

Enantioselective, Palladium-Catalyzed α -Arylation of *N*-Boc Pyrrolidine: *In Situ* React IR Spectroscopy Monitoring, Scope and Synthetic Applications

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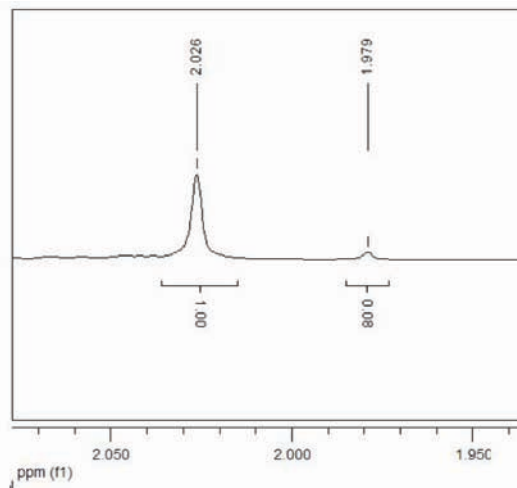
Supporting Information Available: ¹H/¹³C NMR spectra of all compounds and CSP-HPLC data.

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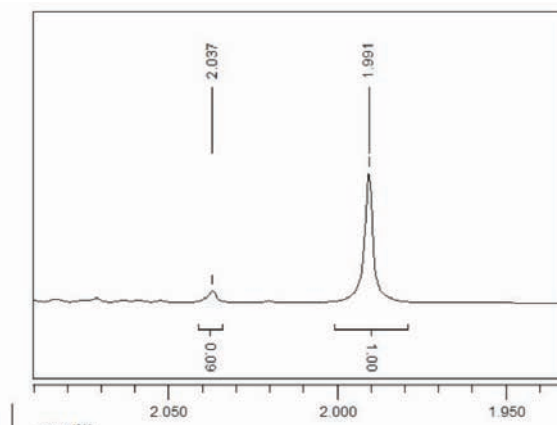
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1. Determination of the enantiomer ratio of (S)-(+)-5-Ethynyl-3-(1-methyl-2-pyrrolidiny)pyridine (S)-SIB1508Y (Scheme 7).

Enantiomer ratio was determined by high resolution ^1H NMR spectroscopy (400 MHz, CDCl_3) in the presence of 4.0 equivalents of (S)-2,2,2-trifluoro-1-(9-anthryl)-ethanol: 92:8 er.

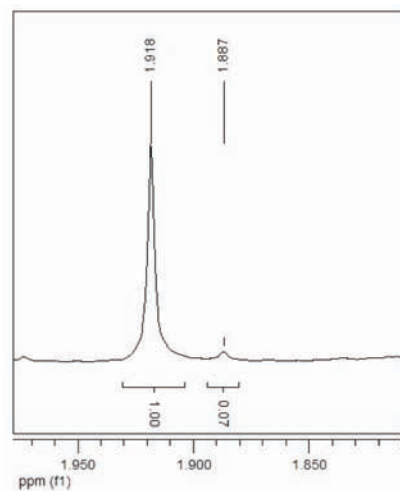


Enantiomer ratio was determined by high resolution ^1H NMR spectroscopy (400 MHz, CDCl_3) in the presence of 4.0 equivalents of (R)-2,2,2-trifluoro-1-(9-anthryl)-ethanol: 92:8 er.

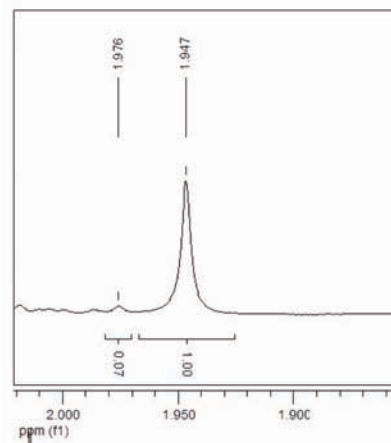


2. Determination of the enantiomer ratio of (S)-Nicotine (Scheme 8).

Enantiomer ratio was determined by high resolution ^1H NMR spectroscopy (400 MHz, CDCl_3) in the presence of 4.0 equivalents of (S)-2,2,2-trifluoro-1-(9-anthryl)-ethanol: 92:8 er.

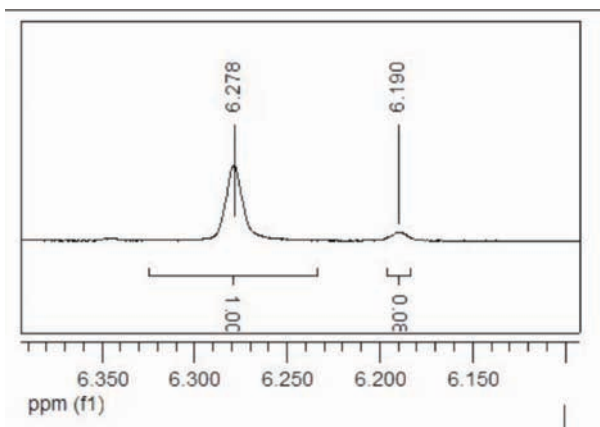


Enantiomer ratio was determined by high resolution ^1H NMR spectroscopy (400 MHz, CDCl_3) in the presence of 4.0 equivalents of (R)-2,2,2-trifluoro-1-(9-anthryl)-ethanol: 92:8 er.

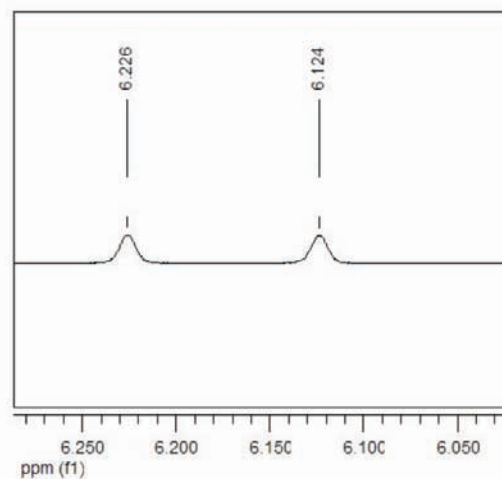


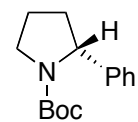
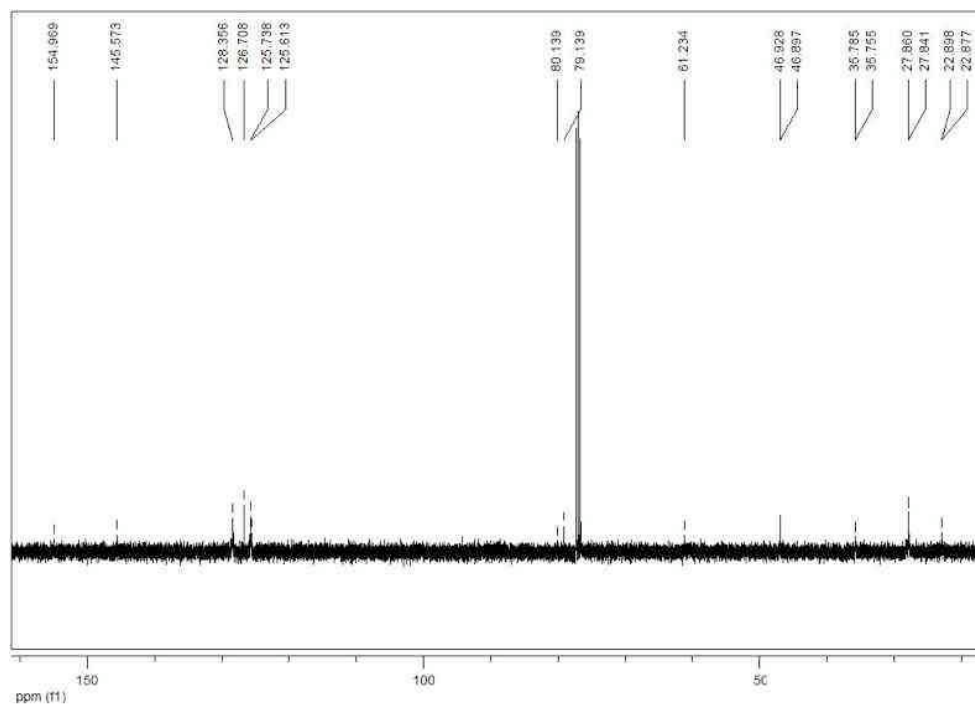
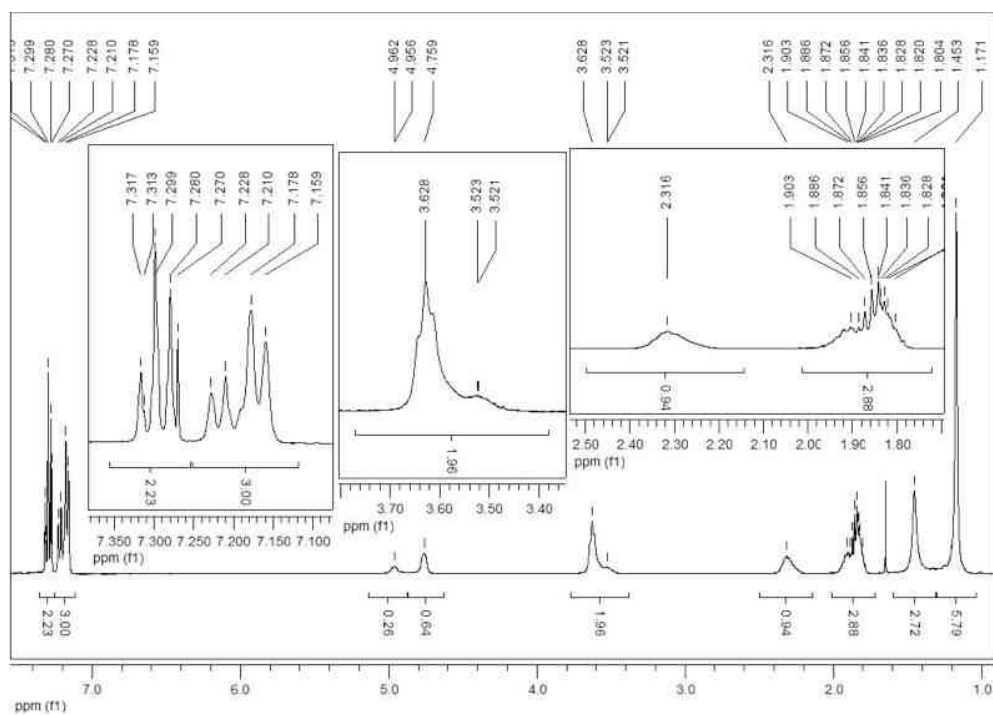
3. Determination of the enantiomer ratio of 1-((*R*)-5-Pyrrolidin-2-yl-3,4-dihydro-2*H*-pyridin-1-yl)ethanone (*R*)-Maackiamine (Scheme 10).

Enantiomer ratio was determined by high resolution ^1H NMR spectroscopy (400 MHz, CDCl_3) in the presence of 4.0 equivalents of (*R*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol: 95:5 er.

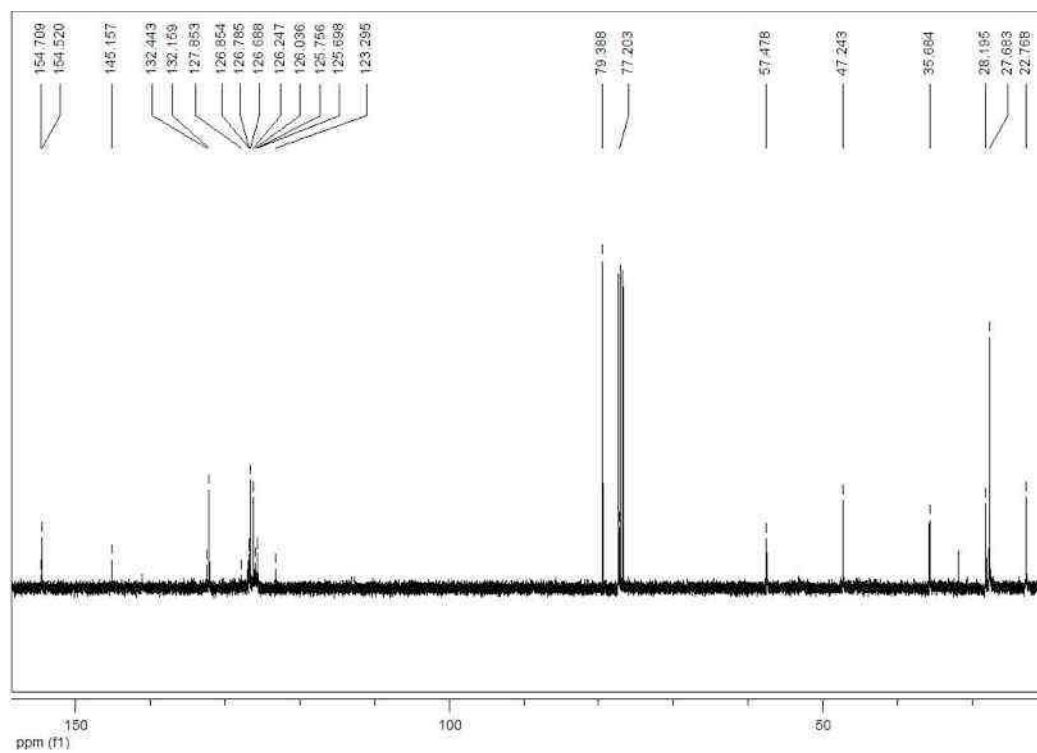
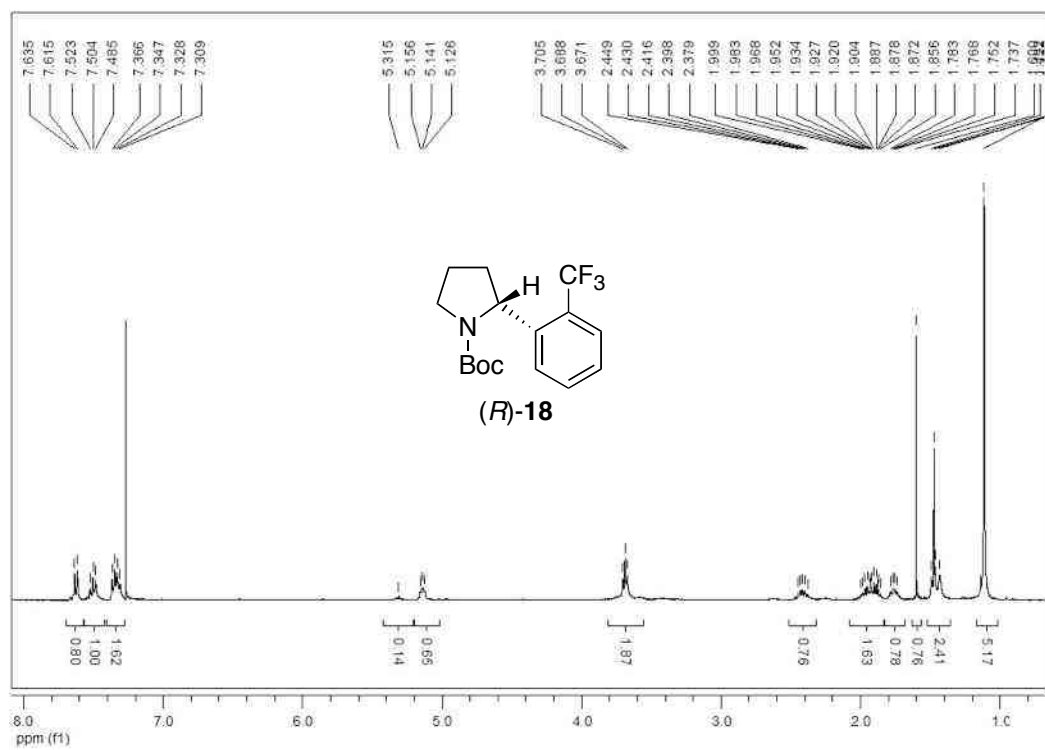


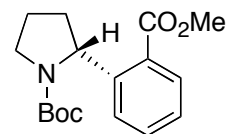
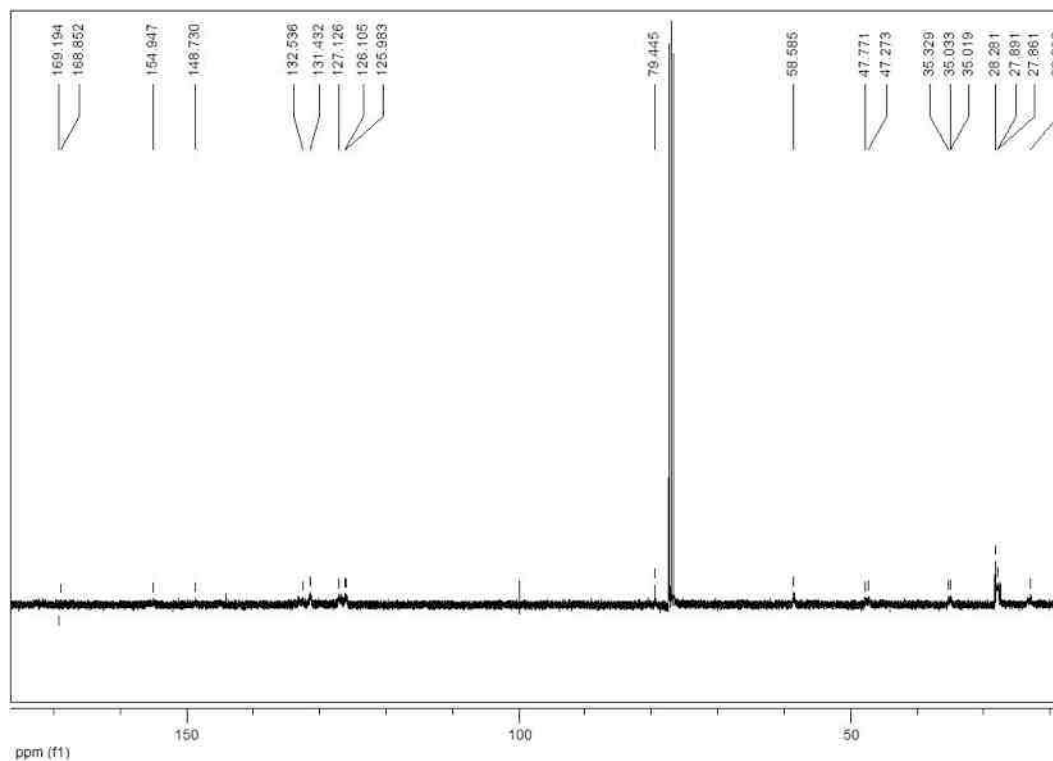
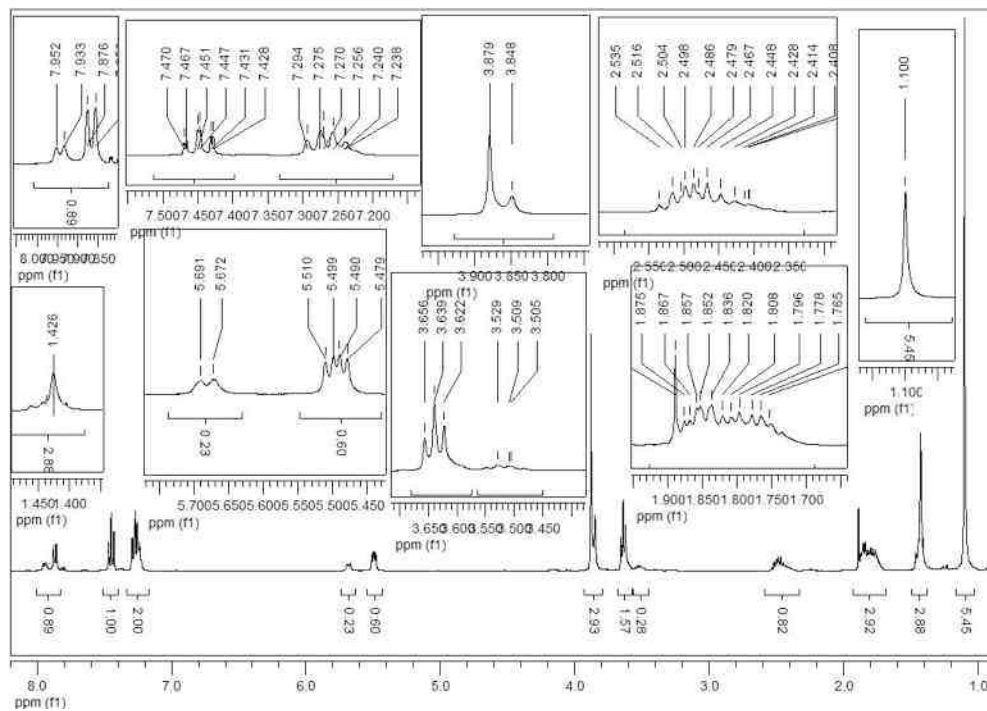
Enantiomer ratio was determined by high resolution ^1H NMR spectroscopy (400 MHz, CDCl_3) in the presence of 4.0 equivalents of (*R*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol: 50:50 er.

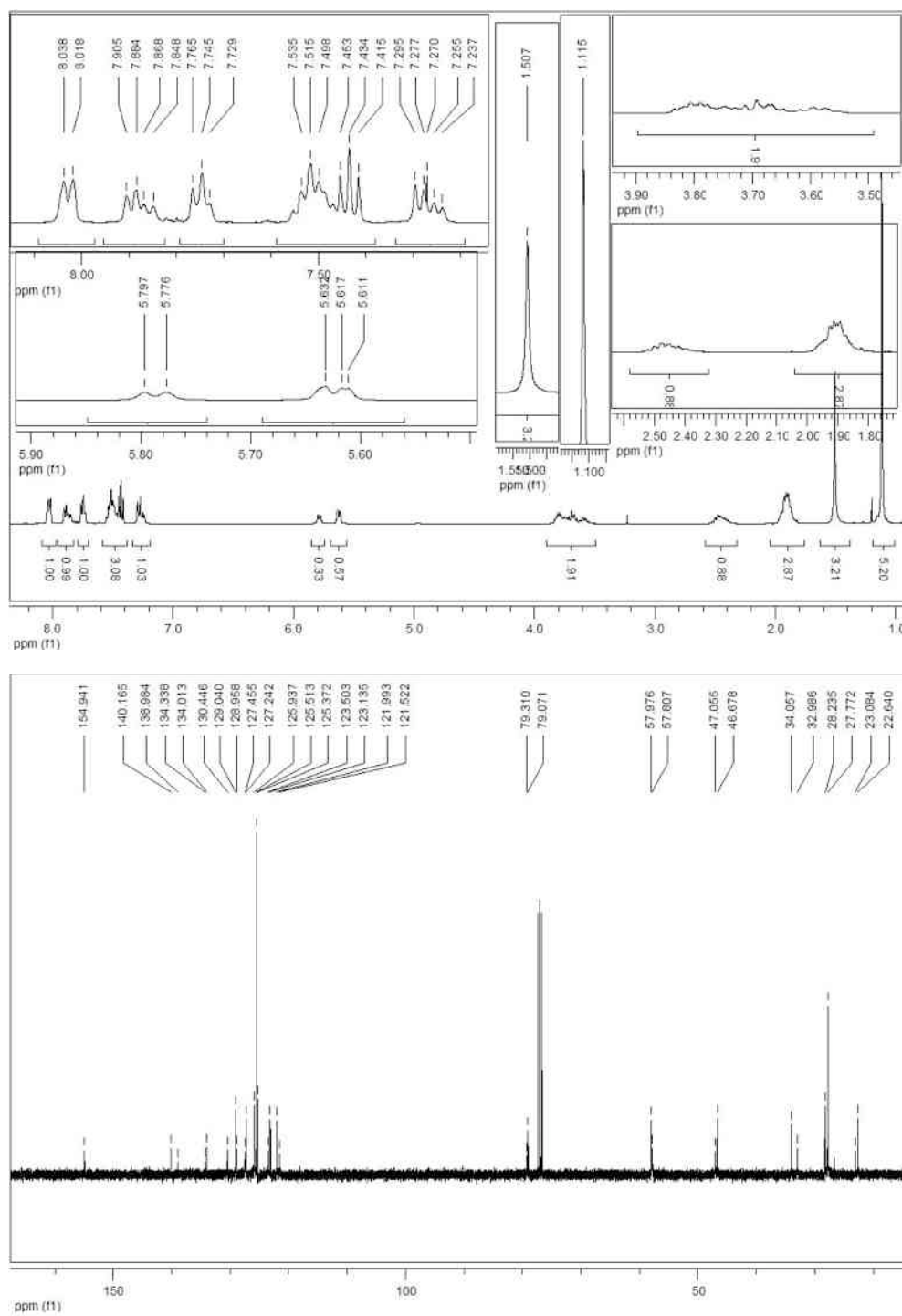
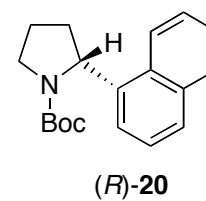


