Supporting Information

The First Example of the Direct Asymmetric Conjugate Addition of Aldehydes to a Methylenemalonate Promoted by an Axially Chiral Amino Diol Catalyst

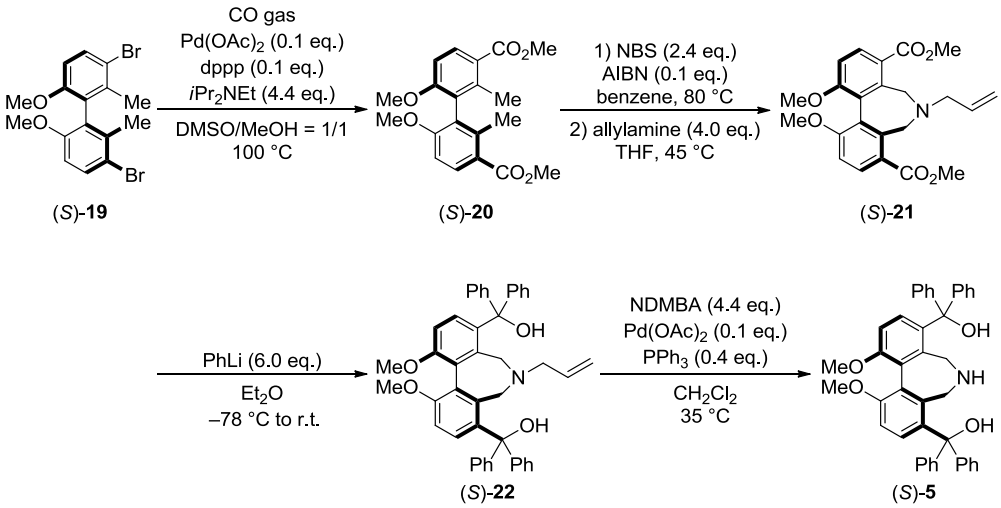
Taichi Kano, Fumitaka Shirozu, Koichi Tatsumi, Yasushi Kubota, and Keiji Maruoka*

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 (400 MHz) spectrometer. Data were reported as follows: chemical shifts in ppm from tetramethylsilane or the residual solvent as an internal standard, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = double-doublet, dq = double quartet, ddd = double double doublet, m = multiplet, br = broad, and app = apparent), coupling constants (Hz), and assignment. ^{13}C NMR spectra were measured on a JEOL JNM-FX400 (100 MHz) 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 20A instruments using Daicel Chiralpak AD-H, AS-H, AD-3, IC and Chiralcel OD-H, OJ-H, OZ-H, OD-3 4.6 mm x 25 cm column. High-resolution mass spectra (HRMS) were performed on Brucker microTOF. 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 neutral silica gel 60N (Kanto Chemical Co. Inc., 40-50μm). For purification with preparative thin layer chromatography (PLC), Merck precoated PLC plates (silica gel 60 GF_{254}, 0.5 mm) were used.

Dichloromethane and toluene were purchased from Kanto Chemical Co. Inc. as "Dehydrated" and further purified by passing through neutral alumina under nitrogen atmosphere. Diethyl ether and tetrahydrofuran were purchased from Kanto Chemical Co. Inc. as "Dehydrated". 1,4-Dioxane, *t*-butyl methyl ether, cyclopentyl methyl ether, vinyltriphenylphosphonium bromide, 4,5-dimethyl-2-thiophenecarboxilyc acid and 2-(2-bromoethyl)-1,3-dioxolane **23** were purchased and used without further purification. The commercially available aldehydes were distilled and stored under argon atmosphere at –17 °C. The commercially available secondary amines were purchased and used without further purification. Binaphthyl-based amines (*S*)-**3**[1] and (*S*)-**4**,[2] 5-benzyloxypentanal,[3] 3-(pyridin-3-yl)propional,[4] cyclohexylacetaldehyde[5] and di-*t*-butyl 2-methylenemalonate[6] were synthesized according to literature procedure and used after purification by column chromatography. (*S*)-3,3'-Dibromo-6,6'-dimethoxy-2,2'-dimethyl-1,1'-biphenyl (*S*)-**19** was provided from Nippon Soda Co, Ltd.[7]

Synthesis and characterization of chiral amino alcohol catalyst (*S*)-5



Diester (*S*)-20: Dibromide (*S*)-**19**[7] (636 mg, 1.6 mmol), $Pd(OAc)_2$ (54 mg, 0.24 mmol), bis(diphenylphosphino)propane (dppp) (98 mg, 0.24 mmol) and *i*Pr_2NEt (1.2 mL, 6.9 mmol) in DMSO (15 mL) and MeOH (15 mL) were charged into autoclave under argon atmosphere. After pressurized with CO (6 atm), the mixture was heated to 100 °C with stirring for 72 h. After cooling to room temperature, the reaction mixture was poured into H_2O and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and then concentrated. The residue was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate = 4/1) to give (*S*)-**20**. [54% yield (306 mg)]. $[\alpha]_D^{27}$ –37.7 (*c* = 1.30, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (2H, d, *J* = 8.8 Hz, Ar-H), 6.83 (2H, d, *J* = 8.8 Hz, Ar-H), 3.87 (6H, s, -CO_2CH_3), 3.72 (6H, s, -OCH_3), 2.16 (6H, s, $ArCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 159.7, 141.0, 132.0, 127.0, 122.7, 107.6, 55.7, 51.6, 17.5; IR (neat) 2949, 1713, 1585, 1431, 1250, 1211, 1186, 1078, 783 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{20}H_{23}O_6$: 359.1489 ($[M + H]^+$), Found: 359.1491 ($[M + H]^+$).

Allylamine (*S*)-21: To a solution of diester (*S*)-**20** (306 mg, 0.85 mmol) in benzene (8.0 mL) were added *N*-bromosuccinimide (365 mg, 2.1 mmol) and azobisisobutylonitrile (20 mg, 0.12 mmol) at room temperature. After 8 h of reflux, the mixture was cooled to room temperature. H_2O was added and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and then concentrated. The residue containing the bromination product was used for the next step without further purifications.

To the mixture obtained above in tetrahydrofuran (9.0 mL) was added allylamine (260 μL, 3.5 mmol) at room temperature. After stirring for 20 h at 45 °C, the mixture was cooled to room temperature. H_2O was added and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and then concentrated. The residue was purificated by flash column chromatography on silica gel (eluting with hexane/ethyl acetate = 5/3) to give (*S*)-**21**. [82% yield

(287 mg)]. $[\alpha]_D^{29}$ 260.8 (*c* = 0.83, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (2H, d, *J* = 8.8 Hz Ar-H), 6.96 (2H, d, *J* = 8.8 Hz, Ar-H), 6.02-5.92 (1H, m, -CH=CH_2), 5.14 (1H, d, *J* = 3.2 Hz, -CH=CHH), 5.10 (1H, s, -CH=CHH), 4.84 (2H, d, *J* = 12.8 Hz, -CHHN-), 3.88 (6H, s, -CO_2CH_3), 3.83 (6H, s, -OCH_3), 3.38 (1H, dd, *J* = 13.6, 5.6 Hz, -NCHHCH-), 2.90 (1H, dd, *J* = 13.6, 7.2 Hz, -NCHHCH-), 2.83 (2H, d, *J* = 12.8 Hz, -CHHN-); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 159.0, 137.4, 136.5, 132.6, 126.6, 122.2, 116.9, 109.3, 58.9, 55.8, 51.9, 49.5; IR (neat) 2947, 1713, 1582, 1485, 1433, 1252, 1186, 1157, 1076, 920, 826, 787, 754 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{23}H_{26}NO_6$: 412.1755 ($[M + H]^+$), Found: 412.1751 ($[M + H]^+$).

Aminoalcohol (*S*)-22: To a solution of (*S*)-**21** (151 mg, 0.37 mmol) in diethyl ether (4.0 mL) was added a 1.9 M dibutyl ether solution of phenyllithium (1.2 mL, 2.3 mmol) at –78 °C. The mixture was stirred for 10 h at room temperature, and saturated NH_4Cl was then carefully added. After extraction with ethyl acetate, the organic layer was washed with brine, dried over Na_2SO_4 and then concentrated. The residue was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate = 1/1) to give (*S*)-**22**. [88% yield (214 mg)]. $[\alpha]_D^{28}$ –131.7 (*c* = 0.98, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.15 (20H, m, Ar-H), 6.69 (2H, d, *J* = 8.4 Hz, Ar-H), 6.60 (2H, d, *J* = 8.8 Hz, Ar-H), 5.77-5.65 (1H, m, -CH=CH_2), 4.84 (1H, d, *J* = 9.2 Hz, -CH=CHH), 4.78 (1H, d, *J* = 16.8 Hz, -CH=CHH), 3.87 (2H, d, *J* = 13.6 Hz, -CHHN-), 3.76 (6H, s, -OCH_3), 3.19 (1H, dd, *J* = 13.6, 4.8 Hz, -NCHHCH-), 2.68 (2H, d, *J* = 13.2 Hz, -CHHN-), 2.51 (1H, dd, *J* = 13.4, 8.6 Hz, -NCHHCH-); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 148.6, 147.3, 138.1, 136.2, 135.3, 130.5, 128.22, 128.20, 127.8, 127.7, 127.4, 126.9, 126.7, 117.1, 108.3, 82.7, 59.1, 55.7, 51.1; IR (neat) 1578, 1483, 1447, 1281, 1269, 1076, 1013, 910, 812, 758, 702 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{45}H_{42}NO_4$: 660.3108 ($[M + H]^+$), Found: 660.3121 ($[M + H]^+$).

Aminoalcohol (*S*)-5: A mixture of (*S*)-**22** (240 mg, 0.36 mmol), *N*,*N*-dimethylbarbituric acid (NDMBA) (256 mg, 1.6 mmol), $Pd(OAc)_2$ (9.5 mg, 0.042 mmol), and triphenylphosphine (43 mg, 0.16 mmol) in CH_2Cl_2 (4.0 mL) was stirred at 35 °C for 15 h under argon atmosphere. After addition of saturated $NaHCO_3$, the mixture was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4 and then concentrated. The residue was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate = 1/2) to give (*S*)-**5**. [90% yield (200 mg)]. $[\alpha]_D^{29}$ –71.6 (*c* = 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.20 (20H, m, Ar-H), 6.72 (2H, d, *J* = 8.8 Hz, Ar-H), 6.64 (2H, d, *J* = 8.8 Hz, Ar-H), 3.88 (2H, d, *J* = 12.8 Hz, -CHH-), 3.79, (6H, s, -OCH_3), 2.77 (2H, d, *J* = 12.8 Hz, -CHH-); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 148.2, 147.4, 137.6, 136.2, 130.5, 128.0, 127.9, 127.82, 127.80, 127.7, 127.0, 126.9, 108.4, 82.7, 55.7, 44.6; IR (neat) 1580, 1485, 1447, 1273, 1084, 908, 812, 758, 732, 702 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{42}H_{38}NO_4$: 620.2795 ($[M + H]^+$), Found: 620.2792 ($[M + H]^+$).

Typical procedure for the organocatalytic conjugate addition of aldehydes

A mixture of di-*t*-butyl methylenemalonate (30.5 mg, 0.13 mmol) and 3-phenylpropanal (53 μL, 0.40 mmol) in diethyl ether (1.3 mL) was stirred at 0 °C. To the mixture was then added (*S*)-**5** (8.3 mg, 0.013 mmol). After stirring for 4 h at 0 °C, MeOH (1.0 mL) and sodium borohydride (50 mg) were added successively. After 0.5 h of vigorous stirring at room temperature, saturated NH_4Cl was added. The resulting mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and then concentrated. The resulting residue was purified by preparative thin layer chromatography (eluting with hexane/ethyl acetate = 3/1) to give di-*t*-butyl (*R*)-2-(2-benzyl-3-hydroxypropyl)malonate (**7**). [94% yield (45.6 mg)].

Di-*t*-butyl (*R*)-2-(2-benzyl-3-hydroxypropyl)malonate (7): $[\alpha]_D^{23}$ 10.4 (*c* = 1.22, $CHCl_3$; 95% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.24 (2H, m, Ar-H), 7.22-7.14 (3H, m, Ar-H), 3.52 (1H, ddd, *J* = 11.2, 4.8, 4.8 Hz, HOCHH-), 3.44 (1H, ddd, *J* = 11.2, 5.6, 5.6 Hz, HOCHH-), 3.29 (1H, app t, *J* = 7.2 Hz, -CH_2CH(CO_2t-Bu)$_2$), 2.67 (1H, dd, *J* = 14.0, 7.6 Hz, -CHHPh), 2.61 (1H, dd, *J* = 14.0, 6.4 Hz, -CHHPh), 2.01-1.78 (4H, m, HOCH_2CHCH_2-), 1.46 (9H, s, -C(CH_3)$_3$), 1.43 (9H, s, -C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 169.1, 140.1, 129.2, 128.3, 126.0, 81.63, 81.56, 63.7, 51.9, 41.0, 37.7, 29.6, 27.9, 27.8; IR (neat) 2978, 1724, 1368, 1254, 1140, 1032, 847, 745, 702 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{21}H_{32}NaO_5$: 387.2142 ([M + Na]$^+$), Found: 387.2127 ([M + Na]$^+$); HPLC analysis: Daicel Chiralcel OD-H, hexane/*i*-PrOH = 20/1, flow rate = 0.5 mL/min, λ = 209 nm, retention time; t_R(minor) = 15.8 min, t_R(major) = 20.8 min.

Di-*t*-butyl (*S*)-2-(3-hydroxy-2-methylpropyl)malonate (7b): $[\alpha]_D^{31}$ –6.92 (*c* = 1.12, $CHCl_3$; 96% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.47 (2H, dd, *J* = 4.4, 4.4 Hz, HOCH_2-), 3.27 (1H, dd, *J* = 8.2, 6.2 Hz, -CH_2CH(CO_2t-Bu)$_2$), 1.96 (1H, m, HOCH_2CHCH_2-), 1.74-1.61 (3H, m, HOCH_2CHCH_2-), 1.46 (18H, s, -C(CH_3)$_3$), 0.95 (3H, d, *J* = 6.4 Hz, -CHCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 169.1, 81.54, 81.51, 67.4, 51.8, 34.1, 31.8, 27.9 (two peaks overlap), 16.6; IR (neat) 2975, 1723, 1456, 1367, 1252, 1141, 1034, 984, 989, 843 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{15}H_{28}NaO_5$: 311.1829 ([M + Na]$^+$), Found: 311.1844 ([M + Na]$^+$); The enantiomeric excess was determined by HPLC after conversion to the corresponding benzoate ester.

Di-*t*-butyl (*S*)-2-(2-(hydroxymethyl)hexyl)malonate (7c): $[\alpha]_D^{30}$ 4.66 (*c* = 0.98, $CHCl_3$; 94% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.55 (1H, d, *J* = 11.6 Hz, HOCHH-), 3.47 (1H, d, *J* = 11.2 Hz, HOCHH-), 3.28 (1H, app t, *J* = 7.0 Hz, -CH_2CH(CO_2t-Bu)$_2$), 1.95-1.75 (3H, m, -CHCH_2CH(CO_2t-Bu)$_2$), 1.46 (18H, s, - C(CH_3)$_3$), 1.35-1.22 (6H, m, -CH_2-), 0.90 (3H, t, *J* = 7.0 Hz, -CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 169.3, 81.6 (two peaks overlap), 64.9, 51.9, 38.9, 30.9, 29.9, 29.1, 27.9 (two peaks overlap), 22.9, 14.0; IR (neat) 3464, 2930, 1726, 1456, 1368, 1254, 1140,

1042, 847 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{18}H_{34}NaO_5$: 353.2298 ($[M + Na]^+$), Found: 353.2284 ($[M + Na]^+$); The enantiomeric excess was determined by HPLC after conversion to the corresponding benzoate ester.

Di-*t*-butyl (*S*)-2-(2-(hydroxymethyl)octyl)malonate (7d): $[\alpha]_D^{29}$ 5.07 (*c* = 0.76, $CHCl_3$; 94% ee); ^1H NMR (400 MHz, $CDCl_3$) δ 3.55 (1H, dd, *J* = 11.2, 4.4 Hz, HOC<u>H</u>H-), 3.46 (1H, dd, *J* = 11.2, 6.0 Hz, HOCH<u>H</u>-), 3.28 (1H, app t, *J* = 7.2 Hz, -$CH_2C\underline{H}(CO_2t\text{-Bu})_2$), 1.93-1.78 (3H, m, -C<u>H</u>C<u>H</u>$_2$CH$(CO_2t\text{-Bu})_2$), 1.46 (18H, s, -C(C<u>H</u>$_3)_3$), 1.37-1.22 (10H, br, -C<u>H</u>$_2$-), 0.88 (3H, t, *J* = 6.0 Hz, -C<u>H</u>$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.40, 169.36, 81.58, 81.56, 64.9, 51.9, 38.9, 31.8, 31.2, 29.9, 29.5, 27.9 (two peaks overlap), 26.9, 22.6, 14.1; IR (neat) 2927, 1723, 1457, 1368, 1249, 1134, 1038, 840, 781, 700 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{20}H_{38}NaO_5$: 381.2611 ($[M + Na]^+$), Found: 381.2623 ($[M + Na]^+$); The enantiomeric excess was determined by HPLC after conversion to the corresponding benzoate ester.

Di-*t*-butyl (*R*)-2-(3-cyclohexyl-2-(hydroxymethyl)propyl)malonate (7e): $[\alpha]_D^{30}$ 6.69 (*c* = 0.53, $CHCl_3$; 86% ee); ^1H NMR (400 MHz, $CDCl_3$) δ 3.55 (1H, dd, *J* = 11.2, 4.4 Hz, HOC<u>H</u>H-), 3.43 (1H, dd, *J* = 11.6, 5.2 Hz, HOCH<u>H</u>-), 3.29 (1H, app t, *J* = 7.4 Hz, -$CH_2C\underline{H}(CO_2t\text{-Bu})_2$), 1.91-1.79 (3H, m, HOC<u>H</u>$_2$C<u>H</u>C<u>H</u>$_2$CH$(CO_2t\text{-Bu})_2$), 1.73-1.64 (5H, m, Cy), 1.46 (18H, s, -C(C<u>H</u>$_3)_3$), 1.27-1.05 (6H, m, Cy), 0.87 (2H, m, -CHC<u>H</u>$_2$Cy); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 169.4, 81.58, 81.56, 65.1, 51.8, 39.1, 35.7, 34.8, 33.60, 33.58, 30.2, 27.92, 27.90, 26.6, 26.29, 26.27; IR (neat) 2920, 1722, 1449, 1367, 1254, 1136, 1021, 849, 762, 690 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{21}H_{38}NaO_5$: 393.2611 ($[M + Na]^+$), Found: 393.2606 ($[M + Na]^+$); The enantiomeric excess was determined by HPLC after conversion to the corresponding benzoate ester.

Di-*t*-butyl (*S*)-2-(3-(benzyloxy)-2-(hydroxymethyl)propyl)malonate (7f): $[\alpha]_D^{31}$ –7.00 (*c* = 0.97, $CHCl_3$; 93% ee); ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.27 (5H, m, Ar-<u>H</u>), 4.51 (2H, s, -OC<u>H</u>$_2$Ph), 3.74-3.62 (2H, m, -CHC<u>H</u>$_2$OCH$_2$Ph), 3.60 (1H, dd, *J* = 9.2, 3.6 Hz, HOC<u>H</u>H-), 3.49 (1H, dd, *J* = 9.2, 6.0 Hz, HOCH<u>H</u>-), 3.26 (1H, app t, *J* = 7.4 Hz, -$CH_2C\underline{H}(CO_2t\text{-Bu})_2$), 2.48 (1H, t, *J* = 5.6 Hz, <u>H</u>OCH$_2$CH-), 1.96-1.79 (3H, m, -C<u>H</u>C<u>H</u>$_2$CH$(CO_2t\text{-Bu})_2$), 1.45 (18H, s, -C(C<u>H</u>$_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.91, 168.88, 138.0, 128.4, 127.7, 127.6, 81.61, 81.57, 73.4, 72.9, 64.7, 51.8, 38.8, 27.9 (two peaks overlap), 27.0; IR (neat) 2978, 1722, 1454, 1368, 1254, 1140, 847, 739, 698 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{22}H_{34}NaO_6$: 417.2248 ($[M + Na]^+$), Found: 417.2254 ($[M + Na]^+$); HPLC analysis: Daicel Chiralcel OD-H, hexane/*i*-PrOH = 40/1, flow rate = 0.5 mL/min, λ = 208 nm, retention time; t_R(minor) = 30.8 min, t_R(major) = 33.2 min.

