Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Antituberculosis agent diaportheone B: Synthesis, absolute configuration assignment, and anti-TB activity of its analogues

Pandrangi Siva Swaroop, Gajanan N. Raut, Rajesh G. Gonnade, Priyanka Verma, Rajesh Gokhale and D. Srinivasa Reddy *

*Corresponding author:

Dr. D. Srinivasa Reddy

National Chemical Laboratory (CSIR, India),

Division of Organic Chemistry,

Dr. Homi Bhabha Road,

Pune 411008, Maharashtra,

India.

E-mail: ds.reddy@ncl.res.in

Tel. +91 20 25902445

Fax. +91 20 25902629

Supporting Information

Reaction Optimization Tables:

Other conditions for the optimization of tandem aldol cascade reaction compiled in below tables.

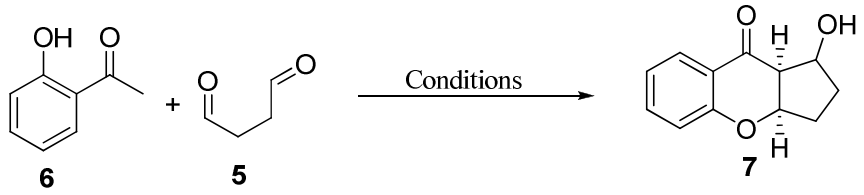


Table-I: Conditions followed for standardization of the cascade reaction

S.No	Base	Solvent	Time (h)	Temp (^{o}C)	Result[a]
1	Pyrrolidine	MeOH	24	50	Product observed
2	DBU	MeOH	24	50	Product observed
3	DABCO	MeOH	24	50	No desired Product
4	Morpholine	MeOH	24	50	No desired Product
5	Proline	MeOH	24	50	No desired Product
6	Pyrrolidine	Toluene	24	50	No desired Product
7	Pyrrolidine	THF	24	50	No desired Product
8	Pyrrolidine	Acetonitrile	24	50	Product observed
9	Pyrrolidine	DMF	24	50	No desired Product
10	Pyrrolidine	DMSO	24	50	Product observed
11	Pyrrolidine	EtOH	24	50	Product observed
12	Pyrrolidine	IPA	24	50	No desired Product
13	Pyrrolidine	BuOH	24	50	No desired Product

(a) reaction monitored by tlc.

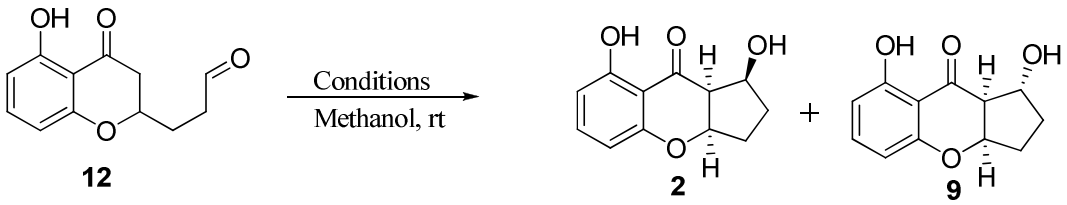


Table-II: Optimization conditions using different bases in methanol solvent

Sr.No	Base	Reaction Time	Dp-B (2)[b]	Epimer (9)[b]	Yield %	Recovered SM %
1	Proline[a]	12h	30	70	38	38
2	DBU	0.5h	27	73	46	18
3	Piperidine	18h	30	70	55	42
4	Proline Diamine[a]	10h	60	40	58	17
5	Pyrrolidine	2.0h	10	90	60	25
6	Pyridine	36h	54	46	72	64
7	2,6-Lutidine	24h	50	50	76	42
8	Prolinol	15h	33	67	79	13
9	DABCO	0.25h	63	37	68	50

(a) 50 mol% of base used. (b) ratio was determined using HPLC

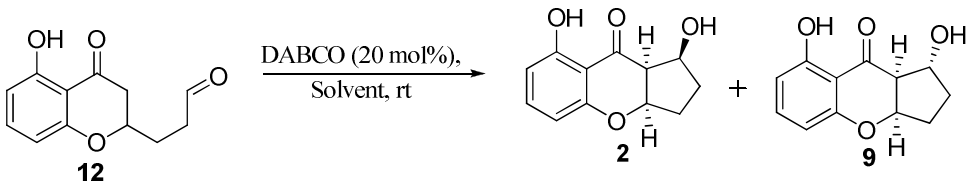


Table-III: Optimization conditions using DABCO in different solvents

S.No	Solvent	Time (h)	Dp-B (2)	Epimer (9)	Yield %	Recovered SM %
1	THF	4.00	68	32	80	14
2	Acetonitrile	3.50	66	34	86	12
3	Benzene	5.50	70	30	87	14
4	MeOH	0.50	63	37	93	50
5	Toluene	6.00	48	52	96	0

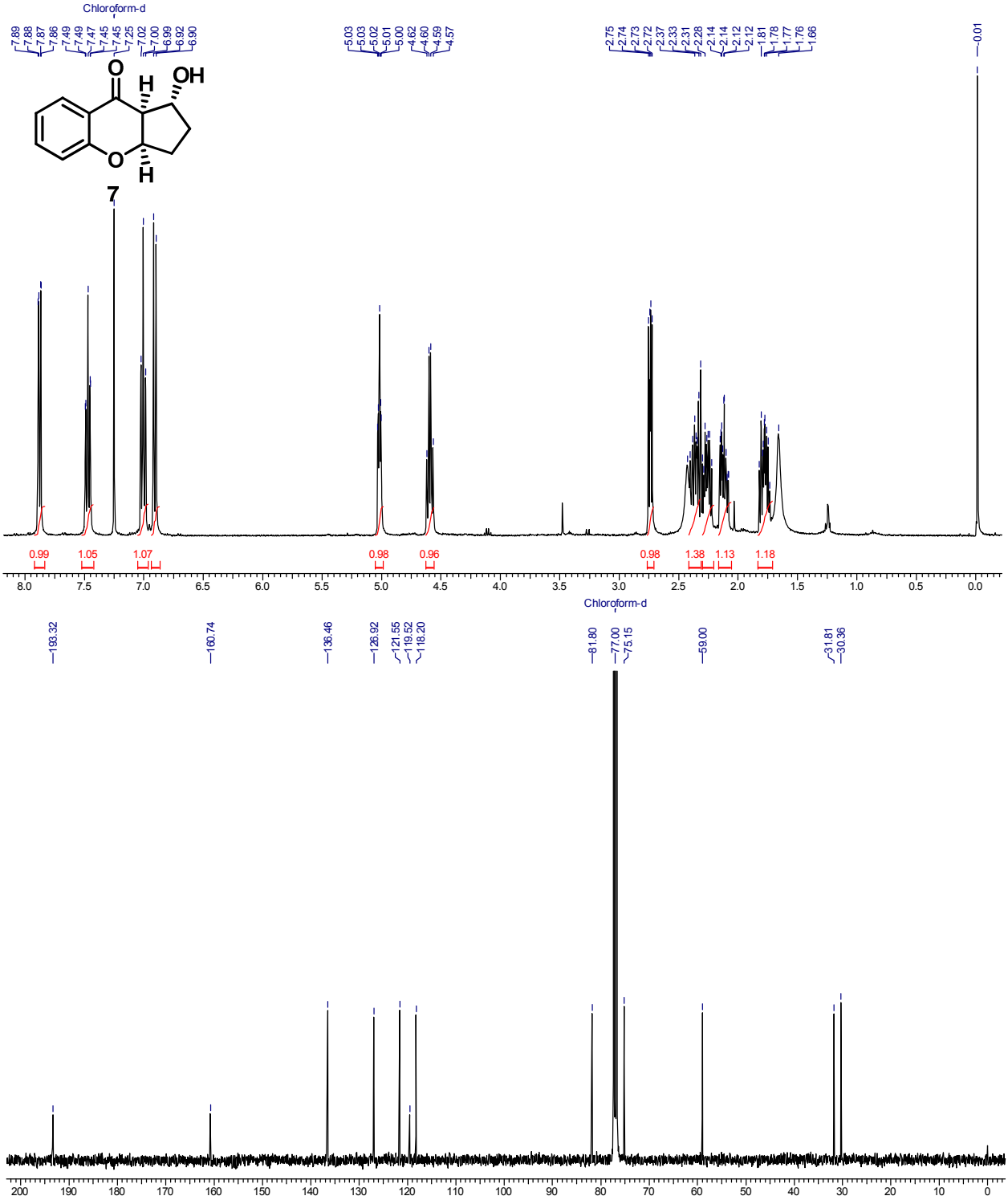
Table IV: ^{1}H NMR data comparison between Reported and synthesized Diaportheone B.

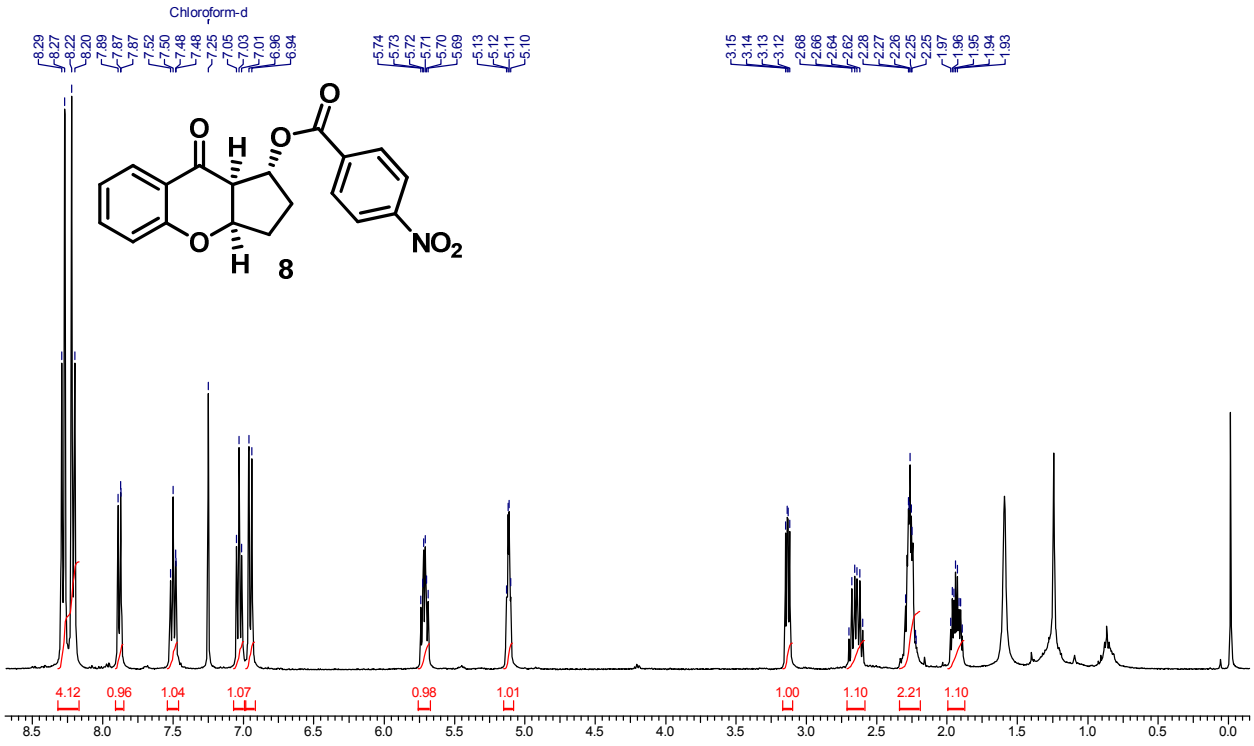
S. N	H	^{1}H NMR of Diaportheone B (Reported)		^{1}H NMR of Diaportheone B (400 MHz) (Synthesized)	
1	1-OH	1.95	1H, d, *J* = 7.0 Hz	1.98-2.09	3H, complex multiplet
2	H-2b	2.02-2.05	1H, overlapped		
3	H-3b	2.05-2.10	1H, overlapped		
4	H-2a	2.23-2.28	1H, m	2.21-2.29	1H, m
5	H-3a	2.37-2.42	1H, m	2.32-2.41	1H, m
6	H-13	2.78	1H, dd, *J* = 5.0, 7.0 Hz	2.78	1H, dd, *J* = 5.2, 6.2 Hz
7	H-1	4.76	1H, ddd, *J* = 2.5, 6.5, 13.0 Hz	4.74	1H, br m
8	H-7	4.97	1H, td, *J* = 3.2, 4.0 Hz	4.95	1H, m
9	H-7	6.40	1H, dd, *J* = 1.5, 8.5 Hz	6.39	1H, d, *J* = 8.2 Hz
10	H-9	6.50	1H, dd, *J* = 1.0, 8.0 Hz	6.48	1H, d, *J* = 8.2 Hz
11	H-8	7.34	1H, t, *J* = 8.0, Hz	7.33	1H, t, *J* = 8.2 Hz
12	10-OH	11.80	1H, s	11.86	1H, s

Table V: ^{13}C NMR data comparison between Reported and synthesized Diaportheone B

S.No	C	^{13}C NMR of Diaportheone B (ppm) (Reported)	^{13}C NMR of Diaportheone B (400 MHz) (ppm) (Synthesized)
1	C-12	198.3	198.3
2	C-10	161.9	161.9
3	C-6	161.3	161.2
4	C-8	138.6	138.5
5	C-9	109.6	109.5
6	C-11	109.3	109.2
7	C-7	107.6	107.6
8	C-4	81.8	81.7
9	C-1	75.5	75.4
10	C-13	55.4	55.4
11	C-2	33.8	33.7
12	C-3	31.8	31.7

Copies of ^{1}H, ^{13}C NMR spectra and HPLC chromatograms:

