

Supporting Information

A modular approach to the bisbenzyloisoquinoline alkaloids tetrandrine and isotetrandrine

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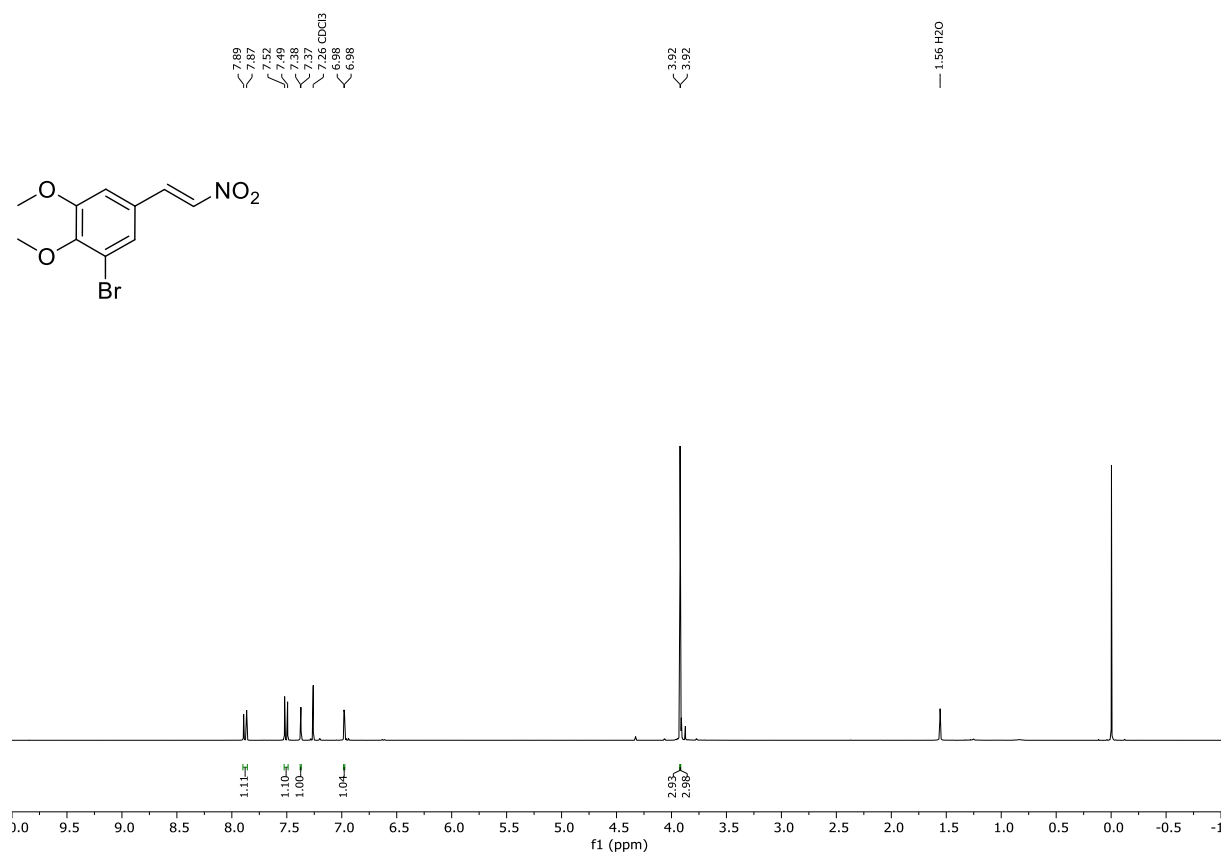
[†]Department of Pharmacy - Center for Drug Research, Ludwig-Maximilians University Munich, Butenandtstr. 5-13, 81377 Munich, Germany

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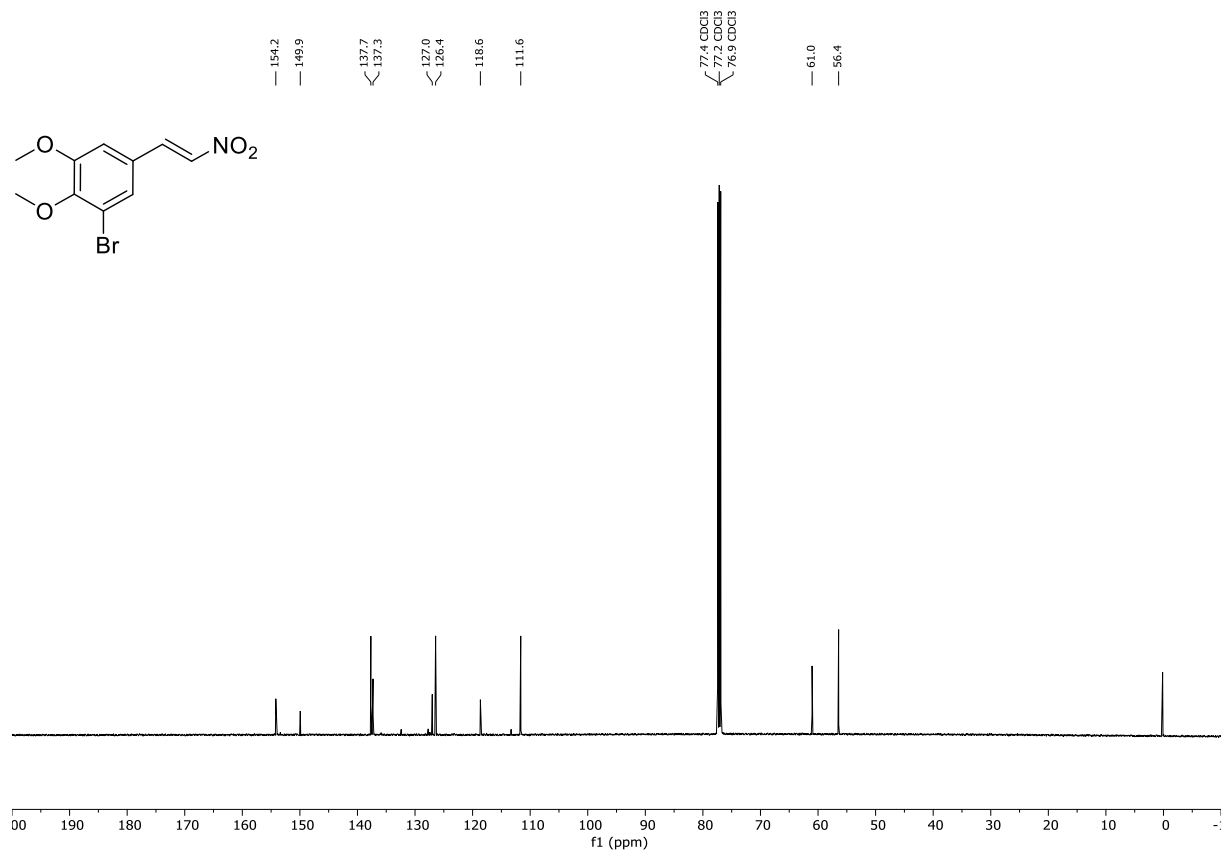
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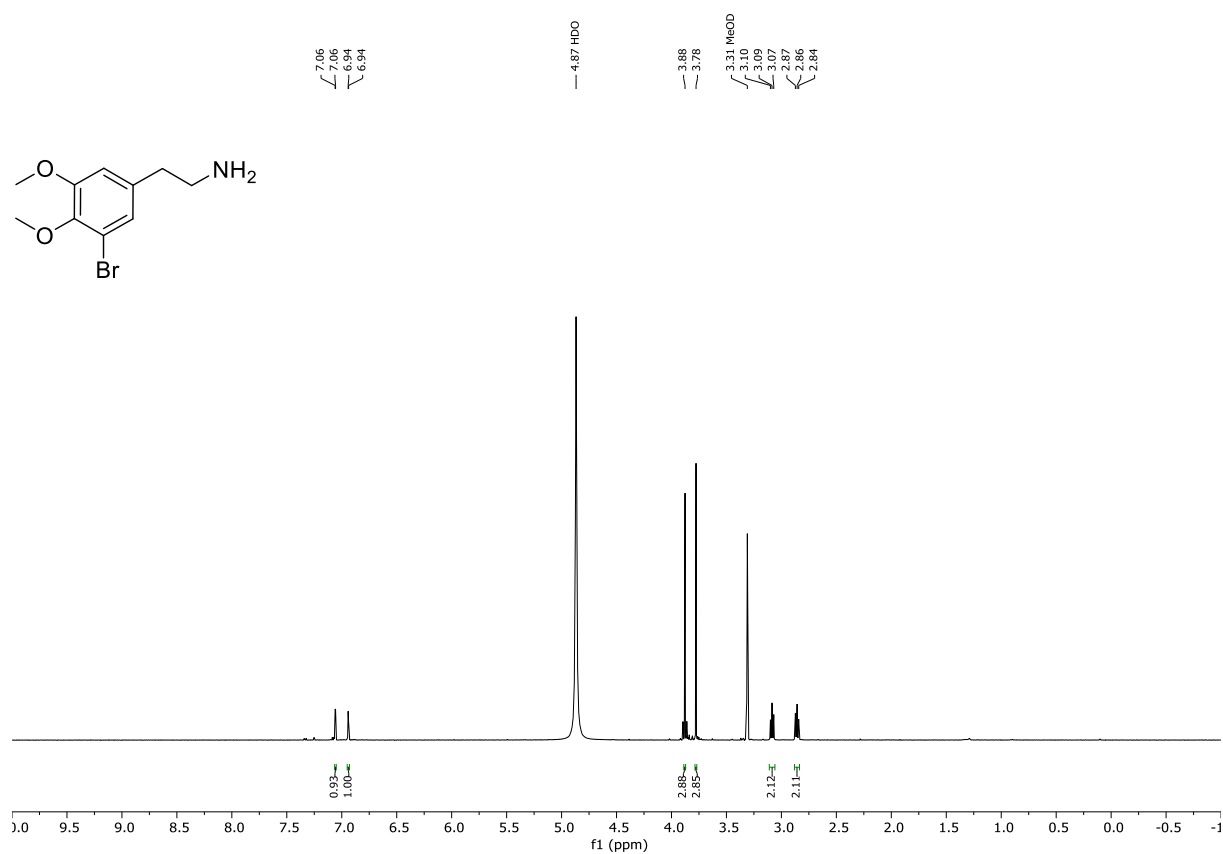
¹H NMR (500 MHz, CDCl₃) of **4**



