



Supporting Information

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Supporting Information for

Enantioselective Activation of Aldehydes by Chiral Phosphoric Acid Catalysts in Aza-Ene Type Reaction of Glyoxylate with Enecarbamates

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1. General Information

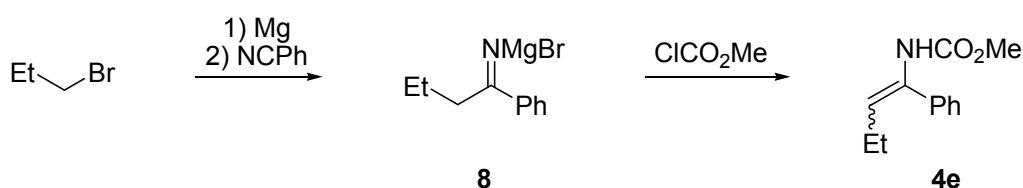
All reactions were carried out in dried glassware. CH_2Cl_2 , diethyl ether and THF were purchased from Kanto Chemical Co., Inc. as “dehydrated solvent system”. Acetone was purchased from Wako Inc. as dried solvent. MeOH and $\text{Me}_2\text{C}(\text{OMe})_2$ was dried over activated MS4A. NEt_3 was dried over KOH. Analytical thin layer chromatography (TLC) was performed on Merck pre-coated TLC plates (silica gel 60 GF₂₅₄, 0.25 mm). Column chromatography was performed on 100-210 μm silica gel 60 N (Kanto Chemical Co., Inc.). Flash column chromatography was performed on 40-50 μm silica gel 60 N (Kanto Chemical Co., Inc.) or 40-63 μm silica gel 60 (Merck). Optical rotations were measured with a Jasco P-1020 digital polarimeter with a sodium lamp and reported as follows; $[\alpha]_{\text{D}}^{25}$ ($c = \text{g}/100 \text{ mL}$, solvent). ^1H - and ^{13}C -NMR spectra were measured with a JEOL GSX-270 (^1H -NMR: 270 MHz, ^{13}C -NMR: 67.8 MHz) or a BRUKER AVANCE-600 spectrometer (^1H -NMR: 600 MHz, ^{13}C -NMR: 150.9 MHz). Data are reported in δ (ppm) from the solvent signals as the internal standard (^1H -NMR: CHCl_3 : 7.26 ppm, $\text{C}_6\text{D}_5\text{H}$: 7.15 ppm; ^{13}C -NMR: CDCl_3 : 77.0 ppm, C_6D_6 : 128.0 ppm). Data are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, br = broad. IR spectra were measured with a Jasco FT/IR-4100 spectrometer. Mass spectra were measured with a Bruker Daltonics APEX III FT-ICR-MS spectrometer at the Instrumental Analysis Center for Chemistry, Graduate School of Science, Tohoku University.

2. Distillation of Ethyl Glyoxylate

Ethyl glyoxylate as a polymer form in toluene (47% concentration) was purchased from Tokyo Kasei Kogyo (TCI). Toluene was evaporated completely. The residue (11.2 g) was distilled over P_2O_5 (224 mg) at 110 °C under 60 mmHg to give monomeric ethyl glyoxylate (7.92 g) as a slightly yellow liquid. The distilled ethyl glyoxylate was stored as an anhydrous CH_2Cl_2 solution (30 WT%) in a refrigerator. The ethyl glyoxylate in CH_2Cl_2 was distilled again prior to use.

3. Synthesis of Enecarbamates

Enecarbamate (*E*)-4e:



To a mixture of Mg (36 mmol, 875 mg) and 1,2-dibromoethane (25 μ L) in diethyl ether (8 mL) was added 1-bromopropane (30 mmol, 2.78 mL) dropwise at room temperature for 15 min under N_2 gas. The resulting mixture was stirred at 45 °C for 5 h. After cooling to room temperature, a solution of propylmagnesium bromide in diethyl ether was transferred to another flask and used for the next step.

To a solution of propylmagnesium bromide in diethyl ether was added a solution of PhCN (2.46 mL, 25 mmol) in diethyl ether (5 mL) dropwise at room temperature for 10 min under N_2 gas. After being stirred for 1 h at 45 °C, the reaction mixture was filtrated and the obtained solid was washed with anhydrous diethyl ether to give **8** as a slightly yellow solid, which was used directly in the next step immediately.

To a suspension of **8** in diethyl ether (10.0 mL) was added a solution of methyl chlorocarbonate (3.25 mL, 40 mmol) in diethyl ether (13 mL) dropwise for 5 min under N_2 gas at room temperature. After being stirred at 45 °C for 1 h, the reaction mixture was quenched with saturated $NaHCO_3$ aq. at 0 °C, and extracted with diethyl ether ($\times 3$). The organic layer was washed with brine, dried over Na_2SO_4 , filtrated and concentrated. The residue was purified with flash column chromatography to give (*E*)-**4e** (*E* / *Z* = <1 / >99, 1.19 g, 5.82 mmol) in 23% yield over 2 steps as a colorless liquid.

Enecarbamate 4a: **4a** (66% yield over 2 steps) was synthesized using methyllithium according to the above procedure.

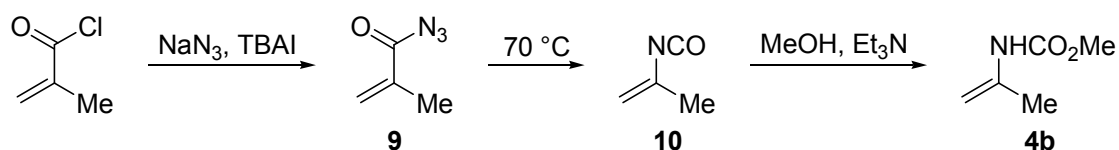
Enecarbamate (*E*)-4c: (*E*)-**4c** (47% yield over 2 steps, *E* / *Z* = 99 / 1) was synthesized using 1-bromoethane according to the above procedure.

Enecarbamate (*Z*)-4e: To a suspension of **8** in diethyl ether was added a solution of methyl

chlorocarbonate (3.25 mL, 40 mmol) in diethyl ether (13 mL) dropwise for 5 min under N₂ gas at room temperature. After being stirred for 1 h at 45 °C, the reaction mixture was quenched with silica gel (25 g) at room temperature. The solution was filtrated, and the silica gel was washed with anhydrous diethyl ether. The filtrate was concentrated, and purified with flash column chromatography to give (Z)-**4e** (*E* / *Z* = <1 / >99, 2.19 g, 10.7 mmol) in 43% yield over 2 steps as a white solid.

Enecarbamate (Z)-4c: (Z)-**4c** (*E* / *Z* = <1 / >99) was synthesized using 1-bromoethane according to the above procedure.

Enecarbamate 4b:



To a solution of NaN₃ (3.18 g, 48 mmol) and tetra-*n*-butylammomium iodide (TBAI) in H₂O (25 mL) was added a solution of metacryloyl chloride (4.88 mL, 40 mmol) in mesitylene (15 mL) dropwise at 0 °C for 5 min. After being stirred for 1 h at 0 °C, the reaction mixture was filtrated. The organic layer was washed with saturated NaHCO₃ aq. (×2) and brine, dried over MgSO₄ and filtrated. The crude solution of **9** was used directly for the next step.

The crude solution of **9** was stirred at 70 °C for 1 h, being vigorous generation of N₂ gas in 5 min. The resulting crude **10** was distilled at 100 °C under 150~300 mmHg to give **10** (1.69 g, 20.4 mmol) in 51% yield over 2 steps as a colorless liquid.

To obtained **10** (1.69 g, 20.4 mmol) were added NEt₃ (142 μL, 1.02 mmol) and MeOH (988 μL, 24.4 mmol) at –60 °C under N₂ gas. After being stirred at –60 °C for 12 h, the reaction mixture was warmed to –15 °C over 2 h, and then stirred at –15 °C for 2 days. The resulting mixture was distilled at 60 °C under 8 mmHg to give **4b** (796 mg, 6.91 mmol) in 34% yield as a colorless liquid.

Enecarbamate (E)-4d: (E)-**4d** (*E* / *Z* = 87 / 13, 3.6% yield over 6 steps) was synthesized using 3-isocyanatopent-2-ene^[1] according to the above procedure, and distilled at 70 °C under 0.1 mmHg.

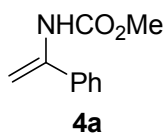
Enecarbamate (Z)-4d: (Z)-**4d** (*E* / *Z* = 4 / 96, 0.66% yield over 6 steps) was synthesized using 3-isocyanatopent-2-ene^[1] according to the above procedure, and purified with column chromatography to give *E*, *Z* mixture of **4d** (*E* / *Z* = 28 / 72). The *E*, *Z* mixture of **4d** (131 mg, 0.915 mmol) was separated by normal phase HPLC to give (Z)- **4d** (39.7 mg, 0.277 mmol).

Enecarbamate 4f: **4f** (5.4% yield over 6 steps) was synthesized as follows. 1-isocyanatocyclohex-1-ene

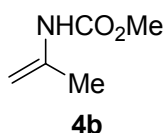
[1] R. Matsubara, Y. Nakamura, S. Kobayashi, *Angew. Chem. Int. Ed.* **2004**, *43*, 3258.

was synthesized using cyclohex-1-enecarbonyl chloride^[2] according to the literature.^[1] Using obtained 1-isocyanatocyclohex-1-ene, **4f** was synthesized according to the above procedure and purified with column chromatography.

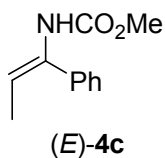
Physical Data of the Enecarbamates



Methyl 1-phenylvinylcarbamate: Yellow liquid; $R_f = 0.63$ (hexane / EtOAc = 1 / 1); ^1H NMR (CDCl_3 , 270 MHz) δ 3.76 (3H, s), 4.97 (1H, s), 5.62 (1H, s), 6.24 (1H, s), 7.35-7.46 (5H, m); ^{13}C NMR (CDCl_3 , 67.8 MHz) δ 52.2, 99.5, 125.9, 128.6, 138.2, 140.5, 154.4, 163.7; IR (ATR): 3324, 3058, 3028, 2998, 2952, 1714, 1634, 1517, 1493 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{10}\text{H}_{11}\text{NO}_2$ ($[\text{M} + \text{Na}]^+$) 200.0688. Found 200.0682.

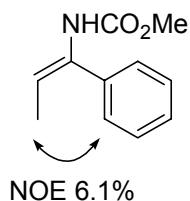


Methyl (*E*)-1-phenylprop-1-enylcarbamate: Colorless liquid; $R_f = 0.68$ (hexane / EtOAc = 1 / 1); ^1H NMR (C_6D_6 , 270 MHz) δ 1.42 (3H, s), 3.34 (3H, s), 4.24 (1H, s), 5.42 (1H, s), 5.50 (1H, brs); ^{13}C NMR (C_6D_6 , 67.8 MHz) δ 21.4, 51.5, 95.4, 137.4, 153.6.

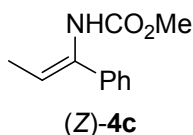


Methyl (*E*)-1-phenylprop-1-enylcarbamate: Slightly yellow liquid; $R_f = 0.54$ (hexane / EtOAc = 2 / 1); ^1H NMR (CDCl_3 , 270 MHz) δ 1.70 (3H, d, $J = 7.3$ Hz), 3.68 (3H, s), 5.98 (1H, s), 6.04 (1H, q, $J = 7.3$ Hz), 7.28-7.42 (5H, m); ^{13}C NMR (CDCl_3 , 67.8 MHz) δ 13.8, 52.2, 112.6, 127.9, 128.2, 128.7, 133.8, 136.5, 154.6; IR (ATR): 3315, 3057, 3025, 2952, 2917, 2859, 1710, 1515, 1493 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{11}\text{H}_{13}\text{NO}_2$ ($[\text{M} + \text{Na}]^+$) 214.0844. Found 214.0838.

Configuration Assignment:

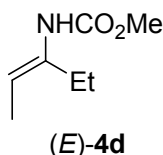
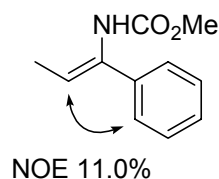


[2] L. Field, P. M. Giles, Jr., *J. Med. Chem.* **1970**, *13*, 317.



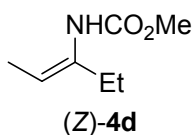
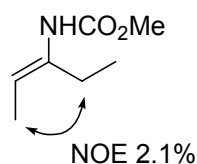
Methyl (Z)-1-phenylprop-1-enylcarbamate: White solid; $R_f = 0.50$ (hexane / EtOAc = 2 / 1); ^1H NMR (CDCl_3 , 270 MHz) δ 1.79 (3H, d, $J = 7.1$ Hz), 3.69 (3H, s), 5.81 (1H, q, $J = 7.1$ Hz), 6.08 (1H, s), 7.24-7.41 (5H, m); ^{13}C NMR (CDCl_3 , 151 MHz) δ 13.6, 52.4, 119.5, 125.3, 127.5, 128.2, 134.1, 138.2, 154.8; IR (ATR): 3222, 3032, 2988, 2938, 2906, 2849, 1685, 1533, 1492 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{11}\text{H}_{13}\text{NO}_2$ ($[\text{M} + \text{Na}]^+$) 214.0844. Found 214.0838.

Configuration Assignment:



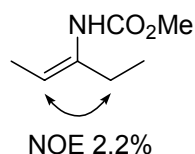
Methyl (E)-pent-2-en-3-ylcarbamate: Slightly yellow liquid; $R_f = 0.45$ (hexane / EtOAc = 2 / 1); ^1H NMR (CDCl_3 , 270 MHz) δ 1.01 (3 H, t, $J = 7.5$ Hz), 1.62 (3 H, d, $J = 7.1$ Hz), 2.21 (2H, q, $J = 7.5$ Hz), 3.66 (3H, s), 5.55 (1H, q, $J = 7.1$ Hz), 5.79 (1H, brs); ^{13}C NMR (CDCl_3 , 67.8 MHz) δ 12.1, 12.3, 22.8, 52.0, 109.1, 135.5, 154.6; IR (ATR): 3325, 2973, 2943, 2924, 2879, 1706 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_7\text{H}_{13}\text{NO}_2$ ($[\text{M} + \text{Na}]^+$) 166.0844. Found 166.0838.

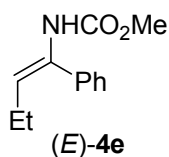
Configuration Assignment:



Methyl (Z)-pent-2-en-3-ylcarbamate: White solid; $R_f = 0.45$ (hexane / EtOAc = 2 / 1); ^1H NMR (CDCl_3 , 270 MHz) δ 1.01 (3H, t, $J = 7.5$ Hz), 1.55 (3H, d, $J = 6.8$ Hz), 2.32 (2H, q, $J = 7.5$ Hz), 3.69 (3H, s), 5.00 (1H, q, $J = 6.8$ Hz), 5.74 (1H, brs); ^{13}C NMR (CDCl_3 , 67.8 MHz) δ 11.9, 12.3, 27.7, 52.2, 111.6, 136.6, 154.4.

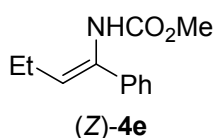
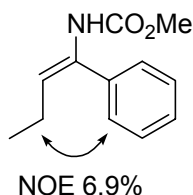
Configuration Assignment:





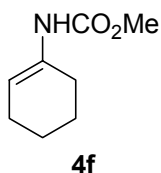
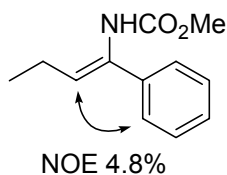
Methyl (E)-1-phenylbut-1-enylcarbamate: Colorless liquid; $R_f = 0.55$ (hexane / EtOAc = 1 / 1); ^1H NMR (CDCl_3 , 270 MHz) δ 1.00 (3H, t, $J = 7.5$ Hz), 2.07 (2H, quin, $J = 7.5$ Hz), 3.67 (3H, s), 5.98-6.01 (2H, brn), 7.30-7.39 (5H, m); ^{13}C NMR (CDCl_3 , 67.8 MHz) δ 14.8, 21.5, 52.0, 119.7, 128.0, 128.3, 128.6, 132.9, 136.9, 154.6; IR (ATR): 3312, 3082, 3058, 3027, 2962, 2932, 2871, 1715, 1520, 1494 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{12}\text{H}_{15}\text{NO}_2$ ($[\text{M} + \text{Na}]^+$) 228.1001. Found 228.0995.

Configuration Assignment:



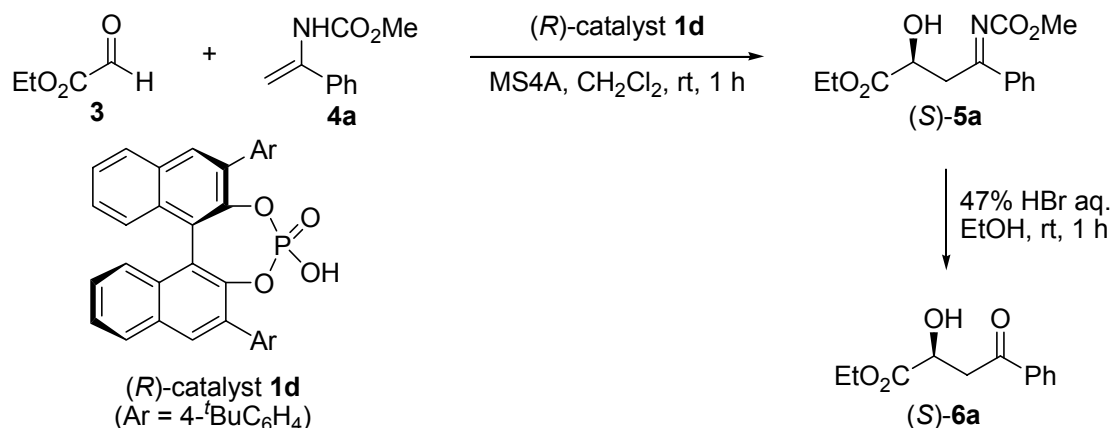
Methyl (Z)-1-phenylbut-1-enylcarbamate: White solid; $R_f = 0.58$ (hexane / EtOAc = 1 / 1); ^1H NMR (CDCl_3 , 270 MHz) δ 1.09 (3H, t, $J = 7.4$ Hz), 2.22 (2H, quin, $J = 7.4$ Hz), 3.69 (3H, s), 5.70 (1H, t, 7.4 Hz), 6.02 (1H, brs), 7.23-7.35 (3H, m), 7.39-7.43 (2H, m); ^{13}C NMR (CDCl_3 , 67.8 MHz) δ 13.3, 21.0, 52.2, 125.3, 126.7, 127.4, 128.1, 132.6, 138.2, 155.1; IR (ATR): 3243, 3032, 2989, 2960, 2930, 2898, 2871, 1690, 1524, 1493 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{12}\text{H}_{15}\text{NO}_2$ ($[\text{M} + \text{Na}]^+$) 228.1001. Found 228.0995.

Configuration Assignment:



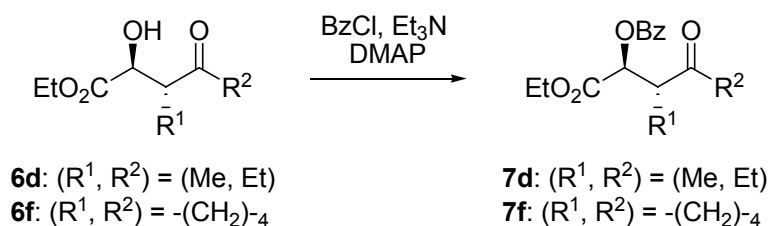
Methyl cyclohex-1-enylcarbamate: White solid; $R_f = 0.53$ (hexane / EtOAc = 1 / 1); ^1H NMR (CDCl_3 , 270 MHz) δ 1.52-1.58 (2H, m), 1.62-1.69 (2H, m), 2.03-2.09 (4H, m), 3.65 (3H, s), 5.79 (2H, brs); ^{13}C NMR (CDCl_3 , 67.8 MHz) δ 22.0, 22.5, 23.8, 27.8, 51.8, 110.3, 132.0, 154.2; IR (ATR): 3328, 2937, 2882, 2859, 2840, 1703 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_8\text{H}_{13}\text{NO}_2$ ($[\text{M} + \text{Na}]^+$) 178.0844. Found 178.0838.

4. Aza-Ene Type Reaction of Glyoxylate with Enecarbamates Catalyzed by Chiral Phosphoric Acids



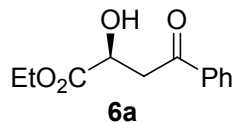
Representative Procedure for Aza-Ene Type Reaction of Aldehyde with Enecarbamates Catalyzed by Chiral Phosphoric Acid: To a suspension of phosphoric acid (*R*)-**1d** (2.5 mg, 5 μ mol) and activated MS4A (<5 micron powder, 85 mg) in CH₂Cl₂ (1 mL) was added freshly distilled ethyl glyoxylate (16.9 μ L, 0.17 mmol) at room temperature under N₂ gas. After being stirred for 5 min, enecarbamate **4a** (18.5 μ L, 0.1 mmol) was introduced, and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with saturated NaHCO₃ aq. at room temperature, and extracted with CH₂Cl₂ ($\times$ 4). The organic layer was dried over Na₂SO₄, filtrated, and concentrated to give crude **5a**. A solution of crude **5a** in EtOH (1.5 mL) was treated with HBr (47% aqueous solution, 150 μ L) at room temperature. After being stirred at room temperature for 1 h, the reaction mixture was quenched with saturated NaHCO₃ aq. at 0 $^{\circ}$ C, and extracted with CH₂Cl₂ ($\times$ 4). The organic layer was dried over Na₂SO₄, filtrated and concentrated. The residue was purified with flash column chromatography to give **6a** (20.6 mg, 0.0927 mmol) in 99% yield as a slightly yellow liquid. The enantioselectivity of **6a** was determined by chiral HPLC to be 98% ee.

Determination of the Enantioselectivity of **6d** and **6f**



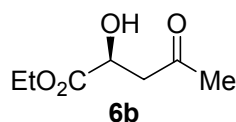
According to the literature,^[1] **6d** and **6f** were converted into **7d** and **7f** respectively, and then their enantioselectivity was determined.

Physical Data of the Products



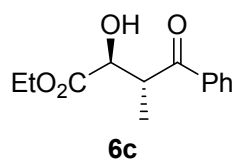
(S)-Ethyl 2-hydroxy-4-oxo-4-phenylbutanoate: Slightly yellow liquid; $R_f = 0.41$ (hexane / EtOAc = 1 / 1); HPLC analysis Chiralpak AD-H (hexane / i PrOH = 80 / 20, 0.5 mL/min, 254 nm, 10 °C) 24.9 min (*S*), 28.2 min (*R*); $[\alpha]_D^{25} = +6.5$ (c 1.9, CHCl₃), $[\alpha]_D^{21} = -8.3$ (c 1.9, EtOH); ^1H NMR (CDCl₃, 270 MHz) δ 1.28 (3H, t, $J = 7.0$ Hz), 3.36 (1H, brd, $J = 5.4$ Hz), 3.45 (1H, dd, $J = 17.6, 5.9$ Hz), 3.56 (1H, dd, $J = 17.6, 4.1$ Hz), 4.27 (2H, q, $J = 7.0$ Hz), 4.66 (1H, ddd, $J = 5.9, 5.4, 4.1$ Hz), 7.48 (2H, tt, $J = 7.3, 1.6$ Hz), 7.59 (1H, tt, $J = 7.3, 1.2$ Hz), 7.96 (2H, d, $J = 7.3$ Hz); ^{13}C NMR (CDCl₃, 67.8 MHz) δ 14.2, 42.2, 61.9, 67.2, 128.1, 128.6, 133.5, 136.2, 173.6, 197.3.

Configuration Assignment: The absolute configuration was determined by the comparison of HPLC retention time^[1] and the optical rotation.^[3]



(S)-Ethyl 2-hydroxy-4-oxopentanoate: Colorless liquid; $R_f = 0.33$ (hexane / EtOAc = 1 / 2); HPLC analysis Chiralpak AD-H (hexane / i PrOH = 98 / 2, 1 mL/min, 220 nm, 10 °C) 48.1 min (*S*), 51.0 min (*R*); $[\alpha]_D^{26} = -2.5$ (c 2.3, CHCl₃); ^1H NMR (CDCl₃, 270 MHz) δ 1.28 (3H, t, $J = 7.1$ Hz), 2.20 (3H, s), 2.89 (1H, dd, $J = 17.4, 6.1$ Hz), 2.98 (1H, dd, $J = 17.4, 4.0$ Hz), 3.20 (1H, d, $J = 5.4$ Hz), 4.24 (2H, q, $J = 7.1$ Hz), 4.46 (1H, ddd, $J = 6.1, 5.4, 4.0$ Hz); ^{13}C NMR (CDCl₃, 67.8 MHz) δ 14.0, 30.4, 46.7, 61.8, 66.9, 173.6, 206.0.

Configuration Assignment: The absolute configuration was determined by analogy.

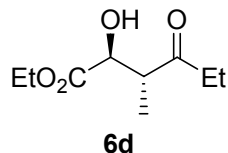


(2*S*,3*R*)-Ethyl 2-hydroxy-3-methyl-4-oxo-4-phenylbutanoate: Slightly yellow liquid; $R_f = 0.35$ (hexane / EtOAc = 1 / 1); HPLC analysis Chiralpak AS-H + AD-H + AD (hexane / i PrOH = 80 / 20, 0.5 mL/min, 254 nm, 25 °C) 49.2 min (2*S*,3*S*), 52.2 min (2*R*,3*R*), 61.0 min (2*S*,3*R*), 71.0 min (2*R*,3*S*) or Mightysil Si 60 250-4.6 (5 μm) + Chiralpak IA (hexane / EtOAc = 85 / 15, 0.4 mL/min, 254 nm, 10 °C) 116.8 min (2*S*,3*R*), 122.9 min (2*S*,3*S*), 127.6 min (2*R*,3*S*), 142.2 min (2*R*,3*R*); $[\alpha]_D^{25} = +17.4$ (c 1.3, CHCl₃); ^1H NMR (CDCl₃, 270 MHz) **anti** δ 1.20 (3H, t, $J = 7.0$ Hz), 1.37 (3H, d, $J = 7.3$ Hz), 3.53 (1H, d, $J = 9.1$ Hz), 3.97 (1H, qd, $J = 7.3, 4.6$ Hz), 4.15 (2H, qd, $J = 7.0, 1.1$ Hz), 4.38 (1H, dd, $J = 9.1, 4.6$ Hz), 7.48 (2H, tt, $J = 7.0, 1.4$ Hz), 7.59 (1H, tt, $J = 7.0, 1.4$ Hz), 7.92 (2H, dt, $J = 7.0, 1.4$ Hz); ^{13}C NMR (CDCl₃, 67.8 MHz) **anti** δ 14.1, 14.3, 44.0, 61.6, 73.2, 128.3, 128.7,

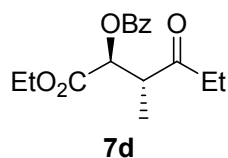
[3] P. Herold, A. F. Indolese, M. Studer, H. P. Jalett, U. Siegrist, H. U. Blaser, *Tetrahedron*, **2000**, 56, 6497.

133.4, 135.8, 173.0, 203.1.

