Supporting information

Direct Enantioselective Aldol Reactions catalyzed by a Proline-Thiourea Host-Guest Complex

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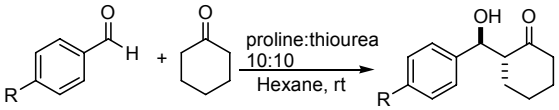
General Information. All commercially available reagents were used without further purification. Purification of products was carried out by flash column chromatography using silica gel 60. Analytical thin layer chromatography was performed on aluminium sheets precoted with silica gel 60F254. Visualization was accomplished with UV light and anisaldehyde followed by heating.

General Procedure for the Enantioselective Direct Aldol Reaction

Proline (0.025 mmol, 2.9 mg), thiourea **4** (0.025 mmol, 12.5 mg) and 1.8 mL hexane were placed in a screw capped vial, then cyclohexanone (4 mmol, 0.4 mL) was added, in which the resulting mixture was stirred for 15 min at ambient temperature followed by addition of aldehyde (0.25 mmol) wherein stirring was continued until the completion of the reaction (TLC monitoring). After completion of the reaction, the reaction mixture was treated with saturated aqueous ammonium chloride solution and the whole mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated to give a crude residue, which was purified with column chromatography over silica gel using hexane-ethyl acetate as an eluent to afford pure product. Diastereoselectivity and conversion were determined by 1H NMR analysis of the crude aldol product. The enantiomeric excess (ee) of **3** was determined by chiral-phase HPLC analysis. The absolute configuration of aldol products were determined by comparing the values with those previously reported in the literature.

Table 2. Enantioselective Direct Aldol Reaction of aldehydes (**2**) and Cyclohexanone (**1**)



2 **1** **3**

entry	aldehyde **R**	time (h)	yield (%)[e]	anti:syn[a]	ee (%)[b]
1	**2a** 4-NO_2Ph [c]	24	75	92:8	>99
2	**2a** 4-NO_2Ph	16	96	90:10	99
3	**2b** 3-NO_2Ph[c]	24	79	93:7	>99
4	**2b** 3-NO_2Ph	16	94	92:8	>99
5	**2c** 4-CNPh	16	98	93:7	99
6	**2d** 4-CF_3Ph	24	93	94:6	99
7	**2e** 4-ClPh	36	91	88:12	99
8	**2f** 4-BrPh	36	87	90:10	99
9	**2g** 2-ClPh	36	83	94:6	99
10	**2h** Ph	48	79	88:12	98
11	**2i**[c] 4-NO_2Ph	16	93	60:40	97

a. Determined from crude NMR spectra

b. Determined by HPLC with appropriate chiral column

c. Toluene is used

d. Cyclopentanone is used

e. After purification

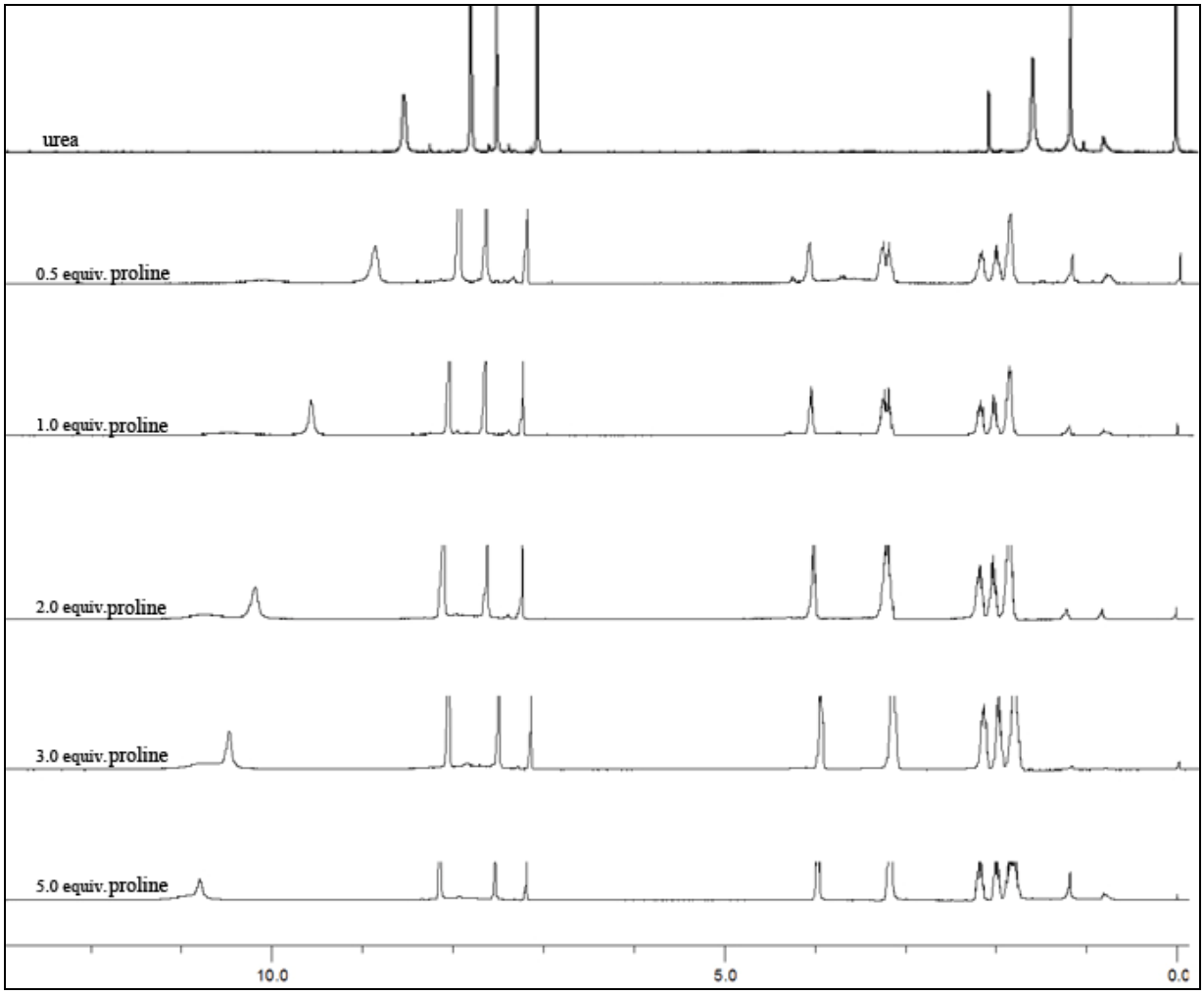
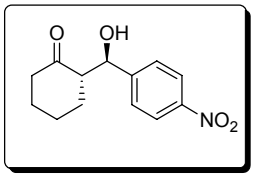
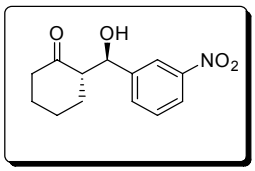


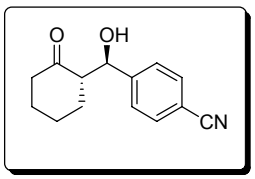
Figure 1. The NMR spectra of proline-thiourea complex



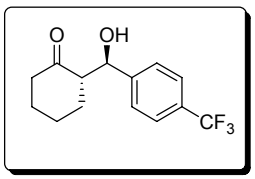
(S)-2-((R)-hydroxy(4-nitrophenyl)methyl)cyclohexan-1-one (3a)[1, 2] : It was obtained in a maximum of >99% ee. The optical purity was determined by HPLC on chiralpak AD-H column [hexane/2-propanol 90.0:10.0]; flow rate 0.5 mL/min.



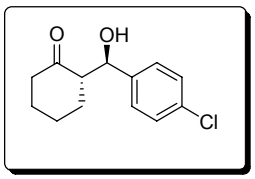
(S)-2-((R)-hydroxy(3-nitrophenyl)methyl)cyclohexan-1-one (3b)[1] : It was obtained in a maximum of >99% ee. The optical purity was determined by HPLC on chiralpak AD-H column [hexane/2-propanol 95.0:5.0]; flow rate 1.0mL/min. *Anti/Syn*= 92/8, *anti*-diastereomer, ^{1}HNMR (400 MHz, $CDCl^3$) δ (ppm) 1.33-2.10 (m, 6H), 2.32-2.48 (m, 2H), 2.58-2.64 (m, 1H), 4.14 (s, 1H), 4.87 (d, J = 8.4 Hz, 1H), 7.50 (t, J = 8.0 Hz, 1H), 7.64 (t, J = 7.6 Hz, 1H), 8.12 (d, J = 7.6 Hz, 1H), 8.18 (d, J = 1.6 Hz, 1H); *syn*-diastereomer, ^{1}HNMR (400 MHz, $CDCl_3$) δ (ppm) 1.48-2.10 (m, 6H), 2.33-2.46 (m, 2H), 2.62-2.66 (m, 1H), 3.27 (s, 1H), 5.44 (d, J = 2.0 Hz, 1H), 7.48 (t, J = 8.0 Hz, 1H), 7.64 (t, J = 7.6 Hz, 1H), 8.06 (t, J = 6.0 Hz, 1H); 8.15 (s, 1H).



