

Supporting Information for:

**Ru-Catalyzed Asymmetric Hydrogenation of Racemic Aldehydes
via Dynamic Kinetic Resolution: Efficient Synthesis of Optically
Active Primary Alcohols**

Jian-Hua Xie, Zhang-Tao Zhou, Wei-Ling Kong, Qi-Lin Zhou*

*State Key Laboratory and Institute of Elemento-organic Chemistry, Nankai University,
Tianjin 300071, China
qlzhou@nankai.edu.cn*

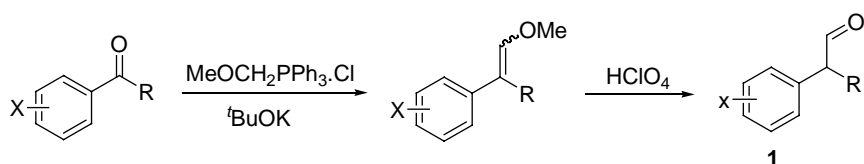
CONTENTS:

(A) Preparation and Physical Data of Racemic α -Arylaldehydes.....	S2
(B) General Procedure for the Preparation of Catalysts 3.....	S7
(C) General Procedure for Asymmetric Hydrogenation.....	S8
(D) Synthesis of (S)-2-(4-Chlorophenyl)-3-methylbutanoic Acid (4).....	S15
(E) Synthesis of BAY \times 1005.....	S15
(F) Hydrogenation of Aldehyde 1c with D ₂	S18
(G) NMR Spectra for New α -Arylaldehydes and Chiral Primary Alcohols	S20
(H) GC or HPLC Chart for Hydrogenation Product and Other Compounds..	S38

General remarks. All reactions and manipulations were performed in an argon-filled glovebox (VAC DRI-LAB HE 493) or using standard Schlenk techniques. ^1H , ^{13}C and ^{31}P NMR spectra were recorded on a Varian Mercury Plus 400 spectrometer at 400 MHz (^1H NMR) and 100 MHz (^{13}C NMR) or a Bruker AV 300 spectrometer at 300 MHz (^1H NMR), 75 MHz (^{13}C NMR) and 121.5 MHz (^{31}P NMR) in CDCl_3 . Chemical shifts were reported in ppm downfield from internal $\text{Si}(\text{CH}_3)_4$ and external 85% H_3PO_4 , respectively. Optical rotations were determined using a Perkin Elmer 341 polarimeter. Mass spectra were recorded on a VG-7070E spectrometer. HRMS were recorded on a VG ZAB-HS mass spectrometer with EI resource or a IonSpec FT-ICR mass spectrometer with MALDI resource. GC analyses were performed using Hewlett Packard Model HP 6890 Series instruments. HPLC analyses were performed using Waters 2996 and Hewlett Packard Model HP 1100 Series instruments. THF and ether were distilled from sodium benzophenone ketyl. 2-Propanol and DMF were freshly distilled from calcium hydride before use. SDP ligands can be obtained from Strem Chemicals Co. Phenylpropionaldehyde (**1a**), (*R,R*)- or (*S,S*)-DACH, and (*R,R*)- and (*S,S*)-DPEN were purchased from Acros or Aldrich chemical company. (*S*)-DAIPEN was synthesized by literature method.^[1] Hydrogen gas (99.999%) was purchased from Boc Gas Inc., Tianjin.

(A) Preparation and Physical Data of Racemic α -Arylaldehydes

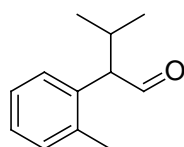
The racemic α -arylaldehydes **1** were synthesized by Wittig methoxymethylation of ketones using (methoxymethyl)triphenylphosphonium chloride ($\text{MeOCH}_2\text{PPh}_3\text{Cl}$) and *t*-BuOK as base, followed by acid catalyzed hydrolysis.^[2]



General procedure: A suspension of $\text{Ph}_3\text{PCH}_2\text{OCH}_3\text{Cl}$ (25.9 g, 75 mmol) in ether (200 mL) was cooled to 0 °C and $t\text{BuOK}$ (80 mmol) was added in portions to give a dark red solution. After stirring for 0.5 h, a solution of ketone (50 mmol) in ether (50 mL) was added dropwise and the mixture was stirred at this temperature for 0.5 h and then warmed up to room temperature. When the reaction completed (TLC monitor) the mixture was poured into water and extracted with AcOEt . The extract was washed with water and brine, dried over MgSO_4 , and concentrated. The residue was purified on a silica gel column with AcOEt /petroleum as eluent to afford the enol-methyl ether.

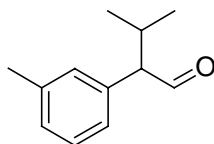
The enol-methyl ether was dissolved in Et_2O (150 mL) and to this solution was slowly added a 70% aqueous solution of HClO_4 (5 mL). After stirring for several minutes (TLC monitor) at room temperature the mixture was added slowly to saturated NaHCO_3 solution (100 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O . The combined organic phase was dried over MgSO_4 , and the solvent was removed under reduced pressure. The residue was purified on a silica gel column with AcOEt /petroleum as eluent to afford the corresponding α -arylaldehyde.

3-Methyl-2-(2-methylphenyl)butanal (1f)



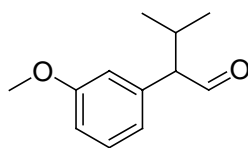
Colorless liquid, 62% yield. ^1H NMR (300 MHz, CDCl_3) δ 0.76 (d, J = 6.6 Hz, 3H), 1.07 (d, J = 6.6 Hz, 3H), 2.33 (s, 3H), 2.36–2.47 (m, 1H), 3.47 (dd, J = 3.6, 9.9 Hz, 1H), 7.12–7.20 (m, 4H), 9.58 (d, J = 3.6 Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 20.0, 20.1, 21.3, 28.9, 62.2, 126.5, 127.2, 128.1, 130.9, 134.0, 137.7, 200.5. HRMS (EI) calcd for $\text{C}_{12}\text{H}_{16}\text{O}$ (M^+): 176.1271. Found: 176.1286.

3-Methyl-2-(3-methylphenyl)butanal (1h)



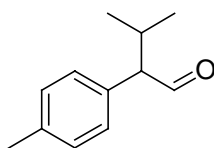
Colorless liquid, 71% yield. ^1H NMR (300 MHz, CDCl_3) δ 0.75 (d, $J = 6.9$ Hz, 3H), 1.01 (d, $J = 6.9$ Hz, 3H), 2.32 (s, 3H), 2.34–2.43 (m, 1H), 3.10 (dd, $J = 3.3, 9.6$ Hz, 1H), 6.95–7.21 (m, 4H), 9.66 (d, $J = 3.0$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 20.1, 21.2, 21.4, 28.7, 66.9, 126.4, 128.2, 128.8, 130.1, 135.5, 138.5, 200.9. HRMS (EI) calcd for $\text{C}_{12}\text{H}_{16}\text{O}$ (M^+): 176.1271. Found: 176.1279

3-Methyl-2-(3-methoxyphenyl)butanal (1i)



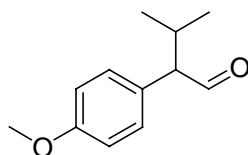
Colorless oil, 63% yield. ^1H NMR (400 MHz, CDCl_3) δ 0.75 (d, $J = 6.8$ Hz, 3H), 1.01 (d, $J = 6.8$ Hz, 3H), 2.33–2.40 (m, 1H), 3.11 (dd, $J = 3.2, 7.2$ Hz, 1H), 3.76 (s, 3H), 6.71–6.81 (m, 3H), 7.24 (t, $J = 8.0$ Hz, 1H), 9.65 (d, $J = 3.6$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 20.3, 21.36, 28.9, 55.3, 67.1, 112.8, 115.3, 121.8, 130.1, 137.3, 160.2, 201.0. HRMS (EI) calcd for $\text{C}_{12}\text{H}_{16}\text{O}_2$ (M^+): 192.1221. Found: 192.1218.

3-Methyl-2-(4-methylphenyl)butanal (1j)



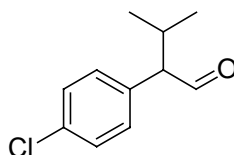
Colorless liquid, 60% yield. ^1H NMR (300 MHz, CDCl_3) δ 0.75 (d, $J = 6.6$ Hz, 3H), 1.02 (d, $J = 6.6$ Hz, 3H), 2.34–2.41 (m, 4H), 3.12 (dd, $J = 3.0, 9.3$ Hz, 1H), 7.05 (d, $J = 8.1$ Hz, 2H), 7.15 (d, $J = 8.1$ Hz, 2H), 9.65 (d, $J = 3.0$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 20.1, 21.0, 21.2, 28.7, 66.5, 129.2, 129.6, 132.4, 137.1, 201.0. HRMS (EI) calcd for $\text{C}_{12}\text{H}_{16}\text{O}$ (M^+): 176.1271. Found: 176.1288.

3-Methyl-2-(4-methoxyphenyl)butanal (1k)



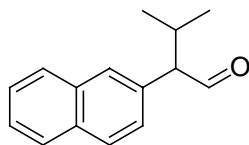
Colorless oil, 75% yield. ^1H NMR (400 MHz, CDCl_3) δ 0.74 (d, $J = 6.4$ Hz, 3H), 1.01 (d, $J = 6.8$ Hz, 3H), 2.34 (m, 1H), 3.10 (dd, $J = 3.2, 9.2$ Hz, 1H), 3.78 (s, 3H), 6.87 (d, $J = 8.8$ Hz, 2H), 7.07 (d, $J = 8.8$ Hz, 2H), 9.64 (d, $J = 3.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.2, 21.4, 28.9, 55.4, 66.2, 114.6, 127.5, 130.5, 159.2, 201.2. HRMS (EI) calcd for $\text{C}_{12}\text{H}_{16}\text{O}_2$ (M^+): 192.1221. Found: 192.1229.

3-Methyl-2-(4-chlorophenyl)butanal (1l)



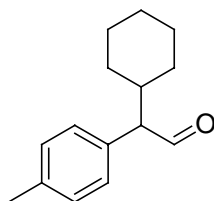
Colorless oil, 58% yield. ^1H NMR (300 MHz, CDCl_3) δ 0.76 (d, $J = 6.9$ Hz, 3H), 1.03 (d, $J = 6.6$ Hz, 3H), 2.34–2.44 (m, 1H), 3.18 (dd, $J = 3.3, 9.6$ Hz, 1H), 7.13 (d, $J = 8.4$ Hz, 2H), 7.33 (d, $J = 8.7$ Hz, 2H), 9.68 (d, $J = 3.3$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 19.9, 21.1, 28.9, 66.0, 129.1, 130.6, 133.5, 134.1, 200.5. HRMS (EI) calcd for $\text{C}_{11}\text{H}_{13}\text{ClO}$ (M^+): 196.0725. Found: 196.0737.

3-Methyl-2-(naphthalen-2-yl)butanal (1m)



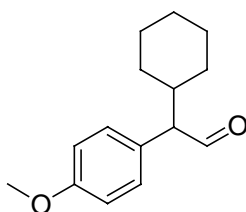
Colorless oil, 70% yield. ^1H NMR (400 MHz, CDCl_3) δ 0.81 (d, $J = 6.8$ Hz, 3H), 1.19 (d, $J = 6.4$ Hz, 3H), 2.65 (m, 1H), 4.09 (m, 1H), 7.38 (m, 1H), 7.46–7.61 (m, 3H), 7.81–7.91 (m, 2H), 8.16 (m, 1H), 9.71 (d, $J = 2.8$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 20.5, 21.8, 29.3, 61.6, 123.5, 125.7, 126.2, 126.8, 128.4, 129.3, 132.0, 133.0, 134.5, 200.5. HRMS (EI) calcd for $\text{C}_{15}\text{H}_{16}\text{O}$ (M^+): 212.1201. Found: 212.1189.

2-Cyclohexyl-2-(4-methylphenyl)acetaldehyde (1n)



Colorless oil, 61% yield. ^1H NMR (300 MHz, CDCl_3) δ 0.75–1.84 (m, 10H), 2.05 (m, 1H), 2.29 (s, 3H), 3.18 (dd, $J = 3.0, 6.3$ Hz, 1H), 7.04 (d, $J = 7.8$ Hz, 2H), 7.12 (d, $J = 7.8$ Hz, 2H), 9.64 (d, $J = 3.3$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 21.0, 26.1, 26.4, 30.2, 31.9, 38.1, 65.4, 129.2, 129.6, 132.2, 137.0, 200.8. HRMS (EI) calcd for $\text{C}_{15}\text{H}_{20}\text{O}$ (M^+): 216.1584. Found: 216.1600.

2-Cyclohexyl-2-(4-methoxyphenyl)acetaldehyde (1o)



White solid, Mp 39–41 °C, 74% yield. ¹H NMR (300 MHz, CDCl₃) δ 0.76–1.84 (m, 10H), 2.03 (m, 1H), 3.20 (dd, *J* = 3.3, 9.6 Hz, 1H), 3.79 (s, 3H), 6.90 (d, *J* = 8.7 Hz, 2H), 7.10 (d, *J* = 8.7 Hz, 2H), 9.65 (d, *J* = 3.6 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 26.1, 26.3, 30.2, 31.8, 38.1, 55.2, 64.9, 114.4, 127.1, 130.3, 159.0, 201.1. HRMS (EI) calcd for C₁₅H₂₀O₂ (M⁺): 232.1463. Found: 232.1450.

(B) General Procedure for the Preparation of Catalysts **3** ^[3]

General procedure: SDP ligand (0.132 mmol) and [(C₆H₆)RuCl₂]₂ (30 mg, 0.06 mmol) were dissolved in anhydrous and degassed DMF (4 mL) under nitrogen. The reaction mixture was heated to 100–110 °C for 3–4 hours, then the solution of 1,2-diamine (0.132 mmol) in 1 mL DMF was added and the reaction was allowed to warm to room temperature while stirring overnight. The solvent was removed under high vacuum at 50 °C, and the residue was dried at room temperature to give the catalysts **3** as orange to red brown solid. The catalysts **3** were used directly in the catalytic reactions without further purification. ³¹P NMR (121 MHz, CDCl₃) of the catalysts:

[RuCl₂((*S*)-DMM-SDP)((*R,R*)-DPEN)] ((*S,RR*)-**3f**): δ 46.43 (s)

[RuCl₂((*R*)-Xyl-SDP)((*S*)-DAIPEN)] ((*R,S*)-**3g**): δ 36.60 (s), 36.65 (s)

[RuCl₂((*S*)-Xyl-SDP)((*S*)-DAIPEN)] ((*S,S*)-**3h**): δ 36.82 (s), 36.76 (s)

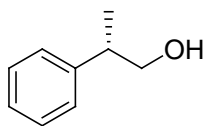
[RuCl₂((*S*)-Xyl-SDP)((*R,R*)-DACH)] ((*S,RR*)-**3i**): δ 47.93 (s), 46.00 (s)

[RuCl₂((*S*)-DMM-SDP)((*R,R*)-DACH)] ((*S,RR*)-**3j**): δ 46.05 (s), 45.36 (s)

(C) General Procedure for Asymmetric Hydrogenation of Aldehydes

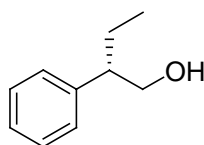
General Procedure: The catalyst (0.002 mmol) was placed in a 30 mL hydrogenation vessel. Anhydrous *i*-PrOH (8.0 mL) was introduced with a syringe and the vessel was purged with hydrogen and pressurized to 20 atm. After released the pressure, α -arylaldehydes (2 mmol) and a solution of *t*-BuOK in *i*-PrOH (0.2 mmol/mL, 2.0 mL, 0.4 mmol) were added. The vessel was purged with hydrogen and pressurized to 50 atm. After stirred at room temperature for 8 h, the reaction was stopped. The reaction mixture was filtered through a short silica gel column, and the filtrate was diluted with acetone and analyzed by GC to determine the conversion. Enantioselectivity of the alcohol was determined by GC or HPLC after flash chromatography on a silica gel column.

(*S*)-2-Phenylpropan-1-ol (2a) ^[4]



Colorless oil, 78% ee, $[\alpha]_{\text{D}}^{20} -10.8$ (*c* 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 1.27 (d, *J* = 6.8 Hz, 3H), 2.93 (m, 1H), 3.70 (m, 2H), 7.25 (m, 3H), 7.33 (m, 2H). The ee value of **2a** was determined by GC analysis using a Supelco β -DEX 225 column [25 m \times 0.25 mm \times 0.25 μ m; N₂ 1 mL/min, programmed from 100 °C to 180 °C at 0.5 °C/min; *t*_R (minor) = 20.97 min, *t*_R (major) = 22.07 min].

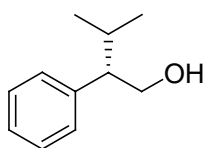
(*S*)-2-Phenylbutan-1-ol (2b) ^[5]



Colorless oil, 86% ee, $[\alpha]_{\text{D}}^{20} -24.7$ (*c* 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ

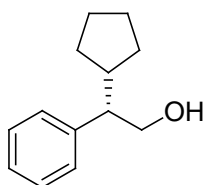
0.84 (t, $J = 8.0$ Hz, 3H), 1.38 (m, 1H), 1.57 (m, 1H), 1.76 (m, 1H), 3.70 (m, 1H), 3.79 (m, 2H), 7.21–7.36 (m, 5H). The ee of **2b** was determined by GC using a Supelco β -DEX 225 column [25 m \times 0.25 mm \times 0.25 μ m; N₂ 1 mL/min, programmed from 100 °C to 180 °C at 0.5 °C/min; t_R (minor) = 26.23 min, t_R (major) = 26.78 min].

(S)-3-Methyl-2-phenylbutan-1-ol (2c) ^[6]



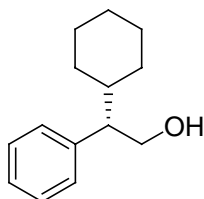
Colorless oil, 96% ee, $[\alpha]_D^{20} +11.3$ (c 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 0.72 (d, $J = 6.8$ Hz, 3H), 1.00 (d, $J = 6.8$ Hz, 3H), 1.92 (m, 1H), 2.51 (m, 1H), 3.83 (m, 1H), 3.93 (m, 1H), 7.18–7.25 (m, 3H), 7.33 (m, 2H). The ee value of **2c** was determined by HPLC analysis using a Daicel Chiralcel AD-H column [25 cm \times 0.46 cm ID; *i*PrOH/Hex = 2:98, 1.0 mL/min, 254 nm; t_R (minor) = 9.09 min, t_R (major) = 9.90 min].

(S)-Cyclopentyl-2-phenylethan-1-ol (2d) ^[7]



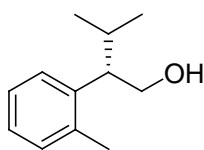
Colorless oil, 92% ee, $[\alpha]_D^{20} +17.5$ (c 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 0.99–2.08 (m, 9H), 2.55 (m, 1H), 3.75 (m, 1H), 3.88 (m, 1H), 7.20–7.33 (m, 5H). The ee value of **2d** was determined by HPLC analysis using a Chiralpak OJ-H column [25 cm \times 0.46 cm ID; *i*PrOH/Hex = 1:99, 0.6 mL/min, 254 nm; t_R (minor) = 23.81 min, t_R (major) = 25.49 min].

(S)-2-Cyclohexyl-2-phenylethan-1-ol (2e) ^[5]



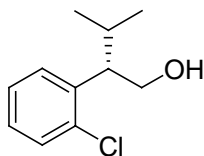
White solid, Mp 49–51 °C, 92% ee, $[\alpha]_{\text{D}}^{20} +5.6$ (*c* 1.2, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 0.75–1.86 (m, 11H), 2.58 (m, 1H), 3.84 (m, 1H), 3.95 (m, 1H), 7.16–7.35 (m, 5H). The ee value of **2e** was determined by HPLC analysis using a Daicel Chiralcel OD-H column [25 cm \times 0.46 cm ID; *i*PrOH/Hex = 1:99, 1.0 mL/min, 254 nm; *t*_R (minor) = 16.59 min, *t*_R (major) = 17.99 min].

(S)-3-Methyl-2-(2-methylphenyl)butan-1-ol (2f)



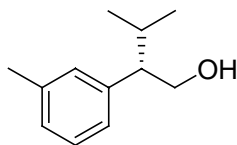
Colorless oil, 95% ee, $[\alpha]_{\text{D}}^{20} +10.5$ (*c* 1.1, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 0.74 (d, *J* = 6.8 Hz, 3H), 1.05 (d, *J* = 6.8 Hz, 3H), 1.91 (m, 1H), 2.35 (s, 3H), 2.85 (m, 1H), 3.72 (m, 1H), 3.87 (m, 1H), 7.10–7.20 (m, 5H); ¹³C NMR (100 MHz, CDCl₃) δ 20.6, 21.1, 21.5, 31.0, 50.0, 65.4, 126.3, 126.4, 126.5, 130.7, 138.0, 140.9; HRMS (EI) calcd for C₁₂H₁₈O: 178.1358. Found: 178.1356. The ee value of **2f** was determined by HPLC analysis using a Daicel Chiralcel OD-H column [25 cm \times 0.46 cm ID; *i*PrOH/Hex = 0.5:99.5, 1.0 mL/min, 254 nm; *t*_R (major) = 25.85 min, *t*_R (minor) = 29.13 min].

(S)-3-Methyl-2-(2-chlorophenyl)butan-1-ol (2j)



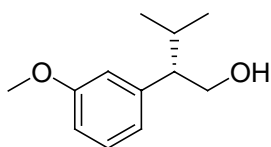
Colorless oil, 93% ee, $[\alpha]_{\text{D}}^{20} +15.7$ (c 1.0, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 0.76 (d, $J = 6.8$ Hz, 3H), 1.03 (d, $J = 6.8$ Hz, 3H), 1.98 (m, 1H), 3.20 (m, 1H), 3.85 (m, 2H), 7.10–7.40 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 20.8, 21.2, 30.2, 50.5, 64.4, 127.1, 127.7, 128.7, 130.0, 135.7, 140.2; HRMS (EI) calcd for $\text{C}_{11}\text{H}_{15}\text{ClO}$: 198.0811. Found: 198.0811. The ee value of **2g** was determined by HPLC analysis using a Chiralpak AD-H column [25 cm \times 0.46 cm ID; $i\text{PrOH/Hex} = 0.5:99.5$, 1.0 mL/min; t_{R} (minor) = 19.28 min, t_{R} (major) = 20.75 min].

(S)-3-Methyl-2-(3-methylphenyl)butan-1-ol (2h)



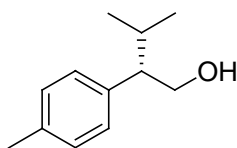
Colorless oil, 89% ee, $[\alpha]_{\text{D}}^{20} +10.4$ (c 1.2, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 0.73 (d, $J = 6.8$ Hz, 3H), 1.00 (d, $J = 6.8$ Hz, 3H), 1.25 (s, 1H), 1.90 (m, 1H), 2.35 (s, 3H), 2.46 (m, 1H), 3.77 (m, 1H), 3.90 (m, 1H), 6.90–7.23 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.2, 21.3, 21.8, 30.3, 56.0, 65.5, 125.9, 127.7, 128.6, 129.8, 138.3, 141.8; HRMS (EI) calcd for $\text{C}_{12}\text{H}_{18}\text{O}$: 178.1358. Found: 178.1356. The ee value of **2h** was determined by HPLC analysis using a Chiralpak AD-H column [25 cm \times 0.46 cm ID; $i\text{PrOH/Hex} = 1:99$, 1.0 mL/min, 254 nm, t_{R} (minor) = 14.63 min; t_{R} (major) = 15.63 min].

(S)-3-Methyl-2-(3-methoxyphenyl)butan-1-ol (2i)



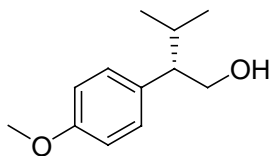
Colorless oil, 93% ee, $[\alpha]_{\text{D}}^{20} +11.5$ (c 1.0, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 0.73 (d, $J = 6.8$ Hz, 3H), 1.00 (d, $J = 6.8$ Hz, 3H), 1.27 (brs, 1H), 1.91 (m, 1H), 2.46 (m, 1H), 3.78 (m, 4H), 3.90 (m, 1H), 6.74–6.79 (m, 3H), 7.25 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.2, 21.3, 30.3, 55.4, 56.1, 65.4, 111.9, 114.9, 121.2, 129.7, 143.7, 159.9; HRMS (EI) calcd for $\text{C}_{12}\text{H}_{18}\text{O}_2$: 194.1307. Found: 194.1305. The ee value of **2i** was determined by HPLC analysis using a Chiralpak AD-H column [25 cm \times 0.46 cm ID; i PrOH/Hex = 1:99, 1.0 mL/min, 254 nm; t_{R} (minor) = 31.23 min, t_{R} (major) = 33.67 min].

(S)-3-Methyl-2-(4-methylphenyl)butan-1-ol (2j)



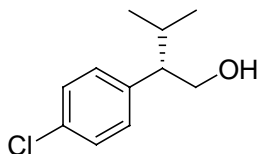
Colorless oil, 93% ee, $[\alpha]_{\text{D}}^{20} +10.3$ (c 1.1, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 0.73 (d, $J = 7.2$ Hz, 3H), 1.00 (d, $J = 7.2$ Hz, 3H), 1.37 (brs, 1H), 1.89 (m, 1H), 2.34 (s, 3H), 2.47 (m, 1H), 3.76 (m, 1H), 3.88 (m, 1H), 7.06–7.14 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.2, 21.3, 30.3, 55.6, 65.4, 128.8, 129.4, 136.4, 138.7; HRMS (EI) calcd for $\text{C}_{12}\text{H}_{18}\text{O}$: 178.1358. Found: 178.1361. The ee value of **2j** was determined by HPLC analysis using a Chiralpak AD-H column [25 cm \times 0.46 cm ID; i PrOH/Hex = 1:99, 1.0 mL/min, 254 nm; t_{R} (minor) = 13.32 min, t_{R} (major) = 16.30 min].

