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Nuclease p1: A new biocatalyst for direct asymmetric aldol reaction under solvent-free conditions

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（Supporting Information）

General method: ^{1}H NMR spectra were recorded on 300 MHz spectrometer. Chemical shifts are expressed in ppm with TMS as internal standard, and coupling constants are reported in Hz. Routine monitoring of reaction was performed by TLC using precoated Haiyang GF254 silica gel TLC plates. All the column chromatography separations were done by using silica gel (100-200 mesh) at increased pressure. Petroleum ether used was of boiling range 60-80 °C. The organic extracts were dried over anhydrous sodium sulfate. Evaporation of solvent was performed at reduced pressure. The enantiomeric excess (ee) of aldol products was determined by chiral HPLC analysis, performed using Chiralcel AD-H, OD-H, AS-H and OJ-H columns. Relative and absolute configurations of the products were determined by comparison with the known ^{1}H NMR and chiral HPLC analysis. Aldol adducts 3a,[1,2] 3b,[1] 3c,[1] 3d,[4,5] 3e,[5] 3f ,[1] 3g,[4] 3h,[1] 3i,[1] 3j,[1] 3k,[1] 3l,[1,3] 3m,[1] 3n[5] and 3o[3]are all known compounds.

Materials: Nuclease P1 from *Penicillium citrinum* (EC 3.1.30.1, 5 U/mg. The activity determination was according to the procedure described by Fujishima *et al.* [6]. The activity was measured in terms of the amount of acid-soluble nucleotides produced by RNA hydrolysis which is catalyzed by nuclease p1. One unit of enzyme activity was defined as the amount of enzyme that produced an increase in the optical density of 1.0 in 1 min at 260 nm.) was purchased from Guangxi Nanning Pangbo Biological Engineering Co. Ltd. (Nanning, China). Unless otherwise noted, all reagents were obtained from commercial suppliers and were used without further purification.

^{1}HNMR and HPLC spectra data of aldol products

***(2S, 1'R)*-2-(Hydroxy-(*p*-tolyl)methyl)cyclohexan-1-one 3a**[1,2]

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.17 (4H, m), 4.75 (1H, d, J = 8.7 Hz), 3.94 (1H, brs), 2.65-2.52 (1H, m), 2.49-2.48 (1H, m), 2.44-2.42 (1H, m), 2.33 (3H, s), 2.10-2.04 (1H, m), 1.79-1.73 (1H, m), 1.64-1.48 (3H, m), 1.34-1.22 (1H, m). Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (9:1 hexane:2-propanol), 25 °C, 220 nm, 0.5 ml/min; major enantiomer tr = 28.2 min, minor enantiomer tr = 30.1 min.

(2*S*, 1'*R*)-2-(Hydroxy(phenyl)methyl)cyclohexan-1-one 3b[1]

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25 (5H, brs), 4.72 (1H, d, J = 7.5 Hz), 3.90 (1H, brs), 2.53-2.51 (1H, m), 2.37-2.25 (2H, m), 2.10-1.97 (1H, m), 1.79-1.75 (1H, m), 1.67-1.57 (3H, m), 1.34-1.18 (1H, m). Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (9:1 hexane:2-propanol), 25 °C, 220 nm, 0.5 ml/min; major enantiomer tr = 17.7 min, minor enantiomer tr = 22.5 min.

(2*S*, 1'*R*)-2-(Hydroxy-(*p*-chlorophenyl)methyl)cyclohexan-1-one 3c[1]

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28 (4H, m), 4.76 (1H, d, J = 8.5 Hz), 4.01 (1H, d, J = 2.2 Hz), 2.60-2.45 (2H, m), 2.42-2.31 (1H, m), 2.12-2.06 (1H, m), 1.82-1.77 (1H, m), 1.73-1.52 (3H, m), 1.35-1.21 (1H, m). Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (9:1 hexane:2-propanol), 25 °C, 220 nm, 1.0 ml/min; major enantiomer tr = 16.1 min, minor enantiomer tr = 14.1 min.

(2*S*, 1'*R*)-2-(Hydroxy-(*o*-chlorophenyl)methyl)cyclohexan-1-one 3d[4,5]

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 (1H, d, J = 7.2 Hz), 7.34-7.18 (3H, m), 5.35 (1H, d, J = 6.7 Hz), 4.06 (1H, brs), 2.84-2.64 (1H, m), 2.49-2.29 (2H, m), 2.10-2.07 (1H, m), 1.83-1.74 (1H, m), 1.70-1.55 (4H, m). Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (95:5 hexane:2-propanol), 25 °C, 220 nm, 0.8 ml/min; major enantiomer tr = 18.2 min, minor enantiomer tr = 21.2 min.

(2*S*, 1'*R*)-2-(Hydroxy-(*m*-chlorophenyl)methyl)cyclohexan-1-one 3e[5]

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (1H, s), 7.26 (2H, d, J = 6.0 Hz), 7.19 (1H, d, J = 4.4 Hz), 4.76 (1H, d, J = 8.4 Hz), 4.02 (1H, brs), 2.61-2.51 (1H, m), 2.46-2.41 (1H, m), 2.39-2.30 (1H, m), 2.12-2.08 (1H, m), 1.88-1.79 (1H, m), 1.72-1.69 (1H, m), 1.64-1.53 (2H, m), 1.37-1.25 (1H, m). Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (95:5 hexane:2-propanol), 25 °C, 220 nm, 1.0 ml/min; major enantiomer tr = 11.1 min, minor enantiomer tr = 13.5 min.

(2*S*, 1'*R*)-2-(Hydroxy-(*2,4*-dichlorophenyl)methyl)cyclohexan-1-one 3f[1]

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50 (1H, d, J = 8.4 Hz), 7.35 (1H, s), 7.29 (1H, d, J = 8.5 Hz), 5.29 (1H, dd, J = 7.0, 2.1 Hz), 4.06 (1H, d, J = 3.8 Hz), 2.67-2.58 (1H, m), 2.48-2.27 (2H, m), 2.12-2.08 (1H, m), 1.85-1.83 (1H, m), 1.72-1.52 (4H, m). Enantiomeric excess was determined by HPLC with a Chiralpak AS –H column (9:1 hexane:2-propanol), 25 °C, 220 nm, 0.5 ml/min; major enantiomer tr = 20.1 min, minor enantiomer tr = 16.9 min.

(2*S*, 1'*R*)-2-(Hydroxy-(*2,6*-dichlorophenyl)methyl)cyclohexan-1-one 3g[4]

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31 (2H, d, J = 8.1 Hz), 7.15 (1H, t, J = 8.0 Hz), 5.84 (1H, d, J = 9.7 Hz),

3.70 (1H, brs), 3.54-3.45 (1H, m), 2.54-2.26 (2H, m), 2.12-2.05 (1H, m), 1.84-1.24 (5H, m). Enantiomeric excess was determined by HPLC with a Chiralpak OJ-H column (95:5 hexane:2-propanol), 25 °C, 220 nm, 1.0 ml/min; major enantiomer tr = 11.1 min, minor enantiomer tr = 9.7 min.

(2*S*, 1'*R*)-2-(Hydroxy-(*p*-bromophenyl)methyl)cyclohexan-1-one 3h[1]

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47 (2H, d, J = 7.9 Hz), 7.20 (2H, d, J = 7.7 Hz), 4.75 (1H, d, J = 8.5 Hz), 3.99 (1H, brs), 2.58-2.32 (3H, m), 2.11-2.07 (1H, m), 1.87-1.52 (4H, m), 1.35-1.23 (1H, m). Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (9:1 hexane:2-propanol), 25 °C, 220 nm, 1.0 ml/min; major enantiomer tr = 17.5 min, minor enantiomer tr = 15.1 min.

(2*S*, 1'*R*)-2-(Hydroxy-(*p*-cyanophenyl)methyl)cyclohexan-1-one 3i[1]

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (2H, d, J = 7.8 Hz), 7.45 (2H, d, J = 7.7 Hz), 4.84 (1H, d, J = 7.0 Hz), 4.07 (1H, d, J = 2.1 Hz), 2.62-2.47 (2H, m), 2.42-2.31 (1H, m), 2.14-2.09 (1H, m), 1.88-1.81 (1H, m), 1.74-1.54 (3H, m), 1.45-1.29 (1H, m). Enantiomeric excess was determined by HPLC with a Chiralpak AD –H column (9:1 hexane:2-propanol), 25 °C, 254 nm, 0.5 ml/min; major enantiomer tr = 68.2 min, minor enantiomer tr = 53.9 min.

(2S,1'R)-2-(Hydroxy-(*p*-(trifluoromethyl)phenyl)methyl)cyclohexan-1-one 3j[1]

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61 (2H, d, J = 7.7 Hz), 7.45 (2H, d, J = 7.7 Hz), 4.85 (1H, d, J = 8.3 Hz), 4.05 (1H, brs), 2.64-2.55 (1H, m), 2.52-2.47 (1H, m), 2.42-2.31 (1H, m), 2.13-2.09 (1H, m), 1.84-1.80 (1H, m), 1.69-1.54 (3H, m), 1.40-1.26 (1H, m). Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (9:1 hexane:2-propanol), 25 °C, 254 nm, 1.0 ml/min; major enantiomer tr = 25.9 min, minor enantiomer tr = 21.3 min.

(2*S*, 1'*R*)-2-(Hydroxy-(*o*-nitrophenyl)methyl)cyclohexan-1-one 3k[1]

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85 (1H, d, J = 8.3 Hz), 7.77 (1H, d, J = 7.9 Hz), 7.64 (1H, t, J = 7.4 Hz), 7.43 (1H, t, J = 7.7 Hz), 5.45 (1H, d, J = 7.1 Hz), 4.12 (1H, d, J = 6.9 Hz), 2.80-2.72 (1H, m), 2.48-2.29 (2H, m), 2.13-2.03 (1H, m), 1.87-1.56 (5H, m). Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (95:5 hexane:2-propanol), 25 °C, 254 nm, 0.5 ml/min; major enantiomer tr = 80.0 min, minor enantiomer tr = 87.2 min.

(2*S*, 1'*R*)-2-(Hydroxy-(*m*-nitrophenyl)methyl)cyclohexan-1-one 3l[1,3]

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.21 (1H, s), 8.17 (1H, d, J = 8.3 Hz), 7.68 (1H, d, J = 7.5 Hz), 7.53 (1H, t, J = 8.1 Hz), 4.90 (1H, d, J = 8.3 Hz), 4.13 (1H, brs), 2.67-2.59 (1H, m), 2.53-2.49 (1H, m), 2.43-2.32 (1H, m), 2.17-2.10 (1H, m), 1.85-1.82 (1H, m), 1.73-1.55 (3H, m), 1.45-1.32 (1H, m). Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (95:5 hexane:2-propanol), 25 °C, 254 nm, 0.5 ml/min; major enantiomer tr = 102.8 min, minor enantiomer tr = 100.2 min.

(2*S*, 1'*R*)-2-(Hydroxy-(*p*-nitrophenyl)methyl)cyclopentan-1-one 3m[1]

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.22 (2H, d, J = 8.1 Hz), 7.54 (2H, d, J = 8.0 Hz), 4.86 (1H, d, J = 9.1 Hz), 4.77 (1H, brs), 2.52-2.16 (3H, m), 2.10-1.94 (1H, m), 1.84-1.69 (2H, m), 1.63-1.48 (1H, m). Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (95:5 hexane:2-propanol), 25 °C, 254 nm, 0.5 ml/min; (anti) major enantiomer tr = 100.4 min, minor enantiomer tr = 97.3 min; (syn) major enantiomer tr = 53.9 min, minor enantiomer tr = 74.2 min.

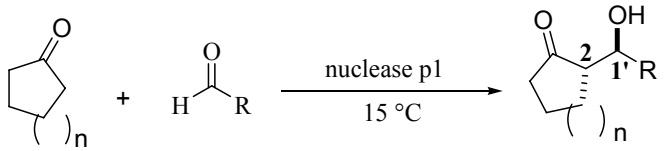
(2*S*, 1'*R*)-2-(Hydroxy-(*p*-cyanophenyl)methyl)cyclopentan-1-one 3n [5]

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64 (2H, d, J = 8.1 Hz), 7.47 (2H, d, J = 8.0 Hz), 4.80 (1H, d, J = 8.9 Hz), 4.74 (1H, s), 2.50-2.39 (1H, m), 2.35-2.12 (2H, m), 2.08-1.91 (2H, m), 1.74-1.68 (2H, m). Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (9:1 hexane:2-propanol), 25 °C, 220 nm, 1.0 ml/min; (anti) major enantiomer tr = 40.8 min, minor enantiomer tr = 46.3 min; (syn) major enantiomer tr = 13.7 min, minor enantiomer tr = 17.5 min.

(2*S*, 1'*R*)-2-(Hydroxy-(*p*-nitrophenyl)methyl)cycloheptan-1-one 3o[3]

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.21 (2H, d, J = 8.3 Hz), 7.53 (2H, d, J = 8.3 Hz), 4.93 (1H, s), 3.71 (1H, brs), 3.01-2.85 (1H, m), 2.67-2.42 (2H, m), 1.89-1.60 (4H, m), 1.50-1.22 (4H, m). Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (9:1 hexane:2-propanol), 25 °C, 254 nm, 0.5 ml/min; major enantiomer tr = 102.2 min, minor enantiomer tr = 43.2 min.

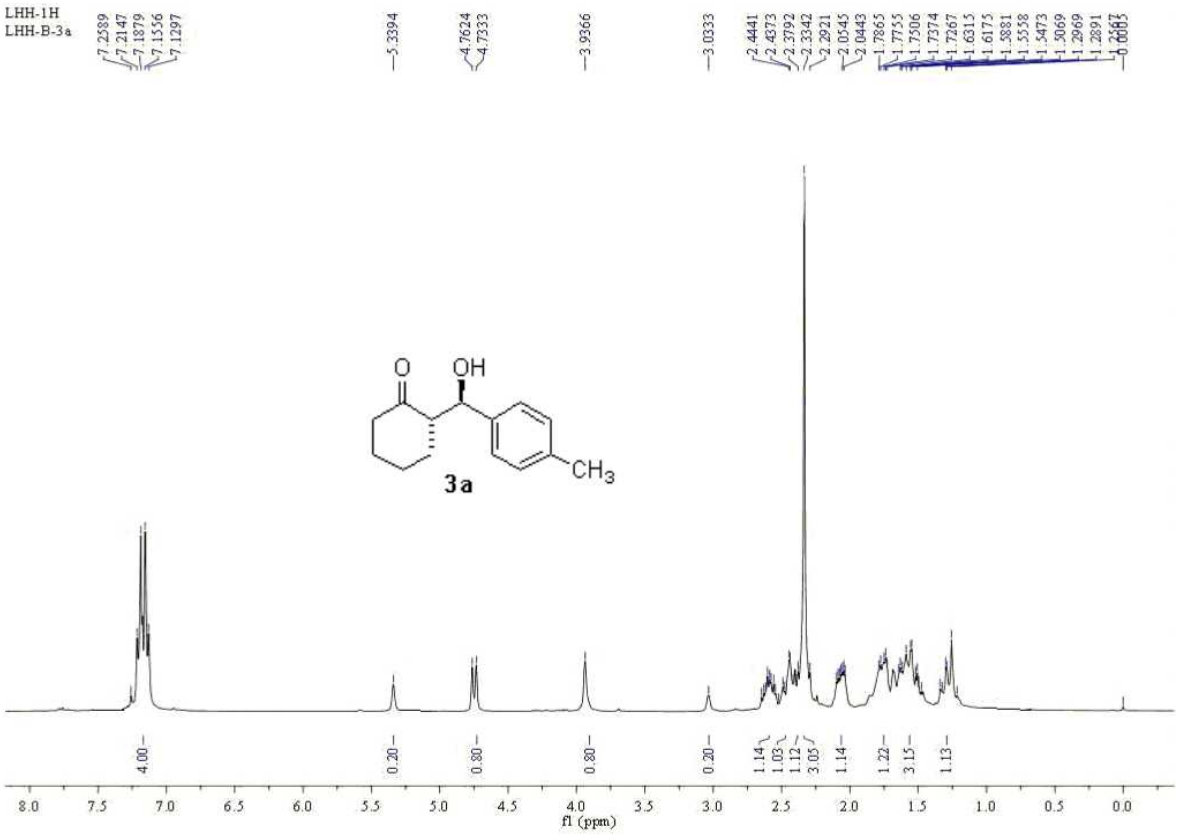
List of the obvious difference between syn-3 and anti-3 on ^{1}H NMR[3]

