Electronic Supplementary Material (ESI) for Chemical Communications

Supplementary Information

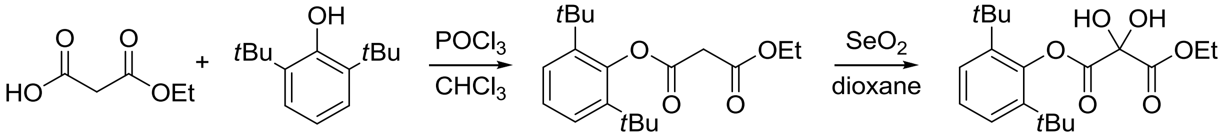
Molecular Recognition of Ketomalonates by Asymmetric Aldol Reaction of Aldehydes with Secondary-Amine Organocatalysts

Taichi Kano, Sunhwa Song and Keiji Maruoka*

Department of Chemistry, Graduate School of Science, Kyoto University
Sakyo, Kyoto 606-8502, Japan

General Information: Infrared (IR) spectra were recorded on a Shimadzu IRPrestige-21 spectrometer. ^{1}H NMR spectra were measured on a JEOL JNM-FX400 (400MHz) spectrometer. Chemical shifts were reported in ppm from tetramethylsilane (in the case of $CDCl_3$) as an internal standard. Data were reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quintet, m = multiplet, br = broad, and app = apparent), and coupling constants (Hz). ^{13}C NMR spectra were recorded on a JEOL JNM-FX400 (100MHz) spectrometer with complete proton decoupling. Chemical shifts were reported in ppm from the residual solvent as an internal standard. High performance liquid chromatography (HPLC) was performed on Shimadzu 10A instruments using Daicel CHIRALPAK AD-H 4.6 mm × 25 cm column. The high-resolution mass spectra (HRMS) were performed on Applied Biosystems Mariner 8295 API-TOF and Bruker microTOF. Optical rotations were measured on a JASCO DIP-1000 digital polarimeter. For thin layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF_{254}, 0.25 mm) were used. The products were purified by flash column chromatography on silica gel 60 (Merck 1.09386.9025, 230-400 mesh). Dichloromethane, acetonitrile and toluene were purchased from Wako Pure Chemistry Co. Inc. Dichloromethane and acetonitrile were stored over 4 Å molecular sieves. Toluene was further purified by passing through neutral alumina under nitrogen atmosphere. Commercially available aldehydes were distilled and stored under argon atmosphere at –17 °C. (*S*)-5-(2-Pyrrolidinyl)-1*H*-tetrazole ((*S*)-**2**) was purchased from Aldrich. Amino sulfonamide (*S*)-**3**[1] was synthesized according to the literature procedure and used after purification by column chromatography. Other simple chemicals were purchased and used as such.

Synthesis of hydrated 1-(2,6-di-*tert*-butylphenyl) 3-ethyl 2-oxomalonate (1c)



To a solution of 2,6-di-*tert*-butylphenol (1.24 g, 6.0 mmol) and ethyl hydrogen malonate (660 μL, 5.0 mmol) in chloroform (12.5 mL) was added $POCl_3$ (2.3 mL, 15.0 mmol) dropwise at room temperature. After 8 h of reflux, the mixture was cooled to 0 °C. The reaction mixture was added $NaHCO_3$ at 0 °C and extracted with CH_2Cl_2.[2] The organic layer was concentrated under vacuum and purified by flash column chromatography on silica gel (hexane/ethyl acetate = 20/1) to afford 2,6-di-*tert*-butylphenyl ethyl malonate (1.33 g, 4.2 mmol, 83% yield). To a solution of the obtained malonate in dioxane (20 mL) was added SeO_2 (702 mg, 6.2 mmol) at room temperature. After 12 h of reflux, the reaction mixture was cooled to room temperature, concentrated and filterated with ethyl acetate.[3] The filtrate was concentrated under vacuum and purified by flash column chromatography on silica gel (hexane/ethyl acetate = 5/1) to afford hydrated oxomalonate **1c** (383 mg, 1.1 mmol, 26% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (1H, d, J = 2.4 Hz, Ar-H), 7.24 (1H, dd, J = 8.4, 2.4 Hz, Ar-H), 6.93 (1H, d, J = 8.4 Hz, Ar-H), 5.02 (2H, s, OH), 4.40 (2H, q, J = 7.2 Hz, $OC\underline{H}_2CH_3$), 1.36 (3H, t, J = 7.2 Hz, $OCH_2C\underline{H}_3$), 1.33 (9H, s, CCH_3), 1.32 (9H, s, CCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 167.4, 149.1, 146.8, 140.1, 124.3, 124.0, 121.7, 90.3, 63.8, 34.7, 34.6, 31.4, 29.9, 13.9; IR (neat) 3447, 2961, 2909, 2870, 1748, 1493, 1209, 1188, 1084 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{19}H_{28}NaO_6$: 375.1778 ($[M + Na]^+$), Found: 375.1783 ($[M + Na]^+$).

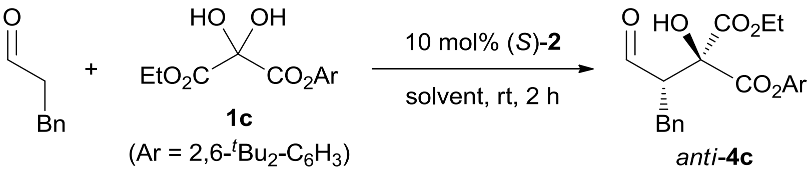
1-(2,6-Dimethylphenyl) 3-ethyl 2-oxomalonate in hydrated form (1a)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11-7.05 (3H, m, Ar-H), 4.91 (2H, s, OH) 4.43 (2H, q, J = 7.2 Hz, $OC\underline{H}_2CH_3$), 2.16 (6H, s, Ar-CH_3), 1.39 (3H, t, J = 7.2 Hz, $OCH_2C\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 166.6, 147.4, 129.9, 128.8, 126.7, 90.2, 64.0, 15.9, 13.9; IR (neat) 3366, 2965, 1775, 1213, 1155, 1088, 789 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{13}H_{16}NaO_6$: 291.0839 ($[M + Na]^+$), Found: 291.0840 ($[M + Na]^+$).

1-(2,6-Di-isopropylphenyl) 3-ethyl 2-oxomalonate in hydrated form (1b)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.24 (1H, m, Ar-H), 7.19 (1H, app s, Ar-H), 7.17 (1H, d, J = 1.2 Hz, Ar-H), 4.90 (2H, s, OH), 4.43 (2H, q, J = 7.2 Hz, $OC\underline{H}_2CH_3$), 2.97 (2H, m, $C\underline{H}CH_3$), 1.42 (3H, t, J = 7.2 Hz, $OCH_2C\underline{H}_3$), 1.18 (12H, d, J = 6.8 Hz $CHC\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 167.5, 144.8, 140.2, 127.4, 124.2, 90.2, 64.1, 26.9, 23.5 (br), 23.0 (br), 13.8; IR (neat) 3447, 2984, 2361, 1746, 1474, 1219, 1157, 1134, 1094, 773 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{17}H_{24}NaO_6$: 347.1465 ($[M + Na]^+$), Found: 347.1460 ($[M + Na]^+$).

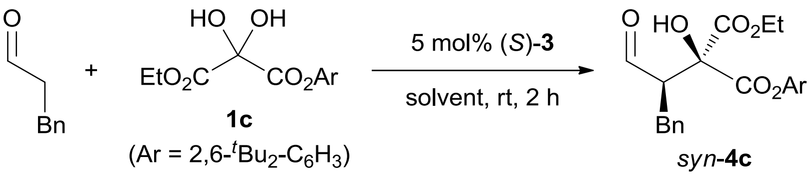
Table S1 *anti*-Selective aldol reactions between 3-phenylpropanal and **1c** catalyzed by (*S*)-**2**[a]



Entry	Solvent	Yield (%)[b]	*anti*/*syn*[c]	ee (%)[d]
1	CH_2Cl_2	88	3.0/1	99
2	Toluene	88	4.1/1	98
3	THF	66	3.6/1	96
4	MeCN	80	3.1/1	98
5	DMF	57	2.6/1	97

[a] The reaction of 3-phenylpropanal (0.125 mmol) with **1c** (0.1 mmol) was performed in the presence of (*S*)-**2** (0.01 mmol) in a solvent (100 μL) at room temperature for 2 h. [b] Isolated yield. [c] Determined by ^{1}H-NMR. [d] The ee of *anti*-**4c** was determined by HPLC using chiral column after conversion to the corresponding γ-lactone.

Table S2 *syn*-Selective aldol reactions between 3-phenylpropanal and **1c** catalyzed by (*S*)-**3** [a]



Entry	Solvent	Yield (%)[b]	*anti*/*syn*[c]	ee (%)[d]
1	CH_2Cl_2	71	1/3.4	92
2	Toluene	90	1/6.2	95
3	THF	74	1/7.3	96
4	MeCN	93	1/2.9	92
5	DMF	82	1/2.8	92

[a] The reaction of 3-phenylpropanal (0.125 mmol) with **1c** (0.1 mmol) was performed in the presence of (*S*)-**3** (0.005 mmol) in a solvent (100 μL) at room temperature for 2 h. [b] Isolated yield. [c] Determined by ^{1}H-NMR. [d] The ee of *syn*-**4c** was determined by HPLC using chiral column after conversion to the corresponding γ-lactone.

General procedure for the *anti*-selective aldol reaction of aldehydes with 1c catalyzed by (*S*)-2

To a stirred solution of hydrated 1-(2,6-di-*tert*-butylphenyl) 3-ethyl 2-oxomalonate **1c** (35 mg, 0.1 mmol) and (*S*)-**2** (1.4 mg, 0.01 mmol) in toluene (100 μL) was added a donor aldehyde (0.125 mmol) at room temperature. After stirring for the time indicated in Table 4, the reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel to afford the corresponding aldol adduct. To a solution of the aldol adduct in dichloromethane (1.0 mL) was added 0.64M solution of L-selectride in THF (0.2 mL, 0.13 mmol) dropwise at –78 °C. After stirring for 1h, the reaction mixture was treated with 1M solution of HCl in diethylether (0.15 mL, 0.15 mmol) and stirred for further 1h. The reaction mixture was then quenched with water and extracted with dichloromethane. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel to afforded the corresponding γ-lactone.

(3*S*,4*R*)-Ethyl 4-methyl-3-hydroxy-2-oxotetrahydrofuran-3-carboxylate (Table 4, entry 1)

$[\alpha]_D^{24}$ –16.2 (*c* 0.2, $CHCl_3$; 95% ee); ^1H NMR (400 MHz, $CDCl_3$) *δ* 4.54 (1H, dd, *J* = 8.8, 7.2 Hz, OC$\underline{H}$H), 4.35 (2H, app qd, *J* = 7.2, 2.0 Hz, OC$\underline{H}_2$$CH_3$), 4.05 (1H, dd, *J* = 8.8, 7.2 Hz, OCH$\underline{H}$), 3.72 (1H, s, OH), 2.99-2.90 (1H, m, CH), 1.33 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$), 1.11 (3H, d, *J* = 7.2 Hz, $CHC\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 170.2, 167.7, 77.4, 72.7, 63.6, 38.7, 14.0, 10.4; IR (neat) 3480, 2963, 2359, 1786, 1746, 1267, 1165, 1017, 772 cm^{-1}; HRMS (ESI-TOF) Calcd. $C_8H_{12}NaO_5$: 211.0577 ($[M + Na]^+$), Found: 211.0575 ($[M + Na]^+$); Daicel Chiralpak AD-H, hexane/2-propanol = 10/1, flow rate 0.5 mL/min, λ = 230 nm, retention time: 23.6 min (minor) and 25.6 min (major).

(3*S*,4*R*)-Ethyl 4-ethyl-3-hydroxy-2-oxotetrahydrofuran-3-carboxylate (Table 4, entry 2)

$[\alpha]_D^{25}$ –10.1 (*c* 0.5, $CHCl_3$; 97% ee); ^1H NMR (400 MHz, $CDCl_3$) *δ* 4.51 (1H, dd, *J* = 8.8, 7.6 Hz, OC$\underline{H}$H), 4.36 (2H, q, *J* = 7.2 Hz, $OC\underline{H}_2CH_3$), 4.10 (1H, app t, 8.8 Hz, OCH$\underline{H}$), 3.79 (1H, s, OH), 2.87-2.79 (1H, m, CH), 1.76-1.65 (1H, m, $C\underline{H}HCH_3$), 1.53-1.42 (1H, m, $CH\underline{H}CH_3$), 1.34 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$), 0.91 (3H, t, *J* = 7.6 Hz, $CH_2C\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 173.2, 170.7, 76.8, 71.3, 63.6, 45.4, 18.5, 14.0, 11.2; IR (neat) 3466, 2970, 2918, 1786, 1738, 1466, 1368, 1256, 1155, 1045, 1007 cm^{-1}; HRMS (ESI-TOF) Calcd. $C_9H_{14}NaO_5$: 225.0733 ($[M + Na]^+$), Found: 225.0720 ($[M + Na]^+$); Daicel Chiralpak AD-H, hexane/2-propanol = 20/1, flow rate 0.5 mL/min, λ = 210 nm, retention time: 37.9 min (minor) and 41.7 min (major).

