Electronic Supplementary Material (ESI) for RSC Advances.

A protecting group free and scalable approach towards total synthesis of (-)-venlafaxine

Subhash P Chavan*, Kailash P Pawar, Sumanta Garai

Division of Organic Chemistry, CSIR-NCL (National Chemical Laboratory),

Pune-411008

sp.chavan@ncl.res.in

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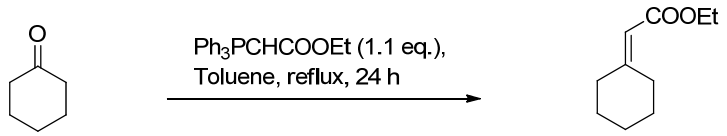
General experimental methods:-

Melting points are recorded using Buchi B-540 and M-560 melting point apparatus in capillary tubes and are uncorrected and the temperatures are in centigrade scale. Unless otherwise stated, commercially available reagents were used as purchased. Triethylamine and toluene were dried and stored over activated 4 Å molecular sieves. Dry tetrahydrofuran was freshly distilled over sodium. Dry dichloromethane was prepared by distillation over phosphorous pentoxide or calcium hydride. All other reagents and solvents were used as received from the manufacturer, unless otherwise specified. All air and water sensitive reactions were performed in flasks flame dried under positive flow of argon and conducted under an argon atmosphere. IR spectra were recorded on a Perkin-Elmer Infrared Spectrophotometer Model 68B or on a Perkin-Elmer 1615 FT Infrared spectrophotometer. ^{1}H (200 and 400 MHz) and ^{13}C (50 and 100 MHz) NMR spectra were recorded on Bruker and Bruker Advance 400 spectrometers, using a 2:1 mixture of $CDCl_3$ and CCl_4 as solvent. The chemical shifts (δ ppm) and coupling constants (Hz) are reported in the standard fashion with reference to chloroform, δ 7.27 (for $_1H$) or the central line (77.0 ppm) of $CDCl_3$ (for ^{13}C). In the C NMR spectra, the nature of the carbons (C, CH, CH_2, or CH_3) was determined by recording the DEPT-135 (Distortionless enhancement by polarization transfer) spectra. The following abbreviations used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. HRMS data were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump. The reaction progress was monitored by the TLC analysis using thin layer plates precoated with silica gel 60 F_{254} (Merck) and visualized by irradiation (254 nm) or iodine or by staining Kägi−Miescher reagent (p-anisaldehyde 2.53 % v/v, acetic acid 0.96 % v/v, ethanol 93.06 % v/v, conc. H_2SO_4 3.45 % v/v) or $KMnO_4$ (3 g $KMnO_4$, 20 g K_2CO_3, 5 mL NaOH (5%), 300 mL H_2O), ninhydrin solution and also 2,4-DNP.

Merck's flash silica gel (300-400 mesh) was used for column chromatography. All small scale dry reactions were carried out using standard syringe-septum technique. Low temperature reactions were carried out using cryostat.

Experimental:-

Ethyl 2-cyclohexylideneacetate (5)

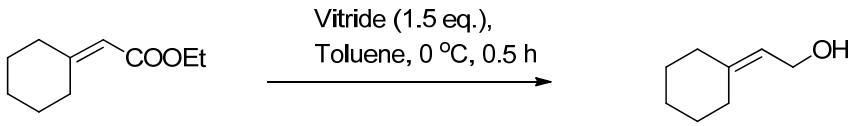


6 **5**

A clean, dry 250 mL round bottom flask was charged with cyclohexanone (5 g, 51.00 mmol) and two-carbon Wittig ylide (19.537 g, 56.1 mmol). Then, temperature of reaction mixture was raised to 120 ^{o}C. The reaction mixture was refluxed for 24 h. After completion of reaction toluene was removed *in vacuo*. After removal of toluene, it was suspended in EA: PE (5:95) system and filtered through 3 cm thick celite bed to remove triphenylphosphine oxide. Filtrate was concentrated under reduced pressure and purification of the residue on a silica gel column using EA: PE (2:98) gave unsaturated ester **4** (24.7 g, 98%) as a clear liquid. R_f (EA: PE/5:95): 0.7.

Yield: 98%; IR ($CHCl_3$): 3020, 1705, 1646, 1215 cm^{-1}; ^{1}H NMR (200 MHz, chloroform-*d*+CCl_4): δ 1.28 (t, *J* = 7.1 Hz, 3 H), 1.50 - 1.76 (m, 7 H), 2.10 - 2.27 (m, 2 H), 2.64 - 3.01 (m, 2 H), 4.13 (q, *J* = 7.1 Hz, 2 H), 5.58 (t, *J* = 1.0 Hz, 1 H); ^{13}C NMR (50 MHz, chloroform-*d*+CCl_4): δ 14.15, 26.14, 27.61, 28.46, 29.55, 37.80, 59.05, 112.96, 162.89, 166.28.

2-cyclohexylideneethan-1-ol (4)

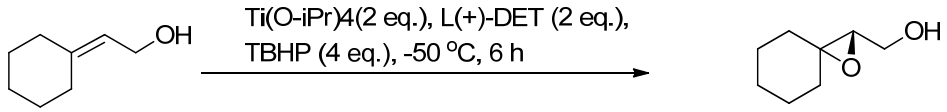


5 **4**

To a solution of the vitride in toluene at 0 °C (115 mg, 1.5 eq), unsaturated ester **5** in toluene was added in drop wise manner, and the solution was stirred at same temperature for 30 min. The reaction was then quenched with saturated sodium potassium tartarate salt by stirring for 3 h. The solution was extracted with ethyl acetate (3 × 100 mL), washed with water followed by brine, dried over anhydrous Na_2SO_4 and filtered. Removal of the ethyl acetate under reduced pressure afforded pure compound **4** as a clear liquid and characterized without any purification (6.1 g, 97%). R_f(EA:PE/2:3): 0.4.

Yield: 97%; IR ($CHCl_3$): 3421, 2934, 1705, 1647, 1265 cm^{-1}; ^1H NMR (200 MHz, chloroform-*d*+ CCl_4): δ 1.48 - 1.69 (m, 6 H), 2.01 - 2.29 (m, 4 H), 3.50 (s, 1 H), 4.13 (d, *J* = 7.1 Hz, 2 H), 5.36 (t, *J* = 7.1 Hz, 1 H); ^{13}C NMR (50 MHz, chloroform-*d*+CCl_4): δ 26.66, 27.76, 28.32, 28.77, 36.98, 58.21, 120.47, 143.76.

(*S*)-(1-Oxaspiro[2.5]octan-2-yl)methanol (3)



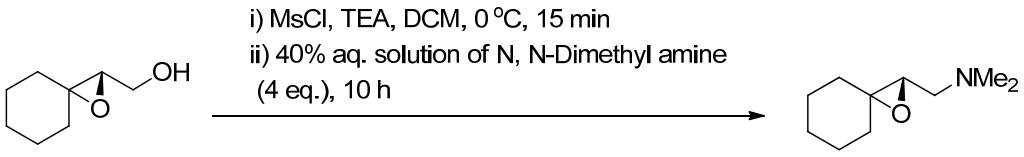
4 **3**

In a clean, dry 250 mL two neck round bottom flask, molecular sieves (4Å) were taken followed by dry DCM (40 mL). To this mixure $Ti(O\text{-}iPr)_4$ (7.88 g, 55.5 mmol) and L(+)-diethyl tartarate (11.46 g, 55.5 mmol) were added sequentially at -10 °C.

After stirring for 10 min, TBHP (4 M in toluene, 10 g, 111.08 mmol) was added drop wise to the mixture. After 30 minutes, temperature of the reaction mixture was lowered to -50 ^{o}C. A solution of allyl alcohol **4** (3.5 g, 27.77 mmol) in DCM was added drop wise to the reaction mixture under nitrogen atmosphere. Reaction mixture was stirred for 6 h. The progress of reaction was monitored on TLC. After completion of reaction, reaction was quenched by adding aqueous NaOH solution and stirring for 2 h at room temperature. Then organic and aqueous layers were separated. Aqueous layer was extracted with DCM (3 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness under reduced pressure. Purification of the residue on a silica gel column using EA: PE (3:7) as eluent furnished the epoxy alcohol **3** (83%) as colorless liquid. R_f(EA: PE/2:3): 0.3.

