

Development of a Robust and Highly-Selective Ru(II)-Catalyzed Dynamic Kinetic Resolution Used to Manufacture AMG 232

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Supporting Information

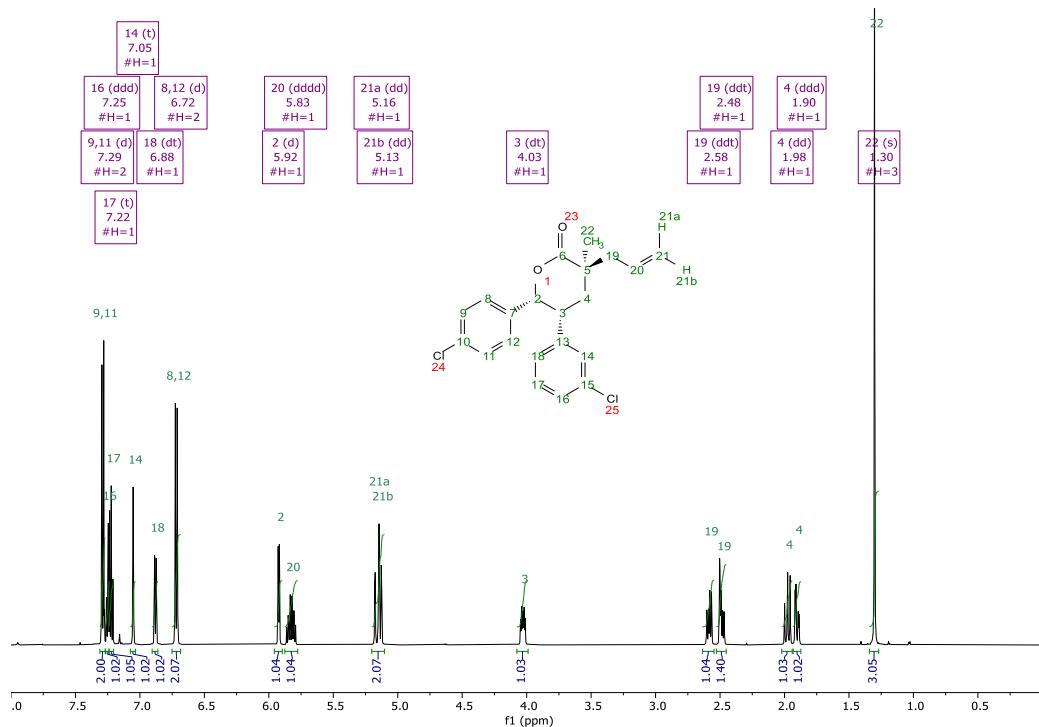
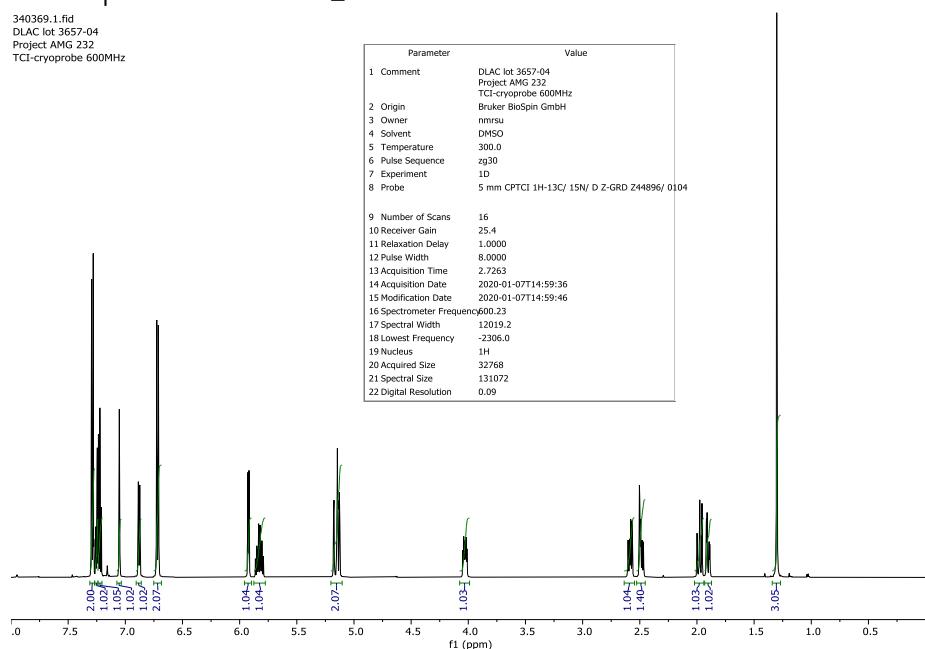
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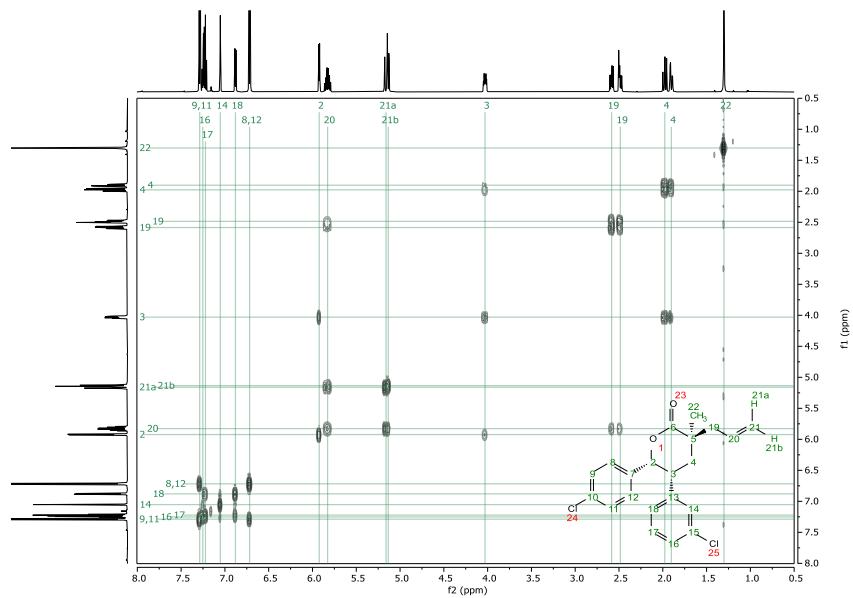
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NMR spectra for DLAC 2

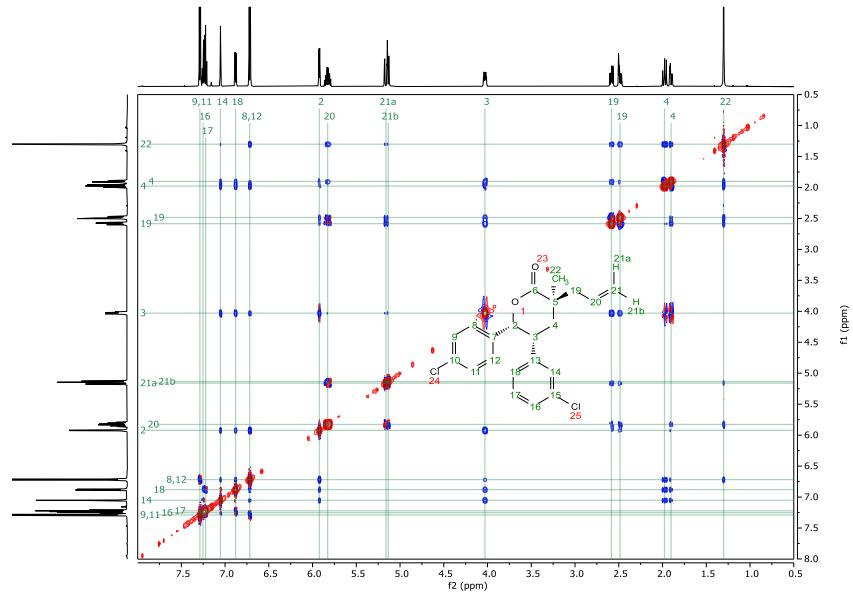
340369.1.fid
DLAC lot 3657-04
Project AMG 232
TCI-cryoprobe 600MHz

Parameter	Value
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2 Origin	Bruker BioSpin GmbH
3 Owner	nmsu
4 Solvent	DMSO
5 Temperature	300.0
6 Pulse Sequence	zg30
7 Experiment	1D
8 Probe	5 mm CPTCI 1H-13C/ 15N/ D Z-GRD 244896/ 0104
9 Number of Scans	16
10 Receiver Gain	25.4
11 Relaxation Delay	1.0000
12 Pulse Width	8.0000
13 Acquisition Time	2.7233
14 Scan Time	100.0000-1-07T14:59:36
15 Modification Date	2020-01-07T14:59:46
16 Spectrometer Frequency	600.23
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21 Spectral Size	131072
22 Digital Resolution	0.09

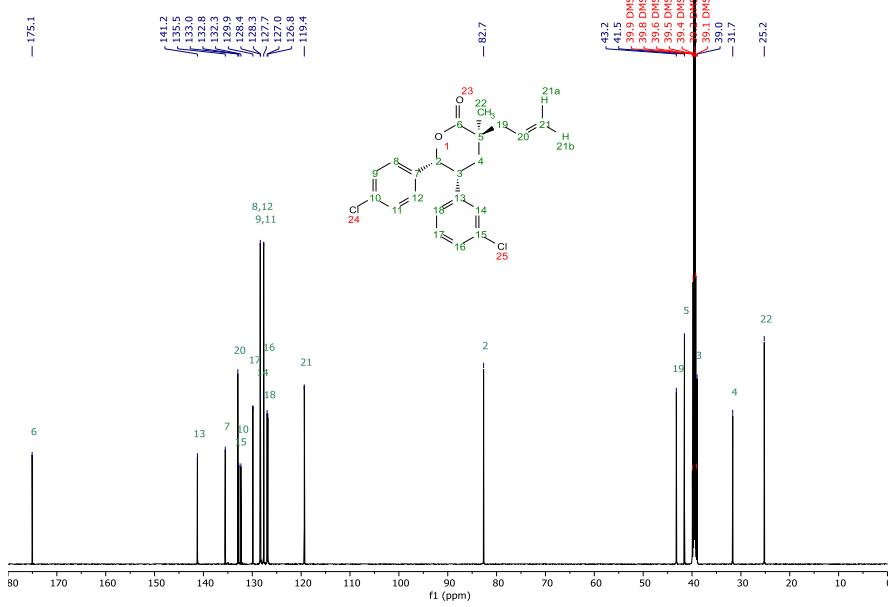




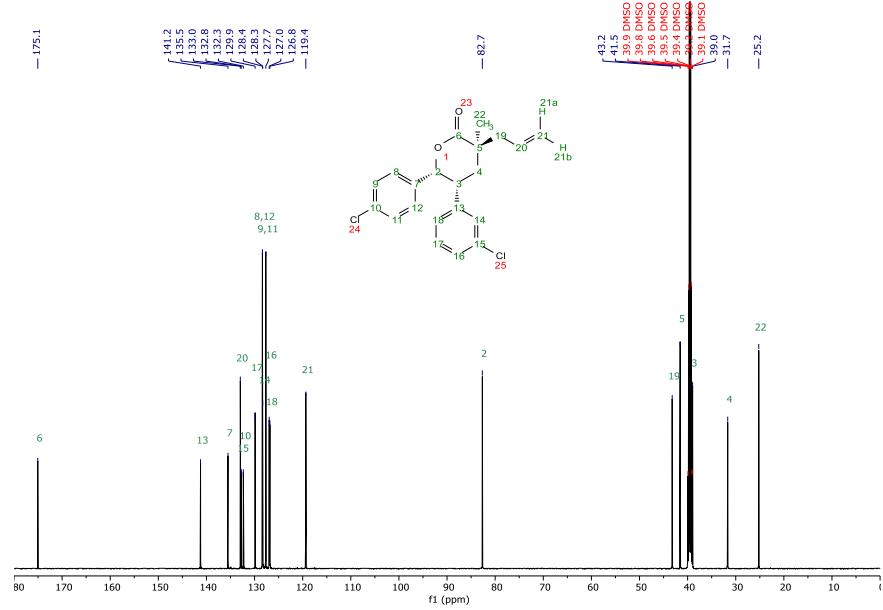
2D ¹H-¹H COSY spectrum of DLAC lot 3657-04 in DMSO-*d*6 at 27 °C (300 K).