(S)-3-Methyl-2-(4-methoxyphenyl)butan-1-ol (2k)^[8]



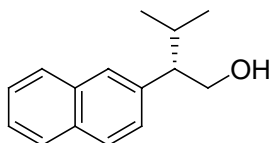
Colorless oil, 94% ee, $[\alpha]_{\text{D}}^{20} +11.3$ (c 1.0, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 0.72 (d, $J = 7.2$ Hz, 3H), 0.98 (d, $J = 7.2$ Hz, 3H), 1.86 (m, 1H), 2.45 (m, 1H), 3.78 (m, 4H), 3.92 (m, 1H), 6.86 (d, $J = 8.8$ Hz, 2H), 7.10 (d, $J = 8.8$ Hz, 2H). The ee value of **2k** was determined by HPLC analysis using a Chiralpak AD-H column [25 cm \times 0.46 cm ID; i PrOH/Hex = 1:99, 1.0 mL/min, 254 nm; t_{R} (minor) = 20.67 min, t_{R} (major) = 24.70 min].

(S)-3-Methyl-2-(4-chlorophenyl)butan-1-ol (2l) ^[9]



Colorless oil, 90% ee, $[\alpha]_{\text{D}}^{20} +8.0$ (c 1.0, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 0.72 (d, $J = 6.8$ Hz, 3H), 1.00 (d, $J = 6.8$ Hz, 3H), 1.89 (m, 1H), 2.48 (m, 1H), 3.79 (m, 1H), 3.91 (m, 1H), 7.13 (d, $J = 8.4$ Hz, 2H); 7.29 (d, $J = 8.4$ Hz, 2H). The ee value of **2l** was determined by HPLC analysis using Chiralpak AD-H column [25 cm \times 0.46 cm ID; i PrOH/Hex = 1:99, 1.0 mL/min, 254 nm]; t_{R} (minor) = 17.59 min, t_{R} (major) = 21.43 min].

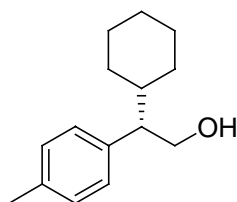
(S)-3-Methyl-2-(naphthalene-2-yl)butan-1-ol (2m) ^[10]



Colorless oil, 89% ee, $[\alpha]_{\text{D}}^{20} +17.2$ (c 1.0, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ

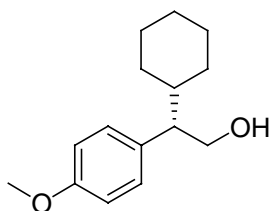
0.79 (d, $J = 6.8$ Hz, 3H), 1.10 (d, $J = 6.8$ Hz, 3H), 2.17 (m, 1H), 3.50 (m, 1H), 4.04 (m, 2H), 7.43-7.54 (m, 4H), 7.76 (d, $J = 8.0$ Hz, 1H), 7.87 (d, $J = 8.0$ Hz, 1H), 8.15 (d, $J = 8.0$ Hz, 1H). The ee value of **2m** was determined by HPLC analysis using a Chiralpak AD-H column [25 cm \times 0.46 cm ID; i PrOH/Hex = 1:99, 1.0 mL/min, 254 nm; t_R (minor) = 28.92 min, t_R (major) = 30.89 min].

(S)-2-Cyclohexyl-2-(4-methylphenyl)ethan-1-ol (2n) ^[11]



White solid, Mp 62–64 °C, 92% ee, $[\alpha]_D^{20} +6.9$ (c 1.0, CHCl₃); ^1H NMR (400 MHz, CDCl₃) δ 0.76–1.74 (m, 10H), 1.84 (m, 1H), 2.32 (s, 3H), 2.52 (m, 1H), 3.79 (m, 1H), 3.92 (m, 1H), 7.06–7.14 (m, 4H). The ee value of **2n** was determined by HPLC analysis using a Chiralcel OD-H column [25 cm \times 0.46 cm ID; i PrOH/Hex = 1:99, 1.0 mL/min, 254nm; t_R (minor) = 21.52 min, t_R (major) = 22.87 min].

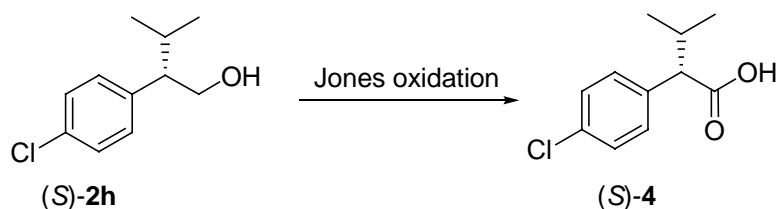
(S)-2-Cyclohexyl-2-(4-methoxyphenyl)ethan-1-ol (2o) ^[11]



White solid, Mp 57–59 °C, 94% ee, $[\alpha]_D^{20} +7.0$ (c 1.0, CHCl₃); ^1H NMR (400 MHz, CDCl₃) δ 0.76–1.75 (m, 10H), 1.85 (m, 1H), 2.53 (m, 1H), 3.75 (m, 1H), 3.80 (s, 3H), 3.92 (m, 1H), 6.87 (d, $J = 8.7$ Hz, 2H), 7.10 (d, $J = 8.7$ Hz, 2H). The ee value of **2o** was determined by HPLC analysis using a Chiralcel OD-H column [25 cm \times 0.46 cm

ID; *i*PrOH/Hex = 1:99, 1.0 mL/min, 254nm; t_R (major) = 21.88 min, t_R (minor) = 26.58 min].

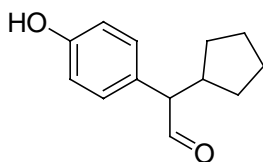
(D) Synthesis of (*S*)-2-(4-Chlorophenyl)-3-methylbutanoic acid (4**)**^[12]



To a stirred solution of (*S*)-2-(4-chlorophenyl)-3-methylbutan-1-ol (**(S)-2I**) (200 mg, 1 mmol) in acetone (10 mL) was added dropwise Jones reagent at 0 °C until the orange color of the mixture disappeared (within 5 min). Then, 1 mL of isopropanol was added to destroy the excess Jones reagent and the solvent was removed under reduced pressure. The residue was poured into 10 mL water, acidified with 1N HCl and extracted with EtOAc (2 × 10 mL). The organic extract was washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by chromatography on a silica gel column (AcOEt/petroleum = 1/5) to give (*S*)-**4** (208 mg, 97% yield) as white solid. Mp 89–91 °C, 90% ee. $[\alpha]_D^{20} +37.3$ (c 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 0.70 (d, J = 6.0 Hz, 3H), 1.06 (d, J = 6.4 Hz, 3H), 2.28 (m, 1H), 3.12 (d, J = 10.4 Hz, 1H), 7.25–7.28 (m, 4H). The ee value of (*S*)-**4** was determined by chiral HPLC after converting to the alcohol.

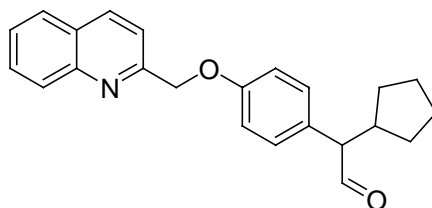
(E) Synthesis of BAY × 1005

Synthesis of 2-cyclopentyl-2-(4-hydroxyphenyl)acetaldehyde



2-Cyclopentyl-2-(4-hydroxyphenyl)acetaldehyde was synthesized from cyclopentyl-(4-(methoxymethoxy)phenyl)methanone using the same procedure as that described in (A). White solid, 64% yield (two steps), Mp 99-101 °C. ^1H NMR (400 MHz, CDCl_3) δ 1.00–2.10 (m, 8H), 2.47 (m, 1H), 3.23 (dd, J = 3.2, 10.4 Hz, 1H), 6.00 (brs, 1H), 6.80 (d, J = 8.4 Hz, 2H), 7.04 (d, J = 8.4 Hz, 2H), 9.61 (d, J = 2.8 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 24.7, 25.5, 30.9, 31.2, 40.3, 64.6, 116.2, 128.0, 130.4, 155.4, 202.1. HRMS (MALDI) calcd for $\text{C}_{13}\text{H}_{16}\text{O}_2$ (M^+ +1): 204.1150. Found: 204.1139.

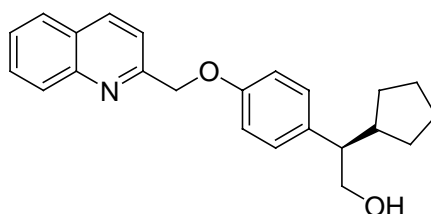
Synthesis of 2-cyclopentyl-2-(4-(quinolin-2-ylmethoxy)phenyl)acetaldehyde (5)



To a mixture of 2-cyclopentyl-2-(4-hydroxyphenyl)acetaldehyde (3.0 g, 15 mmol), anhydrous potassium carbonate (5.0g, 36 mmol) and 25 mL of dry DMF in a three-necked flask equipped with thermometer, stirrer and a condenser, a solution of 2-(chloromethyl)quinoline (3.0 g, 17 mmol) in 20 mL of dry DMF was added under nitrogen atmosphere at 70–80 °C. After the addition (0.5 h), the reaction mixture was kept at 70–80 °C for 5 h to complete the reaction (TLC monitor). The reaction mixture was cooled to room temperature, poured into 150 mL of water, extracted by EtOAc (4 \times 50 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by a flash chromatography on a silica gel column (EtOAc/petroleum ether = 1/5) to provide product **5** (4.6 g, 91%) as a white solid. Mp 79–81 °C. ^1H NMR (400 MHz, CDCl_3) δ 0.82–1.94 (m, 8H), 2.46 (m, 1H), 3.22 (d, J = 10.4 Hz, 1H), 5.36 (s, 2H), 7.00 (d, J =

6.8 Hz, 2H), 7.10 (d, J = 6.8 Hz, 2H), 7.52–7.82 (m, 4H), 8.06 (d, J = 8.4 Hz, 1H), 8.17 (d, J = 8.4 Hz, 1H), 9.61 (d, J = 2.8 Hz, 1H). ^{13}C NMR (100MHz, CDCl_3): δ 24.7, 25.4, 30.8, 31.2, 64.5, 71.5, 115.5, 119.3, 126.7, 127.8, 127.9, 128.9, 129.1, 129.9, 130.4, 137.2, 147.8, 158.0, 200.9. HRMS (MALDI) calcd for $\text{C}_{23}\text{H}_{24}\text{NO}_2$ ($\text{M}^+ + 1$): 346.1807. Found: 346.1797.

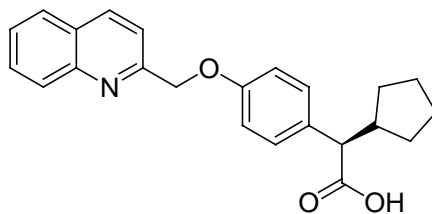
Synthesis of (*R*)-2-cyclopentyl-2-(4-(quinolin-2-ylmethoxy)phenyl)ethanol (**6**)



(*R*)-2-Cyclopentyl-2-(4-(quinolin-2-ylmethoxy)phenyl)ethanol **6** was synthesized by the hydrogenation of aldehyde **5** using (*R,SS*)-**3j** as catalyst according to the same procedure as that for the hydrogenation of α -arylaldehydes.

White solid, Mp 106–108 °C, 97% yield, 90% ee. $[\alpha]_{\text{D}}^{20}$ –10.8 (c 1.0, CHCl_3). ^1H NMR (400MHz, CDCl_3) δ 0.82–1.98 (m, 9H), 2.48 (m, 1H), 3.68 (m, 1H), 3.85 (m, 1H), 5.37 (s, 2H), 6.95 (d, J = 8.4 Hz, 2H), 7.11 (d, J = 8.4 Hz, 2H), 7.55 (t, J = 7.2 Hz, 1H), 7.67–7.76 (m, 2H), 7.82 (d, J = 8.0 Hz, 1H), 8.06 (d, J = 8.4 Hz, 1H), 8.16 (d, J = 8.4 Hz, 1H). ^{13}C NMR (100MHz, CDCl_3): δ 24.7, 25.6, 31.6, 31.9, 42.8, 54.2, 66.8, 71.4, 115.1, 119.3, 126.7, 127.8, 127.9, 129.1, 129.6, 129.9, 135.5, 137.2, 147.7, 157.4, 158.3. HRMS (MALDI) calcd for $\text{C}_{23}\text{H}_{26}\text{NO}_2$ ($\text{M}^+ + 1$): 348.1964. Found: 348.1952. The ee value of **6** was determined by HPLC analysis using a Chiralpak AD-H column [25 cm \times 0.46 cm ID; i PrOH/Hex = 10:90, 1.0 mL/min, 254 nm; t_{R} (major) = 23.73 min, t_{R} (minor) = 26.13 min].

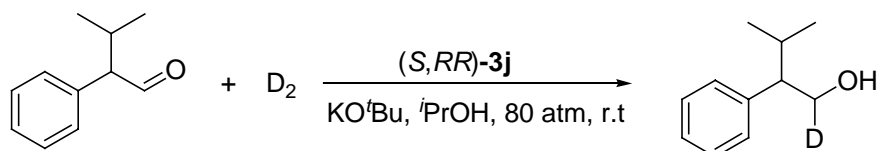
Synthesis of BAY \times 1005 ^[13]



A mixture of **6** (750 mg, 2.2 mmol, 98% ee), TEMPO (7.0 mg, 44 μ mol), MeCN (15 mL), and sodium phosphate (10 mL, 0.67 M, pH = 6.7) is heated to 35°C. The 0.1 mL of bleach (effective Cl >10%) was slowly added, and then a solution of NaClO₂ (450 mg, 5 mmol) in 25 mL water was added dropwise within 30 minutes. The resulted mixture was stirred at 35 °C for 40 h to complete the reaction (TLC monitor). The reaction mixture was extracted with chloroform (3 \times 25 mL) and dried over anhydrous Na₂SO₄. The organic solvent was removed under reduced pressure and the residue was purified by flash chromatography on a silica gel column (EtOAc/petroleum ether = 1/1) to provide product (690 mg, 89%) as a white solid. Mp: 169-171 °C, 98% ee (*R*). $[\alpha]_D^{25} -40.5$ (*c* 1.0, CHCl₃). ¹H NMR (400MHz, CDCl₃) δ 0.95–1.98 (m, 8H), 2.54 (m, 1H), 3.25 (d, *J* = 11.2 Hz, 1H), 5.28 (q, 2H), 6.95 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.4 Hz, 2H), 7.54 (m, 1H), 7.70–7.80 (m, 3H), 8.12–8.21 (m, 2H).

The ee value of BAY \times 1005 was determined by chiral HPLC after converting to the alcohol.

(F) Hydrogenation of Aldehyde **1c** with D₂



The hydrogenation of aldehyde **1c** with D₂ catalyzed by (*R,SS*)-**3j** was carried out using the same procedure as that with H₂. The ¹H NMR analysis showed that the deuteration took place at α -position (58%), and less than 5% deuterium was observed

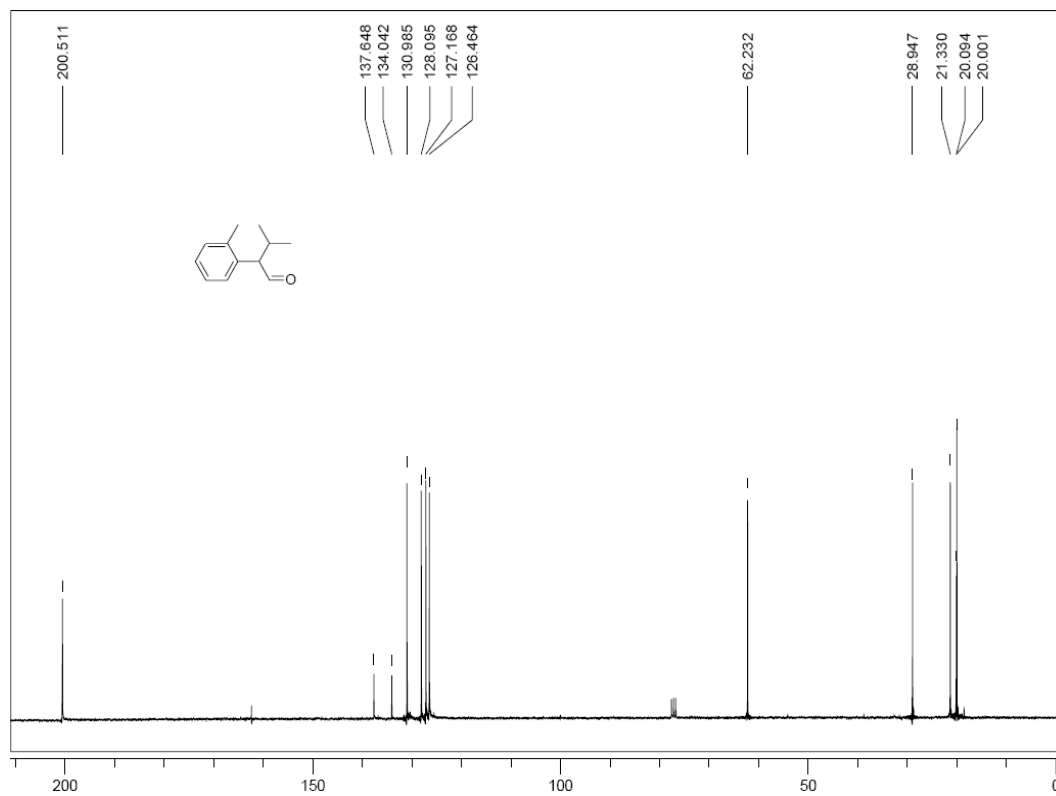
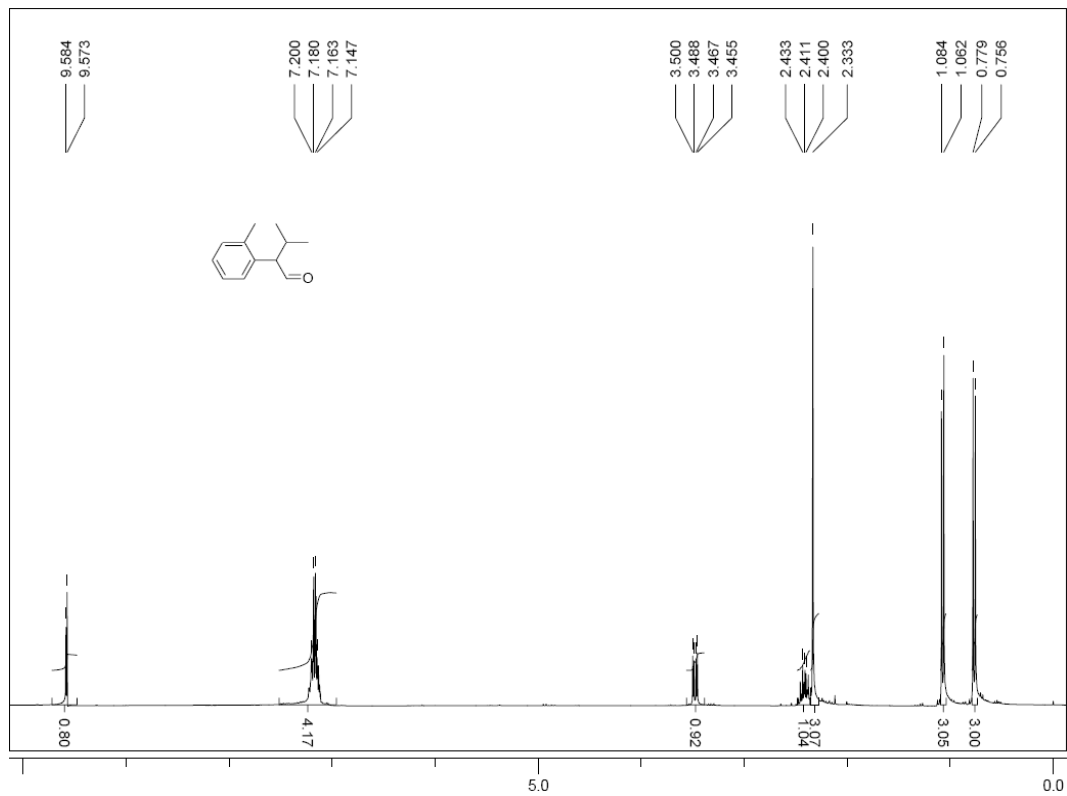
at β -position. ^1H NMR (400 MHz, CDCl_3): δ 0.72 (d, $J = 8.8$ Hz, 3H), 0.99 (d, $J = 8.8$ Hz, 3H), 1.16 (s, 0.87H), 1.94 (m, 1H), 2.51 (m, 0.96H), 3.82 (m, 1H), 3.91 (m, 0.42H), 7.18–7.35 (m, 5H).

Reference:

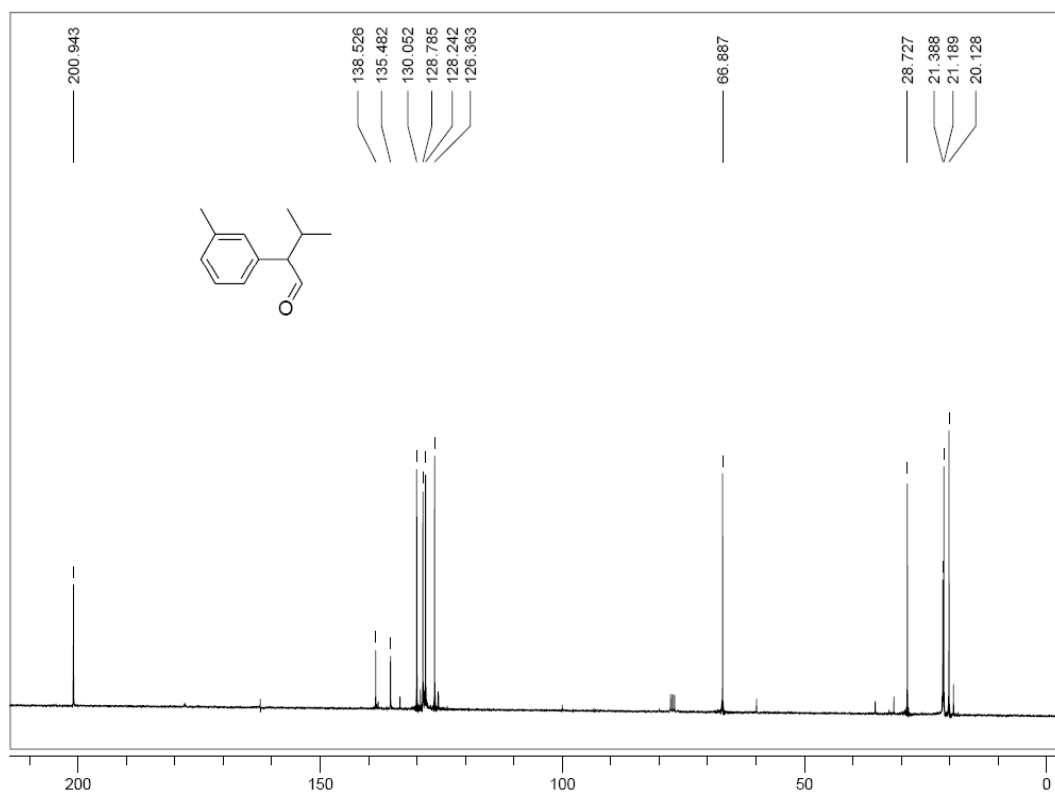
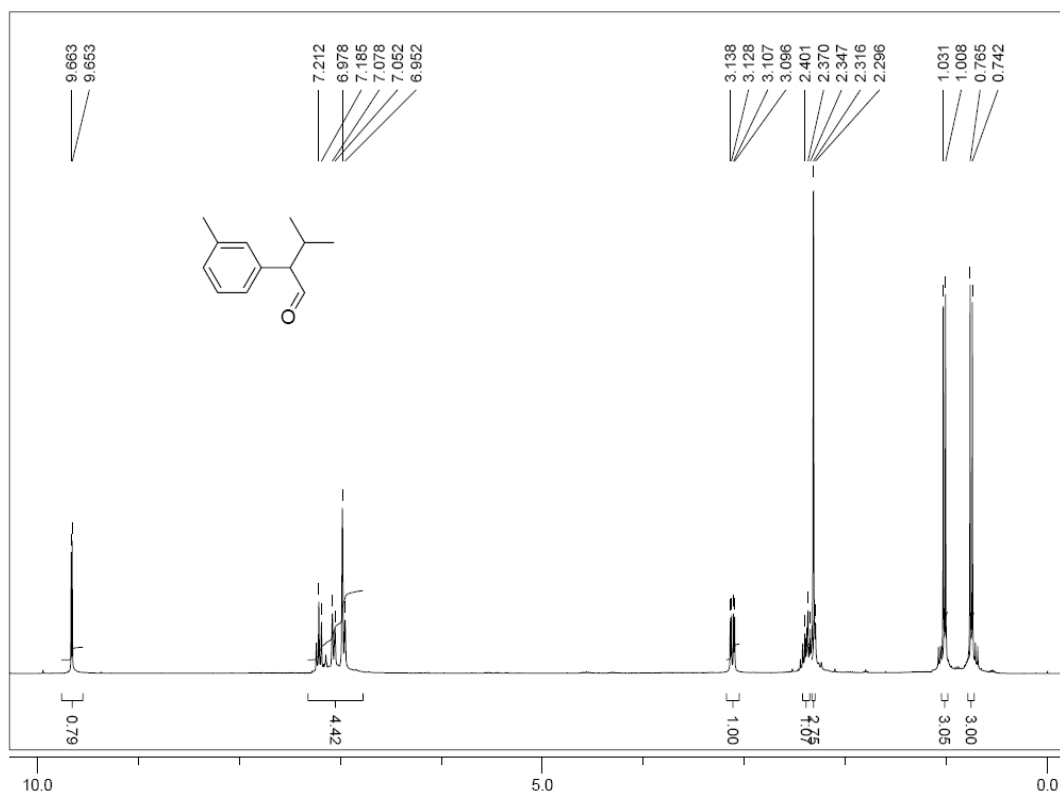
- [1] Wey, S. J.; O'Connor, K. J.; Burrows, C. J. *Tetrahedron Lett.* **1993**, 34, 1905.
- [2] Yamazaki, J.; Watanabe, T. Tanaka, K. *Tetrahedron: Asymmetry* **2001**, 12, 669.
- [3] Xie, J.-H.; Wang, L.-X.; Fu, Y.; Zhu, S.-F.; Fan, B.-M.; Duan, H.-F.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2003**, 125, 4404.
- [4] Uchiyama, M.; Kameda, M.; Mishima, O.; Yokoyama, N.; Koike, M.; Kondo, Y.; Sakamoto, T. *J. Am. Chem. Soc.* **1998**, 120, 493.
- [5] Stratakis, M.; Kalaitzakis, D.; Stavroulakis, D.; Kosmas, G.; Tsangarakis, C. *Org. Lett.* **2003**, 5, 3471.
- [6] Adam, W.; Bosio, S. G.; Turro, N. J.; Wolff, B. T. *J. Org. Chem.* **2004**, 69, 1704.
- [7] Vedso, P.; Chauvin, R.; Li, Z.; Brunet, B.; Vassella, A. *Helv. Chim. Acta.* **1994**, 77, 1631.
- [8] Brenna, E.; Negri, C. D.; Fuganti, C.; Gatti, F. G.; Serra, S. *Tetrahedron: Asymmetry* **2004**, 15, 335.
- [9] Tamaru, Y.; Yamada, K.; Inoue, Y.; Yamamoto, Y.; Yoshida, Z. *J. Org. Chem.* **1983**, 48, 1286.
- [10] Piccolo, O.; Menicagli, R.; Lardicci, L. *Tetrahedron*, **1979**, 35, 1751.
- [11] Vera, K.; Milan, M. *Liebigs Ann. Chem.* **1980**, 11, 1637.
- [12] Beaulieu, C.; Spino, C. *Tetrahedron Lett.*, **1999**, 40, 1637.
- [13] Zhao, M.; Li, J.; Mano, E.; Song, Z.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem.*, **1999**, 64, 2564.

