

# A Chiral Ag-based Catalyst for Practical, Efficient and Highly Enantioselective Additions of Enolsilanes to $\alpha$ -Ketoesters

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## SUPPORTING INFORMATION

**General.** Infrared (IR) spectra are recorded on a Perkin Elmer 781 spectrophotometer,  $\nu_{\max}$  in  $\text{cm}^{-1}$ . Bands are characterized as broad (br), strong (s), medium (m) or weak (w).  $^1\text{H}$  NMR spectra are recorded on a Varian Unity INOVA 400 (400 MHz) spectrometer. Chemical shifts are reported in ppm from the solvent resonance resulting from incomplete deuteration as the internal standard ( $\text{CDCl}_3$ :  $\delta$  7.26). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), and coupling constants.  $^{13}\text{C}$  NMR spectra are recorded on a Varian Unity INOVA 400 (100 MHz) with complete proton decoupling. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ( $\text{CDCl}_3$ :  $\delta$  77.16). Enantiomer ratios are determined by chiral GLC analysis; (Alltech Associates Chiraldex GTA column (30 m x 0.25 mm) or Supelco Betadex 120 column (30 m x 0.25 mm)), or by chiral HPLC analysis (Chiral Technologies Chiralpak OD column (0.46 cm x 25 cm) and AS (0.46 cm x 0.25cm) in comparison with authentic racemic materials. High-resolution mass spectrometry was performed on a Micromass LCT ESI-MS (positive mode) at the Mass Spectrometry Facility at Boston College or at the University of Illinois at Urbana-Champaign. Elemental analyses were carried out at Roberson Microlit Laboratories, Inc. Madison, NJ. Optical rotation values were recorded on a Rudolph Research Analytical Autopol IV polarimeter.

Unless otherwise stated, all reactions were conducted in oven- (135 °C) and flame-dried glassware under an inert atmosphere of dry  $\text{N}_2$ . Solvents were purified under a positive pressure of dry Ar by a modified Advanced ChemTech purification system; dichloromethane was purified through two alumina columns. Tetrahydrofuran was distilled from Na and benzophenone, unless otherwise stated.  $\text{AgF}$  and  $\text{AgF}_2$  were purchased from Aldrich and used without purification. Enolsilanes were purchased from commercial sources (Fluka, Aldrich) and used without purification.  $\alpha$ -Ketoesters were purchased from commercial sources (Aldrich, Lancaster), or synthesized according to previous procedures,<sup>1</sup> and purified by simple distillation.  $\text{EDC}\cdot\text{HCl}$ ,  $\text{HOBT}\cdot\text{H}_2\text{O}$ , 4.0 M solution of HCl in 1,4-dioxane, *n*-butylamine, Boc-protected amino acids, and pyridine carboxaldehydes were purchased from commercial sources (Advanced Chemtech, Nova Biochem) and used without purification. Unless otherwise stated, substrates were synthesized from commercially available starting materials through previously reported protocols.

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1) Rambaud, M.; Bakasse, M.; Duguay, G.; Villieras, J. *Synthesis* **1988**, 7, 564–566.

**(S)-N-((S)-1-(butylamino)1-oxo-3-phenylpropan-2-yl)3,3-dimethyl-2-((E)(6-methylpyridin-2-yl)methyleneamino)butanamide (5d).** Boc-L-Phe-OH (3.00 g, 11.31 mmol) is dissolved in 50 mL of CH<sub>2</sub>Cl<sub>2</sub>, and HOBt•H<sub>2</sub>O (1.90 g, 12.43 mmol), EDC•HCl (2.38 g, 12.43 mmol) and butylamine (2.75 mL, 27.72 mmol) are added successively at 22 °C. The resulting solution is allowed to stir at 22 °C for 4 h. Citric acid (50 mL of a 10 wt. % aqueous solution) is added and the two layers are separated. The aqueous layer is washed twice with 50 mL of CH<sub>2</sub>Cl<sub>2</sub> and the combined organic layers are washed with 50 mL 10 wt. % aqueous citric acid and 50 mL of saturated aqueous NaHCO<sub>3</sub>, followed by 50 mL of a saturated solution of NaCl. The organic layer is dried over MgSO<sub>4</sub> before removal of the volatiles in vacuo to afford Boc-L-Phe-NHBu as a white solid (3.58 g, 11.19 mmol, 90% yield). Hydrochloric acid (4.0 M solution in 1,4-dioxane) is added dropwise to Boc-L-Phe-NHBu (2.0 g, 6.24 mmol) at 0 °C until complete dissolution is achieved. The resulting solution is allowed to warm to 22 °C and stir for 30 min. At this time, the mixture is concentrated in vacuo to afford ClH<sub>3</sub>N-L-Phe-NHBu (1.41 g, 5.49 mmol, 88% yield).

Boc-L-Tle-OH (0.501 g, 1.26 mmol) is dissolved in 10 mL CH<sub>2</sub>Cl<sub>2</sub> and HOBt•H<sub>2</sub>O (0.212 g, 1.39 mmol), EDC•HCl (0.266 g, 1.39 mmol), ClH<sub>3</sub>N-L-Phe-NHBu (0.324 g, 1.26 mmol), and Et<sub>3</sub>N (3.86 mL, 2.77 mmol) are successively added at 22 °C. The resulting solution is allowed to stir at 22 °C for 4 h before quenching and work-up as described above. Boc-L-Tle-L-Phe-NHBu is dissolved in 4.0 M HCl in 1,4-dioxane at 0 °C. The solution is allowed to warm to 22 °C and stirred for 30 min. The mixture is concentrated in vacuo and the resulting solid dissolved in water. NaOH (1 N solution) is added dropwise until pH >10 is achieved, after which the aqueous solution is washed with CH<sub>2</sub>Cl<sub>2</sub> (3 x 20 mL). The combined organic layers are dried over MgSO<sub>4</sub> and concentrated to afford H<sub>2</sub>N-L-Tle-L-Phe-NHBu as a light tan solid (0.357 g, 1.07 mmol, 85% yield). The purity of H<sub>2</sub>N-L-Tle-L-Phe-NHBu is established by inspection of its 400 MHz <sup>1</sup>H NMR spectrum before the final coupling.

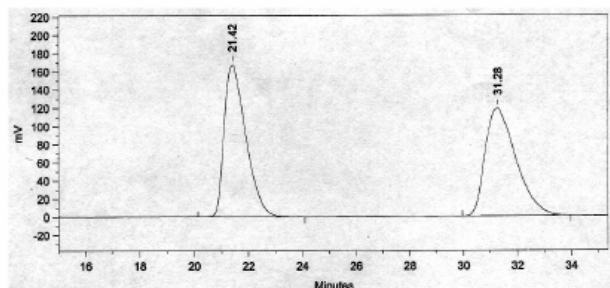
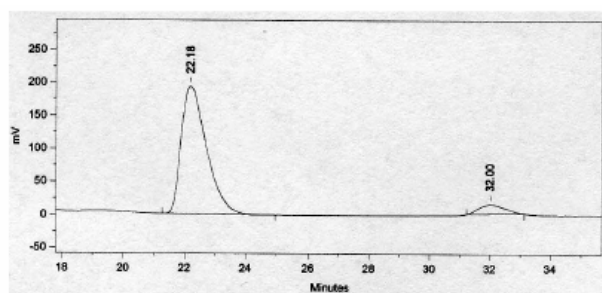
6-Methyl-2-pyridine carboxaldehyde (0.130 g, 1.07 mmol) is dissolved in 5 mL of CH<sub>2</sub>Cl<sub>2</sub>. H<sub>2</sub>N-L-Tle-L-Phe-NHBu (0.357 g, 1.07 mmol) dissolved in 5 mL CH<sub>2</sub>Cl<sub>2</sub> and MgSO<sub>4</sub> are added at 22 °C. The resulting solution is allowed to stir for 3 h, after which MgSO<sub>4</sub> is removed by filtration and the organic filtrate is concentrated in vacuo. The resulting residue is purified by recrystallization (pentane/Et<sub>2</sub>O) to afford **5d** as white crystalline solid (0.252 g, 0.578 mmol, 54% yield). m.p. = 88.2 °C; IR (solid film): 3298 (m), 2958 (m), 2932 (w), 2870 (w), 1646 (s), 1577 (w), 1509 (m), 1457 (w), 1366 (w) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz): δ 8.16 (1H, s), 7.78 (1H, d, *J* = 7.6 Hz), 7.67 (1H, t, *J* = 7.6 Hz), 7.33-7.21 (m, 6H), 7.17 (1H, br d, *J* = 7.6 Hz), 5.79 (1H, br s), 4.65 (1H, q, *J* = 7.6 Hz), 3.54 (1H, s), 3.25-3.20 (1H, m), 3.14-3.02 (3H, m), 2.59 (3H, s), 1.28-1.19 (2H, m), 1.14-1.05 (2H, m), 0.89 (9H, s), 0.76 (3H, t, *J* = 7.2 Hz); <sup>13</sup>C NMR (100 MHz): δ 171.6, 170.6, 163.5, 158.4, 153.3, 137.1, 137.0, 129.5, 128.9, 127.1, 125.0, 118.3, 83.1, 54.3, 39.3, 38.1, 35.5, 31.4, 27.2, 24.4, 20.0, 13.7; HRMS calcd for C<sub>26</sub>H<sub>37</sub>N<sub>4</sub>O<sub>2</sub> (M+H<sup>+</sup>): 437.2925, Found: 437.2917; [ $\alpha$ ]<sub>D</sub><sup>20</sup> = -10.31 (*c* = 0.79, CHCl<sub>3</sub>).

**Representative experimental procedure for enantioselective Ag-catalyzed additions of enolsilanes to  $\alpha$ -ketoesters:** A 16 x 100 mm test tube, equipped with a magnetic stir bar, is

charged with  $\text{AgF}_2$  (1.8 mg, 0.012 mmol) and then chiral ligand **5d** (5.2 mg, 0.012 mmol) followed by tetrahydrofuran (0.40 mL). The resulting solution is allowed to stir while ethyl-2-oxo-4-phenylbutyrate (29  $\mu\text{L}$ , 0.12 mmol) is added, followed by the addition of 0.40 mL of tetrahydrofuran. The test tube is sealed with a septum, purged with  $\text{N}_2$  and allowed to stir for 20 min. At this time, the solution is allowed to cool to  $-78^\circ\text{C}$  in a dry ice/acetone bath and a solution of 1-phenyl-1-trimethylsilyloxyethylene (29  $\mu\text{L}$ , 0.14 mmol) dissolved in 0.40 mL tetrahydrofuran is added dropwise through syringe. The test tube is sealed with teflon tape and the mixture is allowed to warm to  $-30^\circ\text{C}$  in a circulating bath. The mixture is allowed to stir<sup>2</sup> for 24 h at  $-30^\circ\text{C}$ , after which 1 mL of a 2.0 M solution of HCl is added and the mixture is allowed warm to  $22^\circ\text{C}$ . The mixture is allowed to stir for 10 min at  $22^\circ\text{C}$ . The aqueous layer is washed with  $\text{Et}_2\text{O}$  (3 x 1.0 mL) and the combined organic layers are filtered through silica gel and volatiles are removed under reduced pressure to afford pale yellow oil. The oil is purified by silica gel chromatography (5:1 pentane: $\text{Et}_2\text{O}$ ) to give the desired aldol addition product (Table 2, entry 1) as a colorless oil (36 mg, 0.11 mmol, 92% yield).

**Ethyl-(R)-2-hydroxy-4-oxo-2-phenethyl-4-phenylbutanoate (Table 2, entry 1).** The mixture is allowed to stir at  $-40^\circ\text{C}$  for 48 h. Following purification, the desired product is obtained as colorless oil. IR (neat): 3515 (br), 2962 (s), 2923 (w), 1728 (s), 1671 (s), 1451 (w), 1260 (s), 1216 (s), 1090 (s), 1022 (s), 799 (s)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz):  $\delta$  7.94-7.92 (2H, m), 7.59 (1H, tt,  $J = 7.2, 1.6$  Hz), 7.49-7.45 (2H, m), 7.32-7.28 (2H, m), 7.22-7.19 (3H, m), 4.22 (2H, dq,  $J = 7.2, 0.4$  Hz), 3.99 (1H, br s), 3.63 (1H, d,  $J = 17.6$  Hz), 3.49 (1H, d,  $J = 17.6$ ), 2.93-2.86 (1H, m), 2.61-2.53 (1H, m), 2.12-2.08 (2H, m), 1.28 (3H, t,  $J = 7.2$  Hz).  $^{13}\text{C}$  NMR (100 MHz):  $\delta$  198.6, 175.4, 141.6, 136.7, 133.8, 128.8, 128.6, 128.5, 128.3, 126.2, 75.1, 62.0, 47.4, 41.5, 29.6, 14.3; HRMS calcd for  $\text{C}_{20}\text{H}_{22}\text{O}_4\text{Na}$  ( $\text{M}+\text{Na}^+$ ): 349.1416, Found: 349.1436; Anal Calcd for  $\text{C}_{20}\text{H}_{22}\text{O}_4$ : C, 73.60; H, 6.79; Found: C, 73.50; H, 6.36;  $[\alpha]_{\text{D}}^{20} = -26.50$  ( $c = 1.00, \text{CHCl}_3$ ).

Optical purity of the aldol adduct was established by chiral HPLC analysis: Chiralcel OD (0.46 x 25 cm), 96:4 hexanes:*i*-PrOH, 1.0 mL/min,  $\lambda = 254$  nm, 86% *ee*.

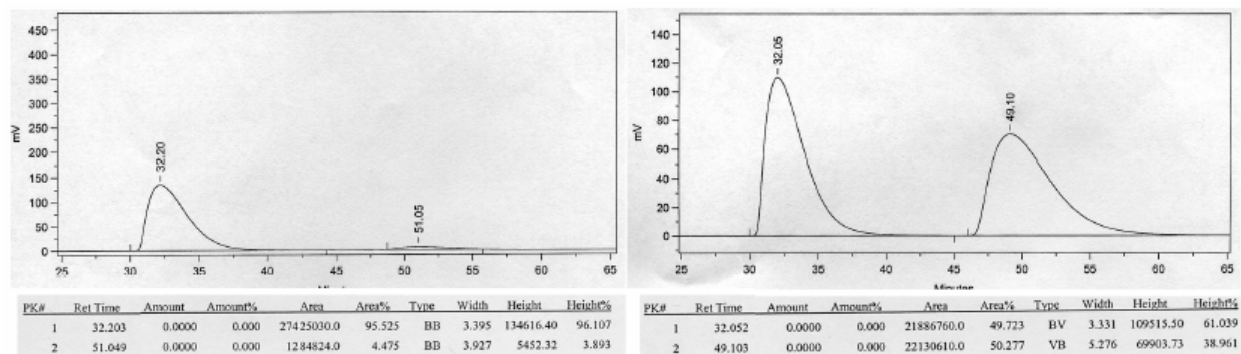


**Dimethyl-(R)-2-hydroxy-2-(2-oxo-2-phenylethyl)pentanedioate (Table 2, entry 2).** The mixture was allowed to stir at  $-30^\circ\text{C}$  for 24 h. Addition of water followed by washing with  $\text{Et}_2\text{O}$  and concentration at reduced pressure affords the desired adduct. The purified product was

2) The heterogeneous mixture requires constant stirring so that >98% conversion can be achieved.