Di-*t*-butyl (*S*)-2-(5-(benzyloxy)-2-(hydroxymethyl)pentyl)malonate (7g): $[\alpha]_D^{33}$ –0.67 (*c* = 0.92,

$CHCl_3$; 95% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.32 (4H, m, Ar-H), 7.26-7.25 (1H, br, Ar-H), 4.49 (2H, s, -OCH_2Ph), 3.54 (1H, dd, *J* = 11.0, 6.2 Hz, HOCHH-), 3.51-3.44 (1H, m, HOCHH-), 3.47 (2H, t, *J* = 6.4 Hz, -CH_2CH_2OCH_2Ph), 3.28 (1H, app t, *J* = 7.4 Hz, -CH_2CH(CO_2*t*-Bu)$_2$), 1.96-1.79 (3H, m, -CHCH_2CH(CO_2*t*-Bu)$_2$), 1.70-1.61 (2H, m, -CH_2-), 1.45 (18H, s, -C(CH_3)$_3$), 1.42-1.32 (2H, m, -CH_2-); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3 (two peaks overlap), 138.5, 128.4, 127.6, 127.5, 81.61, 81.58, 73.0, 70.5, 64.6, 51.8, 38.8, 29.8, 27.9 (two peaks overlap), 27.7, 27.0; IR (neat) 2868, 1723, 1455, 1367, 1254, 1140, 900, 838, 731 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{24}H_{38}NaO_6$: 445.2561 ([M + Na]$^+$), Found: 445.2565 ([M + Na]$^+$); HPLC analysis: Daicel Chiralcel OD-H, hexane/*i*-PrOH = 20/1, flow rate = 0.5 mL/min, λ = 208 nm, retention time; t_R(minor) = 20.6 min, t_R(major) = 22.6 min.

1,1-Di-*t*-butyl 4-methyl (*R*)-3-(hydroxymethyl)butane-1,1,4-tricarboxylate (7h): $[\alpha]_D^{31}$ –0.68 (*c* = 0.93, $CHCl_3$; 86% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (3H, s, -CO_2CH_3), 3.64-3.48 (2H, m, HOCH_2-), 3.26 (1H, app t, *J* = 7.4 Hz, -CH_2CH(CO_2*t*-Bu)$_2$), 2.46 (1H, dd, *J* = 15.6, 7.6 Hz, -CHHCO_2CH_3), 2.36 (1H, dd, *J* = 16.0, 5.6 Hz, -CHHCO_2CH_3), 2.18 (1H, t, *J* = 6.2 Hz, HOCH_2-), 2.10-2.01 (1H, m, HOCH_2CHCH_2-), 2.00-1.87 (1H, m, -CHCHHCH-), 1.85-1.76 (1H, m, -CHCHHCH-), 1.46 (18H, s, -C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 169.0, 168.8, 81.8, 81.8, 64.4, 51.8, 51.7, 36.4, 36.0, 29.6, 27.9 (two peaks overlap); IR (neat) 3539, 2978, 1724, 1439, 1369, 1254, 1140, 847, 745 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{17}H_{30}NaO_7$: 369.1884 ([M + Na]$^+$), Found: 369.1872 ([M + Na]$^+$); The enantiomeric excess was determined by HPLC after conversion to the corresponding 4-benzoate ester.

Di-*t*-butyl (*R*)-2-(3-(((benzyloxy)carbonyl)amino)-2-(hydroxymethyl)propyl)malonate (7i): $[\alpha]_D^{30}$ –15.2 (*c* = 1.19, $CHCl_3$; 84% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.28 (5H, m, Ar-H), 5.28 (1H, br, -CONHCH_2-), 5.11 (2H, s, -CO_2CH_2Ph), 3.61-3.50 (1H, m, -CONHCHHCH-), 3.48-3.28 (3H, m, -CONHCHHCHCH_2OH), 3.23 (1H, app t, *J* = 7.2 Hz, -CH_2CH(CO_2*t*-Bu)$_2$), 3.17-3.07 (1H, m, HOCH_2CHCH_2-), 1.75 (1H, dd, *J* = 7.2, 7.2 Hz, -CHCH_2CH-), 1.454 (9H, s, -C(CH_3)$_3$), 1.451 (9H, -C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 168.9, 157.8, 136.3, 128.5, 128.2, 128.1, 81.9, 81.9, 67.0, 62.0, 51.9, 40.7, 39.9, 27.9 (two peaks over lap), 26.8; IR (neat) 3391, 2976, 1719, 1524, 1368, 1252, 1140, 847, 741 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{23}H_{35}NNaO_7$: 460.2306 ([M + Na]$^+$), Found: 460.2291 ([M + Na]$^+$); HPLC analysis: Daicel Chiralpak AD-3, hexane/*i*-PrOH = 9/1, flow rate = 0.5 mL/min, λ = 208 nm, retention time; t_R(minor) = 20.8 min, t_R(major) = 23.7 min.

Di-*t*-butyl (*R*)-2-(3-hydroxy-2-(pyridine-3-ylmethyl)propyl)malonate (7j): $[\alpha]_D^{32}$ 1.57 (*c* = 0.93, $CHCl_3$; 93% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (1H, s, Ar-H), 8.46 (1H, d, *J* = 5.8 Hz, Ar-H), 7.78 (1H, d, *J* = 8.0 Hz, Ar-H), 7.42 (1H, dd, *J* = 7.8, 5.8 Hz, Ar-H), 3.52-3.38 (2H, m, HOCH_2-),

3.27 (1H, app t, *J* = 7.0 Hz, -$CH_2C\underline{H}(CO_2t\text{-}Bu)_2$), 2.82 (1H, dd, *J* = 14.0, 8.4 Hz, -C<u>H</u>HAr), 2.69 (1H, dd, *J* = 14.0, 6.0 Hz, -CH<u>H</u>Ar), 2.02-1.92 (2H, m, <u>H</u>O$CH_2C\underline{H}$-), 1.87-1.77 (2H, m, -$CHC\underline{H}_2CH$-), 1.47 (9H, s, -$C(C\underline{H}_3)_3$), 1.45 (9H, s, -$C(C\underline{H}_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 168.7, 148.0, 145.3, 139.8, 138.3, 124.9, 82.2, 82.0, 62.2, 51.8, 40.4, 34.5, 29.3, 27.9 (two peaks overlap); IR (neat) 3522, 2978, 2371, 1721, 1369, 1254, 1161, 1140, 845, 745 cm^{-1}; HPLC analysis: Daicel Chiralcel OD-H, hexane/*i*-PrOH = 9/1, flow rate = 0.5 mL/min, λ = 208 nm, retention time; t_R(minor) = 16.1 min, t_R(major) =19.0 min.

Di-*t*-butyl (*R*)-2-(2-(hydroxymethyl)-3-methylbutyl)malonate (7k): $[\alpha]_D^{30}$ 12.3 (*c* = 1.12, $CHCl_3$; 97% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.62 (1H, ddd, *J* = 11.6, 5.8, 5.8 Hz, HOC<u>H</u>H-), 3.54 (1H, ddd, *J* = 11.6, 5.8, 5.8 Hz, HOCH<u>H</u>-), 3.30 (1H, dd, *J* = 8.6, 6.6 Hz, -$CH_2C\underline{H}(CO_2t\text{-}Bu)_2$), 1.95-1.72 (4H, m, $(CH_3)_2C\underline{H}C\underline{H}C\underline{H}_2$-), 1.46 (18H, s, -$C(C\underline{H}_3)_3$), 0.93 (3H, d, *J* = 3.2 Hz, -$CHC\underline{H}_3$), 0.91 (3H, d, *J* = 3.2 Hz, -$CHC\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 169.3, 81.6, 81.5, 63.6, 52.5, 44.7, 28.7, 27.9 (two peaks overlap), 27.2, 19.9, 19.3; IR (neat) 2957, 1721, 1457, 1367, 1253, 1137, 842, 781 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{17}H_{32}NaO_5$: 339.2142 ($[M + Na]^+$), Found: 339.2140 ($[M + Na]^+$); The enantiomeric excess was determined by HPLC after conversion to the corresponding 4-nitrobenzoate ester.

Di-*t*-butyl (*R*)-2-(2-cyclohexyl-3-hydroxypropyl)malonate (7l): $[\alpha]_D^{30}$ 9.73 (*c* = 1.32, $CHCl_3$; 94% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.62 (1H, ddd, *J* = 10.8, 5.4, 5.4 Hz, HOC<u>H</u>H-), 3.54 (1H, ddd, *J* = 10.8, 5.4, 5.4 Hz, HOCH<u>H</u>-), 3.29 (1H, dd, *J* = 8.4, 6.8 Hz, -$CH_2C\underline{H}(CO_2t\text{-}Bu)_2$), 1.97-1.88 (1H, m, -$HOCH_2C\underline{H}$-), 1.86-1.78 (2H, m, -$CHC\underline{H}_2CH$-), 1.77-1.61 (5H, m, Cy), 1.464 (9H, s, -$C(C\underline{H}_3)_3$), 1.461 (9H, s, -$C(C\underline{H}_3)_3$), 1.35-1.00 (6H, m, Cy); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 169.3, 81.6, 81.5, 63.4, 52.5, 44.3, 39.2, 30.2, 29.9, 27.9 (two peaks overlap), 27.5, 26.7, 26.7, 26.6; IR (neat) 2924, 1726, 1368, 1254, 1140, 1040, 847, 745 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{20}H_{36}NaO_5$: 379.2455 ($[M + Na]^+$), Found: 379.2448 ($[M + Na]^+$); HPLC analysis: Daicel Chiralpak IC, hexane/*i*-PrOH = 9/1, flow rate = 0.5 mL/min, λ = 217 nm, retention time; t_R(major) = 17.0 min, t_R(minor) = 27.6 min.

Typical procedure for benzoylation of alcohols

To a solution of di-*t*-butyl (*S*)-2-(3-hydroxy-2-methylpropyl)malonate (20.9 mg, 0.073 mmol) and triethylamine (35 μL, 0.25 mmol) in CH_2Cl_2 (1.0 mL) was added benzoyl chloride (30 μL, 0.26 mmol) at 0 °C. After stirring for 3 h at room temperature, *N*,*N*-dimethyl-1,3-propanediamine (37 μL, 0.29 mmol) was added. The resulting mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and then concentrated. The resulting residue was purified by preparative thin layer chromatography (eluting with hexane/ethyl acetate = 9/1) to give di-*t*-butyl

(*S*)-2-(3-(benzoyloxy)-2-methylpropyl)malonate. [78% yield (22.2 mg)].

Di-*t*-butyl (*S*)-2-(3-(benzoyloxy)-2-methylpropyl)malonate: $[\alpha]_D^{30}$ –0.90 (*c* = 1.48, $CHCl_3$; 96% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (2H, d, *J* = 8.0 Hz, Ar-H), 7.56 (1H, t, *J* = 7.4 Hz, Ar-H), 7.44 (2H, t, *J* = 7.8 Hz, Ar-H), 4.19 (2H, d, *J* = 6.0 Hz, -CO_2CH_2CH-), 3.32 (1H, app t, *J* = 7.8 Hz, -CH_2CH(CO_2t-Bu)$_2$), 2.11-1.93 (2H, m, -CH_2CH(CO_2t-Bu)$_2$), 1.78 (1H, m, -CO_2CH_2CHCH_2-), 1.46 (9H, s, -C(CH_3)$_3$), 1.45 (9H, s, -C(CH_3)$_3$), 1.06 (3H, d, *J* = 6.8 Hz, -CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 168.7, 166.5, 132.9, 130.3, 129.6, 128.3, 81.54, 81.47, 69.2, 51.8, 32.4, 30.9, 27.91, 27.89, 16.8; IR (neat) 2976, 1721, 1452, 1368, 1271, 1138, 978, 847, 712 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{22}H_{32}NaO_6$: 415.2091 ([M + Na]$^+$), Found: 415.2078 ([M + Na]$^+$); HPLC analysis: Daicel Chiralpak AD-H, hexane/*i*-PrOH = 100/1, flow rate = 0.5 mL/min, λ = 227nm, retention time; t_R(major) = 14.7 min, t_R(minor) = 17.5 min.

Di-*t*-butyl (*S*)-2-(2-((benzoyloxy)methyl)hexyl)malonate: $[\alpha]_D^{28}$ 7.08 (*c* = 1.20, $CHCl_3$; 94% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (2H, d, *J* = 7.8 Hz, Ar-H), 7.55 (1H, t, *J* = 7.4 Hz, Ar-H), 7.44 (2H, t, *J* = 7.6 Hz, Ar-H), 4.29 (1H, dd, *J* = 11.6, 4.8 Hz, -CO_2CHHCH-), 4.22 (1H, dd, *J* = 10.4, 5.6 Hz, -CO_2CHHCH-), 3.35 (1H, app t, *J* = 7.8 Hz, -CH_2CH(CO_2t-Bu)$_2$), 1.97 (1H, dd, J = 7.2, 2.4 Hz, -CHCHHCH(CO_2t-Bu)$_2$), 1.95 (1H, dd, *J* = 7.4, 2.2 Hz, -CHCHHCH(CO_2t-Bu)$_2$), 1.81 (1H, app dt, *J* = 6.0, 6.0 Hz, -CO_2CH_2CHCH_2-), 1.46 (9H, s, -C(CH_3)$_3$), 1.45 (9H, s, -C(CH_3)$_3$), 1.42-1.24 (6H, m, -CH_2-), 0.90 (3H, t, *J* = 7.0 Hz, -CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8 (two peaks overlap), 166.6, 132.9, 130.3, 129.6, 128.3, 81.48, 81.46, 67.1, 51.8, 35.5, 31.1, 30.8, 28.8, 27.92, 27.89, 22.8, 14.0; IR (neat) 2976, 2932, 1722, 1452, 1368, 1271, 1138, 847, 712 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{25}H_{38}NaO_6$: 457.2561 ([M + Na]$^+$), Found: 457.2567 ([M + Na]$^+$); HPLC analysis: Daicel Chiralpak AD-H, hexane/*i*-PrOH = 200/1, flow rate = 0.2 mL/min, λ = 227nm, retention time; t_R(major) = 40.0 min, t_R(minor) = 45.1 min.

Di-*t*-butyl (*S*)-2-(2-((benzoyloxy)methyl)octyl)malonate: $[\alpha]_D^{28}$ 2.68 (*c* = 0.94, $CHCl_3$; 94% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (2H, d, *J* = 8.4 Hz, Ar-H), 7.55 (1H, t, *J* = 7.6 Hz, Ar-H), 7.44 (2H, t, *J* = 7.6 Hz, Ar-H), 4.29 (1H, dd, *J* = 11.2, 4.8 Hz, -CO_2CHHCH-), 4.22 (1H, dd, *J* = 11.2, 5.6 Hz, -CO_2CHHCH-), 3.35 (1H, app t, *J* = 7.8 Hz, -CH_2CH(CO_2t-Bu)$_2$), 1.98-1.92 (2H, m, -CHCH_2CH(CO_2t-Bu)$_2$) 1.80 (1H, m, -CO_2CH_2CHCH_2-), 1.46 (9H, s, -C(CH_3)$_3$) 1.44 (9H, s, -C(CH_3)$_3$), 1.42-1.21 (10H, br, -CH_2-), 0.87 (3H, t, *J* = 6.2 Hz, -CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 168.8, 166.6, 132.9, 130.3, 129.6, 128.3, 81.49, 81.47, 67.1, 51.8, 35.6, 31.7, 31.4, 30.8, 29.4, 27.92, 27.90, 26.6, 22.6, 14.0; IR (neat) 2930, 2859, 1722, 1452, 1368, 1271, 1138, 847, 712 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{27}H_{42}NaO_6$ 485.2874 ([M + Na]$^+$), Found: 485.2859 ([M + Na]$^+$); HPLC analysis: Daicel Chiralpak AD-3, hexane/*i*-PrOH = 200/1, flow rate = 0.5 mL/min, λ =

227 nm, retention time; t_R(major) = 18.8 min, t_R(minor) = 20.6 min.

Di-*t*-butyl (*R*)-2-(3-(benzoyloxy)-2-(cyclohexylmethyl)propyl)malonate: $[\alpha]_D^{28}$ 2.81 (*c* = 1.16, $CHCl_3$; 84% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (2H, d, *J* = 7.2 Hz, Ar-H), 7.56 (1H, app t, *J* = 7.4 Hz, Ar-H), 7.44 (2H, app t, *J* = 7.6 Hz, Ar-H), 4.29 (1H, dd, *J* = 11.2, 4.0 Hz, -CO_2CHHCH-), 4.17 (1H, dd, *J* = 11.4, 5.0 Hz, -CO_2CHHCH-), 3.35 (1H, app t, *J* = 7.6 Hz, -CH_2CH(CO_2tBu)$_2$), 2.04-1.85 (3H, m, -CO_2CH_2CHCH_2CH(CO_2tBu)$_2$), 1.79-1.62 (6H, m, Cy), 1.46 (9H, s, -C(CH_3)$_3$), 1.44 (9H, s, -C(CH_3)$_3$), 1.35-1.10 (5H, m, Cy), 0.95-0.80 (2H, m, -CHCH_2Cy); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 168.8, 166.6, 132.9, 130.3, 129.6, 128.3, 81.5, 81.4, 67.4, 51.7, 39.5, 34.7, 33.8, 33.3, 32.5, 31.3, 27.91, 27.89, 26.6, 26.23, 26.20; IR (neat) 2922, 1721, 1450, 1368, 1271, 1136, 847, 712 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{28}H_{42}NaO_6$: 497.2874 ([M + Na]$^+$), Found: 497.2871 ([M + Na]$^+$); HPLC analysis: Daicel Chiralcel AD-3, hexane/*i*-PrOH = 100/1, flow rate = 0.3 mL/min, λ = 227 nm, retention time; t_R(major) = 16.7 min, t_R(minor) = 18.5 min.

1,1-Di-*t*-butyl 4-methyl (*R*)-3-(((4-nitrobenzoyl)oxy)methyl)butane-1,1,4-tricarboxylate: $[\alpha]_D^{32}$ 92.0 (*c* = 0.51, $CHCl_3$; 86% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (2H, d, *J* = 8.8 Hz, Ar-H), 8.20 (2H, d, *J* = 8.8 Hz, Ar-H), 4.39 (1H, dd, *J* = 11.4, 4.6 Hz, -CO_2CHH-), 4.33 (1H, dd, *J* = 11.4, 5.4 Hz, HOCHH-), 3.66 (3H, s, -CO_2CH_3), 3.31 (1H, app t, *J* = 7.6 Hz, -CH_2CH(CO_2t-Bu)$_2$), 2.50-2.38 (3H, m, -CH_2CHC$H_2CO_2CH_3$), 2.10-2.00 (1H, m, -CHCHHCH-), 1.99-1.90 (1H, m, -CHCHHCH-), 1.47 (9H, s, -C(CH_3)$_3$), 1.46 (9H, -C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 168.35, 168.32, 164.5, 135.4, 130.8, 126.3, 123.6, 82.0, 81.9, 67.5, 51.8, 51.5, 36.2, 32.9, 30.2, 27.9 (two peaks overlap); IR (neat) 2978, 1724, 1530, 1368, 1273, 1161, 1140, 845, 721 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{24}H_{33}NaO_{10}$: 518.1997 ([M + Na]$^+$), Found: 518.1998 ([M + Na]$^+$); HPLC analysis: Daicel Chiralpak AD-3, hexane/*i*-PrOH = 9/1, flow rate = 0.5 mL/min, λ = 254 nm, retention time; t_R(minor) = 18.4 min, t_R(major) = 20.5 min.