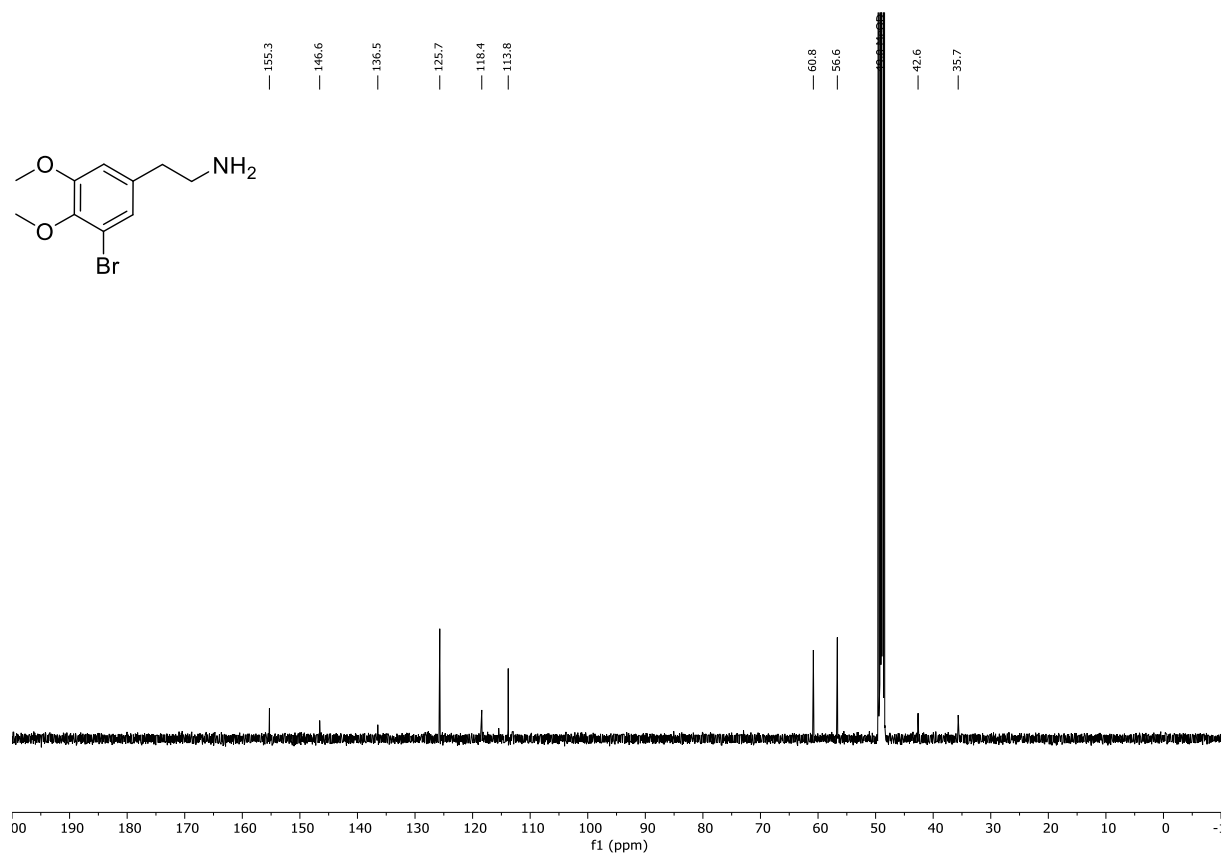
¹³C NMR (126 MHz, CDCl₃) of **4**



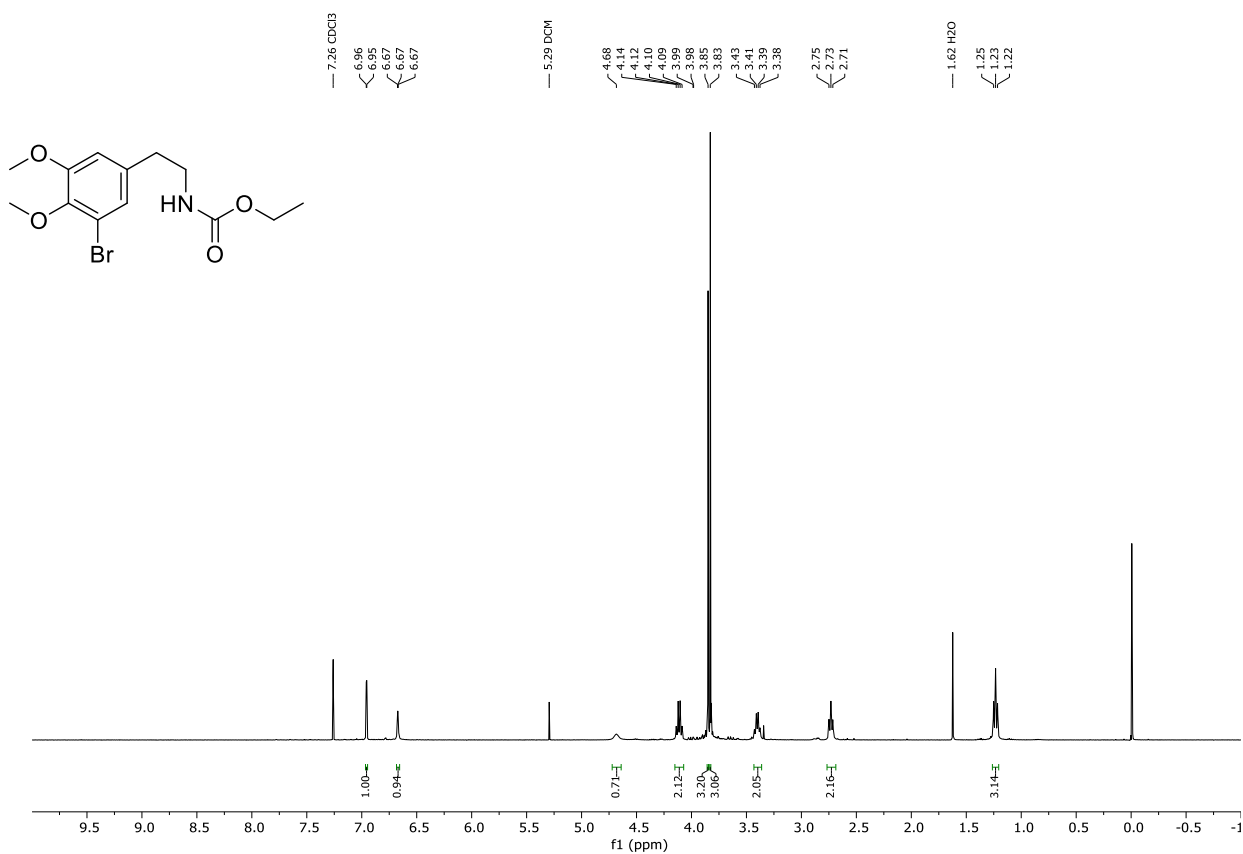
¹H NMR (500 MHz, MeOD) of **5**



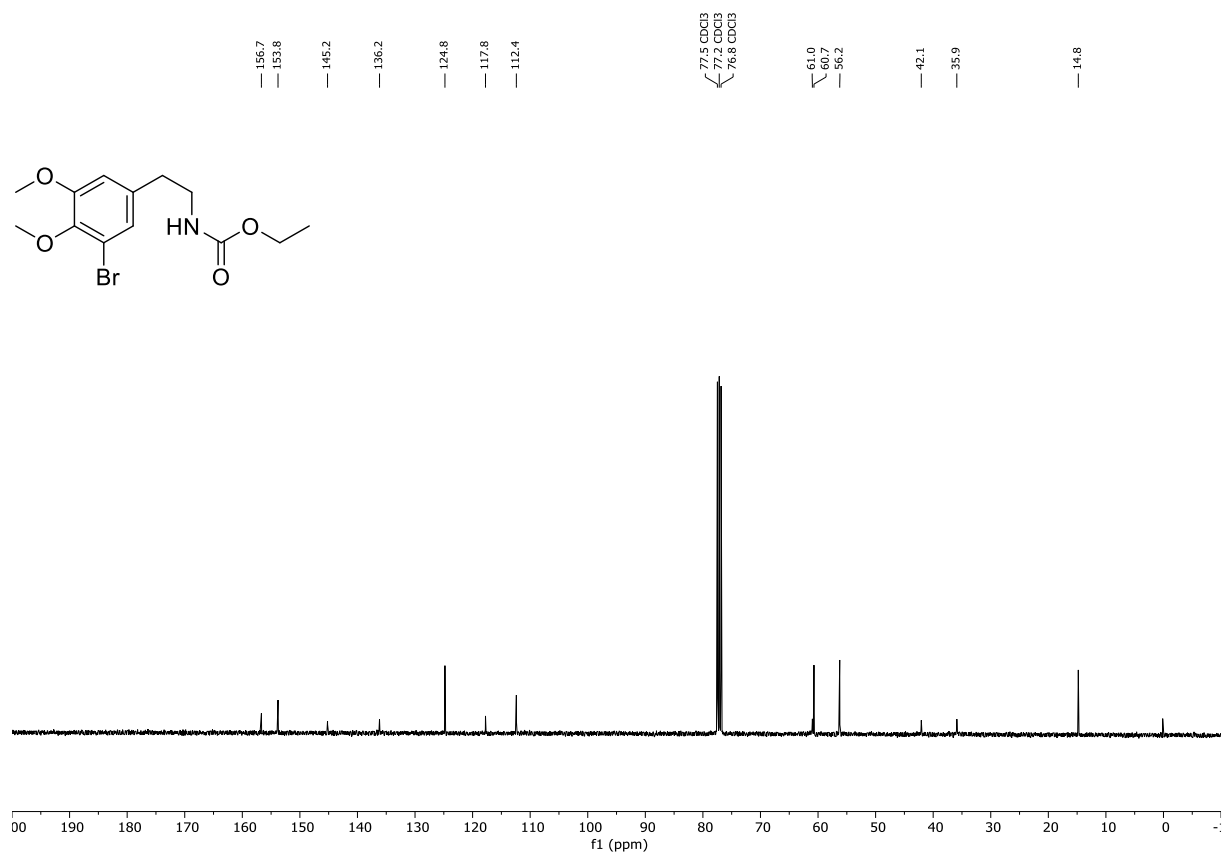
¹³C NMR (126 MHz, MeOD) of **5**



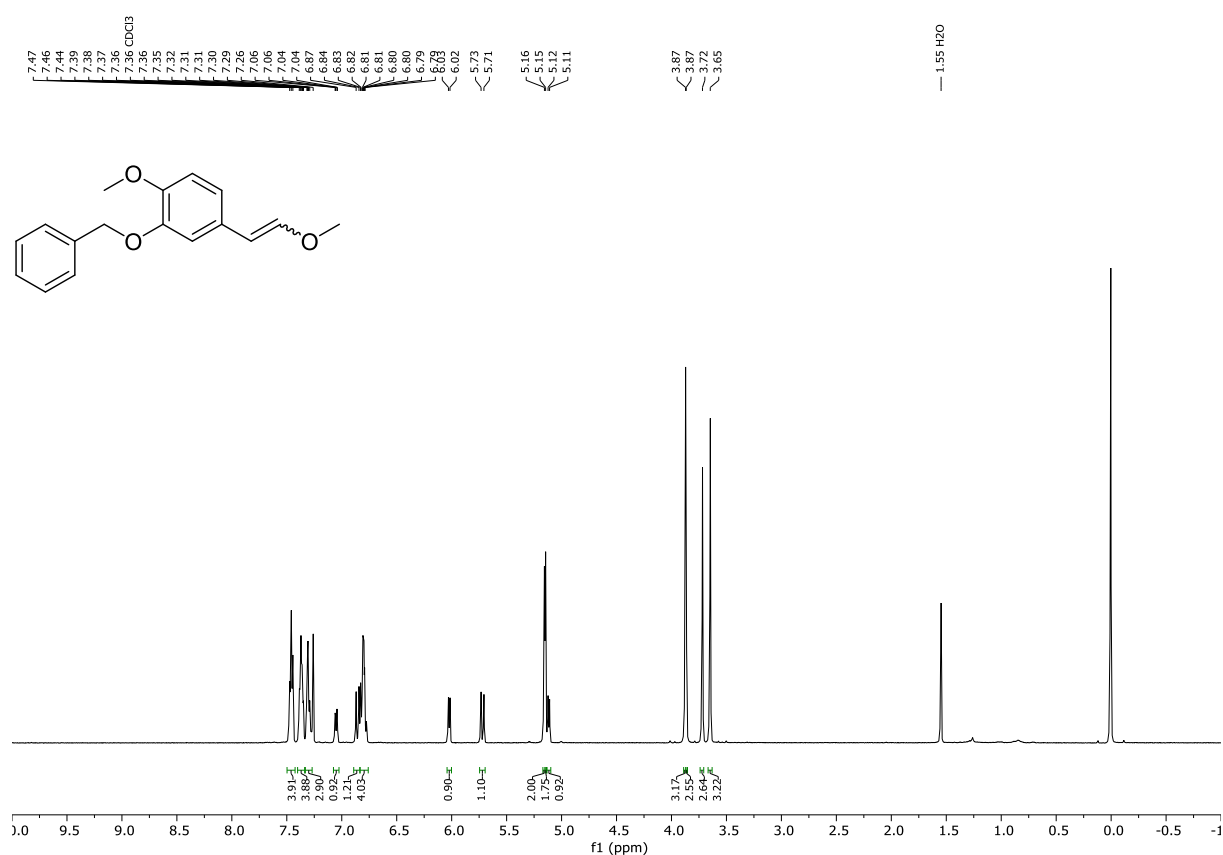
^1H NMR (400 MHz, CDCl_3) of **6**



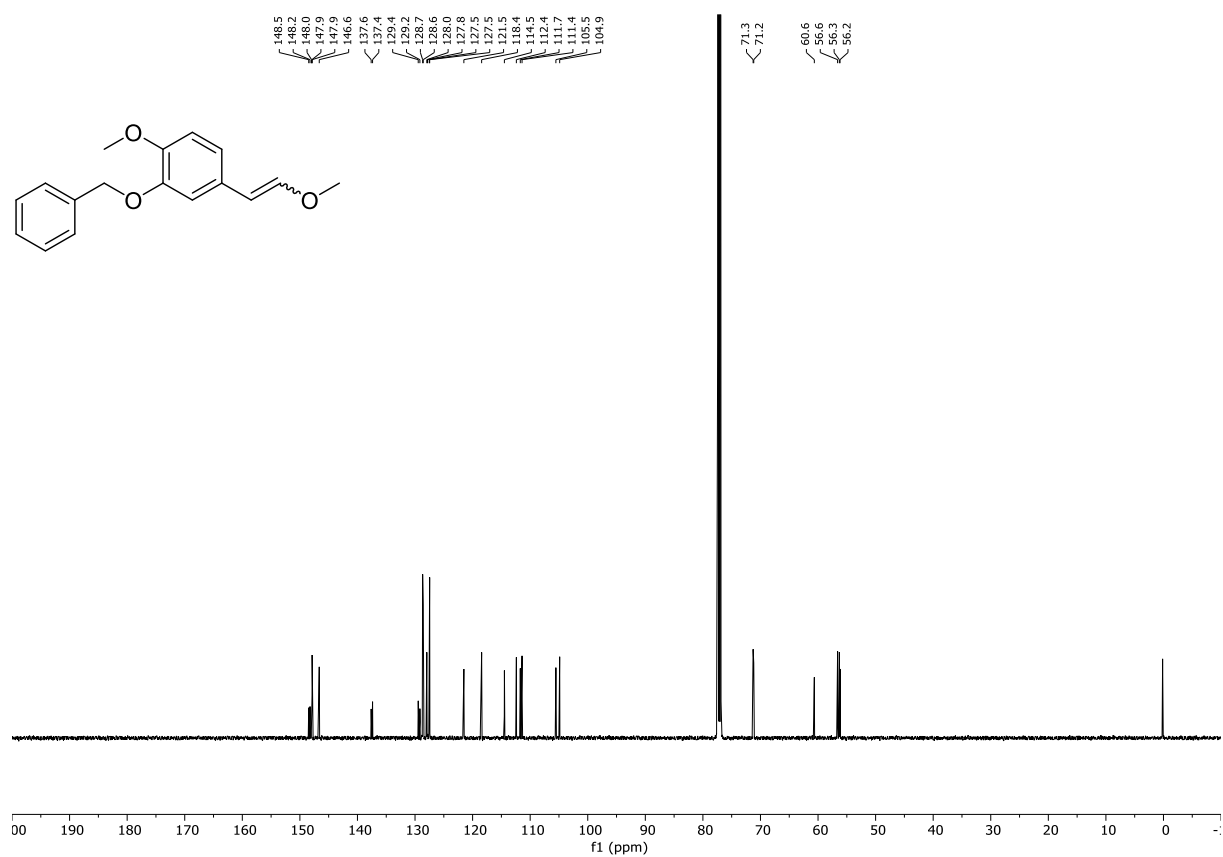
^{13}C NMR (101 MHz, CDCl_3) of **6**



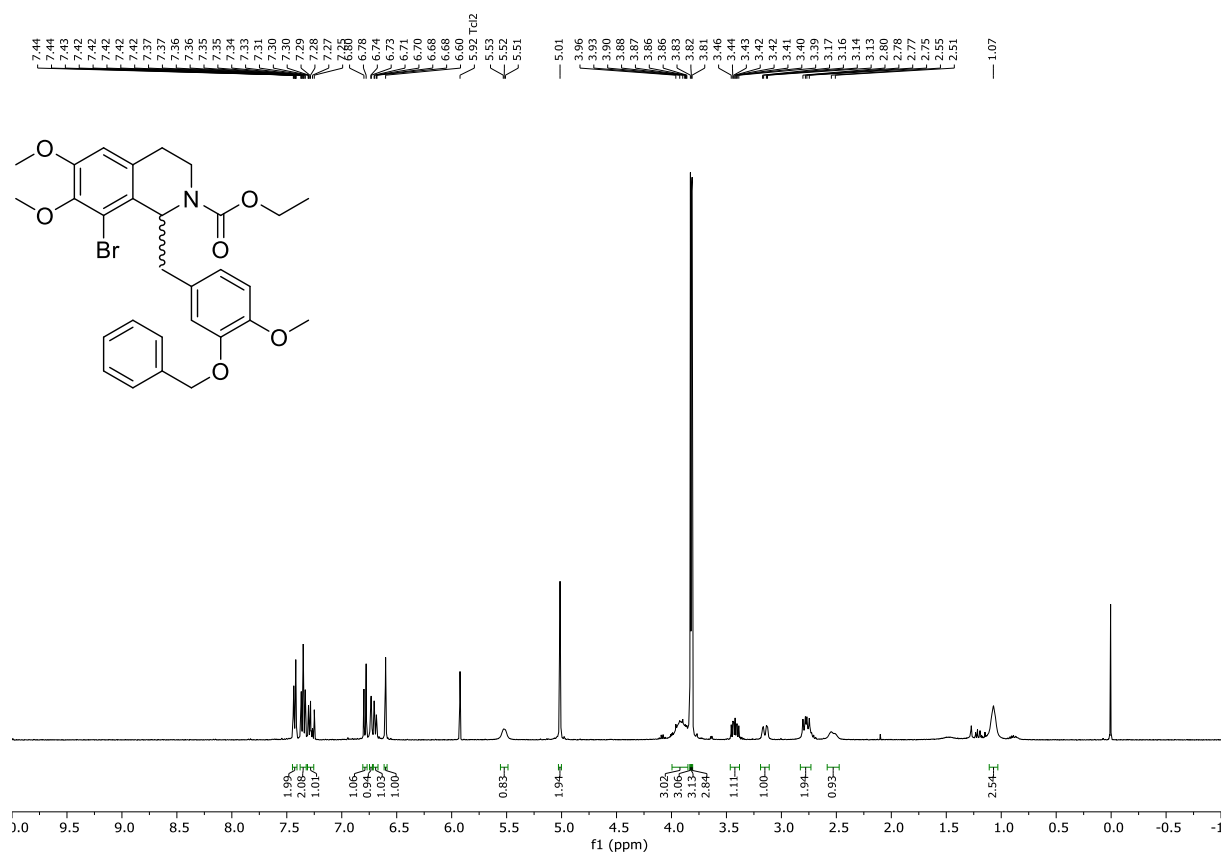
¹H NMR (500 MHz, CDCl₃) of **7**



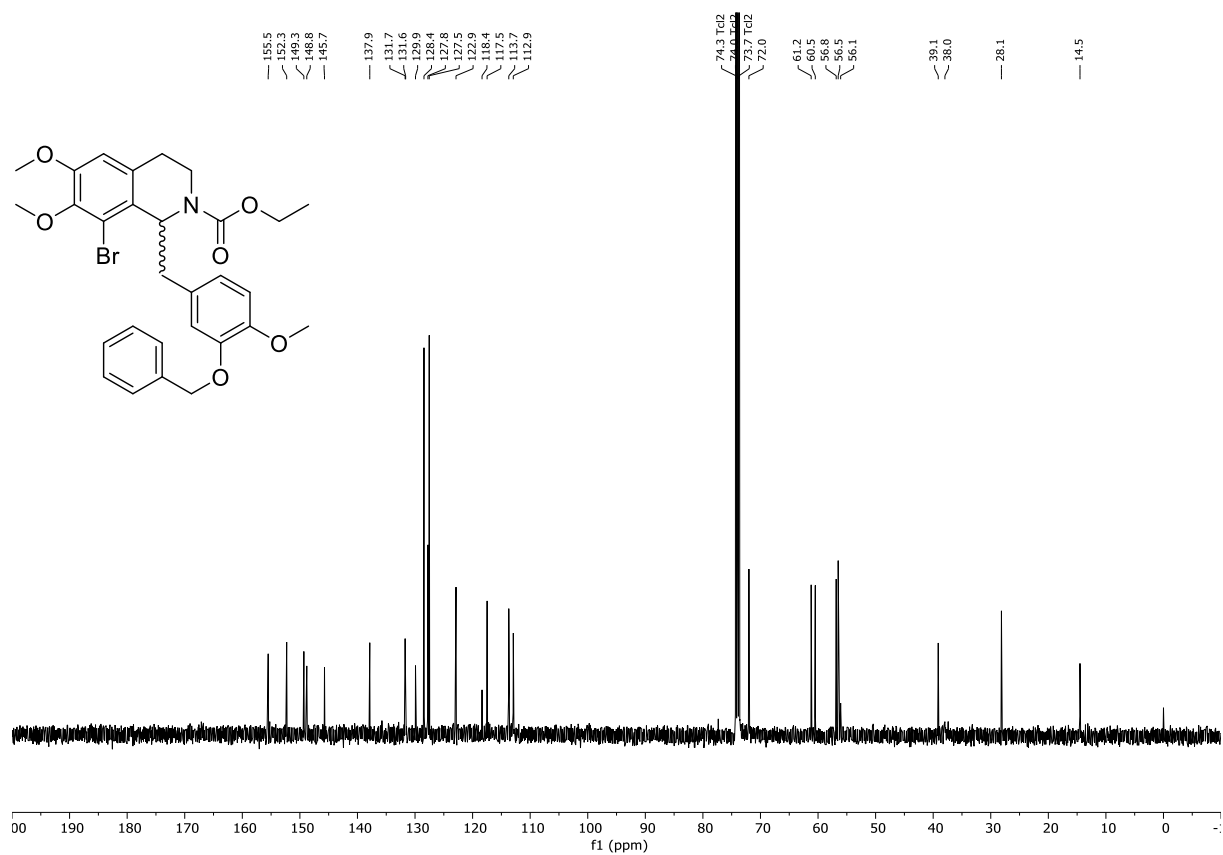
¹³C NMR (126 MHz, CDCl₃) of **7**



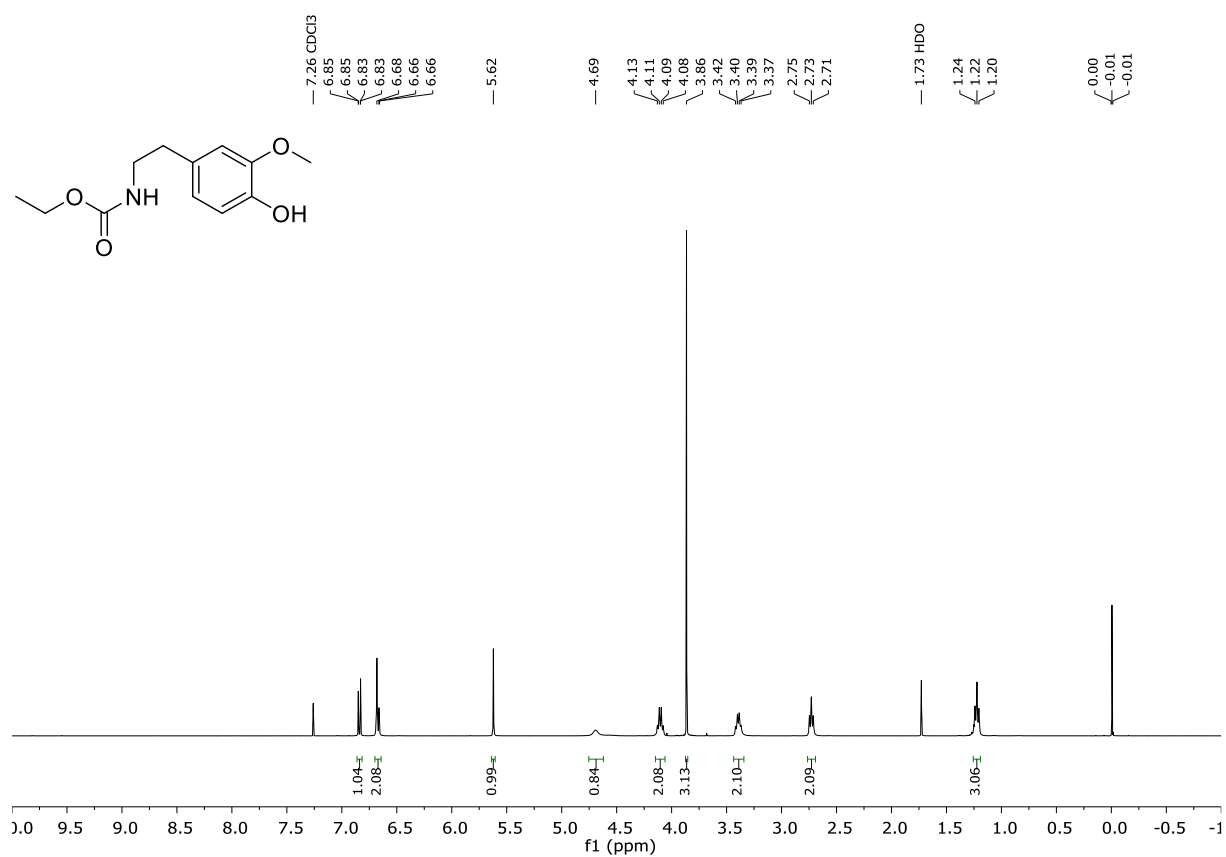
^1H NMR (400 MHz, Tcl_2 , 100°C) of **8**



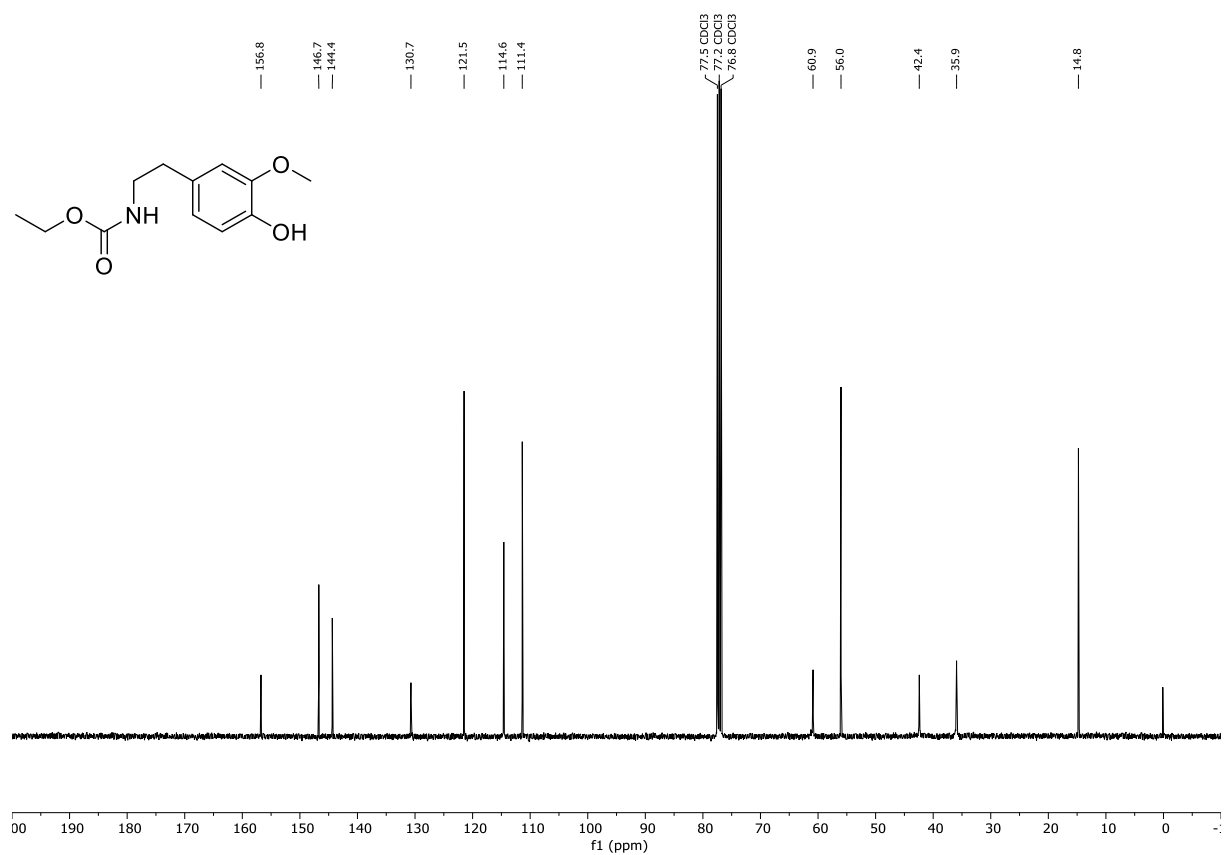
^{13}C NMR (101 MHz, Tcl_2 , 100°C) of **8**