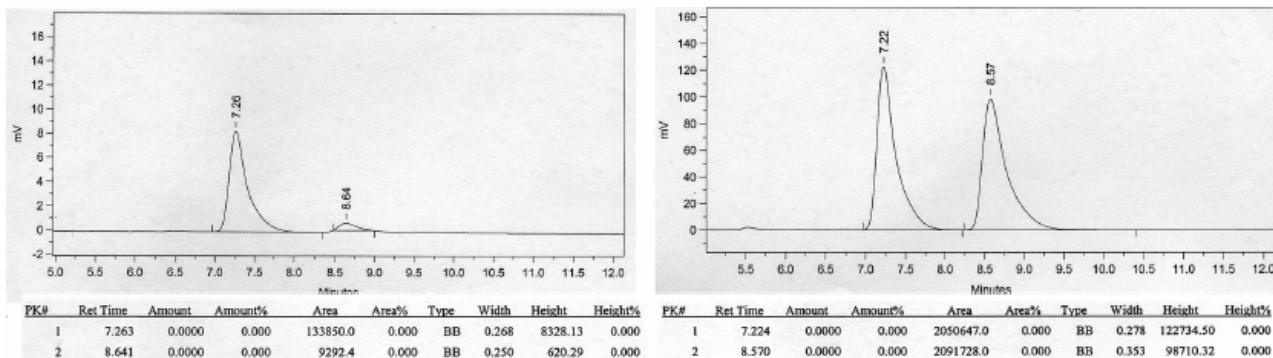
obtained as a white solid. m.p. = 70.5 °C; IR (neat): 3496 (br), 2955 (s), 1734 (s), 1685 (s), 1449 (m), 1218 (s)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz):  $\delta$  7.93-7.91 (2H, m), 7.59 (1H, tt,  $J = 7.2, 1.2$  Hz), 7.49-7.45 (2H, m), 3.90 (1H, br s), 3.71 (3H, s), 3.68 (3H, s), 3.61 (1H, d,  $J = 17.6$  Hz), 3.46 (1H, d,  $J = 17.6$  Hz), 2.63-2.55 (1H, m), 2.38-2.30 (1H, m), 2.16-2.12 (2H, m);  $^{13}\text{C}$  NMR (100 MHz):  $\delta$  198.5, 175.6, 173.7, 136.5, 134.0, 128.9, 128.4, 74.5, 53.1, 52.0, 47.5, 34.3, 28.3; HRMS calcd for  $\text{C}_{15}\text{H}_{18}\text{O}_6\text{Na}$  ( $\text{M}+\text{Na}^+$ ): 317.0991, Found: 317.1001;  $[\alpha]_{\text{D}}^{20} = -24.42$  ( $c = 1.49$ ,  $\text{CHCl}_3$ ).

Optical purity of the product was established by chiral HPLC analysis: Chiracel AS (0.46 x 25 cm), 95:5 hexanes:*i*-PrOH, 1.0 mL/min,  $\lambda = 254$  nm; 92% *ee*.



**Ethyl-(*R*)-2-hydroxy-4-methyl-2-(2-oxo-2-phenylethyl)pentanoate (Table 2, entry 3).** The mixture is allowed to stir at  $-30$  °C for 24 h. Following purification, the desired product is obtained as colorless oil. IR (neat): 3515 (br), 2956 (s), 1736 (s), 1686 (s), 1596 (w), 1449 (m), 1363 (w), 1219 (s)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz):  $\delta$  7.94-7.91 (2H, m), 7.58 (1H, tt,  $J = 7.2, 1.2$  Hz), 7.49-7.44 (2H, m), 4.23 (2H, q,  $J = 7.2$  Hz), 3.88 (1H, s), 3.54 (1H, d,  $J = 17.6$  Hz), 3.39 (1H, d,  $J = 17.6$  Hz), 1.92-1.82 (1H, m), 1.72 (2H, d,  $J = 6.0$  Hz), 1.27 (3H, t,  $J = 7.2$  Hz), 1.01 (3H, d,  $J = 6.4$  Hz), 0.91 (3H, d,  $J = 6.4$  Hz);  $^{13}\text{C}$  NMR (100 MHz):  $\delta$  198.8, 175.9, 136.8, 133.7, 128.8, 128.3, 75.5, 61.8, 48.3, 48.1, 24.6, 24.0, 23.8, 14.3; HRMS calcd for  $\text{C}_{16}\text{H}_{22}\text{O}_4\text{Na}$  ( $\text{M}+\text{Na}^+$ ): 301.1416, Found: 301.1416;  $[\alpha]_{\text{D}}^{20} = -27.38$  ( $c = 0.89$ ,  $\text{CHCl}_3$ ).

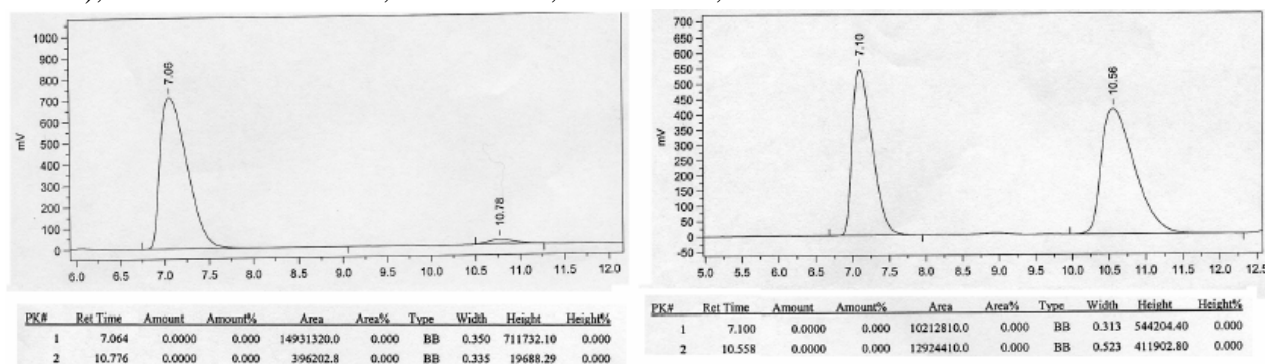
Optical purity of the aldol adduct was established by chiral HPLC analysis: Chiracel OD (0.46 x 25 cm), 95:5 hexanes:*i*-PrOH, 1.0 mL/min,  $\lambda = 254$  nm, 87% *ee*.



**Ethyl-(*S*)-2-hydroxy-2-isopropyl-4-oxo-4-phenylbutanoate (Table 2, entry 4).** The reaction mixture was allowed to stir at  $-30$  °C for 24 h. Following purification, the aldol adduct was

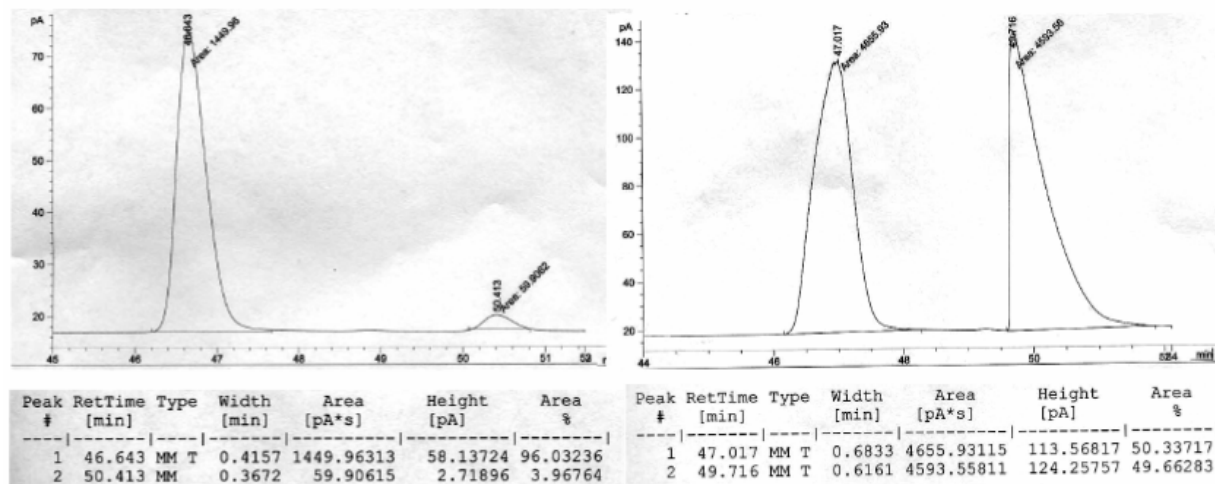
obtained as colorless oil. IR (neat): 3509 (br), 2966 (s), 1732 (s), 1686 (s), 1451 (m), 1350 (m), 1261 (s), 1216 (s), 1039 (s)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz):  $\delta$  7.95-7.92 (2H, m), 7.59 (1H, tt,  $J = 6.8$ , 1.6 Hz), 7.48-7.44 (2H, m), 4.24 (2H, dq,  $J = 7.2$ , 1.2 Hz), 3.79 (1H, s), 3.51 (1H, d,  $J = 17.2$  Hz), 3.45 (1H, d,  $J = 17.2$  Hz), 2.00 (1H, tt,  $J = 6.8$ , 6.8 Hz), 1.26 (3H, t,  $J = 3.6$  Hz), 1.06 (3H, d,  $J = 6.8$  Hz), 0.96 (3H, d,  $J = 6.8$  Hz);  $^{13}\text{C}$  NMR (100 MHz):  $\delta$  199.0, 175.7, 136.9, 133.6, 128.8, 128.2, 77.6, 61.7, 45.0, 35.9, 17.1, 16.7, 14.3; HRMS calcd for  $\text{C}_{15}\text{H}_{20}\text{O}_4\text{Na}$  ( $\text{M}+\text{Na}^+$ ): 287.1259, Found: 287.1252;  $[\alpha]_{\text{D}}^{20} = -28.78$  ( $c = 0.43$ ,  $\text{CHCl}_3$ ).

Optical purity of the aldol adduct was established by chiral HPLC analysis: Chiracel OD (0.46 x 25 cm), 96:4 hexanes:*i*-PrOH, 1.0 mL/min,  $\lambda = 254$  nm; 95% *ee*.



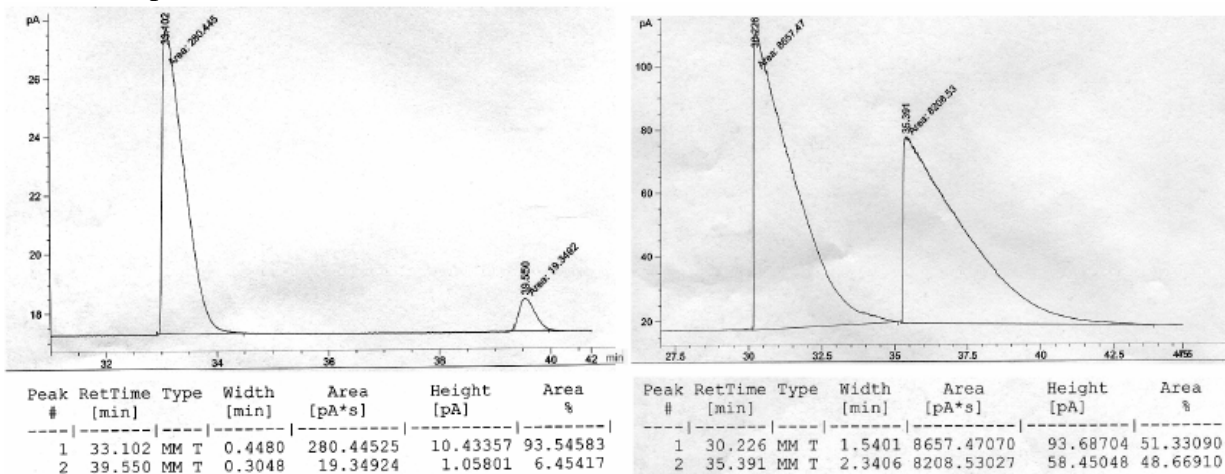
**Ethyl-(*S*)-2-hydroxy-2-isopropyl-5,5-dimethyl-4-oxohexanoate (Table 2, entry 5).** In a 16 x 100 mm test tube under an atmosphere of  $\text{N}_2$  in a glove box,<sup>3</sup>  $\text{AgF}_2$ , chiral ligand **5d**, ethyl-3-methyl-2-oxobutyrate, and tetrahydrofuran are combined as described in the general procedure. The test tube is sealed with a septum and teflon tape, removed from the glove box, and the mixture is allowed to stir for 20 min. The solution is cooled to  $-78$  °C and enolsilane added as described in the general procedure. The reaction mixture is allowed to stir at  $-15$  °C for 48 h. Following purification, the desired product is obtained as colorless oil. IR (neat): 3527 (br), 2967 (s), 2931 (s), 2873 (m), 1732 (s), 1710 (s), 1463 (m), 1394 (m), 1369 (m), 1268 (m), 1214 (s), 1191 (m), 1079 (m), 1048 (m)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz):  $\delta$  4.21 (2H, q,  $J = 6.8$  Hz), 3.69 (1H, s), 3.02 (1H, d,  $J = 17.6$  Hz), 2.92 (1H, d,  $J = 17.6$  Hz), 1.87 (1H, qq,  $J = 6.8$ , 6.8 Hz), 1.25 (3H, t,  $J = 6.8$  Hz), 1.12 (9H, s), 0.96 (3H, d,  $J = 6.8$  Hz), 0.88 (3H, d,  $J = 6.8$  Hz);  $^{13}\text{C}$  NMR (100 MHz):  $\delta$  215.4, 175.7, 77.5, 77.1, 76.8, 61.5, 44.4, 43.4, 35.8, 26.3, 17.1, 16.6, 14.3; HRMS calcd for  $\text{C}_{13}\text{H}_{24}\text{O}_4\text{Na}$  ( $\text{M}+\text{Na}^+$ ): 267.1572, Found: 267.1564;  $[\alpha]_{\text{D}}^{20} = -18.79$  ( $c = 0.45$ ,  $\text{CHCl}_3$ ). Optical purity of the aldol adduct was established by chiral GLC analysis: Chiraldex GTA, 100 °C, 15 psi; 92% *ee*.

<sup>3</sup> For addition of the enolsilane derived from 3,3-dimethyl-2-butanone higher conversion is observed when reactions are prepared under an inert atmosphere in a glove box.



**Ethyl-(S)-2-hydroxy-2-isopropyl-4-oxopentanoate (Table 2, entry 6).** The mixture is allowed to stir at  $-40\text{ }^{\circ}\text{C}$  for 48 h. Following purification, the desired product is obtained as colorless oil. IR (neat): 3503 (br), 2970 (s), 2879 (w), 1731 (s), 1363 (w), 1267 (w), 1213 (w), 1165 (w), 1131 (w), 1041 (w)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz):  $\delta$  4.23 (2H, q,  $J = 7.2$  Hz), 3.65 (1H, br s), 2.97 (1H, d,  $J = 17.6$  Hz), 2.87 (1H, d,  $J = 17.6$  Hz), 2.16 (3H, s), 1.91-1.84 (1H, m), 1.28 (3H, t,  $J = 7.2$  Hz), 0.95 (3H, d,  $J = 7.2$  Hz), 0.87 (3H, d,  $J = 7.2$  Hz);  $^{13}\text{C}$  NMR (100 MHz):  $\delta$  207.8, 175.5, 77.6, 61.8, 49.4, 35.7, 31.0, 17.0, 16.5, 14.3; HRMS calcd for  $\text{C}_{10}\text{H}_{18}\text{O}_4\text{Na}$  ( $\text{M}+\text{Na}^+$ ): 225.1103, Found: 225.1113;  $[\alpha]_{\text{D}}^{20} = -20.62$  ( $c = 0.63$ ,  $\text{CHCl}_3$ ).

