SUPPORTING INFORMATION

Evaluation of the new protocol to enzymatic dynamic kinetic resolution of 3-hydroxy-3-(aryl)propanoic acids

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Experimental

All the chemicals were obtained from commercial sources. The solvents were of analytical grade. Amano lipase PS-C I from *Pseudomonas cepacia* (immobilized on ceramic) and Amano lipase AK from *Pseudomonas fluorescens* were purchased from Sigma-Aldrich. Novozym 435 was purchased from Novo Nordisk. Goose liver was converted to the acetone powder (GLAP) by the method of Connors *et al*.[1] NMR spectra were recorded in $CDCl_3$or DMSO-$D_6$with TMS as an internal standard using 200 and 400 MHz spectrometers. The chemical shifts are reported in ppm (δscale) and the coupling constants (J) are given in hertz(Hz).The HPLC analyses were performed on Chiralcel OD-H, Chiralcel OB, and Chiralcel IA-H chiral columns. (∅ 4.6 mm x 250 mm, from Diacel Chemical Ind., Ltd) equipped with a pre-column (∅ 4mm×10 mm, 5µm) using an LC-6A Varian ProStar apparatus with UV Varian ProStar 330 detector and Chromatopac C-R6A analyser. The mobile phase was hexane/isopropanol and the flow rate 1 mL/min, λ=254 nm. Melting points are uncorrected. Optical rotations were measured in 1-dm cell of 1 mL capacity using Jasco DIP-360 polarimeter operating at 589 nm. The elemental analyses were performed on CHN Perkin-Elmer 240 apparatus. All the reactions were monitored by TLC on Merck silica gel Plates 60 F_{254}. Column chromatography was performed on Merck silica gel 60/230–400 mesh. Enzymatic reactions were performed in a vortex mixture (HeidolphPromax 1020) equipped with incubator (HeidolphInkubator 1000).

Synthesis of ethyl *rac*-3-hydroxy-3-(4-methoxyphenyl)propanoate

Sodium borohydride ($NaBH_4$) (208 mg, 5.05mmol) was added to ethyl 3-(4-methoxyphenyl)-3-oxopropionate (1.11 g. 5.05mmol) in ethanol (30 mL) at 0°C. After 3 hours, reaction was quenched with saturated aqueous ammonium chloride (30 mL) and the separated aqueous phase was extracted with ethyl acetate (3 x 30 mL). The combined organic layer was dried over anhydrous magnesium sulphate ($MgSO_4$) and evaporated in vacuum. The crude product was purified by column chromatography (ethyl acetate/hexanes). Ester was obtained with 77% yield (0.85 g) as a colourless oil;^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, J = 7.2 Hz, 3H), 2.64 (dd, J = 16.4, 4.0 Hz, 1H),2.78 (dd, J = 16.4, 9.2 Hz, 1H),3.40 (br s, 1H),3.78 (s, 3H),4.20 (q, J = 7.2 Hz, 2H),5.05 (dd, J = 9.2, 4.0 Hz, 1H),6.86 (d, J = 8.8 Hz, 2H), 7.27 (d, J = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 43.3, 55.2, 60.7, 69.7, 113.9, 126.8, 134.8, 159.0, 172.3.The ^{1}H and ^{13}C NMR data were in accordance with those reported in the literature.[2] HPLC: Chiralcel OB; hexane/isopropanol (9:1), retention time of the racemic compound (in min):t_R (S) = 14.86, t_R (R) = 25.78.

Synthesis of *rac*-3-hydroxy-3-(4-methoxyphenyl)propanoic acid

General procedure A: Ethyl *rac*-3-hydroxy-3-(4-methoxyphenyl)propanoate (0.4 g, 1.78 mmol) was dissolved in ethanol (1 mL), aqueous solution of NaOH (1N, 10 mL) was added and stirred vigorously for 3 hours at ambient temperature. Ethanol was removed under reduced pressure. Aqueous phase was first washed with ethyl acetate (3x30 mL), acidified with conc. hydrochloric acid to pH 2, and extracted with ethyl acetate (3x30 mL). The combined organic layer was dried over anhydrous magnesium sulfate ($MgSO_4$) and evaporated in vacuum. The crude product was purified by crystallization from ethyl ether/hexanes (98% yield, 0.34 g); mp 81-83 °C (Lit 78-82 °C[3]); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.70-2.85 (m, 2H), 3.84 (s, 3H), 5.15 (dd, J = 4.4, 8.5 Hz, 1H), 6.92 (d, J = 8.8 Hz, 2H), 7.34 (d, J = 8.8 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 43.3, 55.6, 114.3, 127.3, 134.6, 177,2. The ^{1}H and ^{13}C NMR data were in accordance with those reported in the literature.3

Synthesis of ethyl *rac*-3-hydroxy-3-phenylpropanoate

Ethyl 3-oxo-3-phenylpropanoate (2.4 g, 12.5 mmol) was dissolved in ethanol (30 mL), sodium borohydride (425 mg, 12.5mmol) was added portion wise at 0 °C. After the completion of the reaction (TLC, approx. 3 hours) the pH was adjusted to 6.0 with 5% hydrochloric acid (HCl). The ethanol was evaporated in vacuum and the mixture was extracted with DCM (3x50 mL). The combined organic layer was dried over anhydrous magnesium sulphate ($MgSO_4$) and evaporated in vacuum. The crude product was purified by column chromatography (ethyl acetate/hexanes) to yield ester with 85% (2.06 g) as a colourless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.26 (t, 3H, J = 7.2 Hz), 2.71 (dd, J = 16.4, 4.4 Hz, 1H), 2.74 (dd, J = 16.3, 8.3 Hz, 1H),3.36 (br s, 1H), 4.17 (q, 2H, J = 7.2 Hz), 5.13 (dd, J = 8.3, 4.4 Hz,1H), 7.30-7.41 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.4, 43.6, 61.1, 70.6, 125.9, 128.1, 128.8, 142.8, 172.7.The ^{1}H and ^{13}C NMR data were in accordance with those reported in the literature.2HPLC: Chiralcel OD-H; hexane/isopropanol (9:1), retention time of the racemic compound (in min): t_R (S) = 8.67, t_R (R) = 11.27.

Synthesis of *rac*-3-hydroxy-3-phenylpropanoic acid

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[2]Cozzi, P. G.; Benfatti, F.; Capdevila, M. G.; Mignogna, A. *Chem. Commun*. **2008**, 3317- 3318.
[3]Downey, C. W.; Johnson, M. W.; Lawrence, D. H.; Fleisher, A. S.; Tracy, K. J. *J. Org. Chem*. **2010**, *75*, 5351-5354.

rac-3-Hydroxy-3-phenylpropanoic acid was obtained according to **General procedure A** with 99% yield (290 mg) as a white crystals; mp 90-92 °C (Lit 89-90 °C3); ^{1}H NMR (200 MHz,$CDCl_3$) δ 2.70 (dd, J = 5.2, 15.3 Hz, 1H), 2.74 (dd, J = 8.2, 15.3 Hz, 1H), 5.17 (dd, J = 5.2, 8.2 Hz, 1H), 7.28-7.41 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 43.7, 70.1, 125.8, 127.1, 128.1, 143.8, 172.4.The^{1}H and ^{13}C NMR data were in accordance with those reported in the literature.3

Synthesis of ethyl *rac*-3-hydroxy-3-(2-fluorophenyl)propanoate

General procedure B: Triethylamine (0.56 mL, 4.0 mmol, 1 equiv.) was added to a stirred mixture of 2-fluorobenzaldehyde (421 µL, 4.0 mmol, 1 equiv), malonic acid half ethyl ester (582 mg, 4.4 mmol, 1.1 equiv.) and *N*,*N*-dimethylformamide (DMF) (10 mL). This mixture was stirred for 20 hours at 80 °C. Volatile compounds were removed under vacuum. The residue was diluted in ether/dichloromethane (1:1, 40 mL), washed with aqueous saturated sodium bicarbonate ($NaHCO_3$), then with HCl (1 N).The combined organic layer was dried over anhydrous magnesium sulfate ($MgSO_4$)and evaporated in vacuum, and the residue was purified by column chromatography (ethyl acetate/hexanes) to yield ester with 69% (586 mg) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (t, J = 7.2 Hz, 3H), 2.642 (dd, 16.8, 9.2 Hz, 1H), 2.73 (dd, 16.8, 3.4 Hz, 1H), 3.62 (br s, 1H), 4.12 (q, J = 7.2 Hz, 2H), 5.33 (dd, 8.8, 3.4 Hz, 1H), 6.92-6.95 (m, 1H), 7.07-7.11 (m, 1H), 7.19-7.21 (m, 1H), 7.48-7.50 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 41.8,60.9, 64.5, 115.1, 115.3, 124.3, 124.4, 127.2, 127.3, 129.0, 129.1, 129.3, 158.2, 160.6, 172.3. The^{1}H and ^{13}C NMR data were in accordance with those reported in the literature;[4]Elemental Anal.Calcd. for $C_{11}H_{13}FO_3$: C 62.26, H 6.17; Found: C 62.31, H 6.08;MS (ESI): Calcd. for $C_{11}H_{13}FO_3Na$ $[M+Na]^+$, 235.07, Found 235.10; HPLC: Chiralcel OD-H; hexane/isopropanol (9:1), retention time of the racemic compound (in min): t_R (*S*) = 6.60, t_R (*R*) = 9.01.

Synthesis of *rac*-3-hydroxy-3-(2-fluorophenyl)propanoic acid

rac-3-Hydroxy-3-(2-fluorophenyl)propanoic acid was obtained according to **General procedure A** with 96% yield (344 mg) as a white crystals; mp 70-71°C (Lit 68.85°C[5]); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.75-2.82 (m, 2H), 5.38-5.45 (m, 1H), 6.99-7.49 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 42.0, 64.8, 115.4, 115.8, 124.6, 127.4, 129.2, 129.4, 129.5, 129.7, 157.2, 162.1, 177.3;Elemental Anal.Calcd. for $C_9H_9FO_3$: C 58.70, H 4.93; Found: C 58.47, H 5.07;MS (ESI): Calcd. for $C_9H_8FO_3$ $[M-H]^-$, 183.04, Found 183.0.

Synthesis of ethyl *rac*-3-hydroxy-3-(2-bromophenyl)propanoate

Ethyl *rac*-3-hydroxy-3-(2-bromophenyl)propanoate was obtained according to **General procedure B** with 72% yield (786 mg) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, 3H, J = 7.2 Hz), 2.56 (dd, J = 16.8, 9.8 Hz, 1H), 2.87 (dd, J = 16.8, 2.8 Hz, 1H), 3.60 (br s, 1H), 4.21 (q, 2H, J = 7.2 Hz), 5.44 (dd, J = 9.8, 2.8 Hz, 1H), 7.14-7.15 (m, 1H), 7.31-7.34 (m, 1H), 7.50-7.52 (m, 1H), 7.57-7.59 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 41.4, 60.3, 69.2, 121.4, 127.3, 127.8, 129.0, 132.6, 141.4, 172.4. The ^{1}H and ^{13}C NMR data were in accordance with those reported in the literature4; MS (ESI): Calcd. for $C_{11}H_{13}BrO_3Na$ $[M+Na]^+$, 294.9, Found 295.0; HPLC: Chiralcel OD-H; hexane/isopropanol (9:1), retention time of the racemic compound (in min): t_R = 7.77, t_R = 14.56.

Synthesis of *rac*-3-hydroxy-3-(2-bromophenyl)propanoic acid

rac-3-Hydroxy-3-(2-bromophenyl)propanoic acid was obtained according to **General procedure A** with 93% yield (278 mg) as a white crystals; mp90-91 °C (Lit. 89 °C (diethyl ether/hexane)[6]); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.62 (dd, J = 16.8, 10.0 Hz, 1H), 2.93 (dd, J = 16.8, 2.6 Hz, 1H), 5.75 (dd, J = 9.8, 2.6 Hz, 1H), 6.15 (br s, 1H), 7.11-7.18 (m, 1H), 7.30-7.40 (m, 1H), 7.50-7.64 (m, 2H);^{13}C NMR (50 MHz, $CDCl_3$) δ 41.7, 69.4, 121.7, 127.5, 128.2, 129.6, 133.0, 141.3, 177.5; MS (ESI): Calcd. for $C_9H_8BrO_3$ $[M-H]^-$, 242.9, Found 242.9.

Synthesis of ethyl *rac*-3-(4-cyanophenyl)-3-hydroxypropanoate

Ethyl *rac*-3-hydroxy-3-(4-cyanophenyl)propanoatewas obtained according to **General procedure B** with75% yield (658 mg) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, J = 8.0 Hz, 3H), 2.71 (dd, J = 8.0, 4.0 Hz, 2H), 3.65 (br s, 1H), 4.19 (q, J = 8.0 Hz, 2H), 5.17 (dd, J = 8.0, 4.0 Hz, 1H),7.50 (d, 12 Hz, 2H), 7.64 (d, 12 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 42.9, 61.1, 69.5, 111.5, 118.6, 126.3, 132.3, 147.8, 171.9. The ^{1}H and ^{13}C NMR data were in accordance with those reported in the literature[7]; HPLC: Chiralcel OB; hexane/isopropanol (9:1), retention time of the racemic compound (in min): t_R = 14.89, t_R =16.66.

Synthesis of *rac*-3-(4-cyanophenyl)-3-hydroxypropanoic acid

rac-3-Hydroxy-3-(4-cyanophenyl)propanoic acid was obtained according to **General procedure A** with 93% yield (278 mg) as a white crystals; mp 101-102 °C;^{1}H NMR (400 MHz, DMSO-D_6) δ2.50 (dd, J = 8.0, 4.0 Hz, 2H), 5.00 (dd, J = 8.0, 4.0 Hz, 1H),7.54 (d, J = 8.0 Hz), 7.76 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-D_6) δ 44.0, 68.9, 109.7, 118.8, 126.8, 132.0, 150.6, 171.8. The ^{1}H and ^{13}C NMR data were in accordance with those reported in the literature.[8]

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Synthesis of ethyl *rac*-3-hydroxy-3-(4-nitrophenyl)propanoate

To malonic acid monoethyl ester (90mg, 0.66 mmol) in acetonitrile (0.4 mL) was added the aldehyde (100mg, 0.66mmol) and then stirred at 80 °C for 15 h (under nitrogen). Reaction mixture was concentrated. The residue was dissolved in a mixture of diethyl ether/DCM (1/1), washed with saturated sodium bicarbonate, hydrochloric acid (1N), then dried over magnesium sulfate ($MgSO_4$). The organic phase was concentrated. The residue (120 mg) was separated by chromatography on silica gel (ethyl acetate/hexanes). Product was obtained with 76% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, J = 8.0 Hz, 3H), 2.72-2.78 (m, 2H), 3.66 (br s, 1H), 4.20 (q, J = 8.0 Hz, 2H), 5.23 (dd, J = 8.0, 4.0 Hz, 1H), 7.57 (d,J = 8.0 Hz, 2H), 8.21 (d,J = 8.0 Hz, 2H);^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 42.9, 61.2, 69.3, 123.7, 126.4, 147.4, 149.6, 171.9. The ^{1}H and ^{13}C NMR data were in accordance with those reported in the literature.[9]HPLC: Chiralcel IA; hexane/isopropanol (9:1), retention time of the racemic compound (in min): t_R (*S*) = 14.65, t_R (*R*) =16.00.

Synthesis of *rac*-3-hydroxy-3-(4-nitrophenyl)propanoic acid

rac-3-Hydroxy-3-(4-nitrophenyl)propanoic acid was obtained according to **General procedure A** with 92% yield (292 mg) as a white crystals; mp 121-123 ˚C (Lit 119-122 ˚C3); ^{1}H NMR (400 MHz, DMSO-D_6) δ 2.51-2.75 (m, 2H), 3.28 (br s, 1H), 5.05 (dd, J = 8.4, 5.2 Hz, 1H), 7.62 (d, J = 8.8 Hz, 1H), 8.16 (d, J = 8.8 Hz, 1H), 12.1 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-D_6) δ 44.4, 69.1, 123.7, 127.5, 147.0, 153.2, 172.2.The ^{1}H and ^{13}C NMR data were in accordance with those reported in the literature.8

Synthesis of ethyl*rac*-3-hydroxy-3-(2,4-dinitrophenyl)propanoate

Ethyl*rac*-3-hydroxy-3-(2,4-dinitrophenyl)propanoate was obtainedaccording to **General procedure B** with 69% yield (784 mg) as a colourlessoil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30 (t, 3H, J = 8.0 Hz), 2.62 (dd, J = 20.0, 12.0 Hz, 1H), 2.95 (dd, J = 20.0, 4.0 Hz, 1H),4.00 (br s, 1H), 4.34 (q, 2H, J = 8.0 Hz), 5.77 (dd, J = 12.0, 4.0 Hz, 1H), 8.19 (d, J = 8.5 Hz, 1H), 8.47-8.49 (m, 1H), 8.83 (d, J = 8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 41.9, 61.4, 65.9, 120.0, 127.7, 130.2, 144.6, 147.2, 171.8; ElementalAnal.Calcd. for $C_{11}H_{12}N_2O_7$:C 46.48, H 4.26, N 9.86; Found: C 46.52, H 4.19, N 9.75; HRMS (ESI): Exact mass calcd. for $C_{11}H_{12}N_2O_7Na$ $[M+Na]^+$, 307.0542, Found 307.0550; HPLC: Chiralcel AI; hexane/isopropanol (9:1), retention time of the racemic compound (in min): t_R = 24.49, t_R = 29.07.

Synthesis of *rac*-3-hydroxy-3-(2,4-dinitrophenyl)propanoic acid

rac-3-Hydroxy-3-(2,4-dinitrophenyl)propanoic acid was obtained according to **General procedure A** with 98% yield (468 mg) as a semisolid; ^{1}H NMR (400 MHz, $CDCl_3$/$DMSO_{D6}$) δ 2.50 (dd, J = 15.6, 8.8 Hz, 1H), 2.74 (dd, J = 15.6, 3.6 Hz, 1H),5.34 (br s, 1H), 5.54 (dd, J = 8.8, 3.6 Hz, 1H), 6.08 (br s, 1H), 8.14 (d, J = 8.8 Hz, 1H), 8.56-8.59 (m, 1H), 8.73 (d, J = 8.8 Hz, 1H), 12.35 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-D_6) δ 43.9, 65.9, 120.3, 128.3, 131.3, 147.2, 147.4, 148.0, 172.3; HRMS (ESI): Exact mass calcd. for $C_9H_7N_2O_7$[M-H]$^-$, 255.0261, Found 255.0253.