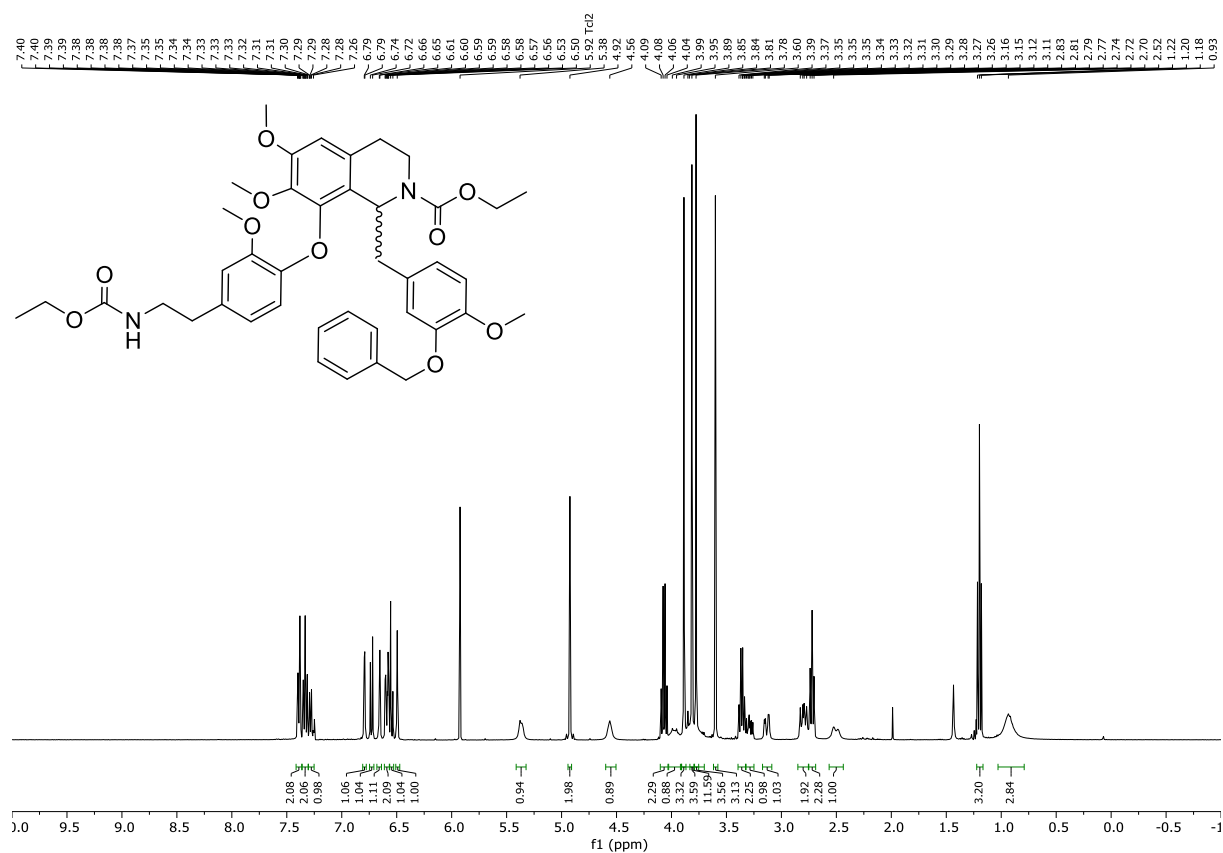
¹H NMR (400 MHz, CDCl₃) of **10**



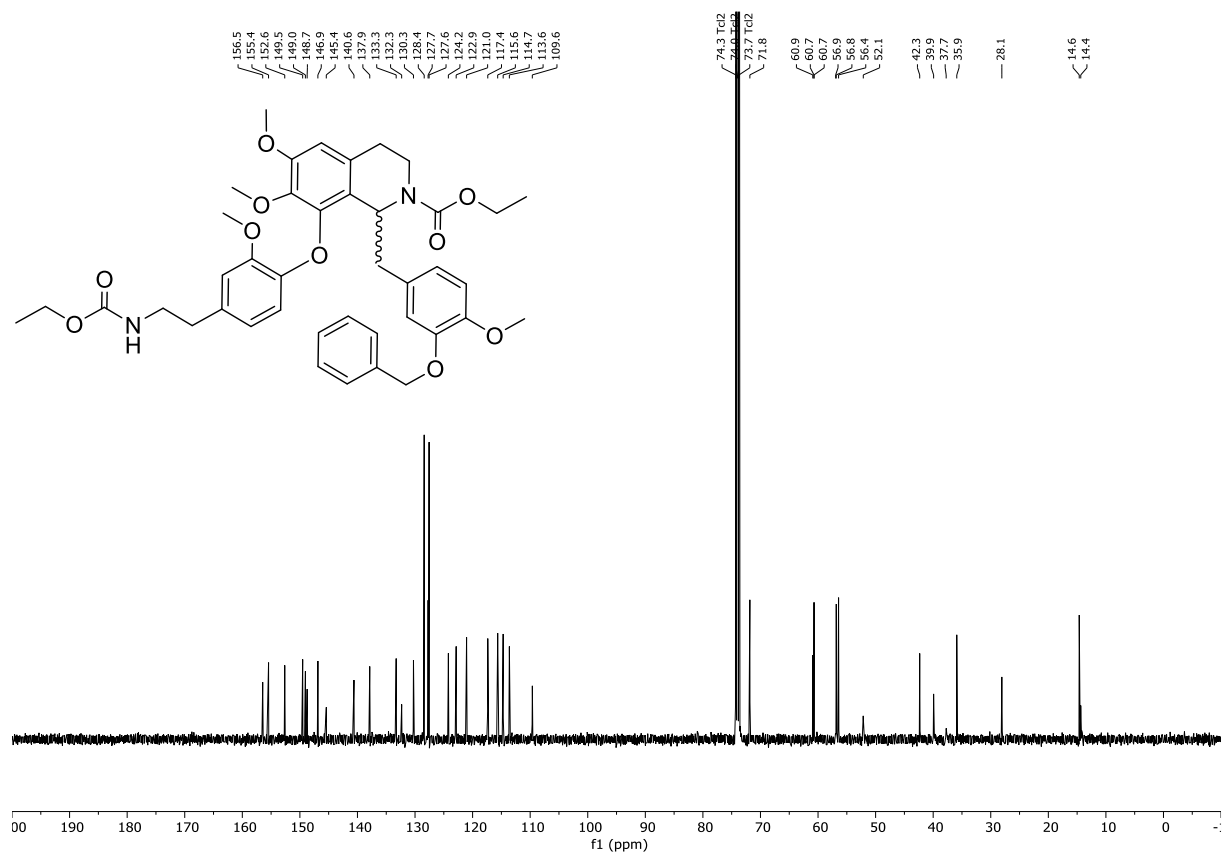
¹³C NMR (101 MHz, CDCl₃) of **10**



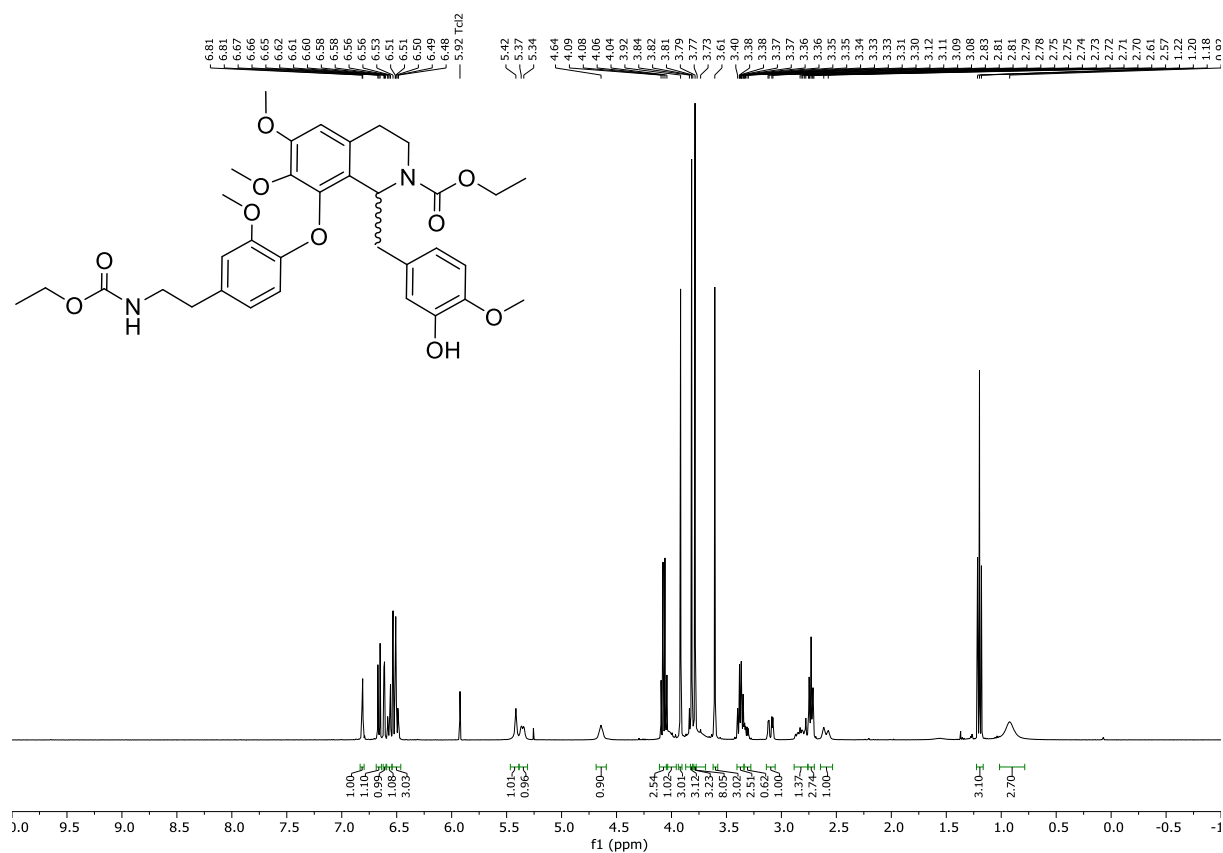
^1H NMR (400 MHz, Tcl_2 , 100°C) of **11**



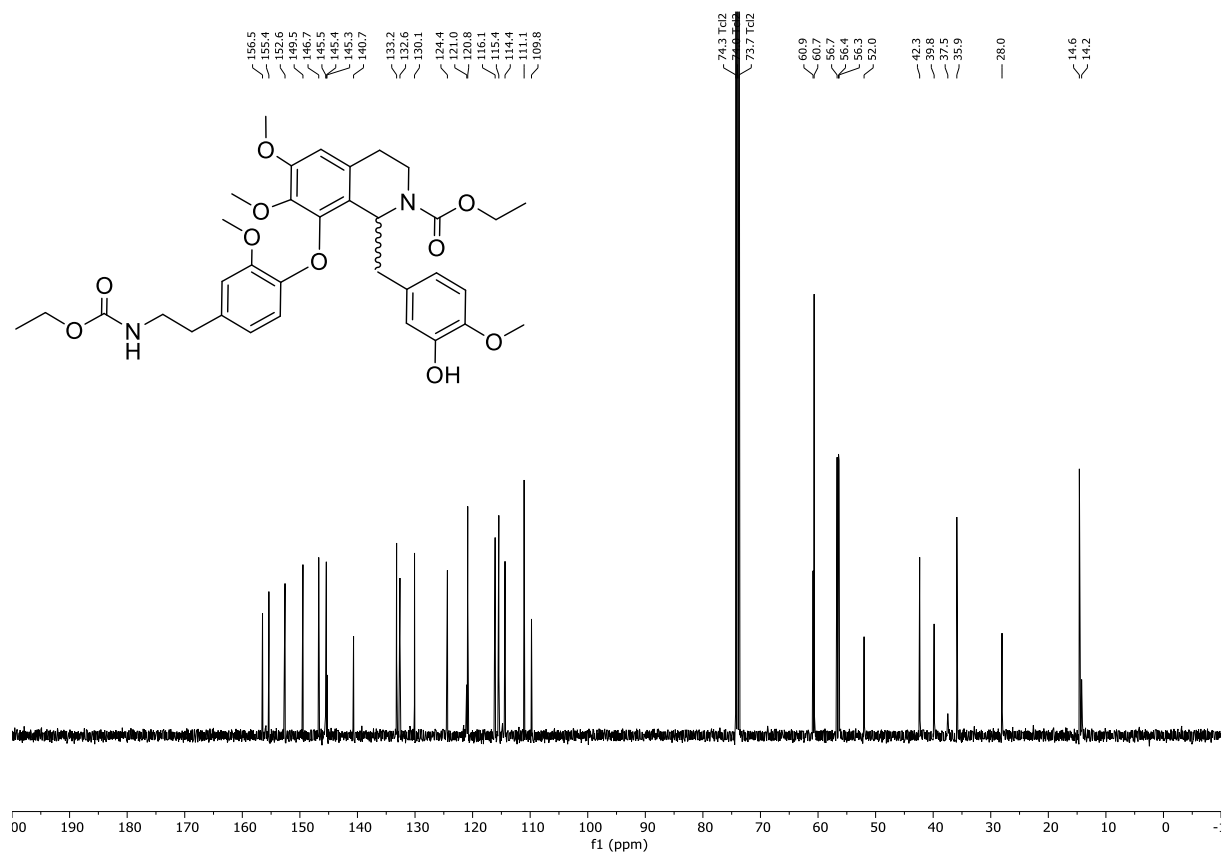
^{13}C NMR (101 MHz, Tcl_2 , 100°C) of **11**



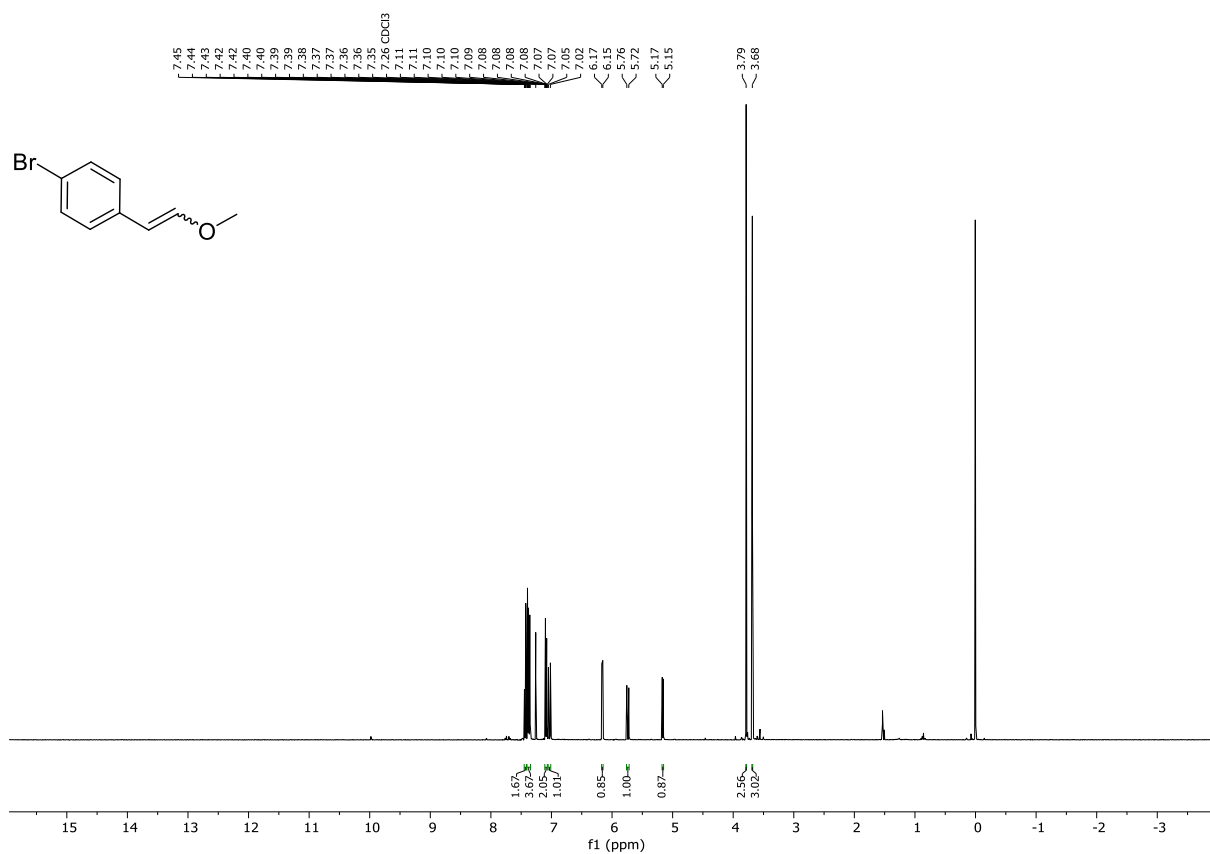
^1H NMR (400 MHz, Tcl_2 , 100°C) of **12**



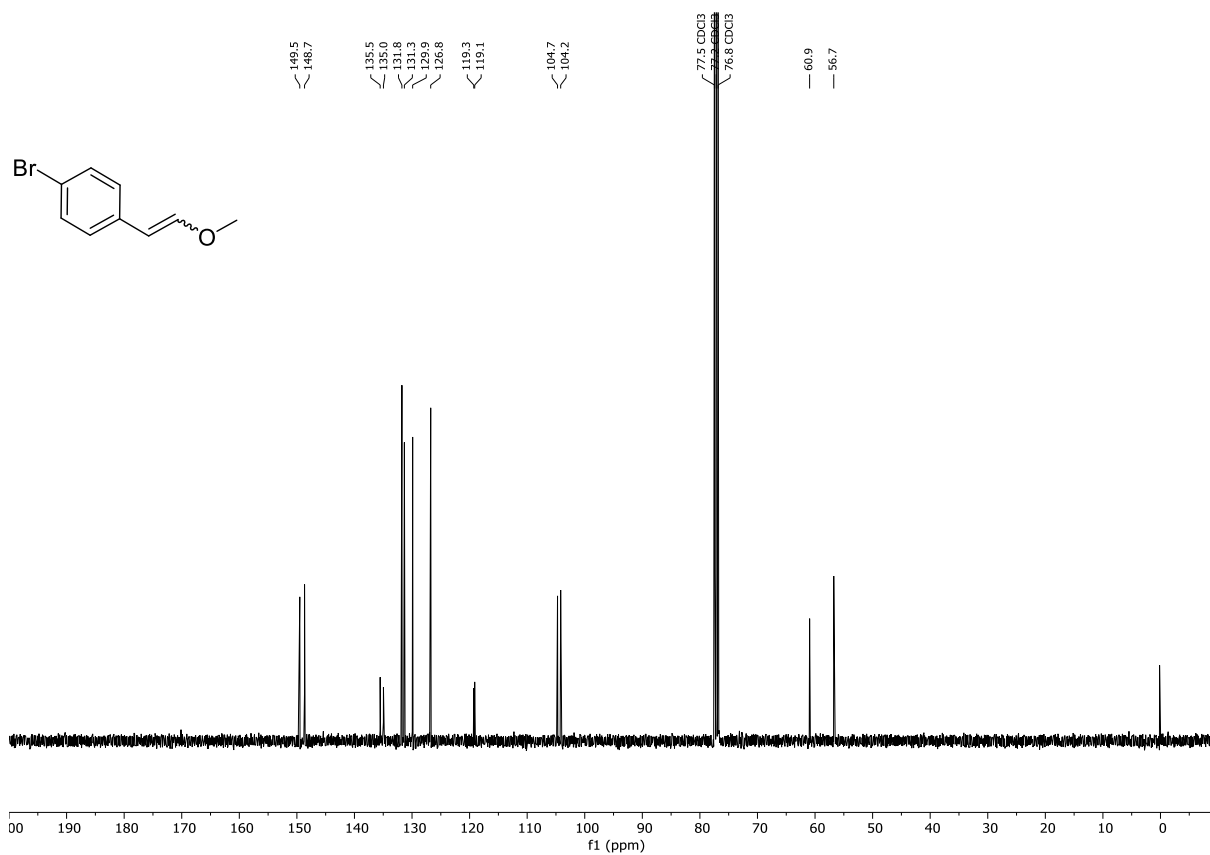
^{13}C NMR (101 MHz, Tcl_2 , 100°C) of **12**



^1H NMR (400 MHz, CDCl_3) of **13**



^{13}C NMR (101 MHz, CDCl_3) of **13**



The figure displays the chemical structure of compound 6 and its corresponding ¹H NMR spectrum. The chemical structure is a complex molecule featuring two chromane-like units linked by a biphenyl moiety. It includes various functional groups such as methoxy, bromine, hydroxyl, and ester groups. The ¹H NMR spectrum shows peaks from -1 to 7.22 ppm, with integration values provided below the baseline.