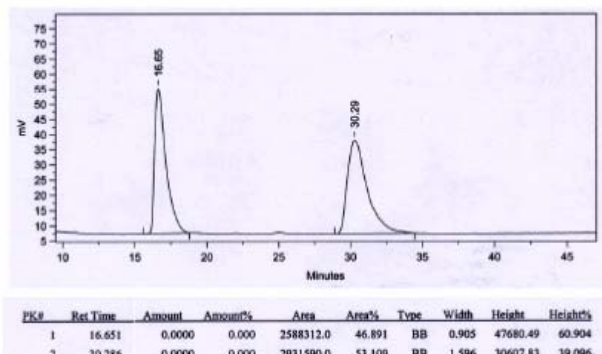
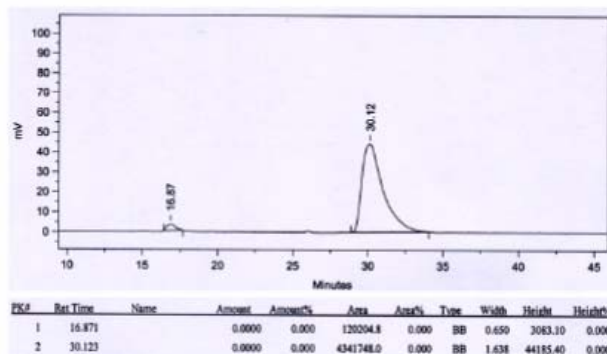
Optical purity of the aldol adduct was established by chiral GLC analysis: Chiraldex GTA,  $100\text{ }^{\circ}\text{C}$ , 15 psi); 88% *ee*.



**Ethyl-(S)-2-cyclohexyl-2-hydroxy-4-oxo-4-phenylbutanoate (Table 2, entry 7).** The mixture is allowed to stir at  $-30\text{ }^{\circ}\text{C}$  for 24 h. Following purification, the desired product is obtained as colorless oil. IR (neat): 3521 (br), 2930 (s), 2855 (m), 1732 (s), 1686 (s), 1596 (w), 1449 (s), 1357 (m), 1218 (s)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz):  $\delta$  7.95-7.92 (2H, m), 7.57 (1H tt,  $J = 6.8, 1.2$  Hz), 7.48-7.44 (2H, m), 4.24 (2H, q,  $J = 1.8$  Hz), 3.81 (1H, br s), 3.52 (1H, d,  $J = 17.2$  Hz), 3.46 (1H, d,  $J = 17.2$  Hz), 1.91-1.78 (3H, m), 1.69-1.57 (3H, m), 1.32-1.16 (8H, m);  $^{13}\text{C}$  NMR (100 MHz):  $\delta$  199.2, 175.6, 137.0, 133.6, 128.8, 128.3, 77.8, 61.7, 45.7, 44.8, 27.2, 26.7, 26.5, 26.4, 26.3,

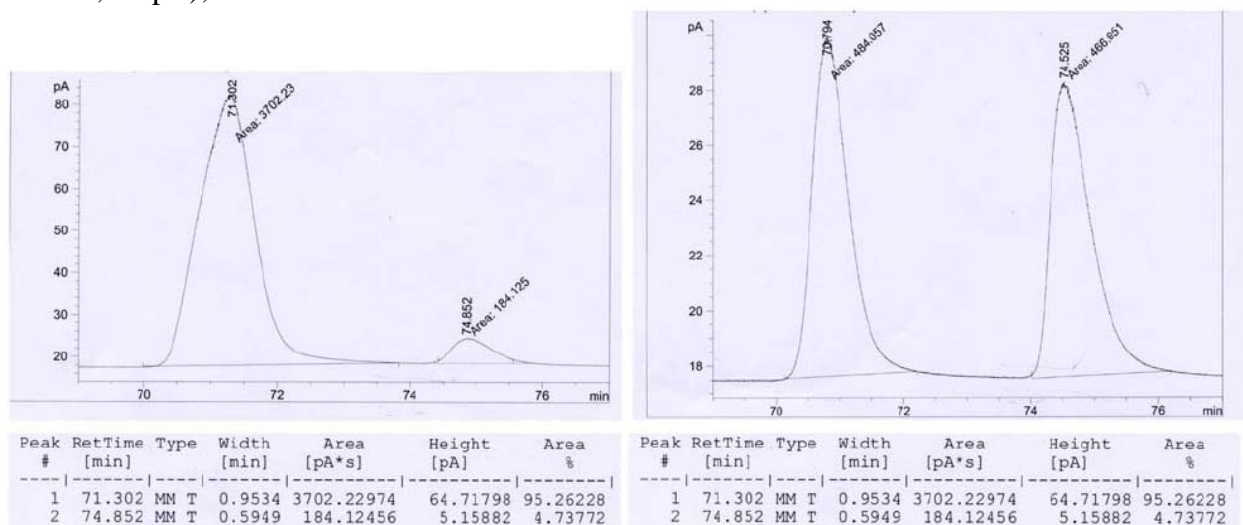
14.3; HRMS calcd for  $C_{18}H_{25}O_4$  ( $M+H^+$ ): 305.1753, Found: 305.1739;  $[\alpha]_D^{20} = -31.54$  ( $c = 0.77$ ,  $CHCl_3$ ).

Optical purity of the aldol adduct was established by diastereoselective reduction ( $BH_3 \cdot THF$ ,  $22\text{ }^\circ\text{C}$ , 15 min;  $NaBH_4$ , 4 h) of the ketone, followed by acid-catalyzed lactonization (acidic workup: addition of a 20% solution of *p*-TsOH in MeOH at  $22\text{ }^\circ\text{C}$  for 1 h; filtration and removal of solvents in vacuo). Optical purity of the derived lactone was established by chiral HPLC analysis in comparison to an authentic racemic sample: Chiracel OD (0.46 x 25 cm), 98:2 hexanes:*i*-PrOH, 1.0 mL/min,  $\lambda = 254\text{ nm}$ ; 95% *ee*.



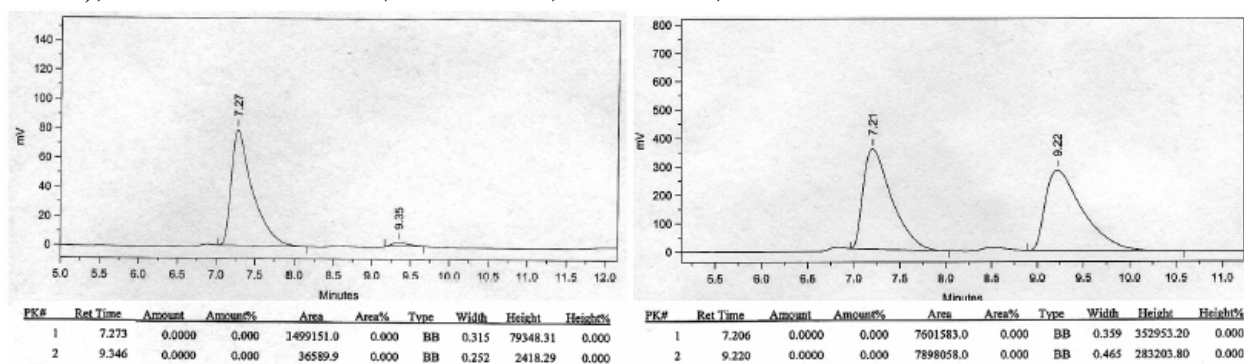
**Ethyl-(*S*)-2-cyclohexyl-2-hydroxy-4-oxopentanoate (Table 2, entry 8).** The mixture is allowed to stir at  $-30\text{ }^\circ\text{C}$  for 24 h. Following purification, the desired product is obtained as colorless oil. IR (neat): 3509 (br), 2931 (s), 2854 (m), 1728 (s), 1451 (w), 1364 (m), 1267 (w), 1212 (s), 1113 (m)  $cm^{-1}$ ;  $^1H$  NMR (400 MHz):  $\delta$  4.33 (2H, q,  $J = 7.2\text{ Hz}$ ), 3.66 (1H, s), 2.97 (1H, d,  $J = 17.2\text{ Hz}$ ), 2.89 (1H, d,  $J = 17.2\text{ Hz}$ ), 2.15 (3H, s), 1.81-1.75 (3H, m), 1.66-1.63 (1H, m), 1.55-1.49 (2H, m), 1.28 (3H, t,  $J = 7.2\text{ Hz}$ ), 1.27-1.07 (5H, m);  $^{13}C$  NMR (100 MHz):  $\delta$  208.0, 175.4, 77.7, 61.8, 45.2, 45.5, 31.0, 27.0, 26.5, 26.4, 26.3, 26.2, 14.3; HRMS calcd for  $C_{13}H_{22}O_4$ : 242.1518, Found: 242.1520;  $[\alpha]_D^{20} = -16.07$  ( $c = 0.87$ ,  $CHCl_3$ ).

Optical purity of the aldol adduct was established by chiral GLC analysis: Chiraldex GTA,  $120\text{ }^\circ\text{C}$ , 15 psi; 90% *ee*.



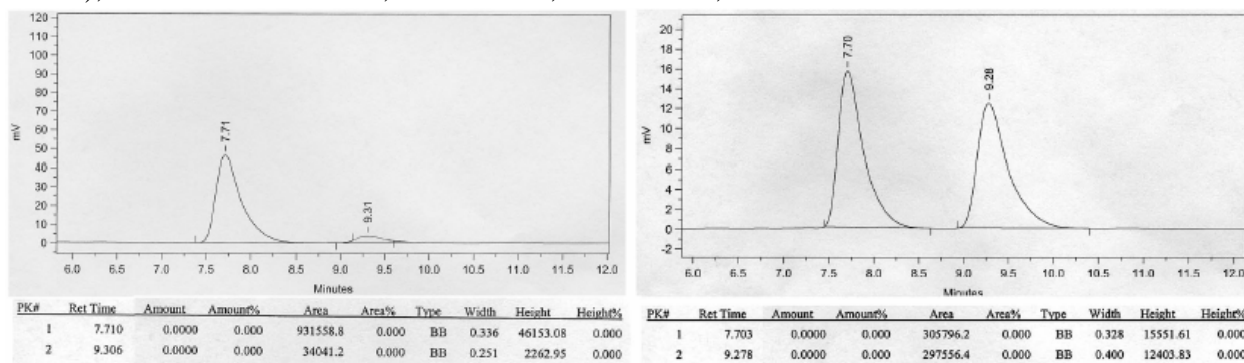
**Ethyl-(S)-2-cyclopropyl-2-hydroxy-4-oxo-4-phenylbutanoate (Table 2, entry 9).** The mixture is allowed to stir at  $-40\text{ }^{\circ}\text{C}$  for 48 h. Following purification, the desired product is obtained as colorless oil. IR (neat): 3503 (br), 2974 (w), 1732 (s), 1686 (s), 1449 (m), 1356 (m), 1276 (m), 1210 (s), 1051 (m)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz):  $\delta$  7.96-7.94 (2H, m), 7.58 (1H, tt,  $J = 7.2, 1.2$  Hz), 7.48-7.44 (2H, m), 4.28 (2H, q,  $J = 7.2$  Hz), 3.63 (1H, dd,  $J = 17.6, 0.4$  Hz), 3.53 (1H, d,  $J = 17.6$  Hz), 3.48 (1H, s), 1.27 (3H, t,  $J = 7.2$  Hz), 1.21-1.13 (1H, m), 0.65-0.54 (2H, m), 0.49-0.42 (1H, m), 0.39-0.33 (1H, m);  $^{13}\text{C}$  NMR (100 MHz):  $\delta$  198.3, 175.9, 136.7, 133.6, 128.8, 128.3, 72.5, 62.0, 47.7, 18.5, 14.3, 0.35,  $-0.23$ ; HRMS calcd for  $\text{C}_{15}\text{H}_{18}\text{O}_4\text{Na}$  ( $\text{M}+\text{Na}^+$ ): 285.1103, Found: 285.1087;  $[\alpha]_{\text{D}}^{20} = -33.19$  ( $c = 1.04, \text{CHCl}_3$ ).

Optical purity of the aldol adduct was established by chiral HPLC analysis: Chiracel OD (0.46 x 25 cm), 95:5 hexanes:*i*-PrOH, 1.0 mL/min,  $\lambda = 254$  nm; 96% *ee*.



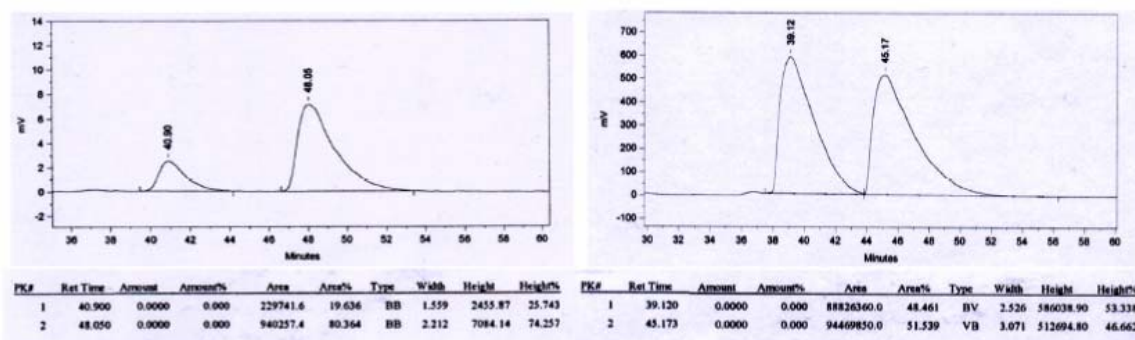
**Ethyl-(S)-2-hydroxy-3-methyl-2-(2-oxo-2-phenylethyl)but-3-enoate (Table 2, entry 10).** The mixture is allowed to stir at  $-40\text{ }^{\circ}\text{C}$  for 48 h. Following purification, the desired product is obtained as colorless oil. IR (neat): 3509 (br), 2980 (m), 2936 (w), 1729 (s), 1686 (s), 1449 (m), 1282 (m), 1283 (m), 1211 (s), 1069 (m), 690 (m);  $^1\text{H}$  NMR (400 MHz):  $\delta$  7.97-7.94 (2H, m), 7.59 (1H, tt,  $J = 7.2, 1.2$  Hz), 7.50-7.45 (2H, m), 5.30-5.29 (1H, m), 5.07-5.06 (1H, m), 4.26 (2H, dq,  $J = 7.2, 1.2$  Hz), 3.77 (1H, d,  $J = 17.2$  Hz), 3.46 (1H, d,  $J = 17.2$  Hz), 1.88-1.87 (3H, m), 1.27 (3H, t,  $J = 7.2$  Hz);  $^{13}\text{C}$  NMR (100 MHz):  $\delta$  199.0, 173.9, 144.1, 136.7, 133.8, 128.8, 128.3, 113.4, 77.6, 62.2, 45.5, 19.0, 14.2; HRMS calcd for  $\text{C}_{15}\text{H}_{18}\text{O}_4\text{Na}$  ( $\text{M}+\text{Na}^+$ ): 285.1103, Found: 285.1099;  $[\alpha]_{\text{D}}^{20} = -14.67$  ( $c = 0.80, \text{CHCl}_3$ ).

Optical purity of the aldol adduct was established by chiral HPLC analysis: Chiracel OD (0.46 x 25 cm), 95:5 hexanes:*i*-PrOH, 1.0 mL/min,  $\lambda = 254$  nm; 90% *ee*.