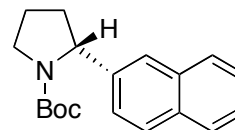
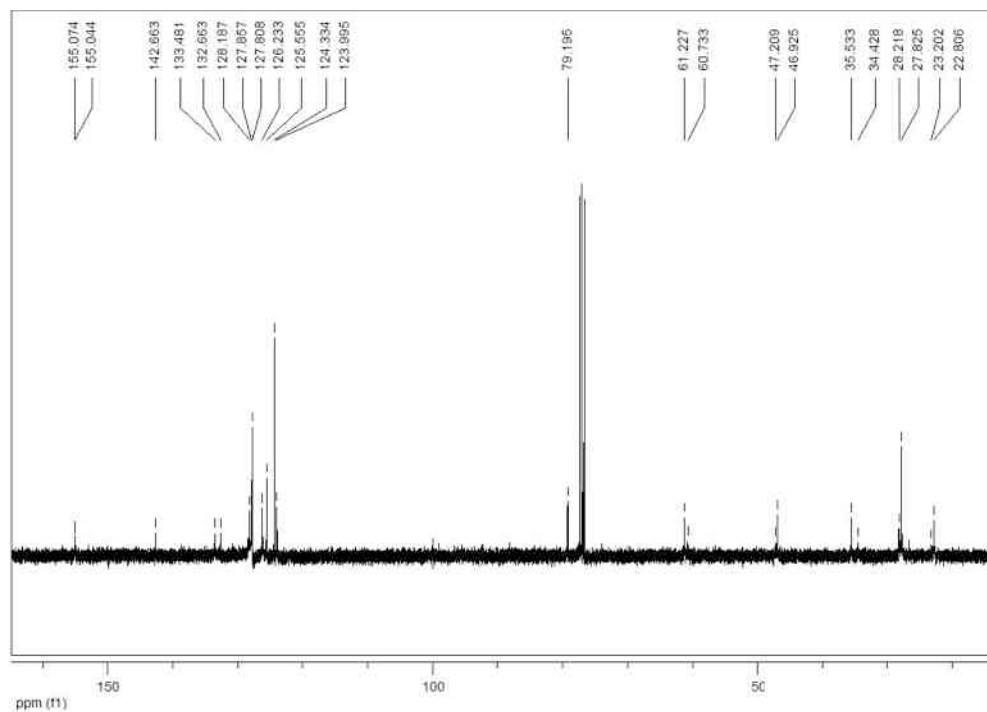
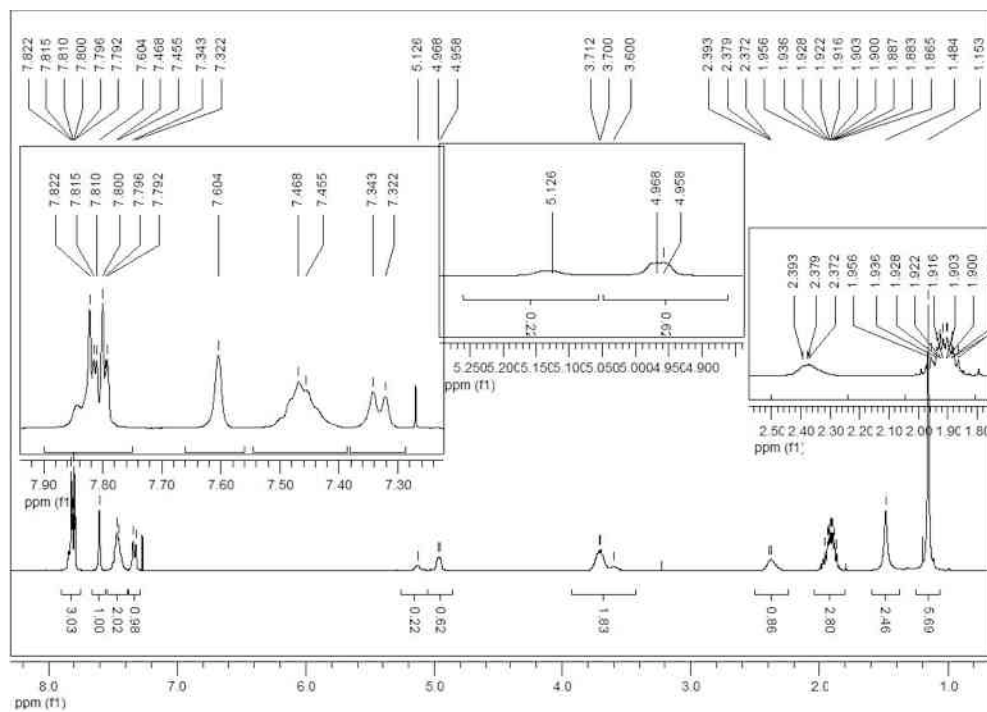
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400 MHz ^1H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; CDCl_3

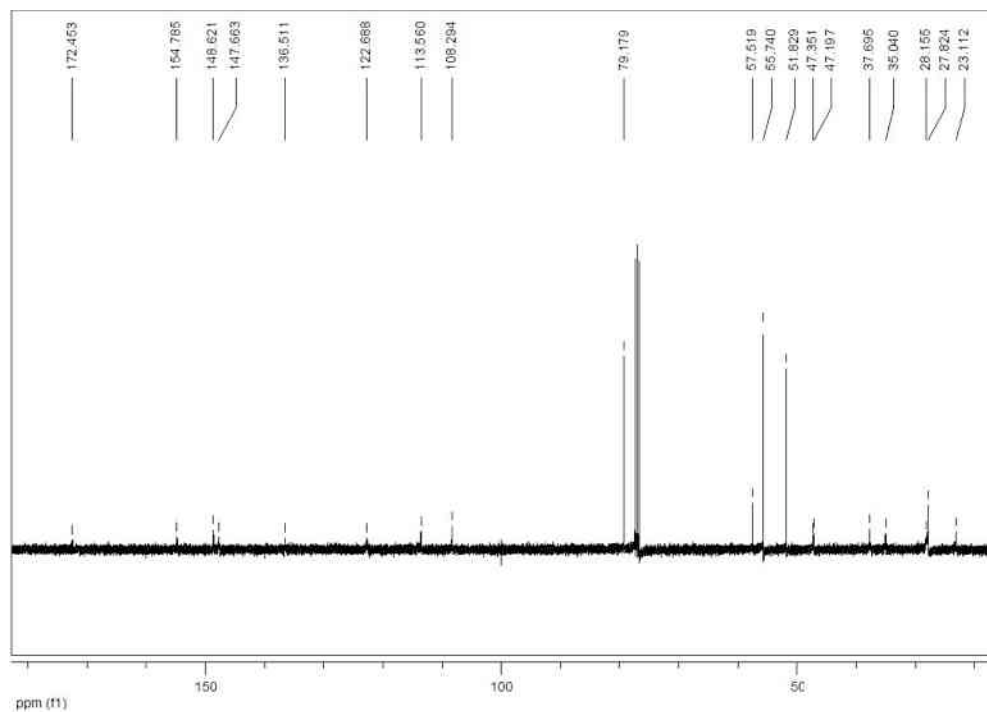
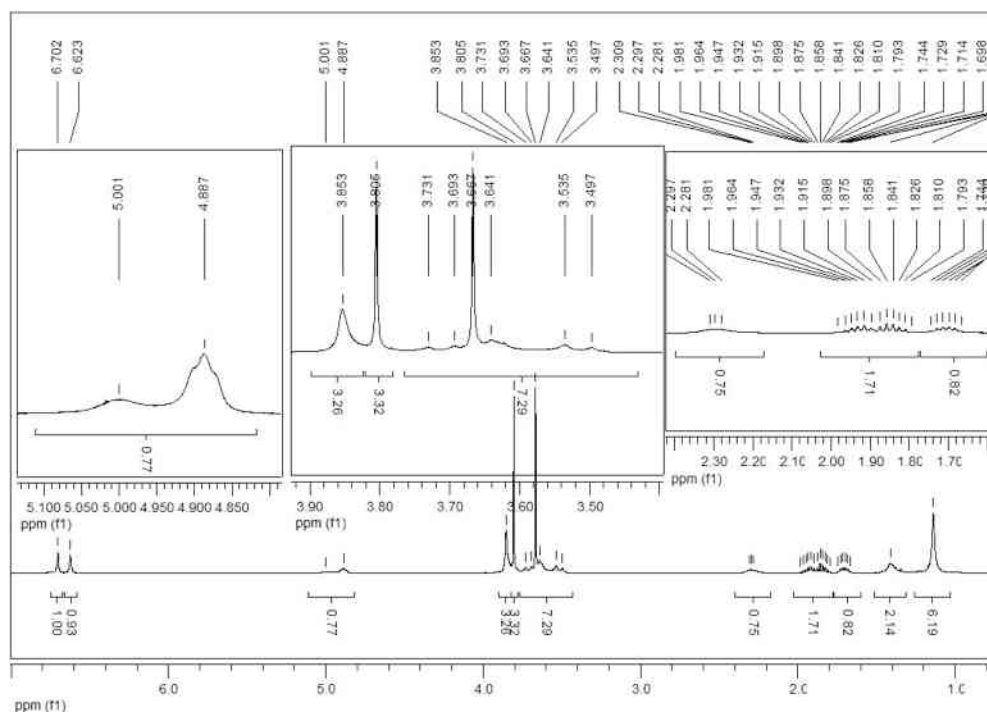
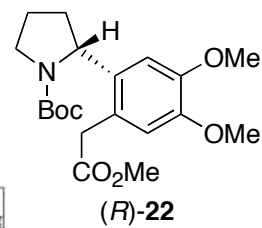


400 MHz ^1H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; CDCl_3 **(R)-19**

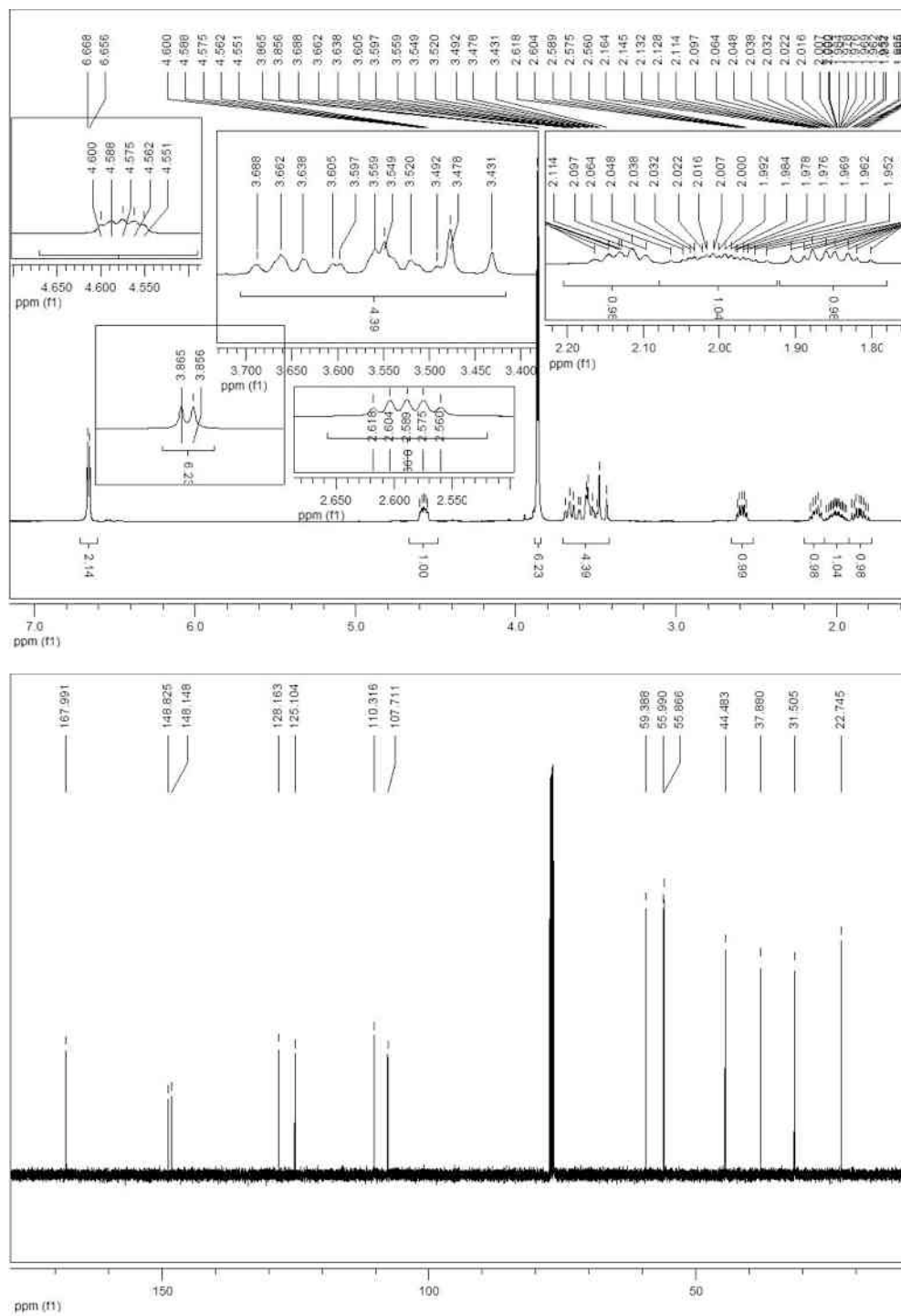
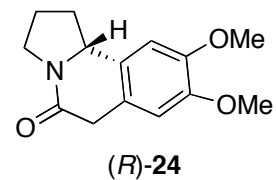
400 MHz ^1H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; CDCl_3 

400 MHz ^1H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; CDCl_3 **(R)-21**

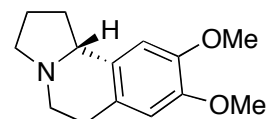
400 MHz ^1H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; CDCl_3



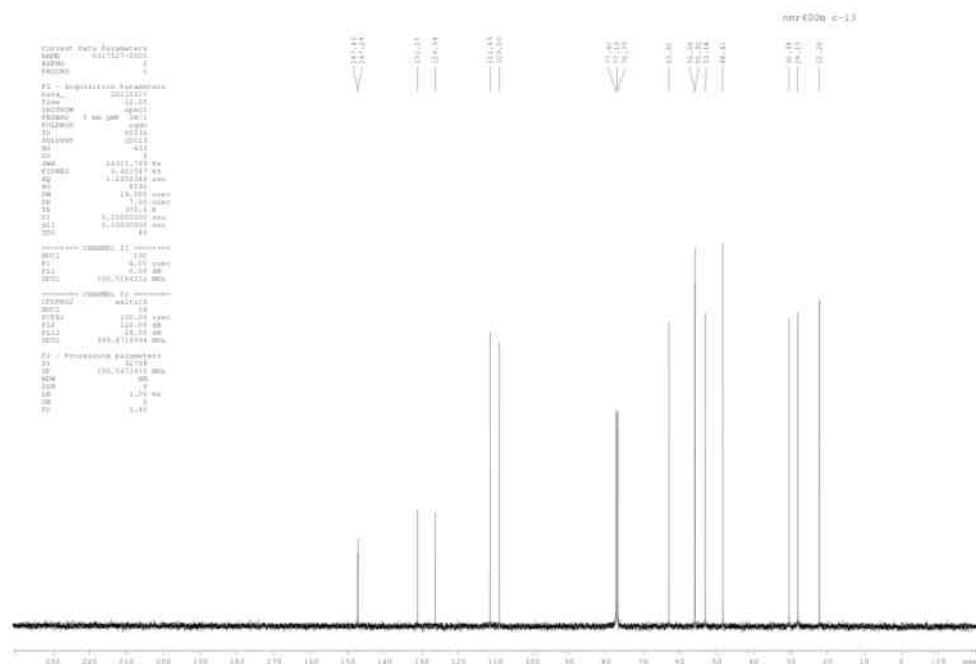
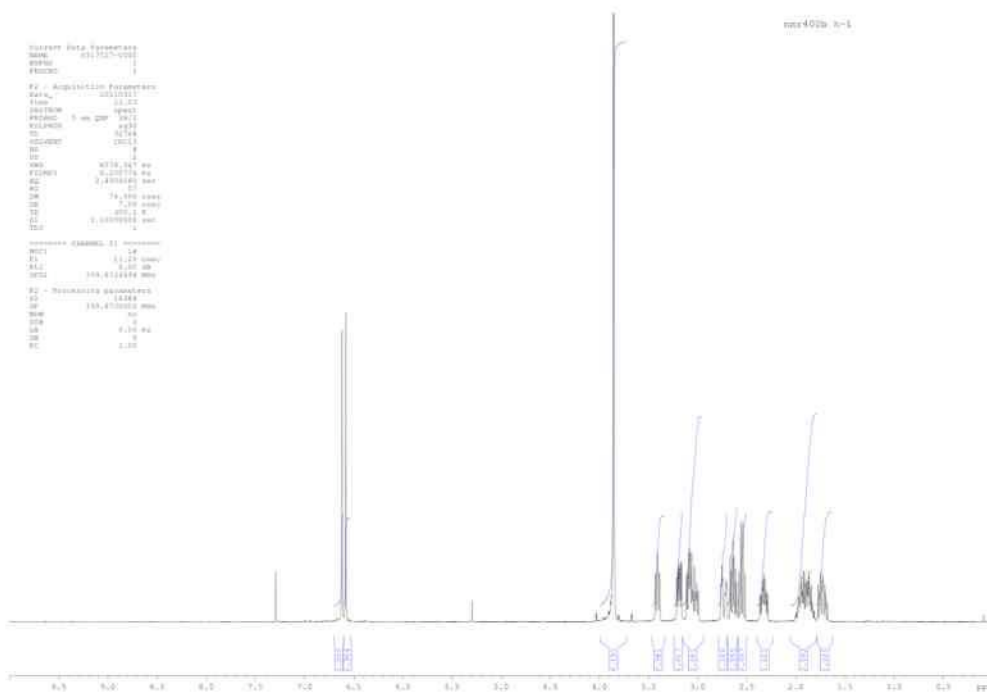
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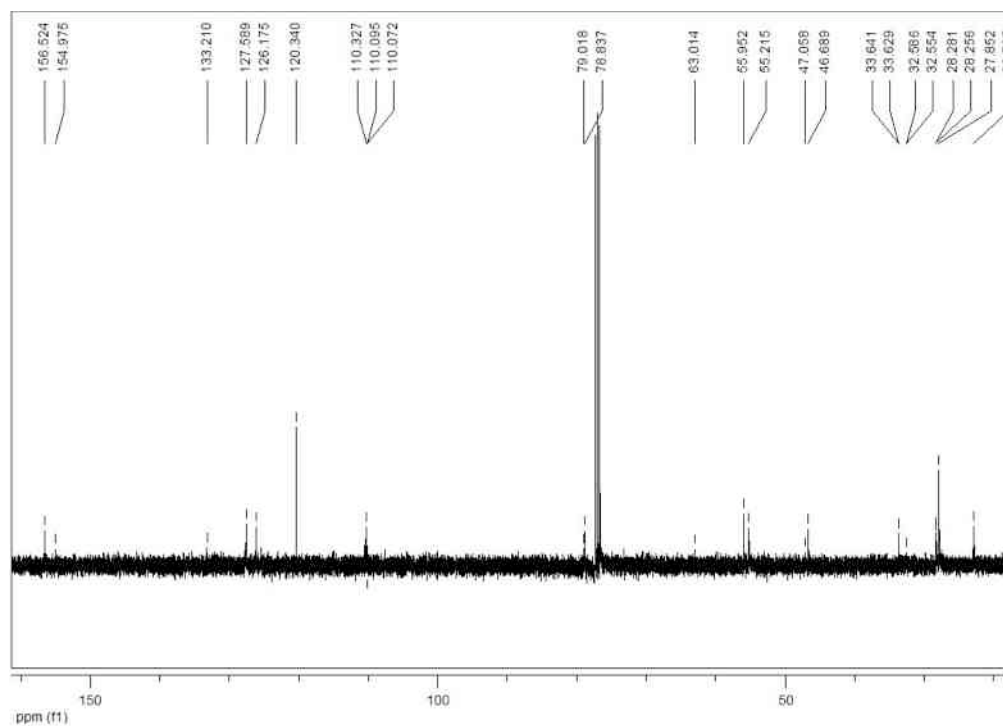
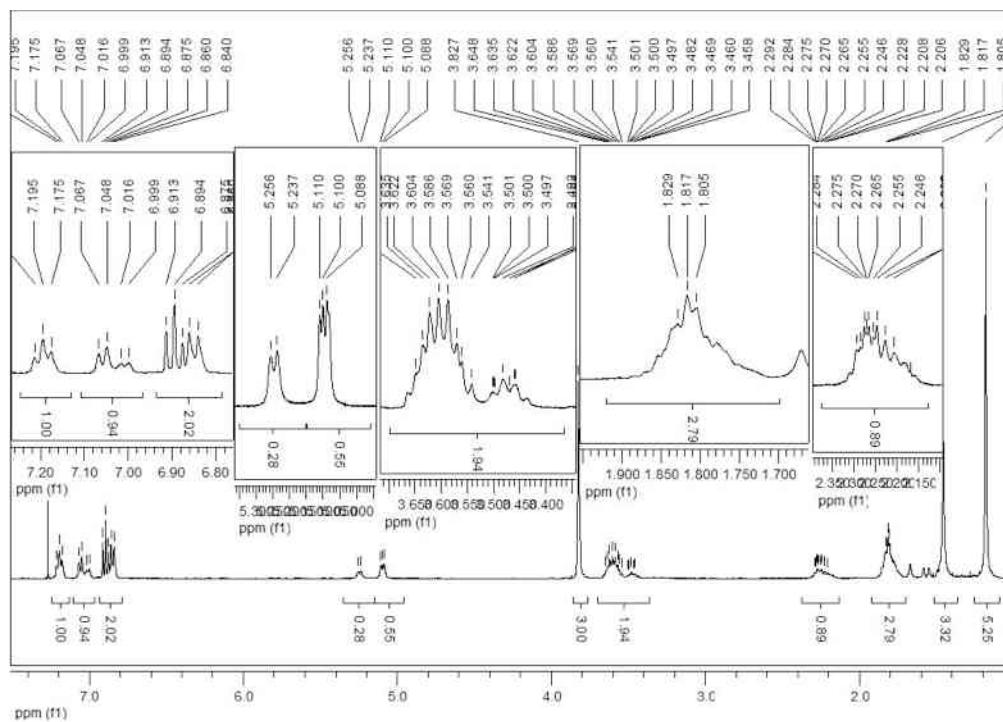
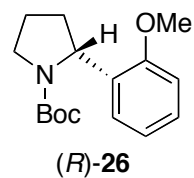


400 MHz ^1H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; CDCl_3

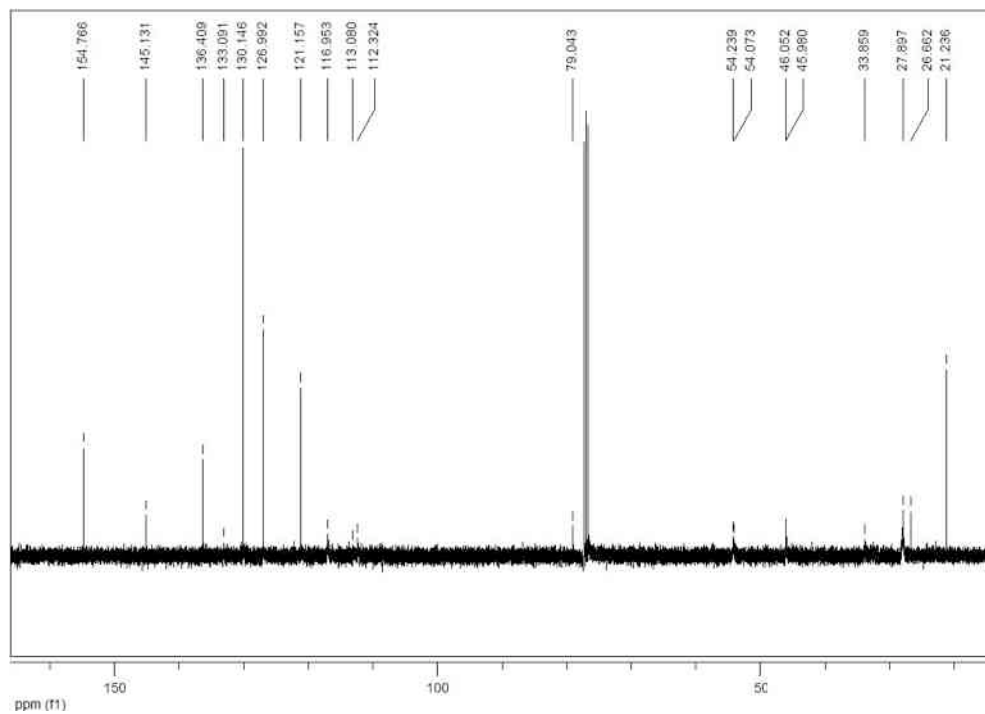
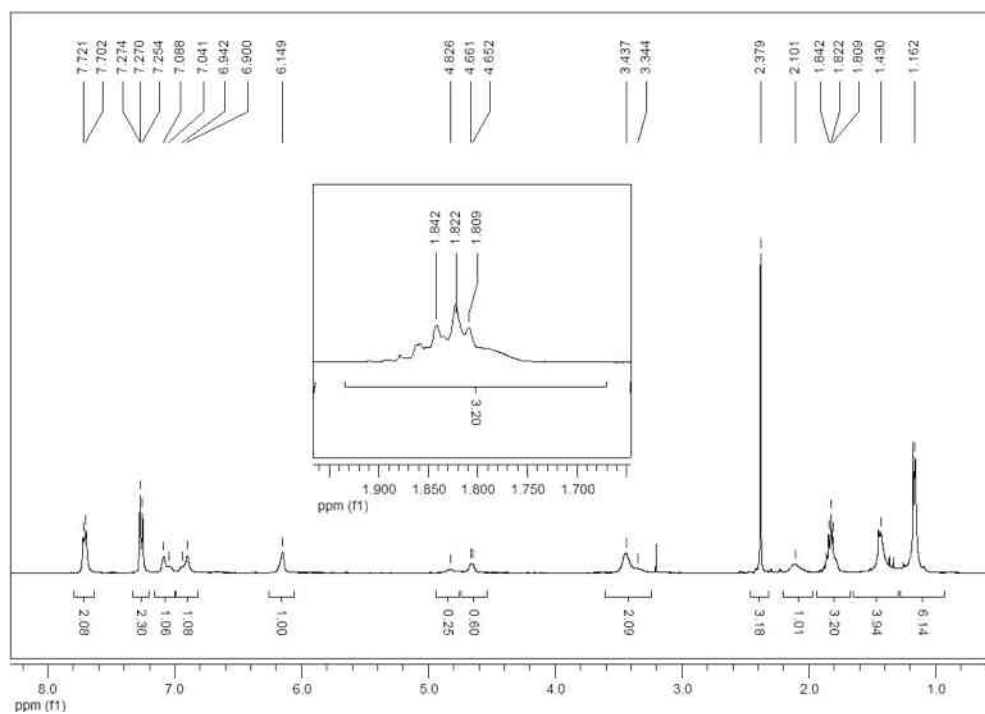
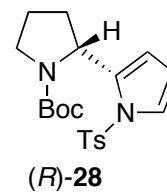


