Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Supporting Information

A modular approach to the bisbenzylisoquinoline alkaloids tetrandrine and isotetrandrine

Ramona Schütz[†], Maximilian Meixner[‡], Iris Antes*[‡] and Franz Bracher*[†]

[†]Department of Pharmacy - Center for Drug Research, Ludwig-Maximilians University Munich, Butenandtstr. 5-13, 81377 Munich, Germany
[‡]TUM School of Life Sciences, Technical University Munich, Emil-Erlenmeyer-Forum 8, 85354 Freising, Germany

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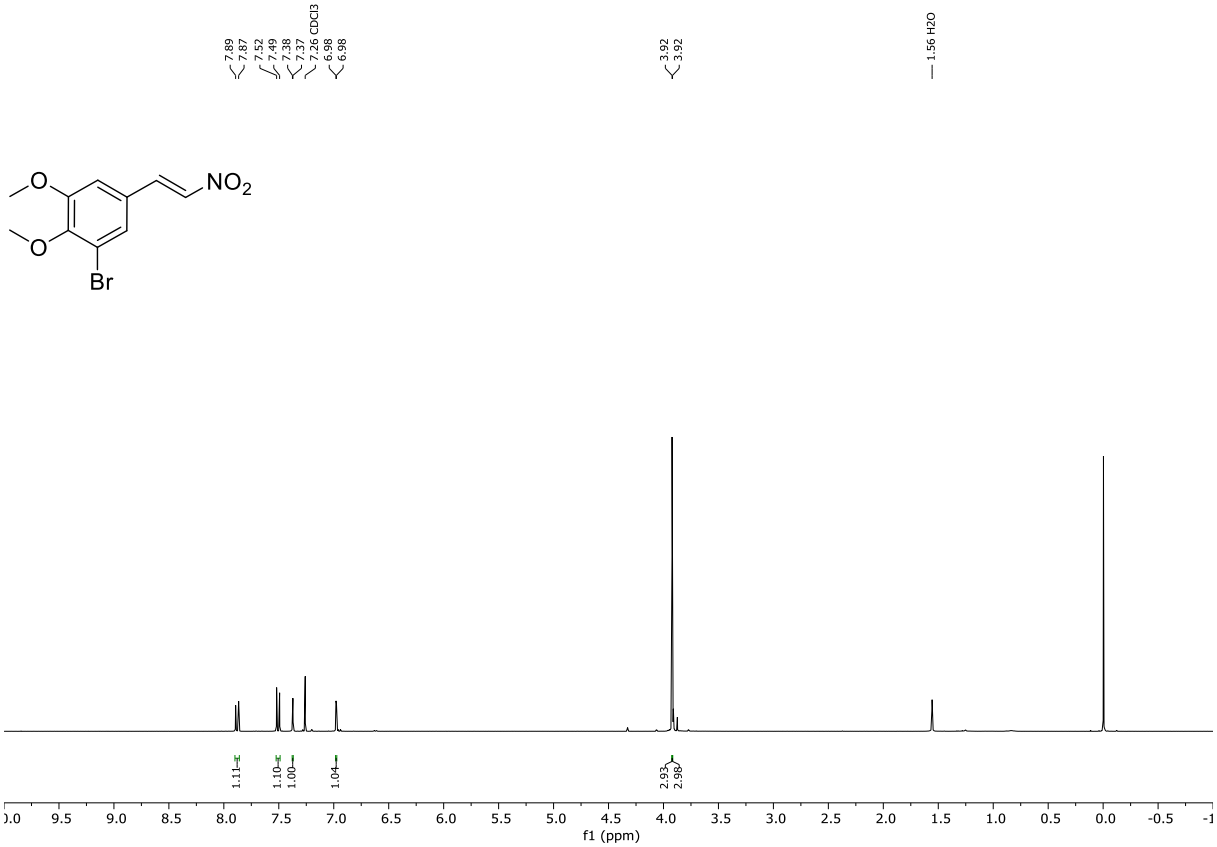
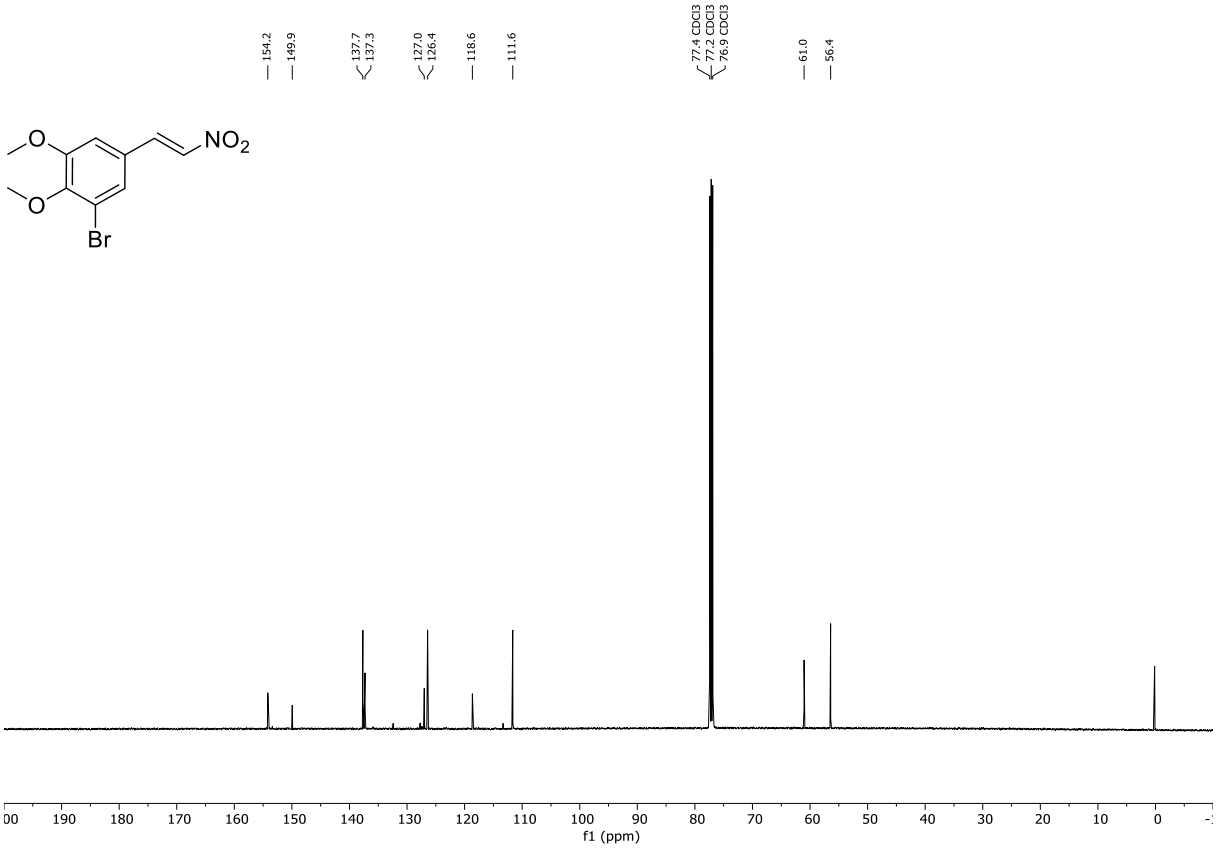
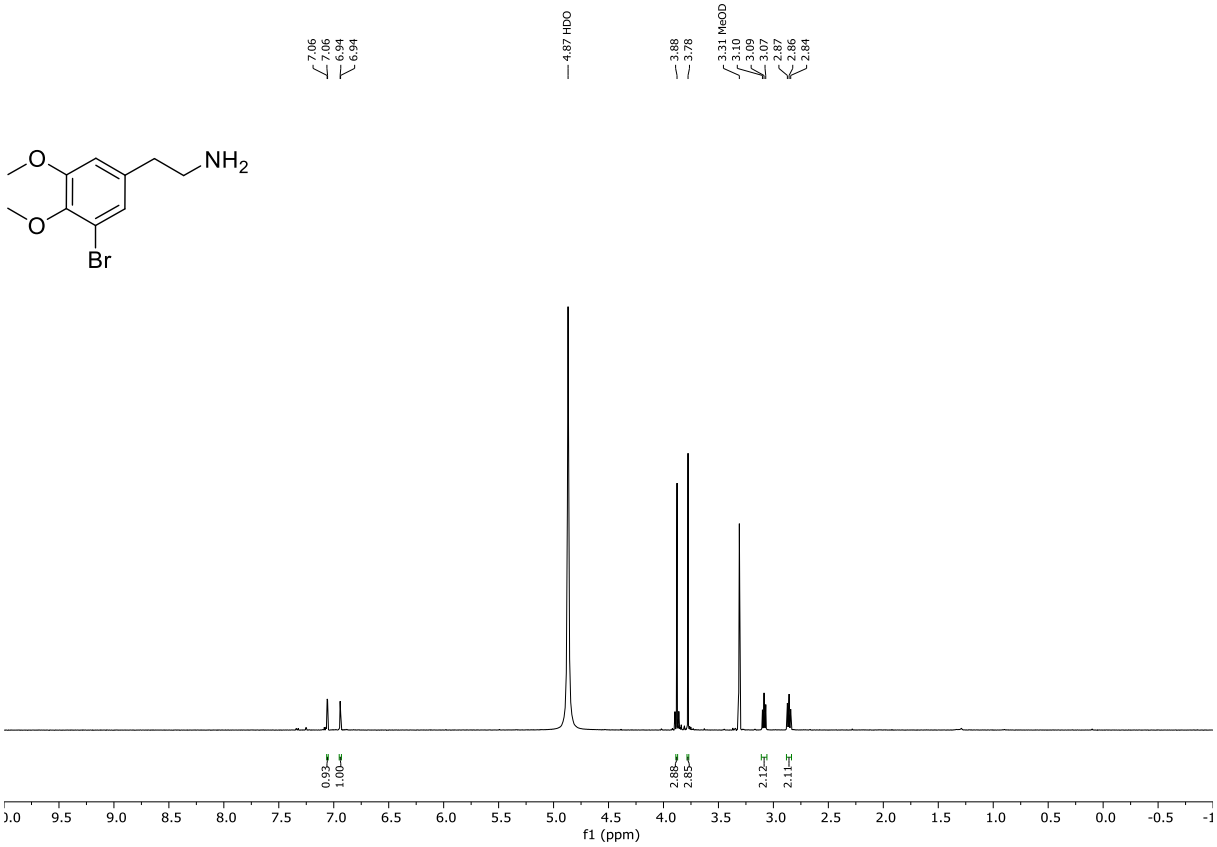
^{1}H NMR (500 MHz, $CDCl_3$) of **4**



