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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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Contents

1. General Information

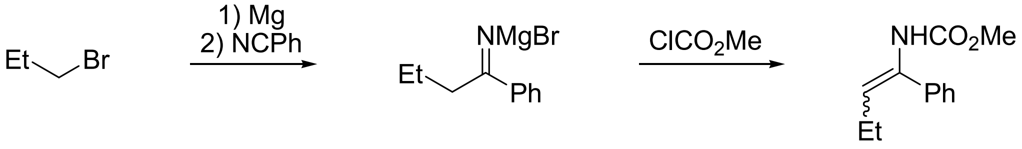
All reactions were carried out in dried glassware. CH_2Cl_2, diethyl ether and THF were purchased from Kanto Chemical Co., Inc. as "dehydrated solvent system". Acetone was purchased from Wako Inc. as dried solvent. MeOH and $Me_2C(OMe)_2$ was dried over activated MS4A. NEt_3 was dried over KOH. Analytical thin layer chromatography (TLC) was performed on Merck pre-coated TLC plates (silica gel 60 GF_{254}, 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; $[\alpha]_D^{T°C}$ (c = g/100 mL, solvent). ^{1}H- and ^{13}C-NMR spectra were measured with a JEOL GSX-270 (^{1}H-NMR: 270 MHz, ^{13}C-NMR: 67.8 MHz) or a BRUKER AVANCE-600 spectrometer (^{1}H-NMR: 600 MHz, ^{13}C-NMR: 150.9 MHz). Data are reported in δ (ppm) from the solvent signals as the internal standard (^{1}H-NMR: $CHCl_3$: 7.26 ppm, C_6D_5H: 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:



8 **4e**

To a mixture of Mg (36 mmol, 875 mg) and 1,2-dibromoethane (25 μL) 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 (×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.

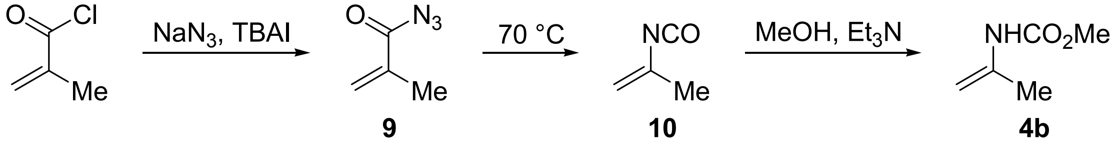
Enecarbamate 4a: **4a** (66% yield over 2 steps) was synthesized using methyllithium according to the above procedure.

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 N_2 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 NaN_3 (3.18 g, 48 mmol) and tetra-*n*-butylammomium iodide (TBAI) in H_2O (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 $NaHCO_3$ aq. (×2) and brine, dried over $MgSO_4$ 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 N_2 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 NEt_3 (142 μL, 1.02 mmol) and MeOH (988 μL, 24.4 mmol) at –60 ºC under N_2 gas. After being stirred at –60 ºC for 12 h, the reaction mixture was warmed to –15 ºC over 2 h, and then stirred at –15 ºC 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

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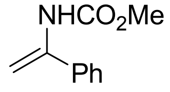
[1] R. Matsubara, Y. Nakamura, S. Kobayashi, *Angew. Chem. Int. Ed.* **2004**, *43*, 3258.

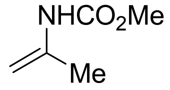
was synthesized using cyclohex-1-enecarbonyl chloride[2] according to the literature.[1] Using obtained 1-isocyanatocyclohex-1-ene, **4f** was synthesized according to the above procedure and purified with column chromatography.

Physical Data of the Enecarbamates



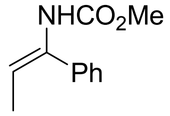
4a

Methyl 1-phenylvinylcarbamate: Yellow liquid; $R_f = 0.63$ (hexane / EtOAc = 1 / 1); ^{1}H 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 $C_{10}H_{11}NO_2$ ([M + Na]$^+$) 200.0688. Found 200.0682.



4b

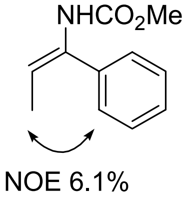
Methyl (*E*)-1-phenylprop-1-enylcarbamate: Colorless liquid; $R_f = 0.68$ (hexane / EtOAc = 1 / 1); ^{1}H NMR (C_6D_6, 270 MHz) δ 1.42 (3H, s), 3.34 (3H, s), 4.24 (1H, s), 5.42 (1H, s), 5.50 (1H, brs); ^{13}C NMR (C_6D_6, 67.8 MHz) δ 21.4, 51.5, 95.4, 137.4, 153.6.



(*E*)-**4c**

Methyl (*E*)-1-phenylprop-1-enylcarbamate: Slightly yellow liquid; $R_f = 0.54$ (hexane / EtOAc = 2 / 1); ^{1}H 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 $C_{11}H_{13}NO_2$ ([M + Na]$^+$) 214.0844. Found 214.0838.

Configuration Assignment:



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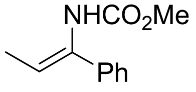
[2] L. Field, P. M. Giles, Jr., *J. Med. Chem.* **1970**, *13*, 317.



(*Z*)-**4c**

Methyl (*Z*)-1-phenylprop-1-enylcarbamate: White solid; R_f = 0.50 (hexane / EtOAc = 2 / 1); ^{1}H 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 $C_{11}H_{13}NO_2$ ([M + Na]$^+$) 214.0844. Found 214.0838.

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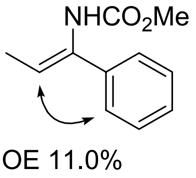
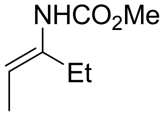
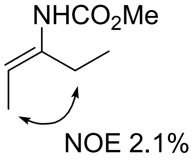


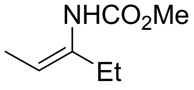


(*E*)-**4d**

Methyl (*E*)-pent-2-en-3-ylcarbamate: Slightly yellow liquid; R_f = 0.45 (hexane / EtOAc = 2 / 1); ^{1}H 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 $C_7H_{13}NO_2$ ([M + Na]$^+$) 166.0844. Found 166.0838.

Configuration Assignment:

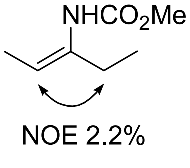


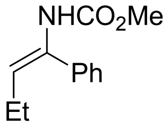


(*Z*)-**4d**

Methyl (*Z*)-pent-2-en-3-ylcarbamate: White solid; R_f = 0.45 (hexane / EtOAc = 2 / 1); ^{1}H 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:

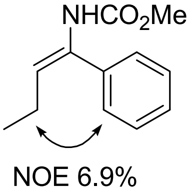


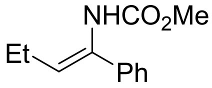


(*E*)-**4e**

Methyl (*E*)-1-phenylbut-1-enylcarbamate: Colorless liquid; R_f = 0.55 (hexane / EtOAc = 1 / 1); ^{1}H 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, brm), 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 $C_{12}H_{15}NO_2$ ([M + Na]$^+$) 228.1001. Found 228.0995.

Configuration Assignment:

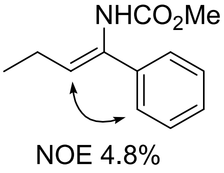


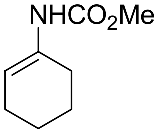


(*Z*)-**4e**

Methyl (*Z*)-1-phenylbut-1-enylcarbamate: White solid; R_f = 0.58 (hexane / EtOAc = 1 / 1); ^{1}H 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 $C_{12}H_{15}NO_2$ ([M + Na]$^+$) 228.1001. Found 228.0995.

Configuration Assignment:

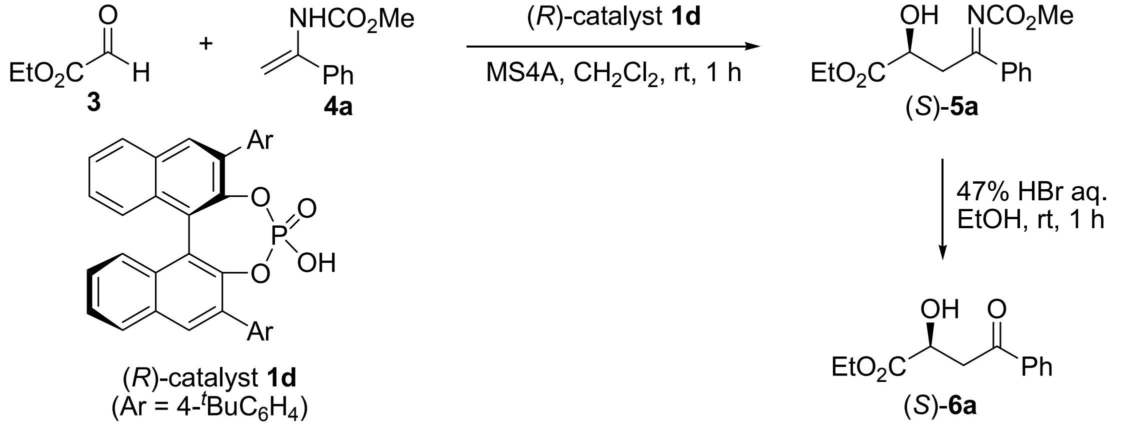




4f

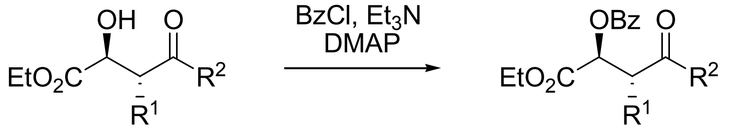
Methyl cyclohex-1-enylcarbamate: White solid; R_f = 0.53 (hexane / EtOAc = 1 / 1); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.52-1.58 (2H, m), 1.62-1.69 (2H, m), 2.03-2.09 (4H, m), 3.65 (3H, s), 5.79 (2H, brs); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 22.0, 22.5, 23.8, 27.8, 51.8, 110.3, 132.0, 154.2; IR (ATR): 3328, 2937, 2882, 2859, 2840, 1703 cm^{-1}; HRMS (ESI) Calcd for $C_8H_{13}NO_2$ ([M + 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 μmol) and activated MS4A (<5 micron powder, 85 mg) in CH_2Cl_2 (1 mL) was added freshly distilled ethyl glyoxylate (16.9 μL, 0.17 mmol) at room temperature under N_2 gas. After being stirred for 5 min, enecarbamate **4a** (18.5 μL, 0.1 mmol) was introduced, and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with saturated $NaHCO_3$ aq. at room temperature, and extracted with CH_2Cl_2 (×4). The organic layer was dried over Na_2SO_4, 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 μL) at room temperature. After being stirred at room temperature for 1 h, the reaction mixture was quenched with saturated $NaHCO_3$ aq. at 0 °C, and extracted with CH_2Cl_2 (×4). The organic layer was dried over Na_2SO_4, 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

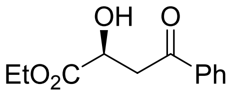


6d: (R^1, R^2) = (Me, Et) **7d**: (R^1, R^2) = (Me, Et)

6f: (R^1, R^2) = $-(CH_2)_4$ **7f**: (R^1, R^2) = $-(CH_2)_4$

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

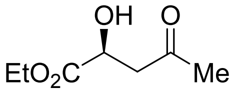
Physical Data of the Products



6a

(*S*)-Ethyl 2-hydroxy-4-oxo-4-phenylbutanoate: Slightly yellow liquid; R_f = 041 (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*); $[\alpha]^{25}_{D}$ = +6.5 (*c* 1.9, $CHCl_3$), $[\alpha]^{21}_{D}$ = -8.3 (*c* 1.9, EtOH); ^{1}H NMR ($CDCl_3$, 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 ($CDCl_3$, 67.8 MHz) δ 14.2, 42.2, 61.9, 67.2, 128.1, 128.6, 133.5, 136.2, 173.6, 197.3.

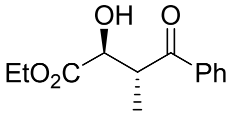
Configuration Assignment: The absolute configuration was determined by the comparison of HPLC retention time[1] and the optical rotation.[3]



6b

(*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*); $[\alpha]^{26}_{D}$ = -2.5 (*c* 2.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 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 ($CDCl_3$, 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.



6c

(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*); $[\alpha]^{25}_{D}$ = +17.4 (*c* 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 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 ($CDCl_3$, 67.8 MHz) ***anti*** δ 14.1, 14.3, 44.0, 61.6, 73.2, 128.3, 128.7,

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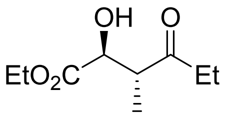
[3] P. Herold, A. F. Indolese, M. Studer, H. P. Jalett, U. Siegrist, H. U. Blaser, *Tetrahedron,* **2000**, *56*, 6497.

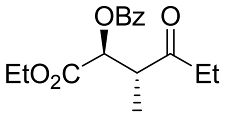
133.4, 135.8, 173.0, 203.1.

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



6d

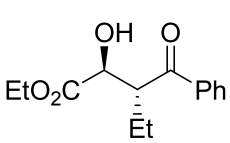
(2*S*,3*R*)-Ethyl 2-hydroxy-3-methyl-4-oxohexanoate: Colorless liquid; R_f = 0.39 (hexane / EtOAc = 1 / 1); $[\alpha]^{25}_D$ = +28.5 (*c* 1.3, $CHCl_3$); ^{1}H NMR (C_6D_6, 270 MHz) ***anti*** δ 0.87 (3H, td, *J* = 7.0, 0.6 Hz), 0.88 (3H, t, *J* = 7.2 Hz), 0.98 (3H, d, *J* = 7.2 Hz), 1.99 (2H, q, *J* = 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}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 $C_9H_{16}O_4$ ([M + Na]$^+$) 211.0946. Found 211.0941.



7d

(2*S*,3*R*)-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 (2*R*,3*S*), 59.8 min (2*S*,3*R*), **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}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}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 $C_{16}H_{20}O_5$ ([M + Na]$^+$) 315.1208. Found 315.1203.

Configuration Assignment: The absolute configuration was determined by analogy.

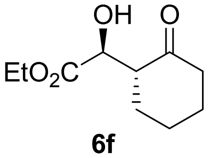


6e

(2*S*,3*R*)-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 (2*S*,3*S*), 27.1 min (2*R*,3*R*), 30.9 min (2*S*,3*R*), 49.5 min (2*R*,3*S*); $[\alpha]^{27}_D$ = +50.9 (*c* 3.8, $CHCl_3$); ^{1}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.

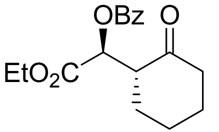
Configuration Assignment: The absolute and relative configurations were determined by analogy.



6f

(2*S*,1'*R*)-Ethyl 2-hydroxy-2-(2-oxocyclohexyl)acetate: Colorless liquid; R_f = 0.31 (hexane / EtOAc = 1 / 1); $[\alpha]^{25}_D$ = +36.8 (*c* 1.8, $CHCl_3$); ^{1}H 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 ^{1}H & ^{13}C NMR Spectra.[4]



7f

(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*); $[\alpha]^{27}_D$ = +28.7 (*c* 1.0, $CHCl_3$); ^{1}H 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.

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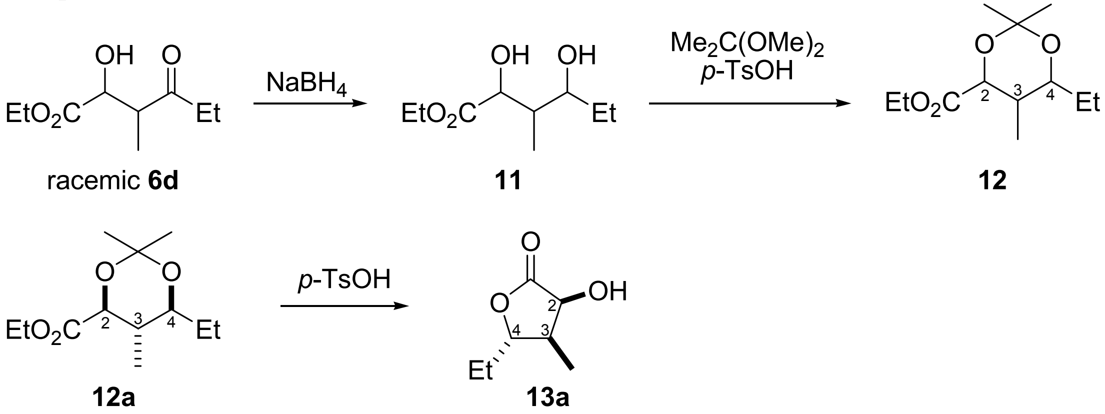
[4] a) S. Tsuboi, E. Nishiyama, M. Utaka, A. Takeda, *Tetrahedron Lett.* **1986**, *27*, 1915. Also see: b) S. Tsuboi, E. Nishiyama, H. Fukutani, M. Utaka, A. Takeda, *J. Org. Chem.* **1987**, *52*, 1359.

5. Determination of Relative Configuration of 6d

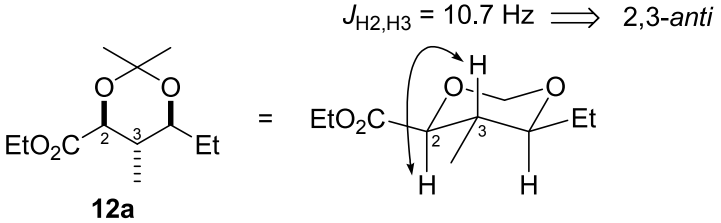
5.1. Preparation of Authentic 13a



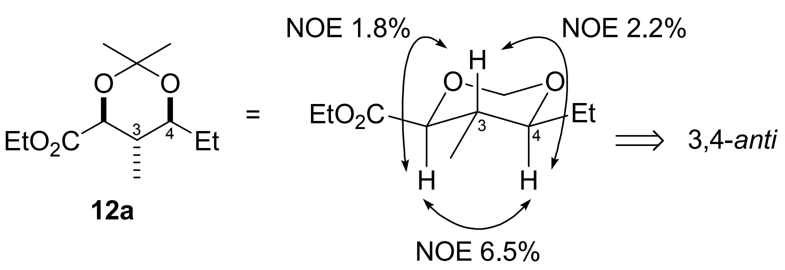
To the solution of racemic **6d** (955 mg, 5.07 mmol, 1:1 diastereomeric mixture)[5] in MeOH / CH_2Cl_2 = 1 / 2 (100 mL) was added $NaBH_4$ (426 mg, 10.1 mmol) at 0 °C. After being stirred at 0 °C for 15 min, the reaction mixture was quenched with saturated NH_4Cl aq. at 0 °C, and extracted with CH_2Cl_2 (×4). The organic layer was dried over Na_2SO_4, 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 $Me_2C(OMe)_2$ (7.48 mL, 60.8 mmol) and *p*-toluenesulfonic acid monohydrate (14.6 mg, 0.076 mmol) at 0 °C under N_2 gas. After being stirred at 0 °C for 15 min. the reaction mixture was quenched with saturated $NaHCO_3$ aq. at 0 °C, and extracted with CH_2Cl_2 (×4). The organic layer was dried over Na_2SO_4, 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



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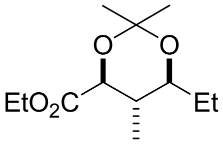
[5] S. Shirakawa, K. Maruoka, *Tetrahedron Lett.* **2003**, *44*, 281.

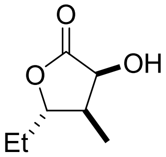
To a solution of **12a** (21.3 mg, 0.0925 mmol) in CH_2Cl_2 (3 mL) was added *p*-toluenesulfonic acid monohydrate (3.52 mg, 18.5 μmol) at room temperature. After being stirred at room temperature for 1 h, the reaction mixture was quenched with saturated $NaHCO_3$ aq. at room temperature, and extracted with CH_2Cl_2 (×4). The organic layer was dried over Na_2SO_4, 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

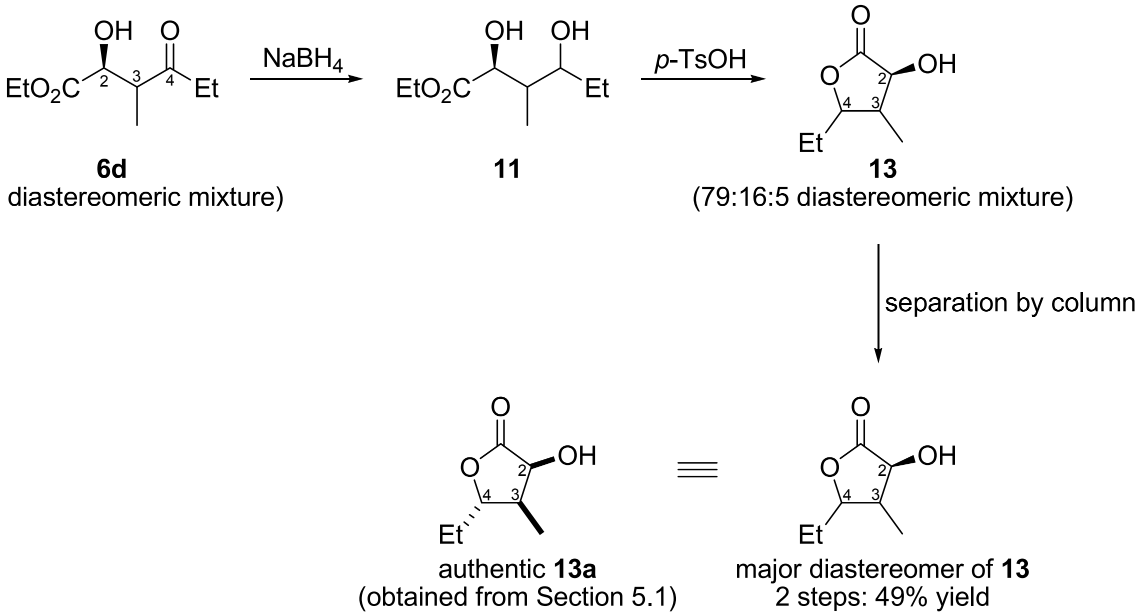
(4*S**, 5*S**, 6*S**)-4-Ethoxycarbonyl-6-ethyl-2,2,5-trimethyl-1,3-dioxane: Colorless liquid; R_f = 0.36 (hexane / EtOAc = 4 / 1); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.81 (3H, d, *J* = 6.6 Hz), 0.92 (3H, t, *J* = 7.4 Hz), 1.29 (3H, t, *J* = 7.1 Hz), 1.41-1.46 (1H, m), 1.44 (6H, s), 1.62-1.76 (1H, m), 1.69 (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); ^{13}C NMR ($CDCl_3$, 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 $C_{12}H_{22}O_4$ ($[M + Na]^+$) 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); ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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 $C_7H_{12}O_3$ ($[M + Na]^+$) 167.0684. Found 167.0679.

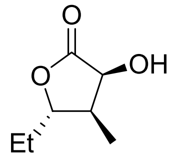
5.2. Transformation of Diastereomerically Enriched 6d (93:7 Diastereomeric Mixture) to Stereochemically Determined 13a



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 (×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



chiral **13a**

$[\alpha]^{27}_{D}$ = -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.

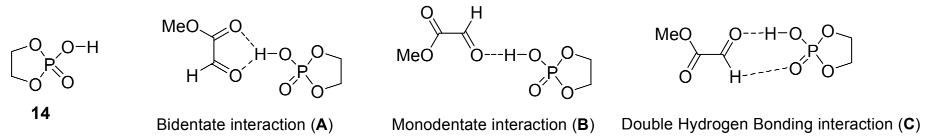
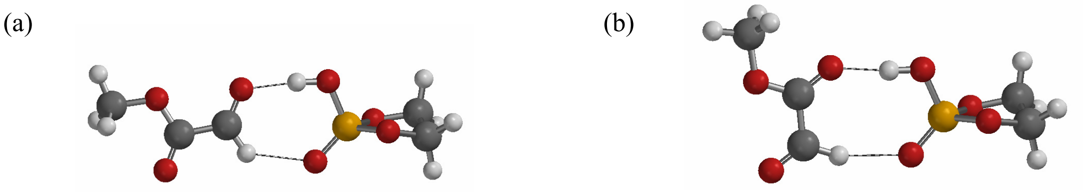


Figure I. Plausible modes of hydrogen bonding interaction between phosphoric acid (**14**) and glyoxylate (**3'**).



C (-1063.9456012 au)

D (-1063.9461961 au)

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

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[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.

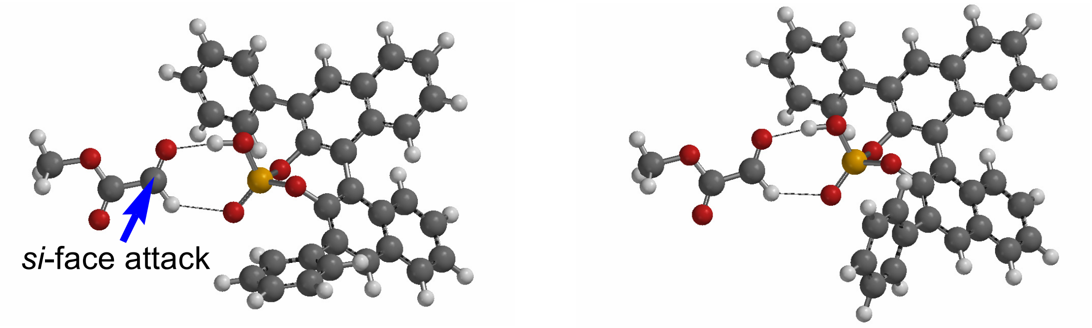
[8] A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648.

[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':

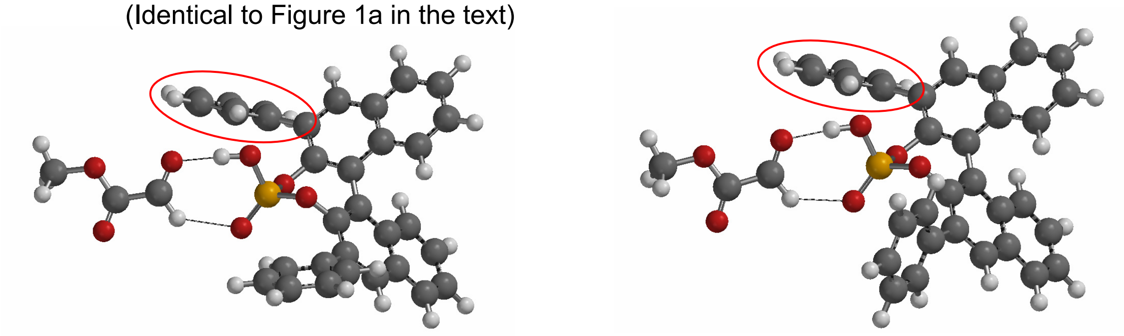
Inspection of Figure III and Table I reveals that associate **E** was optimized as the lowest energy conformer and **F**-**H** were obtained as local minima of (*R*)-**1a**/**3'**. In the conformer **E**, the nucleophiles (enecarbamate) are fully accessible to one enantiotopic face (*si*-face) of aldehyde (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.



E (0.00 kcal/mol)

F (0.5 kcal/mol)

(Identical to Figure 1a in the text)



G (1.37 kcal/mol)

H (1.47 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.

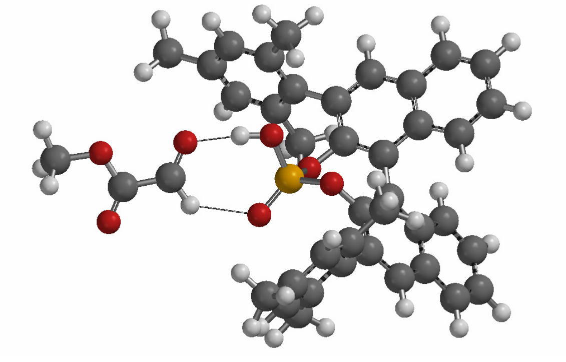
Table I: Computational data for the double hydrogen bonding pairs of (*R*)-**1a**/**3'**.