$[\alpha]_D^{25}$ -17.02 (c = 1.03, $CHCl_3$); Lit. $[\alpha]_D^{25}$ -16.01 (c = 1.0, $CHCl_3$); Yield: 83%; Chiral GC (Supelco β-Dex 120 column, oven temp. 140 ^{o}C for 60 min (isothermal), injection temp. 220 ^{o}C, Detection temp. 300 ^{o}C, $t_{(-)}$ = 23.38, $t_{(+)}$ = 24.57 showed 85% ee; IR ($CHCl_3$): 3421, 2934, 1705, 1647, 1265 cm^{-1}; ^{1}H NMR (200 MHz, chloroform-d+CCl_4): δ 1.44 - 1.90 (m, 11 H), 2.94 (dd, J = 6.63, 4.48 Hz, 1 H), 3.53 - 3.98 (m, 2 H); ^{13}C NMR (50 MHz, chloroform-*d*+CCl_4): δ 24.68, 25.45, 29.31, 35.22, 60.52, 63.29, 64.31.; HRMS: 165.0887 $[M+Na]^+$, Exact mass: 142.0994.

(*S*)-*N, N*-Dimethyl-1-(1-oxaspiro[2.5]octan-2-yl)methanamine



3 **2**

To a solution of epoxy alcohol **3** (2.5 gm, 17.6 mmol) in anhydous CH_2Cl_2 (5 mL) at 0 °C were added Et_3N (5.3 g, 7.32 mL, 52.81 mmol) and methanesulphonyl chloride (3.0 g, 2.15 mL, 26.4 mmol) sequentially in dropwise manner. Progress of the reaction was monitored by TLC. After completion, the reaction was quenched with

water (5 mL) and the organic layer was washed with aq $NaHCO_3$ (2 %, 10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The crude compound was used directly in the next reaction. To crude mesylate epoxide (4 g, 18.18 mmol) was added 40% aqueous solution of *N, N*-dimethyl amine (72.72 mmol) and stirred at room temperature for 10 h. The reaction mixture was directly concentrated under reduced pressure at 60 ^oC to furnish crude (-)-epoxyamine **2**. It was purified by silica gel column chromatography to get 95 % of **2** as yellow oil. R_f(100% EtOAc): 0.2.

$[\alpha]_D^{25}$ = - 18.41 (c = 1.4, $CHCl_3$); Yield: 95%; ^{1}H NMR (200 MHz, chloroform- d+ CCl_4): δ 1.40 - 1.80 (m, 10 H), 2.20 - 2.39 (m, 7 H), 2.56 - 2.73 (m, 1 H), 2.84 (dd, J = 6.25, 3.98 Hz, 1 H); ^{13}C NMR (50 MHz, chloroform-*d* +CCl_4): δ 24.42, 24.49, 25.42, 29.26, 35.11, 45.54, 57.70, 61.06, 62.43.
HRMS: 170.1539 $[M+H]^+$, Exact mass; 169.1467

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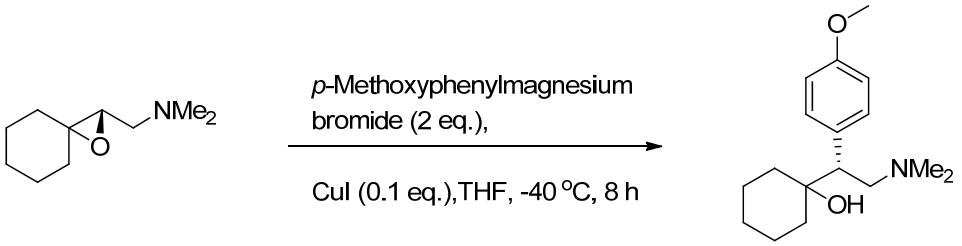
Synthesis of (-)- venlafaxine (1)



2 **1**

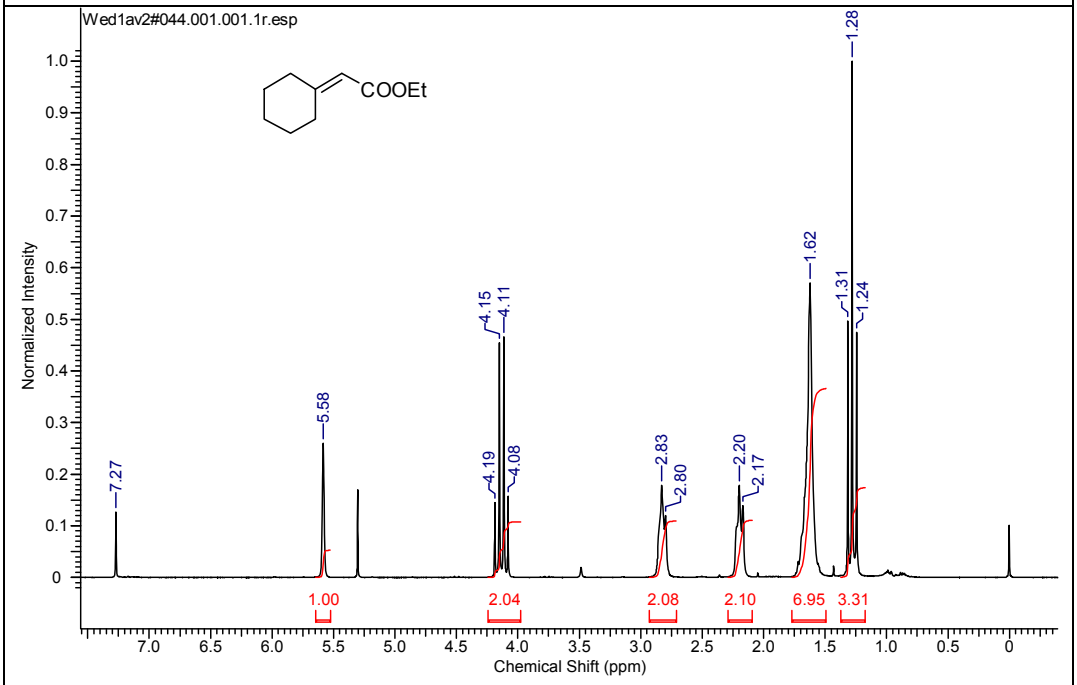
4-Bromoanisole (1.66 g, 8.86 mmol) was added to the suspension of Mg metal turnings (425 mg, 17.7 mmol) in dry THF and the resulting mixture was allowed to stir under heating until all magnesium metal disappeared. To this solution was added copper iodide (112 mg, 0.59 mmol) and allowed to stir for 15 min. This suspension was cooled to -40 ^oC. A solution of (-)-epoxyamine **2** (1 g, 5.9 mmol) in THF (40 mL) was added slowly to the above reagent and the mixture was stirred at -40 ^oC for 8 h.

Progress of reaction was monitored on TLC. After completion of reaction, it was quenched with a saturated solution of NH_4Cl. The organic layer and aqueous layers were separated. Aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated to dryness under reduced pressure. Purification of the residue on a silica gel column using ethyl acetate as eluent furnished the (-)-venlafaxine **1** (after recrystallization in ethyl acetate) as white solid.

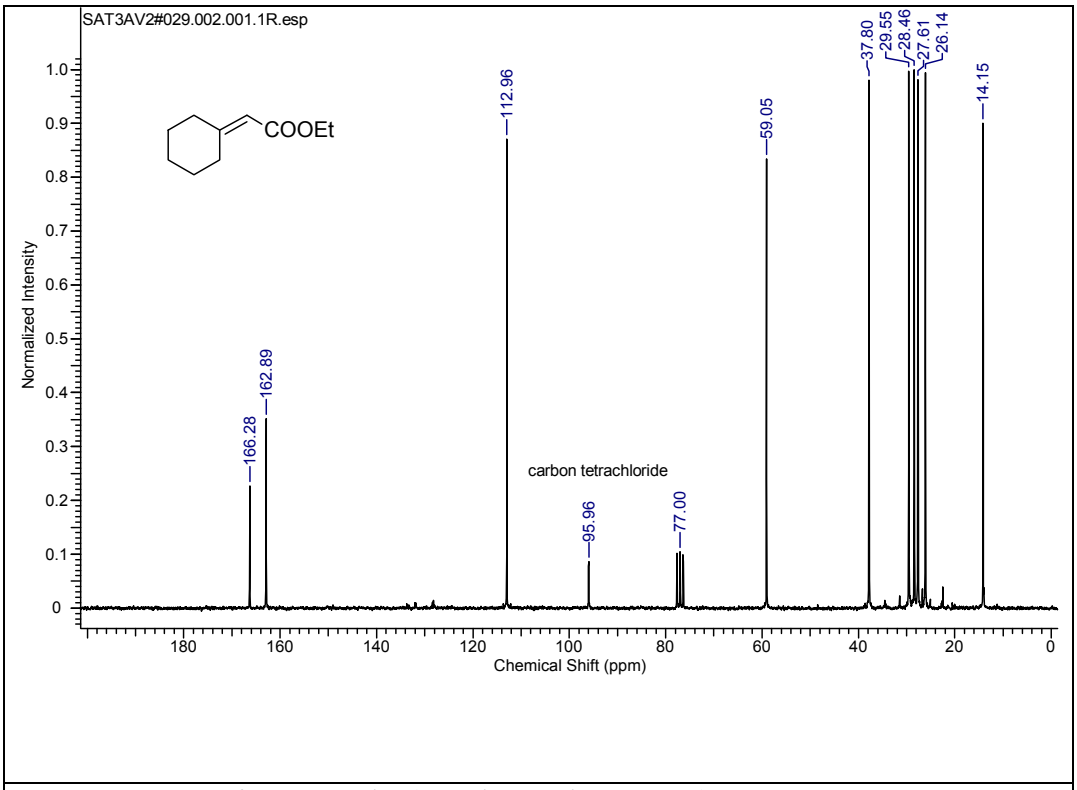
R_f (100% EtOAc): 0.2 (long tail); Yield: 71%; $[\alpha]_D^{25}$: −24.285 (*c* = 1.04, EtOH) Literature; *R*-(-)-venlafaxine $[\alpha]_D^{25}$= -29.9 (c = 1.04, EtOH); mp: 101-103 ^oC; IR ($CHCl_3$): 3164, 2982, 2938, 2860, 2782, 1610 cm^{-1}; ^1H NMR (400 MHz, chloroform-*d*+CCl_4): δ 0.73 - 1.11 (m, 2 H), 1.33 - 1.74 (m, 8 H), 2.35 - 2.51 (m, 7 H), 3.01 (d, 1 H), 3.00 (dd, *J* = 11.9, 2.9 Hz, 1 H), 3.41 (t, *J* = 11.9 Hz, 1 H), 3.79 (s, 3 H), 5.49 (s, 1 H), 6.79 (d, *J* = 8.8 Hz, 2 H), 7.04 (d, 2 H); ^{13}C NMR (100 MHz, chloroform-*d*+CCl_4): δ 21.36, 21.54, 25.90, 31.29, 37.84, 45.35, 51.74, 55.06, 61.15, 74.22, 76.68, 77.31, 113.49, 130.08, 132.32, 158.44; HRMS: 278.2115 $[M+H]^+$, Exact mass : 277.2042.