Chemical Structure:

CCOC(=O)N1Cc2cc(OC)c(OC)c(Oc3ccc(CCN1C(=O)OCC)cc3Oc4cc(OC)c(OC)c(O)c4)c2Cc5ccc(Br)cc5

¹H NMR Spectrum Data:

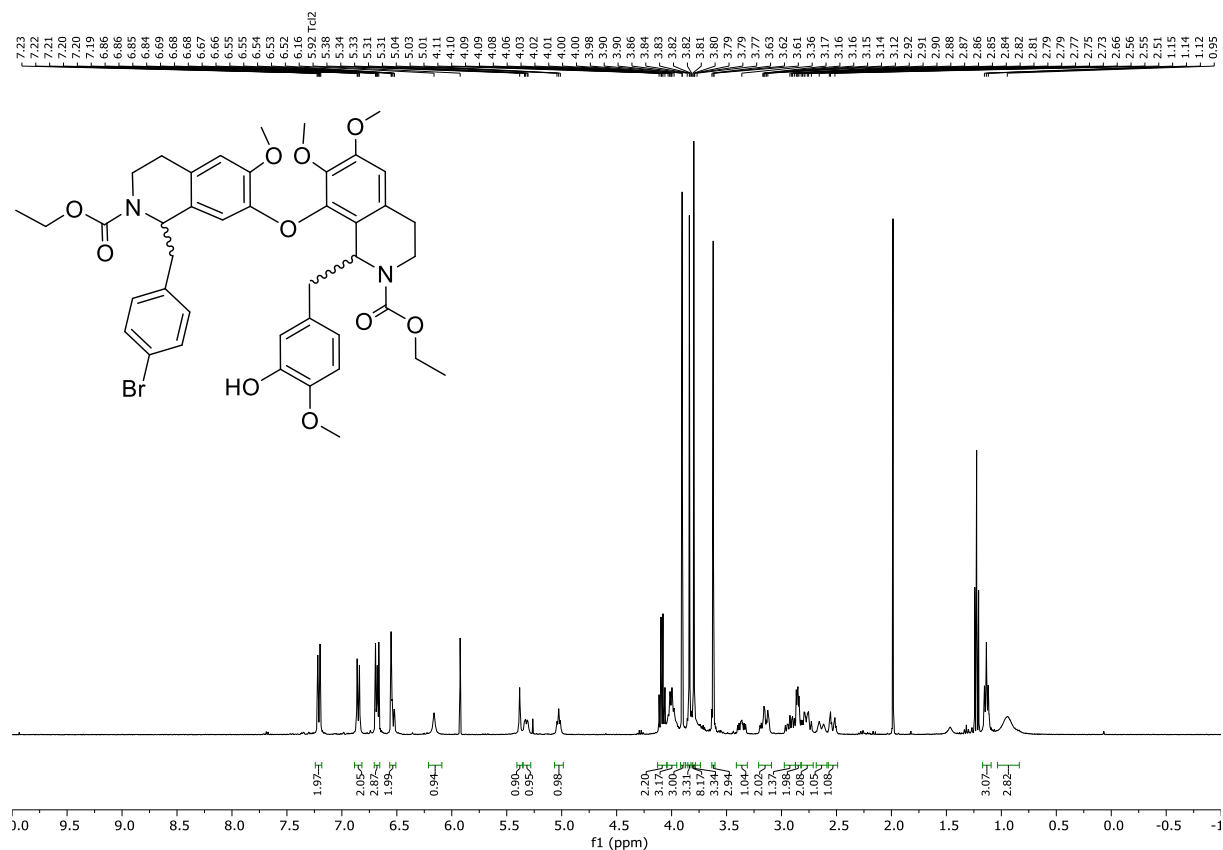
Chemical Shift (ppm)	Integration
7.22	1.93
7.21	1.93
7.20	0.86
7.19	0.86
7.18	0.86
7.17	0.86
7.16	0.86
7.15	0.86
7.14	0.86
7.13	0.86
7.12	0.86
7.11	0.86
7.10	0.86
7.09	0.86
7.08	0.86
7.07	0.86
7.06	0.86
7.05	0.86
7.04	0.86
7.03	0.86
7.02	0.86
7.01	0.86
7.00	0.86
6.99	0.86
6.98	0.86
6.97	0.86
6.96	0.86
6.95	0.86
6.94	0.86
6.93	0.86
6.92	0.86
6.91	0.86
6.90	0.86
6.89	0.86
6.88	0.86
6.87	0.86
6.86	0.86
6.85	0.86
6.84	0.86
6.83	0.86
6.82	0.86
6.81	0.86
6.80	0.86
6.79	0.86
6.78	0.86
6.77	0.86
6.76	0.86
6.75	0.86
6.74	0.86
6.73	0.86
6.72	0.86
6.71	0.86
6.70	0.86
6.69	0.86
6.68	0.86
6.67	0.86
6.66	0.86
6.65	0.86
6.64	0.86
6.63	0.86
6.62	0.86
6.61	0.86
6.60	0.86
6.59	0.86
6.58	0.86
6.57	0.86
6.56	0.86
6.55	0.86
6.54	0.86
6.53	0.86
6.52	0.86
6.51	0.86
6.50	0.86
6.49	0.86
6.48	0.86
6.47	0.86
6.46	0.86
6.45	0.86
6.44	0.86
6.43	0.86
6.42	0.86
6.41	0.86
6.40	0.86
6.39	0.86
6.38	0.86
6.37	0.86
6.36	0.86
6.35	0.86
6.34	0.86
6.33	0.86
6.32	0.86
6.31	0.86
6.30	0.86
6.29	0.86
6.28	0.86
6.27	0.86
6.26	0.86
6.25	0.86
6.24	0.86
6.23	0.86
6.22	0.86
6.21	0.86
6.20	0.86
6.19	0.86
6.18	0.86
6.17	0.86
6.16	0.86
6.15	0.86
6.14	0.86
6.13	0.86
6.12	0.86
6.11	0.86
6.10	0.86
6.09	0.86
6.08	0.86
6.07	0.86
6.06	0.86
6.05	0.86
6.04	0.86
6.03	0.86
6.02	0.86
6.01	0.86
6.00	0.86
5.99	0.86
5.98	0.86
5.97	0.86
5.96	0.86
5.95	0.86
5.94	0.86
5.93	0.86
5.92	0.86
5.91	0.86
5.90	0.86
5.89	0.86
5.88	0.86
5.87	0.86
5.86	0.86
5.85	0.86
5.84	0.86
5.83	0.86
5.82	0.86
5.81	0.86
5.80	0.86
5.79	0.86
5.78	0.86
5.77	0.86
5.76	0.86
5.75	0.86
5.74	0.86
5.73	0.86
5.72	0.86
5.71	0.86
5.70	0.86
5.69	0.86
5.68	0.86
5.67	0.86
5.66	0.86
5.65	0.86
5.64	0.86
5.63	0.86
5.62	0.86
5.61	0.86
5.60	0.86
5.59	0.86
5.58	0.86
5.57	0.86
5.56	0.86
5.55	0.86
5.54	0.86
5.53	0.86
5.52	0.86
5.51	0.86
5.50	0.86
5.49	0.86
5.48	0.86

Chemical structure of compound 10b is shown above the ^{13}C NMR spectrum. The structure is a dimeric molecule consisting of two 6-methoxy-2-(4-methoxyphenyl)-2,3-dihydro-1H-benzopyran units linked by a central ether bridge. Each unit is substituted with a 4-bromophenyl group and an ethyl ester group.

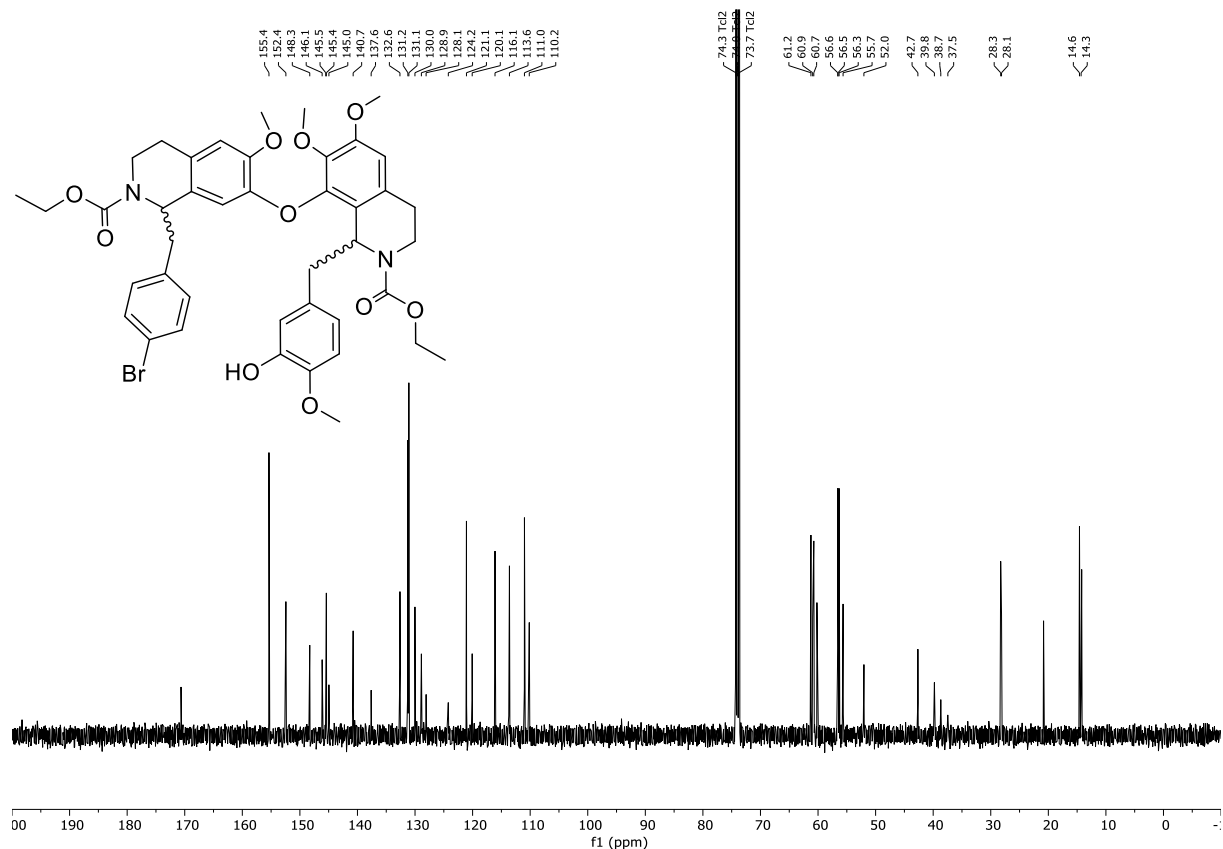
The ^{13}C NMR spectrum (ppm) shows the following peaks (labeled from left to right):

- 155.4
- 152.5
- 148.2
- 146.2
- 145.5
- 145.4
- 145.0
- 140.6
- 137.4
- 136.6
- 131.2
- 131.1
- 130.0
- 128.8
- 128.3
- 124.3
- 124.0
- 120.2
- 116.0
- 114.0
- 113.7
- 111.0
- 110.1
- 74.3 Td2
- 73.7 Td2
- 61.2
- 60.9
- 60.7
- 56.7
- 56.5
- 56.4
- 55.6
- 52.0
- 42.6
- 39.8
- 38.9
- 37.3
- 28.2
- 28.0
- 14.2

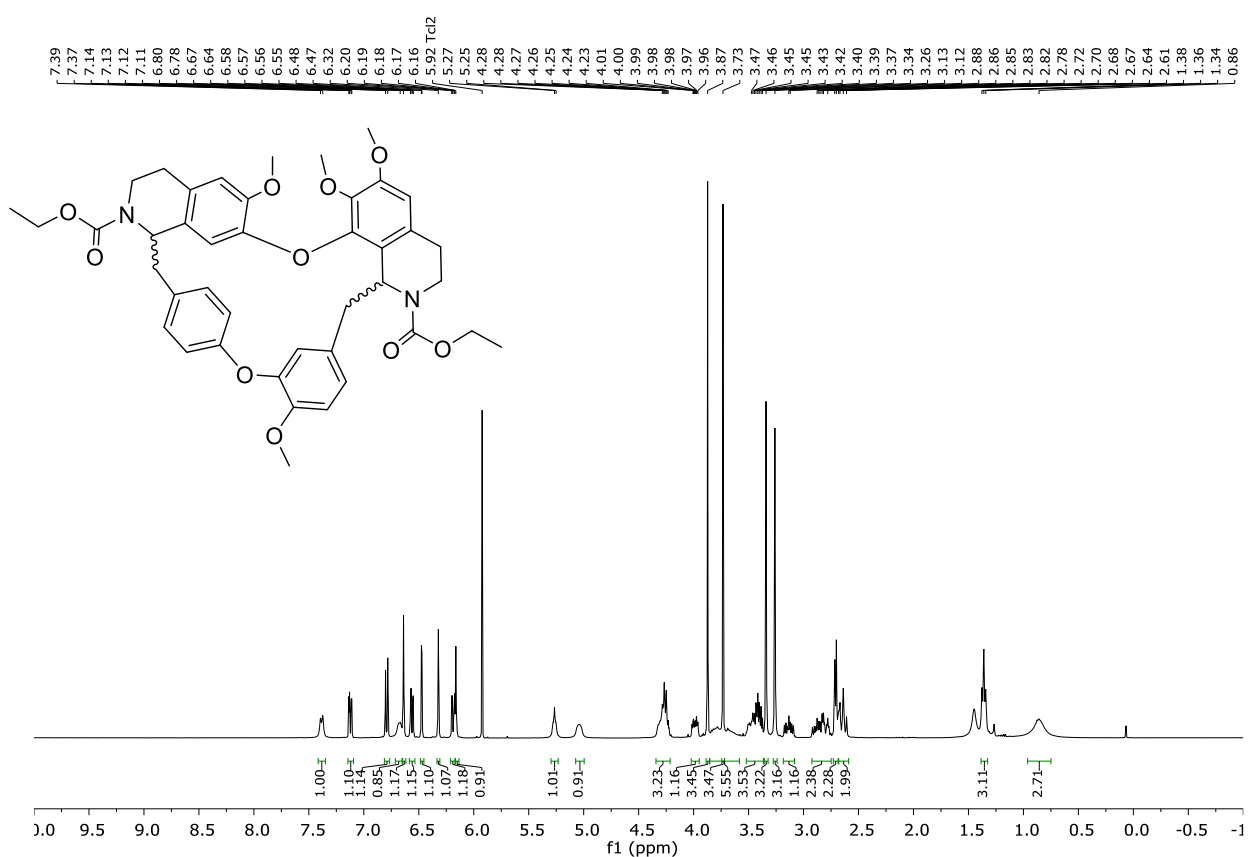
^1H NMR (400 MHz, Tcl_2 , 100°C) of **14b** ((1*R*,1'*S*)/(1*S*,1'*R*) isomers)



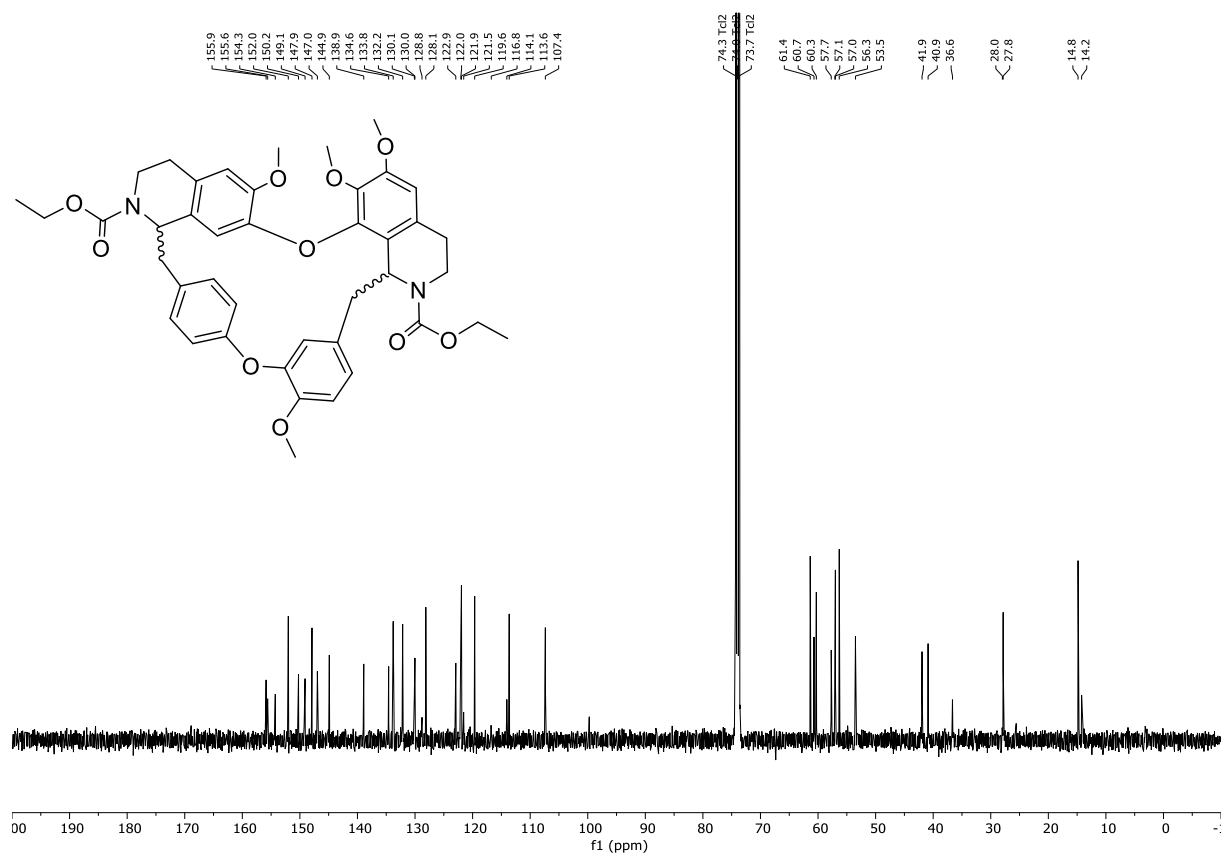
^{13}C NMR (101 MHz, Tcl_2 , 100°C) of **14b** ((1*R*,1'*S*)/(1*S*,1'*R*) isomers)



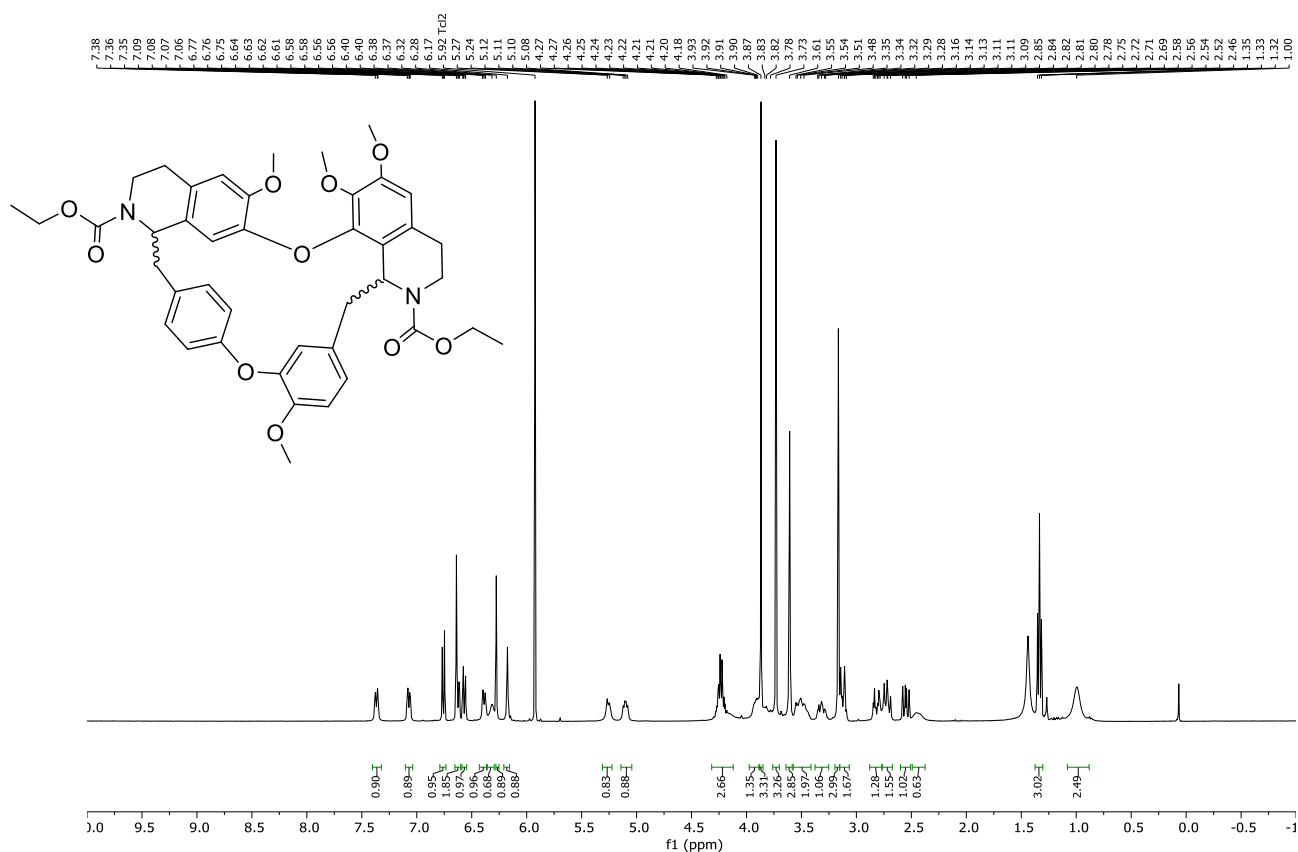
^1H NMR (400 MHz, CDCl_3 , 100°C) of **15a** ((1*R*,1'*R*)/(1*S*,1'*S*) isomers)



