

Diastereoselective Multicomponent Cascade Reaction Leading to [3.2.0]-Heterobicyclic Compounds

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Estonia

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Estonia

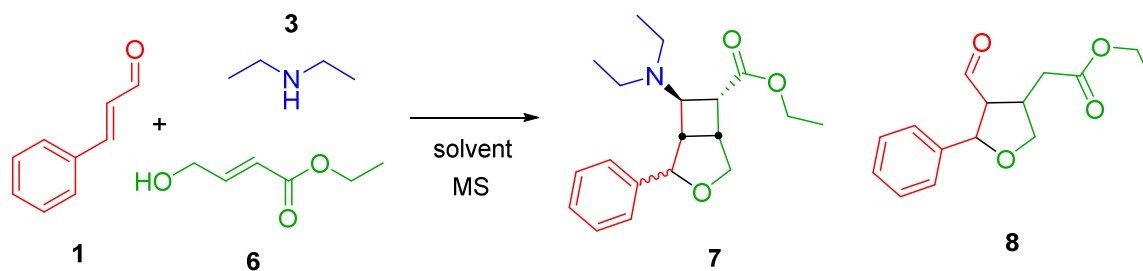
kanger@chemnet.ee

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1. Screening of reaction conditions

Table 1. Solvent screening to improve diastereoselectivity. ^[a]

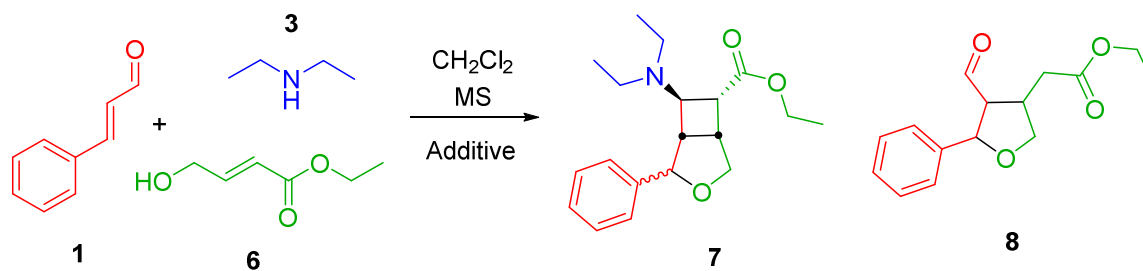


Entry	Solvent	6/7/8 ^[b]	d.r. ^[c]
1	CH ₃ CN	49/46/5	3:1
2	Toluene	22/58/20	1.8:1
3	THF	42/47/11	3.5:1
4	CH ₂ Cl ₂	0/96/4	5:1
5 ^[d]	CH ₃ Cl	0/85/15	3.5:1
6	CCl ₄	40/40/20	1.6:1
7	1,2-dichloroethane	19/75/6	4:1
8	Dioxan	45/35/20	2.3:1
9	<i>t</i> -AmylOH	57/32/11	2.1:1

^[a] Cinnamaldehyde (2 equiv), Et₂NH (2 equiv), and hydroxycrotonate (1 equiv) were stirred in an appropriate solvent at rt for 48 h, with MS.

^[b] Ratios were determined by ¹H NMR in relation to the major diastereomer. ^[c] Ratio of [3.2.0]-oxabicyclo heptane **7** 2-*exo* and 2-*endo* diastereoisomers determined by ¹H NMR. ^[d] Reaction time 24h

Table 1. Screening of additives to improve diastereoselectivity. ^[a]

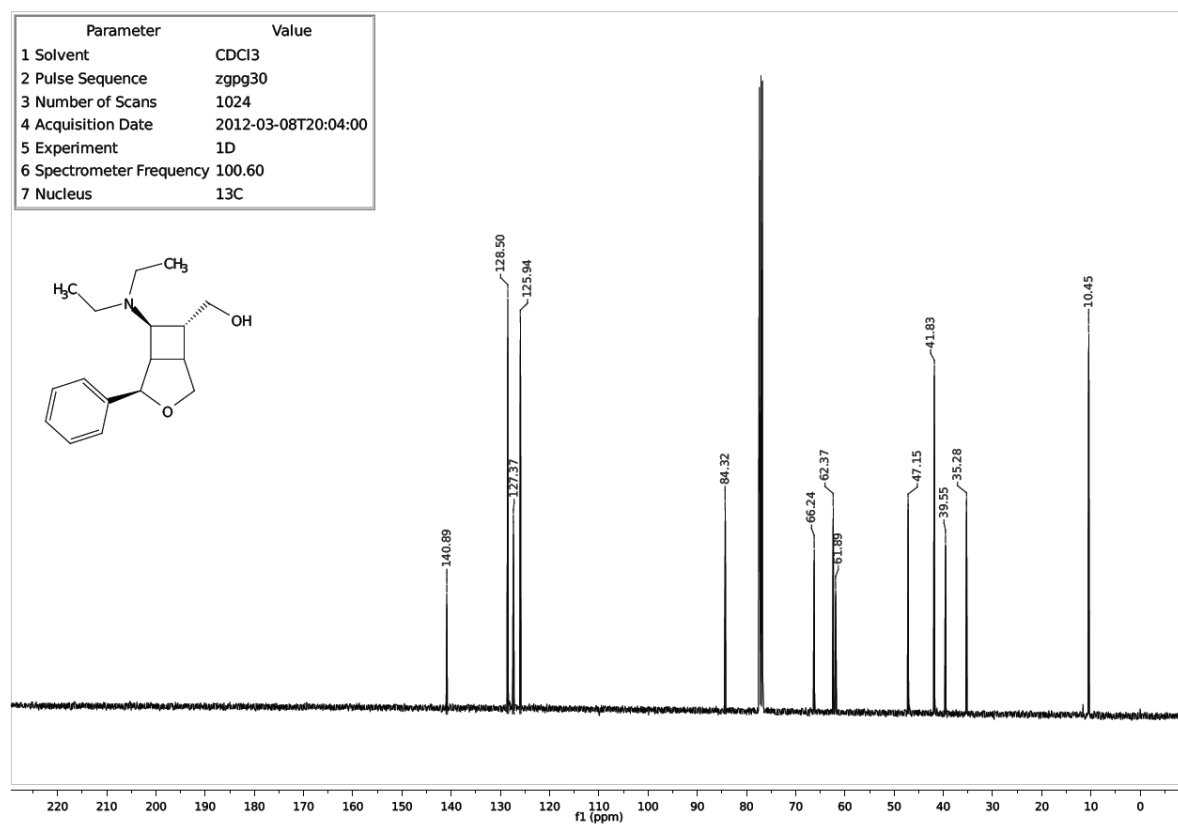
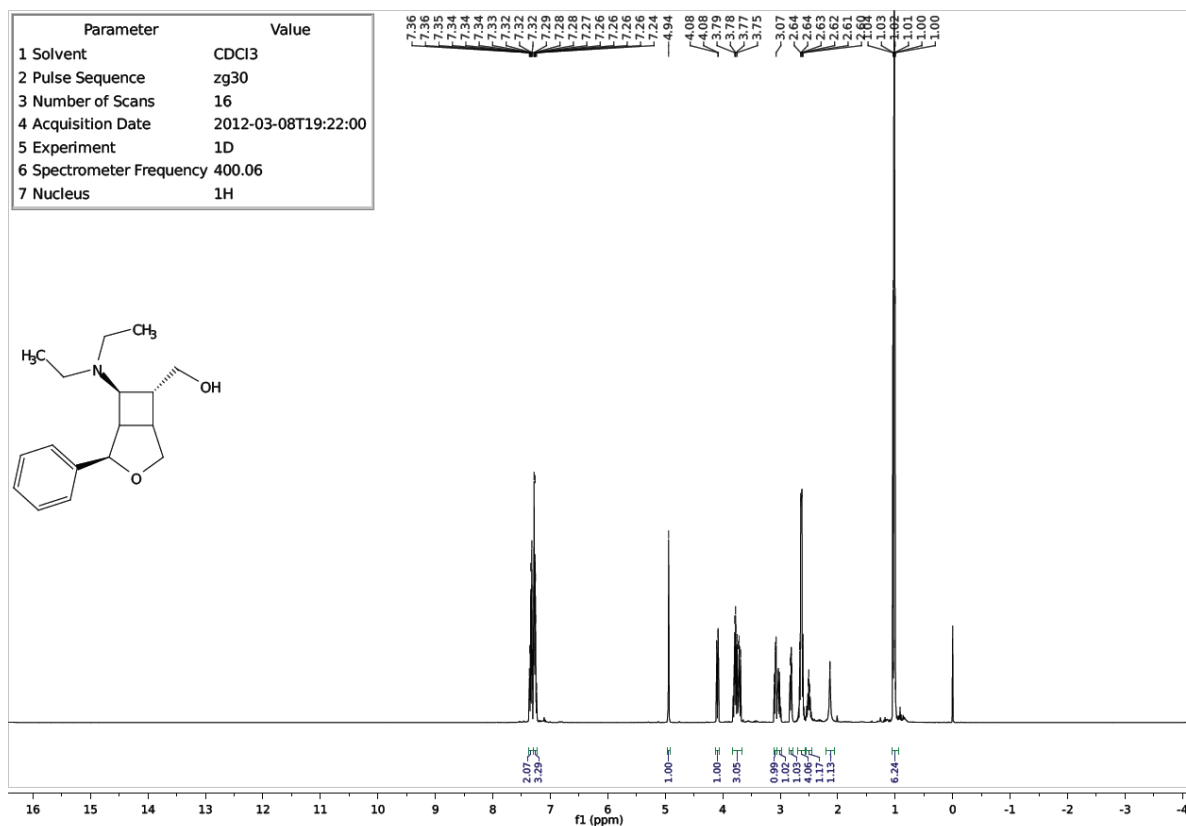


Entry	Additive	6/7/8 ^[b]	d.r. ^[c]
1	NaOAc	15/79/6	5:1
2	Benzoic acid	25/47/28	3:1
3	<i>p</i> -NO ₂ -benzoic acid	44/13/43	n.d
4	TFA	47/13/40	1.6:1
5 ^[d]	Benzoic acid	17/64/19	3.5:1
6 ^[e]	Et ₂ NH	20/73/7	3.6:1

^[a] Cinnamaldehyde (2 equiv), Et₂NH (2 equiv), additive (1eq) and hydroxycrotonate (1 equiv) were stirred in an appropriate solvent at rt for 48 h, with MS. ^[b] Ratios were determined by ¹H NMR in relation to the major diastereomer. ^[c] Ratio of [3.2.0]-oxabicyclo heptane **7** 2-*exo* and 2-*endo* diastereoisomers determined by ¹H NMR. ^[d] 20 mol% of the additive ^[e] 3 equiv of Et₂NH was used.

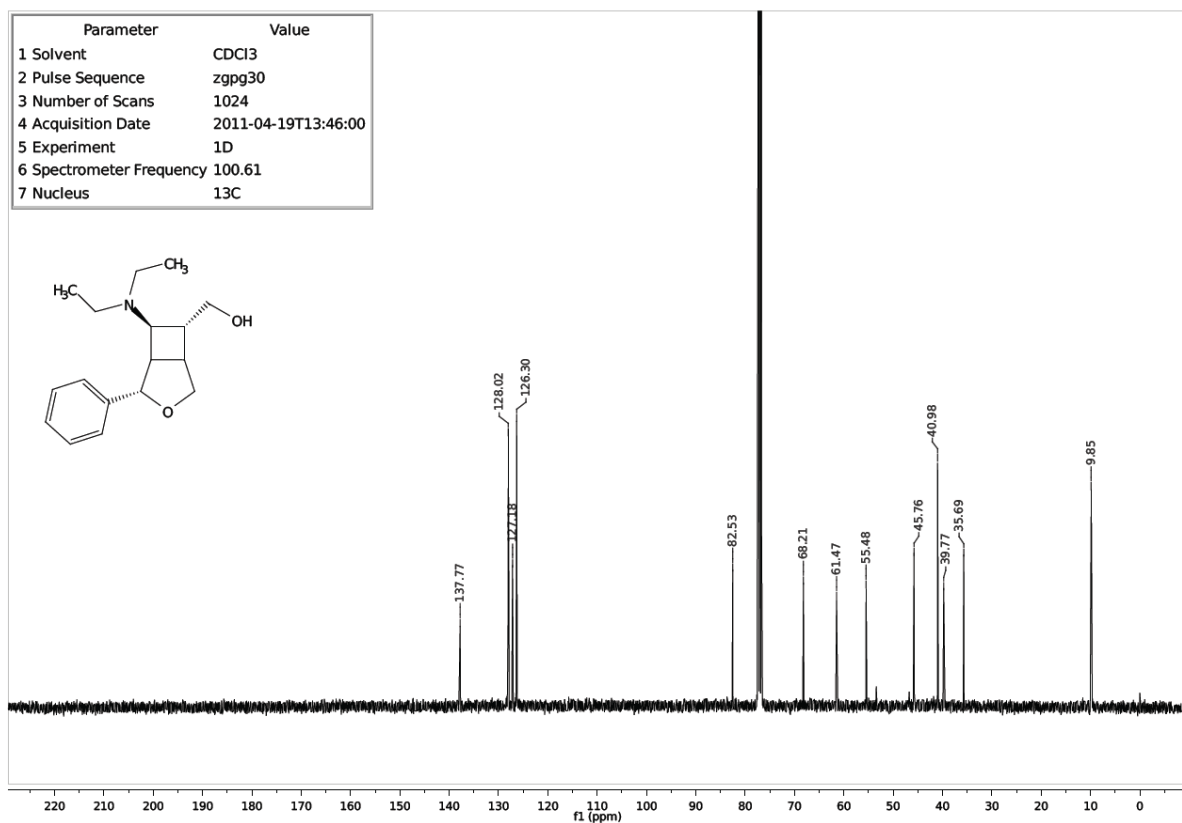
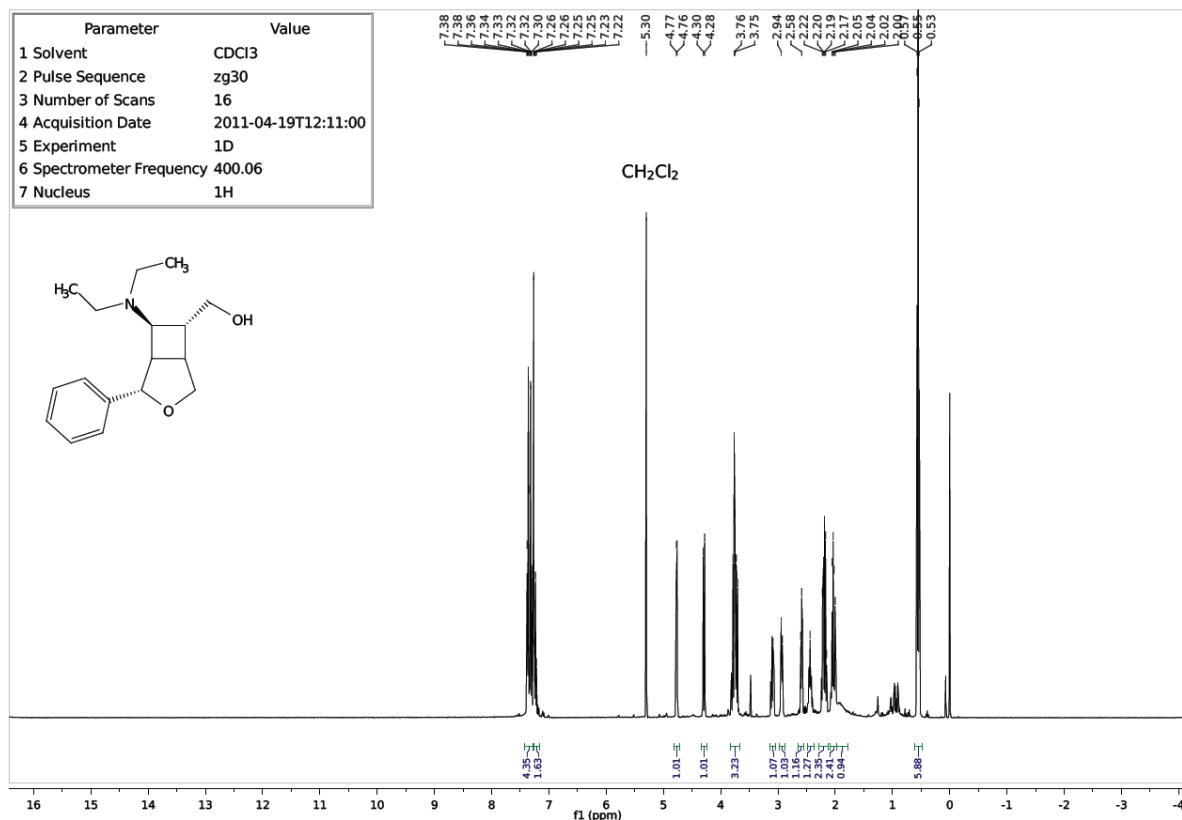
2. Spectral Data (^1H and ^{13}C spectra)

9a (7-*exo*-(Diethylamino)-2-*exo*-phenyl-3-oxabicyclo[3.2.0]heptan-6-*endo*-yl)methanol



