

A Convenient Enantioselective CBS-Reduction of Arylketones in Flow-Microreactor Systems

Sonia De Angelis,^a Maddalena De Renzo,^a Claudia Carlucci,^a

Leonardo Degennaro,^{*,a} and Renzo Luisi^{*,a}

^a Department of Pharmacy ó Drug Sciences, University of Bari ðA. Moroö; FLAME-Lab ó Flow Chemistry and Microreactor Technology Laboratory, Via E. Orabona 4, I-70125.

E-mail renzo.luisi@uniba.it; leonardo.degennaro@uniba.it

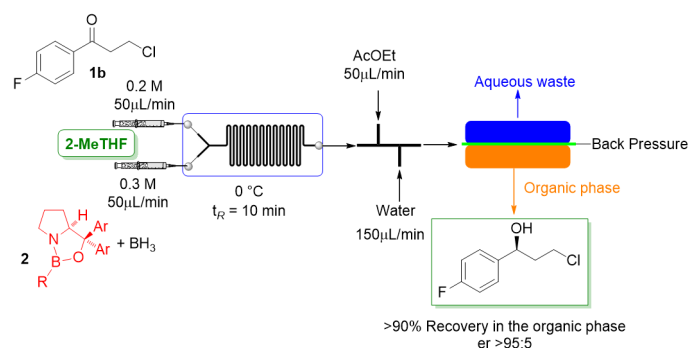
Phone: (+39)-080-5442762; fax: (+39)-080-5442739

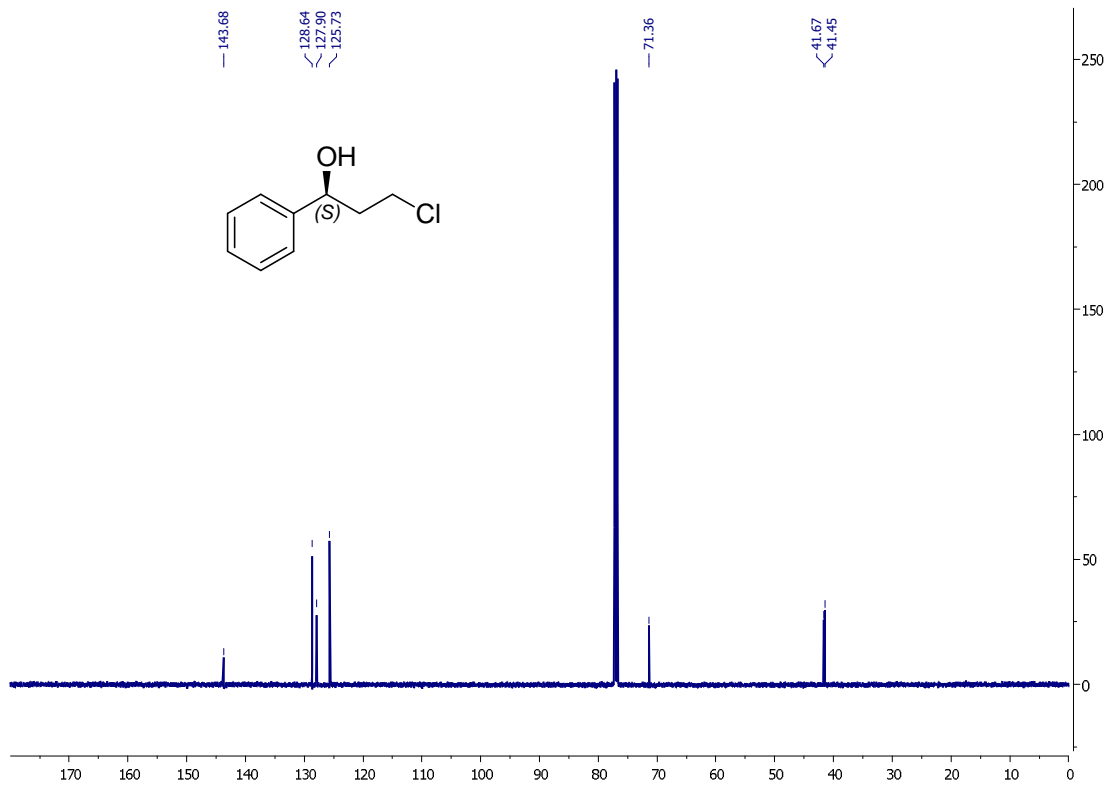
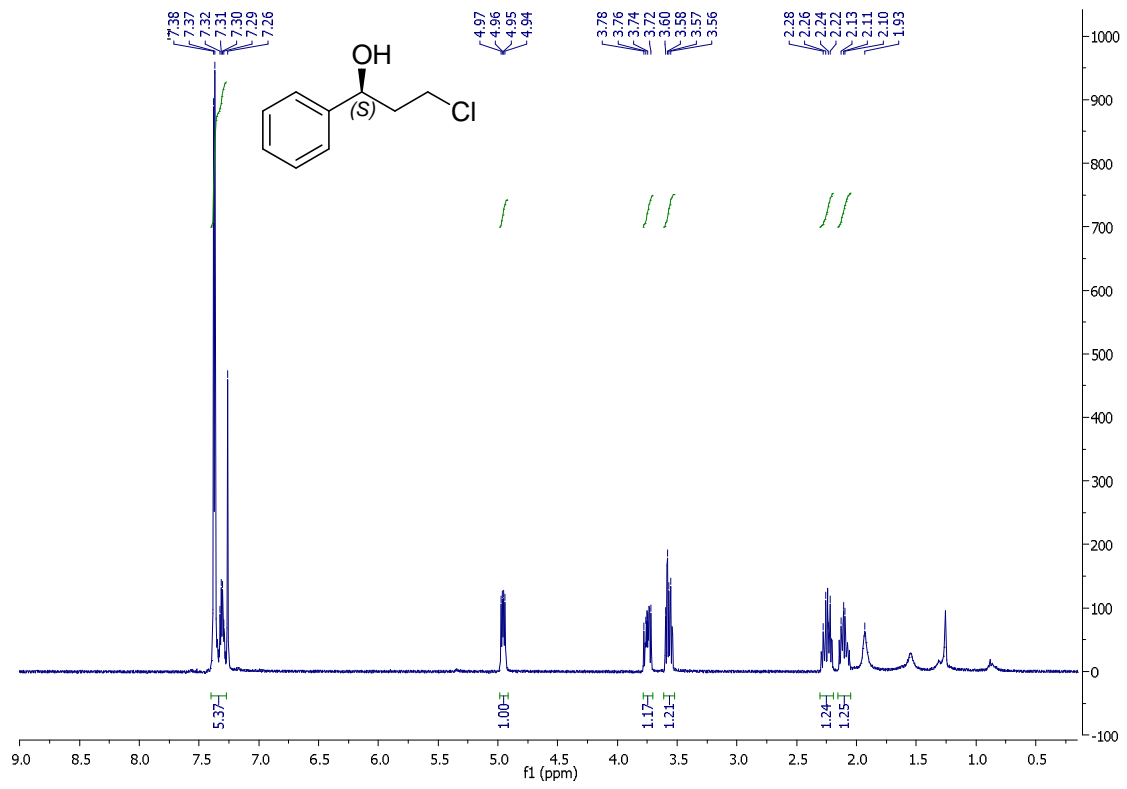
Contents:

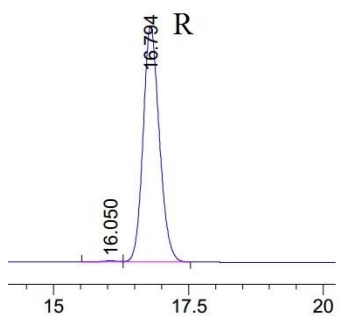
Procedure for the continuous flow reduction and in-line liquid/liquid extraction	S2
NMR spectra and HPLC traces	S3-S35

Procedure for the continuous flow reduction and in-line liquid/liquid extraction

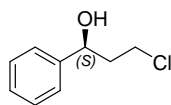
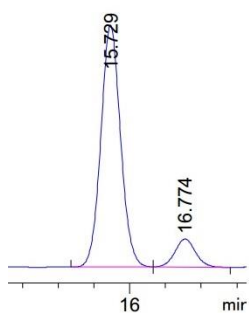
The process was executed using Asia[®] syringe pumps by Syrris that continuously deliver solutions of reactants from stock containers of suitable volume (minimum 50 mL). The following solutions were prepared and filtered with PTFE filters with a porosity of 0.2 μm : (i) 10 mL, 0.2 M in 2-MeTHF of ketone **1b** (2 mmol, 372 mg); (ii) 10 mL, 0.3 M of BH_3 in 85% 2-MeTHF, obtained by diluting with 2-MeTHF a 1 M commercial solution of BH_3 in THF. To solution (ii), the catalyst (*R*)-CBS 2 (8 mol% with respect to ketone **1b**) was added, and cooled at 0° C with an ice bath. Those solutions were pumped into the microreactor kept at 0°C with an ice bath at a flow rate of 50 $\mu\text{L}/\text{min}$. The solutions were delivered simultaneously into the flow system and, under steady state conditions (after 20 minutes), the output stream was introduced in a T-shaped micromixer fed with AcOEt (50 $\mu\text{L}/\text{min}$) before the introduction into the FLLEX system fed with water 150 $\mu\text{L}/\text{min}$. The organic and aqueous streams were separated keeping a pressure of 1 torr and a ΔP (0.1 torr). The desired alcohol was obtained after removal of organic phase and flash chromatography (86% yield, er > 95/5).



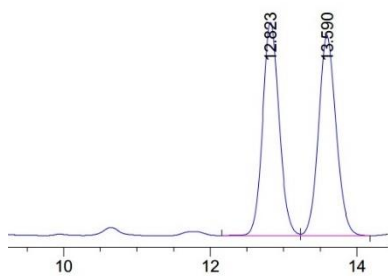




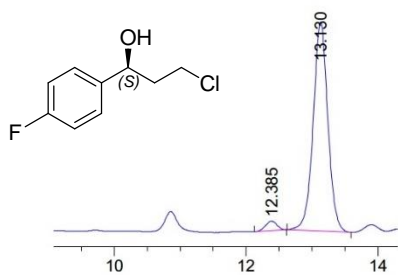
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.050	BV	0.3041	35.03330	1.70215	0.5021
2	16.794	VB	0.3194	6942.76758	332.71973	99.4979



