Supplementary Information

Asymmetric direct aldol reaction catalyzed by chiral amine macrocycle-metal(II) complex under solvent-free conditions

Koichi Tanaka,*[,a] Azusa Asakura, [a] Toshihide Muraoka,[a] Przemysław Kalicki, [b] and Zofia Urbanczyk-Lipkowska[b]
[a] Department of Chemistry and Materials Engineering, Faculty of Chemistry, Materials and Bioengineering, Kansai University, Suita, Osaka 564-8680, Japan.
[b] Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warszawa, Poland.

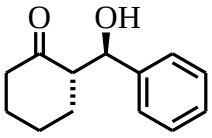
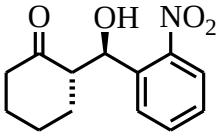
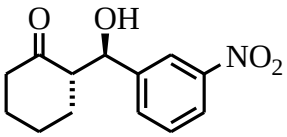
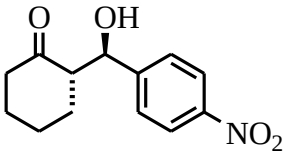
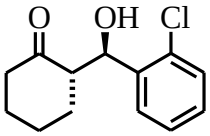
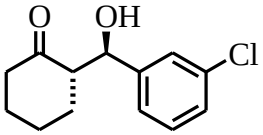
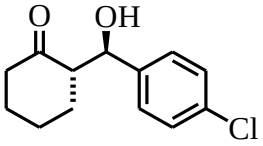
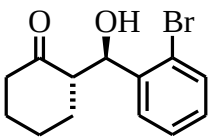
General

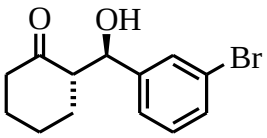
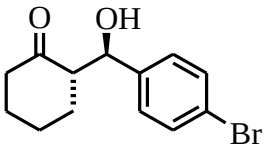
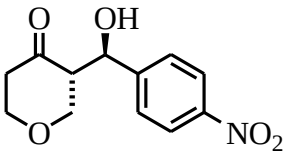
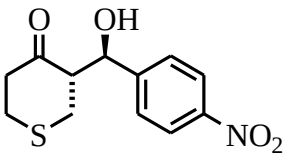
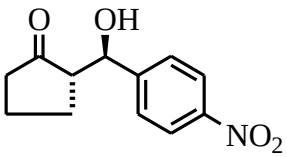
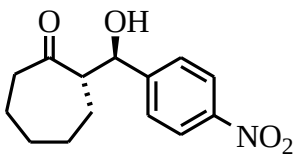
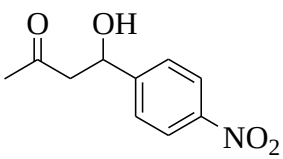
All reagents were purchased from commercial suppliers. ^{1}H-NMR spectra were recorded on a JEOL JNM-AL 400 spectrometer with tetramethylsilane as the internal standard. The diastereoselectivity of the reaction was determined by 1H-NMR spectroscopy of the crude product. Enantiomeric excesses were determined by high-performance liquid chromatography (HPLC) either on Chiralpak OD or Chiralpak AD-H column (Daisel). The absolute configuration of aldol products was determined by comparison with published HPLC retention times. Reactions in the ball mill were conducted using a Fritsch Planetary Micro Mill model "Pulverisette 7".

Typical procedure for the solvent-free asymmetric aldol reaction between cyclohexanone and 4-nitrobenzaldehyde in a ball mill:

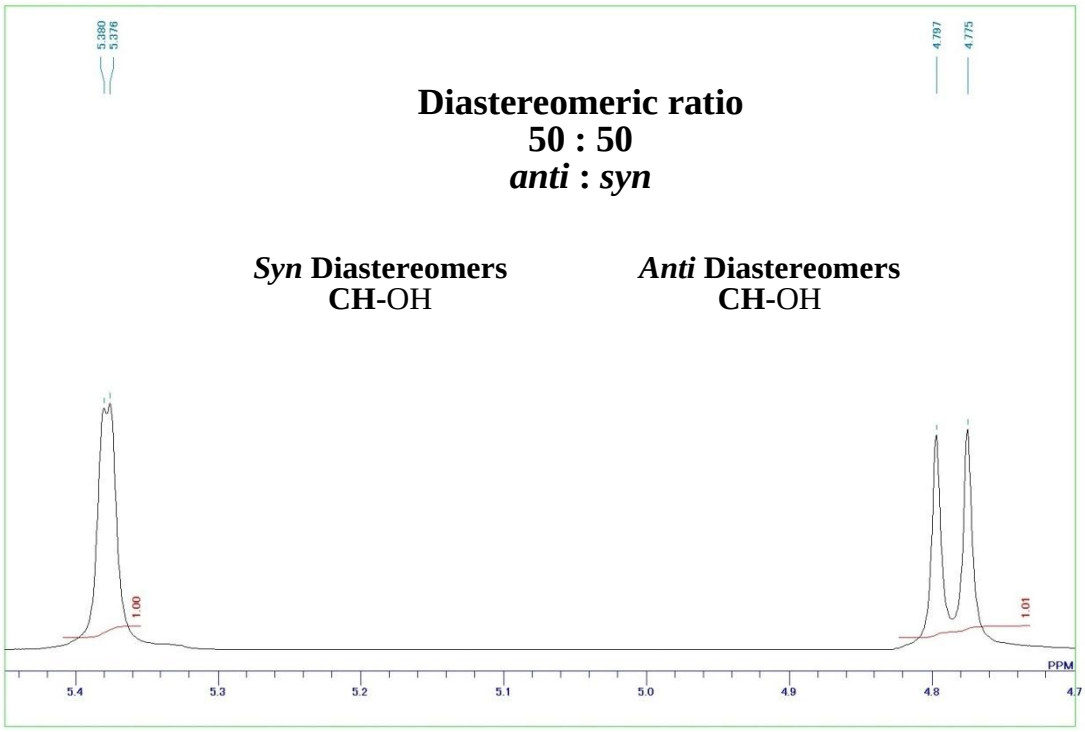
A mixture of (*S,S,S,S,S,S*)-**1** (0.13 g, 0.02 mmol), $CoBr_2$ (0.087 g, 0.04 mmol), cyclohexanone **8** (2.0 mmol) and 4-nitrobenzaldehyde **9** (0.151g, 1.0 mmol) was milled for 24 h at 100 rpm at room temperature using a planetary ball mill (Fritsch P-7). The crude reaction mixture was purified by column chromatography (silica gel, hexane/EtOAc = 2:1) to afford a mixture of *syn*- and *anti*-aldol reaction products (*1'R, 2S*)-**10** (*anti/syn* = 71:29) in 82% yield with the enantioselectivity of 93% ee. The diastereoselectivity was determined by ^{1}H NMR of the crude product. The ee was determined by chiral HPLC using Chiralpak AD-H column (hexane:2-PrOH (90:10), 1 mL min^{-1}).

Table S1. ^{1}H-NMR spectroscopic data for diastereoisomers and HPLC data for diastereoisomers of compounds obtained in the asymmetric aldol reactions.

compound	^{1}H-NMR /$CDCl_3$ (C***H***OH) in ppm *syn* *anti*	HPLC column eluent / flow rate	retention time (min) *anti-major enantiomer*	retention time (min) *anti-minor enantiomer*
	5.38 4.78	CHIRALPAK OD Hexane : 2-PrOH (95 : 5) / 0.5 mL min^{-1}	19.32	20.72
	5.95 5.45	CHIRALPAK AD-H Hexane : 2-PrOH (90 : 10) / 1 mL min^{-1}	18.94	25.01
	5.41 5.05	CHIRALPAK AD-H Hexane : 2-PrOH (95 : 5) / 0.8 mL min^{-1}	9.64	12.15
	5.49 4.92	CHIRALPAK AD-H Hexane : 2-PrOH (90 : 10) / 1 mL min^{-1}	28.60	21.79
	5.34 4.75	CHIRALPAK AD-H Hexane : 2-PrOH (95 : 5) / 0.5 mL min^{-1}	29.29	24.17
	5.71 5.35	CHIRALPAK AD-H Hexane : 2-PrOH (90 : 10) / 0.5 mL min^{-1}	22.45	25.32
	5.34 4.77	CHIRALPAK AD-H Hexane : 2-PrOH (90 : 10) / 1 mL min^{-1}	10.05	8.68
	5.63 5.31	CHIRALPAK OD Hexane : 2-PrOH (95 : 5) / 1 mL min^{-1}	10.55	13.07

	5.38 4.78	CHIRALPAK AD-H Hexane : 2-PrOH (90 : 10) / 0.5 mL min^{-1}	26.14	27.75
	5.34 4.91	CHIRALPAK AD-H Hexane : 2-PrOH (90 : 10) / 0.5 mL min^{-1}	33.09	28.5
	5.53 5.07	CHIRALPAK AD-H Hexane : 2-PrOH (90 : 10) / 1 mL min^{-1}	24.34	26.88
	5.06 4.84	CHIRALPAK AD-H Hexane : 2-PrOH (90 : 10) / 1 mL min^{-1}	22.12	29.12
	5.56 4.85	CHIRALPAK AD-H Hexane : 2-PrOH (95 : 5) / 1 mL min^{-1}	50.04	47.59
	5.29 4.95	CHIRALPAK AD-H Hexane : 2-PrOH (95 : 5) / 1 mL min^{-1}	86.19	38.39
	5.70	CHIRALPAK AS Hexane : 2-propanol (70 : 30) / 1mL min-1	11.96	14.35

