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

An Efficient Access to Enantiopure 1,3-disubstituted Isoindolines from Selective Catalytic Fragmentation of Original Desymmetrized Rigid Overbred Template

Ganesh Pandey,* Rajesh R Varkhedkar, Divya Tiwari

Supporting Information

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Single Crystal X-ray Diffraction Analysis for compound **13…**…….S49-S52

General Information:

All the commercially available chemicals have been purchased from Sigma Aldrich Co., Merck Co., Alfa Aesar Co. or Spectrochem chemicals. The dry solvents required for anhydrous reaction has been purified and were dried according to Perrin *et al.*[1]. Wherever necessary, air or moisture sensitive reactions were carried out under inert atmosphere of argon.

All reactions were monitored by analytical thin layer chromatography (TLC) on TLC Silica gel 60 F_{254} plate obtained from Merck KGaA and visualized under UV lamp of 254 nm followed by staining with iodine, ninhydrin solution in alcohol or aqueous $KMnO_4$. Separations were performed by column chromatography on silica gel 60-120/ 100-200/ 230-400 mesh obtained from Rankem Co. Ltd.

All the melting points were recorded in degree Celsius and recorded on Buchi Melting Point M-560 apparatus.IR Spectras were recorded on Perkin Elmer FT-IR spectrometer. ^{1}H NMR were recorded on Avance Bruker 400 MHz spectrometer and Bruker 800 MHz spectrometer using deuterated solvents. ^{13}C NMR were recorded on Avance Bruker 400 MHz operating at 100 MHz spectrometer and Bruker 800 MHz operating at 200 MHz. Chemical shifts are reported in ppm with the solvent resonance as the internal standard (chloroform-d: 7.27 ppm for ^{1}H NMR and 77 ppm for ^{13}C) and proton coupling constant (*J*) is reported as absolute value in Hz and corresponding multiplicities are (br, broadened; s, singlet; d, doublet; t, triplet; m, multiplet). High-resolution mass spectra (HRMS) were obtained in ESI mode by using Agilent Technology LCMS-HRMS instrument. Analytical HPLC were performed using Agilent Technologies HPLC 1260 Infinity series instruments.

Abbreviations:

AcOH	Acetic Acid
DCM	Dichloromethane
DMSO	Dimethylsulfoxide
EtOAc	Ethyl Acetate
EtOH	Ethanol
iPrOH	Isopropanol
MeOH	Methanol
rt	room temperature
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography

References:

1) Perrin, D. D.; Armarego, W. L. F. Purification of Laboratory Chemicals, 3rd. Ed., Pergamon, New York, 1988.

2) Doubling/broadening of signals in NMR spectra is due to the isomerisation by restricted rotation around C–N bond, see: In Applications of NMR Spectroscopy in Organic Chemistry; Jackman, L. M., Sternhell, S., Eds.; Pergamon: Elmsford, NY, 1978; p 361.

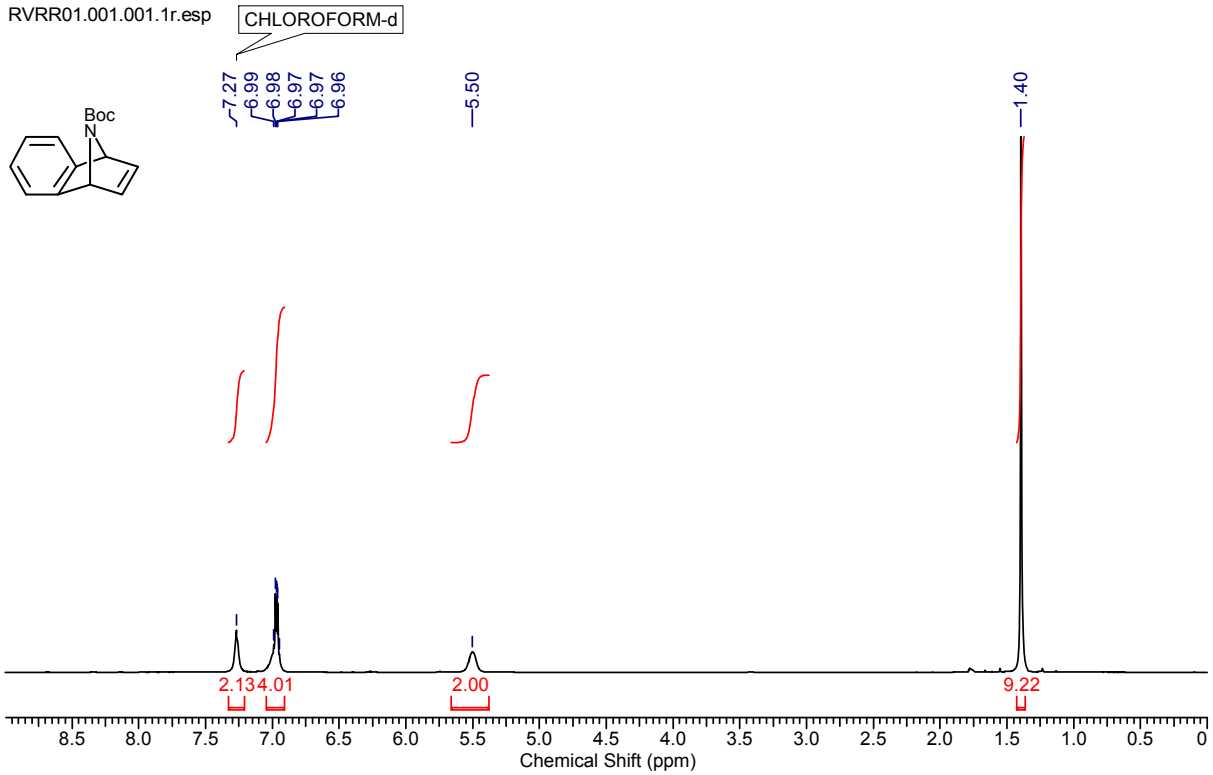


Figure: ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)

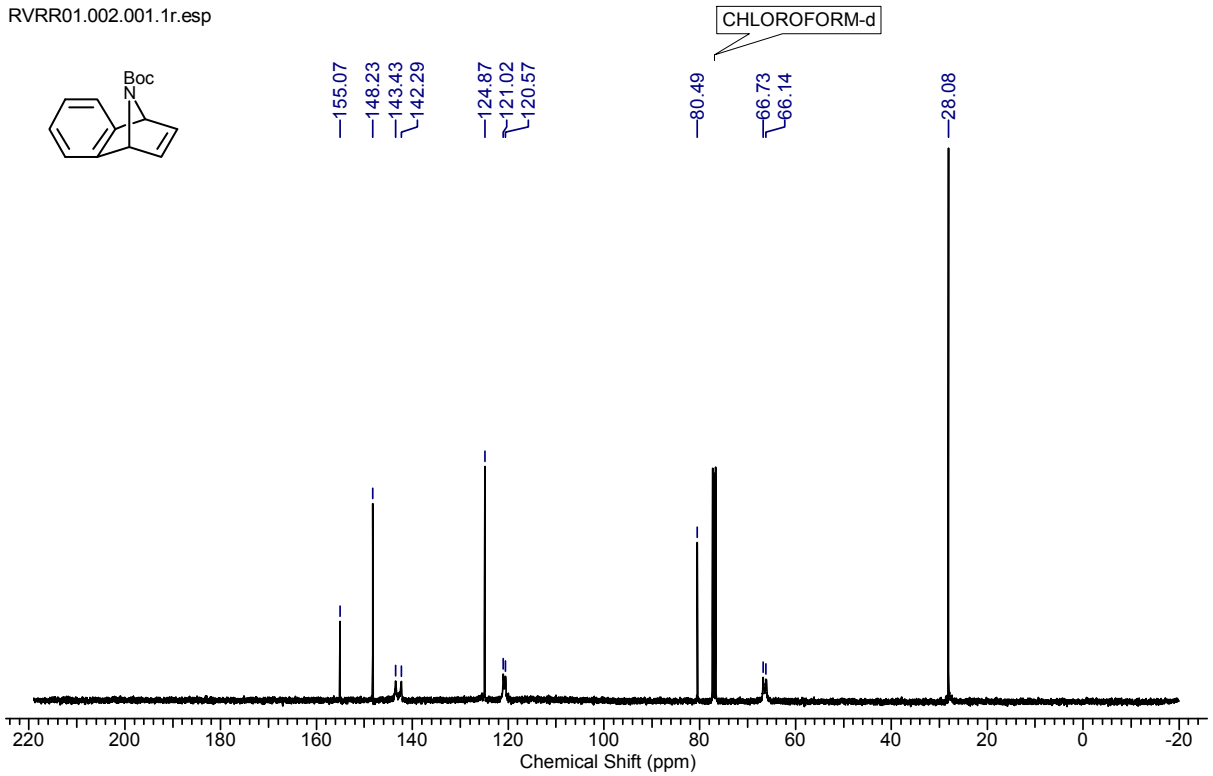


Figure: ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

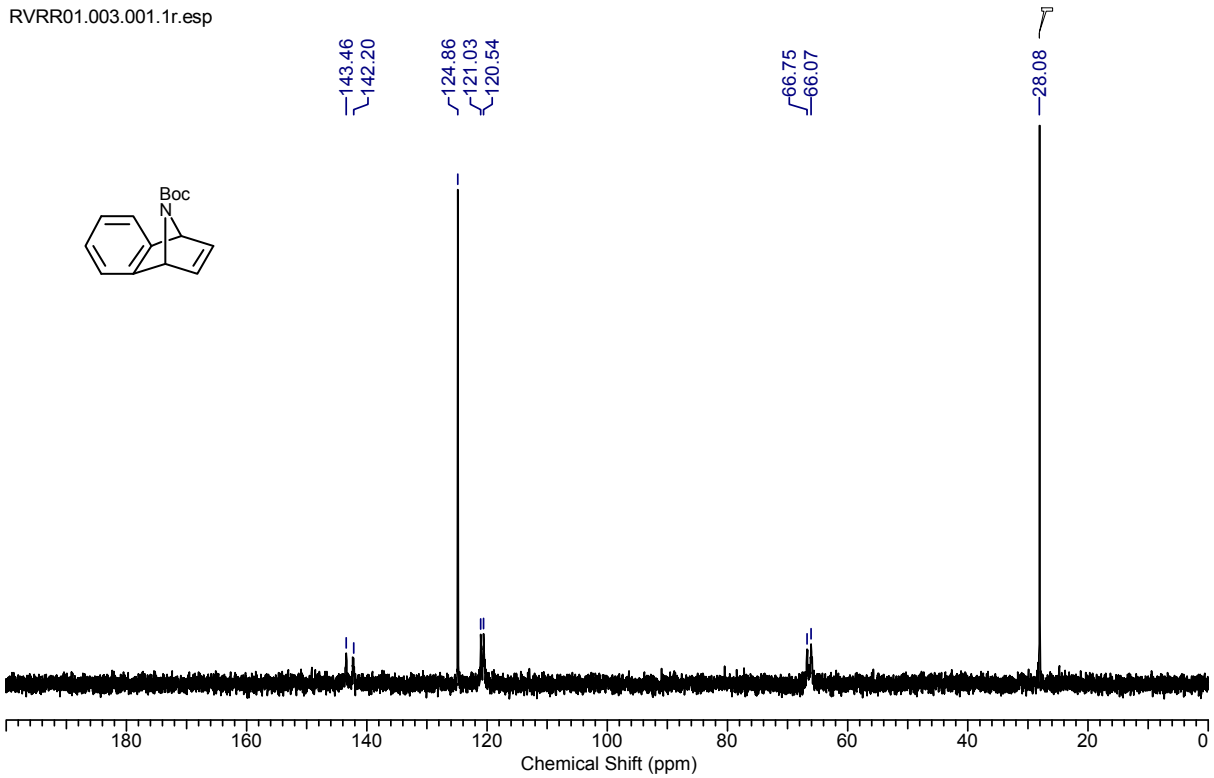


Figure: ^{13}C DEPT NMR Spectrum (100 MHz, $CDCl_3$)

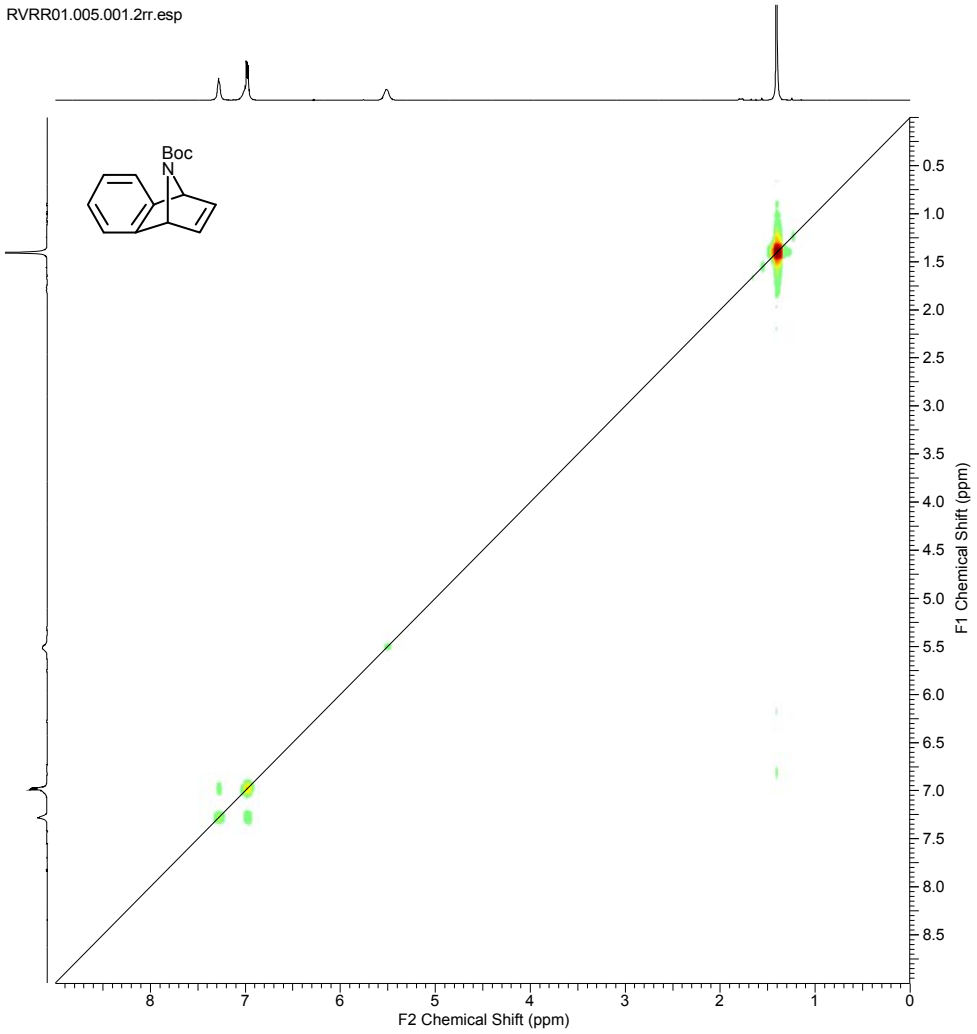


Figure: COSEY NMR Spectrum

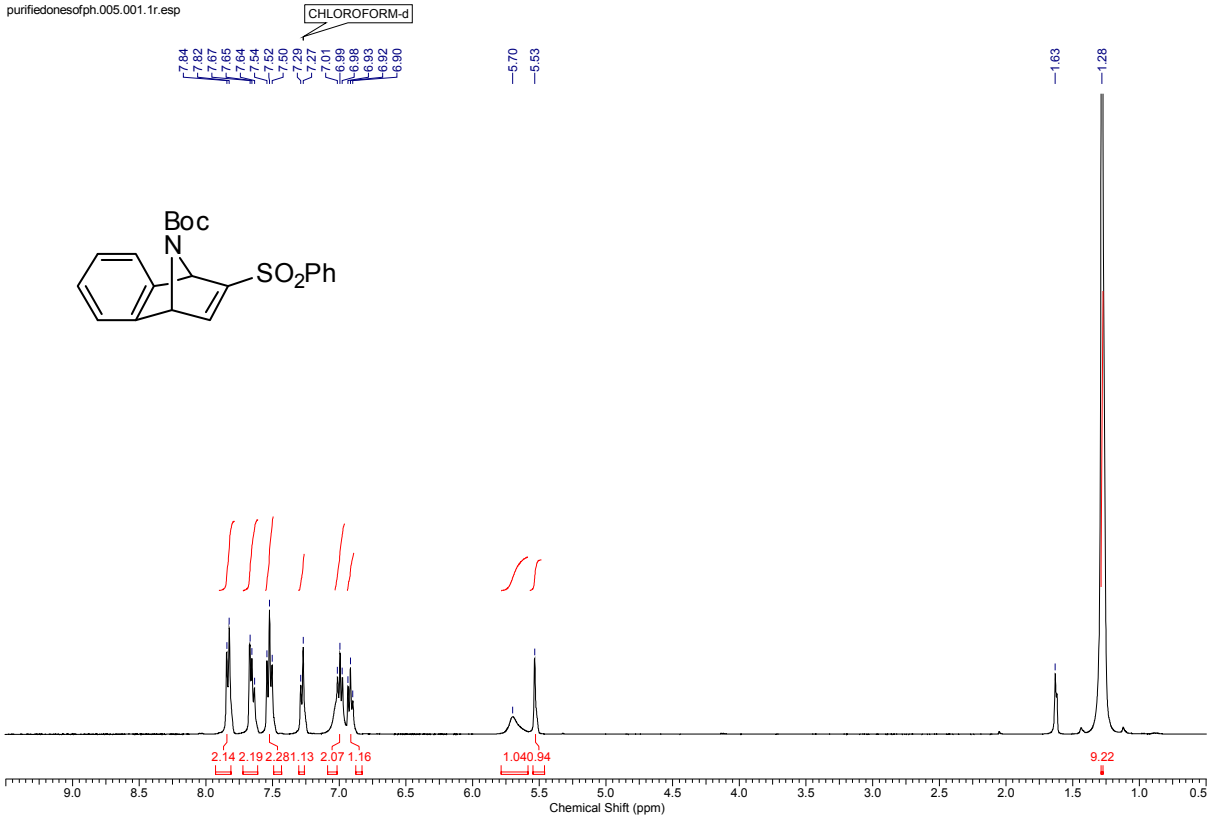


Figure ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)

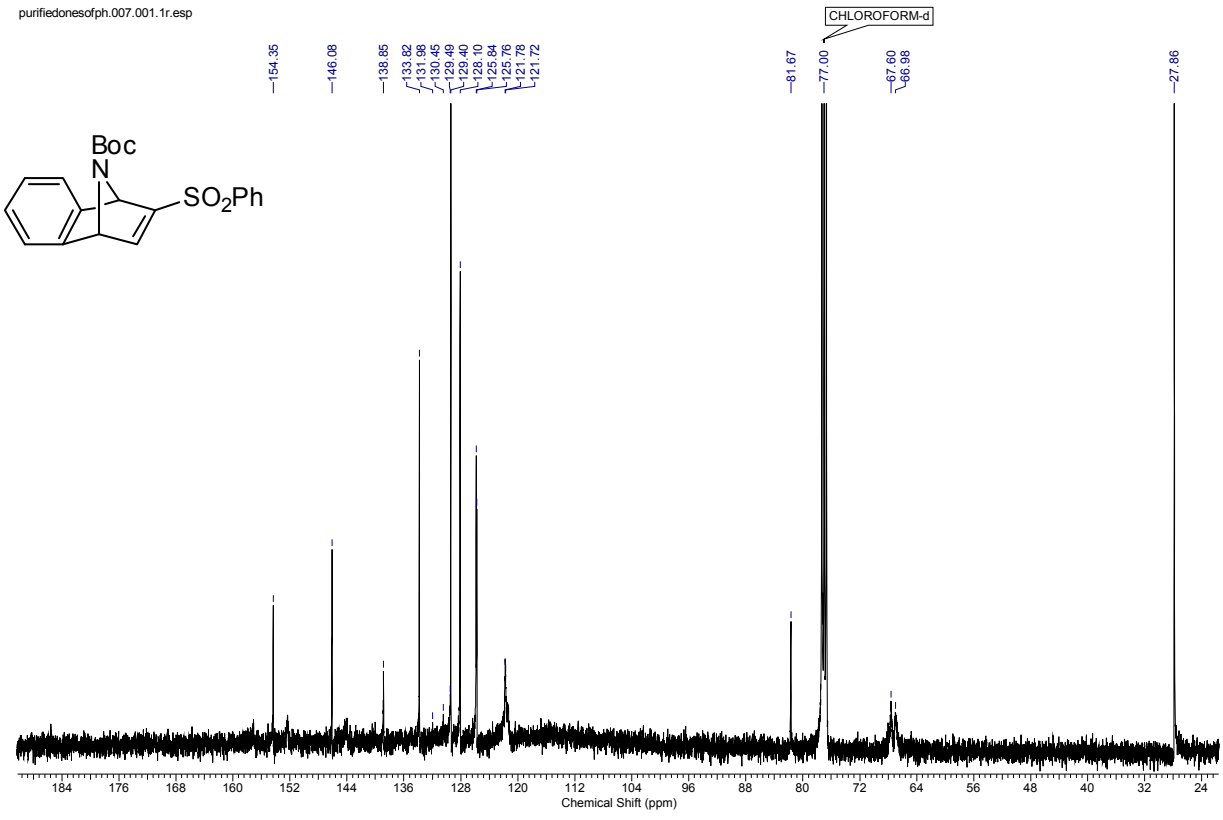


Figure ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

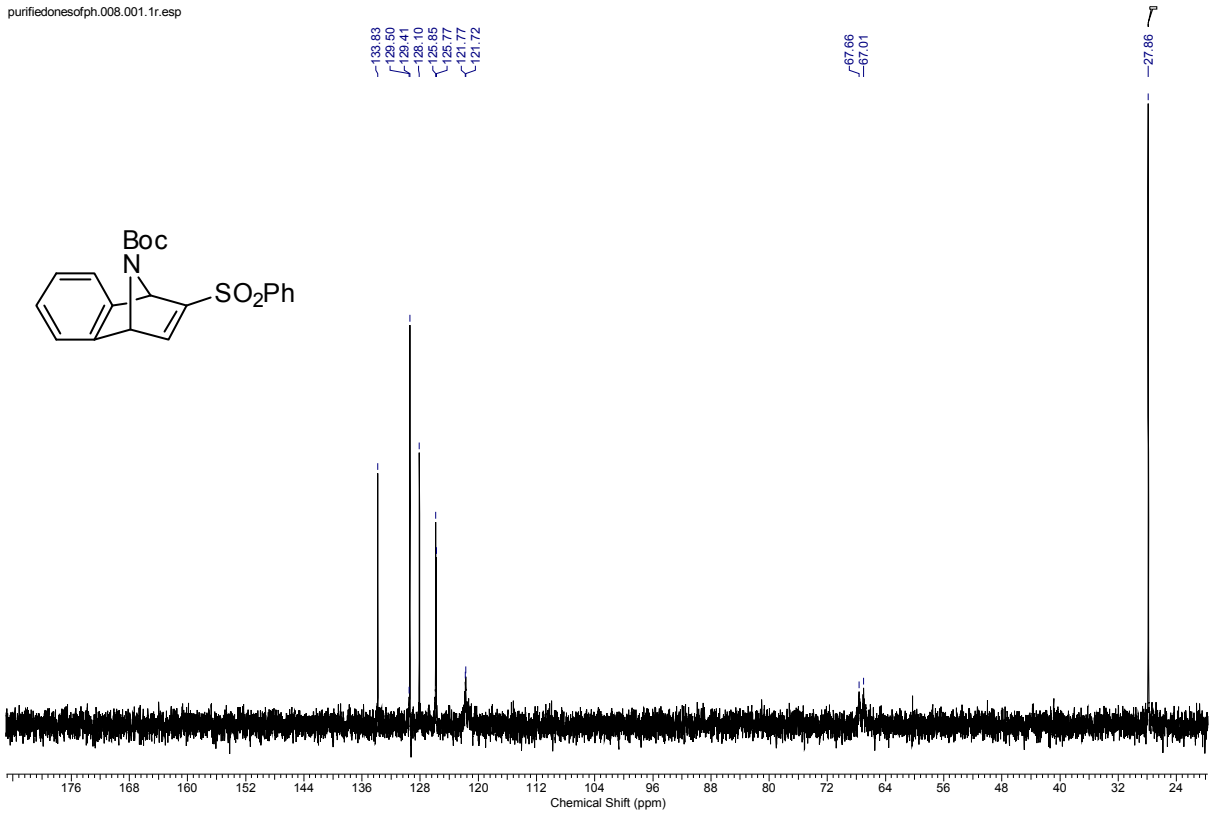
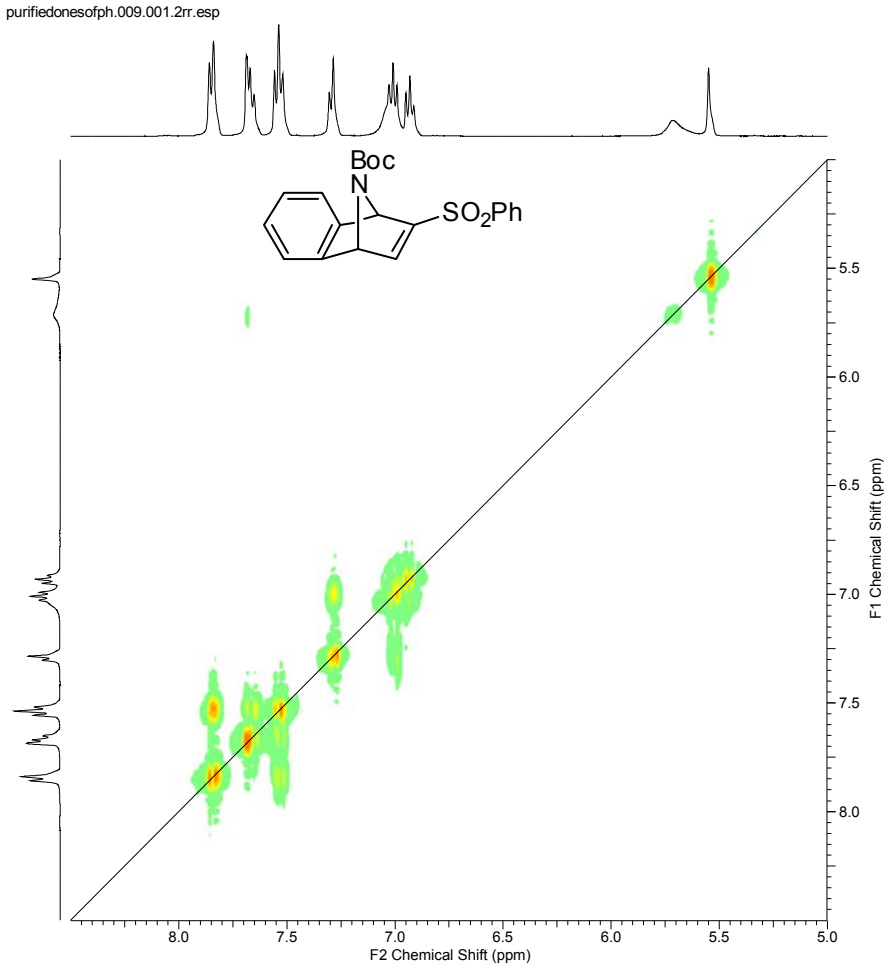


Figure ^{13}C-DEPT NMR Spectrum (100 MHz, $CDCl_3$)