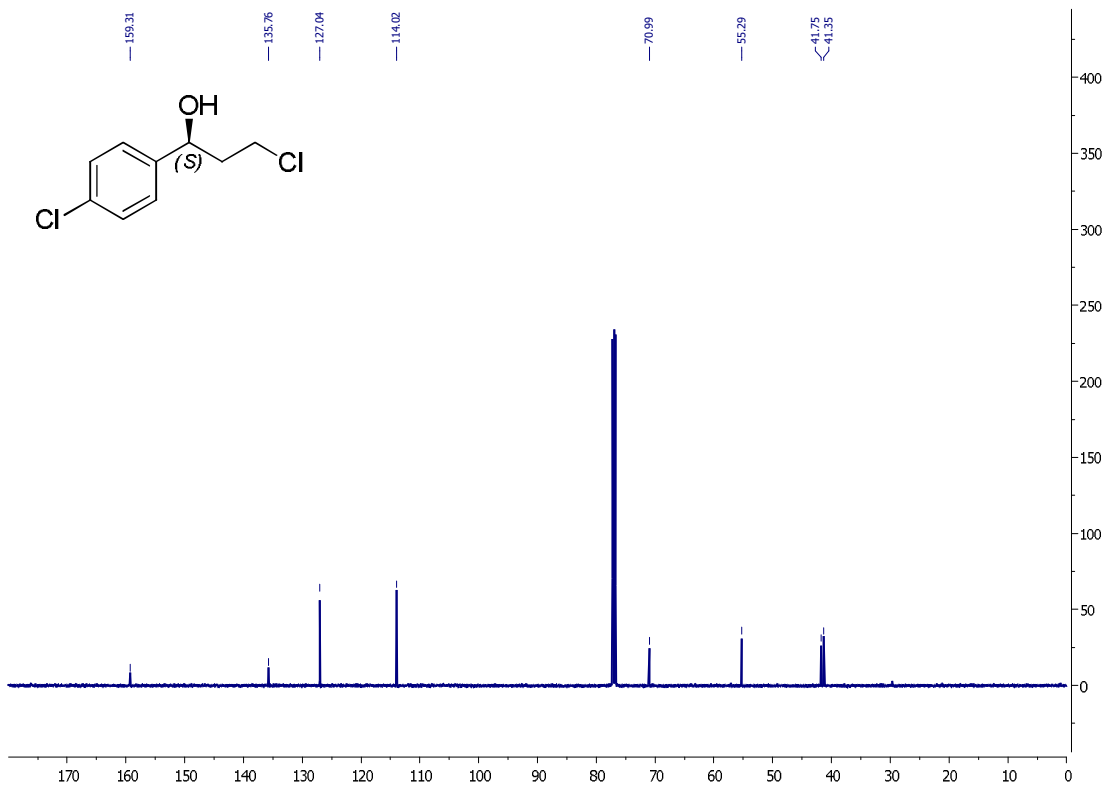
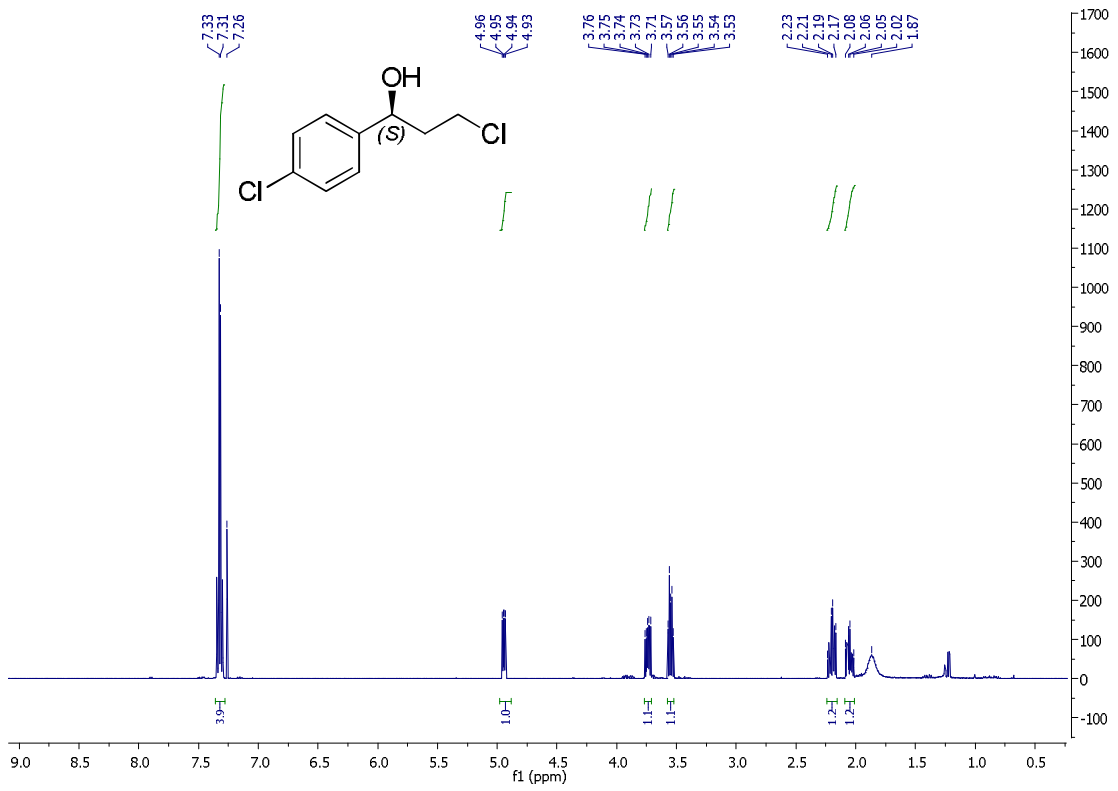
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.729	BV	0.2972	5069.79053	264.94327	89.0632
2	16.774	VB	0.3092	622.56281	30.87845	10.9368

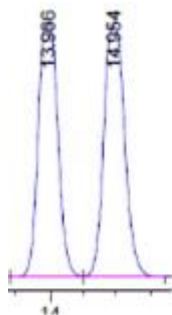


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.823	BV	0.2424	4975.47363	318.22211	49.7979
2	13.590	VB	0.2570	5015.86621	300.04425	50.2021

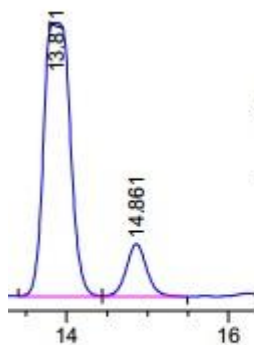


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.385	BB	0.1885	26.13958	2.14016	3.4891
2	13.130	BB	0.2371	723.03394	46.58212	96.5109

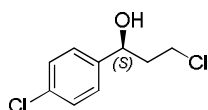


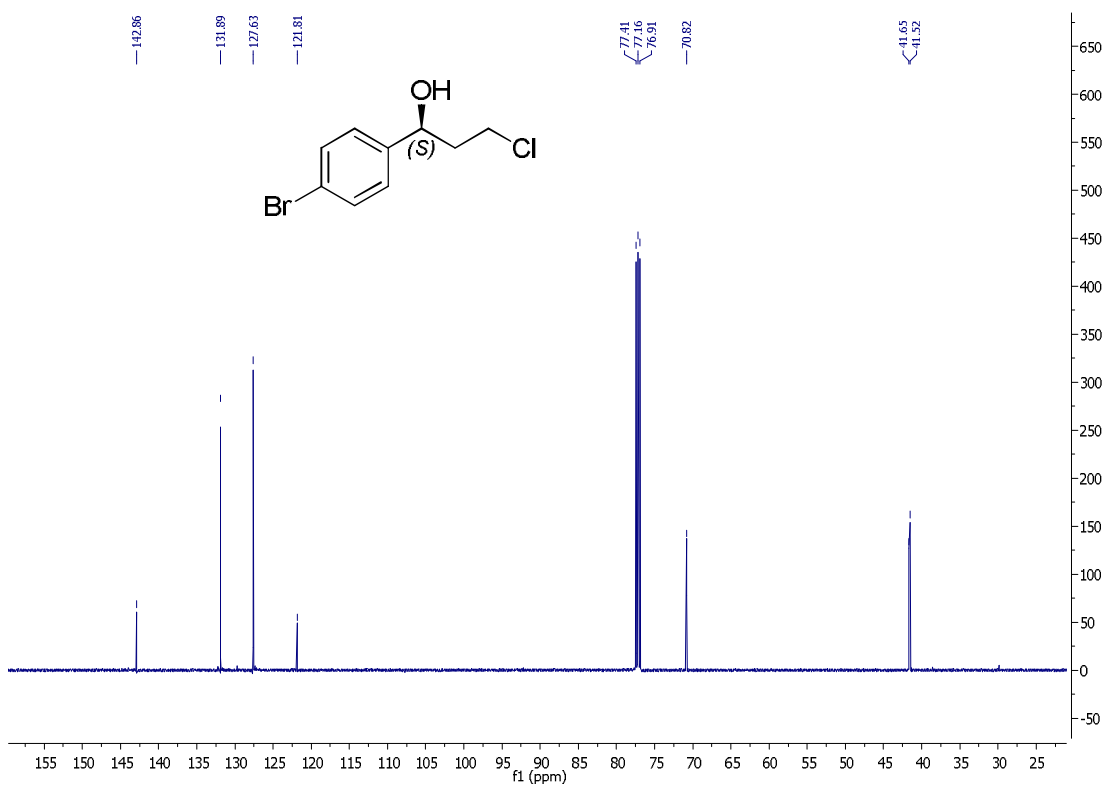
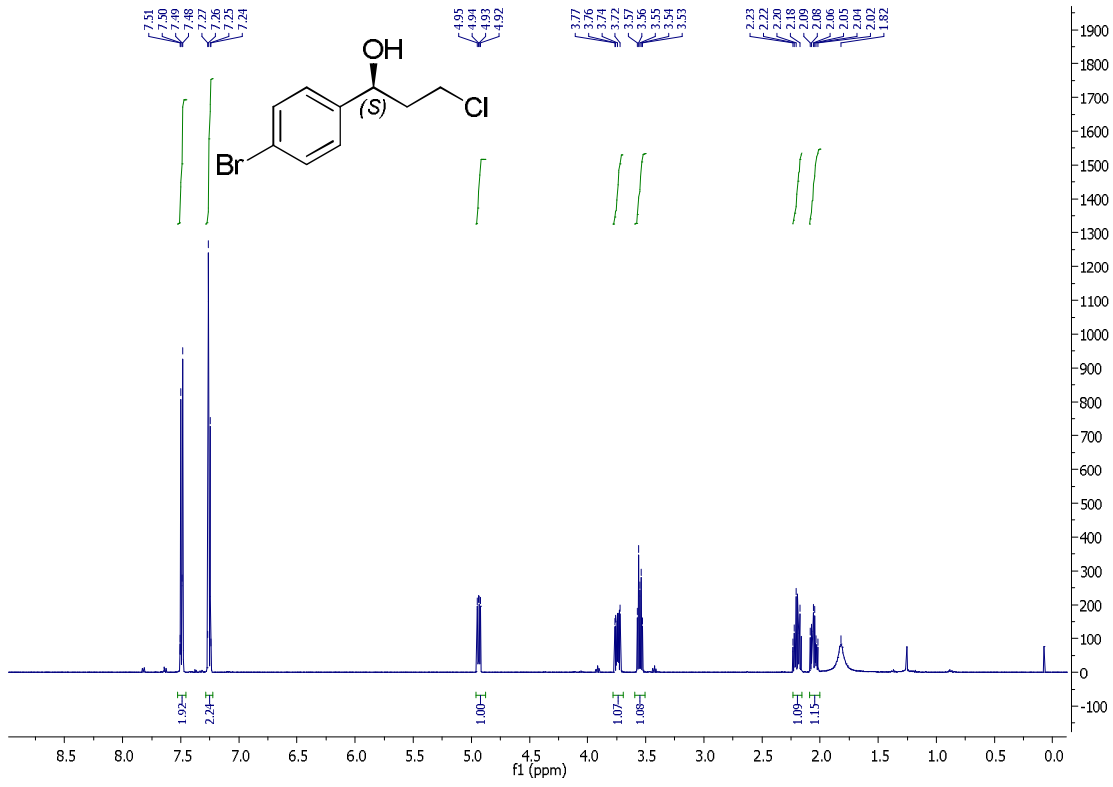


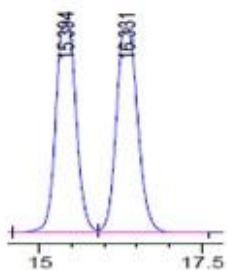
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
13	13.966	BV	0.3222	4.39156e4	2151.36133	44.7532
14	14.954	VB	0.3391	4.60031e4	2120.48169	46.8805



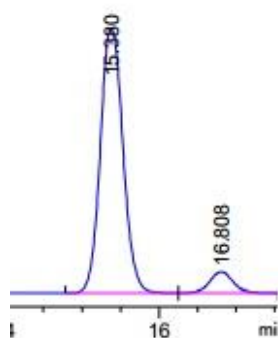
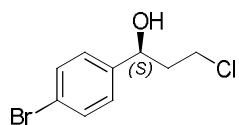
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.871	VV	0.3573	4.94490e4	2190.84448	87.0755
2	14.861	VB	0.2677	7339.62305	420.44351	12.9245