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



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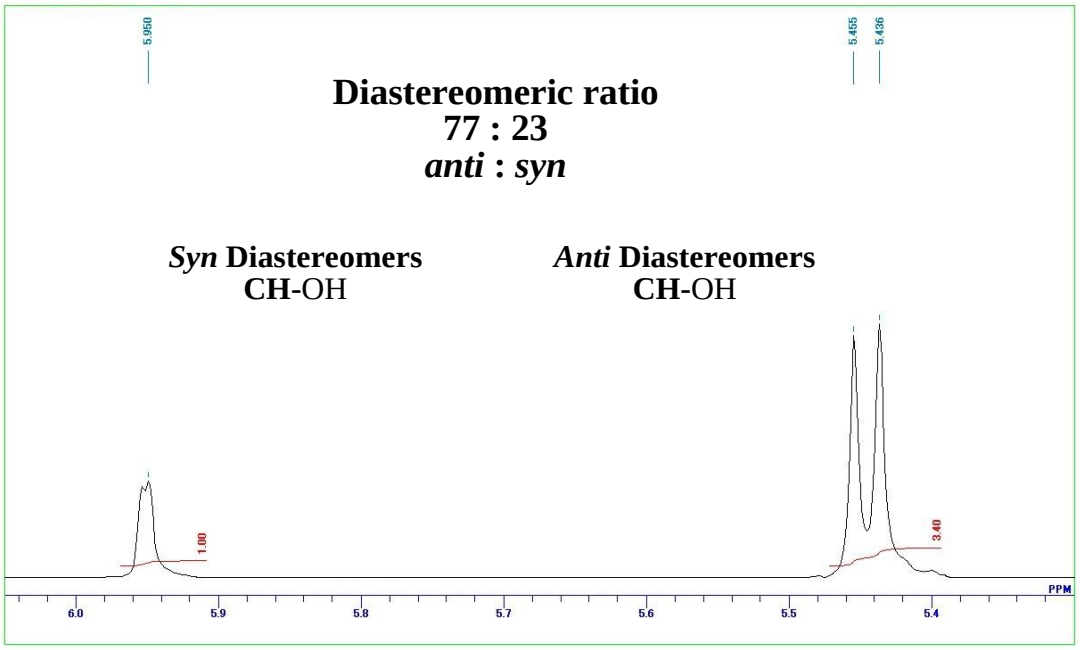

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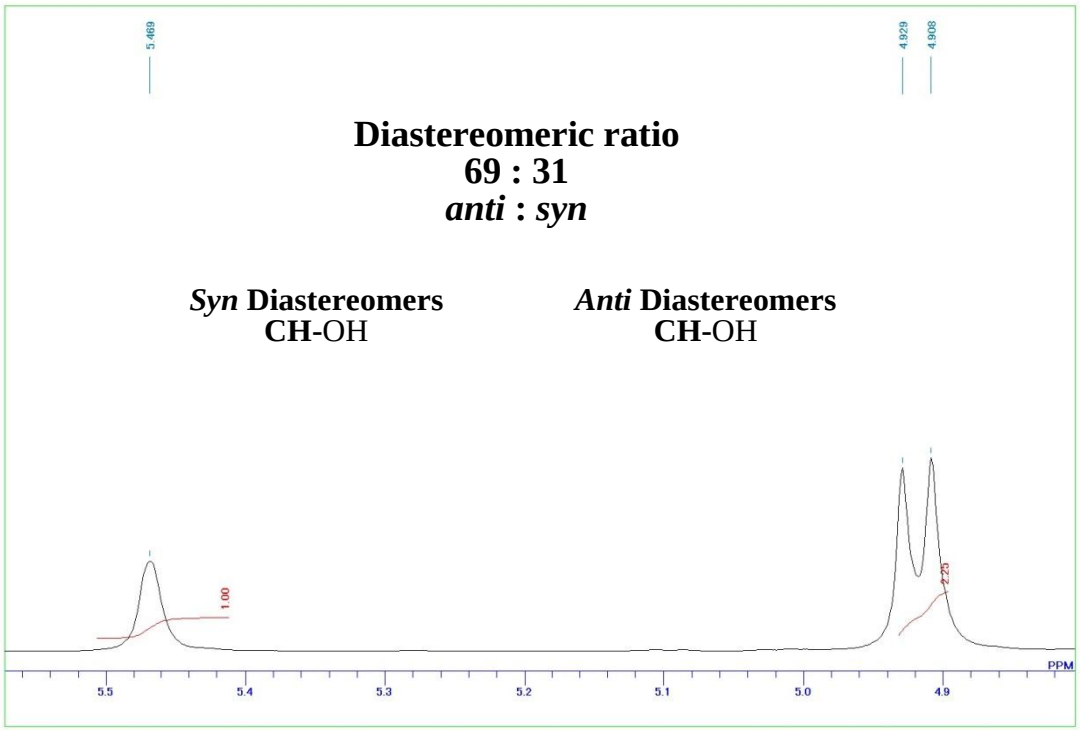

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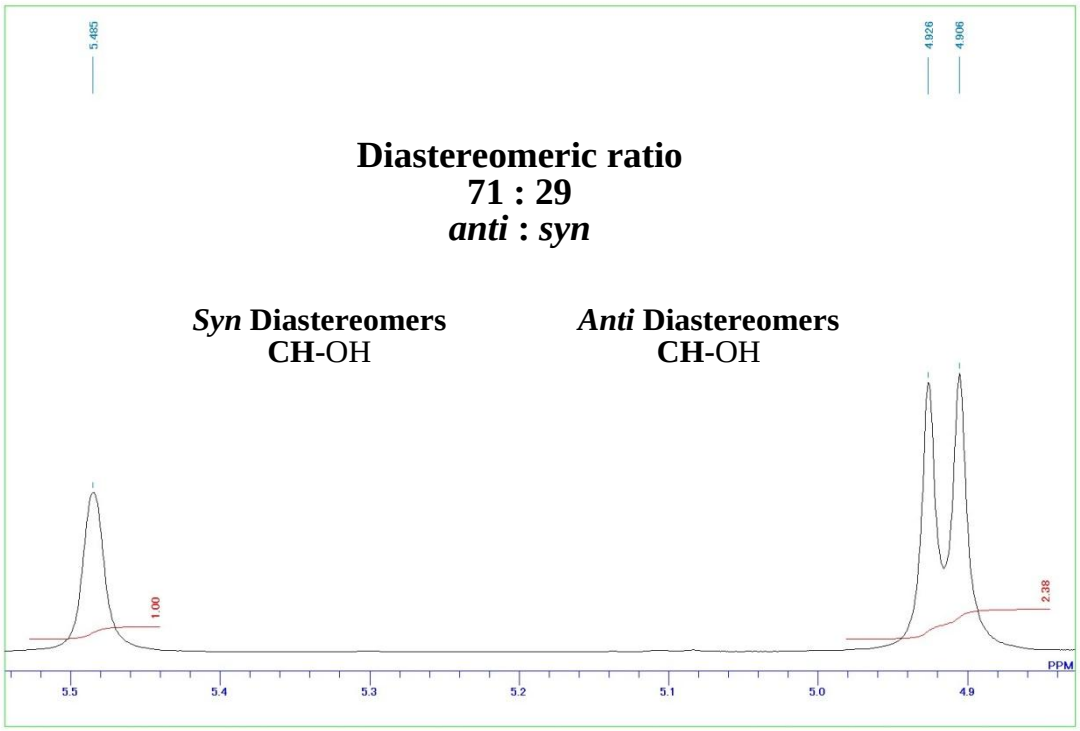

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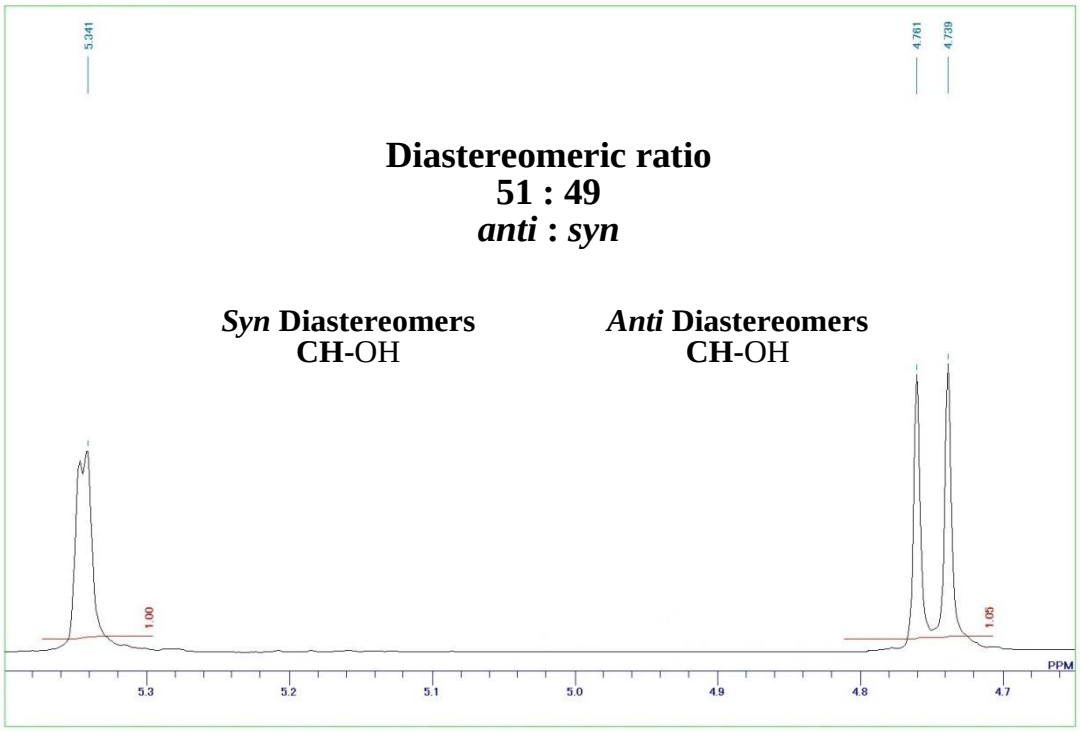

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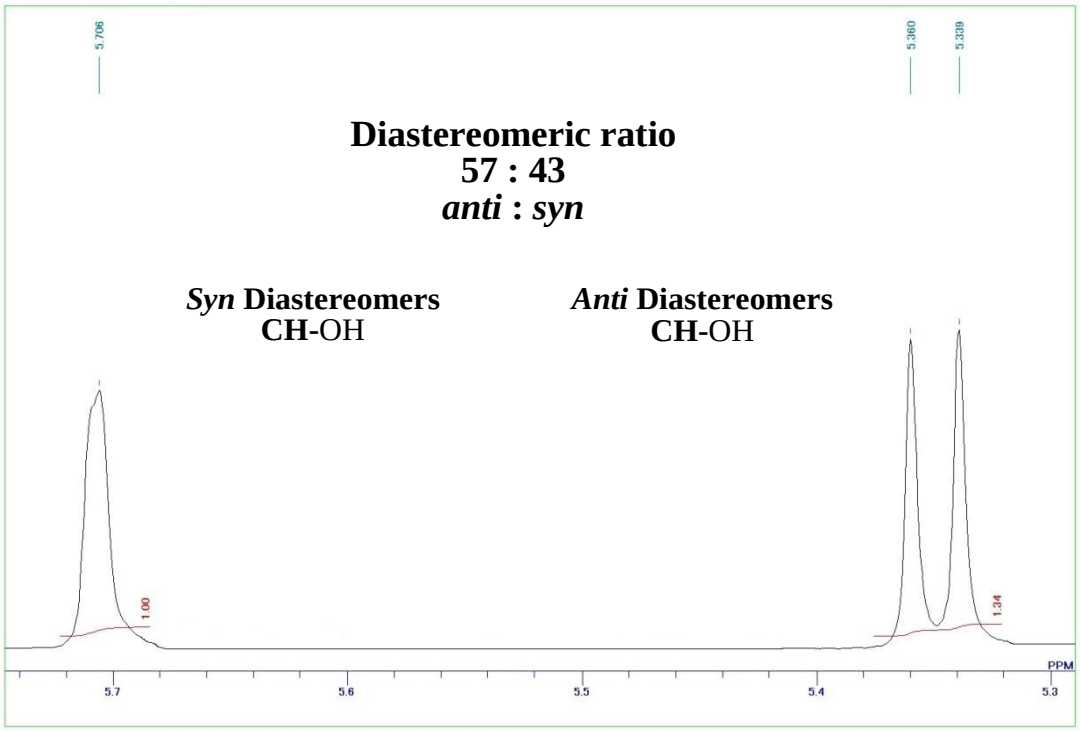