(*R*)-Crispine A

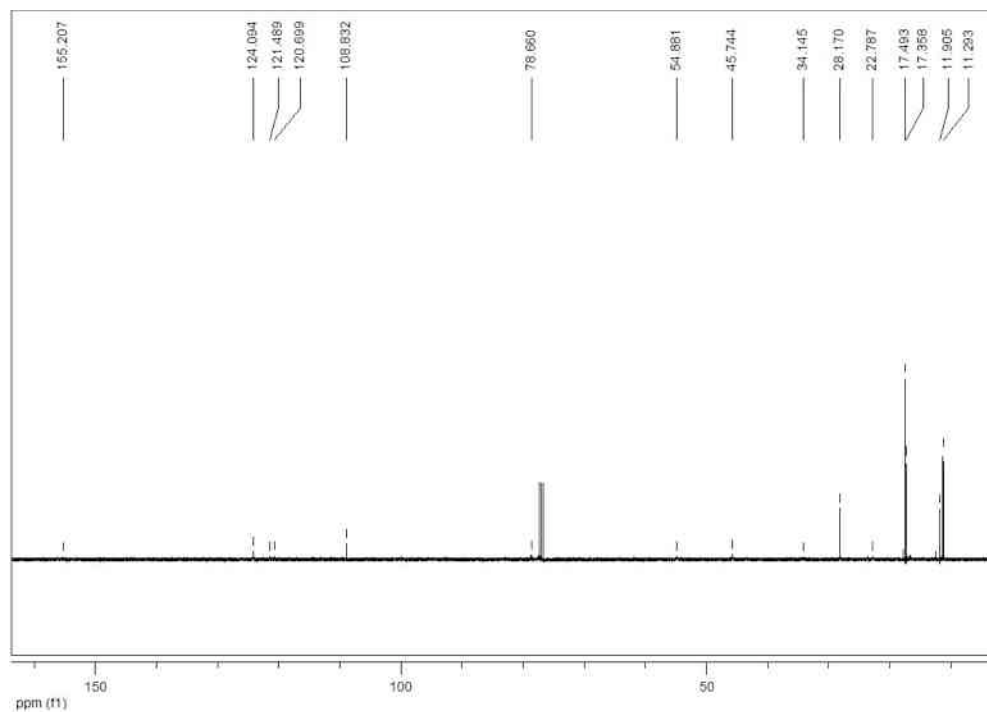
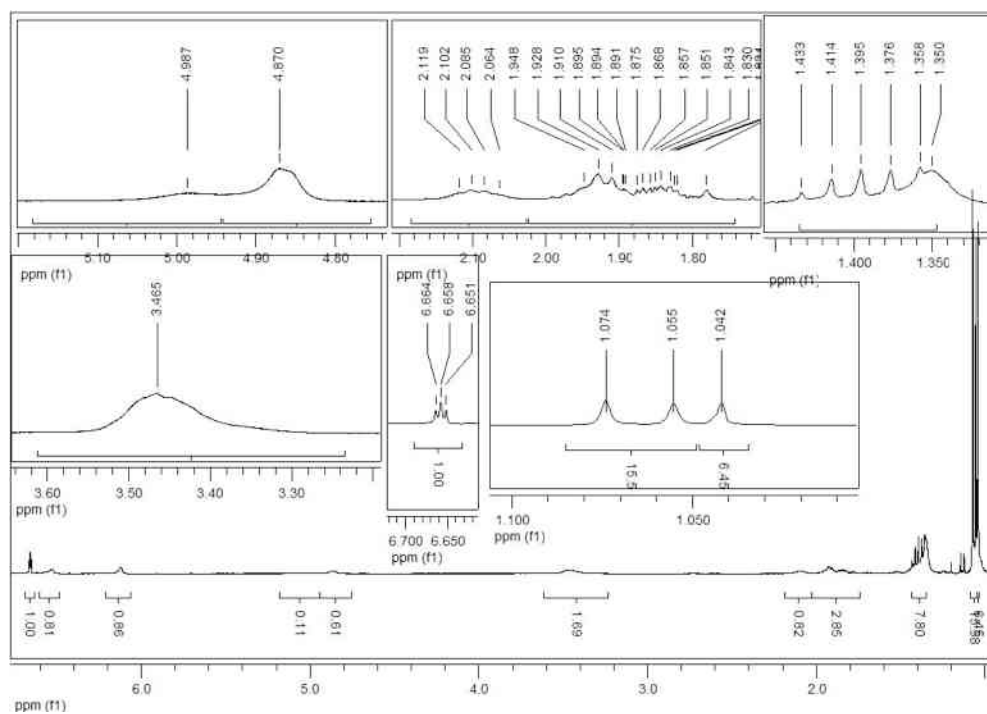
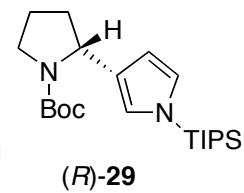


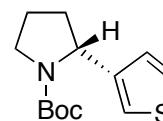
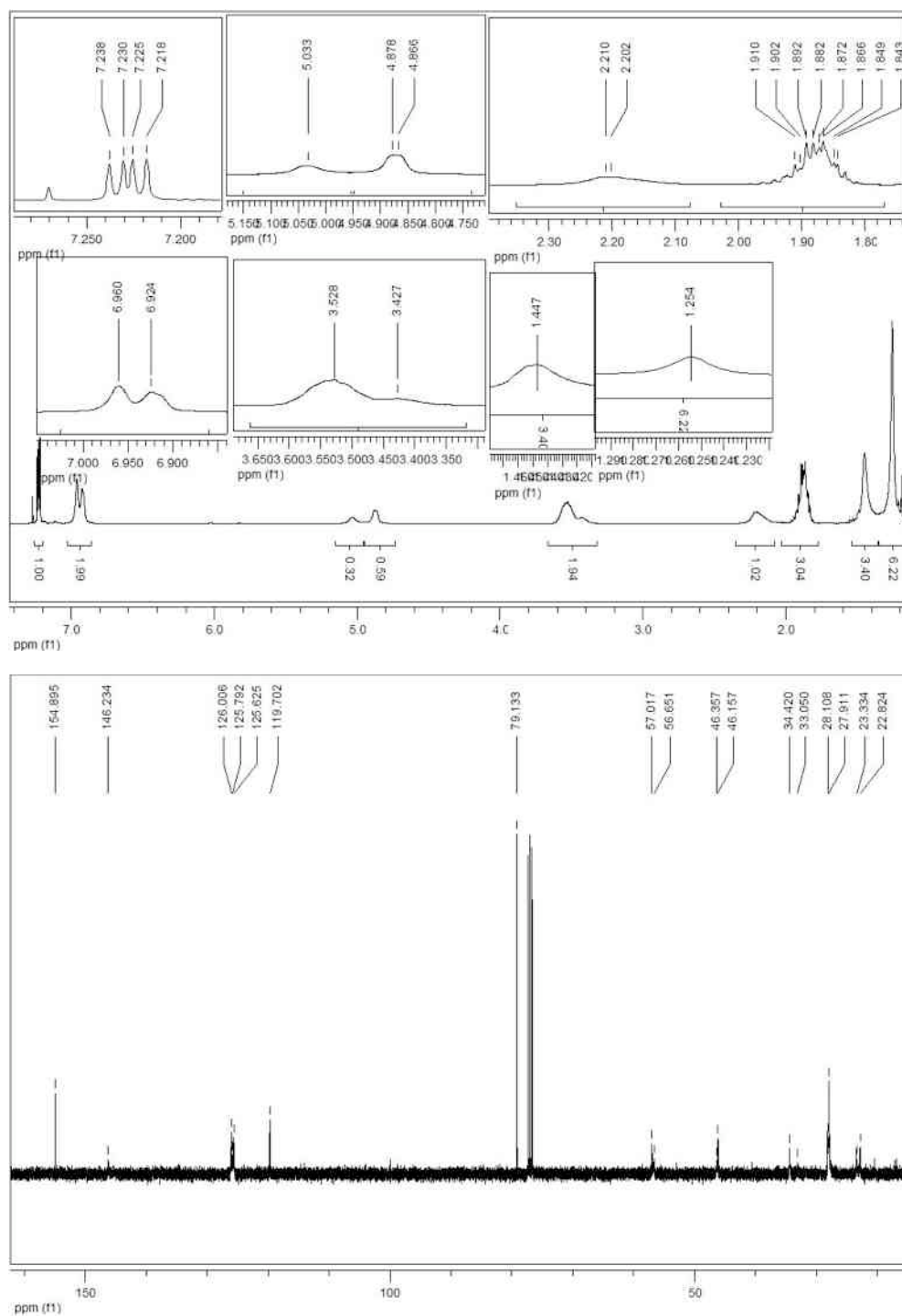
400 MHz ^1H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; CDCl_3 

400 MHz ^1H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; CDCl_3

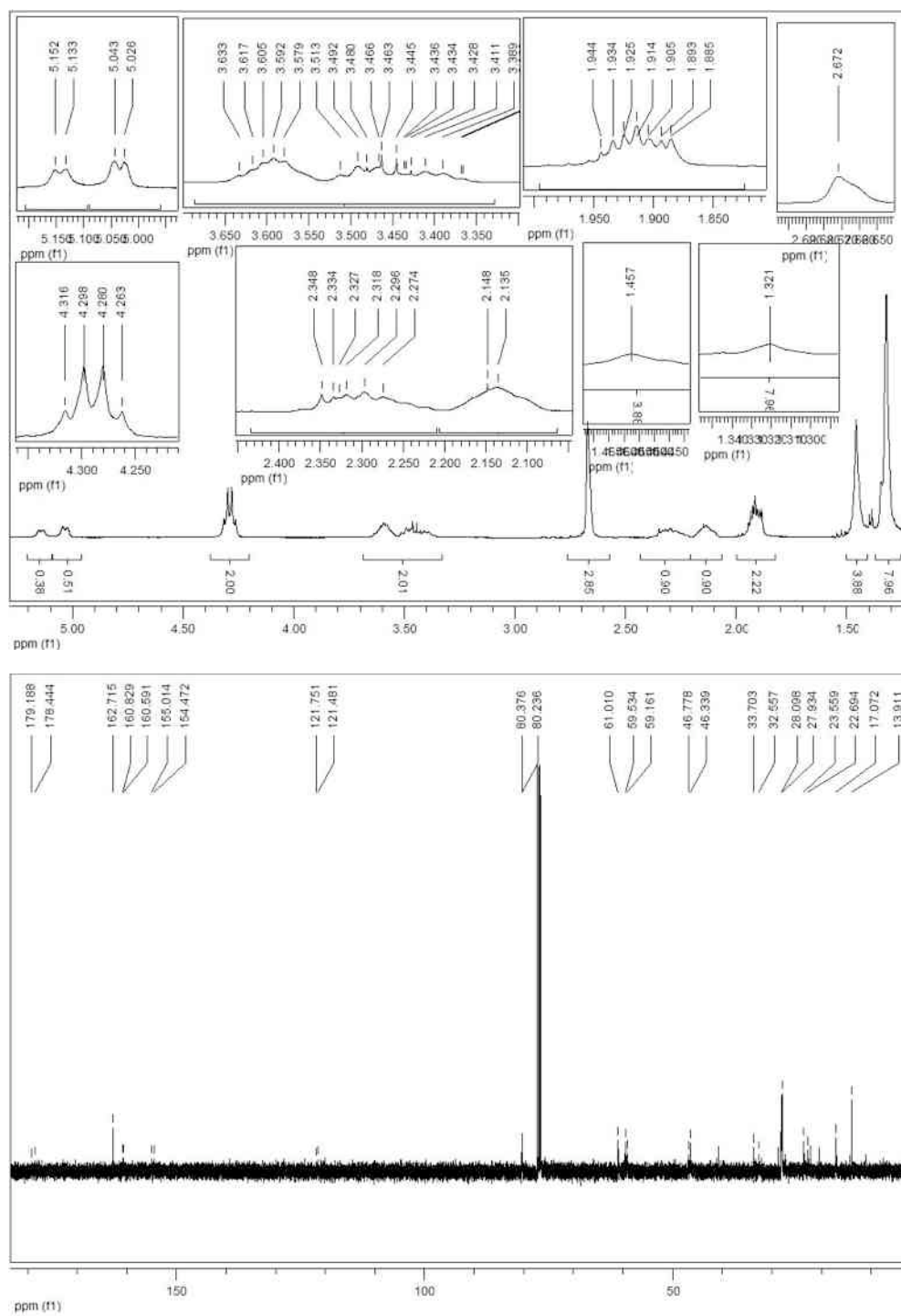
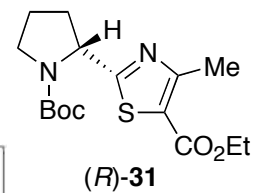


400 MHz ^1H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; CDCl_3

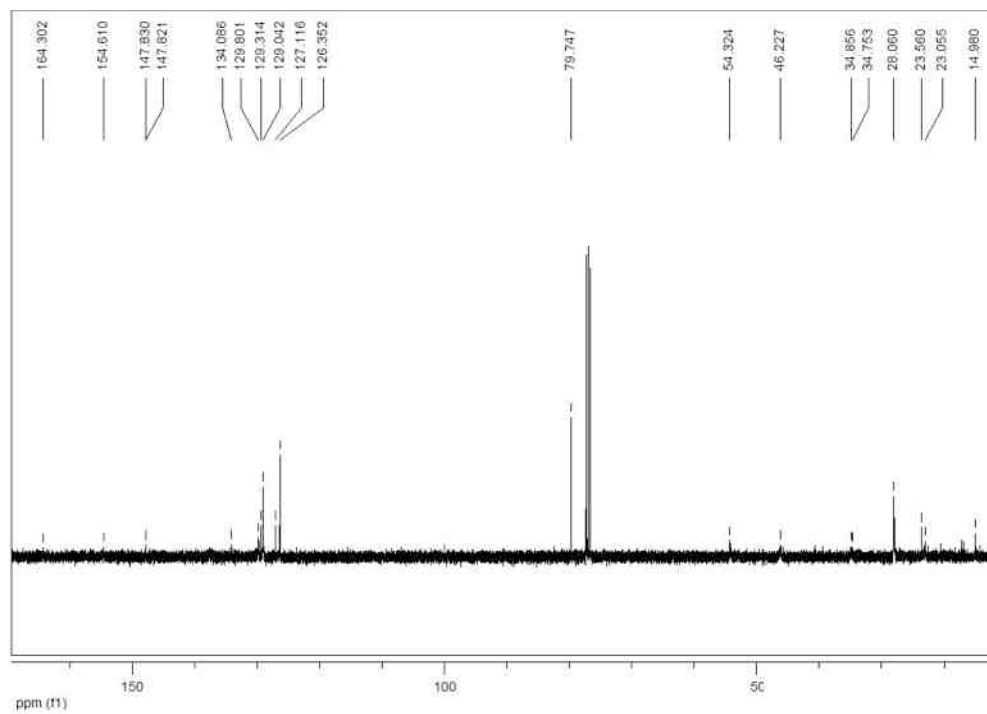
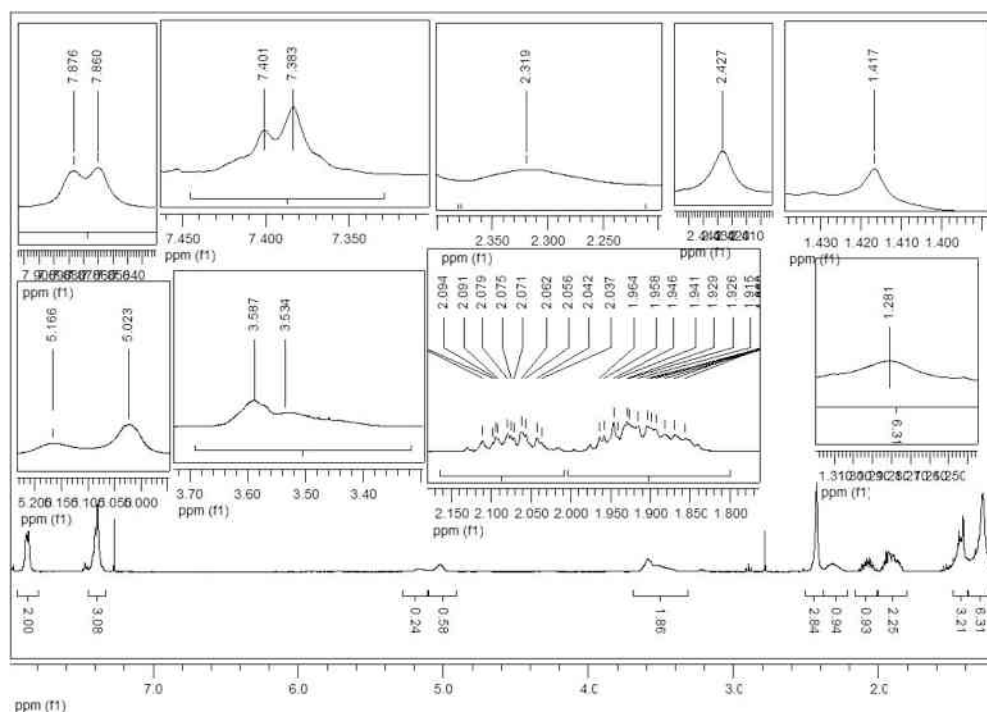
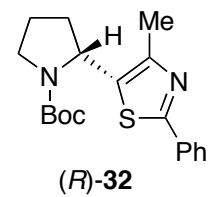


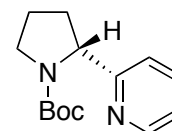
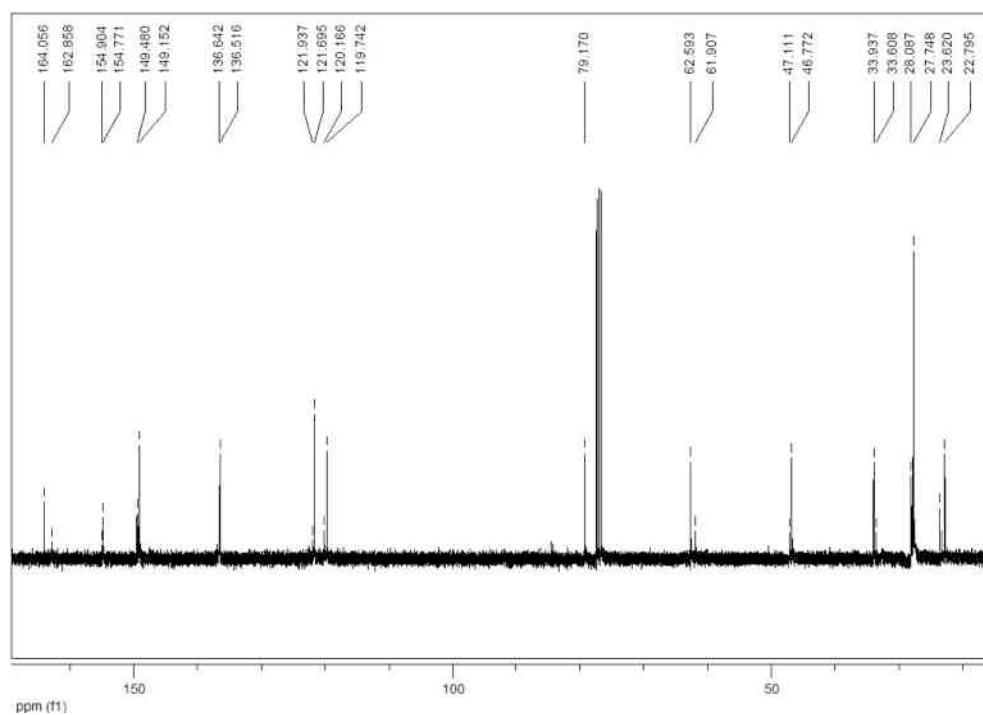
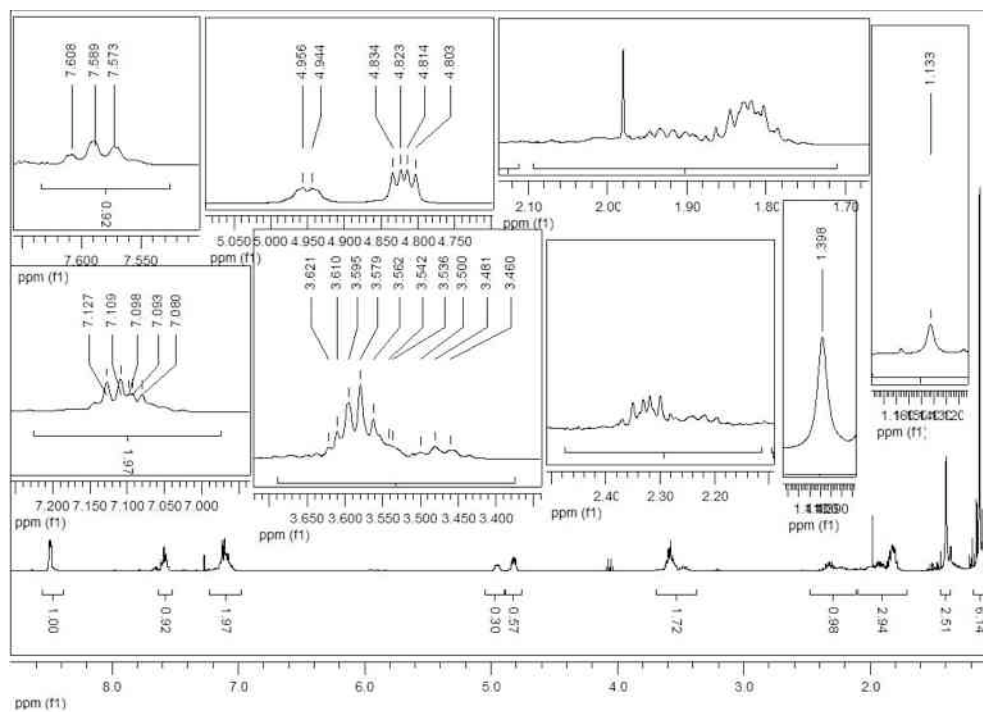
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400 MHz ^1H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; CDCl_3