(3*S*,4*R*)-Ethyl 4-benzyl-3-hydroxy-2-oxotetrahydrofuran-3-carboxylate (Table 4, entry 3)

$[\alpha]_D^{25}$ 13.0 (*c* 0.7, $CHCl_3$; 98% ee); ^1H NMR (400 MHz, $CDCl_3$) *δ* 7.30-7.26 (2H, m, Ar-H), 7.24-7.16 (3H, m, Ar-H), 4.46 (1H, dd, *J* = 8.8, 7.6 Hz, OC$\underline{H}$H), 4.19 (1H, app t, *J* = 8.8 Hz, OCH$\underline{H}$), 4.11 (1H, dq, *J* = 10.8, 7.2 Hz, $OC\underline{H}HCH_3$), 4.02 (1H, dq, *J* = 10.8, 7.2 Hz, $OCH\underline{H}CH_3$), 3.88 (1H, s, OH), 3.26-3.17 (1H, m, CH), 2.99 (1H, dd, *J* = 14.0, 8.4 Hz, C$\underline{H}$HPh), 2.70 (1H, dd, *J* = 14.0, 7.2 Hz, CH$\underline{H}$Ph), 1.14 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 172.8, 169.8, 137.5, 129.0, 128.6, 126.9, 76.6, 70.9, 63.4, 45.7, 31.0, 13.8 ; IR (neat) 3462, 2970, 2361, 1740, 1368, 1229, 1020, 746, 702 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{14}H_{16}NaO_5$: 287.0890 ($[M + Na]^+$), Found: 287.0886 ($[M + Na]^+$); Daicel Chiralpak AD-H, hexane/2-propanol = 10/1, flow rate 0.5 mL/min, λ = 210 nm, retention time: 25.8 min (major) and 29.5 min (minor).

(3*S*,4*R*)-Ethyl 4-(cyclohexylmethyl)-3-hydroxy-2-oxotetrahydrofuran-3-carboxylate (Table 4, entry 4)

$[\alpha]^{18}_{D}$ 7.4 (*c* 0.5, $CHCl_3$; 96% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.48 (1H, dd, *J* = 8.8, 7.6 Hz, OC<u>H</u>H), 4.35 (2H, app qd, *J* = 7.2, 1.2 Hz, OCH_2CH_3), 4.06 (1H, dd, *J* = 9.2, 8.8 Hz, OCH<u>H</u>), 3.75 (1H, s, OH), 3.07-2.99 (1H, m, CH), 1.70-1.66 (5H, m, CH_2<u>Cy</u>), 1.60-1.53 (1H, m, C<u>H</u>HCy), 1.34 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$), 1.34-1.11 (5H, m, CH_2<u>Cy</u>, CH<u>H</u>Cy), 0.91-0.82 (2H, m, CH_2<u>Cy</u>); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 170.7, 76.8, 71.8, 63.5, 41.1, 35.0, 33.5, 33.2, 32.4, 26.3, 26.1 (two peaks overlap), 14.0; IR (neat) 3468, 2924, 2851, 2359, 1788, 1738, 1449, 1267, 1252, 1225, 1182, 1155, 1020, 773 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{14}H_{22}NaO_5$: 293.1359 ($[M + Na]^+$), Found: 293.1360 ($[M + Na]^+$); Daicel Chiralpak AD-H, hexane/2-propanol = 10/1, flow rate 0.5 mL/min, λ = 230 nm, retention time: 19.2 min (major) and 28.6 min (minor).

(3*S*,4*R*)-Ethyl 3-hydroxy-4-isopropyl-2-oxotetrahydrofuran-3-carboxylate (Table 4, entry 5)
$[\alpha]^{25}_{D}$ 18.1 (*c* 0.9, $CHCl_3$; 96% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.50 (1H, dd, *J* = 8.8, 7.6 Hz, OC<u>H</u>H), 4.38 (1H, dq, *J* = 10.8, 7.2 Hz, OC<u>H</u>HCH_3), 4.34 (1H, dq, *J* = 10.8, 7.2 Hz, OCH<u>H</u>CH_3), 4.14 (1H, dd, *J* = 10.0, 8.8 Hz, OCH<u>H</u>), 3.83 (1H, s, OH), 2.68-2.61 (1H, m, CH), 2.12-2.03 (1H, m, $C\underline{H}(CH_3)_2$), 1.34 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$), 0.90 (3H, d, *J* = 6.8 Hz, $CH(C\underline{H}_3)(CH_3)$), 0.87 (3H, d, *J* = 6.8 Hz, $CH(CH_3)(C\underline{H}_3)$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 171.1, 76.8, 70.9, 63.5, 50.5, 25.4, 20.5, 19.6, 14.0; IR (neat) 3466, 2967, 2874, 1786, 1738, 1474, 1366, 1260, 1223, 1157, 1111, 1020 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{10}H_{16}NaO_5$: 239.0890 ($[M + Na]^+$), Found: 239.0892 ($[M + Na]^+$); Daicel Chiralpak AD-H, hexane/2-propanol = 20/1, flow rate 0.5 mL/min, λ = 208 nm, retention time: 17.8 min (major) and 19.2 min (minor).

General procedure for the *syn*-selective aldol reaction of aldehydes with 1c catalyzed by (*S*)-3

To a stirred solution of hydrated 1-(2,6-di-*tert*-butylphenyl) 3-ethyl 2-oxomalonate **1c** (35 mg, 0.1 mmol) and (*S*)-**3** (2.0 mg, 0.005 mmol) in toluene (100 μL) was added a donor aldehyde (0.125 mmol) at room temperature. After stirring for the time indicated in Table 4, the reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel to afford the corresponding aldol adduct. To a solution of the aldol adduct in dichloromethane (2.0 mL) was added 0.64M solution of L-selectride in THF (0.2 mL, 0.13 mmol) dropwise at –78 °C. After stirring for 1h, the reaction mixture was quenched with water and extracted with dichloromethane. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel to affored the corresponding γ-lactone.

(3*S*,4*S*)-Ethyl 4-methyl-3-hydroxy-2-oxotetrahydrofuran-3-carboxylate (Table 4, entry 6)
$[\alpha]^{24}_{D}$ –4.7 (*c* 0.1, $CHCl_3$; 97% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.46 (1H, app t, *J* = 8.8 Hz, OC<u>H</u>H), 4.40 (1H, qd, *J* = 7.2, 3.6 Hz, OC<u>H</u>HCH_3), 4.34 (1H, qd, *J* = 7.2, 3.6 Hz, OCH<u>H</u>CH_3), 4.09 (1H, dd, 11.2, 8.8 Hz, OCH<u>H</u>), 3.81 (1H, s, OH), 2.86-2.79 (1H, m, CH), 1.35 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$), 1.10 (3H, d, *J* = 6.8

Hz, $CHCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4 168.8, 79.3, 70.7, 63.5, 41.4, 14.2, 11.3; IR (neat) 2969, 2361, 2340, 1788, 1746, 1262, 1219, 1020, 768 cm^{-1}; HRMS (ESI-TOF) Calcd. $C_8H_{12}NaO_5$: 211.0577 ($[M + Na]^+$), Found: 211.0579 ($[M + Na]^+$); Daicel Chiralpak AD-H, hexane/2-propanol = 10/1, flow rate 0.5 mL/min, λ = 230 nm, retention time: 32.6 min (minor) and 34.5 min (major).

(3*S*,4*S*)-Ethyl 4-ethyl-3-hydroxy-2-oxotetrahydrofuran-3-carboxylate (Table 4, entry 7)

$[\alpha]_D^{25}$ –67.6 (*c* 0.2, $CHCl_3$; 95% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.50 (1H, dd, *J* = 8.8, 8.4 Hz, OCHH), 4.39 (1H, dq, *J* = 10.8, 7.2 Hz, $OCHHCH_3$), 4.33 (1H, dq, *J* = 10.8, 7.2 Hz, $OCHHCH_3$), 4.09 (1H, dd, 11.2, 8.8 Hz, OCHH), 3.78 (1H, s, OH), 2.73-2.64 (1H, m, CH), 1.69-1.58 (1H, m, $CHHCH_3$), 1.45-1.36 (1H, m, $CHHCH_3$), 1.35 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 0.98 (3H, t, *J* = 7.6 Hz, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 168.9, 79.2, 70.0, 63.4, 48.0, 20.1, 14.1, 11.6; IR (neat) 3478, 2969, 2938, 2359, 1786, 1748, 1117, 1017, 912, 744 cm^{-1}; HRMS (ESI-TOF) Calcd. $C_9H_{14}NaO_5$: 225.0733 ($[M + Na]^+$), Found: 225.0730 ($[M + Na]^+$); Daicel Chiralpak AD-H, hexane/2-propanol = 10/1, flow rate 0.5 mL/min, λ = 235 nm, retention time: 29.4 min (minor) and 34.6 min (major).

(3*S*,4*S*)-Ethyl 4-benzyl-3-hydroxy-2-oxotetrahydrofuran-3-carboxylate (Table 4, entry 8)

$[\alpha]_D^{25}$ –157.6 (*c* 0.1, $CHCl_3$; 95% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.23 (3H, m, Ar-H), 7.15-7.13 (2H, m, Ar-H), 4.47 (1H, dq, *J* = 10.8, 7.2 Hz, $OCHHCH_3$), 4.39 (1H, dq, *J* = 10.8, 7.2 Hz, $OCHHCH_3$), 4.26 (1H, app t, *J* = 8.4 Hz, OCHH), 4.22 (1H, dd, *J* = 9.6, 9.2 Hz, OCHH), 3.84 (1H, s, OH), 3.09-3.03 (1H, m, CH), 3.03 (1H, dd, *J* = 14.8, 4.8 Hz, CHHPh), 2.54 (1H, dd, *J* = 14.8, 11.6 Hz, CHHPh), 1.41 (3H, t, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 168.7, 136.9, 128.9, 128.4, 127.1, 78.8, 69.8, 63.7, 48.0, 33.0, 14.2; IR (neat) 3462, 2980, 2918, 2359, 1786, 1746, 1140, 1018, 747, 702 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{14}H_{16}NaO_5$: 287.0890 ($[M + Na]^+$), Found: 287.0886 ($[M + Na]^+$); Daicel Chiralpak AD-H, hexane/2-propanol = 10/1, flow rate 0.5 mL/min, λ = 210 nm, retention time: 30.1 min (minor) and 32.9 min (major).

(3*S*,4*S*)-Ethyl 4-(cyclohexylmethyl)-3-hydroxy-2-oxotetrahydrofuran-3-carboxylate (Table 4, entry 9)

$[\alpha]_D^{18}$ –55.0 (*c* 0.2, $CHCl_3$; 95% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.47 (1H, app t, *J* = 8.8 Hz, OCHH), 4.39 (1H, dq, *J* = 10.8, 7.2 Hz, $OCHHCH_3$), 4.33 (1H, dq, *J* = 10.8, 7.2 Hz, $OCHHCH_3$), 4.09 (1H, dd, *J* = 11.2, 8.8 Hz, OCHH), 3.77 (1H, s, OH), 2.91-2.82 (1H, m, CH), 1.71-1.66 (5H, m, CH_2Cy), 1.49-1.43 (1H, m, CHHCy), 1.34 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 1.28-1.12 (5H, m, CH_2Cy, CHHCy), 0.92-0.85 (2H, m, CH_2Cy); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 169.0, 79.2, 70.3, 63.4, 43.9, 35.2, 34.6, 33.6, 33.1, 26.3, 26.0 (two peaks overlap), 14.1; IR (neat) 3466, 2924, 2851, 2361, 1786, 1749, 1449, 1136, 1016, 772 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{14}H_{22}NaO_5$: 293.1359 ($[M + Na]^+$), Found: 293.1360 ($[M + Na]^+$); Daicel Chiralpak AD-H, hexane/2-propanol = 10/1, flow rate 0.5 mL/min, λ = 240 nm, retention time: 29.0 min (major) and 31.8 min (minor).

(3*S*,4*S*)-Ethyl 3-hydroxy-4-isopropyl-2-oxotetrahydrofuran-3-carboxylate (Table 4, entry 10)

$[\alpha]_D^{25}$ –76.3 (*c* 0.3, $CHCl_3$; 96% ee); ^1H NMR (400 MHz, $CDCl_3$) δ 4.47 (1H, dd, *J* = 8.8, 8.4 Hz, OC<u>H</u>H), 4.38 (1H, dq, *J* = 10.8, 7.2 Hz, OC<u>H</u>HCH_3), 4.34 (1H, dq, *J* = 10.8, 7.2 Hz, OCH<u>H</u>CH_3), 4.14 (1H, dd, *J* = 10.8, 8.8 Hz, OCH<u>H</u>), 3.75 (1H, s, OH), 2.47-2.40 (1H, m, CH), 1.77-1.68 (1H, m, C<u>H</u>$(CH_3)_2$), 1.34 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$), 1.01 (3H, d, *J* = 6.8 Hz, $CH(C\underline{H}_3)(CH_3)$), 0.91 (3H, d, *J* = 6.8 Hz, $CH(CH_3)(C\underline{H}_3)$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 169.1, 79.1, 69.7, 63.4, 53.0, 28.1, 20.8, 20.6, 14.1; IR (neat) 3476, 2967, 2878, 2359, 2340, 1786, 1749, 1123, 1018, 912, 744 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{10}H_{16}NaO_5$: 239.0890 ($[M + Na]^+$), Found: 239.0893 ($[M + Na]^+$); Daicel Chiralpak AD-H, hexane/2-propanol = 10/1, flow rate 0.5 mL/min, λ = 220 nm, retention time: 23.5 min (major) and 25.0 min (minor).

