Supporting Information

for

Asymmetric Hydrogenation of Aryl Ketones Mediated by a Copper Catalyst

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General. Reactions were carried out under a nitrogen atmosphere containing a Teflon coated stirrer bar. Methanol and isopropyl alcohol were distilled from Mg and CaH_2, respectively, prior to use. All the aryl ketones were distilled prior to use. $[Cu(NO_3)(PPh_3)_2]$ was synthesized according to the literature.[1] $[CuH(PPh_3)]_6$ was purchased from Aldrich. $Cu(NO_3)_2{\cdot}3H_2O$ and NaO-*t*-Bu was purchased from Nacalai Tesque Inc. and Merck, respectively. Tris(3,5-dimethylphenyl)phosphine ($P(3,5\text{-xylyl})_3$) was synthesized according to the literature.[2] Other phosphine ligands were purchased from: Strem Chemicals, Inc. ((*S*,*S*)-BDPP, (*S*,*S*)-CHIRAPHOS), Fuji Chemical Industries, Ltd. ((*S*,*S*)-BPPM), Sigma-Aldrich Inc. ((*R*,*R*)-DIOP), Tokyo Kasei Kogyo Co., Ltd. (PPh_3), Takasago International Corporation ((*R*)-BINAP), Azmax Co., Ltd. ((*R*)-(*S*)-Josiphos). Acetophenone, 2'-methylacetophenone, 3'-methylacetophenone, 4'-methylacetophenone, 2'-methoxyacetophenone and acetpnaphtone were purchased from Tokyo Kasei Kogyo Co., Ltd. and distilled prior to use. 2'-Bromoacetophenone and 2'-(trifluoromethyl)acetophenone were purchased from Sigma-Aldrich Inc. and Apollo Scientific Ltd., respectively and distilled prior to use. Racemic compounds of the reduced products were synthesized using $LiAlH_4$ or purchased from Tokyo Kasei Kogyo Co., Ltd. GC analyses were carried out using Hewlett Packard HP5890 equipped with CP-Chirasil-DEX CB (df = 0.25 μm, 0.25 mm i.d. x 25 m (Varian); carrirer gas, helium (138 kPa), injection temp. 220 °C, detection temp. 250 °C.). NMR Spectra were obtained on Varian Mercury plus 300. IR spectra were obtained using Avatar 360 FT-IR. Optical rotation was obtained on Jasco P-1020. Melting points were obtained on Yanaco MP500D. HRMS was obtained on Shimadzu LCMS-IT-TOF.

Preparation of Nitratobis(tris(3,5-dimethylphenyl)phosphine)copper (I) ($[Cu(NO_3)(P(3,5\text{-xylyl})_3)_2]$). Modification of the procedure for $[Cu(NO_3)(PPh_3)_2]$[1]: Under nitrogen atmosphere, $Cu(NO_3)_2{\cdot}3H_2O$ (2.79 g, 11.5 mmol) was added to a mixture of $P(3,5\text{-xylyl})_3$ (10.0 g, 28.9 mmol) and MeOH (100 mL) at 60 °C. The reaction mixture was refluxed for 10 min, then gradually cooled to 5 °C. The white precipitate was filtered, washed with MeOH (10 mL) and Et_2O (10 mL) and dried under vacuum to give the titled compound (3.22 g, 34%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00 – 6.80 (m, 18H), 2.13 (s, 36H); ^{31}P NMR (121 MHz, $CDCl_3$) δ -0.62 (s); ^{13}C NMR (76 MHz, $CDCl_3$) δ 138.0, 131.9, 131.8, 131.3, 21.2; IR (KBr) ν 1457, 1384, 1283; HRMS (ESI+) *m*/*z* calc. for $[C_{48}H_{54}CuNO_3P_2 - NO_3]^+$: 755.2997; found: 755.2990; mp. 207 – 209 °C.

Asymmetric hydrogenation of acetophenone (Method A); Table 1, entry 1. To a 100-mL stainless steel autoclave equipped with a glass inner lining and a Teflon coated stirrer bar was placed CuCl (3.0 mg, 0.030 mmol), (*S*,*S*)-BDPP (13.2 mg, 0.030 mmol). The atmosphere was replaced with nitrogen gas, followed by addition of *i*-PrOH solution (0.090 M) of NaO-*t*-Bu (2.0 mL, 0.18 mmol) and acetophenone (1.05 mL, 9.0 mmol). Hydrogen was initially introduced into the autoclave at a pressure of 1.0 MPa, before being reduced to 0.1 MPa by carefully releasing the stop valve. After this procedure was repeated three times, hydrogen was introduced at 5.0 MPa and the solution was stirred at 30 °C for 16 h. GC analysis (column temp. 115 °C; ^{t}R = 9.0 min for (*R*), 9.7 min for (*S*)) indicated that (*S*)-1-phenylethanol was obtained in 21% conversion and 40% ee.

Table 1, entry 2. According to method A, PPh_3 (23.6 mg, 0.090 mmol) was placed together with CuCl and (*S*,*S*)-BDPP. GC analysis indicated that (*S*)-1-phenylethanol was obtained in >99% conversion and 47% ee.

Table 1, entry 3. According to method A, the following amounts were used: $[CuH(PPh_3)]_6$ (5.9 mg, 0.0030 mmol), PPh_3 (4.7 mg, 0.018 mmol), (*S*,*S*)-BDPP (7.9 mg, 0.018 mmol), *i*-PrOH (2.0 mL) and acetophenone (1.05 mL, 9.0 mmol). *i*-PrOH was added in place of *i*-PrOH solution (0.090M) of NaO-*t*-Bu. GC analysis indicated that (*S*)-1-phenylethanol was obtained in >99% conversion and 48% ee.

Table 1. entry 4. According to method A, the following amounts were used: $[Cu(NO_3)(PPh_3)_2]$ (11.7 mg, 0.018 mmol), (*S*,*S*)-BDPP (7.9 mg, 0.018 mmol), *i*-PrOH solution (0.090 M) of NaO-*t*-Bu (2.0 mL, 0.18 mmol), *i*-PrOH (2.0 mL) and acetophenone (2.10 mL, 18.0 mmol). *i*-PrOH was added together with *i*-PrOH solution (0.090 M) of NaO-*t*-Bu. GC analysis indicated that (*S*)-1-phenylethanol was obtained in >99% conversion and 47% ee.

Table 1, entry 5. To a 100-mL stainless steel autoclave equipped with a glass inner lining and a Teflon coated stirrer bar was placed $[Cu(NO_3)(PPh_3)_2]$ (11.7 mg, 0.018 mmol), PPh_3 (14.1 mg, 0.054 mmol) and (*S*,*S*)-BDPP (7.9 mg, 0.018 mmol). The atmosphere was replaced with nitrogen gas, followed by addition of *i*-PrOH solution (0.090 M) of NaO-*t*-Bu (2.0 mL, 0.18 mmol) and *i*-PrOH (10.6 mL) and acetophenone (6.30 mL, 54.0 mmol). Hydrogen was initially introduced into the autoclave at a pressure of 1.0 MPa, before being reduced to 0.1 MPa by carefully releasing the stop valve. After this procedure was repeated three times, hydrogen was introduced at 5.0 MPa and the solution was stirred at 30 °C. The reaction was monitored by sampling the reaction mixture. The sampling was carried out via syringe after releasing hydrogen followed by streaming with nitrogen. After sampling, hydrogen was introduced again at 5.0 MPa and the solution was stirred at 30 °C. Conversions and ee's were as follows: 20% and 45% ee at 17 h; 48% and 46% ee at 40 h; 75% and 46% ee at 64 h; 96% and 47% ee at 96 h. Flash silica gel column chromatography (ethyl acetate / hexane = 1 / 1) after removal of the solvent, followed by distillation under vacuum (92 °C/10 mm Hg) afforded (*S*)-1-phenylethanol (6.20 g, 94%, 48% ee). $[\alpha]_D^{20}$ –22.0° (*c* 1.05, CH_2Cl_2) (lit. $[\alpha]_D^{22}$ +41.9° (*c* 1.05, CH_2Cl_2) for 87% ee (*R*))[3]

Table 1, entry 6. According to method A, the following amounts were used: $[Cu(NO_3)(P(3,5\text{-xylyl})_3)_2]$ (14.7 mg, 0.018 mmol), (*S*,*S*)-BDPP (7.9 mg, 0.018 mmol), *i*-PrOH solution (0.090M) of NaO-*t*-Bu (2.0 mL, 0.18 mmol) and acetophenone (1.05 mL, 9.0 mmol). GC analysis indicated that (*S*)-1-phenylethanol was obtained in >99% conversion and 56% ee.

Ligand screening. According to method A, the following amounts were used: $[Cu(NO_3)(PPh_3)_2]$ (11.7 mg, 0.018 mmol), Ligand (0.018 mmol), *i*-PrOH solution (0.090 M) of NaO-*t*-Bu (2.0 mL, 0.18 mmol), and acetophenone (1.05 mL, 9.0 mmol). The amounts of ligand, conversion and ee (configuration) of the product were as follows, respectively: (*S*,*S*)-CHIRAPHOS (7.7 mg, 2% conversion), (*R*)-BINAP (11.2 mg, 17% conversion and 24% ee (*R*), (*R*,*R*)-DIOP (9.0 mg, >99% conversion and 12% ee (*R*)), (*S*,*S*)-BPPM (10.0 mg, >99% conversion, 27% ee (*R*)), (*R*)-(*S*)-Josiphos (10.7 mg, 99% conversion, 45% ee (*S*)).