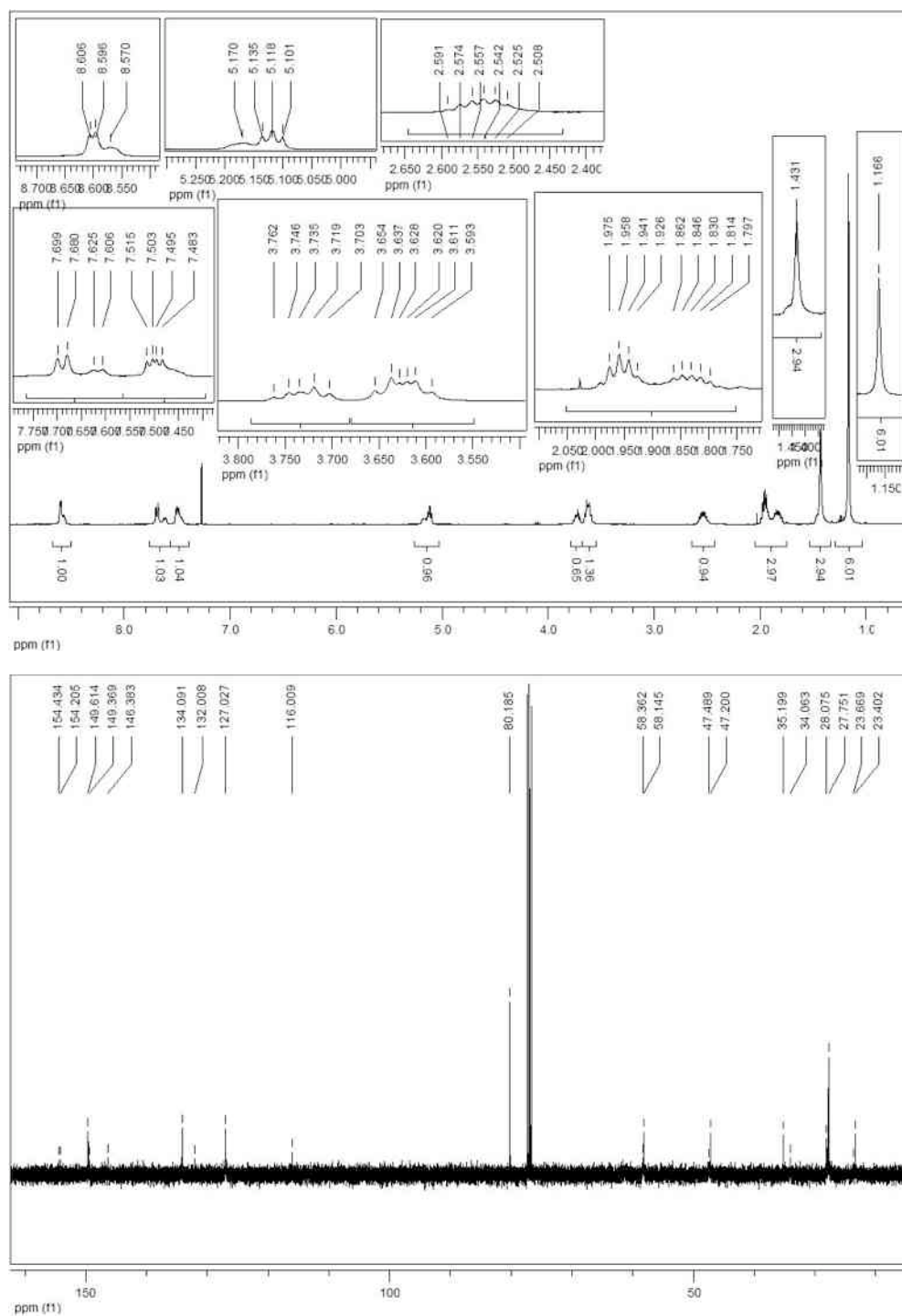
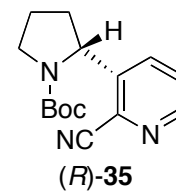


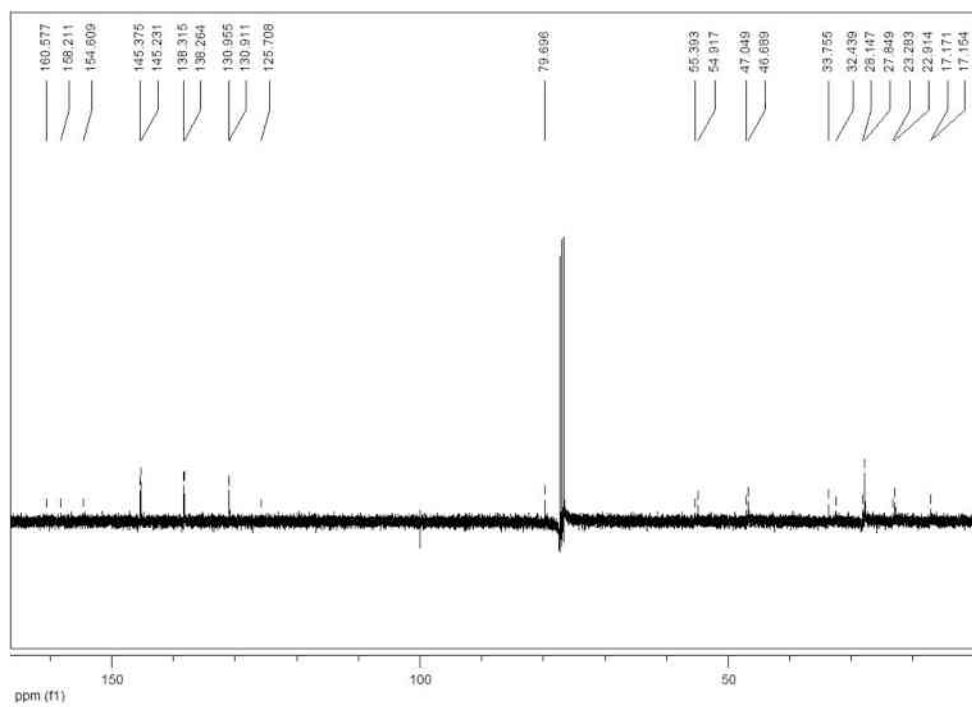
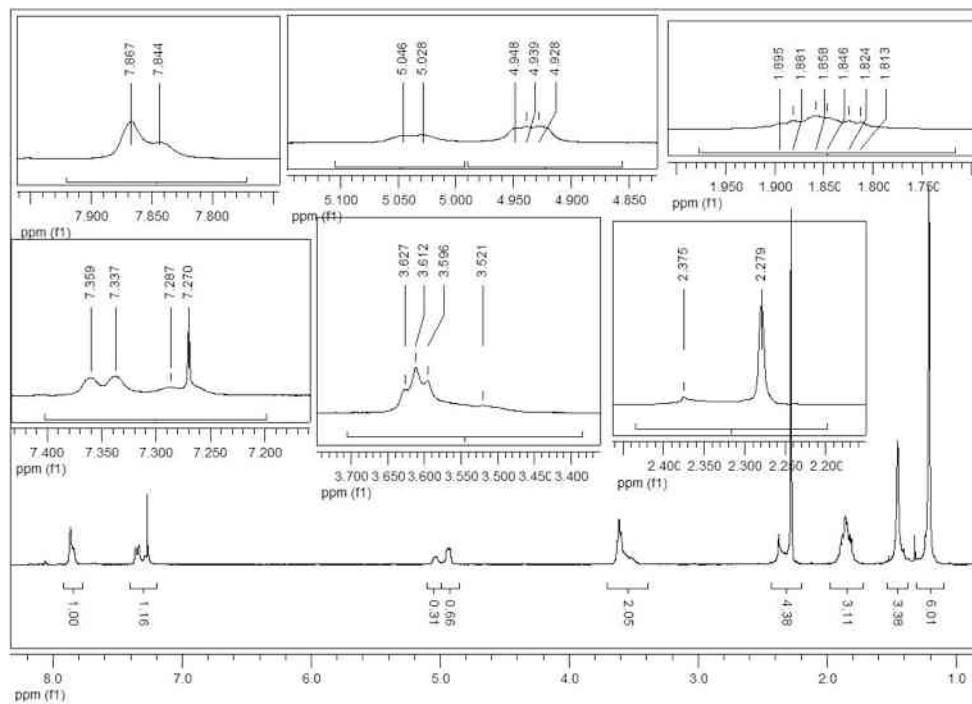
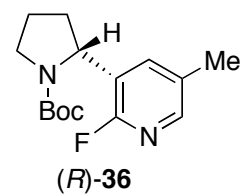
400 MHz ^1H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; CDCl_3



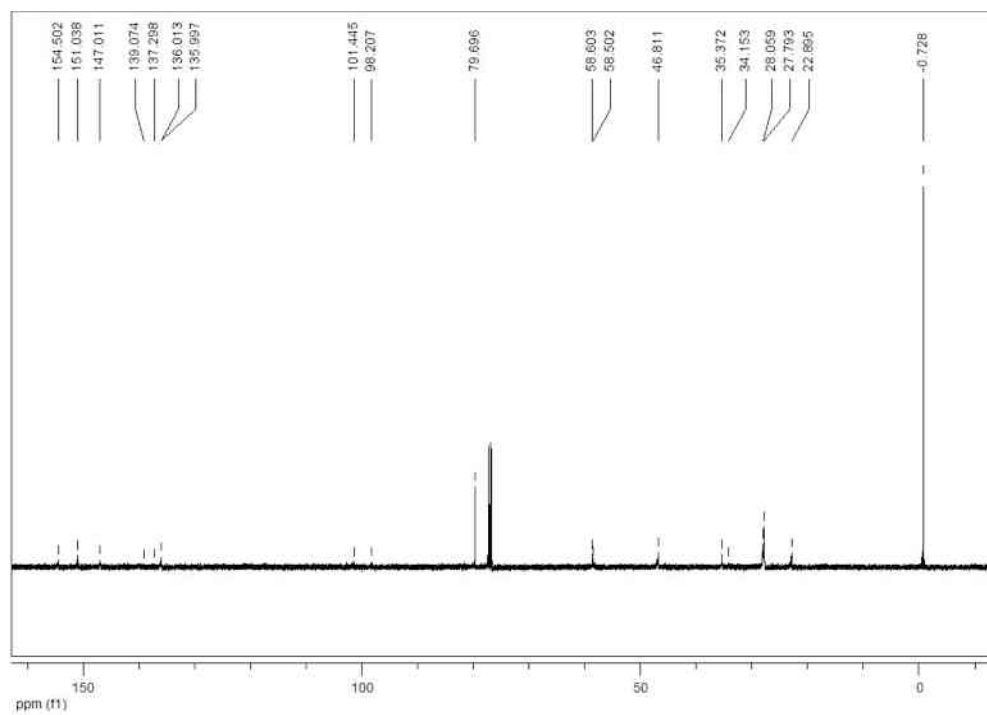
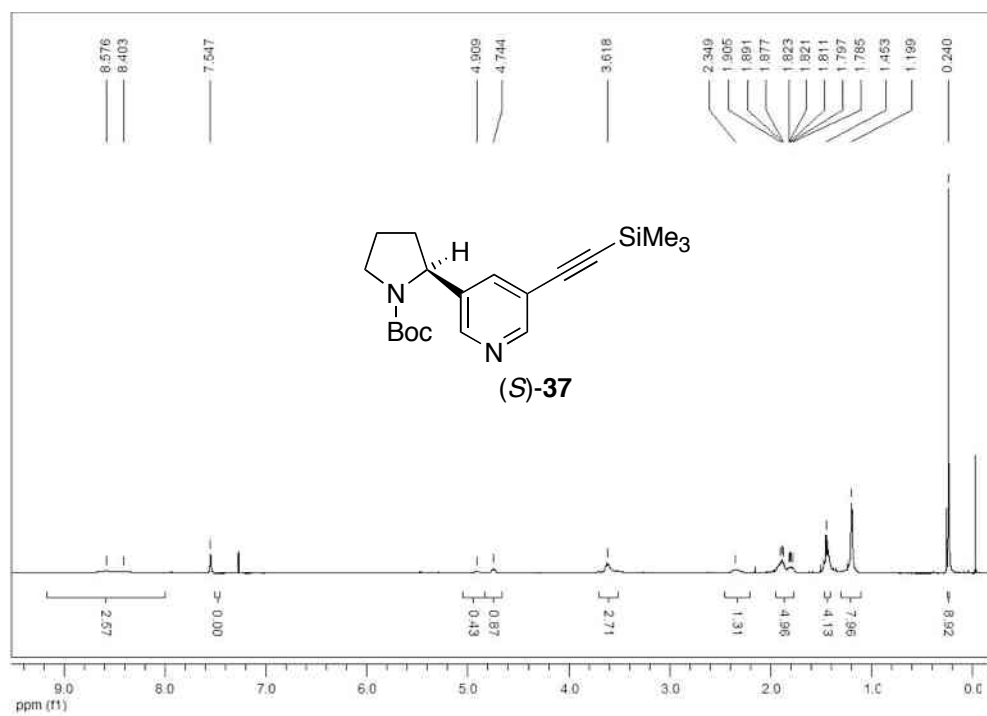
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400 MHz ^1H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; CDCl_3

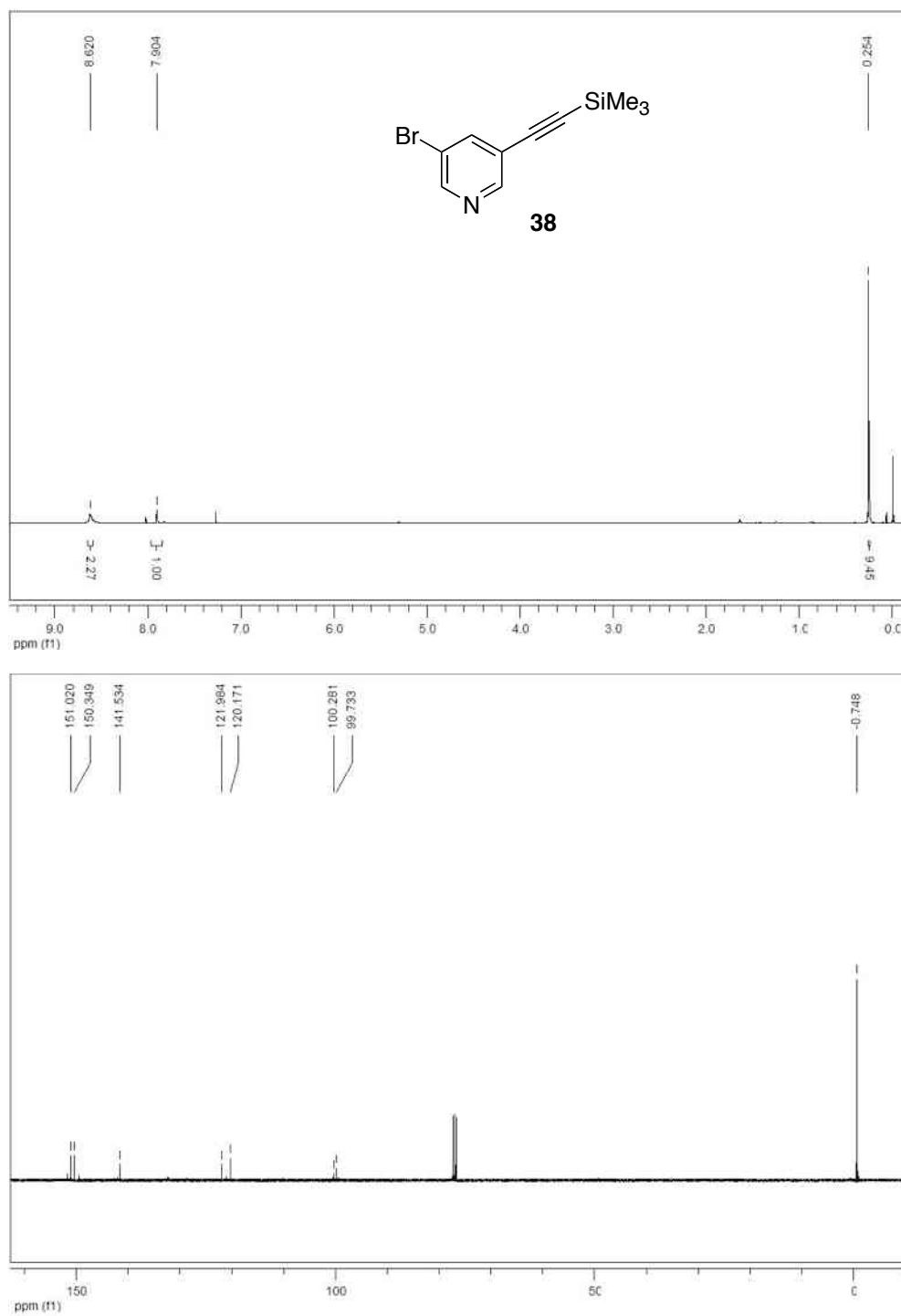


400 MHz ^1H NMR spectrum; CDCl_3 

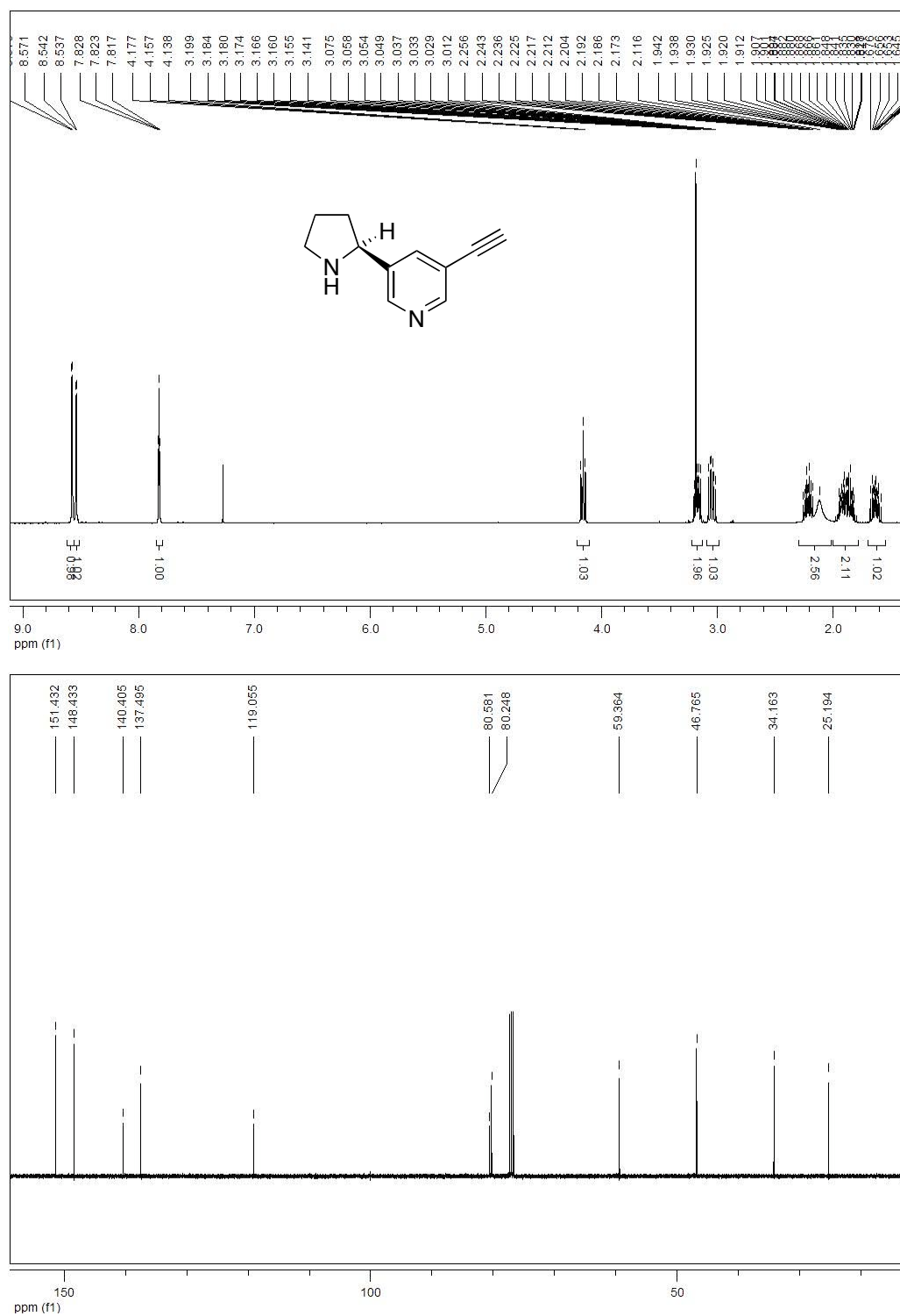
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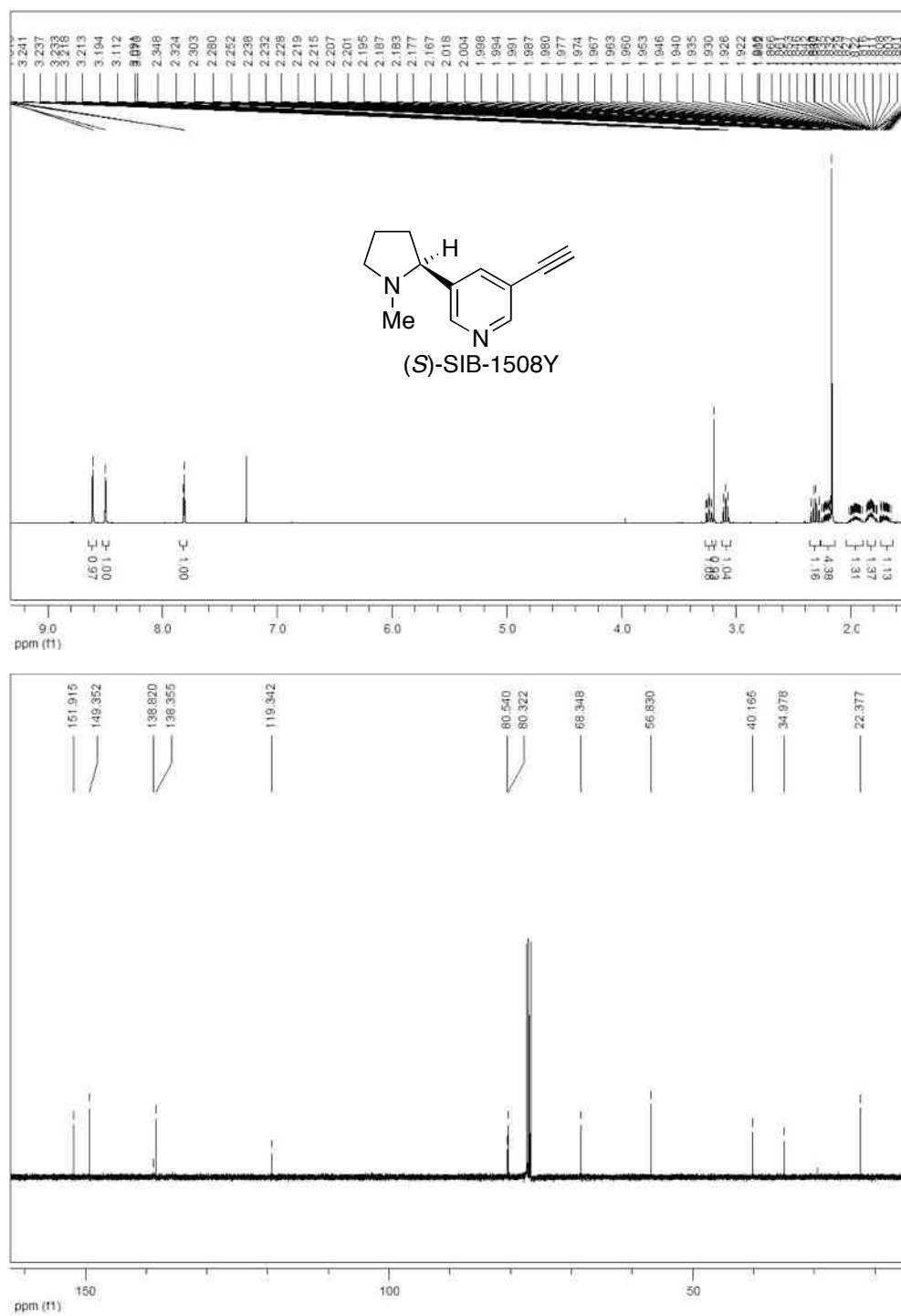
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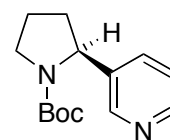
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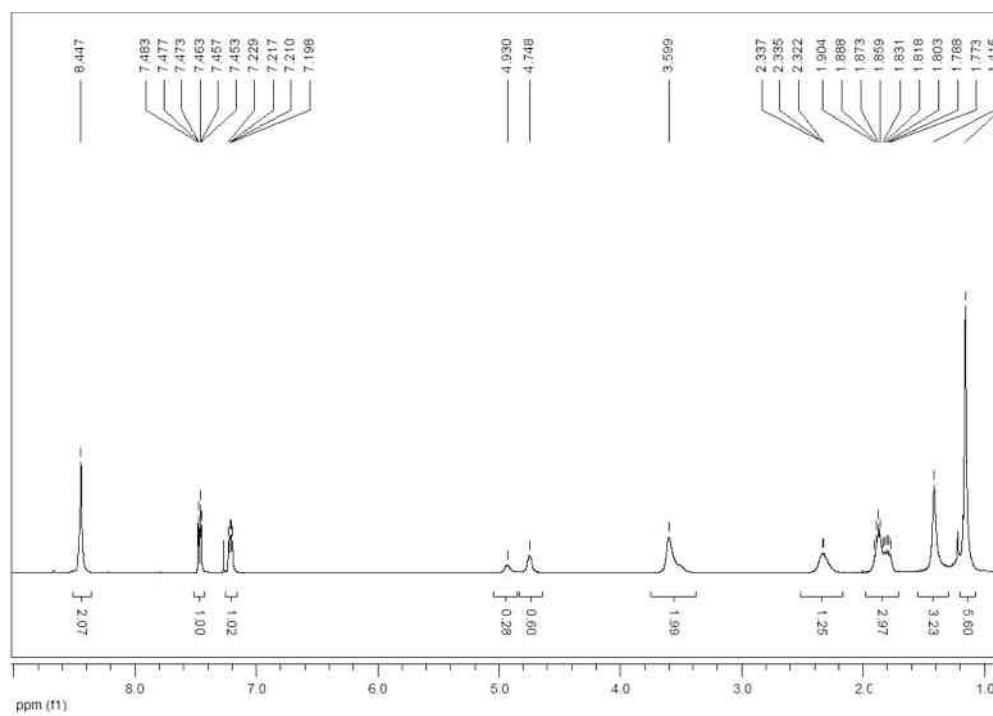
400 MHz ^1H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; CDCl_3