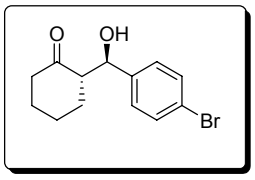
(S)-2-((R)-hydroxy(4-cyanophenyl)methyl)cyclohexan-1-one (3c)[1] : It was obtained in a maximum of 99% ee. The optical purity was determined by HPLC on chiralpak OD-H column [hexane/2-propanol 90.0:10.0]; flow rate 0.5 mL/min. *Anti/Syn*= 93/7, *anti*-diastereomer, ^{1}HNMR (400 MHz, $CDCl_3$) δ (ppm) 1.31-2.11 (m, 6H), 2.30-2.48 (m, 2H), 2.53-2.59 (m, 1H), 4.07 (s, 1H), 4.82 (d, J = 8.4 Hz, 1H), 7.43 (d, J = 8.4 Hz, 2H), 7.62 (d, J = 8.0 Hz, 2H); *syn*-diastereomer, ^{1}HNMR (400 MHz, $CDCl_3$) δ (ppm) 1.52-2.12 (m, 6H), 2.33-2.48 (m, 2H), 2.57-2.61 (m, 1H), 3.19 (s, 1H), 5.42 (s, 1H), 7.42 (d, J = 8.0 Hz, 2H), 7.62 (d, J = 8.4 Hz, 2H).



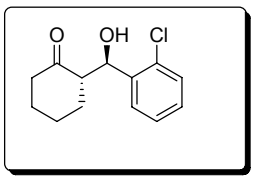
(S)-2-((R)-(4-(trifluoromethyl)phenyl)(hydroxy)methyl)cyclohexan-1-one (3d)[3] : It was obtained in a maximum of 99% ee. The optical purity was determined by HPLC on chiralpak OD-H column [hexane/2-propanol 95.0:5.0]; flow rate 1.0mL/min.



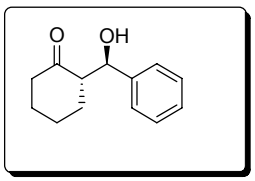
(S)-2-((R)-hydroxy(4-chlorophenyl)methyl)cyclohexan-1-one (3e)[1] : It was obtained in a maximum of 99% ee. The optical purity was determined by HPLC on chiralpak AD-H column [hexane/2-propanol 90.0:10.0]; flow rate 0.5 mL/min.



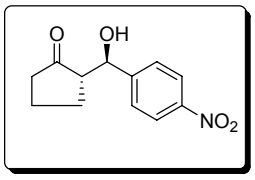
(S)-2-((R)-hydroxy(4-bromophenyl)methyl)cyclohexan-1-one (3f)[1] : It was obtained in a maximum of 99% ee. The optical purity was determined by HPLC on chiralpak AD-H column [hexane/2-propanol 90.0:10.0]; flow rate 0.5 mL/min.



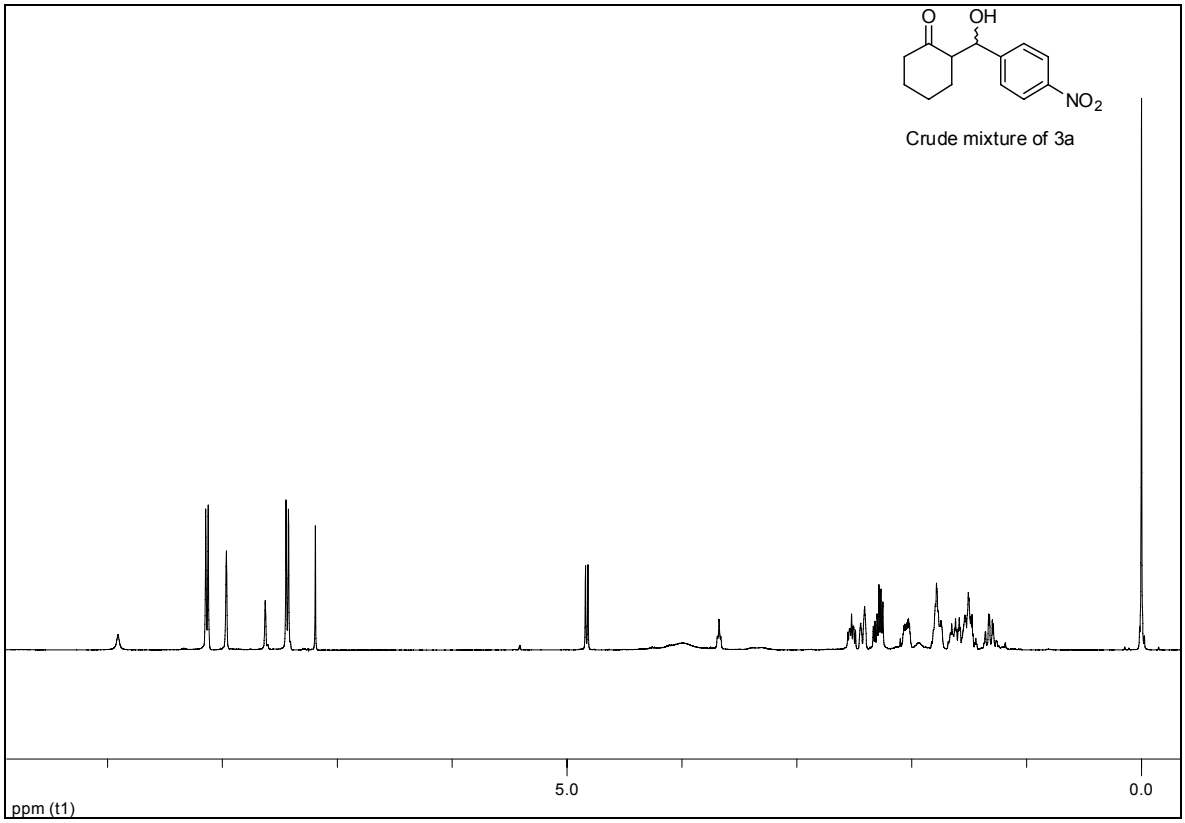
(S)-2-((R)-hydroxy(2-chlorophenyl)methyl)cyclohexan-1-one (3g)[4] : It was obtained in a maximum of 99% ee. The optical purity was determined by HPLC on chiralpak OD-H column [hexane/2-propanol 95.0:5.0]; flow rate 0.5 mL/min.



(S)-2-((R)-hydroxy(phenyl)methyl)cyclohexan-1-one (3h)[1] : It was obtained in a maximum of 98% ee. The optical purity was determined by HPLC on chiralpak OD-H column [hexane/2-propanol 90.0:10.0]; flow rate 1.0 mL/min.