Synthesis of ethyl *rac*-3-hydroxy-3-(2-nitro-4-fluorophenyl)propanoate

Ethyl *rac*-3-hydroxy-3-(2-nitro-4-fluorophenyl)propanoate was obtained according to **General procedure B** with78% yield (803 mg) as a colourless oil;^{1}H NMR (200 MHz, $CDCl_3$) δ 1.27 (t, 3H, J= 7.2 Hz), 2.60 (dd, J = 16.8, 9.2 Hz, 1H), 2.93 (dd, J = 16.8, 2.8 Hz, 1H), 3.90 (br s, 1H), 4.20 (q, 2H, J = 7.2 Hz), 5.63 (dd, J = 3.4, 2.4 Hz, 1H), 7.34-7.43 (m, 1H), 7.66-7.72 (m, 1H), 7.87-7.94 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.4, 42.6, 61.5, 65.9, 111.9, 112.5, 121.2, 121.6, 130.4, 130.5, 172.6; Elemental Anal Calcd. for $C_{11}H_{12}NO_5F$: C 51.37, H 4.70, N 5.45; Found: C 51.15, H 4.82, N 5.37; HRMS (ESI): Exact mass calcd. for $C_{11}H_{12}NO_5NaF$ $[M+Na]^+$, 280.0597, Found 280.0599; HPLC: Chiralcel OD-H; hexane/isopropanol (9:1), retention time of the racemic compound (in min): t_R = 10.91, t_R = 13.73.

Synthesis of *rac*-3-hydroxy-3-(2-nitro-4-fluorophenyl)propanoic acid

rac-3-Hydroxy-3-(2-nitro-4-fluorophenyl)propanoic acid was obtained according to **General procedure A** with 94% yield (306 mg) as a semisolid;^{1}H NMR (200 MHz, $CDCl_3$) δ 2.61 (dd, J = 16.8, 9.2 Hz, 1H), 2.93 (dd, J = 16.8, 2.8 Hz, 1H), 5.70-5.76 (m, 1H), 7.38-7.42 (m, 1H), 7.62-7.71 (m, 1H), 7.82-7.92 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 42.9, 69.9, 115.5, 127.6, 140.0, 163.5, 172.2; Elemental Anal.Calcd. for $C_9H_8FNO_5$: C 47.17, H 3.52, N 6.11; Found: C 46.82, H 3.78, N 5.96; MS (ESI): Calcd. for $C_9H_7FNO_5$ [M-H]$^-$, 228.03, Found 228.0.

Synthesis of ethyl 3-hydroxy-3-(2-nitro-4-trifluoromethylphenyl)propanoate

Ethyl *rac*-3-hydroxy-3-(2-nitro-4-trifluoromethylphenyl)propanoate was obtained according to **General procedure B** with 72% yield (885 mg) as a colourless oil;^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (t, 3H, J = 8.0 Hz), 2.62 (dd, J = 16.0, 12.0 Hz, 1H), 2.98 (dd, J = 16.0, 4.0 Hz, 1H), 4.02 (br s, 1H), 4.24 (q, 2H, J = 8.0 Hz), 5.77 (d,J = 8.0 Hz, 1H), 8.20 (d, J = 8.0 Hz,1H), 8.50 (dd, J = 8.0 Hz, 1H), 8.83 (d,J = 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 42.1, 61.3, 65.9, 121.8, 121.9, 129.5, 130.1, 131.4, 141.9, 172.0;Elemental Anal.Calcd. for $C_{12}H_{12}F_3NO_5$: C 46.91, H 3.94, N 4.56; Found: C 47.02, H 3.90, N 4.33; HRMS (ESI): Exact mass calcd. for $C_{12}H_{12}$ F_3NO_5Na $[M+Na]^+$, 330.0565, Found 330.0559; HPLC: Chiralcel OB; hexane/isopropanol (9:1), retention time of the racemic compound (in min): t_R = 8.41, t_R =10.64.

Synthesis of *rac*-3-hydroxy-3-(2-nitro-4-trifluoromethylphenyl)propanoic acid.

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rac-3-Hydroxy-3-(2-nitro-4-trifluoromethylphenyl)propanoic acid was obtained according to **General procedure A** with 89% yield (275 mg) as a semisolid;[1]H NMR (400 MHz, DMSO-D_6) δ 2.57 (dd, *J* = 12.0, 8.0 Hz, 1H), 2.73 (dd, *J* = 12.0, 4.0 Hz, 1H), 5.50 (dd, *J* = 8.4, 4.0 Hz, 1H), 5.98 (br s, 1H), 8.10 (d, *J* = 8 Hz, 1H), 8.15 (dd, *J* = 8.4, 1.2 Hz, 1H), 8.33 (d, *J* = 1.2 Hz, 1H), 12.3 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-D_6) δ43.6, 65.5, 130.6, 148.0, 171.9; HRMS (ESI): Exact mass calcd. for $C_{10}H_7F_3NO_5$ [M-Na]$^-$, 278.0275, Found 278.0276.

Enzymatic kinetic resolution of *rac*-3-hydroxy-3-(aryl)propanoic acids

To the solution of acid **1a-h** (0.1 mmol) in organic solvent (2 mL), triethylorthobenzoate (2 equiv.) and enzyme (native 5 mg or immobilized 10 mg) were added in 5mL screwed vial. The reaction mixture was stirred for 72 hours at 40°C in a vortex mixture (HeidolphPromax 1020) equipped with incubator (HeidolphInkubator 1000). After cooling crude product was isolated and purified by column chromatography (ethyl acetate/hexanes). The ^{1}H NMR data were in accordance with those recorded for racemates; (*R*)-(+)-**2a**: $[\alpha]_D^{20}$= +21.5 (c 1.00 $CHCl_3$, 60% *ee*), Lit (*R*) enantiomer: $[\alpha]_D^{20}$ = +28.8 (c 1.0, $CHCl_3$);[10](*R*)-(+)-**2b**: $[\alpha]_D^{20}$= +40.2 (c 1.00 $CHCl_3$, 63% *ee*), Lit (*R*) enantiomer: $[\alpha]_D^{20}$ = +48.9 (c 0.89, $CHCl_3$);[11] (*R*)-(+)-**2c**: $[\alpha]_D^{20}$= +34.6 (c 1.00 $CHCl_3$, 68% *ee*), Lit (*S*) enantiomer: $[\alpha]_D^{20}$ = -49.7 (c 2.71, $CHCl_3$);9 (+)-**2g**: $[\alpha]_D^{20}$= +25.2 (c 1.00 $CHCl_3$, 83% *ee*); (+)-**2h**: $[\alpha]_D^{20}$= +16.3 (c 1.00 $CHCl_3$, 52% *ee*); (+)-**2i**: $[\alpha]_D^{20}$= +12.8 (c 1.00 $CHCl_3$, 62% *ee*).

Synthesis (dynamic kinetic resolution) of ethyl (*S*)-3-hydroxy-3-(4-nitrophenyl)propanoate and ethyl (*R*)-3-hydroxy-3-(4-nitrophenyl)propanoate

To the solution of acid (0.1 mmol) in organic solvent (2 mL), triethylorthobenzoate (2 equiv.), enzyme (native 5 mg or immobilized 10 mg) and metal catalyst (10 mol%) were added in 5mL vial. The reaction mixture was stirred for 72 hours at 40°C in vortex mixture (HeidolphPromax 1020) equipped with incubator (HeidolphInkubator 1000). After cooling, crude product was isolated and purified by column chromatography (ethyl acetate/hexanes). The ^{1}H NMR data were in accordance with those recorded for racemates;(*S*)-(-)-**2f**: $[\alpha]_D^{20}$= −59.5 (*c* 1.5, $CHCl_3$); Lit (*R*) enantiomer: $[\alpha]_D^{20}$ = +23.1 (c 1.0, $CHCl_3$).[12]

Racemization of ethyl (S)-3-hydroxy-3-(4-nitrophenyl)propanoate ((S)-2a)

To the solution of ester (*S*)-**2a** (0.1 mmol) in TBME (2 mL) were added (see Table 4 in main Text);triethylorthobenzoate (2 mmol), enzyme (native 5 mg or immobilized 10 mg) and metal catalyst (10 mol%) were added in 5mL vial. The reaction mixture was stirred for 24 hours at 40°C in vortex mixture (HeidolphPromax 1020) equipped with incubator (HeidolphInkubator 1000). After cooling, crude product was purified by column chromatography (ethyl acetate/hexanes) and analysed on HPLC: Chiralcel IA; hexane/isopropanol (9:1), retention time of the racemic compound (in min): t_R (*S*) = 14.65, t_R (*R*) =16.00.

Synthesis ethyl (*S*)-3-hydroxy-3-(4-nitrophenyl)propanoate- preparative scale

To the solution of acid **1a**(212 mg, 1 mmol) in TBME (20 mL), triethylorthobenzoate (2 mmol), Amano AK (50 mg) and rhodium(II) acetate (10 mol%) was stirred for 72 hours at 40°C in vortex mixture (HeidolphPromax 1020) equipped with incubator (HeidolphInkubator 1000). Enzyme and catalyst were separated by filtration and washed with ethyl acetate. Combined organic phases were evaporated in vacuum and purified by column chromatography (ethyl acetate/hexanes). Product (*S*)-**2a** was obtained with 94% yield (225 mg) as a yellow oil.

Synthesis ethyl (*R*)-3-hydroxy-3-(2,4-nitrophenyl)propanoate- preparative scale

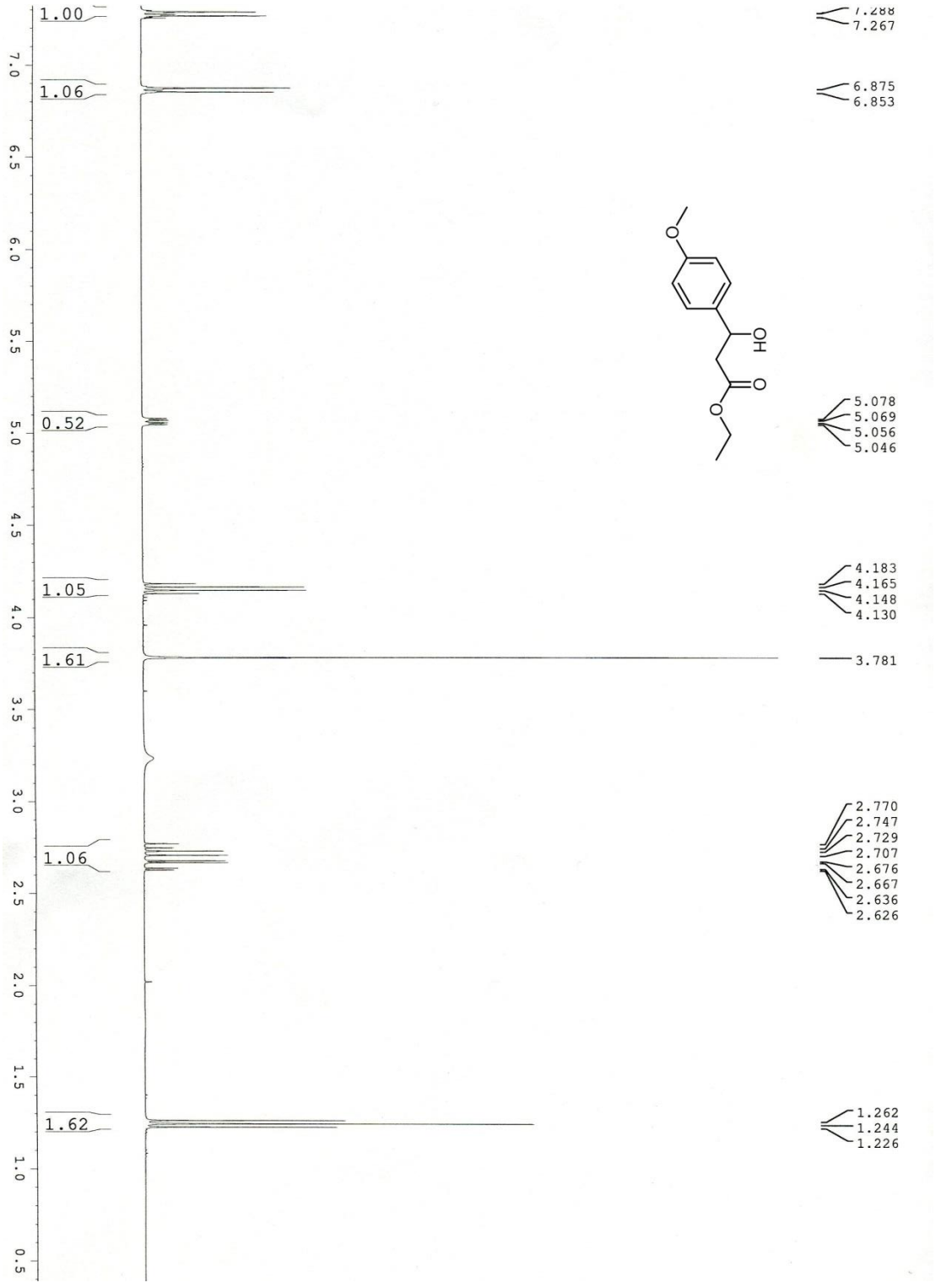
To the solution of acid **1c** (200 mg, 0.8mmol) in organic solvent (20 mL), triethylorthobenzoate (2 mmol), Novozyme 435 (90 mg) and rhodium(II) acetate (10 mol%) was stirred for 72 hours at 40°C in vortex mixture (HeidolphPromax 1020) equipped with incubator (HeidolphInkubator 1000). Enzyme and catalyst were separated by filtration and washed with ethyl acetate. Combined organic phases were evaporated in vacuum and purified by column chromatography (ethyl acetate/hexanes). Product (*S*)-**2c** was obtained with 98% yield (228 mg) as a yellow oil.

Synthesis ethyl (*R*)-3-hydroxy-3-(phenyl)propanoate- preparative scale

To the solution of acid **1i** (200 mg, 1.2mmol) in organic solvent (20 mL), triethylorthobenzoate (2 mmol), Novozyme 435 (100 mg) and rhodium(II) acetate (10 mol%) was stirred for 72 hours at 40°C in vortex mixture (HeidolphPromax 1020) equipped with incubator (HeidolphInkubator 1000). Enzyme and catalyst were separated by filtration and washed with ethyl acetate. Combined organic phases were evaporated in vacuum and purified by column chromatography (ethyl acetate/hexanes). Product (*S*)-**2i** was obtained with 98% yield (246 mg) as a colourless oil.

[10]Brem, J.;Naghi, M.;Tosa, M. –I.;Boros, Z.; Poppe, L.;Irimie, F, -D.; Paizs, C. *Tetrahedron: Asymmetry***2011**, *22*, 1672-1679.
[11]Kitanosono, T.; Xu, P.; Kobayashi, S. *Chem. Asian J*. **2014**, *9*, 179-188.
[12]Xu, Ch.; Yuan, Ch. *Tetrahedron* **2005**, *61*, 2169-2186.

- **^{1}H and ^{13}C NMR spectra for 1a-i and 2a-i:**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1.06
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7.288
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6.875
6.853
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5.069
5.056
5.046
4.183
4.165
4.148
4.130
3.781
2.770
2.747
2.729
2.707
2.676
2.667
2.636
2.626
1.262
1.244
1.226
OH
O
O
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

