

Supporting Information

Bisoxazolidine-catalyzed Enantioselective Reformatsky Reaction

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1. Synthetic Procedures

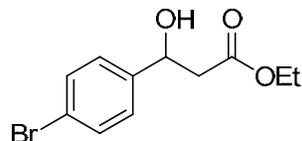
All commercially available reagents and solvents were used without further purification. NMR spectra were obtained at 400 MHz (^1H NMR) and 100 MHz (^{13}C NMR). Chemical shifts are reported in ppm relative to TMS. Reaction products were purified by column chromatography on silica gel (particle size 32 – 63 μm). Aldehydes were purified prior to use by distillation under reduced pressure or by flash chromatography on silica gel using 4% ethyl acetate in hexanes as mobile phase. Bisoxazolidine **1** was synthesized as described previously.¹

Reformatsky Reaction Procedure

A 150 mL three-neck flask was fitted with a CaCl_2 drying tube sealed with a stopper. Bisoxazolidine **4** (9.6 mg, 0.024 mmol) was dissolved in 5.0 mL of anhydrous Et_2O at room temperature, transferred into the flame-dried flask and the solution was stirred for five minutes under inert atmosphere until ethyl iodoacetate (59.1 μL , 0.50 mmol) was added. After five minutes, $\text{B}(\text{OMe})_3$ (27.9 μL , 0.25 mmol) was added. Then, the reaction was opened to the atmosphere by removing the stopper from the CaCl_2 drying tube. After another five minutes, 1.2 M Me_2Zn in toluene (0.85 mL, 1.0 mmol) was added at once followed immediately by dropwise addition of the substrate (0.25 mmol) in 1.0 mL of anhydrous Et_2O using a syringe pump (10 μL drops over 10 minutes). After four minutes within the automated addition, another portion of 1.2 M Me_2Zn in toluene (0.85 mL, 1.0 mmol) was added to the reaction flask. The reaction was allowed to proceed for one hour and was quenched with 10 mL of 1 M HCl . The mixture was extracted with three portions of Et_2O , dried over MgSO_4 and solvents were removed in vacuo. The product was purified by flash chromatography on silica gel as described below.

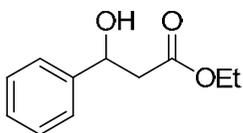
2. Product Characterization

Ethyl 3-(4-bromophenyl)-3-hydroxypropanoate (**3**)²



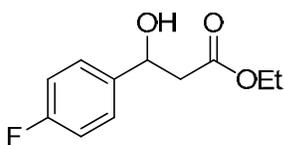
Ethyl 3-(4-bromophenyl)-3-hydroxypropanoate, **3**, was obtained after purification by flash chromatography (pentane: Et_2O : EtOH = 300:100:4) as a colorless oil (90% yield, 76% ee). ^1H NMR (400 MHz, CDCl_3) δ = 1.26 (t, J = 7.2 Hz, 3H), 2.65 – 2.74 (m, 2H), 3.46 (bs, 1H), 4.17 (q, J = 7.2 Hz, 2H), 5.08 (m, 1H), 7.25 (d, J = 8.3 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ = 13.1, 42.1, 60.0, 68.6, 120.6, 126.4, 130.6, 140.5, 171.2. Ee determination by chiral HPLC analysis on Chiralpak AS using hexanes:*i*-PrOH (98:2) as mobile phase; retention times: t_1 (minor) = 11.3 min, t_2 (major) = 13.4 min.

Ethyl 3-hydroxy-3-phenylpropanoate (**5**)²



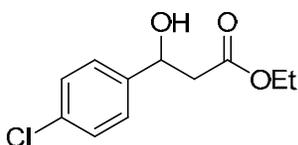
Ethyl 3-hydroxy-3-phenylpropanoate, **5**, was obtained after purification by flash chromatography (pentane:Et₂O:EtOH = 300:100:4) as a colorless oil (79% yield, 77% ee). ¹H NMR (400 MHz, CDCl₃) δ = 1.25 (t, *J* = 7.1 Hz, 3H), 2.67 – 2.79 (m, 2H), 3.31 (d, *J* = 3.5 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 5.12 (m, 1H), 7.25 – 7.39 (m, 5H). ¹³C NMR (100 MHz, CDCl₃) δ = 14.1, 43.3, 60.8, 70.2, 125.6, 127.7, 128.5, 142.5, 172.4. Ee determination by chiral HPLC analysis on Chiralcel OD using hexanes:*i*-PrOH (90:10) as mobile phase; retention times: *t*₁ (major) = 13.8 min, *t*₂ (minor) = 15.6 min.

Ethyl 3-(4-fluorophenyl)-3-hydroxypropanoate (**6**)³



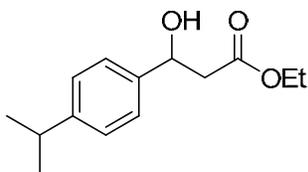
Ethyl 3-(4-fluorophenyl)-3-hydroxypropanoate, **6**, was obtained after purification by flash chromatography (pentane:Et₂O:EtOH = 300:100:4) as a colorless oil (70% yield, 76% ee). ¹H NMR (400 MHz, CDCl₃) δ = 1.26 (t, *J* = 7.2 Hz, 3H), 2.64 – 2.76 (m, 2H), 3.39 (bs, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 5.09 (m, 1H), 7.03 (dd, *J* = 8.6 Hz, 8.6 Hz, 2H), 7.34 (dd, *J* = 5.6 Hz, 8.4 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃) δ = 14.1, 43.3, 60.9, 69.6, 115.3 (d, *J*_{C-F} = 21.4 Hz), 127.3 (d, *J*_{C-F} = 8.1 Hz), 138.3 (d, *J*_{C-F} = 3.1 Hz), 162.2 (d, *J*_{C-F} = 245.7 Hz), 172.2. Ee determination by chiral HPLC analysis on Chiralpak AS using hexanes:*i*-PrOH (98:2) as mobile phase; retention times: *t*₁ (minor) = 10.5 min, *t*₂ (major) = 12.1 min.

Ethyl 3-(4-chlorophenyl)-3-hydroxypropanoate (**7**)²



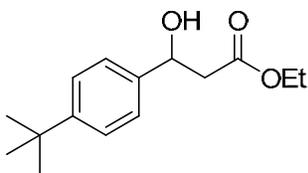
Ethyl 3-(4-chlorophenyl)-3-hydroxypropanoate, **7**, was obtained after purification by flash chromatography (pentane:Et₂O:EtOH = 300:100:4) as a colorless oil (86% yield, 78% ee). ¹H NMR (400 MHz, CDCl₃) δ = 1.25 (t, *J* = 7.1 Hz, 3H), 2.65 – 2.74 (m, 2H), 3.44 (bs, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 5.10 (m, 1H), 7.21 - 7.41 (m, 4H). ¹³C NMR (100 MHz, CDCl₃) δ = 14.1, 43.2, 61.0, 69.6, 127.0, 128.6, 133.4, 141.0, 172.2. Ee determination by chiral HPLC analysis on Chiralpak AS using heptanes:*i*-PrOH (95:5) as mobile phase; retention times: *t*₁ (minor) = 21.1 min, *t*₂ (major) = 26.4 min.

Ethyl 3-hydroxy-3-(4-isopropylphenyl)propanoate (**8**)²



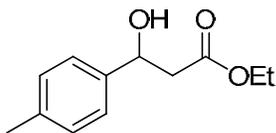
Ethyl 3-hydroxy-3-(4-isopropylphenyl)propanoate, **8**, was obtained after purification by flash chromatography (pentane:Et₂O:EtOH = 300:100:4) as a colorless oil (82 % yield, 79 % ee). ¹H NMR (400 MHz, CDCl₃) δ = 1.24 (d, *J* = 6.9 Hz, 6H), 1.26 (t, *J* = 7.1 Hz, 3H), 2.66 – 2.80 (m, 2H), 2.90 (sept, *J* = 6.9 Hz, 1H), 3.18 (d, *J* = 3.3 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 5.11 (m, 1H), 7.21 (d, *J* = 8.0 Hz, 2H) 7.30 (d, *J* = 8.0 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃) δ = 14.1, 23.9, 33.8, 43.3, 60.8, 70.2, 125.7, 126.6, 139.9, 148.5, 172.4. Ee determination by chiral HPLC analysis on Chiralpak AS using hexanes:*i*-PrOH (96:4) as mobile phase; retention times: *t*₁ (minor) = 20.1 min, *t*₂ (major) = 22.7 min.

Ethyl 3-(4-*tert*-butylphenyl)-3-hydroxypropanoate (**9**)²



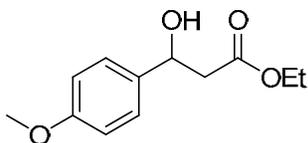
Ethyl 3-(4-*tert*-butylphenyl)-3-hydroxypropanoate, **9**, was obtained after purification by flash chromatography (pentane:Et₂O:EtOH = 300:100:4) as a colorless oil (79 % yield, 79 % ee). ¹H NMR (400 MHz, CDCl₃) δ = 1.26 (t, *J* = 7.2 Hz, 3H), 1.31 (s, 9H), 2.67 – 2.80 (m, 2H), 3.17 (d, *J* = 3.3 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 5.11 (m, 1H), 7.31 (d, *J* = 8.2 Hz, 2H), 7.38 (d, *J* = 8.3 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃) δ = 14.1, 31.3, 34.5, 43.2, 60.8, 70.1, 125.4, 139.5, 150.7, 172.4. Ee determination by chiral HPLC analysis on Chiralpak AS using hexanes:*i*-PrOH (96:4) as mobile phase; retention times: t₁ (minor) = 18.3 min, t₂ (major) = 20.8 min.