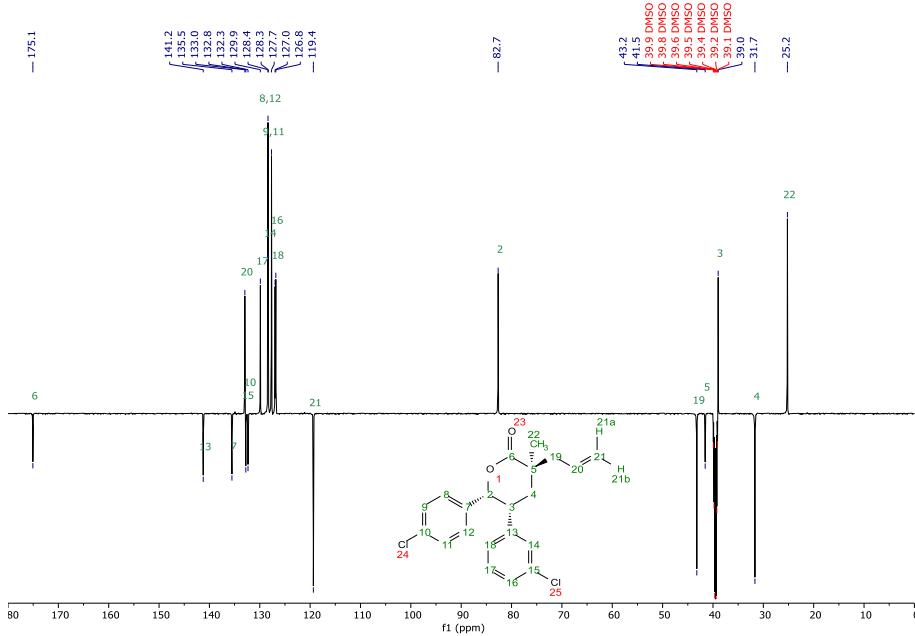
2D ¹H-¹H ROESY spectrum of DLAC lot 3657-04 in DMSO-*d*6 at 27 °C (300 K).



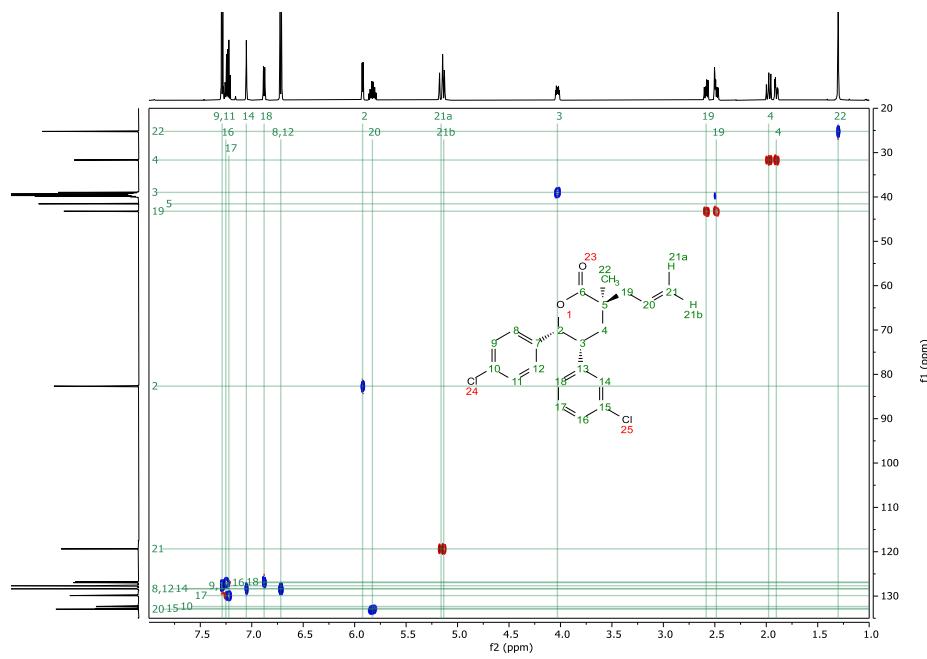
^{13}C NMR spectrum of DLAC lot 3657-04 in $\text{DMSO}-d_6$ at $27\text{ }^\circ\text{C}$ (300 K) with assignments.



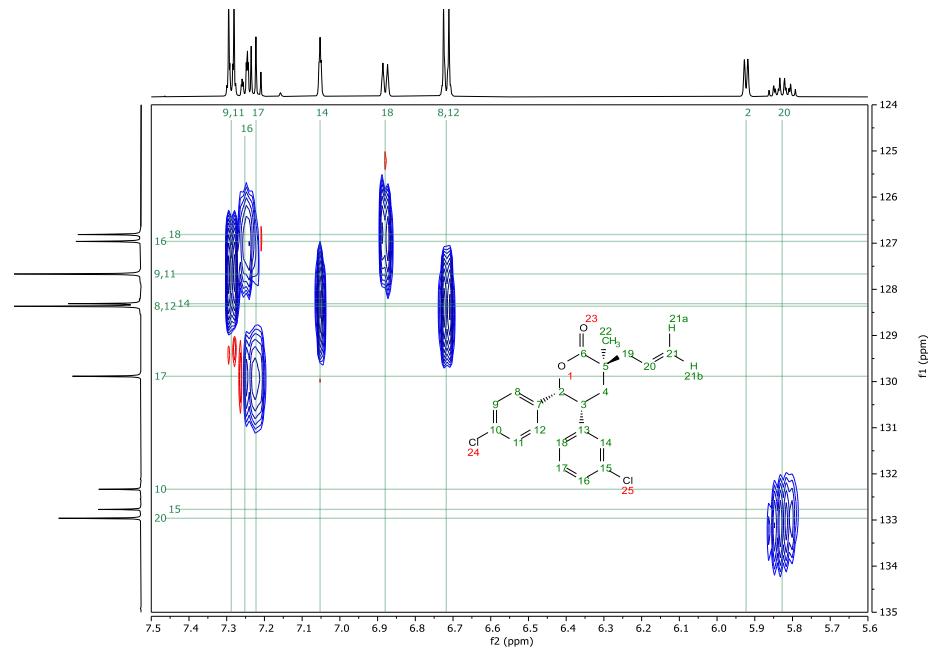
Aromatic region of the ^{13}C NMR spectrum of DLAC lot 3657-04 in $\text{DMSO}-d_6$ at $27\text{ }^\circ\text{C}$ (300 K) with assignments.



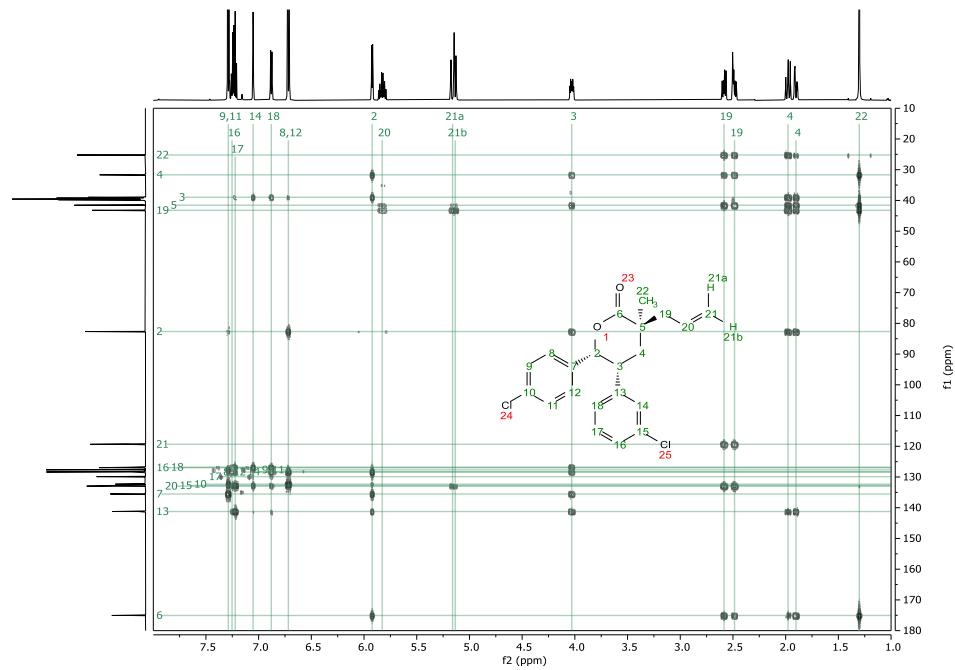
^{13}C DEPTQ spectrum of DLAC lot 3657-04 in $\text{DMSO}-d_6$ at $27\text{ }^\circ\text{C}$ (300 K) with assignments.



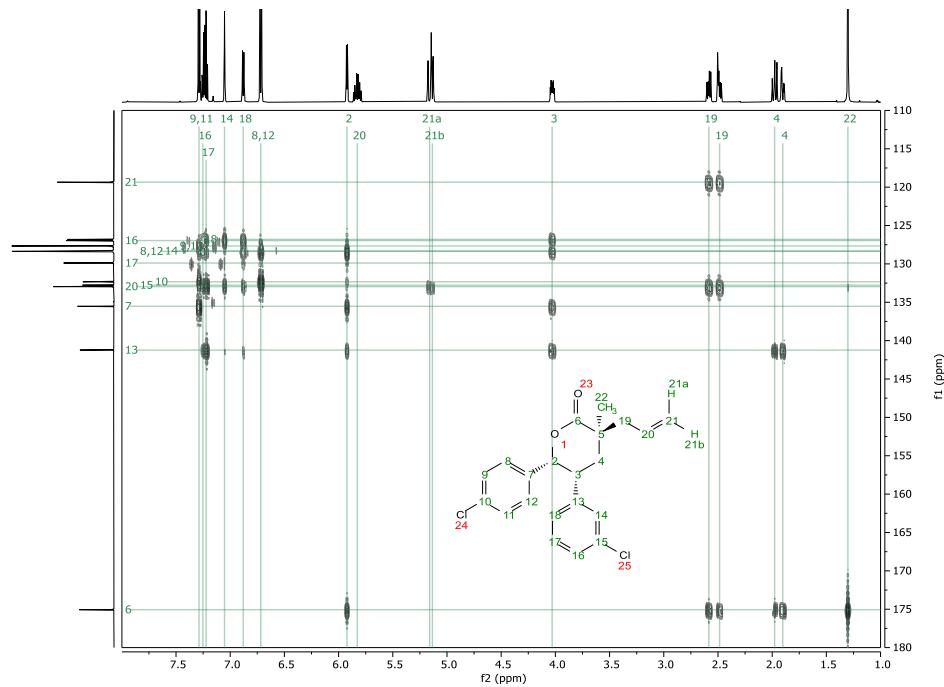
2D ^1H - ^{13}C HSQC spectrum of DLAC lot 3657-04 in $\text{DMSO}-d_6$ at $27\text{ }^\circ\text{C}$ (300 K). The ^1H and ^{13}C traces are from Figures 1 and 4.



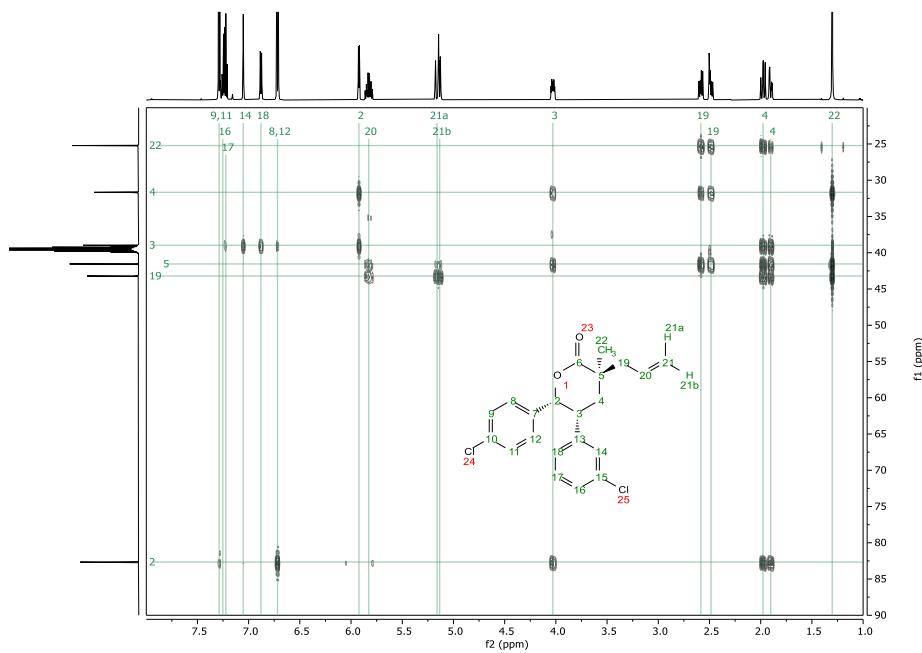
Aromatic region of the 2D ^1H - ^{13}C HSQC spectrum of DLAC lot 3657-04 in $\text{DMSO}-d_6$ at 27°C (300 K).



2D ^1H - ^{13}C HMBC spectrum of DLAC lot 3657-04 in $\text{DMSO}-d_6$ at 27°C (300 K).



Expansion of the 2D ¹H-¹³C HMBC spectrum of DLAC lot 3657-04 in DMSO-*d*6 at 27 °C (300 K).