(G) NMR Spectra for New α -Arylaldehydes and Chiral Primary Alcohols

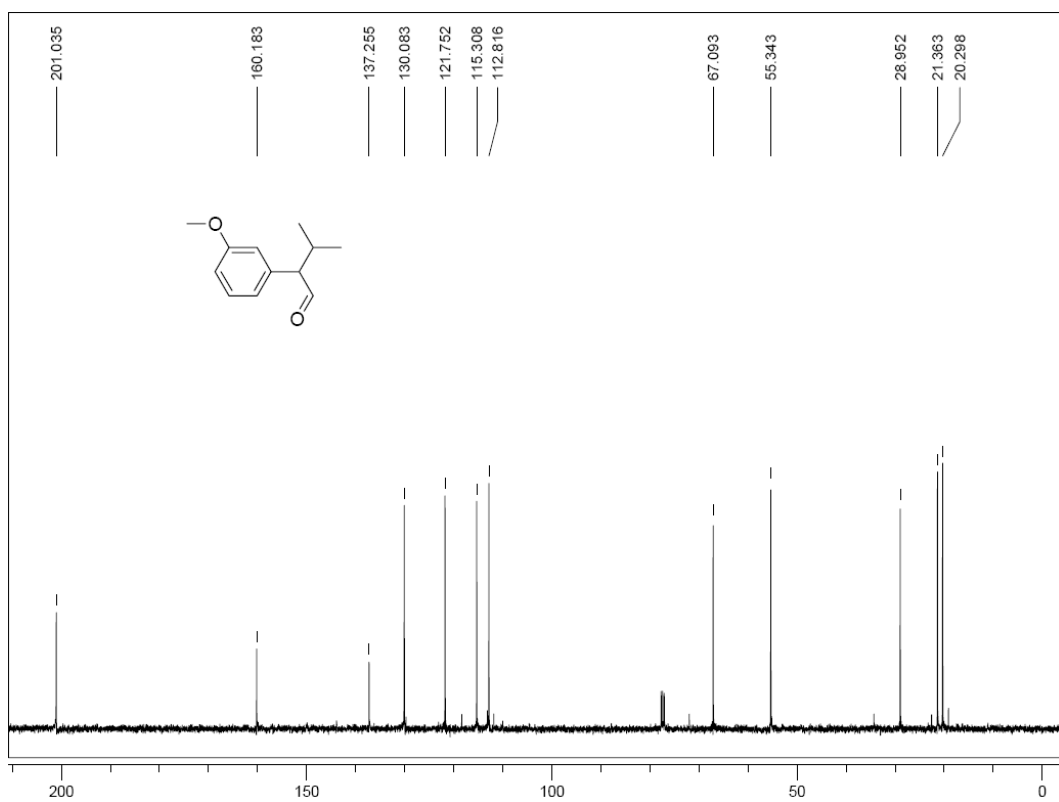
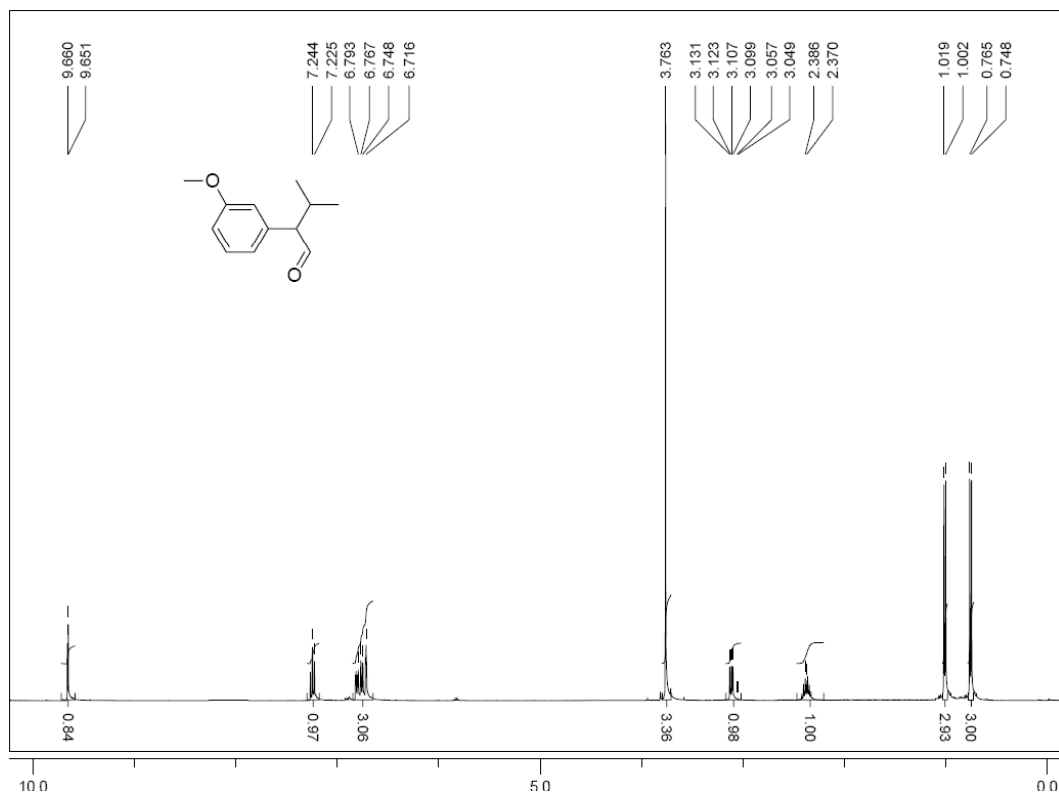
3-Methyl-2-(2-methylphenyl)butanal (1f)



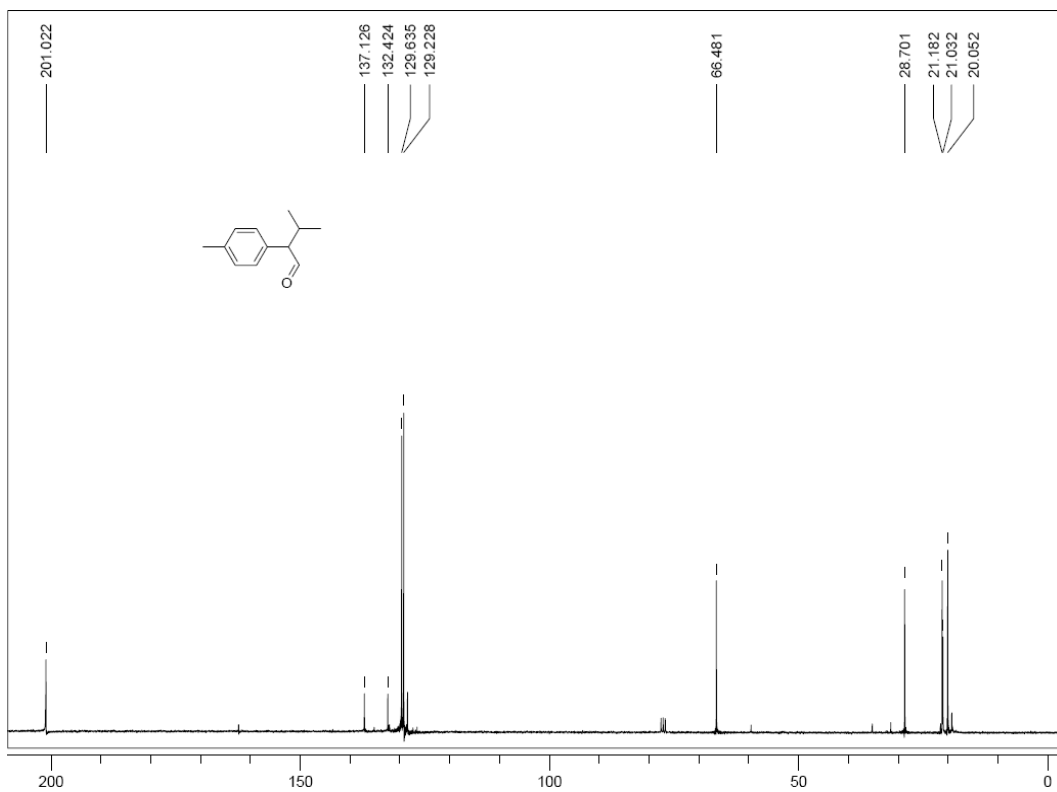
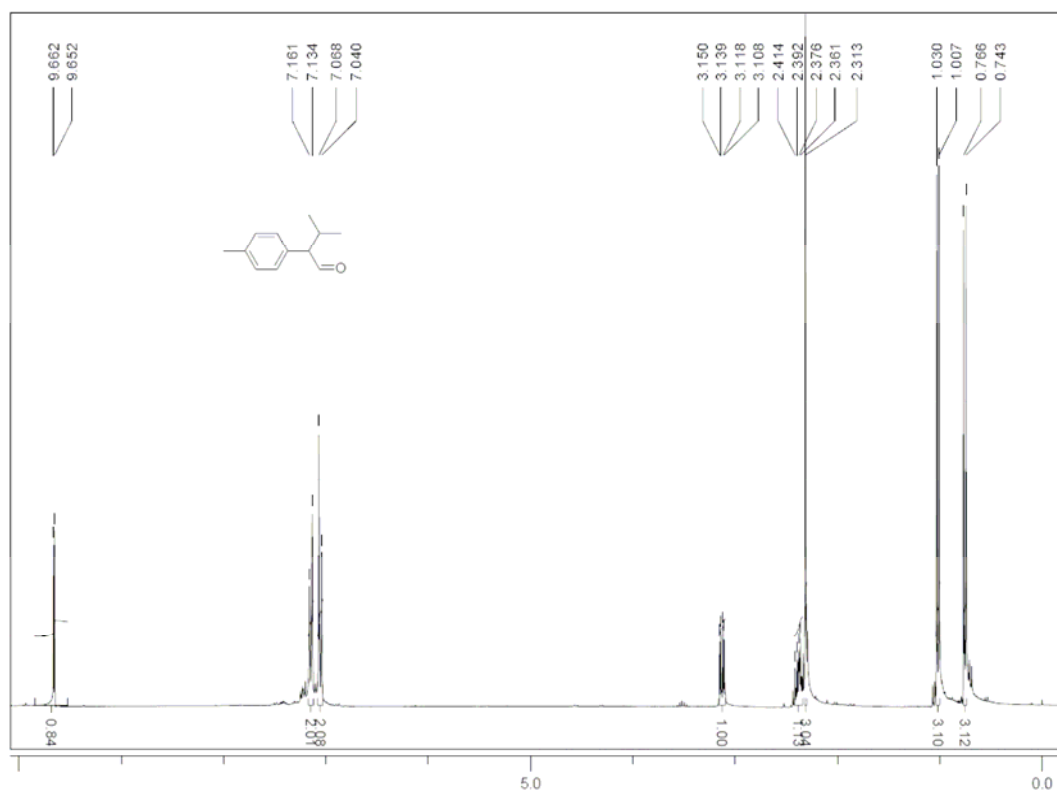
3-Methyl-2-(3-methylphenyl)butanal (1h)



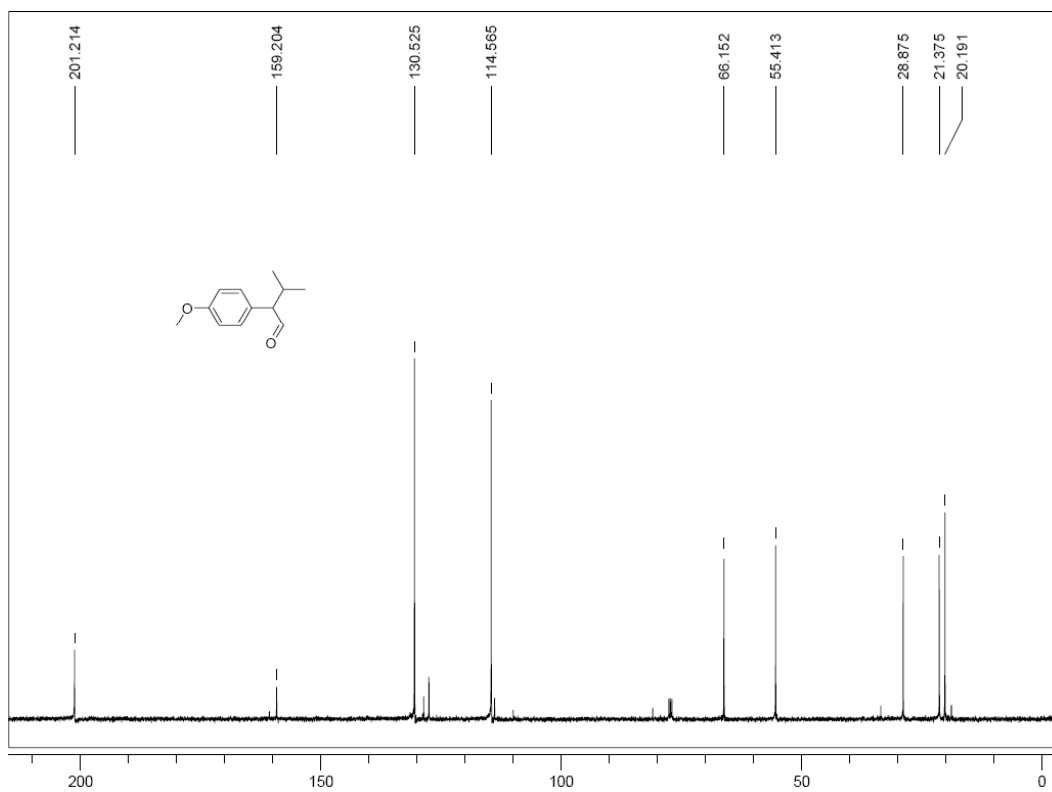
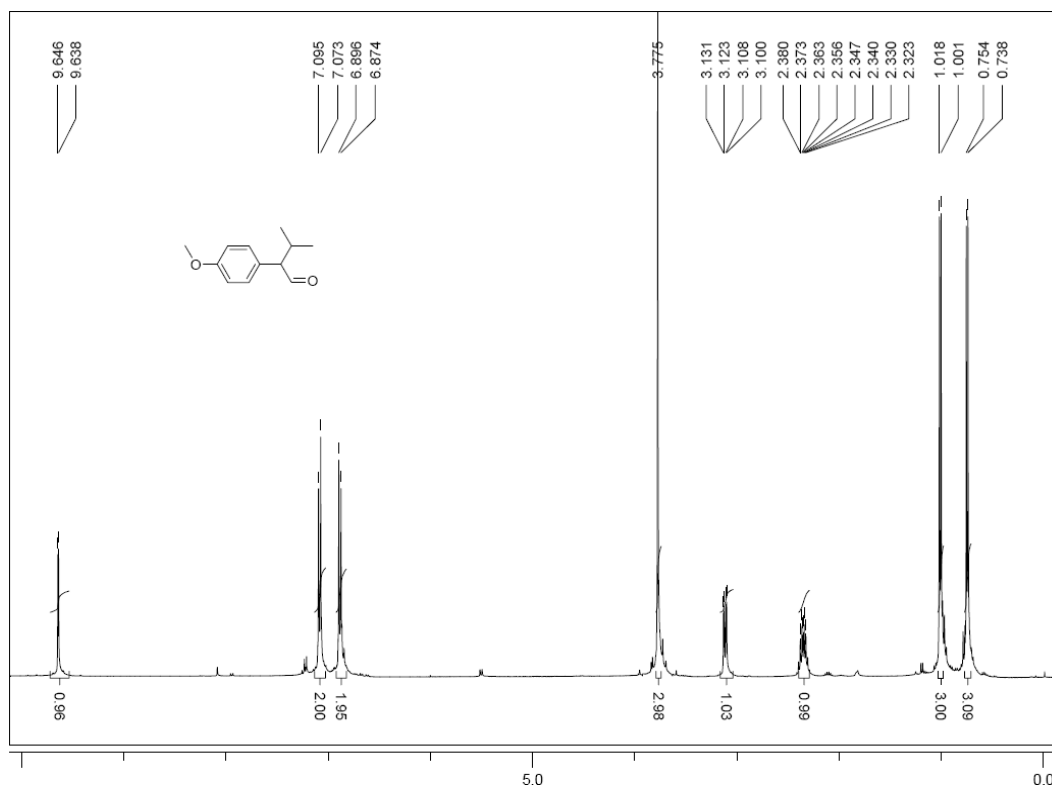
3-Methyl-2-(3-methoxyphenyl)butanal (1i)



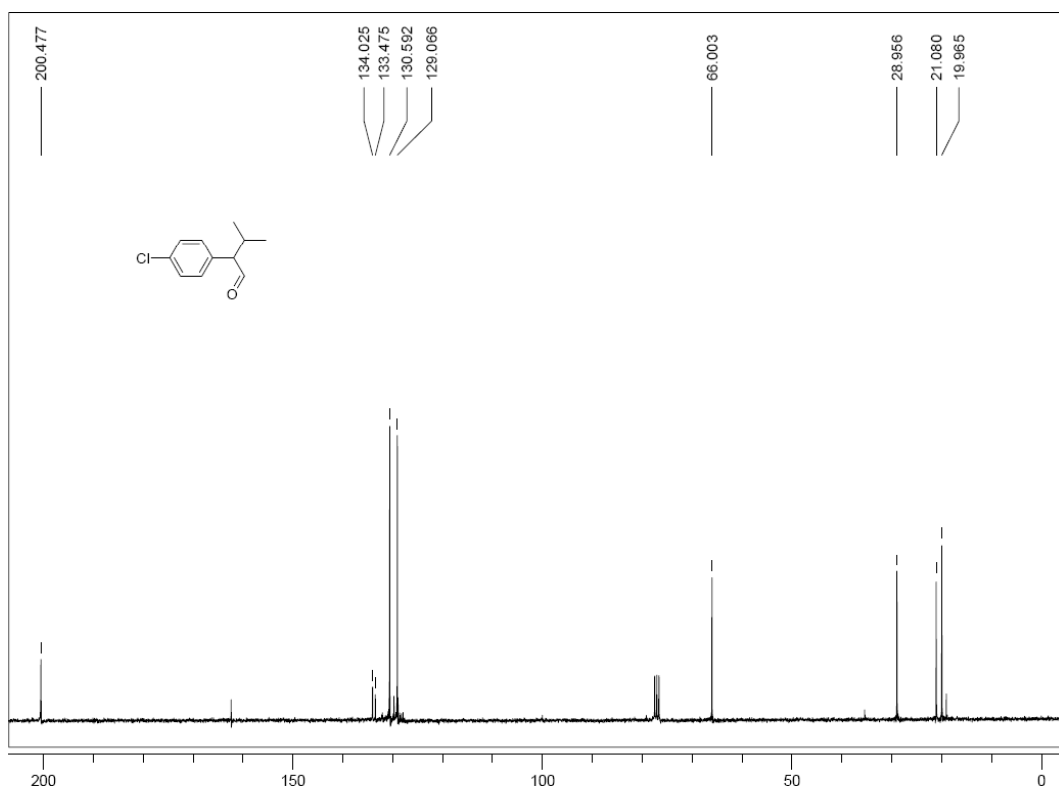
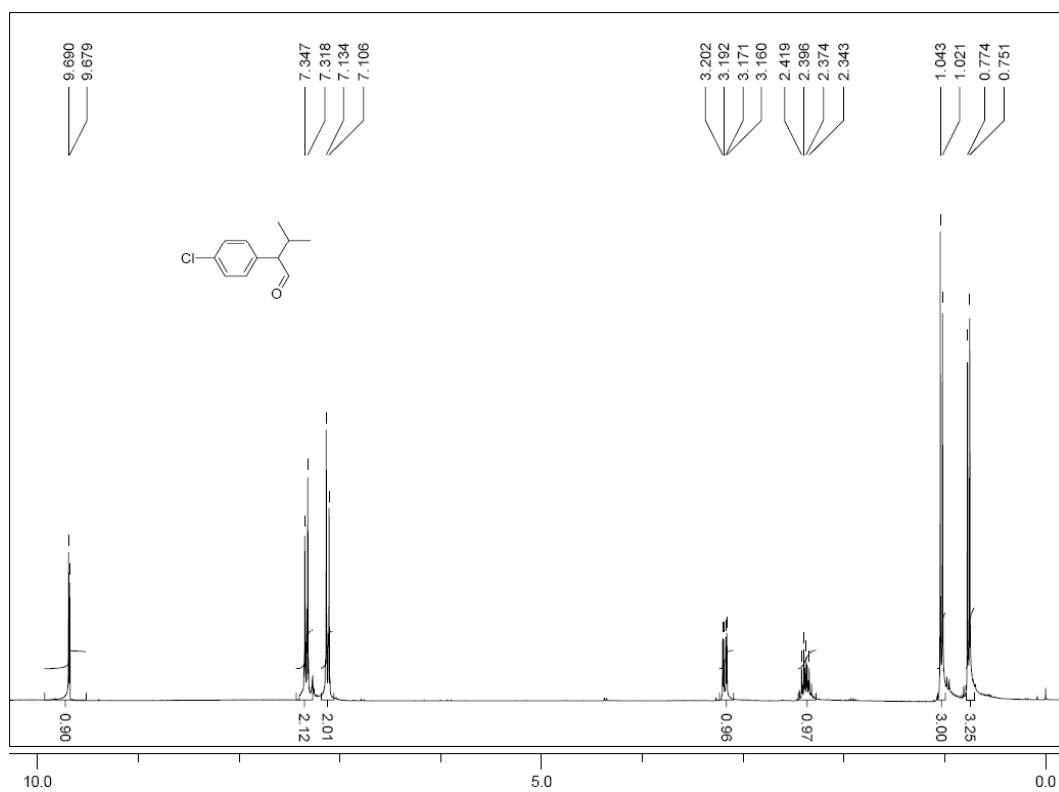
3-Methyl-2-(4-methylphenyl)butanal (1j)