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O
O
H
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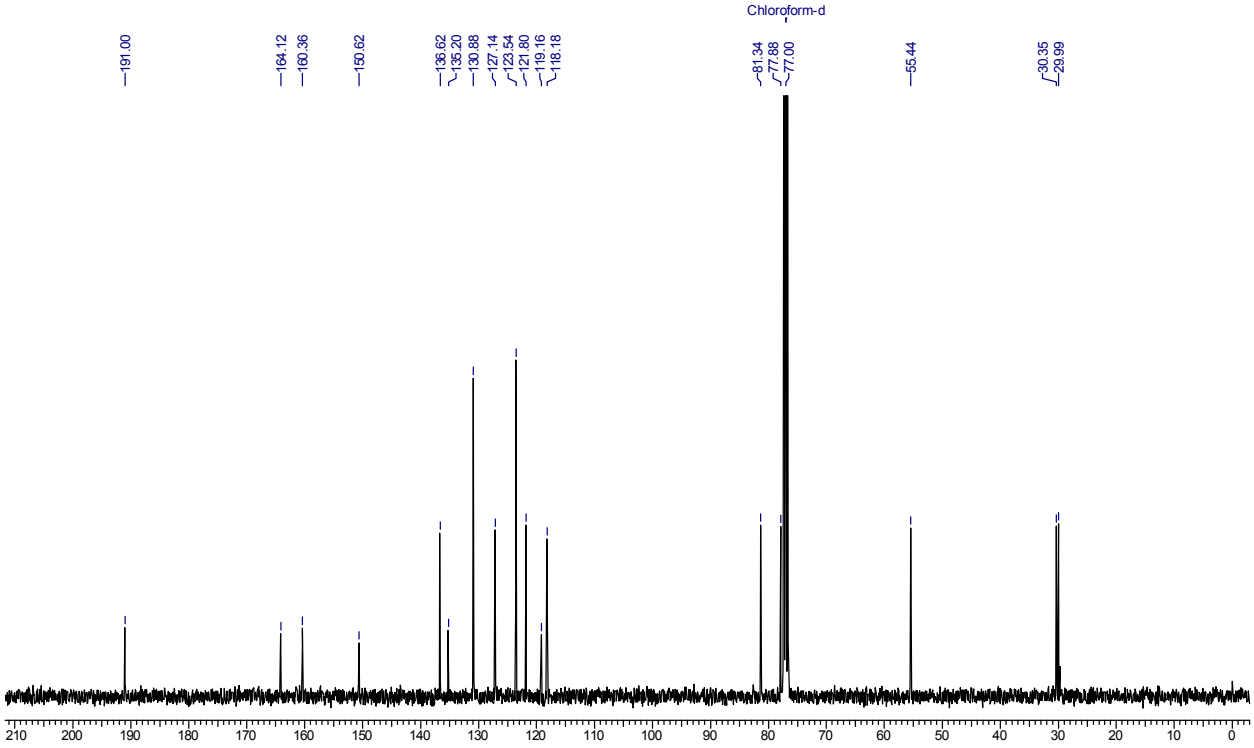
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81.34
77.88
77.00
55.44
30.35
29.99
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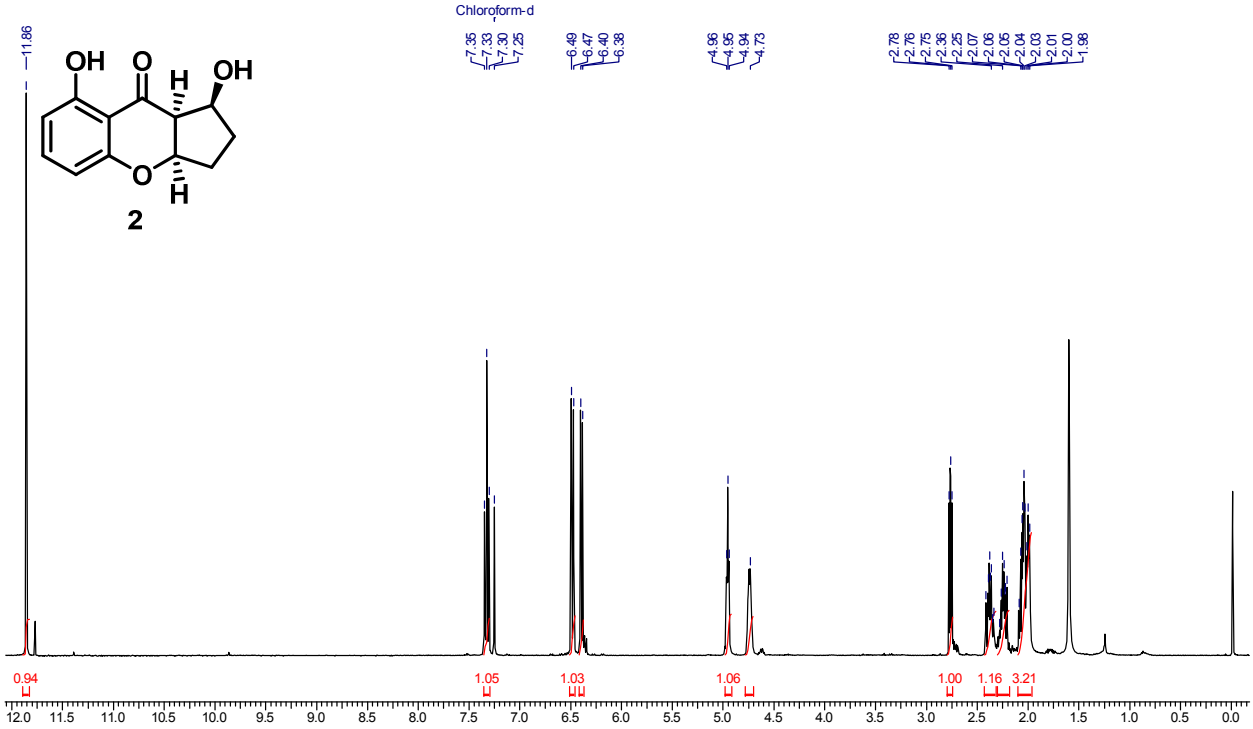

