

Supporting Information

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

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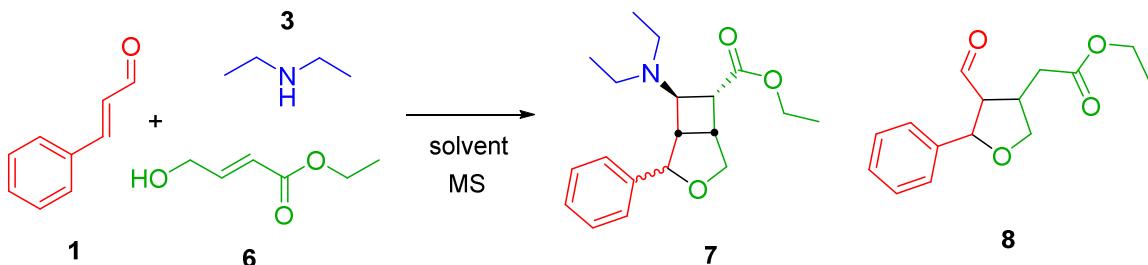
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## 1. Screening of reaction conditions

**Table 1.** Solvent screening to improve diastereoselectivity. <sup>[a]</sup>

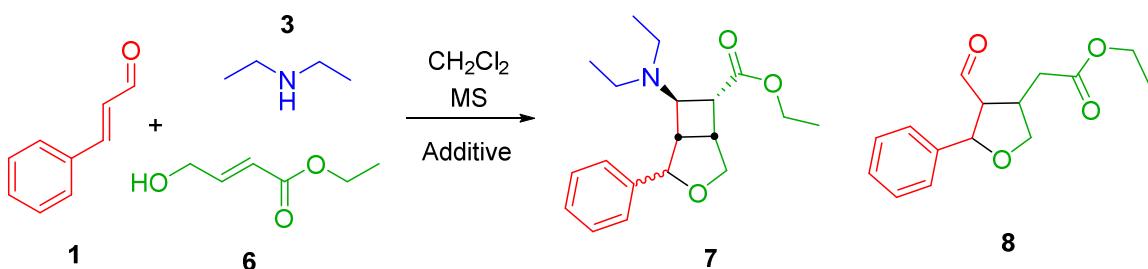


Entry	Solvent	6/7/8 <sup>[b]</sup>	d.r. <sup>[c]</sup>
1	CH <sub>3</sub> CN	49/46/5	3:1
2	Toluene	22/58/20	1.8:1
3	THF	42/47/11	3.5:1
4	CH <sub>2</sub> Cl <sub>2</sub>	0/96/4	5:1
5 <sup>[d]</sup>	CH <sub>3</sub> Cl	0/85/15	3.5:1
6	CCl <sub>4</sub>	40/40/20	1.6:1
7	1,2-dichloroethane	19/75/6	4:1
8	Dioxan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

<sup>[a]</sup> Cinnamaldehyde (2 equiv), Et<sub>2</sub>NH (2 equiv), and hydroxycrotonate (1 equiv) were stirred in an appropriate solvent at rt for 48 h, with MS.

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

**Table 1.** Screening of additives to improve diastereoselectivity. <sup>[a]</sup>

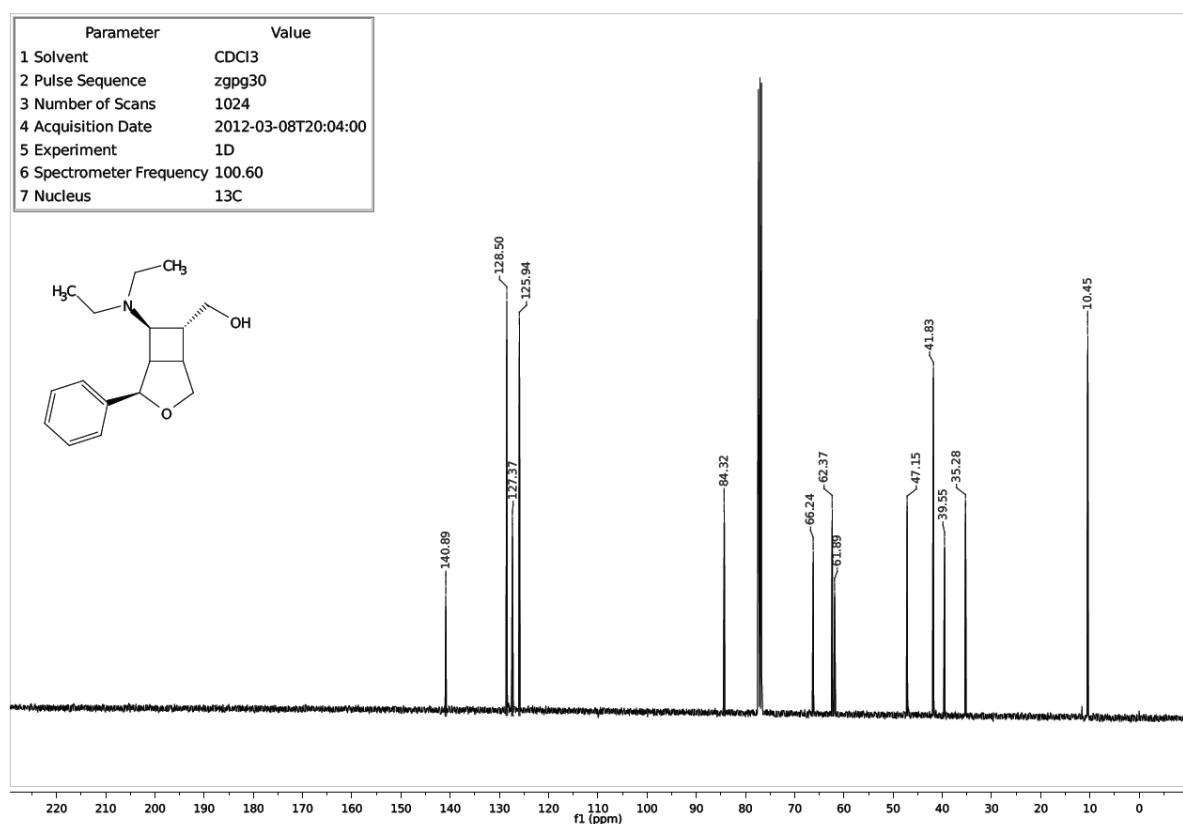
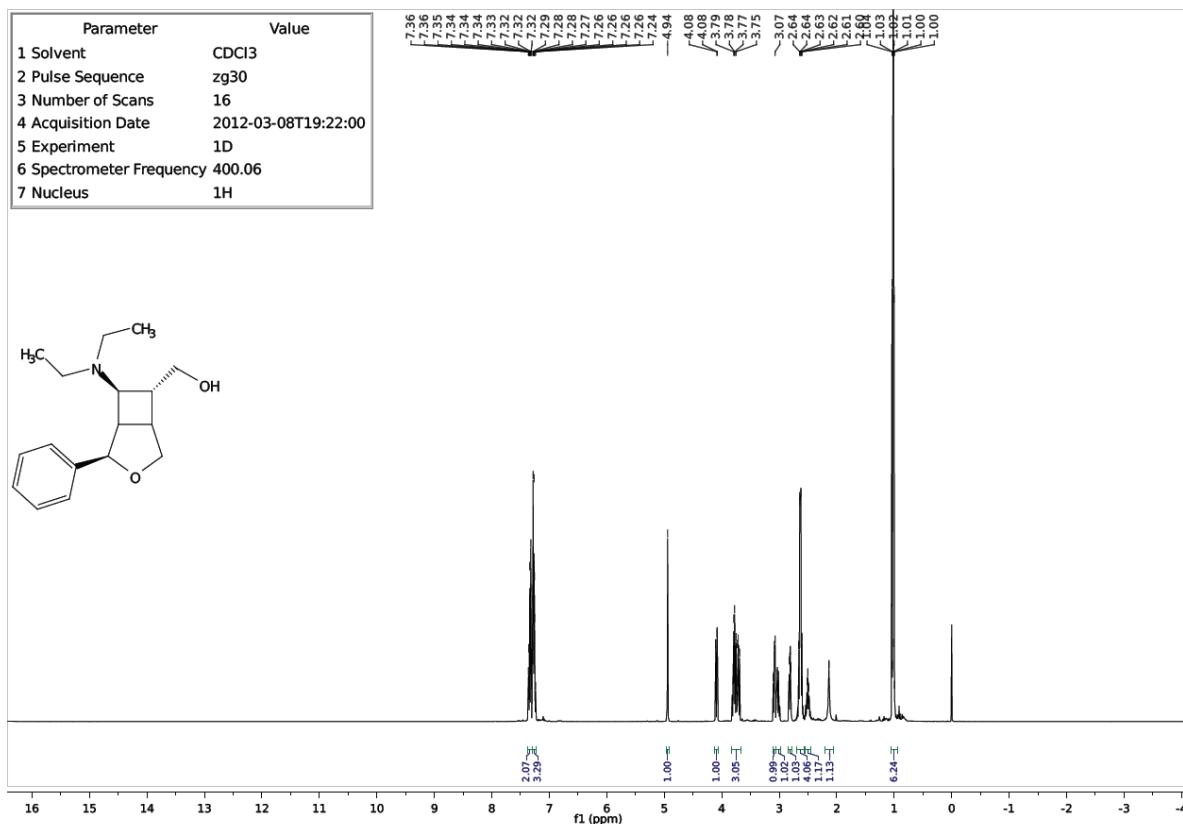


Entry	Additive	6/7/8 <sup>[b]</sup>	d.r. <sup>[c]</sup>
1	NaOAc	15/79/6	5:1
2	Benzoic acid	25/47/28	3:1
3	<i>p</i> -NO <sub>2</sub> -benzoic acid	44/13/43	n.d
4	TFA	47/13/40	1.6:1
5 <sup>[d]</sup>	Benzoic acid	17/64/19	3.5:1
6 <sup>[e]</sup>	Et <sub>2</sub> NH	20/73/7	3.6:1

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

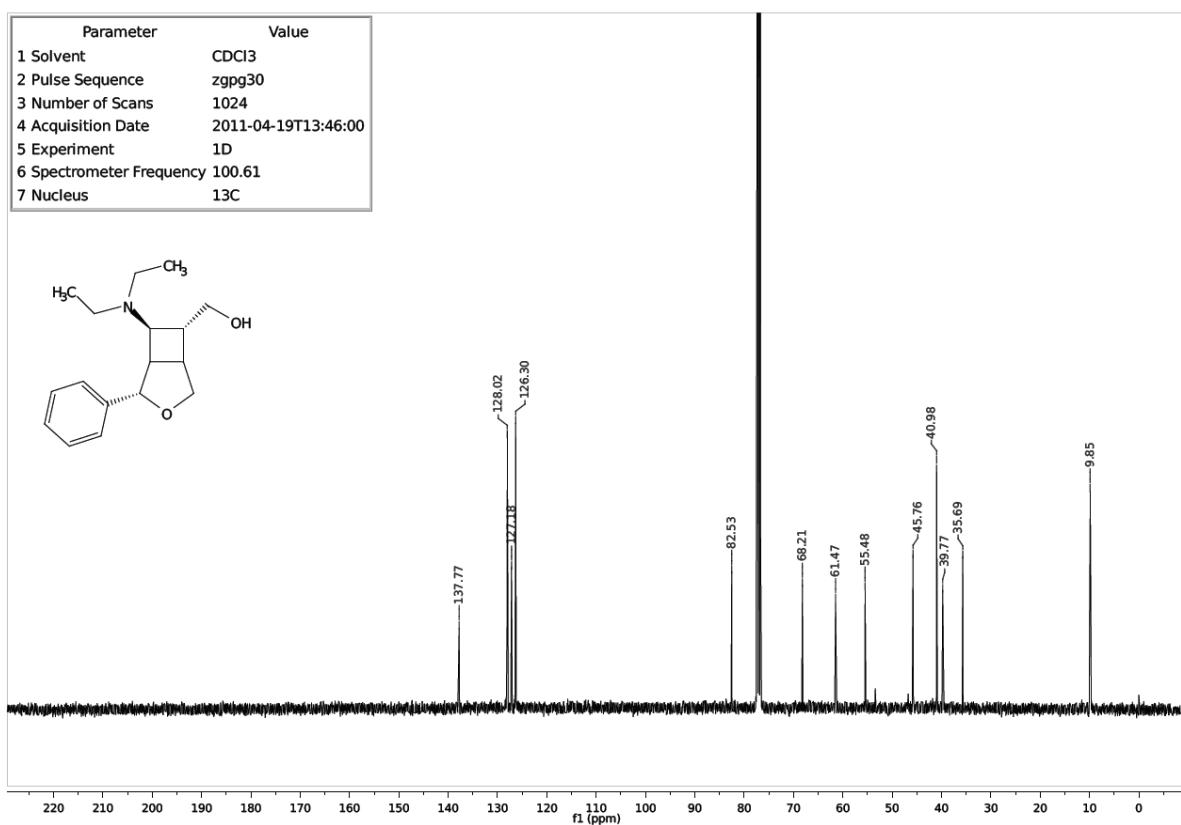
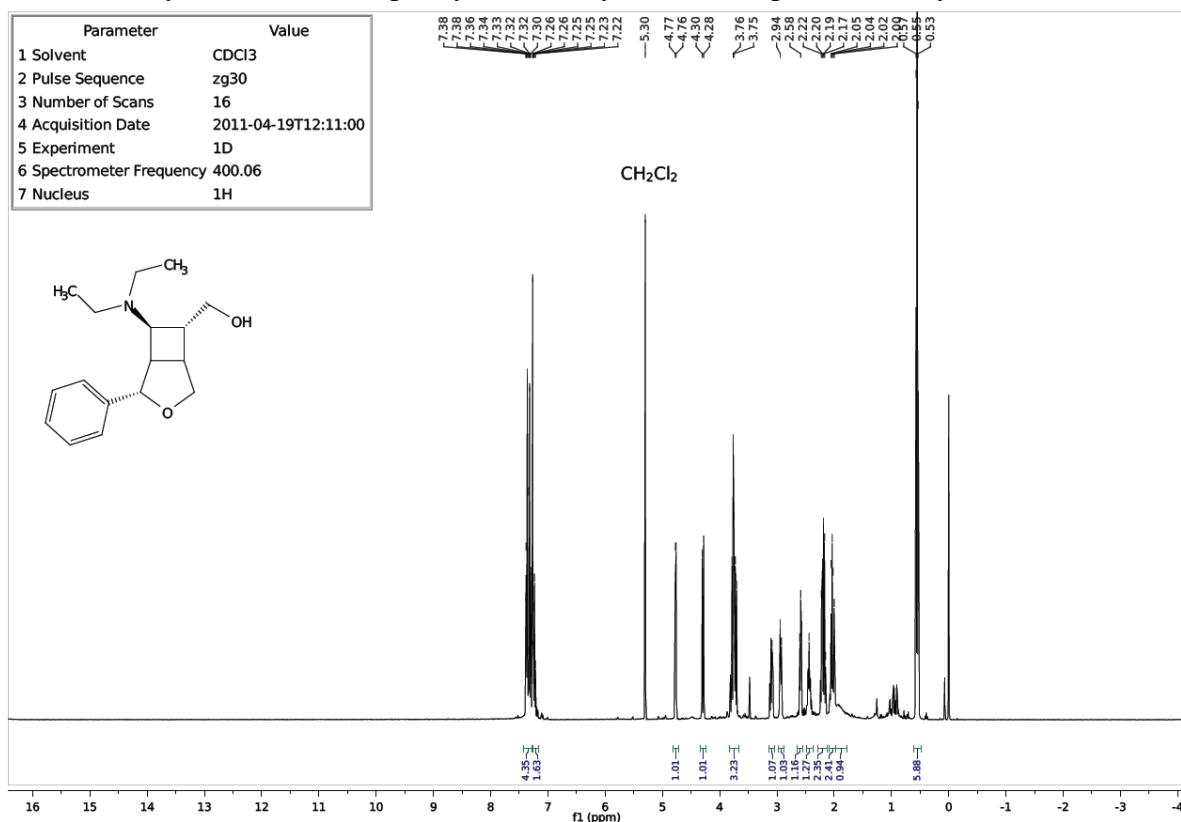
## 2. Spectral Data (<sup>1</sup>H and <sup>13</sup>C spectra)