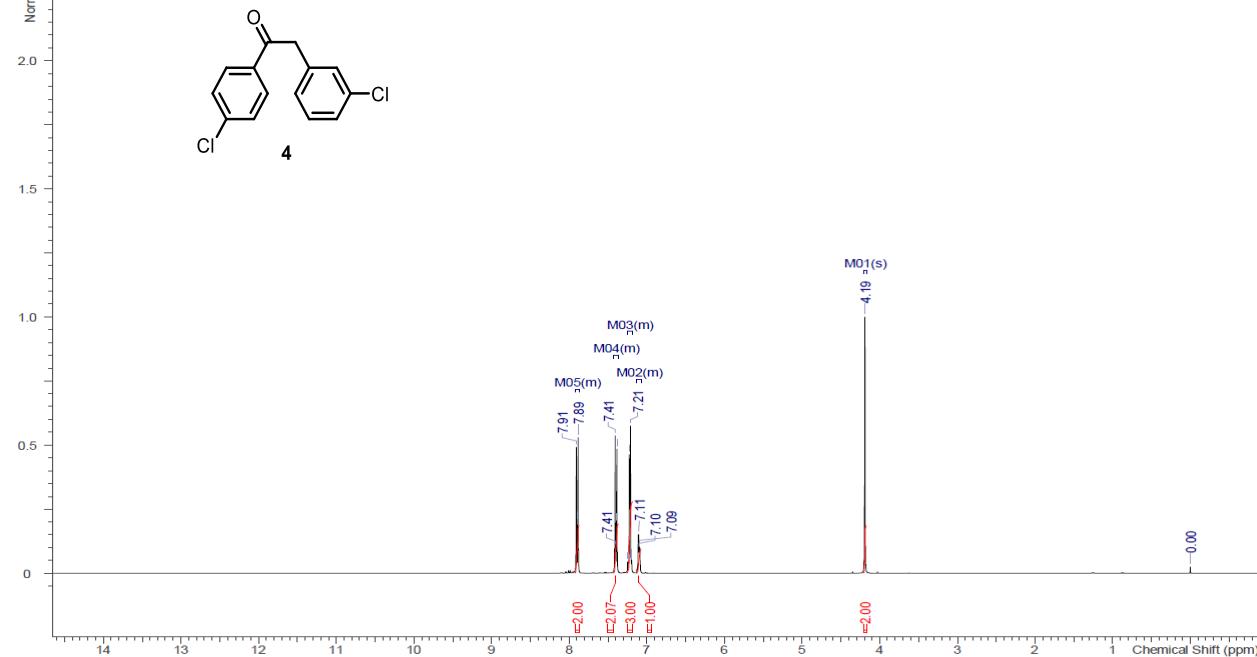


Expansion of the 2D ¹H-¹³C HMBC spectrum of DLAC lot 3657-04 in DMSO-*d*6 at 27 °C (300 K).

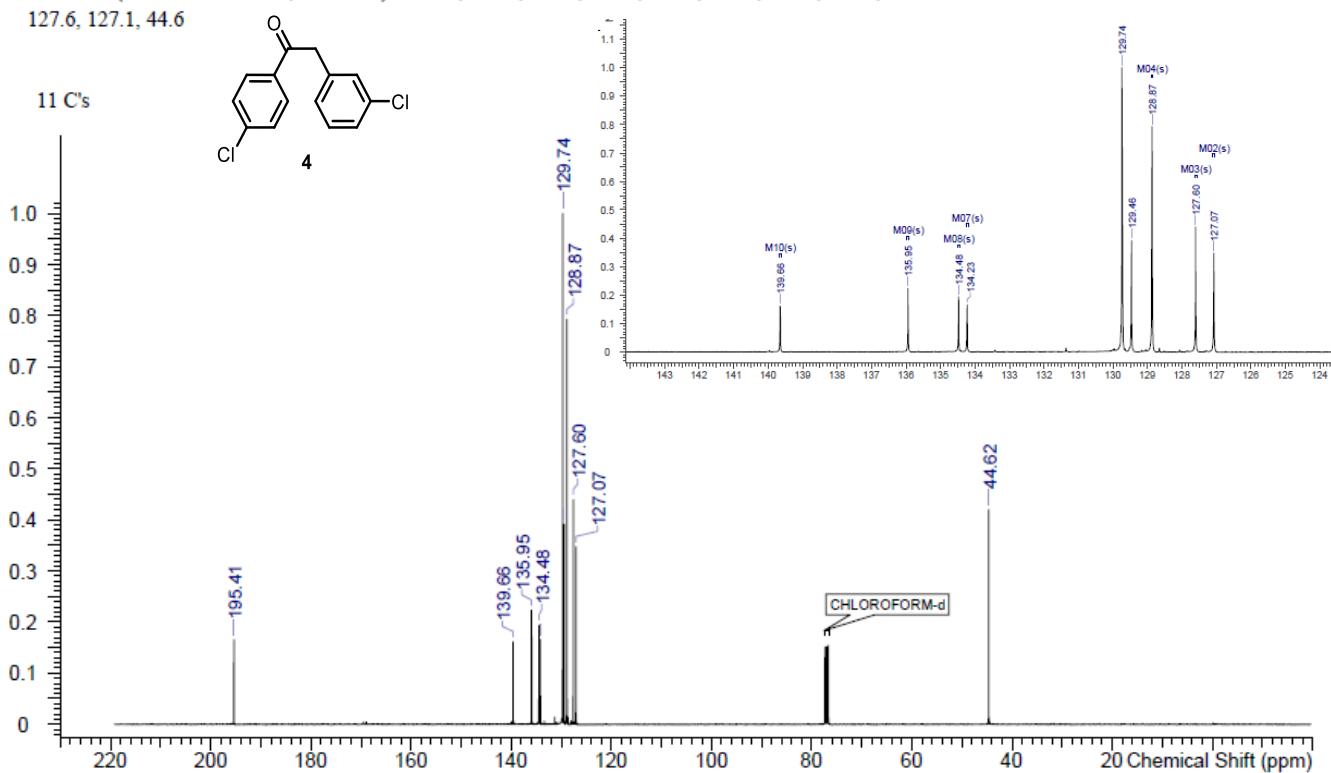
NMR spectra for 4

¹H NMR (400 MHz, CHLOROFORM-d) δ ppm 4.19 (s, 2 H) 7.07 - 7.13 (m, 1 H) 7.18 - 7.26 (m, 3 H) 7.36 - 7.43 (m, 2 H) 7.87 - 7.92 (m, 2 H)

ausmith.01-175-10_10.ESRVerticalScaleFactor = 1



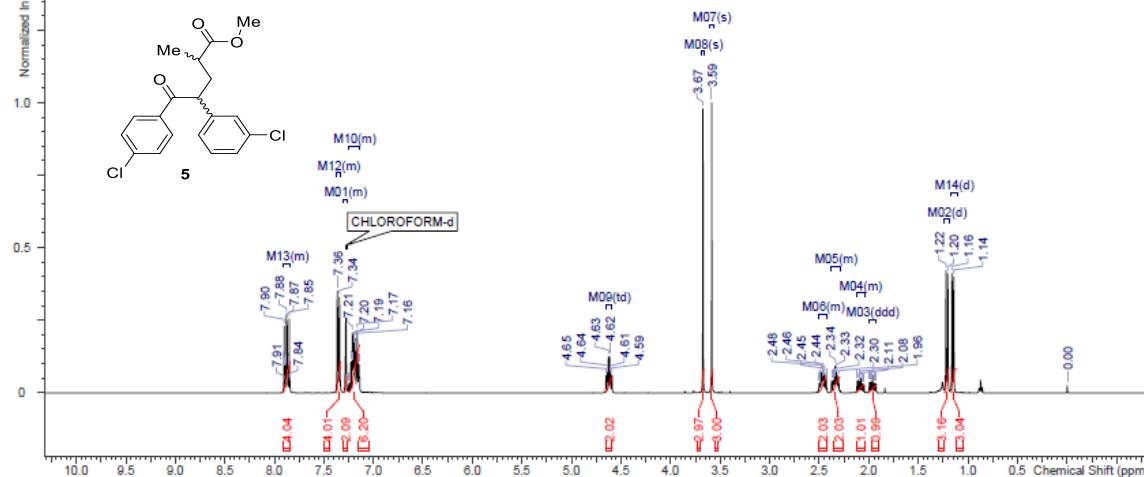
¹³C NMR (CHLOROFORM-d, 101 MHz) δ 195.4, 139.7, 135.9, 134.5, 134.2, 129.7, 129.5, 128.9, 127.6, 127.1, 44.6



NMR spectra for 5

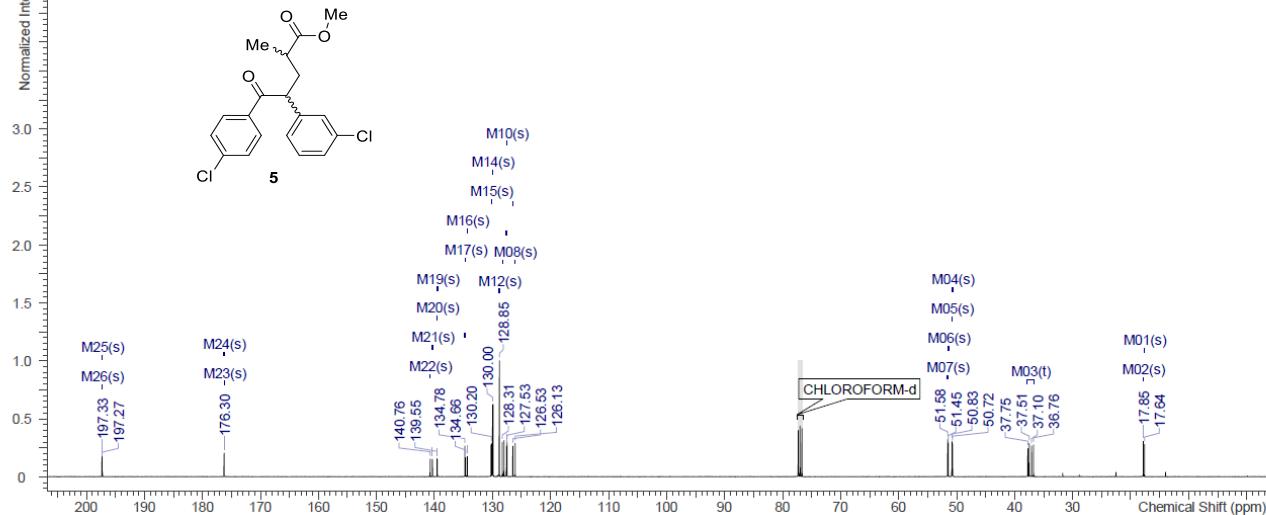
¹H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.15 (d, *J*=7.05 Hz, 3 H) 1.21 (d, *J*=7.05 Hz, 3 H) 1.96 (ddd, *J*=13.79, 9.02, 4.56 Hz, 1 H) 2.05 - 2.12 (m, 1 H) 2.29 - 2.38 (m, 2 H) 2.42 - 2.51 (m, 2 H) 3.59 (s, 3 H) 3.67 (s, 3 H) 4.62 (td, *J*=9.07, 5.49 Hz, 2 H) 7.14 - 7.25 (m, 6 H) 7.26 - 7.31 (m, 2 H) 7.33 - 7.38 (m, 4 H) 7.84 - 7.91 (m, 4 H)

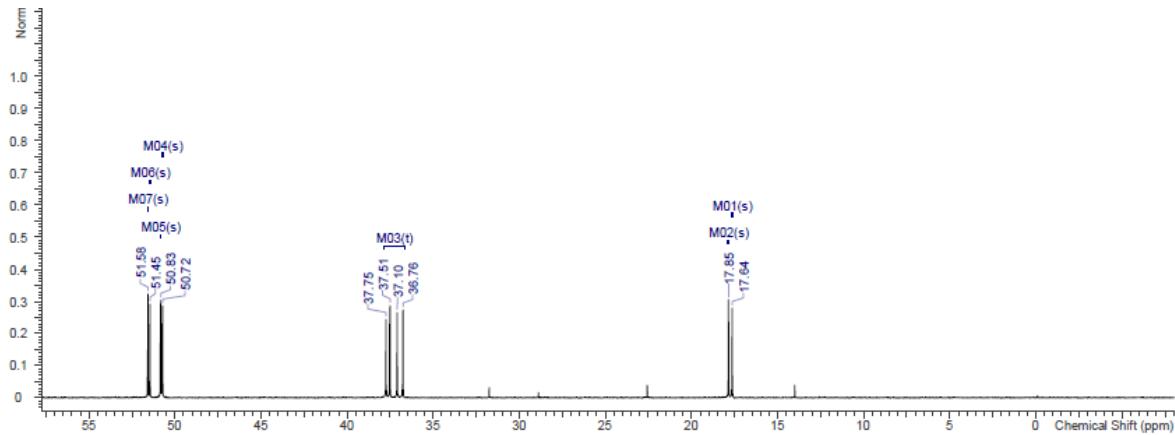
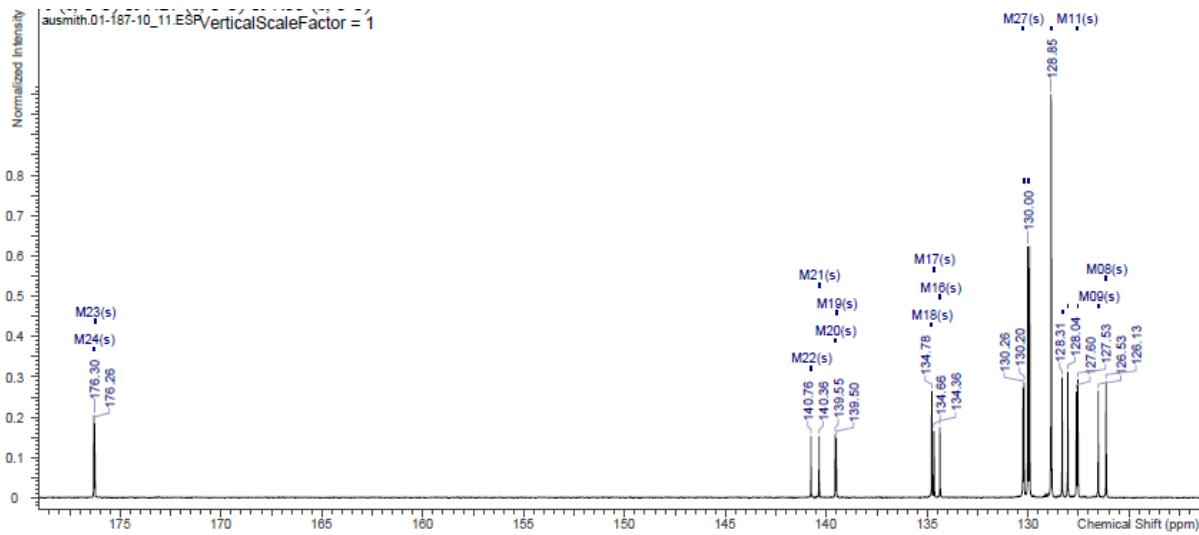
ausmith.01-187-10_10.ESP VerticalScaleFactor = 1



