Enantioselective synthesis of an octahydroindolizine (indolizidine) alcohol using an enzymatic resolution

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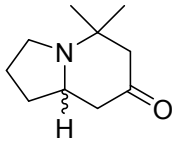
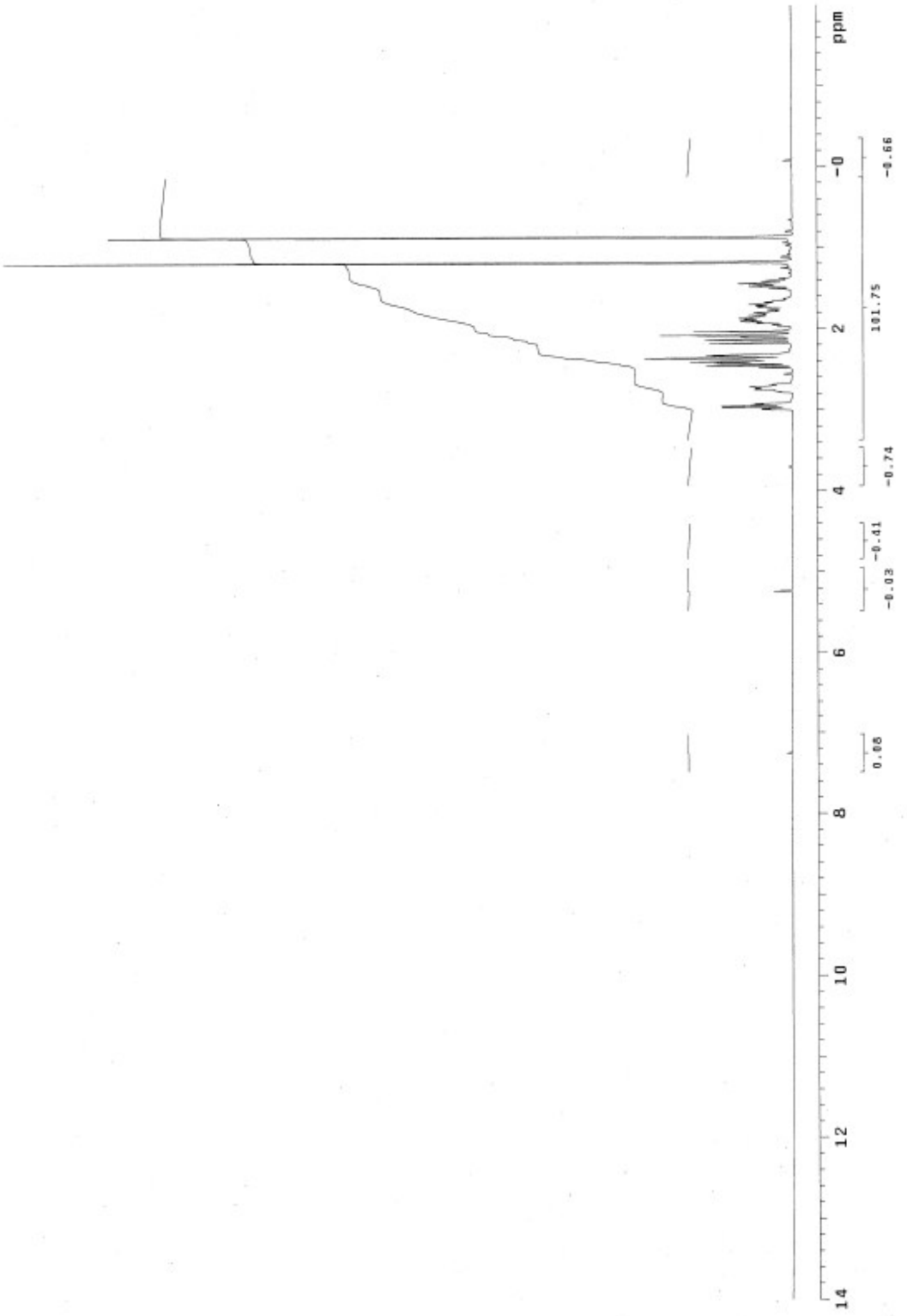
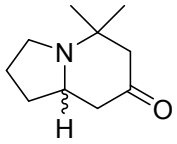
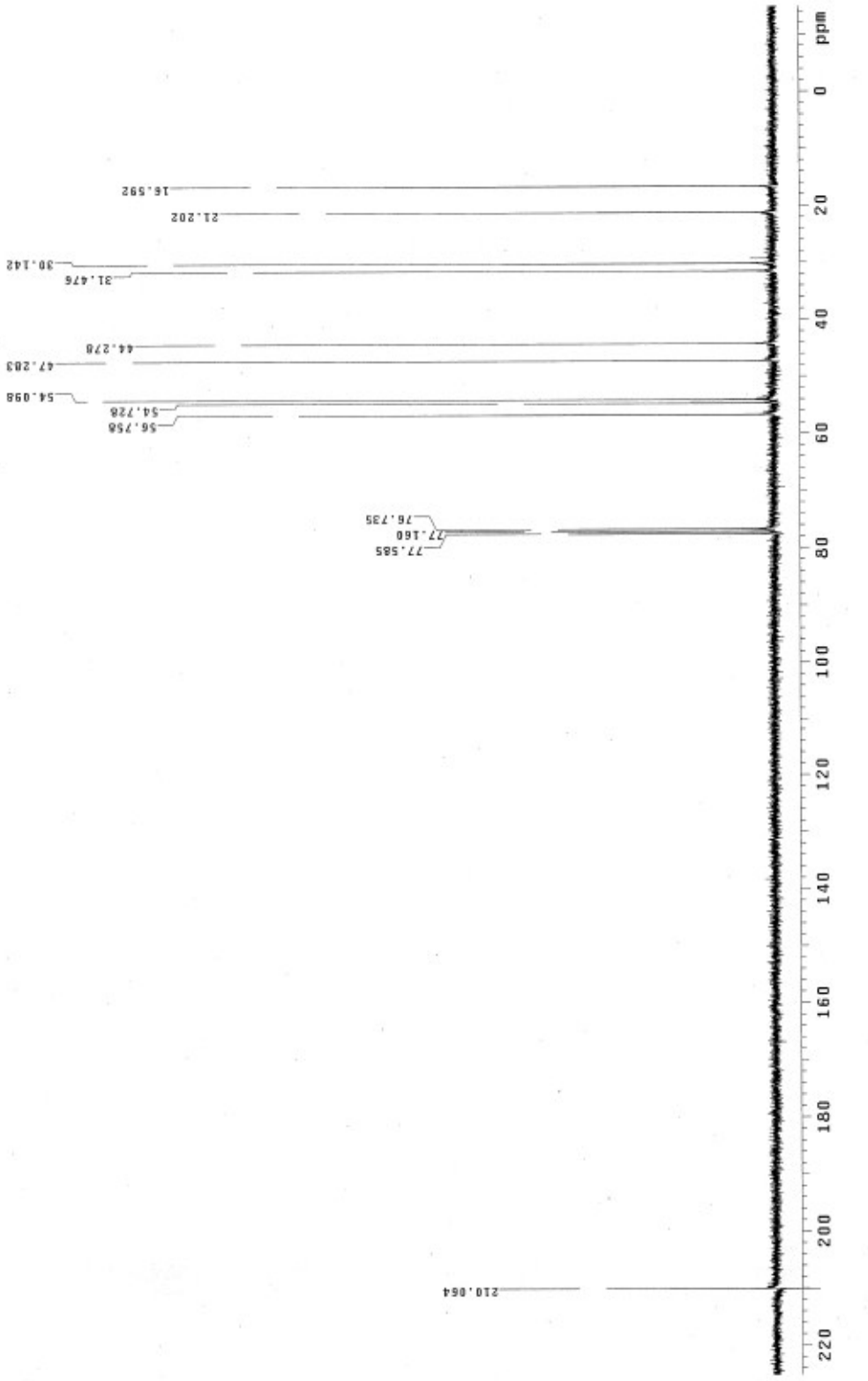




^{13}C NMR FOR (±)-HEXAHYDRO-5,5-DIMETHYLINDOLIZIN-(1*H*)-ONE 10





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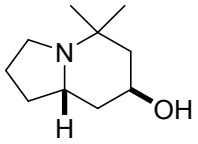

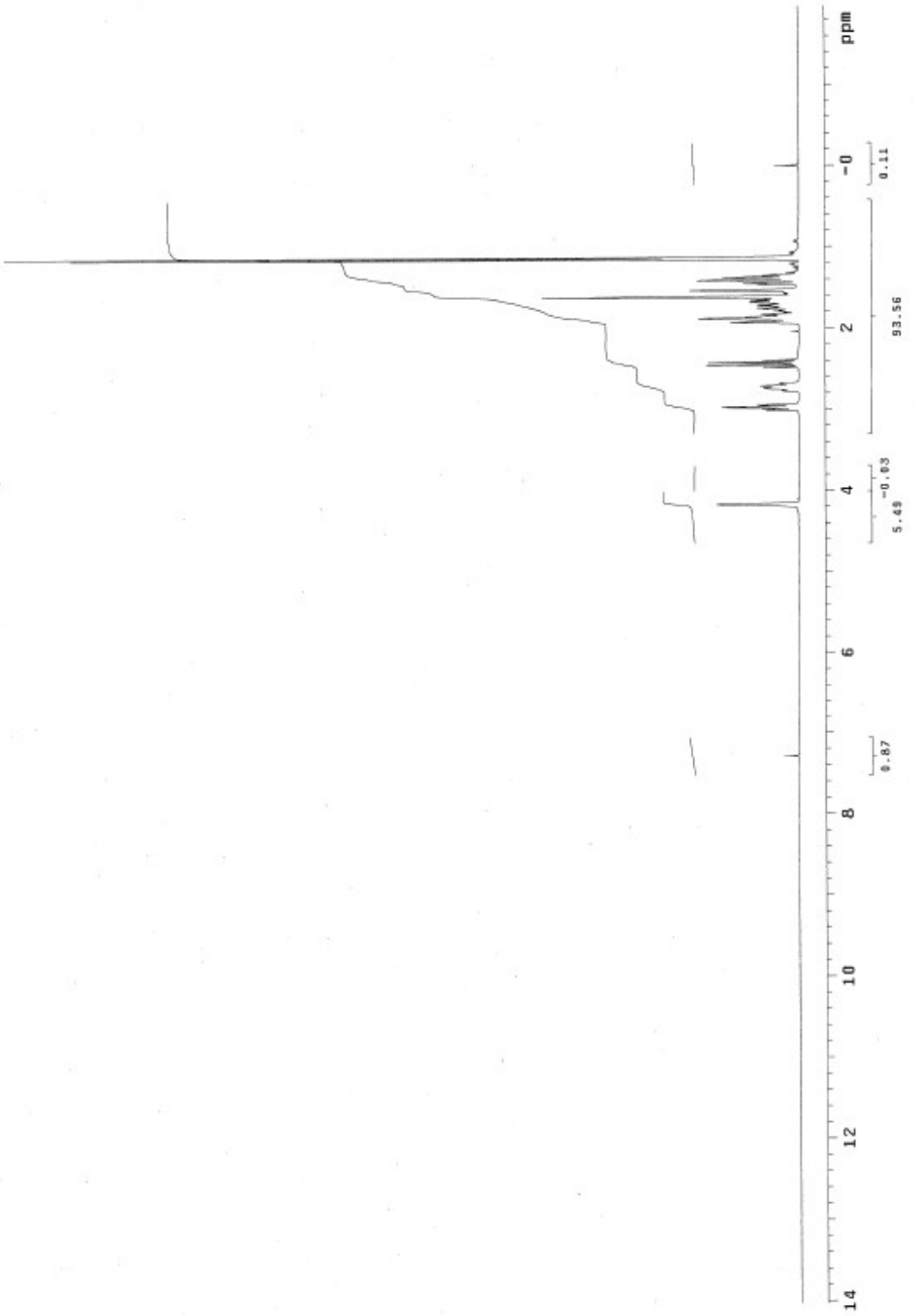

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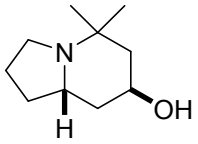

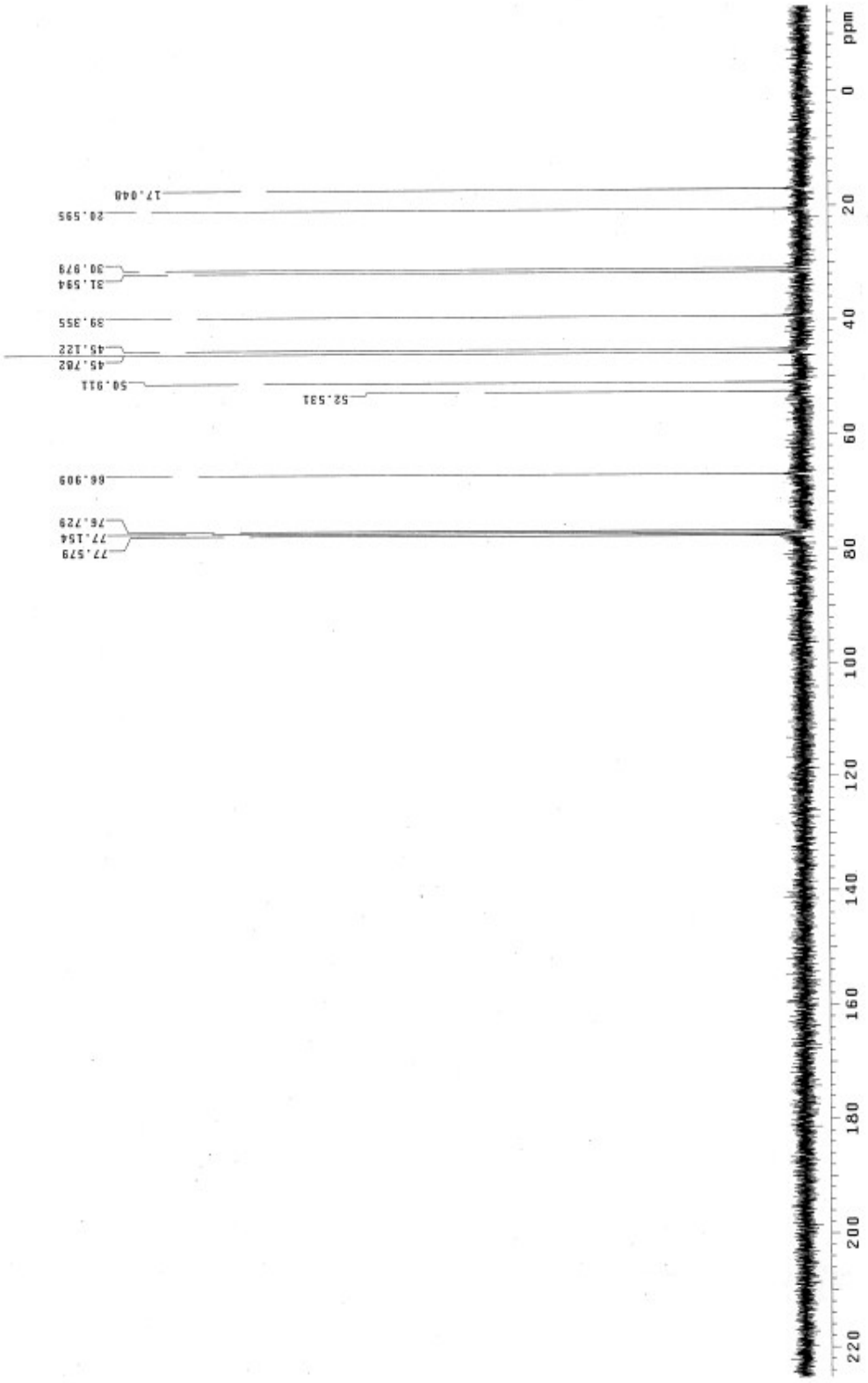

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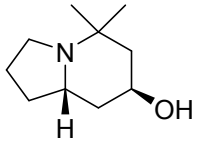

