-2-enal (**6**)



Entry[a]	Ligand	Yield (%)[b]	dr (8a/8b)[c]	er (8a)[d]
1	dppbenz	40	nd	-
2	dppe	25	nd	-
3	dppf	41	nd	-
4	(+)-Binap	23	100/0	52:48
5	Josiphos (*R*,*S*)-PPF-Pcy_2	25	100/0	59:41
6	Josiphos (*R*,*S*)-cy_2PF-P*t*Bu_2	22	100/0	56:44
7[e]	Josiphos (*R*,*S*)-cy_2PF-P*t*Bu_2	25	100/0	55:45

[a]Reaction conditions: **5** (0.1 mmol), DME (0.8 mL), Molecular sieves 4 Å (100 mg), **6** (0.11 mmol), 30 °C, 4 h, then $[RhOH(cod)]_2$ (10 mol %), CsF (0.3 mmol), ligand (20 mol %), 85 °C. [b]Yield of isolated product. [c]Calculated by ^1H NMR analysis of the crude reaction mixture. [d]Determined by HPLC analysis on a chiral stationary phase. [e]The reaction was carried out in toluene. nd: not determined.

Table 4. Comparison of our data with literature:



Assignment	**This Work** ^{13}C NMR, 50 MHz $CDCl_3$	**Jia et al. Report** [1] (±)-*cis*-Clavicipitic acid methyl ester ^{13}C NMR, 100 MHz $CDCl_3$	**Chemical Shift Difference** $\Delta\delta = \delta$ (this work) - δ (Jia et al. Report)
C2	121.5	121.5	0
C3	112.9	113.0	0.1
C4	137.0	137.0	0
C5	117.7	117.8	0.1
C6	121.5	121.5	0
C7	109.3	109.4	0.1
C8	137.3	137.4	0.1
C9	125.0	125.0	0
C10	33.7	33.7	0
C11	62.2	62.2	0
C12	174.5	174.6	0.1
C13	52.4	52.4	0
C14	61.9	61.9	0
C15	127.4	127.4	0
C16	134.3	134.4	0.1
C17	25.8	25.8	0
C18	18.3	18.4	0.1

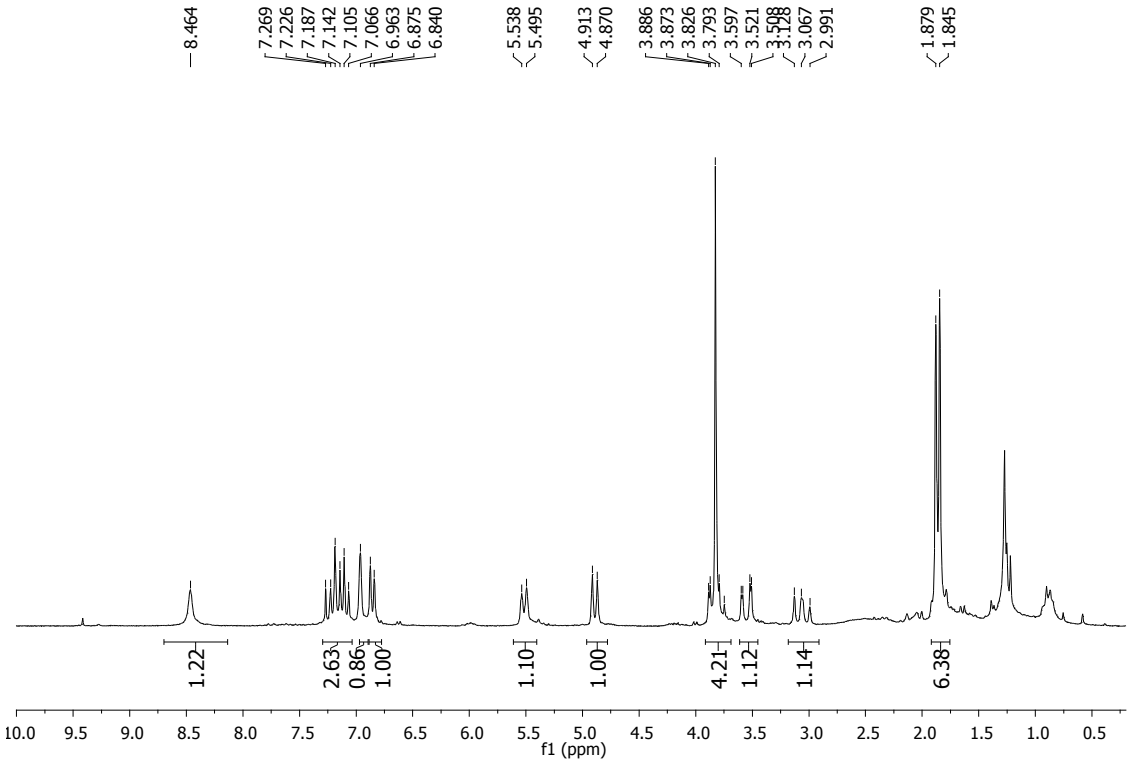
Table 5. Comparison of our data with literature:

This Work ^{1}H NMR, 200 MHz $CDCl_3$	**Jia et al. Report** [1] (±)-*cis*-Clavicipitic acid methyl ester ^{1}H NMR, 400 MHz $CDCl_3$
1.85 (d, J = 1.0 Hz, 3H)	1.84 (d, J = 1.2 Hz, 3H)
1.89 (d, J = 1.0 Hz, 3H)	1.88 (d, J = 1.2 Hz, 3H)
2.68 (br s, 1H)	2.53 (br s, 1H)
3.07 (ddd, J_1 = 15.5 , J_2 = 12.0, J_3 = 1.0 Hz, 1H)	3.06 (ddd, J_1 = 15.2 , J_2 = 12.0, J_3 = 1.2 Hz, 1H)
3.56 (dd, J_1 = 15.5 , J_2 = 2.5 Hz, 1H)	3.54 (dd, J_1 = 15.2 , J_2 = 2.8 Hz, 1H)
3.83 (s, 3H)	3.82 (s, 3H)
3.84 (dd, J_1 = 12.0 , J_2 = 2.5 Hz, 1H)	3.84 (dd, J_1 = 12.0 , J_2 = 2.8 Hz, 1H)
4.90 (d, J = 9.0 Hz, 1H)	4.89 (d, J = 8.8 Hz, 1H)
5.52 (d, J = 9.0 Hz, 1H)	5.51 (d, J = 8.8 Hz, 1H)
6.87 (d, J = 7.5 Hz, 1H)	6.85 (d, J = 8.0 Hz, 1H)
6.97 (s, 1H)	6.94 (s, 1H)
7.11 (t, J = 7.5 Hz, 1H)	7.10 (t, J = 8.0 Hz, 1H)
7.21 (d, J = 7.5 Hz, 1H)	7.17 (d, J = 8.0 Hz, 1H)
8.44 (br s, 1H)	8.44 (br s, 1H)