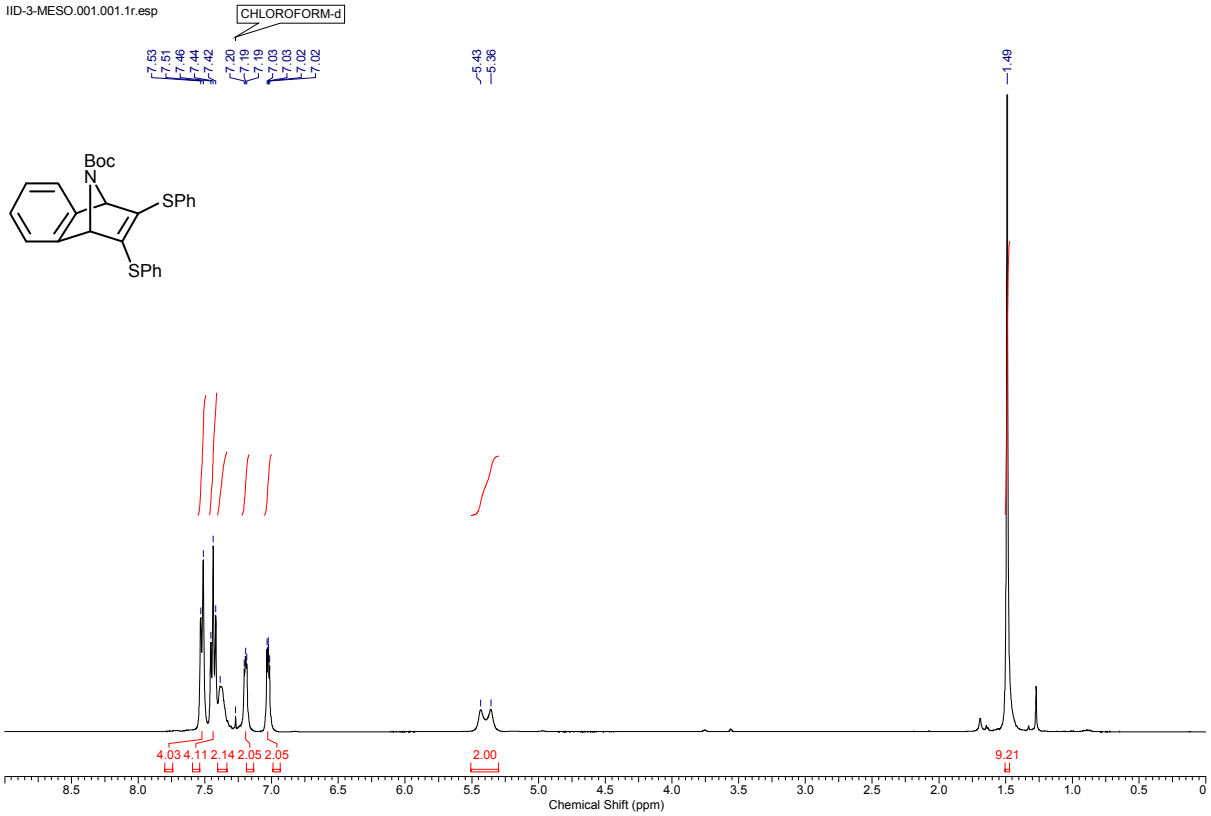


Figure ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)

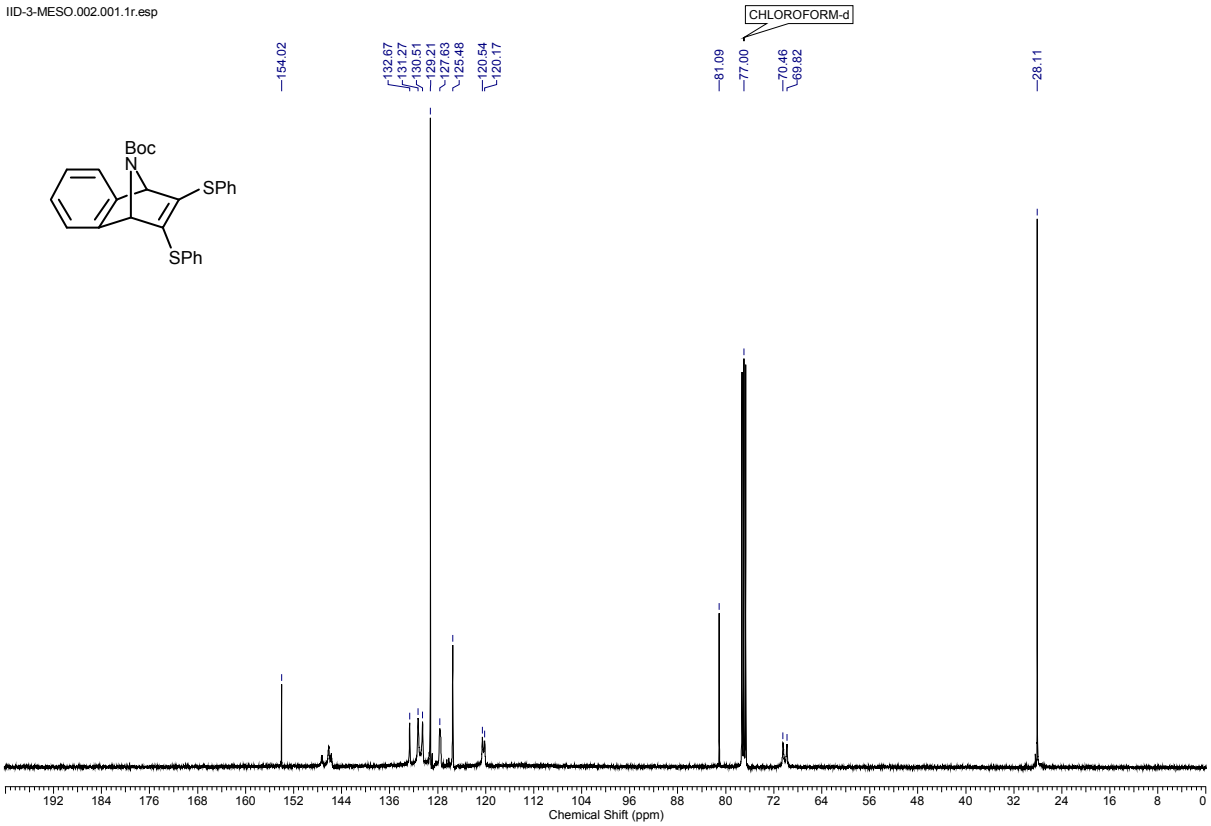


Figure ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

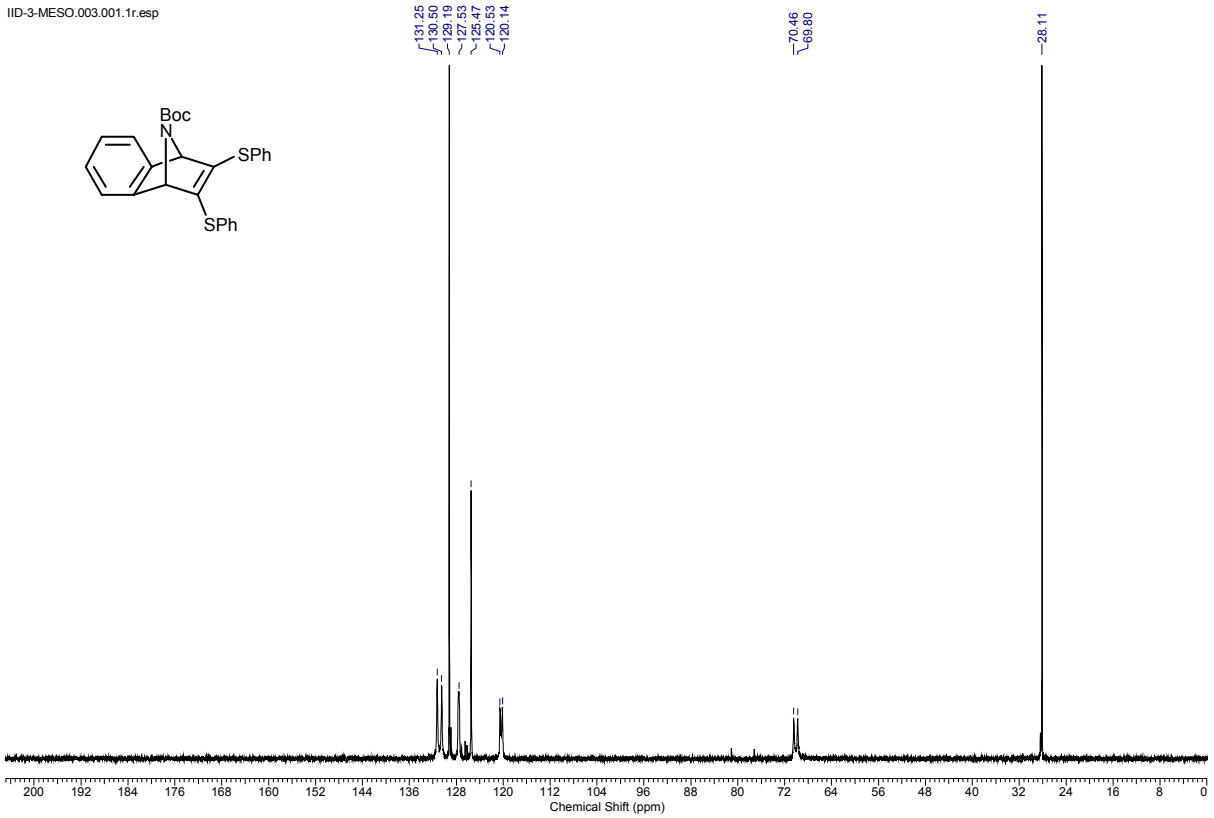


Figure ^{13}C-DEPT NMR Spectrum (100 MHz, $CDCl_3$)

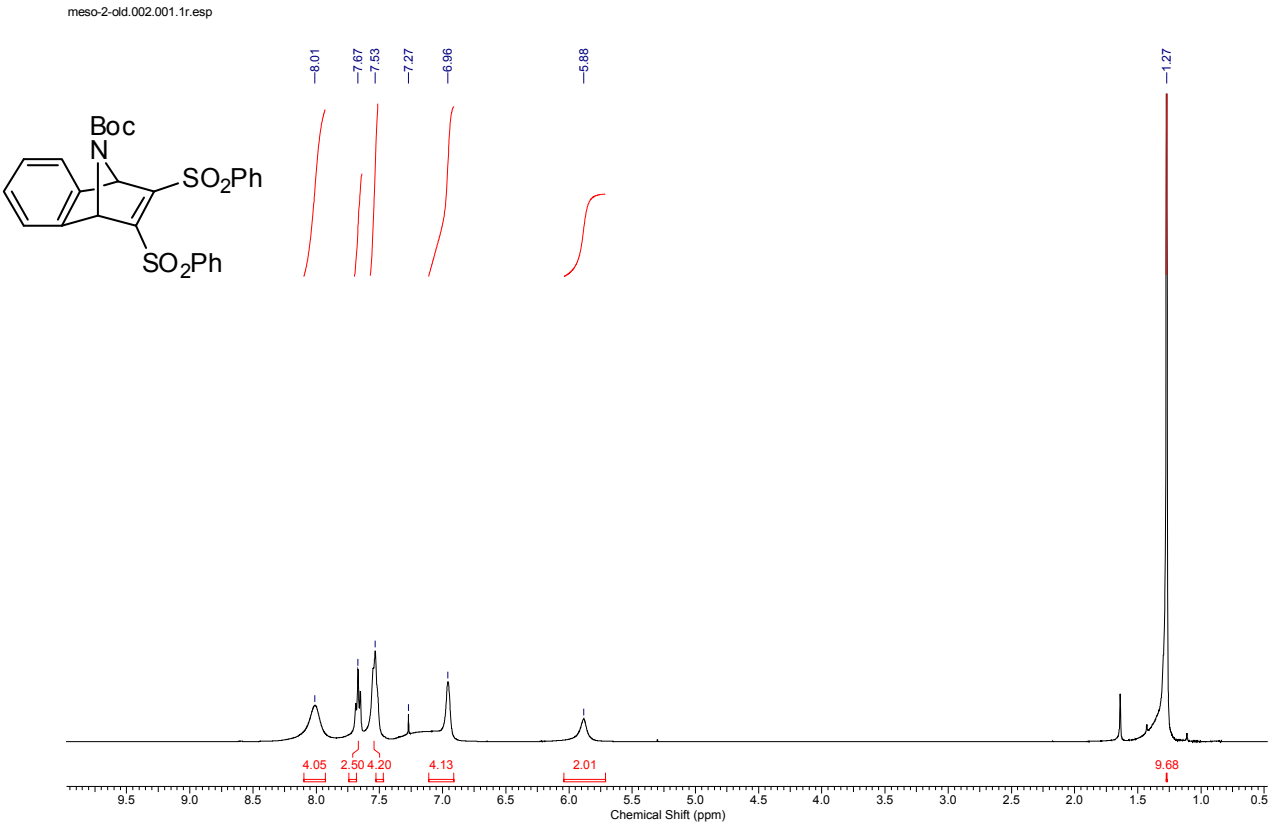


Figure ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)

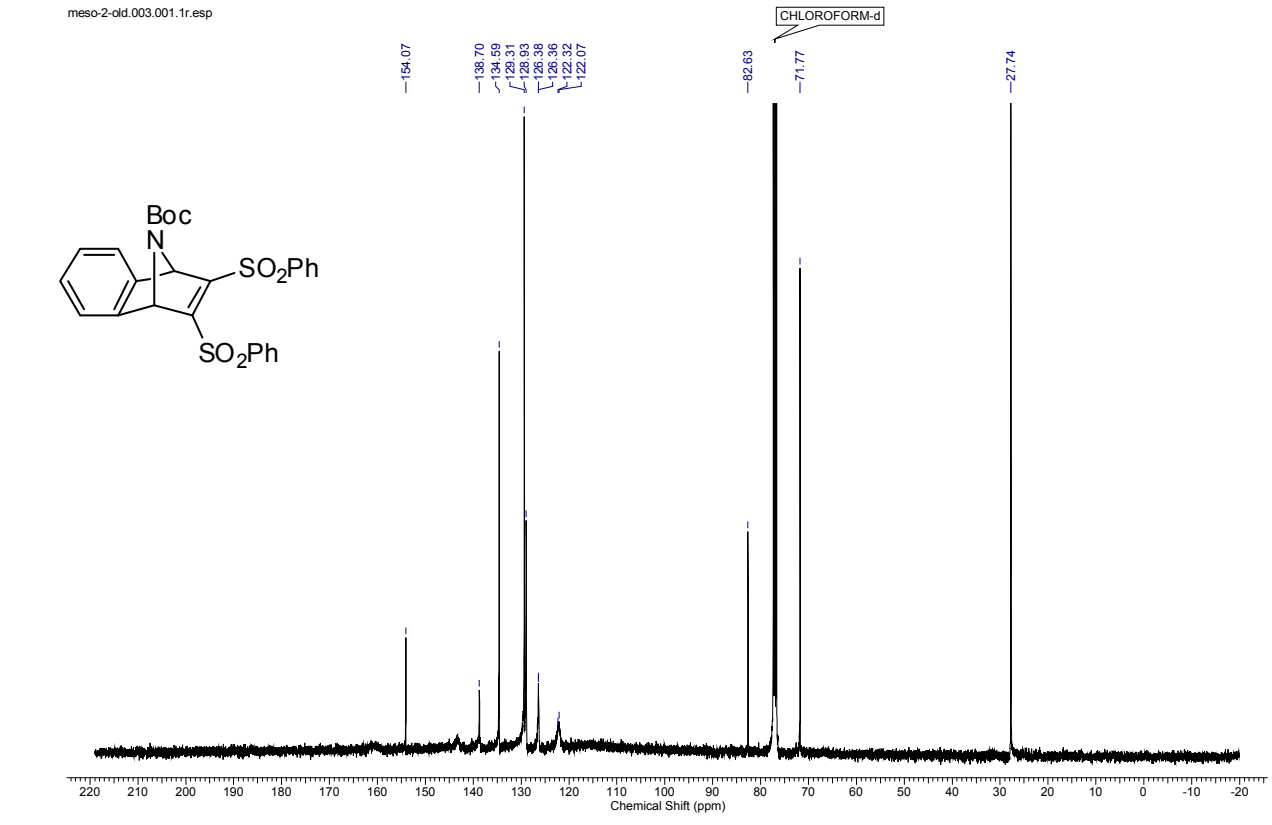


Figure ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

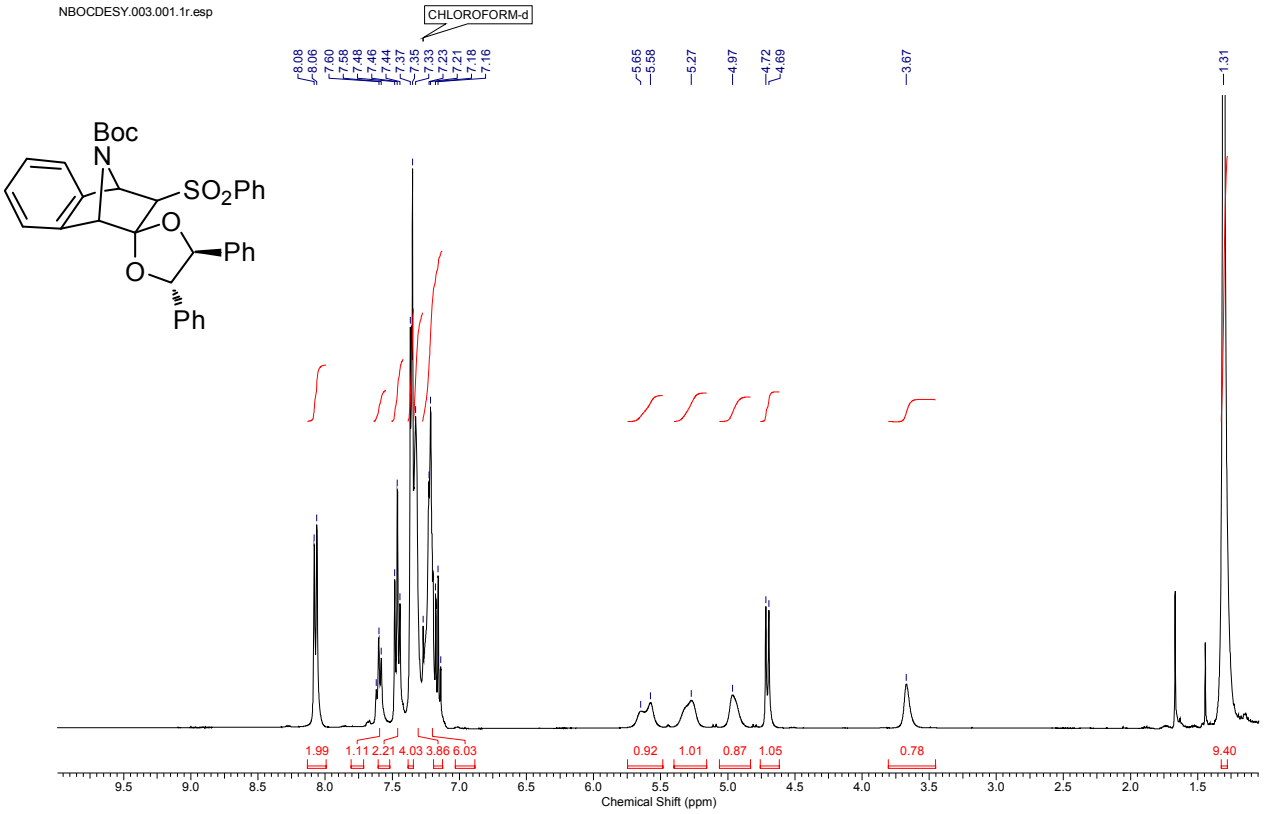


Figure 1H NMR Spectrum (400 MHz, $CDCl_3$)

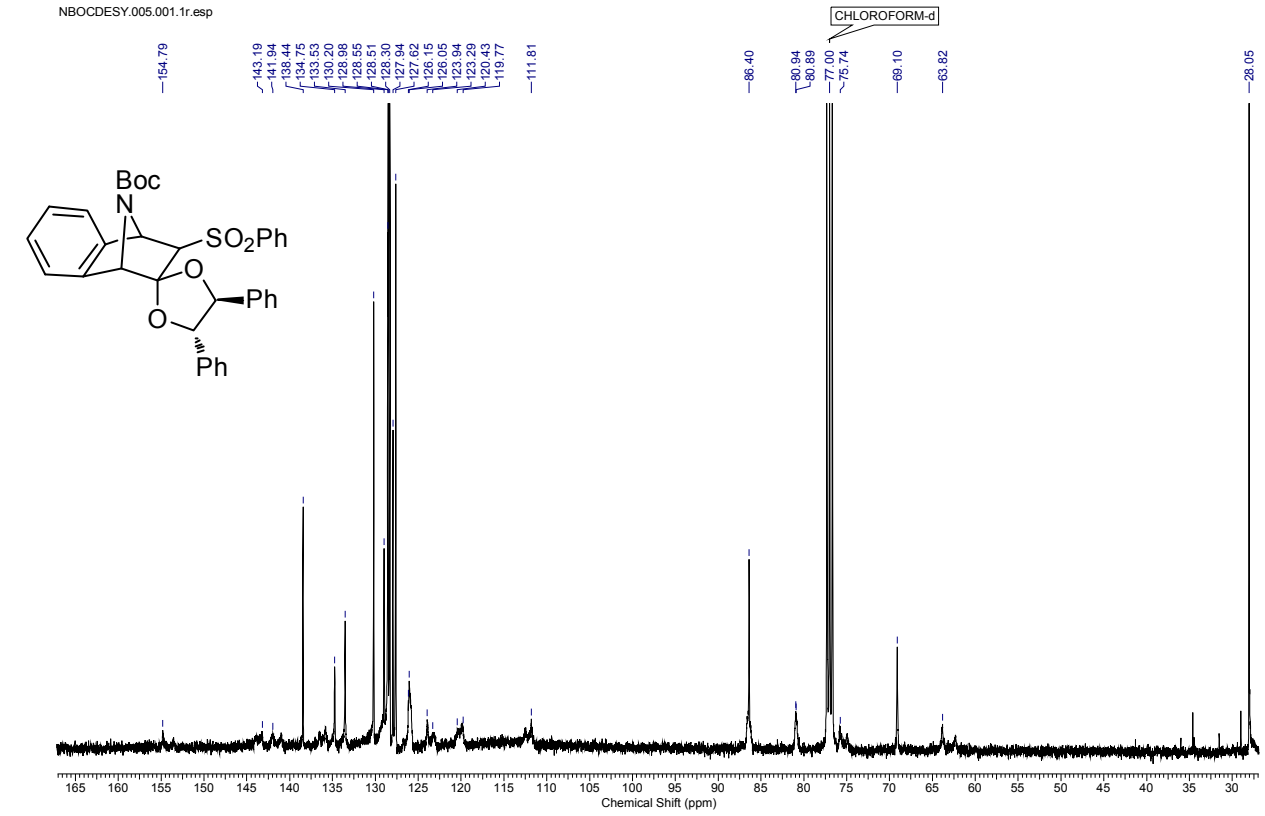
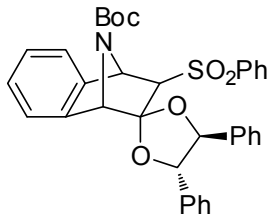


Figure ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

HPLC for Desymmetrization of *N*-Boc-*Meso* at -78 °C:



CBMR

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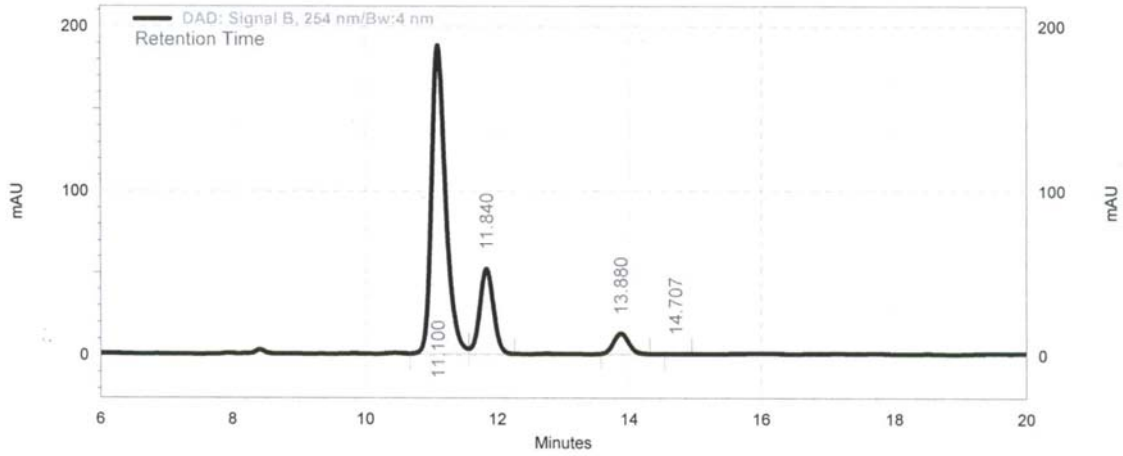


DAD: Signal B,
254 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
11.100	5844541	74.67	393956	74.62
11.840	1567733	20.03	108090	20.47
13.880	412434	5.27	25740	4.88
14.707	2066	0.03	153	0.03
Totals	7826774	100.00	527939	100.00

Column: Atlantis T3 5um
Solvent: MeOH:H2O (80:20)
Wavelength-254nm
Flow Rate- 1ML/min
Pressure: 1250 psig
Operator :RAJESH

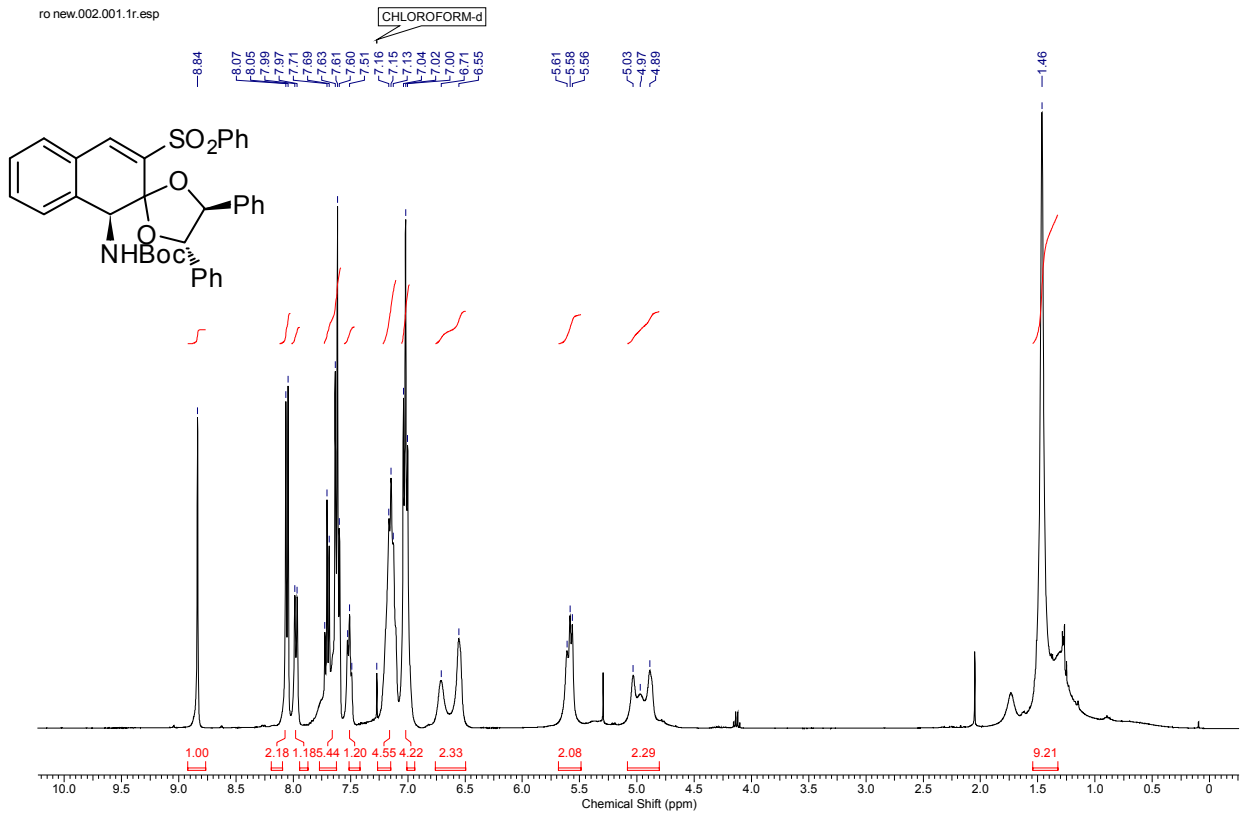


Figure ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)

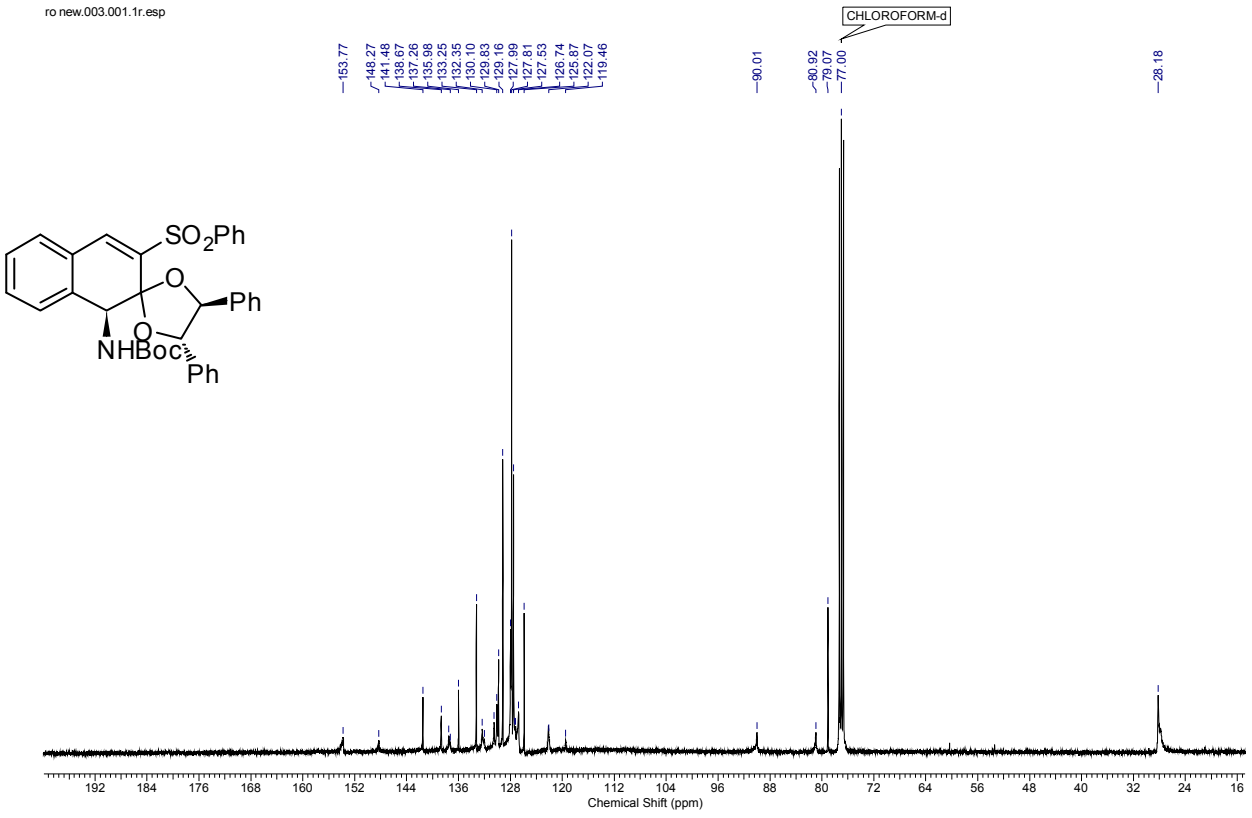
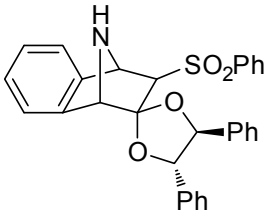


Figure ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

Desymmetrization of NH-*Meso* :



At rt.

