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Graphical Abstract

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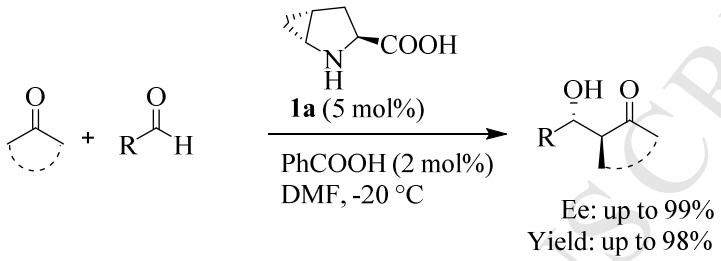

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ABSTRACT

The 4,5-methano-L-proline was studied for the direct asymmetric aldol reaction of acetone or cyclohexanone with various aromatic and aliphaticaldehydes at -20 °C or 0 °C. A loading of only 5mol% of derivative **1a** was employed in this catalytic system, and excellent enantioselectivities (up to 99% ee) and yields (up to 98% yield) could be achieved.

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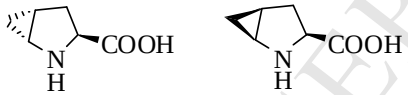
1. Introduction

The asymmetric direct aldol reaction is one of the most important carbon-carbon bond forming reactionsin organic synthesis, in particular in the synthesis of β-hydroxycarbonyl structural unit found in many natural products.[1] Since the publication of apioneering work by List and Barbas,[2] the asymmetric aldol reaction catalyzed by L-proline has been a representative reaction in the field of organocatalysis, after which extraordinary progress has been sought in order to find more selective and efficient catalytic systems for these direct aldol reaction.[3,4] A number of catalysts have been reported with a modified pyridine ring moiety of L-proline, making it effecting in asymmetric reactions. For example, the groups of Alexakis,[5] Wang,[6] Hayashi,[7] Zhao,[8] Palomo,[9] Jacobsen,[10] Chen,[11] and Loh,[12] among many others,[13,14] have developed a series of efficient proline-like catalysts (moleculescontaining a proline moiety) to improve the stereoselectivity in asymmetric reactions. However, the catalytic systems retain several shortcomings, such as: the low reaction activity, high catalyst loading requirements and unsatisfactory results. Thus, the search for highly efficient proline-like organocatalysts still remains a worthwhile endeavor.

The Hanessian group[15] had reported the synthesis of 4,5-methano-L-prolines and the enzymatic activity of the corresponding N-(3-mereapto-2-(R)-methyl-propionyl) analogs as inhibitors of angiotensin converting enzyme (Figure1). We found that these proline-like compounds are unique for their rigid bicyclic structure with two H atoms attached to the bridgehead C atoms lying on the same side of the ring. The X-ray structure and solid state conformational characteristics of its revealed considerable flattening of the pyrrolidine ring compared to L-proline. To the best of our knowledge, 4,5-methanoproline as a catalysis can surpass the venerable proline in conjugate additions of nitroalkanesto cyclic enonesin many cases.[15a] Recently, our group have used it as chiral organocatalysts in asymmetric Michael addition of aldehydes to nitroolefins, which afforded excellent diastereo- and enantioselectivities in high yields for a series of aldehydes and nitroolefins.[16] This paper concerns the application of 4,5-methano-L-prolines to asymmetric direct aldol reaction of various aldehydes with acetone or cyclohexanone. *trans*-4,5-methano-L-proline **1a** showed excellent catalytic behavior for these asymmetric reactions.



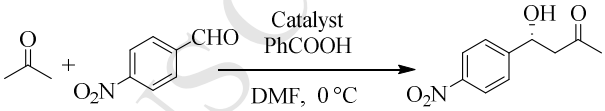
1a **1b**

Figure1. The structure of *trans*-4,5-methano-L-proline (**1a**) and *cis*-4,5-methano-L-proline (**1b**).

2. Results and discussion

We first applied **1a** and **1b** in the direct aldol reaction between acetone and *p*-nitrobenzaldehyde as the model reaction in DMF to determine the effect of different configurations of the catalyst used in the reaction. The results showed that high yields and excellent enantioselectivities could be obtained in the presence of catalyst **1a**, whereas a poorer yield and a moderate *ee* value were obtained with catalyst **1b** (Table 1, entries 1 and 2). Next, the effect of additive of this reaction was investigated. All of the acid additives dramatically improved the yield and enantioselectivity in the reaction (Table 1, entries 4-8). The best results were obtained with benzoic acid as the additive. The addition of trifluoroaceticacid also gave similar results with benzoic acid (entries 4 and 5). It could be concluded that the combination of organocatalyst **1a** and benzoic acid is crucial for the reactivity of this catalytic system. For further details, the loading of the additive was also studied. The reaction afforded a good *ee* value but only a moderate yield when a larger amount of additive was used (20 mol%; Table 1, Entry 13). However, a much higher yield was obtained when this reaction was carried out with 2-10 mol % of benzoic acid (Table 1, Entries 6, 14, and 15). Then, we tested a lower loading of catalyst **1a** in DMF. To our delight, the decreased catalyst loading (from 30 to 10 mol%) could still maintain the product yield and enantioselectivity (Table 1, Entries 4, 9 and 10). When further decreasing the amount of catalyst **1a** to 5 mol%, up to 85% yield and 95% enantioselectivity were obtained by extending the reaction time. Even with 2 mol% of catalyst **1a**, similar results were still obtained in this reaction (Table 1, Entry 12). Thus, the most efficient catalytic system involved 5 mol% of catalyst **1a** and 2 mol% of benzoic acid in DMF.

Table1. Influence of catalysts and additives for aldol reaction between acetone and 4-nitrobenzaldehyde[a]



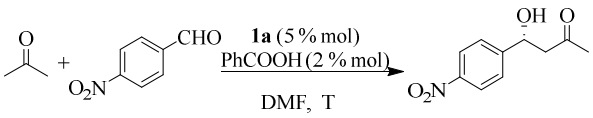
Entry	Catalyst (mol%)	Time (h)	Additive (mol%)	Yield (%)[b]	Ee (%)[c]
1	**1a** (30)	14	-	80	89
2	**1b** (30)	14	-	78	73
3[d]	**Proline**	14	-	68	76
4	**1a** (30)	6	PhCOOH (10)	90	98
5	**1a** (30)	6	TFA (10)	89	95
6	**1a** (30)	10	CH_3COOH (10)	85	90
7	**1a** (30)	9	TsOH (10)	86	90
8	**1a** (30)	11	TfOH (10)	75	92
9	**1a** (20)	8	PhCOOH (10)	91	96
10	**1a** (10)	7	PhCOOH (10)	89	95
11	**1a** (5)	9	PhCOOH (10)	85	95
12	**1a** (2)	12	PhCOOH (10)	83	92
13	**1a** (5)	9	PhCOOH (20)	70	91
14	**1a** (5)	9	PhCOOH (5)	84	92
15	**1a** (5)	9	PhCOOH (2)	82	95
16	**Proline**	9	PhCOOH (2)	85	92

[a]The reaction was carried out with acetone(2.5 mmol) and 4-nitrobenzaldehyde(0.5 mmol) at 0 °C in DMF (1 mL) according tothe general procedure.[b]Isolated yield.[c]Determined by chiralHPLC analysis by using a Chiralpak AS-H column, and the configurationwas assigned as R by comparison with the literaturedata.[d] The date come from ref. 2.

Influence of solvents on the reaction was further explored and the aldol reaction was successful in many organic solvents. The best enantioselectivity (95% ee) was achieved in DMF (Table 2,

entry 1). Although a slight difference in enantioselectivity was observed in THF and $CHCl_3$ (Table 2, entries 2 and 6), the reaction required longer reaction time. However, the enantiomeric excess decreased further when water was used as a solvent (Table 2, entry 4). When decreasing the reaction temperature to -20 °C, product 3a was obtained with 99% ee. It was found that the reaction temperature have an effect on improving the enantioselectivity of the aldol product.

Table 2.Influence of solvents and temperature for aldol reaction between acetone and 4-nitrobenzaldehyde catalyzed by **1a**[a]

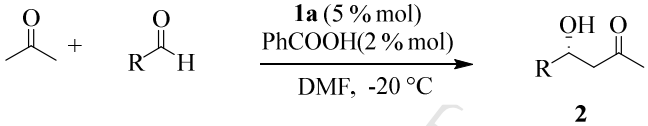


Entry	Solvent	Temp. (°C)	Time (h)	Yield (%)[b]	Ee (%)[c]
1	DMF	0	9	82	95
2	THF	0	11	82	91
3	MeCN	0	11	75	72
4	Water	0	14	73	45
5	Acetone	0	9.5	47	67
6	Chloroform	0	12	56	90
7	Toluene	0	13	80	58
8	DMF	-20	12	85	99

[a]The reaction was carried out with acetone(2.5 mmol) and 4-nitrobenzaldehyde(0.5 mmol) in solvent at suitable temperature according to the general procedure. [b]Isolated yield. [c]Determined by chiral HPLC analysis by using a Chiralpak AS-H column, and the configurationwas assigned as R by comparison with the literature data.

To increase the scope of the methodology, the aldol reaction was extended to several aromatic and aliphatic aldehydes and the results are summarized in Table 3. The reaction of acetone with aromatic aldehydes bearing electron-withdrawing group led to excellent enantioselectivities (97-99%) and high yields (85-92%) due to the strong electrophilicity of the substrates (Table 2, entries 2-9). The effect of steric hindrance on the reaction outcome has been tested. When an electron-withdrawing group was introduced at the ortho-position of the phenyl ring, product remain in high enantioselectivity (97-98%)(Table 2, entries 2, 4 and 6). Weak electrophilic aldehydes, such as 4-methylbenzaldhyde, required a longer reaction time to give the corresponding aldol products in moderate yield (Table 2, entry 10). The benzaldehyde and 2-naphthaldehyde reacted with acetone to generate the aldol product with extremely high enantioselectivities (Table 2, entries 1 and 12; ee up to 95% and 98%, respectively). Nevertheless, as for less-reactive aliphatic aldehydes such as isobutyraldehyde, only a trace amount of the aldol adduct could be obtained in this system (Table 2, entries 11 and 15). This may be due to the fact that the formation of imidazolidinethiones between isobutyraldehyde and the organocatalyst occurs more quickly in this reaction system. To expand the range of the substrates, compounds containing heterocyclessuch as furyl rings were also employed in this reaction, which proceeded with excellent enantioselectivities (up to 80% ee, entry 13). To show the practicality of the method, the reaction was testedat a large scale. Acetone (3.69 mL, 50.3 mmol) was allowed to react with benzaldehyde (1.27 mL, 12.5mmol) by using the catalyst **1a**(32 mg, 0.25 mmol) with benzoic acid as an additive in DMF (12.5 mL) at 0 °C. The reaction was complete in 16 h, and the aldol product was obtained in 86% yield and 93% ee (Table 2, entry 14).

Table 3. Scope of direct asymmetric aldol reactions of acetone with various aldehydes catalyzed by**1a**[a]

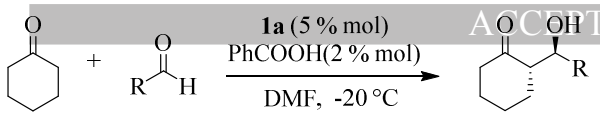


Entry	Product	R	Time (h)	Yield (%)[b]	Ee (%)[c]
1	**2a**	Ph	14	90	95
2	**2b**	2-$NO_2C_6H_4$	12	87	97
3	**2c**	4-$NO_2C_6H_4$	12	85	99
4	**2d**	2-BrC_6H_4	12.5	86	97
5	**2e**	4-BrC_6H_4	12.5	87	98
6	**2f**	2-$CF_3C_6H_4$	12	92	97
7	**2g**	4-$CF_3C_6H_4$	12	95	99
8	**2h**	4-FC_6H_4	13.5	88	98
9	**2i**	4-ClC_6H_4	13.5	92	97
10	**2j**	4-$CH_3C_6H_4$	15	81	98
11	**2k**	*i*Pr	15	<6	-
12	**2l**	2-Naphthyl	8.5	82	95
13	**2m**	2-Furyl	15	75	80
14[d]	**2n**	Ph	16	86	93
15[e]	**2o**	*i*Pr	12	<17	-
16	**2p**	4-$CO_2C_6H_4$	12	35	<5

[a]The reaction was carried out with acetone(2.5 mmol) and various aldehydes (0.5 mmol) in DMF at -20 °C according tothe general procedure. [b]Isolated yield. [c]Determined by chiral HPLC analysis by using a Chiralpak AS-H column, and the configurationwas assigned as R by comparison with the literaturedata. [d]The reaction was conducted with acetone (3.69 mL, 50.3 mmol) and benzaldehyde (40.0 mmol)) in the presence of catalyst **1a** (32 mg, 0.25 mmol) with benzoic acid as an additive in DMF (12.5 mL) at -20 °C. [e]The reaction was carried out at 25 °C.

Finally, to further examine the generality of this catalyticsystem, cyclohexanone was used as the aldol donor with different aromatic aldehydes. Up to 93% yield and excellent diastereoselectivity and enantioselectivity(86-99% ee) were obtained under the optimal reaction conditions (Table 4). For others type of ketone, such as 2,2-dimethyl-1,3-dioxan-5-one and 3,4-dihydronaphthalen-1(2H)-onewas also reacted with *p*-nitrobenzaldehyde to generate the aldol product with extremely high enantioselectivities (Figure.2, ee up to 96% and 91%, respectively).

Table 4. Scope of direct asymmetric aldol reactions of cyclohexanone with various aldehydes catalyzed by**1a**[a]



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Entry	Product	R	Time (h)	Yield (%)[b]	*Anti/sync*[c]	Ee (%)[d]
1	**3a**	Ph	18	93	98:2	95
2	**3b**	4-$CH_3OC_6H_4$	16	87	97:3	96
3	**3c**	4-$NO_2C_6H_4$	21	90	96:4	99
4	**3d**	4-ClC_6H_4	19	86	97:3	97
5	**3e**	4-$CF_3C_6H_4$	17	87	96:4	98
6	**3f**	2-Naphthyl	15	92	94:6	96
7	**3g**	2-Furyl	16	91	93:7	86

[a]The reaction was carried out with cyclohexanone(2.5 mmol) and various aldehydes(0.5 mmol) in DMF at -20 °C according to the general procedure. [b]Isolated yield. [c]Determined by ^{1}H NMR of the crudeproduct. [d]Determined by chiral-phase HPLC analysis of the *anti* product.

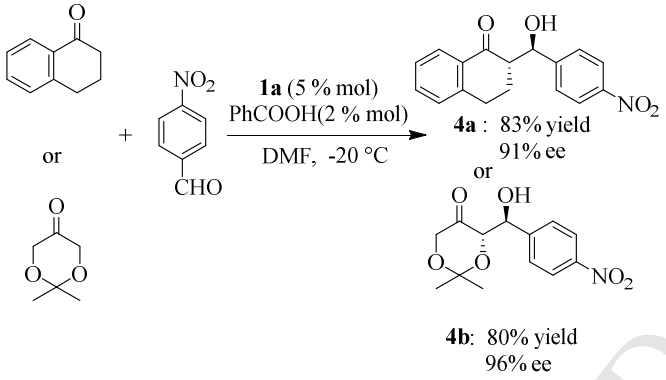

Figure2. The 2,2-dimethyl-1,3-dioxan-5-one and 3,4-dihydronaphthalen-1(2H)-one reacted with *p*-nitrobenzaldehyde.

3. Conclusion

In summary, *trans*-4,5-methano-L-proline **1a** is a very highly efficient chiral organocatalyst for the asymmetric aldol reactions of various aldehydes with acetone or cyclohexanone. Moreover, it is worthwhile to highlight that thereactions could achieve high enantioselectivity ranging from 84 to 99%*ee* and up to 98% yield by employing only 5 mol% of organocatalyst **1a**. The advantages of this catalytic system are clear, and it is to some extent a green and atom economical approach. Further application of 4,5-methano-L-prolineorganocatalysts to other important asymmetric reactions is underway.

4. Experimental section

4.1. General

All ^{1}H NMR spectra were recorded on Bruker AV 300 or Varianmercury Plus 400 using $CDCl_3$ as solvent and TMS as internal standard unless otherwise noted, chemicalshifts are given in(ppm) and coupling constants (*J*) in Hz. HRMS was performed on Analysis Center of Shanghai Institute of Technology University. The Enantioselectivity was measured by high performance liquid chromatography (HPLC) using chiral column (Chiralcel OD, AD, AS, OJ, OZ) with hexane/2-propyl alcohol as eluent. Column chromatography was performed using 300-400 mesh silica gel. All commercially available substrates were used as received.

4.2. General Procedure for the asymmetric aldol reaction

To amixture of catalyst **1a** and benzoic acid in DMF (1 mL) was addedacetone (0.2 mL, 2.5 mmol, 5 equiv.). Then, the aldehyde(0.5 mmol, 1 equiv.) was added at 0 °C. After TLC analysis indicatedcomplete consumption of the starting material, the reactionmixture was quenched with saturated NH_4Cl aqueous solution, extracted with EtOAc, and dried with anhydrous Na_2SO_4. The crude product was purified by flash silica gel chromatography (hexane/EtOAc) to afford pure aldol products. All aldol products are knowncompounds, and their spectroscopic data are identical to those reportedin the literature. The *ee* values were determined by chiral HPLC analysis.

4.2.1.(R)-4-Hydroxy-4-phenyl-butan-2-one (**2a**).[17]

According to the general procedureto give pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.18 (s, 3H), 2.82 (m, 2H), 3.37 (brs, 1H), 5.15 (m, 1H), 7.28-7.35 (m,5H). Enantiomeric excess: 95%, determined by HPLC (Daicel Chiralpak AS-H, *i*-PrOH/Hexane =15/ 85), UV 220 nm, flow rate 1.0 mL/min. *R*-isomer, t_R= 10.1 min and *S*-isomer, t_R= 11.5 min.

4.2.2.(R)-4-Hydroxy-4-(2'-nitrophenyl)-butan-2-one (**2b**).[17]

According to the general procedureto give pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.23 (s, 3H), 2.73-3.10 (m, 2H), 3.79 (brs, 1H), 5.65-5.67(m, 1H), 7.41(t, 1H), 7.66 (t, 1H), 7.87-7.96 (dd, *J* = 8.1, 25.5 Hz, 2H). Enantiomeric excess: 99%, determined by HPLC (Daicel Chiralpak AS-H, *i*-PrOH/Hexane = 30/70), UV 220 nm, flow rate 1.0 mL/min. *R*-isomer, t_R =13.1min and *S*-isomer, t_R = 9.5 min.

4.2.3.(R)-4-Hydroxy-4-(2'-nitrophenyl)-butan-2-one (**2c**).[18]

According to the general procedureto give pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.19 (s, 3H), 2.83-2.84 (m, 2H), 3.68 (brs, 1H), 5.24 (m, 1H), 7.50-7.52(d, *J*= 8.4 Hz, 2H), 8.14-8.16 (d, *J* = 8.4 Hz, 2H). Enantiomeric excess: 95%, determined by HPLC (Daicel Chiralpak AS-H, *i*-PrOH/Hexane=30/70), UV 254 nm, flow rate 1.0 mL/min. *R*-isomer, t_R= 17.2min and *S*-isomer, t_R=23.1 min.

4.2.4.(R)-4-Hydroxy-4-(2'-bromophenyl)-butan-2-one (**2d**).[18]

According to the general procedureto give pale yellow oil.^{1}H NMR (400 MHz, $CDCl_3$): δ 2.12(s, 3H), 2.52-2.61(m, 1H), 2.86-2.92(m, 1H) 3.58-3.59 (d, *J* = 3.2 Hz,1H), 5.34-5.37(m, 1H), 7.02-7.07(t, 1H), 7.23-7.28 (t,1H), 7.40-7.53(dd, *J*= 7.7, 32.2 Hz, 2H) .Enantiomeric excess: 98%, determined by HPLC (Daicel Chiralpak AS-H, i-PrOH/Hexane=15/85), UV 220 nm, flow rate 1.0 mL/min. *R*-isomer, t_R = 13.0 min and *S*-isomer, t_R = 9.3 min.

4.2.5.(R)-4-Hydroxy-4-(4'-bromophenyl)-butan-2-one (**2e**).[19]

According to the general procedure to give pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.24 (s, 3H), 2.73-2.75 (m, 1H), 3.12-3.17 (m, 1H), 3.70 (m, 1H), 5.67-5.69 (m, 1H), 7.44-7.46 (d, *J* = 8.4 Hz, 2H), 7.89-7.97 (d, *J*= 8.4 Hz, 2H). Enantiomeric excess: 96%, determined by HPLC (Daicel Chiralpak AS-H, *i*-PrOH/Hexane=10/90), UV 220 nm, flow rate 1.0mL/min. *R*-isomer, t_R = 17.7 min and *S*-isomer, t_R = 23.4 min.