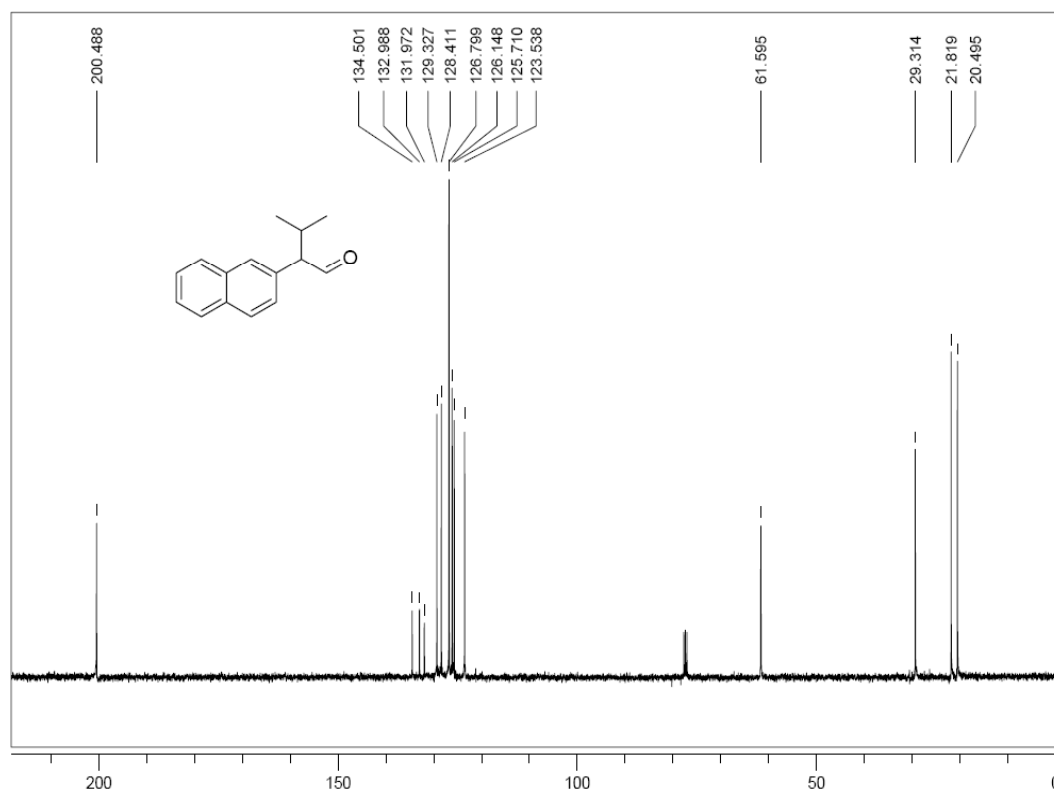
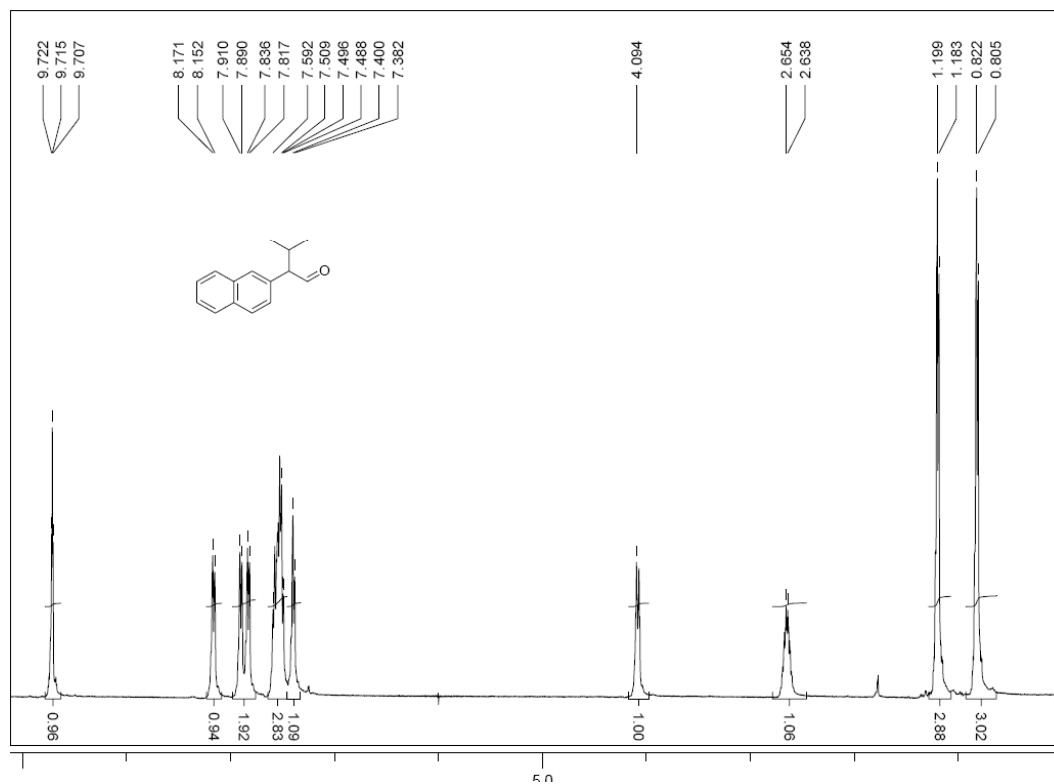
3-Methyl-2-(4-methoxyphenyl)butanal (1k)



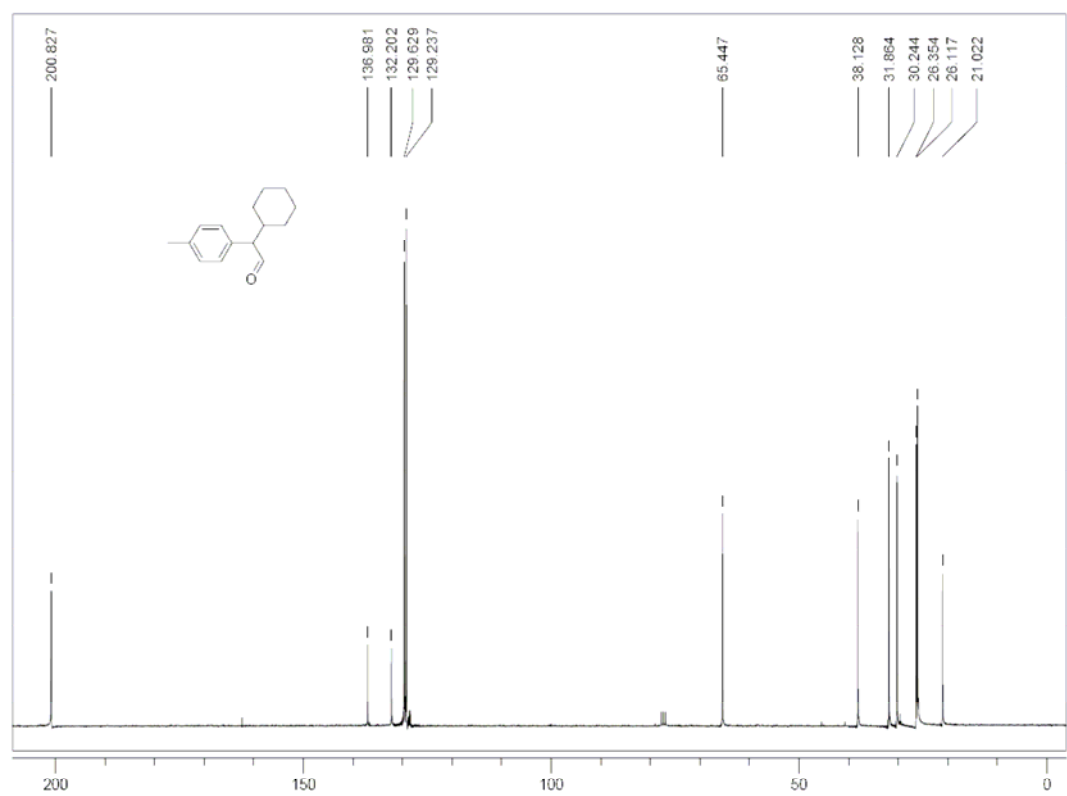
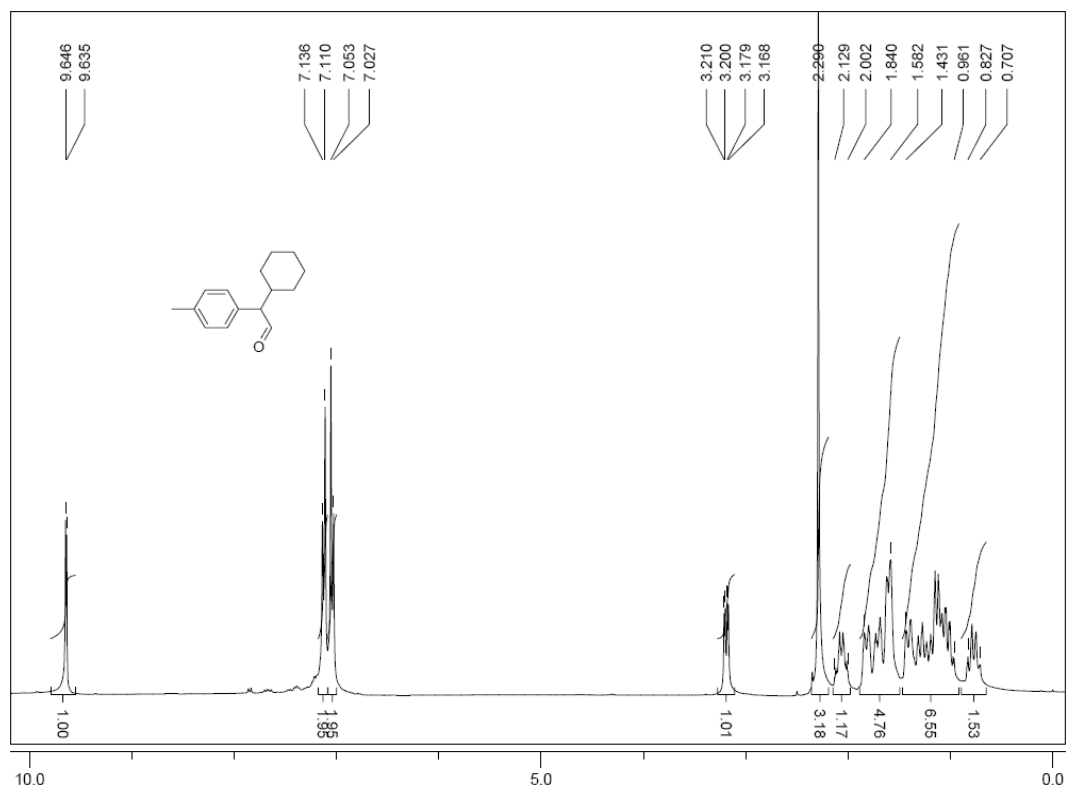
3-Methyl-2-(4-chlorophenyl)butanal (11)



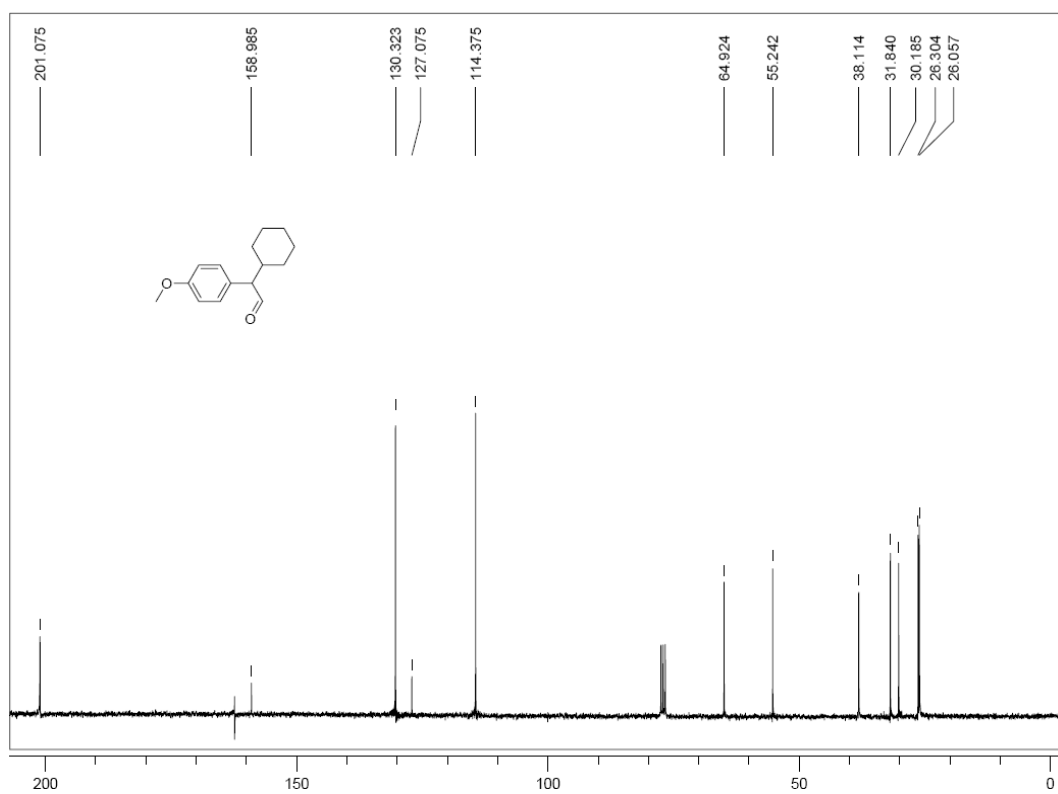
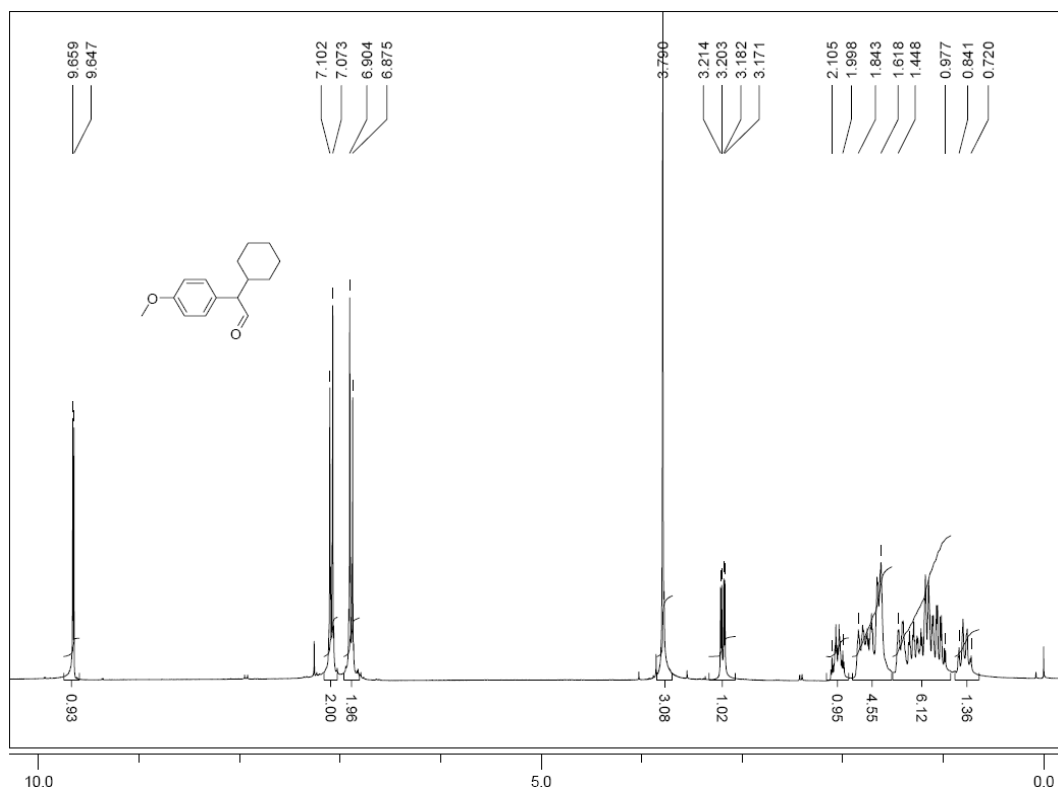
3-Methyl-2-(naphthalen-2-yl)butanal (1m)



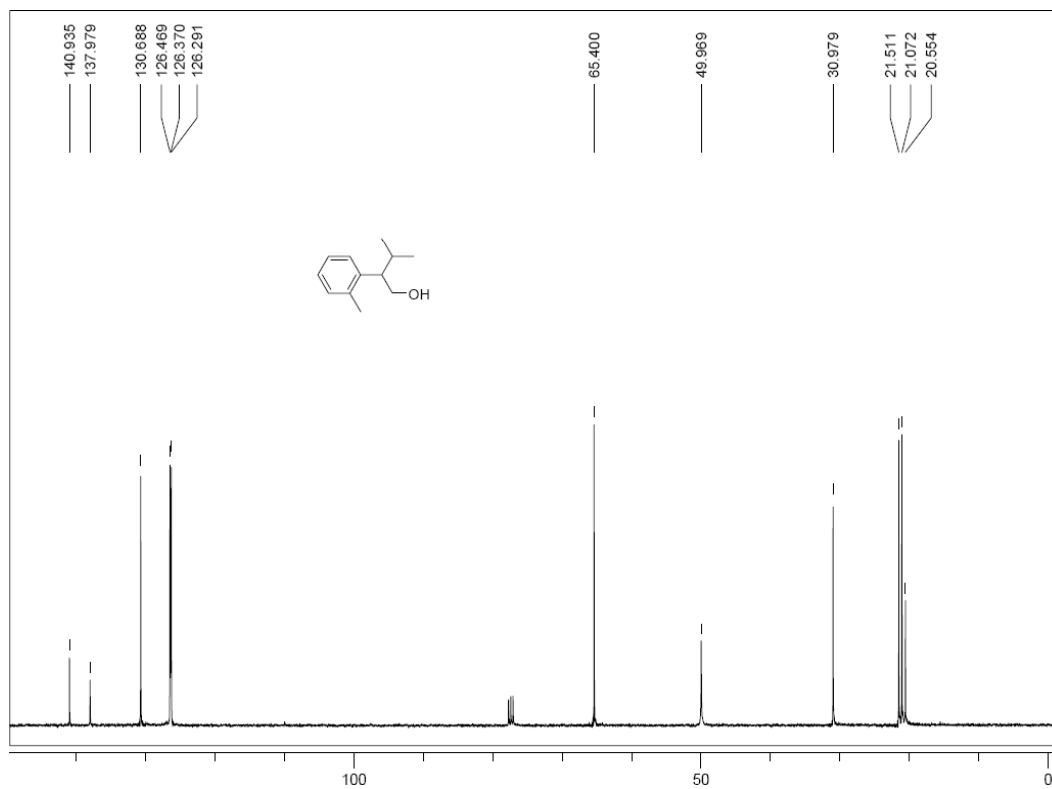
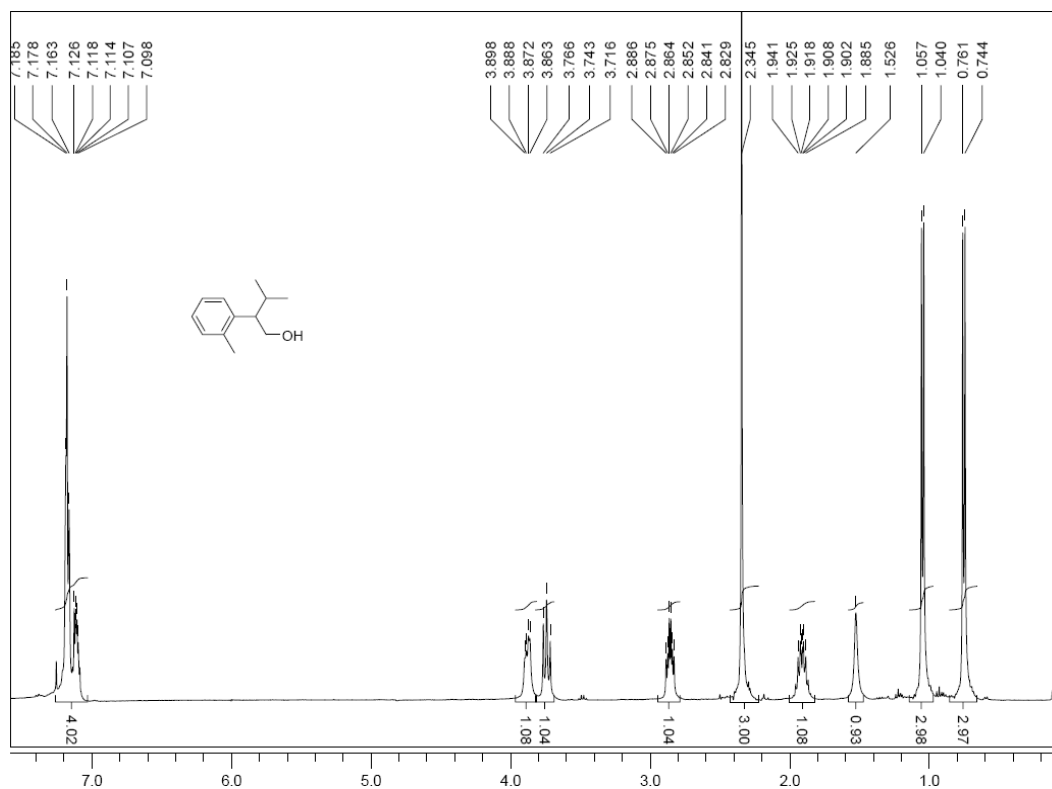
2-Cyclohexyl-2-(4-methylphenyl)acetaldehyde (1n)



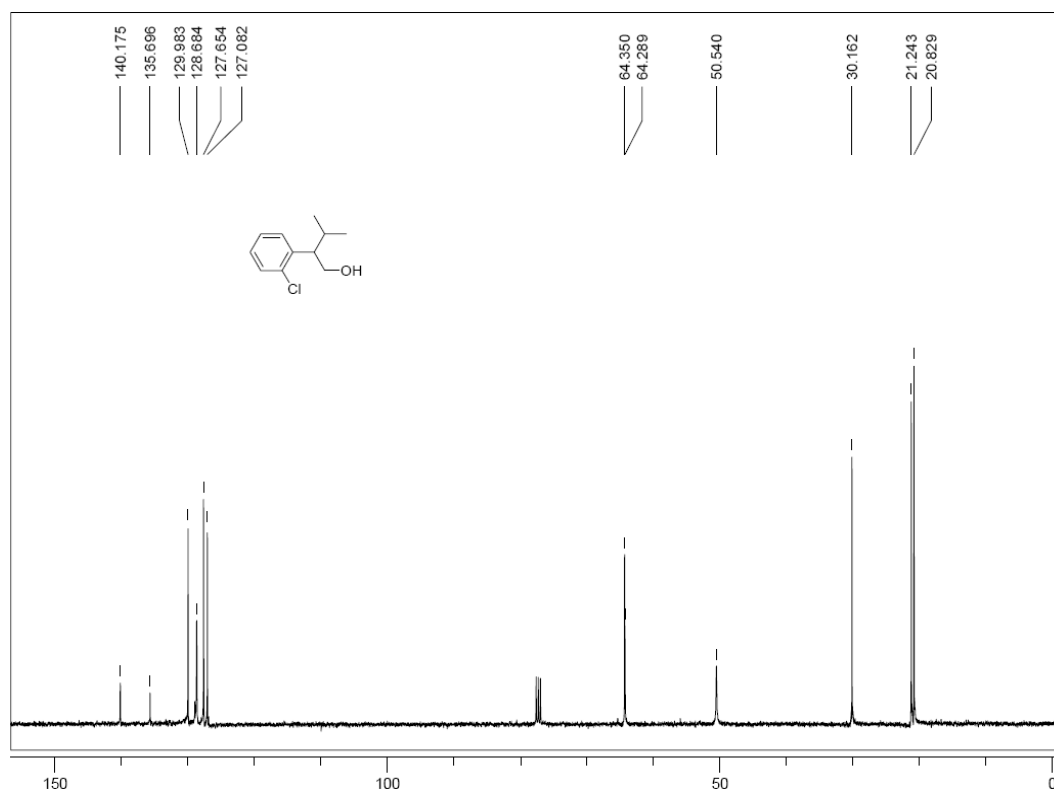
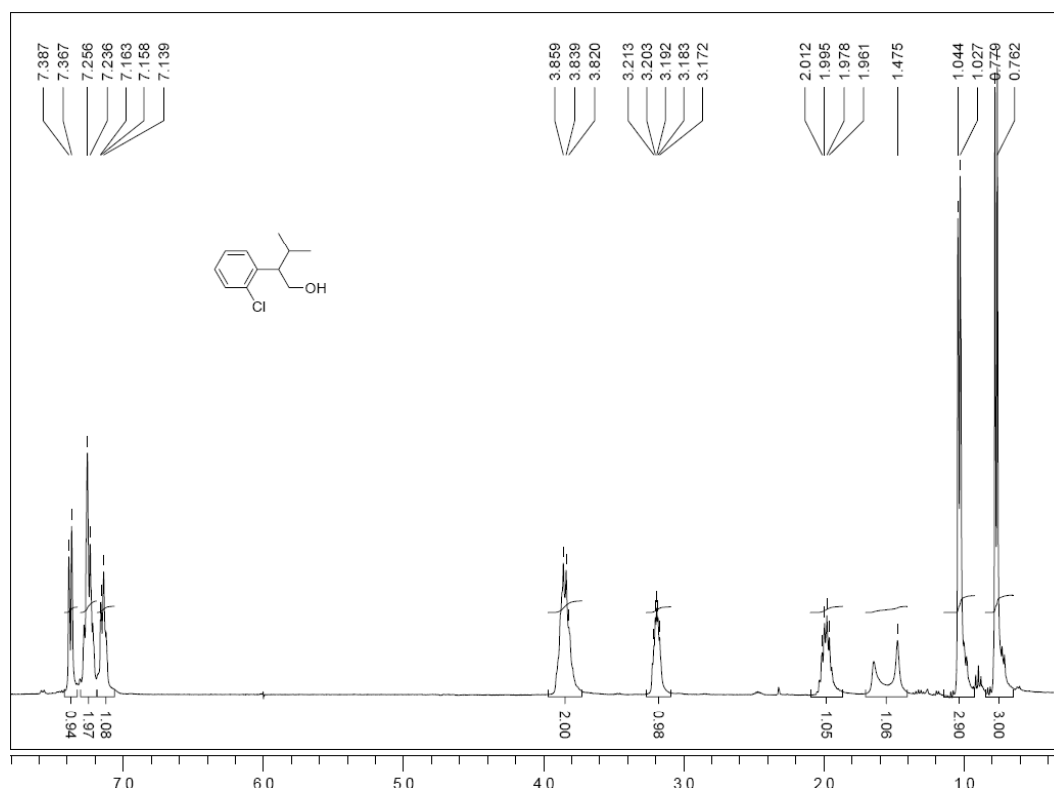
2-Cyclohexyl-2-(4-methoxyphenyl)acetaldehyde (1o)



