

Supporting Information

Atroposelective Total Syntheses of Naphthylisoquinoline Alkaloids with P-Configuration

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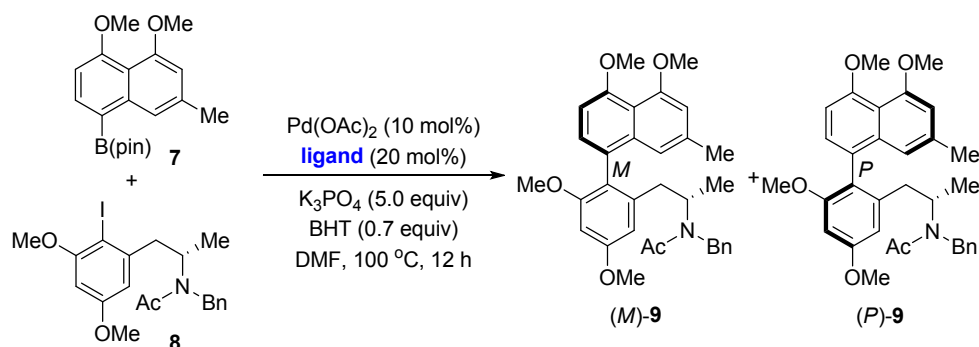
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1. Optimization of Reaction Conditions

1-1. Ligand Screening

Table S1. Ligand Screening in Atroposelective Suzuki-Miyaura Coupling Reaction



Entry	Ligand	Yield ^a of M+P	Ratio ^b of M:P
1	XantPhos	89%	8 : 1
2	(±)-BINAP	-	N.D. ^c
3	dppf	-	N.D. ^c

^a Isolated yield of a mixture of M and P isomers.

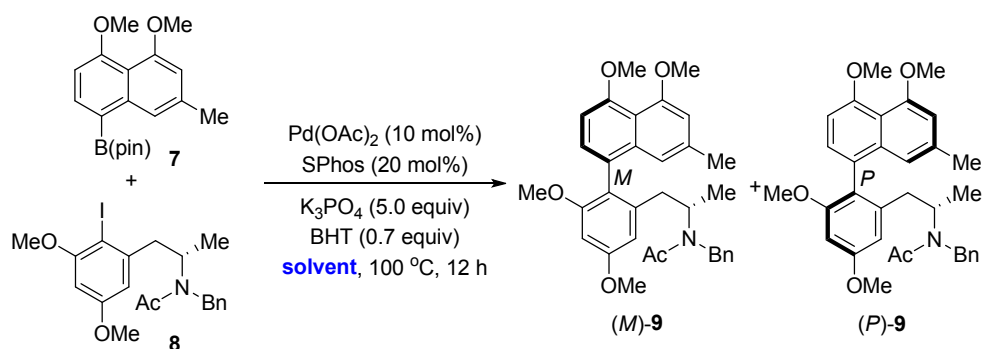
^b Determined by ¹H NMR analysis of a mixture of M and P isomers.

^c Not determined.

The effect of bidentate phosphine ligands on the atropodiastereoselective Suzuki-Miyaura coupling reaction was investigated (Table S1). The choice of the bidentate phosphine ligand exerted a considerable influence on the efficiency of this coupling reaction. When XantPhos was used as a ligand for this reaction, the coupling product **9** was obtained as a mixture of M and P atropisomers with 8:1 ratio in 89% yield (entry 1). However, other bidentate ligands, such as BINAP and dppf, did not provide the coupling product **9** (entries 2 and 3).

1-2. Solvent Screening

Table S2. Solvent Screening in Atroposelective Suzuki-Miyaura Coupling Reaction



Entry	Solvent	Yield ^a of M+P	Ratio ^b of M:P
1	DMF	95%	1 : 3
2	MeCN	93%	1 : 3
3	DMSO	92%	1 : 1
4	DMA	89%	1 : 1.5
5	Toluene	47%	1 : 2.5
6	THF	42%	1 : 2.5

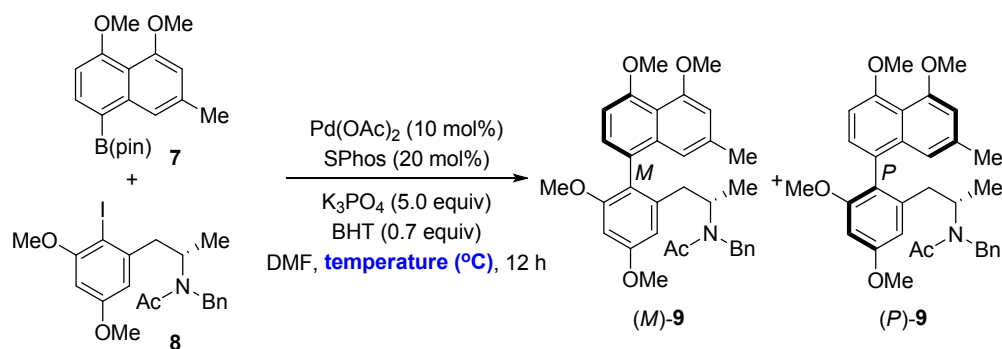
^a Isolated yield of a mixture of M and P isomers.

^b Determined by ¹H NMR analysis of a mixture of M and P isomers.

The effect of solvent on the atropodiastereoselective Suzuki-Miyaura coupling reaction was investigated (Table S2). The choice of solvent played a considerable role in the reactivity and atroposelectivity of this reaction. The P-isomer, (*P*)-**9**, was obtained as the major product (M:P = 1:3) from the reactions in DMF and acetonitrile (entries 1 and 2). However, reactions in DMSO and DMA provided the desired product **9** with lower atroposelectivity (entries 3 and 4). When relatively non-polar solvents, such as toluene and THF, were used as the reaction media, the desired product **9** was obtained in much lower yield and with slightly reduced atroposelectivity (entries 5 and 6).

1-3. Temperature Screening

Table S3. Temperature Screening in Atroposelective Suzuki-Miyaura Coupling Reaction



Entry	Temperature ($^{\circ}\text{C}$)	Yield ^a of M+P	Ratio ^b of M:P
1	80	89%	1 : 3
2	100	95%	1 : 3
3	120	94%	1 : 3

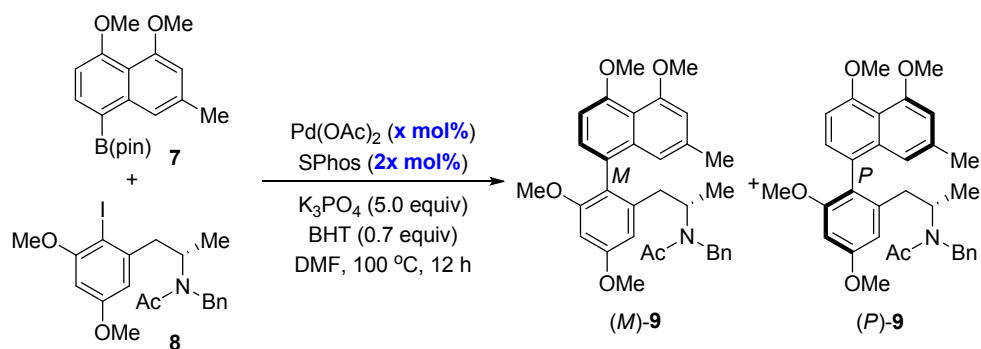
^a Isolated yield of a mixture of M and P isomers.

^b Determined by ^1H NMR analysis of a mixture of M and P isomers.

The effect of temperature on the atropodistereoselective Suzuki-Miyaura coupling reaction was explored (Table S3). It was found that the reaction temperature has little effect on the cross-coupling reaction; the desired coupled product **9** was obtained in similar yields and atroposelectivity regardless of the reaction temperature (entries 1-3).

1-4. Catalyst Loading Screening

Table S4. Catalyst Loading Screening in Atroposelective Suzuki-Miyaura Coupling Reaction



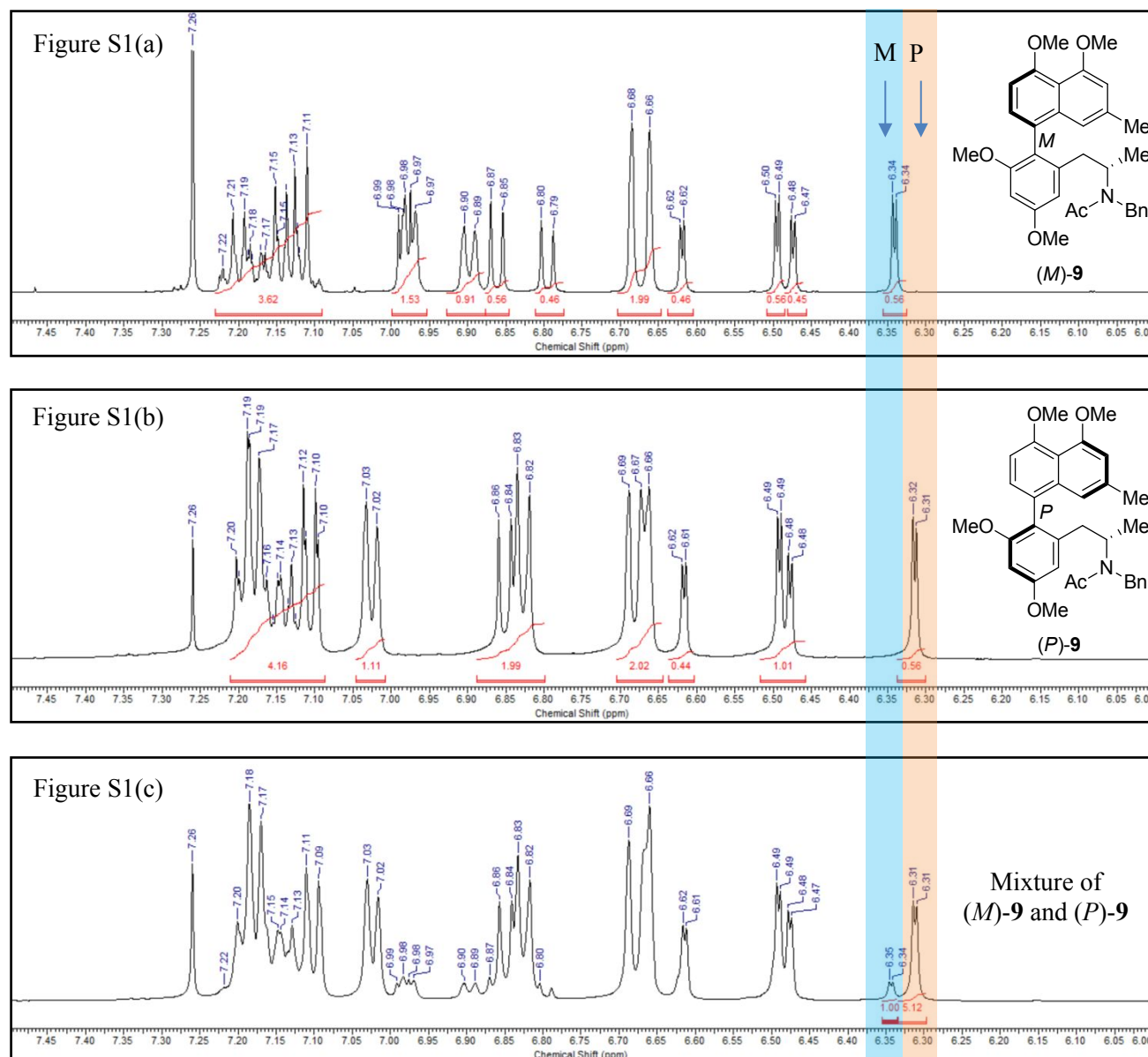
Entry	x	Yield ^a of M+P	Ratio ^b of M:P
1	20	94%	1 : 3
2	10	95%	1 : 3
3	5	93%	1 : 2
4	3	87%	1 : 1.8