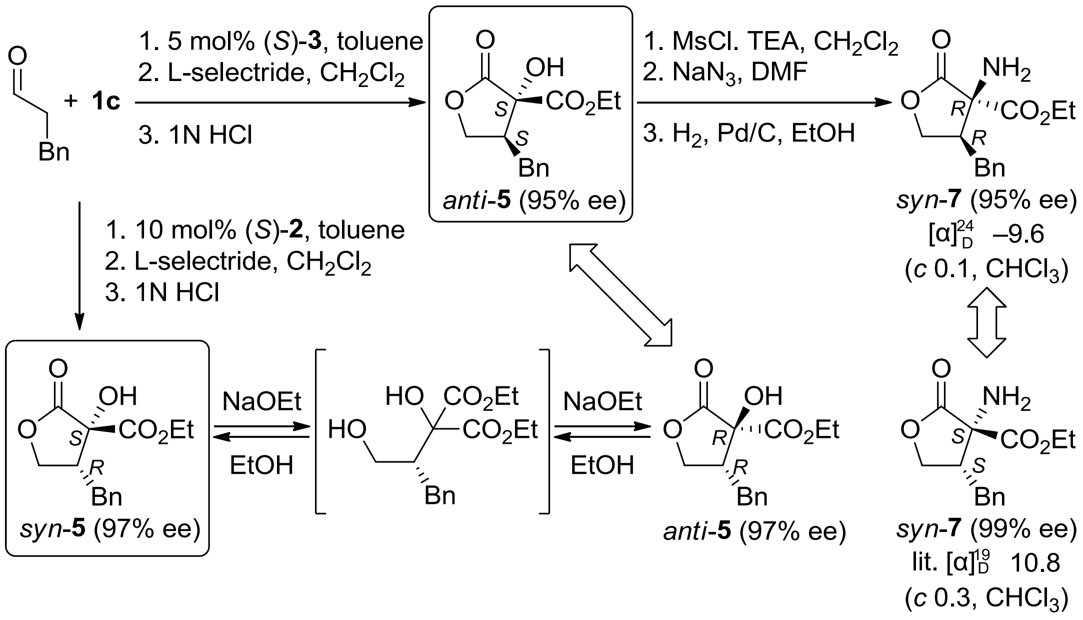
Synthesis of ethyl (3*R*,4*R*)-3-amino-4-benzyl-2-oxotetrahydrofuran-3-carboxylate (*syn*-7)

To a solution of γ-lactone *anti*-**5** (14 mg, 0.05 mmol) and triethylamine (15 μL, 0.115 mmol) in dichloromethane (80 μL) was added $MeSO_2Cl$ (4.6 μL, 0.06 mmol) dropwise at 0 °C argon atmosphere. After stirring at 0 °C for 12 h, the reaction mixture was added NH_4Cl and extracted with CH_2Cl_2. The organic layer was concentrated under vacuum and purified by flash column chromatography on silica gel (hexane/ethyl acetate = 5/1) to afford the mesylated γ-lactone *anti*-**6** (10.6 mg, 0.031 mmol, 62% yield).

To a solution of obtained *anti*-**6** (1.8mg, 0.005 mmol) in anhydrous DMF (25 μL) was added NaN_3 (1.0 mg, 0.015 mmol) at room temperature. After stirring for 24 h, the reaction mixture was added NH_4Cl to quench excess azide and extracted with EtOAc. The organic layer was concentrated under vacuum and roughly purified by flash column chromatography on silica gel (hexane/ethyl acetate = 5/1) to afford the corresponding α-azido-γ-lactone. To a solution of the obtained α-azido-γ-lactone and 10% Pd/C (0.2 mg) in EtOH (0.1 mL) was stirred at room temperature under hydrogen atmosphere for 24 h. After filtration through celite, the filtrate was concentrated under vacuum and purified by flash column chromatography on silica gel (hexane/ethyl acetate = 3/1) to afford amino lactone (1.3 mg, 0.005 mmol, 99% yield for two steps). ^1H NMR, ^{13}C NMR and IR match those reported in the literature.[4] $[\alpha]_D^{24}$ –9.6 (*c* = 0.1, $CHCl_3$; 95% ee); HPLC analysis: Daicel Chiralpak AS-H, hexane/2-propanol = 10/1, flow rate 0.5 mL/min, λ = 210 nm, retention time: 56.1 min (minor) and 71.4 min (major).

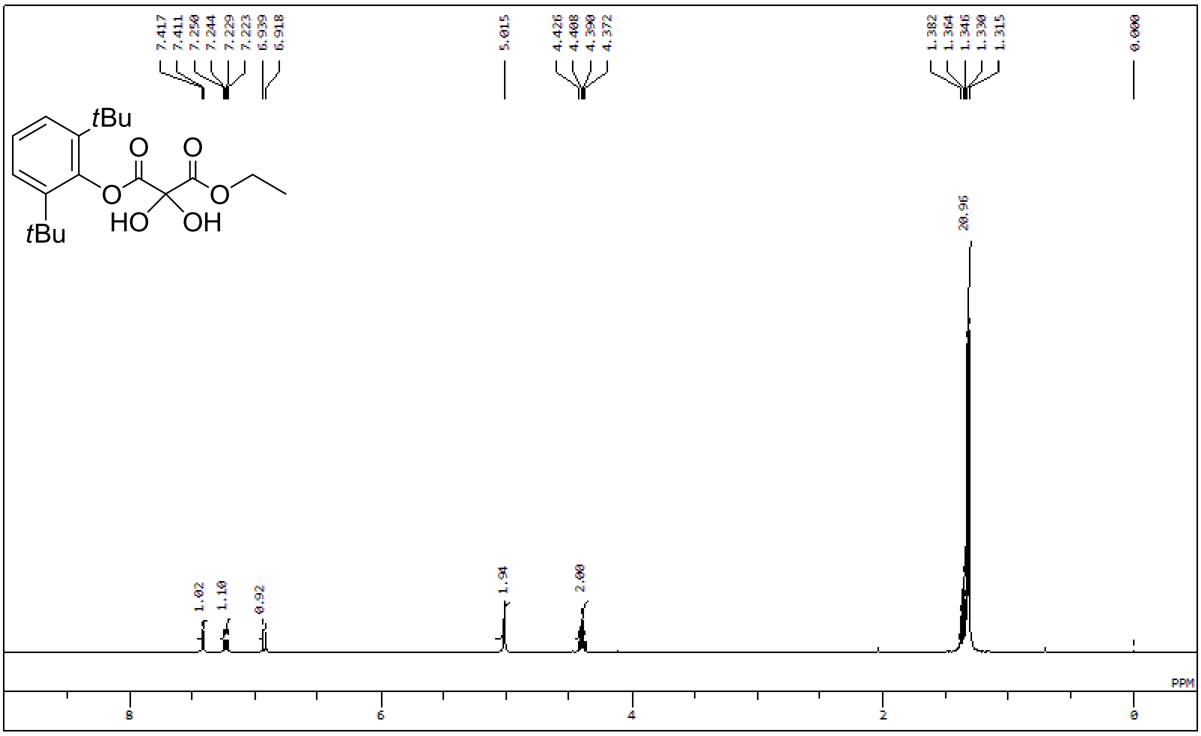
Determination of the absolute stereochemistry of *syn*-5 and *anti*-5

The relative and absolute configuration of *anti*-**5** was determined to be (3*S*,4*S*) by converting to *syn*-**7** as described above and by comparison of the sign of the optical rotation with the reported value.[4] Based on this information, the absolute configuration of *syn*-**5** obtained in the reaction catalyzed by (*S*)-**2** was determined to be (3*S*,4*R*) by converting to *anti*-**5** using NaOEt and by comparison of the HPLC retention times.