Representative Procedure for the catalytic asymmetric hydrogenation of aryl ketones. (*S*)-1-(2-Methylphenyl)ethanol (Method B); Table 2, entry 1. To a 100-mL stainless steel autoclave equipped with a glass inner lining and a Teflon coated stirrer bar was placed $[Cu(NO_3)(P(3,5\text{-xylyl})_3)_2]$

(16.4 mg, 0.020 mmol), P(3,5-xylyl)$_3$ (41.6 mg, 0.12 mmol) and (*S*,*S*)-BDPP (8.8 mg, 0.020 mmol). The atmosphere was replaced with nitrogen gas, followed by addition of *i*-PrOH solution (0.077 M) of NaO-*t*-Bu (2.6 mL, 0.20 mmol) and 2'-methylacetophenone (1.31 mL, 10 mmol). Hydrogen was initially introduced into the autoclave at a pressure of 1.0 MPa, before being reduced to 0.1 MPa by carefully releasing the stop valve. After this procedure was repeated three times, hydrogen was introduced at 5.0 MPa and the solution was stirred at 30 °C for 16 h. Silica gel chromatography afforded the titled compound (1.21 g, 98% yield, 86 % ee). Conversion and % ee were determined by Chiral GC (columun temp. 130 °C; ^tR = 8.1 min for (*R*), 9.4 min for (*S*)).; $[\alpha]_D^{20}$ –61.8° (*c* 0.51, $CHCl_3$) (lit. $[\alpha]_D^{29}$ –72.1° (*c* 0.535, $CHCl_3$) for 91% ee (*S*))[4]

(*S*)-1-(3-Methylphenyl)ethanol; Table 2, entry 2. According to Method B, 3'-methylacetophenone (1.36 mL, 10 mmol) was used in place of 2'-methylacetophenone. Silica gel chromatography afforded the titled compound (1.25 g, 92% yield, 64% ee). Conversion and % ee were determined by Chiral GC (columun temp. 130 °C; ^tR = 6.6 min for (*R*), 6.9 min for (*S*)). $[\alpha]_D^{20}$ –27.2° (*c* 0.57, $CHCl_3$) (lit. $[\alpha]_D^{26}$ –42.6° (*c* 0.62, $CHCl_3$) for 84% ee (*S*))[4]

(*S*)-1-(4-Methylphenyl)ethanol; Table 2, entry 3. According to Method B, 4'-methylacetophenone (1.34 mL, 10 mmol) was used in place of 2'-methylacetophenone. Silica gel chromatography (AcOEt / Hexane = 1 / 5) afforded the titled compound (1.25 g, 92% yield, 62% ee). Conversion and % ee were determined by Chiral GC (columun temp. 130 °C; ^tR = 6.0 min for (*R*), 6.6 min for (*S*)). $[\alpha]_D^{20}$ –27.3° (*c* 0.54, $CHCl_3$) (lit. $[\alpha]_D^{27}$ –53.0° (*c* 0.55, $CHCl_3$) for 92% ee (*S*))[4]

(*S*)-1-(2-Methoxyphenyl)ethanol; Table 2, entry 4. According to Method B, 2'-methoxyacetophenone (1.37 mL, 10 mmol) was used in place of 2'-methylacetophenone. Silica gel chromatography afforded the titled compound (1.40 g, 92% yield, 91% ee). Conversion and % ee were determined by Chiral GC (columun temp. 130 °C; ^tR = 11.6 min for (*S*), 13.0 min for (*R*)). $[\alpha]_D^{20}$ –17.5° (*c* 0.75, $CHCl_3$) (lit. $[\alpha]_D^{23}$ +11.5° (*c* 1.1, $CHCl_3$) for 73.2% ee (*R*))[5]

(*S*)-1-(2-Trifluoromethylphenyl)ethanol; Table 2, entry 5. According to Method B, 2'-trifluoromethylacetophenone (1.20 g, 8.0 mmol) in place of 2'-methylacetophenone and *i*-PrOH solution (0.077 M) of NaO-*t*-Bu (7.8 mL, 0.60 mmol) were used. Silica gel chromatography afforded the titled compound (1.15 g, 76% yield, 90% ee). Conversion and % ee were determined by Chiral GC (column temp. 110 °C; ^tR = 14.0 min for (*R*), 15.8 min for (*S*)). $[\alpha]_D^{20}$ –35.4° (*c* 0.70, MeOH) (lit. $[\alpha]_D^{20}$ –43.4° (*c* 0.74, MeOH) for 91% ee (*S*))[6]

(*S*)-1-(2-Bromophenyl)ethanol; Table 2, entry 6. According to Method B, 2'-bromoacetophenone (1.35 mL, 10 mmol) in place of 2'-methylacetophenone and *i*-PrOH solution (0.077 M) of NaO-*t*-Bu (7.8 mL, 0.60 mmol) were used. Silica gel chromatography afforded the titled compound (1.64 g, 82% yield, 81 % ee). Conversion and % ee were determined by Chiral GC (column temp. 150 °C; ^tR = 7.4 min for (*R*), 9.1 min for (*S*).). $[\alpha]_D^{20}$ -39.5° (*c* 0.96, $CHCl_3$) (lit. $[\alpha]_D^{20}$ –52.1° (*c* 0.93, $CHCl_3$) for 94% ee (*S*))[6]

(*S*)-1-(1-Naphthyl)ethanol; Table 2, entry 7. According to Method B, 1-acetonaphthone (1.52 mL, 10 mmol) was used in place of 2'-methylacetophenone. Silica gel chromatography afforded the title compound (1.51 g, 88% yield, 63% ee). Conversion and % ee were determined by Chiral GC (column temp. 160 °C; ^tR = 13.5 min for (*S*), 14.9 min for (*R*).). $[\alpha]_D^{20}$ –46.4° (*c* 0.98, Et_2O) (lit. $[\alpha]_D^{23}$ +75.8° (*c* 0.99, Et_2O) for 95% ee (*R*))[3]

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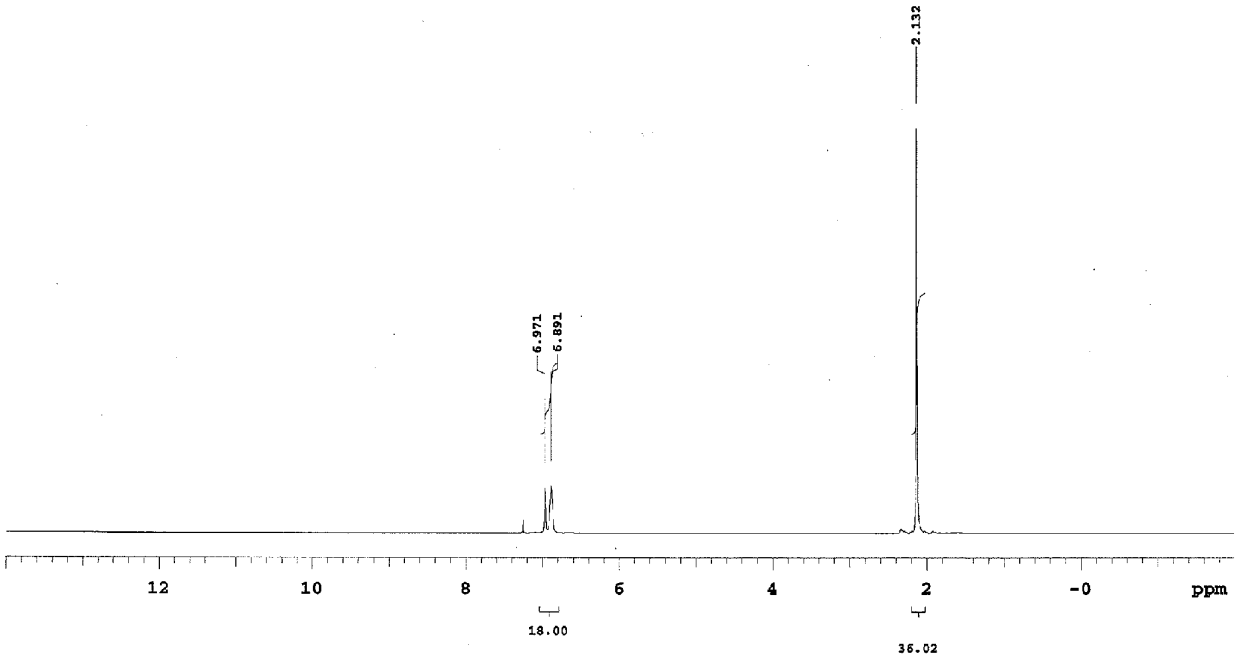
^{1}H NMR [Cu(NO$_3$)(P(3,5-xylyl)$_3$)$_2$]



