Supplementary material for "**Acid Controlled Diastereoselectivity in Asymmetric Aldol Reaction of Cycloketone to Aldehyde with Enamine-based Organocatalysts**"

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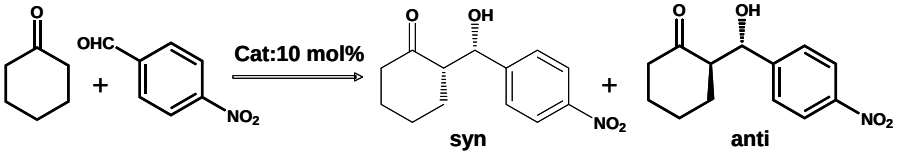
General Information: Unless otherwise stated, materials were purchased from commercial suppliers and used without purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian 400 (400 MHz) spectrophotometers. Flash column chromatography was performed using 200-300 mesh silica gel. High resolution mass spectra were done by a Micromass Q-Tof instrument (ESI). Chiral HPLC was performed on Agilent 1100 series with chiral columns (Chiralpak AD-H, Chiralcel OD-H). The chiral amines **1a** [1], **1b** [2], **1c** [3], **1d** [4], **1e** [5], **1f** [5], were prepared according to literature procedures.

A typical procedure for the aldol reaction

The chiral amine **1a** (0.0125 mmol) together with succinic acid (0.0125 mmol) were in cyclohexanone (0.2 mL) for 20 min. The 4-nitrobenzaldehyde (0.125 mmol) was added and the mixture was stirred for 24 h. Then the reaction mixture was directly purified by flash column chromatography to afford the aldol adducts. The enantiomeric excess was determined by HPLC (chiralpak AD-H column, 254 nm, 2-propanol/n-hexane=20:80 as eluent, 25 ^{o}C, 0.5 mL/min), anti enantiomer t_R=24.8 and 31.7; syn enantiomer t_R=21 and 22.7 min

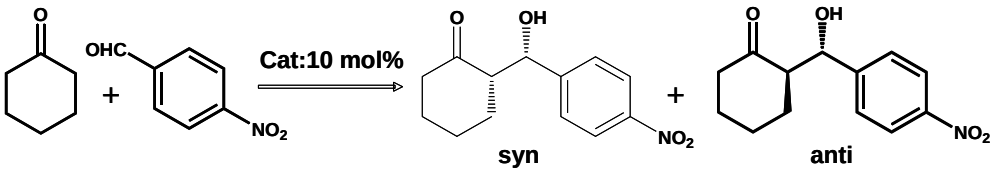
Table S1. Screening the catalyst of the direct aldol reaction[a].

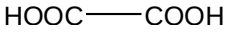
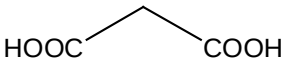
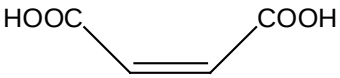
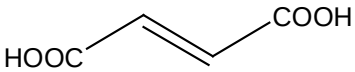
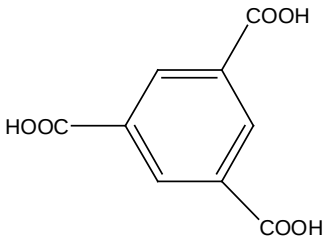


Entry	catalyst	Yield%[b]	Syn/anti[c]	Ee% (anti)[c]
1	**1a**	95	11/89	97
2	**1b**	96	47/53	-93
3	**1c**	90	43/57	-93
4	**1d**	82	25/75	-95
5	**1e**	65	37/63	-90
6	**1f**	71	35/65	92
7	**1g**	95	46/54	86
8[d]	**1a**	58	31/69	83

[a] Reaction conditions: chiral diamine: 10 mol%; TFA: 10 mol%; cyclohexanone: 0.2 mL; 4-nitrobenzaldehyde: 0.125 mmol; RT, 2 h. [b] Isolated yield, [c] Determined by HPLC. [d] 2 mol% of the catalyst was used, and the reaction time is 240 h.

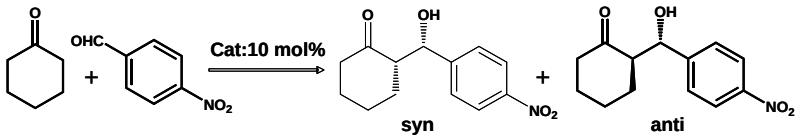
Table S2. Effect of various acids on direct aldol reactions[a].



Entry	acid	Yield%[b]	Syn/anti[c]	Ee% (syn)[c]
1		95	19/81	96 (anti)
2		94	21/79	96 (anti)
3		96	24/76	96 (anti)
4		95	62/38	83
5	L-(-)-tartaric acid	90	40/60	92 (anti)
6	D-(-)-tartaric acid	86	30/70	92 (anti)
7	L-(-)-Di-p-toluoyltartaric acid	96	45/55	86 (anti)
8	DL-malic acid	90	40/60	94 (anti)
9		trace	n.d.	n.d.

[a] Reaction conditions: chiral diamine **1a**: 10 mol%; acid: 10 mol%; cyclohexanone: 0.2 mL; 4-nitrobenzaldehyde: 0.125 mmol; RT, 5-24 h. [b] Isolated yield, [c] Determined by HPLC, and the syn product had a (1'S, 2 S) configuration, the anti product had a (1'S, 2R) configuration.

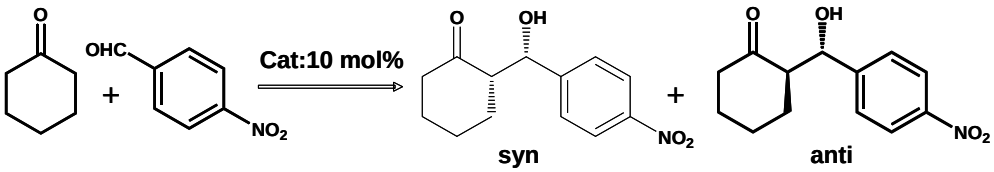
Table S3. Screening the reaction condition of the direct aldol reactions[a].



entry	Acid/**1a**	solvent	Yield%[b]	Syn/anti[c]	ee% (syn) [c]
1	0.5	neat	75	68/32	78
2	1.0	neat	94	75/25	84
3	1.5	neat	89	67/33	76
4	2.0	neat	85	69/31	74
5	1.0	NMP	26	78/22	80
6	1.0	DMF	30	74/26	80
7	1.0	n-hexane	37	68/32	87
8	1.0	THF	35	70/30	77
9	1.0	CH_2Cl_2	40	60/40	79
10	1.0	H_2O	97	18/82	90 (anti)

[a] Reaction conditions: chiral diamine **1a**: 10 mol%; succinic acid; cyclohexanone: 0.1 mL; solvent: 0.1 mL; 4-nitrobenzaldehyde: 0.125 mmol; RT, 24 h. [b] Isolated yield, [c] Determined by HPLC.

Table S4. Screening chiral amines of the direct aldol reaction[a].

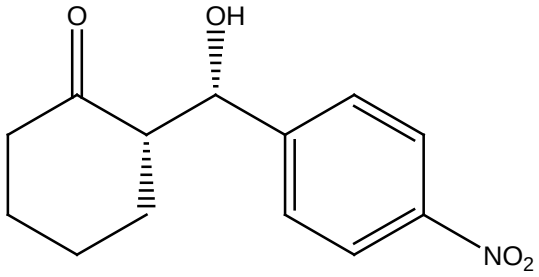


Entry	catalyst	Yield%[b]	Syn/anti[c]	Ee% (syn)[c]
1	**1a**	94	75/25	84
2	**1b**	95	80/20	73
3	**1c**	94	78/22	73
4	**1d**	97	62/38	-56
5	**1e**	58	58/42	-62
6	**1f**	56	58/42	73
7	**1g**	96	70/30	11

[a] Reaction conditions: chiral diamine: 10 mol%; succinic acid: 10 mol%; cyclohexanone: 0.2 mL; 4-nitrobenzaldehyde: 0.125 mmol; RT, 24 h. [b] Isolated yield, [c] Determined by HPLC.