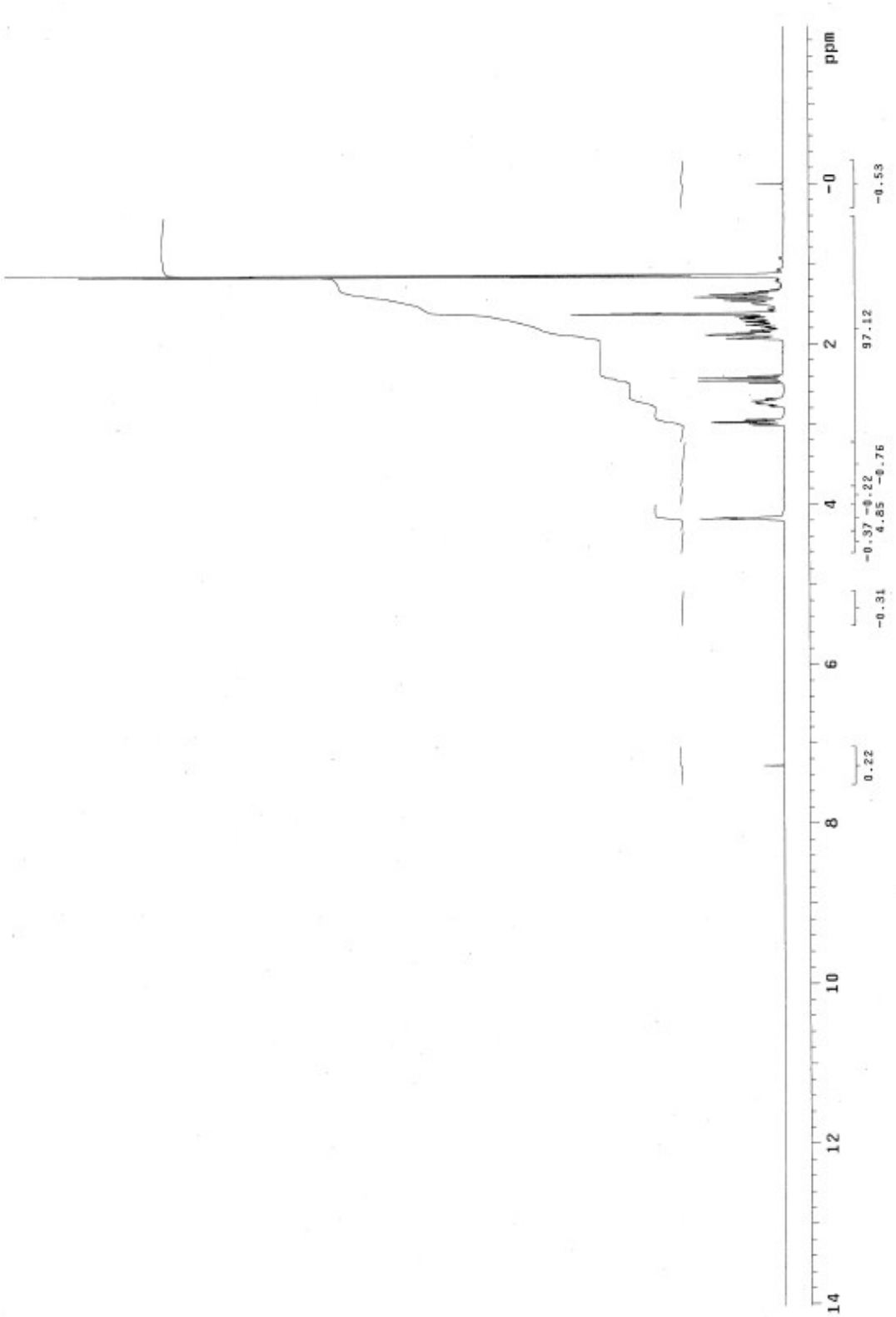

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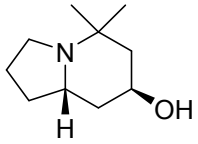
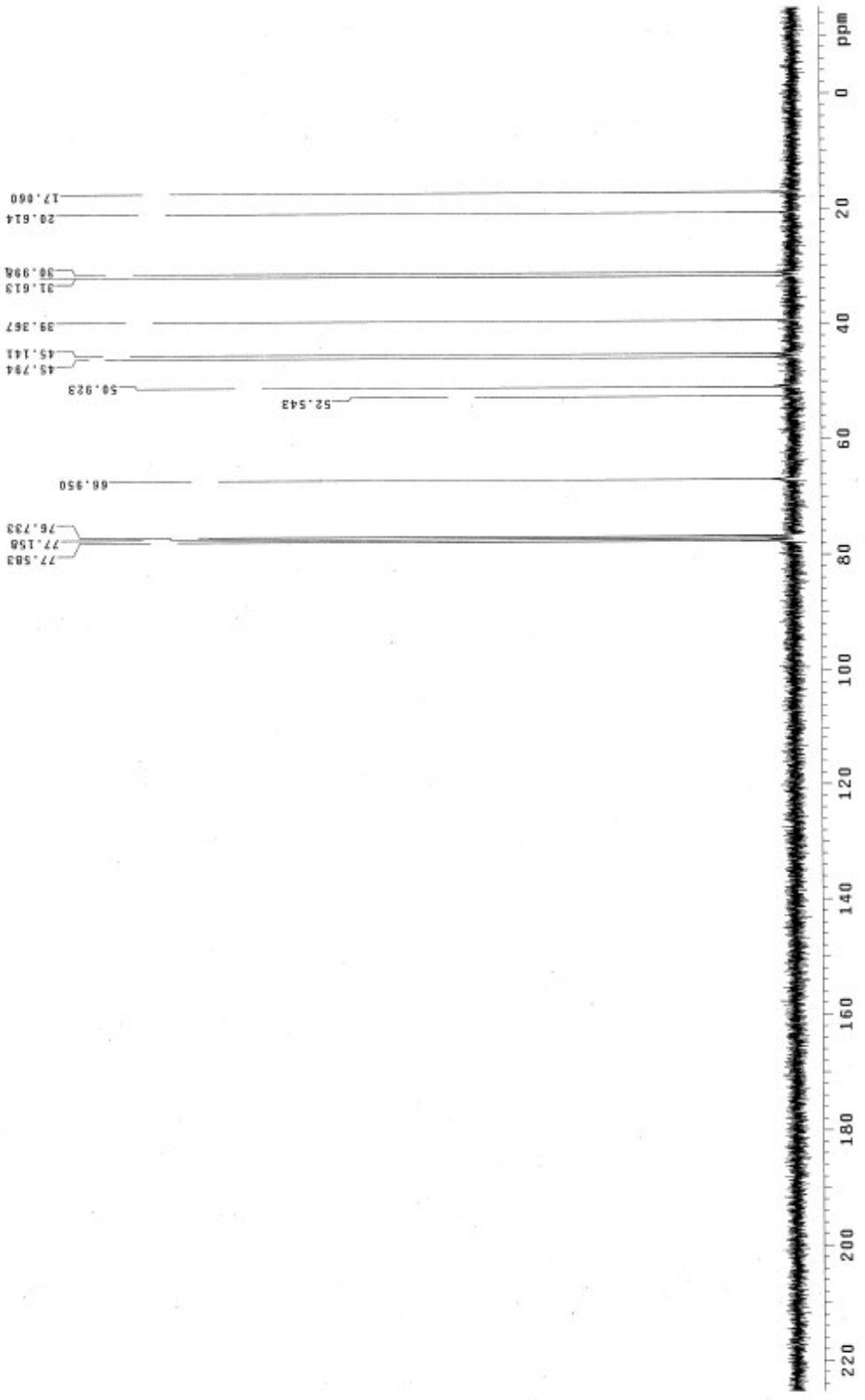
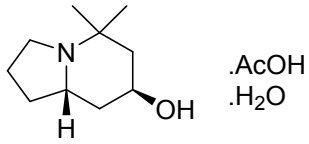