Di-*t*-butyl (*R*)-2-(3-methyl-2-(((4-nitrobenzoyl)oxy)methyl)butyl)malonate: $[\alpha]_D^{30}$ 18.0 (*c* = 1.30, $CHCl_3$; 97% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (2H, d, *J* = 9.2 Hz, Ar-H), 8.22 (2H, d, *J* = 9.2 Hz, Ar-H), 4.40 (1H, dd, *J* = 11.4, 5.4 Hz, -CO_2CHHCH-), 4.28 (1H, dd, *J* = 11.4, 6.2 Hz, -CO_2CHHCH-), 3.33 (1H, dd, *J* = 9.2, 6.4 Hz, -CH_2CH(CO_2t-Bu)$_2$), 2.03 (1H, m, -CHCH(CH_3)$_2$), 1.94-1.84 (2H, m, -CHCH_2CH(CO_2t-Bu)$_2$), 1.70 (1H, m, -CHCH(CH_3)$_2$), 1.46 (9H, s, -C(CH_3)$_3$), 1.45 (9H, s, -C(CH_3)$_3$), 1.00 (3H, d, *J* = 6.8 Hz, -CHCH_3), 0.98 (3H, d, *J* = 7.2 Hz, -CHCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 168.7, 164.7, 150.6, 135.7, 130.8, 123.6, 81.7, 81.6, 66.7, 52.2, 41.1, 29.0, 27.94, 27.92, 27.85, 19.5, 19.2; IR (neat) 2974, 1724, 1530, 1368, 1348, 1273, 1138, 847, 719 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{24}H_{35}NNaO_8$: 488.2255 ([M + Na]$^+$), Found: 488.2256 ([M + Na]$^+$); HPLC analysis: Daicel Chiralpak AS-H, hexane/*i*-PrOH = 40/1, flow rate = 0.2 mL/min, λ

= 254 nm, retention time; t_R(minor) = 25.3 min, t_R(major) = 26.4 min.

Synthesis of (*R*)-5-benzyltetrahydro-2*H*-pyran-2-one (9)

To a solution of (*R*)-di-*t*-butyl 2-(3-hydroxy-2-benzylpropyl)malonate (**7**) (14.4 mg, 0.040 mmol) in toluene (1.0 mL) was added trifluoroacetic acid (13 μL, 0.16 mmol) at room temperature. After stirring for 48 h at 80 °C, the mixture was diluted with H_2O (2.0 mL). The resulting mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and then concentrated. The resulting residue was purified by preparative thin layer chromatography (eluting with hexane/ethyl acetate = 3/1) to give (*R*)-5-benzyltetrahydro-2*H*-pyran-2-one (**9**). [99% yield (7.6 mg)].

(*R*)-5-Benzyltetrahydro-2*H*-pyran-2-one (9): ^{1}H NMR, ^{13}C NMR and IR match those reported in the literature.[8] $[\alpha]_D^{30}$ –1.06 (*c* = 0.83, $CHCl_3$; 95% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.28 (2H, m, Ar-H), 7.25-7.21 (1H, m, Ar-H), 7.18-7.13 (2H, m, Ar-H), 4.31 (1H, ddd, *J* = 11.2, 4.4, 1.8 Hz, -CO_2CHH-), 4.02 (1H, dd, *J* = 11.2, 9.6 Hz, -CO_2CHH-), 2.70-2.56 (3H, m, -O_2CCHH-, -CH_2Ph), 2.49 (1H, ddd, *J* = 18.0, 9.6, 7.6 Hz, -O_2CCHH-), 2.28-2.16 (1H, m, -CHCH_2Ph), 2.03-1.98 (1H, m, -O_2CCH_2CHH-), 1.67-1.56 (1H, m, -O_2CCH_2CHH-); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 138.4, 128.8, 128.7, 126.7, 73.1, 37.9, 34.7, 29.0, 25.3; IR (neat) 2924, 1734, 1456, 1246, 1182, 1053, 914, 746, 702 cm^{-1}; HPLC analysis: Daicel Chiralcel OD-H, hexane/*i*-PrOH = 9/1, flow rate = 0.5 mL/min, λ = 207 nm, retention time; t_R(minor) = 47.3 min, t_R(major) = 54.6 min.

Synthesis of di-*t*-butyl (*S*)-4-benzyldihydrofuran-2,2(3*H*)-dicarboxylate (10) [9]

To a solution of di-*t*-butyl (*R*)-2-(3-hydroxy-2-benzylpropyl)malonate (**7**) (16.3 mg, 0.045 mmol) in chloroform (5.0 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (68 μL, 0.46 mmol), and the mixture was stirred for 0.5 h at 0 °C. One equivalent of trifluoromethanesulfonyl chloride (4.8 μL, 0.045 mmol) was added five times in every 3 h at 0 °C (total 0.23 mmol of trifluoromethanesulfonyl chloride). The mixture was then stirred for 8 h at room temperature. The reaction mixture was quenched and washed with H_2O. The organic layer was dried over Na_2SO_4 and then concentrated. The resulting residue was purified by preparative thin layer chromatography (eluting with hexane/ethyl acetate = 3/1) to give di-*t*-butyl (*S*)-4-benzyldihydrofuran-2,2(3*H*)-dicarboxylate (**10**). [70% yield (11.4 mg)].

Di-*t*-butyl (*S*)-4-benzyldihydrofuran-2,2(3*H*)-dicarboxylate (10): $[\alpha]_D^{27}$ –17.2 (*c* = 0.76, $CHCl_3$; 95% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.25 (2H, m, Ar-H), 7.23-7.19 (1H, m, Ar-H), 7.19-7.13 (2H, m, Ar-H), 4.08 (1H, dd, *J* = 8.2, 6.6 Hz, -OCHHCH-), 3.71 (1H, dd, *J* = 8.4, 3.6 Hz, -OCHHCH-), 2.73-2.59 (3H, m, -CHHCHCH_2Ph), 2.52 (1H, dd, *J* = 13.2, 7.6 Hz, -CHHCH-), 2.06

(1H, dd, *J* = 13.2, 8.0 Hz, -CHCH$_2$Ph), 1.49 (9H, s, -C(CH$_3$)$_3$), 1.46 (9H, s, -C(CH$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 168.6, 140.1, 128.6, 128.5, 126.2, 87.2, 82.23, 82.15, 75.0, 40.8, 38.6, 38.3, 27.9, 27.8; IR (neat) 2978, 1732, 1369, 1300, 1252, 1146, 1113, 845, 702 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{21}H_{30}NaO_5$: 385.1985 ([M + Na]$^+$), Found: 385.1987 ([M + Na]$^+$); HPLC analysis: Daicel Chiralpak AD-H, hexane/*i*-PrOH = 40/1, flow rate = 0.5 mL/min, λ = 208 nm, retention time; t_R(minor) = 14.9 min, t_R(major) = 18.4 min.

Synthesis of di-*t*-butyl (*R*)-2-(2-benzyl-3-(benzylamino)propyl)malonate (11)

A mixture of di-*t*-butyl methylenemalonate (34.0 mg, 0.15 mmol) and 3-phenylpropanal (61 μL, 0.46 mmol) in diethyl ether (1.5 mL) was stirred at 0 °C. To the mixture was then added (*S*)-**5** (8.6 mg, 0.014 mmol). After stirring for 4 h at 0 °C, benzylamine (52 μL, 0.48 mmol) was added. After stirring for 3 h at 0 °C, MeOH (1.0 mL) and sodium borohydride (30 mg) were added successively, and the mixture was vigorously stirred for 0.5 h at room temperature. The reaction mixture was quenched with saturated NH_4Cl. The resulting mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and then concentrated. The residue was purified by preparative thin layer chromatography (eluting with hexane/ethyl acetate = 3/1) to give di-*t*-butyl (*R*)-2-(2-benzyl-3-(benzylamino)propyl)malonate (**11**). [99% yield (66.9 mg)].

Di-*t*-butyl (*R*)-2-(2-benzyl-3-(benzylamino)propyl)malonate (11): $[\alpha]_D^{31}$ 10.4 (*c* = 1.61, $CHCl_3$; 93% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.10 (10H, m, Ar-H), 3.72 (1H, d, *J* = 13.2 Hz, PhCHHNH-), 3.69 (1H, d, *J* = 13.2 Hz, PhCHHNH-), 3.32 (1H, app t, *J* = 7.6 Hz, -CH$_2$CH(CO$_2$*t*-Bu)$_2$), 2.64 (2H, m, -CHCH$_2$Ph), 2.53 (2H, m, -NHCH$_2$CH-), 1.96-1.76 (3H, m, -CHCH$_2$CH(CO$_2$*t*-Bu)$_2$), 1.45 (9H, s, -C(CH$_3$)$_3$), 1.34 (9H, s, -C(CH$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0 (two peaks overlap), 140.7, 140.5, 129.2, 128.3 (two peaks overlap), 128.1, 126.8, 125.9, 81.3, 81.2, 54.0, 52.0, 51.9, 39.0, 38.3, 31.4, 27.94, 27.86; IR (neat) 2976, 2930, 1722, 1452, 1367, 1254, 1138, 847, 741, 698 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{28}H_{40}NO_4$: 454.2952 ([M + H]$^+$), Found: 454.2955 ([M + H]$^+$); HPLC analysis: Daicel Chiralcel OD-H, hexane/*i*-PrOH = 40/1, flow rate = 0.5 mL/min, λ = 206 nm, retention time; t_R(minor) = 13.9 min, t_R(major) = 16.4 min.

Synthesis of (*R*)-1,5-dibenzylpiperidin-2-one (12)

To a solution of di-*t*-butyl (*R*)-2-(2-benzyl-3-(benzylamino)propyl)malonate (**11**) (36.5 mg, 0.081 mmol) in toluene (1.0 mL) was added trifluoroacetic acid (25 μL, 0.33 mmol) at room temperature. After stirring for 48 h at 100 °C, the mixture was diluted with H_2O (2.0 mL). The resulting mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and then concentrated. The residue was purified by preparative thin layer chromatography (eluting with hexane/ethyl acetate = 2/1) to give (*R*)-1,5-dibenzylpiperidin-2-one (**12**). [91% yield (20.3 mg)].

(*R*)-1,5-Dibenzylpiperidin-2-one (12): ^{1}H NMR, ^{13}C NMR and IR match those reported in the literature.[10] $[\alpha]_D^{33}$ –39.0 (*c* = 1.00, $CHCl_3$; 93% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.17 (8H, m, Ar-H), 7.05 (2H, d, *J* = 7.6 Hz, Ar-H), 4.63 (1H, d, *J* = 14.8 Hz, PhCHHN-), 4.49 (1H, d, *J* = 14.8 Hz, PhCHHN-), 3.19 (1H, ddd, *J* = 12.4, 5.2, 1.6 Hz, -NCHHCH-), 2.95 (1H, dd, *J* = 12.2, 9.8 Hz, -NCHHCH-), 2.62-2.47 (3H, m, -NCOCHH-, -CH_2Ph), 2.39 (1H, ddd, *J* = 18.6, 11.2, 6.6 Hz, -NCOCHH-), 2.13-2.02 (1H, br, -CHCH$_2$Ph), 1.92-1.83 (1H, br, -CHCHHCH$_2$-), 1.66-1.44 (1H, m, -CHCHHCH$_2$-); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 139.1, 137.2, 128.9, 128.6, 128.5, 128.1, 127.4, 126.3, 52.3, 50.3, 39.4, 35.7, 31.3, 26.9; IR (neat) 2924, 2853, 1721, 1454, 1260, 739, 700 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{19}H_{22}NO$: 280.1696 ([M + H]$^+$), Found: 280.1694 ([M + H]$^+$); HPLC analysis: Daicel Chiralcel OJ-H, hexane/*i*-PrOH = 9/1, flow rate = 0.3 mL/min, λ = 208 nm, retention time; t_R(minor) = 60.8 min, t_R(major) = 63.2 min.

Synthesis of di-*t*-butyl (*S*)-1,4-dibenzylpyrrolidine-2,2-dicarboxylate (13)[11]

To a solution of di-*t*-butyl (*R*)-2-(2-benzyl-3-(benzylamino)propyl)malonate (**11**) (30.0 mg, 0.066 mmol) and iodosobenzene diacetate (33.0 mg, 0.10 mmol) in THF (2.0 mL) was added tetrabutylammonium iodide (38.0 mg, 0.10 mmol). After stirring for 15 h at room temperature, the mixture was concentrated under reduced pressure. The resulting residue was purified by preparative thin layer chromatography (eluting with hexane/ethyl acetate = 20/1) to give di-*t*-butyl (*S*)-1,4-dibenzylpyrrolidine-2,2-dicarboxylate (**13**). [61% yield (18.3 mg)].

Di-*t*-butyl (*S*)-1,4-dibenzylpyrrolidine-2,2-dicarboxylate (13): $[\alpha]_D^{28}$ –4.24 (*c* = 1.18, $CHCl_3$; 93% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (2H, d, *J* = 7.6 Hz, Ar-H), 7.32-7.28 (2H, t, *J* = 7.6 Hz, Ar-H), 7.24-7.18 (3H, m, Ar-H), 7.16-7.08 (3H, m, Ar-H), 3.98 (2H, s, PhCH_2N-), 2.84 (1H, dd, *J* = 8.2, 6.6 Hz, -CHCHHN-), 2.68 (2H, d, *J* = 6.8 Hz, -CHCH_2Ph), 2.61-2.45 (3H, m, -CH_2CHCHHN-), 2.12-2.02 (1H, m, -CHCH$_2$Ph), 1.50 (9H, s, -C(CH_3)$_3$), 1.46 (9H, s, -C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 169.9, 140.9, 140.6, 128.7, 128.3, 128.11, 128.09, 126.6, 125.8, 81.7, 81.5, 75.5, 57.1, 54.7, 40.6, 40.5, 37.5, 28.11, 28.06; IR (neat) 2976, 1724, 1454, 1368, 1254, 1144, 847, 737, 700 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{28}H_{38}NO_4$: 452.2795 ([M + H]$^+$), Found: 452.2776 ([M + H]$^+$); HPLC analysis: Daicel Chiralcel OZ-H, hexane/*i*-PrOH = 400/1, flow rate = 0.5 mL/min, λ = 204 nm, retention time; t_R(major) = 10.5 min, t_R(minor) = 11.7 min.

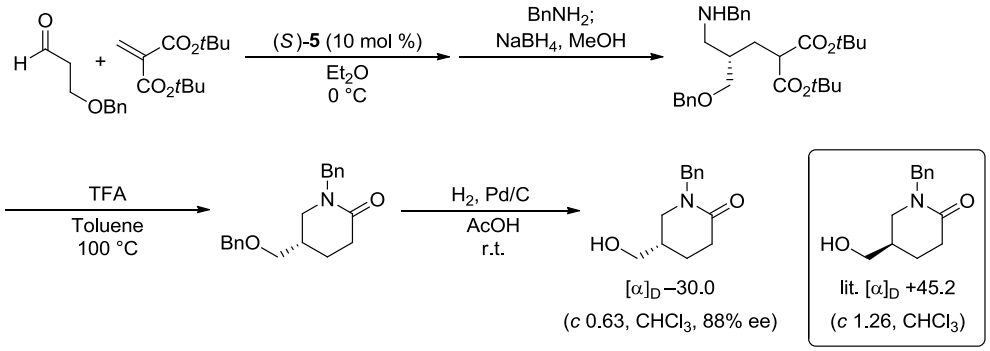
Synthesis of di-*t*-butyl (*S*)-5-benzylcyclohex-3-ene-1,1-dicarboxylate (14)[12]

A mixture of di-*t*-butyl methylenemalonate (16.7 mg, 0.073 mmol) and 3-phenylpropanal (13.1 μL, 0.099 mmol) in diethyl ether (0.8 mL) was stirred at 0 °C. To the mixture was then added (*S*)-**5** (5.0 mg, 7.4 μmol). The mixture was stirred for 4 h at 0 °C, and diluted with THF (0.8 mL). To the

mixture were added vinyltriphenylphosphonium bromide (92.0 mg, 0.25 mmol) and sodium hydride (20.0 mg, 0.50 mmol) were added at –78 °C. The whole mixture was stirred for 2 h at –78 °C, and quenched with saturated NH_4Cl (2.0 mL) was added. The resulting mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and then concentrated. The residue was purified by preparative thin layer chromatography (eluting with hexane/ethyl acetate = 8/1) to give di-*t*-butyl (*S*)-5-benzylcyclohex-3-ene-1,1-dicarboxylate (**14**). [61% yield (31.0 mg)].

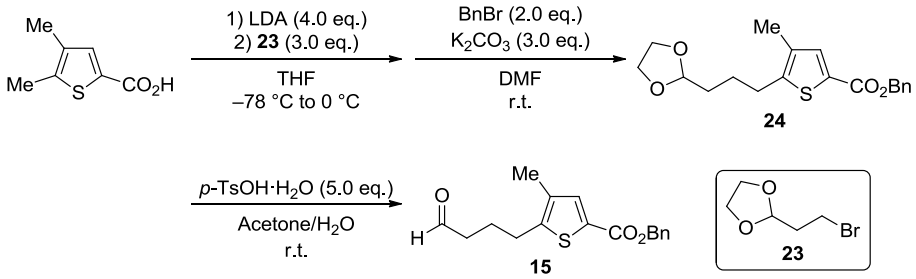
Di-*t*-butyl (*S*)-5-benzylcyclohex-3-ene-1,1-dicarboxylate (14): $[\alpha]_D^{31}$ 21.1 (*c* = 1.20, $CHCl_3$; 92% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.28 (2H, m, Ar-H), 7.22-7.13 (3H, m, Ar-H), 5.69-5.63 (1H, m, -CH_2CH=CHCH-), 5.55 (1H, d, *J* = 10.0 Hz, -CH_2CH=CHCH-), 2.72-2.55 (3H, m, -CHHCH=CH-, -CH_2Ph), 2.48-2.36 (1H, br, -CH-), 2.26-2.13 (2H, m, -CHHCH=CHCHCHH-,), 1.55-1.43 (1H, m, -CHCHHCCH_2-), 1.42 (9H, s, -C(CH_3)$_3$), 1.39 (9H, s, -C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 170.0, 140.0, 130.2, 129.0, 128.2, 126.0, 124.4, 81.2, 80.7, 54.5, 42.3, 34.8, 34.0, 27.84, 27.77; IR (neat) 2976, 2928, 1726, 1368, 1256, 1167, 1142, 1082, 847, 700 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{23}H_{32}NaO_4$: 395.2193 ($[M + Na]^+$), Found: 395.2199 ($[M + Na]^+$); HPLC analysis: Daicel Chiralcel OD-3, hexane/*i*-PrOH = 400/1, flow rate = 0.5 mL/min, λ = 210 nm, retention time; t_R(minor) = 17.2 min, t_R(major) = 18.2 min.

Determination of absolute stereochemistry of the conjugate addition product



The optical rotaion of (*R*)-1-benzyl-5-(hydroxymethyl)piperidin-2-one was reported.[13] Based on this information, the absolute configuration of the product obtained in the (*S*)-**5** catalyzed conjugate addition between 3-benzyloxypropanal and di-*t*-butyl 2-methylenemalonate was determined to be *S* by converting to 1-benzyl-5-(hydroxymethyl)piperidin-2-one and by comparison of the sign of the optical rotation.