NMR Spectra

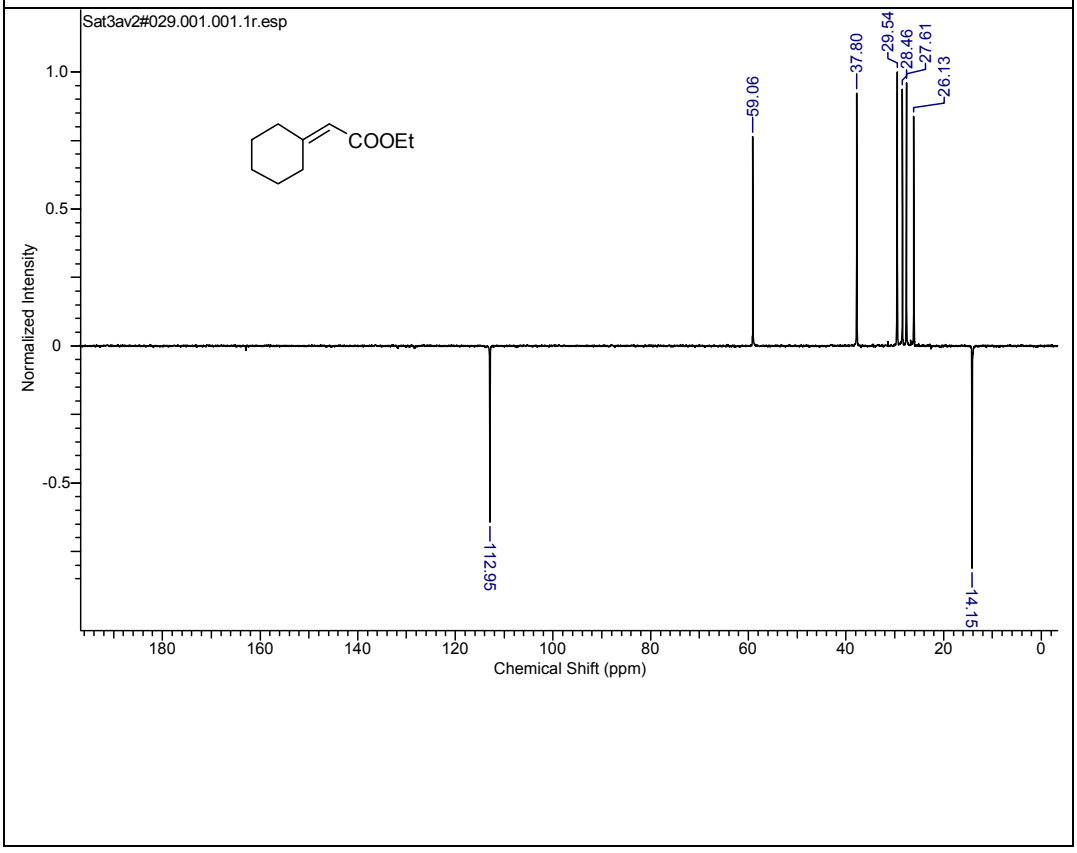
^{1}H NMR spectrum of compound **5** ($CDCl_3$+CCl_4, 200 MHz)



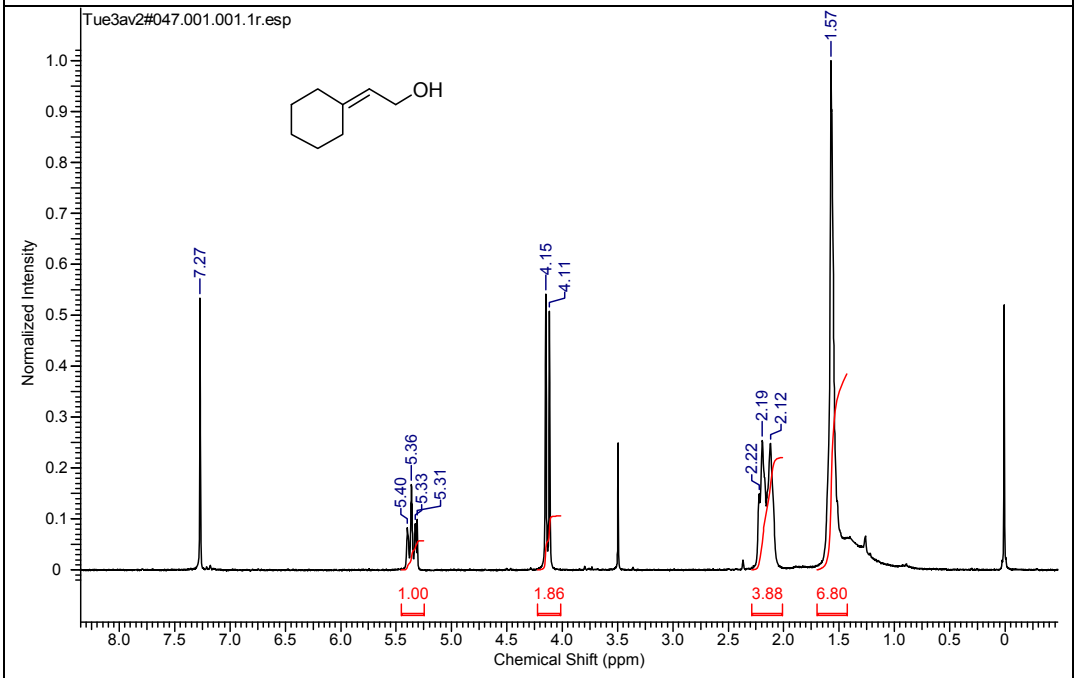
^{13}C NMR spectrum of compound **5** ($CDCl_3$ + CCl_4, 50 MHz)