200
180
160
140
120
100
80
60
40
20
0
ppm
OH
O
O
O
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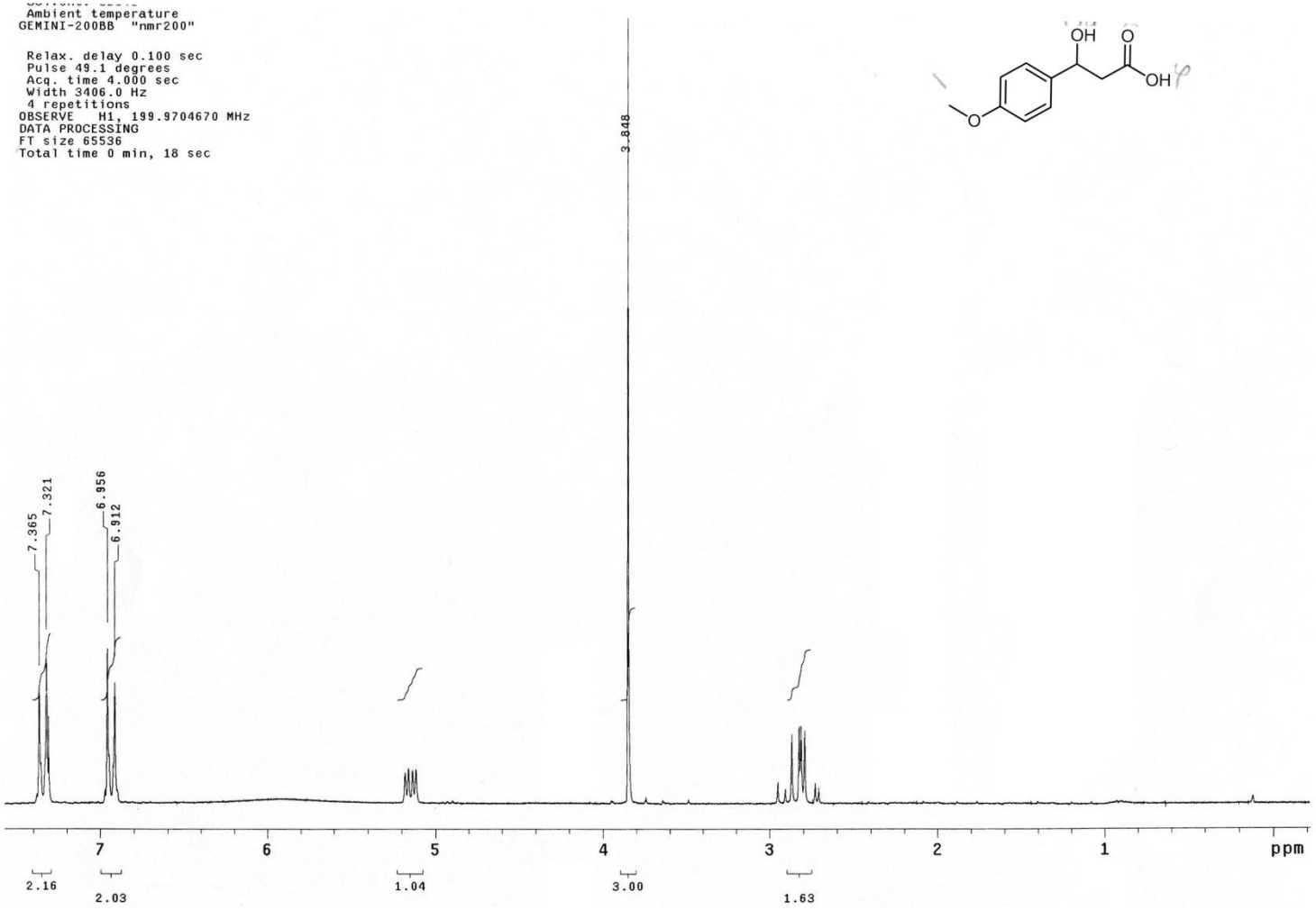
134.81
77.36
77.05
76.73
69.95
60.77
55.25
43.37
14.12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Width 3406.0 Hz
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OH
O
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7.321
6.956
6.912
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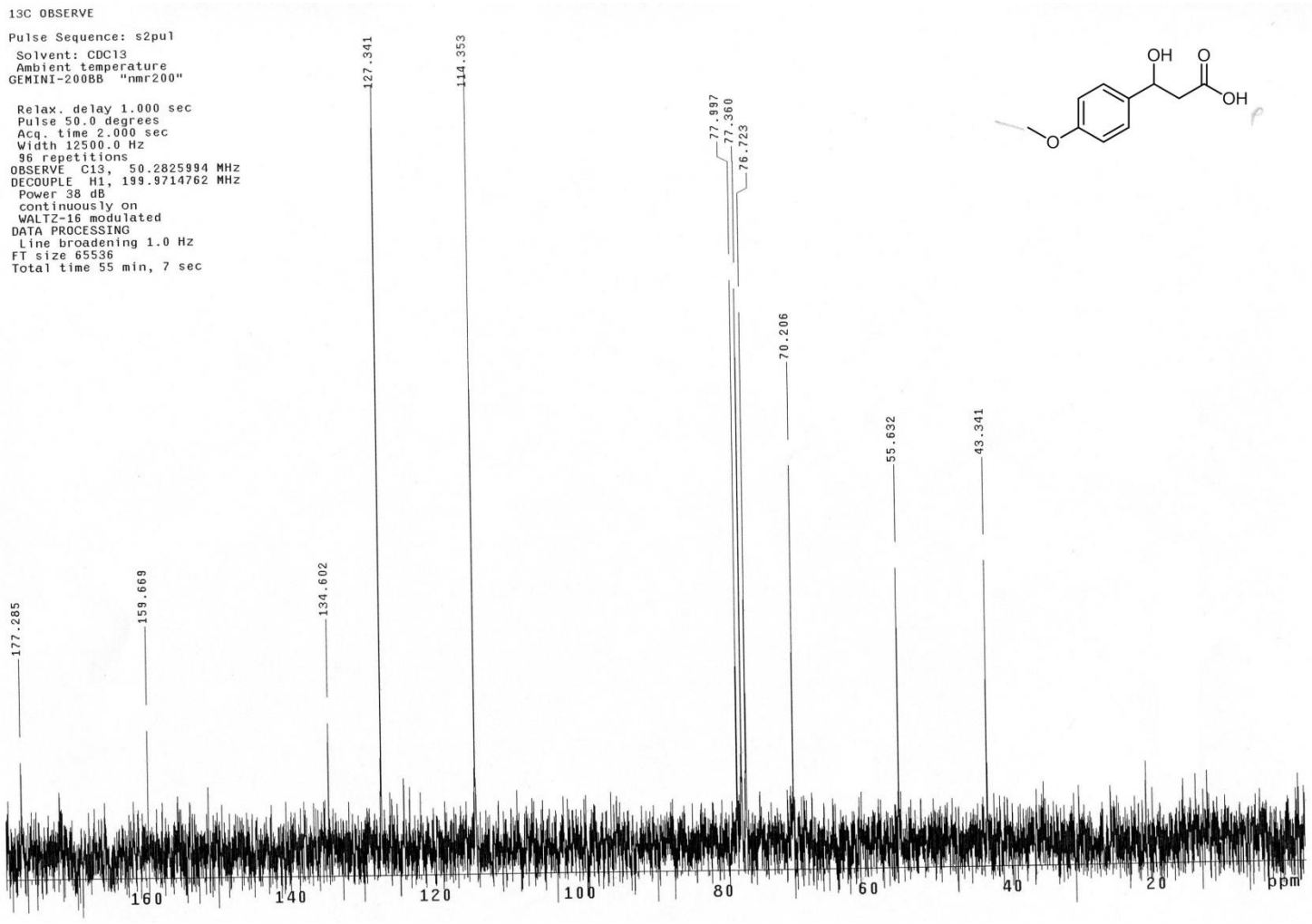
7
6
5
4
3
2
1
ppm
2.16
2.03
1.04
3.00
1.63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Pulse 50.0 degrees
Acq. time 2.000 sec
Width 12500.0 Hz
96 repetitions
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DECOUPLE H1, 199.9714762 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 55 min, 7 sec
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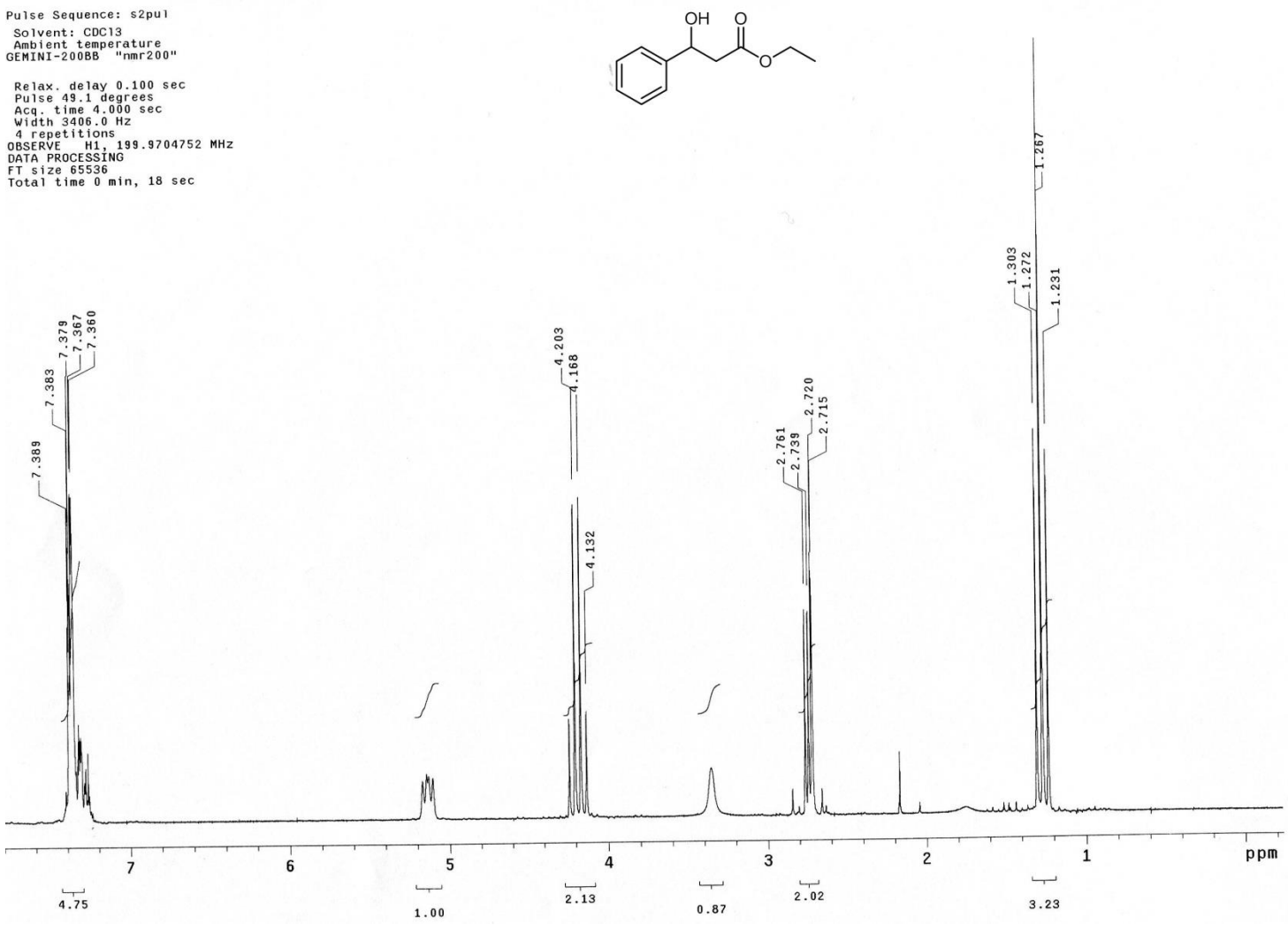
159.669
134.602
127.341
114.353
77.997
77.360
76.723
70.206
55.632
43.341
OH
O
OH
O
160
140
120
100
80
60
40
20
ppm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Solvent: CDCl3
Ambient temperature
GEMINI-200BB "nmr200"
Relax. delay 0.100 sec
Pulse 49.1 degrees
Acq. time 4.000 sec
Width 3406.0 Hz
4 repetitions
OBSERVE H1, 199.9704752 MHz
DATA PROCESSING
FT size 65536
Total time 0 min, 18 sec
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O
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7.383
7.379
7.367
7.360
4.203
4.168
4.132
2.761
2.739
2.720
2.715
1.303
1.272
1.267
1.231
7
6
5
4
3
2
1
ppm
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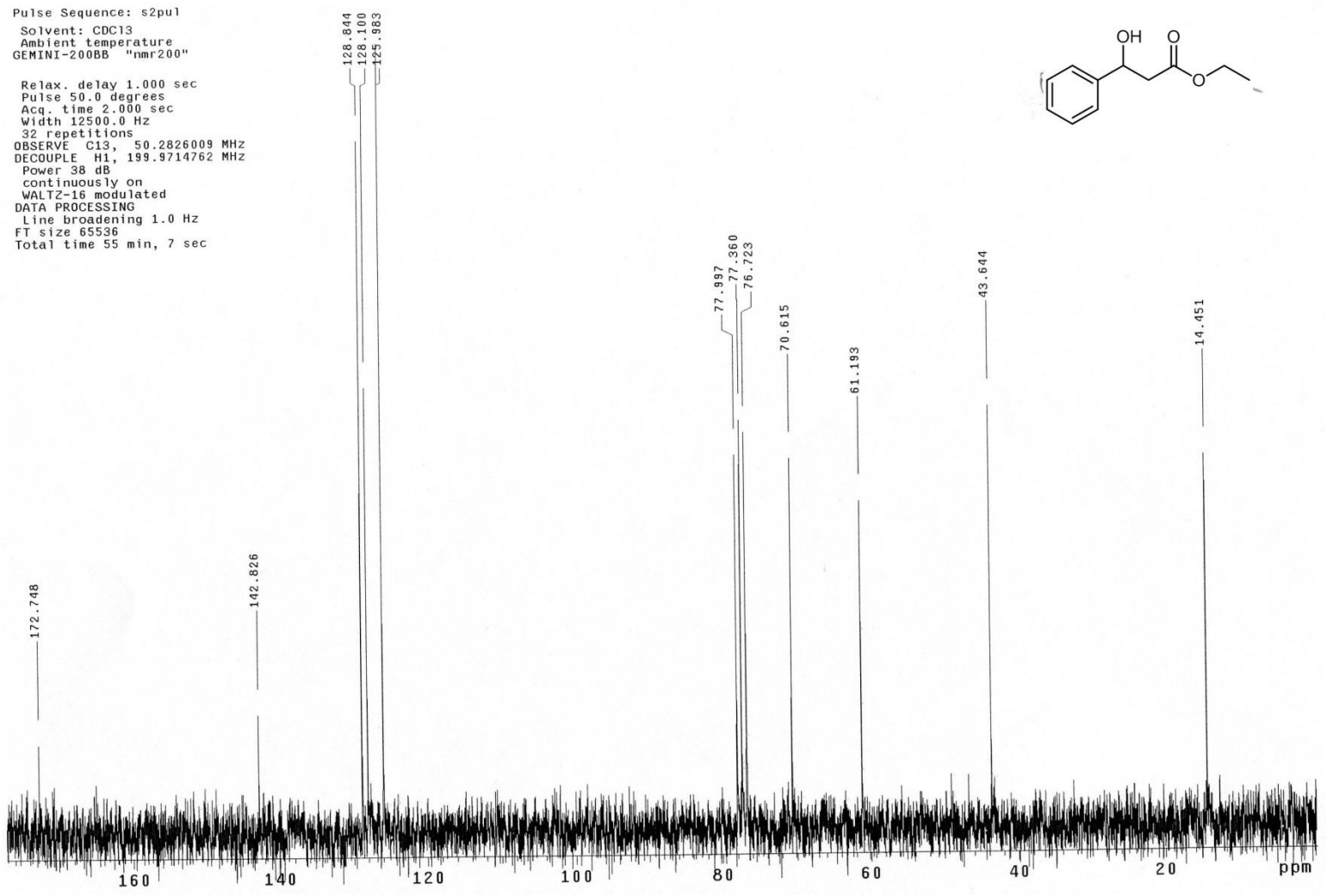
1.00
2.13
0.87
2.02
3.23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Ambient temperature
GEMINI-200BB "nmr200"
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Pulse 50.0 degrees
Acq. time 2.000 sec
Width 12500.0 Hz
32 repetitions
OBSERVE C13, 50.2826009 MHz
DECOUPLE H1, 199.9714762 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 55 min, 7 sec
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128.100
125.983
77.997
77.360
76.723
70.615
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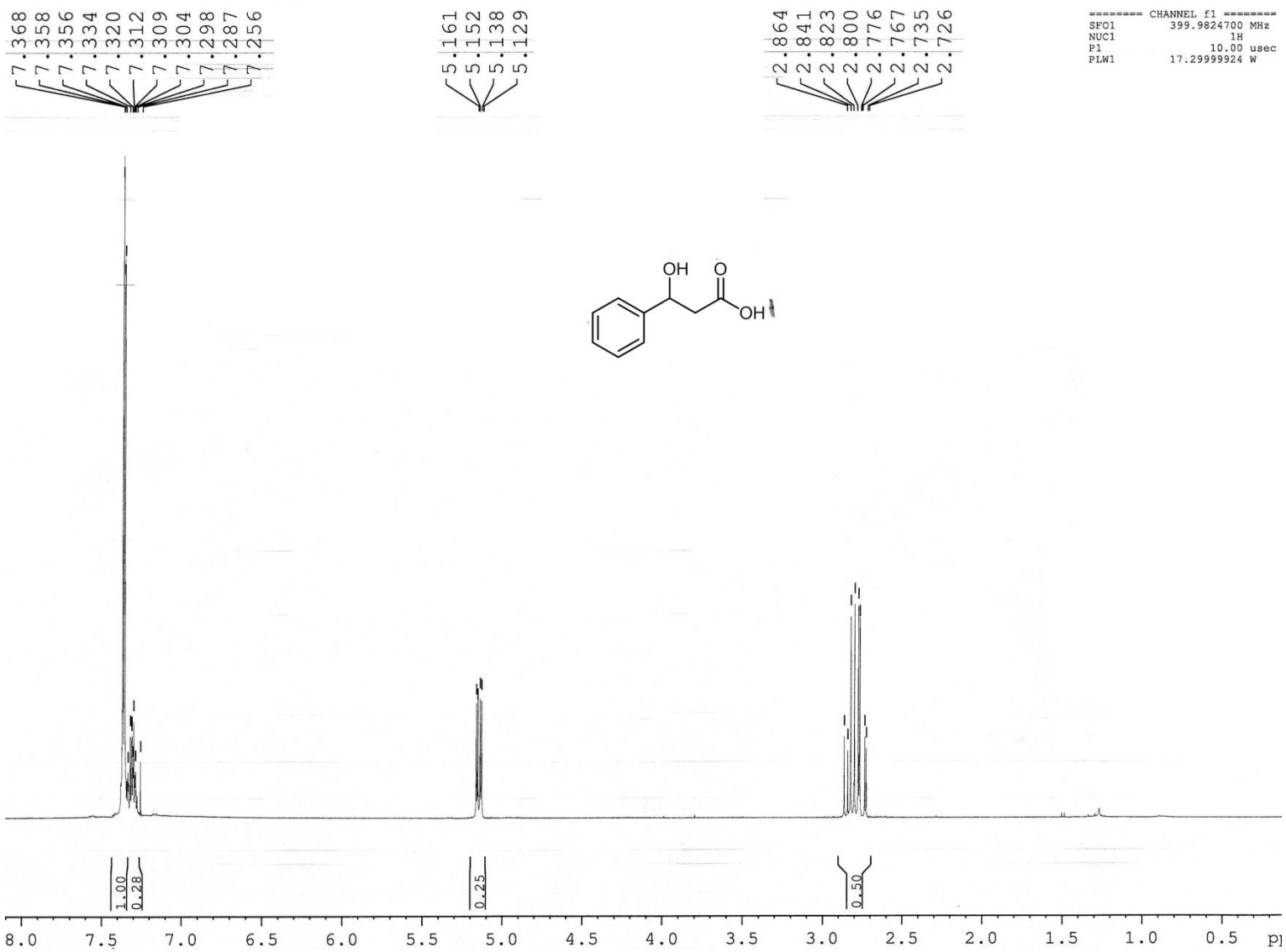
172.748
142.826
OH
O
O
160
140
120
100
80
60
40
20
ppm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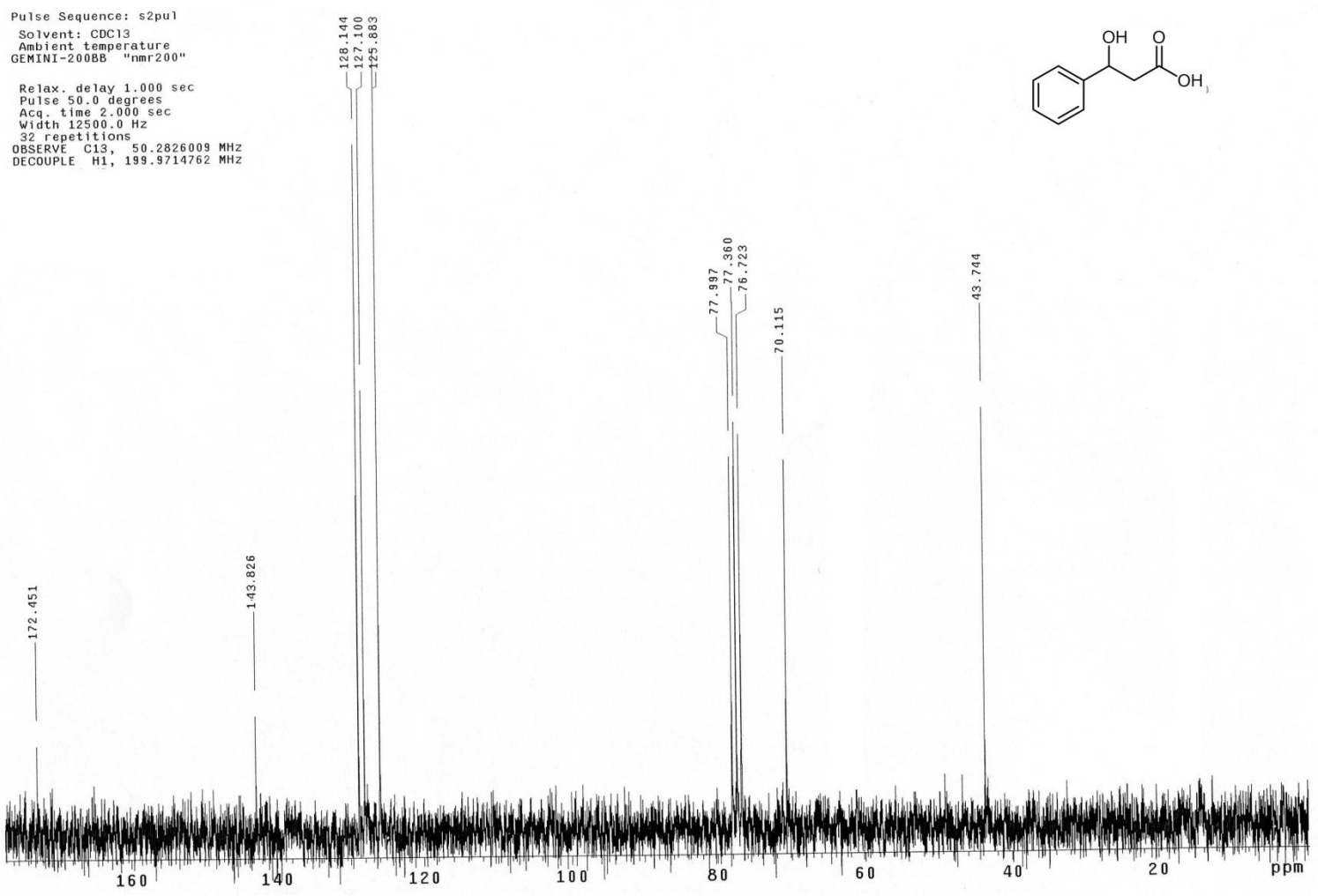
7.256
5.161
5.152
5.138
5.129
2.864
2.841
2.823
2.800
2.776
2.767
2.735
2.726
======== CHANNEL f1 ========
SFO1 399.9824700 MHz
NUC1 1H
P1 10.00 usec
PLW1 17.29999924 W
OH
O
OH
1.00
0.28
0.25
0.50
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
p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Solvent: CDCl3
Ambient temperature
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Relax. delay 1.000 sec
Pulse 50.0 degrees
Acq. time 2.000 sec
Width 12500.0 Hz
32 repetitions
OBSERVE C13, 50.2826009 MHz
DECOUPLE H1, 199.9714762 MHz
128.144
127.100
125.883
77.997
77.360
76.723
70.115
43.744
172.451
143.826
OH
O
OH
160
140
120
100
80
60
40
20
ppm