Configuration Assignment: The absolute and relative configurations were determined by the comparison of HPLC retention time.^[1]

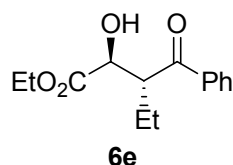


(2S,3R)-Ethyl 2-hydroxy-3-methyl-4-oxohexanoate: Colorless liquid; $R_f = 0.39$ (hexane / EtOAc = 1 / 1); $[\alpha]^{25}_D = +28.5$ (c 1.3, CHCl_3); $^1\text{H NMR}$ (C_6D_6 , 270 MHz) **anti** δ 0.87 (3H, td, $J = 7.0, 0.6$ Hz), 0.88 (3H, t, $J = 7.2$ Hz), 0.98 (3H, d, $J = 7.2$ Hz), 1.99 (2H, q, $J = 7.2$ Hz), 2.67 (1H, qd, $J = 7.2, 4.6$ Hz), 3.26 (1H, d, $J = 7.2$ Hz), 3.78-4.00 (2H, m), 4.07 (1H, dd, $J = 7.2, 4.6$ Hz); **distinguishable syn peaks** δ 2.97 (1H, d, $J = 4.6$ Hz), 4.38 (1H, t, $J = 4.6$ Hz); $^{13}\text{C NMR}$ (C_6D_6 , 67.8 MHz) **anti** δ 7.8, 13.0, 14.2, 34.7, 49.5, 61.4, 73.0, 173.4, 211.1; IR (ATR): 2979, 2940, 2921, 1738, 1715, 1235, 1095 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_9\text{H}_{16}\text{O}_4$ ($[\text{M} + \text{Na}]^+$) 211.0946. Found 211.0941.



(2S,3R)-Ethyl 2-benzoyloxy-3-methyl-4-oxohexanoate: Colorless liquid; $R_f = 0.29$ (hexane / EtOAc = 4 / 1); HPLC analysis Chiralpak **anti** AD-H + AD-H (hexane / i PrOH = 95 / 5, 0.5 mL/min, 254 nm, 10 °C) 48.1 min (2R,3S), 59.8 min (2S,3R), **syn** AD-H + AD-H (hexane / i PrOH = 98 / 2, 0.5 mL/min, 254 nm, 30 °C) 73.1 min, 79.5 min; $[\alpha]^{27}_D = -5.5$ (c 1.1, CHCl_3); $^1\text{H NMR}$ (CDCl_3 , 270 MHz) **anti** δ 1.10 (3H, t, $J = 7.3$ Hz), 1.25 (3H, t, $J = 7.0$ Hz), 1.28 (3H, d, $J = 7.0$ Hz), 2.61 (2H, q, $J = 7.3$ Hz), 3.24 (1H, quin, $J = 7.0$ Hz), 4.24 (2H, q, $J = 7.0$ Hz), 5.41 (1H, d, $J = 7.0$ Hz), 7.44 (2H, t, $J = 7.3$ Hz), 7.58 (1H, t, $J = 7.3$ Hz), 8.01 (2H, d, $J = 7.3$ Hz); **distinguishable syn peaks** δ 5.71 (1H, d, $J = 4.9$ Hz); $^{13}\text{C NMR}$ (CDCl_3 , 67.8 MHz) **anti** δ 7.7, 12.7, 14.2, 35.1, 47.1, 61.6, 73.9, 128.3, 129.0, 129.8, 133.4, 165.5, 168.8, 209.5; IR (ATR): 2980, 2941, 2909, 2884, 1755, 1722, 1096 cm^{-1} ; HRMS (ESI) Calcd for $\text{C}_{16}\text{H}_{20}\text{O}_5$ ($[\text{M} + \text{Na}]^+$) 315.1208. Found 315.1203.

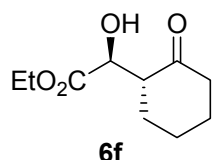
Configuration Assignment: The absolute configuration was determined by analogy.



(2S,3R)-Ethyl 2-hydroxy-3-benzoyl-pentanoate: Slightly yellow liquid; $R_f = 0.49$ (hexane / EtOAc = 1 / 1); HPLC analysis Chiralpak AS-H (hexane / i PrOH = 80 / 20, 0.5 mL/min, 254 nm, 10 °C) 22.4 min (2S,3S), 27.1 min (2R,3R), 30.9 min (2S,3R), 49.5 min (2R,3S); $[\alpha]^{27}_D = +50.9$ (c 3.8, CHCl_3); $^1\text{H NMR}$ (CDCl_3 , 270 MHz)

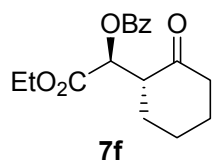
anti δ 1.04 (3H, t, $J = 7.2$ Hz), 1.14 (3H, t, $J = 7.1$ Hz), 1.87 (2H, quin, $J = 7.2$ Hz), 3.69 (1H, d, $J = 9.9$ Hz), 3.82 (1H, td, $J = 7.2, 4.0$ Hz), 4.09 (2H, q, $J = 7.1$ Hz), 4.43 (1H, dd, $J = 9.9, 4.0$ Hz), 7.48 (2H, t, $J = 7.2$ Hz), 7.59 (1H, tt, $J = 7.2, 1.2$ Hz), 7.92 (2H, d, $J = 7.2$ Hz); ^{13}C NMR (CDCl_3 , 67.8 MHz) *anti* δ 12.0, 13.9, 22.3, 50.1, 61.4, 71.3, 128.3, 128.7, 133.5, 136.7, 173.4, 203.9.

Configuration Assignment: The absolute and relative configurations were determined by analogy.



(2*S*,1'*R*)-Ethyl 2-hydroxy-2-(2-oxocyclohexyl)acetate: Colorless liquid; $R_f = 0.31$ (hexane / EtOAc = 1 / 1); $[\alpha]_D^{25} = +36.8$ (c 1.8, CHCl_3); ^1H NMR (C_6D_6 , 270 MHz) *anti* δ 0.95 (3H, t, $J = 7.1$ Hz), 1.03-1.18 (2H, m), 1.33-1.37 (2H, m), 1.56-1.85 (3H, m), 2.05-2.12 (1H, m), 2.66 (1H, dddd, $J = 9.3, 6.0, 3.0, 1.0$ Hz), 3.35-3.37 (1H, brm), 3.83 (1H, brs), 4.02 (2H, q, $J = 7.1$ Hz); **distinguishable *syn* peaks** δ 0.88 (3H, t, $J = 7.3$ Hz), 2.38 (1H, dddd, $J = 9.3, 6.1, 2.8, 0.8$ Hz), 2.94 (1H, brs); ^{13}C NMR (C_6D_6 , 67.8 MHz) *anti* δ 14.3, 24.9, 26.7, 30.2, 41.9, 53.8, 61.4, 71.3, 173.5, 209.2.

Configuration Assignment: The absolute and relative configurations were determined by the comparison of the optical rotation and ^1H & ^{13}C NMR Spectra.^[4]

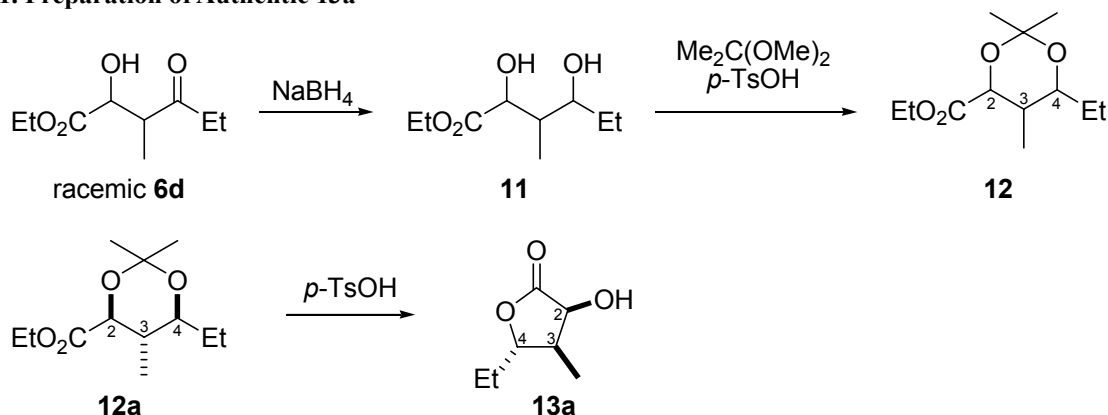


(2*S*,1'*R*)-Ethyl 2-benzoyloxy-2-(2-oxocyclohexyl)acetate: Slightly yellow liquid; $R_f = 0.35$ (hexane / EtOAc = 2 / 1); HPLC analysis Chiralpak AD-H + AS-H (hexane / i PrOH = 90 / 10, 0.9 mL/min, 254 nm, 10 °C) 33.5 min (2*S*,1'*R*), 36.5 min (*syn*), 41.0 min (2*R*,1'*S*), 51.5 min (*syn*); $[\alpha]_D^{27} = +28.7$ (c 1.0, CHCl_3); ^1H NMR (CDCl_3 , 270 MHz) *anti* δ 1.25 (3H, t, $J = 7.1$ Hz), 1.65-1.83 (3H, m), 1.94-1.98 (1H, m), 2.08-2.17 (2H, m), 2.32-2.42 (1H, m), 2.48-2.53 (1H, m), 3.22 (1H, dt, $J = 10.8, 5.3$ Hz), 4.23 (2H, qd, $J = 7.1, 1.8$ Hz), 5.50 (1H, d, $J = 5.5$ Hz), 7.44 (2H, tt, $J = 7.8, 1.4$ Hz), 7.57 (1H, tt, $J = 7.8, 1.4$ Hz), 8.05 (2H, dd, $J = 7.8, 1.4$ Hz); **distinguishable *syn* peaks** δ 1.26 (3H, t, $J = 7.3$ Hz), 2.99-3.12 (1H, m), 5.86 (1H, d, $J = 3.2$ Hz); ^{13}C NMR (CDCl_3 , 126 MHz) *anti* δ 14.0, 24.6, 26.8, 29.5, 41.8, 51.7, 61.6, 71.0, 128.4, 130.0, 133.3, 166.0, 169.2, 207.5; **distinguishable *syn* peaks** δ 14.1, 23.4, 26.8, 29.7, 41.0, 51.6, 60.5, 70.2, 128.5, 129.8, 130.2, 133.6, 166.1, 169.6, 207.3.

[4] a) S. Tsuboi, E. Nishiyama, M. Utaka, A. Takeda, *Tetrahedron Lett.* **1986**, 27, 1915. Also see: b) S. Tsuboi, E. Nishiyama, H. Fukutani, M. Utaka, A. Takeda, *J. Org. Chem.* **1987**, 52, 1359.

5. Determination of Relative Configuration of **6d**

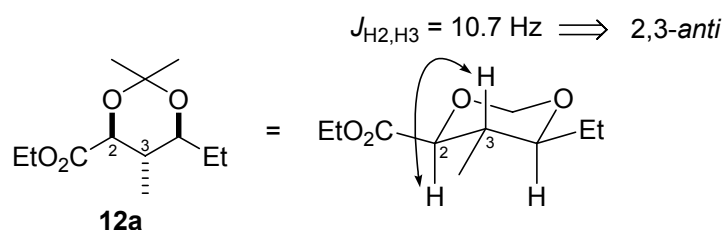
5.1. Preparation of Authentic **13a**



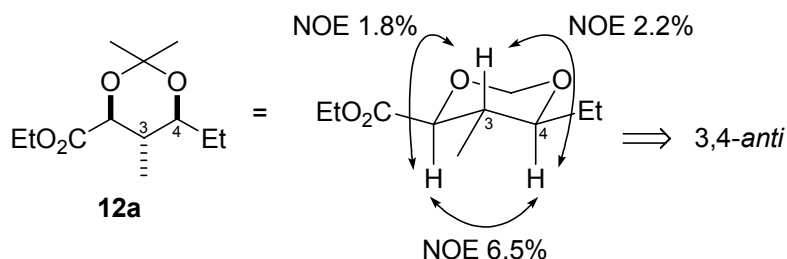
To the solution of racemic **6d** (955 mg, 5.07 mmol, 1:1 diastereomeric mixture)^[5] in MeOH / CH₂Cl₂ = 1 / 2 (100 mL) was added NaBH₄ (426 mg, 10.1 mmol) at 0 °C. After being stirred at 0 °C for 15 min, the reaction mixture was quenched with saturated NH₄Cl aq. at 0 °C, and extracted with CH₂Cl₂ (×4). The organic layer was dried over Na₂SO₄, filtrated and concentrated. The residue was purified with flash column chromatography to give **11** (580 mg, 3.05 mmol) in 60% yield as a colorless liquid.

To a solution of **11** (289 mg, 1.52 mmol) in acetone (30 mL) were added Me₂C(OMe)₂ (7.48 mL, 60.8 mmol) and *p*-toluenesulfonic acid monohydrate (14.6 mg, 0.076 mmol) at 0 °C under N₂ gas. After being stirred at 0 °C for 15 min, the reaction mixture was quenched with saturated NaHCO₃ aq. at 0 °C, and extracted with CH₂Cl₂ (×4). The organic layer was dried over Na₂SO₄, and concentrated to give a crude diastereomer mixture of **12** (**12a** / **12b** / **12c** = 31 / 26 / 43). The mixture of diastereomers was separated with flash column chromatography. The relative configuration of **12a** was determined to be 2,3-*anti*, 3,4-*anti* by the following NMR analysis.

Determination of the C2,3 Configuration



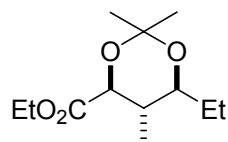
Determination of the C3,4 Configuration



[5] S. Shirakawa, K. Maruoka, *Tetrahedron Lett.* **2003**, 44, 281.

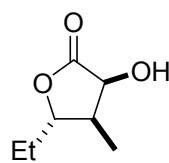
To a solution of **12a** (21.3 mg, 0.0925 mmol) in CH₂Cl₂ (3 mL) was added *p*-toluenesulfonic acid monohydrate (3.52 mg, 18.5 μmol) at room temperature. After being stirred at room temperature for 1 h, the reaction mixture was quenched with saturated NaHCO₃ aq. at room temperature, and extracted with CH₂Cl₂ (×4). The organic layer was dried over Na₂SO₄, filtrated and concentrated. The residue was purified with flash column chromatography to give **13a** (13.0 mg, 0.0902 mmol) in 98% yield as a slightly yellow liquid.

Physical Data of 12a and 13a



12a

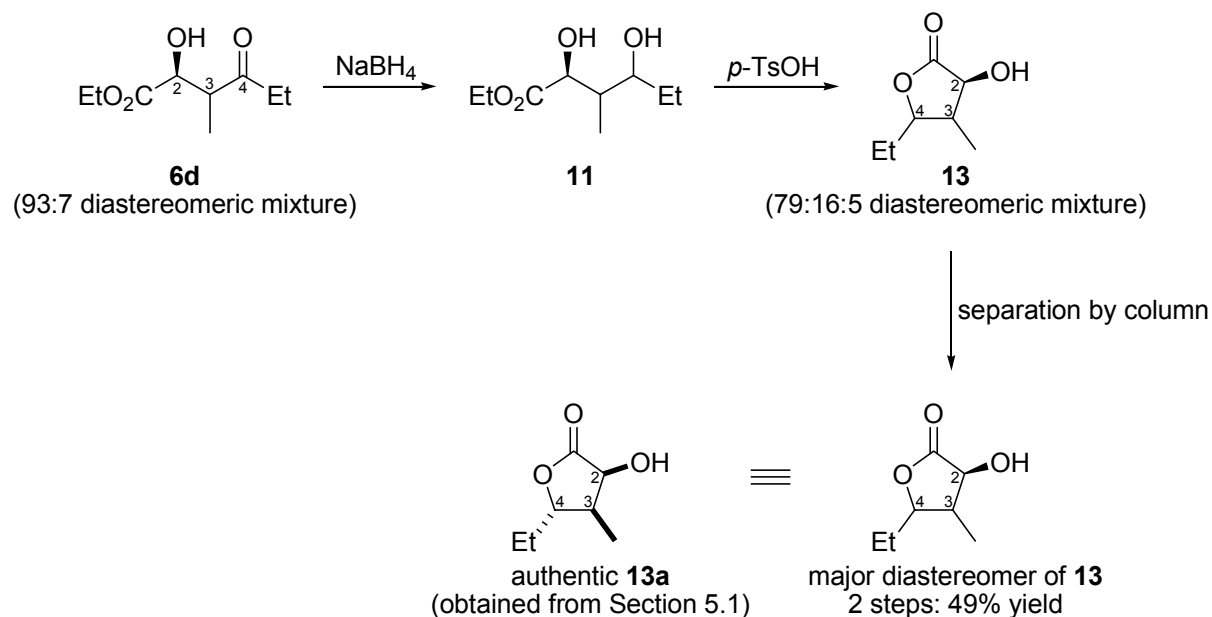
(4*S*^{*}, 5*S*^{*}, 6*S*^{*})-4-Ethoxycarbonyl-6-ethyl-2,2,5-trimethyl-1,3-dioxane: Colorless liquid; *R*_f = 0.36 (hexane / EtOAc = 4 / 1); ¹H NMR (CDCl₃, 270 MHz) δ 0.81 (3H, d, *J* = 6.6 Hz), 0.92 (3H, t, *J* = 7.4 Hz), 1.29 (3H, t, *J* = 7.1 Hz), 1.41-1.46 (1H, m), 1.44 (6H, s), 1.62-1.76 (1H, m), 1.69 (1H, ddd, *J* = 10.7, 10.3, 6.6 Hz), 3.44 (1H, ddd, *J* = 10.3, 7.6, 2.6 Hz), 4.07 (1H, d, *J* = 10.7 Hz), 4.22 (2H, q, *J* = 7.1 Hz); ¹³C NMR (CDCl₃, 67.8 MHz) δ 9.0, 11.9, 14.1, 19.5, 25.6, 29.8, 35.2, 61.0, 74.9, 75.8, 98.7, 170.4; IR (ATR): 2980, 2938, 2879, 1749, 1201, 1187, 1172 cm⁻¹; HRMS (ESI) Calcd for C₁₂H₂₂O₄ ([M + Na]⁺) 253.1416. Found 253.1410.



13a

(3*S*^{*}, 4*S*^{*}, 5*S*^{*})-5-Ethyl-3-hydroxy-4-methyl-2-cyclopentanone: Slightly yellow liquid; *R*_f = 0.26 (hexane / EtOAc = 1 / 1); ¹H NMR (CDCl₃, 270 MHz) δ 1.03 (3H, t, *J* = 7.5 Hz), 1.11 (3H, d, *J* = 7.3 Hz), 1.57-1.80 (2H, m), 2.39 (1H, quind, *J* = 7.3, 4.0 Hz), 2.78 (1H, brs), 4.15 (1H, ddd, *J* = 7.8, 5.6, 4.0 Hz), 4.45 (1H, d, *J* = 7.3 Hz); ¹³C NMR (CDCl₃, 67.8 MHz) δ 10.0, 11.6, 27.2, 39.1, 69.7, 87.3, 177.3; IR (ATR): 3421, 2968, 2924, 2882, 2852, 1759, 1458, 1135 cm⁻¹; HRMS (ESI) Calcd for C₇H₁₂O₃ ([M + Na]⁺) 167.0684. Found 167.0679.

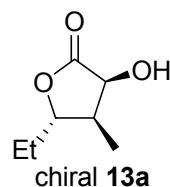
5.2. Transformation of Diastereomerically Enriched **6d** (93:7 Diastereomeric Mixture) to Stereochemically Determined **13a**



Diastereomerically enriched **6d** (28.7 mg, 0.152 mmol, 93:7 diastereomeric mixture) was transformed to diol **11**, according to the above procedure. The crude **11** obtained was used in the next step without purification.

To a solution of the crude **11** in CH_2Cl_2 (15 mL) was added *p*-toluenesulfonic acid monohydrate (5.78 mg, 0.0304 mmol) at room temperature. After being stirred at room temperature for 8 h, the reaction mixture was quenched with saturated NaHCO_3 aq. at room temperature, and extracted with CH_2Cl_2 ($\times 4$). The organic layer was dried over Na_2SO_4 , filtrated and concentrated. The diastereomeric mixtures of **13** (79 / 16 / 5) was separated with flash column chromatography to give a major isomer of **13** as a single diastereomer (10.7 mg, 0.074 mmol) in 49% yield over 2 steps (slightly yellow liquid). The NMR chart of the major isomer of **13** thus purified was consistent with that of authentic **13a**. The major diastereomer of **6d** (Table 2, entry 2) was determined to be *anti* based on the configuration of **13a**.

Physical Data of Optically Active **13a**



$[\alpha]_{\text{D}}^{27} = -67.2$ (c 1.0, CHCl_3)

6. DFT Computational Analysis of Hydrogen Bonding Pairs of Phosphoric Acid with Glyoxylate

6.1. Computational Details.

Geometries of all stationary points were optimized using analytical energy gradients of self-consistent-field^[6] and density functional theory (DFT).^[7] The latter utilized Beck's three-parameter exchange-correction functional^[8] including the nonlocal gradient corrections described by Lee-Yang-Parr (LYP),^[9] as implemented in the Spartan '04 program package for Windows (Wavefunction Inc.). Geometry optimizations of all conformers were performed using the B3LYP/6-31G** basis set.

6.2. Model Studies.

We initially investigated the mode of hydrogen bonding interaction between a simplified phosphoric acid and methyl glyoxylate (**3'**) as a model system. In model studies, BINOL-derived chiral phosphoric acid was replaced by 2-hydroxy-1,3,2-dioxaphospholane-2-oxide (**14**). As shown in Figure I, we generated three initial conformers, such as bidentate (**A**), monodentate (**B**), and double hydrogen bonding models (**C**). After thorough optimization of these conformers, all of the initial structures converged to the double hydrogen bonding model (**C**), as shown in Figure IIa. In addition, a double hydrogen bonding model (**D**) was optimized as the lowest energy conformer (Figure IIb), however one of the hydrogen bonds was formed between the O-H proton of phosphoric acid (**14**) and the ester carbonyl oxygen of **3'**. It is obvious that aldehyde is not activated by the phosphoric acid in conformer **D**. And hence **C** was employed to further computational studies.

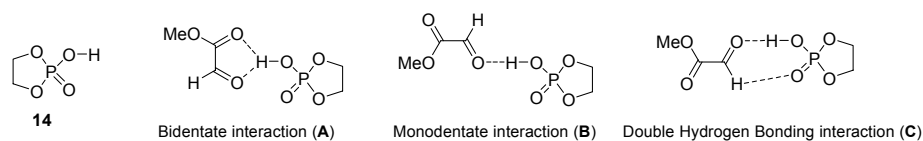


Figure I. Plausible modes of hydrogen bonding interaction between phosphoric acid (**14**) and glyoxylate (**3'**).

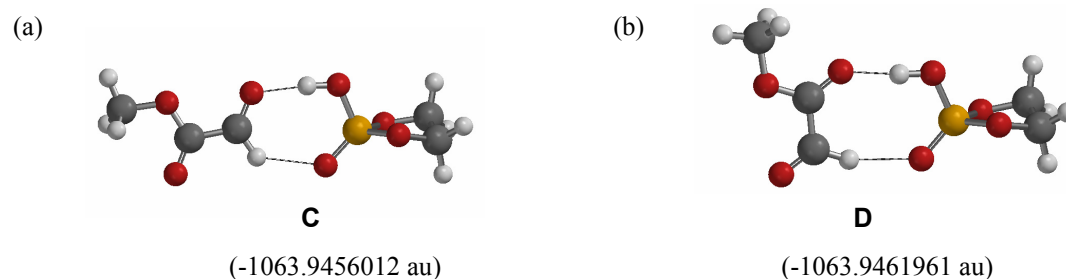


Figure II. Optimized 3D-structures of model system. P Tan, O Red, C Gray, H White. Absolute energies in hartrees are in parentheses.

6.3. DFT Computational Analysis of Double Hydrogen Bonding Pairs of (*R*)-1/3'.

In an effort to gain mechanistic insight of the high enantioselectivity observed in the aza-ene type reaction, we

[6] P. Pulay, *In Modern Theoretical Chemistry*; H. F. Ed. Schaefer, Plenum: New York, 1977; Vol. 4, pp. 153.

[7] R. G. Parr, W. Yang, *Density Functional Theory of Atoms and Molecules*; Oxford University Press: New York, 1989.

[8] A. D. Becke, *J. Chem. Phys.* **1993**, 98, 5648.

[9] C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1993**, 37, 785.

conducted computational analysis of the chiral version of hydrogen bonding pairs formed between the BINOL-derived catalysts (**1**) and methyl glyoxylate (**3'**) at the B3LYP/6-31G** level of theory. The optimized 3D-structures of the associates (*R*)-**1a/3'** and (*R*)-**1h/3'** are shown in Figures III and IV, respectively.

6.3.1. Computational Analysis of Double Hydrogen Bonding Pairs of (*R*)-**1a/3'**:

Inspection of Figure III and Table I reveals that associate **E** was optimized as the lowest energy conformer and **F-H** were obtained as local minima of (*R*)-**1a/3'**. In the conformer **E**, the nucleophiles (enecarbamate) are fully accessible to one enantiotopic face (*si*-face) of aldehyde (blue arrow indicated in **E**) and the other face (*re*-face) of aldehyde is effectively shielded by one of the phenyl rings. If the reaction would proceed via the lowest energy conformer **E**, (*S*)-product could be obtained. The absolute configuration thus expected from the most stable conformer is identical to that observed experimentally. The conformer **F** is energetically close to the conformer **E**, however both enantiotopic faces of the aldehyde are well shielded by the two phenyl rings in the conformer **F**. The other geometrically distinct conformers **G** and **H** were optimized as local minima. In these conformers, *re*-face of aldehyde, especially for the formyl oxygen side, is congested owing to the horizontally arranged phenyl rings (red circle indicated in **G** and **H**). This steric congestion would make the formation of cyclic transition states difficult on the *re*-face and hence the formation of the (*R*)-enantiomer could be prevented. In addition, these conformers, **G** and **H**, are relatively unfavourable as compared with the conformer **E**, though energy differences are not large, less than 2 kcal/mol.

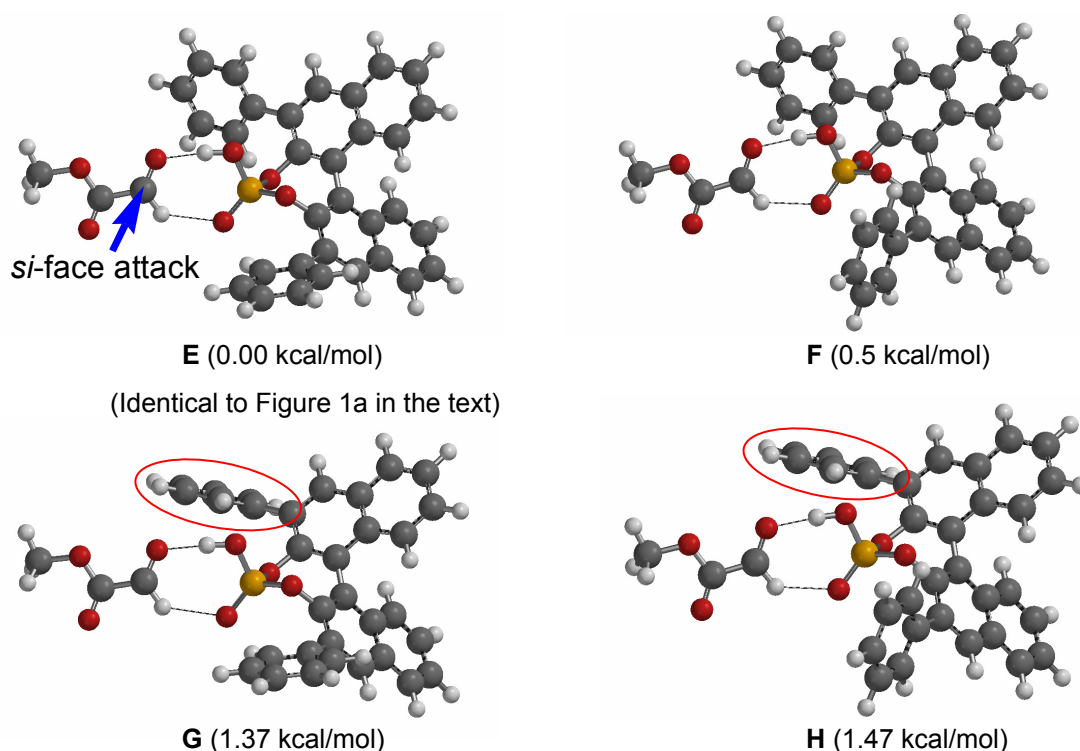


Figure III. 3D-structures for the optimized geometries (at the B3LYP/6-31G** level of theory) of the D-H bonding pairs of (*R*)-**1a** (Ar = Ph) with **3'**. P Tan, O Red, C Gray, H White. **E**: The lowest energy conformer of (*R*)-**1a/3'**; **F-H**: Local minima of (*R*)-**1a/3'**. Relative energies are shown in parentheses.