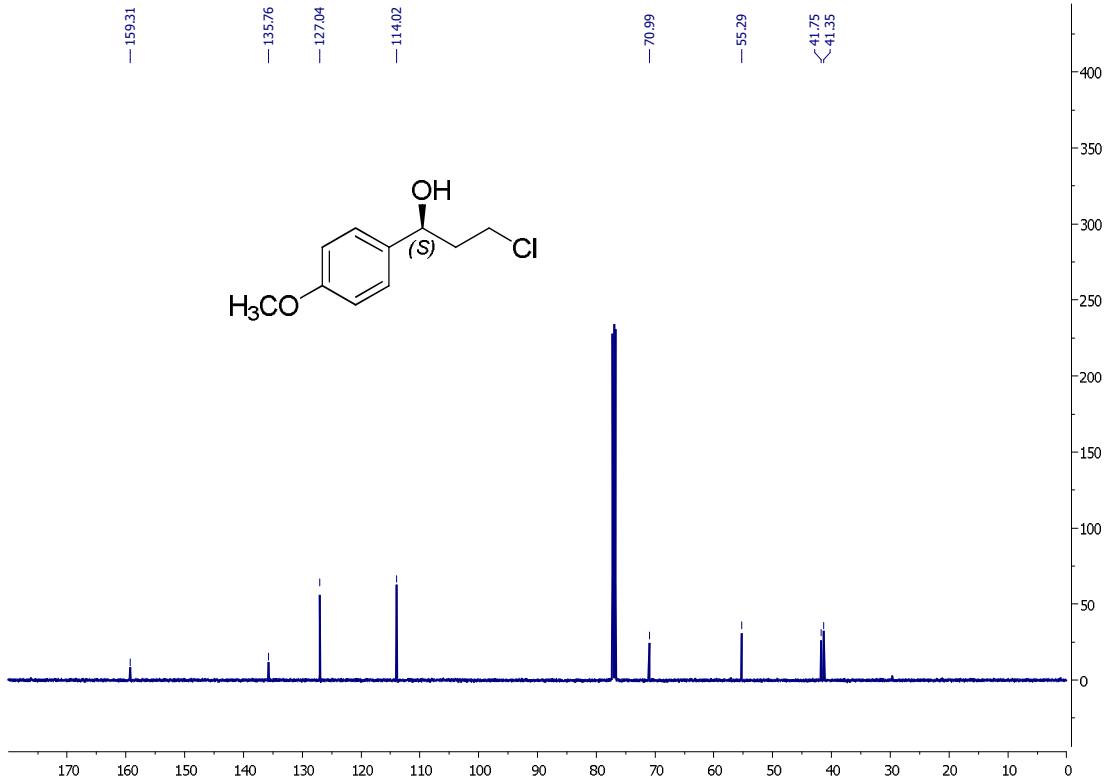
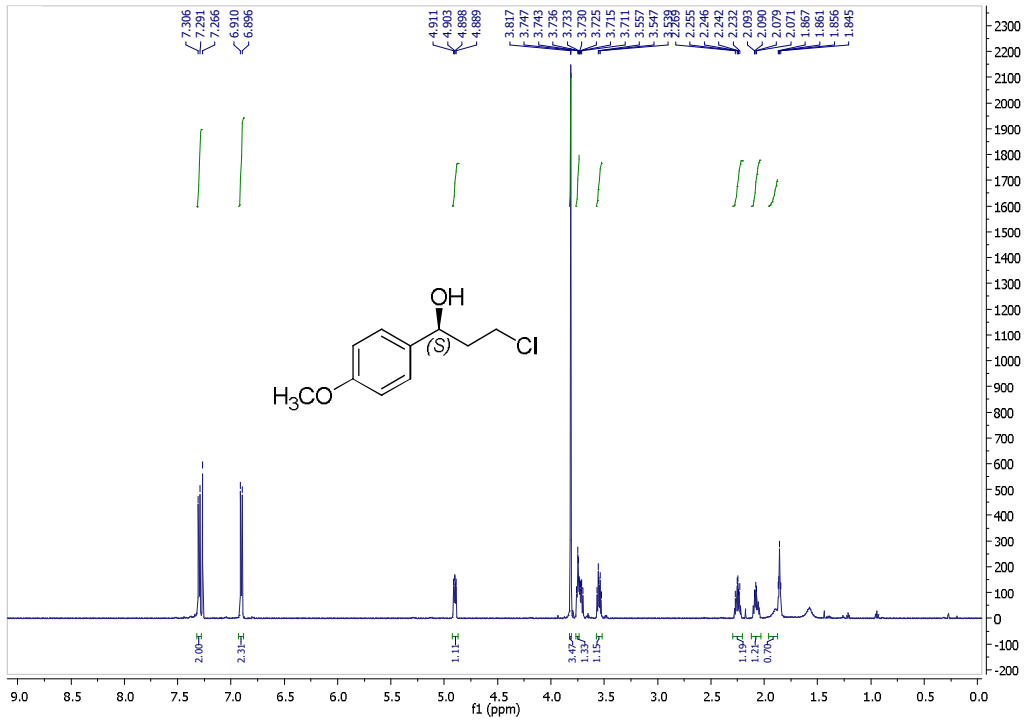


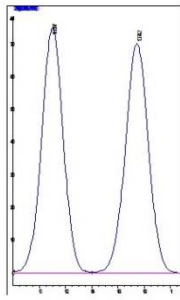


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
10	15.394	BV	0.3402	4.31828e4	1997.52930	46.1031
11	16.331	VB	0.3557	4.43357e4	1947.04236	47.3339

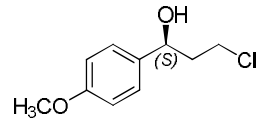
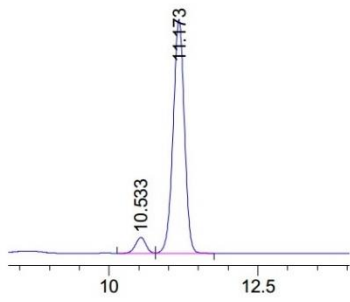


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.380	BB	0.3179	4.32572e4	2121.40161	92.3278
2	16.808	BB	0.3209	3594.55957	171.22899	7.6722

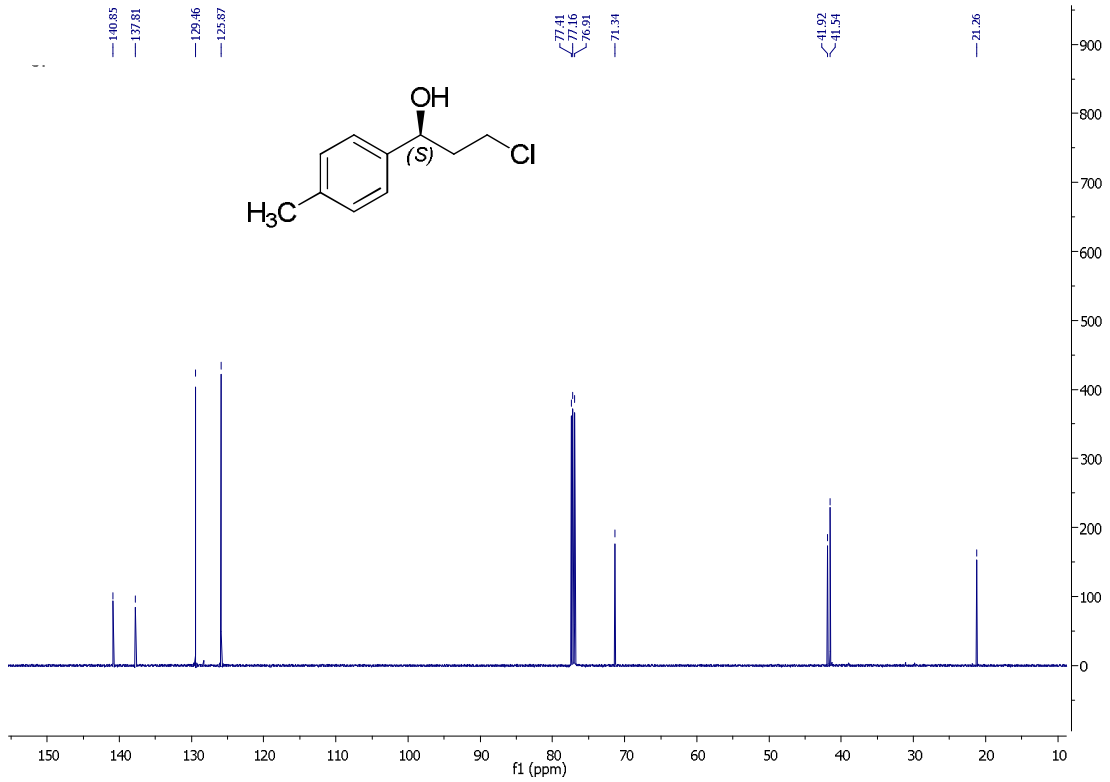
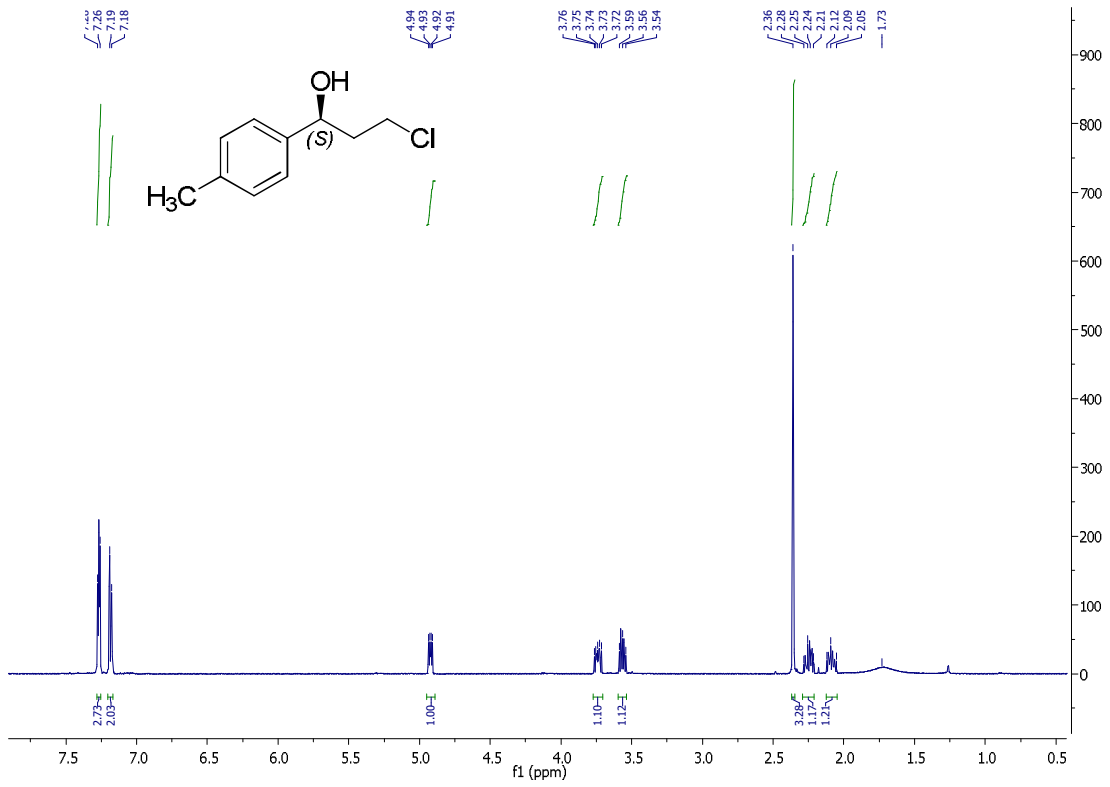


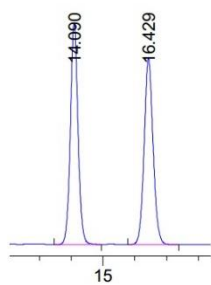


#	Time	Area	Height	Width	Area%	Symmetry
1	10.097	8692.3	750.1	0.1812	49.903	1.003
2	10.742	8726.1	703.5	0.1927	50.097	1.004

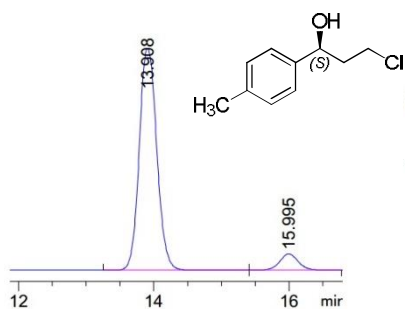


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.533	BV	0.1895	422.00433	34.31686	5.9269
2	11.173	VB	0.2041	6698.12207	507.04840	94.0731