Desymmetrization of NH-meso at R.T.

Area % Report

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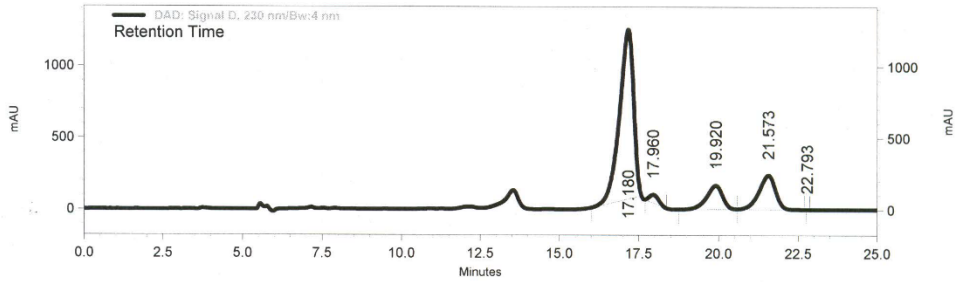
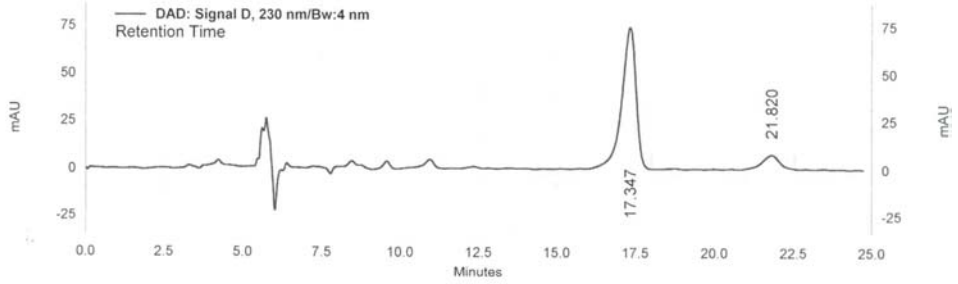


DAD: Signal D,
230 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
17.180	76203918	70.27	2477058	71.99
17.960	2395843	2.21	118391	3.44
19.920	12000014	11.07	347734	10.11
21.573	17839631	16.45	497554	14.46
22.793	131	0.00	34	0.00

Totals				
	108439537	100.00	3440771	100.00

At 0°C

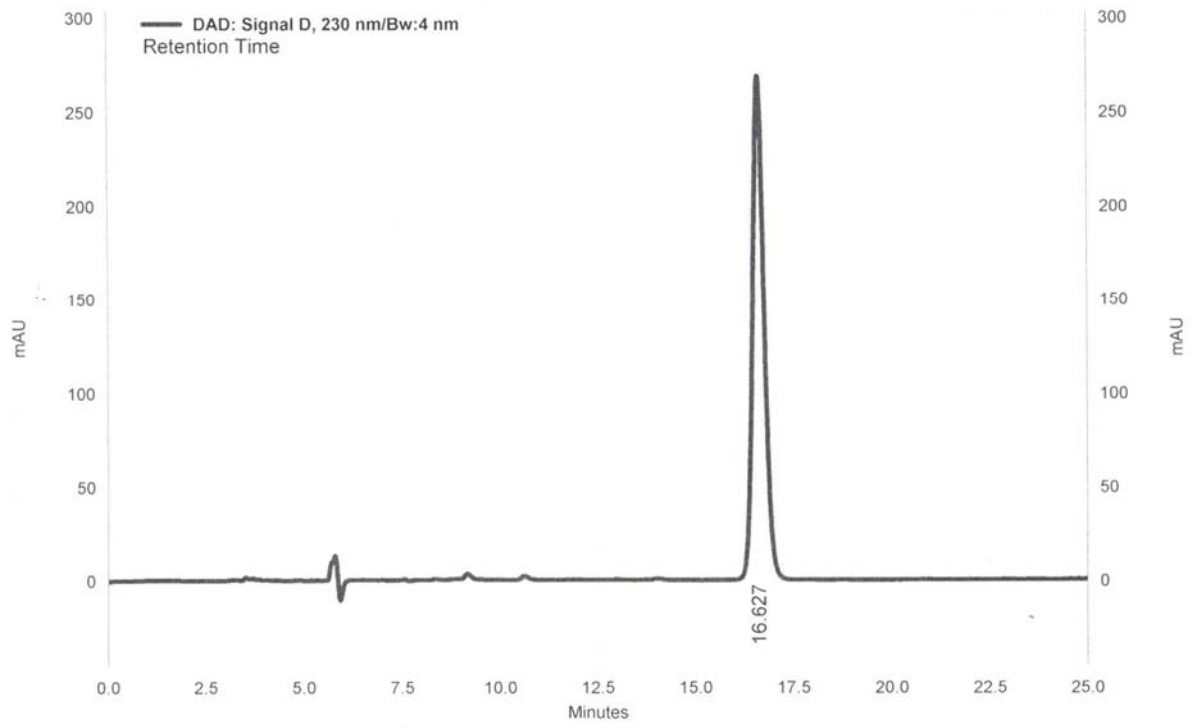


DAD: Signal D,
230 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
17.347	4919878	89.30	155813	90.95
21.820	589410	10.70	15498	9.05

Totals				
	5509288	100.00	171311	100.00

At – 20 °C



DAD: Signal D,
230 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
16.627	11412328	100.00	562587	100.00

Totals	11412328	100.00	562587	100.00

Column: ATLANTIS
Solvent: MeOH:H2O = 80:20
WAVELENGTH-230 NM
Flow Rate : 0.5 mL/min
Pressure: 135 bar
Operator : RAJESH

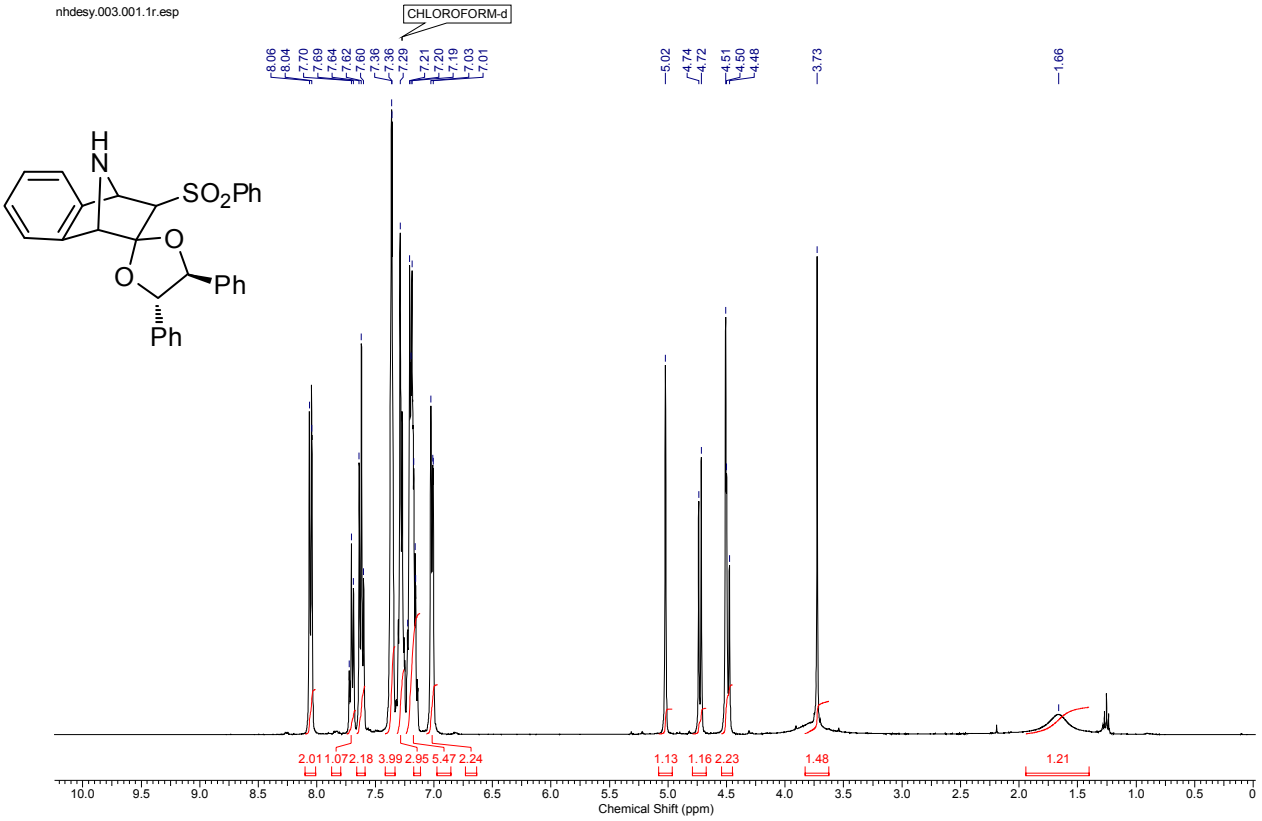


Figure 1H NMR Spectrum (400 MHz, $CDCl_3$)

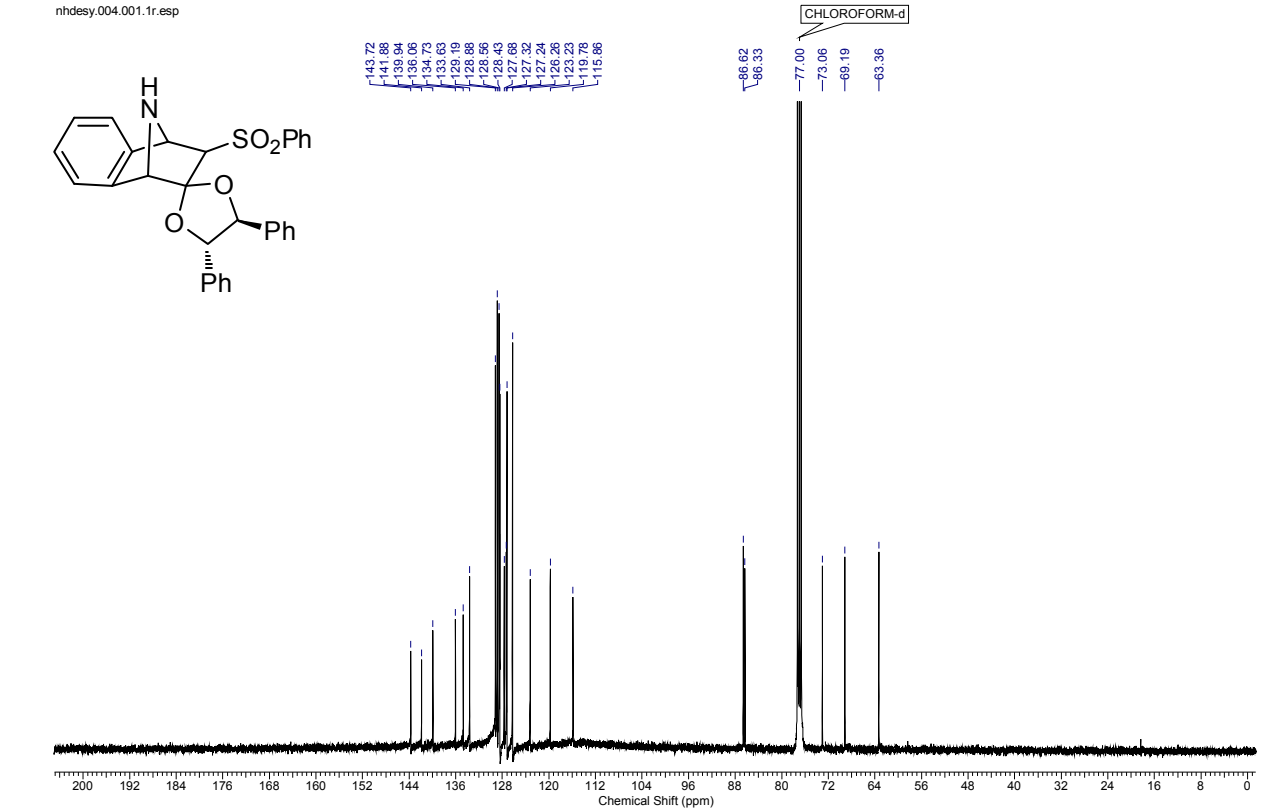


Figure ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

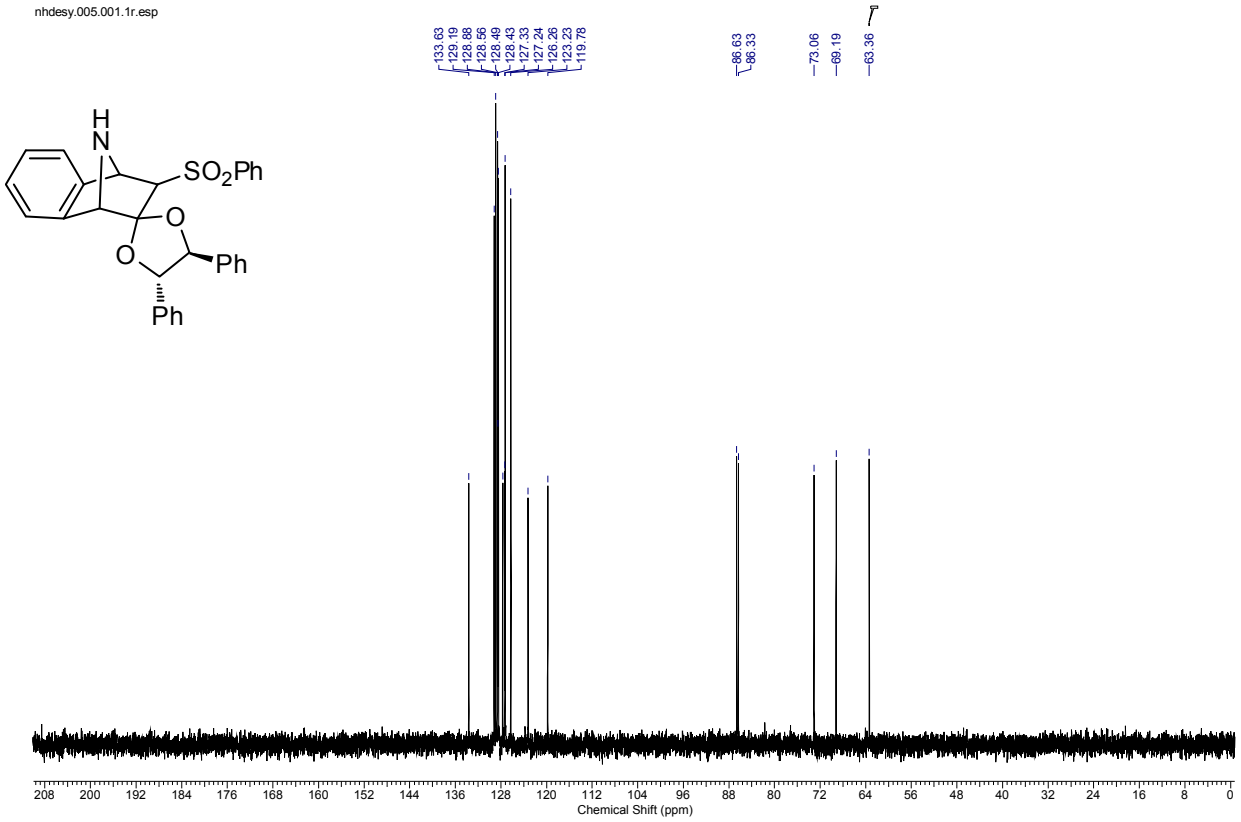


Figure ^{13}C-DEPT NMR Spectrum (100 MHz, $CDCl_3$)

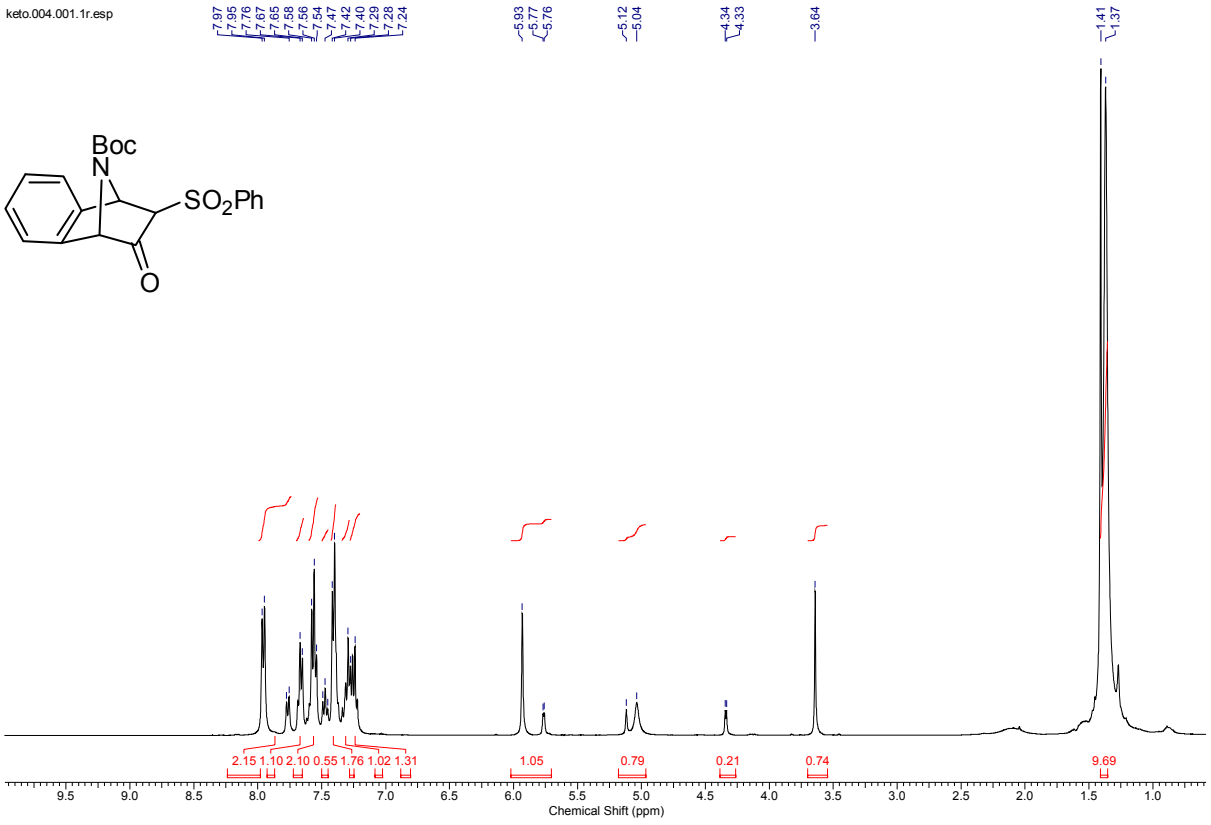


Figure ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)

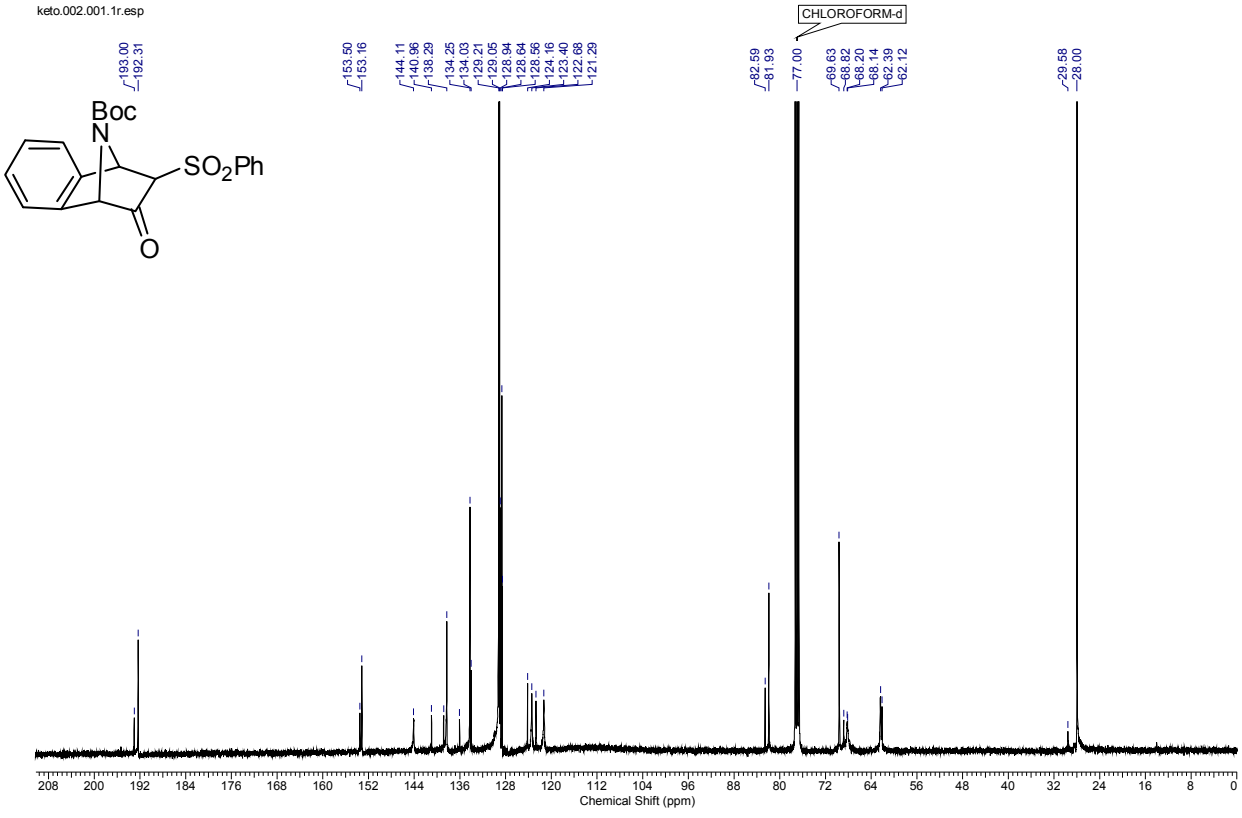


Figure ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

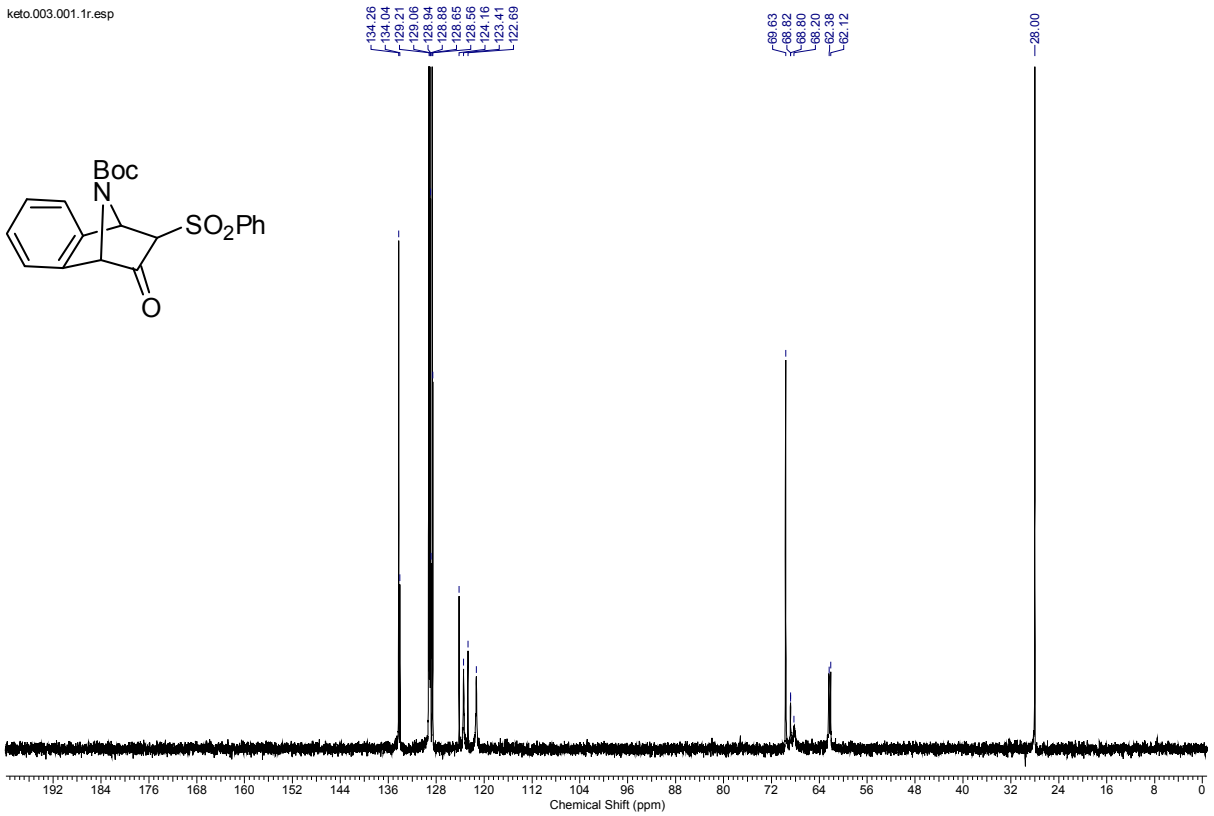
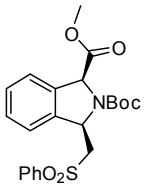
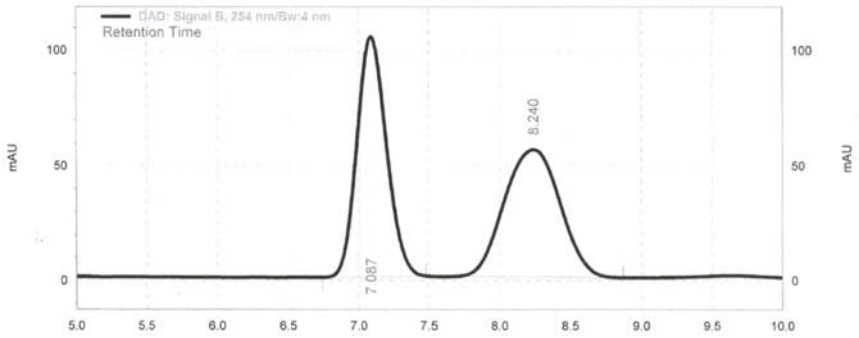


Figure ^{13}C-DEPT NMR Spectrum (100 MHz, $CDCl_3$)

HPLC REPORTS





DAD: Signal B,
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Results

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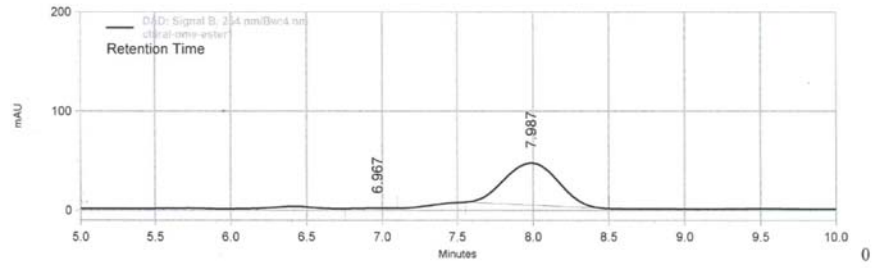
8.240	3185725	49.80
Totals	6396895	100.00



DAD: Signal B,
254 nm/Bw:4 nm
Results

S.No.	Retention Time	Area	Area %
1	6.97	5952	0.27
2	7.99	2205668	99.73
Totals		2211620	100.00

Column: CHIRALPAK AS-H
Solvent Hexane:Isopropanol (90:10)
Wavelenght 254 nm
Flow Rate - 1.5 mL/min
Pressure 60bar
Operator: Rajesh.