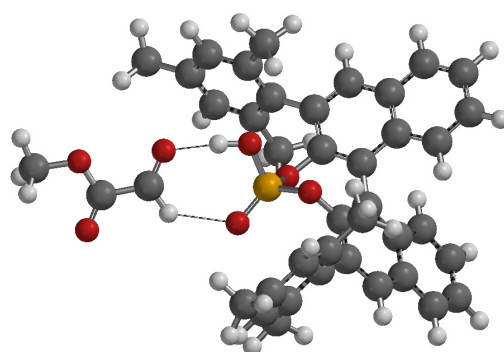
Table I: Computational data for the double hydrogen bonding pairs of (*R*)-**1a/3'**.

Conformer	Absolute energy [au]	Relative energy [kcal/mol]	<i>si</i> -face ^[a]	<i>re</i> -face ^[a]
			[(<i>S</i>)-product]	[(<i>R</i>)-product]
E ^[b]	-2216.8544231	0.00	accessible	inaccessible
F	-2216.8536237	0.50	inaccessible	inaccessible
G	-2216.8522432	1.37	accessible	unfavourable
H	-2216.8520746	1.47	inaccessible	unfavourable

[a] Accessibility to enantiotopic faces of glyoxylate (**3'**). [b] Identical to Figure 1a in the text.

6.3.2. Computational Analysis of Double Hydrogen Bonding Pairs of (*R*)-**1h/3'**:

In contrast to the D-H bonding pairs of **1a/3'** as described above, conformational analysis of **1h/3'** afforded **I** as an only conformer as shown in Figure IV. In the conformer **I**, both enantiotopic faces of aldehyde are well shielded by the two mesityl rings.



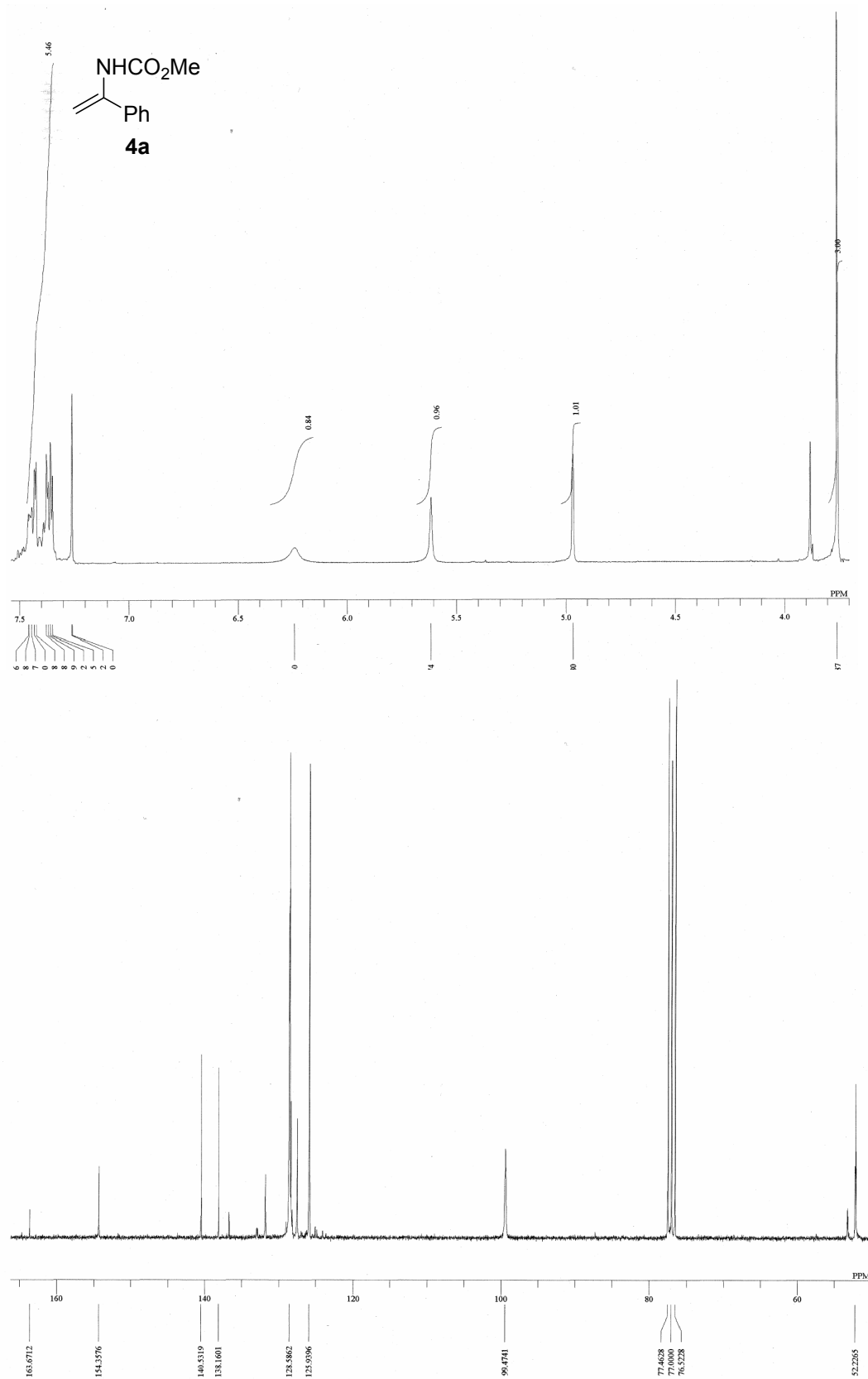
I (-2452.7711522 au)

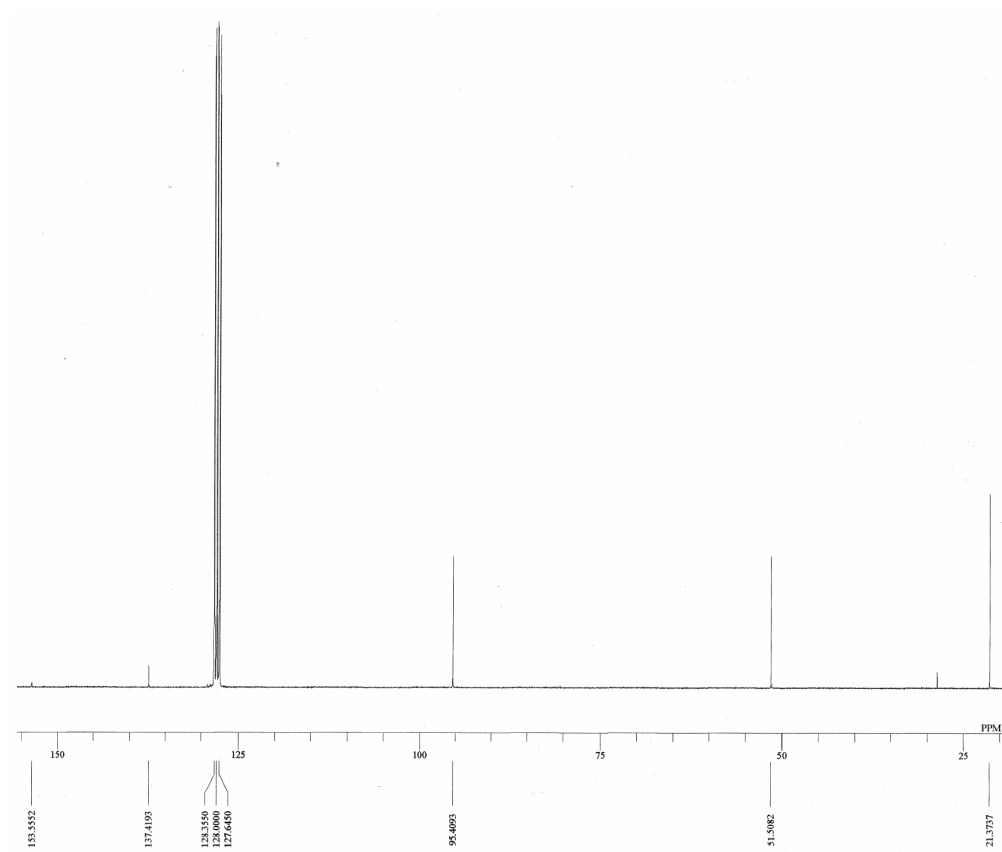
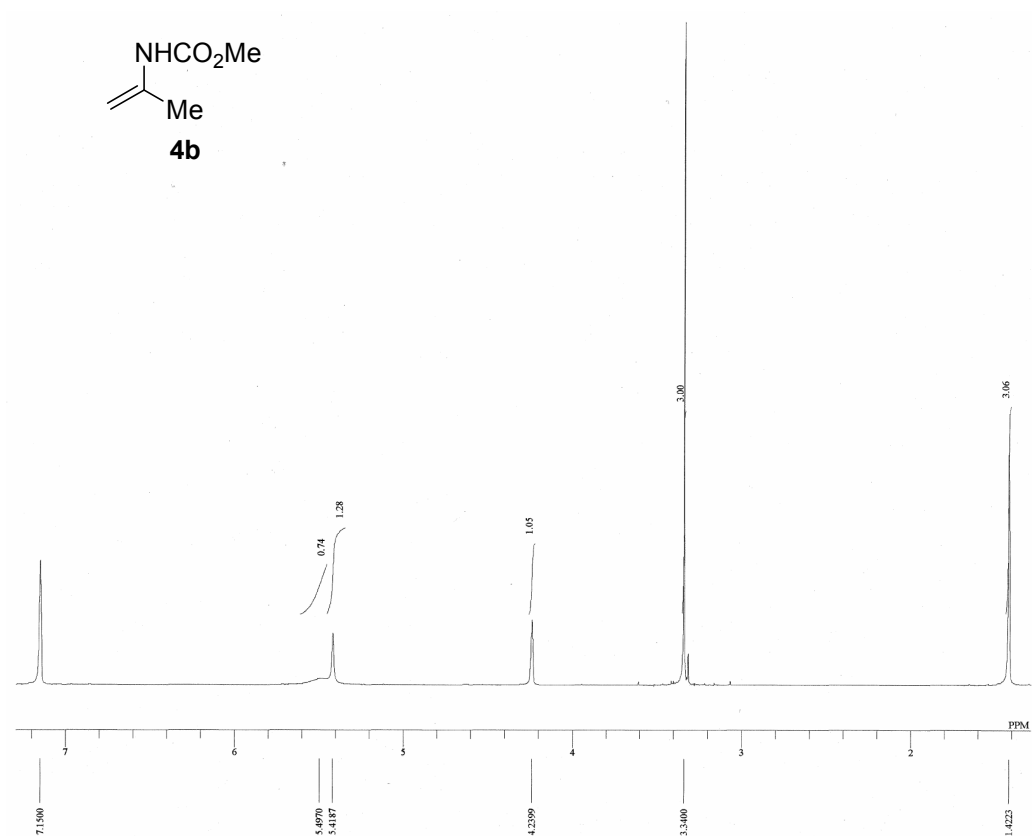
(Identical to Figure 1b in the text)

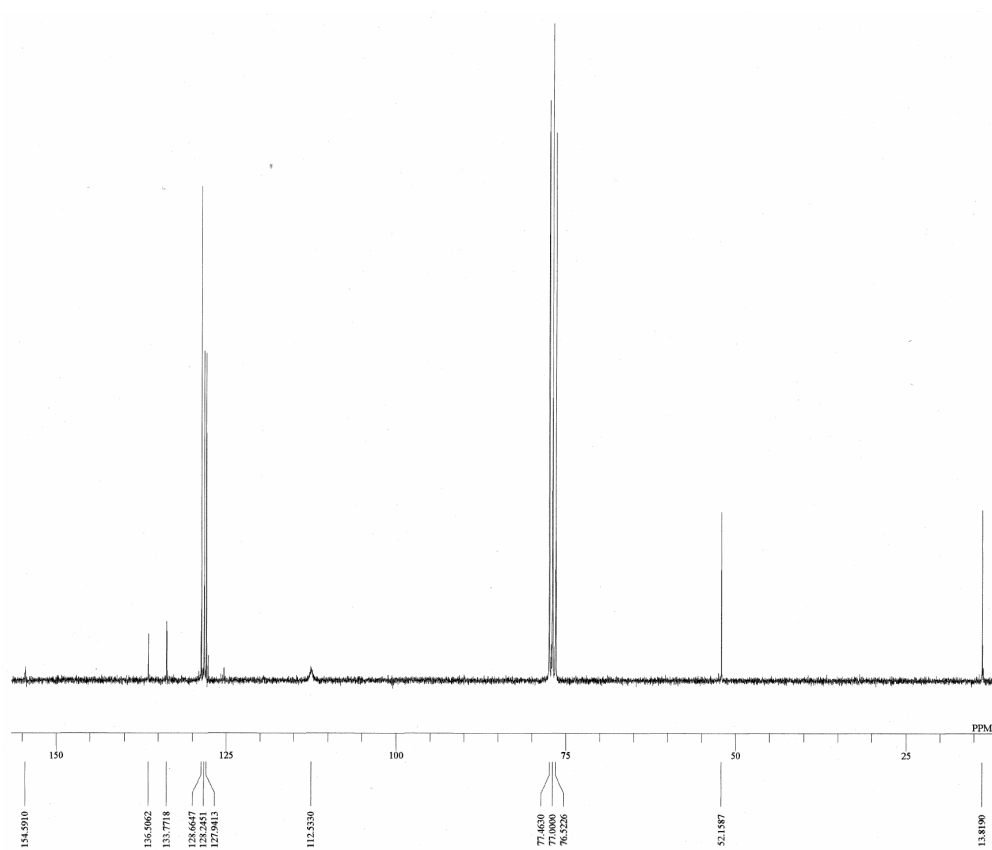
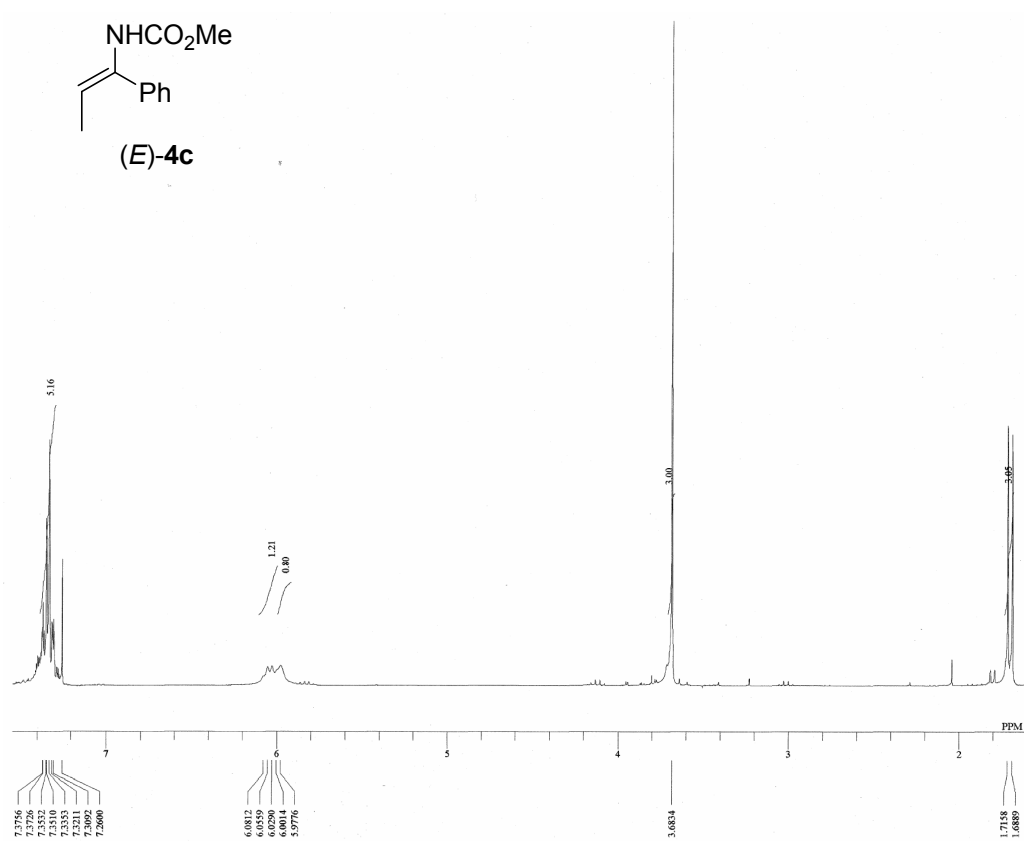
Figure IV. 3D-structure for the optimized geometry (at the B3LYP/6-31G** level of theory) of the D-H bonding pairs of (*R*)-**1h** (Ar = mesityl) with **3'**. P Tan, O Red, C Gray, H White. Absolute energy in hartrees is in parenthesis.

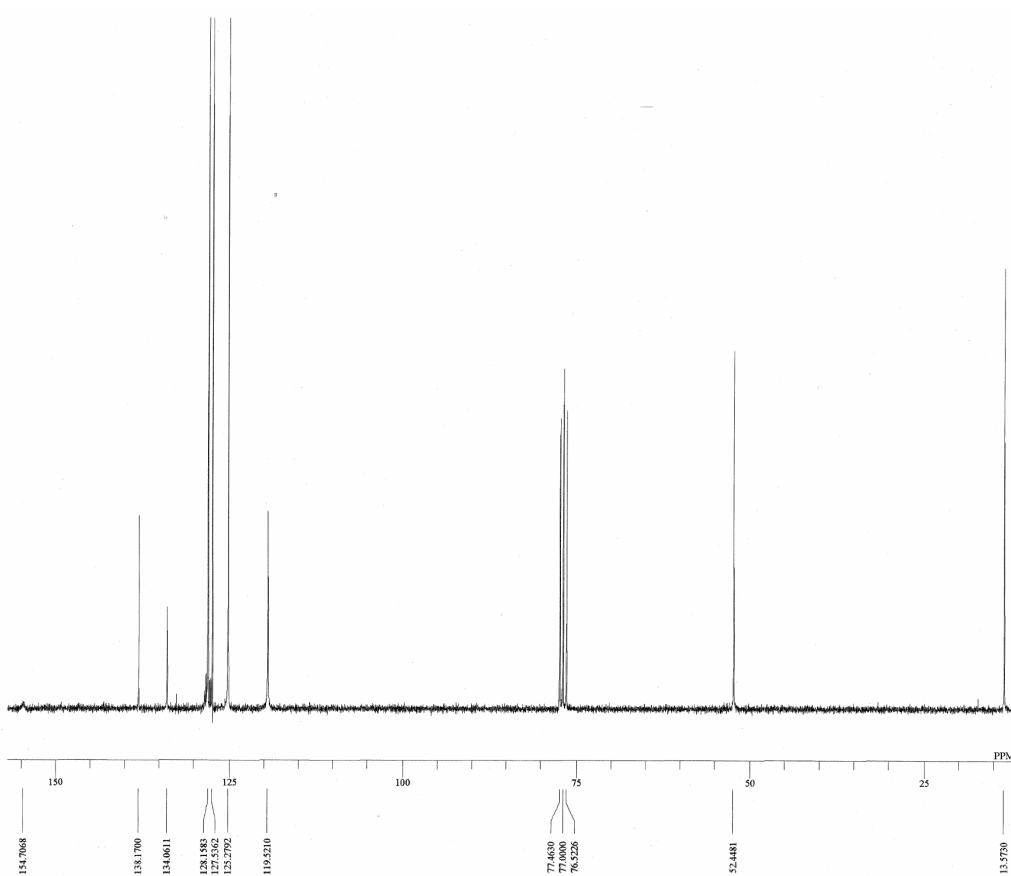
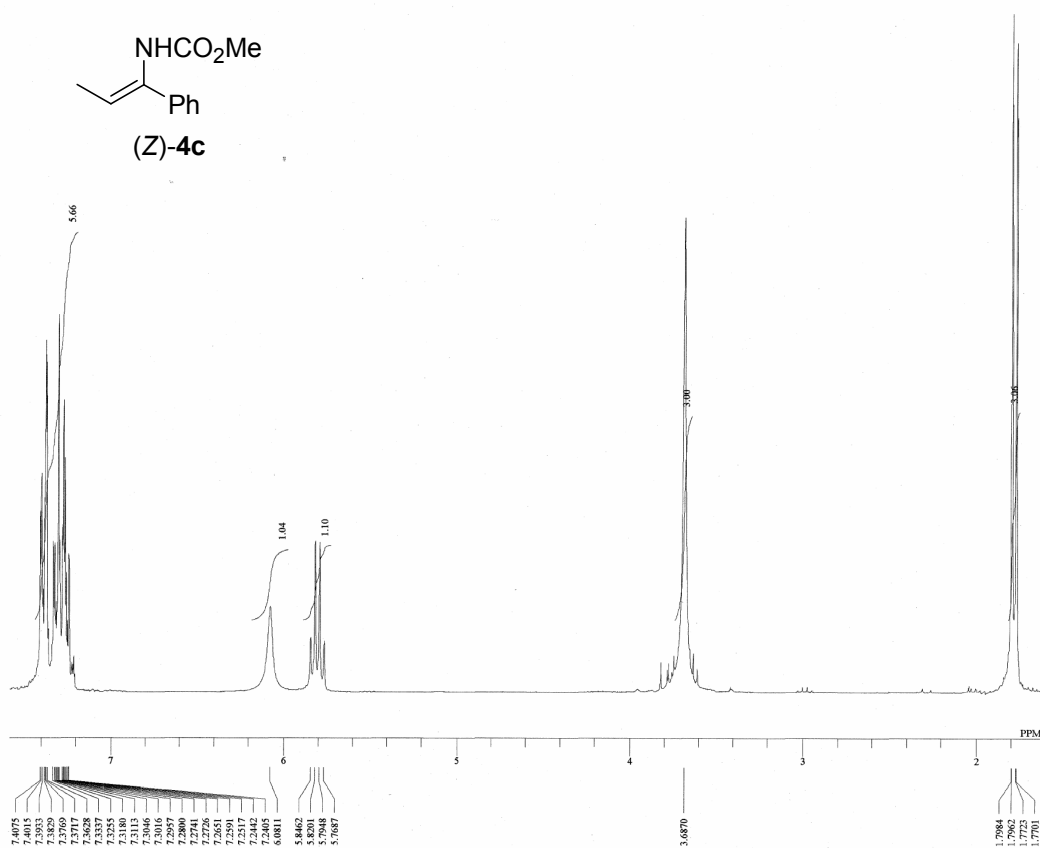
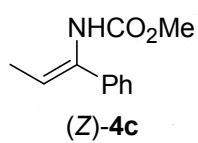
7. ^1H & ^{13}C NMR Spectra and HPLC Charts

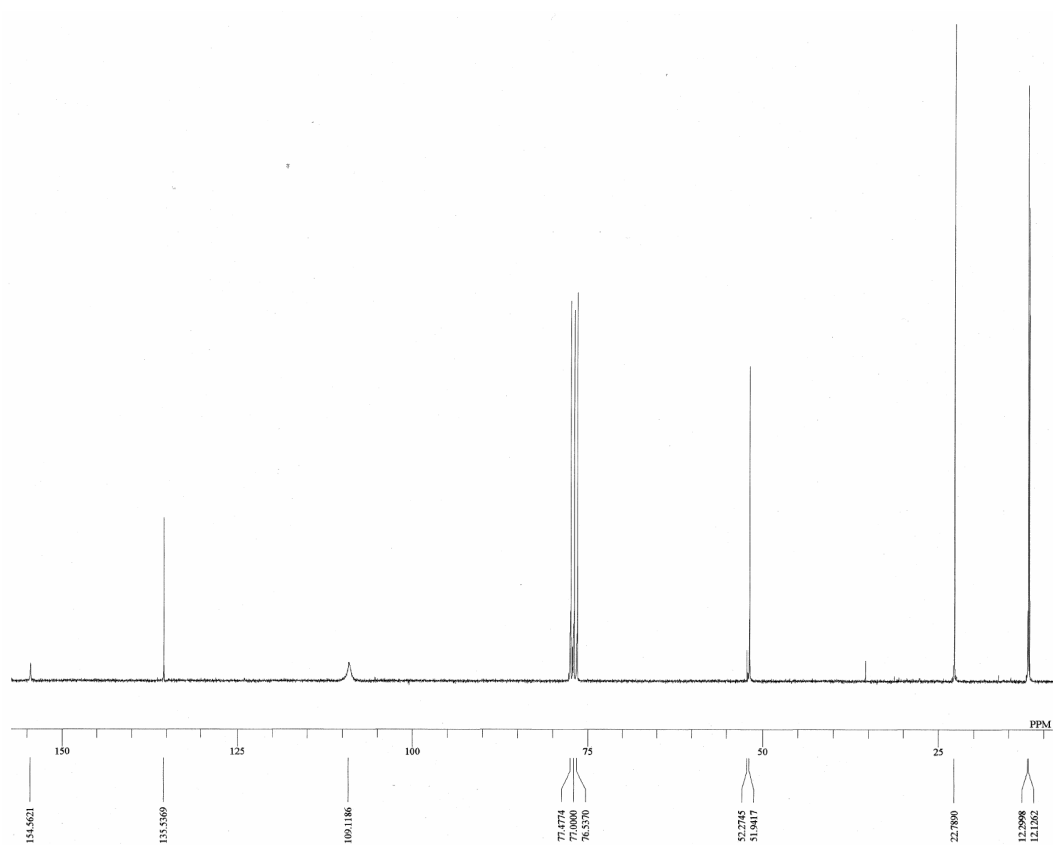
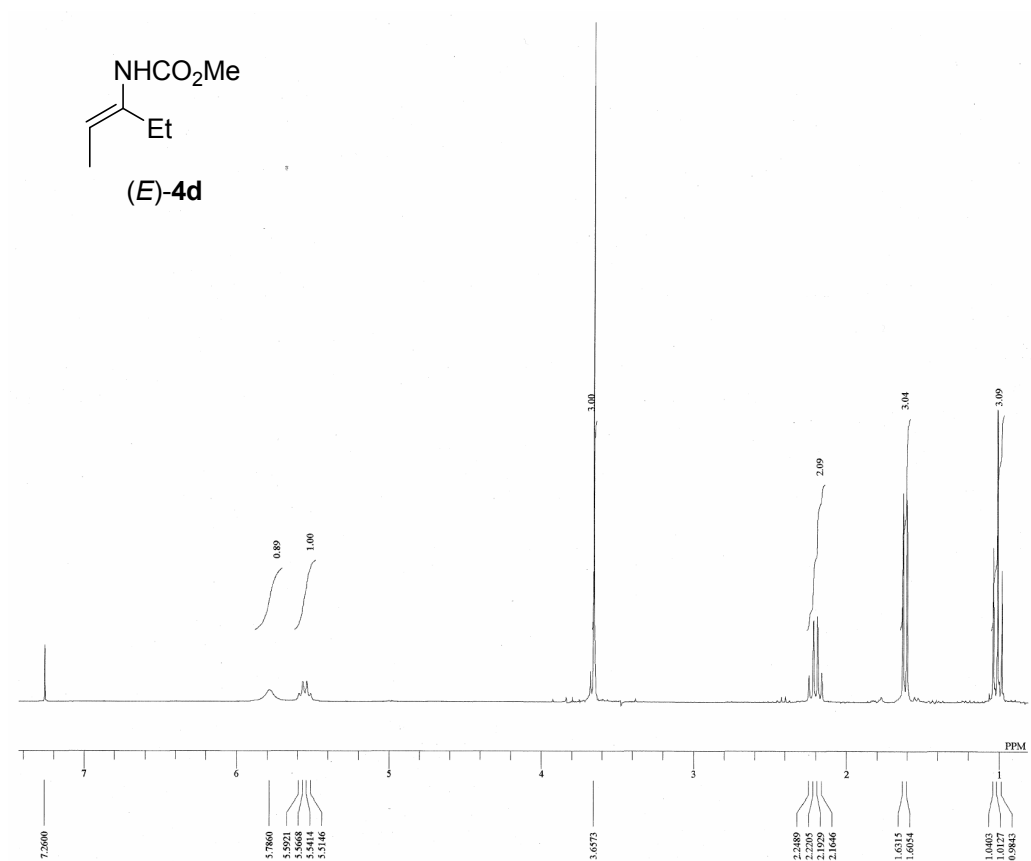
^1H & ^{13}C NMR of Enecarbamates