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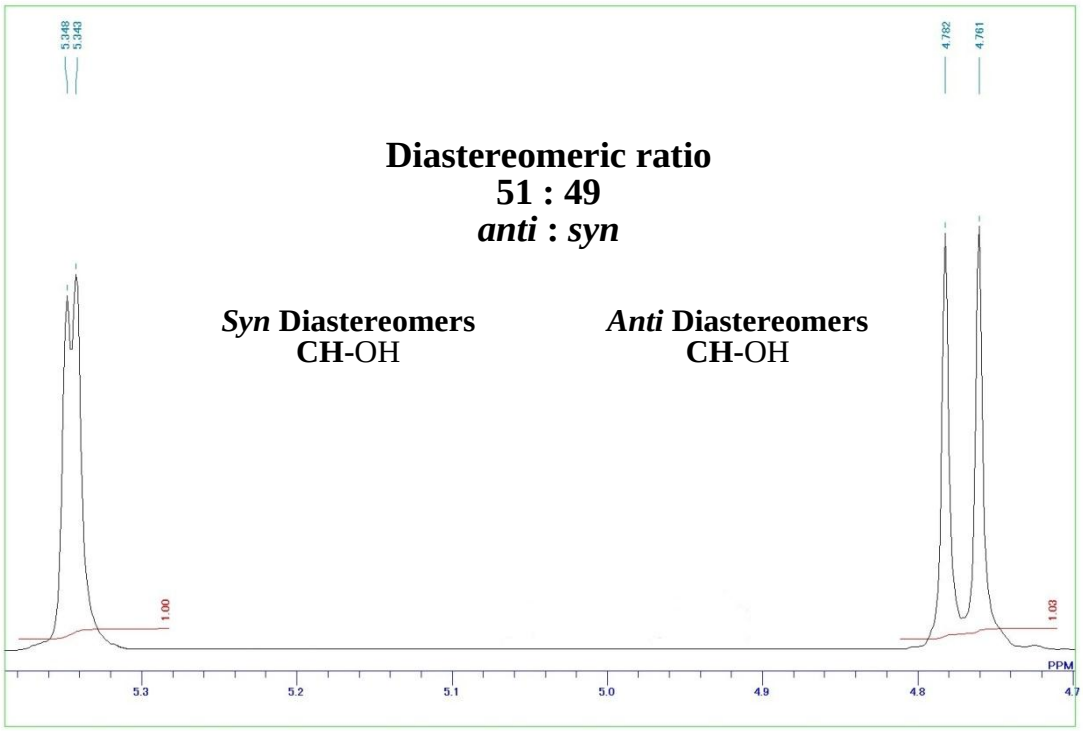

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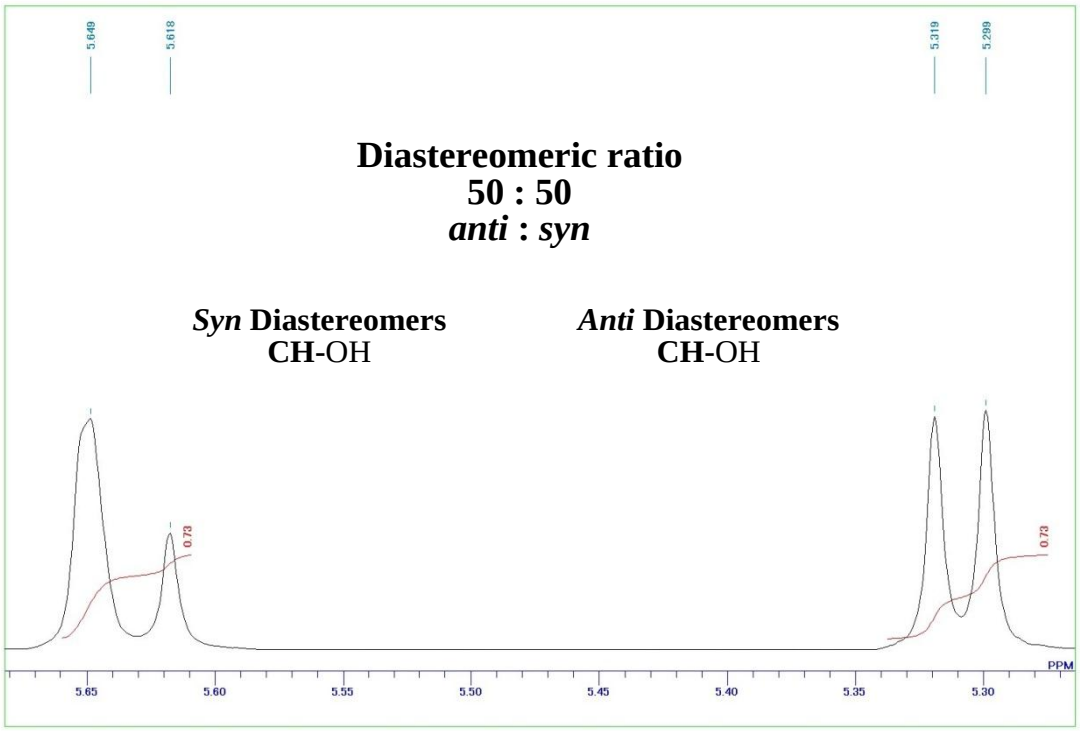

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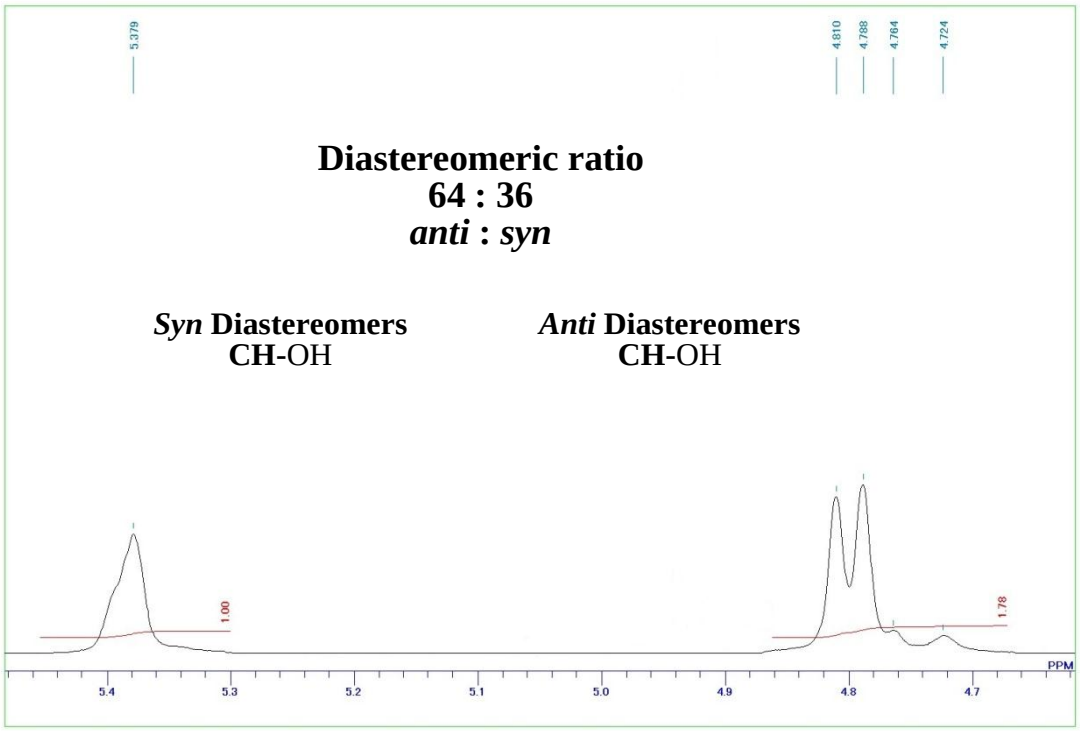

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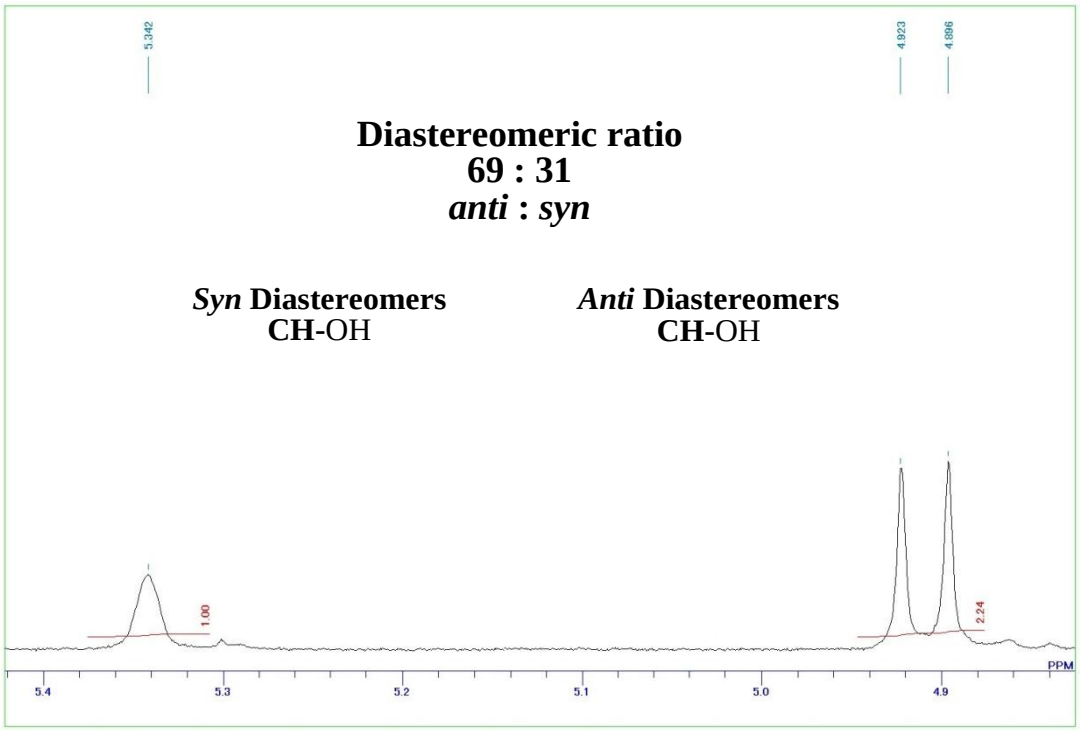