Synthesis and characterization of aldehyde 15[14]



Acetal 24: To a solution of diisopropylamine (1.13 mL, 8.0 mmol) in tetrahydrofuran (10 mL) was added a 1.6 M hexane solution of *n*-butyllithium (5.0 mL, 8.0 mmol) at –78 °C. The mixture was stirred for 1 h at 0 °C. A solution of 4,5-dimethyl-2-thiophenecarboxylic acid (309 mg, 2.0 mmol) in tetrahydrofuran (4.0 mL) was added to the mixture at –78 °C. After stirring for 1 h at 0 °C, 2-(2-bromoethyl)-1,3-dioxolane (**23**) (720 μL, 6.1 mmol) was added to the mixture. The mixture was stirred for 2 h at room temperature. After addition of saturated NH_4Cl, the mixture was acidified with 1 N HCl. After extraction with ethyl acetate, the organic layer was washed with brine, dried over Na_2SO_4 and then concentrated. The residue containing the alkylation product was used for the next step without further purifications.

To the mixture obtained above in DMF (20 mL) were added potassium carbonate (830 mg, 6.0 mmol) and benzylbromide (470 μL, 3.9 mmol) at room temperature. The mixture was stirred for 5 h at room temperature. After addition of H_2O, the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and then concentrated. The residue was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate = 4/1) to give **24**. [83% yield (575 mg)].

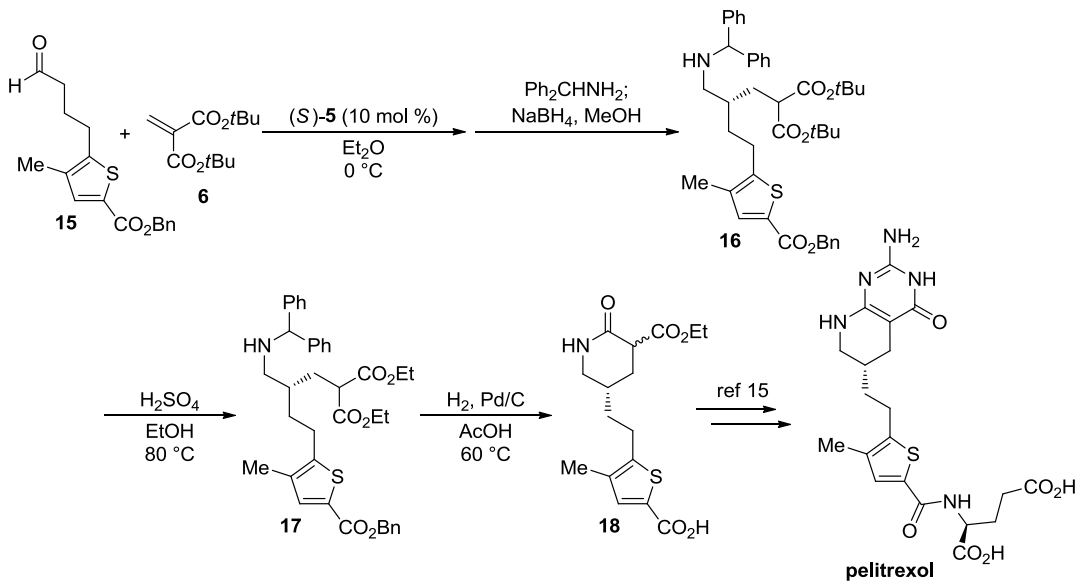
Benzyl 5-(3-(1,3-dioxolan-2-yl)propyl)-4-methylthiophene-2-carboxylate (24): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (1H, s, Ar-H), 7.45-7.29 (5H, m, Ar-H), 5.29 (2H, s, -CO_2CH_2Ph), 4.87 (1H, app t, *J* = 4.4 Hz, -$CH_2CH(OCH_2)_2$, 4.00-3.90 (2H, m, -OCHHCHHO-), 3.90-3.80 (2H, m, -OCHHCHHO-), 2.78 (2H, t, *J* = 7.0 Hz, -CH_2Ar), 2.14 (3H, s, ArCH_3), 1.84-1.67 (4H, m, -$CHCH_2CH_2CH_2$-); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 147.3, 136.5, 136.1, 134.1, 128.53, 128.46, 128.1, 128.0, 104.1, 66.4, 64.9, 33.1, 28.3, 25.2, 13.6; IR (neat) 2951, 2882, 2359, 1705, 1456, 1279, 1242, 1059, 750, 698 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{19}H_{22}NaO_4S$: 369.1131 ([M + Na]$^+$), Found: 369.1138 ([M + Na]$^+$).

Aldehyde 15: To a solution of acetal **24** (79.7 mg, 0.23 mmol) in acetone (4.0 mL) and H_2O (2.0 mL) was added *p*-toluenesulfonic acid monohydrate (930 mg, 4.9 mmol) at room temperature. After stirring for 30 h at room temperature, the mixture was cooled to room temperature. The reaction mixture was quenched with H_2O and extracted with dichloromethane. The organic layer was dried

over Na_2SO_4 and then concentrated. The residue was purificated by flash column chromatography on silica gel (eluting with hexane/ethyl acetate = 4/1) to give **15**. [93% yield 64.7 mg)].

Benzyl 4-methyl-5-(4-oxobutyl)thiophene-2-carboxylate (15): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (1H, t, *J* = 1.2 Hz, -C<u>H</u>O), 7.53 (1H, s, Ar-<u>H</u>), 7.45-7.30 (5H, m, Ar-<u>H</u>), 5.30 (2H, s, -$CO_2C\underline{H}_2$Ph), 2.79 (2H, t, *J* = 7.8 Hz, -$C\underline{H}_2$Ar), 2.52 (2H, td, *J* = 7.2, 1.2 Hz, -$C\underline{H}_2$CHO), 2.15 (3H, s, Ar$C\underline{H}_3$), 1.97 (2H, tt, *J* = 7.4, 7.4 Hz, -$CH_2C\underline{H}_2CH_2$-); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.4, 162.1, 146.0, 136.5, 136.0, 134.6, 128.9, 128.6, 128.2, 128.1, 66.5, 42.8, 27.5, 23.2, 13.6; IR (neat) 2947, 2359, 1705, 1454, 1279, 1242, 1061, 748 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{17}H_{18}NaO_3S$: 325.0874 ([M + Na]$^+$), Found: 325.0873 ([M + Na]$^+$).

Formal Synthesis of Pelitrexol



Amine 16: A mixture of di-*t*-butyl methylenemalonate (51.0 mg, 0.22 mmol) and aldehyde **15** (102 mg, 0.34 mmol) in diethyl ether (2.0 mL) was stirred at 0 °C. To the mixture was then added (*S*)-**5** (14 mg, 0.023 mmol). After stirring for 4 h at 0 °C, benzhydrylamine (78 μL, 0.46 mmol) was added. After stirring for 3 h at 0 °C, MeOH (2.0 mL) and sodium borohydride (30 mg) were added successively, and the mixture was vigorously stirred for 0.5 h at room temperature. The reaction mixture was quenched with saturated NH_4Cl. The resulting mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and then concentrated. The residue was purified by preparative thin layer chromatography (eluting with hexane/ethyl acetate = 6/1) to give **16**. [72% yield (110.5 mg)].

Di-*t*-butyl (*R*)-2-(2-((benzhydrylamino)methyl)-4-(5-((benzyloxy)carbonyl)-3-methylthiophen-2-yl)butyl) malonate (16): $[\alpha]_D^{21}$ –4.02 (*c* = 1.22, $CHCl_3$; 94% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (1H, s, Ar-H), 7.44-7.30 (10H, m, Ar-H), 7.30-7.24 (3H, m, Ar-H), 7.18 (2H, m, Ar-H), 5.29 (2H, s, -CO_2CH_2Ph), 4.74 (1H, s, Ph_2CHNH-), 3.27 (1H, app t, *J* = 7.6 Hz, -$CH_2CH(CO_2t$-Bu)$_2$), 2.68 (2H, t, *J* = 8.0 Hz, -CH_2CH_2Ar), 2.54 (2H, d, *J* = 4.8 Hz, -NHCH_2CH-), 2.10 (3H, s, ArCH_3), 1.96-1.50 (5H, m, -$CH_2CHCH_2CH_2$Ar), 1.43 (9H, s, -C(CH_3)$_3$), 1.41 (9H, s, -C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.94, 168.92, 162.2, 147.7, 144.2 (two peaks overlap), 136.5, 136.1, 134.0, 128.53, 128.48, 128.46, 128.3, 128.13, 128.05, 127.24, 127.21, 127.0 (two peaks overlap), 81.4 (two peaks overlap), 67.9, 66.4, 51.8, 50.7, 36.3, 33.5, 31.4, 27.9 (two peaks overlap), 25.8, 13.6; IR (neat) 2976, 1711, 1452, 1244, 1161, 1140, 748, 700 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{42}H_{52}NO_6S$: 698.3510 ($[M + H]^+$), Found: 698.3504 ($[M + H]^+$); HPLC analysis: Daicel Chiralcel OD-H(triple), hexane/*i*-PrOH = 9/1, flow rate = 0.3 mL/min, λ = 287 nm, retention time; t_R(major) = 74.1 min, t_R(minor) = 79.8 min.

Ester 17: To a solution of amine **16** (98.1 mg, 0.14 mmol) in ethanol (25 mL) were added five drops of conc. sulfonic acid at room temperature. The mixture was stirred for 72 h at 80 °C. After neutralized with saturated $NaHCO_3$, the mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate, washed with H_2O and brine, dried over Na_2SO_4, and then concentrated. The residue was purified by preparative thin layer chromatography (eluting with hexane/ethyl acetate = 3/1) to give **17**. [83% yield (75.0 mg)].

Diethyl (*R*)-2-(2-((benzhydrylamino)methyl)-4-(5-((benzyloxy)carbonyl)-3-methylthiophen-2-yl)butyl) malonate (17): $[\alpha]_D^{22}$ –3.75 (*c* = 0.70, $CHCl_3$; 94% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (1H, s, Ar-H), 7.45-7.23 (13H, m, Ar-H), 7.19 (2H, t, *J* = 7.2 Hz, Ar-H), 5.30 (2H, s, -CO_2CH_2Ph), 4.73 (1H, s, Ph_2CHNH-), 4.25-4.06 (4H, m, -$CO_2CH_2CH_3$), 3.51 (1H, app t, *J* = 7.6 Hz, -$CH_2CH(CO_2Et)_2$), 2.69 (2H, t, *J* = 7.8 Hz, -CH_2CH_2Ar), 2.54 (2H, d, *J* = 5.6 Hz, -NHCH_2CH-), 2.10 (3H, s, ArCH_3), 2.02-1.90 (2H, m, -$CHCH_2CH(CO_2Et)_2$), 1.85-1.53 (3H, m, -$CHCH_2CH_2$Ar), 1.24 (3H, t, *J* = 6.8 Hz, - $CO_2CH_2CH_3$), 1.22 (3H, t, *J* = 7.0 Hz, -$CO_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 169.5, 162.1, 147.5, 144.13, 144.10, 136.5, 136.1, 134.0, 128.53, 128.47 (two peaks overlap), 128.3, 128.1, 128.0, 127.20, 127.18, 127.0 (two peaks overlap), 67.9, 66.4, 61.42, 61.40, 50.8, 50.0, 36.3, 33.5, 31.6, 25.7, 14.0(two peaks overlap), 13.5; IR (neat) 2932, 1728, 1705, 1450, 1277, 1242, 1180, 1063, 748, 700 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{38}H_{44}NO_6S$: 642.2884 ($[M + H]^+$), Found: 642.2881 ($[M + H]^+$); HPLC analysis: Daicel Chiralpak AD-H, hexane/*i*-PrOH = 9/1, flow rate = 0.5 mL/min, λ = 288 nm, retention time; t_R(minor) = 37.7 min, t_R(major) = 45.6 min.

Lactam 18: To a solution of ethyl ester **17** (45 mg, 0.070 mmol) in acetic acid (2.0 mL) was added palladium on carbon (15 mg) at room temperature. Hydrogen gas (balloon) was then charged to the reaction flask, and the mixture was stirred for 2 h at 60 °C. The reaction mixture was filtered through celite with acetic acid, and concentrated. The residue was purified by preparative thin layer chromatography (eluting with ethyl acetate/acetic acid = 100/1) to give **18**. [64% yield (15.2 mg)].

5-(2-((3*S*)-5-(ethoxycarbonyl)-6-oxopiperidin-3-yl)ethyl)-4-methylthiophene-2-carboxylic acid (18) (1/1 diastereo mixture): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (1H, s, Ar-H), 4.28-4.17 (2H, m, -$CO_2CH_2CH_3$), 3.51-3.35 (2H, m, -$NHCH_2CH$-), 3.14-2.94 (1H, m, -CH_2CHCO_2Et), 2.88-2.70 (2H, m, -CH_2CH_2Ar), 2.30-2.10 (1H, br, -CH_2CHCH_2-), 2.16 (3H, s, $ArCH_3$), 1.96-1.64 (4H, m, -CH_2CHCH_2-), 1.30 (1.5H, t, *J* = 7.4 Hz, -$CO_2CH_2CH_3$), 1.28 (1.5H, t, *J* = 7.4 Hz, -$CO_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 170.2, 169.1, 168.9, 166.39, 166.35, 146.9, 146.7, 137.3, 137.2, 134.5 (two peaks overlap), 128.9 (two peaks overlap), 61.8, 61.6, 48.6, 47.3, 47.2, 46.8, 34.2, 33.8, 32.0, 30.8, 30.1, 29.4, 25.8, 25.7, 14.1 (two peaks overlap), 13.62, 13.60; IR (neat) 3292, 2926, 2361, 2340, 1732, 1670, 1460, 1260, 1184, 1051, 760 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{16}H_{21}NNaO_5S$: 362.1033 ($[M + Na]^+$), Found: 362.1032 ($[M + Na]^+$). The enantiomeric excess was determined by HPLC after conversion to the corresponding methyl ester (94/94 % ee).

References

1) T. Ooi, M. Kameda and K. Maruoka, *J. Am. Chem. Soc.*, 2003, **125**, 5139.

2) T. Kano, M. Ueda, J. Takai and K. Maruoka, *J. Am. Chem. Soc.*, 2006, **128**, 6046.

3) P. M. Pihko and J. E. Aho, *Org. Lett.*, 2004, **6**, 3849.

4) J. E. Baldwin, T. D. W. Claridge, A. J. Culshaw, F. A. Heupel, S. Smrcková and R. C. Whitehead, *Tetrahedron Lett.*, 1996, **37**, 6919.

5) M. Stratakis, R. Nencka and C. Rabalakos, *J. Org. Chem.*, 2002, **67**, 8758.

6) A. Bugarin, K. D. Jones and B. T. Connell, *Chem. Commun.*, 2010, 1715.

7) Y. G. Wang, M. Ueda, X. Wang, Z. Han and K. Maruoka, *Tetrahedron*, 2007, **63**, 6042.

8) L. Wang, K. Thai and M. Gravel, *Org. Lett.*, 2009, **11**, 891.

9) G. H. Hakimelahi and G. Just, *Tetrahedron Lett.*, 1979, **20**, 3645.

10) G. Satyanarayana and M. E. Maier, *Tetrahedron*, 2008, **64**, 356.

11) (*a*) Y. Ye, C. Zheng and R. Fan, *Org. Lett.*, 2009, **11**, 3156; (*b*) R. Fan, H. Wang, Y. Ye and J. Gan, *Tetrahedron Lett.*, 2010, **51**, 453.

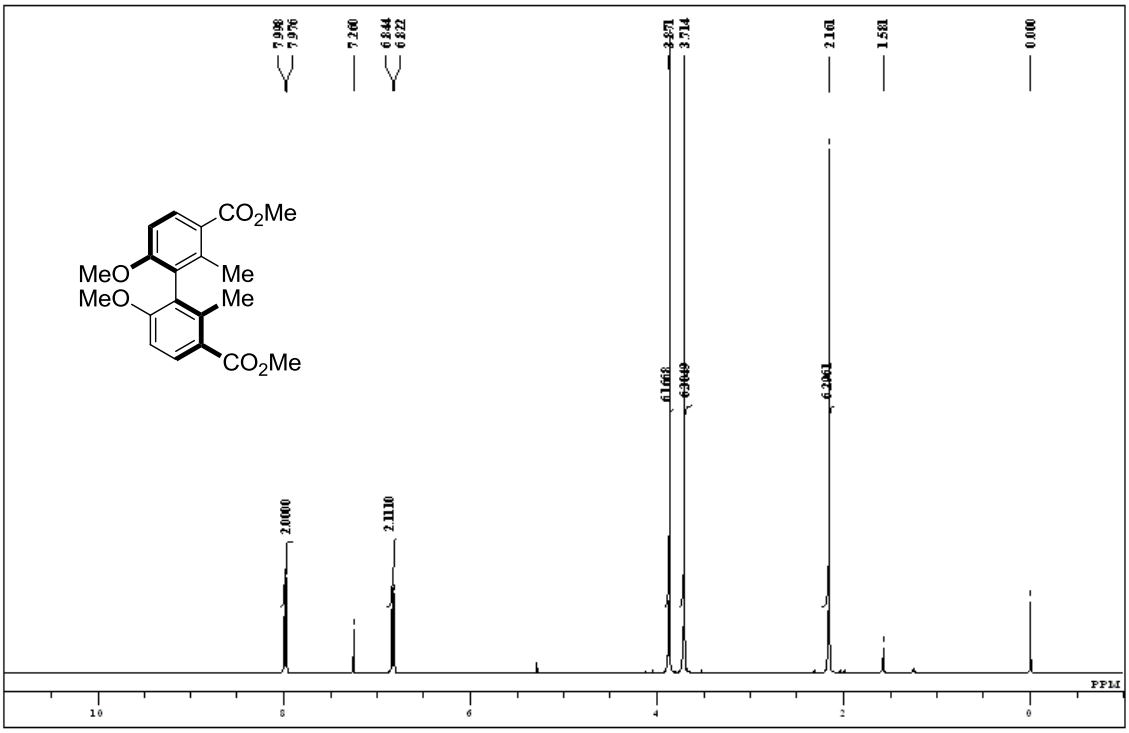
12) M. E. Kuehne and P. J. Reider, *J. Org. Chem.*, 1985, **50**, 1464.