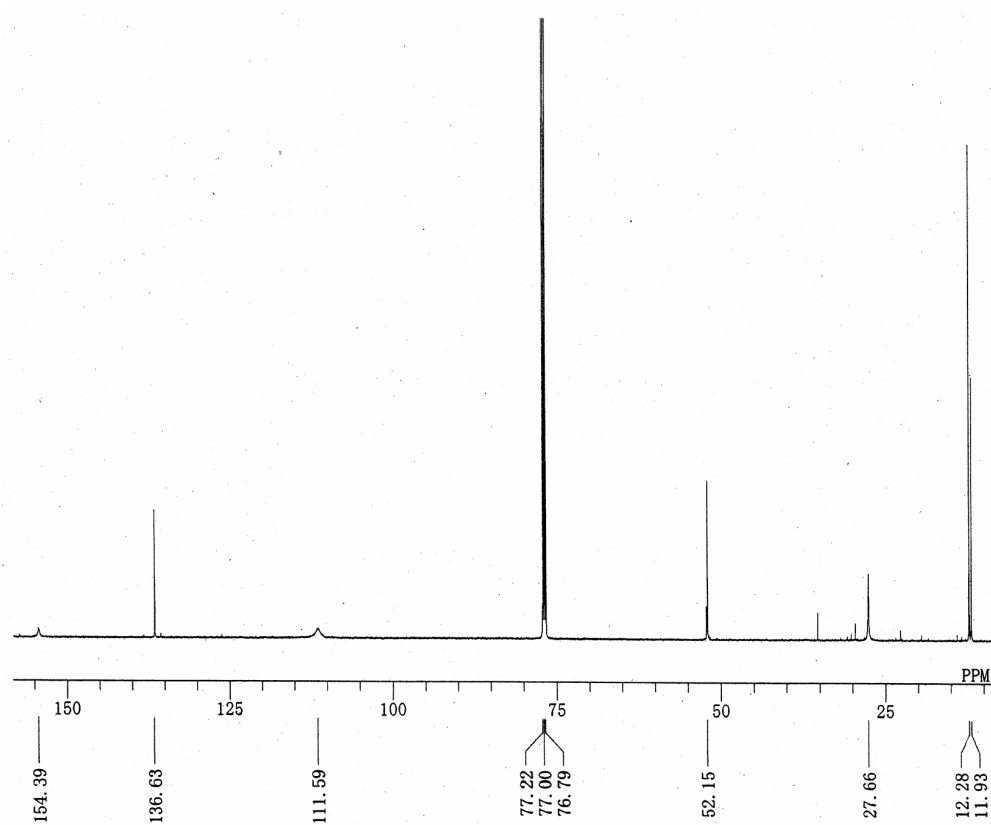
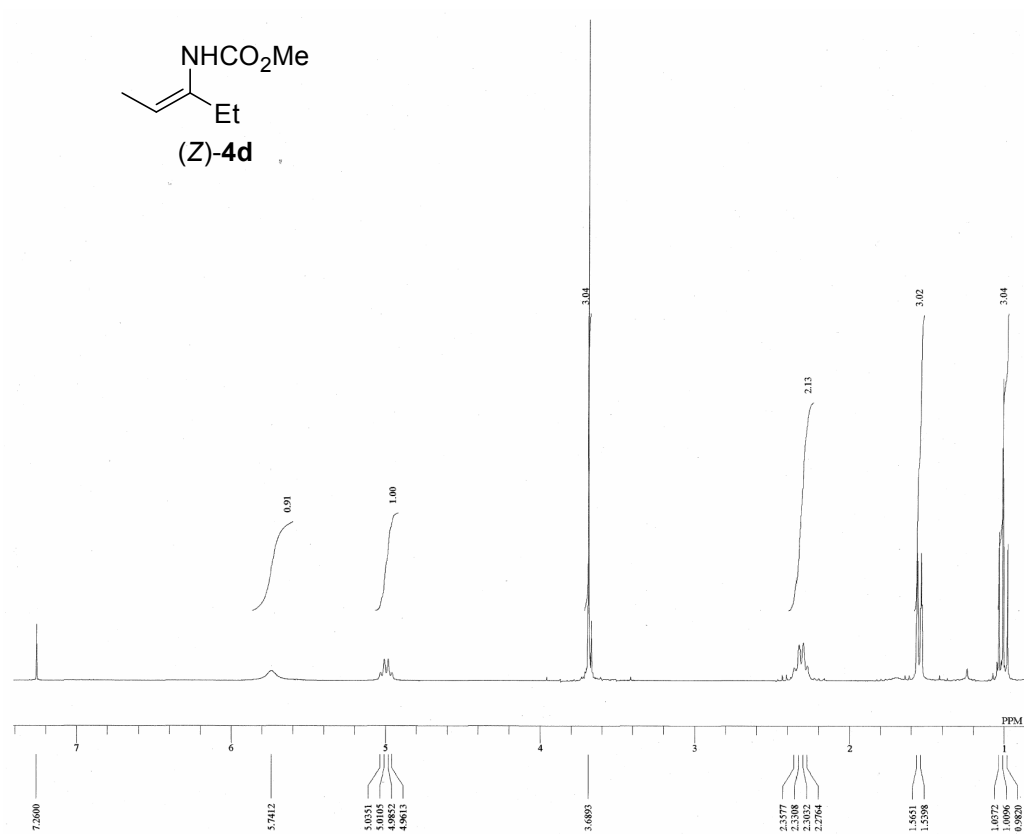


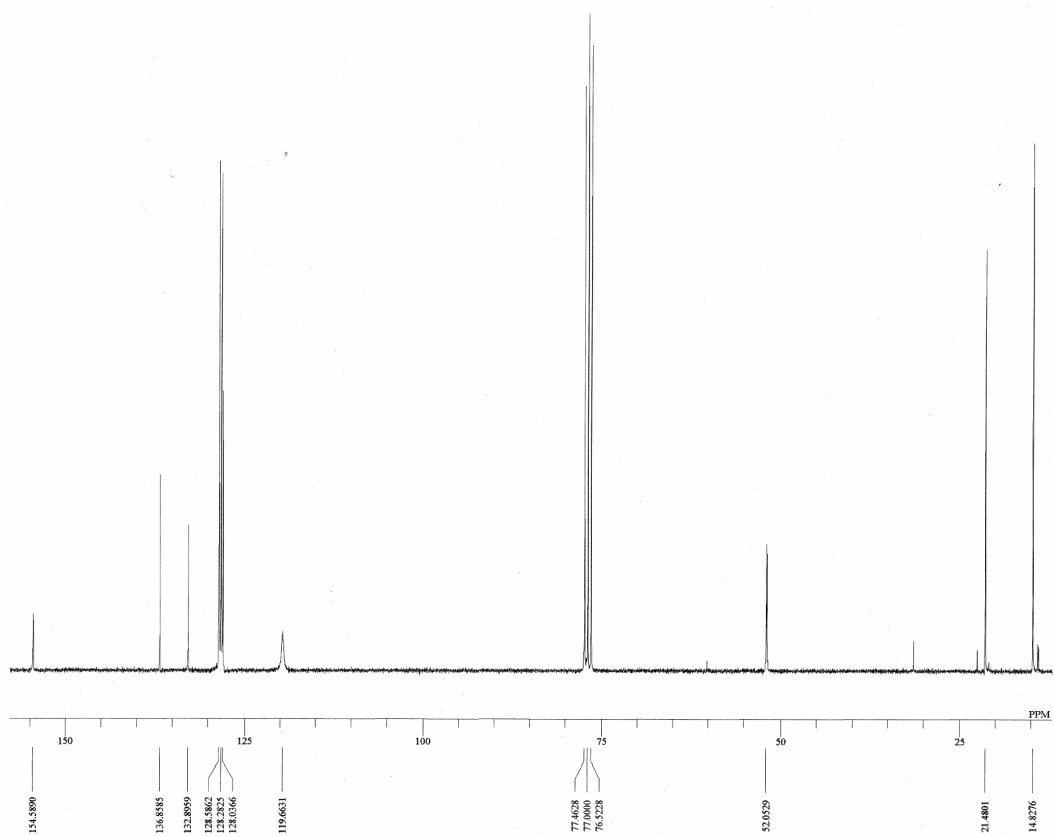
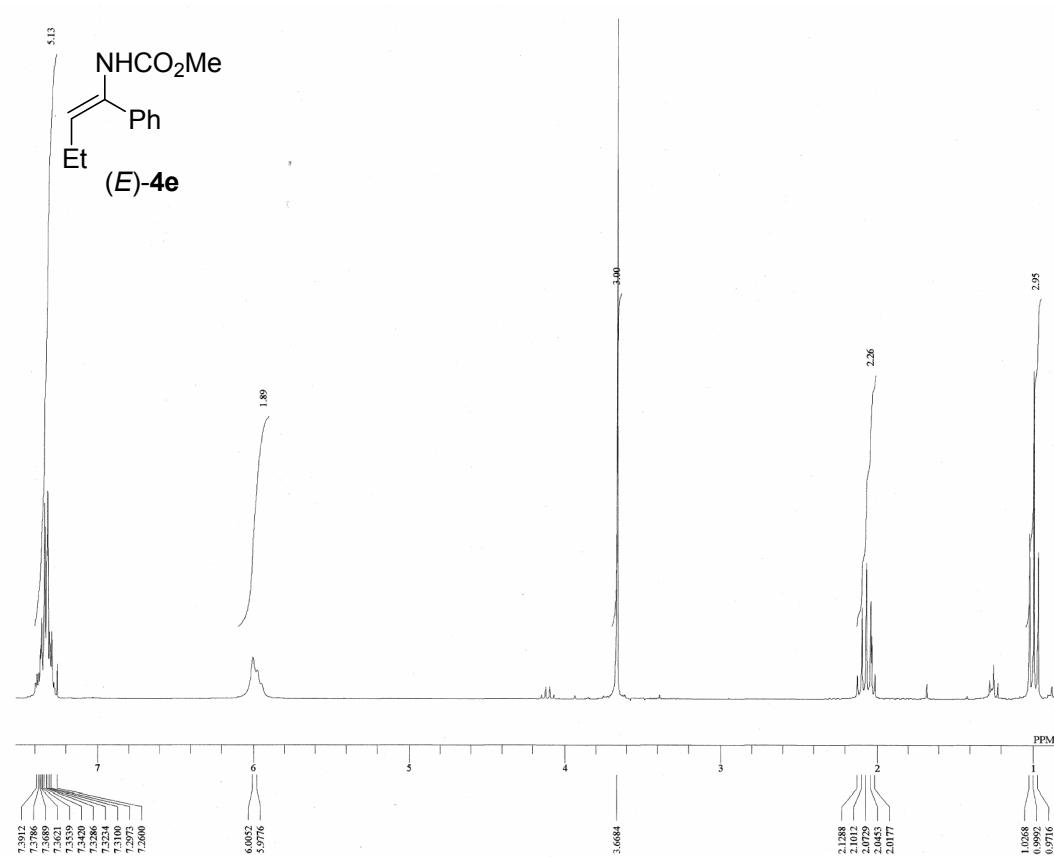


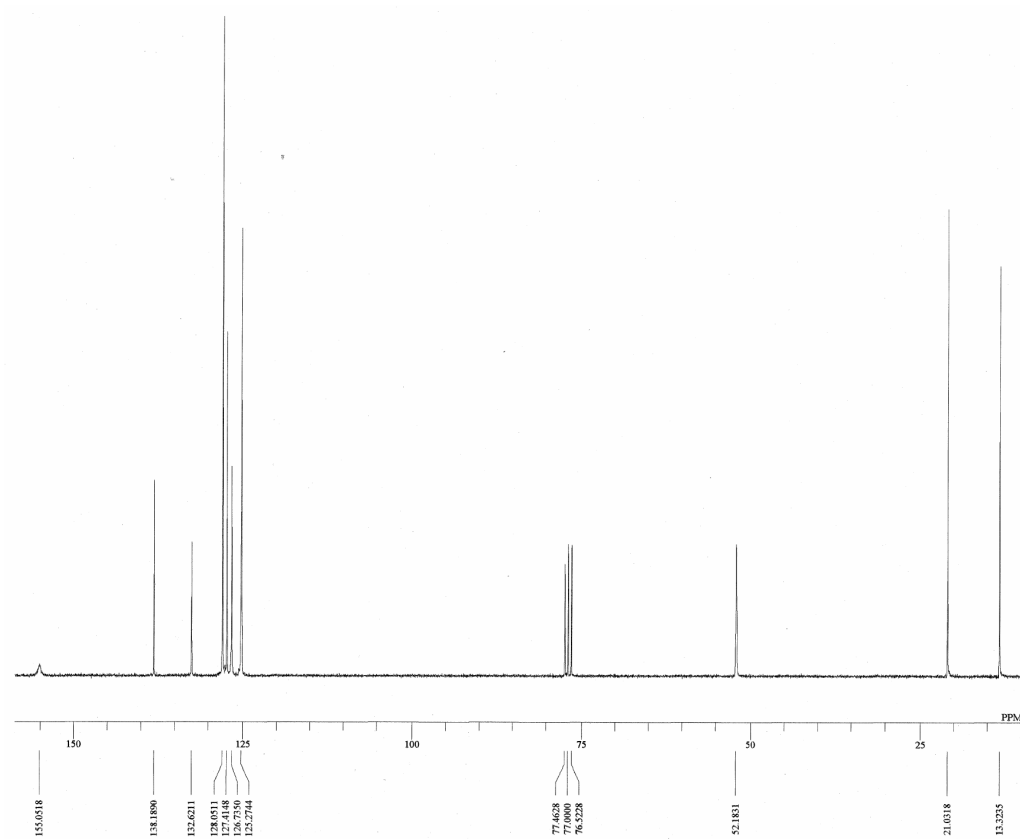
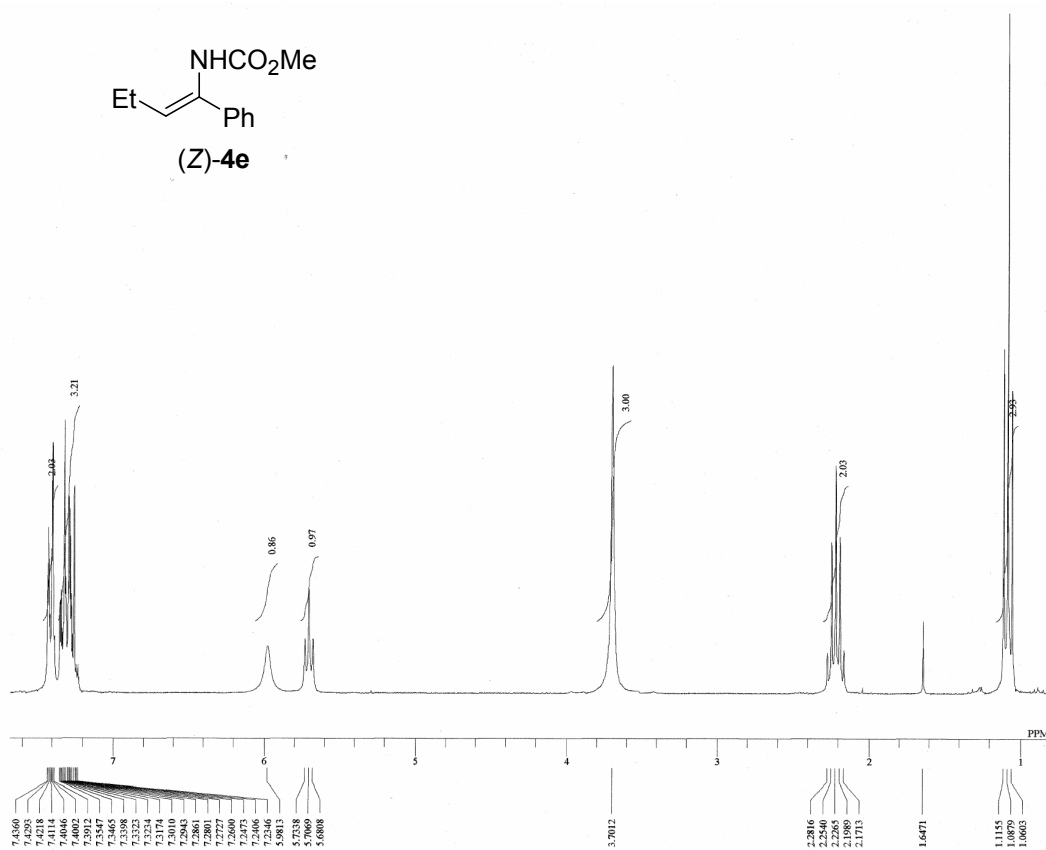
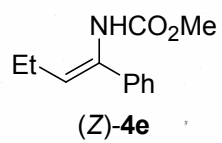


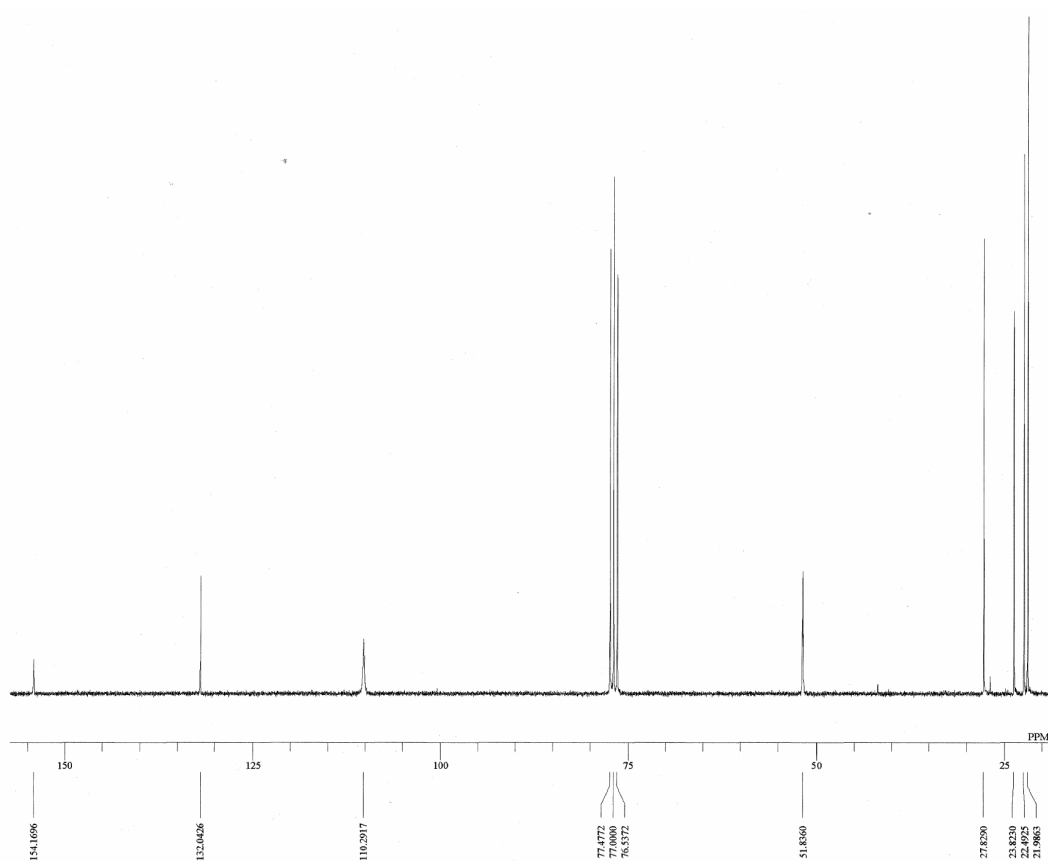
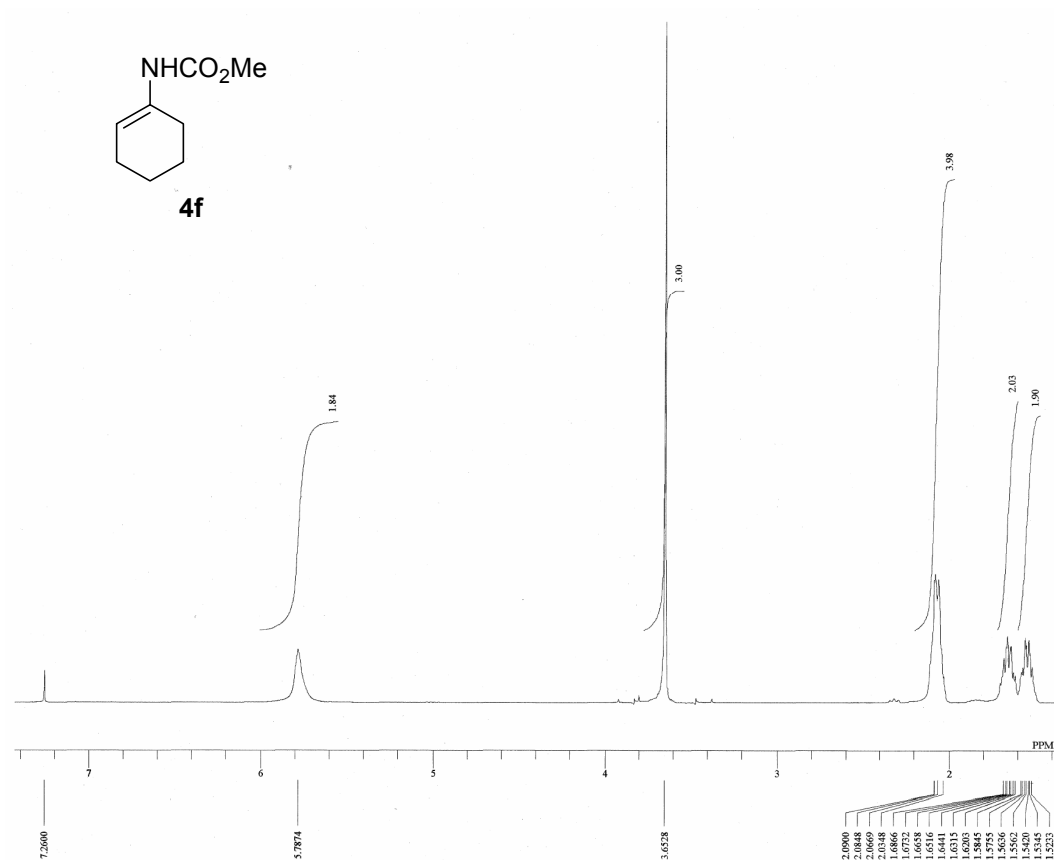




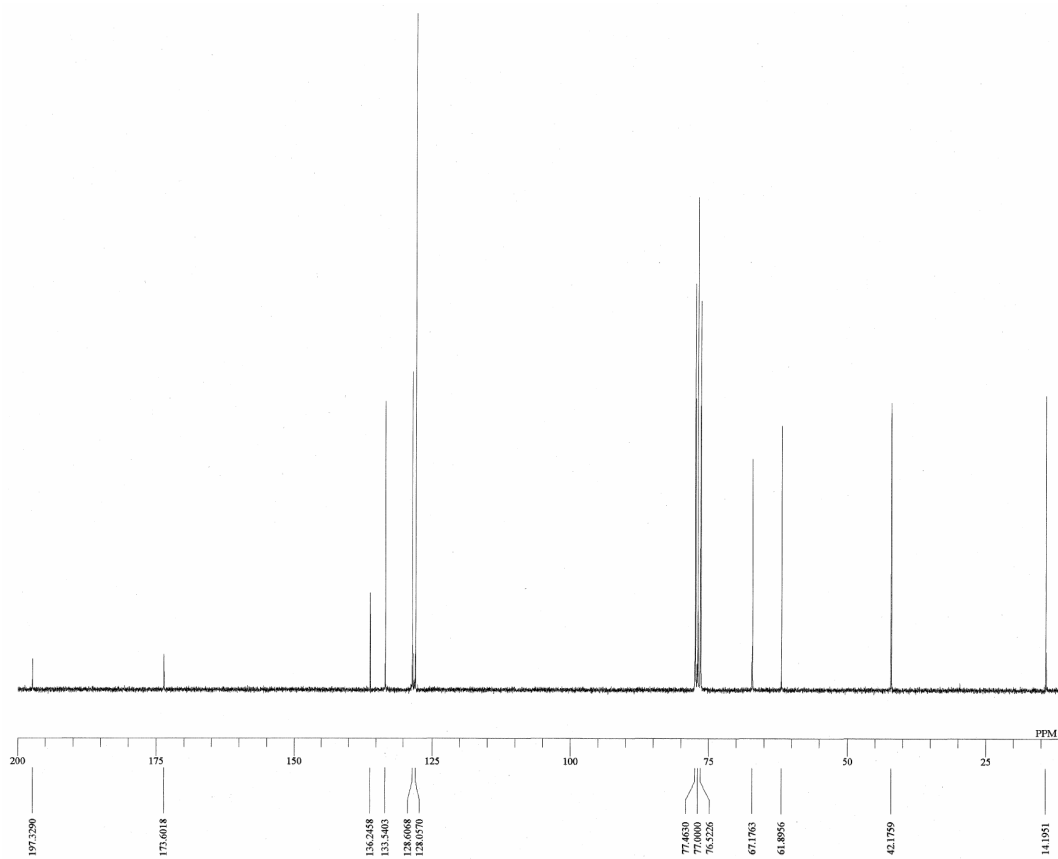
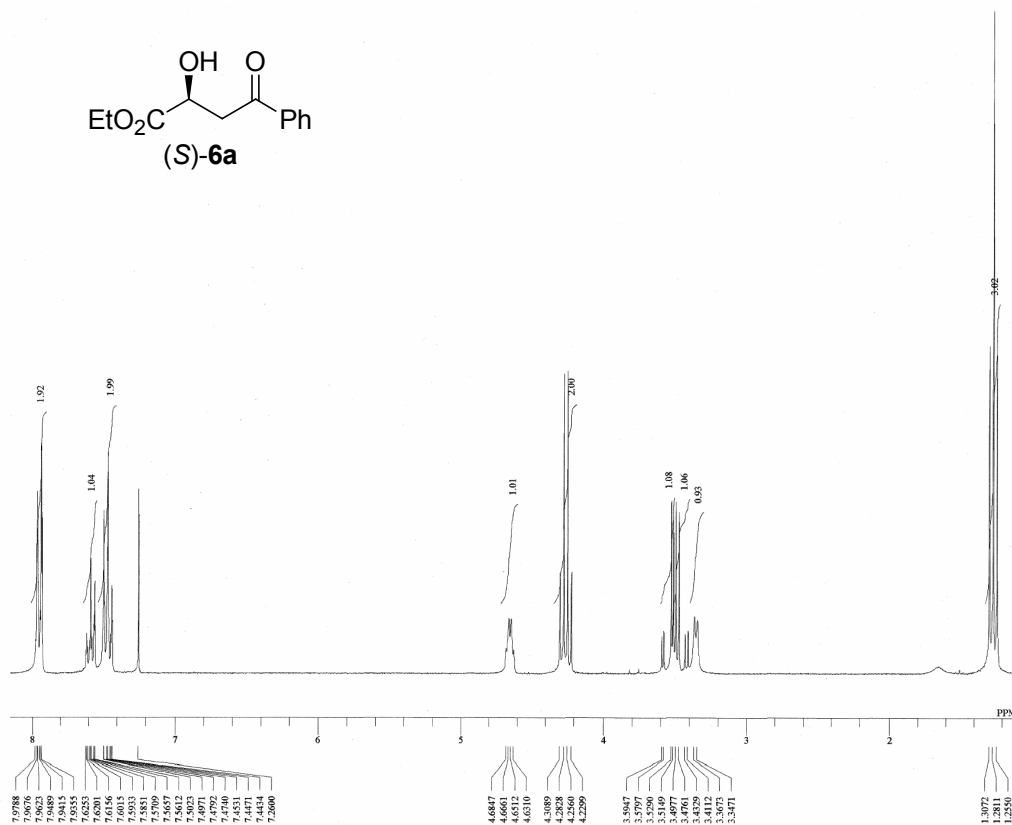
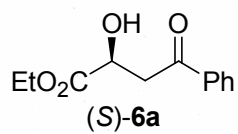