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



**9a 2-endo diastereoisomer**

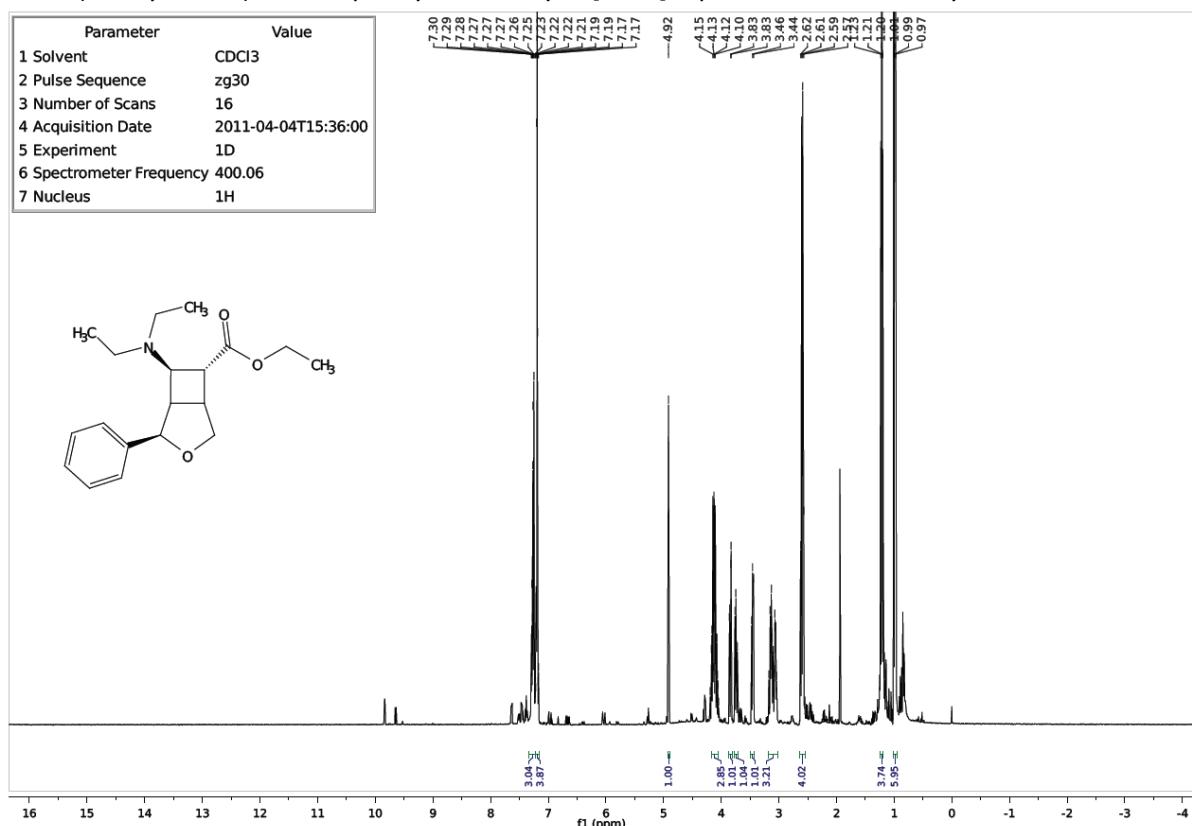
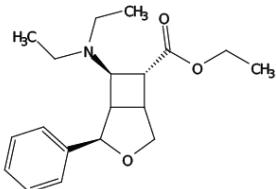
(7-*exo*-(Diethylamino)-2-*endo*-phenyl-3-oxabicyclo[3.2.0]heptan-6-*endo*-yl)methanol



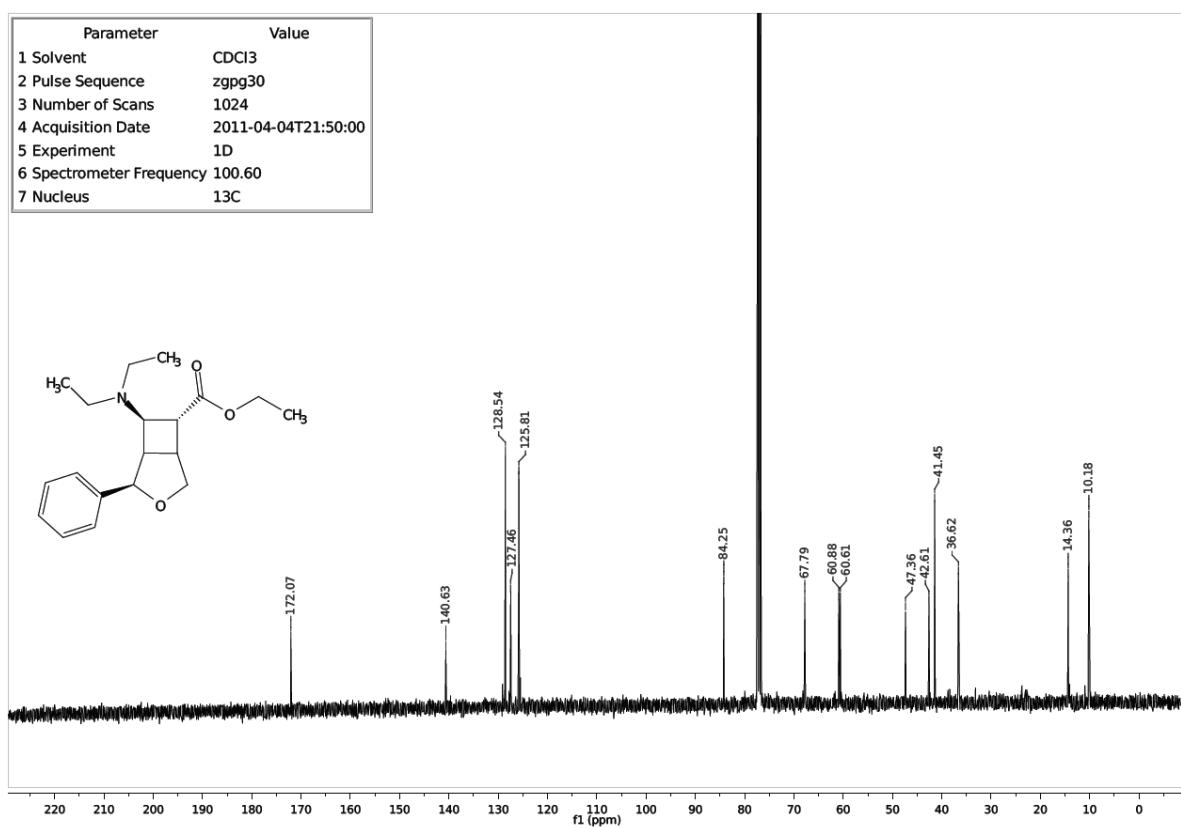
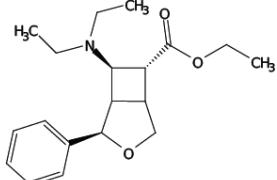
## 7 2-exo ester

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

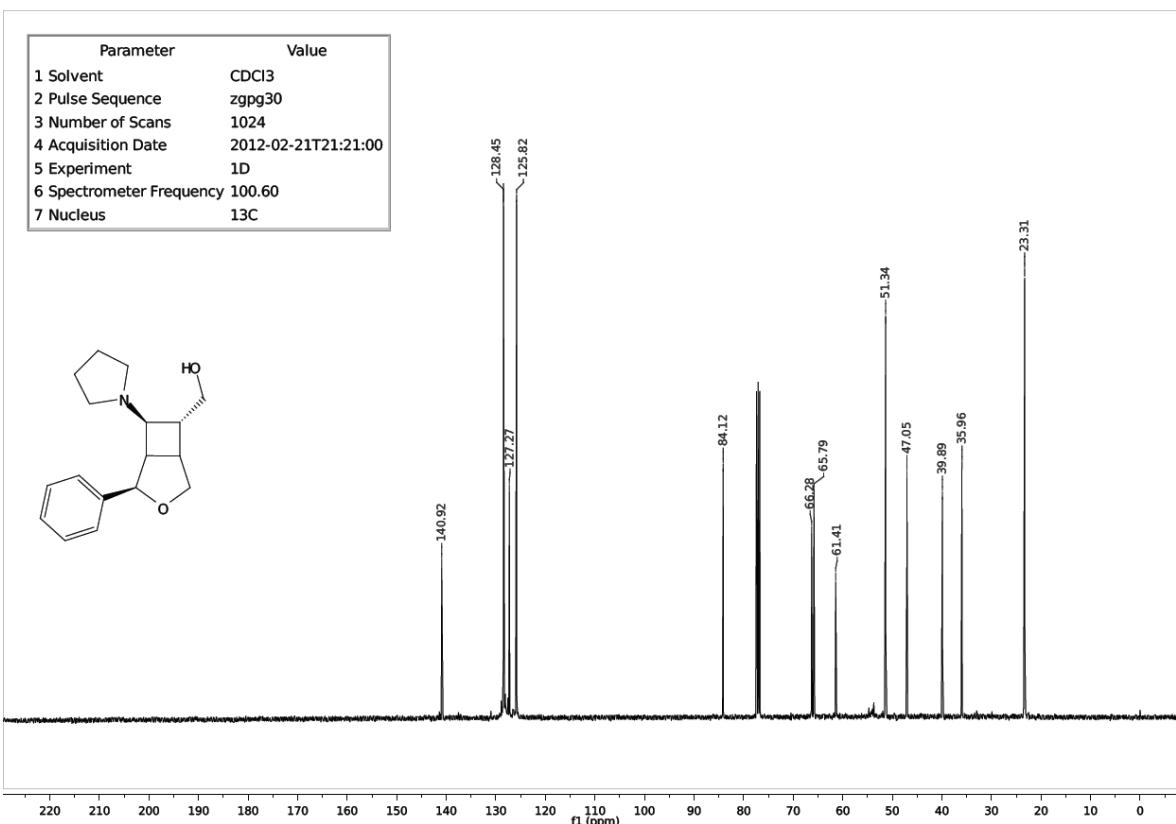
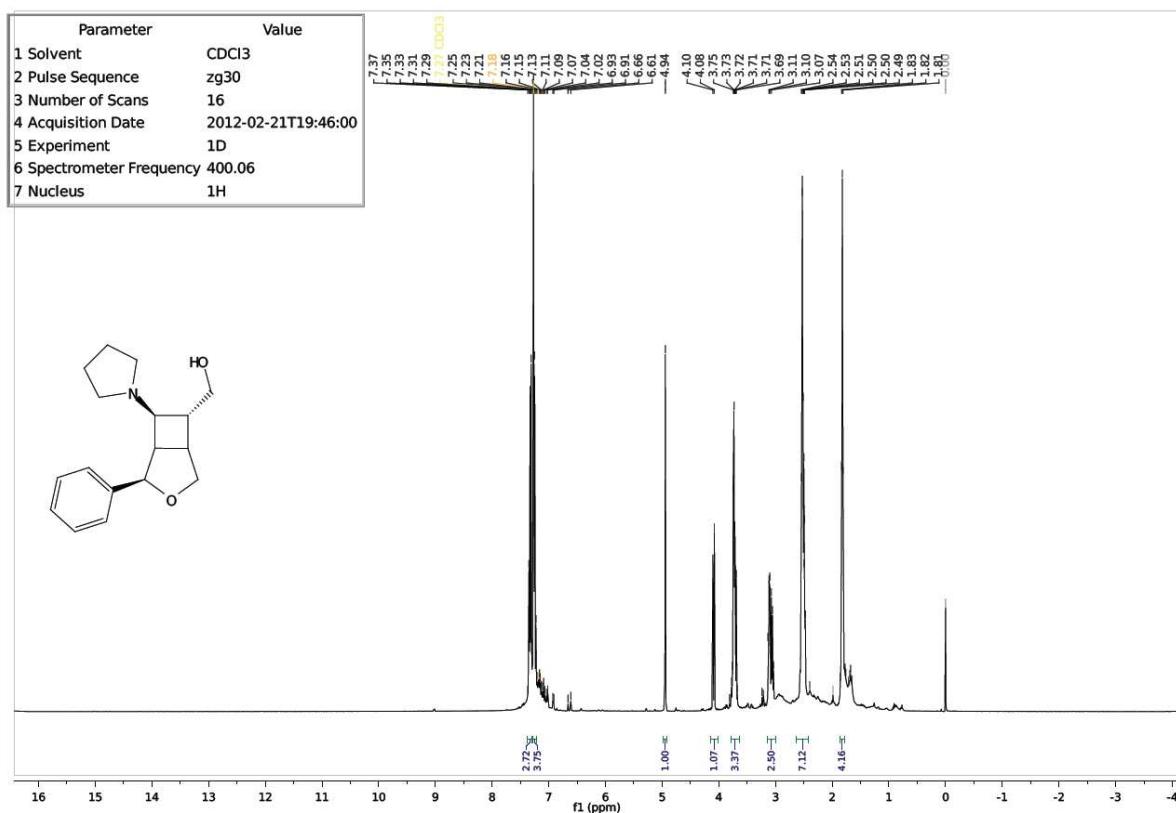
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4 Acquisition Date	2011-04-04T15:36:00
5 Experiment	1D
6 Spectrometer Frequency	400.06
7 Nucleus	1H



Parameter	Value
1 Solvent	CDCl3
2 Pulse Sequence	zgpg30
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5 Experiment	1D
6 Spectrometer Frequency	100.60
7 Nucleus	13C

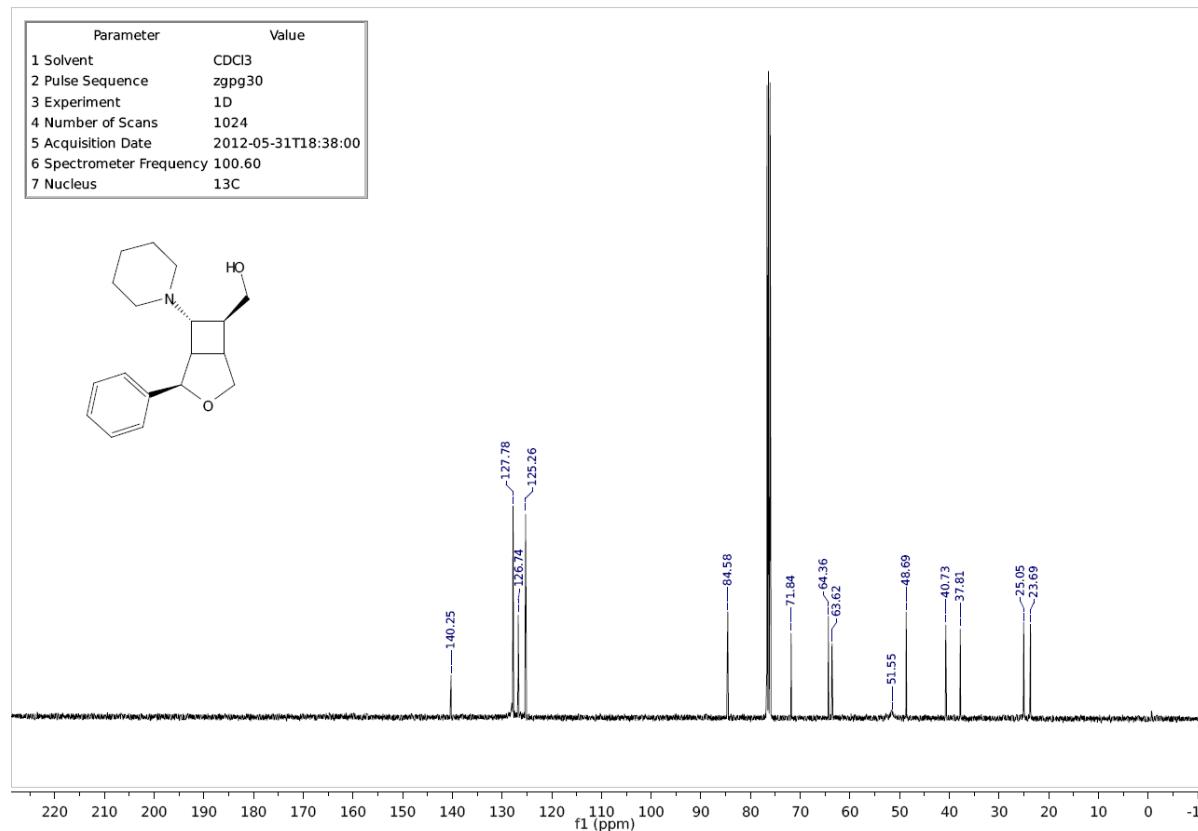
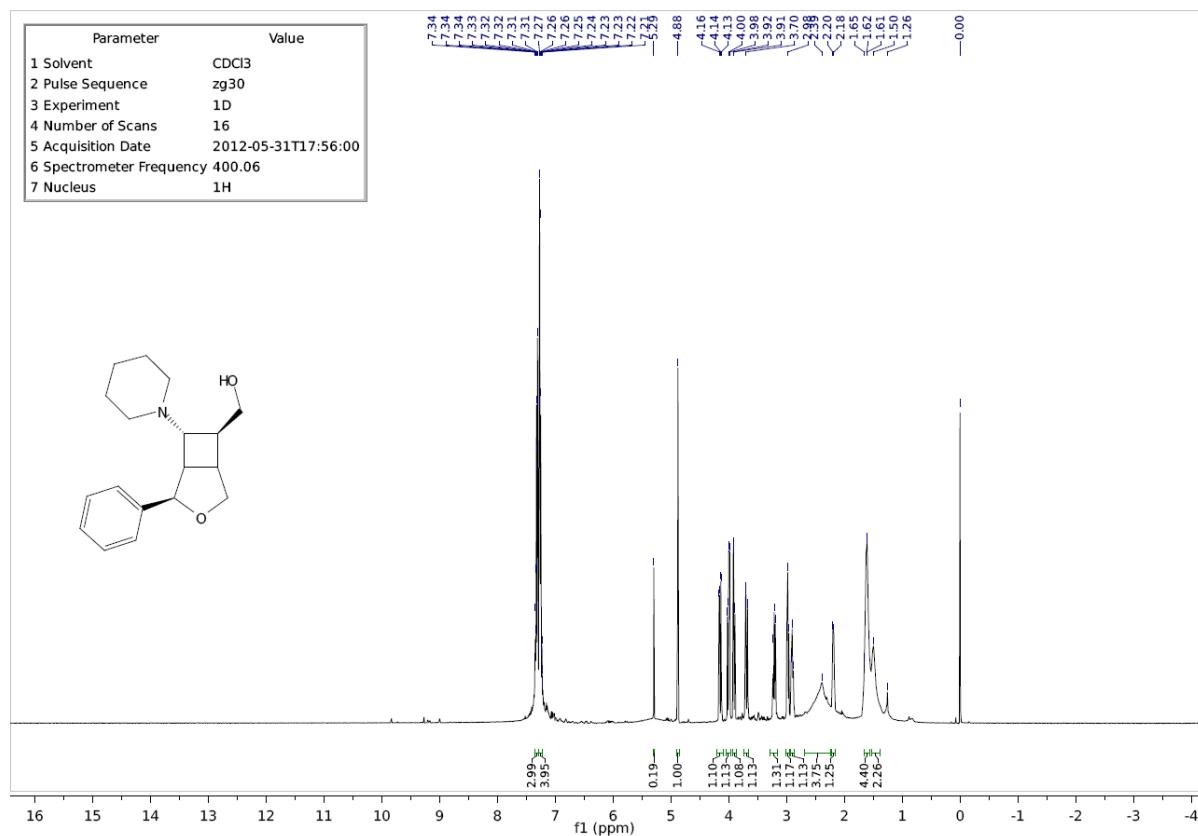