4.2.6.(R)-Hydroxy-4-(2'-(trifluoromethyl)phenyl)-butan-2-one(**2f**).[19]

According to the general procedure to give pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.19(s, 3H), 2.75-2.78(m, 2H), 3.66-3.67 (m, 1H), 5.55-5.57(m, 1H), 7.37-7.40(t, 1H), 7.59-7.62(m, 2H), 7.80-7.82 (m, 1H). Enantiomeric excess: 99%, determined

by HPLC (Daicel Chiralpak AS-H, *i*-PrOH/Hexane=10/90), UV 254 nm, flow rate 1.0 mL/min. *R*-isomer, t_R = 11.6min and *S*-isomer, t_R = 7.4 min.

4.2.7.(R)-Hydroxy-4-(4'-(trifluoromethyl)phenyl)-butan-2-one (**2g**).[19]

Accordingto the general procedure to give pale yellow oil.^{1}H NMR (400 MHz, $CDCl_3$): δ 2.20 (s, 3H), 2.84 (d, *J*= 6.3 Hz, 2H), 3.48 (d, *J* = 3.2 Hz, 1H), 5.21 (m, 1H), 7.48(d, *J*= 8.1 Hz, 2H), 7.61 (d, *J* = 8.1 Hz, 2H). Enantiomeric excess: 98%, determined by HPLC (Daicel Chiralpak AS-H, i-PrOH/Hexane=10/90), UV 254 nm, flow rate 1.0 mL/min. *R*-isomer, t_R = 9.2 min and *S*-isomer, t_R = 7.8 min. = 7.4Hz, 3H).

4.2.8.(R)- 4-Hydroxy-4-(4'-fluorophenyl)-butan-2-one (**2h**).[19]

According to the general procedure to give pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.19 (s, 3H), 2.74-2.90 (m, 2H), 3.32 (brs, 1H), 5.13 (m, 1H), 7.03 (m, 2H), 7.30 (m, 2H). Enantiomeric excess: 98%, determined by HPLC (Daicel Chiralpak AS-H, *i*-PrOH/Hexane =10/90), UV 220 nm, flow rate 1.0 mL/min. *R*-isomer, t_R =12.4 min and *S*-isomer, t_R =13.8 min.

4.2.9.(R)-4-Hydroxy-4-(4'-chlorophenyl)-butan-2-one (**2i**).[19]

According to thegeneral procedure to give pale yellow oil. ^{1}H NMR (400 MHz,$CDCl_3$): δ 2.18 (s, 3H), 2.82 (m, 2H), 3.46 (brs, 1H), 5.11 (m, 1H), 7.29 (m, 4H). Enantiomeric excess: 98%, determined by HPLC (Daicel Chiralpak AS-H, *i*-PrOH/Hexane =10/90), UV220 nm, flow rate 1.0 mL/min. *R*-isomer, t_R = 16.9 min and *S*-isomer, t_R = 20.9 min.

4.2.10.(R)-4-Hydroxy-4-(4-methylphenyl)-butan-2-one (**2j**).[19]

According to the general procedure to give pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.20 (s, 3H), 2.35 (s, 3H) 2.77-2.88 (m, 2H), 3.32 (s, 1H), 5.25 (d, *J* = 8.7Hz, 2H), 7.17 (d, *J* = 7.8 Hz, 2H), 7.26 (d, *J* = 7.8 Hz, 2H). Enantiomeric excess: 98%, determined by HPLC (Daicel Chiralpak AS-H, *i*-PrOH/Hexane = 10/90), UV 220 nm, flow rate 1.0 mL/min. *R*-isomer, t_R = 10.6 min and *S*-isomer, t_R = 13.4 min.

4.2.11.(R)-4-Hydroxy-4-(naphthalene-2-yl)butan-2-one (**2l**).[19]

According to the general procedure to give pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.21 (s, 3H), 2.95 (m, 2H), 3.44 (brs, 1H), 5.34 (m,1H), 7.43 (m, 1H),7.83 (m, 4H), 7.94-8.01(m, 2H). Enantiomeric excess: 96%, determined by HPLC (Daicel Chiralpak AS-H, *i*-PrOH/Hexane=30/70), UV 254nm, flow rate 1.0 mL/min. *R*-isomer, t_R = 15.0 min and *S*-isomer, t_R = 16.8 min.

4.2.12.(R)-4-Hydroxy-4-(2'-furyl) -butan-2-one (**2m**).[19]

According to the general procedure to give pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.13(s, 3H), 2.75-2.78(m, 2H) 3.66-3.67 (m, 1H), 4.98-5.05(m, 1H),6.37-6.40(m, 1H), 6.47-6.51(m, 1H) 7.67-7.72 (m,1H). Enantiomeric excess: 84%, determined by HPLC (Daicel Chiralpak AS-H, *i*-PrOH/Hexane=30/70), UV 254nm, flow rate 1.0 mL/min. *R*-isomer, t_R = 6.9min and *S*-isomer, t_R = 9.3 min.

4.2.13.(2S,1'R)-2-(hydroxy(phenyl) methyl) cyclohexan-1-one (**3a**).[20]

According to the general procedureto give pale yellow oil. ^{1}H NMR (400 MHz,$CDCl_3$): δ 7.50-7.24 (5H, m), 4.80(1H, d, *J* = 9.0 Hz), 4.00 (1H, m), 2.70-2.56 (1H, m), 2.55-2.44 (1H, m), 2.34 (1H, td, *J* = 12.3, 5.4Hz), 2.16-2.03 (1H, m), 1.87-1.73 (1H, m), 1.72-1.50 (3H, m), 1.40-1.22 (1H, m). Enantiomeric excess: 96%, determined by HPLC (Daicel Chiralpak OD-H, *i*-PrOH/Hexane= 10/90), UV 254nm, flow rate 0.5 mL/min. t_R *(major) = 22.3 min,* t_R *(minor) = 31.9 min.*

4.2.14.(2S,1'R)-2-(hydroxy(4-methoxyphenyl)methyl) cyclohexan-1-one (**3b**).[20]

According to the general procedure to give pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 (2H, d, *J* =8.4 Hz), 6.88 (2H, d, *J* = 8.7 Hz), 4.74 (1H, dd, *J* = 8.7, 2.4 Hz), 3.93 (1H, d, *J* = 2.7 Hz), 3.80 (3H, s), 2.65-2.49 (1H, m), 2.52-2.43 (1H, m), 2.35 (1H, td, *J* = 12.9, 5.4 Hz), 2.15-2.04 (1H, m),1.84-1.73 (1H, m), 1.70-1.45 (3H, m), 1.36-1.24 (1H, m). Enantiomeric excess: 97%, determined by HPLC (Daicel Chiralpak AS-H, *i*-PrOH/Hexane = 10/90), UV 254nm, flow rate 0.5 mL/min. t_R *(major) = 60.9 min,* t_R *(minor) = 64.2 min.*

4.2.15.(2S,1'R)-2-(hydroxy(4-Nitrophenyl) methyl) cyclohexan-1-one (**3c**).[20]

According to the general procedure to give pale yellow oil. ^{1}H NMR (400MHz, $CDCl_3$): δ 8.21 (2H, d, *J* = 8.7 Hz), 7.51 (2H, d, *J* = 8.7 Hz), 4.90 (1H, dd, *J* = 8.4, 3.0 Hz), 4.09 (1H, d, *J* = 3.0 Hz), 2.65-2.45 (2H,m), 2.36 (1H, td, *J* = 13.2, 5.7 Hz), 2.17-2.06 (1H, m), 1.87-1.78 (1H, m), 1.67-1.51 (3H, m),1.45-1.31 (1H, m). Enantiomeric excess: 90%, determined by HPLC (Daicel Chiralpak AD-H, *i*-PrOH/Hexane= 20/80), UV 254nm, flow rate 0.5 mL/min. t_R *(major) = 41.3min,* t_R *(minor) = 52.6 min.*

4.2.16.(2S,1'R)- 2-(4-chlorophenyl)(hydroxy) methyl) cyclohexan-1-one (**3d**).[20]

According to the general procedure to give pale yellow oil. ^{1}H NMR (400MHz, $CDCl_3$): δ 7.29 (4H, dd, *J* = 20.4,8.4 Hz), 4.76 (1H, dd, *J* = 8.7, 2.7 Hz), 3.99 (1H, d, *J* = 3.0 Hz), 2.61-2.44 (2H, m), 2.35 (1H, td, *J* = 12.9, 5.4 Hz), 2.15-2.05 (1H, m), 1.85-1.75 (1H, m), 1.70-1.50 (3H, m), 1.37-1.20 (1H, m). Enantiomeric excess: 98%, determined by HPLC (Daicel Chiralpak AD-H, *i*-PrOH/Hexane= 10/90), UV 254 nm, flow rate 0.5 mL/min. t_R *(major) = 26.5 min,* t_R *(minor) = 31.8 min.*

4.2.17.(2S,1'R)-2-(hydroxyl(4-trifluoromethyl)phenyl)methyl)cyclohexan-1-one (**3e**).[21]

According to the general procedure to give pale yellow oil. ^{1}H NMR (400MHz, CDCl3): δ 7.74-7.55 (3H, m), 7.40-7.38(1H, t, *J* = 7.2 Hz), 5.30 (1H, d, *J* = 9.3 Hz), 4.03 (1H, t, *J* = 3.0 Hz), 2.81-2.69 (1H, m), 2.55-2.45(1H, m), 2.37 (1H, td, *J* = 12.9, 4,8 Hz), 2.15-2.03 (1H, m), 1.81-149 (3H, m), 1.48-1.23 (1H, m). Enantiomeric excess: 97%, determined by HPLC (Daicel Chiralpak AD-H, *i*-PrOH/Hexane= 10/90), UV 254nm, flow rate 0.5 mL/min. t_R *(major) = 32.9 min,* t_R *(minor) = 35.2 min.*

4.2.18.(2S,1'R)-2-(hydroxy(naphthalene-2-yl) methyl) cyclohexan-1-one (**3f**).[21]

According to the general procedure to give pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87-7.78 (3H, m), 7.75 (1H, s), 7.47 (3H, d, *J* = 7.2 Hz), 4.96 (1H, d, *J* = 8.7 Hz), 4.08 (1H, s), 2.77-2.65 (1H, m),2.55-2.44 (1H, br-d, *J* = 13.8 Hz), 2.36 (1H, td, *J* = 12.9, 5.7 Hz), 2.14-2.00 (1H, m), 1.80-1.36 (5H, m). Enantiomeric excess: 93%, determined by HPLC (Daicel Chiralpak AD-H, *i*-PrOH/Hexane= 10/90), UV 254nm, flow rate 0.5 mL/min. t_R *(major) = 47.5 min,* t_R *(minor) = 54.7 min.*

4.2.19.(2S,1'R)-2-furan-2-yl(hydroxy)methyl) cyclohexan-1-one (**3g**).[21]

According to the general procedure to give pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (1H, d, J = 0.6 Hz), 6.33 (1H, dd, J = 3.0, 1.8 Hz), 6.28 (1H, d, J = 3.0 Hz), 4.83 (1H, dd, J = 8.4, 3.9 Hz), 3.88 (1H, d,J = 3.9 Hz), 2.97-2.86 (1H, m), 2.52-2.30 (2H, m), 2.17-2.04 (1H, m), 1.89-1.78 (1H, m), 1.75-1.56 (3H, m), 1.44-1.30 (1H, m). Enantiomeric excess: 94%, determined by HPLC (Daicel Chiralpak AD-H, *i*-PrOH/Hexane= 10/90), UV 254nm, flow rate 0.5 mL/min. t_R *(major) = 41.0 min*, t_R *(minor) = 43.8 min.*

4.2.20. (S)-4-((S)-Hydroxy(4-nitrophenyl)methyl)-2,2-dimethyl-1,3-dioxan-5-one (**4b**). [22]

According to the general procedureto give pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz), δ 8.19 (d, J =8.8 Hz, 2H), 7.60 (d,J = 8.6 Hz, 2H), 4.98 (d, J = 7.9 Hz, 1H), 4.28 (dd, J= 1.4,17.7 Hz, 1H), 4.09 (d, J = 17.7 Hz, 1H),3.82 (bs, 1H), 1.38 (s,3H), 1.21 (s,3H). Enantiomeric excess: 96%, determined by HPLC(Daicel Chiralpak AD-H, *i*-PrOH/Hexane= 10/90), UV 254nm, flow rate 0.5 mL/min. t_R *(major) = 27.8 min*, t_R *(minor) = 32.3 min.*

4.2.21(S)-2-((R)-hydroxy(4-nitrophenyl)methyl)-3,4dihydronaphthalen-1(2H)-on(**4a**).[23]

According to the general procedure to give pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (d, J = 8.8 Hz, 2H), 8.06 (d, J = 8.0 Hz, 2H), 7.59 (d, J = 8.8 Hz, 2H), 7.53-7.23 (m, 3H), 5.12 (d, J = 8.0 Hz, 1H), 5.03 (s, 1H), 2.90 (m, 2H),2.76 (m, 1H), 1.69 (m, 2H). Enantiomeric excess: 91%, determined by HPLC (Daicel Chiralpak AD-H, *i*-PrOH/Hexane= 10/90), UV 254nm, flow rate 0.5 mL/min. t_R *(major) = 35.7 min*, t_R *(minor) = 43.8 min.*

Acknowledgments

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Supplementary Material

Supplementary data related to this article can be found onlineat http://dx.doi.org/XXX

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Supporting Information for

The 4,5-methano-L-proline as a chiral Organocatalysts in Direct Asymmetric Aldol Reactions

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Table of Contents

1. Copies of NMR spectra of the product

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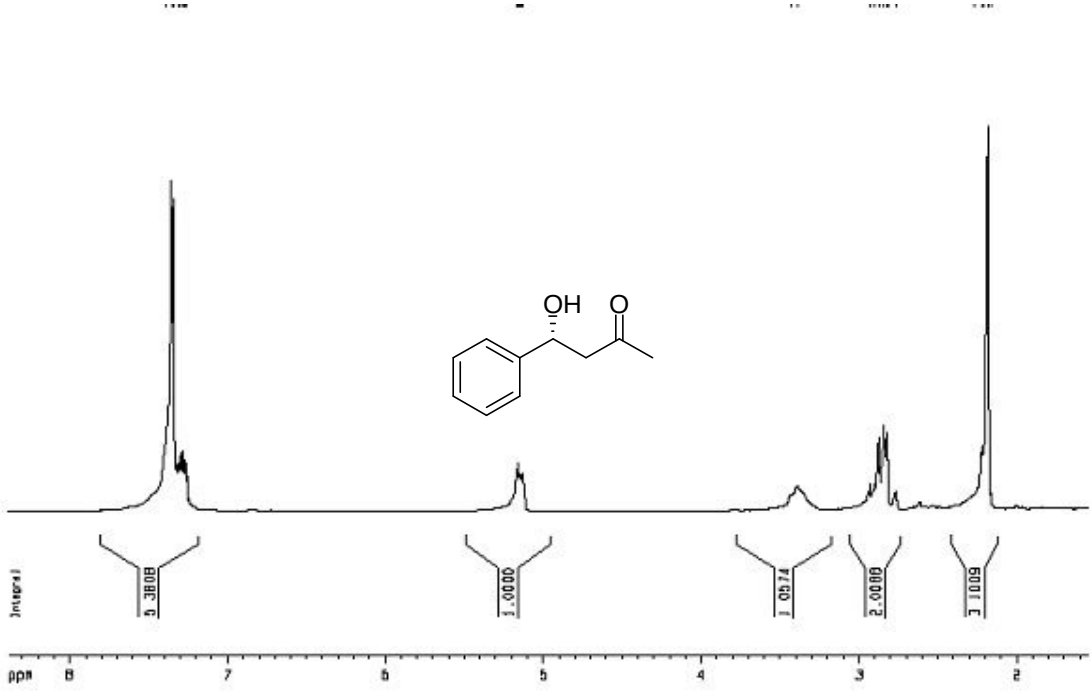

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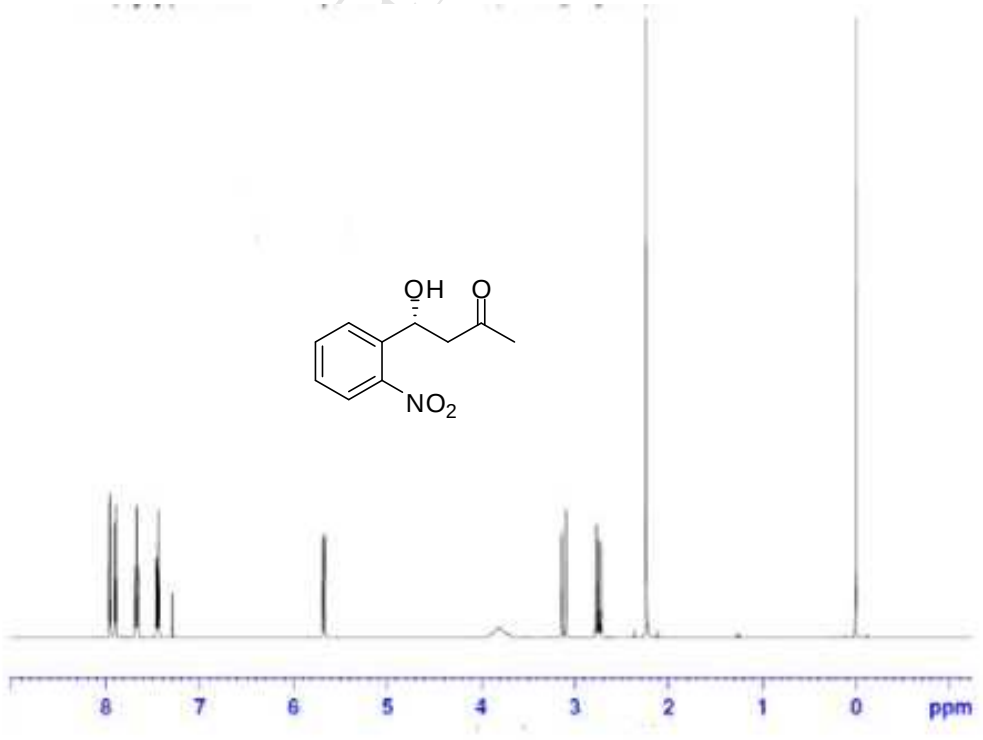

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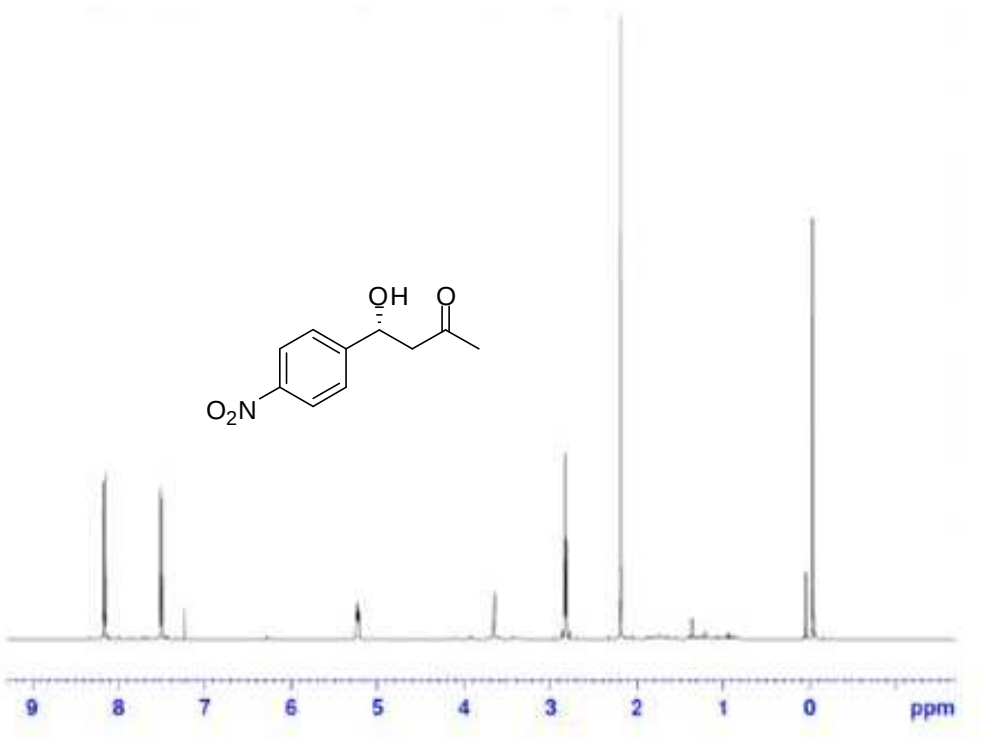