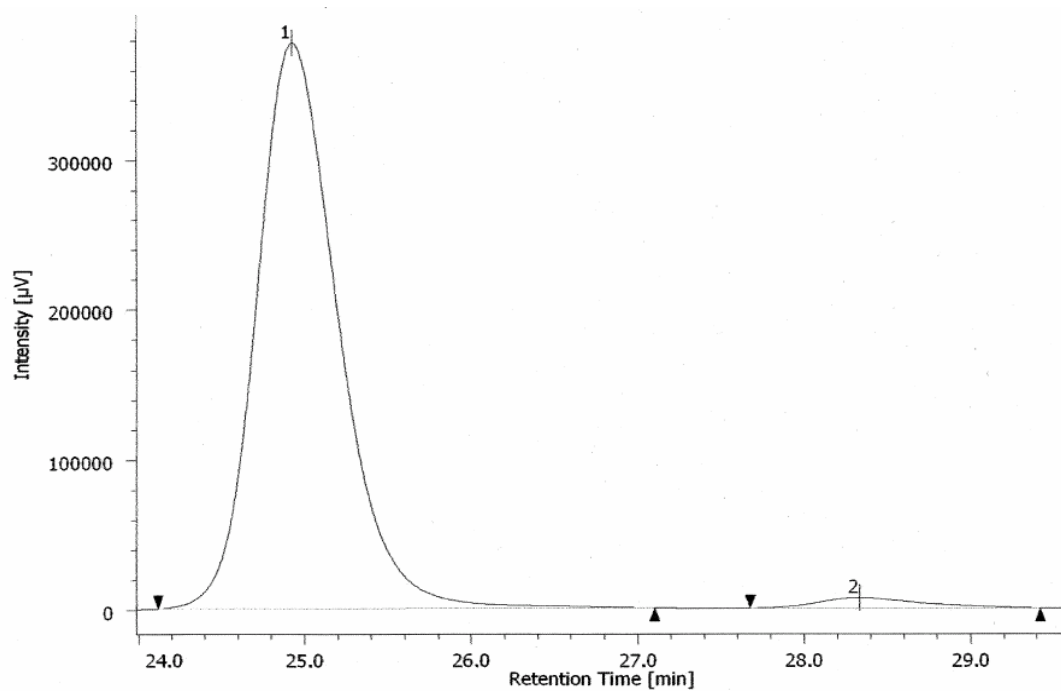
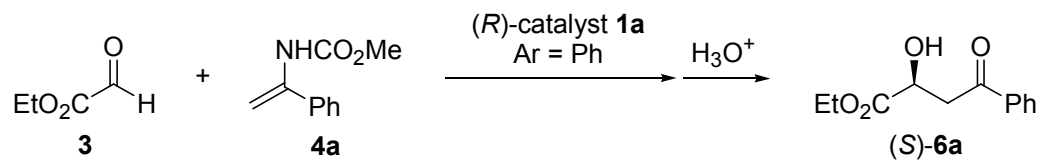
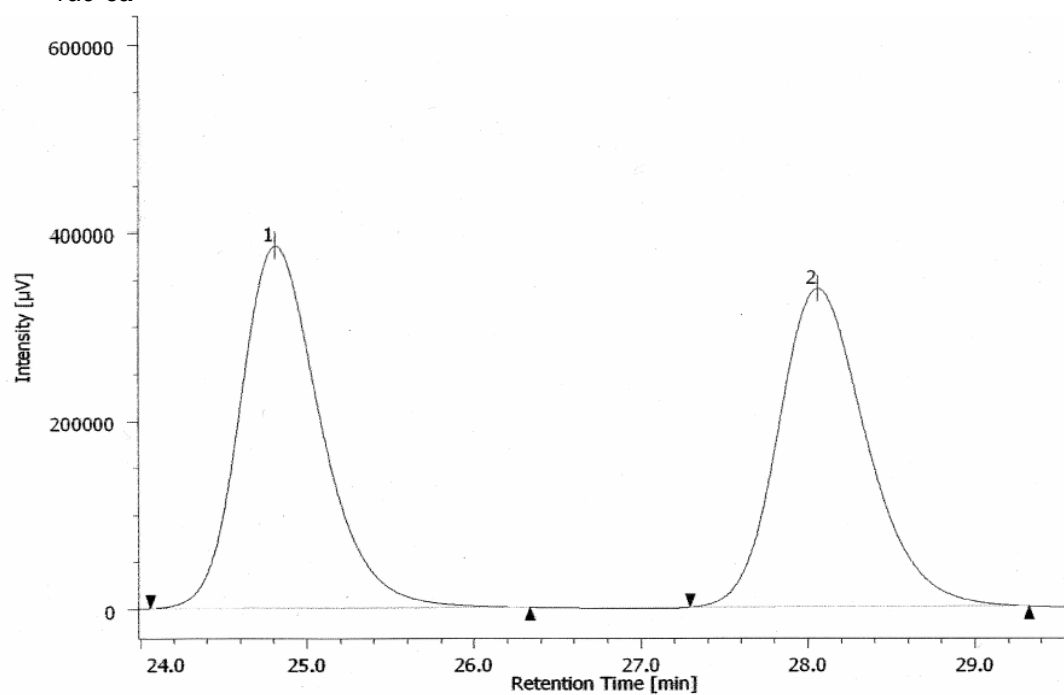
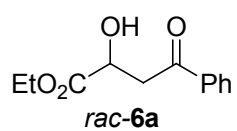


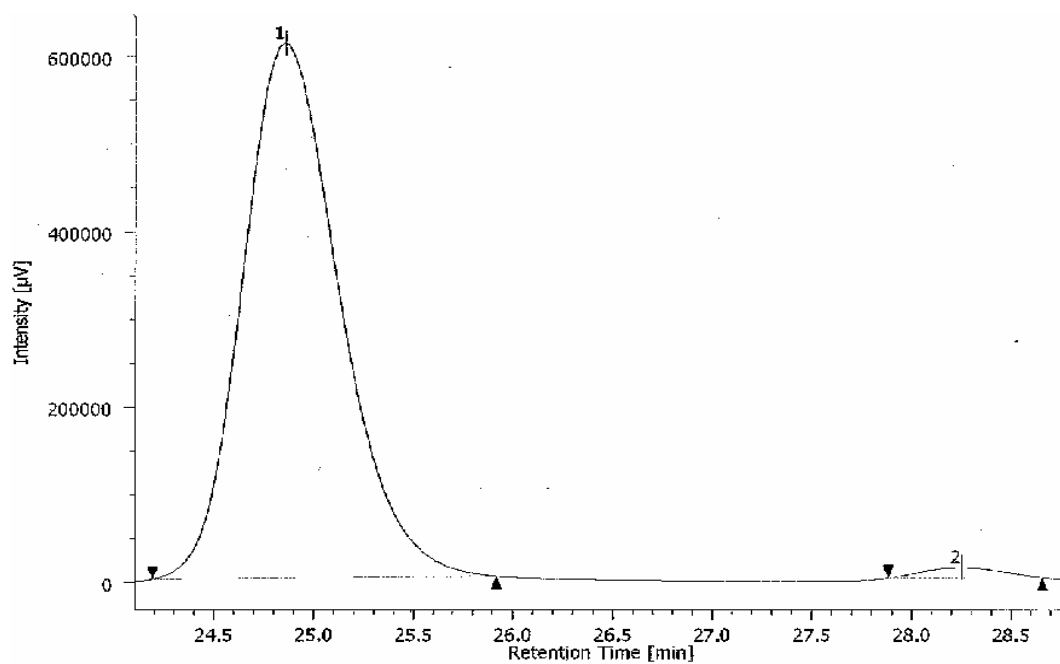
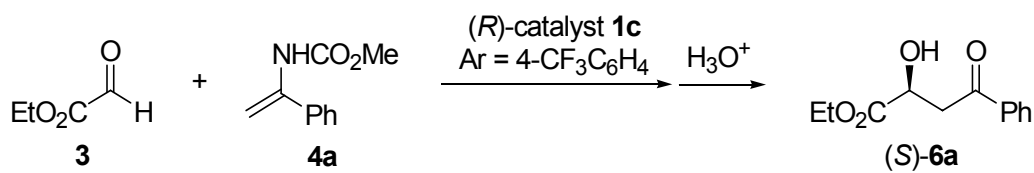
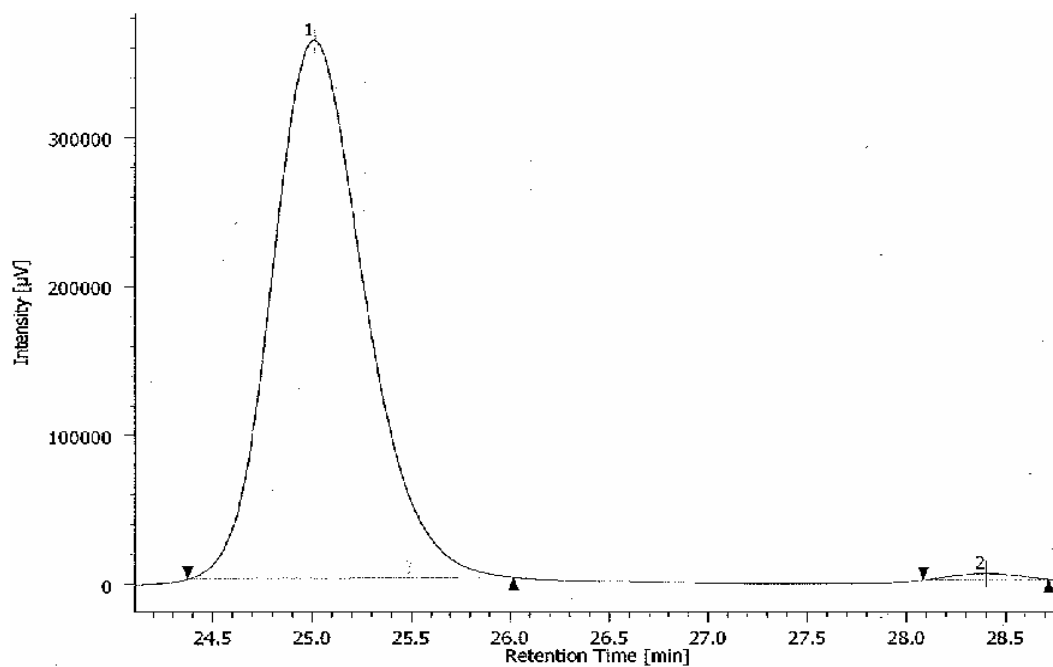
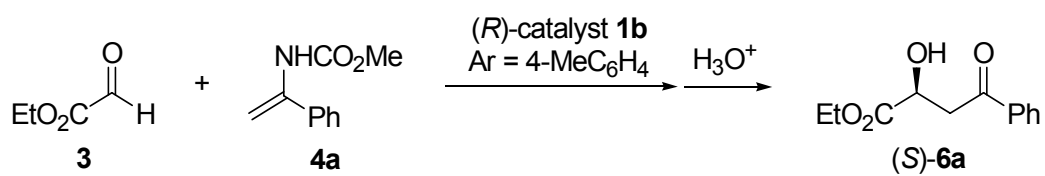


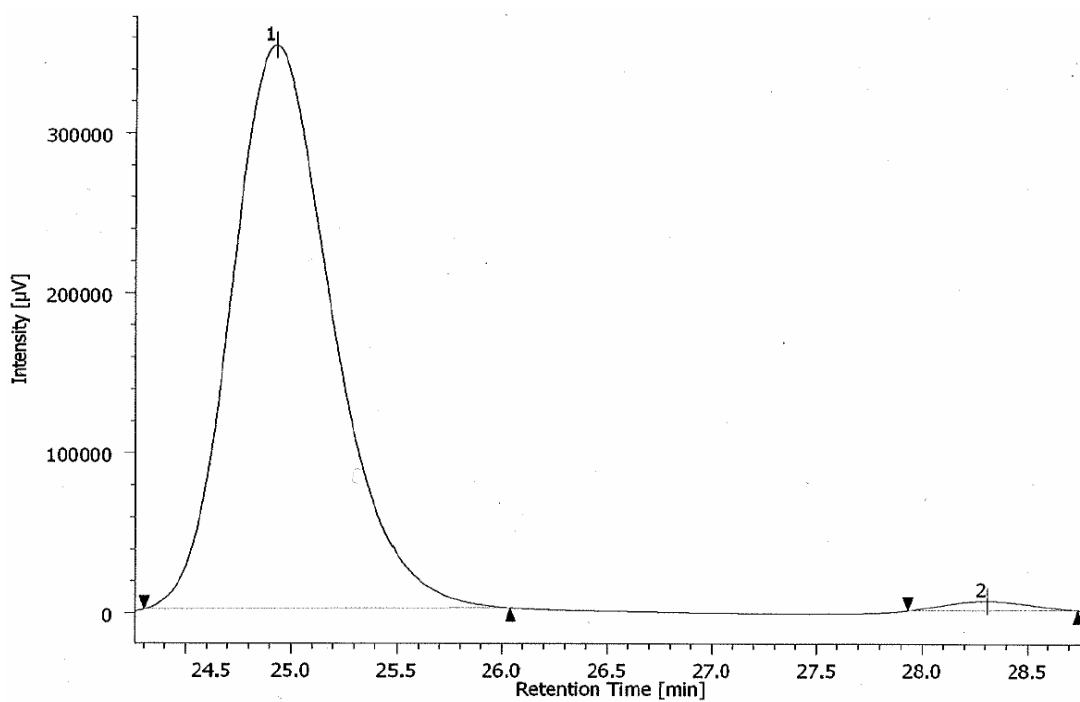
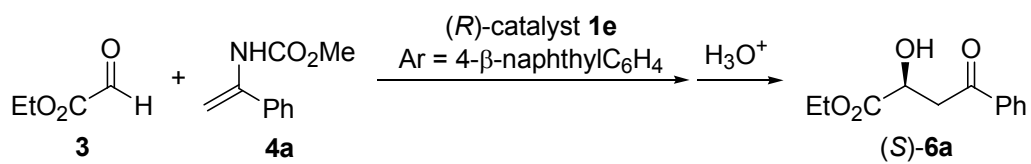
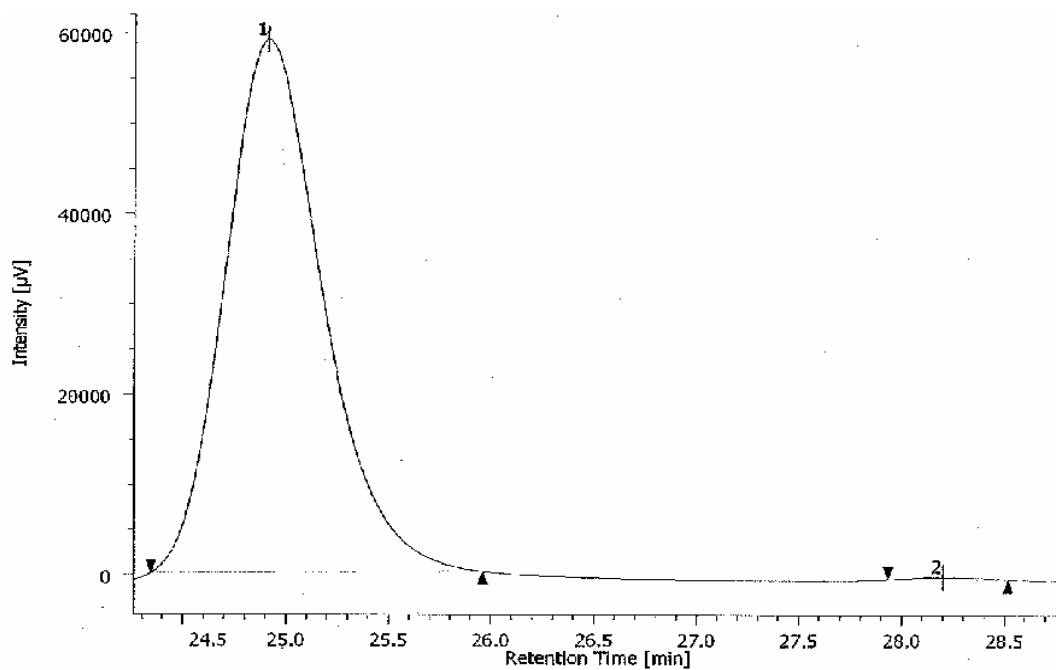
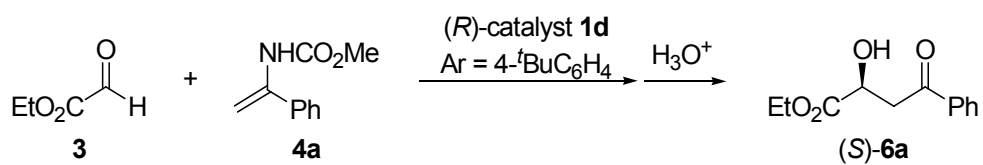


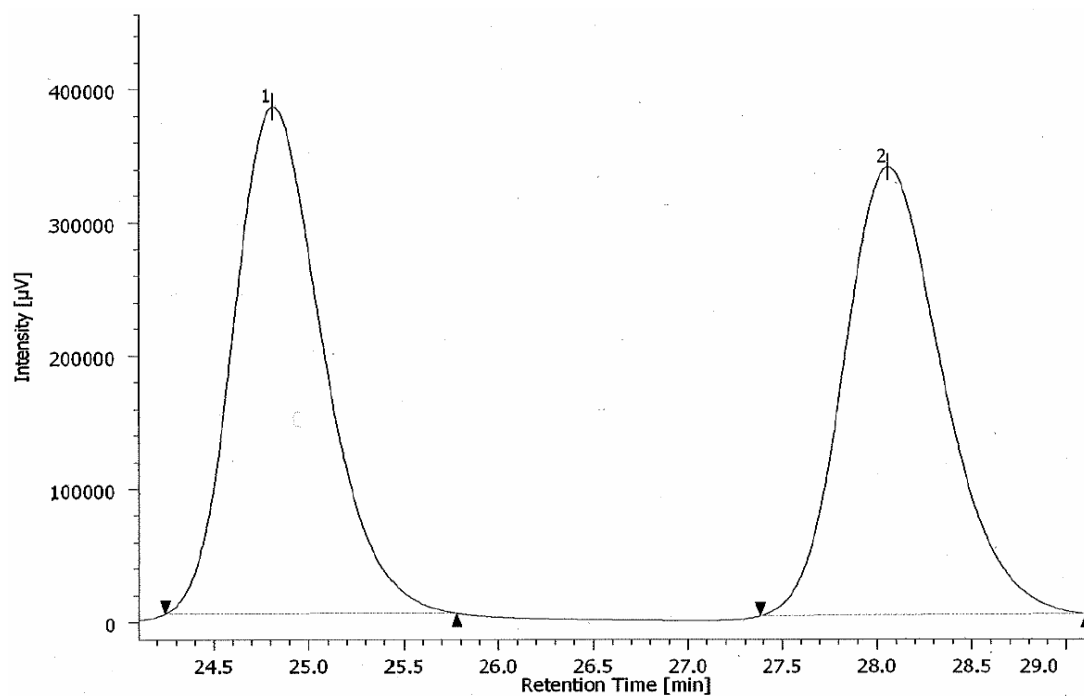
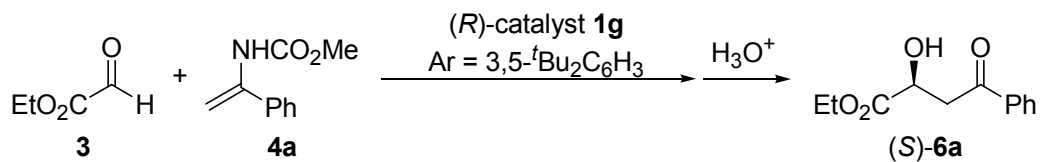
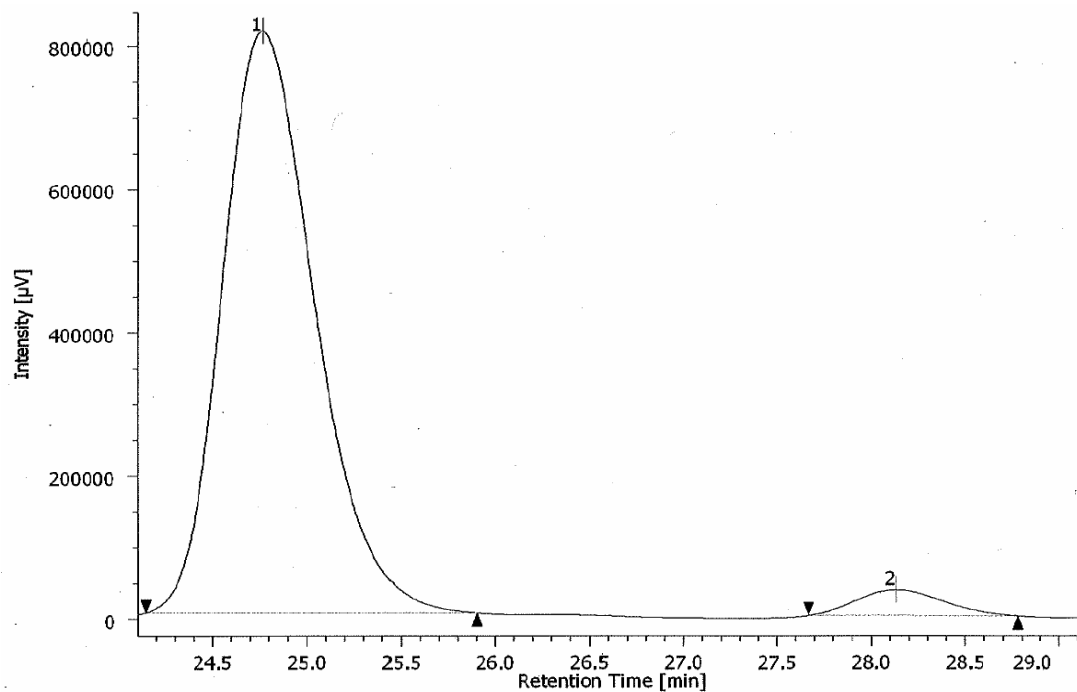
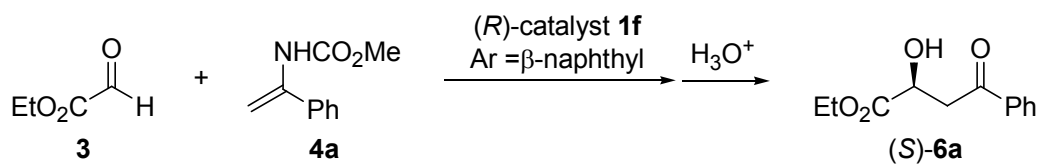
¹H & ¹³C NMR Spectra and HPLC Charts of Products

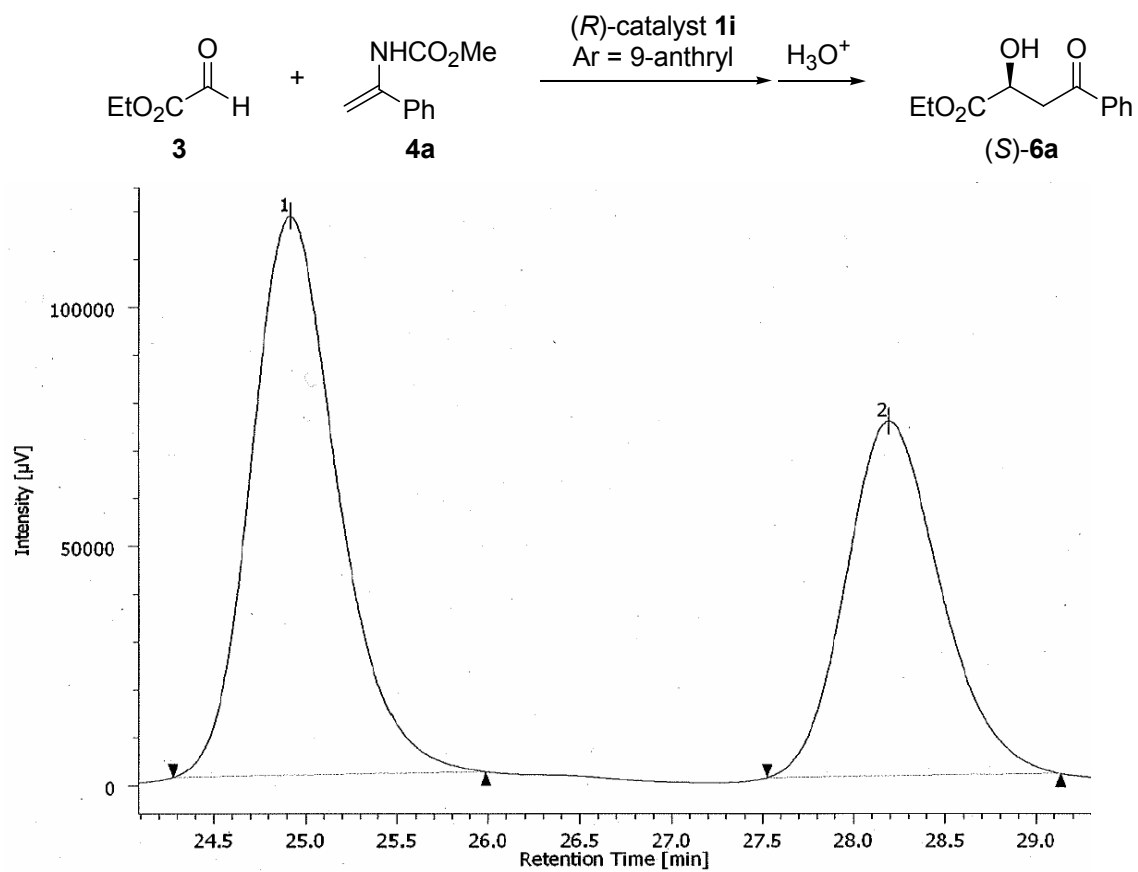
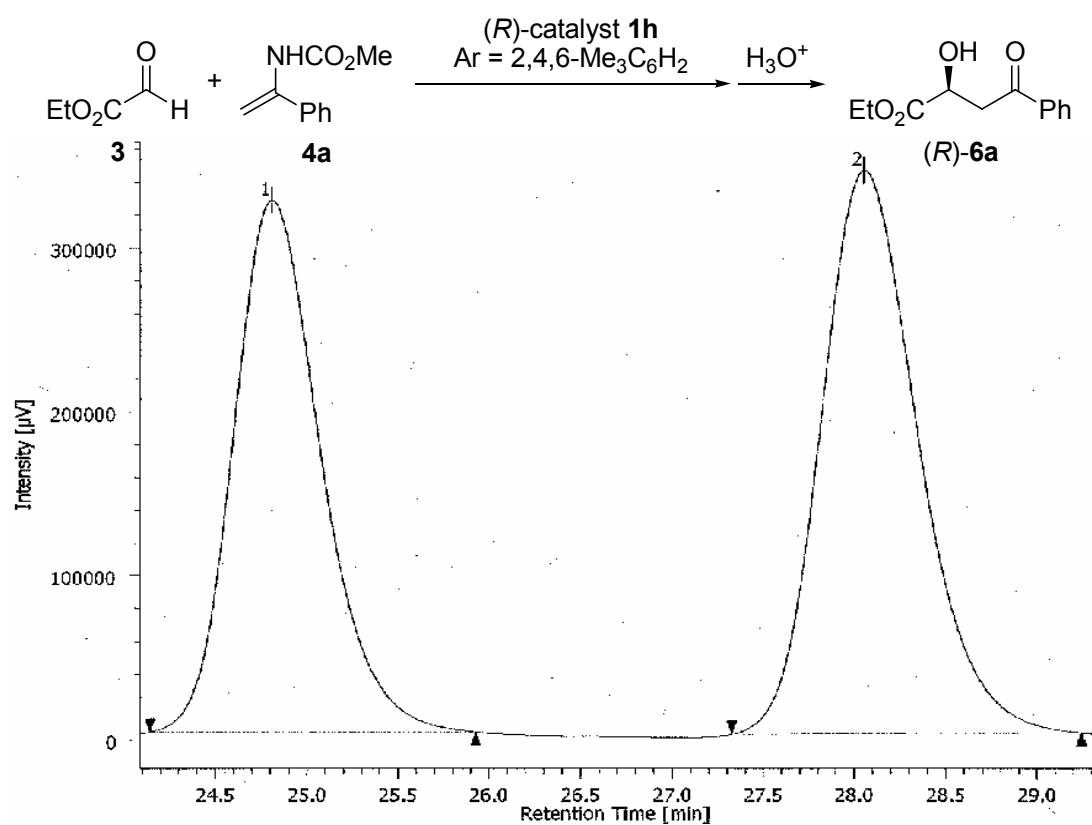