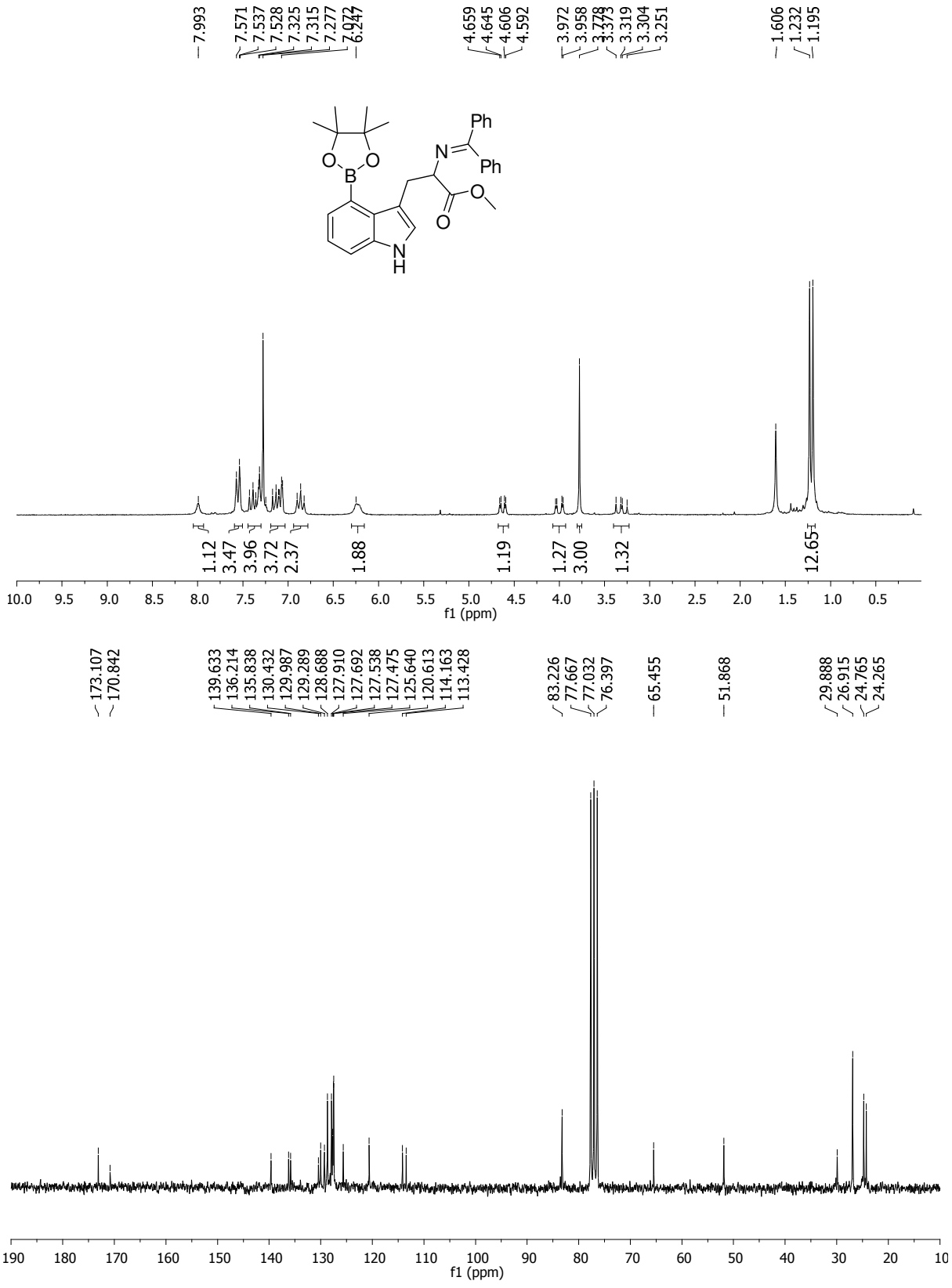
References.

(1) Xu, Z.; Hu, W.; Liu, Q.; Zhang, L.; Jia, Y. *J. Org. Chem.* **2010**, *75*, 7626.