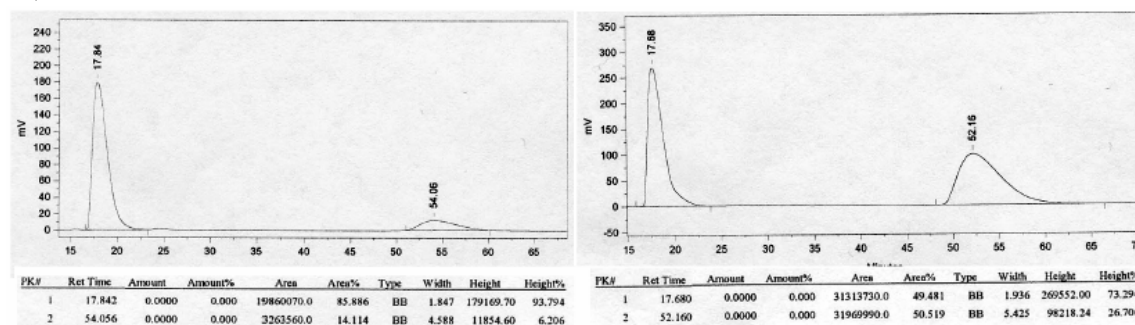
**Ethyl-(S)-2-hydroxy-4-oxo-2,4-diphenylbutanoate (Table 2, entry 11).** The mixture is allowed to stir at  $-30\text{ }^{\circ}\text{C}$  for 24 h. Following purification, the desired product is obtained as colorless oil. IR (neat): 3515 (br), 3055 (w), 2974 (m), 1730 (s), 1683 (s), 1448 (m), 1267 (m), 1213 (s), 1180 (m), 1060 (m)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz):  $\delta$  7.98-7.95 (2H, m), 7.69-7.67 (2H, m), 7.60 (1H, tt,  $J = 6.8, 1.2$  Hz), 7.50-7.45 (2H, m), 7.42-7.38 (2H, m), 7.36-7.32 (1H, m), 4.51 (1H, s), 4.26 (2H, q,  $J = 7.2$  Hz), 4.07 (1H, d,  $J = 17.6$  Hz), 3.58 (1H, d,  $J = 17.6$  Hz), 1.25 (3H, t,  $J = 7.2$  Hz);  $^{13}\text{C}$  NMR (100 MHz):  $\delta$  198.7, 174.1, 140.8, 136.4, 133.8, 128.8, 128.6, 128.3, 128.2, 125.2, 76.5, 62.3, 49.1, 14.1; HRMS calcd for  $\text{C}_{18}\text{H}_{18}\text{O}_4\text{Na}$  ( $\text{M}+\text{Na}^+$ ): 321.1103, Found: 321.1110; Anal Calcd for  $\text{C}_{18}\text{H}_{18}\text{O}_4$ : C, 72.47; H, 6.08; Found: C, 72.51; H, 6.36;  $[\alpha]_{\text{D}}^{20} = -36.79$  ( $c = 0.90, \text{CHCl}_3$ ).

Optical purity of the aldol adduct was established by chiral HPLC analysis: Chiracel OD (0.46 x 25 cm), 98:2 hexanes:*i*-PrOH, 0.5 mL/min,  $\lambda = 254$  nm; 60% *ee*.



**Ethyl-(R)-2-hydroxy-4-oxo-4-phenyl-2-(thiophen-2-yl)butanoate (Table 2, entry 12).** The mixture is allowed to stir at  $-30\text{ }^{\circ}\text{C}$  for 48 h. Following purification, the desired product is obtained as pale yellow oil. IR (neat): 3483 (br), 3062 (w), 2980 (m), 1737 (s), 1680 (s), 1597 (s), 1449 (m), 1352 (m), 1266 (m), 1214 (s), 1115 (m), 1061 (m)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz):  $\delta$  7.97-7.95 (2H, m), 7.60 (1H, tt,  $J = 6.8, 1.6$  Hz), 7.50-7.46 (2H, m), 7.29 (1H, dd,  $J = 5.3, 1.2$  Hz), 7.15 (1H, dd,  $J = 4.0, 1.2$  Hz), 7.01 (1H, dd,  $J = 5.3, 4.0$  Hz), 4.60 (1H, s), 4.29 (2H, q,  $J = 7.2$  Hz), 4.02 (1H, d,  $J = 17.6$  Hz), 3.78 (1H, d,  $J = 17.6$  Hz), 1.28 (3H, t,  $J = 7.2$  Hz);  $^{13}\text{C}$  NMR (100 MHz):  $\delta$  197.7, 173.3, 145.7, 136.4, 134.0, 128.9, 128.4, 127.3, 125.7, 124.1, 75.4, 62.8, 49.8, 14.2; HRMS calcd for  $\text{C}_{16}\text{H}_{16}\text{O}_4\text{SNa}$  ( $\text{M}+\text{Na}^+$ ): 327.0667, Found: 327.0676;  $[\alpha]_{\text{D}}^{20} = -33.59$  ( $c = 0.77, \text{CHCl}_3$ ).

Optical purity of the aldol adduct was established by chiral HPLC analysis: Chiracel AS (0.46 x 25 cm), 95:5 hexanes:*i*-PrOH, 1.0 mL/min,  $\lambda = 254$  nm; 72% *ee*.

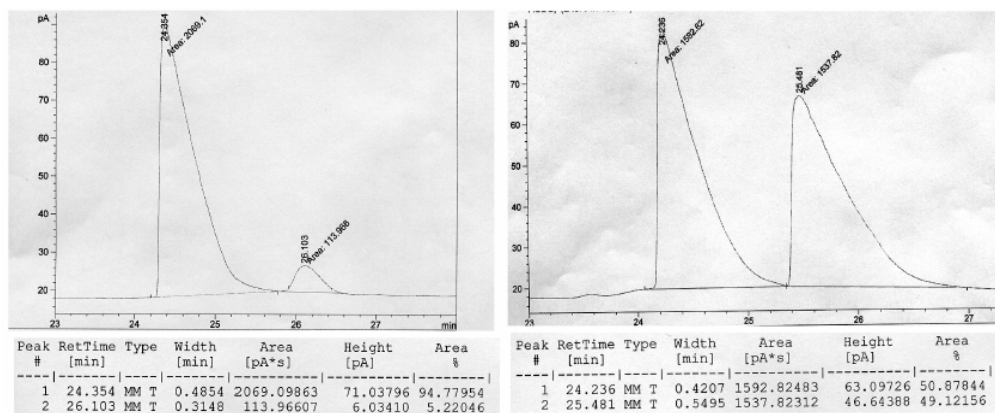


**Methyl-(*R*)-5-oxo-2-(2-oxo-2-phenylethyl)tetrahydrofuran-2-carboxylate (eq 1).** The mixture is allowed to stir at  $-30\text{ }^{\circ}\text{C}$  for 24 h after which 1 mL of a 2 N solution of HCl is added; the resulting solution is allowed to stir for 4 h. The mixture is washed with  $\text{Et}_2\text{O}$ , as described in the general procedure. The purified product is obtained as a white solid. m. p. =  $70.5\text{ }^{\circ}\text{C}$ ; IR (neat): 1785 (s), 1746 (m), 1687 (m), 1451 (w), 1369 (w), 1173 (s), 1064 (s);  $^1\text{H}$  NMR (400 MHz):  $\delta$  7.93 (2H, d,  $J = 7.6$  Hz), 7.60 (1H, t,  $J = 7.2$  Hz), 7.48 (2H, t,  $J = 7.6$  Hz), 3.83 (1H, d,  $J = 17.6$  Hz), 3.82 (3H, s), 3.68 (1H, d,  $J = 17.6$  Hz), 2.84-2.59 (3H, m), 2.38-2.27 (1H, m);  $^{13}\text{C}$  NMR (100 MHz):  $\delta$  195.2, 175.9, 171.3, 136.2, 134.0, 129.0, 128.3, 83.7, 53.4, 46.1, 31.4, 28.1; HRMS calcd for  $\text{C}_{14}\text{H}_{14}\text{O}_5\text{Na}$  ( $\text{M}+\text{Na}^+$ ): 285.0739, Found: 285.0758;  $[\alpha]_{\text{D}}^{20} = +11.96$  ( $c = 1.02$ ,  $\text{CHCl}_3$ ).

**Representative experimental procedure for enantioselective Ag-catalyzed hetero-Diels-Alder (HDA) reactions of  $\alpha$ -ketoesters:** A 16 x 100 mm test tube equipped with a magnetic stir bar is charged with  $\text{AgF}_2$  (1.8 mg, 0.012 mmol), chiral ligand **5d** (5.2 mg, 0.012 mmol) and tetrahydrofuran (0.40  $\mu\text{L}$ ) is added. The resulting solution is allowed to stir while ethyl-3-methyl-2-oxobutyrate (17  $\mu\text{L}$ , 0.12 mmol) is added followed by the addition of 0.40  $\mu\text{L}$  of tetrahydrofuran. The tube is capped with a septum, purged with  $\text{N}_2$ , and allowed to stir for 20 min, after which the solution is allowed to cool to  $-78\text{ }^{\circ}\text{C}$ , and *trans*-1-methoxy-3-(trimethylsiloxy)1,3-butadiene (27  $\mu\text{L}$ , 0.14 mmol) dissolved in THF (0.40 mL) is added in a dropwise fashion (syringe). The test tube is sealed with teflon tape and warmed to  $-30\text{ }^{\circ}\text{C}$  in a circulating bath. The mixture is allowed to stir for 24 h at  $-30\text{ }^{\circ}\text{C}$ , after which 1 mL of a 2.0 M aqueous solution of HCl is added and the mixture is allowed to warm to  $22\text{ }^{\circ}\text{C}$  and stir for 1 h. The aqueous layer is washed with  $\text{Et}_2\text{O}$  (3 x 1.0 mL) and the combined organic layers are filtered through silica and concentrated under reduced pressure to afford pale yellow oil, which is purified by silica gel chromatography (5:1 pentane: $\text{Et}_2\text{O}$ ) to deliver the desired unsaturated pyranone as a colorless oil (17 mg, 0.08 mmol, 66% yield).

**Ethyl-(*S*)-2-isopropyl-4-oxo-3,4-dihydro-2H-pyran-2-carboxylate (eq 3,  $\text{R} = i\text{-Pr}$ ).** The mixture is allowed to stir at  $-30\text{ }^{\circ}\text{C}$  for 24 h. Following purification, the desired cycloadduct is obtained as colorless oil. IR (neat): 2967 (m), 2817 (s), 2848 (m), 1734 (s), 1682 (s), 1597 (s), 1463 (m), 1400 (m), 1274 (s), 1218 (m), 1174 (m)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz):  $\delta$  7.37 (1H, d,  $J = 6.1$  Hz), 5.40 (1H, dd,  $J = 6.1, 1.2$  Hz), 4.22 (2H, tt,  $J = 7.2, 7.2$  Hz), 2.89 (1H, dd,  $J = 16.8, 1.2$  Hz), 2.76 (1H, d,  $J = 16.8$  Hz), 2.22 (1H, tt,  $J = 6.8, 6.8$  Hz), 1.26 (3H, t,  $J = 6.8$  Hz), 1.02 (3H, d,  $J = 6.8$  Hz), 1.01 (3H, d,  $J = 6.8$  Hz);  $^{13}\text{C}$  NMR (100 MHz):  $\delta$  190.8, 170.6, 162.5, 107.6, 88.7, 62.3, 40.7, 34.9, 16.9, 16.7, 14.3; HRMS calcd for  $\text{C}_{11}\text{H}_{17}\text{O}_4$  ( $\text{M}+\text{H}^+$ ): 213.1120, Found: 213.1127;  $[\alpha]_{\text{D}}^{20} = -125.15$  ( $c = 0.93$ ,  $\text{CHCl}_3$ ).

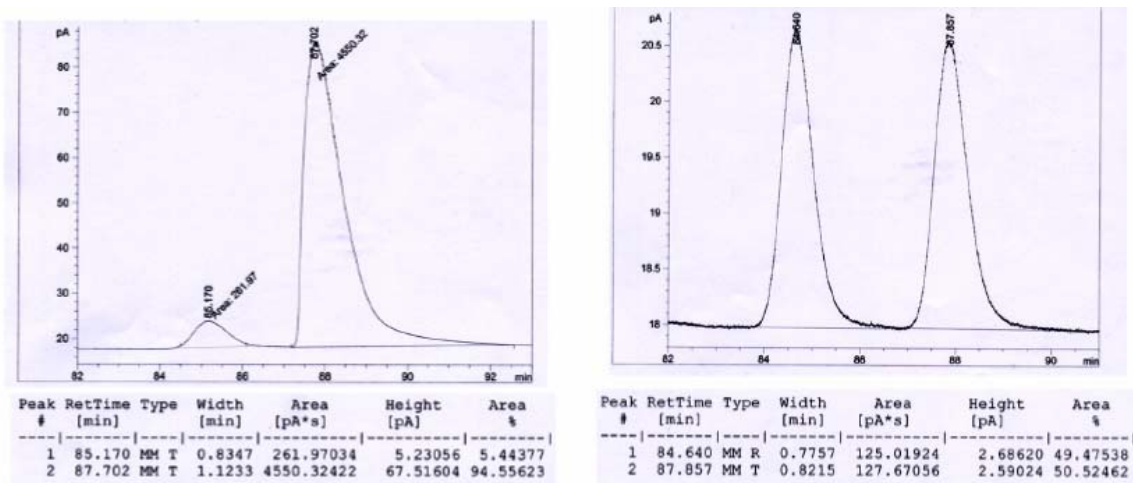
Optical purity of the cycloadduct was established by chiral GLC analysis: Chiraldex GTA,  $130\text{ }^{\circ}\text{C}$ , 15 psi); 90% *ee*.



**Ethyl-(S)-2-(2-cyclohexyl-4-oxo-3,4-dihydro-2H-pyran-2-yl)-2-oxoacetate (eq 3, R = Cy).**

The mixture is allowed to stir at  $-30\text{ }^{\circ}\text{C}$  for 24 h. Following purification, the desired cycloadduct is obtained as colorless oil. IR (neat): 2929 (s), 2854 (m), 1733 (s), 1684 (s), 1597 (s), 1451 (w), 1401 (m), 1273 (s), 1221 (m), 1181 (m), 1026 (m)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz):  $\delta$  7.50 (1H, d,  $J = 6.0$  Hz), 5.39 (1H, dd,  $J = 6.0, 1.2$  Hz), 4.21 (2H, q,  $J = 6.8$  Hz), 2.87 (1H, dd,  $J = 16.4, 1.2$  Hz), 2.79 (1H, d,  $J = 16.4$  Hz), 1.90-1.68 (6H, m), 1.31-1.03 (8H, m);  $^{13}\text{C}$  NMR (100 MHz):  $\delta$  191.0, 170.7, 162.5, 107.6, 88.7, 62.3, 44.6, 40.8, 27.1, 26.9, 26.3, 26.2, 14.4; HRMS calcd for  $\text{C}_{14}\text{H}_{20}\text{O}_4$ : 252.1362, Found: 252.1358;  $[\alpha]_{\text{D}}^{20} = -106.34^{\circ}$  ( $c = 0.04, \text{CHCl}_3$ ).

Optical purity of the cycloadduct was established by chiral GLC analysis: Chiraldex GTA,  $140\text{ }^{\circ}\text{C}$ , 15 psi); 90% *ee*.

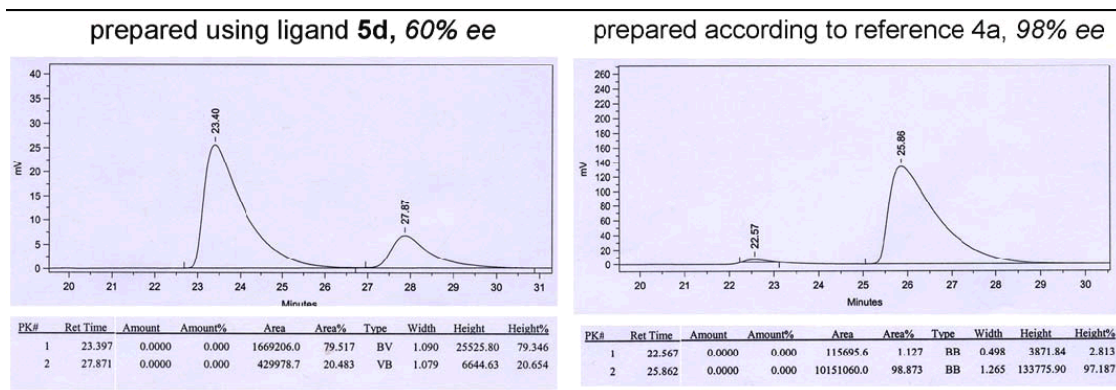
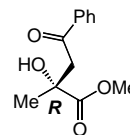


**Proof of absolute stereochemistry.** The spectral data for methyl-(*R*)-2-hydroxy-2-methyl-4-oxo-4-phenylbutanoate are consistent with those reported in the literature.<sup>4</sup> Moreover, as summarized in the Table below, the optical rotation measurements correspond to the (*R*) enantiomer being formed as the major enantiomer with chiral ligand **5d**.