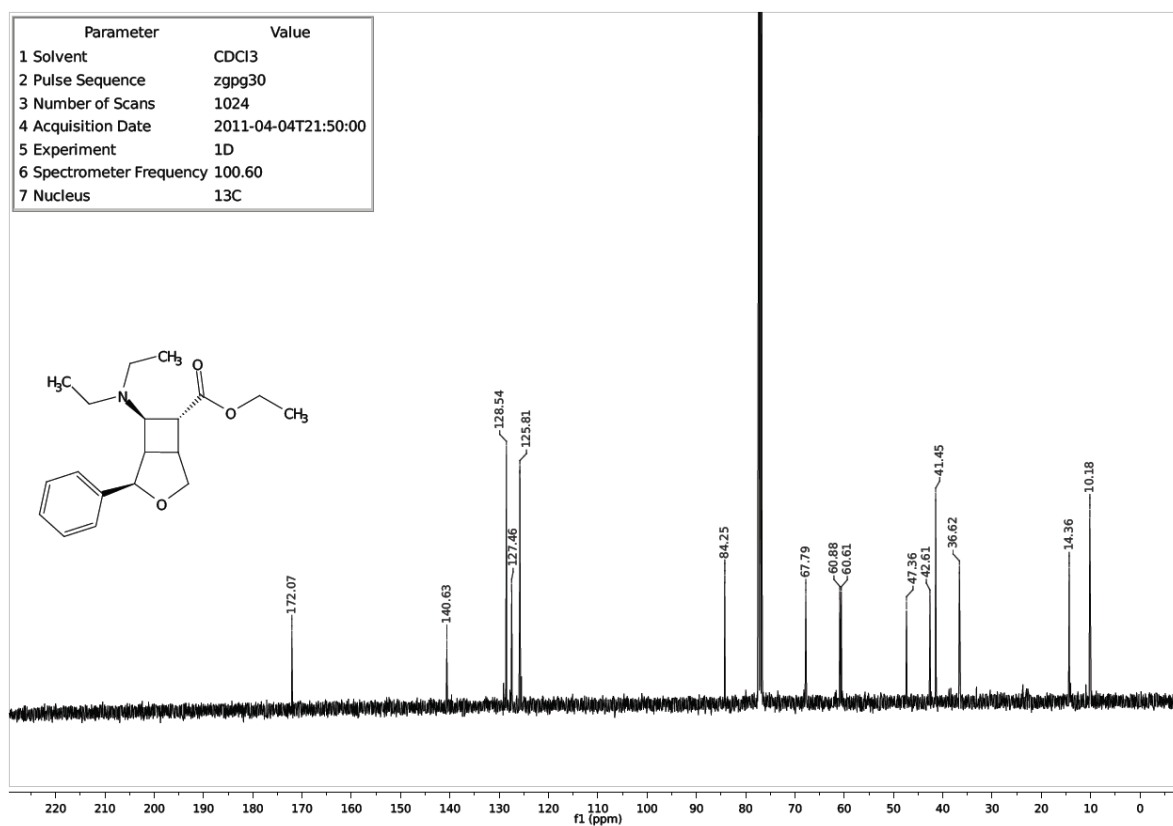
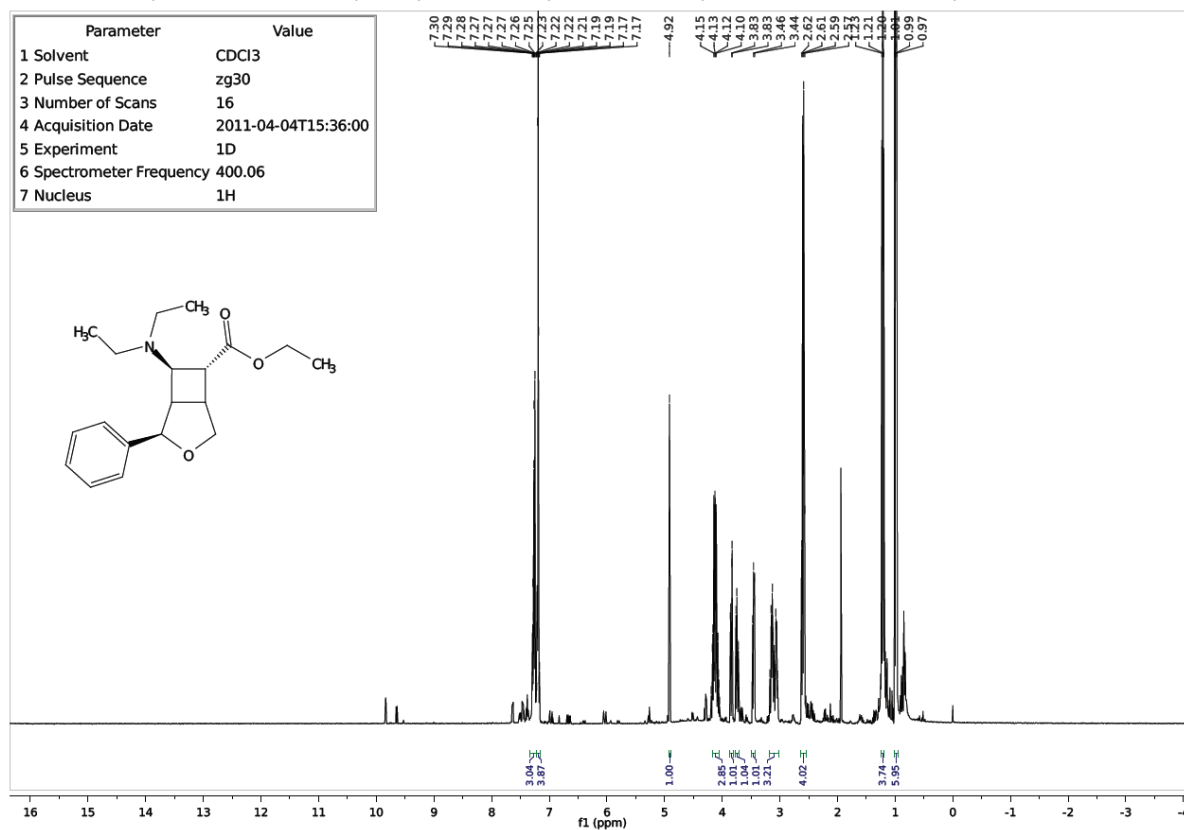
9a 2-endo diastereoisomer

(7-*exo*-(Diethylamino)-2-*endo*-phenyl-3-oxabicyclo[3.2.0]heptan-6-*endo*-yl)methanol

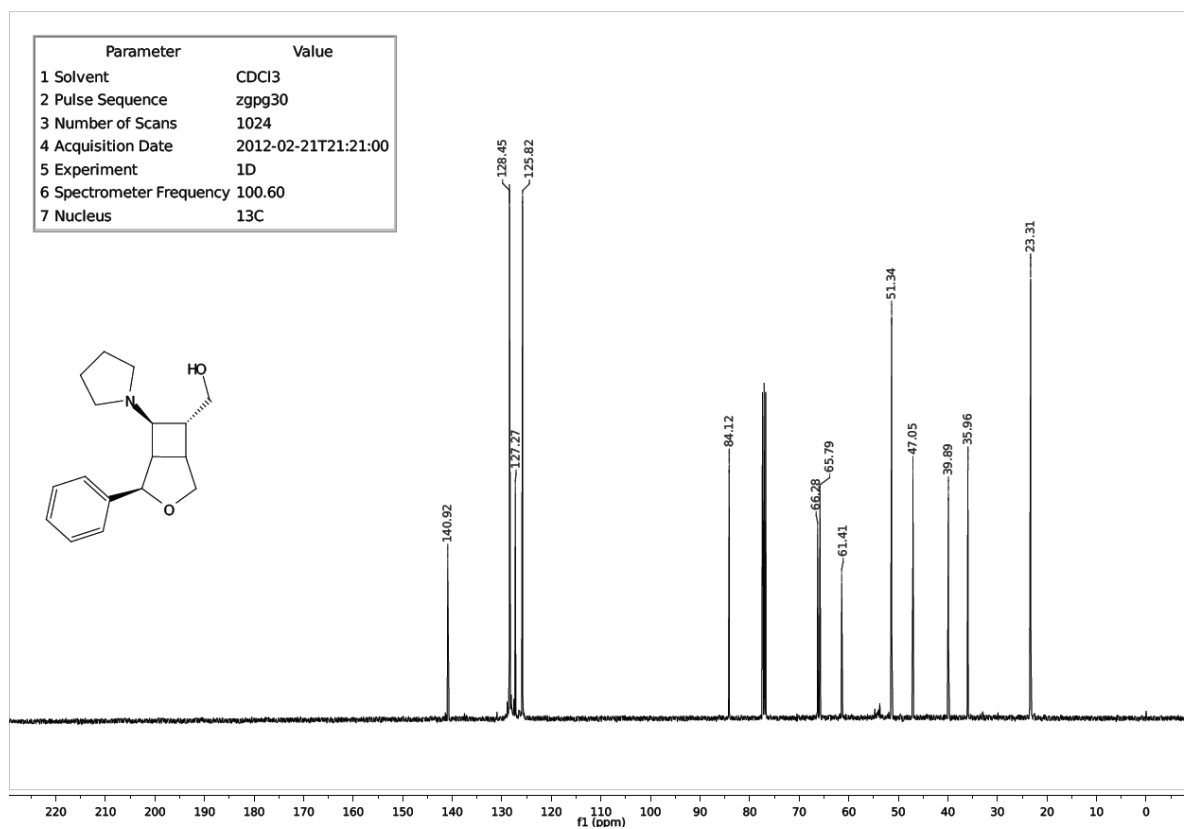
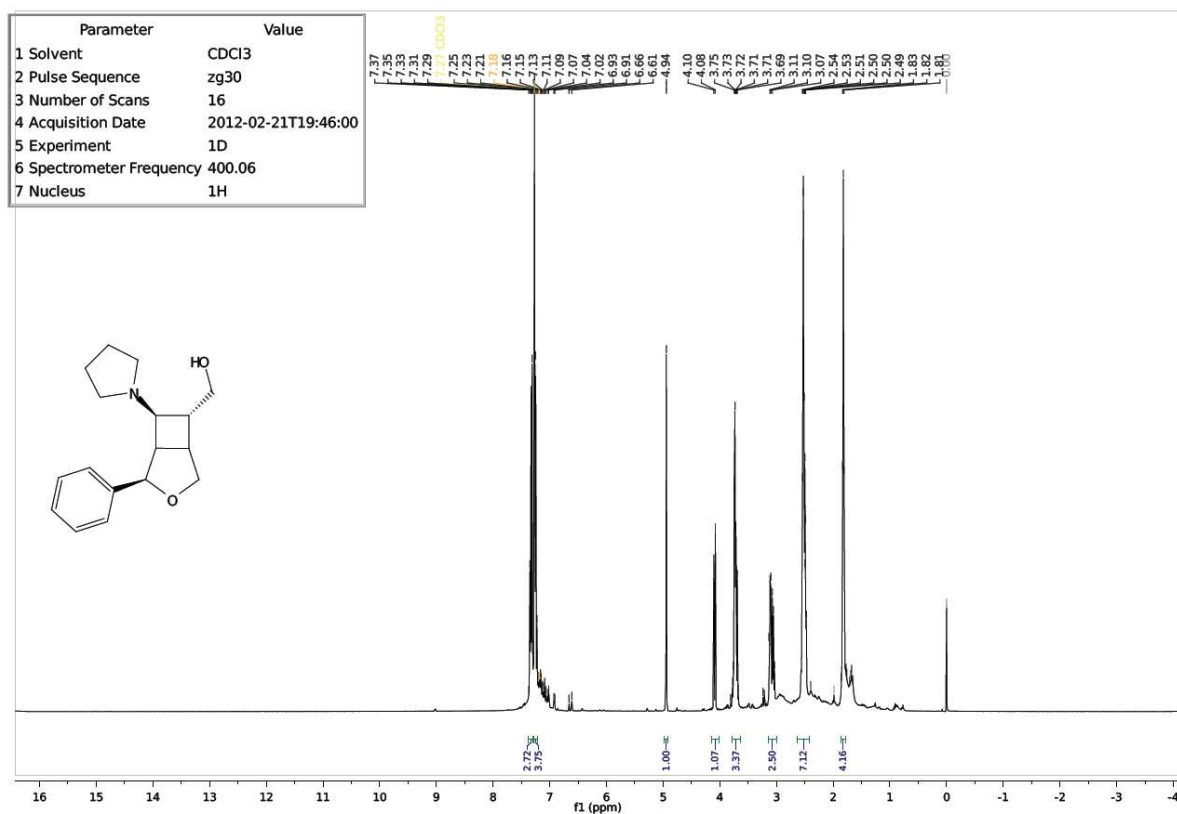


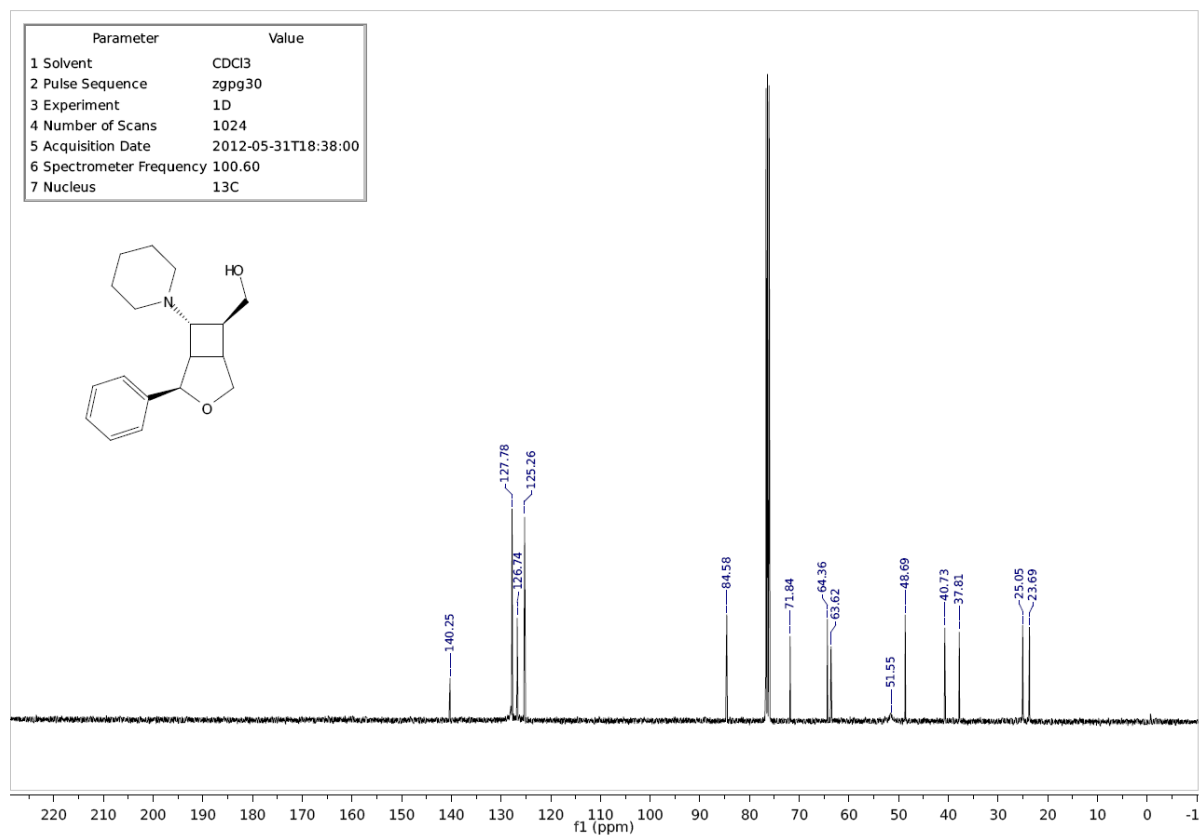
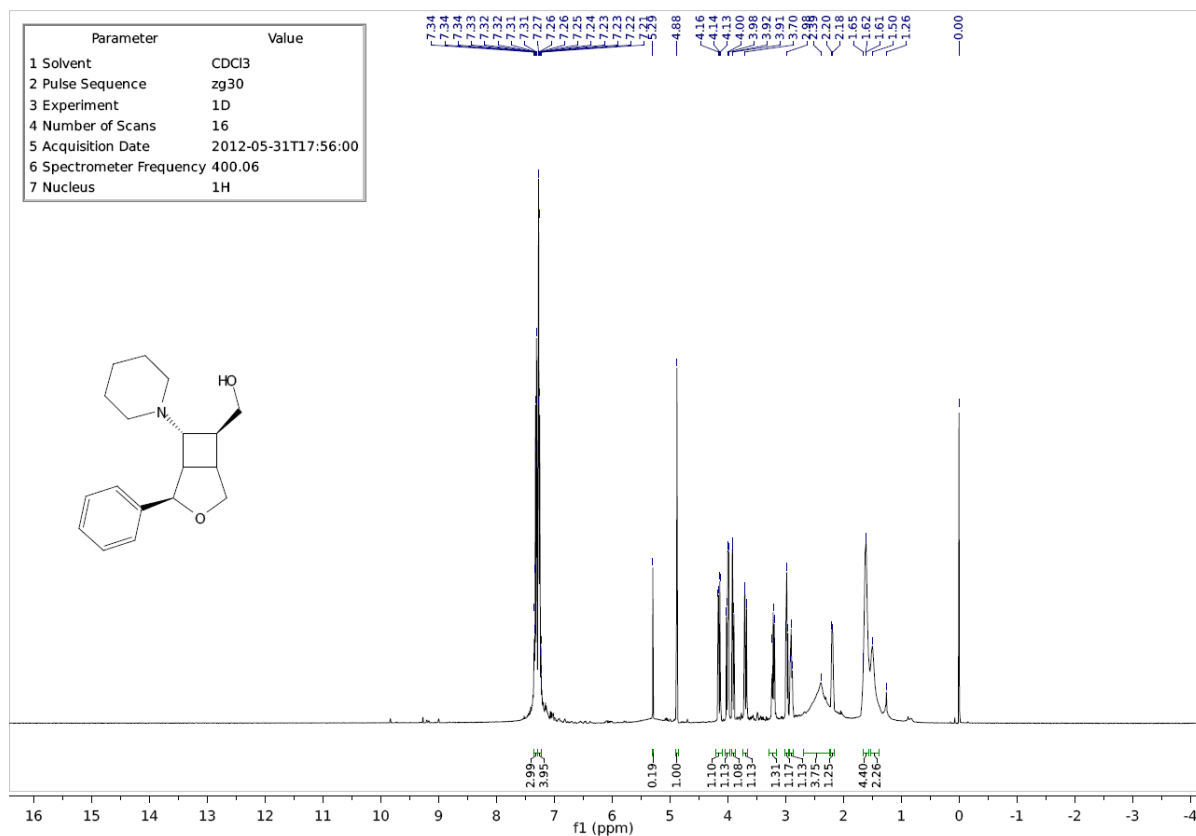
7 2-exo ester

7-*exo*-(diethylamino)-2-*endo*-phenyl-3-oxabicyclo[3.2.0]heptane-6-*endo*-carboxylate