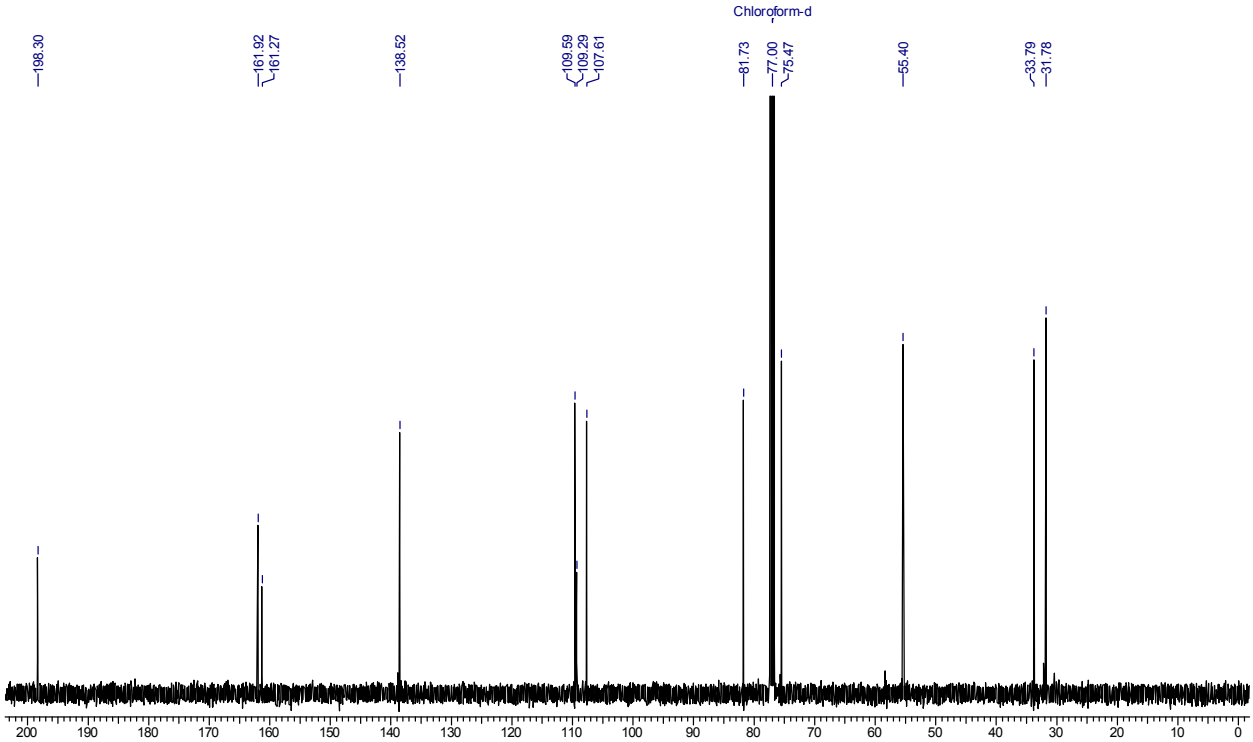

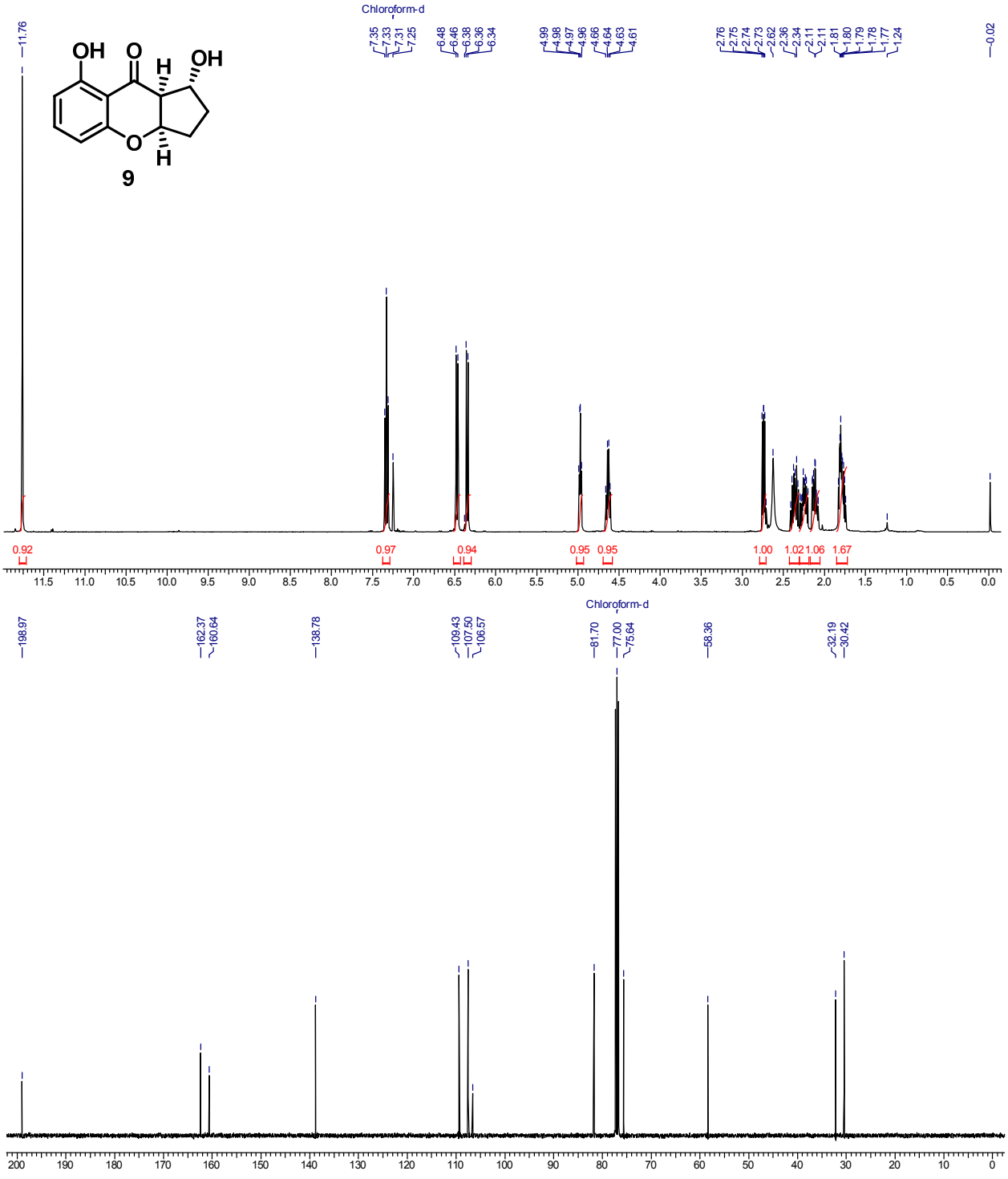

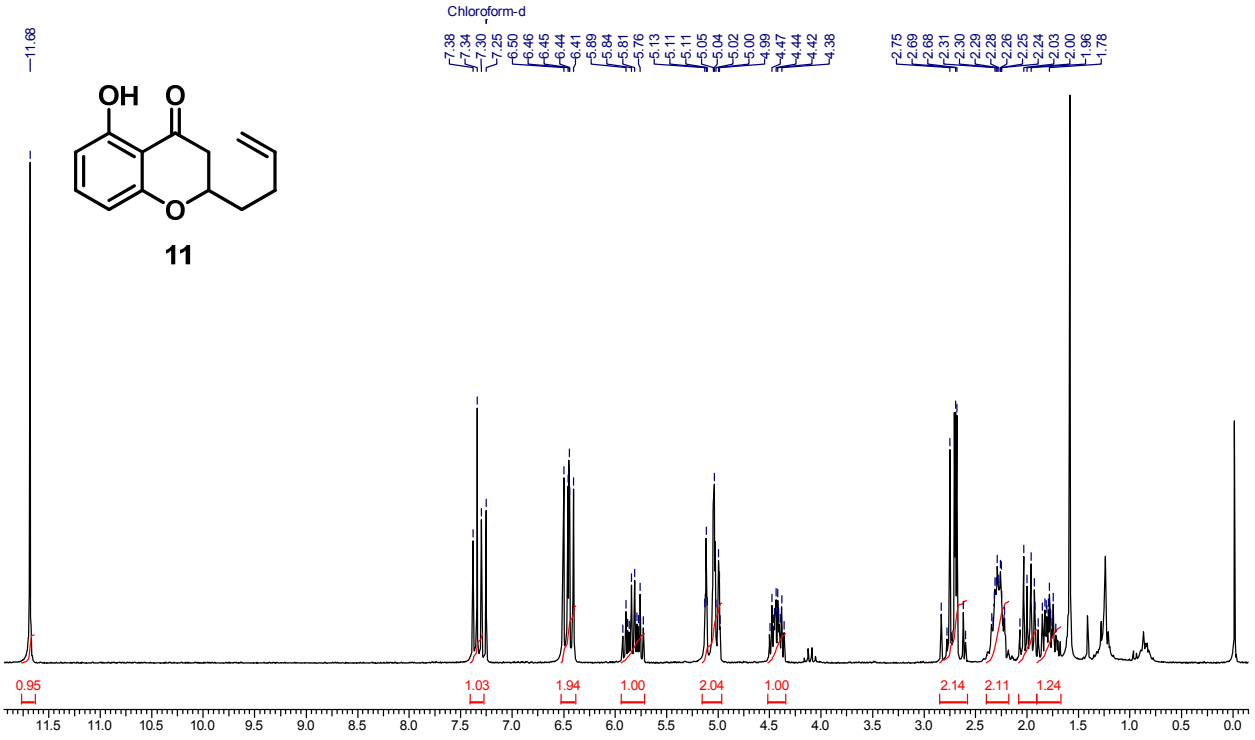

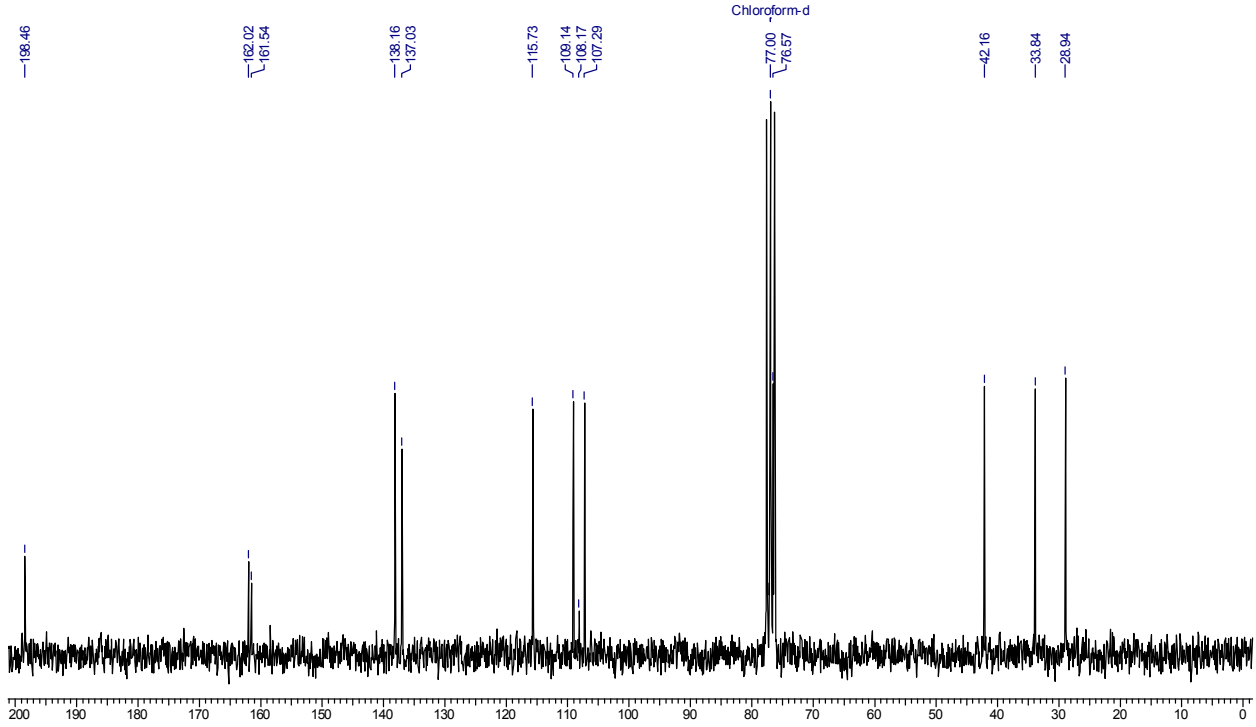

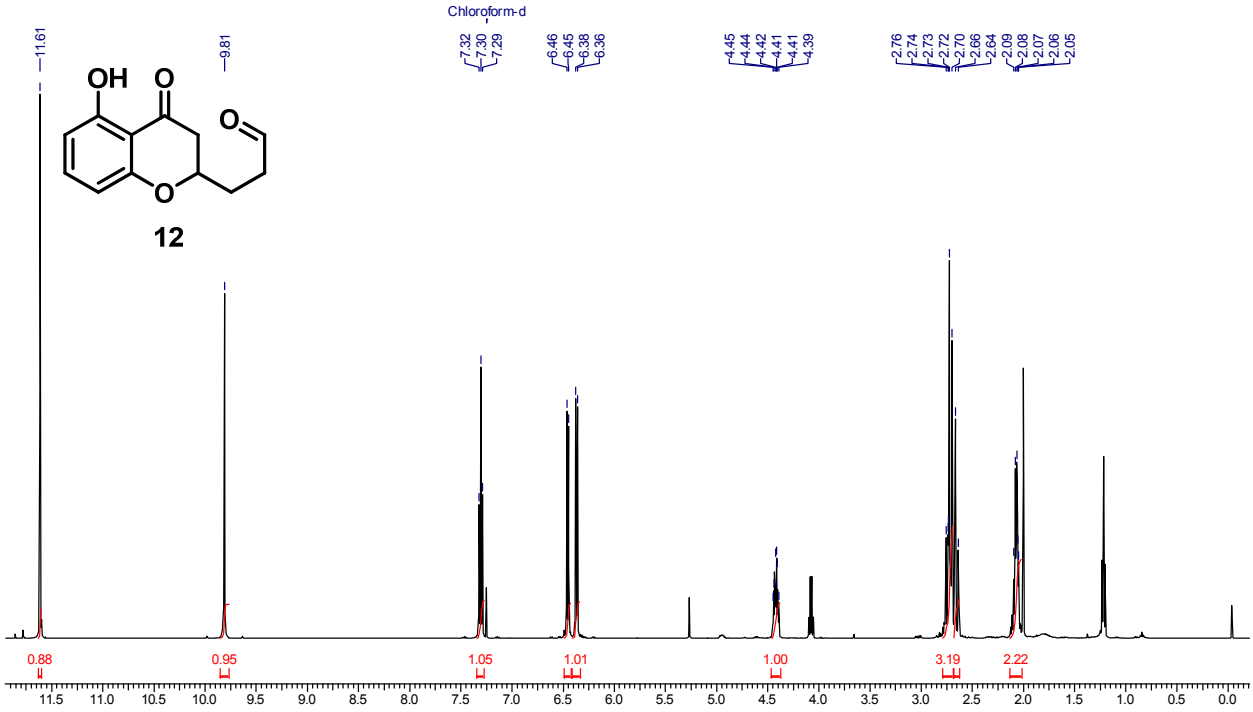

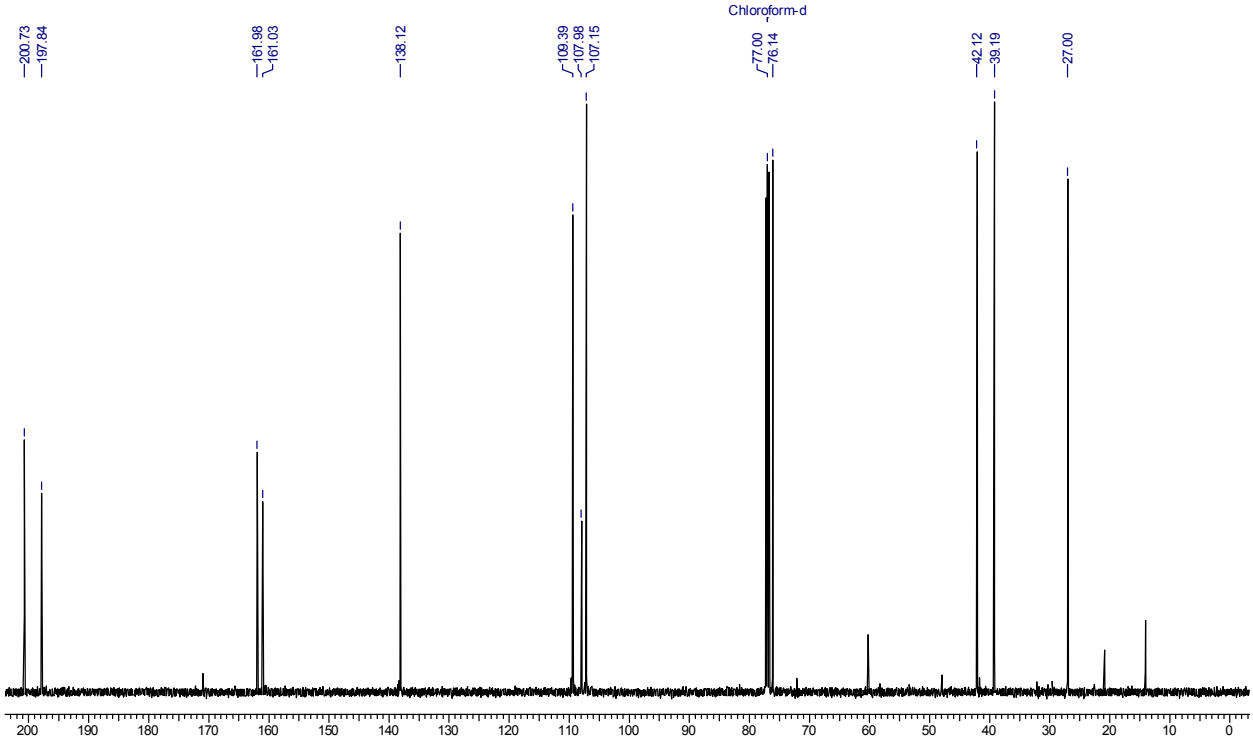

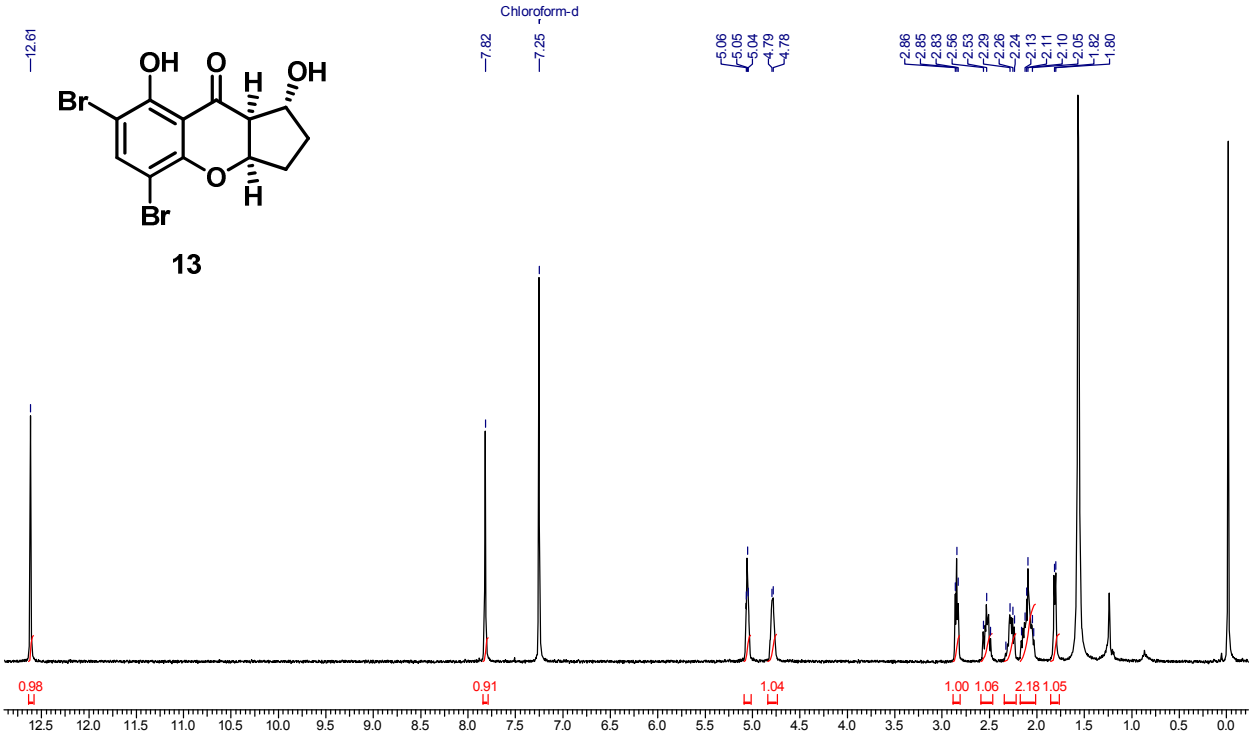

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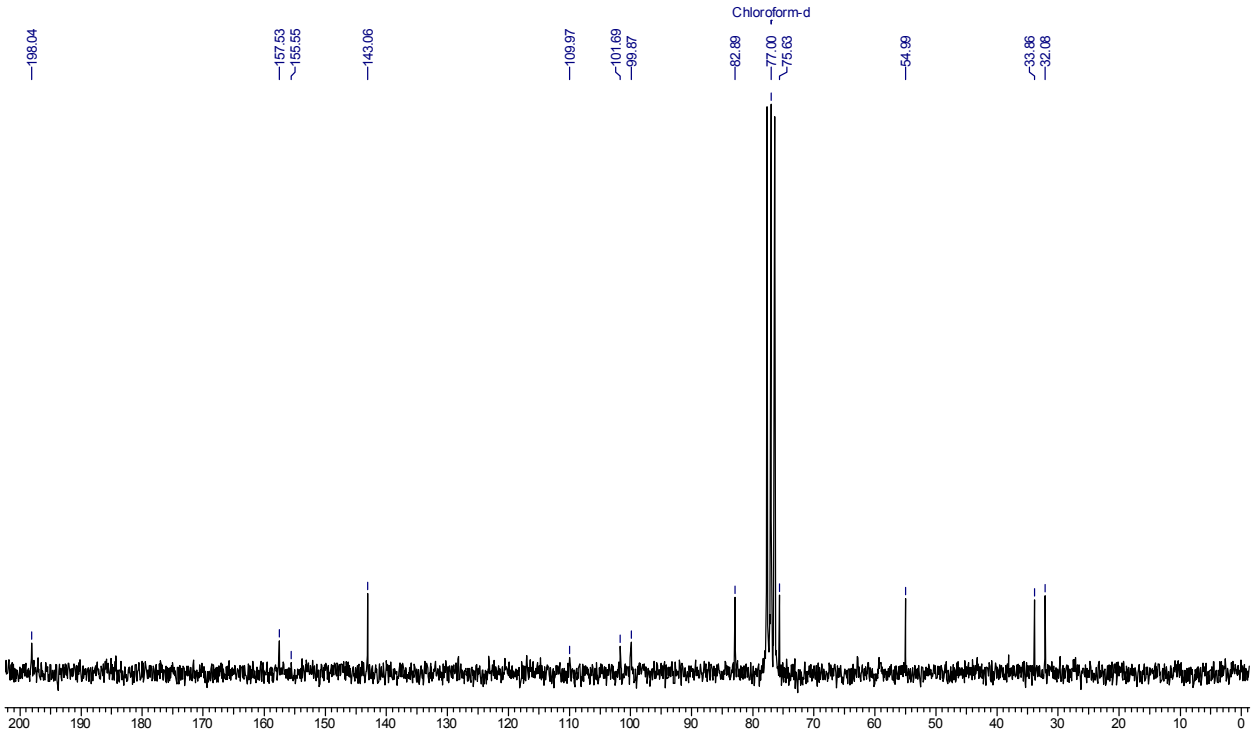