¹³C NMR (101 MHz, CHLOROFORM-d) δ ppm 17.64 (s, 1 C) 17.85 (s, 1 C) 37.28 (t, *J*=49.52 Hz, 1 C) 50.72 (s, 1 C) 50.83 (s, 1 C) 51.45 (s, 1 C) 51.58 (s, 1 C) 126.13 (s, 1 C) 126.53 (s, 1 C) 127.53 (s, 1 C) 127.60 (s, 1 C) 128.31 (s, 1 C) 128.85 (s, 1 C) 130.00 (s, 1 C) 130.20 (s, 1 C) 134.36 (s, 1 C) 134.66 (s, 1 C) 134.78 (s, 1 C) 139.50 (s, 1 C) 139.55 (s, 1 C) 140.36 (s, 1 C) 140.76 (s, 1 C) 176.26 (s, 1 C) 176.30 (s, 1 C) 197.27 (s, 1 C) 197.33 (s, 1 C)

ausmith.01-187-10_11.ESP VerticalScaleFactor = 1

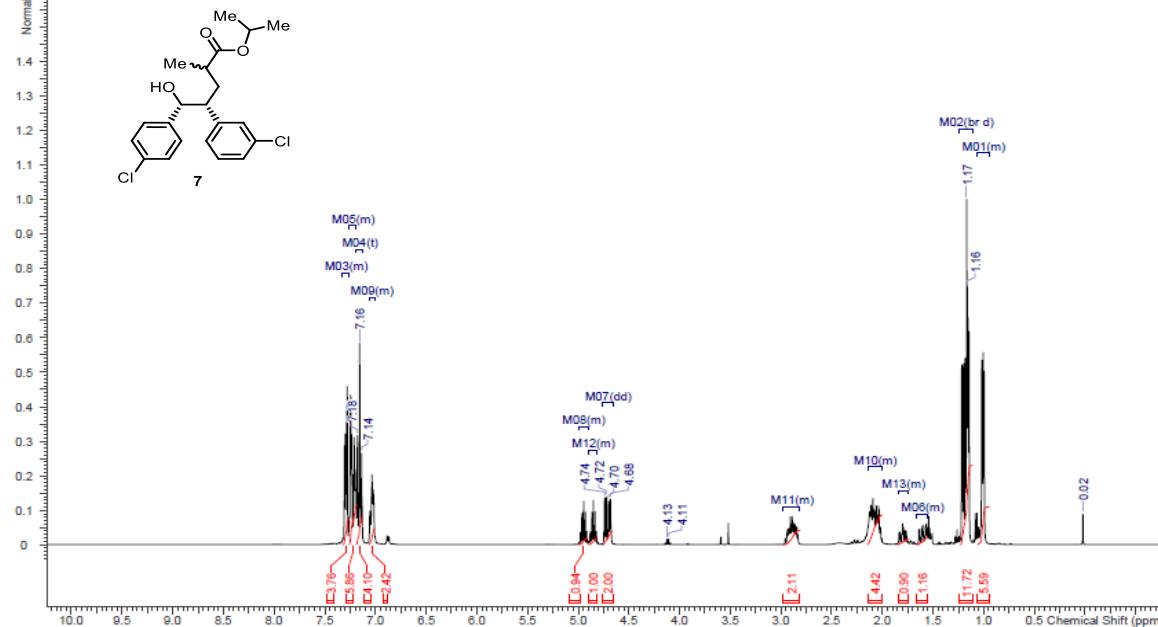




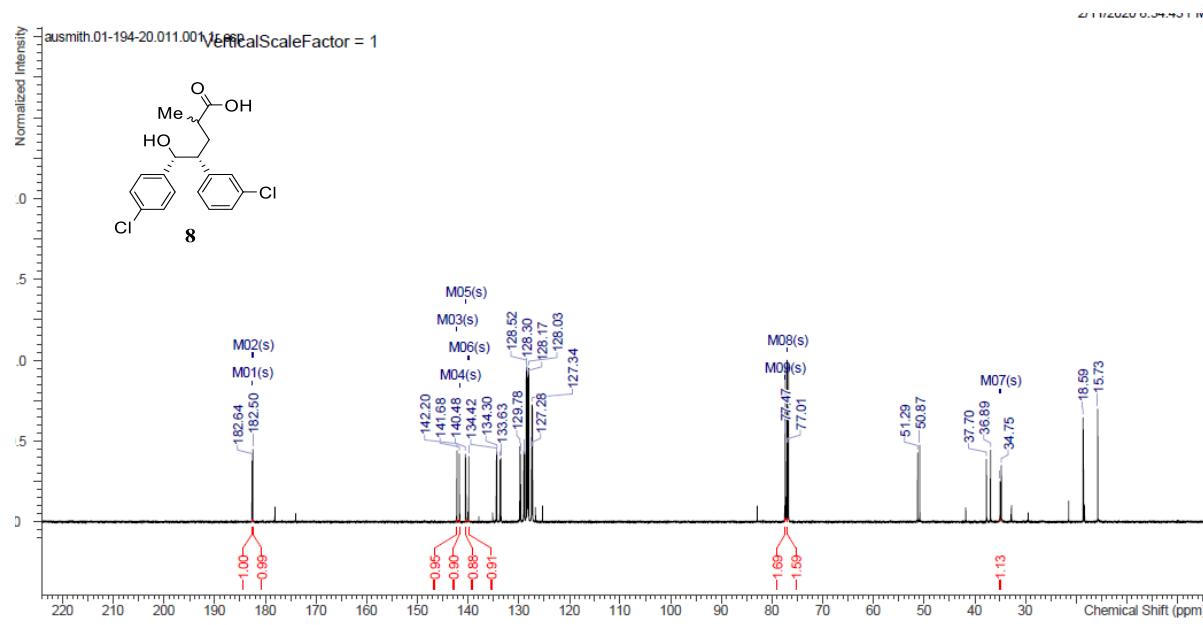
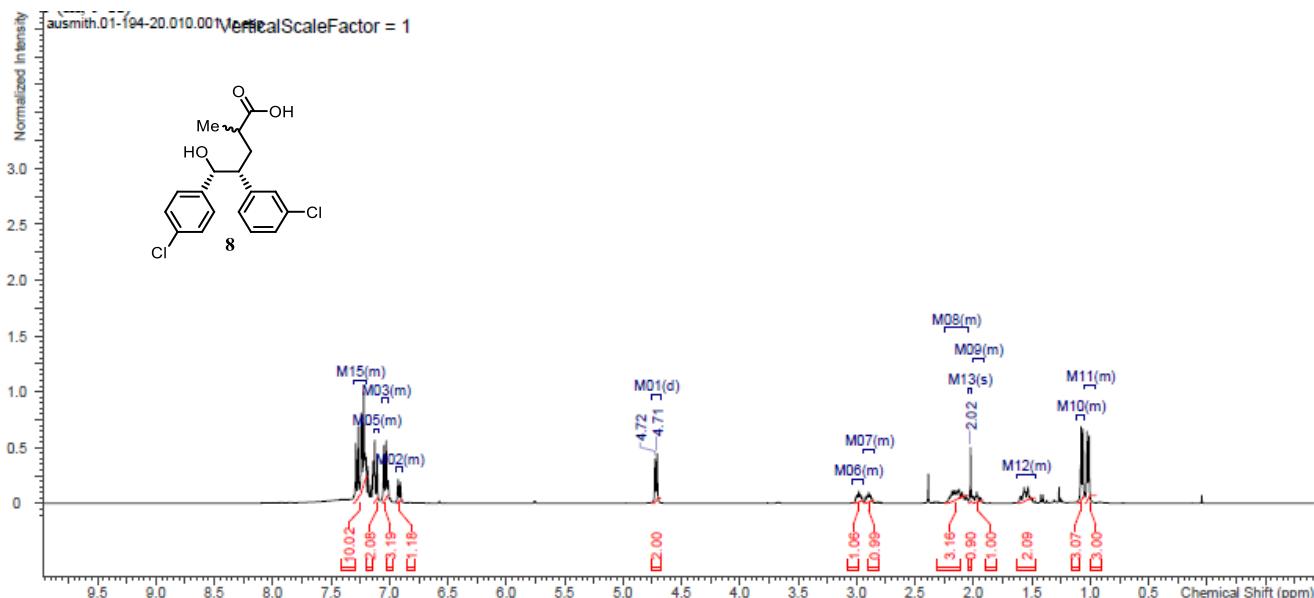
NMR spectra for 7

¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.95 - 1.06 (m, 6 H) 1.16 (br d, *J*=2.70 Hz, 12 H) 1.55 - 1.66 (m, 1 H) 1.74 - 1.85 (m, 1 H) 2.00 - 2.14 (m, 4 H) 2.81 - 2.98 (m, 2 H) 4.71 (dd, *J*=15.55, 7.26 Hz, 2 H) 4.81 - 4.90 (m, 1 H) 4.90 - 5.00 (m, 1 H) 7.01 - 7.06 (m, 2 H) 7.16 (t, *J*=8.50 Hz, 4 H) 7.19 - 7.26 (m, 6 H) 7.26 - 7.33 (m, 4 H)