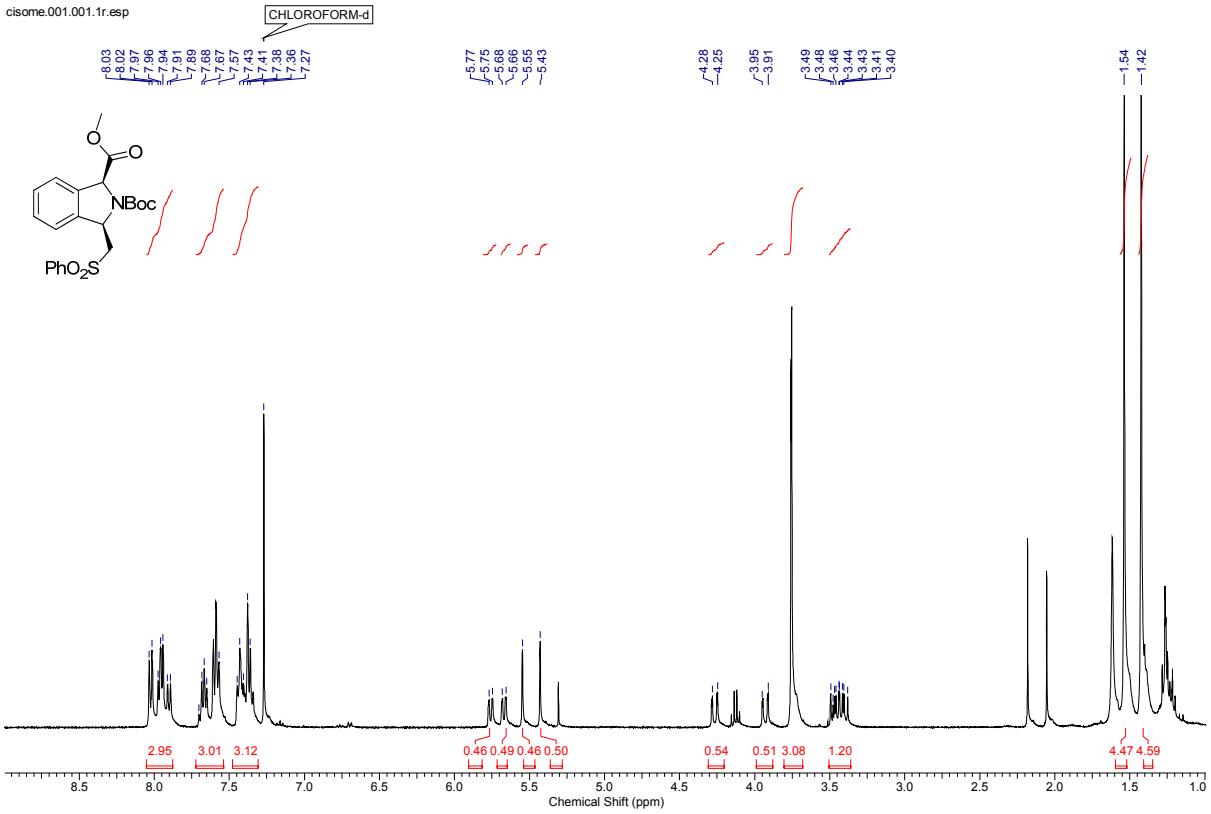


Figure 1H NMR Spectrum (400 MHz, $CDCl_3$)

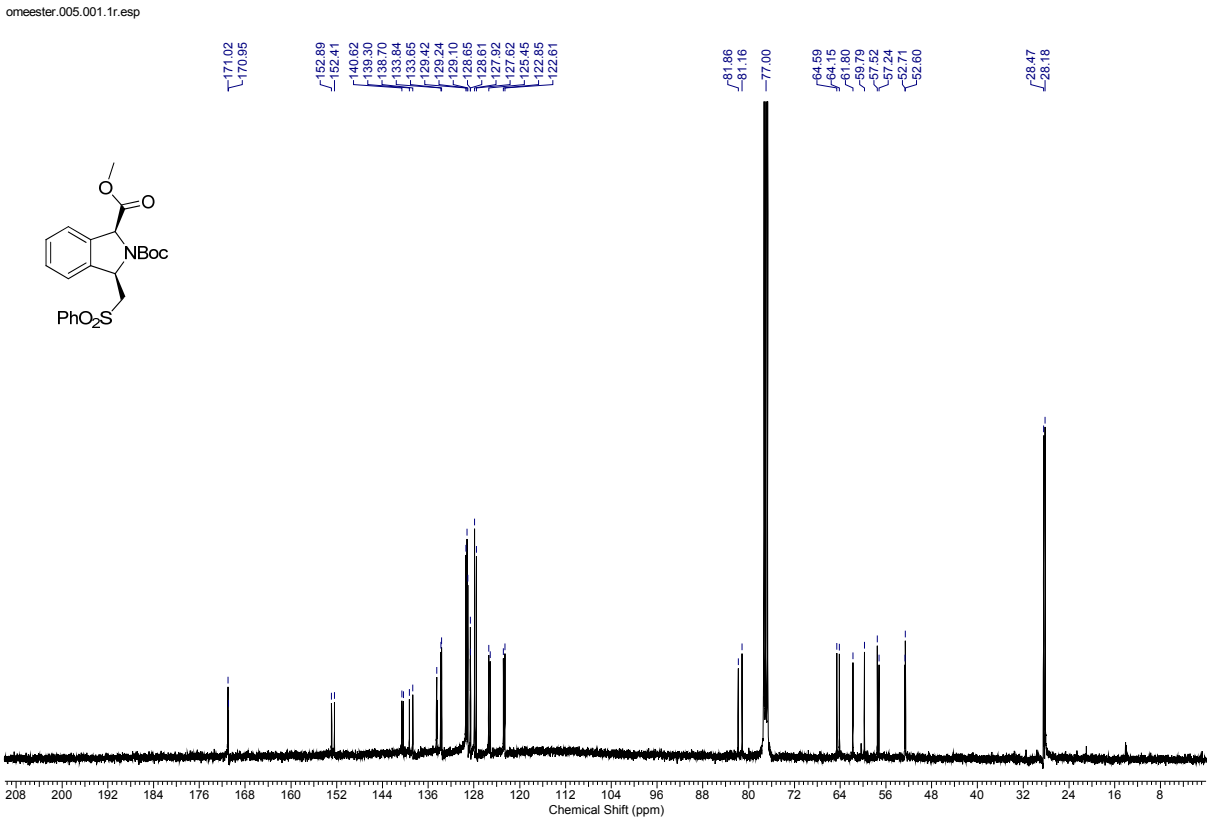


Figure ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

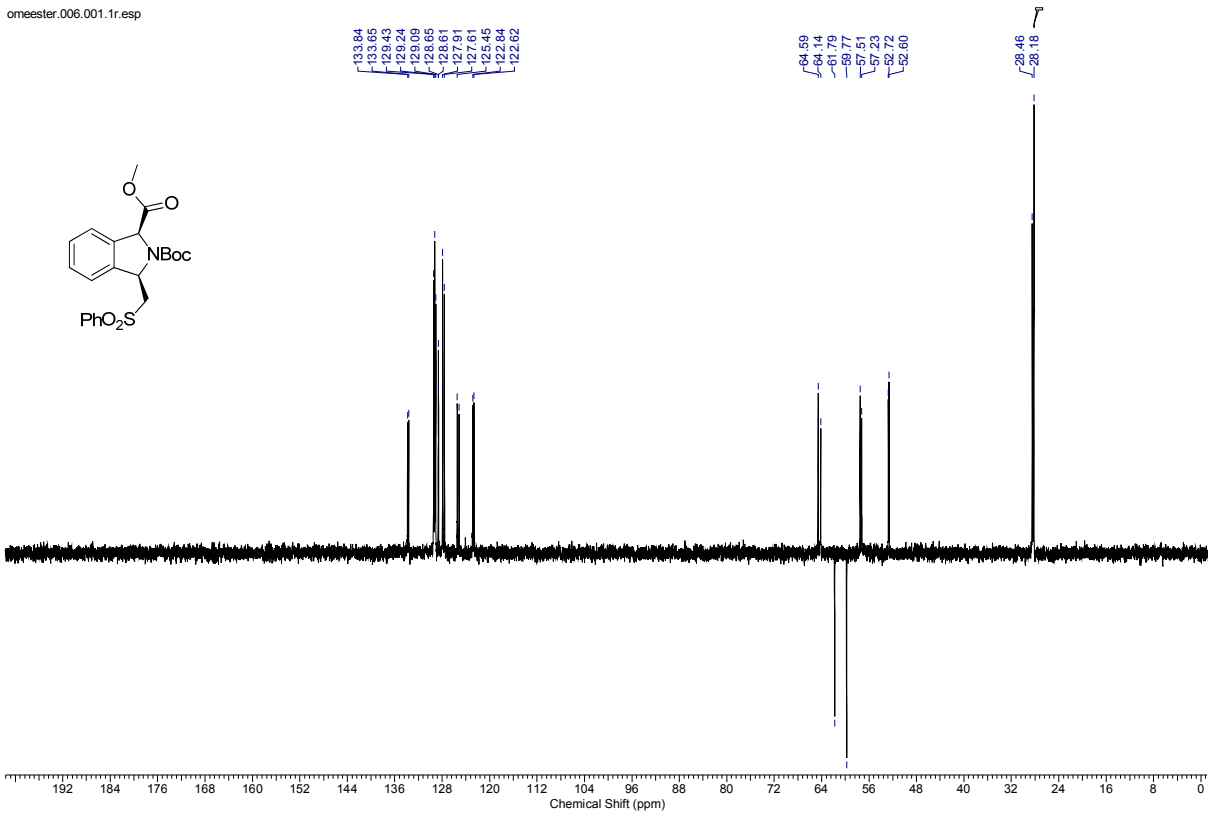
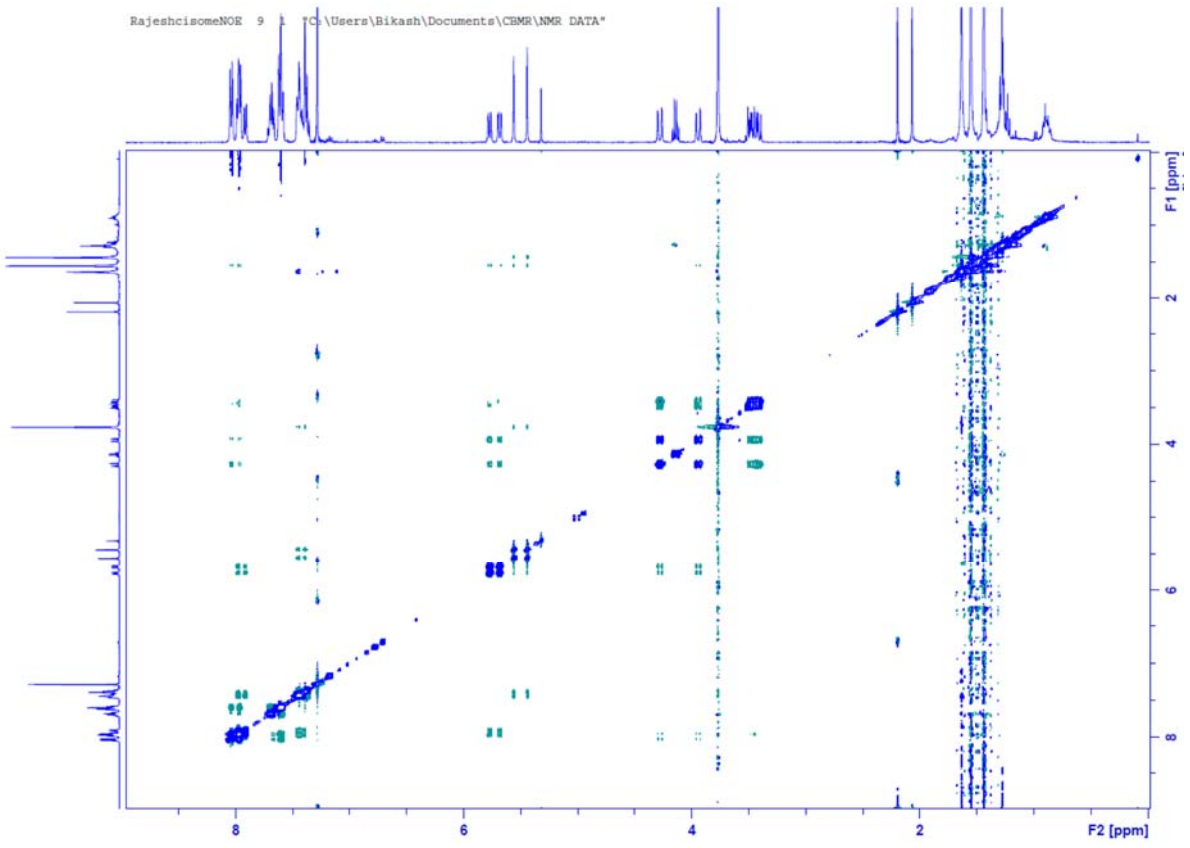


Figure ^{13}C-DEPT NMR Spectrum (100 MHz, $CDCl_3$)

NOE:



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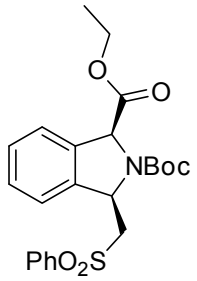
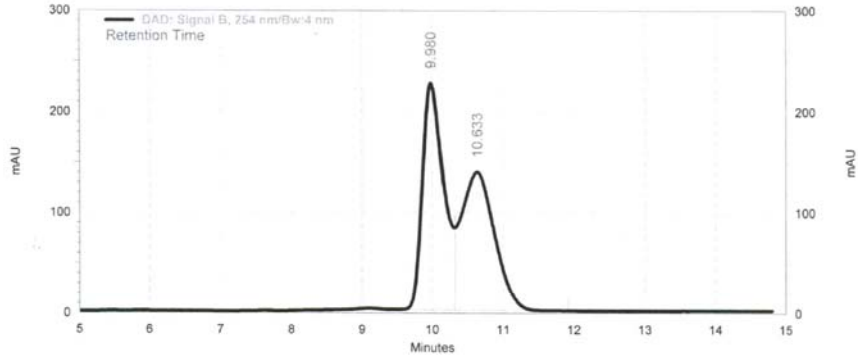
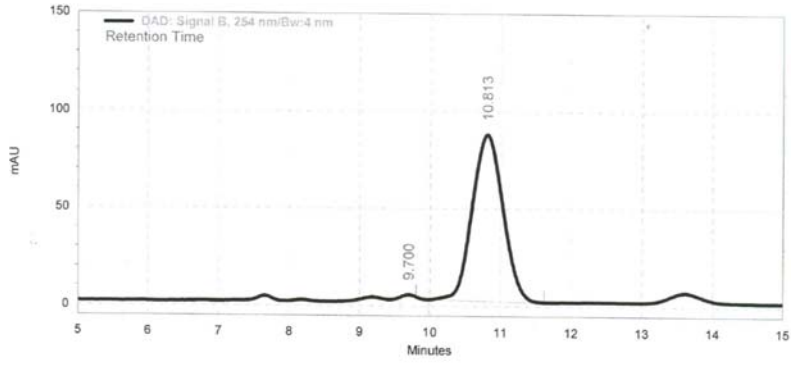




DAD: Signal B,
254 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
9.980	9776035	50.82	471551	62.09
10.633	9460095	49.18	287921	37.91
Totals	19236130	100.00	759472	100.00



DAD: Signal B,
254 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
9.700	19607	0.36	2273	1.26
10.813	5431904	99.64	178762	98.74
Totals	5451511	100.00	181035	100.00

Column: CHIRALPAK AS-H
Solvent: Hexane:Isopropanol (95:5)
Wavelength-254nm
Flow Rate-1.5ML/min
Pressure: 45 bar
Operator :RAJESH

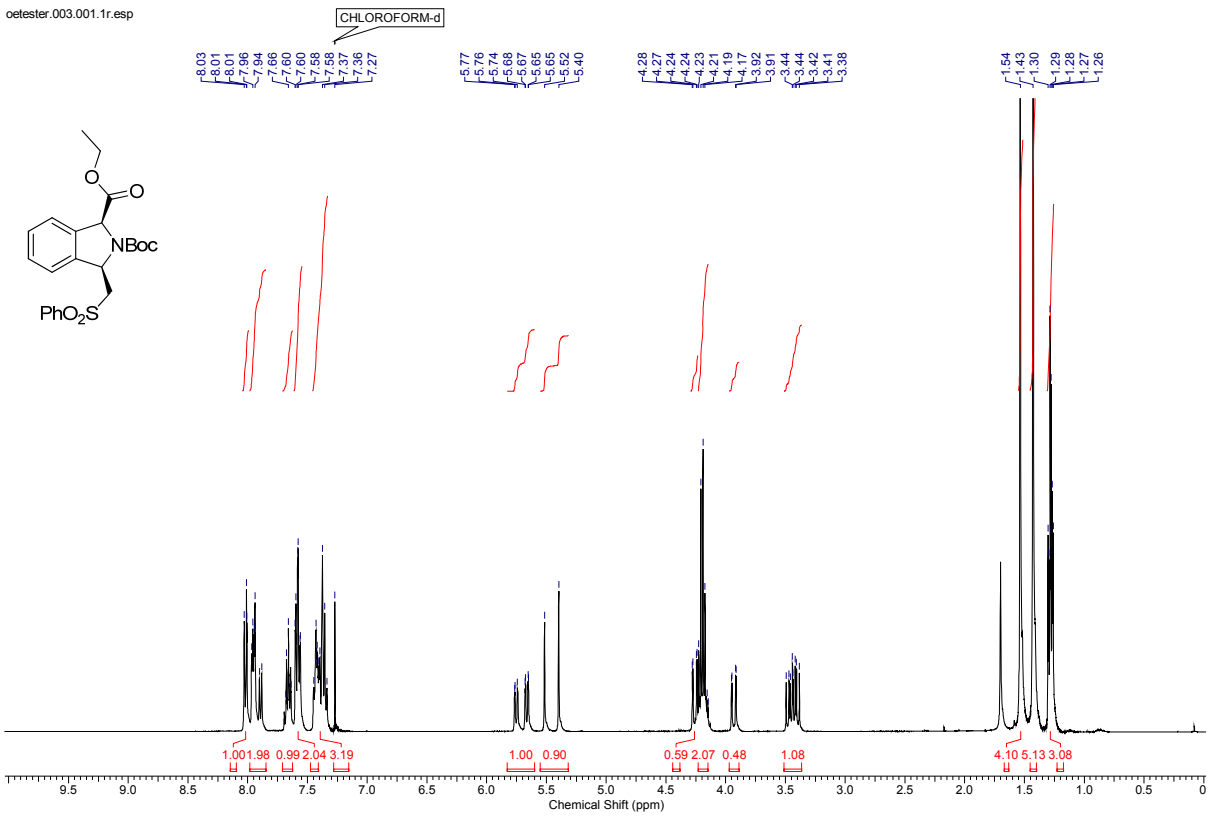


Figure 1H NMR Spectrum (400 MHz, $CDCl_3$)

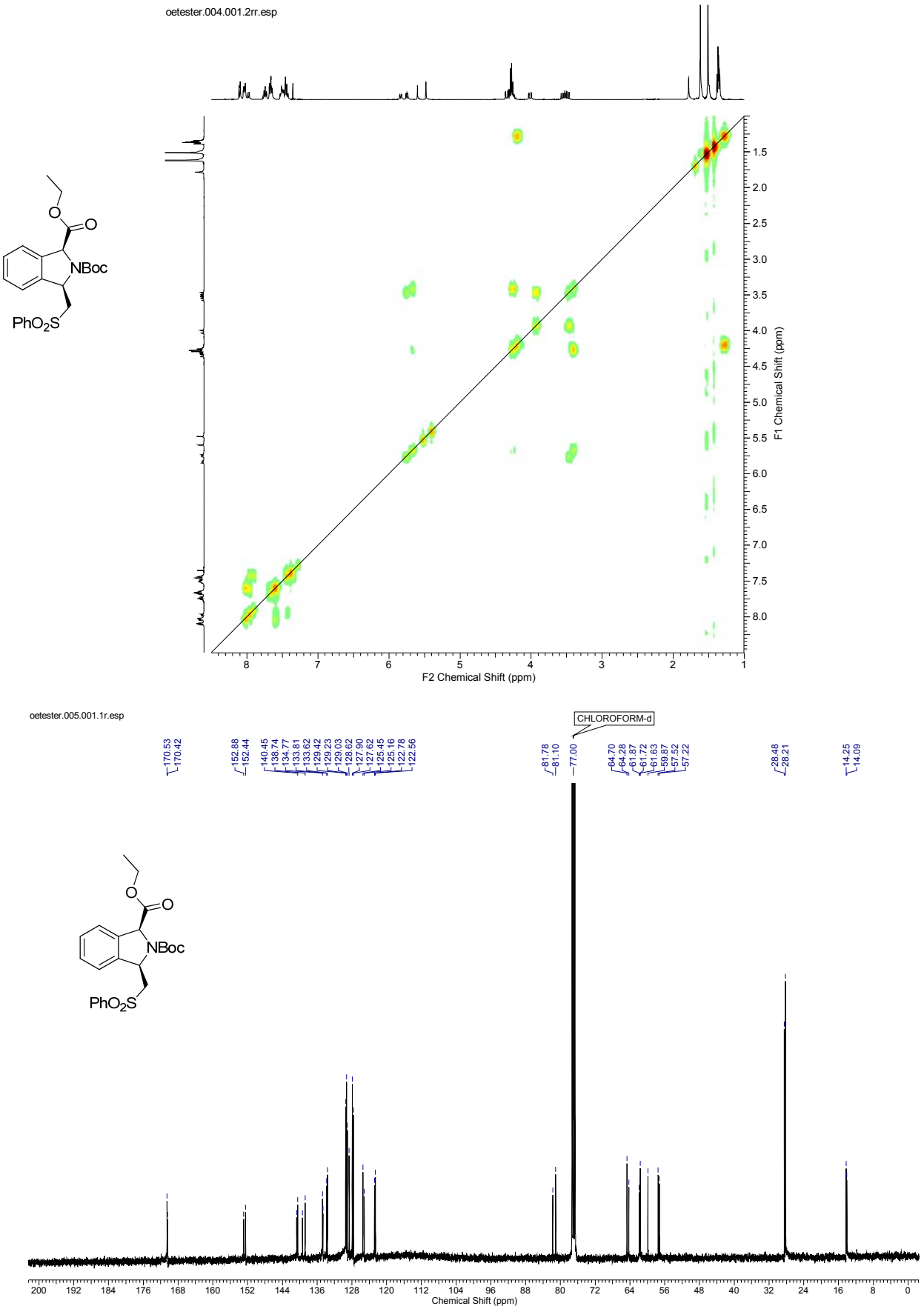


Figure ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

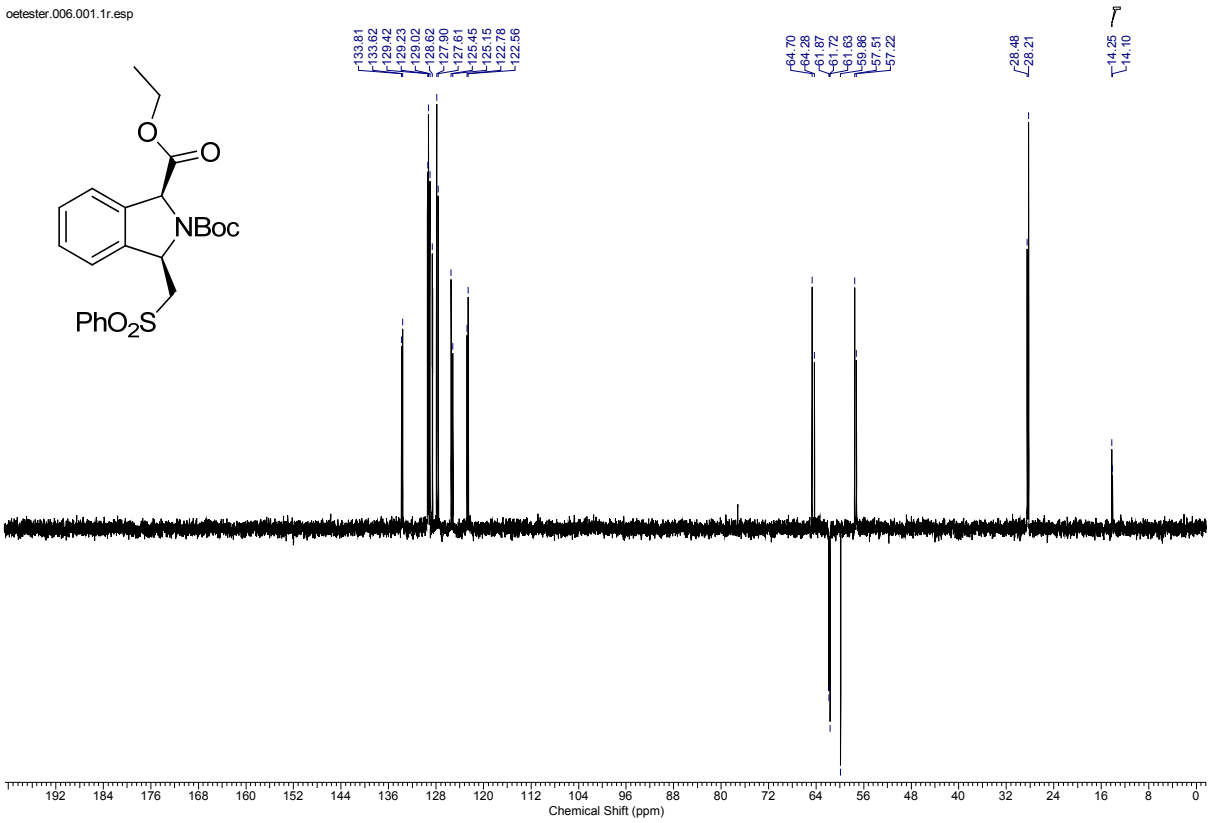
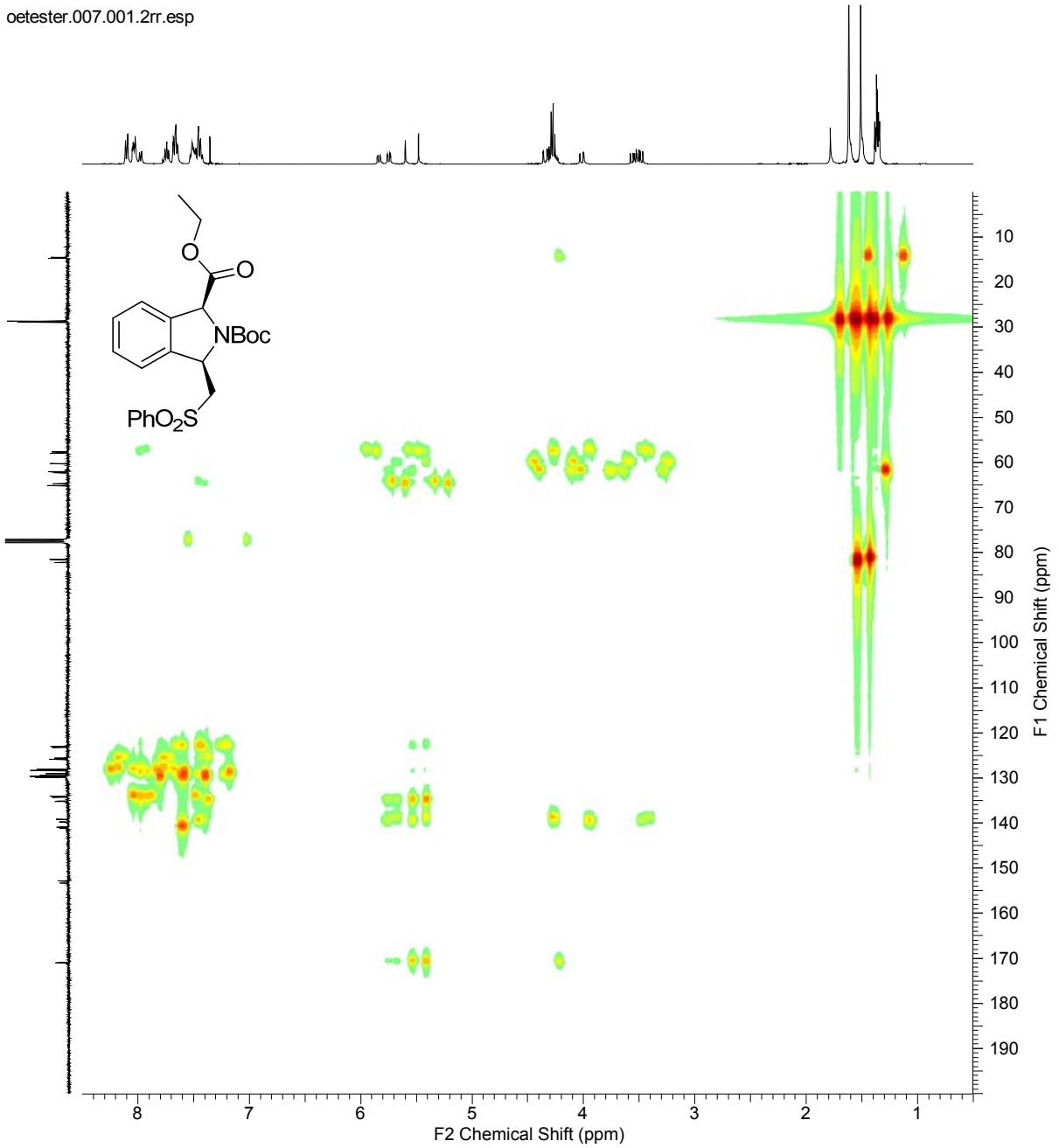