**9b** (2-*exo*-Phenyl-7-*exo*-(pyrrolidin-1-yl)-3-oxabicyclo[3.2.0]heptan-6-*endo*-yl)methanol



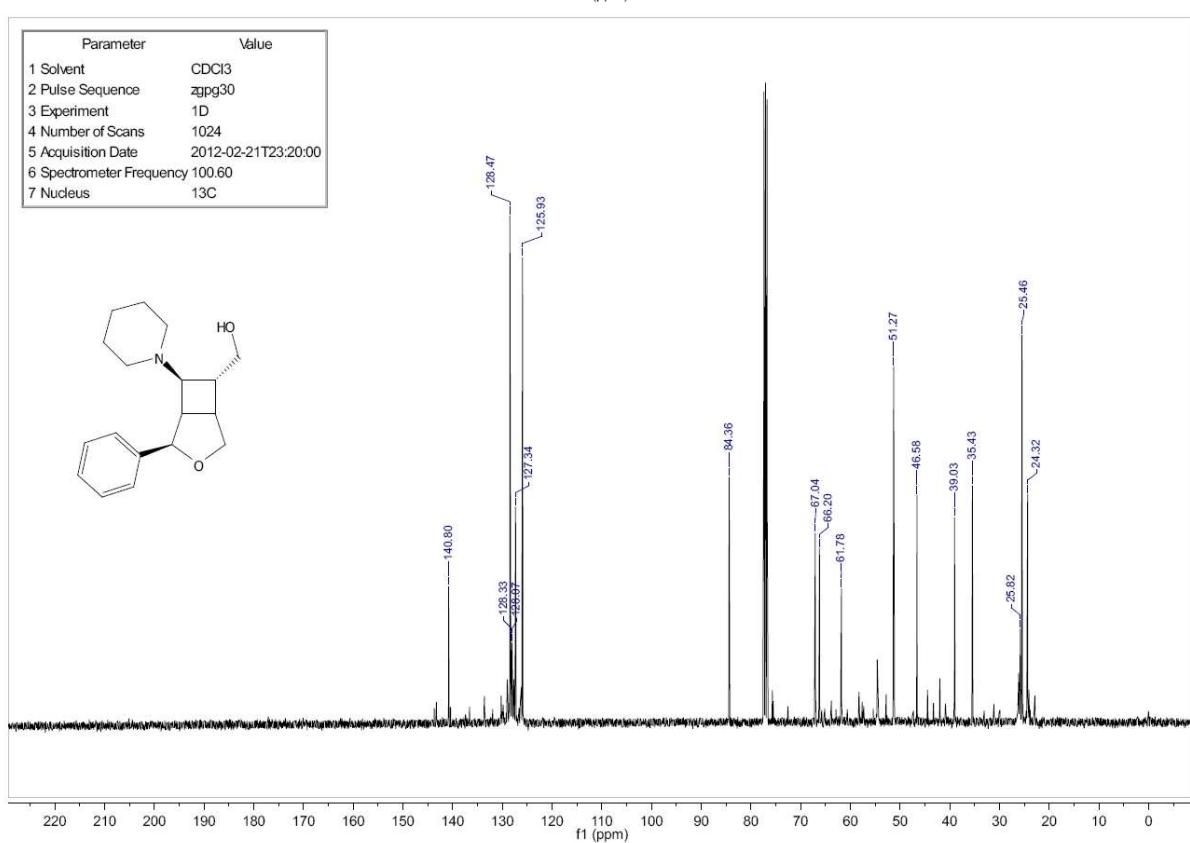
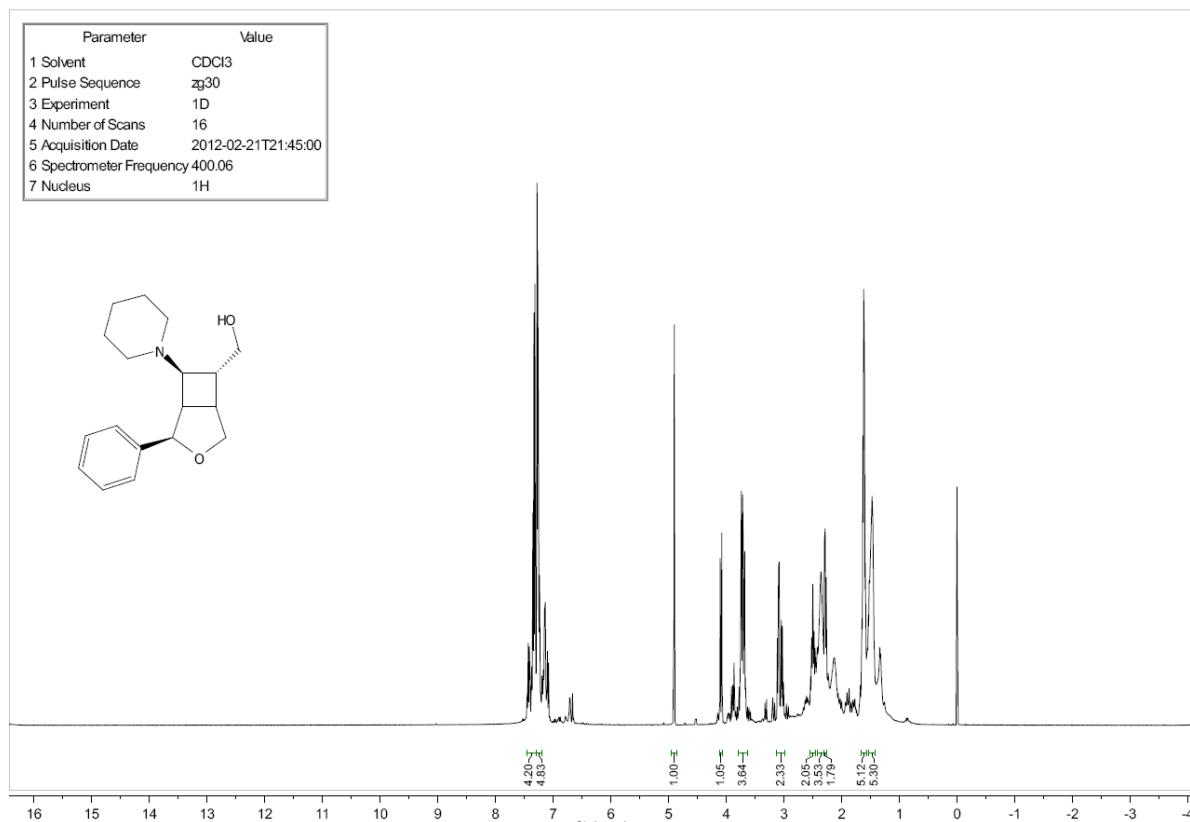
### 9c 2-exo-7-endo-6-exo diastereoisomer

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



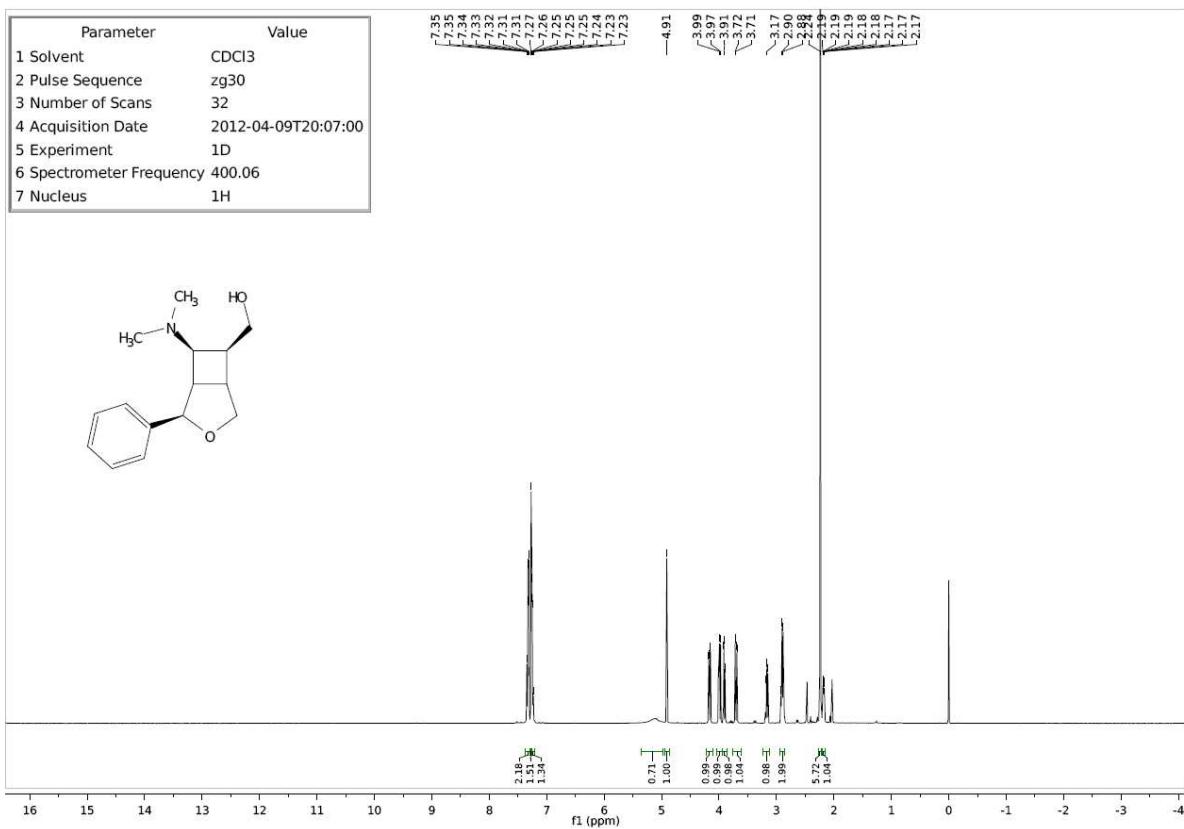
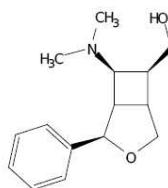
**9c 2-exo-7-exo-6-endo diastreoisomer**

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

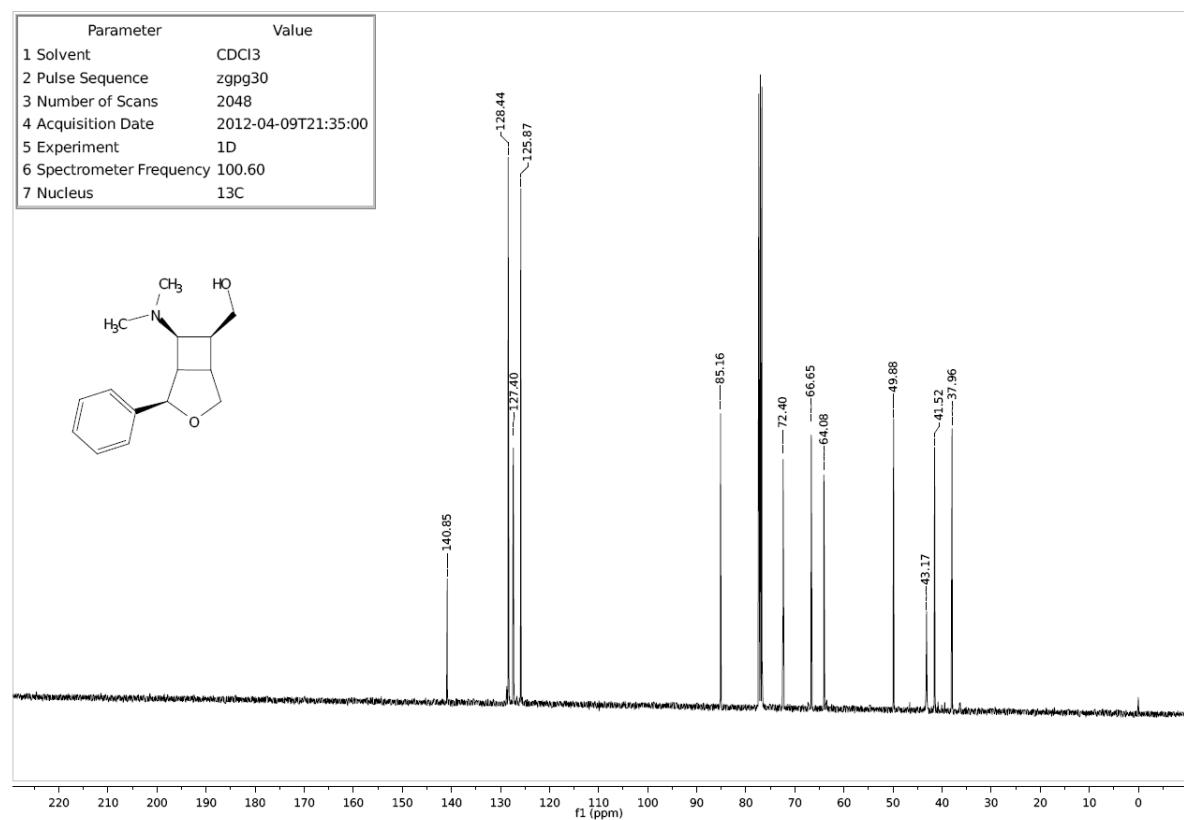
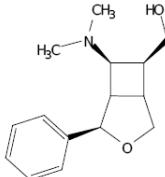


**9d** (*7*-*exo*-(Dimethylamino)-*2*-*exo*-phenyl-*3*-oxabicyclo[3.2.0]heptan-*6*-*exo*-yl)methanol

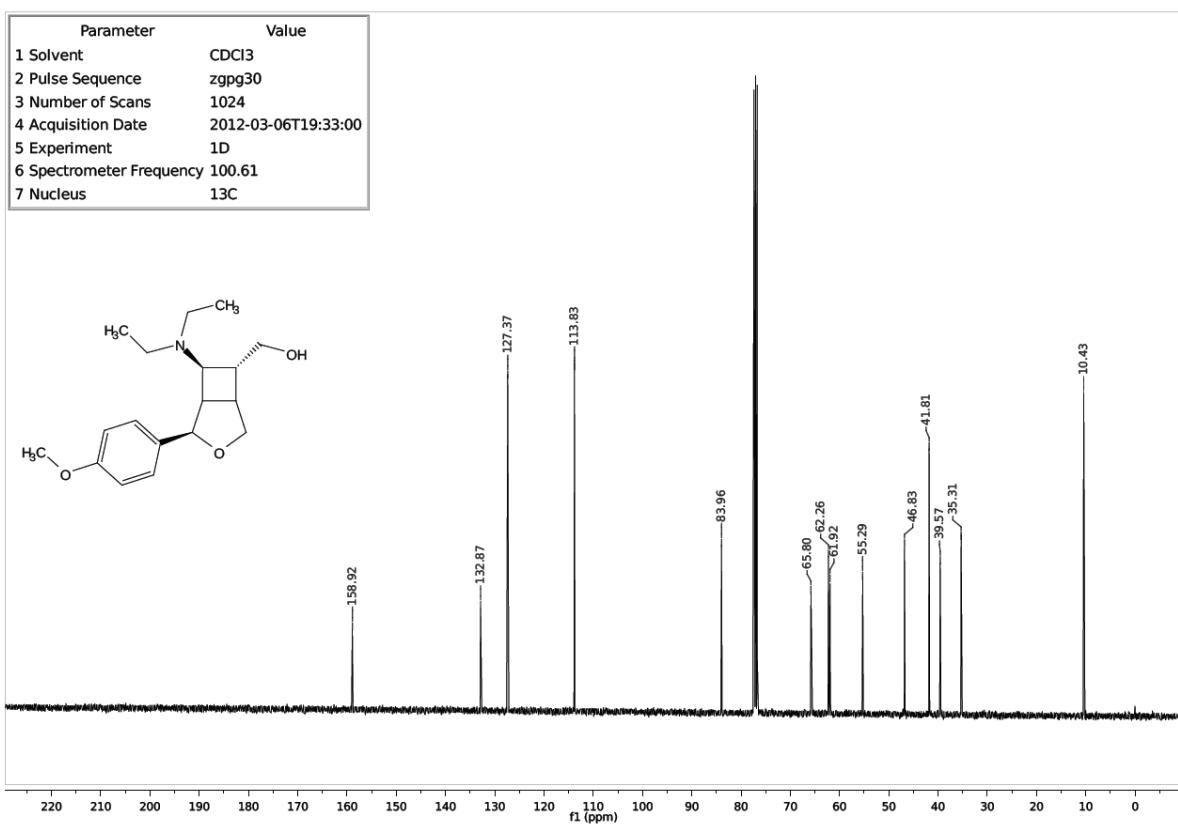
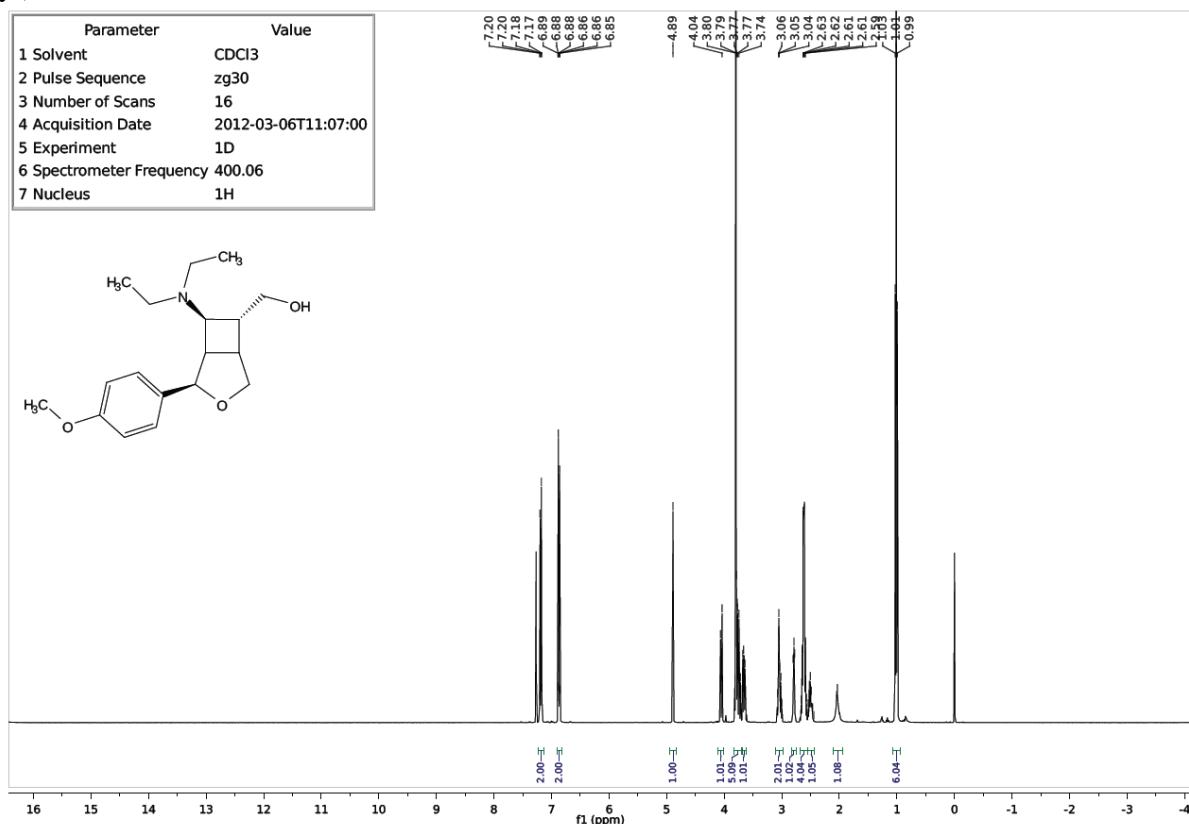
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5 Experiment	1D
6 Spectrometer Frequency	400.06
7 Nucleus	1H