(S)-2-((R)-hydroxy(4-nitrophenyl)methyl)cyclopentan-1-one (3i)[5] : It was obtained in a maximum of >97% ee. The optical purity was determined by HPLC on chiralpak AD-H column [hexane/2-propanol 95.0:5.0]; flow rate 0.5 mL/min.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OH
NO2
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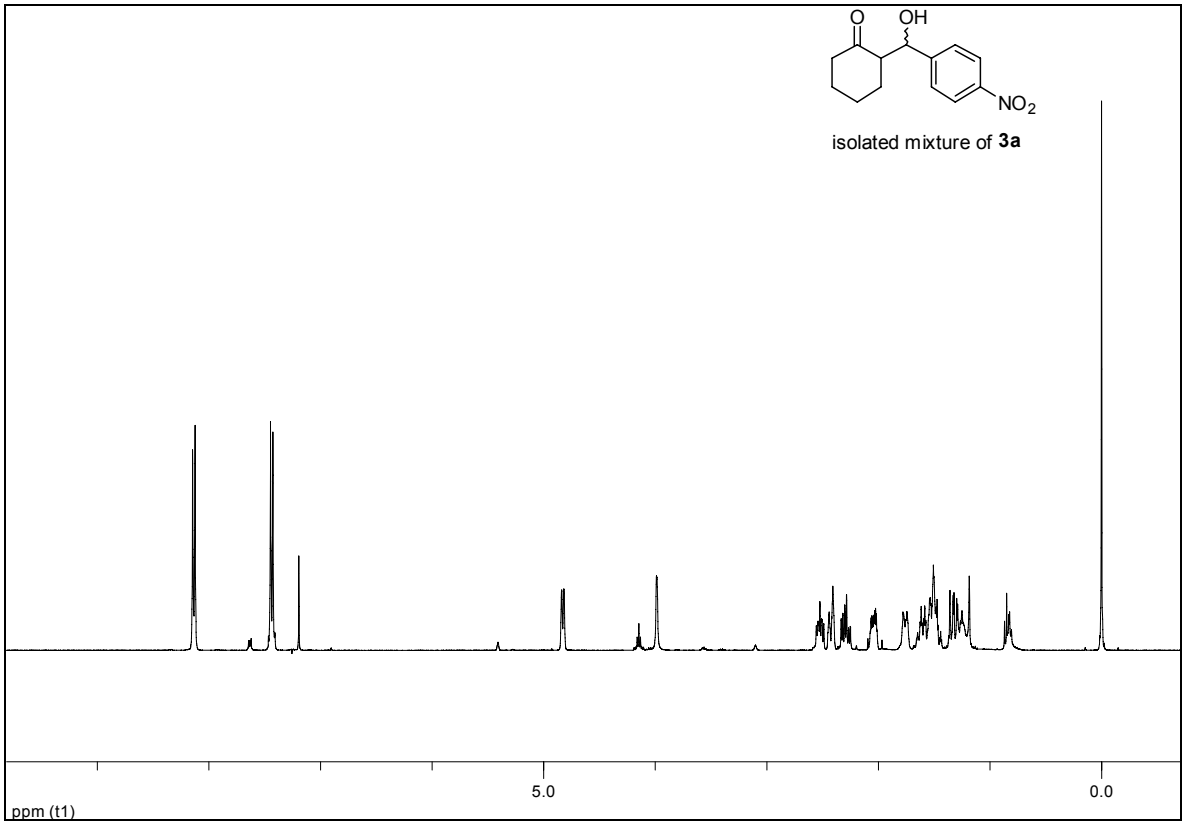
5.0
0.0
ppm (t1)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OH
NO2
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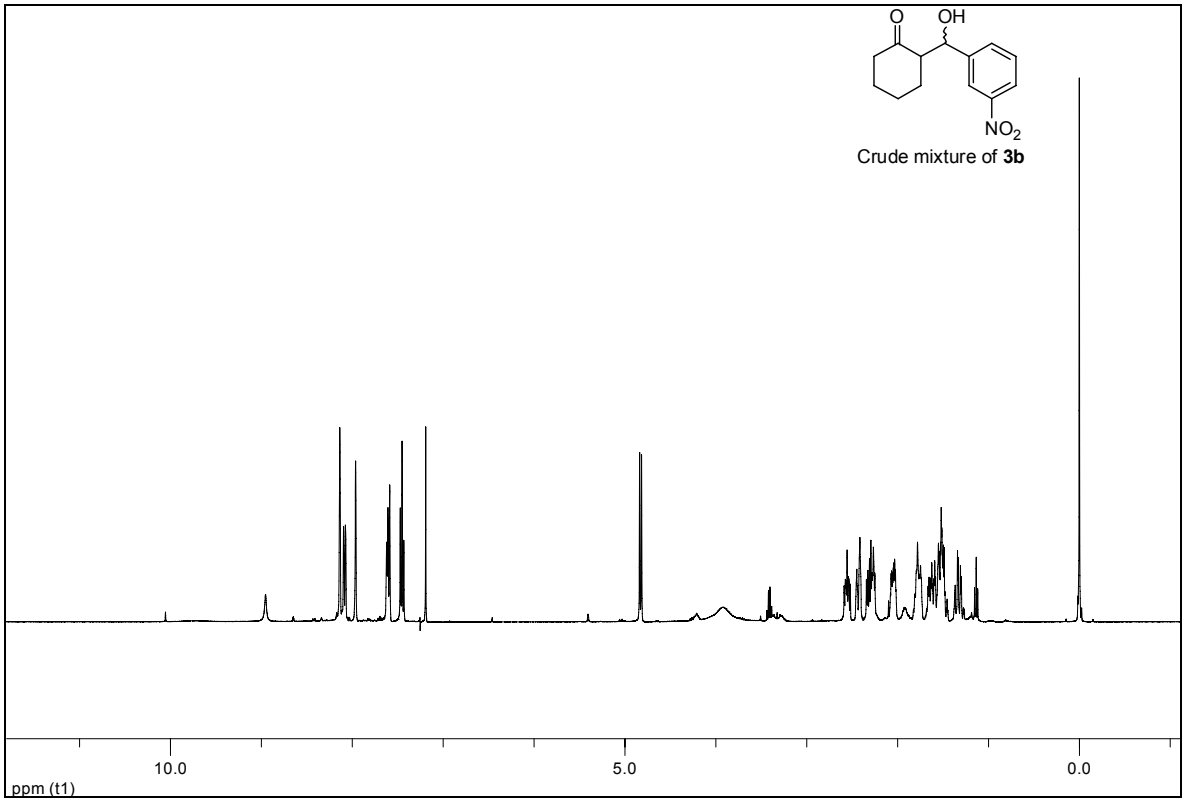
ppm (t1)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NO2
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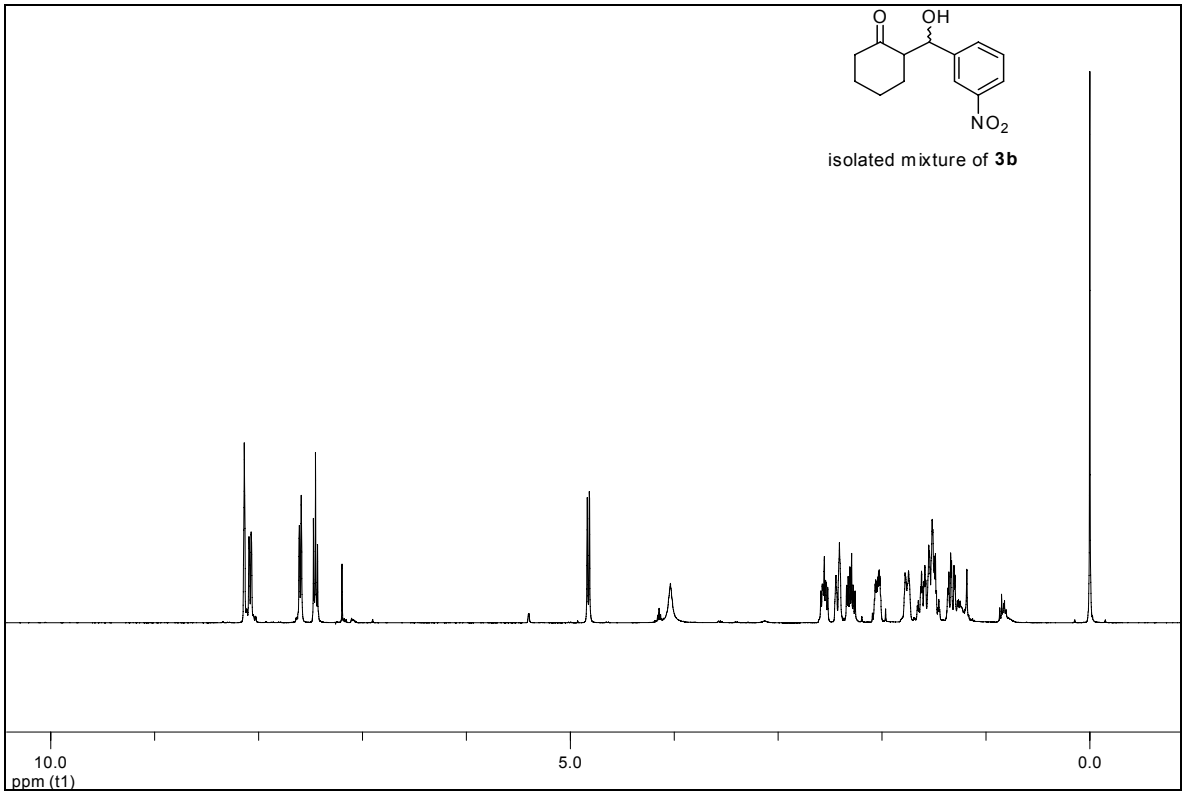
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OH
NO2
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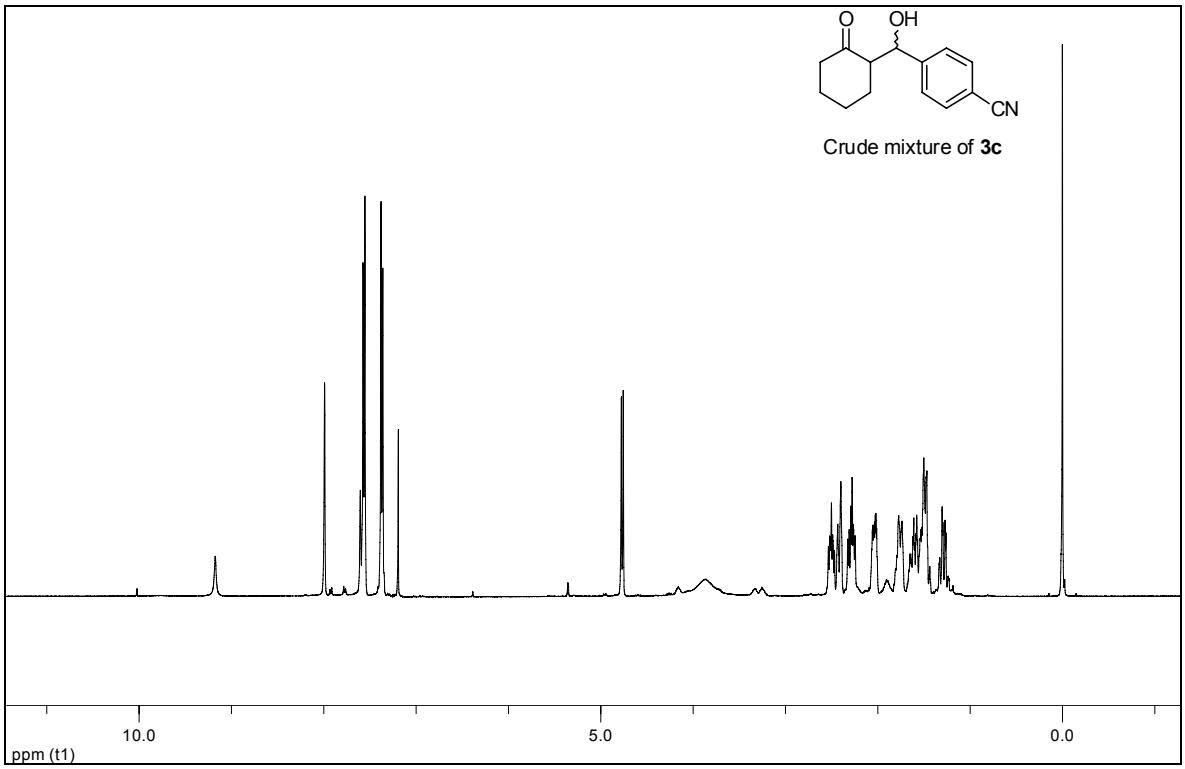
5.0
0.0
ppm (t1)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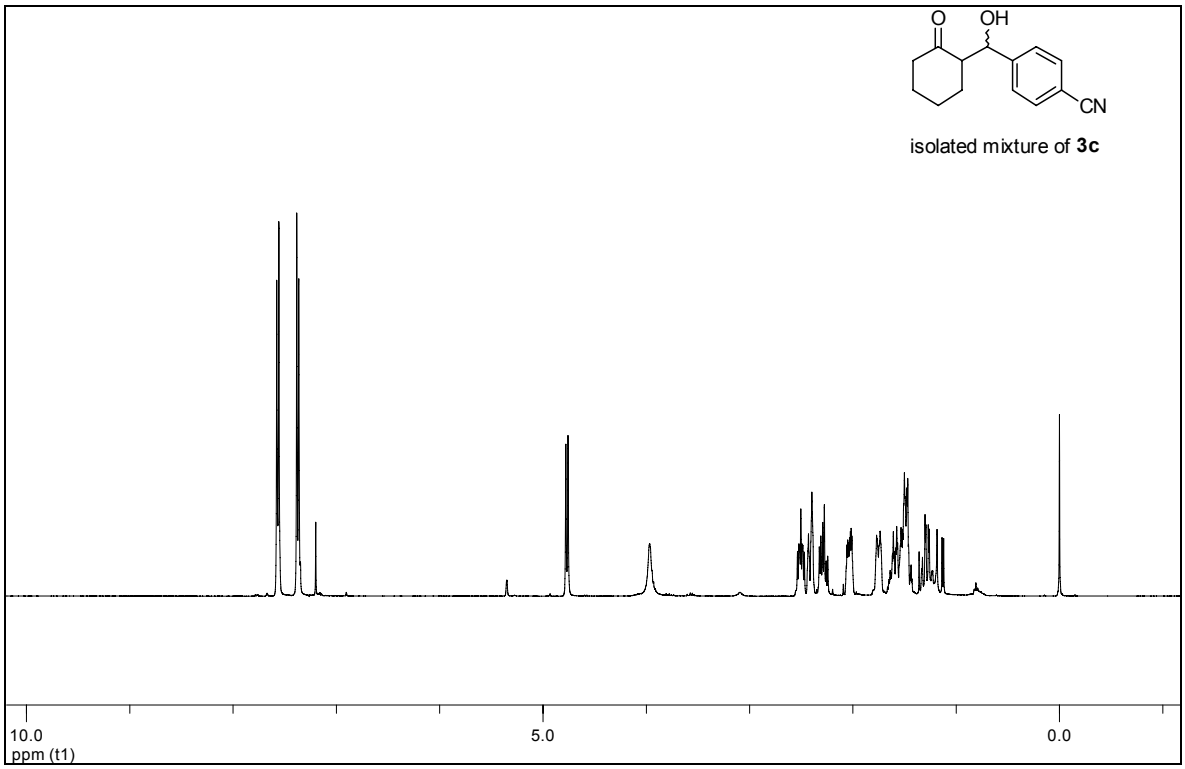
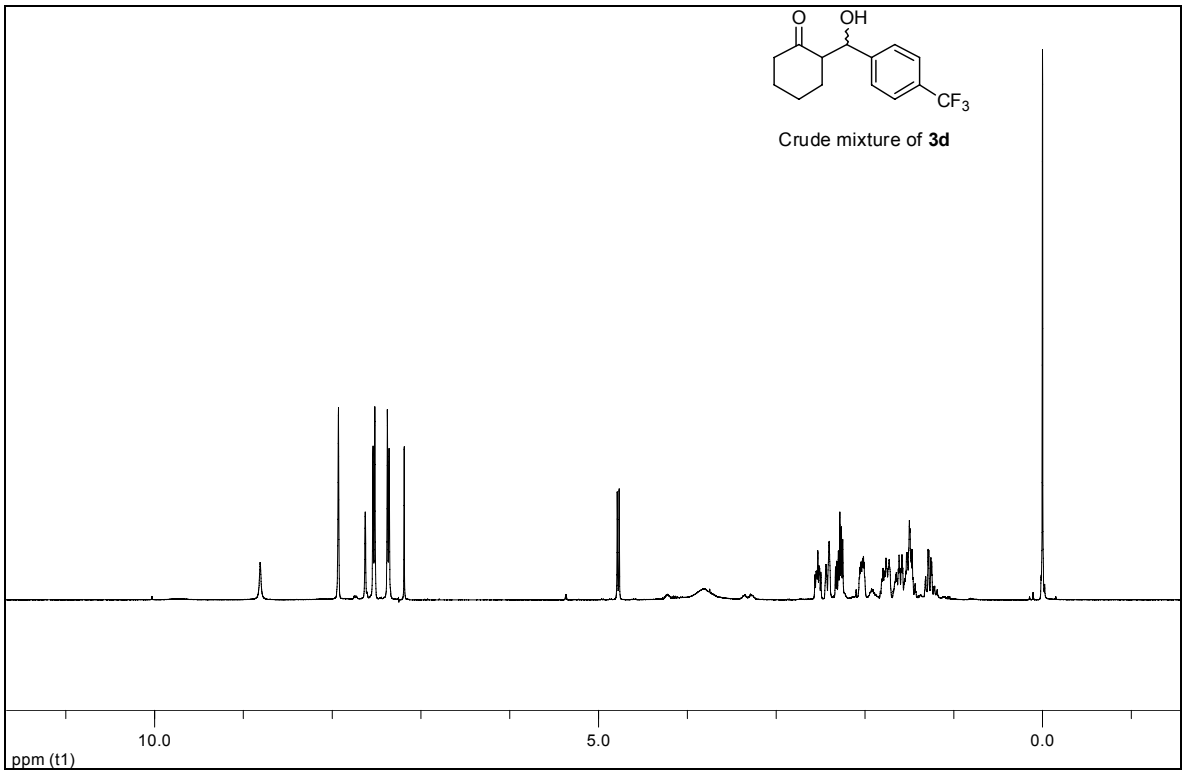
OH
CN
Crude mixture of 3c
10.0
5.0
0.0
ppm (t1)