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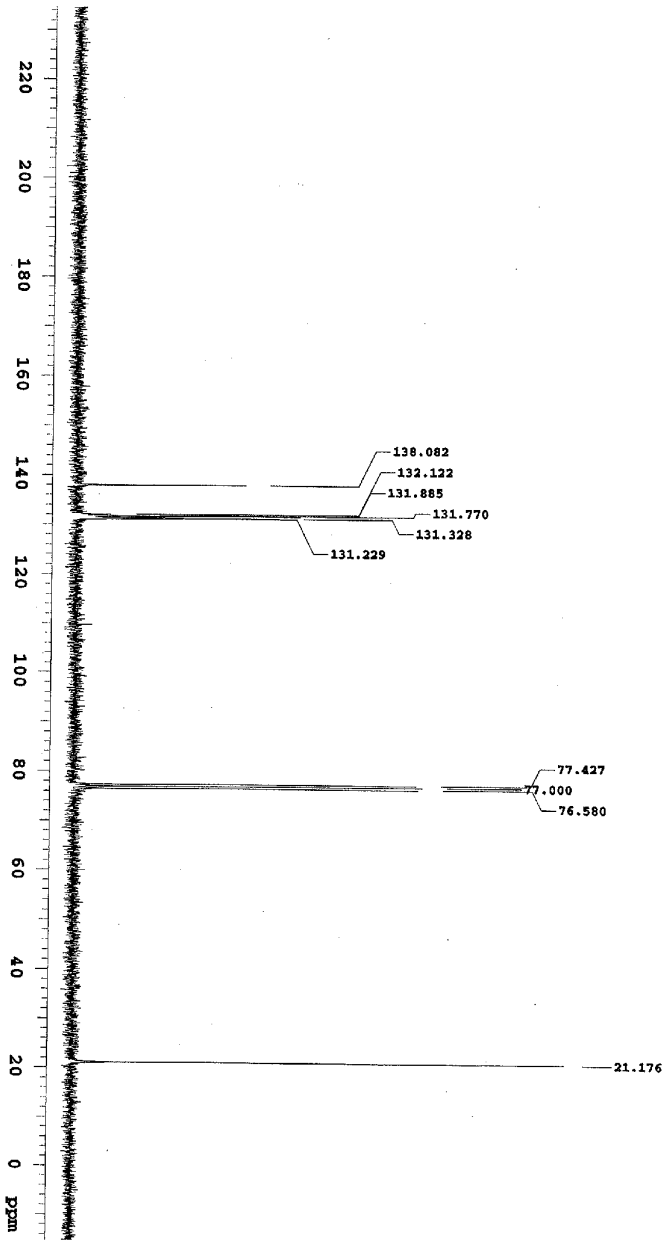
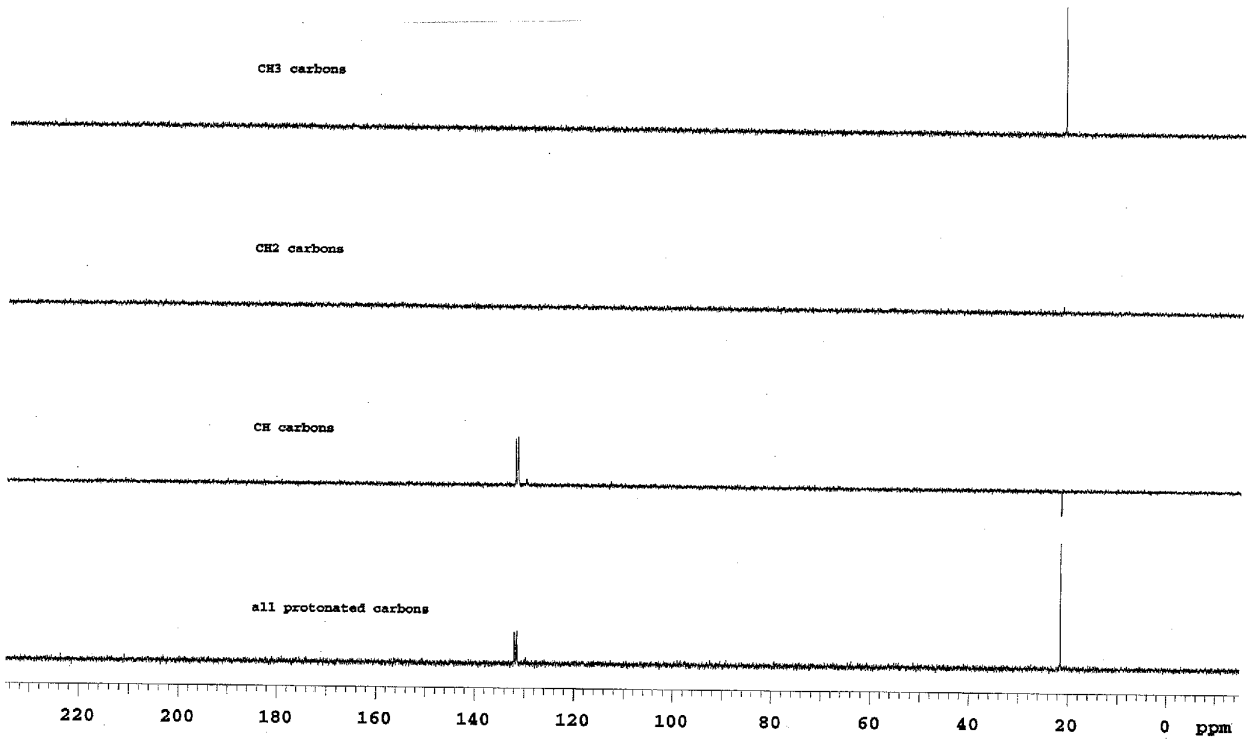
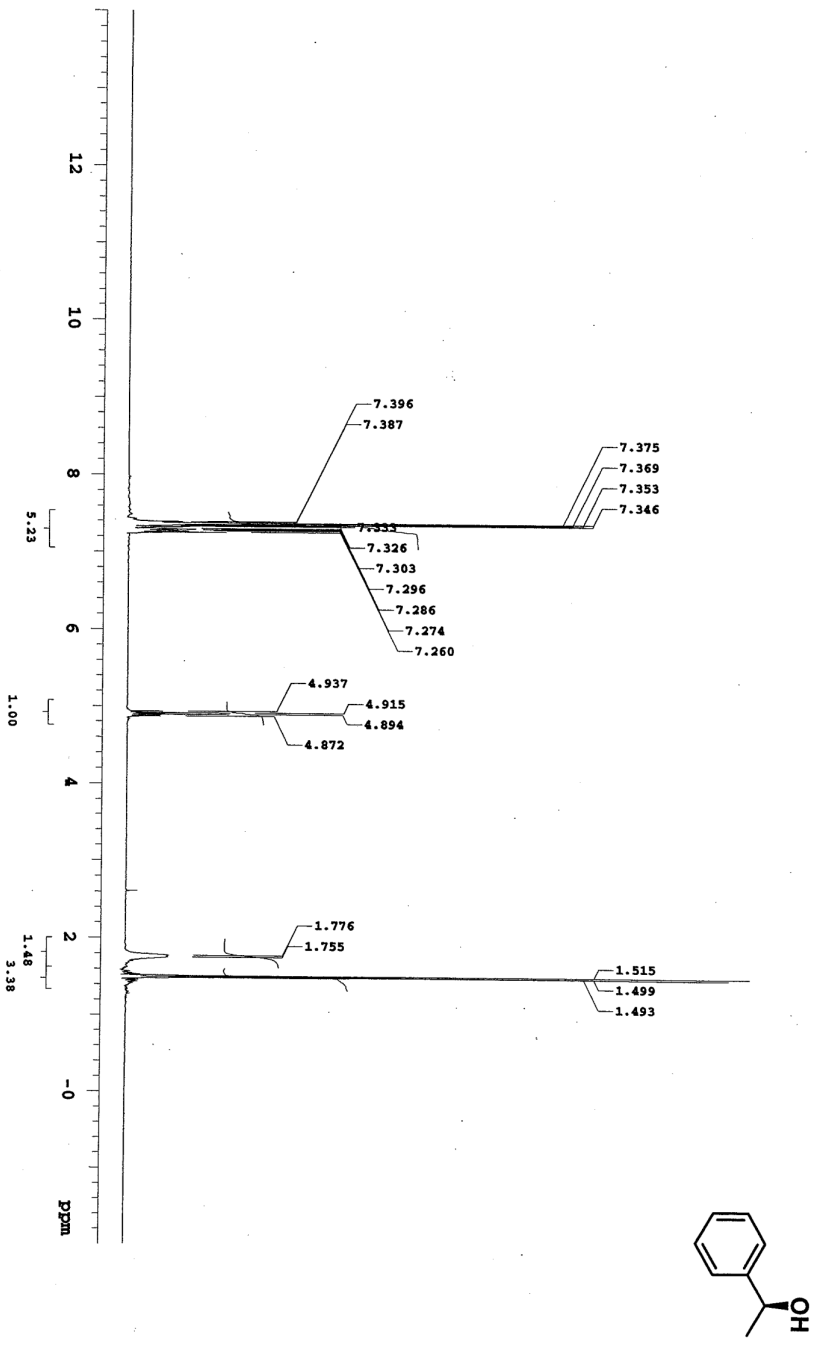


^{13}C NMR [Cu(NO$_3$)(P(3,5-xylyl)$_3$)$_2$]

DEPT [Cu(NO$_3$)(P(3,5-xylyl)$_3$)$_2$]