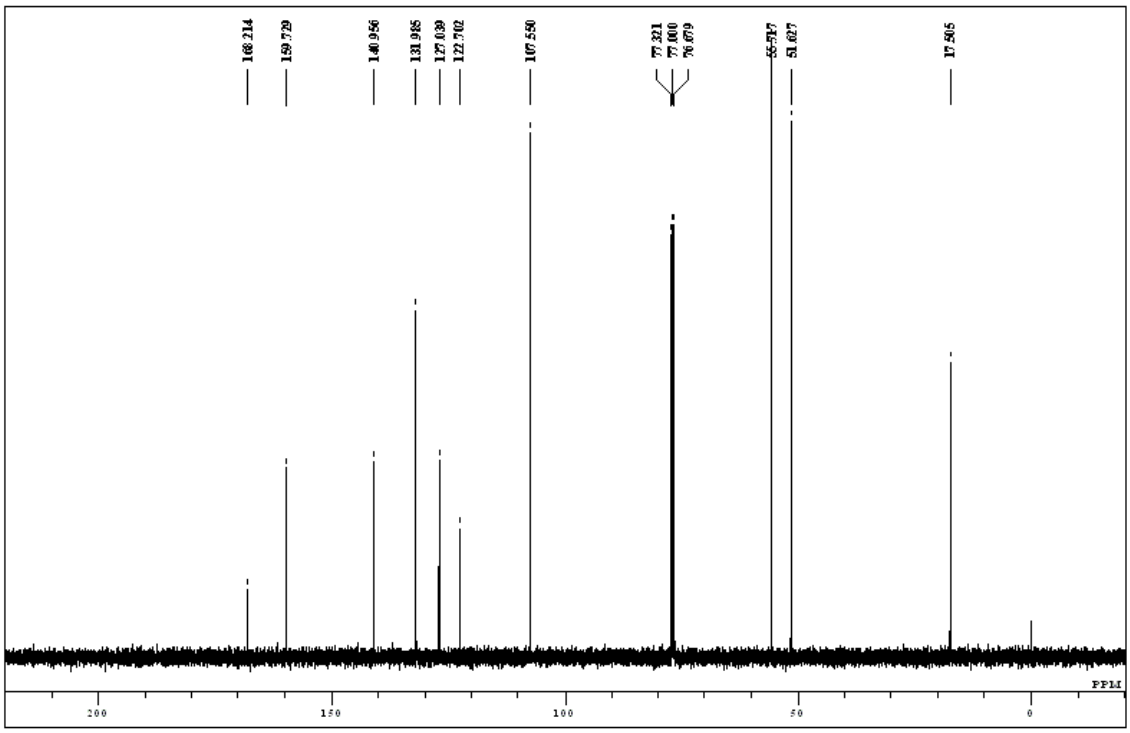
13) D. Gray and T. Gallagher, *Angew. Chem., Int. Ed.*, 2006, **45**, 2419.

14) N. P. Gould and T.-J. Lee, *J. Org. Chem.*, 1980, **45**, 4528.

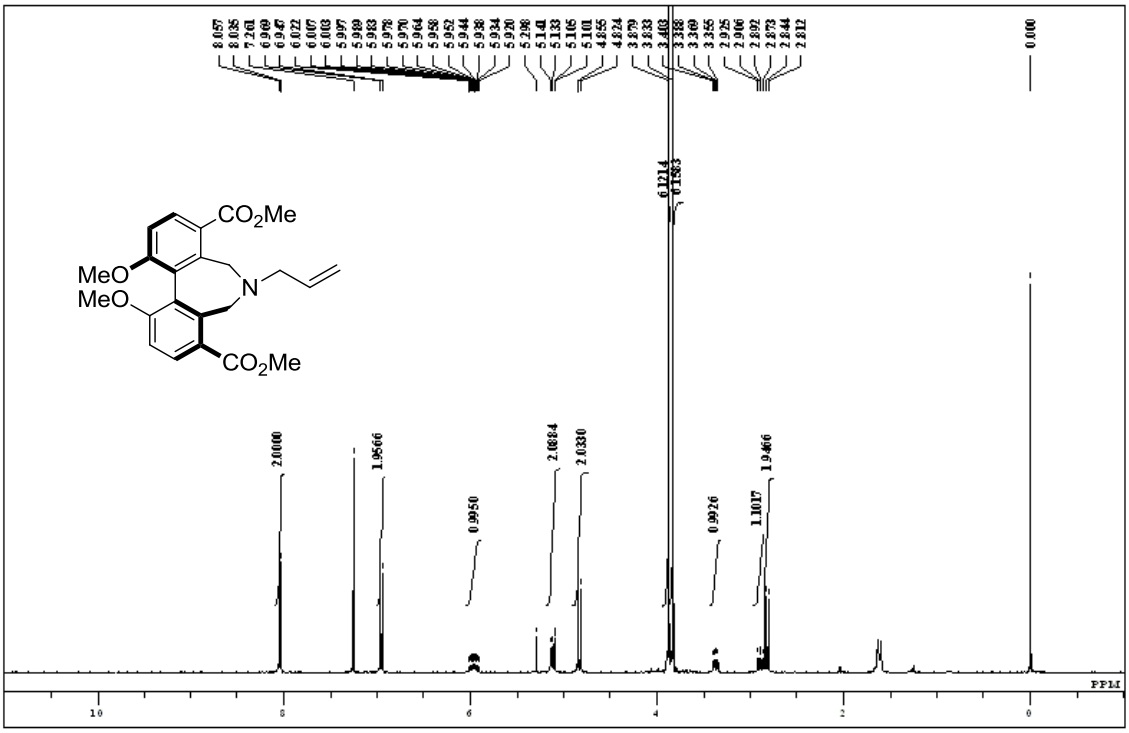
15) *WO*, 074083, 2003.

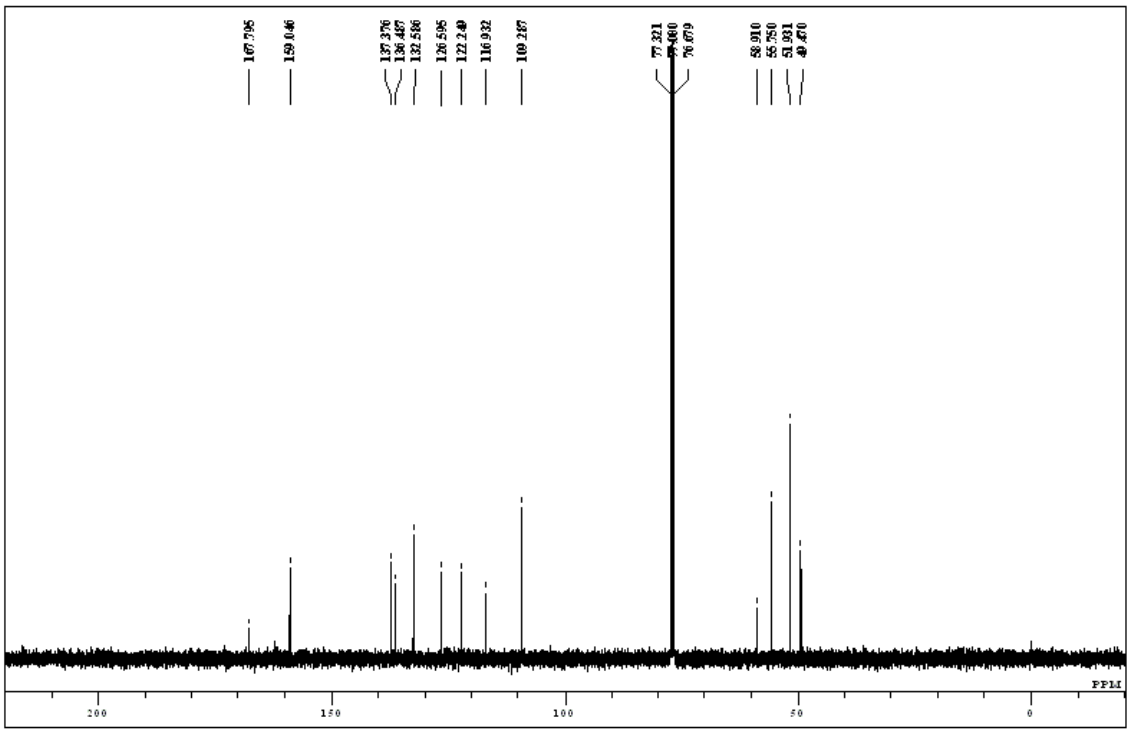
Diester (*S*)-20


7.998
7.976
7.260
6.844
6.822
3.871
3.714
2.161
1.581
0.000
CO2Me
MeO
Me
MeO
Me
CO2Me
2.0000
2.1110
6.1668
6.3049
6.2961
PPM
10
8
6
4
2
0