O
OH
CN
isolated mixture of 3c
10.0
5.0
0.0
ppm (t1)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OH
CF3
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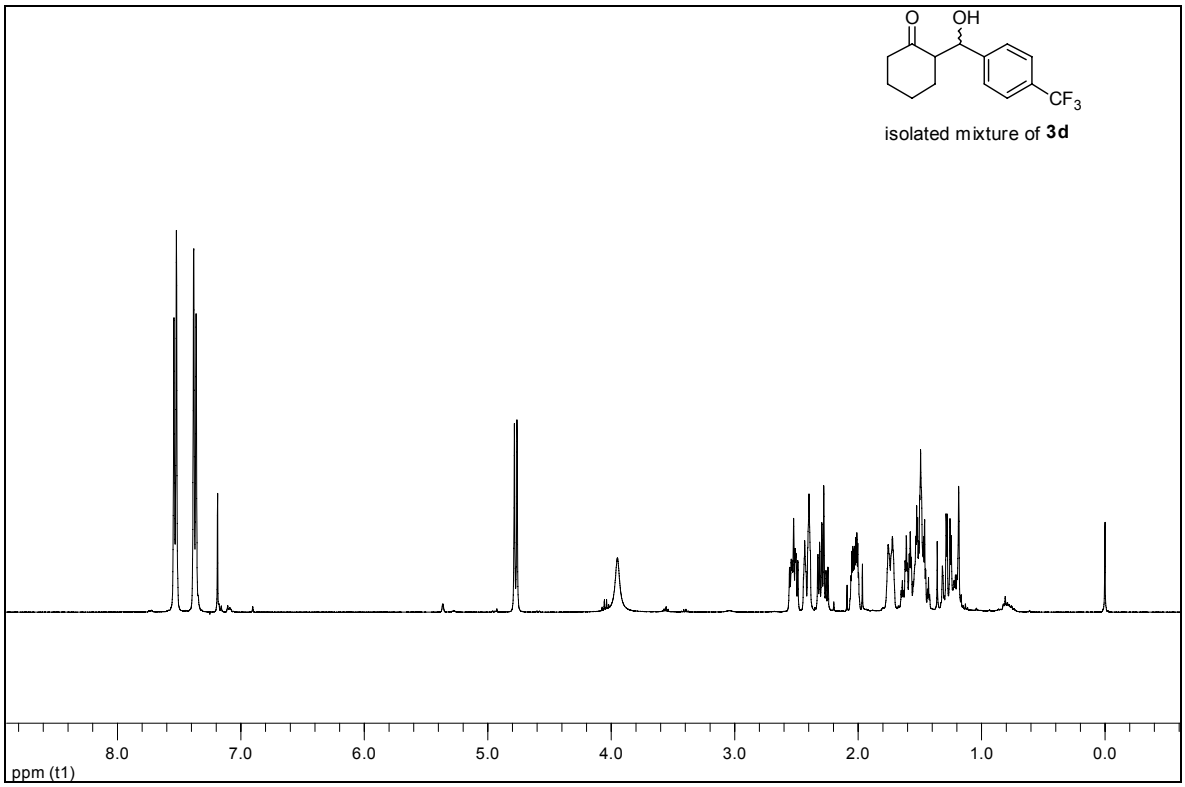
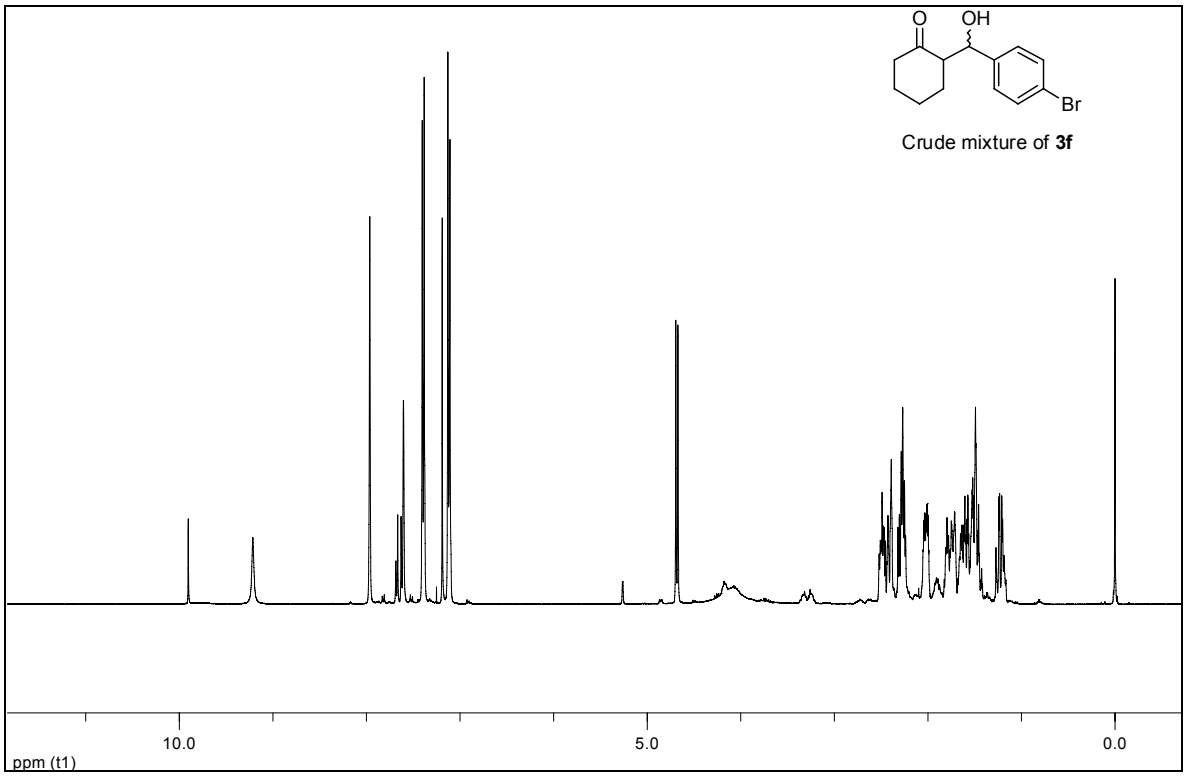
10.0
5.0
0.0
ppm (t1)