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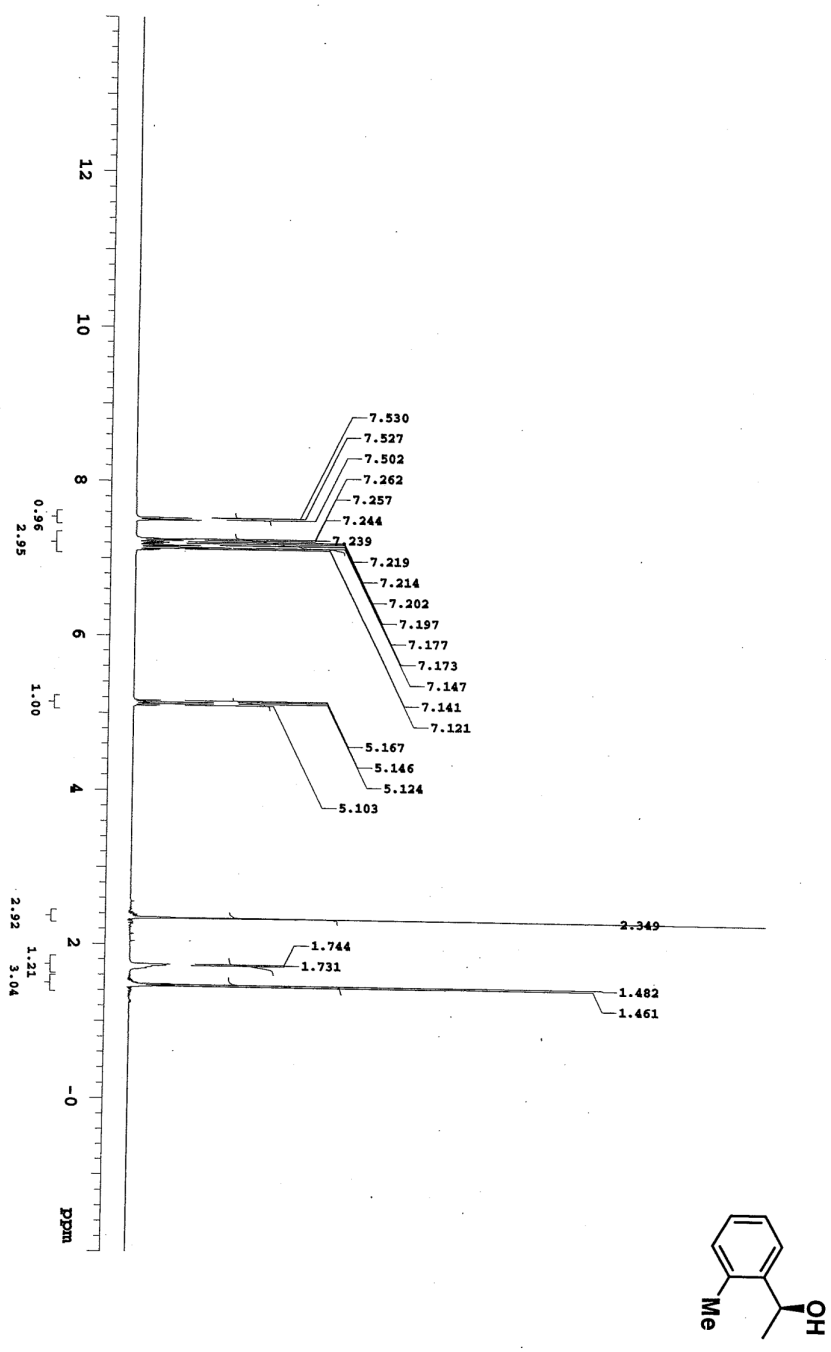
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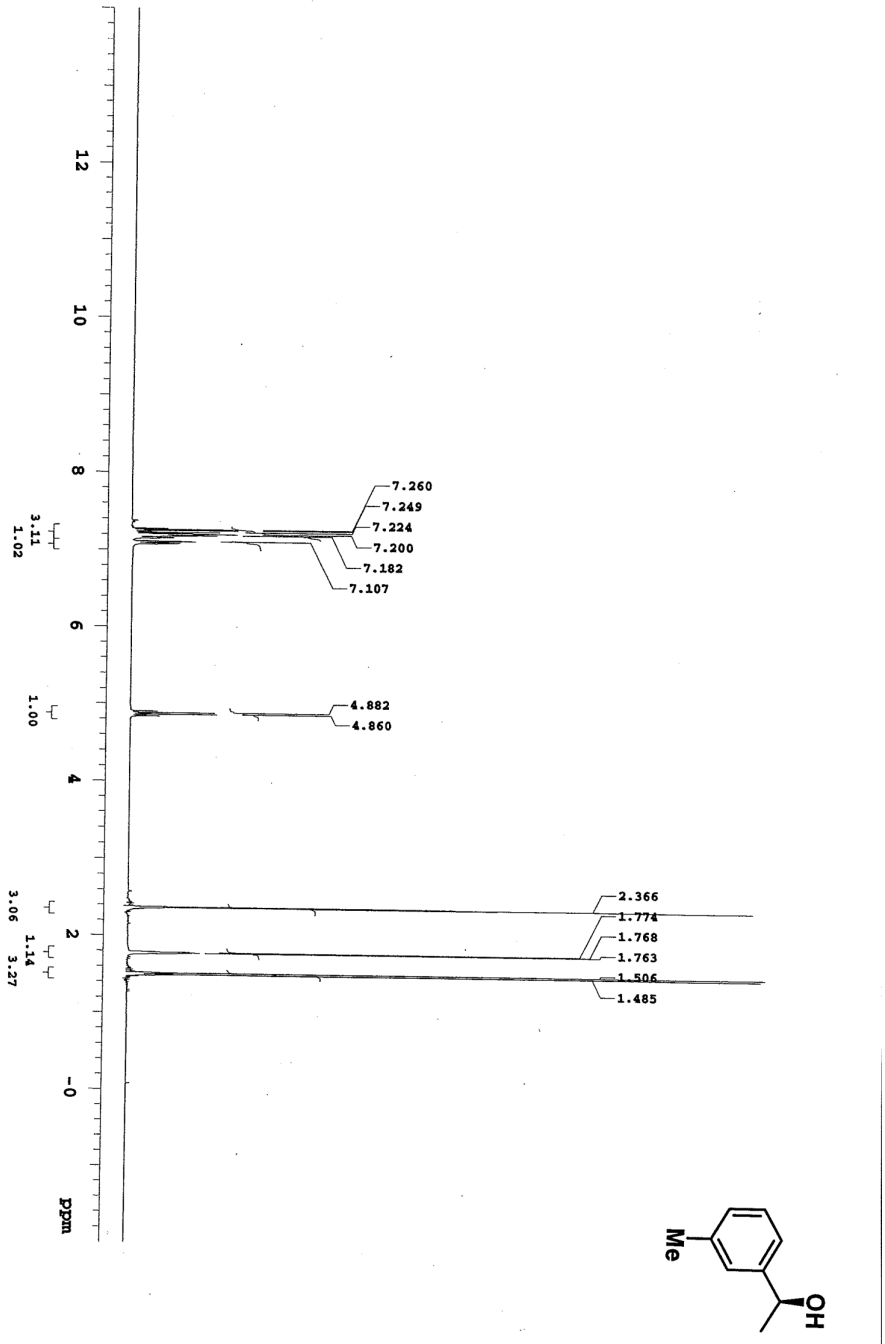
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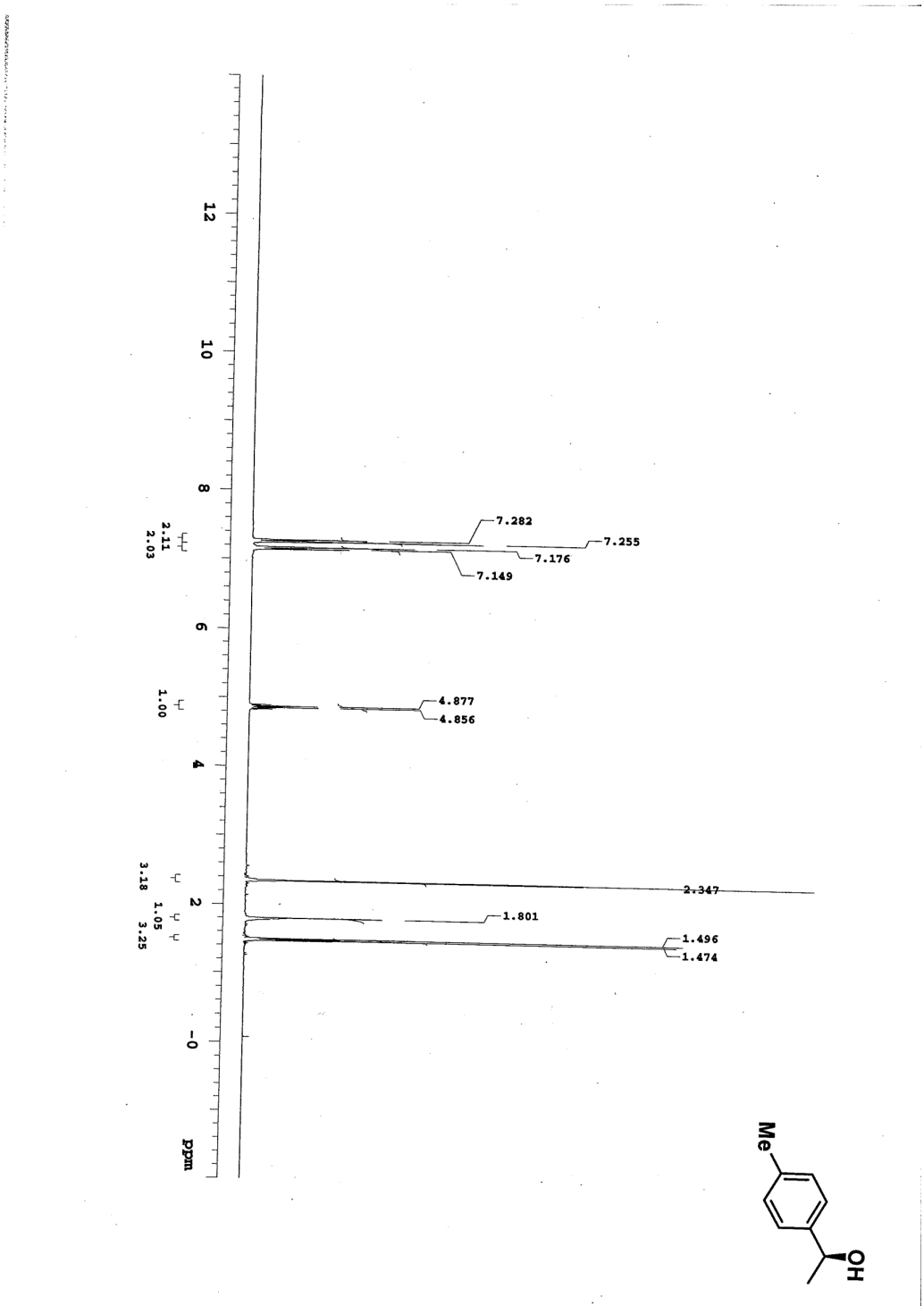
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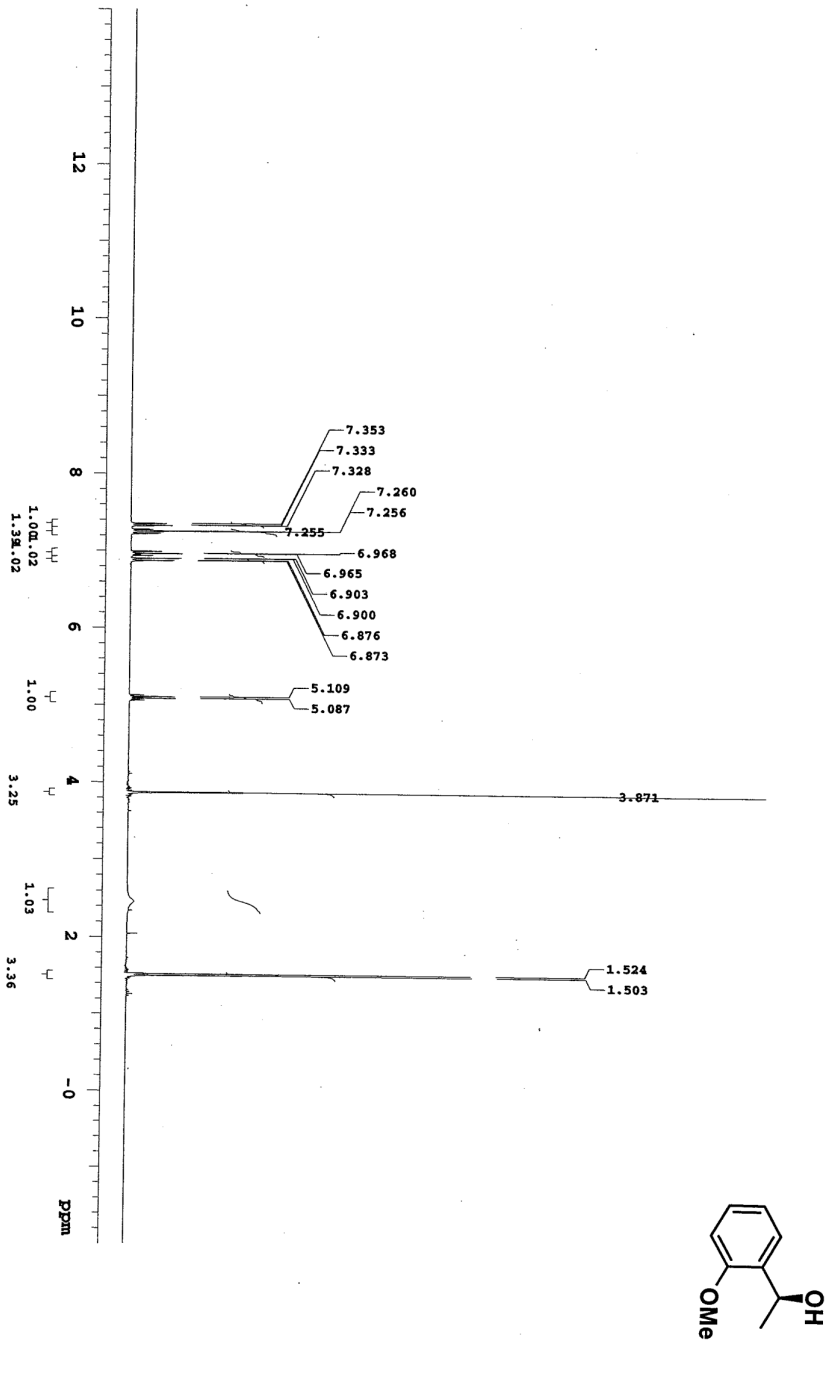
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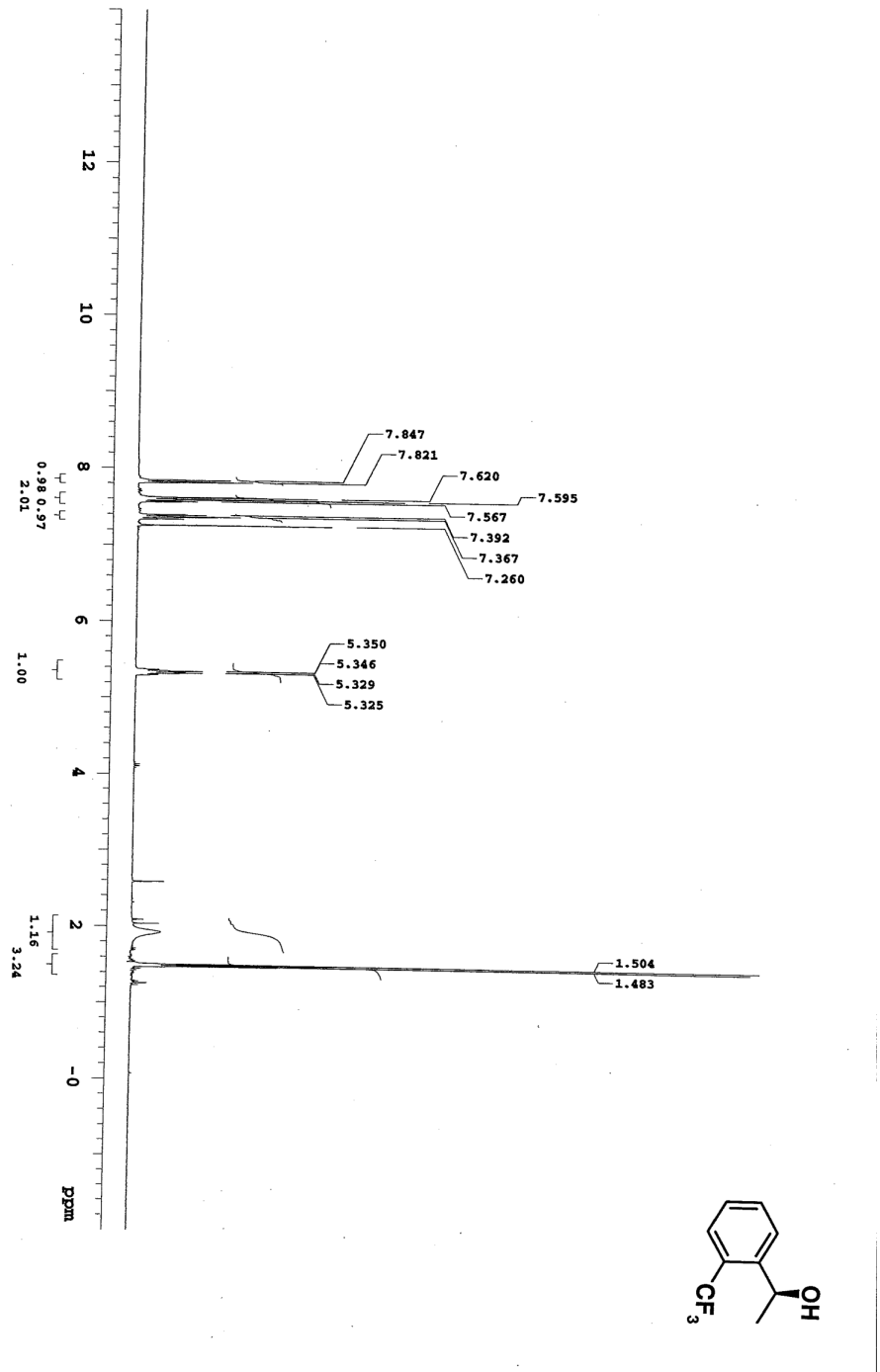
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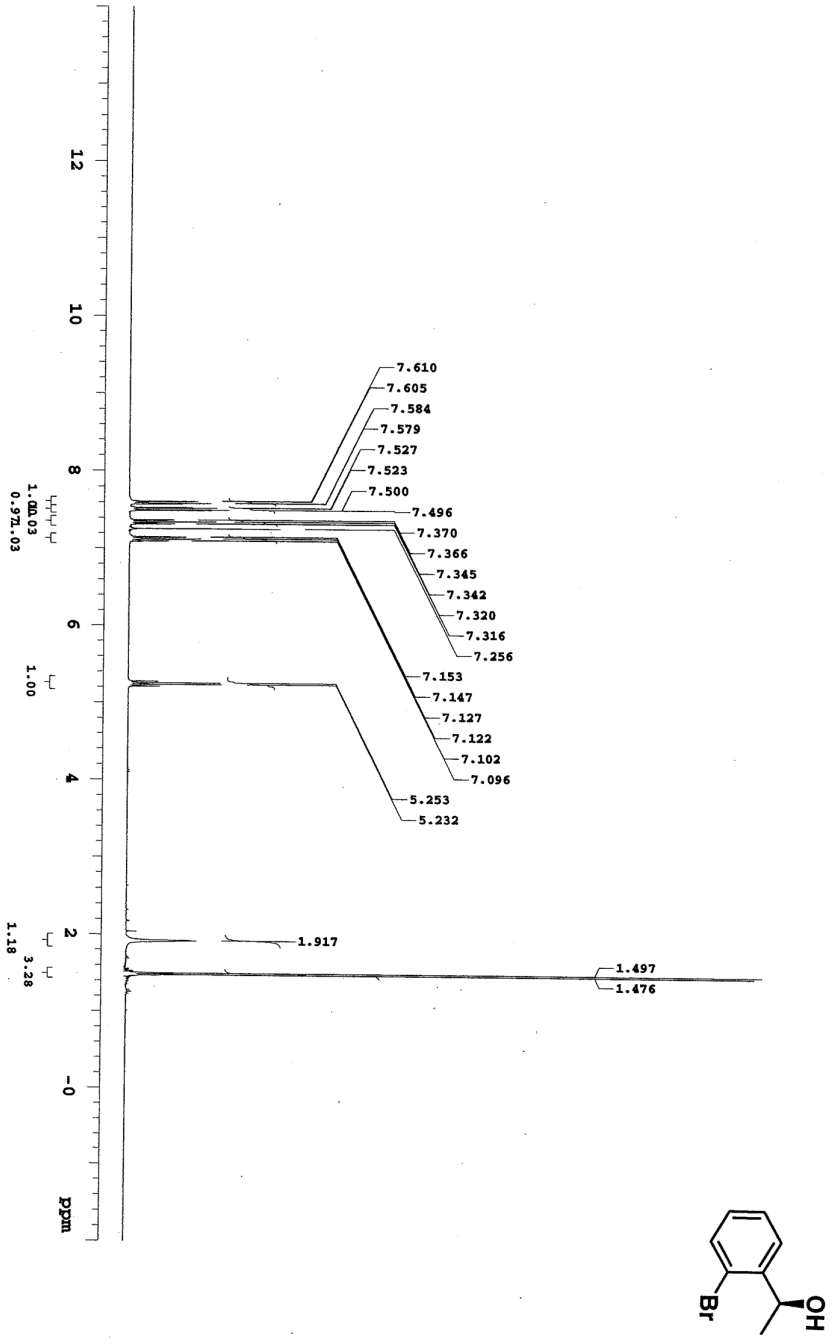
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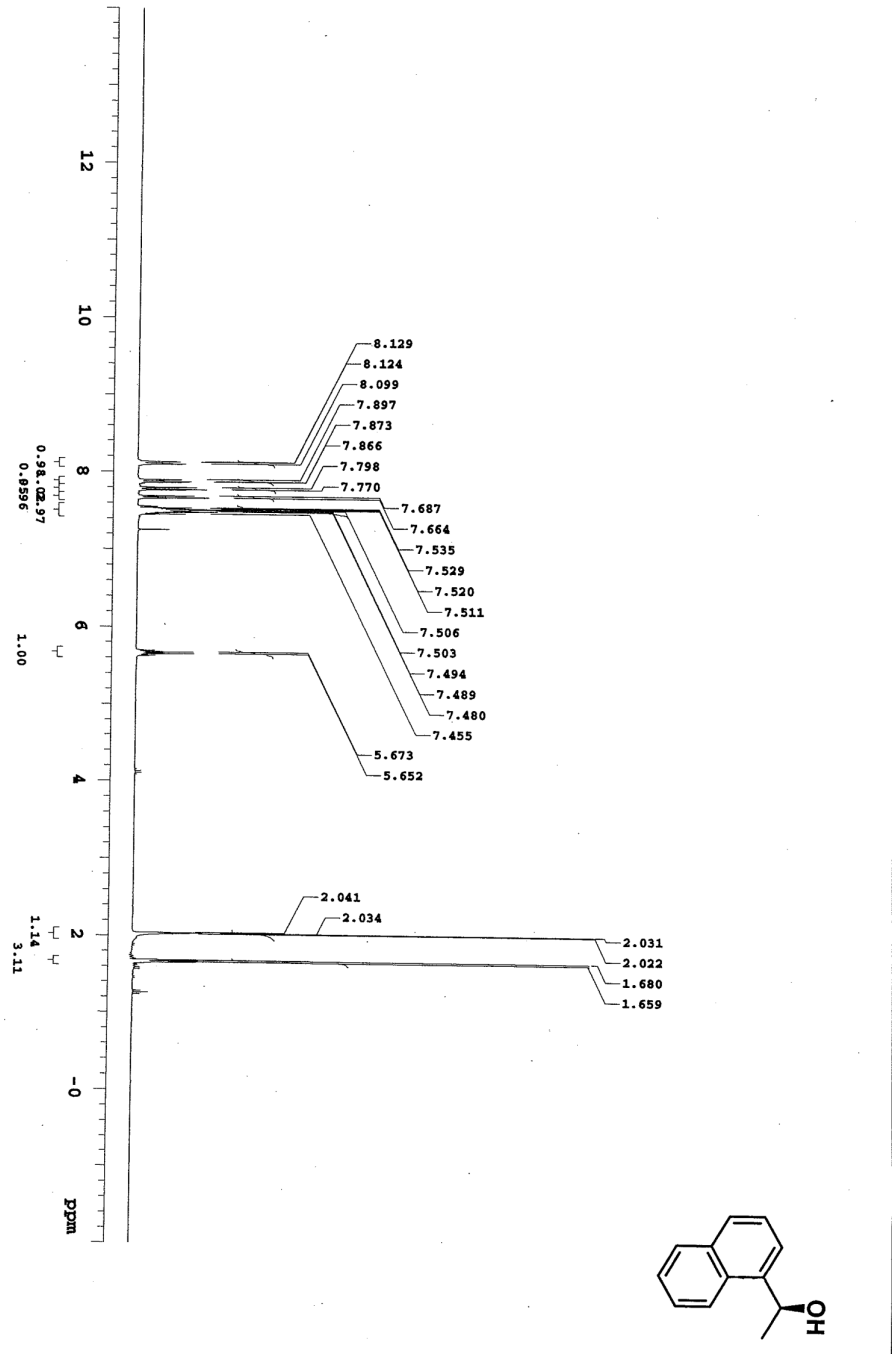
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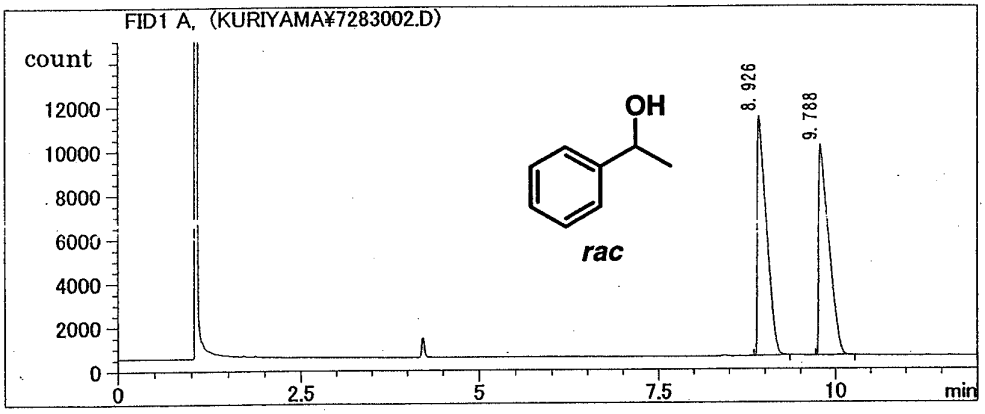