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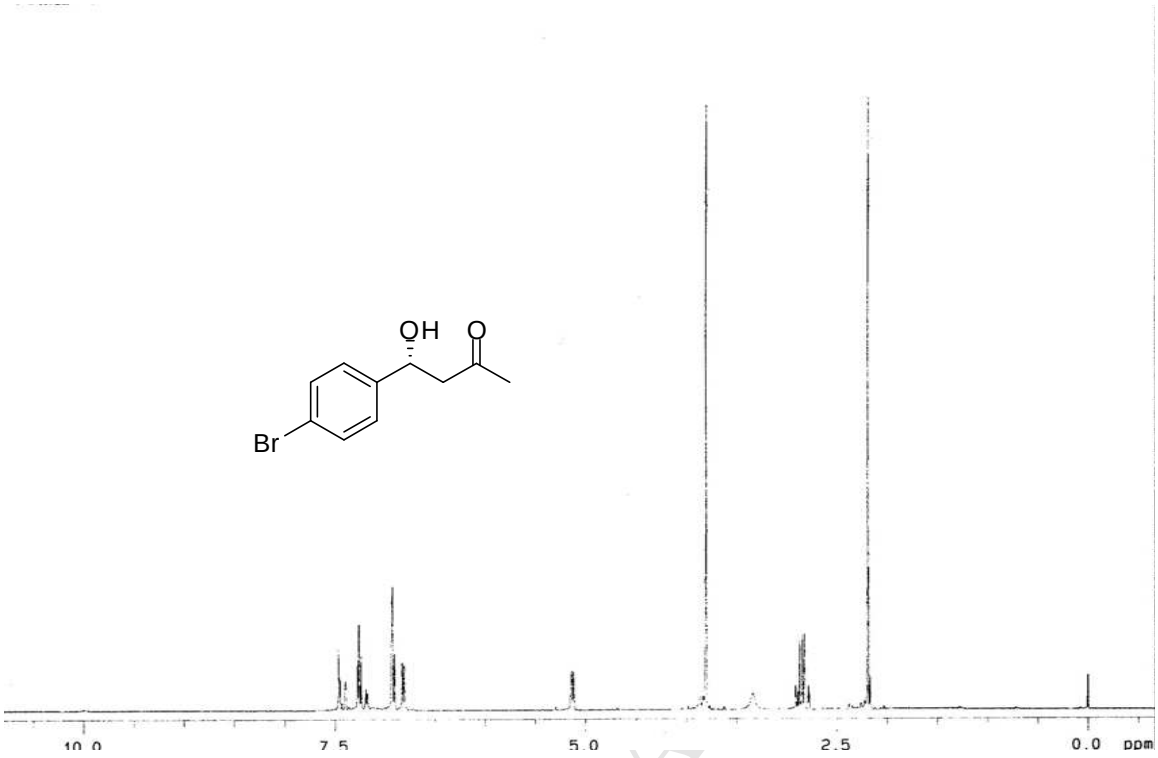

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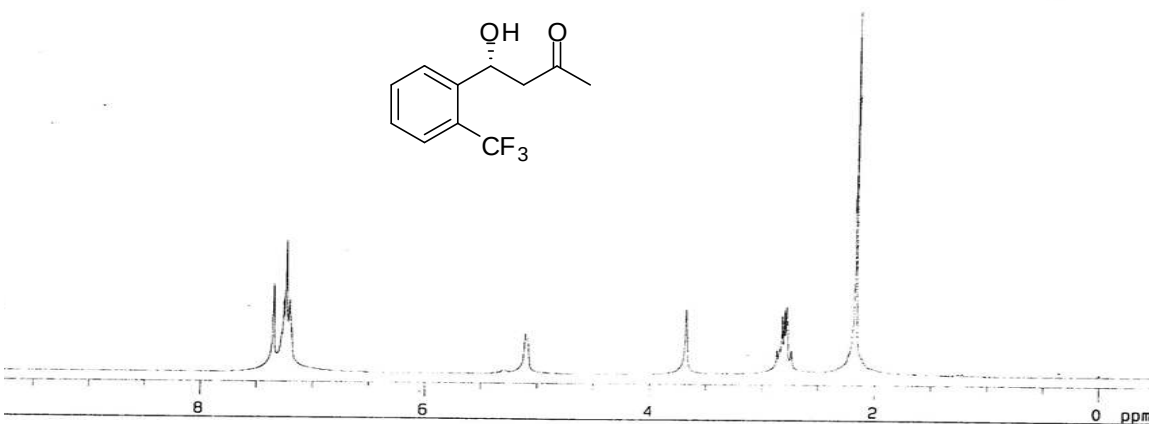

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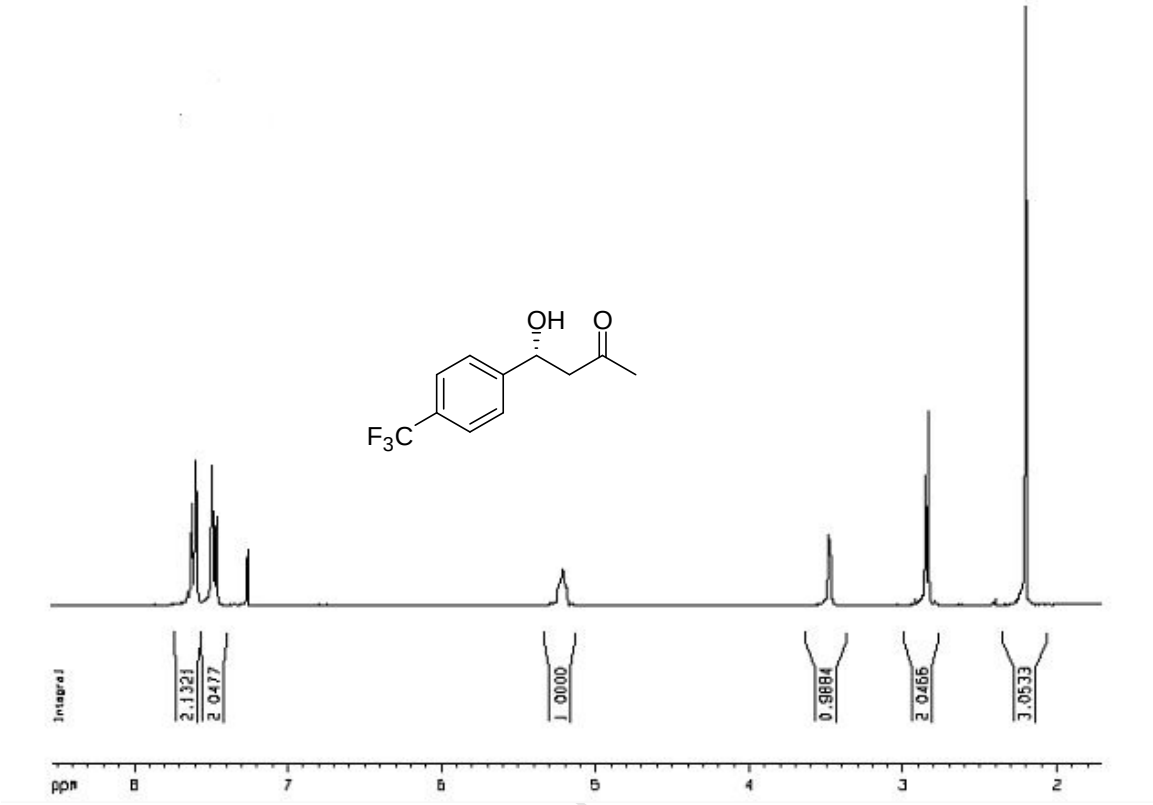

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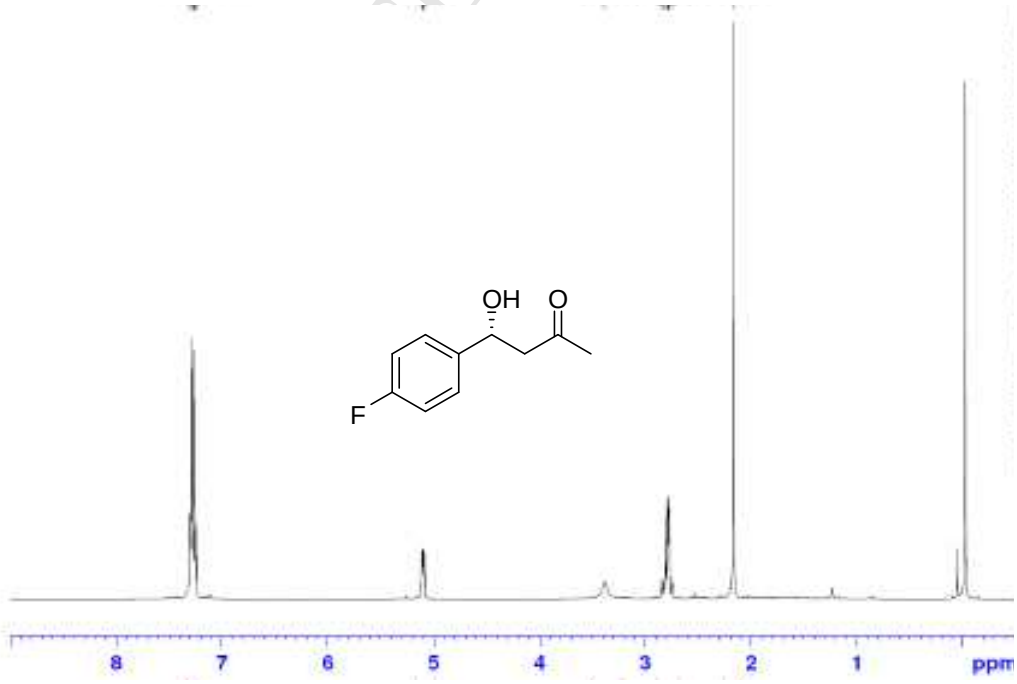

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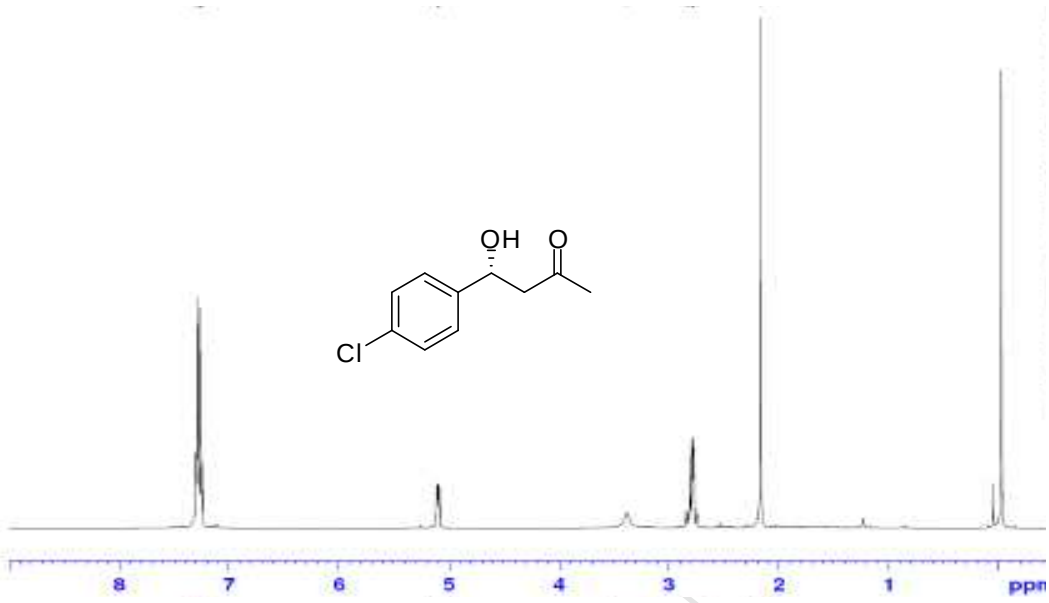

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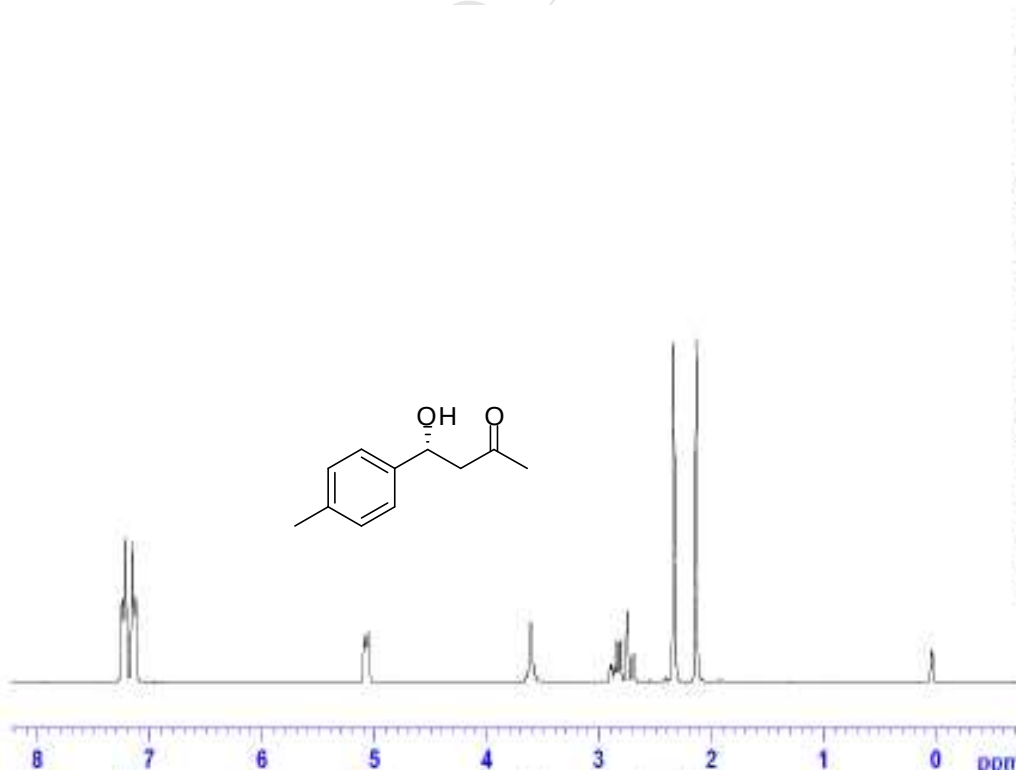

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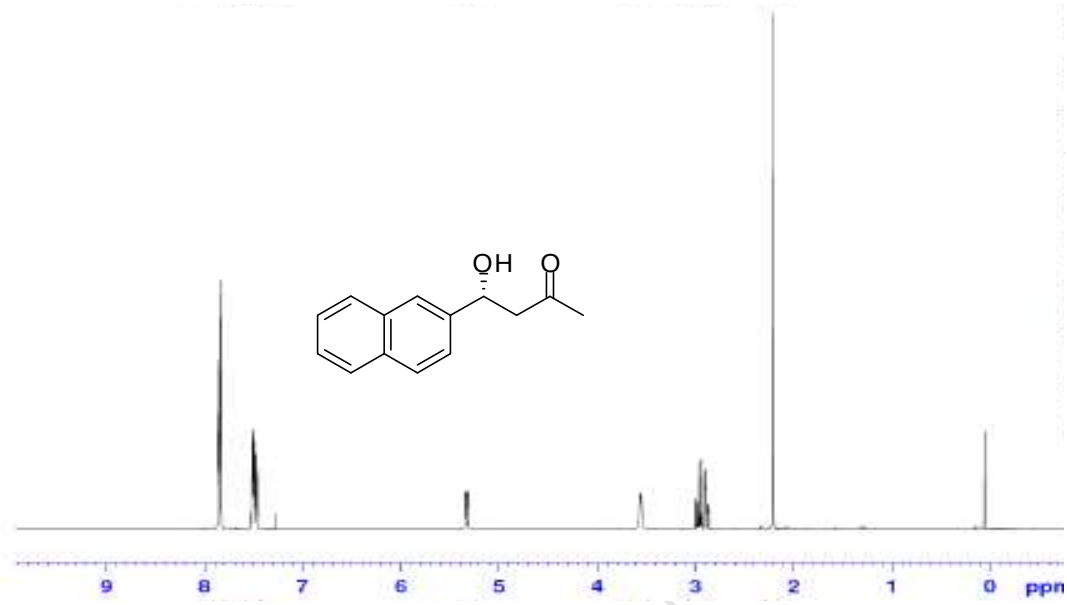
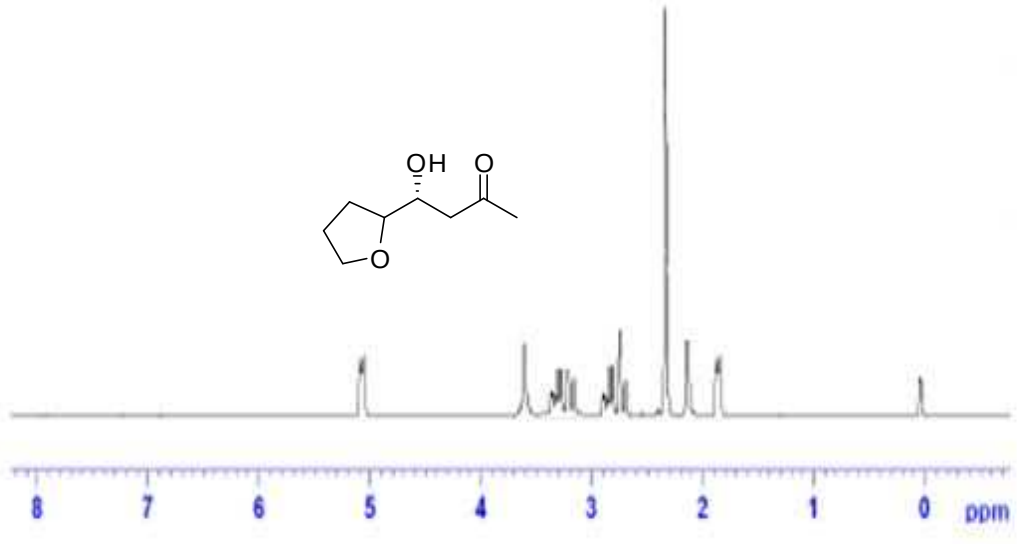
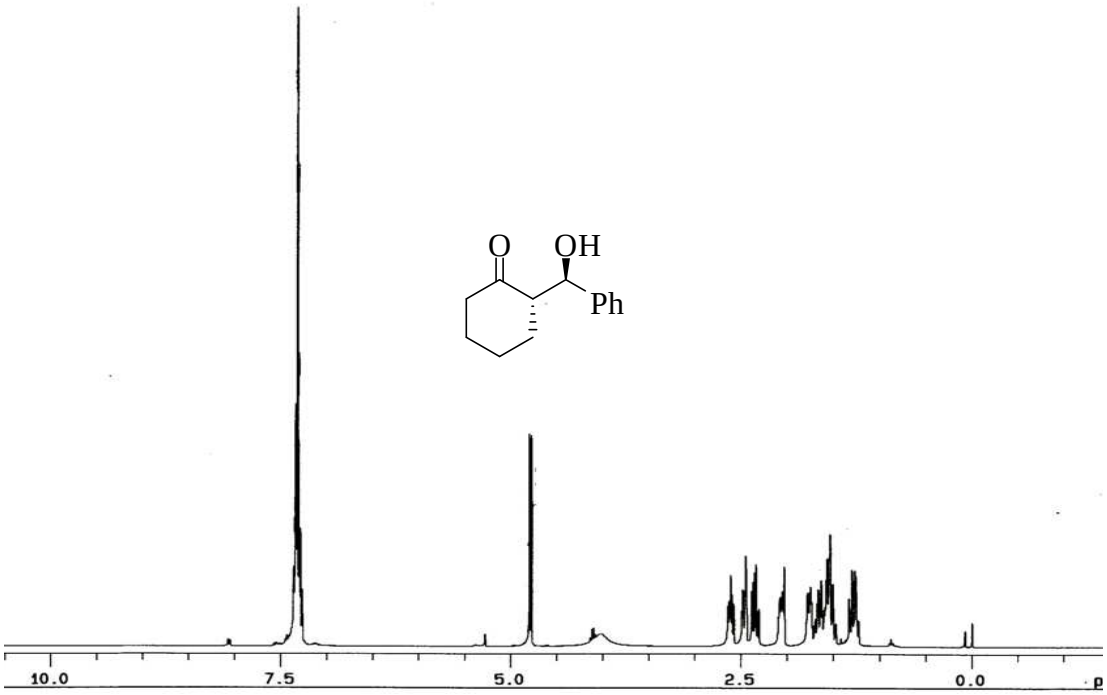