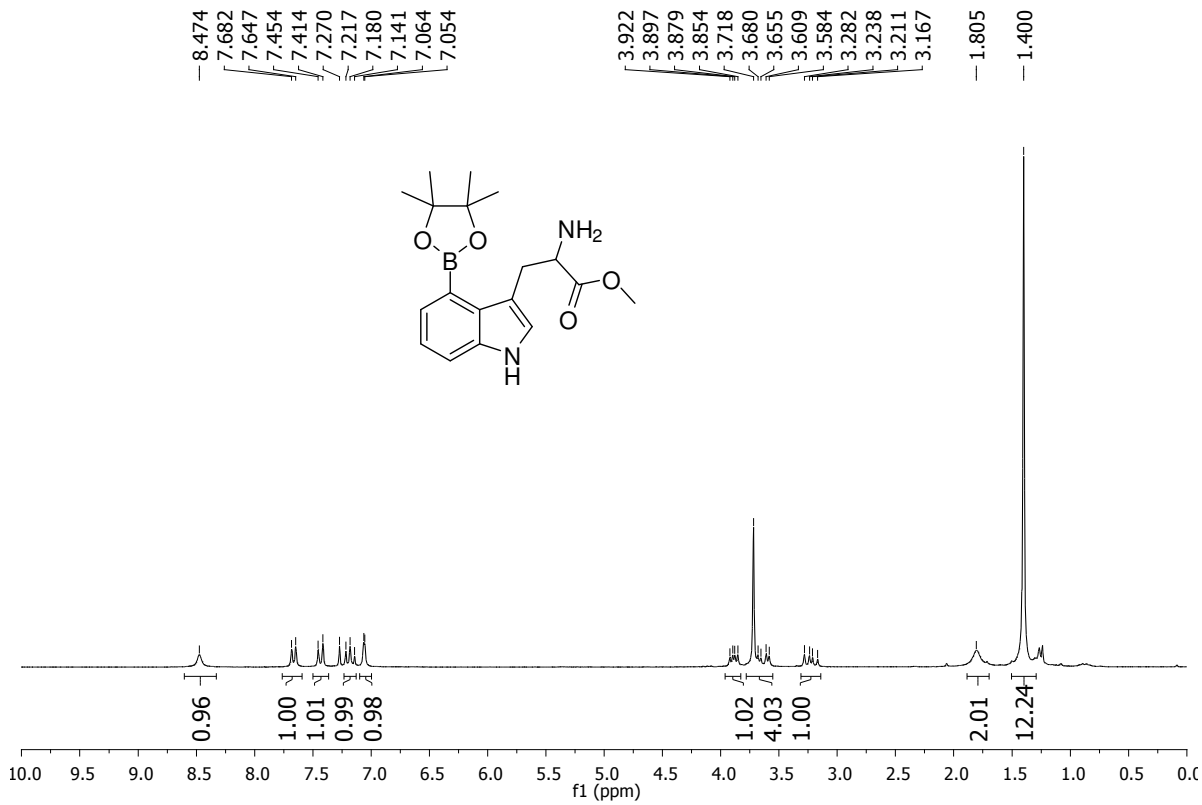
^{1}H NMR of the crude of intramolecular Rh(I)-catalyzed hydroarylation of **5** and 3-methylbut-2-enal (**6**)