^a Isolated yield of a mixture of M and P isomers.

^b Determined by ¹H NMR analysis of a mixture of M and P isomers.

The effect of catalyst loading on the atropodiastereoselective Suzuki-Miyaura coupling reaction was examined (Table S4). The catalyst loading did not affect the efficiency of the coupling reaction when it was higher than 10 mol% (entries 1 and 2). However, when the catalyst loading was used less than 10 mol%, the atroposelectivity of the coupling product **9** was decreased although the no considerable decrease in the yield was observed (entries 3 and 4).

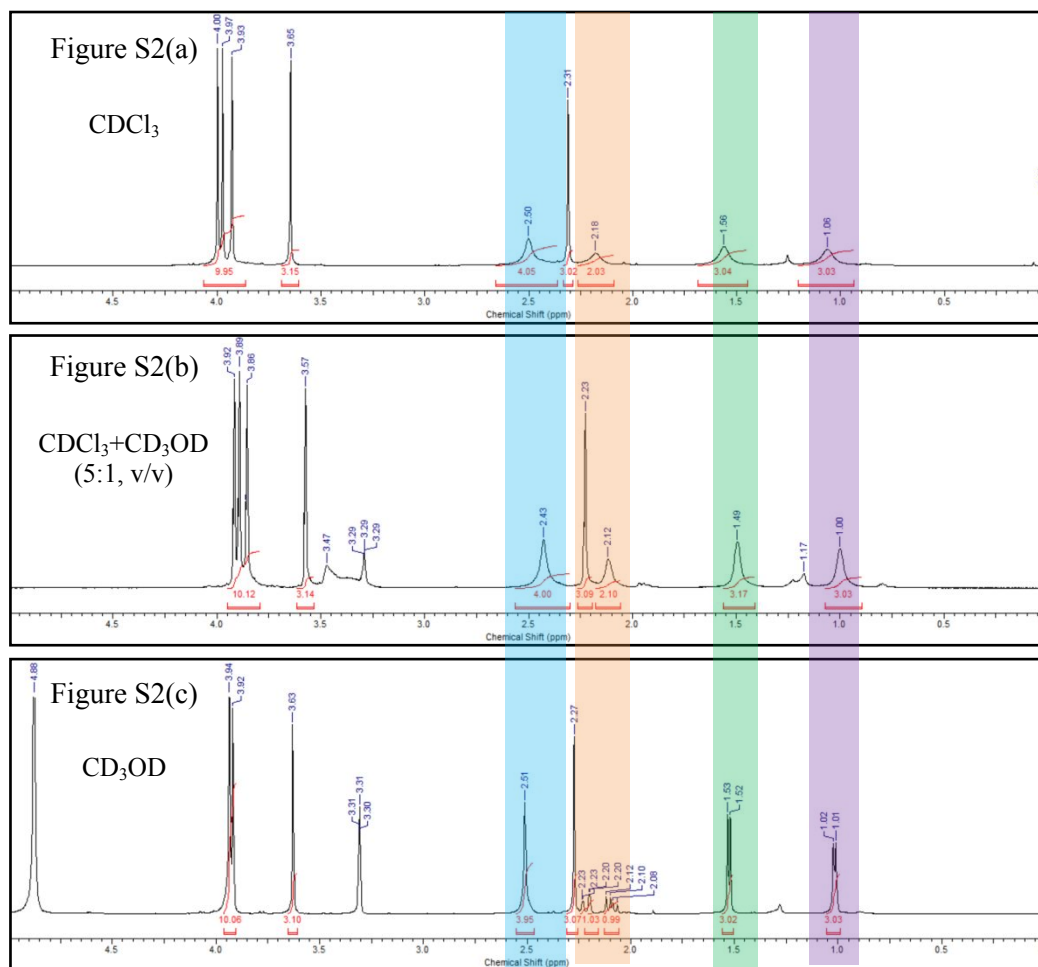
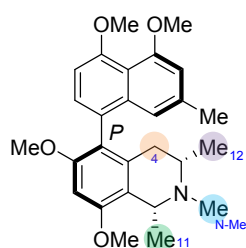
2. Determination of Ratio of (*M*)-**9** and (*P*)-**9**



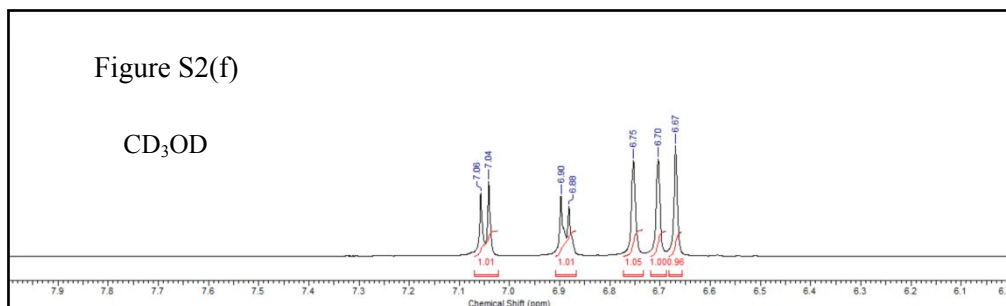
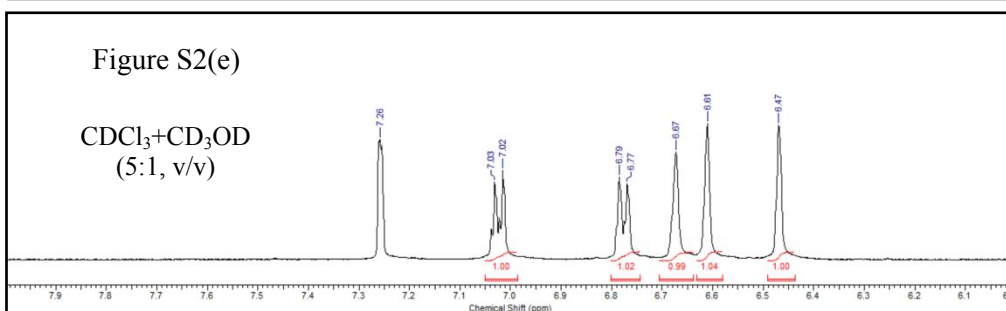
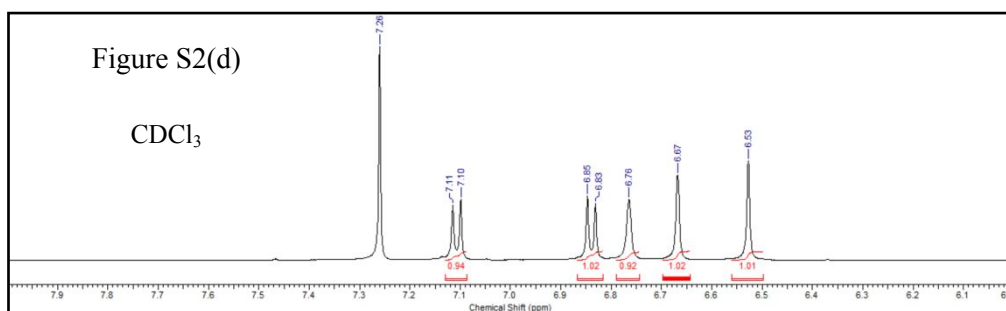
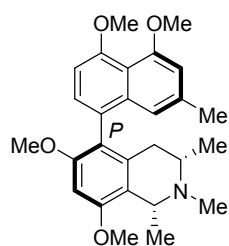
Since the coupling product **9** possesses both axial chirality and tertiary amide moiety, it is very difficult to directly analyze the ratio of two atropisomers, (*M*)-**9** and (*P*)-**9** from the reaction mixture. Thus, the ratio of (*M*)-**9** and (*P*)-**9** was determined by ¹H NMR analysis after purified as a mixture of two atropisomers. As shown the above spectra, the two atropisomers display rather characteristic peaks; (*M*)-**9** has a peak at 6.34 ppm, while (*P*)-**9** has one at 6.31 ppm. By the comparison of these two peaks in the ¹H NMR spectrum of the mixture of two atropisomers, the ratio of the two atropisomers could be determined. As demonstrated in Figure S1(c), the ratio of (*M*)-**9** to (*P*)-**9** was determined as 1:5 (entry 9 in Table 1).