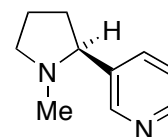
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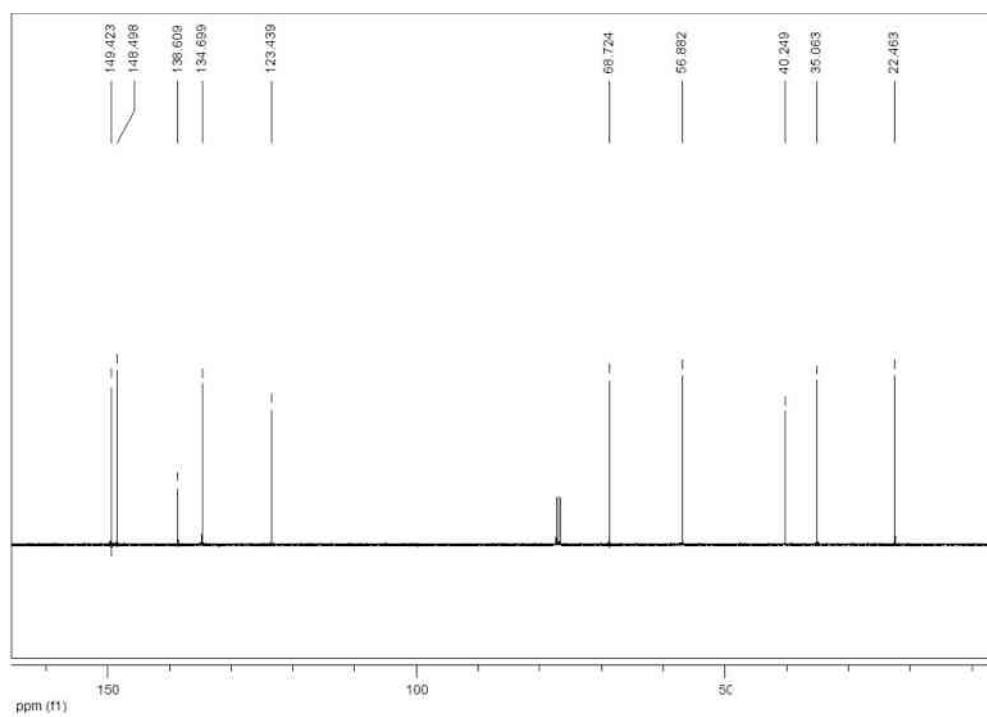
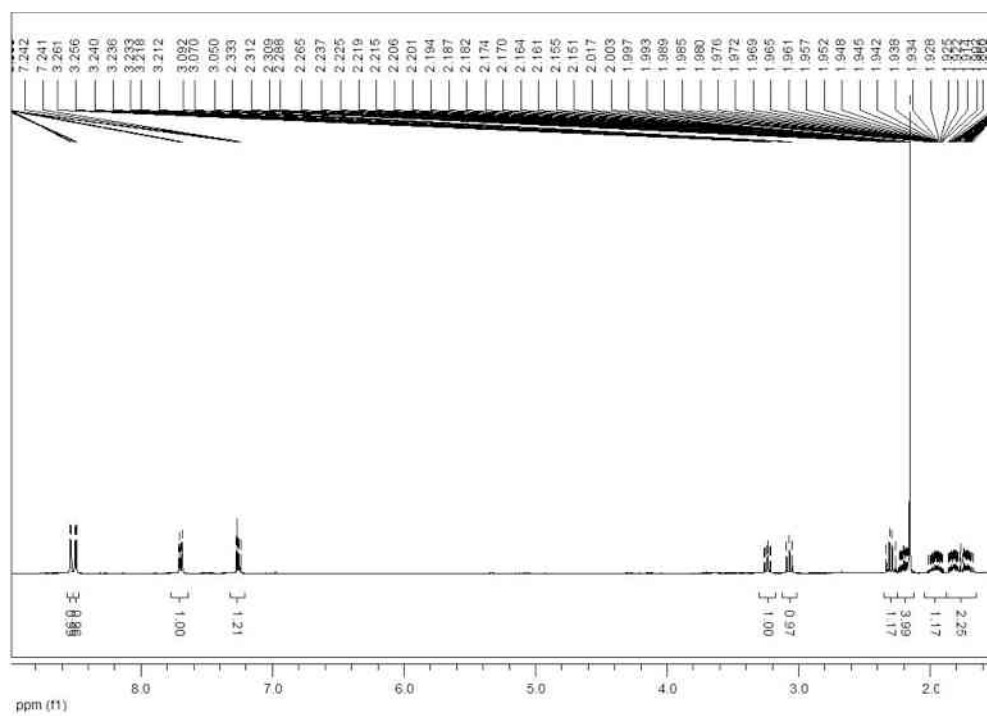
(S)-33

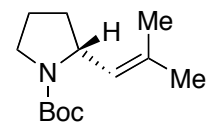
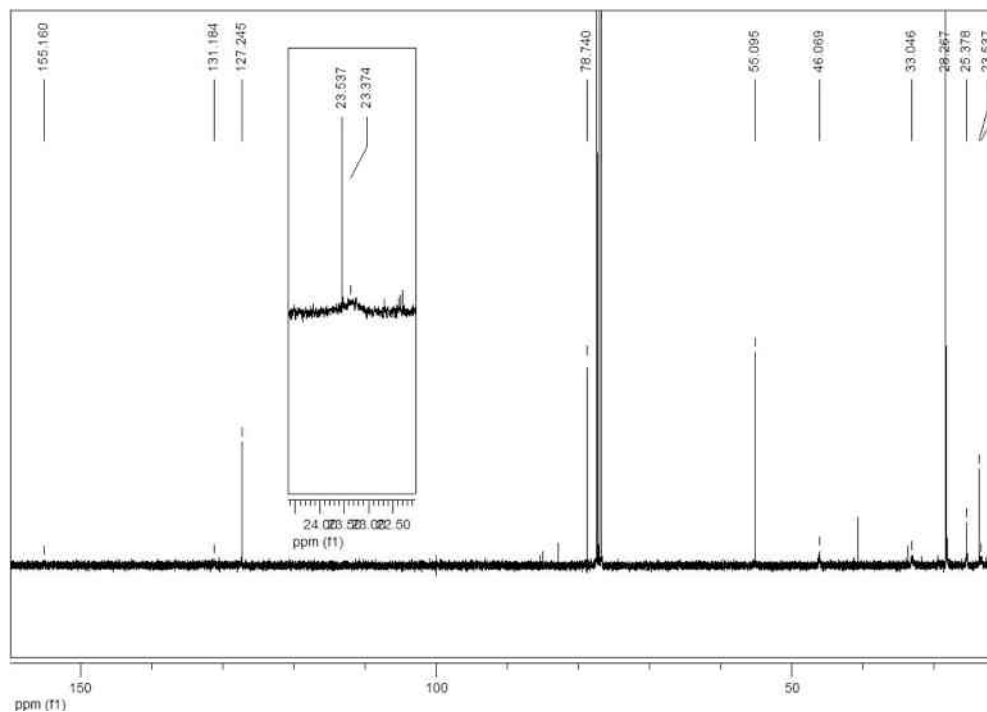
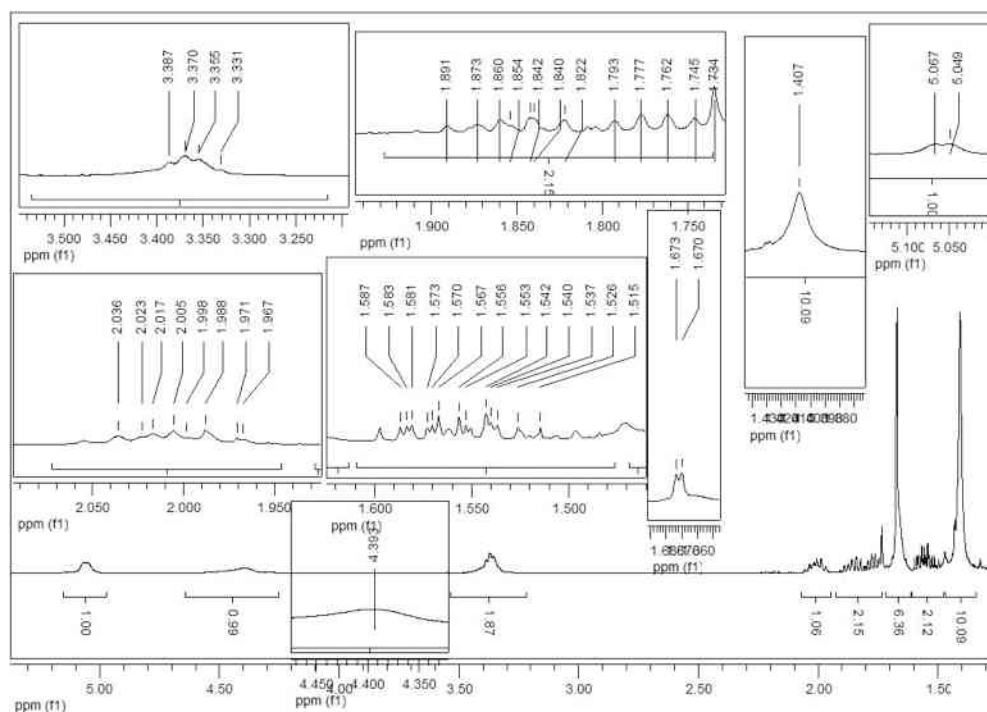


400 MHz ^1H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; CDCl_3

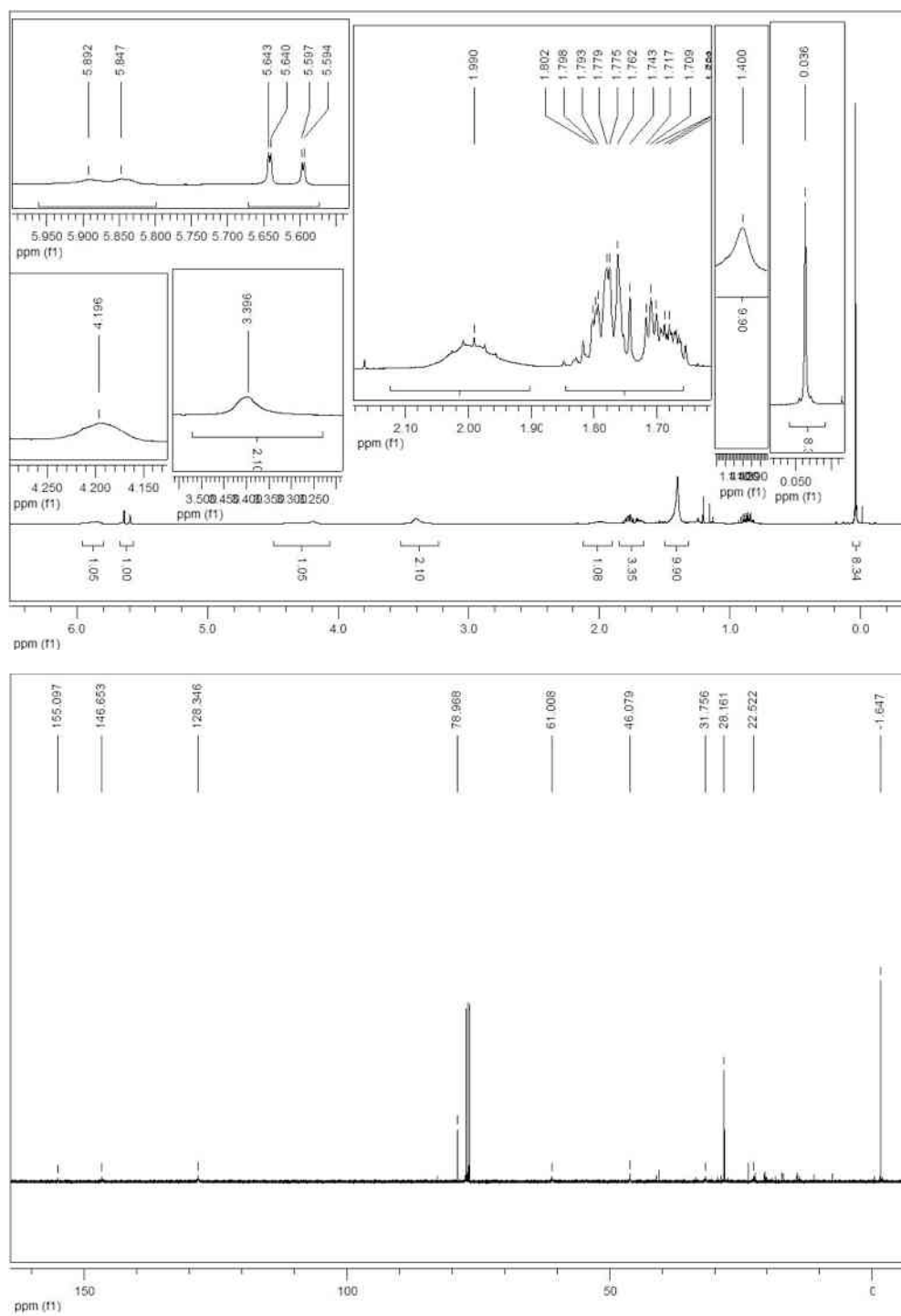
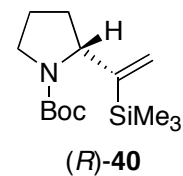


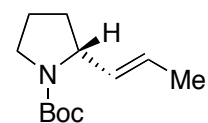
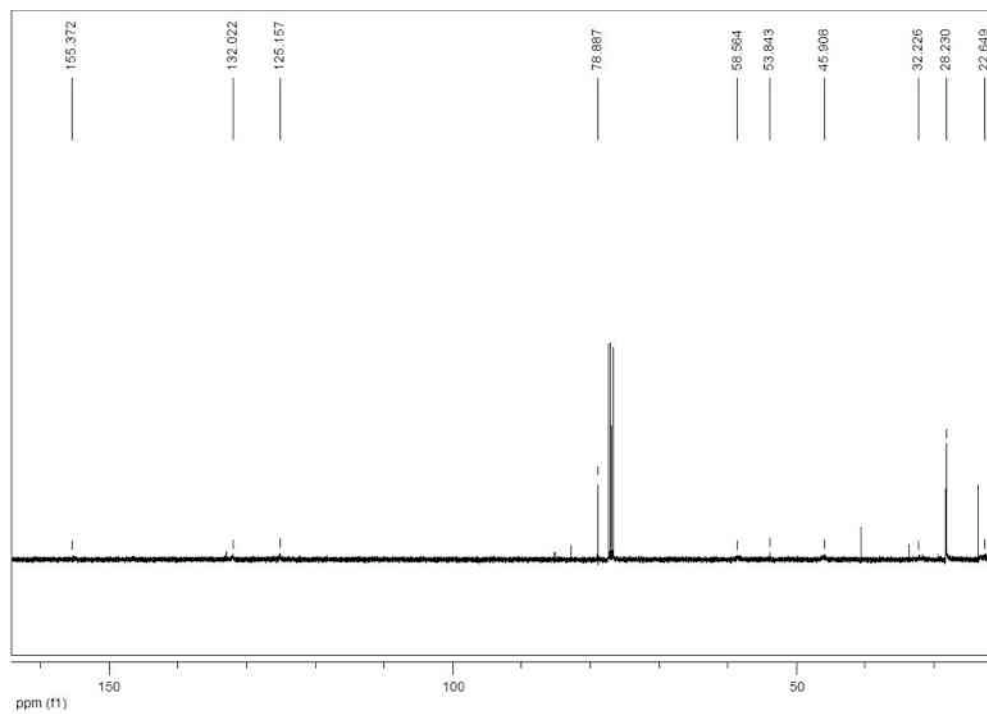
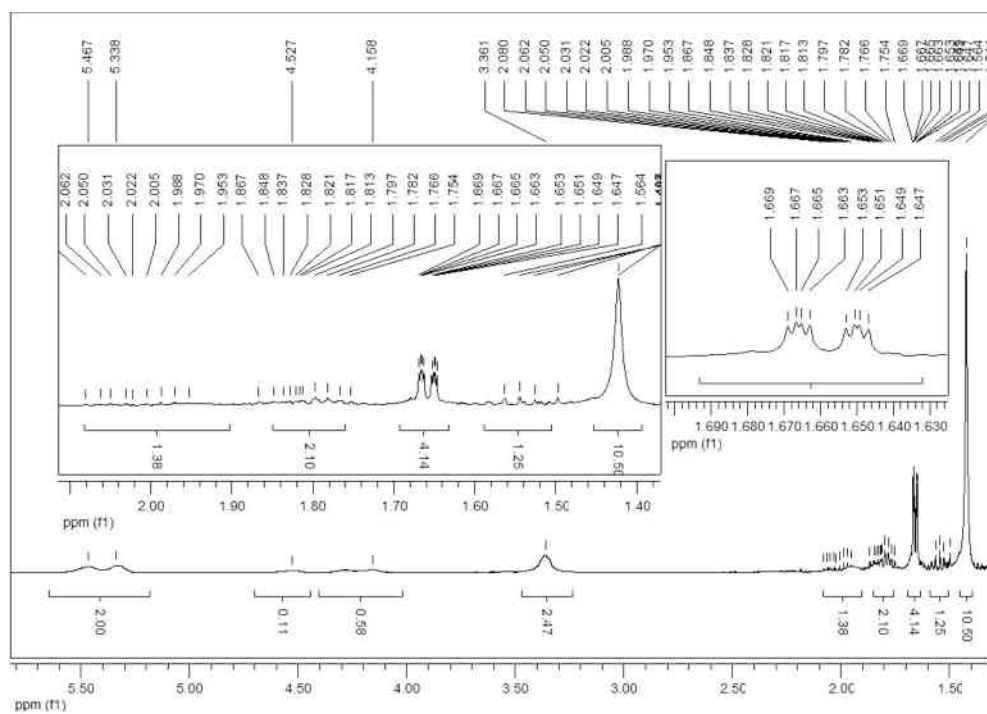
(S)-Nicotine

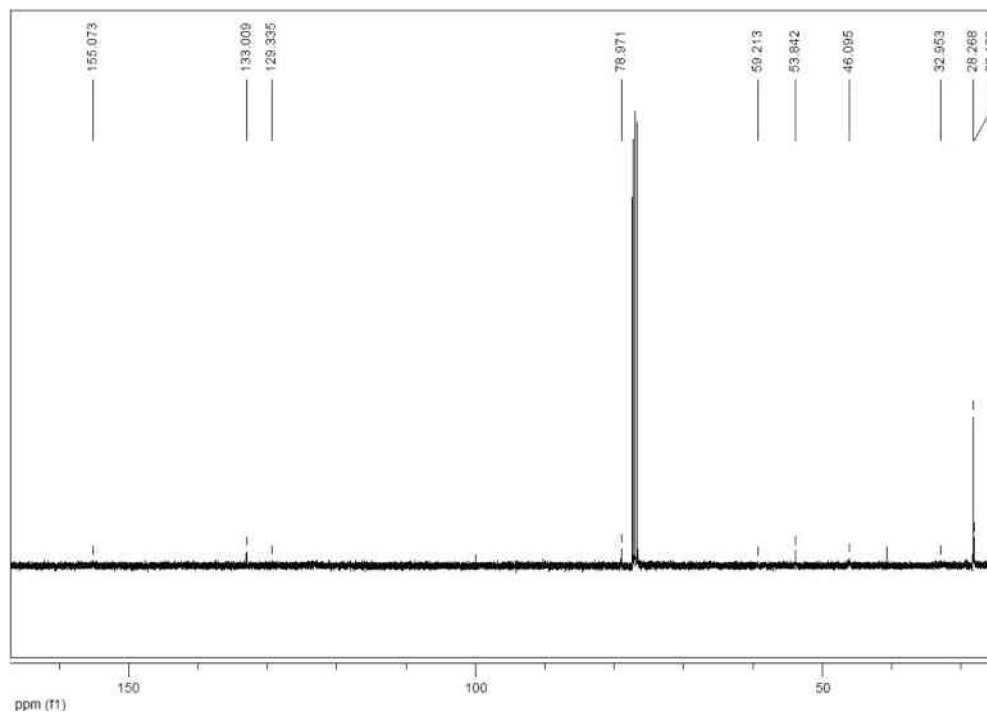
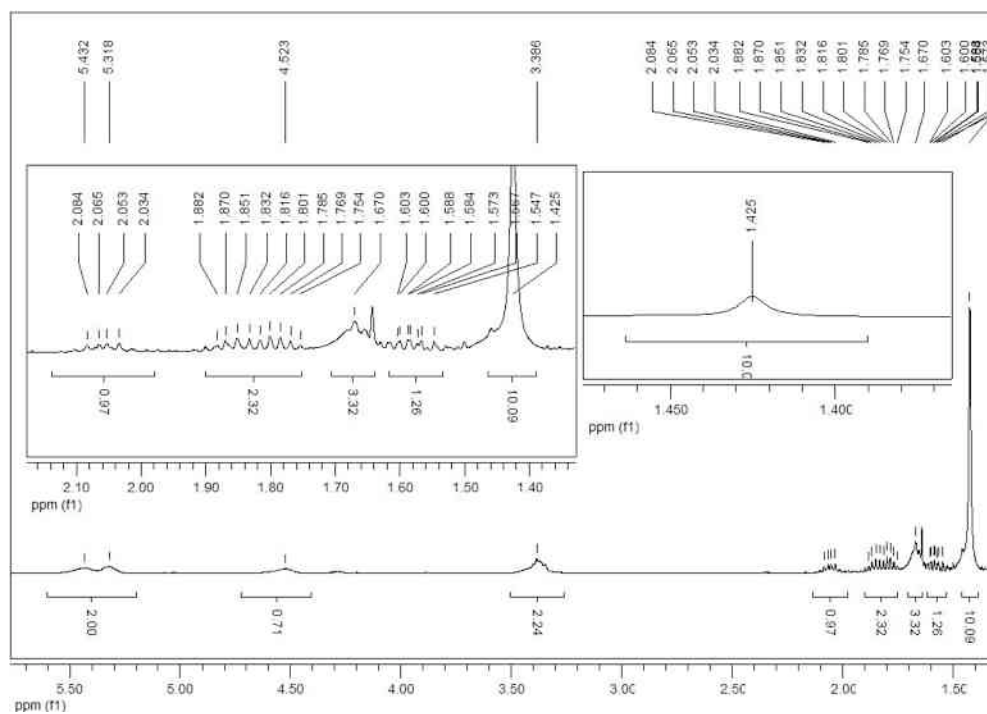
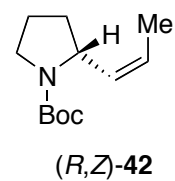