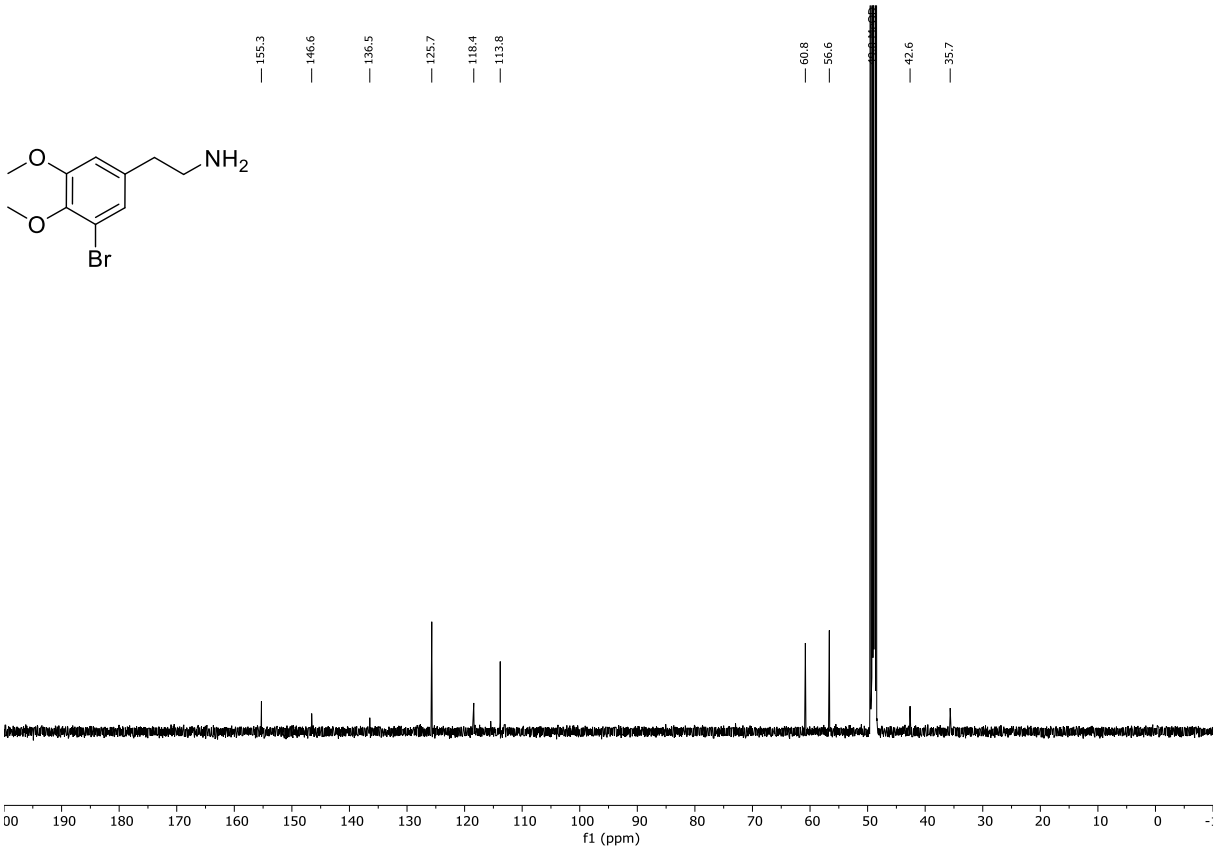
^{13}C NMR (126 MHz, $CDCl_3$) of **4**



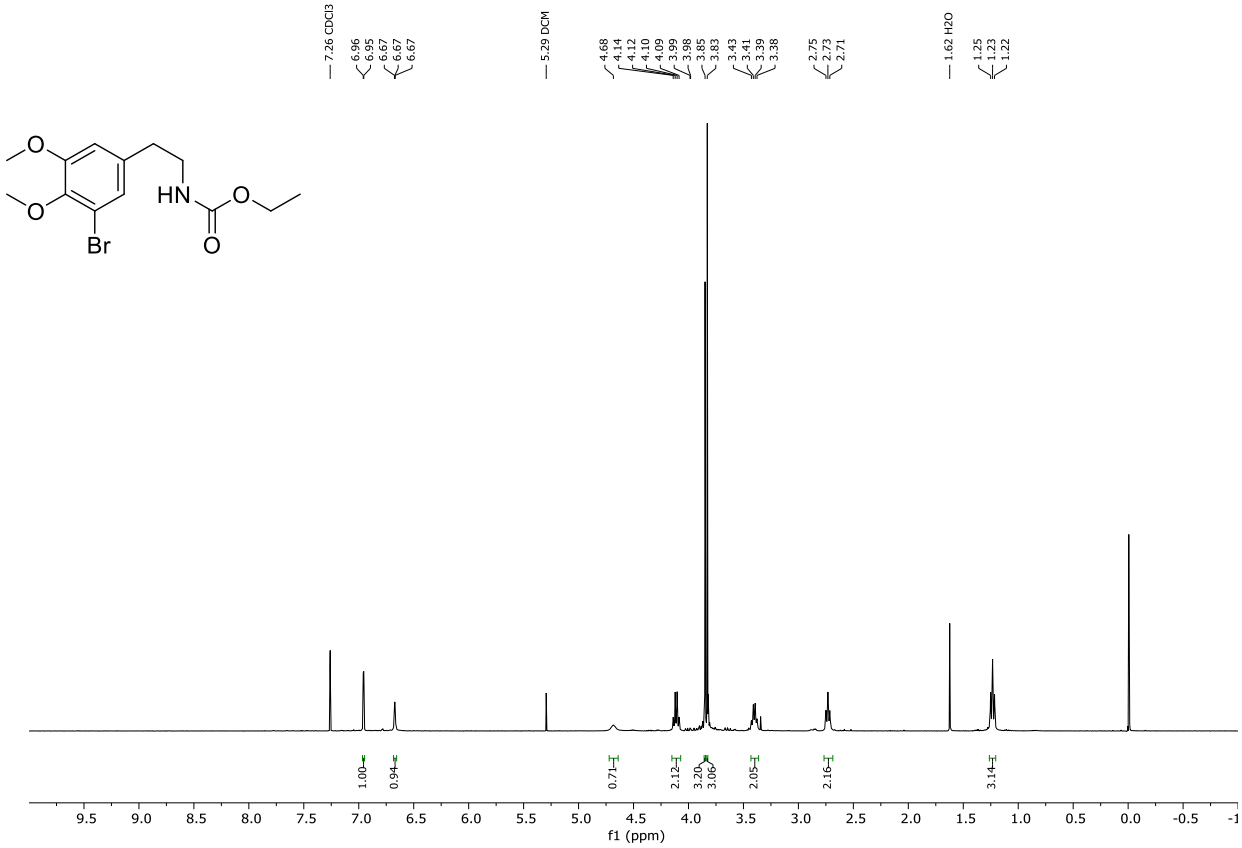
^{1}H NMR (500 MHz, MeOD) of **5**



^{13}C NMR (126 MHz, MeOD) of **5**



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



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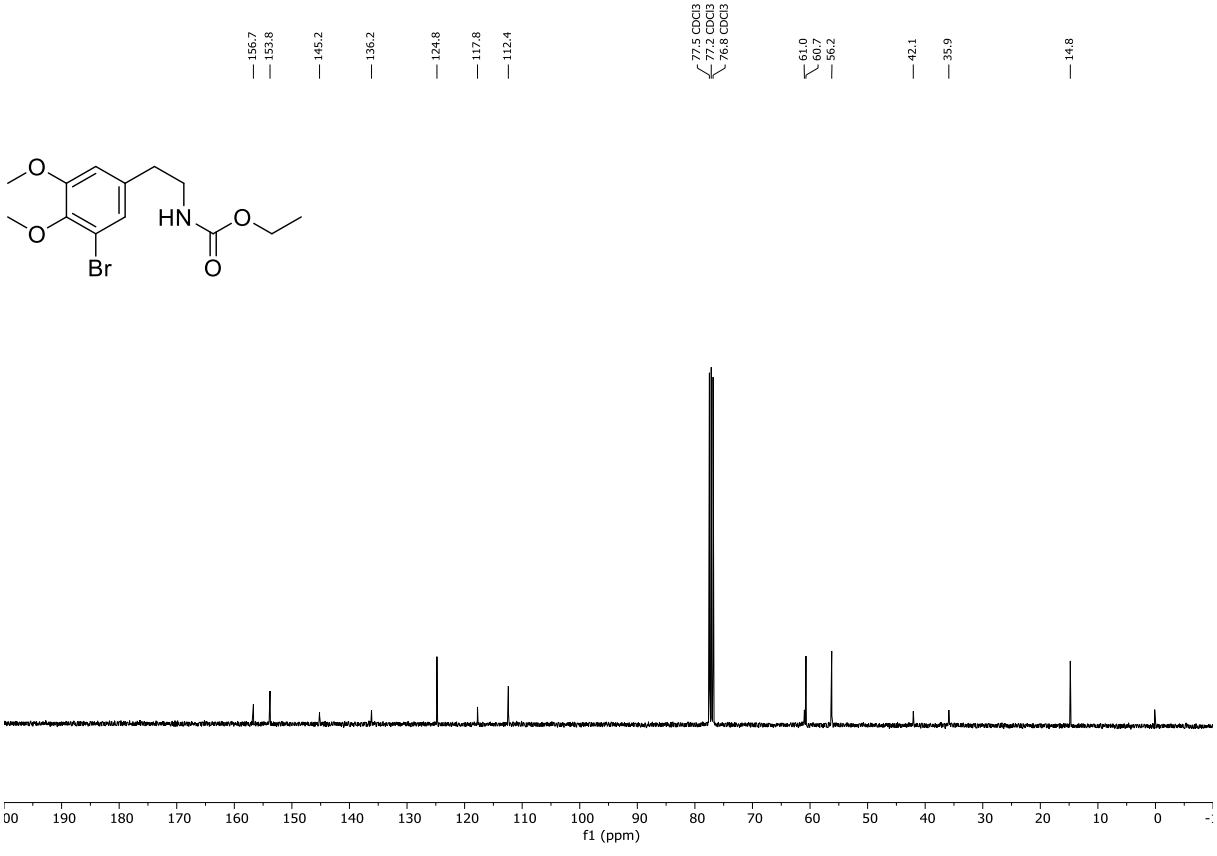
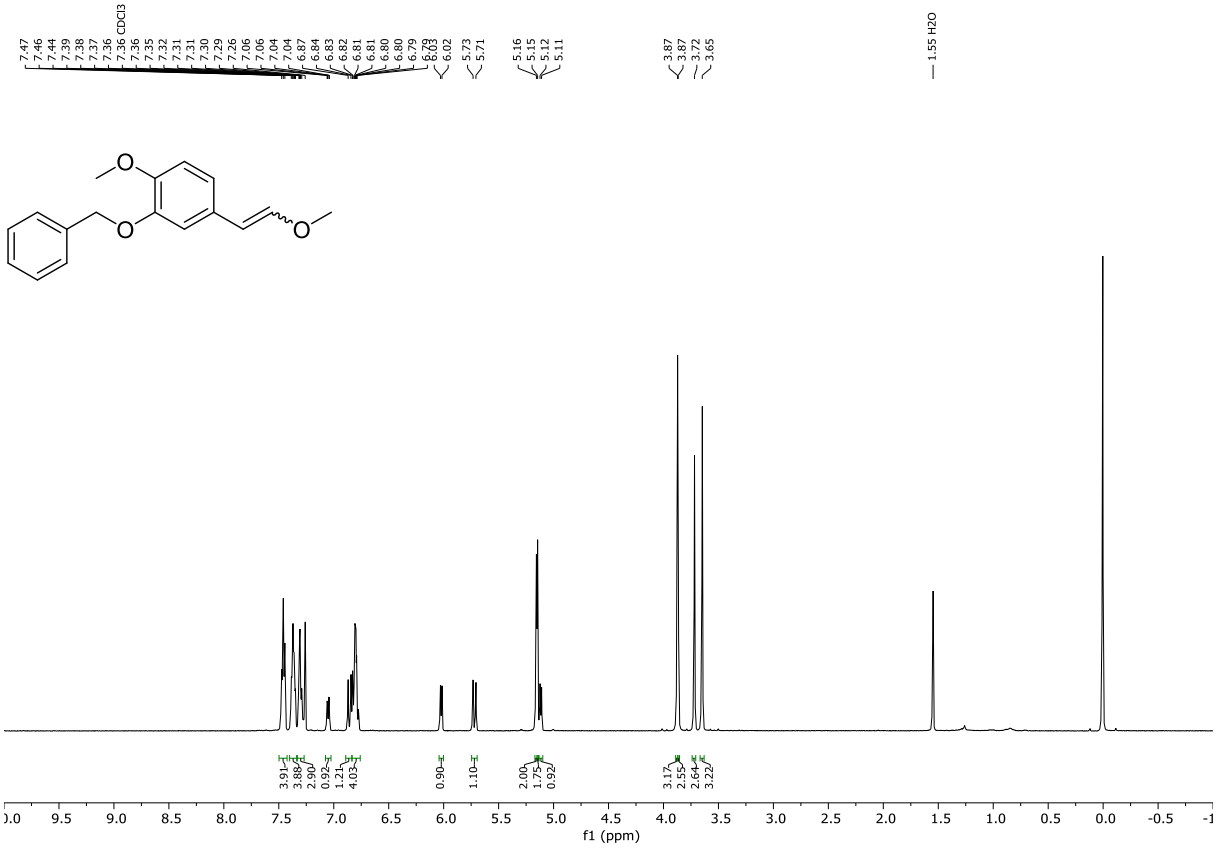
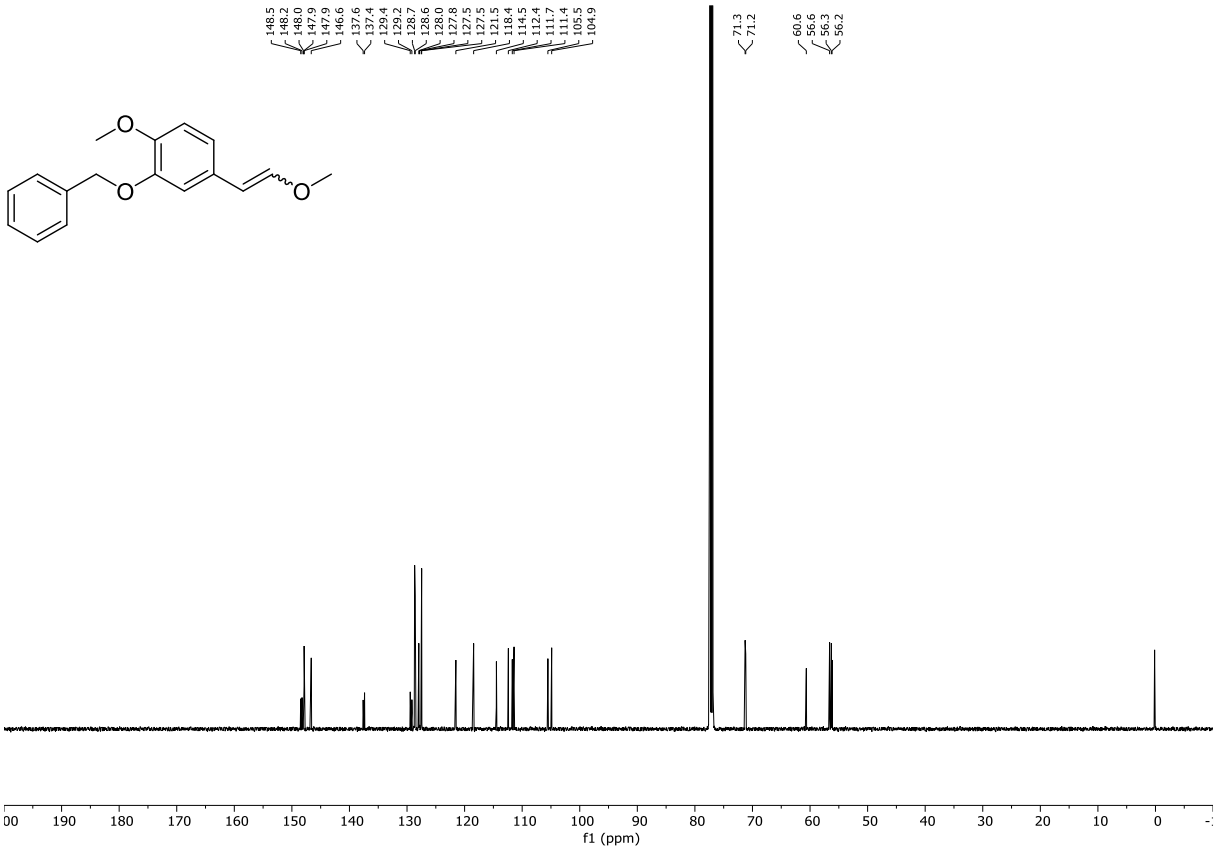


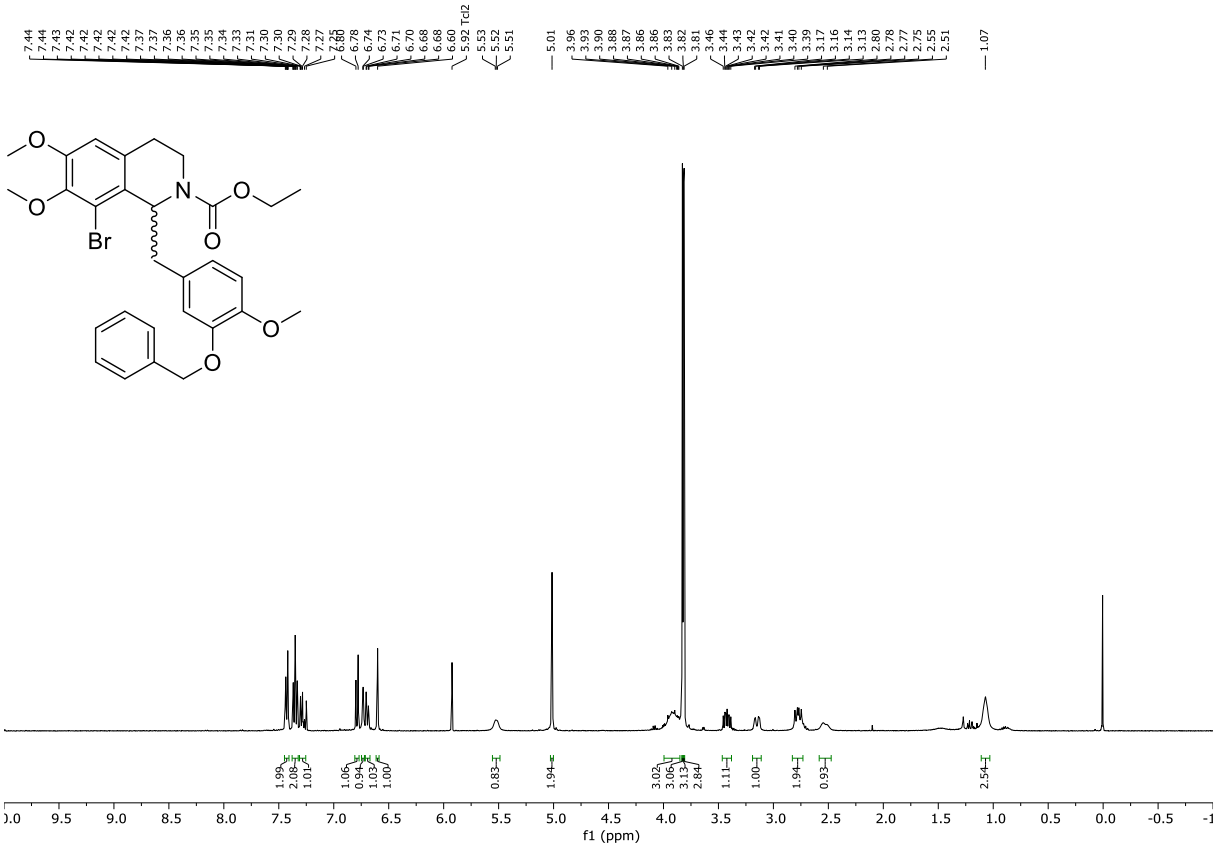
^{1}H NMR (500 MHz, $CDCl_3$) of **7**



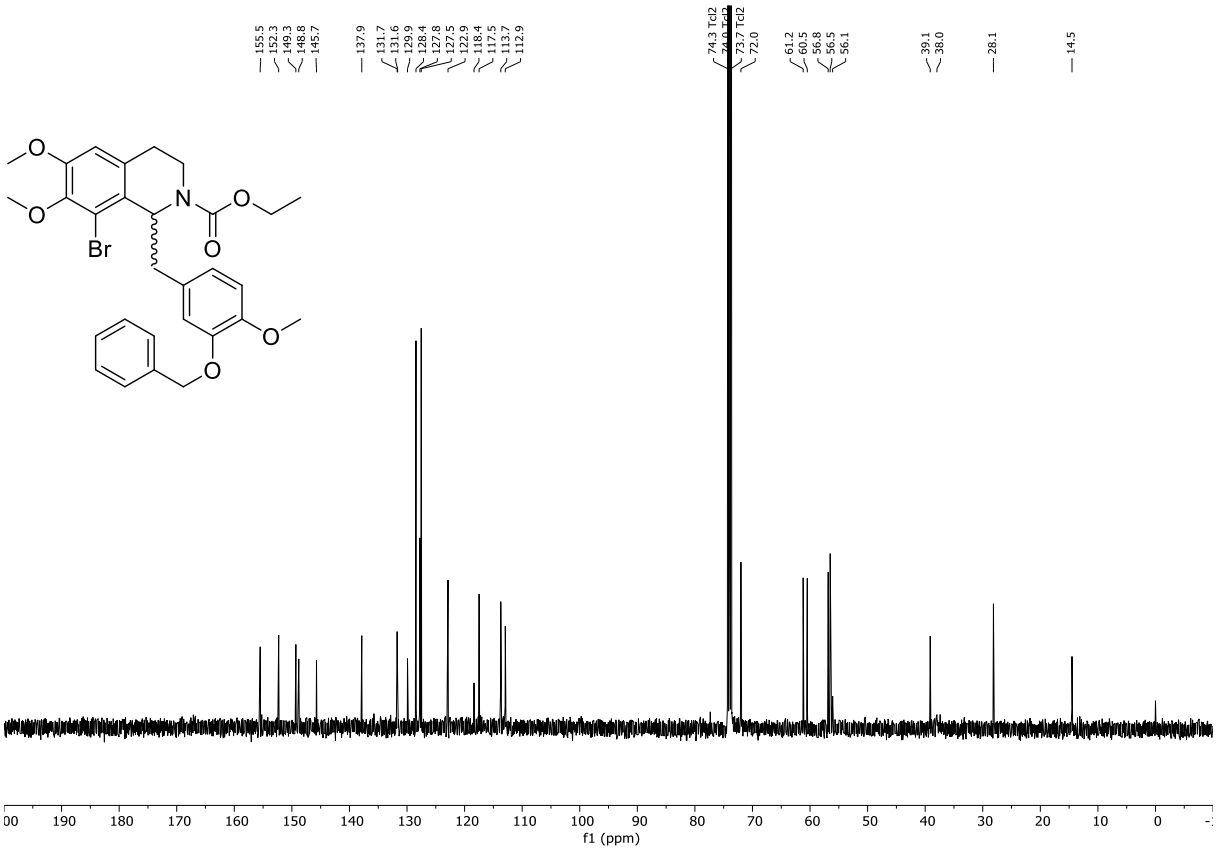
^{13}C NMR (126 MHz, $CDCl_3$) of **7**



^{1}H NMR (400 MHz, TcI_2, 100°C) of **8**



^{13}C NMR (101 MHz, TcI_2, 100°C) of **8**



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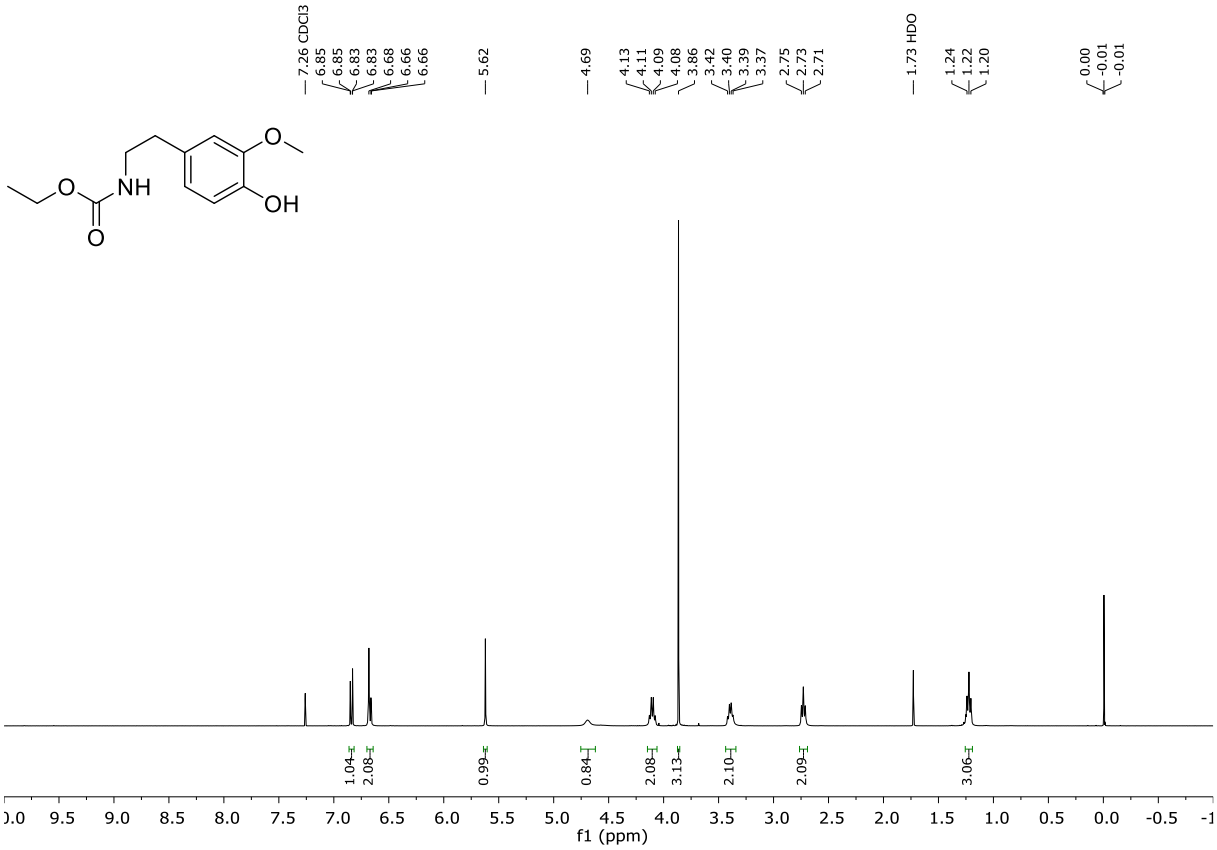

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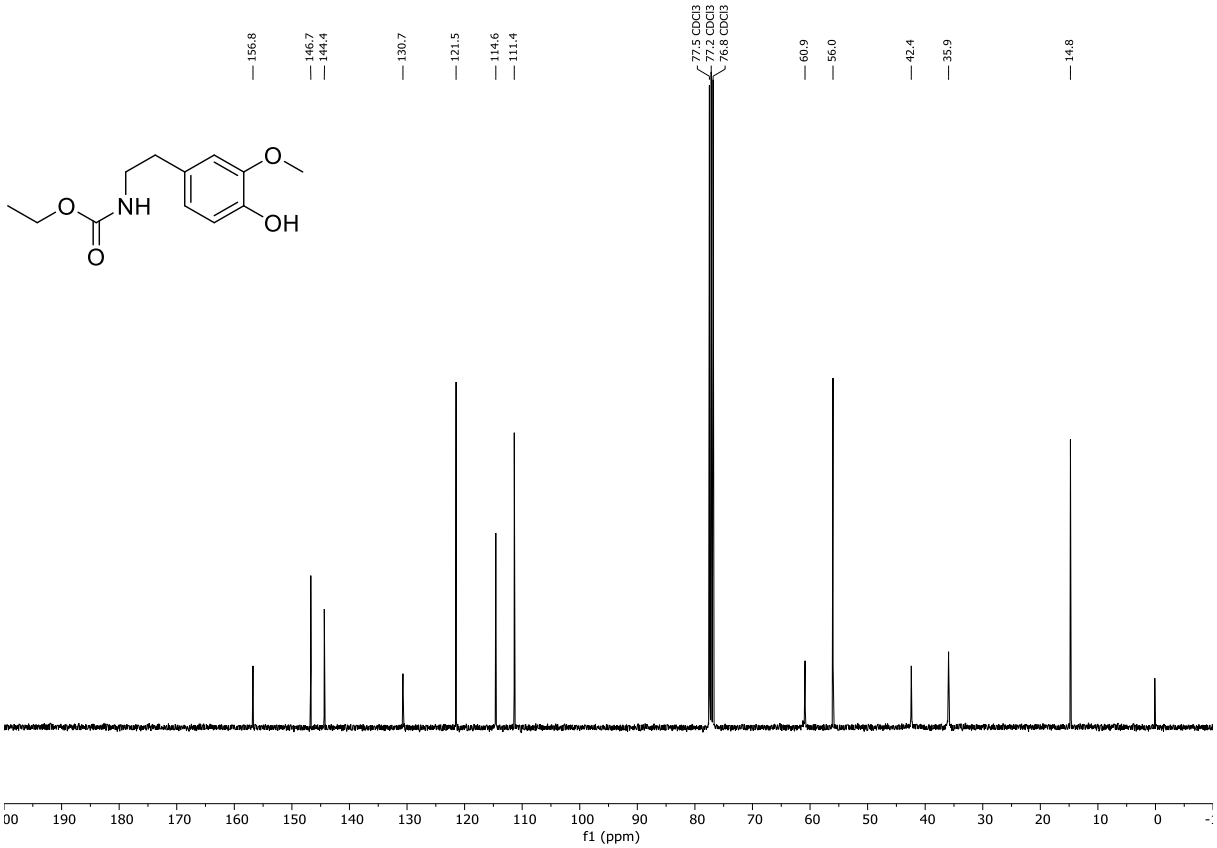
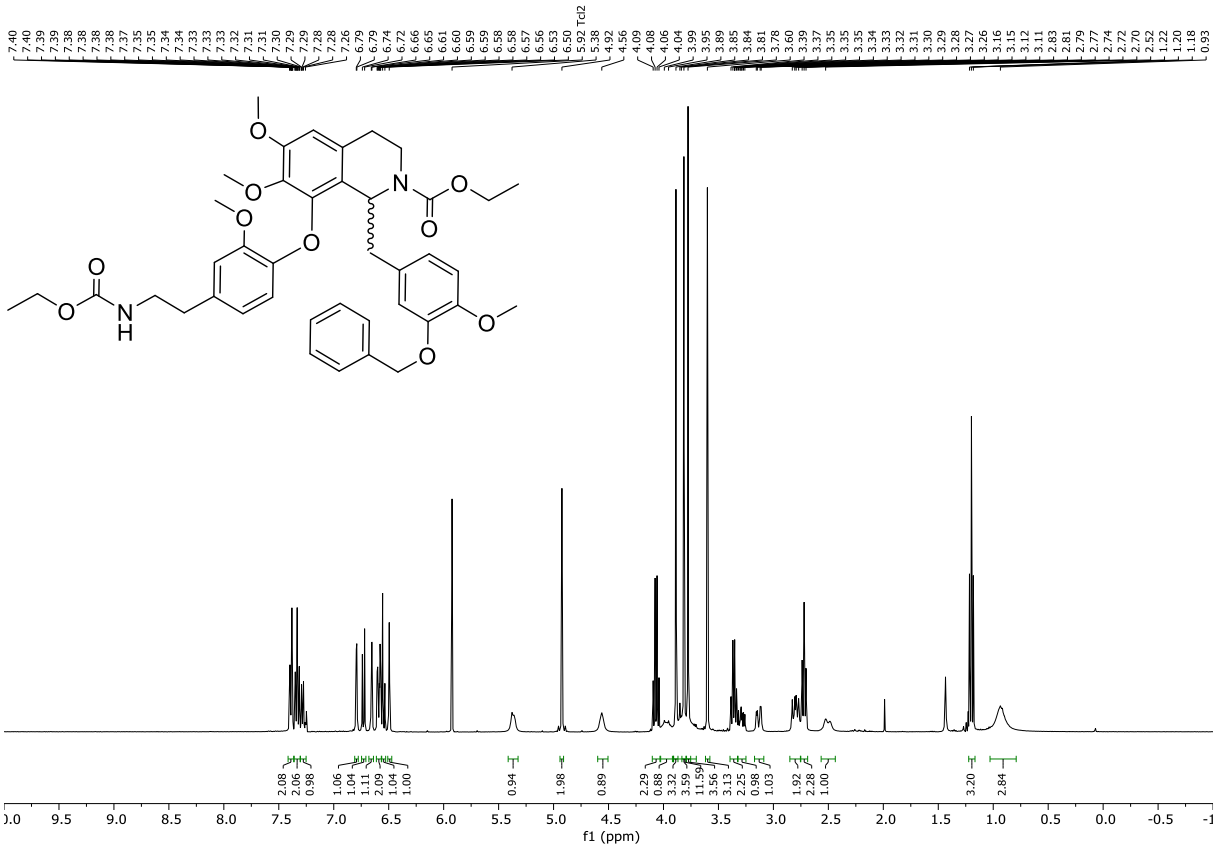
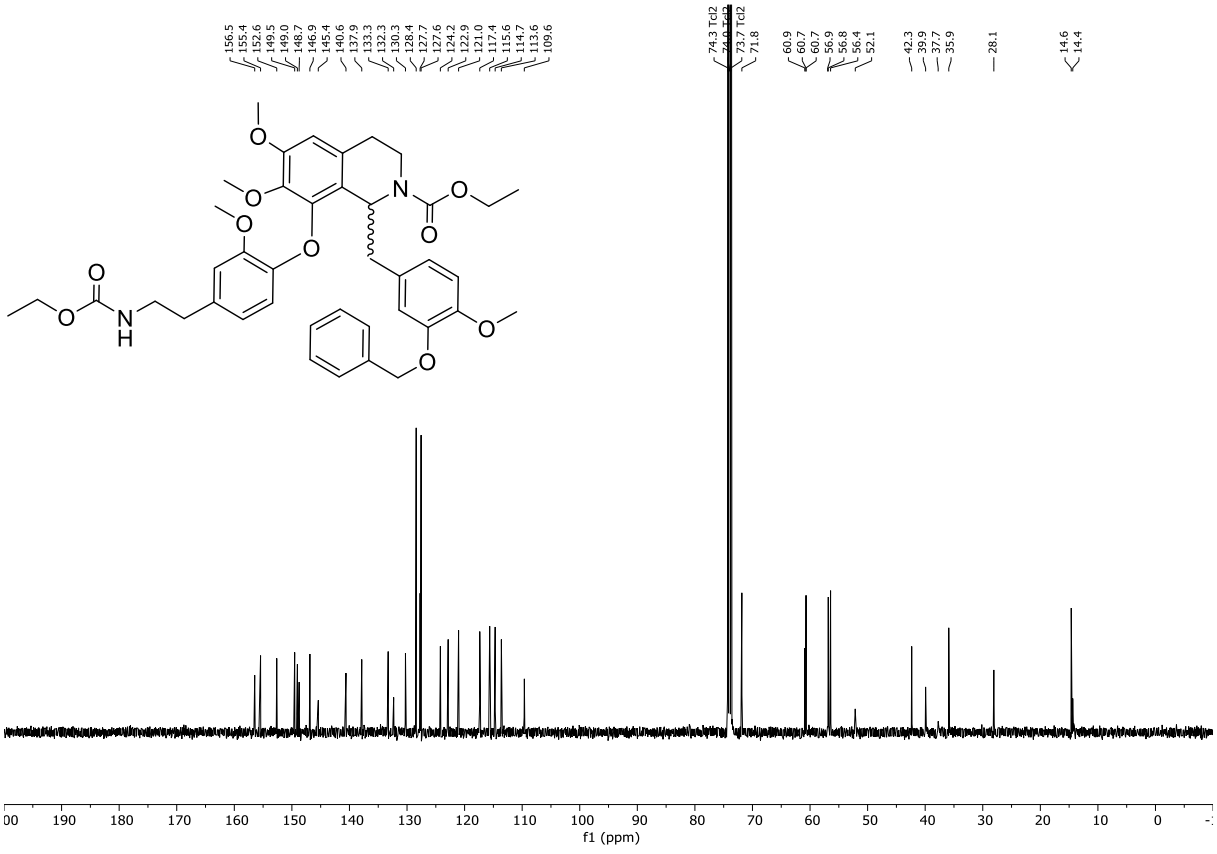