O
OH
CF3
isolated mixture of 3d
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)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OH
Br
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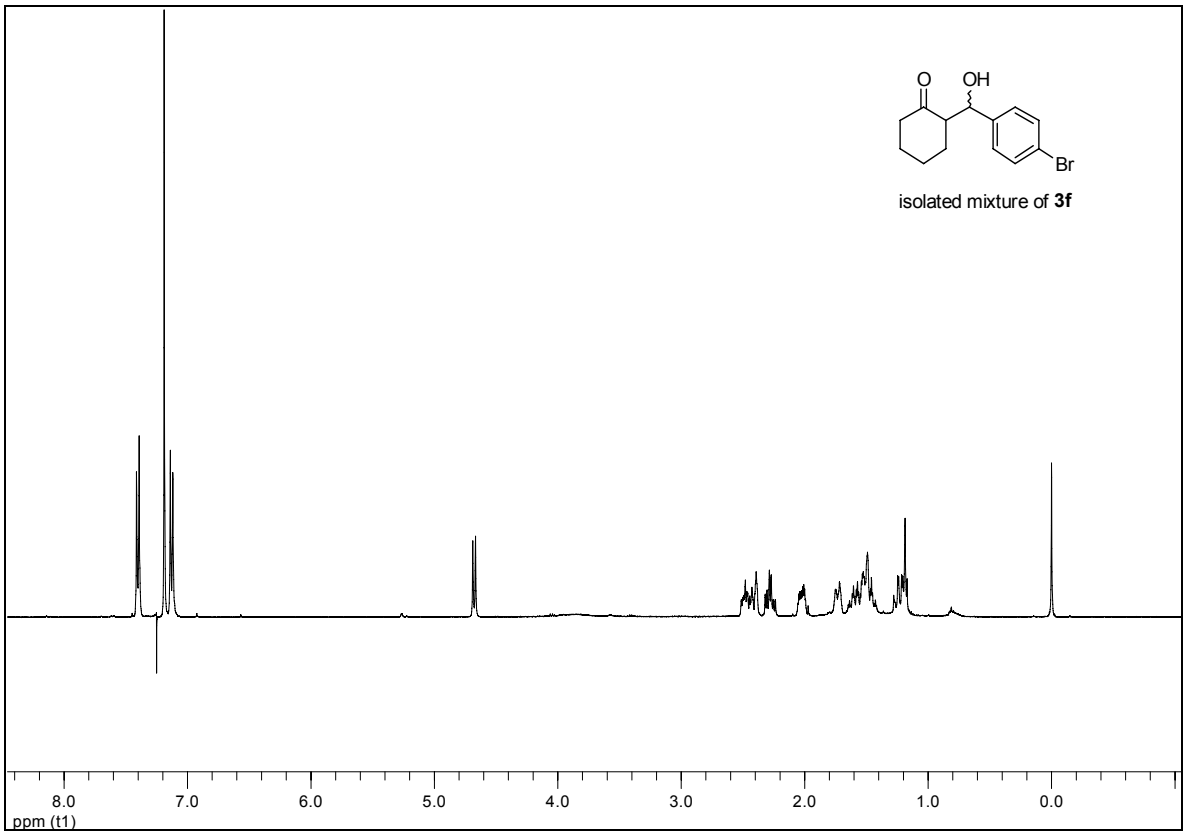
5.0
0.0
ppm (t1)


O
OH
Br
isolated mixture of 3f
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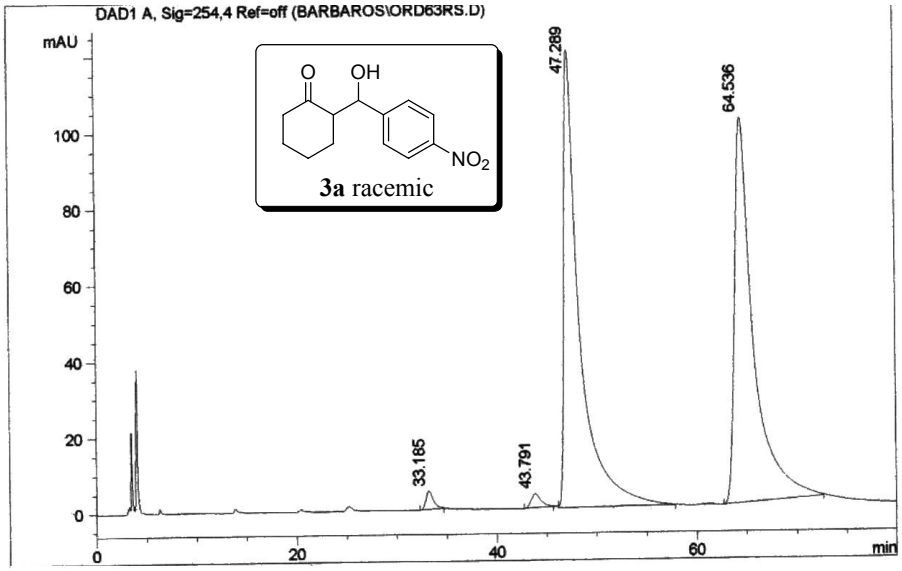
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)



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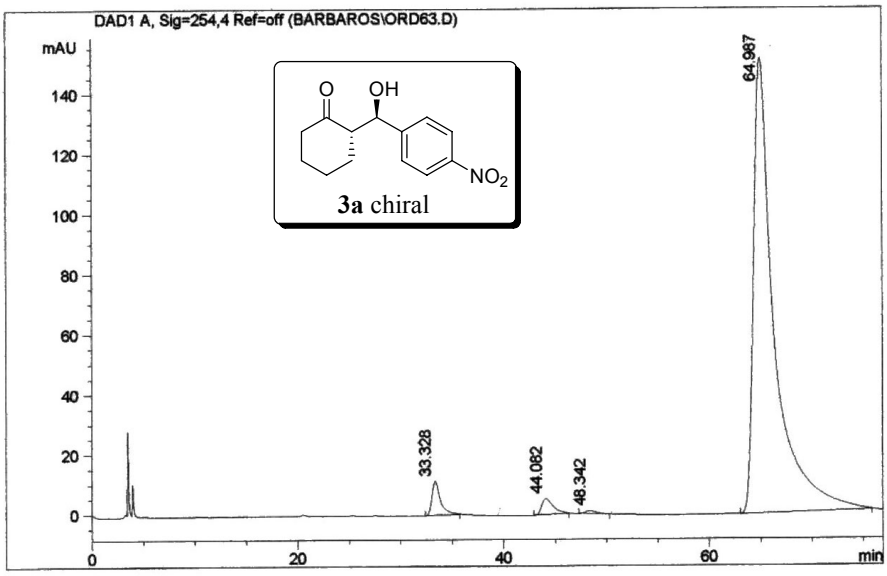
2	43.791	1.004	263.721	0.984	
3	47.289	1.809	13081.641	48.814	
4	64.536	1.869	13185.832	49.202	