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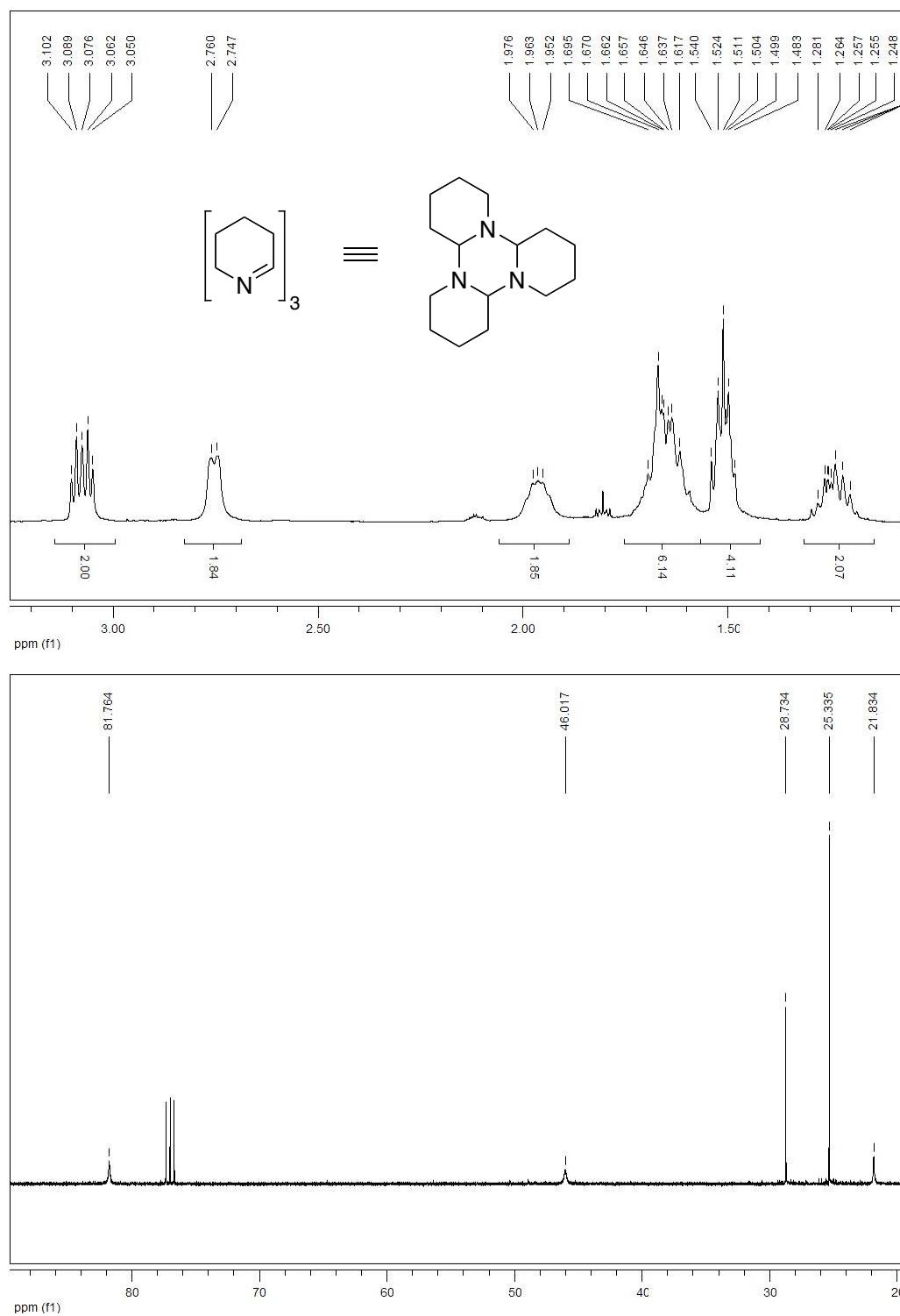
400 MHz ^1H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; CDCl_3

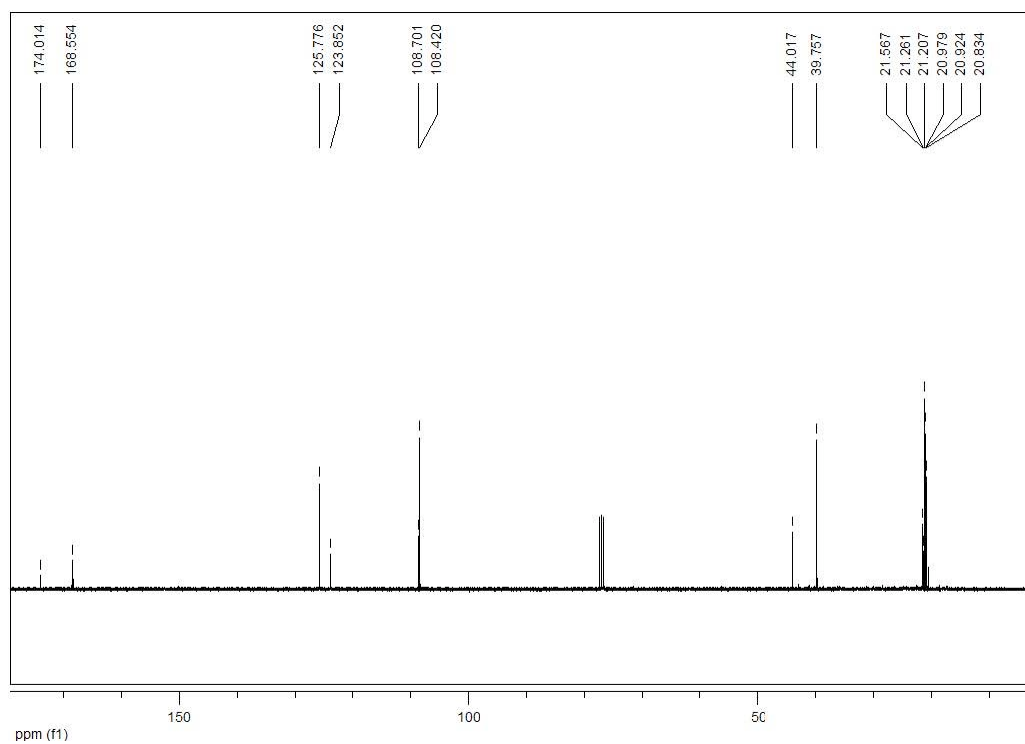
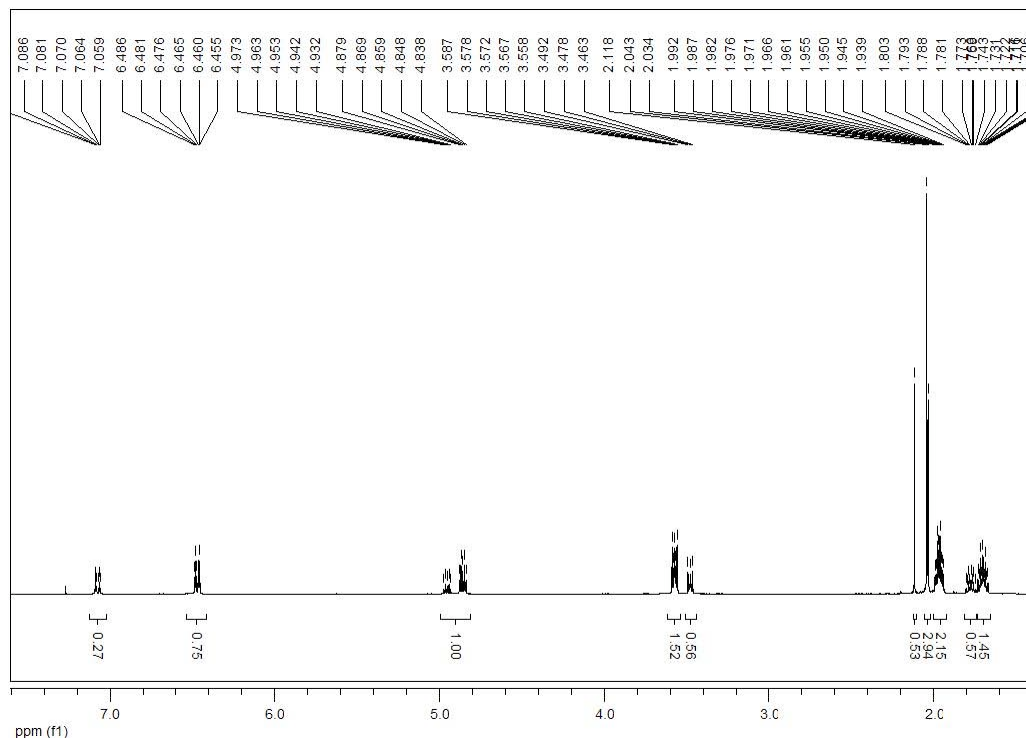
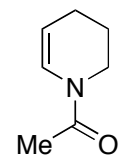


400 MHz ^1H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; CDCl_3 **(*R,E*)-41**

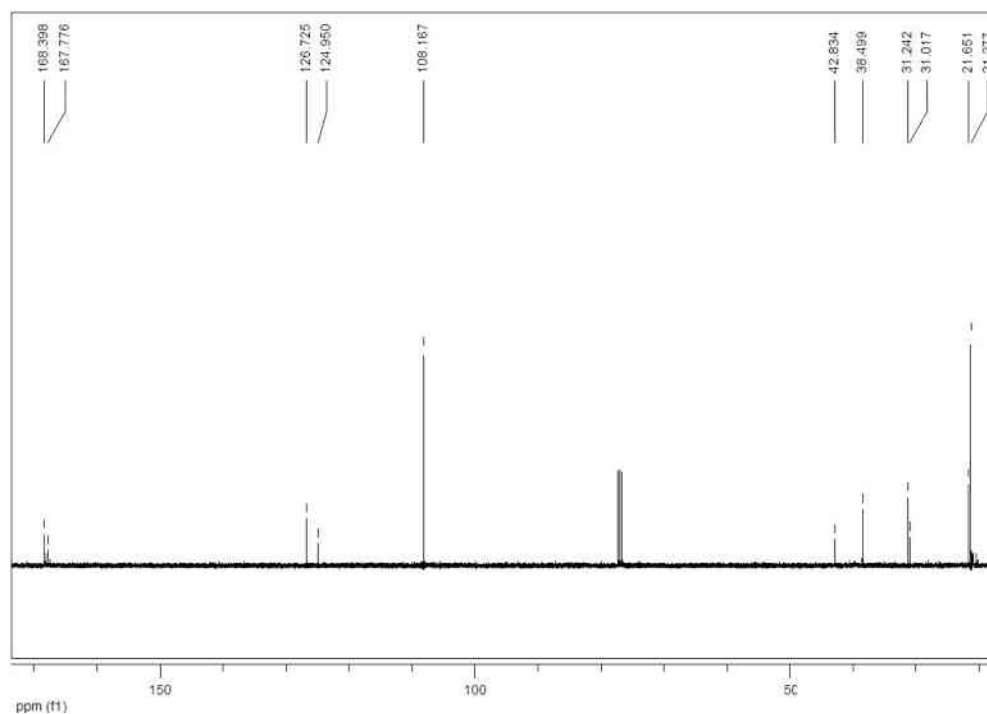
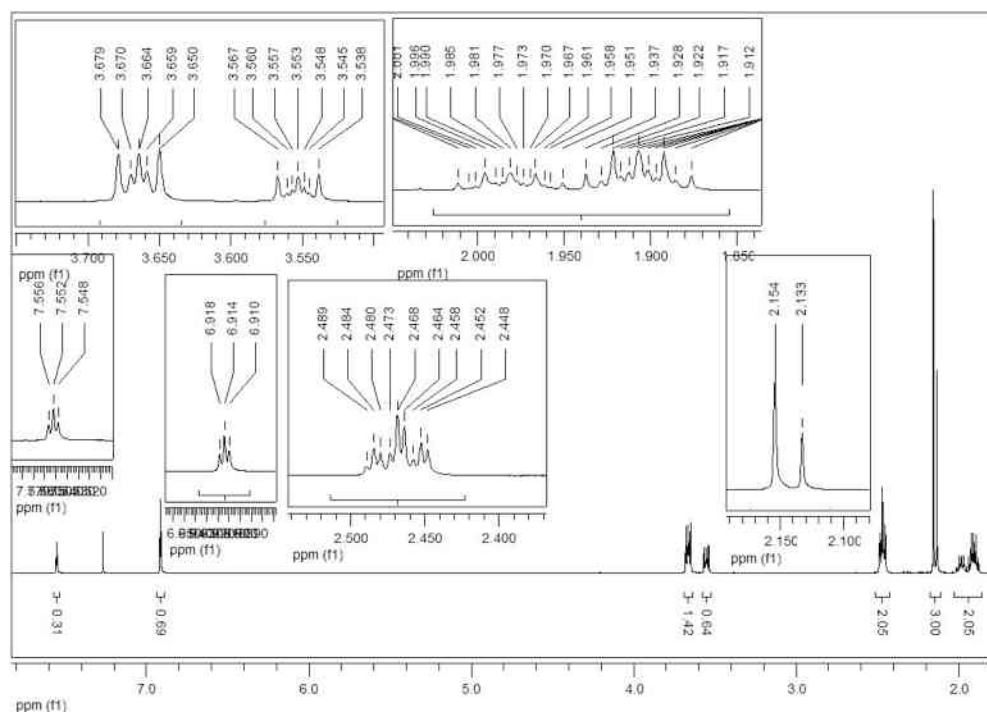
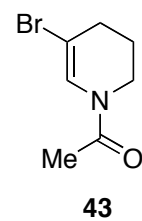
400 MHz ^1H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; CDCl_3 

400 MHz ^1H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; CDCl_3

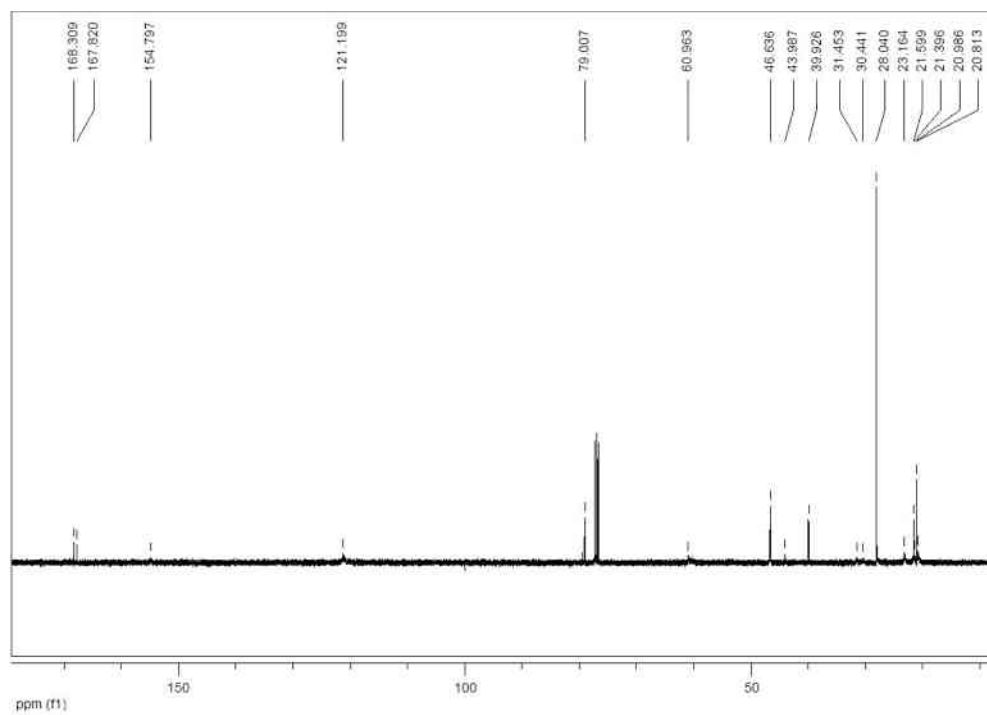
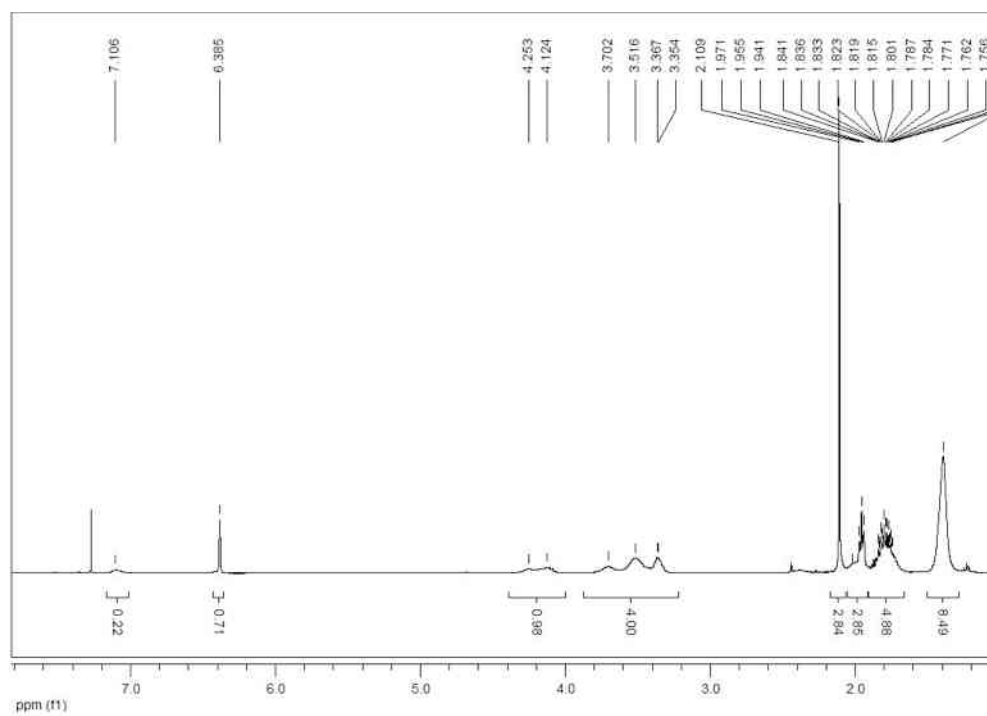
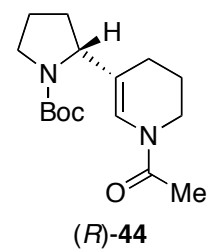


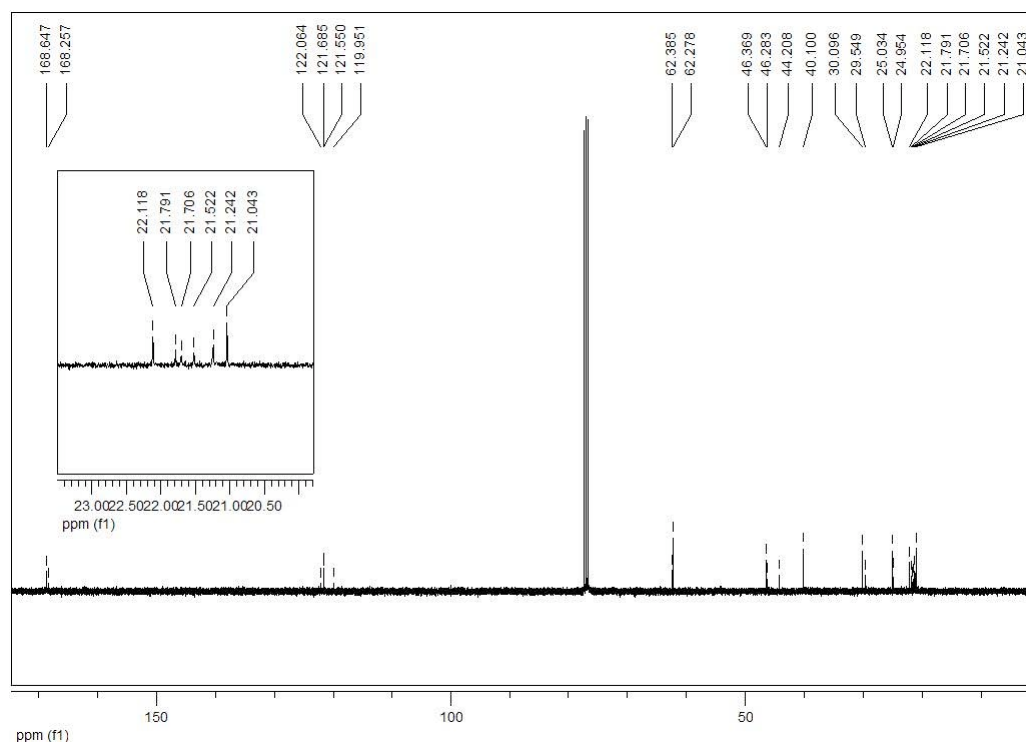
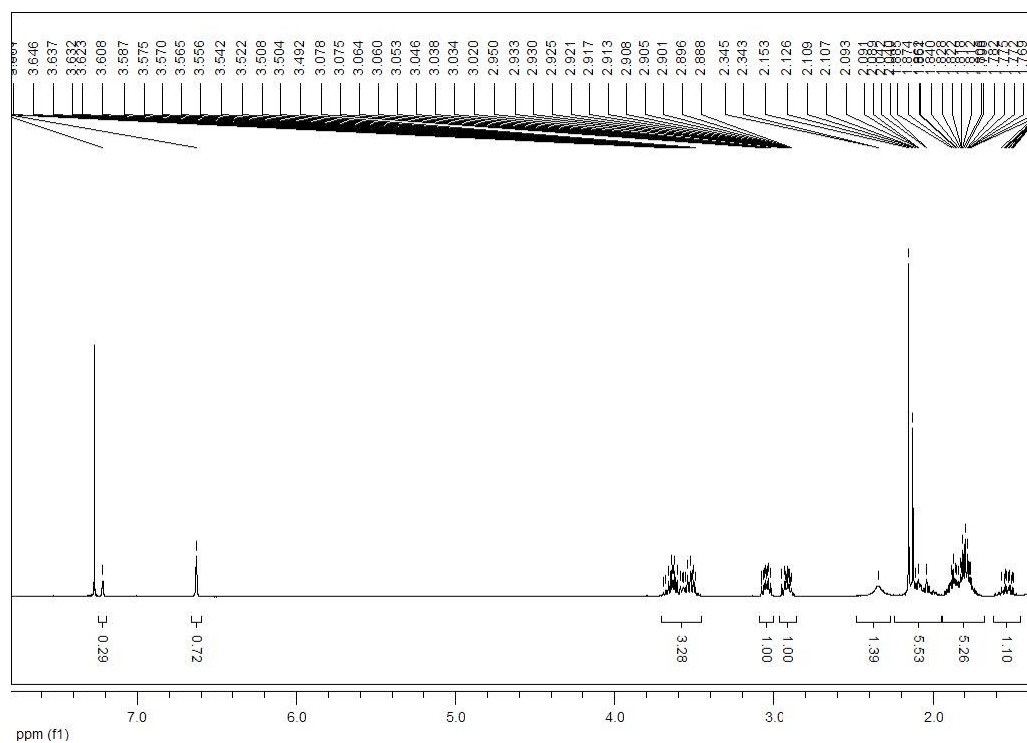
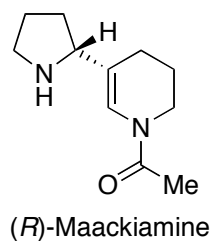
400 MHz ^1H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; CDCl_3 

400 MHz ^1H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; CDCl_3



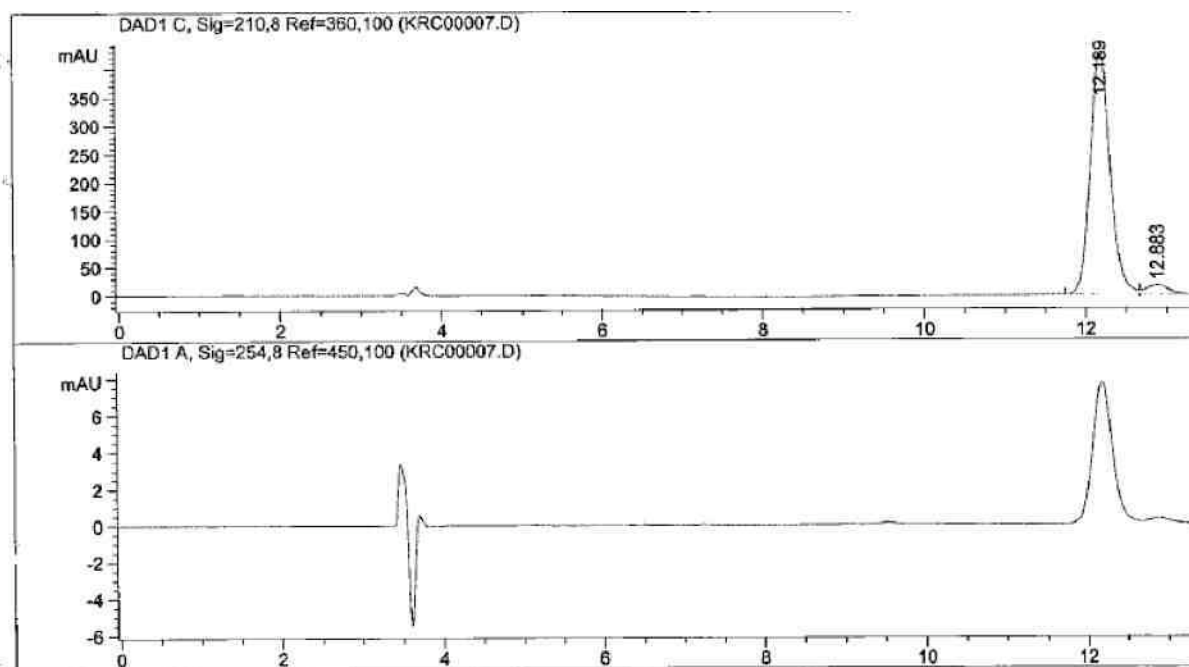
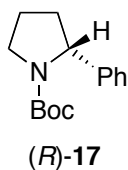
400 MHz ^1H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; CDCl_3



400 MHz ^1H NMR spectrum; 100.6 MHz ^{13}C NMR spectrum; CDCl_3 

5. CSP-HPLC dataCSP-HPLC for (*R*)-17

96:4 er (Table 1, entry 1)