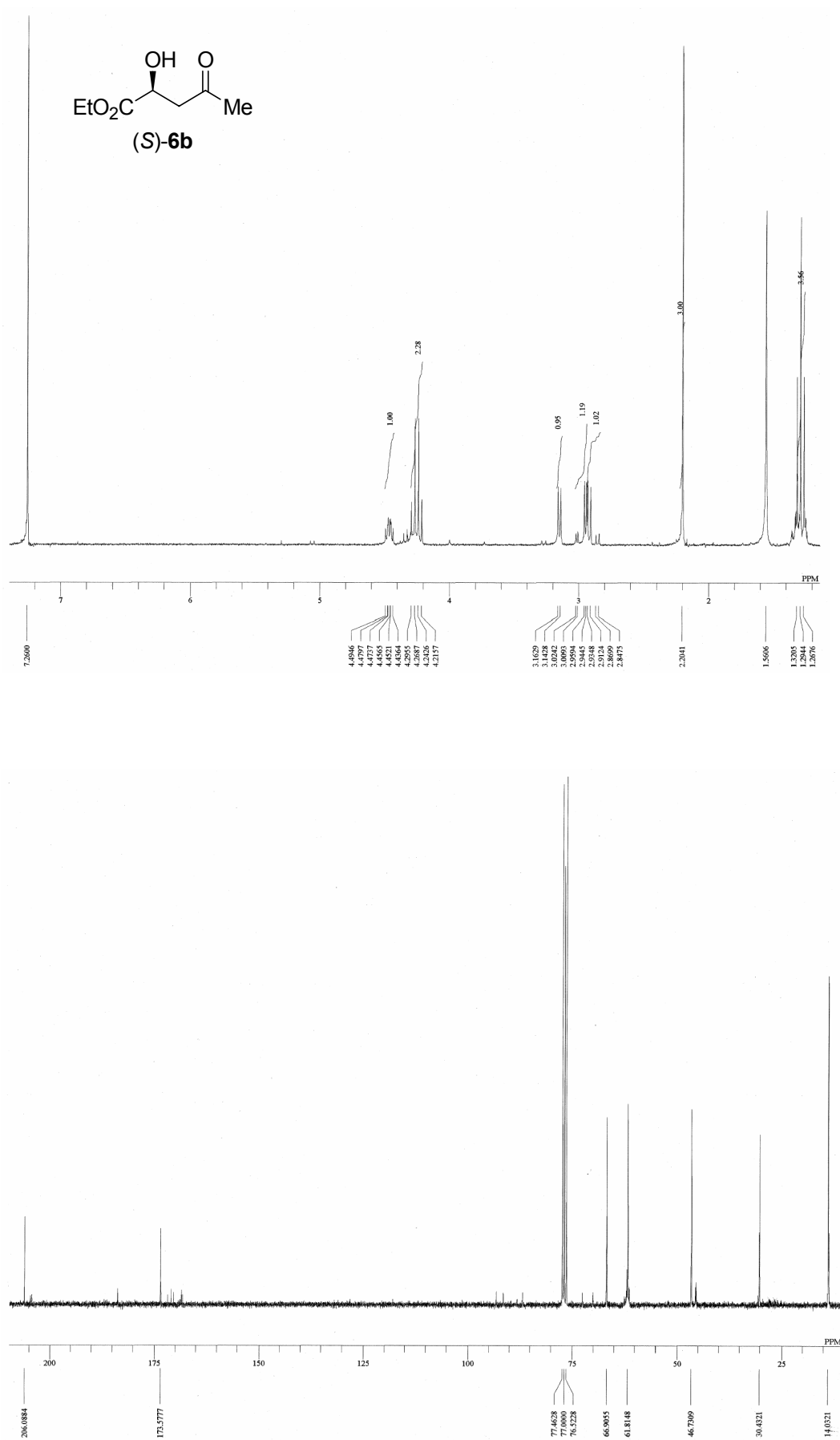


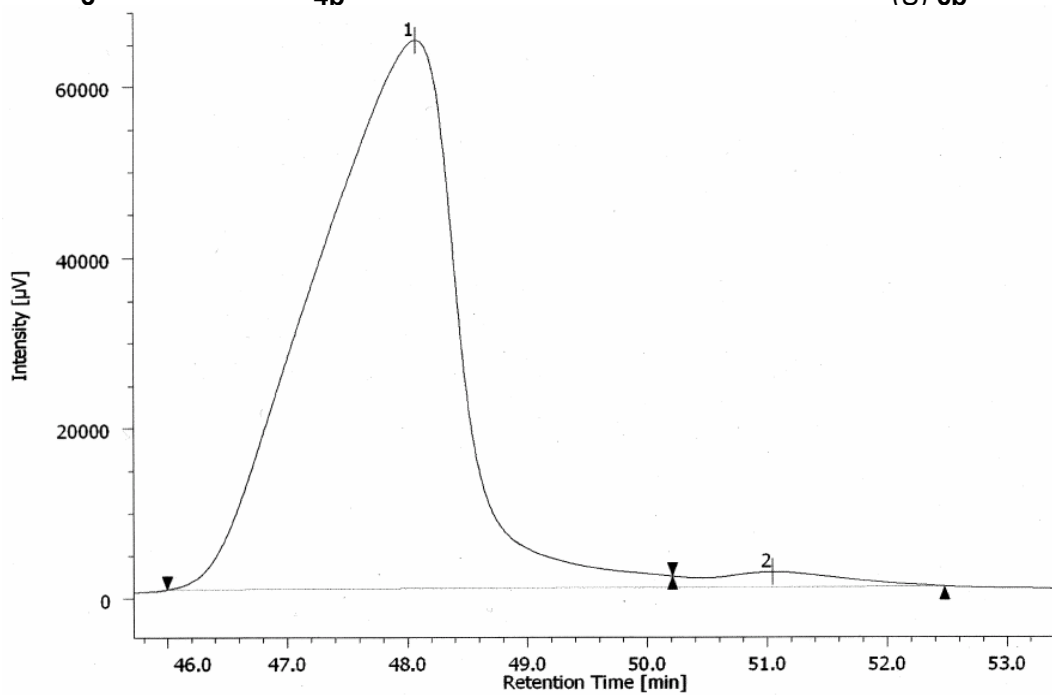
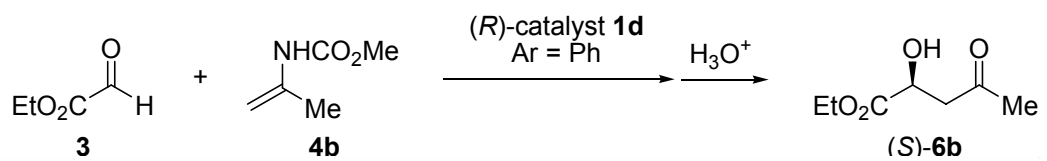
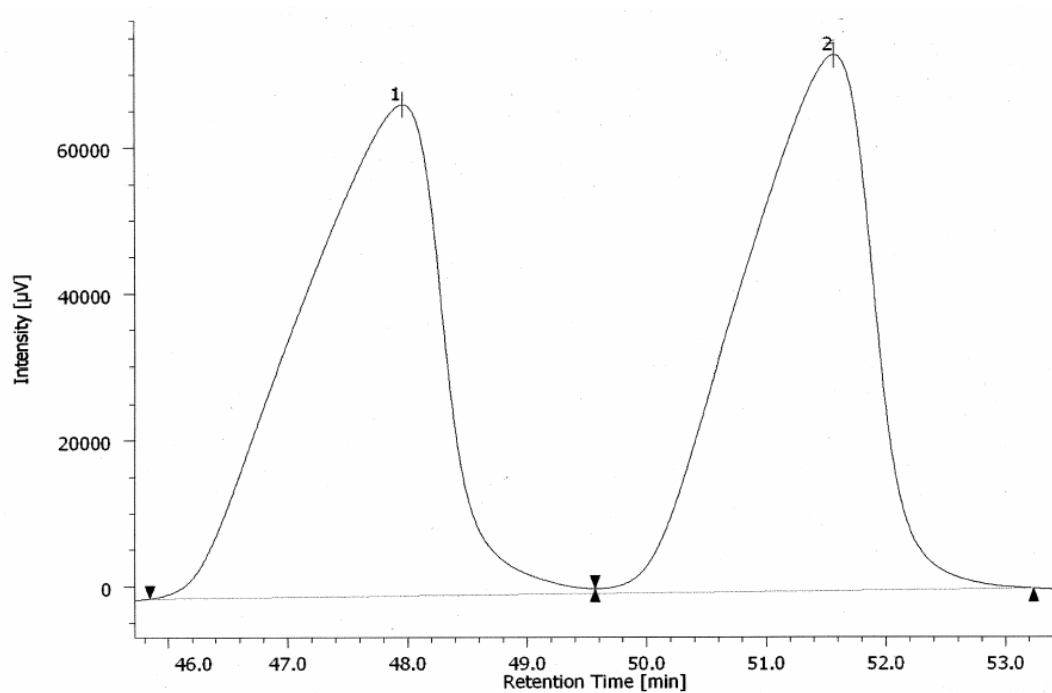
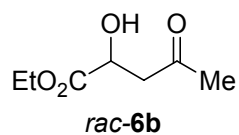


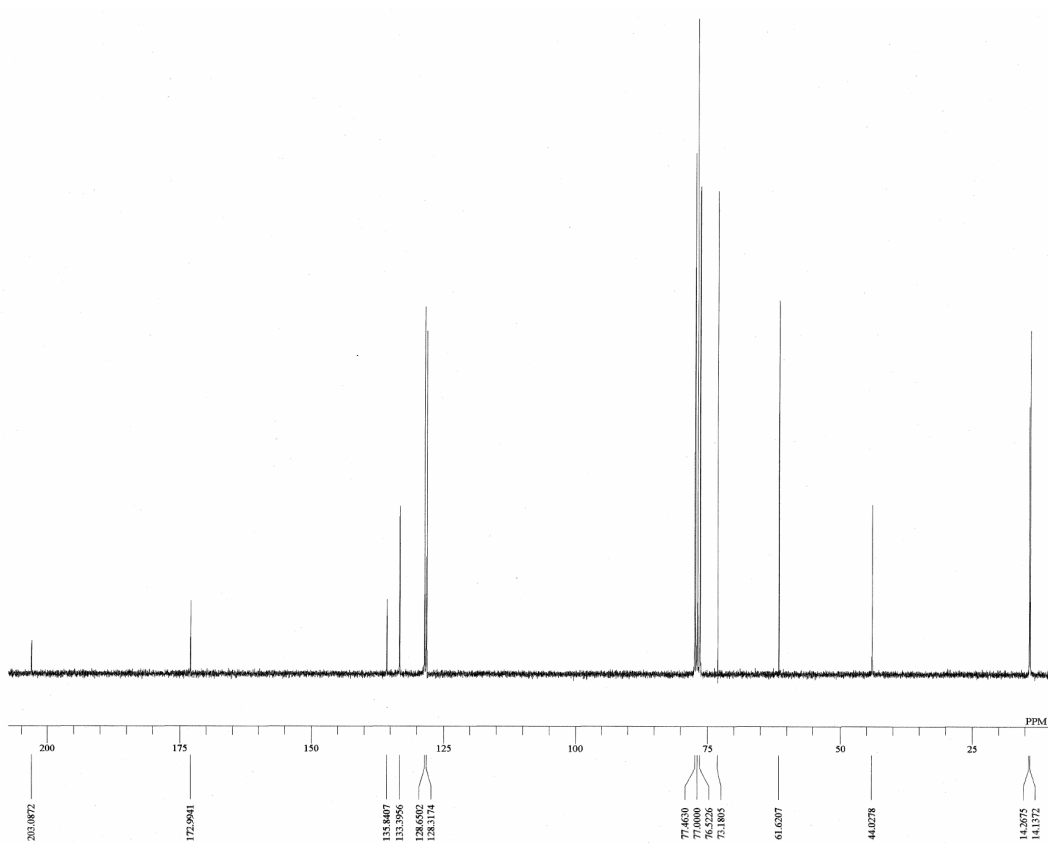
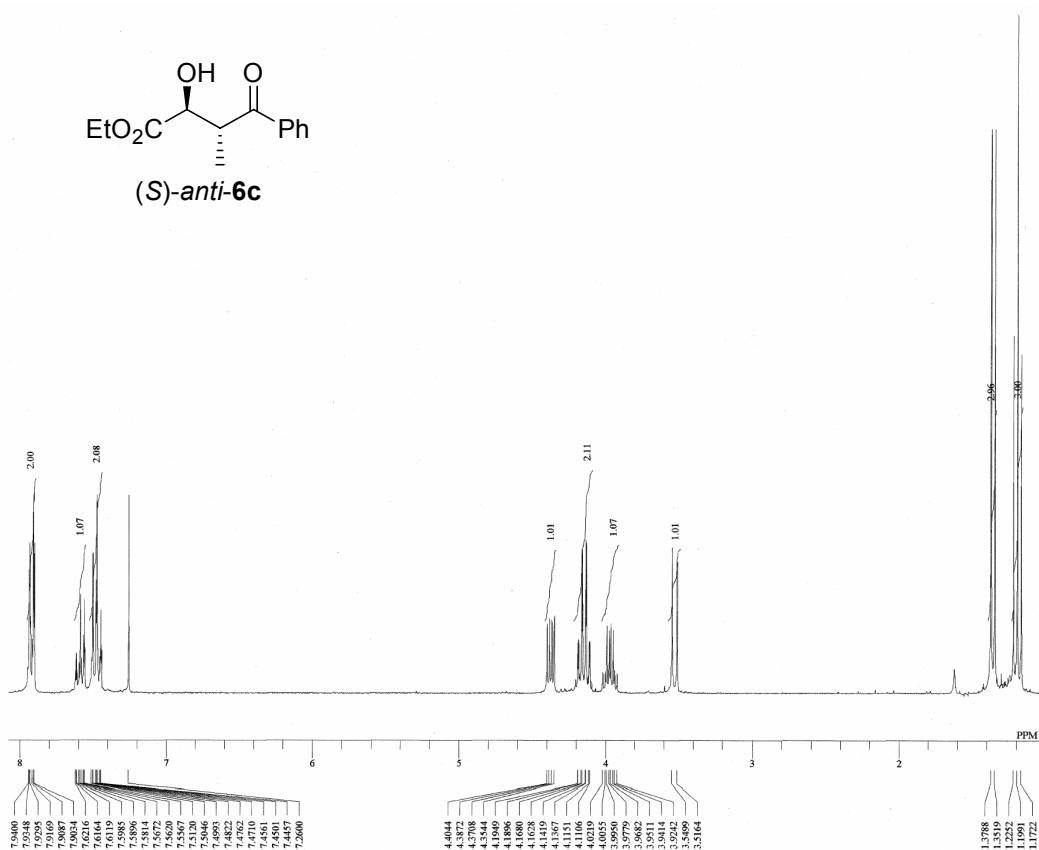
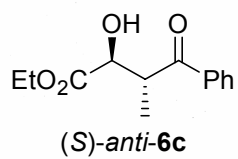


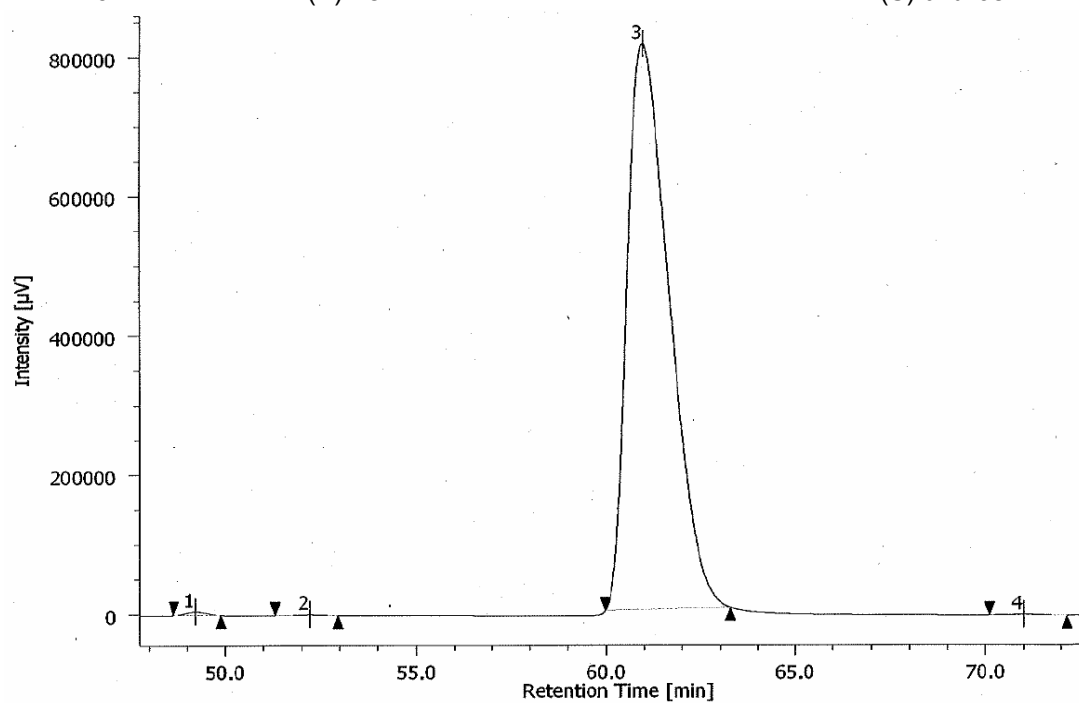
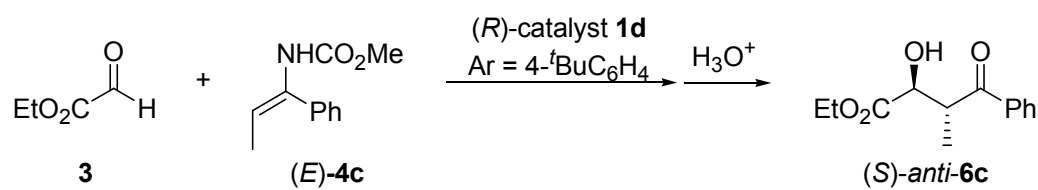
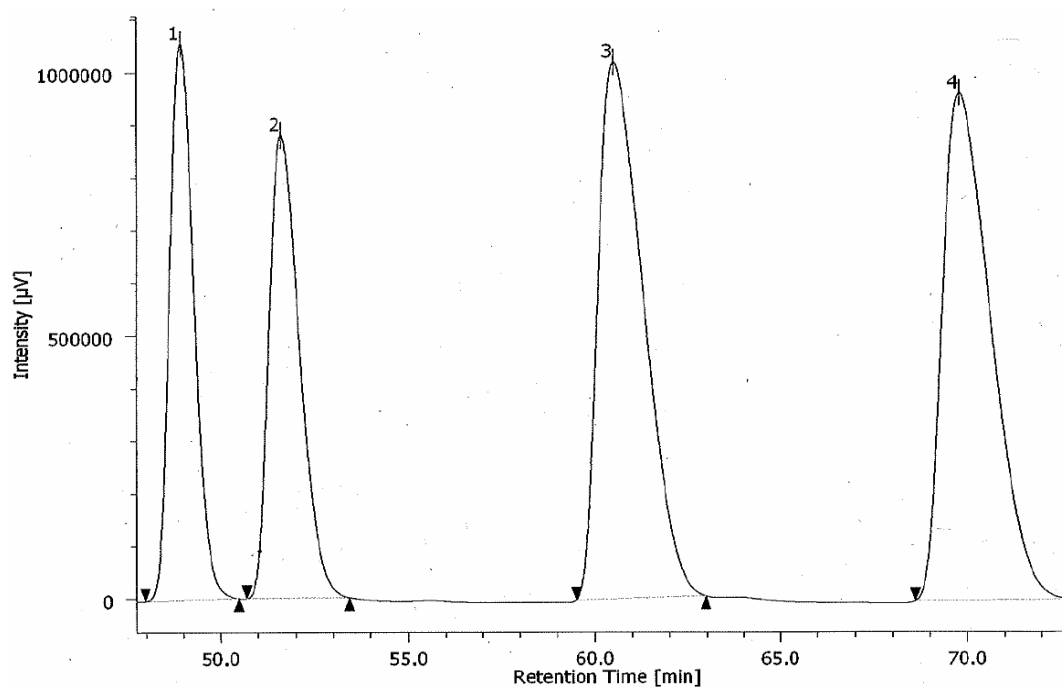
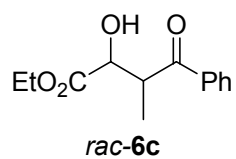


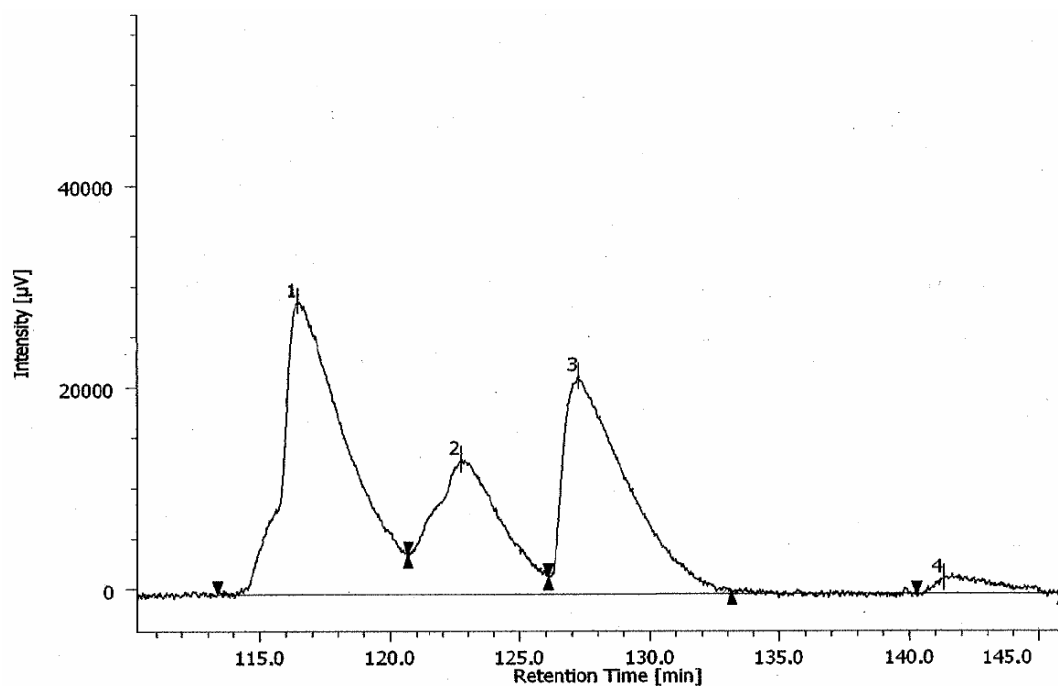
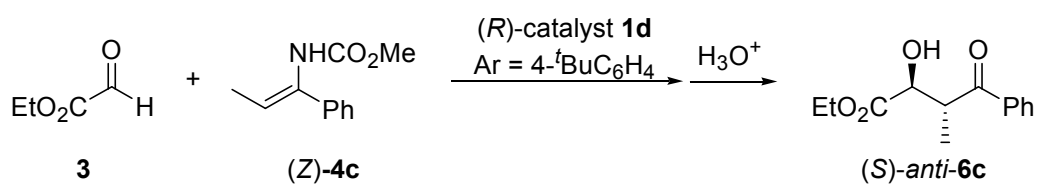
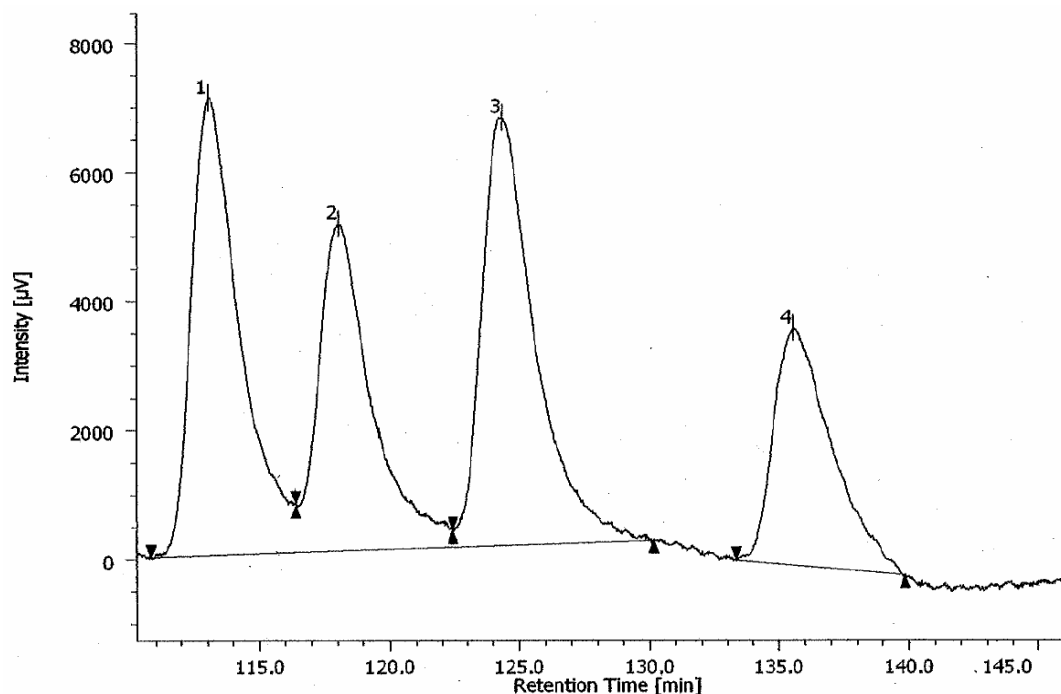
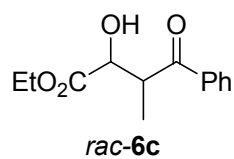