Figure ^{13}C-DEPT NMR Spectrum (100 MHz, $CDCl_3$)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O
NBoc
PhO2S
F2 Chemical Shift (ppm)
F1 Chemical Shift (ppm)

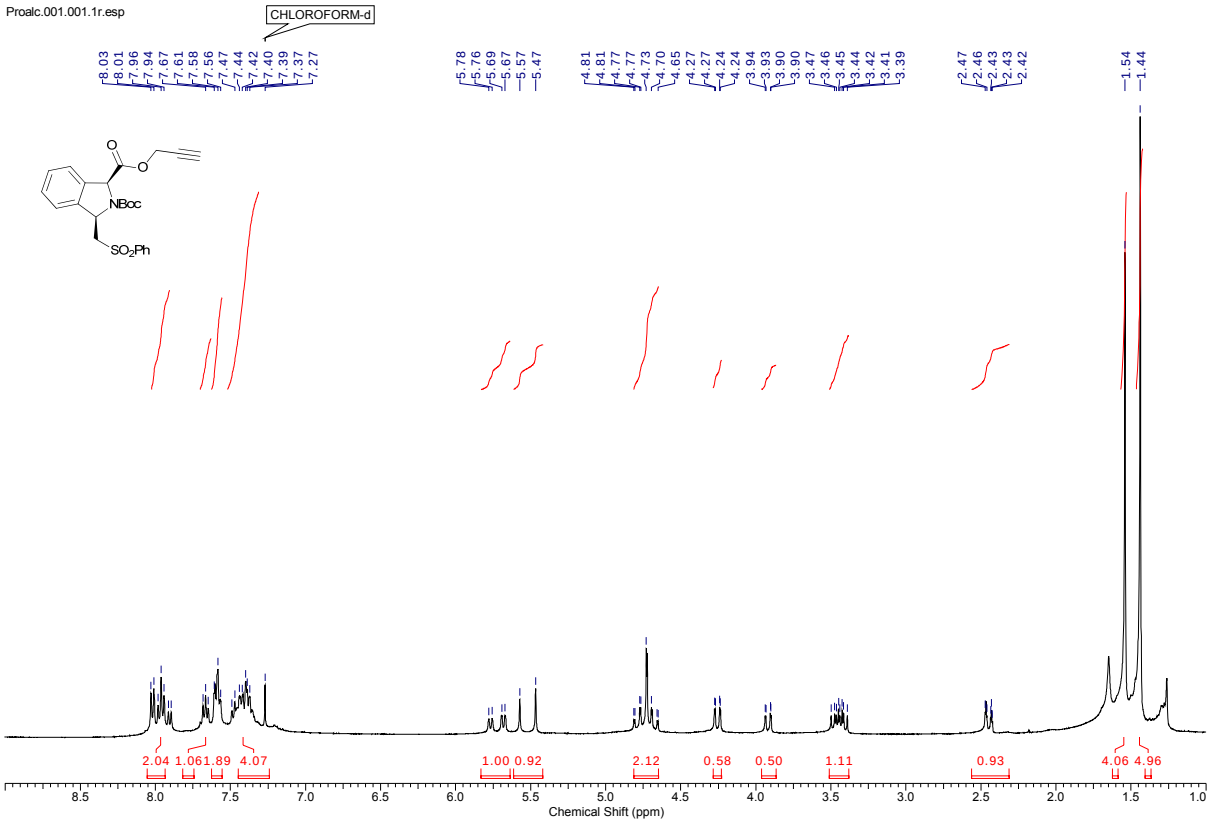


Figure ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)

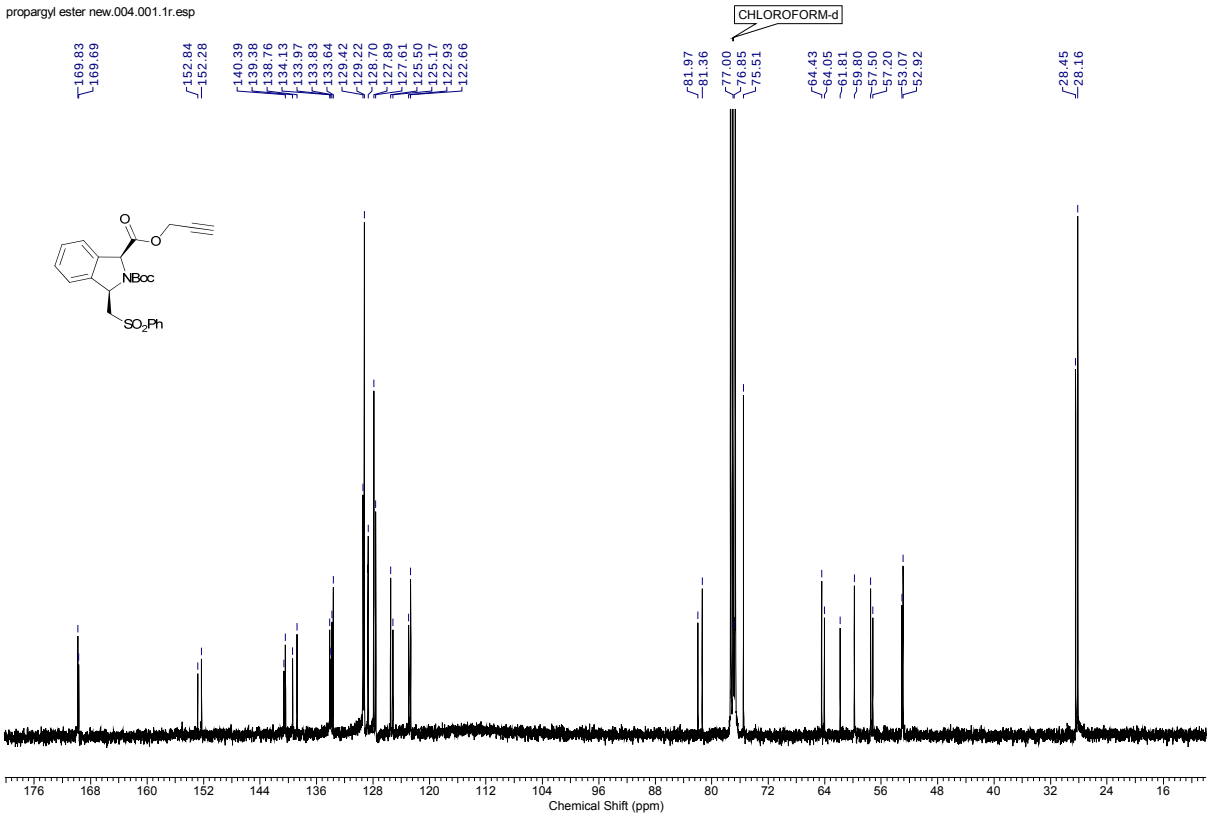


Figure ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

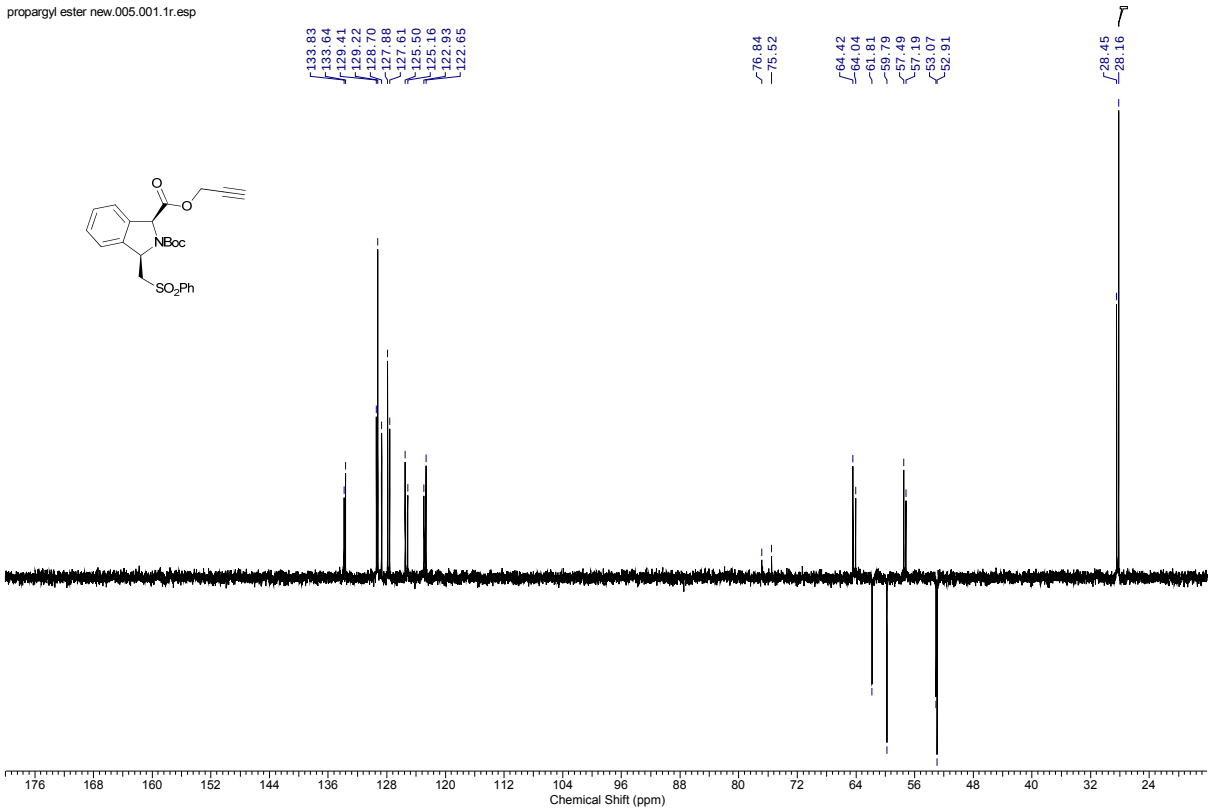


Figure ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

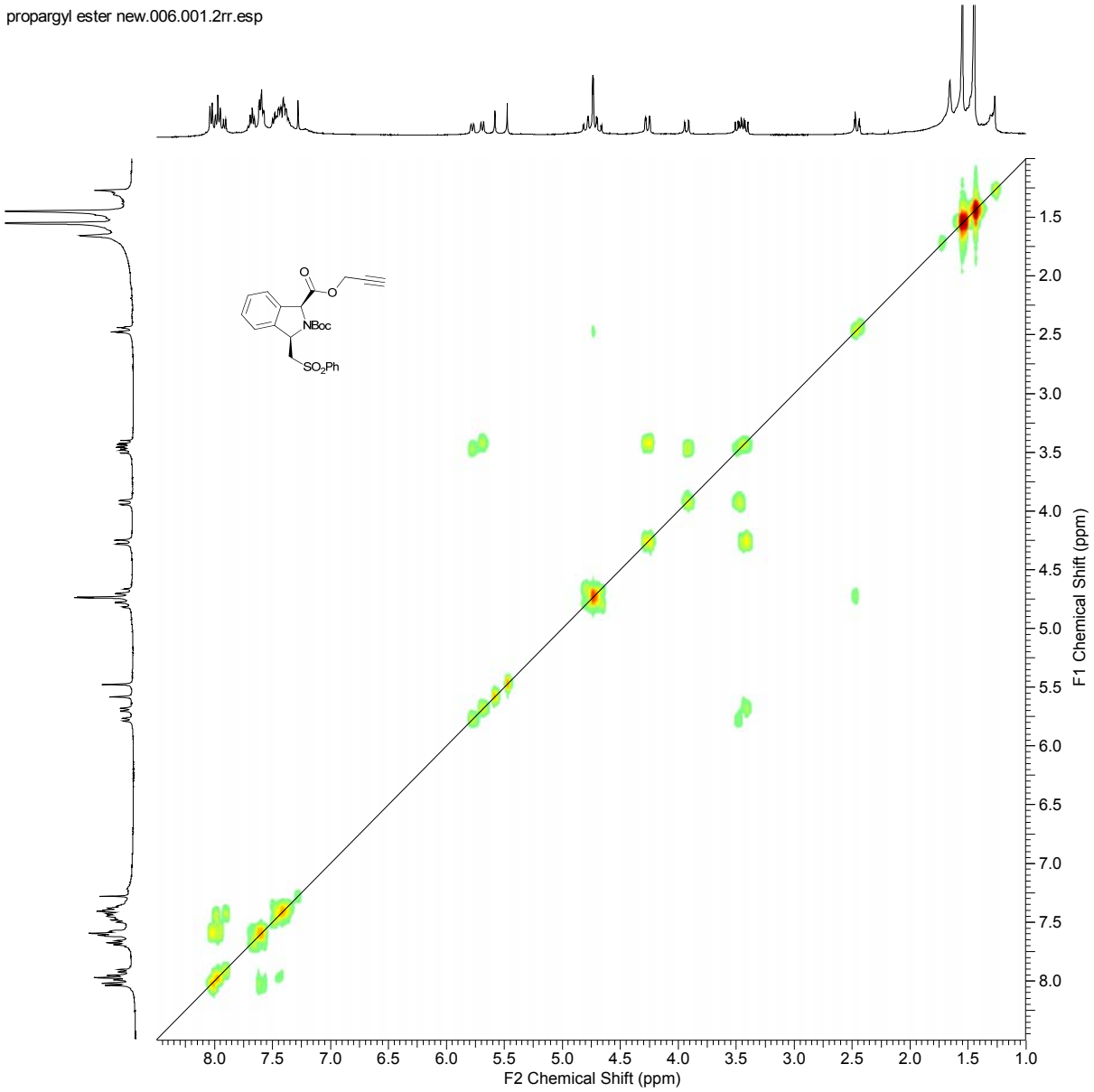


Figure: COSEY NMR Spectrum (400 MHz, $CDCl_3$)

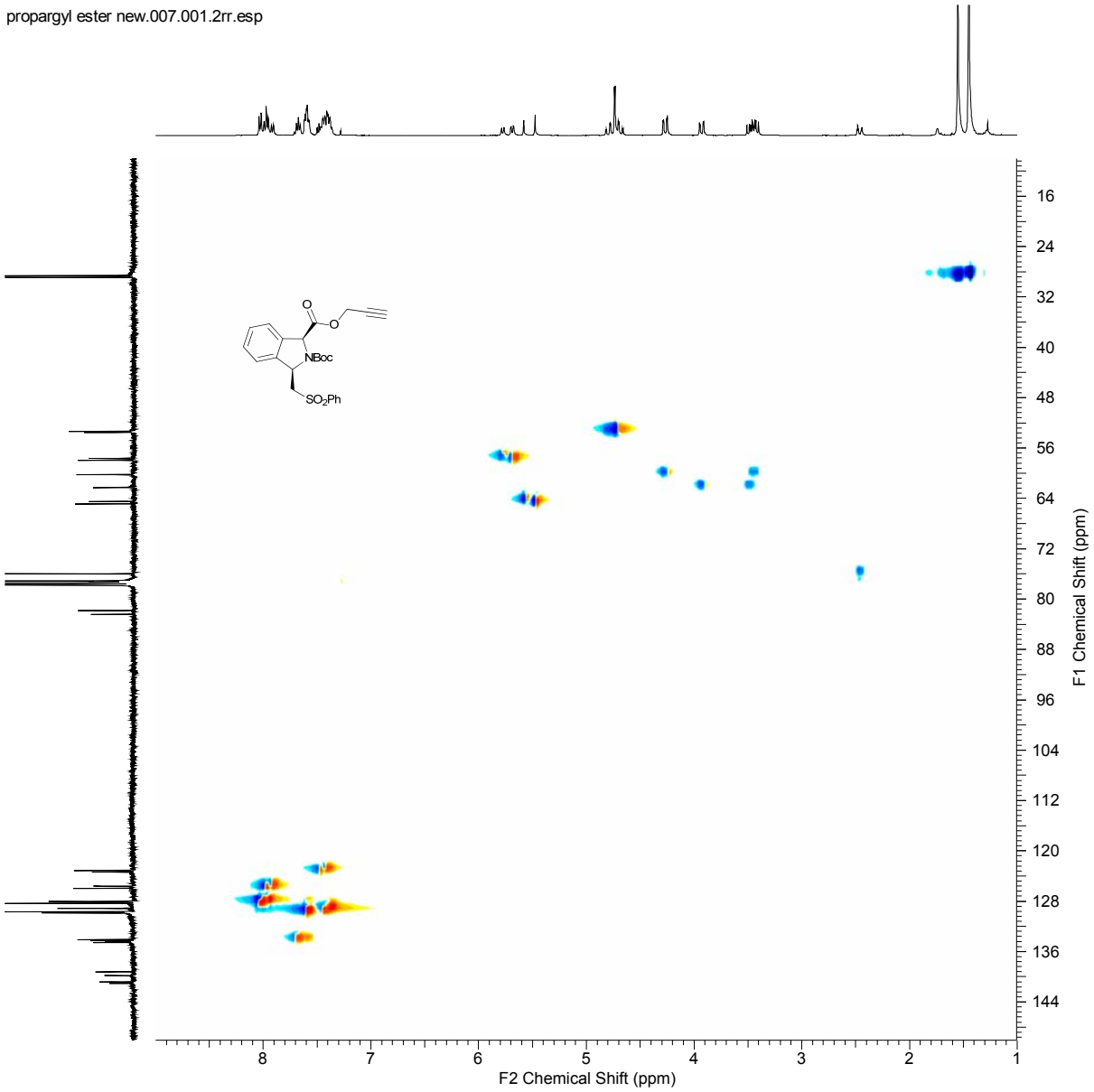
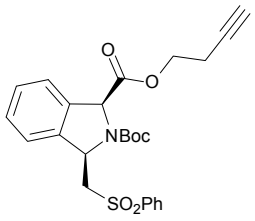
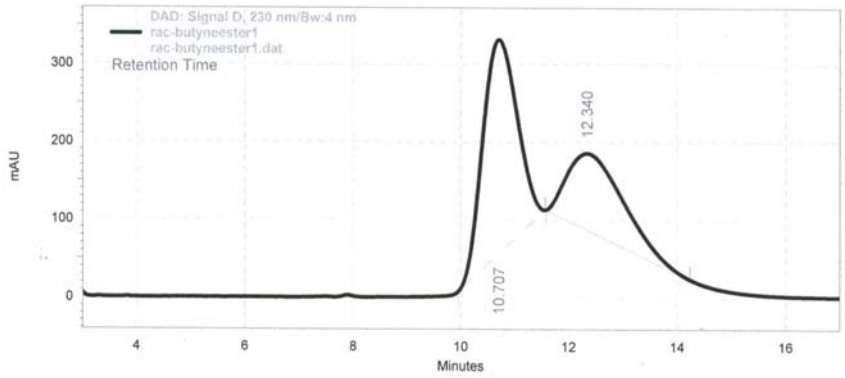


Figure HETCOR NMR Spectrum (400 MHz, $CDCl_3$)

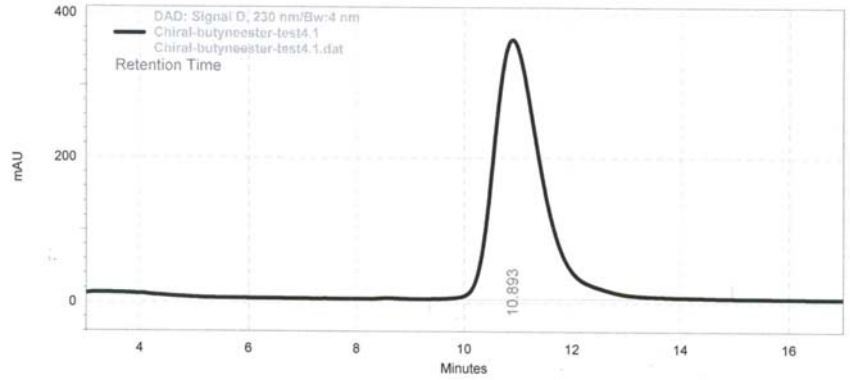
HPLC Data:





DAD: Signal D,
230 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
10.707	25447106	62.53	574976	73.54
12.340	15249632	37.47	206892	26.46
Totals	40696738	100.00	781868	100.00



DAD: Signal D,
230 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
10.893	45785314	100.00	752088	100.00
Totals	45785314	100.00	752088	100.00

Column: CHIRALPAK AS-H
Solvent: Hexane:Isopropanol (80:00)
Wavelength-230 nm
Flow Rate-1.5ML/min
Pressure:75 bar
Operator :RAJESH

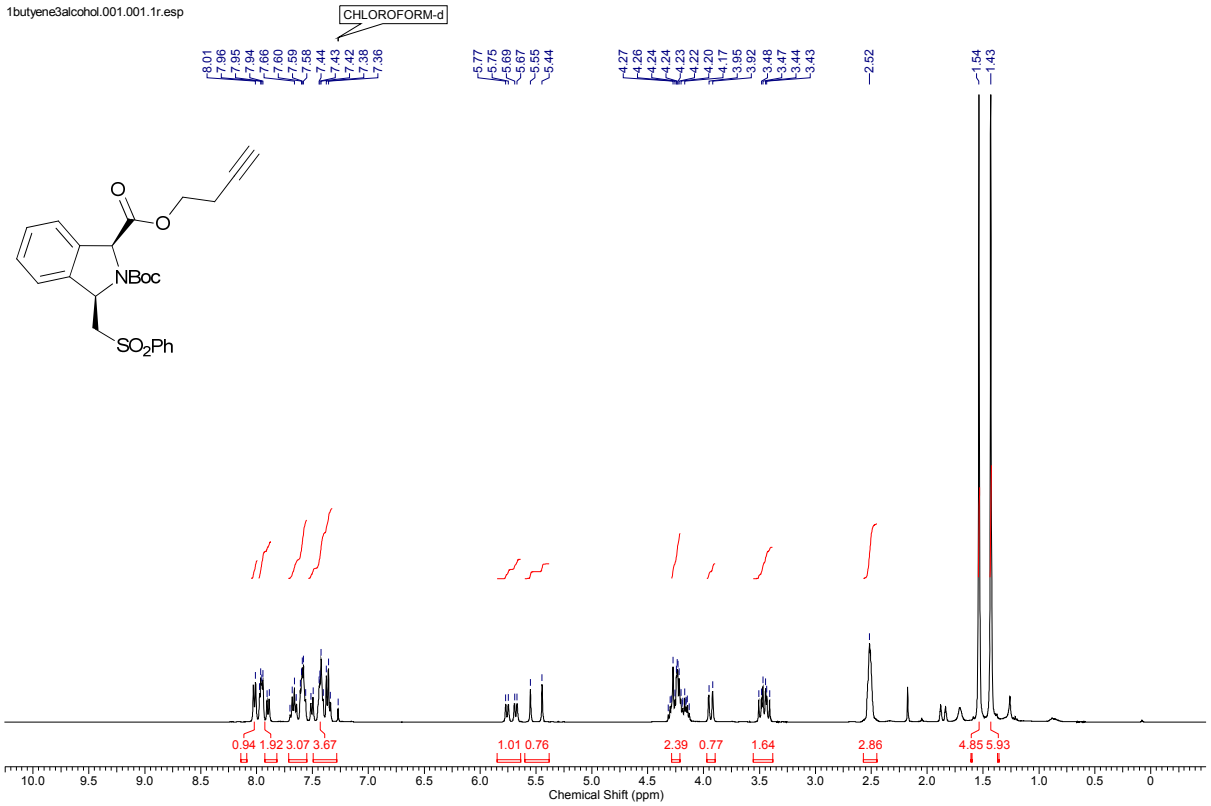


Figure 1H NMR Spectrum (400 MHz, $CDCl_3$)