3. Comparison of NMR Data of Ancistrobertsonine C (2) in Different Solvents

3-1. ^1H NMR Spectra of Ancistrobertsonine C (2) in Different Solvents (Aliphatic Region)

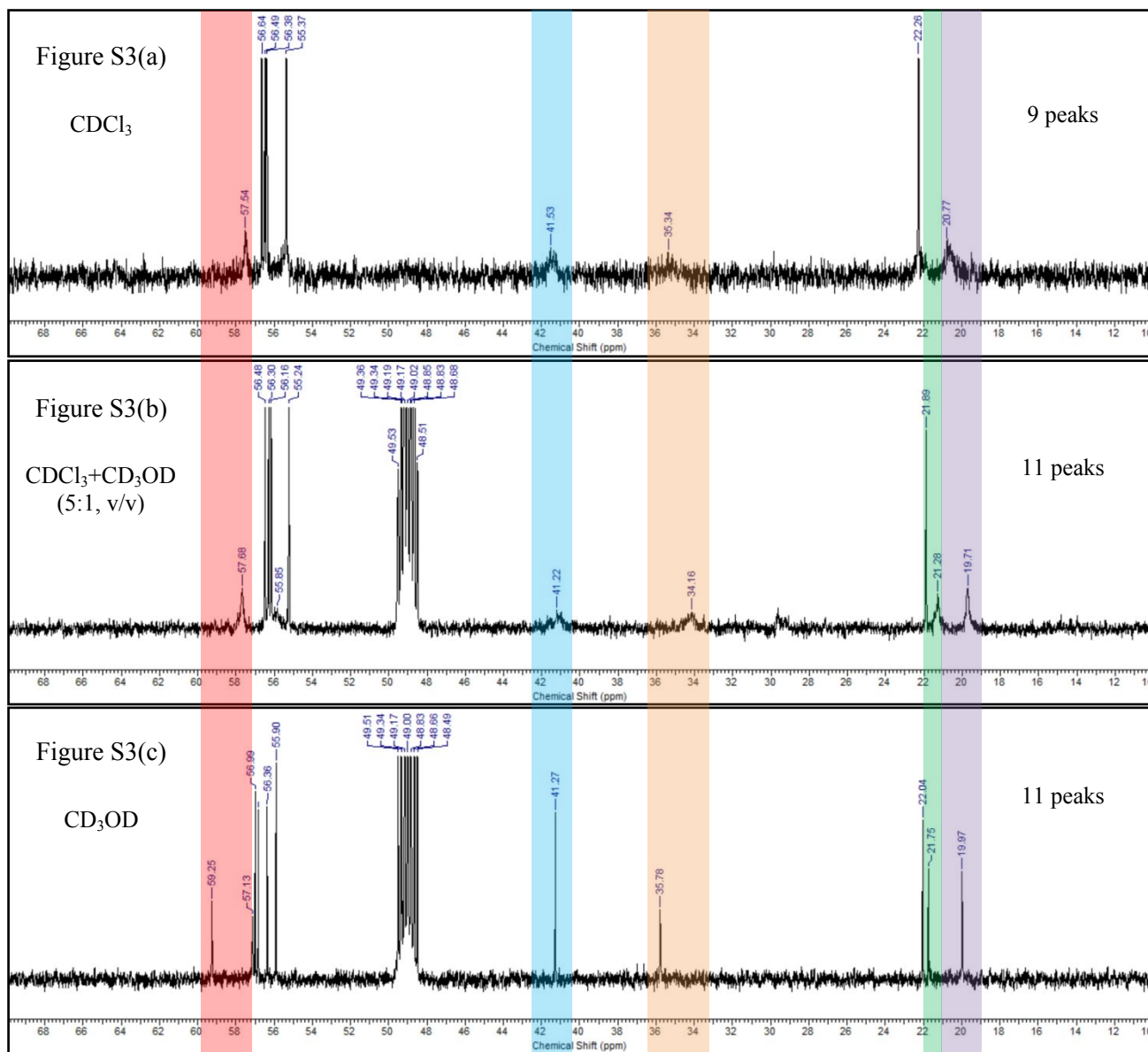
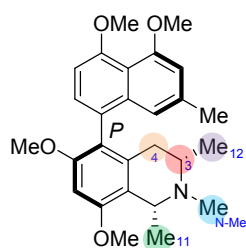


b) ^1H NMR Spectra of Ancistrobertsonine C (**2**) in Different Solvents (Aromatic Region)

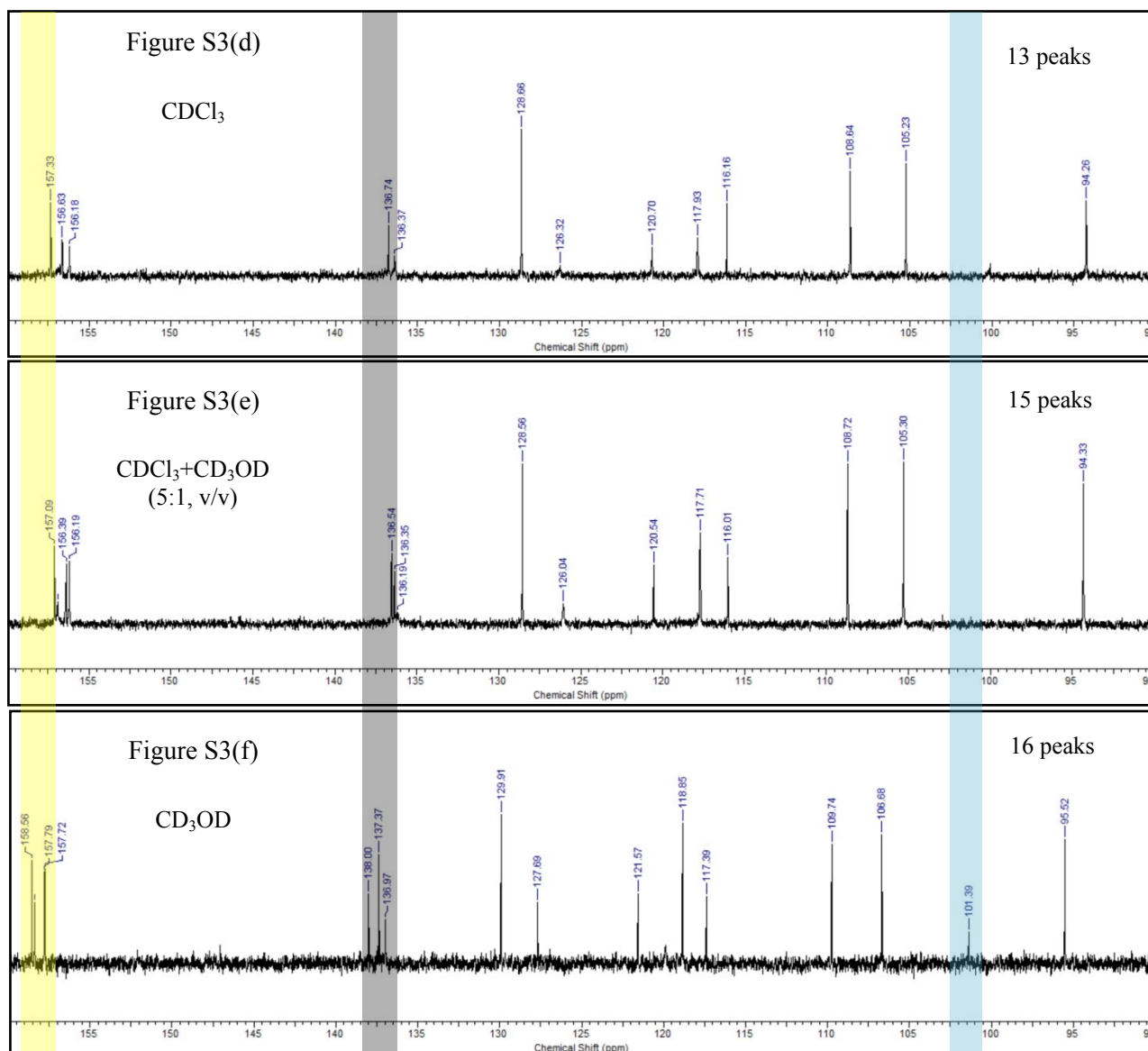
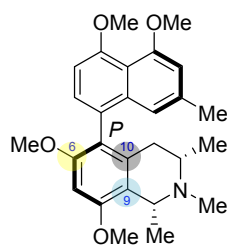


3-2. ^{13}C NMR Spectra of Ancistrobertsonine C (**2**) in Different Solvents

a) Aliphatic Region



b) Aromatic Region of ^{13}C NMR



^{13}C NMR data of compound **2** in CDCl_3 did not match the reported HRMS formula; the number of peaks in ^{13}C NMR spectrum of compound **2** in CDCl_3 was smaller than expected. It was believed that the reason why the number of peaks was small in ^{13}C NMR spectra of these compounds would be due to the rapid molecular motion of a nitrogen atom in the isoquinoline ring of compound **2**. Thus, it was expected that if the conformation of compound **2** were locked, broadening of peaks in ^1H NMR

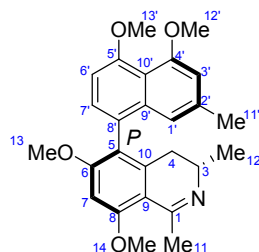
spectrum would disappear. At the same time, the number of peaks in ^{13}C NMR would be matched with the HRMS data.

Thus, we re-measured ^1H and ^{13}C NMR spectra of compound **2** in a different NMR solvent. ^1H NMR spectrum of compound **2** in CDCl_3 showed broad peaks in the aliphatic region and there were only 22 peaks in ^{13}C NMR spectrum, which was much smaller than expected from the HMRS data. When we measured the NMR data of compound **2** in a mixture of CDCl_3 and CD_3OD (5:1), much sharp peaks of the ^1H NMR spectrum were obtained, and more peaks (25 peaks) in ^{13}C NMR spectrum were found. Furthermore, when CD_3OD was used the NMR solvent, very sharp peaks and all the peaks from each carbon from compound **2** were observed in ^1H NMR and ^{13}C NMR spectrum, respectively.

Based on these results, although there was the small number of peaks in ^{13}C NMR spectrum of compound **2** in CDCl_3 , we believed that this is not because of the purity of compound **2** but because of rapid molecular motion in the isoquinoline ring.