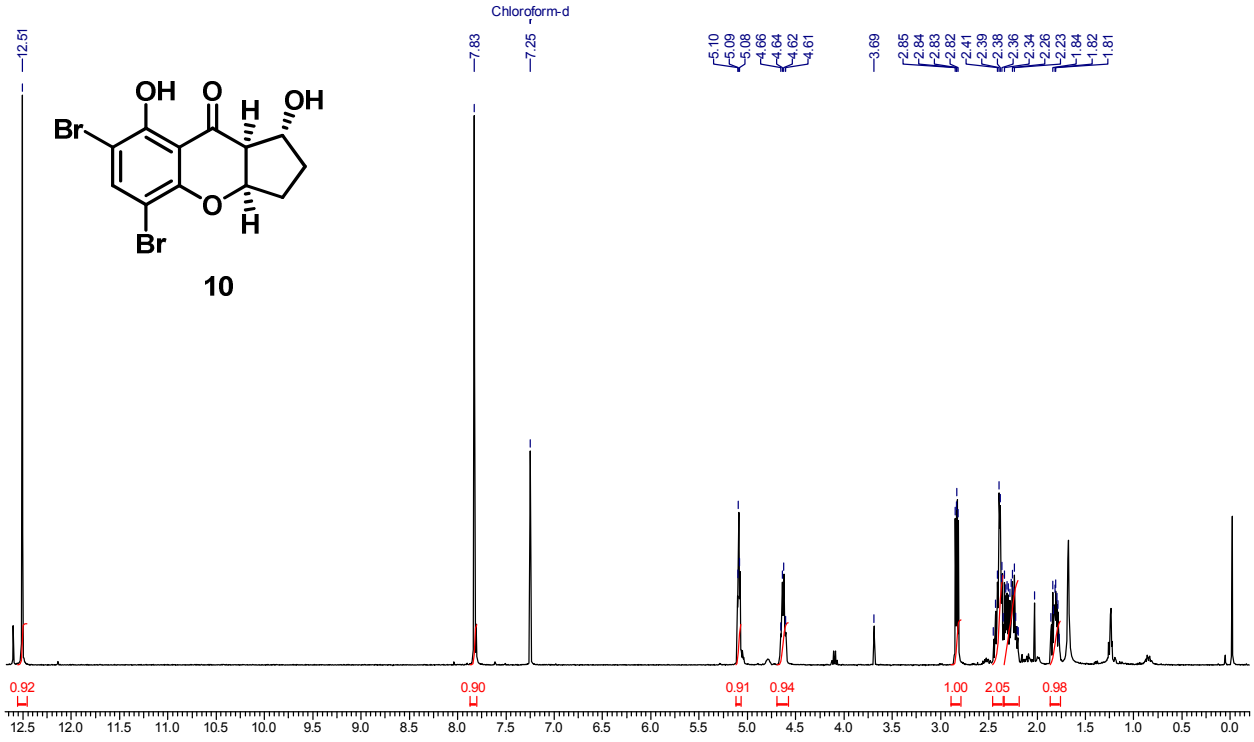

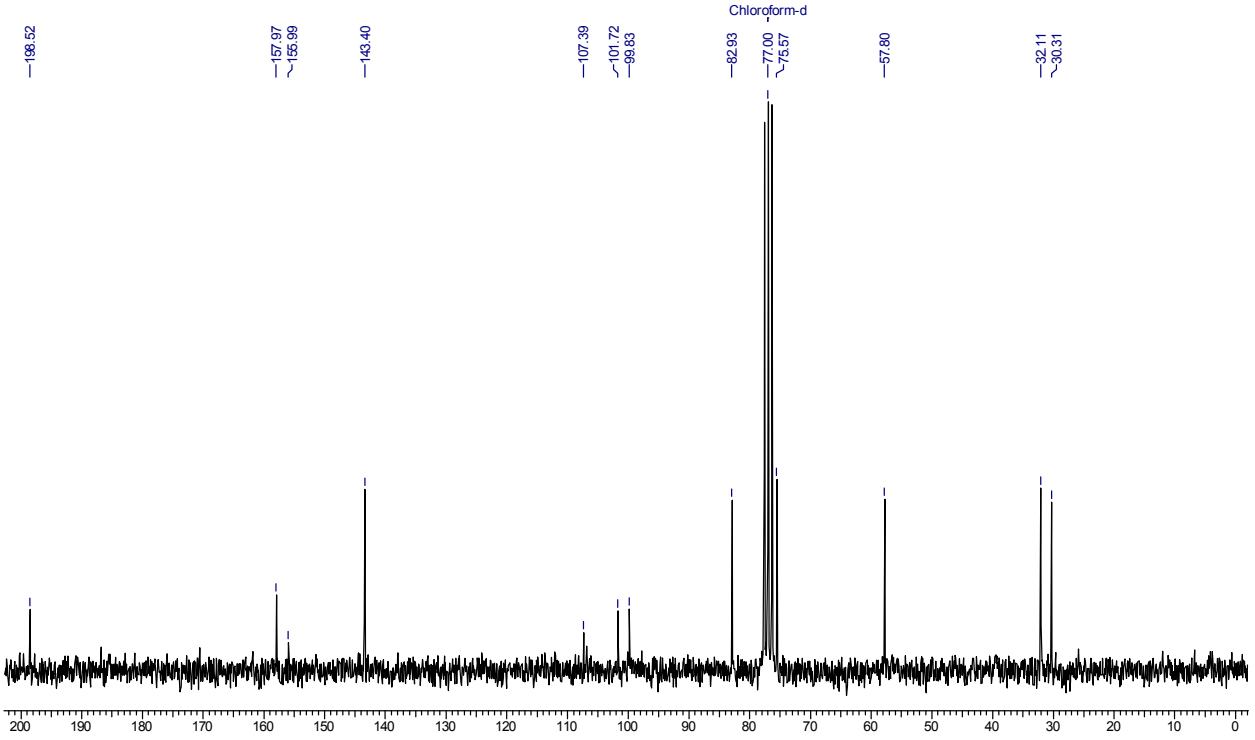

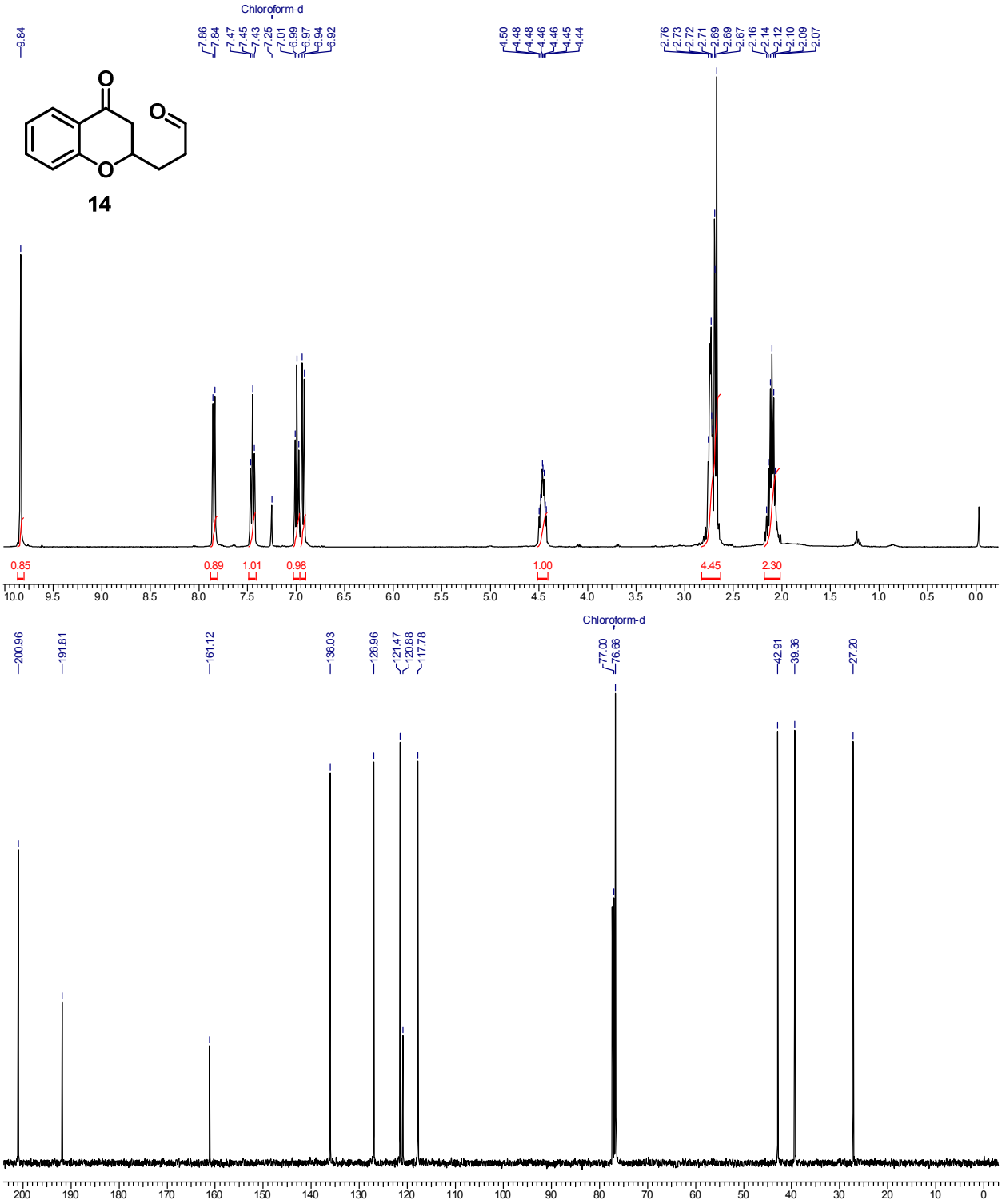
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2.09
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O
O
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0.98
1.00
4.45
2.30
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
Chloroform-d
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126.96
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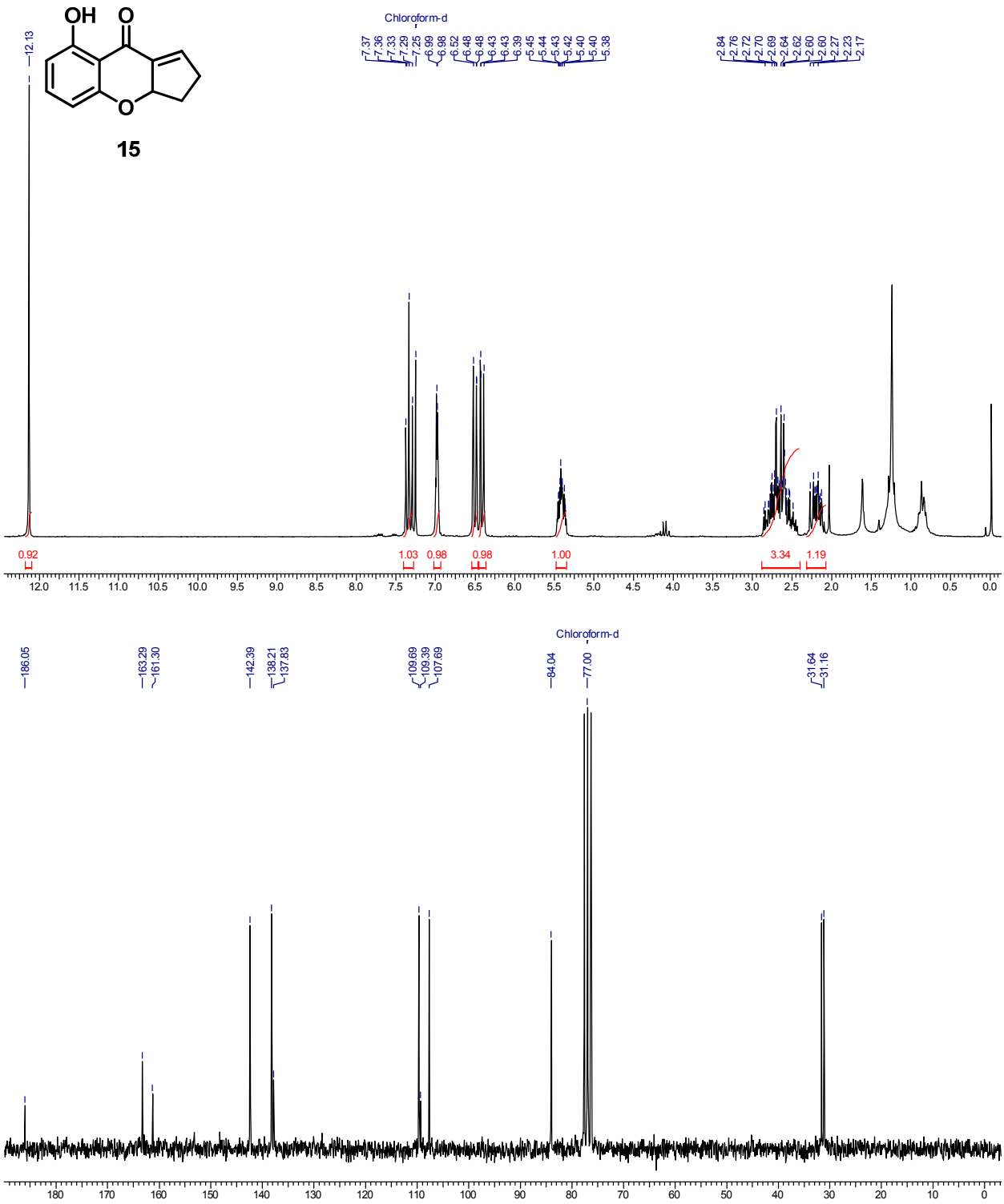