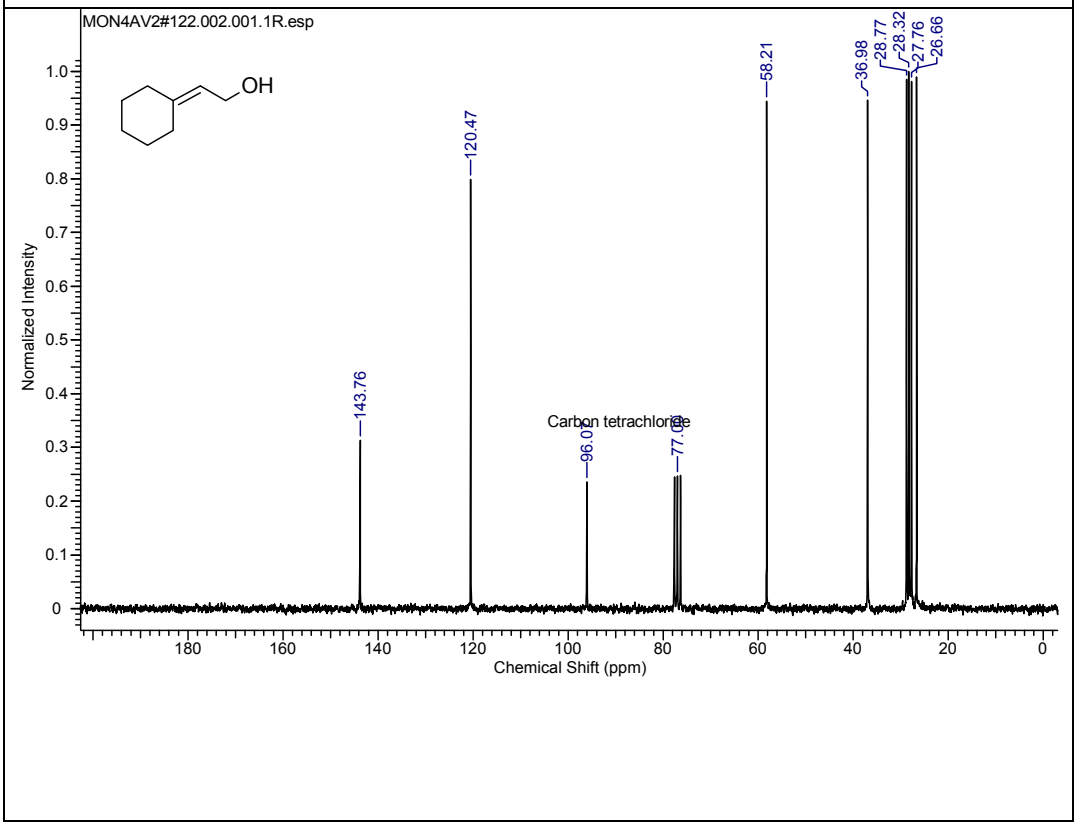
DEPT spectrum of compound **5** ($CDCl_3$ + CCl_4, 50 MHz)



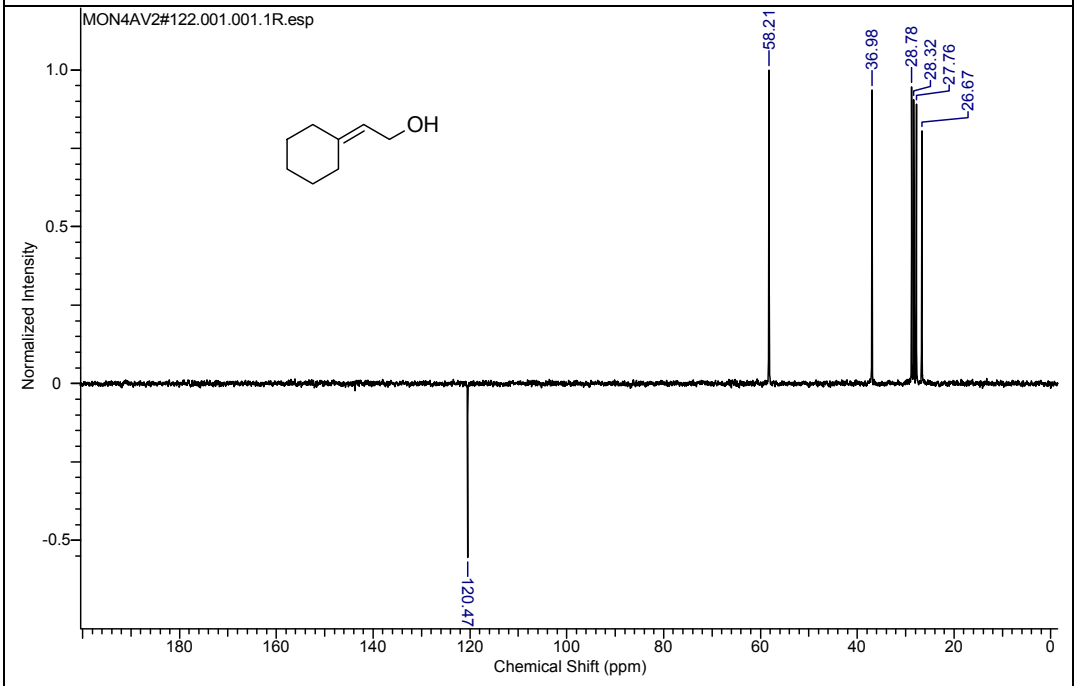
^{1}H NMR spectrum of compound **4** ($CDCl_3$+CCl_4, 200 MHz)



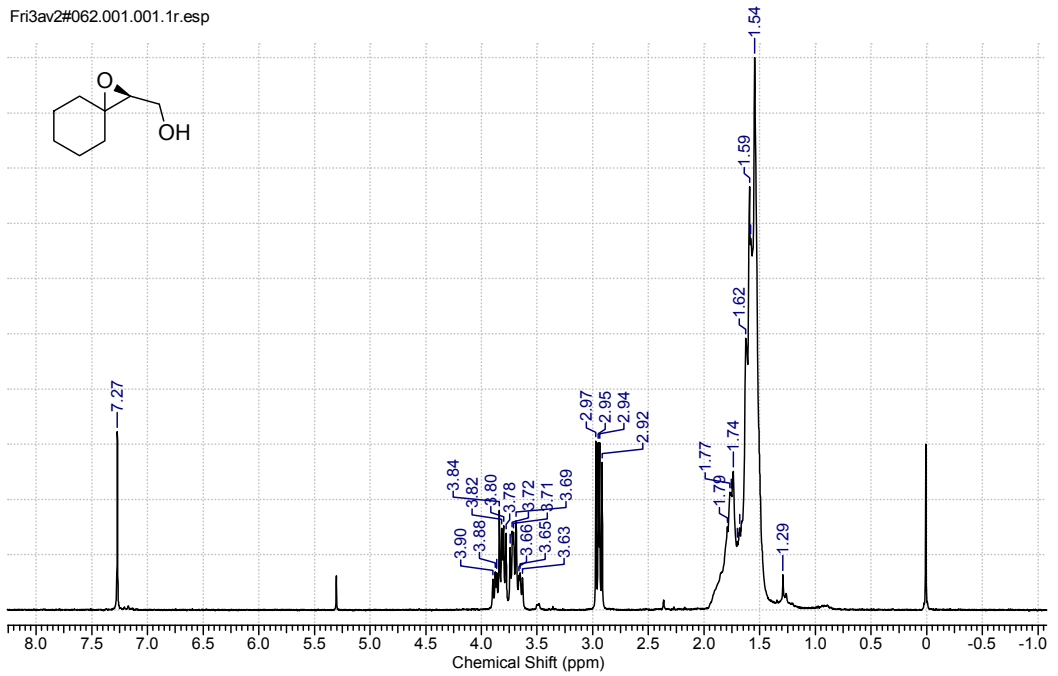
^{13}C NMR spectrum of compound **4** ($CDCl_3$ + CCl_4, 50 MHz)



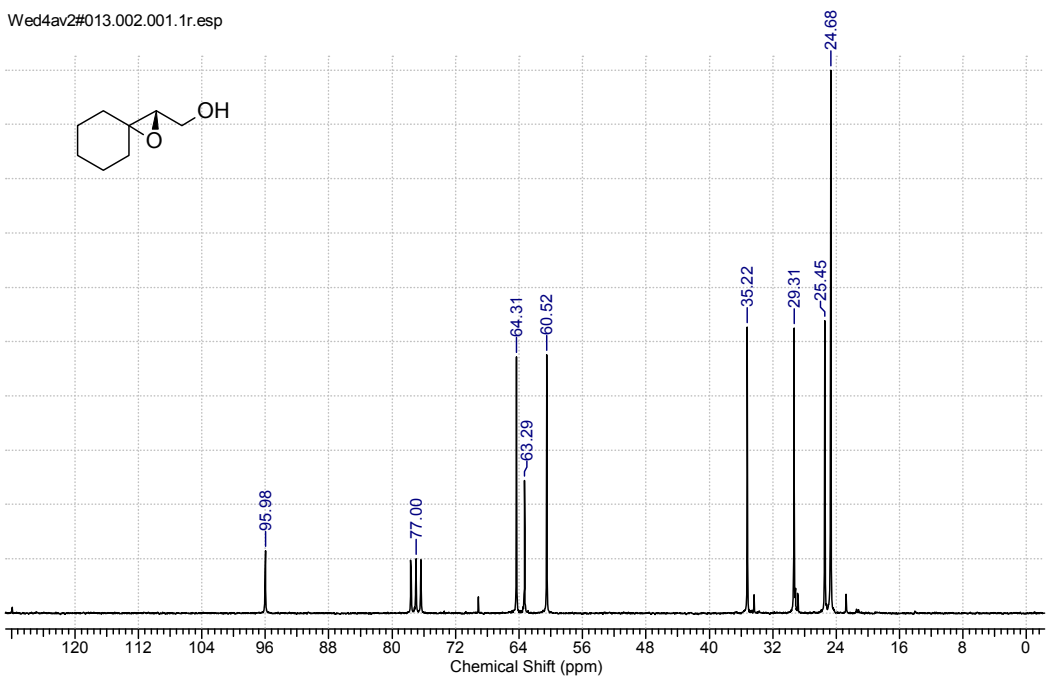
DEPT spectrum of compound **4** ($CDCl_3$ + CCl_4, 50 MHz)