References

1. Y.-G.Wang and K. Maruoka, *Org. Process Res. Dev.*, 2007, **11**, 628.
2. (*a*) I. Jabin, G. Revial, N. Monnier-Benoit and P. Netchitaïlo, *J. Org. Chem.*, 2001, **66**, 256; (*b*) M. Black, J. I. G. Cadogan and H. McNab, *Org. Biomol. Chem.*, 2010, **8**, 2961.
3. S. Astin, A. C. C. Newman and H. L. Riley, *J. Chem. Soc.*, 1933, 391.
4. T. Kano, S. Song, Y. Kubota and K. Maruoka, *Angew. Chem. Int. Ed.*, 2012, **51**, 1191.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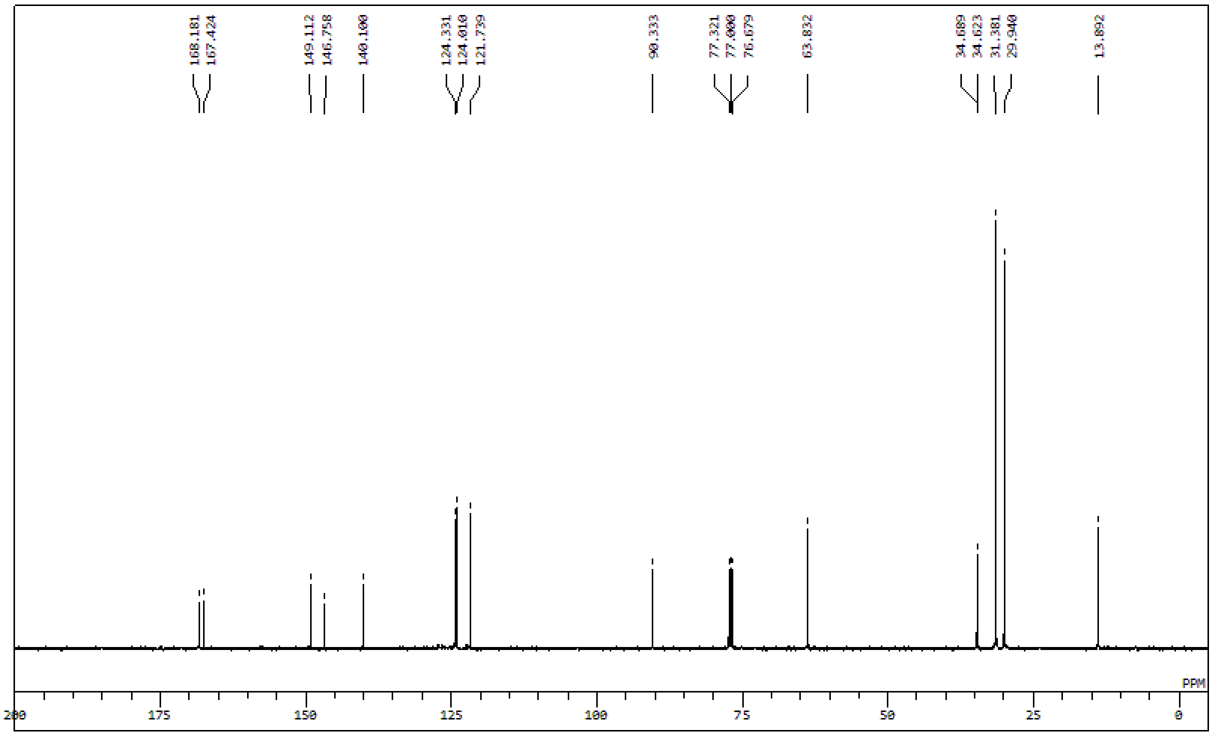
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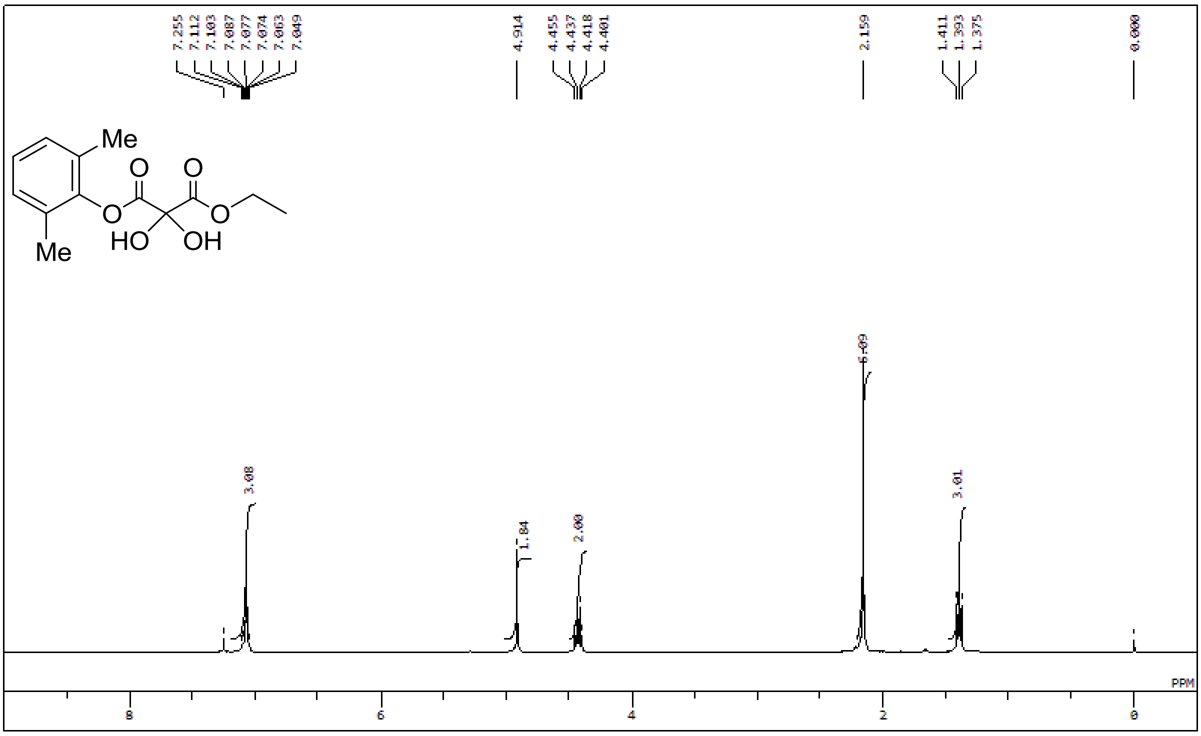
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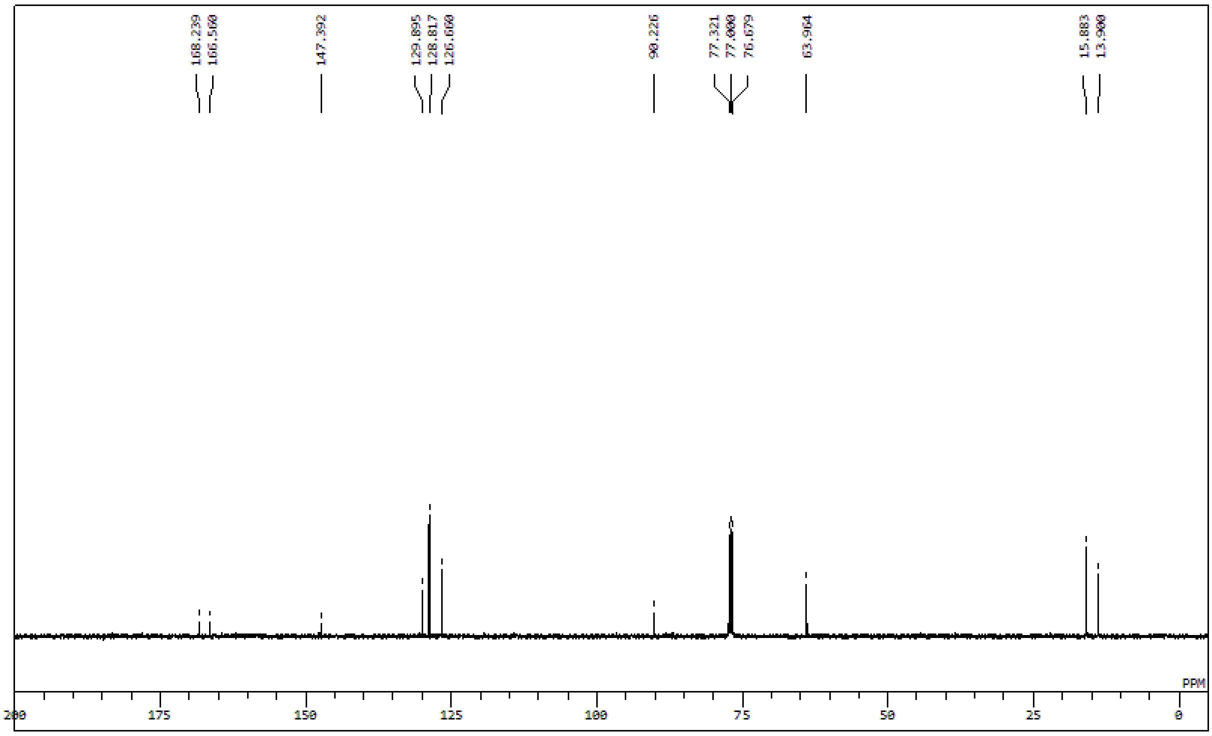