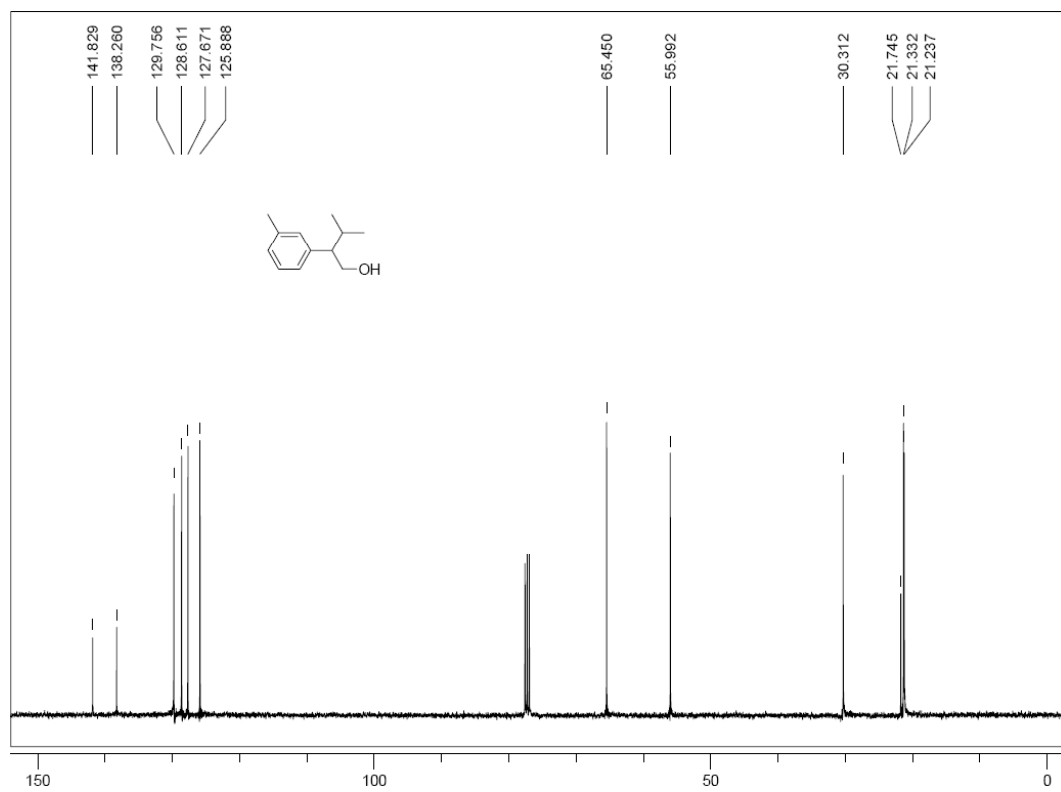
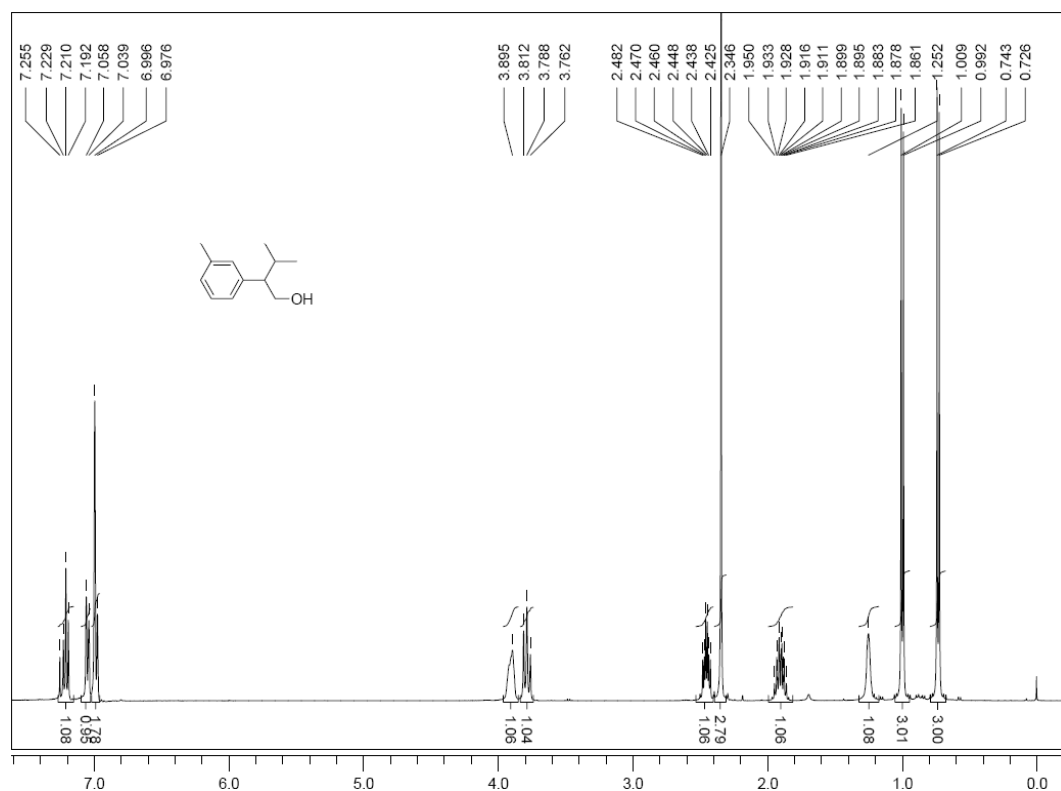
(S)-3-Methyl-2-(2-methylphenyl)butan-1-ol (2f)



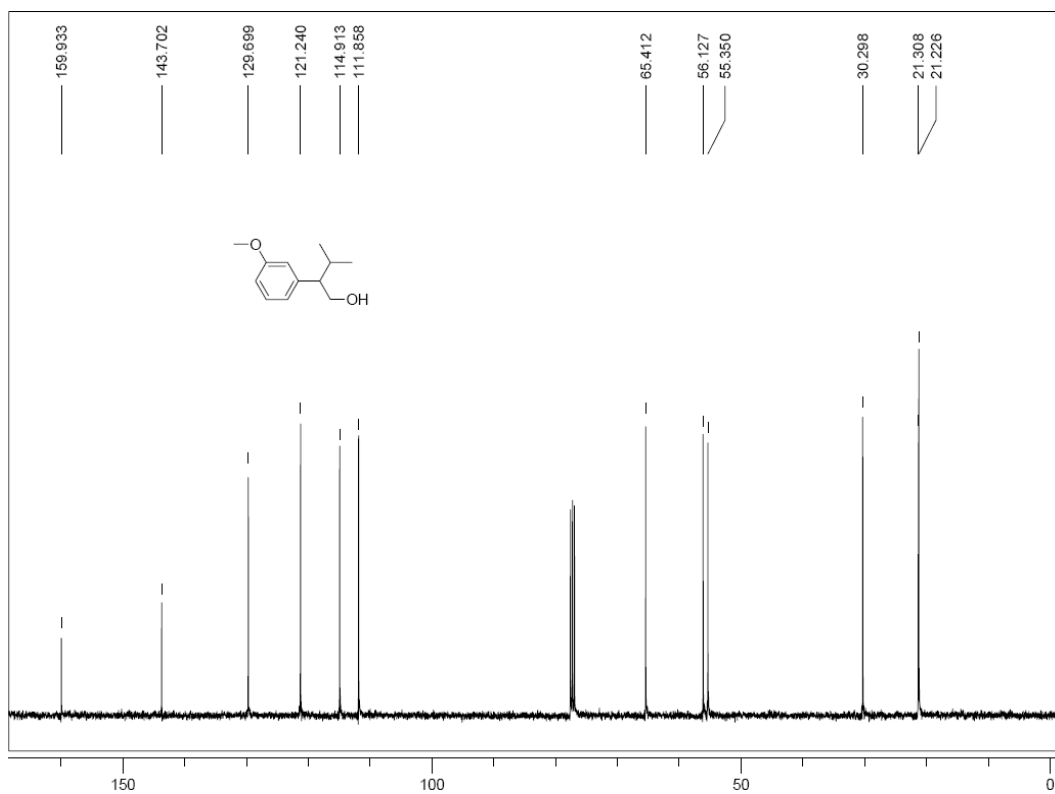
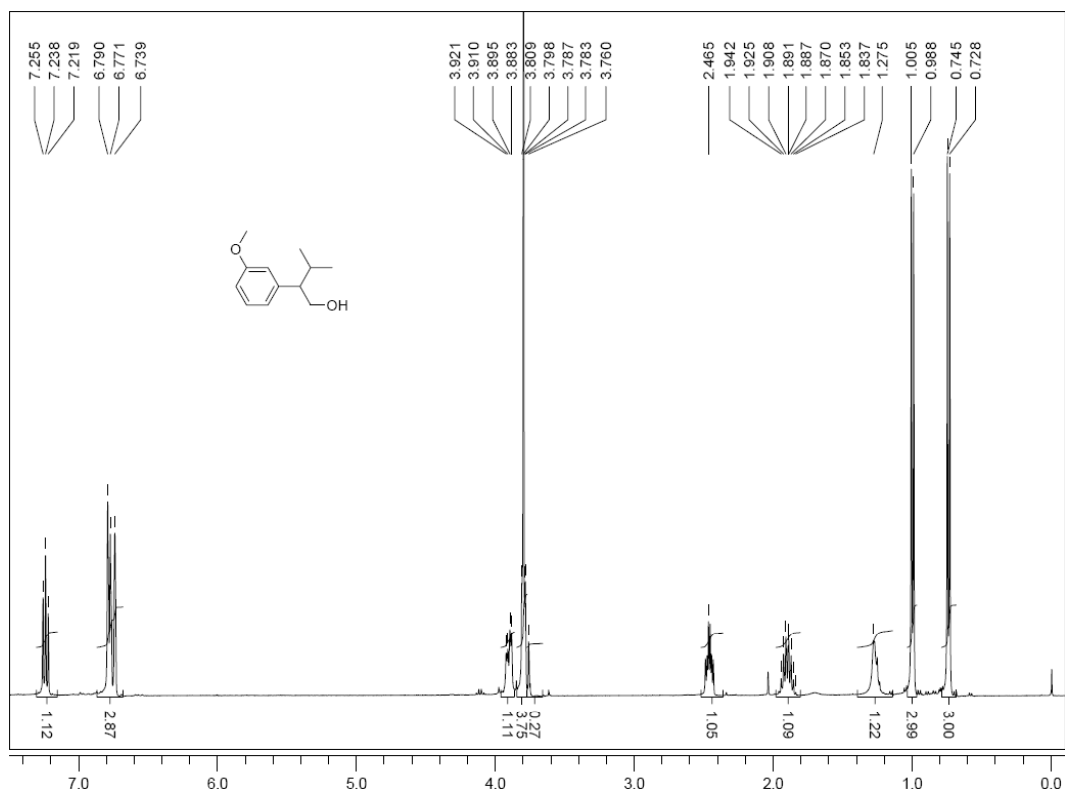
(S)-3-Methyl-2-(2-chlorophenyl)butan-1-ol (2g)



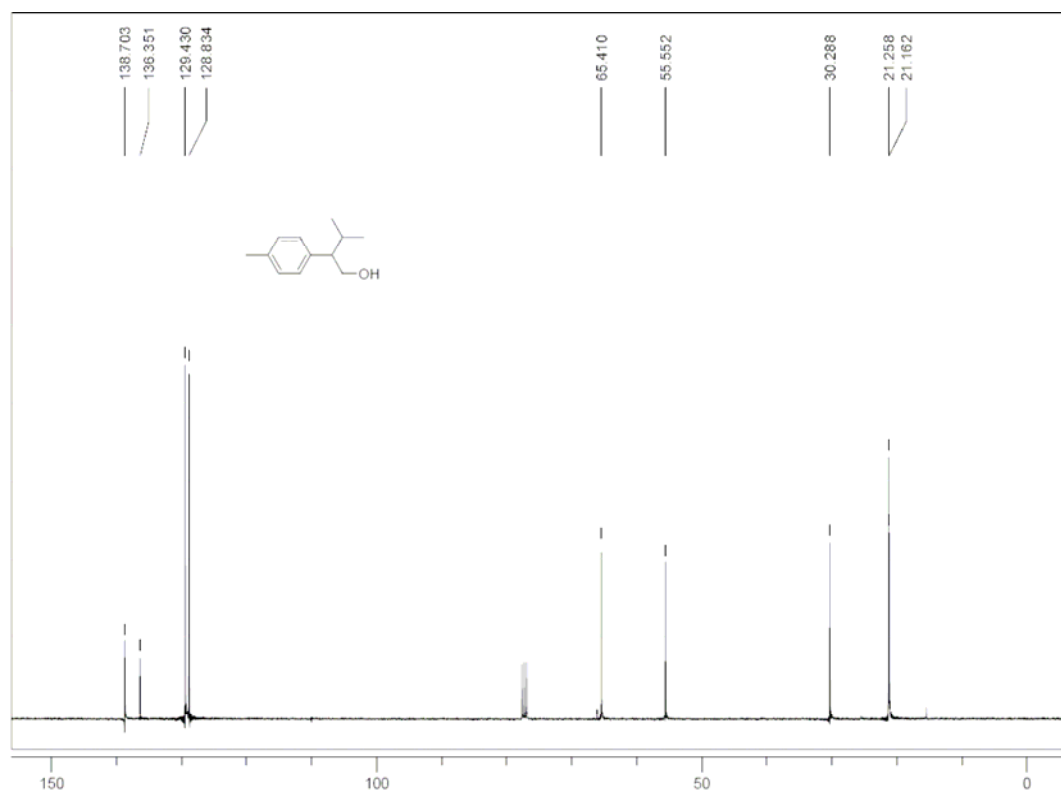
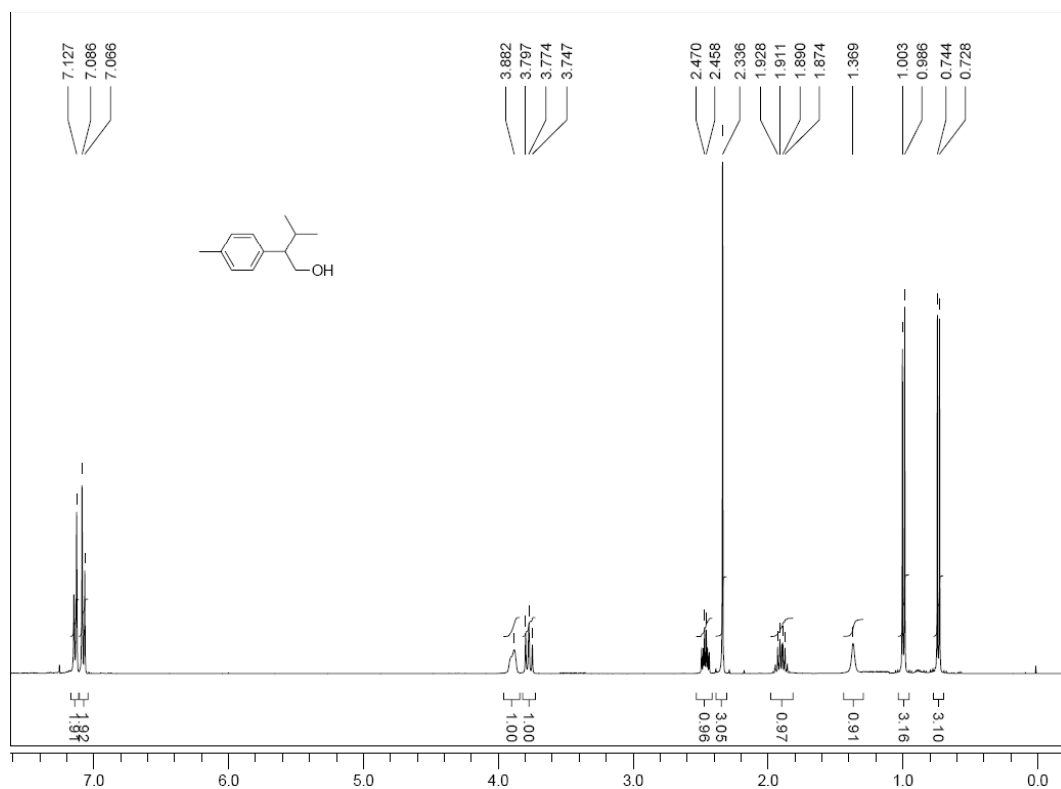
(S)-3-Methyl-2-(3-methylphenyl)butan-1-ol (2h)



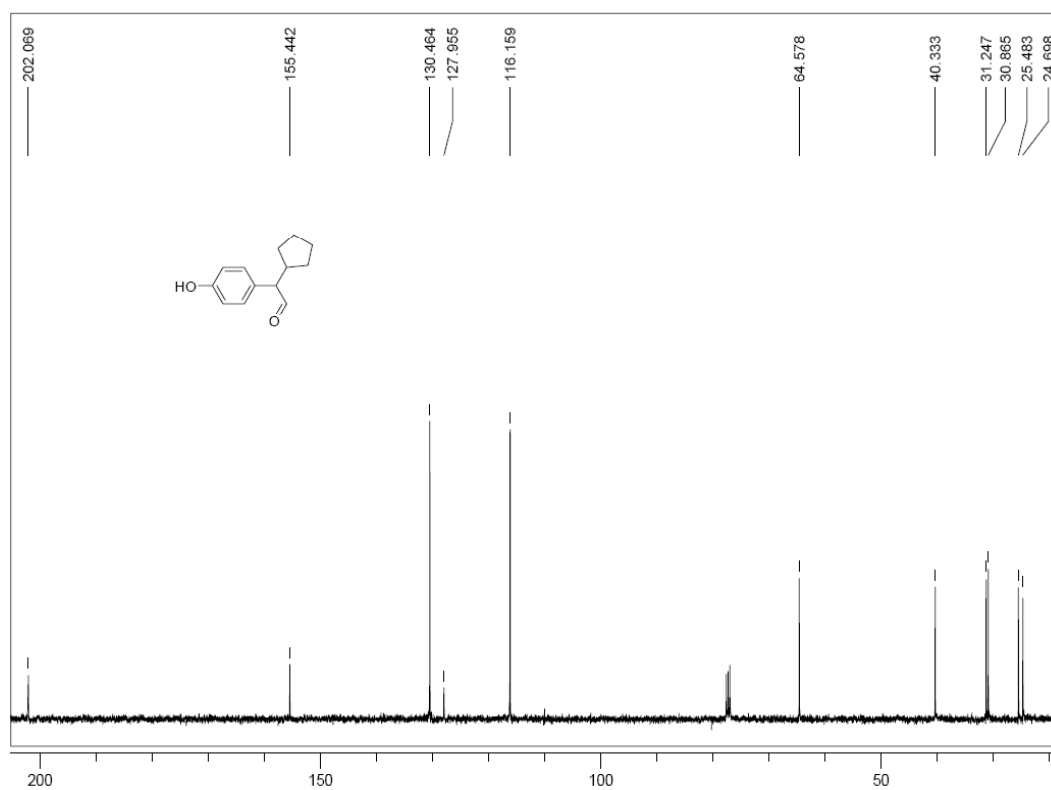
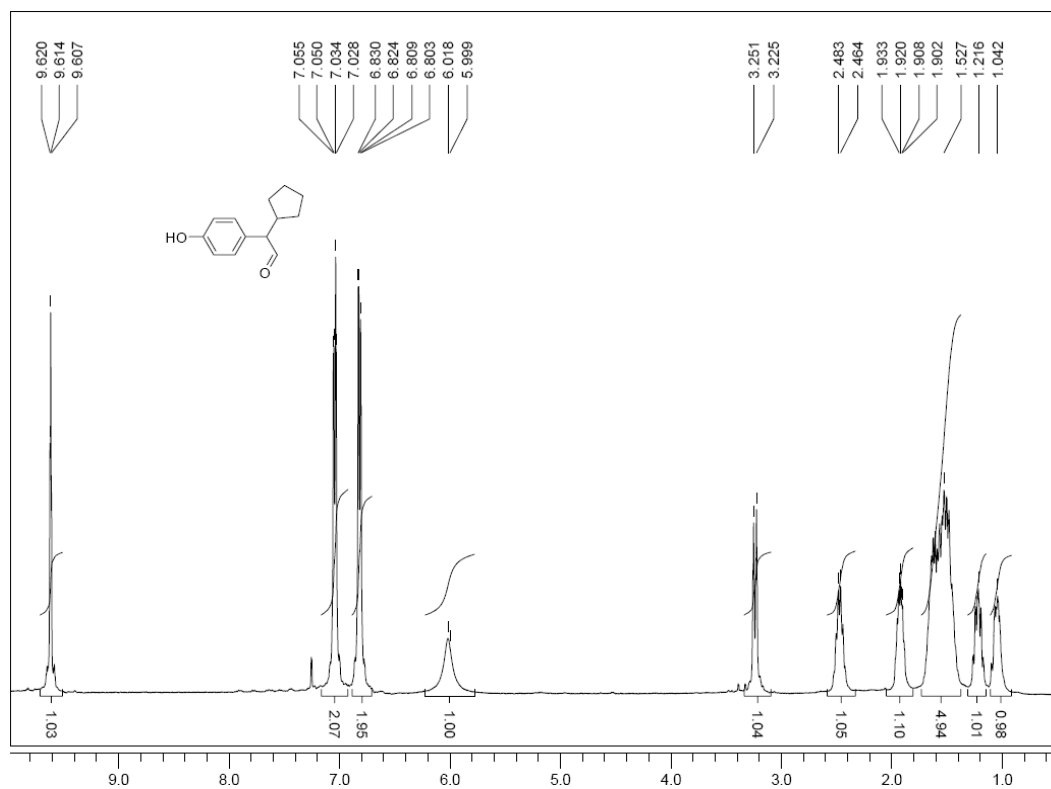
(S)-3-Methyl-2-(3-methoxyphenyl)butan-1-ol (2i)



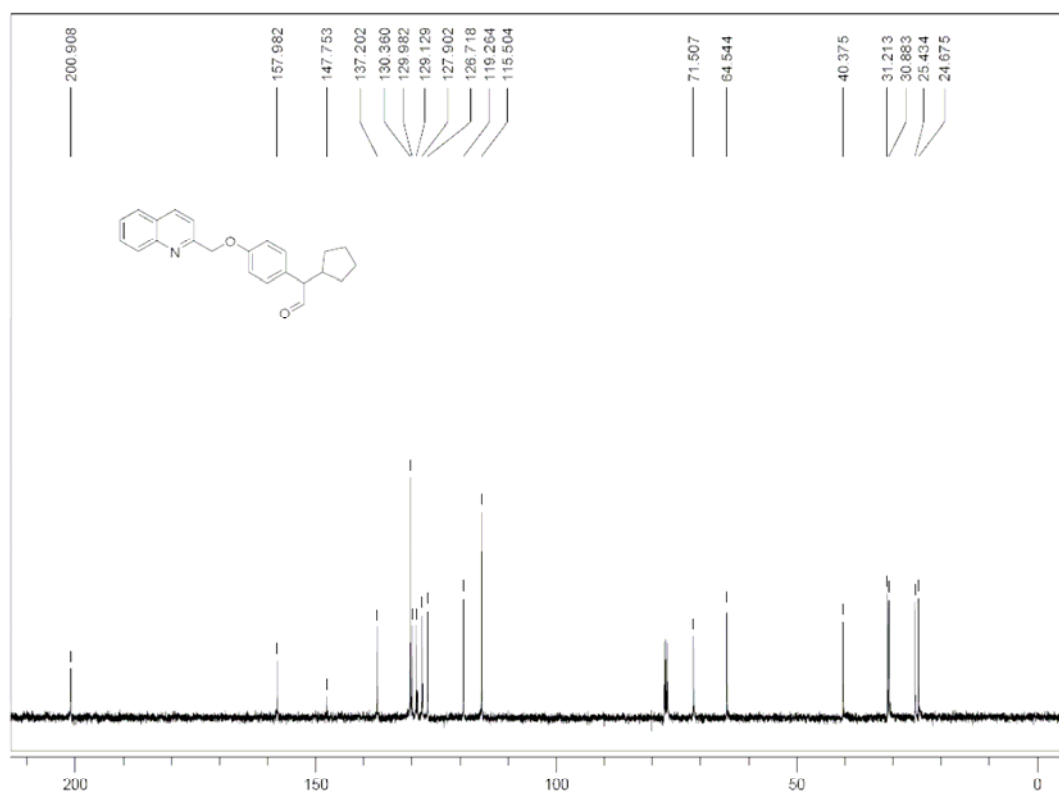
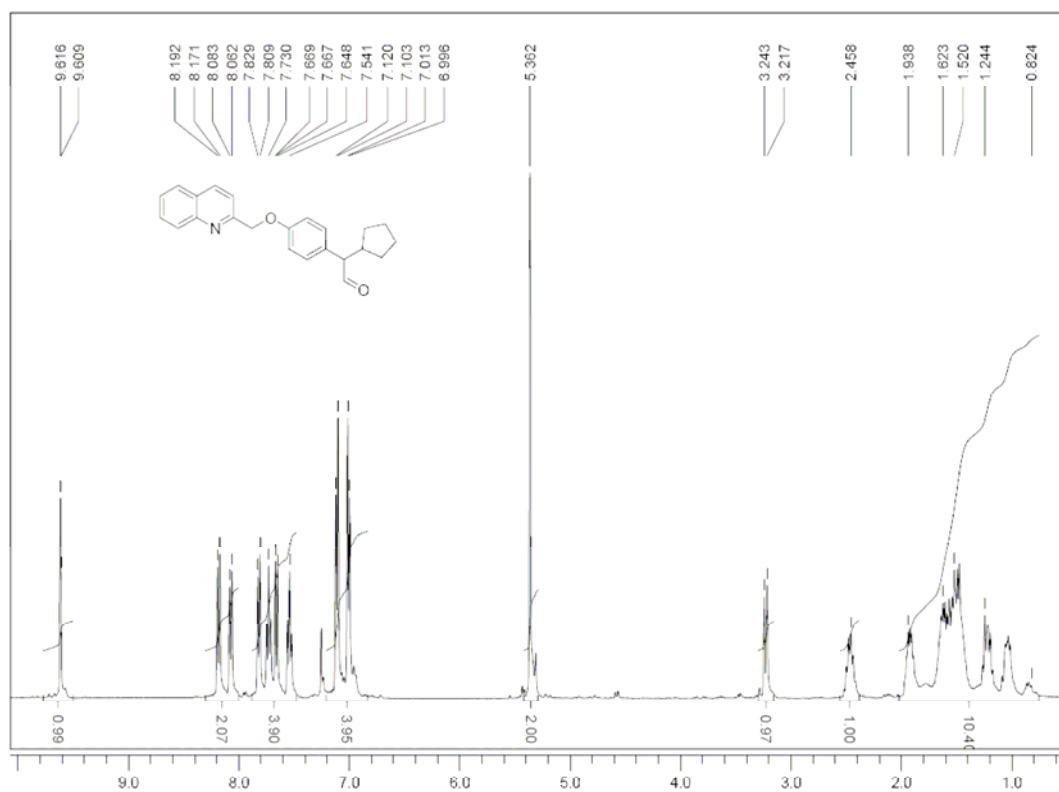
(S)-3-Methyl-2-(4-methylphenyl)butan-1-ol (2j)