7.108
7.092
7.089
7.073
7.070
6.975
6.972
6.955
6.952
6.949
6.946
6.928
6.925
5.356
5.348
5.334
5.325
4.144
4.126
4.108
4.091
3.392
2.756
2.747
2.715
2.706
2.676
2.654
2.635
2.612
1.210
1.192
1.174
1.00
1.21
1.01
1.01
0.98
2.03
0.86
2.13
3.29
F
OH
O
OEt
ppm

172.39
160.69
158.25
129.39
129.16
129.07
127.24
127.20
124.36
124.32
115.33
115.12
64.62
64.59
60.92
41.87
41.86
14.10
F
OH
O
OEt
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
GEMINI-200BB "nmr200"

Relax. delay 0.100 sec
Pulse 49.1 degrees
Acq. time 4.000 sec
Width 3406.0 Hz
4 repetitions
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DATA PROCESSING
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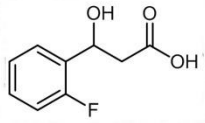
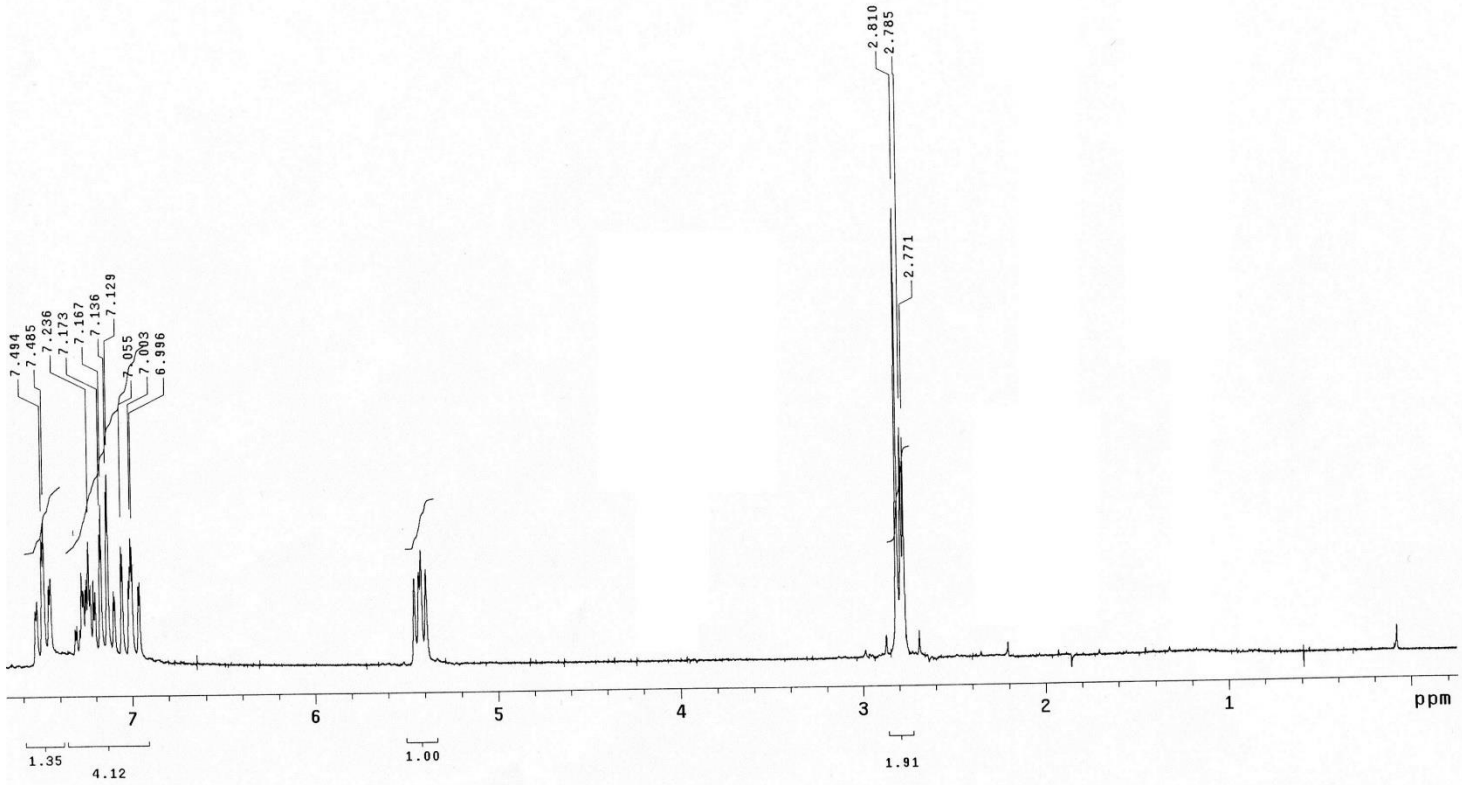
Total time 0 min, 18 sec





Ambient temperature
GEMINI-200BB "nmr200"
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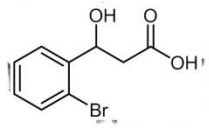
Pulse 50.0 degrees
Acq. time 2.000 sec
Width 12500.0 Hz
48 repetitions
OBSERVE C13, 50.2826017 MHz
DECOUPLE H1, 199.9714762 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 55 min, 7 sec
177.315
162.142
157.256
129.
129.
129.
129.
127.
127.
124.
124.
115.
115.
77.990
77.360
76.723
64.
64.
42.
180
160
140
120
100
80
60
40
20
ppm
F
OH
O
OH

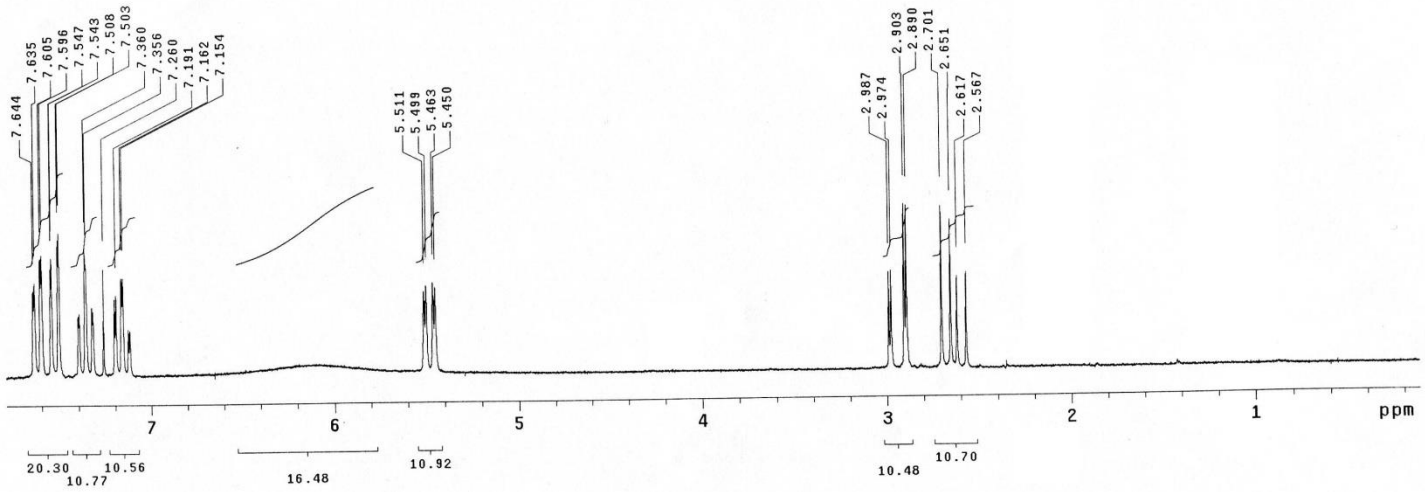

7.369
7.354
7.352
7.350
7.335
7.334
7.332
7.331
7.168
7.164
7.164
7.149
7.145
5.455
5.450
5.431
5.426
4.238
4.220
4.202
4.184
2.900
2.893
2.858
2.852
2.598
2.574
2.557
2.533
1.301
1.283
1.265
0.96
0.95
0.99
0.95
0.94
2.00
1.00
1.00
3.01
Br
OH
O
OEt
ppm

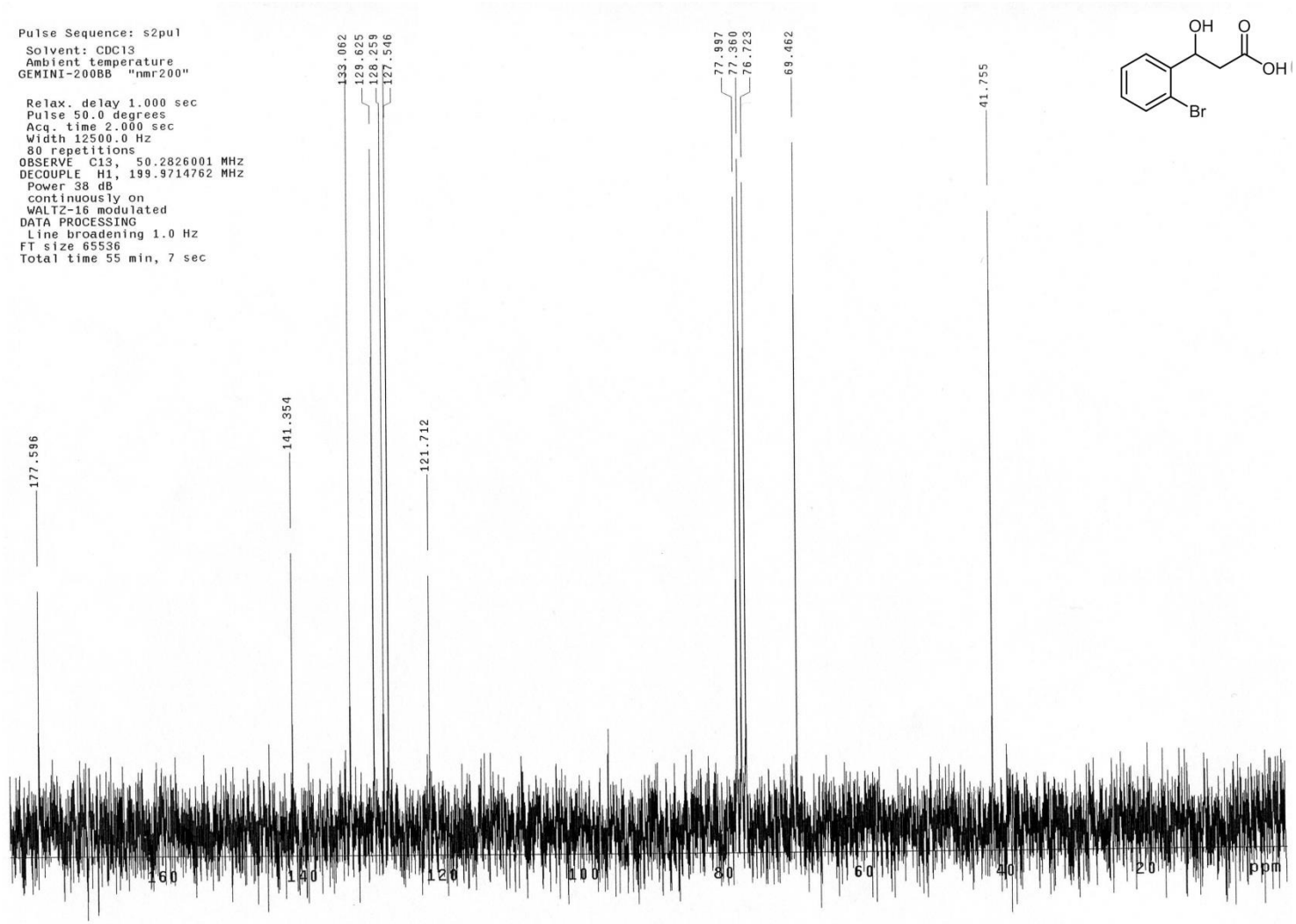
172.45
141.40
132.65
129.07
127.81
127.32
121.42
69.27
60.97
41.47
14.13
Br
OH
O
OEt
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
ppm

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
GEMINI-200BB "nmr200"

Relax. delay 0.100 sec
Pulse 49.1 degrees
Acq. time 4.000 sec
Width 3406.0 Hz
4 repetitions
OBSERVE H1, 199.9704770 MHz
DATA PROCESSING
FT size 65536
Total time 0 min, 18 sec






Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
GEMINI-200BB "nmr200"
Relax. delay 1.000 sec
Pulse 50.0 degrees
Acq. time 2.000 sec
Width 12500.0 Hz
80 repetitions
OBSERVE C13, 50.2826001 MHz
DECOUPLE H1, 199.9714762 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 55 min, 7 sec
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141.354
133.062
129.625
128.259
127.546
121.712
77.997
77.360
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69.462
41.755
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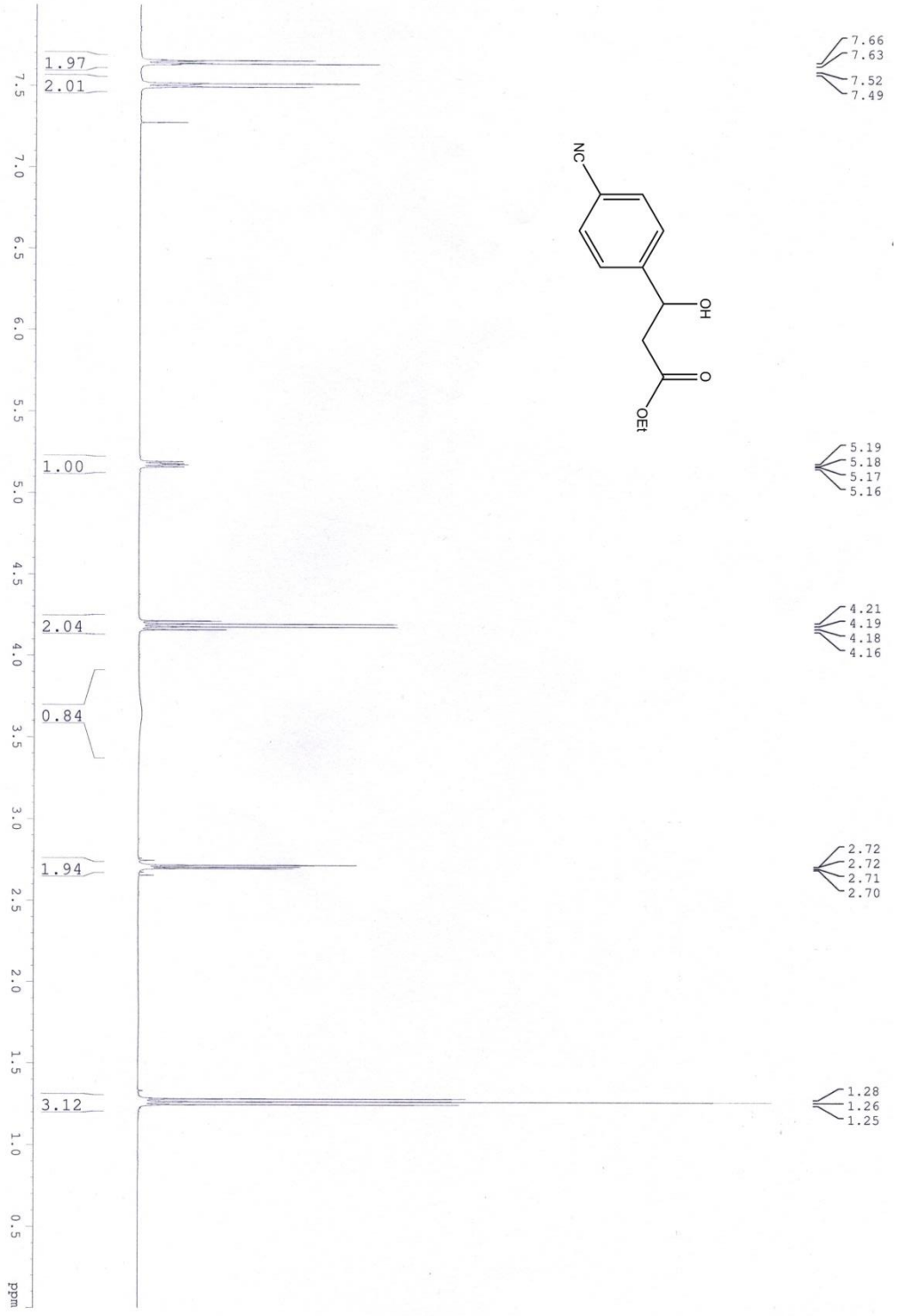
O
OH
Br
160
140
120
100
80
60
40
20
ppm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1.00
2.04
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6.5
6.0
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5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
NC
OH
O
OEt
7.66
7.63
7.52
7.49
5.19
5.18
5.17
5.16
4.21
4.19
4.18
4.16
2.72
2.72
2.71
2.70
1.28
1.26
1.25