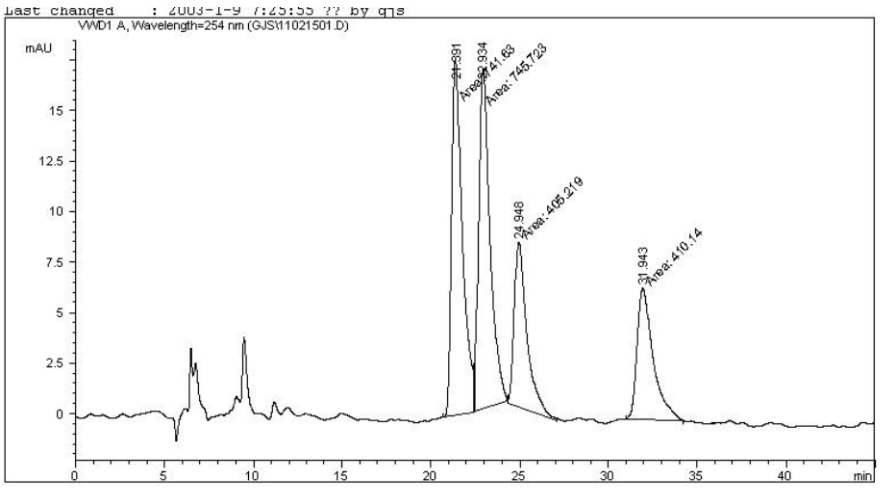
HPLC data for aldol products

(2S,1'S)-2-(Hydroxy(4-nitrophenyl)methyl)cyclohexan-1-one



Syn/anti=75/25, ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.5-2.1 (m, 6H), 2.3-2.65 (m, 3H), 3.18 (syn-OH, 1H), 4.08 (anti-OH, 1H), 4.90 (anti-CH*OH, 1H), 5.48 (syn-CH*OH, 1H), 7.48 (2H), 8.19 (2H); ^{13}C NMR (400 NMR, $CDCl_3$) δ (ppm) 24.9, 26.1, 28, 29.9, 42.8, 56.9, 70.3, 73, 76.8, 77.2, 123.6, 126.7, 128, 147, 149, 214; HRMS (MNa^{+}) Calcd. For: $C_{13}H_{15}NO_4Na$: 272.0899. Found: 272.0899. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (80:20 Hexane:2-propanol), 0.5 mL/min; λ=254 nm; anti enantiomer t_R=24.8 and 31.7 min; syn enantiomer t_R=21.2 and 22.7 min (major syn-product) [6].

Racemate:



RetTime [min]	k'	Area mAU *s	Height [mAU]	Symm.	Width [min]	Plates	Resolution	Selectivity
21.391	-	741.62994	17.76575	0.48	0.6018	6999	-	-
22.934	-	745.72266	16.96035	0.47	0.6503	6889	1.45	1.07
24.948	-	405.21930	8.15961	0.62	0.6843	7363	1.77	1.09
31.943	-	410.14008	6.49033	0.53	0.8882	7166	5.23	1.28

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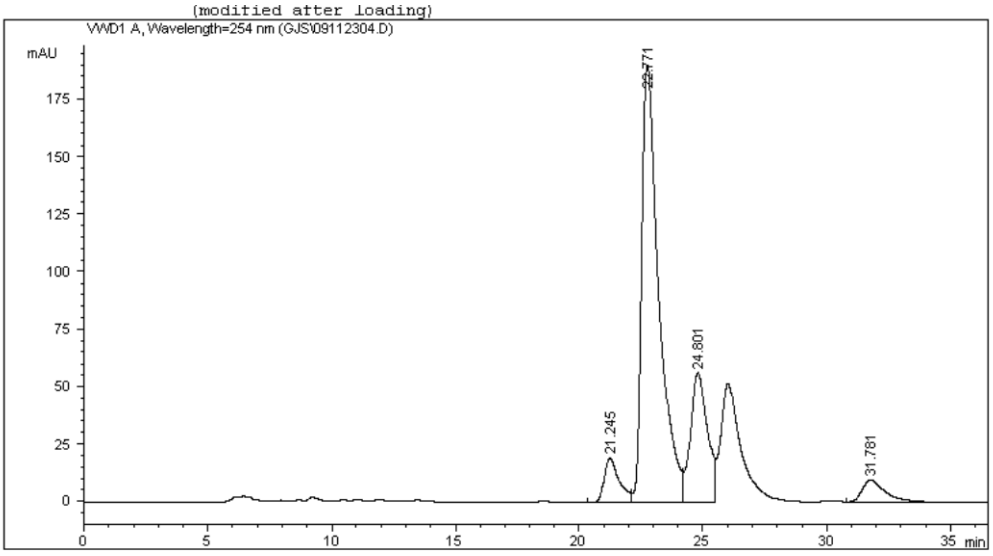
Chiral:



RetTime [min]	k'	Area mAU *s	Height [mAU]	Symm.	Width [min]	Plates	Resolution	Selectivity
21.245	-	796.52838	19.03592	0.57	0.6115	6686	-	-
22.771	-	9088.98145	188.10114	0.47	0.6746	6312	1.39	1.07
24.801	-	2690.48633	56.10231	0.77	0.7571	5944	1.67	1.09
31.781	-	667.89594	9.76560	0.50	0.9173	6650	4.90	1.28

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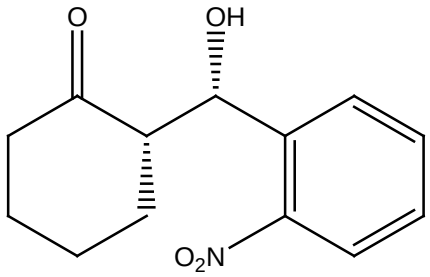
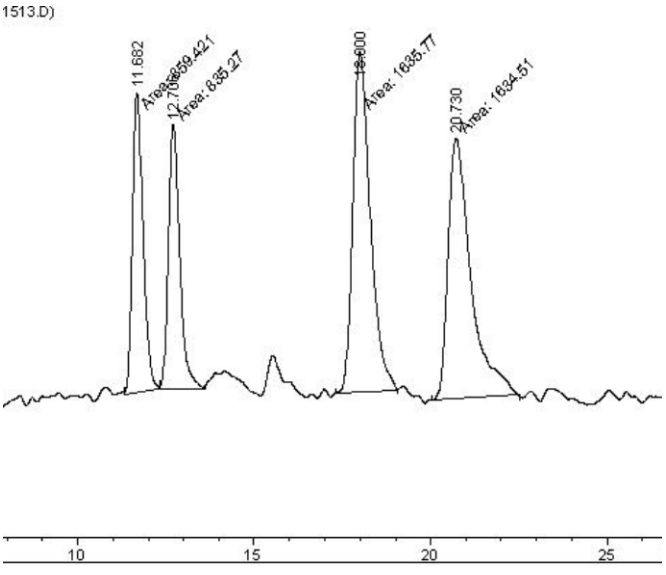
(2S,1'S)-2-(Hydroxy(2-nitrophenyl)methyl)cyclohexan-1-one