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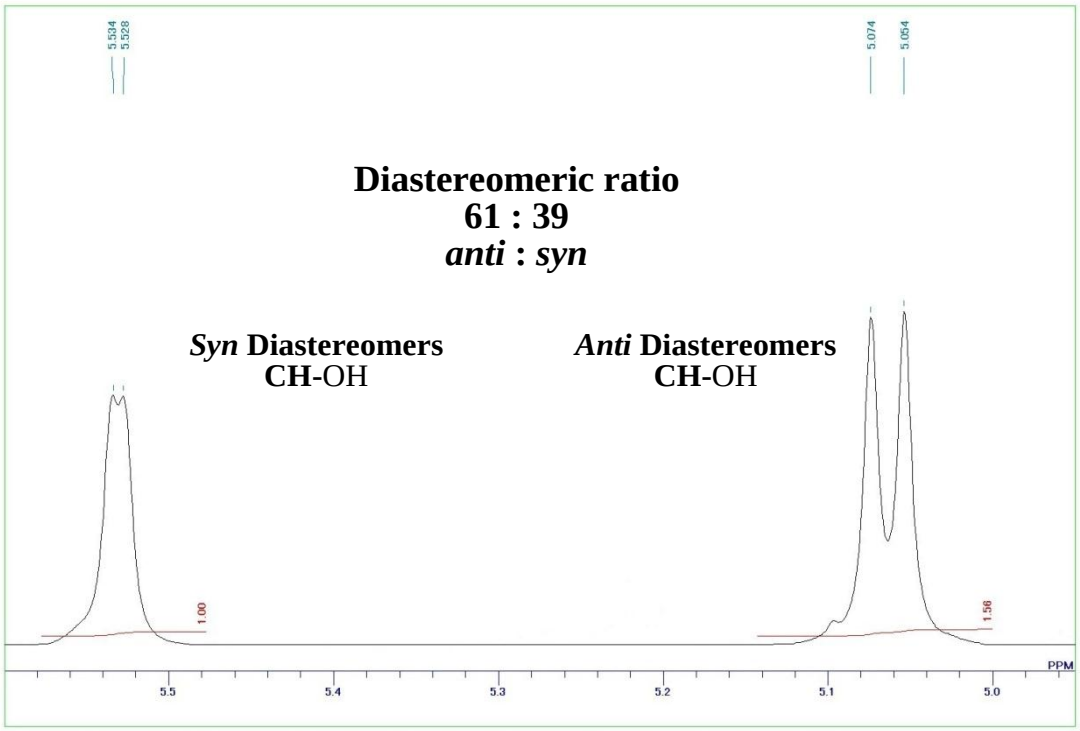

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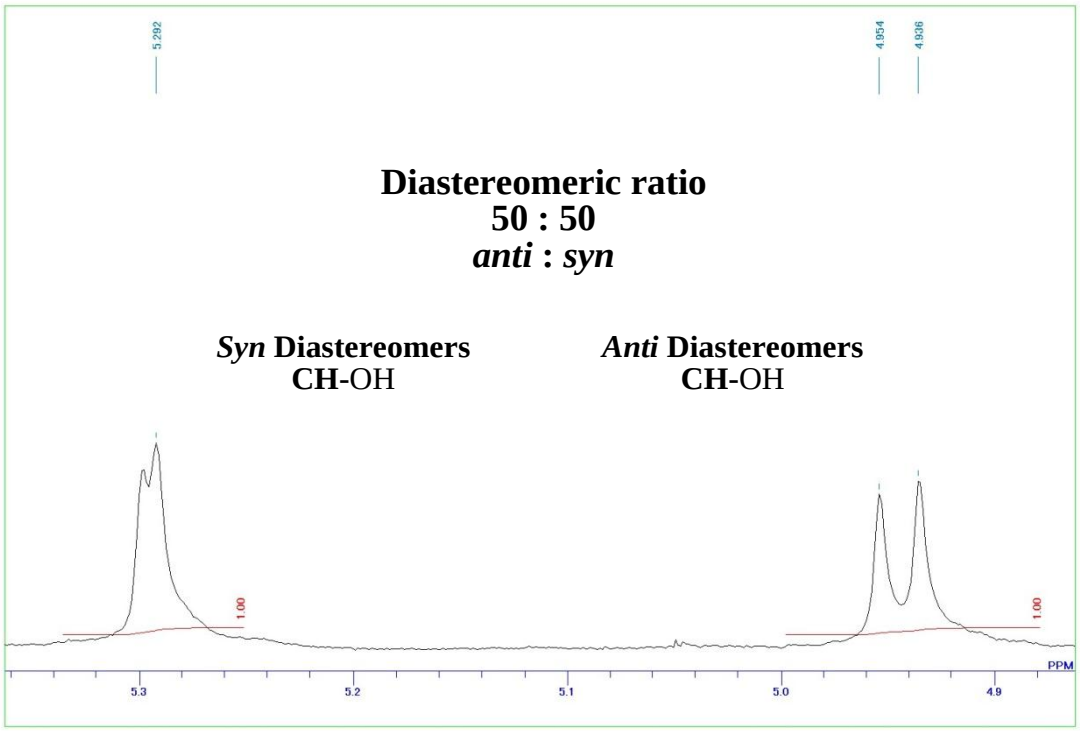

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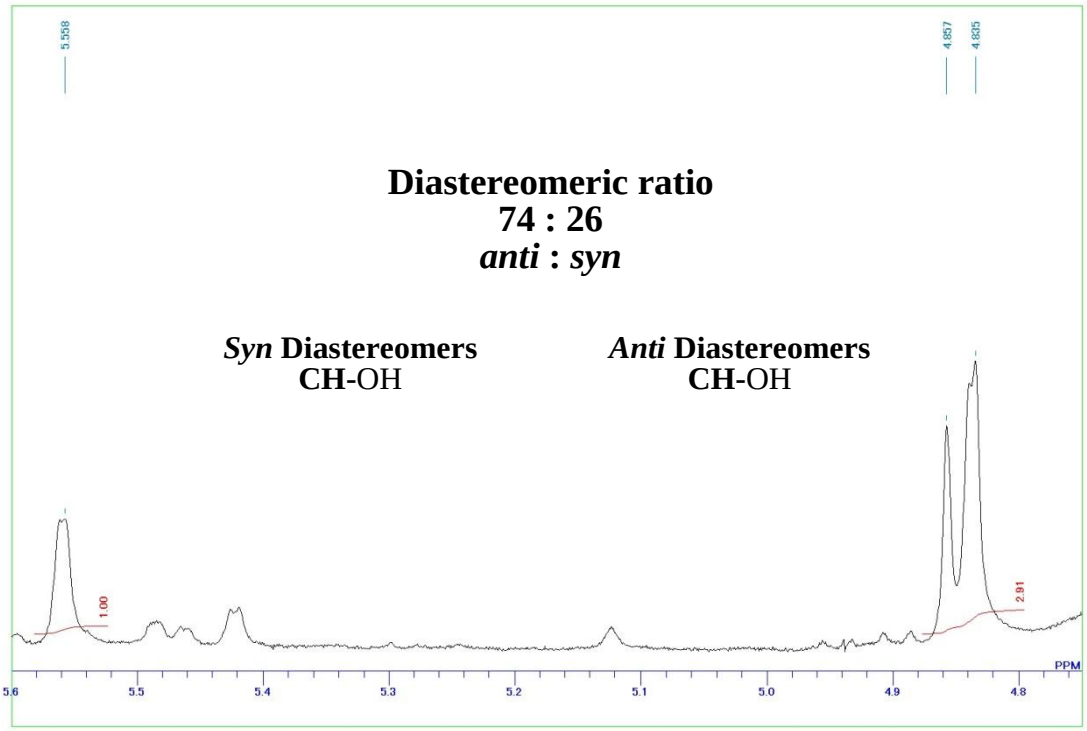

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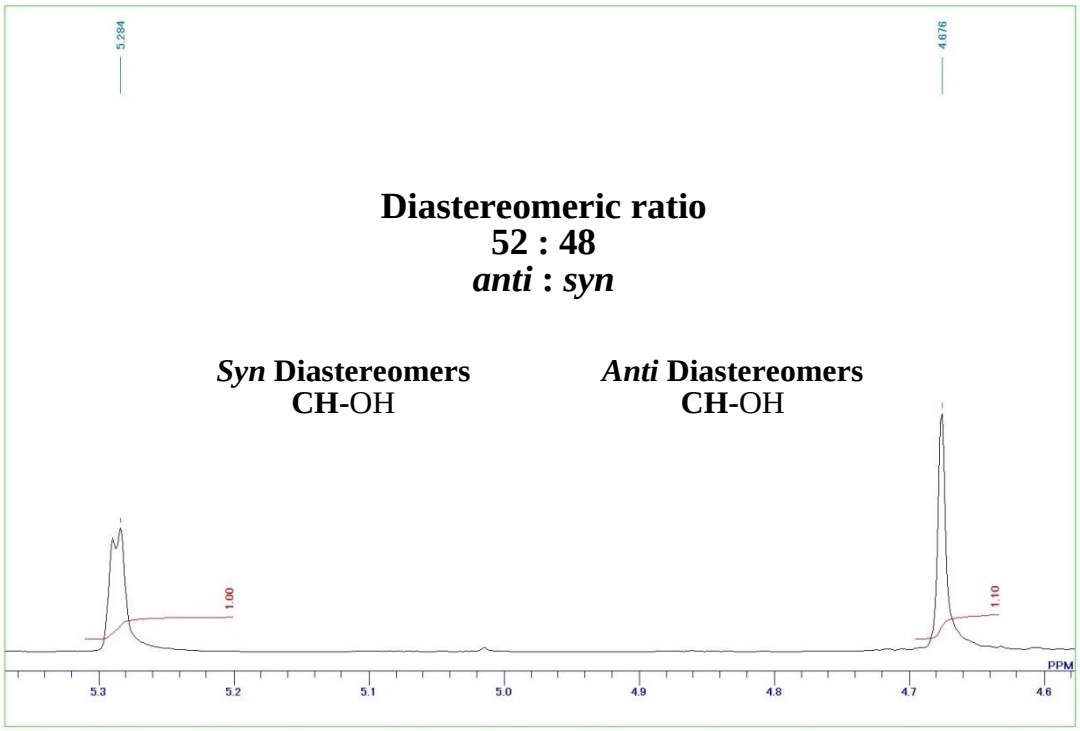