180
160
140
120
100
80
60
40
20
ppm
171.93
147.82
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77.04
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OH
O
OEt

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1.94
1.00
2.29
7.77
7.75
7.55
7.53
5.01
5.00
4.99
4.98
2.60
2.59
2.57
2.55
2.53
2.51
2.49
2.48
2.48
2.47
2.47
NC
OH
O
OH
ppm

180
160
140
120
100
80
60
40
20
ppm
171.84
150.62
132.09
126.85
118.89
109.75
68.90
44.01
40.15
39.94
39.74
39.53
39.32
39.11
38.90
NC
OH
O
OH

1.94
1.98
1.00
2.02
0.95
2.05
3.18
8.22
8.20
7.58
7.56
5.25
5.24
5.23
5.22
5.21
4.23
4.21
4.19
4.17
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3.66
2.78
2.75
2.74
2.74
2.72
2.68
1.29
1.27
1.25
O2N
OH
O
OEt
ppm

O2N
OH
O
OEt
171.94
149.68
147.46
126.49
123.75
77.33
77.01
76.69
69.36
61.21
42.91
14.09
200
180
160
140
120
100
80
60
40
20
0
ppm

O2N
OH
O
OH
0.81
1.92
1.95
1.00
1.06
1.78
1.11
8.179
8.157
7.637
7.615
5.070
5.057
5.049
5.036
3.289
2.632
2.619
2.594
2.581
2.552
2.531
2.514
2.493
2.489
2.484
2.480
2.475
2.471
ppm

172.24
153.22
147.03
127.56
123.74
69.17
44.48
O2N
OH
O
OH
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
ppm

1.00
1.08
1.09
1.08
2.06
1.08
1.12
1.13
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8.52
8.51
8.49
8.49
8.21
8.19
7.27
5.78
5.76
4.26
4.24
4.22
4.20
4.02
4.01
3.00
2.99
2.95
2.95
2.68
2.65
2.64
2.61
1.32
1.30
1.28
O2N
NO2
OH
O
OEt
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8.5
8.0
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7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

180
160
140
120
100
80
60
40
20
ppm
171.81
147.23
144.64
130.21
127.69
120.06
77.32
77.00
76.68
65.93
61.48
41.99
14.07
O2N
NO2
OH
O
OEt

12.355
8.739
8.734
8.591
8.585
8.569
8.563
8.154
8.132
6.084
5.565
5.556
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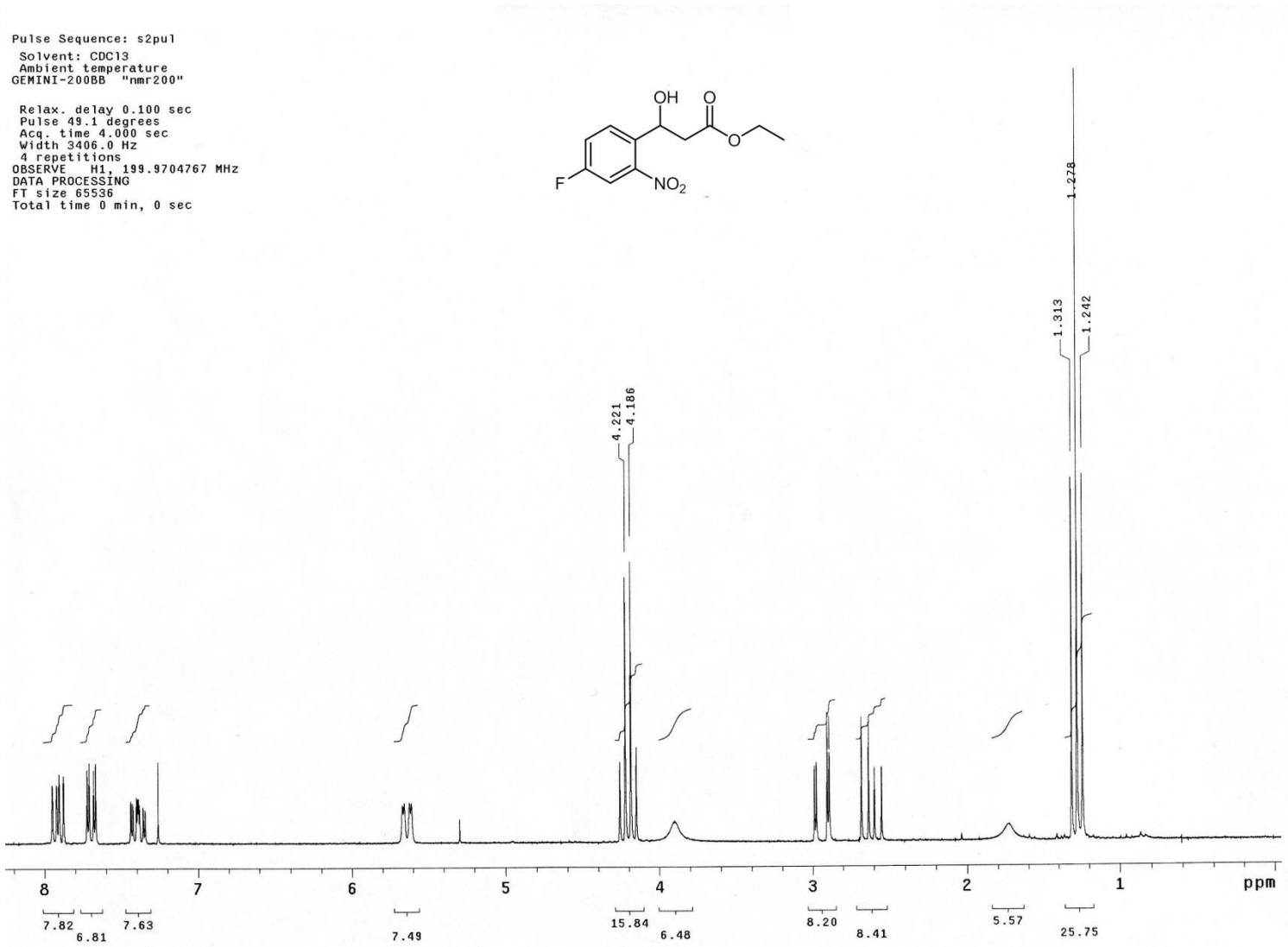
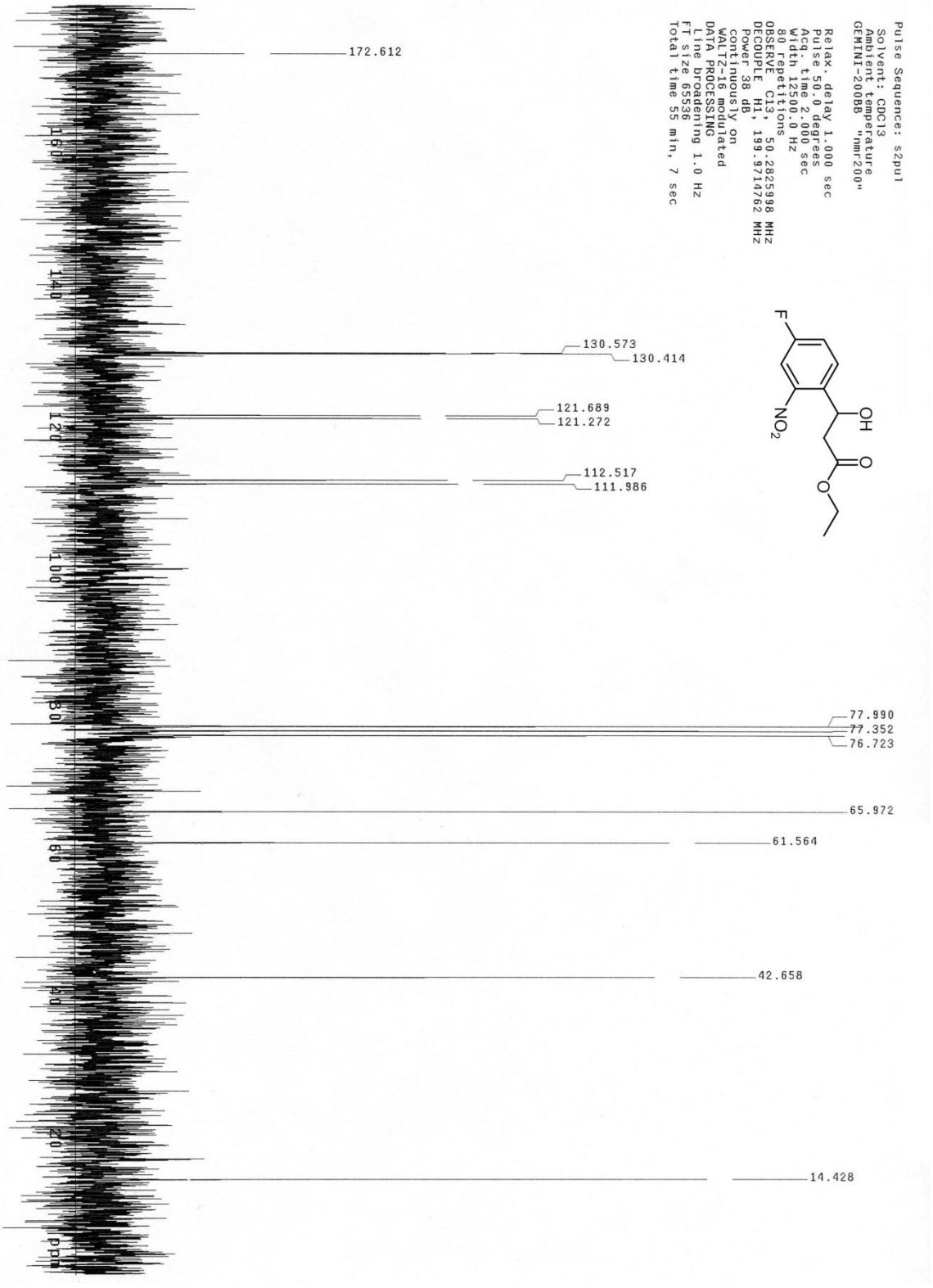
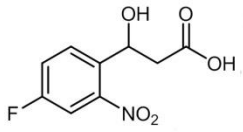
2.730
2.721
2.605
2.583
2.566
2.549
2.544
2.540
2.535
2.531
0.84
0.94
1.01
1.00
0.81
1.00
0.97
0.78
ppm

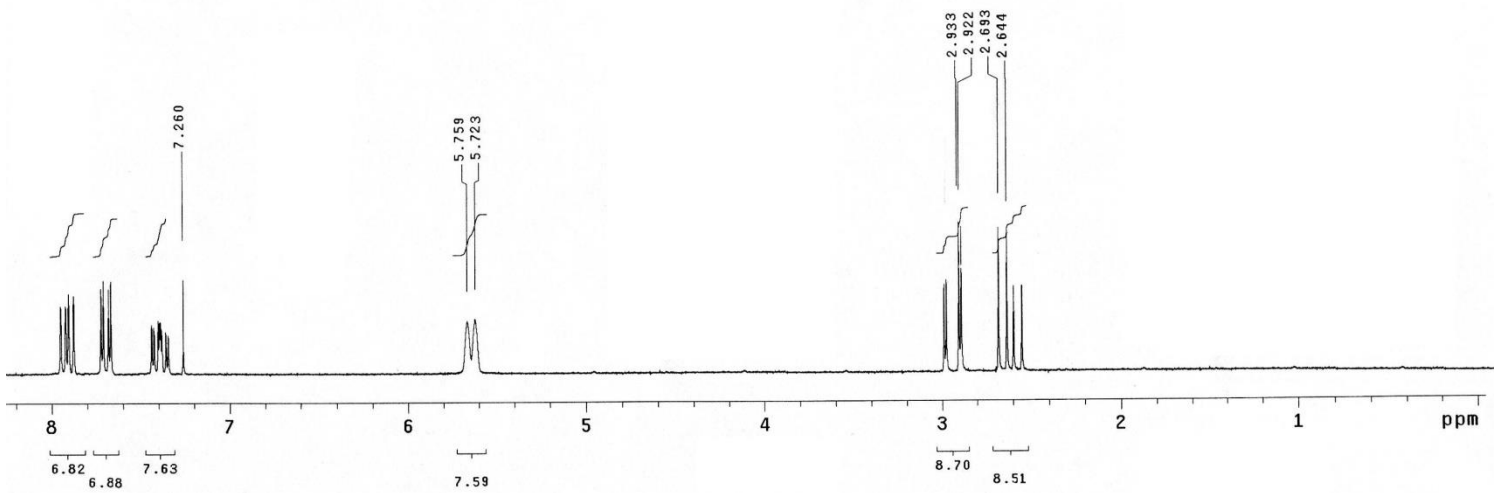
200
180
160
140
120
100
80
60
40
20
0
ppm
172.31
148.09
147.43
147.21
131.33
128.30
120.36
65.99
43.96

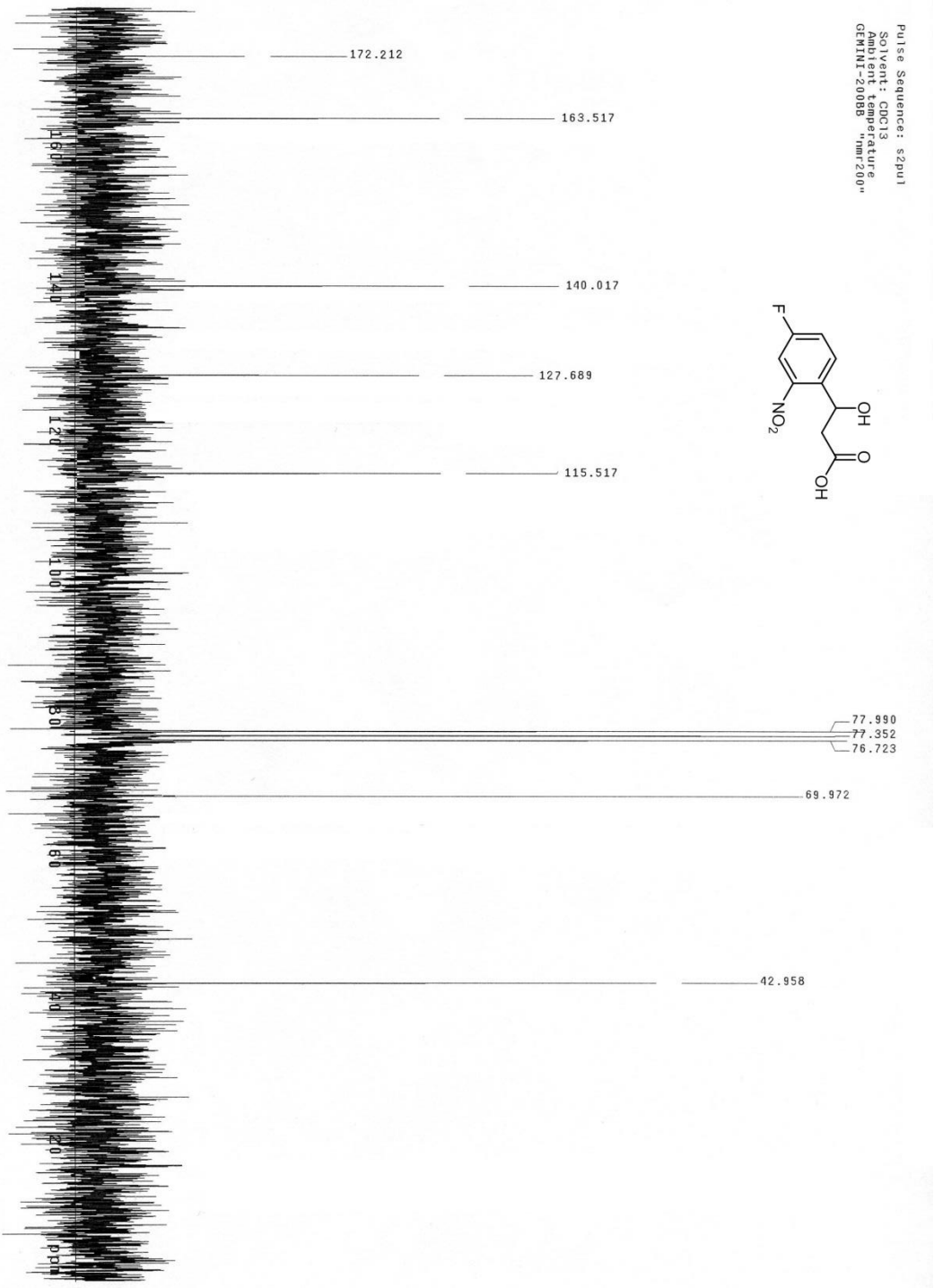

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
GEMINI-200BB "nmr200"
Relax. delay 0.100 sec
Pulse 49.1 degrees
Acq. time 4.000 sec
Width 3406.0 Hz
4 repetitions
OBSERVE H1, 199.9704767 MHz
DATA PROCESSING
FT size 65536
Total time 0 min, 0 sec
OH
O
O
F
NO2
1.278
1.313
1.242
4.221
4.186
8
7
6
5
4
3
2
1
ppm
7.82
6.81
7.63
7.49
15.84
6.48
8.20
8.41
5.57
25.75