Conformer	Absolute energy [au]	Relative energy [kcal/mol]	*si*-face[a] [(*S*)-product]	*re*-face[a] [(*R*)-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.

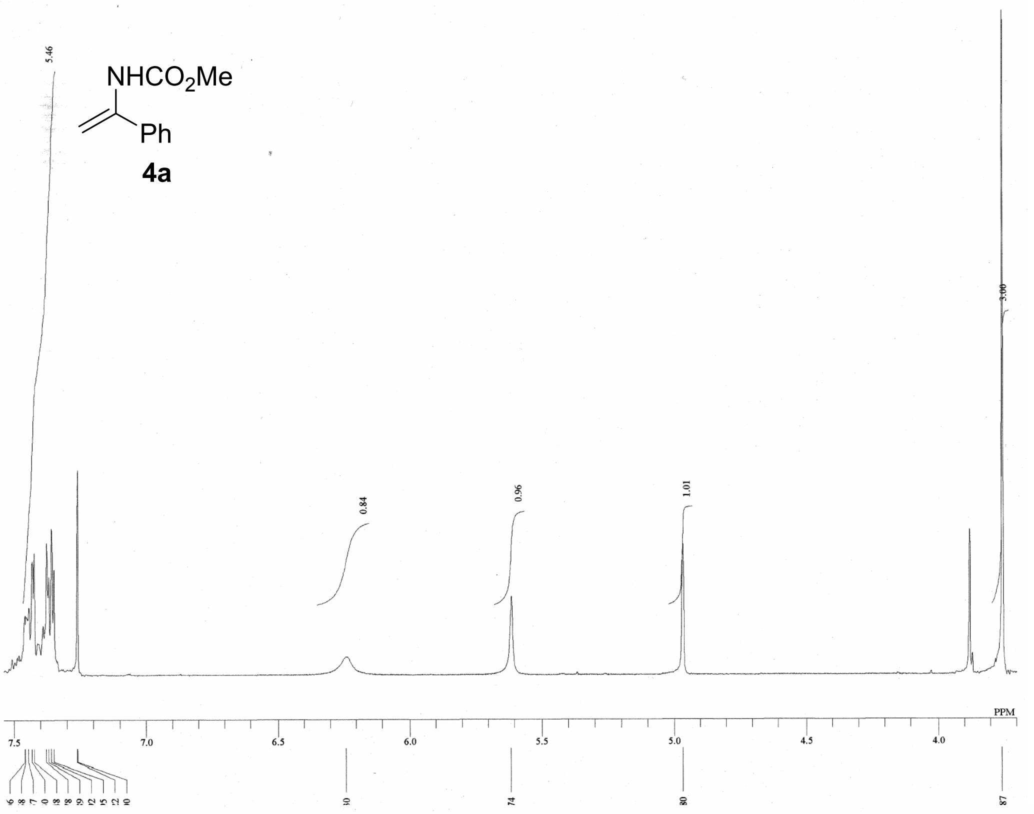


I (-2452.7711522 au)
(Identical to Figure 1b in the text)

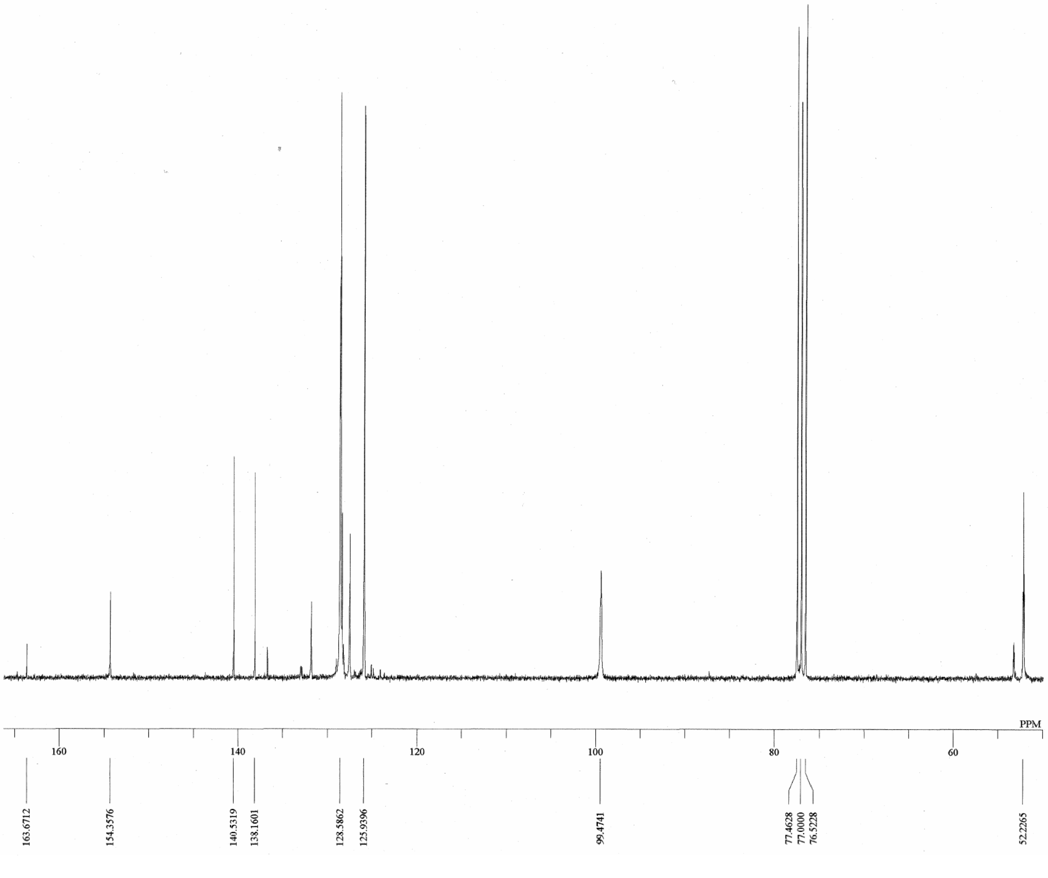
Figure IV. 3D-structure for the optimized geometry (at the B3LYP/6-31G** level of theory) of the D-H bonding pairs of (*R*)-**1h** (Ar = mesityl) with **3'**. P Tan, O Red, C Gray, H White. Absolute energy in hartrees is in parenthesis.

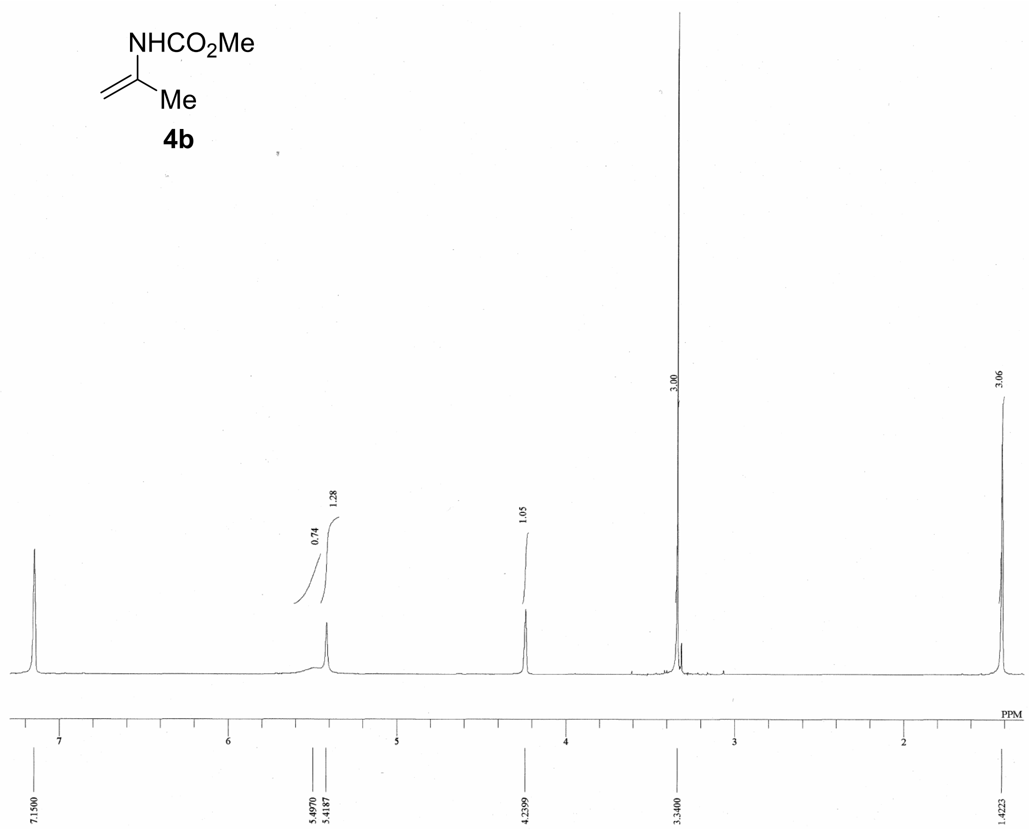
7. ^{1}H & ^{13}C NMR Spectra and HPLC Charts

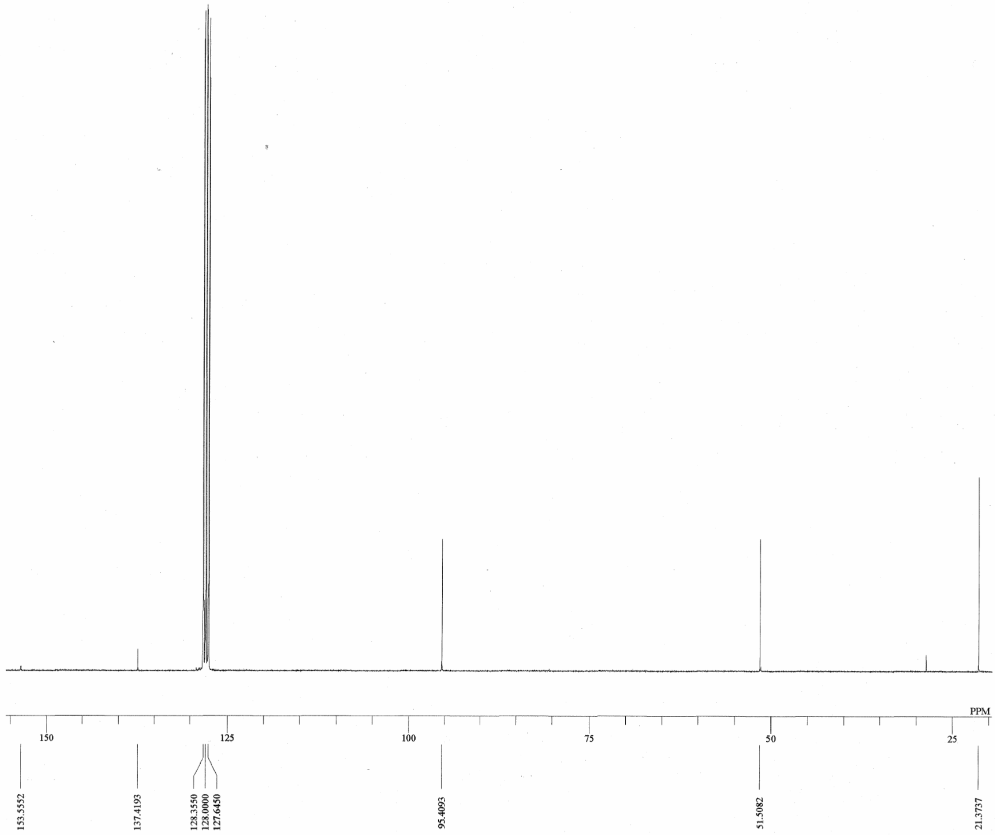
^{1}H & ^{13}C NMR of Enecarbamates

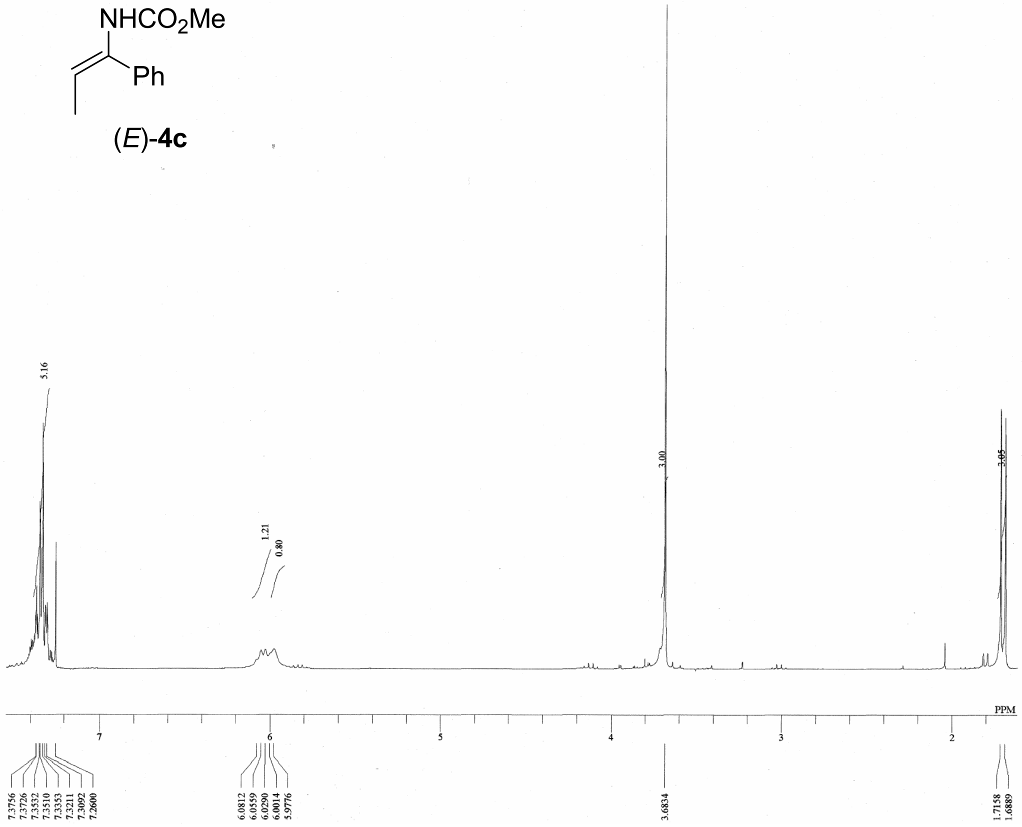


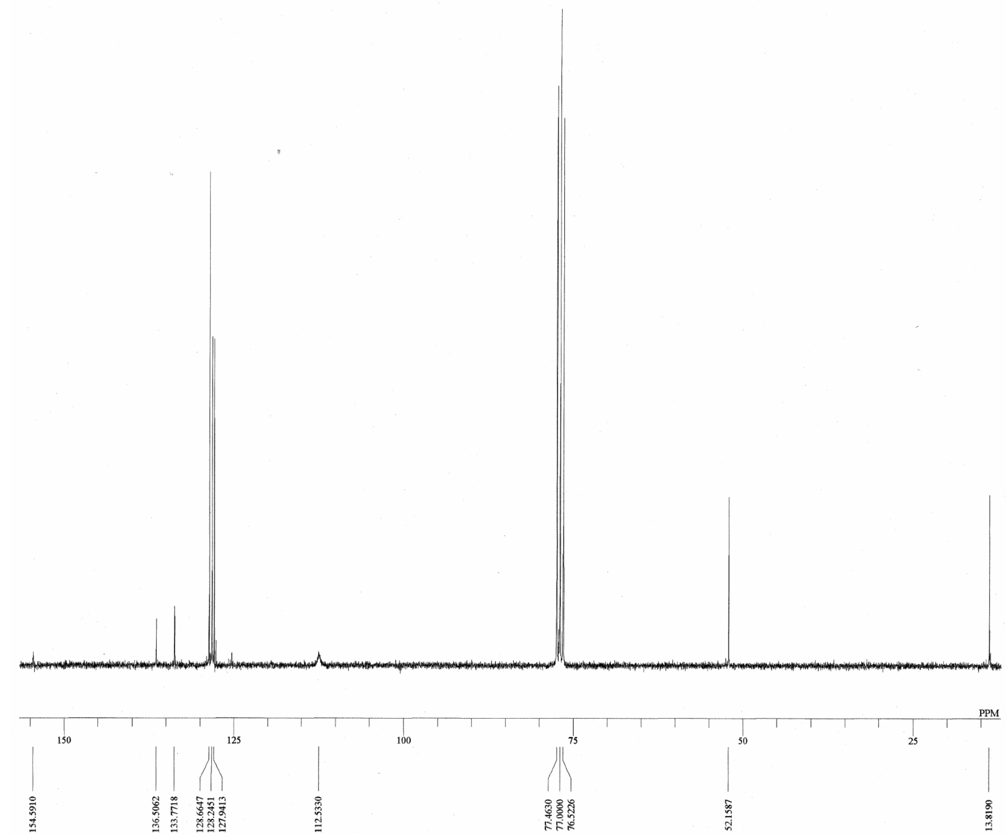
4a

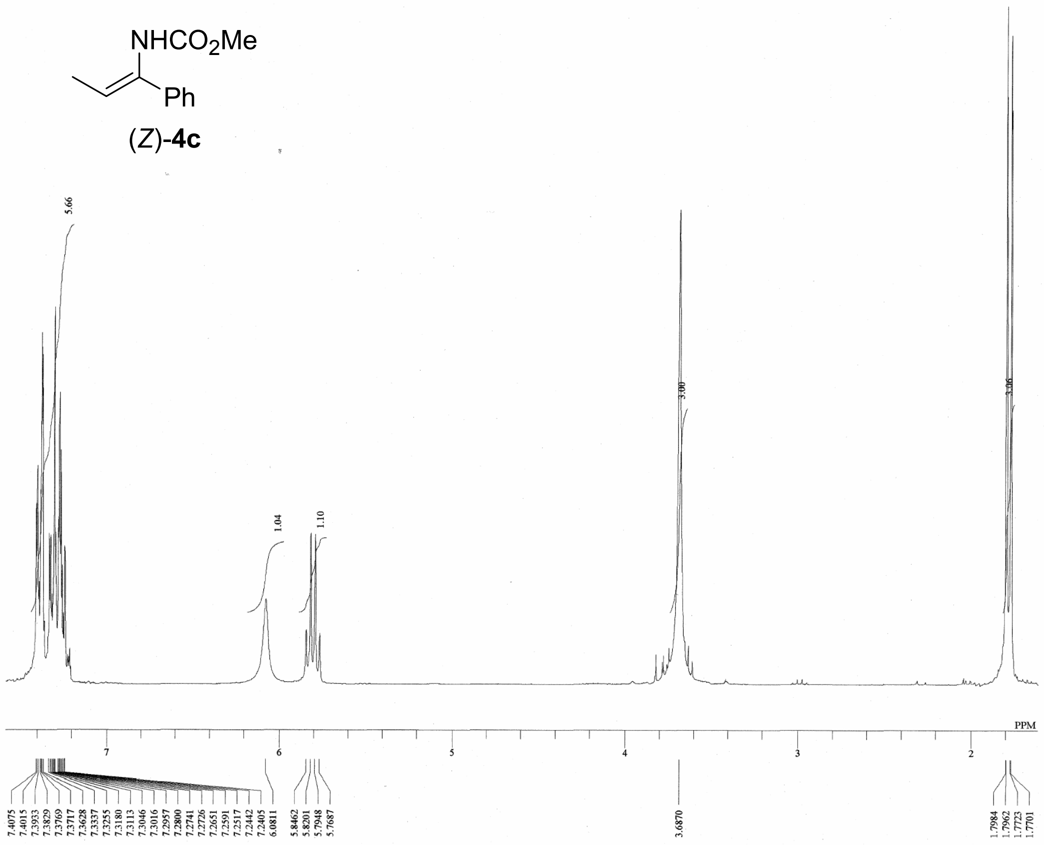



NHCO$_2$Me
Me
4b
0.74
1.28
1.05
3.00
3.06
PPM
7
6
5
4
3
2
7.1500
5.4970
5.4187
4.2399
3.3400
1.4223


PPM
150
125
100
75
50
25
153.5552
137.4193
128.3550
128.0000
127.6450
95.4093
51.5082
21.3737


(*E*)-**4c**
NHCO2Me
Ph
5.16
1.21
0.80
3.00
3.05
PPM
7
6
5
4
3
2
7.3756
7.3726
7.3532
7.3510
7.3353
7.3211
7.3092
7.2600
6.0812
6.0559
6.0290
6.0014
5.9776
3.6834
1.7158
1.6889


PPM
150
125
100
75
50
25
154.5910
136.5062
133.7718
128.6647
128.2451
127.9413
112.5330
77.4630
77.0000
76.5226
52.1587
13.8190


(*Z*)-**4c**

NHCO2Me
Ph
5.66
1.04
1.10
3.00
3.06
PPM
7
6
5
4
3
2
7.4075
7.4015
7.3933
7.3829
7.3769
7.3717
7.3628
7.3337
7.3255
7.3180
7.3113
7.3046
7.3016
7.2957
7.2800
7.2741
7.2726
7.2651
7.2591
7.2517
7.2442
7.2405
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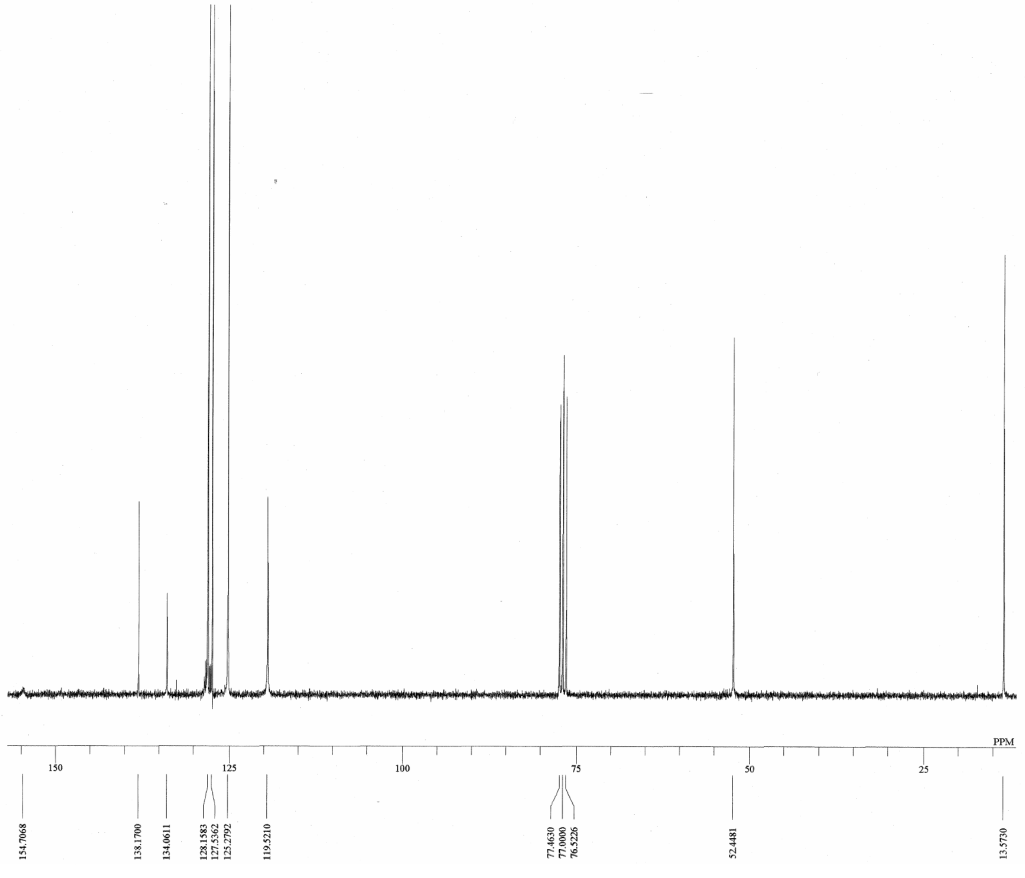
1.7962
1.7723
1.7701