^{1}H NMR FOR (7*S*, 8*AS*)-HEXAHYDRO-5,5-DIMETHYLINDOLIZIN-7-OL 9, ACETIC ACID SALT MONOHYDRATE**



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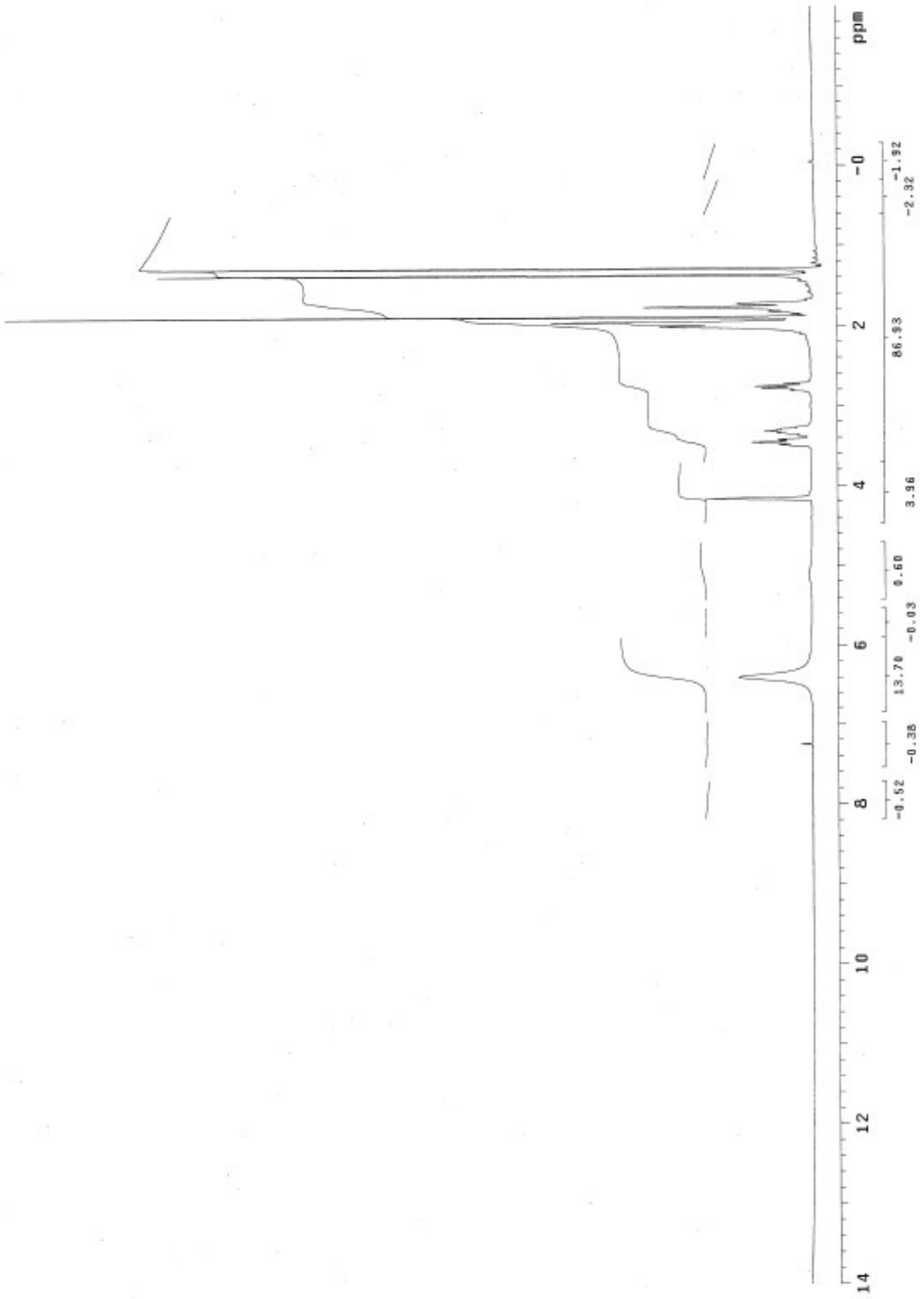
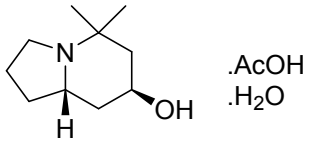
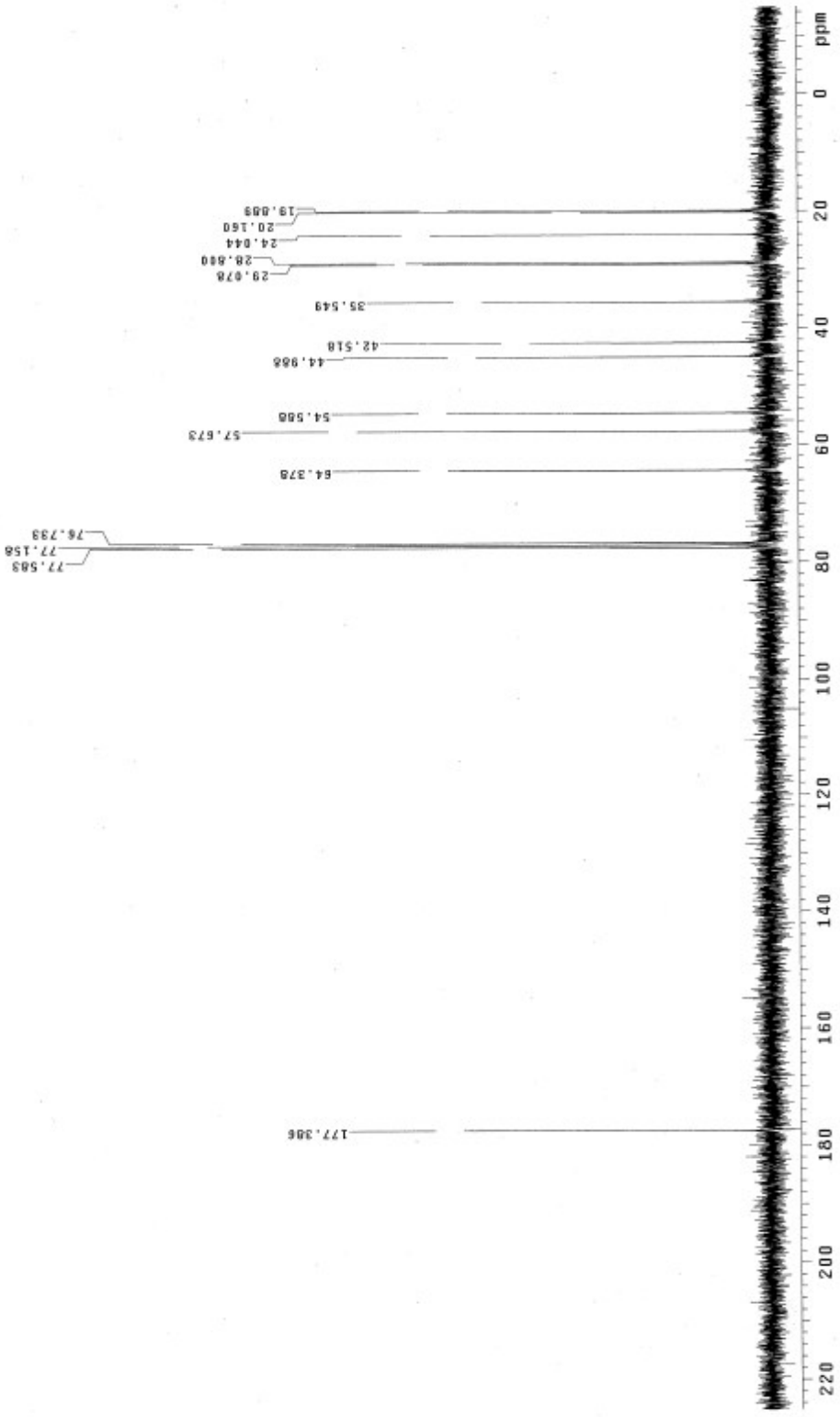
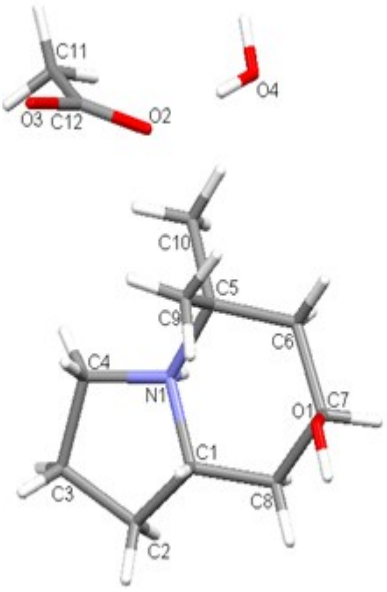


^{13}C NMR FOR (7*S*, 8*AS*)-HEXAHYDRO-5,5-DIMETHYLINDOLIZIN-7-OL 9, ACETIC ACID SALT MONOHYDRATE

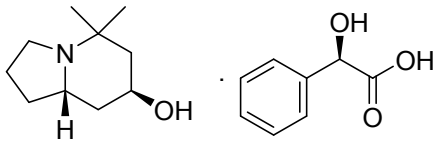


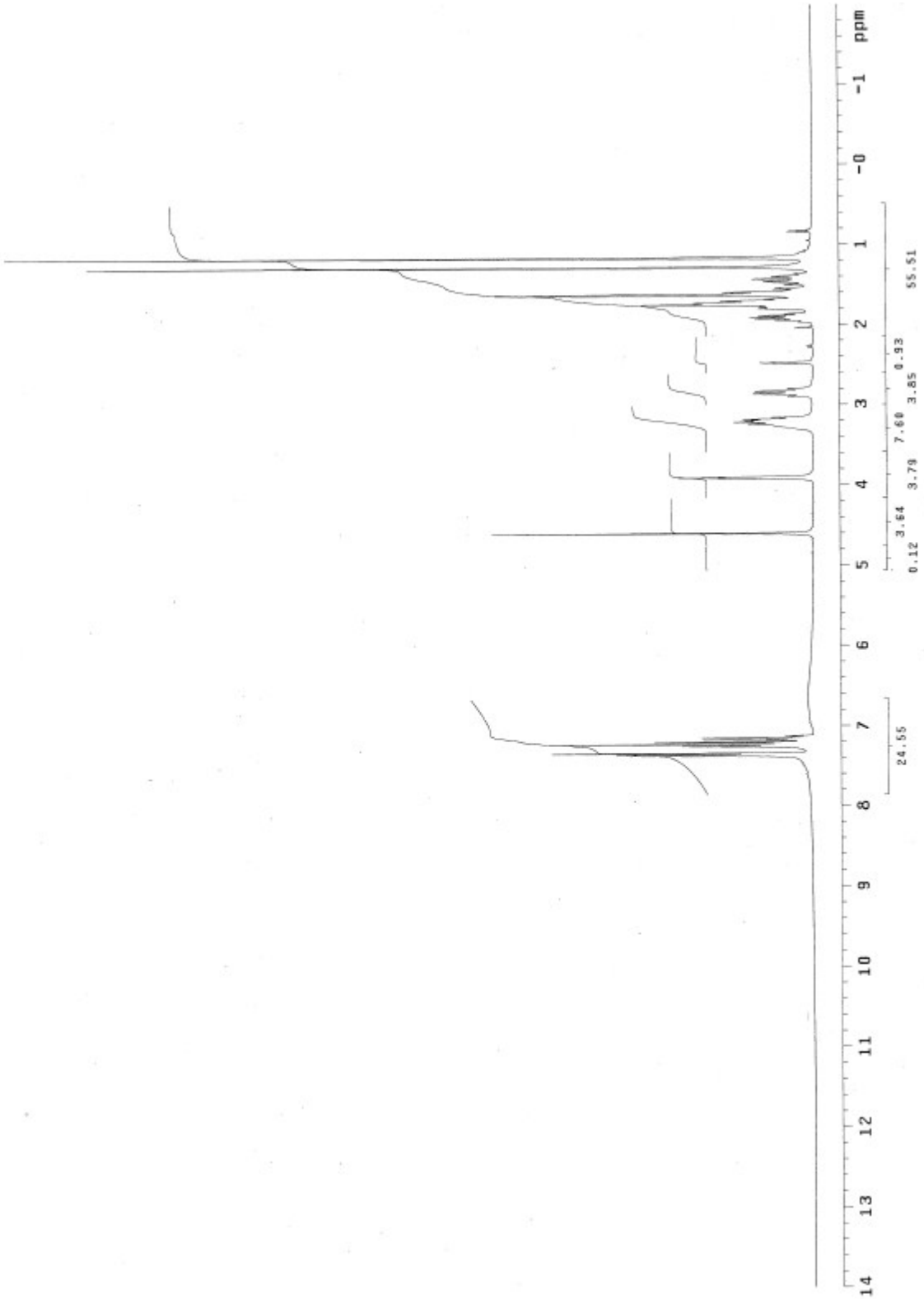


X-RAY STRUCTURE FOR (7*S*, 8*AS*)-HEXAHYDRO-5,5-DIMETHYLINDOLIZIN-7-OL 9, ACETIC ACID SALT MONOHYDRATE (NOTE: SEPARATE CIF FILE ALSO IN SUPPLEMENTAL INFORMATION)**

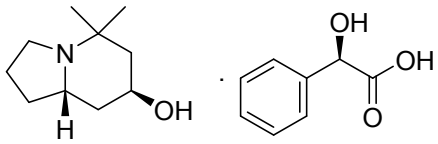


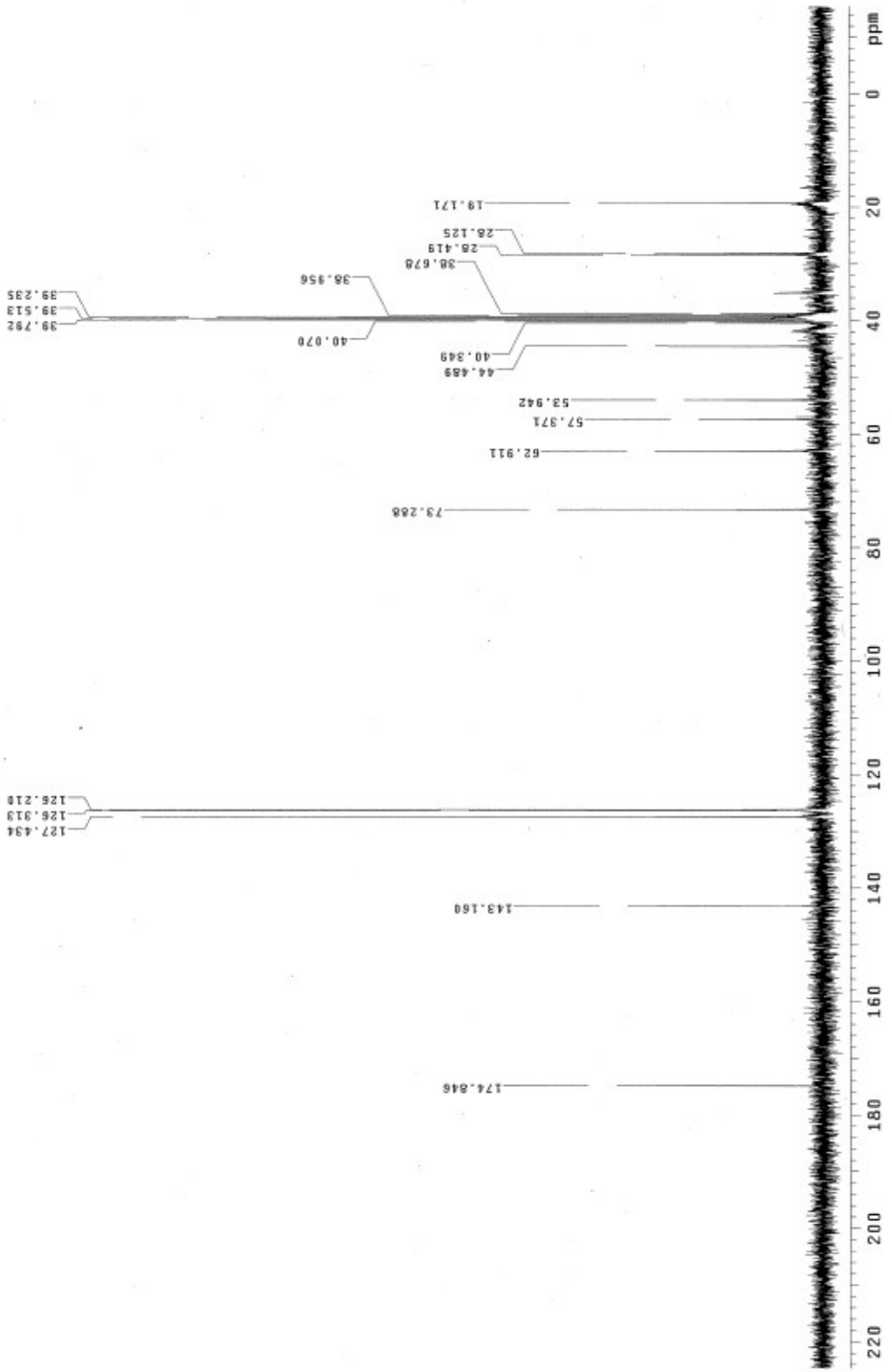
^{1}H NMR FOR (7*S*, 8*AS*)-HEXAHYDRO-5,5-DIMETHYLINDOLIZIN-7-OL 9, MANDELIC ACID SALT