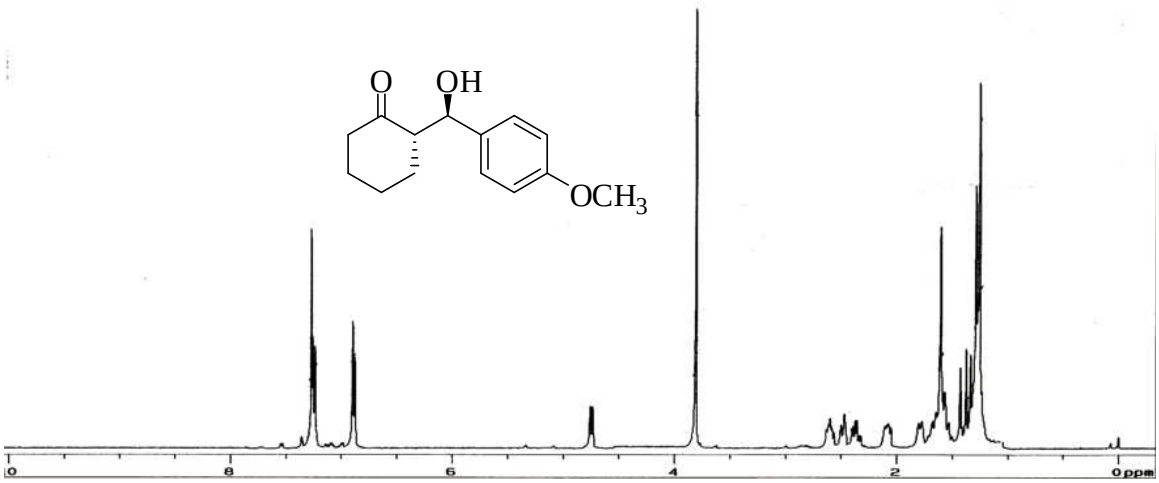
^{1}H NMR of 2m



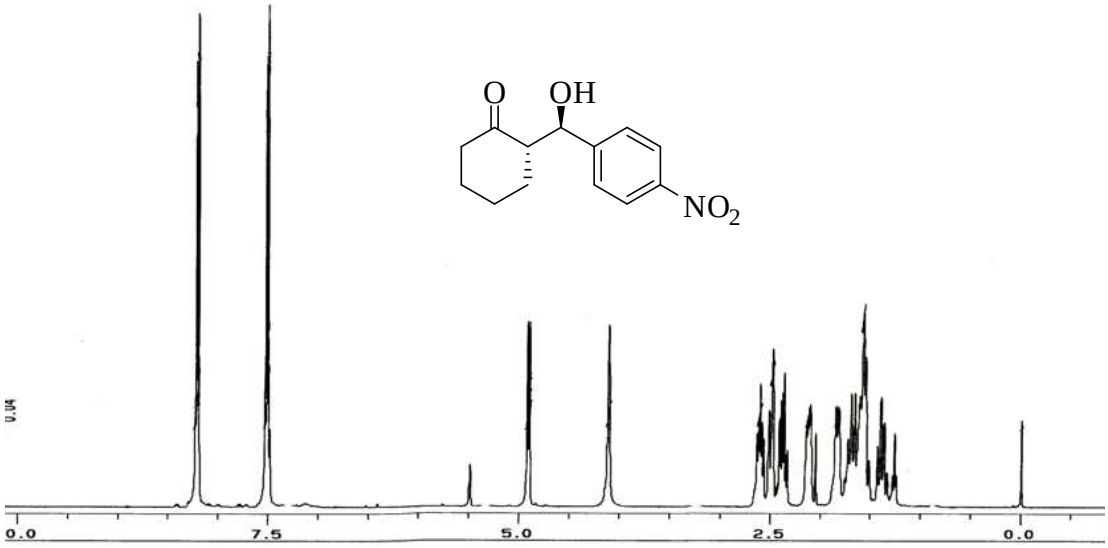
^{1}H NMR of 3a



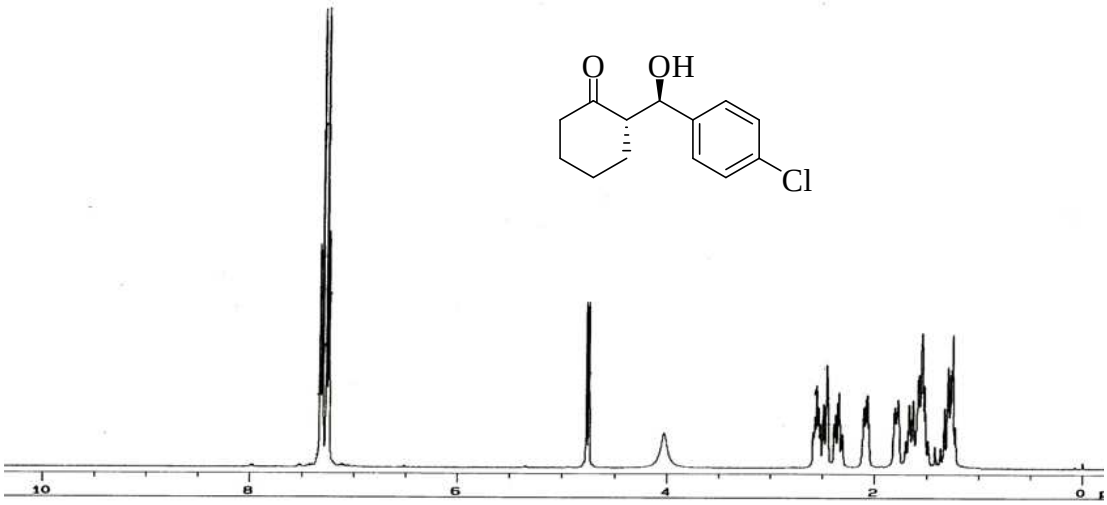
^{1}H NMR of 3 b



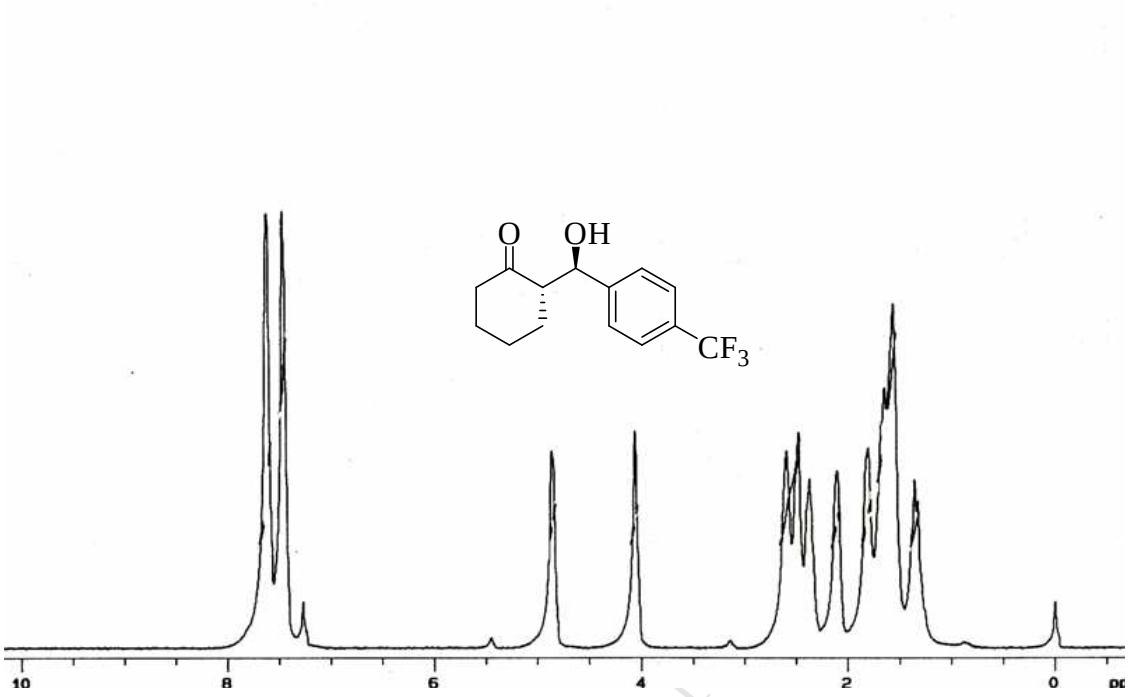
^{1}H NMR of 3 c



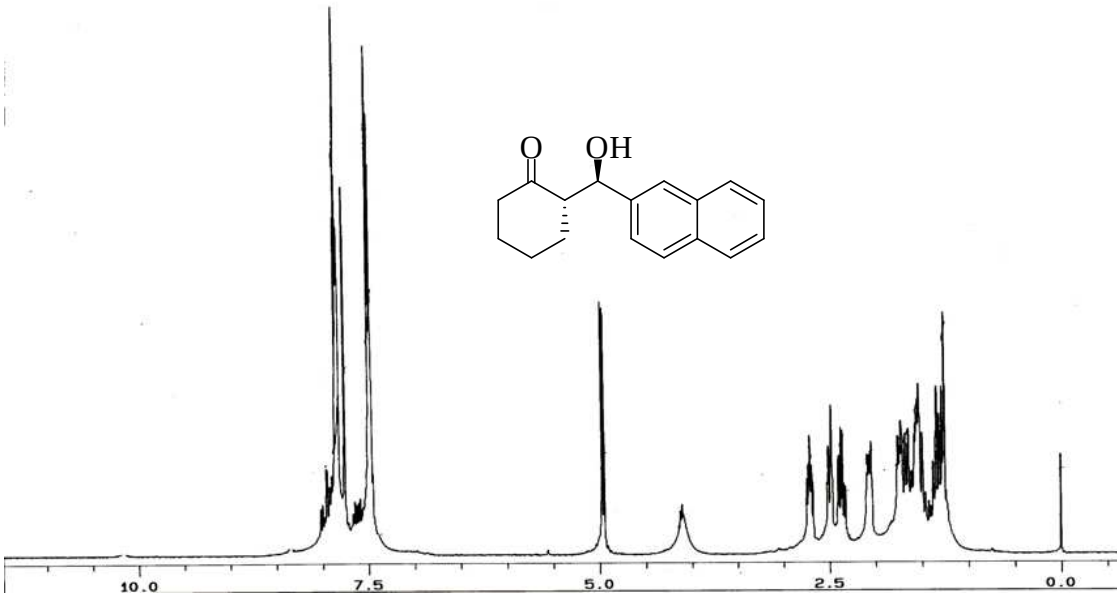
^{1}H NMR of 3 d



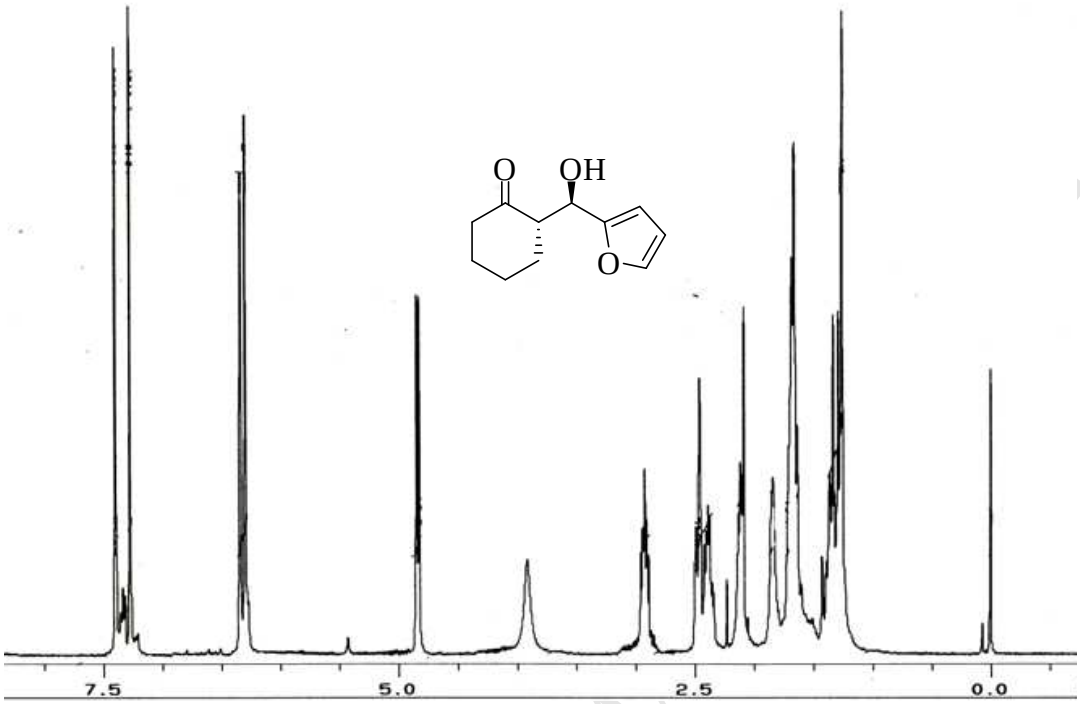
^{1}H NMR of 3 e



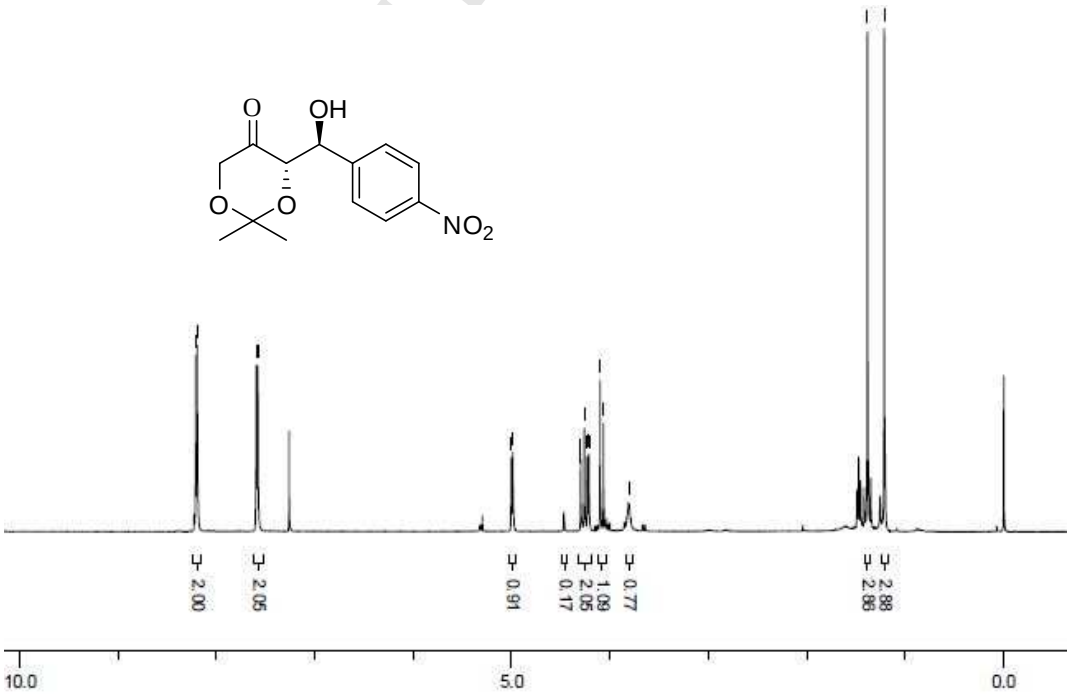
^{1}H NMR of 3 f



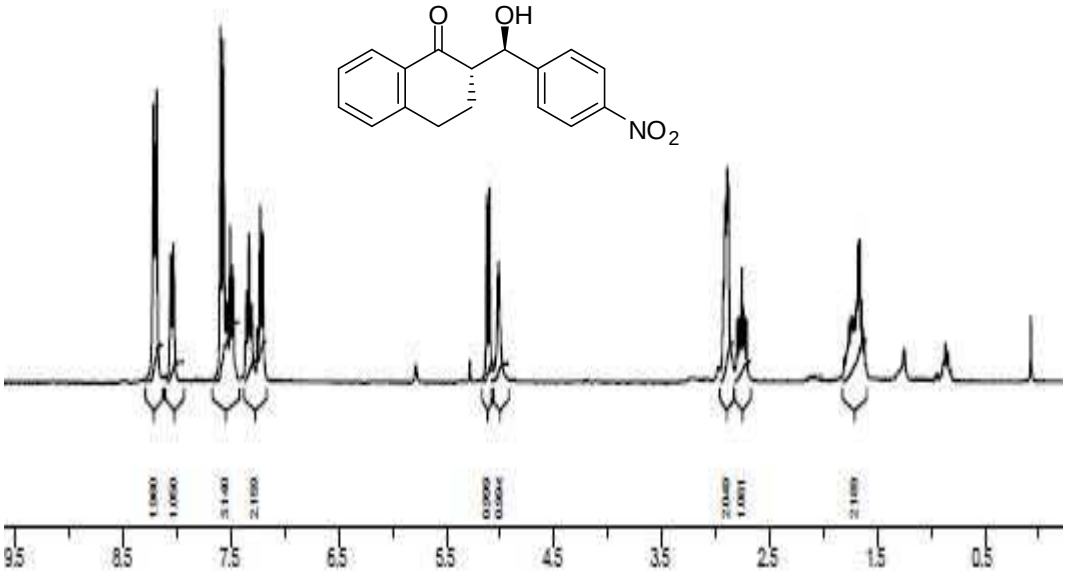
^{1}H NMR of 3g



^{1}H NMR of 4a



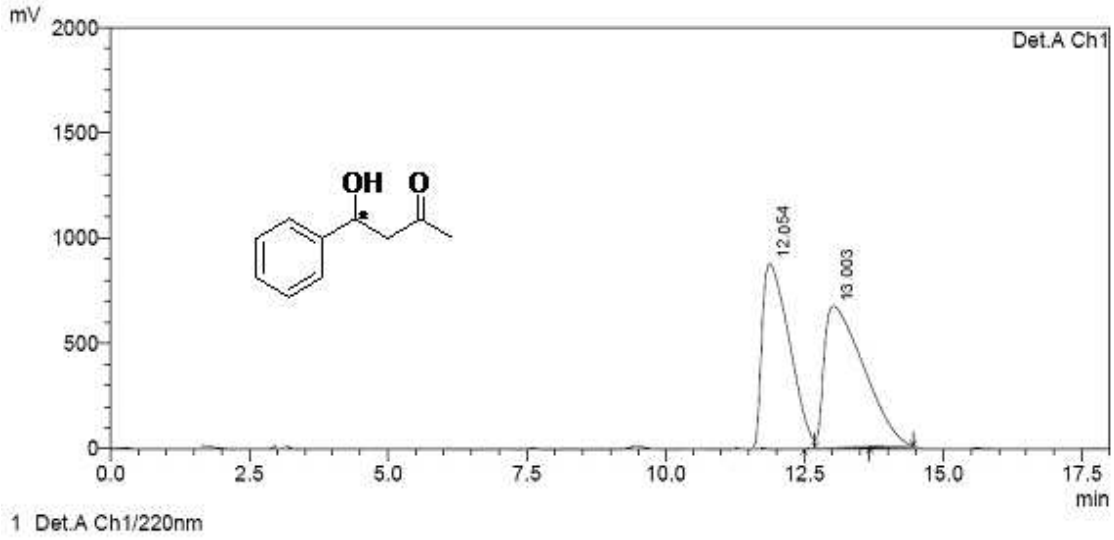
^{1}H NMR of 4b



HPLC Data of Products

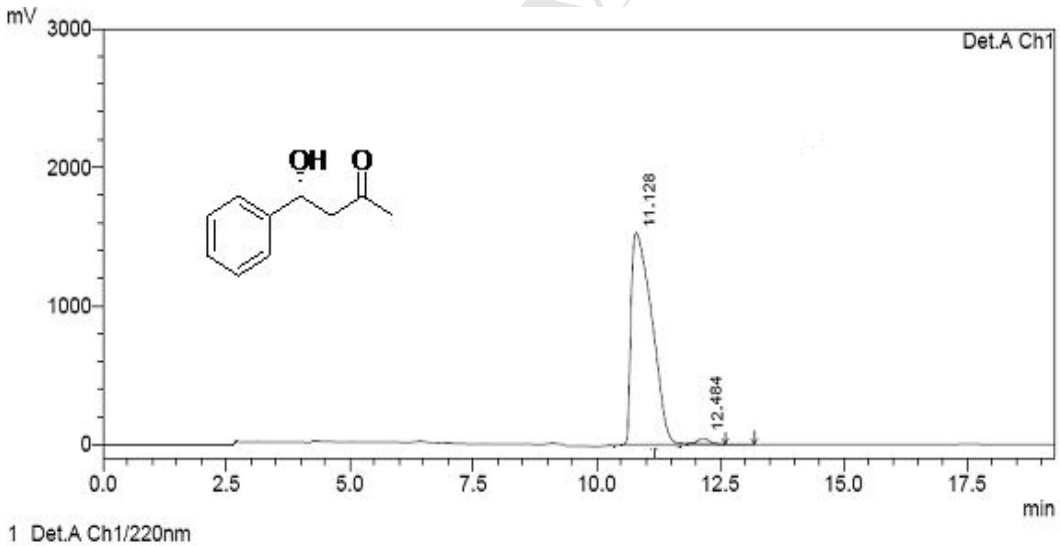
HPLC data of 2a

Racemic Sample



PeakTable

Catalytical Sample

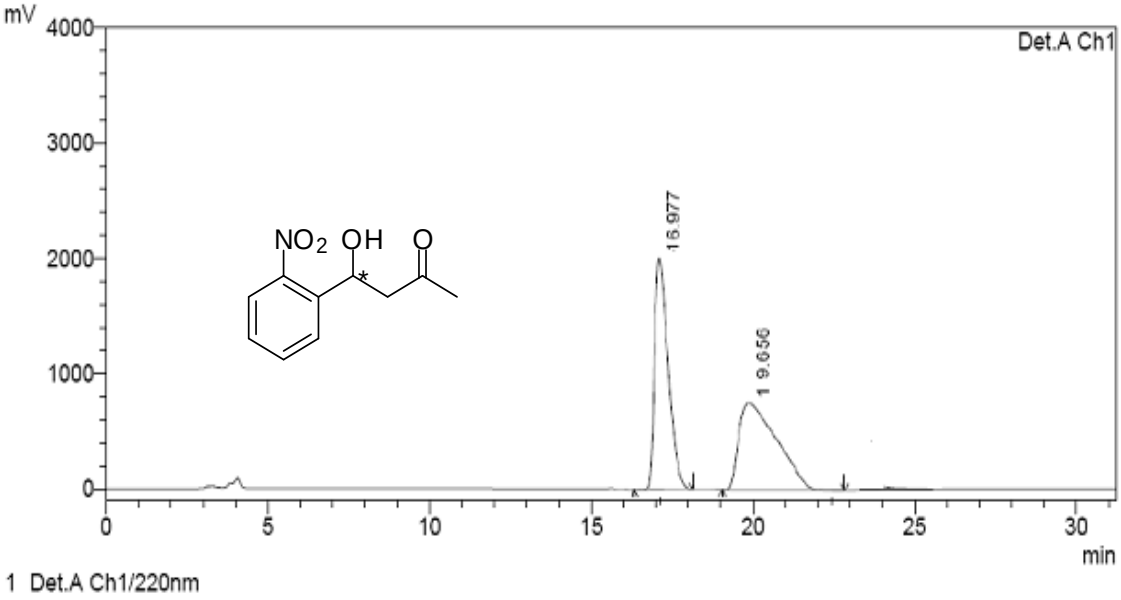


PeakTable

Peak#	Ret.Time	Area	Height	Area %	Height %
1	11.128	44564846	1526475	98.268	96.700
2	12.484	667042	671688	2.732	3.300
Total		45231888	1562414	100.000	100.000