4) (a) Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.* **1999**, *121*, 686–699. (b) Bolm, C.; Langner, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 5984–5987.

**Table.** Comparison of Specific Rotation Values

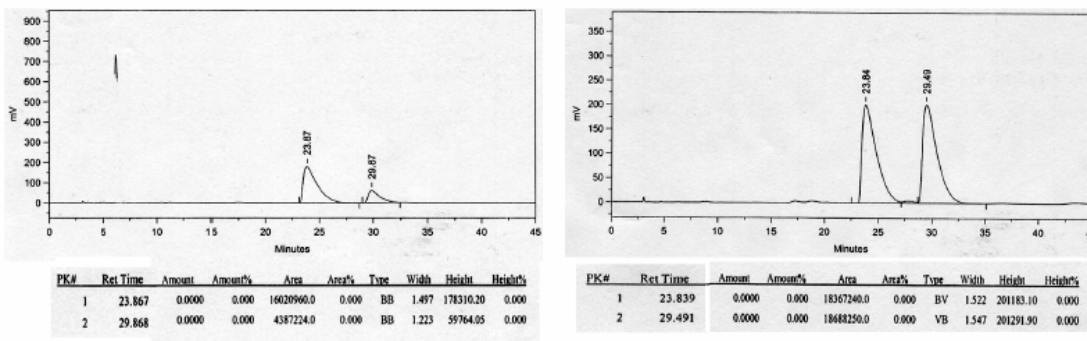
study	product ee (%)	specific rotation $[(\alpha)_D]$	absolute configuration
Evans (ref 4a)	99	+84.4 ( $c = 3.5, \text{CHCl}_3$ )	S
Bolm (ref 4b)	98	-86.7 ( $c = 1.0, \text{CHCl}_3$ )	R
this study	60	-39.6 ( $c = 3.5, \text{CHCl}_3$ )	R



A sample of optically enriched methyl-2-hydroxy-2-methyl-4-oxo-4-phenylbutanoate was prepared through the use of  $\text{Cu}(\text{OTf})_2$  and (*S,S*)-bis(*tert*-butyloxazoline), according to procedures described by Evans in reference 4a. Comparison of chiral HPLC data vs the optically enriched sample of the same compound obtained through Ag-catalyzed aldol addition confirms enrichment of the opposite enantiomer and the aforementioned stereochemical assignment (Chiracel OD (0.46 x 25 cm), 98:2 hexanes:*i*-PrOH, 1.0 mL/min,  $\lambda = 254$  nm; (*R*) enantiomer  $t_r = 23.4$  min, (*S*) enantiomer  $t_r = 27.9$  min).

**Methyl-(*R*)-2-hydroxy-2-methyl-4-oxo-4-phenylbutanoate.** The mixture is allowed to stir at  $-30$  °C for 24 h. Following purification, the aldol adduct is obtained as a colorless oil. IR (neat): 3521 (br), 2980 (m), 2955 (m), 1740 (s), 1682 (s), 1450 (m), 1216 (s), 1114 (m)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz):  $\delta$  7.94-7.91 (2H, m), 7.58 (1H t,  $J = 7.2$  Hz), 7.48-7.44 (2H, m), 3.97 (1H, br s), 3.76 (3H, s), 3.66 (1H, d,  $J = 17.6$  Hz), 3.34 (1H, d,  $J = 17.6$  Hz), 1.50 (3H, s);  $^{13}\text{C}$  NMR (100 MHz):  $\delta$  202.8, 199.12, 136.5, 134.0, 128.9, 128.4, 72.9, 53.0, 48.2, 26.7; HRMS calcd for  $\text{C}_{12}\text{H}_{14}\text{O}_4\text{Na}$  ( $\text{M}+\text{Na}^+$ ): 245.0790, Found: 245.0806;  $[\alpha]_D^{20} = -39.58$  ( $c = 3.5, \text{CHCl}_3$ ).

Optical purity of the aldol adduct was established by chiral HPLC analysis: Chiracel OD (0.46 x 25 cm), 98:2 hexanes:*i*-PrOH, 1.0 mL/min,  $\lambda = 254$  nm; 60% ee.



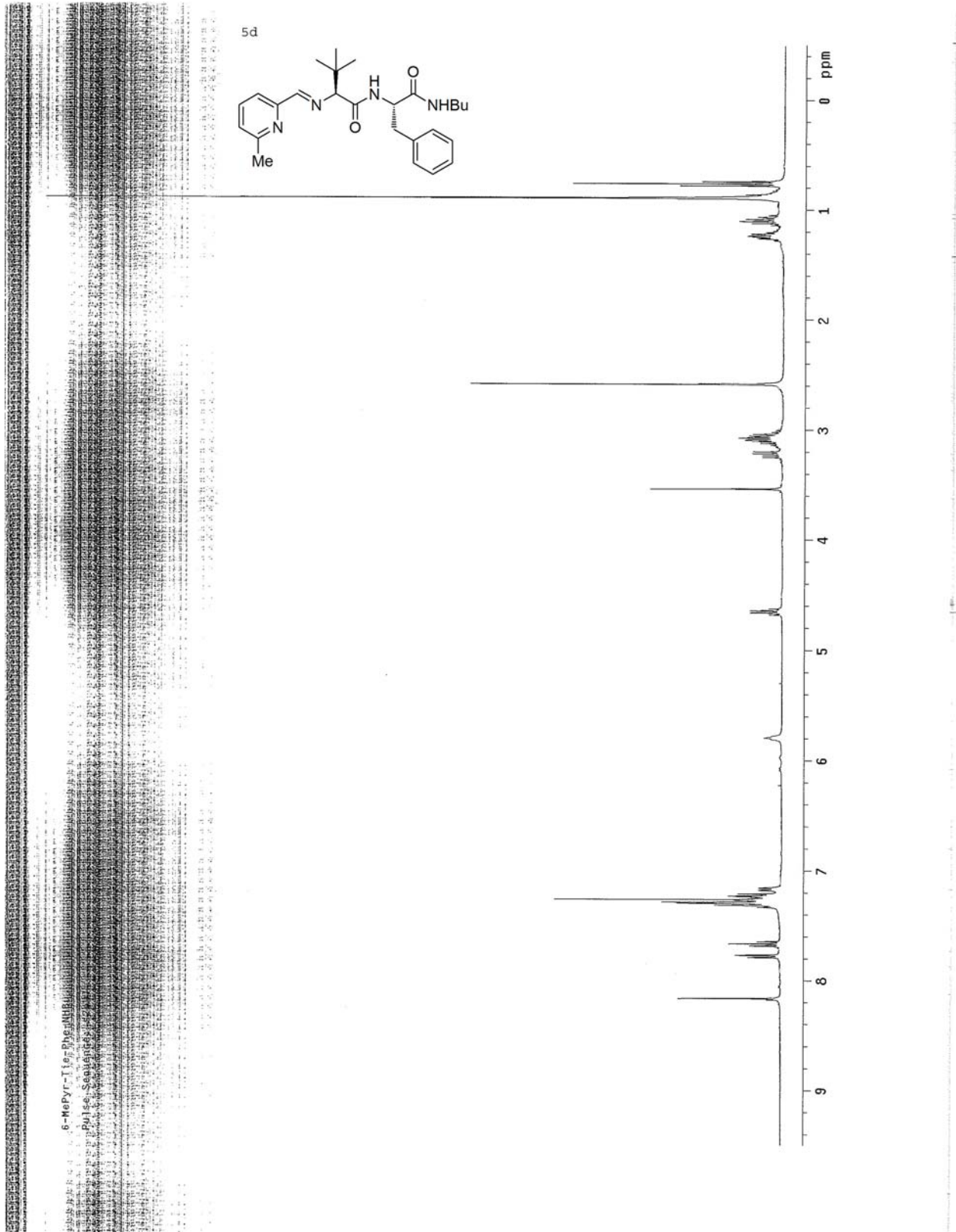
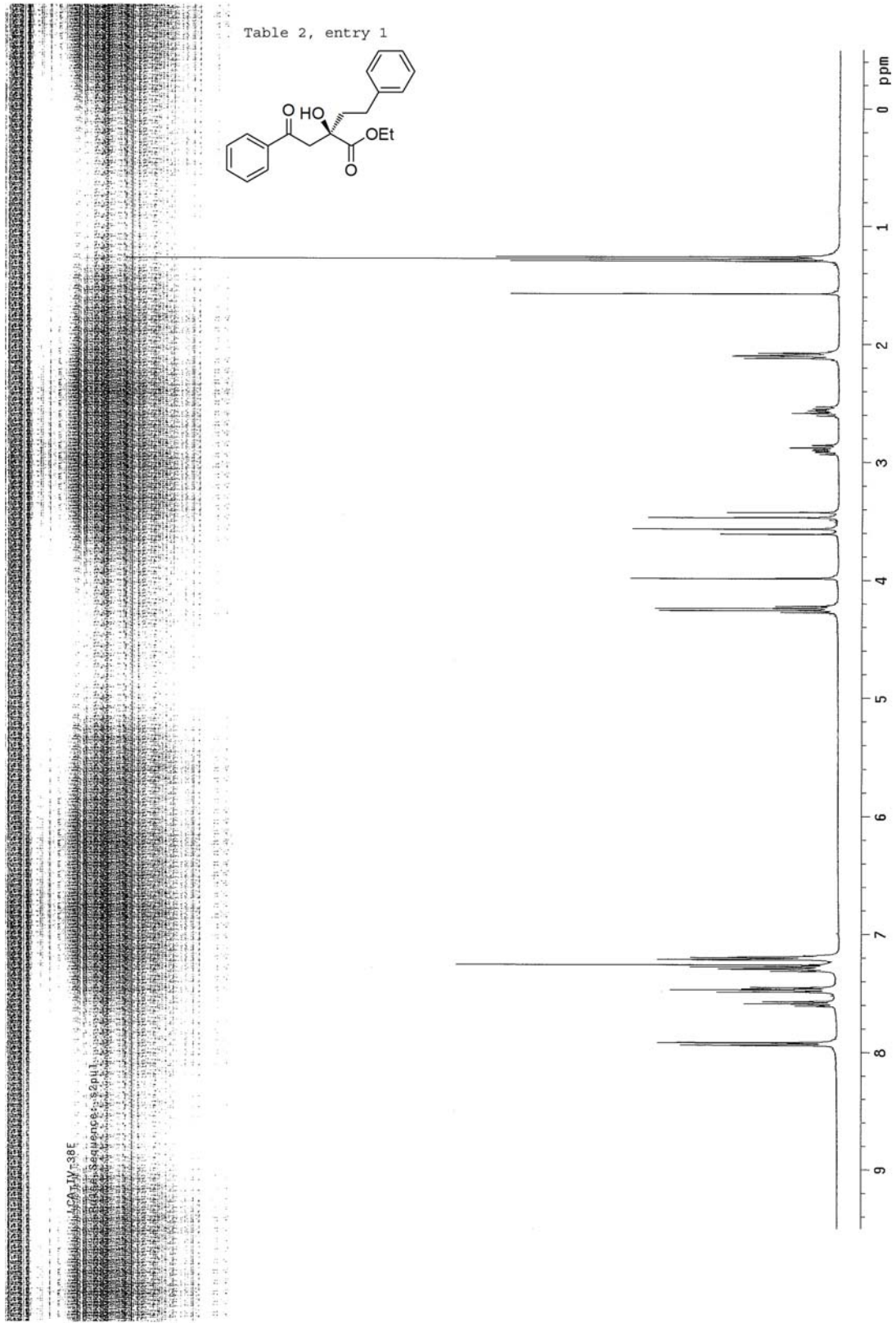
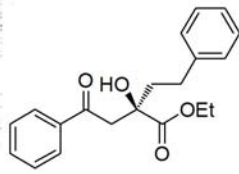