PPM
150
125
100
75
50
25
154.7068
138.1700
134.0611
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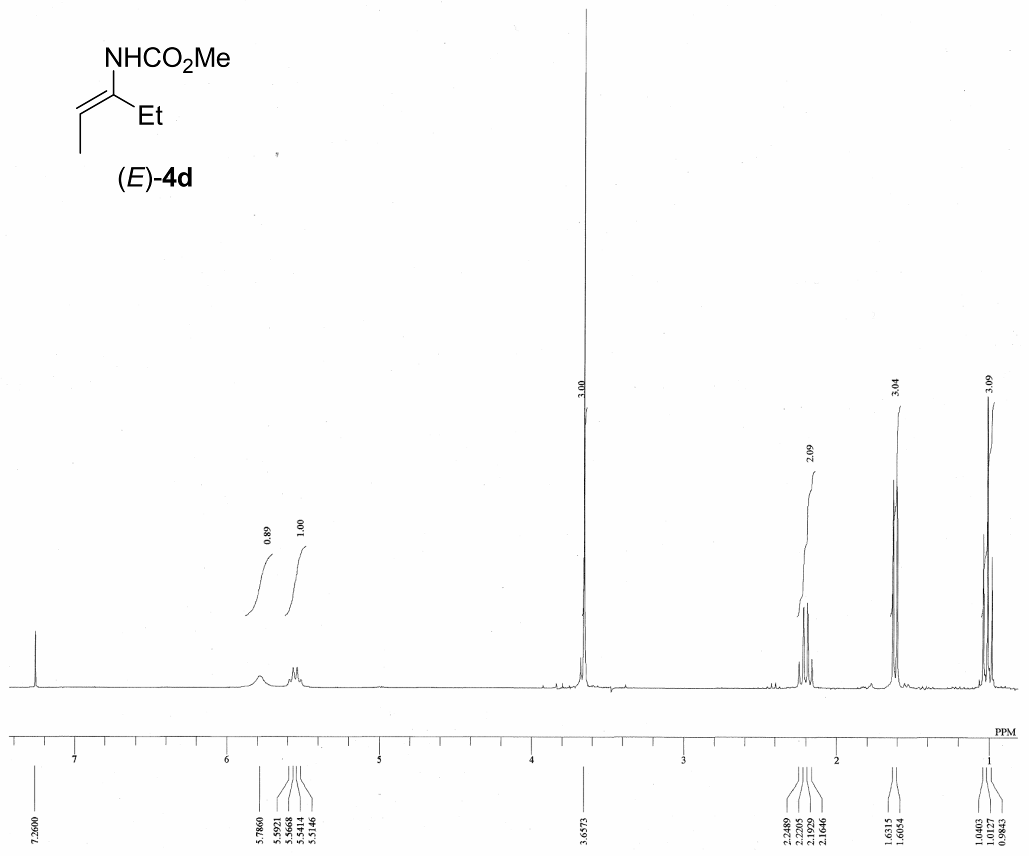
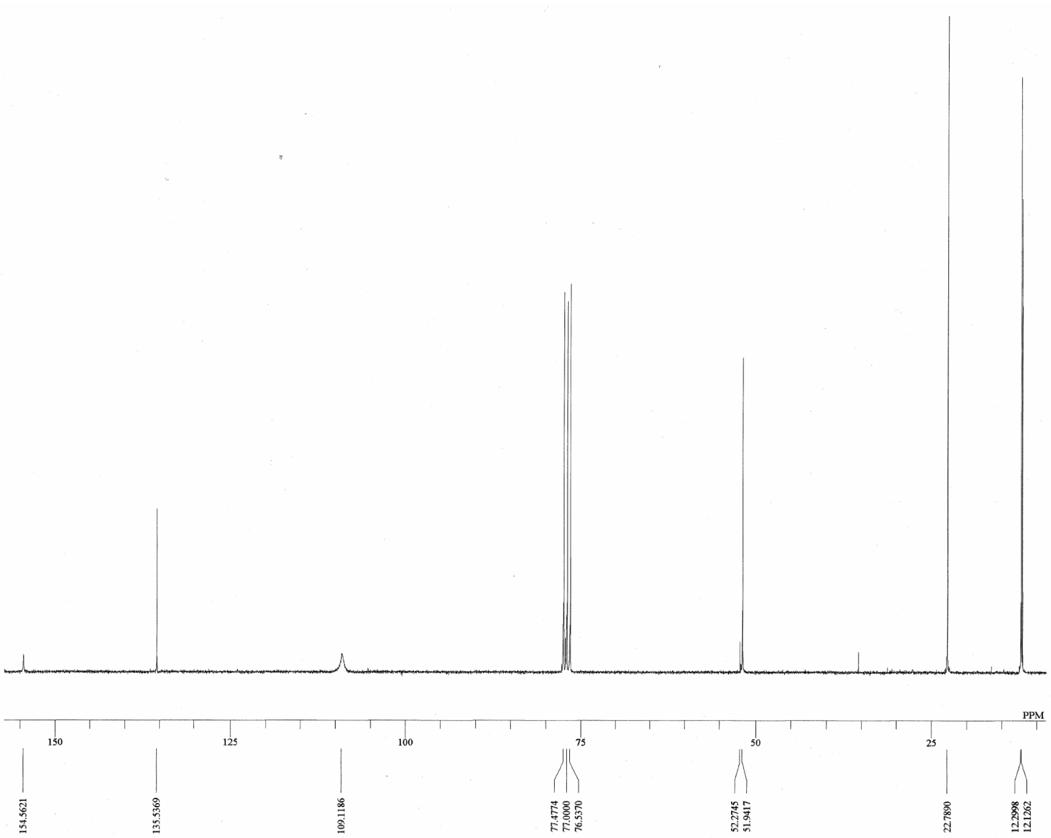
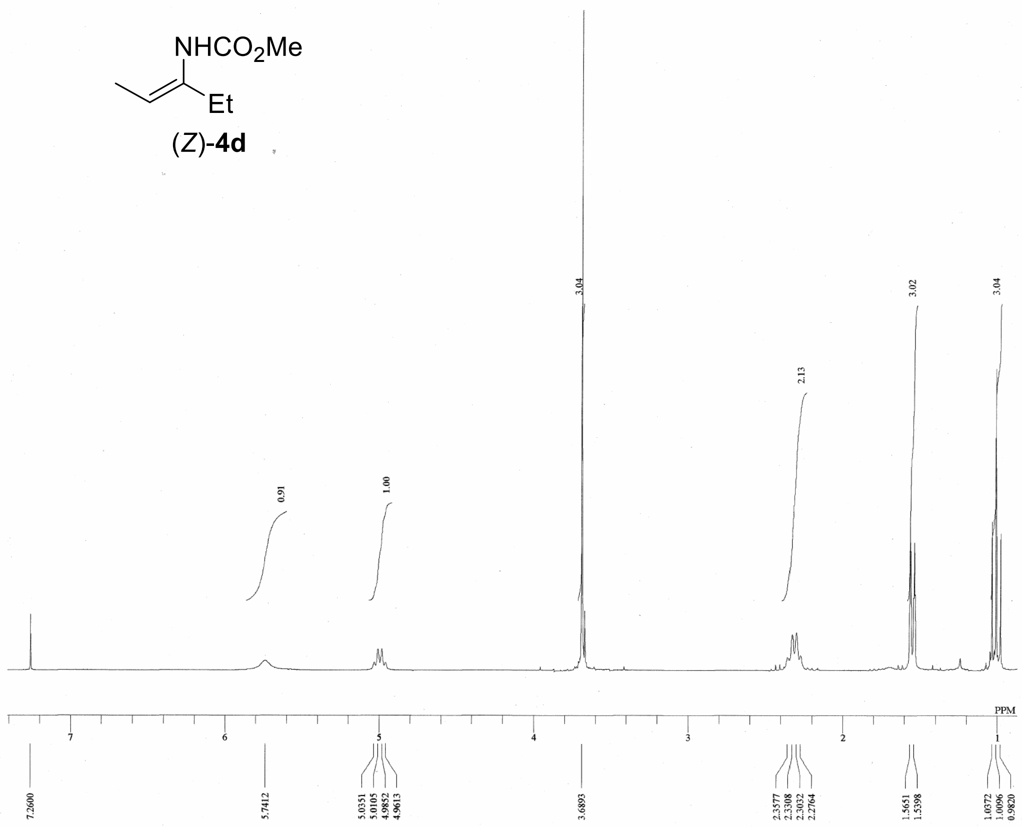
127.5362
125.2792
119.5210
77.4630
77.0000
76.5226
52.4481
13.5730

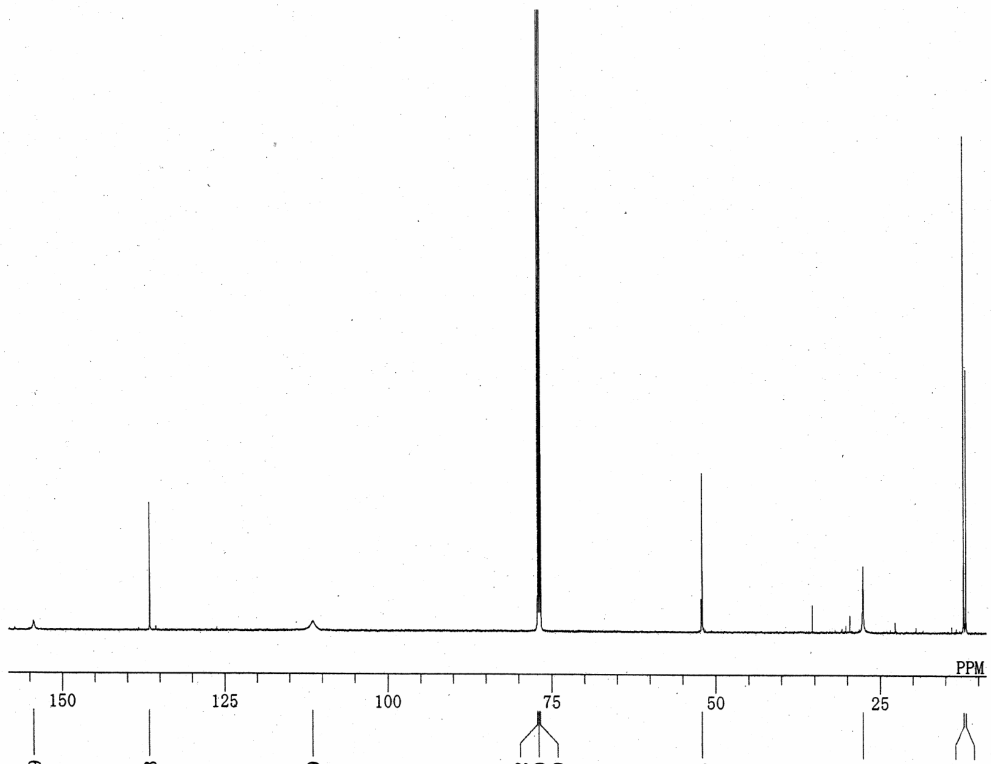

(*E*)-**4d**

NHCO2Me
Et
0.89
1.00
3.00
2.09
3.04
3.09
PPM
7
6
5
4
3
2
1
7.2600
5.7860
5.5921
5.5668
5.5414
5.5146
3.6573
2.2489
2.2205
2.1929
2.1646
1.6315
1.6054
1.0403
1.0127
0.9843



PPM
150
125
100
75
50
25
154.5621
135.5369
109.1186
77.4774
77.0000
76.5370
52.2745
51.9417
22.7890
12.2998
12.1262


NHCO2Me
Et
(Z)-4d
0.91
1.00
3.04
2.13
3.02
3.04
PPM
7
6
5
4
3
2
1
7.2600
5.7412
5.0351
5.0105
4.9852
4.9613
3.6893
2.3577
2.3308
2.3032
2.2764
1.5651
1.5398
1.0372
1.0096
0.9820


PPM
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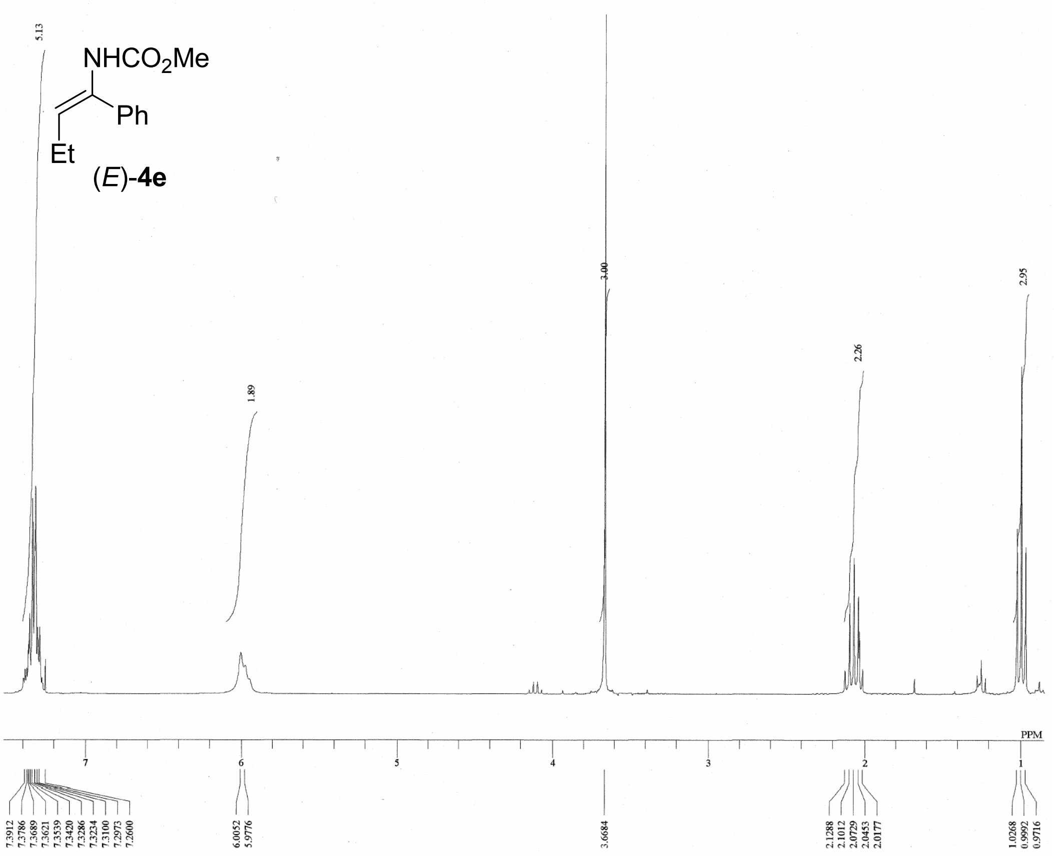
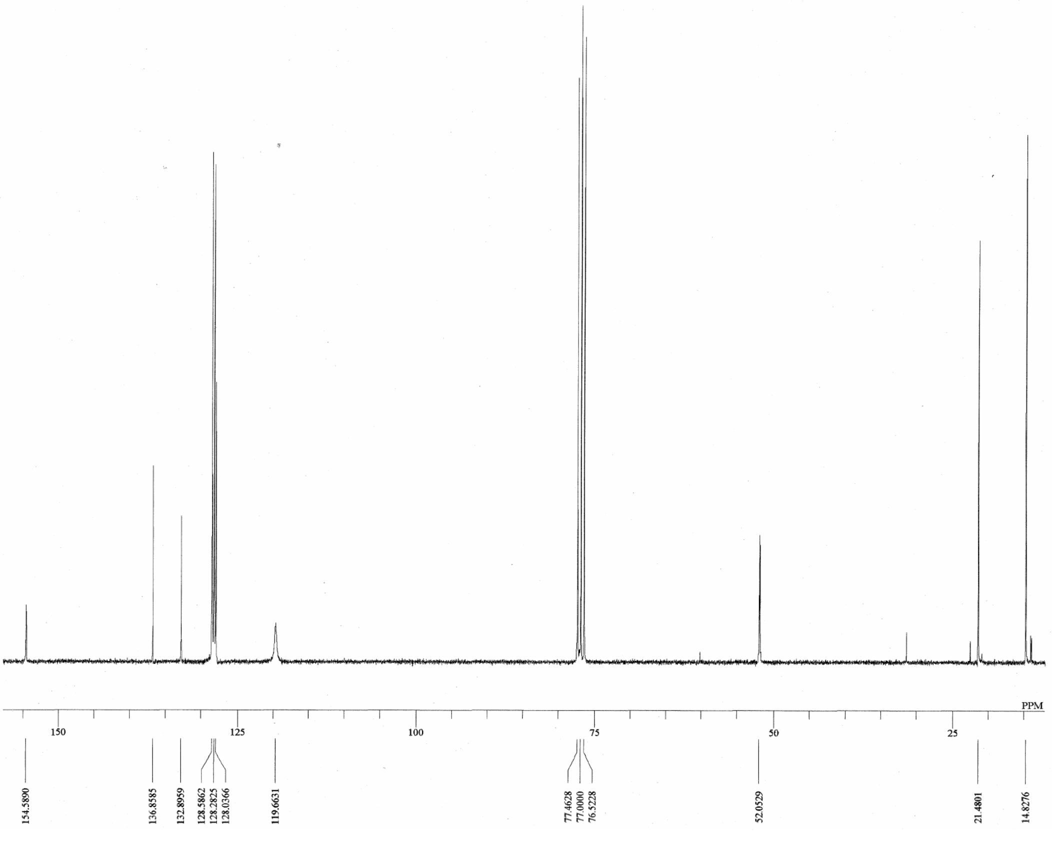
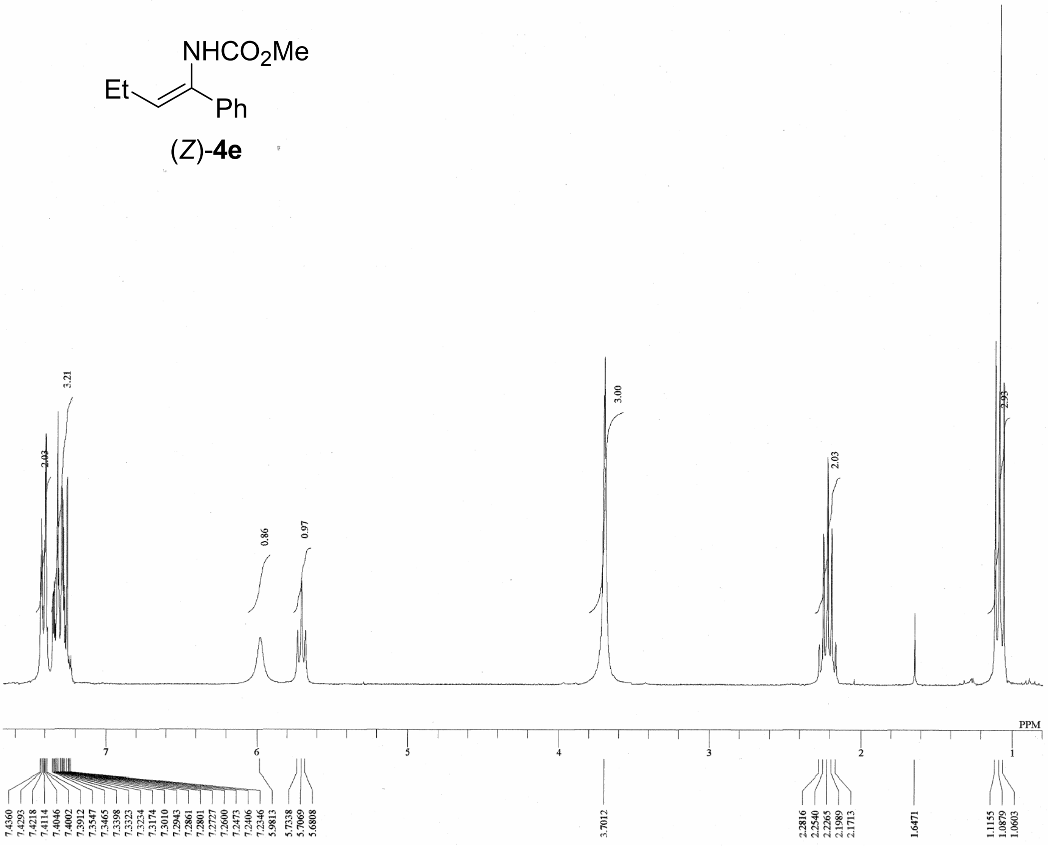
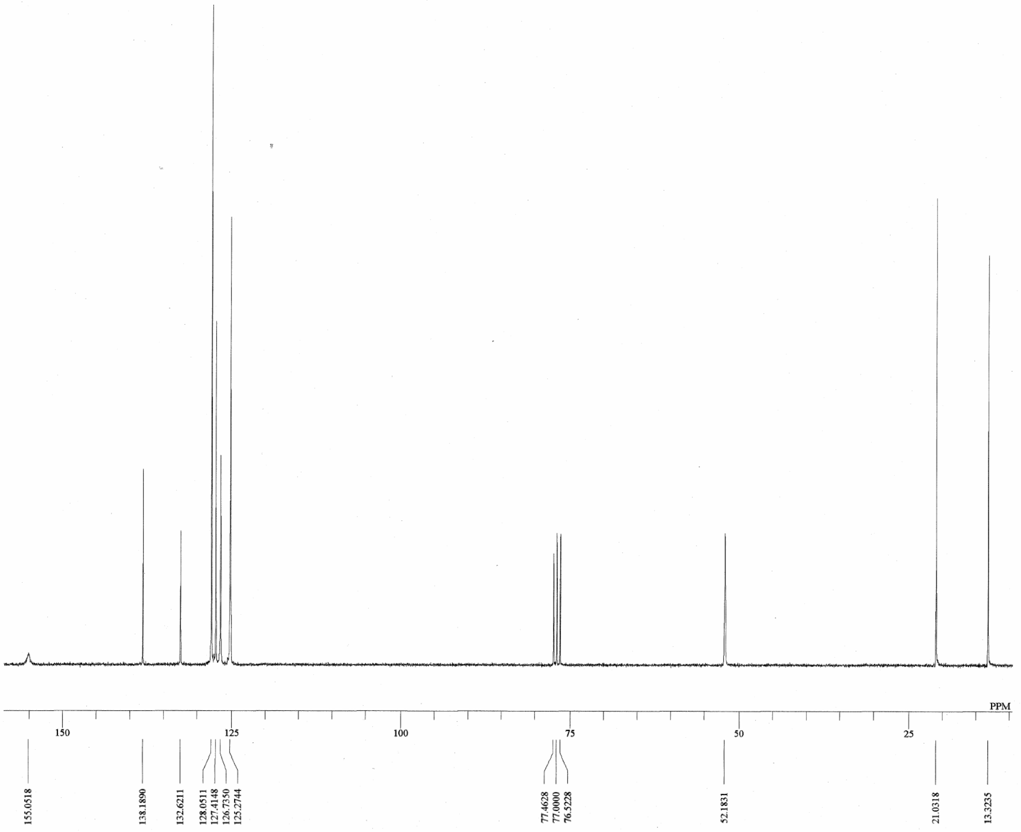
125
100
75
50
25
154.39
136.63
111.59
77.22
77.00
76.79
52.15
27.66
12.28
11.93


NHCO2Me
Ph
Et
(E)-4e
5.13
1.89
3.00
2.26
2.95
PPM
7
6
5
4
3
2
1
7.3912
7.3786
7.3689
7.3621
7.3539
7.3420
7.3286
7.3234
7.3100
7.2973
7.2600
6.0052
5.9776
3.6684
2.1288
2.1012
2.0729
2.0453
2.0177
1.0268
0.9992
0.9716


PPM
150
125
100
75
50
25
154.5890
136.8585
132.8959
128.5862
128.2825
128.0366
119.6631
77.4628
77.0000
76.5228
52.0529
21.4801
14.8276


NHCO$_2$Me
Et
Ph
2.03
3.21
0.86
0.97
3.00
2.03
2.93
PPM
7
6
5
4
3
2
1
7.4360
7.4293
7.4218
7.4114
7.4046
7.4002
7.3912
7.3547
7.3465
7.3398
7.3323
7.3234
7.3174
7.3010
7.2943
7.2861
7.2801
7.2727
7.2600
7.2473
7.2406
7.2346
5.9813
5.7338
5.7069
5.6808
3.7012
2.2816
2.2540
2.2265
2.1989
2.1713
1.6471
1.1155
1.0879
1.0603

(*Z*)-**4e**


PPM
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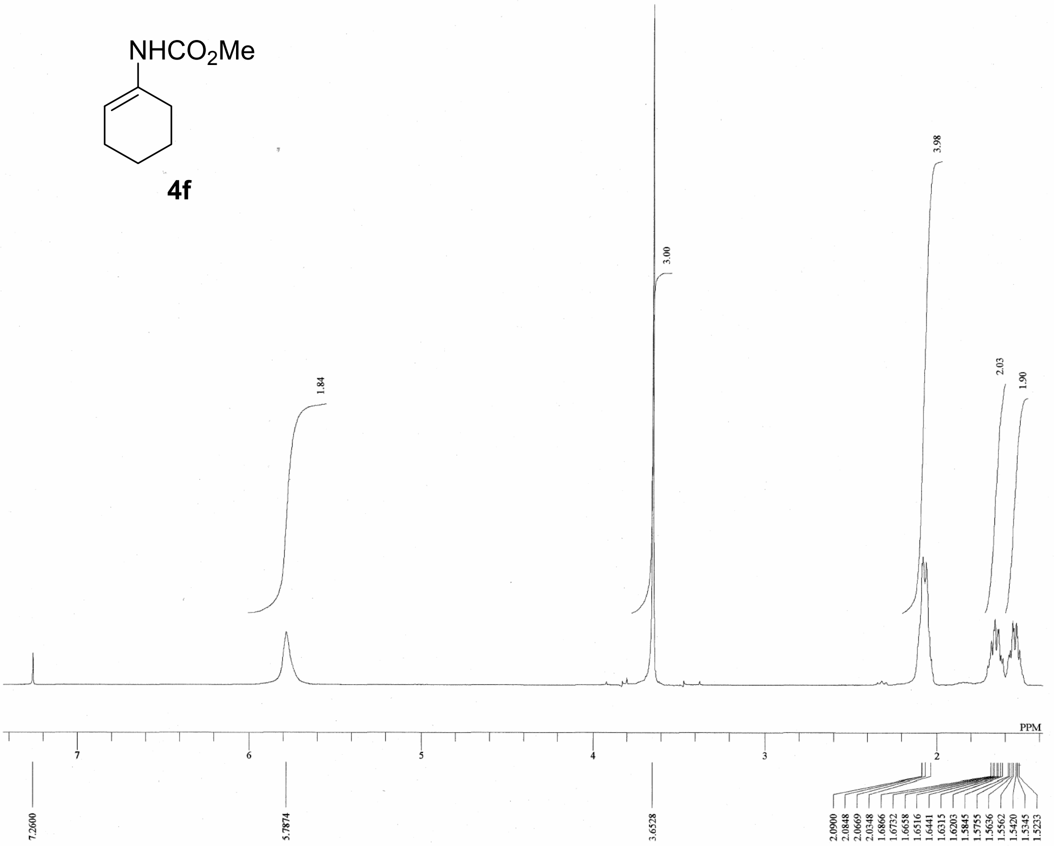
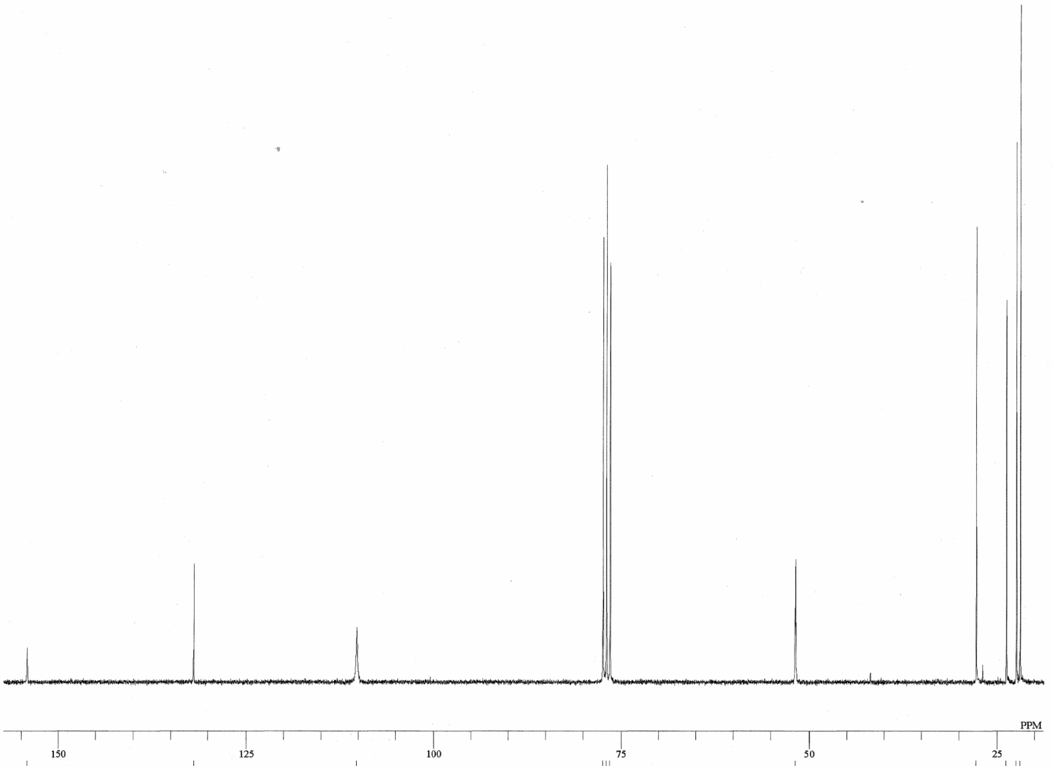
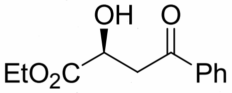
125
100
75
50
25
155.0518
138.1890
132.6211
128.0511
127.4148
126.7350
125.2744
77.4628
77.0000
76.5228
52.1831
21.0318
13.3235

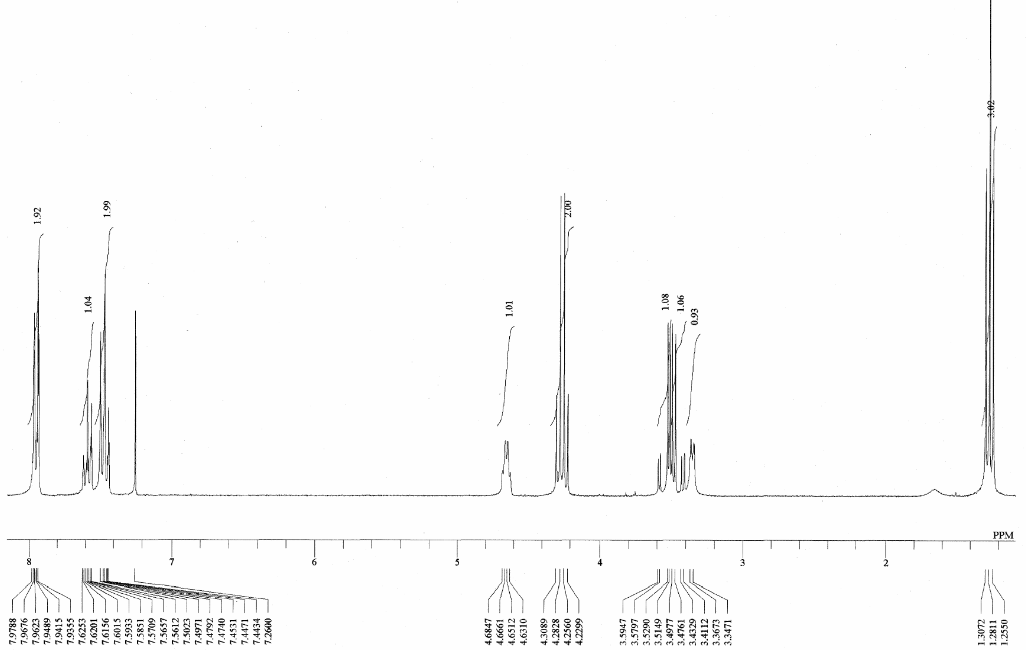

NHCO2Me
4f
1.84
3.00
3.98
2.03
1.90
PPM
7
6
5
4
3
2
7.2600
5.7874
3.6528
2.0900
2.0848
2.0669
2.0348
1.6866
1.6732
1.6658
1.6516
1.6441
1.6315
1.6203
1.5845
1.5755
1.5636
1.5562
1.5420
1.5345
1.5233