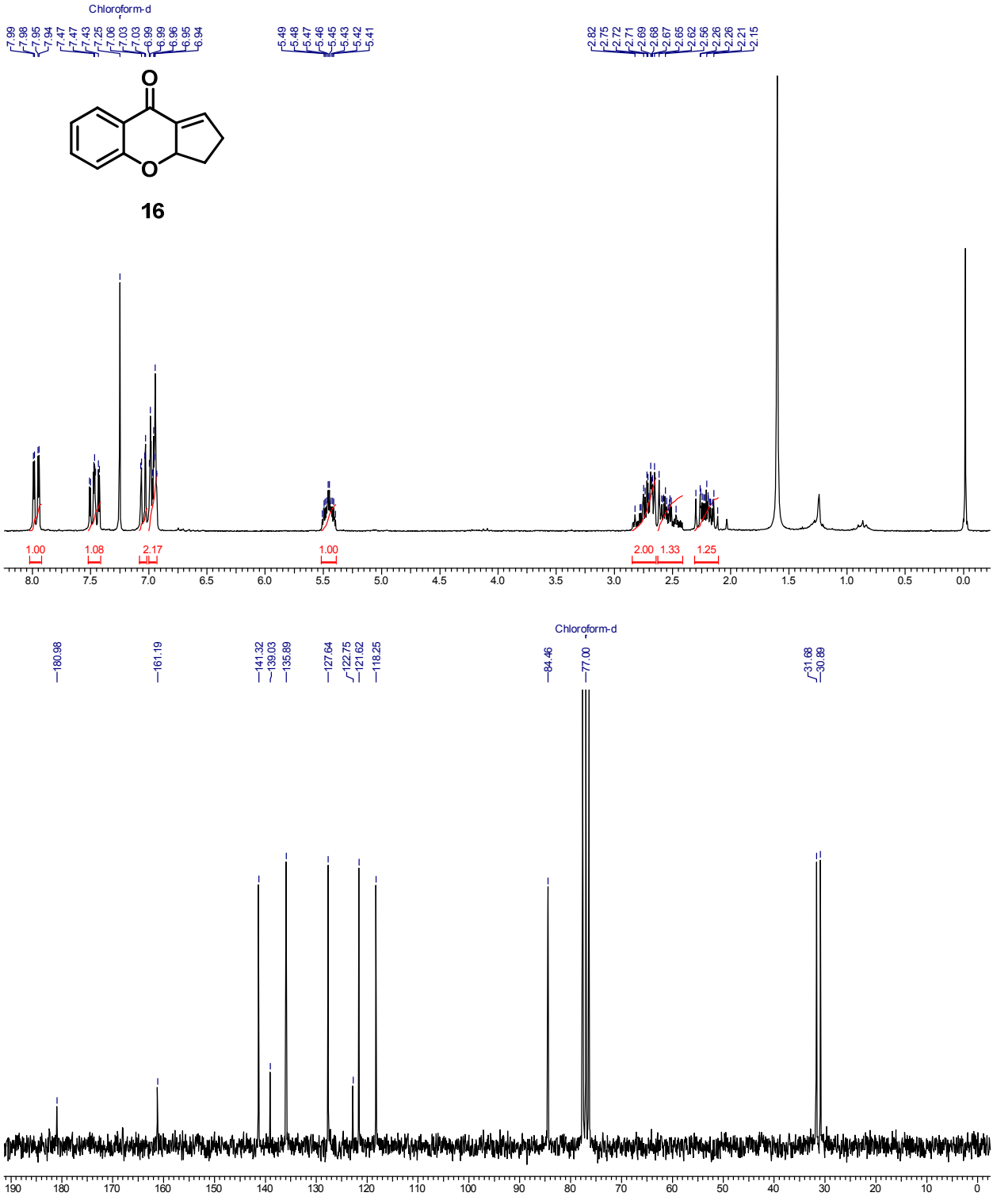

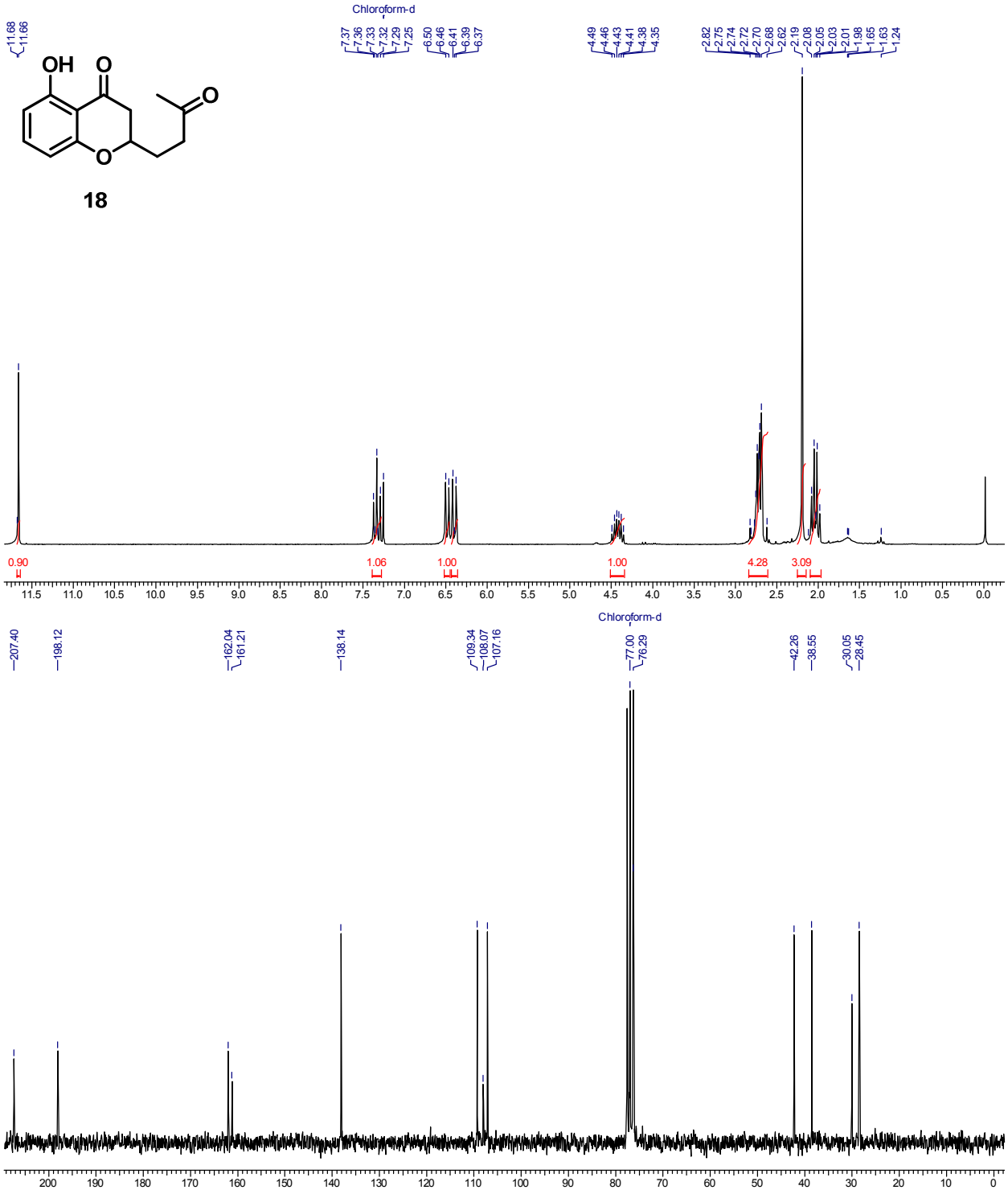

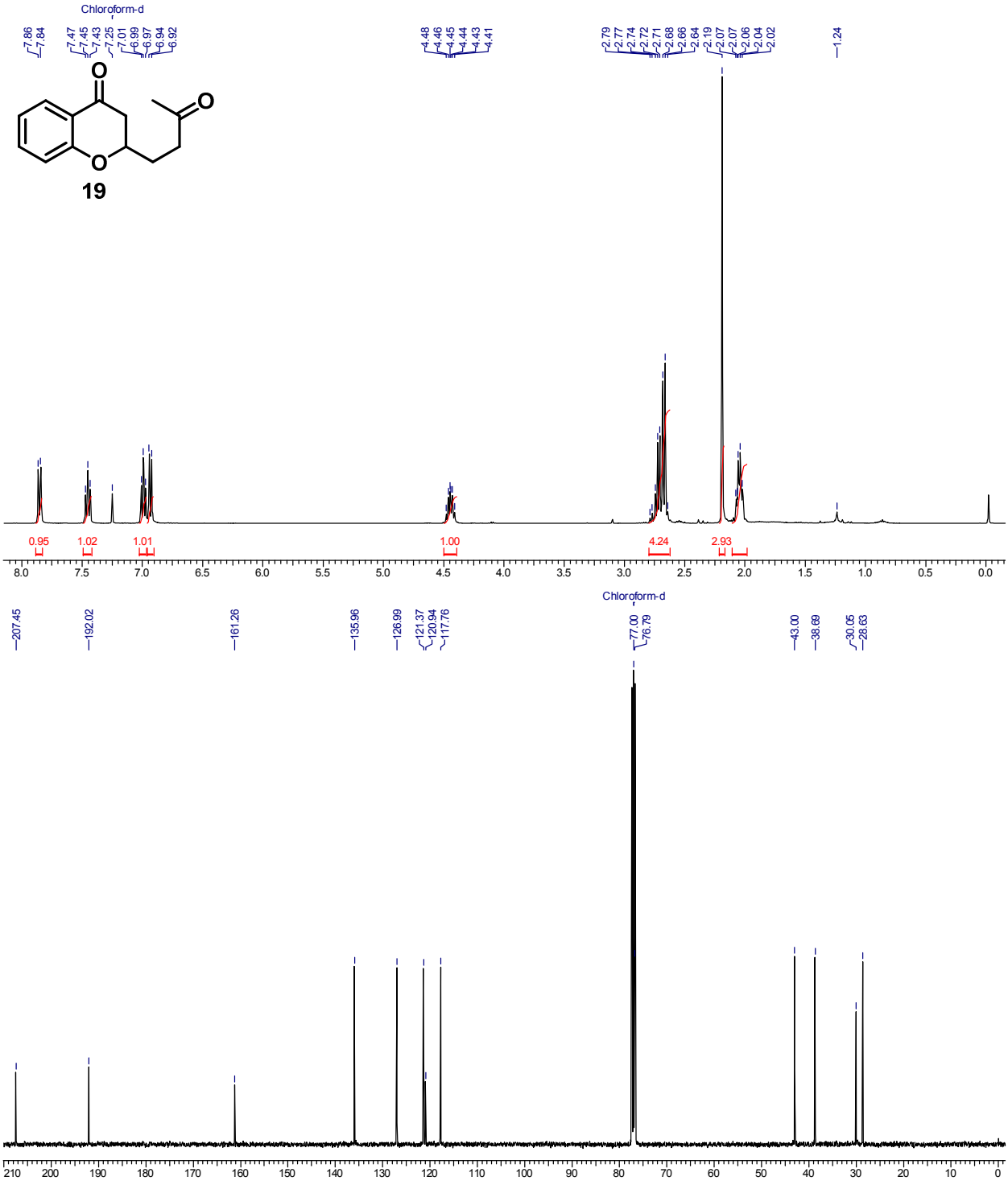

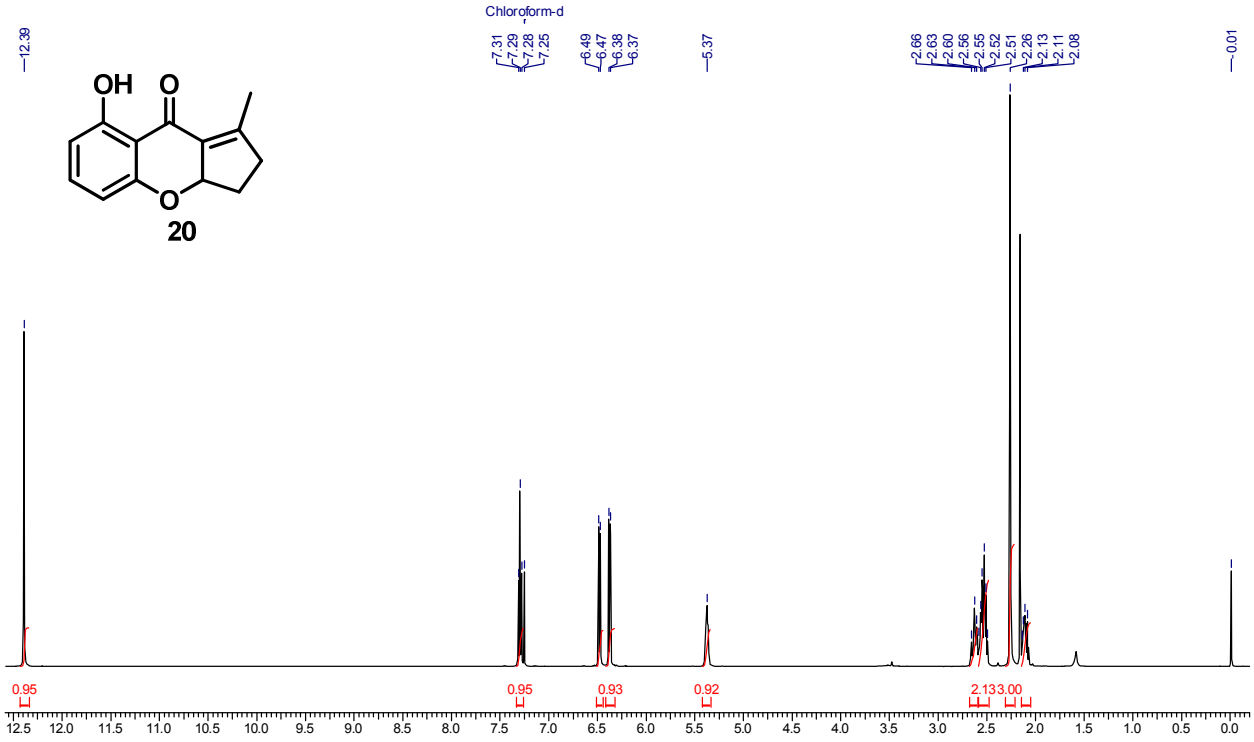

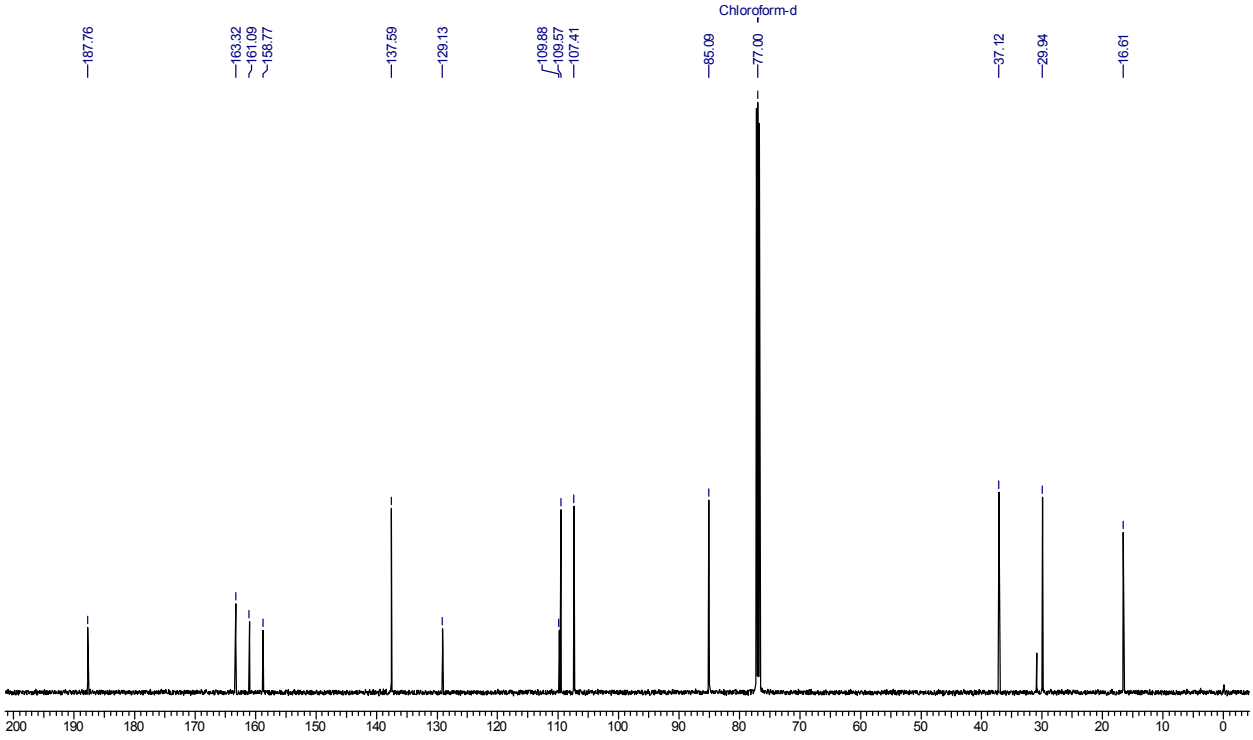

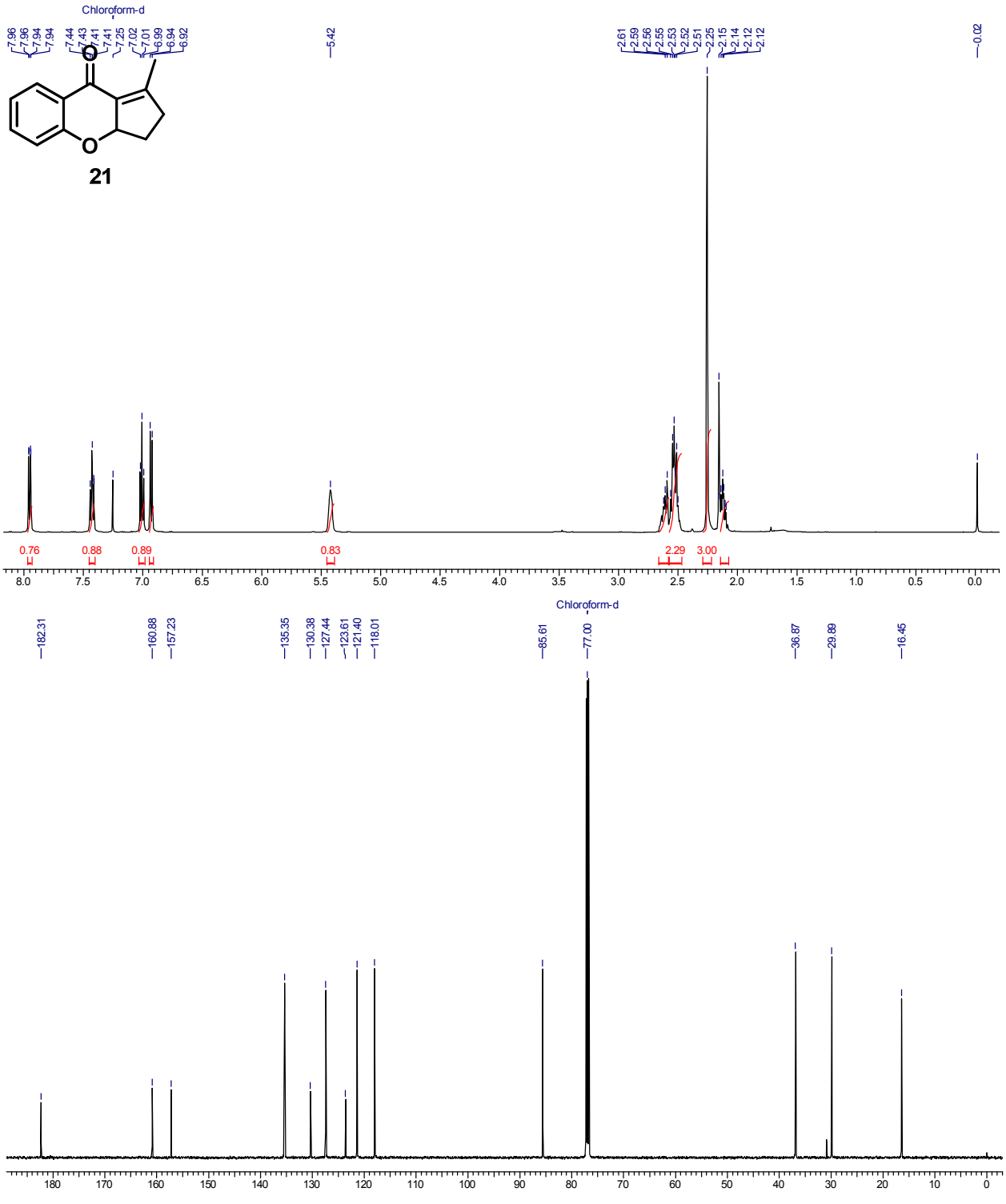