Syn/anti=64/36, ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.5-2.8 (m, 6H), 2.2-2.9 (m, 3H), 5.45 (anti-CH*OH, 1H), 5.96 (syn-CH*OH, 1H), 7.4-7.6 (2H), 7.8-8.0 (2H); ^{13}C NMR (400 NMR, $CDCl_3$) δ (ppm) 25.1, 26.7, 28.0, 29.9, 31.4, 42.8, 55.0, 57.5, 66.9, 70.0, 76.9, 77.2, 77.6, 124.3, 124.9, 128.2, 128.6, 129.2, 129.8, 133.3, 137.2, 214.3, 215.2; HRMS (MNa^+) Calcd. For: $C_{13}H_{15}NO_4Na$: 272.0899. Found: 272.0902. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (95:5 Hexane:2-propanol), 1.0 mL/min; λ=254 nm; anti enantiomer t_R=18.4 and 20.7 min; syn enantiomer t_R=11.8 (major syn-pruduct) and 12.9 min. [7]

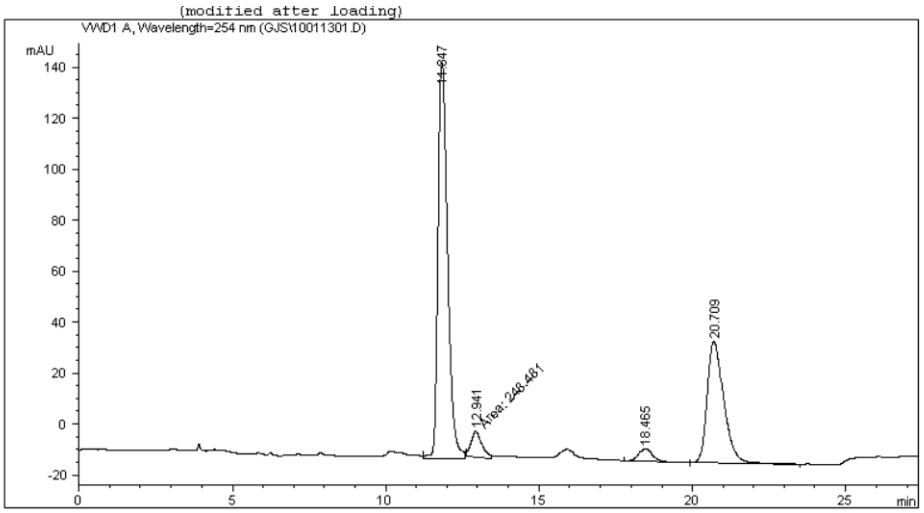
Racemate:



RetTime [min]	k'	Area mAU *s	Height [mAU]	Symm.	Width [min]	Plates	Resolution	Selectivity
11.682	-	859.42133	41.82713	0.92	0.3106	7836	-	-
12.706	-	835.27014	36.78238	0.91	0.3397	7749	1.85	1.09
18.000	-	1635.76807	47.28149	0.71	0.5145	6782	7.28	1.42
20.730	-	1634.50732	36.29799	0.57	0.6261	6073	2.81	1.15

*** End of Report ***

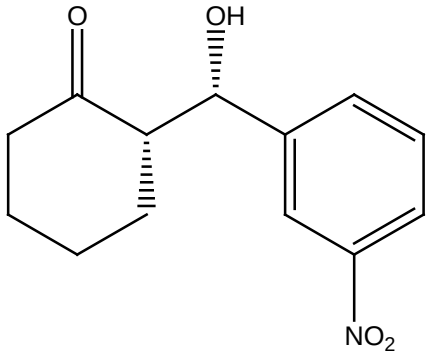
Chiral:



RetTime [min]	k'	Area mAU *s	Height [mAU]	Symm.	Width [min]	Plates	Resolution	Selectivity
11.847	-	3297.36548	152.74306	0.72	0.3203	7578	-	-
12.941	-	248.48138	10.05526	0.83	0.3689	6819	1.86	1.09
18.465	-	167.84442	5.01066	0.88	0.4902	7861	7.56	1.43
20.709	-	1799.42102	47.35897	0.65	0.5678	7369	2.49	1.12

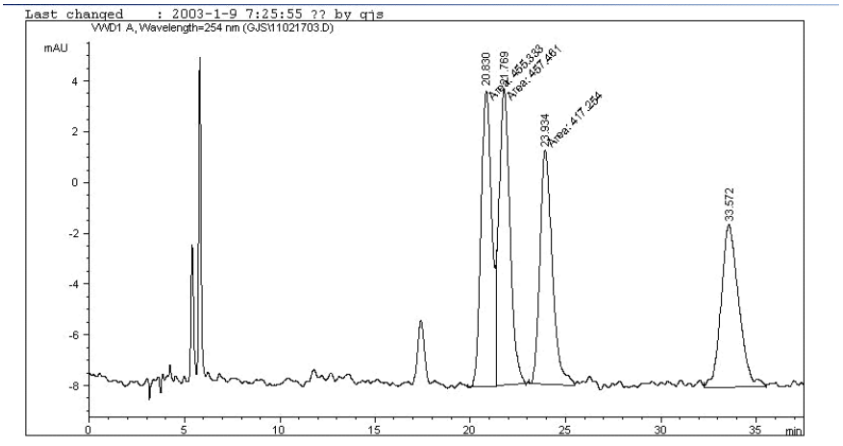
*** End of Report ***

(2S,1'S)-2-(Hydroxy(3-nitrophenyl)methyl)cyclohexan-1-one



Syn/anti=66/34, ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.5-2.1 (m, 6H), 2.4-2.68 (m, 3H), 3.29(syn-OH, 1H), 4.1 (anti-OH, 1H), 4.90 (anti-CH*OH, 1H), 5.48 (syn-CH*OH, 1H), 7.5-7.7 (2H), 8.1-8.2 (2H); ^{13}C NMR (400 NMR, $CDCl_3$) δ (ppm) 24.8, 26.1, 27.8, 28.4, 29.8, 30.9, 42.7, 56.9, 57.3, 70.0, 74.1, 76.9, 77.2, 77.5, 121.0, 122.2, 123.0, 129.3, 132.1, 133.4, 144.0, 148.4, 214.3, 215.1; HRMS (MNa^+) Calcd. For: $C_{13}H_{15}NO_4Na$: 272.0899. Found: 272.0898. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (95:5 Hexane:2-propanol), 1.0 mL/min; λ=254 nm; anti enantiomer t_R=23.8 and 32.7 min; syn enantiomer t_R=20.6 and 21.6 min (major syn-product) [7].

Racemate:



RetTime [min]	k'	Area mAU *s	Height [mAU]	Symm.	Width [min]	Plates	Resolution	Selectivity
20.830	-	455.33347	11.72084	0.68	0.6212	6229	-	-
21.769	-	457.46088	11.69538	0.83	0.6625	5982	0.86	1.05
23.934	-	417.25424	9.25202	0.85	0.6601	7284	1.92	1.10
33.572	-	415.25781	6.40810	0.76	0.9610	6762	6.99	1.40