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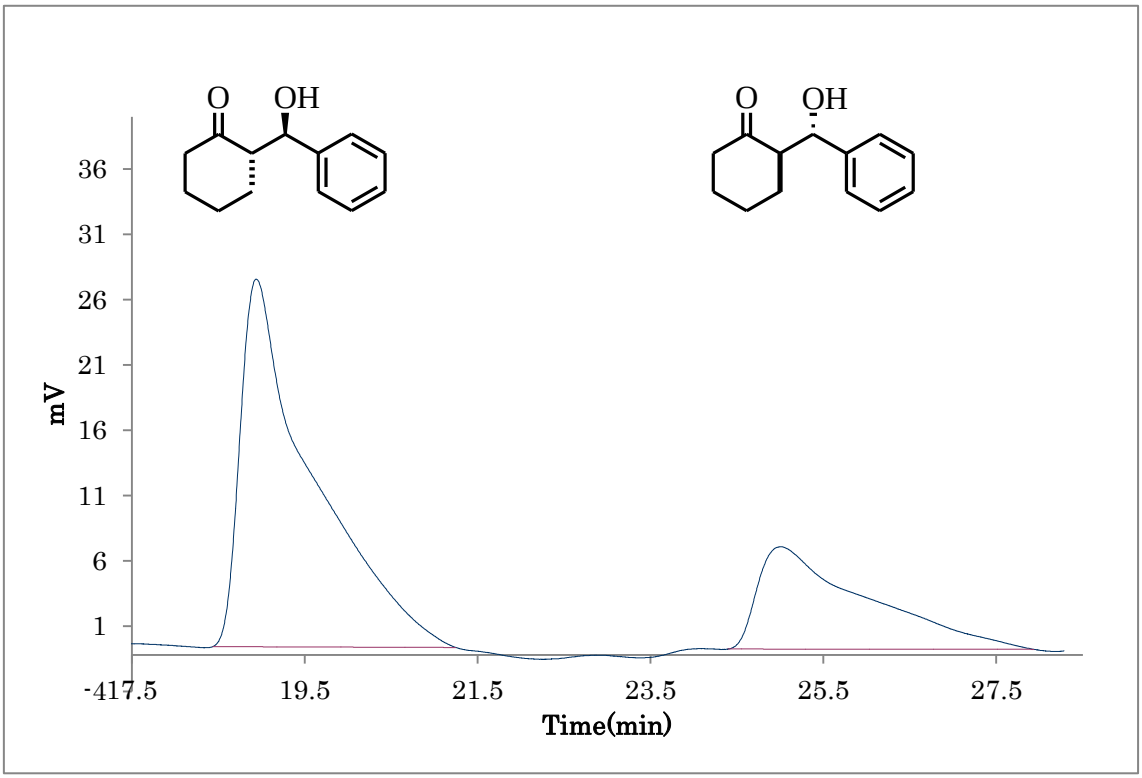
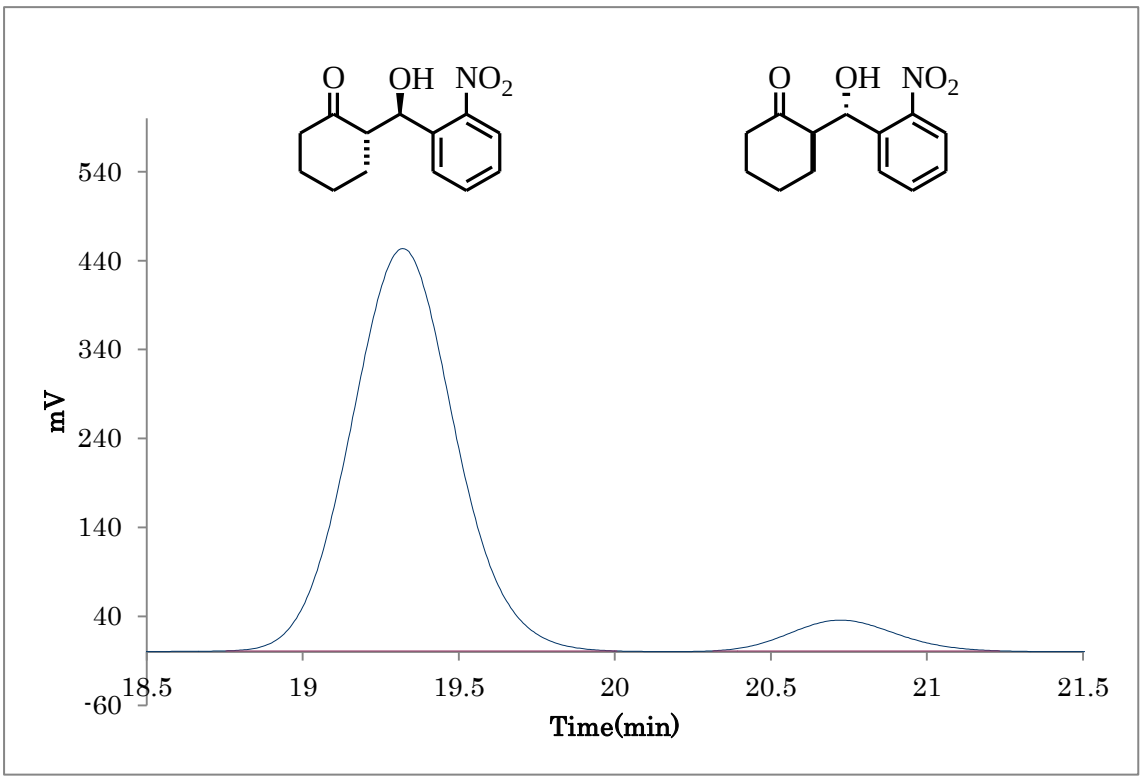


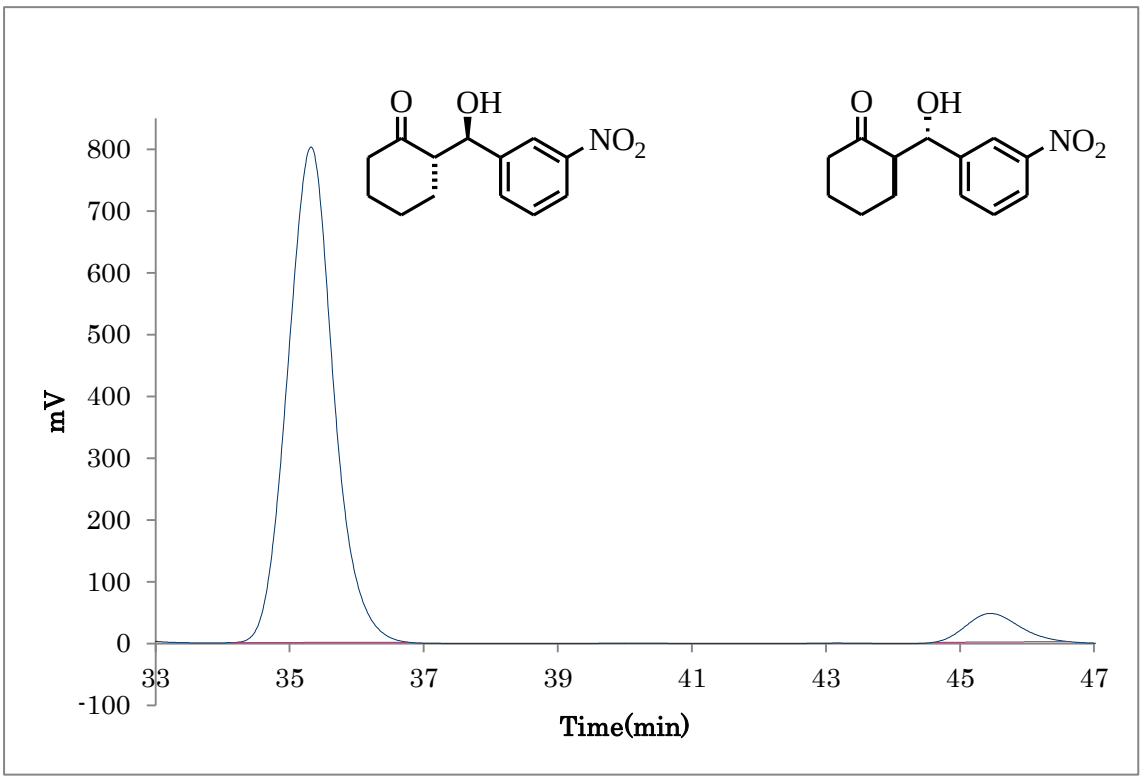
Peak	Retention time(min)	Area(%)	Ee(%)
1	18.94	70.5184	
2	25.01	29.4816	41.0368

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



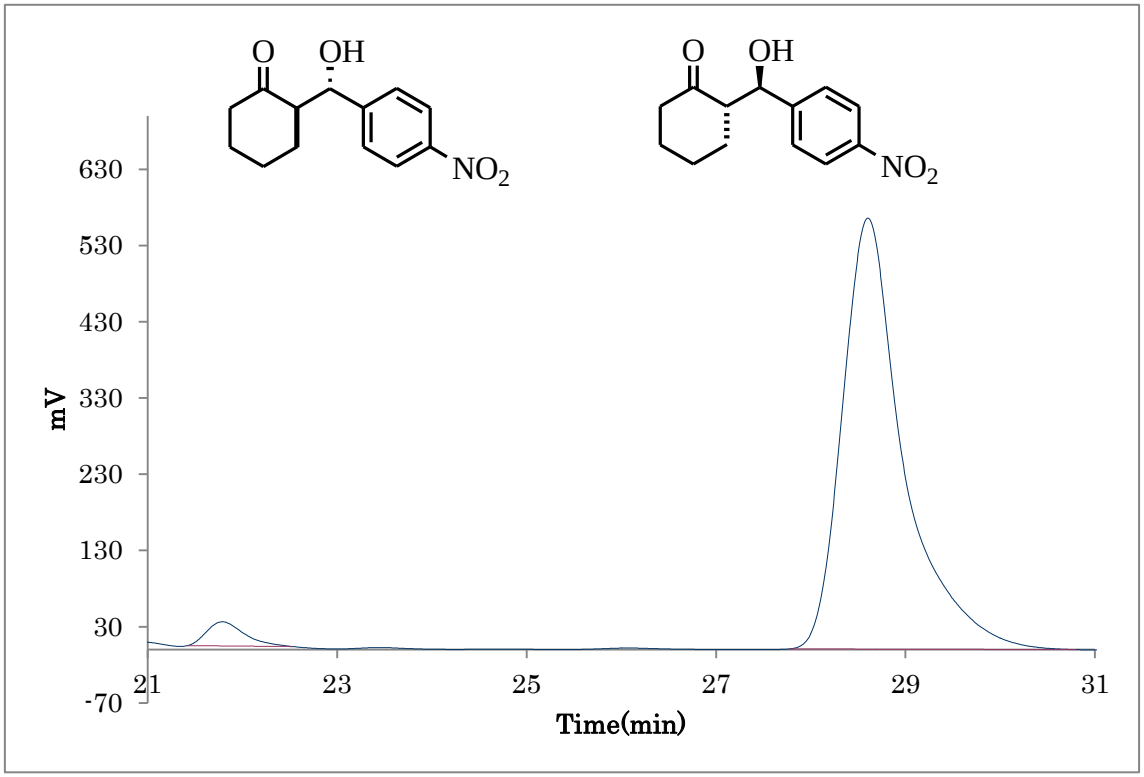
Peak	Retention time(min)	Area(%)	Ee(%)
1	19.32	92.7821	
2	20.72	7.2179	85.5642