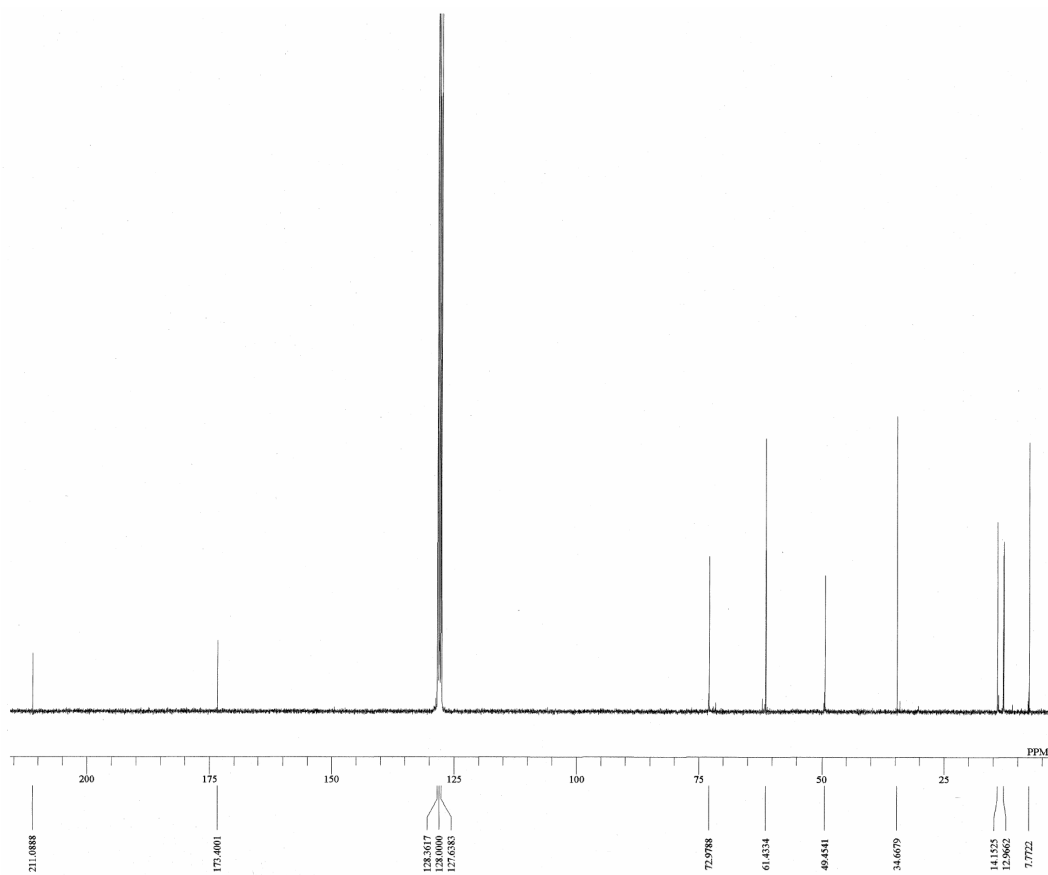
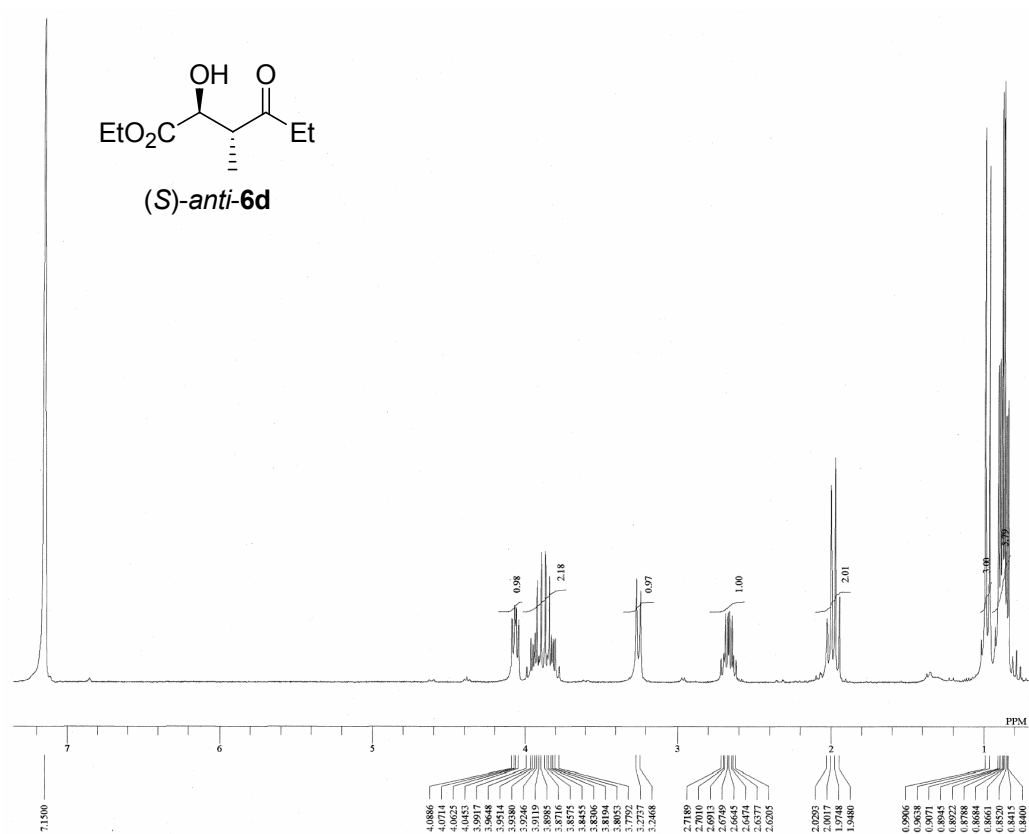


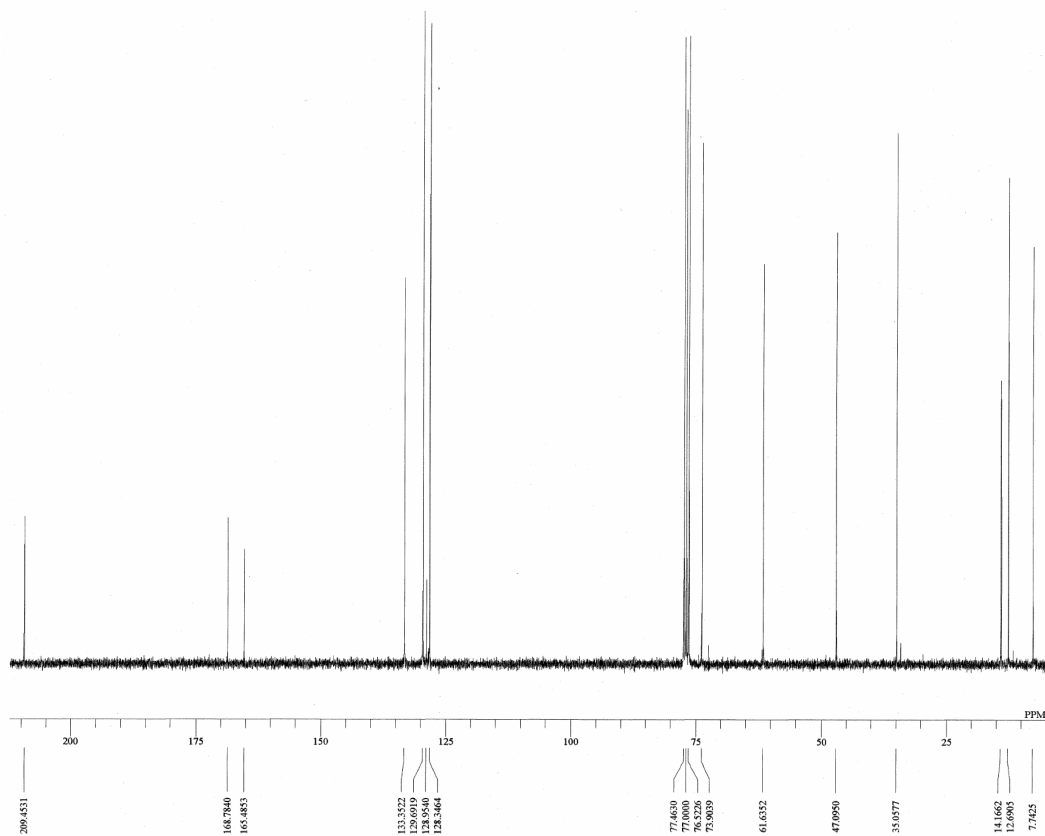
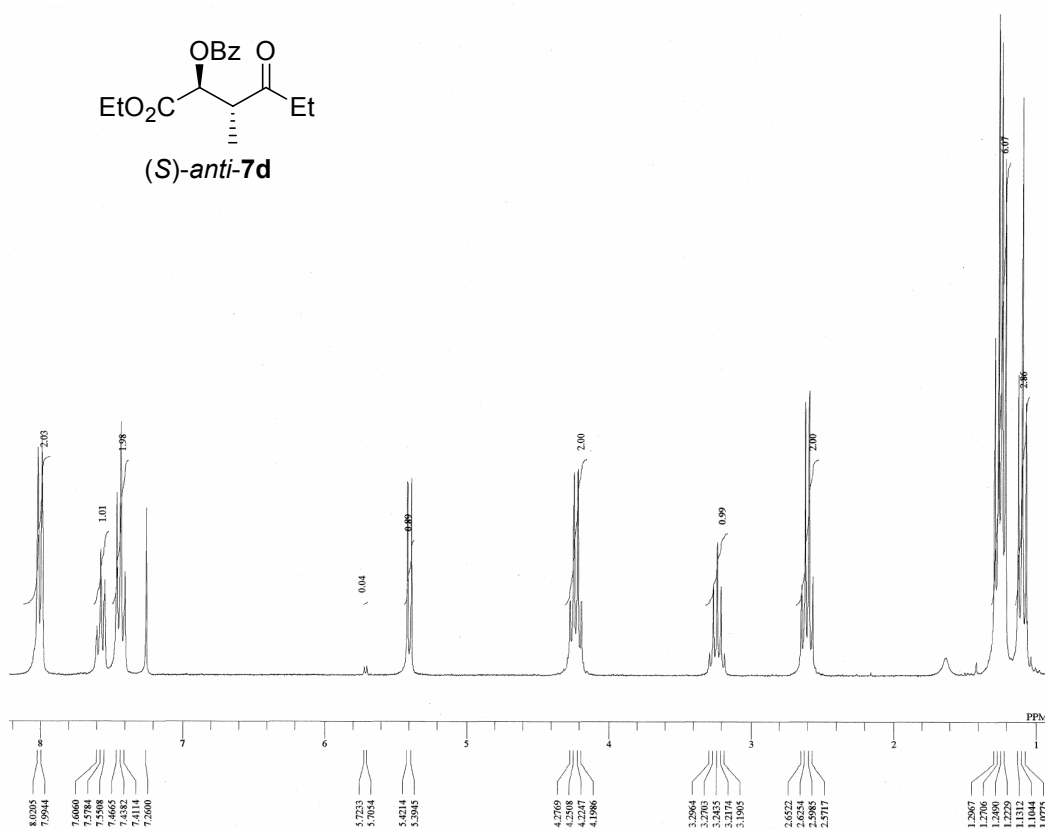
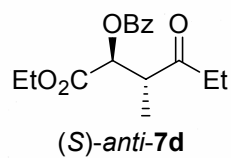


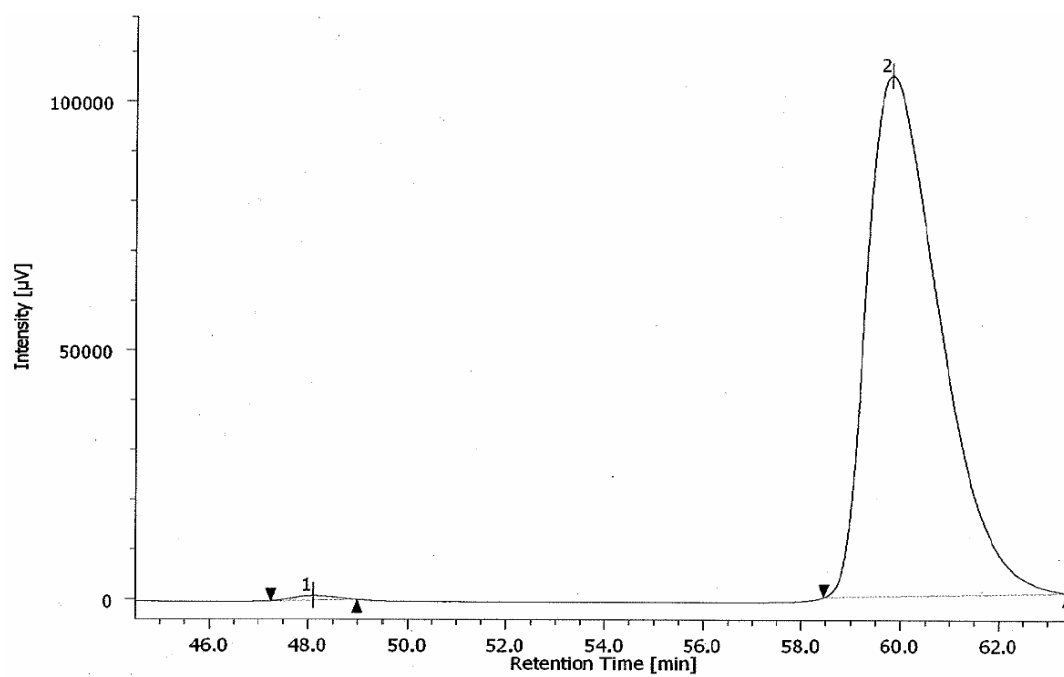
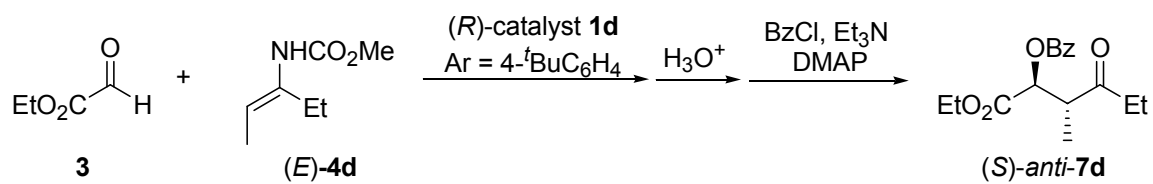
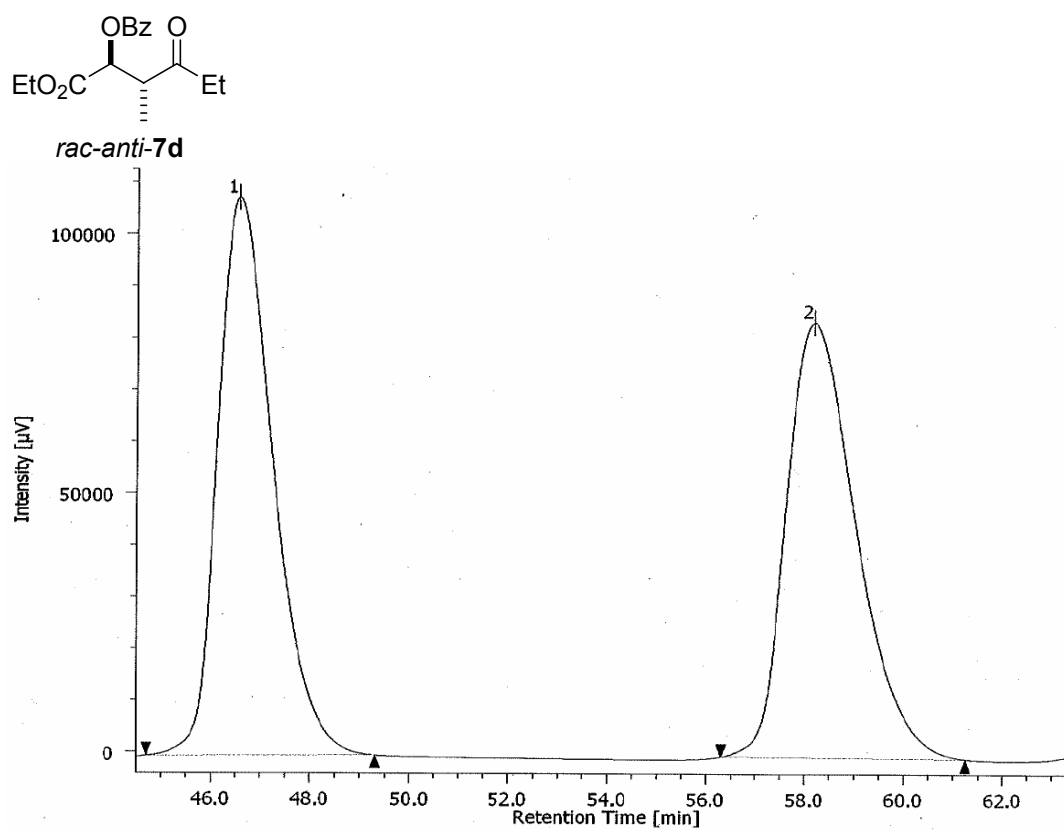


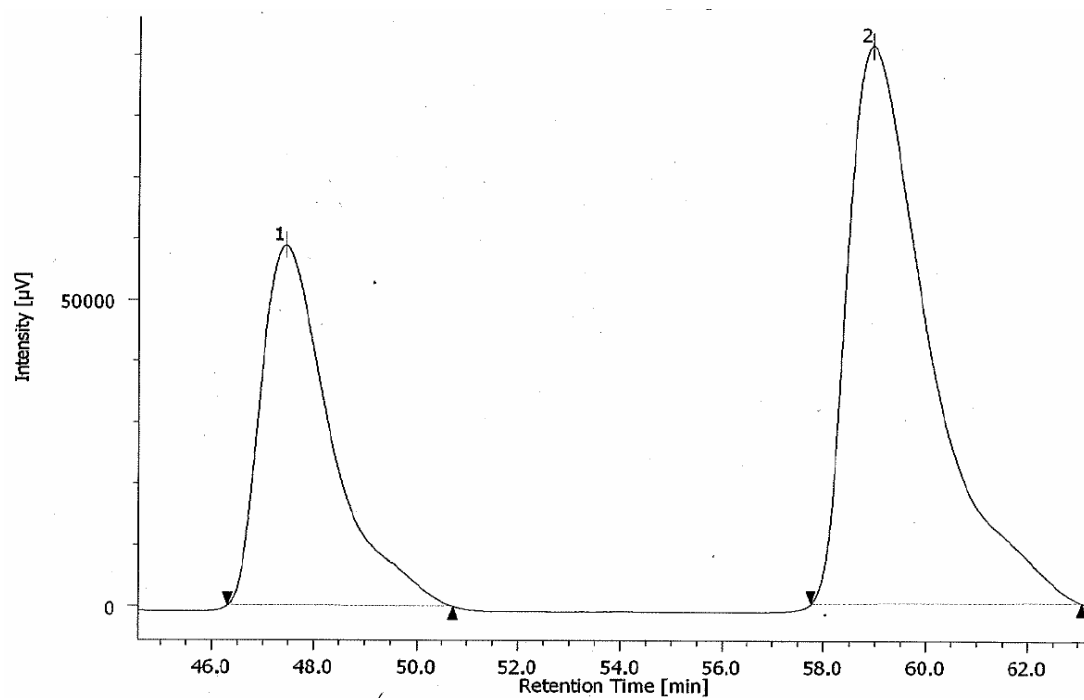
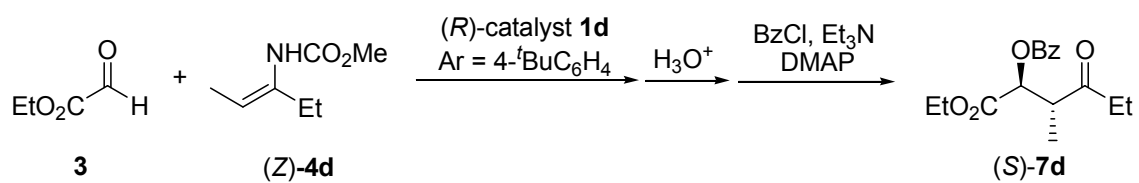


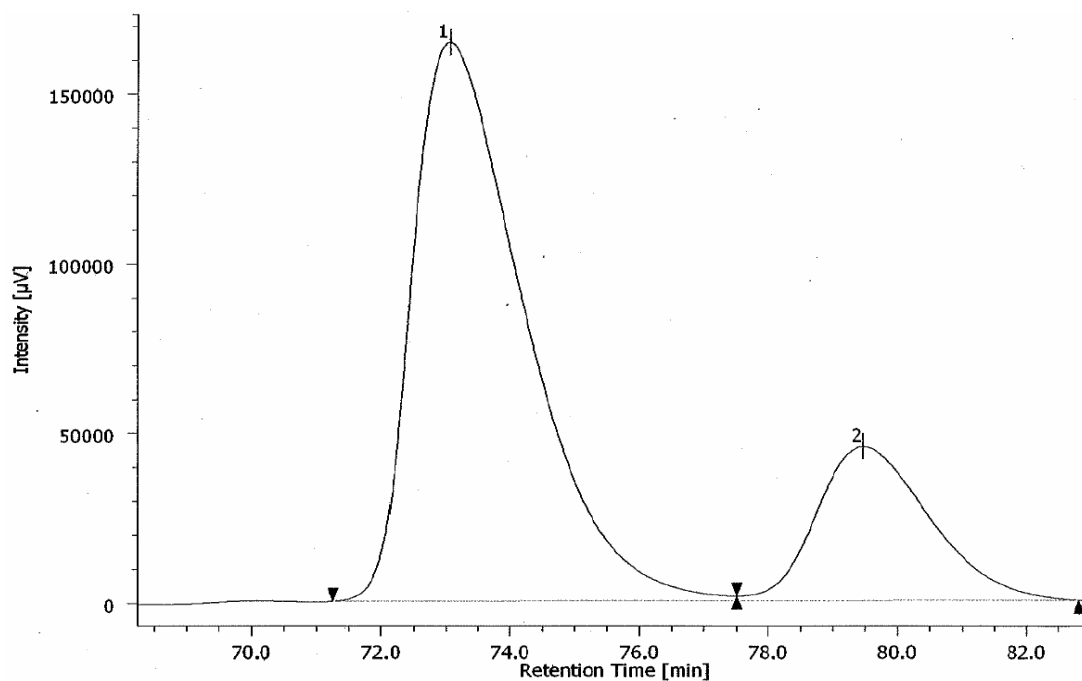
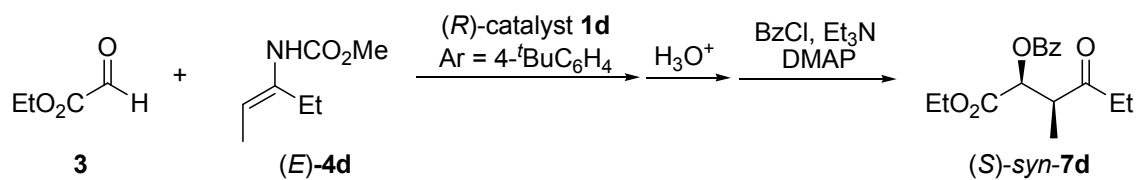
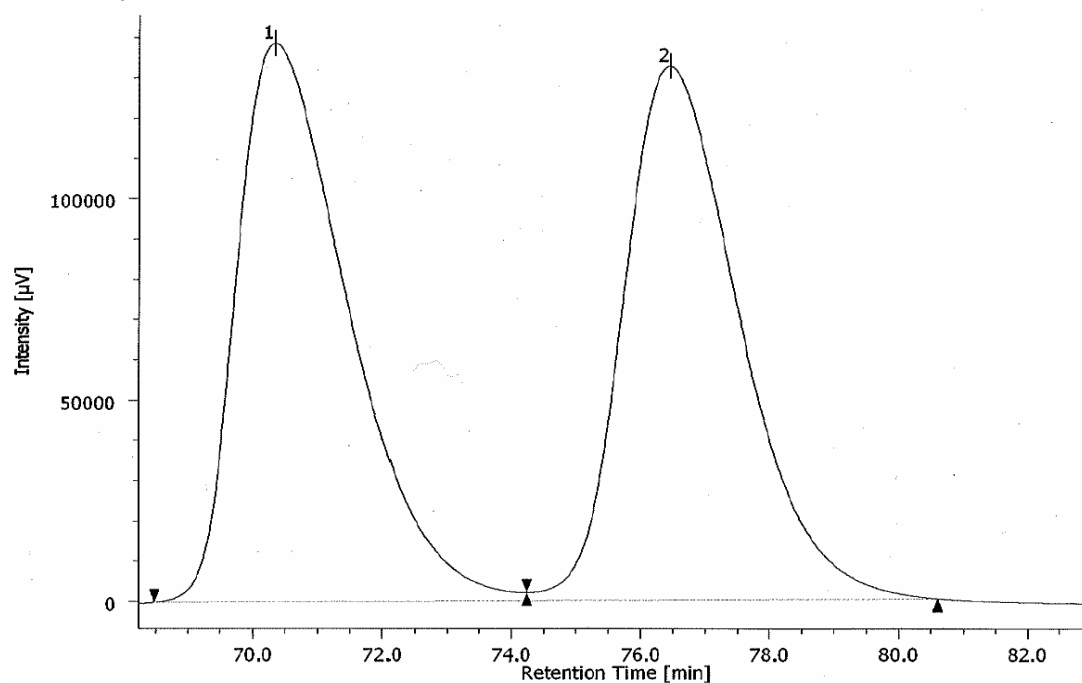
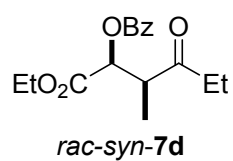