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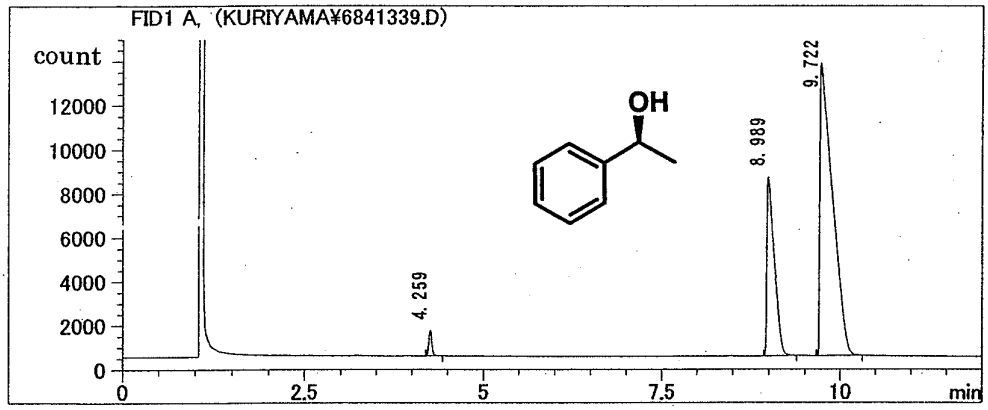
rac-1-Phenylethanol