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



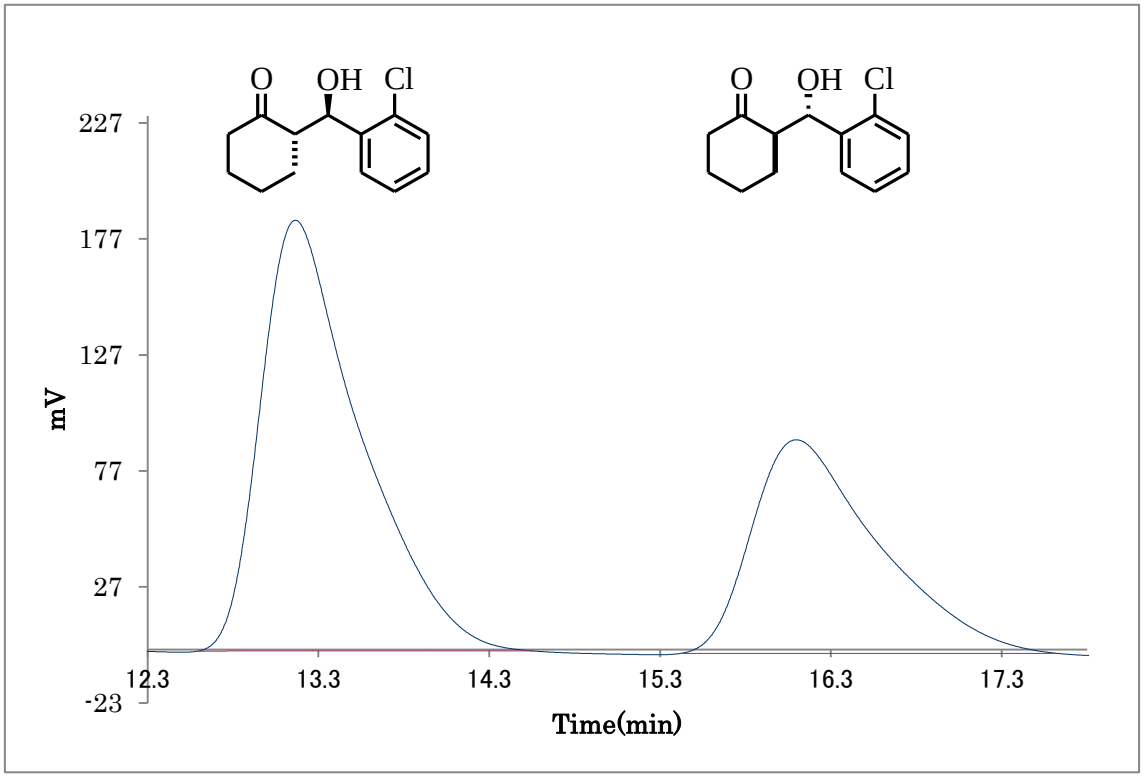
Peak	Retention time(min)	Area(%)	Ee(%)
1	35.32	93.7521	
2	45.46	6.2479	87.5042

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



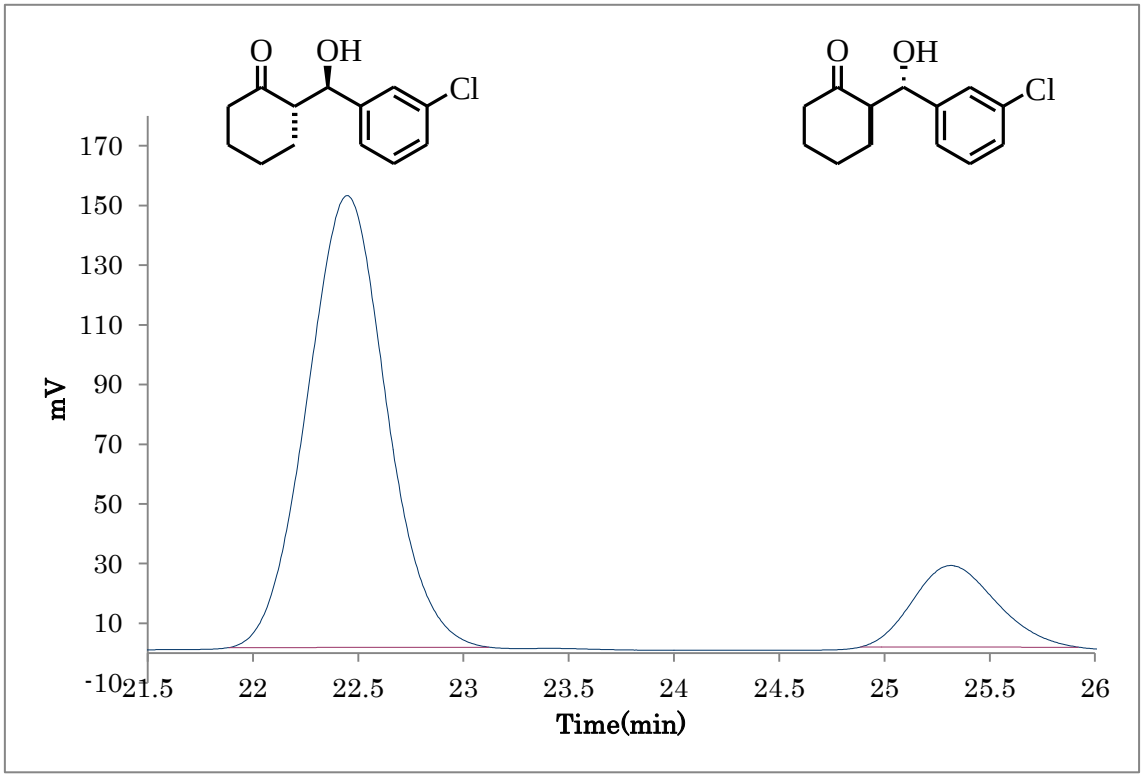
Peak	Retention time(min)	Area(%)	Ee(%)
1	21.79	3.3639	
2	28.6	96.6361	93.2722

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



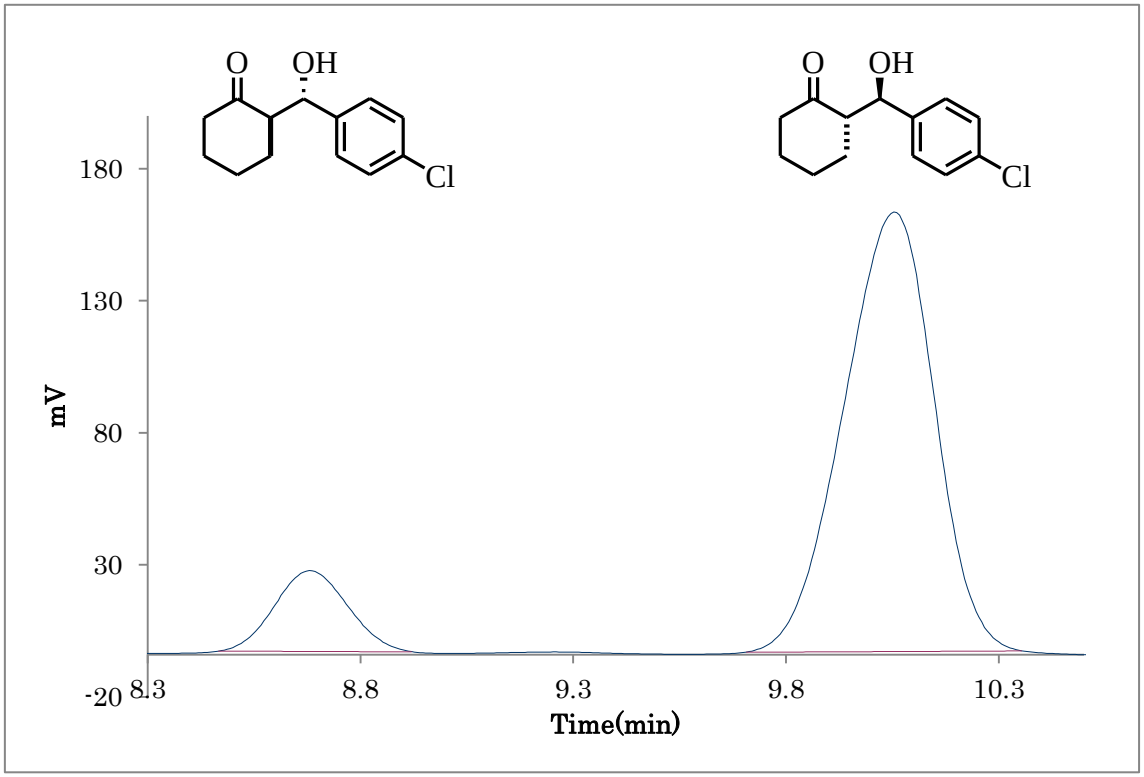
Peak	Retention time(min)	Area(%)	Ee(%)
1	13.16	61.4326	
2	16.1	38.5674	22.8652