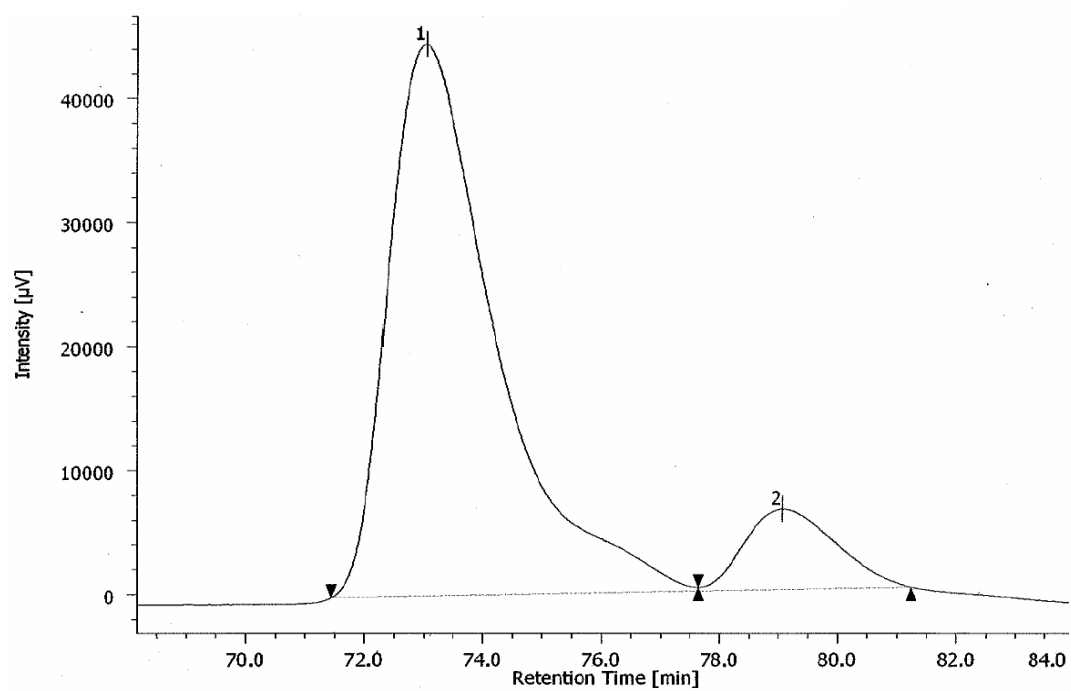
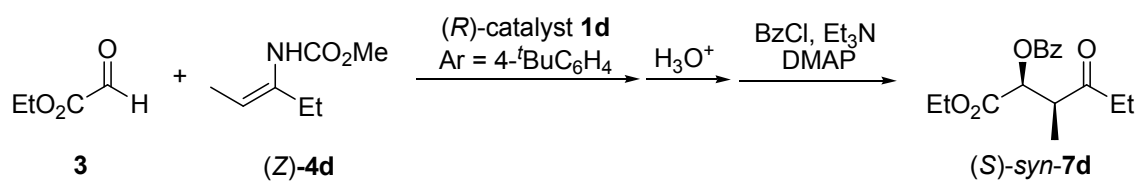


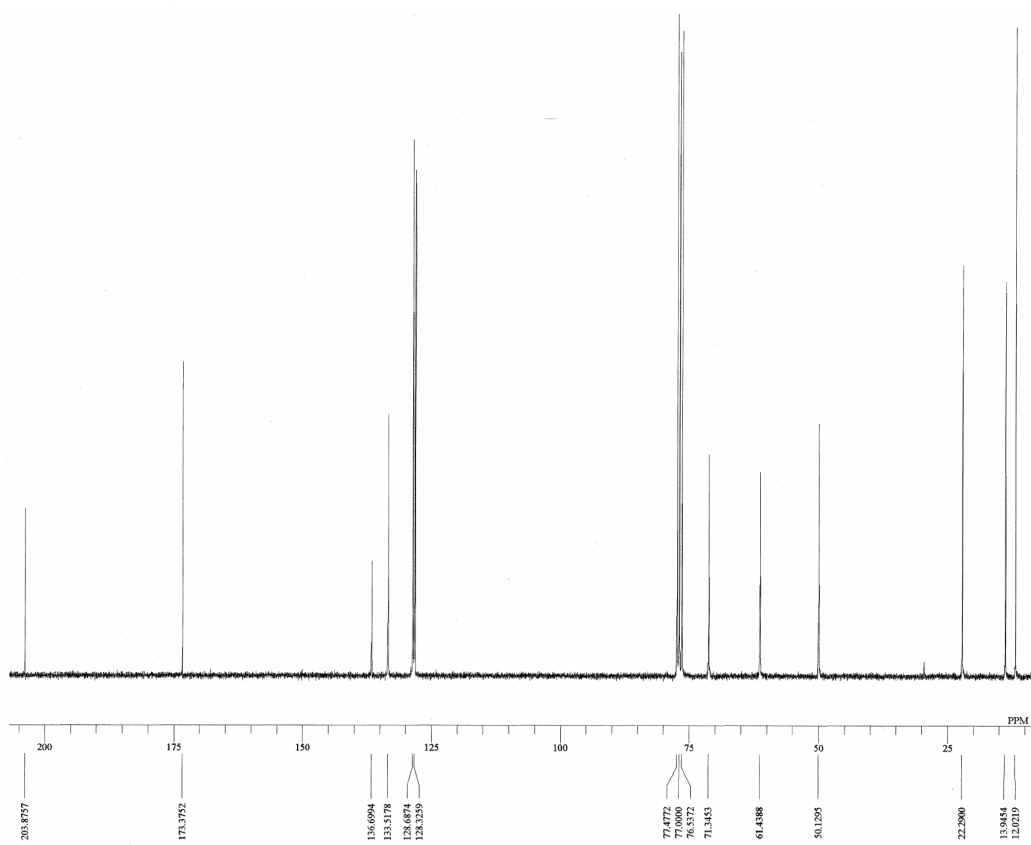
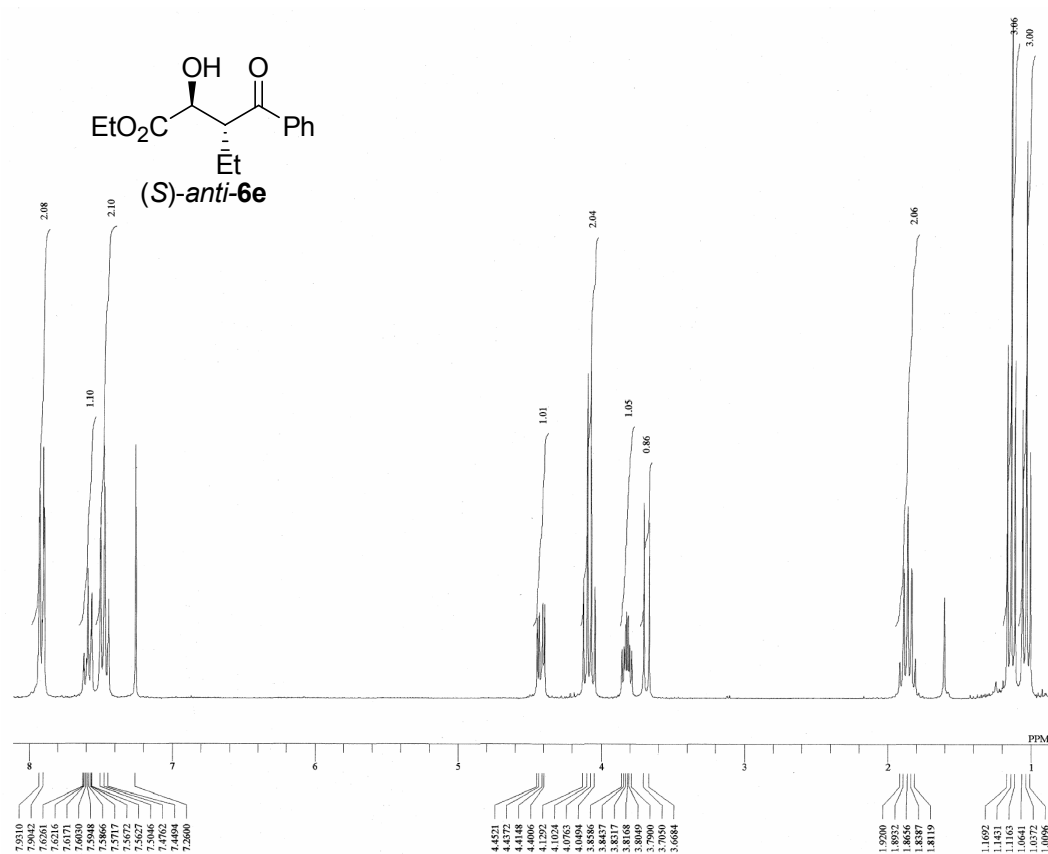


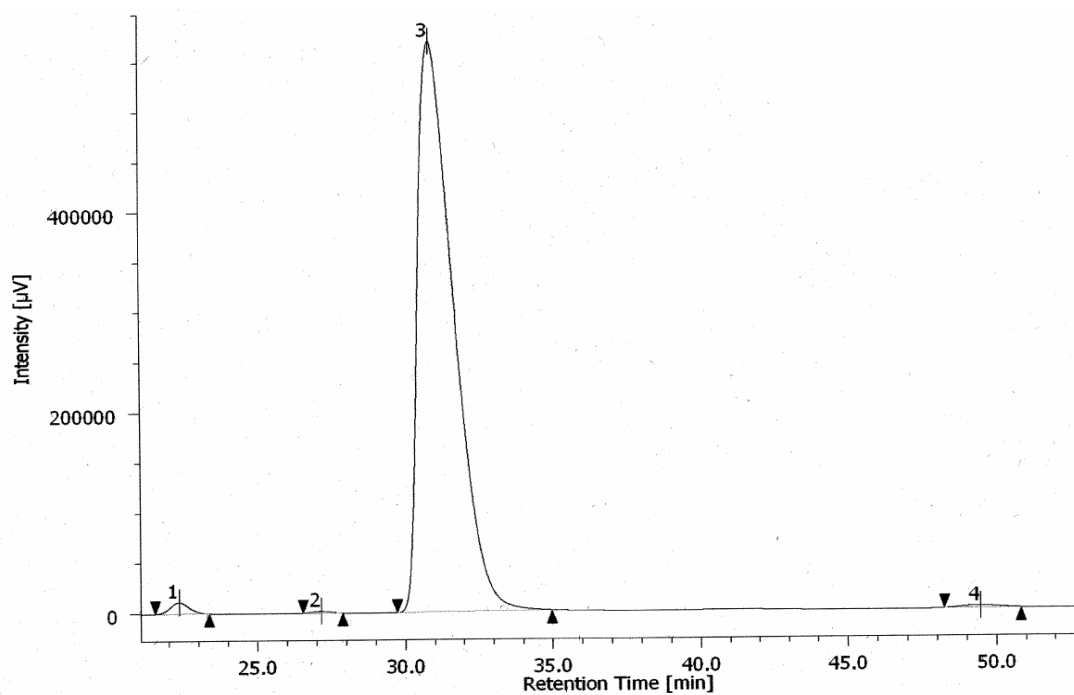
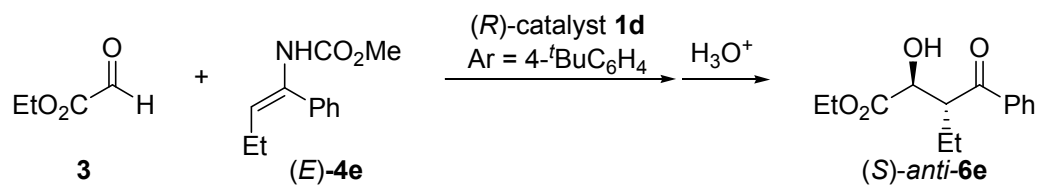
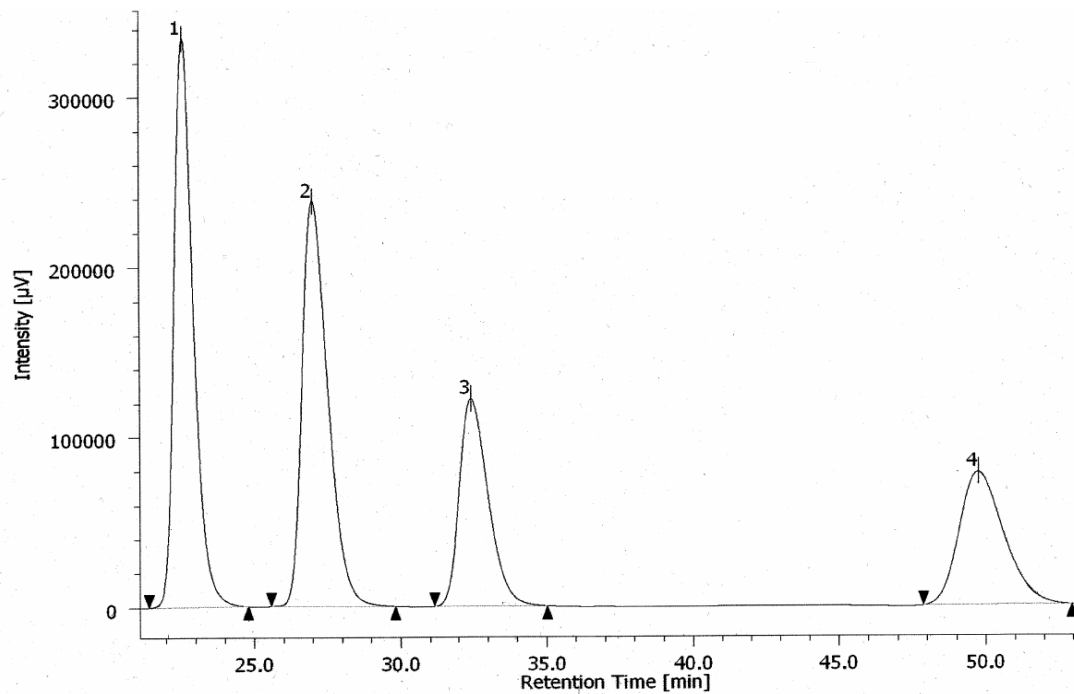
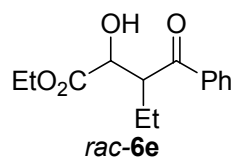


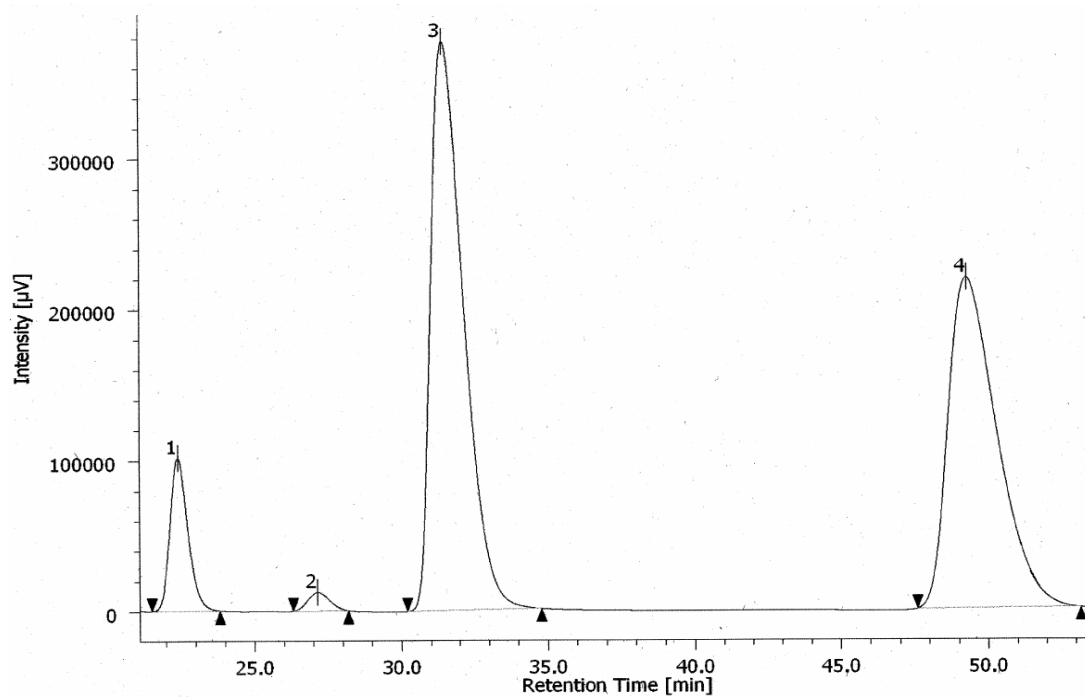
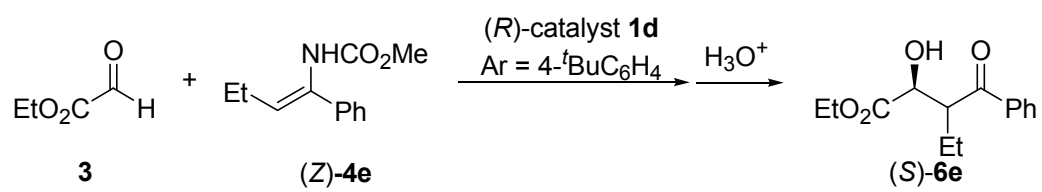


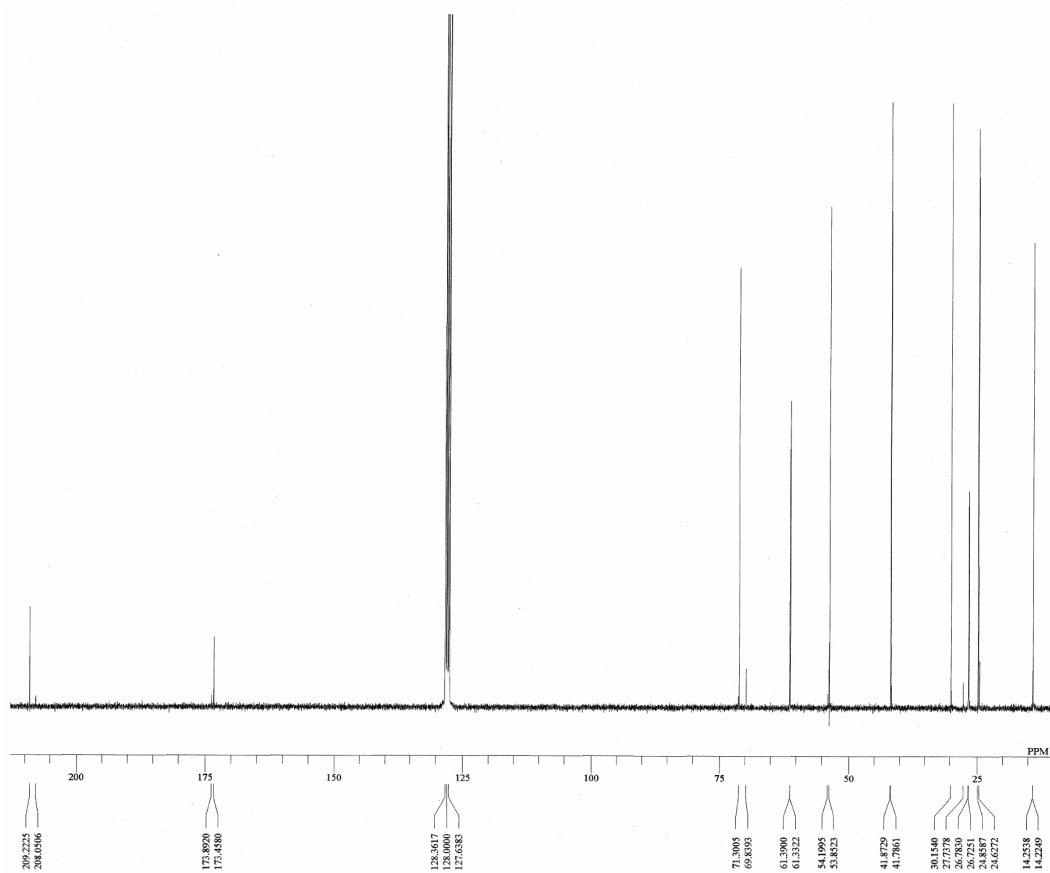
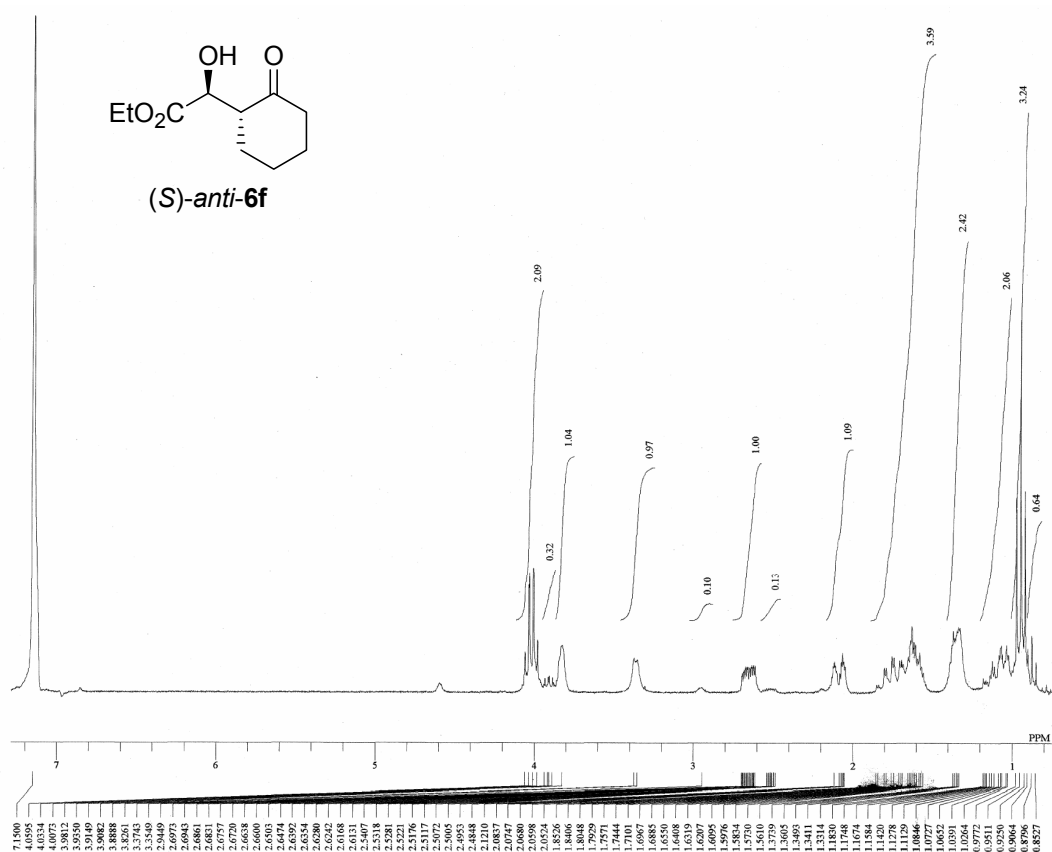


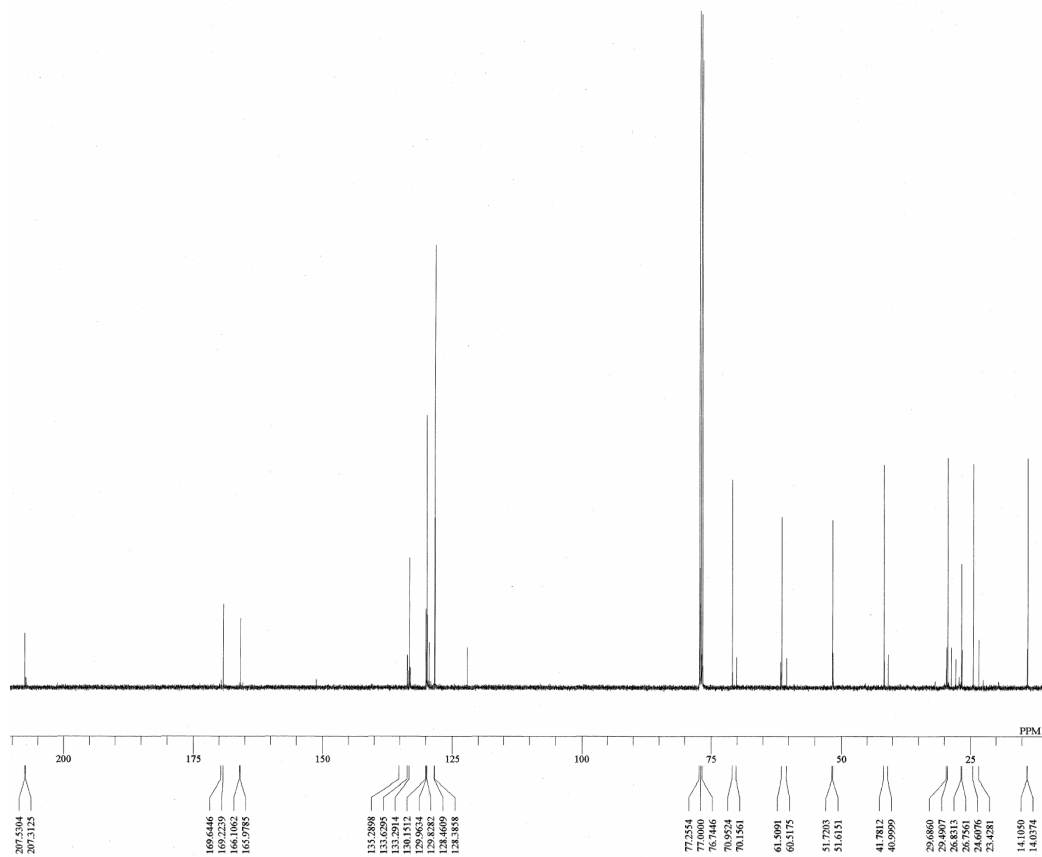
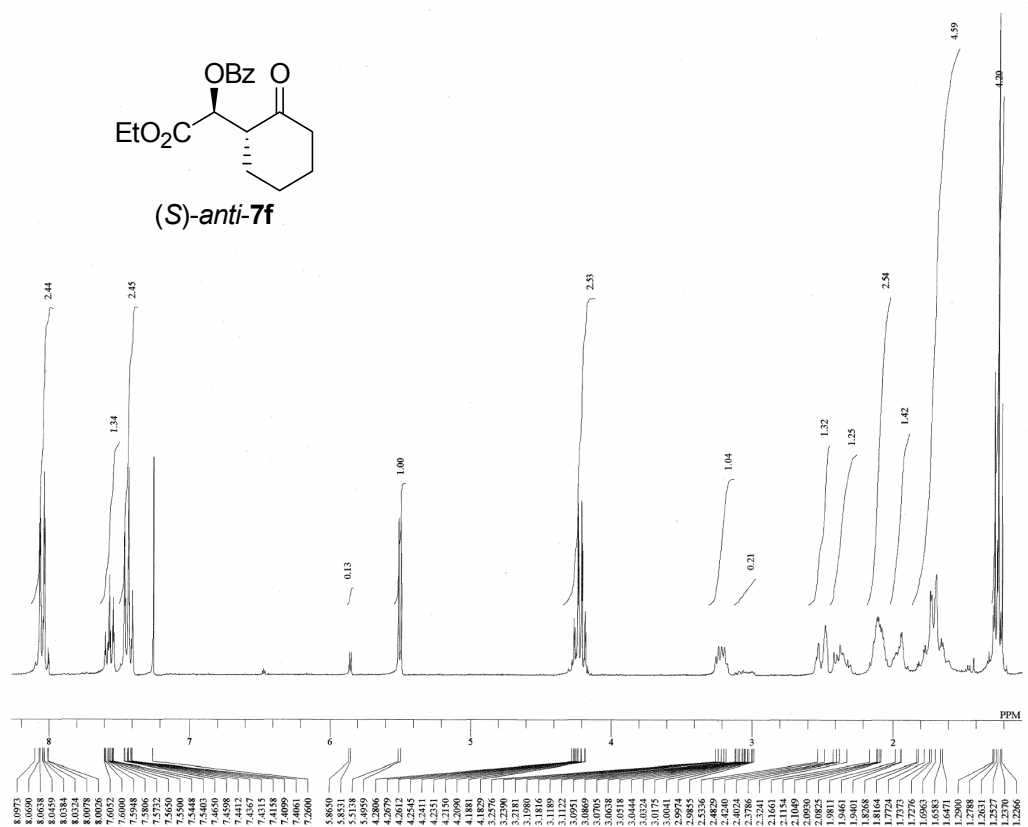
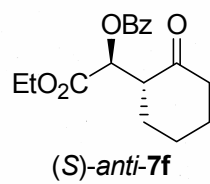


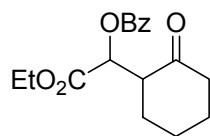












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