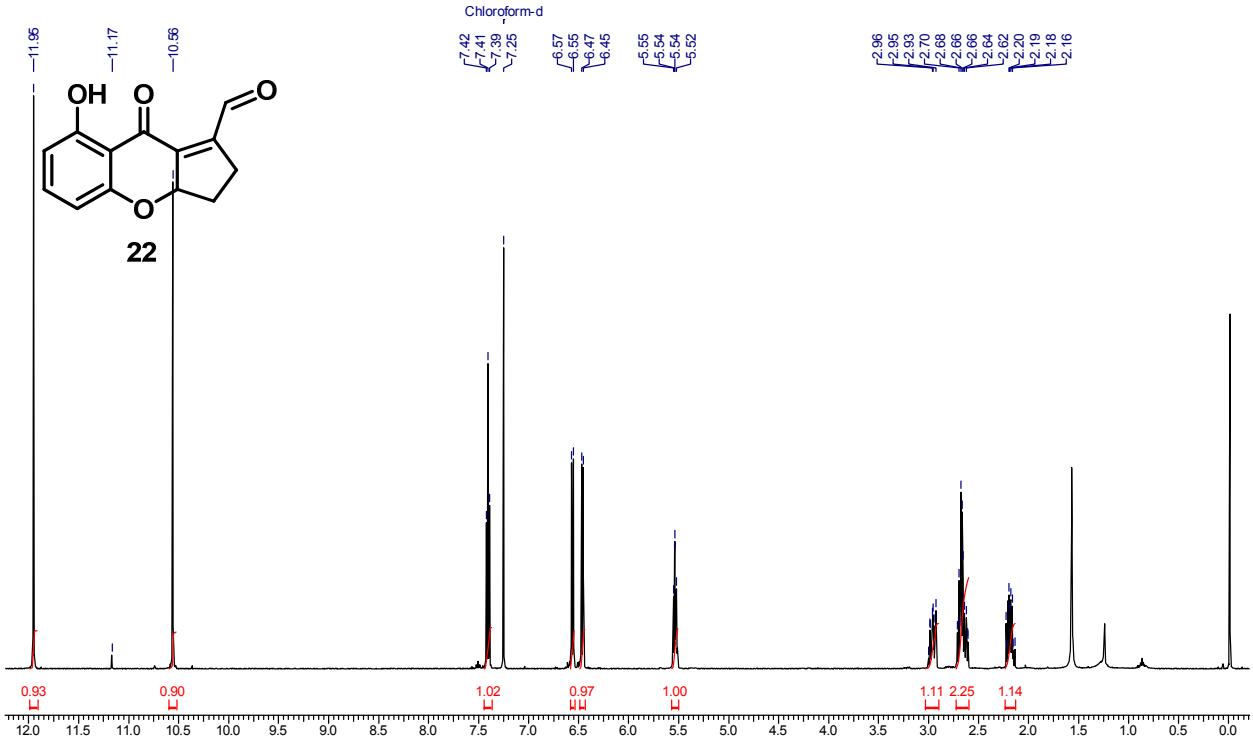
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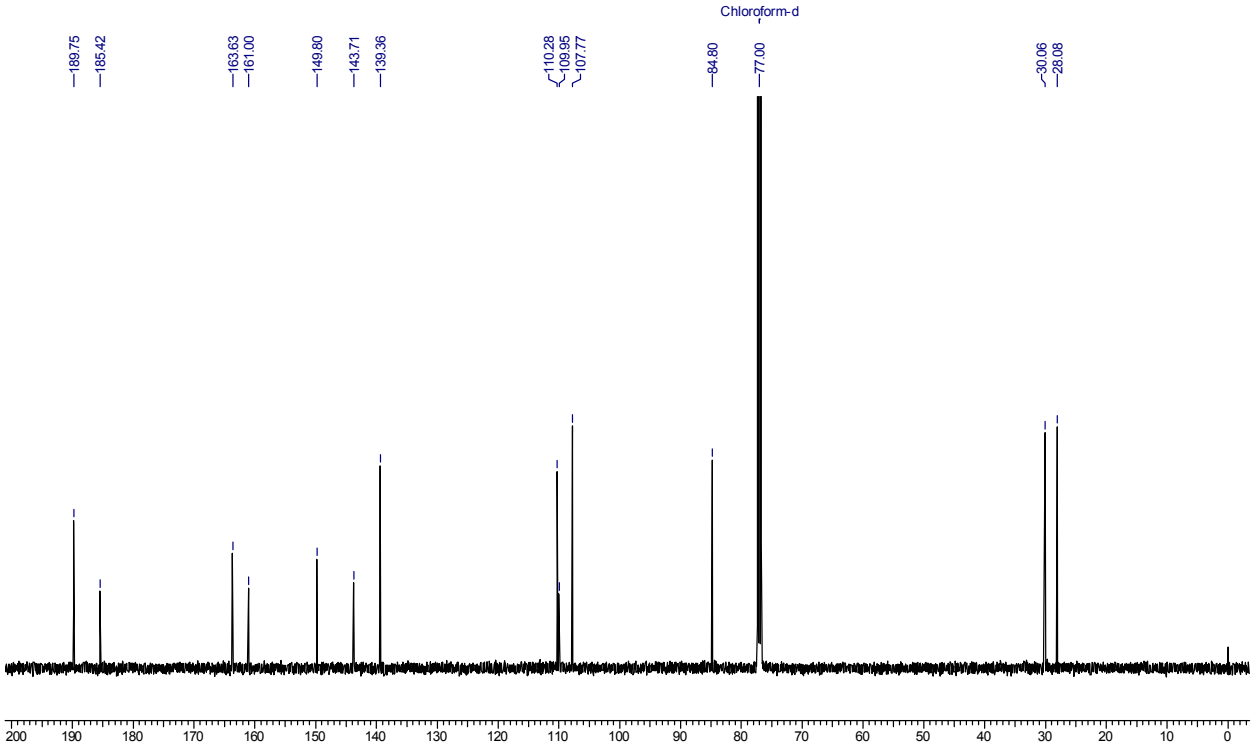
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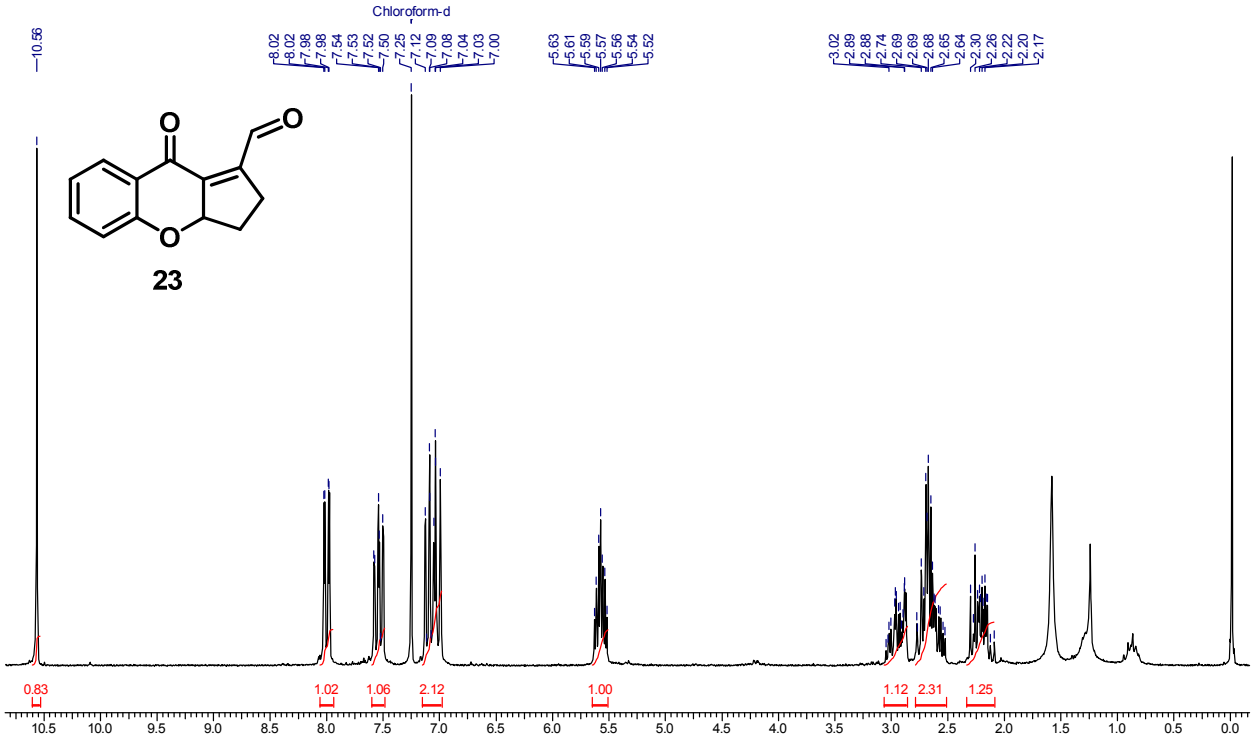