Ethyl 3-hydroxy-3-(4-tolyl)propanoate (**10**)³



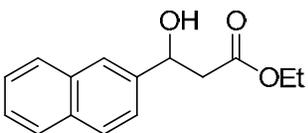
Ethyl 3-hydroxy-3-(4-tolyl)propanoate, **10**, was obtained after purification by flash chromatography (pentane:Et₂O:EtOH = 300:100:4) as a colorless oil (83 % yield, 78 % ee). ¹H NMR (400 MHz, CDCl₃) δ = 1.26 (t, *J* = 7.1 Hz, 3H), 2.34 (s, 3H), 2.66 – 2.74 (m, 2H), 3.22 (bs, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 5.08 (m, 1H), 7.15 (d, *J* = 7.8 Hz, 2H), 7.26 (d, *J* = 7.8 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃) δ = 14.1, 21.1, 43.3, 60.8, 70.2, 125.6, 129.2, 137.4, 139.6, 172.4. Ee determination by chiral HPLC analysis on Chiralpak AS using hexanes:*i*-PrOH (95:5); retention times: t₁ (minor) = 18.4 min, t₂ (major) = 21.1 min.

Ethyl 3-hydroxy-3-(4-methoxyphenyl)propanoate (**11**)²



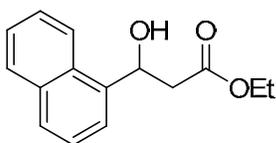
Ethyl 3-hydroxy-3-(4-methoxyphenyl)propanoate, **11**, was obtained after purification by flash chromatography (pentane:Et₂O:EtOH = 300:100:4) as a colorless oil (77% yield, 77% ee). ¹H NMR (400 MHz, CDCl₃) δ = 1.26 (t, *J* = 7.2 Hz, 3H), 2.64 – 2.79 (m, 2H), 3.19 (d, *J* = 3.1 Hz, 1H), 3.81 (s, 3H), 4.18 (q, *J* = 7.2 Hz, 2H), 5.08 (m, 1H), 6.88 (d, *J* = 8.7 Hz, 2H), 7.30 (d, *J* = 8.6 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃) δ = 14.1, 43.3, 55.2, 60.8, 69.9, 113.9, 126.9, 134.7, 159.2, 172.4. Ee determination by chiral HPLC analysis on Chiralpak AS using hexanes:*i*-PrOH (95:5); retention times: t₁ (minor) = 10.4 min, t₂ (major) = 14.6 min.

Ethyl 3-hydroxy-3-(2-naphthyl)propanoate (**12**)²



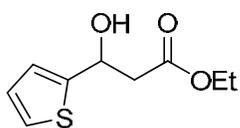
Ethyl 3-hydroxy-3-(2-naphthyl)propanoate, **12**, was obtained after purification by flash chromatography (pentane:Et₂O:EtOH = 300:100:4) as a colorless oil (89% yield, 79% ee). ¹H NMR (400 MHz, CDCl₃) δ = 1.25 (t, *J* = 7.1 Hz, 3H), 2.76 – 2.86 (m, 2H), 3.44 (s, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 5.29 (m, 1H), 7.46 – 7.48 (m, 3H), 7.81 – 7.83 (m, 4H). ¹³C NMR (100 MHz, CDCl₃) δ = 14.1, 43.3, 60.9, 70.4, 123.7, 124.4, 125.9, 126.2, 127.6, 128.0, 128.3, 133.0, 133.2, 139.9, 172.4. Ee determination by chiral HPLC analysis on Chiralpak AS using hexanes:*i*-PrOH (95:5); retention times: t₁ (minor) = 29.8 min, t₂ (major) = 34.6 min.

Ethyl 3-hydroxy-3-(1-naphthyl)propanoate (**13**)⁴



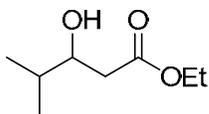
Ethyl 3-hydroxy-3-(1-naphthyl)propanoate, **13**, was obtained after purification by flash chromatography (pentane:Et₂O:EtOH = 300:100:4) as a colorless oil (94% yield, 80% ee). ¹H NMR (400 MHz, CDCl₃) δ = 1.27 (t, *J* = 7.1 Hz, 3H), 2.79 – 2.92 (m, 2H), 3.44 (s, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 5.91 (m, 1H), 7.45 – 7.53 (m, 3H), 7.69 (d, *J* = 7.1 Hz, 1H), 7.78 (d, *J* = 8.2 Hz, 1H), 7.86 (d, *J* = 7.7 Hz, 1H), 8.05 (d, *J* = 8.2 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃) δ = 14.2, 42.7, 61.0, 67.3, 122.8, 122.9, 125.5, 125.6, 126.2, 128.2, 129.0, 130.0, 133.7, 138.0, 172.7. Ee determination by chiral HPLC analysis on Chiralcel OD using heptanes:*i*-PrOH (90:10); retention times: *t*₁ (major) = 16.2 min, *t*₂ (minor) = 21.3 min.

Ethyl 3-hydroxy-3-(2-thienyl)propanoate (**14**)²



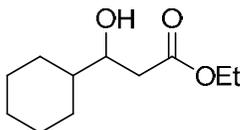
Ethyl 3-hydroxy-3-(thiophen-2-yl)propanoate, **14**, was obtained after purification by flash chromatography (pentane:Et₂O:EtOH = 300:100:4) as a colorless oil (77% yield, 75% ee). ¹H NMR (400 MHz, CDCl₃) δ = 1.27 (t, *J* = 7.2 Hz, 3H), 2.82 – 2.91 (m, 2H), 3.47 (d, *J* = 4.2 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 5.37 (m, 1H), 6.95 – 6.98 (m, 2H), 7.25 (m, 1H). ¹³C NMR (100 MHz, CDCl₃) δ = 14.1, 43.1, 66.5, 69.1, 123.6, 124.8, 126.7, 146.2, 171.9. Ee determination by chiral HPLC analysis on Chiralcel OD using heptanes:*i*-PrOH (90:10); retention times: *t*₁ (major) = 11.7 min, *t*₂ (minor) = 30.3 min.

Ethyl 3-hydroxy-4-methylpentanoate (**15**)⁵



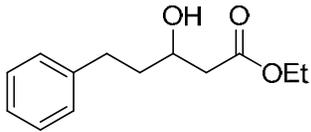
Ethyl 3-hydroxy-4-methylpentanoate, **15**, was obtained after purification by flash chromatography (pentane:Et₂O:EtOH = 500:100:6) as a colorless oil (89% yield, 51% ee). ¹H NMR (400 MHz, CDCl₃) δ = 0.92 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.71 (m, 1H), 2.40 (dd, *J* = 9.5 Hz, 16.3 Hz, 1H), 2.50 (dd, *J* = 2.8 Hz, 16.3 Hz, 1H), 2.89 (d, *J* = 3.2 Hz, 1H), 3.78 (m, 1H), 4.18 (q, *J* = 7.2 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃) δ = 14.1, 17.7, 18.3, 33.1, 38.4, 60.6, 72.6, 173.4. Ee determination by chiral GC analysis on Lipodex E (25 m x 0.25 mm). Initial temperature 50 °C for 60 min, then 10 °C/min until 70 °C, then 70 °C for 20 min; retention times: *t*₁ (major) = 69.3 min, *t*₂ (minor) = 69.9 min.

Ethyl 3-cyclohexyl-3-hydroxypropanoate (**16**)⁶



Ethyl 3-cyclohexyl-3-hydroxypropanoate, **16**, was obtained after purification by flash chromatography (pentane:Et₂O:EtOH = 500:100:6) as a colorless oil (86% yield, 36% ee). ¹H NMR (400 MHz, CDCl₃) δ = 0.96 – 1.31 (m, 5H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.38 (m, 1H), 1.62 – 1.71 (m, 2H), 1.71 – 1.81 (m, 2H), 1.86 (m, 1H), 2.41 (dd, *J* = 9.5 Hz, 16.3 Hz, 1H), 2.51 (dd, *J* = 2.9 Hz, 16.3 Hz), 2.87 (d, *J* = 3.8 Hz, 1H), 3.78 (m, 1H), 4.17 (q, *J* = 7.2 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃) δ = 14.1, 26.0, 26.1, 26.4, 28.2, 28.8, 38.6, 43.0, 60.6, 72.1, 173.5. Ee determination by chiral GC analysis on 6-O-TBDMS-2,3-di-O-methyl-β-cyclodextrin (5 m x 0.25 mm). Temperature at 60 °C; retention times: *t*₁ (major) = 150 min, *t*₂ (minor) = 175 min.