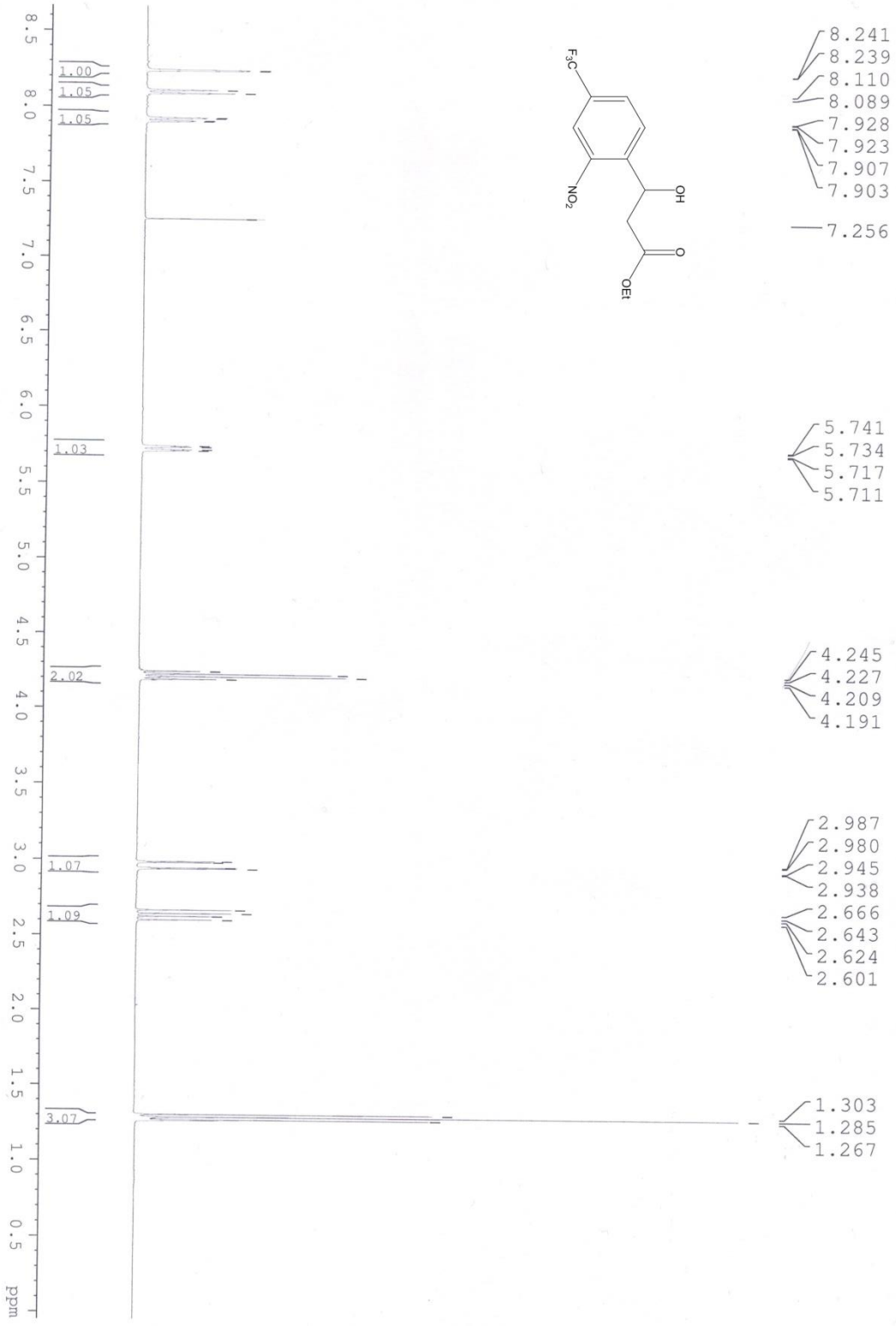

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
GEMINI-200BB "nmr200"
Relax. delay 1.000 sec
Pulse 50.0 degrees
Acq. time 2.000 sec
Width 12500.0 Hz
80 repetitions
OBSERVE C13, 50.2825998 MHz
DECOUPLE H1, 199.9714762 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 55 min, 7 sec
172.612
130.573
130.414
121.689
121.272
112.517
111.986
77.990
77.352
76.723
65.972
61.564
42.658
14.428
F
NO2
OH
O
O
160
140
120
100
80
60
40
20
ppm

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
GEMINI-200BB "nmr200"

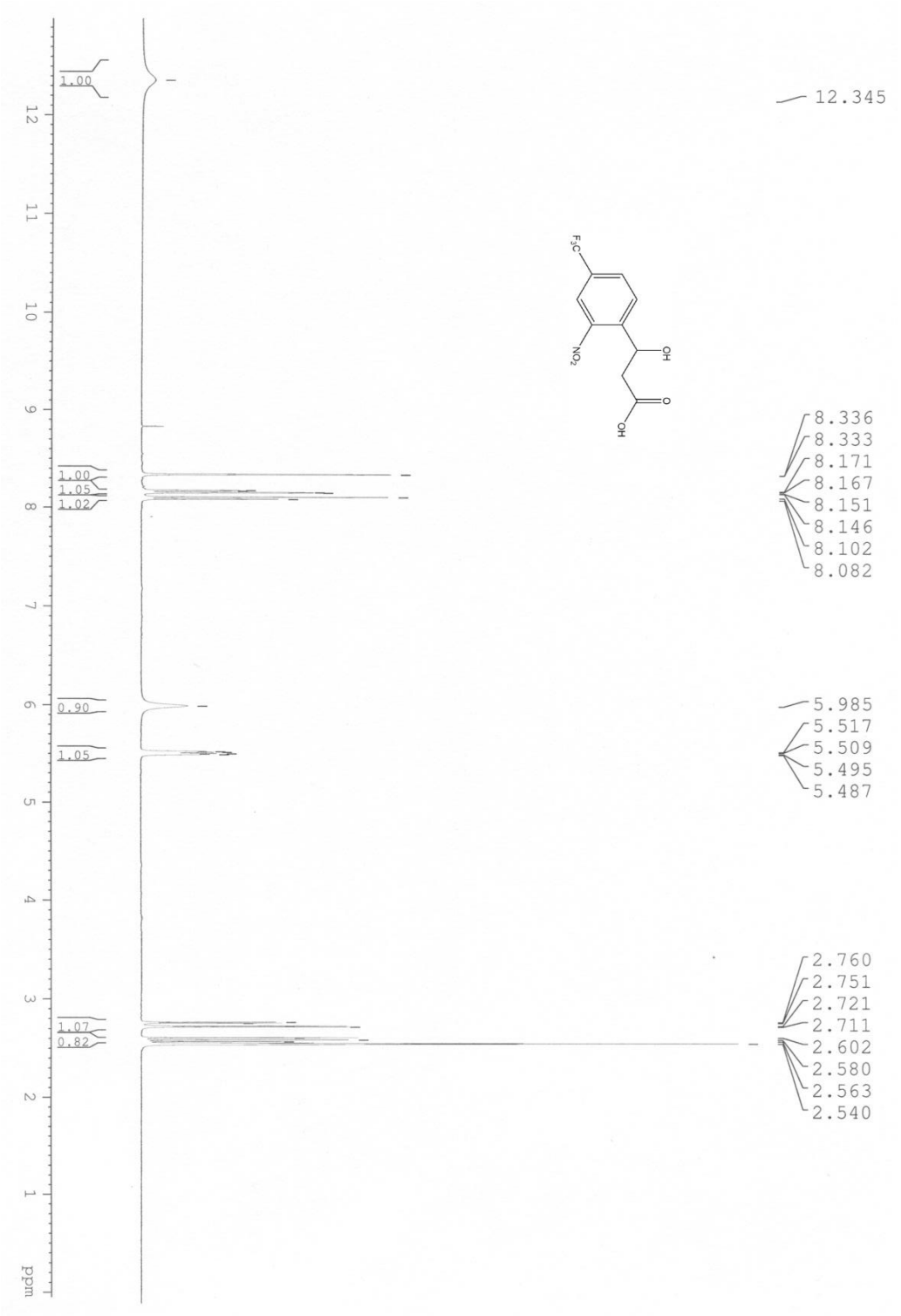


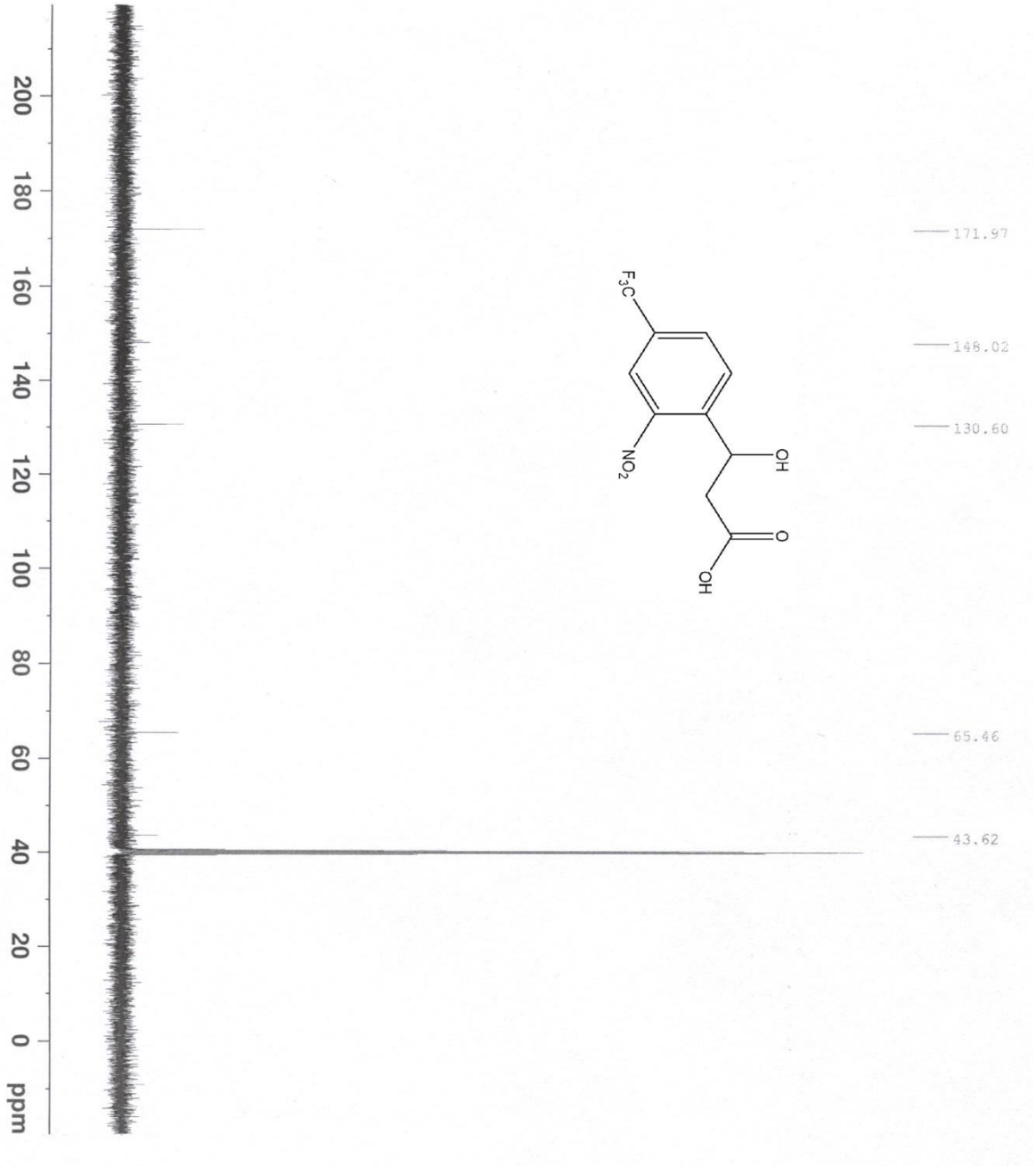



Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
GEMINI-200BB "nmr200"
172.212
163.517
140.017
127.689
115.517
77.990
77.352
76.723
69.972
42.958
F
NO2
OH
O
OH
160
140
120
100
80
60
40
20
ppm

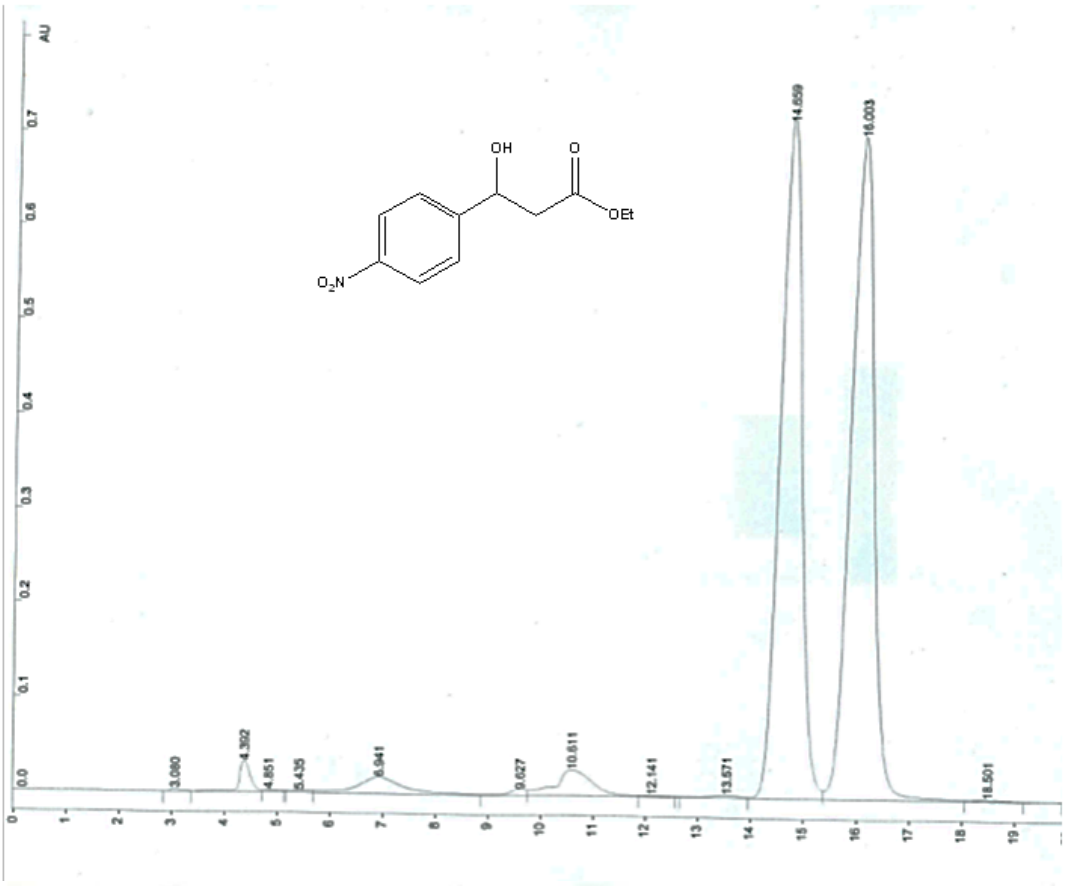

8.241
8.239
8.110
8.089
7.928
7.923
7.907
7.903
7.256
5.741
5.734
5.717
5.711
4.245
4.227
4.209
4.191
2.987
2.980
2.945
2.938
2.666
2.643
2.624
2.601
1.303
1.285
1.267
1.00
1.05
1.05
1.03
2.02
1.07
1.09
3.07
F3C
NO2
OH
O
OEt
ppm

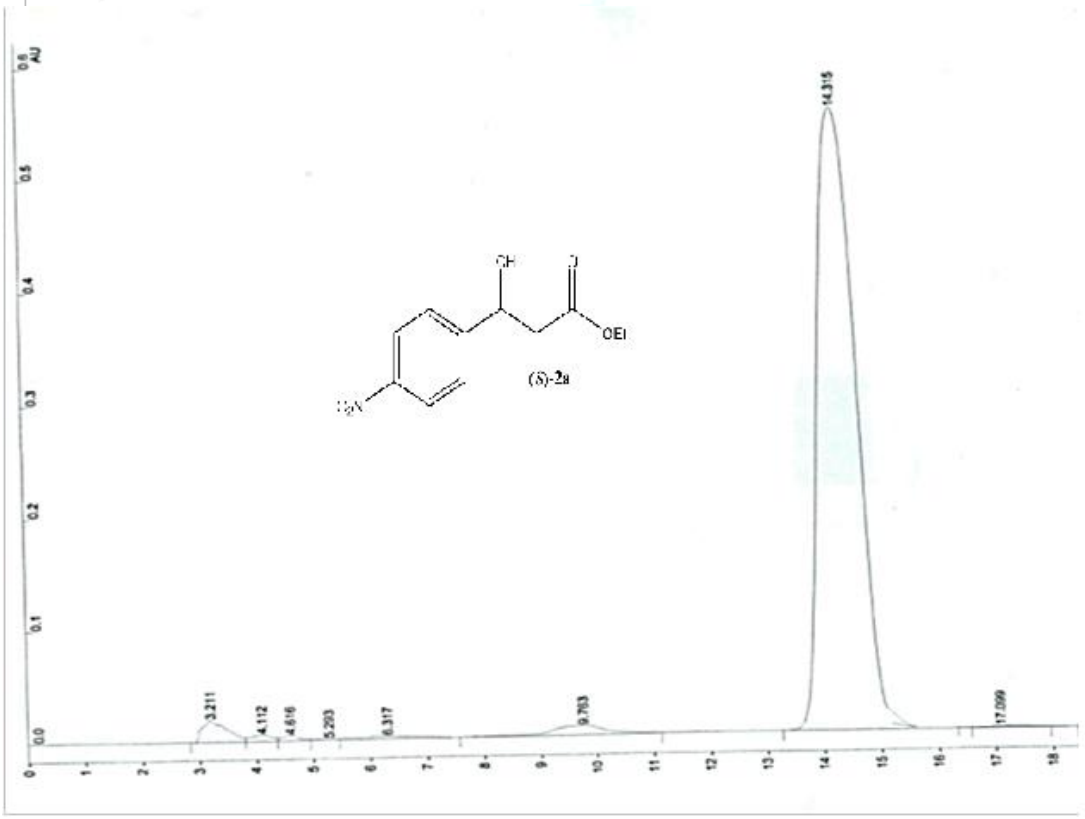
172.030
141.941
131.373
130.169
129.542
121.883
121.840
65.866
61.347
42.102
14.085
F3C
NO2
OH
O
OEt
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