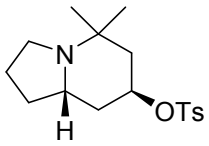


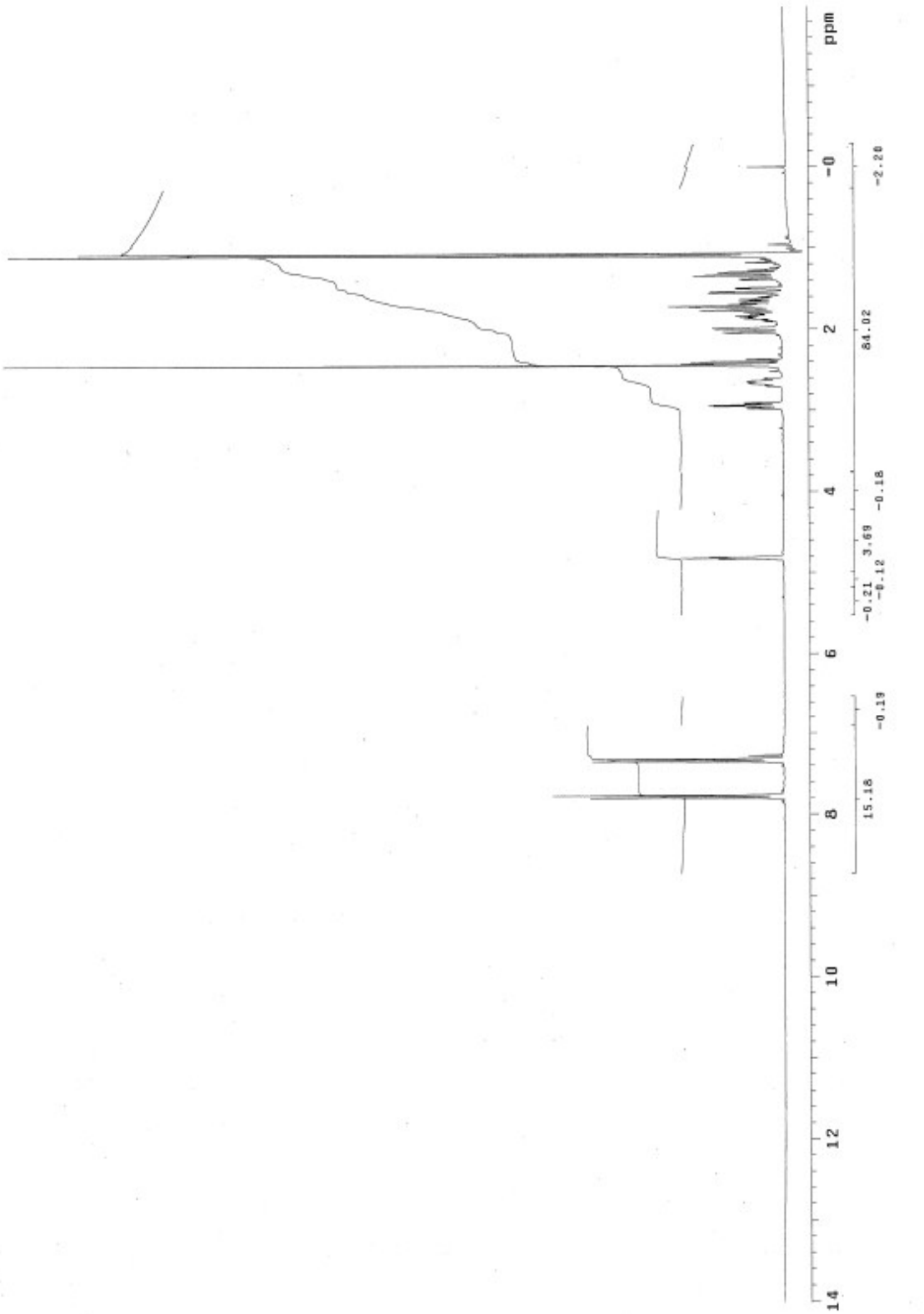
^{13}C NMR FOR (7*S*, 8*aS*)-HEXAHYDRO-5,5-DIMETHYLINDOLIZIN-7-OL 9, MANDELIC ACID SALT





^{1}H NMR FOR (7*S*, 8*AS*)-HEXAHYDRO-5,5-DIMETHYLINDOLIZIN-4-METHYLBENZENESULFONATE 17





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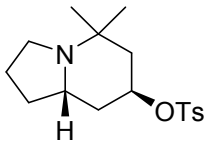
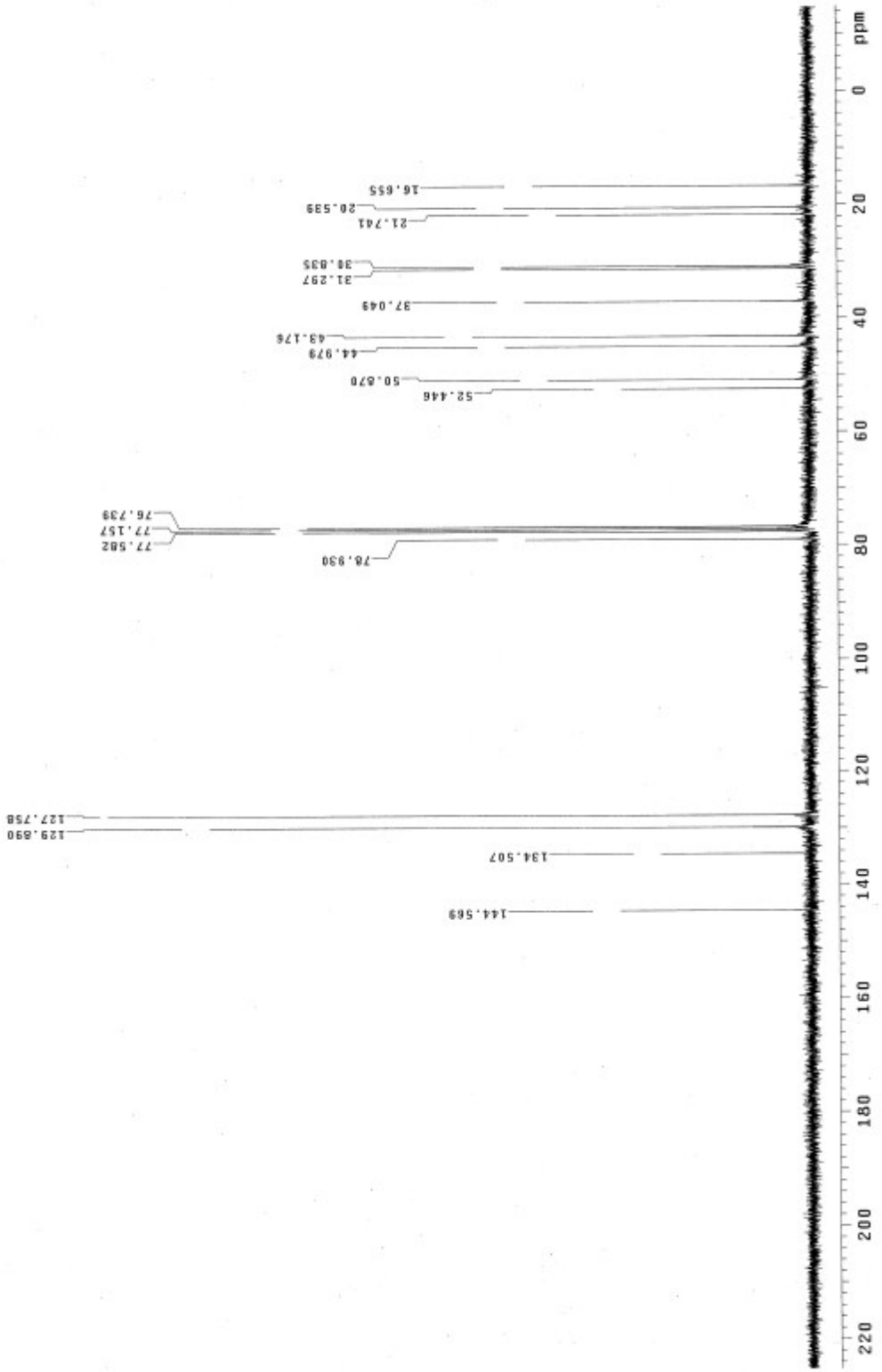
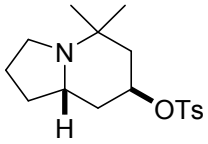
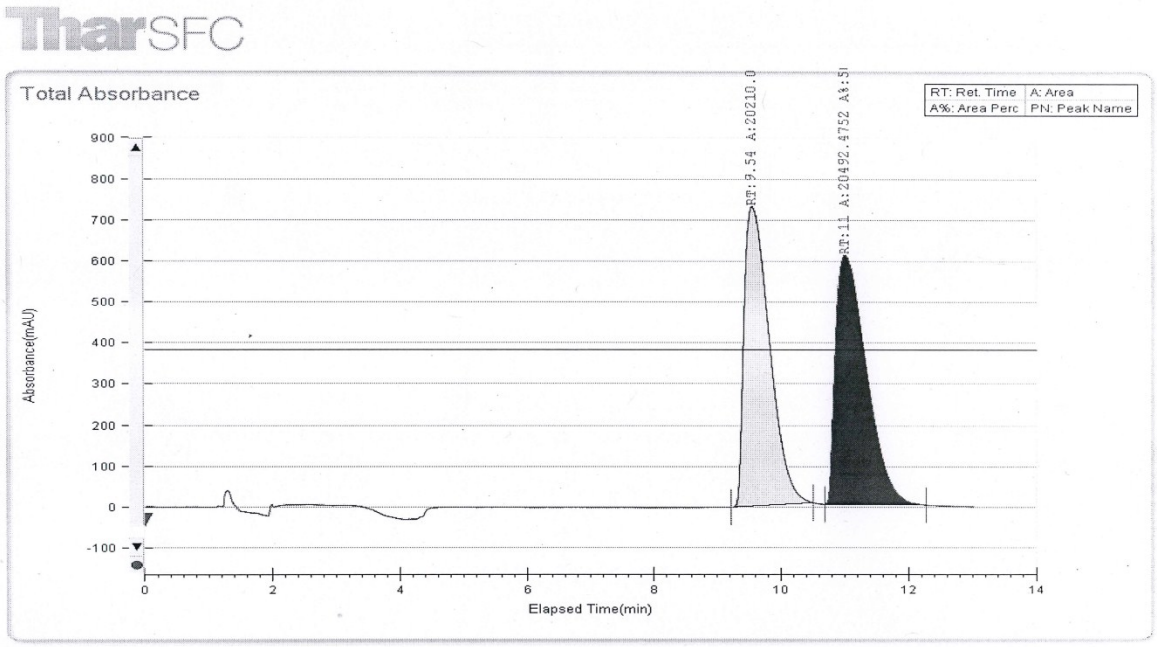




COPY OF CHIRAL SFC FOR RACEMIC (±)-HEXAHYDRO-5,5-DIMETHYLINDOLIZIN-4-METHYLBENZENESULFONATE





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Report By	current_User		

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Inj Vol	10	Flow	3
Solvent	IPA (0.1% DEA)	% Modifier	8
Column	AD-H 4.6mm	Pressure	100
Sample	1740-151A		
Well location	P1: 5A		

Peak Info

Peak No	% Area	Area	RT (min)	Height (mV)	K'
1	49.6531	20210.0644	9.54	731.5293	0.011
2	50.3469	20492.4752	11	608.8674	0.0127
Total:	100	40702.5396			

Column: Daicel Chemical Industries, Chiralcel AD-H, 4.6x250 mm

Mobile phase: 8% Isopropanol (IPA contains 0.1% diethylamine) / 92% CO_2; isocratic

Flow rate: 3 ml/min

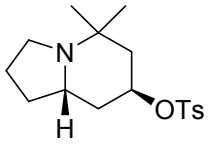
Run time: 13-15 minutes

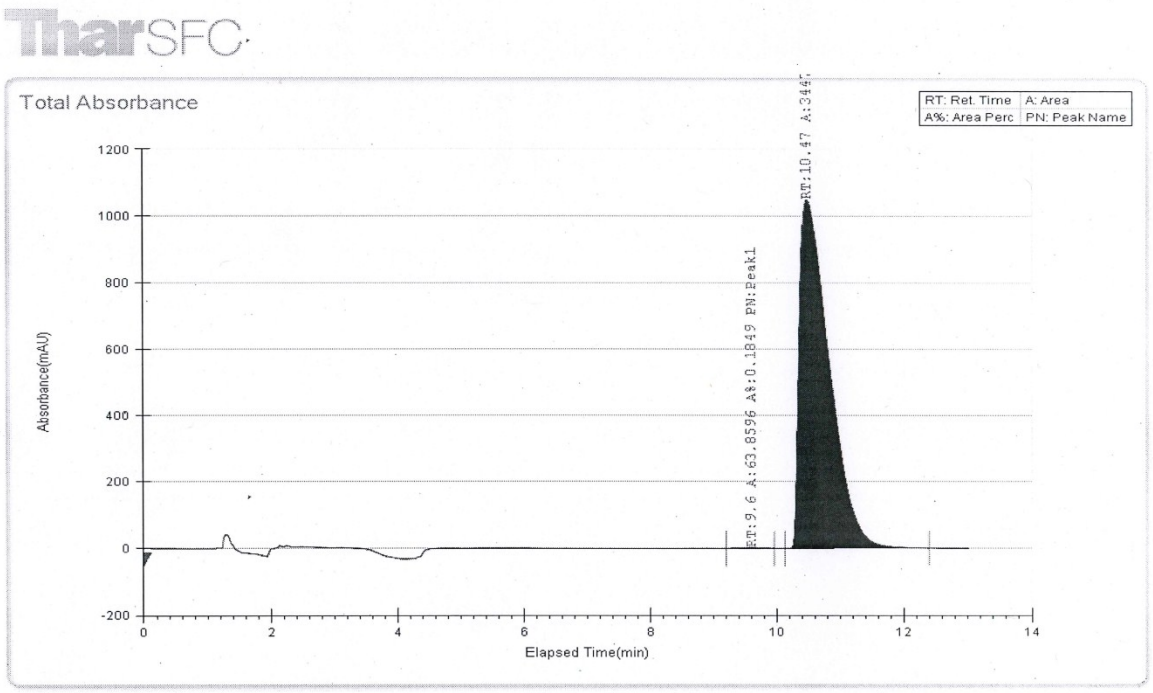
Temperature: 26.7°C

Detection: 254nm

SFC: TharSFC Investigator

COPY OF CHIRAL SFC FOR (7*S*, 8*AS*)-HEXAHYDRO-5,5-DIMETHYLINDOLIZIN-4-METHYLBENZENESULFONATE 17





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Solvent	IPA (0.1% DEA)	**% Modifier**	8
Column	AD-H 4.6mm	**Pressure**	100
Sample	1740-151B		
Well location	P1: 6A		