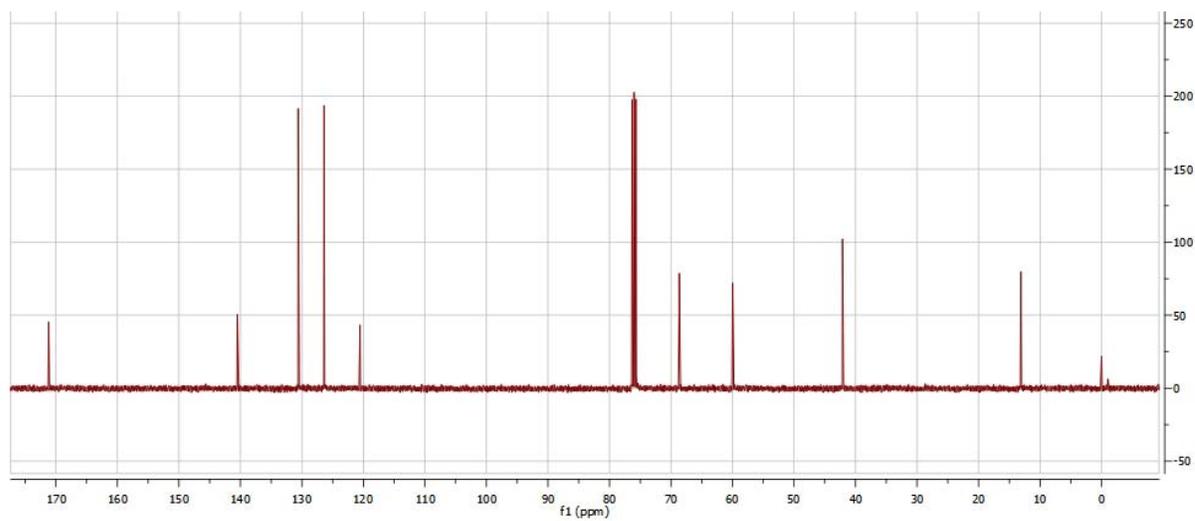
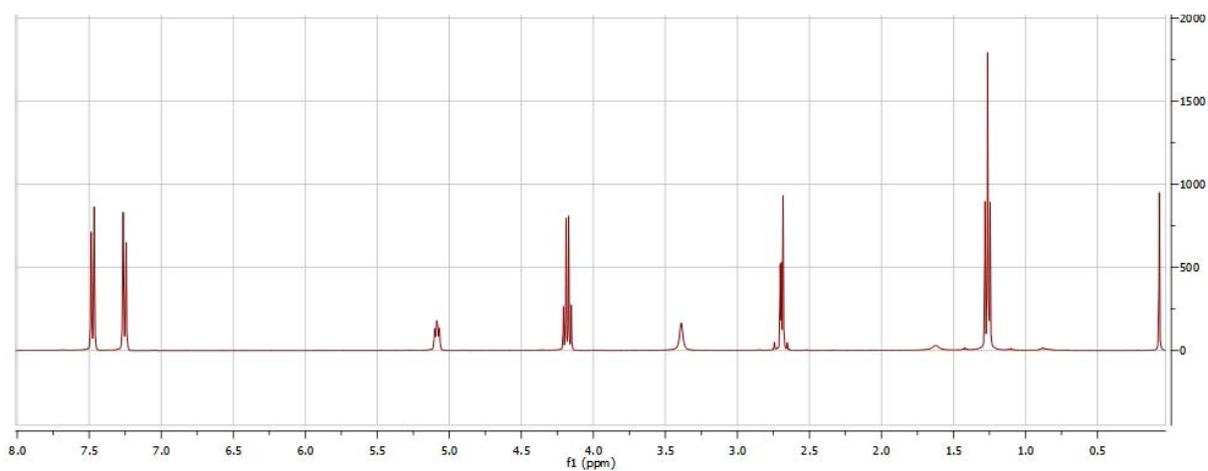
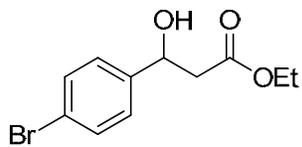
Ethyl 3-hydroxy-5-phenylpentanoate (**17**)⁷



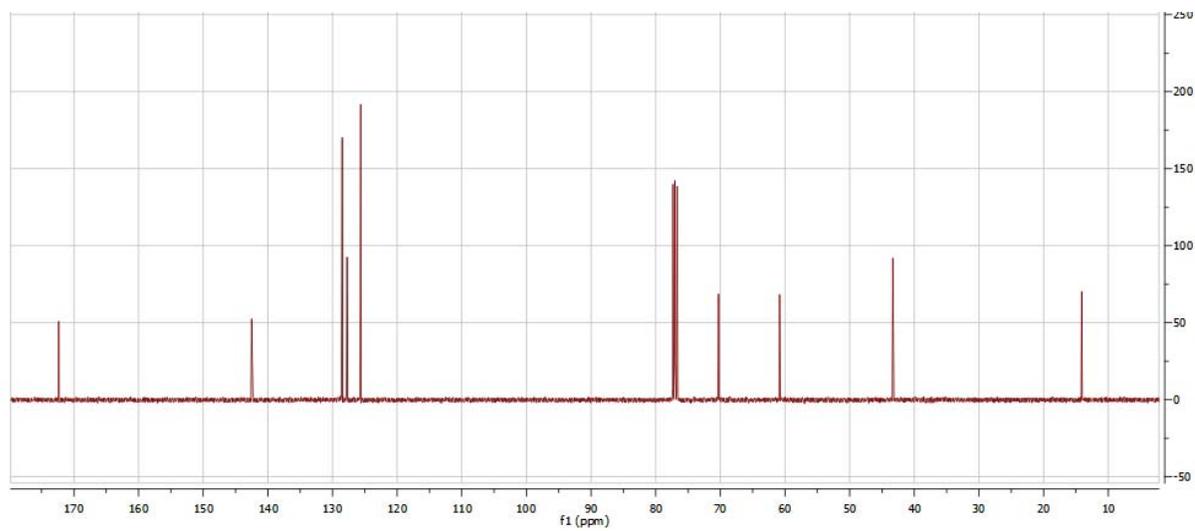
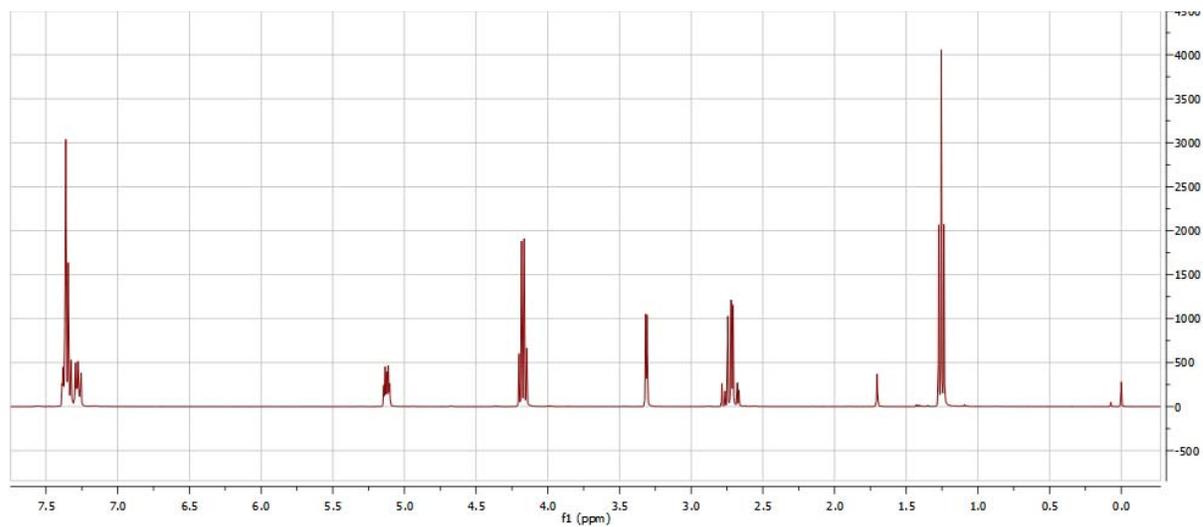
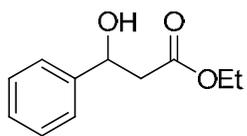
Ethyl 3-hydroxy-5-phenylpentanoate, **17**, was obtained after purification by flash chromatography (pentane:Et₂O:EtOH = 500:100:6) as a colorless oil (75% yield, 26% ee). ¹H NMR (400 MHz, CDCl₃) δ = 1.26 (t, *J* = 7.2 Hz, 3H), 1.74 (m, 1H), 1.85 (m, 1H), 2.44 (dd, *J* = 8.6 Hz, 16.6 Hz, 1H), 2.50 (dd, *J* = 3.5 Hz, 16.5 Hz, 1H), 2.70 (m, 1H), 2.83 (m, 1H), 3.09 (bs, 1H), 4.02 (m, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 7.16 – 7.20 (m, 3H), 7.25 – 7.30 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ = 14.1, 31.7, 38.1, 41.3, 60.7, 67.1, 125.9, 128.3, 128.4, 141.7, 173.0. Ee determination by chiral HPLC analysis on Chiralcel OD using heptanes:*i*-PrOH (90:10); retention times: t₁ (major) = 12.1 min, t₂ (minor) = 14.2 min.