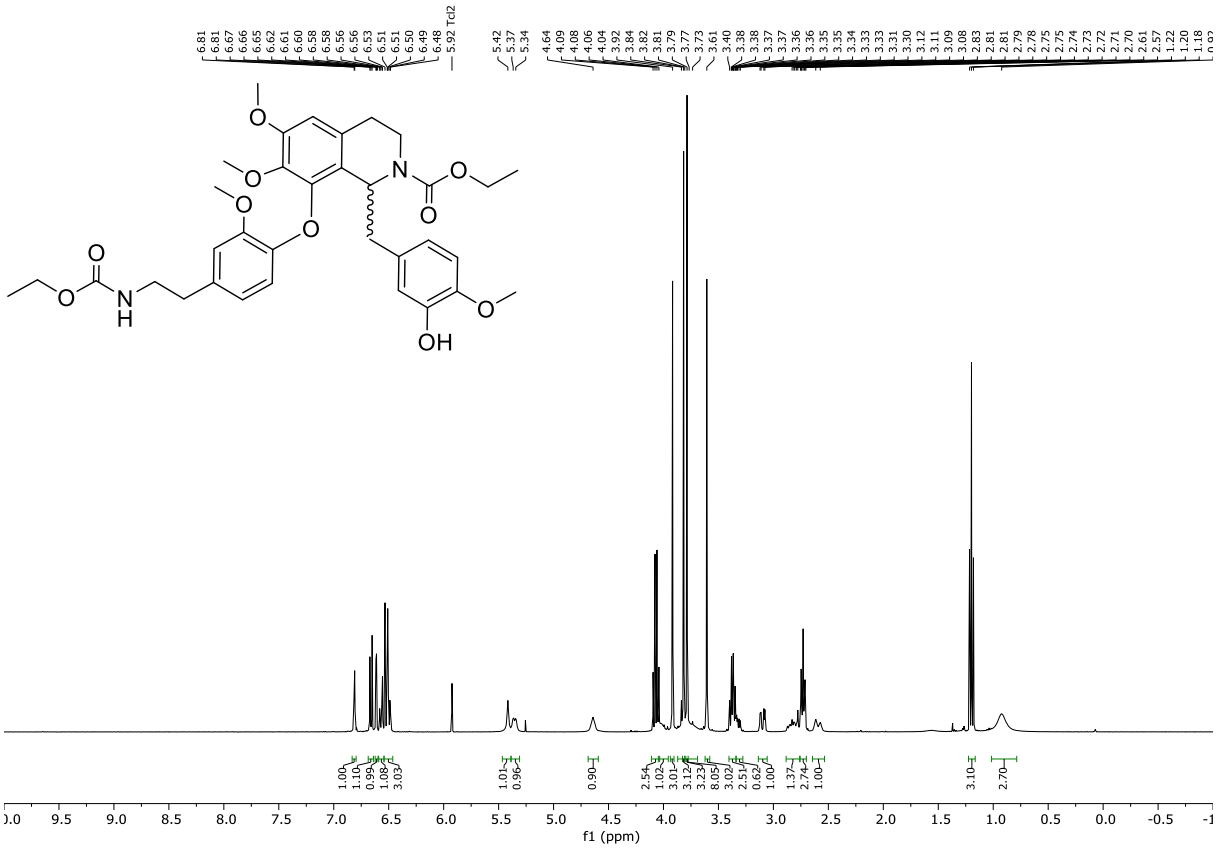
^{1}H NMR (400 MHz, Tcl_2, 100°C) of **11**



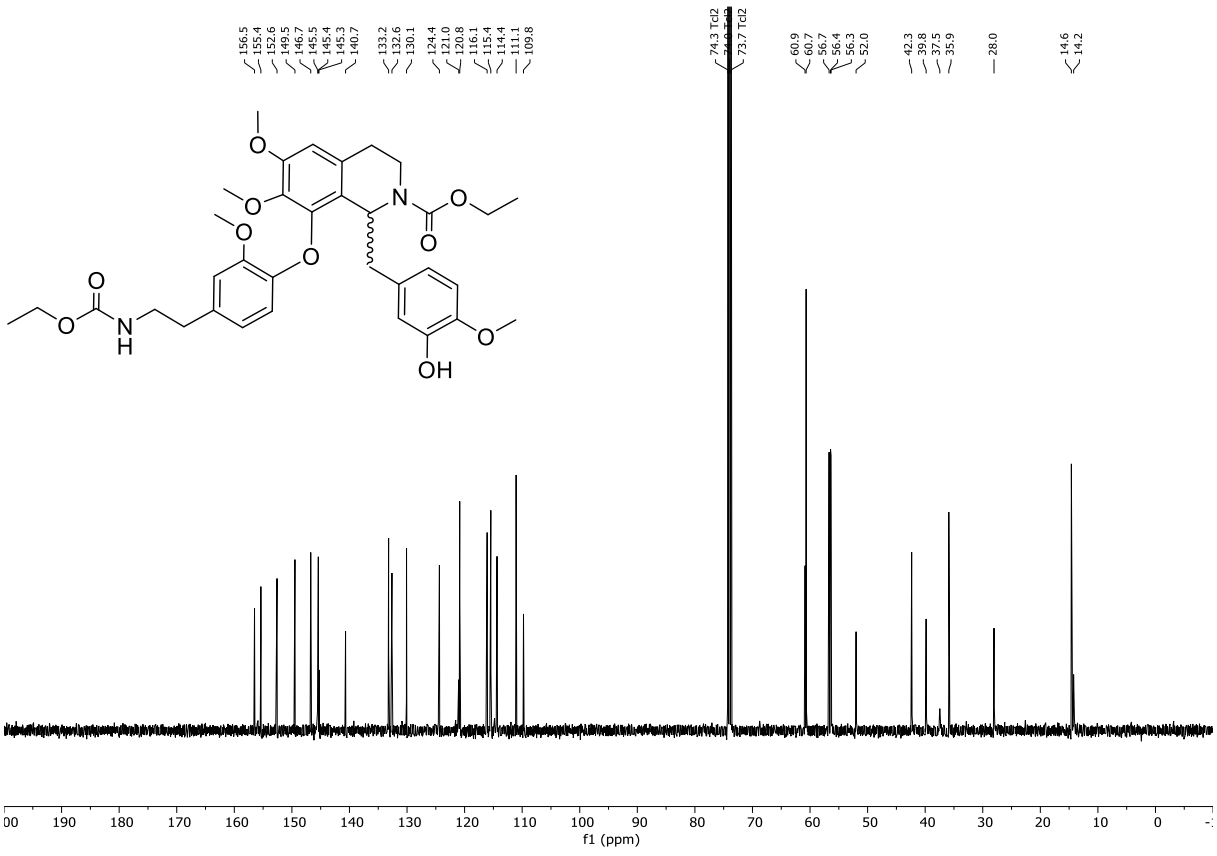
^{13}C NMR (101 MHz, Tcl_2, 100°C) of **11**



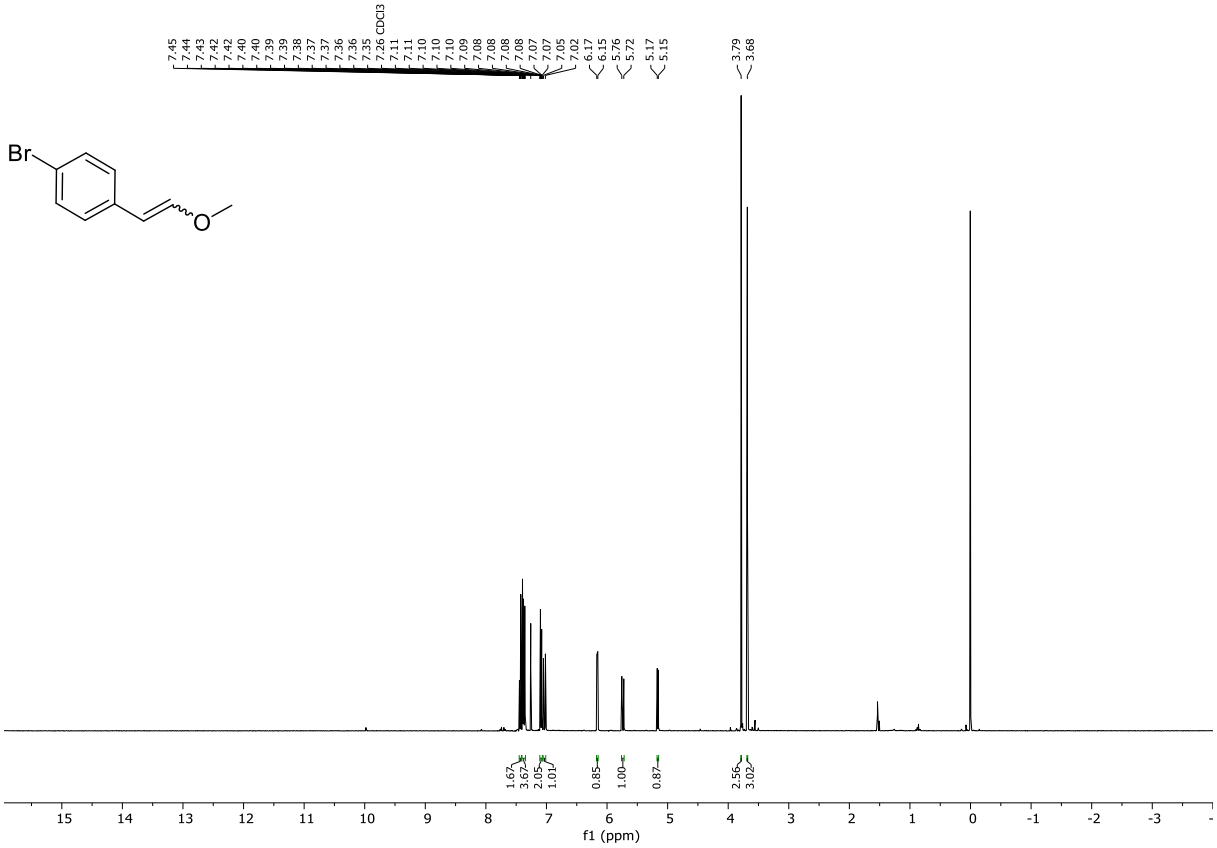
^{1}H NMR (400 MHz, TcI_2, 100°C) of **12**



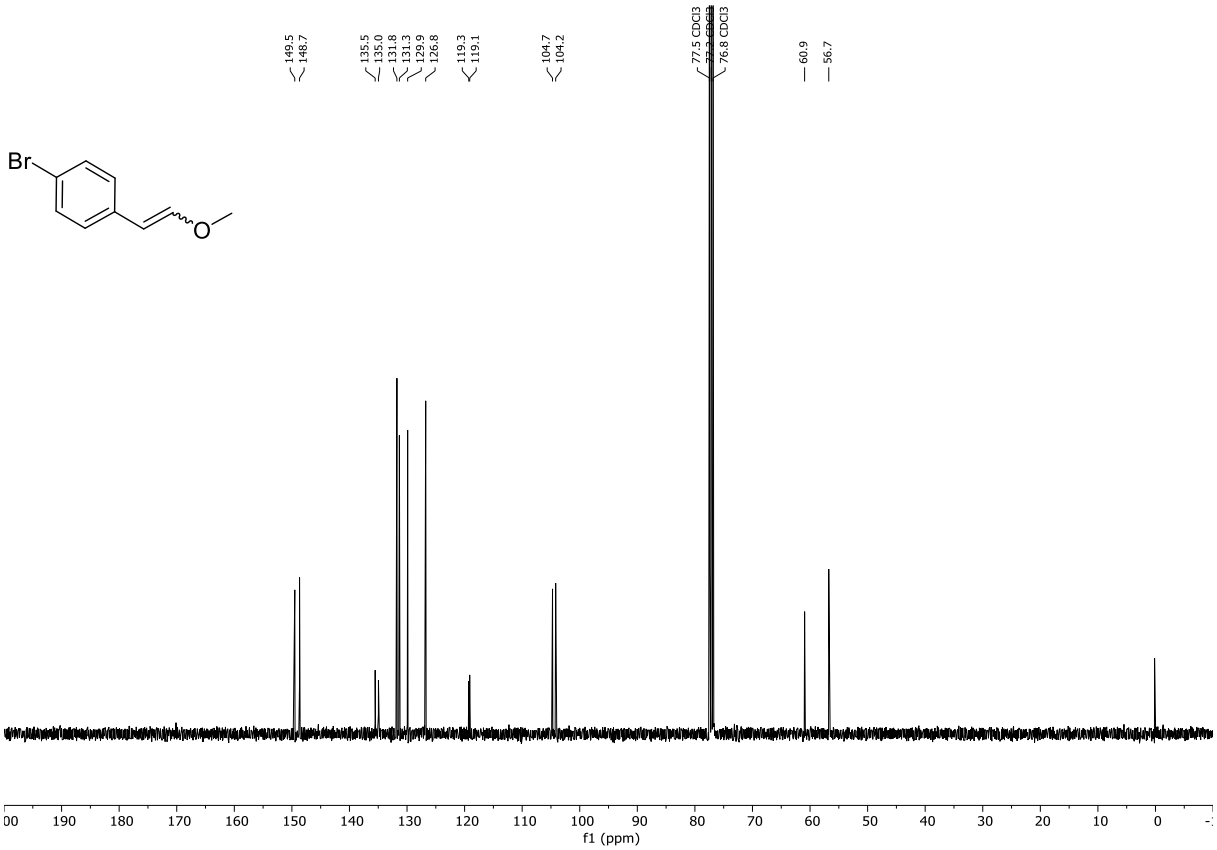
^{13}C NMR (101 MHz, TcI_2, 100°C) of **12**



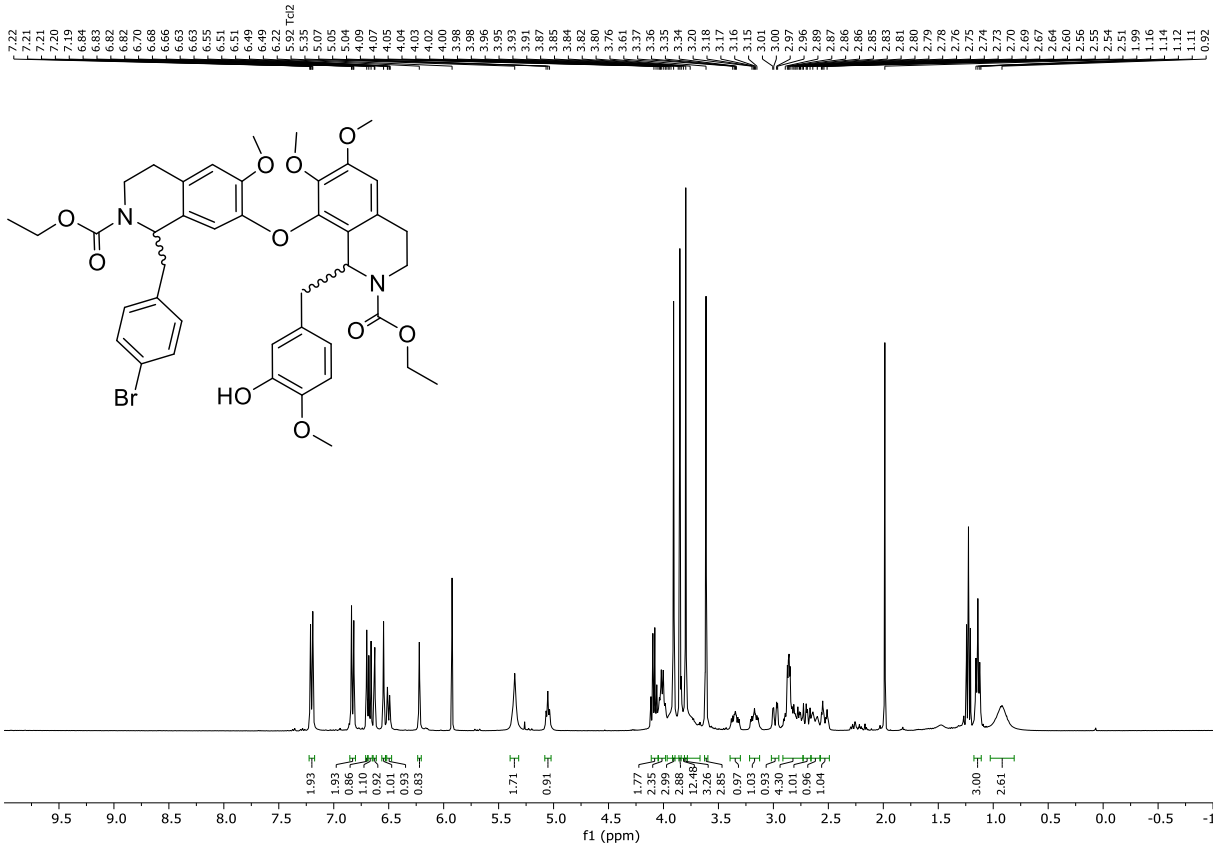
^{1}H NMR (400 MHz, $CDCl_3$) of **13**



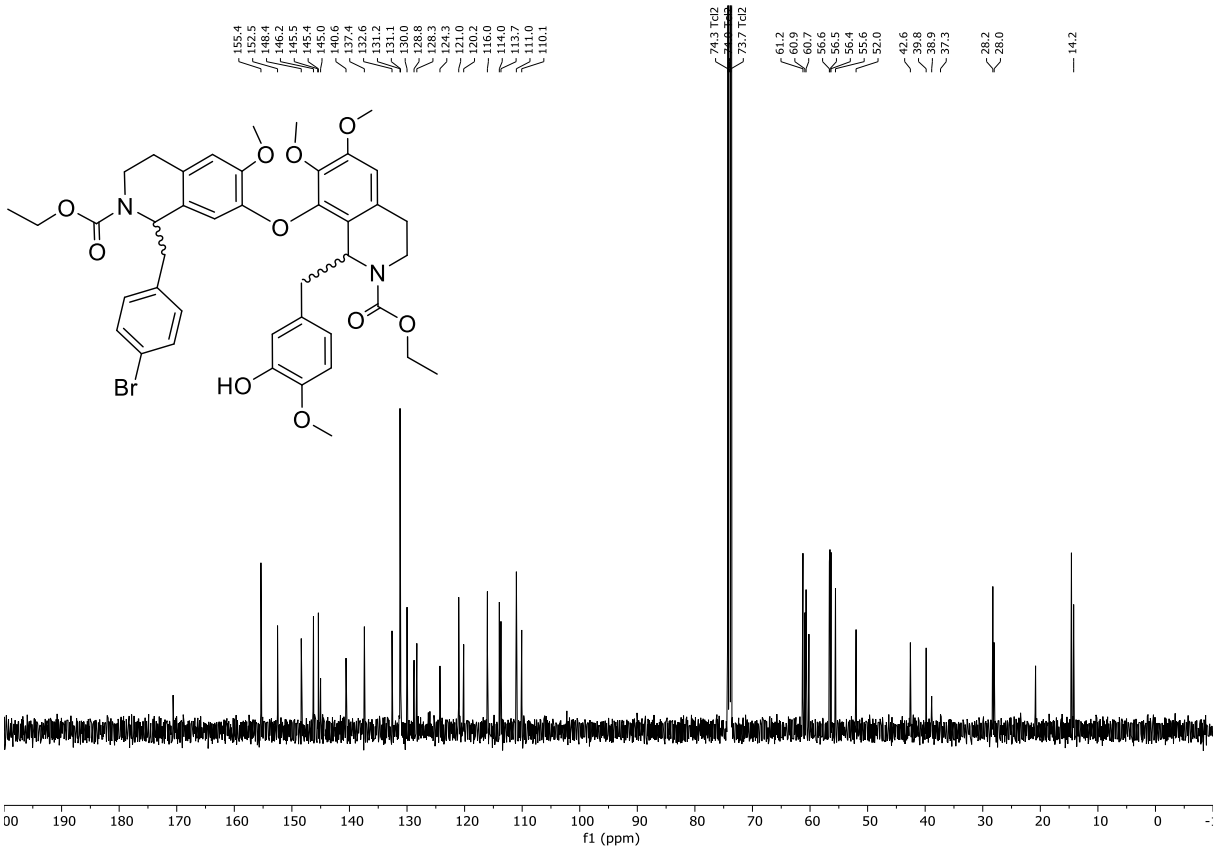
^{13}C NMR (101 MHz, $CDCl_3$) of **13**