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3	BB	48.342	0.869	80.054	0.356	
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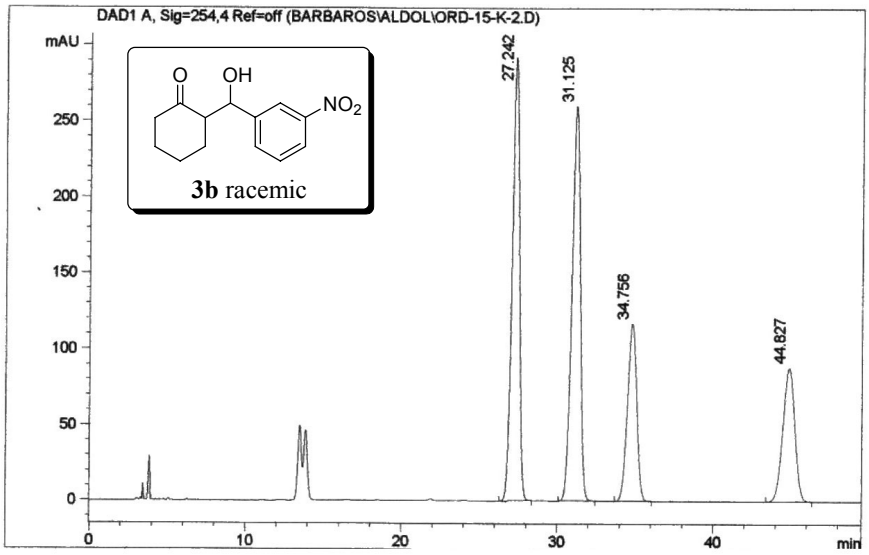

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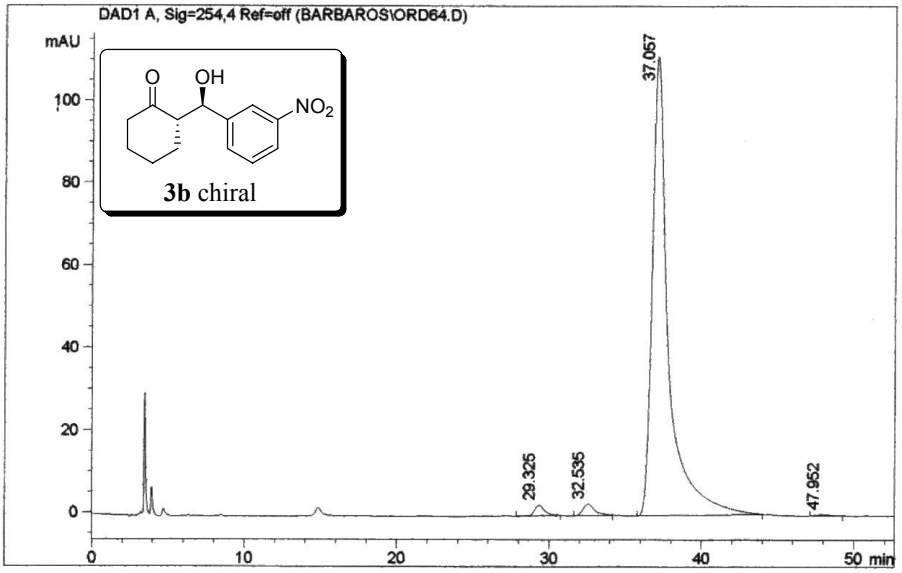
2	31.125	BB	0.590	9777.838	33.982	
3	34.756	BB	0.646	4832.918	16.796	
4	44.827	BB	0.835	4712.805	16.379	



Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	Type	RT [min]	Width [min]	Area	Area %
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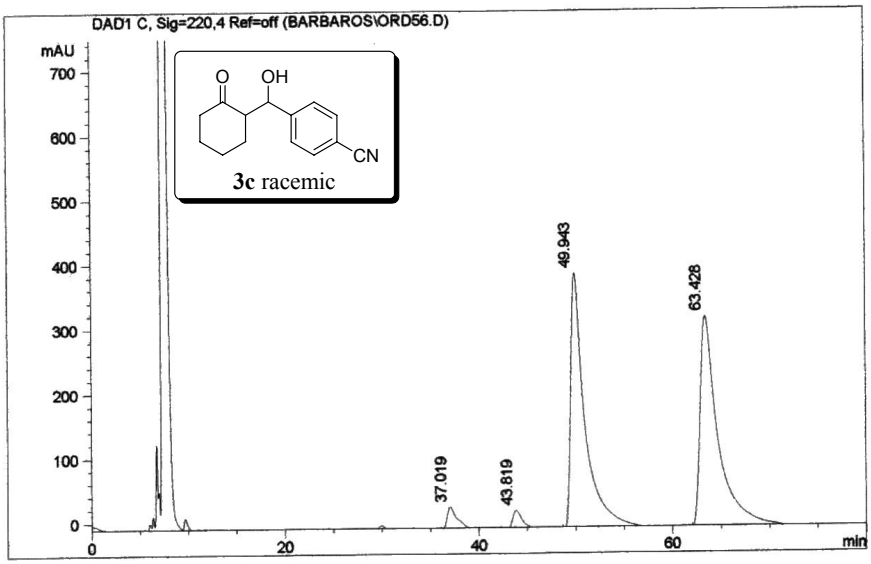
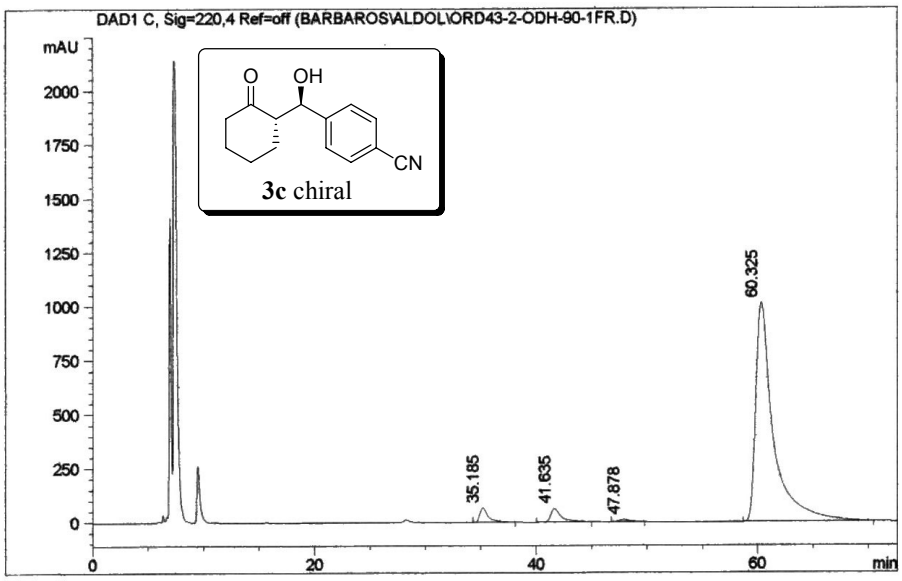
2	BB	32.535	0.769	160.480	1.862
3	BB	37.057	1.073	8297.462	96.284
4	BB	47.952	0.854	24.320	0.282



Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak #	RT [min]	Width [min]	Area	Area %
1	37.019	1.340	3110.373	3.393
2	43.819	1.237	2836.616	3.094
3	49.943	1.505	42695.516	46.570
4	63.428	2.178	43038.531	46.944



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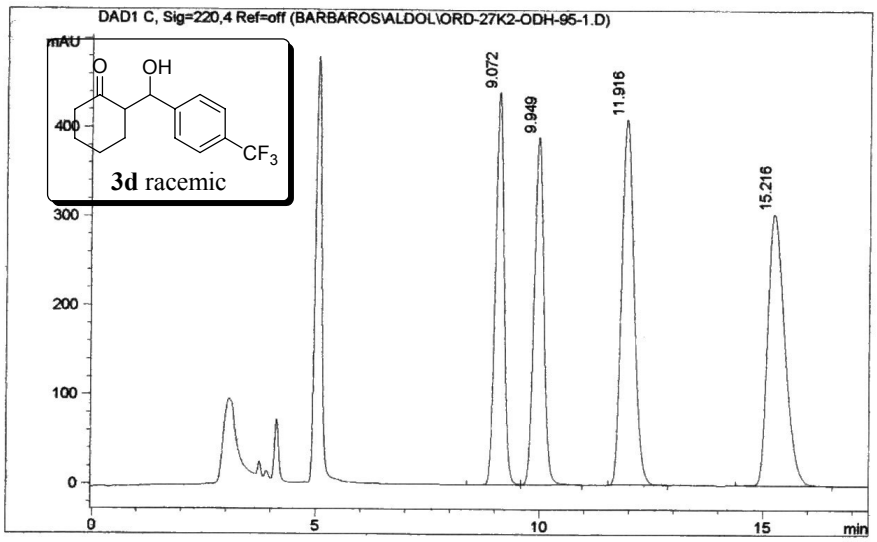

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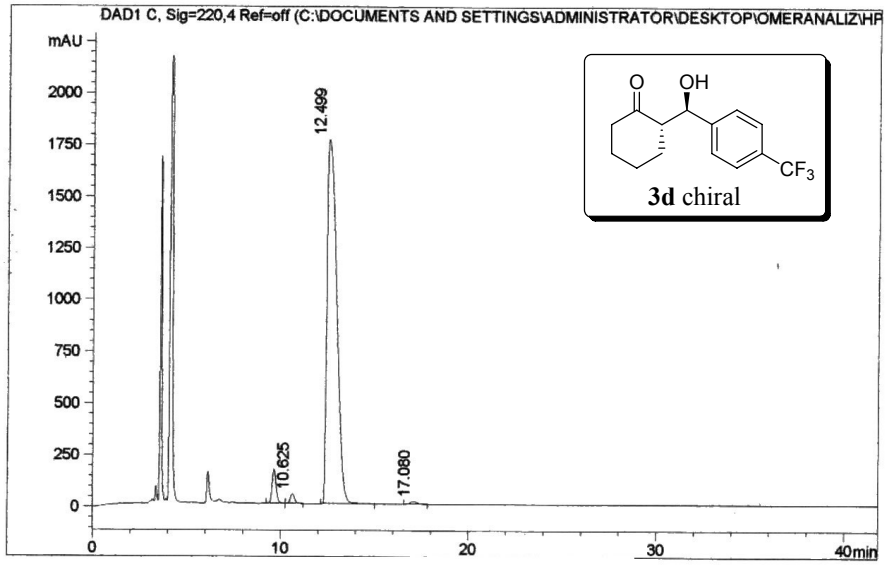
2	9.949	VB	0.236	5899.665	21.157
3	11.916	BB	0.302	7966.257	28.568
4	15.216	BB	0.410	8098.664	29.043