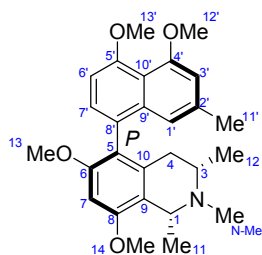
4. Summary of Spectroscopic Data of Natural Products 1 and 2

4-1. Ancistroealaine A (1) (¹H NMR 500 MHz / ¹³C NMR 125 MHz)

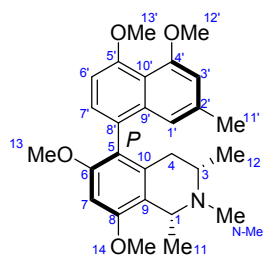


Pos.	¹ H NMR		¹³ C NMR	
	Lit. ¹ (CDCl ₃)	Synthetic (CDCl ₃)	Lit. ¹ (CDCl ₃)	Synthetic (CDCl ₃)
1	-	-	173.5	171.0
2	-	-	-	-
3	3.76, m	3.70, m	47.8	48.0
4	2.34, dd (16.9, 9.8), 2.42, dd (16.9, 5.6)	2.11, dd (16.8, 8.4) 2.48, dd (16.8, 5.5)	31.9	31.5
5	-	-	122.7	122.2
6	-	-	165.9	165.0
7	6.51, s	6.53, s	93.8	94.0
8	-	-	163.5	162.7
9	-	-	108.4	108.7
10	-	-	140.2	140.4
11	2.87, s	2.88, s	24.2	25.1
12	1.28, d (6.8)	1.22, d (6.7)	17.4	18.2
13	3.77, s	3.75, s	56.1	56.3
14	4.05, s	4.04, s	55.9	56.1
1'	6.51, s	6.52, s	116.5	116.7
2'	-	-	137.1	136.9
3'	6.69, s	6.66, s	108.9	108.8
4'	-	-	157.7	157.5
5'	-	-	157.5	157.3
6'	6.81, d (8.0)	6.81, d (8.1)	104.9	104.9
7'	6.99, d (8.0)	7.04, d (7.9)	128.7	128.7
8'	-	-	116.1	116.0
9'	-	-	135.8	135.9
10'	-	-	123.3	123.7
11'	2.31, s	2.29, s	22.1	22.1
12'	3.96, s	3.94, s	56.3	56.3
13'	3.98, s	3.97, s	56.6	56.5

a) ¹H NMR Data of Ancistrobertsonine C (**2**) (500 MHz)



¹ H NMR				
Pos.	Lit. ² (CDCl ₃)	Synthetic (CDCl ₃)	Synthetic (CDCl ₃ +CD ₃ OD)	Synthetic (CD ₃ OD)
1	3.81, q (6.4)	3.97, m	3.86, m	3.94, m
2	-	-	-	-
3	2.39, m	2.50, m	2.44, m	2.51, m
4	1.99, dd (14.9, 1.9), 2.27, dd (14.8, 10.9)	2.18, m 2.18, m	2.12, m 2.12, m	2.15, m 2.21, m
5	-	-	-	-
6	-	-	-	-
7	6.49, s	6.53, s	6.47, s	6.67, s
8	-	-	-	-
9	-	-	-	-
10	-	-	-	-
11	1.47, d (6.4)	1.56, br	1.49, br	1.53, d (6.4)
12	0.99, d (5.1)	1.06, br	1.00, br	1.02, d (6.4)
13	3.62, s	3.65, s	3.57, s	3.63, s
14	3.93, s	3.93, s	3.86, s	3.92, s
1'	6.69, s	6.76, s	6.67, s	6.75, s
2'	-	-	-	-
3'	6.68, s	6.67, s	6.61, s	6.70, s
4'	-	-	-	-
5'	-	-	-	-
6'	6.84, d (8.0)	6.84, d (7.9)	6.78, d (7.9)	6.89, d (7.9)
7'	7.15, d (8.0)	7.11, d (7.9)	7.02, d (7.9)	7.05, d (7.9)
8'	-	-	-	-
9'	-	-	-	-
10'	-	-	-	-
11'	2.32, s	2.31, s	2.23, s	2.27, s
12'	4.00, s	4.00, s	3.92, s	3.94, s
13'	3.97, s	3.97, s	3.89, s	3.94, s
N-Me	2.45, s	2.50, br	2.43, br	2.51, s

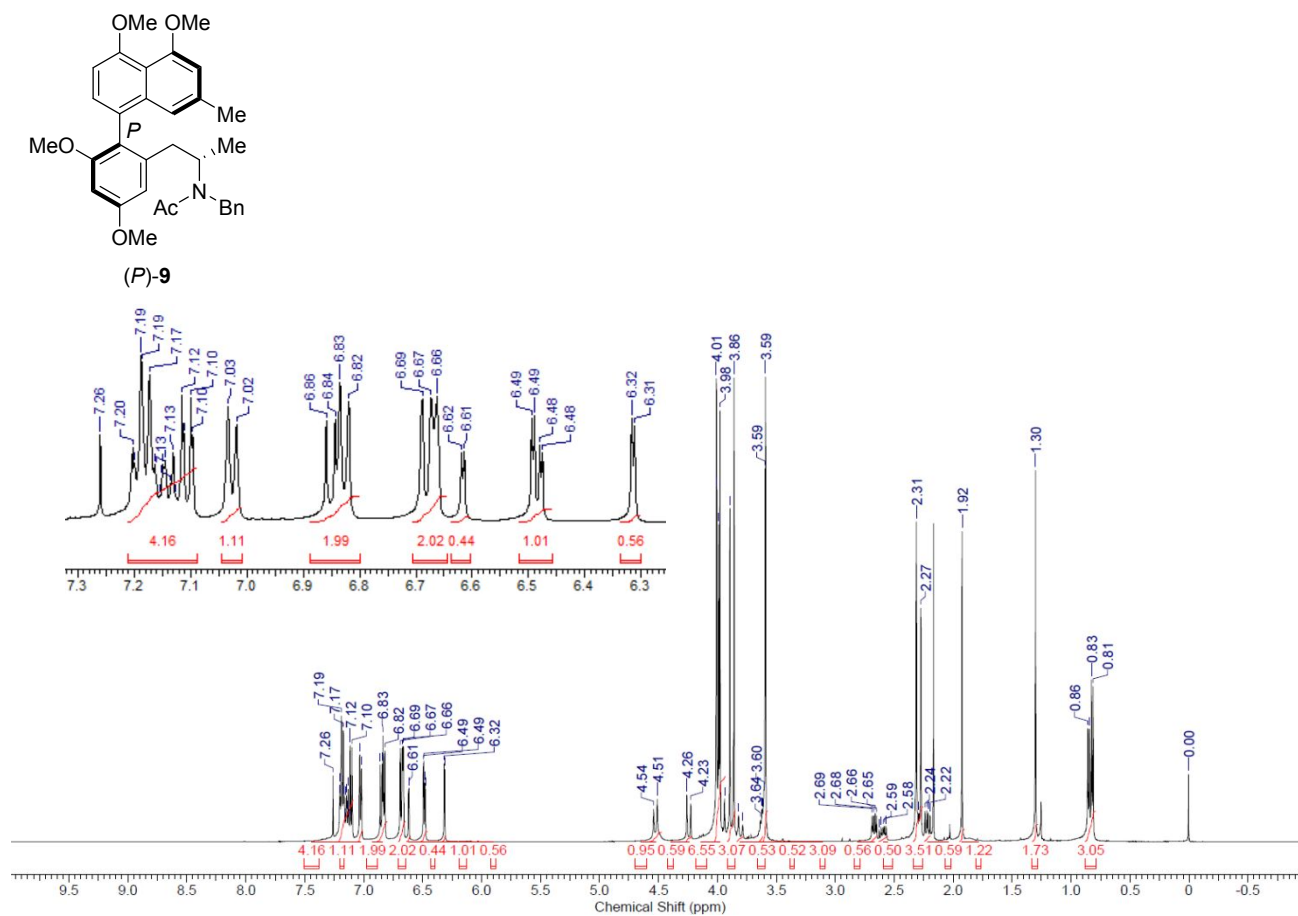
b) ¹³C NMR Data of Ancistrobertsonine C (**2**) (500 MHz)

¹³ C NMR				
Pos.	Lit. ² (CDCl ₃)	Synthetic (CDCl ₃)	Synthetic (CDCl ₃ +CD ₃ OD)	Synthetic (CD ₃ OD)
1	57.4	57.5	57.7	59.3
2	-	-	-	-
3	55.5	-	55.9	57.1
4	36.4	35.3	34.2	35.8
5	120.3	120.7	120.5	118.9
6	156.5	-	156.9	158.4
7	93.6	94.3	94.3	95.5
8	156.0	156.2	156.2	157.7
9	120.5	-	-	121.6
10	137.2	-	136.5	138.0
11	22.5	-	21.9	22.0
12	20.9	20.8	19.7	20.0
13	55.2	55.4	55.2	55.9
14	56.1	56.4	56.2	56.4
1'	117.9	117.9	117.7	117.4
2'	135.8	136.4	136.2	137.0
3'	108.5	108.6	108.7	106.7
4'	157.1	157.3	157.1	158.6
5'	156.4	156.6	156.4	157.8
6'	105.2	105.2	105.3	101.4
7'	128.9	128.7	128.6	129.9
8'	126.5	126.3	126.0	127.7
9'	136.3	136.7	136.4	137.4
10'	115.9	116.2	116.0	109.7
11'	22.0	22.3	21.3	21.8
12'	56.2	56.5	56.3	56.8
13'	56.6	56.6	56.5	57.0
N-Me	41.2	41.5	41.2	41.3