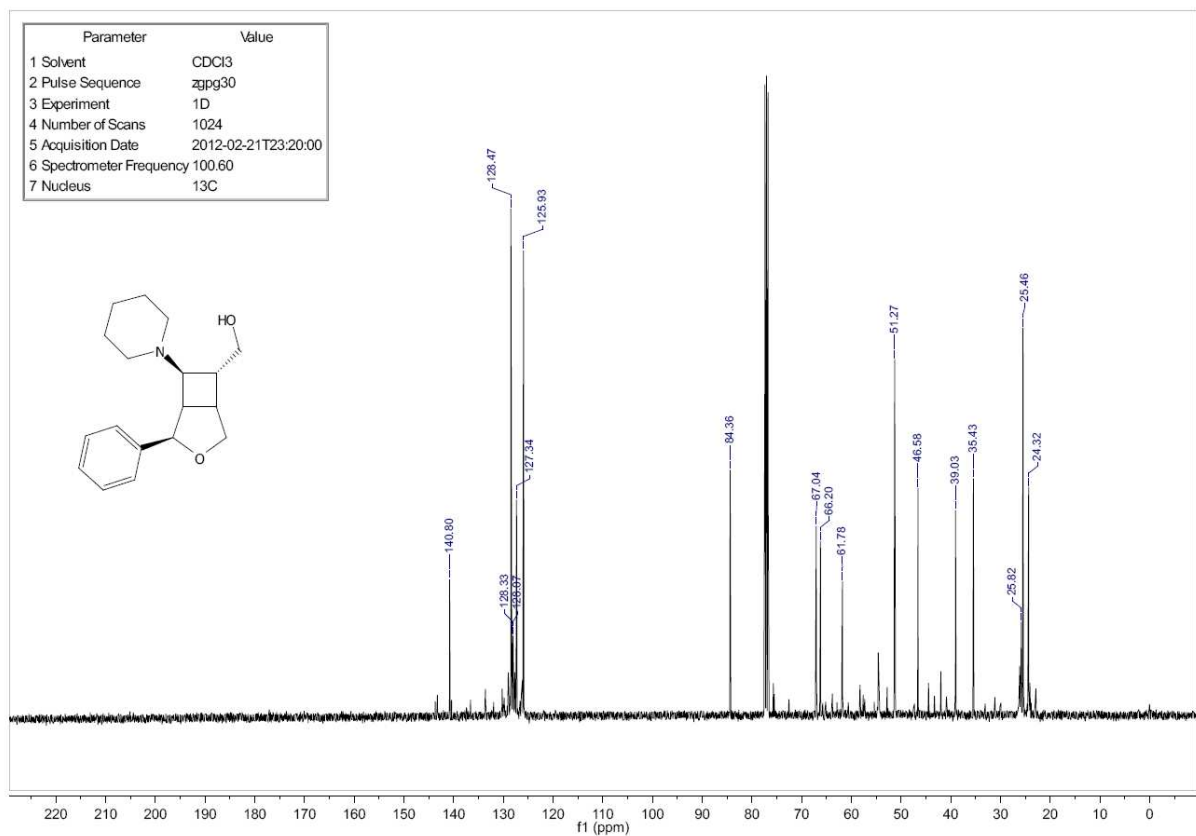
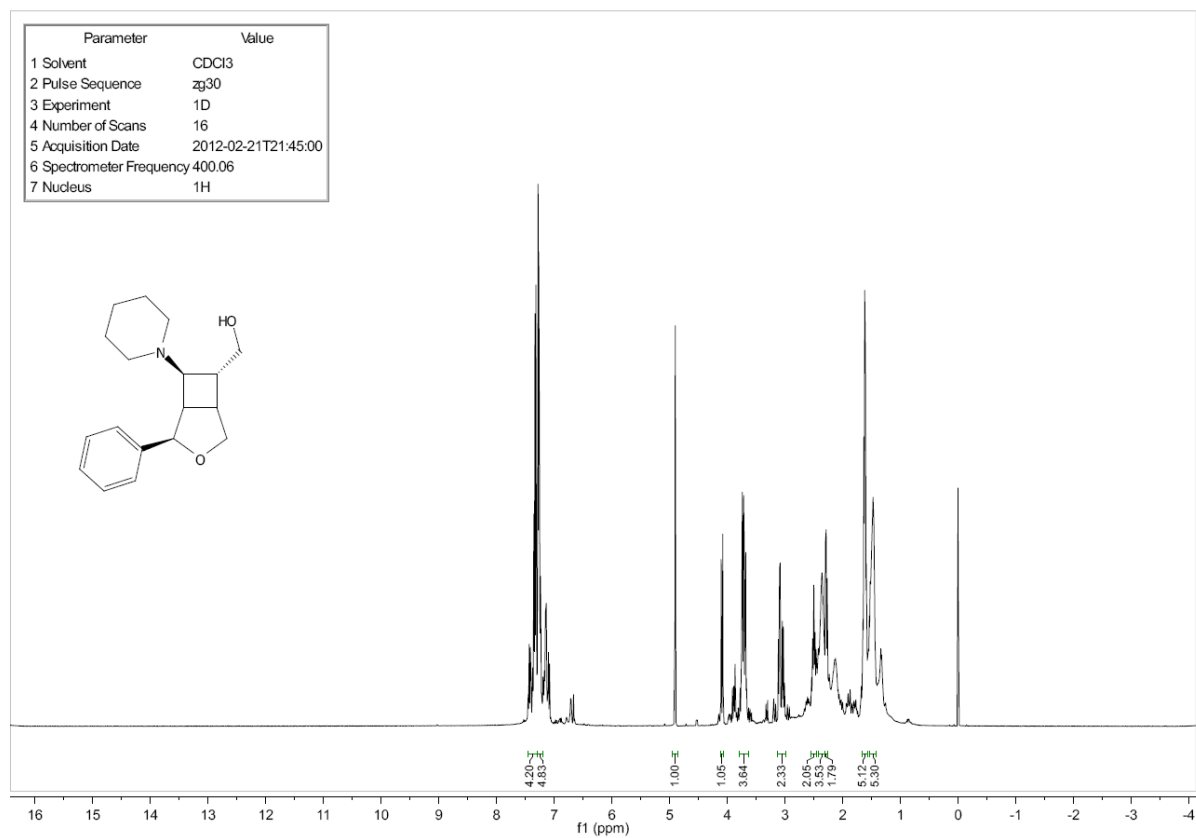
9b (2-*exo*-Phenyl-7-*exo*-(pyrrolidin-1-yl)-3-oxabicyclo[3.2.0]heptan-6-*endo*-yl)methanol



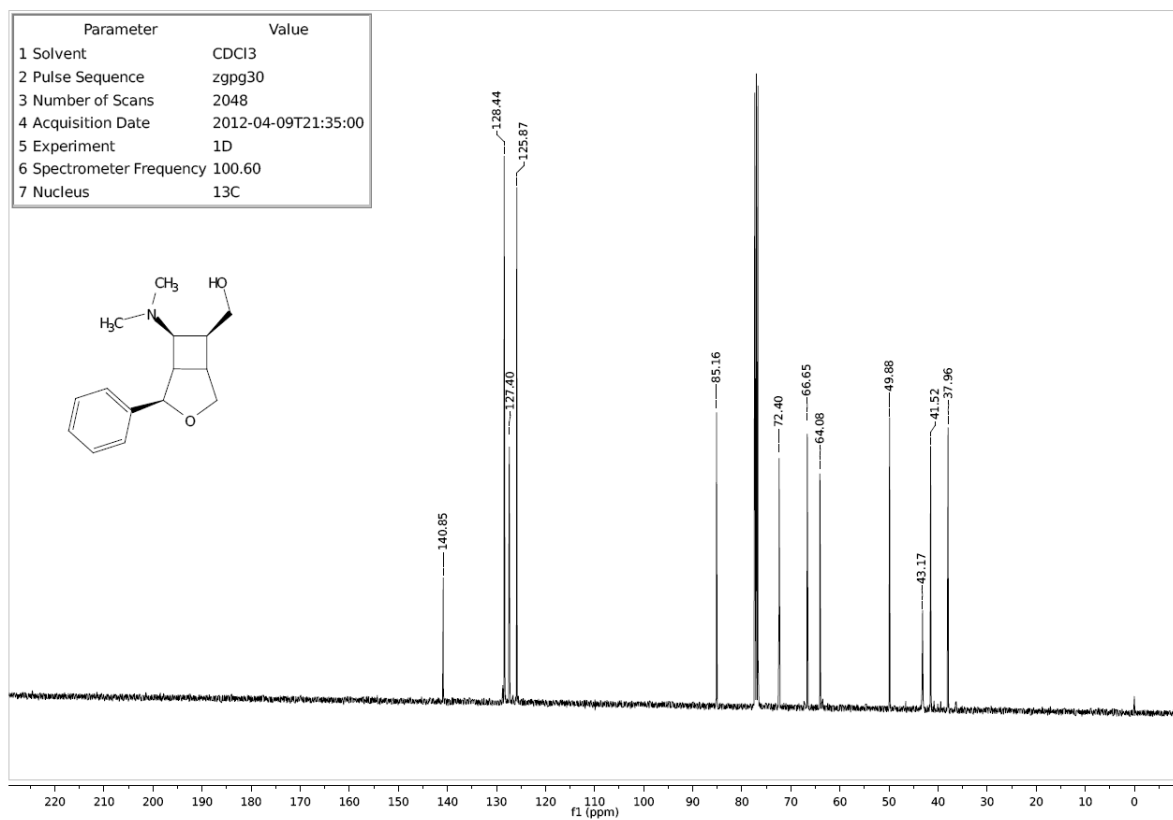
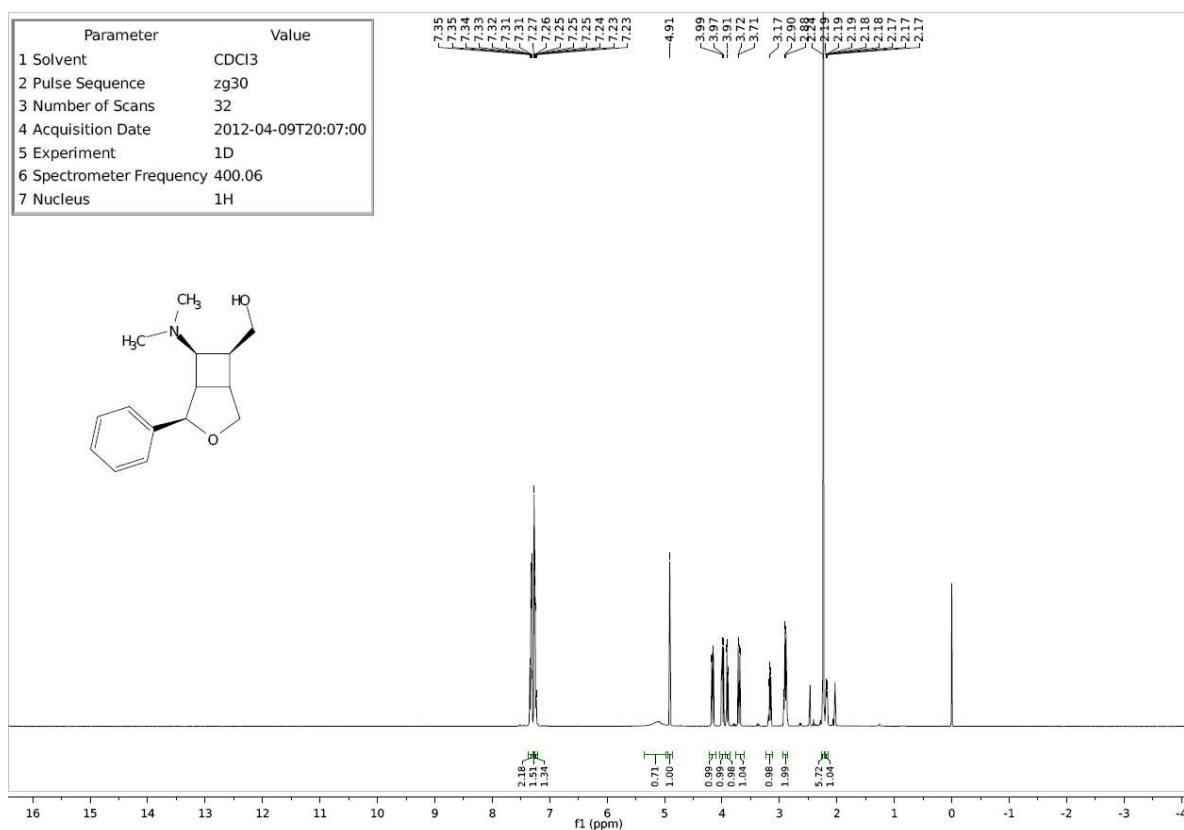
9c 2-exo-7-endo-6-exo diastereoisomer**(2-exo-Phenyl-7-endo-(piperidin-1-yl)-3-oxabicyclo[3.2.0]heptan-6-exo-yl)methanol**

9c 2-*exo*-7-*exo*-6-*endo* diastreoisomer

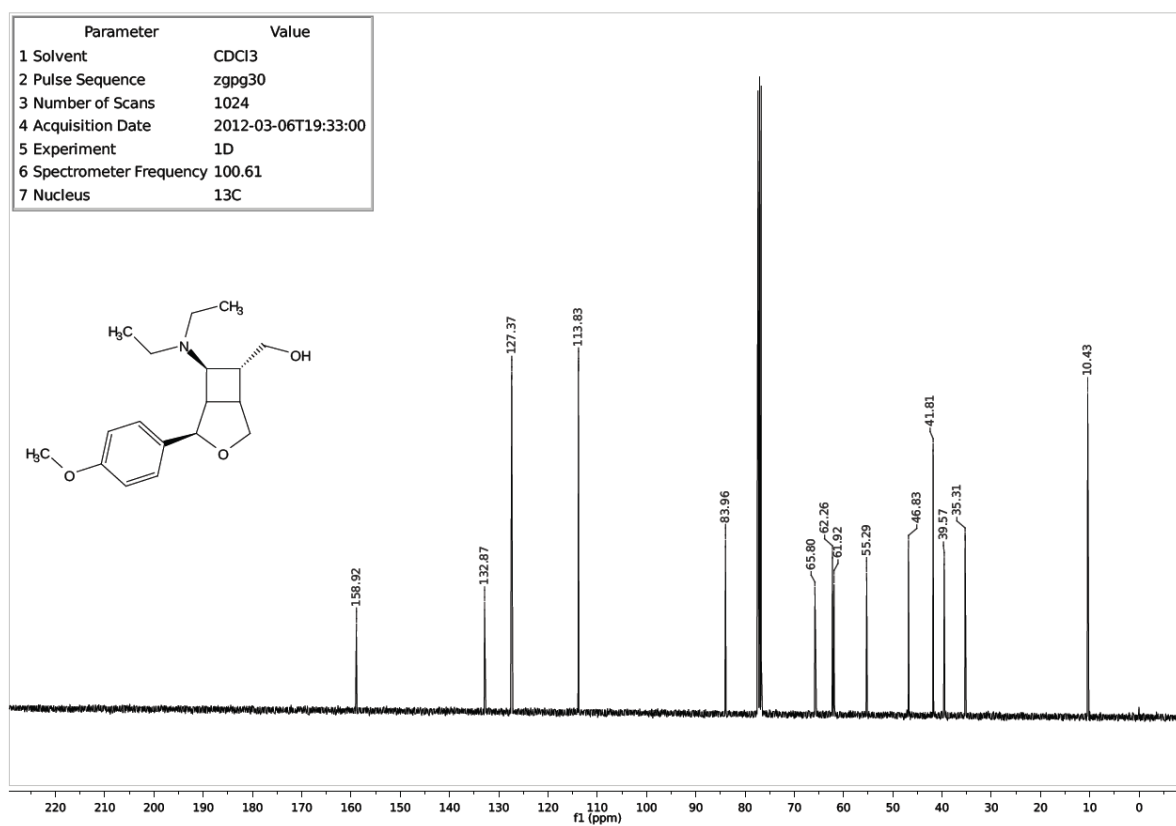
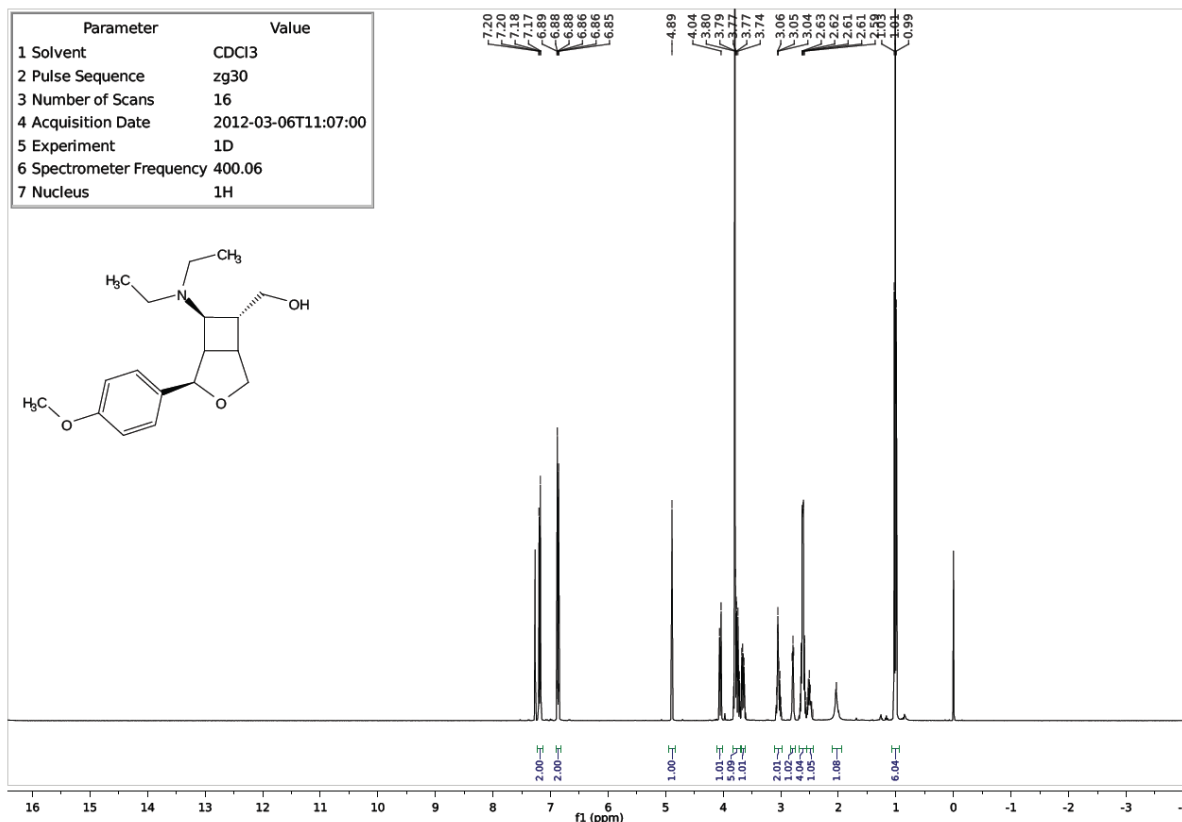
(2-*exo*-Phenyl-7-*exo*-(piperidin-1-yl)-3-oxabicyclo[3.2.0]heptan-6-*endo*-yl)methanol