3. NMR Spectroscopy

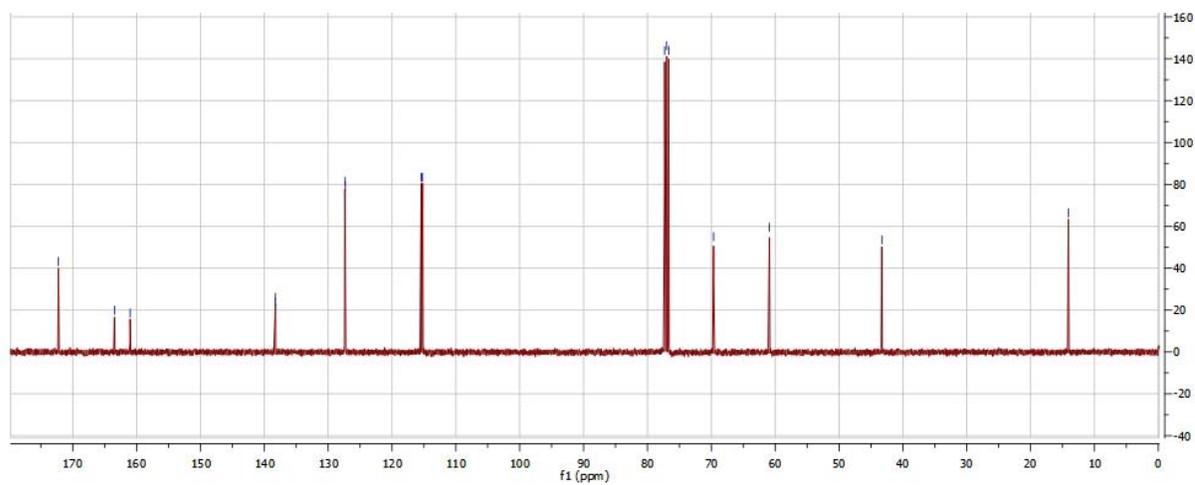
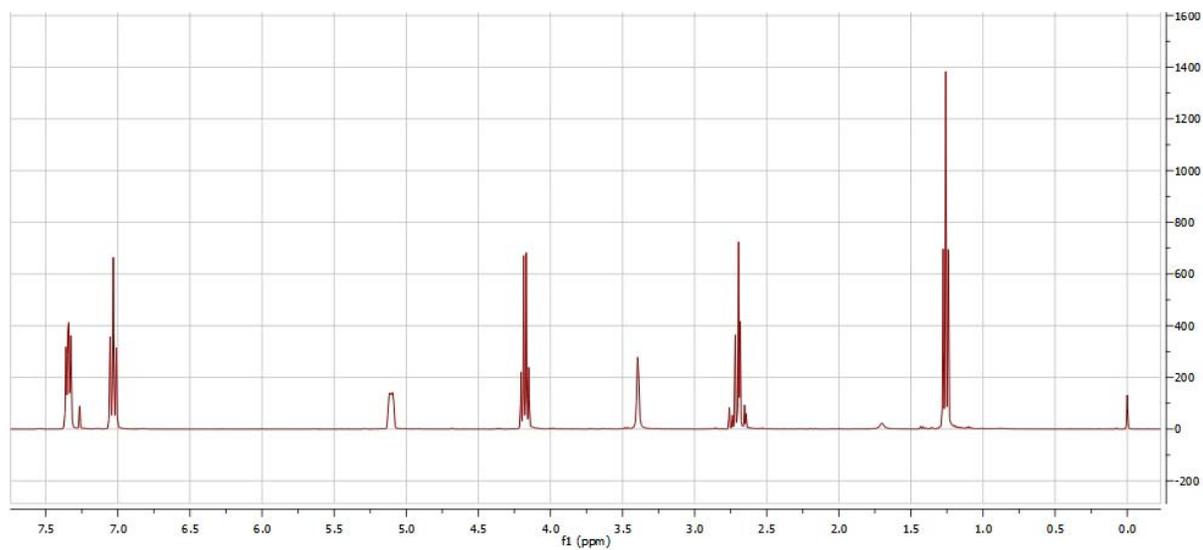
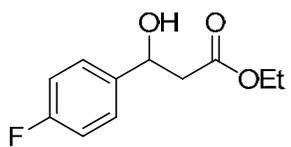
Ethyl 3-(4-bromophenyl)-3-hydroxypropanoate (**3**)



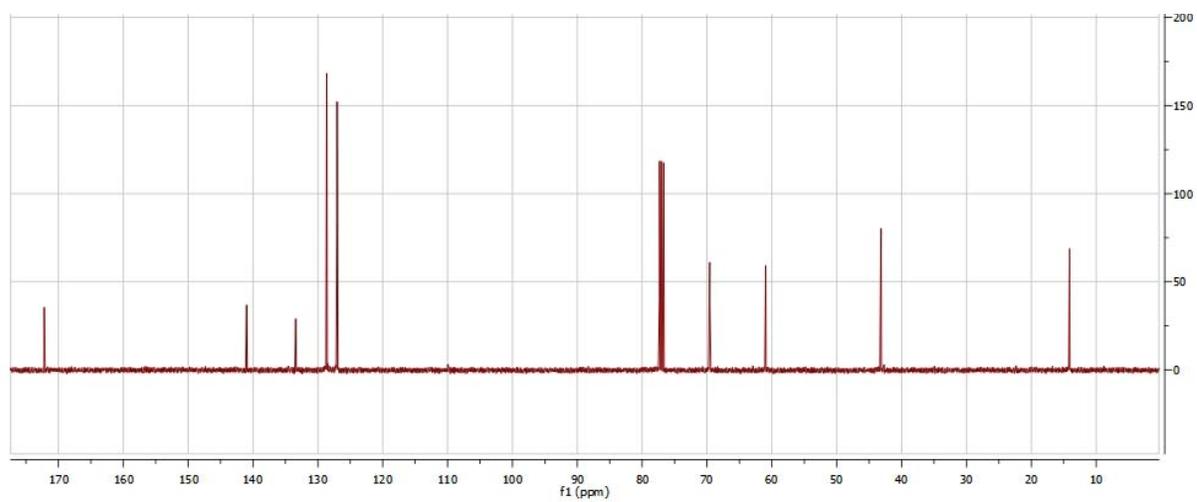
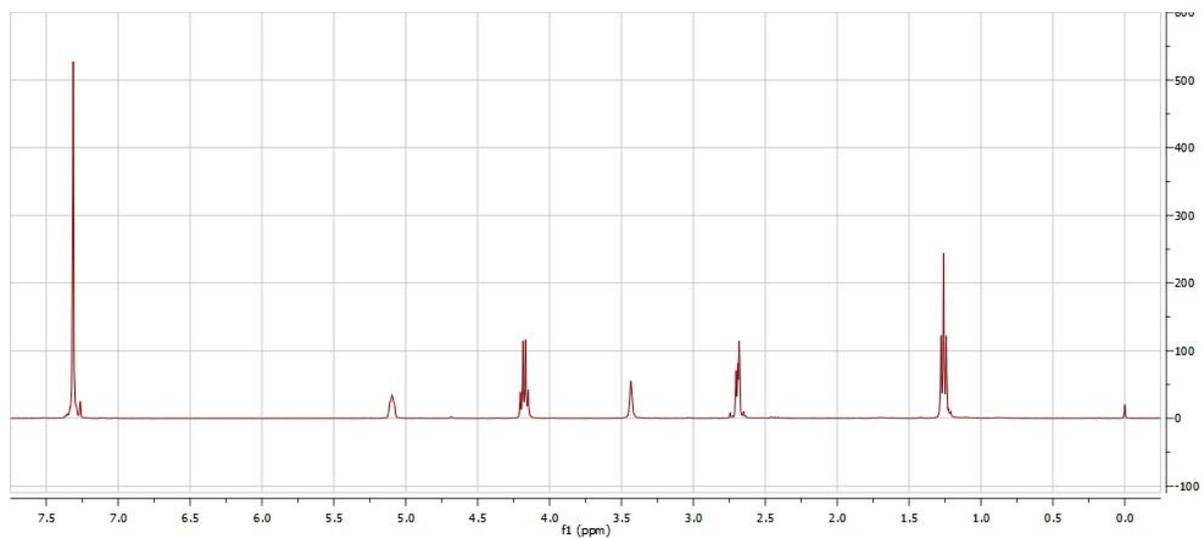
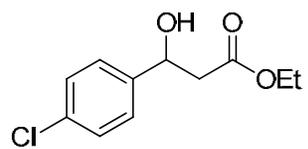
Ethyl 3-hydroxy-3-phenylpropanoate (**5**)



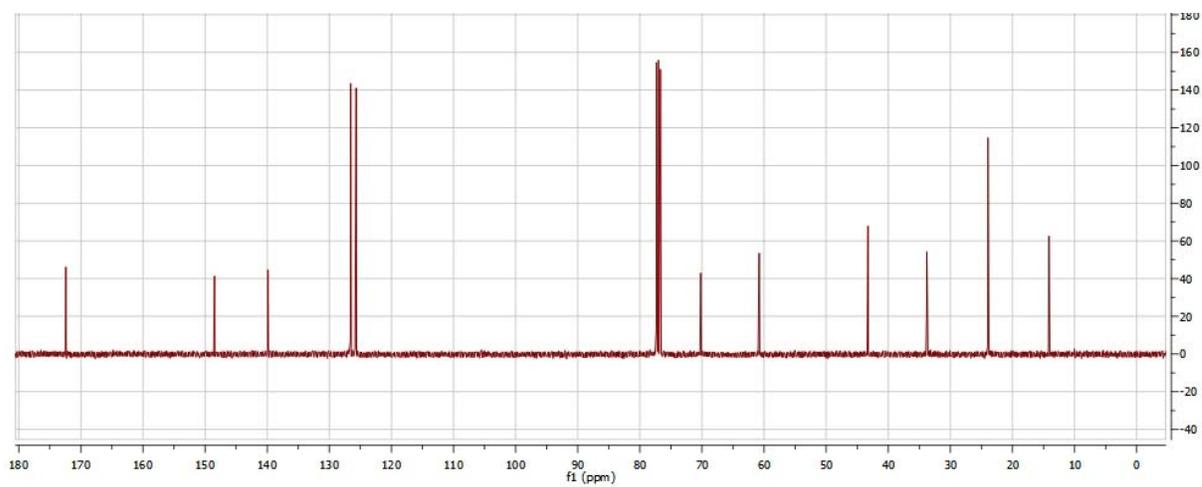
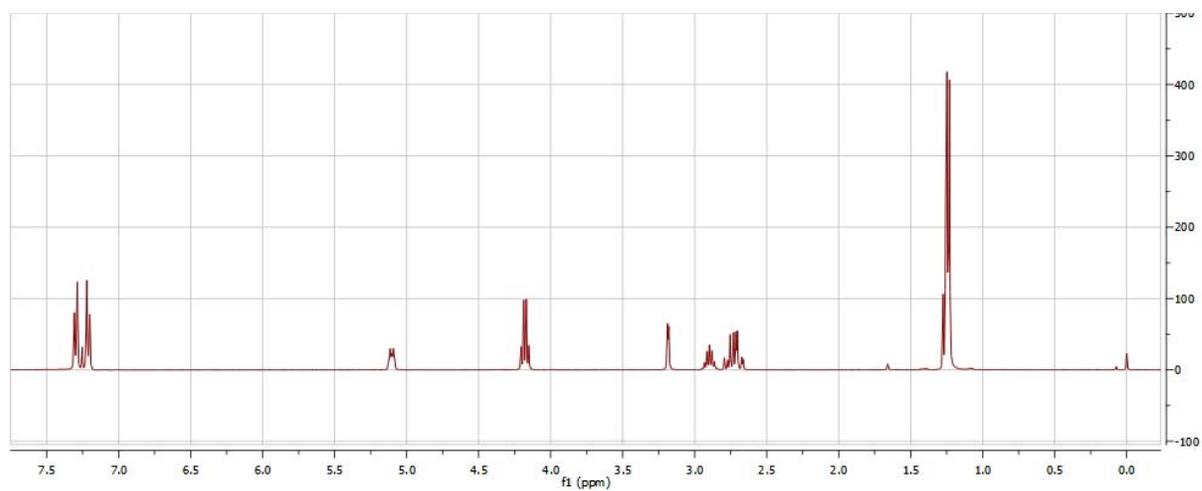
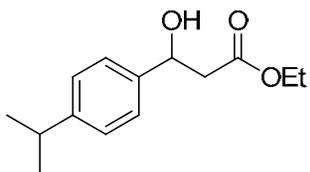
Ethyl 3-(4-fluorophenyl)-3-hydroxypropanoate (6)