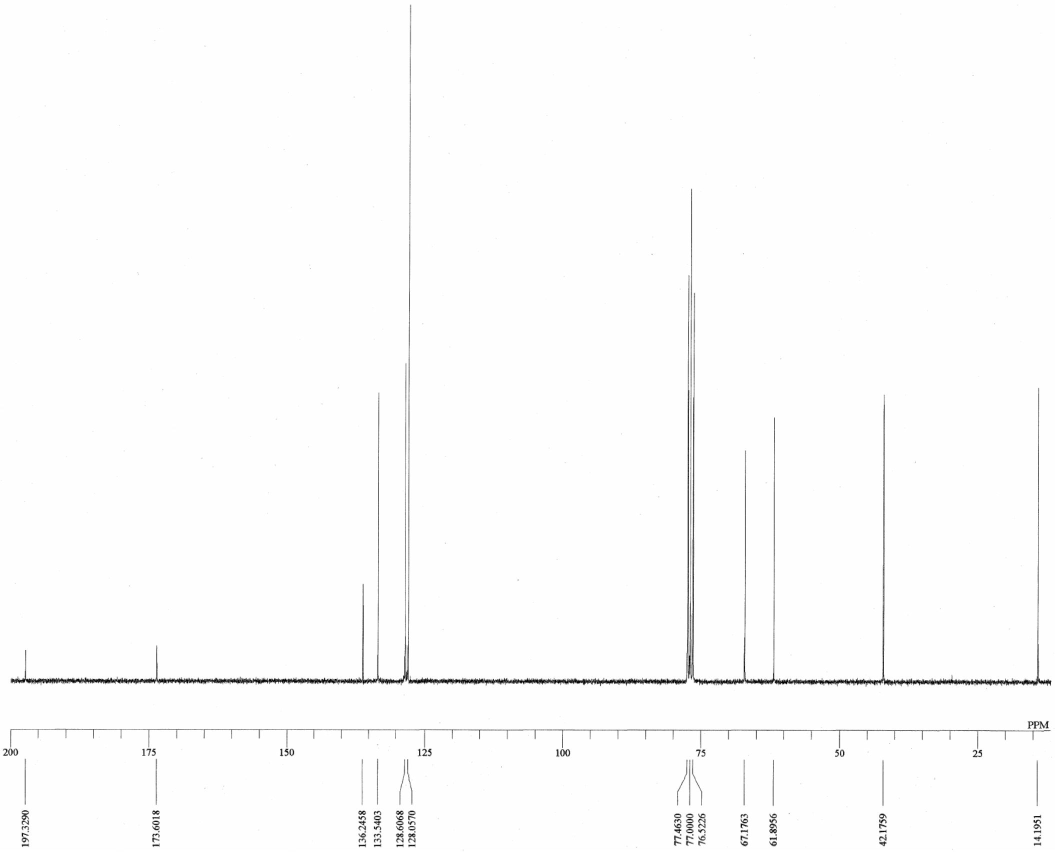

PPM
150
125
100
75
50
25
154.1696
132.0426
110.2917
77.4772
77.0000
76.5372
51.8360
27.8290
23.8230
22.4925
21.9863

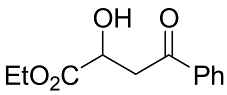
H & ^{13}C NMR Spectra and HPLC Charts of Products



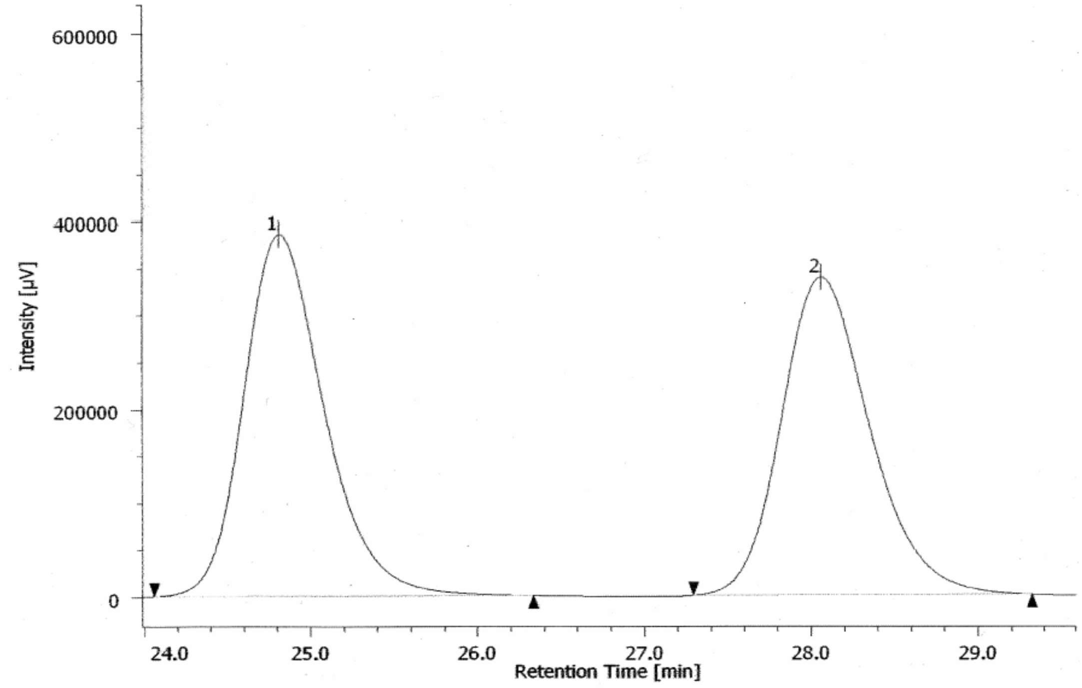
(*S*)-**6a**

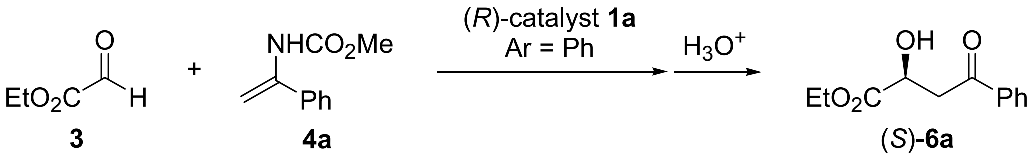


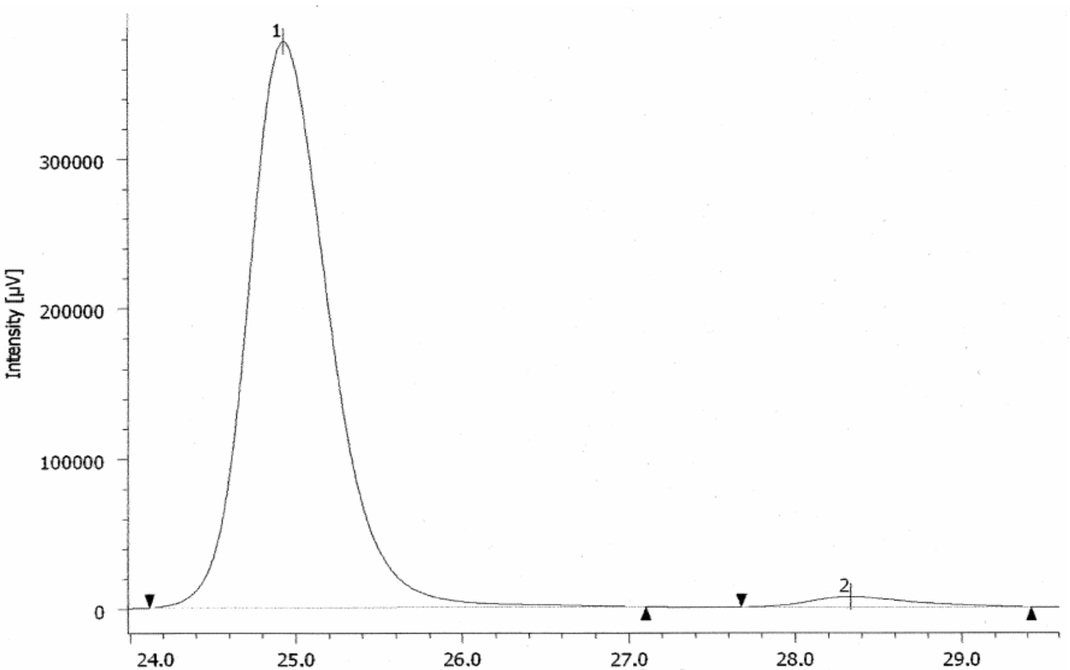




rac-**6a**


600000
400000
200000
0
Intensity [μV]
1
2
24.0
25.0
26.0
27.0
28.0
29.0
Retention Time [min]


(*R*)-catalyst **1a**
Ar = Ph
H_3O^+
3
4a
(*S*)-**6a**


300000
200000
100000
0
Intensity [μV]
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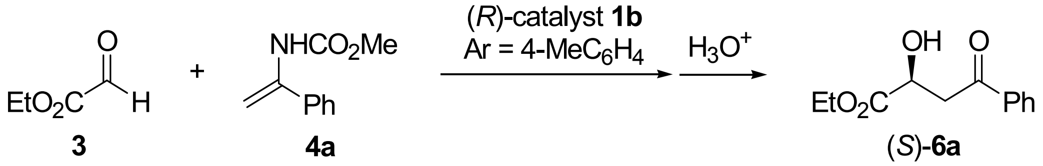
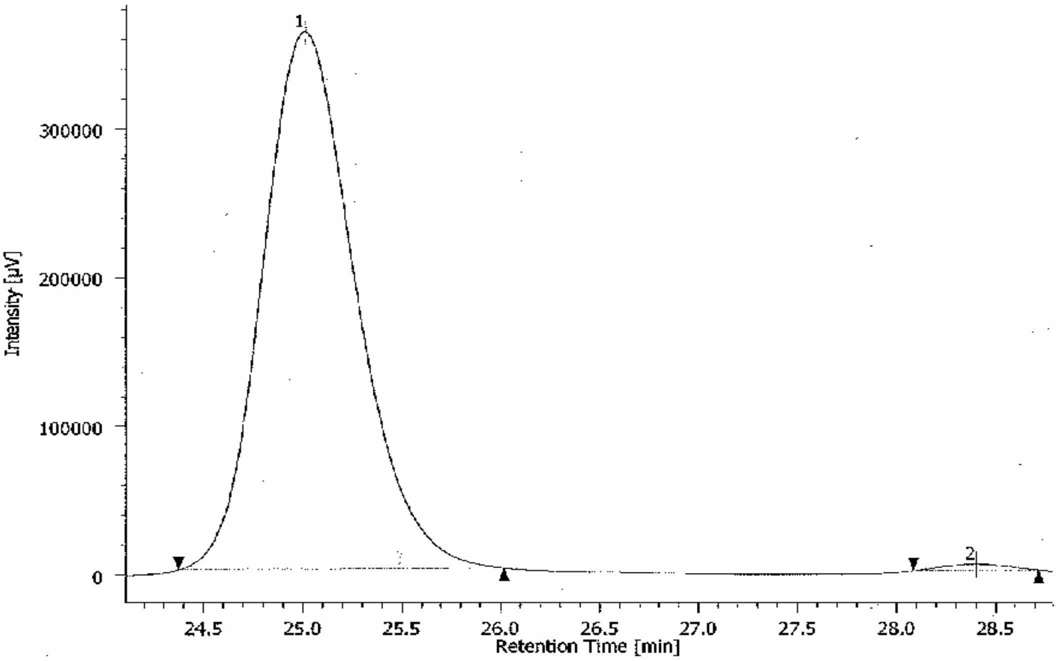
2
24.0
25.0
26.0
27.0
28.0
29.0
Retention Time [min]


(R)-catalyst 1b
Ar = 4-MeC6H4
H3O+
EtO2C
H
O
+
NHCO2Me
Ph
OH
O
EtO2C
Ph
3
4a
(S)-6a


Intensity [µV]
300000
200000
100000
0
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2
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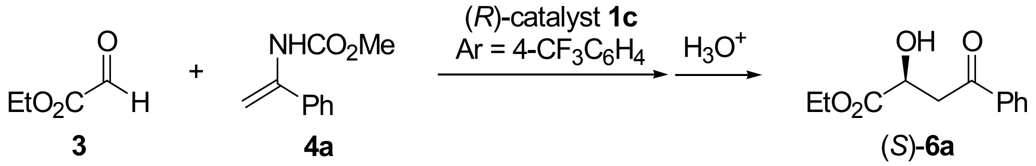
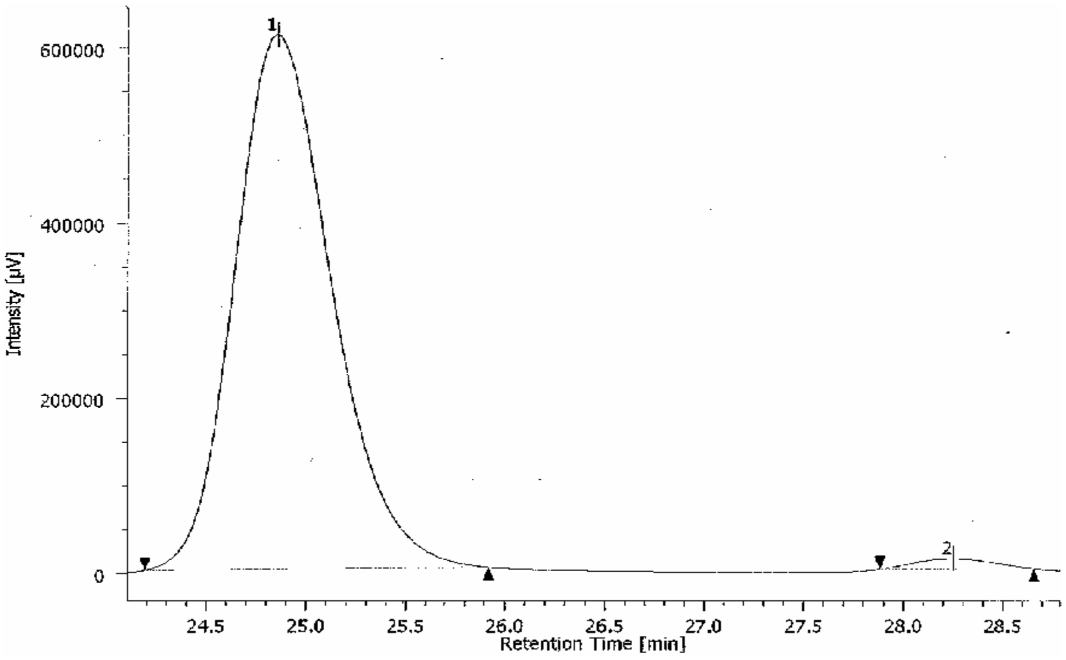
25.0
25.5
26.0
26.5
27.0
27.5
28.0
28.5
Retention Time [min]


(R)-catalyst 1c
Ar = 4-CF3C6H4
H3O+
EtO2C
H
O
+
NHCO2Me
Ph
OH
O
EtO2C
Ph
3
4a
(S)-6a


Intensity [µV]
600000
400000
200000
0
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2
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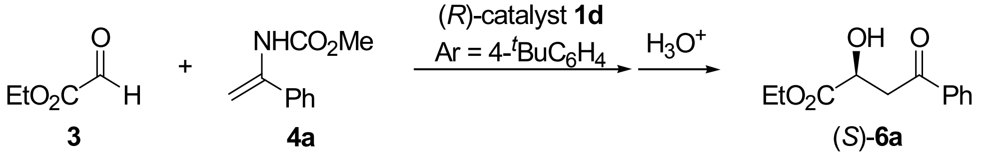
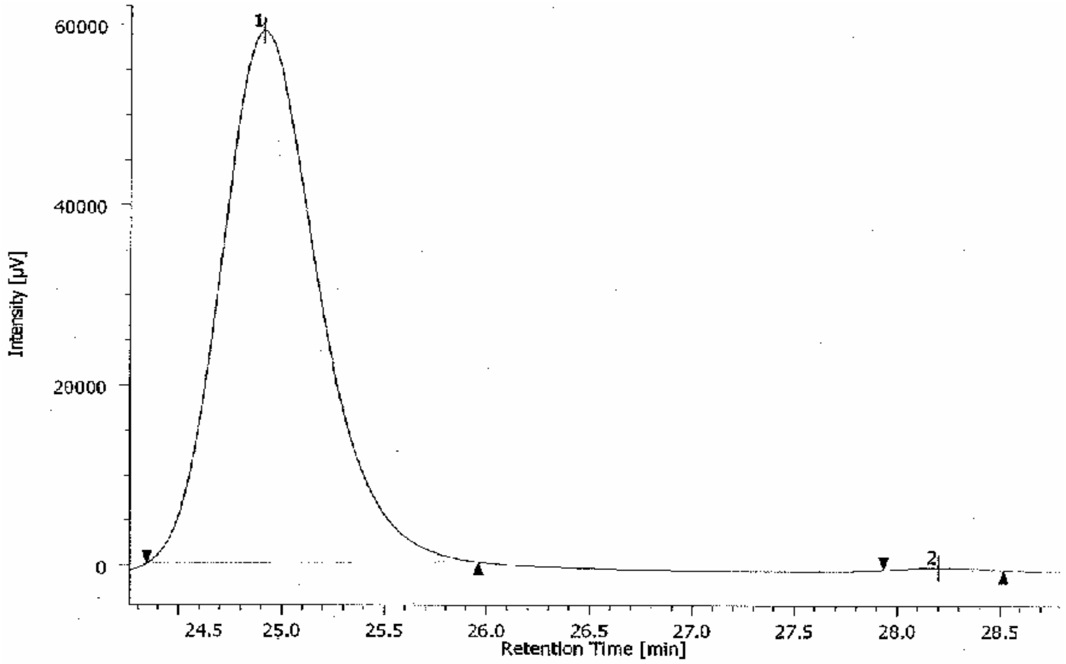
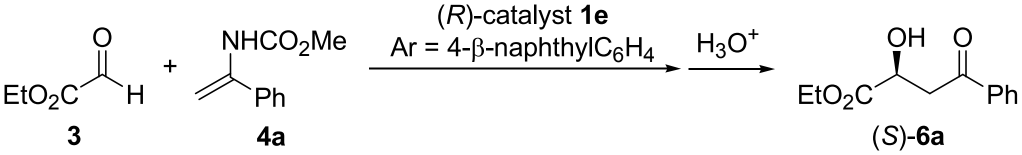
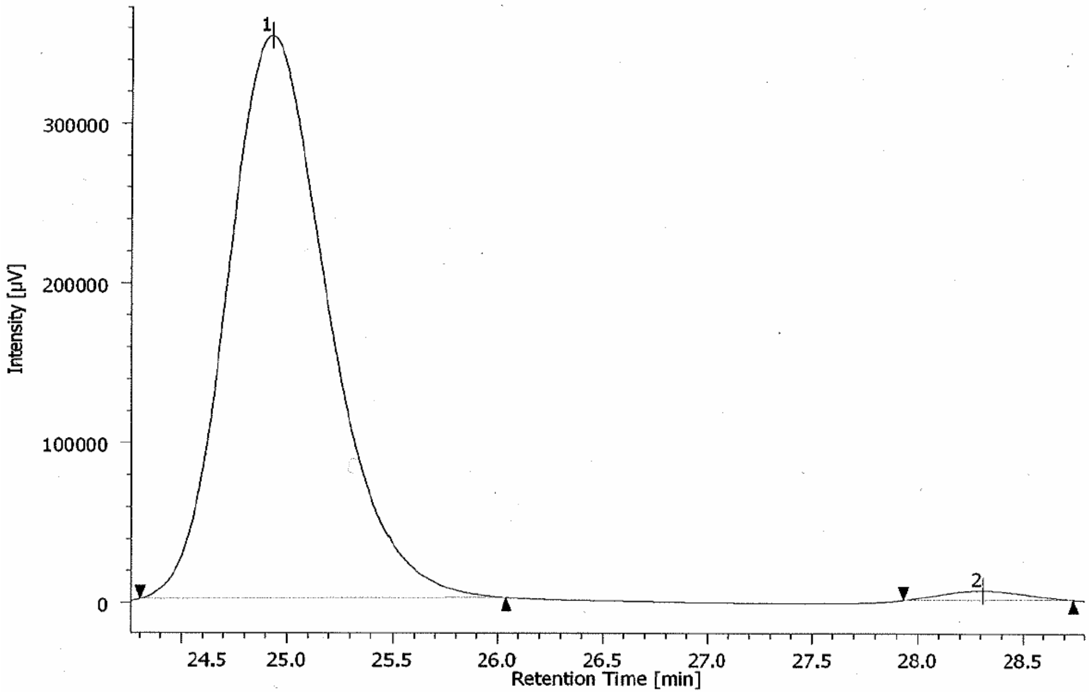
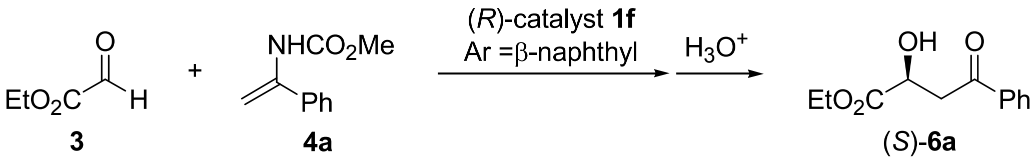
25.0
25.5
26.0
26.5
27.0
27.5
28.0
28.5
Retention Time [min]


(R)-catalyst 1d
Ar = 4-tBuC6H4
H3O+
EtO2C
H
NHCO2Me
Ph
OH
O
3
4a
(S)-6a

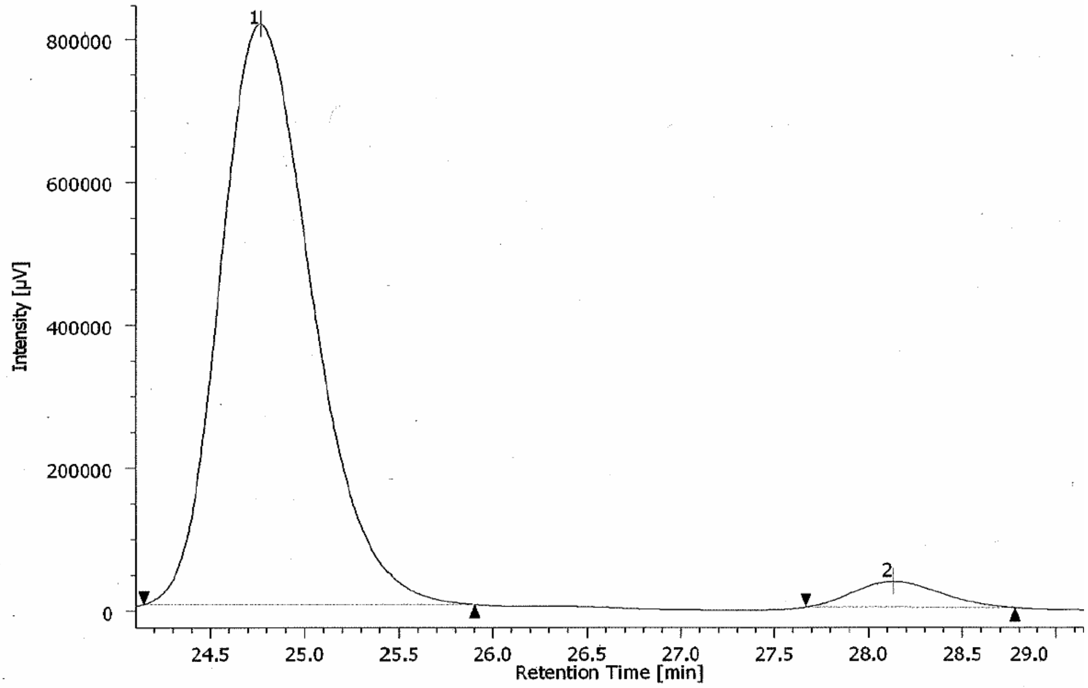

60000
40000
20000
0
Intensity [μV]
1
2
24.5
25.0
25.5
26.0
26.5
27.0
27.5
28.0
28.5
Retention Time [min]


(R)-catalyst 1e
Ar = 4-β-naphthylC6H4
H3O+
EtO2C
H
NHCO2Me
Ph
OH
O
3
4a
(S)-6a

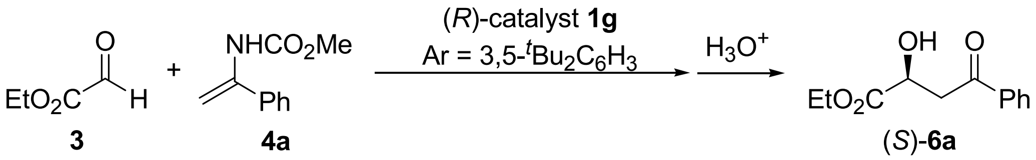

300000
200000
100000
0
Intensity [μV]
1
2
24.5
25.0
25.5
26.0
26.5
27.0
27.5
28.0
28.5
Retention Time [min]



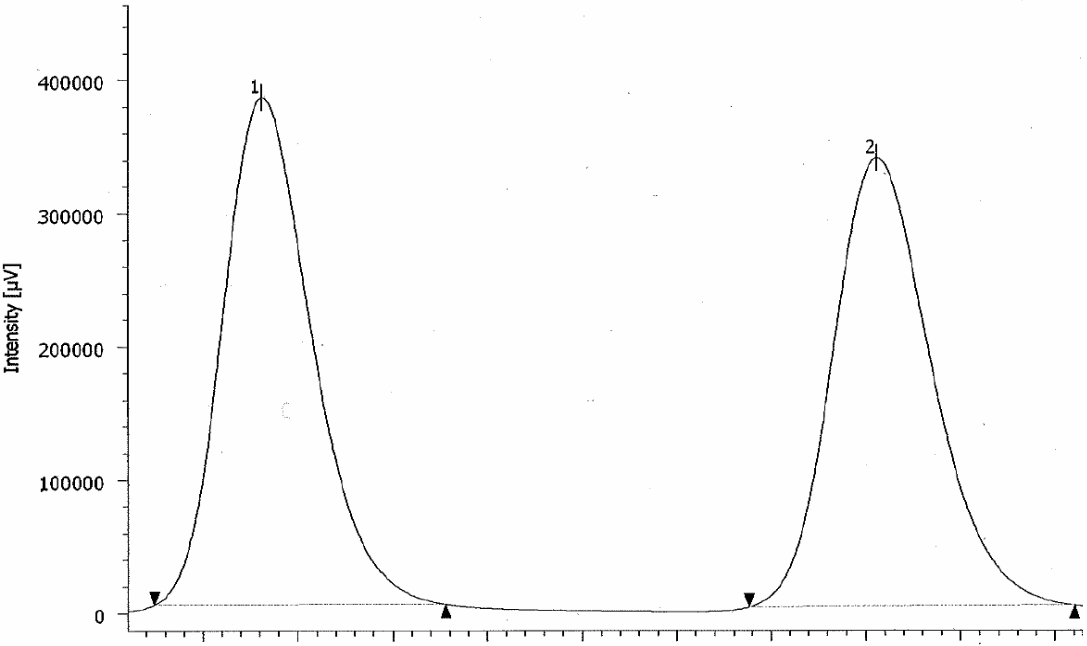
EtO2C H
3
NHCO2Me
Ph
4a
(R)-catalyst 1f
Ar =β-naphthyl
H3O+
OH O
EtO2C Ph
(S)-6a