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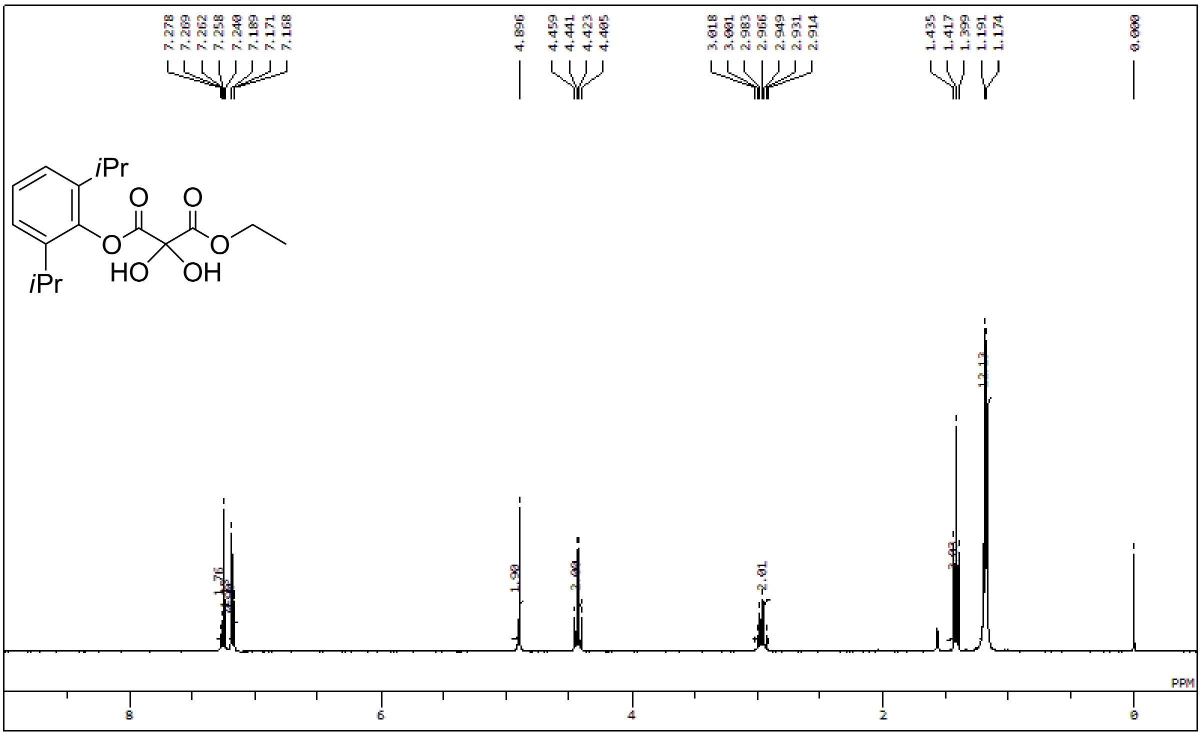
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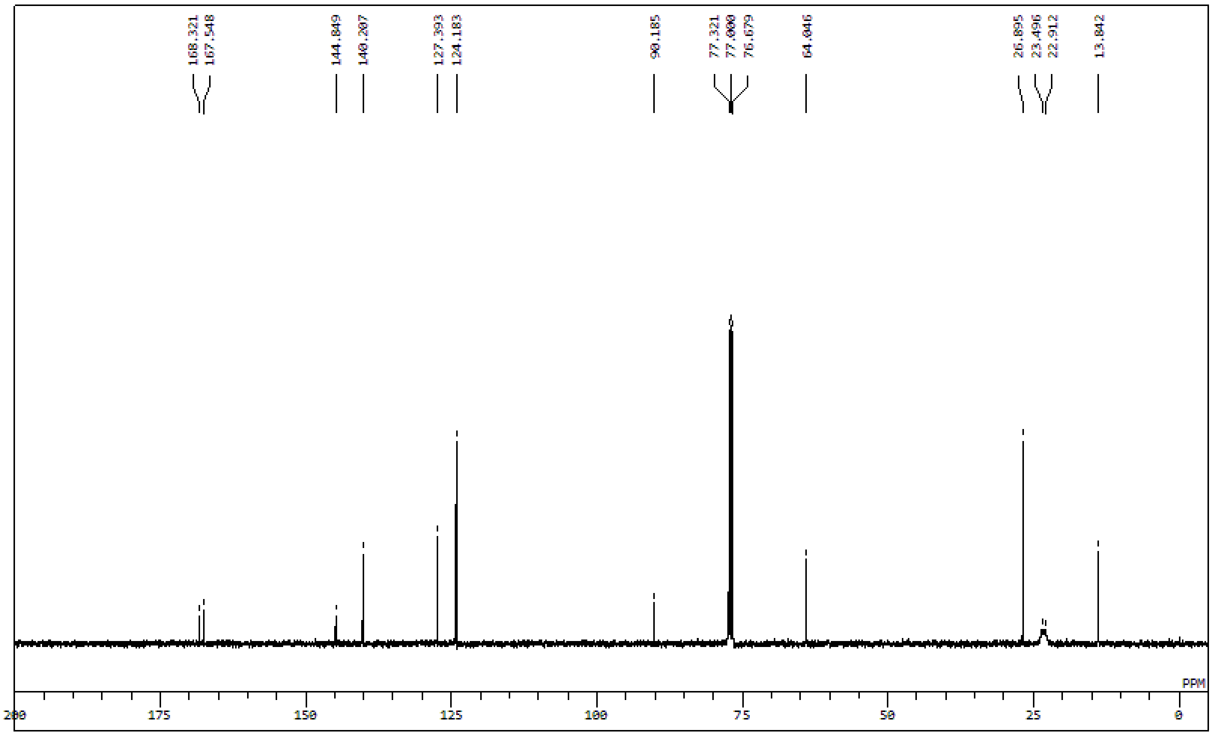
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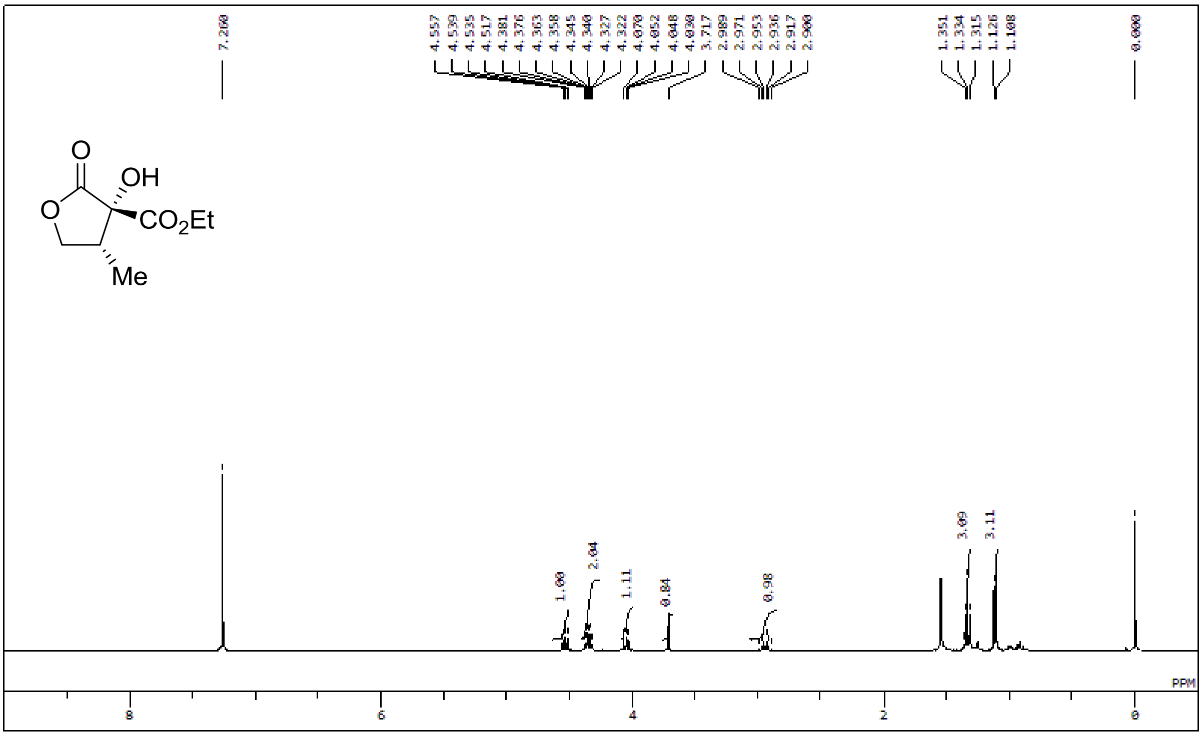
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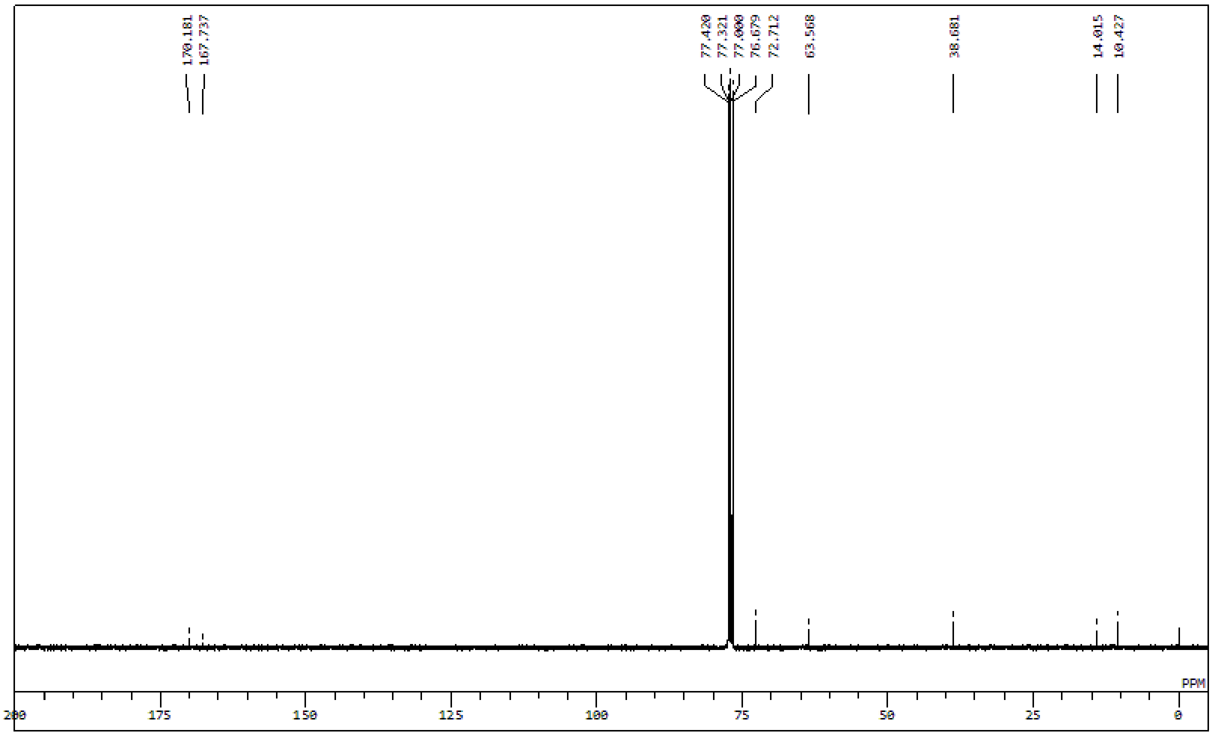
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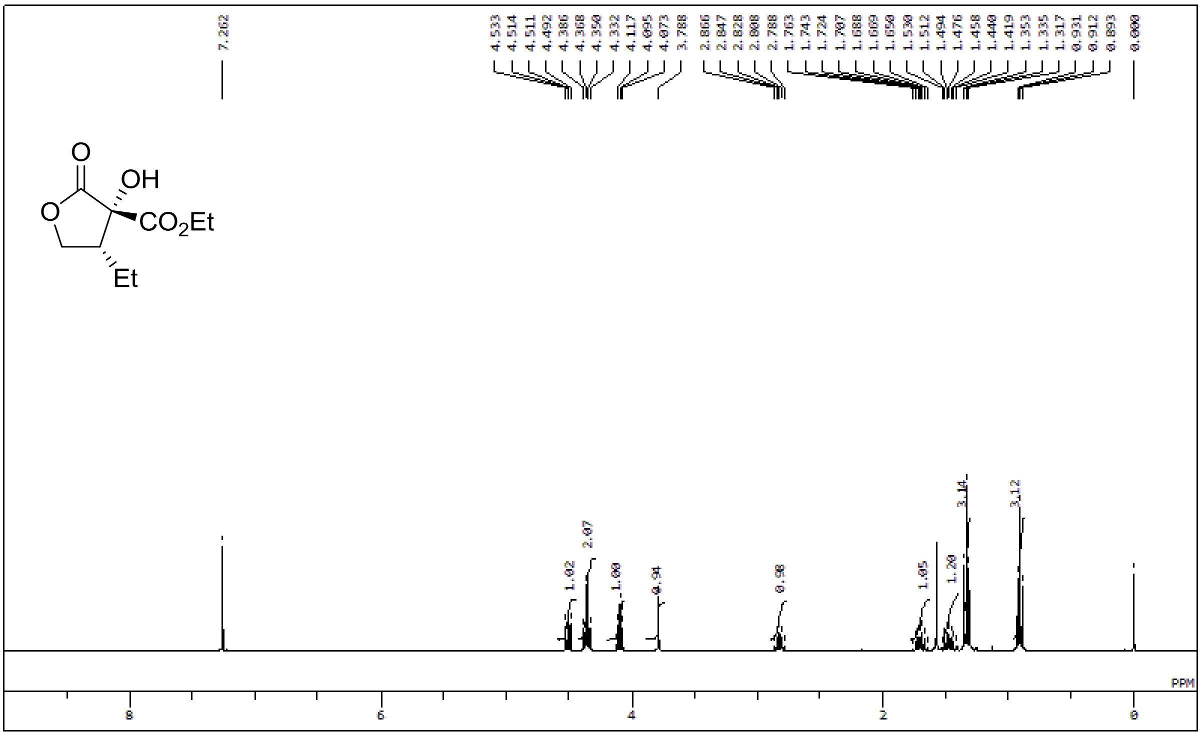
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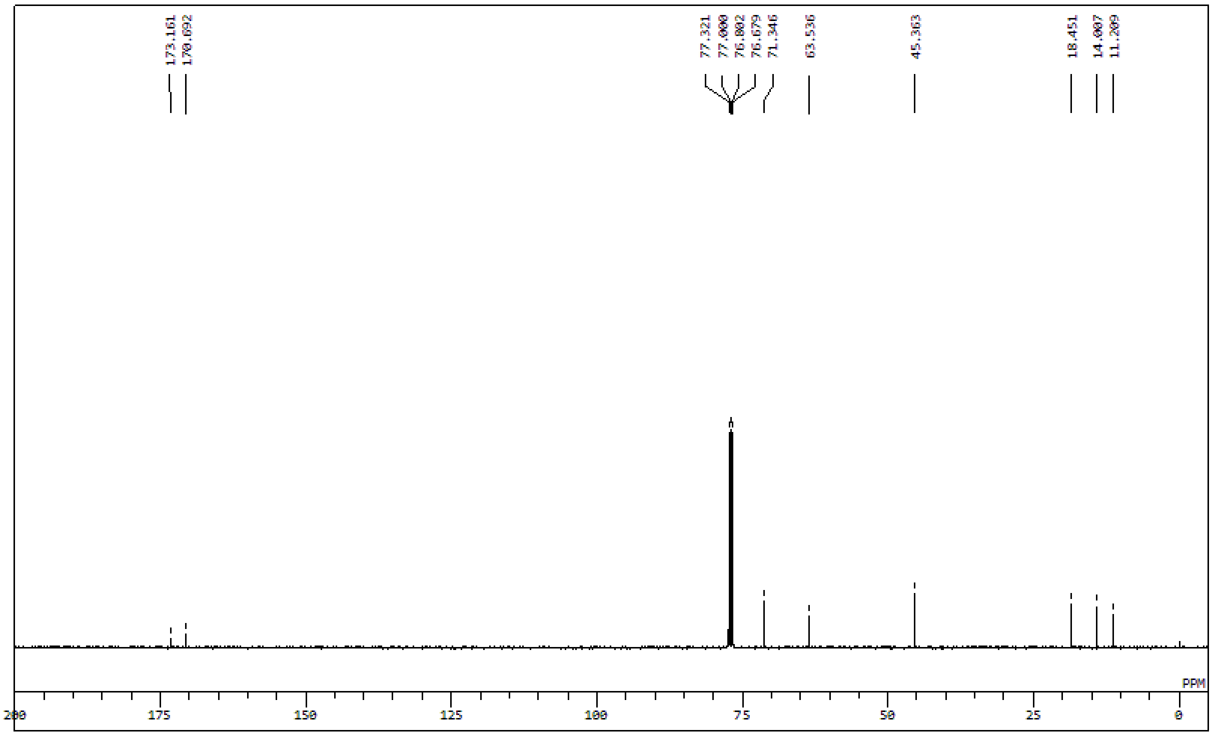
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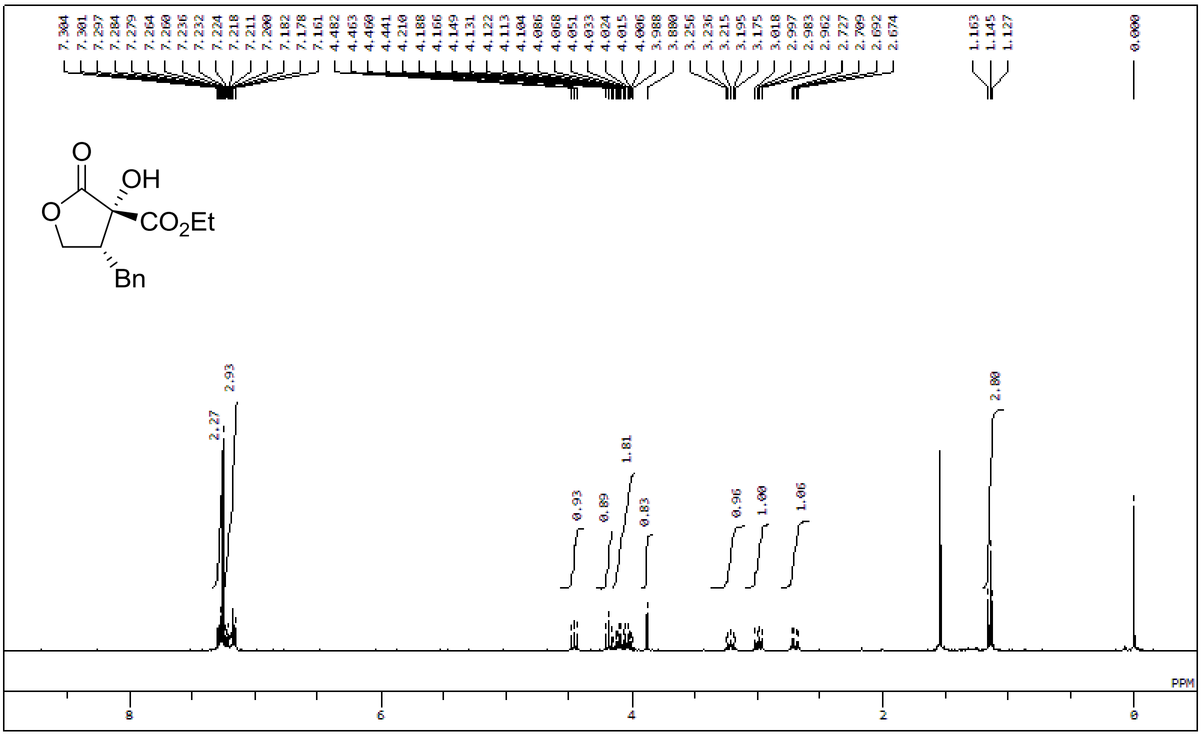