HPLC data of 2b

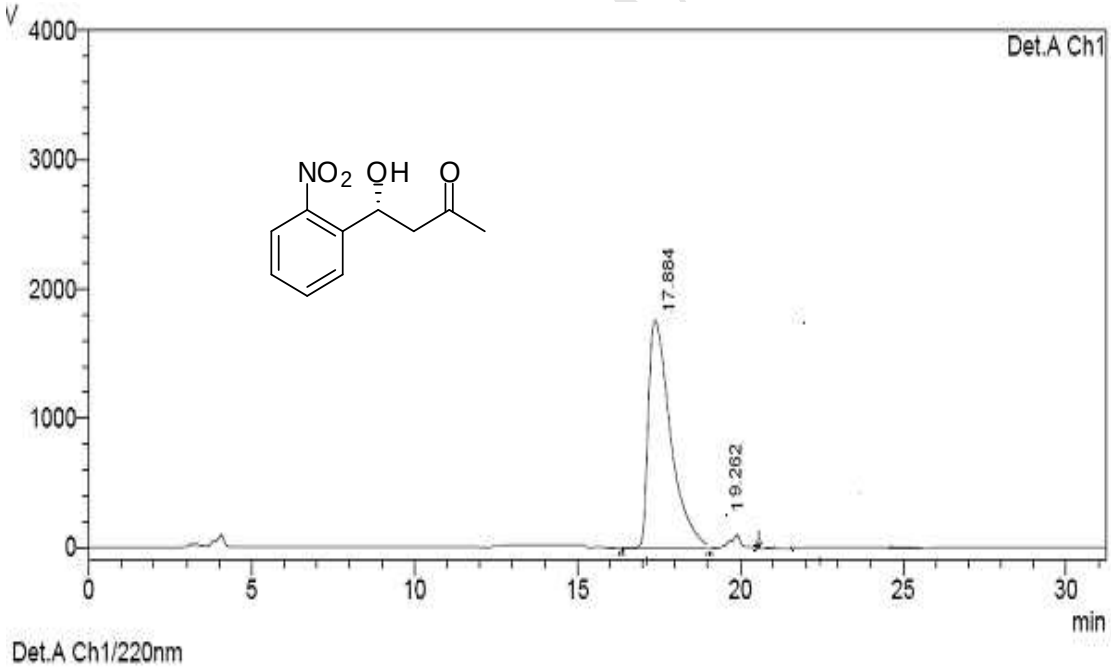
Racemic Sample



1 Det.A Ch1/220nm

PeakTable

Catalytical Sample

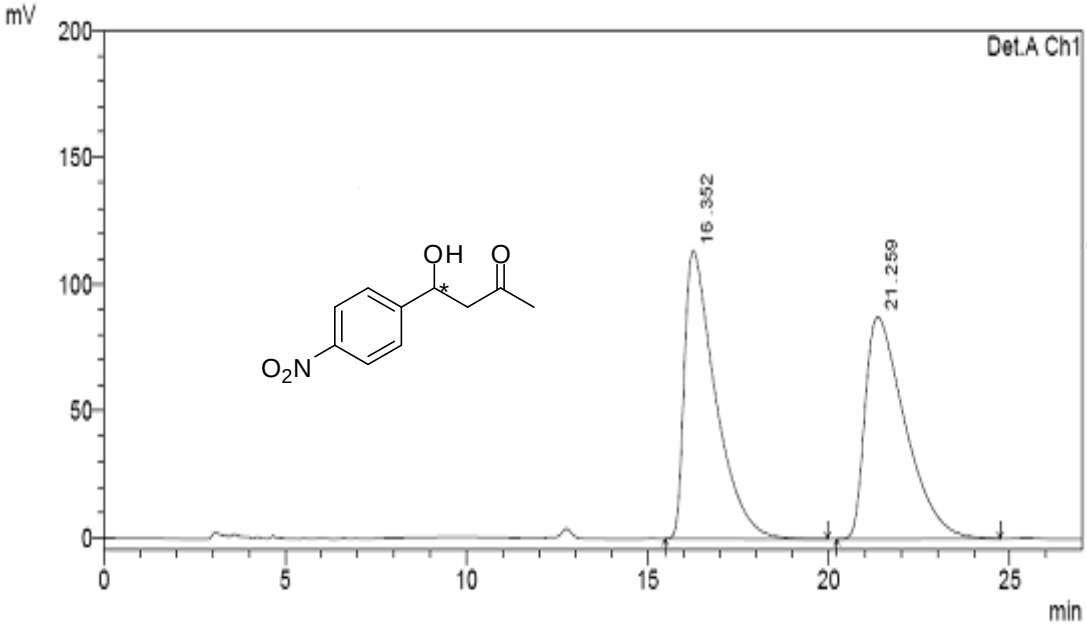


Det.A Ch1/220nm

Peak#	Ret.Time	Area	Height	Area %	Height %
1	17.884	54574655	1676788	98.868	97.700
2	19.202	766242	777665	1.132	2.300
Total		55340897	2454454	100.000	100.000

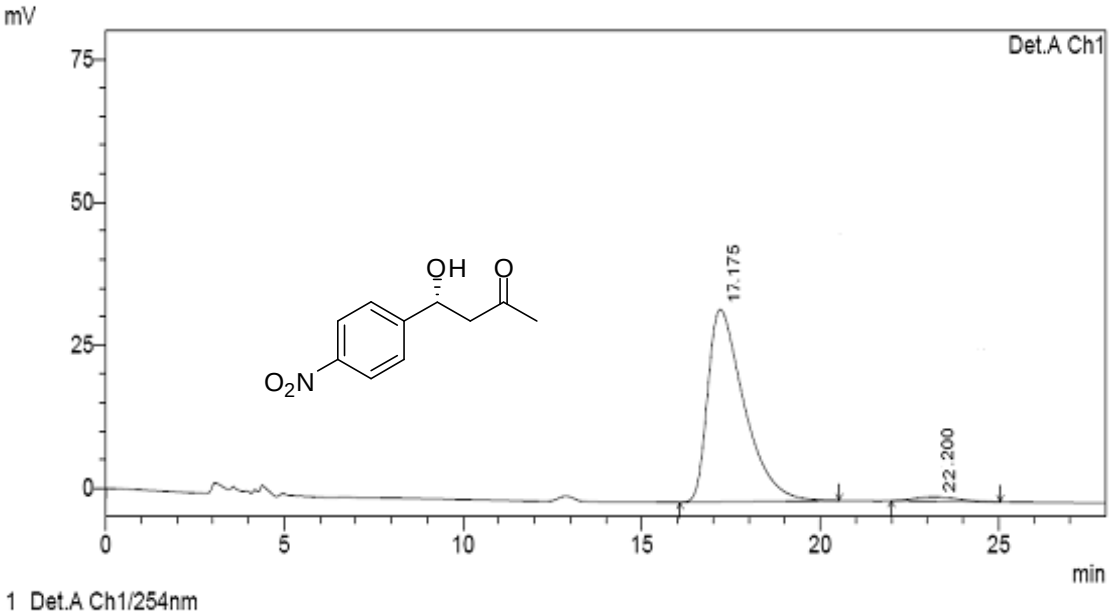
HPLC data of 2c

Racemic Sample



1 Det.A Ch1/254nm

Catalytical Sample

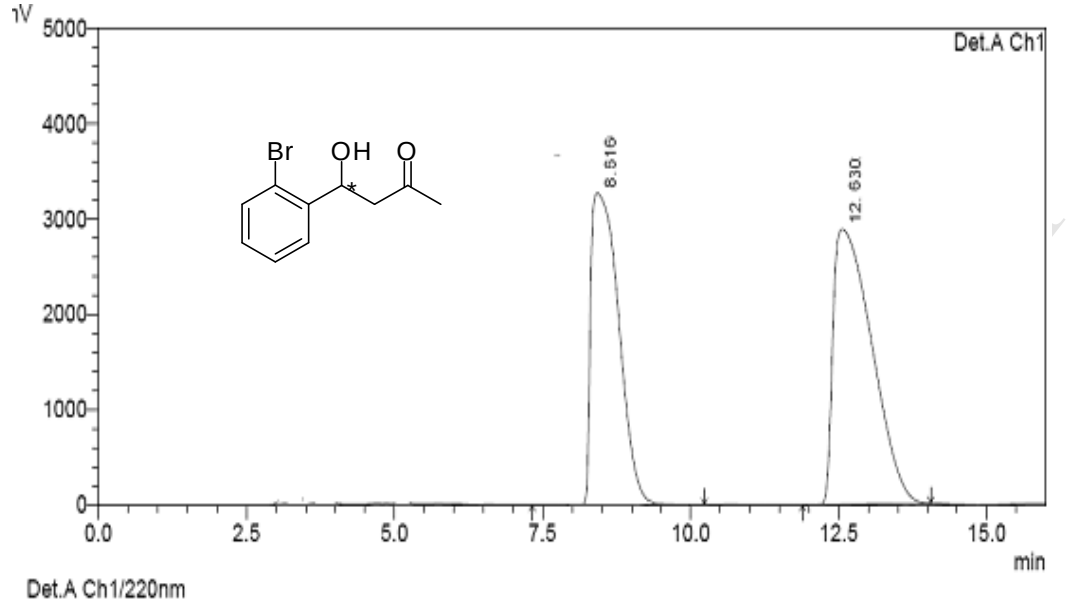


1 Det.A Ch1/254nm

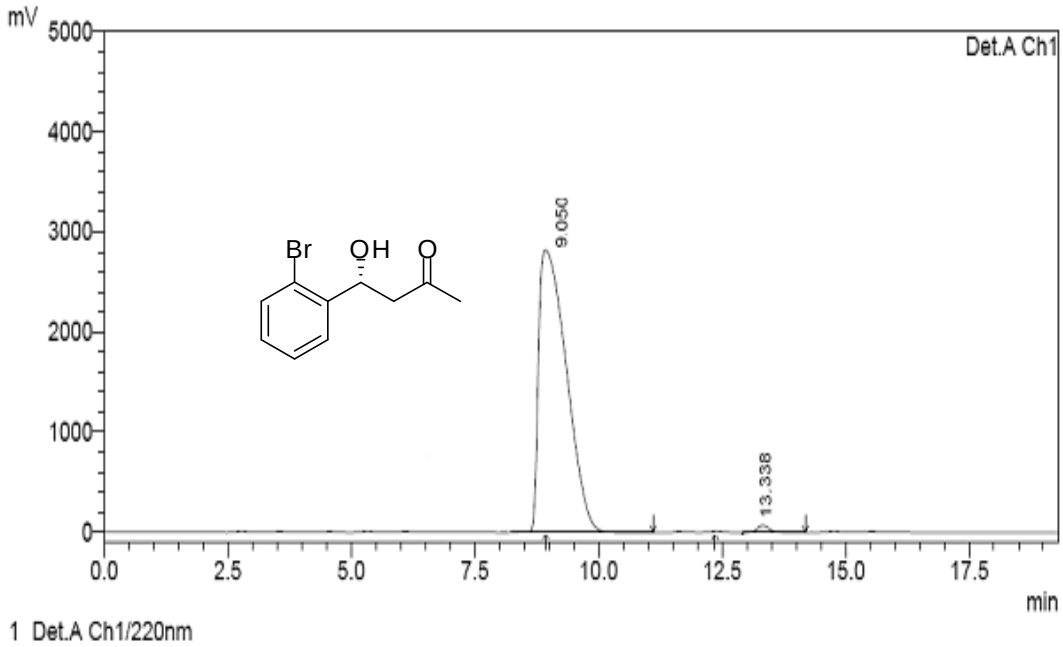
Peak#	Ret.Time	Area	Height	Area %	Height %
1	17.175	2385801	33650	99.591	97.772
2	22.200	61398	767	0.409	2.228
Total		2447199	34417	100.000	100.000

HPLC data of 2d

Racemic Sample



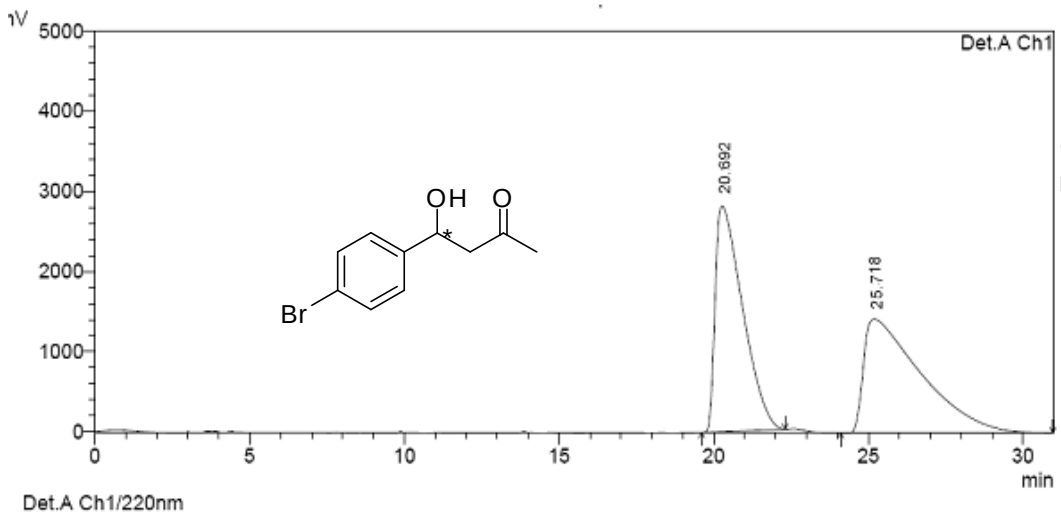
Catalytical Sample



Peak#	Ret.Time	Area	Height	Area %	Height %
1	9.050	117895300	2934839	98.763	97.532
2	13.338	2361753	73542	1.237	2.468
Total		120157053	3008381	100.000	100.000

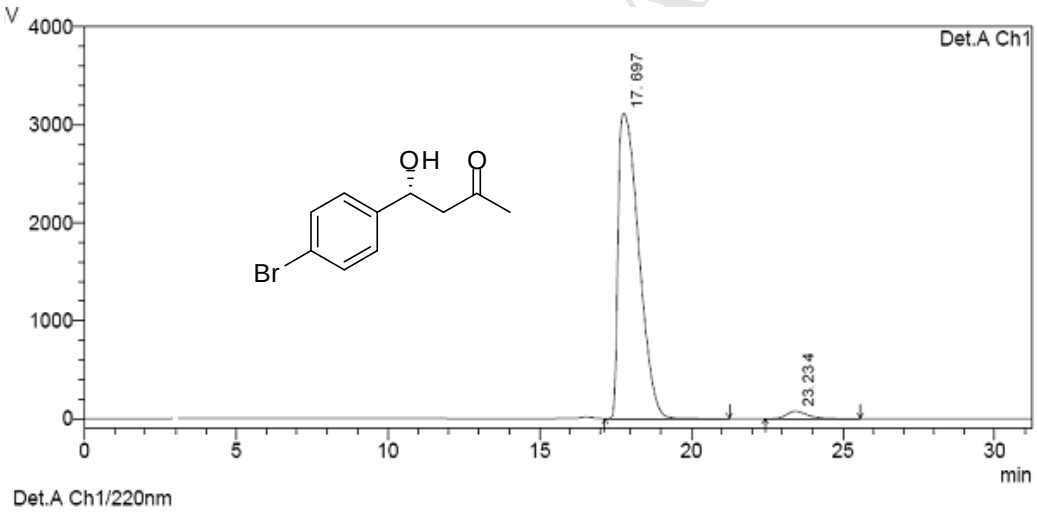
HPLC data of 2e

Racemic Sample



PeakTable

Catalytical Sample

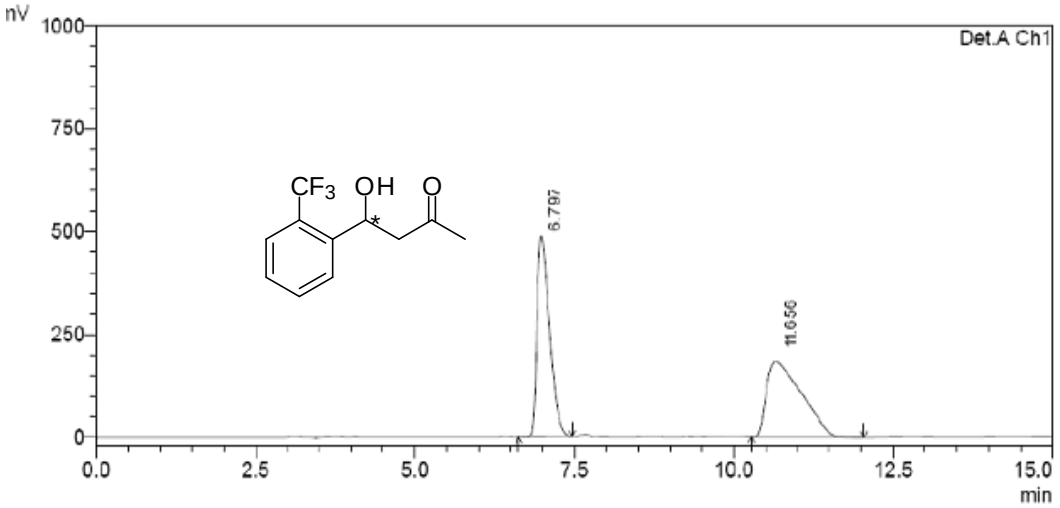


PeakTable

Peak#	Ret.Time	Area	Height	Area %	Height %
1	17.697	157384334	3231354	99.347	98.578
2	23.234	3123687	71012	1.653	1.422
Total		160508021	3302366	100.000	100.000

HPLC data of 2f

Racemic Sample

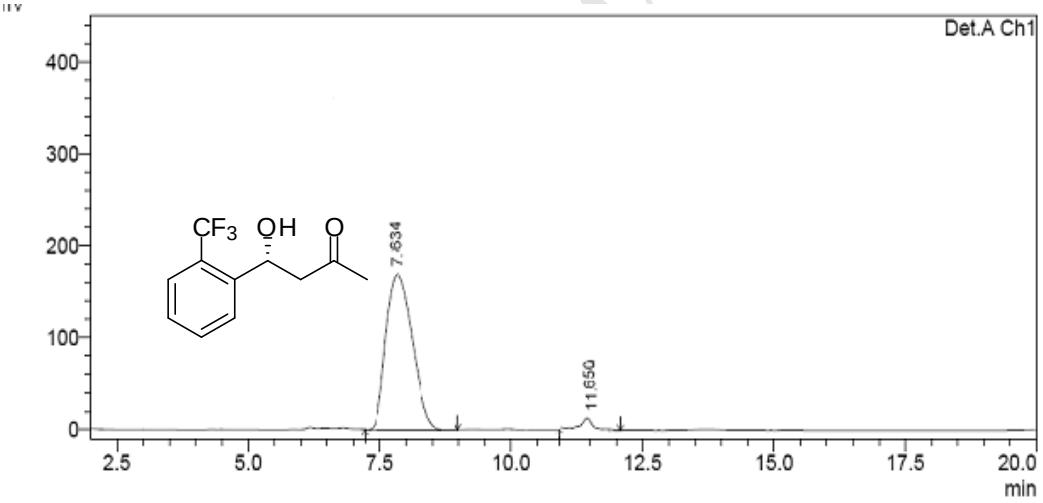


Det.A Ch1/254nm

PeakTable

Detector A Ch1 254nm

Catalytical Sample



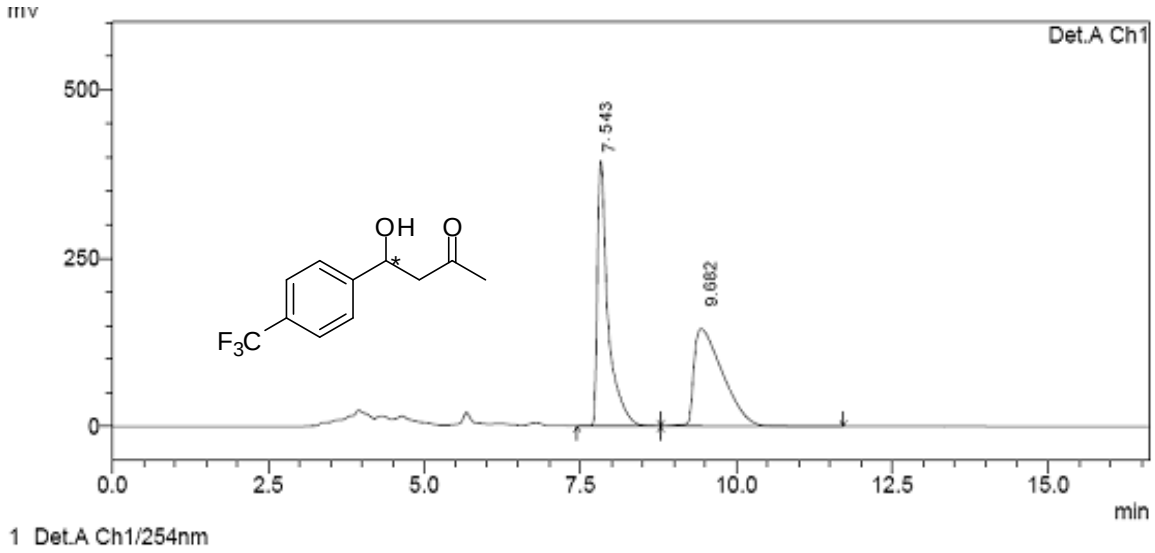
Det.A Ch1/254nm

PeakTable

Peak#	Ret.Time	Area	Height	Area %	Height %
1	7.634	6457164	171126	98.567	98.243
2	11.650	31534	2932	1.433	1.757
Total		6488698	174058	100.000	100.000