5. Spectroscopic Data

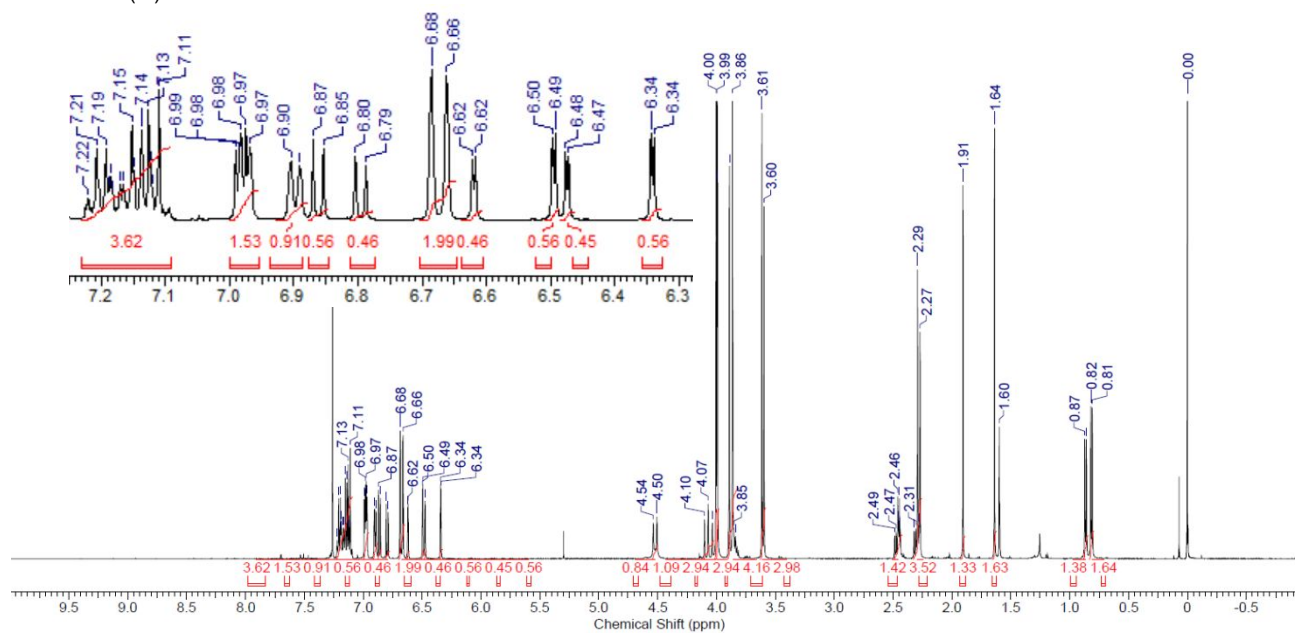
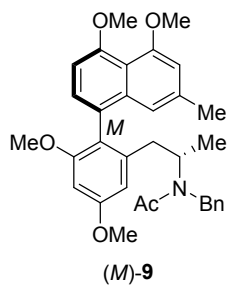
5-1. NMR Spectrum of Compound (*P*)-9

a) ^1H NMR Spectrum (in CDCl_3 , 500 MHz)



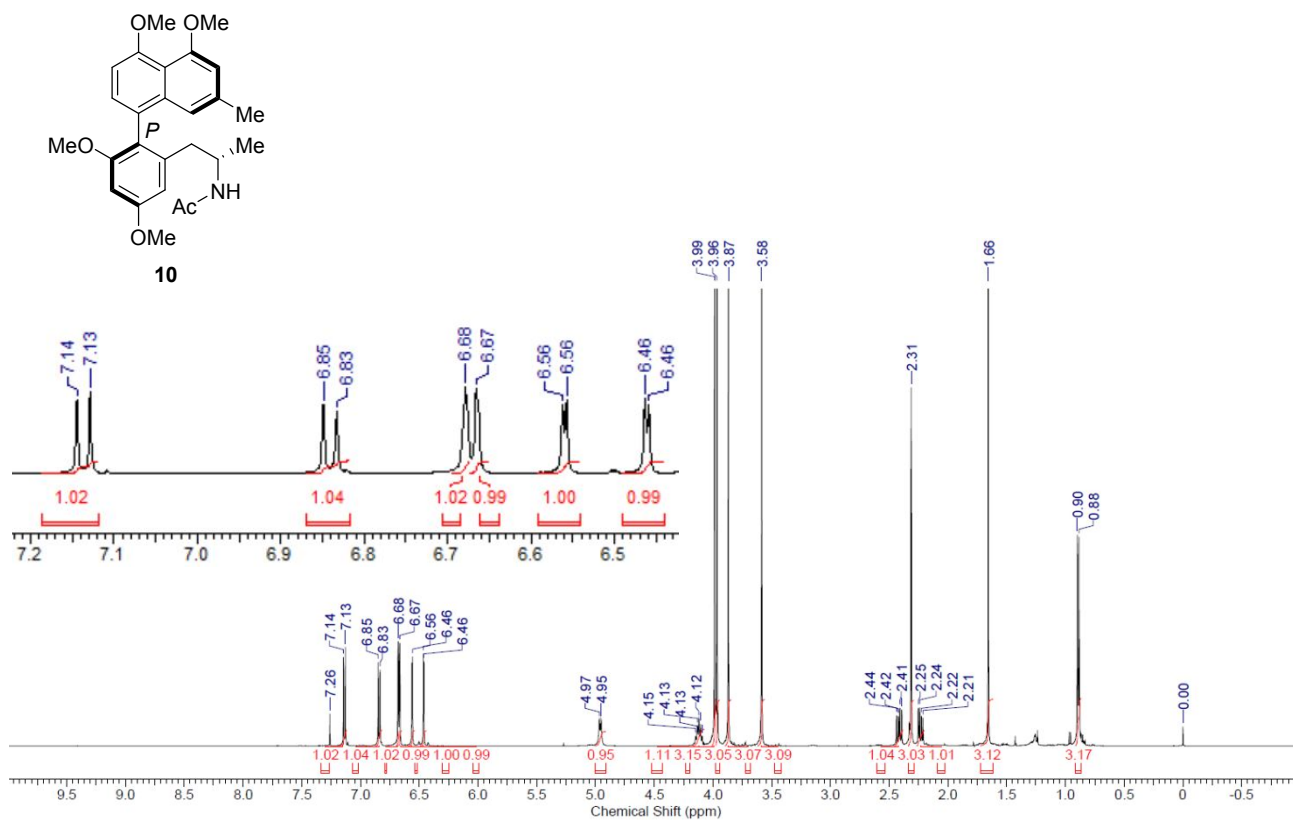
5-2. NMR Spectrum of Compound (M)-9

a) ^1H NMR Spectrum (in CDCl_3 , 500 MHz)

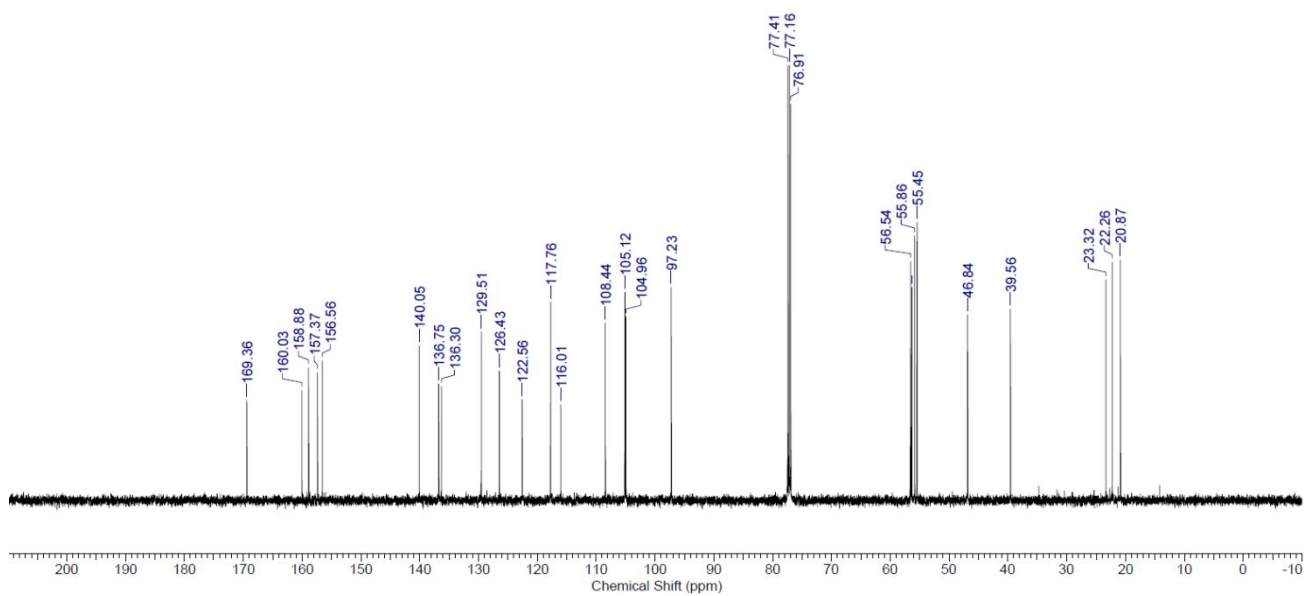


5-3. NMR Spectra of Compound **10**

a) ^1H NMR Spectrum (in CDCl_3 , 500 MHz)