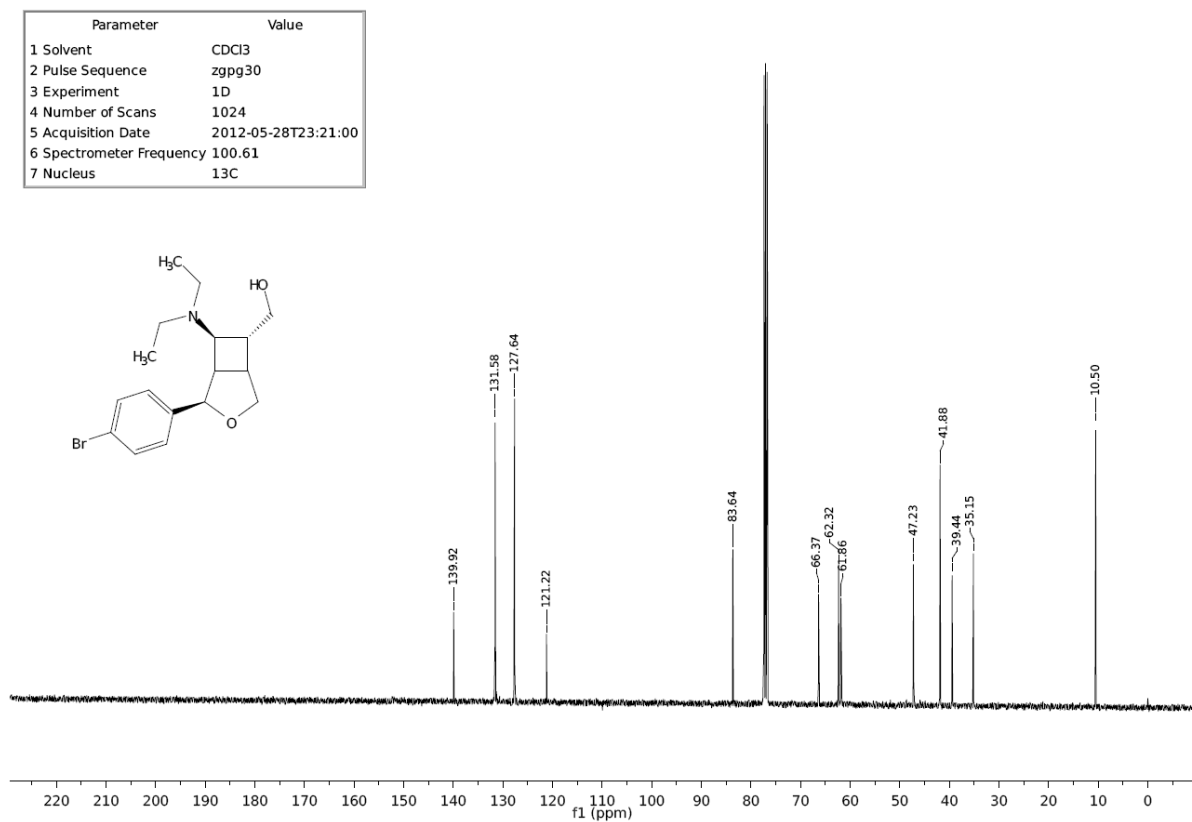
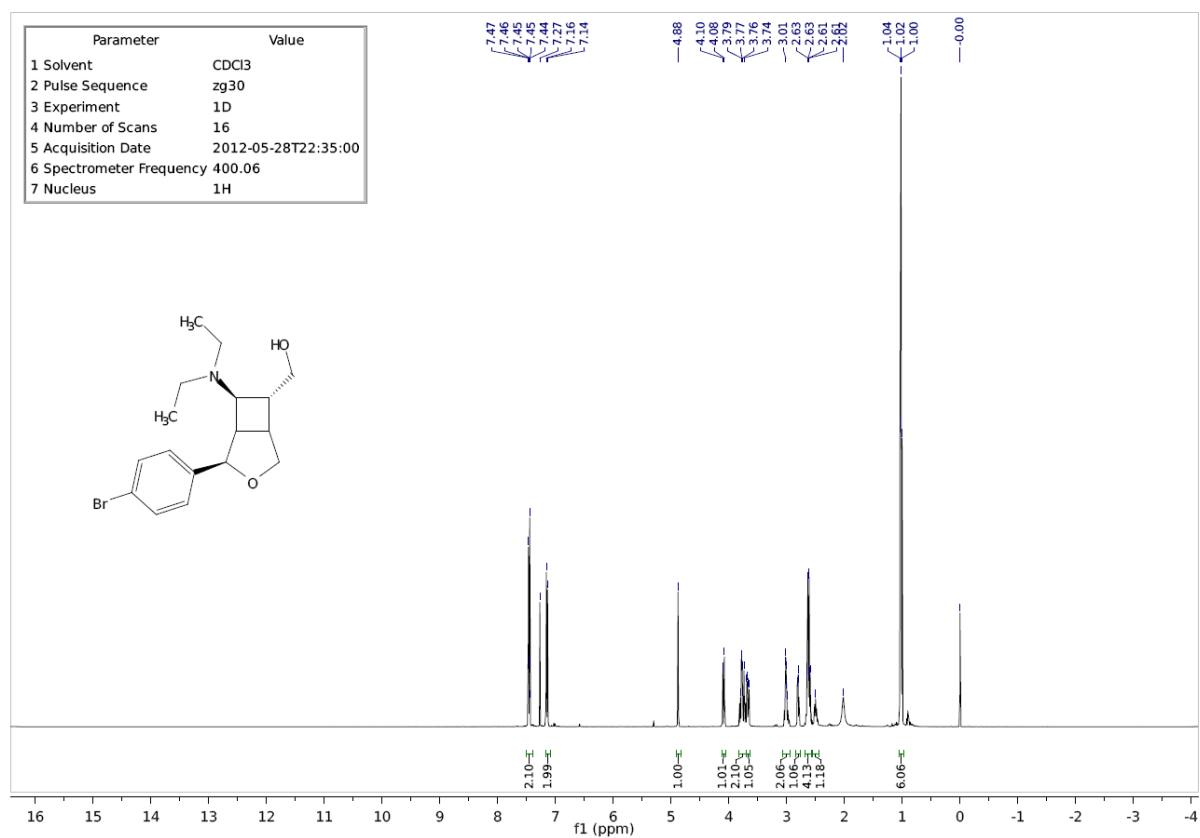
9d (7-*exo*-(Dimethylamino)-2-*exo*-phenyl-3-oxabicyclo[3.2.0]heptan-6-*exo*-yl)methanol



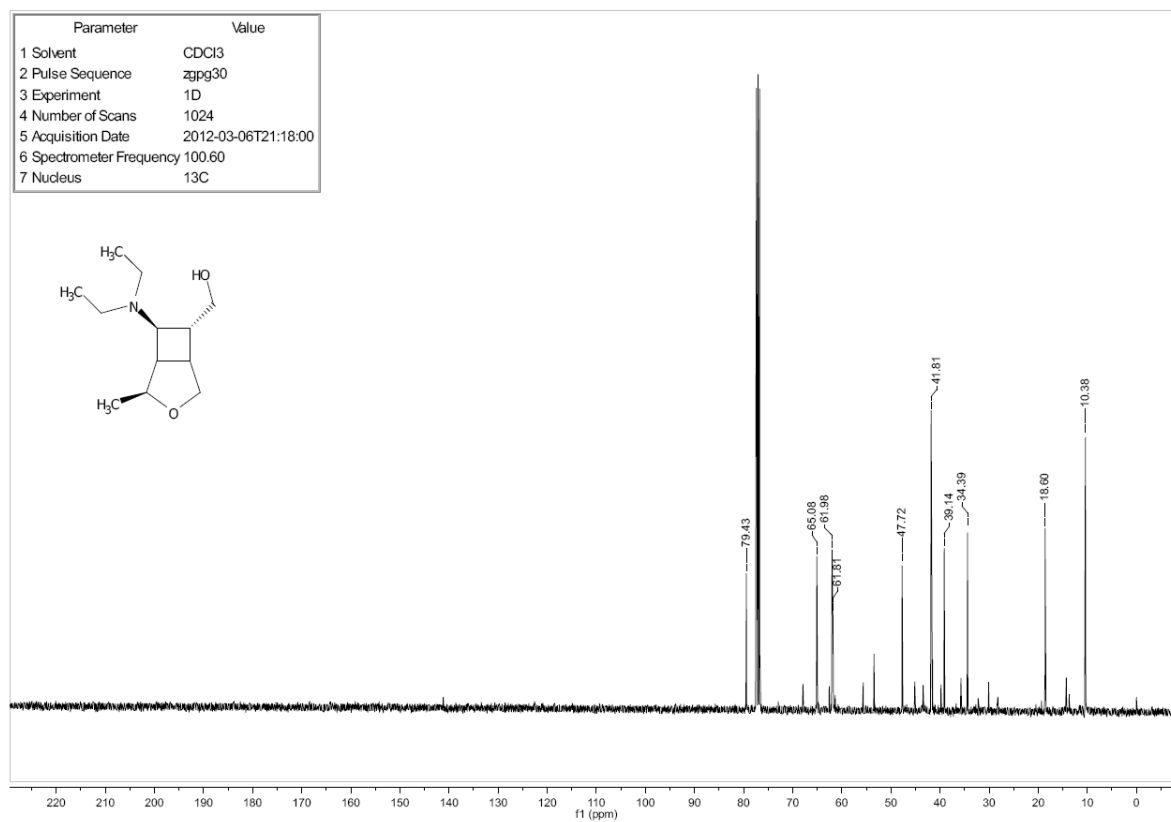
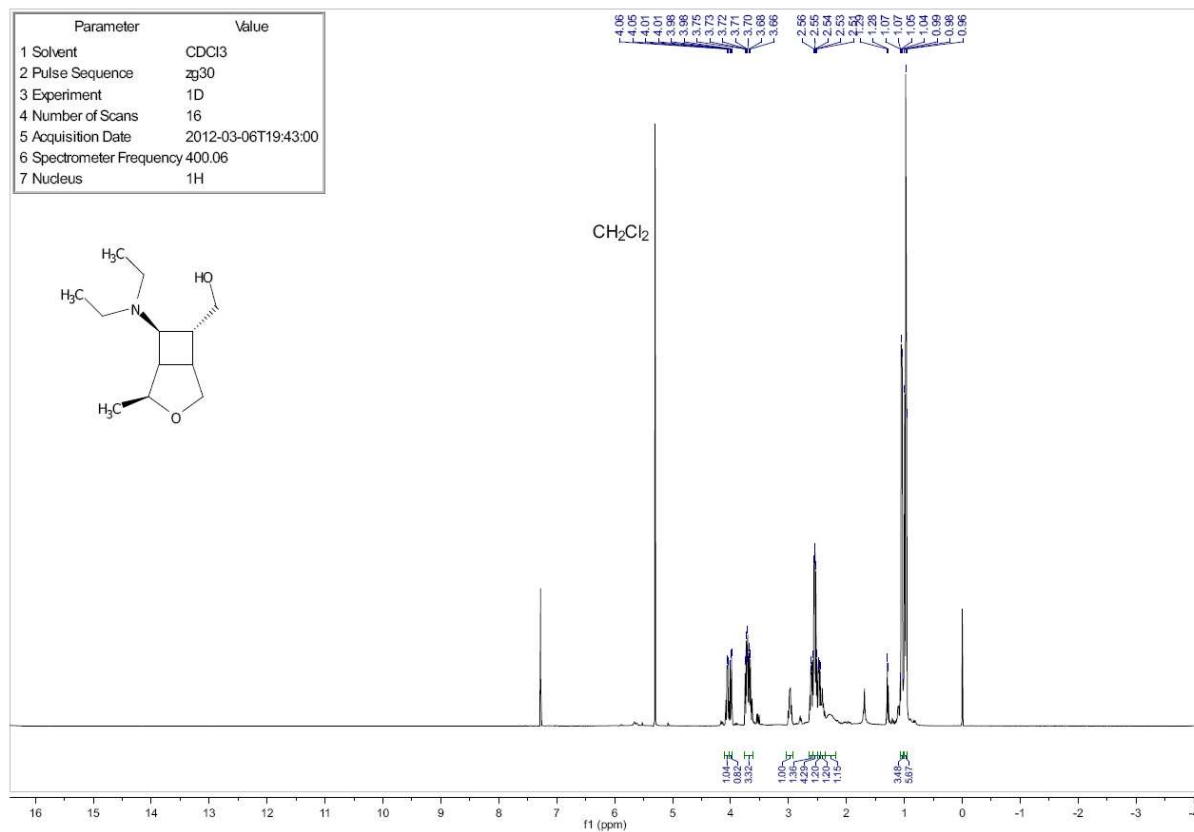
9e (7-*exo*-(Diethylamino)-2-*exo*-(4-methoxyphenyl)-3-oxabicyclo[3.2.0]heptan-6-*endo*-yl)methanol



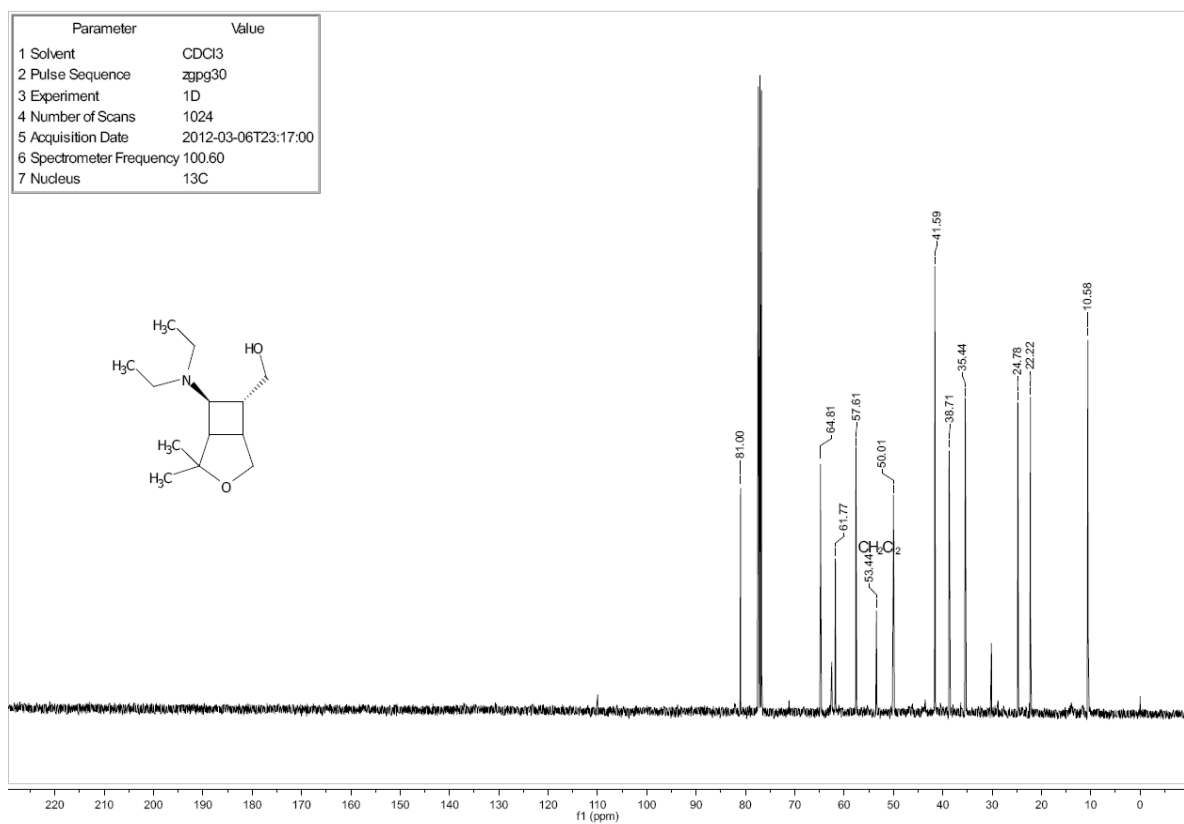
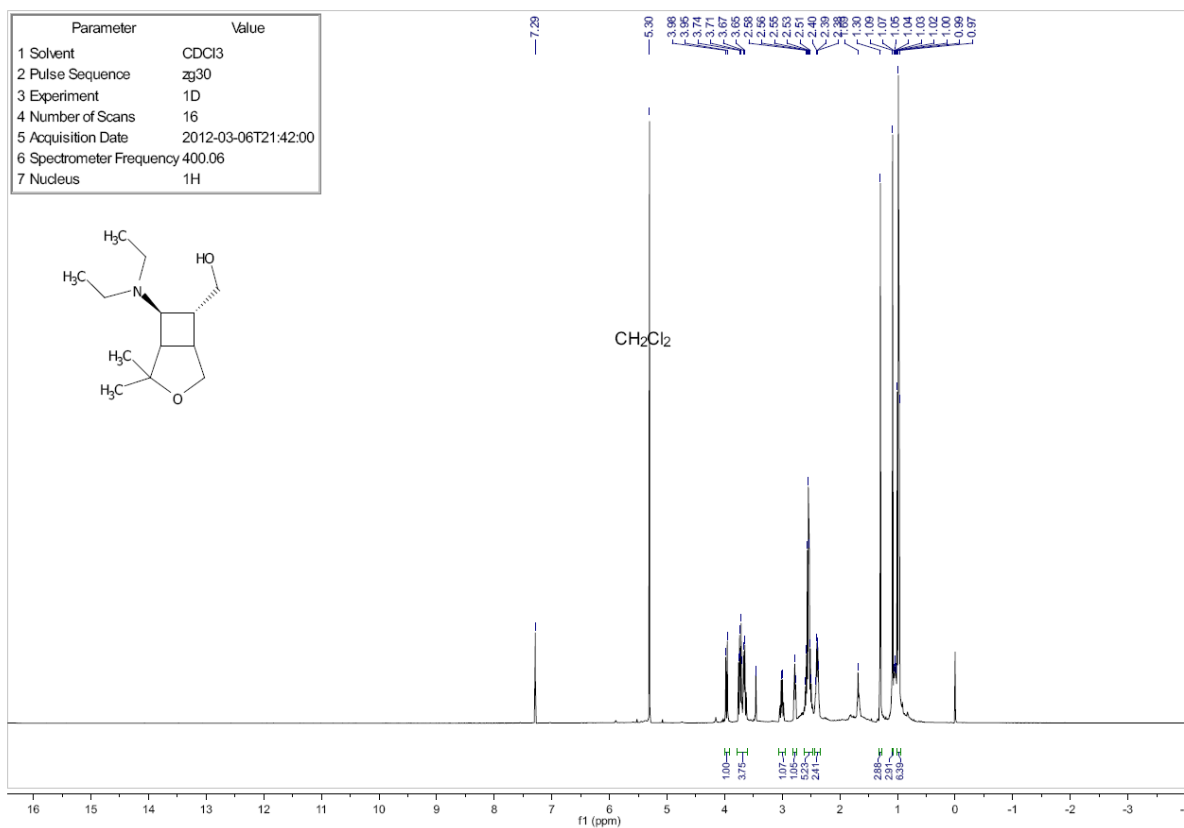
9f (2-*exo*-(4-Bromophenyl)-7-*exo*-(diethylamino)-3-oxabicyclo[3.2.0]heptan-6-*endo*-yl)methanol



9h (7-*exo*-(Diethylamino))-2-*exo*-methyl-3-oxabicyclo[3.2.0]heptan-6-*endo*-yl)methanol