Peak Info

Peak No	% Area	Area	RT (min)	Height (mV)	K'
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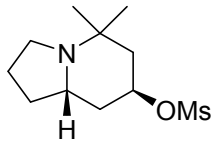
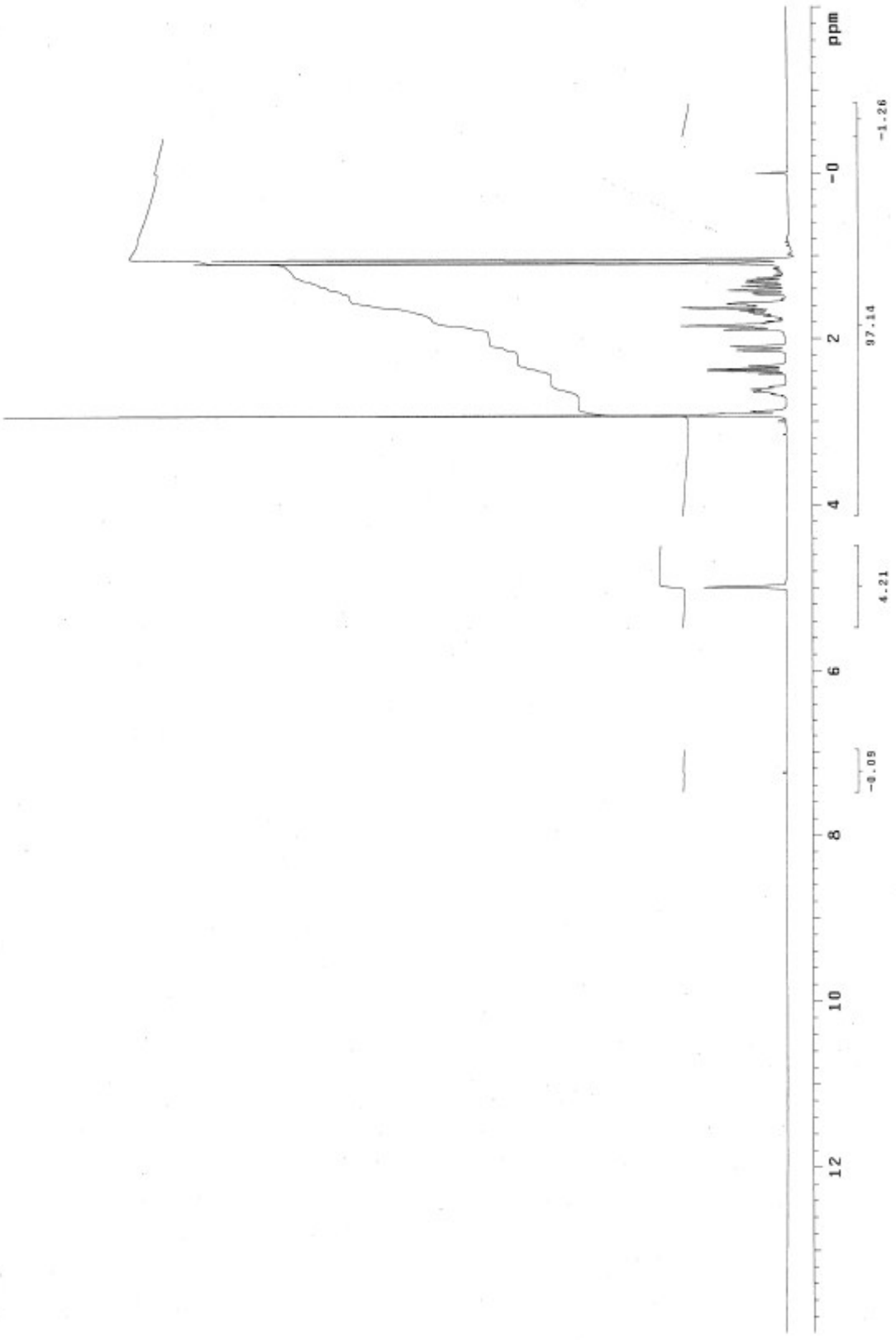
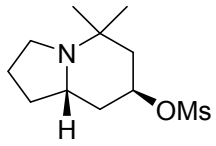
2	99.8151	34475.2386	10.47	1047.97	0.0119
Total:	100	34539.0982			

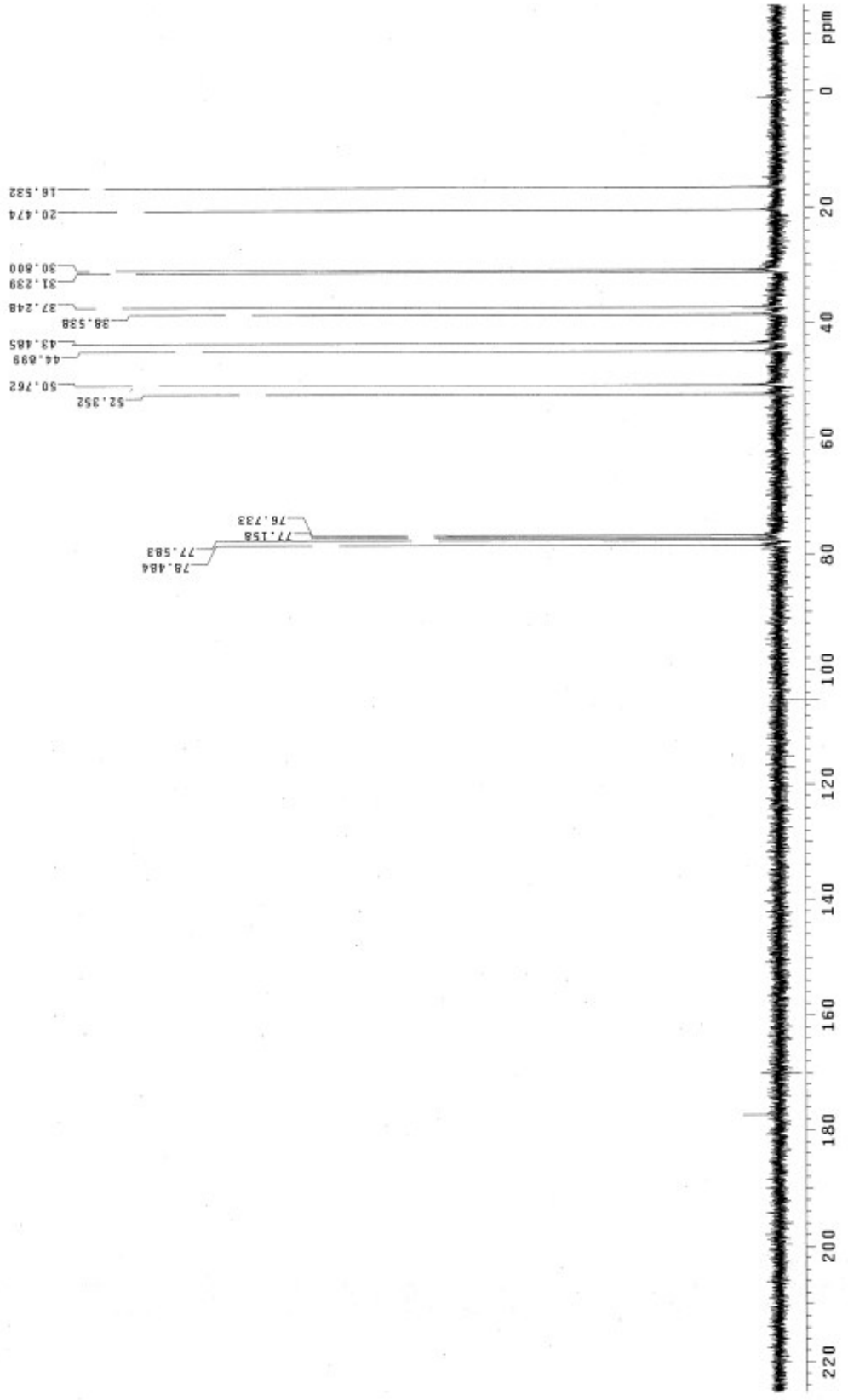
^{1}H NMR FOR (7*S*, 8*AS*)-HEXAHYDRO-5,5-DIMETHYLINDOLIZIN-4-METHANESULFONATE 18



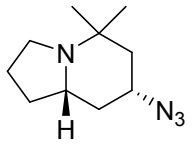


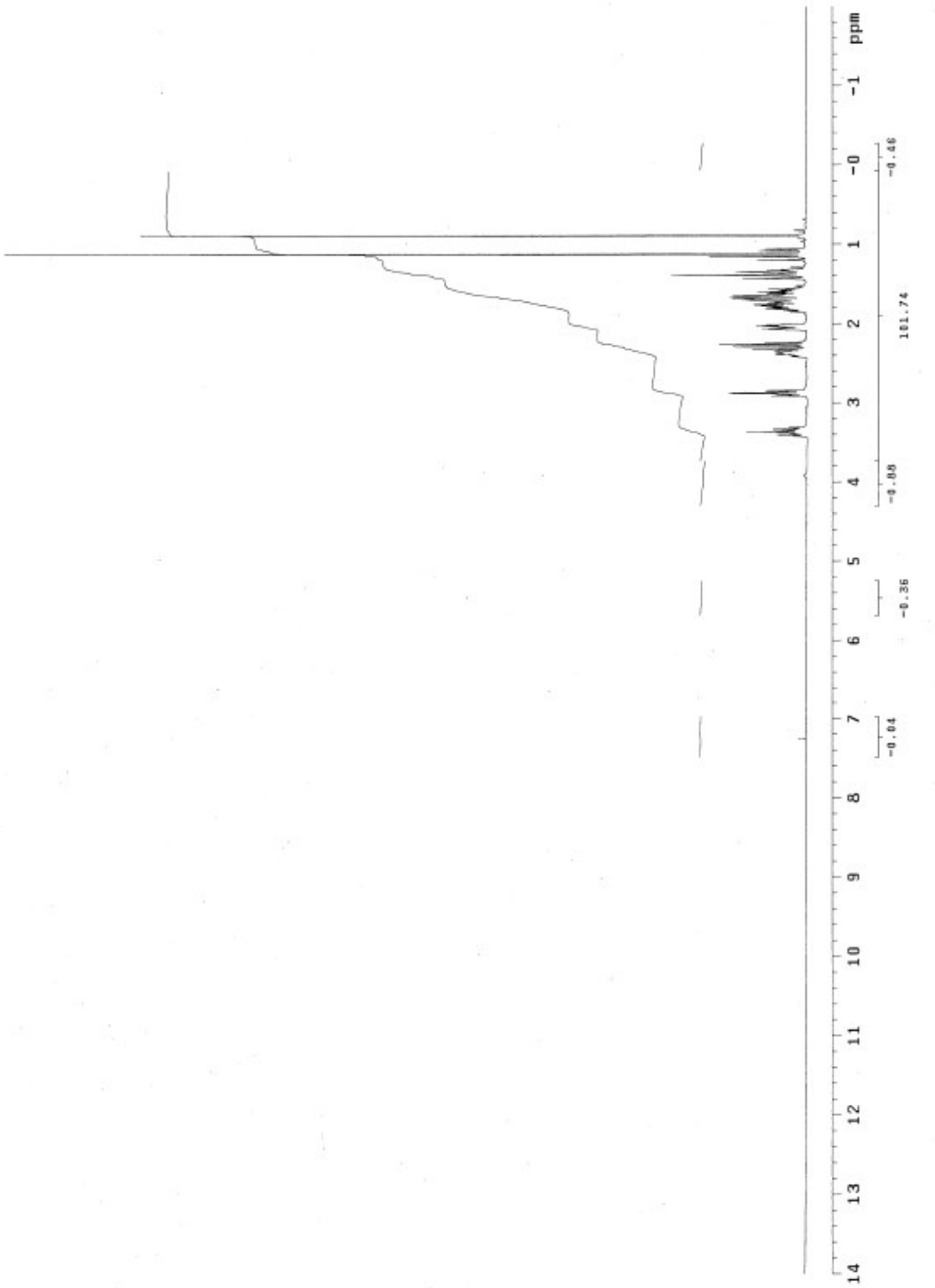
^{13}C NMR FOR (7*S*, 8*AS*)-HEXAHYDRO-5,5-DIMETHYLINDOLIZIN-4-METHANESULFONATE 18**