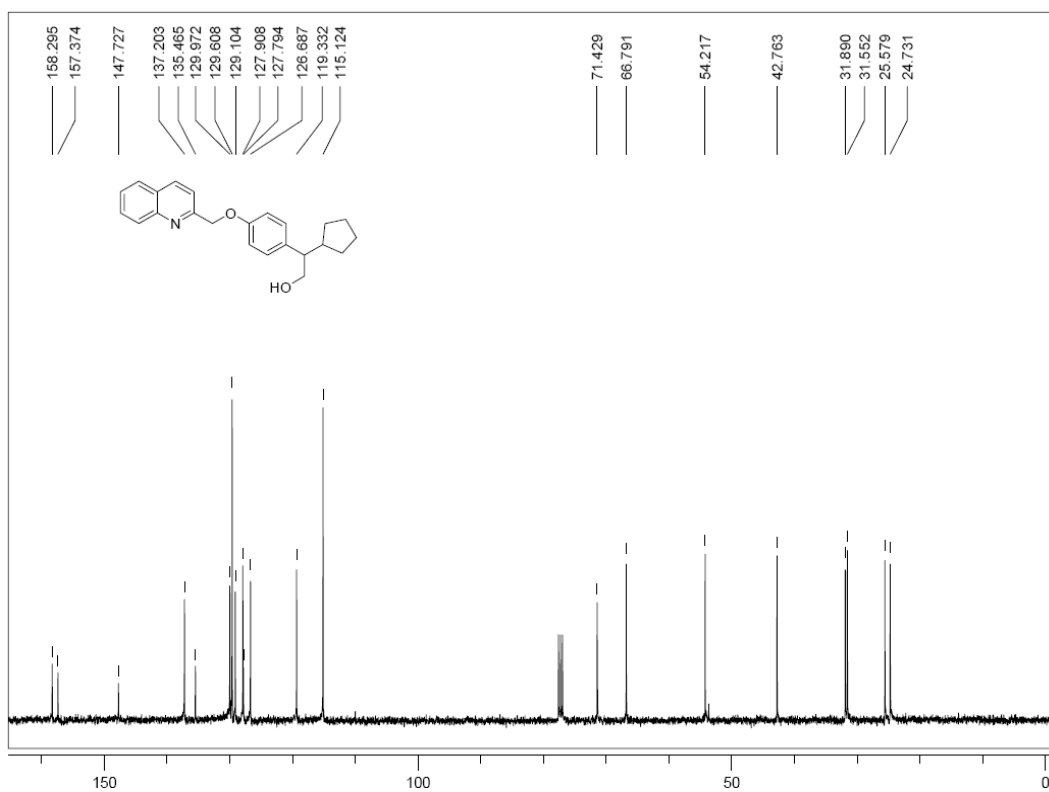
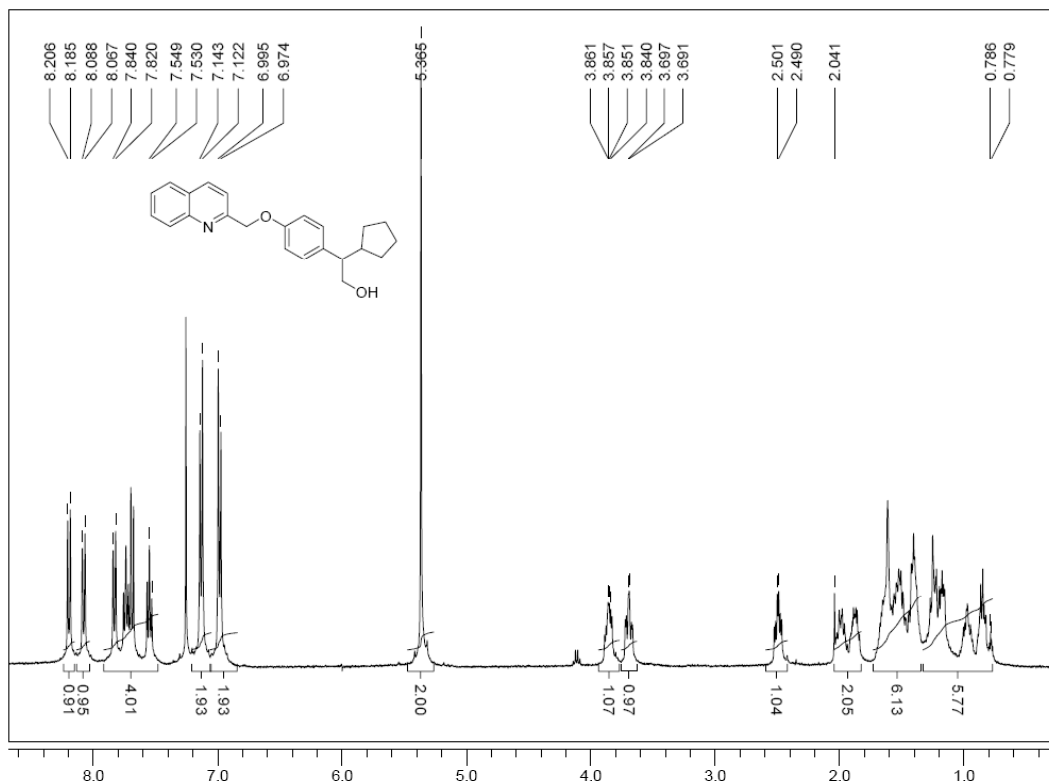
2-Cyclopentyl-2-(4-hydroxyphenyl)acetaldehyde



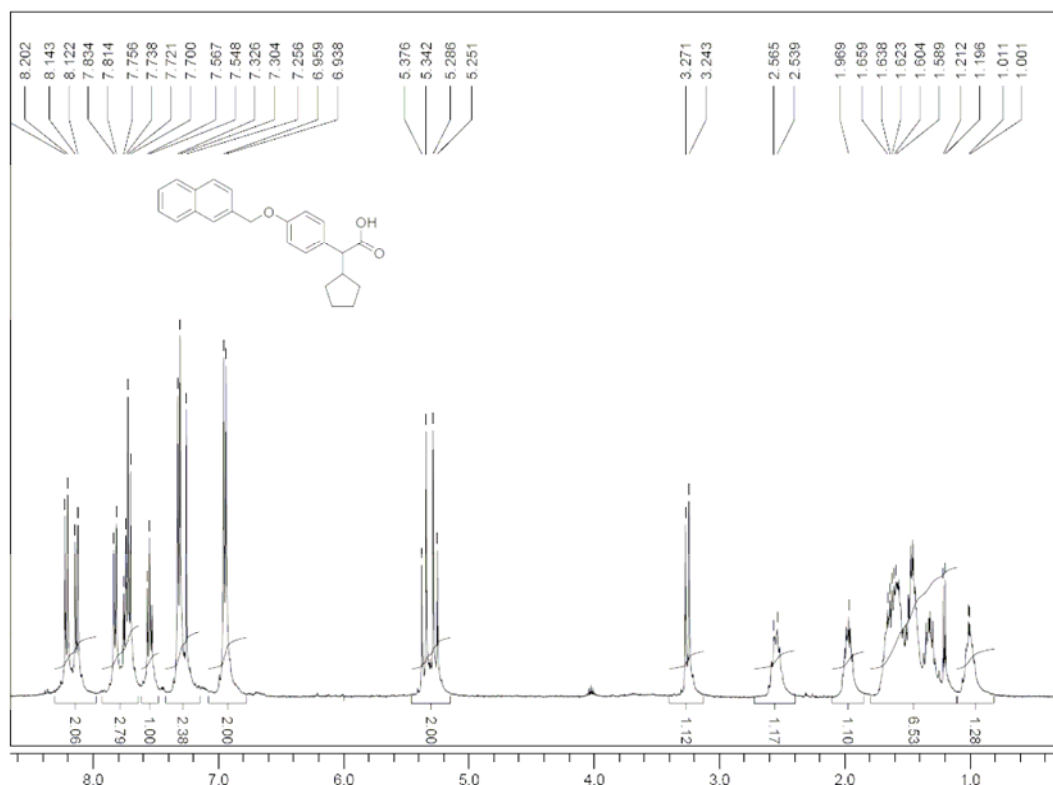
2-Cyclopentyl-2-(4-(quinolin-2-ylmethoxy)phenyl)acetaldehyde 5



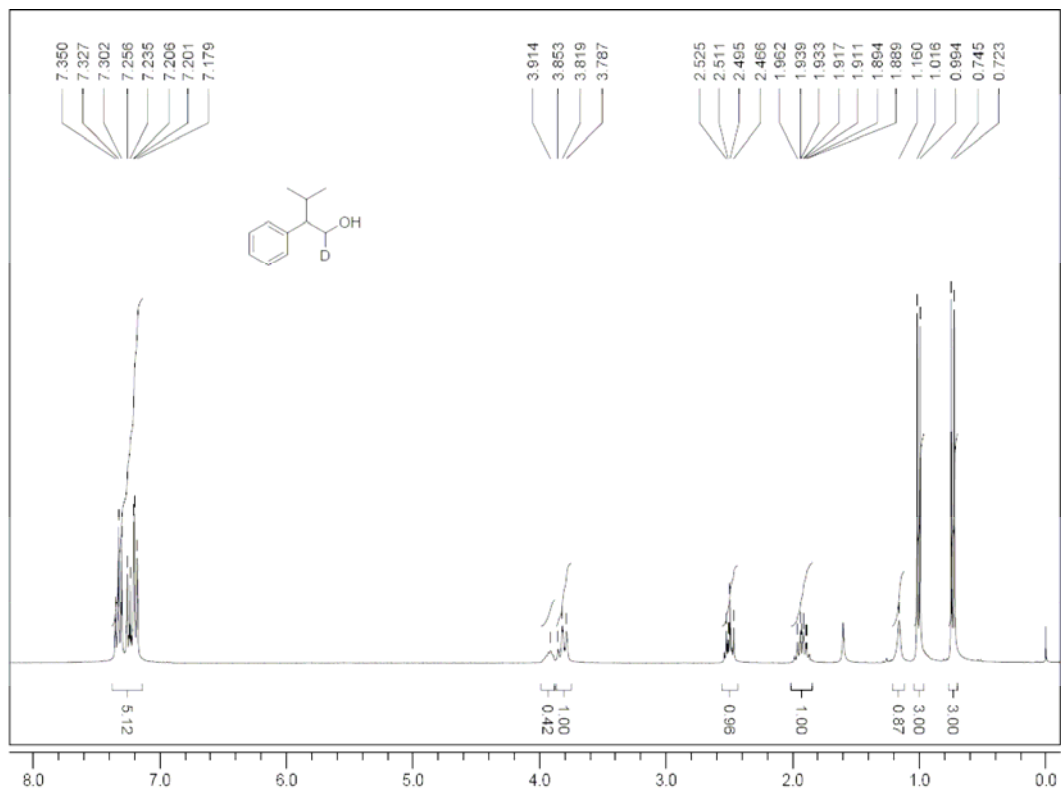
2-Cyclopentyl-2-(4-(quinolin-2-ylmethoxy)phenyl)ethanol **6**



BAY × 1005

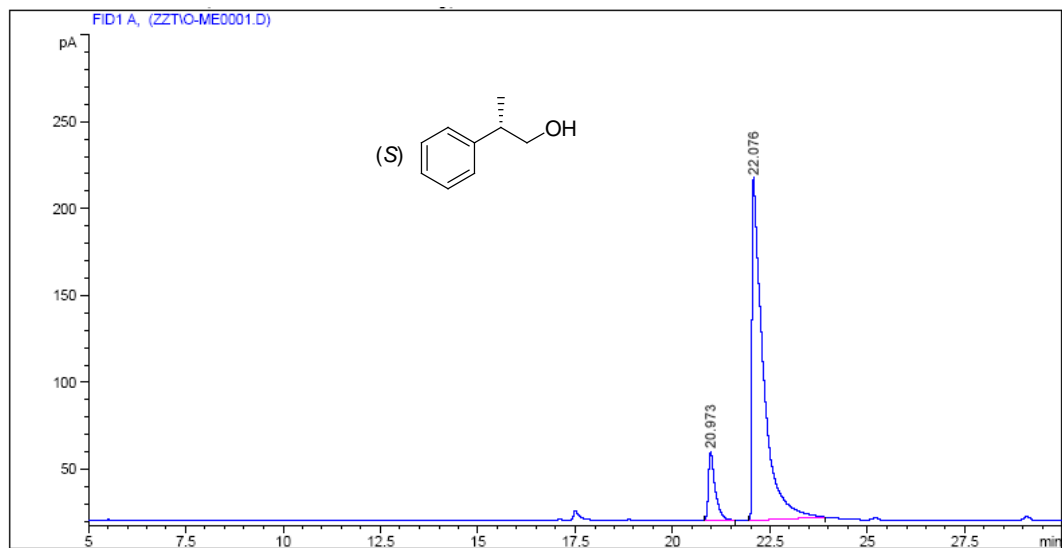
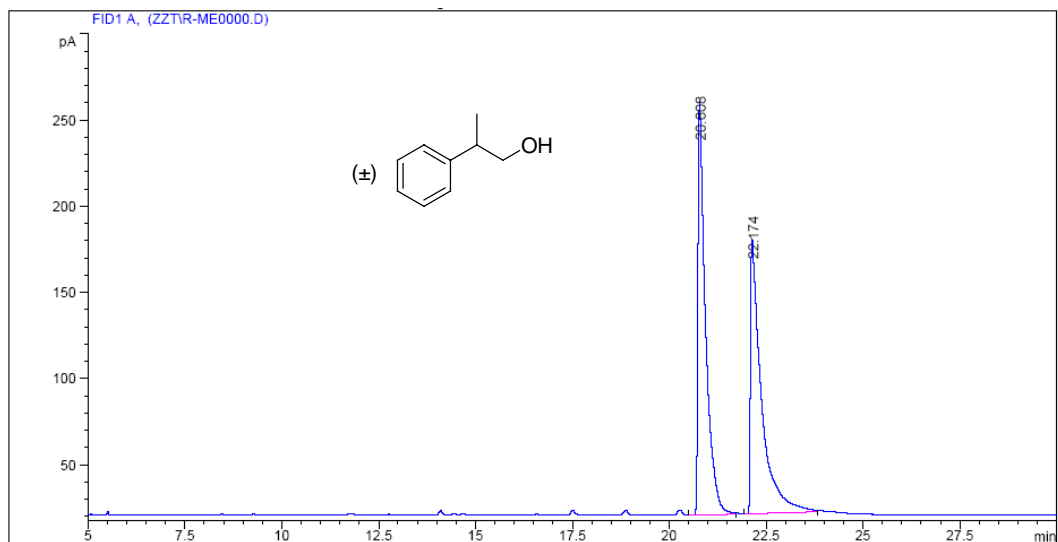


The ^1H NMR of the deuteration product



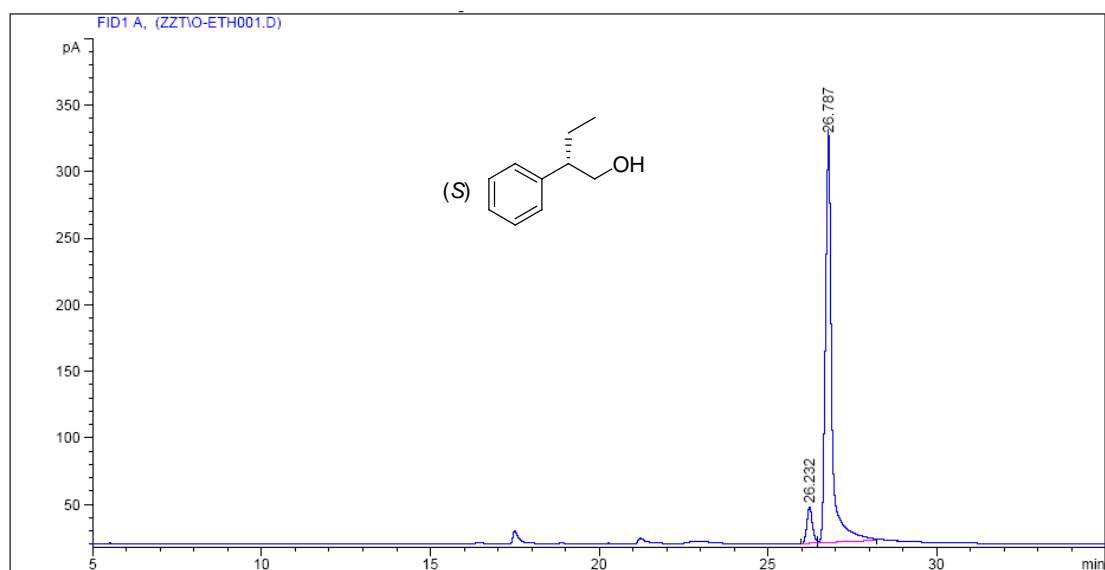
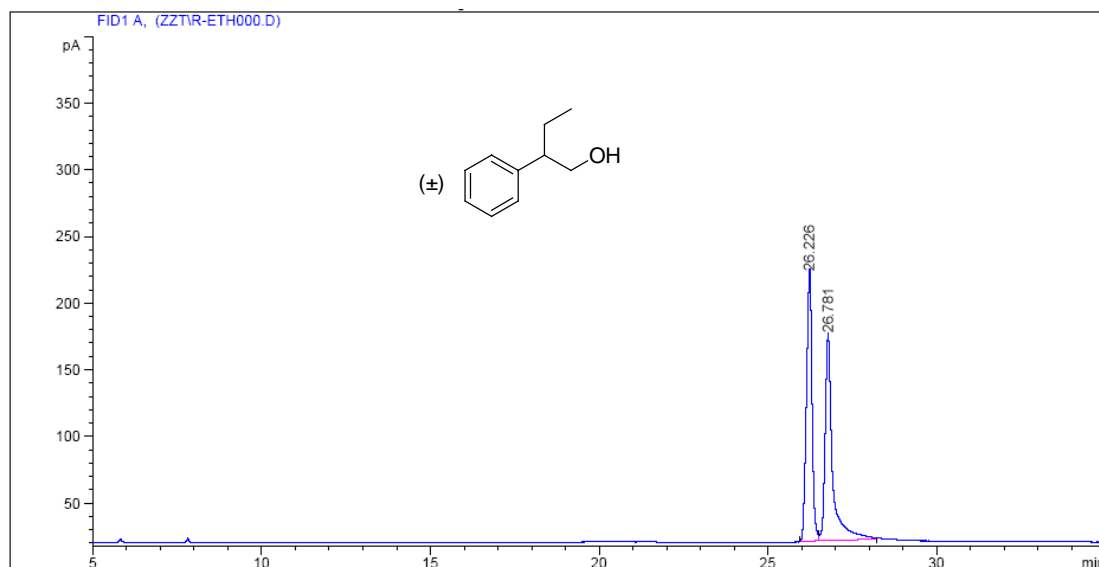
(H) GC or HPLC Chart for Hydrogenation Product and Other Compounds

(S)-2-Phenylpropan-1-ol (2a)



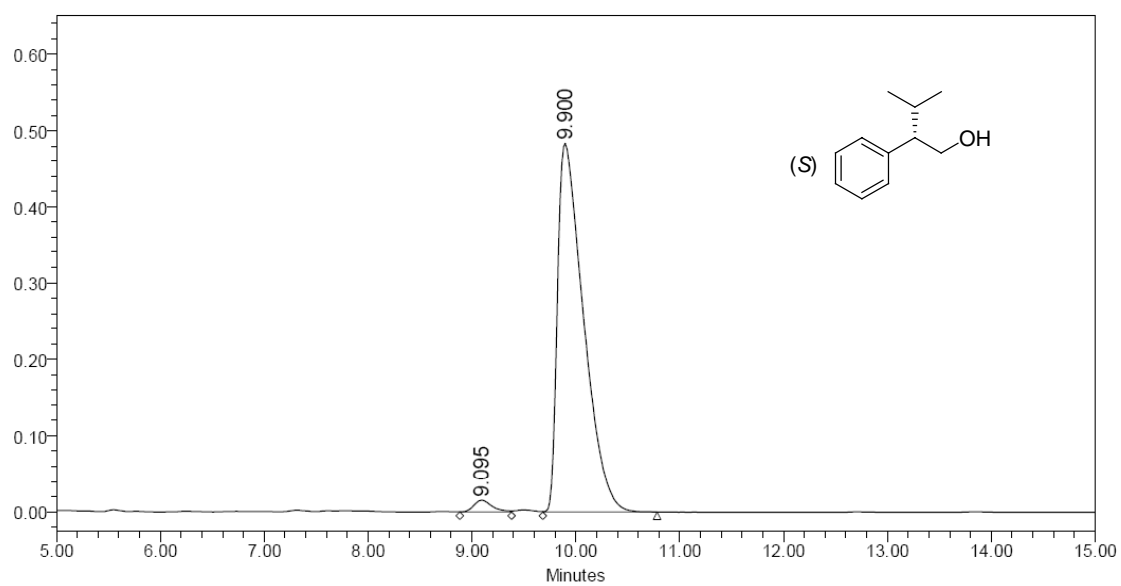
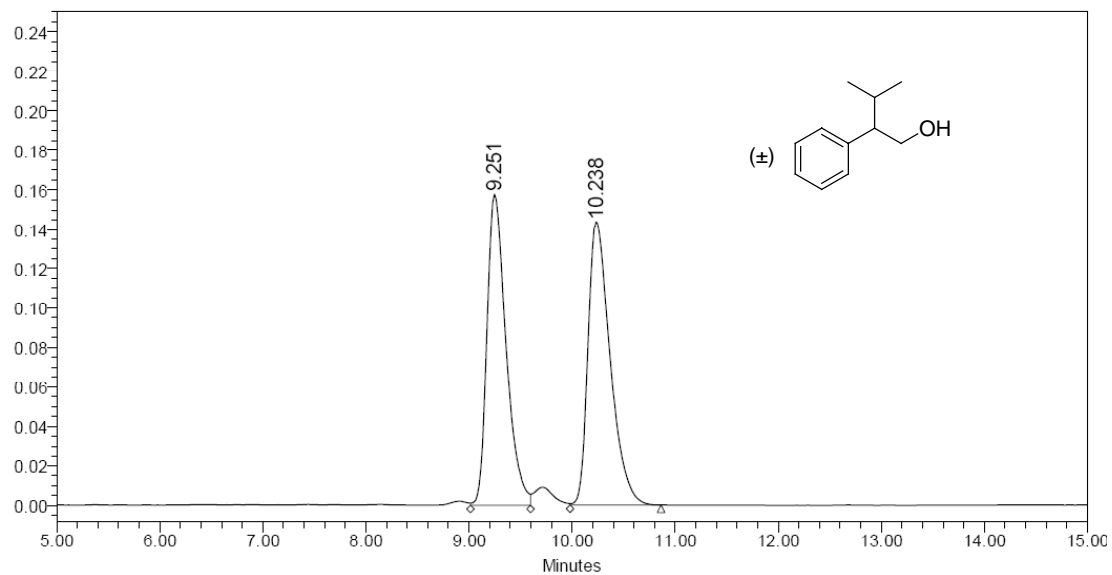
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	20.973	PB	0.1528	476.95105	39.64929	10.86034
2	22.076	PB	0.2477	3914.72412	196.69812	89.13966

(S)-2-Phenylbutan-1-ol (2b)



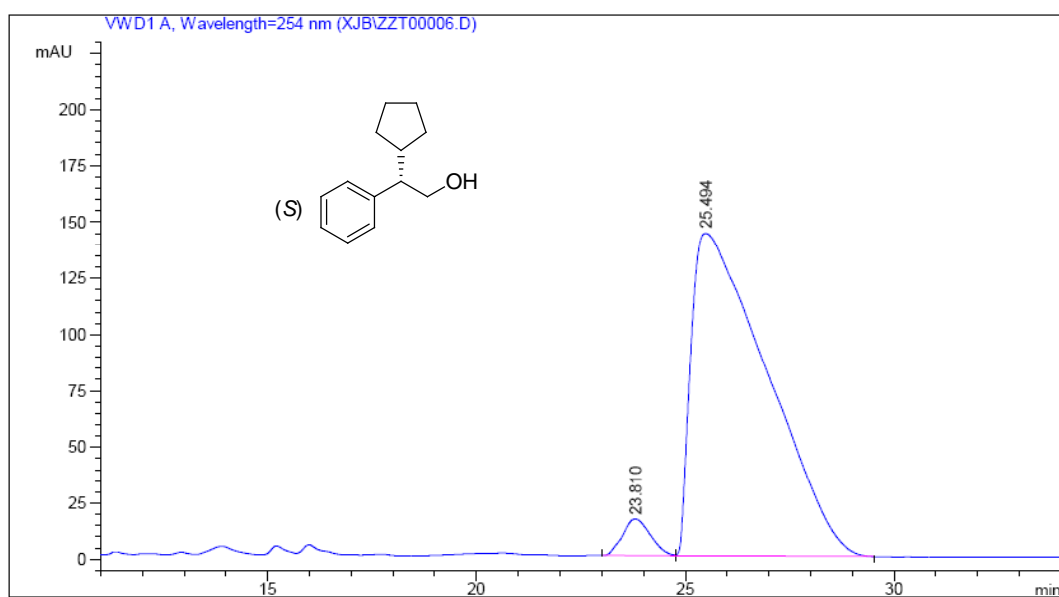
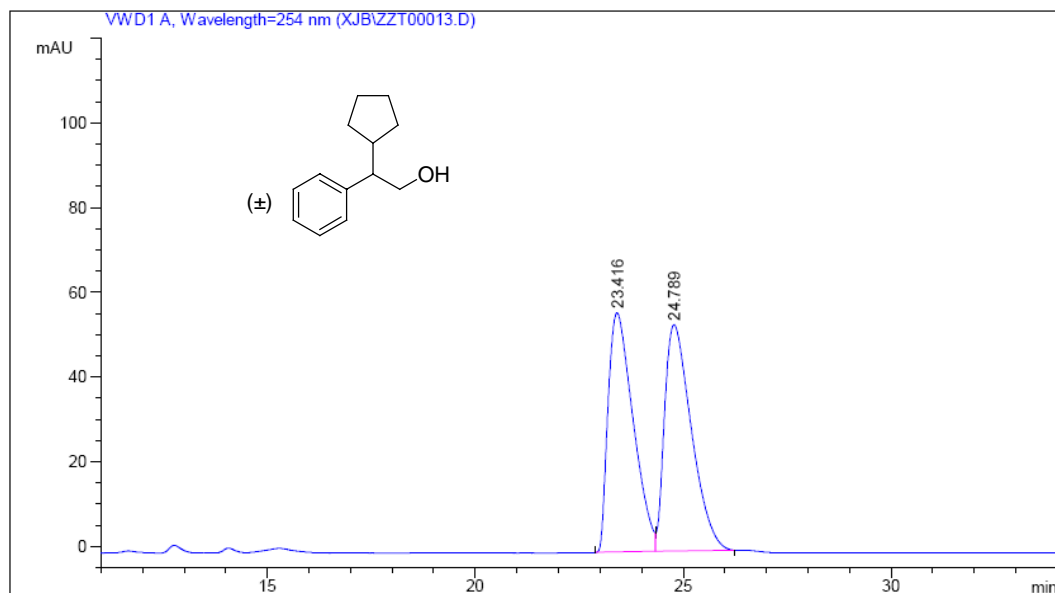
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	26.232	PV	0.1911	309.79544	26.75042	7.09225
2	26.787	VB	0.2113	4058.28833	304.82428	92.90775
Totals :				4368.08377	331.57470	