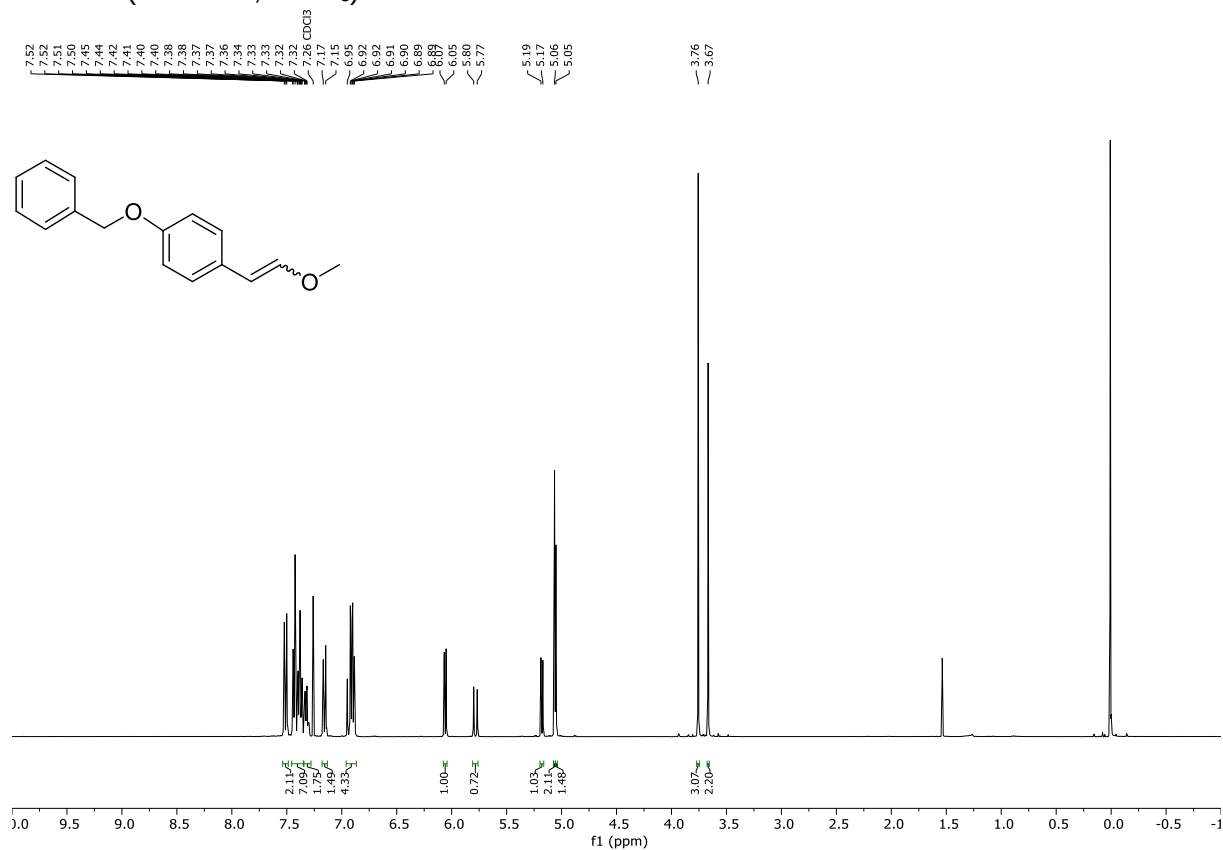
^{13}C NMR (101 MHz, CDCl_3 , 100°C) of **15a** ((1*R*,1'*R*)/(1*S*,1'*S*) isomers)



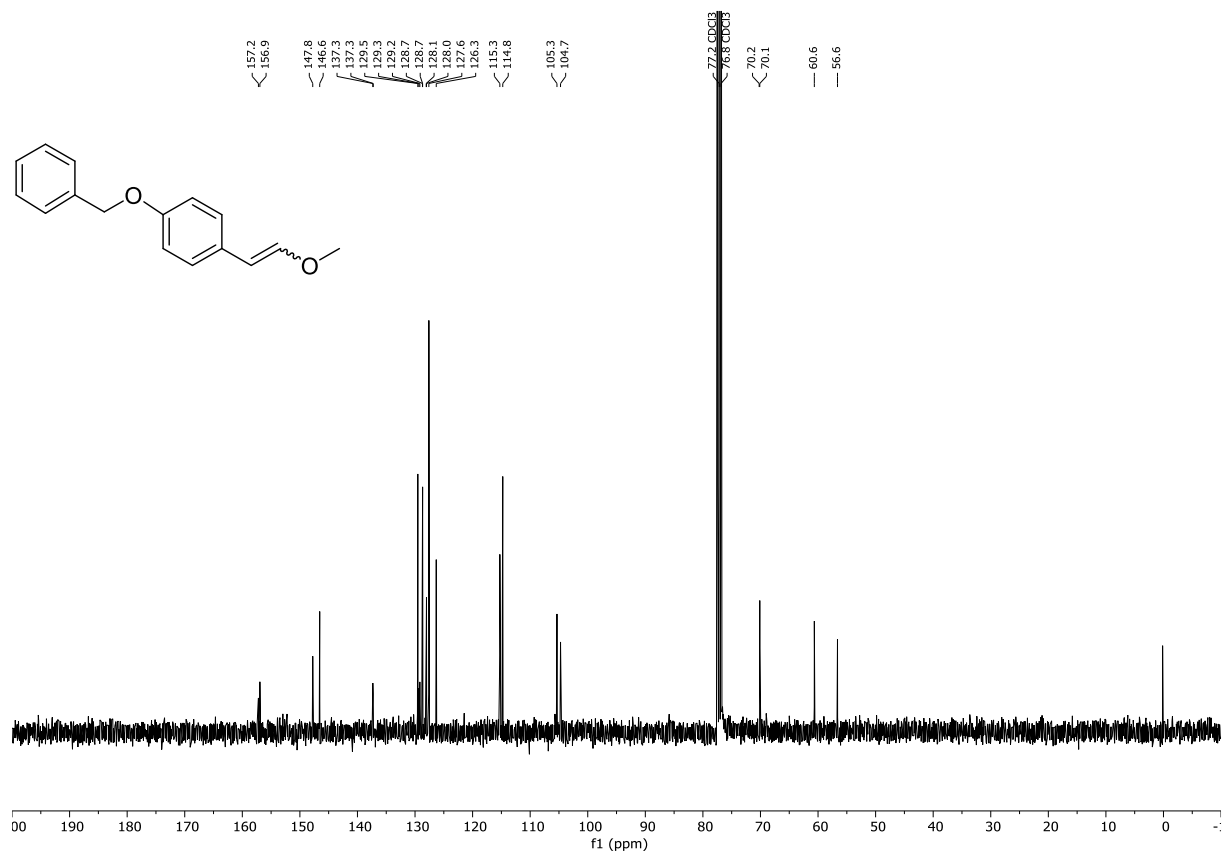
^1H NMR (400 MHz, CDCl_3 , 100°C) of **15b** ((1*R*,1'*S*)/(1*S*,1'*R*) isomers)



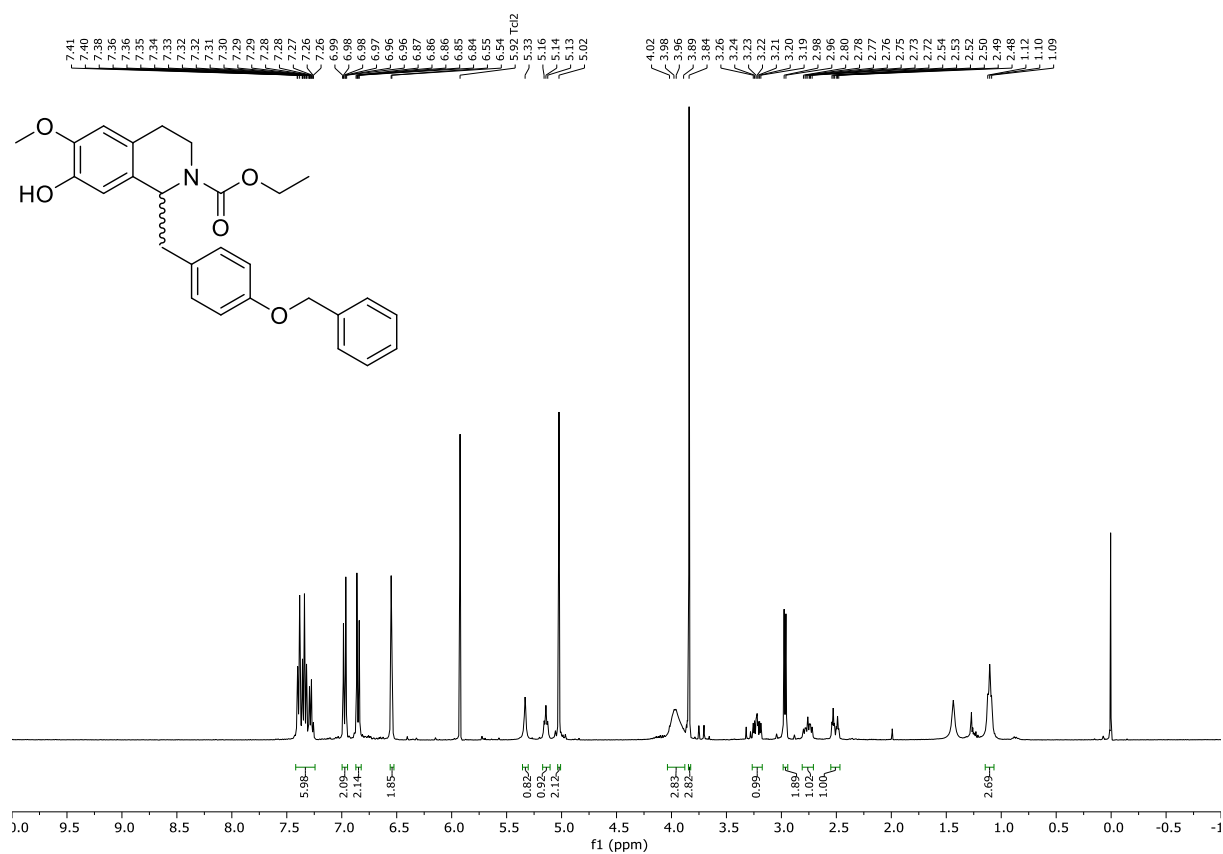
^1H NMR (400 MHz, CDCl_3) of **16**



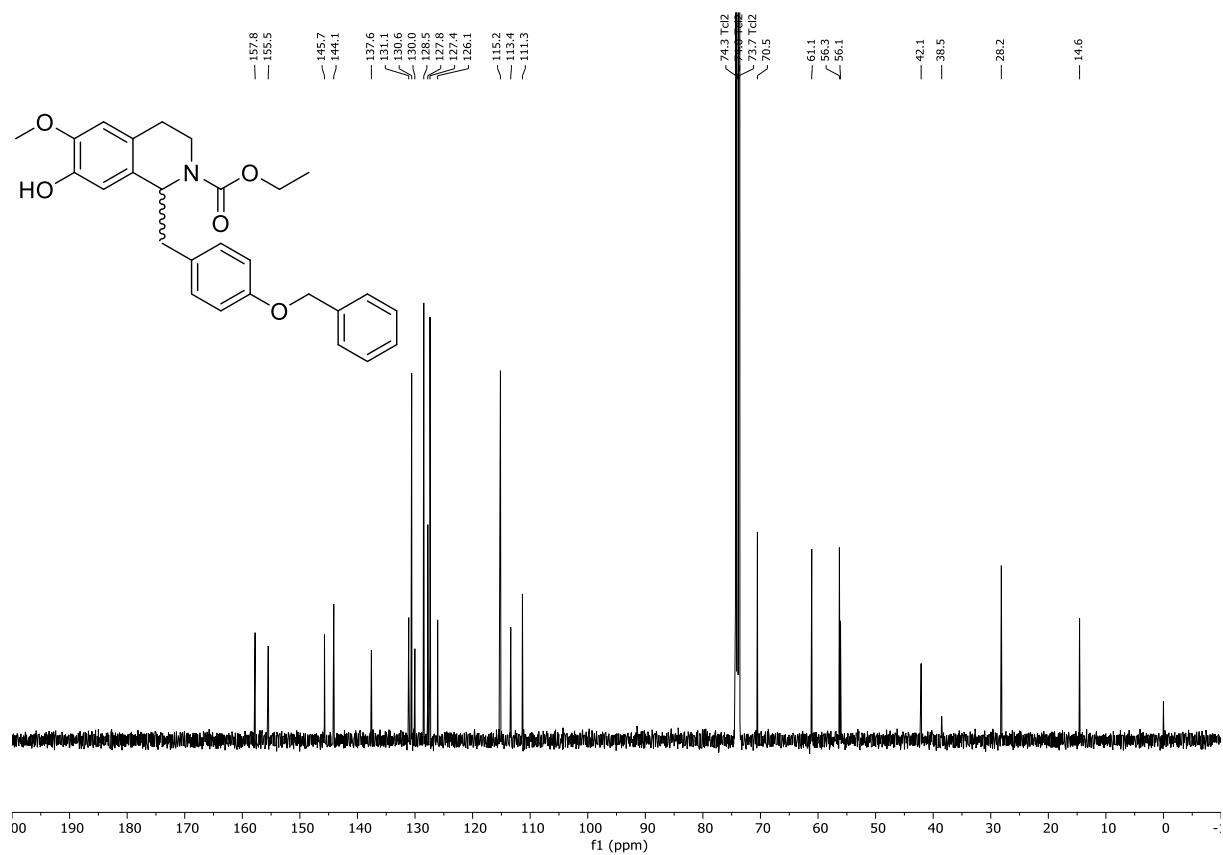
^{13}C NMR (101 MHz, CDCl_3) of **16**



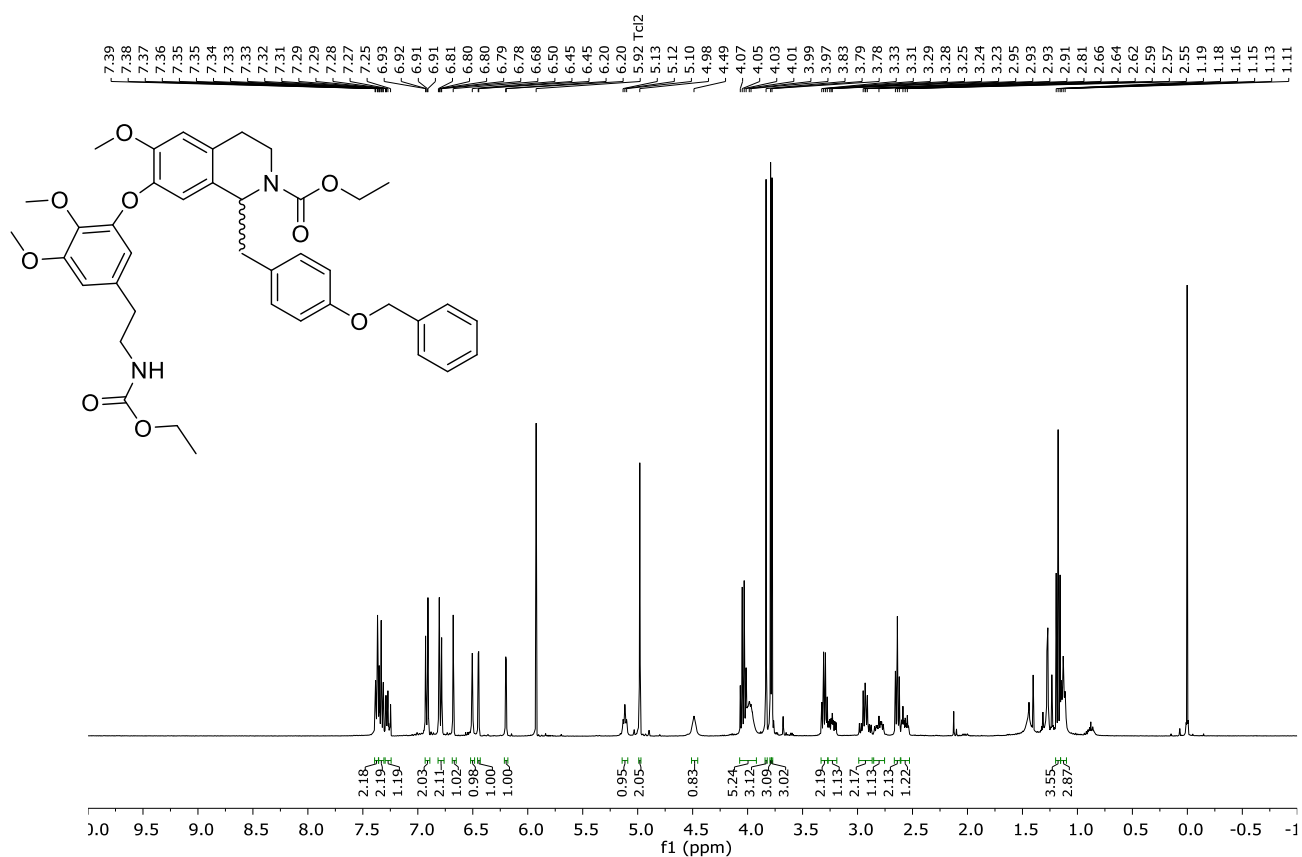
^1H NMR (400 MHz, Tcl_2 , 100°C) of **17**



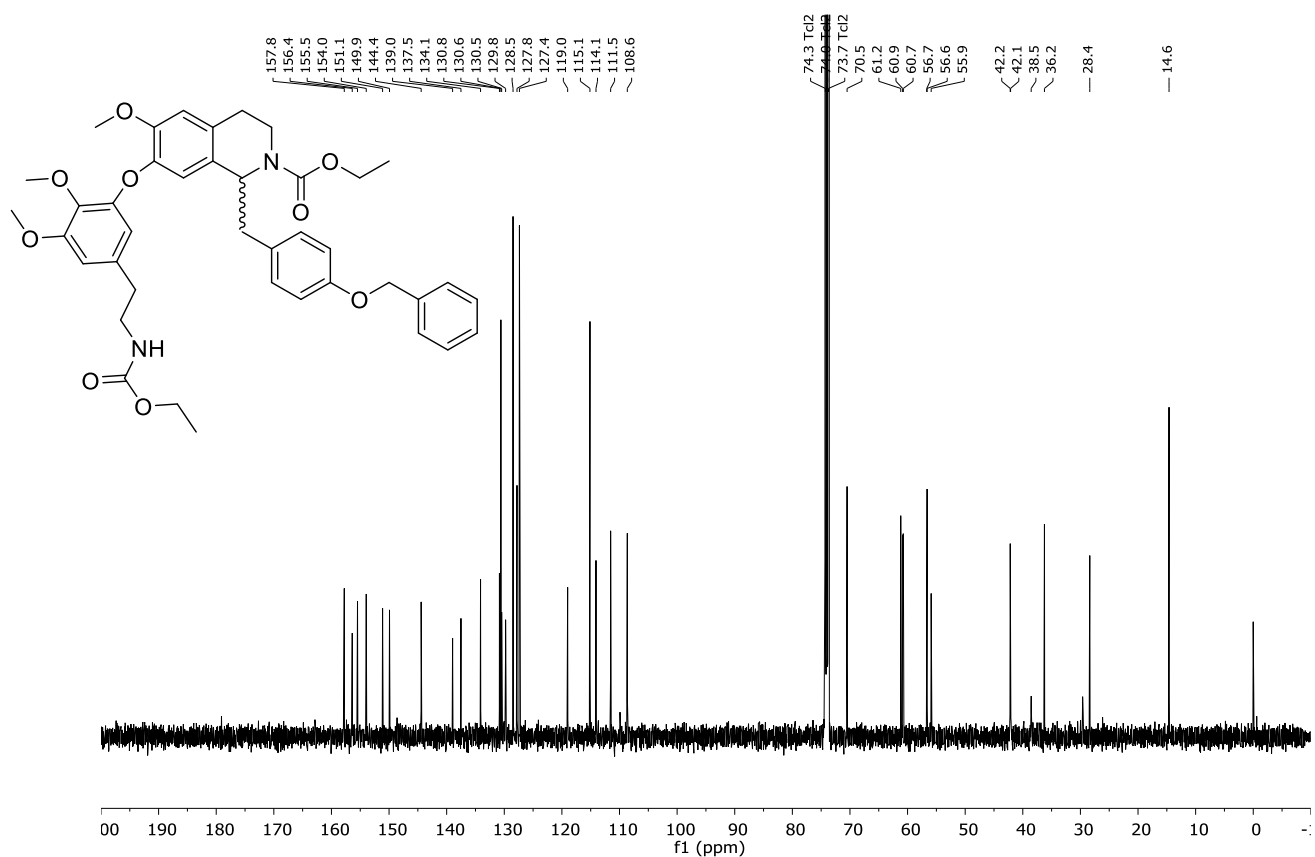
^{13}C NMR (101 MHz, Tcl_2 , 100°C) of **17**