Table 2, entry 1



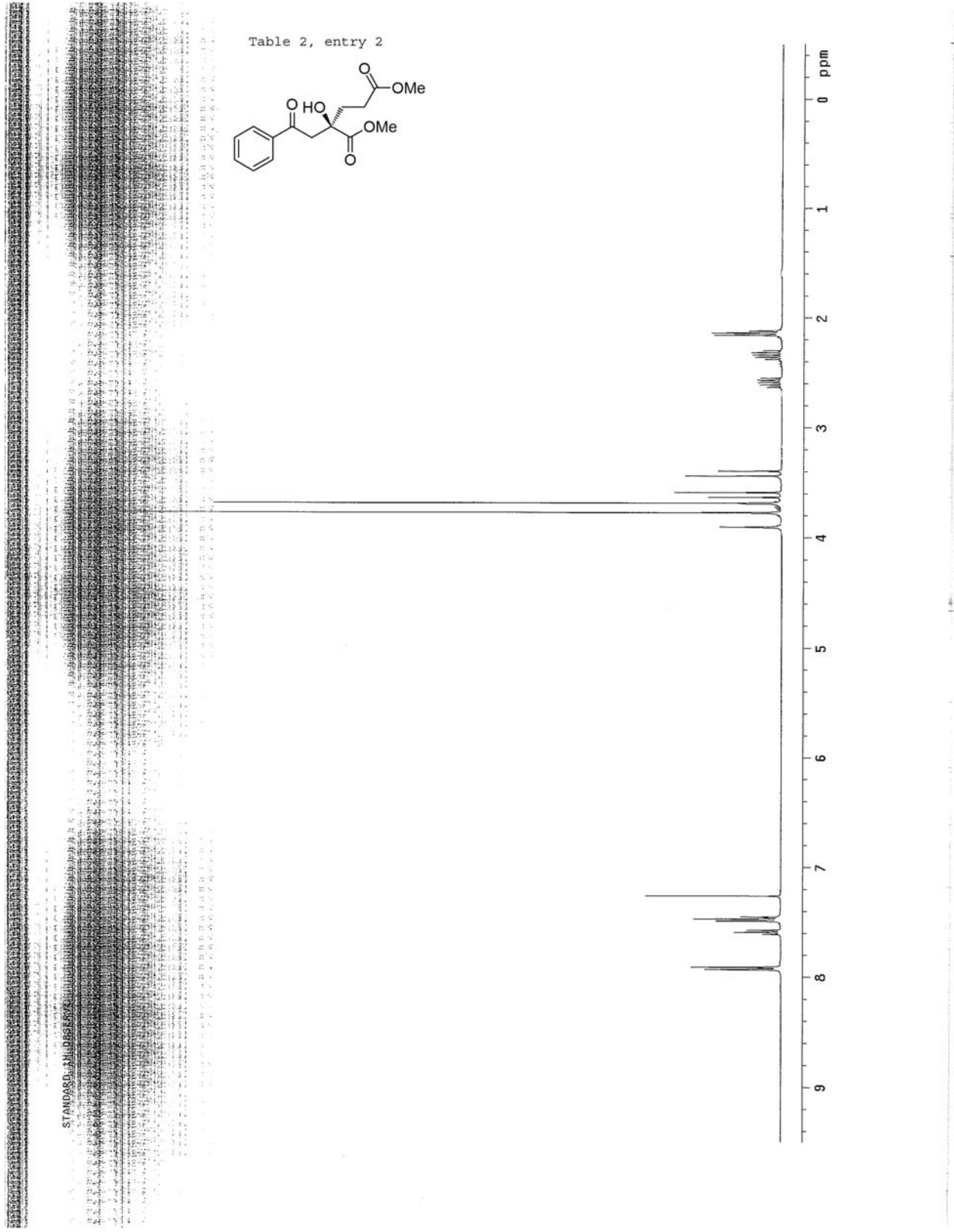
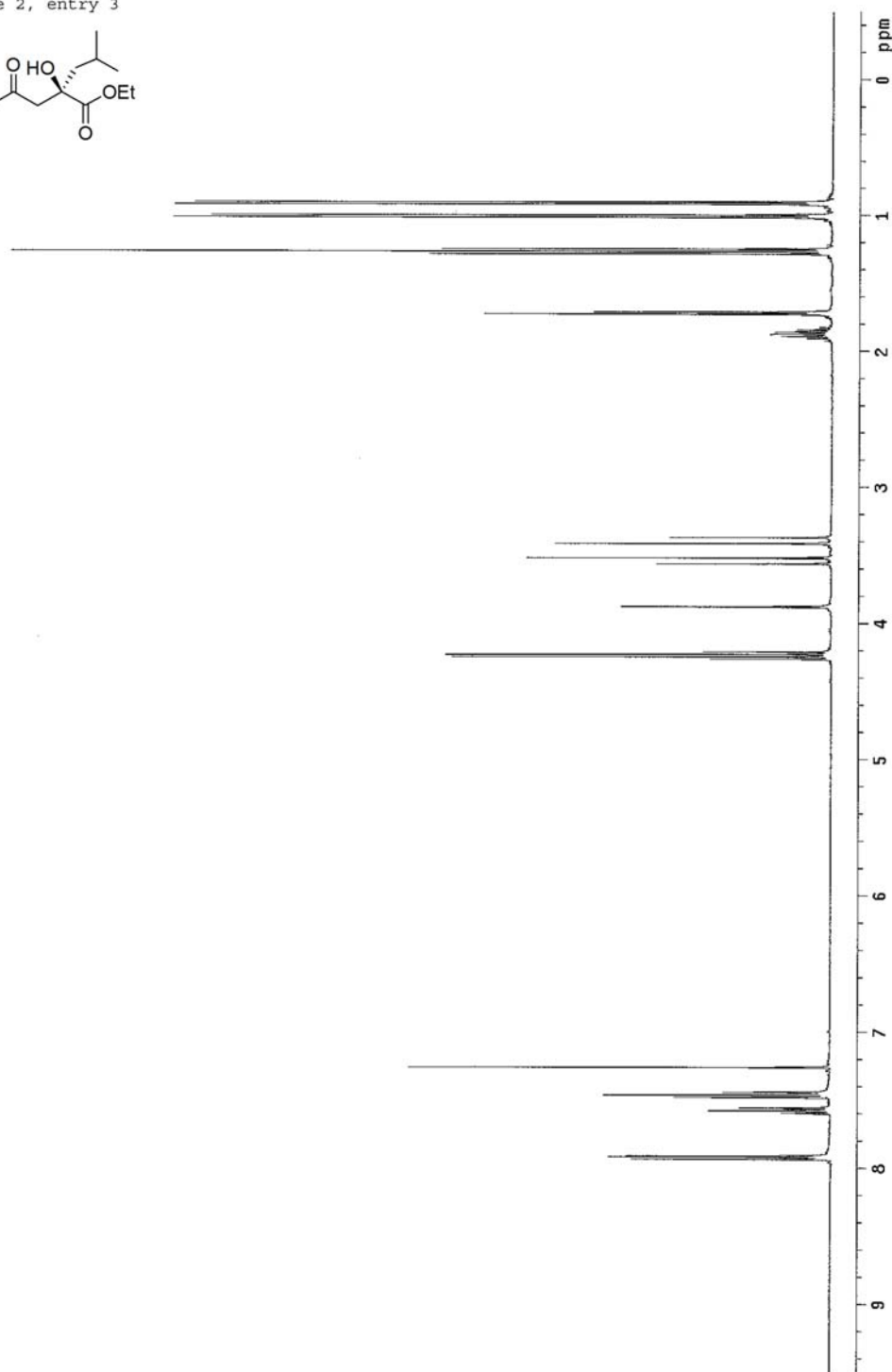
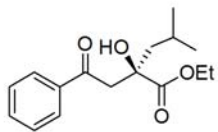


Table 2, entry 3



1H NMR spectrum (ppm) showing peaks at approximately 7.2-7.4, 4.1-4.5, 3.5-4.0, 2.0-2.5, 1.0-1.5, and 0.8-1.0 ppm.

LCN-TV-38C  
Pulse Sequence: zgpg30

1H NMR spectrum (400 MHz, CDCl3) of the compound shown in Table 2, entry 4. The spectrum displays peaks in the aromatic region (7.2-7.8 ppm), a multiplet for the methine proton (4.2-4.8 ppm), a quartet for the ethoxy methyl protons (3.7-3.9 ppm), and a doublet for the ethoxy methylene protons (1.1-1.3 ppm). Integration values are provided below the peaks.

Table 2, entry 4

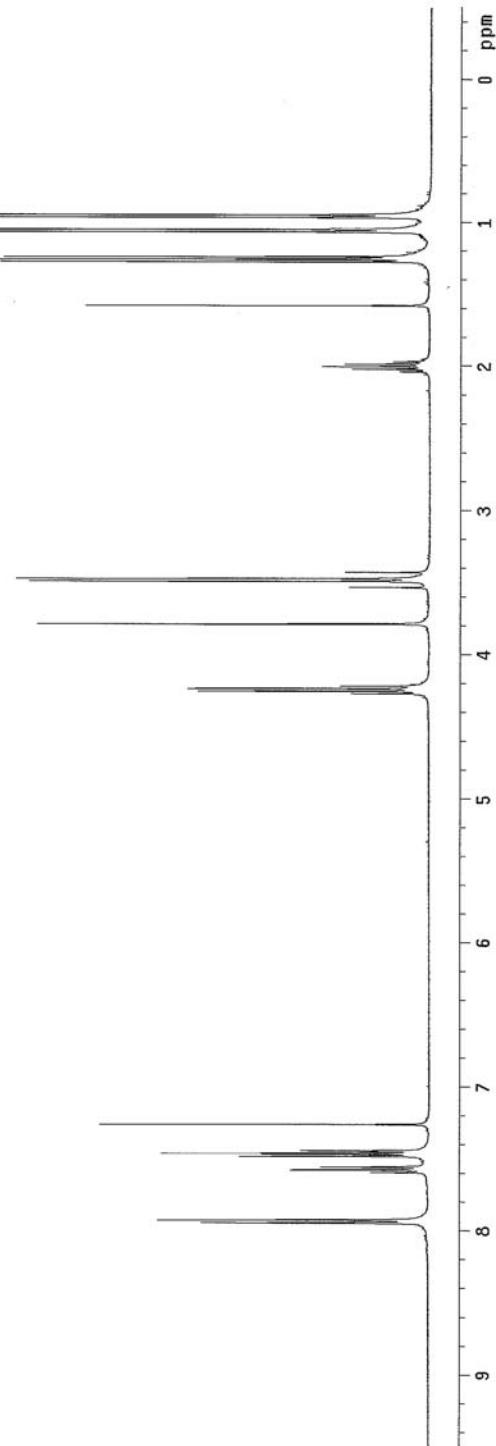
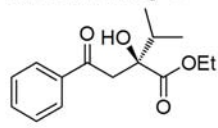


Table 2, entry 5

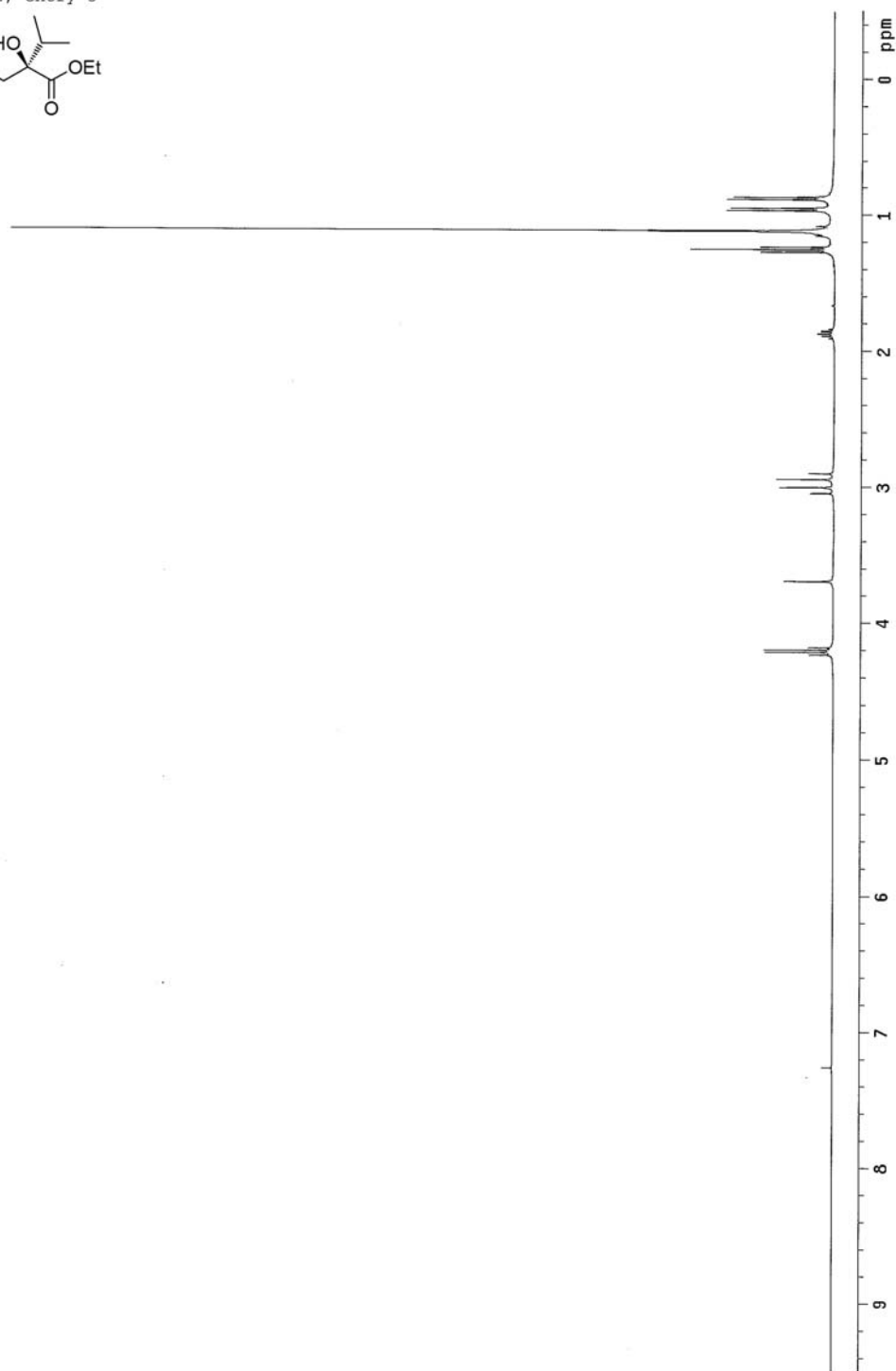
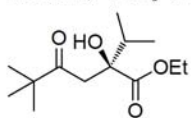


Table 2, entry 6

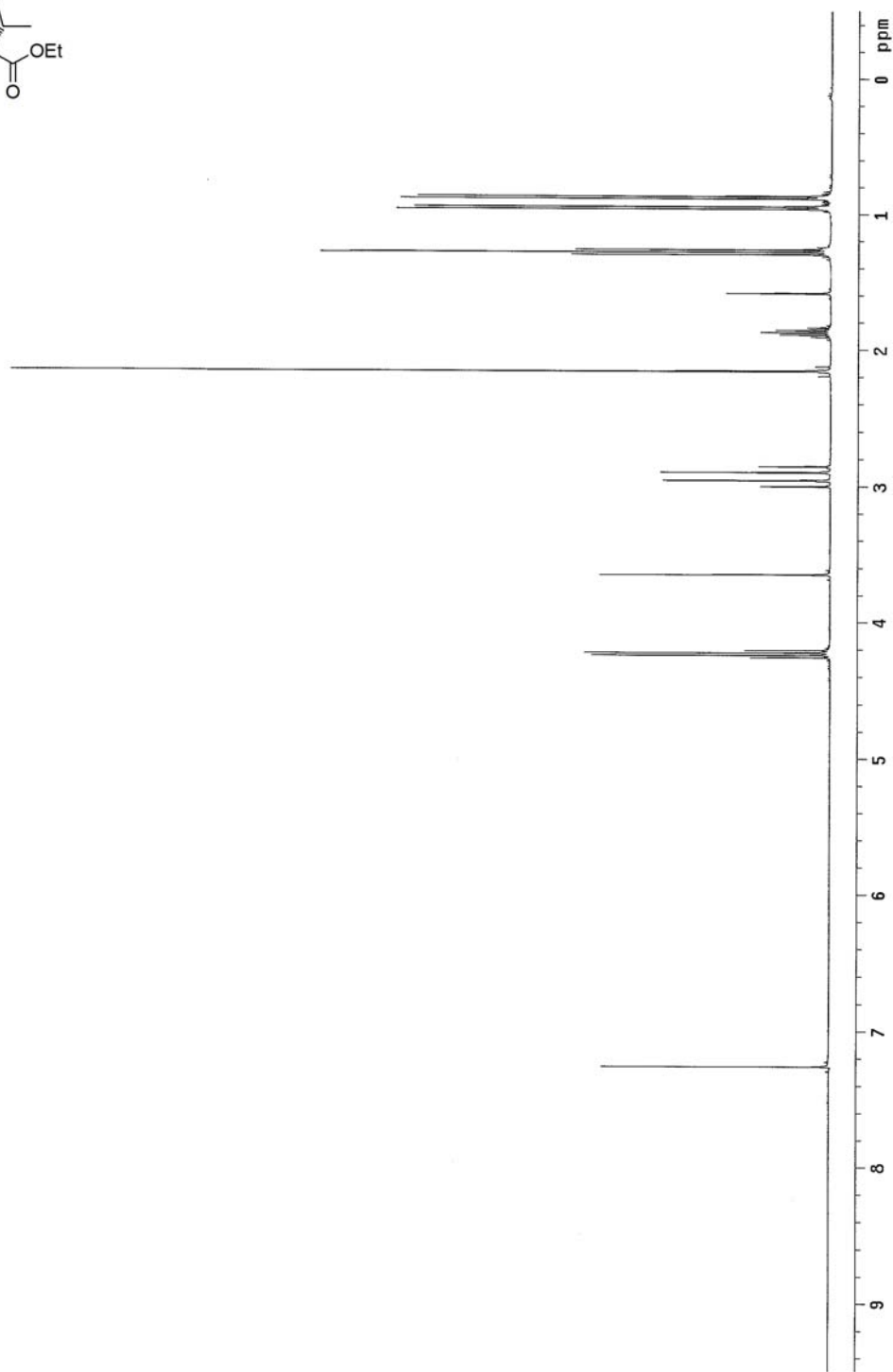
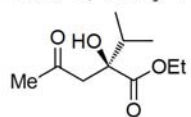