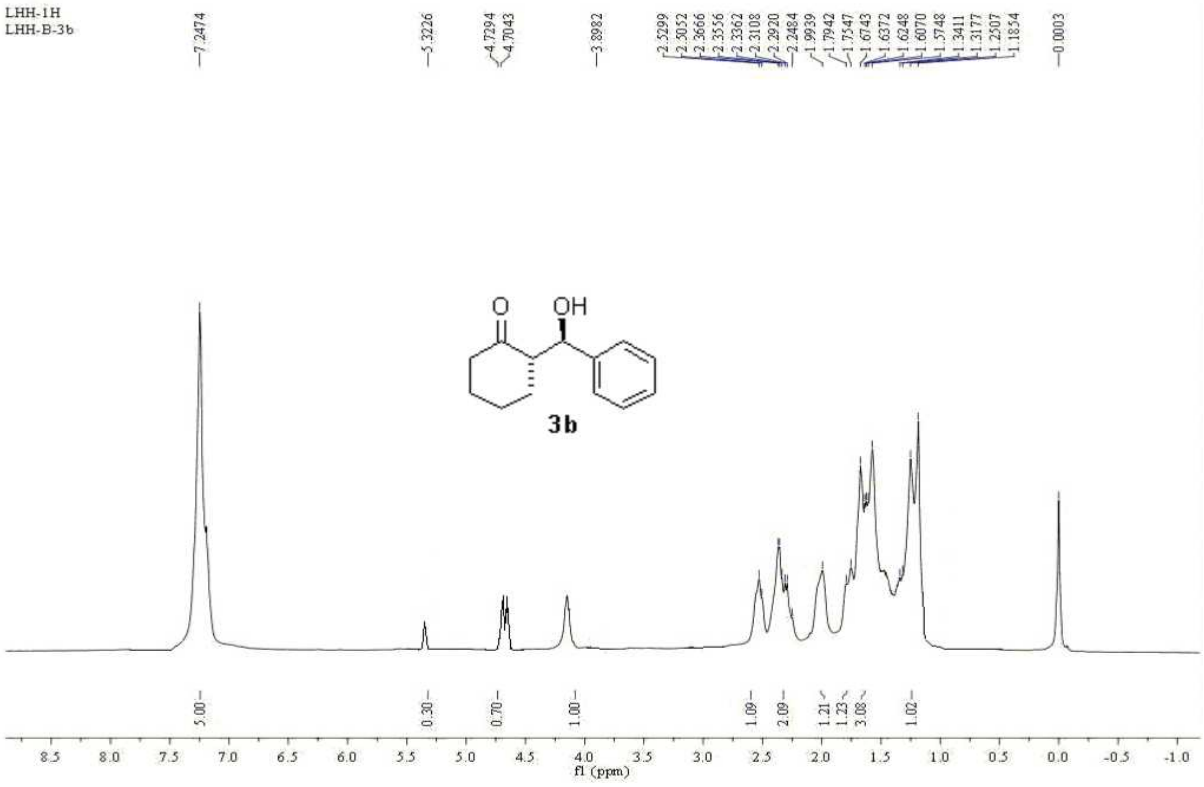


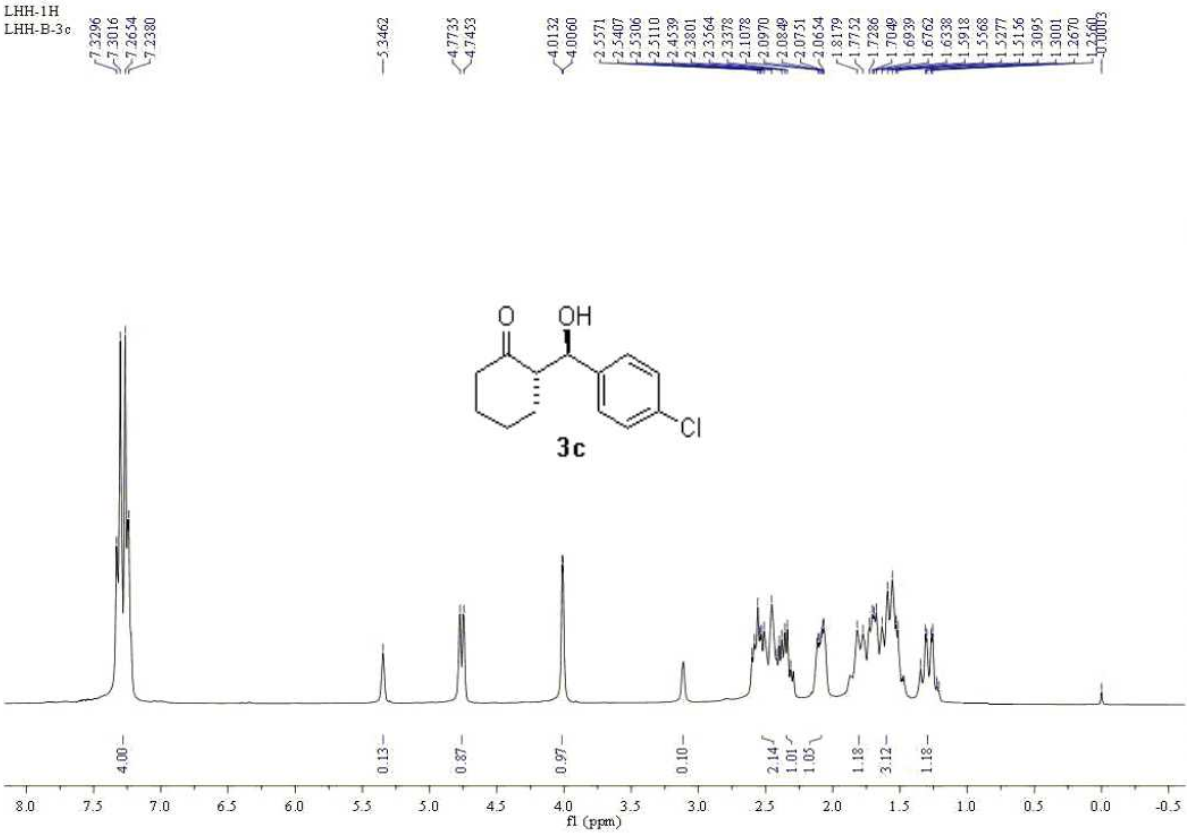
1 **2** **3**

Entry	R_1	n	Product	^{1}HNMR (-C<u>H</u>OH) [ppm]	
				syn	**anti**
1	4-Me-C_6H_4-	2	**3a**	5.34 (brs)	4.75 (d, J = 8.7 Hz)
2	C_6H_4-	2	**3b**	5.32 (brs)	4.72 (d, J = 7.5 Hz)
3	4-Cl-C_6H_4-	2	**3c**	5.35 (brs)	4.76 (d, J = 8.5 Hz)
4	2-Cl-C_6H_4-	2	**3d**	5.48 (brs)	4.90 (dd, J = 8.5, 2.8 Hz)
5	3-Cl-C_6H_4-	2	**3e**	5.36 (brs)	4.76 (d, J = 8.4 Hz)
6	2,4-Cl_2-C_6H_3-	2	**3f**	5.65 (brs)	5.29 (dd, J = 7.0, 2.1 Hz)
7	2,6-Cl_2-C_6H_3-	2	**3g**	6.20 (brs)	5.84 (d, J = 9.7 Hz)
8	4-Br-C_6H_4-	2	**3h**	5.34 (brs)	4.75 (d, J = 8.5 Hz)
9	4-CN-C_6H_4-	2	**3i**	5.43 (brs)	4.84 (d, J = 7.0 Hz)
10	4-CF_3-C_6H_4-	2	**3j**	5.45 (brs)	4.85 (d, J = 8.3 Hz)
11	2-NO_2-C_6H_4-	2	**3k**	5.96 (brs)	5.45 (d, J = 7.1 Hz)
12	3-NO_2-C_6H_4-	2	**3l**	5.48 (brs)	4.90 (d, J = 8.3 Hz)
13	4-NO_2-C_6H_4-	1	**3m**	5.42 (brs)	4.86 (d, J = 9.1 Hz)
14	4-CN-C_6H_4-	1	**3n**	5.36 (brs)	4.80 (d, J = 8.9 Hz)
15	4-NO_2-C_6H_4-	3	**3o**	5.31 (brs)	4.93 (s)