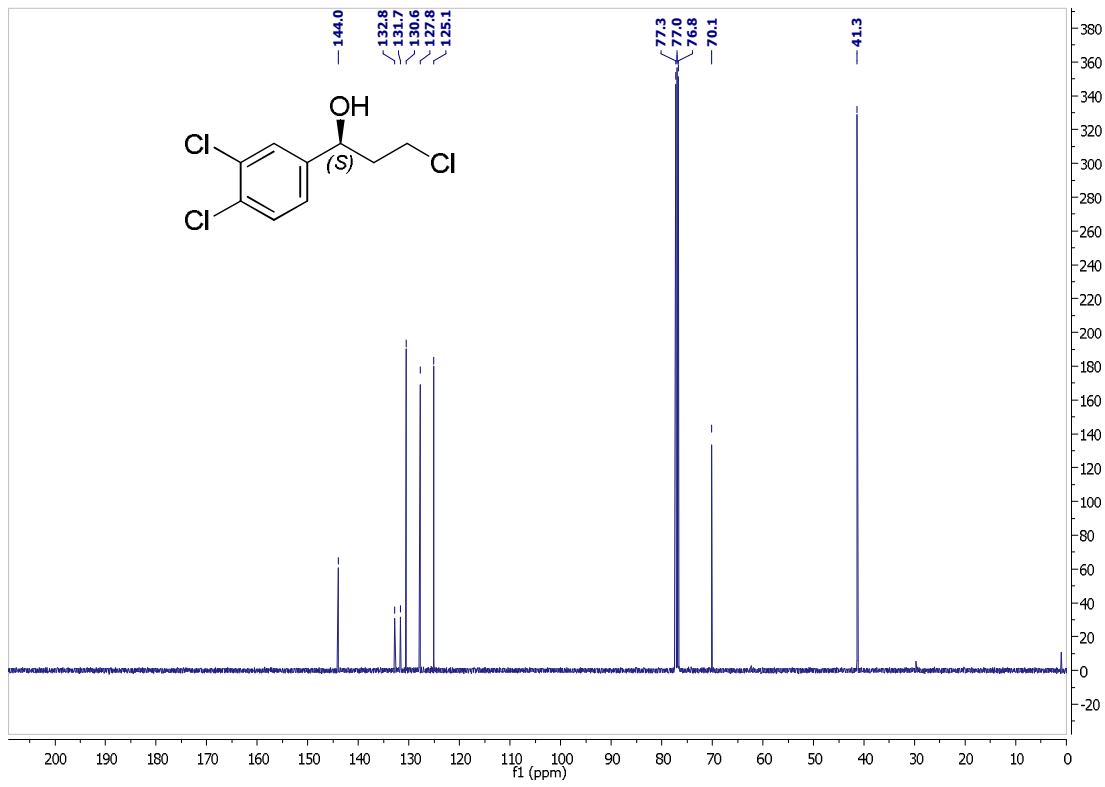
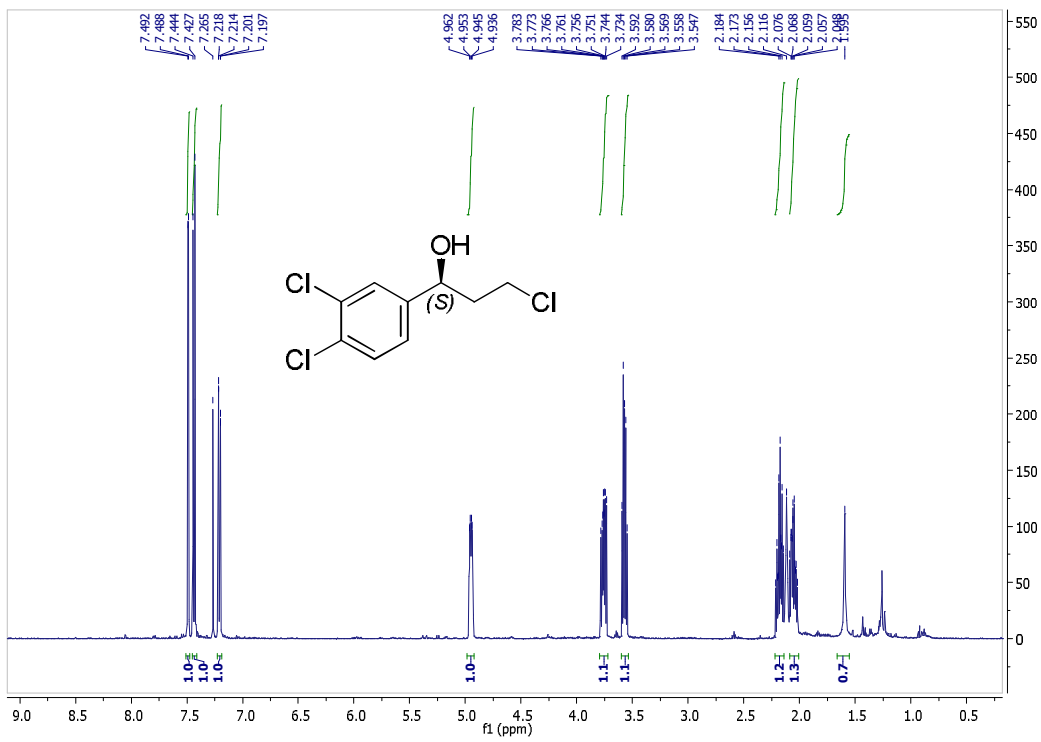


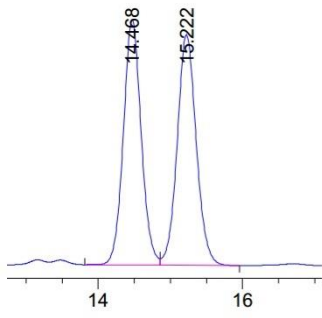


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.090	BB	0.2520	8088.68359	486.53348	50.2839
2	16.429	BB	0.2982	7997.34619	408.78867	49.7161

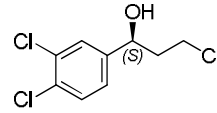
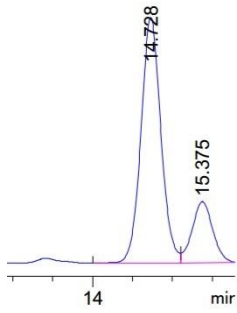


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.908	BB	0.2793	3.50544e4	1953.63452	92.8624
2	15.995	BB	0.2869	2694.37427	143.62955	7.1376

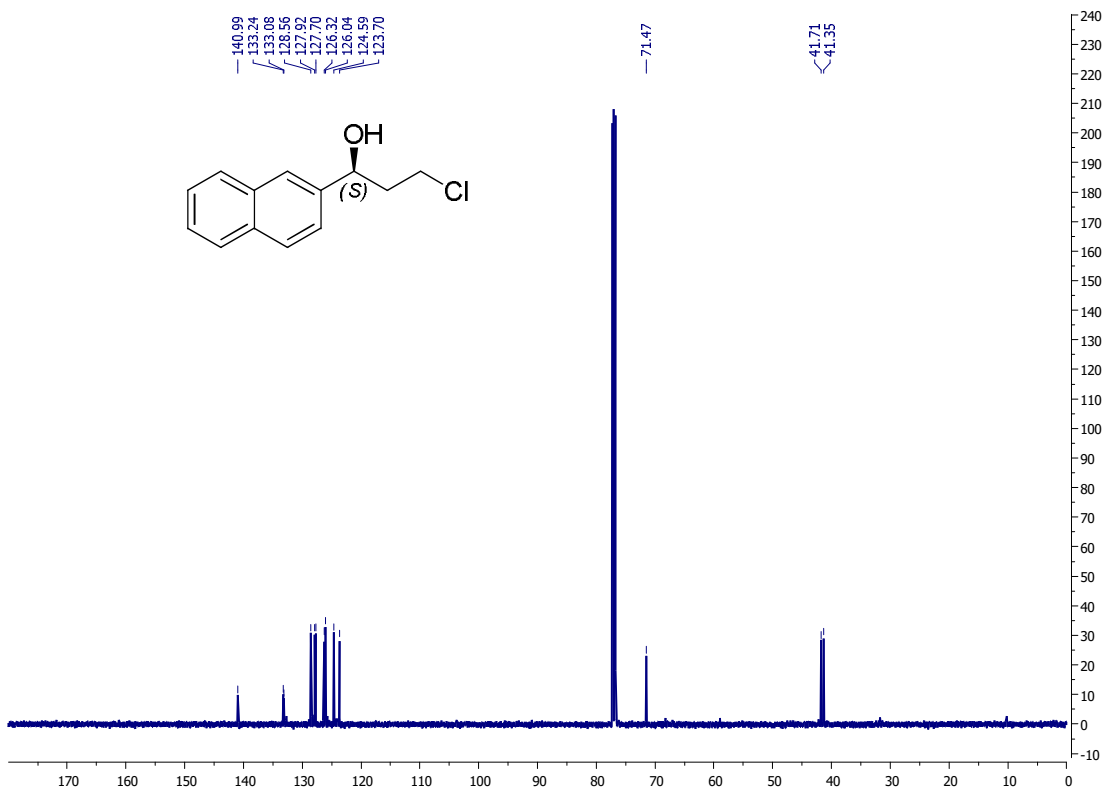
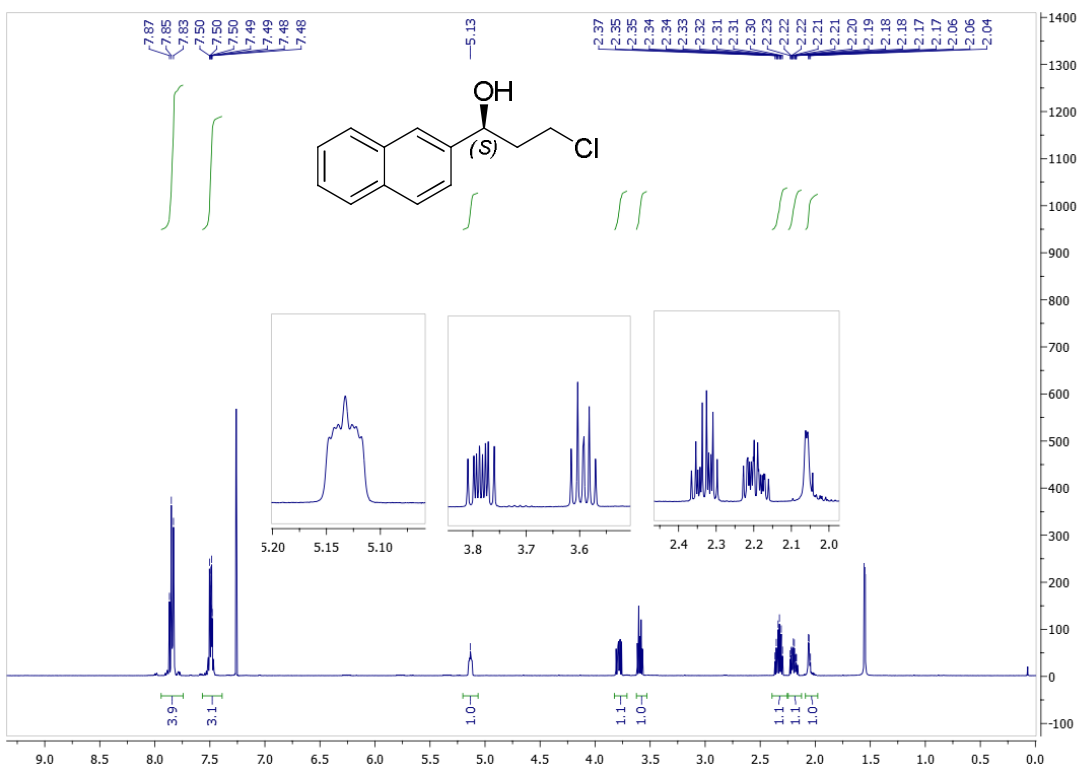


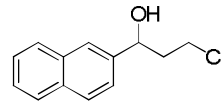
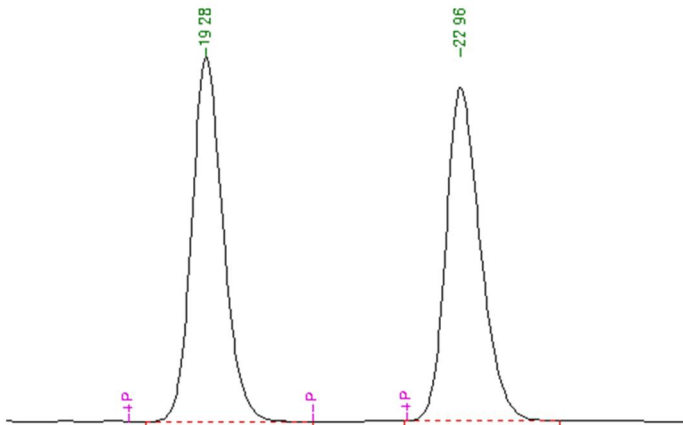


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.468	BV	0.2624	1.84230e4	1072.29700	49.9479
2	15.222	VB	0.2820	1.84614e4	1006.66528	50.0521



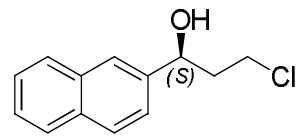
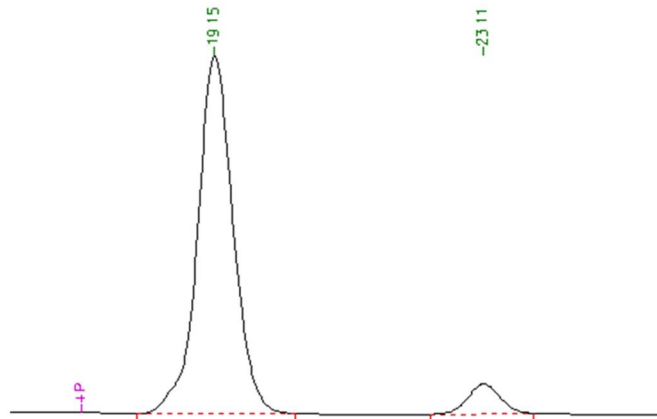
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.728	BV	0.2643	1.21734e4	701.99182	79.4229
2	15.375	VBA	0.2740	3153.92041	175.19295	20.5771