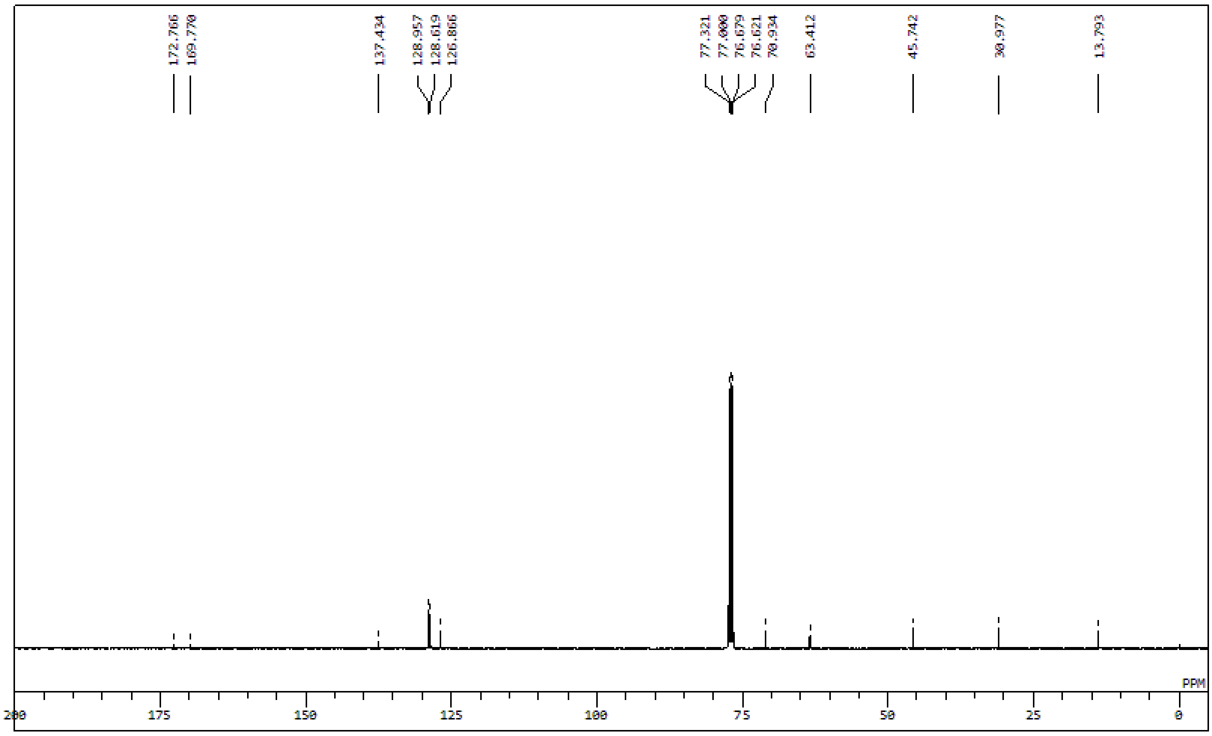

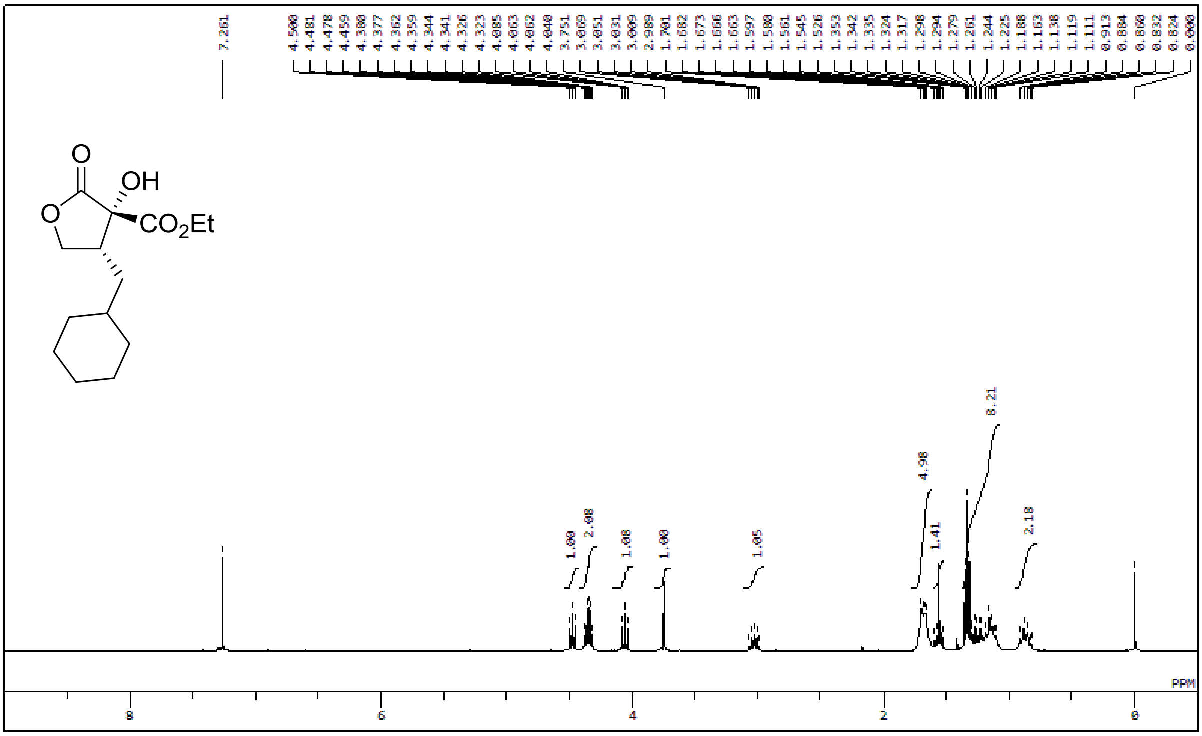

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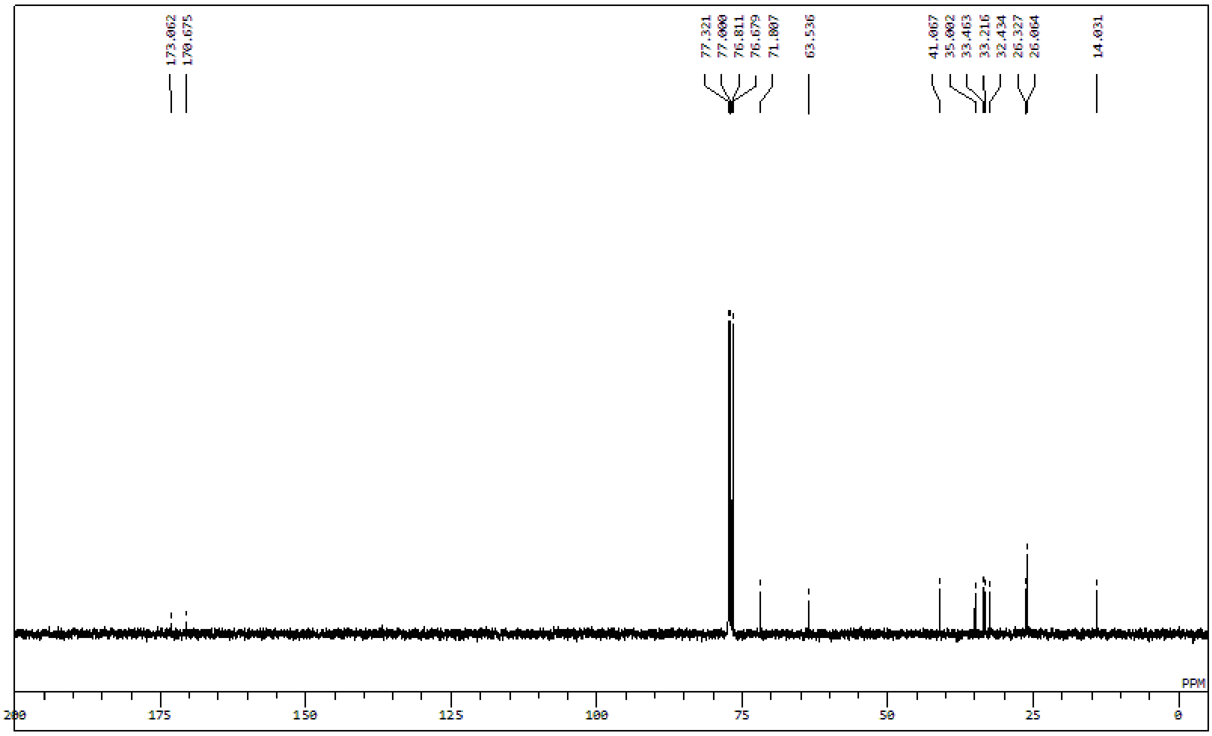

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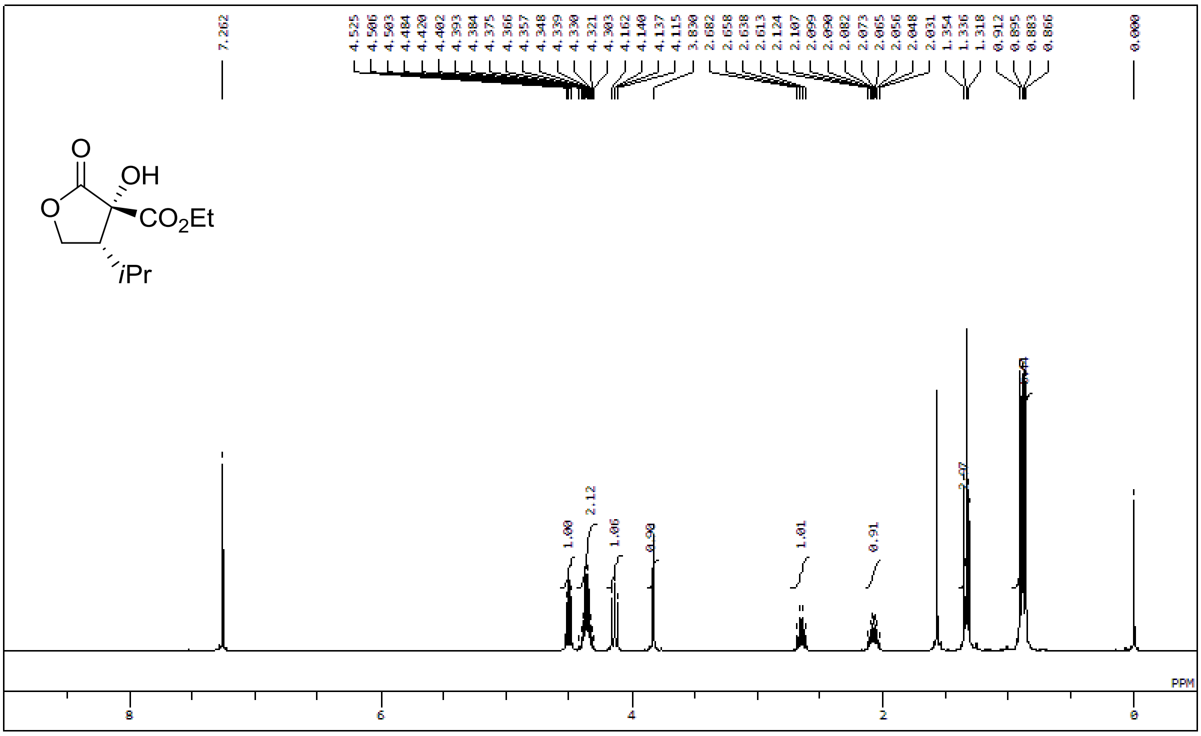
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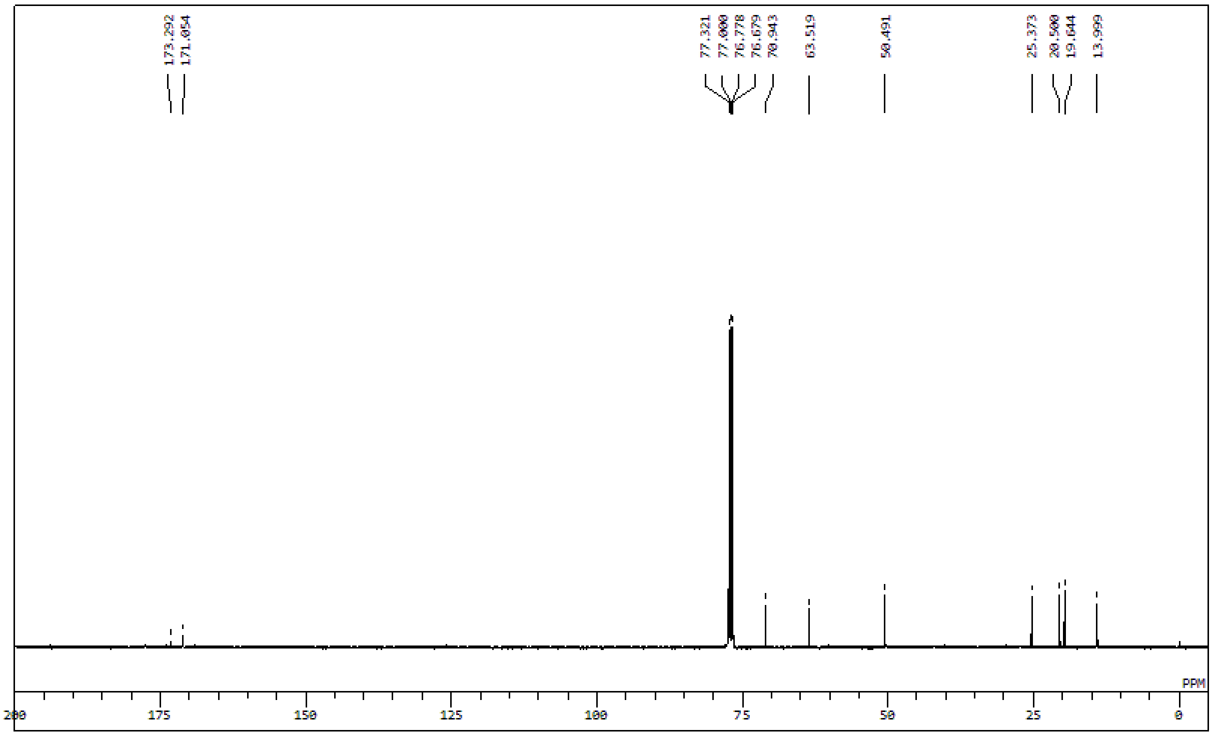
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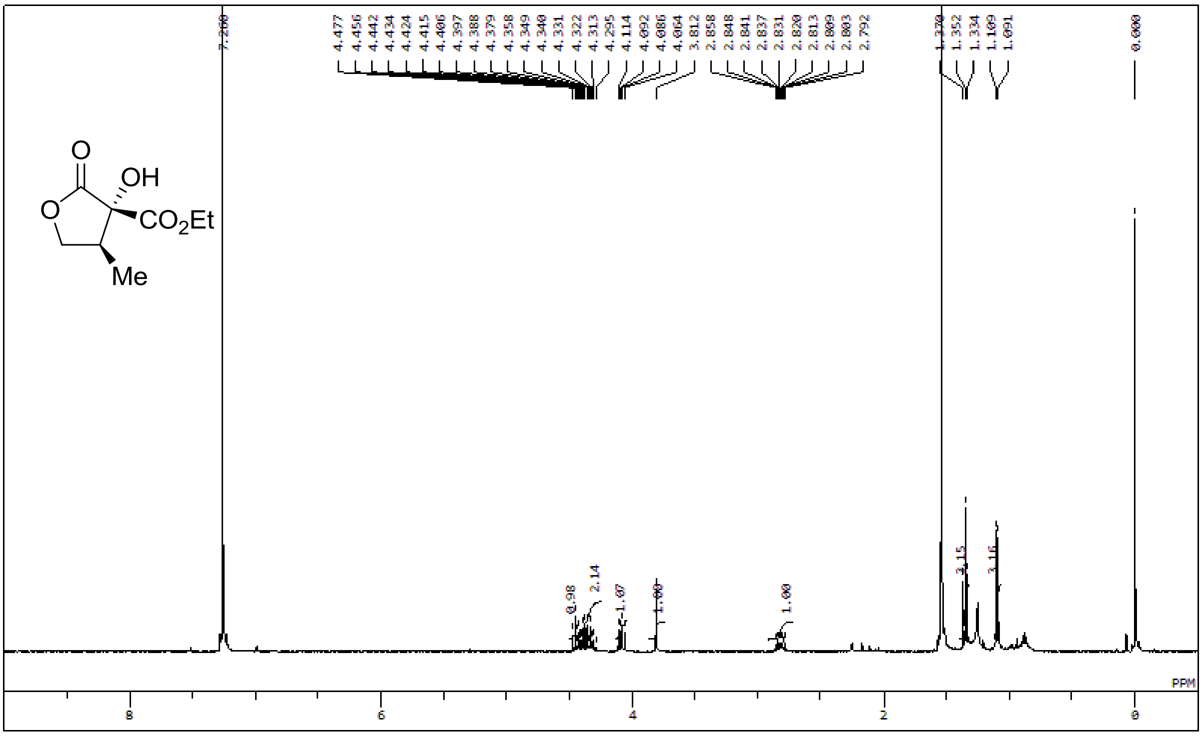