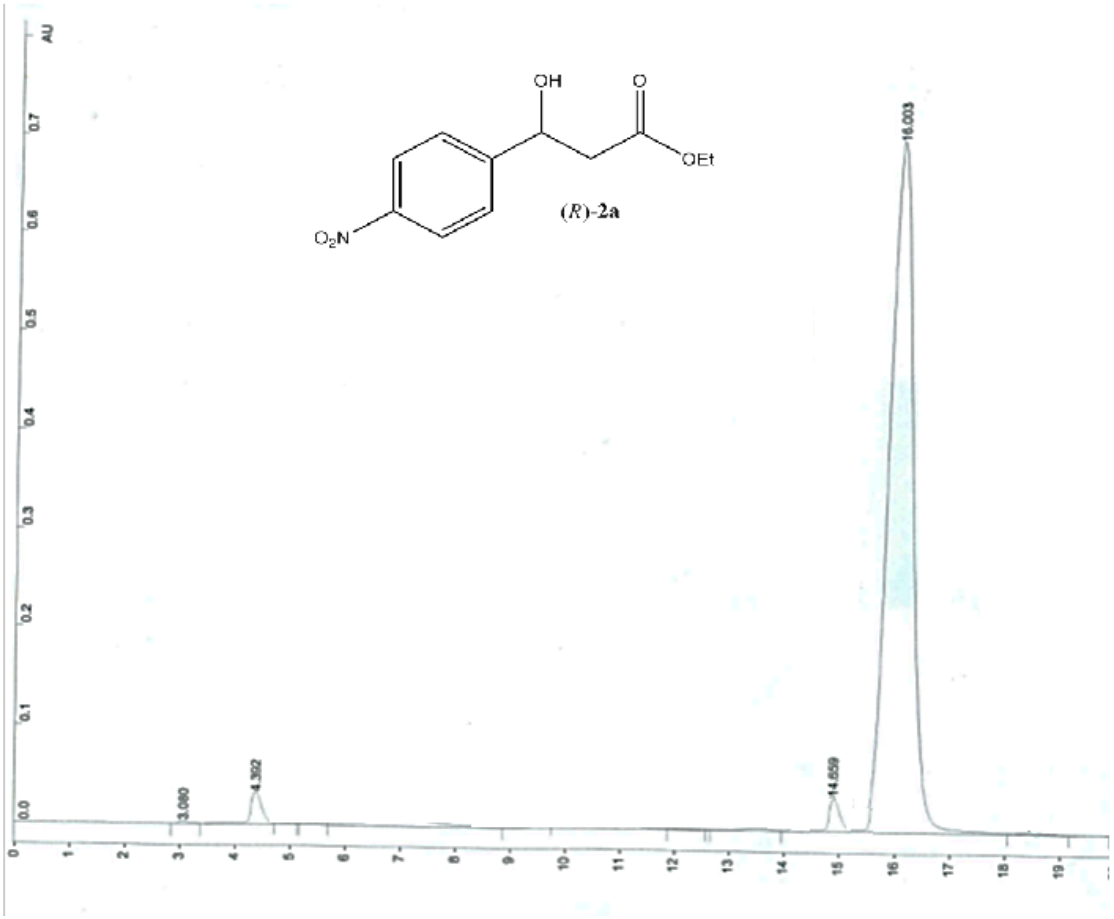

12.345
8.336
8.333
8.171
8.167
8.151
8.146
8.102
8.082
5.985
5.517
5.509
5.495
5.487
2.760
2.751
2.721
2.711
2.602
2.580
2.563
2.540
1.00
1.00
1.05
1.02
0.90
1.05
1.07
0.82
F3C
NO2
OH
O
OH
ppm

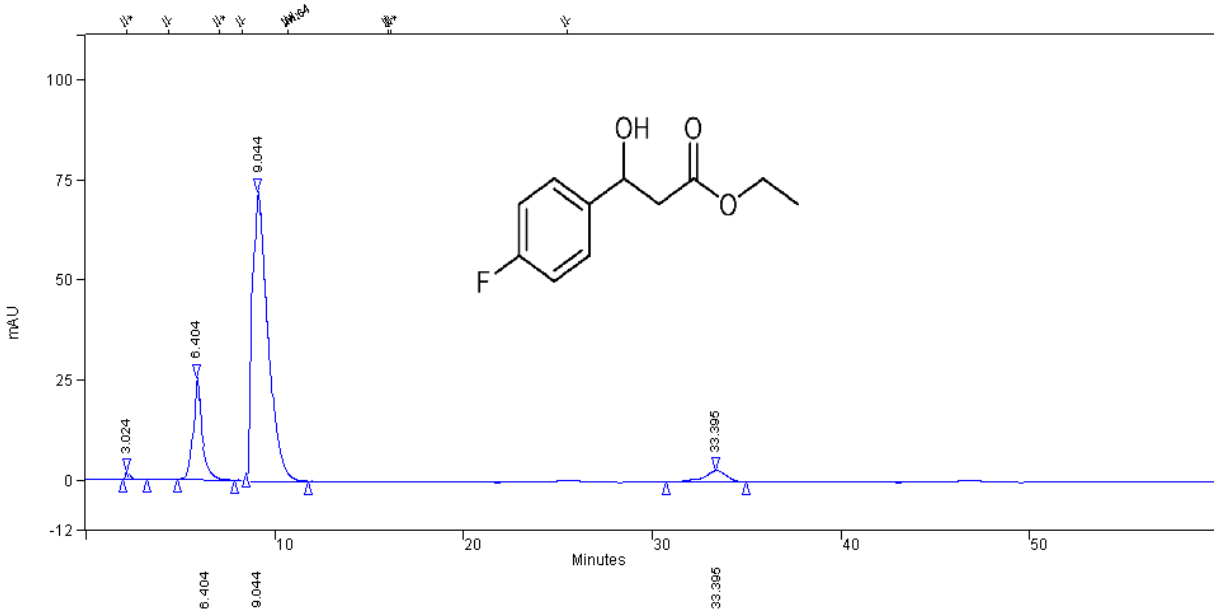


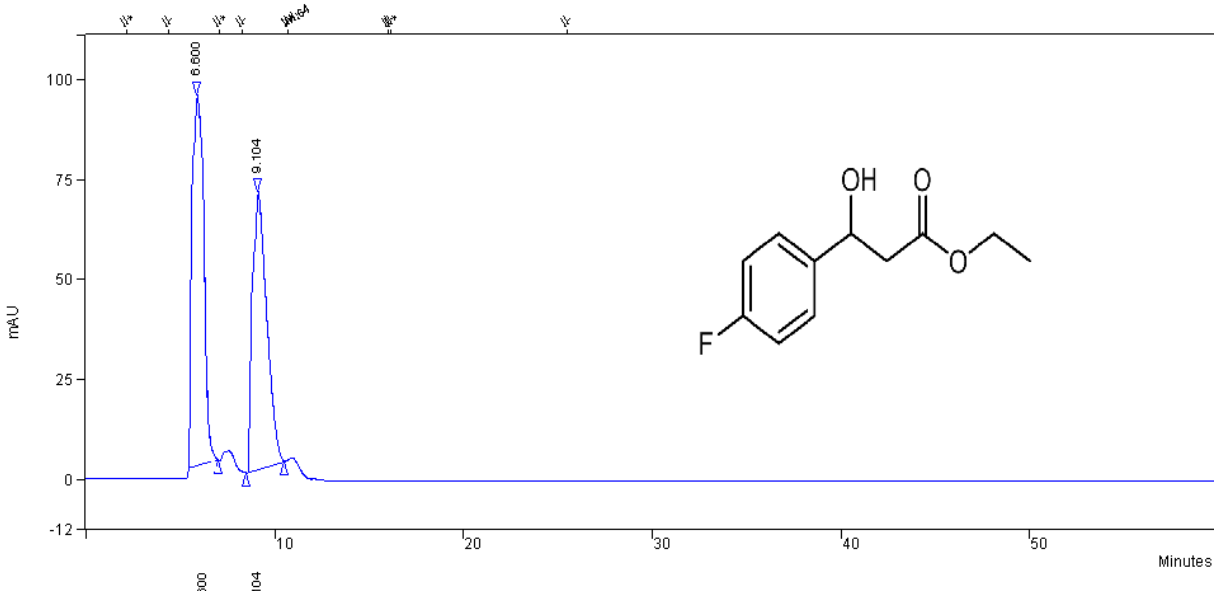
- **HPLC tracers for racemic and enantiomerically enriched esters 2a-i:**