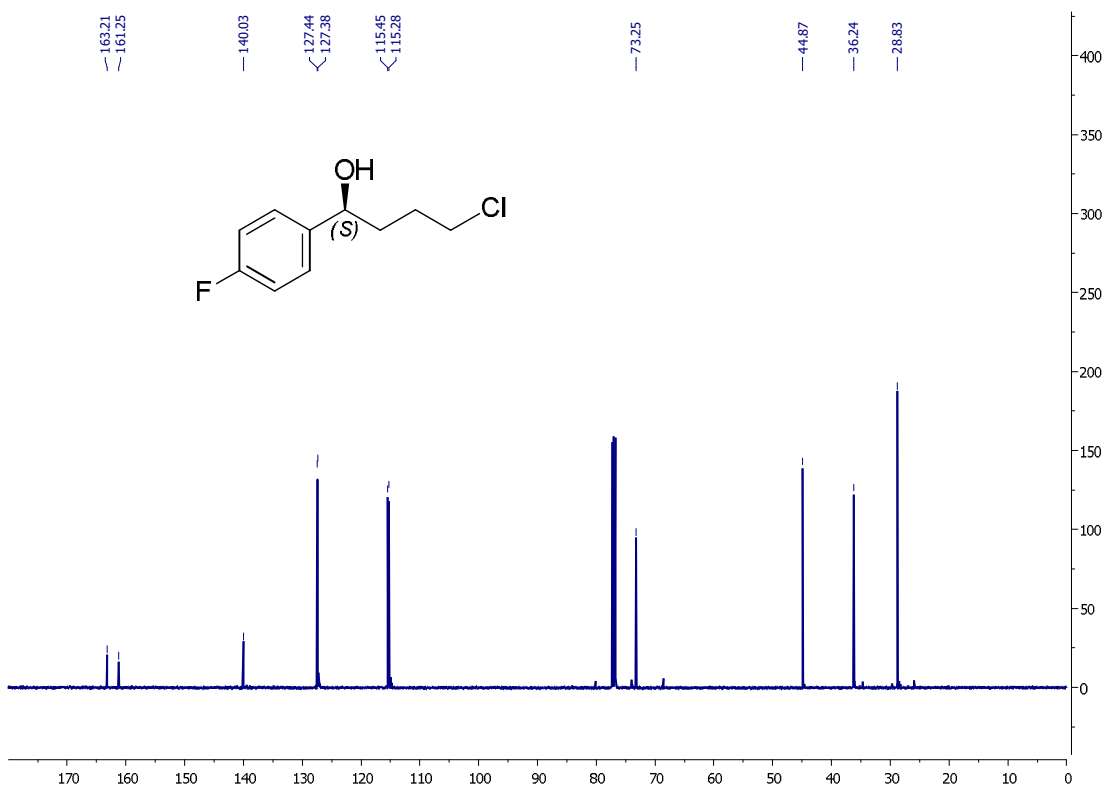
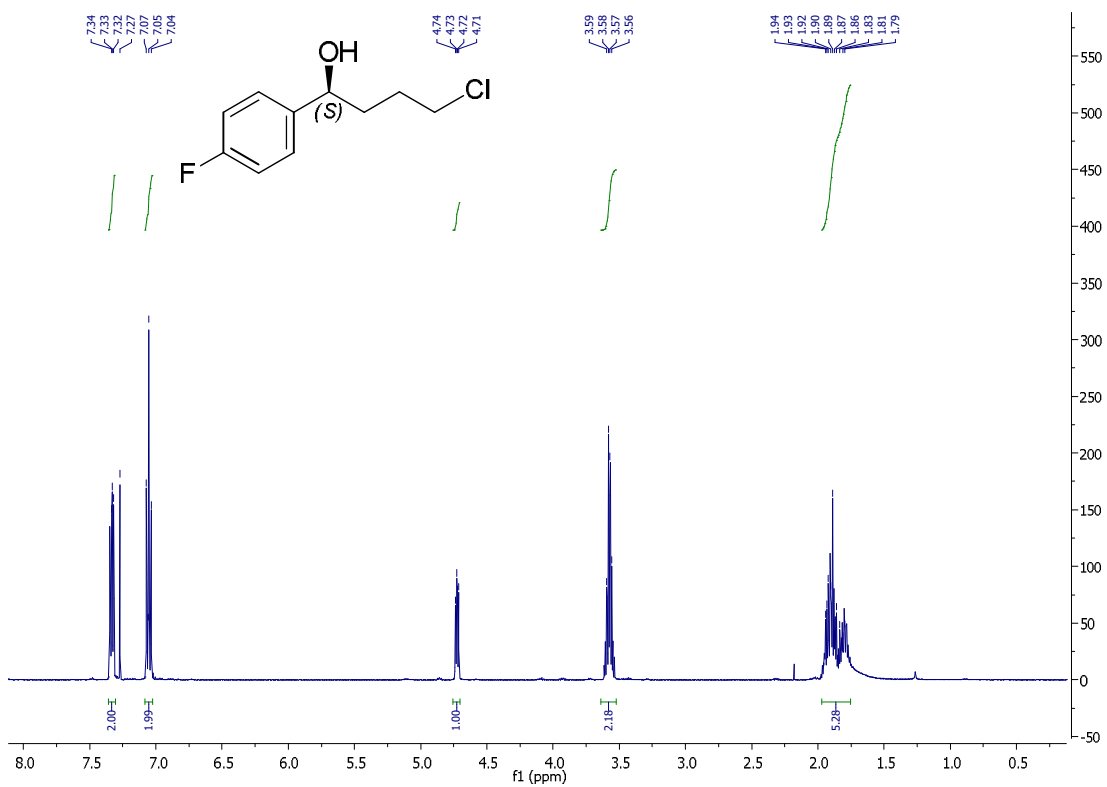
LP12

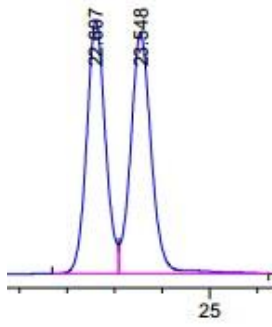
Peak #	Time [min]	Area [$\mu\text{V}\cdot\text{s}$]	Height [μV]	Area [%]	Norm. Area [%]	Area BL	Area/Height [s]
1	19.276	5143363.50	163087.16	50.06	0.00	BB	31.54
2	22.962	5131886.00	148729.07	49.94	0.00	BB	34.50



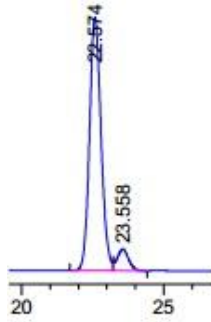
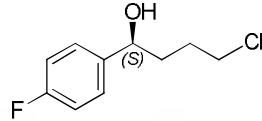
LP12

Peak #	Time [min]	Area [$\mu\text{V}\cdot\text{s}$]	Height [μV]	Area [%]	Norm. Area [%]	Area BL	Area/Height [s]
1	19.147	4342772.00	119433.34	93.01	0.00	BB	36.36
2	23.105	326412.00	9858.05	6.99	0.00	BB	33.11

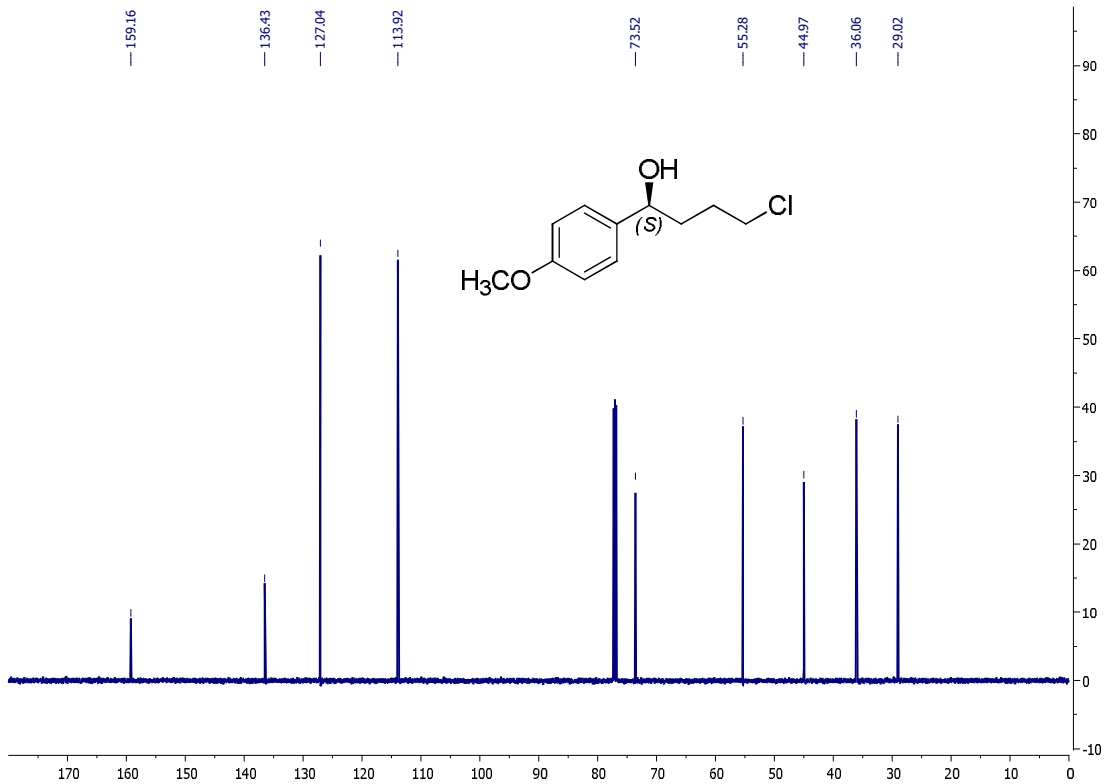
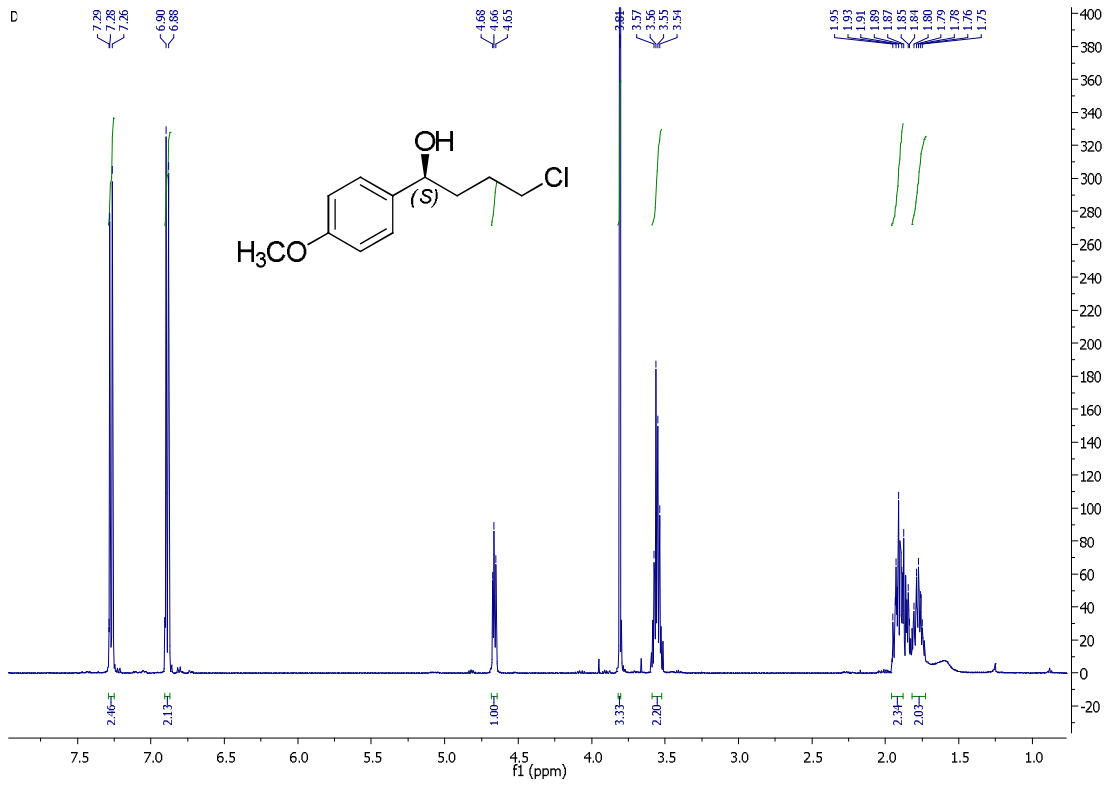


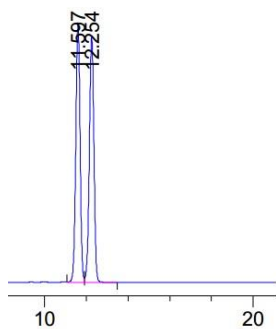


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.607	BV	0.4184	2870.47998	105.18634	48.6184
2	23.548	VB	0.4571	3033.62207	100.22219	51.3816

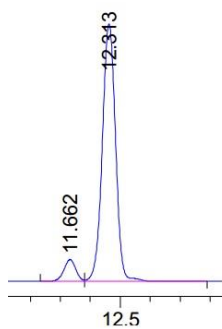
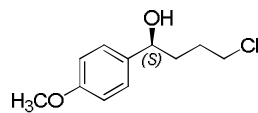


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.574	BV	0.4392	6148.41602	217.92923	92.2448
2	23.558	VB	0.4239	516.90601	18.50671	7.7552