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Area Percent Report
=====

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

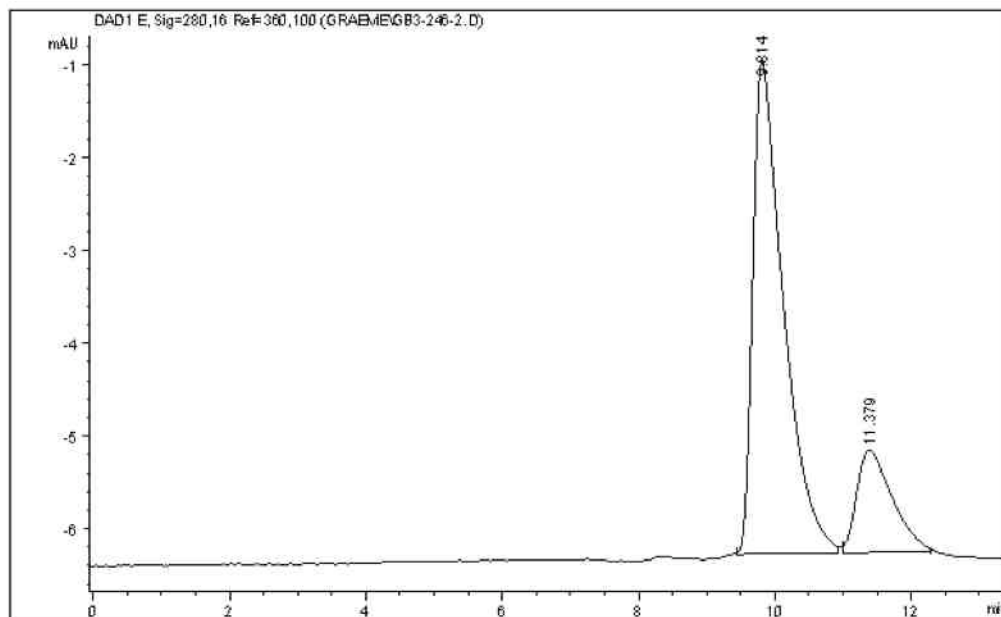
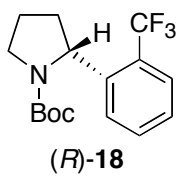
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.189	BV	0.2681	7373.95703	425.77893	96.0975
2	12.883	VB	0.2806	299.45142	15.98518	3.9025

92% er

CSP-HPLC for (*R*)-**18**

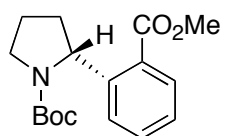
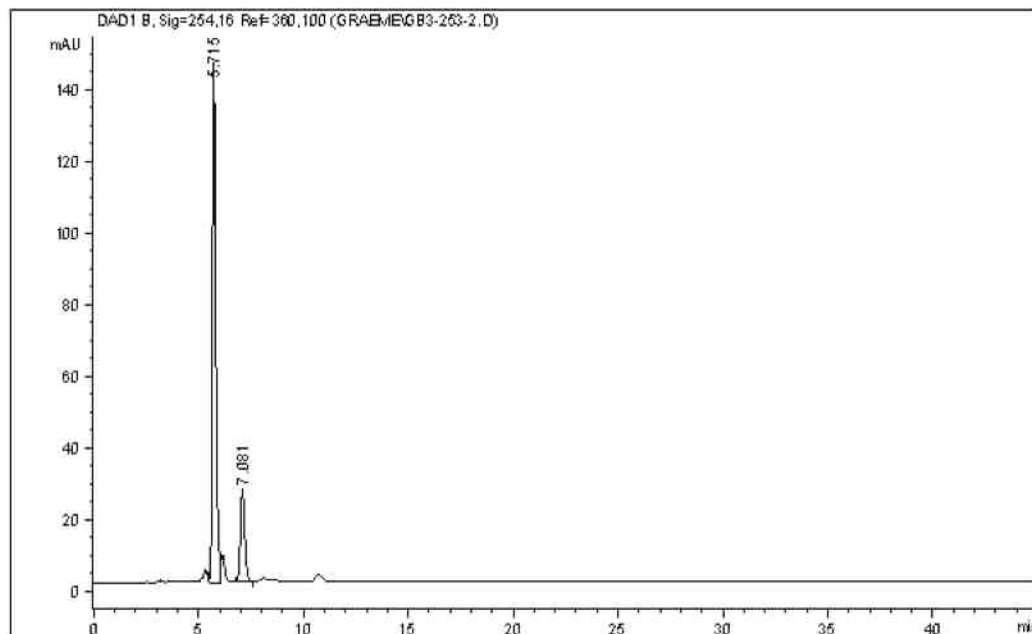
80:20 er (Table 2, entry 2)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.814	BB	0.4364	165.95007	5.31263	80.5763
2	11.379	BB	0.4524	40.00386	1.10492	19.4237

CSP-HPLC for (*R*)-**19**

81:19 er (Table 2, entry 4)

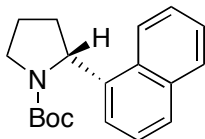
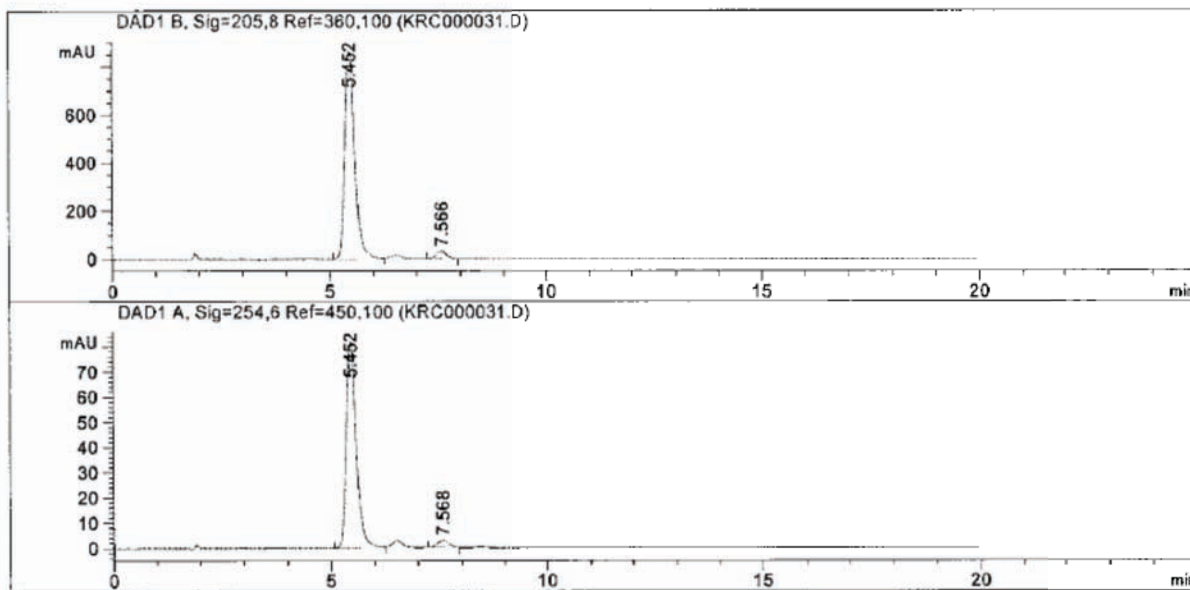
*(R)*-**19**

Signal 1: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.715	VV	0.1726	1650.36365	145.21695	81.2764
2	7.081	BV	0.2232	380.19266	25.90643	18.7236

CSP-HPLC for (*R*)-**20**

96:4 er (Table 1, entry 9)

*(R)*-**20**=====
Area Percent Report
=====

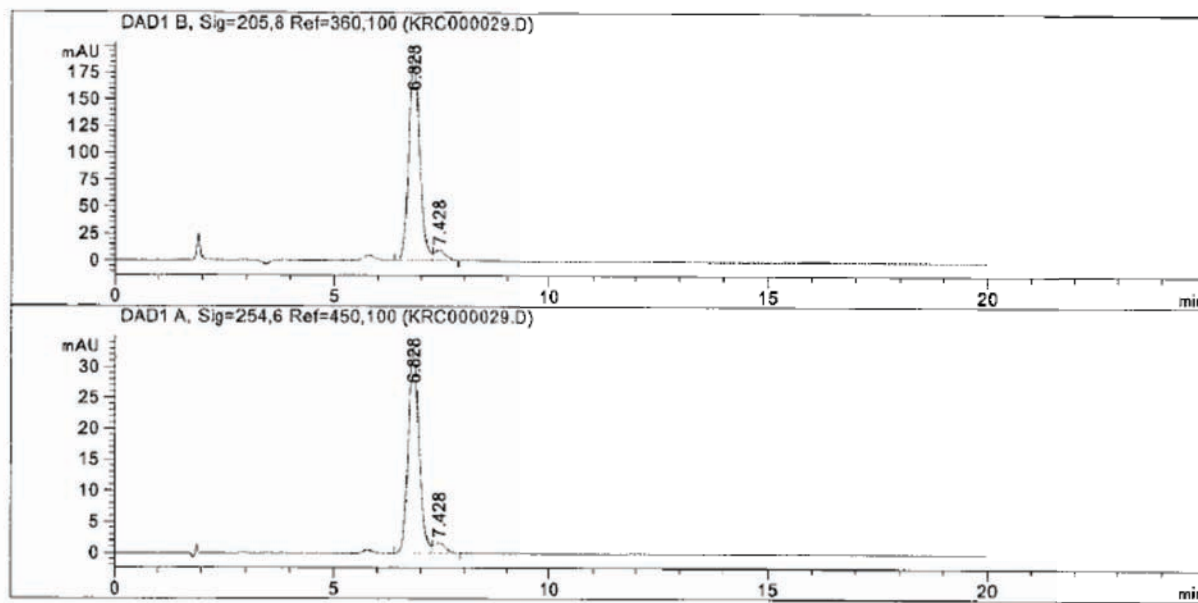
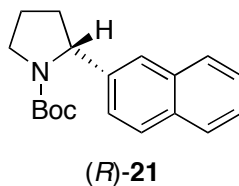
Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 B, Sig=205,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.452	MF	0.2603	1.34624e4	862.05835	96.2568
2	7.566	MM	0.2884	523.52539	30.25759	3.7432

CSP-HPLC for (*R*)-**21**

95:5 er (Table 1, entry 10)

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Area Percent Report
=====

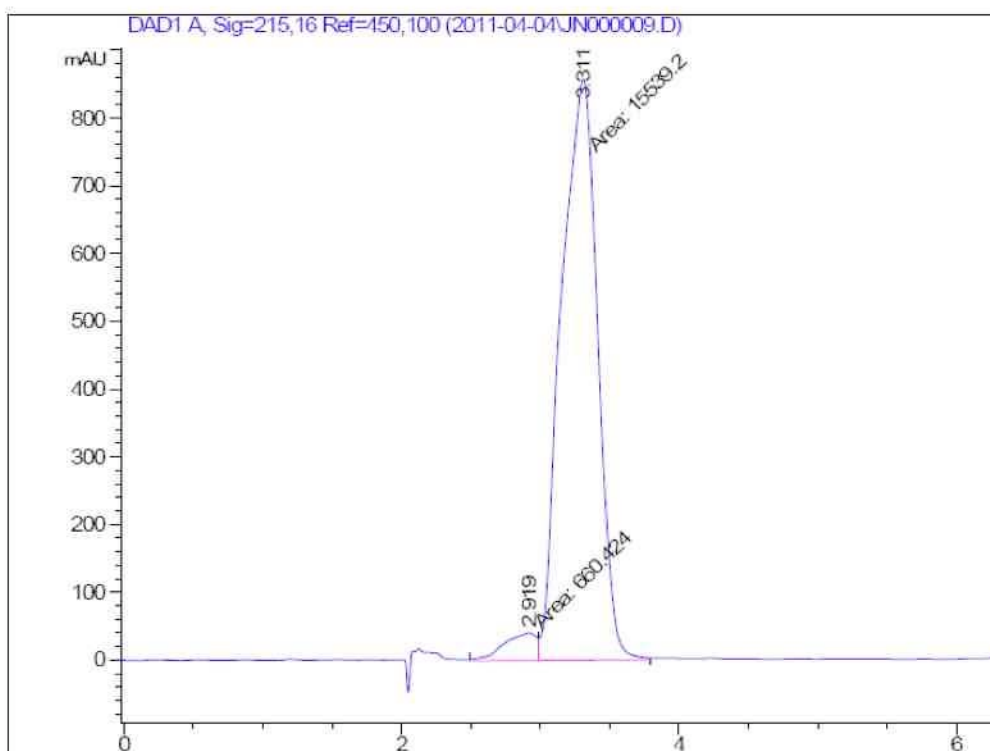
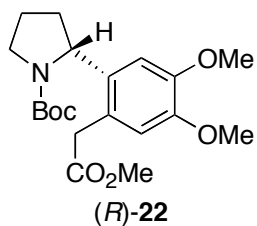
Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 B, Sig=205,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.828	MF	0.2892	3343.40015	192.64951	94.9344
2	7.428	PM	0.3103	178.39935	9.58354	5.0656

CSP-HPLC for (*R*)-**22**

96:4 er (Scheme 4)



Area Percent Report

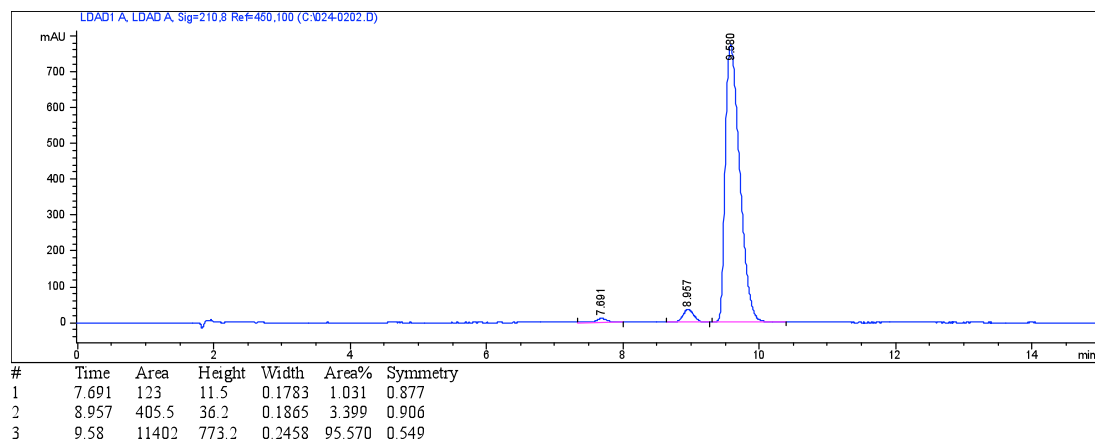
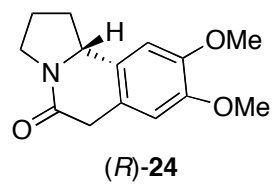
Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=215,16 Ref=450,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.919	MF	0.2702	660.42432	40.74096	4.0768
2	3.311	FM	0.3021	1.55392e4	857.37701	95.9232

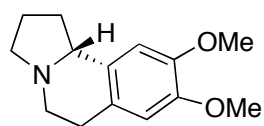
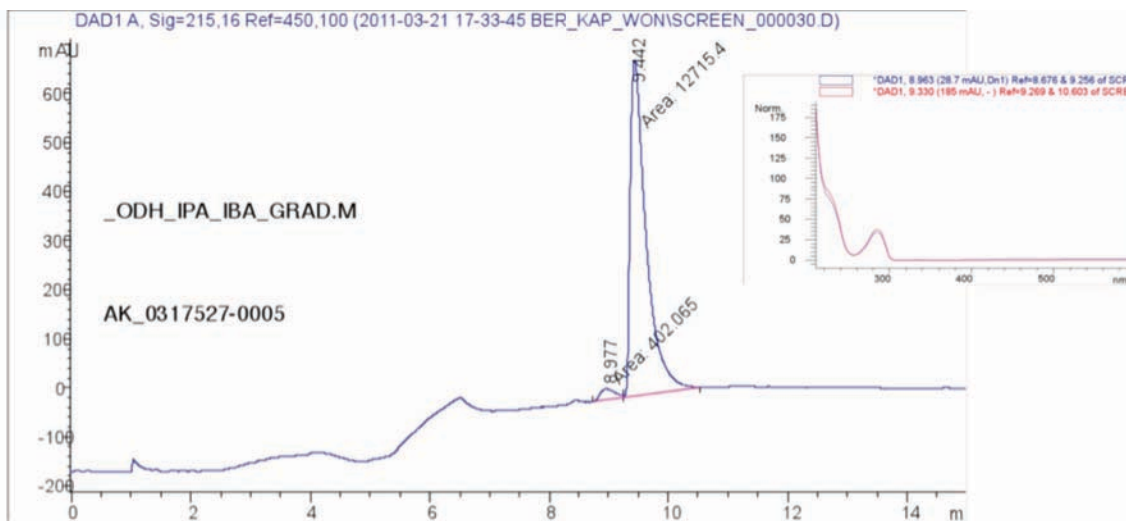
CSP-HPLC for (*R*)-**24**

96:4 er (Scheme 4)



CSP-HPLC for (*R*)-crispine A

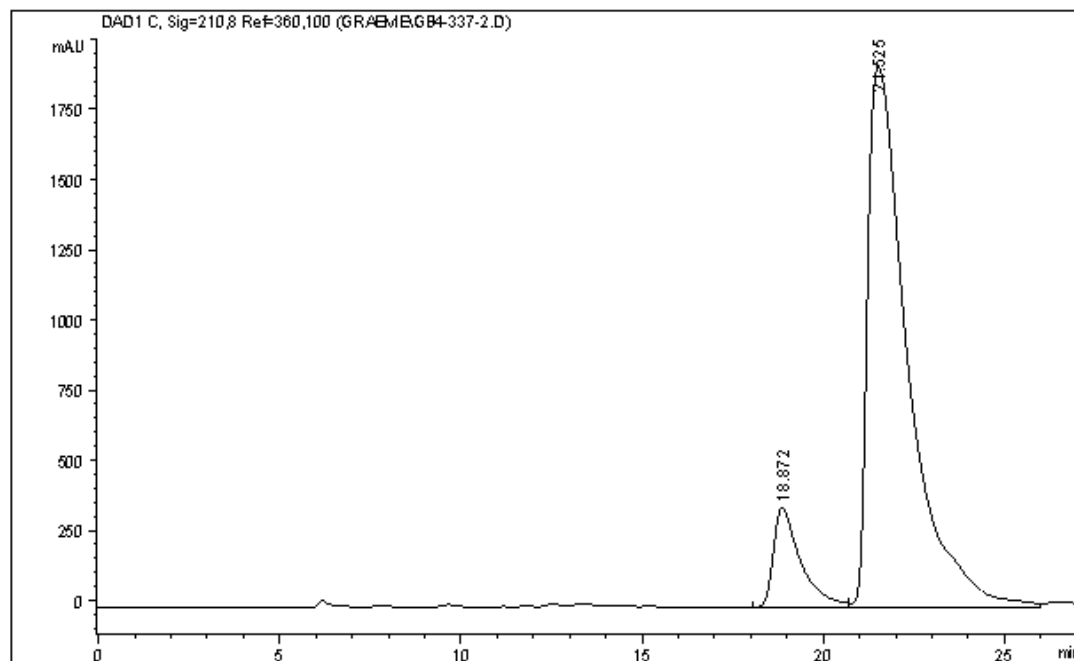
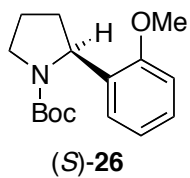
97:3 er (Scheme 4)

*(R)*-Crispine A

#	Time	Area	Height	Width	Area%	Symmetry
1	8.977	402.1	23	0.2915	3.065	0.879
2	9.442	12715.4	685.9	0.309	96.935	0.388

CSP-HPLC for (S)-**26**

89:11 er (Scheme 5)

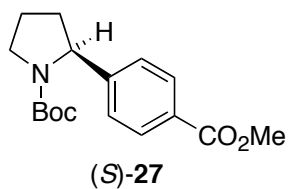


Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.872	VV	0.7522	1.85472e4	355.77158	11.1322
2	21.525	VV	1.1444	1.48062e5	1926.94873	88.8678

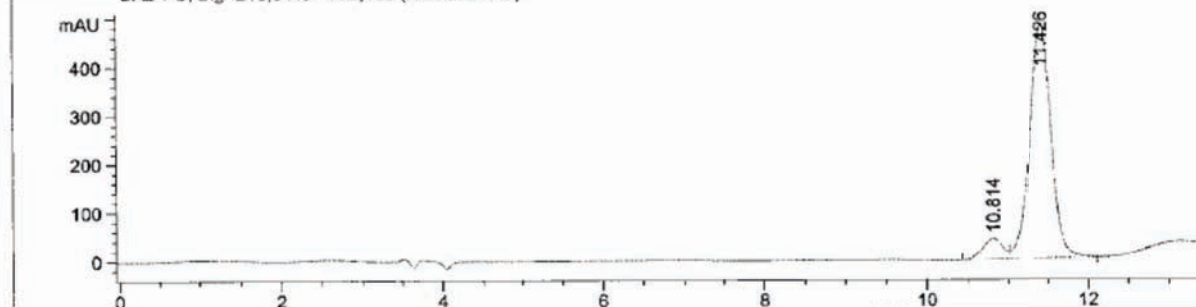
CSP-HPLC for (*S*)-**27**

93:7 er (Table 2, entry 8)

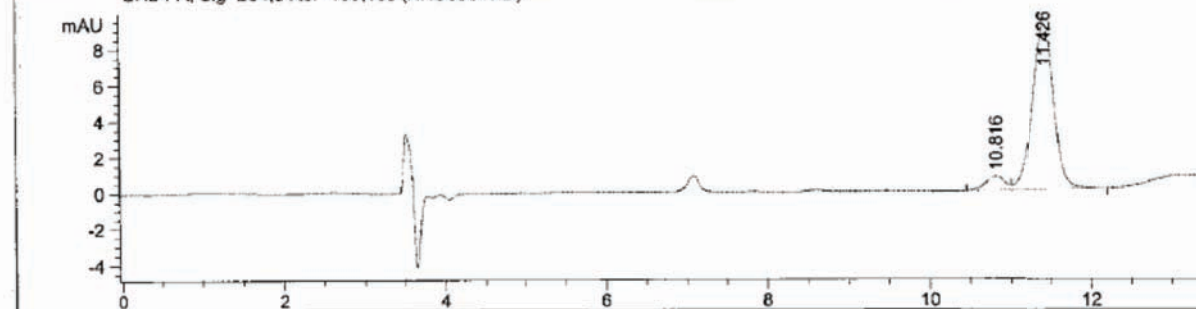


AD-H isocratic 2% iPA-Heptane

DAD1 C, Sig=210,8 Ref=360,100 (KRC00043.D)



DAD1 A, Sig=254,8 Ref=450,100 (KRC00043.D)



Area Percent Report

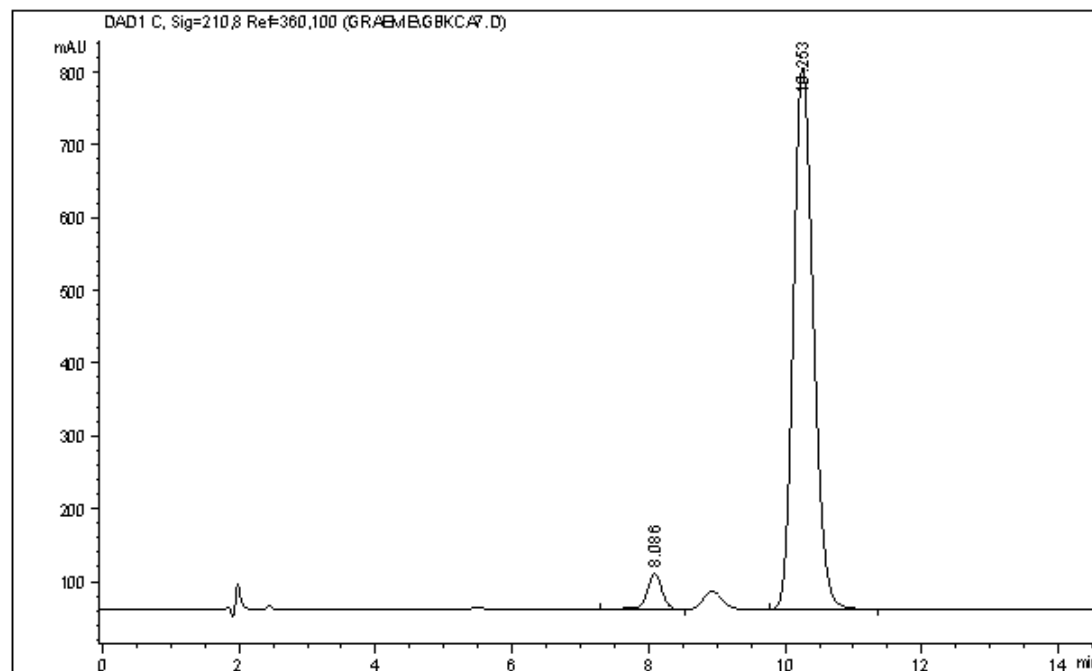
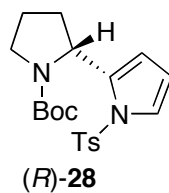
Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.814	MF	0.2771	707.09485	42.52843	7.3171
2	11.426	FM	0.3091	8956.52734	482.99701	92.6829