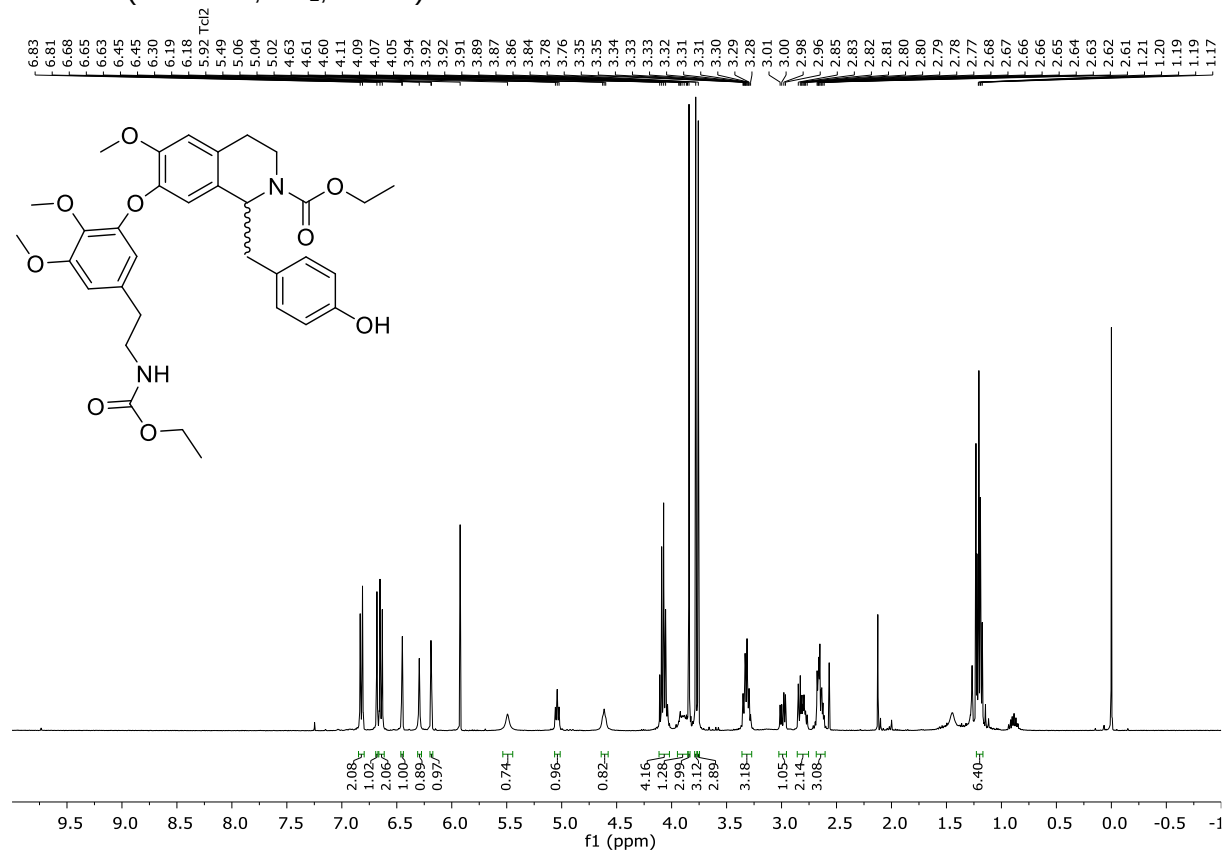
¹H NMR (400 MHz, TcCl₂, 100°C) of **18**



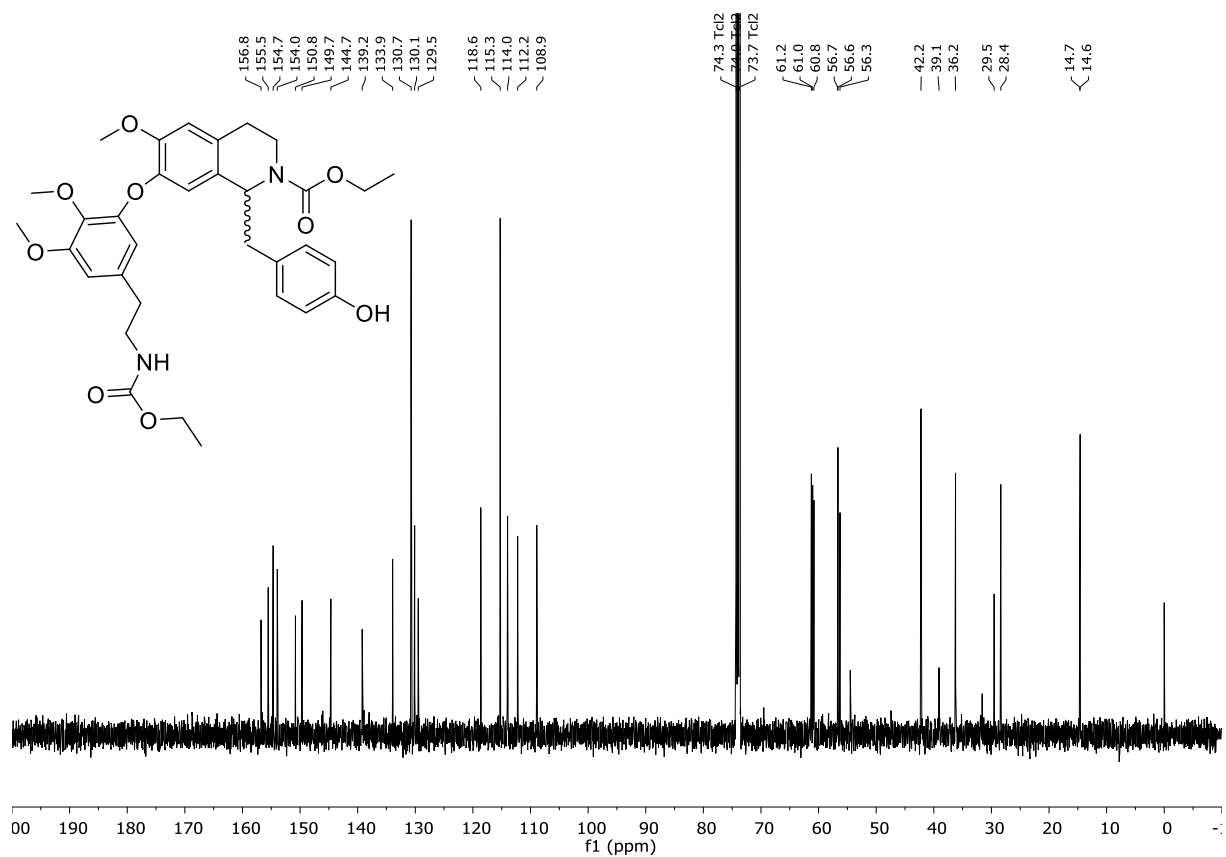
¹³C NMR (101 MHz, TcCl₂, 100°C) of **18**



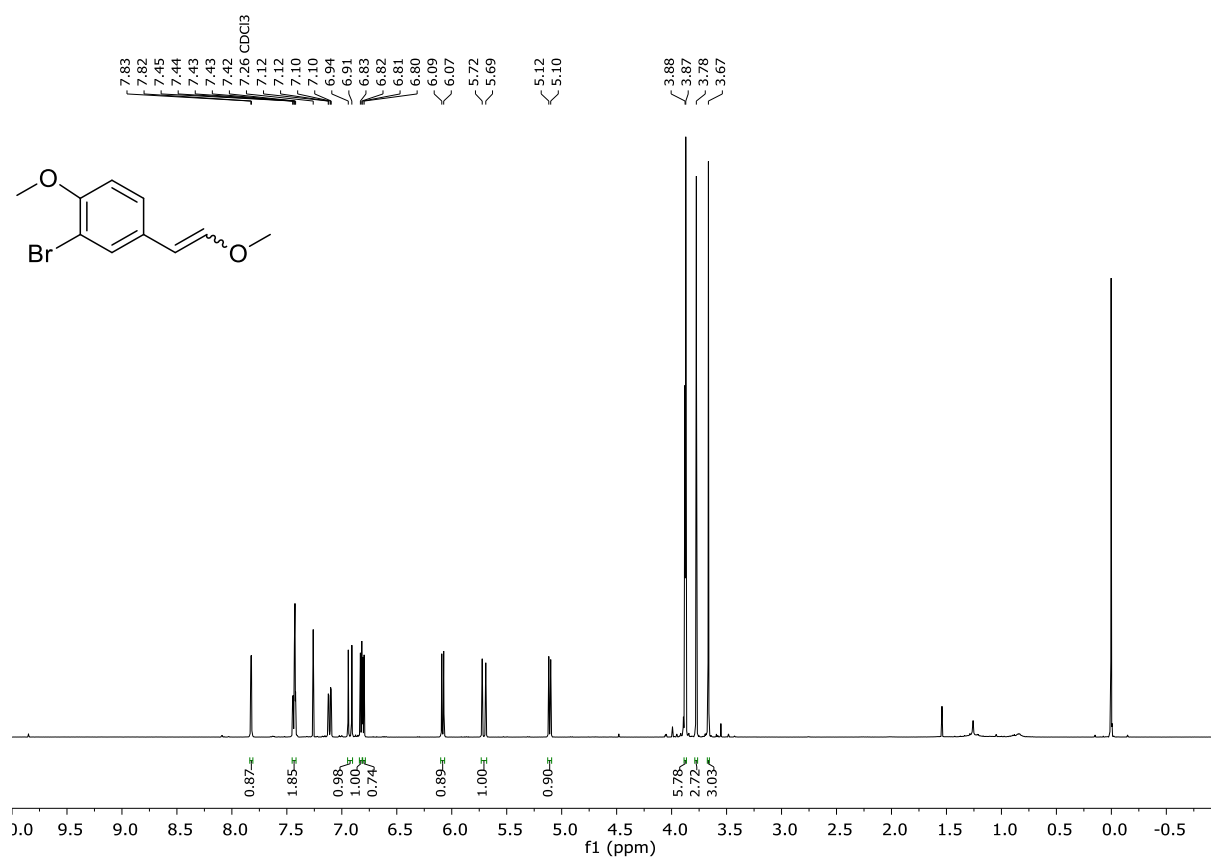
¹H NMR (400 MHz, TcCl₂, 100°C) of **19**



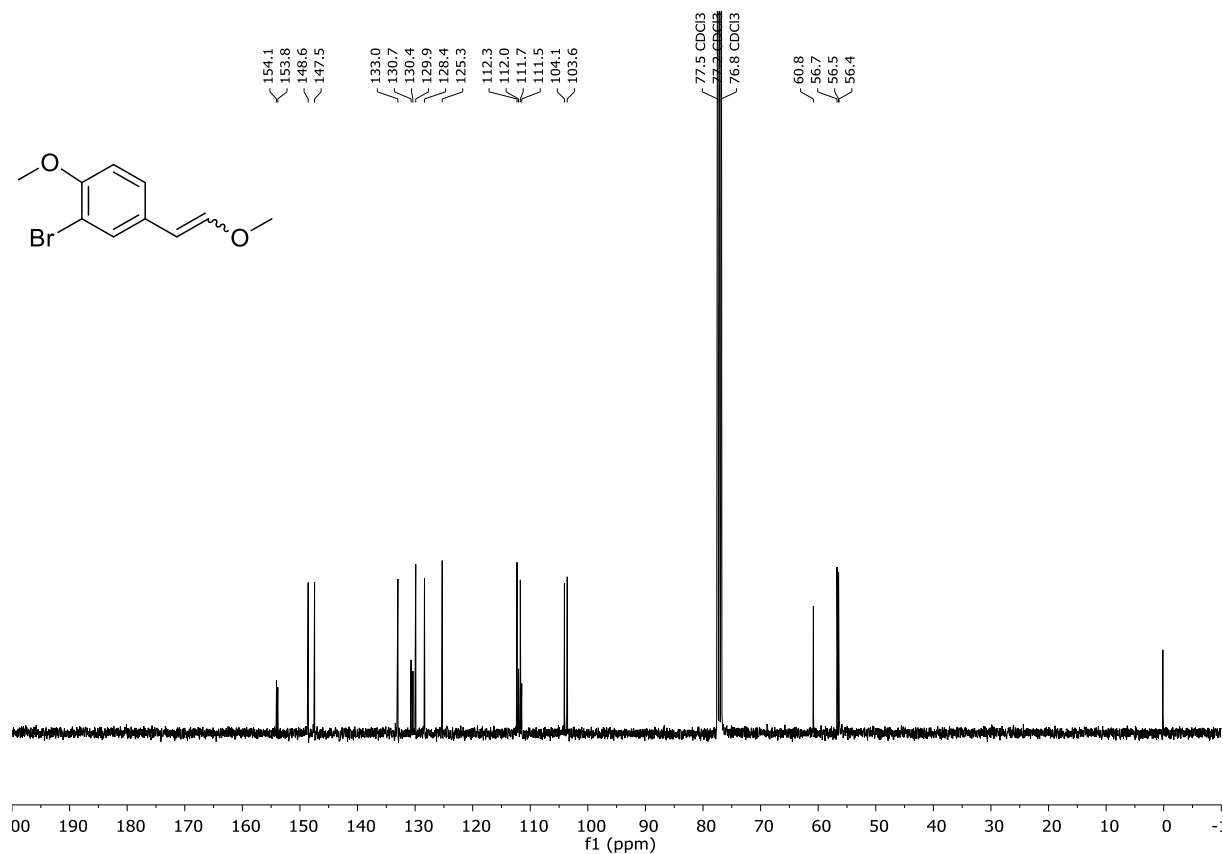
¹³C NMR (101 MHz, TcCl₂, 100°C) of **19**