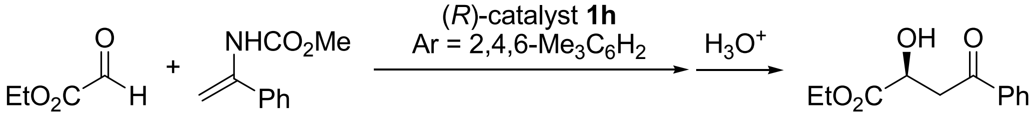
Intensity [µV]
800000
600000
400000
200000
0
1
2
24.5
25.0
25.5
26.0
26.5
27.0
27.5
28.0
28.5
29.0
Retention Time [min]



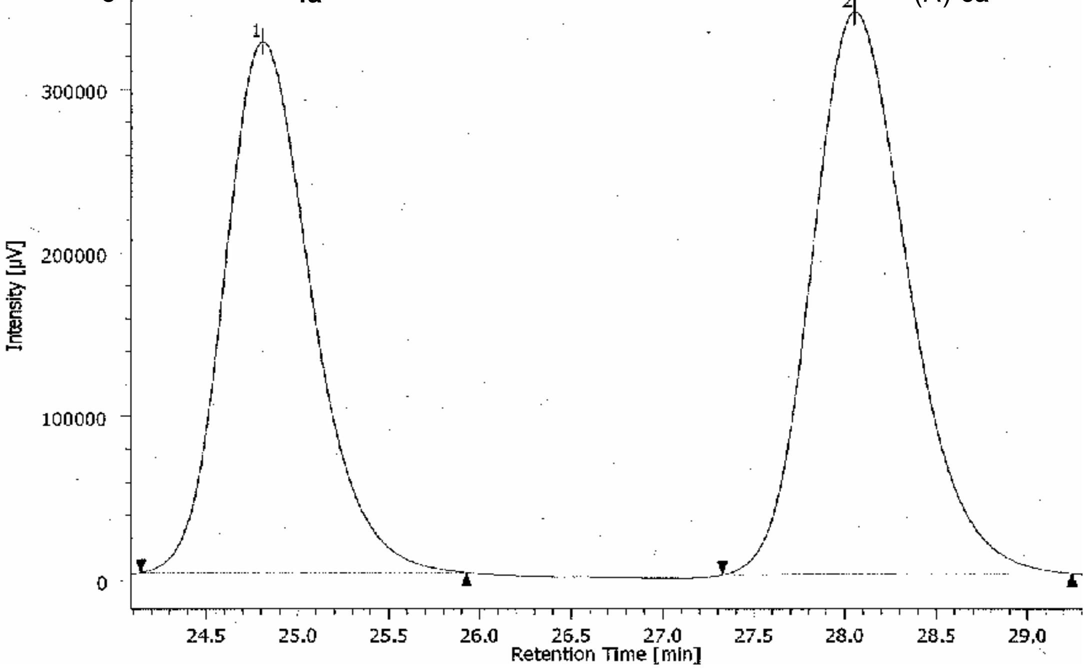
EtO2C H
3
NHCO2Me
Ph
4a
(R)-catalyst 1g
Ar = 3,5-tBu2C6H3
H3O+
OH O
EtO2C Ph
(S)-6a

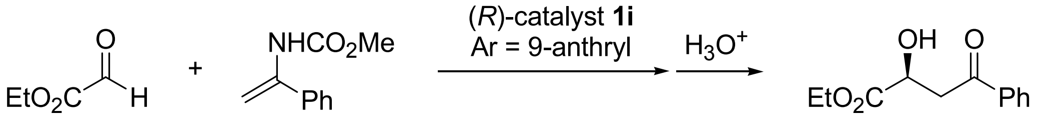


Intensity [µV]
400000
300000
200000
100000
0
1
2
24.5
25.0
25.5
26.0
26.5
27.0
27.5
28.0
28.5
29.0
Retention Time [min]

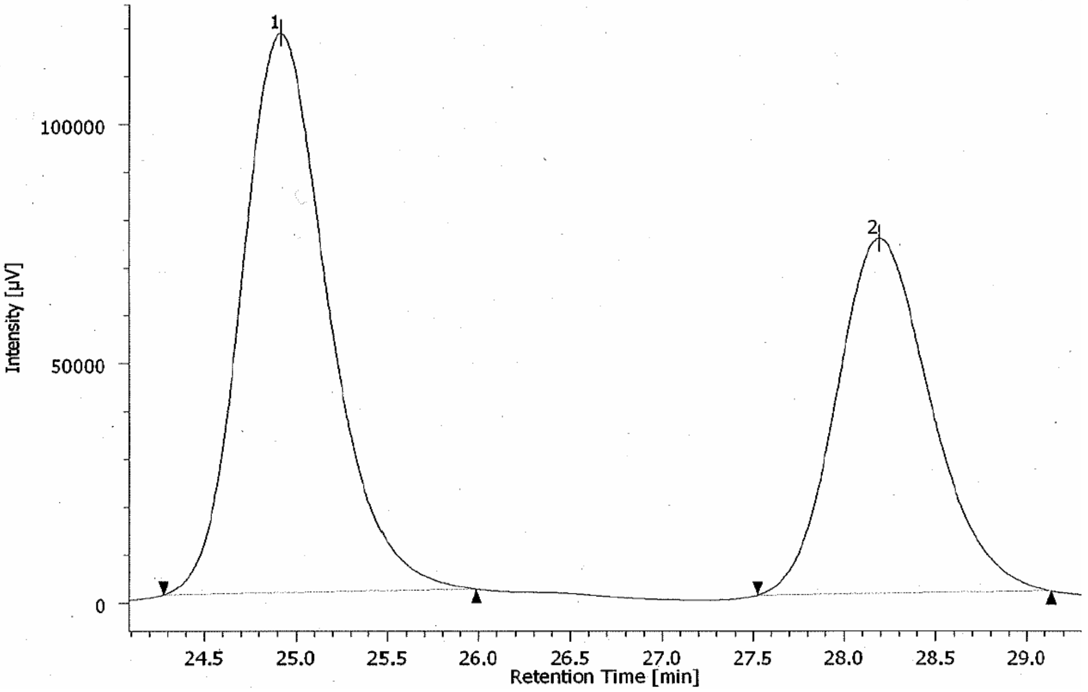


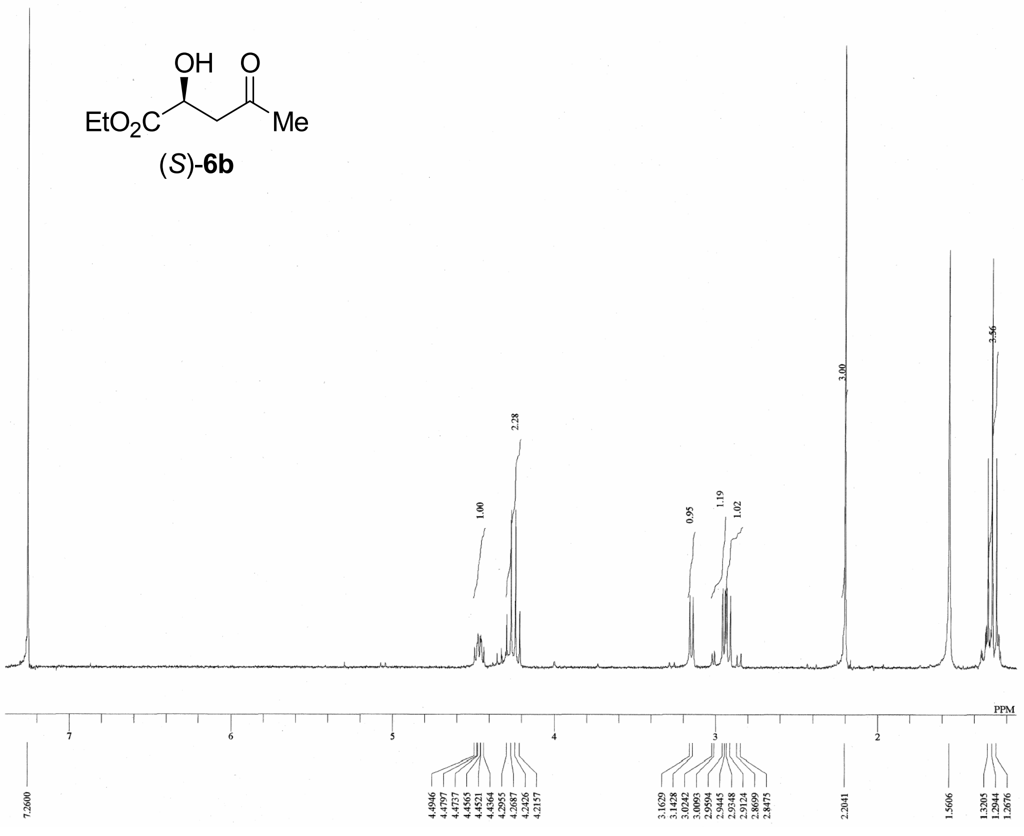
3 **4a** (*R*)-**6a**

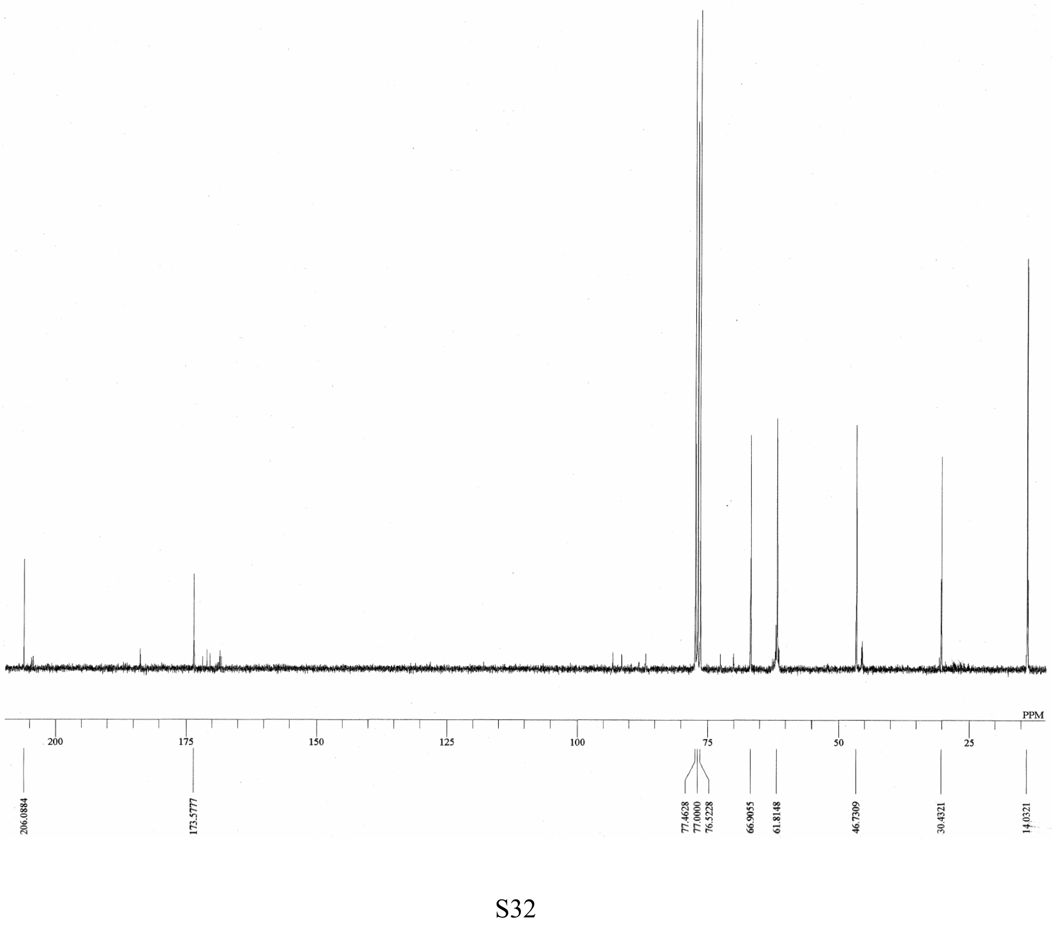


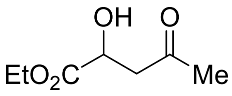


3 **4a** (*S*)-**6a**

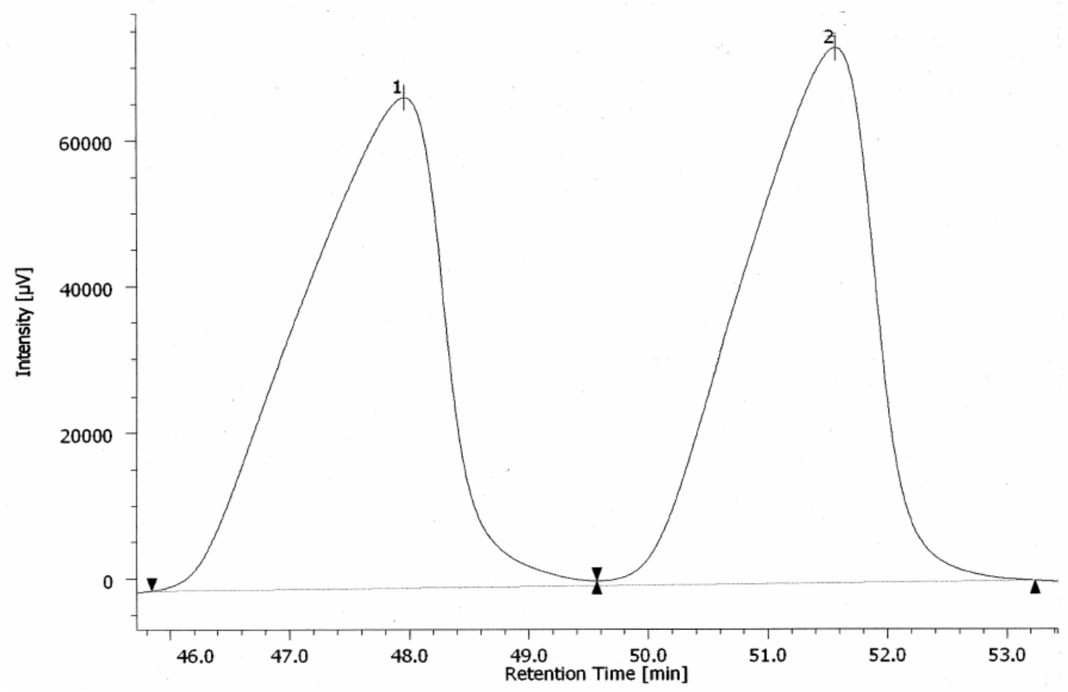


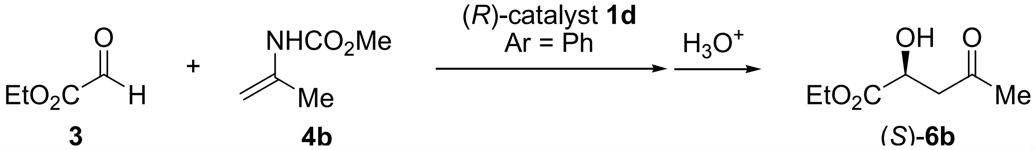

OH
O
EtO2C
Me
(S)-6b
1.00
2.28
0.95
1.19
1.02
3.00
3.56
7
6
5
4
3
2
PPM
7.2600
4.4946
4.4797
4.4737
4.4565
4.4521
4.4364
4.2955
4.2687
4.2426
4.2157
3.1629
3.1428
3.0242
3.0093
2.9594
2.9445
2.9348
2.9124
2.8699
2.8475
2.2041
1.5606
1.3205
1.2944
1.2676

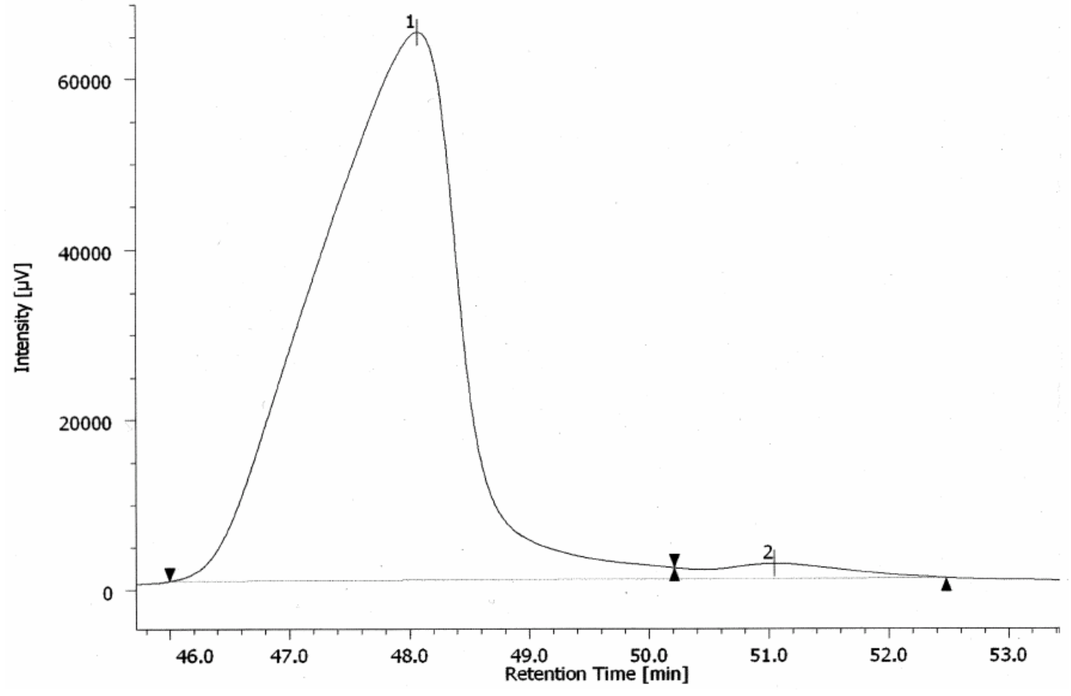

200
175
150
125
100
75
50
25
PPM
206.0884
173.5777
77.4628
77.0000
76.5228
66.9055
61.8148
46.7309
30.4321
14.0321

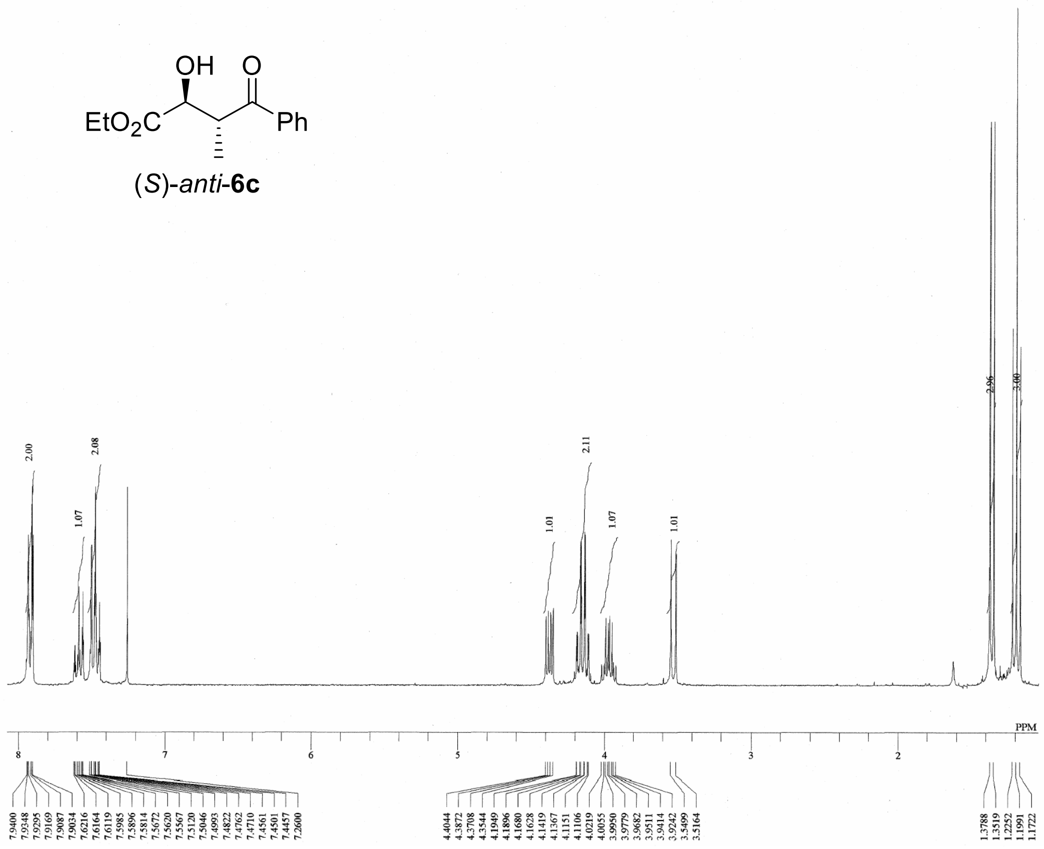

OH
O
EtO2C
Me

rac-**6b**

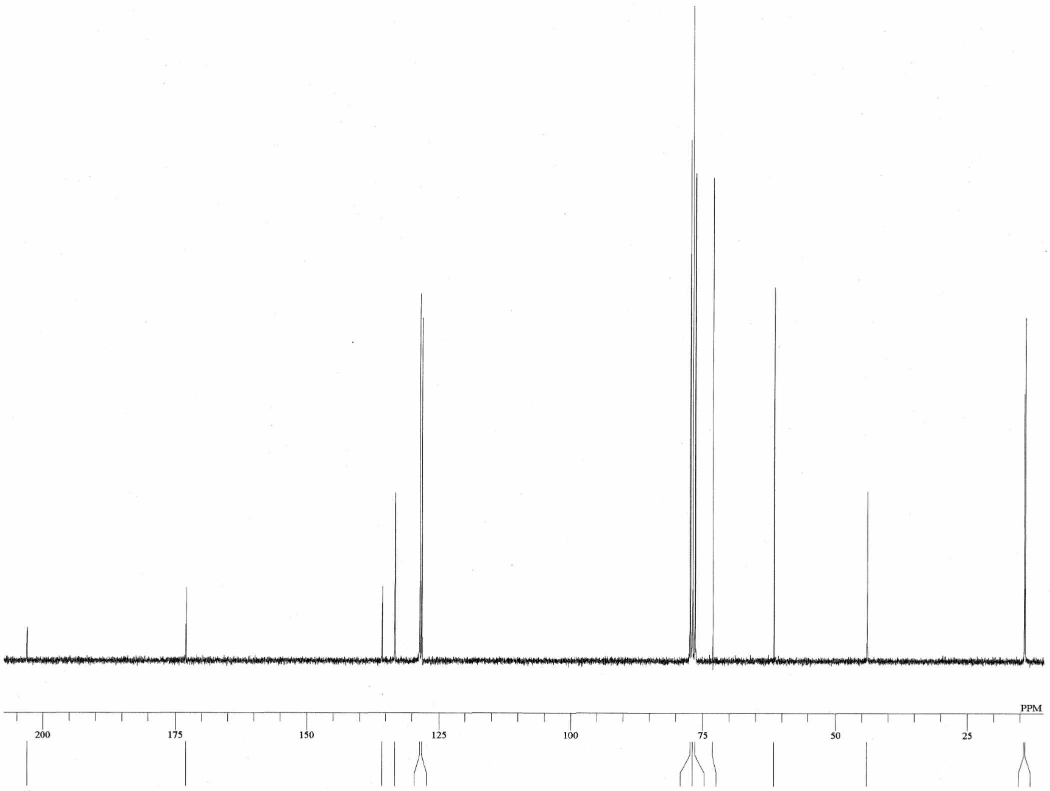

1
2
60000
40000
20000
0
Intensity [µV]
46.0
47.0
48.0
49.0
50.0
51.0
52.0
53.0
Retention Time [min]

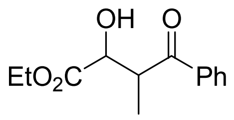

O
EtO2C
H
3
+
NHCO2Me
Me
4b
(R)-catalyst 1d
Ar = Ph
H3O+
OH
O
EtO2C
Me
(S)-6b


1
2
60000
40000
20000
0
Intensity [µV]
46.0
47.0
48.0
49.0
50.0
51.0
52.0
53.0
Retention Time [min]

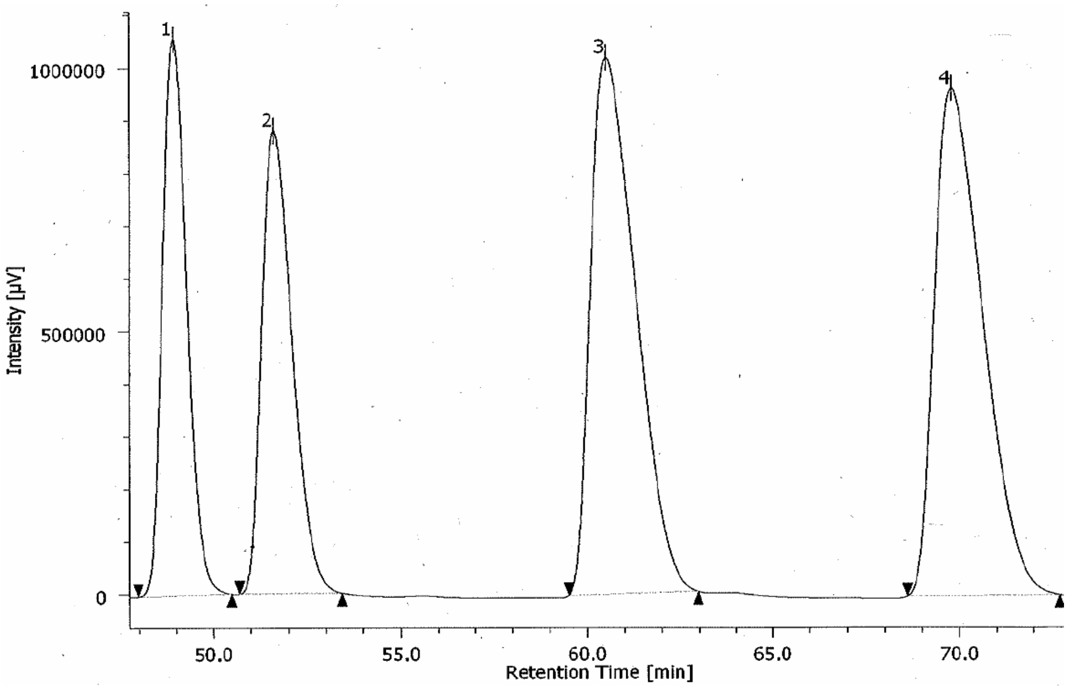

OH
O
EtO2C
Ph
2.00
1.07
2.08
1.01
2.11
1.07
1.01
2.96
3.00
8
7
6
5
4
3
2
PPM
7.9400
7.9348
7.9295
7.9169
7.9087
7.9034
7.6216
7.6164
7.6119
7.5985
7.5896
7.5814
7.5672
7.5620
7.5567
7.5120
7.5046
7.4993
7.4822
7.4762
7.4710
7.4561
7.4501
7.4457
7.2600
4.4044
4.3872
4.3708
4.3544
4.1949
4.1896
4.1680
4.1628
4.1419
4.1367
4.1151
4.1106
4.0219
4.0055
3.9950
3.9779
3.9682
3.9511
3.9414
3.9242
3.5499
3.5164
1.3788
1.3519
1.2252
1.1991
1.1722

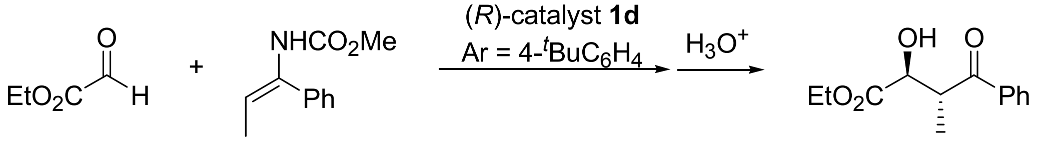
(*S*)-*anti*-**6c**


200
175
150
125
100
75
50
25
PPM
203.0872
172.9941
135.8407
133.3956
128.6502
128.3174
77.4630
77.0000
76.5226
73.1805
61.6207
44.0278
14.2675
14.1372