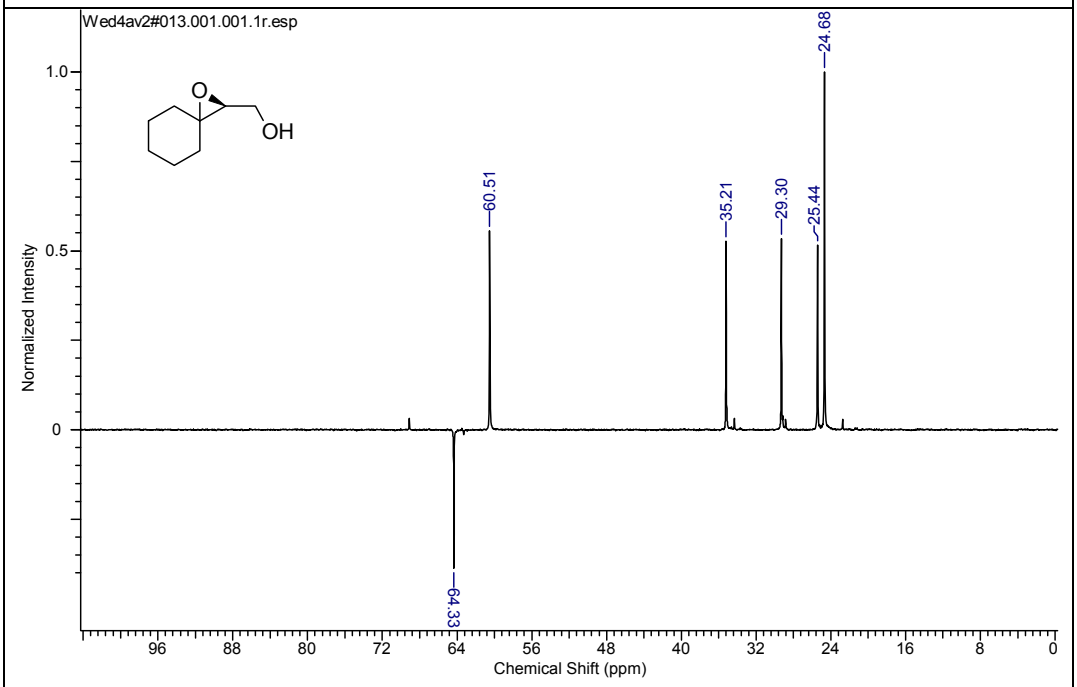
^{1}H NMR spectrum of compound **3** ($CDCl_3$, 200 MHz)



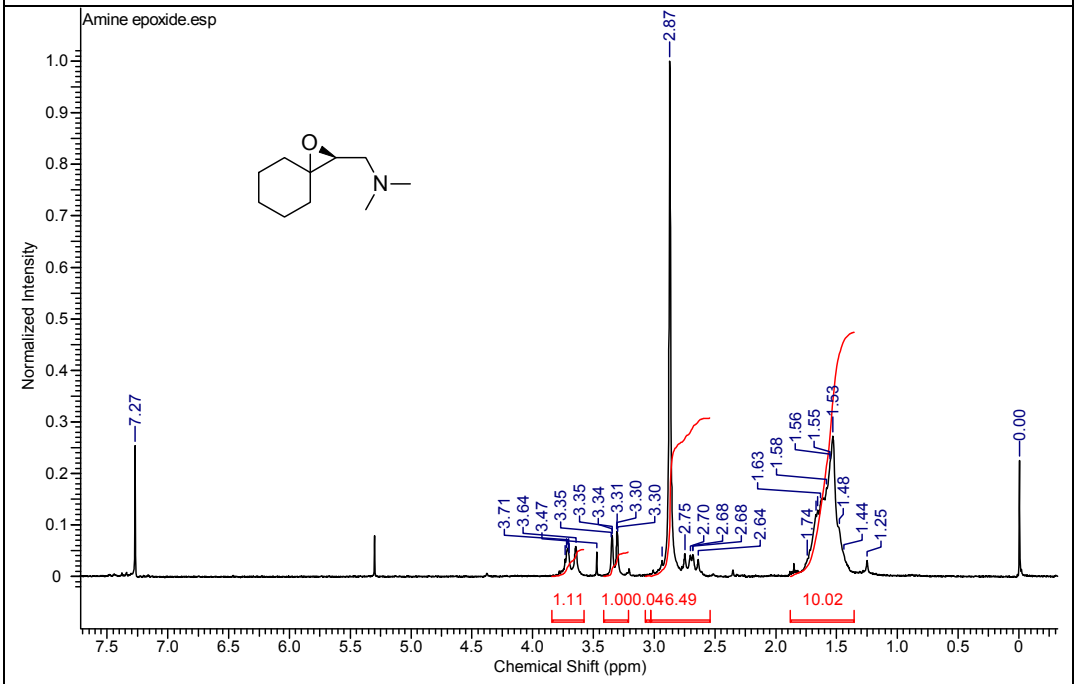
^{13}C NMR spectrum of compound **3** ($CDCl_3$, 50 MHz)



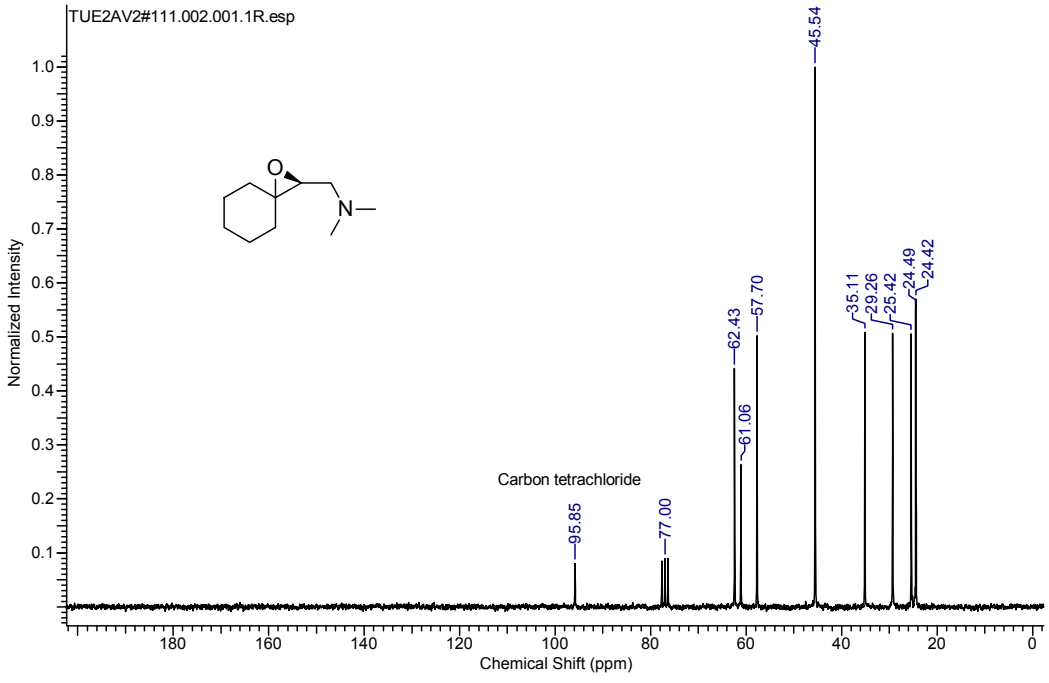
DEPT spectrum of compound **3** ($CDCl_3$, 50 MHz)