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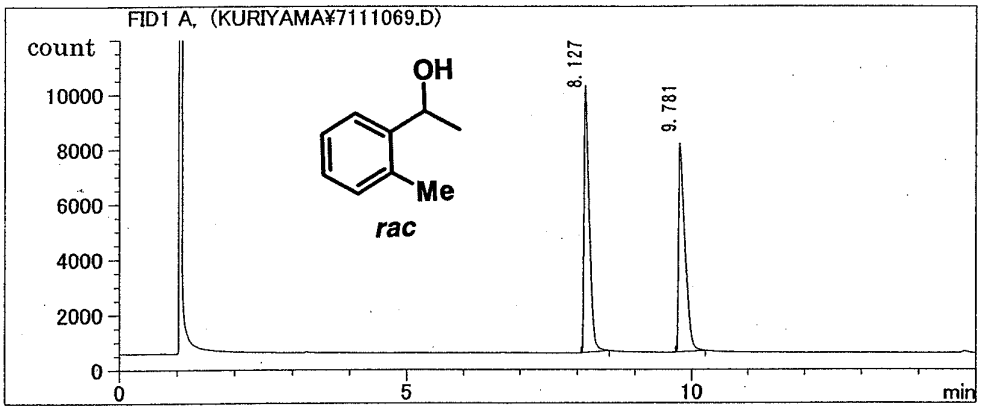

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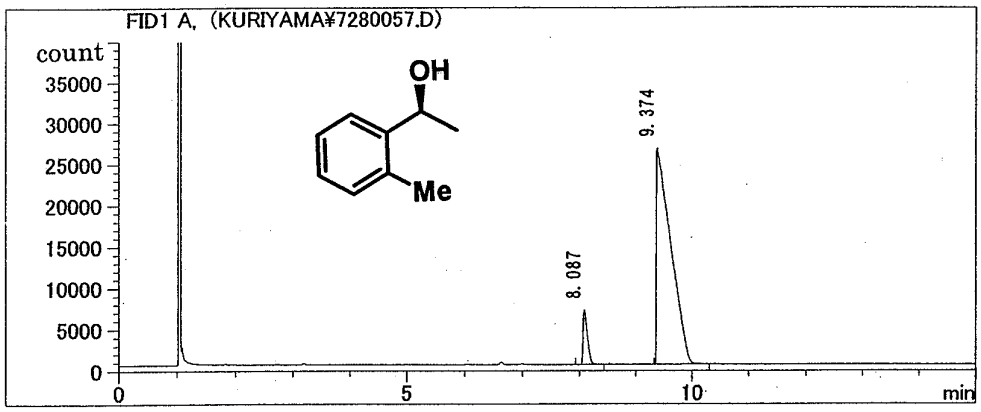
rac-1-(2-Methylphenyl)ethanol