AU
OH
O
OEt
O_2N
14.659
16.003
3.080
4.302
4.851
5.435
6.941
9.027
10.611
12.141
13.571
18.501

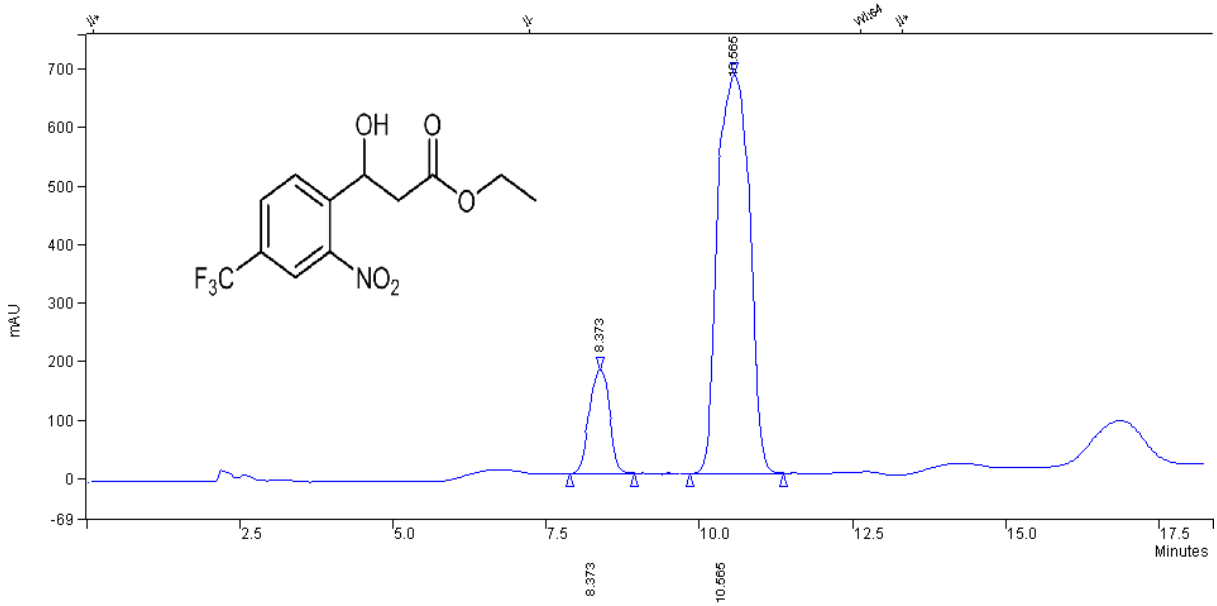

AU
OH
O
OEt
O_2N
(S)-2a
14.315
3.211
4.112
4.616
5.293
6.317
9.763
17.099


AU
OH
O
OEt
O2N
(R)-2a
16.003
14.659
4.392
3.080

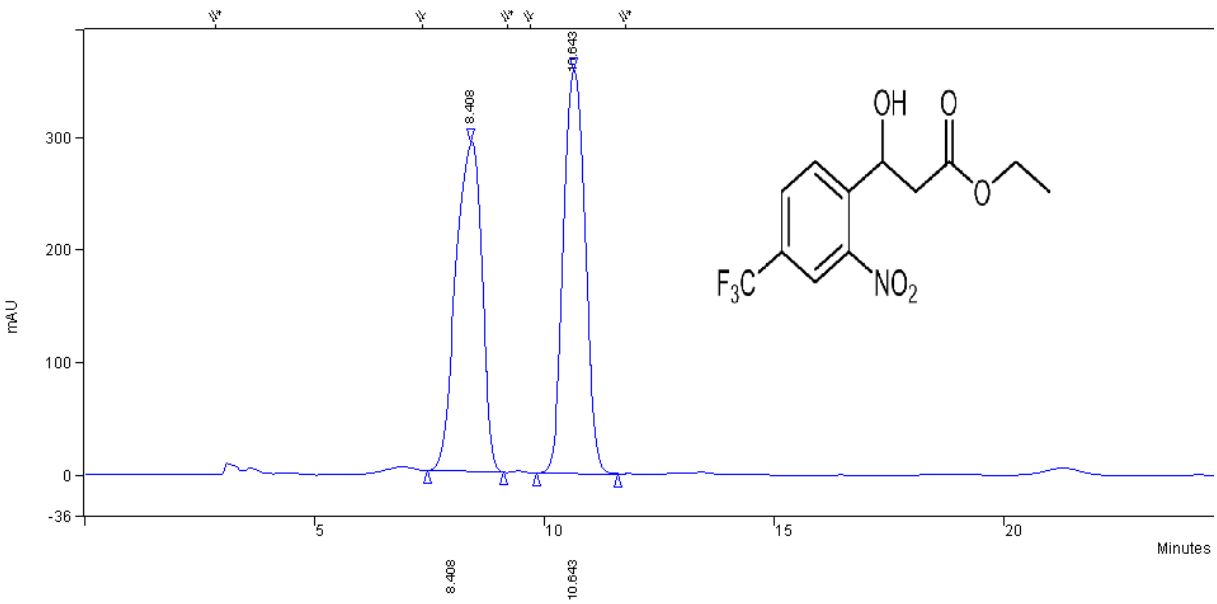

mAU
OH
O
O
F
9.044
6.404
3.024
33.395
Minutes



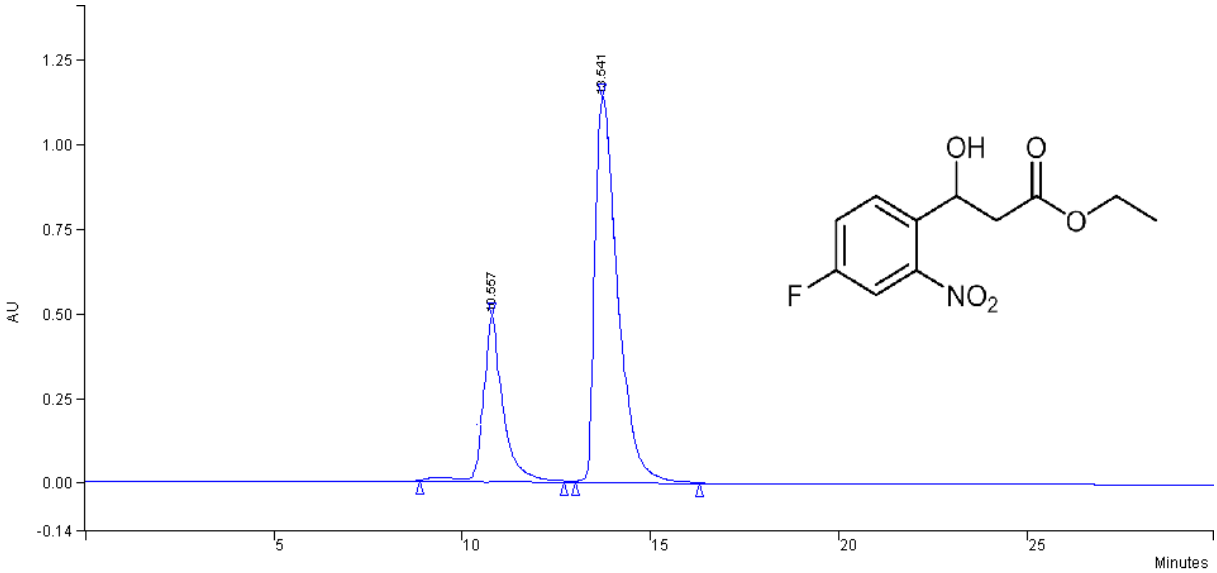
6.600 9.104

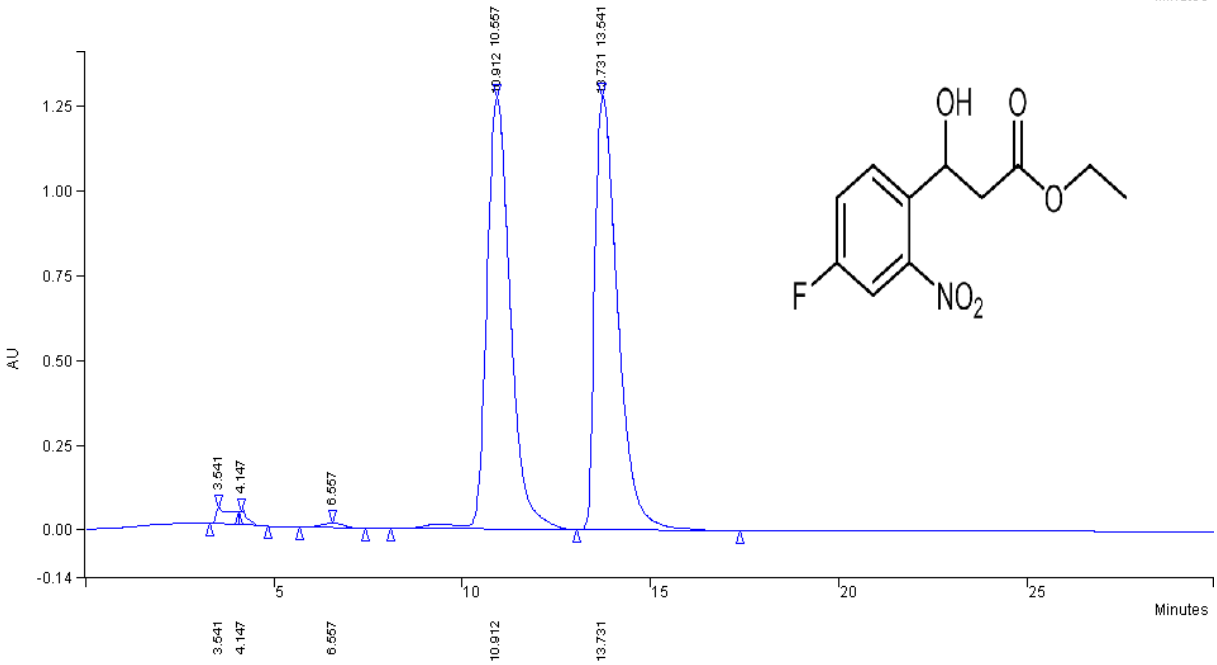


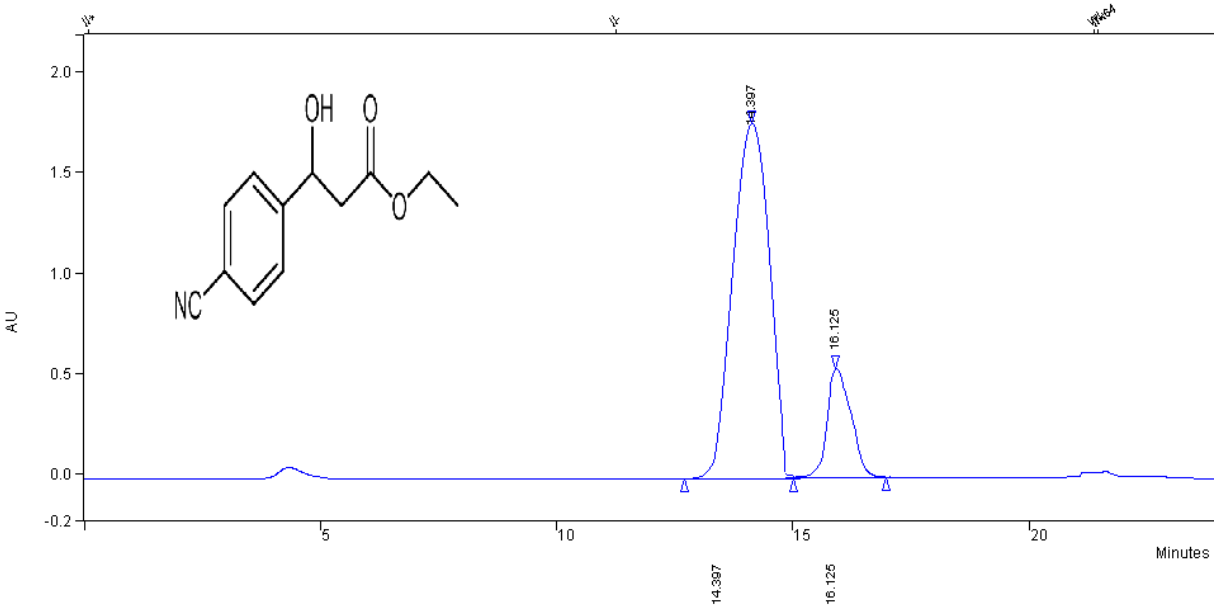
8.373 10.565

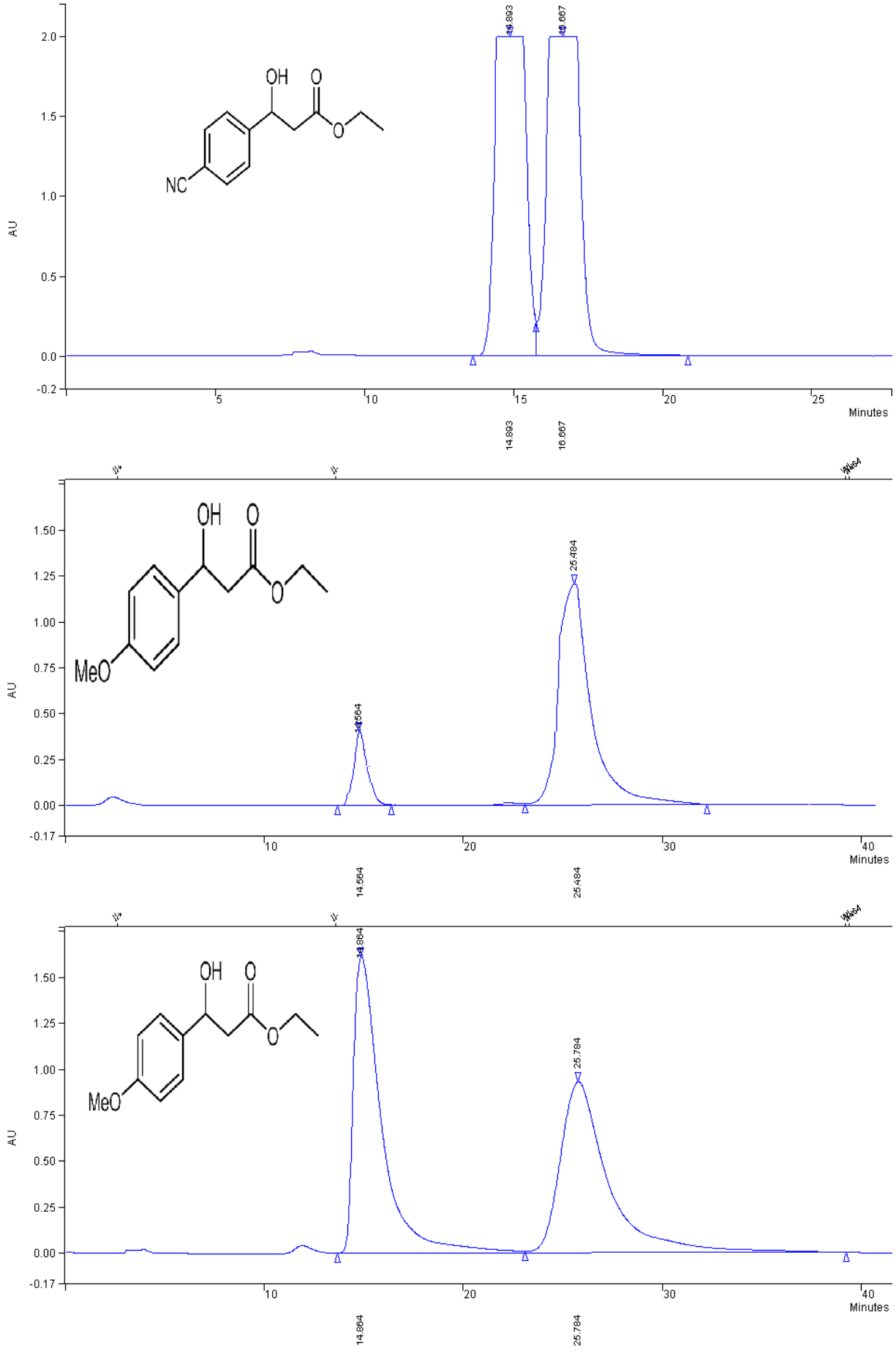


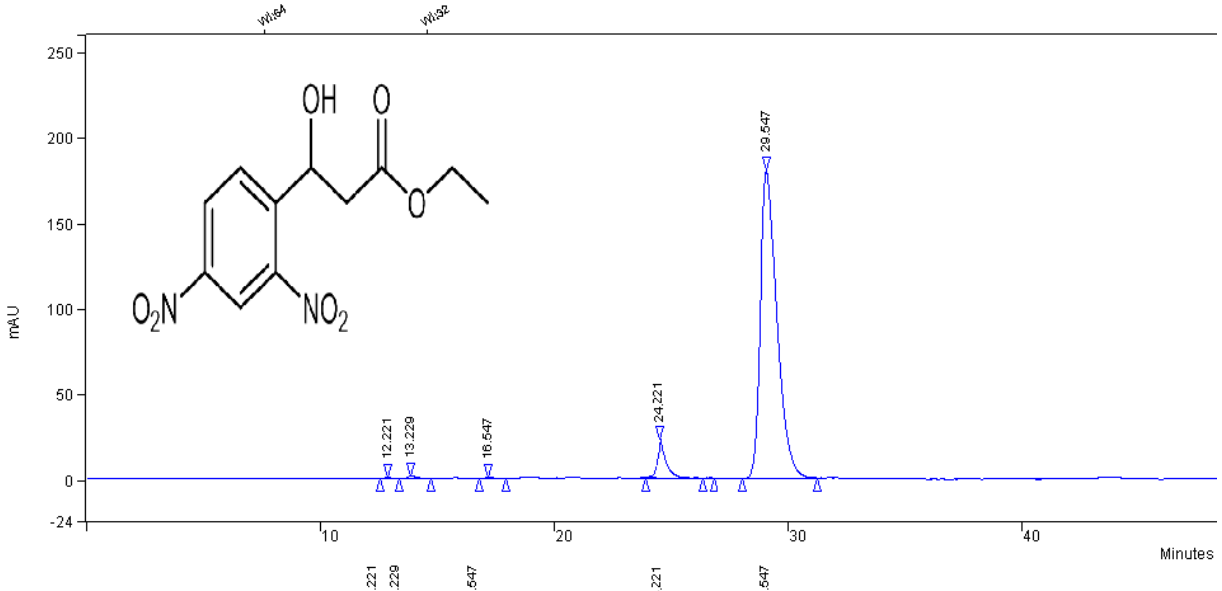
8.408 10.643

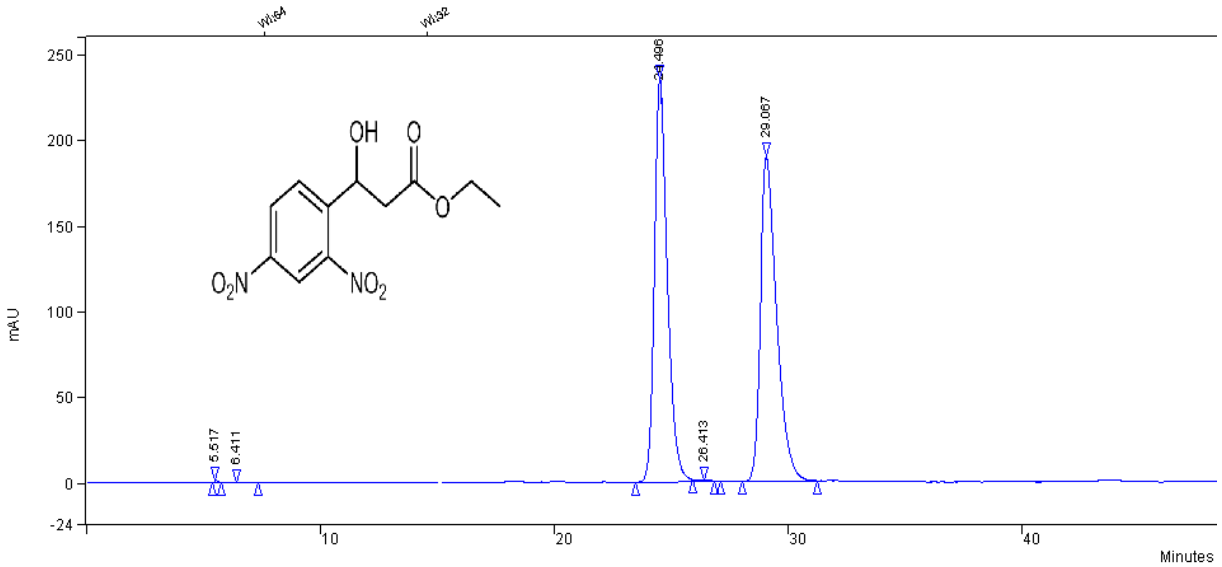

AU
1.25
1.00
0.75
0.50
0.25
0.00
-0.14
5
10
15
20
25
Minutes
10.557
13.541
OH
O
O
F
NO2

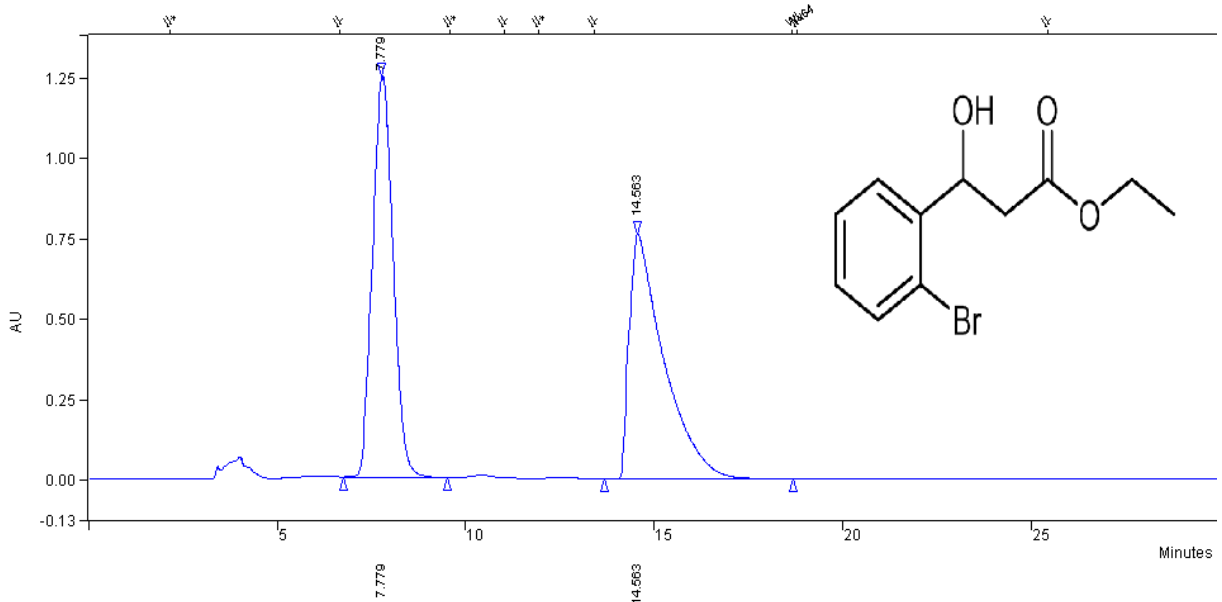

AU
1.25
1.00
0.75
0.50
0.25
0.00
-0.14
5
10
15
20
25
Minutes
3.541
4.147
6.557
10.912
10.557
13.731
13.541
OH
O
O
F
NO2

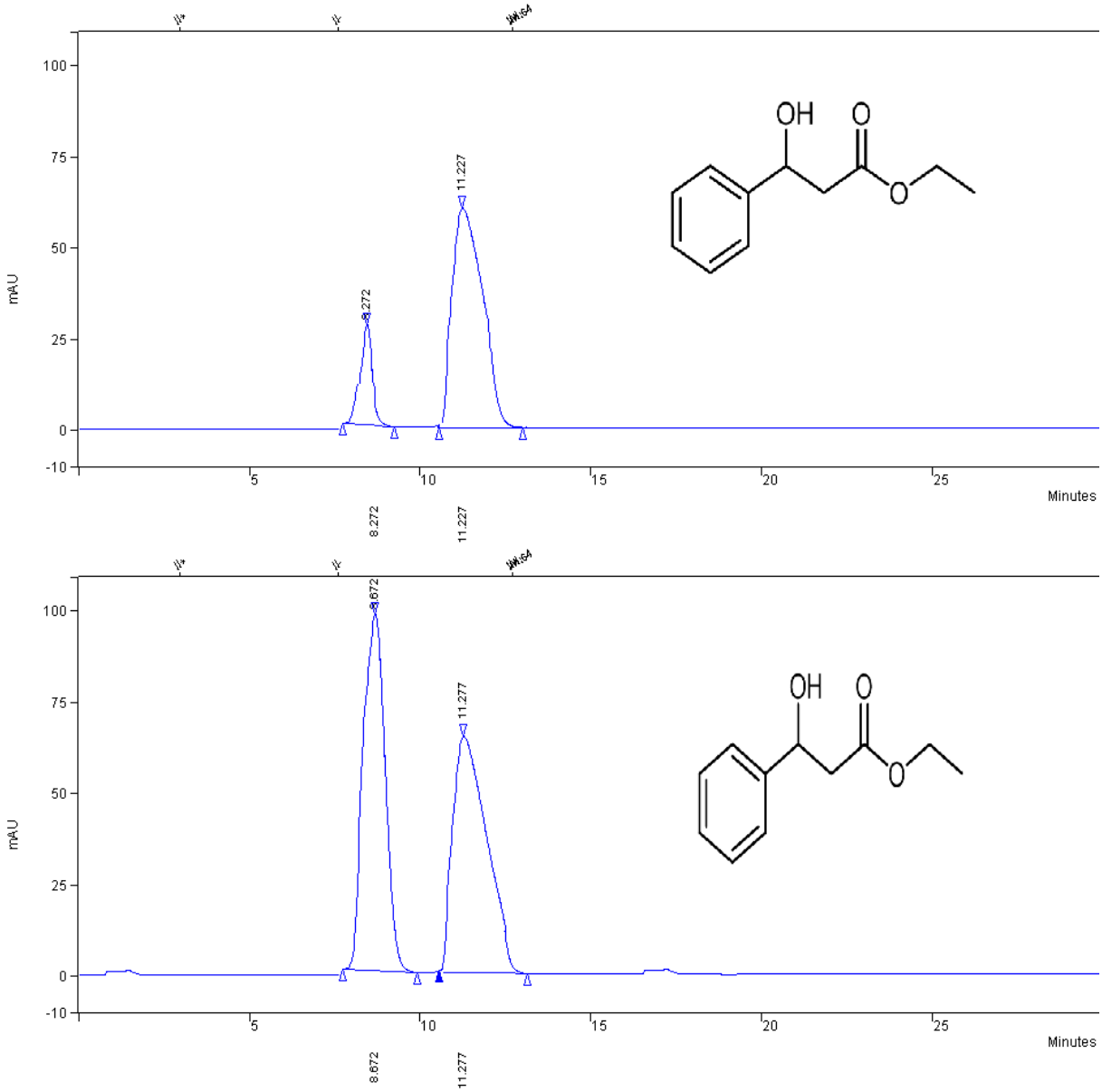

AU
2.0
1.5
1.0
0.5
0.0
-0.2
5
10
15
20
Minutes
14.397
16.125
OH
O
O
NC


OH
O
O
NC
AU
2.0
1.5
1.0
0.5
0.0
-0.2
5
10
15
20
25
Minutes
14.893
16.667
OH
O
O
MeO
AU
1.50
1.25
1.00
0.75
0.50
0.25
0.00
-0.17
10
20
30
40
Minutes
14.564
25.484
OH
O
O
MeO
AU
1.50
1.25
1.00
0.75
0.50
0.25
0.00
-0.17
10
20
30
40
Minutes
14.864
25.784


WVL:64
WVL:32
mAU
Minutes
12.221
13.229
16.547
24.221
29.547
OH
O
O
O_2N
NO_2


WVL:64
WVL:32
mAU
Minutes
5.517
6.411
24.496
26.413
29.067
OH
O
O
O_2N
NO_2


WVL:64
AU
Minutes
7.779
14.563
OH
O
O
Br


mAU
100
75
50
25
0
-10
5
10
15
20
25
Minutes
8.272
11.227
OH
O
O
mAU
100
75
50
25
0
-10
5
10
15
20
25
Minutes
8.672
11.277
OH
O
O