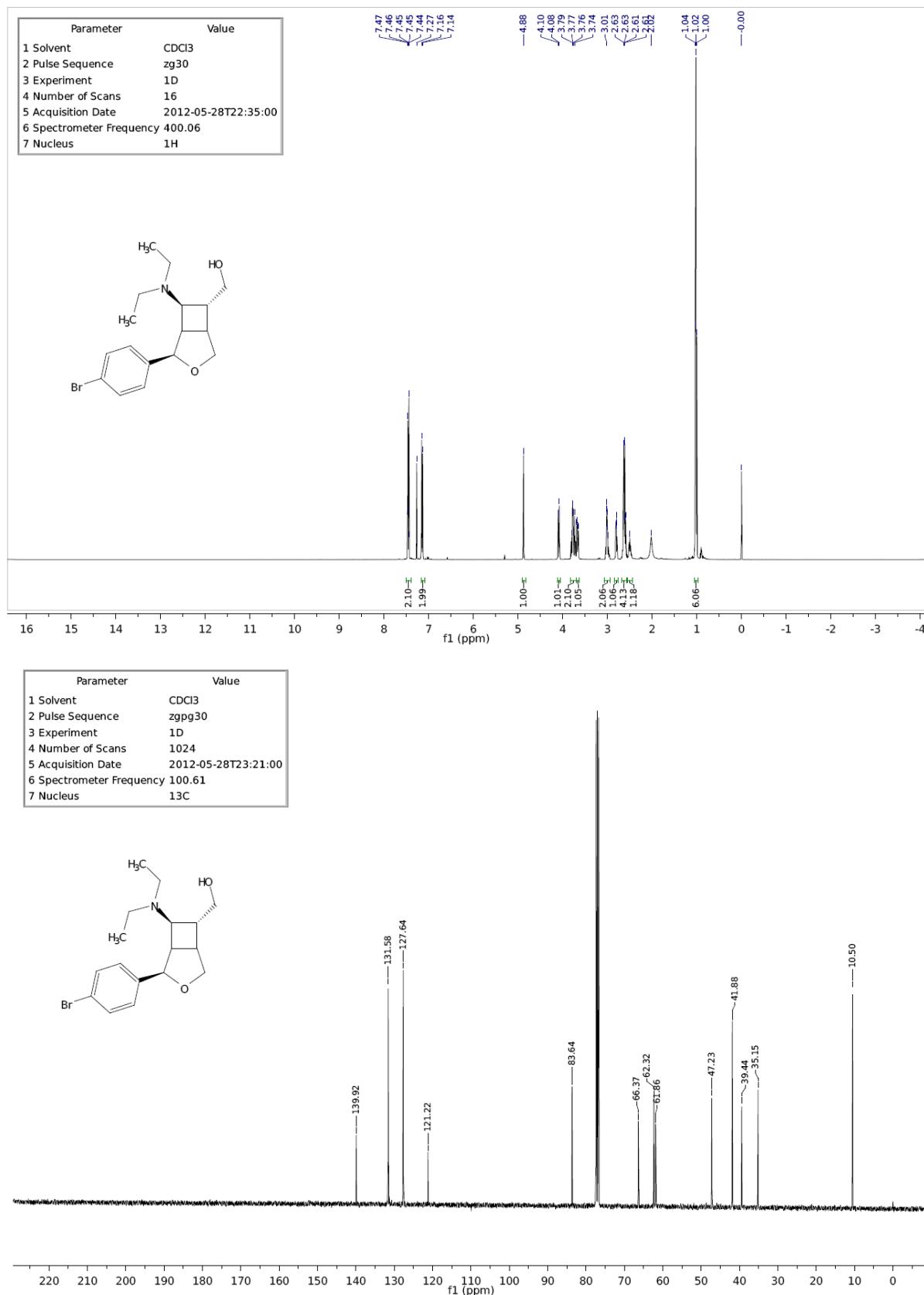
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2 Pulse Sequence	zgpg30
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5 Experiment	1D
6 Spectrometer Frequency	100.60
7 Nucleus	13C



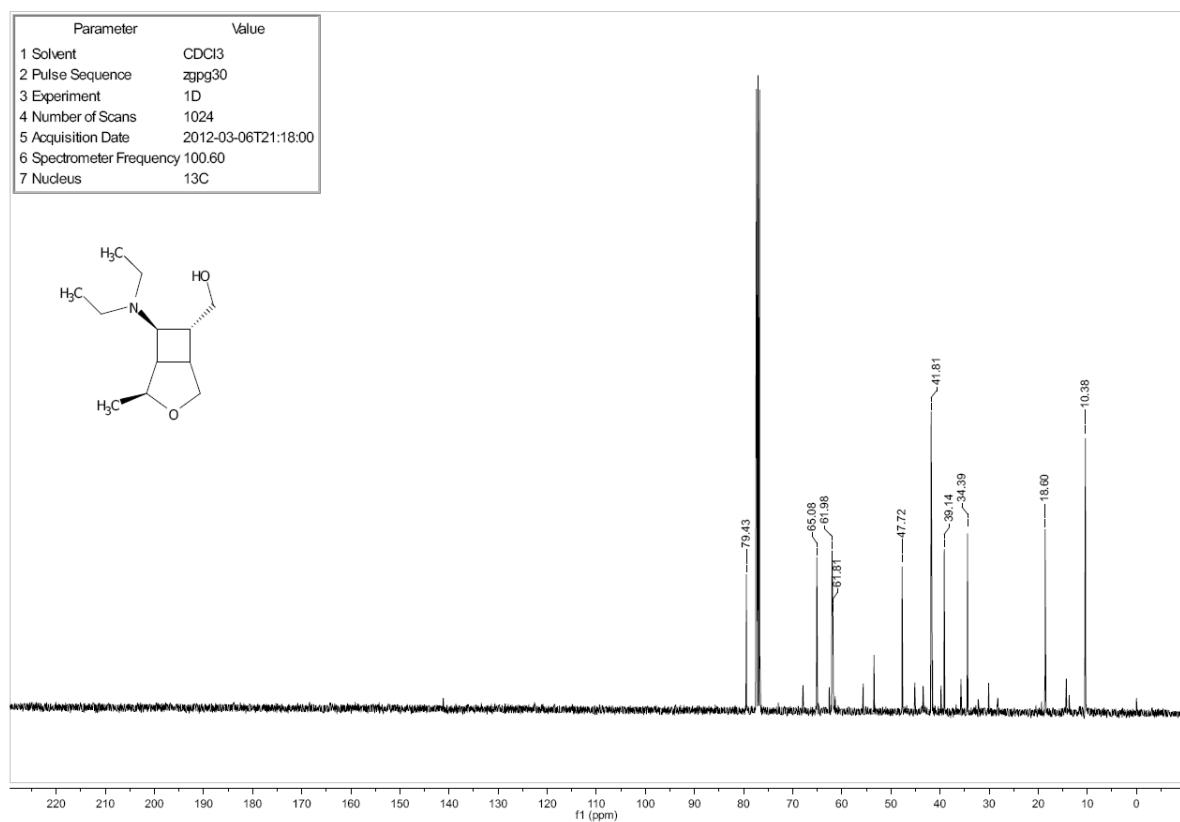
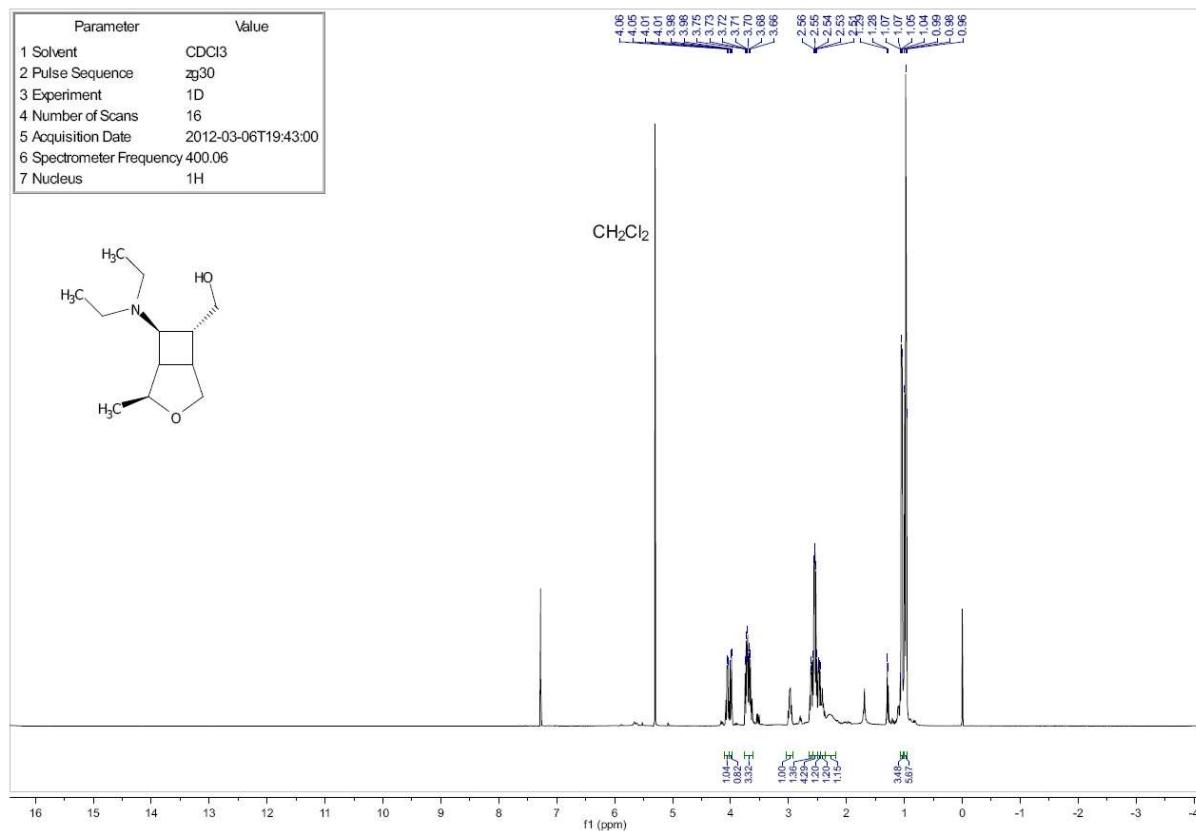
**9e** (*7-exo*-(Diethylamino)-*2-exo*-(4-methoxyphenyl)-3-oxabicyclo[3.2.0]heptan-6-*endo*-yl)methanol



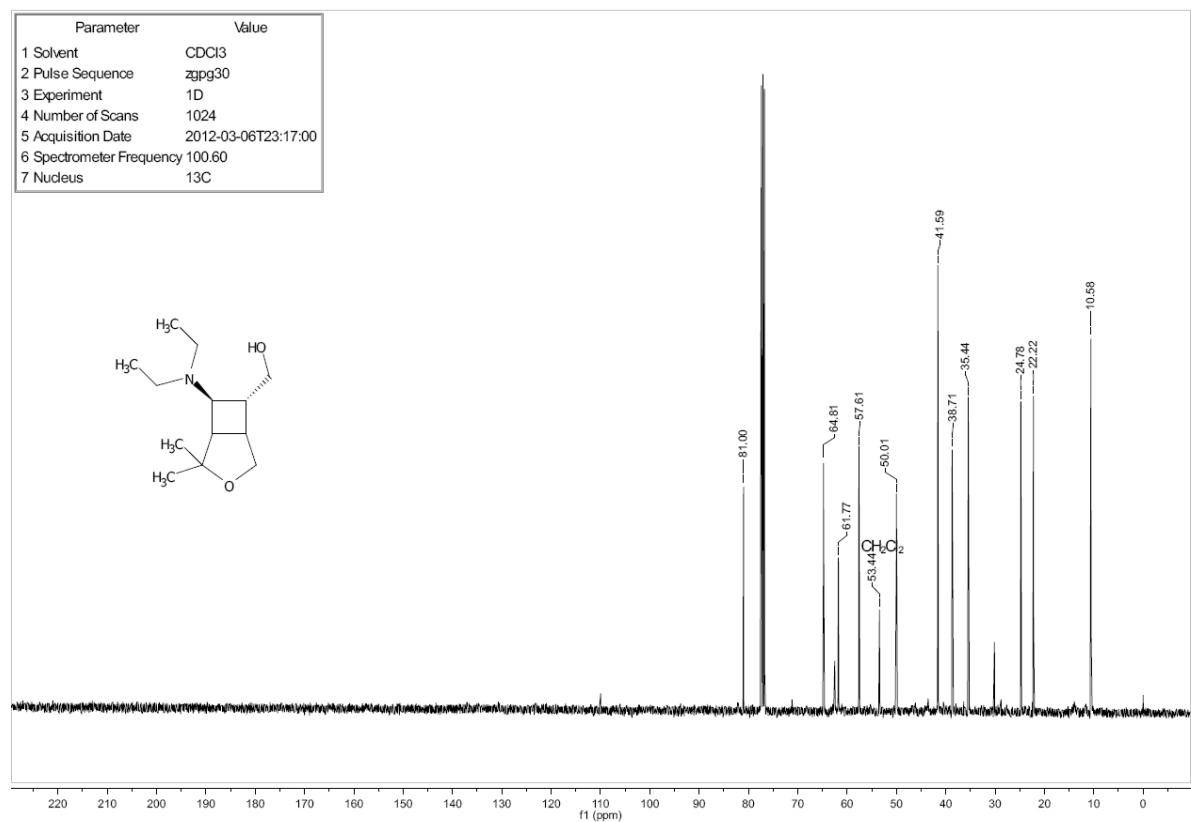
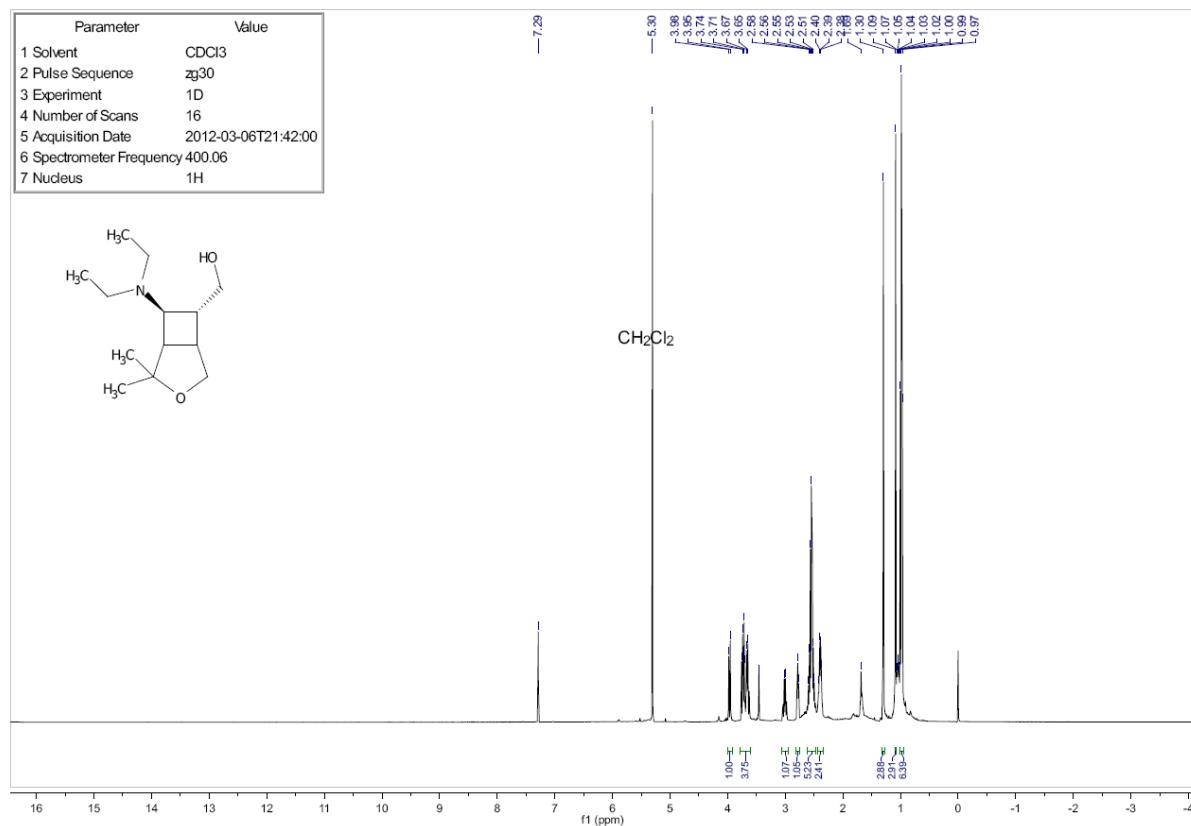
**9f** (2-*exo*-(4-Bromophenyl)-7-*exo*-(diethylamino)-3-oxabicyclo[3.2.0]heptan-6-*endo*-yl)methanol