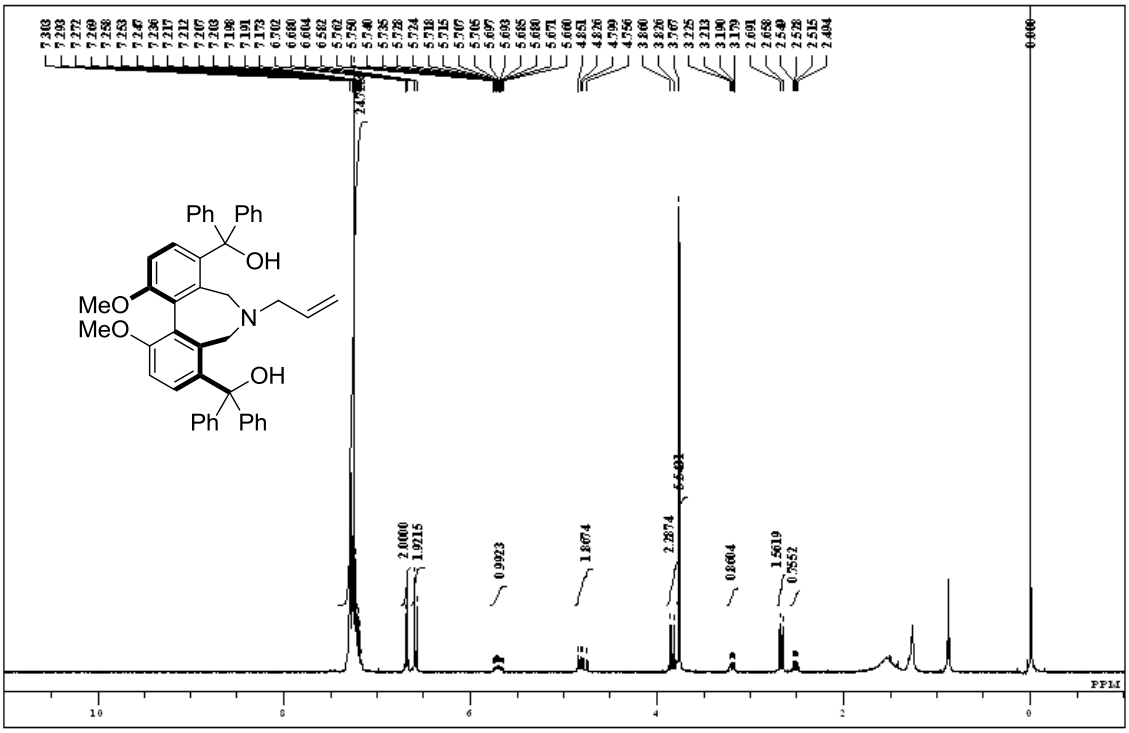

168.214
159.729
140.956
131.985
127.639
122.702
107.550
77.321
77.000
76.679
55.727
51.627
17.505
PPM
200
150
100
50
0

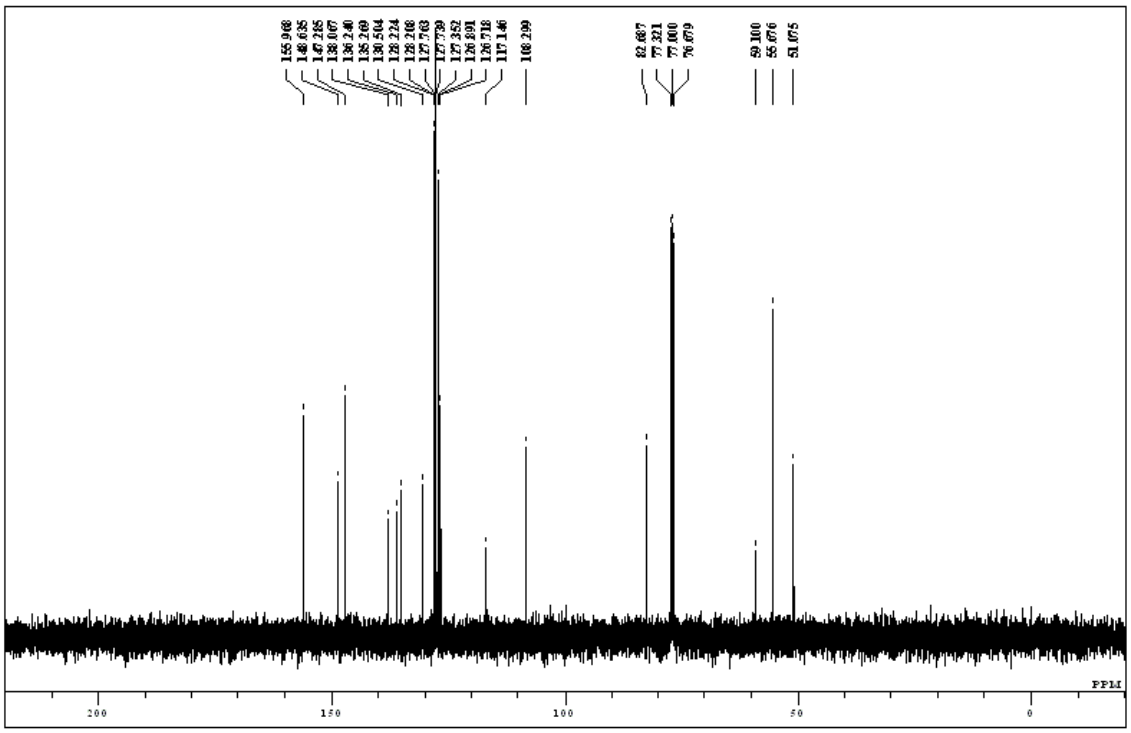
Allylamine (*S*)-21



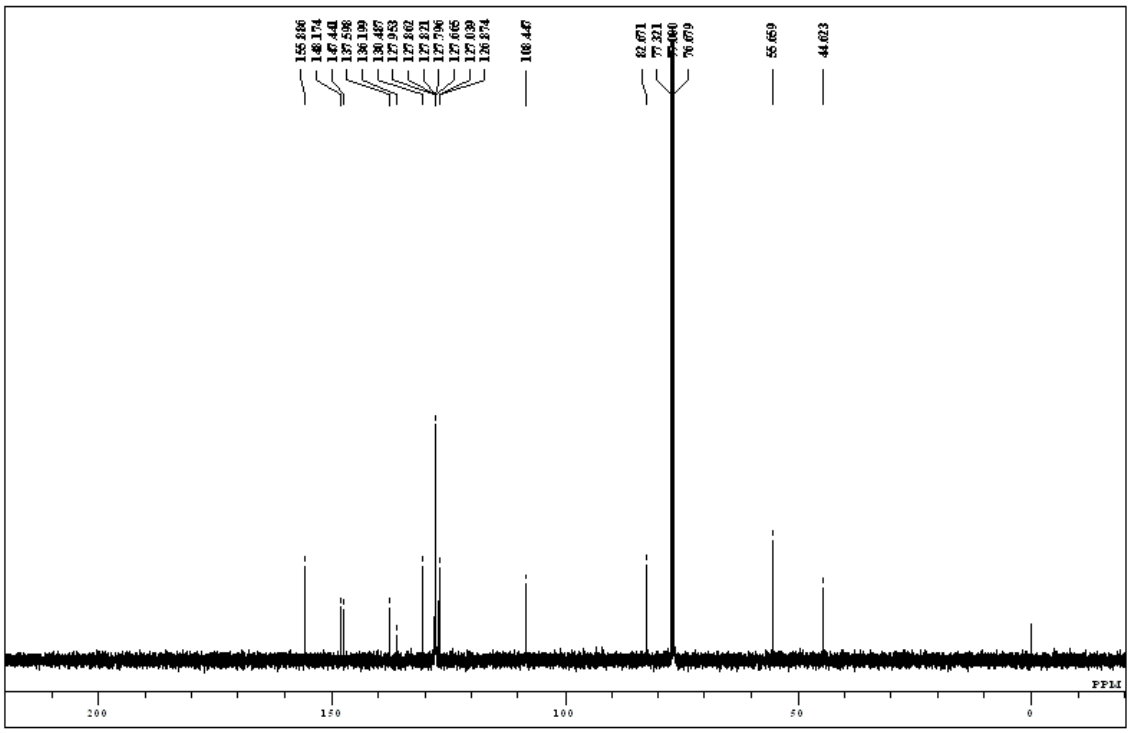


Aminoalcohol (*S*)-22

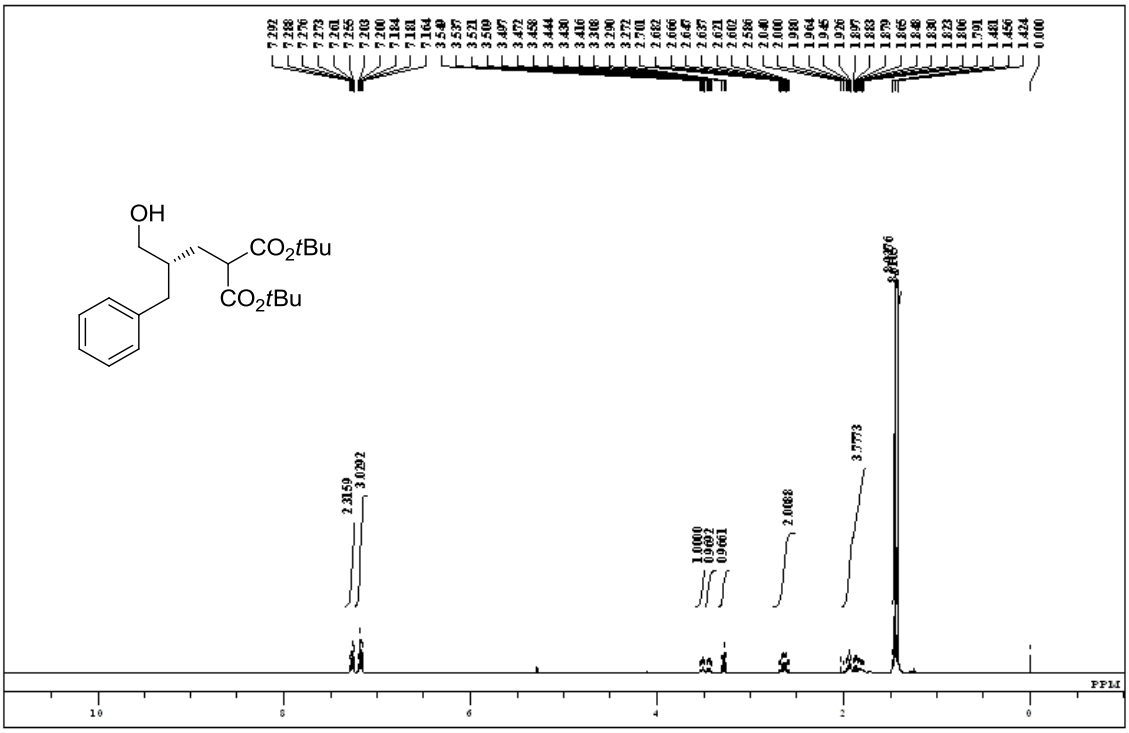


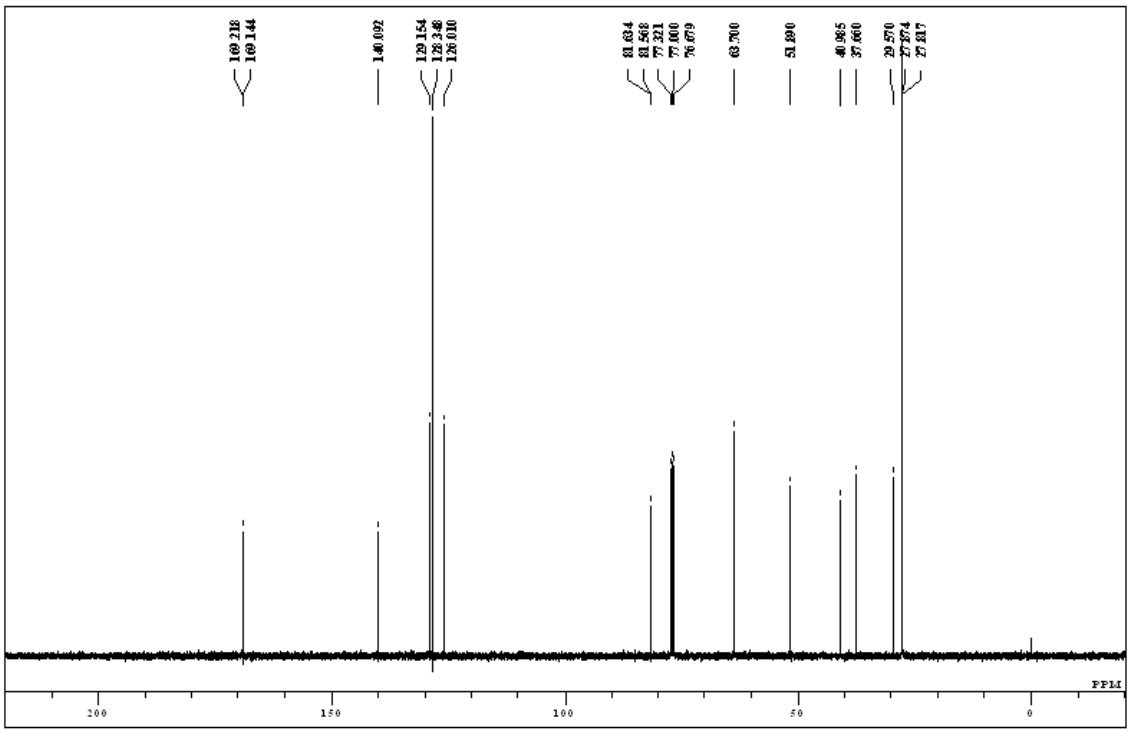


Aminoalcohol (*S*)-5

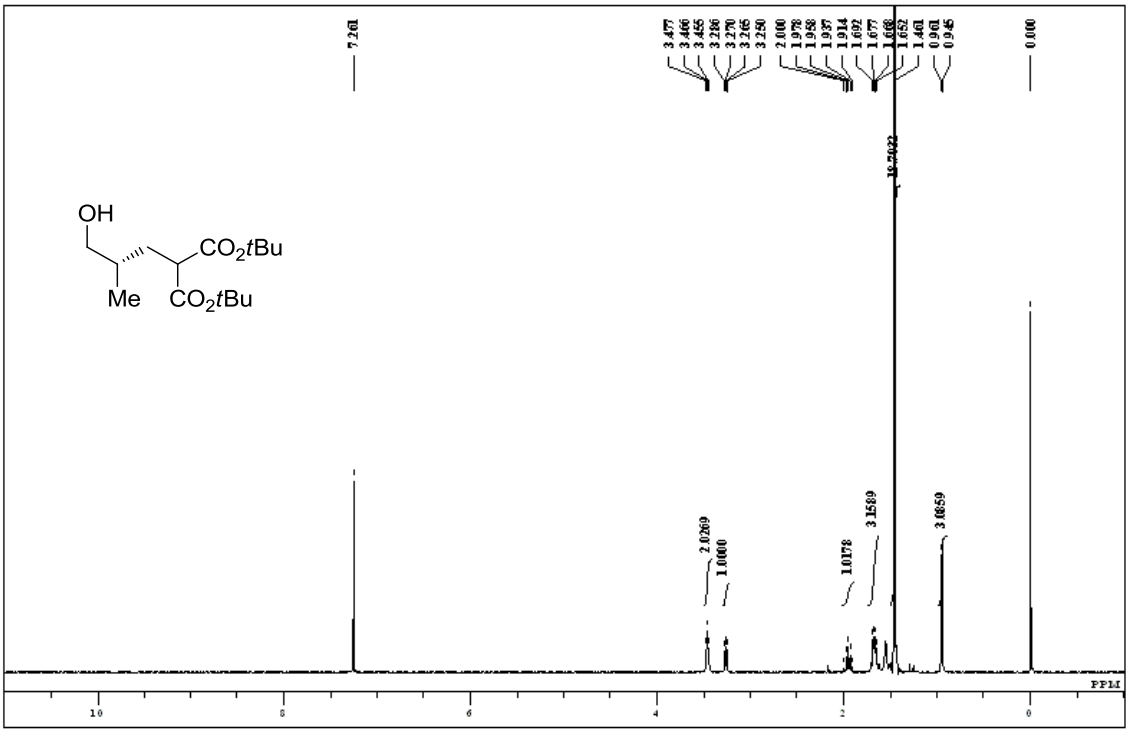


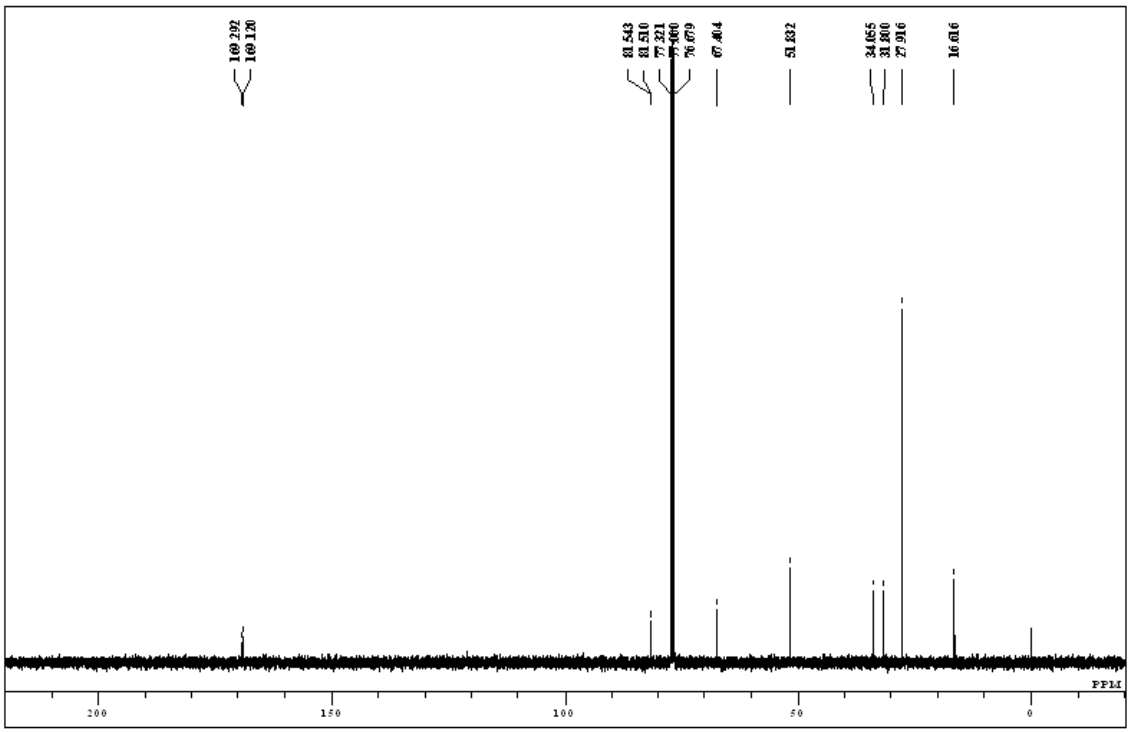
Di-*t*-butyl (*R*)-2-(2-benzyl-3-hydroxypropyl)malonate (7)



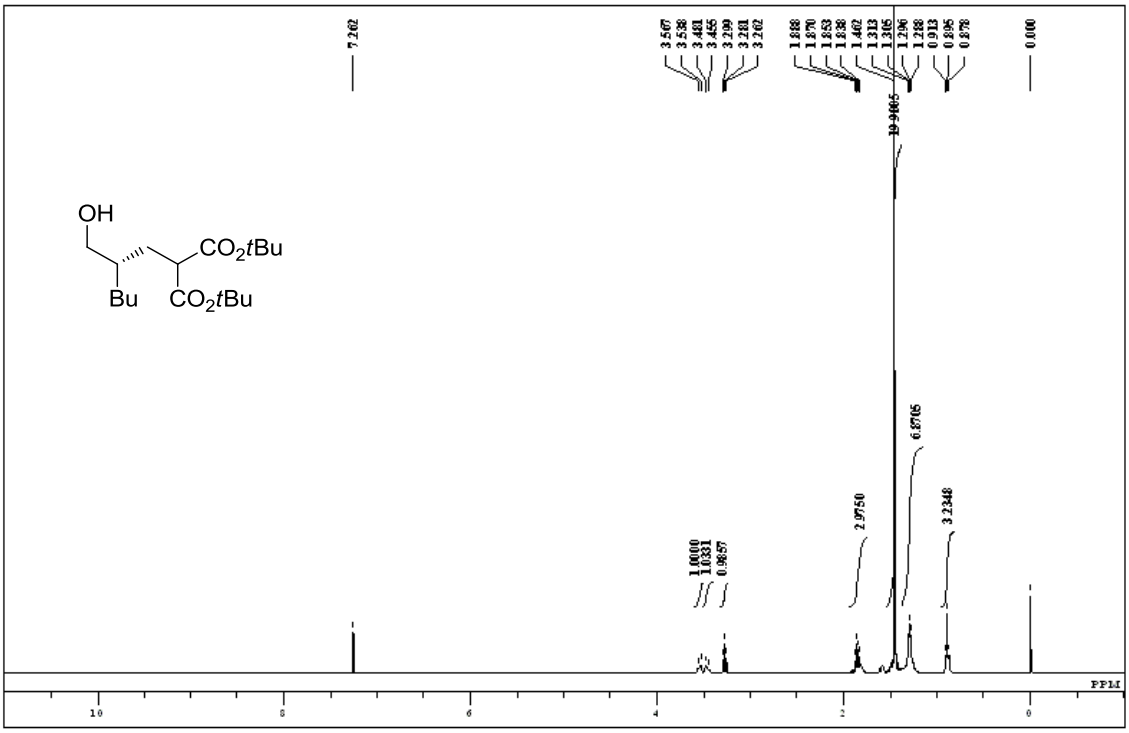


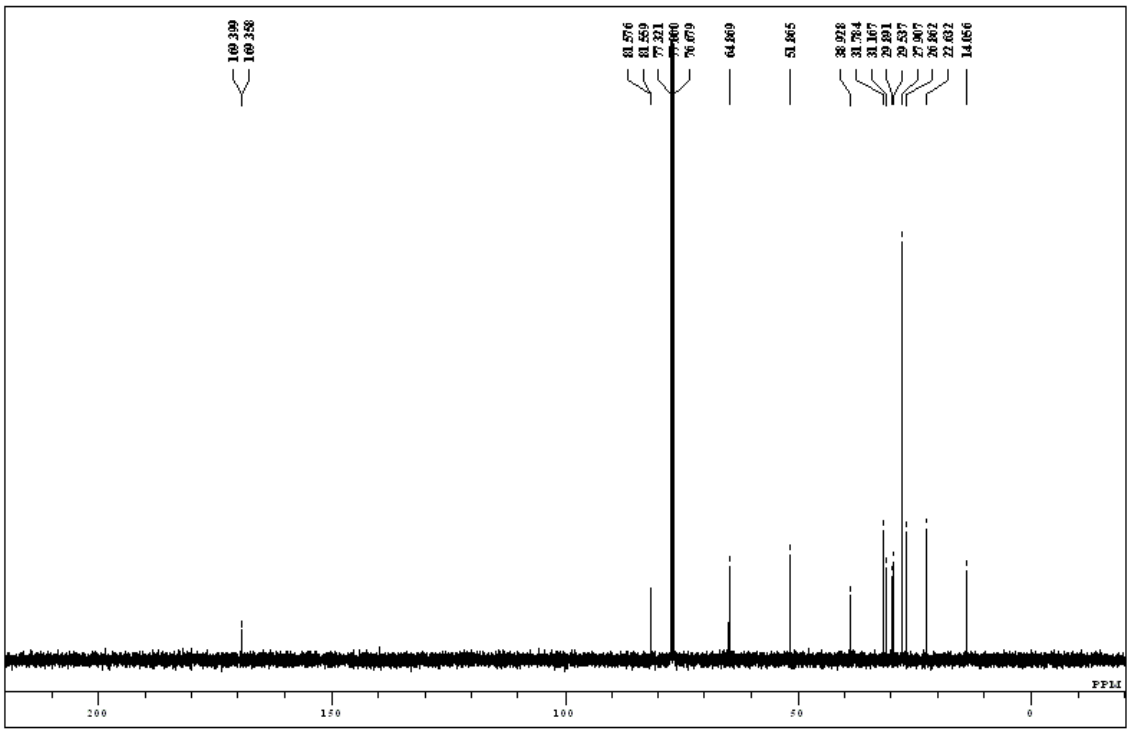
Di-*t*-butyl (*S*)-2-(3-hydroxy-2-methylpropyl)malonate (7b)



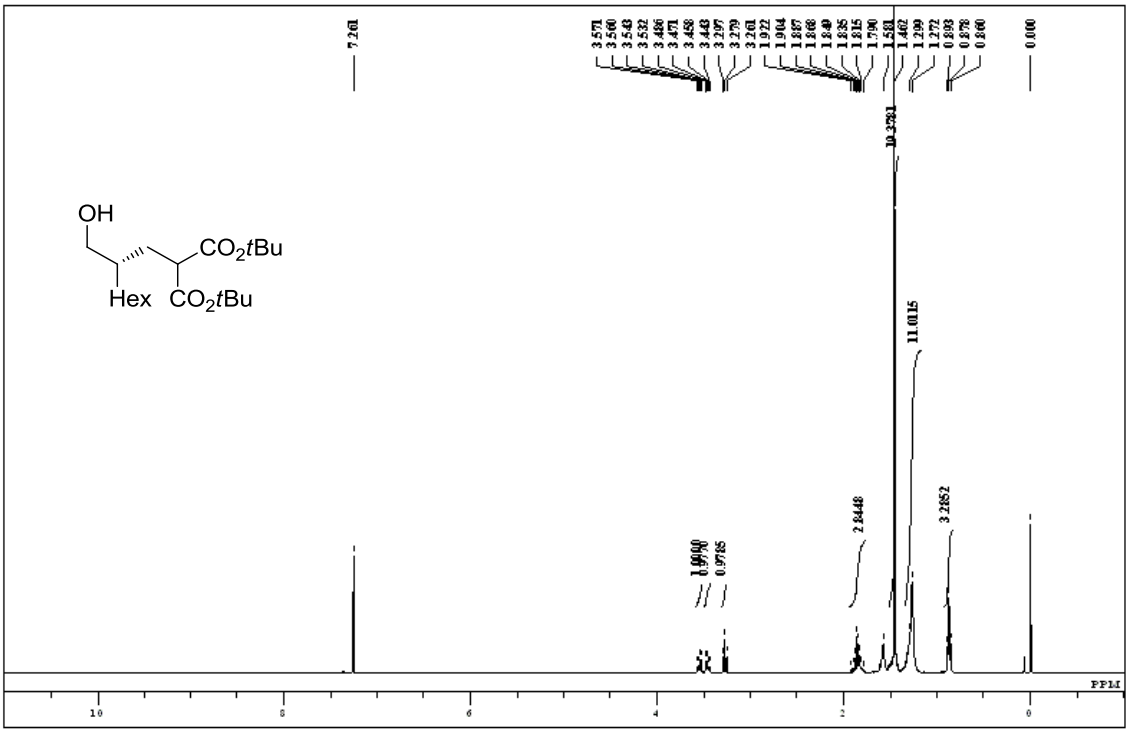


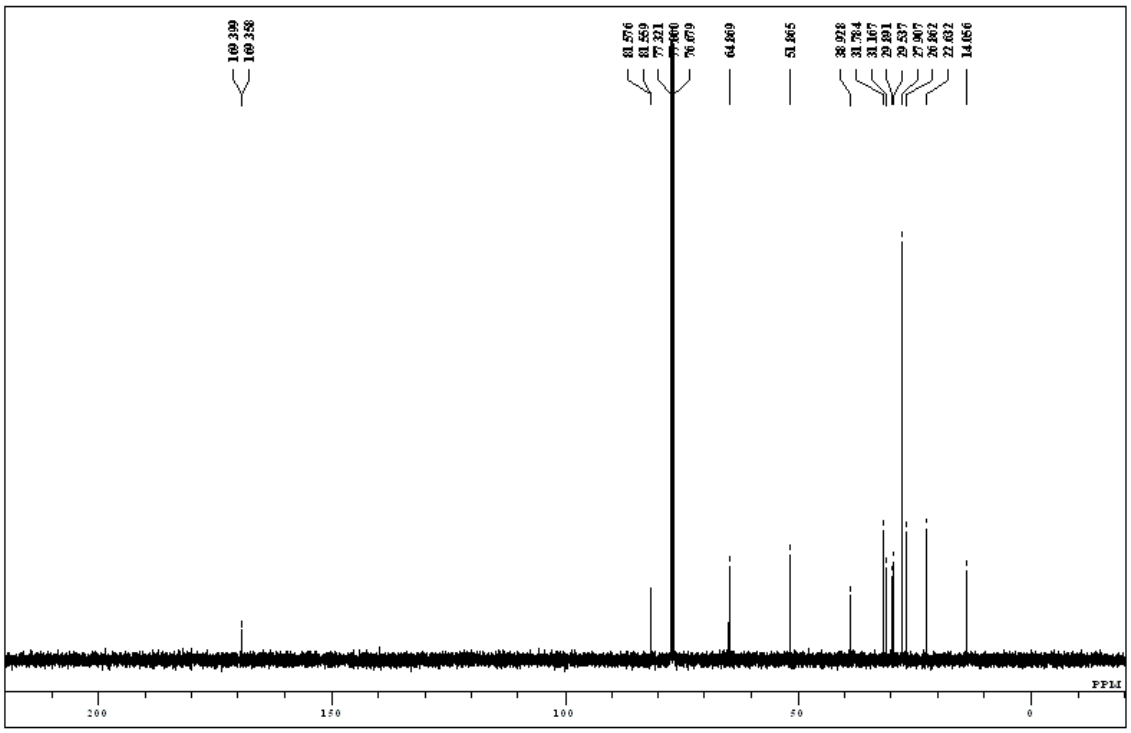
Di-*t*-butyl (*S*)-2-(2-(hydroxymethyl)hexyl)malonate (7c)