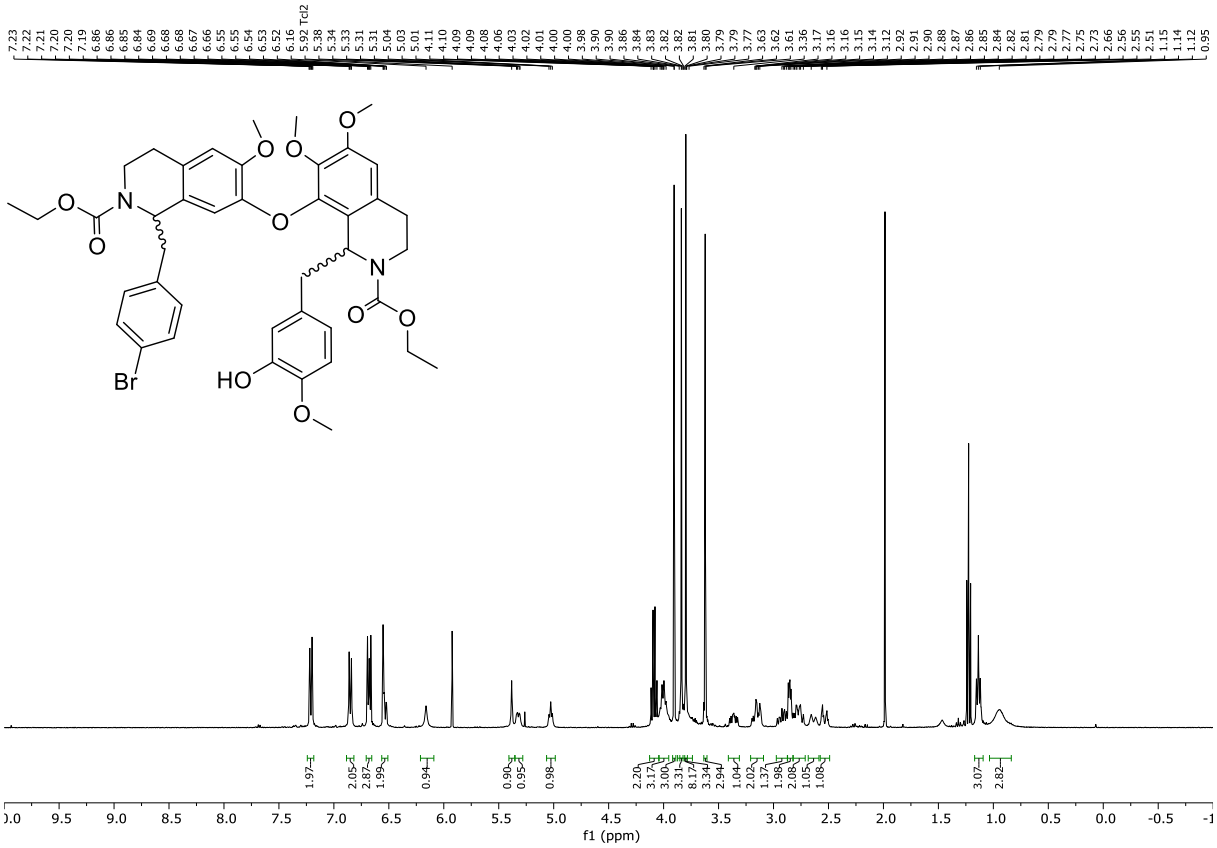
^{1}H NMR (400 MHz, TcI_2, 100°C) of **14a** ((1*R*,1'*R*)/(1*S*,1'*S*) isomers)



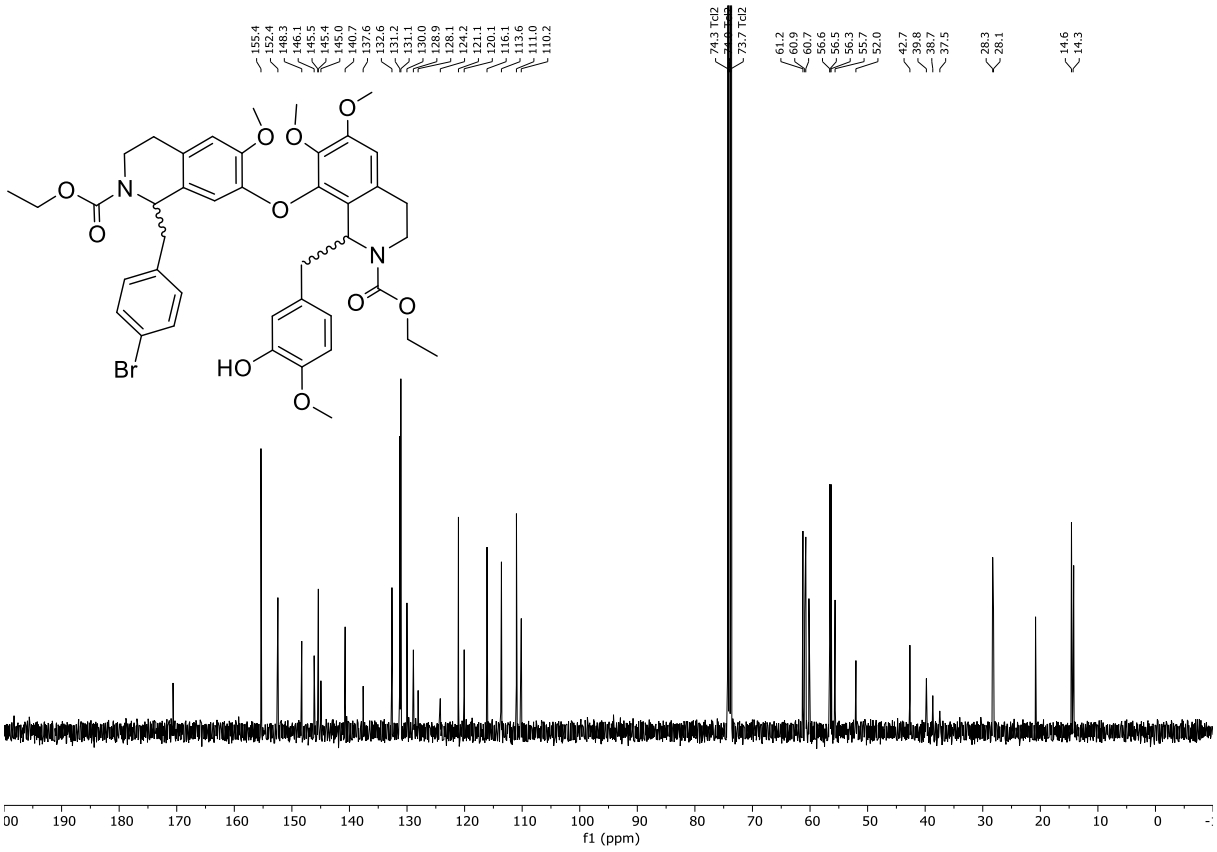
^{13}C NMR (101 MHz, TcI_2, 100°C) of **14a** ((1*R*,1'*R*)/(1*S*,1'*S*) isomers)



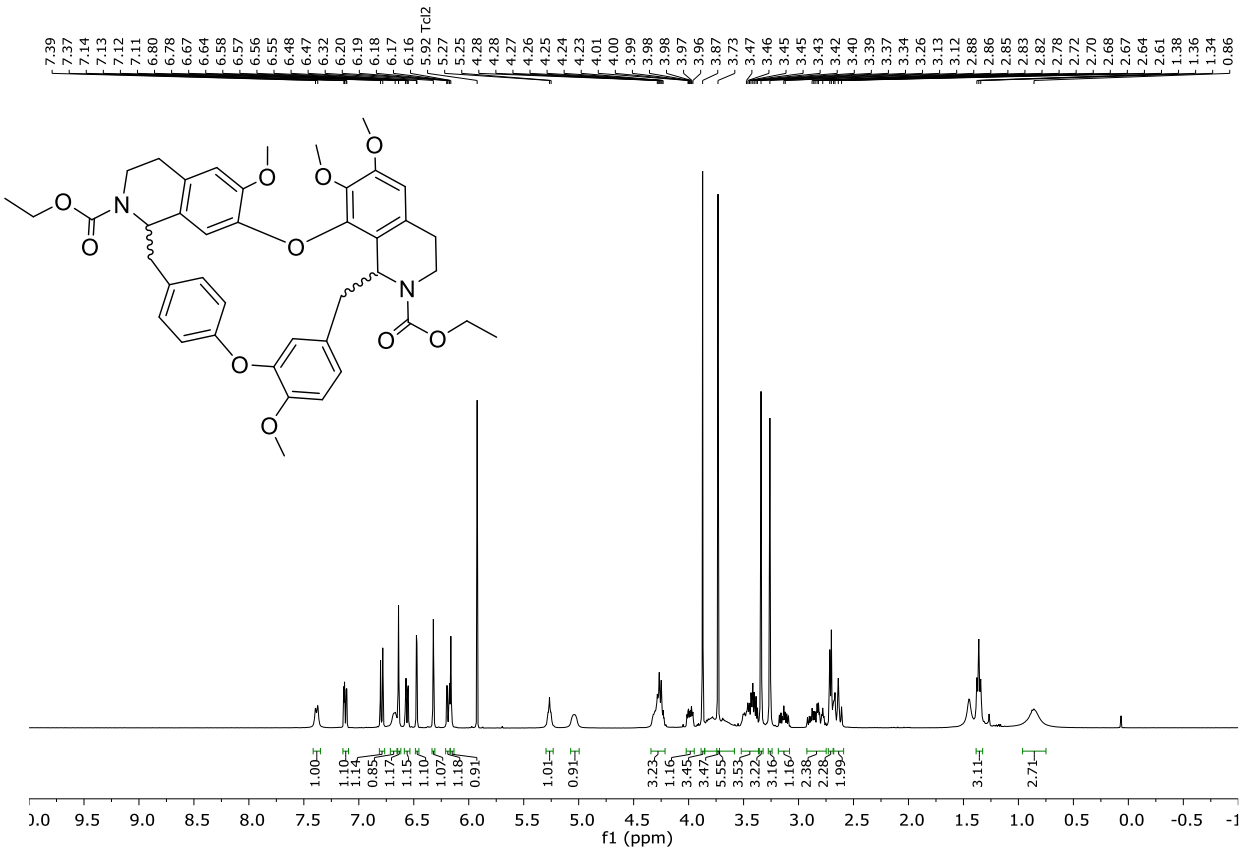
^{1}H NMR (400 MHz, TcI_2, 100°C) of **14b** ((1*R*,1'*S*)/(1*S*,1'*R*) isomers)



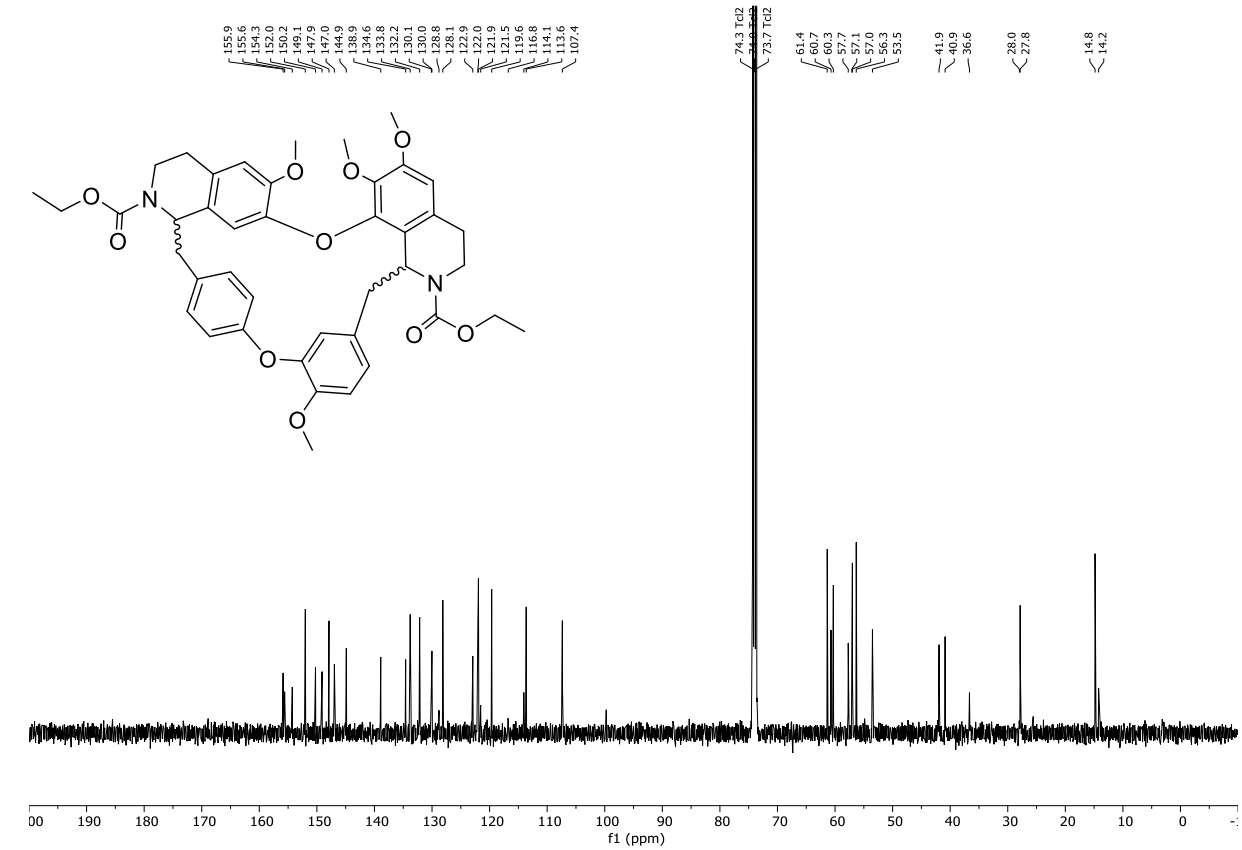
^{13}C NMR (101 MHz, TcI_2, 100°C) of **14b** ((1*R*,1'*S*)/(1*S*,1'*R*) isomers)



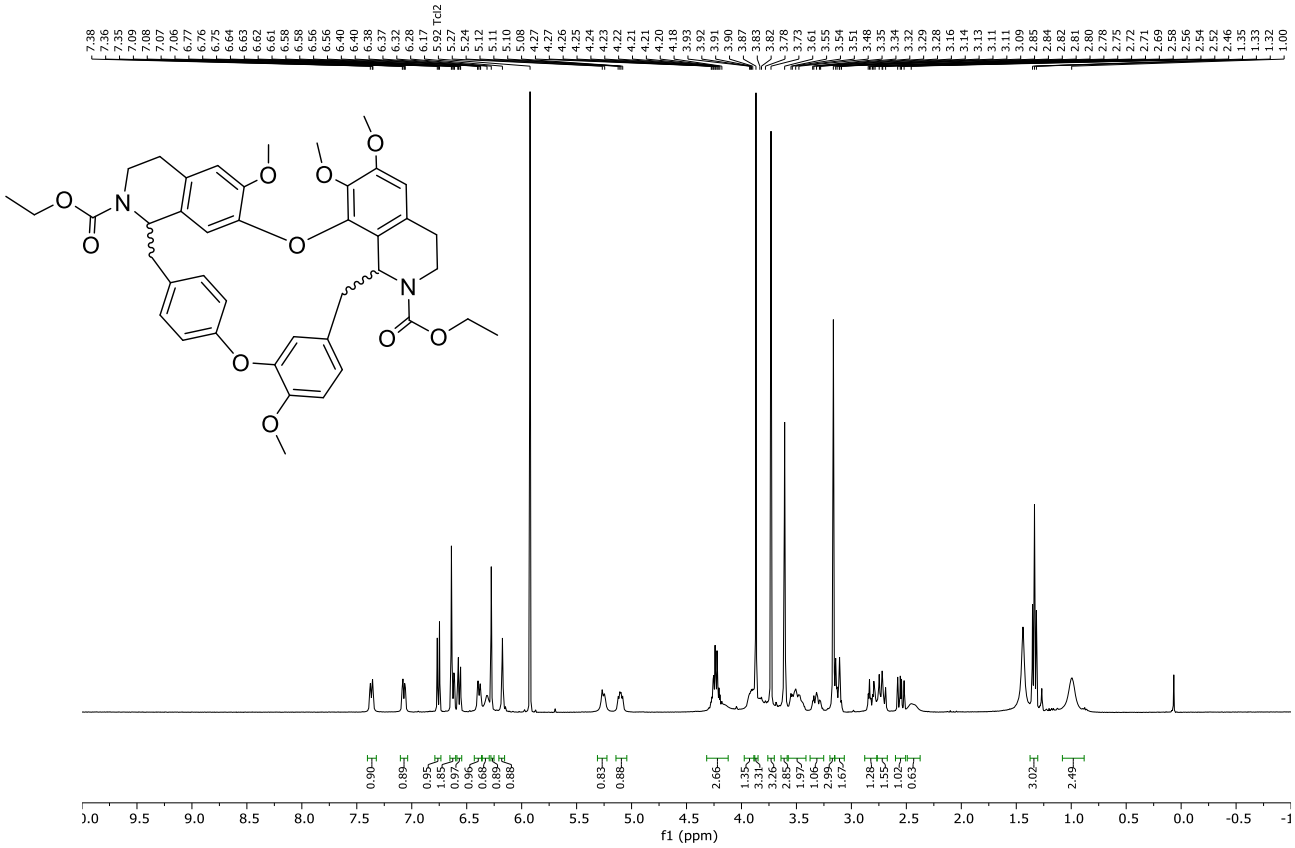
^{1}H NMR (400 MHz, TcI_2, 100°C) of **15a** ((1*R*,1'*R*)/(1*S*,1'*S*) isomers)