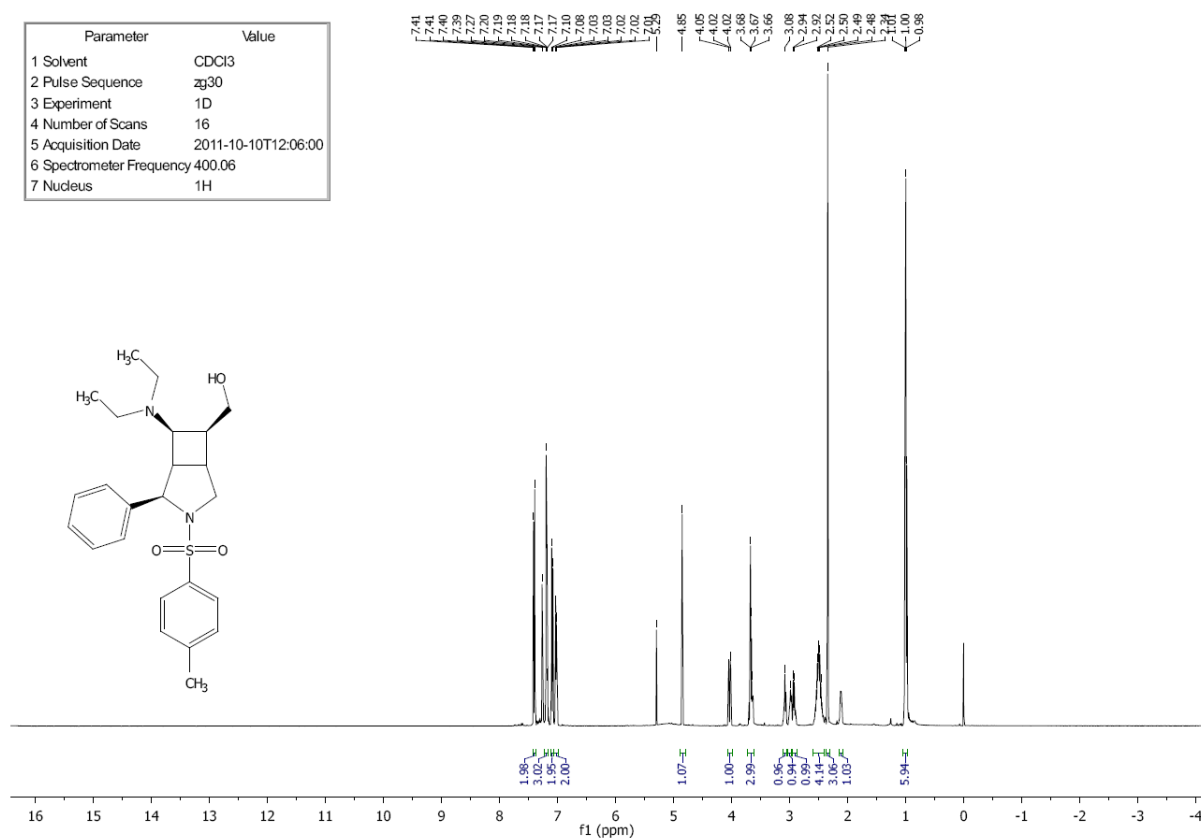


9i (7-*exo*-(Diethylamino)-2,2-dimethyl-3-oxabicyclo[3.2.0]heptan-6-*endo*-yl)methanol

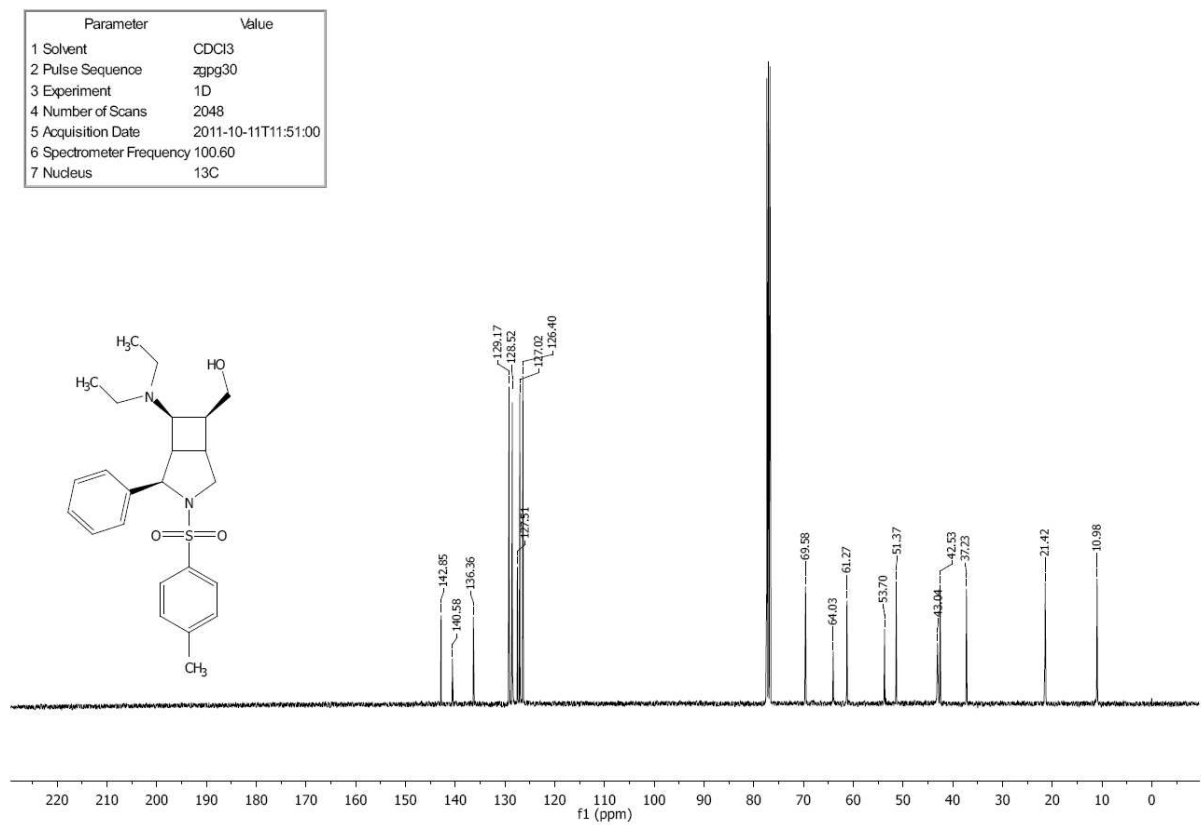


10a (7-*exo*-(Diethylamino)-2-*exo*-phenyl-3-tosyl-3-azabicyclo[3.2.0]heptan-6-*exo*-yl)methanol

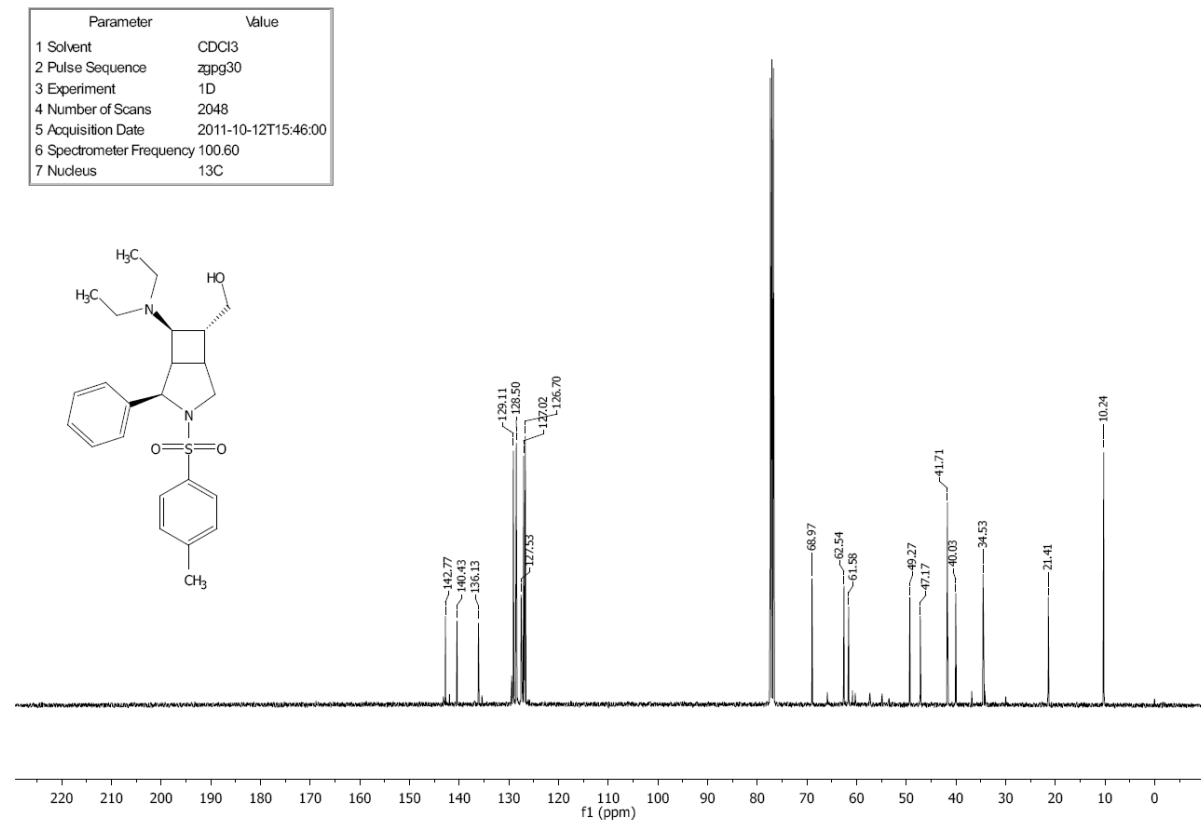
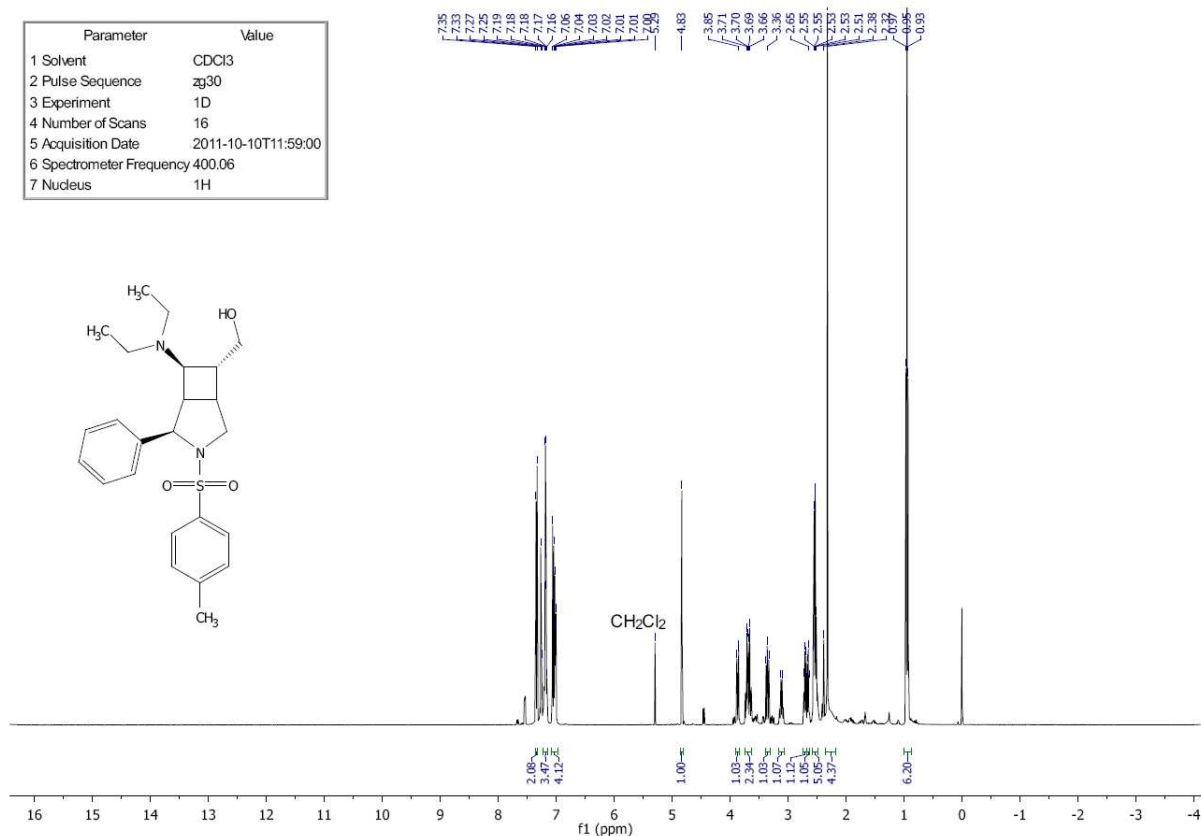
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2 Pulse Sequence	zg30
3 Experiment	1D
4 Number of Scans	16
5 Acquisition Date	2011-10-10T12:06:00
6 Spectrometer Frequency	400.06
7 Nucleus	¹ H



Parameter	Value
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2 Pulse Sequence	zgpg30
3 Experiment	1D
4 Number of Scans	2048
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6 Spectrometer Frequency	100.60
7 Nucleus	¹³ C

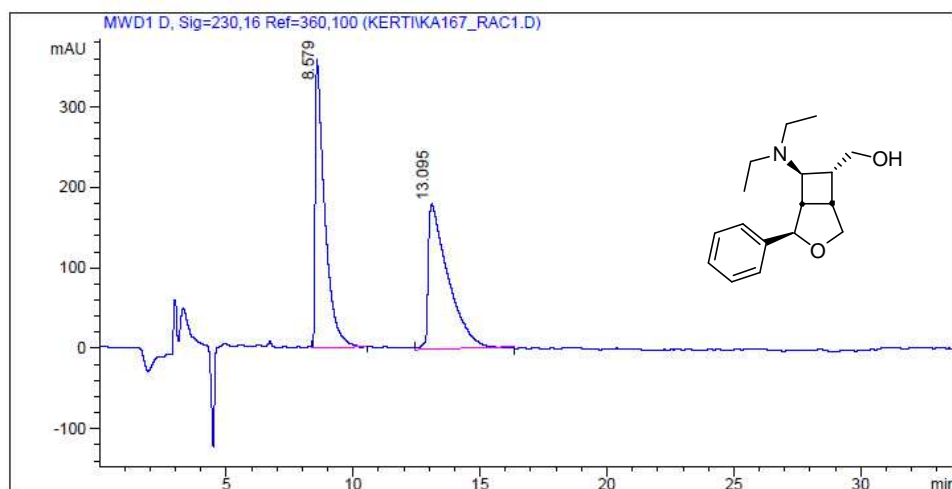


10b (7-*exo*-(Diethylamino)-2-*exo*-phenyl-3-tosyl-3-azabicyclo[3.2.0]heptan-6-*endo*-yl)methanol



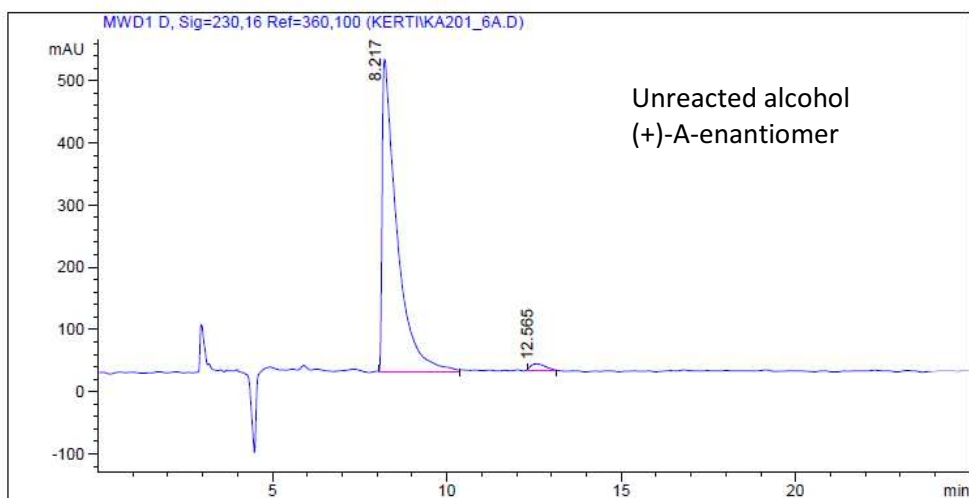
3. HPLC chromatograms for the kinetic resolutions with CALB

9a



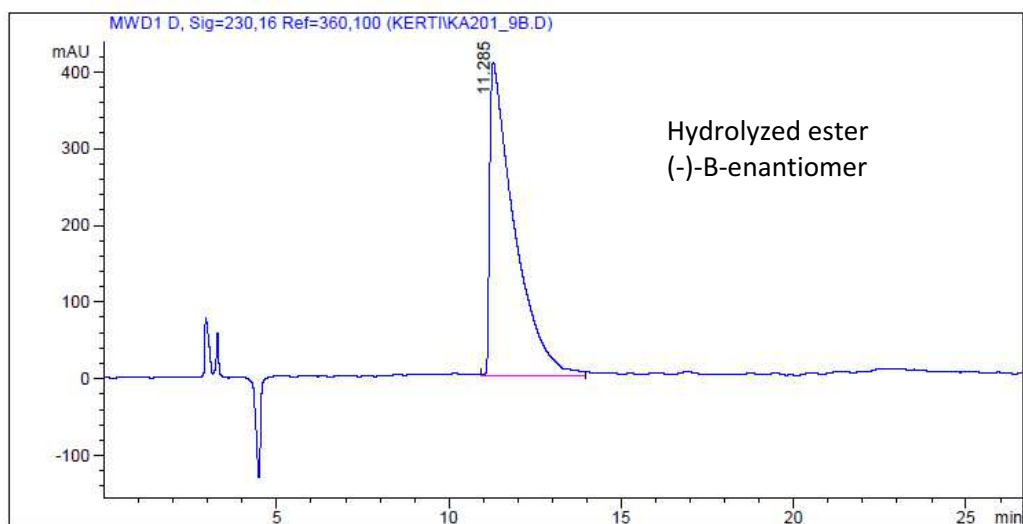
Signal 1: MWD1 D, Sig=230,16 Ref=360,100

Peak no	RT [min]	Peak Type	Width [min]	Area	Area %	Name
1	8.579	MM	0.435	9379.784	48.842	
2	13.095	MM	0.907	9824.573	51.158	