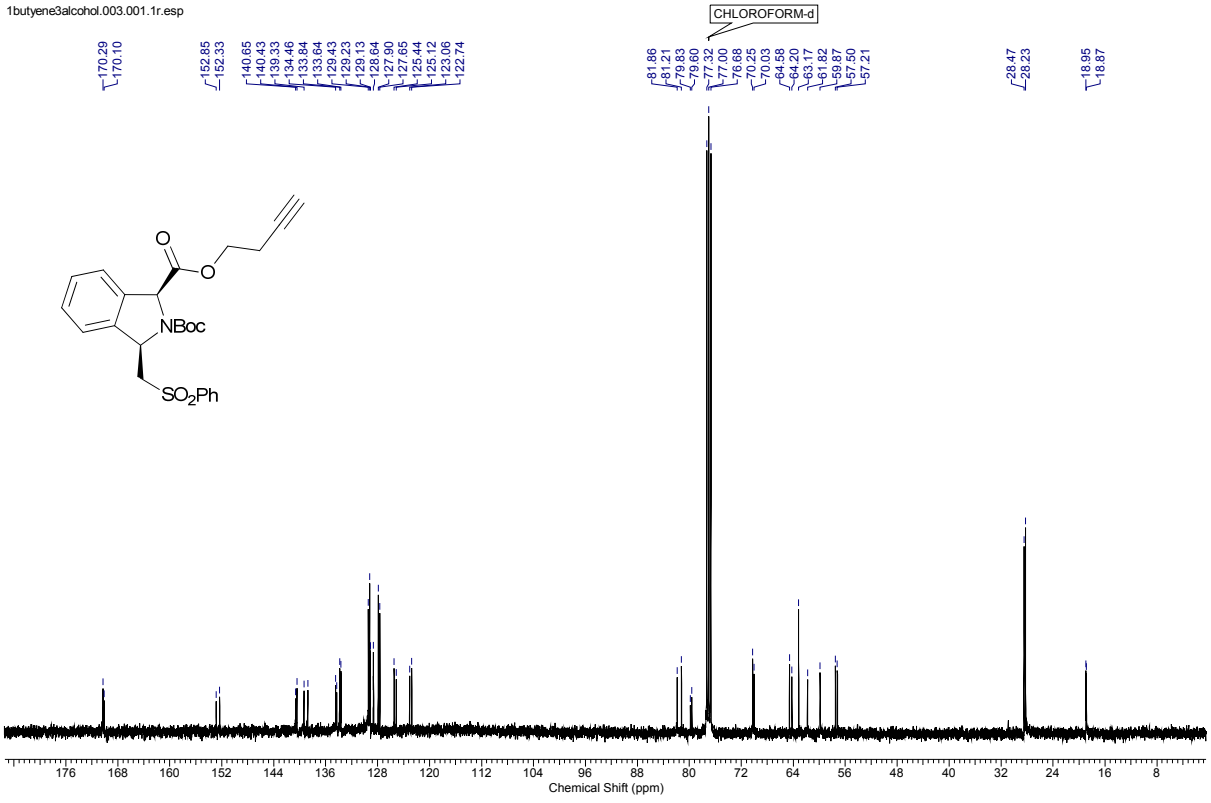


Figure ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

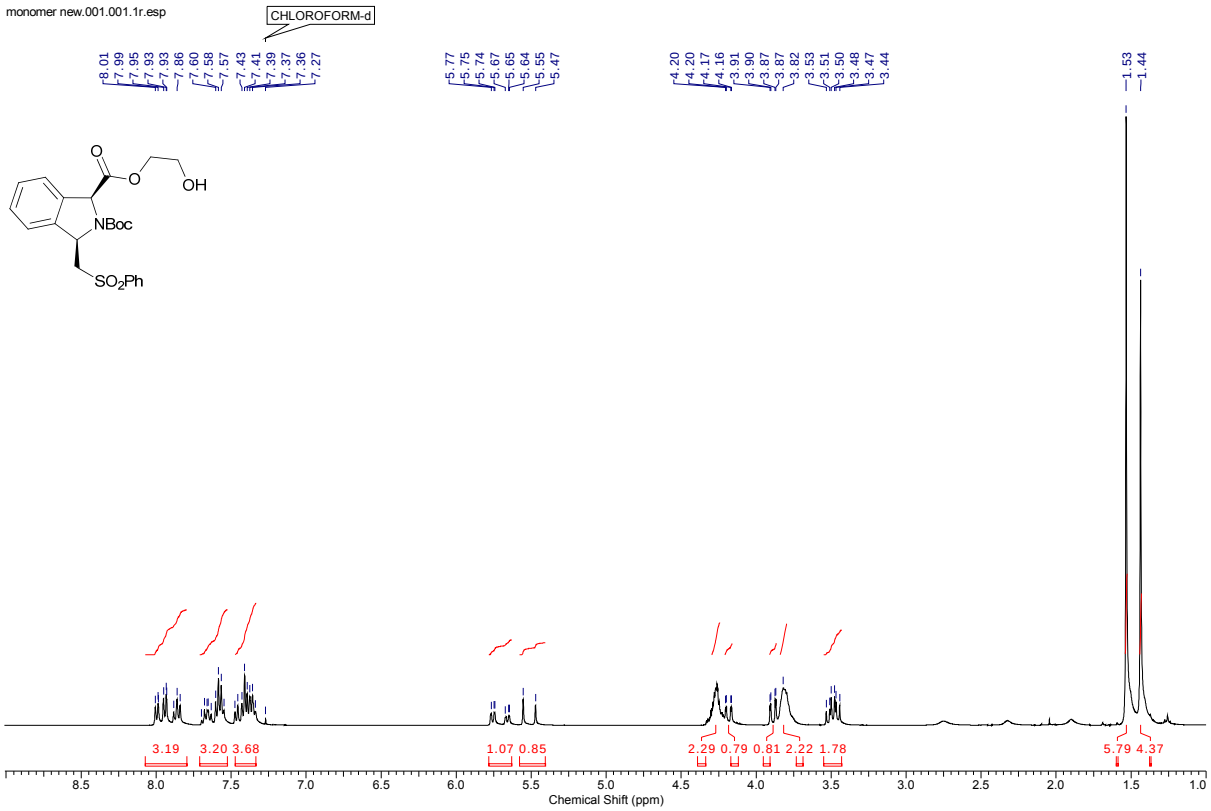


Figure ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)

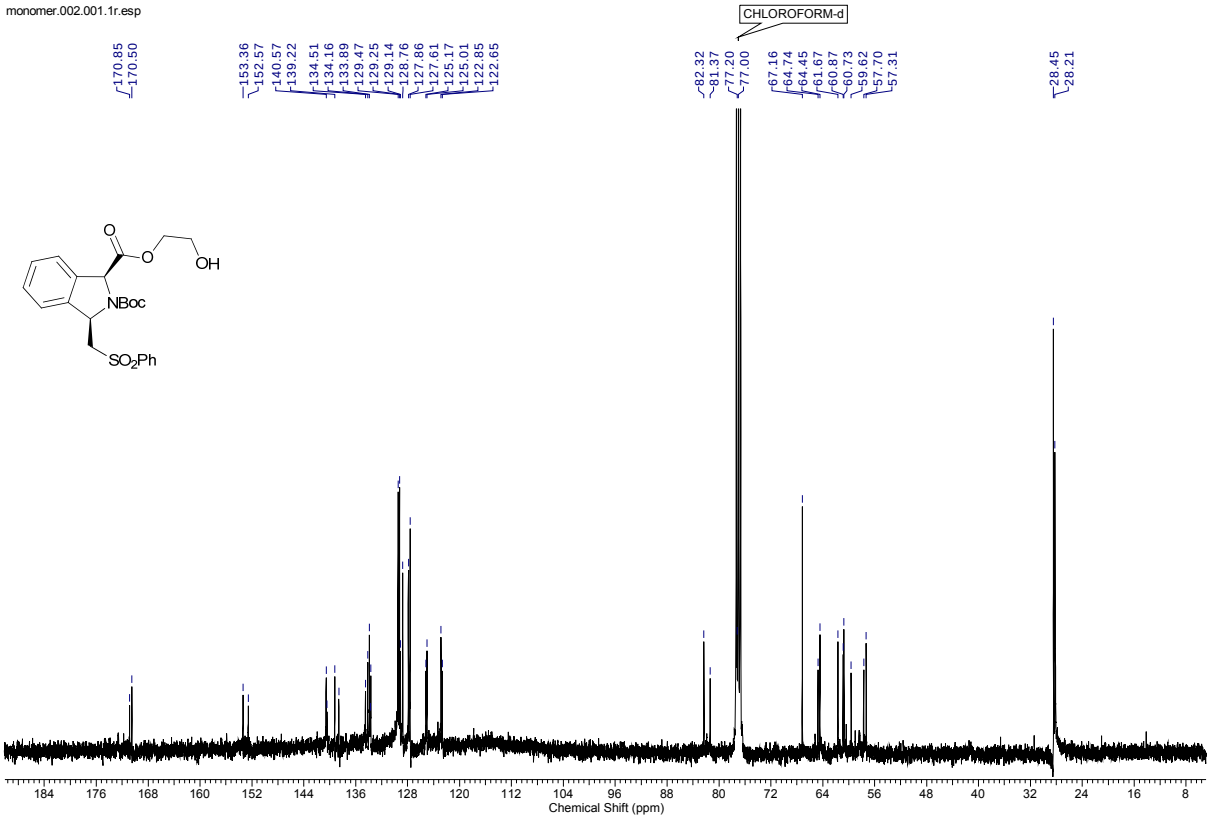


Figure ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

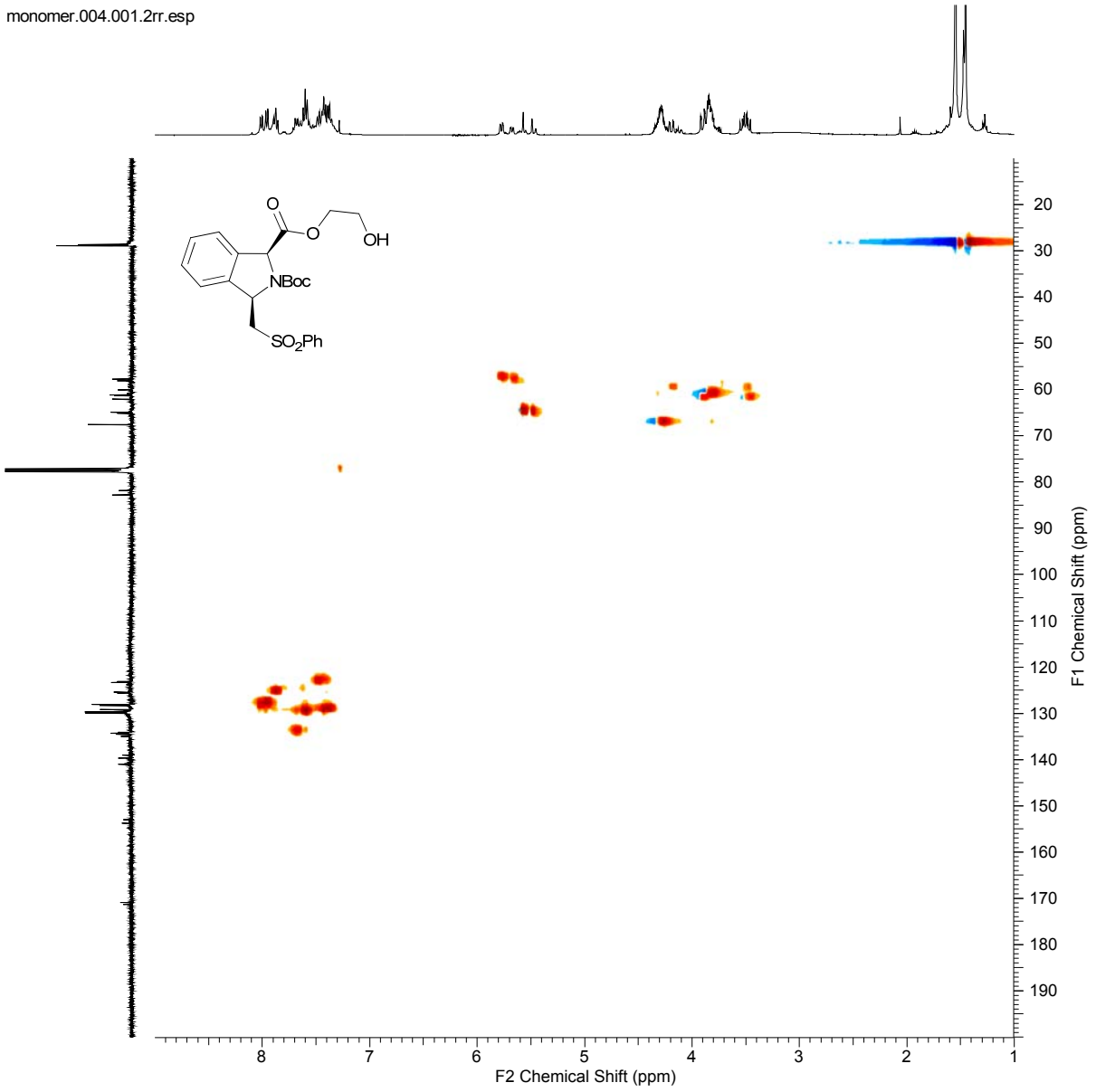


Figure HETCOR NMR Spectrum

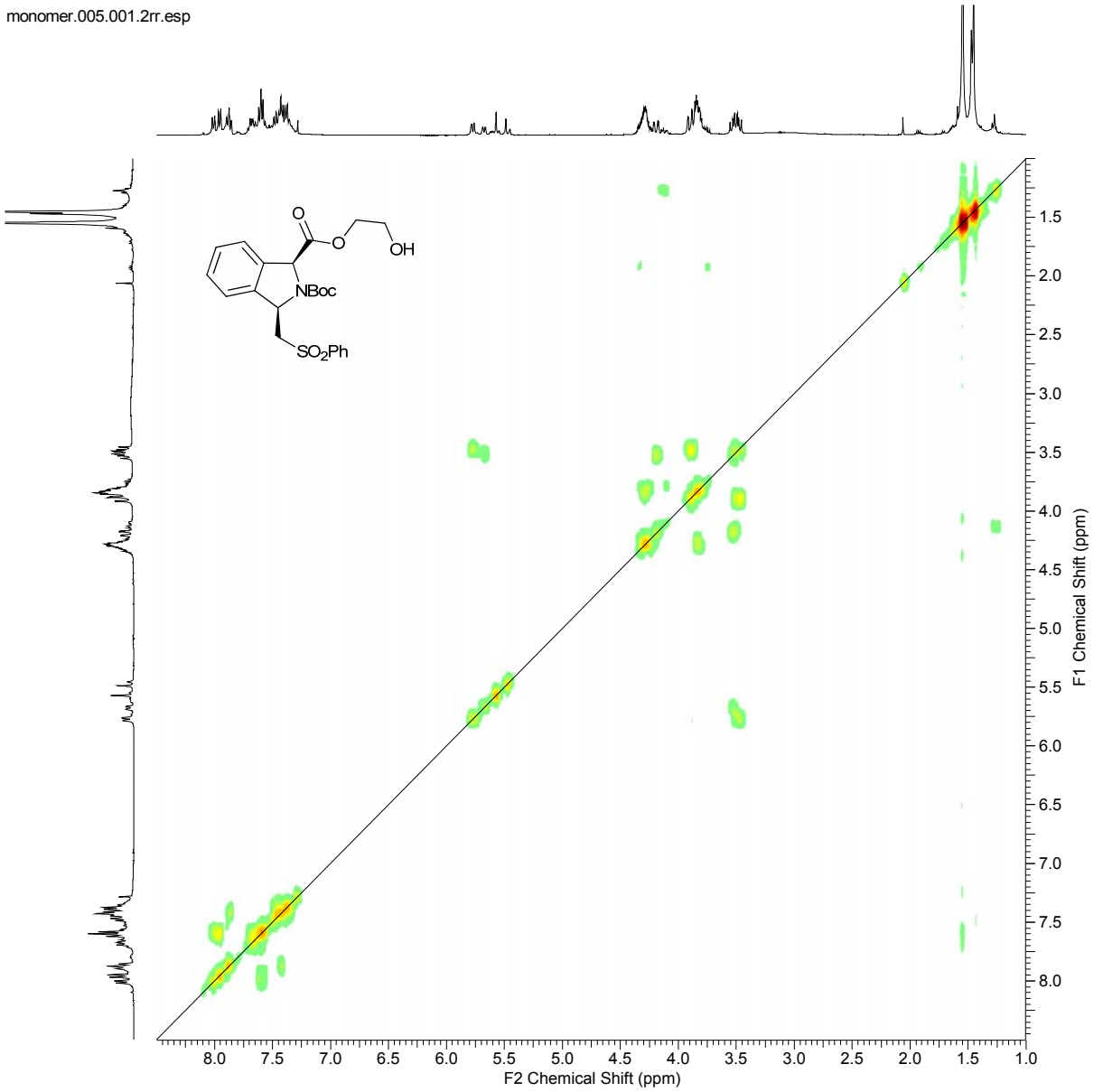


Figure COSEY NMR Spectrum (400 MHz, $CDCl_3$)

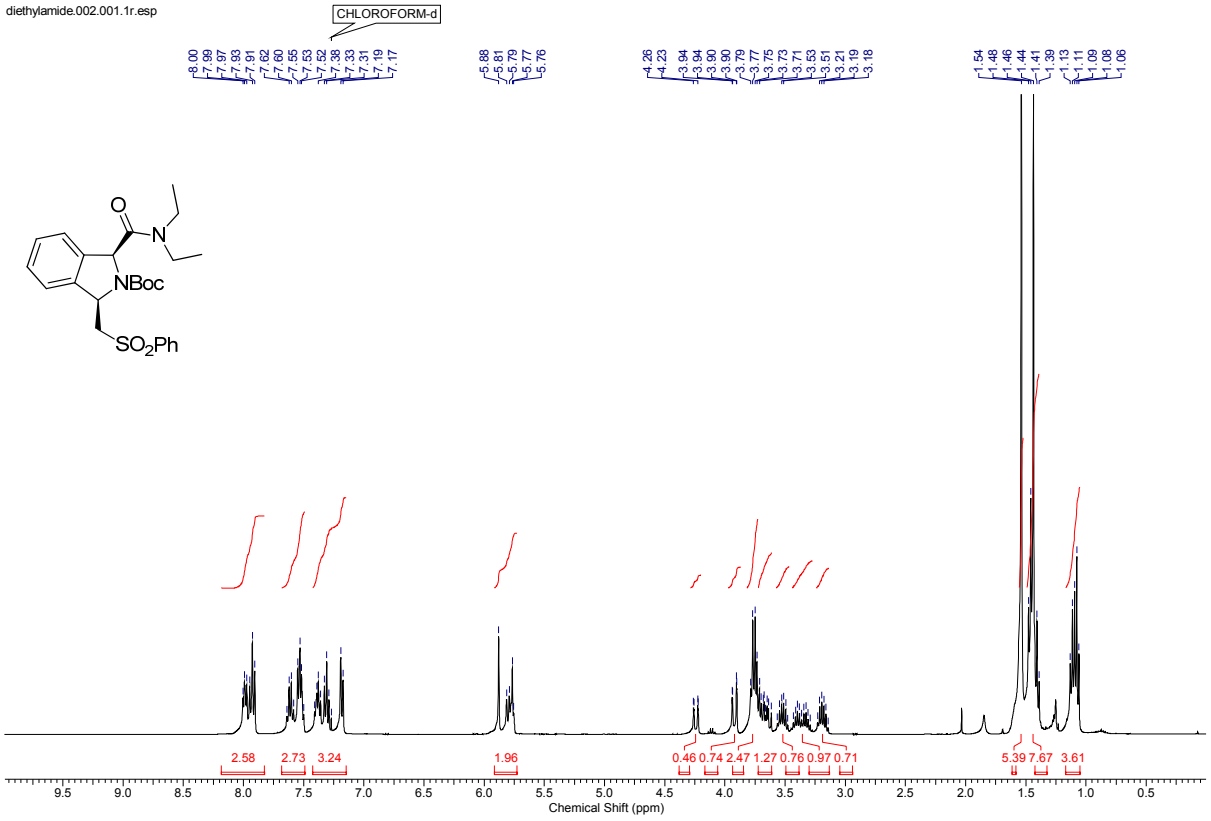


Figure ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)

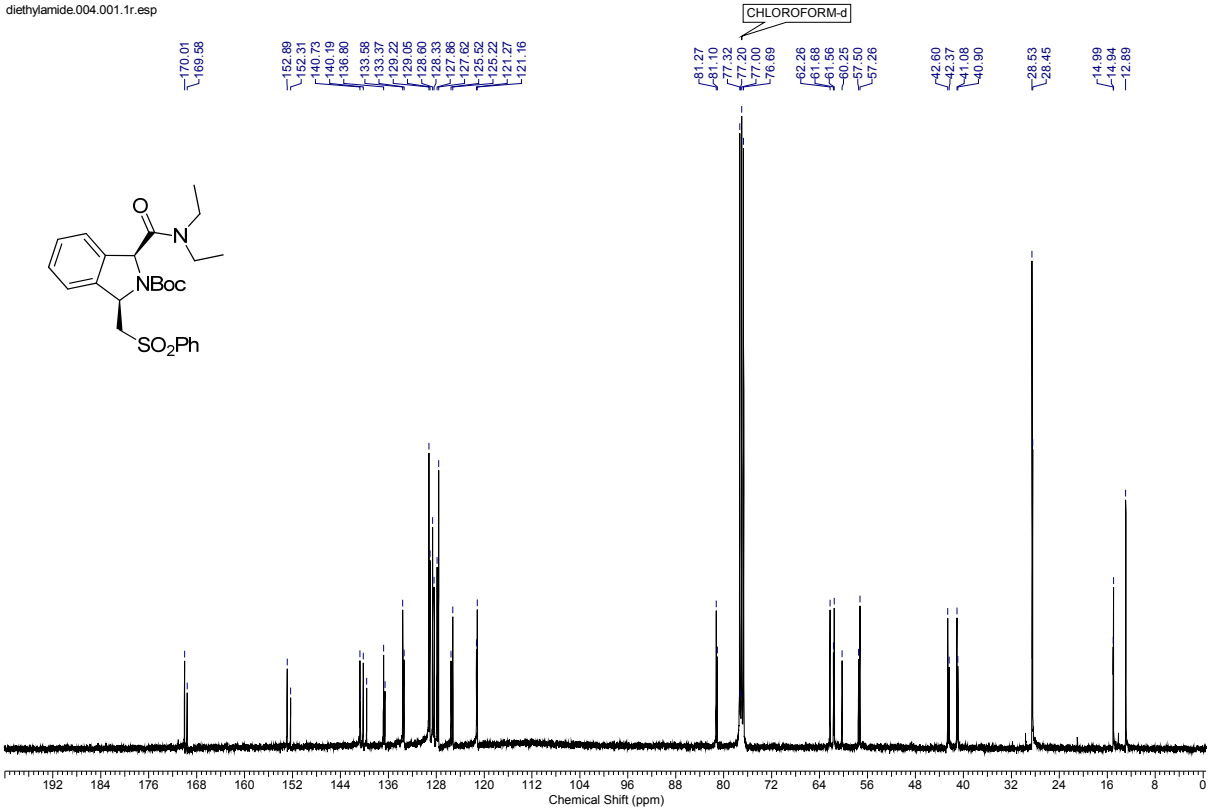


Figure ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

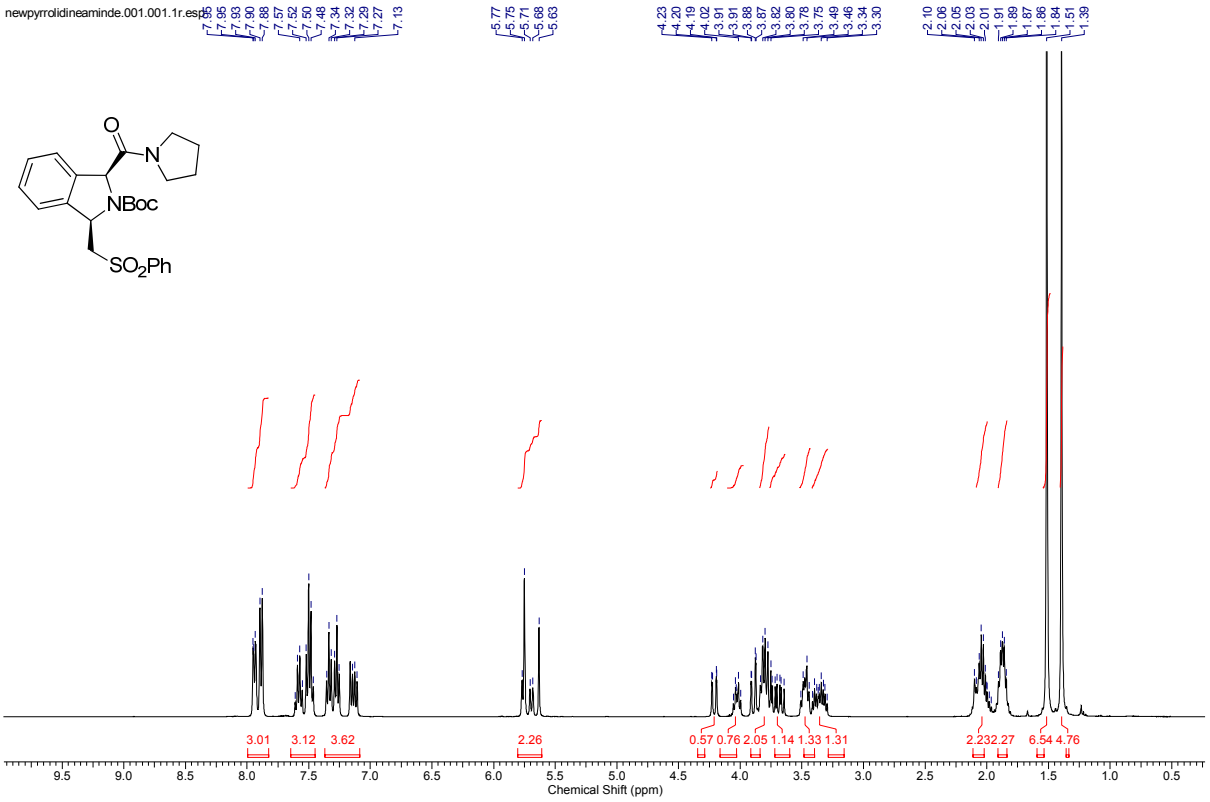


Figure 1H NMR Spectrum (400 MHz, $CDCl_3$)

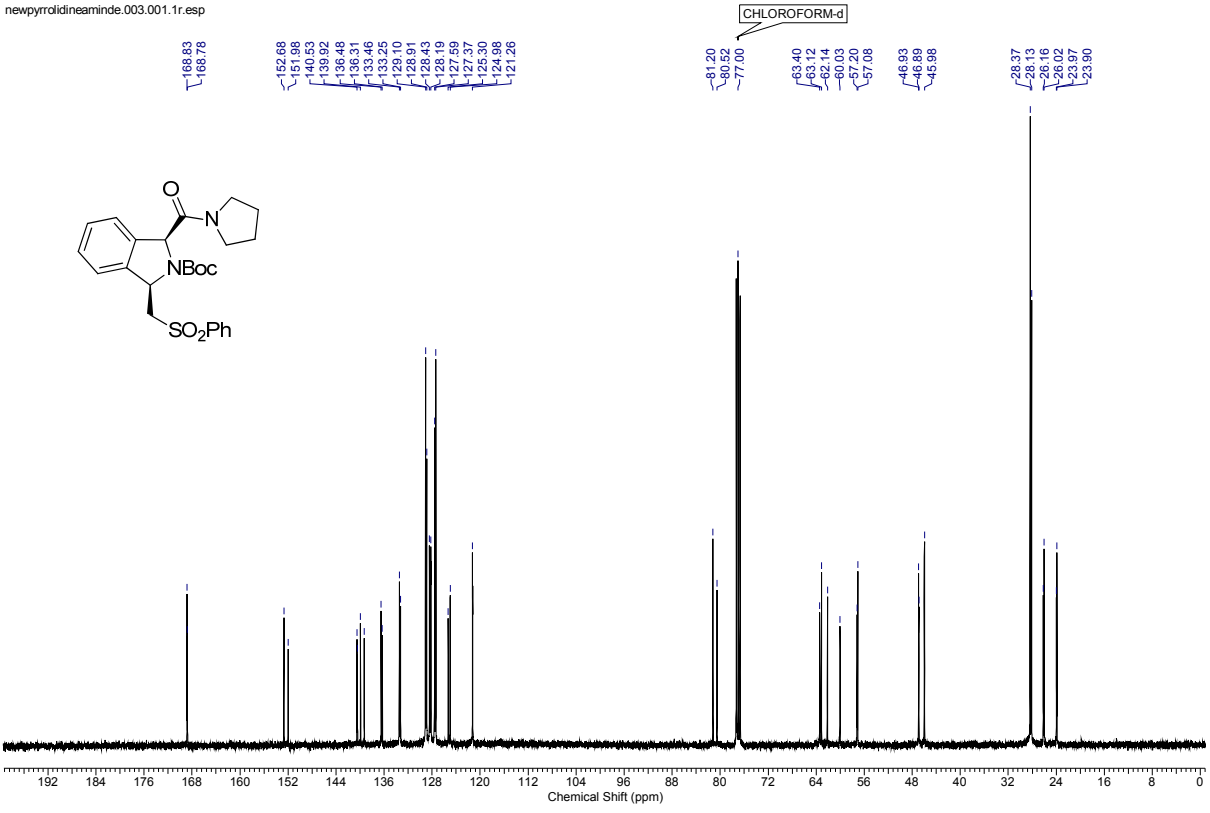
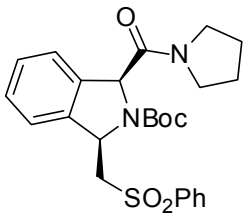
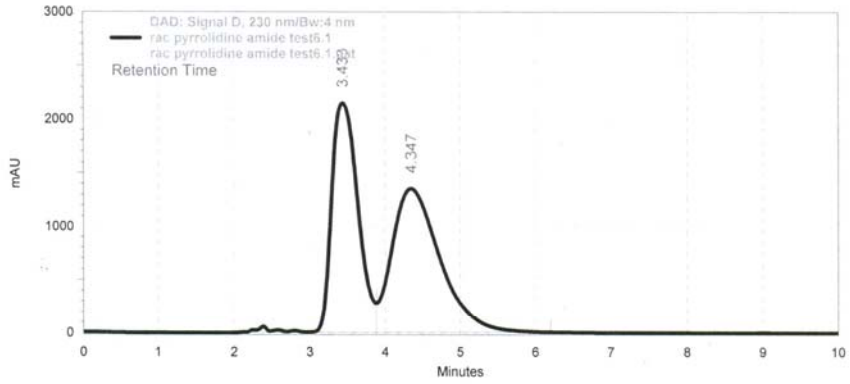