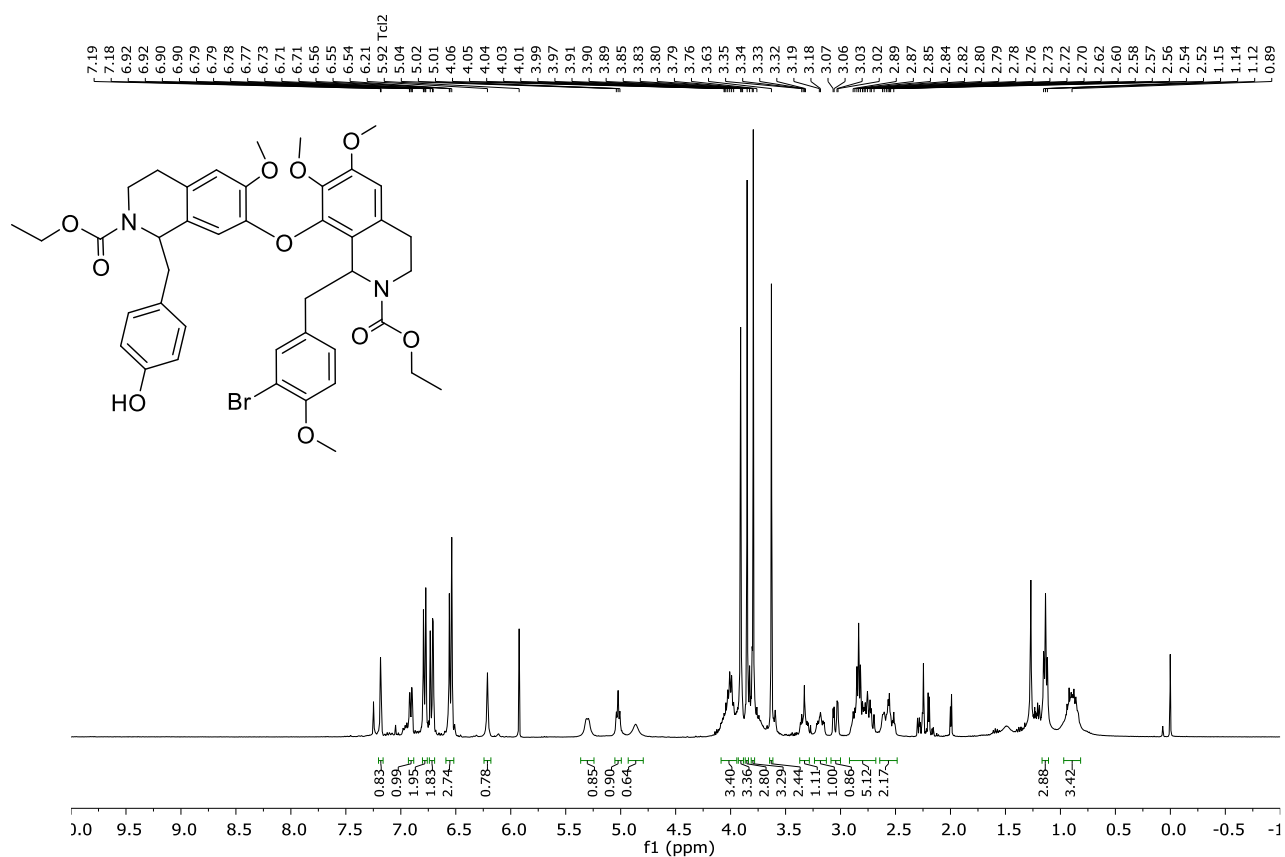
^1H NMR (400 MHz, CDCl_3) of **20**



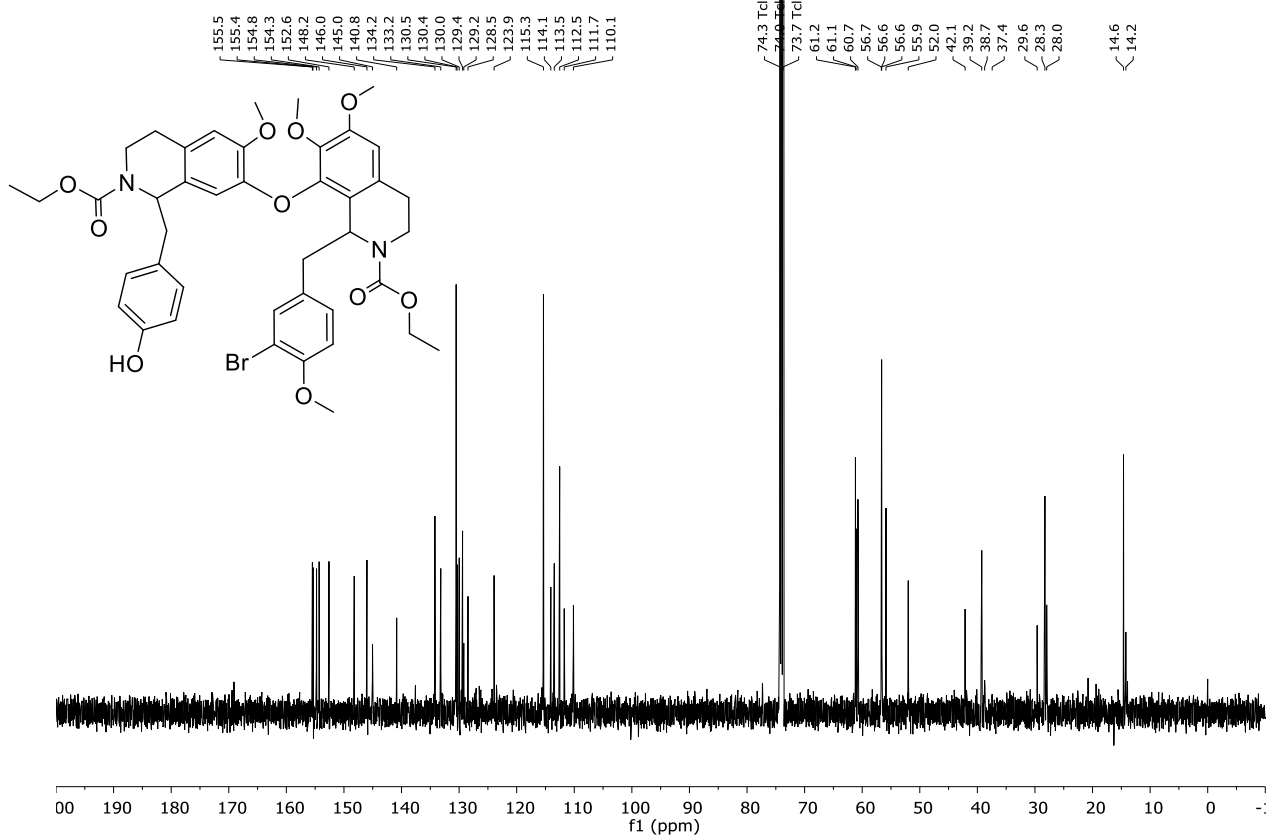
^{13}C NMR (101 MHz, CDCl_3) of **20**



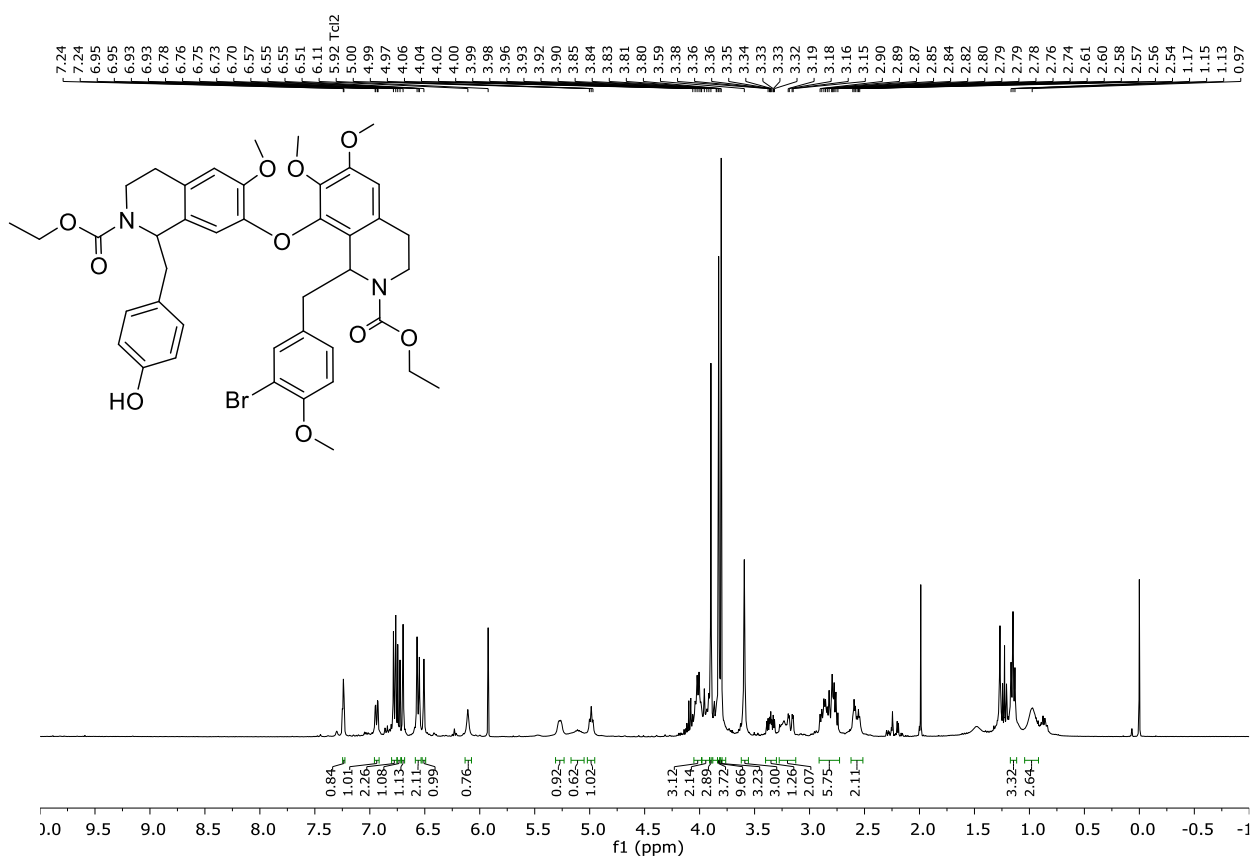
^1H NMR (400 MHz, Tcl_2 , 100°C) of **21a** ((1*R*,1'*R*)/(1*S*,1'*S*) isomers)



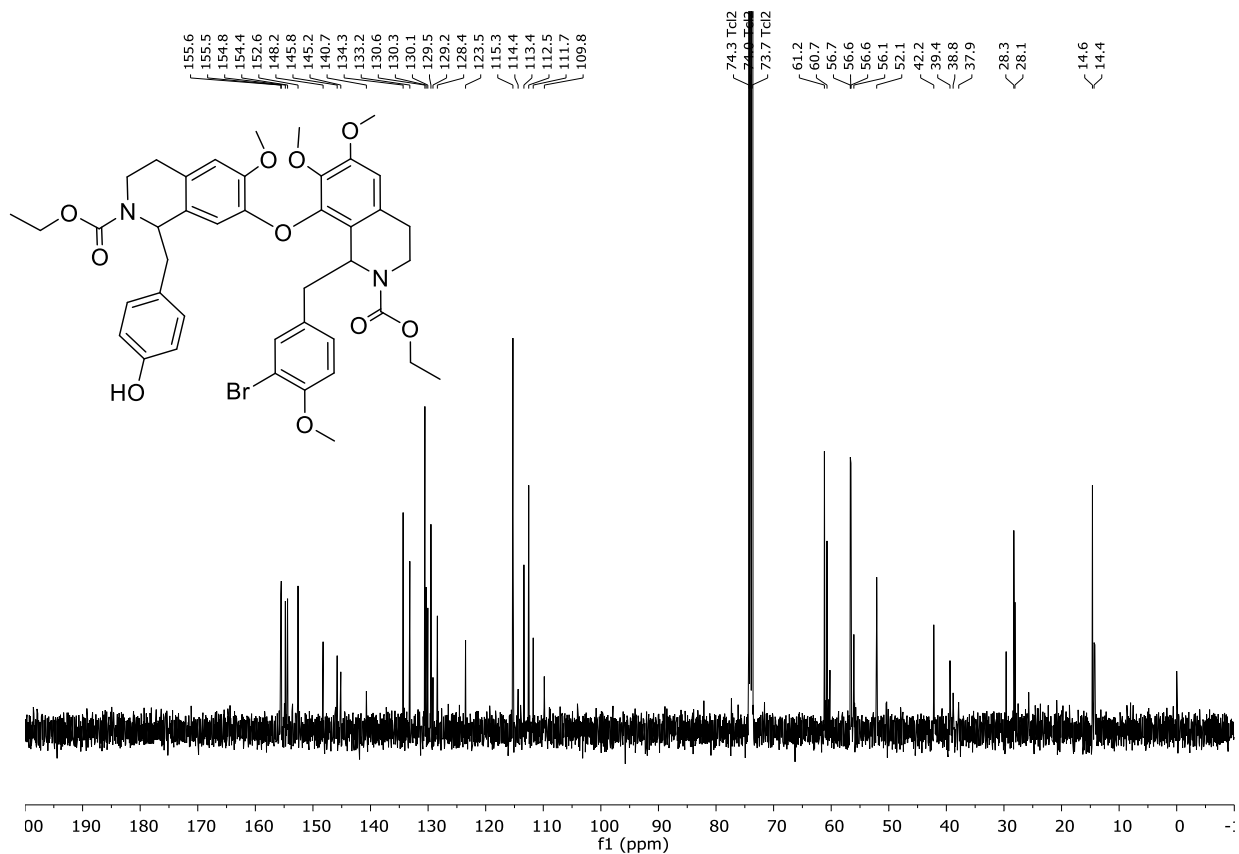
^{13}C NMR (101 MHz, Tcl_2 , 100°C) of **21a** ((1*R*,1'*R*)/(1*S*,1'*S*) isomers)



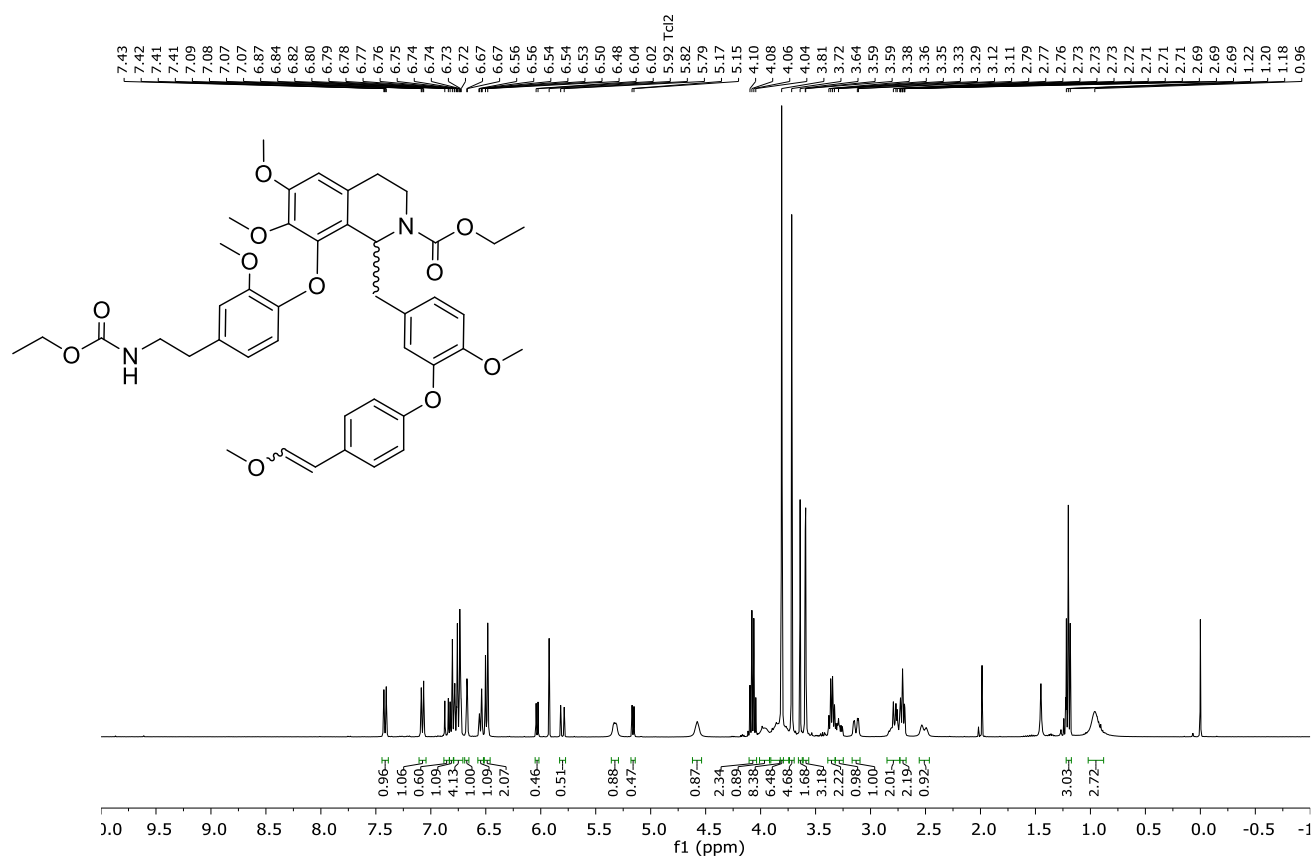
^1H NMR (400 MHz, Tcl_2 , 100°C) of **21b** ((1*R*,1'*S*)/(1*S*,1'*R*) isomers)



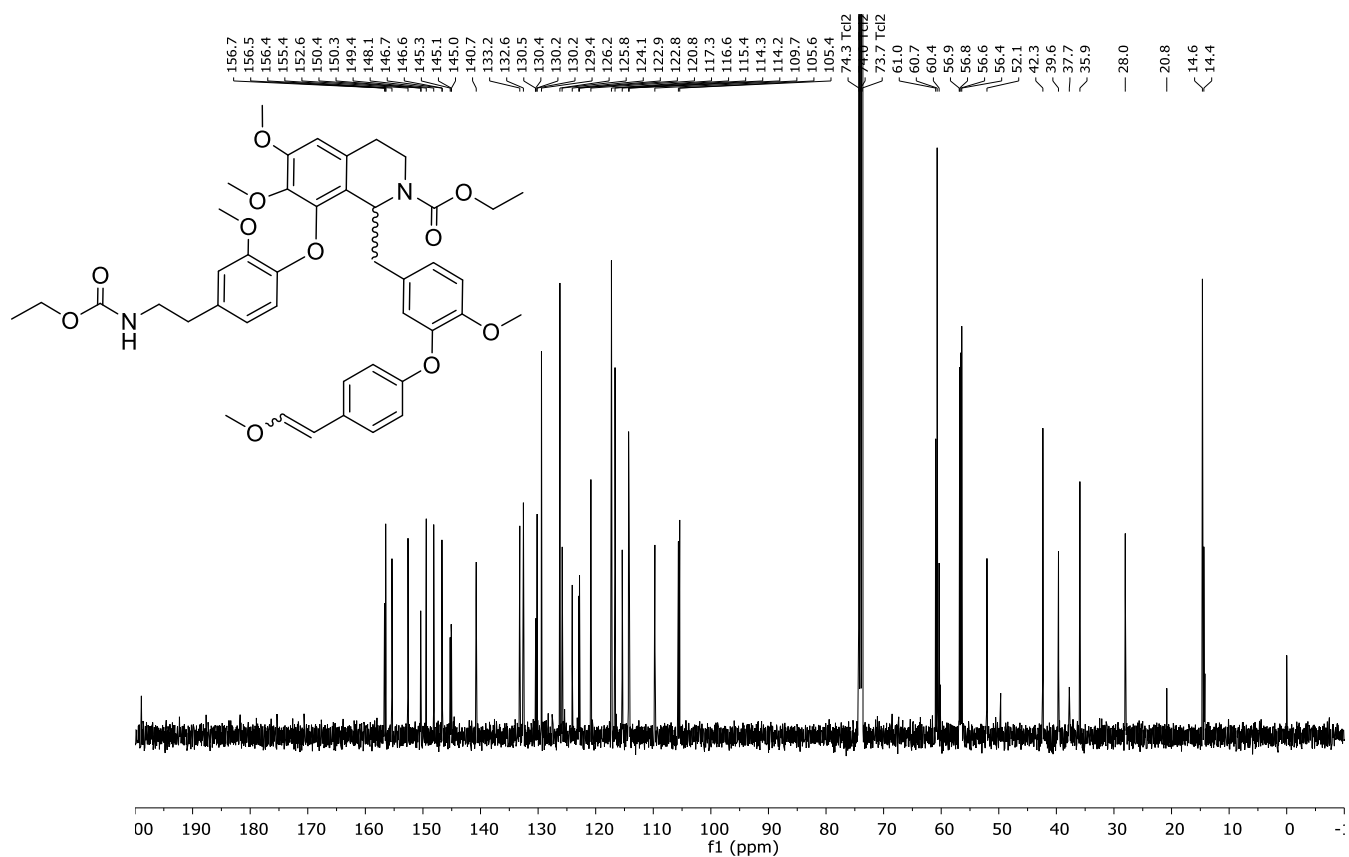
^{13}C NMR (101 MHz, Tcl_2 , 100°C) of **21b** ((1*R*,1'*S*)/(1*S*,1'*R*) isomers)



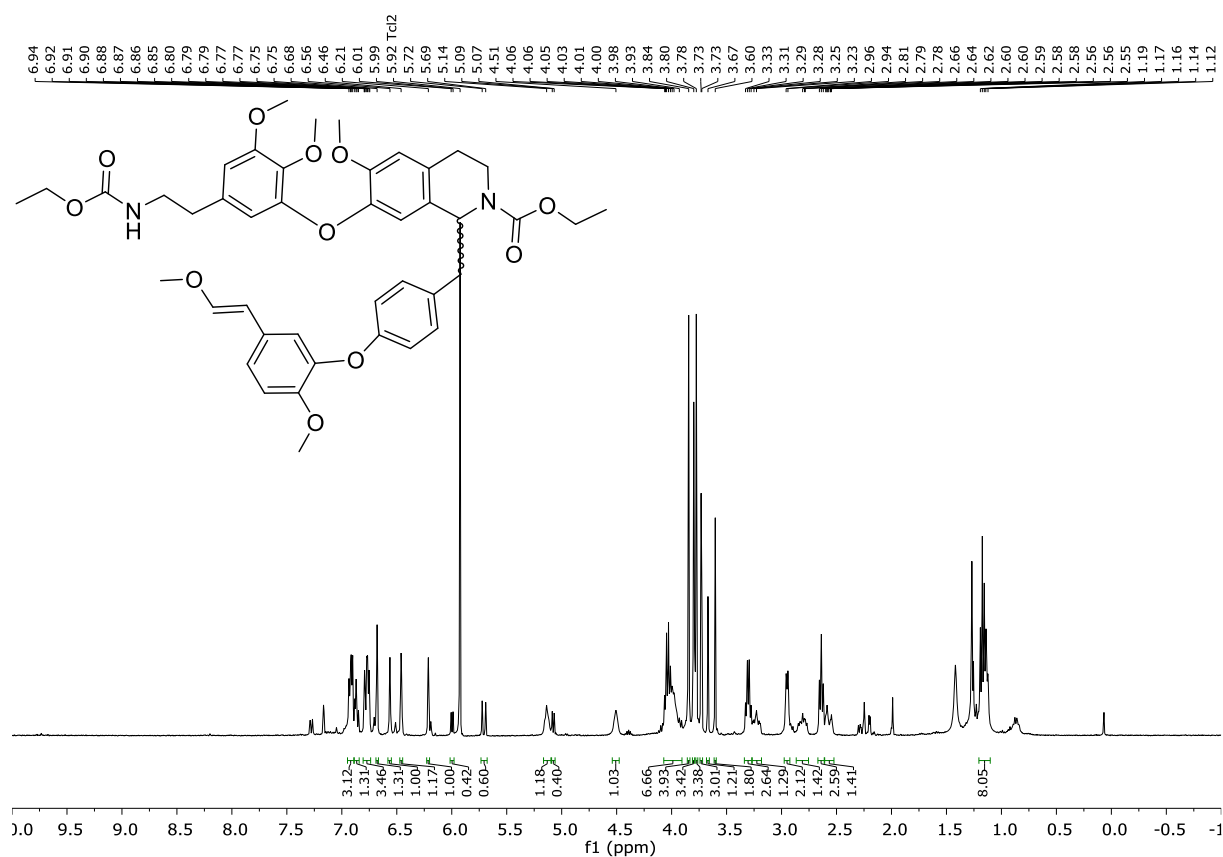
^1H NMR (400 MHz, CDCl_3 , 100°C) of **22**