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

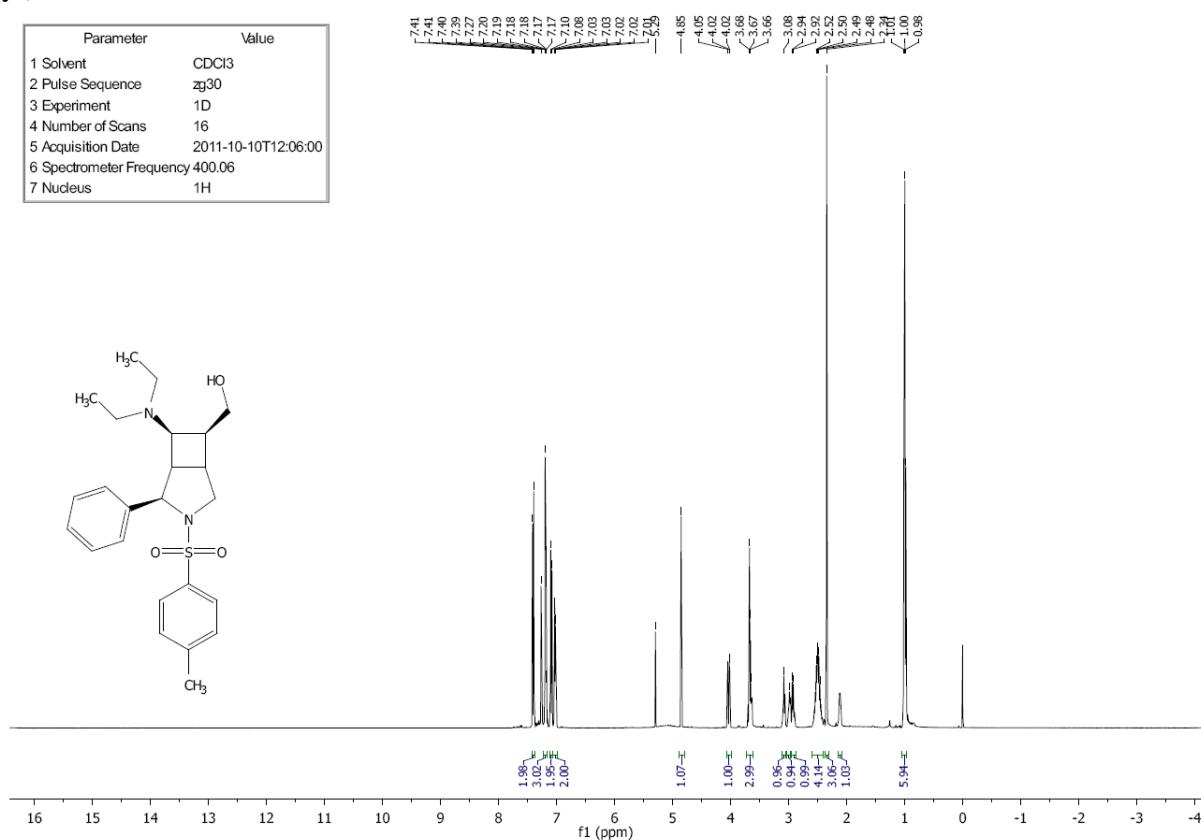


**9i** (7-*exo*-(Diethylamino)-2,2-dimethyl-3-oxabicyclo[3.2.0]heptan-6-*endo*-yl)methanol

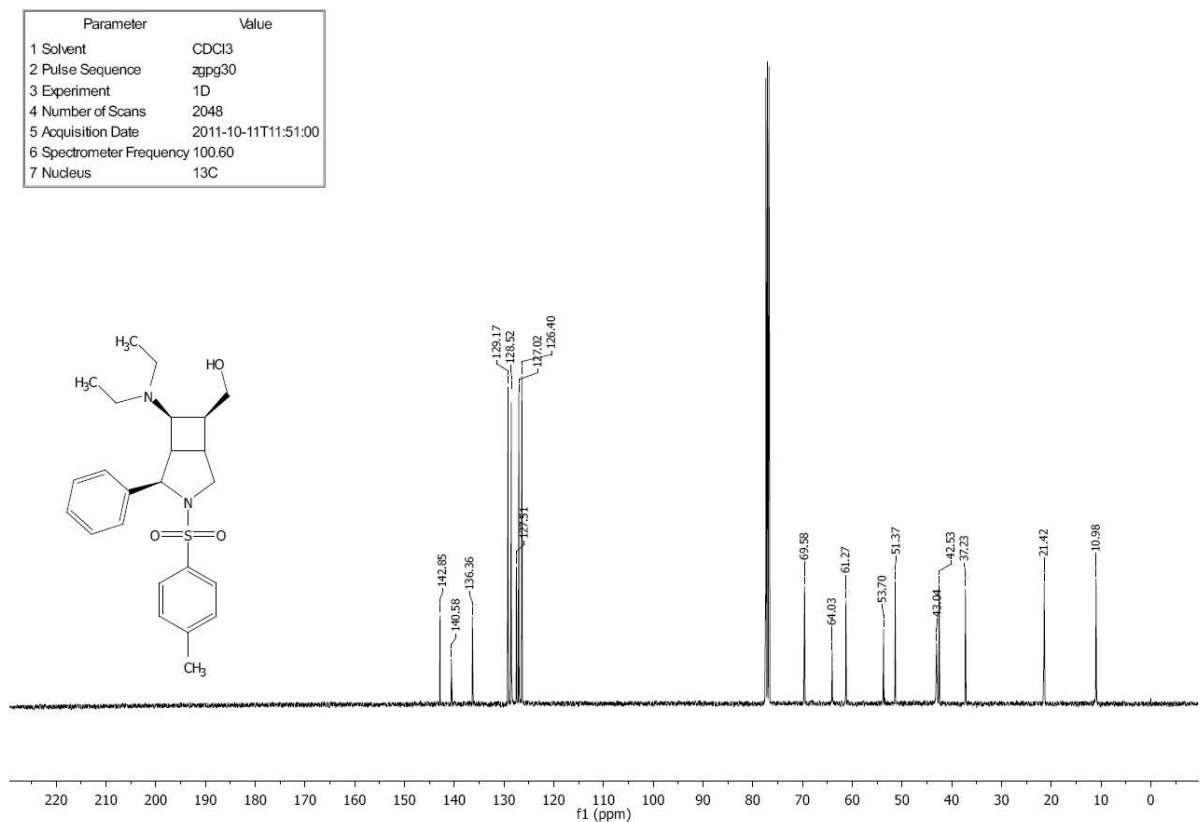


**10a** (*7*-*exo*-(Diethylamino)-*2*-*exo*-phenyl-*3*-tosyl-*3*-azabicyclo[3.2.0]heptan-*6*-*exo*-yl)methanol

Parameter	Value
1 Solvent	CDCl <sub>3</sub>
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	1H

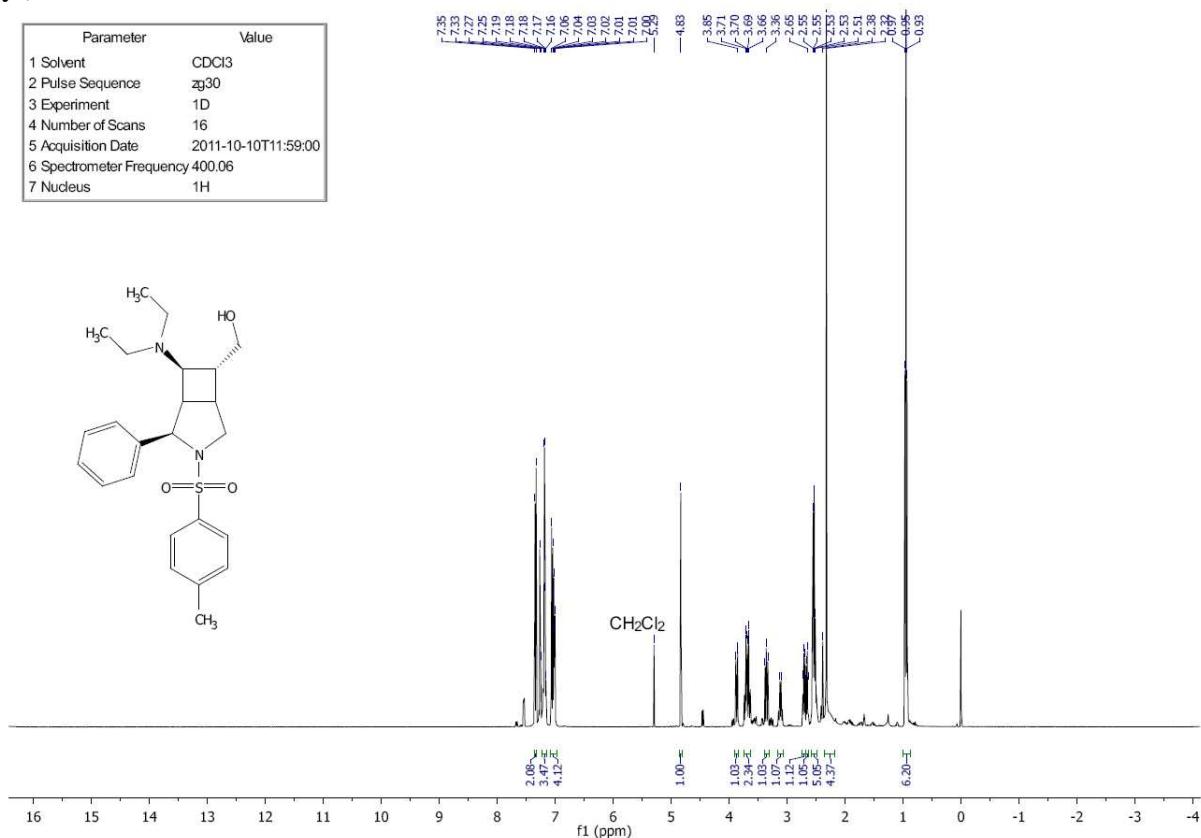


Parameter	Value
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2 Pulse Sequence	zgpg30
3 Experiment	1D
4 Number of Scans	2048
5 Acquisition Date	2011-10-11T11:51:00
6 Spectrometer Frequency	100.60
7 Nucleus	13C

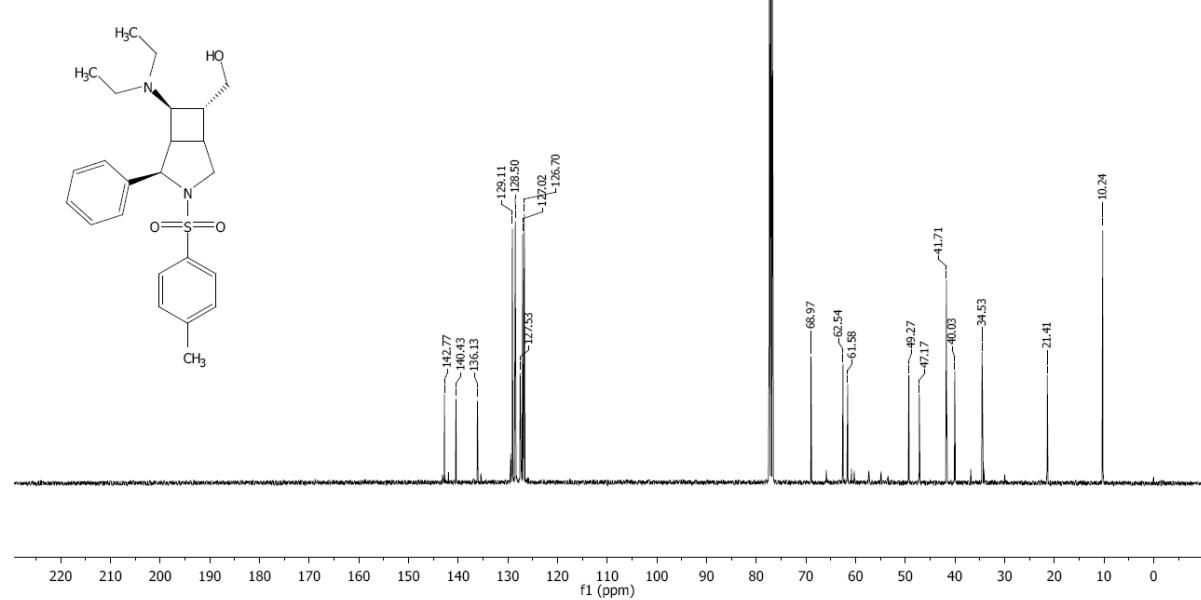


**10b** (*7*-*exo*-(Diethylamino)-*2*-*exo*-phenyl-*3*-tosyl-*3*-azabicyclo[3.2.0]heptan-*6*-*endo*-yl)methanol

Parameter	Value
1 Solvent	CDCl <sub>3</sub>
2 Pulse Sequence	zg30
3 Experiment	1D
4 Number of Scans	16
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6 Spectrometer Frequency	400.06
7 Nucleus	1H

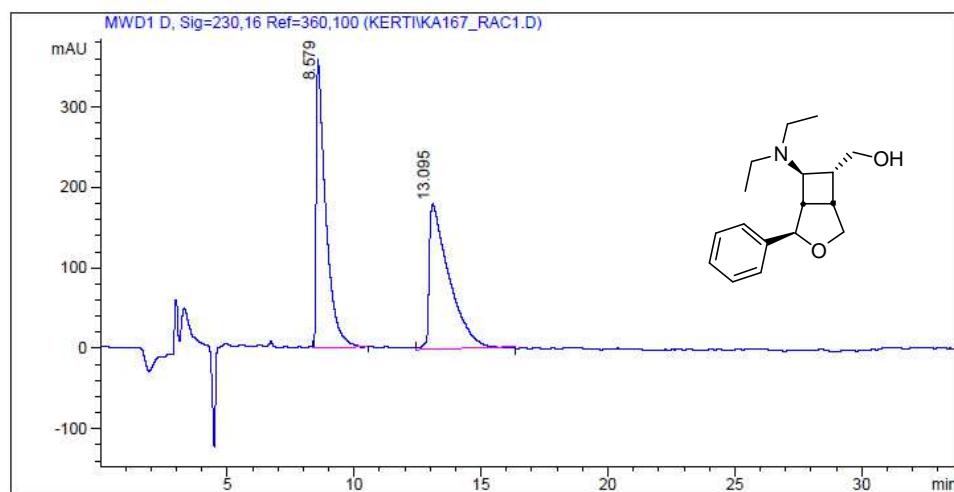


Parameter	Value
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2 Pulse Sequence	zgpg30
3 Experiment	1D
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6 Spectrometer Frequency	100.60
7 Nucleus	13C



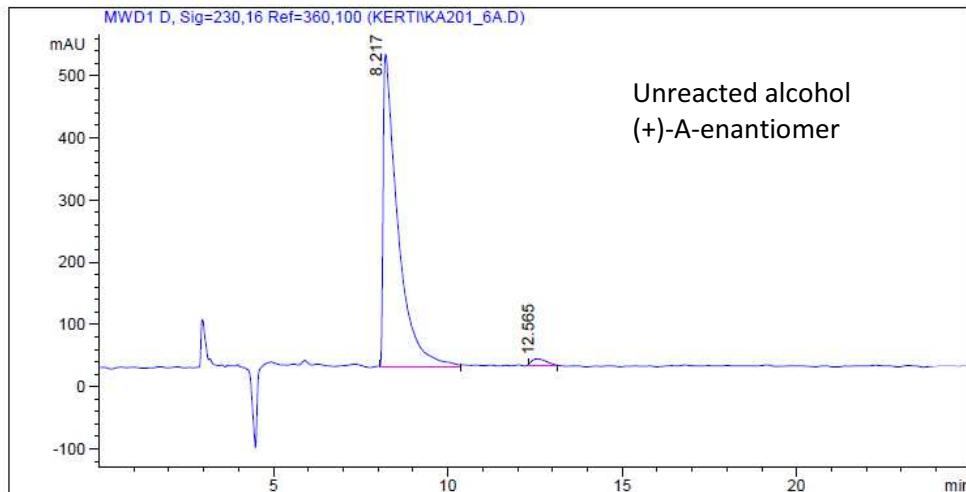
### 3. HPLC chromatograms for the kinetic resolutions with CALB

9a



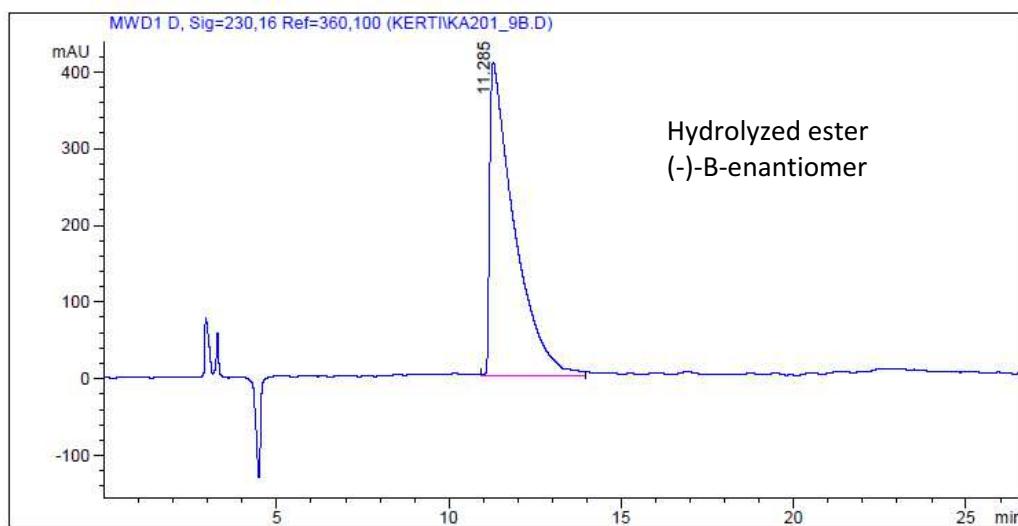
Signal 1: MWD1 D, Sig=230,16 Ref=360,100