(S)-3-Methyl-2-phenylbutan-1-ol (2c)



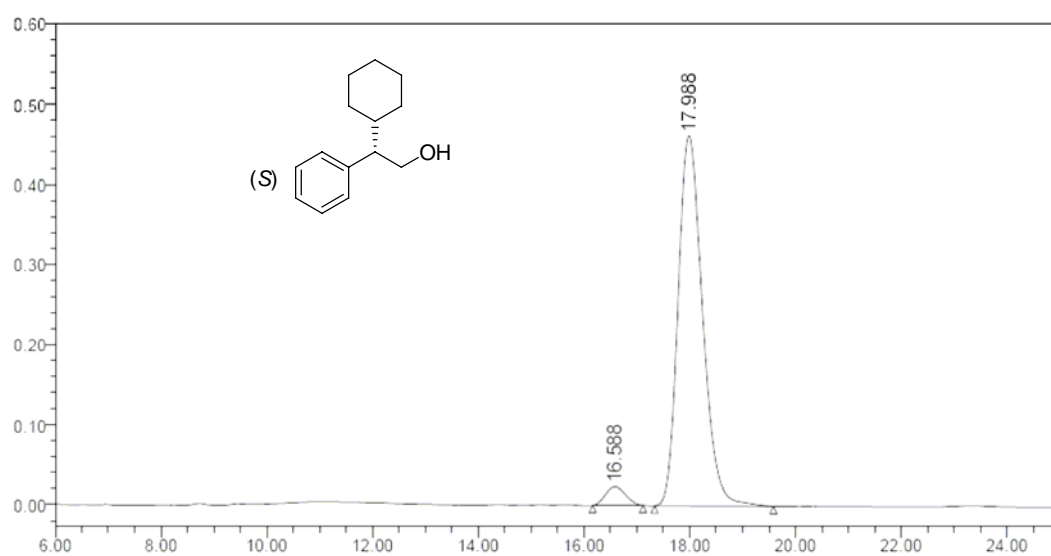
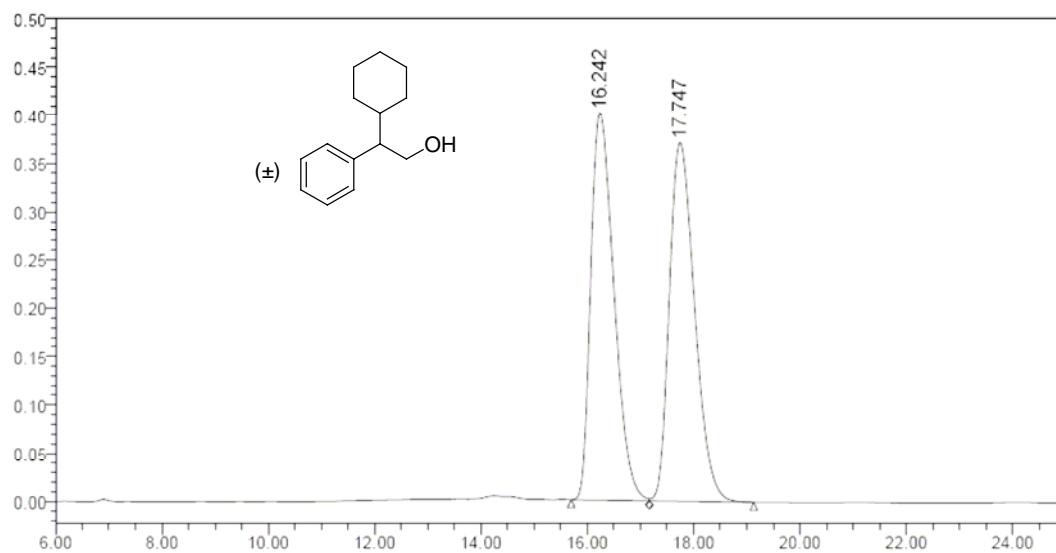
	RT	Area	% Area	Height
1	9.095	189294	2.21	15460
2	9.900	8390285	97.79	484381

(S)-Cyclopentyl-2-phenylethan-1-ol (2d)



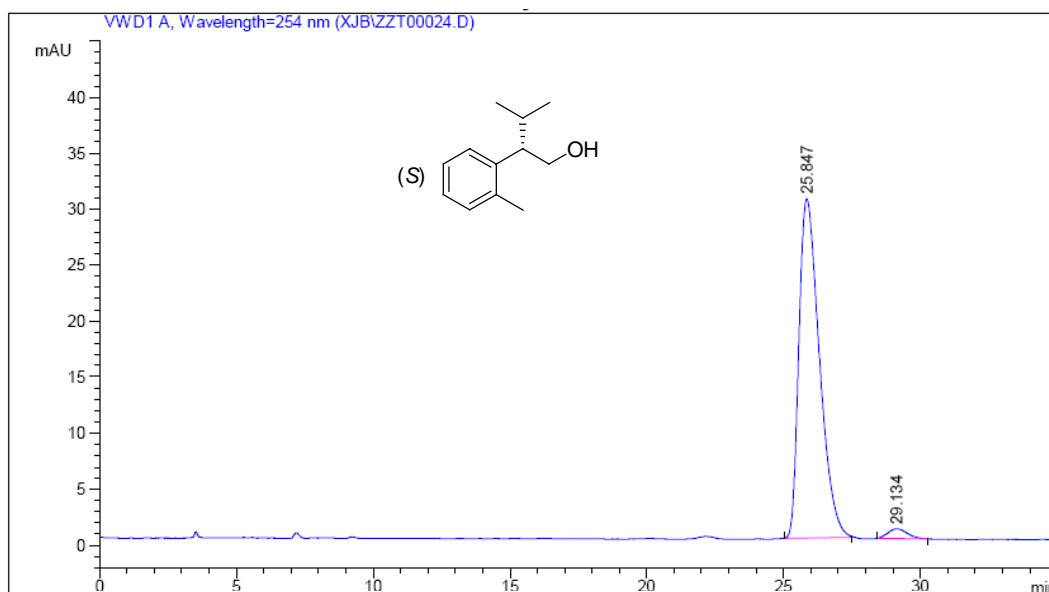
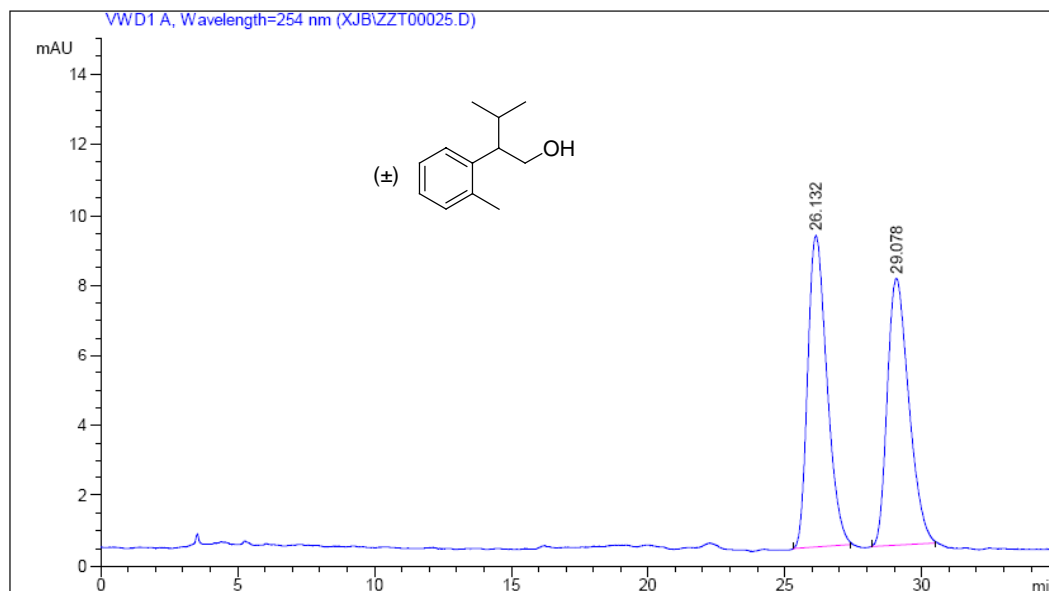
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	23.810	PV	0.7001	755.04626	16.31492	3.9924
2	25.494	VB	1.7188	1.81570e4	143.55157	96.0076

(S)-2-Cyclohexyl-2-phenylethan-1-ol (2e)



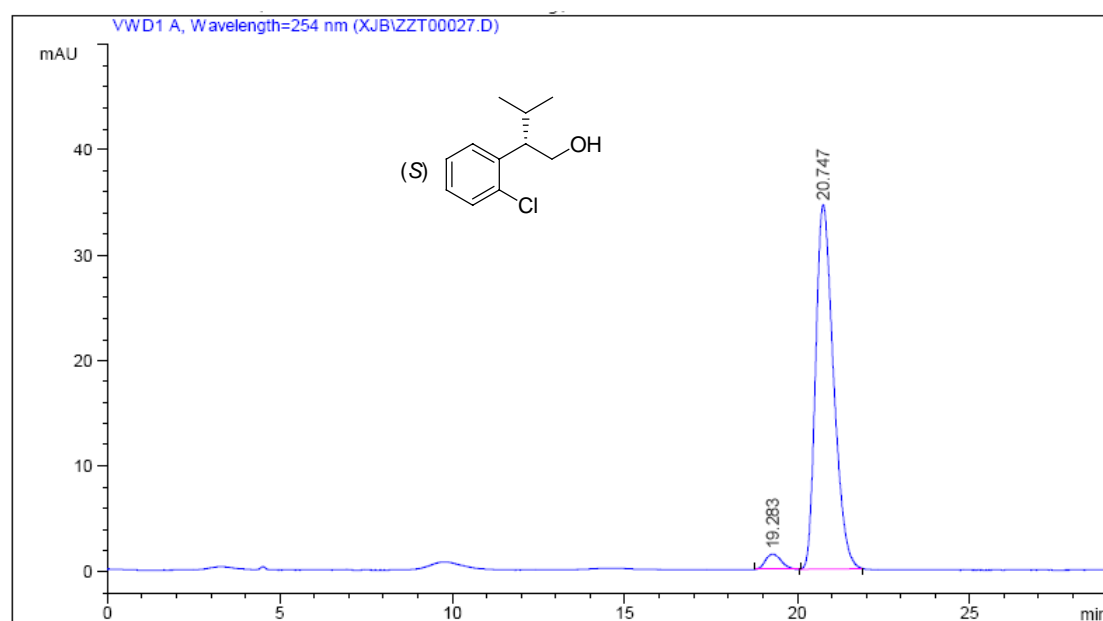
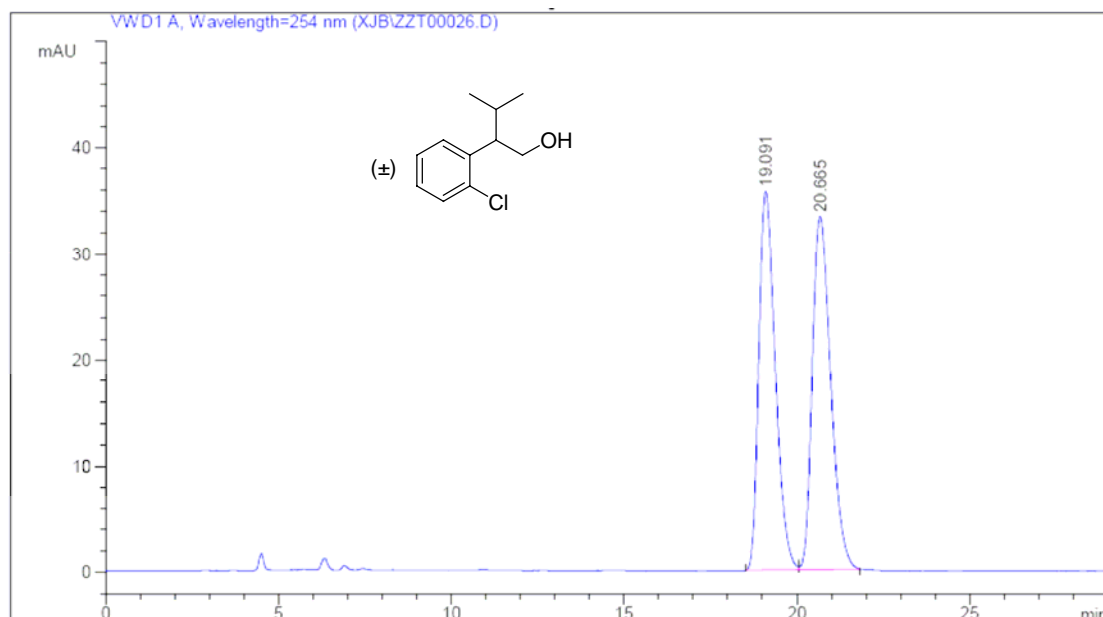
	RT	Area	% Area	Height
1	16.588	614030	3.97	23483
2	17.988	14852272	96.03	461991

(S)-3-Methyl-2-(2-methylphenyl)butan-1-ol (2f)



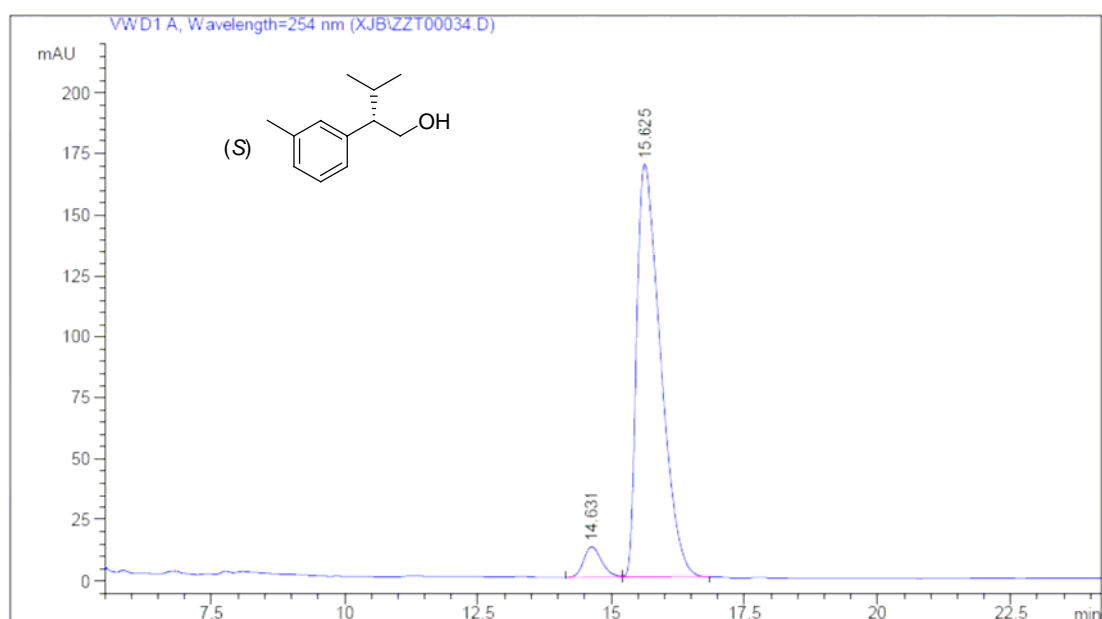
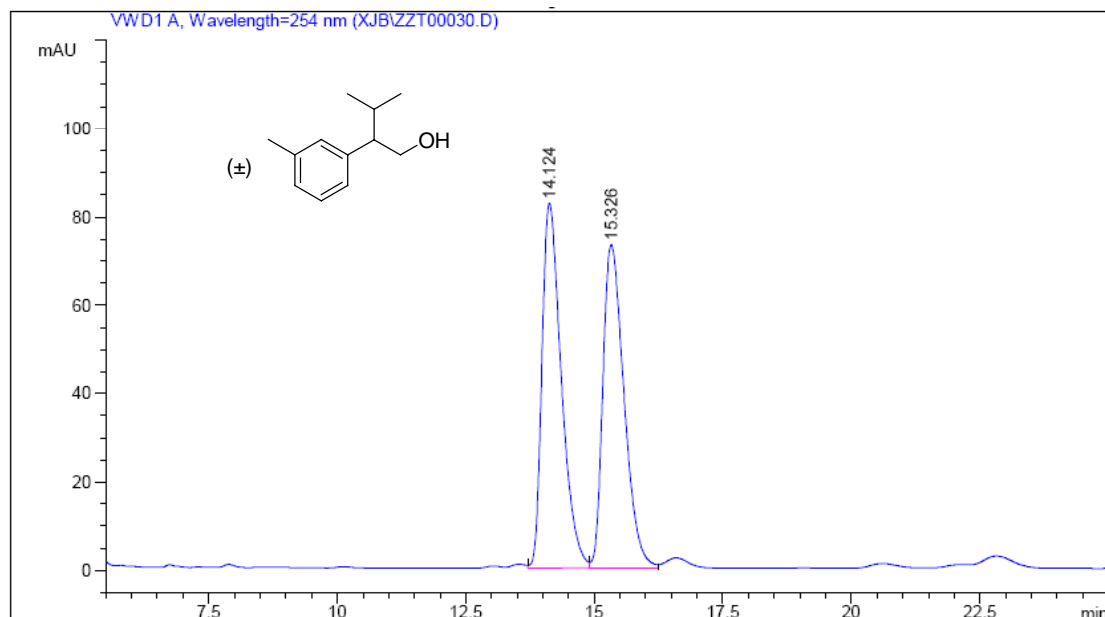
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	25.847	BB	0.7923	1574.00635	30.30404	97.3295
2	29.134	BB	0.5907	43.18676	8.72314e-1	2.6705

(S)-3-Methyl-2-(2-chlorophenyl)butan-1-ol (2j)



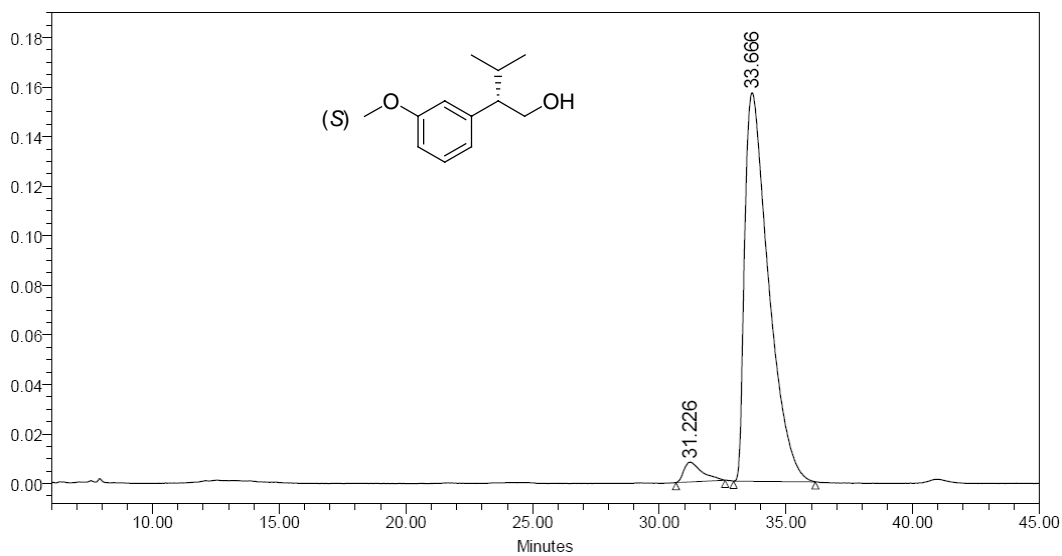
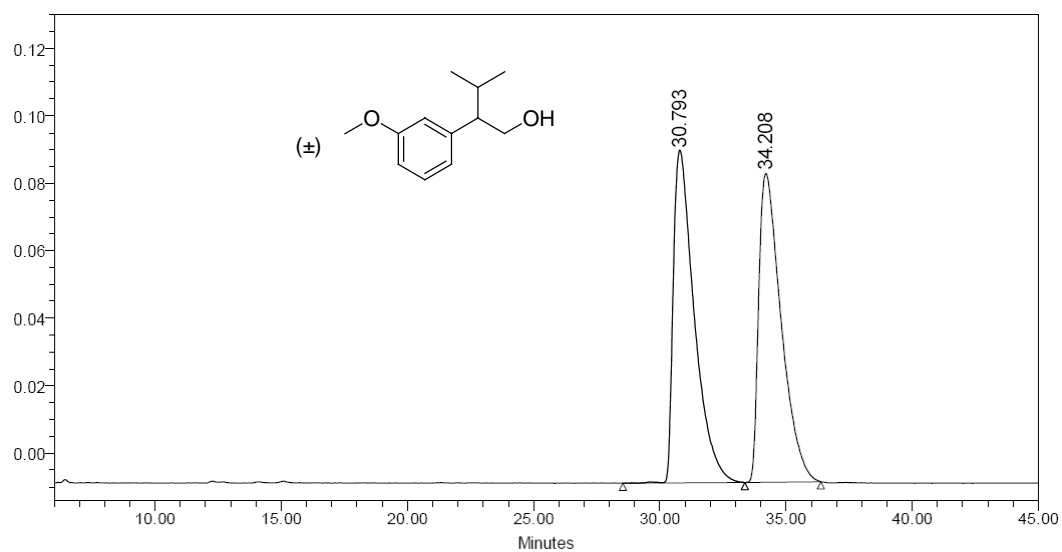
Peak #	RetTime [min]	Type	Width [min]	Area mAU*s	Height [mAU]	Area %
1	19.283	BB	0.4670	48.22871	1.54727	3.7168
2	20.747	BB	0.5539	1249.34753	34.58657	96.2832

(S)-3-Methyl-2-(3-methylphenyl)butan-1-ol (2h)



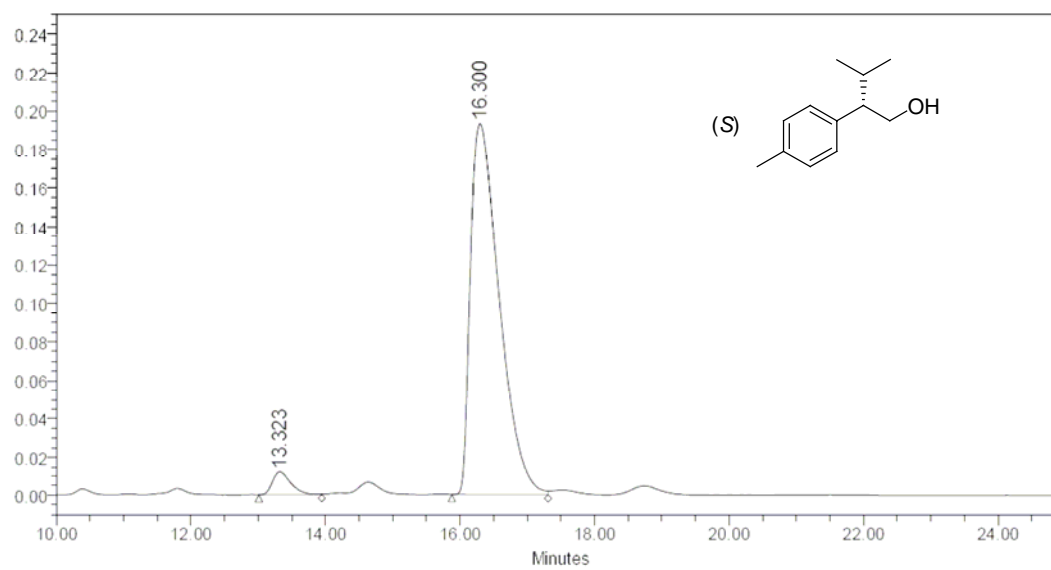
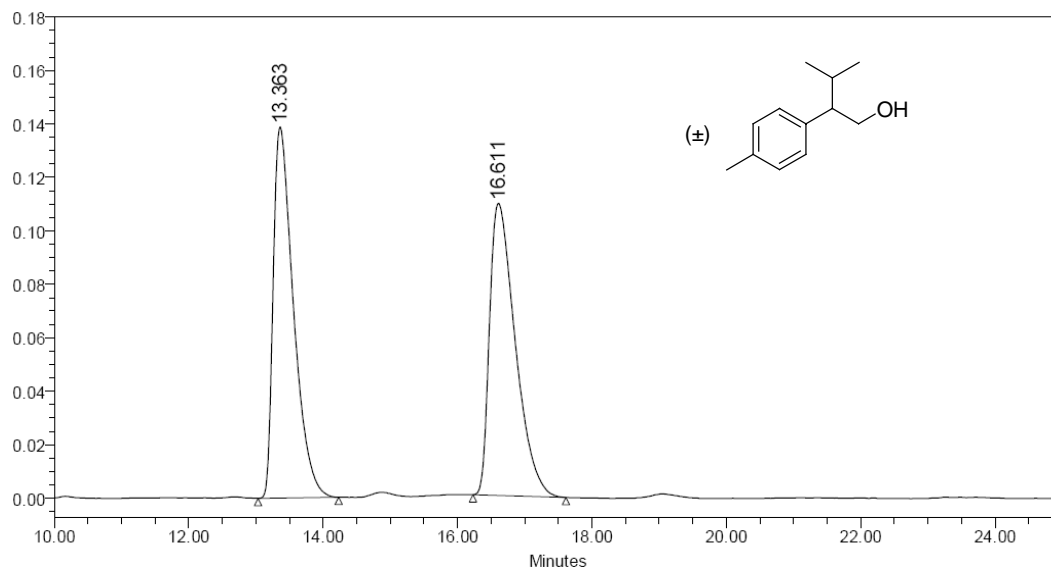
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	14.631	PV	0.3655	297.41977	12.47386	5.3528
2	15.625	VB	0.4907	5258.95850	169.21422	94.6472