Table 2, entry 7

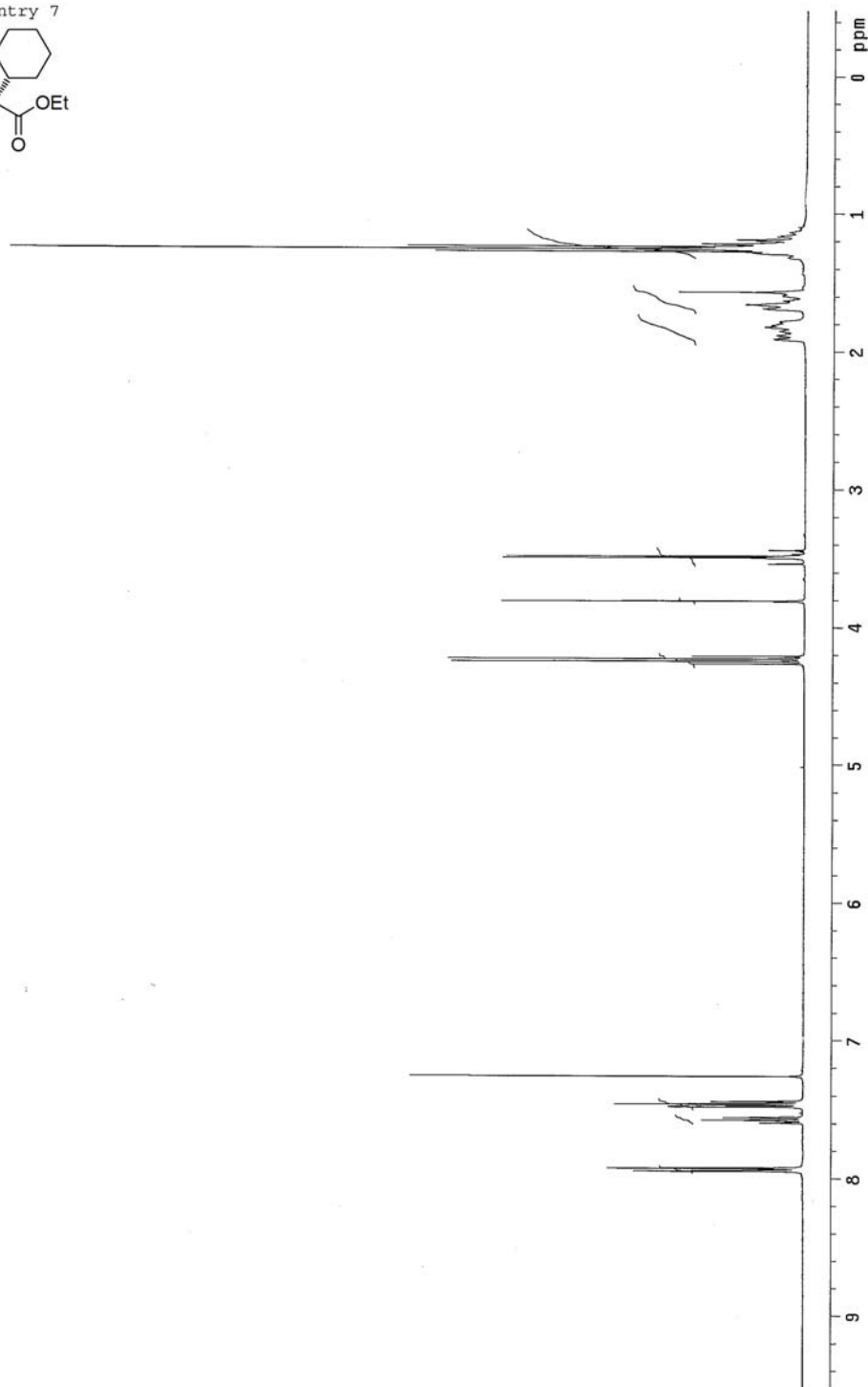
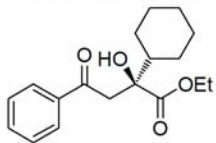


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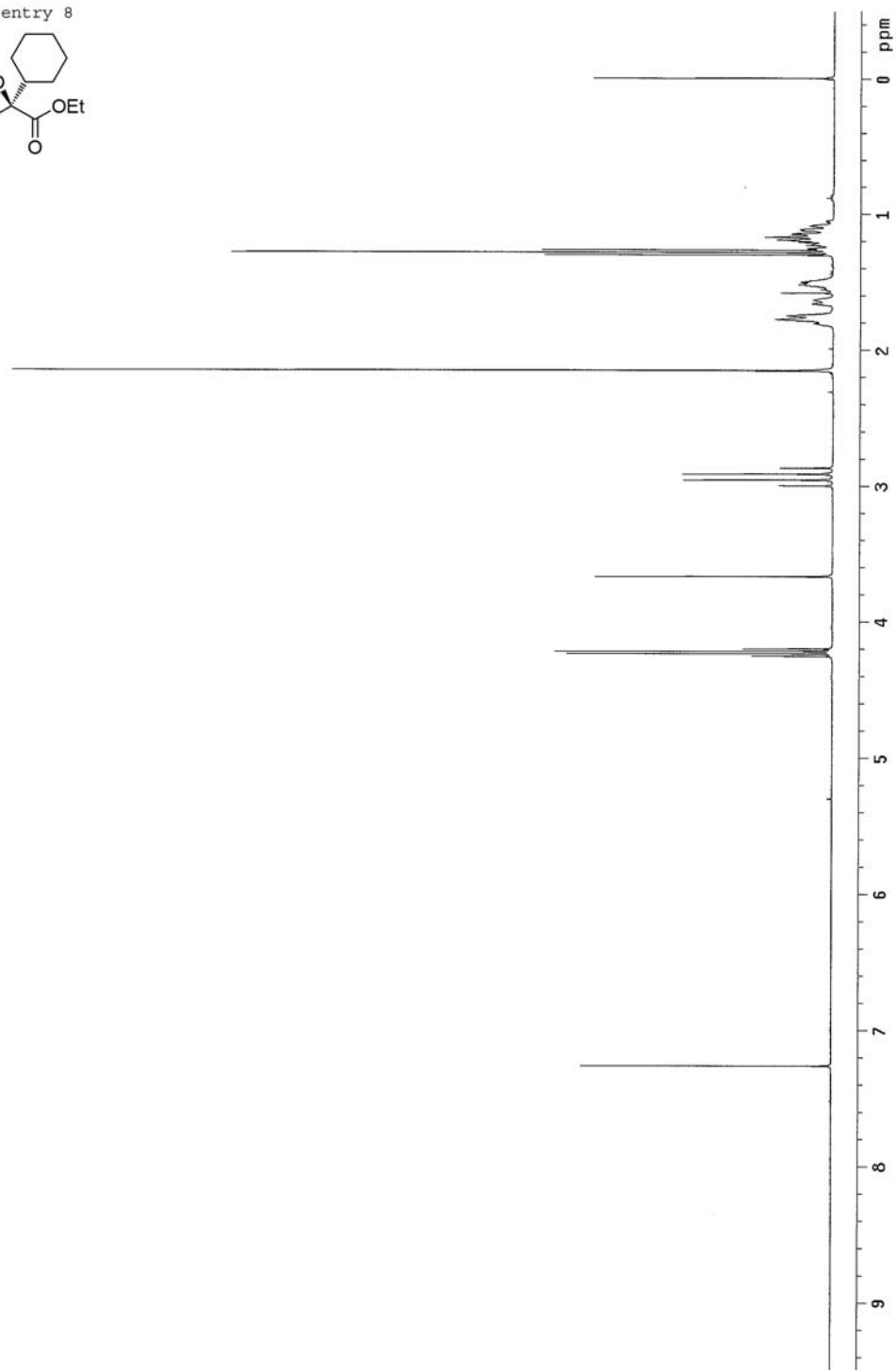
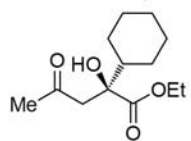


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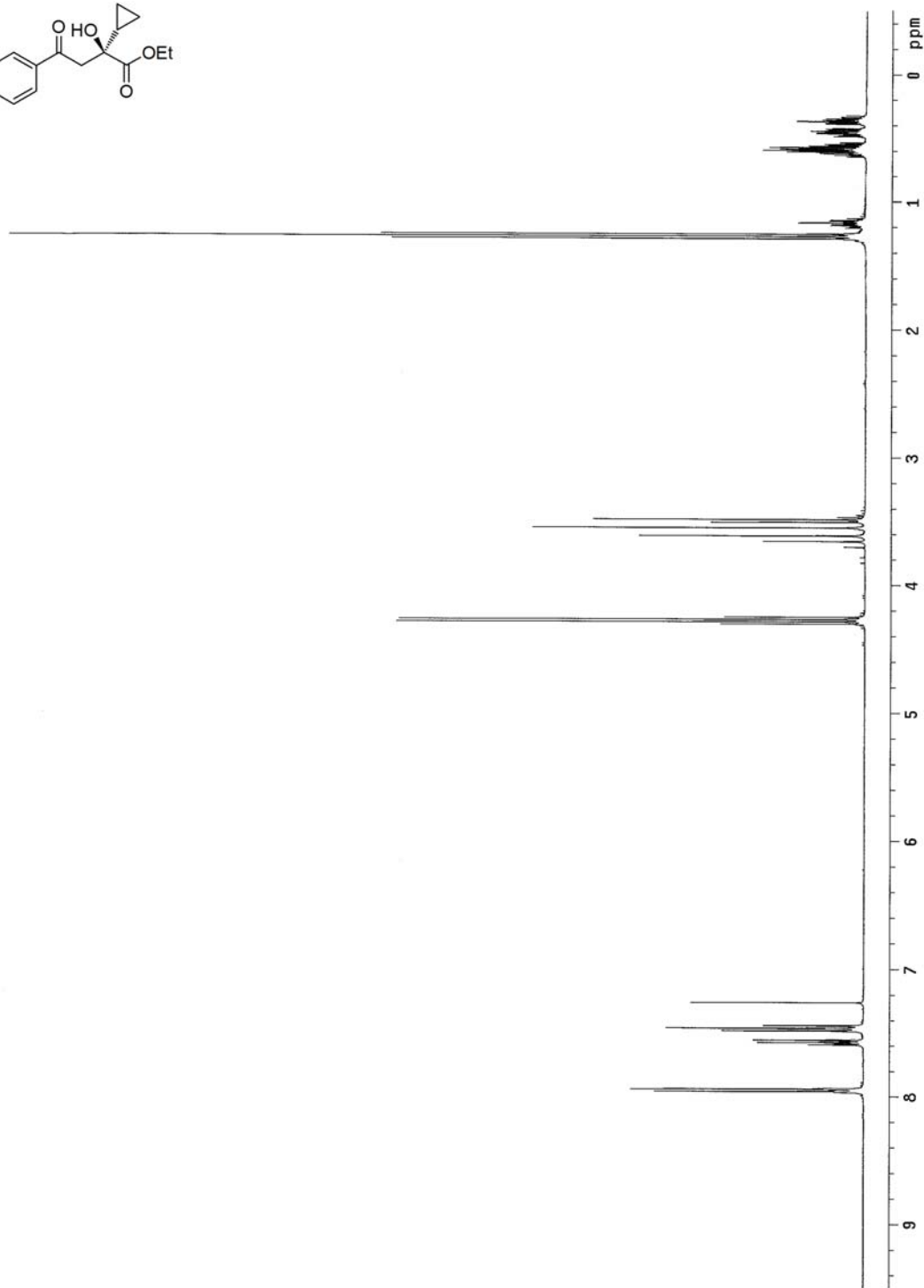
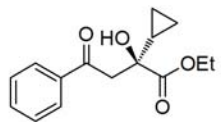


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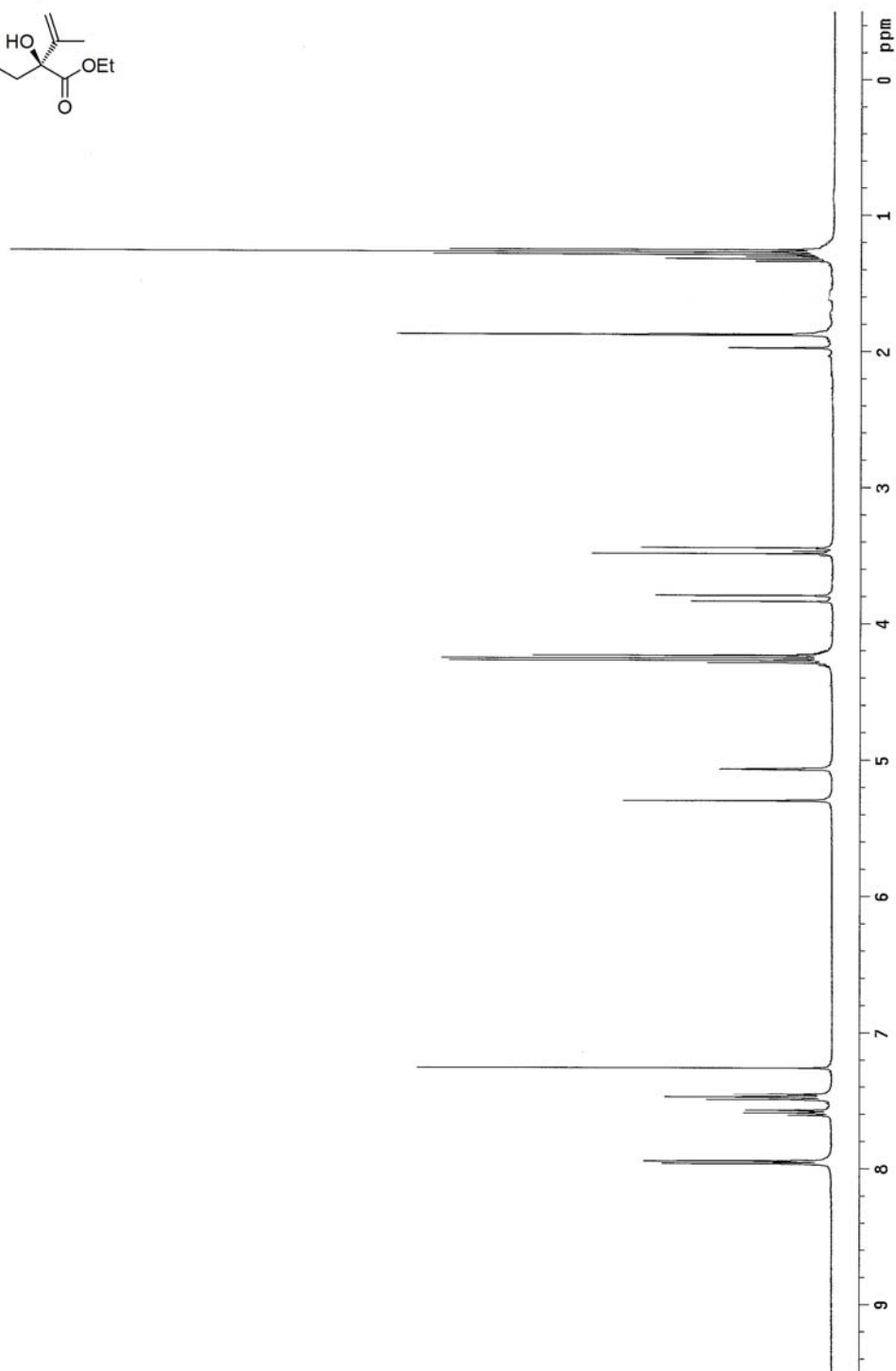
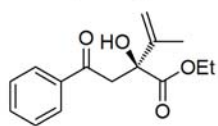