Figure ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

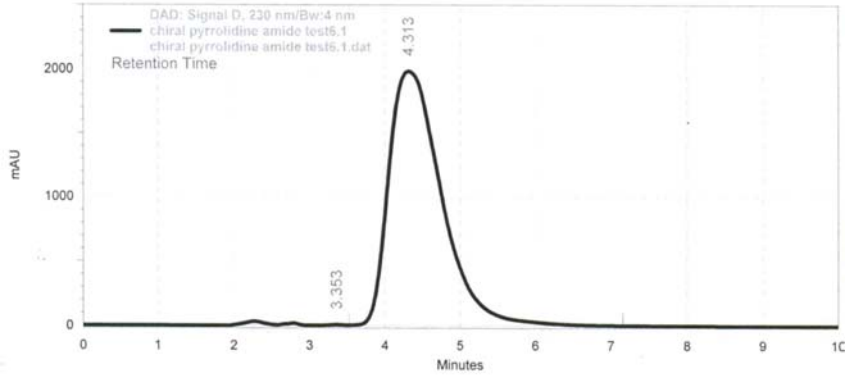
HPLC:





DAD: Signal D,
230 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
3.433	108470977	46.20	4495517	61.37
4.347	126297379	53.80	2829312	38.63
Totals	234768356	100.00	7324829	100.00



DAD: Signal D,
230 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
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4.313	202490247	99.95	4156598	99.79
Totals	202594000	100.00	4165437	100.00

Column: CHIRALPAK AS-H
Solvent: Hexane:Isopropanol (60:40)
Wavelength-230nm
Flow Rate-1.5ML/min
Pressure:110 bar
Operator :RAJESH

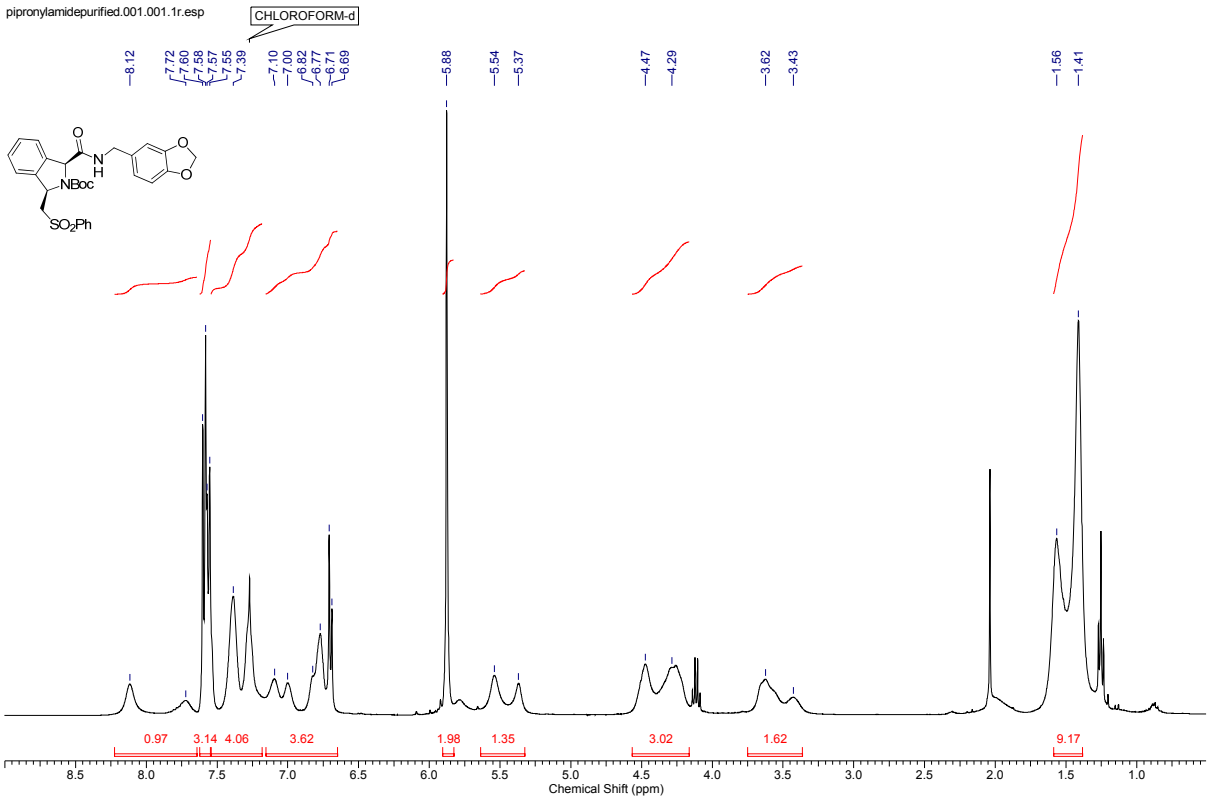


Figure ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)

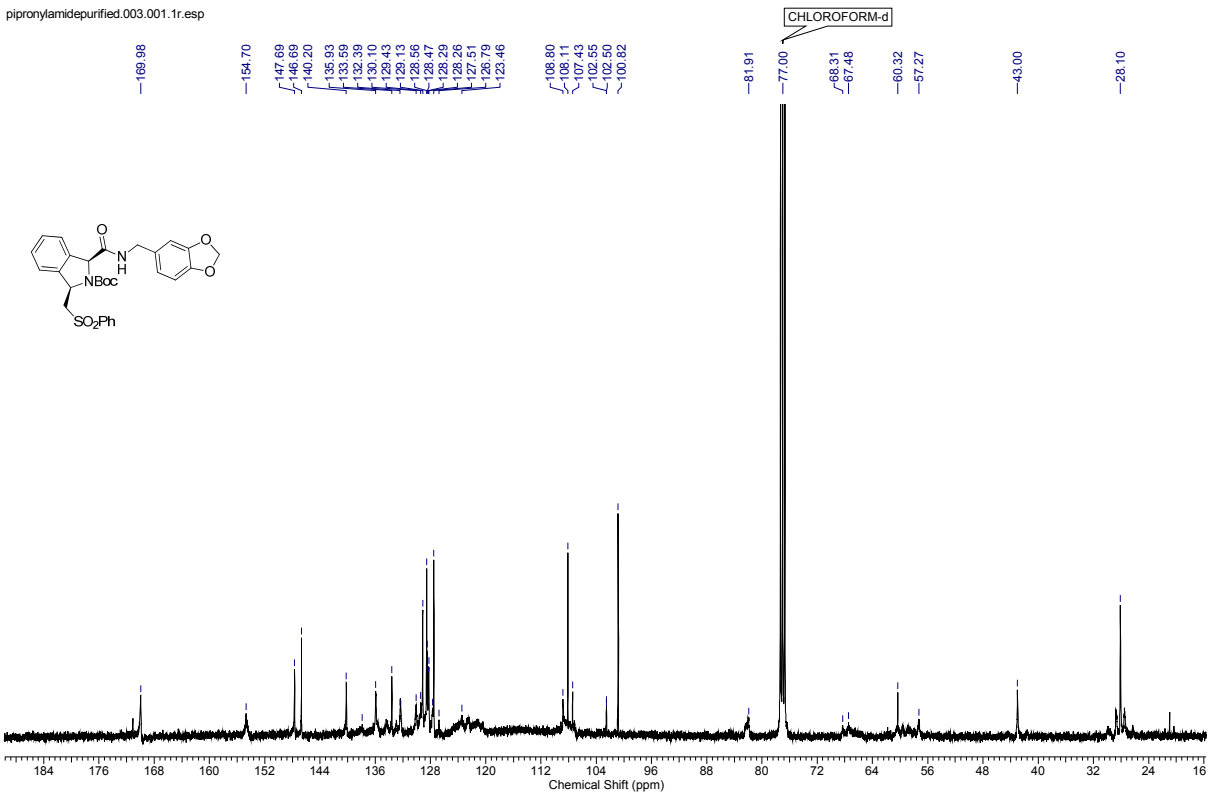
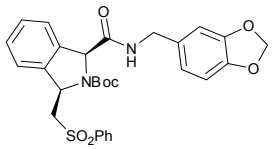
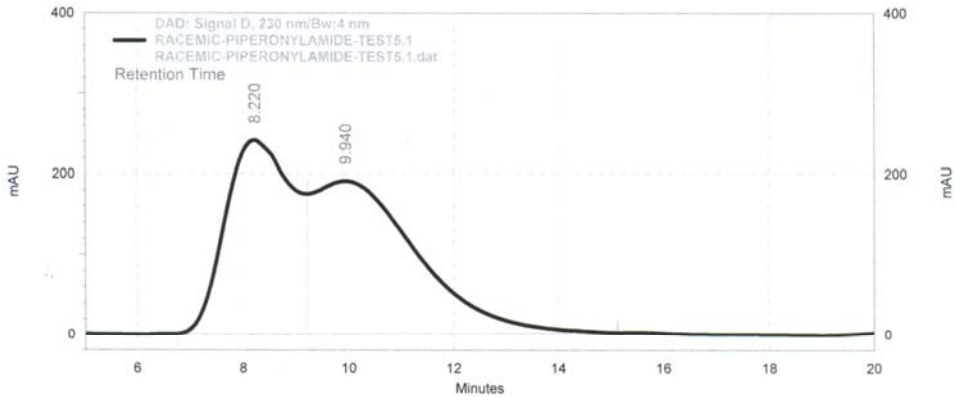


Figure ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

HPLC Report:





DAD: Signal D,
230 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
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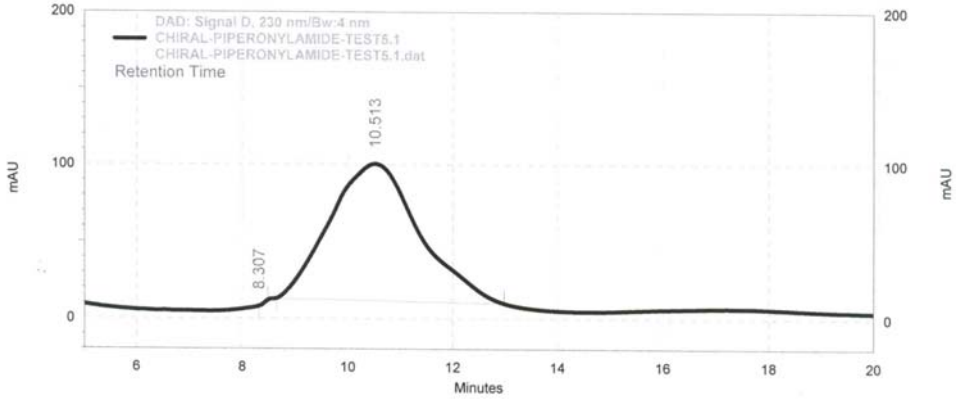
Totals	99743662	100.00	900680	100.00



DAD: Signal D,
230 nm/Bw:4 nm
Results

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8.307	6199	0.03	0	0.00
10.513	22019674	99.97	186241	100.00
Totals	22025873	100.00	186241	100.00

Column: CHIRALPAK AS-H
Solvent: Hexane:Isopropanol (60:40)
Wavelength-230nm
Flow Rate-1.5ML/min
Pressure:110 bar
Operator :RAJESH

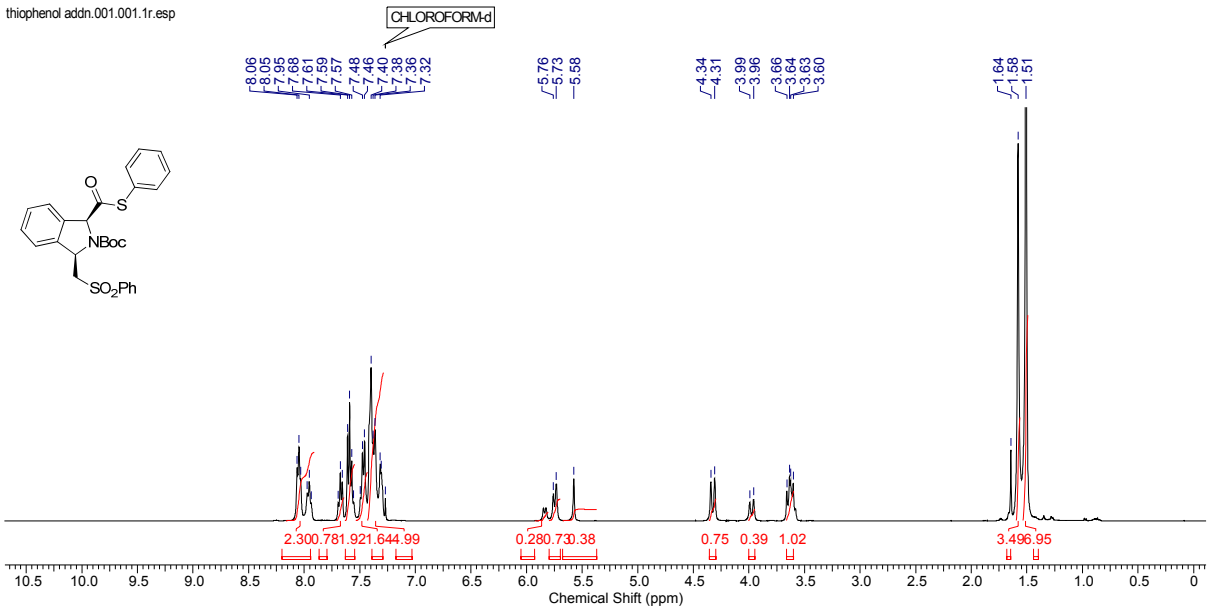


Figure 1H NMR Spectrum (400 MHz, $CDCl_3$)

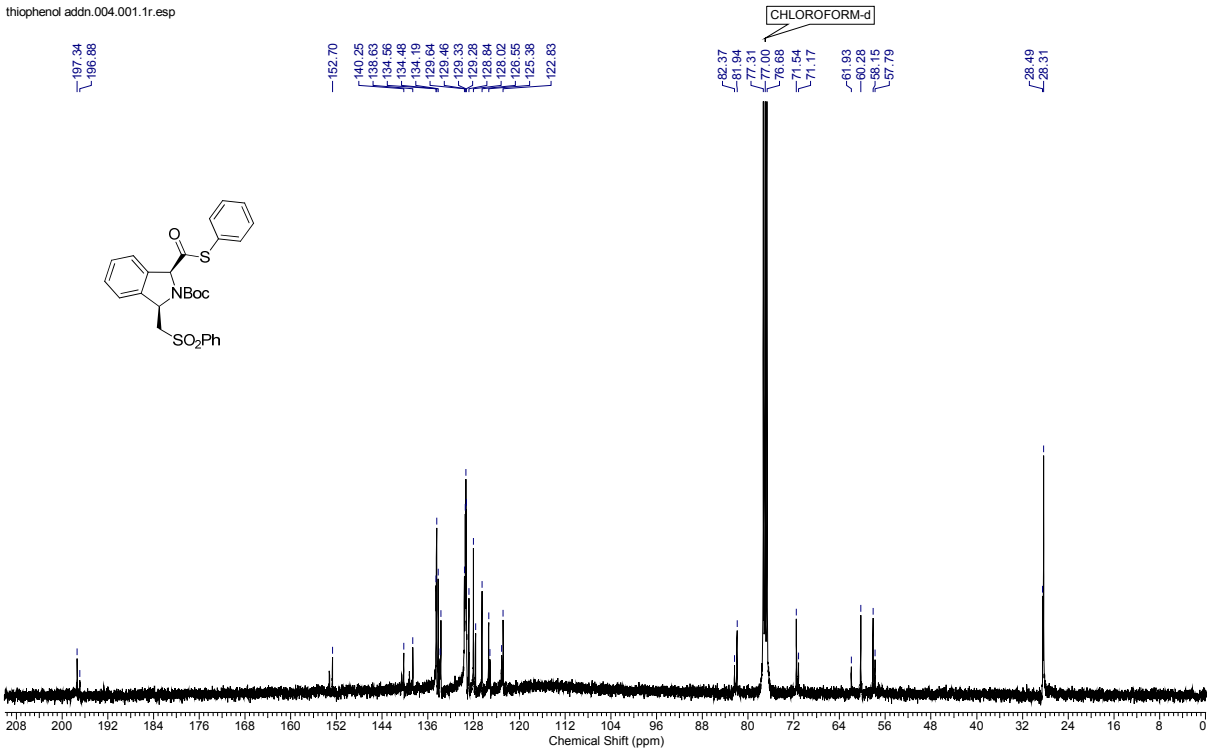


Figure ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

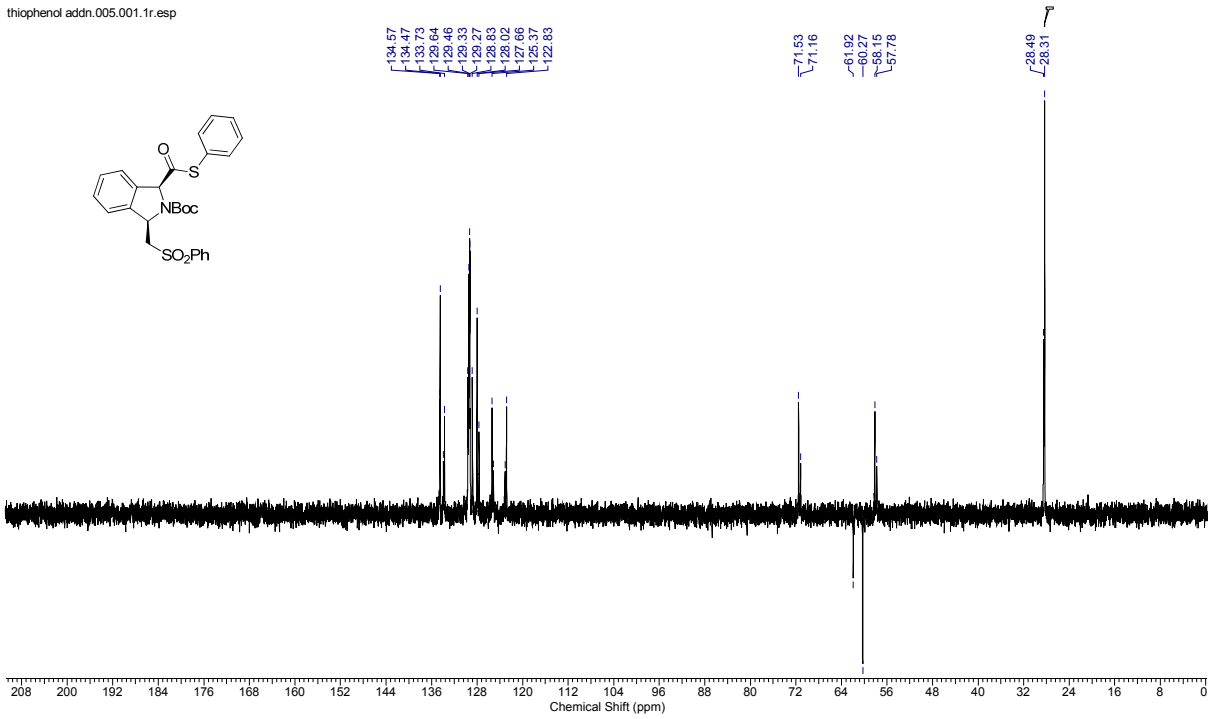


Figure ^{13}C DEPT NMR Spectrum (100 MHz, $CDCl_3$)

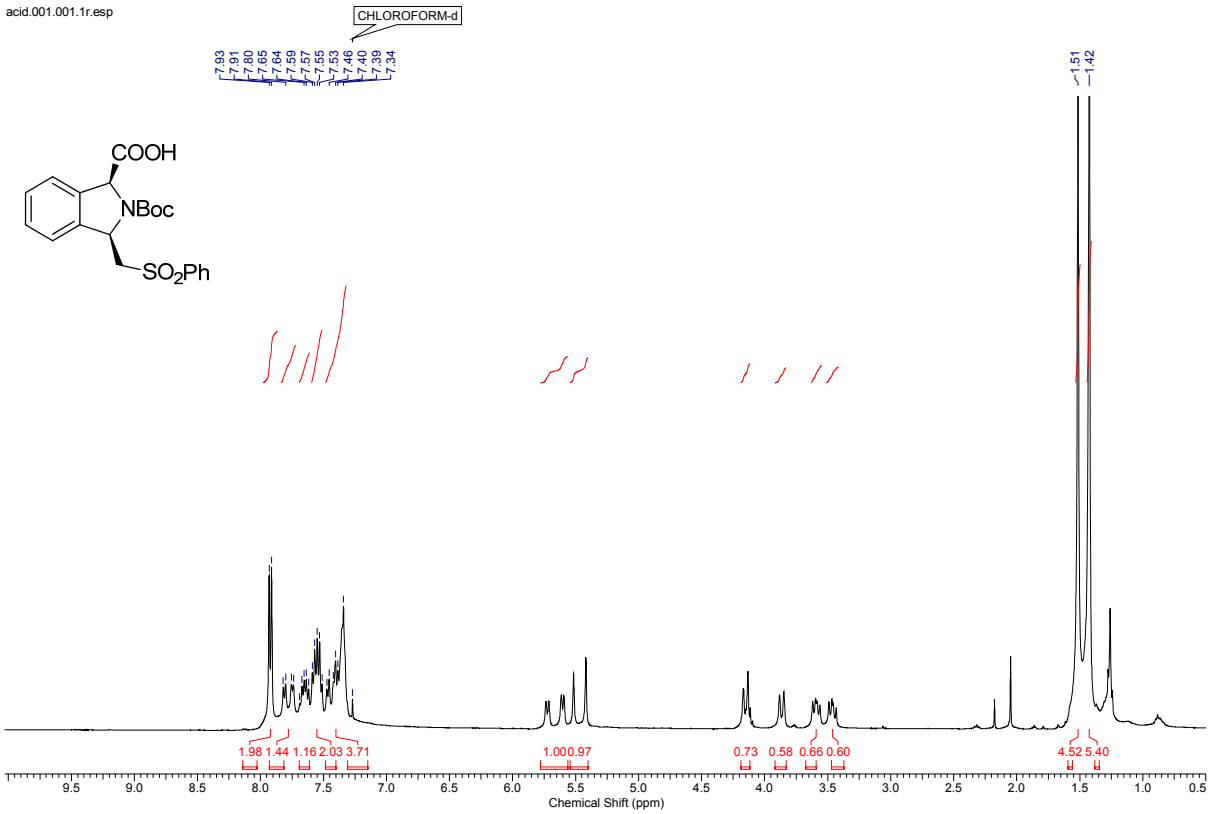


Figure 1H NMR Spectrum (400 MHz, $CDCl_3$)

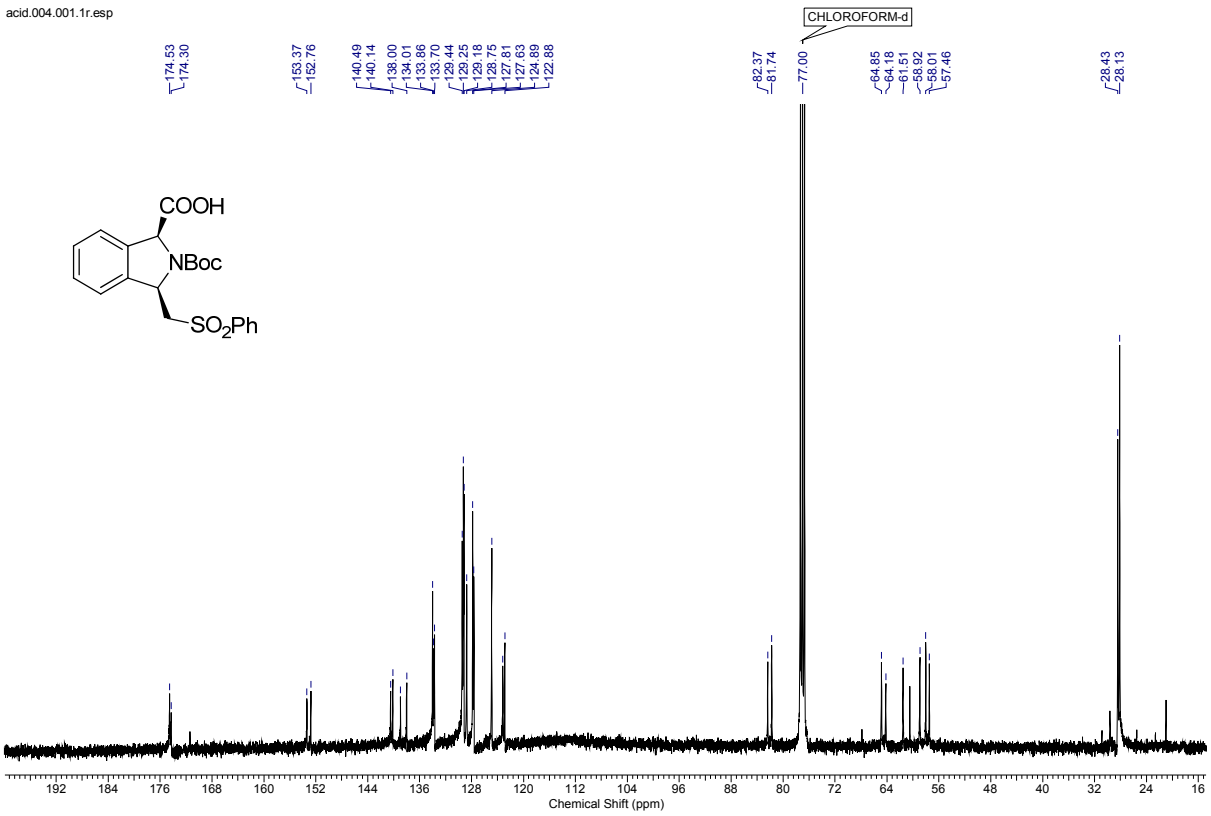


Figure ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

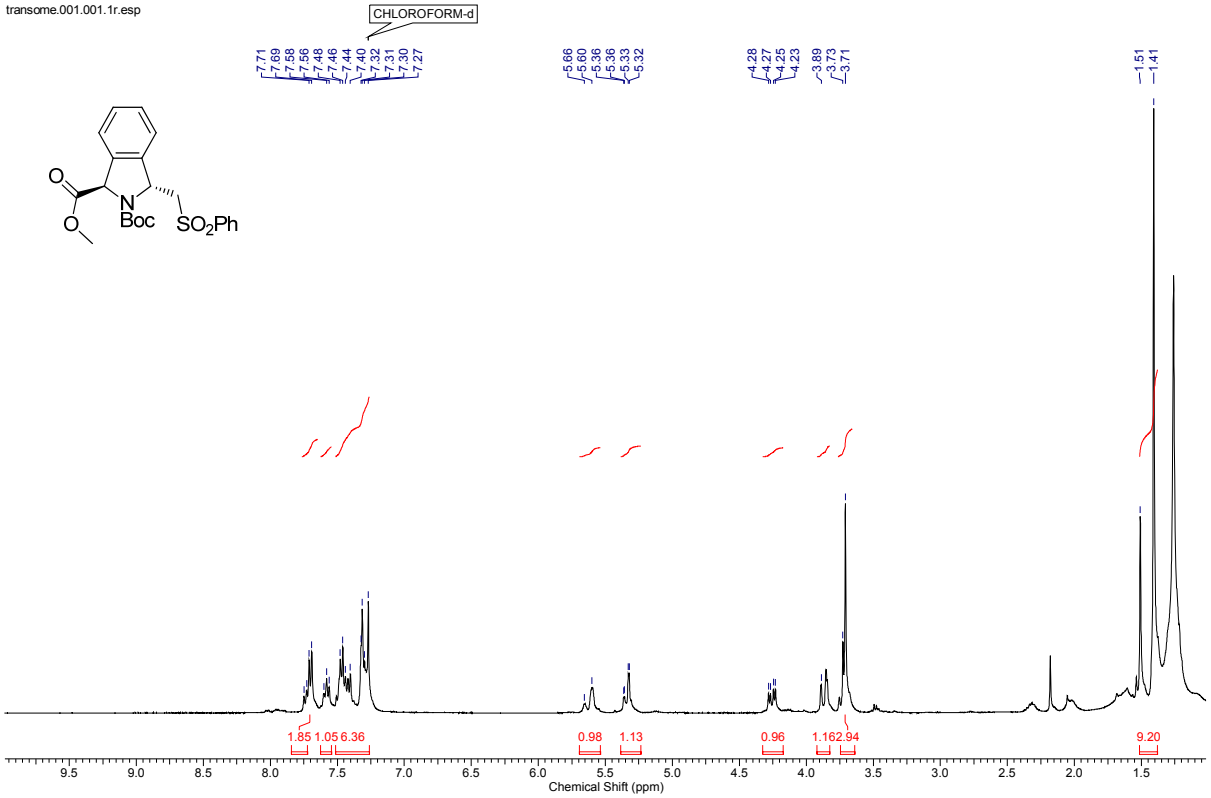


Figure ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)