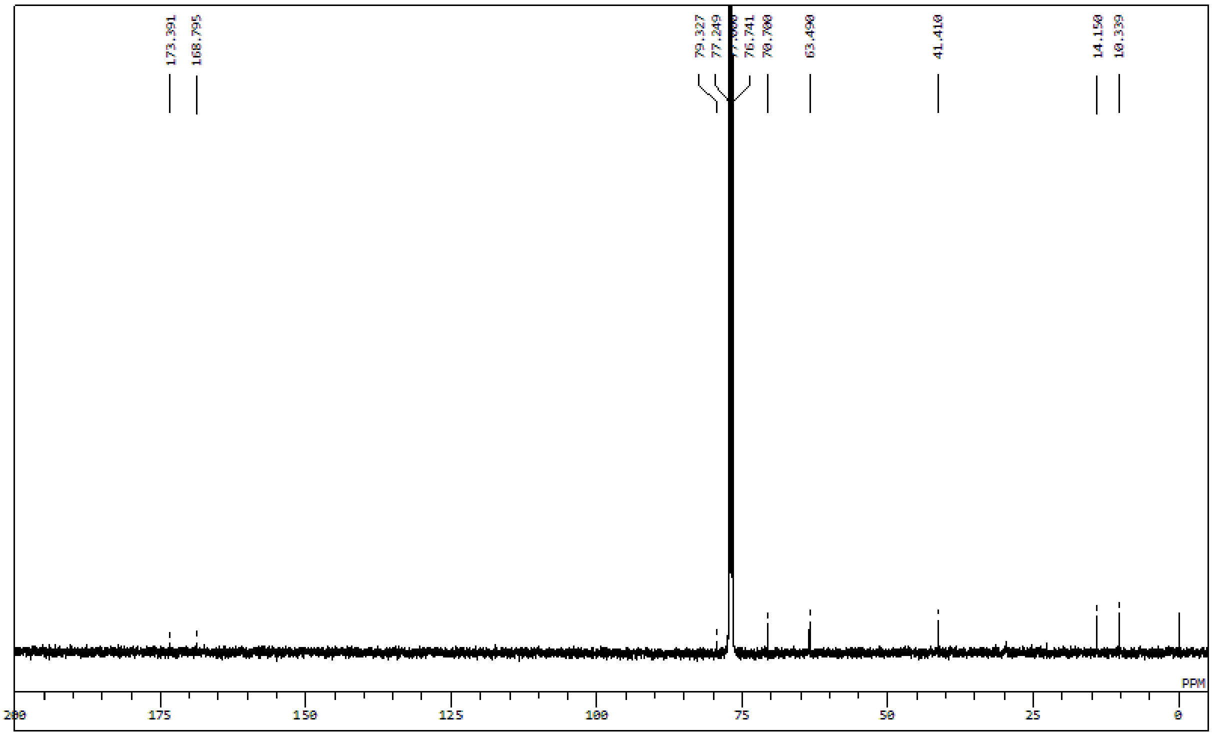

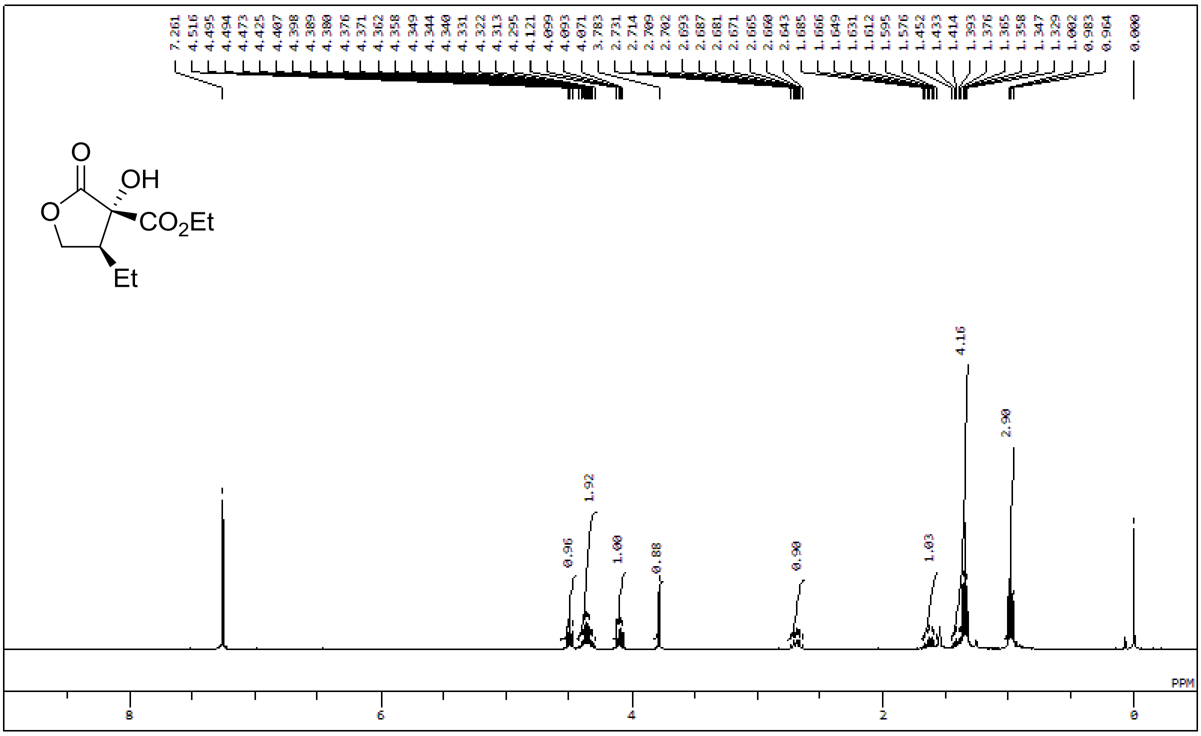
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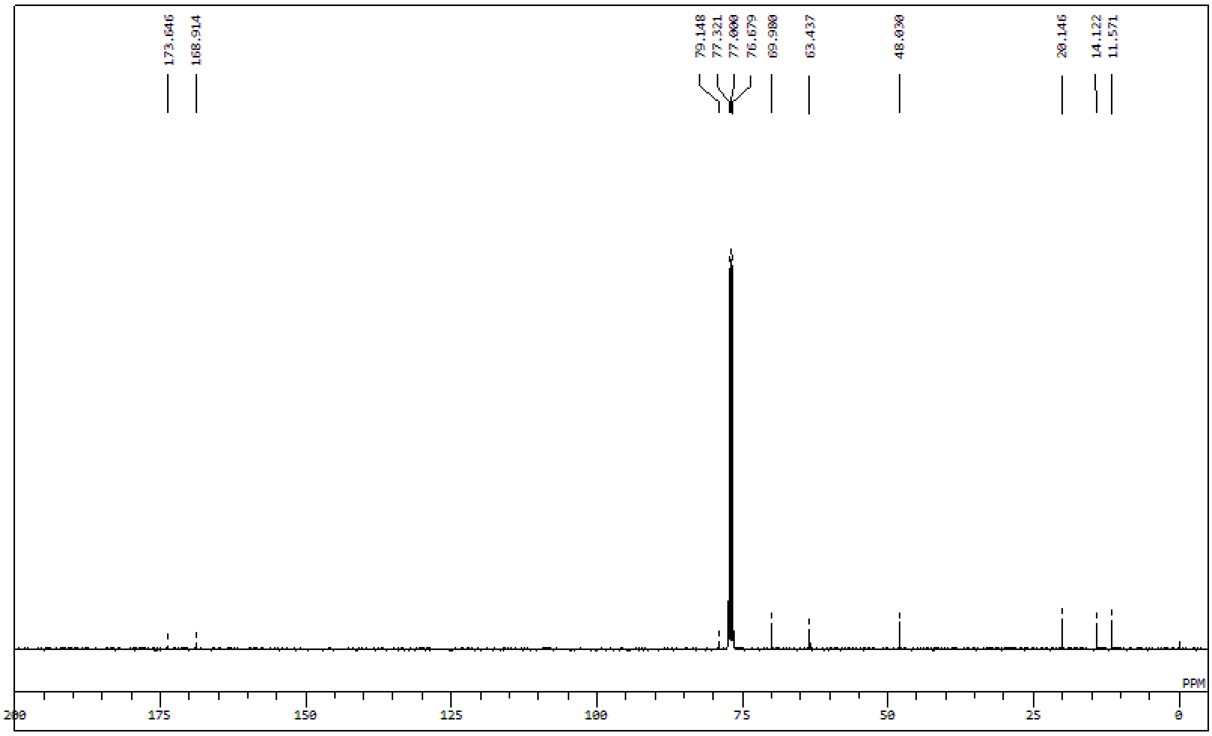
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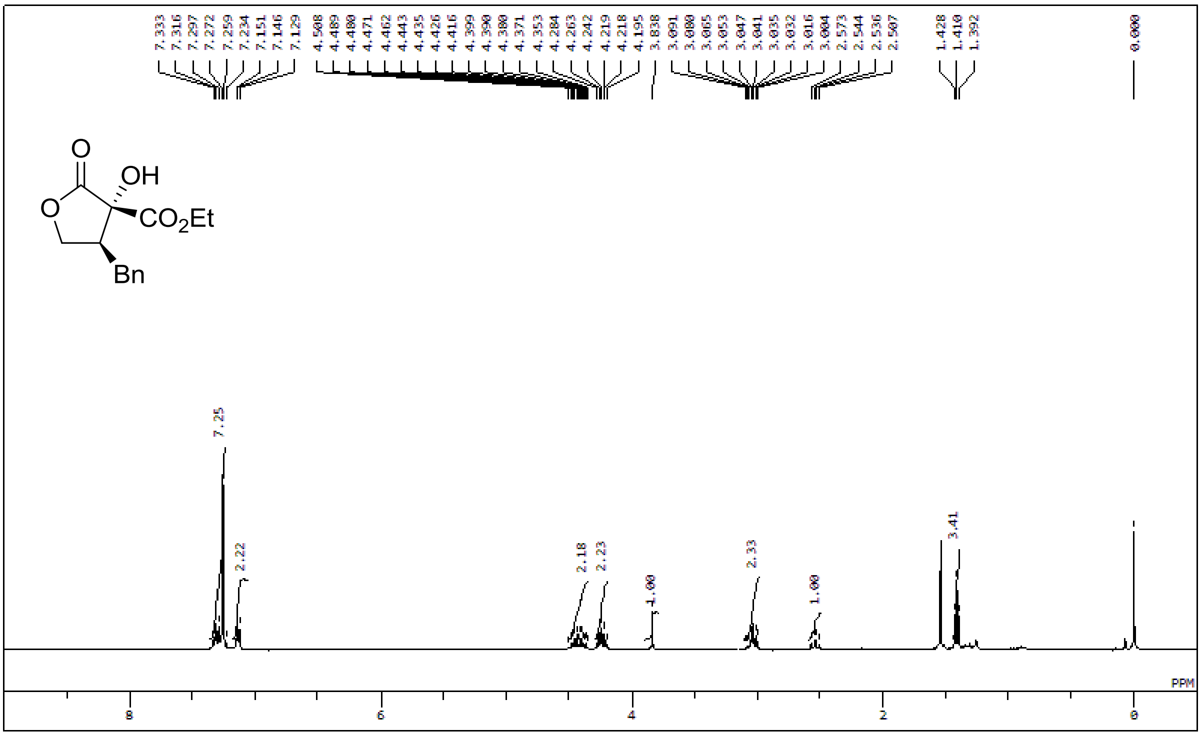