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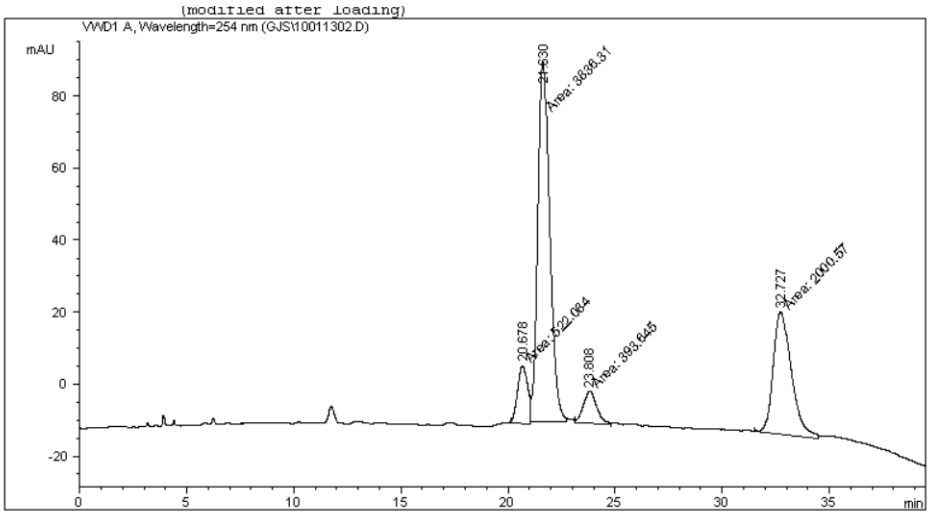
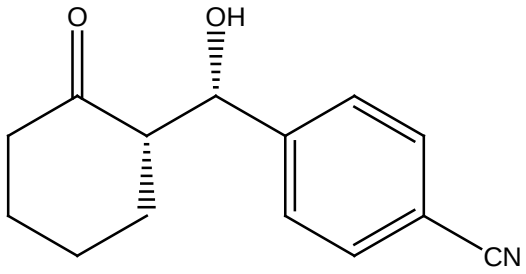
Chiral:



RetTime [min]	k'	Area mAU *s	Height [mAU]	Symm.	Width [min]	Plates	Resolution	Selectivity
20.678	-	522.08411	16.14416	0.91	0.5654	7409	-	-
21.630	-	3836.30811	100.04895	0.92	0.5824	7641	0.97	1.05
23.808	-	393.64481	8.98480	0.81	0.6455	7537	2.08	1.10
32.727	-	2000.57141	33.91225	0.79	0.8882	7522	6.83	1.37

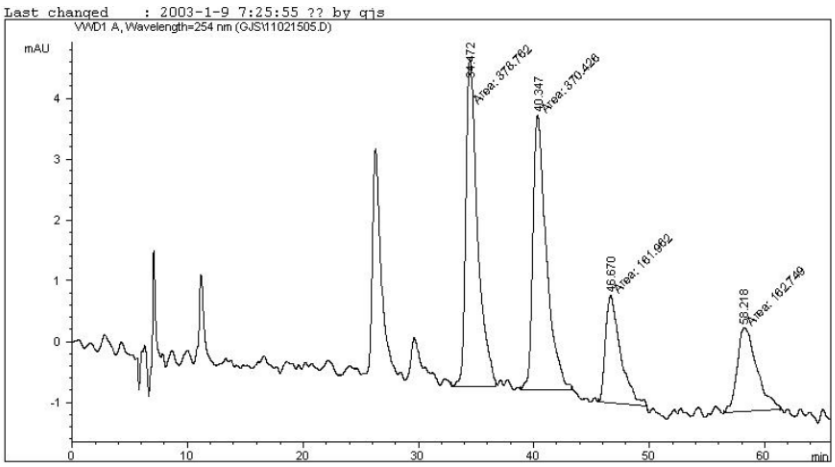
*** End of Report ***

(2S,1'S)-2-(Hydroxy(4-cyanophenyl)methyl)cyclohexan-1-one



Syn/anti=69/31, ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.5-2.1 (m, 6H), 2.3-2.7 (m, 3H), 4.85 (anti-CH*OH, 1H), 5.43 (syn-CH*OH, 1H), 7.42 (2H), 7.63 (2H); ^{13}C NMR (400 NMR, $CDCl_3$) δ (ppm) 24.9, 26.1, 28, 30.9, 42.8, 57.0, 70.4, 74.4, 76.9, 77.2, 111, 119.1, 126.7, 128.0, 130.8, 132.2, 147.2, 214.4; HRMS (MNa^{+}) Calcd. For: $C_{14}H_{15}NO_2Na$: 252.1000. Found: 252.1005. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (90:10 Hexane:2-propanol), 0.5 mL/min; λ=254 nm; anti enantiomer t_R=47.0 and 58.8 min; syn enantiomer t_R=34.7 and 40.5 min (major syn-product) [8].

Racemate:



RetTime [min]	k'	Area mAU *s	Height [mAU]	Symm.	Width [min]	Plates	Resol ution	Select ivity
34.472	-	378.76221	5.39652	0.51	0.9707	6987	-	-
40.347	-	370.42554	4.51371	0.58	1.1891	6379	3.20	1.17
46.670	-	161.96198	1.77071	0.55	1.2958	7186	2.99	1.16
58.218	-	162.74921	1.37424	0.56	1.7666	6017	4.43	1.25

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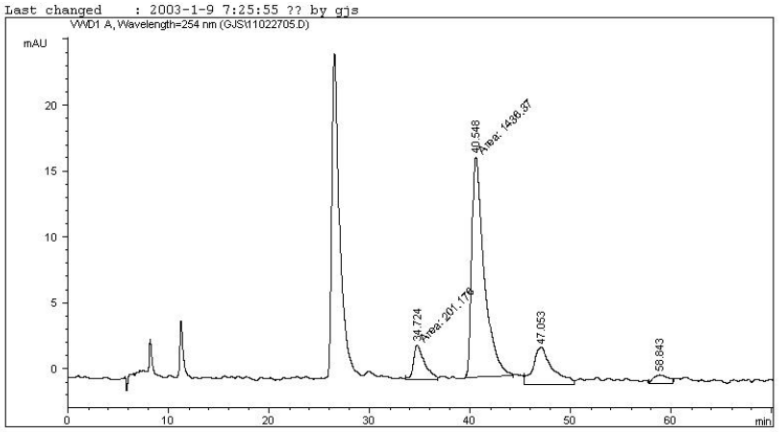
Chiral:



RetTime [min]	k'	Area mAU *s	Height [mAU]	Symm.	Width [min]	Plates	Resol ution	Select ivity
34.724	-	201.17650	2.62804	0.49	1.0629	5913	-	-
40.548	-	1436.37097	16.76122	0.47	1.2036	6287	3.02	1.17
47.053	-	377.32501	2.84129	0.66	1.6841	4325	2.65	1.16
58.843	-	65.69677	6.41719e-1	0.67	2.1194	4271	3.64	1.25

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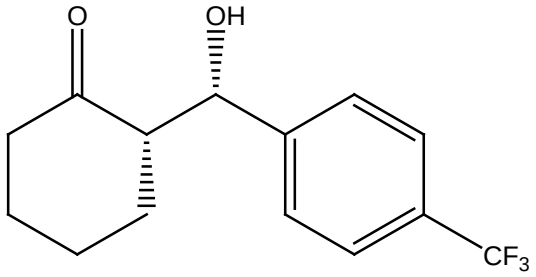
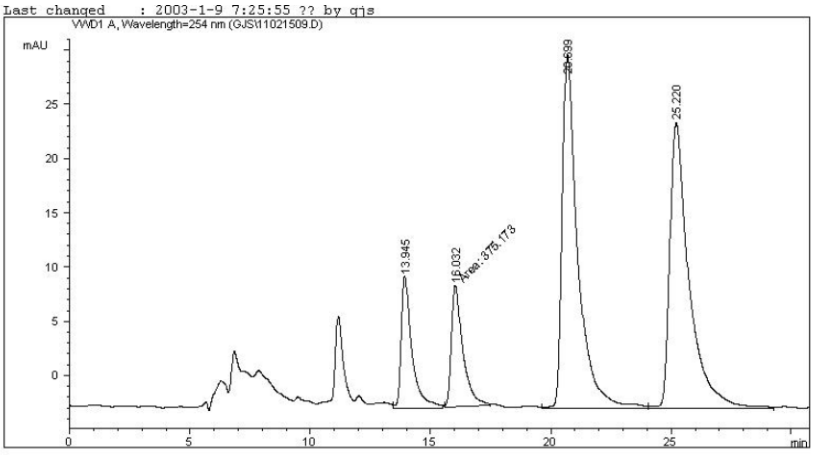
(2S,1'S)-2-(Hydroxy(4-trifluoromethylphenyl)methyl)cyclohexan-1-one