CSP-HPLC for (*R*)-**28**

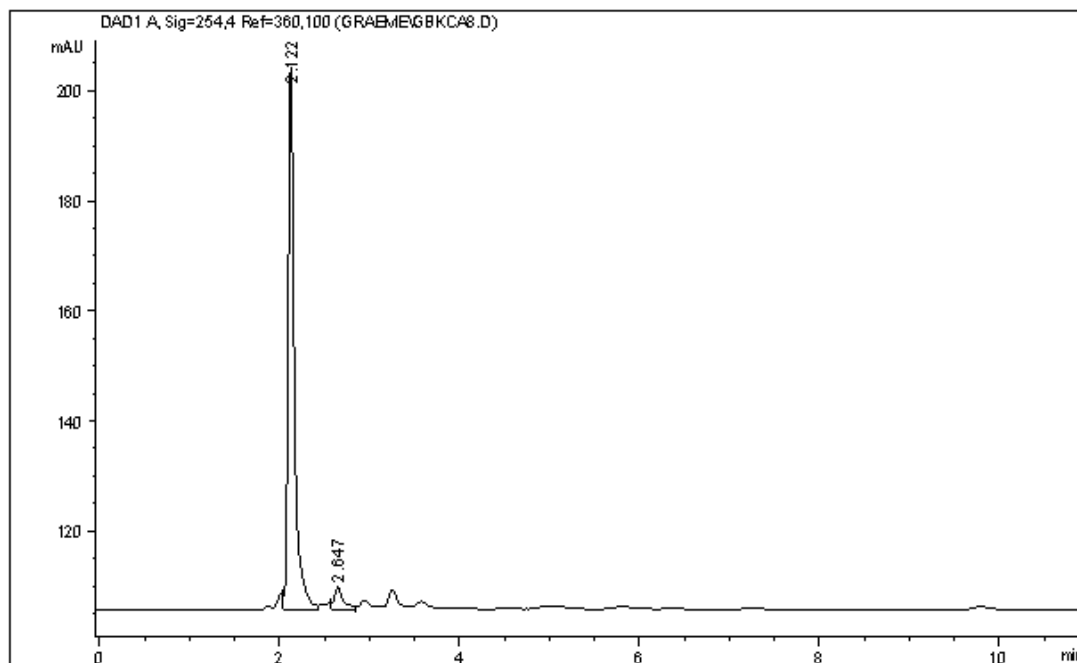
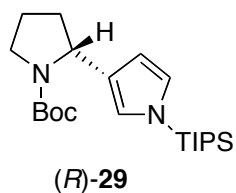
95:5 er (Scheme 6)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.086	BV	0.2384	790.78601	50.02863	4.9482
2	10.253	BB	0.3179	1.51906e4	744.84204	95.0518
Totals :				1.59814e4	794.87067	

CSP-HPLC for (*R*)-**29**

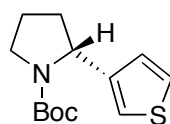
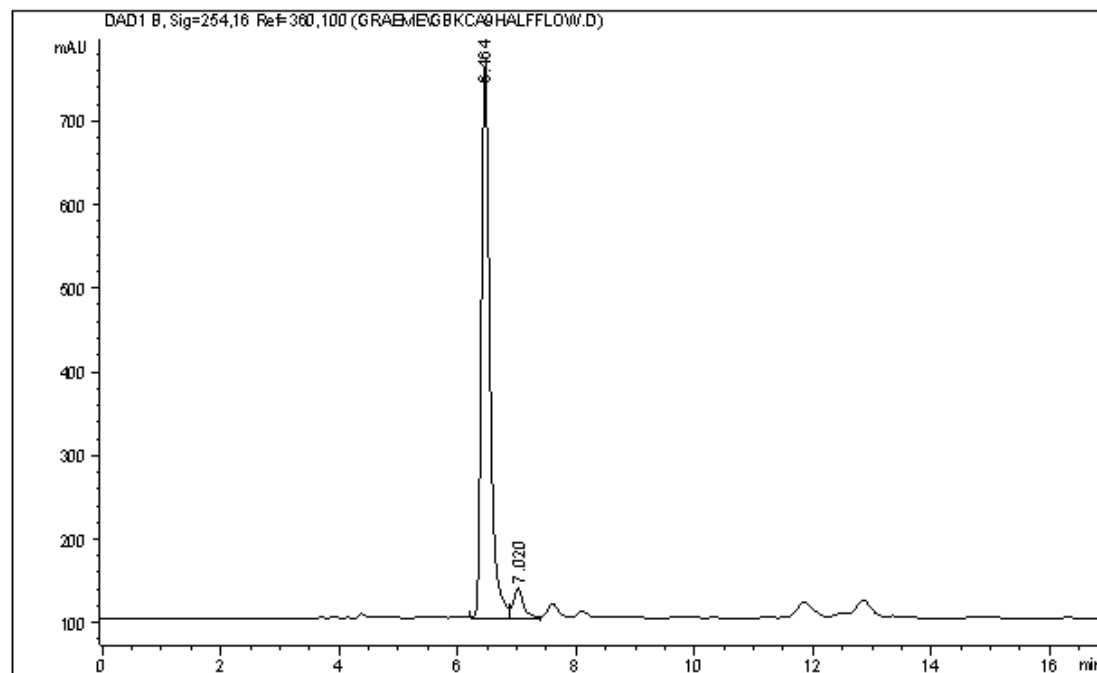
94:6 er (Scheme 6)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.122	VV	0.0717	473.49725	99.11206	94.3799
2	2.647	VV	0.0989	28.19583	4.06858	5.6201
Totals :				501.69308	103.18065	

CSP-HPLC for (*R*)-**30**

94:6 er (Scheme 6)

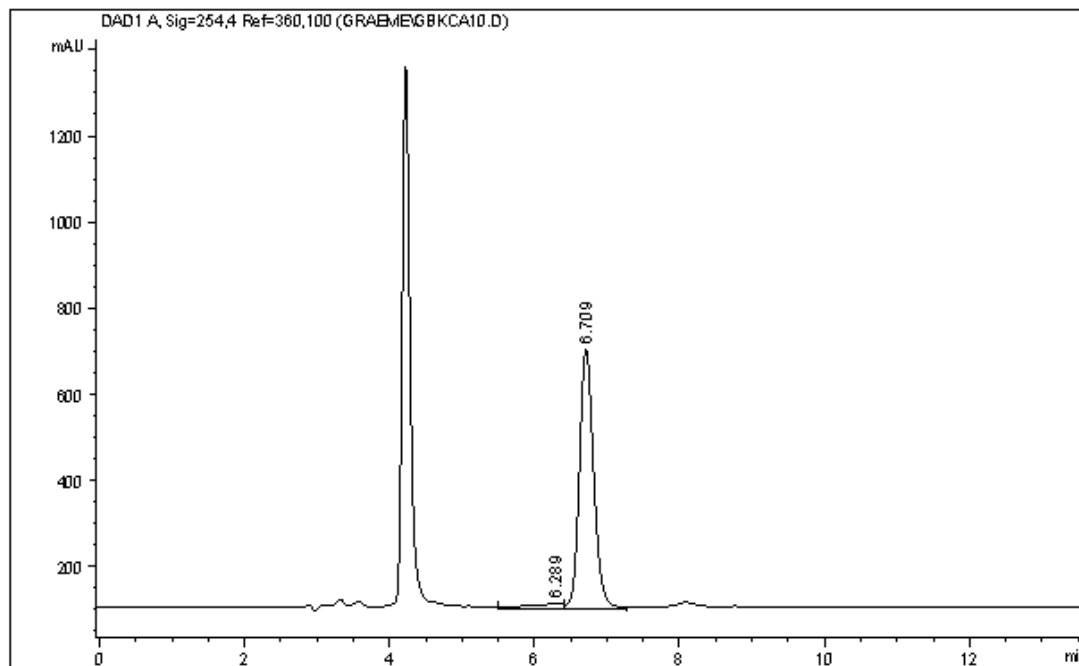
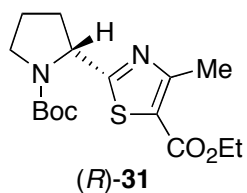
**(*R*)-30**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.464	VV	0.1538	6656.19824	659.27527	94.0697
2	7.020	VV	0.1718	419.61673	35.51915	5.9303

Totals : 7075.81497 694.79442

CSP-HPLC for (*R*)-**31**

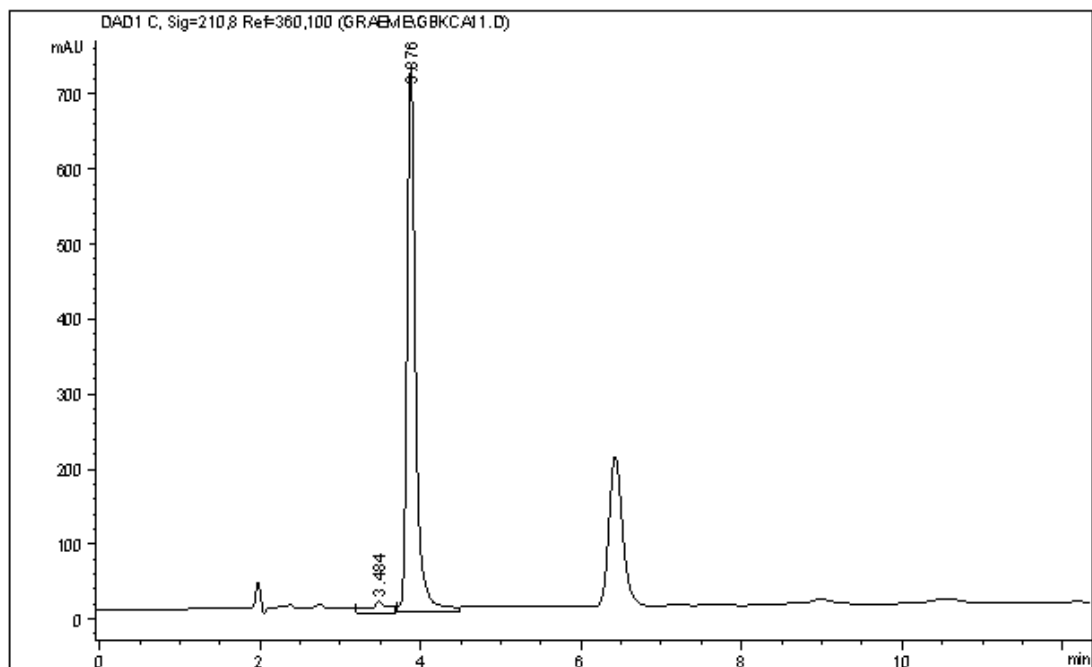
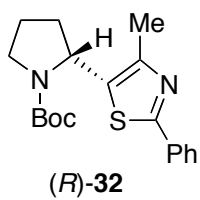
94:6 er (Scheme 6)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.289	BV	0.4796	551.93439	15.05926	6.1809
2	6.709	VV	0.2140	8377.72168	603.46490	93.8191
Totals :				8929.65607	618.52416	

CSP-HPLC for (*R*)-**32**

95:5 er (Scheme 6)

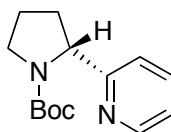
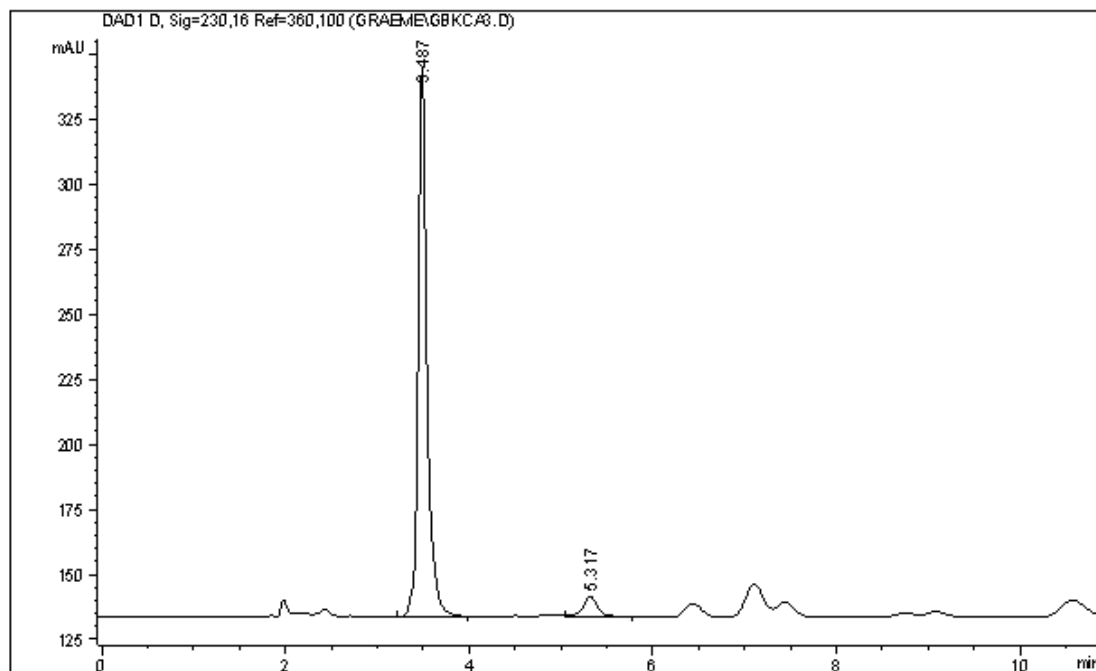


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.484	BB	0.2134	256.30411	15.62017	4.4987
2	3.876	BB	0.1111	5440.93115	729.07861	95.5013

Totals : 5697.23526 744.69879

CSP-HPLC for (*R*)-**34**

94:6 er (Scheme 6)

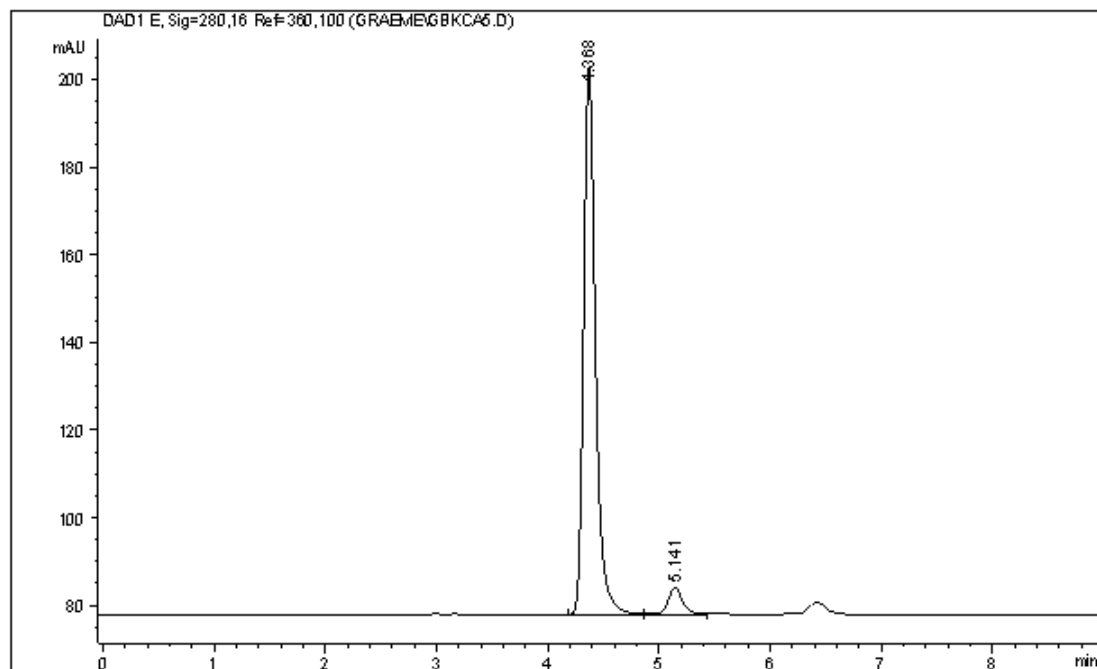
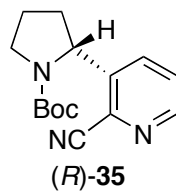
**(*R*)-34**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.487	VB	0.0979	1416.47241	212.05295	93.8705
2	5.317	VB	0.1742	92.49261	7.92538	6.1295

Totals : 1508.96502 219.97833

CSP-HPLC for (*R*)-**35**

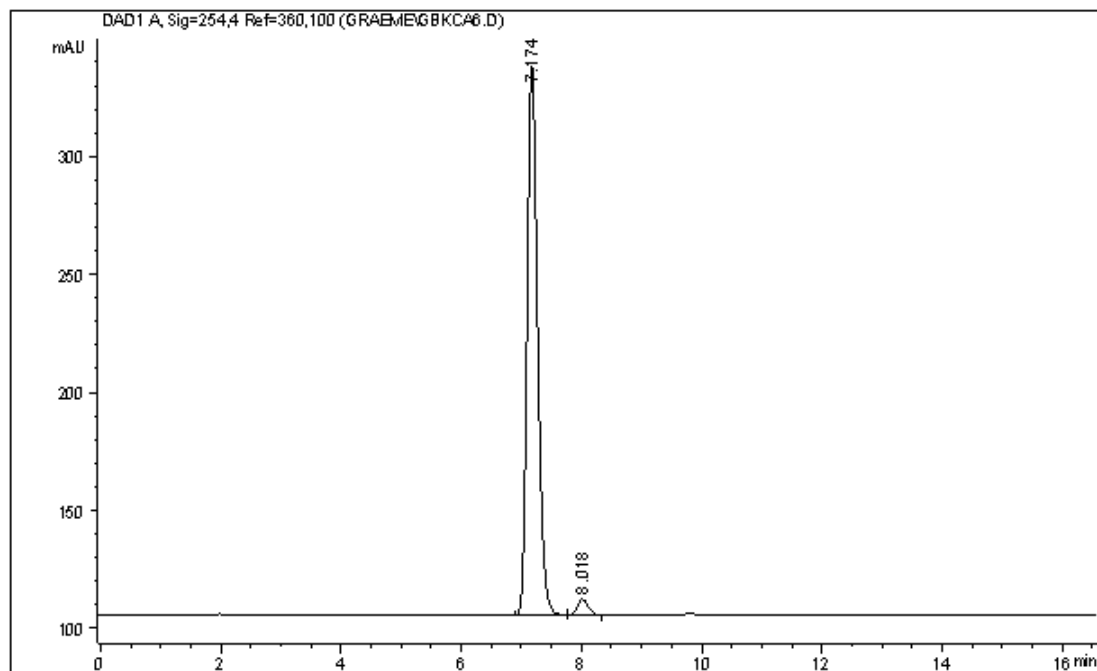
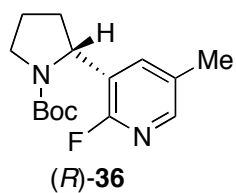
94:6 er (Scheme 6)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.368	BV	0.1125	928.55933	125.21604	94.1881
2	5.141	VV	0.1399	57.29731	6.19571	5.8119
Totals :				985.85664	131.41175	

CSP-HPLC for (*R*)-**36**

97:3 er (Scheme 6)

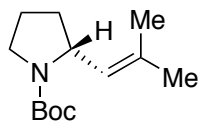
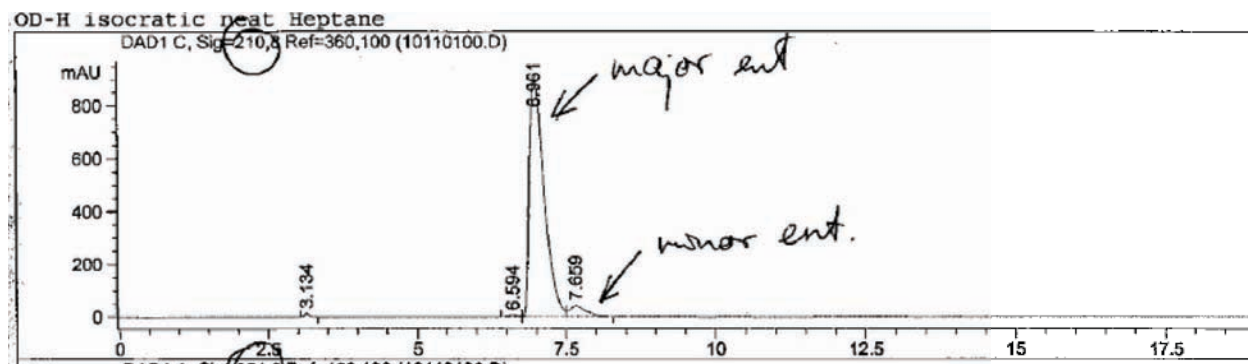


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.174	BV	0.1851	2819.88696	233.08038	96.8246
2	8.018	VV	0.2048	92.47945	6.88065	3.1754

Totals : 2912.36641 239.96104

CSP-HPLC for (*R*)-39

95:5 er (Scheme 9)

*(R)*-39

Area Percent Report

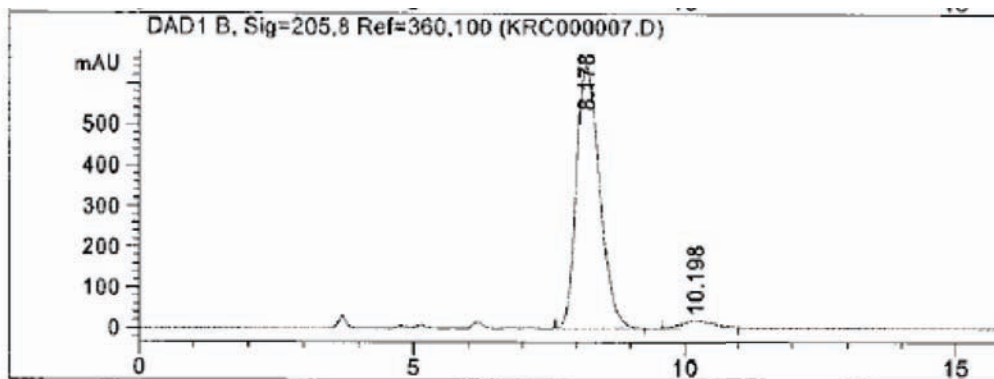
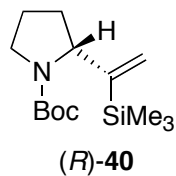
Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.134	BP	0.0833	64.19637	11.82797	0.3767
2	6.594	BV	0.1637	68.69412	6.37782	0.4030
3	6.961	VV	0.2703	1.61270e4	921.06824	94.6213
4	7.659	VB	0.2616	783.84241	42.41903	4.5990

CSP-HPLC for (*R*)-40

97:3 er (Scheme 9)

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Area Percent Report
=====

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

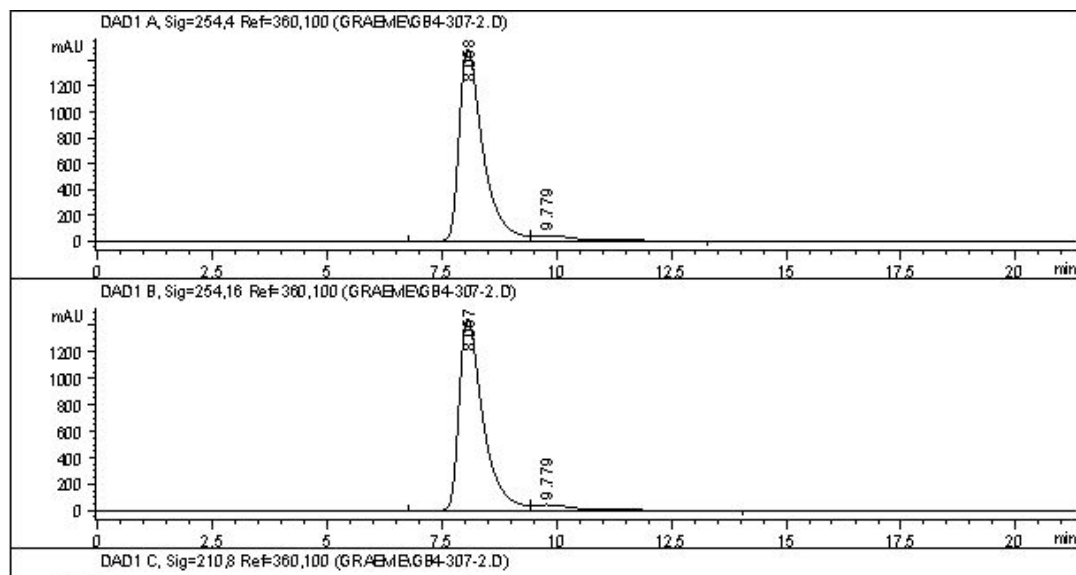
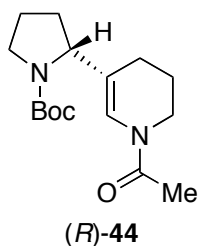
Signal 1: DAD1 A, Sig=254,6 Ref=450,100

Signal 2: DAD1 B, Sig=205,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.178	BB	0.4740	1.95447e4	644.04871	96.6590
2	10.198	MM	0.6495	675.56854	17.33514	3.3410

CSP-HPLC for (*R*)-44

95:5 er (Scheme 10)



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.058	VV	0.5391	5.34556e4	1488.12866	95.1469
2	9.779	VB	0.9150	2726.55347	43.04678	4.8531

Totals : 5.61822e4 1531.17544

Signal 2: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.057	VV	0.5399	5.23360e4	1454.17102	95.1102
2	9.779	VB	0.9237	2690.67603	42.21072	4.8898

Totals : 5.50267e4 1496.38174