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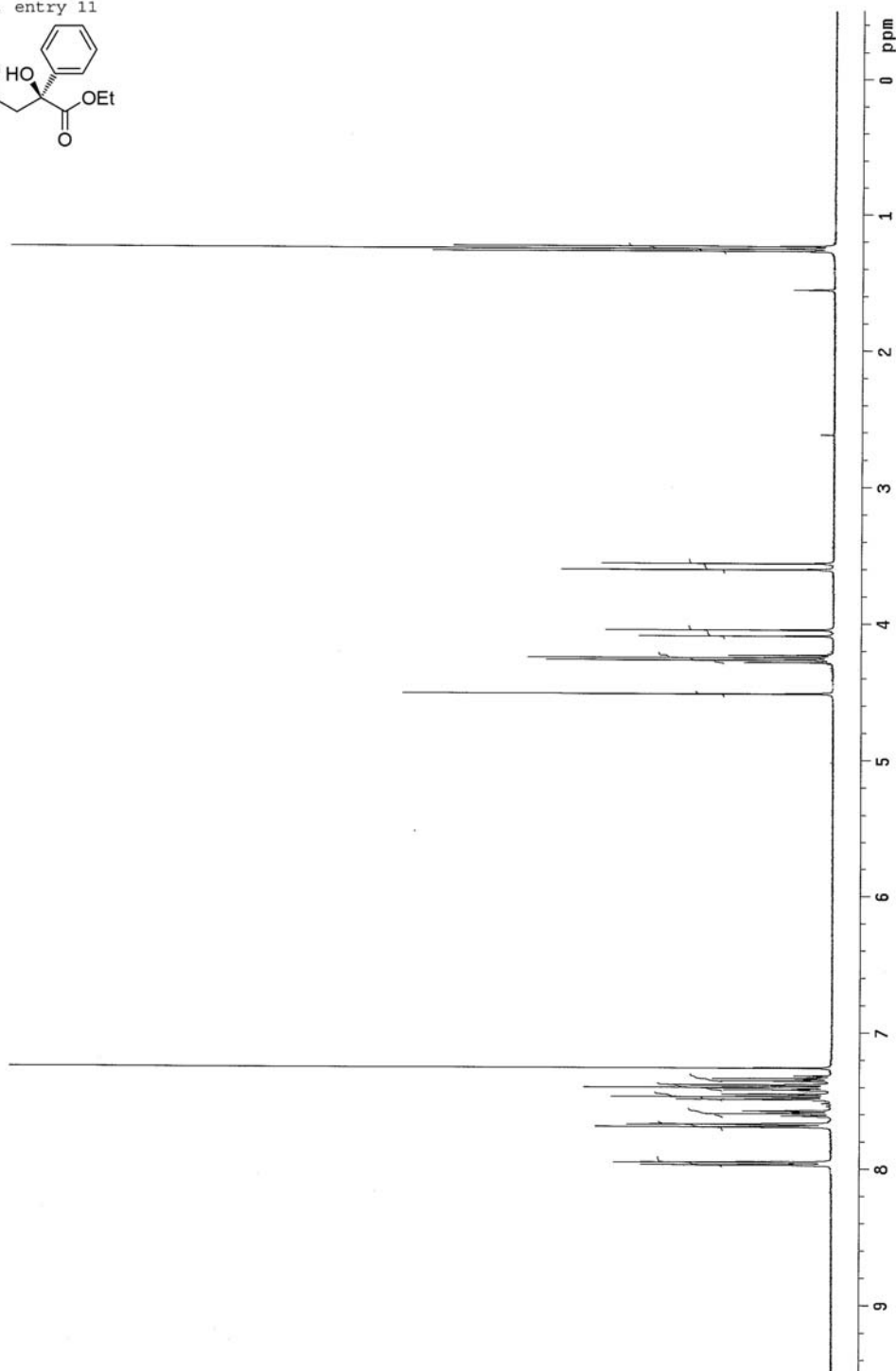
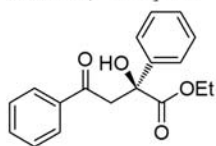
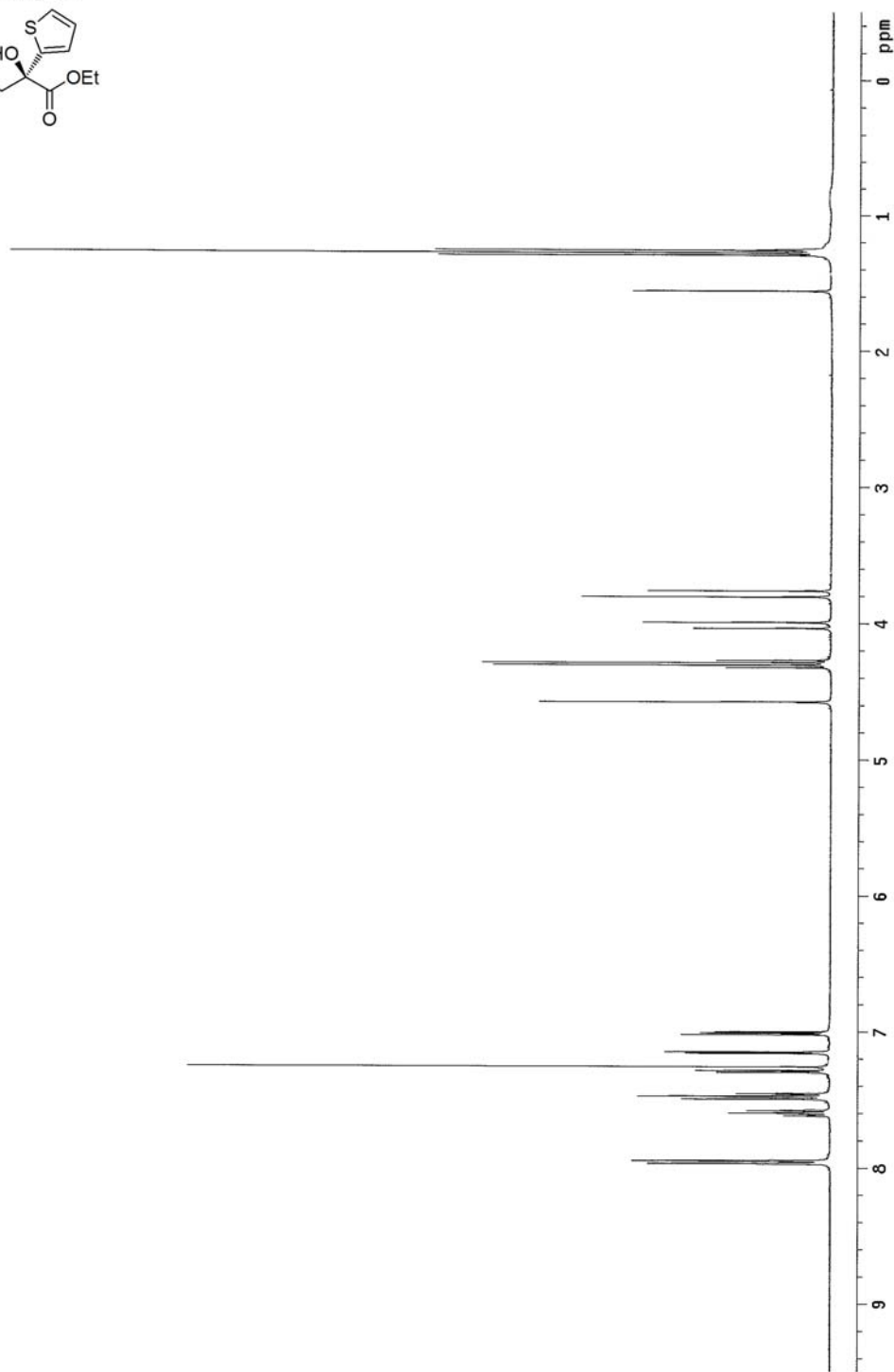
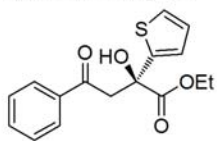
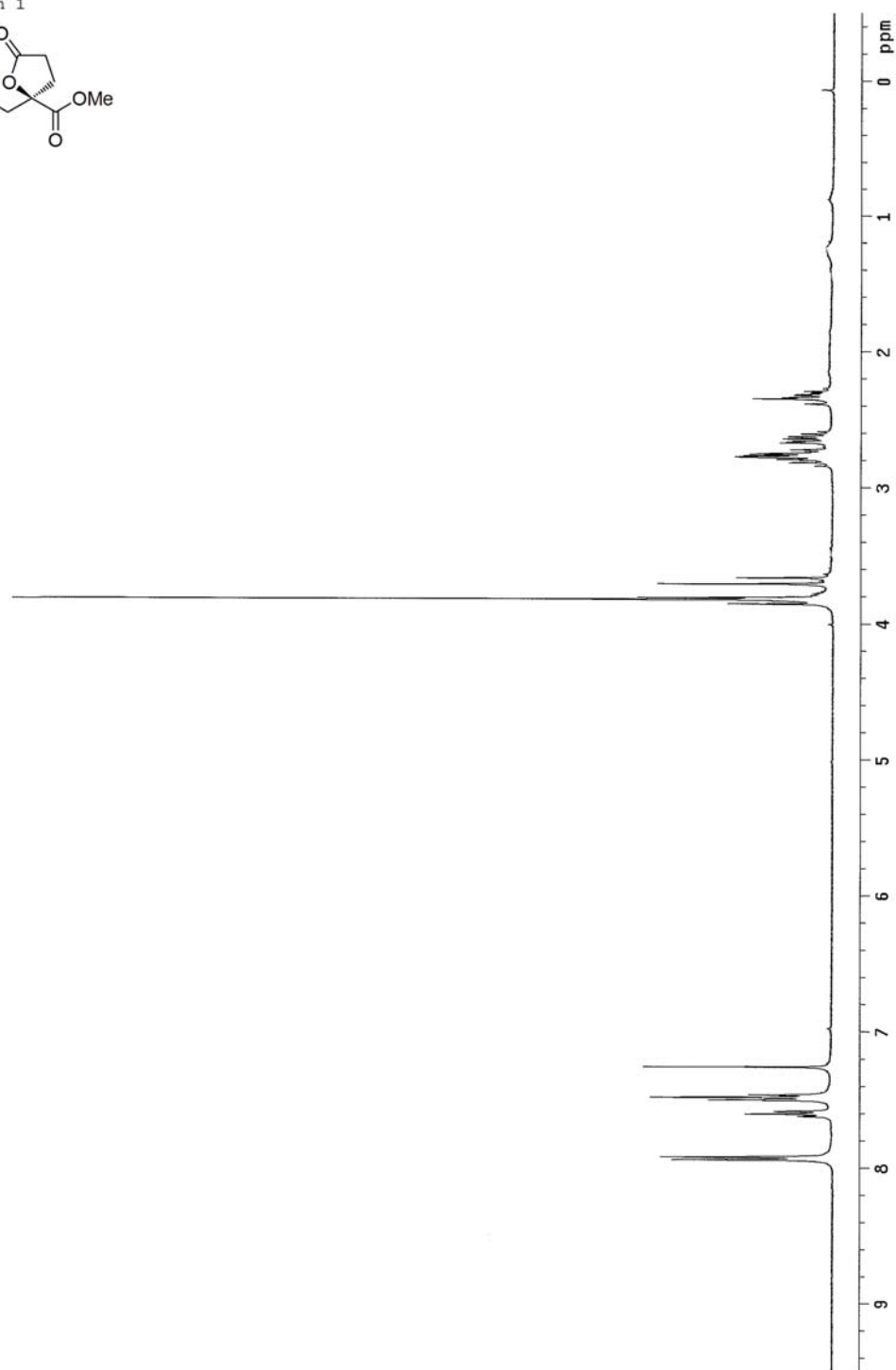
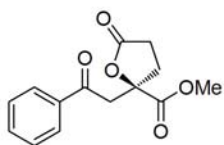


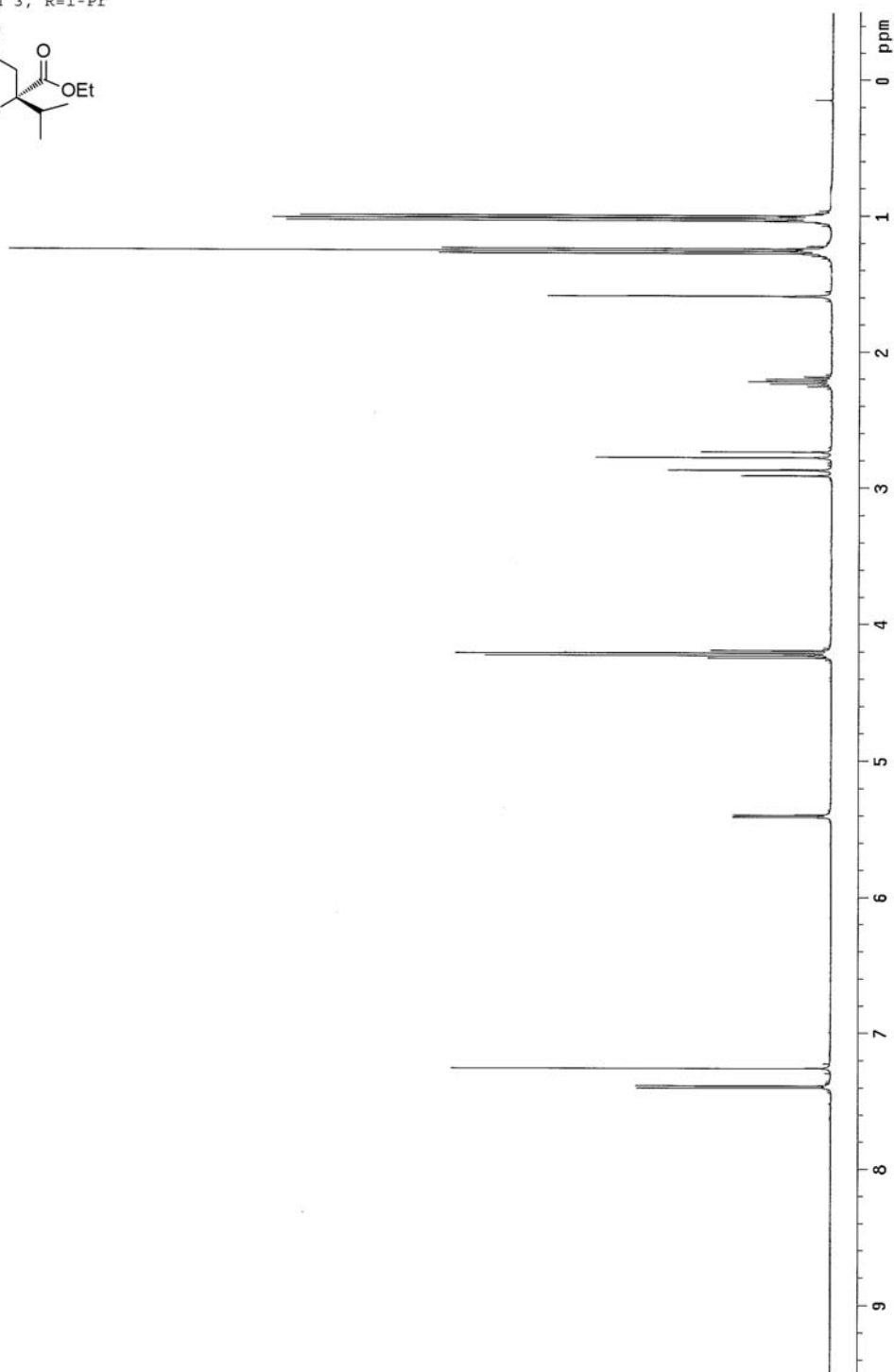
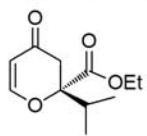
Table 2, entry 12



equation 1



equation 3, R=i-Pr



equation 3, R=Cy