[1]HNMR spectra for aldol products 3a-3o



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Cl
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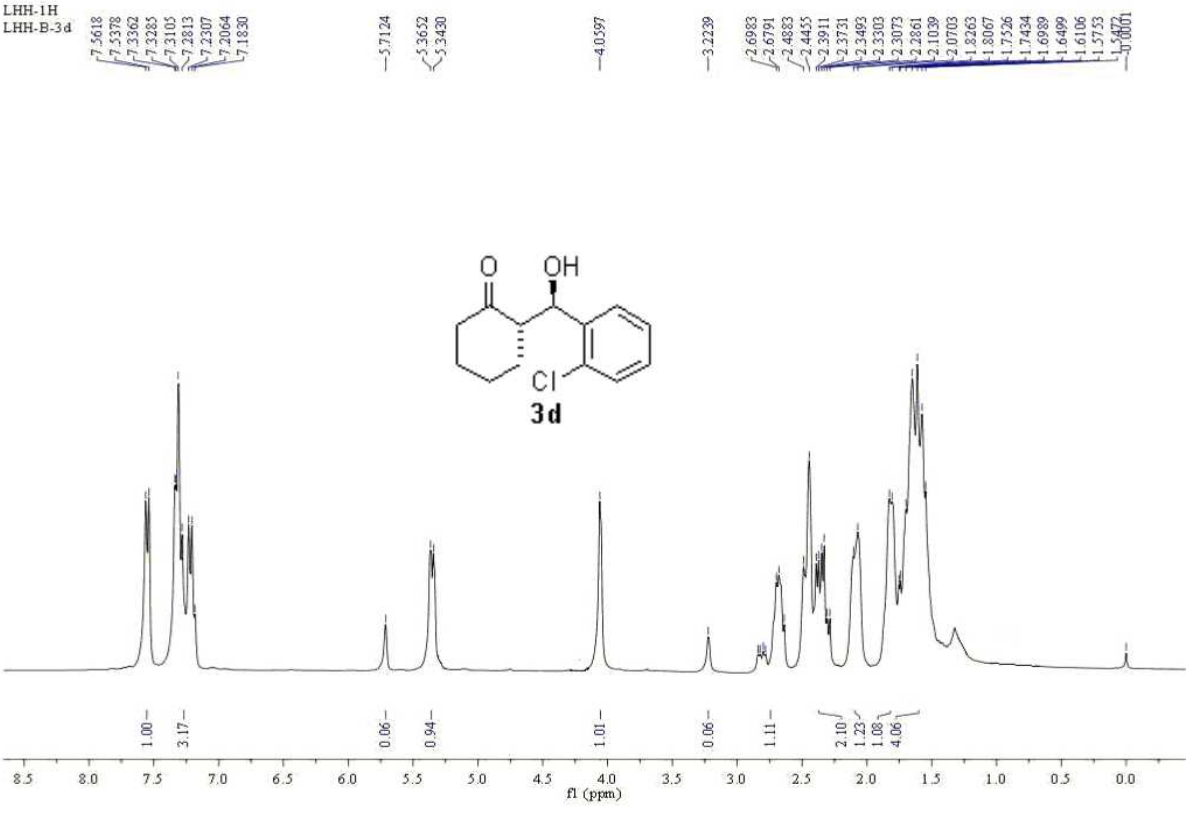
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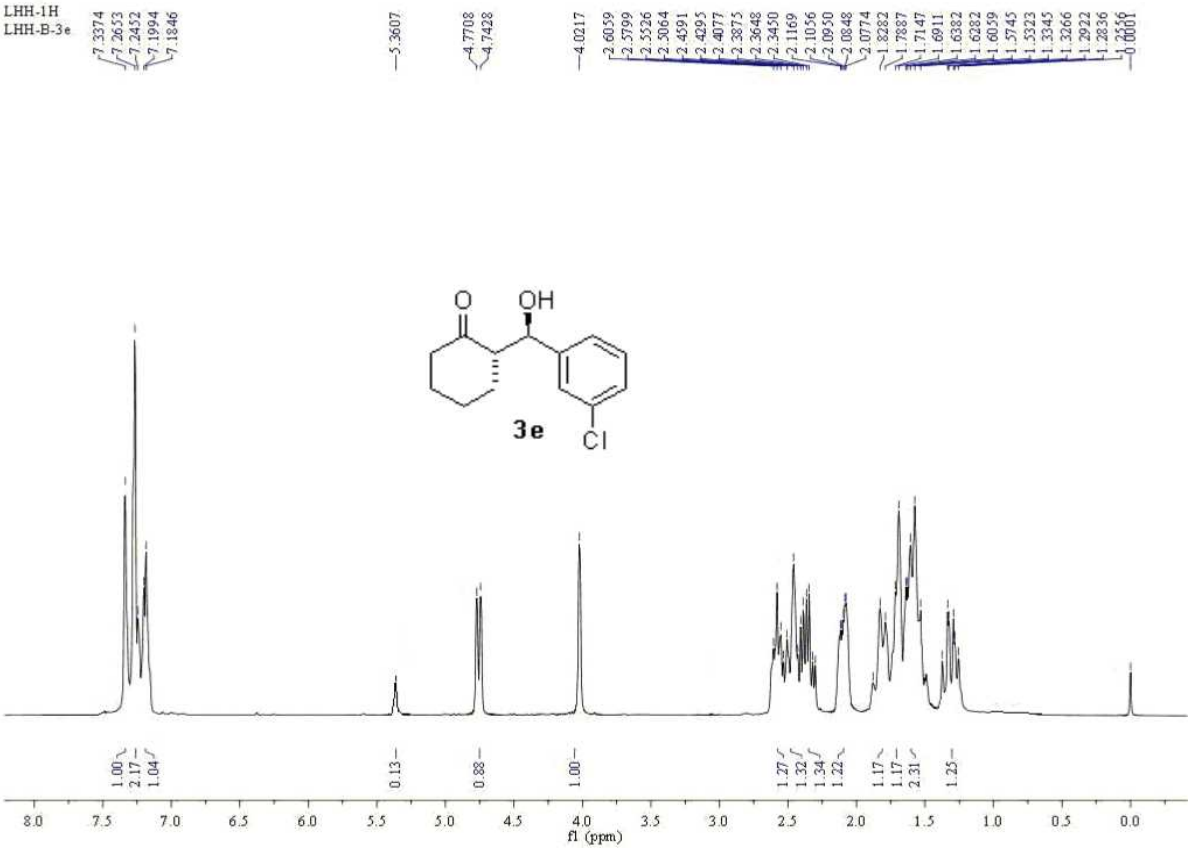
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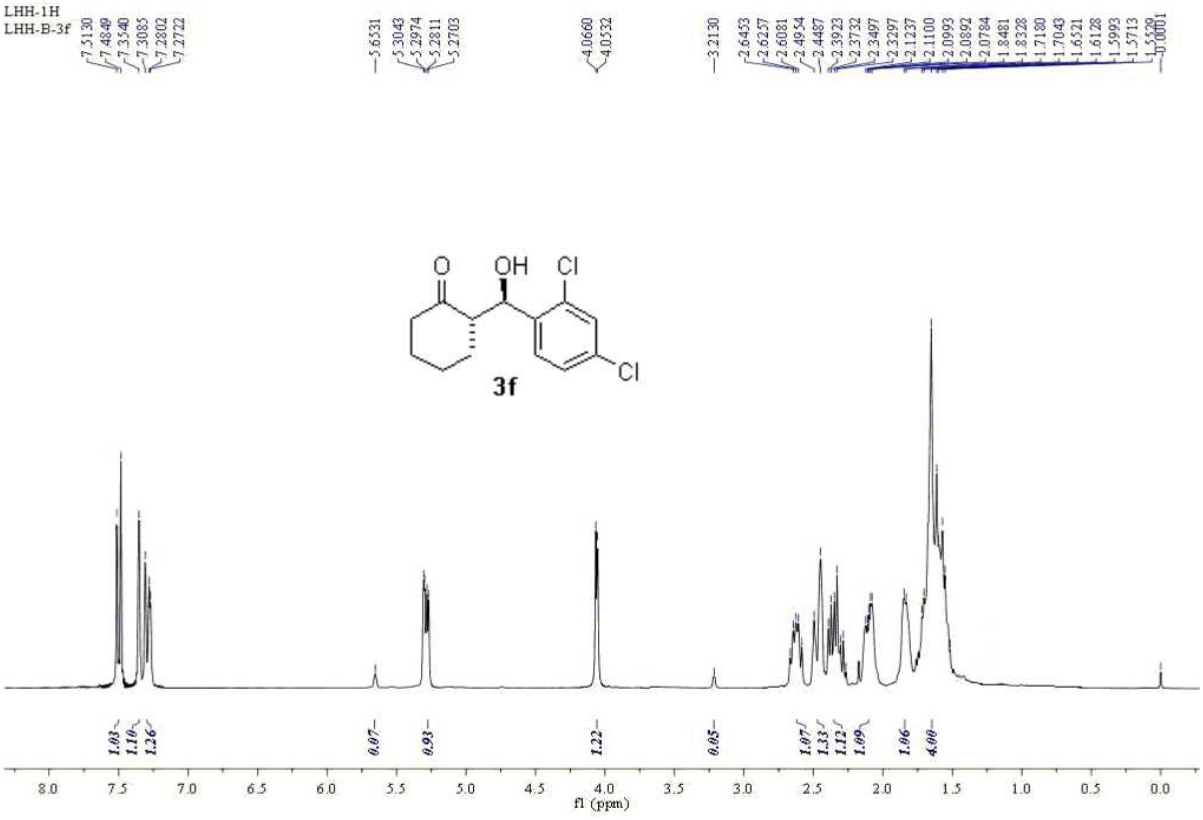
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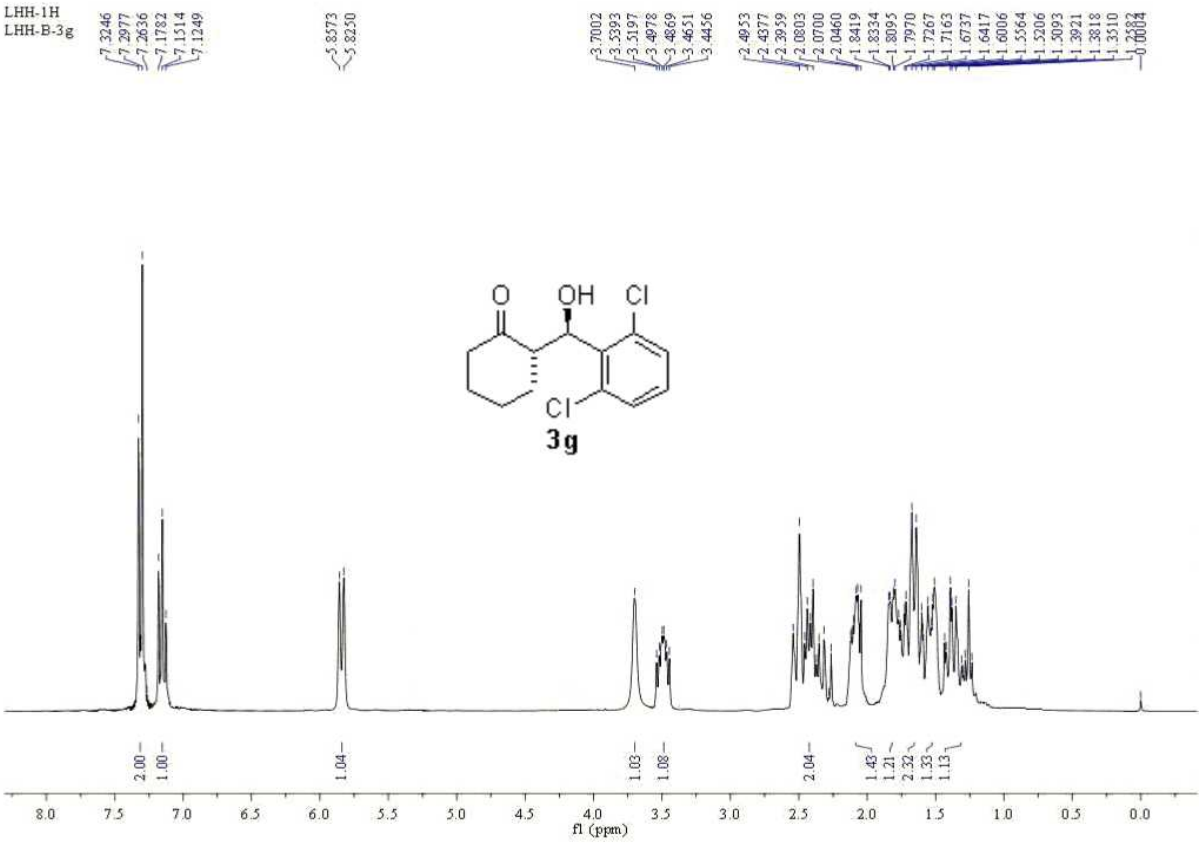
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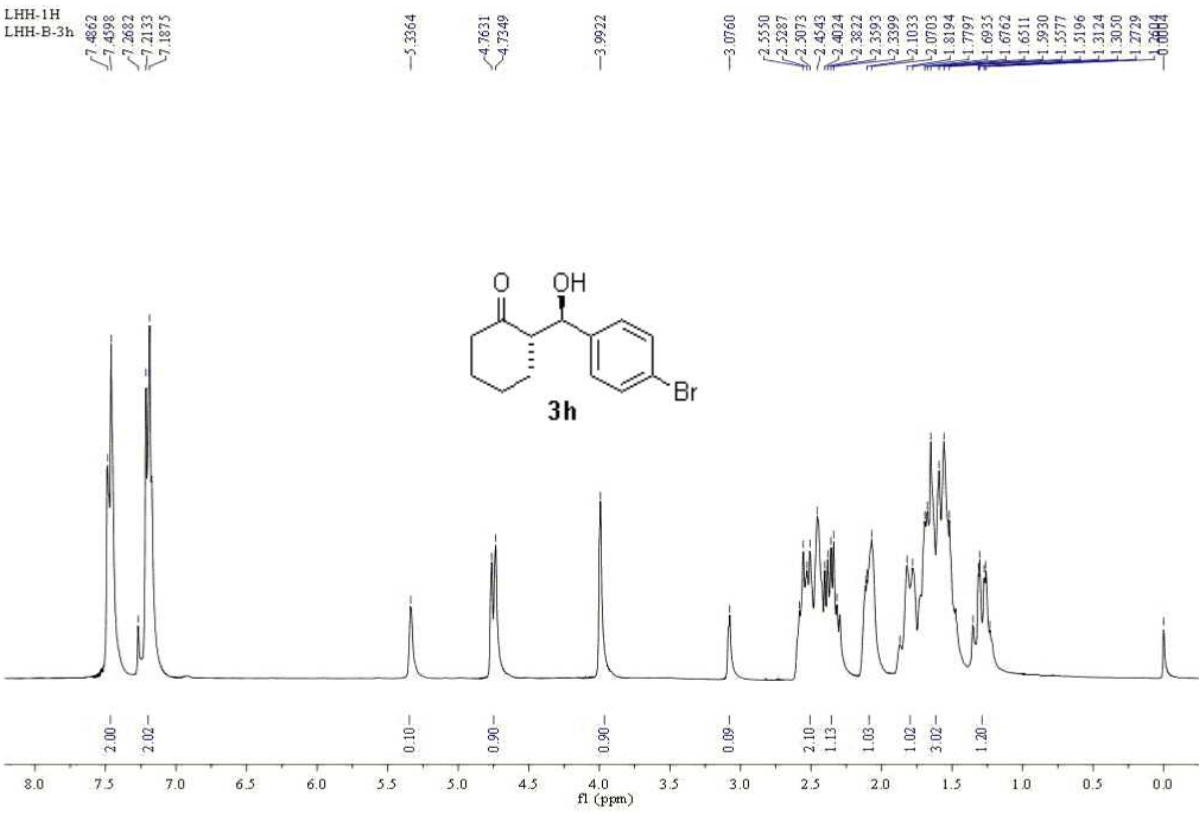
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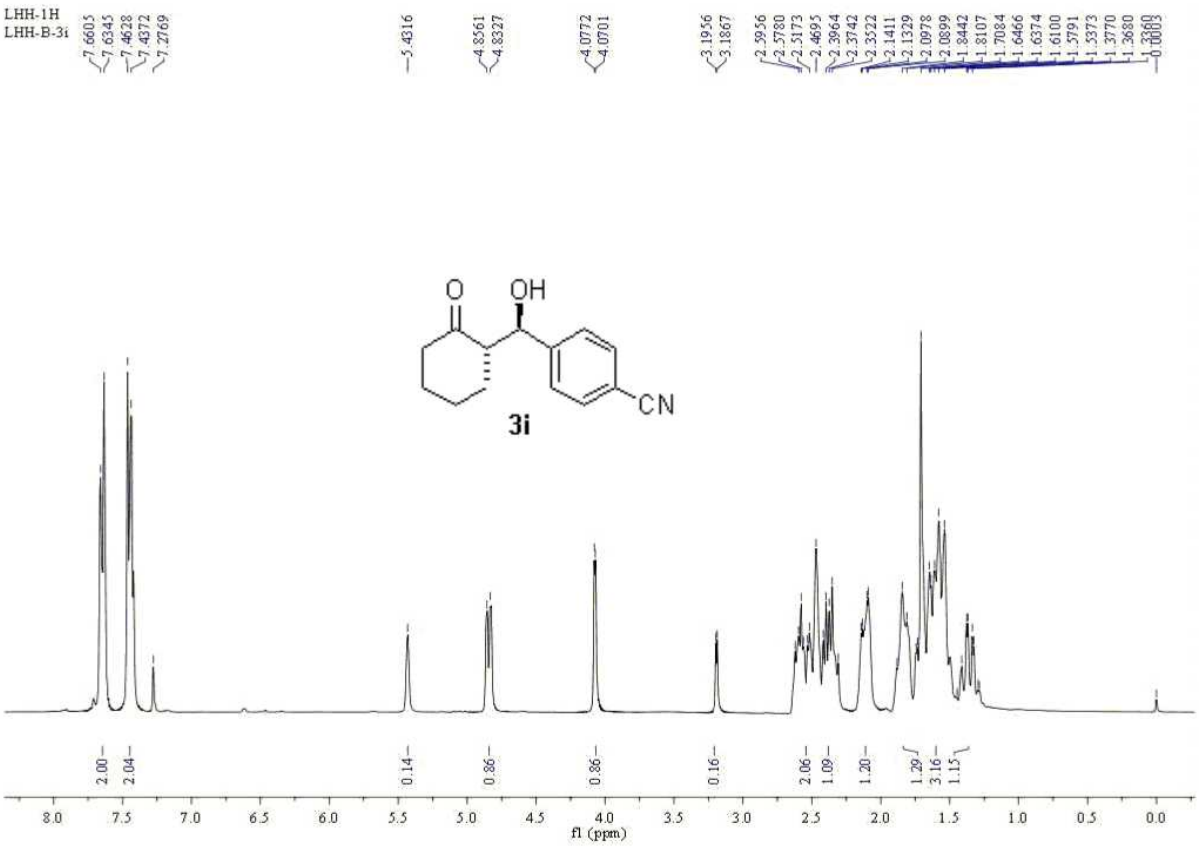
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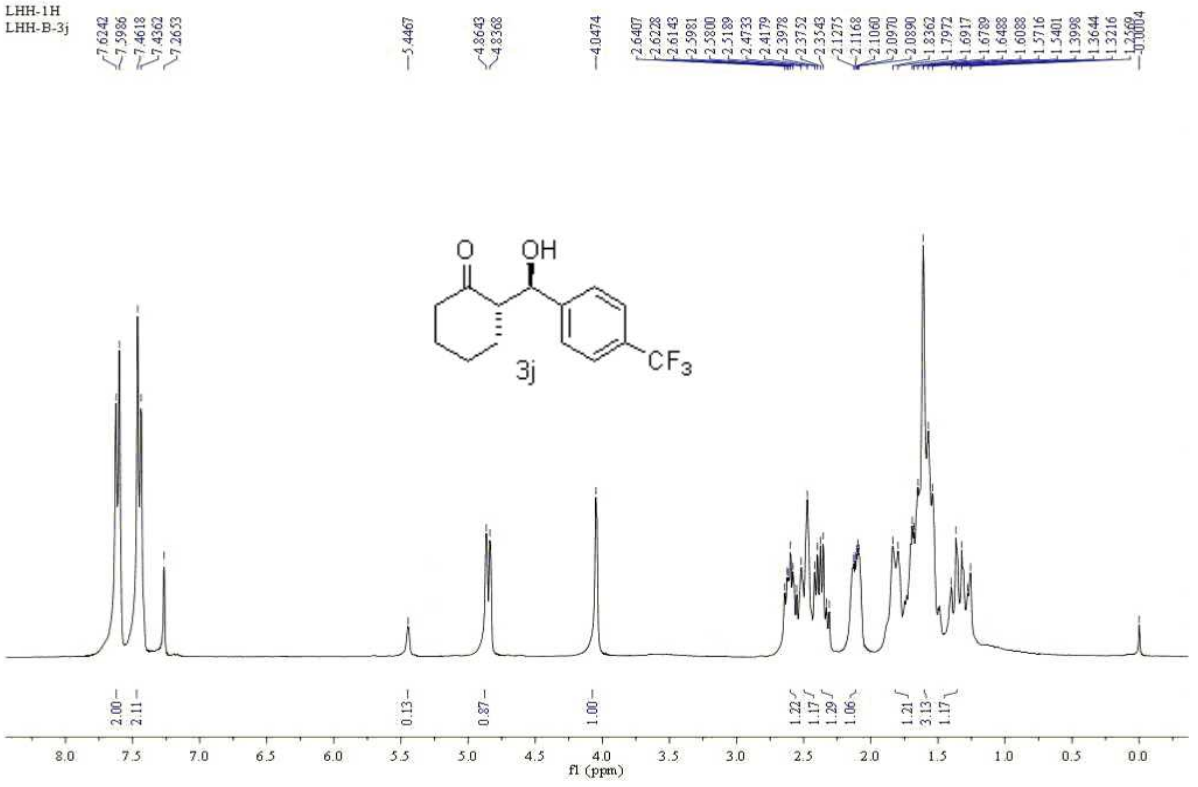
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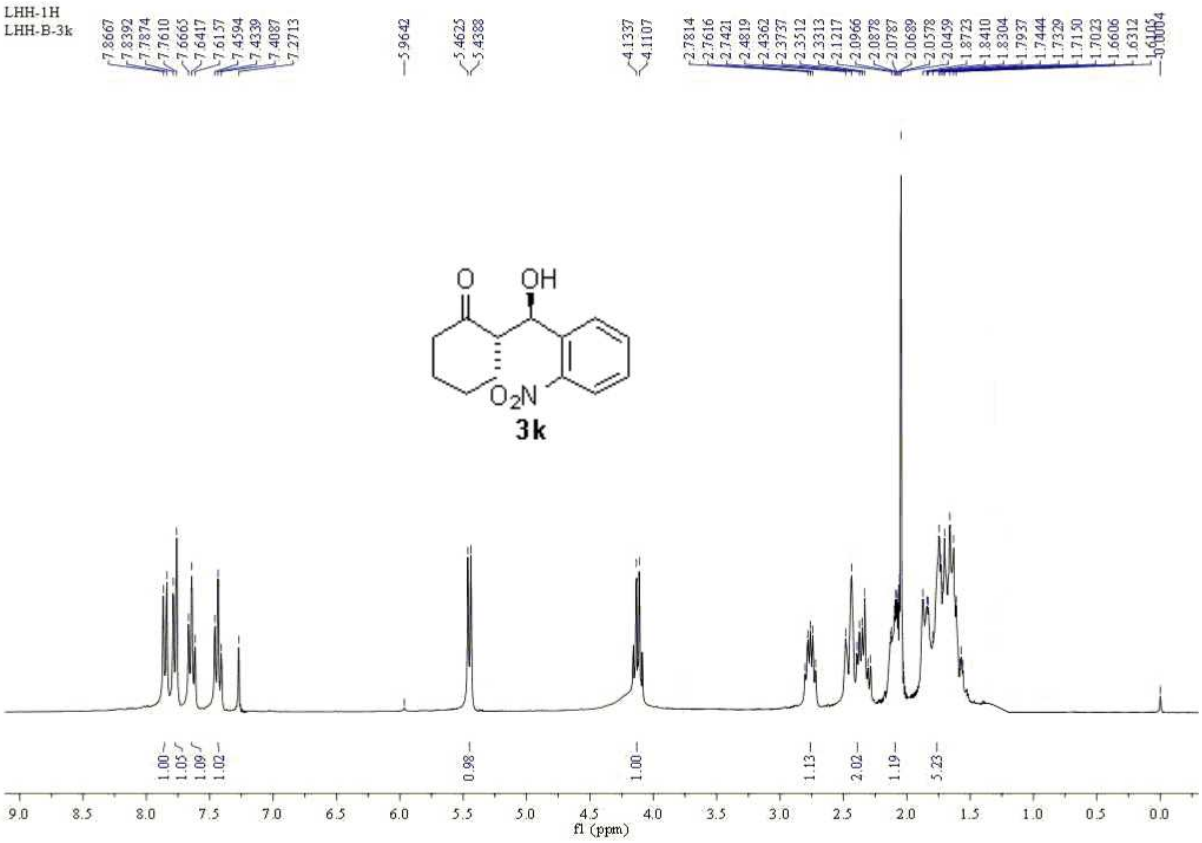
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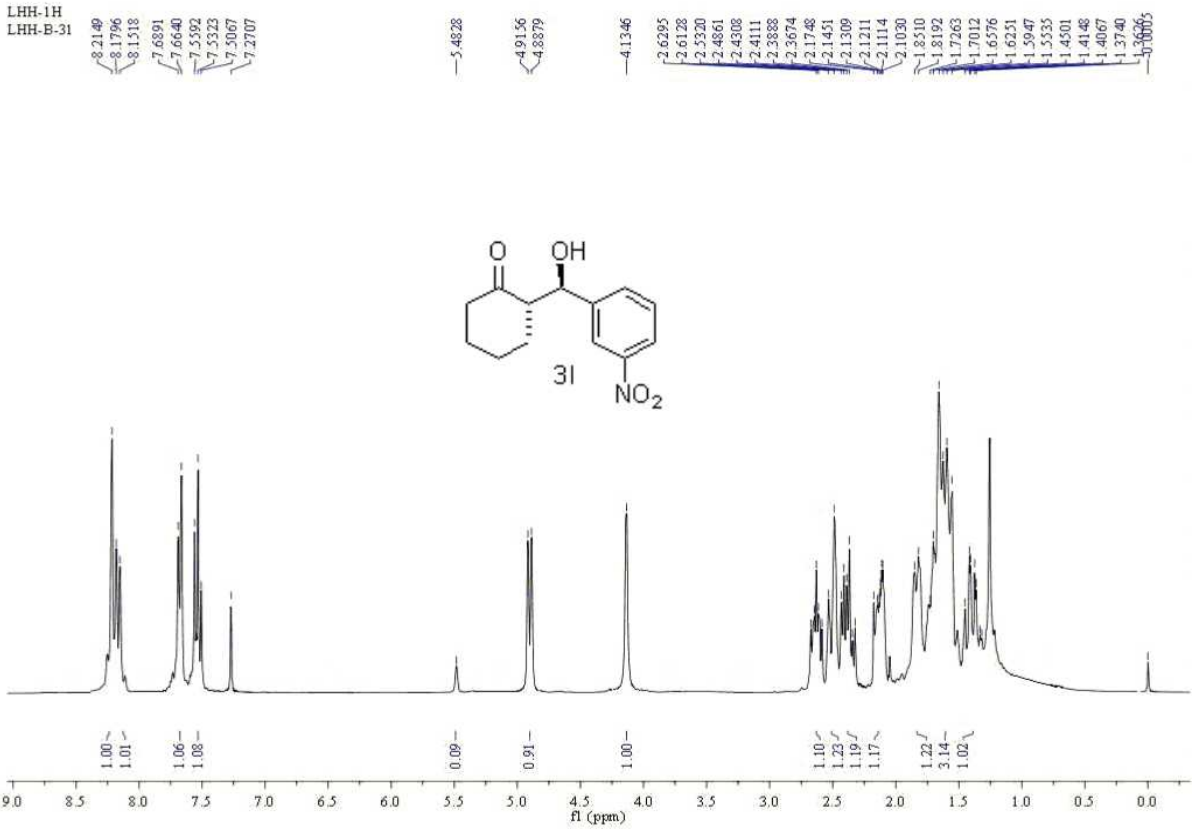
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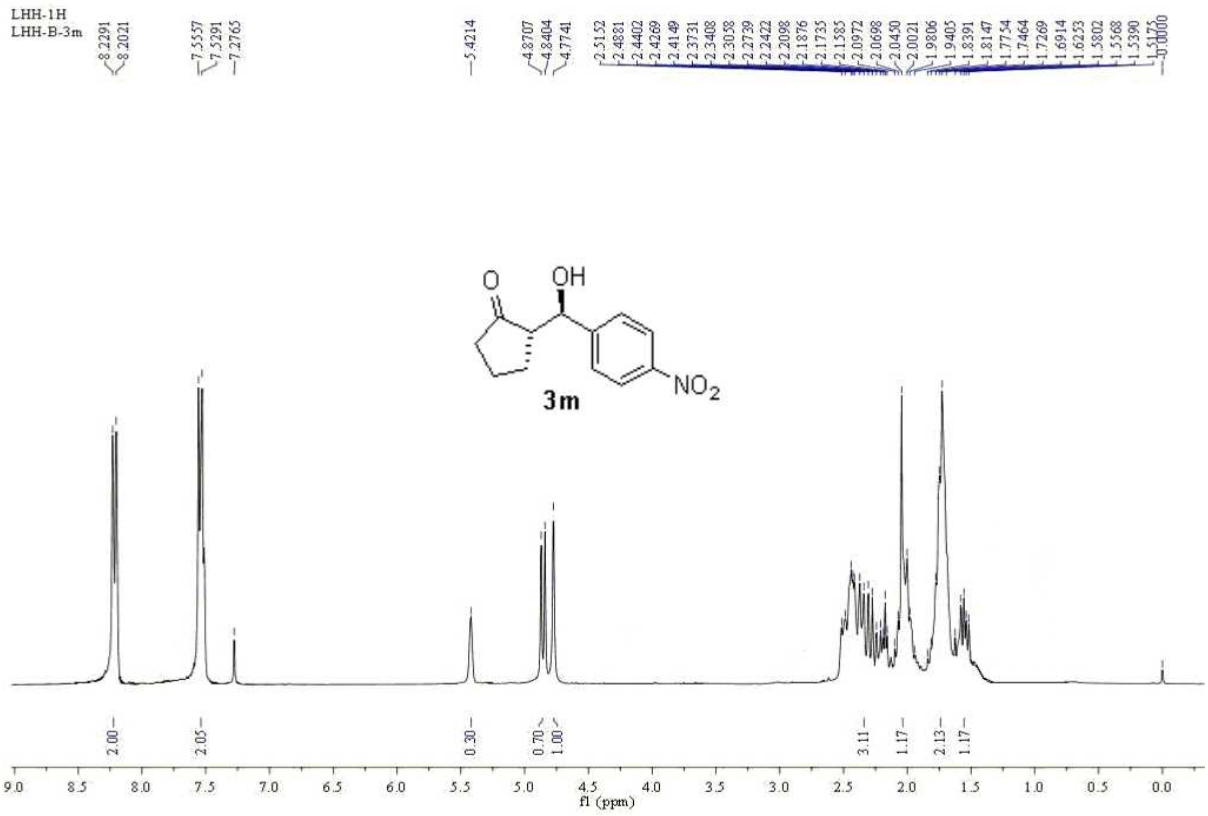
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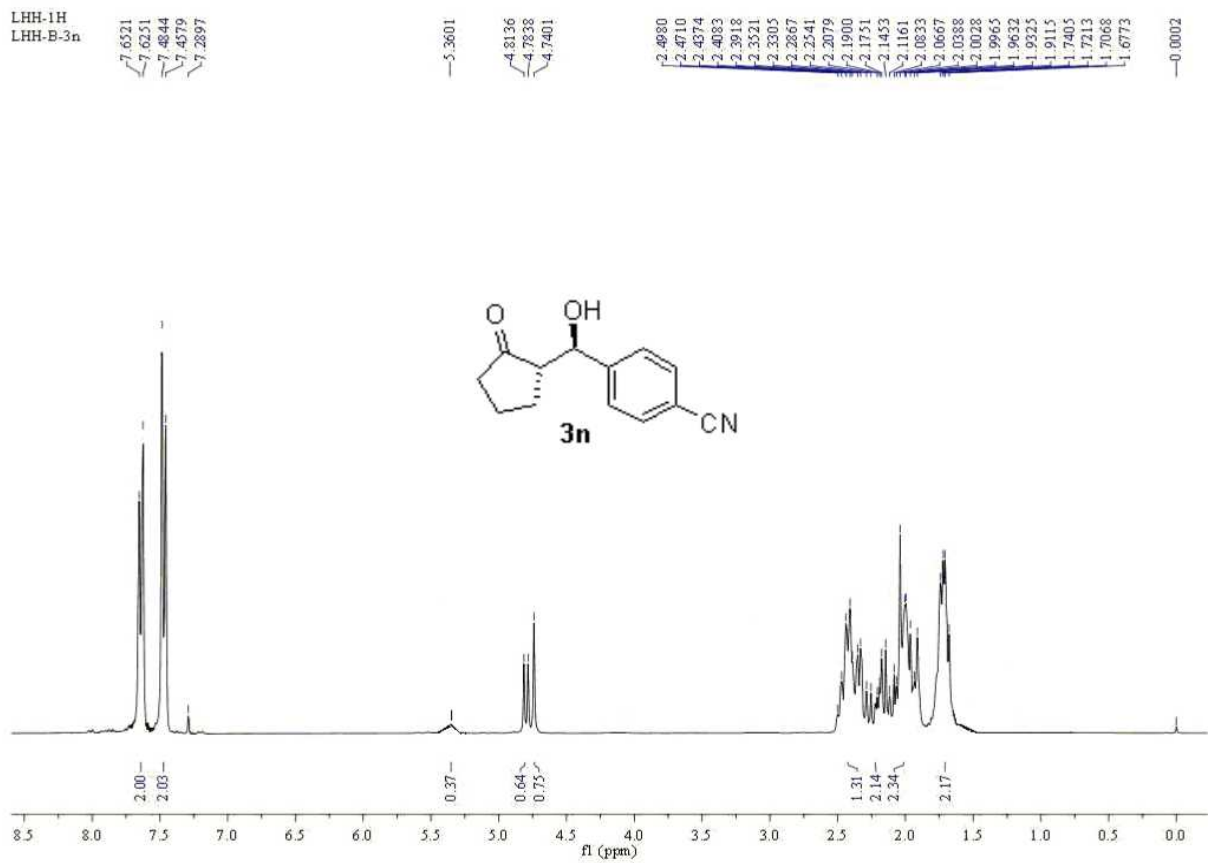
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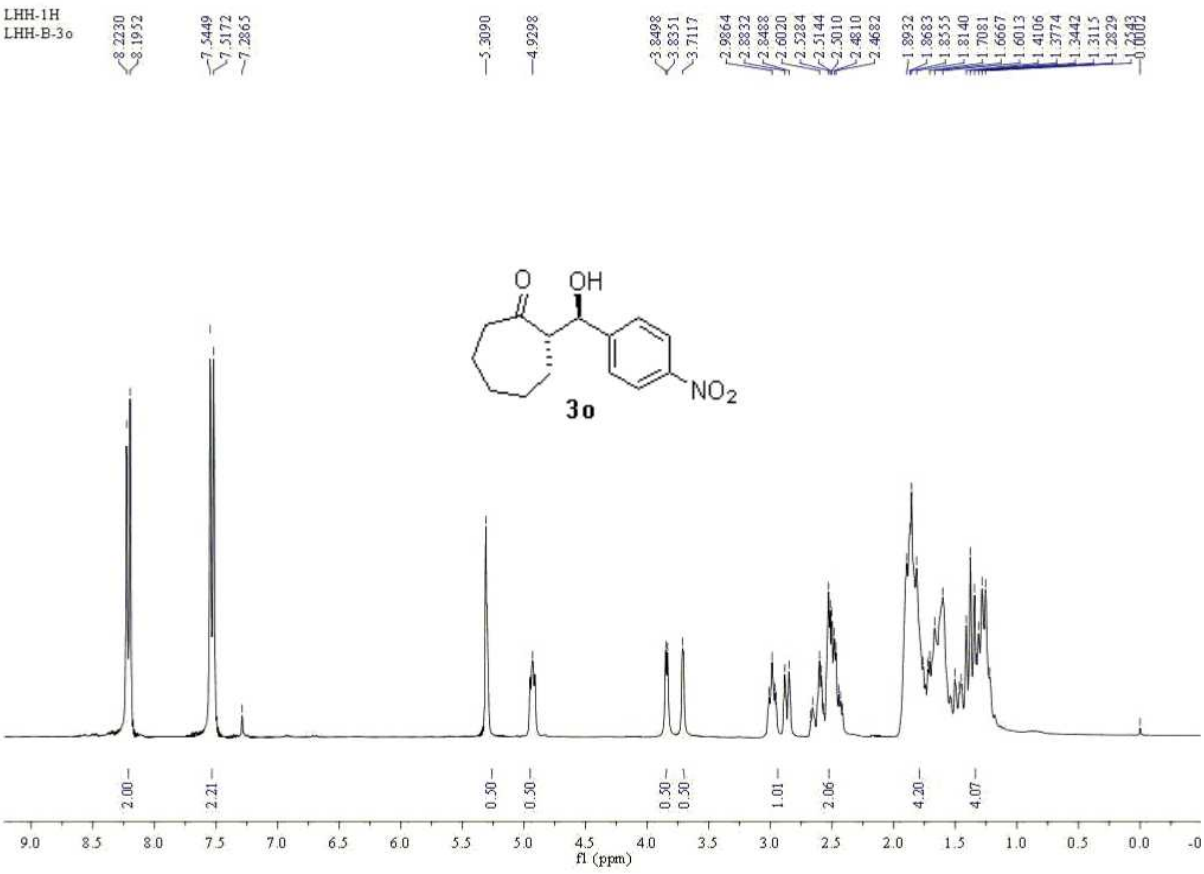
f1 (ppm)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1.01
2.06
4.20
4.07
9.0
8.5
8.0
7.5
7.0
6.5
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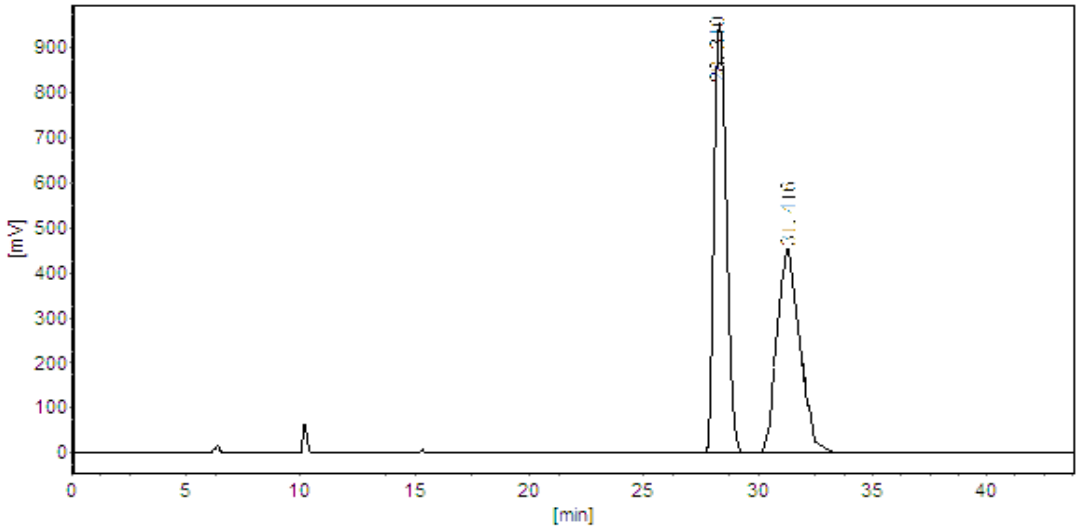
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0
f1 (ppm)