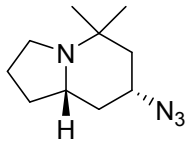


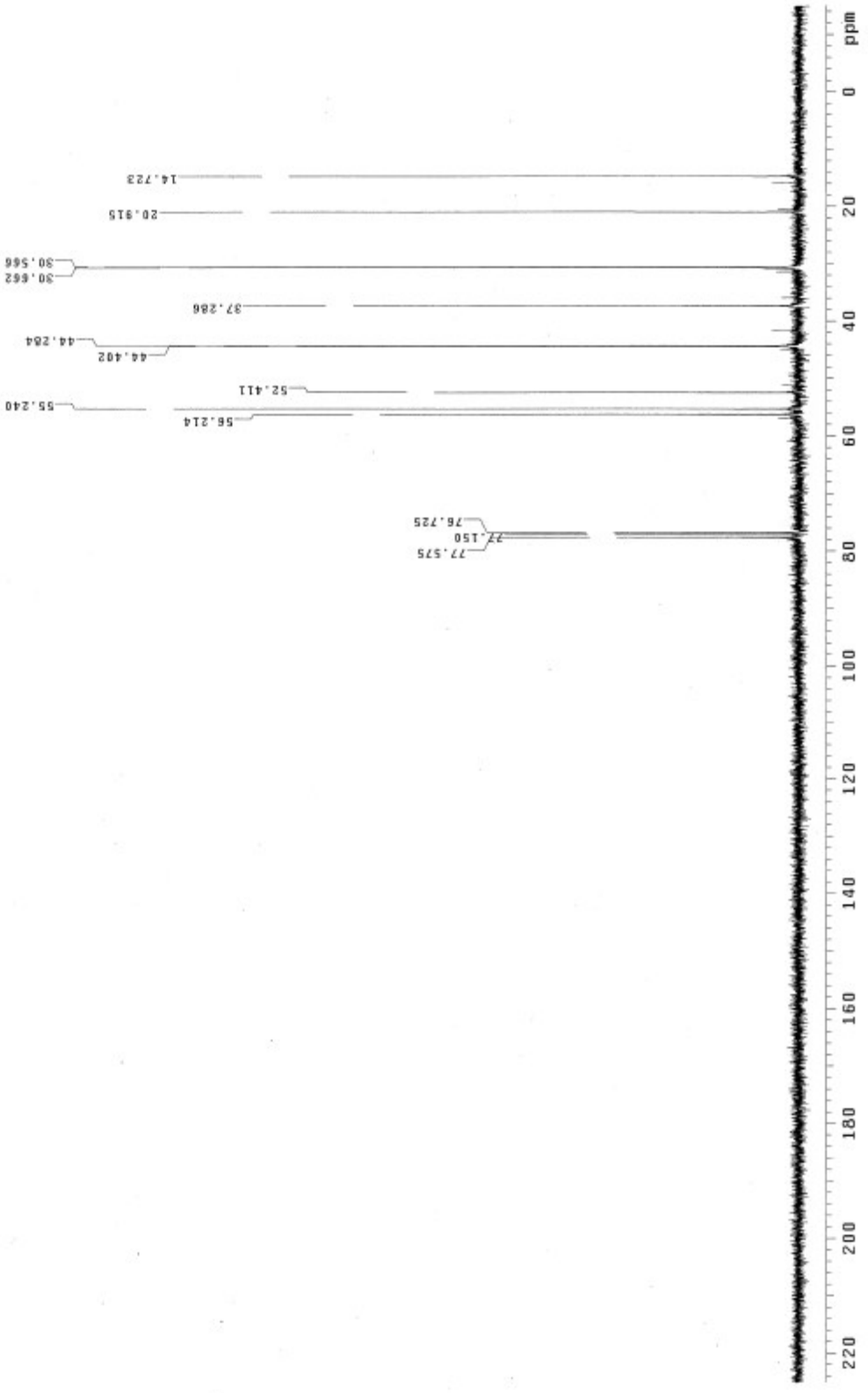
^{1}H NMR FOR (7*R*,8*AS*)-7-AZIDO-OCTAHYDRO-5,5-DIMETHYLINDOLIZINE 19**



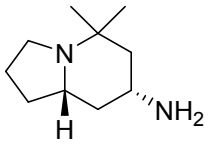


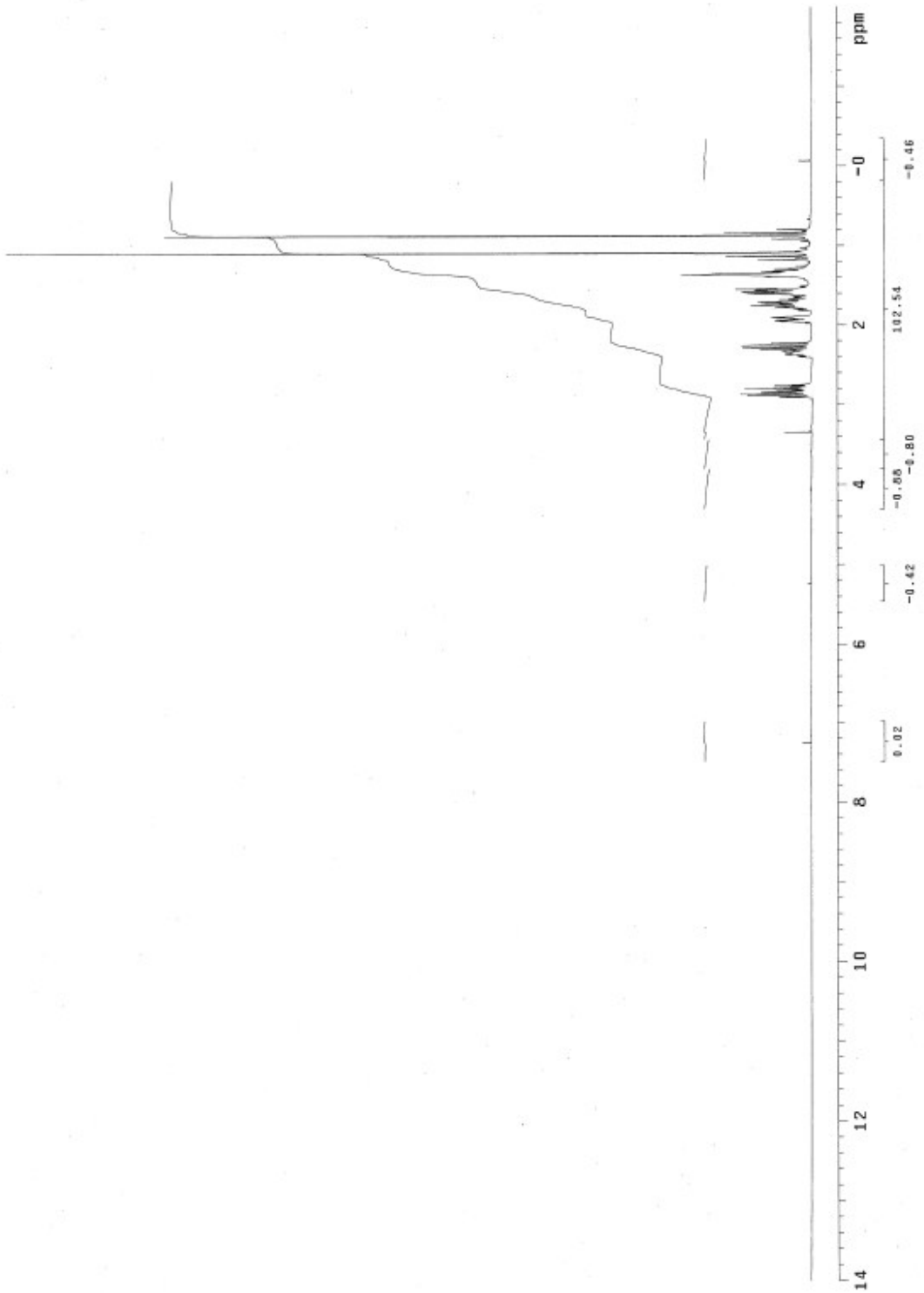
^{13}C NMR FOR (7*R*,8*AS*)-7-AZIDO-OCTAHYDRO-5,5-DIMETHYLINDOLIZINE 19**



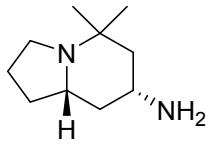


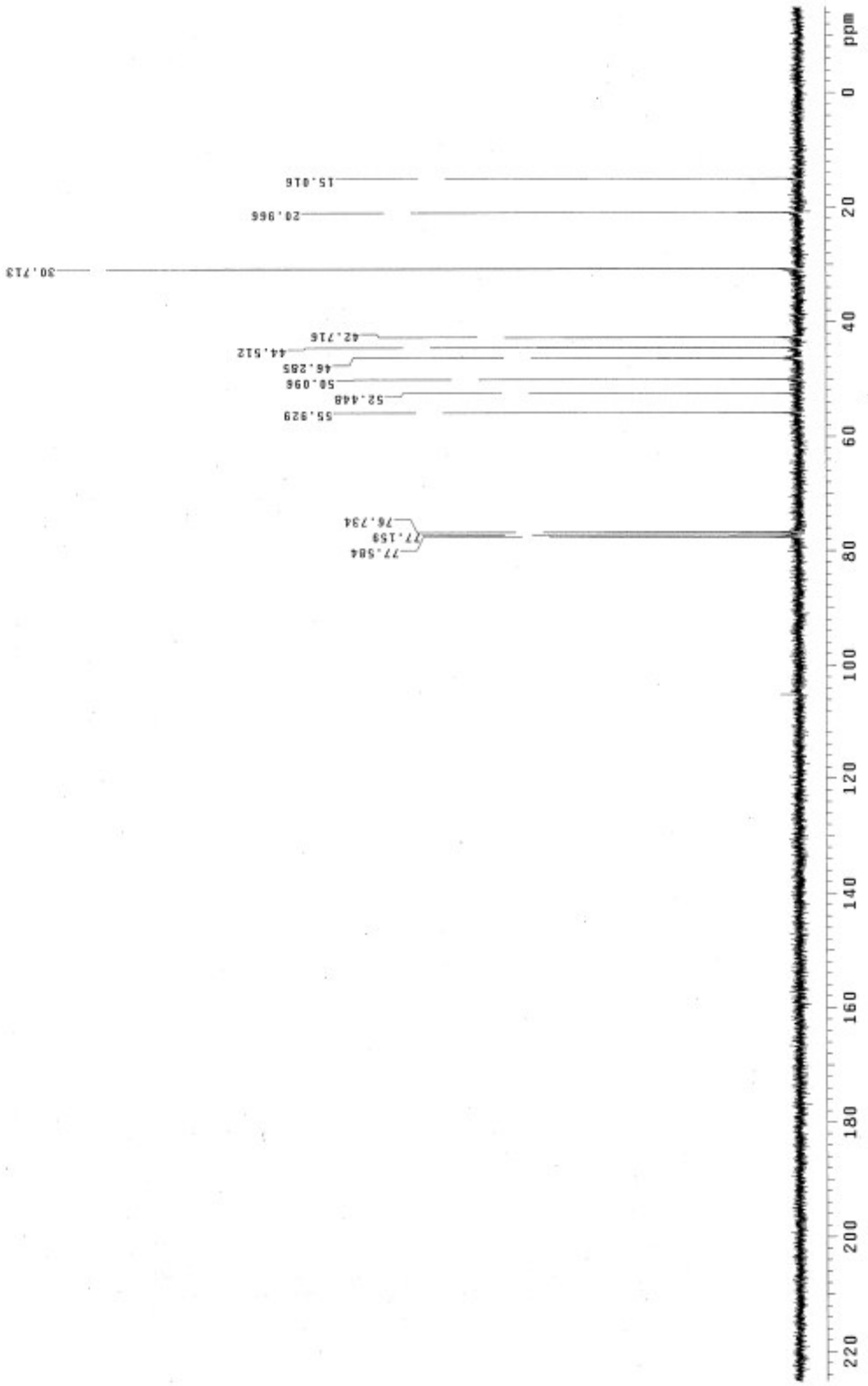
^{1}H NMR FOR (7*R*,8*AS*)-OCTAHYDRO-5,5-DIMETHYLINDOLIZIN-7-AMINE 8**



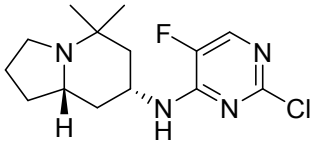


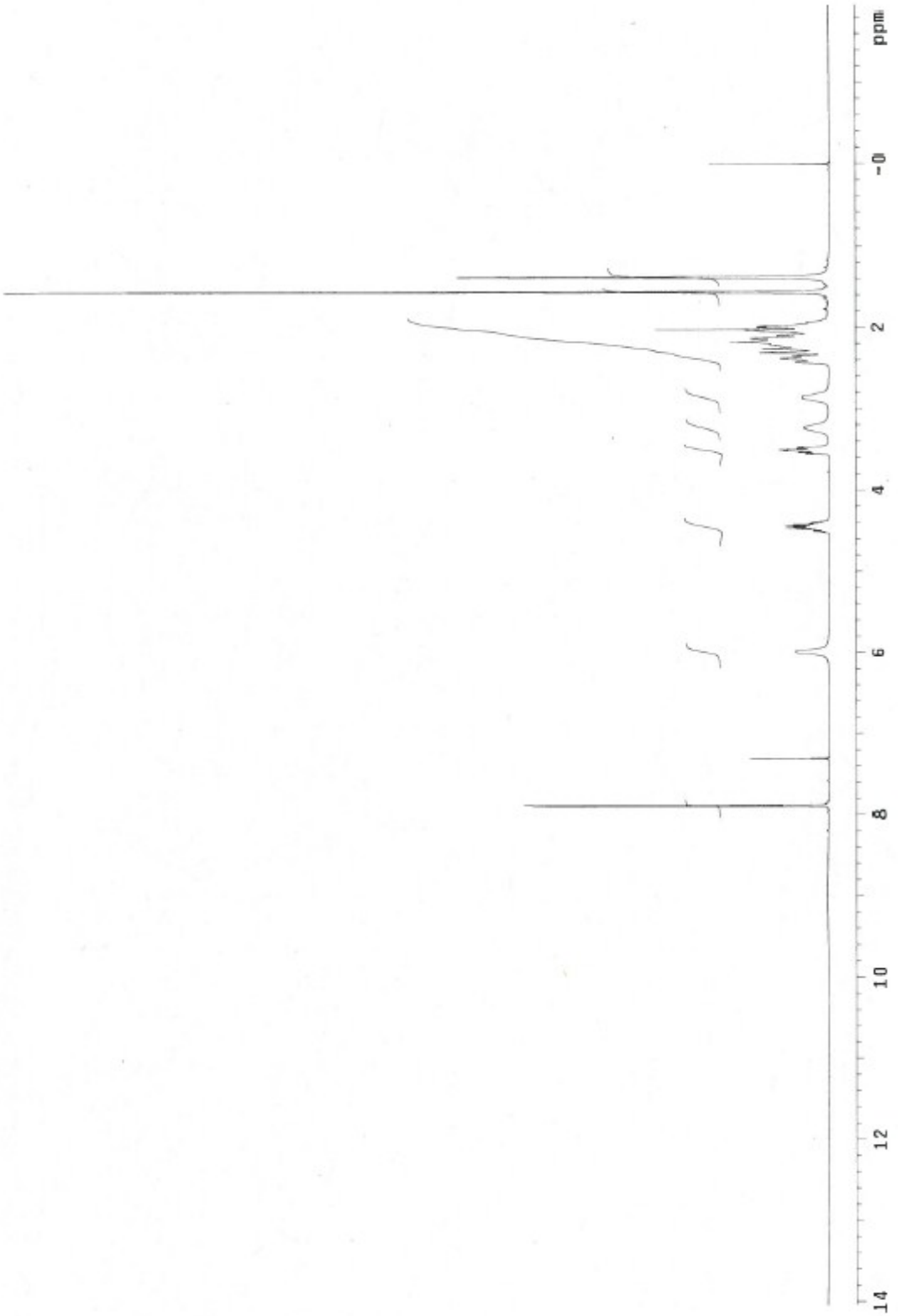
^{13}C NMR FOR (7*R*,8*AS*)-OCTAHYDRO-5,5-DIMETHYLINDOLIZIN-7-AMINE 8**



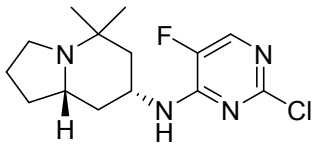


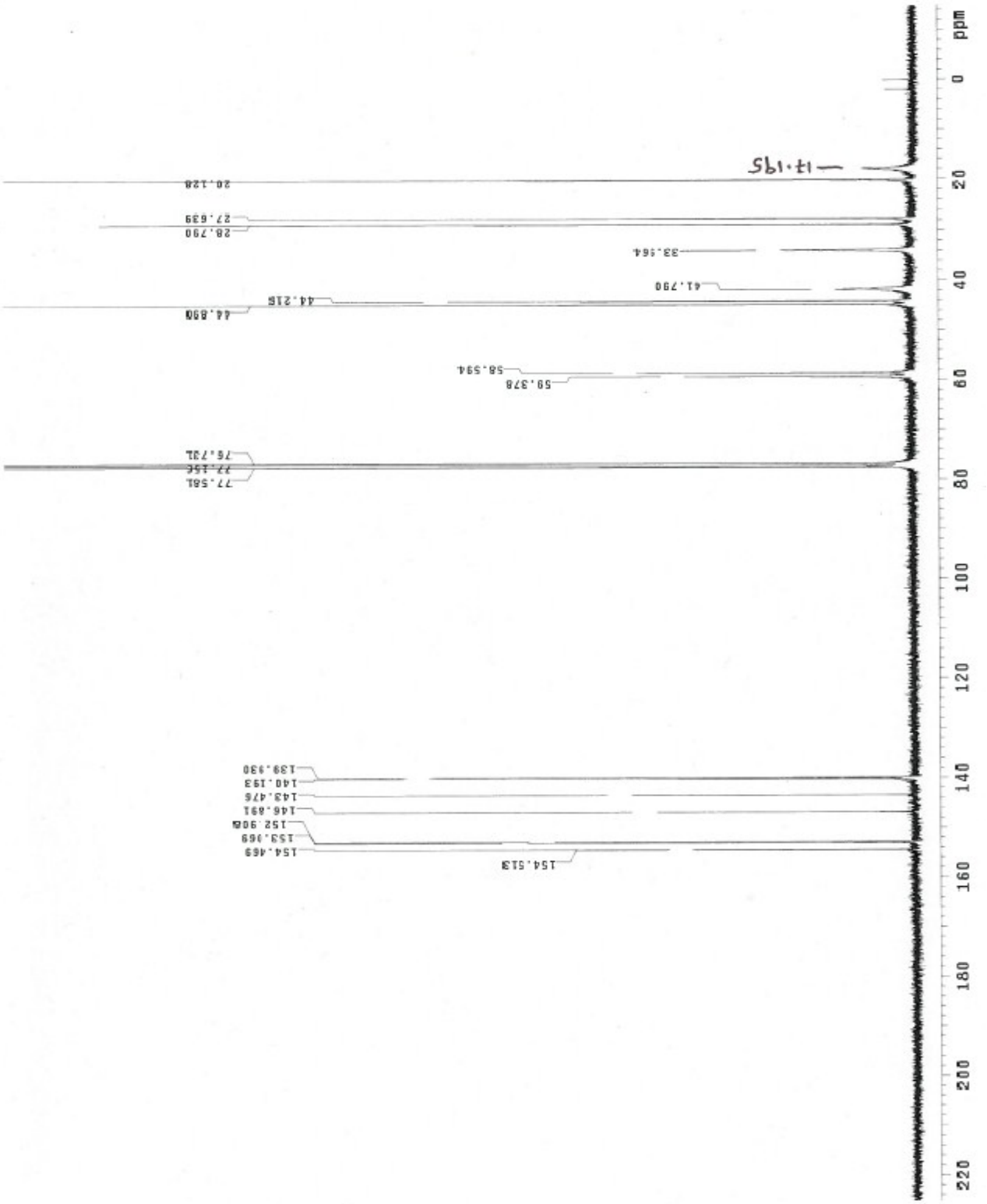