HPLC data of 2g

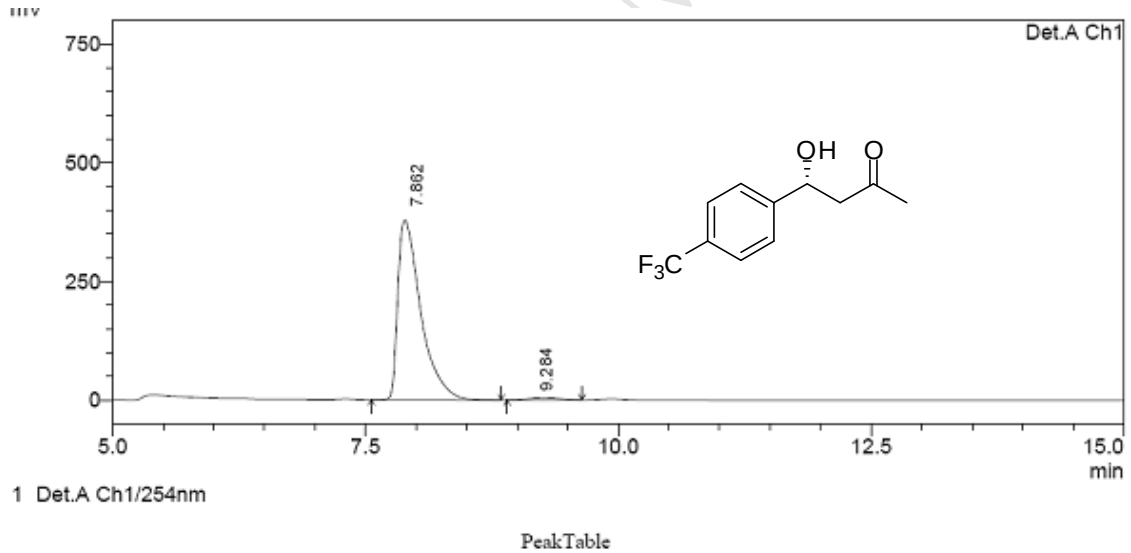
Racemic Sample



1 Det.A Ch1/254nm

PeakTable

Catalytical Sample



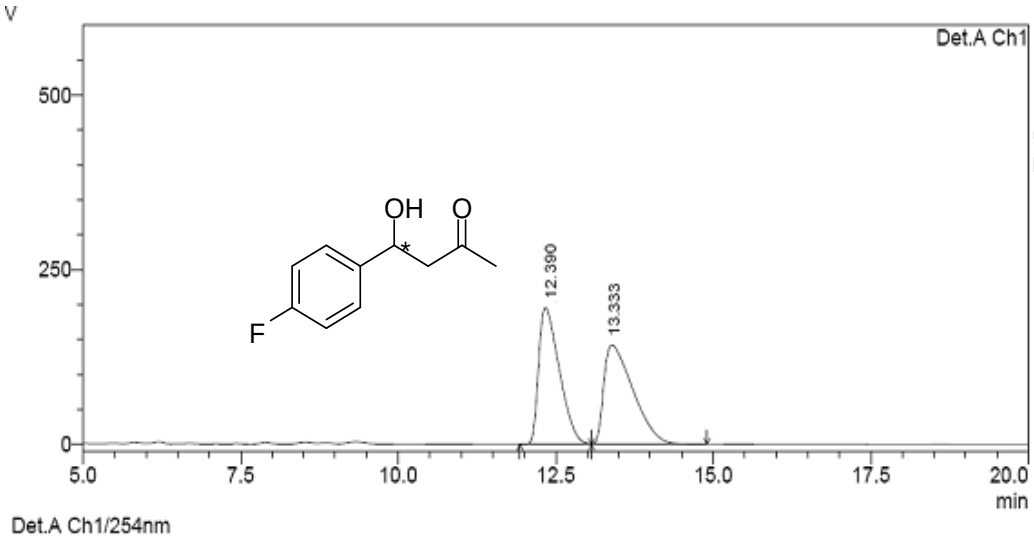
1 Det.A Ch1/254nm

PeakTable

Peak#	Ret.Time	Area	Height	Area %	Height %
1	7.862	5985463	384963	99.561	98.973
2	9.284	74651	3916	0.439	1.027
Total		6060114	398879	100.000	100.000

HPLC data of 2h

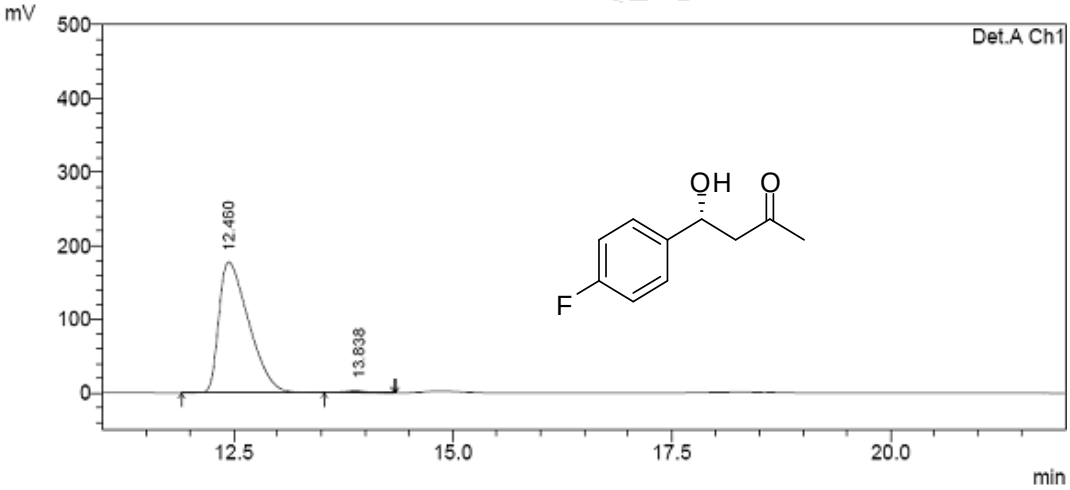
Racemic Sample



Det.A Ch1/254nm

PeakTable

Catalytical Sample



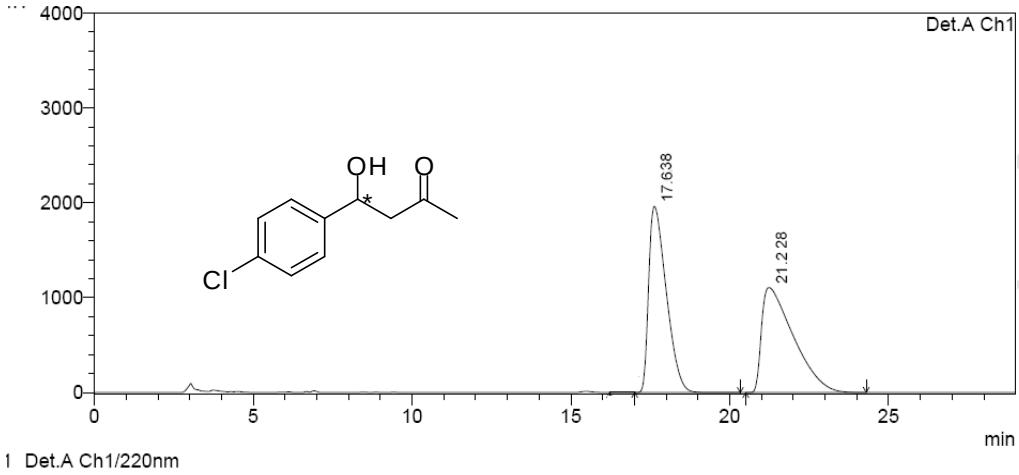
1 Det.A Ch1/254nm

PeakTable

Peak#	Ret.Time	Area	Height	Area %	Height %
1	12.460	4245177	189166	98.914	98.773
2	13.838	46582	2312	1.086	1.227
Total		4291759	191478	100.000	100.000

HPLC data of 2i

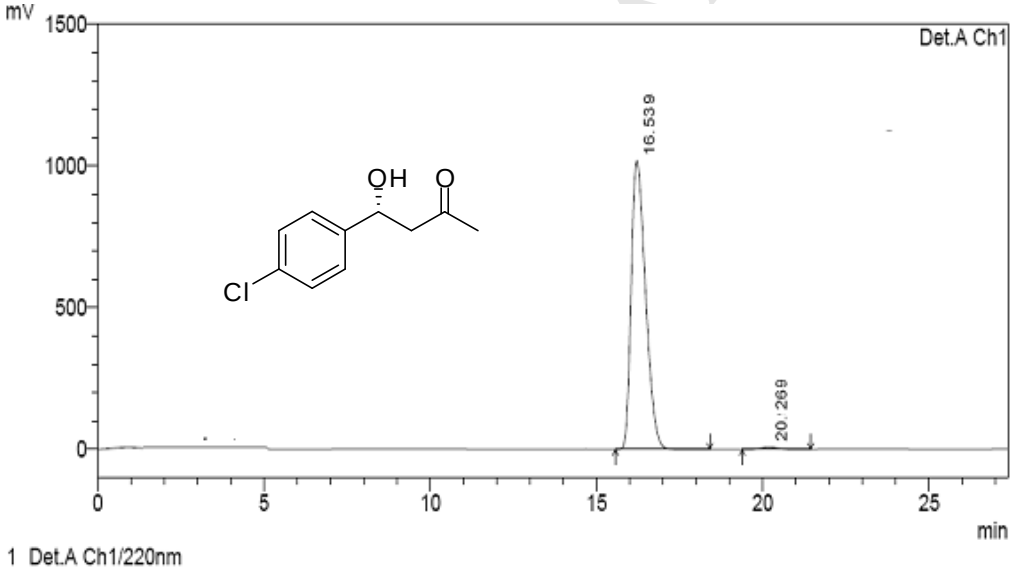
Racemic Sample



1 Det.A Ch1/220nm

PeakTable

Catalytical Sample



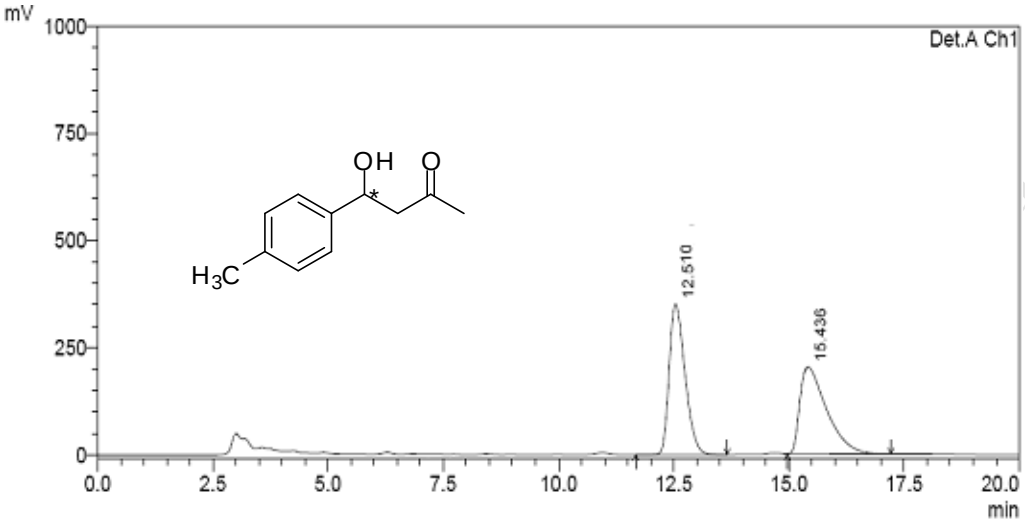
1 Det.A Ch1/220nm

PeakTable

Peak#	Ret.Time	Area	Height	Area %	Height %
1	16.639	30611732	1018748	98.874	99.364
2	20.269	295786	8265	1.126	0.636
Total		30817518	1027013	100.000	100.000

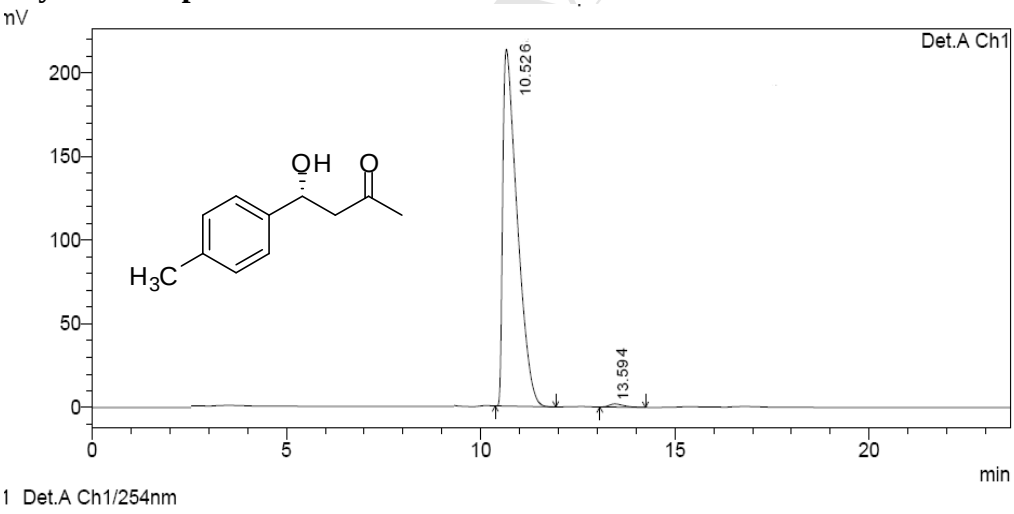
HPLC data of 2j

Racemic Sample



PeakTable

Catalytical Sample

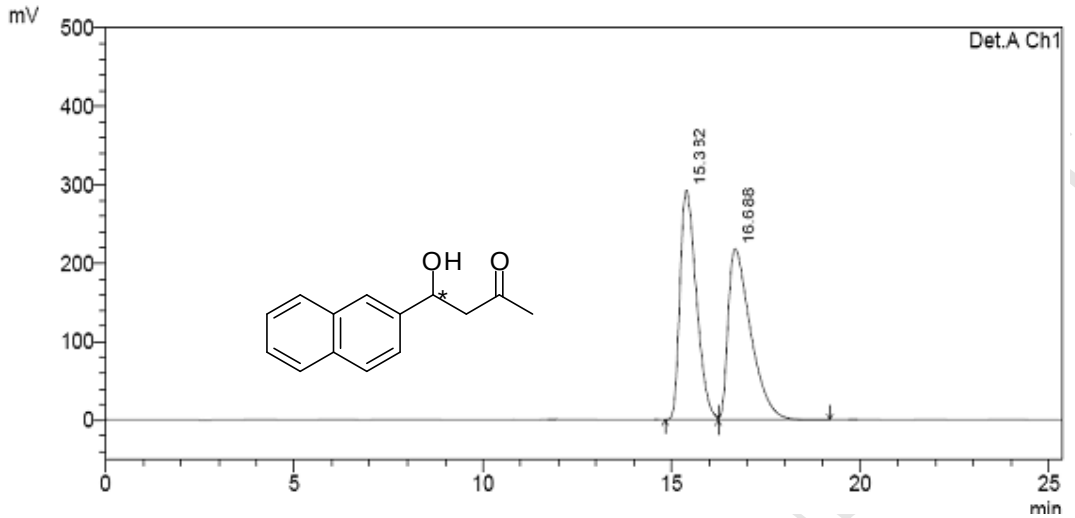


PeakTable

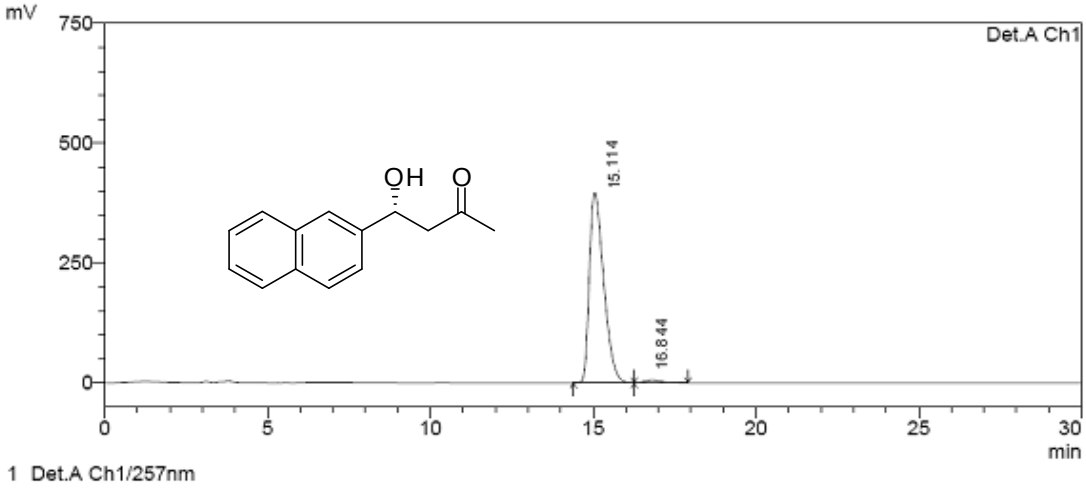
Peak#	Ret.Time	Area	Height	Area %	Height %
1	10.526	5523686	214563	99.653	99.124
2	13.452	50312	1911	1.347	0.876
Total		5574998	215474	100.000	100.000

HPLC data of 2l

Racemic Sample



Catalytical Sample

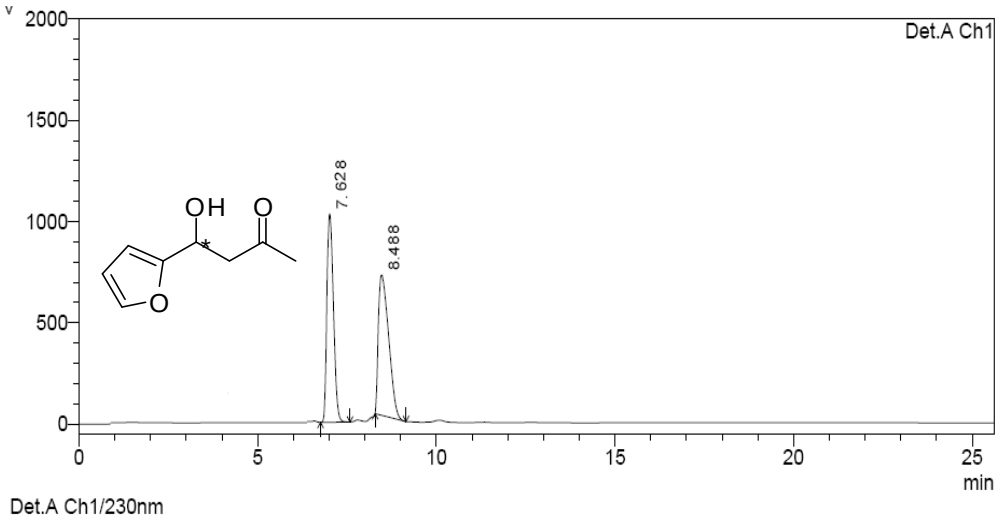


PeakTable

Peak#	Ret.Time	Area	Height	Area %	Height %
1	15.114	12048198	396914	97.534	98.593
2	16.844	269651	6301	2.466	1.407
Total		12317749	403215	100.000	100.000