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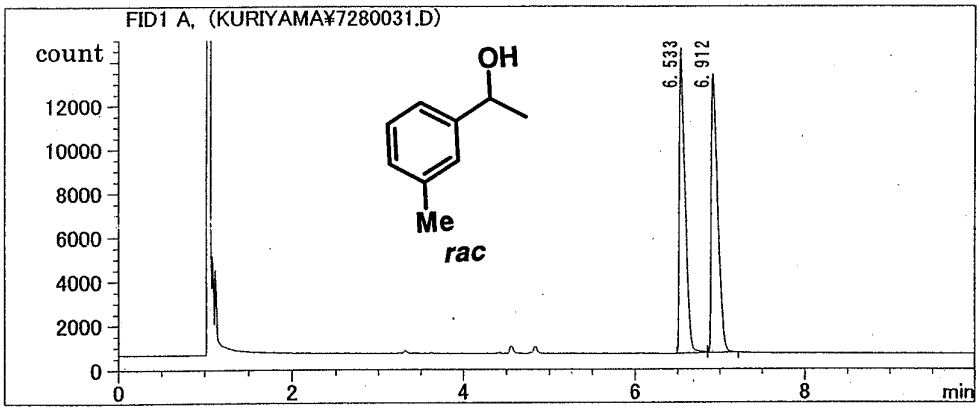
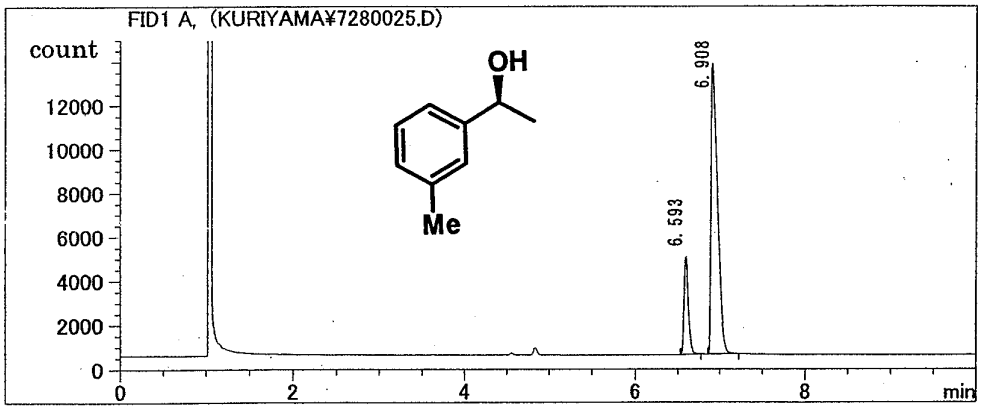


signal 1: FID1 A,

peak #	RT [min]	peak type	width [min]	area	area %
1	6.533	BV	0.062	65022.312	49.527
2	6.912	VB	0.070	66264.227	50.473

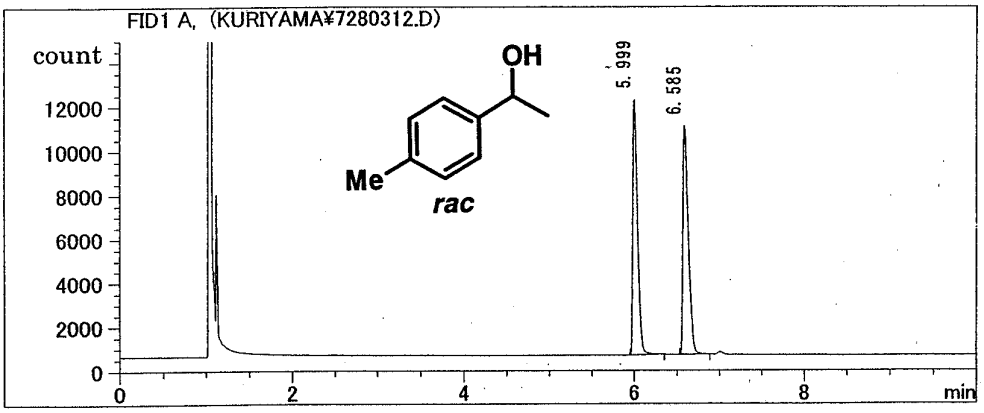
rac-1-(3-Methylphenyl)ethanol



signal 1: FID1 A,

peak #	RT [min]	peak type	width [min]	area	area %
1	6.593	PB	0.054	15588.375	18.207
2	6.908	PB	0.072	70027.195	81.793

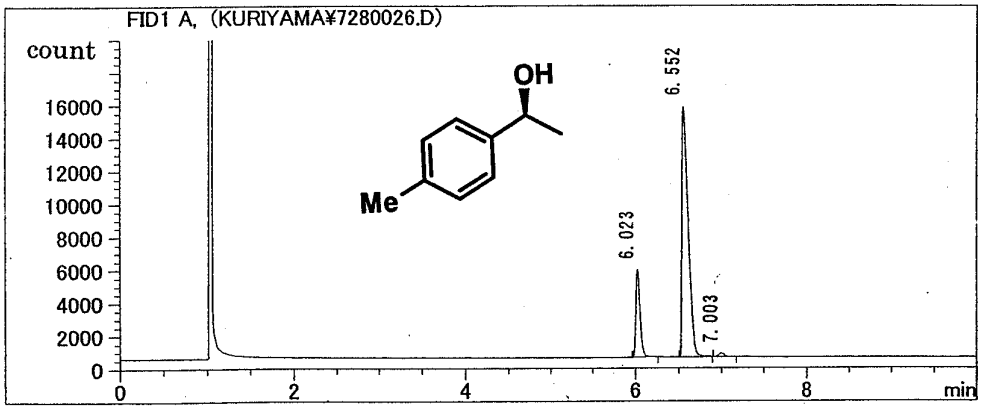
(*S*)-1-(3-Methylphenyl)ethanol (Table 2, Entry 2)



signal 1: FID1 A,

peak #	RT [min]	peak type	width [min]	area	area %
1	5. 999	PB	0. 058	43488. 191	49. 047
2	6. 585	PB	0. 062	45178. 383	50. 953

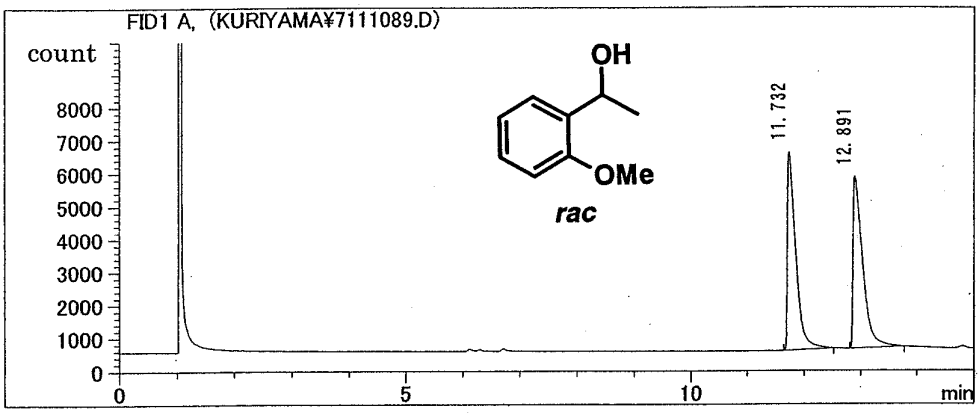
rac-(4-Methylphenyl)ethanol



signal 1: FID1 A,

peak #	RT [min]	peak type	width [min]	area	area %
1	6. 023	PB	0. 050	17554. 943	18. 581
2	6. 552	PB	0. 069	75852. 555	80. 284
3	7. 003	BB	0. 073	1072. 945	1. 136

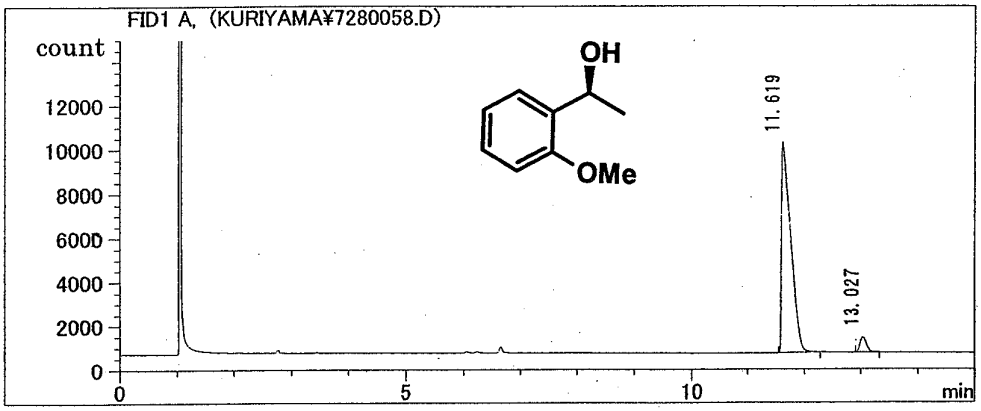
(*S*)-1-(4-Methylphenyl)ethanol (Table 2, Entry 3)



signal 1: FID1 A,

peak #	RT [min]	peak type	width [min]	area	area %
1	11.732	PB	0.138	61258.535	49.589
2	12.891	PB	0.163	62274.309	50.411