Signal 1: MWD1 D, Sig=230,16 Ref=360,100

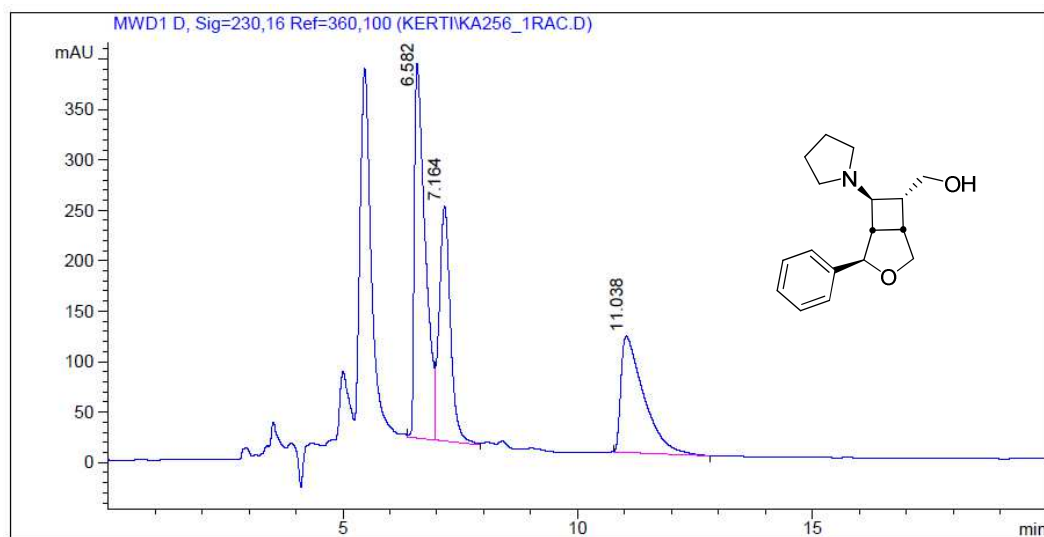
Peak no	RT [min]	Peak Type	Width [min]	Area	Area %	Name
1	8.217	MM	0.490	1.480e4	97.863	
2	12.565	MM	0.492	323.222	2.137	



Signal 1: MWD1 D, Sig=230,16 Ref=360,100

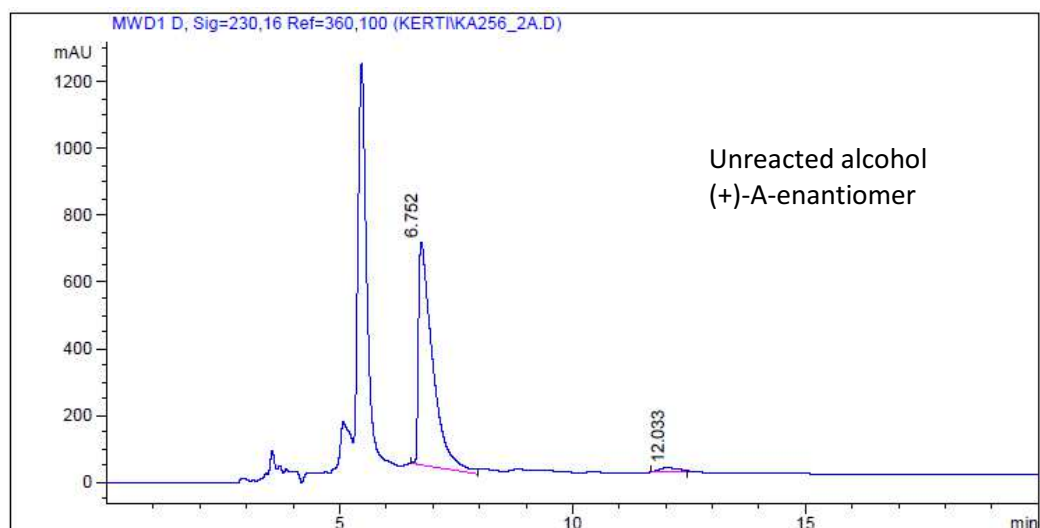
Peak no	RT [min]	Peak Type	Width [min]	Area	Area %	Name
1	11.285	MM	0.818	2.004e4	100.000	

9b



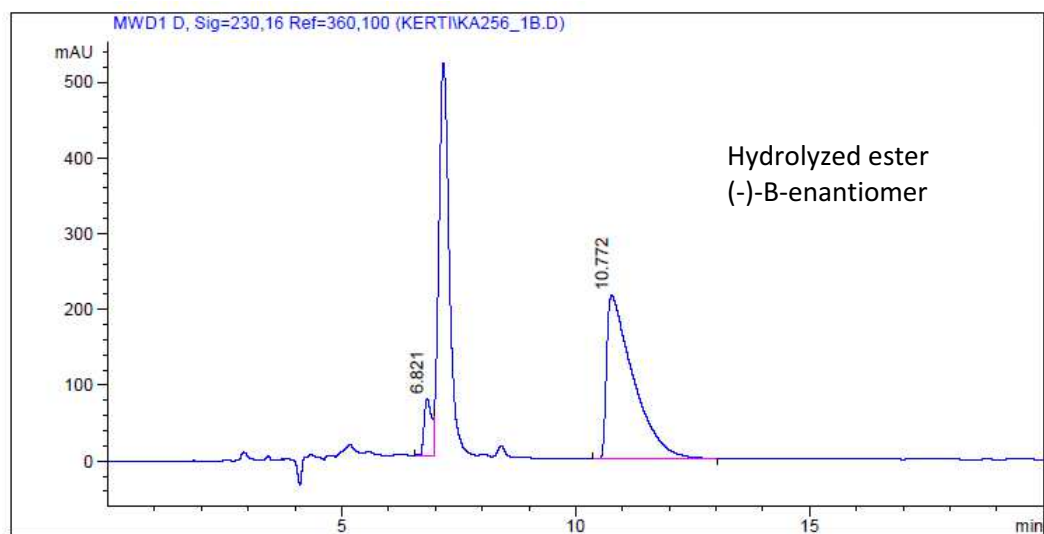
Signal 1: MWD1 D, Sig=230,16 Ref=360,100

Peak no	RT [min]	Peak Type	Width [min]	Area	Area %	Name
1	6.582	MF	0.268	5982.600	43.403	
2	7.164	FM	0.279	3894.729	28.256	
3	11.038	MM	0.564	3906.355	28.340	



Signal 1: MWD1 D, Sig=230,16 Ref=360,100

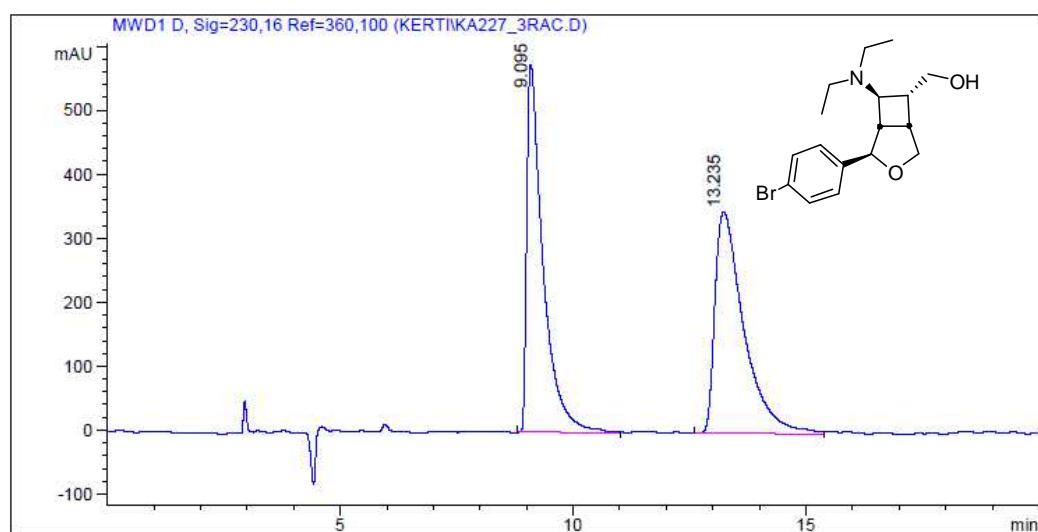
Peak no	RT [min]	Peak Type	With [min]	Area	Area %	Name
1	6.752	MM	0.352	1.409e4	97.635	
2	12.033	MM	0.469	341.338	2.365	



Signal 1: MWD1 D, Sig=230,16 Ref=360,100

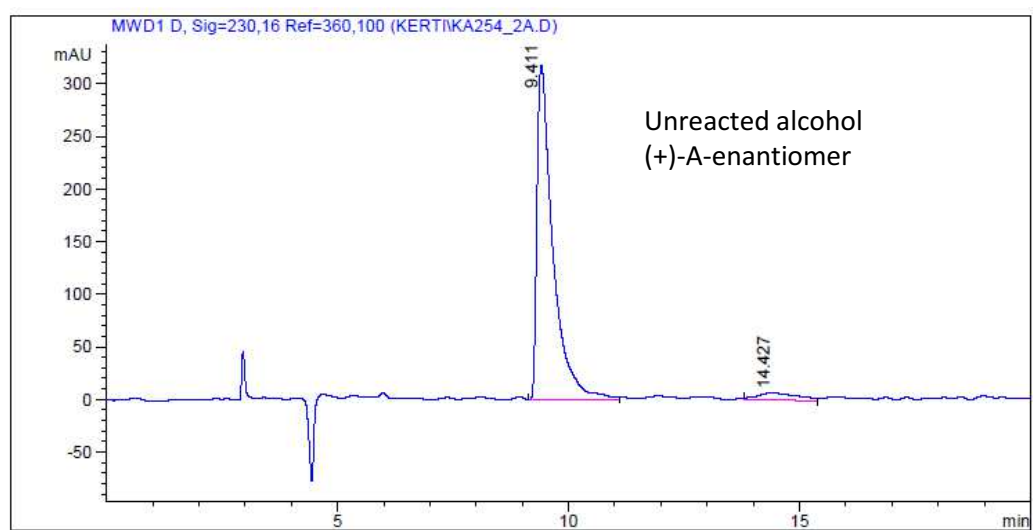
Peak no	RT [min]	Peak Type	With [min]	Area	Area %	Name
1	6.821	MF	0.203	927.087	9.792	
2	10.772	VB	0.553	8541.022	90.208	

9f



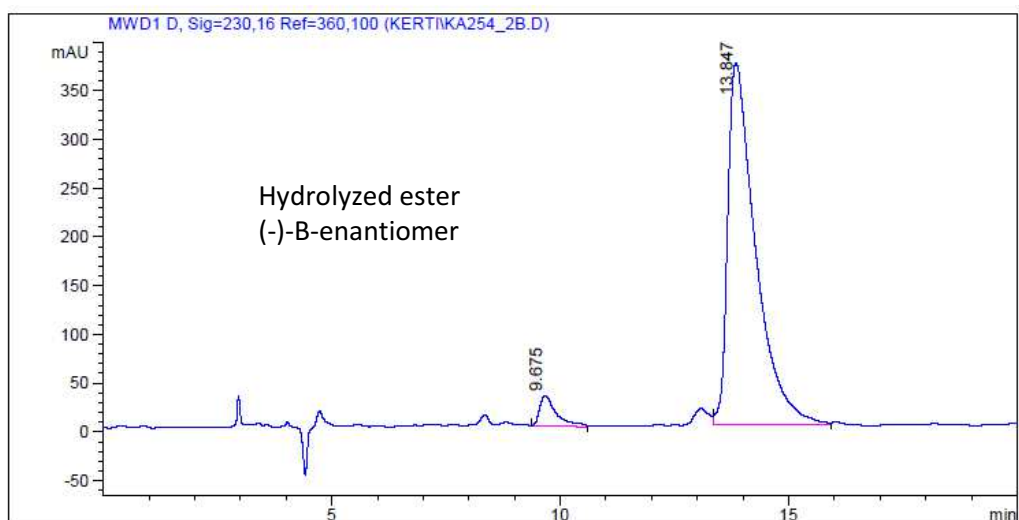
Signal 1: MWD1 D, Sig=230,16 Ref=360,100

Peak no	RT [min]	Peak Type	With [min]	Area	Area %	Name
1	9.095	MM	0.406	1.397e4	48.210	
2	13.235	VV	0.643	1.500e4	51.790	



Signal 1: MWD1 D, Sig=230,16 Ref=360,100

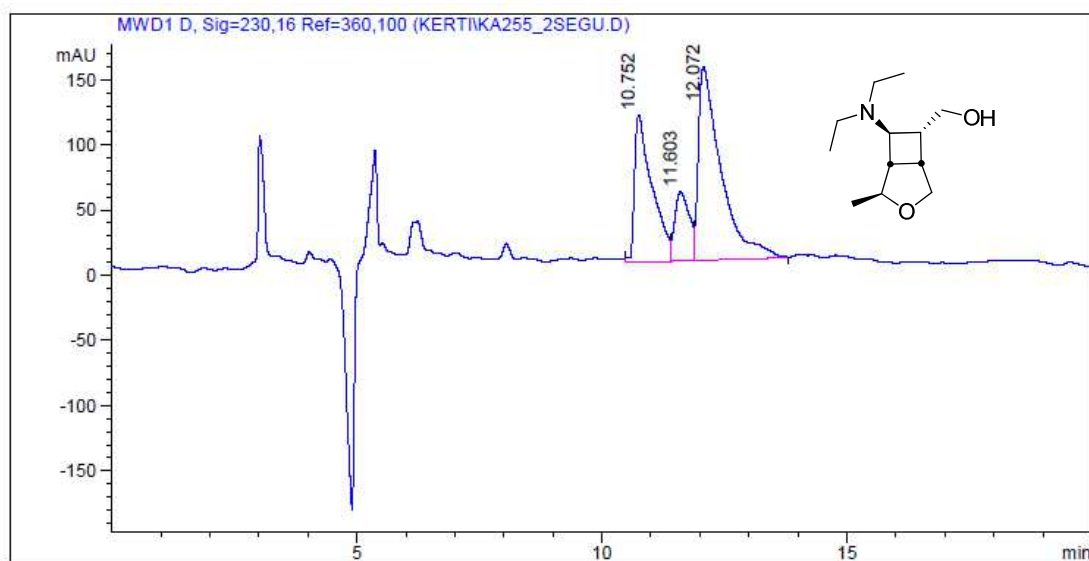
Peak no	RT [min]	Peak Type	With [min]	Area	Area %	Name
1	9.411	MM	0.396	7553.762	95.179	
2	14.427	MM	0.961	382.631	4.821	



Signal 1: MWD1 D, Sig=230,16 Ref=360,100

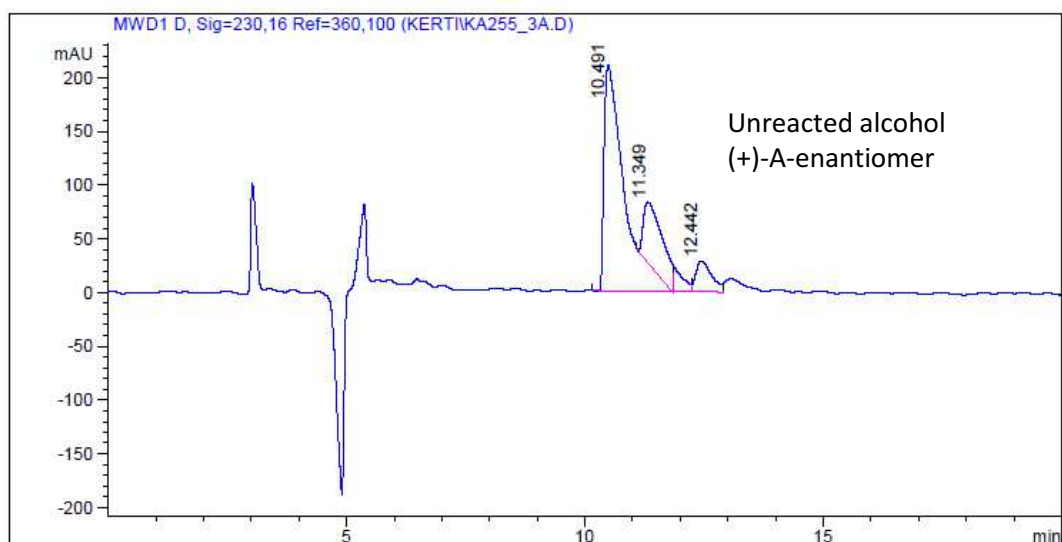
Peak no	RT [min]	Peak Type	With [min]	Area	Area %	Name
1	9.675	MM	0.424	782.315	4.716	
2	13.847	FM	0.708	1.581e4	95.284	

9h



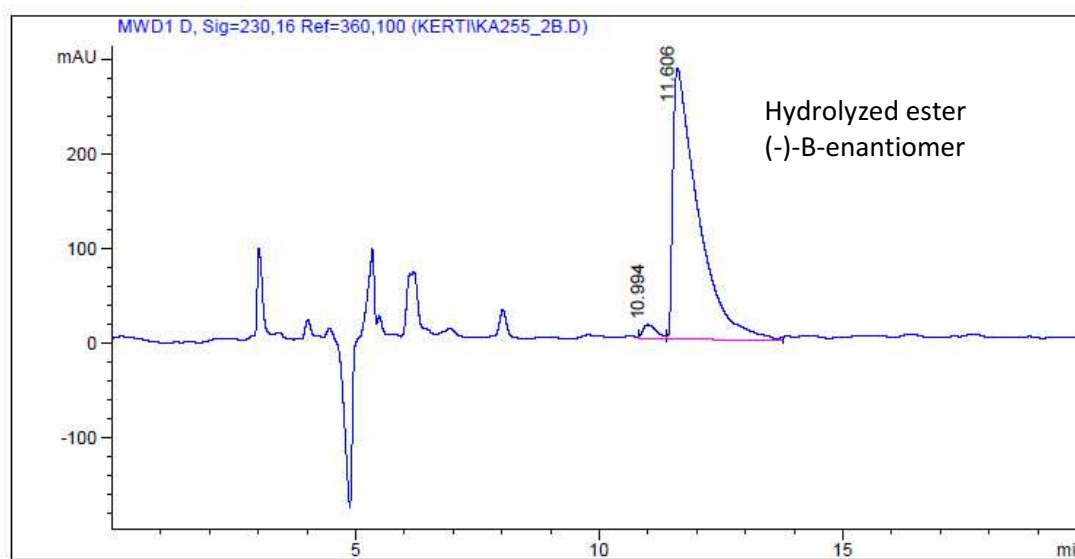
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Peak no	RT [min]	Peak Type	With [min]	Area	Area %	Name
1	10.752	MF	0.415	2817.316	32.386	
2	11.603	MF	0.349	1107.983	12.737	
3	12.072	FM	0.534	4773.858	54.877	