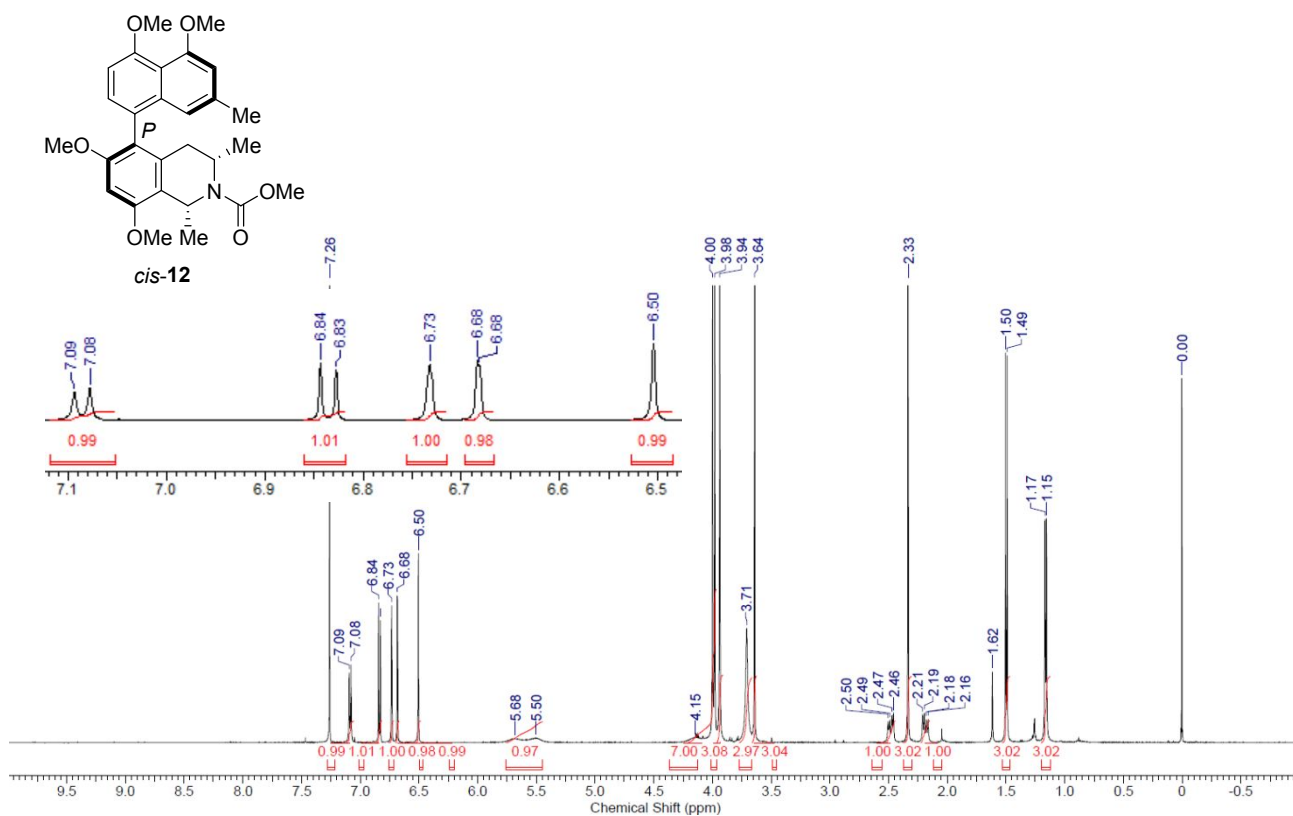


b) ^{13}C NMR Spectrum (in CDCl_3 , 125 MHz)

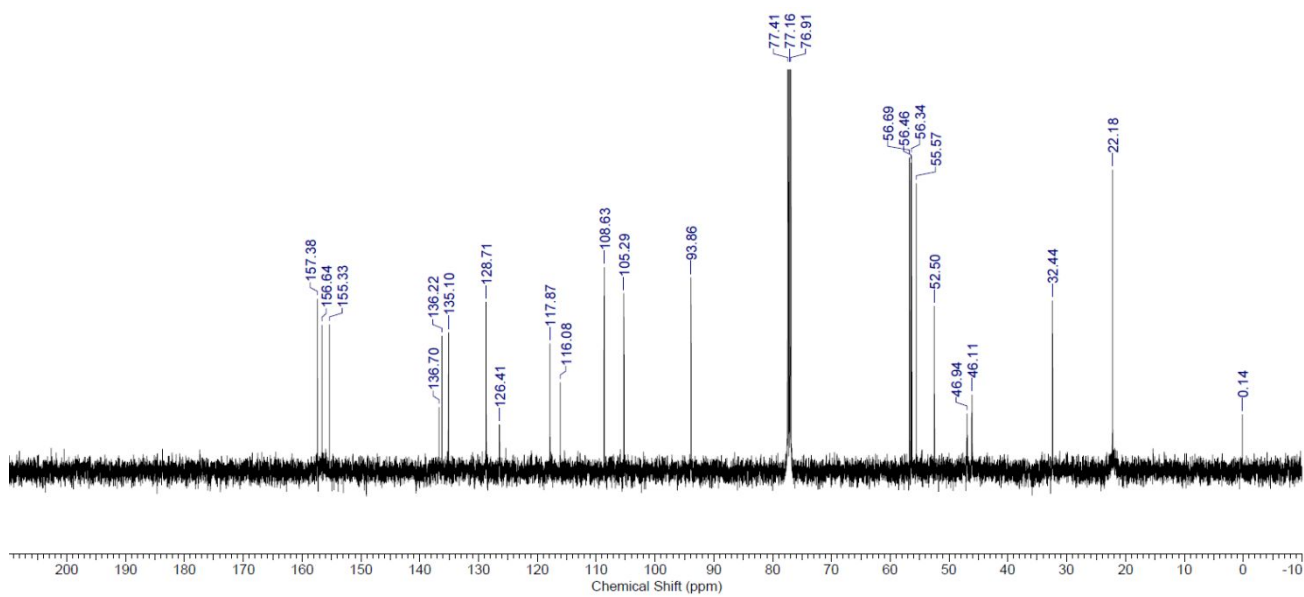


5-5. NMR Spectra of Compound *cis*-12

a) ^1H NMR Spectrum (in CDCl_3 , 500 MHz)

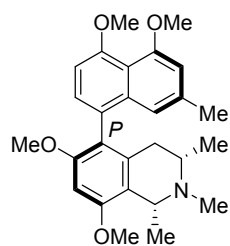


b) ^{13}C NMR Spectrum (in CDCl_3 , 125 MHz)

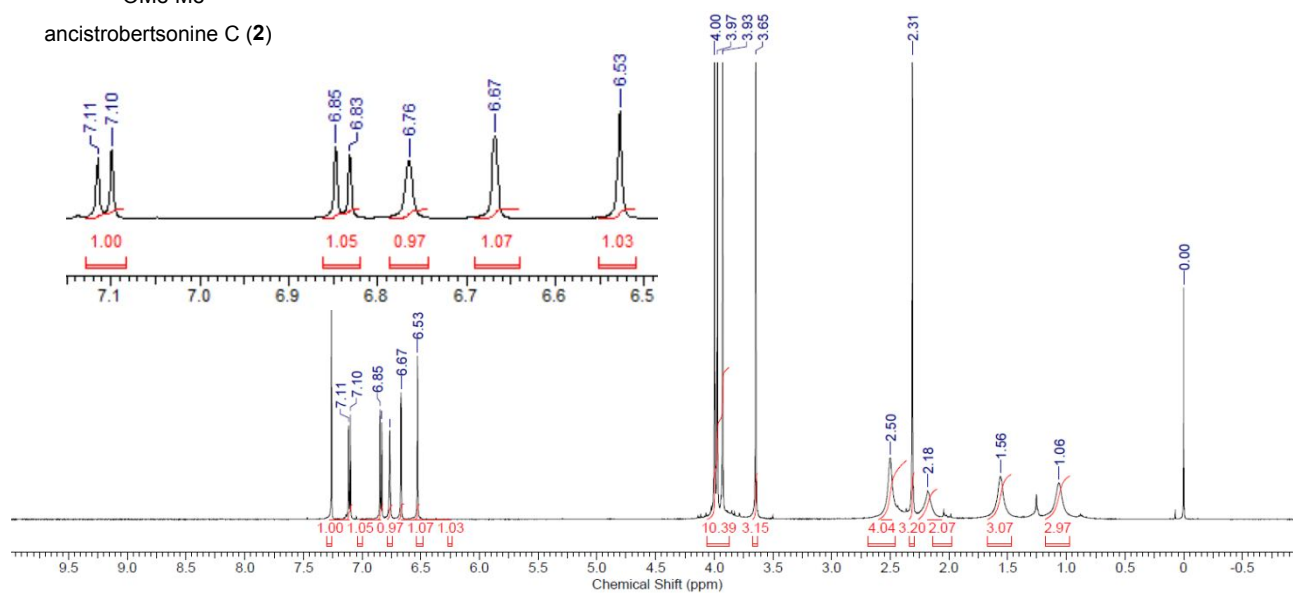


5-6. NMR Spectra of Ancistrobertsonine C (2)

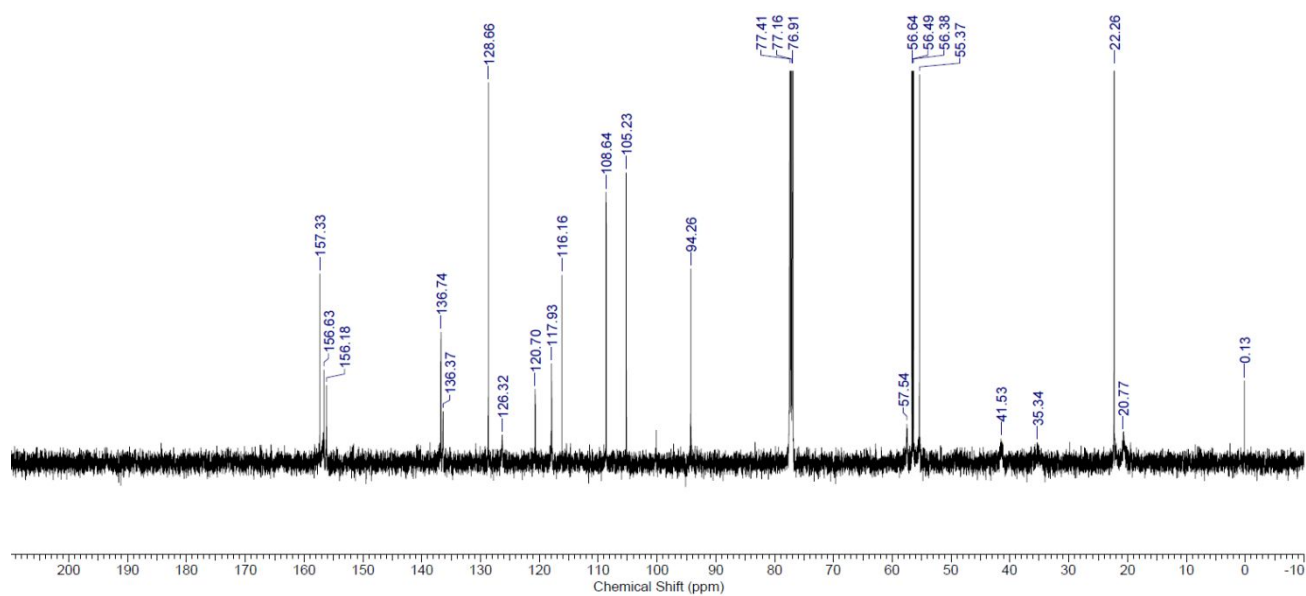
a) ^1H NMR Spectrum (in CDCl_3 , 500 MHz)



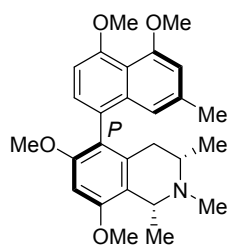
ancistrobertsonine C (2)