^{1}H NMR FOR (7*R*,8*AS*)-*N*-(2-CHLORO-5-FLUOROPYRIMIDIN-4-YL)-OCTAHYDRO-5,5-DIMETHYLINDOLIZIN-7-AMINE 20**



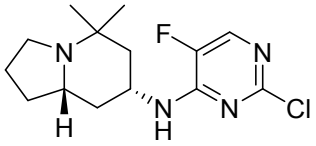


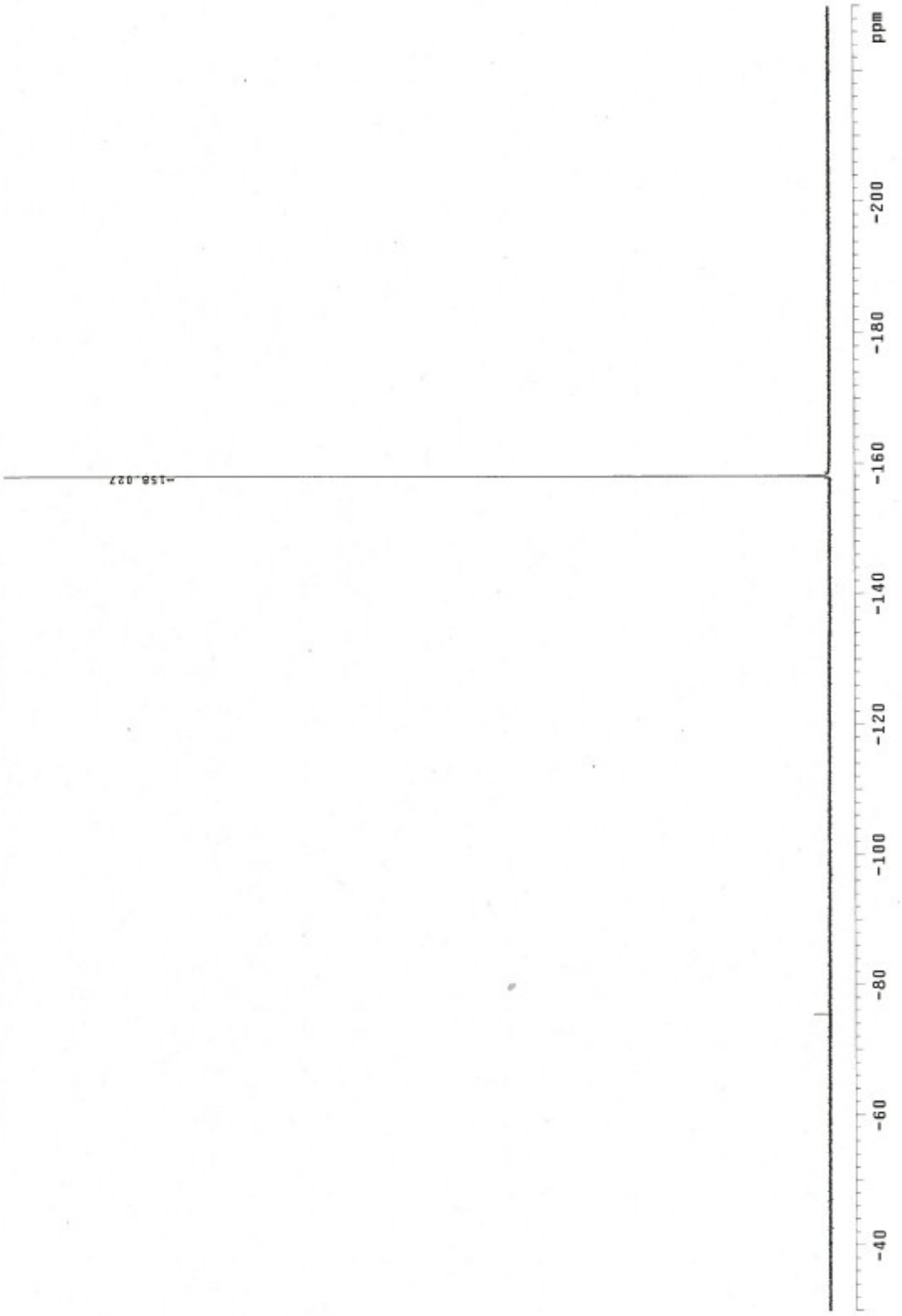
^{1}H NMR FOR (7*R*,8*AS*)-*N*-(2-CHLORO-5-FLUOROPYRIMIDIN-4-YL)-OCTAHYDRO-5,5-DIMETHYLINDOLIZIN-7-AMINE 20**



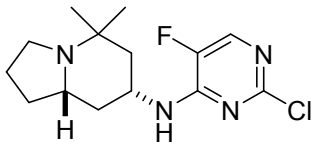


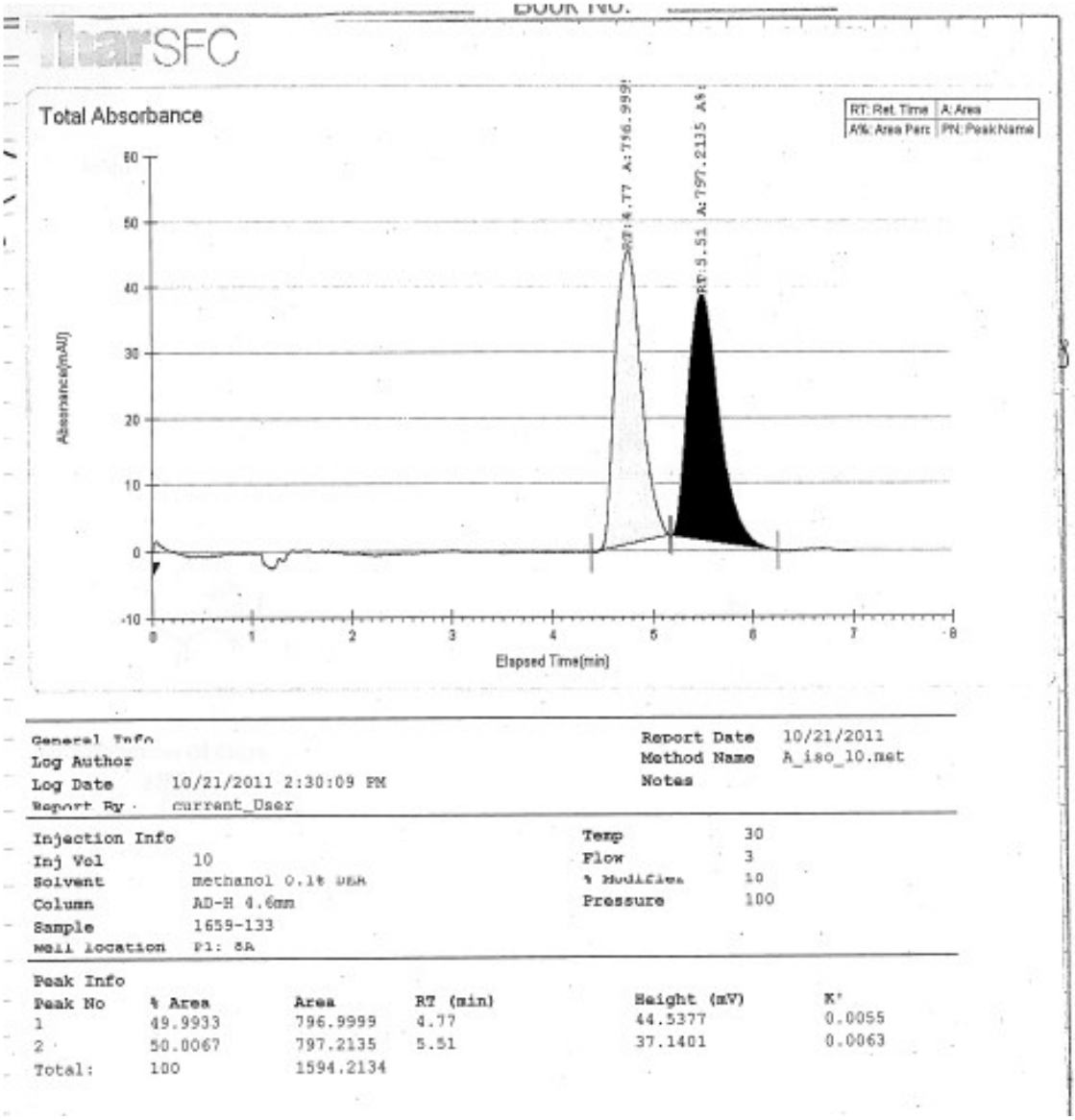
^{19}F NMR FOR (7*R*,8*AS*)-*N*-(2-CHLORO-5-FLUOROPYRIMIDIN-4-YL)-OCTAHYDRO-5,5-DIMETHYLINDOLIZIN-7-AMINE 20**





COPY OF CHIRAL SFC FOR RACEMIC *N*-(2-CHLORO-5-FLUOROPYRIMIDIN-4-YL)-OCTAHYDRO-5,5-DIMETHYLINDOLIZIN-7-AMINE





Column: Daicel Chemical Industries, Chiralcel AD-H, 4.6x250 mm

Mobile phase: 10% Methanol (MeOH contains 0.1% diethylamine) / 90% CO_2; isocratic