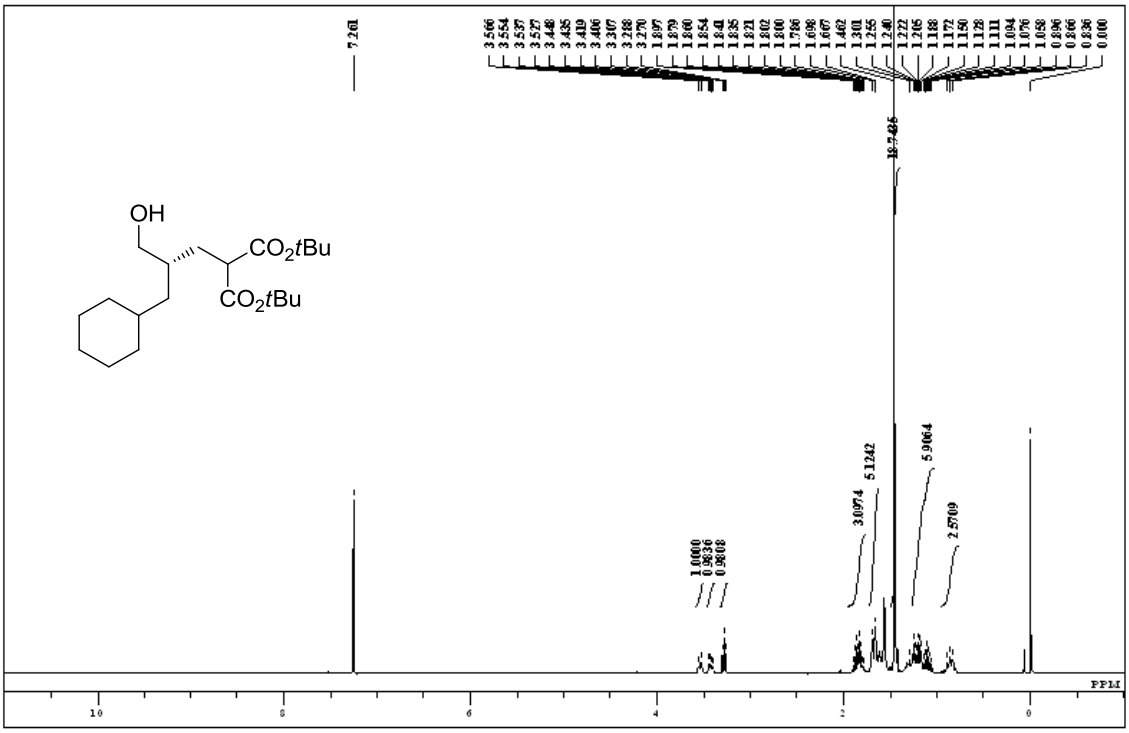


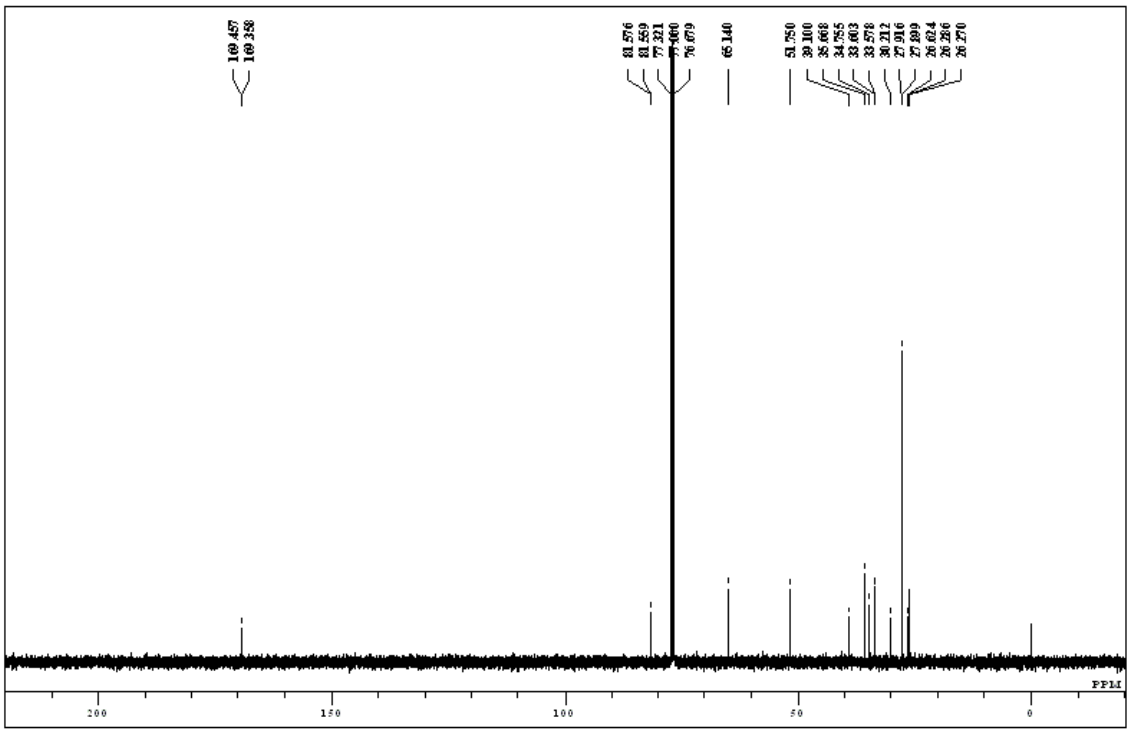
Di-*t*-butyl (*S*)-2-(2-(hydroxymethyl)octyl)malonate (7d)



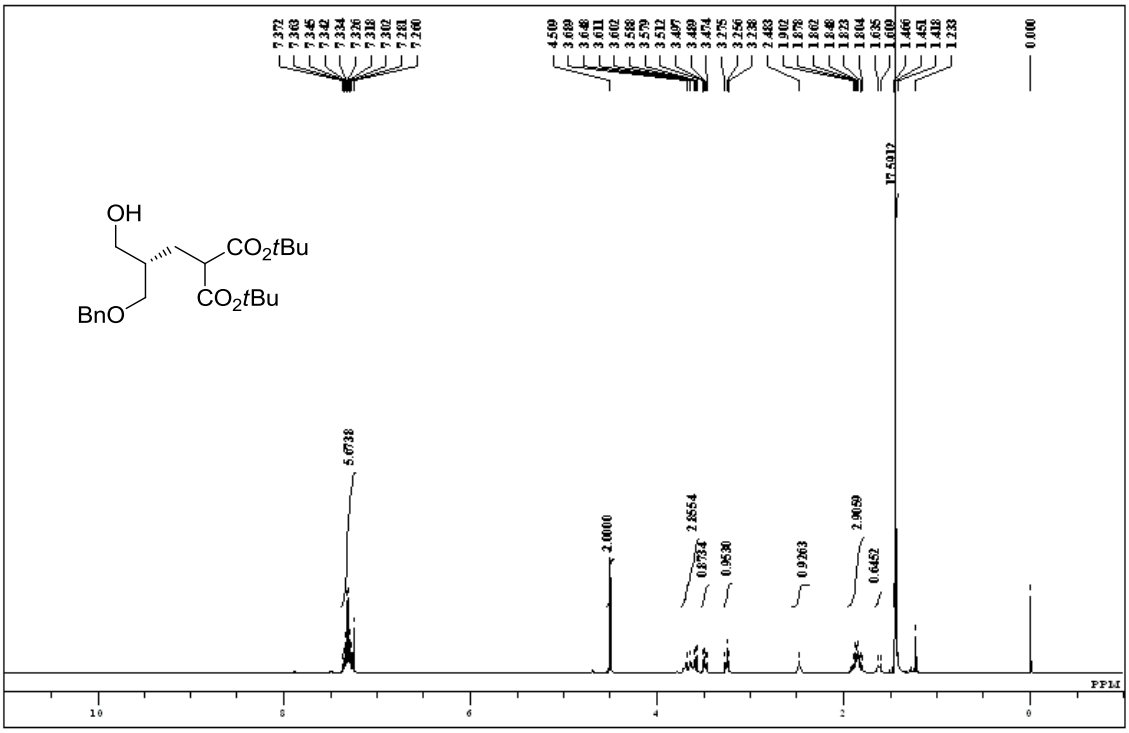


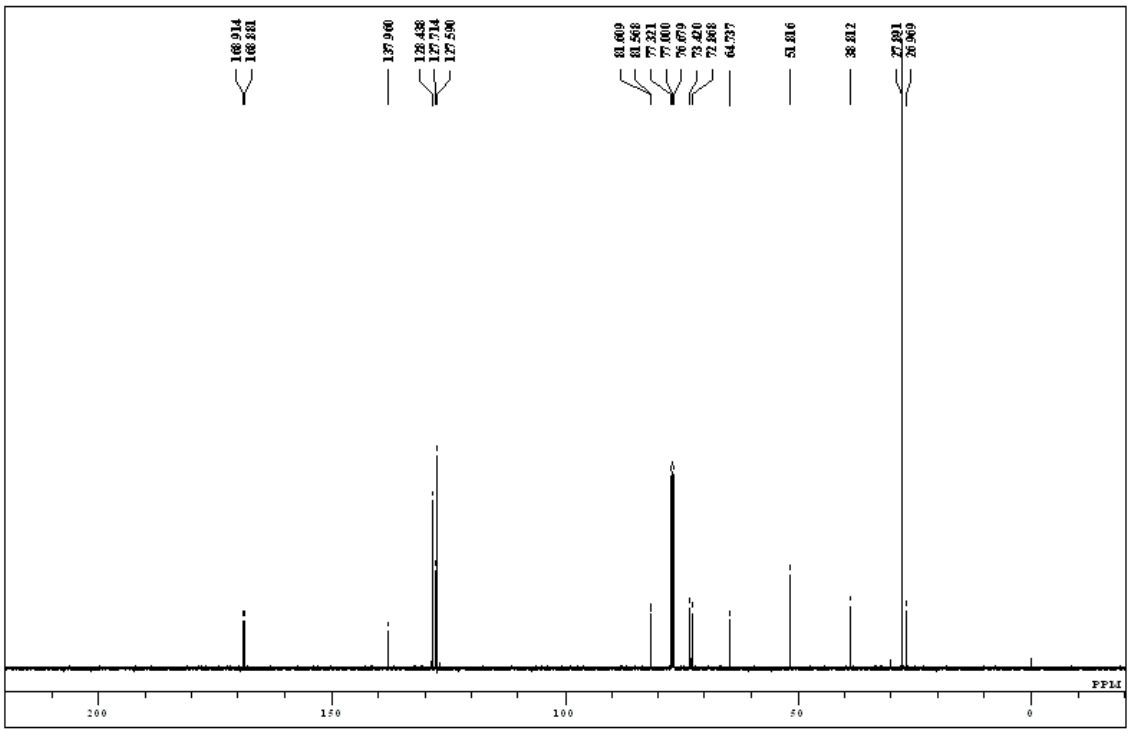
Di-*t*-butyl (*R*)-2-(3-cyclohexyl-2-(hydroxymethyl)propyl)malonate (7e)



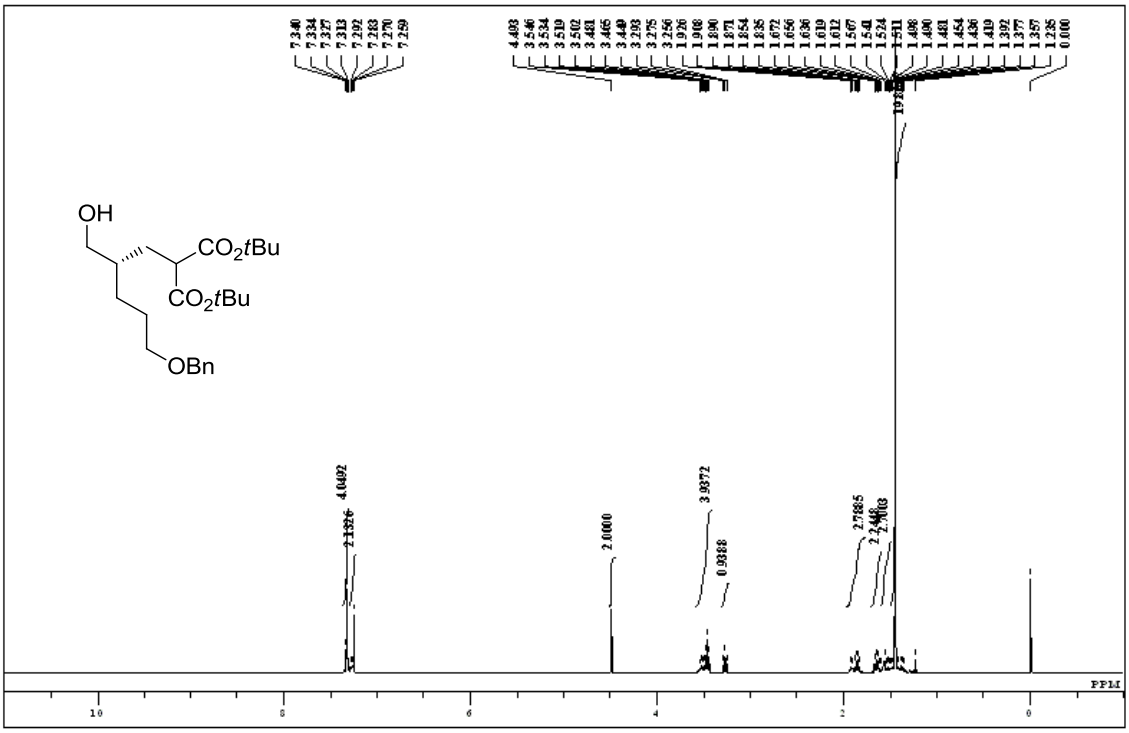


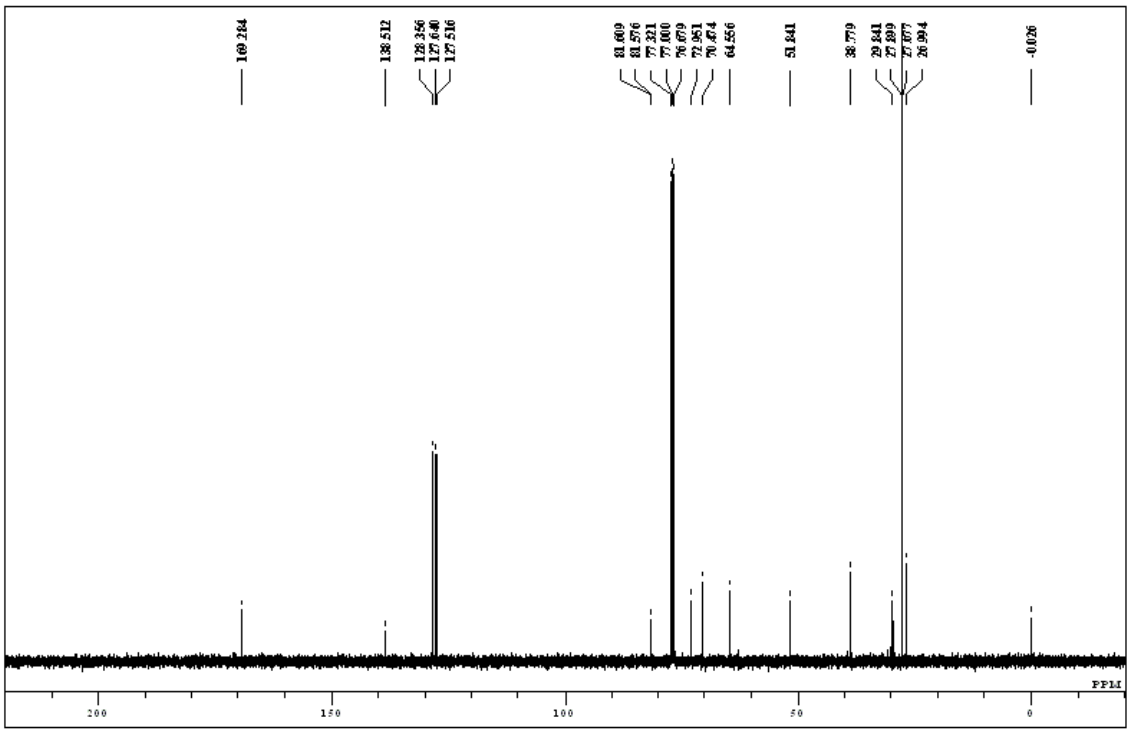
Di-*t*-butyl (*S*)-2-(3-(benzyloxy)-2-(hydroxymethyl)propyl)malonate (7f)



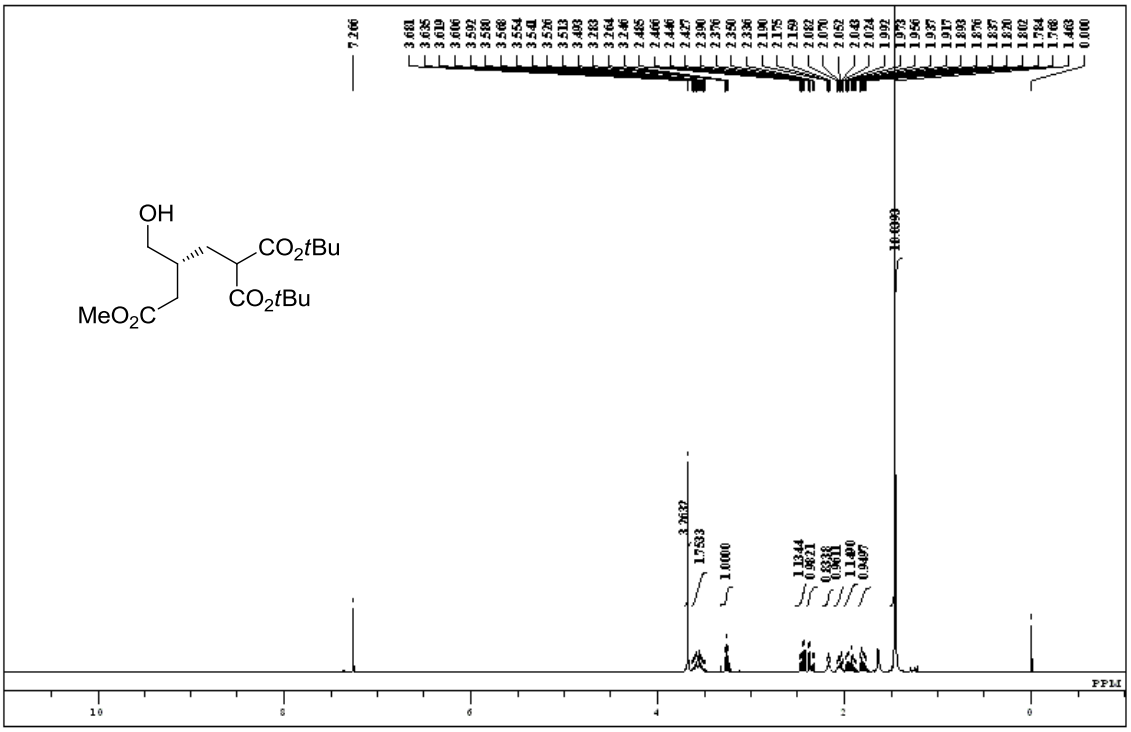


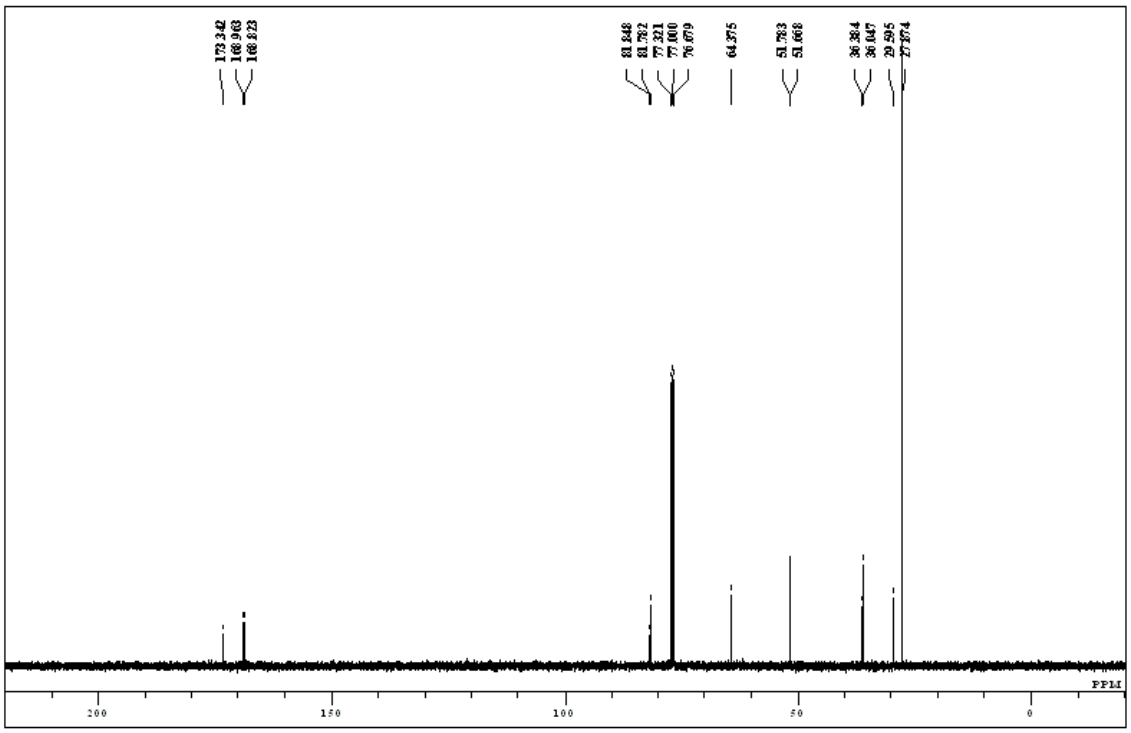
Di-*t*-butyl (*S*)-2-(5-(benzyloxy)-2-(hydroxymethyl)pentyl)malonate (7g)