Syn/anti=64/36, ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.5-2.1 (m, 6H), 2.3-2.6 (m, 3H), 3.18 (syn-OH, 1H), 4.07 (anti-OH, 1H), 4.84 (anti-CH*OH, 1H), 5.44 (syn-CH*OH, 1H), 7.43 (2H), 7.59 (2H); ^{13}C NMR (400 NMR, $CDCl_3$) δ (ppm) 24.9, 26.1, 27.9, 29.9, 31.0, 42.8, 57.1, 70.4, 74.5, 76.9, 77.2, 125.3, 126.3, 127.6, 145.8, 149, 214.6, 215.3; HRMS (MNa^+) Calcd. For: $C_{14}H_{15}O_2F_3Na$: 295.0922. Found: 295.0930. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (90:10 Hexane:2-propanol), 0.5 mL/min; λ=254 nm; anti enantiomer t_R=20.2 and 24.6 min; syn enantiomer t_R=13.6 and 15.7 min (major syn-product) [8].

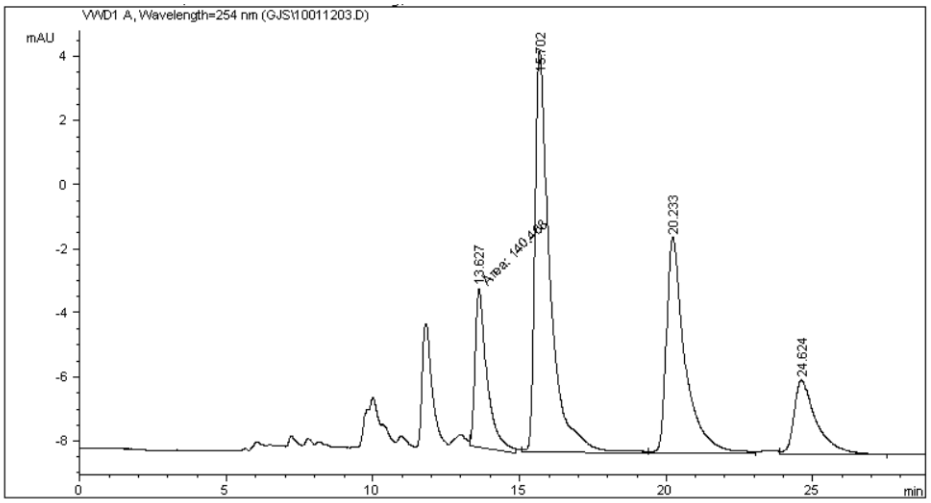
Racemate:



RetTime [min]	k'	Area mAU *s	Height [mAU]	Symm.	Width [min]	Plates	Resolution	Selectivity
13.945	-	373.12479	12.05669	0.49	0.4028	6639	-	-
16.032	-	375.17255	11.21222	0.67	0.4514	6990	2.87	1.15
20.699	-	1476.72656	32.36541	0.46	0.6018	6554	5.21	1.29
25.220	-	1472.10364	26.29125	0.45	0.7474	6308	3.94	1.22

*** End of Report ***

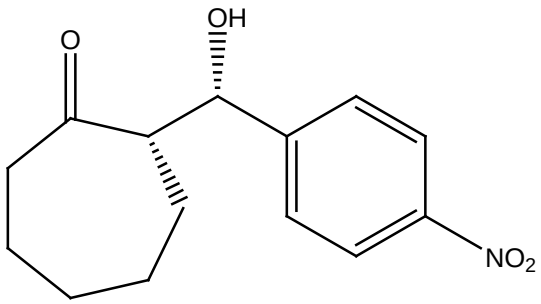
Chiral:



RetTime [min]	k'	Area mAU *s	Height [mAU]	Symm.	Width [min]	Plates	Resolution	Selectivity
13.627	-	140.46758	4.97499	0.53	0.3786	7179	-	-
15.702	-	453.92279	12.29983	0.46	0.4805	5916	2.84	1.15
20.233	-	295.81152	6.69252	0.47	0.5824	6686	5.01	1.29
24.624	-	119.95596	2.27647	0.49	0.7183	6511	3.97	1.22

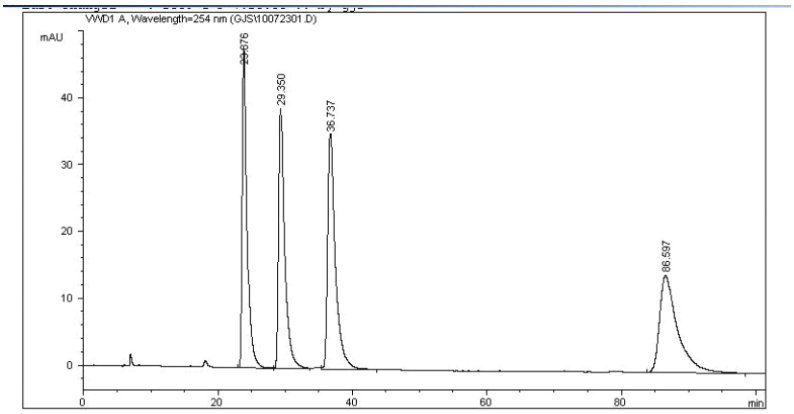
*** End of Report ***

(2S,1'S)-2-(Hydroxy(4-nitrophenyl)methyl)cycloheptan-1-one



Syn/anti=71/29, ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.6-2.06 (m, 8H), 2.5-2.89 (m, 3H), 3.6 (syn-OH, 1H), 4.15 (anti-OH, 1H), 4.93 (anti-CH*OH, 1H), 5.32 (syn-CH*OH, 1H), 7.53 (2H), 8.22 (2H); ^{13}C NMR (400 NMR, $CDCl_3$) δ (ppm) 23.2, 23.8, 29.1, 44, 57, 58, 72.5, 75, 76.8, 77.2, 123.7, 126.9, 127.8, 149, 217; HRMS (MNa^+) Calcd. For: $C_{14}H_{17}NO_4Na$: 286.1055. Found: 286.1053. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (90:10 Hexane:2-propanol), 0.5 mL/min; λ=254 nm; anti enantiomer t_R=36.6 and 86 min; syn enantiomer t_R=23.9 and 29.3 min (major syn-product) [9, 10].

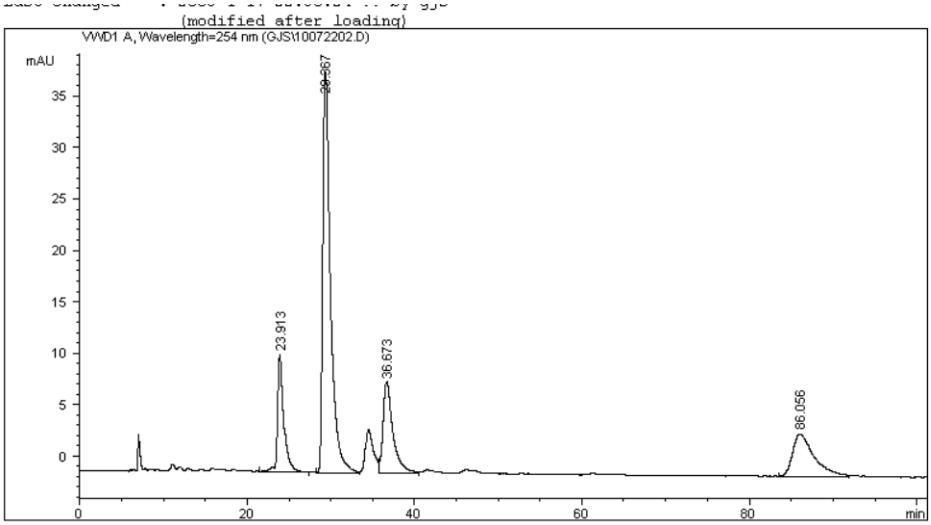
Racemate:



RetTime [min]	k'	Area mAU *s	Height [mAU]	Symm.	Width [min]	Plates	Resolution	Selectivity
23.876	-	2412.09595	47.82505	0.48	0.6843	6744	-	-
29.350	-	2422.04297	38.95824	0.47	0.8445	6692	4.21	1.23
36.737	-	2760.76855	35.12834	0.48	1.0629	6618	4.55	1.25
86.597	-	2732.67114	14.56970	0.46	2.5529	6375	16.20	2.36

*** End of Report ***

Chiral:



RetTime [min]	k'	Area mAU *s	Height [mAU]	Symm.	Width [min]	Plates	Resolution	Selectivity
23.913	-	606.09351	11.37281	0.57	0.6843	6765	-	-
29.367	-	2417.83057	38.72247	0.47	0.8445	6699	4.19	1.23
36.673	-	717.26404	8.83688	0.52	1.0774	6418	4.47	1.25
86.056	-	759.01685	4.16856	0.49	2.5189	6466	16.13	2.35

*** End of Report ***

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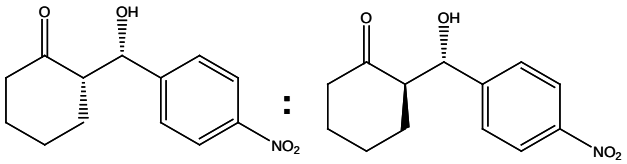
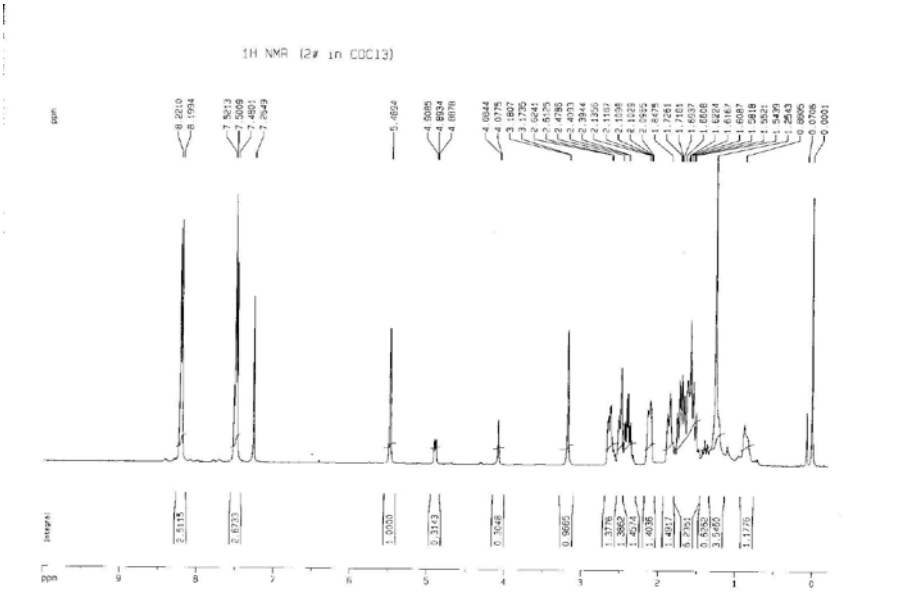
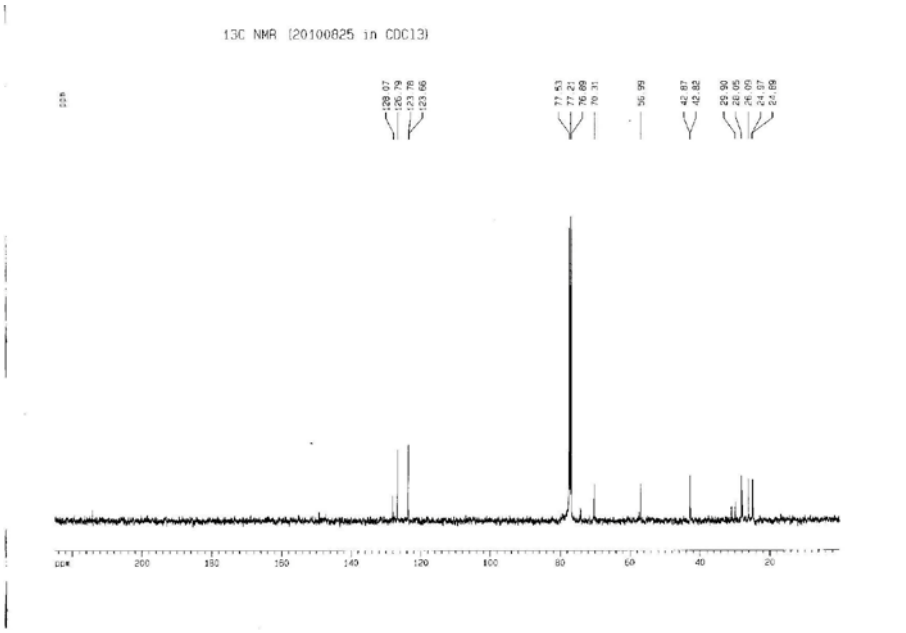
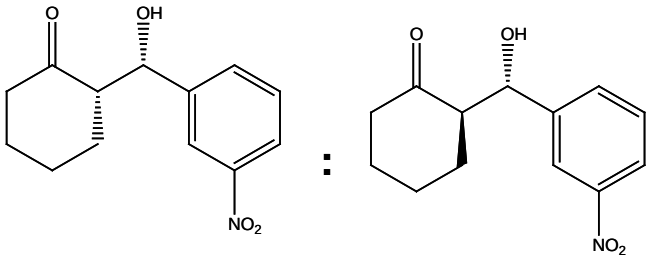
NMR Spectra