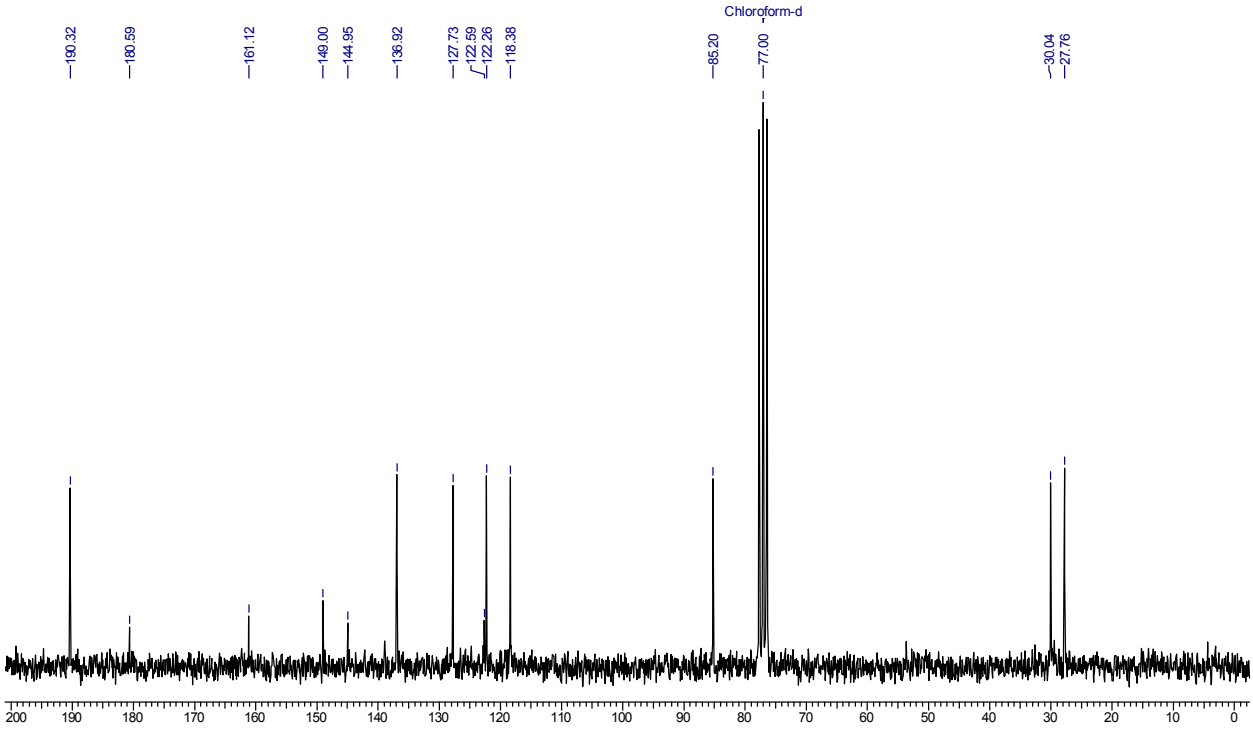

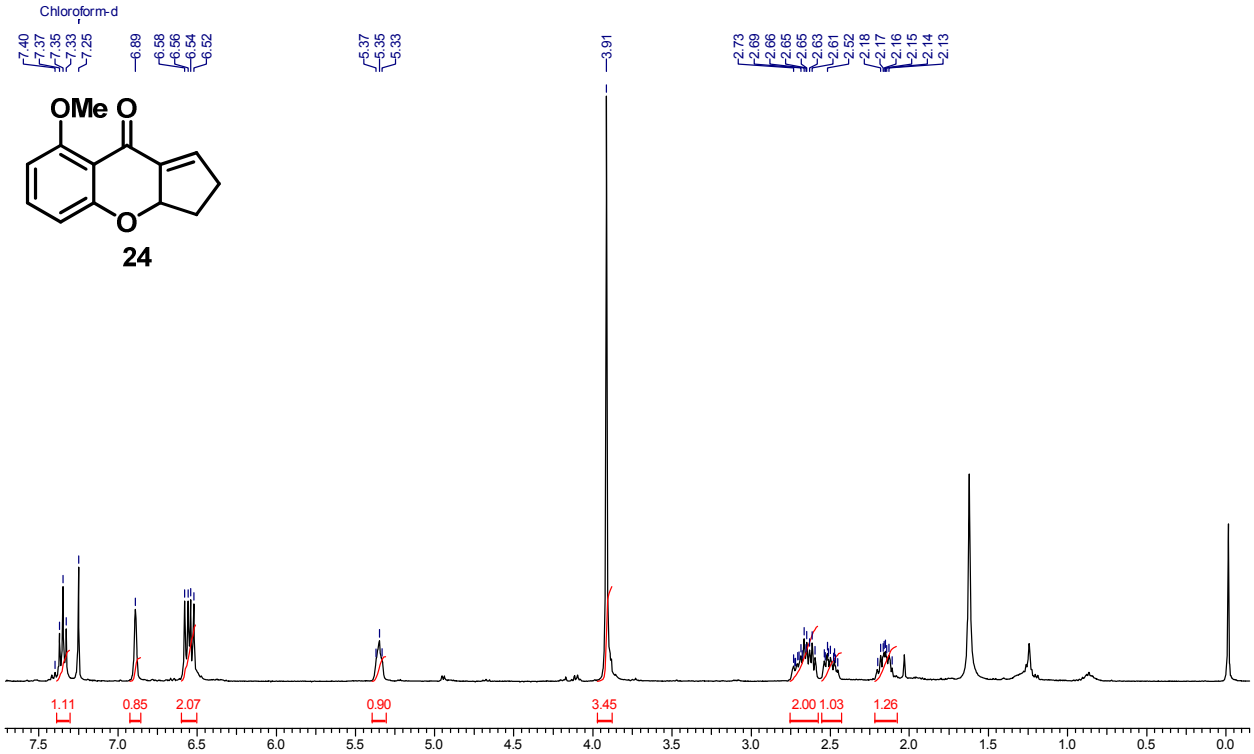
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2.61
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2.16
2.15
2.14
2.13
OMe O
O
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0.90
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2.00
1.03
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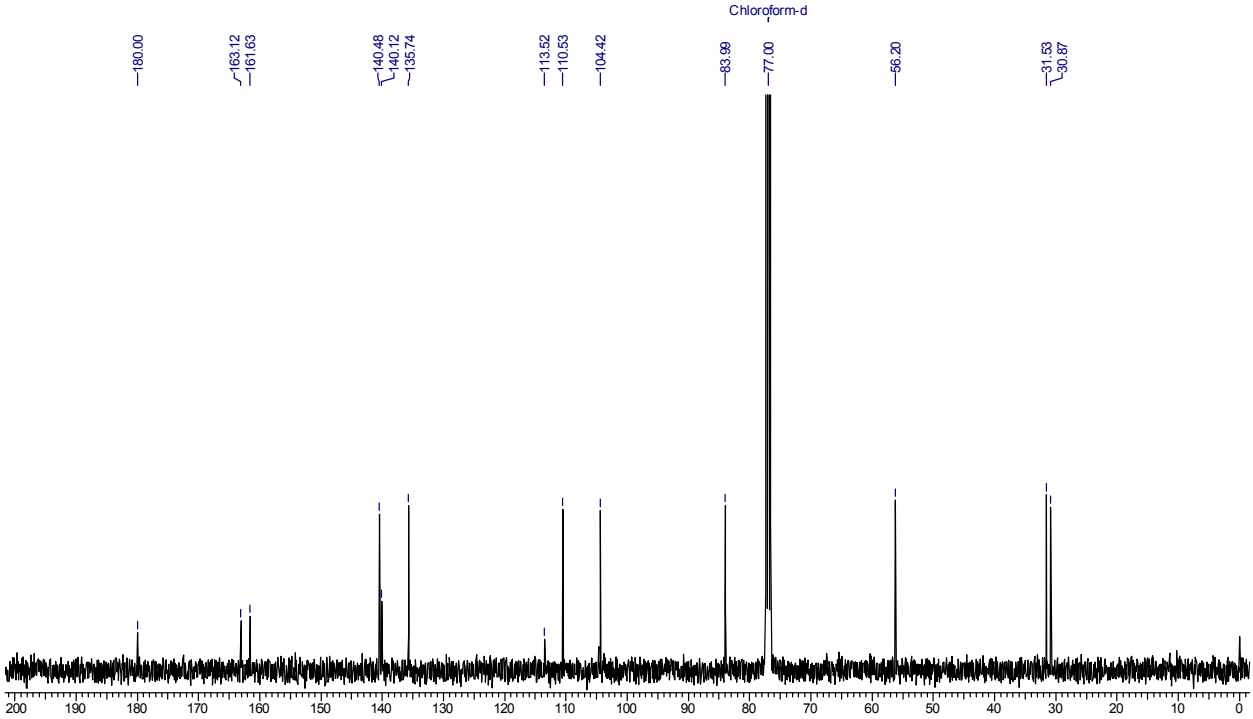
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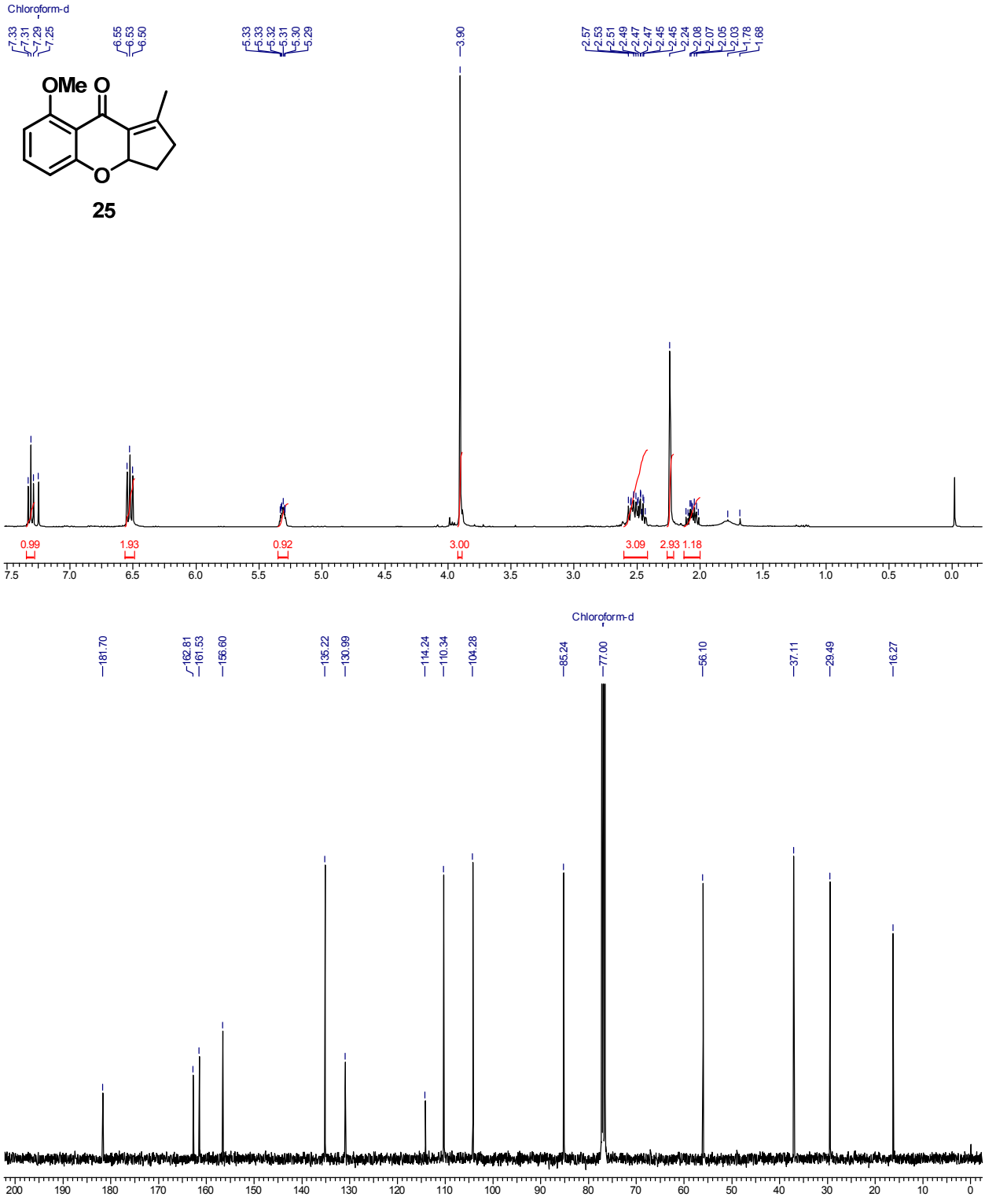

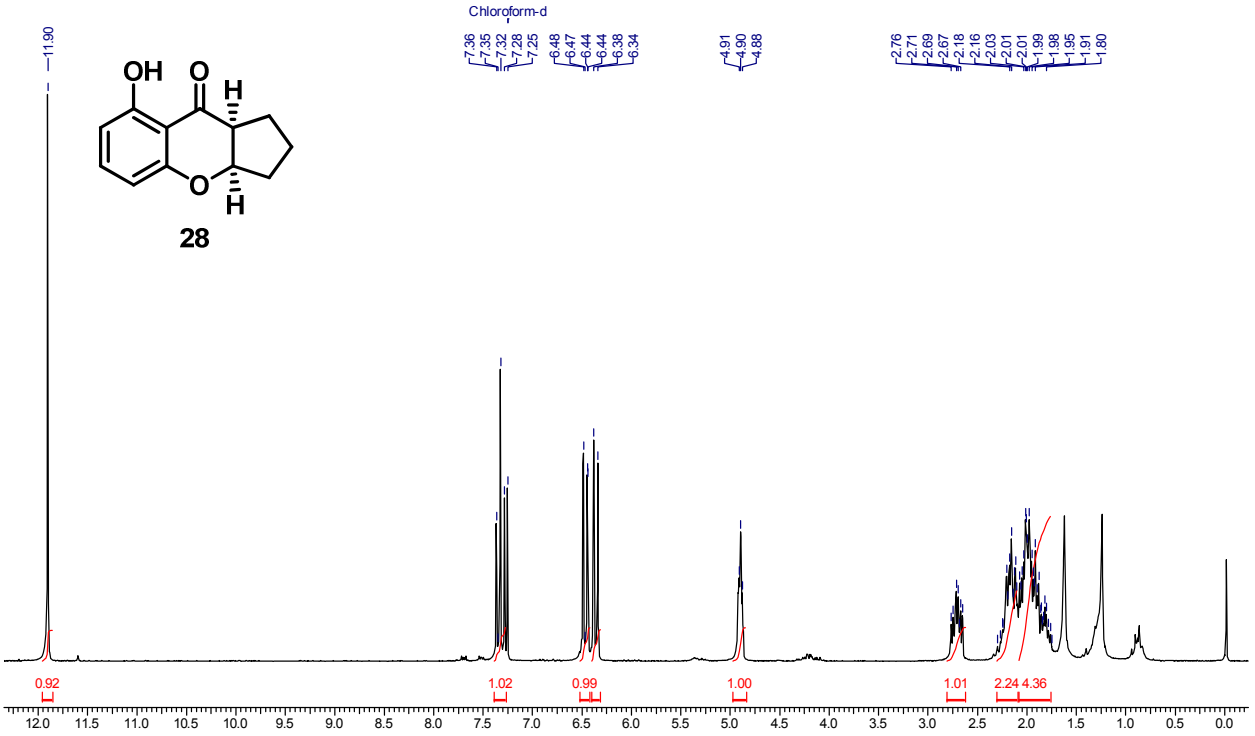

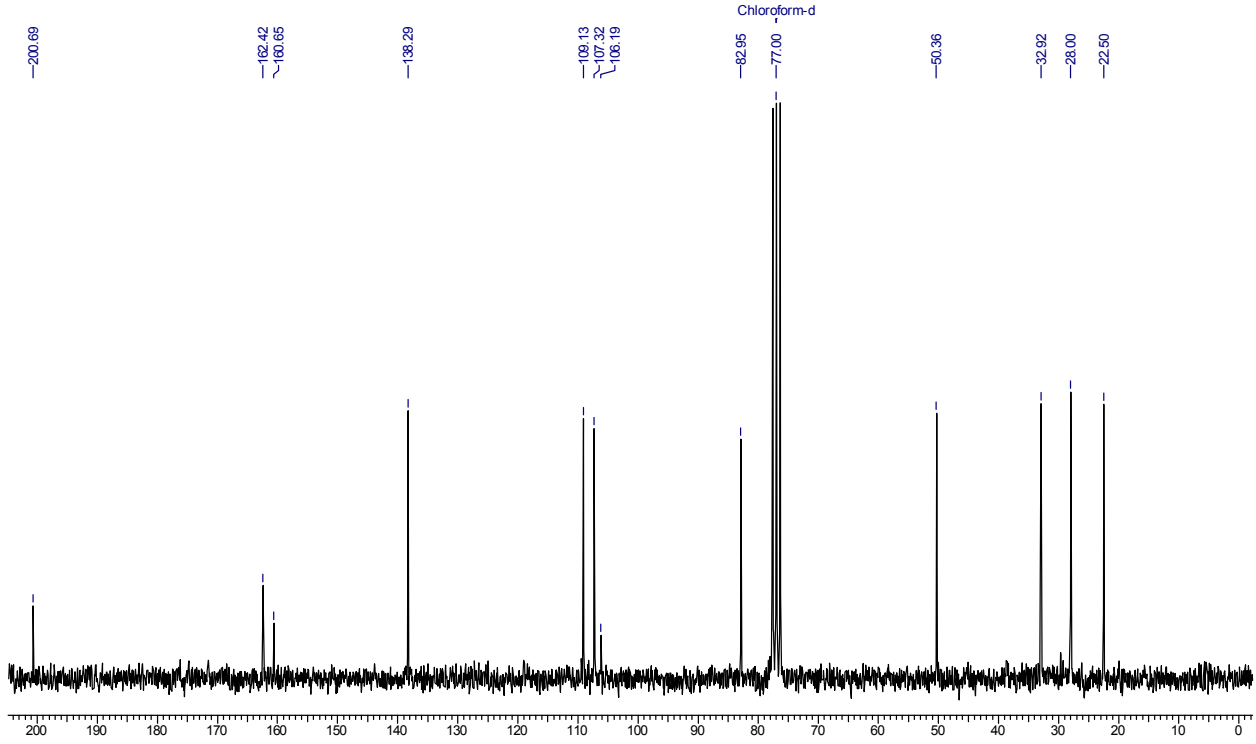

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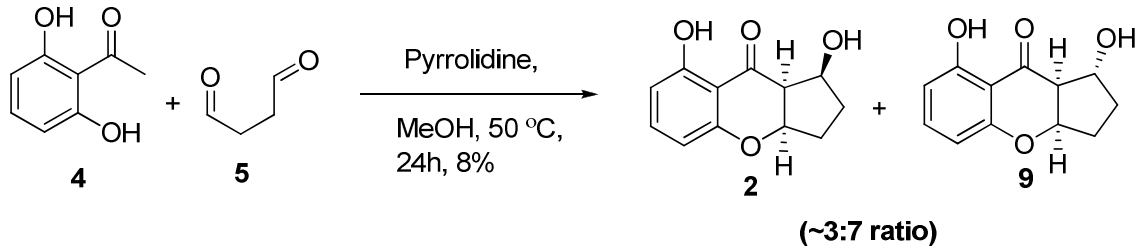