Flow rate: 3 ml/min

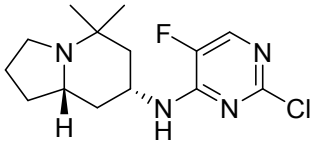
Run time: 8 minutes

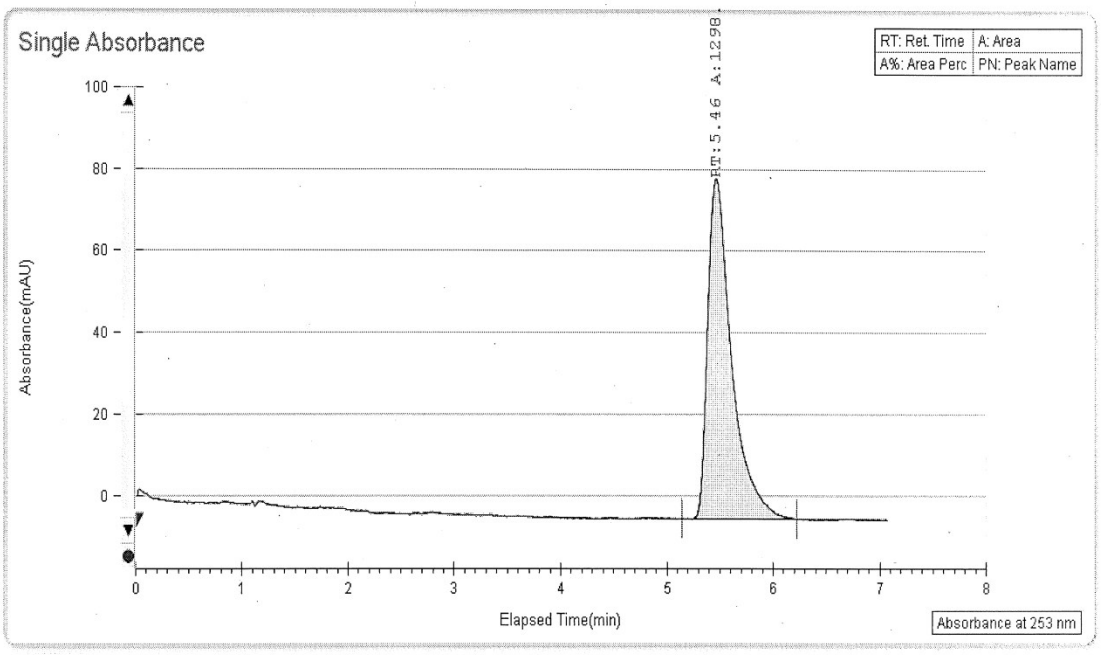
Temperature: 30°C

Detection: 254nm

SFC: TharSFC Investigator

COPY OF CHIRAL SFC FOR (7*R*,8*A**S*)-*N*-(2-CHLORO-5-FLUOROPYRIMIDIN-4-YL)-OCTAHYDRO-5,5-DIMETHYLINDOLIZIN-7-AMINE **20**





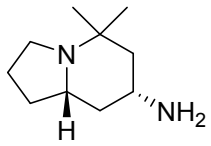
General Info		**Report Date**	11/3/2011
Log Author		**Method Name**	A_iso_10.met
Log Date	11/3/2011 4:17:18 PM	**Notes**	
Report By	current_User		

Injection Info		**Temp**	30
Inj Vol	10	**Flow**	3
Solvent	methanol 0.1% DEA	**% Modifier**	10
Column	AD-H 4.6mm	**Pressure**	101
Sample	1662-130A		
Well location	P1: 5D		

Peak Info

Peak No	% Area	Area	RT (min)	Height (mV)	K'
1	100	1298.4313	5.46	83.4421	0.0056
Total:	100	1298.4313			

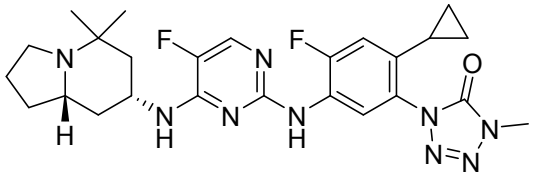
DETERMINATION OF ABSOLUTE CONFIGURATION FOR AMINE 8



Amine **8**

The absolute stereochemistry of amine **8** was determined *via* two (2) independent methods. As background, homochiral compound **S1** below, could be prepared from molecule **20** [note: a racemic version of **S1** was also available from (±)-**12**]. The following were then undertaken.

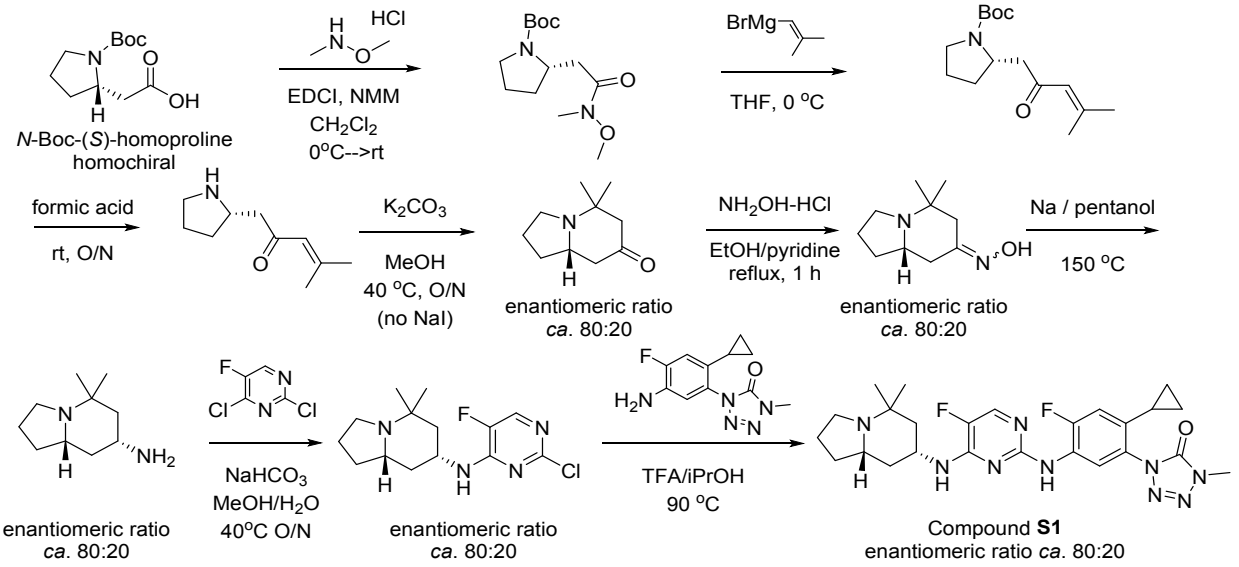
1. A co-crystal structure of PKC-theta protein with compound **S1**, indicated that compound **S1** possessed the (7*R*, 8*aS*)-stereochemistry[1]



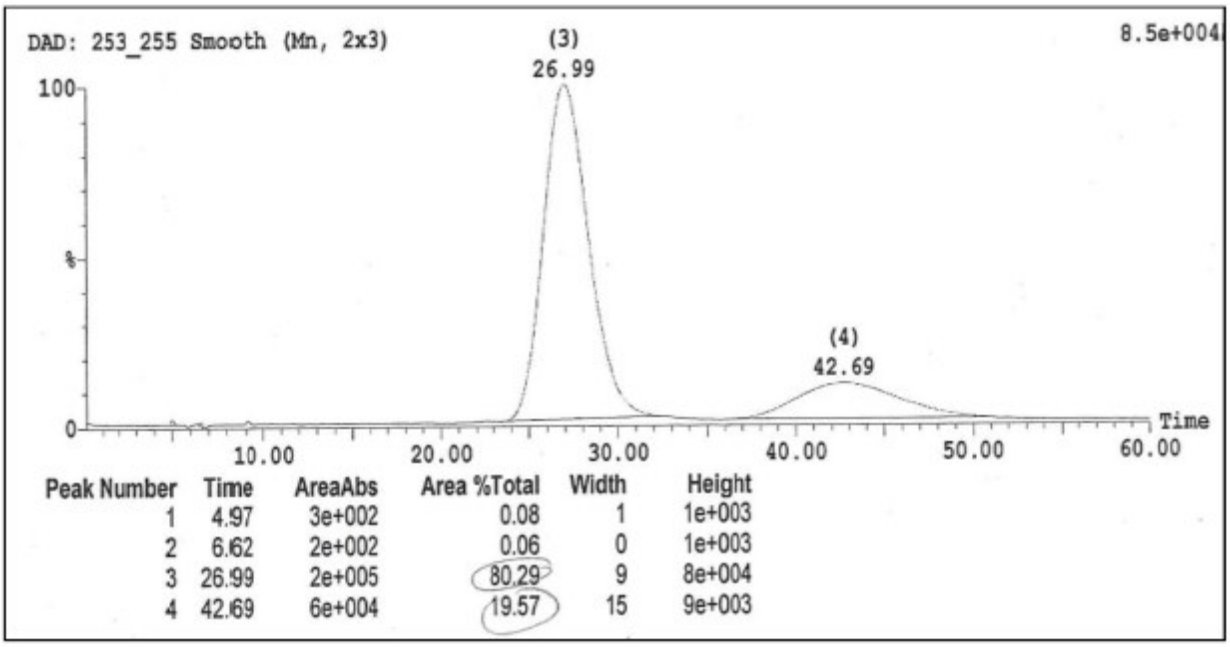
Compound **S1**
Co-crystal structure with PKC-theta indicated (7*R*, 8*aS*)-stereochemistry

2. An independent synthesis of compound **S1**, starting from homochiral *N*-Boc-(*S*)-homoproline, also known as L-Boc-homoproline (see Scheme S1).[2,3]

Scheme S1. Synthesis of compound **S1** from homochiral *N*-Boc-(*S*)-homoproline.[2,3]

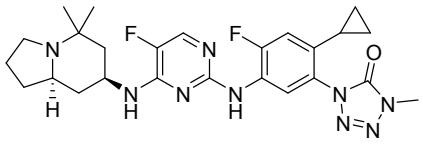


Synthesis as outlined in Scheme S1, gave compound **S1** as a *ca*. 80:20 mixture of enantiomers (see below). The partial-racemization from this synthesis is thought to occur during the cyclization step (K_2CO_3 in MeOH), consistent with observations from the literature.[2]



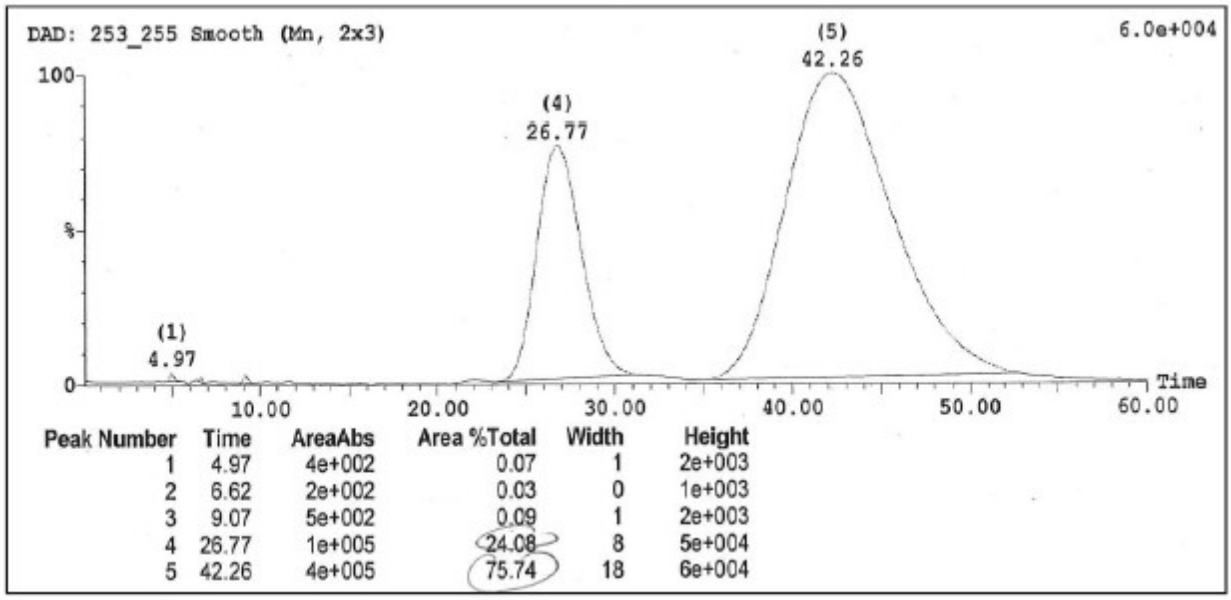
Peak Number	Time	AreaAbs	Area %Total	Width	Height
1	4.97	3e+002	0.08	1	1e+003
2	6.62	2e+002	0.06	0	1e+003
3	26.99	2e+005	80.29	9	8e+004
4	42.69	6e+004	19.57	15	9e+003

The peak at 26.99 min (from an HPLC employing a chiral stationary-phase) was matched to compound **S1**. The peak at 42.69 min was matched to the enantiomeric compound **S2**, which was also available as a reference.



Compound **S2**

Similarly, compound **S2** could also be prepared using the method outlined in Scheme S1, except starting from homochiral *N*-Boc-(*R*)-homoproline (D-Boc-homoproline). This gave compound **S2** as a *ca*. 75:25 mixture of enantiomers (with compound **S1** being the other component - see HPLC trace below).



Peak Number	Time	AreaAbs	Area %Total	Width	Height
1	4.97	4e+002	0.07	1	2e+003
2	6.62	2e+002	0.03	0	1e+003
3	9.07	5e+002	0.09	1	2e+003
4	26.77	1e+005	24.08	8	5e+004
5	42.26	4e+005	75.74	18	6e+004

The peak at 26.77 min was matched to compound **S1**. The peak at 42.26 min was matched to the isomeric compound **S2**.

References and notes

1. R. Singh, M. Duncton, J. Zhang, S. Alvarez, K. Tso, S. Holland, R. Yen, R. Kolluri, T. Heckrodt, Y. Chen, E. Masuda, H. Li, D. G. Payan, R. Kelley, *PCT Int. Appl.*, WO2013152198, 2013; *Chem. Abstr.*, 2013, **159**, 608680.
2. We used the methodology as outlined in M. J. Niphakis, B. J. Turunen, G. I. Georg, *J. Org. Chem*., 2010, **75**, 6793-6805.
3. We thank Rose Yen for technical assistance with this work.