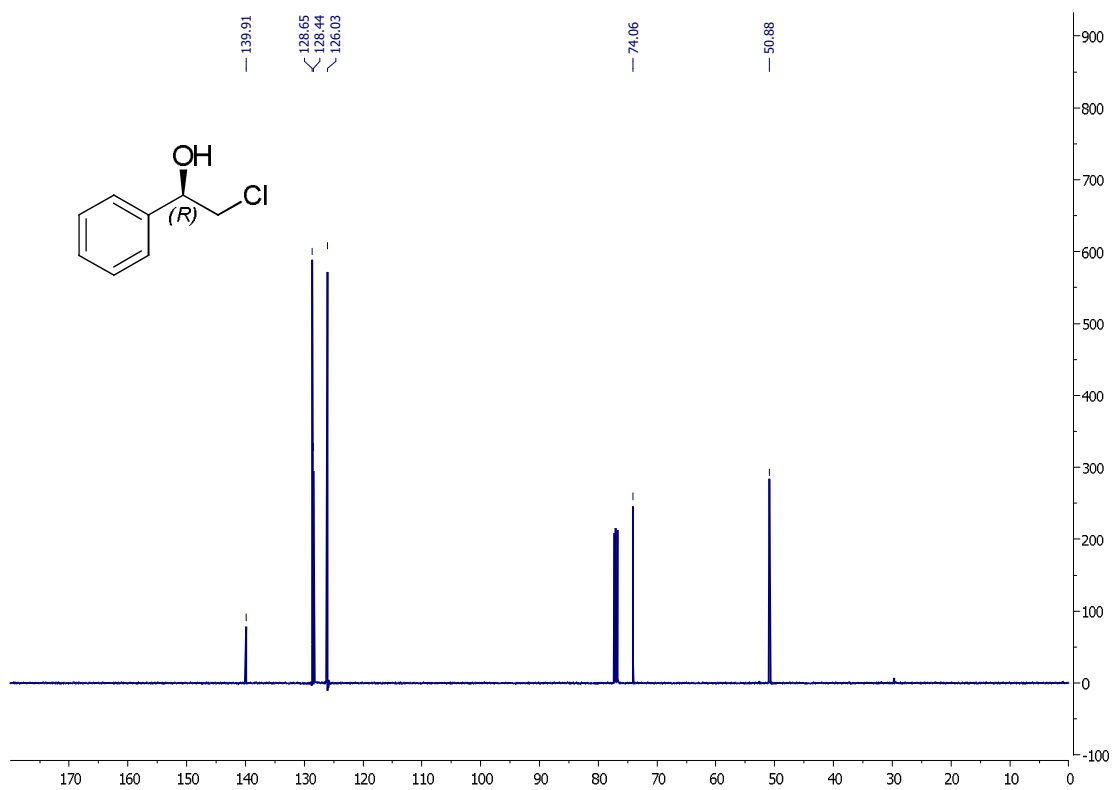
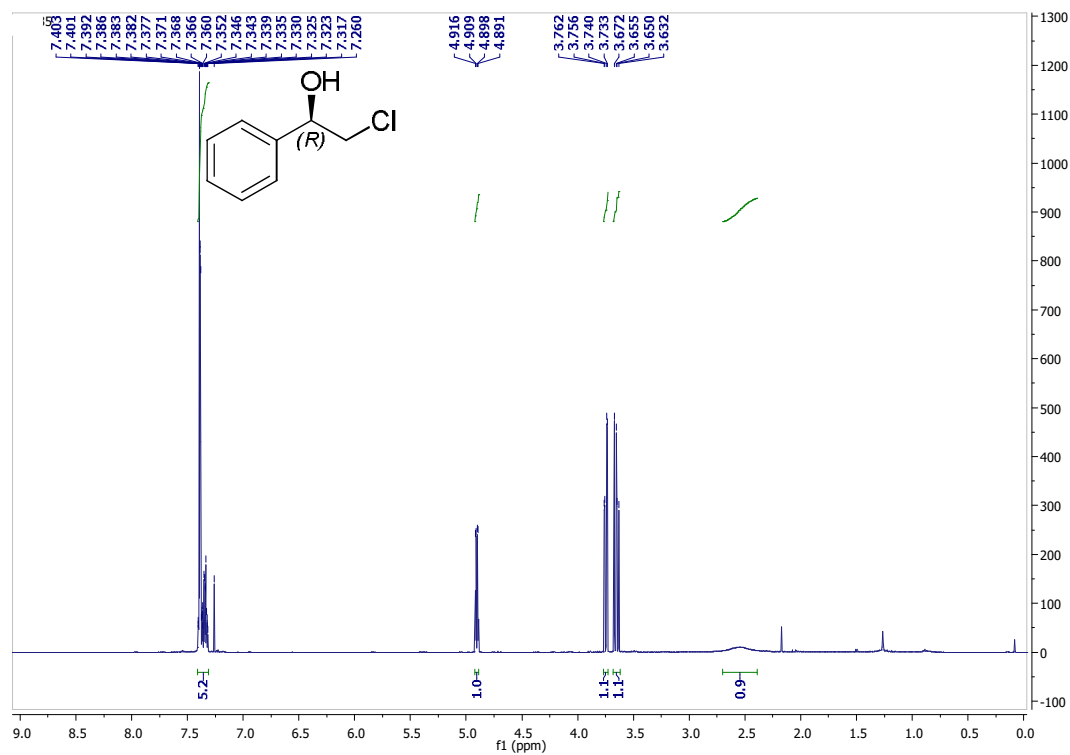


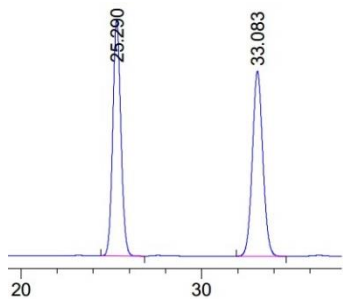


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.597	VV	0.2227	2.10360e4	1472.54492	49.8172
2	12.254	VB	0.2376	2.11904e4	1392.21570	50.1828

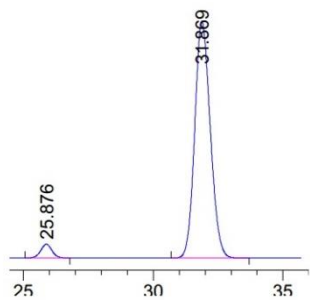
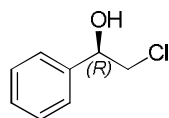


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.662	BV	0.2163	1677.61365	120.58468	7.1570
2	12.313	VB	0.2388	2.17627e4	1419.95532	92.8430

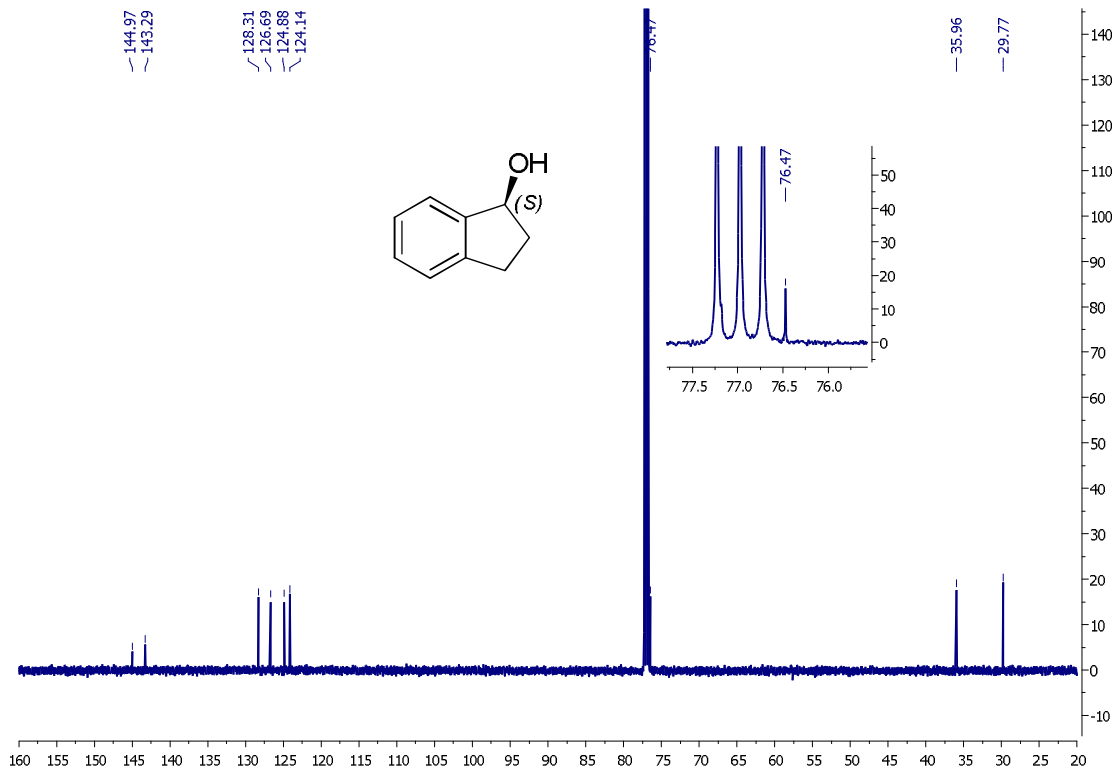
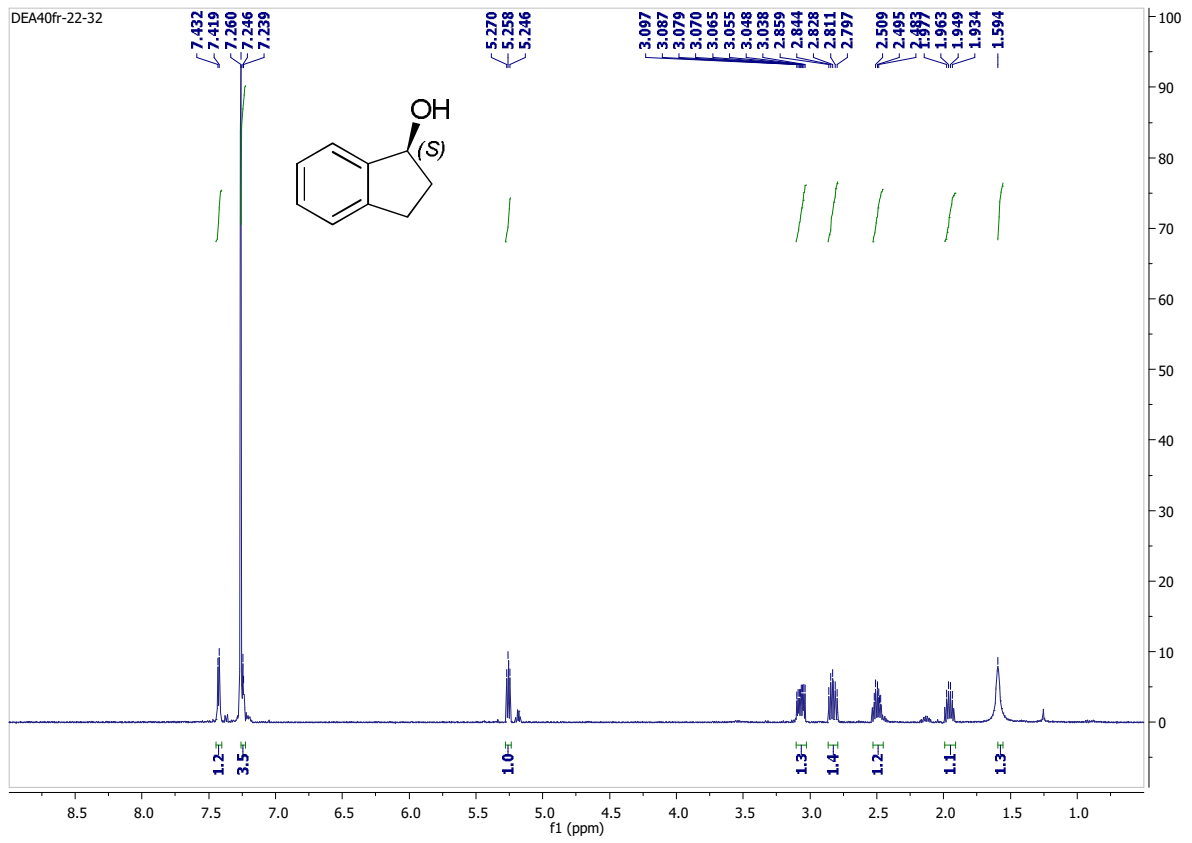


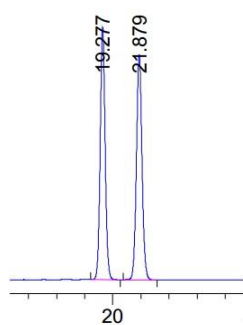


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.290	BB	0.4787	9178.95020	295.23572	49.6248
2	33.083	BB	0.6244	9317.74219	231.11127	50.3752

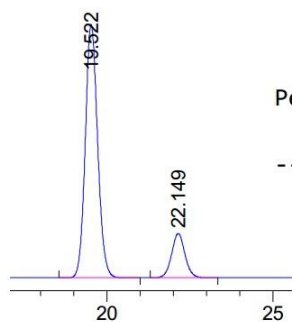
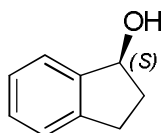


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.876	BB	0.4518	1012.23993	33.95287	3.9875
2	31.869	BB	0.6420	2.43729e4	585.08148	96.0125