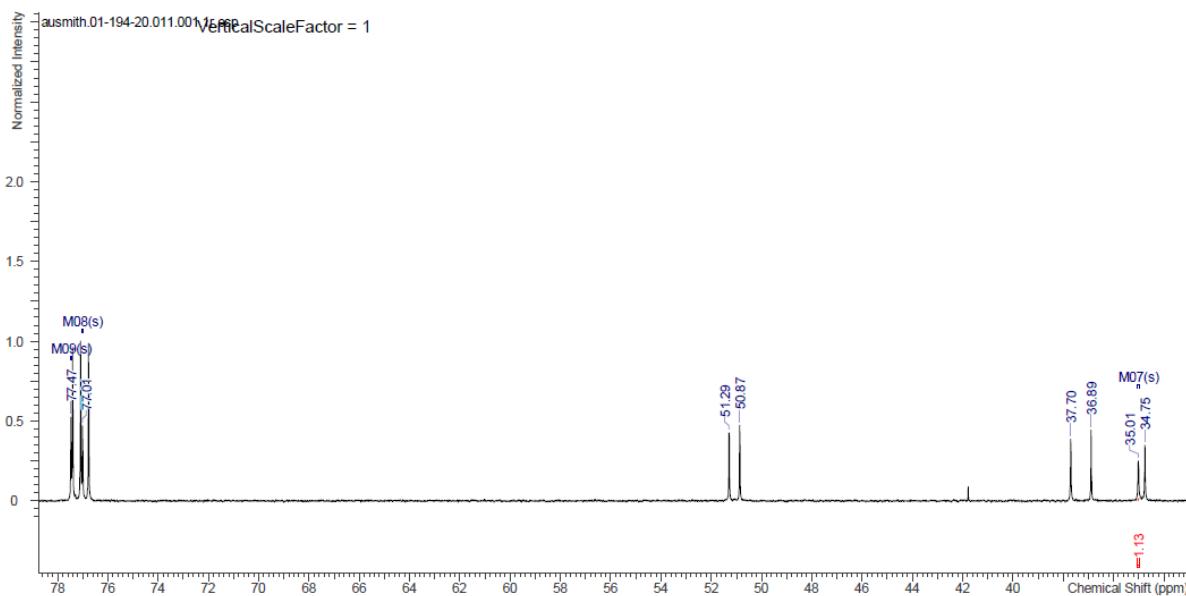
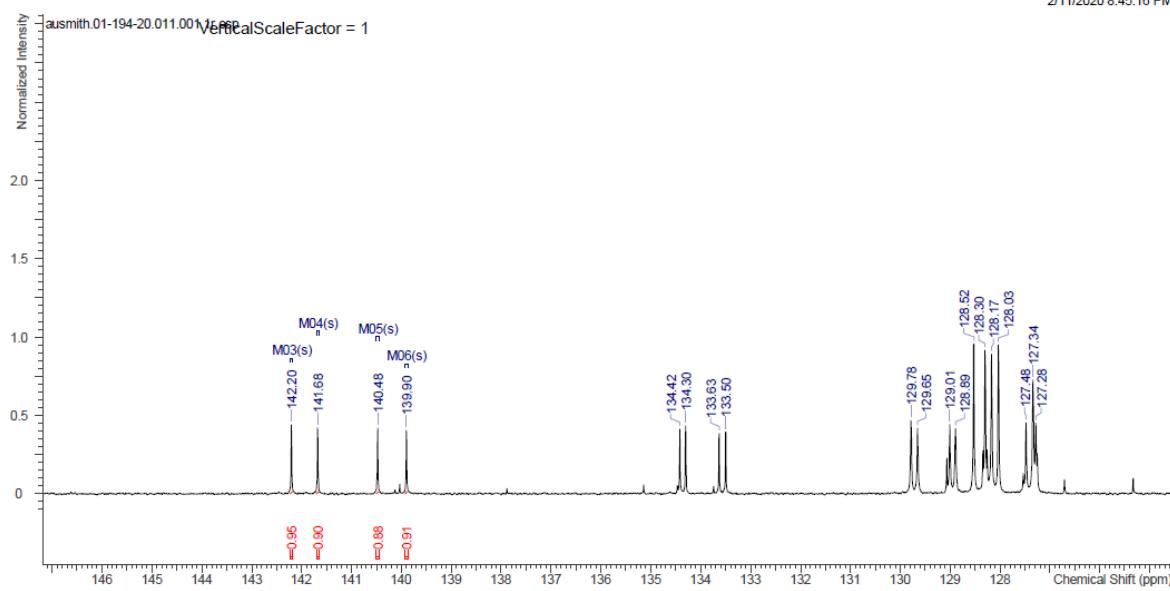
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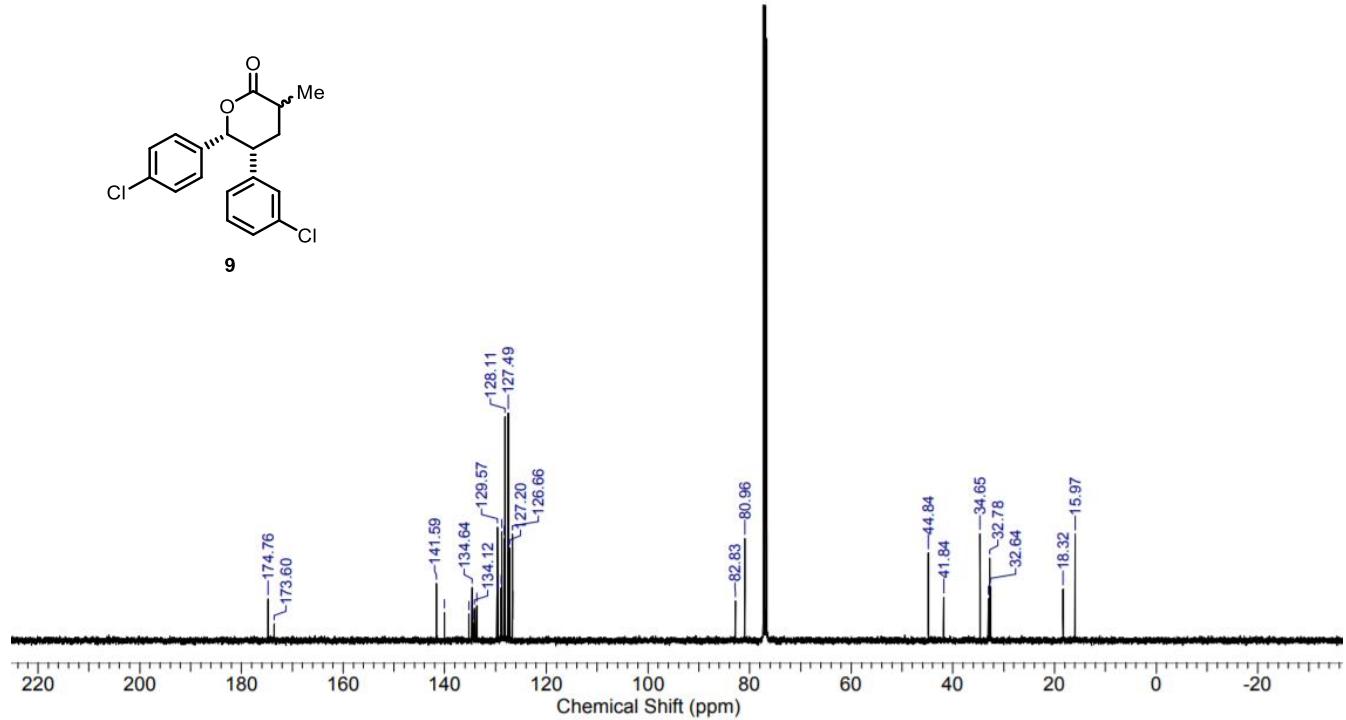
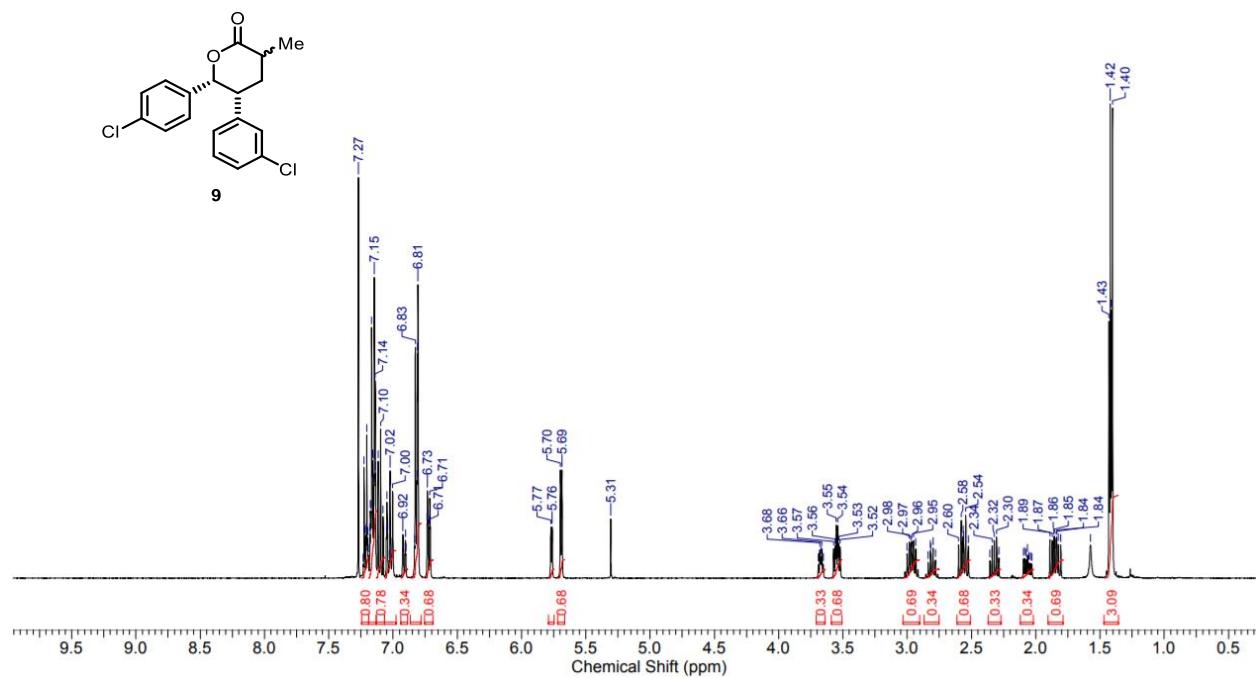
NMR spectra for **8**



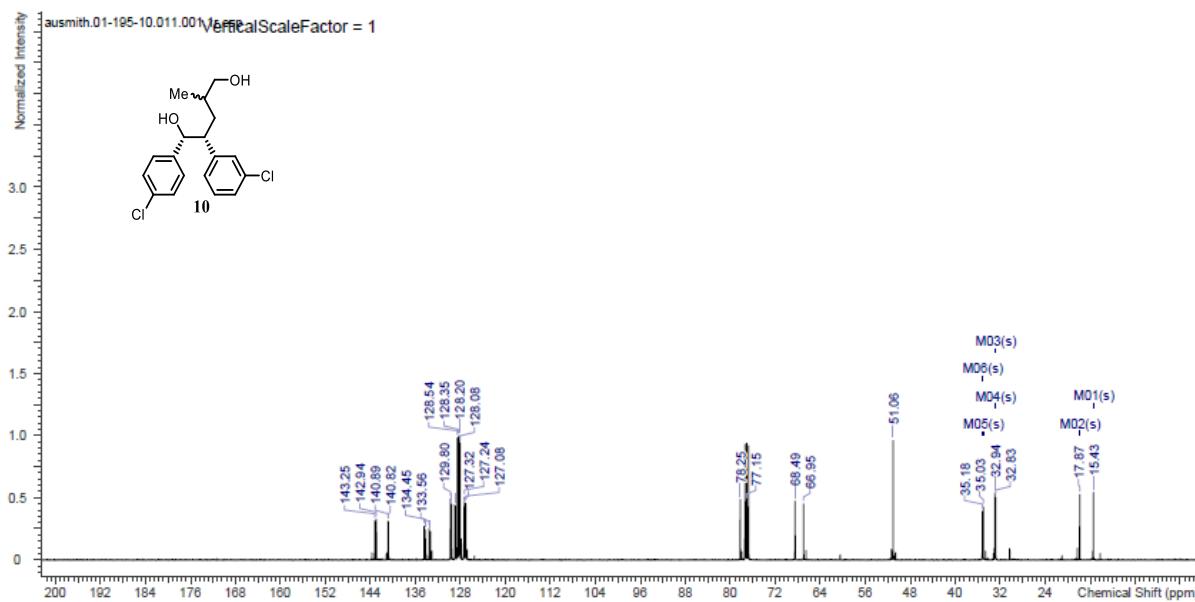
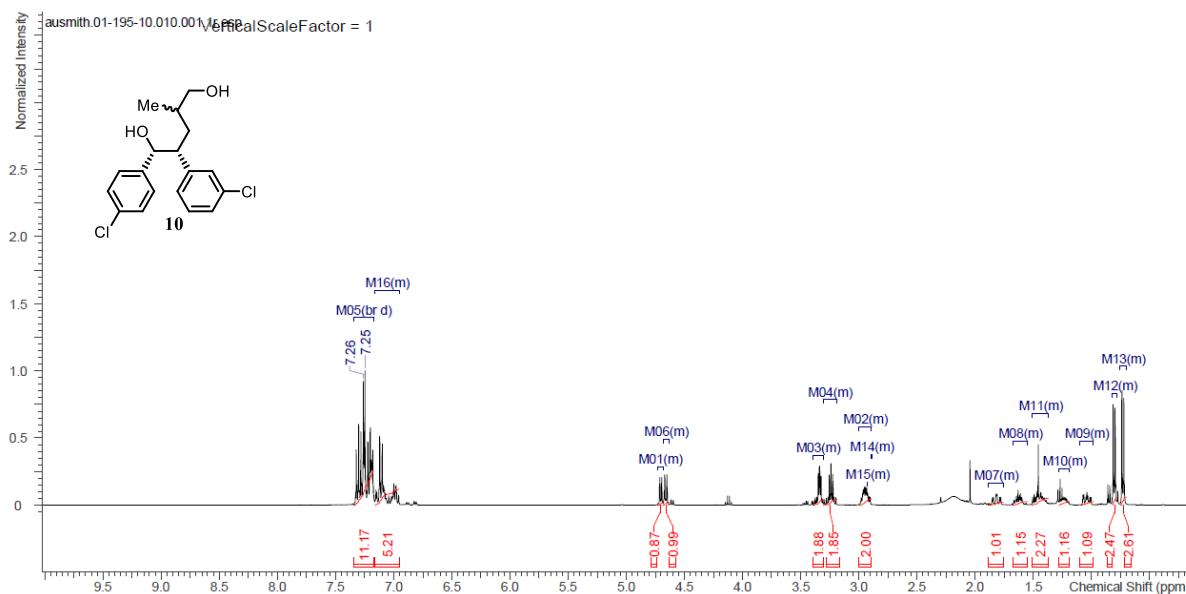
2/11/2020 8:45:16 PM



NMR spectra for **9**



NMR spectra for **10**

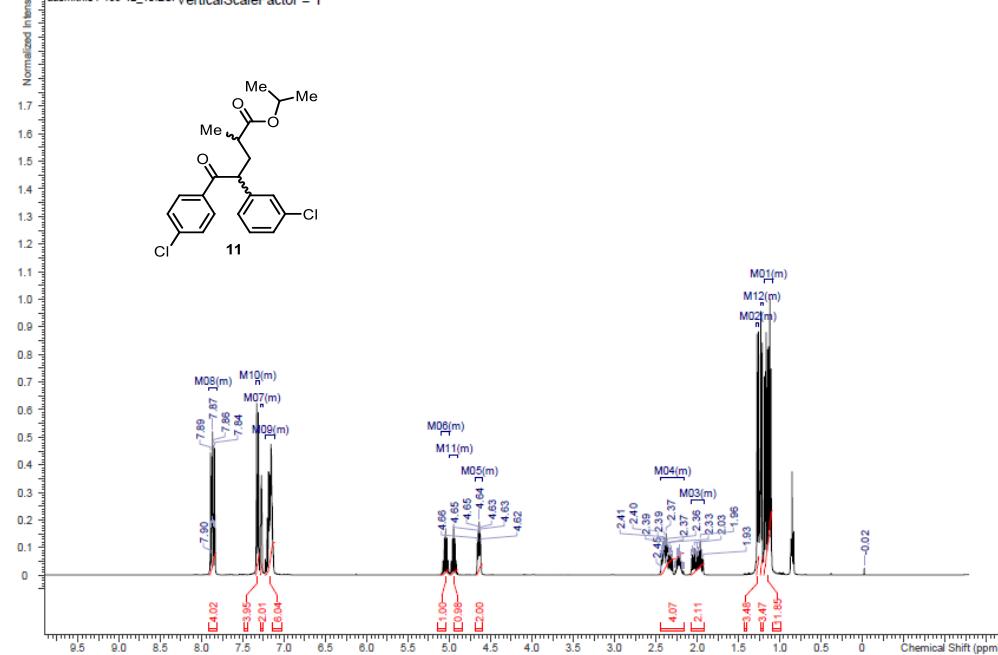


MS (ESI+): m/z 361.1 ($M + Na$).