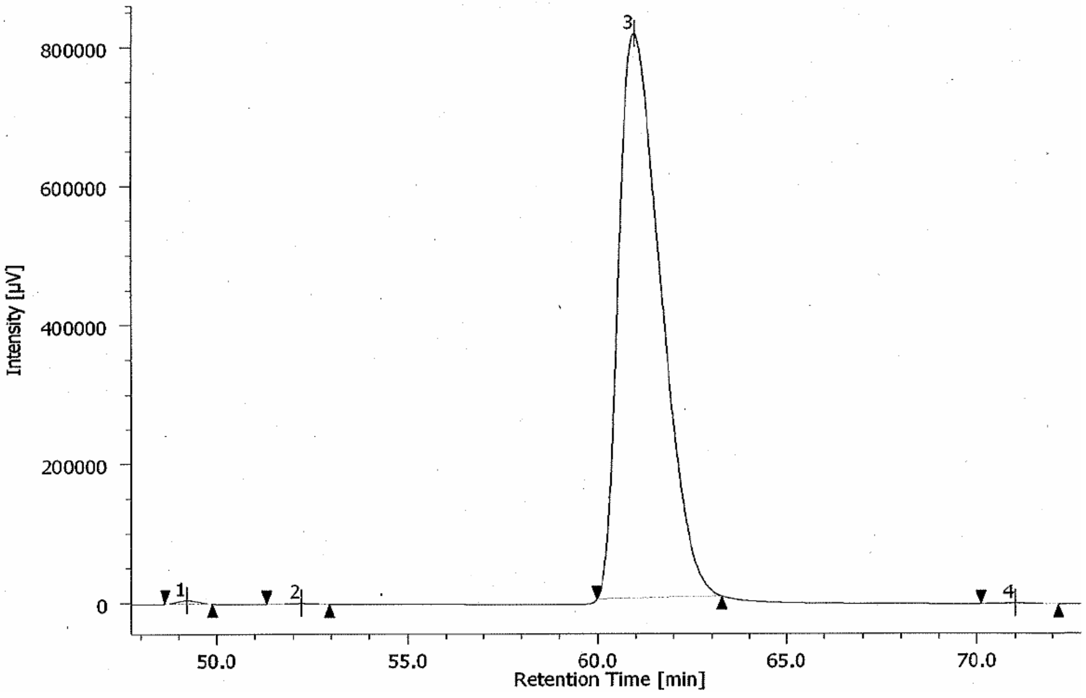


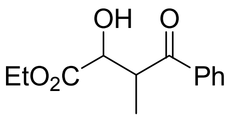
rac-**6c**



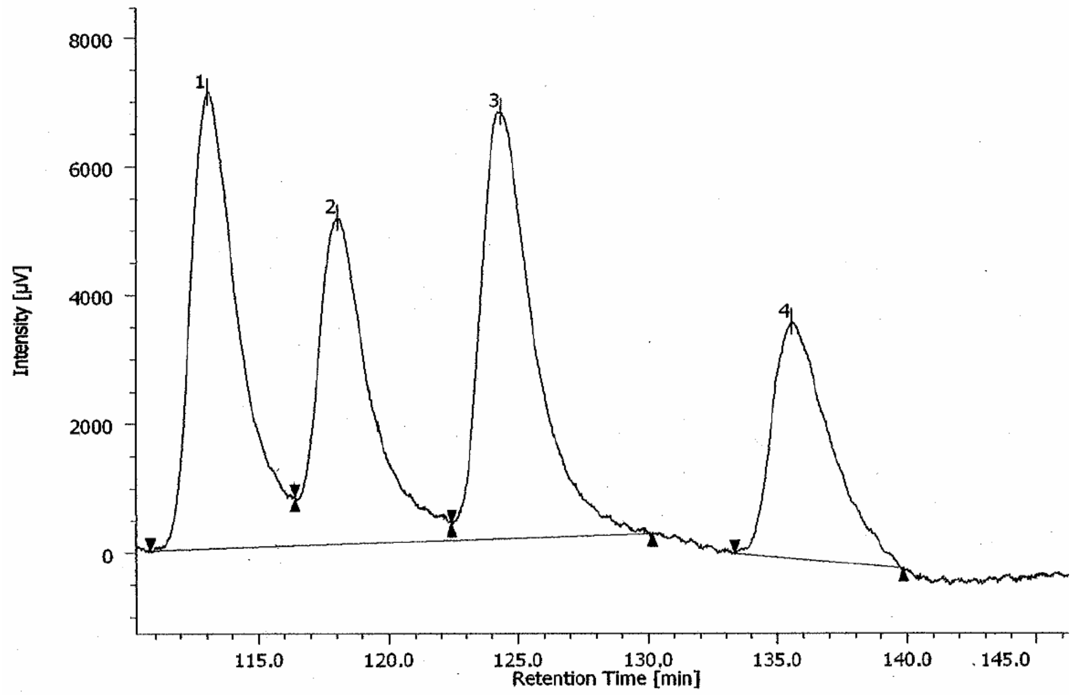


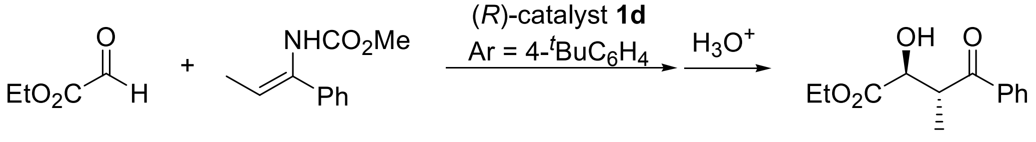
3 (*E*)-**4c** (*S*)-*anti*-**6c**



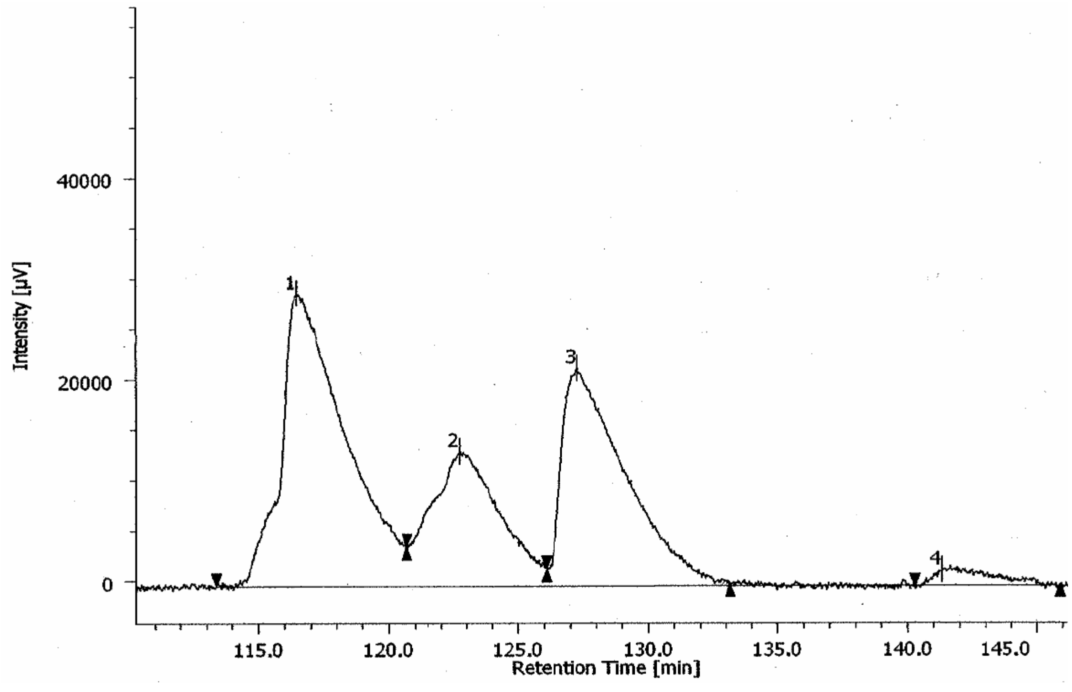


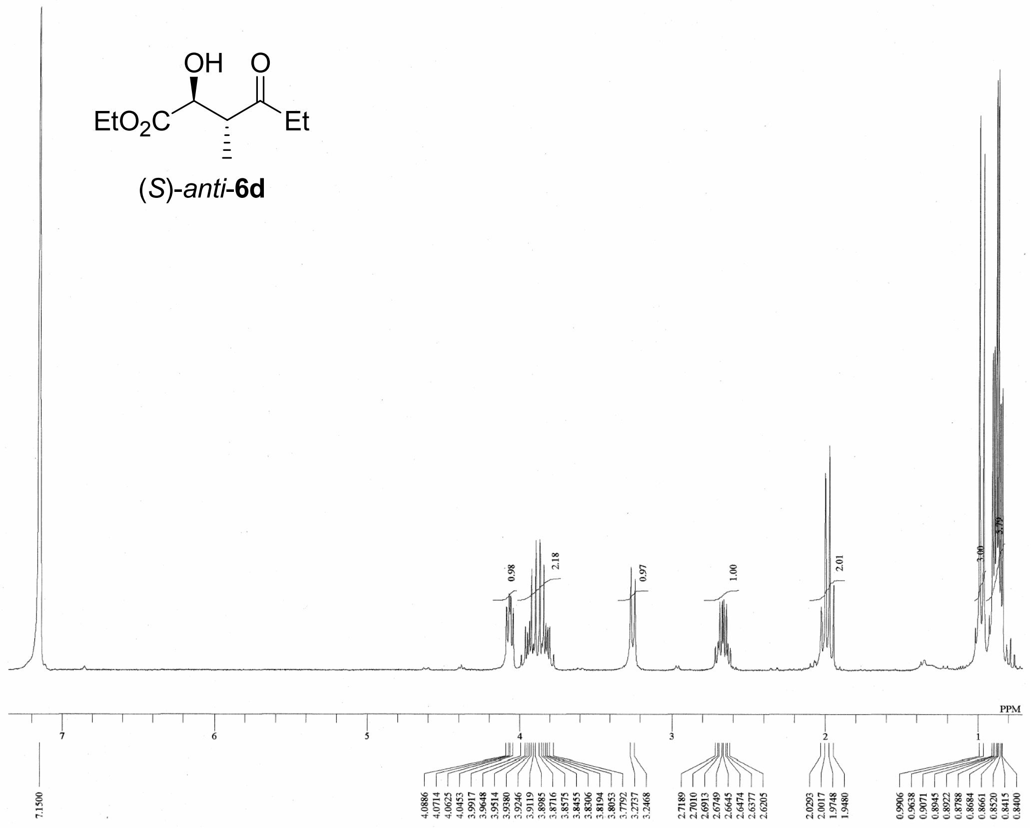
rac-**6c**



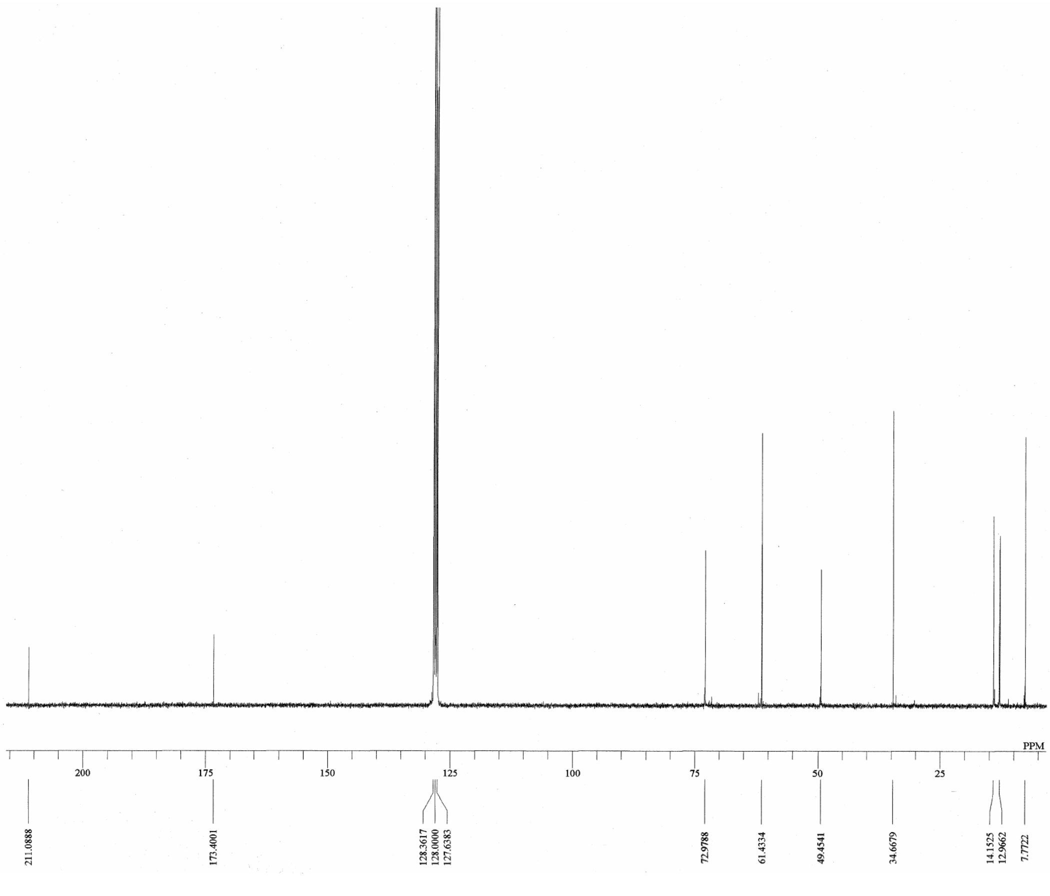


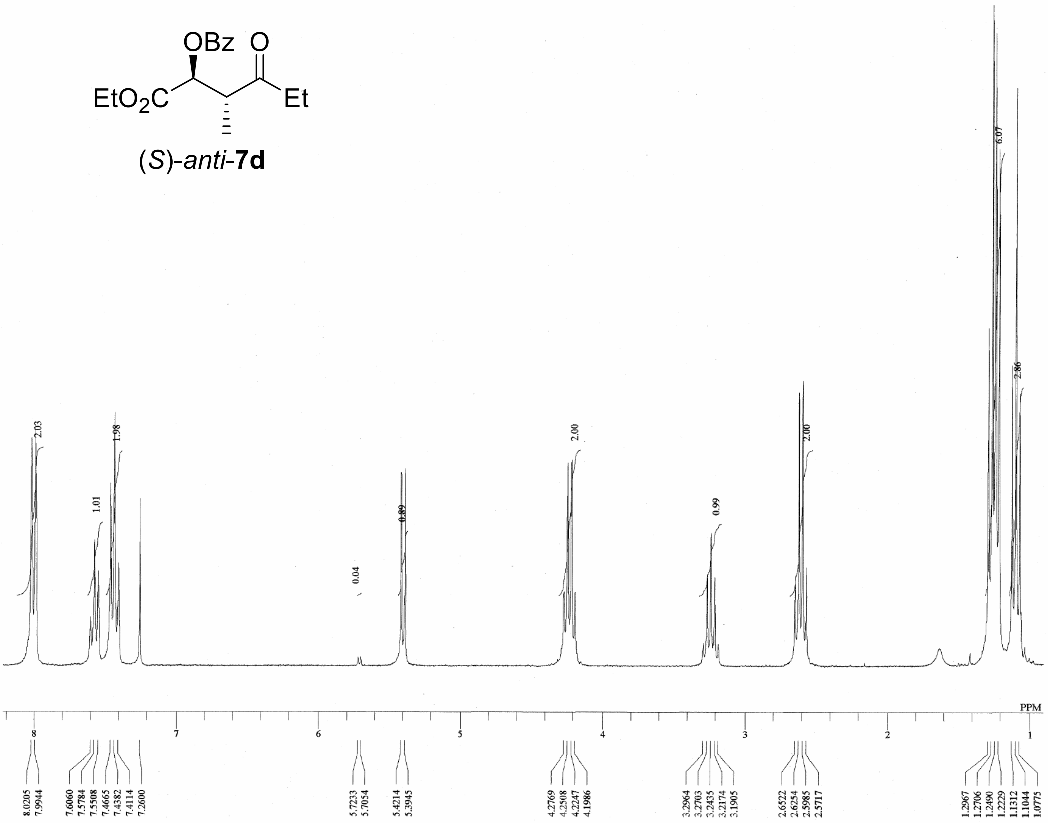
3 (*Z*)-**4c** (*S*)-*anti*-**6c**

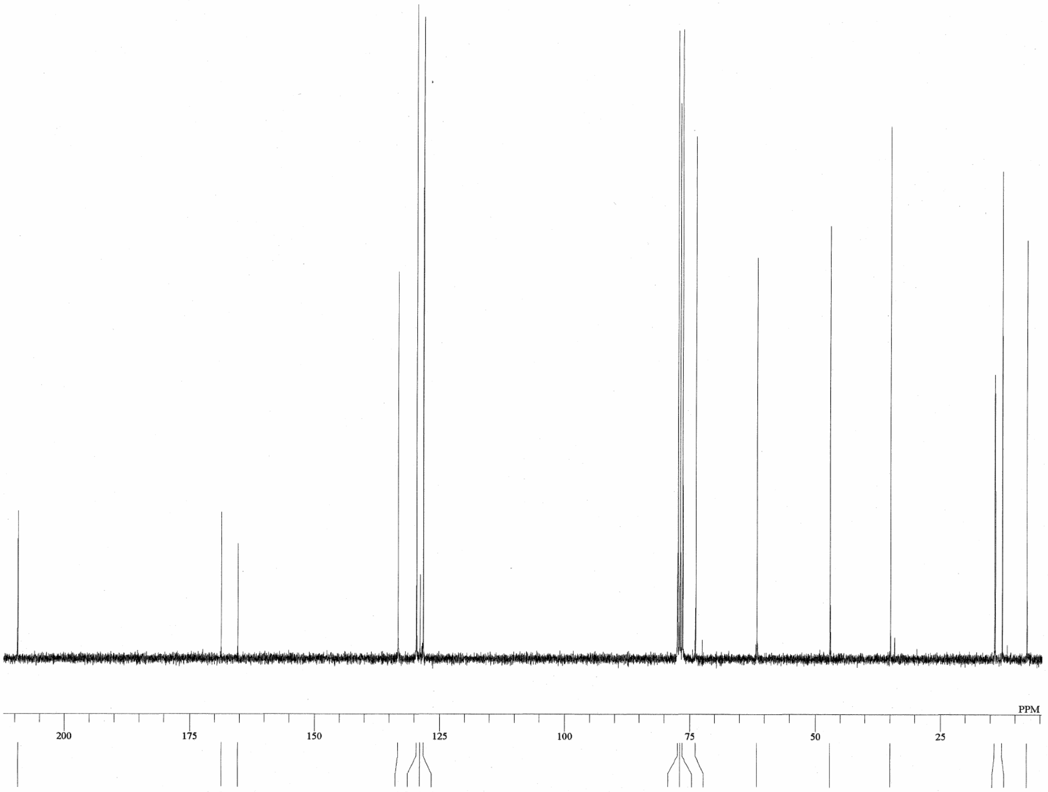


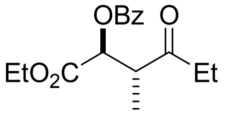

OH
O
EtO$_2$C
Et
0.98
2.18
0.97
1.00
2.01
3.00
3.79
PPM
7
6
5
4
3
2
1
7.1500
4.0886
4.0714
4.0625
4.0453
3.9917
3.9648
3.9514
3.9380
3.9246
3.9119
3.8985
3.8716
3.8575
3.8455
3.8306
3.8194
3.8053
3.7792
3.2737
3.2468
2.7189
2.7010
2.6913
2.6749
2.6645
2.6474
2.6377
2.6205
2.0293
2.0017
1.9748
1.9480
0.9906
0.9638
0.9071
0.8945
0.8922
0.8788
0.8684
0.8661
0.8520
0.8415
0.8400

(*S*)-*anti*-**6d**

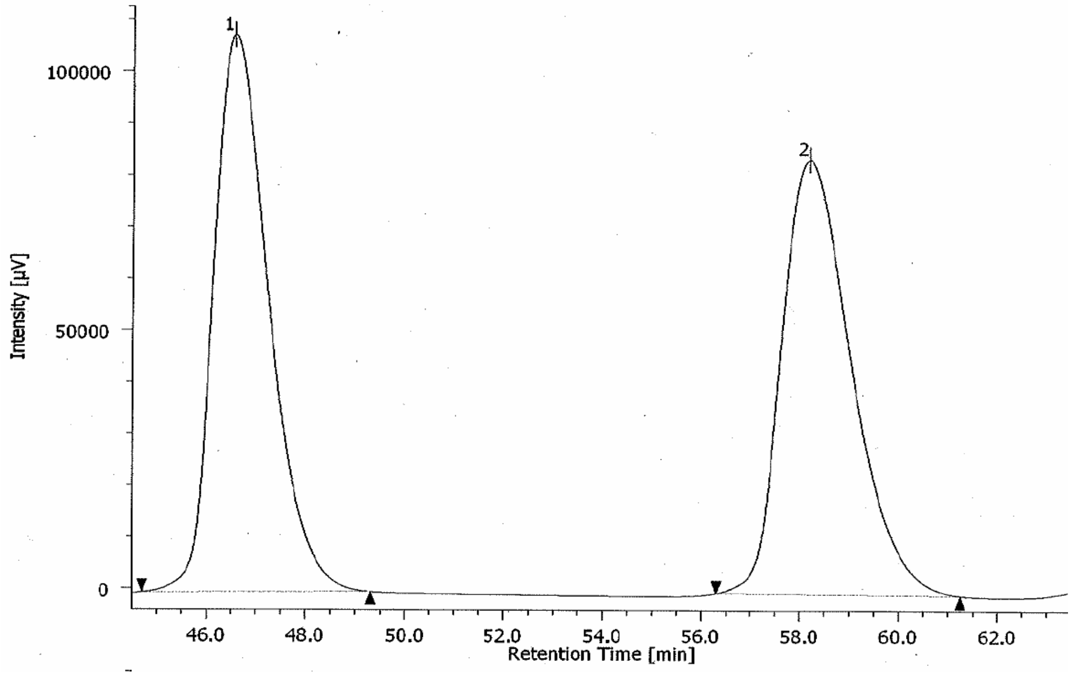

PPM
200
175
150
125
100
75
50
25
211.0888
173.4001
128.3617
128.0000
127.6383
72.9788
61.4334
49.4541
34.6679
14.1525
12.9662
7.7722

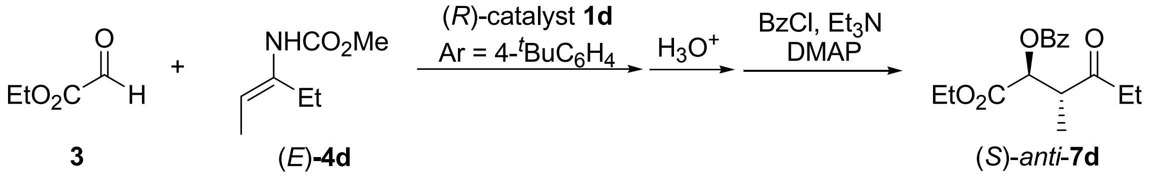

OBz
O
EtO2C
Et
(S)-anti-7d
2.03
1.01
1.98
0.04
0.89
2.00
0.99
2.00
6.07
2.86
PPM
8
7
6
5
4
3
2
1
8.0205
7.9944
7.6060
7.5784
7.5508
7.4665
7.4382
7.4114
7.2600
5.7233
5.7054
5.4214
5.3945
4.2769
4.2508
4.2247
4.1986
3.2964
3.2703
3.2435
3.2174
3.1905
2.6522
2.6254
2.5985
2.5717
1.2967
1.2706
1.2490
1.2229
1.1312
1.1044
1.0775

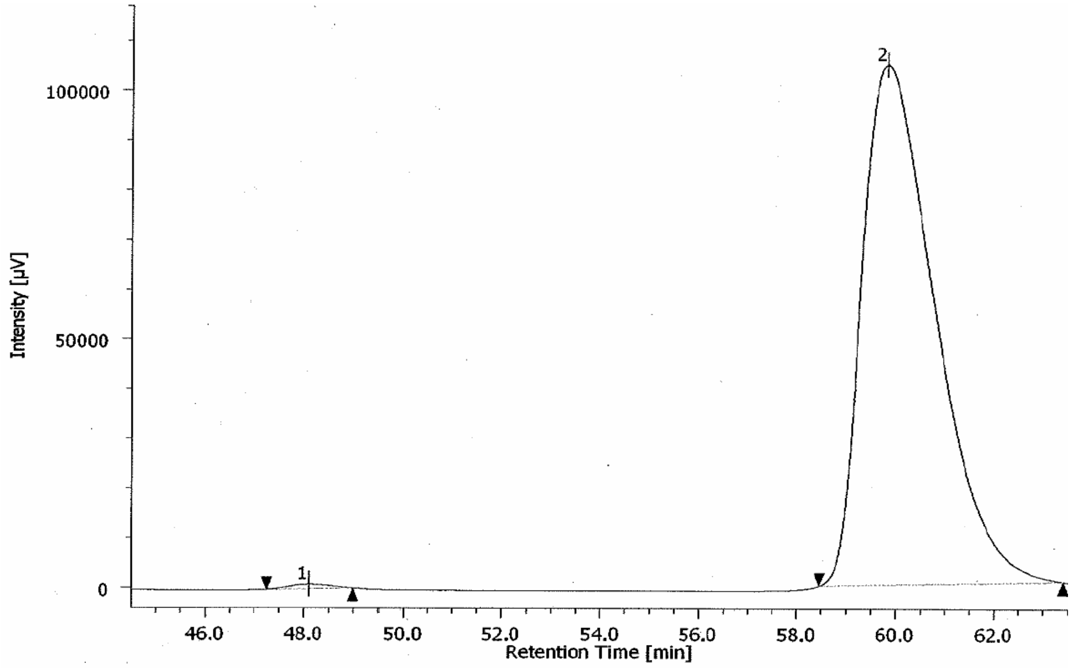

PPM
200
175
150
125
100
75
50
25
209.4531
168.7840
165.4853
133.3522
129.6919
128.9540
128.3464
77.4630
77.0000
76.5226
73.9039
61.6352
47.0950
35.0577
14.1662
12.6905
7.7425

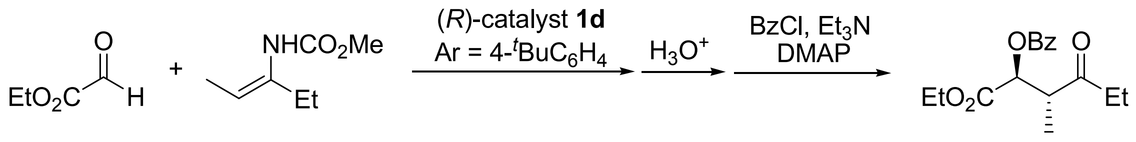

OBz
O
EtO2C
Et

rac-*anti*-**7d**

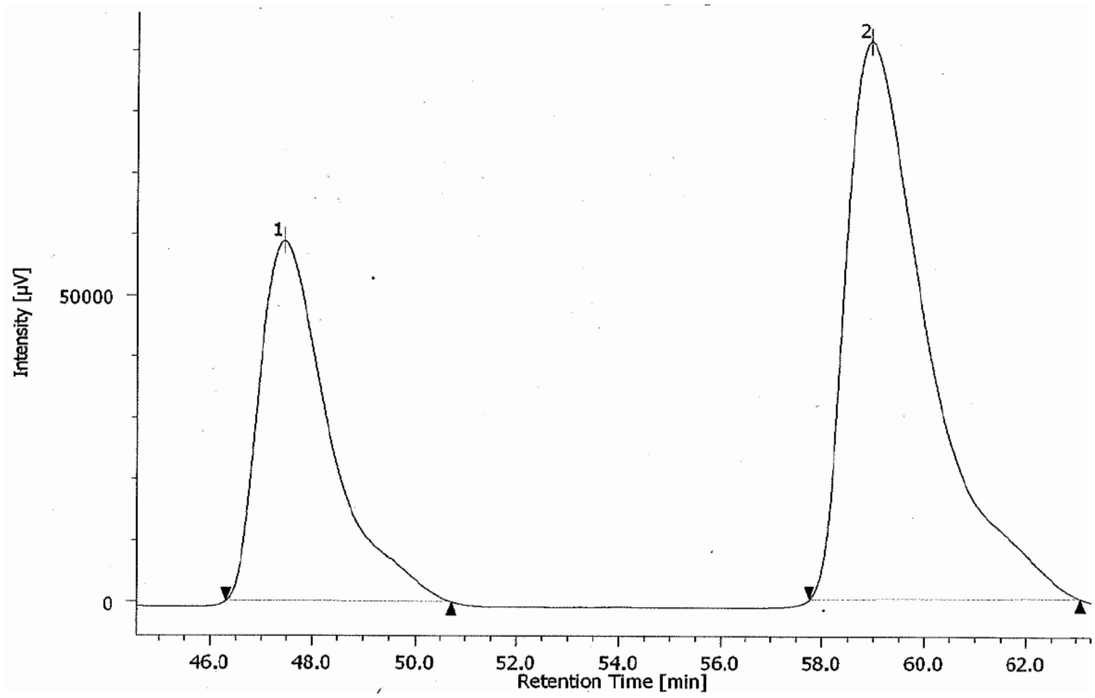

1
2
100000
50000
0
Intensity [µV]
46.0
48.0
50.0
52.0
54.0
56.0
58.0
60.0
62.0
Retention Time [min]