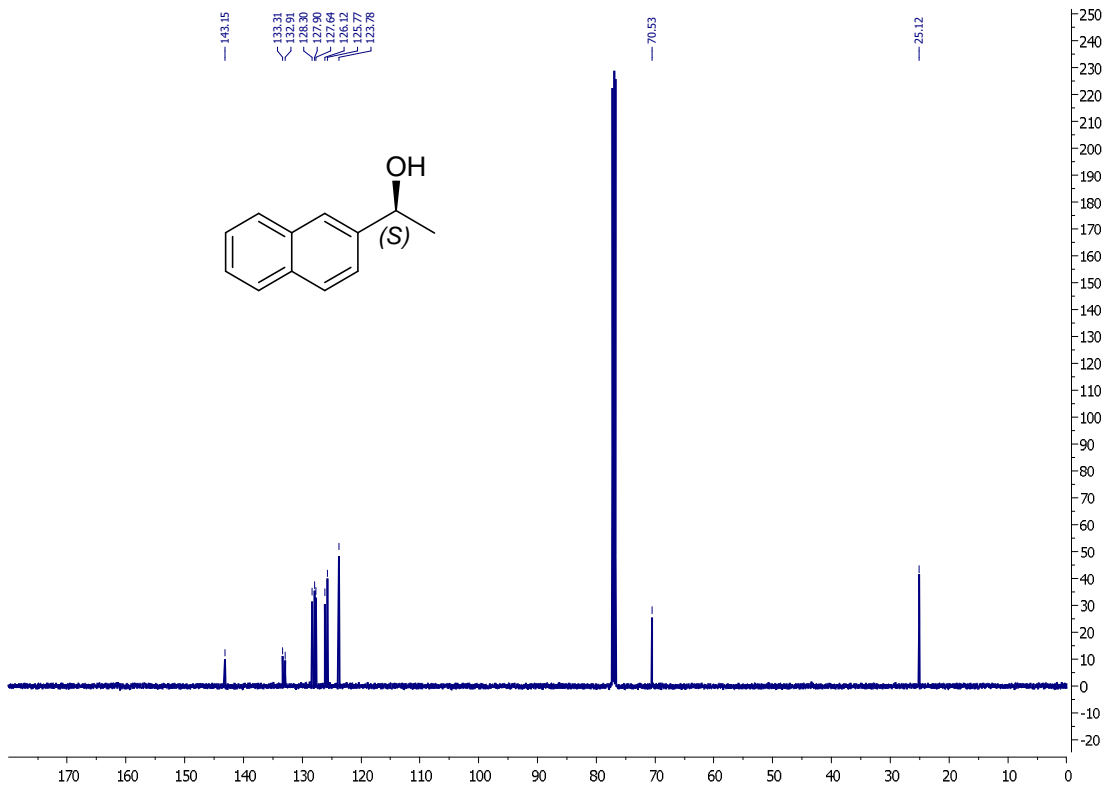
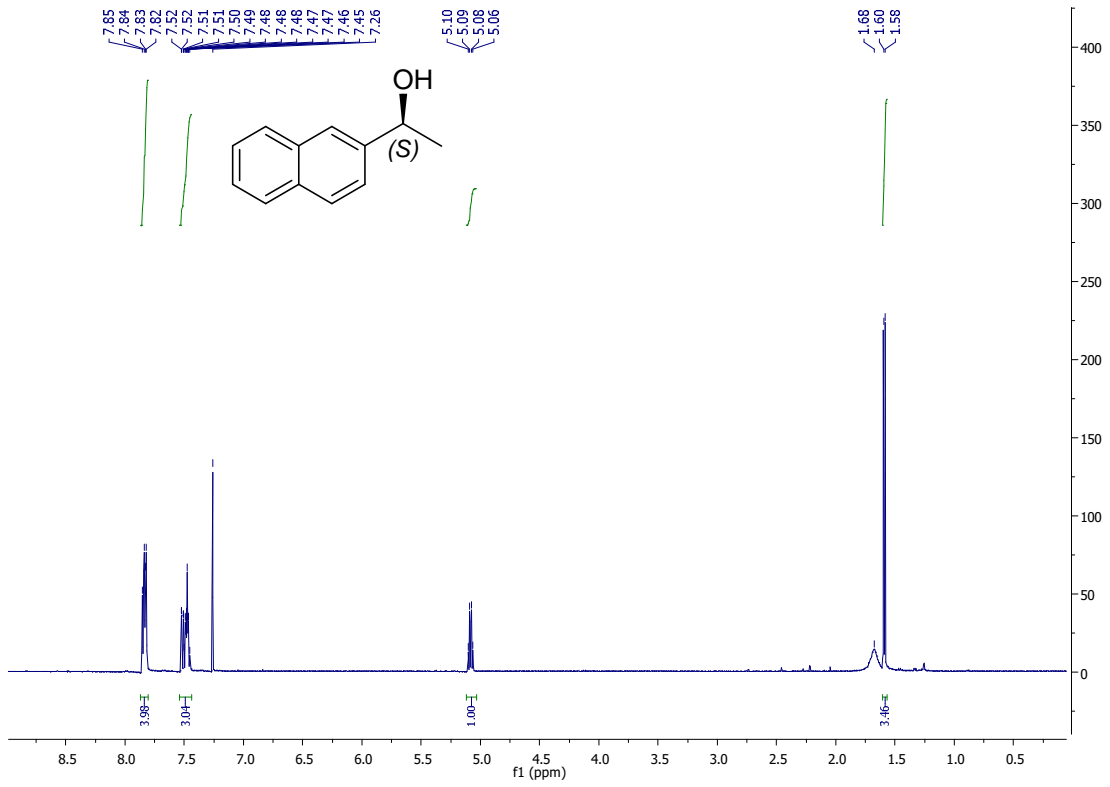


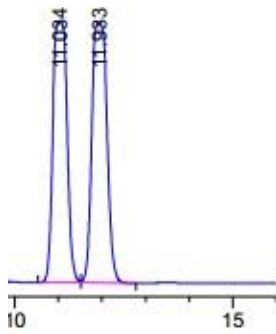


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.277	BB	0.3777	6842.16797	279.43628	49.8776
2	21.879	BB	0.4235	6875.75781	249.54065	50.1224

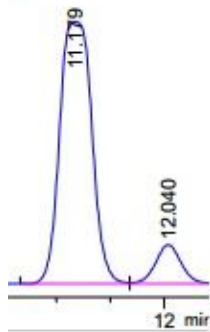
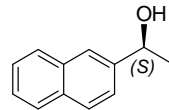


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.522	BB	0.3964	2.05695e4	798.92810	84.1938
2	22.149	BB	0.4254	3861.62573	139.29750	15.8062

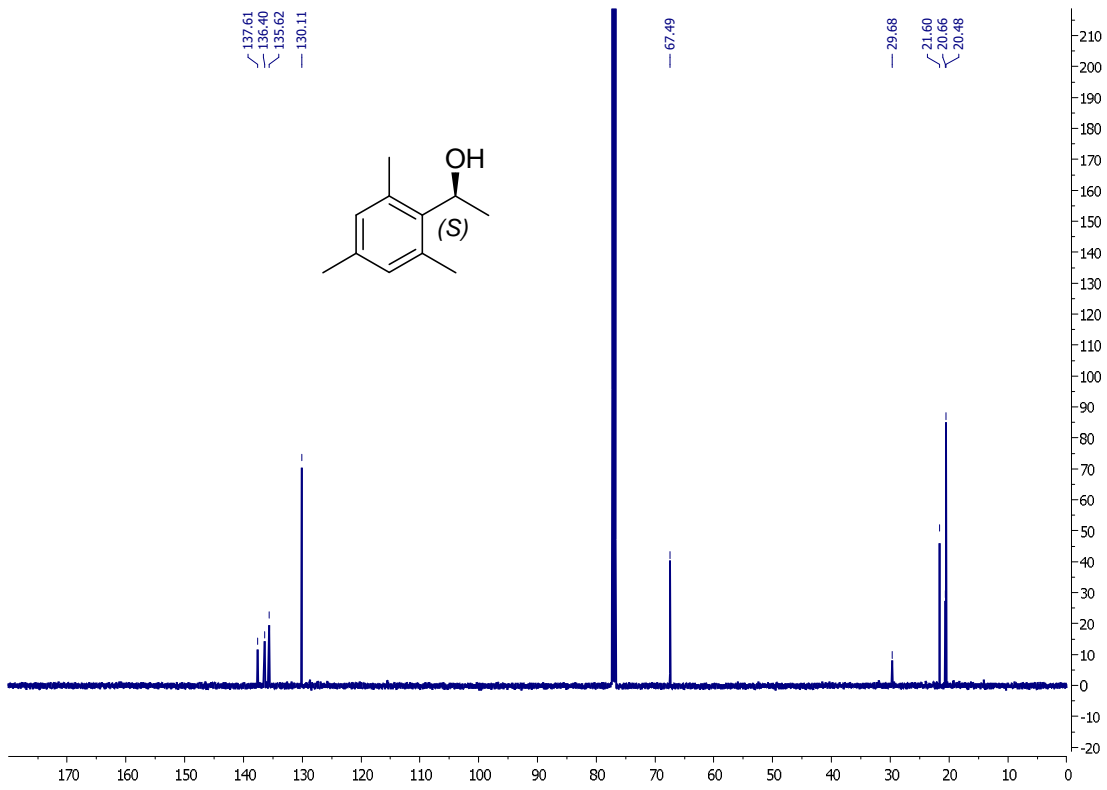
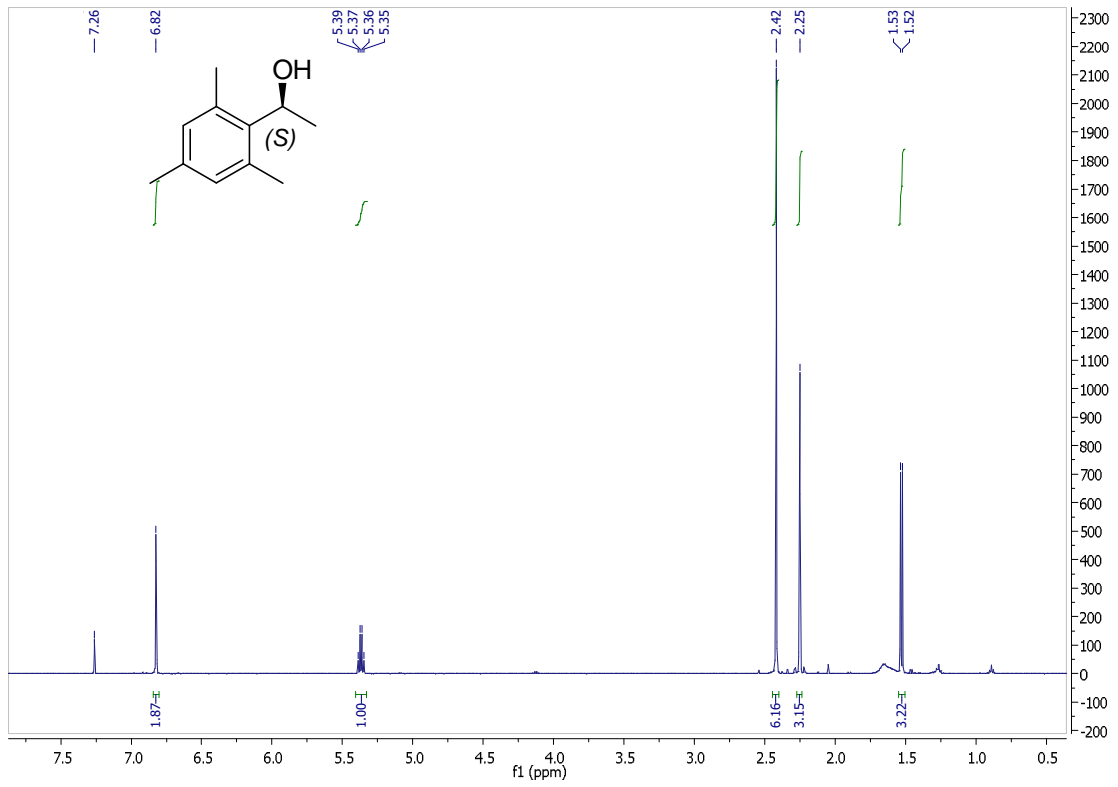


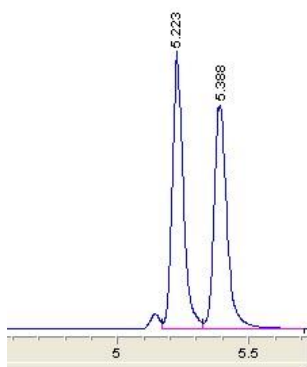


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.034	BV	0.3599	4.78676e4	2131.96582	48.4943
2	11.933	VB	0.3840	5.08401e4	2118.25513	51.5057

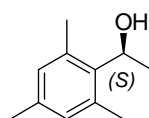
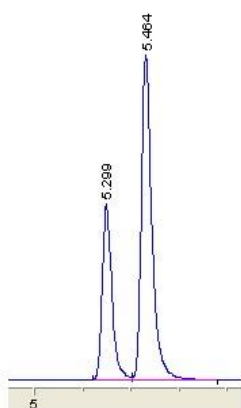