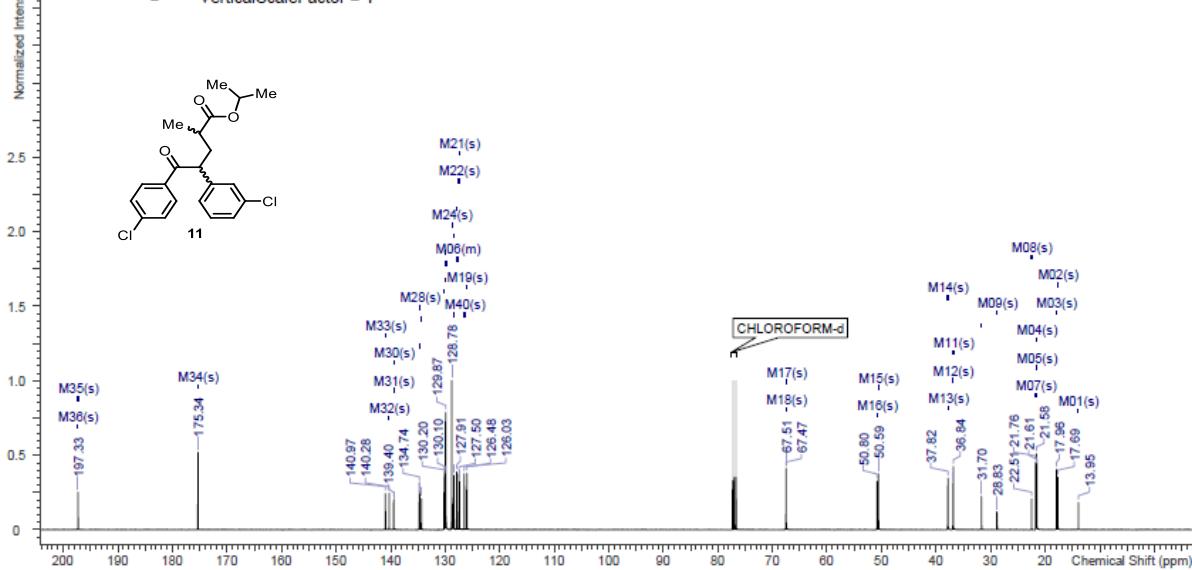
NMR spectra for 11

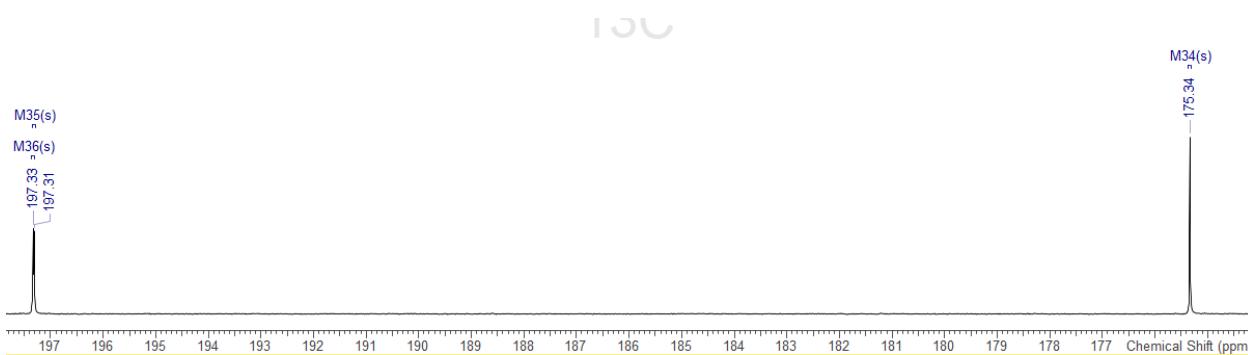
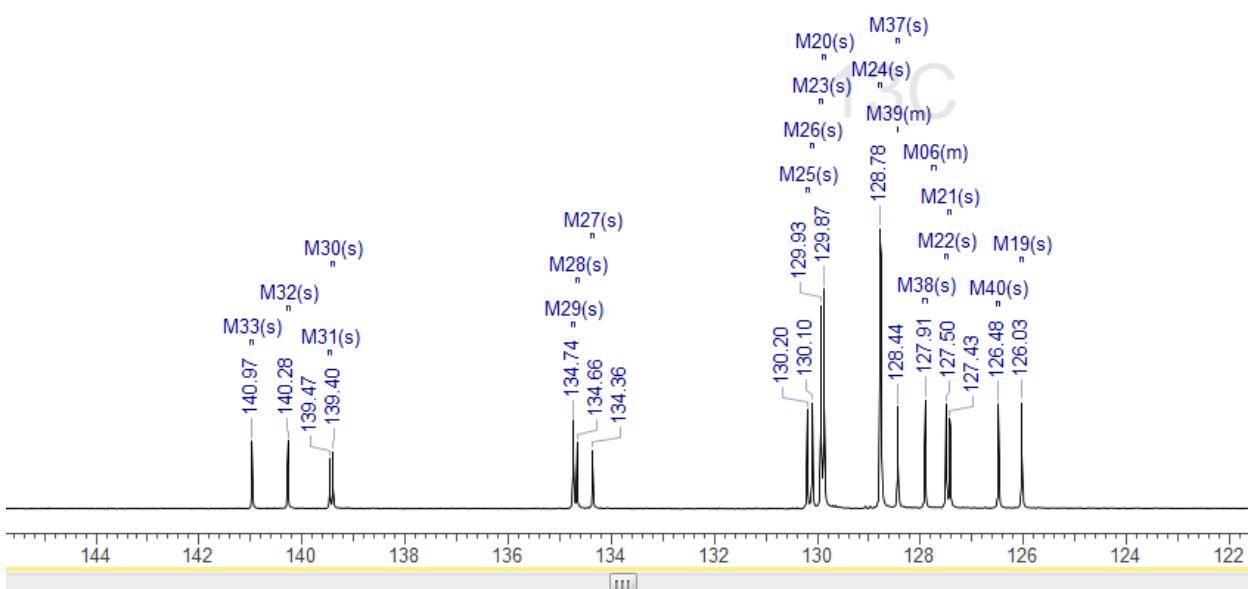
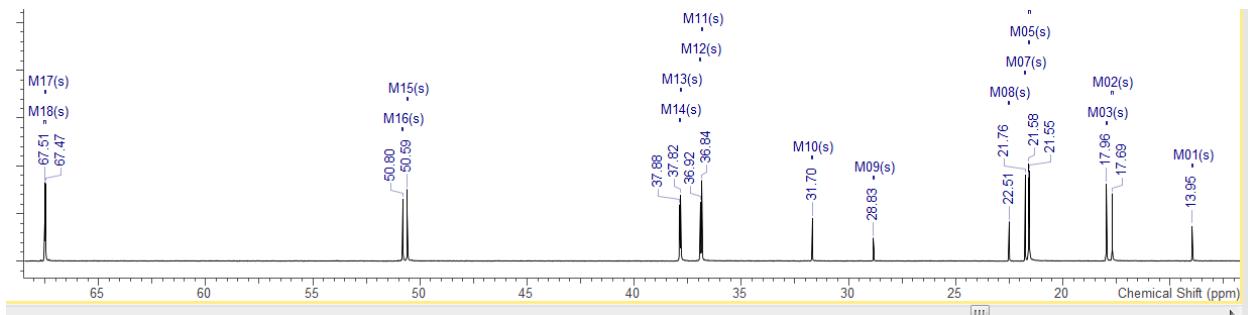
¹H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.09 - 1.19 (m, 12 H) 1.21 - 1.23 (m, 3 H) 1.25 - 1.28 (m, 3 H) 1.92 - 2.08 (m, 2 H) 2.16 - 2.45 (m, 4 H) 4.60 - 4.68 (m, 2 H) 4.90 - 5.00 (m, 1 H) 5.00 - 5.10 (m, 1 H) 7.11 - 7.23 (m, 6 H) 7.25 - 7.29 (m, 2 H) 7.30 - 7.35 (m, 4 H) 7.82 - 7.91 (m, 4 H)

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ausmith.01-185-12_11.ESP VerticalScaleFactor = 1

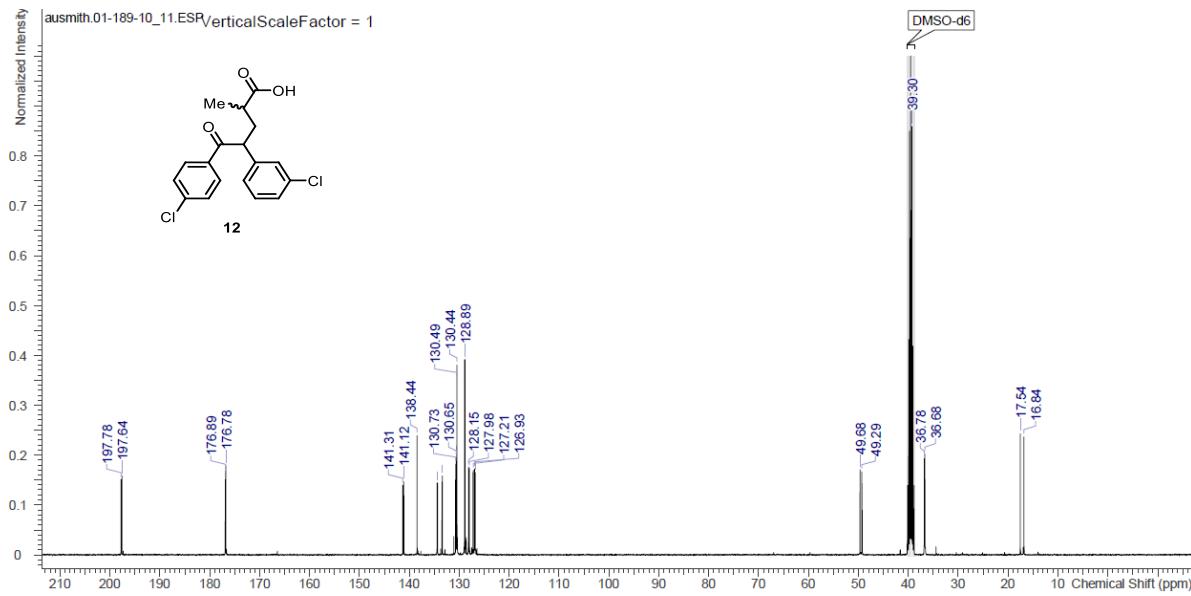
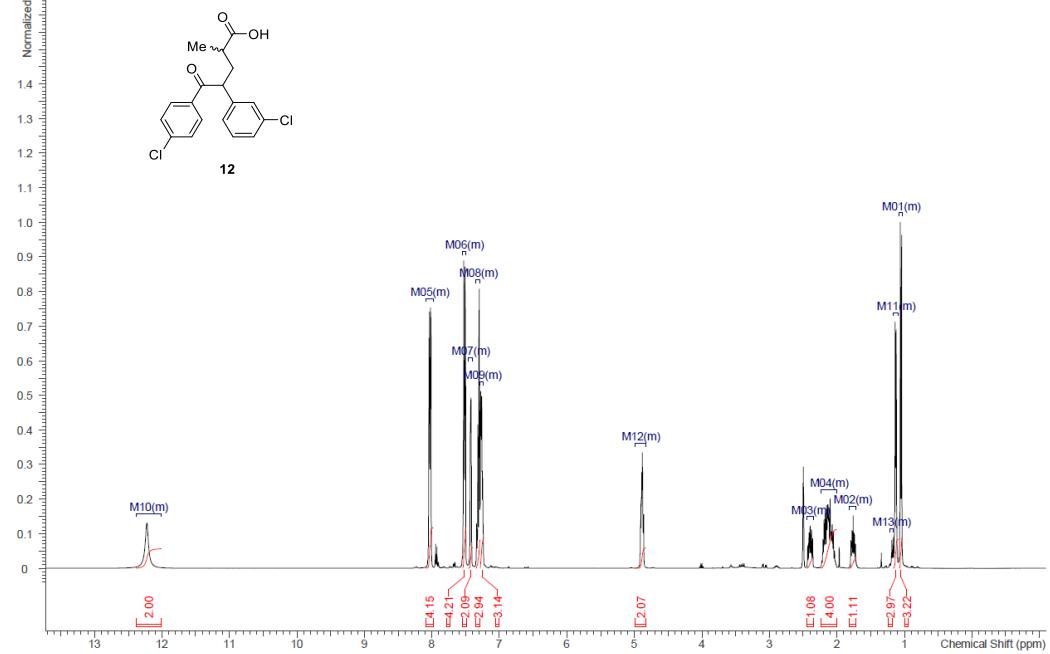