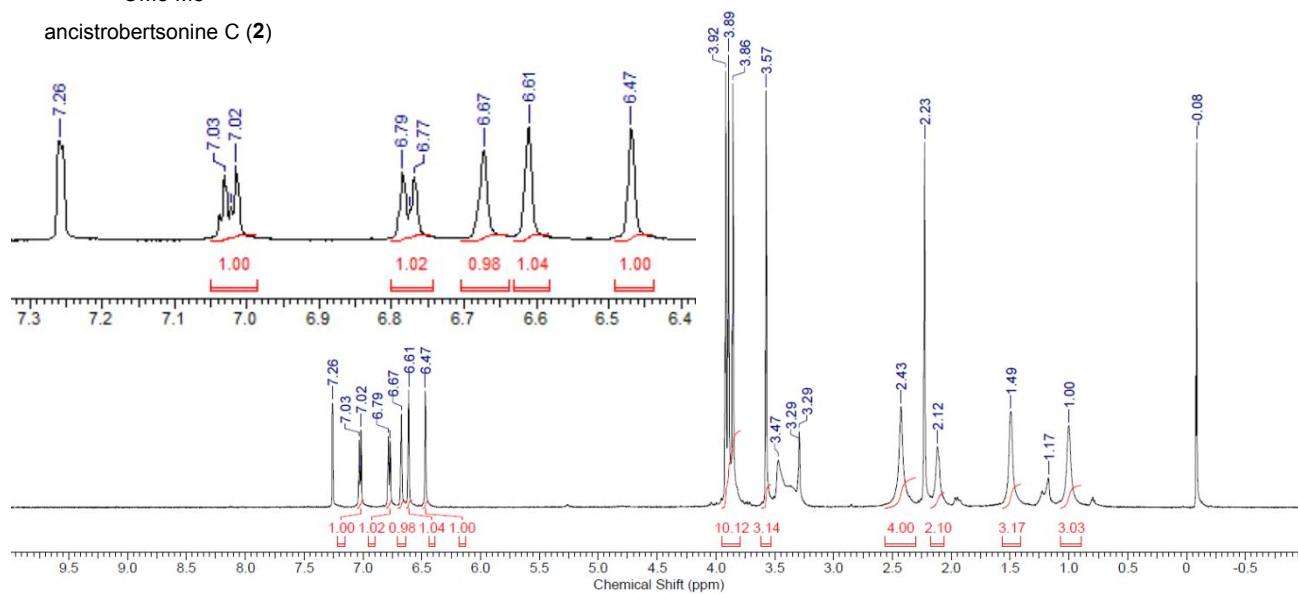
b) ^{13}C NMR Spectrum (in CDCl_3 , 125 MHz)



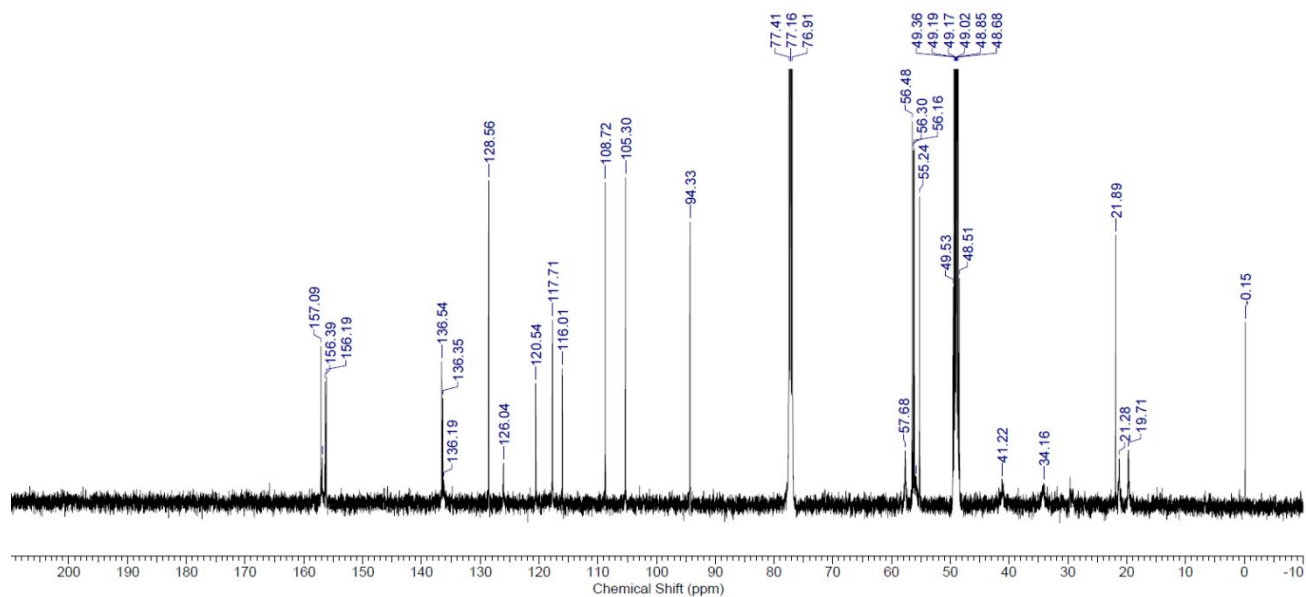
c) ^1H NMR Spectrum (in $\text{CDCl}_3+\text{CD}_3\text{OD}$ (5:1, v/v), 500 MHz)



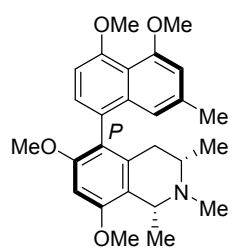
ancistrobertsonine C (2)



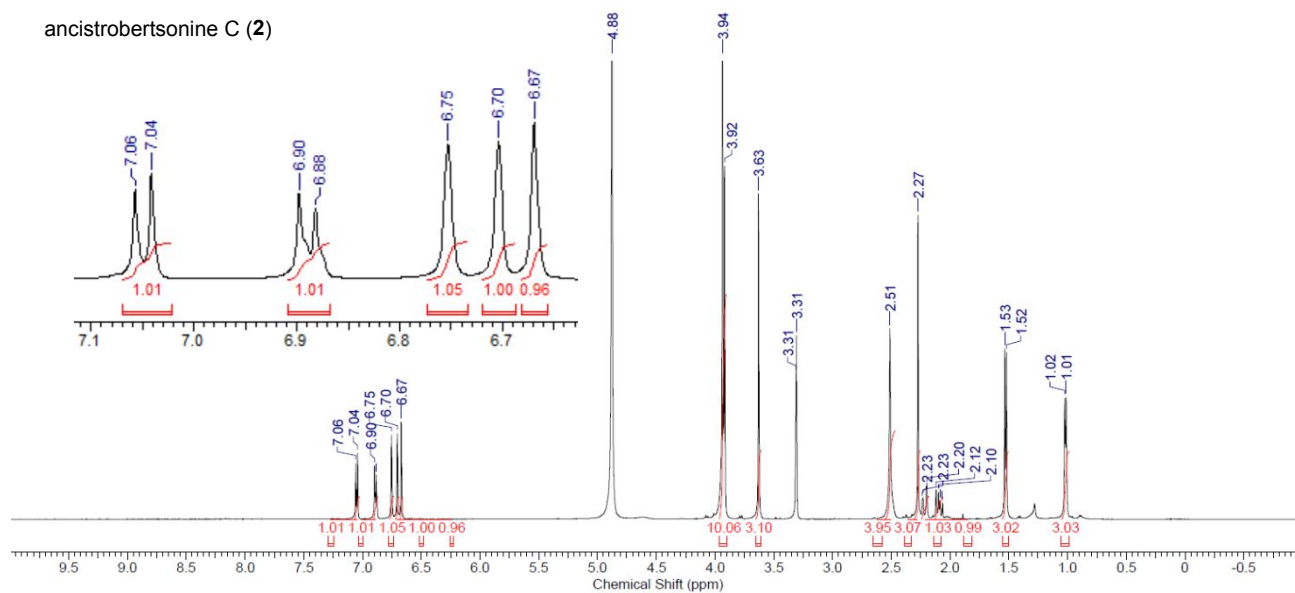
d) ^{13}C NMR Spectrum (in $\text{CDCl}_3+\text{CD}_3\text{OD}$ (5:1, v/v), 125 MHz)



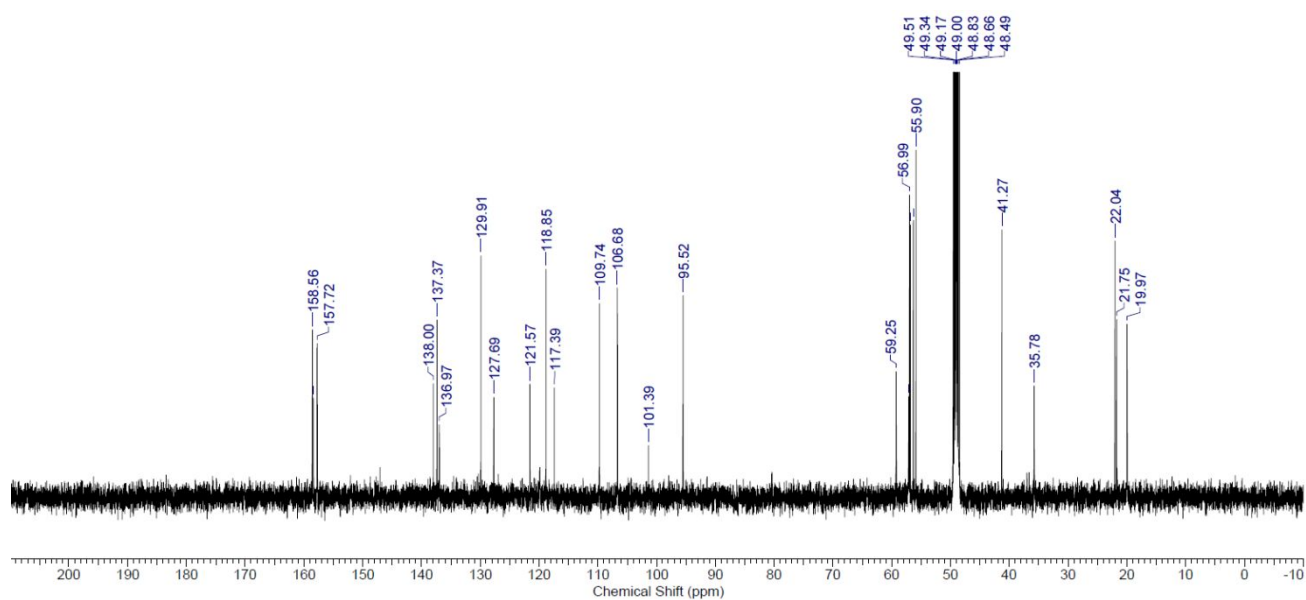
e) ^1H NMR Spectrum (in MeOD, 500 MHz)



ancistrobertsonine C (2)