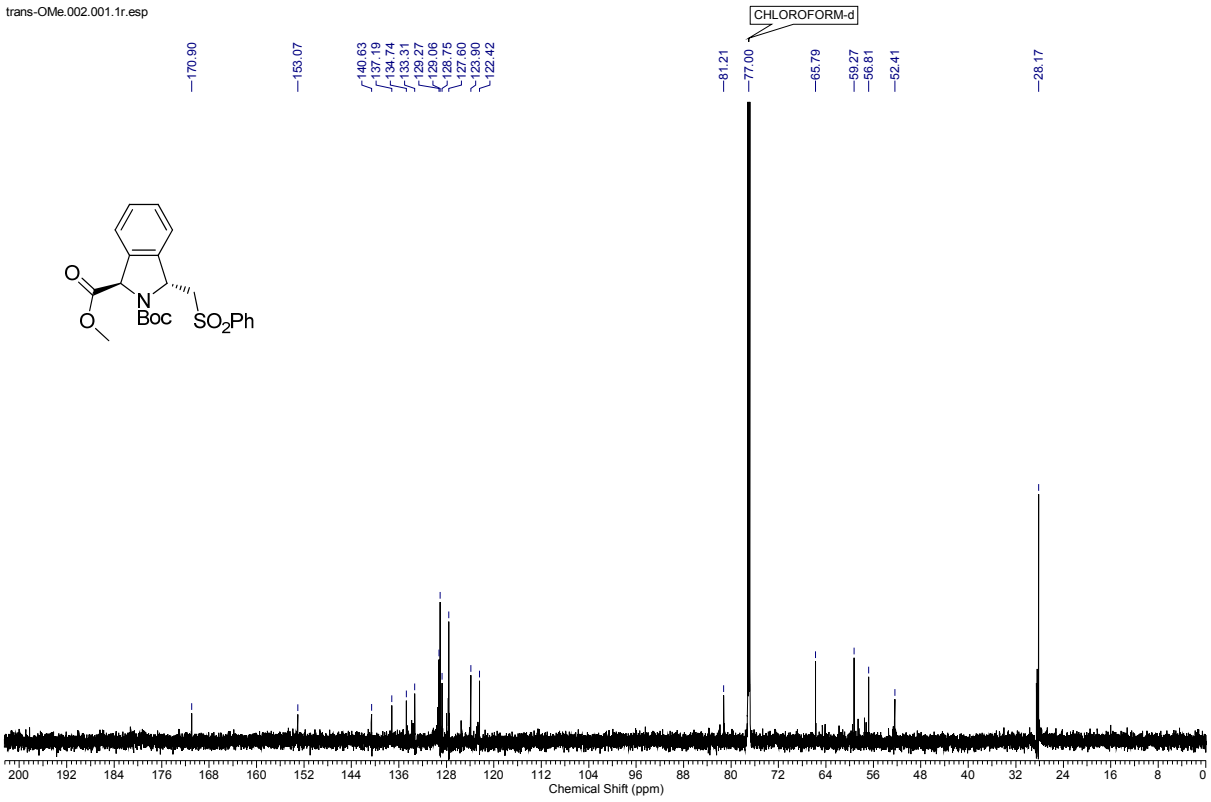
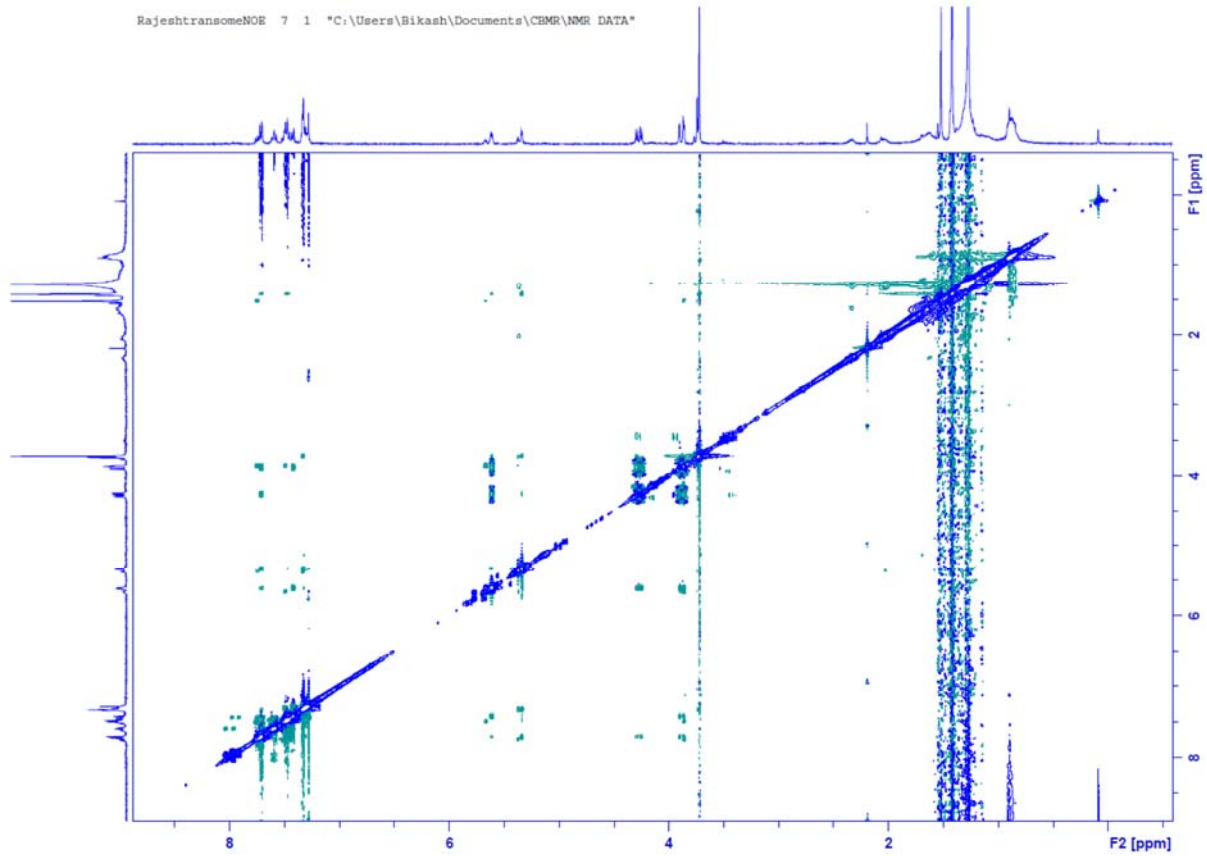


Figure ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

NOE: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F2 [ppm]
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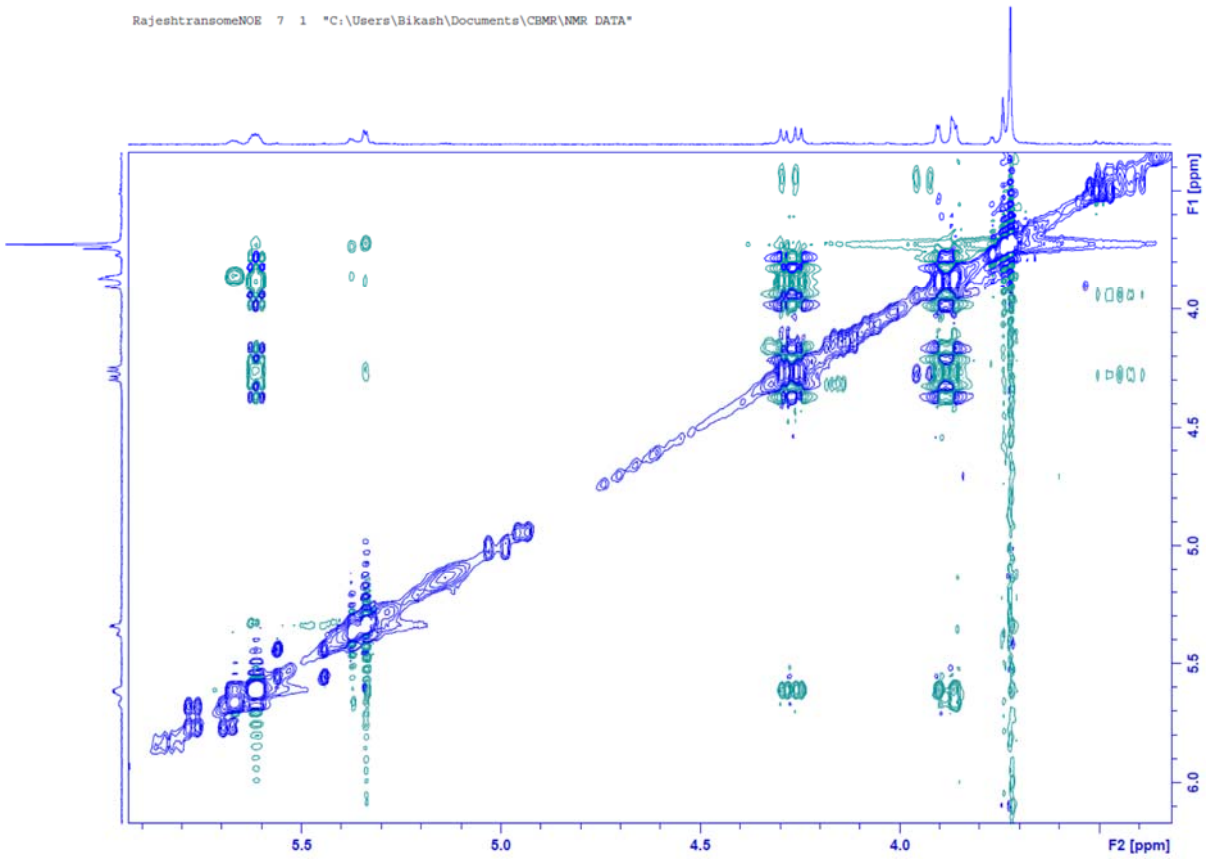
6
4
2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F1 [ppm]
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5.0
4.5
4.0
6.0

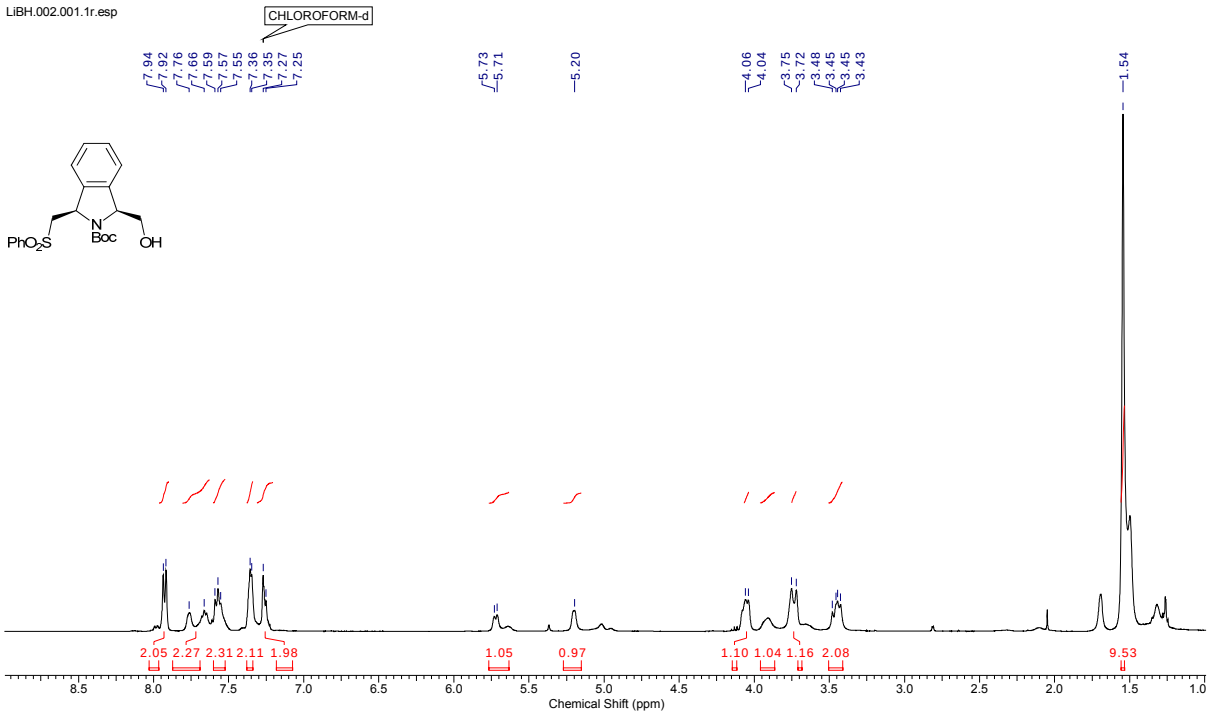

Figure ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)

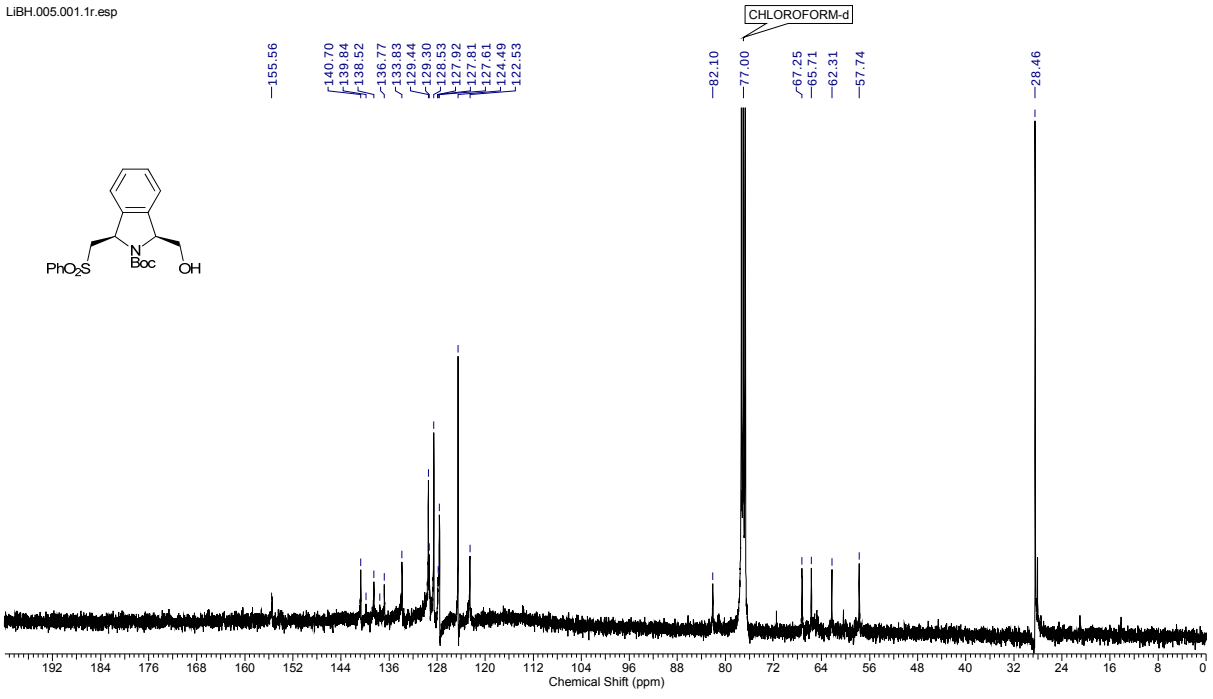

Figure ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

Single Crystal X-ray Diffraction for 13:

X-ray intensity data measurements of compound **13** was carried out on a Bruker SMART APEX II CCD diffractometer with graphite-monochromatized (MoK_α= 0.71073Å) radiation at room temperature. The X-ray generator was operated at 50 kV and 30 mA. A preliminary set of cell constants and an orientation matrix were calculated from three sets of 36 frames. Data were collected with ω scan width of 0.5° at different settings of φ and 2θ with a frame time of 10 secs keeping the sample-to-detector distance fixed at 5.00 cm. The X-ray data collection was monitored by APEX2 program (Bruker, 2006).[1] All the data were corrected for Lorentzian, polarization and absorption effects using SAINT and SADABS programs (Bruker, 2006). SHELX-97 was used for structure solution and full matrix least-squares refinement on F^2.[2] All the hydrogen atoms were placed in geometrically idealized position and constrained to ride on their parent atoms. An *ORTEP* III[3] view of both compounds were drawn with 30% probability displacement ellipsoids and H atoms are shown as small spheres of arbitrary radii.

Crystal data of **13** $C_{35}H_{33}N_1O_6$, M = 595.68, colorless block, 0.32 x 0.28 x 0.25 mm^3, orthorhombic, space group $P2_12_12_1$, a = 10.5513(6) Å, b = 13.4479(7) Å, c = 21.7370(12) Å, V = 3084.3(3) $Å^3$, Z = 4, T = 296(2) K, $2\theta_{max}$=50.00°, D_{calc} (g cm^{-3}) = 1.283, $F(000)$ = 1256, μ (mm^{-1}) = 0.152, 19534 reflections collected, 5387 unique reflections (R_{int}=0.0471), 4027 observed ($I > 2\sigma(I)$) reflections, multi-scan absorption correction, T_{min} = 0.953, T_{max} = 0.963, 391 refined parameters, S = 0.0916, $R1$ = 0.0485, $wR2$ = 0.0830 (all data R = 0.0743, $wR2$ = 0.0916), maximum and minimum residual electron densities; $\Delta\rho_{max}$ = 0.13, $\Delta\rho_{min}$= -0.21 (e $Å^{-3}$).

References

(1) Bruker (2006). *APEX2*, *SAINT* and *SADABS*. Bruker AXS Inc., Madison, Wisconsin, USA.

(2) G. M. Sheldrick, *Acta Crystallogr.*, 2008, A**64**, 112.

(3) L. J. Farrugia, *J. Appl. Cryst.* 1997, **30**, 565–565.

checkCIF/PLATON (standard)

You have not supplied any structure factors. As a result the full set of tests cannot be run.
THIS REPORT IS FOR GUIDANCE ONLY. IF USED AS PART OF A REVIEW PROCEDURE FOR PUBLICATION, IT SHOULD NOT REPLACE THE EXPERTISE OF AN EXPERIENCED CRYSTALLOGRAPHIC REFEREE.

No syntax errors found. CIF dictionary
Please wait while processing ....
Interpreting this report

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Bond precision: C-C = 0.0046 A Wavelength=0.71073
Cell: a=10.5513(6) b=13.4479(7) c=21.7370(12)
alpha=90 beta=90 gamma=90
Temperature: 296 K

	Calculated	Reported
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Space group	P 21 21 21	P2(1)2(1)2(
Hall group	P 2ac 2ab	?
Moiety formula	C35 H33 N O6 S	C35 H33 N O6 S
Sum formula	C35 H33 N O6 S	C35 H33 N O6 S
Mr	595.68	595.68
Dx,g cm-3	1.283	1.283
Z	4	4
Mu (mm-1)	0.152	0.152
F000	1256.0	1256.0
F000'	1257.08	
h,k,lmax	12,15,25	12,15,25
Nref	5426[3067]	5387
Tmin,Tmax	0.953,0.963	0.953,0.963
Tmin'	0.953	

Correction method= MULTI-SCAN
Data completeness= 1.76/0.99 Theta(max)= 25.000
R(reflections)= 0.0485(4027) wR2(reflections)= 0.0916(5387)
S = 1.035 Npar= 391

The following ALERTS were generated. Each ALERT has the format **test-name_ALERT_alert-type_alert-level**.
Click on the hyperlinks for more details of the test.

Alert level C

PLAT230_ALERT_2_C Hirshfeld Test Diff for O6 -- C31 .. 5.5 su
PLAT230_ALERT_2_C Hirshfeld Test Diff for N1 -- C31 .. 5.5 su
PLAT242_ALERT_2_C Low Ueq as Compared to Neighbors for ..... C32 Check
PLAT340_ALERT_3_C Low Bond Precision on C-C Bonds ..... 0.0046 Ang.

Alert level G

PLAT005_ALERT_5_G No _iucr_refine_instructions_details in the CIF Please Do !
PLAT066_ALERT_1_G Predicted and Reported Tmin&Tmax Range Identical ? Check
PLAT791_ALERT_4_G The Model has Chirality at C1 ..... S Verify
And 4 other PLAT791 Alerts
More ...
PLAT899_ALERT_4_G SHELXL97 is Deprecated and Succeeded by SHELXL 2014 Note

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0 **ALERT level A** = Most likely a serious problem - resolve or explain
0 **ALERT level B** = A potentially serious problem, consider carefully
4 **ALERT level C** = Check. Ensure it is not caused by an omission or oversight
8 **ALERT level G** = General information/check it is not something unexpected

1 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
3 ALERT type 2 Indicator that the structure model may be wrong or deficient
1 ALERT type 3 Indicator that the structure quality may be low
6 ALERT type 4 Improvement, methodology, query or suggestion
1 ALERT type 5 Informative message, check

It is advisable to attempt to resolve as many as possible of the alerts in all categories. Often the minor alerts point to easily fixed oversights, errors and omissions in your CIF or refinement strategy, so attention to these fine details can be worthwhile. In order to resolve some of the more serious problems it may be necessary to carry out additional measurements or structure refinements. However, the purpose of your study may justify the reported deviations and the more serious of these should normally be commented upon in the discussion or experimental section of a paper or in the "special_details" fields of the CIF. checkCIF was carefully designed to identify outliers and unusual parameters, but every test has its limitations and alerts that are not important in a particular case may appear. Conversely, the absence of alerts does not guarantee there are no aspects of the results needing attention. It is up to the individual to critically assess their own results and, if necessary, seek expert advice.

Publication of your CIF in IUCr journals

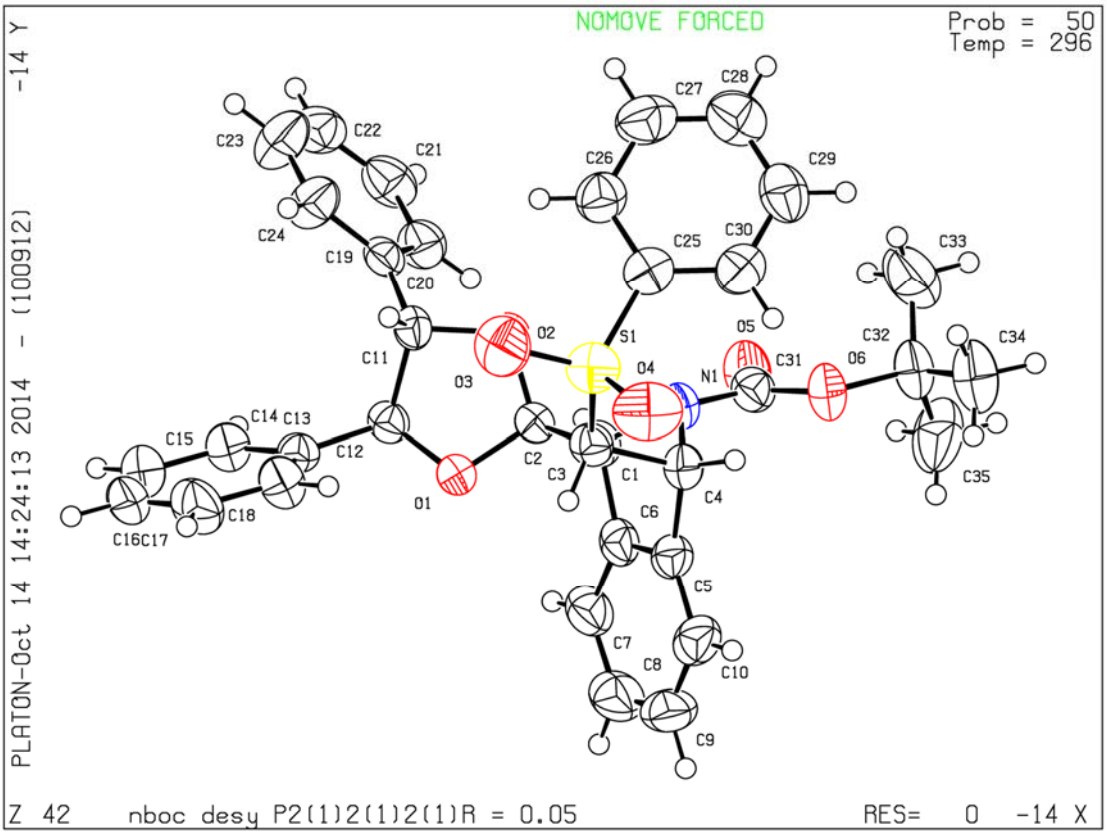
A basic structural check has been run on your CIF. These basic checks will be run on all CIFs submitted for publication in IUCr journals (*Acta Crystallographica*, *Journal of Applied Crystallography*, *Journal of Synchrotron Radiation*); however, if you intend to submit to *Acta Crystallographica Section C* or *E*, you should make sure that full publication checks are run on the final version of your CIF prior to submission.

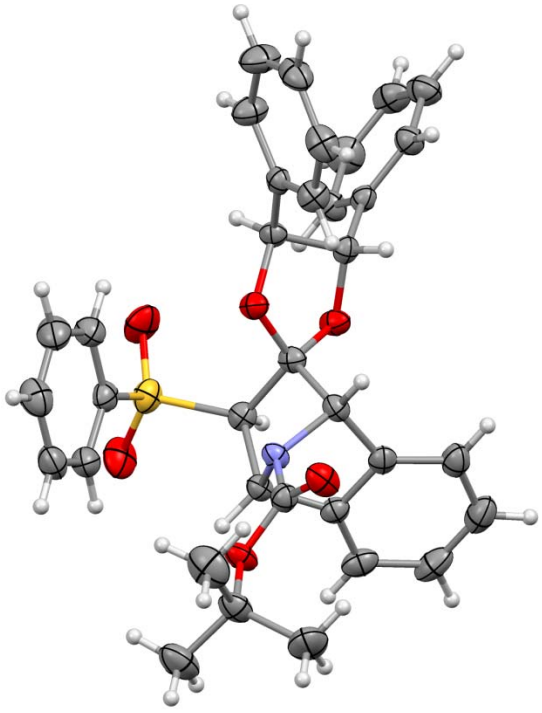
Publication of your CIF in other journals

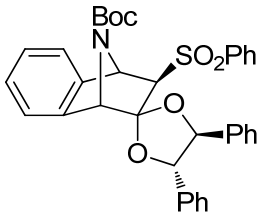
Please refer to the *Notes for Authors* of the relevant journal for any special instructions relating to CIF submission.

PLATON version of 20/08/2014; check.def file version of 18/08/2014

Datablock nboc_desy_0m - ellipsoid plot







ORTEP DIAGRAM