Signal 1: MWD1 D, Sig=230,16 Ref=360,100

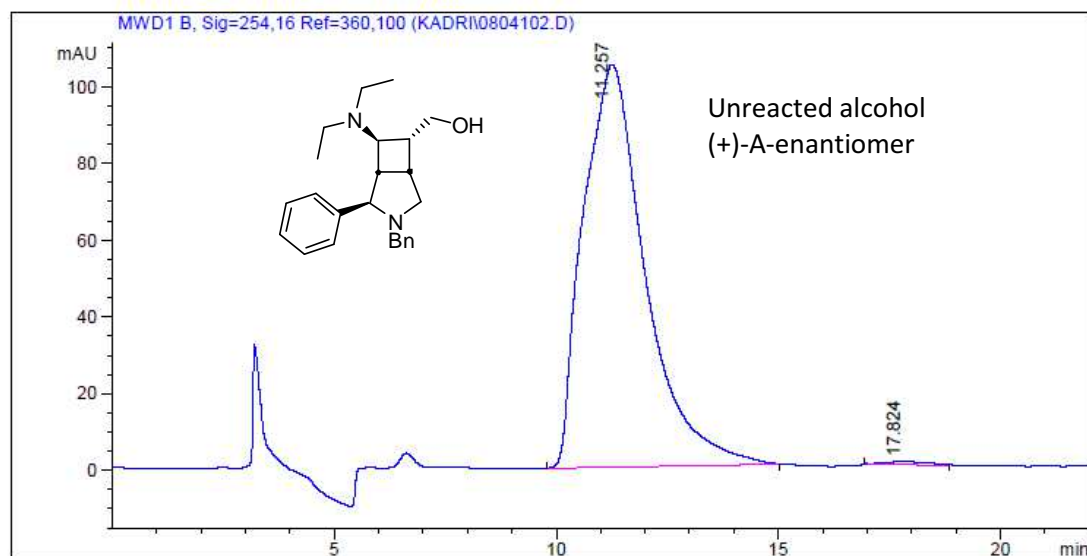
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1	10.491	MF R	0.516	6509.392	73.508	
2	11.349	MM T	0.506	1687.747	19.059	
3	12.442	MF	0.385	658.208	7.433	



Signal 1: MWD1 D, Sig=230,16 Ref=360,100

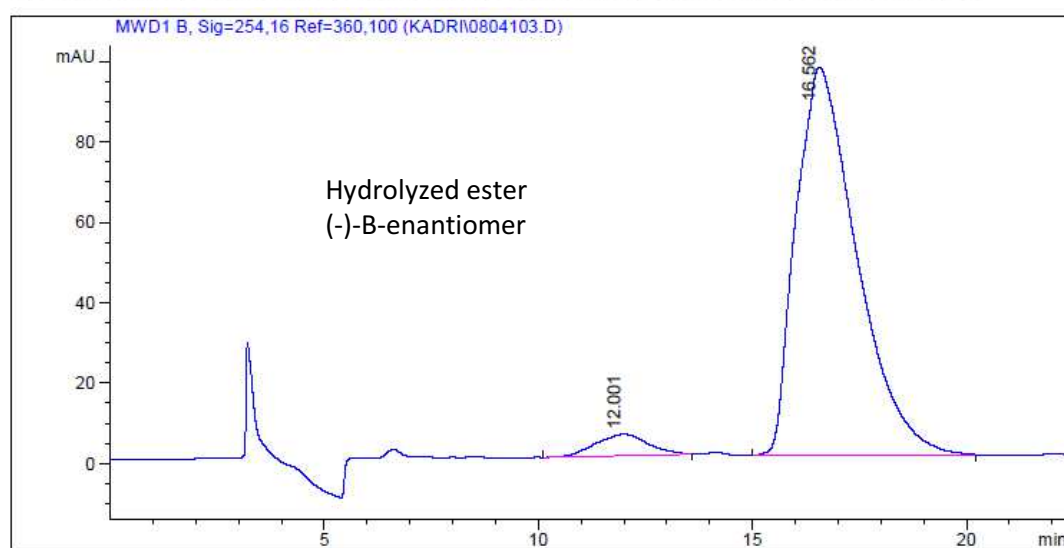
Peak no	RT [min]	Peak Type	With [min]	Area	Area %	Name
1	10.994	MF	0.321	281.093	2.672	
2	11.606	FM	0.594	1.024e4	97.328	

9j



Signal 1: MWD1 B, Sig=254,16 Ref=360,100

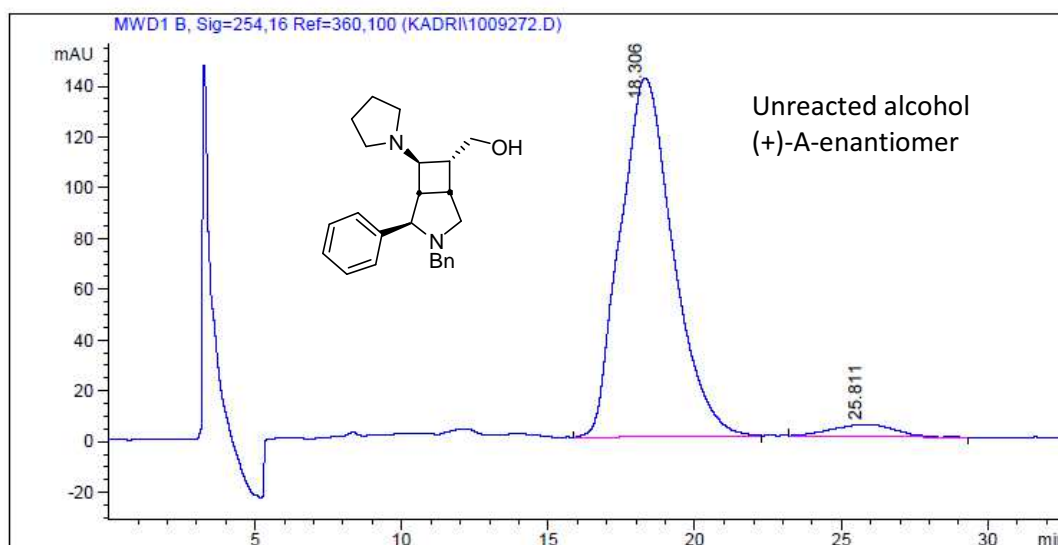
Peak no	RT [min]	Peak Type	With [min]	Area	Area %	Name
1	11.257	BB	1.327	1.015e4	99.438	
2	17.824	MM	1.158	57.413	0.562	



Signal 1: MWD1 B, Sig=254,16 Ref=360,100

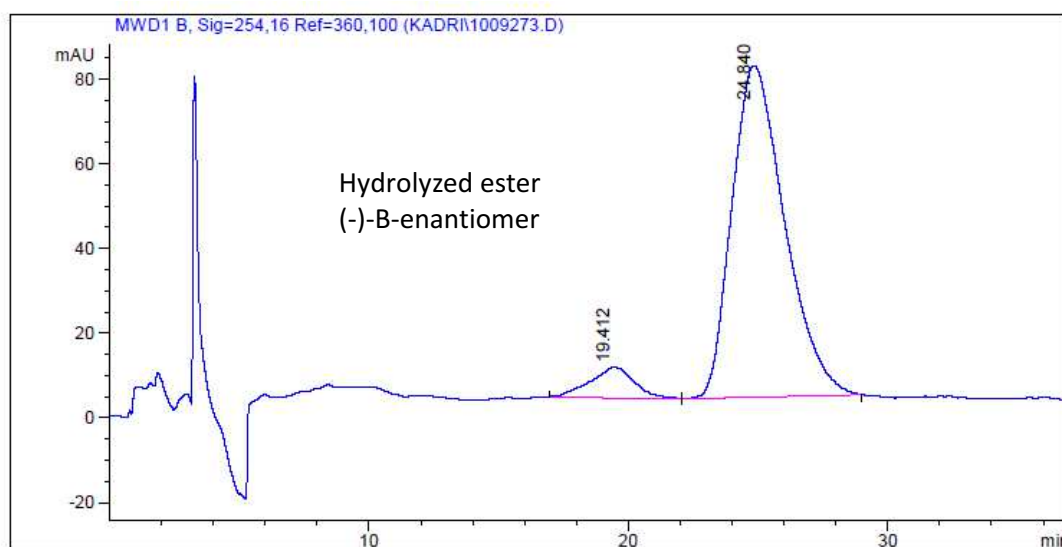
Peak no	RT [min]	Peak Type	With [min]	Area	Area %	Name
1	12.001	BV	1.078	461.719	4.623	
2	16.562	BB	1.392	9526.273	95.377	

9k



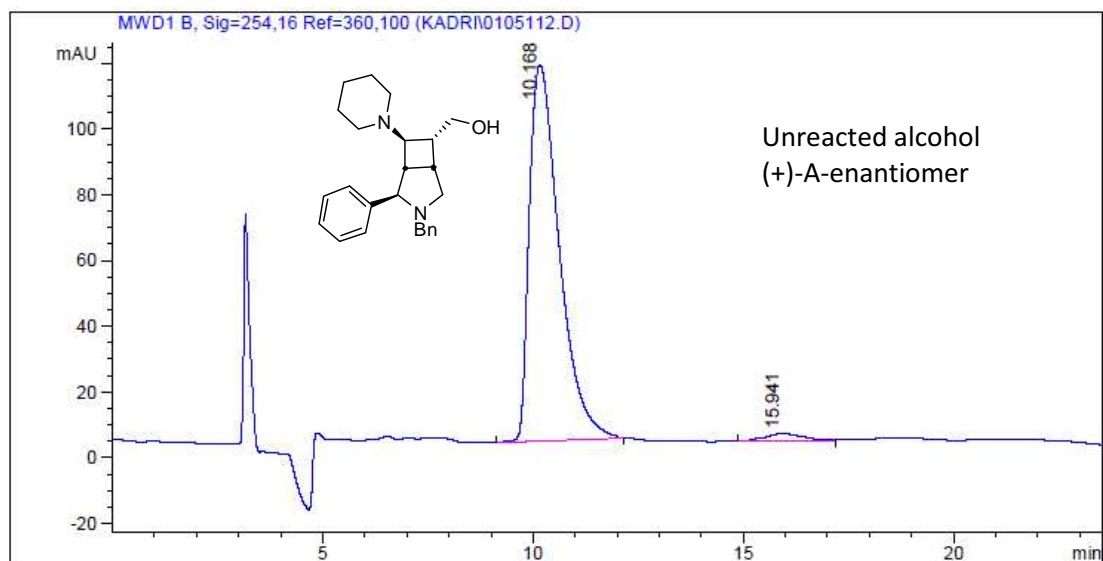
Signal 1: MWD1 B, Sig=254,16 Ref=360,100

Peak no	RT [min]	Peak Type	With [min]	Area	Area %	Name
1	18.306	VB	1.756	1.771e4	96.085	
2	25.811	BV	1.746	721.524	3.915	



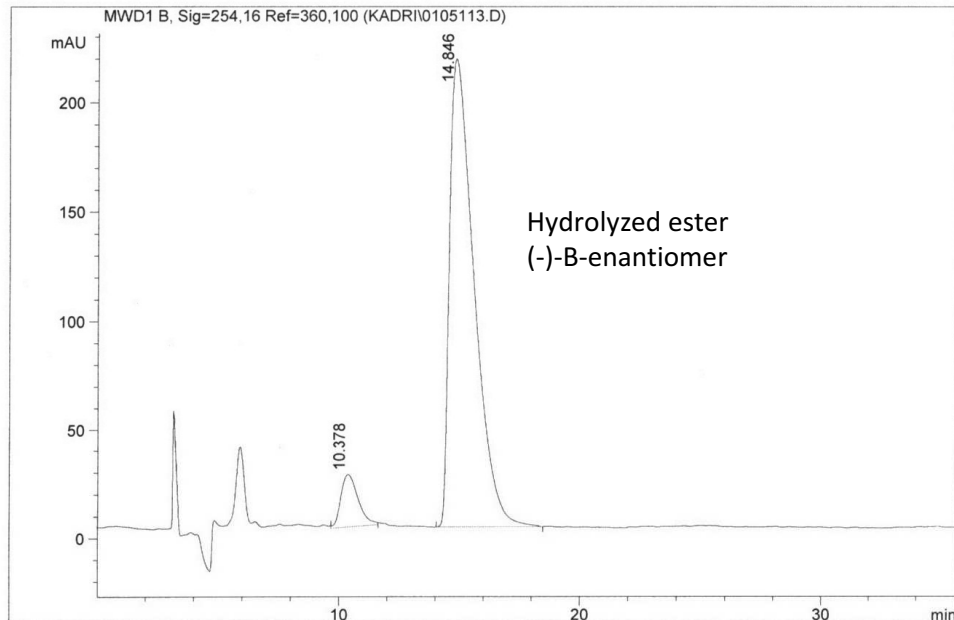
Signal 1: MWD1 B, Sig=254,16 Ref=360,100

Peak no	RT [min]	Peak Type	With [min]	Area	Area %	Name
1	19.412	BV	1.459	858.704	7.196	
2	24.840	VB	2.023	1.107e4	92.804	



Signal 1: MWD1 B, Sig=254,16 Ref=360,100

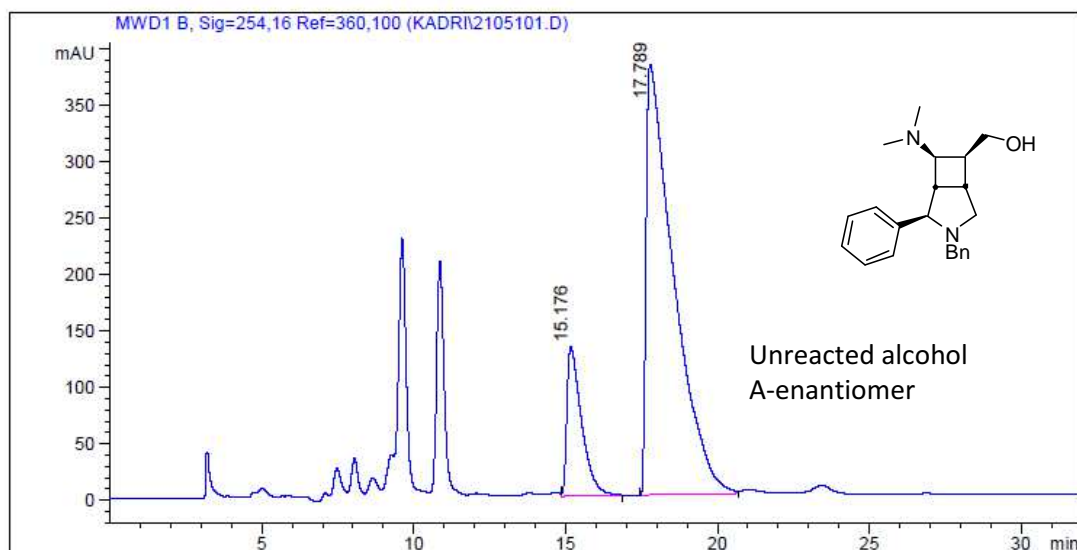
Peak no	RT [min]	Peak Type	With [min]	Area	Area %	Name
1	10.168	BB	0.765	5683.885	97.695	
2	15.941	BV	0.735	134.114	2.305	



Signal 1: MWD1 B, Sig=254,16 Ref=360,100

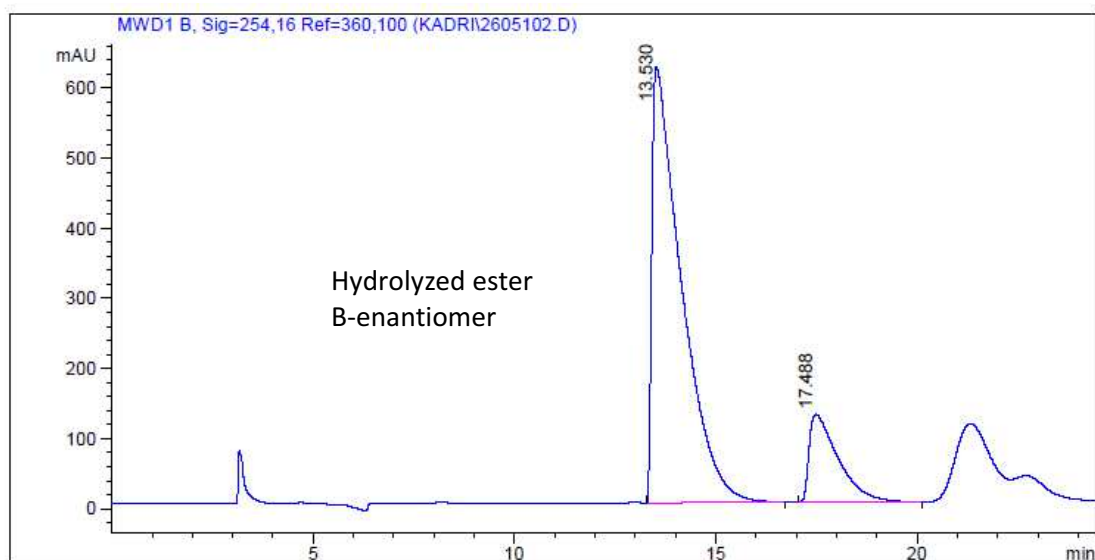
Peak No	RT [min]	Type	With [min]	Area	Area %	Name
1	10.378	MM	0.828	1182.099	7.191	
2	14.846	BB	1.079	1.526e4	92.809	~ 85,6%

9m



Signal 1: MWD1 B, Sig=254,16 Ref=360,100

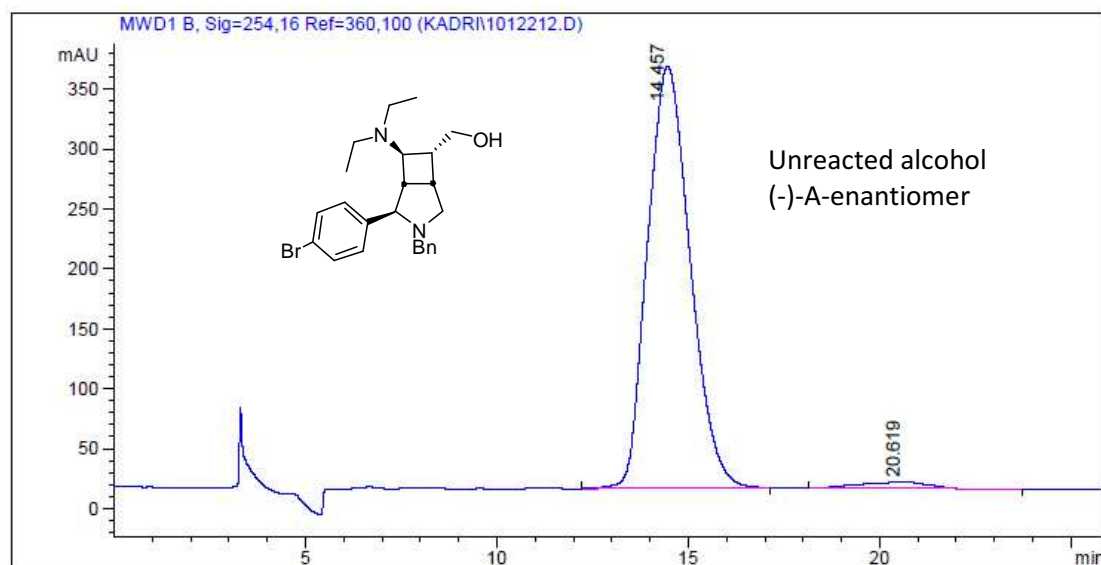
Peak no	RT [min]	Peak Type	With [min]	Area	Area %	Name
1	15.176	VB	0.494	4431.535	15.546	
2	17.789	BB	0.881	2.408e4	84.454	