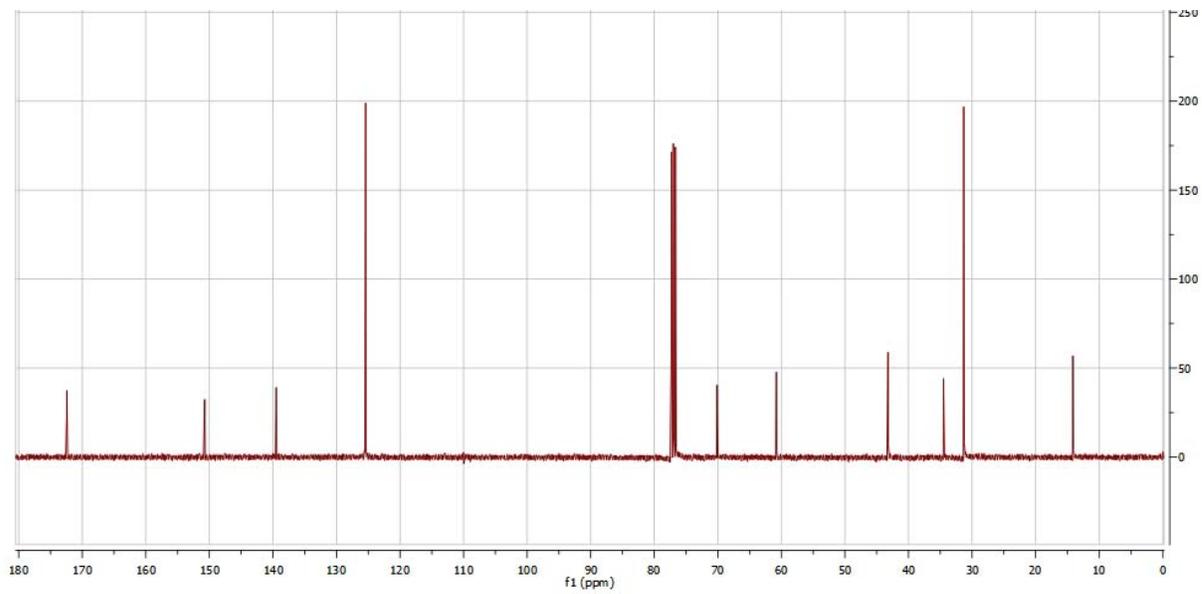
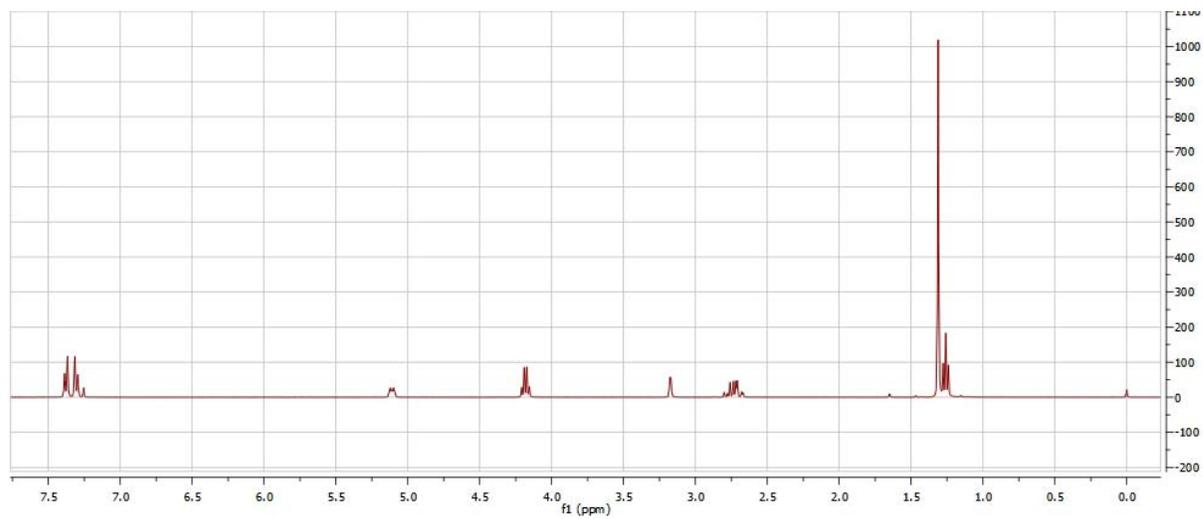
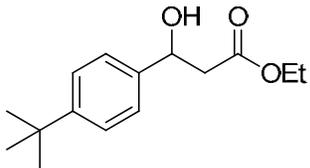
Ethyl 3-(4-chlorophenyl)-3-hydroxypropanoate (7)



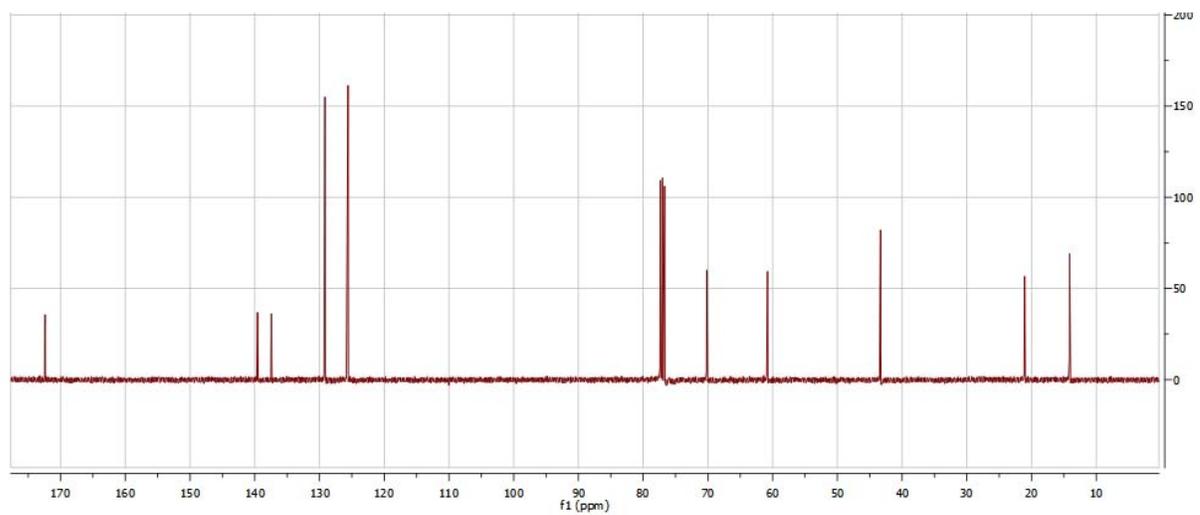
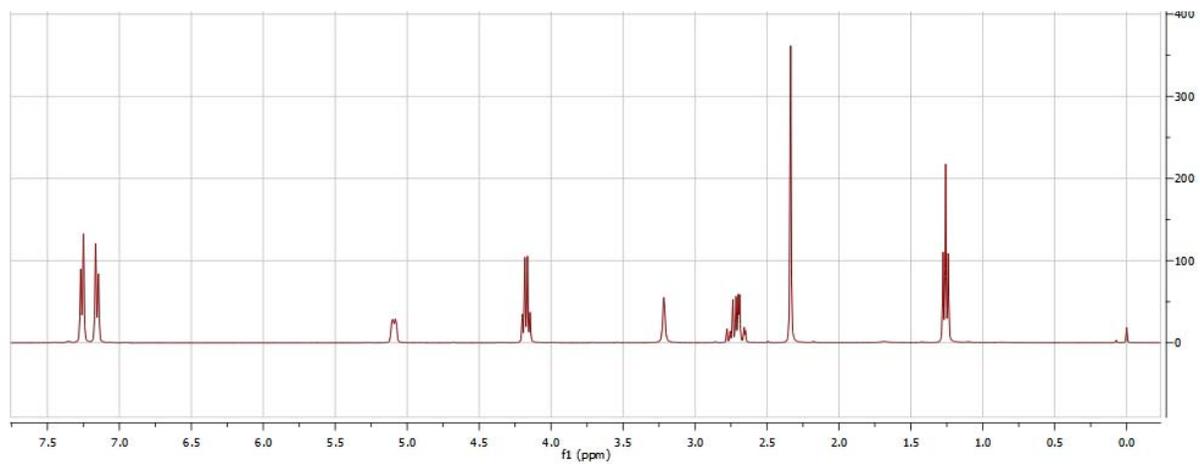
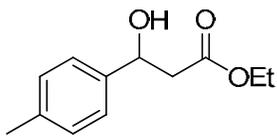
Ethyl 3-hydroxy-3-(4-isopropylphenyl)propanoate (**8**)