Peak no	RT [min]	Peak Type	With [min]	Area	Area %	Name
11	8.579	MM	0.435	9379.784	48.842	
12	13.095	MM	0.907	9824.573	51.158	



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

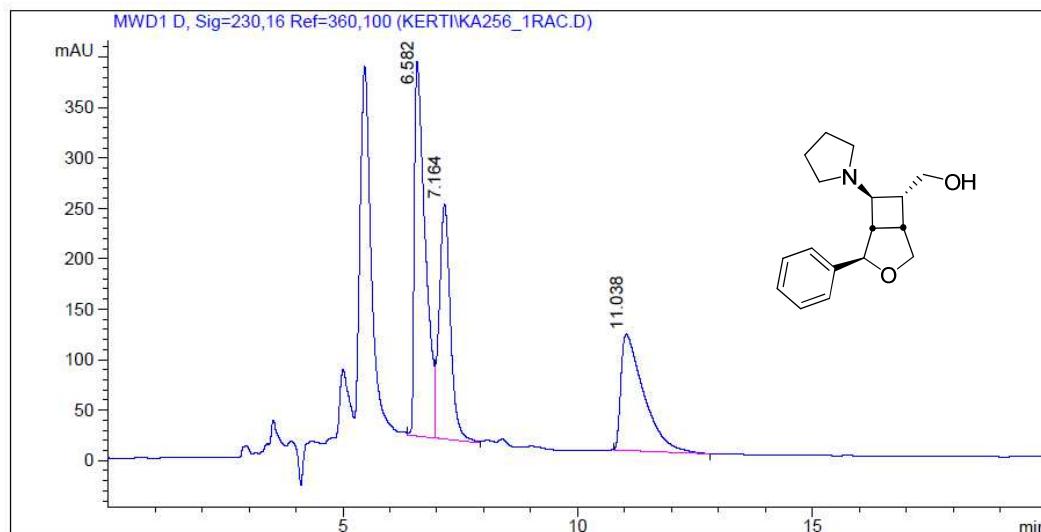
Peak no	RT [min]	Peak Type	With [min]	Area	Area %	Name
1	8.217	MM	0.490	1.480e4	97.863	
2	12.565	MM	0.492	323.222	2.137	



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

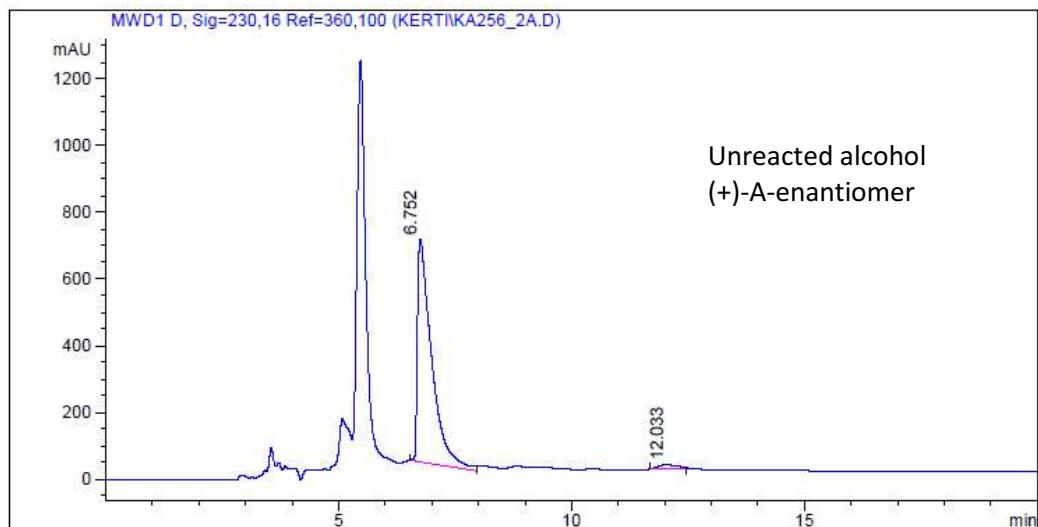
Peak no	RT [min]	Peak Type	With [min]	Area	Area %	Name
1	11.285	MM	0.818	2.004e4	100.000	

### 9b



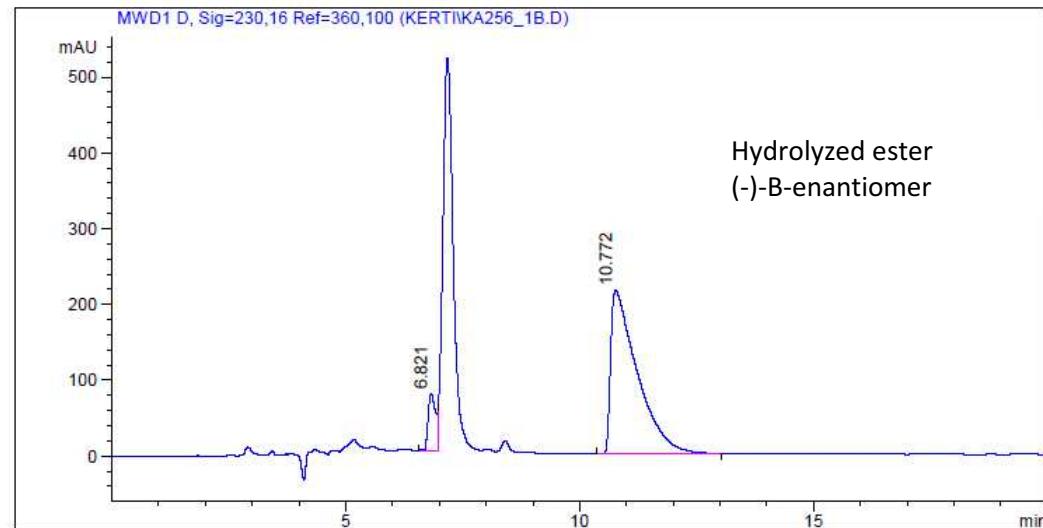
Signal 1: MWD1 D, Sig=230,16 Ref=360,100

Peak no	RT [min]	Peak Type	With [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

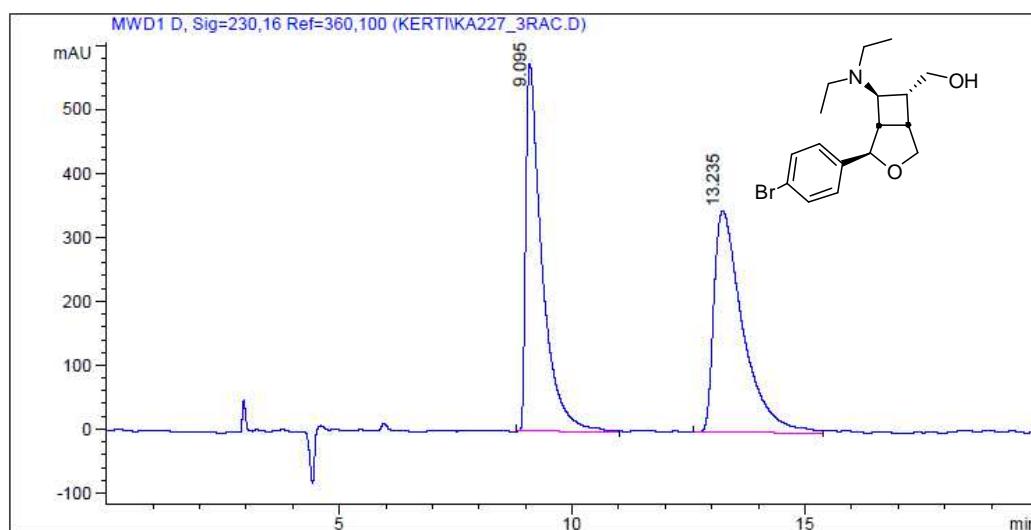
Peak no	RT [min]	Peak Type	With [min]	Area	Area %	Name
1	6.752	MM	0.352	1.409e4	97.635	
2	12.033	MM	0.469	341.338	2.365	



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

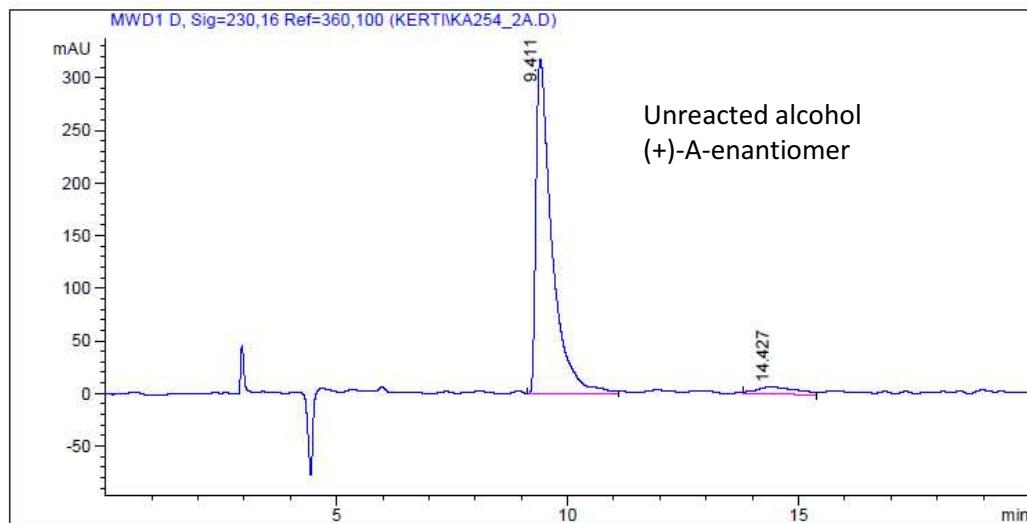
Peak no	RT [min]	Peak Type	With [min]	Area	Area %	Name
1	6.821	MF	0.203	927.087	9.792	
2	10.772	VB	0.553	8541.022	90.208	

9f



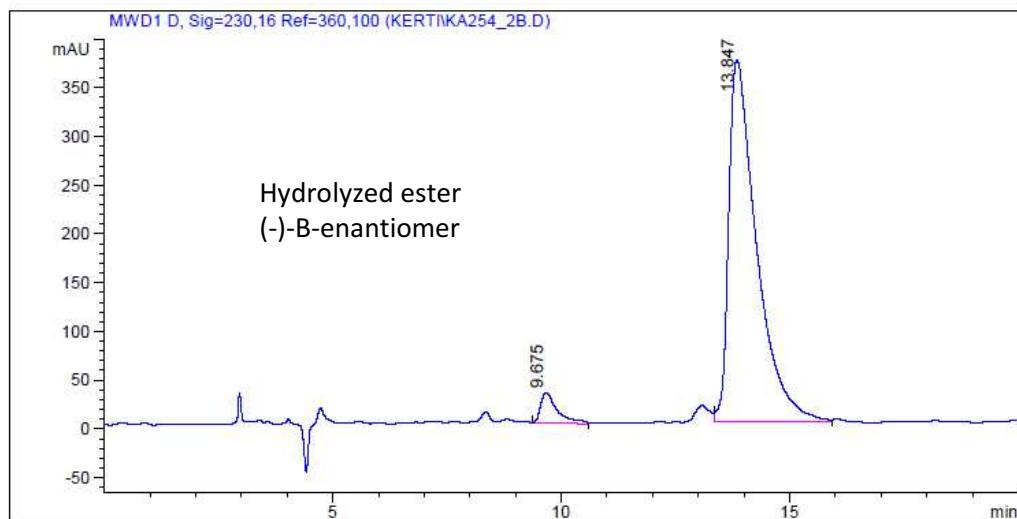
Signal 1: MWD1 D, Sig=230,16 Ref=360,100

Peak	RT	Peak	With	Area	Area	Name
no	[min]	Type	[min]		%	
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

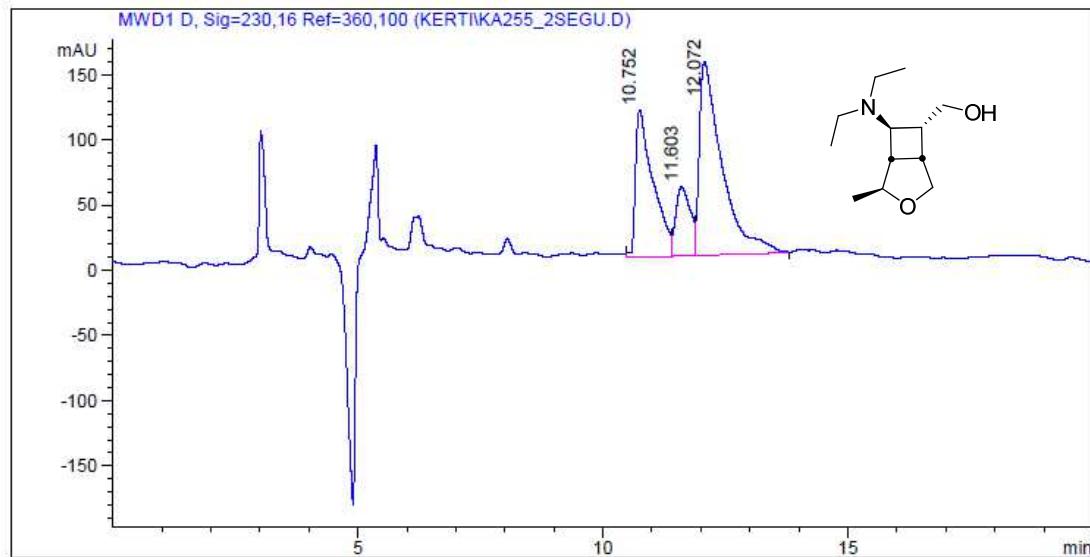
Peak	RT	Peak	With	Area	Area	Name
no	[min]	Type	[min]		%	
1	9.411	MM	0.396	7553.762	95.179	
2	14.427	MM	0.961	382.631	4.821	



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

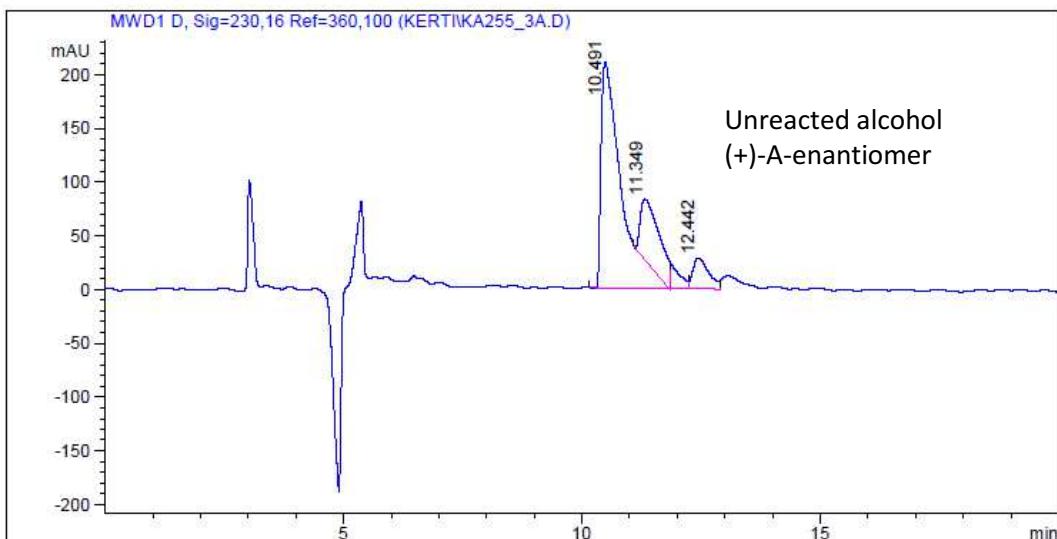
Peak no	RT [min]	Peak Type	With [min]	Area	Area %	Name
1	9.675	MM	0.424	782.315	4.716	
2	13.847	FM	0.708	1.581e4	95.284	

9h



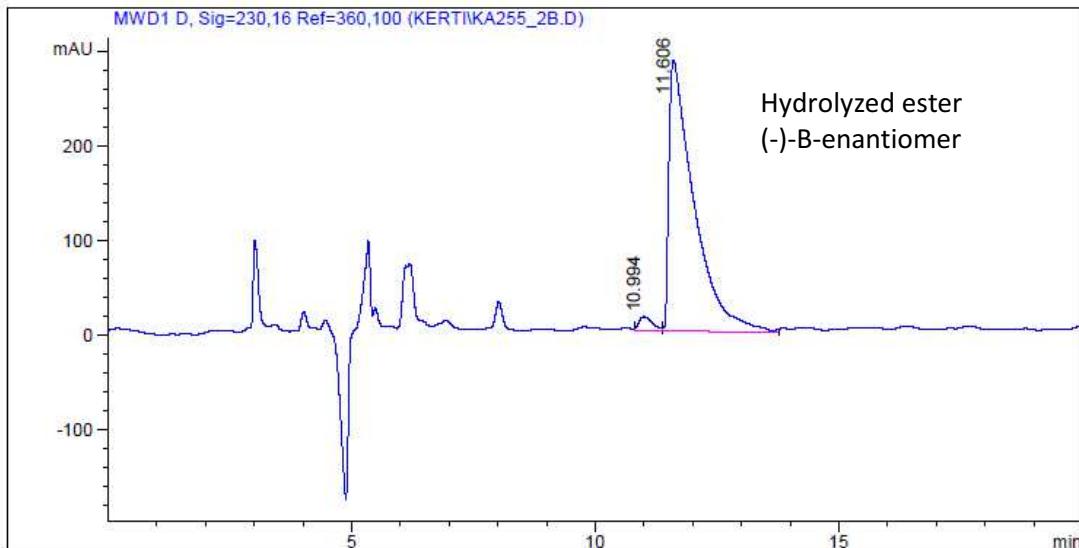
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1	10.752	MF	0.415	2817.316	32.386	
2	11.603	MF	0.349	1107.983	12.737	
3	12.072	FM	0.534	4773.858	54.877	