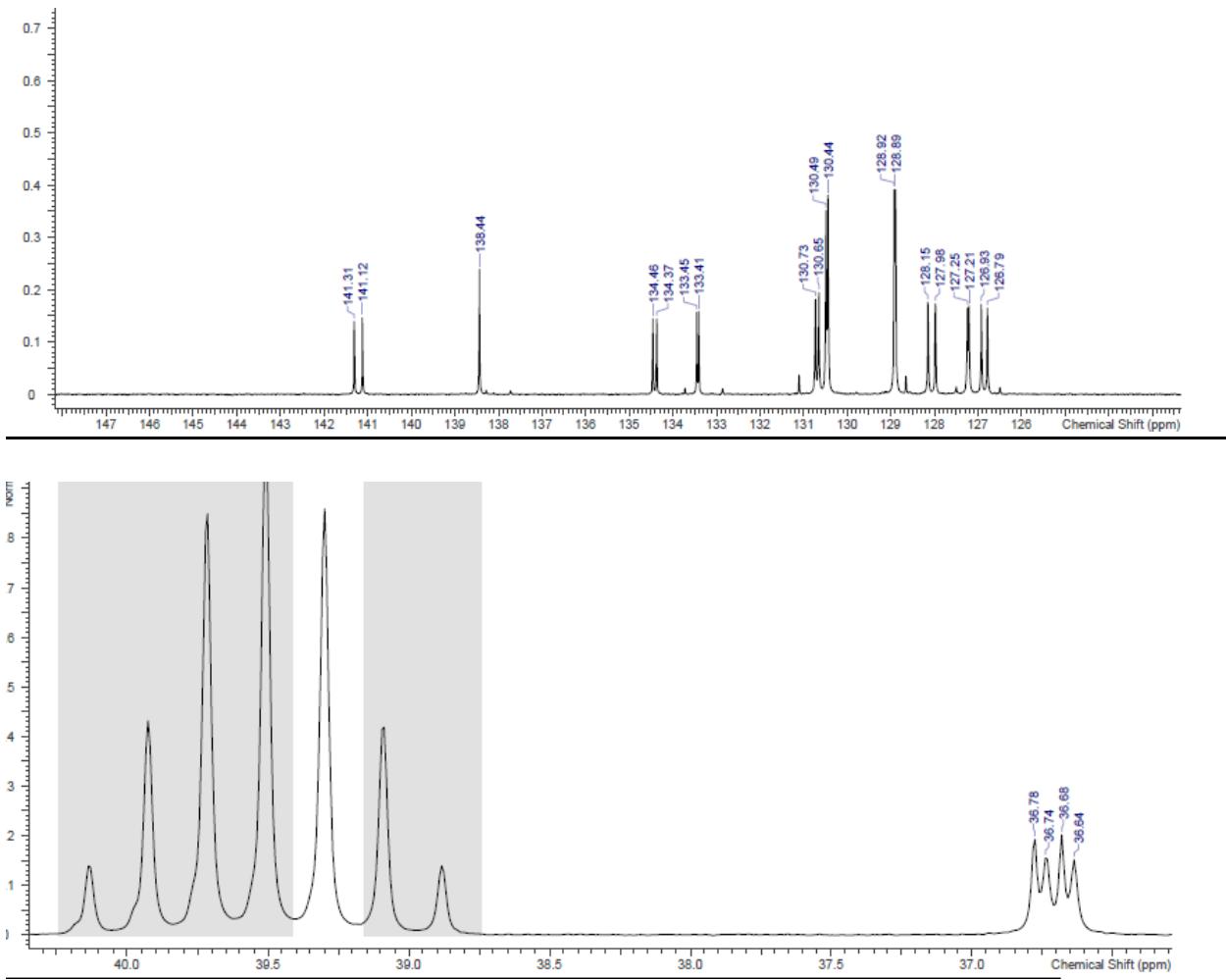
NMR spectra for **12**

¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.03 - 1.07 (m, 3 H) 1.09 - 1.16 (m, 3 H) 1.16 - 1.22 (m, 1 H) 1.71 - 1.82 (m, 1 H) 2.00 - 2.23 (m, 4 H) 2.35 - 2.44 (m, 1 H) 4.83 - 4.99 (m, 2 H) 7.24 - 7.28 (m, 3 H) 7.29 - 7.35 (m, 3 H) 7.40 - 7.46 (m, 2 H) 7.50 - 7.54 (m, 4 H) 7.98 - 8.09 (m, 4 H) 12.01 - 12.38 (m, 2 H)

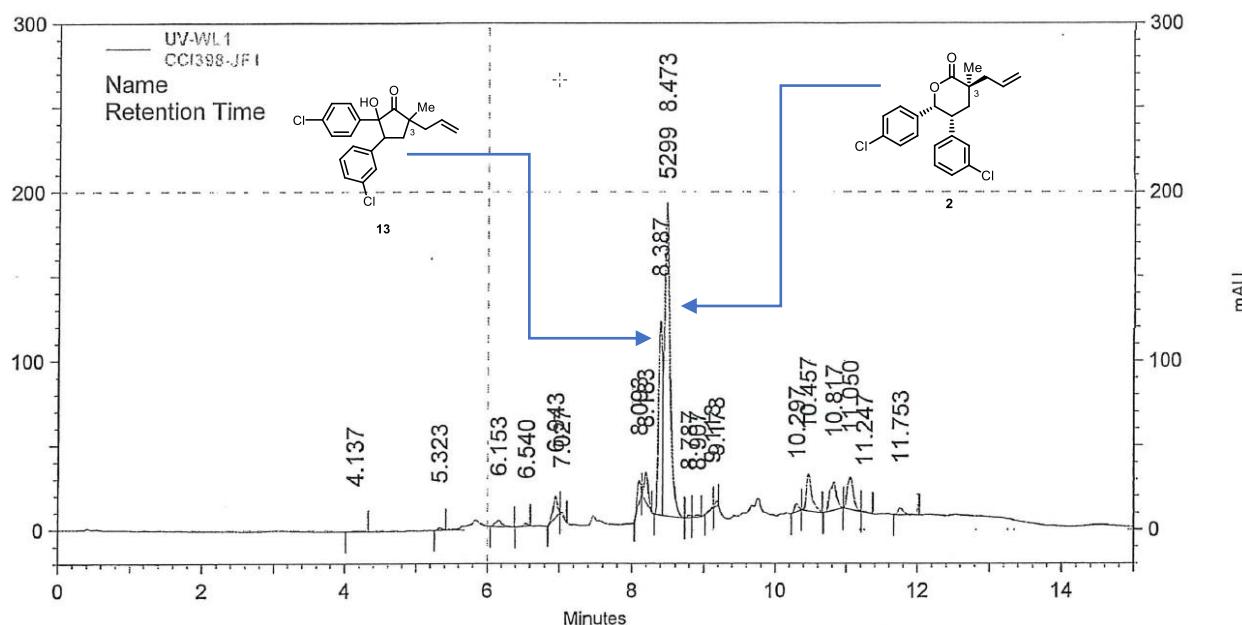
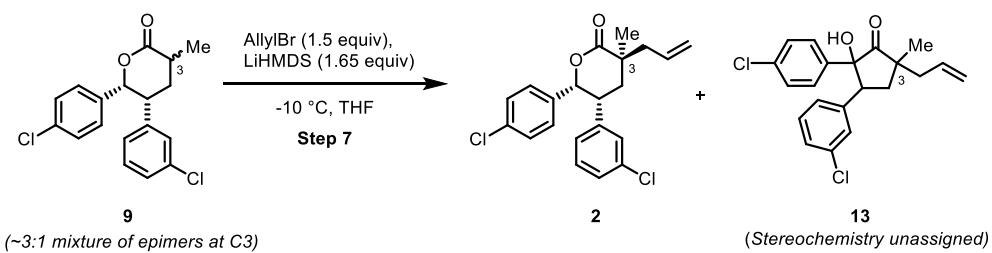
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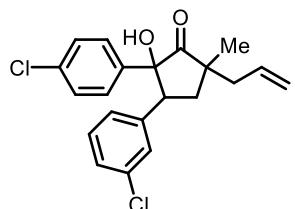
MS (ESI+): *m/z* 351.1 ($M + 1$).



NMR spectra and structural elucidation of **13**



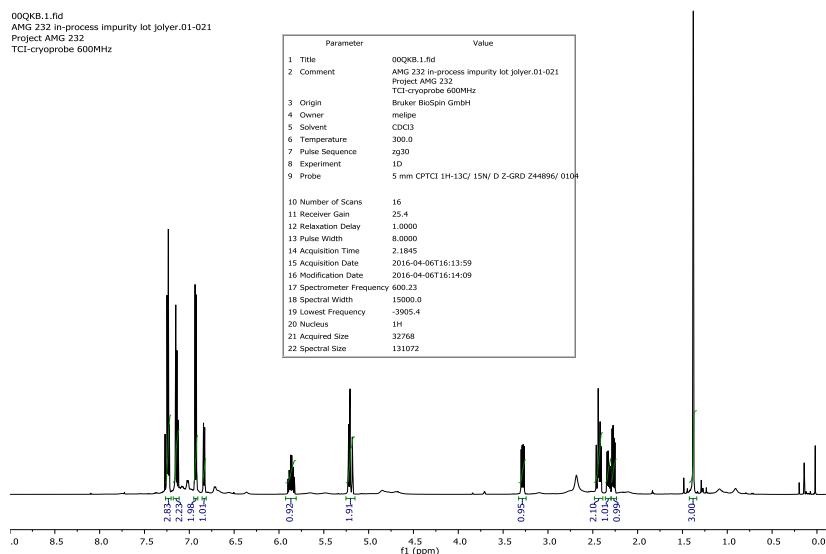
Alkylation of **9** to Produce **2** and LC Chromatogram of Mother Liquors Showing Overlap of **2** and **13**



13

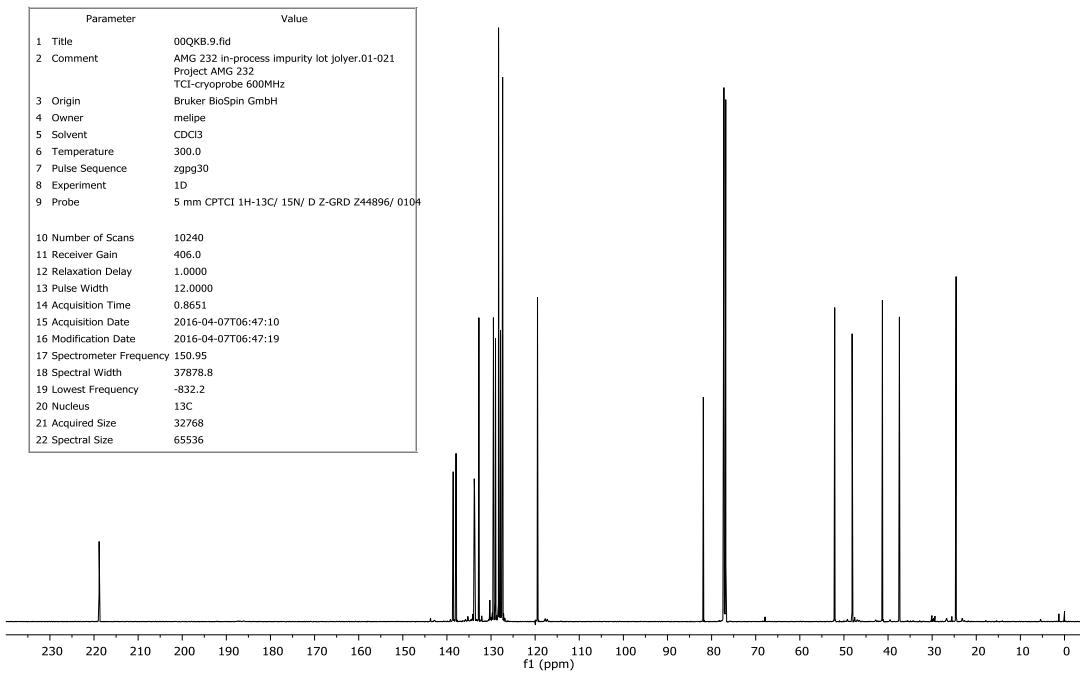
00QKB.1.fid
AMG 232 in-process impurity lot jolyer.01-021
Project AMG 232
TCI-cryoprobe 600MHz