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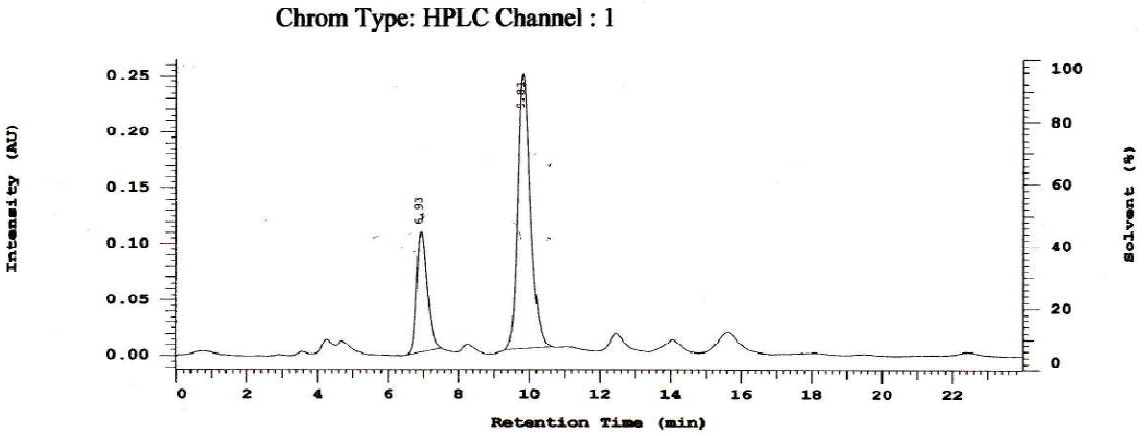

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2	9.81	122636	3069198	73.614
		176340	4169330	100.000

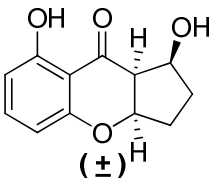
Column: Atlantis RP-18 (250 x 4.6 mm)

Mobile phase: MeOH:H_2O (50:50)

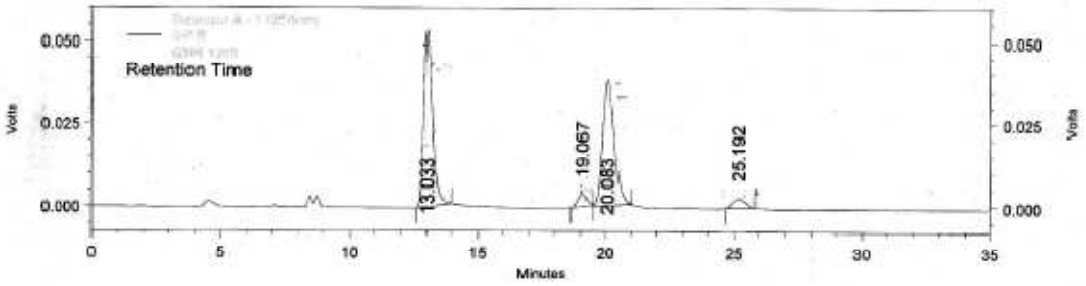
Wavelength: 254 nm

Flow rate: 1mL/min (2900 psi)

Sample conc: 1mg/mL (Inj vol – 10 µL)

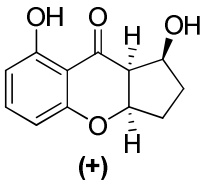


(±)



Detector A - 1 (254nm)

Retention Time	C Area	Area %
13.033	1149396	45.451
19.067	101063	3.996
20.083	1177268	46.553
25.192	101158	4.000
Totals	2528885	100.000



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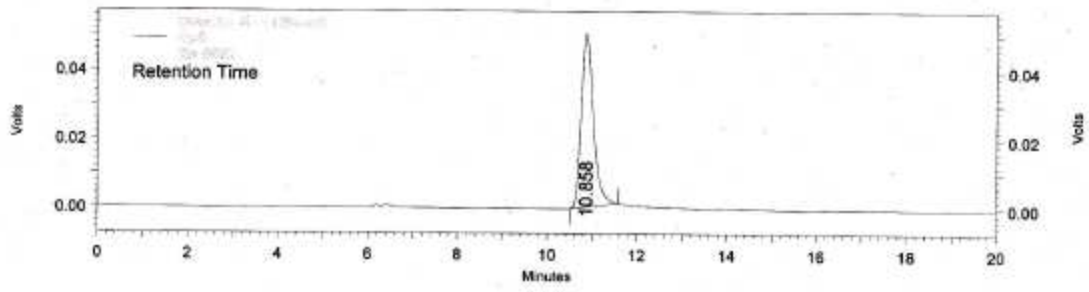
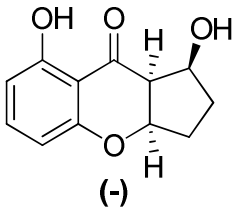


Detector A - 1 (254nm)

Retention Time	C Area	Area %
10.858	944985	100.000
Totals	944985	100.000



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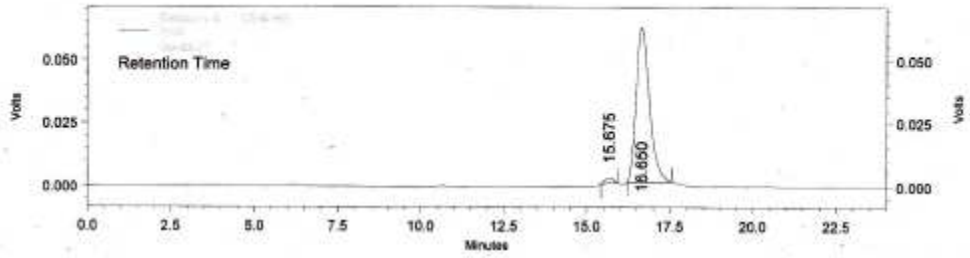


Detector A - 1 (254nm)

Retention Time	C Area	Area %
15.675	35815	2.046
16.650	1714609	97.954
Totals	1750424	100.000

Column: Kromasil 5-AmyCoat (250 x 4.6 mm)

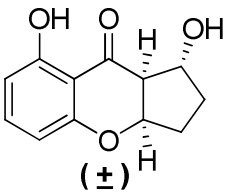
Mobile phase: IPA:n-Hexane (15:85)

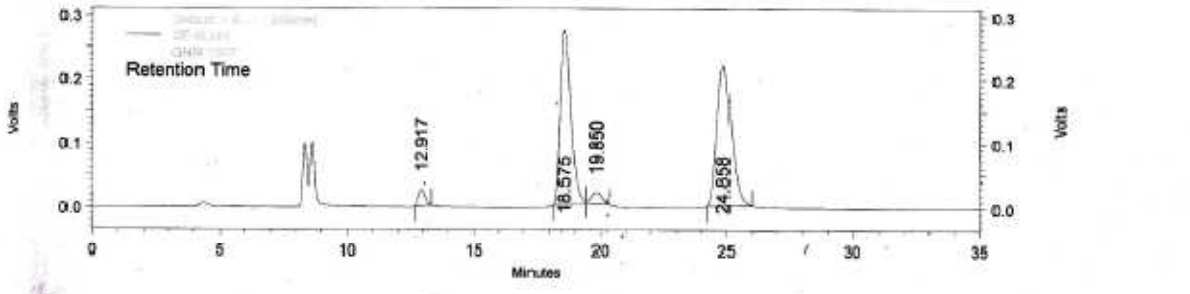
Wavelength: 254 nm

Flowrate: 0.7 mL/min 470 psi

Conc: 1.0 mg/mL

Inj vol: 10μL





Detector A - 1 (254nm)

Retention Time	C Area	Area %
12.917	478538	2.733
18.575	8190720	46.787
19.850	500415	2.858
24.858	8336871	47.621
Totals	17506544	100.000

Column: Kromasil 5-AmyCoat (250 x 4.6 mm)

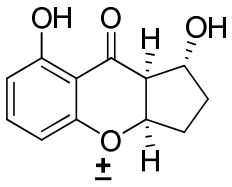
Mobile phase: IPA:n-Hexane (15:85)

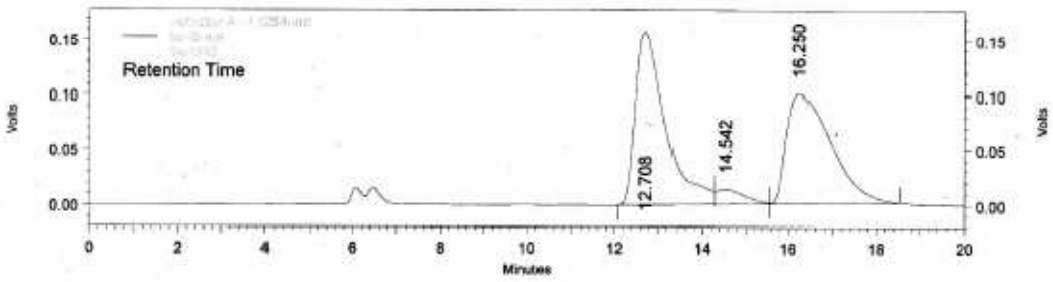
Wavelength: 254 nm

Flowrate: 0.7 mL/min 470 psi

Conc: 1.0 mg/mL

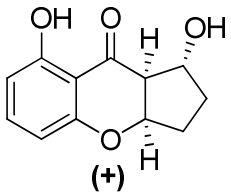
Inj vol: 10µL

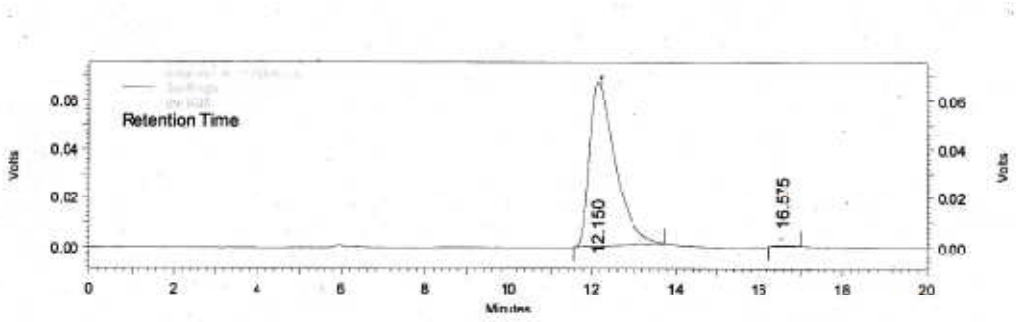




Detector A - 1 (254nm)

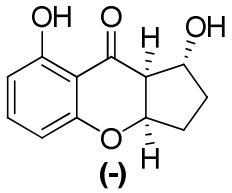
Retention Time	C Area	Area %
12.708	7493670	49.773
14.542	618361	4.107
16.250	6943620	46.120
Totals	15055651	100.000





Detector A - 1 (254nm)

Retention Time	C Area	Area %
12.150	2781270	99.531
15.575	13104	0.469
Totals	2794374	100.000



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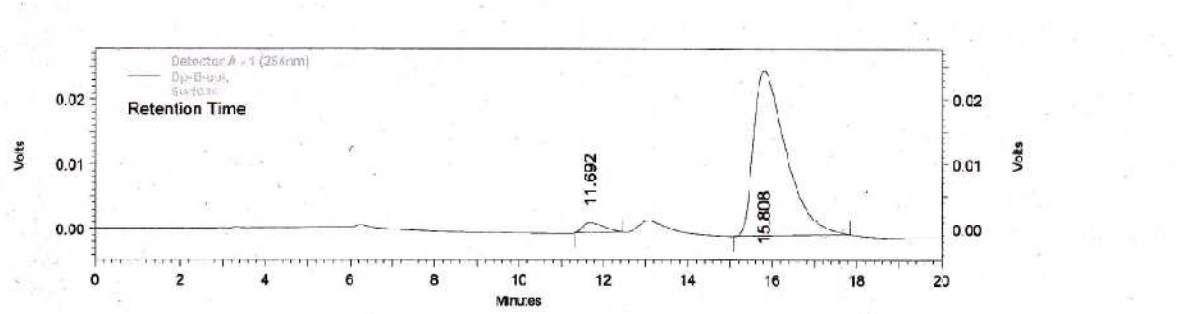

Detector A - 1 (254nm)

Retention Time	C Area	Area %
11.692	54087	3.802
15.808	1368417	96.198
Totals	1422504	100.000

Column: Chiralcel- OD (250 x 4.6 mm)

Mobile phase: IPA:n-Hexane (9:91)

Wavelength: 254 nm

Flowrate: 1 mL/min 560 psi

Conc: 20.0 mg/mL

Inj vol: 7.5 µL

Details of X-Ray Crystal Structure analysis

Single crystals of compounds **8, 10** and **13** were obtained from DCM/Pentane by diffusion crystallization method. X-ray intensity data were collected on an X-ray diffractometer with graphite-monochromatized (Mo Kα=0.71073 Å) radiation at room temperature.

Crystallographic data for 8: ($C_{19}H_{15}N_1O_6$): M = 353.32, Crystal dimensions 0.49 x 0.16 x 0.10 mm^3, monoclinic, space group $P\ 2_1/c$, a = 8.0391(17), b = 18.123(3), c = 11.275(2) Å, β = 105.499(9), V = 1582.9(5) $Å^3$, Z = 4, ρ_{calcd} = 1.483 gcm^{-3}, μ (Mo-K_α) = 0.112 mm^{-1}, *F(000)* = 736, $2\theta_{max}$ = 50.00°, T = 100(2) K, 9119 reflections collected, 2705 unique, 2128 observed ($I > 2\sigma(I)$) reflections, 236 refined parameters, R value 0.0718, $wR2$ = 0.1112, (all data R = 0.0967, $wR2$ = 0.1192), S = 1.171, minimum and maximum transmission 0.9472 and 0.9889; maximum and minimum residual electron densities +0.225 and –0.236 e $Å^{-3}$.

Crystallographic data for 10: ($C_{12}H_{10}Br_2O_4$): M = 378.02, Crystal dimensions 0.56 x 0.07 x 0.07 mm^3, triclinic, space group P -1, a = 7.6833(5), b = 12.1129(8), c = 13.7371(9) Å, α = 97.440(3), β = 97.440(3), γ = 102.311(3), V = 1222.16(14) $Å^3$, Z' = 2, Z = 4, ρ_{calcd} = 2.054 gcm^{-3}, μ (Mo-K_α) = 6.636 mm^{-1}, *F(000)* = 736, $2\theta_{max}$ = 54.00°, T = 100(2) K, 20413 reflections collected, 5313 unique, 4563 observed ($I > 2\sigma(I)$) reflections, 329 refined parameters, R value 0.0225, $wR2$ = 0.0492, (all data R = 0.0306, $wR2$ = 0.0521), S = 1.045, minimum and maximum transmission 0.1186 and 0.6538; maximum and minimum residual electron densities +0.682 and –0.638 e $Å^{-3}$.

Crystallographic data for 13: ($C_{12}H_{10}Br_2O_4$): M = 378.02, Crystal dimensions 0.35 x 0.10 x 0.03 mm^3, orthorhombic, space group $P\ 2_12_12_1$, a = 13.574(6), b = 17.699(8), c = 21.533(9) Å, V = 5173(4) $Å^3$, Z' = 4, Z = 16, ρ_{calcd} = 1.942 gcm^{-3}, μ (Mo-K_α) = 6.271 mm^{-1}, *F(000)* = 2944, $2\theta_{max}$ = 50.00°, T = 100(2) K, 79943 reflections collected, 9365 unique, 6701 observed ($I > 2\sigma(I)$) reflections, 657 refined parameters, R value 0.0352, $wR2$ = 0.0513, (all data R = 0.0702, $wR2$ = 0.0589), S = 1.020, minimum and maximum transmission 0.2176 and 0.8342; maximum and minimum residual electron densities +0.413 and –0.382 e $Å^{-3}$. The absolute configuration was established by anomalous dispersion effect (Flack parameter of -0.0032 (65)) in X-ray diffraction measurements which is caused by the presence of bromine atom in the molecule.