(S)-3-Methyl-2-(3-methoxyphenyl)butan-1-ol (2i)



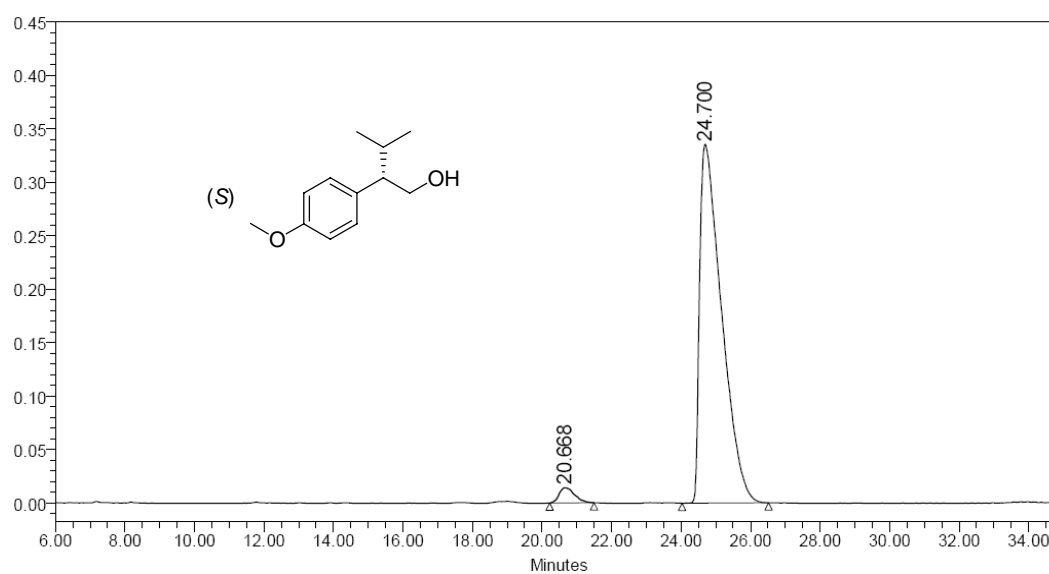
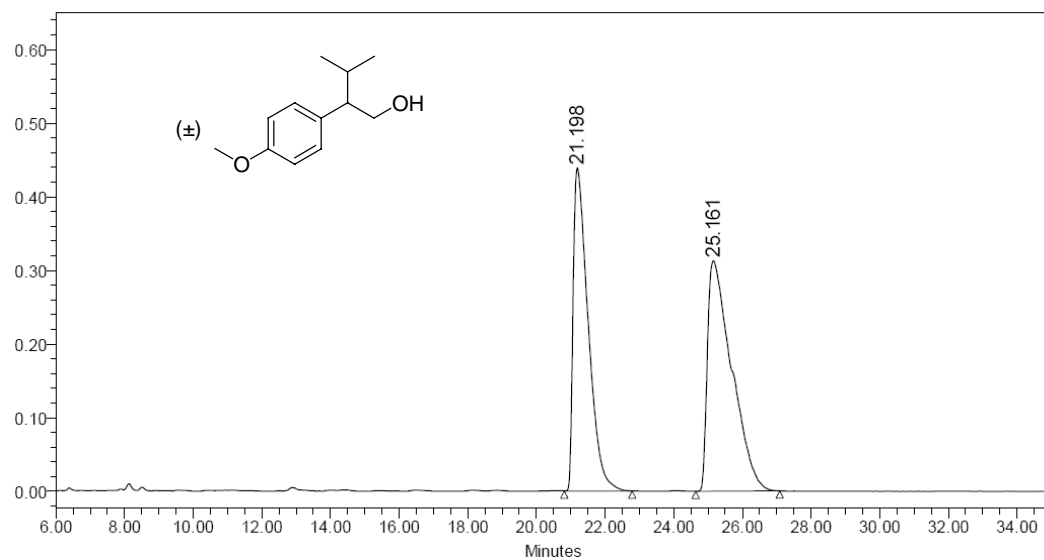
	RT	Area	% Area	Height
1	31.226	394480	3.70	7922
2	33.666	10272133	96.30	156775

(S)-3-Methyl-2-(4-methylphenyl)butan-1-ol (2j)



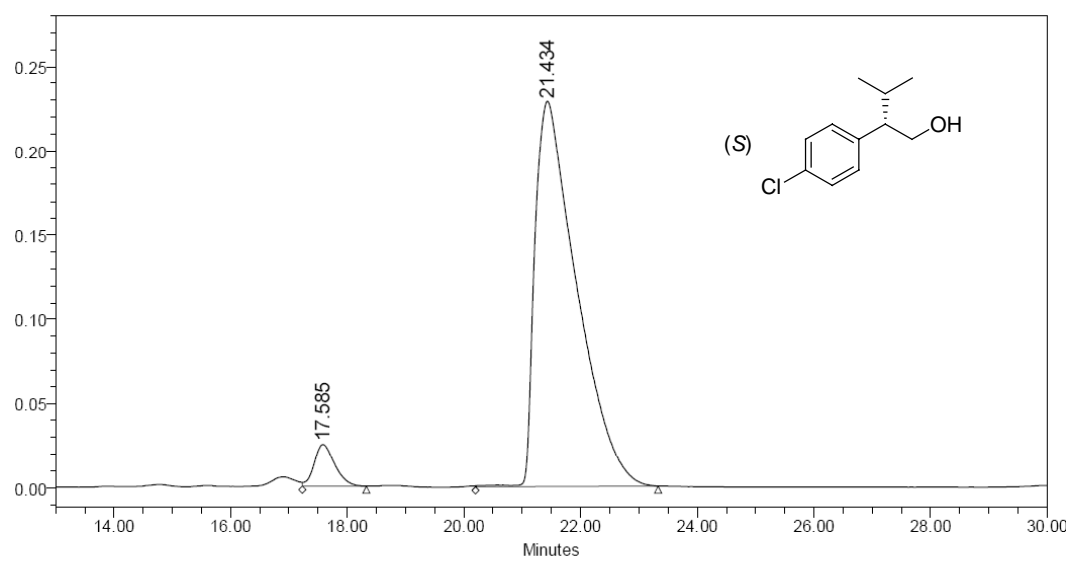
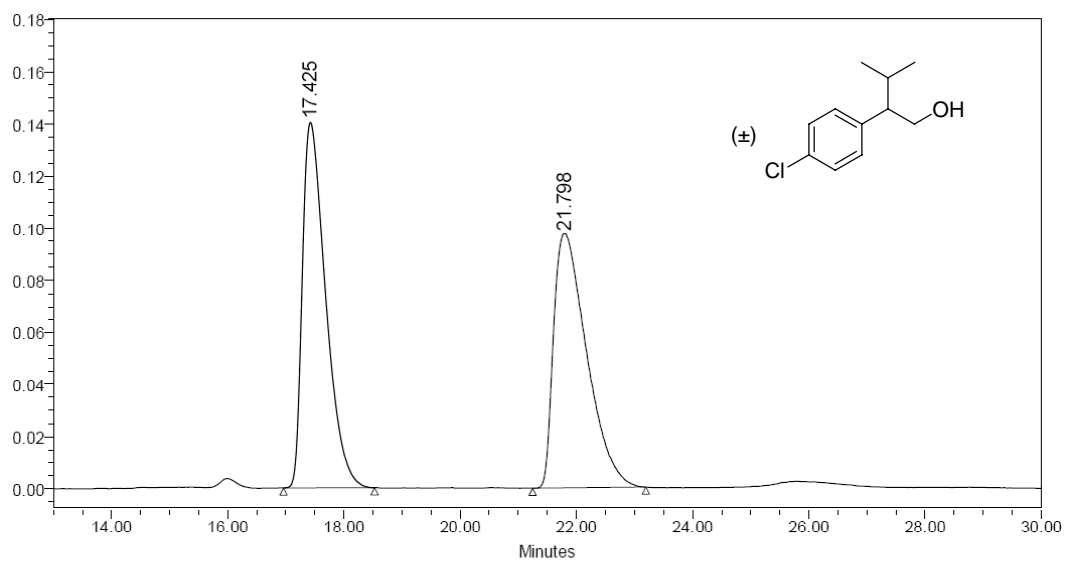
	RT	Area	% Area	Height
1	31.226	394480	3.70	7922
2	33.666	10272133	96.30	156775

(S)-3-Methyl-2-(4-methoxyphenyl)butan-1-ol (2k)



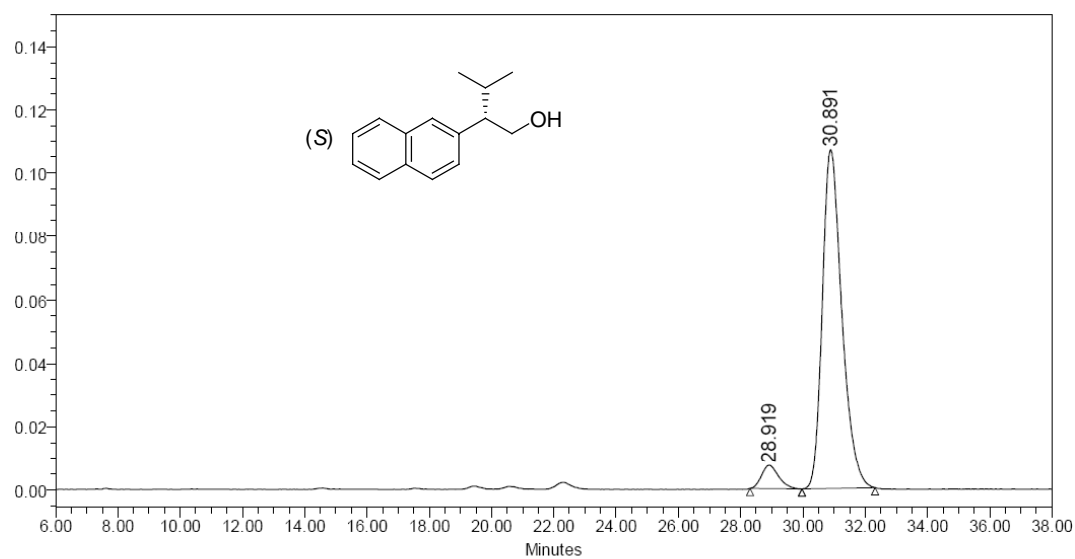
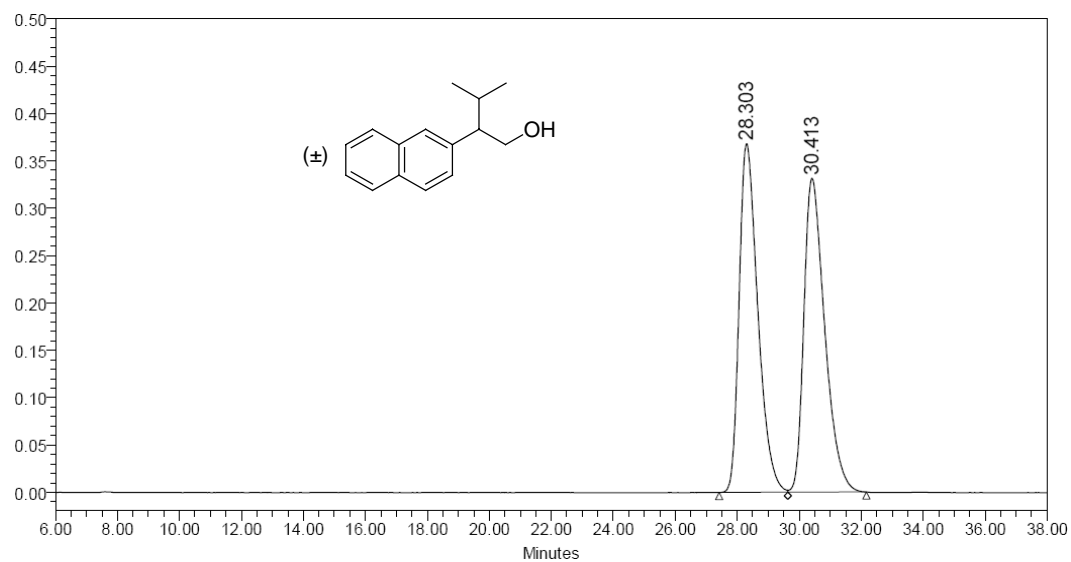
	RT	Area	% Area	Height
1	20.668	439393	2.91	14249
2	24.700	14662133	97.09	335391

(S)-3-Methyl-2-(4-chlorophenyl)butan-1-ol (2I)



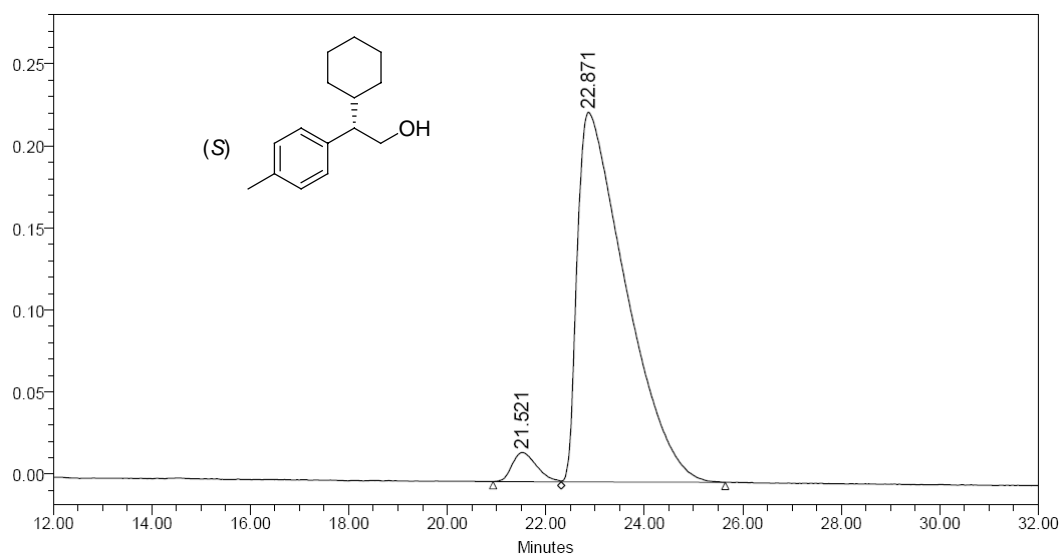
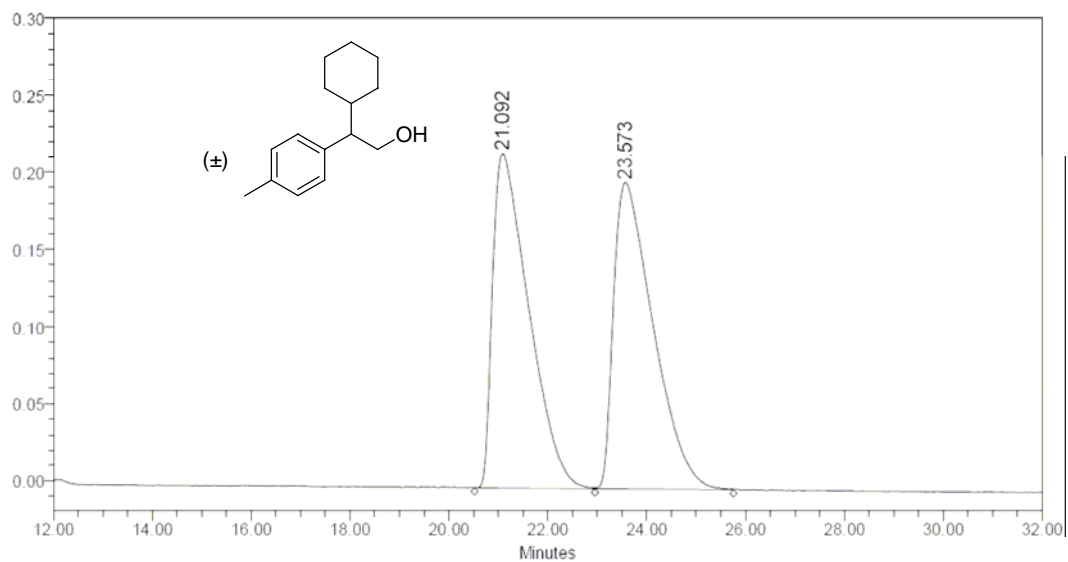
	RT	Area	% Area	Height
1	17.585	607193	5.08	24925
2	21.434	11348509	94.92	228703

(S)-3-Methyl-2-(naphthene-2-yl)butan-1-ol (2m)



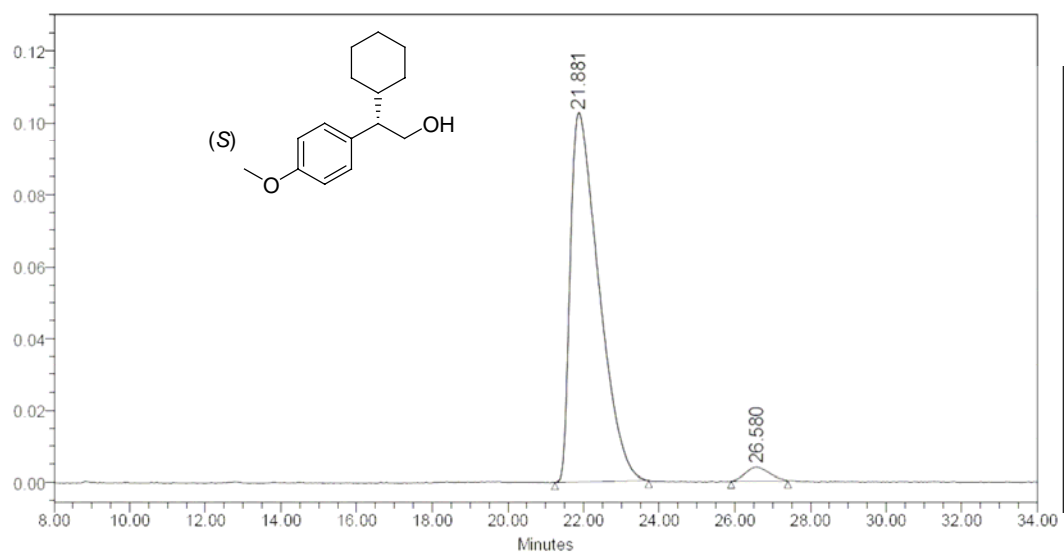
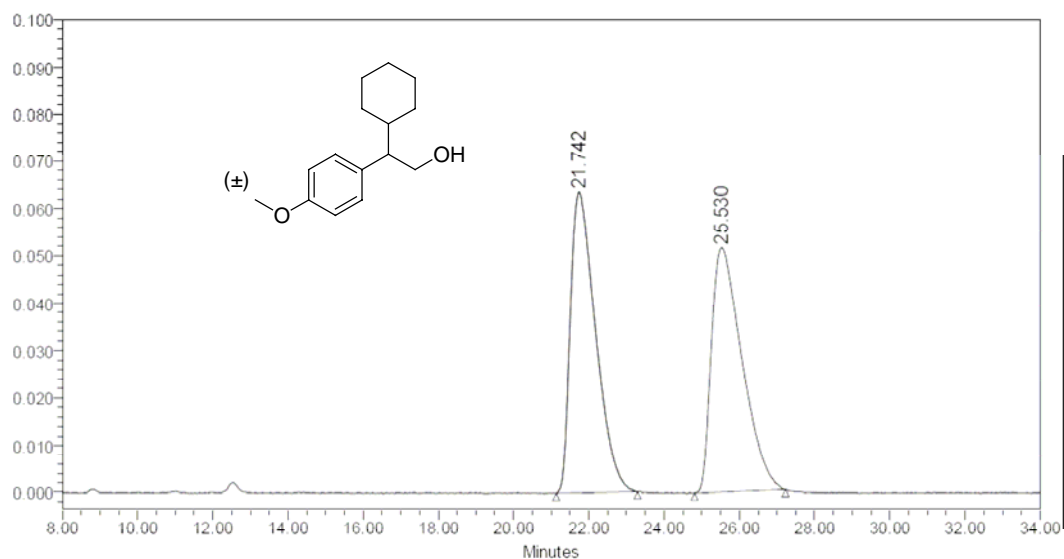
	RT	Area	% Area	Height
1	28.919	277710	5.62	7327
2	30.891	4662848	94.38	107107

(S)-2-Cyclohexyl-2-(4-methylphenyl)ethan-1-ol (2n)



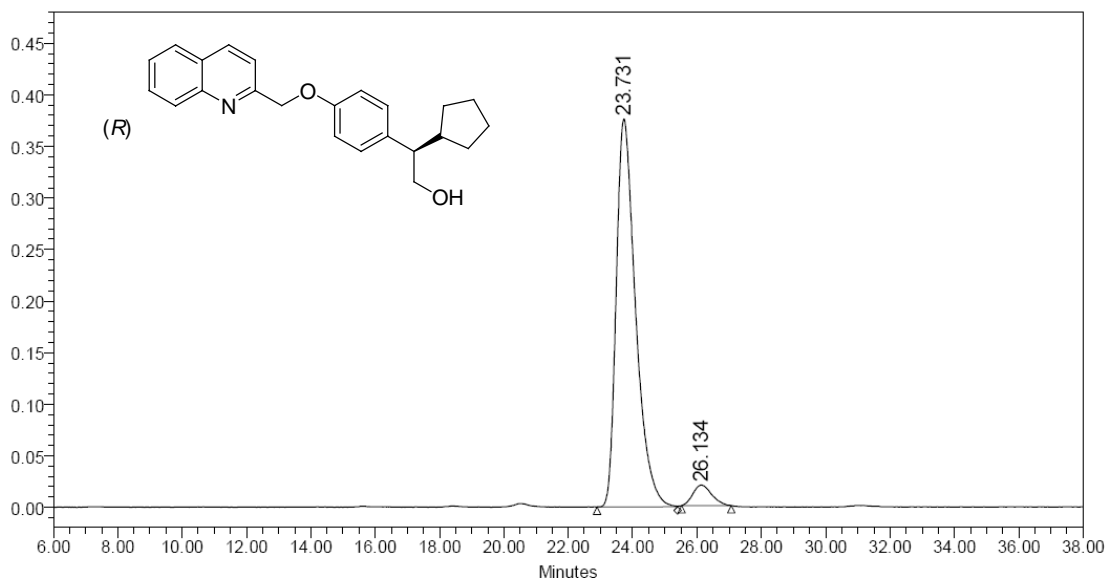
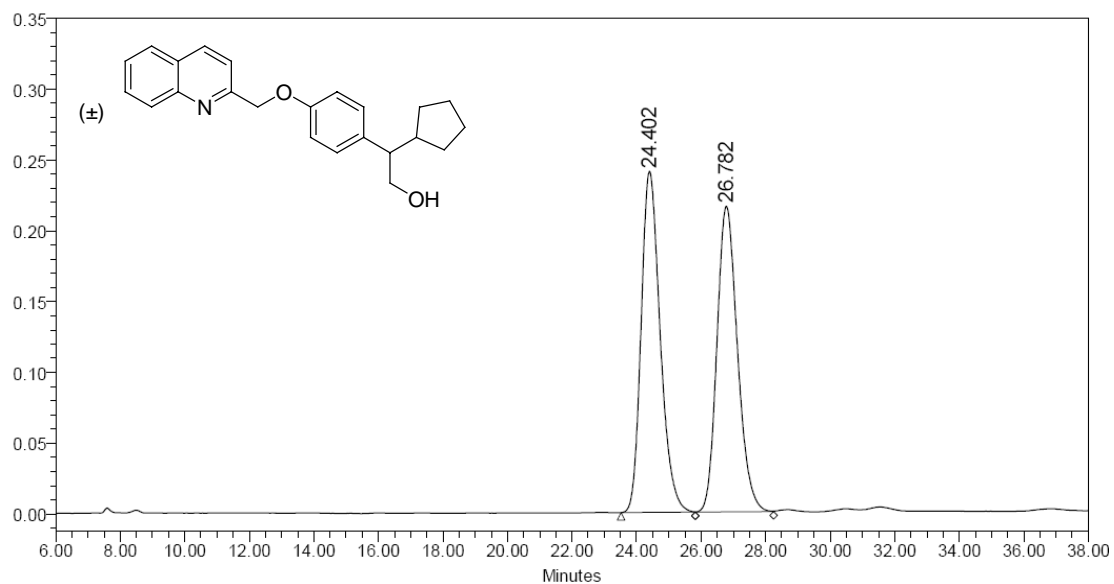
	RT	Area	% Area	Height
1	21.521	615407	3.84	17802
2	22.871	15391042	96.16	225309

(S)-2-Cyclohexyl-2-(4-methoxyphenyl)ethan-1-ol (2o)



	RT	Area	% Area	Height
1	21.881	5371238	97.08	102790
2	26.580	161660	2.92	3709

(R)-2-Cyclopentyl-2-(4-(quinolin-2-ylmethoxy)phenyl)ethanol 6



	RT	Area	% Area	Height
1	23.731	15699742	95.11	376004
2	26.134	807430	4.89	19817