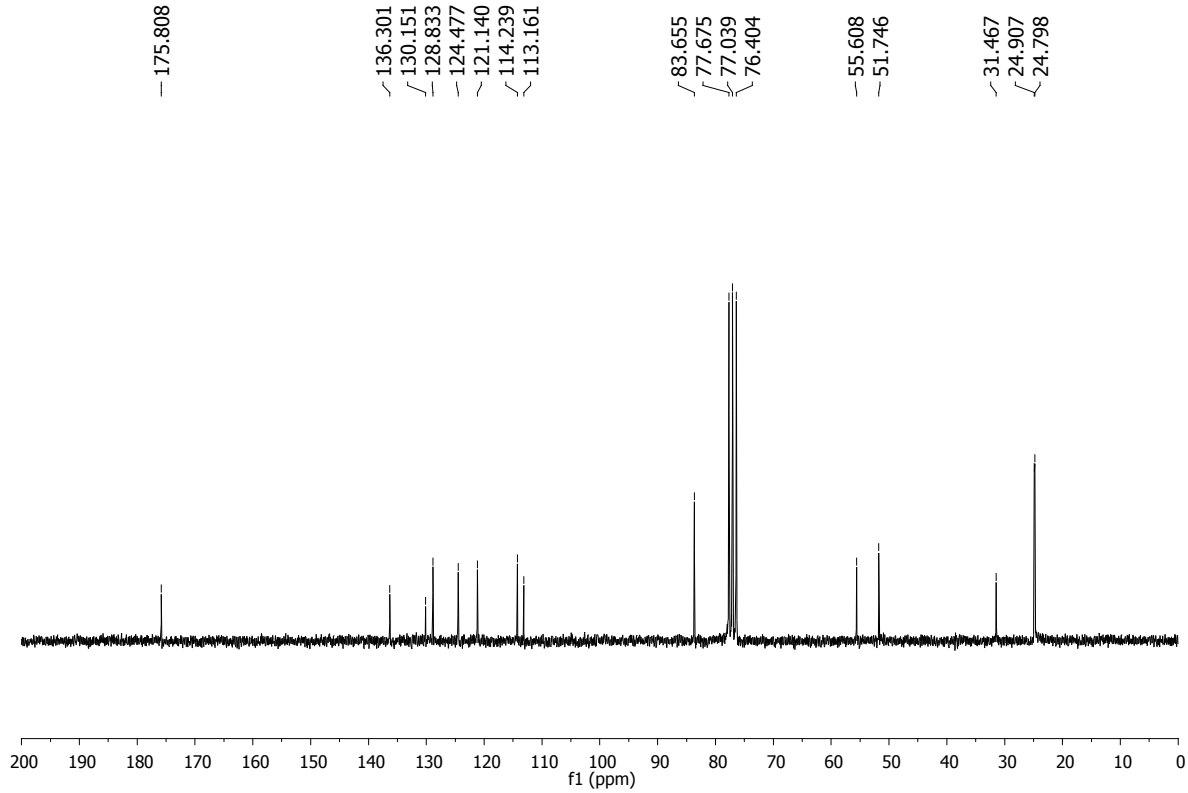


^{1}H and ^{13}C NMR Spectra of Compound **4**

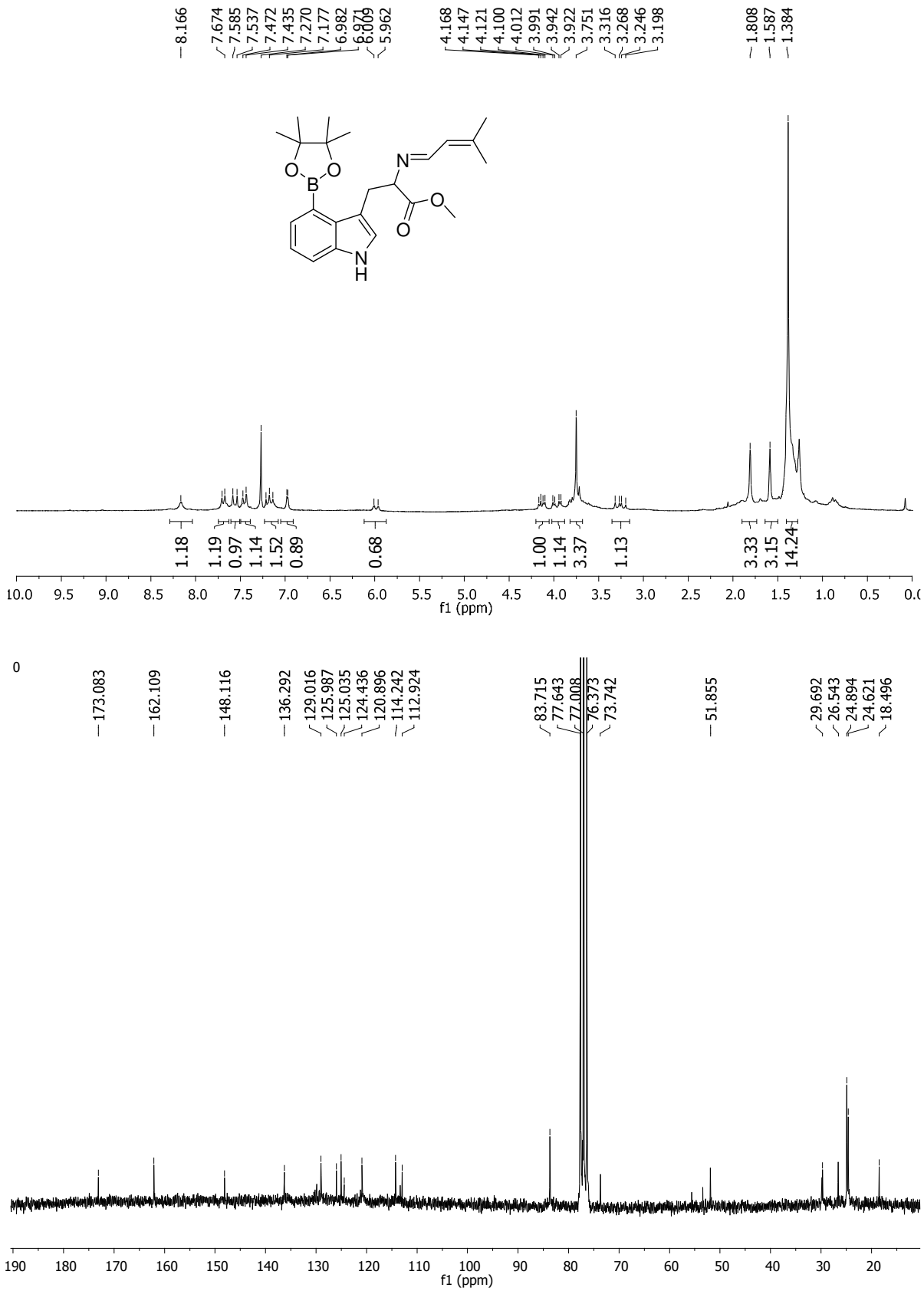