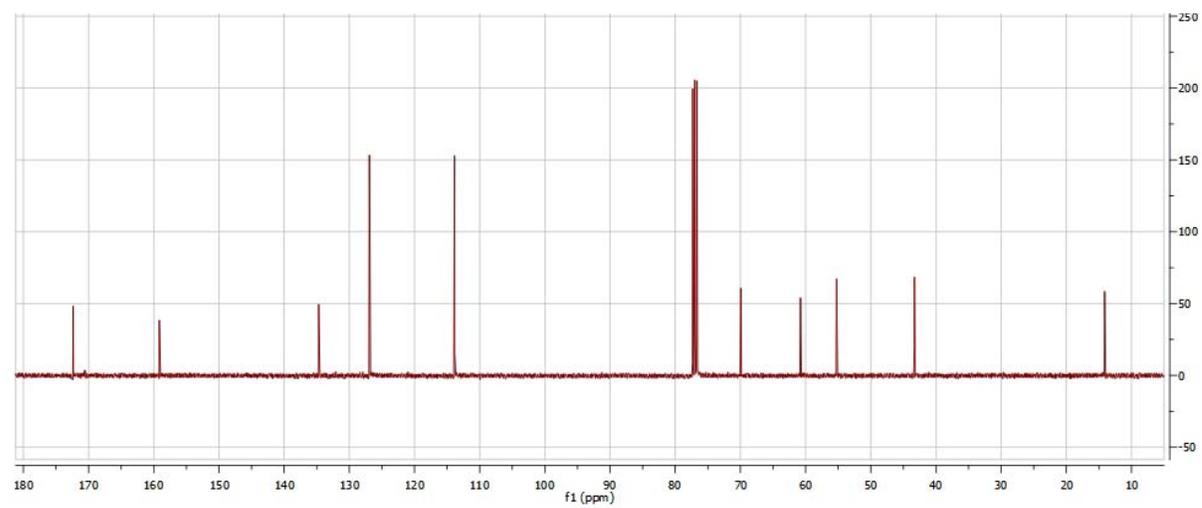
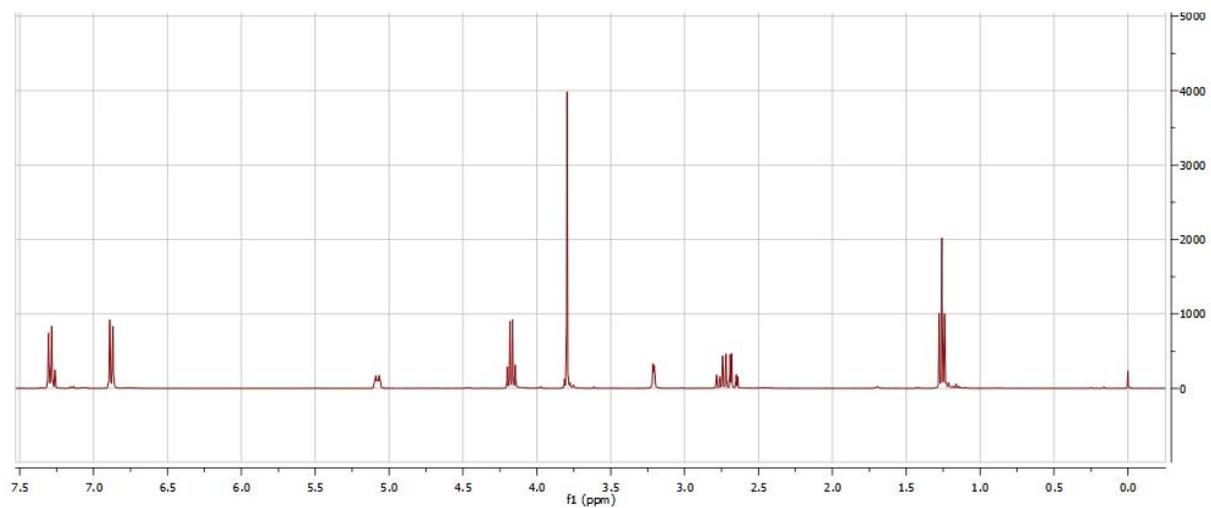
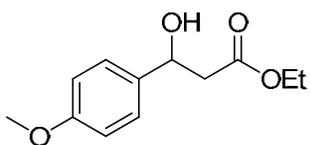
Ethyl 3-(4-*tert*-butylphenyl)-3-hydroxypropanoate (**9**)



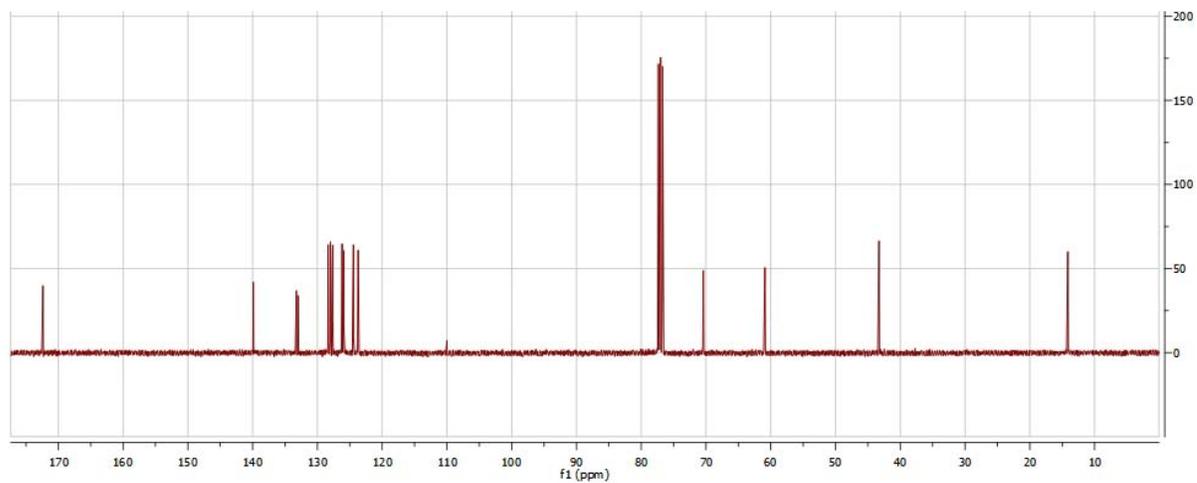
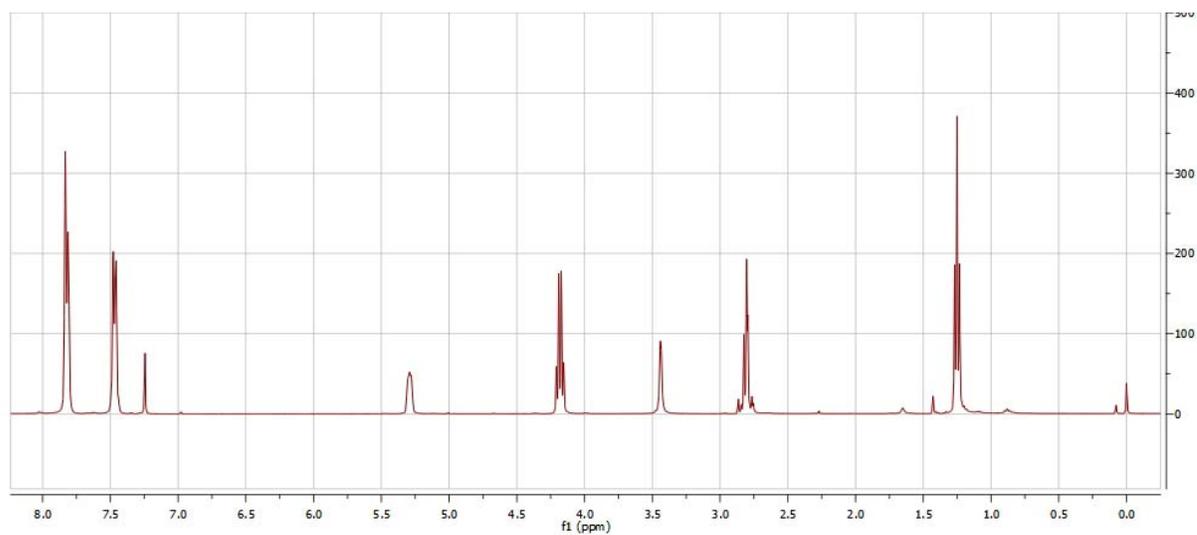
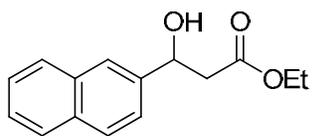
Ethyl 3-hydroxy-3-(4-tolyl)propanoate (**10**)