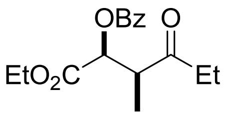

O
EtO2C
H
+
NHCO2Me
Et
(R)-catalyst 1d
Ar = 4-tBuC6H4
H3O+
BzCl, Et3N
DMAP
OBz
O
EtO2C
Et
3
(E)-4d
(S)-anti-7d


1
2
100000
50000
0
Intensity [µV]
46.0
48.0
50.0
52.0
54.0
56.0
58.0
60.0
62.0
Retention Time [min]

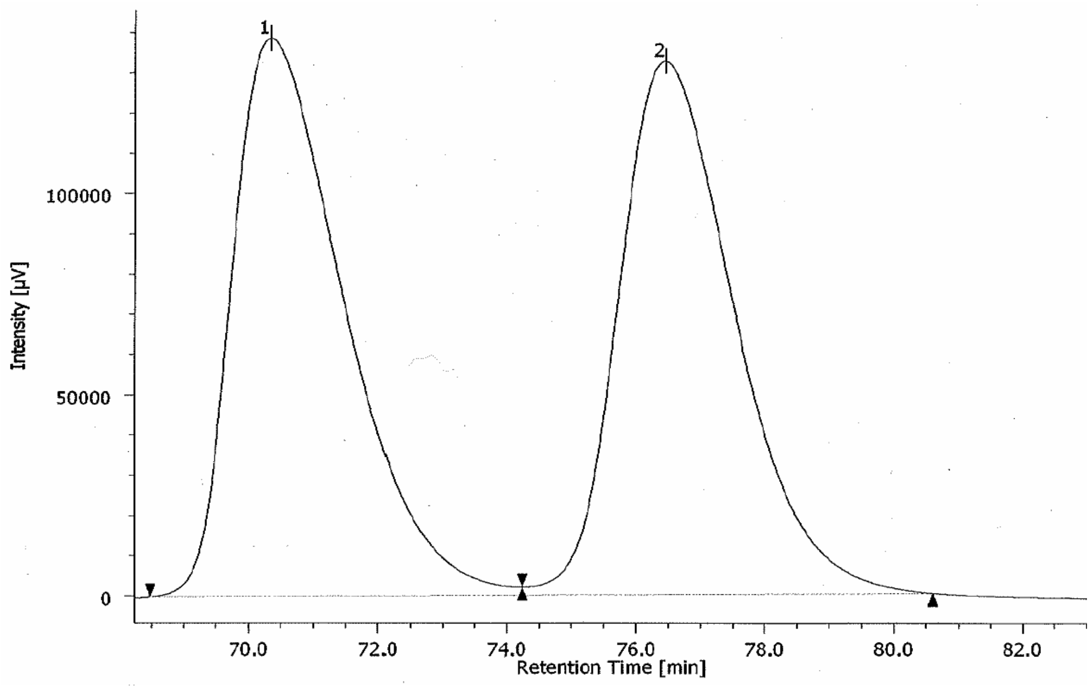

(*R*)-catalyst **1d**
Ar = 4-^{t}BuC$_6$H$_4$
H_3O^+
BzCl, Et_3N
DMAP
EtO_2C
H
O
NHCO$_2$Me
Et
+
OBz
O
Et

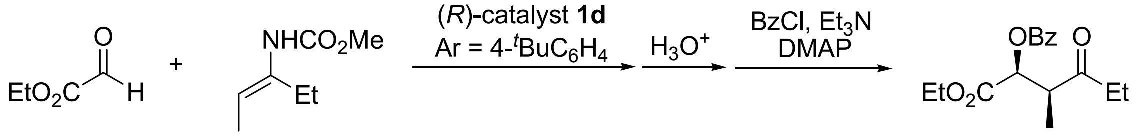
3 (*Z*)-**4d** (*S*)-**7d**


Intensity [µV]
50000
0
1
2
46.0
48.0
50.0
52.0
54.0
56.0
58.0
60.0
62.0
Retention Time [min]

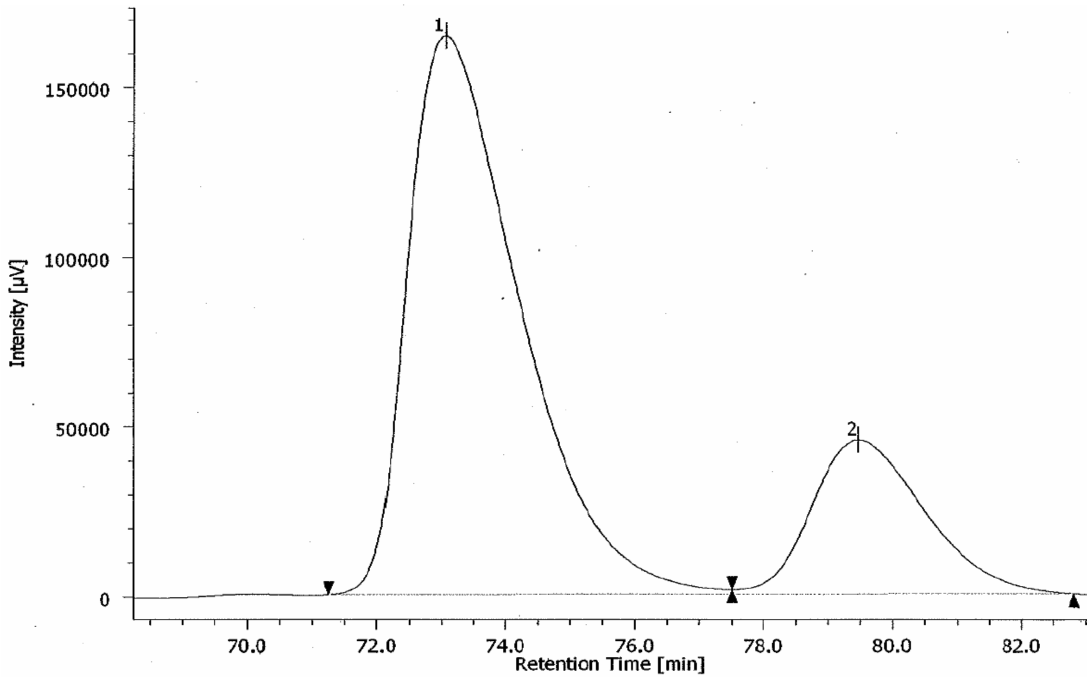


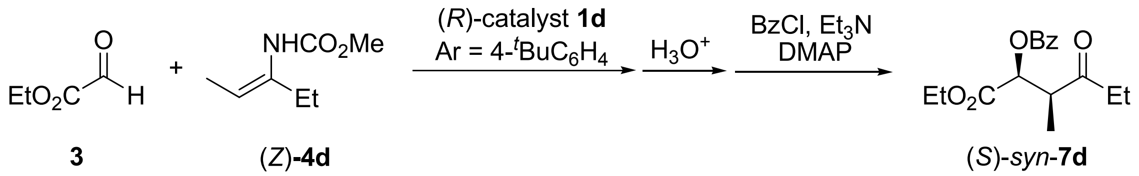
rac-*syn*-**7d**

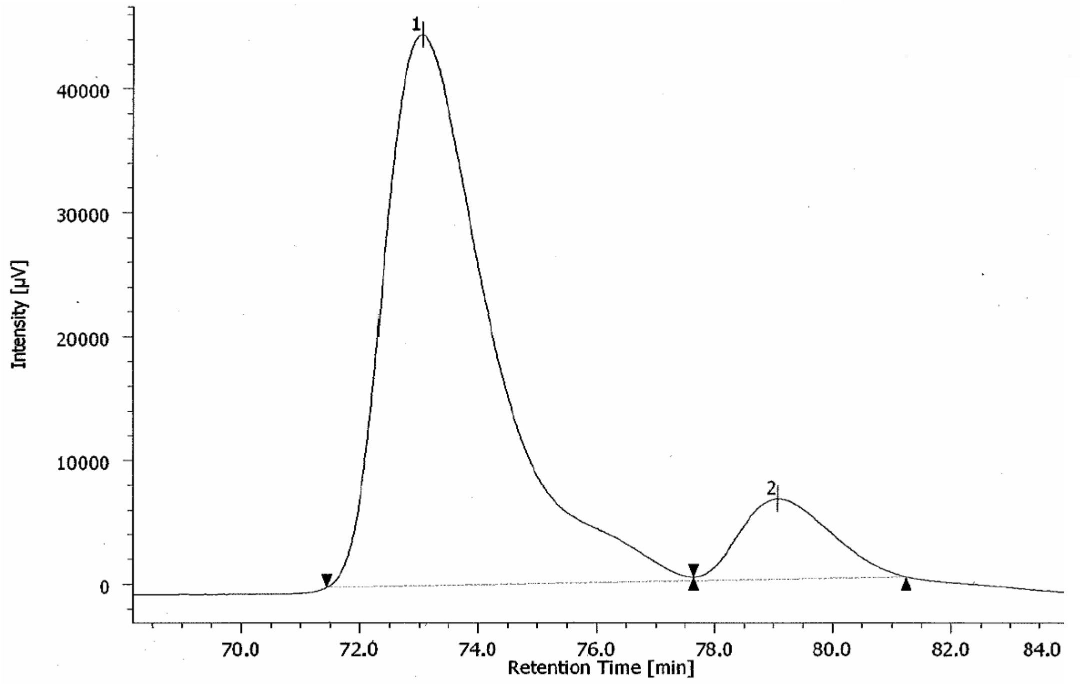


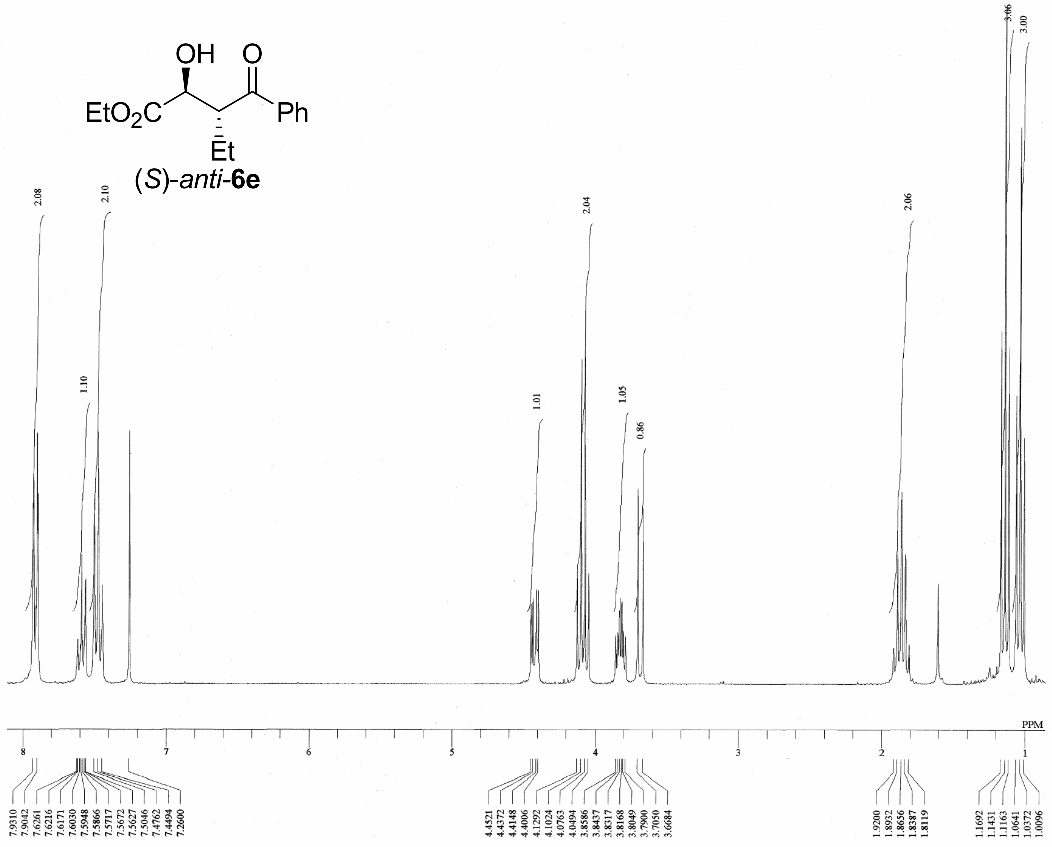


3 (*E*)-**4d** (*S*)-*syn*-**7d**

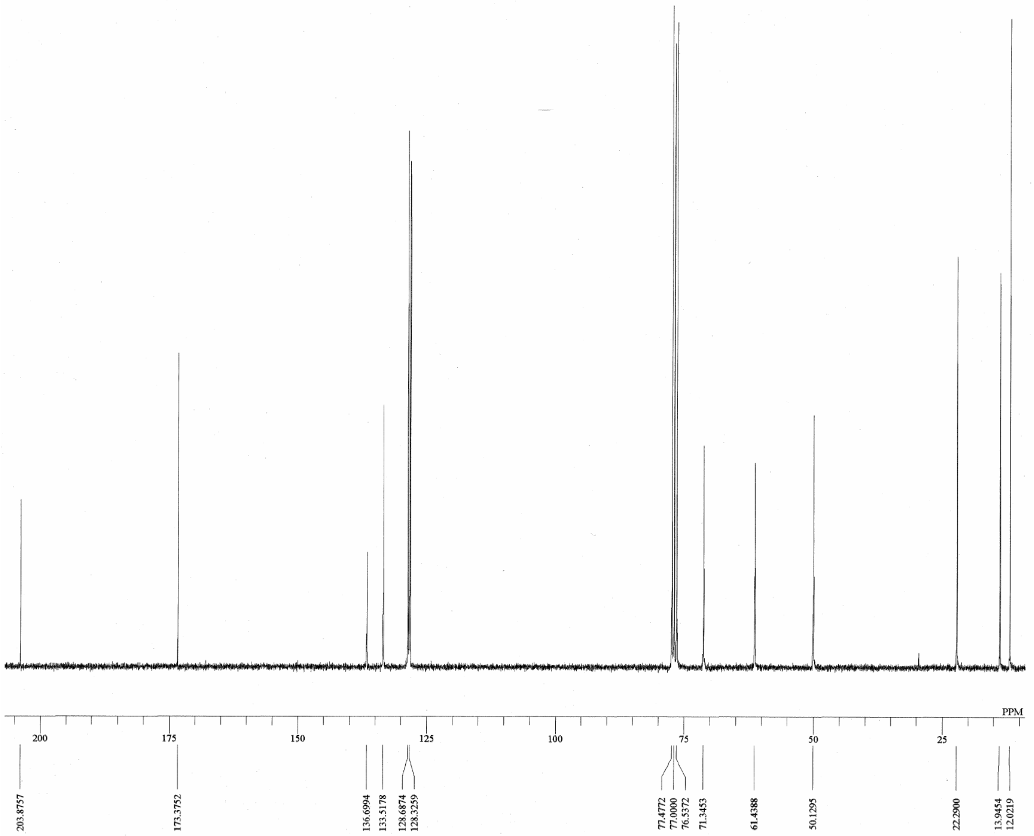


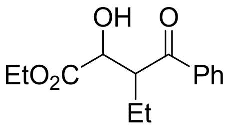

EtO2C
O
H
+
NHCO2Me
Et
(R)-catalyst 1d
Ar = 4-tBuC6H4
H3O+
BzCl, Et3N
DMAP
OBz
O
EtO2C
Et
3
(Z)-4d
(S)-syn-7d


1
2
Intensity [µV]
40000
30000
20000
10000
0
70.0
72.0
74.0
76.0
78.0
80.0
82.0
84.0
Retention Time [min]

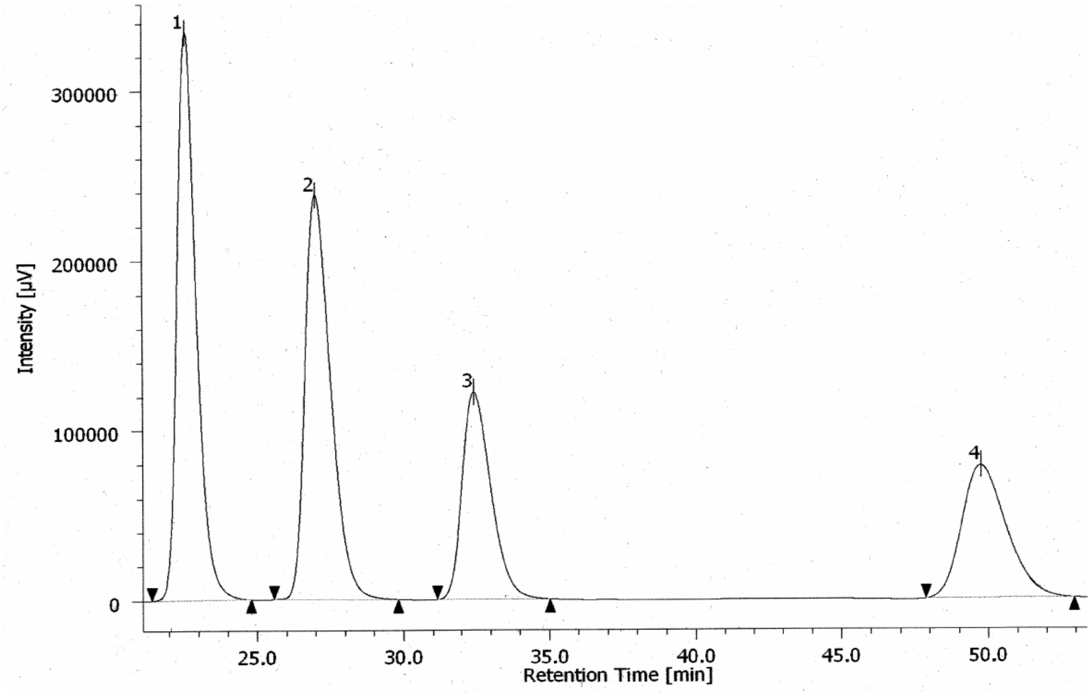

(*S*)-*anti*-**6e**

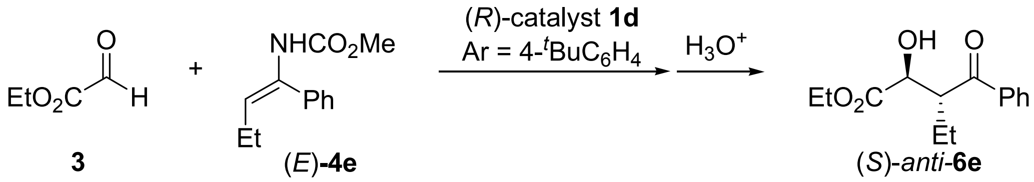
OH
O
EtO_2C
Ph
Et
2.08
1.10
2.10
1.01
2.04
1.05
0.86
2.06
3.06
3.00
PPM
8
7
6
5
4
3
2
1
7.9310
7.9042
7.6261
7.6216
7.6171
7.6030
7.5948
7.5866
7.5717
7.5672
7.5627
7.5046
7.4762
7.4494
7.2600
4.4521
4.4372
4.4148
4.4006
4.1292
4.1024
4.0763
4.0494
3.8586
3.8437
3.8317
3.8168
3.8049
3.7900
3.7050
3.6684
1.9200
1.8932
1.8656
1.8387
1.8119
1.1692
1.1431
1.1163
1.0641
1.0372
1.0096


PPM
200
175
150
125
100
75
50
25
203.8757
173.3752
136.6994
133.5178
128.6874
128.3259
77.4772
77.0000
76.5372
71.3453
61.4388
50.1295
22.2900
13.9454
12.0219

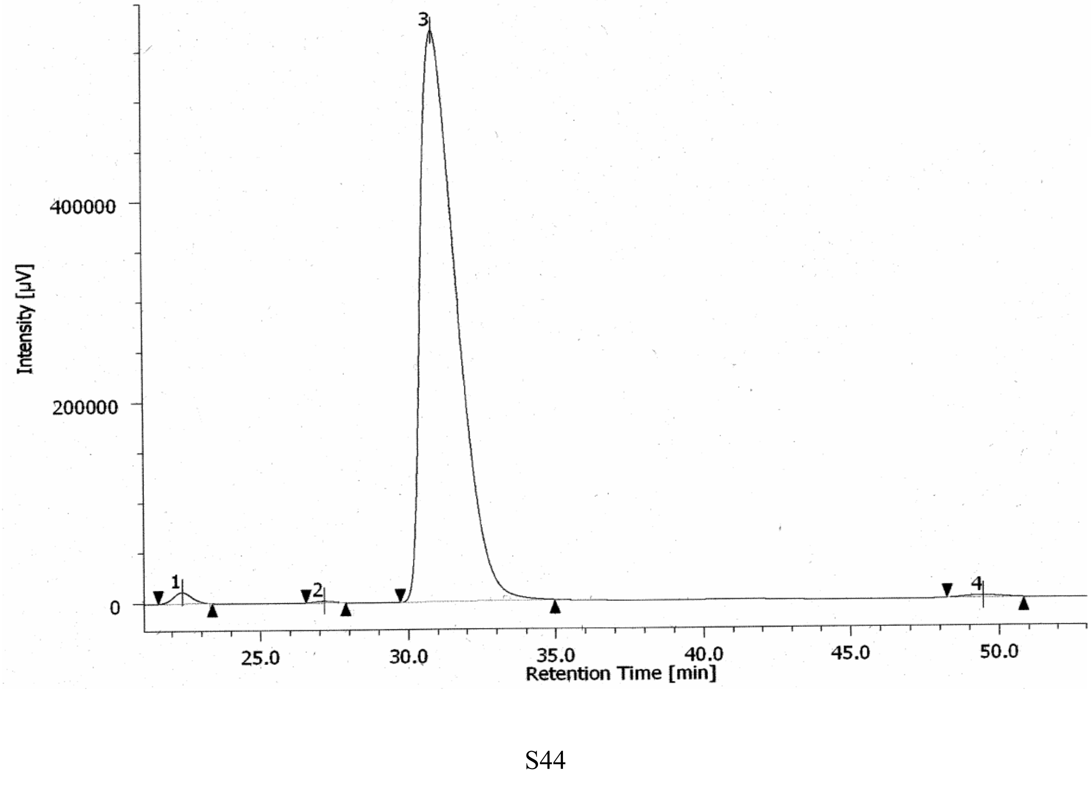


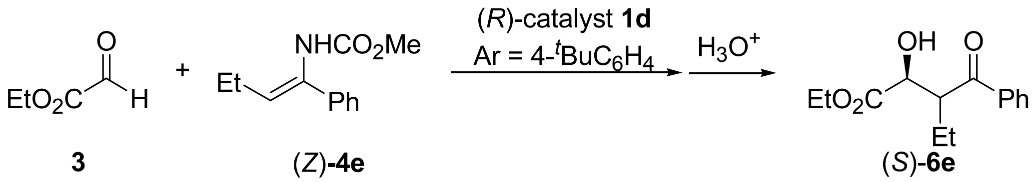
rac-**6e**

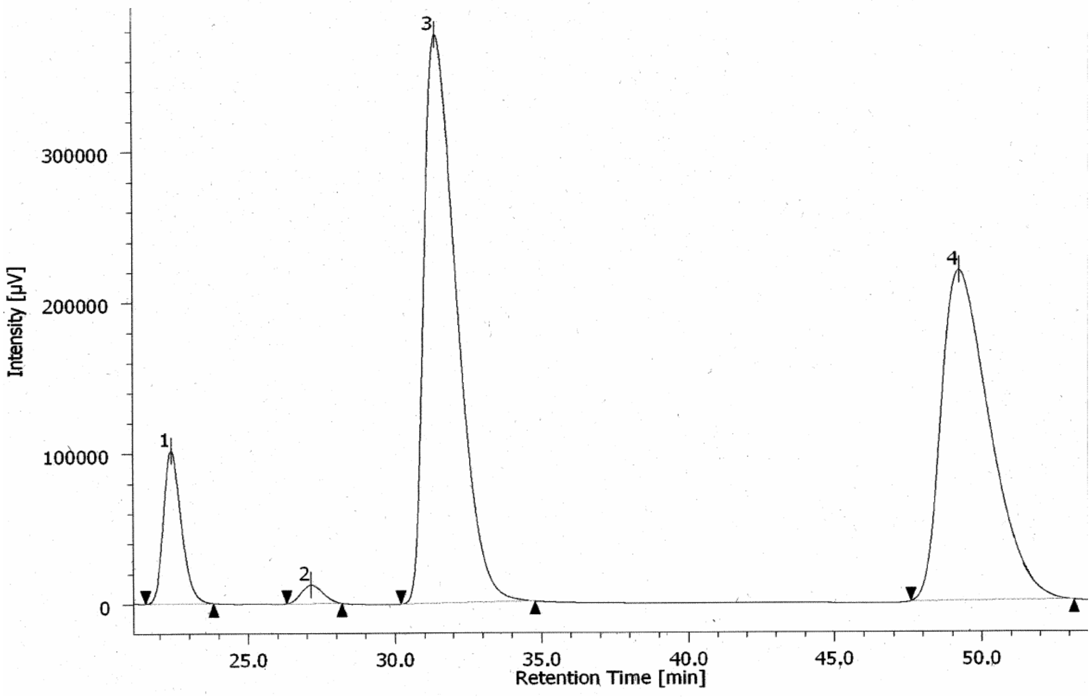


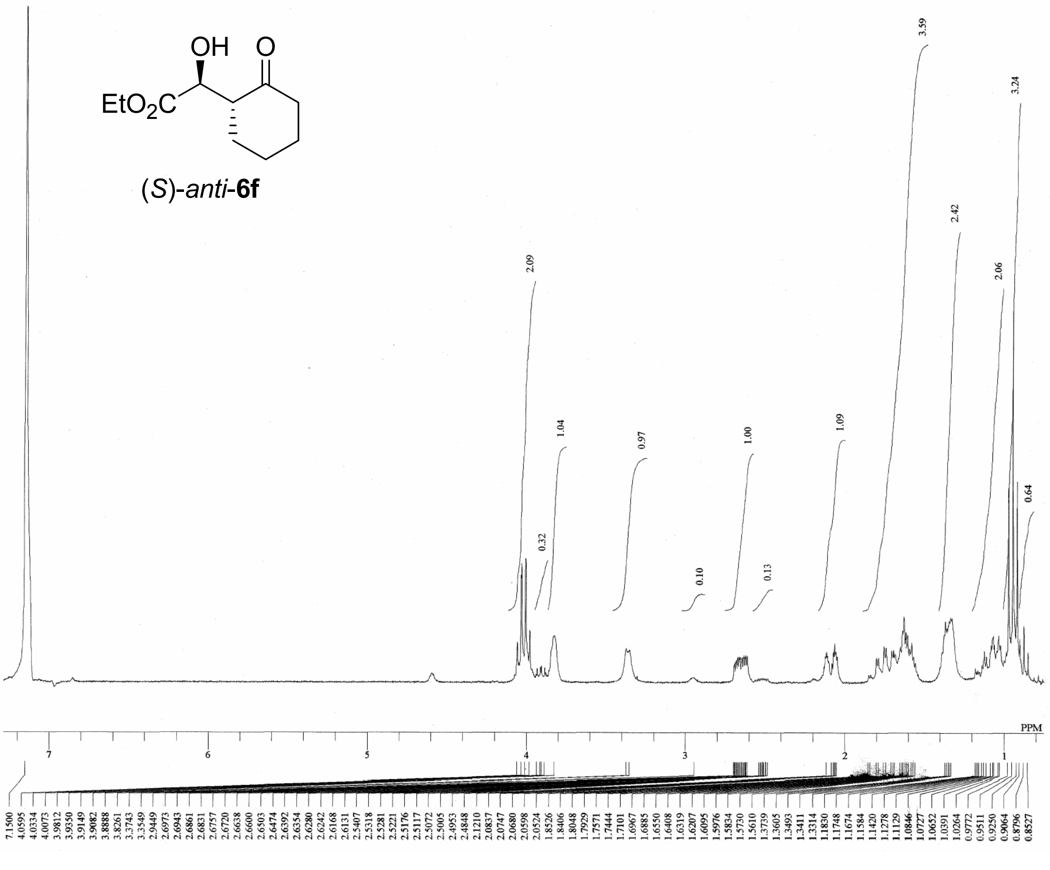


3 (*E*)-**4e** (*S*)-*anti*-**6e**




EtO$_2$C
H
O
3
+
Et
NHCO$_2$Me
Ph
(Z)-4e
(R)-catalyst 1d
Ar = 4-^{t}BuC$_6$H$_4$
H$_3$O$^+$
OH
O
EtO$_2$C
Ph
Et
(S)-6e