Signal 1: MWD1 B, Sig=254,16 Ref=360,100

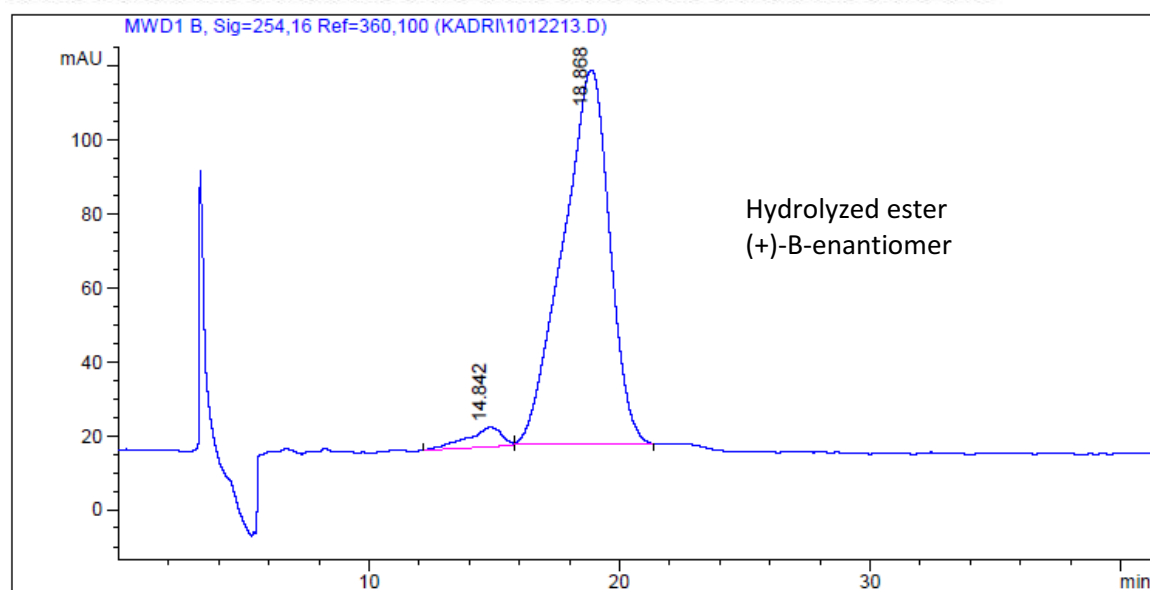
Peak no	RT [min]	Peak Type	With [min]	Area	Area %	Name
1	13.530	BB	0.698	3.156e4	83.393	
2	17.488	BB	0.734	6285.290	16.607	

90



Signal 1: MWD1 B, Sig=254,16 Ref=360,100

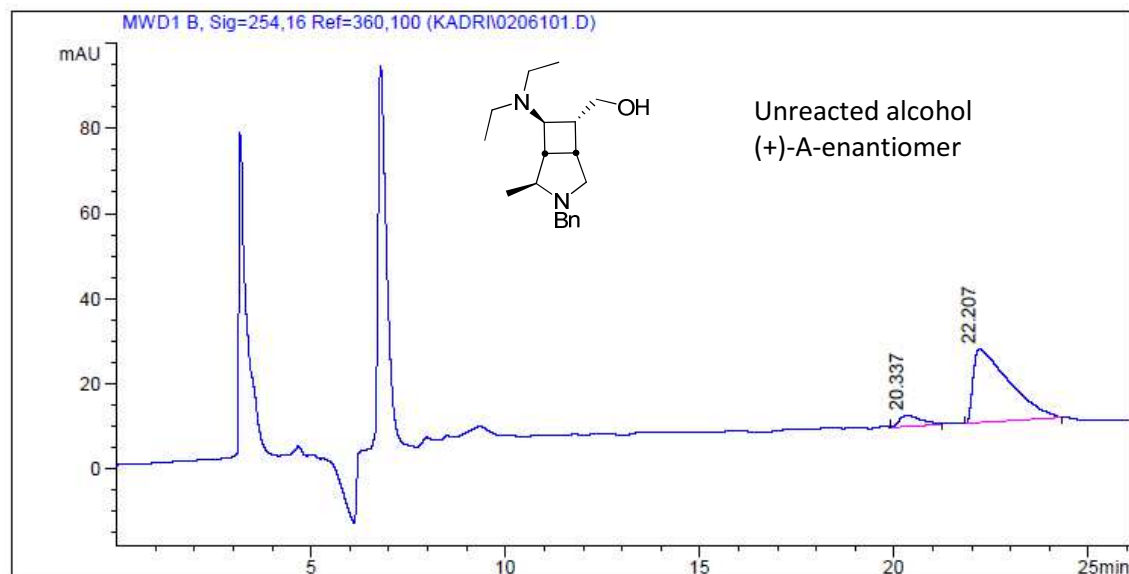
Peak no	RT [min]	Peak Type	With [min]	Area	Area %	Name
1	14.457	BB	1.269	2.726e4	97.737	
2	20.619	BB	1.372	631.209	2.263	



Signal 1: MWD1 B, Sig=254,16 Ref=360,100

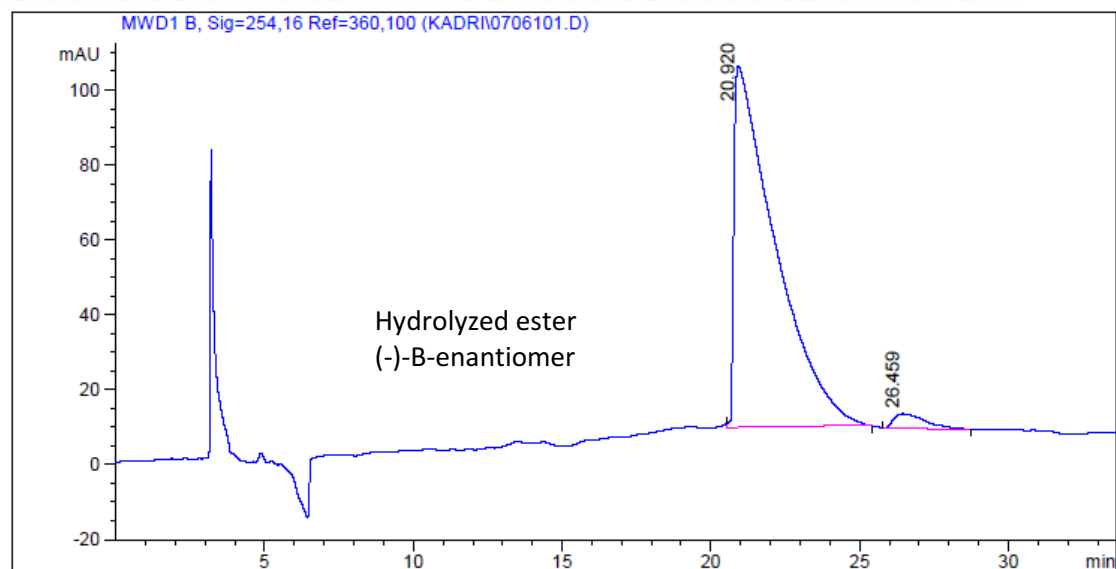
Peak no	RT [min]	Peak Type	With [min]	Area	Area %	Name
1	14.842	MM	1.626	509.865	3.750	
2	18.868	MM	2.156	1.309e4	96.250	

9r



Signal 1: MWD1 B, Sig=254,16 Ref=360,100

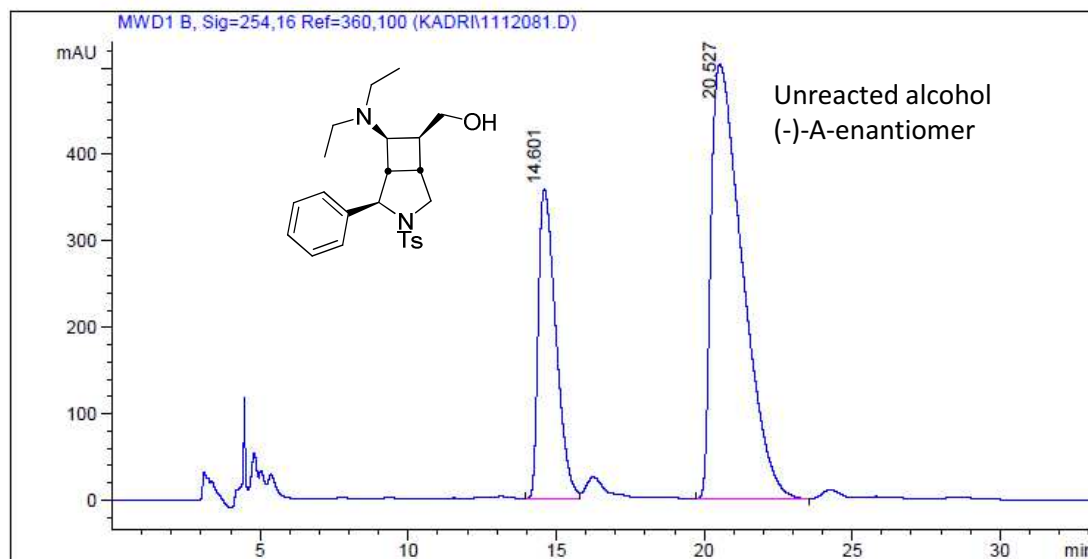
Peak no	RT [min]	Peak Type	With [min]	Area	Area %	Name
1	20.337	VV	0.577	99.148	8.221	
2	22.207	BB	0.843	1106.814	91.779	



Signal 1: MWD1 B, Sig=254,16 Ref=360,100

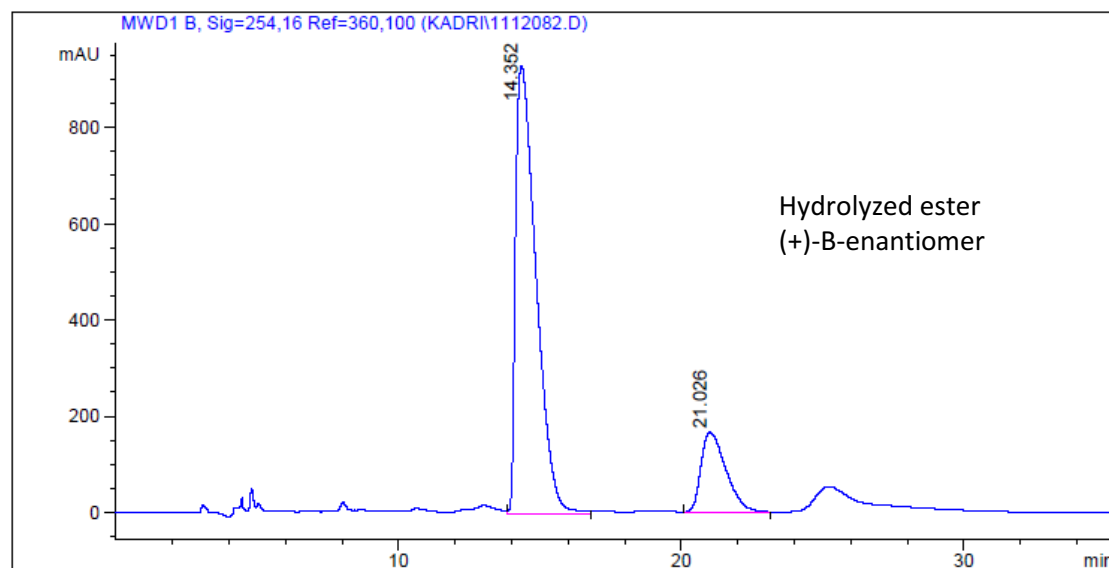
Peak no	RT [min]	Peak Type	With [min]	Area	Area %	Name
1	20.920	MM	1.600	9268.885	96.982	
2	26.459	BV	0.881	288.393	3.018	

10a



Signal 1: MWD1 B, Sig=254,16 Ref=360,100

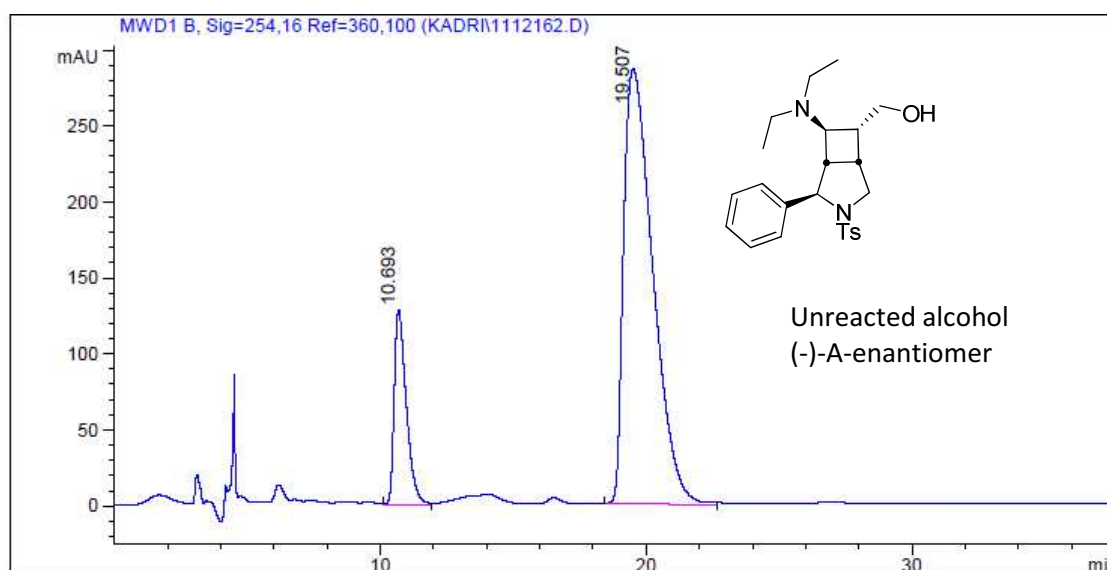
Peak no	RT [min]	Peak Type	With [min]	Area	Area %	Name
1	14.601	VV	0.639	1.471e4	28.261	
2	20.527	VB	1.091	3.733e4	71.739	



Signal 1: MWD1 B, Sig=254,16 Ref=360,100

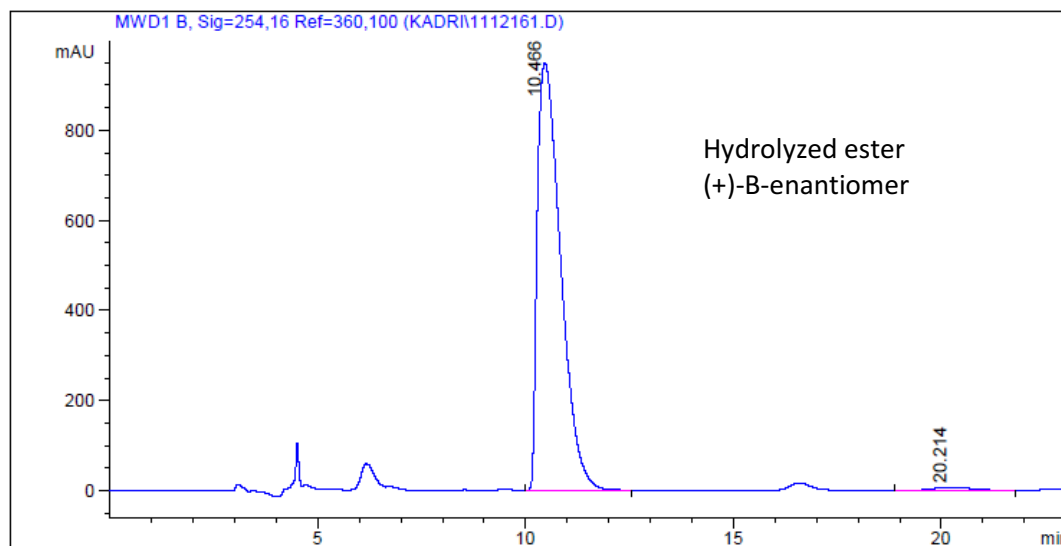
Peak no	RT [min]	Peak Type	With [min]	Area	Area %	Name
1	14.352	VB	0.753	4.675e4	82.069	
2	21.026	VB	0.937	1.022e4	17.931	

10b



Signal 1: MWD1 B, Sig=254,16 Ref=360,100

Peak no	RT [min]	Peak Type	With [min]	Area	Area %	Name
1	10.693	MM	0.530	4084.323	15.769	
2	19.507	MM	1.269	2.182e4	84.231	



Signal 1: MWD1 B, Sig=254,16 Ref=360,100

Peak no	RT [min]	Peak Type	With [min]	Area	Area %	Name
1	10.466	VB	0.605	3.684e4	98.819	
2	20.214	BB	0.871	440.420	1.181	

4. Crystal Structure Data for **9f** A-enantiomer

Single crystals of **9f**, A enantiomer were grown at room temperature by slow evaporation of a solution of the compound in ethyl acetate. Diffraction data was collected on a Bruker SMART X2S at 200 K. The crystallographic data were deposited with the Cambridge Crystallographic Data Centre (CCDC 900224) and are included in the supporting information.

Crystal data. $C_{17}H_{24}BrNO_2$, $M = 354.28$, monoclinic, $a = 8.9677(9)$, $b = 5.2389(7)$, $c = 17.839(2)$ Å, $\beta = 94.853(4)^\circ$, $V = 835.10(17)$ Å³, $T = 200$ K, space group $P2_1$ (no. 4), $Z = 2$, reflections measured 5287, unique 2876 ($R_{\text{int}} = 0.0395$), Flack parameter $x = 0.004(10)$, final $R1 = 0.0433$ and $wR2 = 0.0804$ for all data.

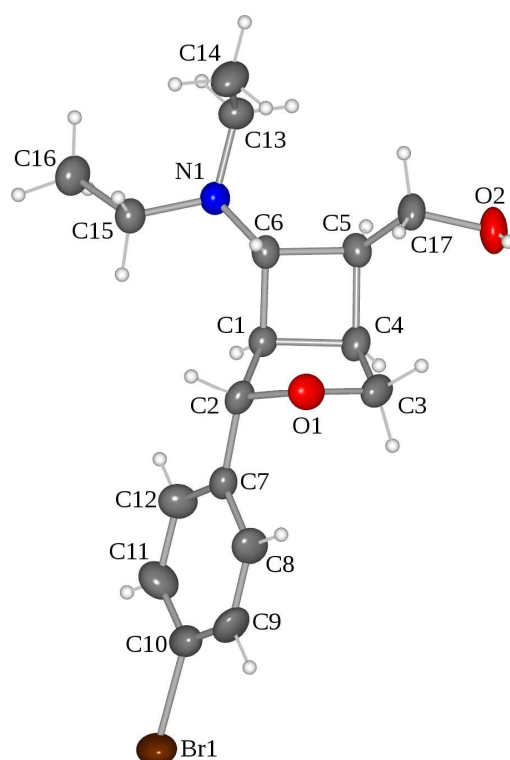


Figure 1. Molecular moiety in the crystal structure of **9f**, A enantiomer. Displacement ellipsoids are drawn at the 50% probability level.