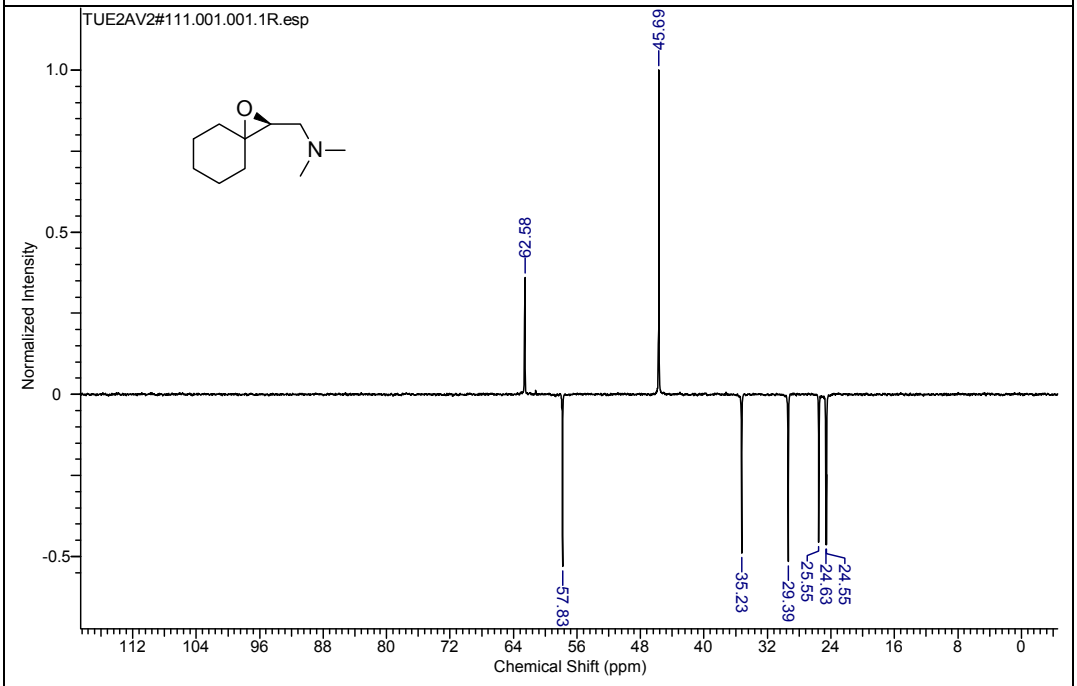
^{1}H NMR spectrum of compound **2** ($CDCl_3$+CCl_4, 200 MHz)



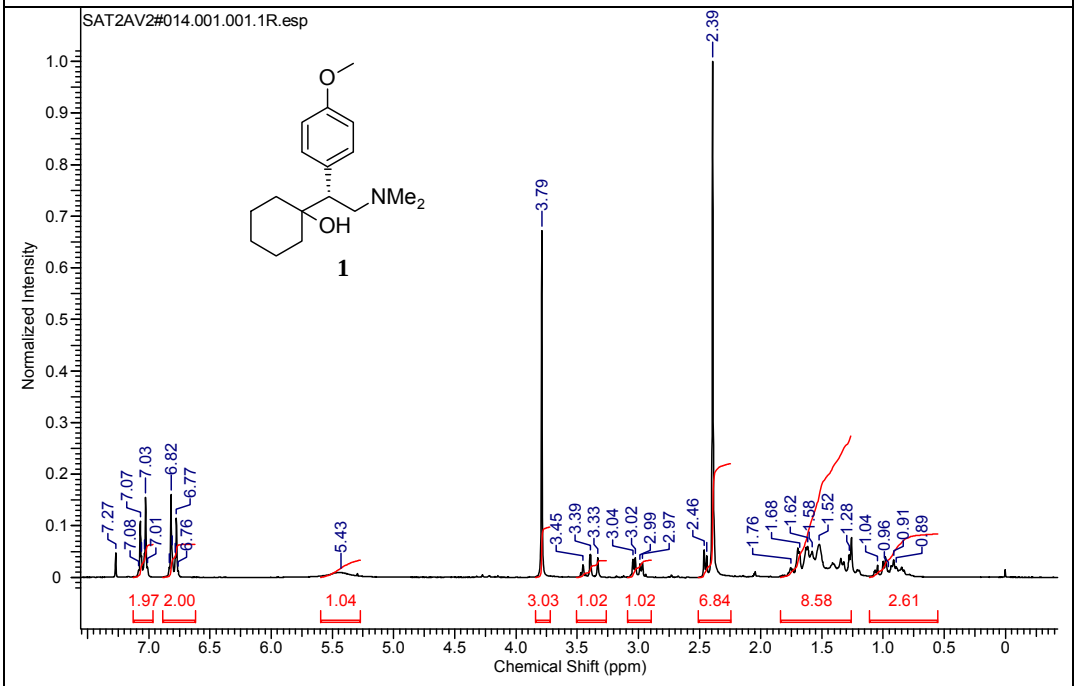
^{13}C NMR spectrum of compound **2** ($CDCl_3$ + CCl_4, 50 MHz)



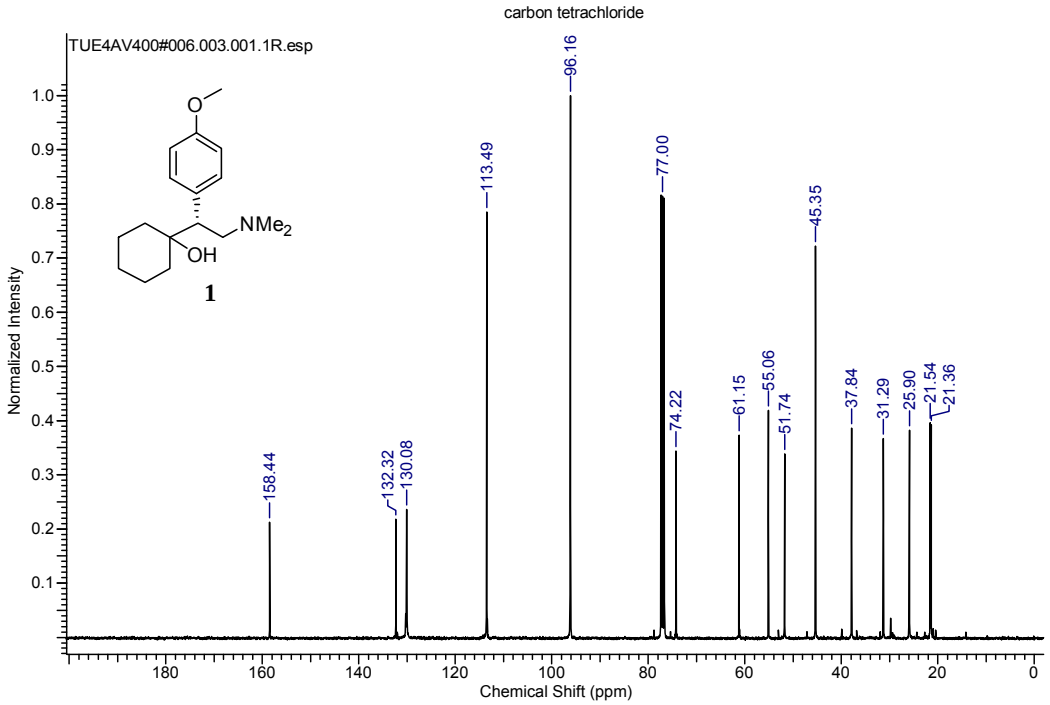
DEPT spectrum of compound **2** ($CDCl_3$ + CCl_4, 50 MHz)



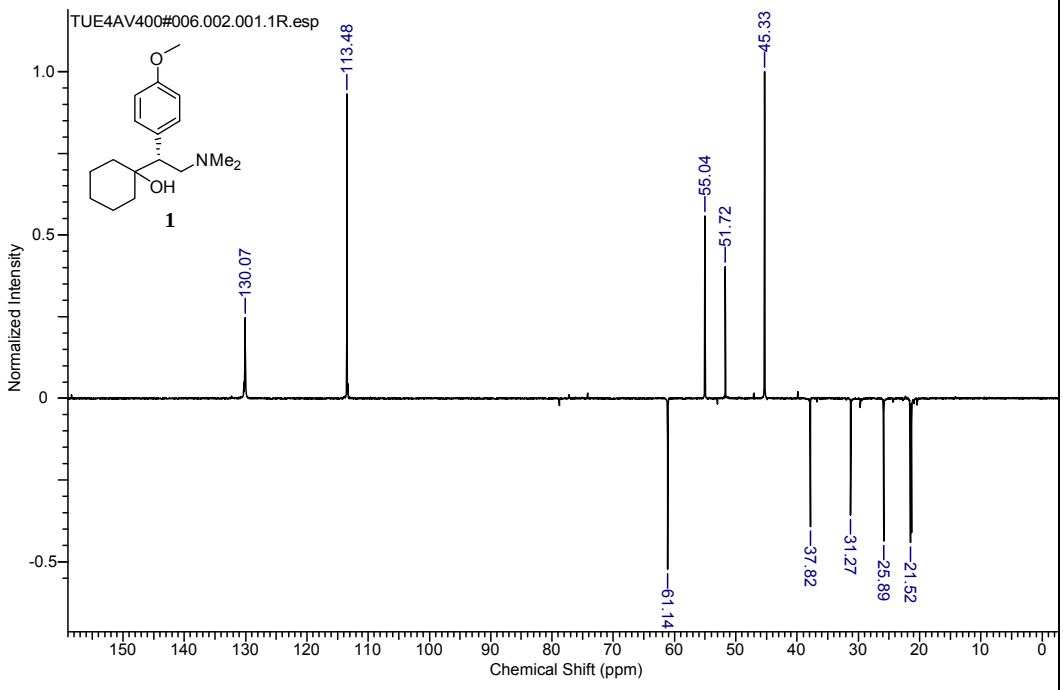
^{1}H NMR spectrum of compound **1** ($CDCl_3$ + CCl_4, 400MHz)