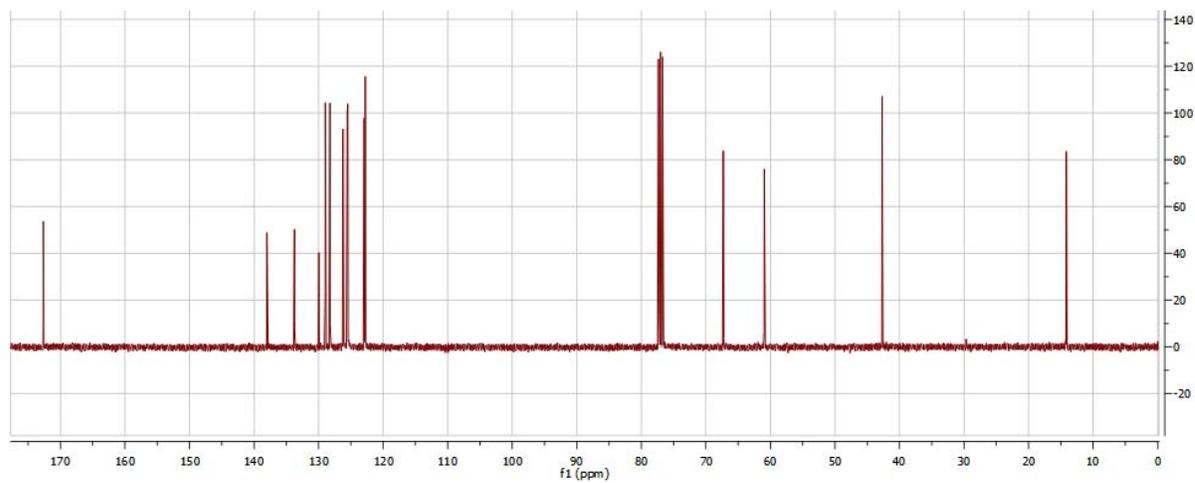
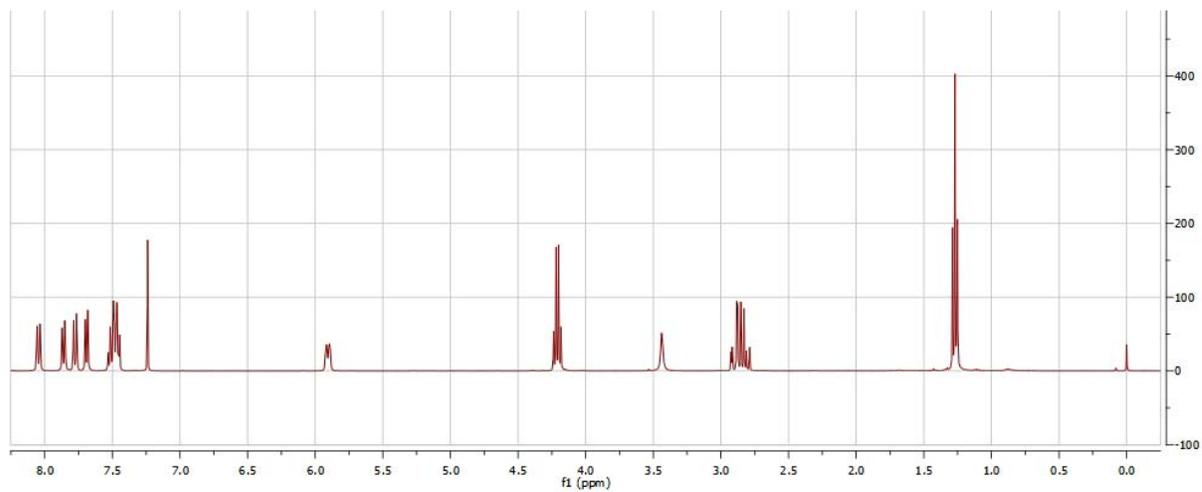
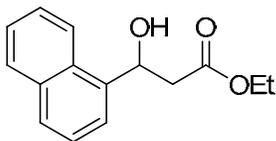
Ethyl 3-hydroxy-3-(4-methoxyphenyl)propanoate (**11**)



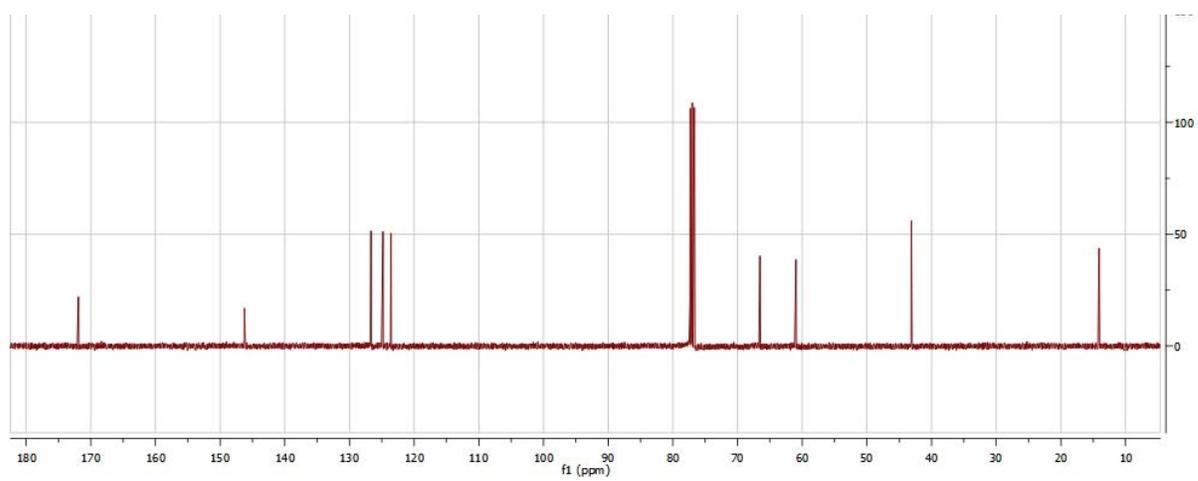
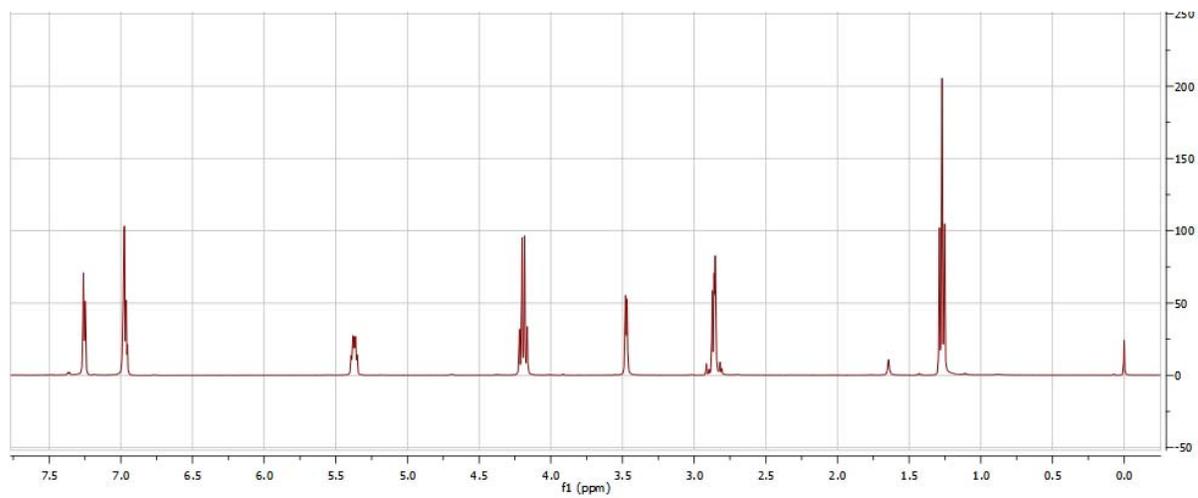
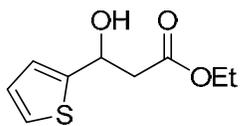
Ethyl 3-hydroxy-3-(2-naphthyl)propanoate (**12**)



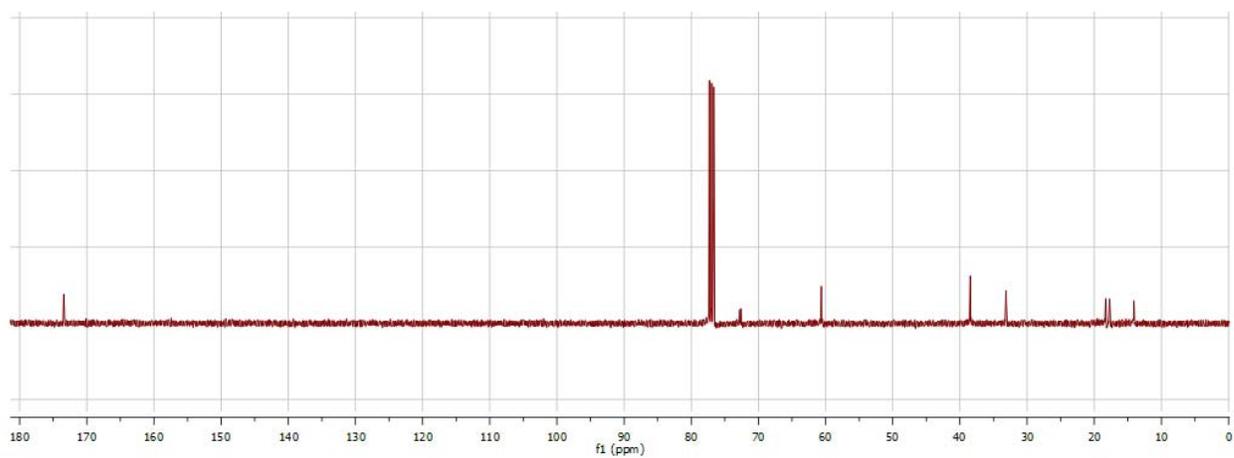
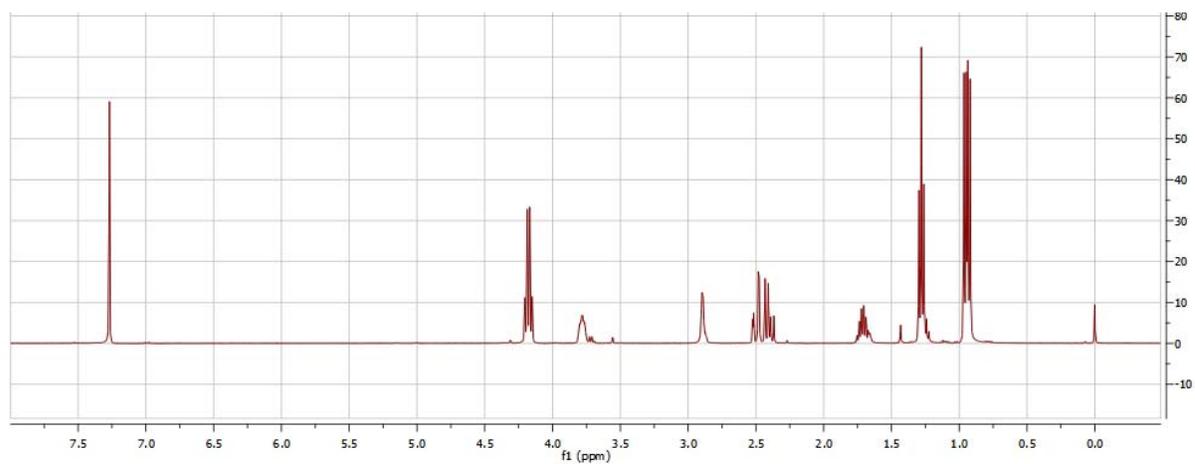
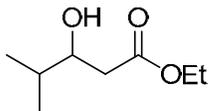
Ethyl 3-hydroxy-3-(1-naphthyl)propanoate (**13**)