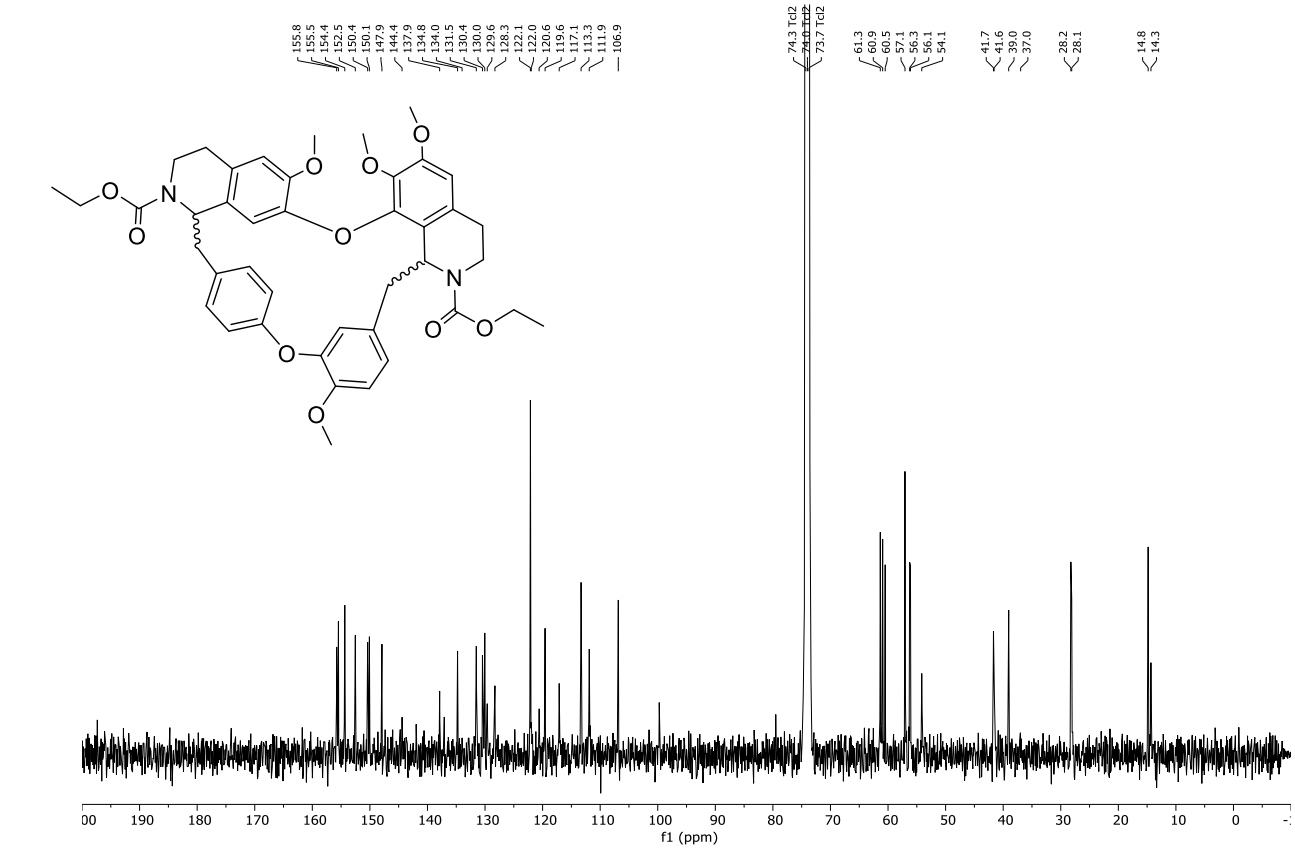
^{13}C NMR (101 MHz, TcI_2, 100°C) of **15a** ((1*R*,1'*R*)/(1*S*,1'*S*) isomers)



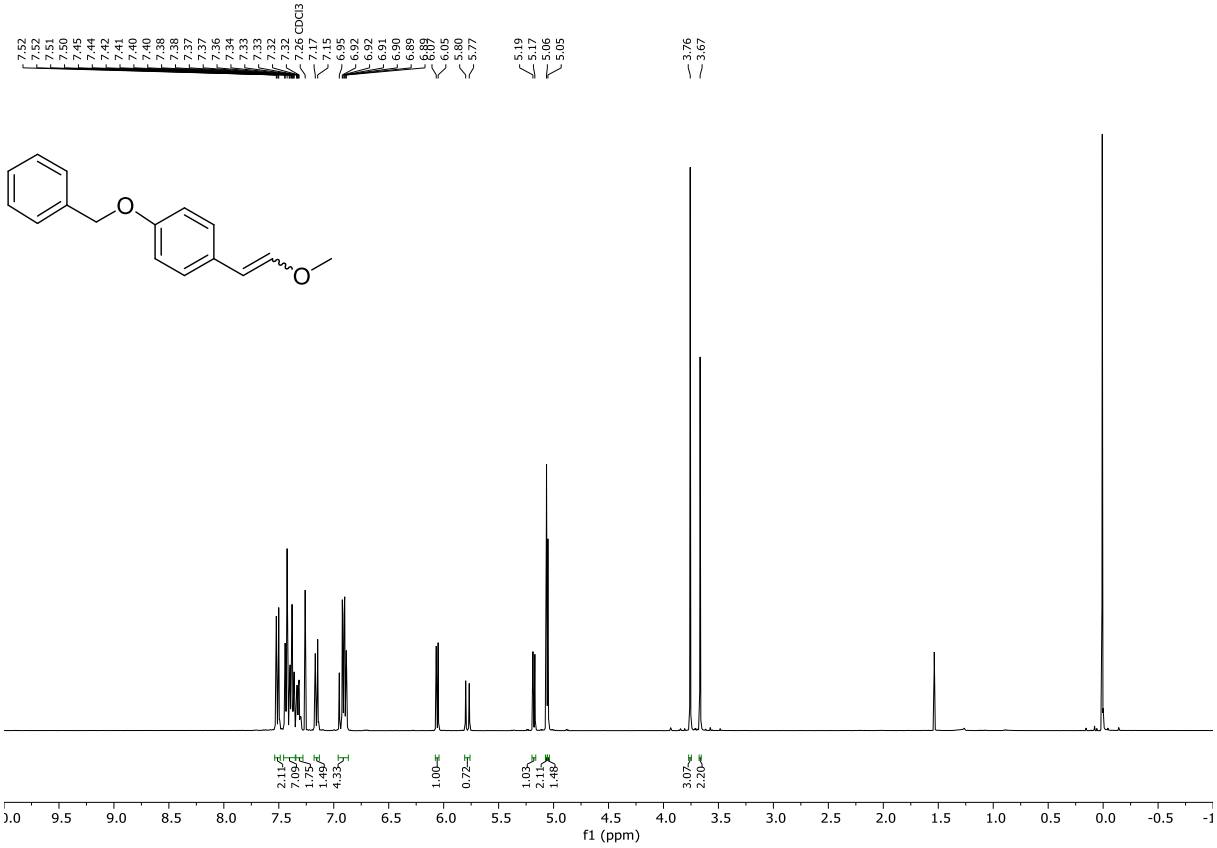
^{1}H NMR (400 MHz, TcI_2, 100°C) of **15b** ((1*R*,1'*S*)/(1*S*,1'*R*) isomers)



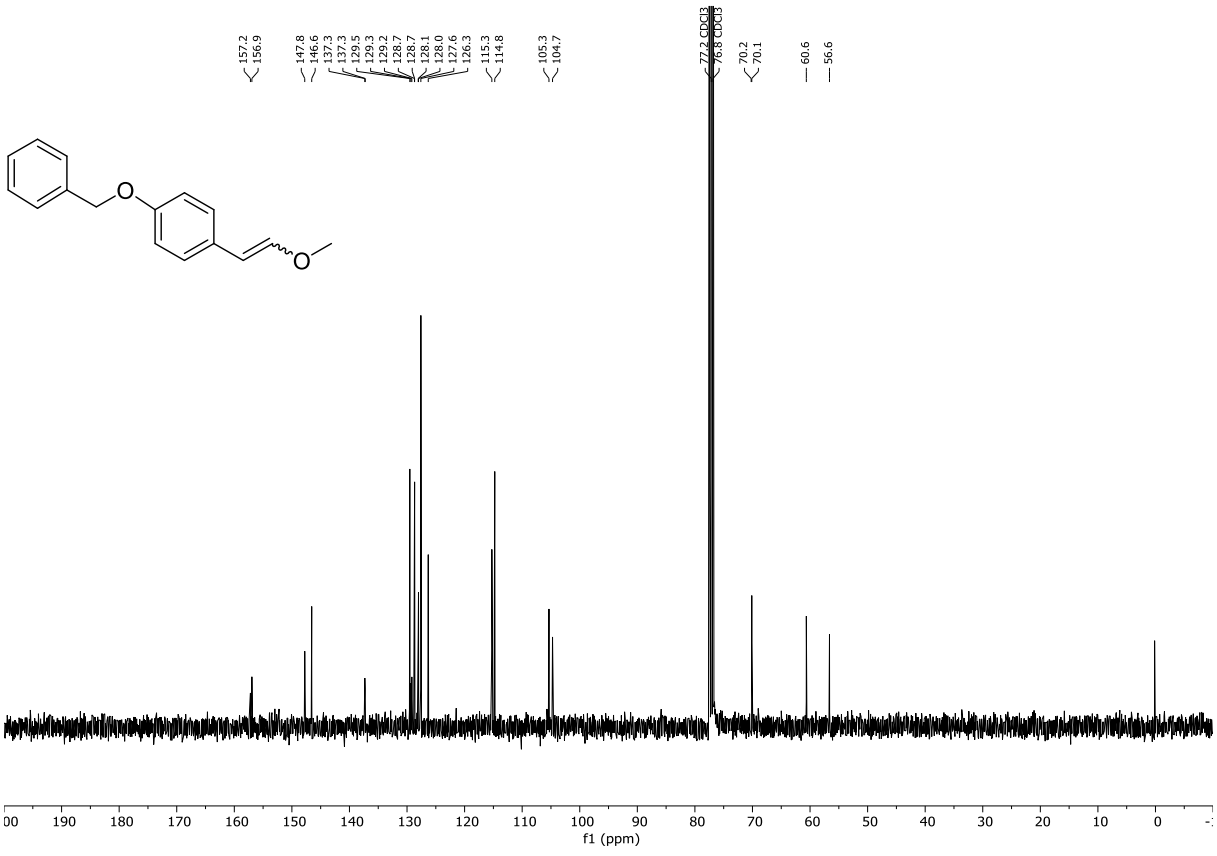
^{13}C NMR (101 MHz, TcI_2, 100°C) of **15b** ((1*R*,1'*S*)/(1*S*,1'*R*) isomers)



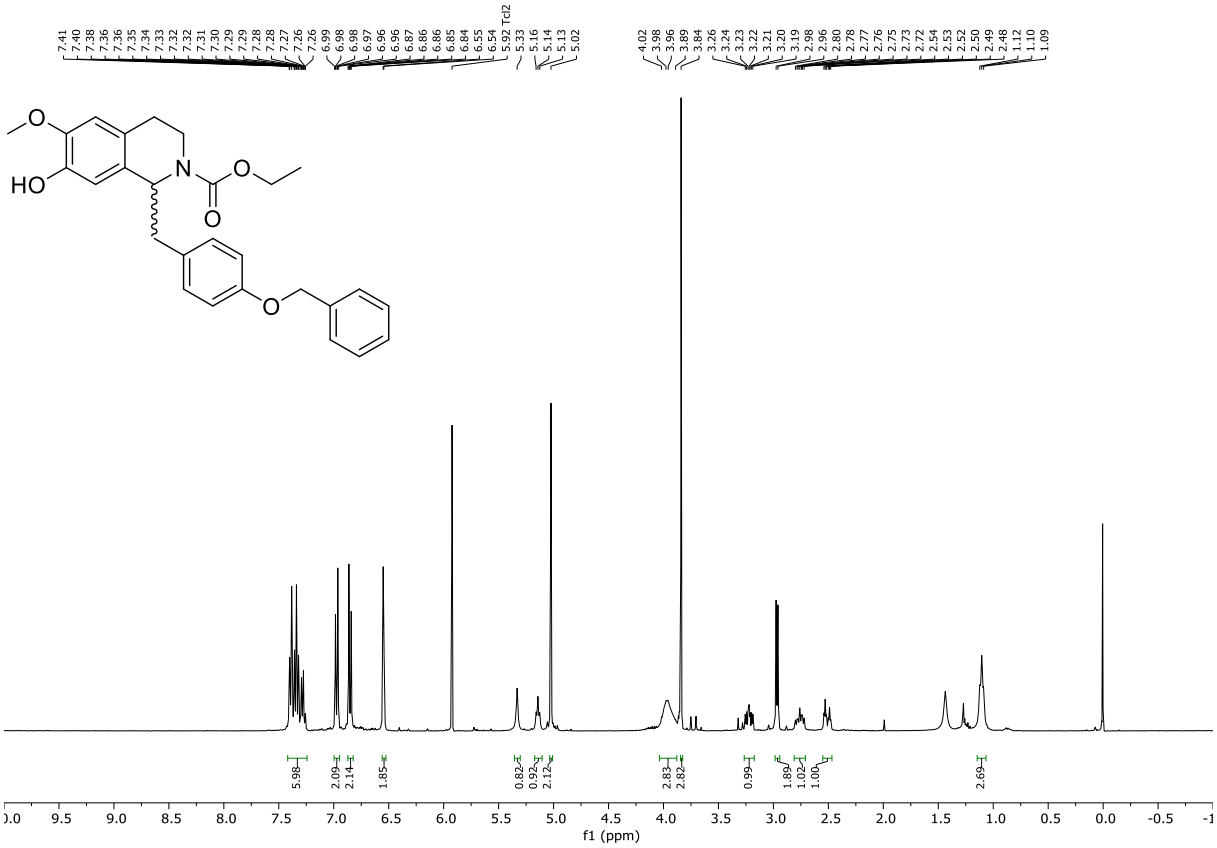
^{1}H NMR (400 MHz, $CDCl_3$) of **16**



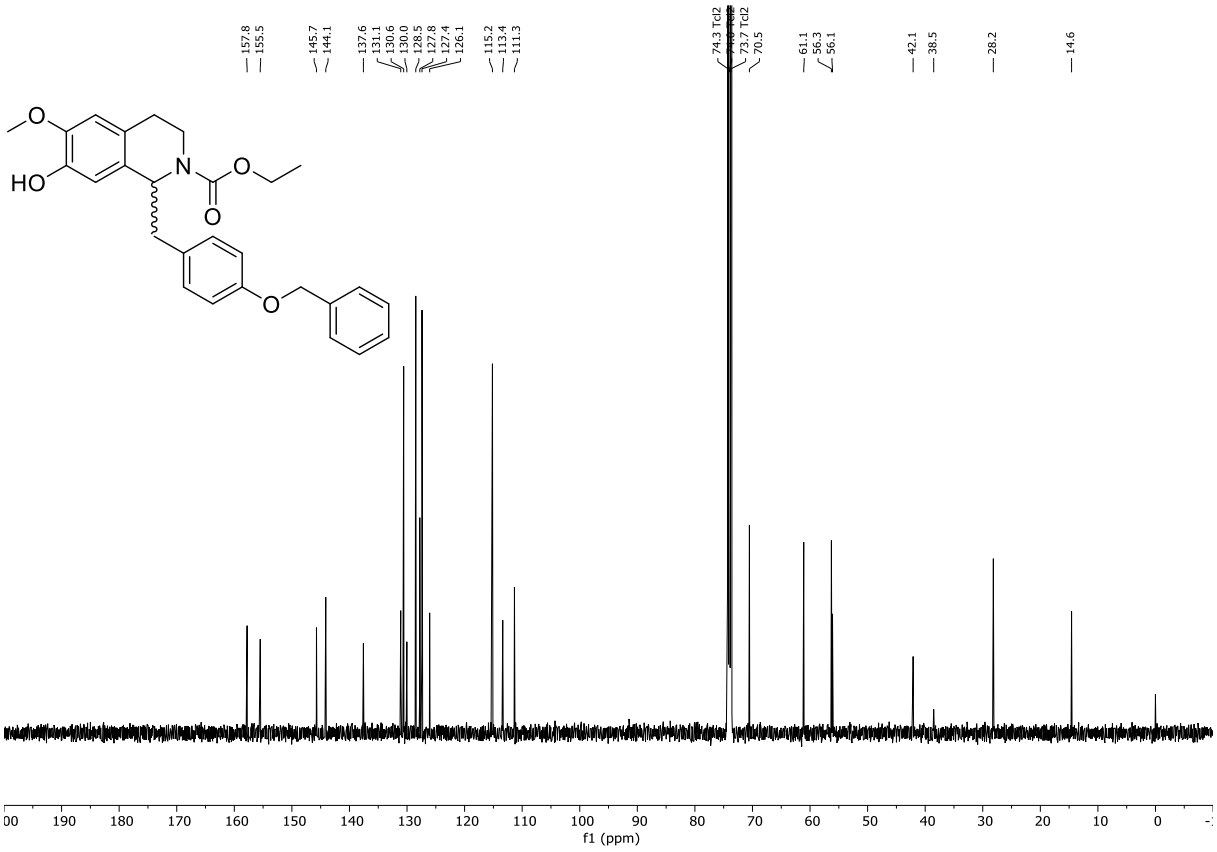
^{13}C NMR (101 MHz, $CDCl_3$) of **16**



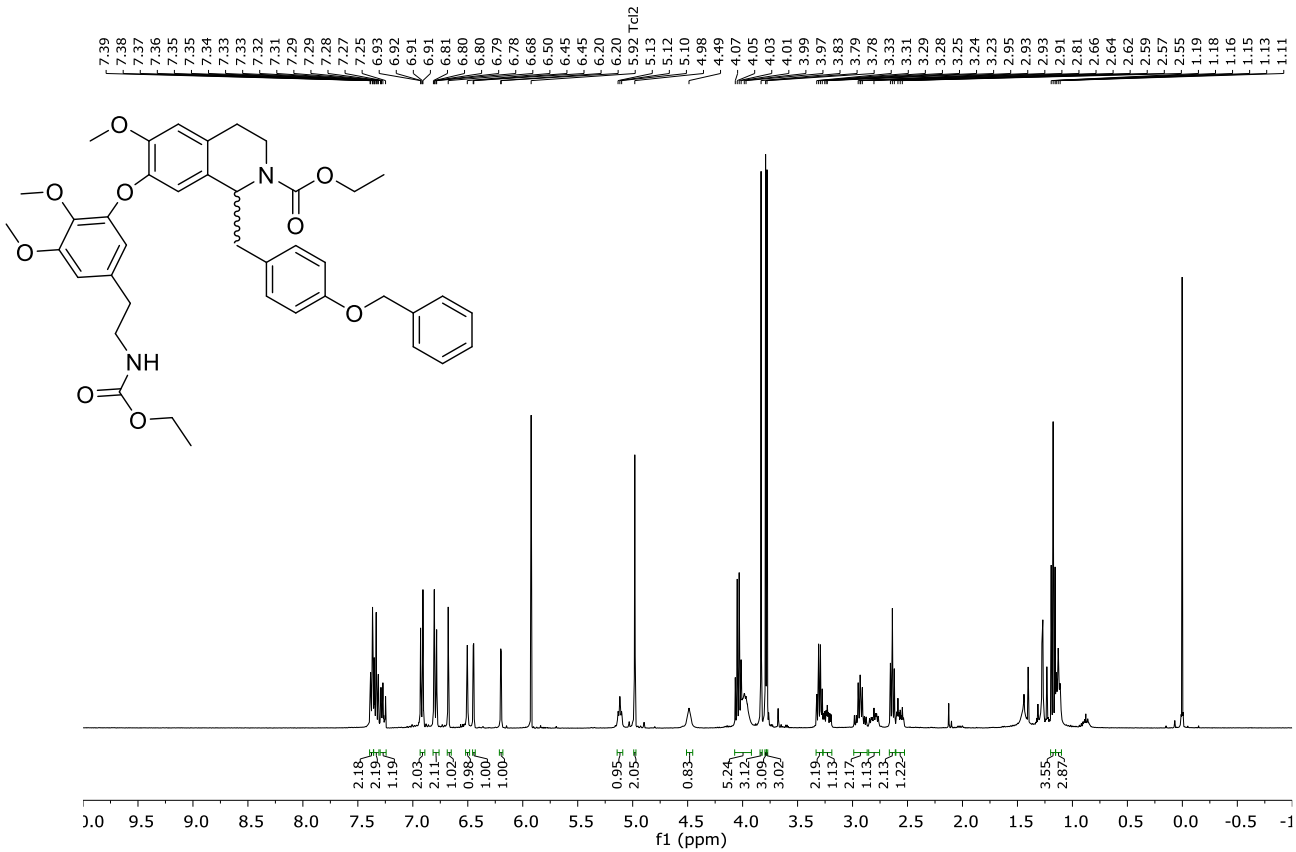
^{1}H NMR (400 MHz, TcI_2, 100°C) of **17**