Parameter	Value
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4 Owner	melppe
5 Solvent	CDCl ₃
6 Temperature	300.0
7 Pulse Sequence	zg30
8 Experiment	1D
9 Probe	5 mm CPTCI 1H-13C/ 15N/ D Z-GRD 244896/ 010
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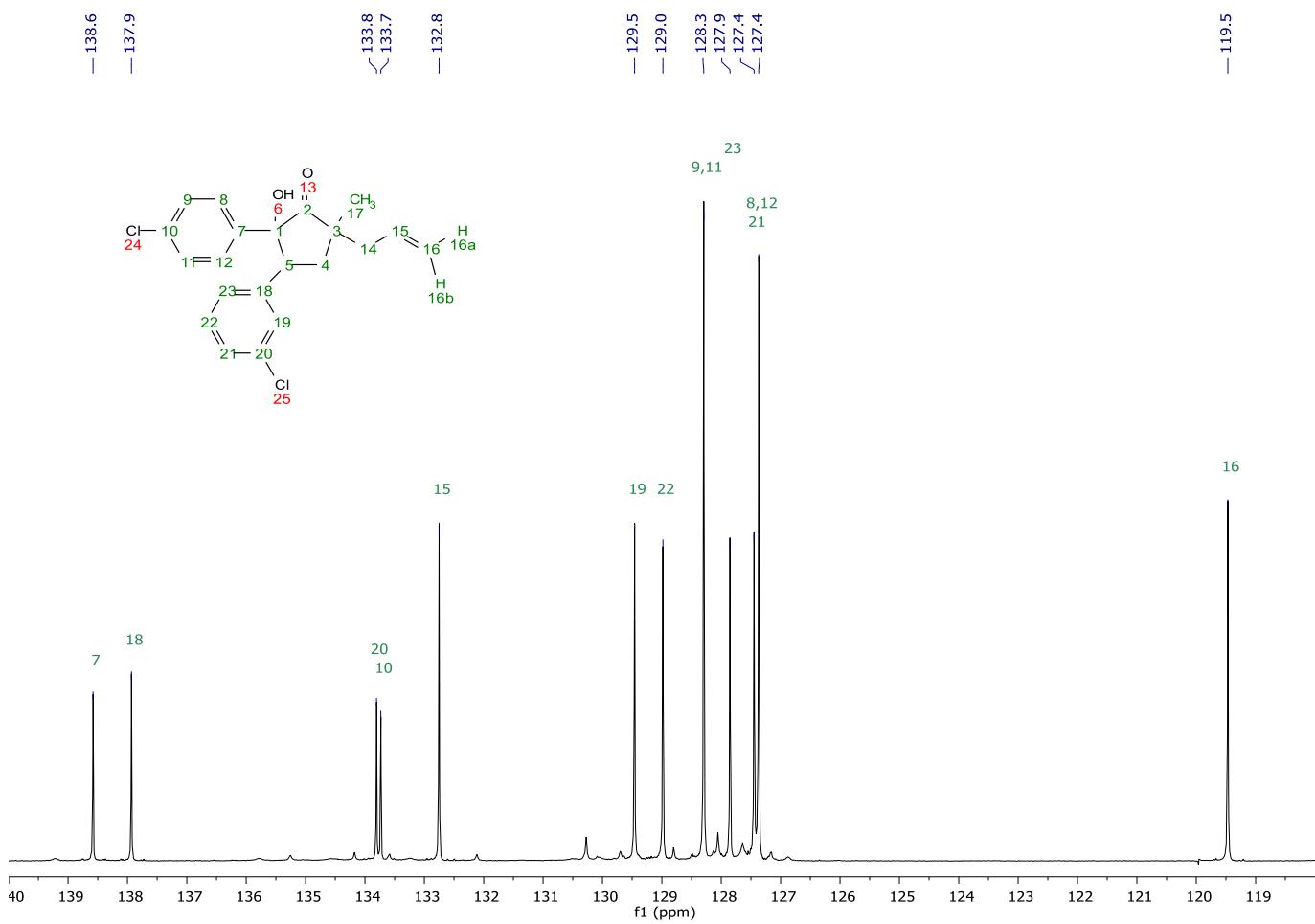


¹H NMR spectrum of AMG 232 in process impurity in CDCl₃ at 27 °C (300 K) with experimental parameters.

00QKB.9.fid
AMG 232 in-process impurity lot jolyer.01-021
Project AMG 232
TCI-cryoprobe 600MHz



¹³C NMR spectrum of AMG 232 in process impurity lot in CDCl₃ at 27 °C (300 K) with experimental parameters.



Aromatic region of the ^{13}C NMR spectrum of AMG 232 in process impurity lot in CDCl_3 at 27 °C (300 K) with assignments.

MS (ESI-): m/z 373.1 (M – 1).

Chiral HPLC data for DLAC 2

Chiral Analytical Method Conditions

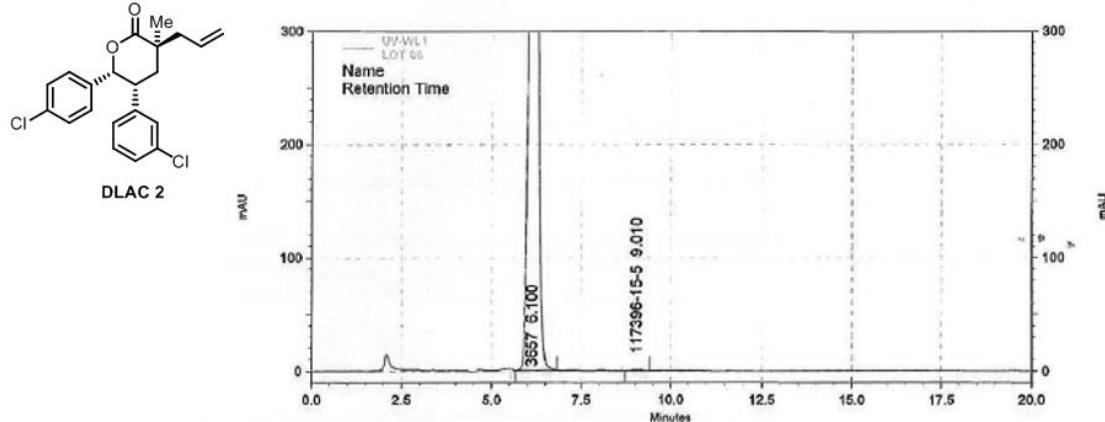
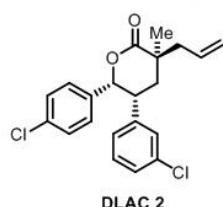
Column: CHIRALPACK AD-H, 4.6 x 250 mm, 5 μ M

Eluent: 3% EtOH in n-heptane, 1.5mL/min,

Column temperature: 30 °C,

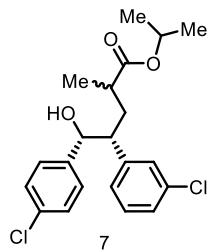
Wavelength: 220 nm,

Diluent: 100% 2-PrOH



UV-WL1 Results			
Retention Time	Area	Name	Area Percent
6.10	71423589	3657	99.91
9.01	62521	117396-15-5	0.09
Totals	71486110		100.00

Chiral HPLC data for 7

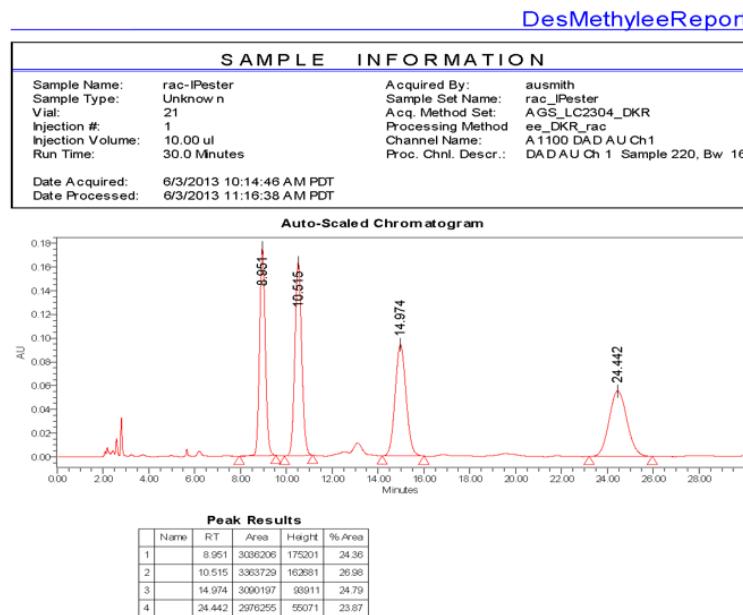


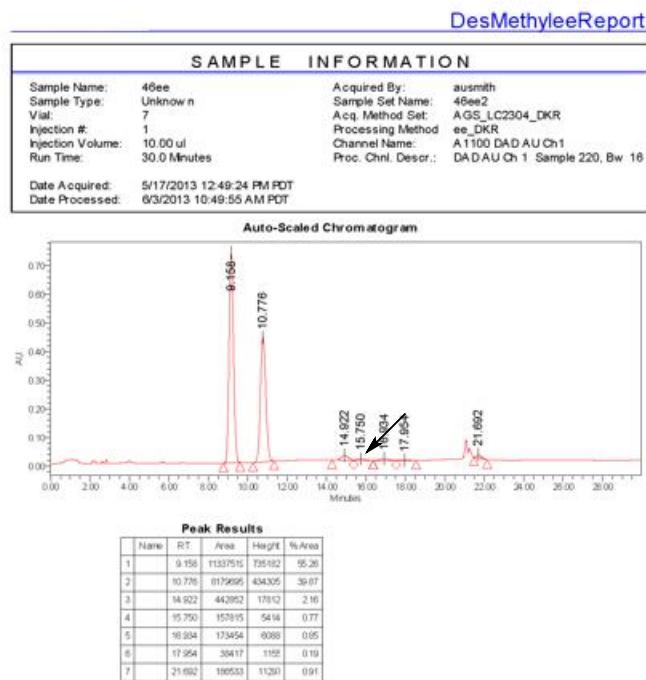
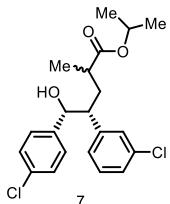
Chiral Analytical Method Conditions

Column: AD-H, 4.6 x 250 mm, 5 μ M
 Eluent: 2% EtOH in n-Hexane 1.5mL/min
 Column temperature: 20 °C
 Wavelength: 220 nm
 Diluent 50% IPA/50% n-Hexane

Racemic mixture

8.951 min: Isomer 1
 10.515 min: Isomer 2
 14.974 min: Isomer 2
 24.442 min: Isomer 1





Reported by User: Austin Smith (ausmith)
 Report Method: DesMethyleeReport
 Report Method ID: 28312
 Page: 1 of 1

Project Name: MDM212705932 (AMG 232)
 Date Printed: 6/3/2013
 10:51:32 AM US/Pacific

Peak	RT	Area Percent
Isomer 1, major enantiomer	9.158 min	55.26
Isomer 2, major enantiomer	10.776 min	39.87
Isomer 2, minor enantiomer	15.75 min	0.77
Isomer 1, minor enantiomer	21.692 min	0.91

Isomer 1 e.r.

$$55.26 \text{ (major)} / 0.91 \text{ (minor)} = 60.7$$

$$\text{Major (x) / minor (y)} = 60.7; \quad x = 60.7y$$

$$x + y = 100; \quad 60.7y + y = 100; \quad 61.7y = 100; \quad 100 / 61.7 = y; \quad y = 1.62$$

$$x + 1.62 = 100; \quad x = 98.38$$

Isomer 1 e.r. = 98.4 : 1.6

Isomer 2 e.r.

$$39.87 \text{ (major)} / 0.77 \text{ (minor)} = 51.8$$

$$\text{Major (x) / minor (y)} = 51.8; \quad x = 51.8y$$

$$x + y = 100; \quad 51.8y + y = 100; \quad 52.8y = 100; \quad 100 / 52.8 = y; \quad y = 1.89$$

$$x + 1.89 = 100; \quad x = 98.1$$

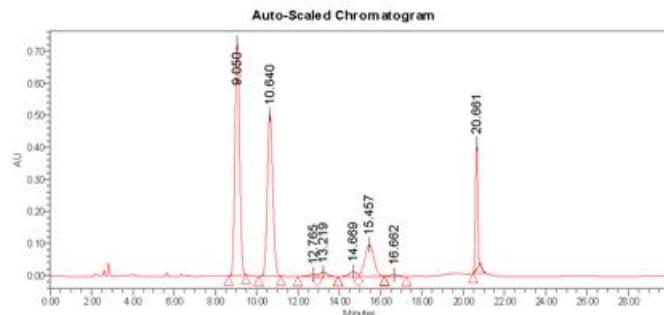
Isomer 2 e.r. = 98.1 : 1.9

Average e.r., Isomer 1 and 2 = 98.3: 1.7

Enantioenriched **7**, spiked with racemic **7**

DesMethyleeReport

SAMPLE INFORMATION	
Sample Name:	46eespiked
Sample Type:	Unknown
Vial:	7
Injection #:	1
Injection Volume:	10.00 μ l
Run Time:	30.0 Minutes
Acquired By:	ausmith
Sample Set Name:	46ee2
Acq. Method Set:	AGS_LC2304_DKR
Processing Method:	ee_DKR_spiked
Channel Name:	A1100 DAD AU Ch1
Proc. Chnl. Descr.:	DAD AU Ch 1 Sample 220, Bw 16
Date Acquired:	5/17/2013 1:21:09 PM PDT
Date Processed:	6/3/2013 11:41:50 AM PDT



Peak Results

Name	RT	Area	Height	%Area
1	9.050	1115786	726229	40.73
2	10.640	9277703	604457	33.85
3	12.765	187751	7421	0.69
4	13.219	343330	12648	1.25
5	14.689	357389	14817	1.30
6	15.457	2996603	99010	10.95
7	16.662	133384	5055	0.49
8	20.661	2940663	388331	10.74

Reported by User: Austin Smith (ausmith)
 Report Method: DesMethyleeReport
 Report Method ID: 28312
 Page: 1 of 1

Project Name: MDM22705932 (AMG 232)
 Date Printed:
 6/3/2013
 11:43:38 AM US/Pacific