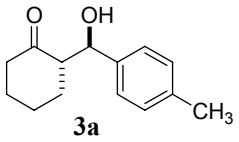
HPLC spectra for aldol products 3a-3o

3a (Racemic)

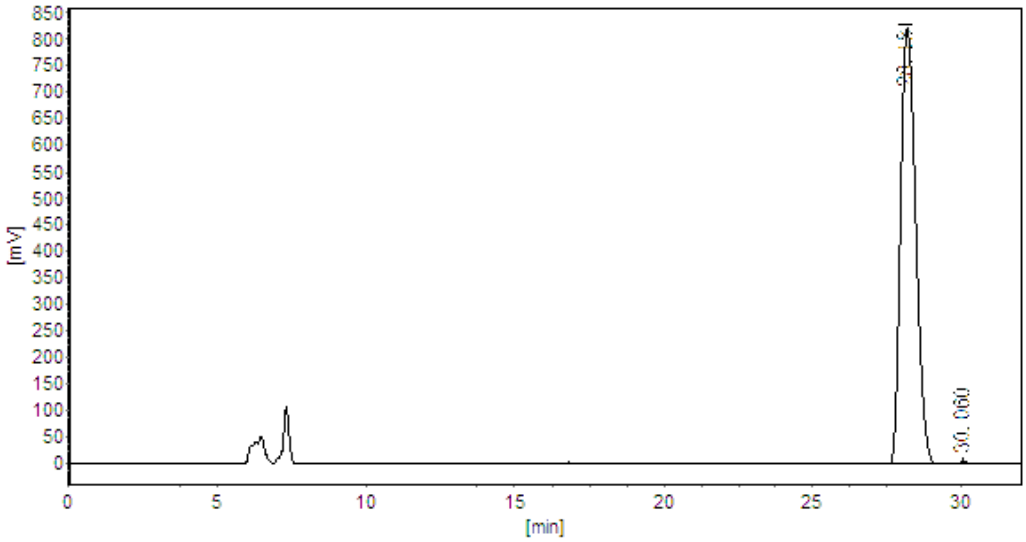
3a



3a (Chiral)



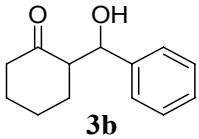
3a



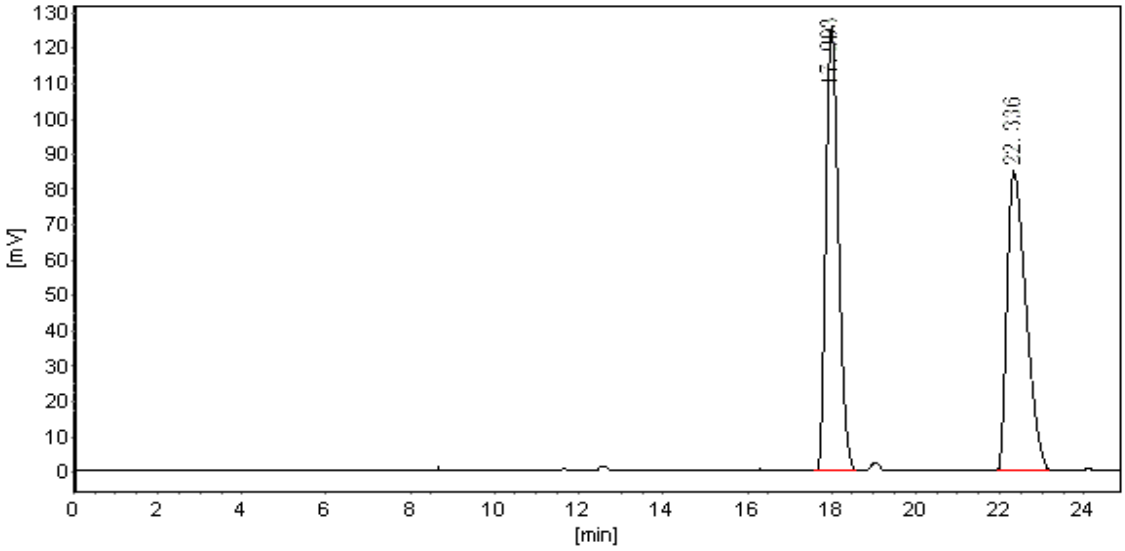
DEFAULT REPORT

Peak #	Time [min]	Area [µv.s]	Height [µv]	Area [%]
1	28.181	28931374	818377	99.83285
2	30.060	48439	4020	0.16715