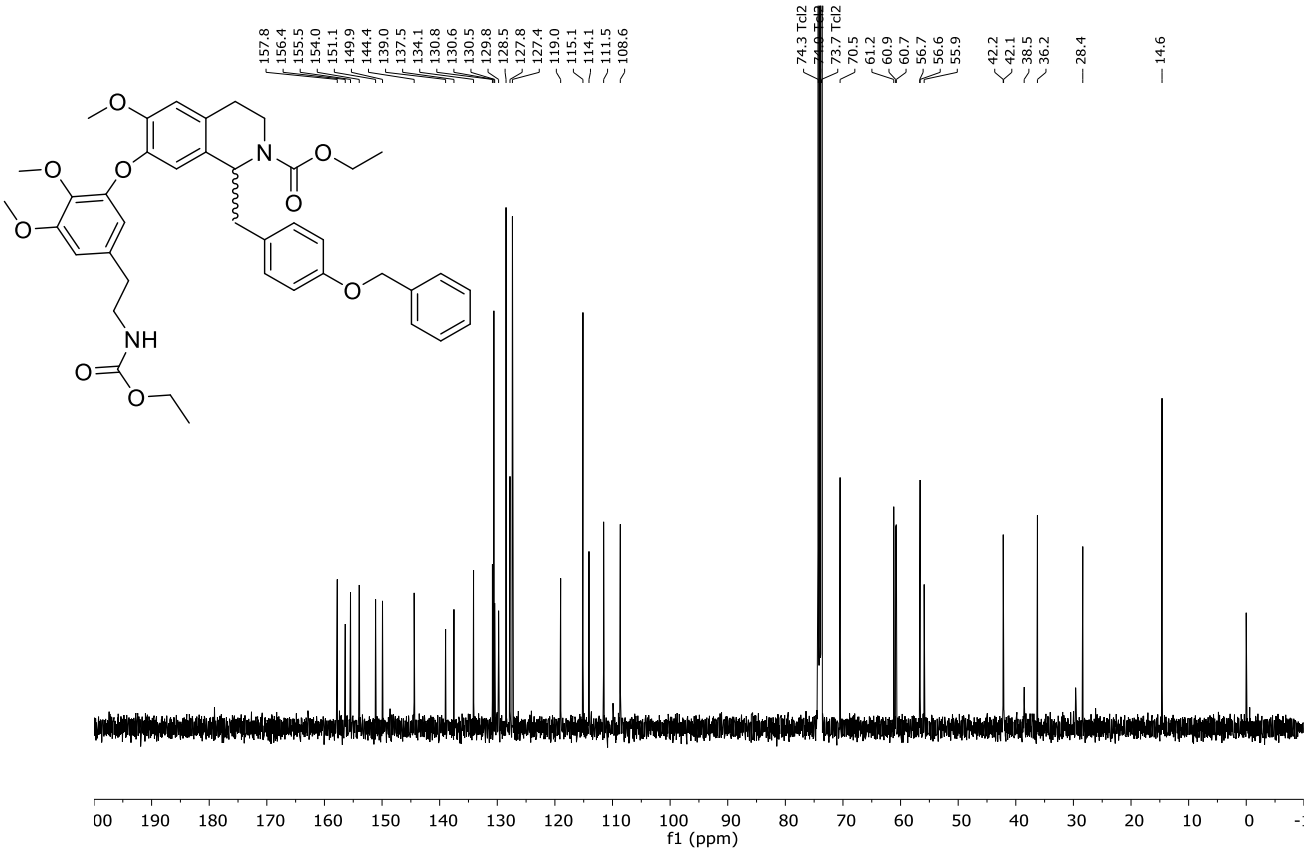
^{13}C NMR (101 MHz, TcI_2, 100°C) of **17**



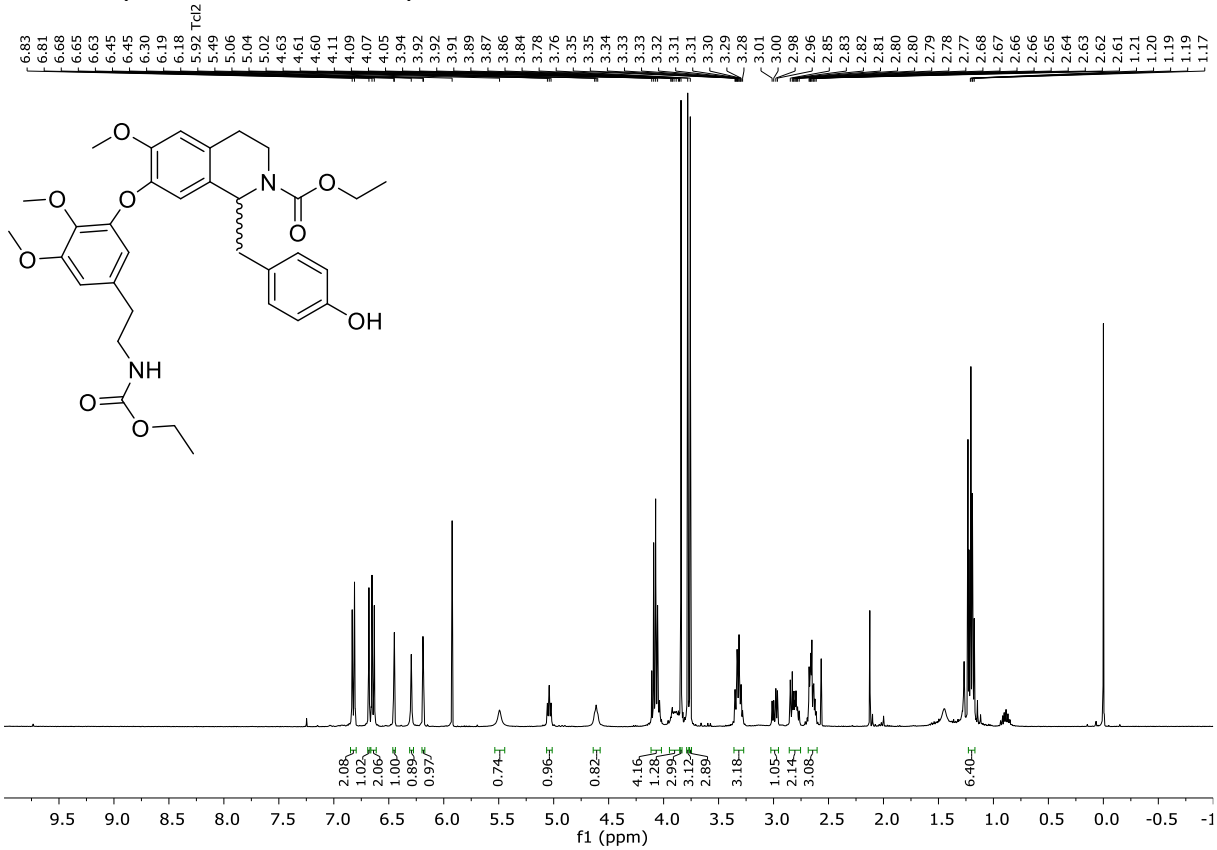
^{1}H NMR (400 MHz, TcI_2, 100°C) of **18**



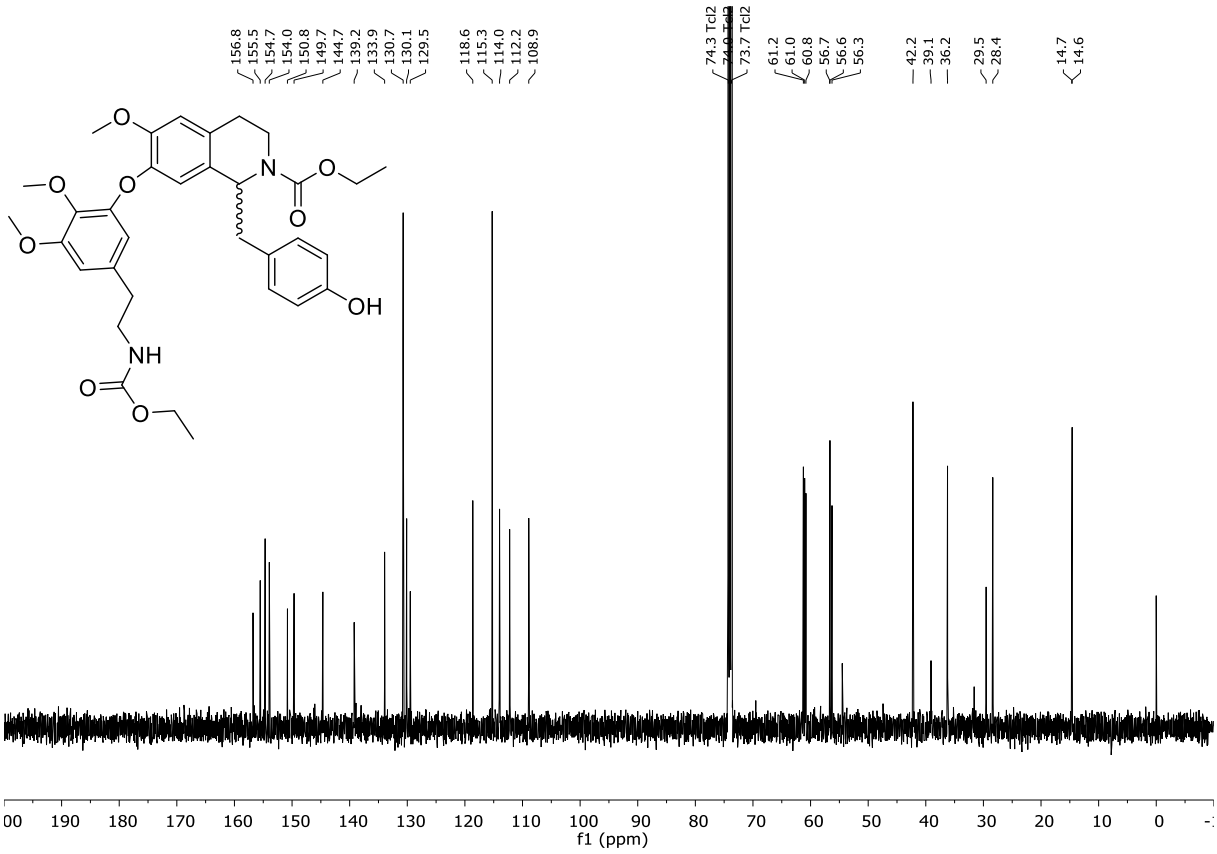
^{13}C NMR (101 MHz, TcI_2, 100°C) of **18**



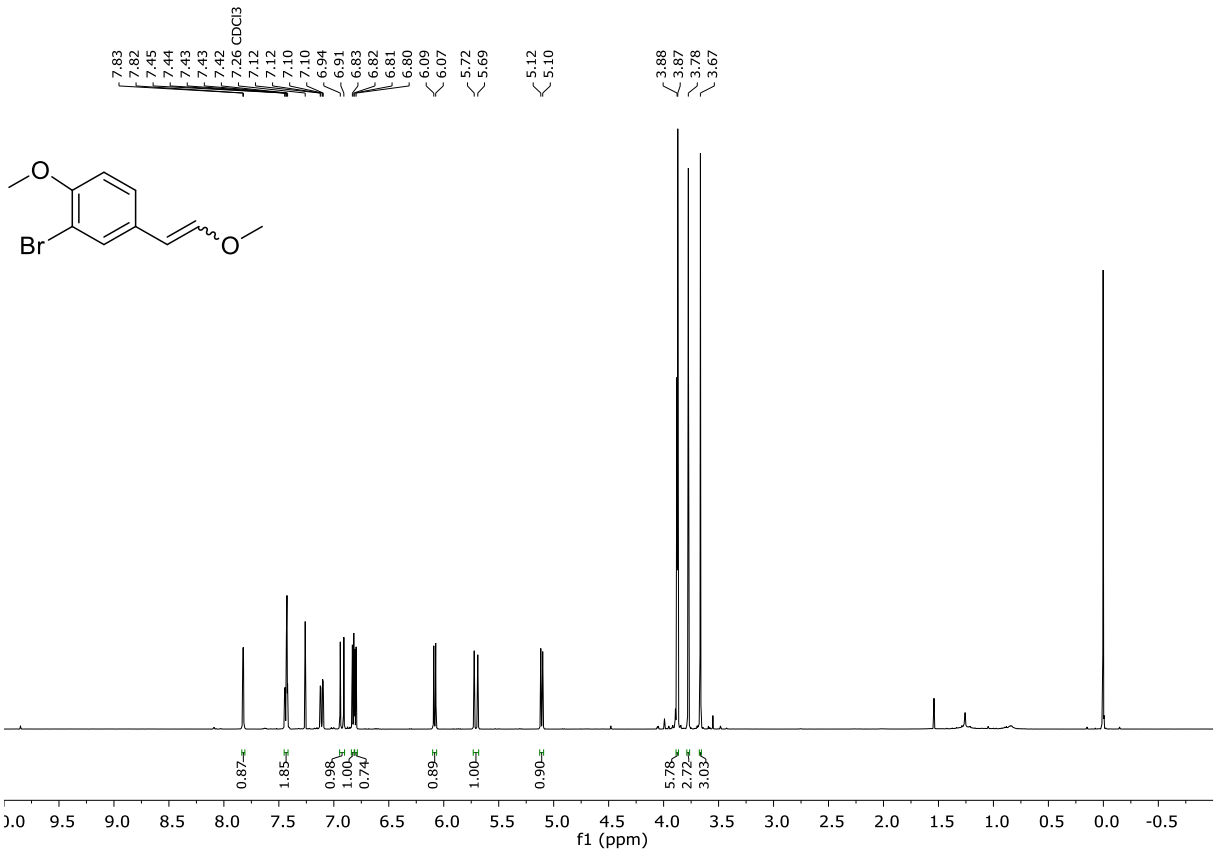
^{1}H NMR (400 MHz, TcI_2, 100°C) of **19**



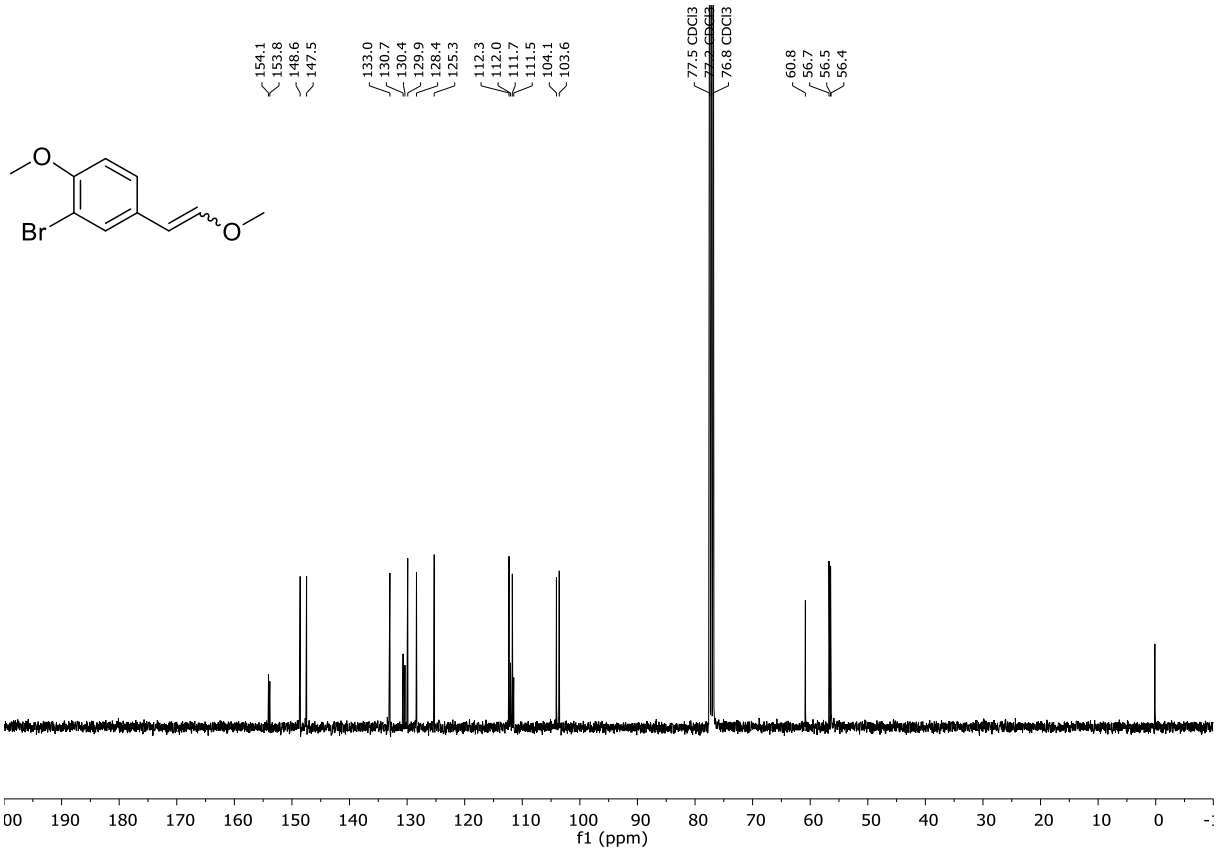
^{13}C NMR (101 MHz, TcI_2, 100°C) of **19**



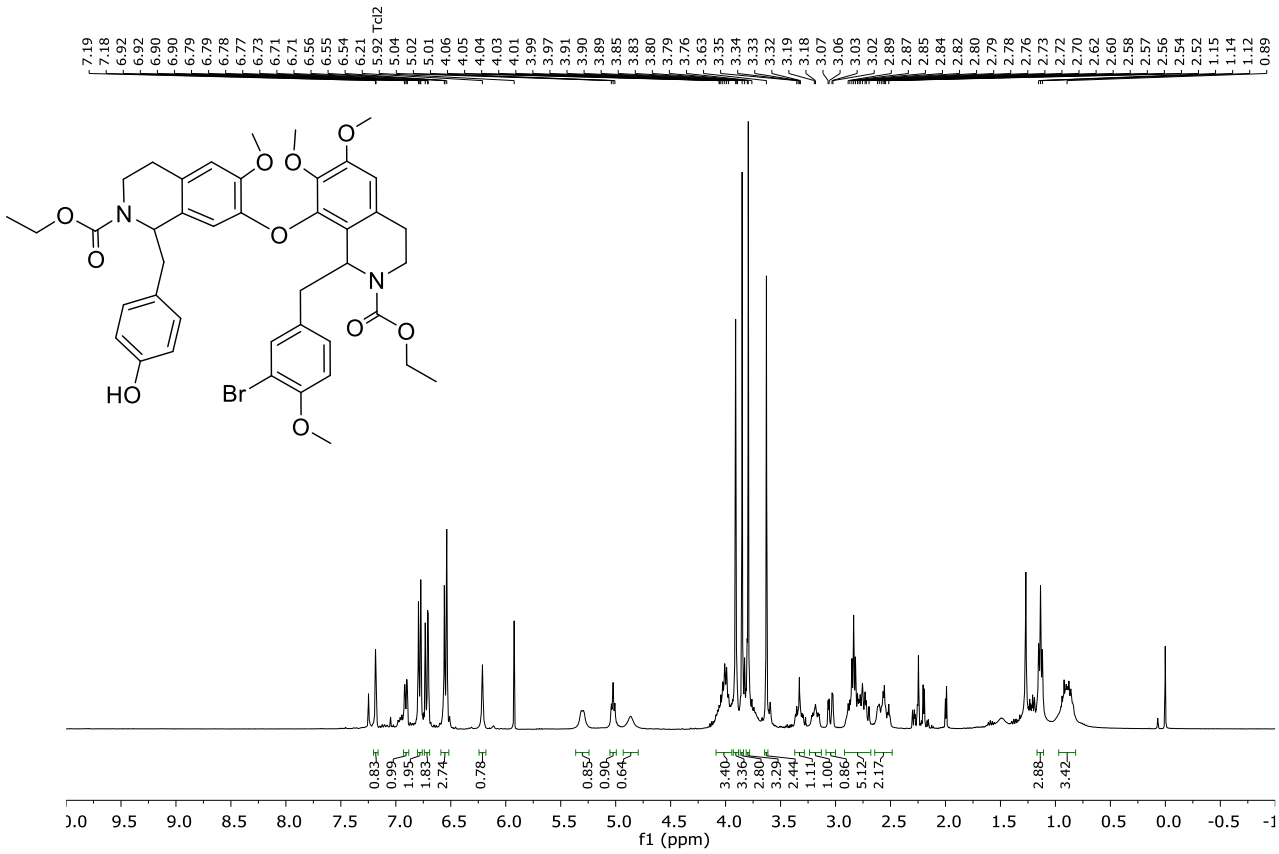
^{1}H NMR (400 MHz, $CDCl_3$) of **20**



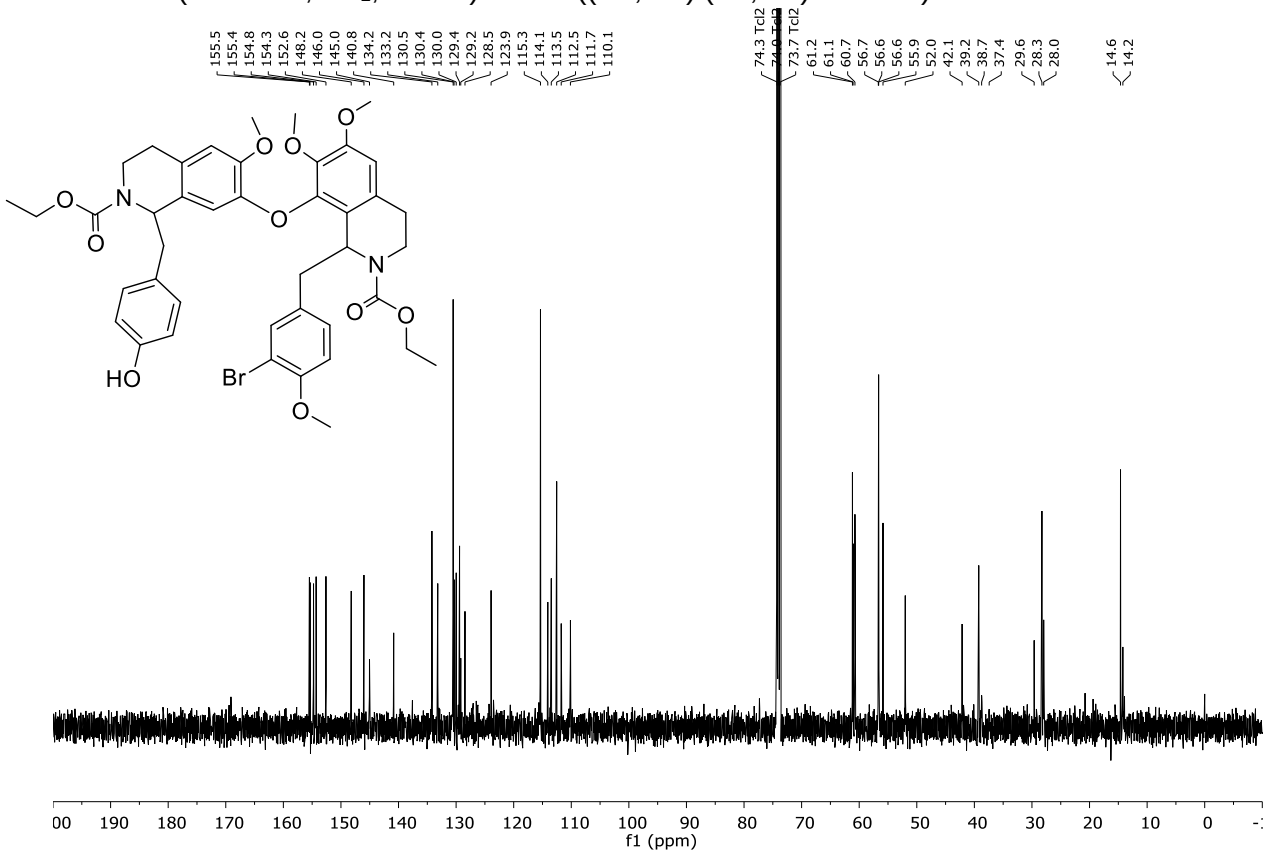
^{13}C NMR (101 MHz, $CDCl_3$) of **20**