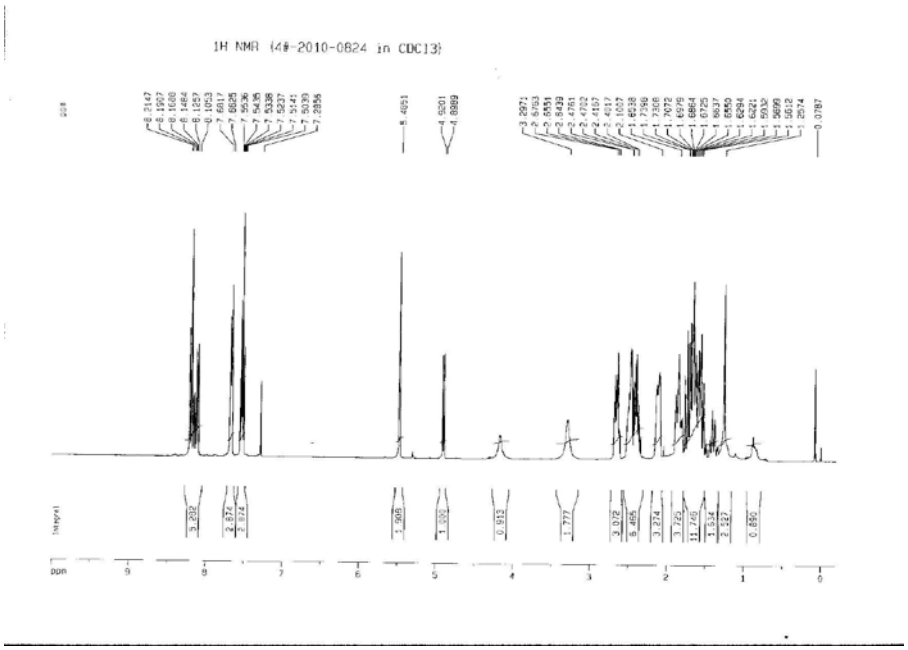
75 : 25






O
OH
NO2
:
O
OH
NO2

66 : 34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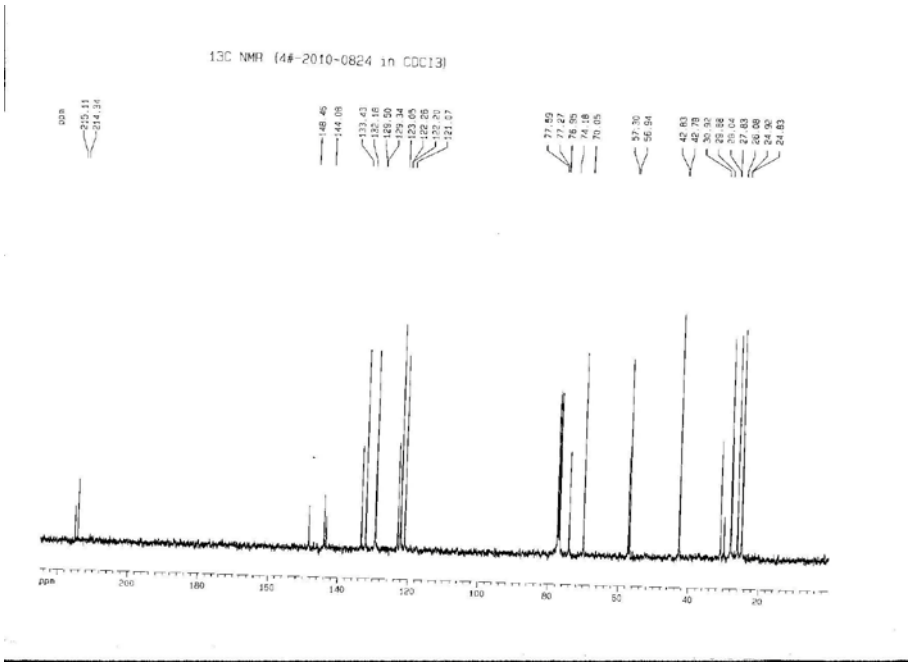
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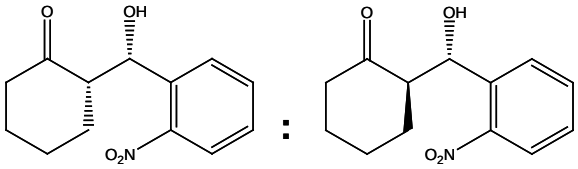
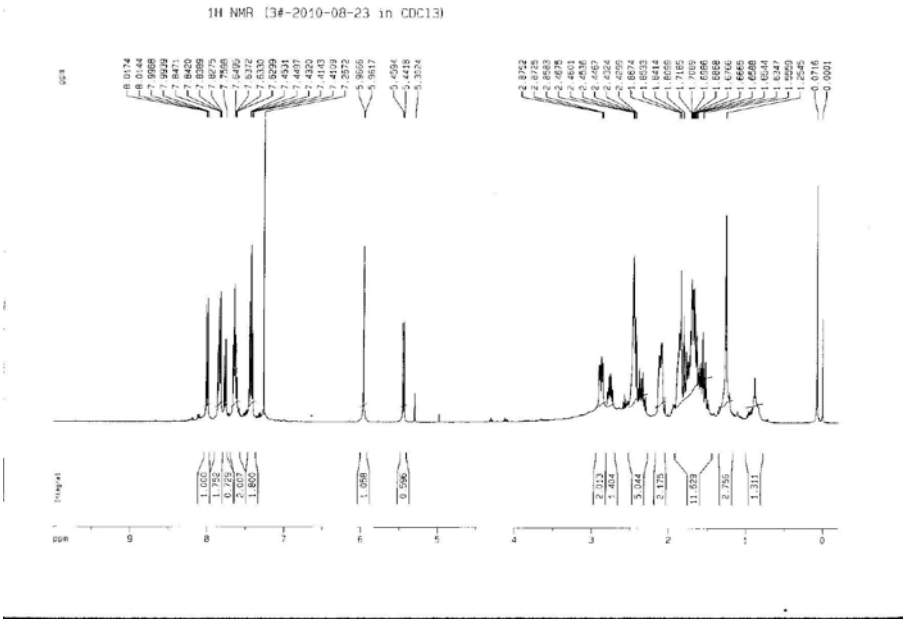

O
OH
O2N
:
O
OH
O2N

64 : 36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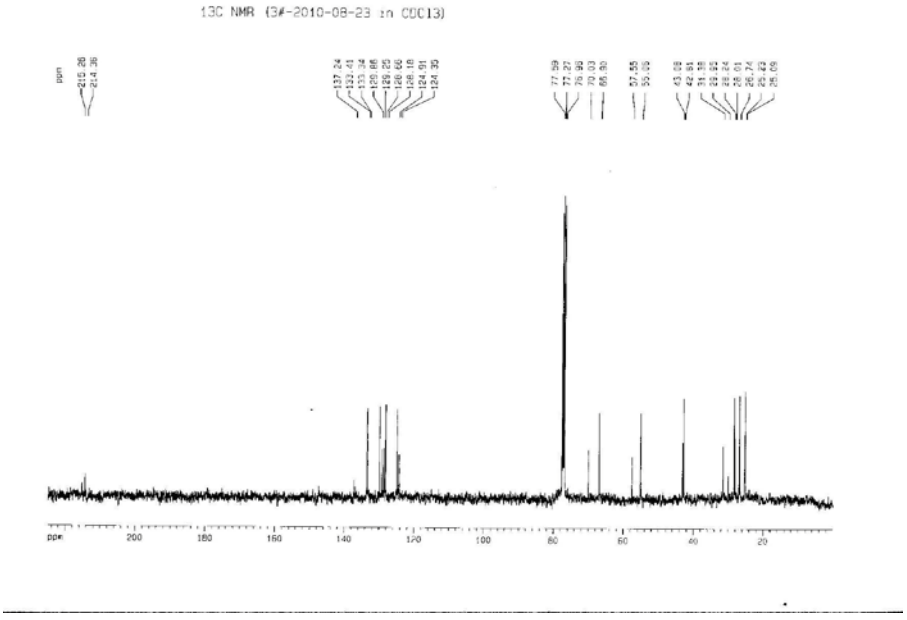
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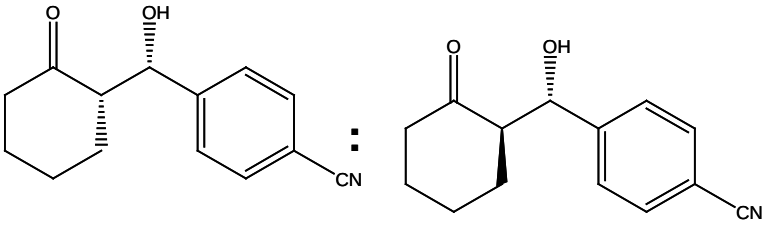
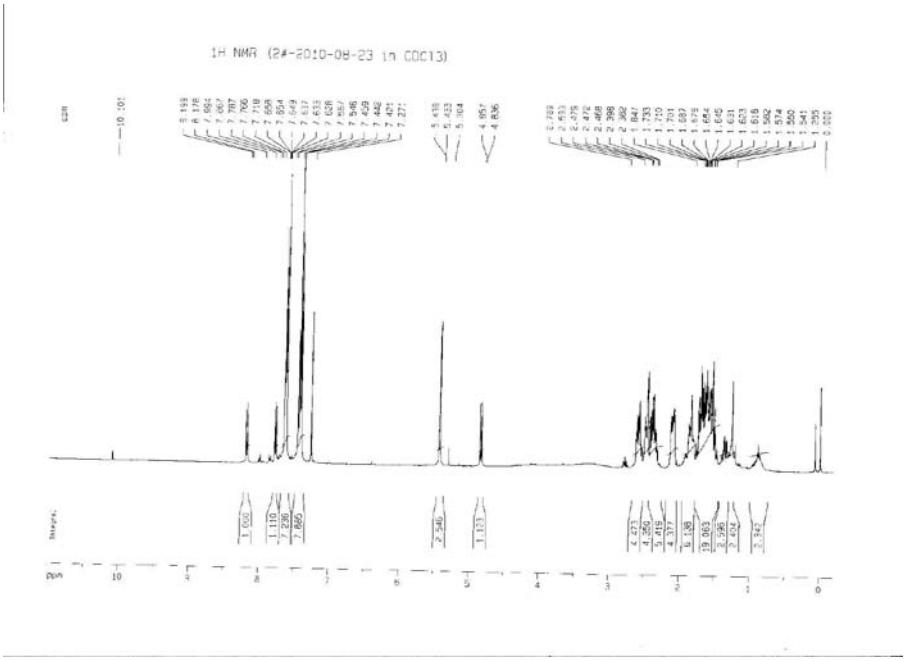