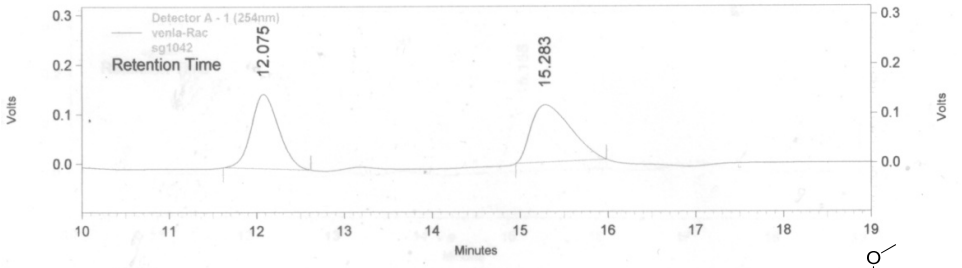
^{13}C NMR spectrum of compound **1** ($CDCl_3$ + CCl_4, 100 MHz)

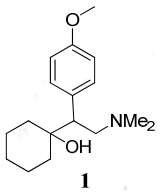


DEPT spectrum of compound **1** ($CDCl_3$+CCl_4, 50 MHz)



Scanned HPLC chromatogram of racemic venlafaxine **1**





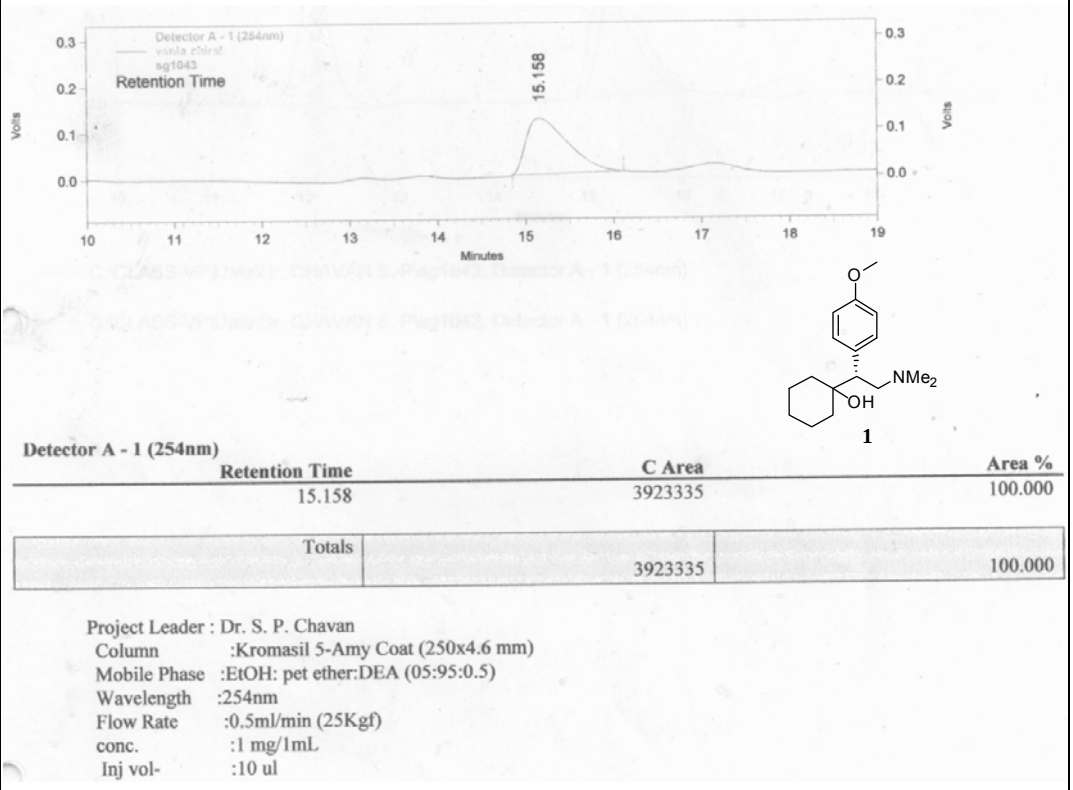
1

Detector A - 1 (254nm)

Retention Time	C Area	Area %
12.075	3291874	47.587
15.283	3625754	52.413
Totals	6917628	100.000

Project Leader : Dr. S. P. Chavan
Column :Kromasil 5-Amy Coat (250x4.6 mm)
Mobile Phase :EtOH: pet ether:DEA (05:95:0.5)
Wavelength :254nm
Flow Rate :0.5ml/min (25Kgf)
conc. :1 mg/1mL
Inj vol- :10 ul

Scanned HPLC chromatogram of chiral (−)-venlafaxine **1**

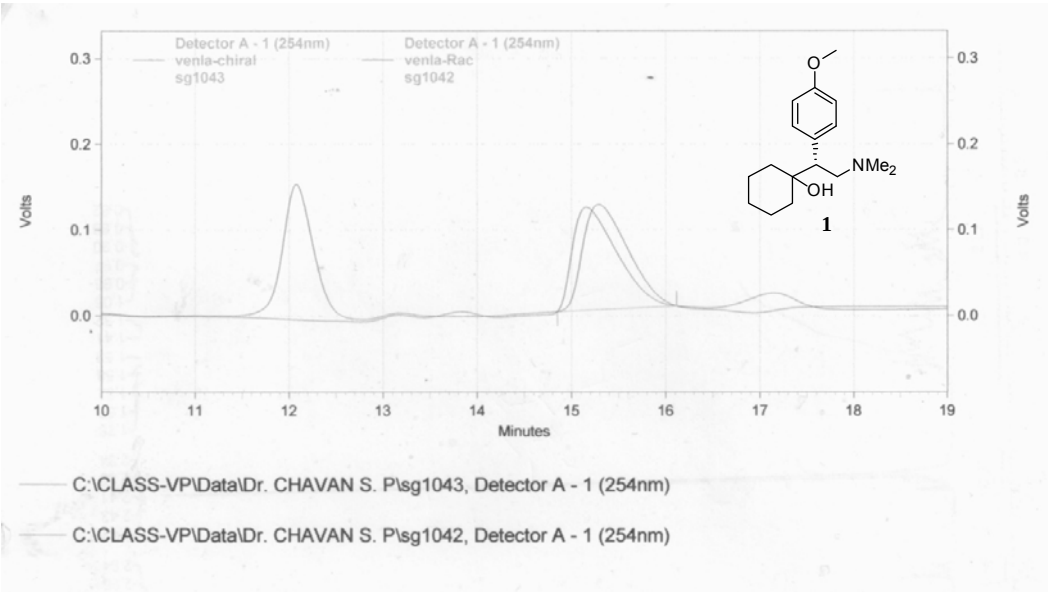


Detector A - 1 (254nm)

Retention Time	C Area	Area %
15.158	3923335	100.000
Totals	3923335	100.000

Project Leader : Dr. S. P. Chavan
Column :Kromasil 5-Amy Coat (250x4.6 mm)
Mobile Phase :EtOH: pet ether:DEA (05:95:0.5)
Wavelength :254nm
Flow Rate :0.5ml/min (25Kgf)
conc. :1 mg/1mL
Inj vol- :10 ul

Scanned HPLC overlapping chromatogram of both racemic venlafaxine **1** and chiral (−)-venlafaxine **1**



Chromatogram racemic:-

Shimadzu CLASS-VP V6.12 SP5
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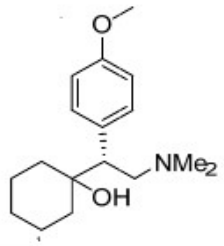
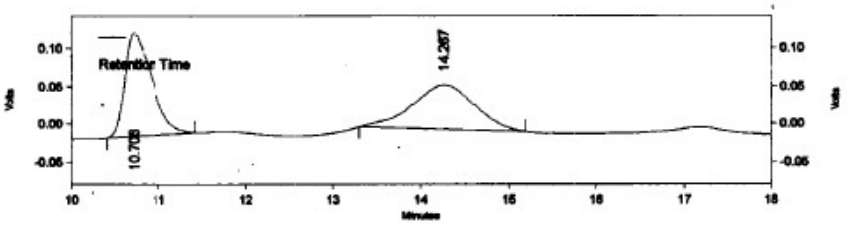
Data Name: C:\CLASS-VP\Data\Dr. CHAVAN S. P\KP 1005
User: System
Acquired: 8/8/13 4:57:29 PM
Printed: 8/8/13 6:06:06 PM
Sample Name KP-Rac