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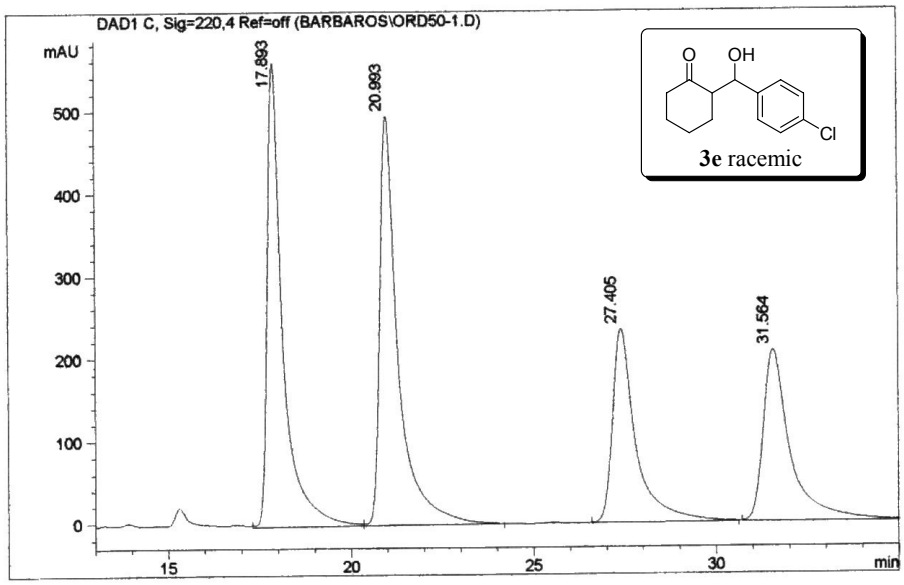
4	17.080	BB	0.425	385.224	0.577



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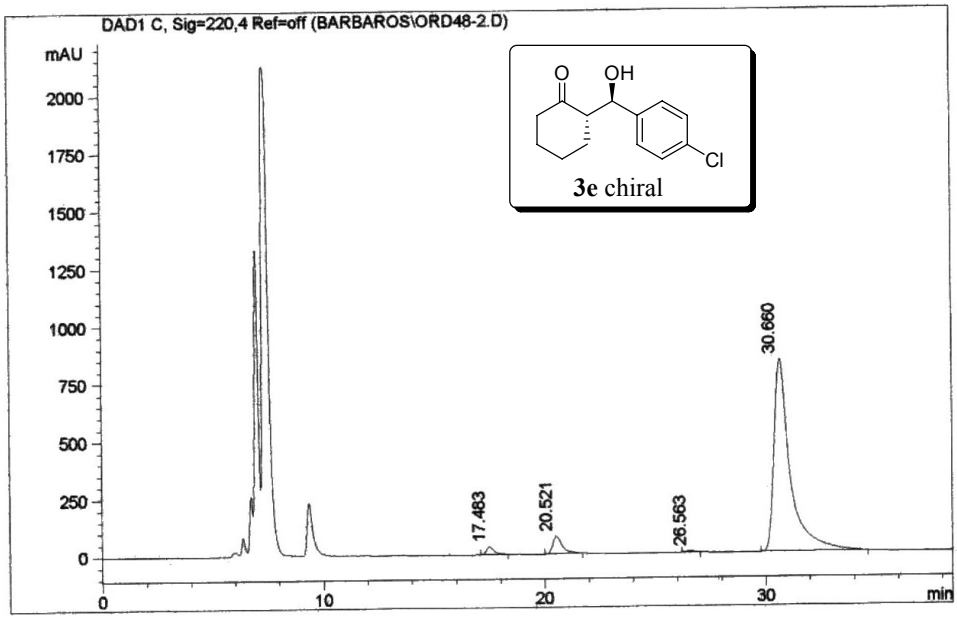
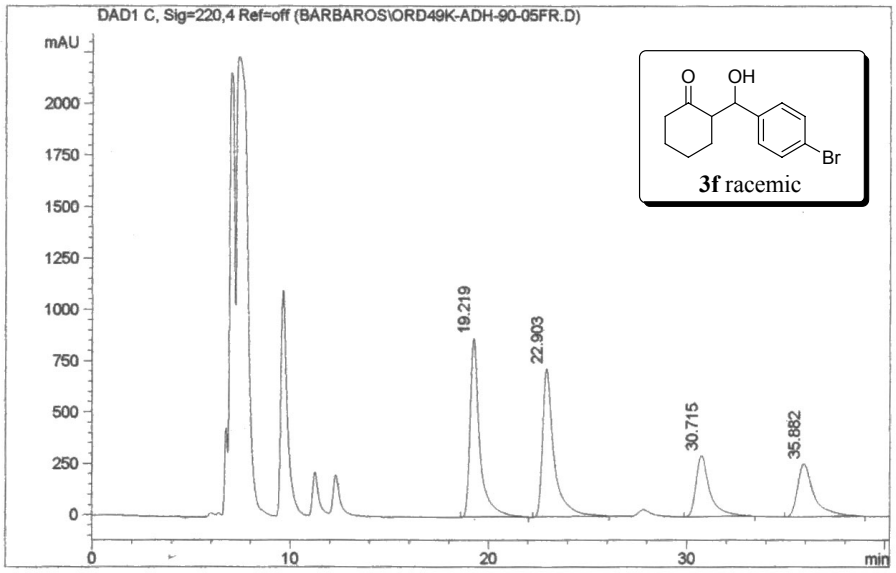


5	17.483	BB	0.369	862.576	1.869
6	20.521	BB	0.443	2328.896	5.045
7	26.563	MM	0.468	149.401	0.324
8	30.660	BB	0.740	42823.004	92.763



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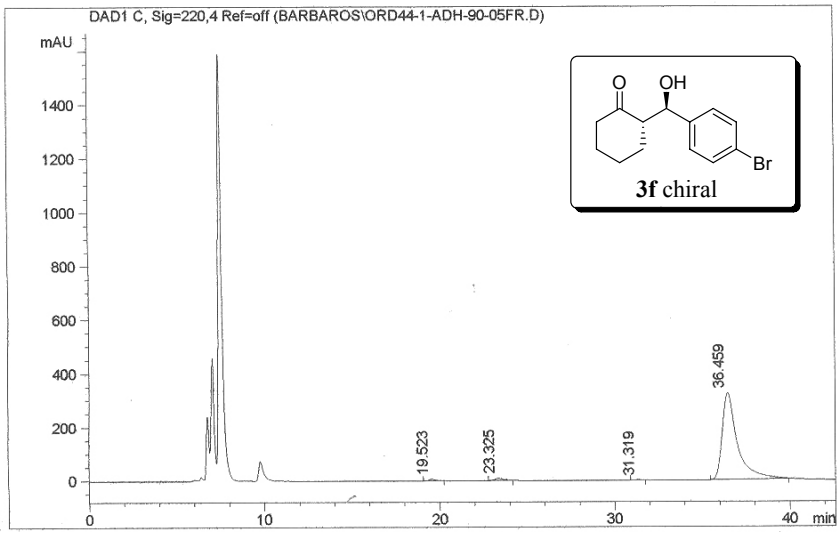
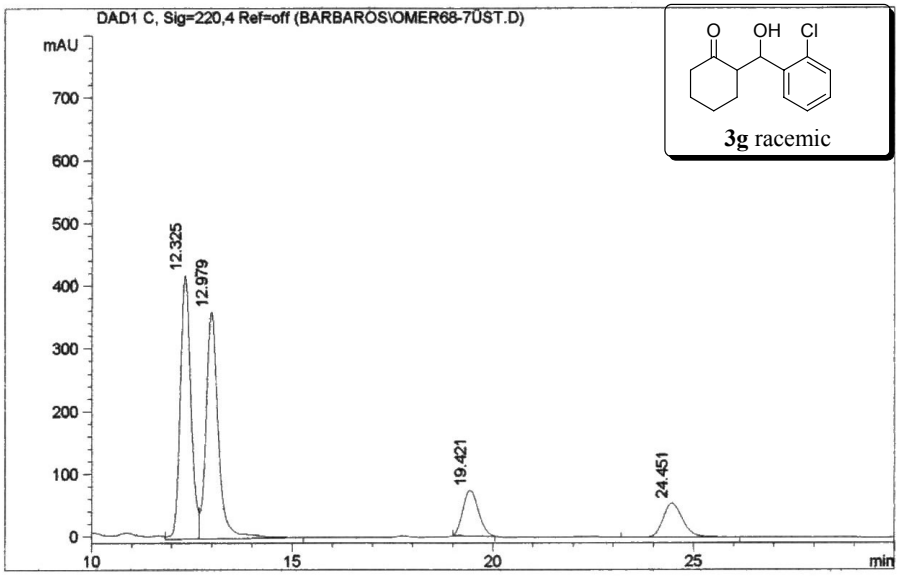
7	30.715	BB	0.727	15024.604	16.766	
8	35.882	BB	0.867	15398.444	17.183	