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



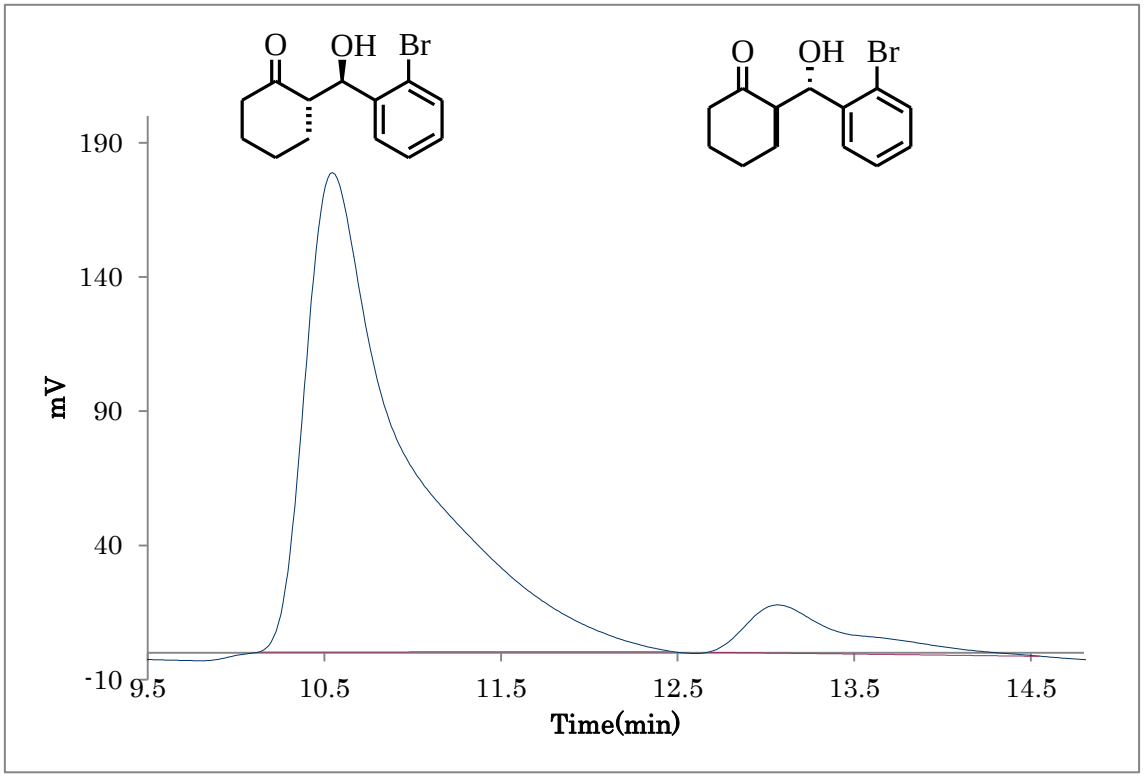
Peak	Retention time(min)	Area(%)	Ee(%)
1	22.45	84.0194	
2	25.32	15.9806	68.0388

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



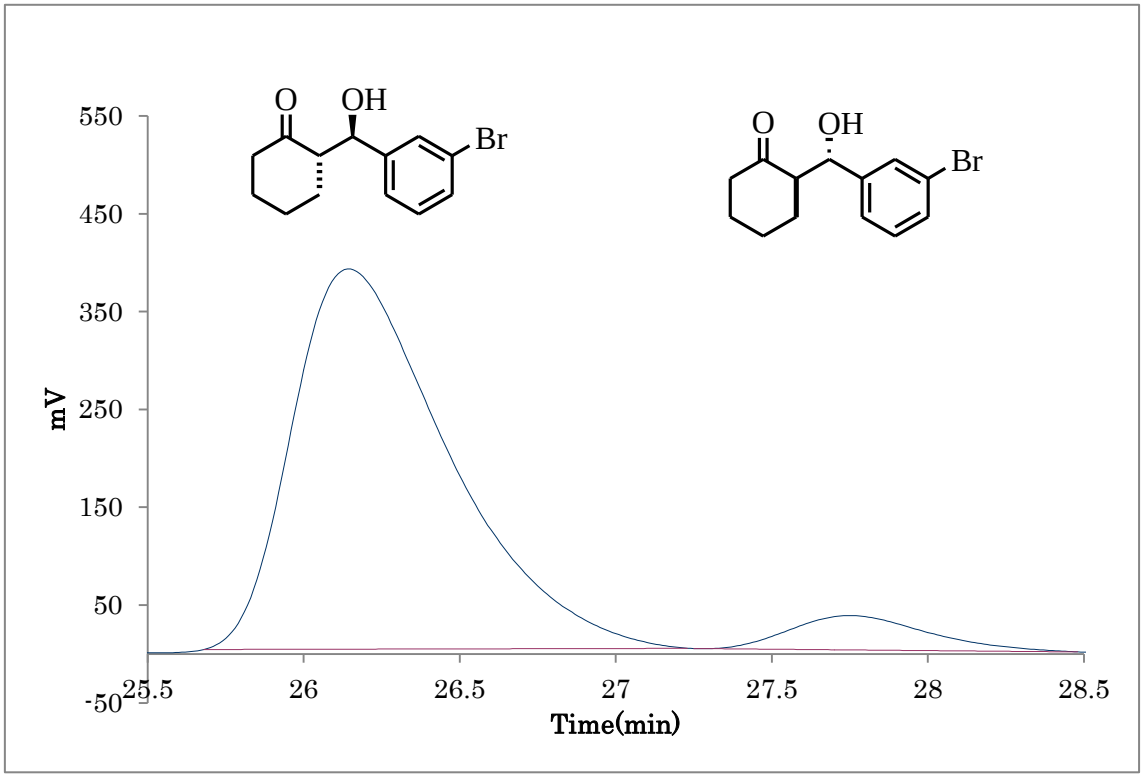
Peak	Retention time(min)	Area(%)	Ee(%)
1	8.68	12.8839	
2	10.05	87.1161	74.2322

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



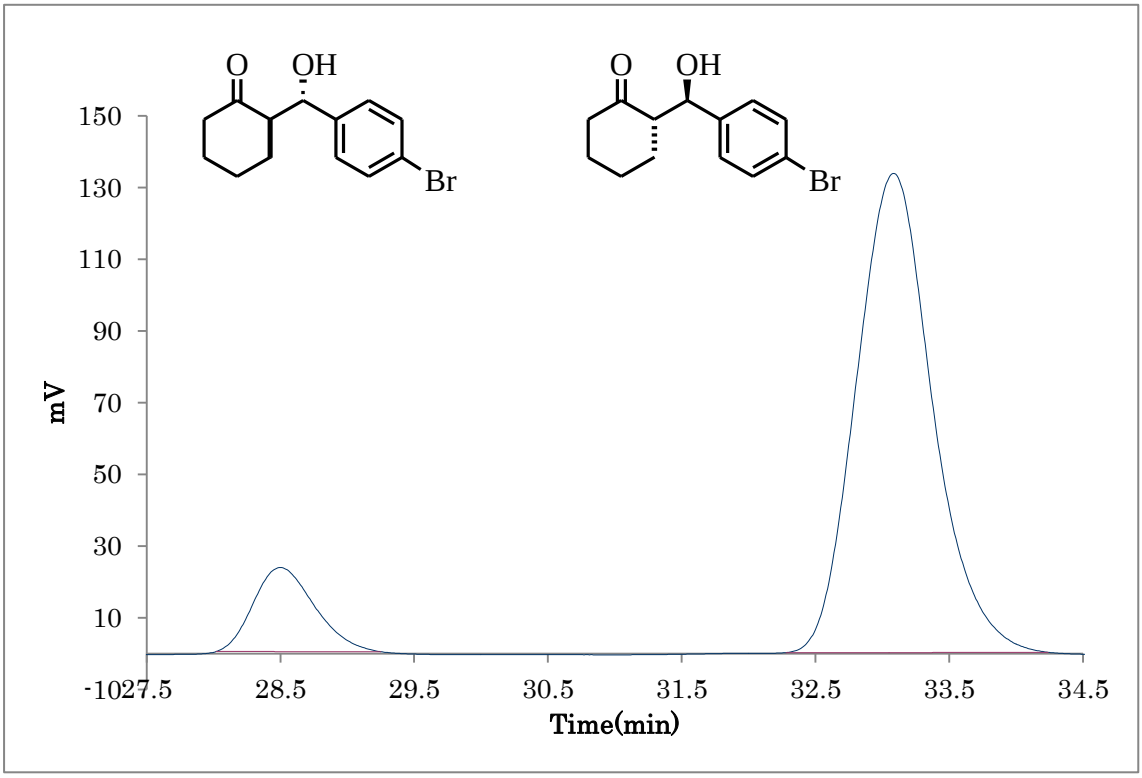
Peak	Retention time(min)	Area(%)	Ee(%)
1	10.55	90.6656	
2	13.07	9.3344	81.3312

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



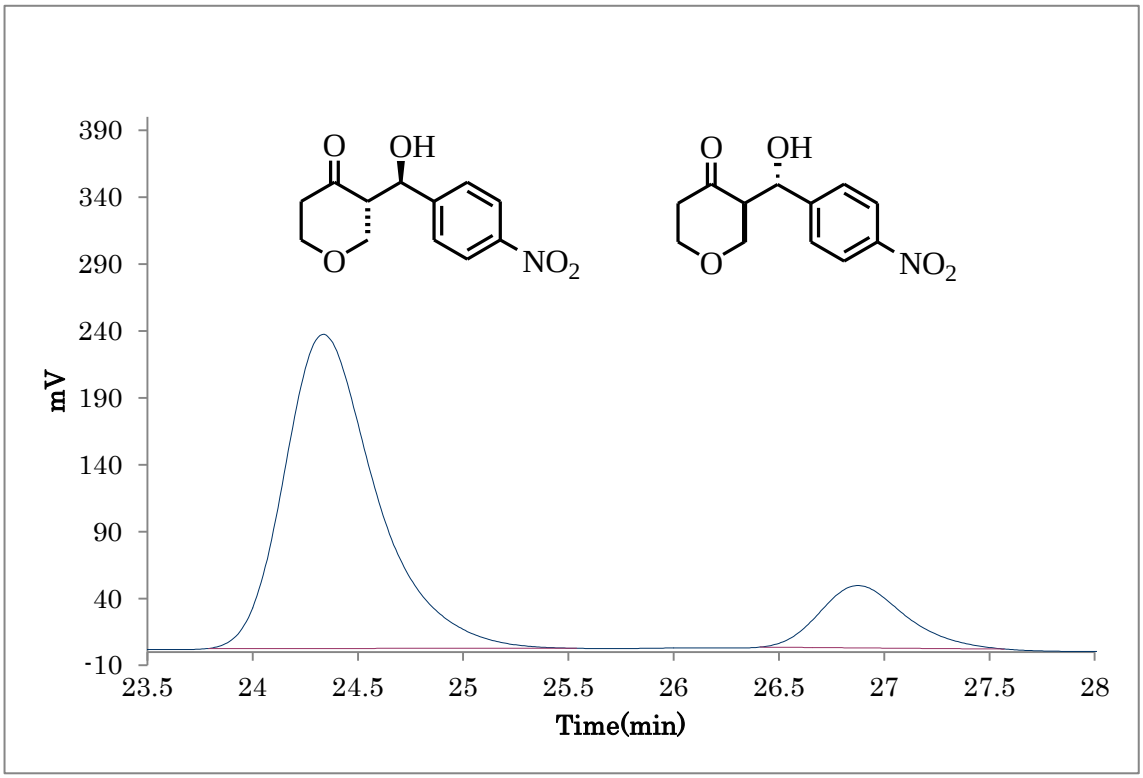
Peak	Retention time(min)	Area(%)	Ee(%)
1	26.14	92.6941	
2	27.75	7.3059	85.3882