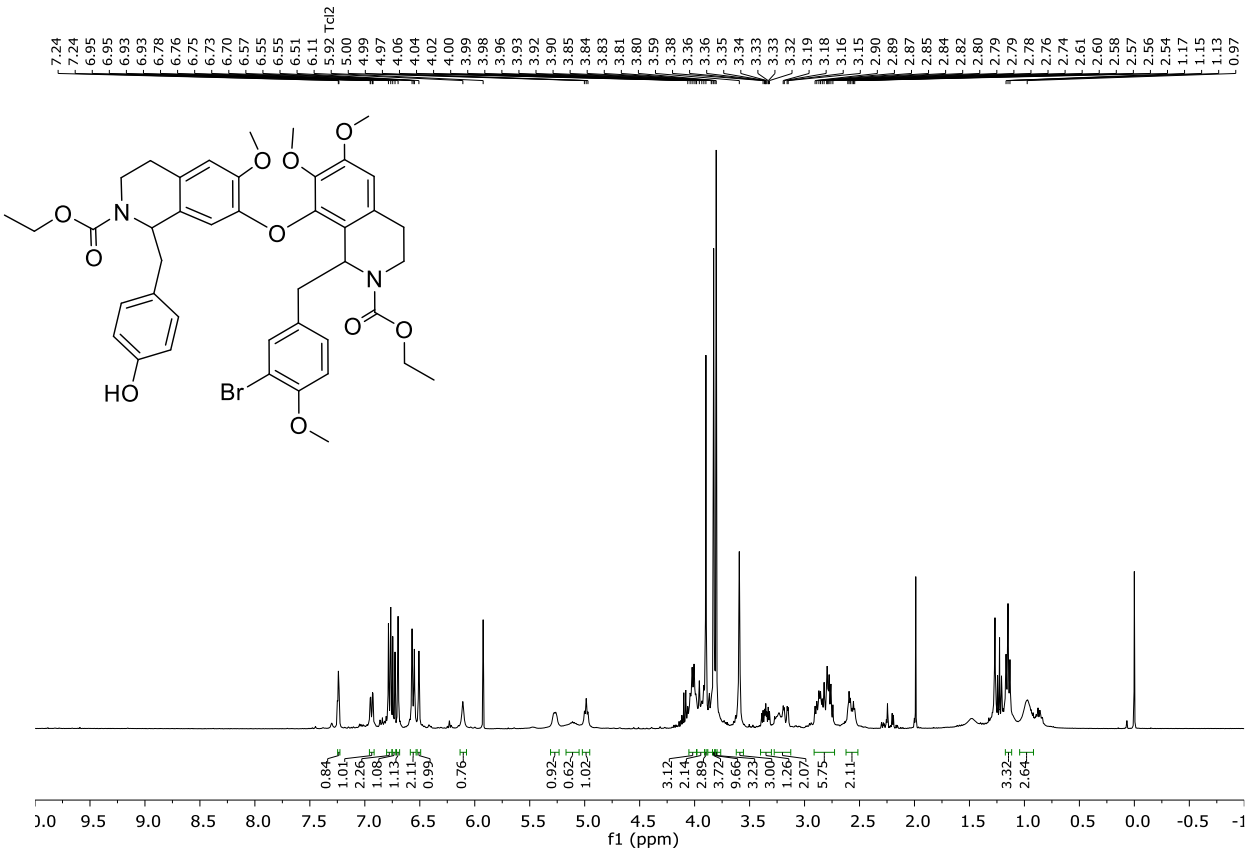
^{1}H NMR (400 MHz, $TcCl_2$, 100°C) of **21a** ((1*R*,1'*R*)/(1*S*,1'*S*) isomers)



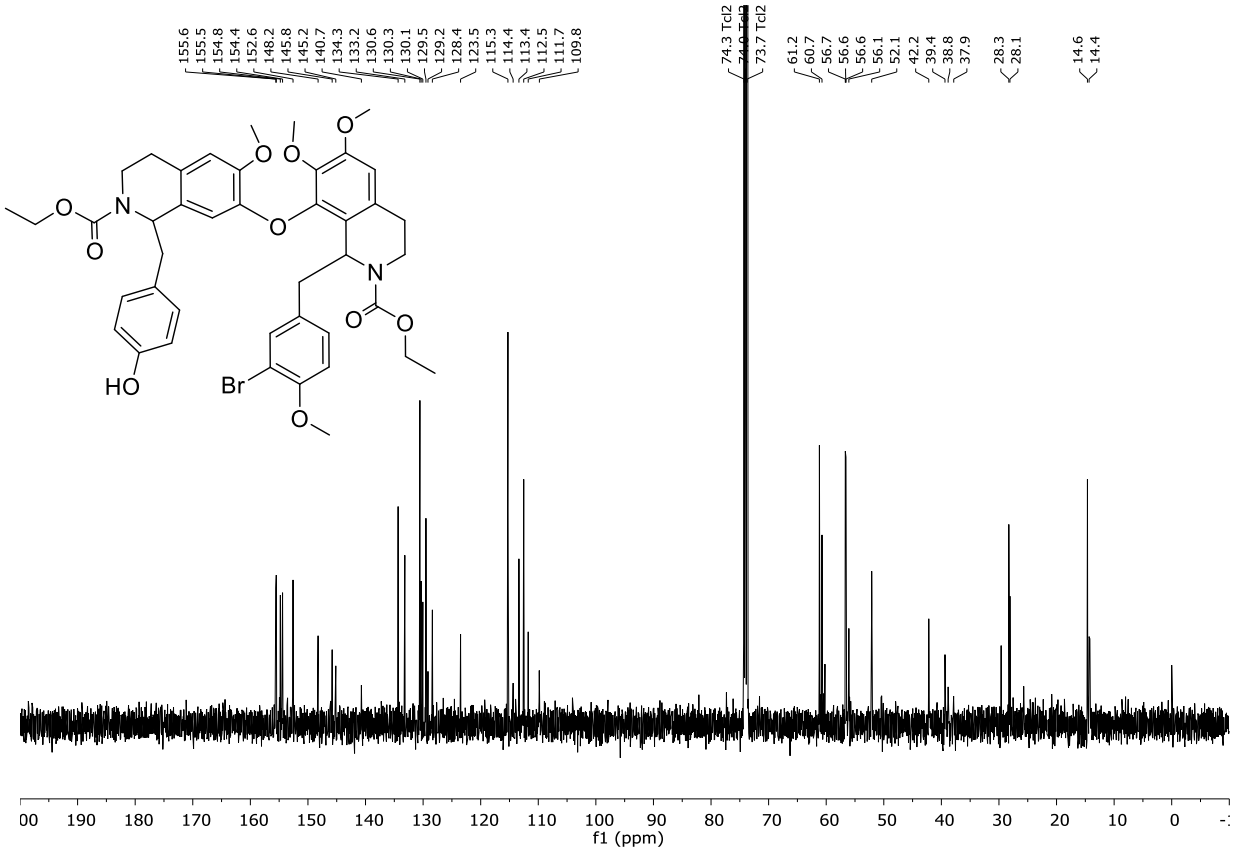
^{13}C NMR (101 MHz, $TcCl_2$, 100°C) of **21a** ((1*R*,1'*R*)/(1*S*,1'*S*) isomers)



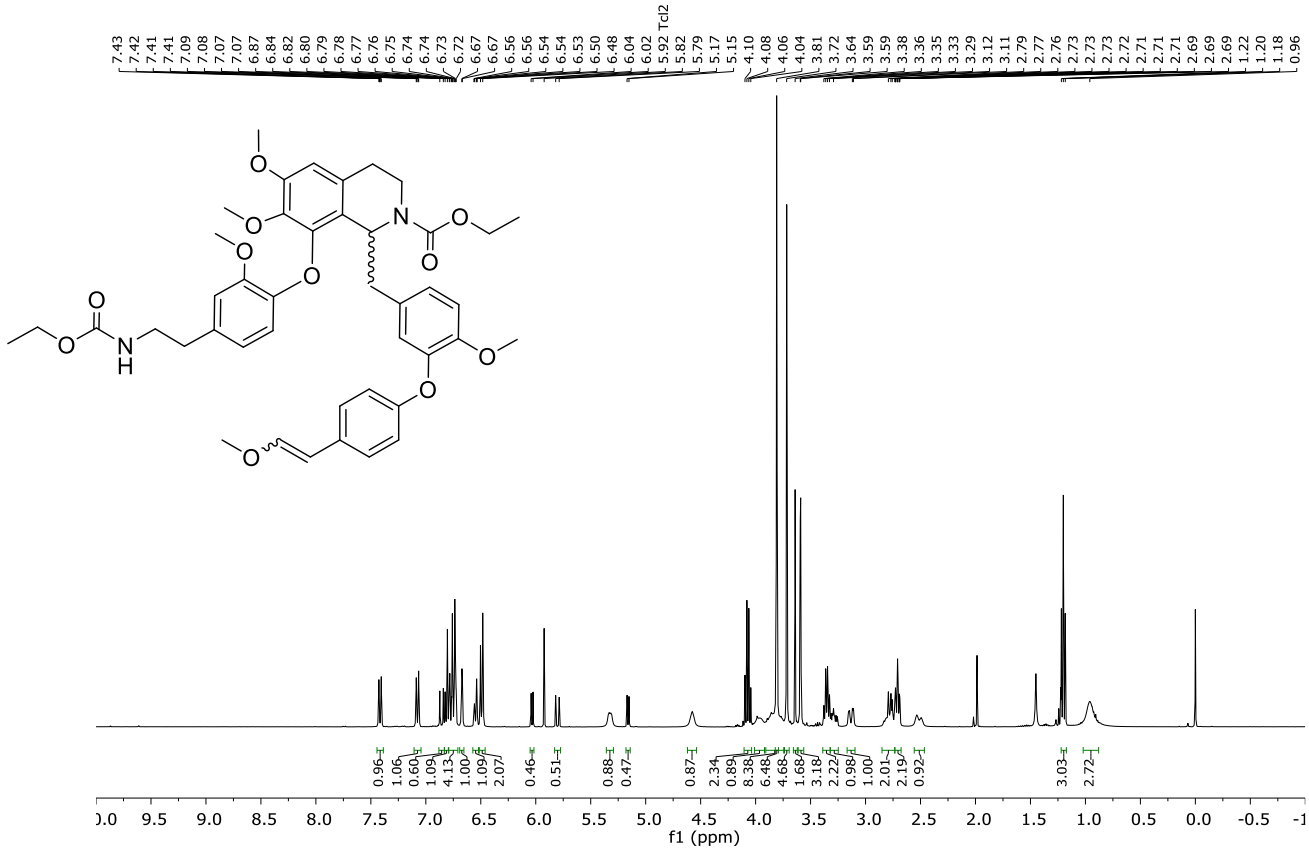
^{1}H NMR (400 MHz, TcI_2, 100°C) of **21b** ((1*R*,1'*S*)/(1*S*,1'*R*) isomers)



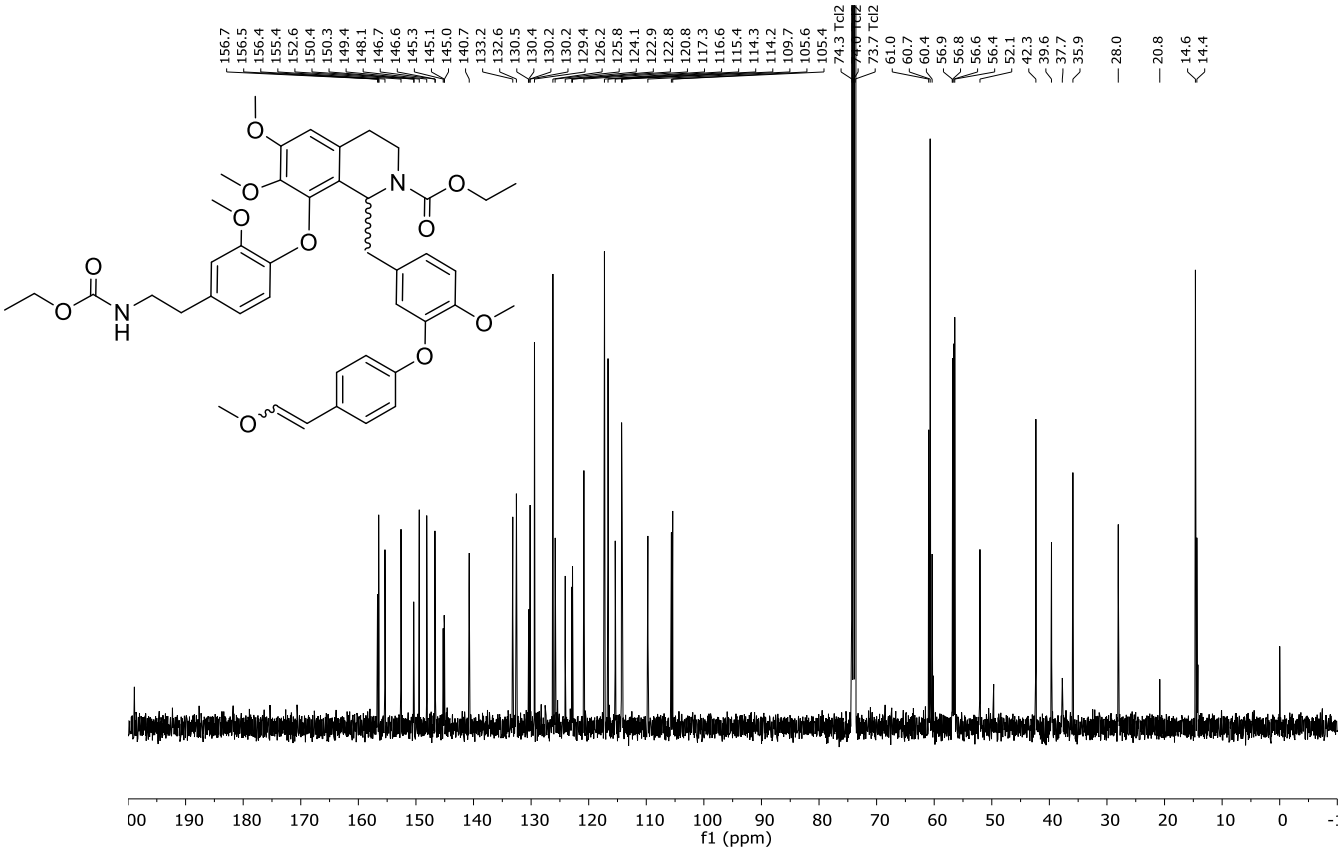
^{13}C NMR (101 MHz, TcI_2, 100°C) of **21b** ((1*R*,1'*S*)/(1*S*,1'*R*) isomers)



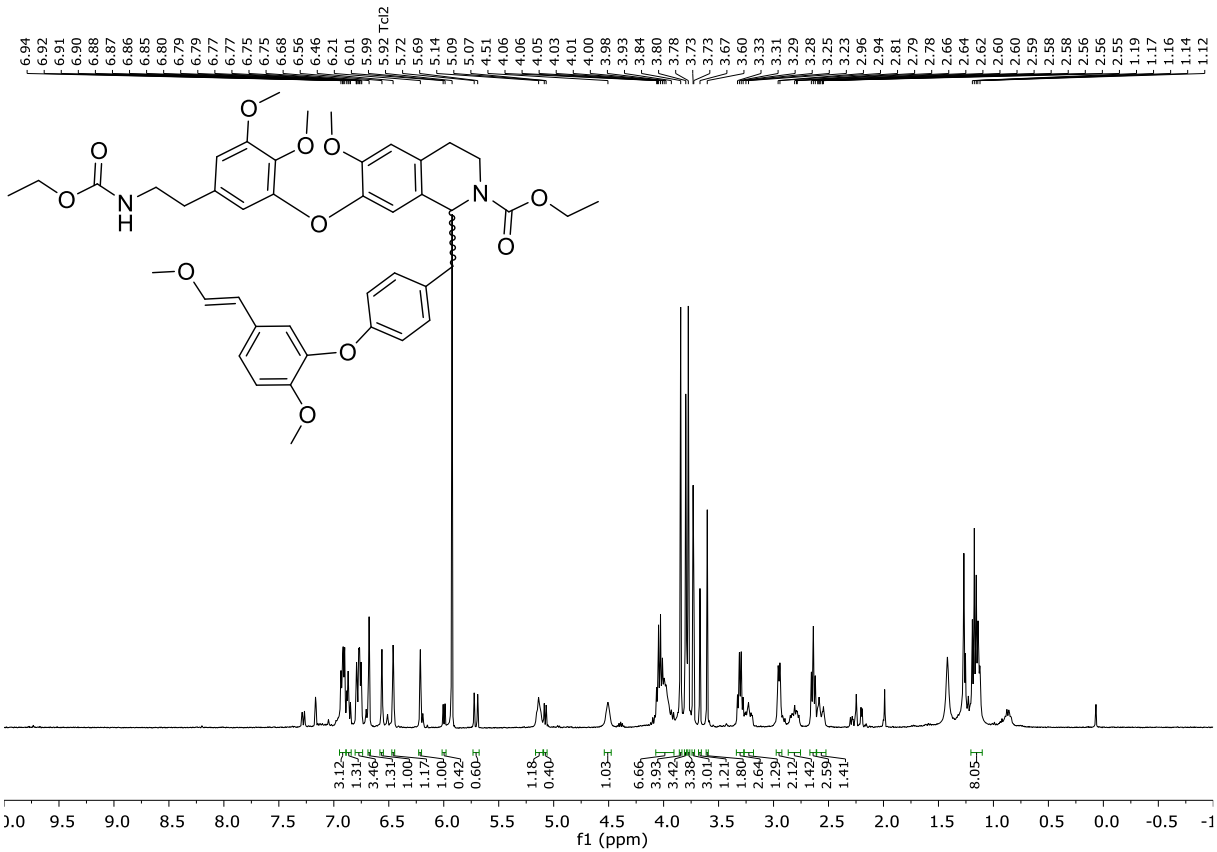
^{1}H NMR (400 MHz, TcI_2, 100°C) of **22**



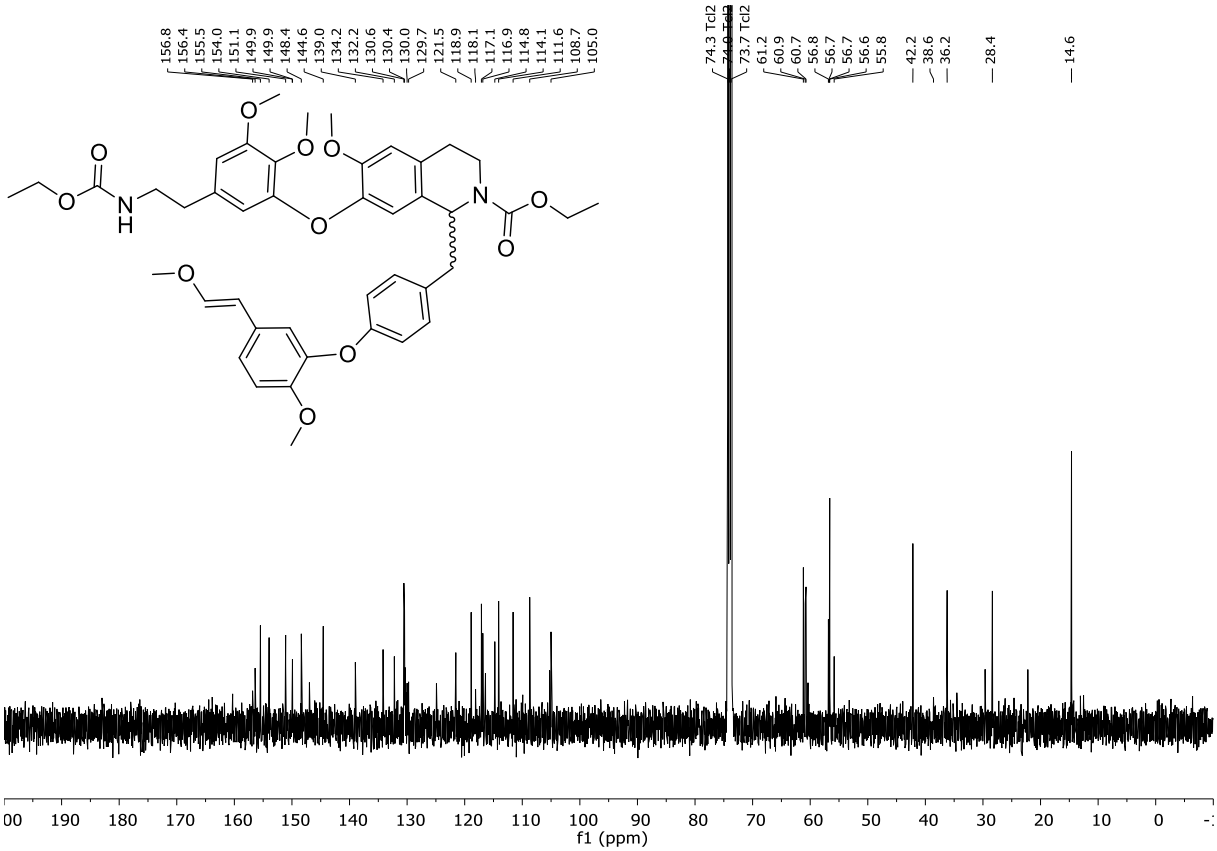
^{13}C NMR (101 MHz, TcI_2, 100°C) of **22**