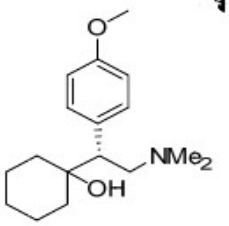
Detector A - 1 (254nm)

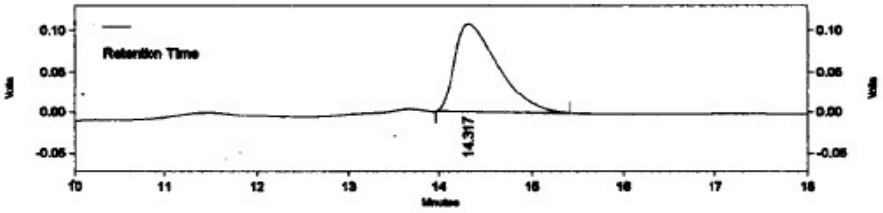
Retention Time	C Area	Area %
10.708	2950167	50.501
14.267	2891670	49.499
Totals	5841837	100.000

Project Leader : Dr. S P Chavan
Column :Kromasil 5-AmyCoat (250 x4.6mm)
Mobile Phase :ETOH:PET ETHER:DEA (5:95:0.5)
Wavelength : 254 nm
Flow Rate :0.5/min
Conc. :1 mg/ 1.0 ml
Inj vol- :20ul.

Chromatogram Chiral:-

Shimadzu CLASS-VP V6.12 SP5
Method Name: C:\CLASS-VP\Data\Dr. CHAVAN S P\PAPAL FH10 % IPAPE
Data Name: C:\CLASS-VP\Data\Dr. CHAVAN S P\KP 1006
User: System
Acquired: 8/8/13 5:29:46 PM
Printed: 8/8/13 6:02:43 PM
Sample Name KP-Chi





Detector A - 1 (254nm)

Retention Time	C Area	Area %
14.317	3514022	100.000
Totals	3514022	100.000

Project Leader : Dr. S P Chavan
Column :Kromasil 5-AmyCoat (250 x4.6mm)
Mobile Phase :ETOH:PET ETHER:DEA (5:95:0.5)
Wavelength : 254 nm
Flow Rate :0.5/min
Conc. :1 mg/ 1.0 ml
Inj vol- :20ul.

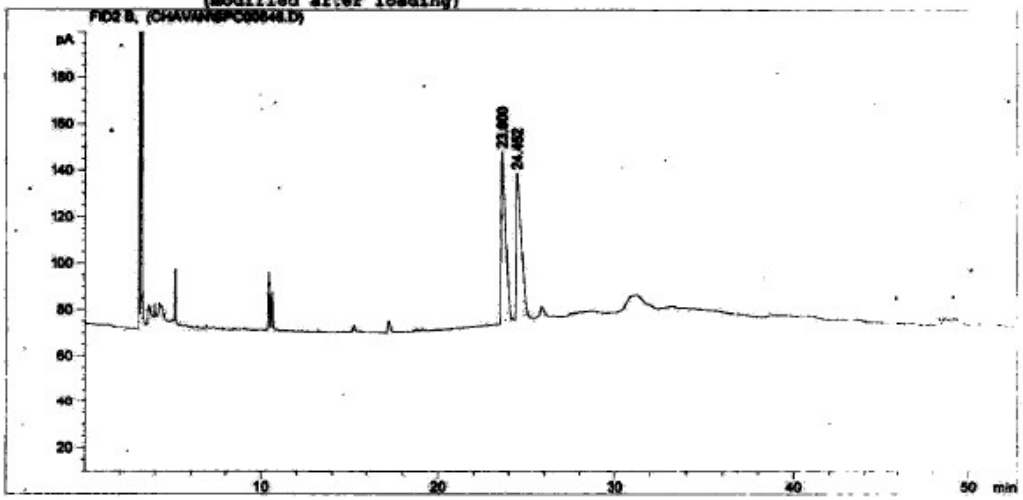
Racemic GC:-

Data File C:\HPCHEM\1\DATA\CHAVAN\SPC00646.D Sample Name: 2-8-13 R

140Deg(60min);ON 6890N Agilent DET-300 DEG INJ.220 DEG,
COL: supelco beta dex120 flow: 1.5
Sample is Dissolved in DCM

Injection Date : 8/2/2013 11:25:22 AM
Sample Name : 2-8-13 R
Acq. Operator : BORIKAR
Location : Vial 2
Inj : 1
Inj Volume : Manually

Acq. Method : C:\HPCHEM\1\METHODS\REGFID.M
Last changed : 8/2/2013 11:23:36 AM by BORIKAR
(modified after loading)
Analysis Method : C:\HPCHEM\1\METHODS\COOLFID.M
Last changed : 8/12/2013 12:17:25 PM by BORIKAR
(modified after loading)



Area Percent Report

Sorted By : Signal
Calib. Data Modified : Thursday, July 31, 2008 2:25:40 PM
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: FID2 B,

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Area %	Name
1	23.600	PB	0.2044	1202.62329	50.60380	?
2	24.452	PB	0.2233	1173.92395	49.39620	?

Totals : 2376.54724

Results obtained with enhanced integrator!

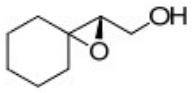
GC ECD 8/12/2013 12:19:03 PM BORIKAR Page 1 of 2

Chiral GC:-

Data File C:\HPCHEM\1\DATA\CHAVAN\SPC00647.D

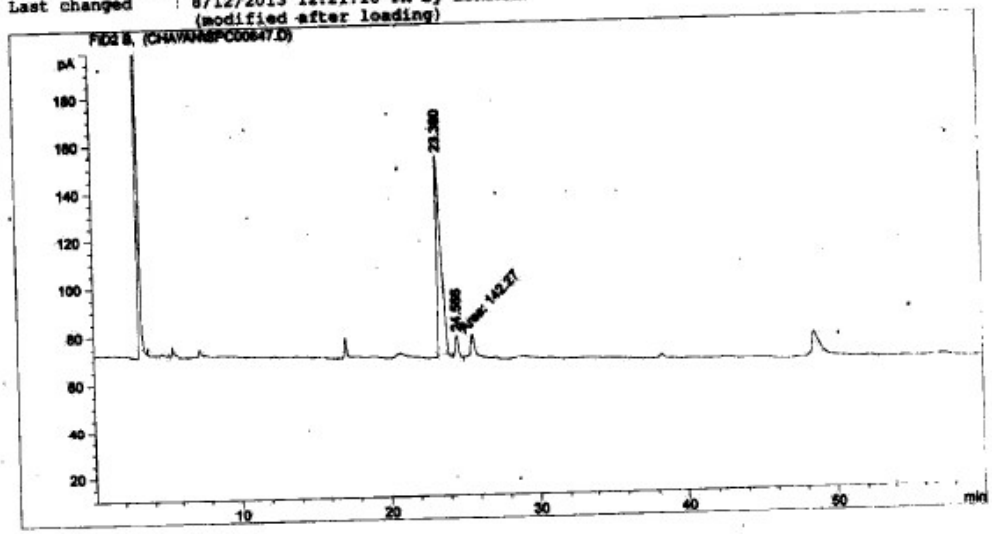
Sample Name: 2-8-13 chi

140Deg(60min);ON 5890N Agilent DET-300 DEG INJ.220 DEG.
COL: supelco beta dex120 flow: 1.5
Sample is Dissolved in DCM



Injection Date : 8/2/2013 12:20:21 PM
Sample Name : 2-8-13 chi
Acq. Operator : BORIKAR
Location : Vial 2
Inj : 1
Inj Volume : Manually

Acq. Method : C:\HPCHEM\1\METHODS\REGFID.M
Last changed : 8/2/2013 12:18:50 PM by BORIKAR
(modified after loading)
Analysis Method : C:\HPCHEM\1\METHODS\COOLFID.M
Last changed : 8/12/2013 12:21:10 PM by BORIKAR
(modified after loading)



Area Percent Report

Sorted By : Signal
Calib. Data Modified : Thursday, July 31, 2008 2:25:40 PM
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: FID2 B,

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Area %	Name
1	23.380	PB	0.2346	1588.59827	91.78044	?
2	24.566	MM	0.2617	142.26976	8.21956	?

Totals : 1730.86803

Results obtained with enhanced integrator!

GC ECD 8/12/2013 12:21:33 PM BORIKAR

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