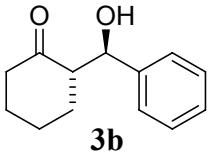
3b (Racemic)



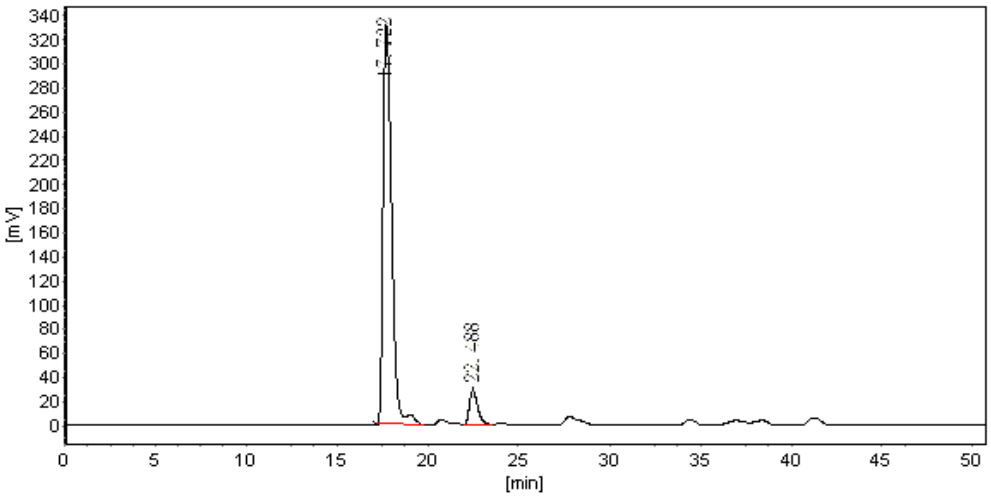
3b



3b (Chiral)



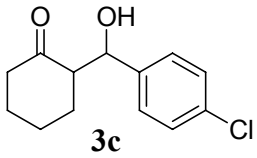
3b



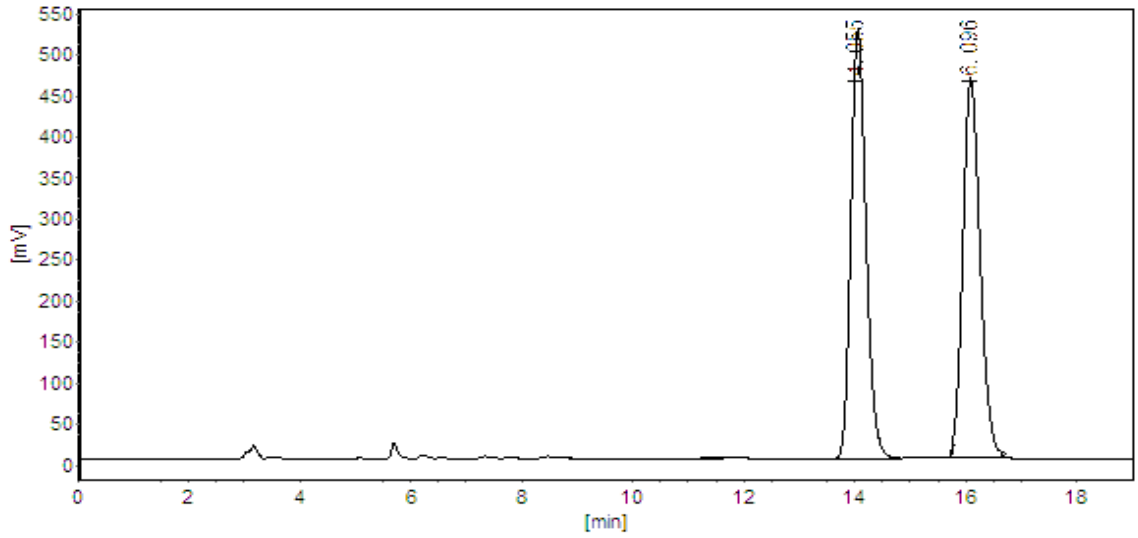
DEFAULT REPORT

Peak #	Time [min]	Area [µv.s]	Height [µv]	Area [%]
1	17.722	10923479	329720	92.39088
2	22.488	899635	28842	7.60912

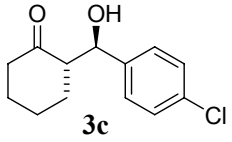
3c (Racemic)



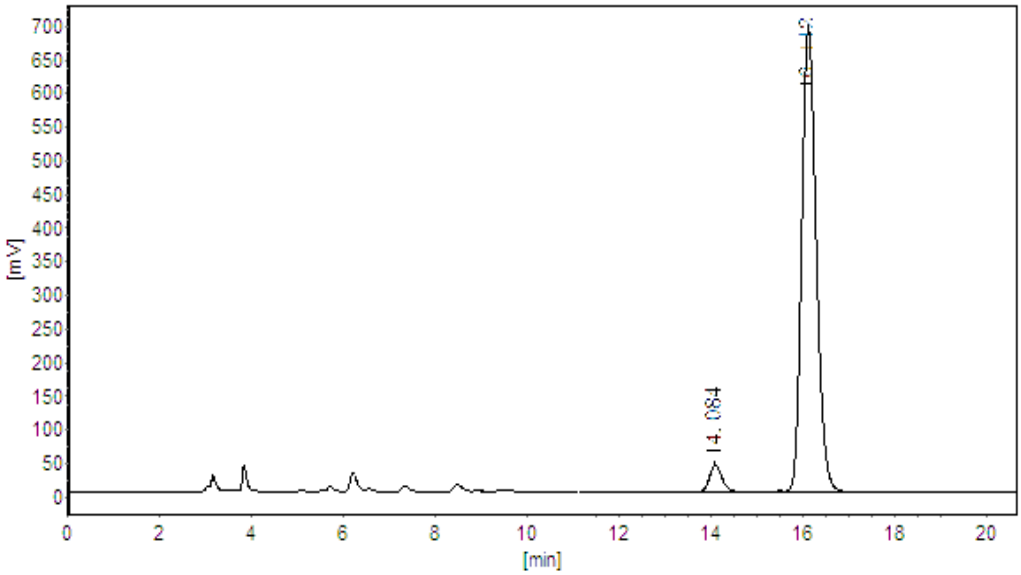
3c



3c (Chiral)



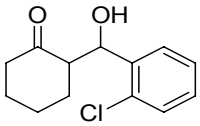
3c



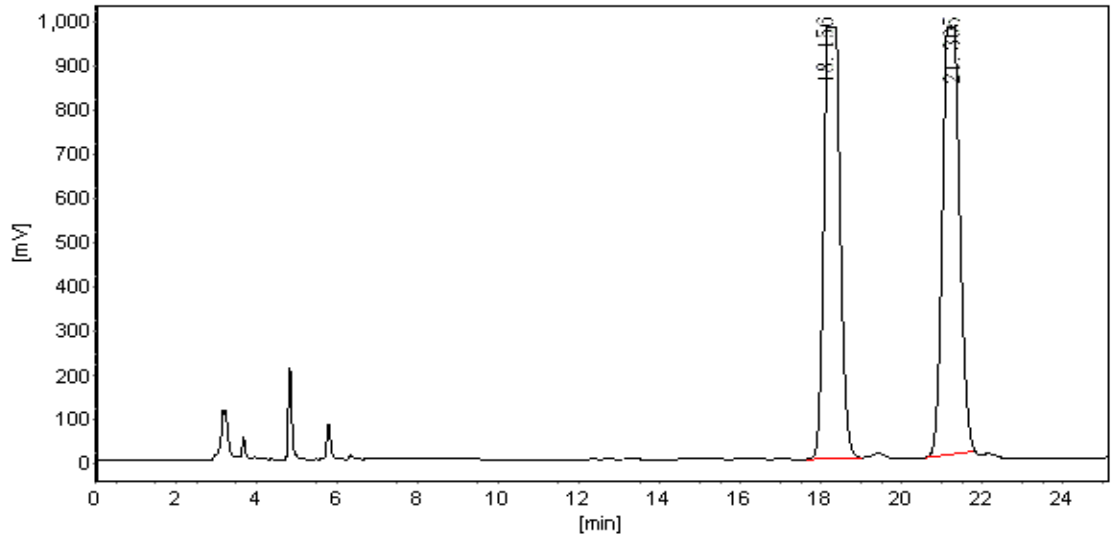
DEFAULT REPORT

Peak #	Time [min]	Area [µv.s]	Height [µv]	Area [%]
1	14.084	739177	39537	4.64978
2	16.112	15157865	689339	95.35022

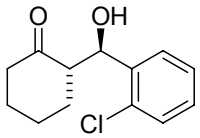
3d (Racemic)



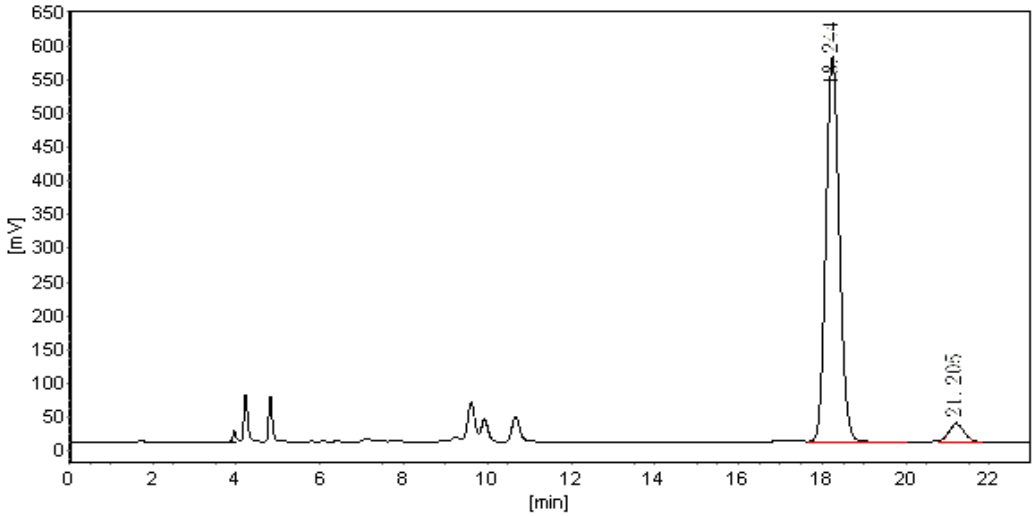
3d



3d (Chiral)



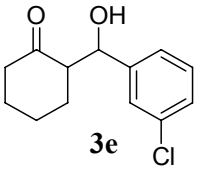
3d



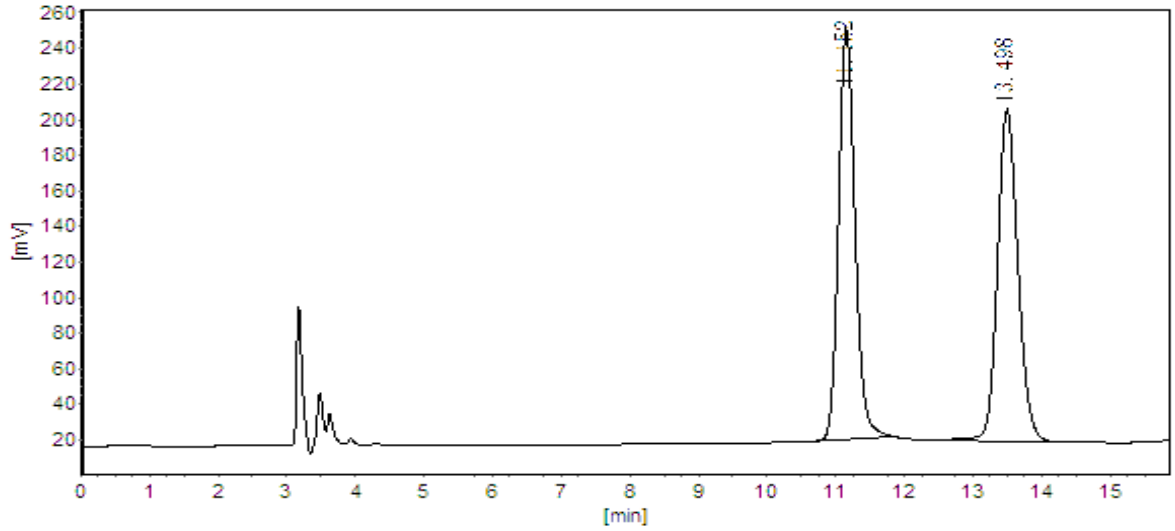
DEFAULT REPORT

Peak #	Time [min]	Area [µv.s]	Height [µv]	Area [%]
1	18.244	12738831	567882	96.59982
2	21.205	448389	21370	3.40018

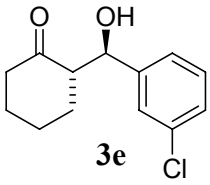
3e (Racemic)



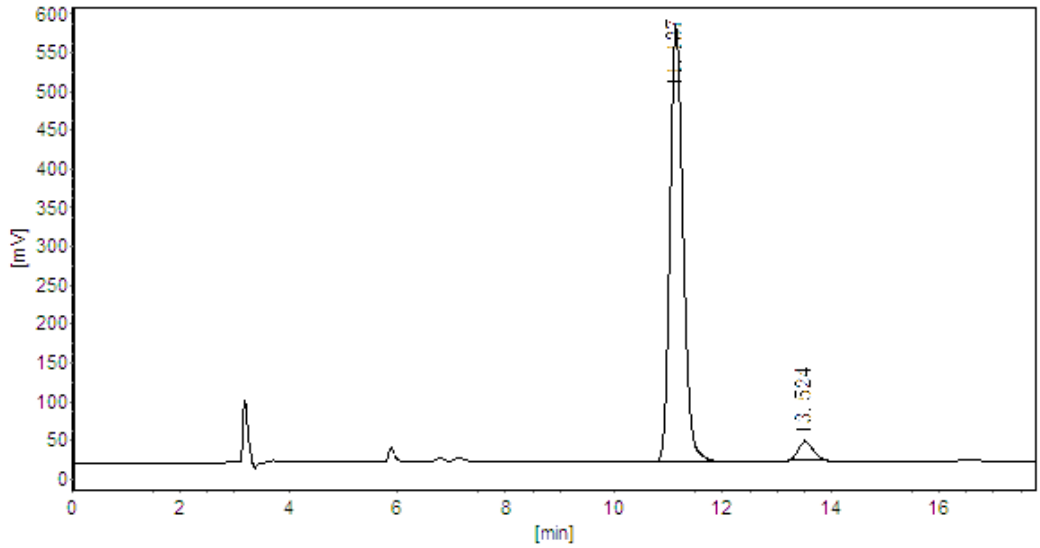
3e



3e (Chiral)



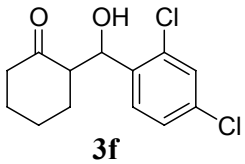
3e



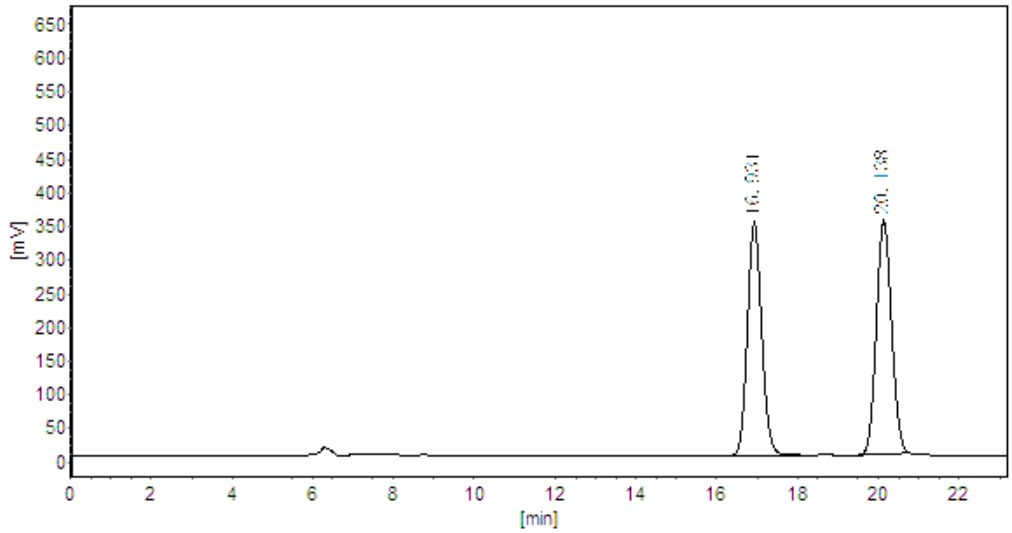
DEFAULT REPORT

Peak #	Time [min]	Area [µv.s]	Height [µv]	Area [%]
1	11.137	9461608	558351	95.66029
2	13.524	429234	23047	4.33971