1
2
3
4
Intensity [μV]
0
100000
200000
300000
25.0
30.0
35.0
40.0
45.0
50.0
Retention Time [min]


(*S*)-*anti*-**6f**
OH
O
EtO2C
2.09
0.32
1.04
0.97
0.10
1.00
0.13
1.09
3.59
2.42
2.06
3.24
0.64
PPM
7
6
5
4
3
2
1
7.1500
4.0595
4.0334
4.0073
3.9812
3.9350
3.9149
3.9082
3.8888
3.8261
3.3743
3.3549
2.9449
2.6973
2.6943
2.6861
2.6831
2.6757
2.6720
2.6638
2.6600
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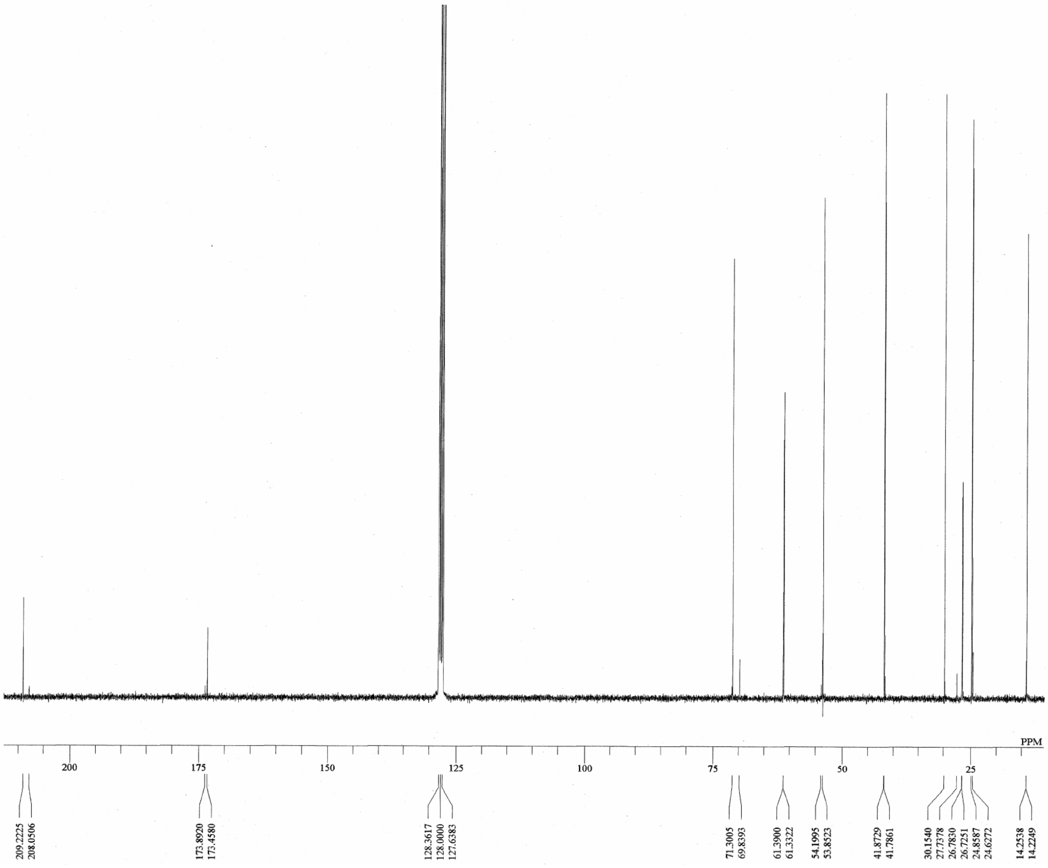
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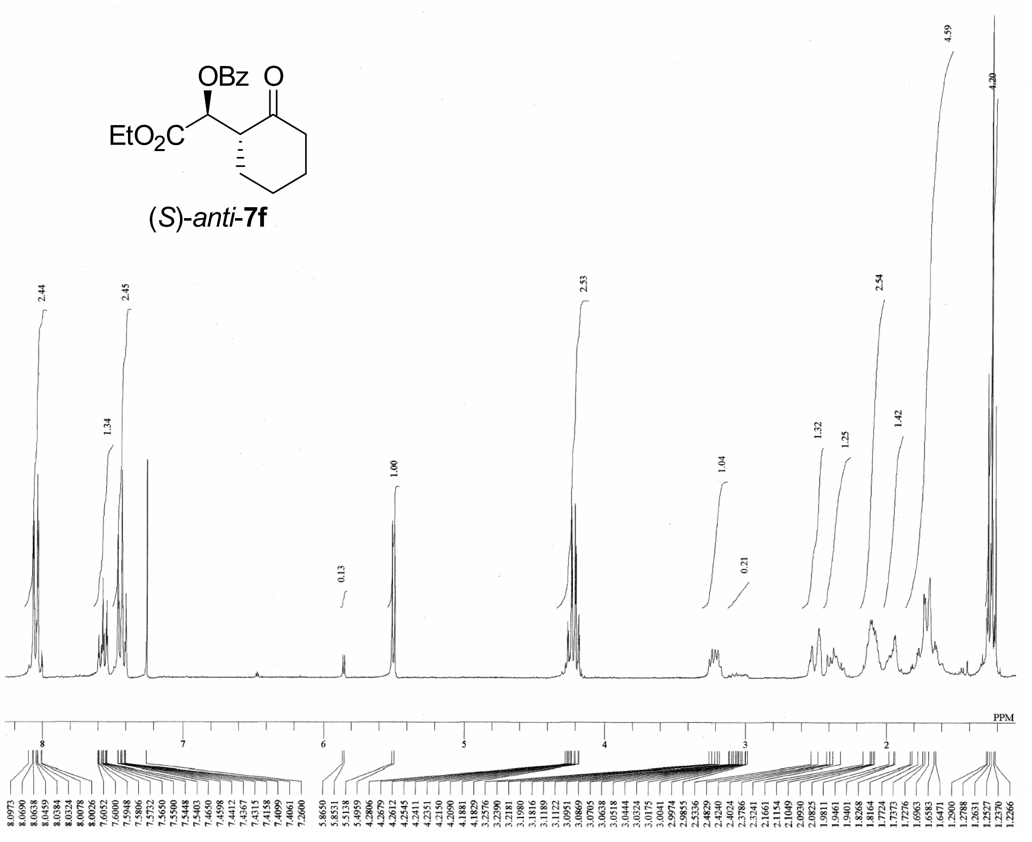
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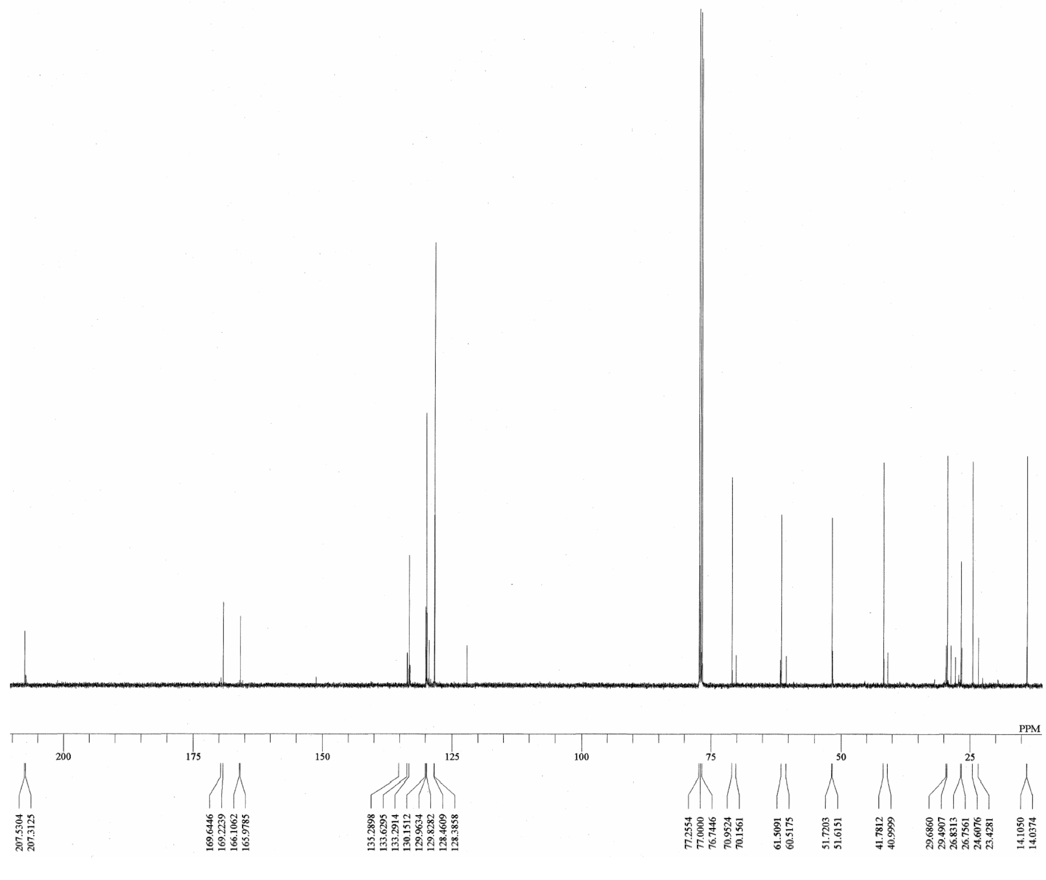
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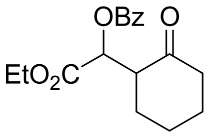
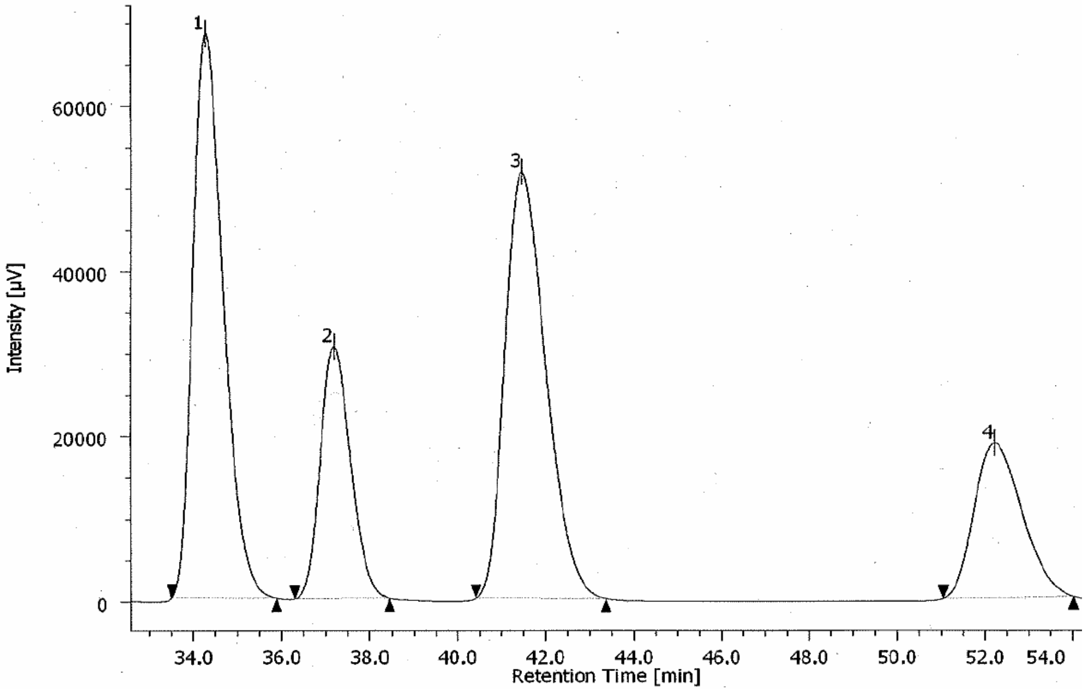
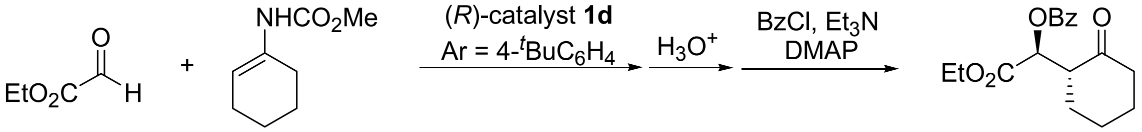
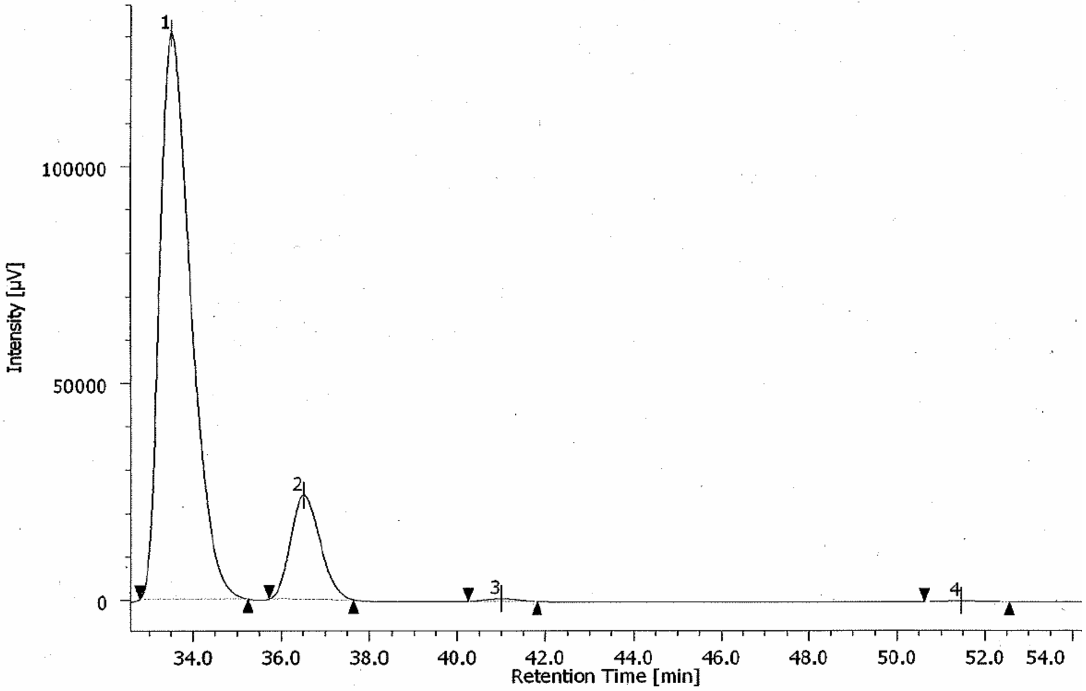


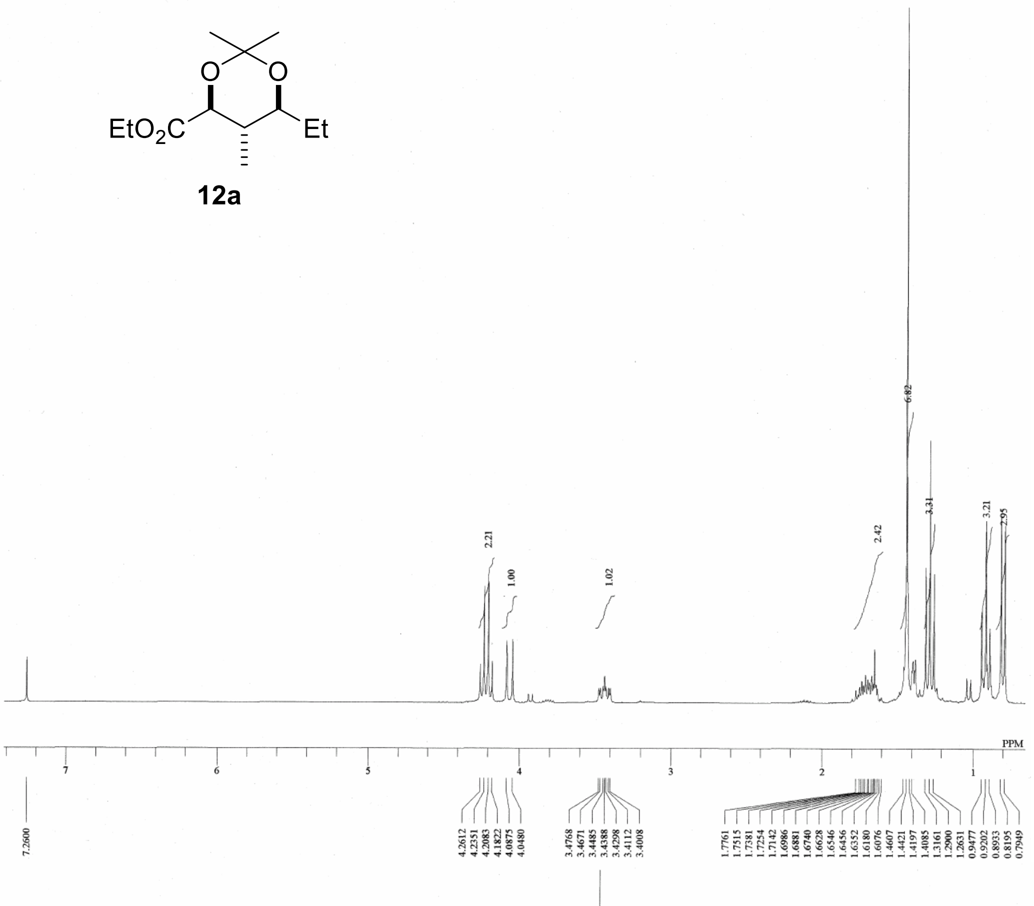
rac-**7f**





3 **4f** (*S*)-*anti*-**7f**





12a

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7
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5
4
3
2
1
PPM
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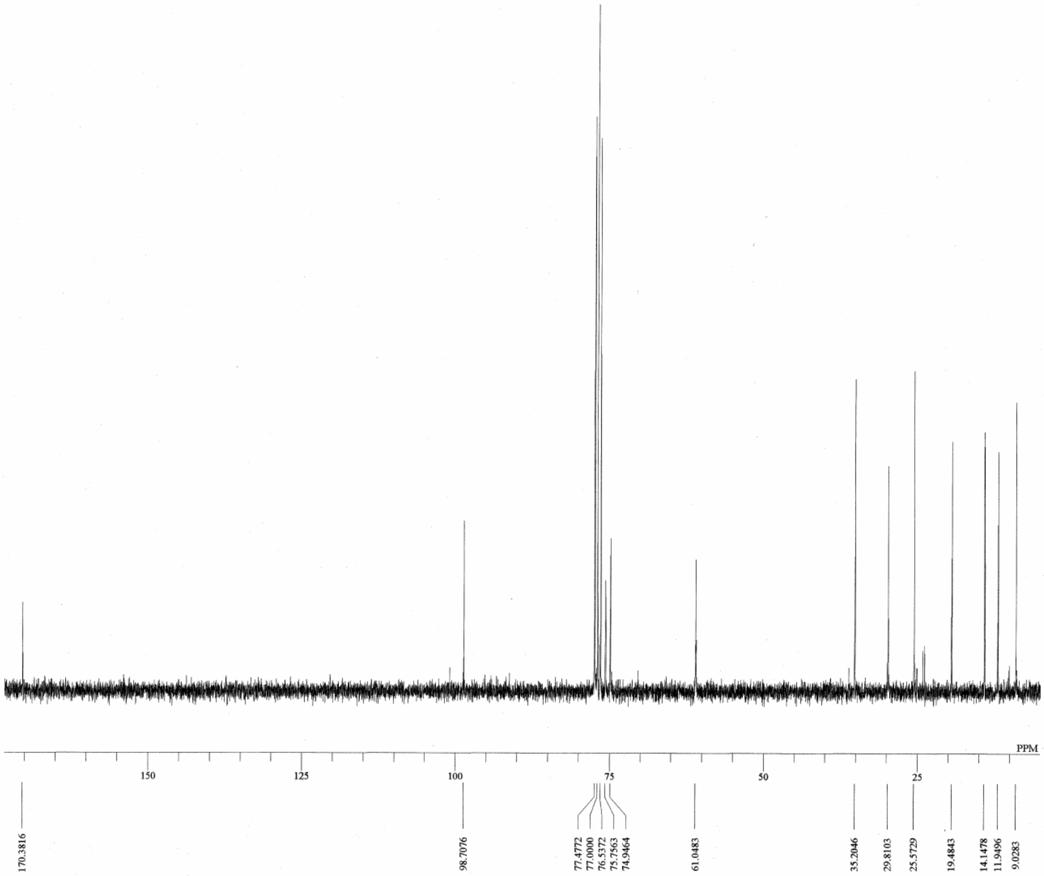

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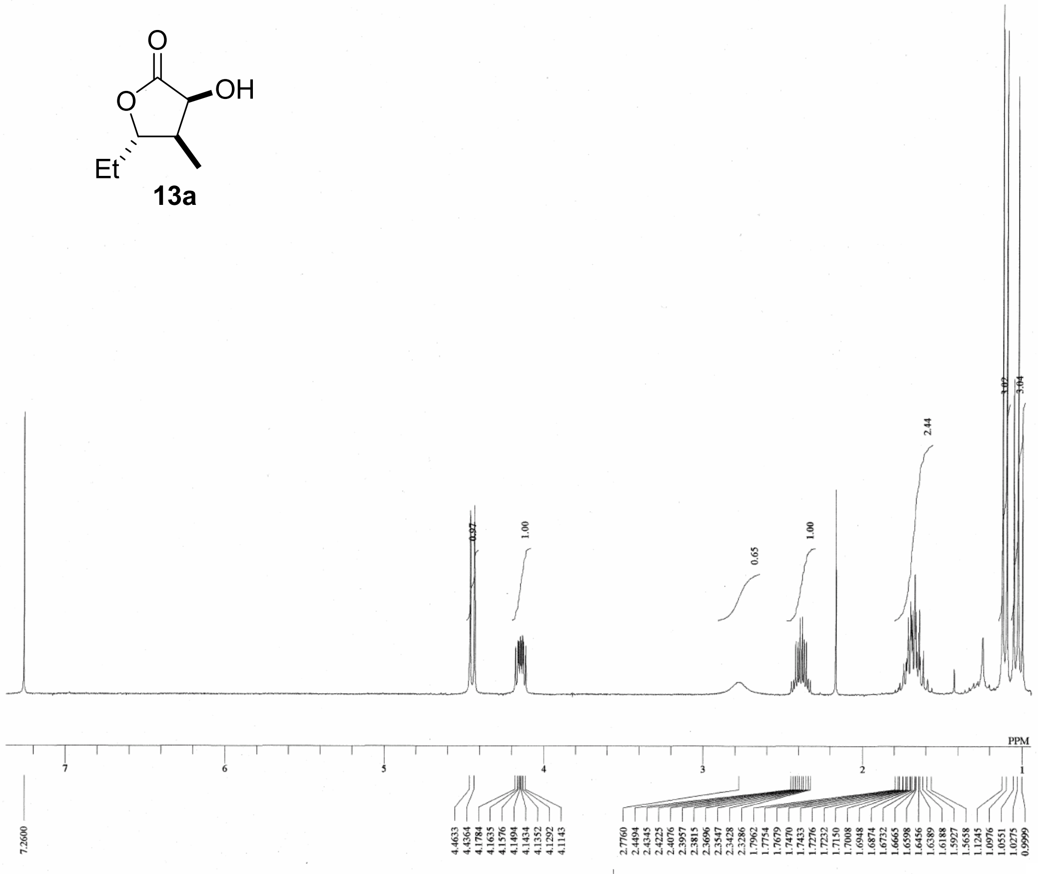
13a

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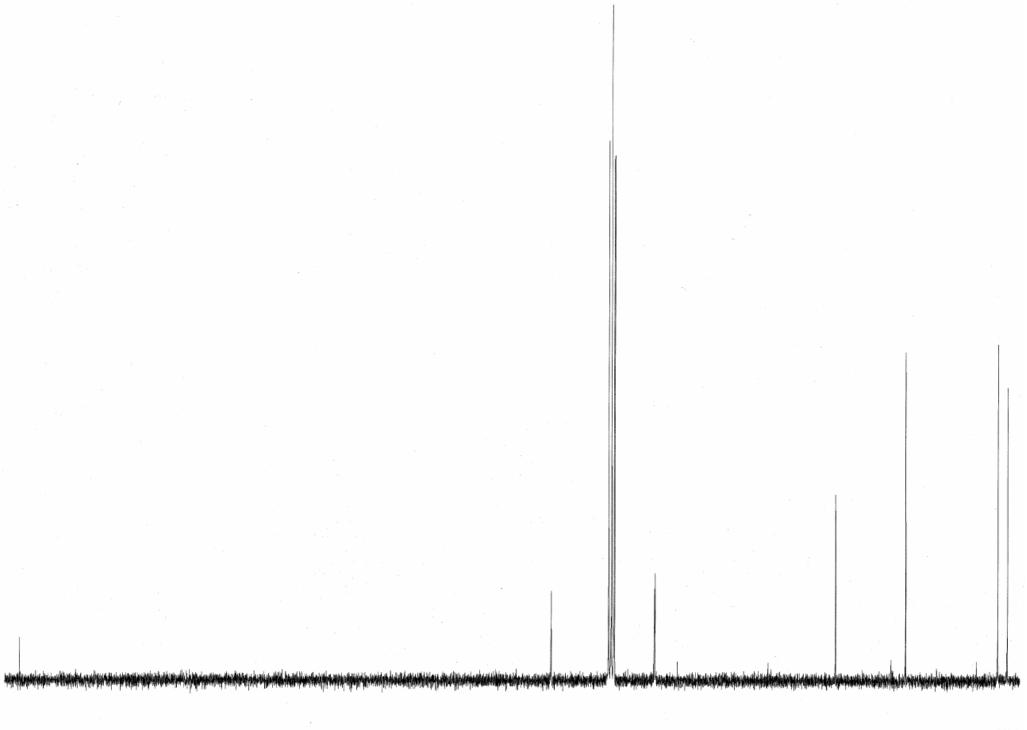
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