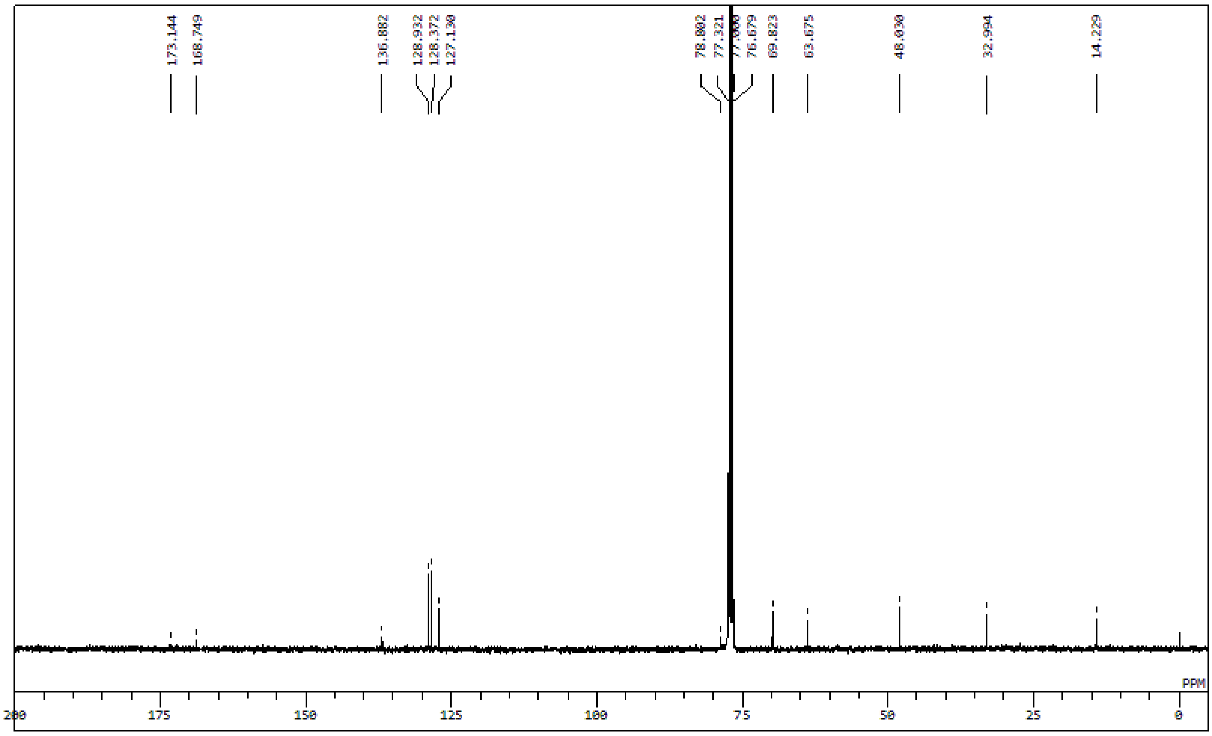

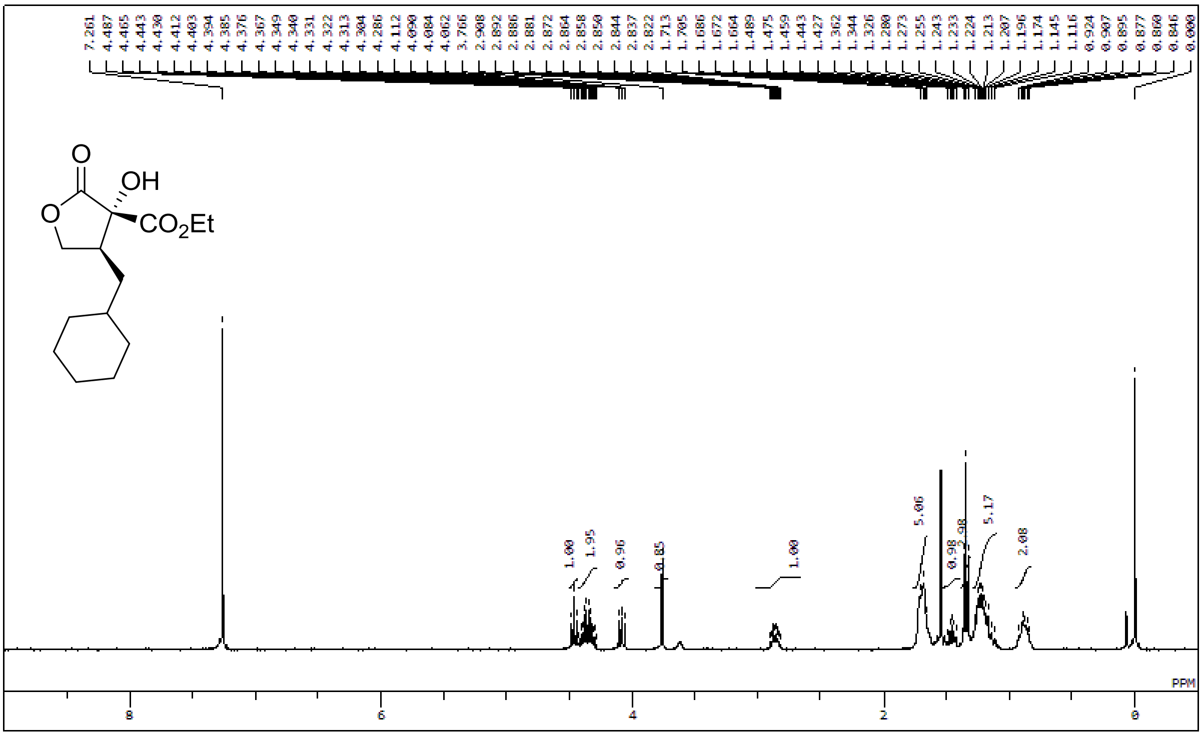

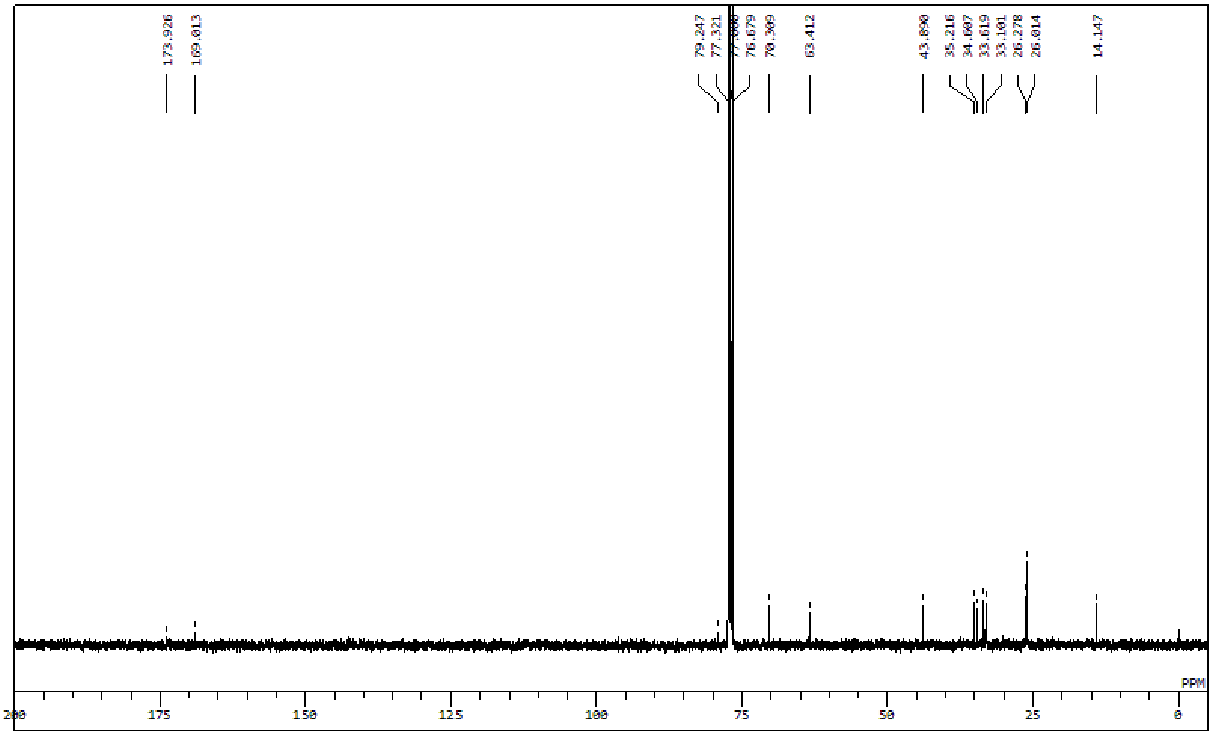

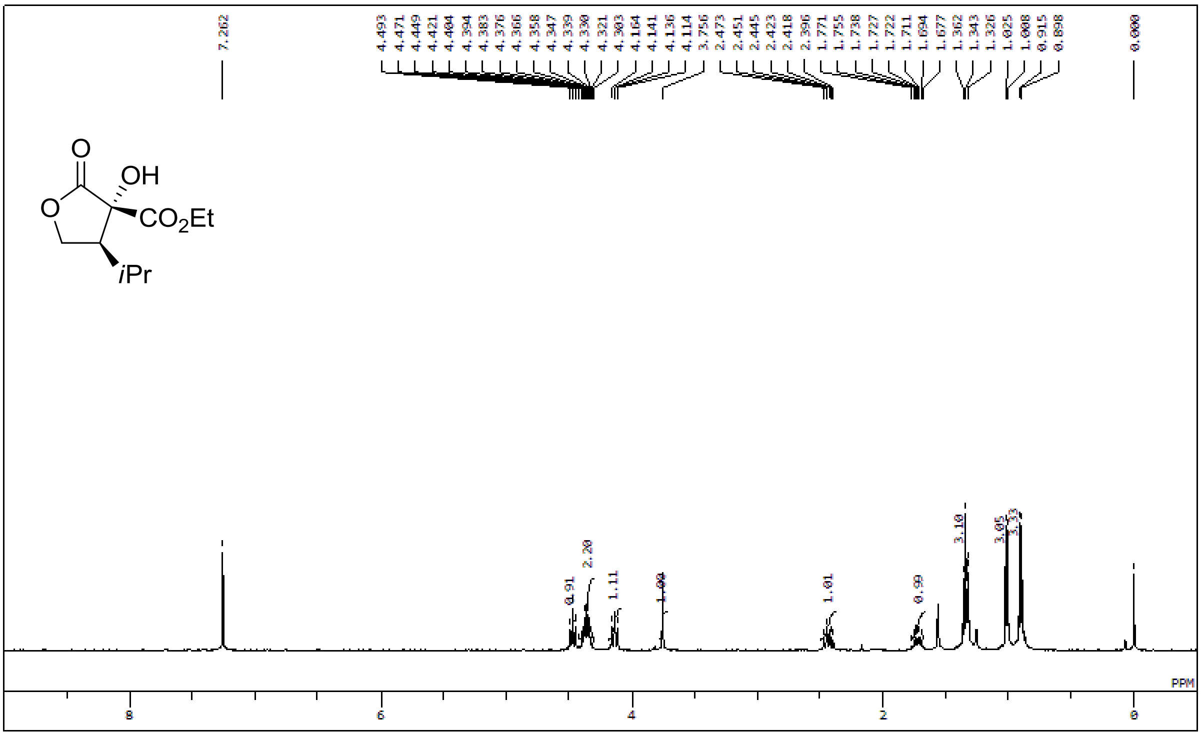
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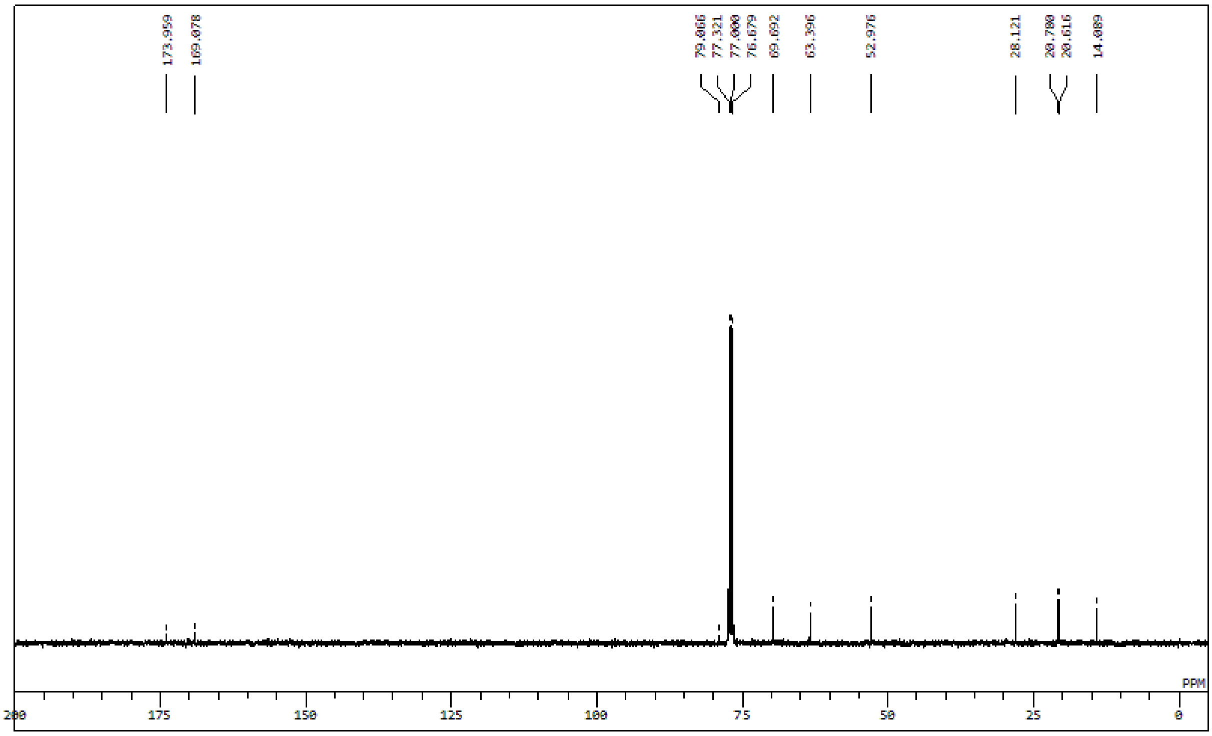
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