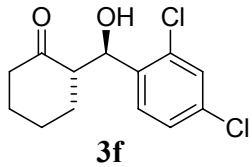
3f (Racemic)



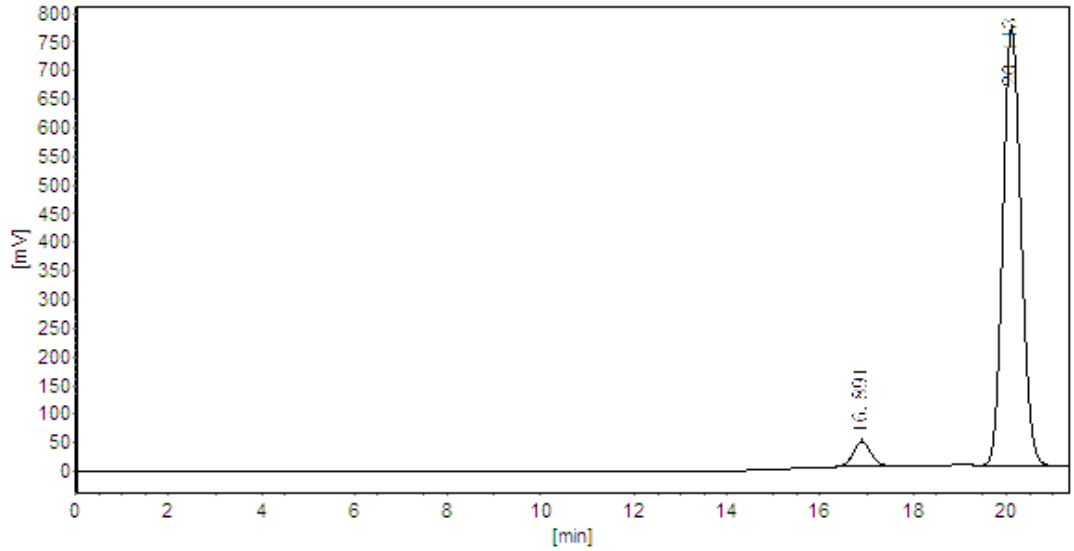
3f



3f (Chiral)



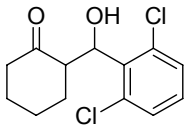
3f



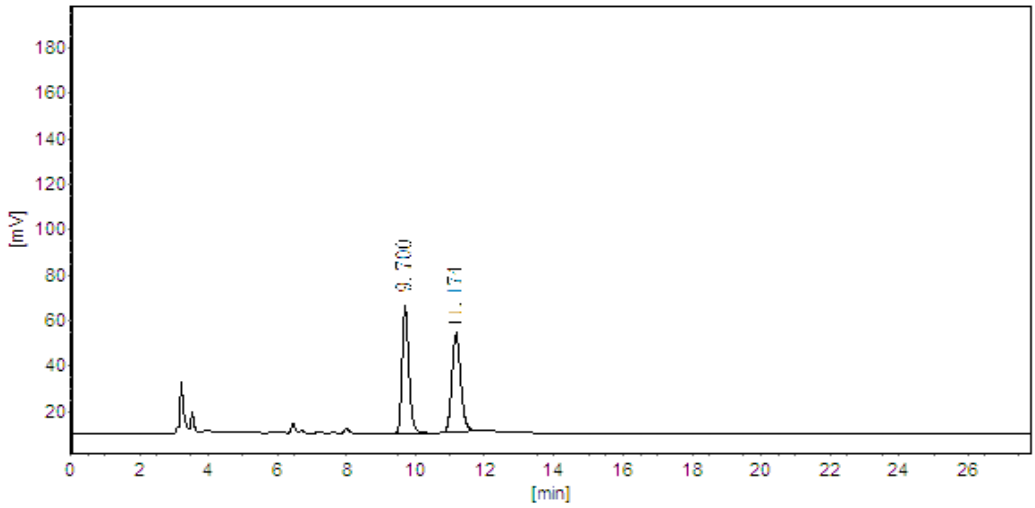
DEFAULT REPORT

Peak #	Time [min]	Area [µv.s]	Height [µv]	Area [%]
1	16.891	1070562	41592	4.92815
2	20.113	20652833	763861	95.07185

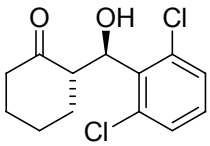
3g (Racemic)



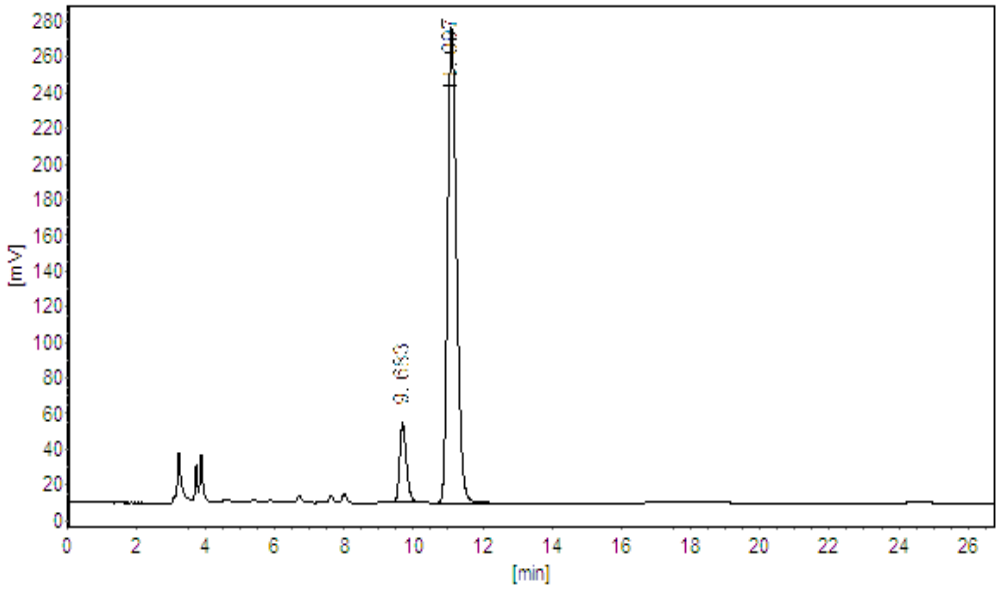
3g



3g (Chiral)



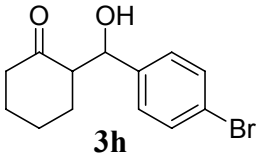
3g



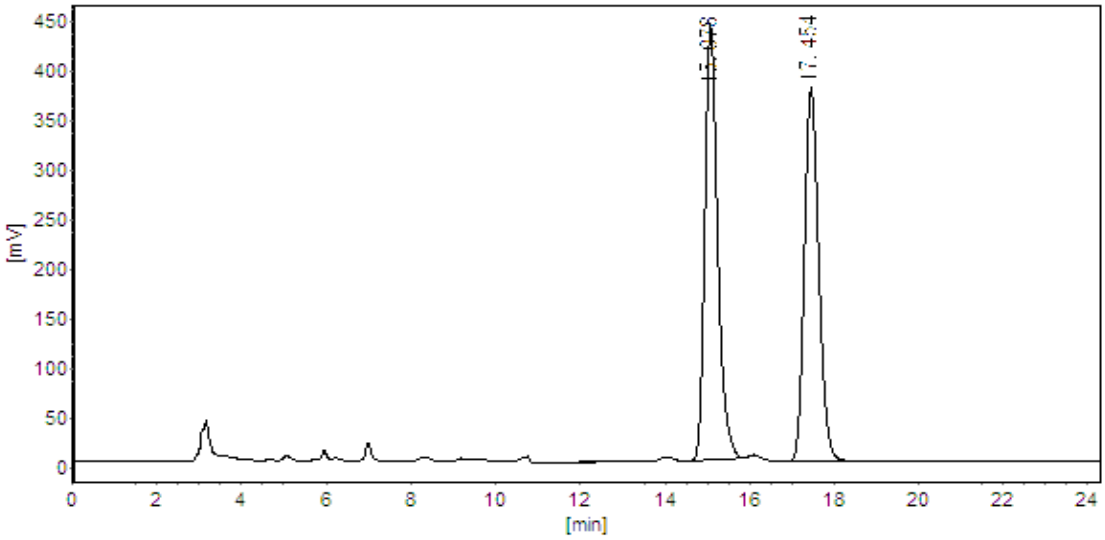
DEFAULT REPORT

Peak #	Time [min]	Area [µv.s]	Height [µv]	Area [%]
1	9.683	502311	40509	9.53614
2	11.097	4765137	265439	90.46386

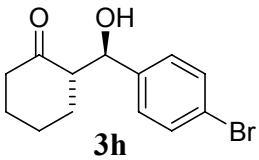
3h (Racemic)



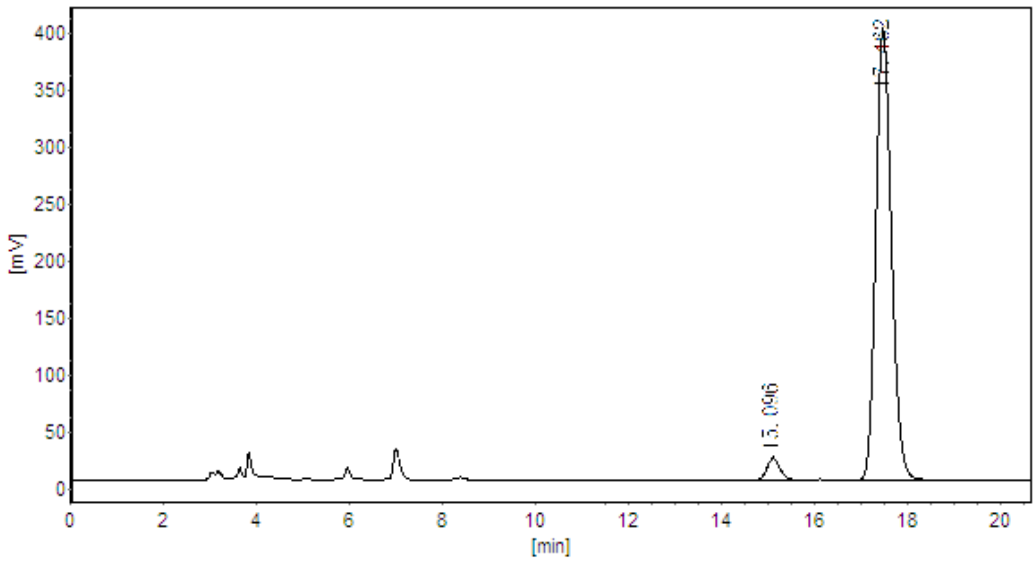
3h



3h (Chiral)



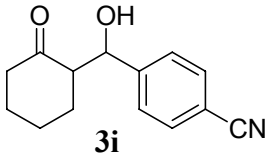
3h



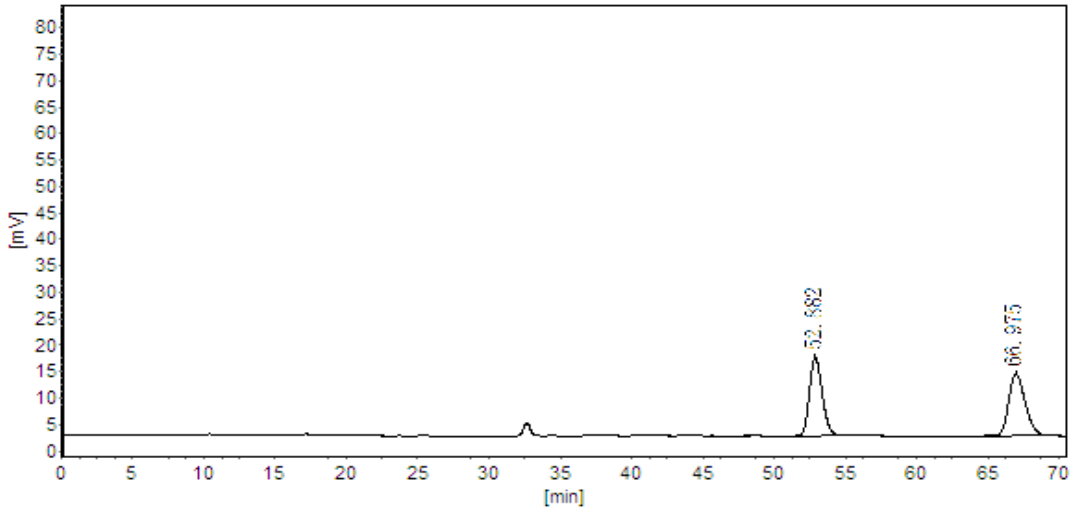
DEFAULT REPORT

Peak #	Time [min]	Area [µv.s]	Height [µv]	Area [%]
1	15.096	367953	18581	3.81327
2	17.462	9281320	395157	96.18673

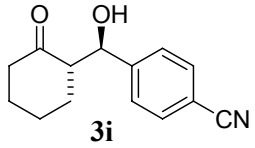
3i (Racemic)



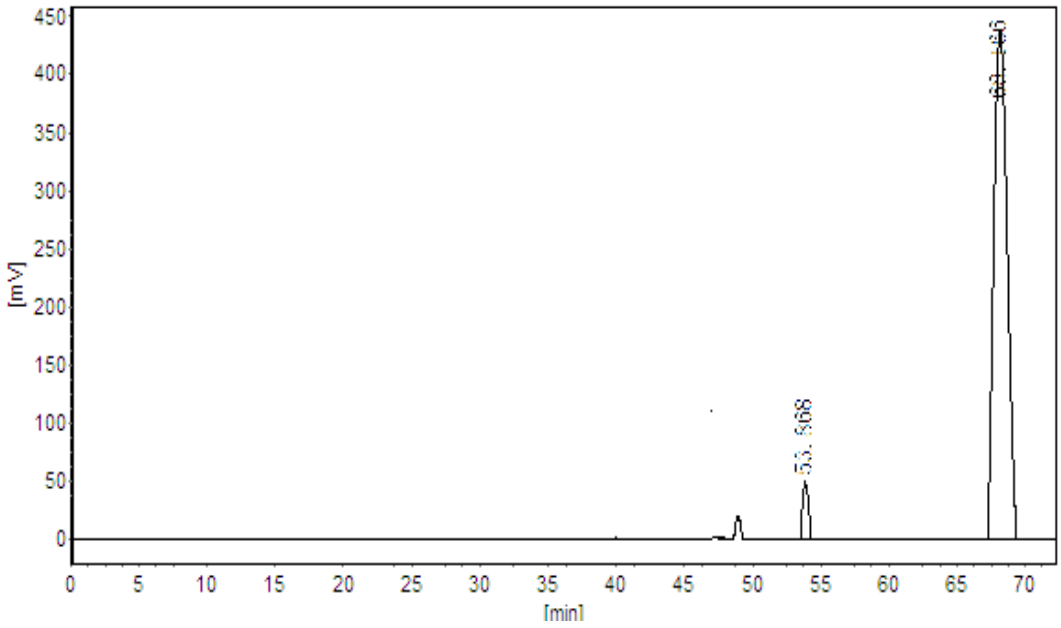
3i



3i (Chiral)



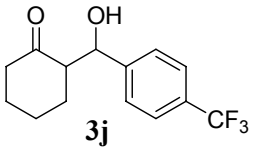
3i



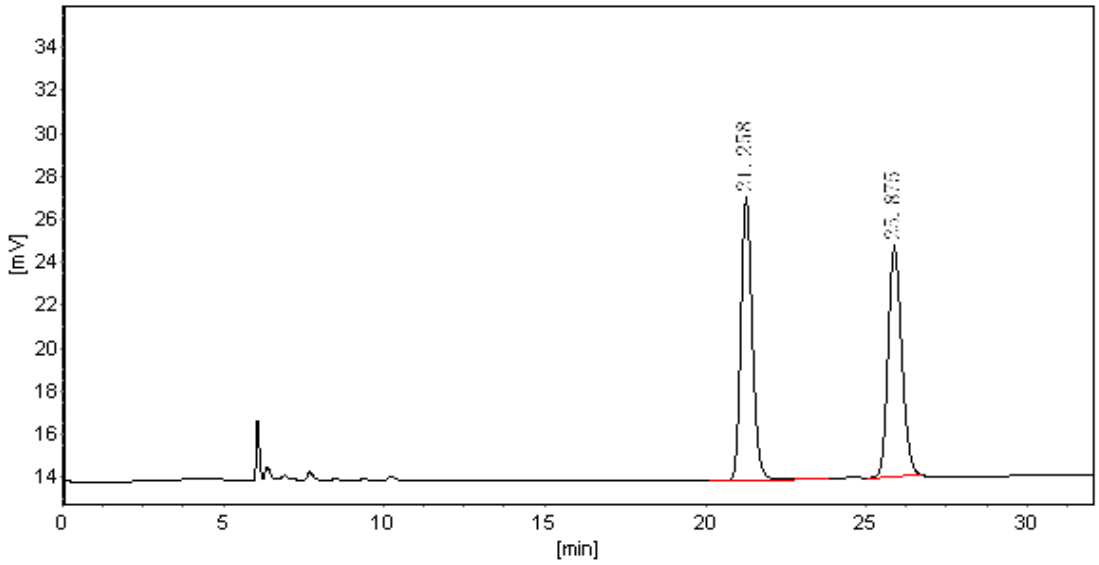
DEFAULT REPORT

Peak #	Time [min]	Area [µv.s]	Height [µv]	Area [%]
1	53.868	1451107	47158	4.65934
2	68.166	29692937	436219	95.34066