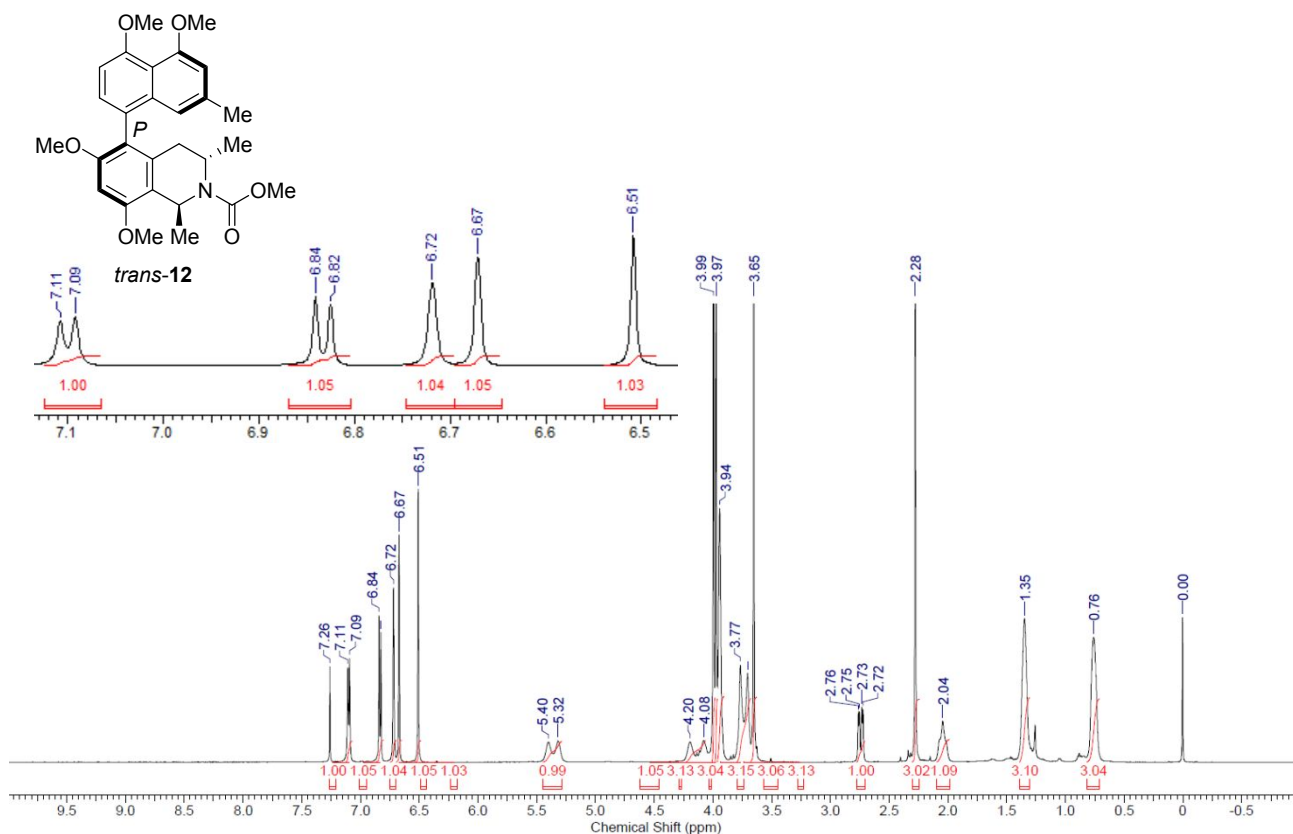


f) ^{13}C NMR Spectrum (in MeOD, 125 MHz)

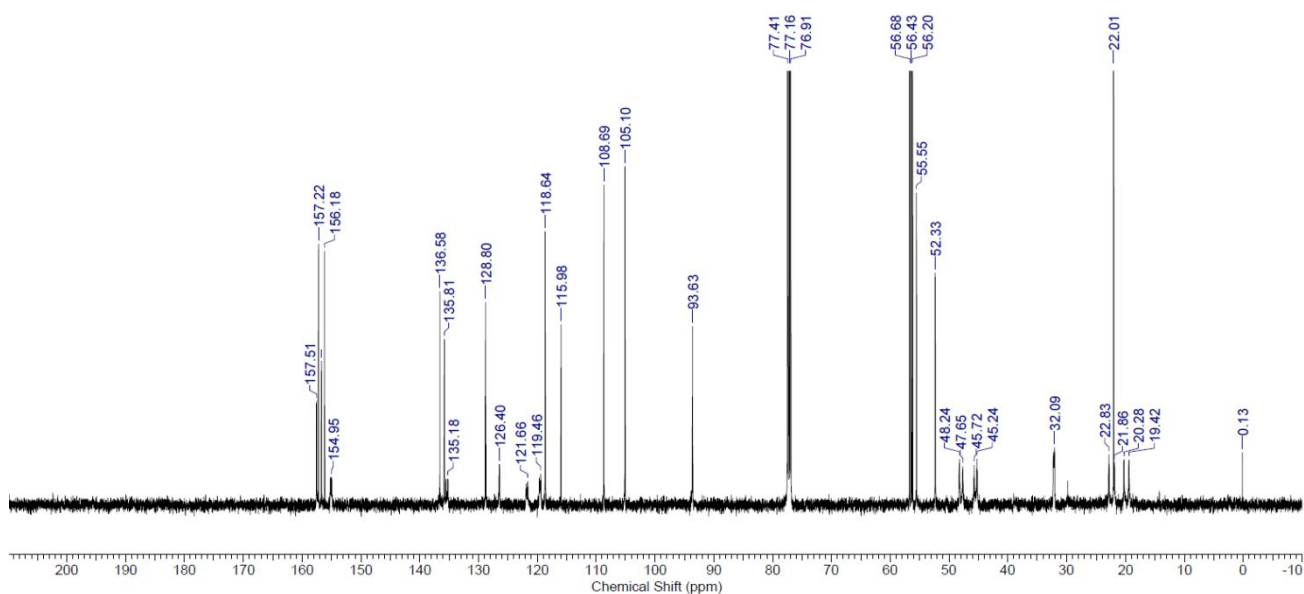


5-7. NMR Spectra of Compound *trans*-12

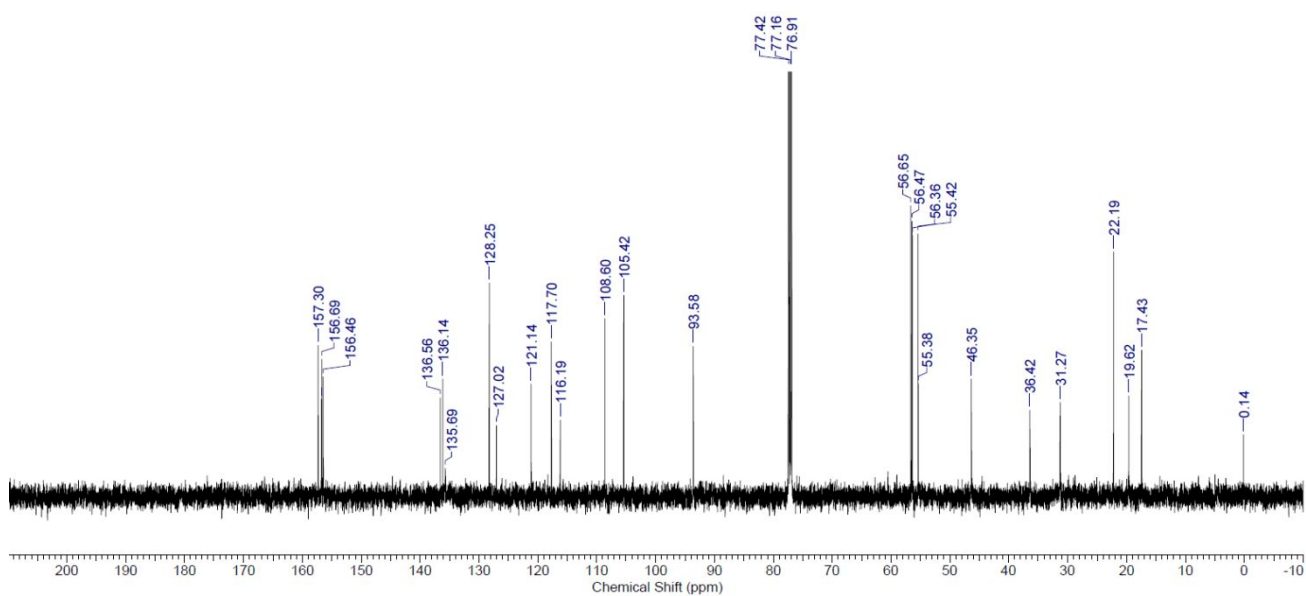
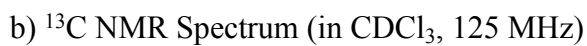
a) ^1H NMR Spectrum (in CDCl_3 , 500 MHz)



b) ^{13}C NMR Spectrum (in CDCl_3 , 125 MHz)



a) ^1H NMR Spectrum (in CDCl_3 , 500 MHz)



6. References

1. Bringmann, G.; Hamm, A.; Günther, C.; Michel, M.; Brun, R.; Mudogo, V. Ancistrocalines A and B, Two New Bioactive Naphthylisoquinolines, and Related Naphthoic Acids from *Ancistrocladus ealaensis*. *J. Nat. Prod.* **2000**, *63*, 1465.
2. Bringmann, G.; Teltschik, F.; Michel, M.; Busemann, S.; Rückert, M.; Haller, R.; Bär, S.; Robertson, S. A.; Kaminsky, R. Ancistrobertsonines B, C, and D as well as 1,2-Didehydroancistrobertsonine D from *Ancistrocladus robertsoniorum*. *Phytochemistry* **1999**, *52*, 321.