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

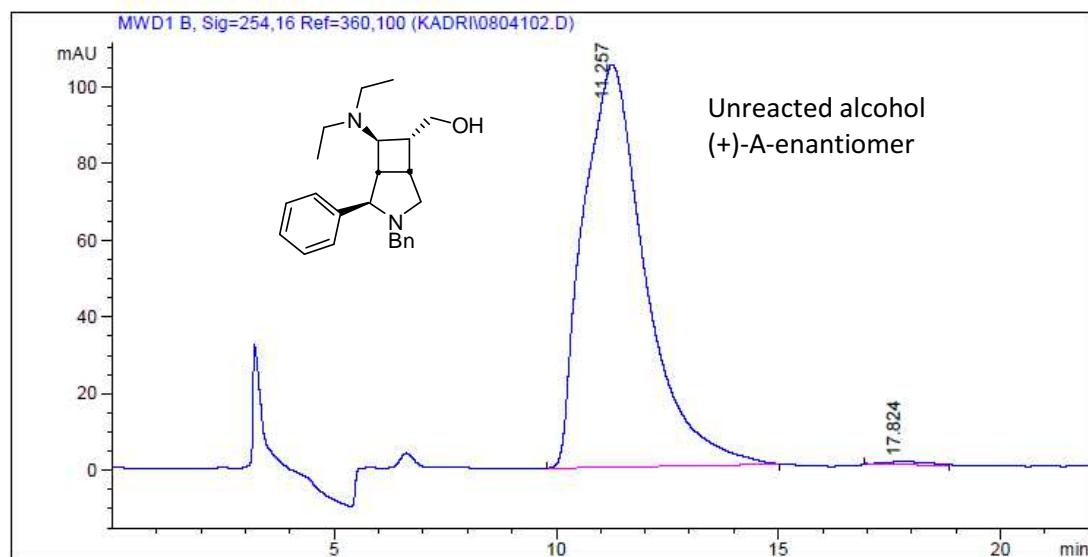
Peak no	RT [min]	Peak Type	With [min]	Area	Area %	Name
1	10.491	MF R	0.516	6509.392	73.508	
2	11.349	MM T	0.506	1687.747	19.059	
3	12.442	MF	0.385	658.208	7.433	



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

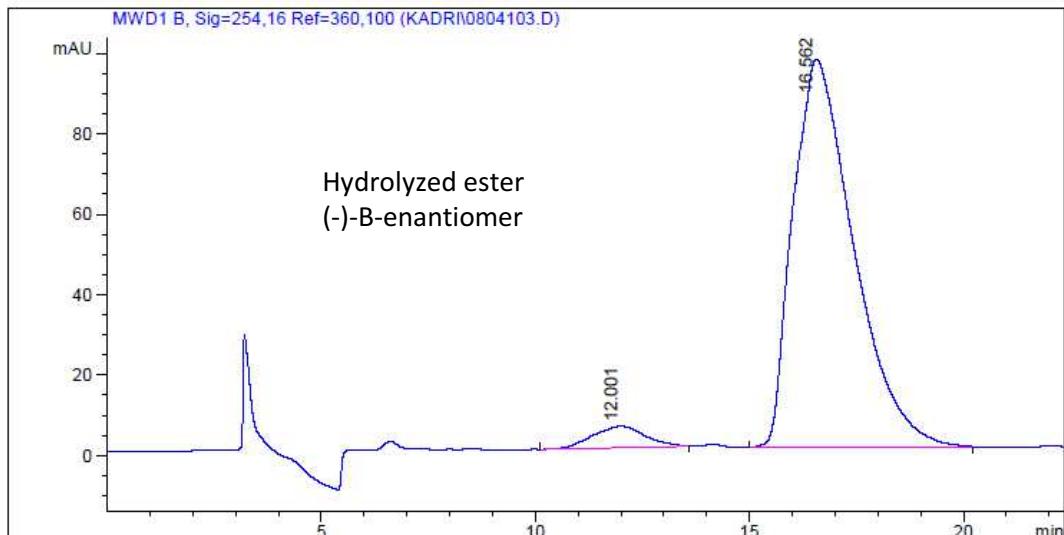
Peak no	RT [min]	Peak Type	With [min]	Area	Area %	Name
1	10.994	MF	0.321	281.093	2.672	
2	11.606	FM	0.594	1.024e4	97.328	

9j



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

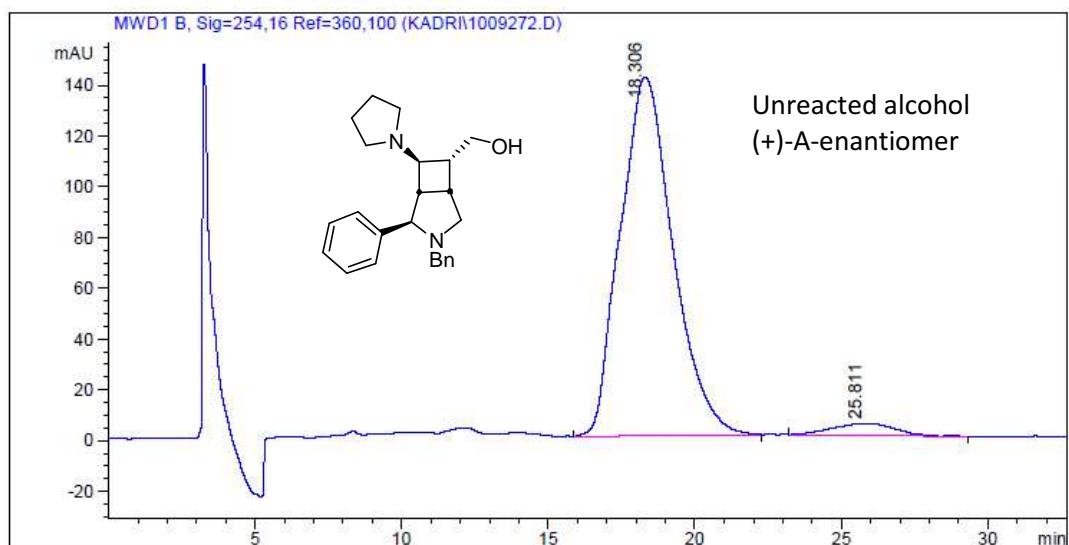
Peak no	RT [min]	Peak Type	With [min]	Area	Area %	Name
1	11.257	BB	1.327	1.015e4	99.438	
2	17.824	MM	1.158	57.413	0.562	



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

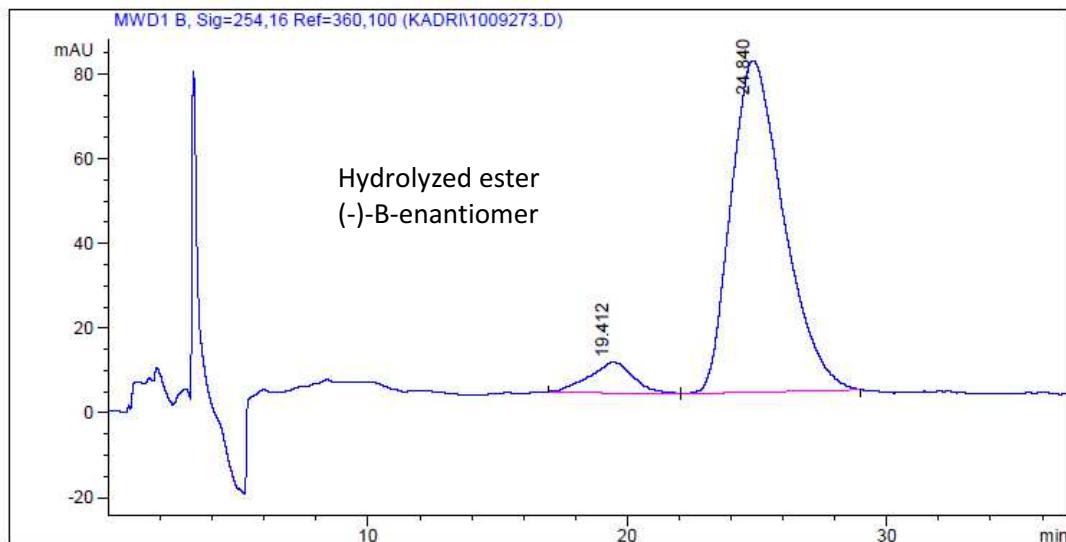
Peak no	RT [min]	Peak Type	With [min]	Area	Area %	Name
1	12.001	BV	1.078	461.719	4.623	
2	16.562	BB	1.392	9526.273	95.377	

9k



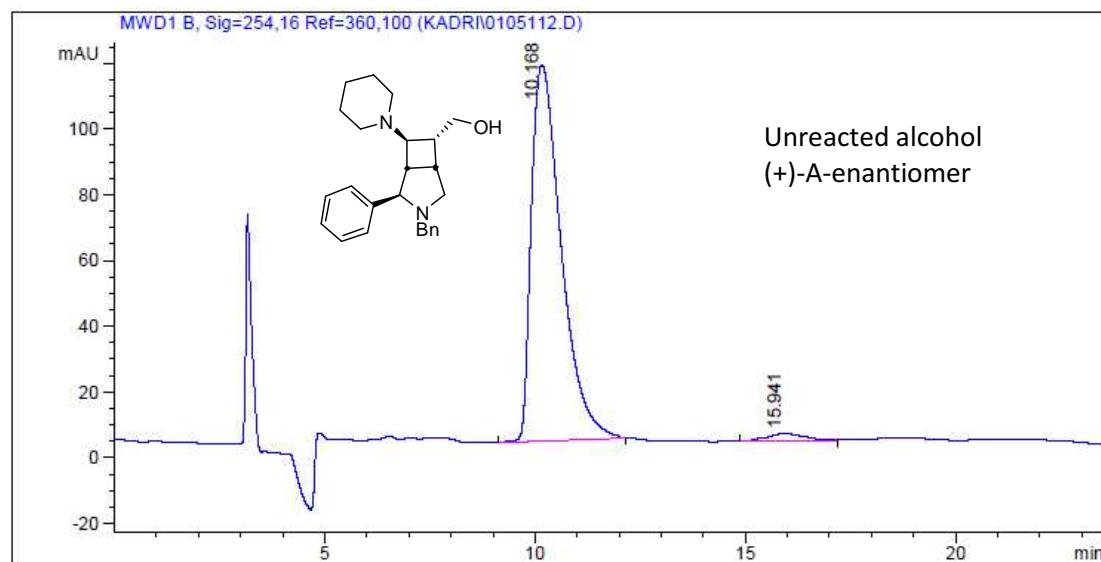
Signal 1: MWD1 B, Sig=254,16 Ref=360,100

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	



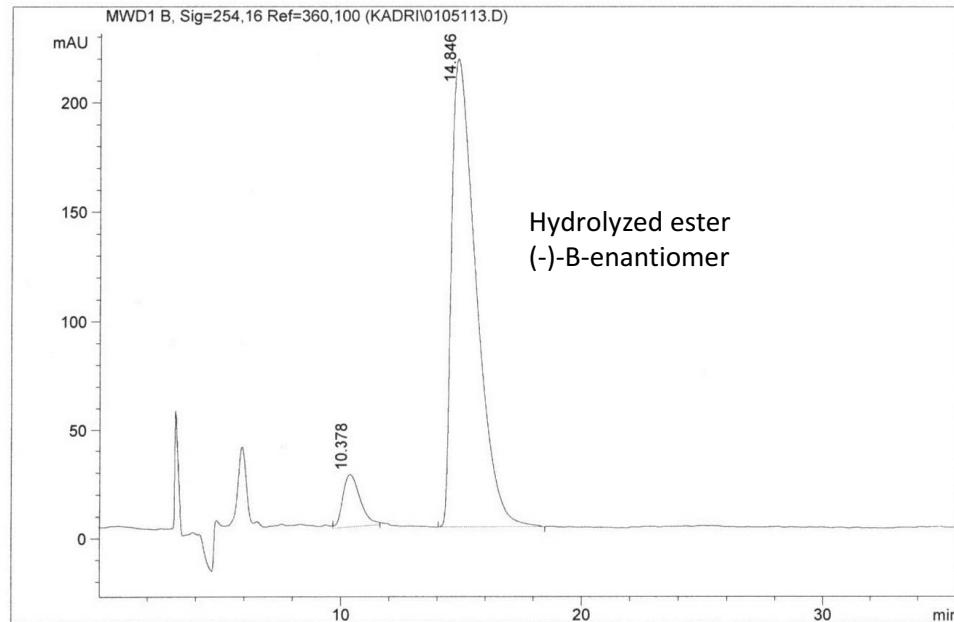
Signal 1: MWD1 B, Sig=254,16 Ref=360,100

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



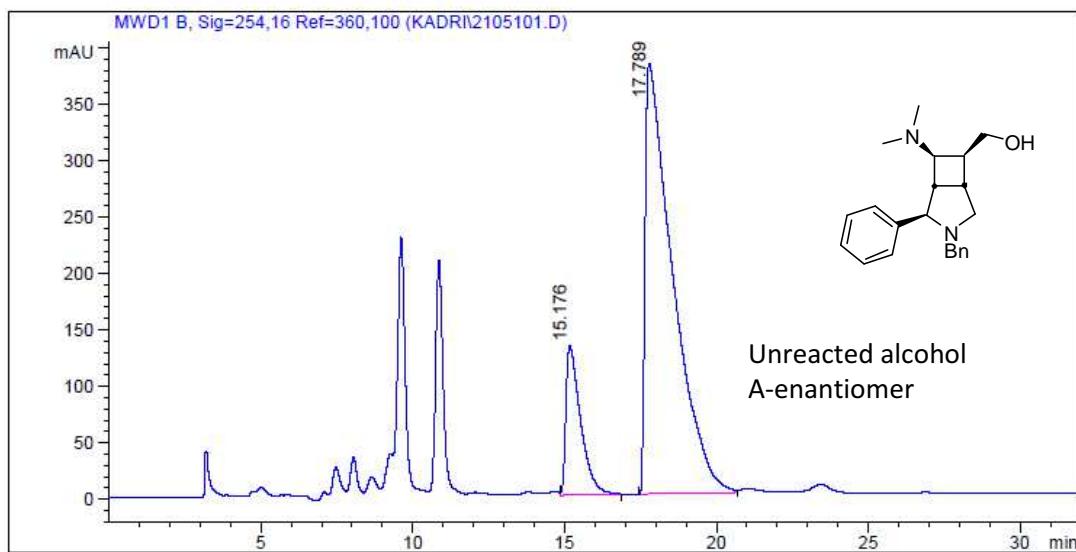
Signal 1: MWD1 B, Sig=254,16 Ref=360,100

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	



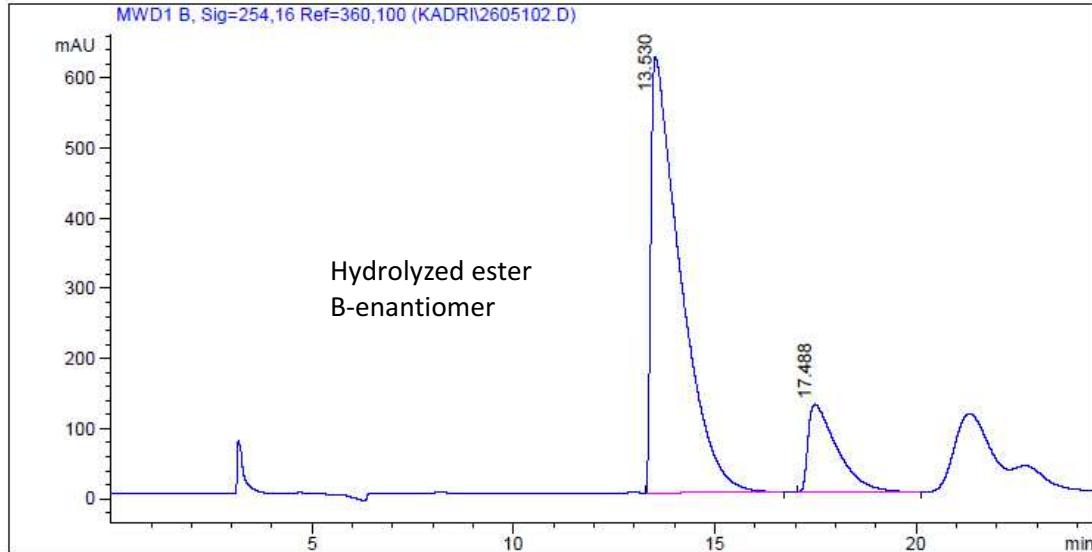
Signal 1: MWD1 B, Sig=254,16 Ref=360,100