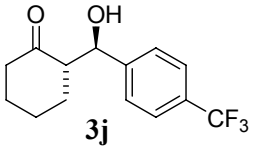
3j (Racemic)



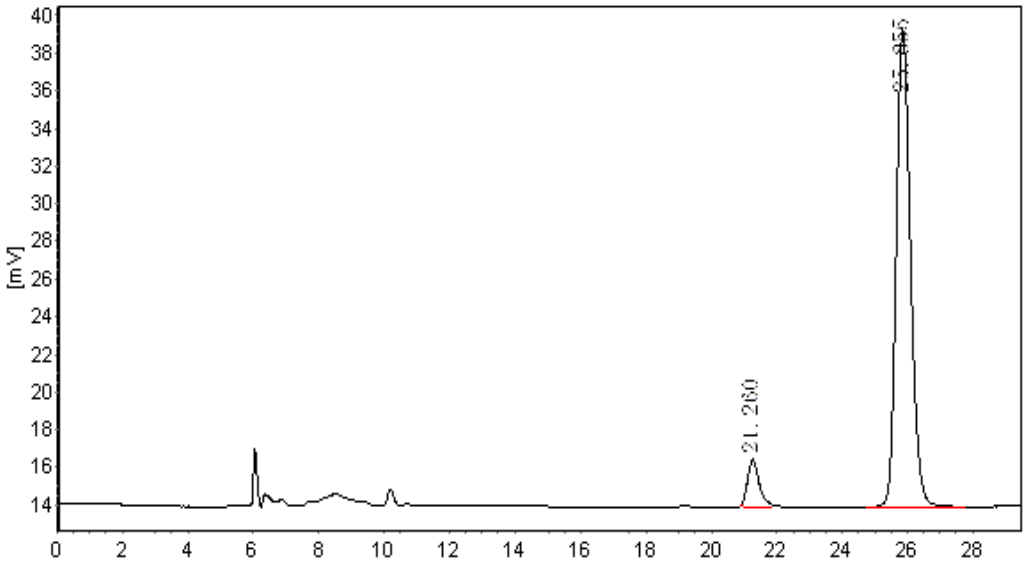
3j



3j (Chiral)



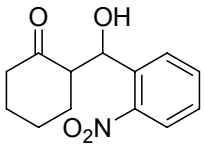
3j



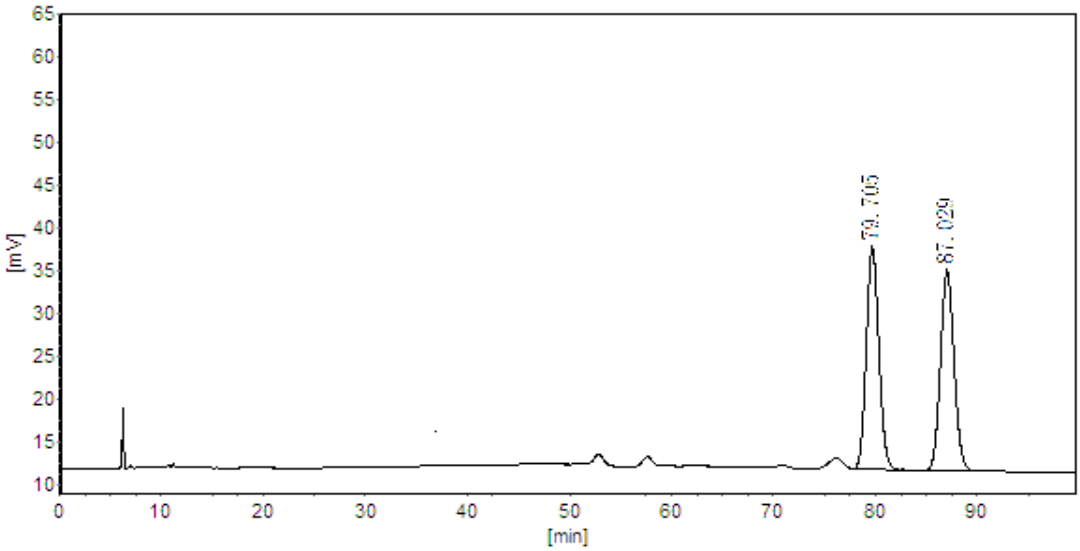
DEFAULT REPORT

Peak #	Time [min]	Area [µv.s]	Height [µv]	Area [%]
1	21.260	40728	2048	5.00944
2	25.855	772302	25350	94.99056

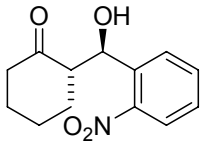
3k (Racemic)



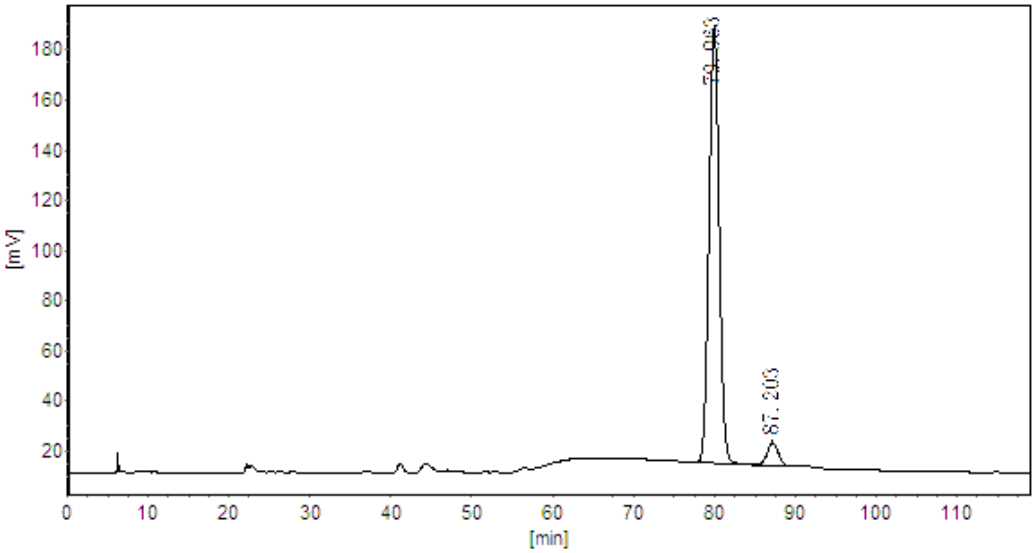
3k



3k (Chiral)



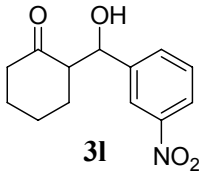
3k



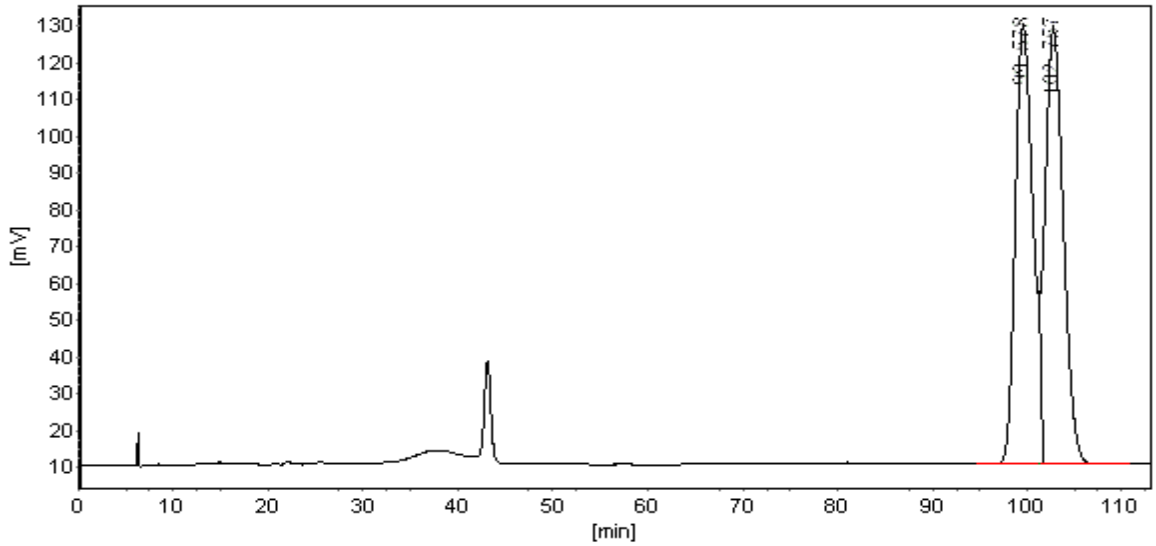
DEFAULT REPORT

Peak #	Time [min]	Area [µv.s]	Height [µv]	Area [%]
1	79.963	15198340	173800	94.53621
2	87.203	878399	9044	5.46379

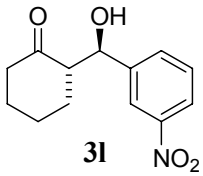
3l (Racemic)



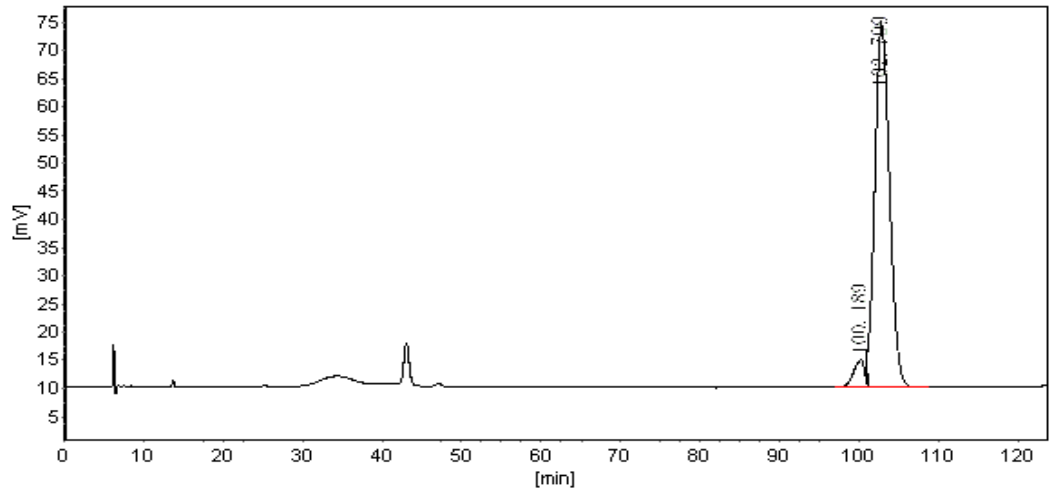
3l



3l (Chiral)



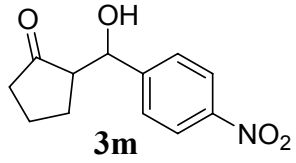
3l



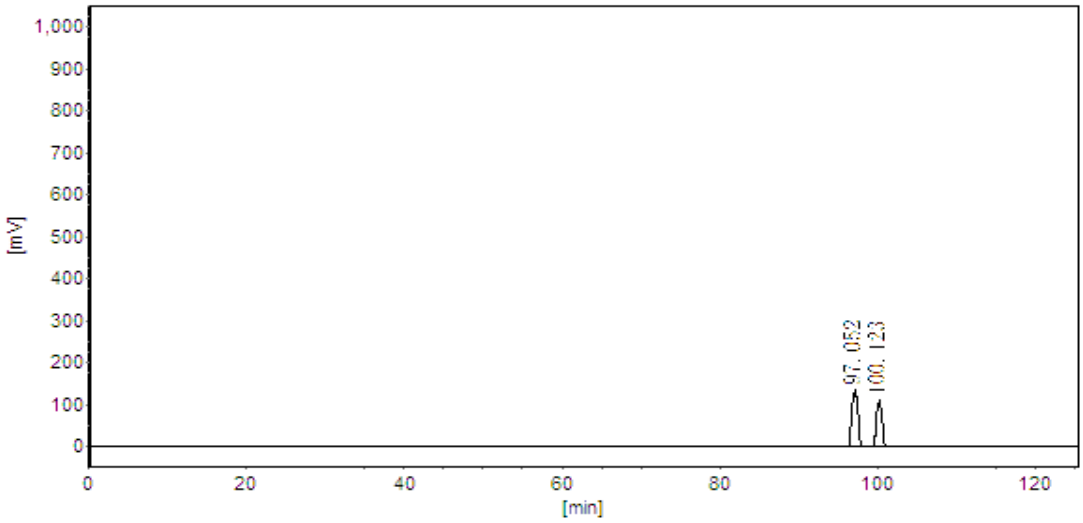
DEFAULT REPORT

Peak #	Time [min]	Area [µv.s]	Height [µv]	Area [%]
1	100.189	376051	4614	4.24758
2	102.799	8477235	64154	95.75242

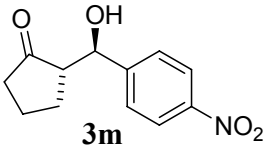
3m-anti (Racemic)



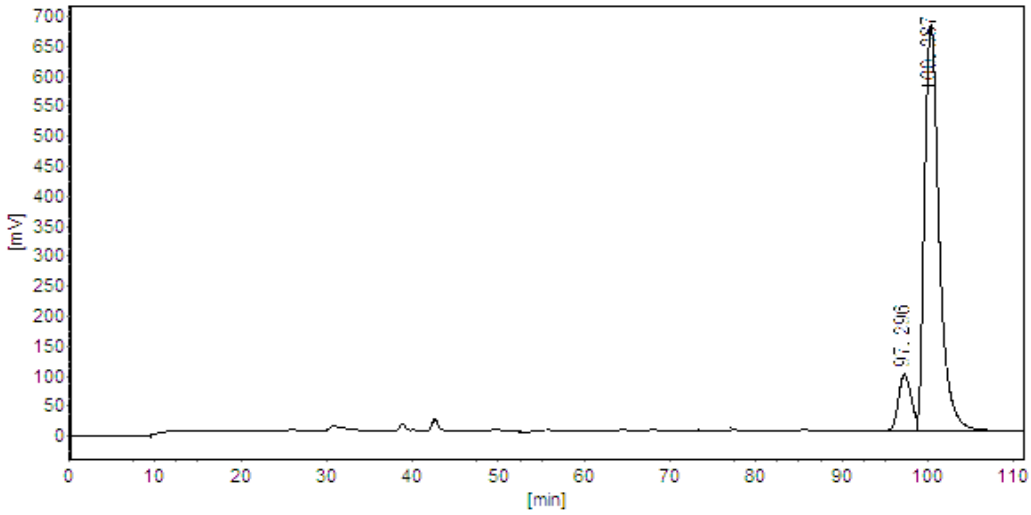
3m



3m-anti (Chiral)



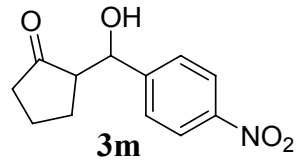
3m



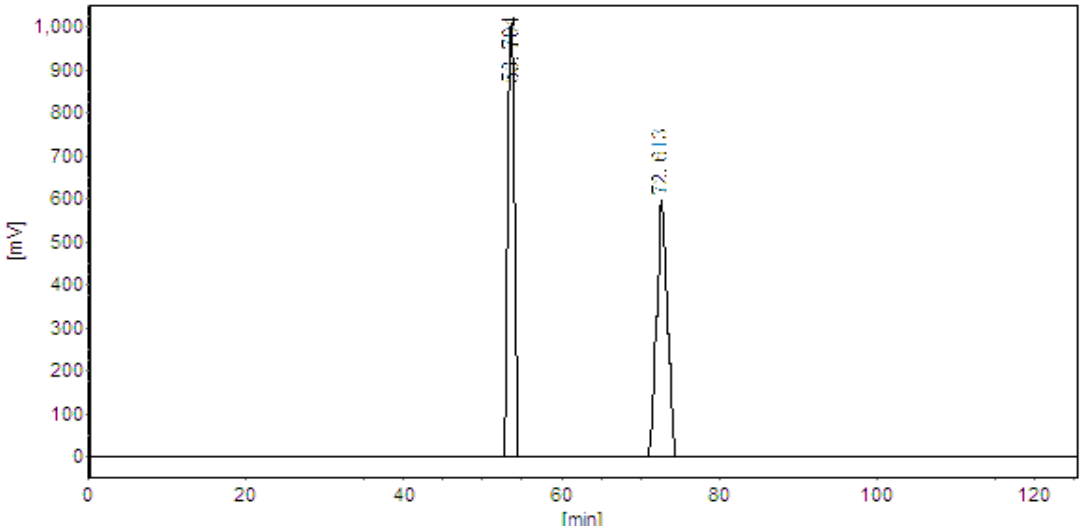
DEFAULT REPORT

Peak #	Time [min]	Area [µv.s]	Height [µv]	Area [%]
1	97.296	9718019	93390	10.77049
2	100.387	80510209	674544	89.22951