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.179	BV	0.3286	4.20617e4	2039.81995	89.5425
2	12.040	VBA	0.2499	4912.29199	301.81052	10.4575

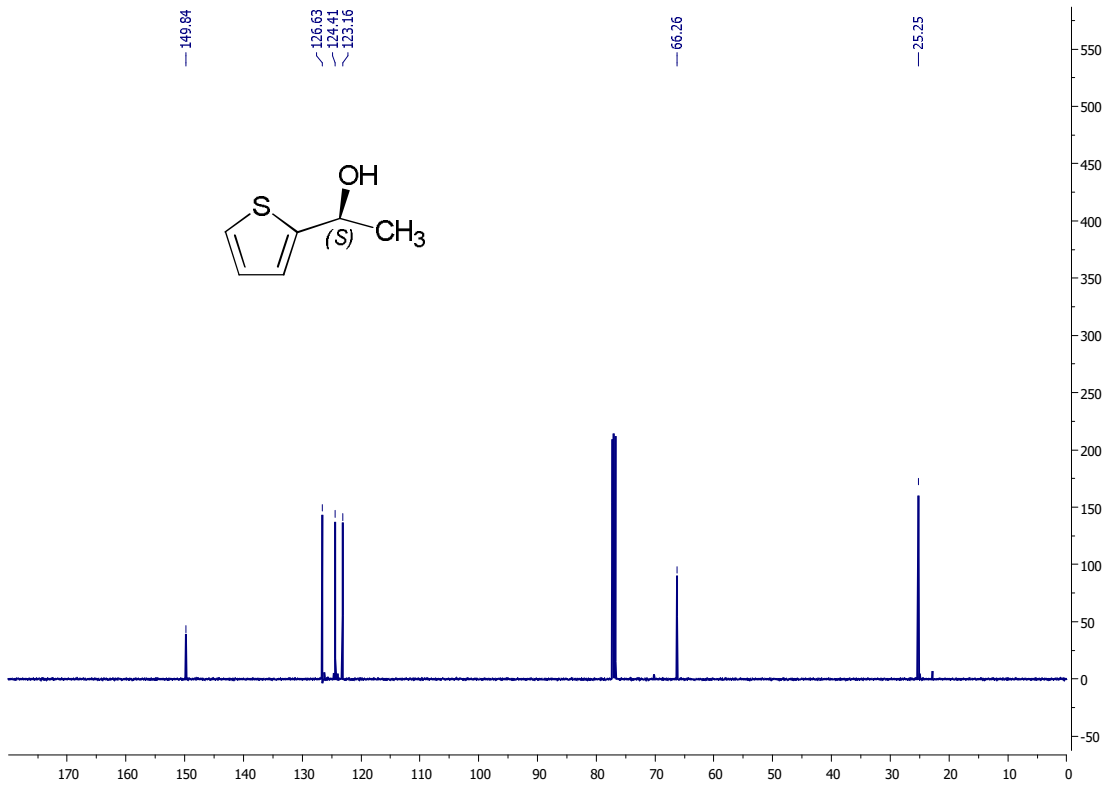
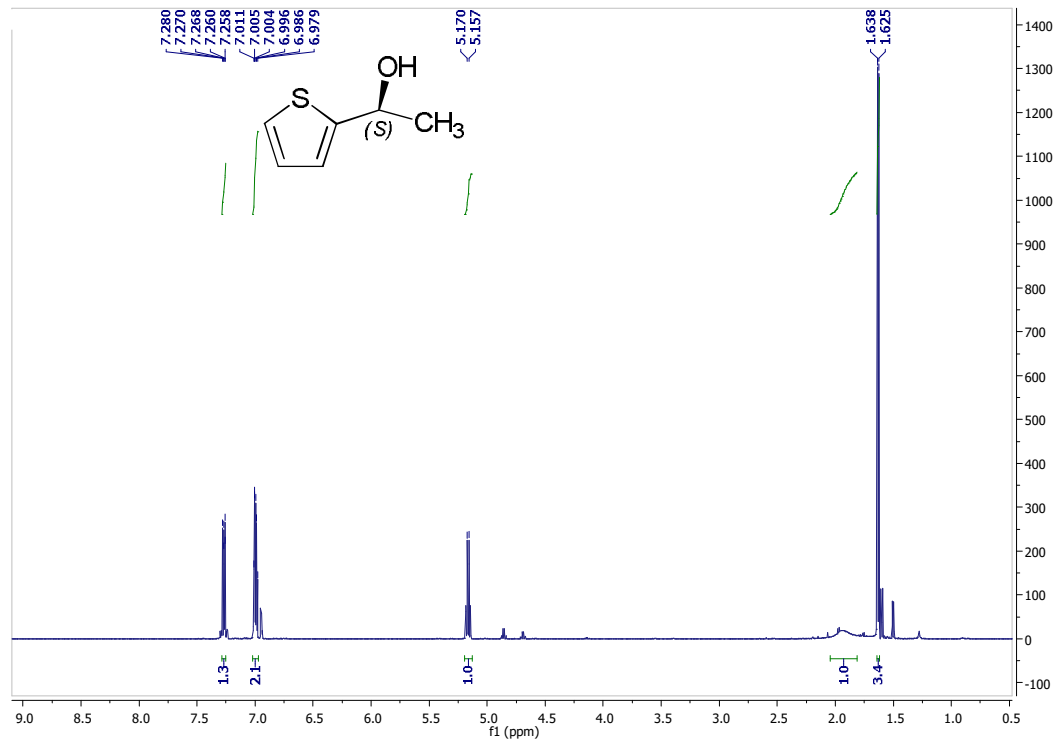


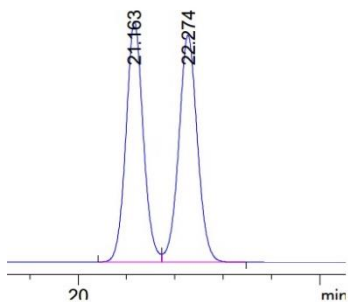


#	Time	Area	Height	Width	Area%	Symmetry
1	1.319	118601.4	78084.6	0.0212	99.573	0.816
2	5.223	257.3	89	0.0367	0.216	0.67
3	5.388	251.5	71.8	0.0449	0.211	0.839

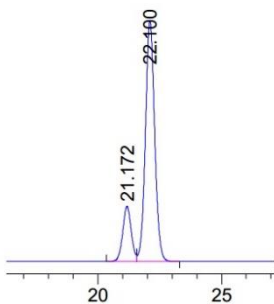
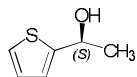


#	Time	Area	Height	Width	Area%	Symmetry
1	1.328	101248.6	88091.7	0.0164	99.526	0.371
2	5.299	158.8	56.8	0.0361	0.156	0.69
3	5.464	323	104.7	0.0445	0.317	0.654

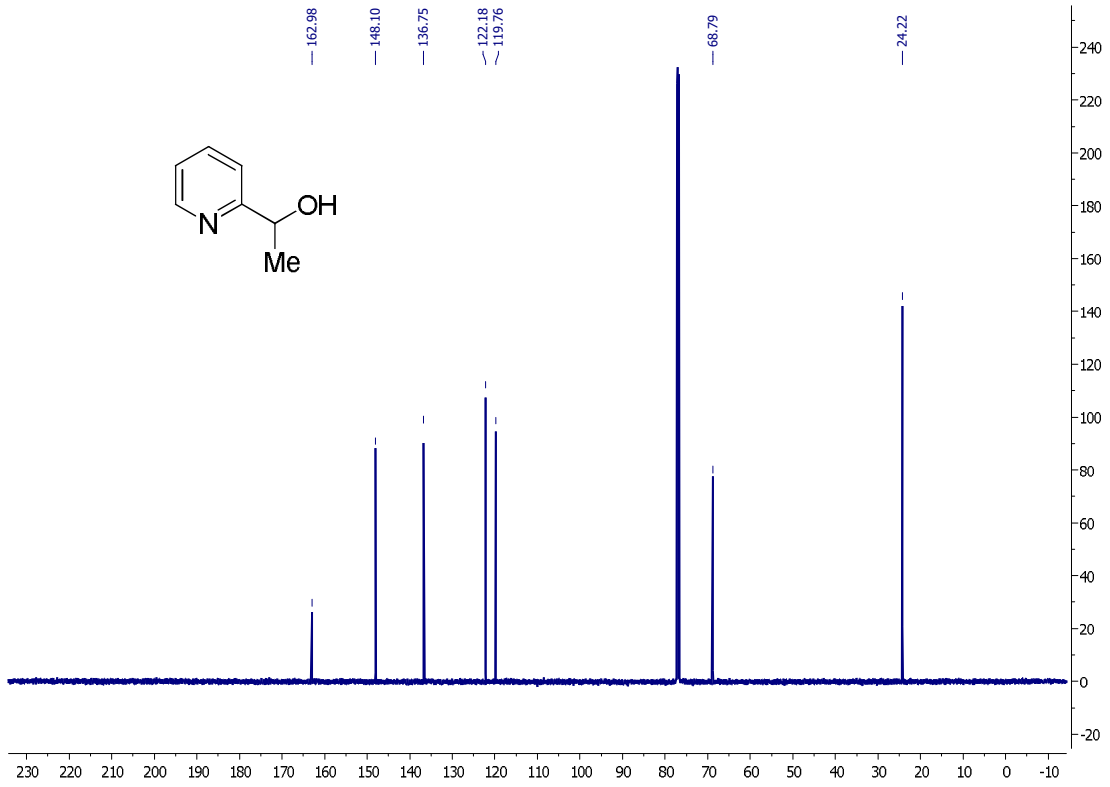
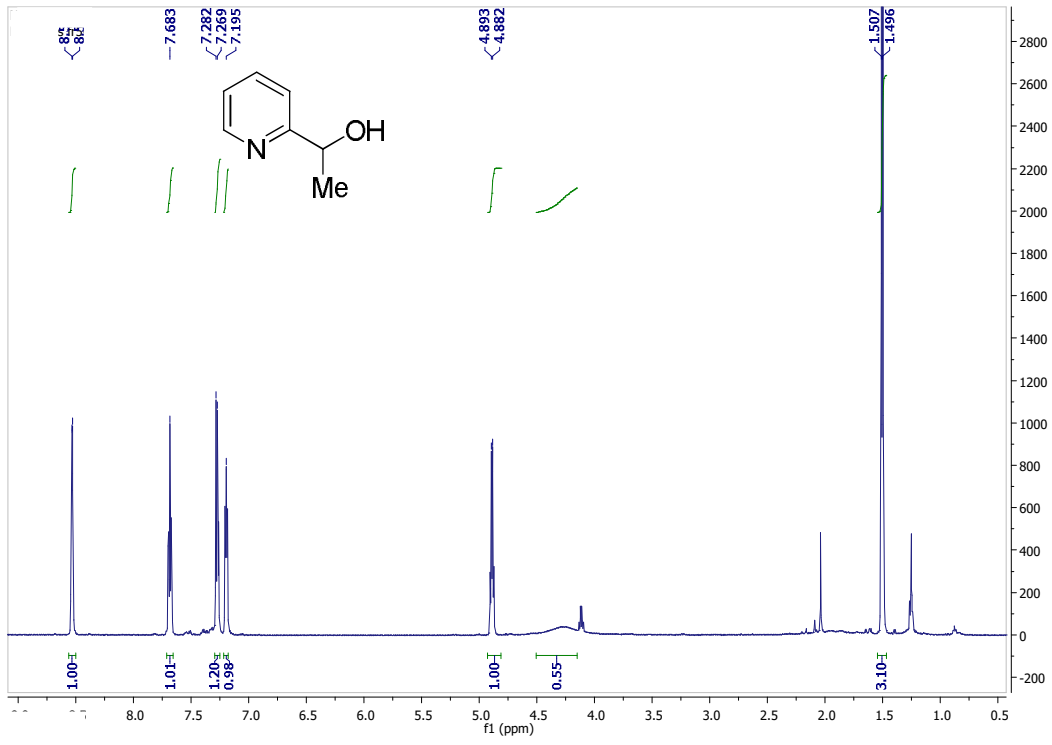


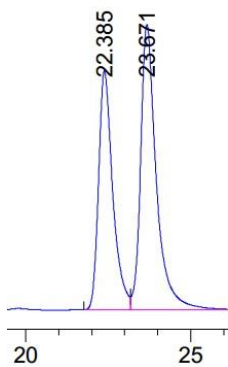
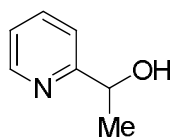


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.163	BV	0.3847	1.60421e4	643.78979	49.6882
2	22.274	VB	0.4098	1.62434e4	607.70911	50.3118



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.172	BV	0.3705	5224.03271	217.26282	17.5327
2	22.100	VB	0.3973	2.45719e4	951.40051	82.4673





Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.385	BV	0.4434	1608.07446	54.00879	43.0782
2	23.671	VB	0.4846	2124.84668	64.45042	56.9218