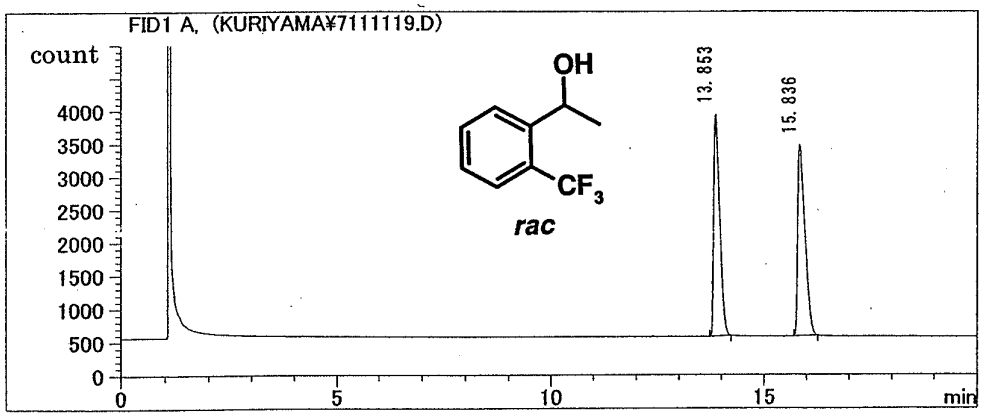
rac-1-(2-Methoxyphenyl)ethanol



signal 1: FID1 A,

peak #	RT [min]	peak type	width [min]	area	area %
1	11.619	PB	0.143	106826.055	95.362
2	13.027	BB	0.117	5195.649	4.638

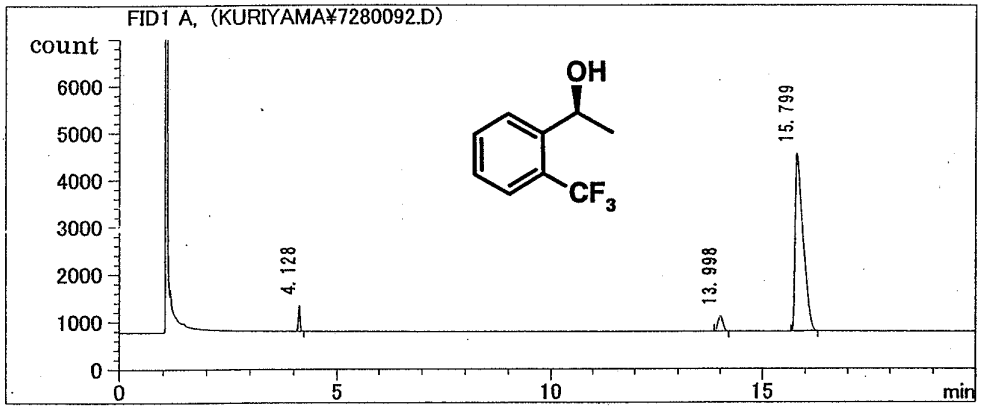
(*S*)-1-(2-Methoxyphenyl)ethanol (Table 2, Entry 4)



signal 1: FID1 A,

peak #	RT [min]	peak type	width [min]	area	area %
1	13.853	PB	0.134	32850.980	49.900
2	15.836	BB	0.156	32982.313	50.100

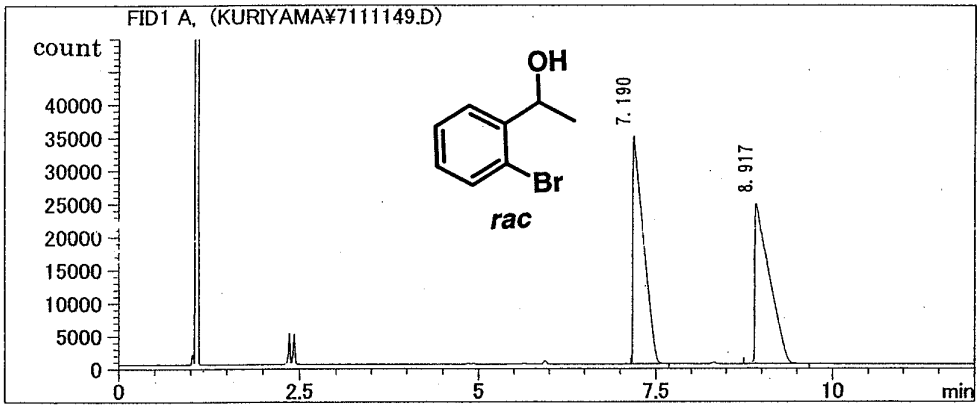
rac-1-(2-Trifluoromethylphenyl)ethanol



signal 1: FID1 A,

peak #	RT [min]	peak type	width [min]	area	area %
1	4.128	BP	0.040	1369.806	2.661
2	13.998	BP	0.096	2491.283	4.840
3	15.799	BP	0.163	47615.105	92.499

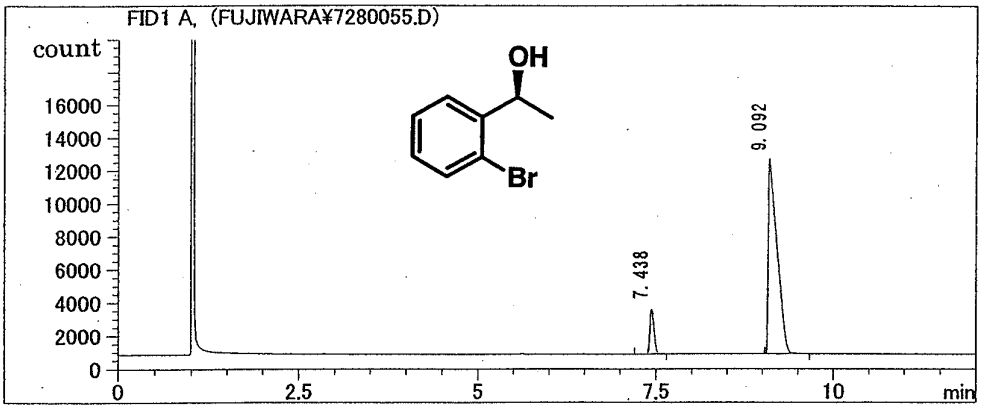
(*S*)- 1-(2-Trifluoromethylphenyl)ethanol (Table 2, Entry 5)



signal 1: FID1 A,

peak #	RT [min]	peak type	width [min]	area	area %
1	7.190	VV	0.123	344520.531	50.098
2	8.917	PB	0.173	343172.688	49.902

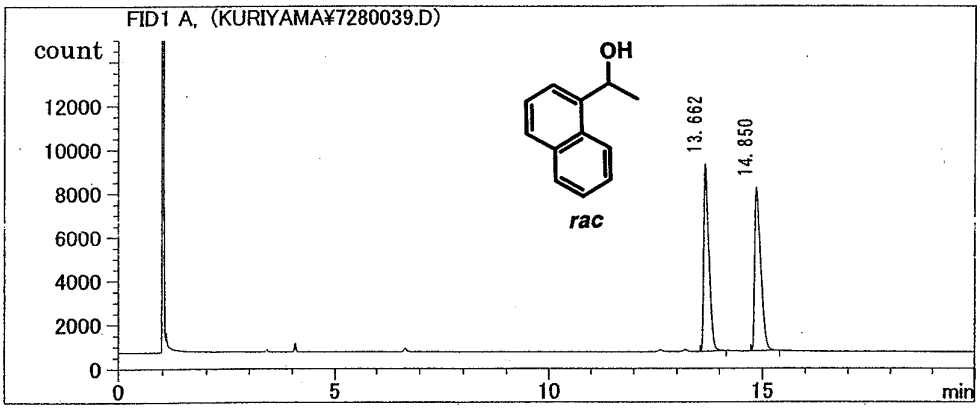
rac-1-(2-Bromophenyl)ethanol



signal 1: FID1 A,

peak #	RT [min]	peak type	width [min]	area	area %
1	7.438	PV	0.061	10322.010	9.256
2	9.092	VB	0.113	101198.992	90.744

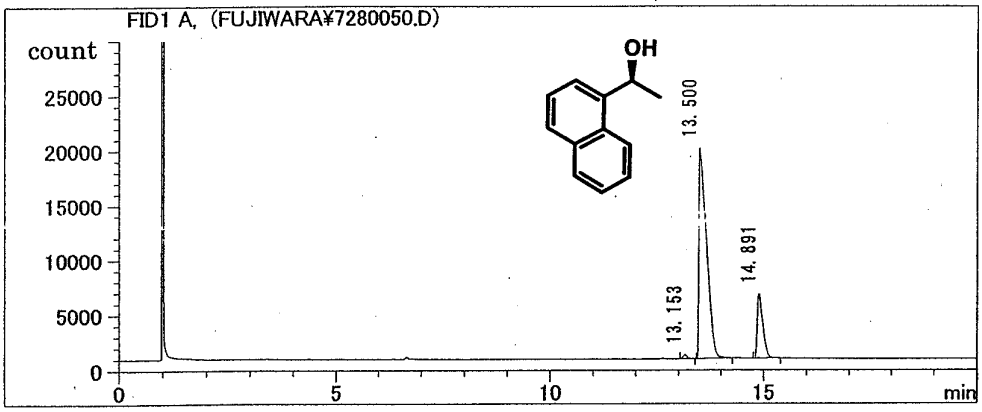
(*S*)- 1-(2-Bromophenyl)ethanol (Table 2, Entry 6)



signal 1: FID1 A,

peak #	RT [min]	peak type	width [min]	area	area %
1	13. 662	PB	0. 114	70461. 422	49. 540
2	14. 850	PB	0. 126	71770. 805	50. 460

rac-1-(1-Naphthyl)ethanol



signal 1: FID1 A,

peak #	RT [min]	peak type	width [min]	area	area %
1	13. 153	BB	0. 088	2391. 284	0. 824
2	13. 500	PB	0. 155	235076. 938	81. 014
3	14. 891	PB	0. 125	52699. 020	18. 162

(*S*)-1-(1-Naphthyl)ethanol (Table 2, Entry 7)