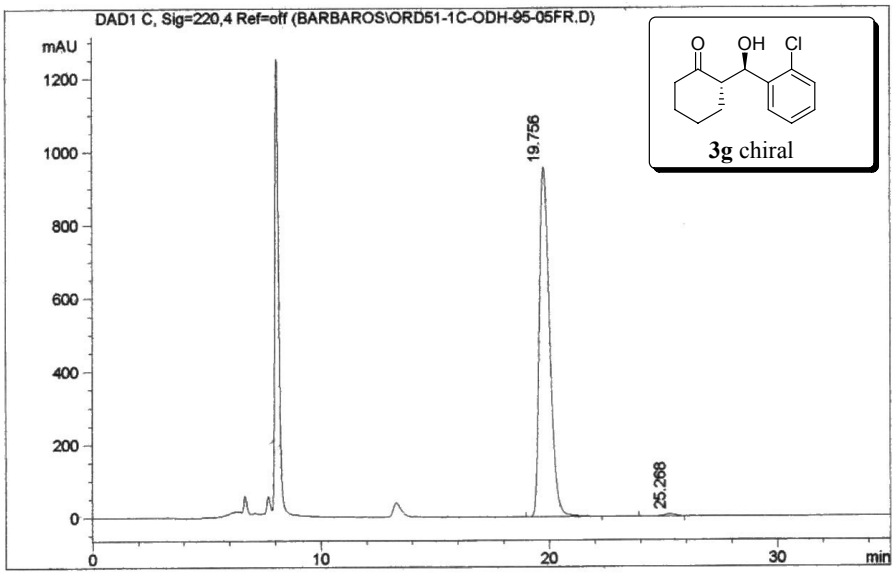


5	19.523	BB	0.407	186.792	0.922	
6	23.325	BB	0.495	331.351	1.636	
7	31.319	MM	0.503	53.499	0.264	
8	36.459	BB	0.885	19681.922	97.178	

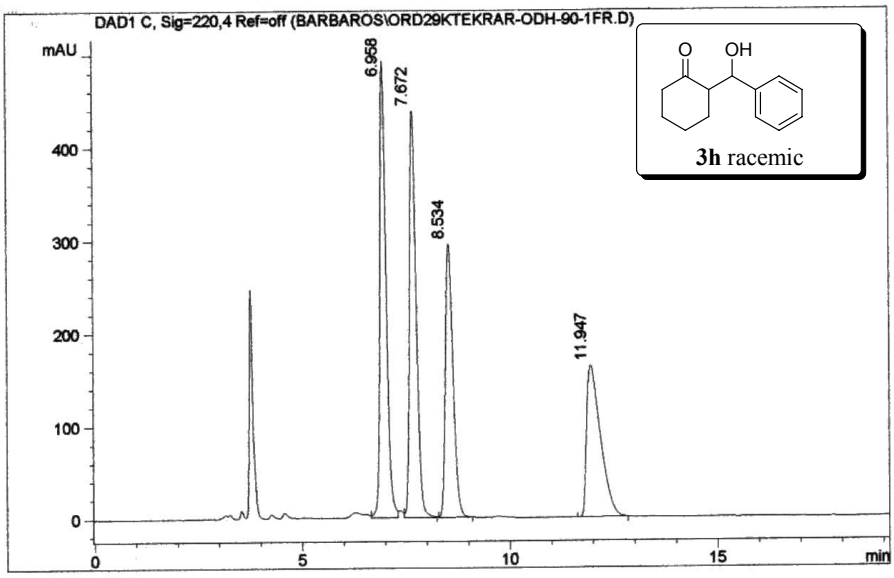


Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak #	RT [min]	Width [min]	Area	Area %
1	12.325	0.283	7764.859	40.028
2	12.979	0.322	7756.875	39.987
3	19.421	0.456	2014.495	10.385
4	24.451	0.527	1862.190	9.600

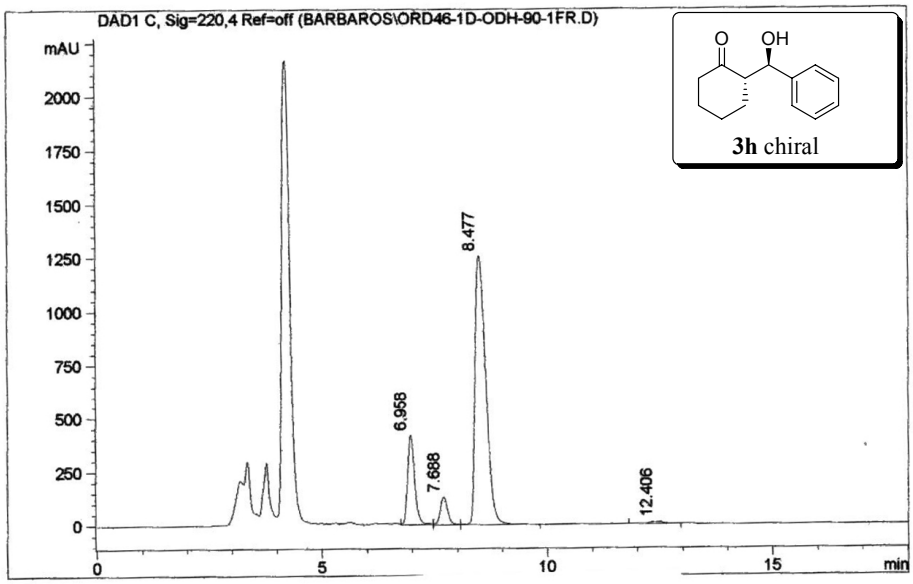


Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	19.756	BB	0.495	30105.145	99.228	
2	25.268	BV	0.533	234.336	0.772	



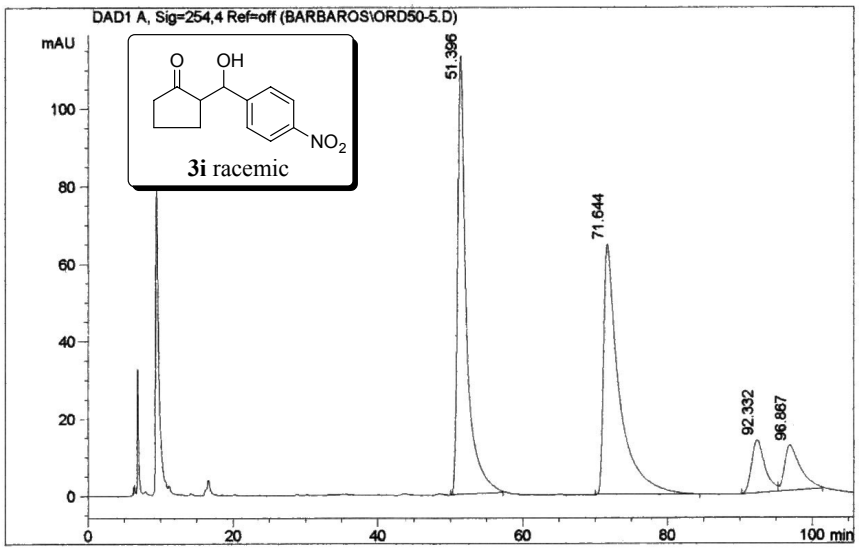
Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak #	RT [min]	Type	Width [min]	Area	Area %	Name
1	6.958	VV	0.159	5118.946	28.968	
2	7.672	VB	0.173	4922.461	27.857	
3	8.534	BB	0.200	3803.570	21.525	
4	11.947	BB	0.349	3825.760	21.650	



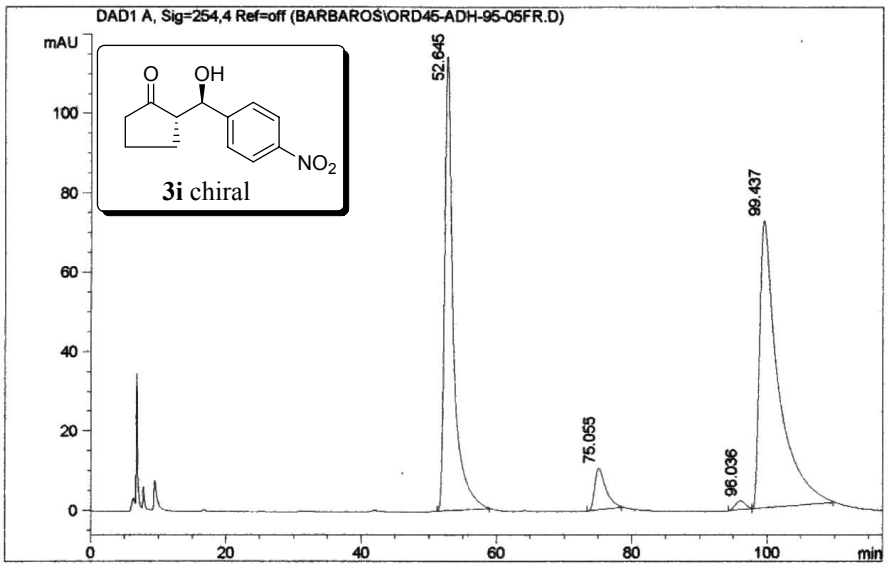
Signal 1: DAD1 C, Sig=220,4 Ref=off

Peak #	RT [min]	Type	Width [min]	Area	Area %
1	6.958	VV	0.169	4641.419	16.999
2	7.688	VV	0.180	1544.454	5.656
3	8.477	VV	0.262	20888.770	76.503
4	12.406	BB	0.316	229.775	0.842



Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RT [min]	Width [min]	Area	Area %
1	51.396	1.248	9799.221	42.353
2	71.644	2.495	9710.574	41.970
3	92.332	1.593	1790.325	7.738
4	96.867	2.080	1836.856	7.939



Signal 1: DAD1 A, Sig=254,4 Ref=off

Type	Peak #	RT [min]	Width [min]	Area	Area %
BB	1	52.645	1.306	10344.775	40.011
BB	2	75.055	1.651	1238.169	4.789
BV	3	96.036	1.332	256.218	0.991
VB	4	99.437	2.611	14015.356	54.209

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