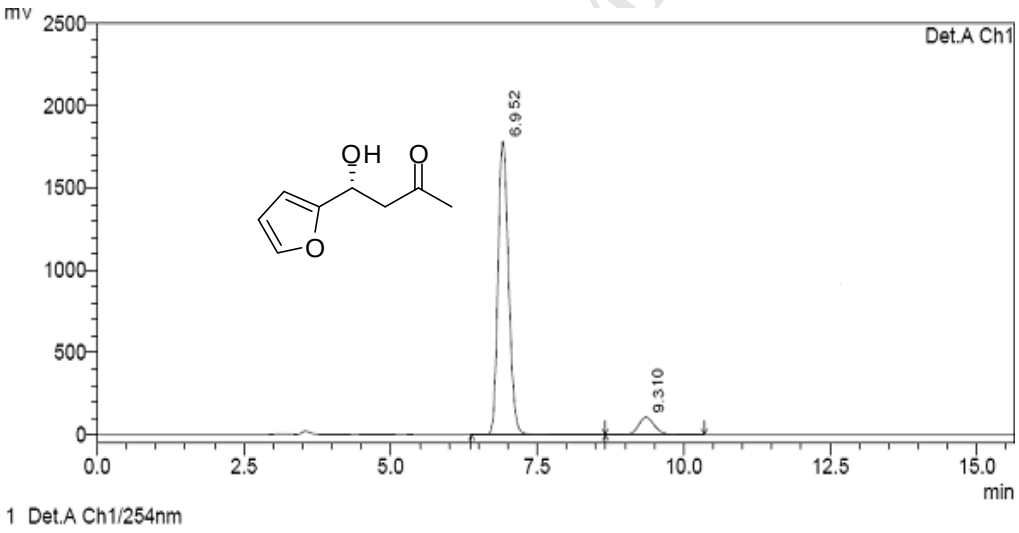
HPLC data of 2m

Racemic Sample



PeakTable

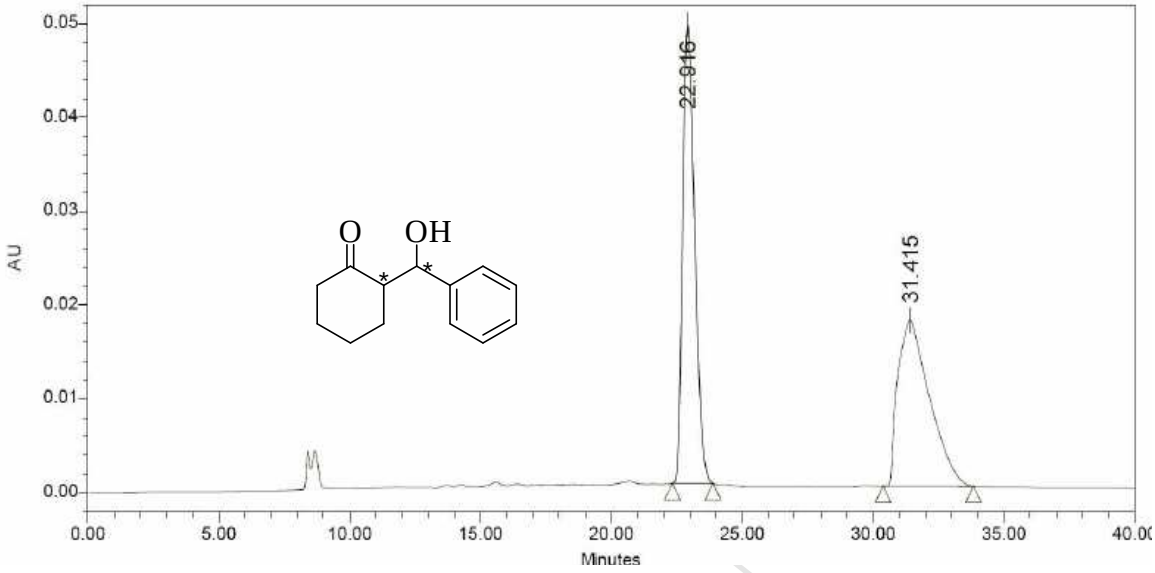
Catalytical Sample



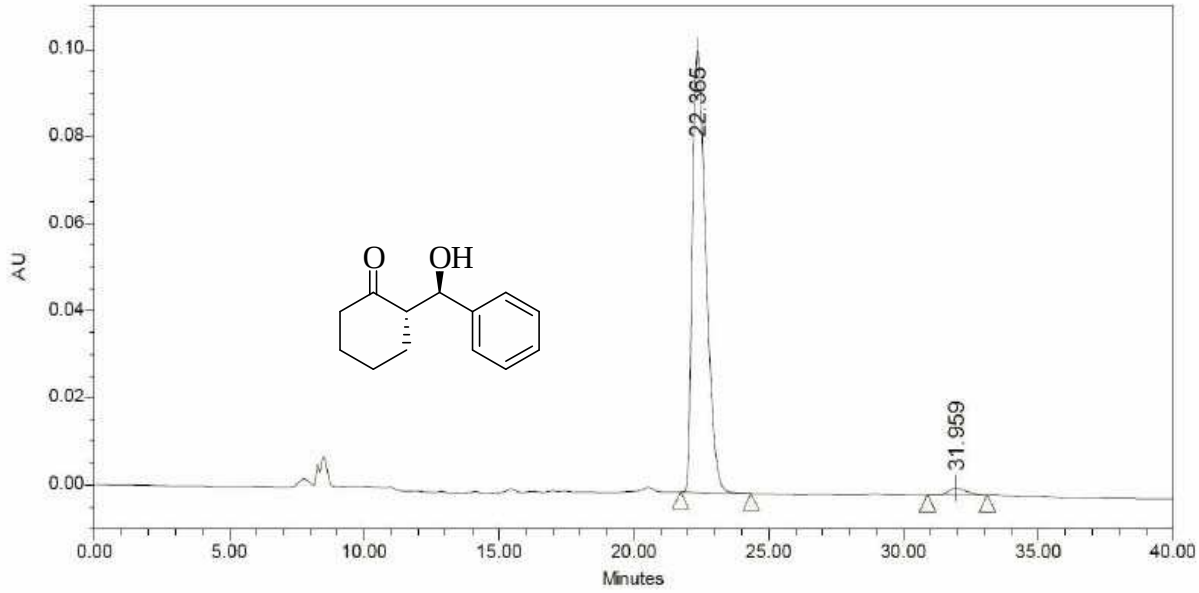
PeakTable

Peak#	Ret.Time	Area	Height	Area %	Height %
1	6.952	23216352	1865321	95.467	94.651
2	9.352	1992137	111234	4.533	5.349
Total		24208499	1976555	100.000	100.000

HPLC data of 3a
Racemic Sample

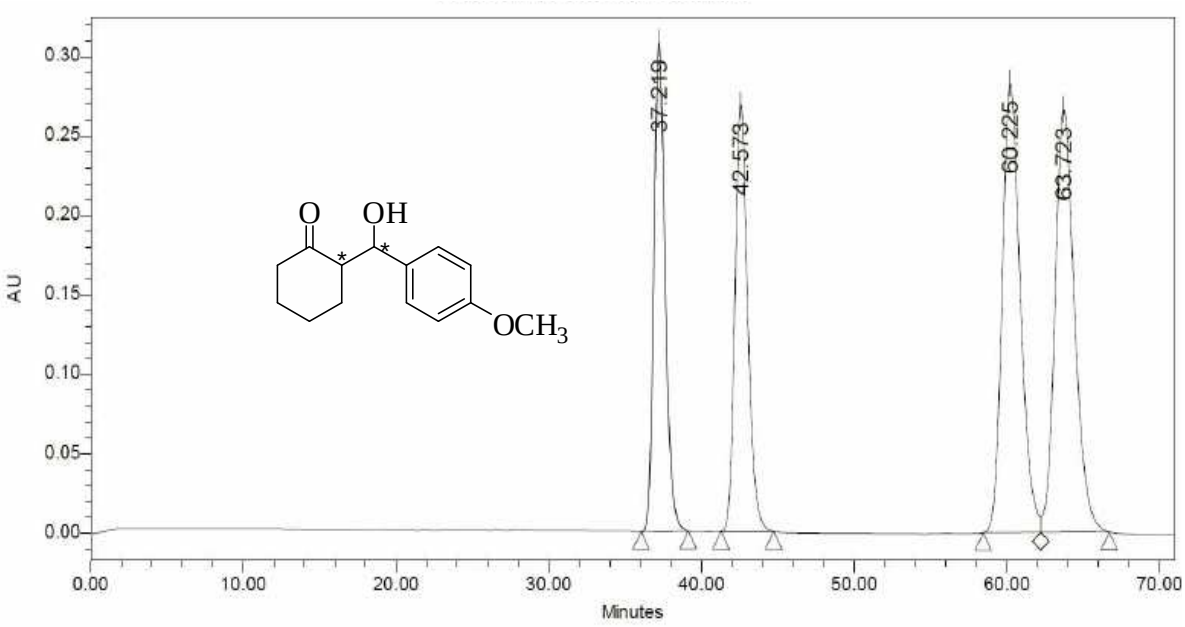


Catalytical Sample

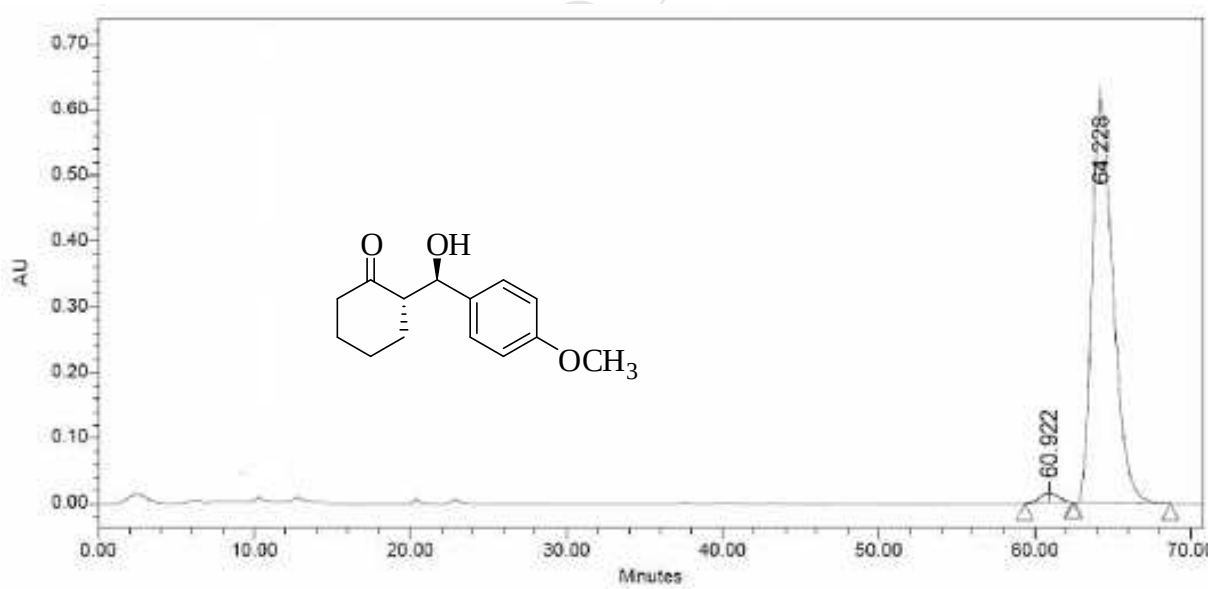


Peak#	Ret.Time	Area	Height	Area %	Height %
1	22.365	3506344	101399	97.98	98.10
2	31.959	70484	1964	2.02	1.90
Total		3576828	10 3363	100.000	100.000

HPLC data of 3b
Racemic Sample



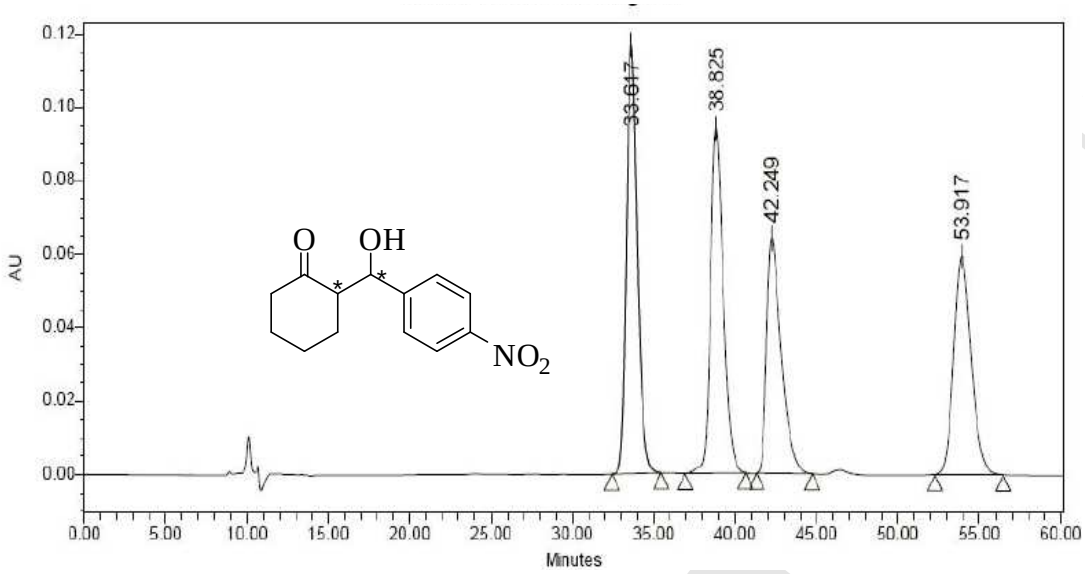
Catalytical Sample



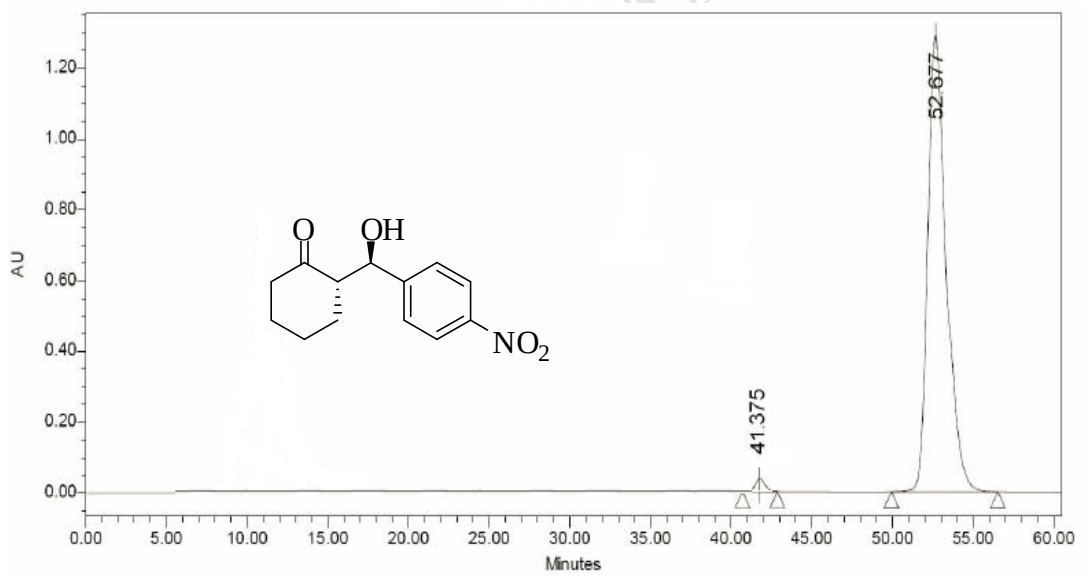
Peak#	Ret.Time	Area	Height	Area %	Height %
1	60.922	1140154	14286	1.97	2.29
2	64.228	58751209	610719	98.03	97.71
Total		59891363	62 4995	100.000	100.000

HPLC data of 3c

Racemic Sample

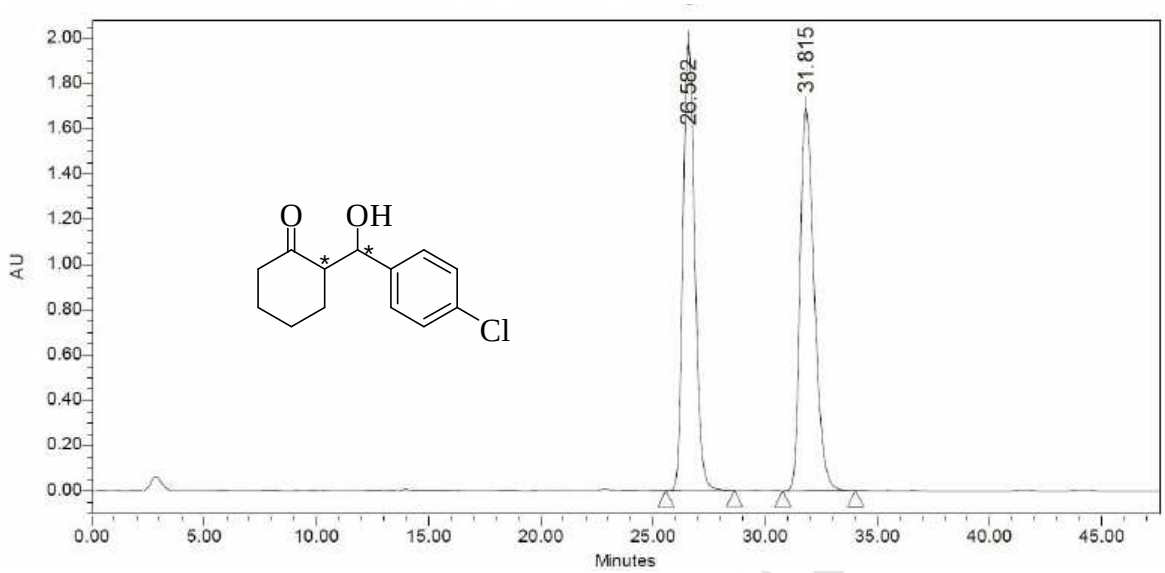


Catalytical Sample

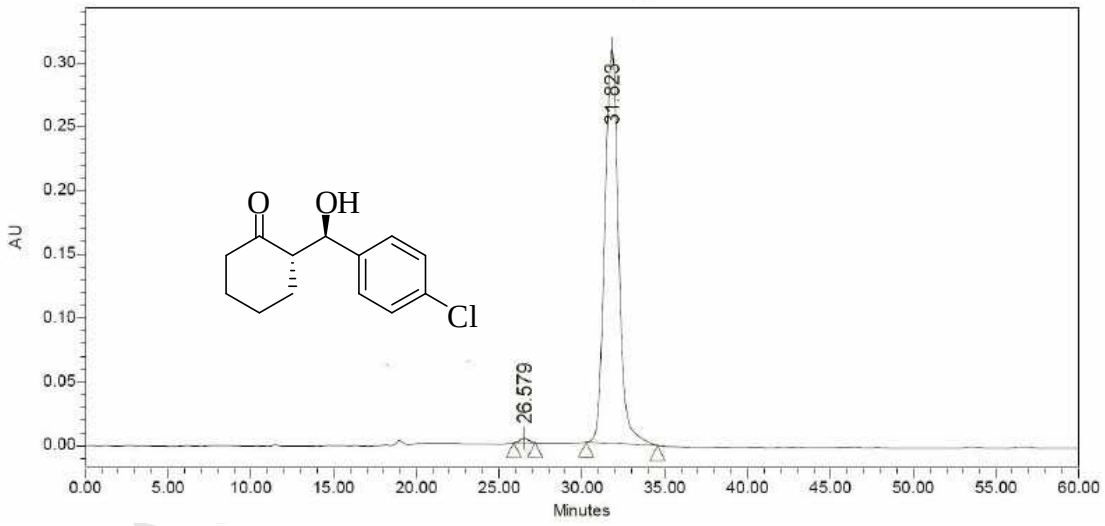


Peak#	Ret.Time	Area	Height	Area %	Height %
1	41.375	197801	908	0.19	0.07
2	52.677	102131840	1286584	99.81	99.93
Total		59891363	1287492	100.000	100.000