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

**9m**

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

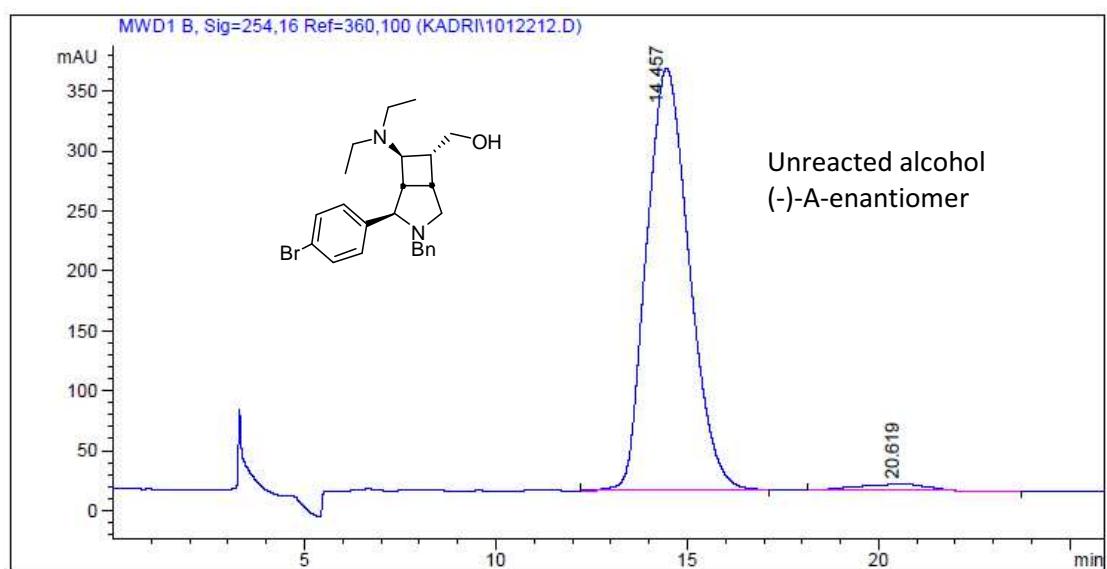
Peak no	RT [min]	Peak Type	With [min]	Area	Area %	Name
1	15.176	VB	0.494	4431.535	15.546	
2	17.789	BB	0.881	2.408e4	84.454	



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

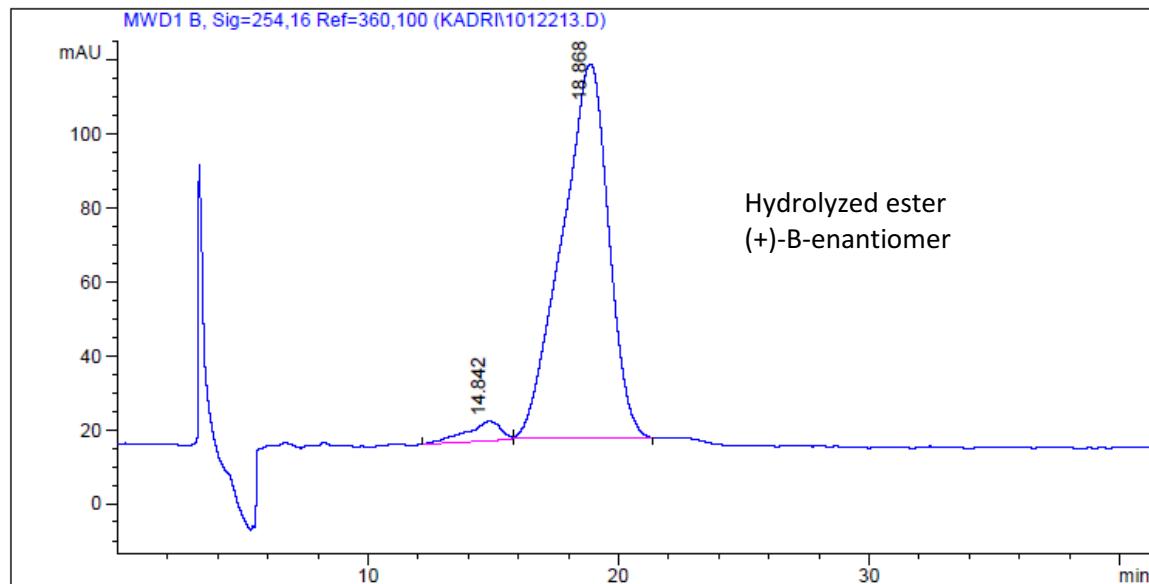
Peak no	RT [min]	Peak Type	With [min]	Area	Area %	Name
1	13.530	BB	0.698	3.156e4	83.393	
2	17.488	BB	0.734	6285.290	16.607	

90



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

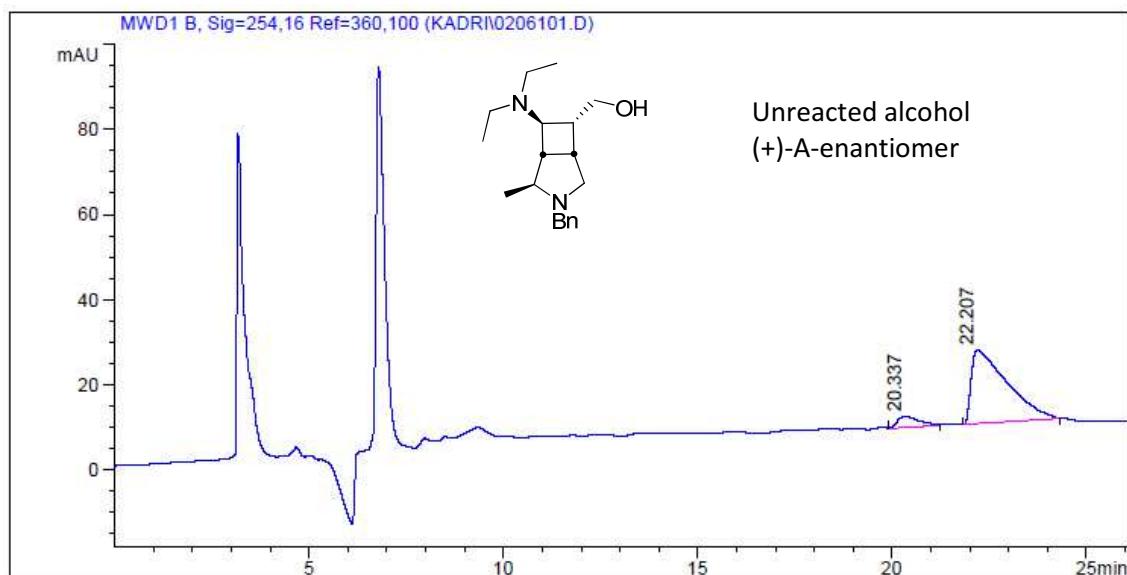
Peak no	RT [min]	Peak Type	With [min]	Area	Area %	Name
1	14.457	BB	1.269	2.726e4	97.737	
2	20.619	BB	1.372	631.209	2.263	



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

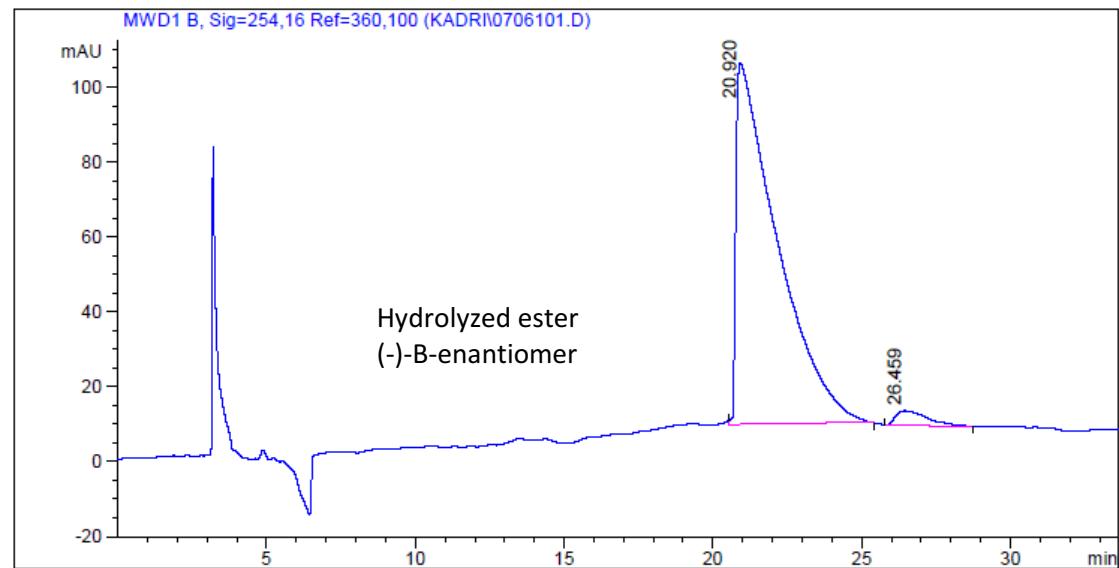
Peak no	RT [min]	Peak Type	With [min]	Area	Area %	Name
1	14.842	MM	1.626	509.865	3.750	
2	18.868	MM	2.156	1.309e4	96.250	

9r



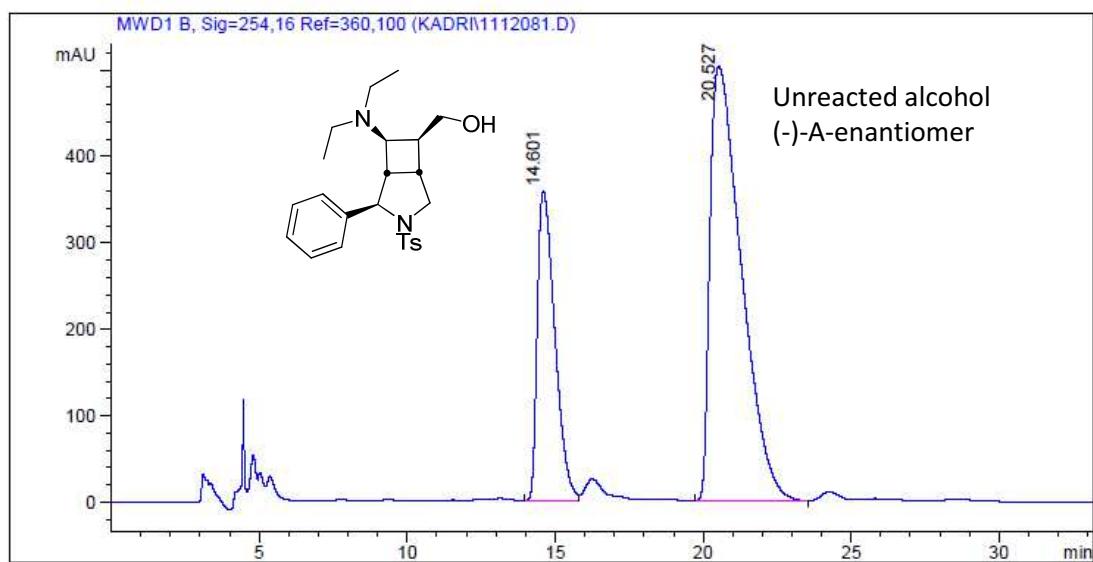
Signal 1: MWD1 B, Sig=254,16 Ref=360,100

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	



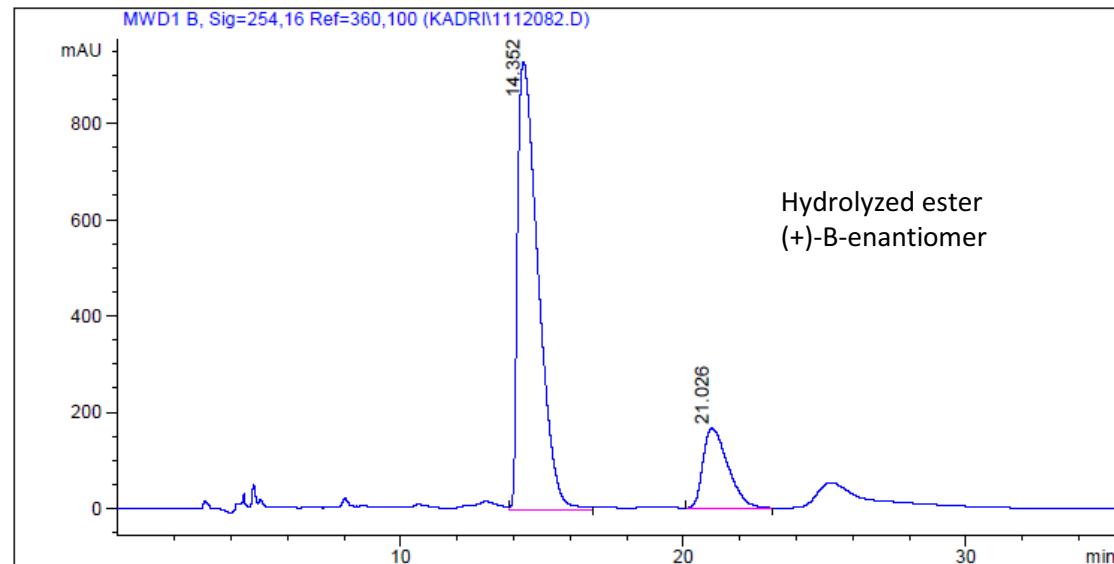
Signal 1: MWD1 B, Sig=254,16 Ref=360,100

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**

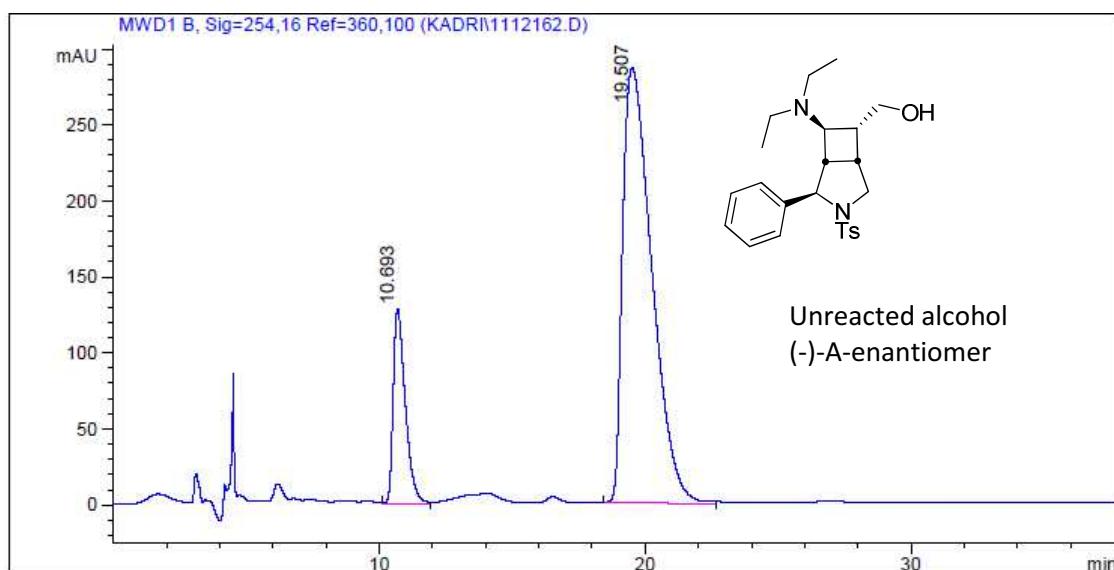
Signal 1: MWD1 B, Sig=254,16 Ref=360,100

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	



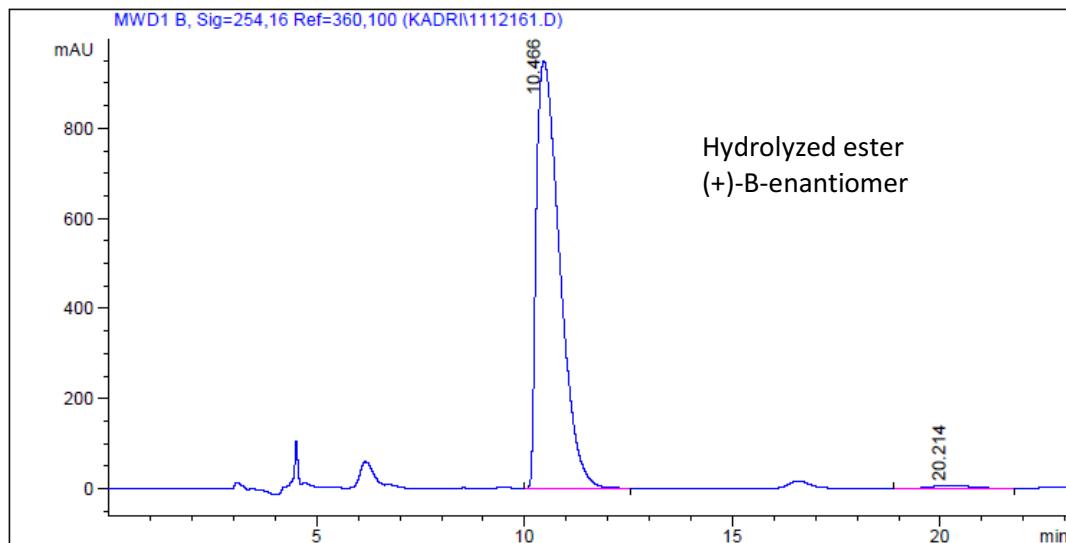
Signal 1: MWD1 B, Sig=254,16 Ref=360,100

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,  $\beta = 94.853(4)^\circ$ ,  $V = 835.10(17)$  Å<sup>3</sup>,  $T = 200$  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.

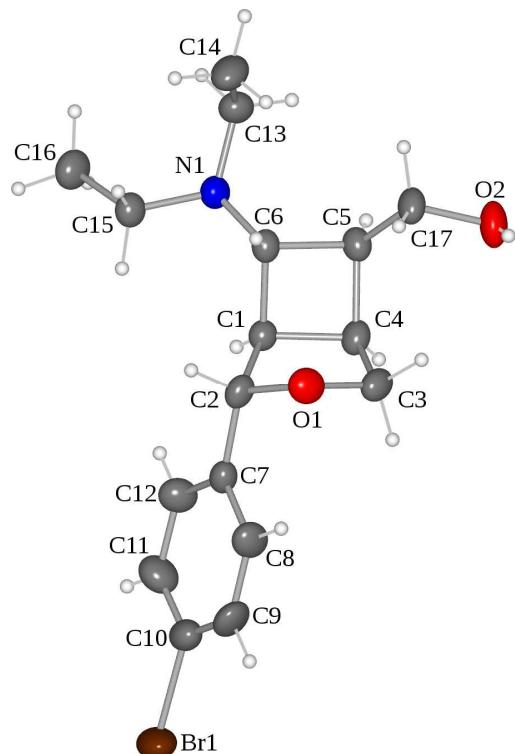


Figure 1. Molecular moiety in the crystal structure of **9f**, A enantiomer. Displacement ellipsoids are drawn at the 50% probability level.