O
OH
CN
:
O
OH
CN

69 : 31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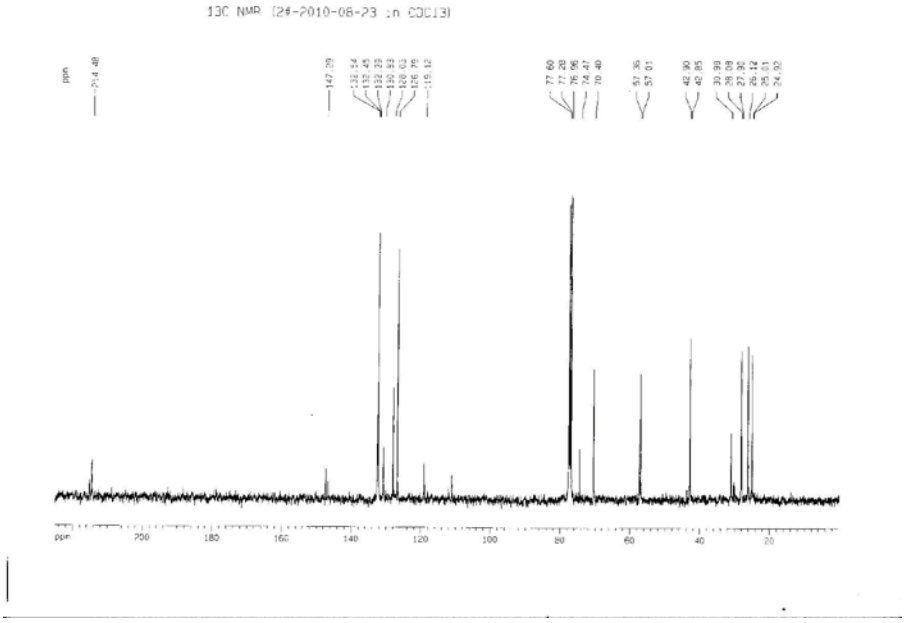
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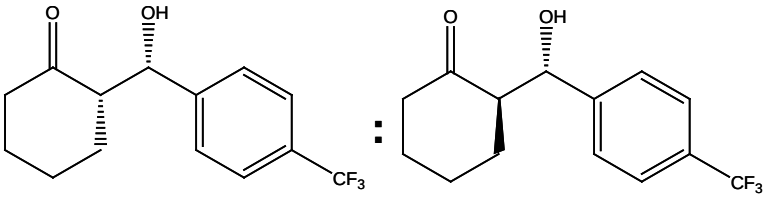
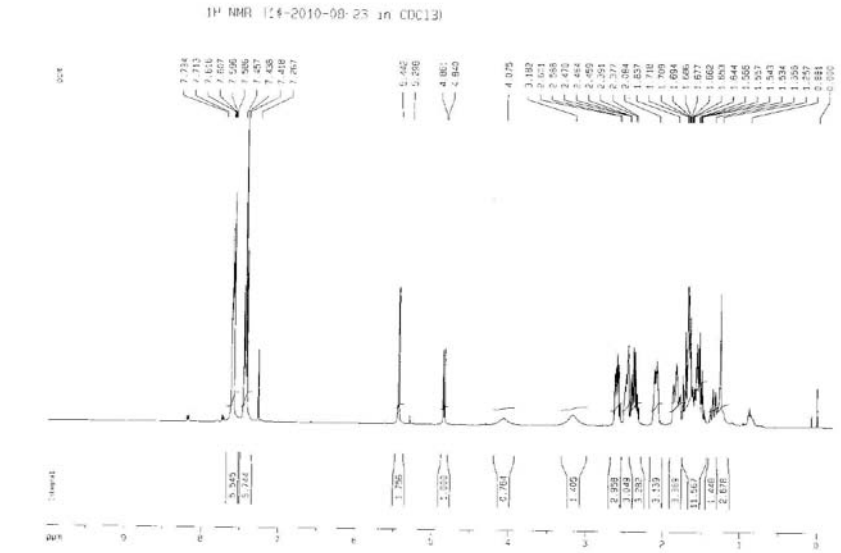
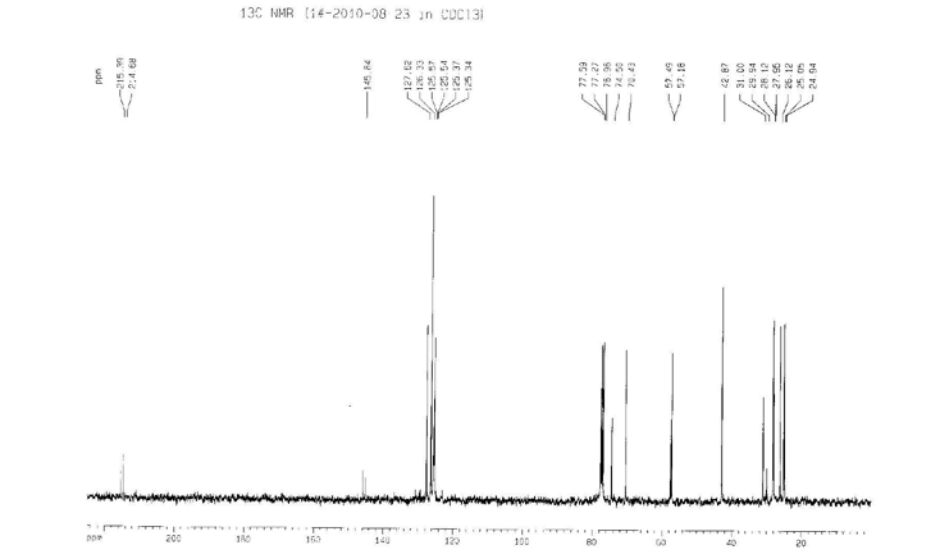
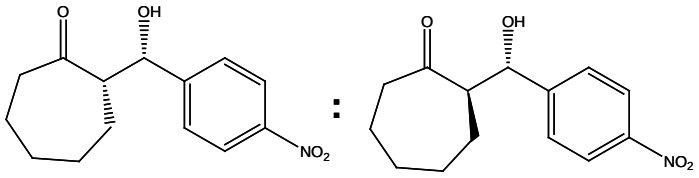


64 : 36







71 : 29