HPLC data of 3d
Racemic Sample



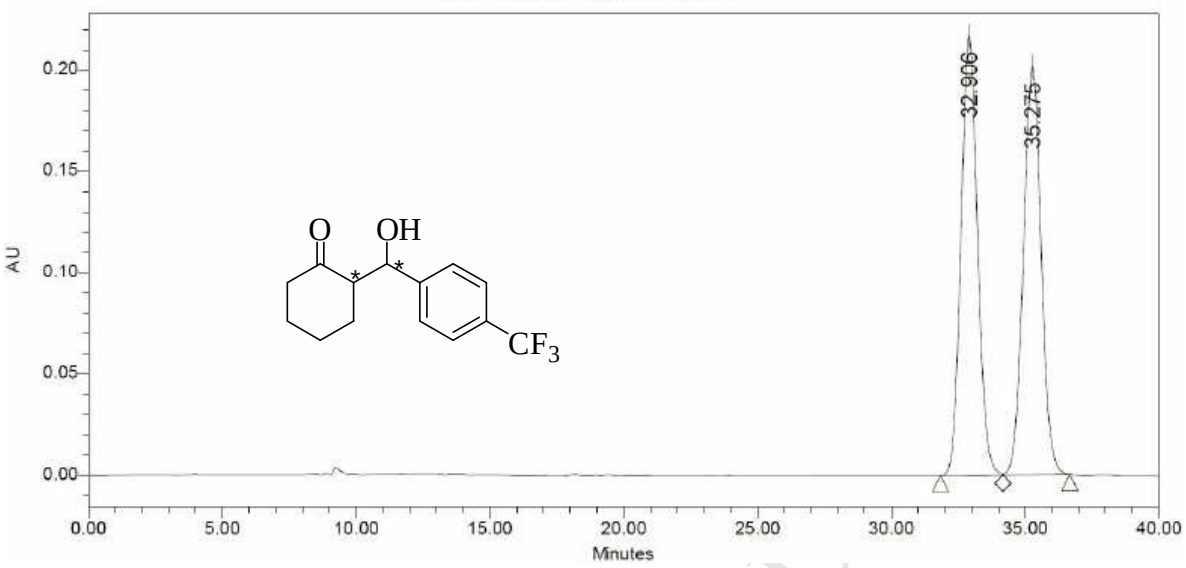
Catalytical Sample



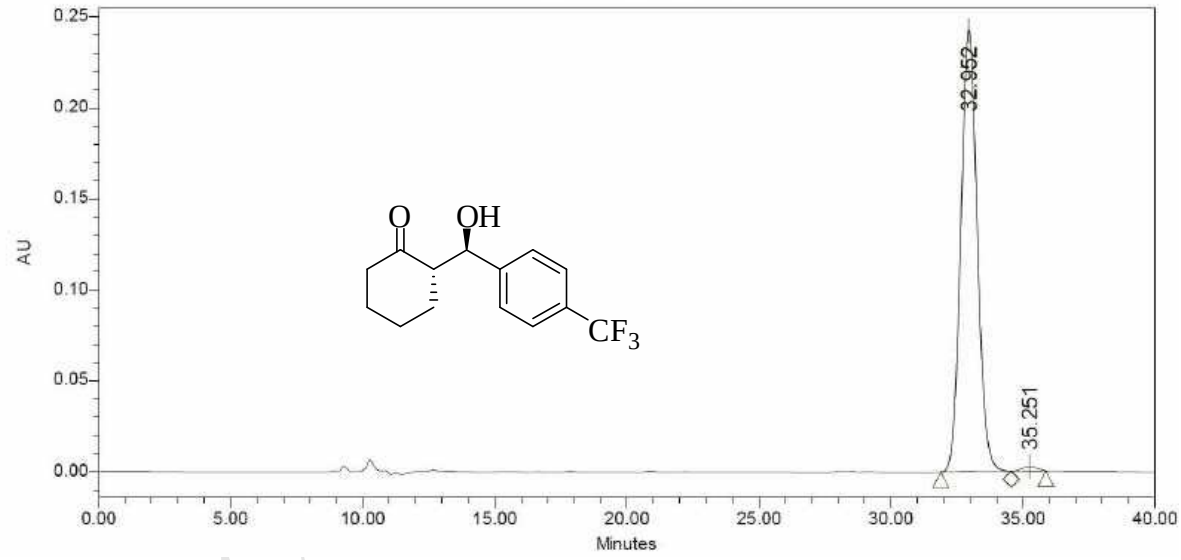
Peak#	Ret.Time	Area	Height	Area %	Height %
1	26.579	124225	3287	1.20	1.05
2	31.823	17967800	310153	98.80	98.95
Total		18092025	313440	100.000	100.000

HPLC data of 3e

Racemic Sample



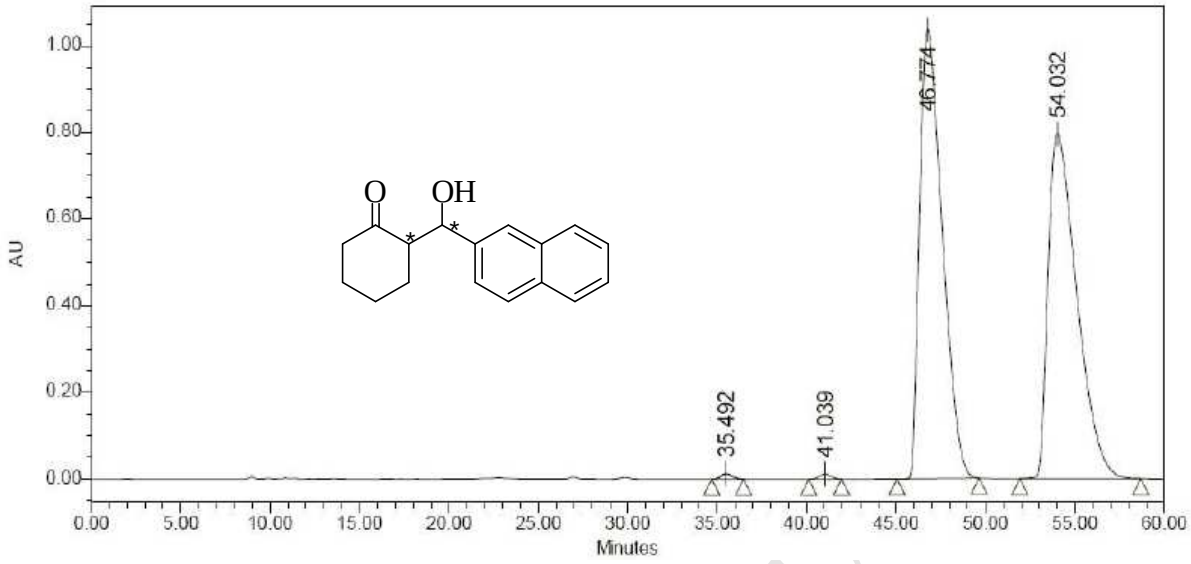
Catalytical Sample



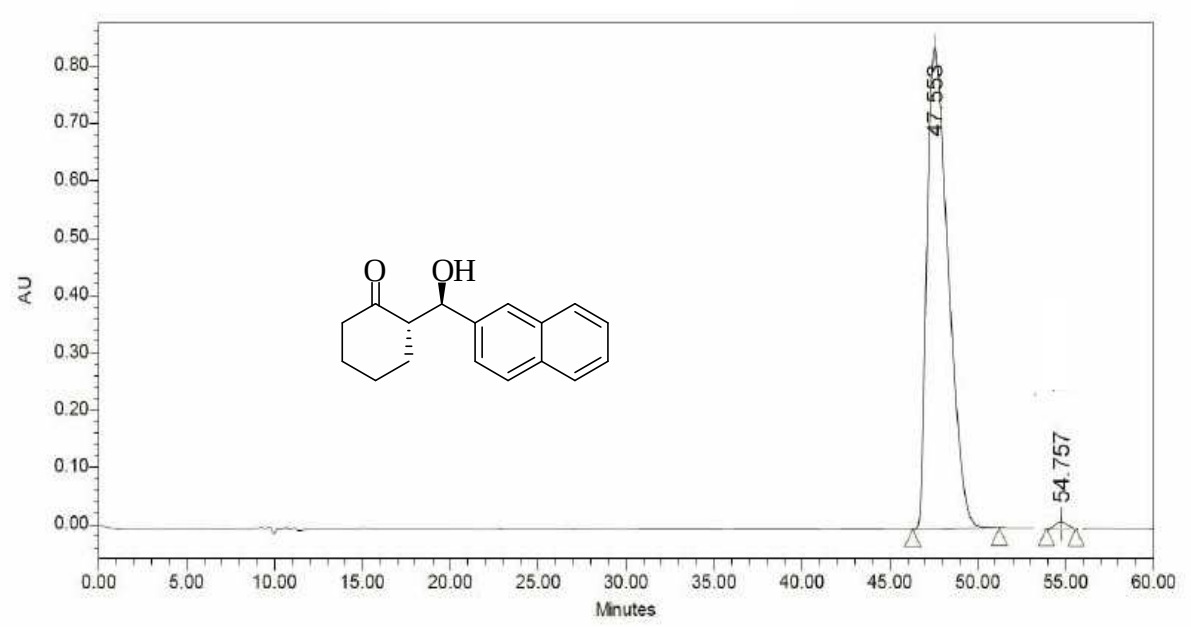
Peak#	Ret.Time	Area	Height	Area %	Height %
1	32.952	10487716	242485	99.30	99.14
2	35.251	73598	2103	0.70	0.88
Total		10561314	244588	100.000	100.000

HPLC data of 3f

Racemic Sample

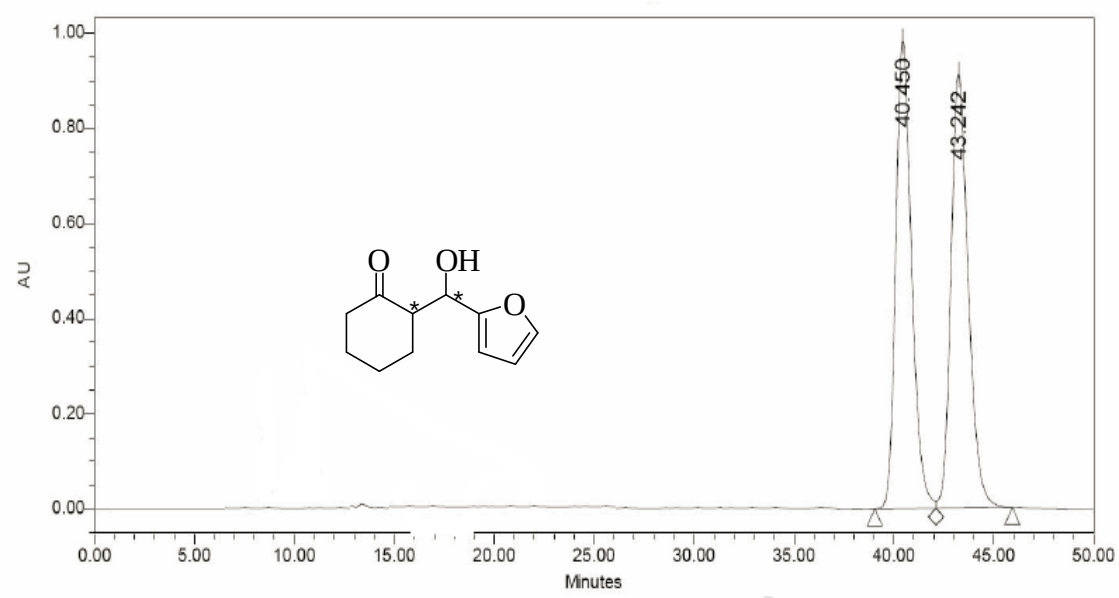


Catalytical Sample

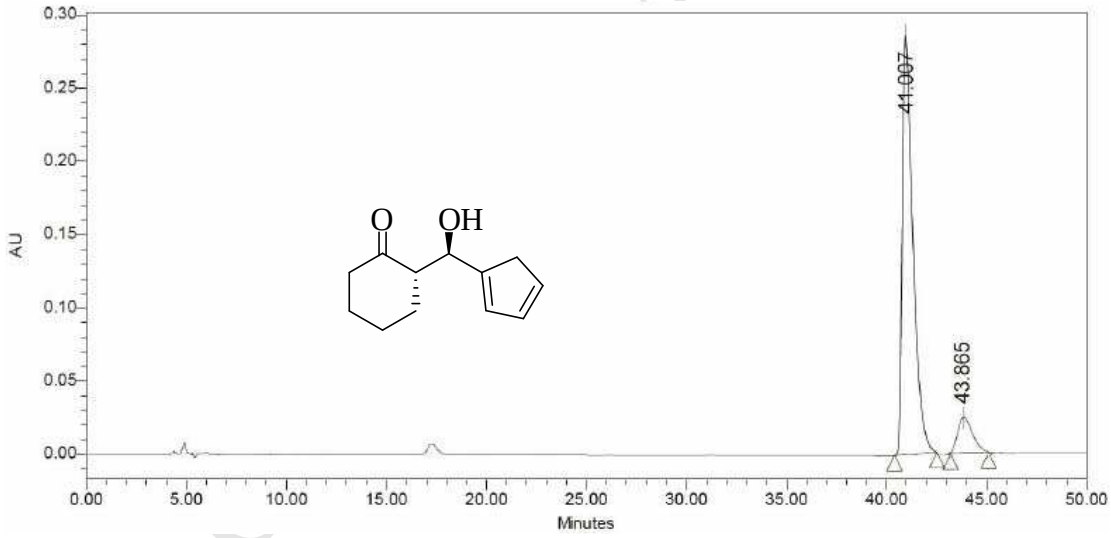


Peak#	Ret.Time	Area	Height	Area %	Height %
1	47.553	69640863	839579	98.92	99.76
2	54.757	1464344	2054	2.08	0.24
Total		71005107	841633	100.000	100.000

HPLC data of 3g
Racemic Sample



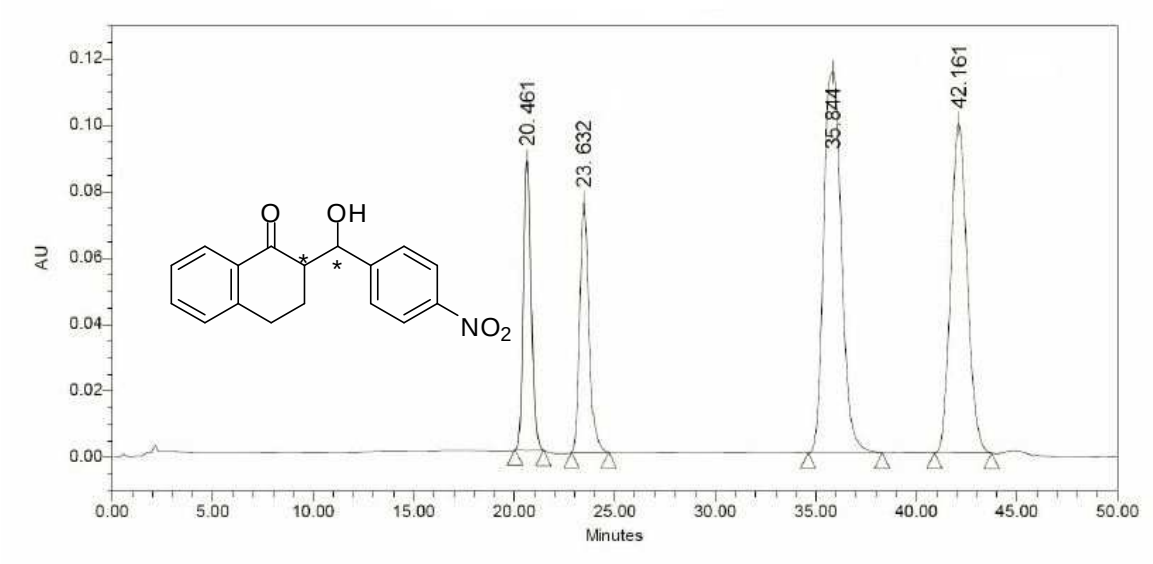
Catalytical Sample



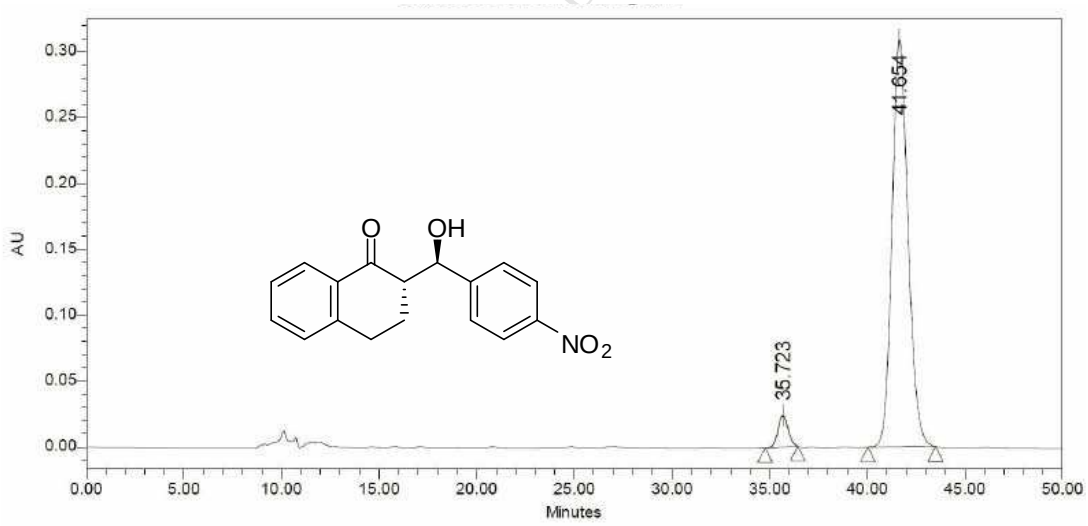
Peak#	Ret.Time	Area	Height	Area %	Height %
1	41.007	12582599	286707	93.48	92.08
2	43.865	877606	24665	6.52	7.92
Total		13460205	311372	100.000	100.000

HPLC data of 4a

Racemic Sample

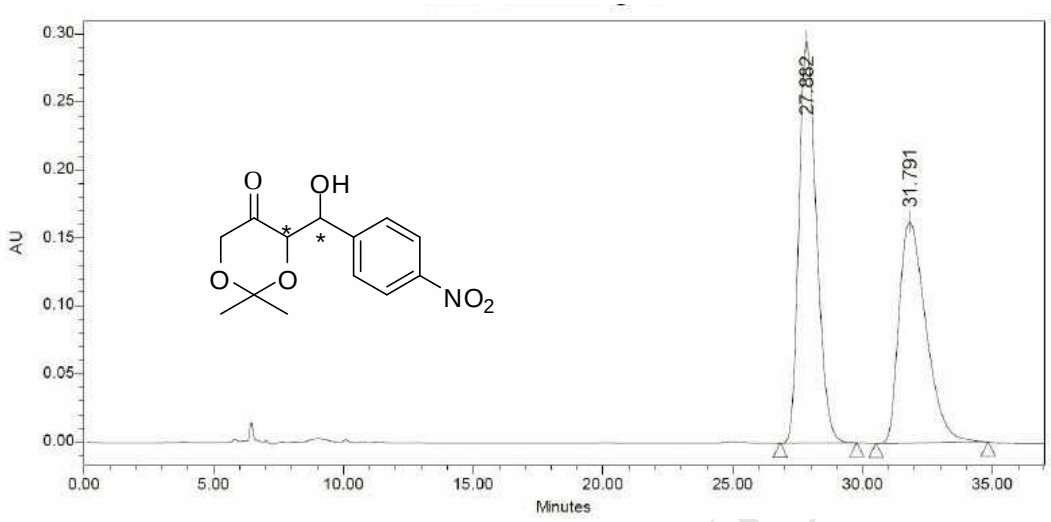


Catalytical Sample

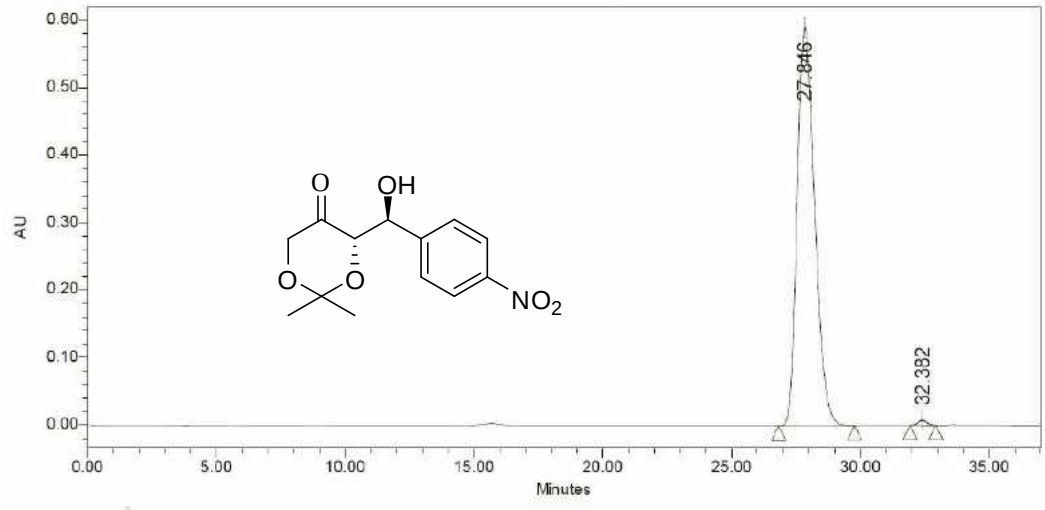


Peak#	Ret.Time	Area	Height	Area %	Height %
1	35.723	823318	14199	4.41	4.40
2	43.865	17846004	308652	95.59	95.60
Total		18669322	322851	100.000	100.000

HPLC data of 4a
Racemic Sample



HPLC data of 4a
Racemic Sample



Peak#	Ret.Time	Area	Height	Area %	Height %
1	27.846	27871933	590886	98.36	98.74
2	32.382	178625	7553	1.64	1.26
Total		28049558	598439	100.000	100.000