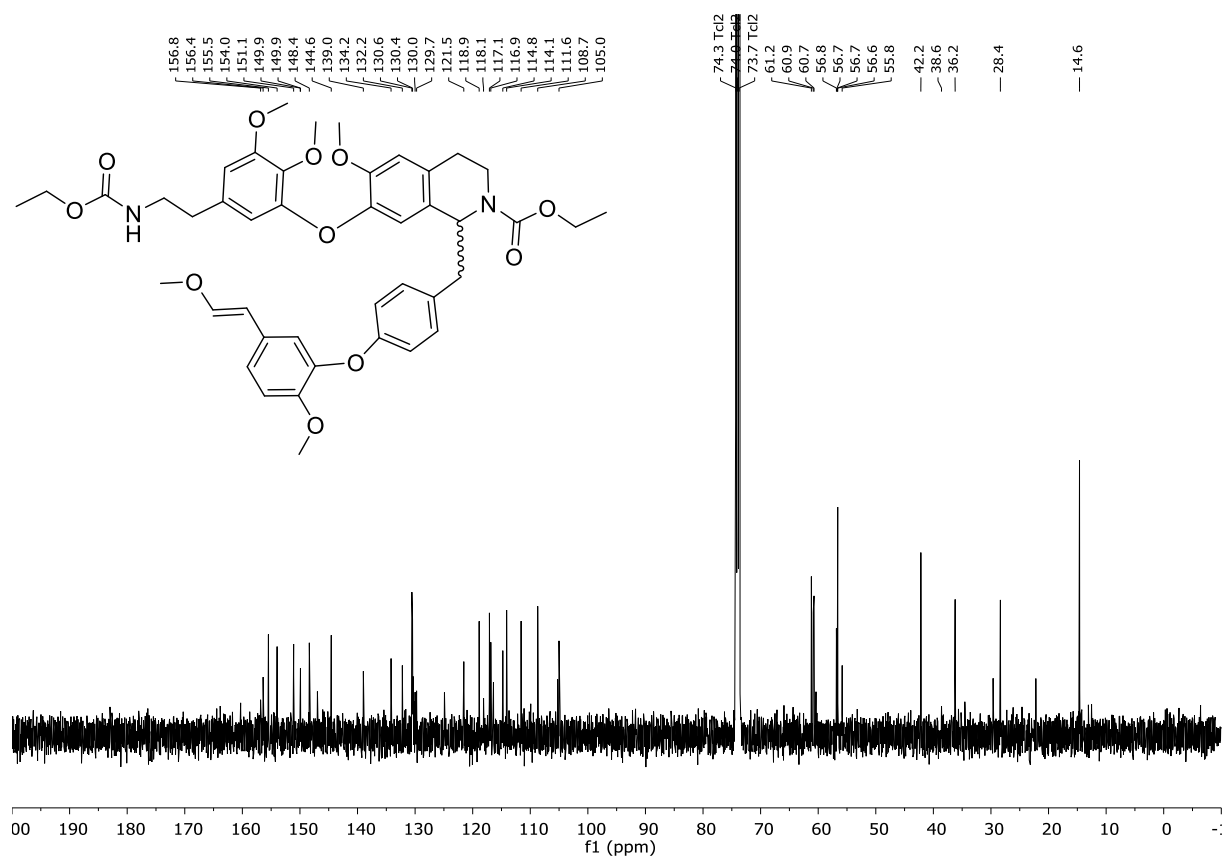
^{13}C NMR (101 MHz, CDCl_3 , 100°C) of **22**



^1H NMR (400 MHz, CDCl_3 , 100°C) of **23**



^{13}C NMR (101 MHz, CDCl_3 , 100°C) of **23**

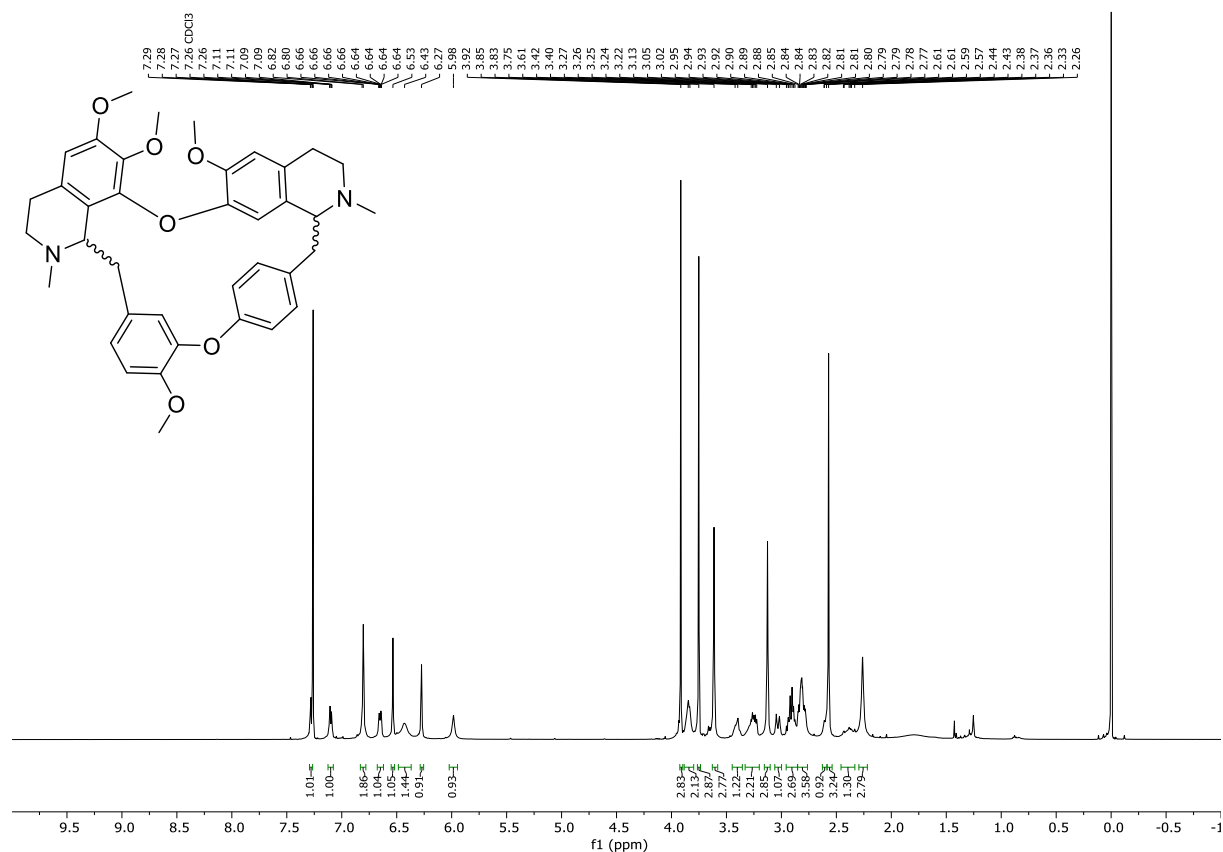


[illegible]

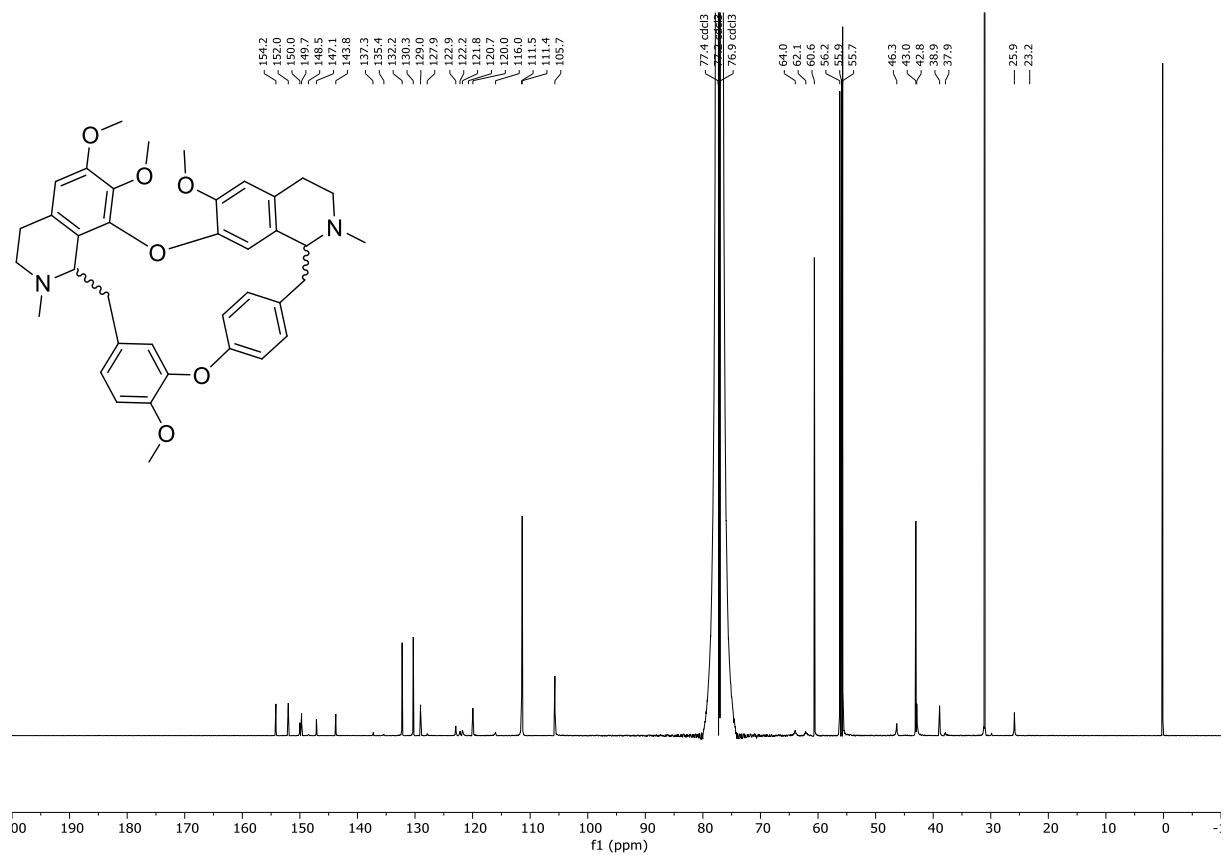
Chemical structure of compound 10 is shown above the ¹³C NMR spectrum. The spectrum displays peaks corresponding to the chemical shifts of the carbon atoms in the molecule, with the following labeled values (ppm):

- 153.9, 151.5, 149.5, 148.7, 148.6, 147.2, 146.6, 138.0, 135.4, 135.1, 132.8, 130.3, 128.3, 128.2, 128.1, 123.1, 122.9, 122.1, 122.0, 120.3, 118.5, 116.5, 116.4, 112.9, 111.7, 105.9, 77.4 (CDCl₃), 76.9 (CDCl₃), 64.1, 61.6, 60.4, 56.3, 56.0, 56.0, 45.4, 44.3, 42.8, 42.5, 42.1, 38.4, 25.4, 22.2.

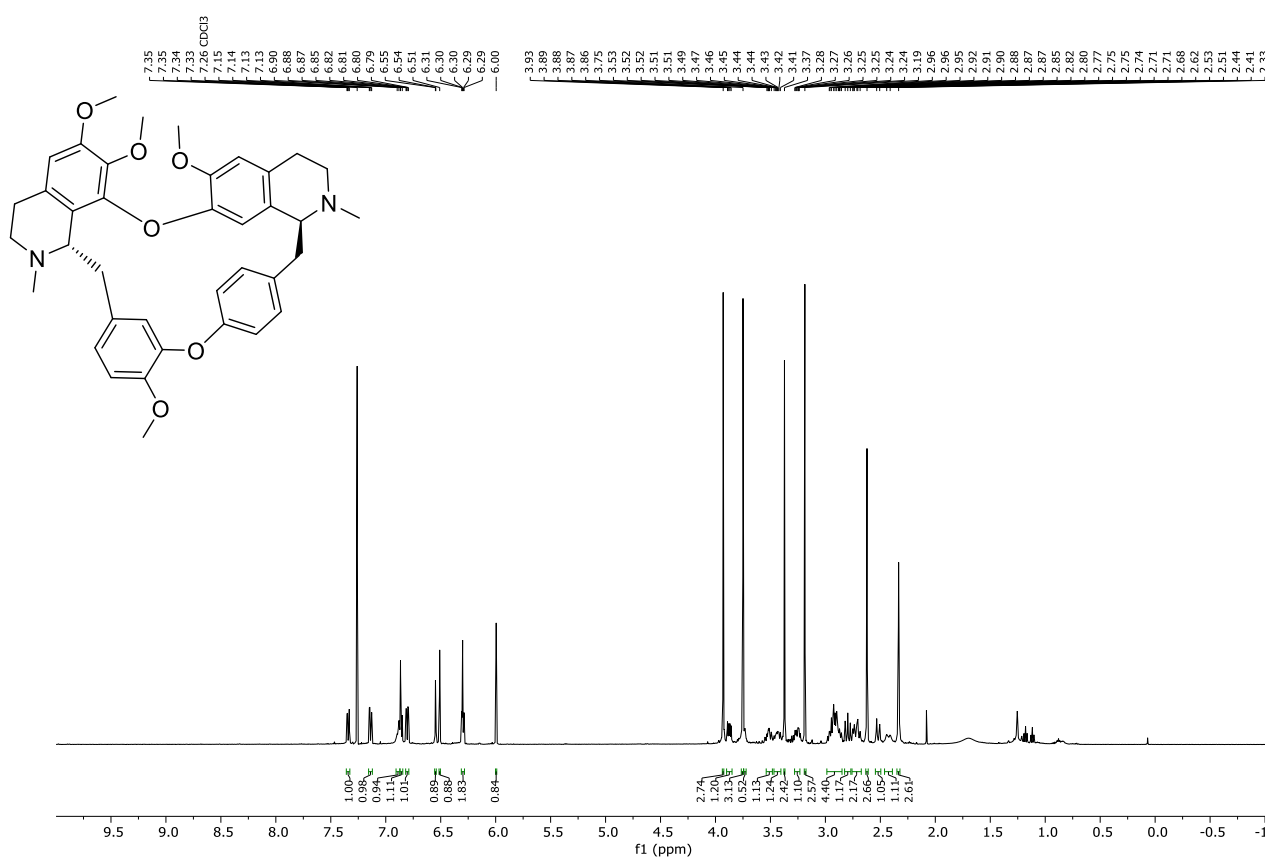
^1H NMR (500 MHz, CDCl_3) of synthetic racemic isotetrandrine (*rac*-2)



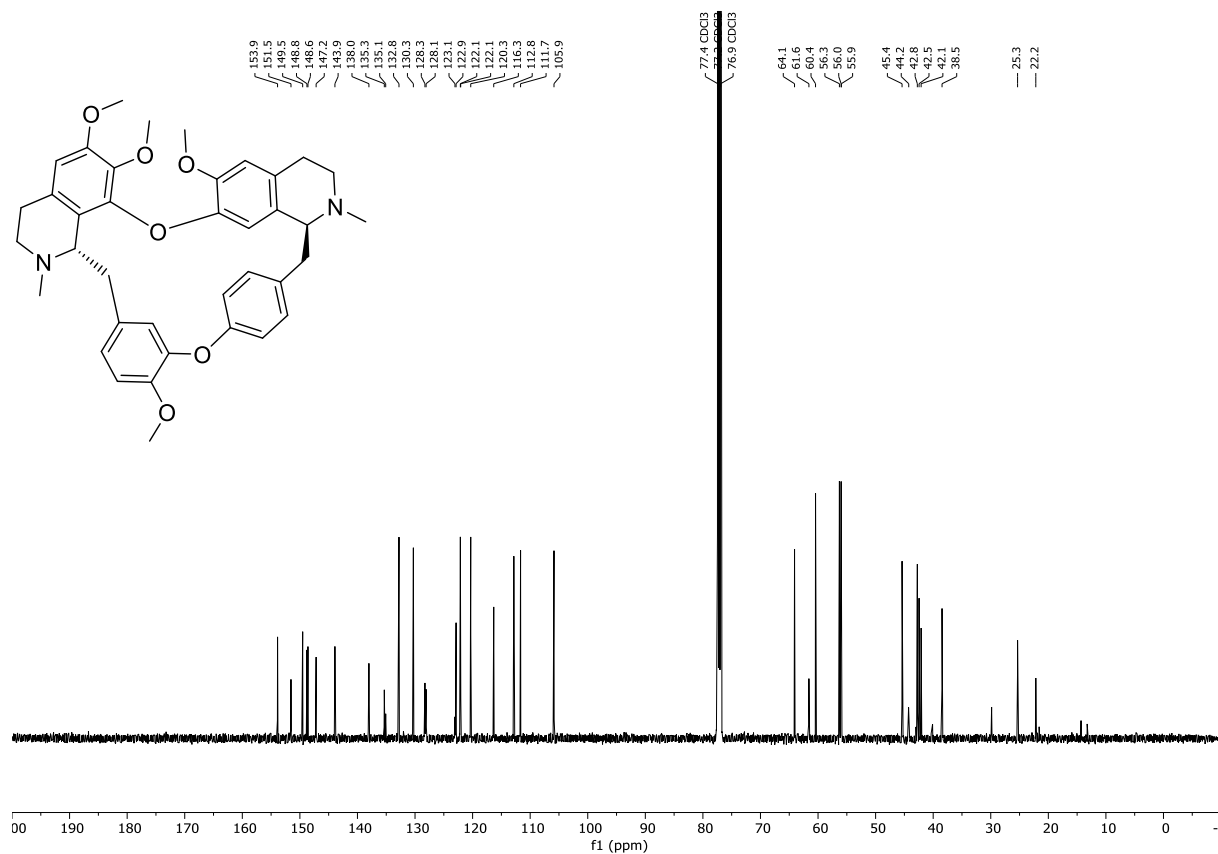
^{13}C NMR (151 MHz, CDCl_3) of synthetic racemic isotetrandrine (*rac*-2)



^1H NMR (500 MHz, CDCl_3) of natural tetrandrine (**1**)



^{13}C NMR (151 MHz, CDCl_3) of natural tetrandrine (**1**)



Computational details

Table S1. Summary table of the conformational analysis performed on the first 150 (all) conformations of the pre-reaction ensembles for routes 2a and 2b. Out of 150 (547) pre-reaction conformations of route 2a, a total number of 111 (391) were oriented towards a final set of configurations leading to tetrandrine-like isomers (red; C-1R and C-1' pre-R: 24 (90); C-1S and C-1' pre-S: 87 (301)), while 39 (156) obtained orientations yielding isotetrandrine-like isomers with opposite configurations on both stereocenters (blue; C-1R and C-1' pre-S: 34 (130); C-1S and C-1' pre-R: 5 (26)). Similarly, out of 150 pre-reaction conformations sampled for route 2b a total number of 58 structures were oriented towards final sets of configurations corresponding to tetrandrine-like isomers (red; C-1 pre-R and C'1-R: 28; C-1 pre-S and C'1-S: 30) and 92 to isotetrandrine-like isomers (blue; C-1 pre-R and C'1-S: 48; C-1 pre-S and C'1-R: 44), respectively. With respect to the total amount of pre-reaction conformers the estimated computational ratio tetrandrine:isotetrandrine was achieved and is listed in Table 4.

route 2a (22 → 15)				route 2b (23 → 15)		
intermediate	expected configuration of C-1' (pre-S/R)	number of structures		intermediate	expected configuration of C-1 (pre-S/R)	number of structures
C-1R	S	34	(130)	C-1'R	S	44
	R	24	(90)		R	28
C-1S	S	87	(301)	C-1'S	S	30
	R	5	(26)		R	48
Total amount		150	(547)	Total amount		150

Energies and coordinates:

During the parameterization procedure (see Computational Details in the main text) the final set of point charges were derived using a multi-configurational RESP fitting with 10 conformations per intermediate. The following table lists the total energies calculated, no imaginary frequencies were obtained.

Molecule	Conformation	Total energy [Hartree]	Unscaled zero-point energy correction [Hartree]	Coordinate File
C-1R intermediate	1	-2475.13095019	0.898796	A0
	2	-2475.12927231	0.898836	A1
	3	-2475.13334919	0.897540	A2
	4	-2475.13366428	0.899806	A3
	5	-2475.12878976	0.898353	A4
	6	-2475.12909161	0.898103	A5
	7	-2475.12688317	0.899054	A6
	8	-2475.11290140	0.899519	A7
	9	-2475.13466874	0.897995	A8
	10	-2475.12732177	0.898047	A9
C-1S intermediate	1	-2475.12283903	0.899664	B0
	2	-2475.11855262	0.898763	B1
	3	-2475.12138472	0.899924	B2
	4	-2475.12708388	0.899706	B3
	5	-2475.12787330	0.898355	B4
	6	-2475.12122737	0.900077	B5
	7	-2475.12217170	0.900050	B6
	8	-2475.13096803	0.898153	B7
	9	-2475.12752179	0.899471	B8
	10	-2475.12129848	0.898981	B9
C-1'R intermediate	1	-2475.13281809	0.897841	C0
	2	-2475.13100116	0.897114	C1
	3	-2475.13255862	0.897356	C2
	4	-2475.13108209	0.898632	C3
	5	-2475.13331046	0.898004	C4
	6	-2475.12371658	0.898619	C5
	7	-2475.13076949	0.899022	C6
	8	-2475.13690739	0.898570	C7
	9	-2475.12614835	0.898367	C8
	10	-2475.12568964	0.898300	C9
C-1'S intermediate	1	-2475.12817518	0.898150	D0
	2	-2475.13732446	0.898990	D1
	3	-2475.13093231	0.897567	D2
	4	-2475.13344391	0.897520	D3
	5	-2475.12723351	0.897860	D4
	6	-2475.13260197	0.897940	D5
	7	-2475.13393679	0.897831	D6
	8	-2475.13727757	0.899142	D7
	9	-2475.12580821	0.898636	D8
	10	-2475.13552101	0.899065	D9
DCM	-	-957.985177114	0.032043	E