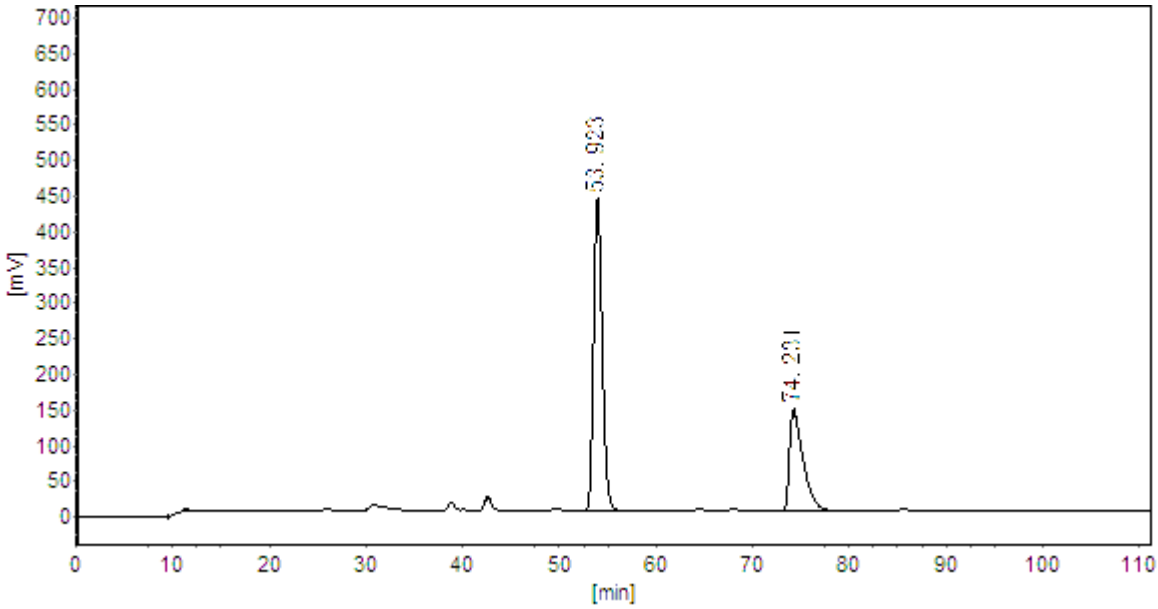
3m-syn (Racemic)



3m



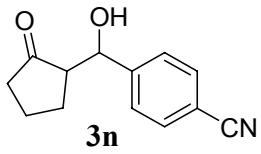
3m-syn (Chiral)



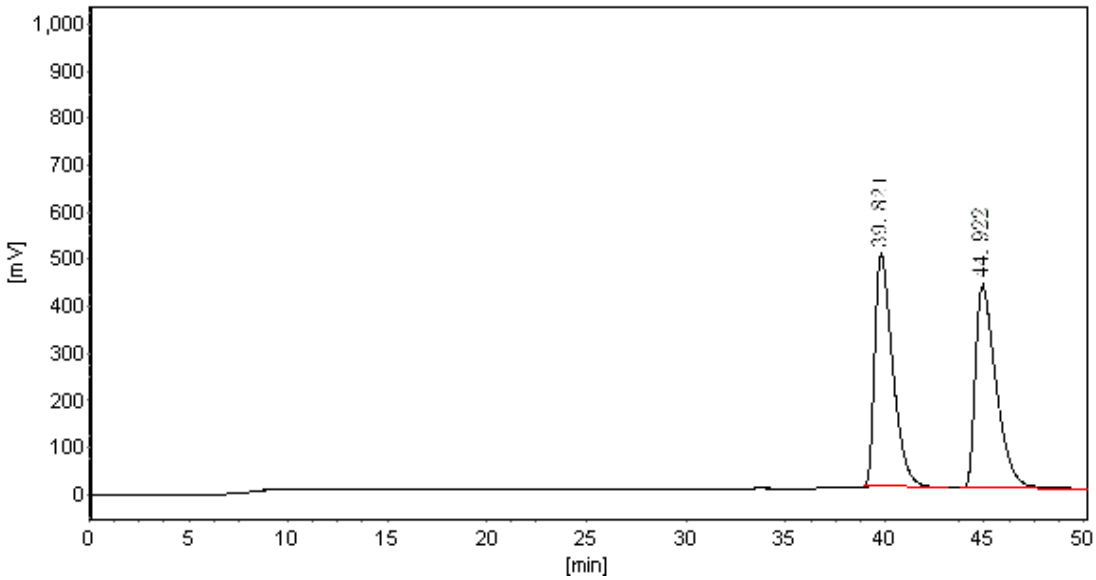
DEFAULT REPORT

Peak #	Time [min]	Area [µv.s]	Height [µv]	Area [%]
1	53.923	27106584	434703	66.26426
2	74.231	13800210	139488	33.73574

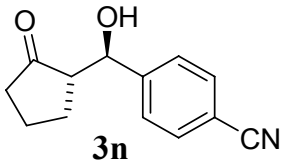
3n-anti (Racemic)



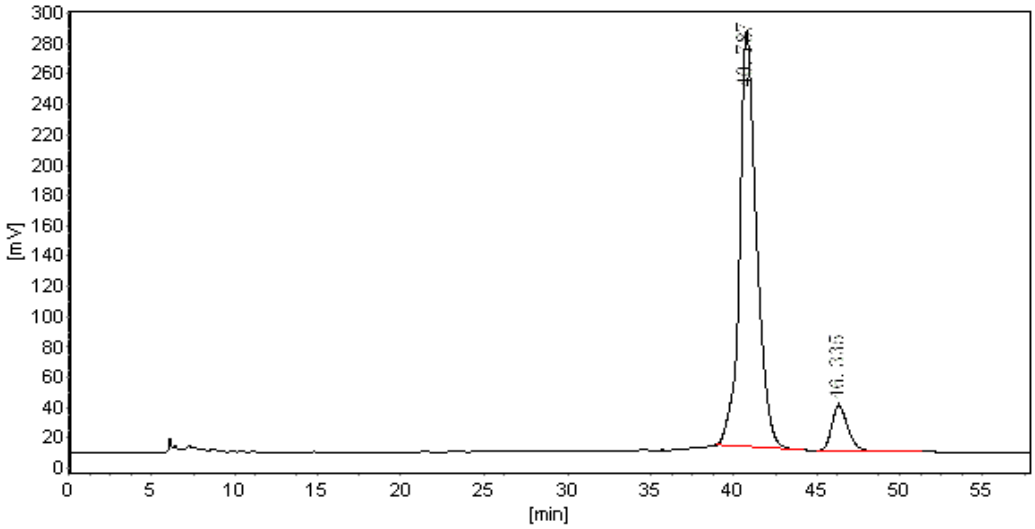
3n



3n-anti (Chiral)



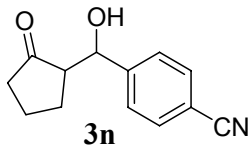
3n



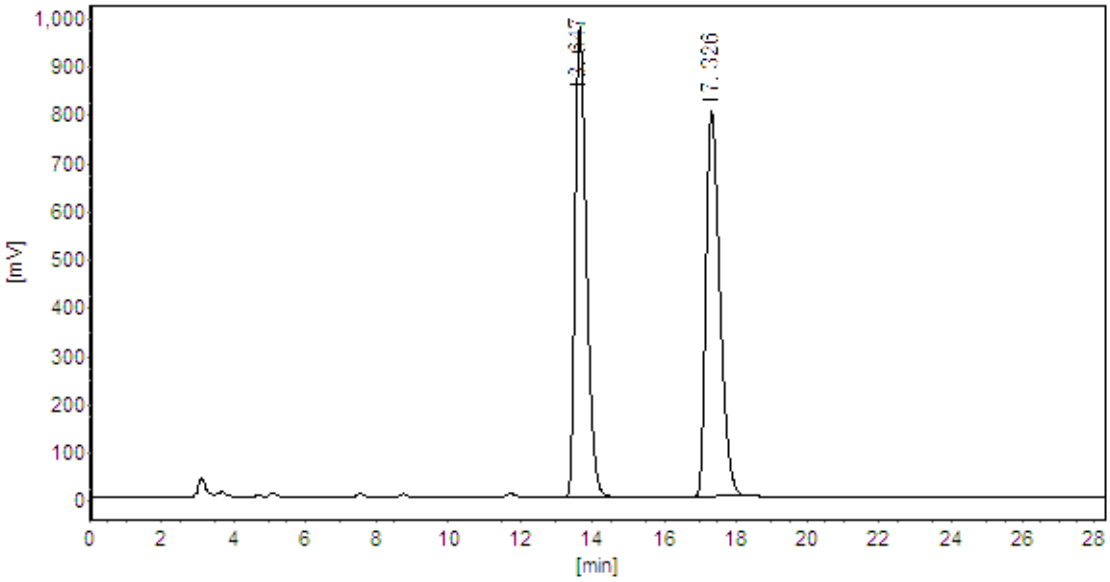
DEFAULT REPORT

Peak #	Time [min]	Area [µv.s]	Height [µv]	Area [%]
1	40.787	19453875	273494	90.70693
2	46.335	1993081	29344	9.29307

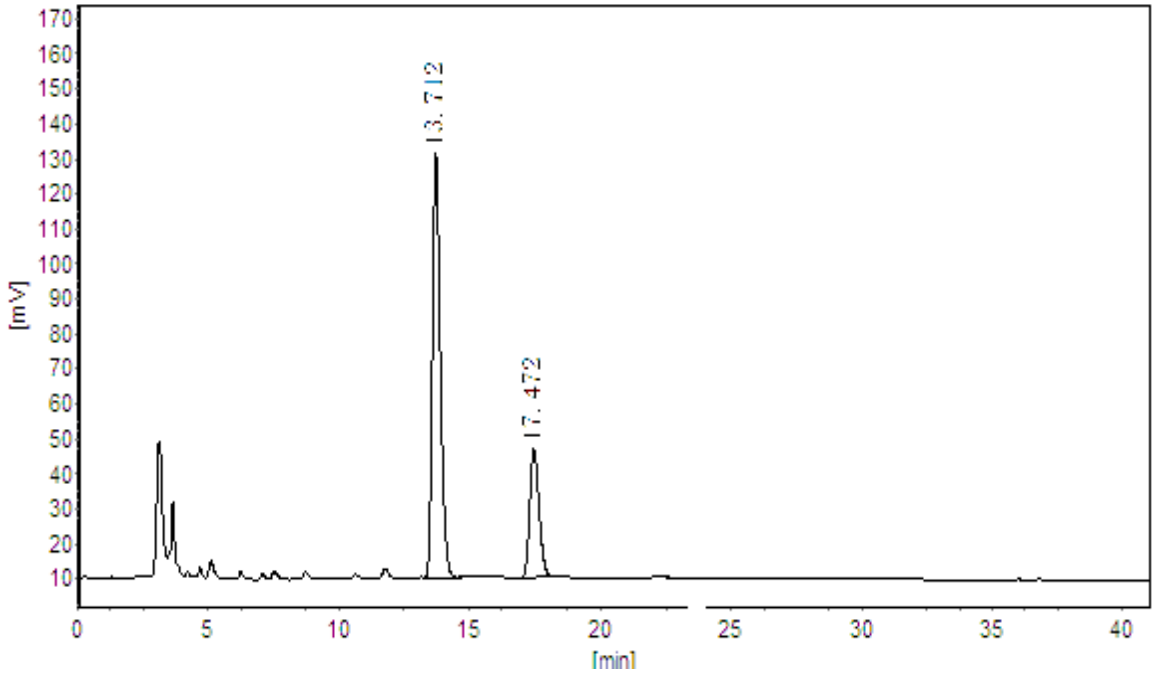
3n-syn (Racemic)



3n



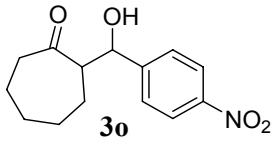
3n-syn (Chiral)



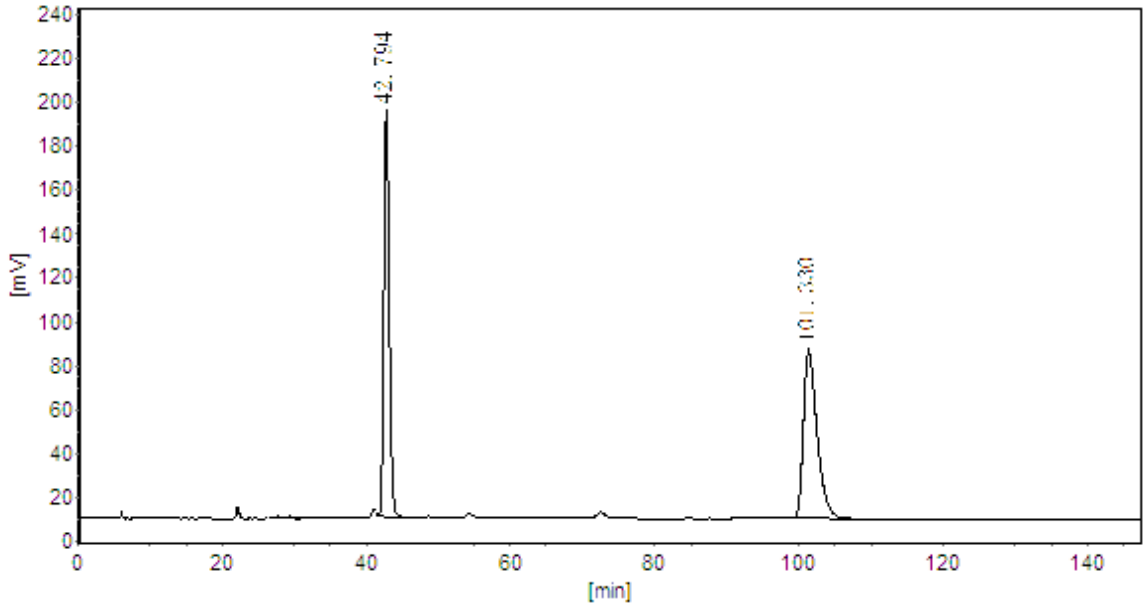
DEFAULT REPORT

Peak #	Time [min]	Area [µv.s]	Height [µv]	Area [%]
1	13.712	2545875	120419	73.68226
2	17.472	909332	36365	26.31774

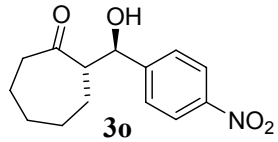
3o (Racemic)



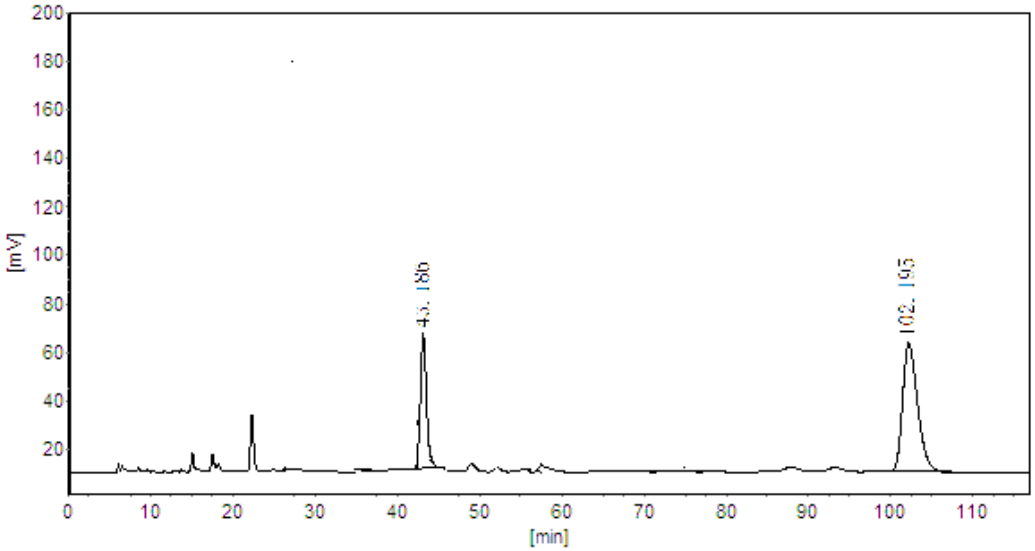
3o



3o (Chiral)



3o



DEFAULT REPORT

Peak #	Time [min]	Area [µv.s]	Height [µv]	Area [%]
1	43.186	2295360	49182	25.49841
2	102.195	6706615	52659	74.50159

References

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