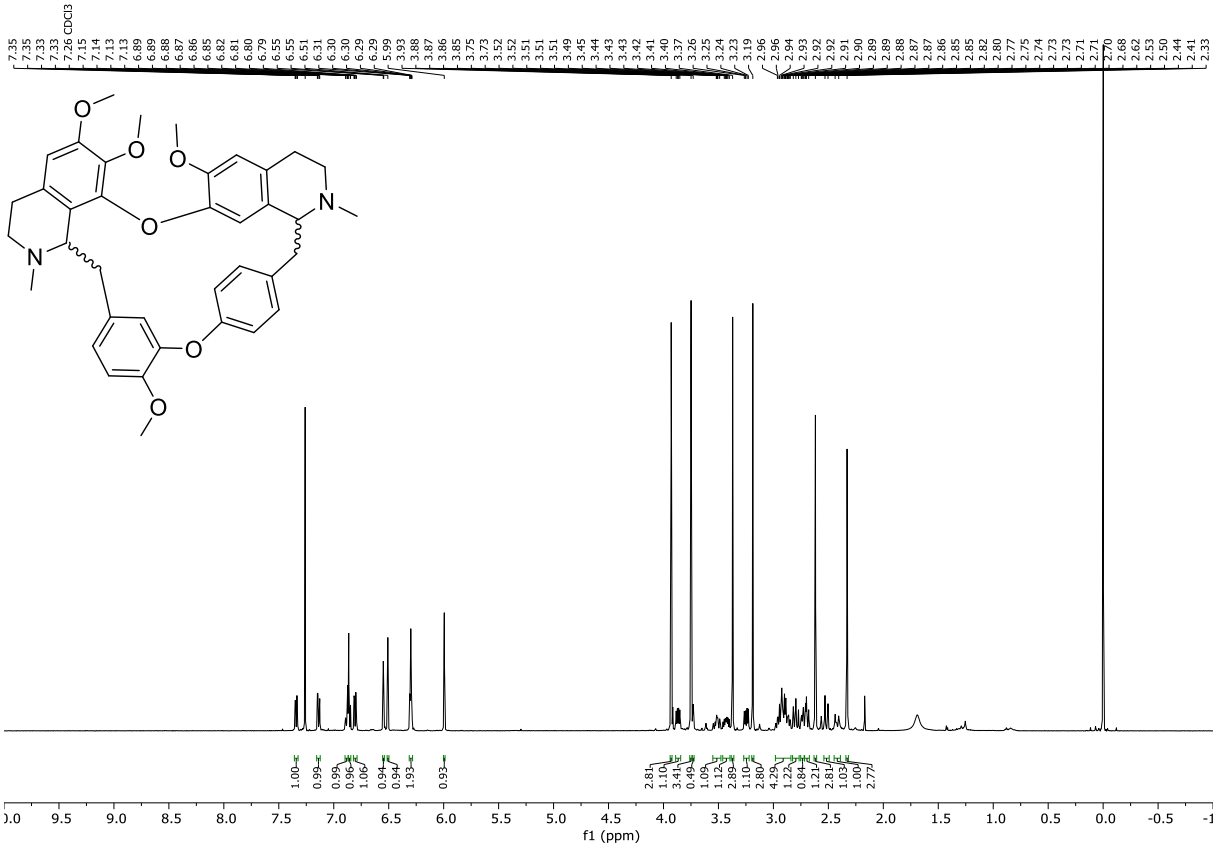
^{1}H NMR (400 MHz, TcI_2, 100°C) of **23**



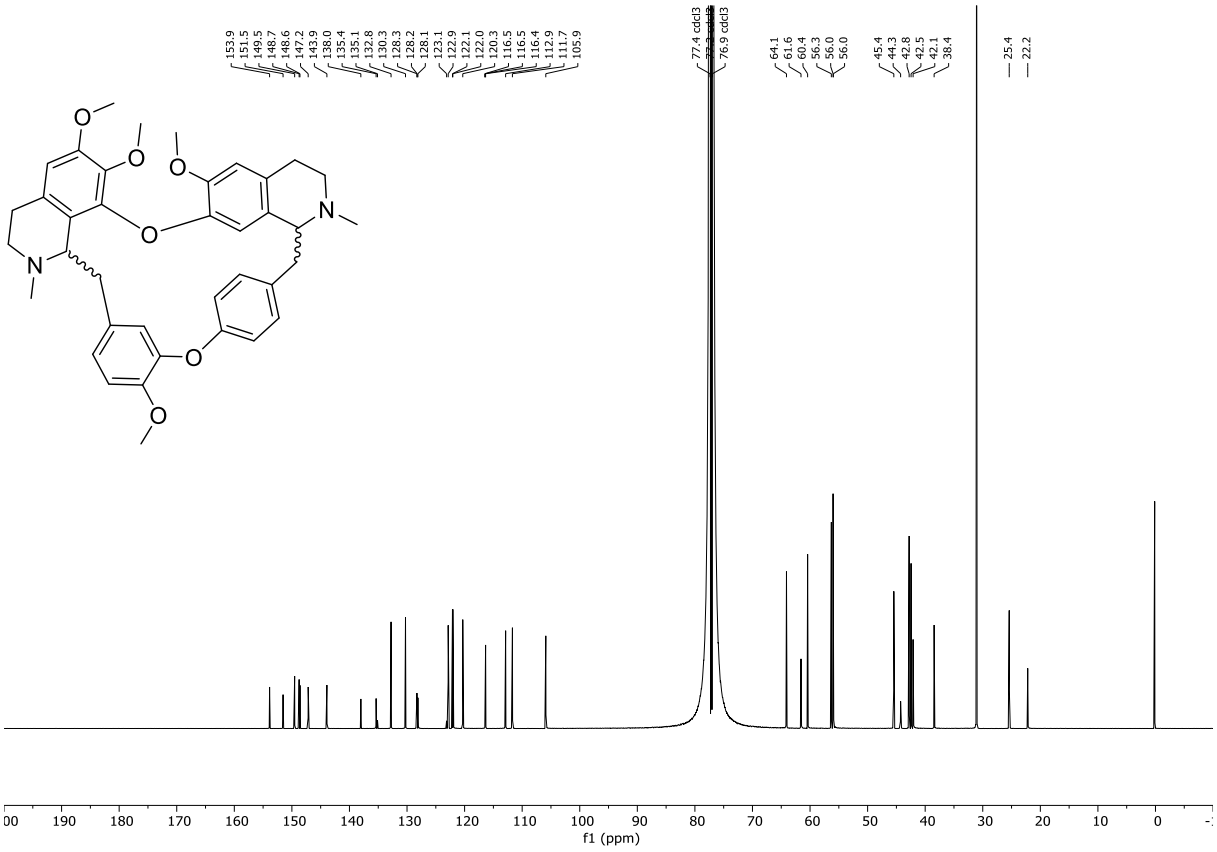
^{13}C NMR (101 MHz, TcI_2, 100°C) of **23**



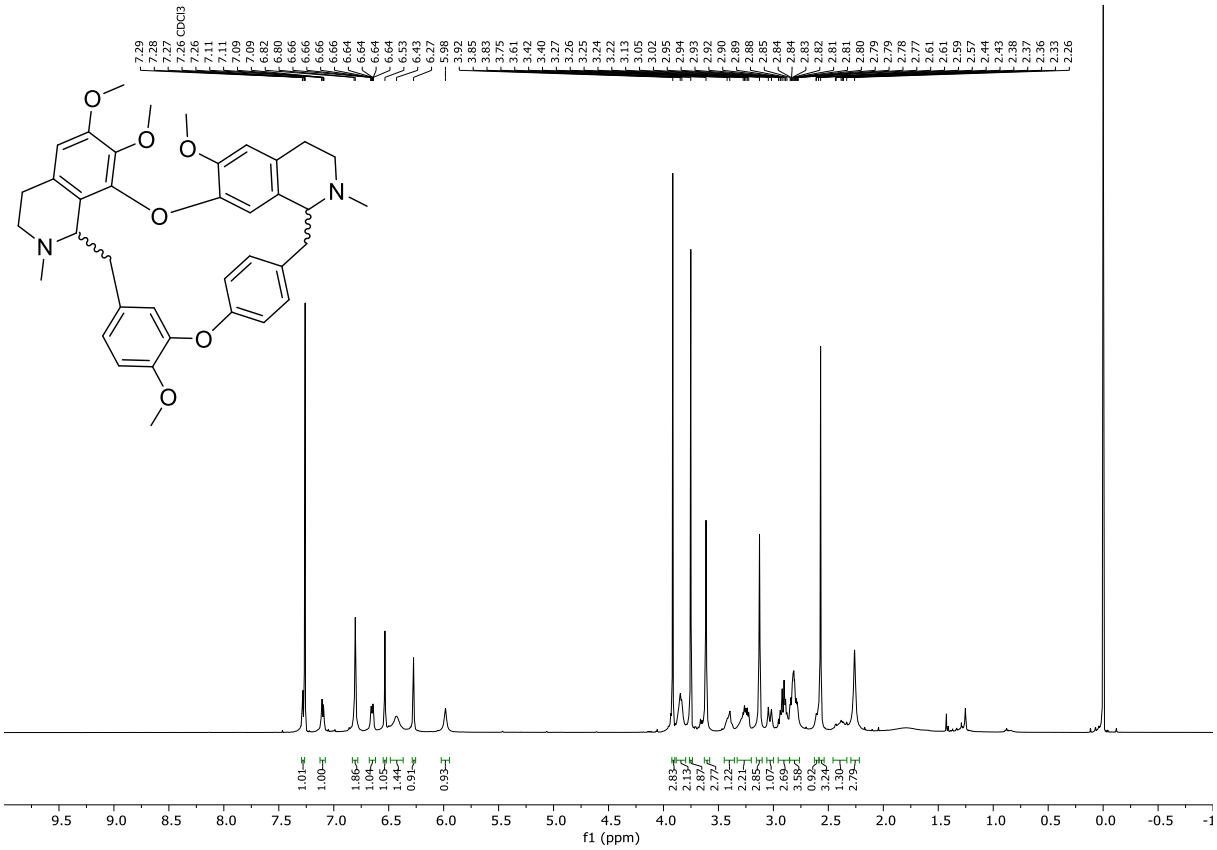
^{1}H NMR (500 MHz, $CDCl_3$) of synthetic racemic tetrandrine (*rac*-**1**)



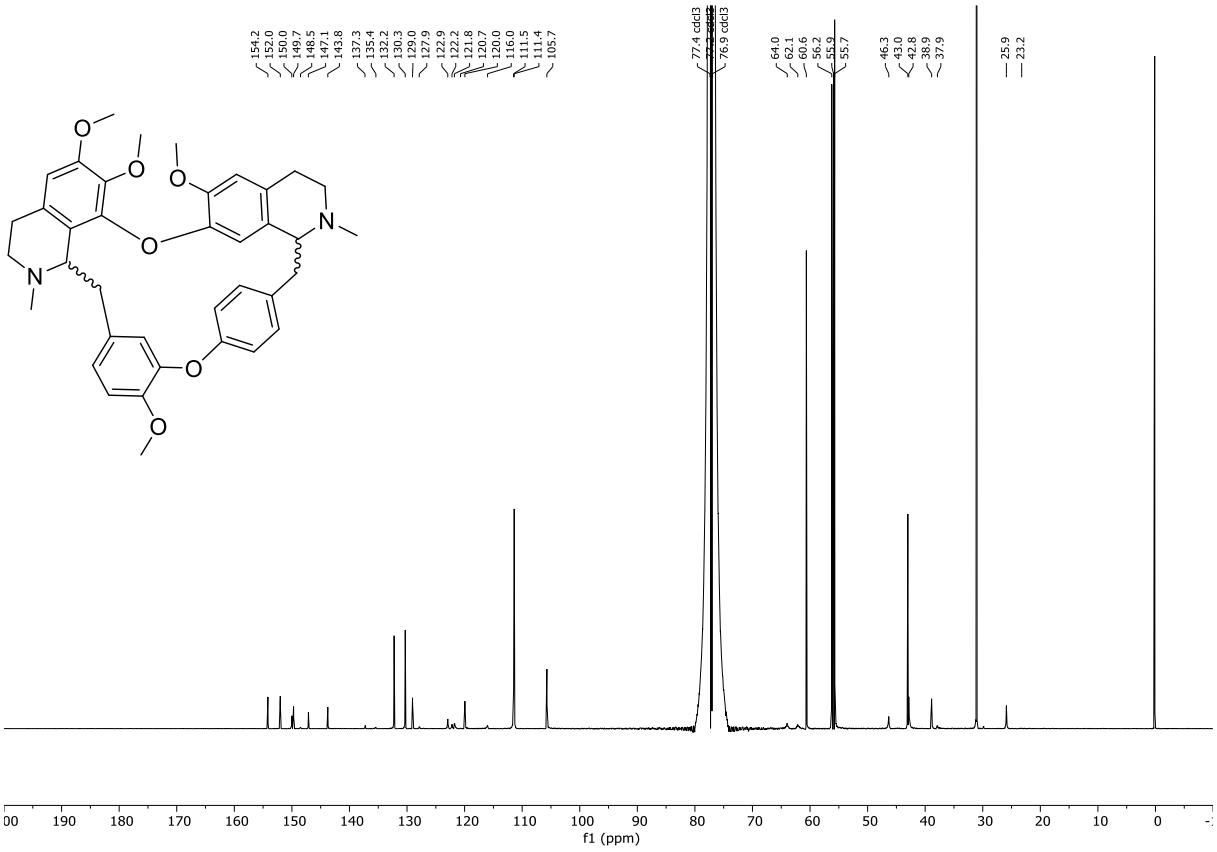
^{13}C NMR (151 MHz, $CDCl_3$) of synthetic racemic tetrandrine (*rac*-**1**)



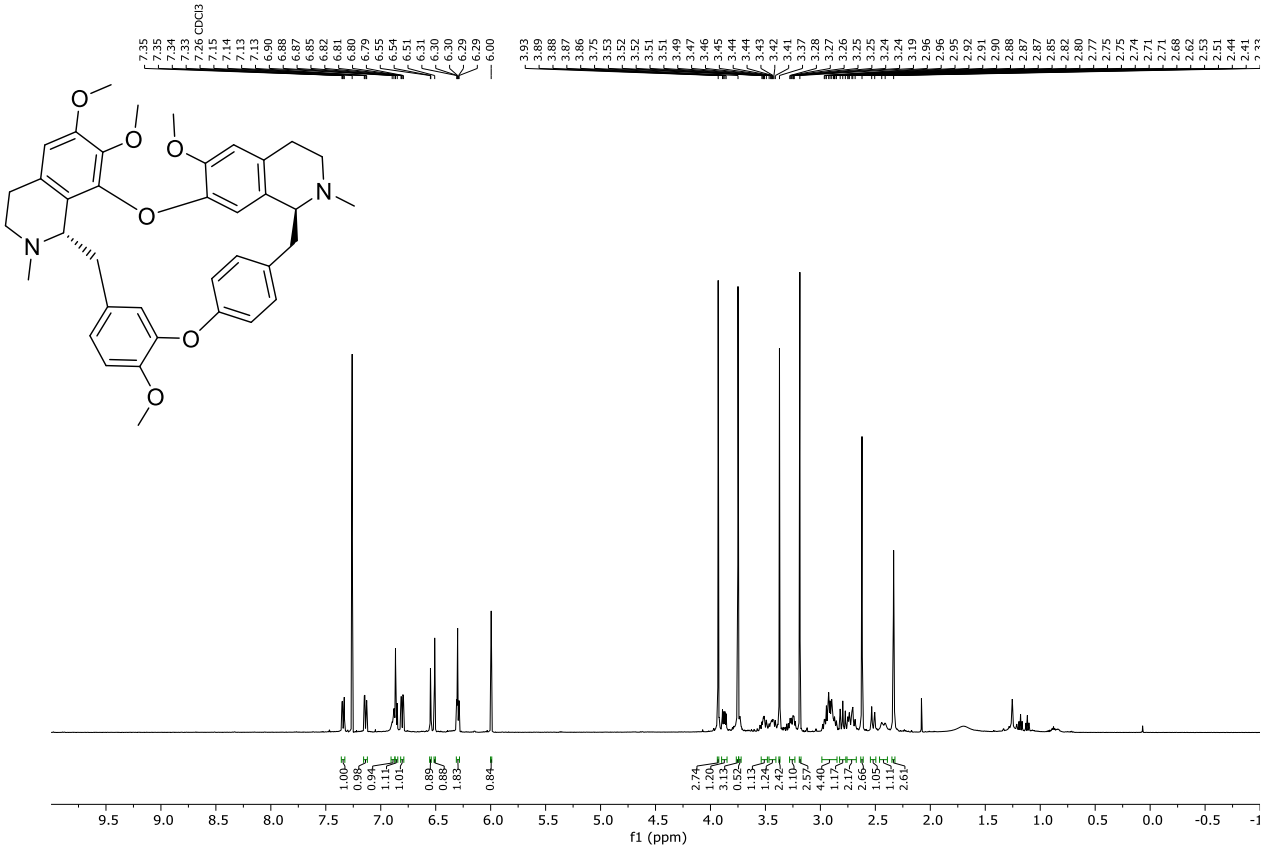
^{1}H NMR (500 MHz, $CDCl_3$) of synthetic racemic isotetrandrine (*rac*-**2**)



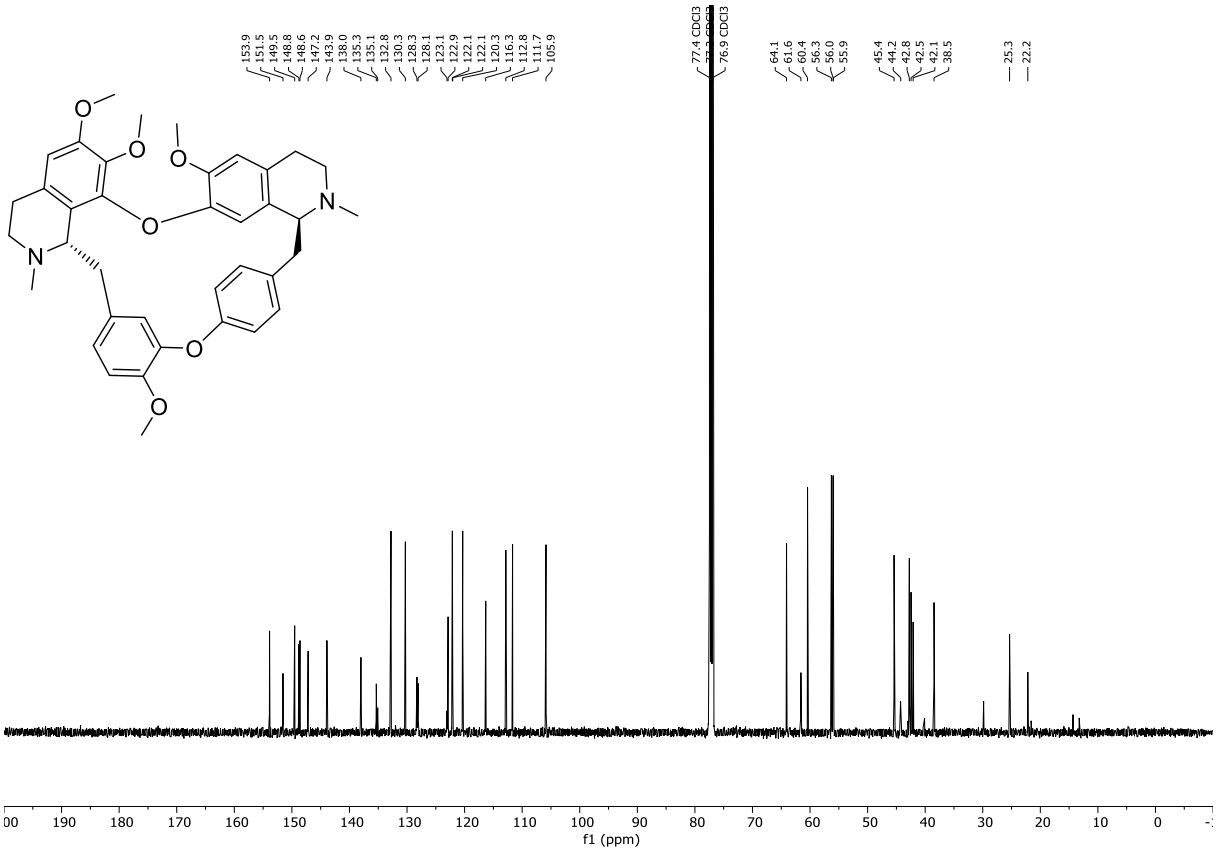
^{13}C NMR (151 MHz, $CDCl_3$) of synthetic racemic isotetrandrine (*rac*-**2**)



^{1}H 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'-1S: 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-1*R*	*S*	34	(130)	C-1'*R*	*S*	44
	R	24	(90)		*R*	28
C-1*S*	*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-1*R* 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-1*S* 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