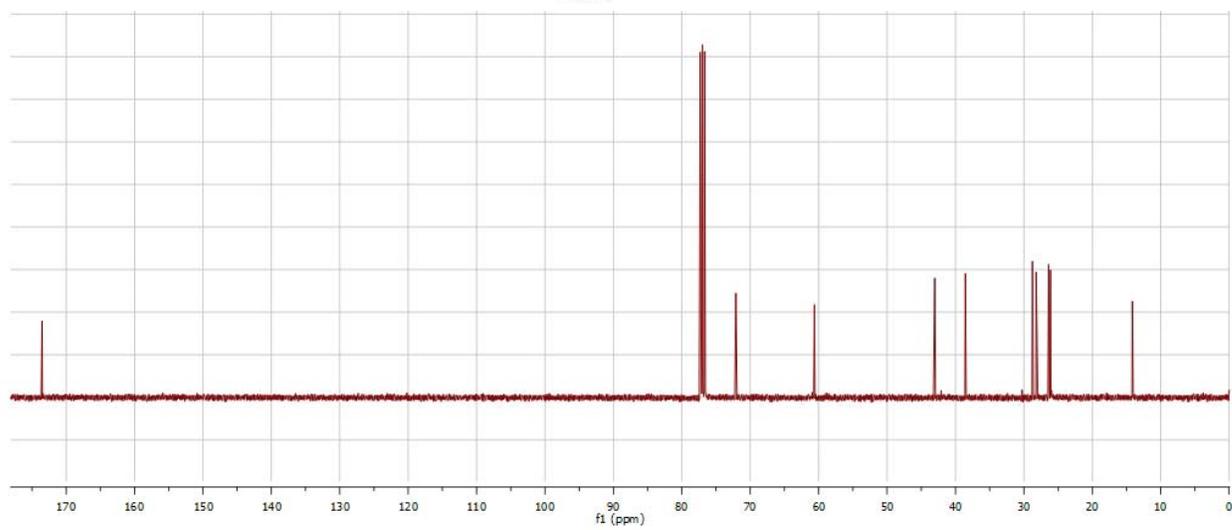
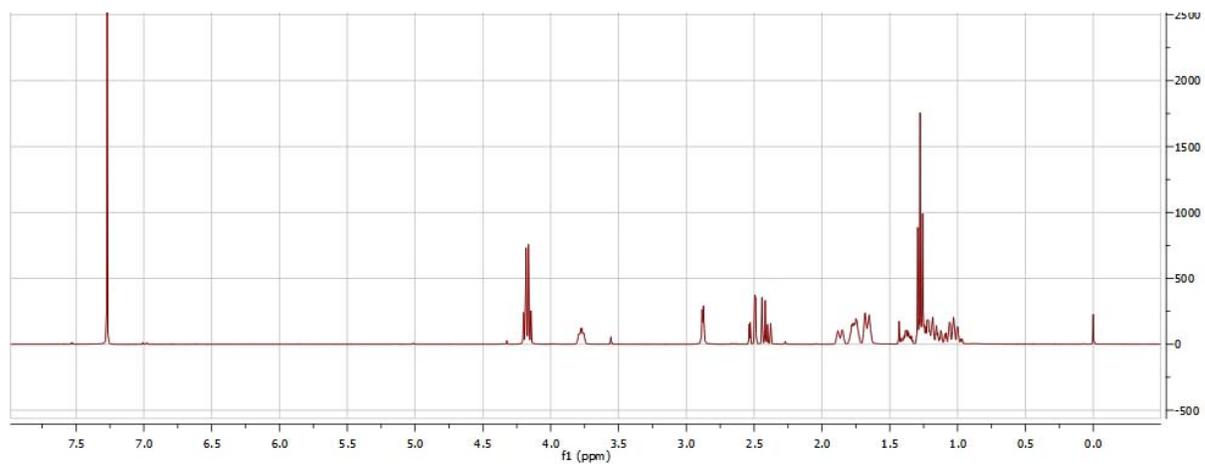
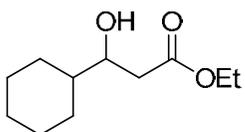
Ethyl 3-hydroxy-3-(2-thienyl)propanoate (**14**)



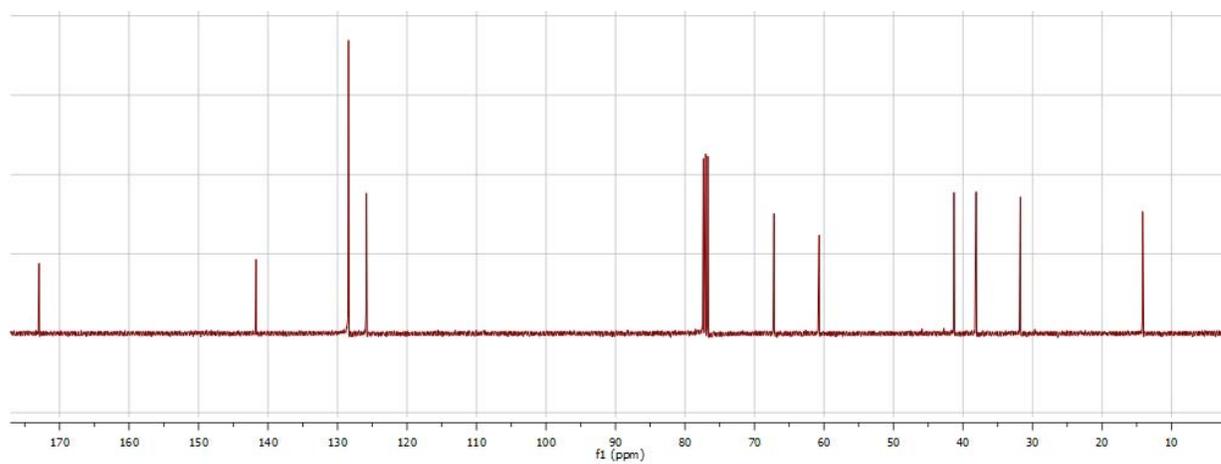
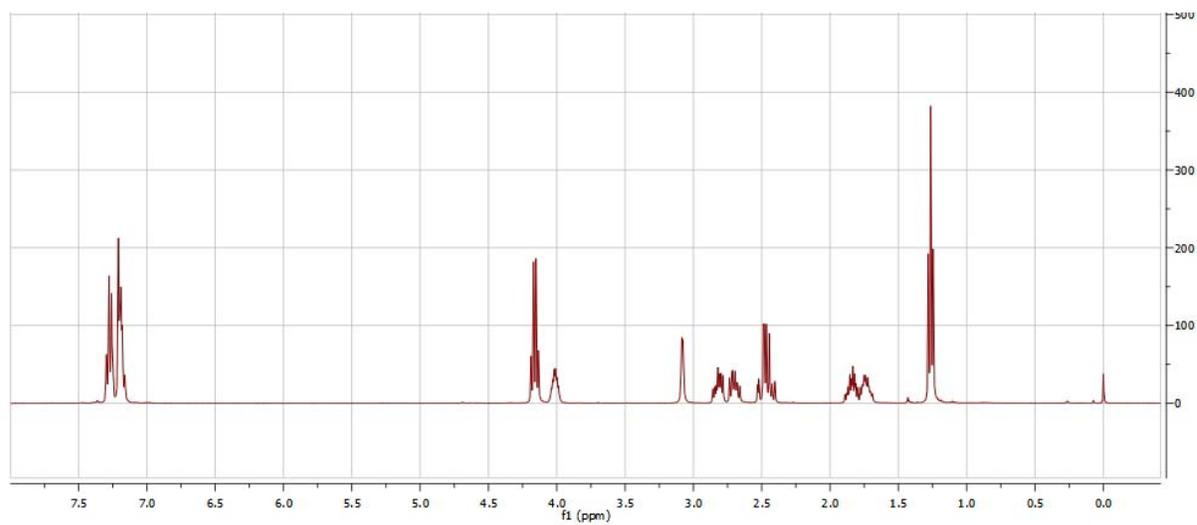
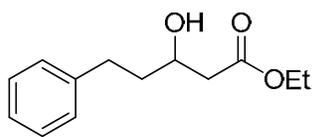
Ethyl 3-hydroxy-4-methylpentanoate (**15**)



Ethyl 3-cyclohexyl-3-hydroxypropanoate (**16**)



Ethyl 3-hydroxy-5-phenylpentanoate (**17**)



4. References

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