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



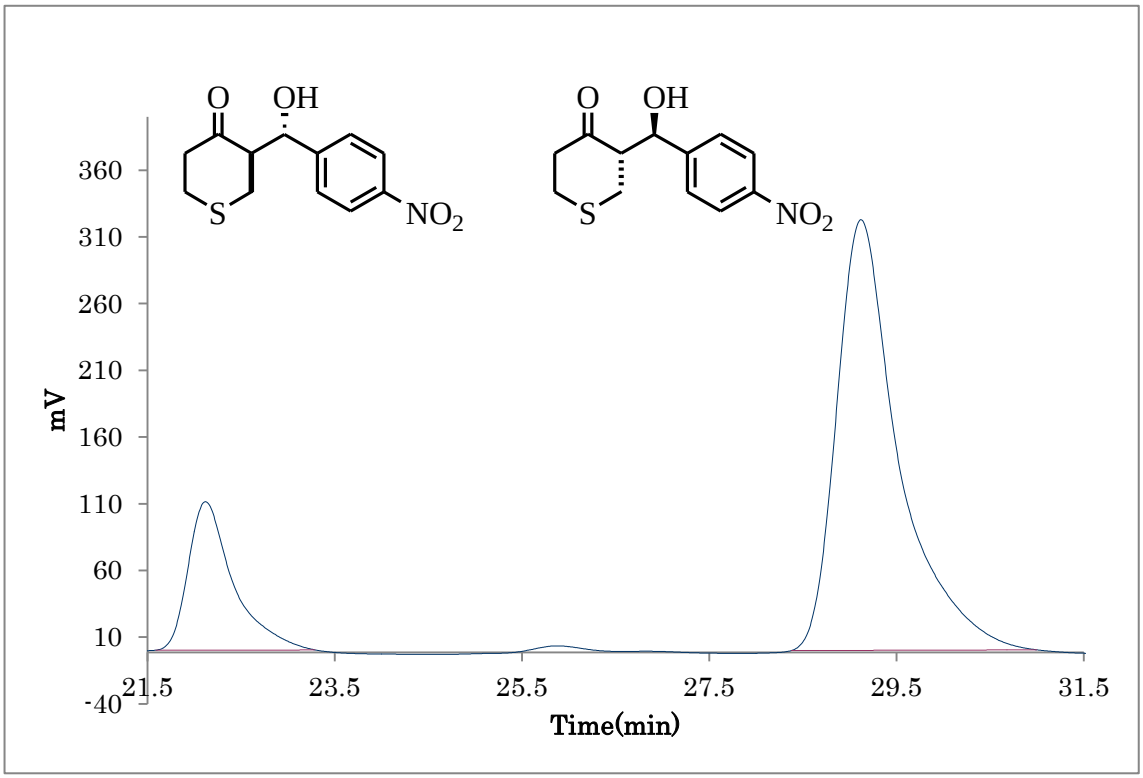
Peak	Retention time(min)	Area(%)	Ee(%)
1	28.5	12.3366	
2	33.09	87.6634	75.3268

(*2S,1'R*)-2-[1'-Hydroxy-1'-(4-nitrophenyl)methyl]-tetrahydro-4-H-pyran-4-one



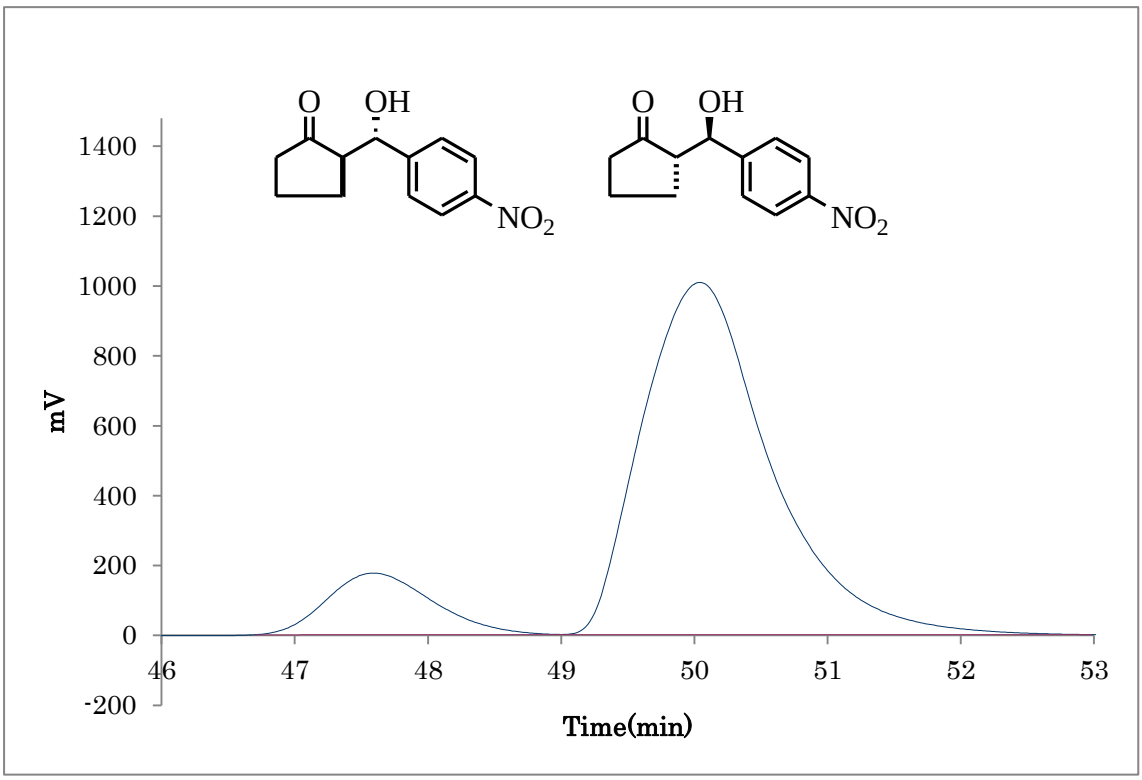
Peak	Retention time(min)	Area(%)	Ee(%)
1	24.34	84.437	
2	26.88	15.563	68.874

(*2S,1'R*)-2-[1'-Hydroxy-1'-(4-nitrophenyl)methyl]-tetrahydro-4-H-thiopyran-4-one



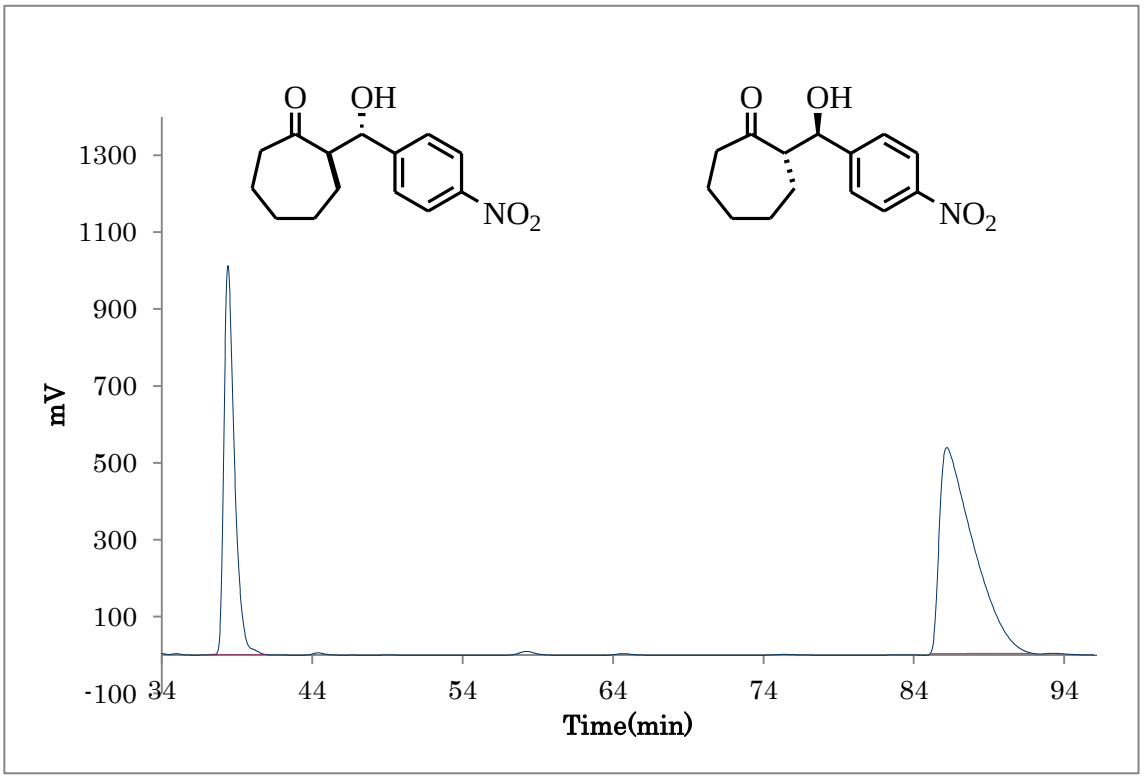
Peak	Retention time(min)	Area(%)	Ee(%)
1	22.12	20.032	
2	29.12	79.968	59.936

(*2S,1'R*)-2-[1'-Hydroxy-1'-(4-nitrophenyl)methyl]cyclopentan-1-one



Peak	Retention time(min)	Area(%)	Ee(%)
1	47.59	12.6381	
2	50.04	87.3619	74.7238

(*2S,1'R*)-2-[1'-Hydroxy-1'-(4-nitrophenyl)methyl]cycloheptan-1-one



Peak	Retention time(min)	Area(%)	Ee(%)
1	38.39	36.9422	
2	86.19	63.0578	26.1156

4-hydroxy-4-(4-nitrophenyl)butan-2-one