^{1}H and ^{13}C NMR Spectra of Compound **5**

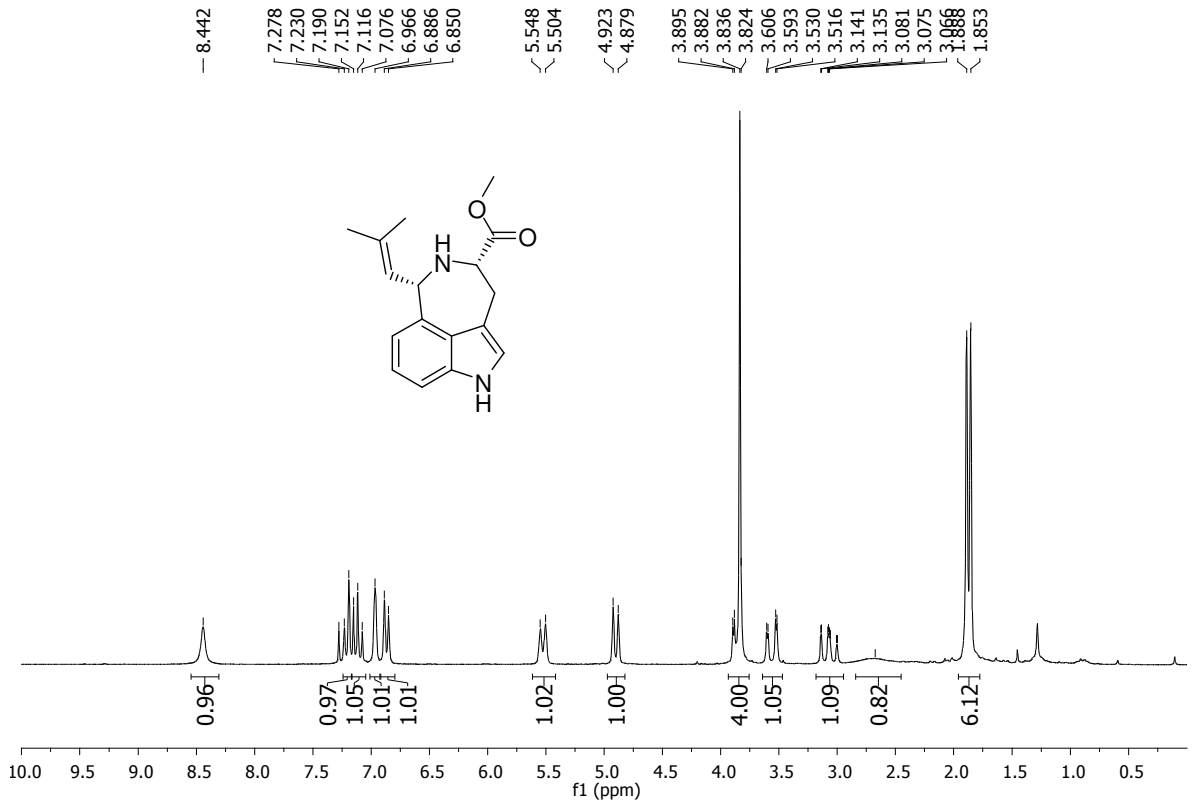


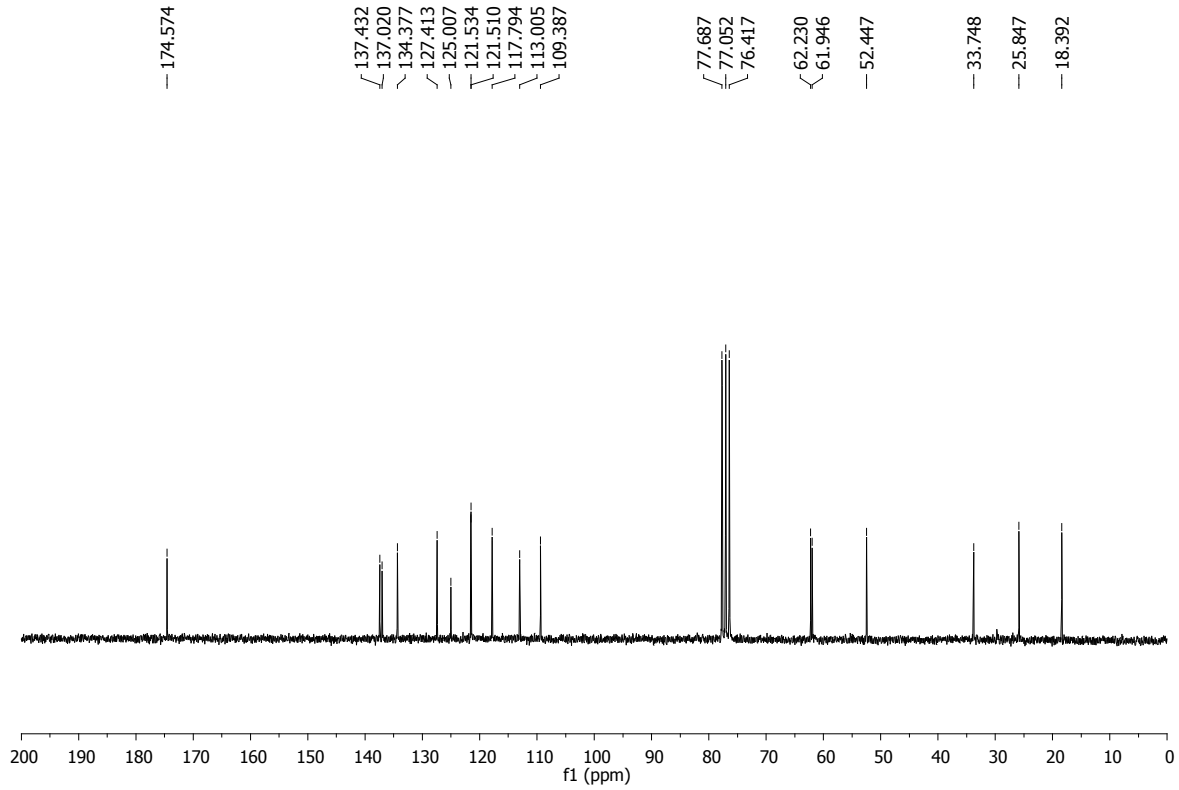


^{1}H and ^{13}C NMR Spectra of Compound **7**



^{1}H and ^{13}C NMR Spectra of Compound **8a**





^{1}H and ^{13}C NMR Spectra of Compound **1a**