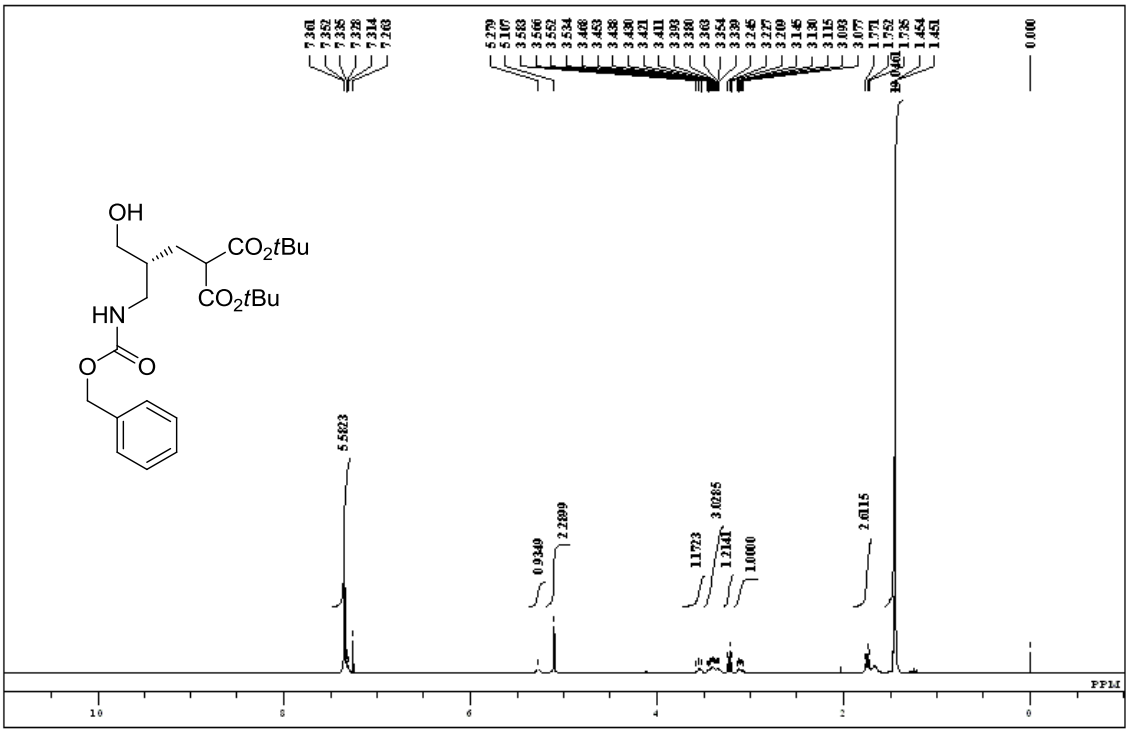


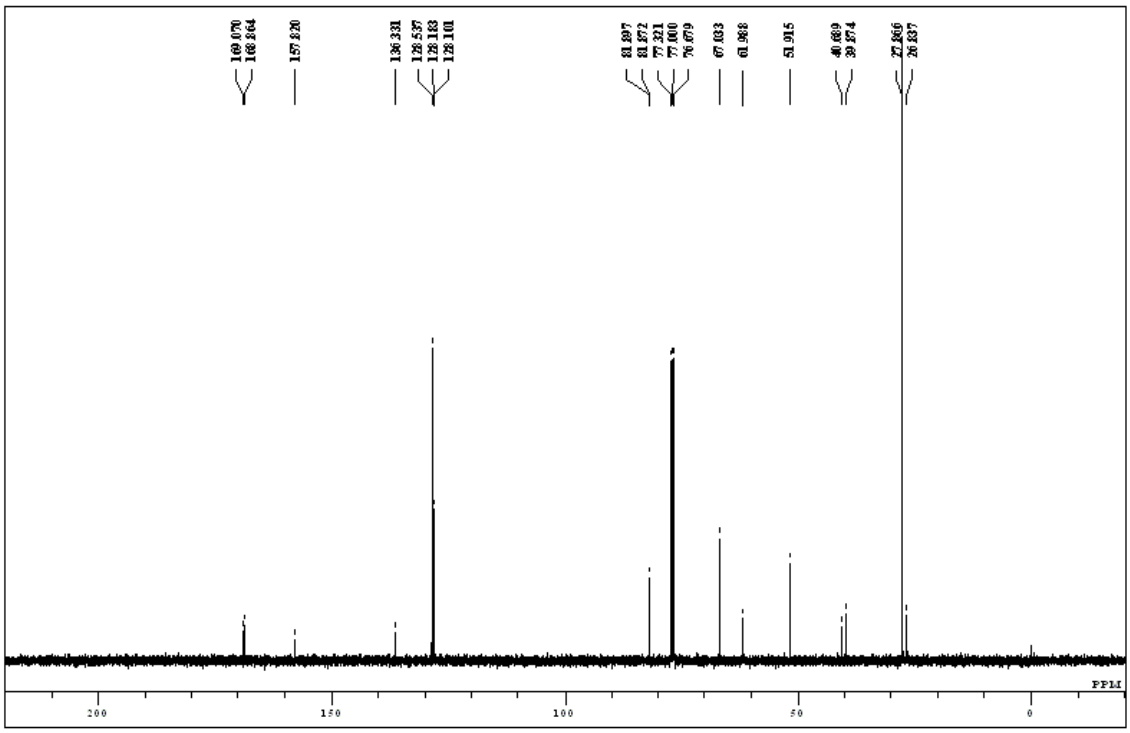
1,1-Di-*t*-butyl 4-methyl (*R*)-3-(hydroxymethyl)butane-1,1,4-tricarboxylate (7h)



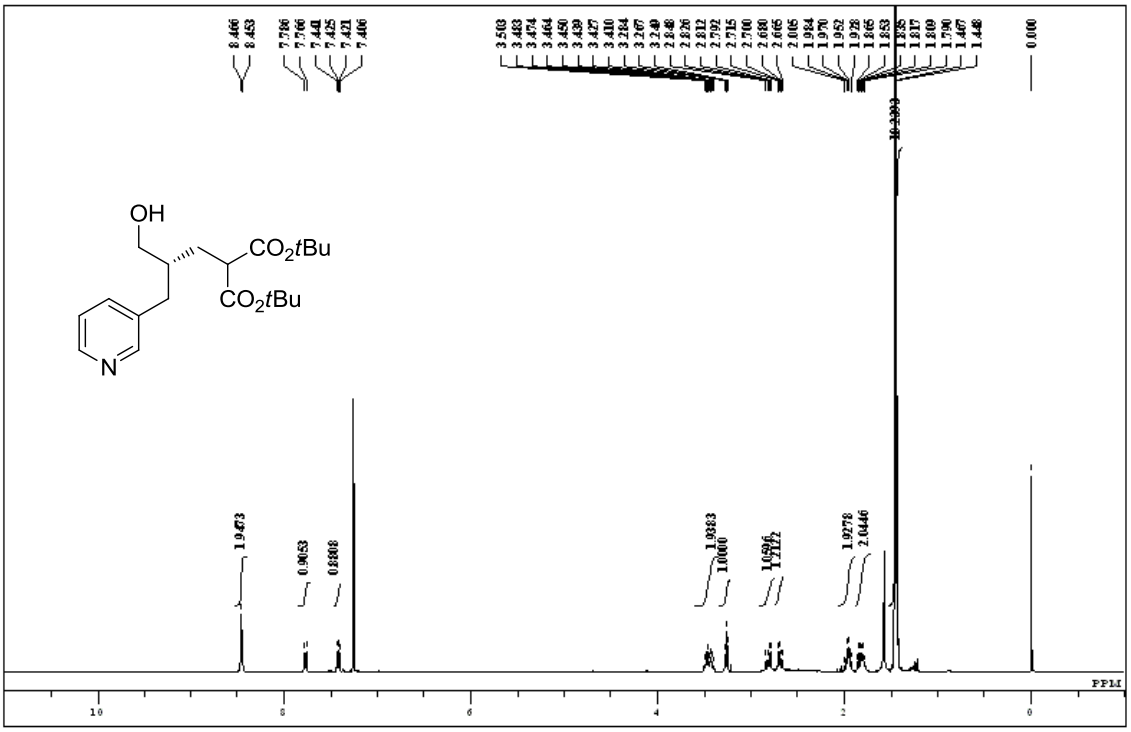


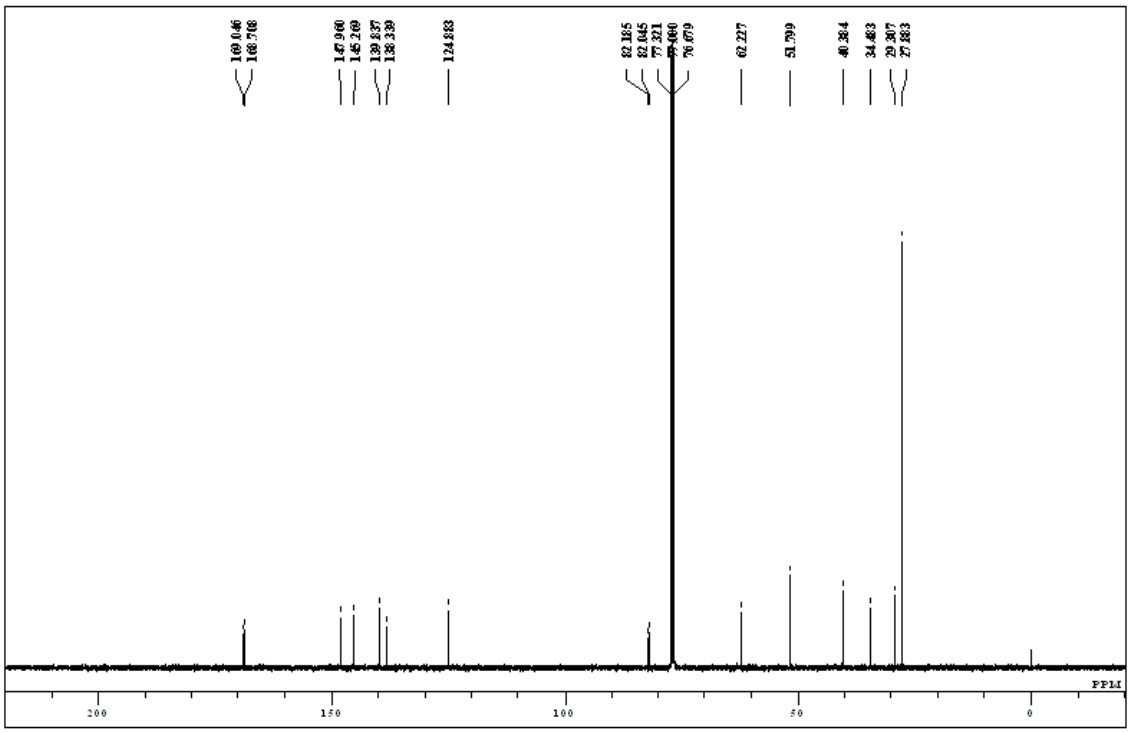
Di-*t*-butyl (*R*)-2-(3-(((benzyloxy)carbonyl)amino)-2-(hydroxymethyl)propyl)malonate (7i)



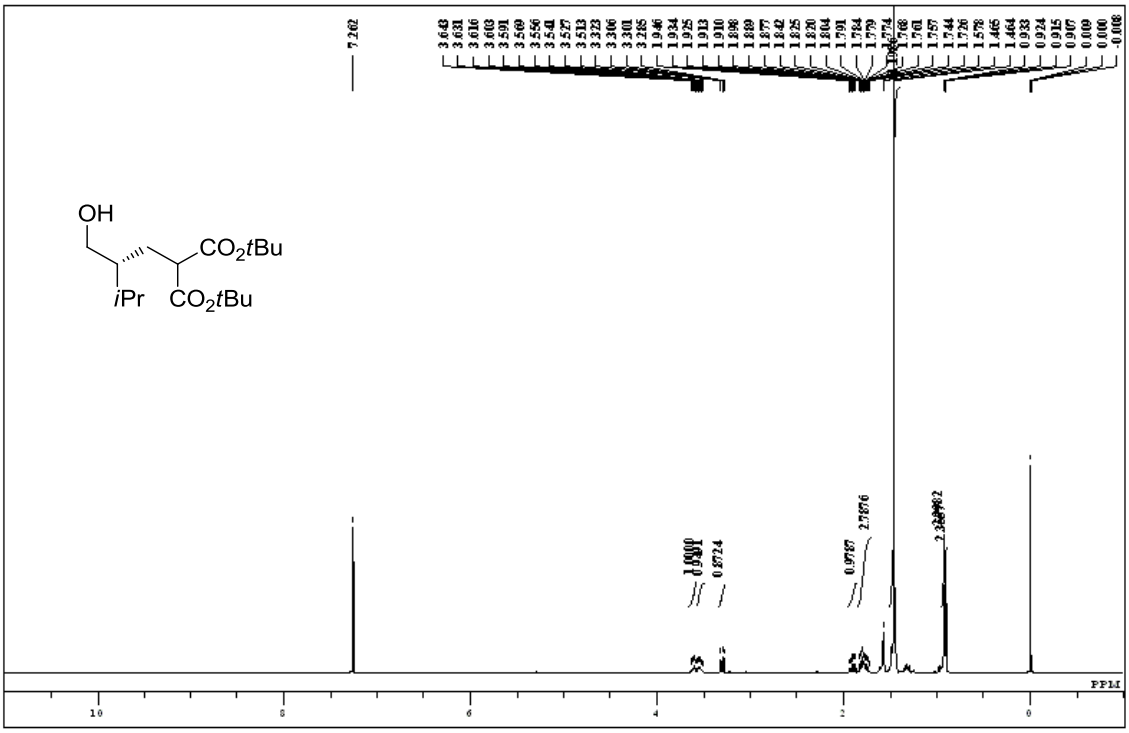


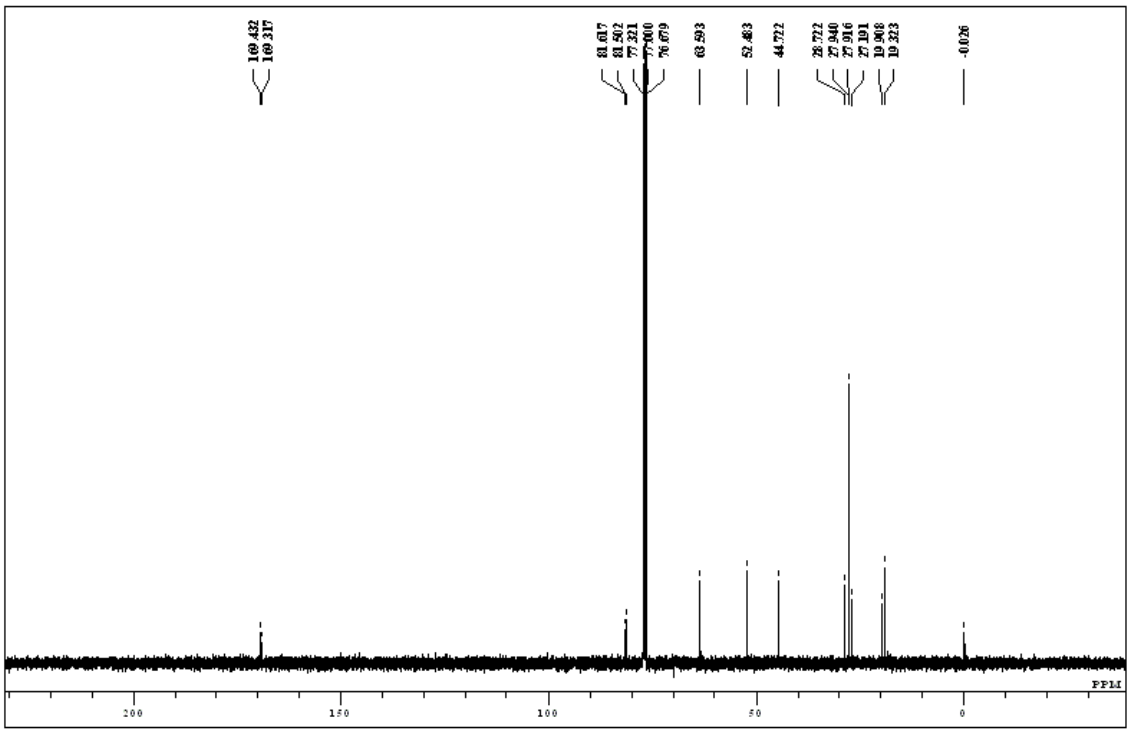
Di-*t*-butyl (*R*)-2-(3-hydroxy-2-(pyridin-3-ylmethyl)propyl)malonate (7j)



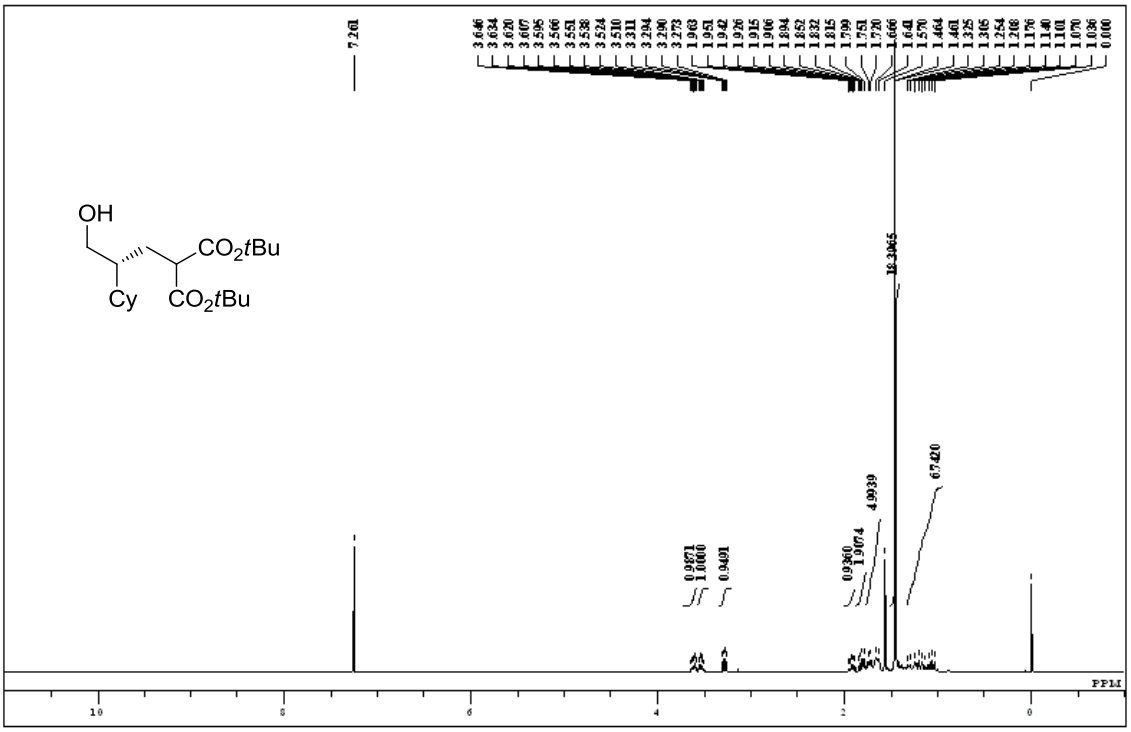


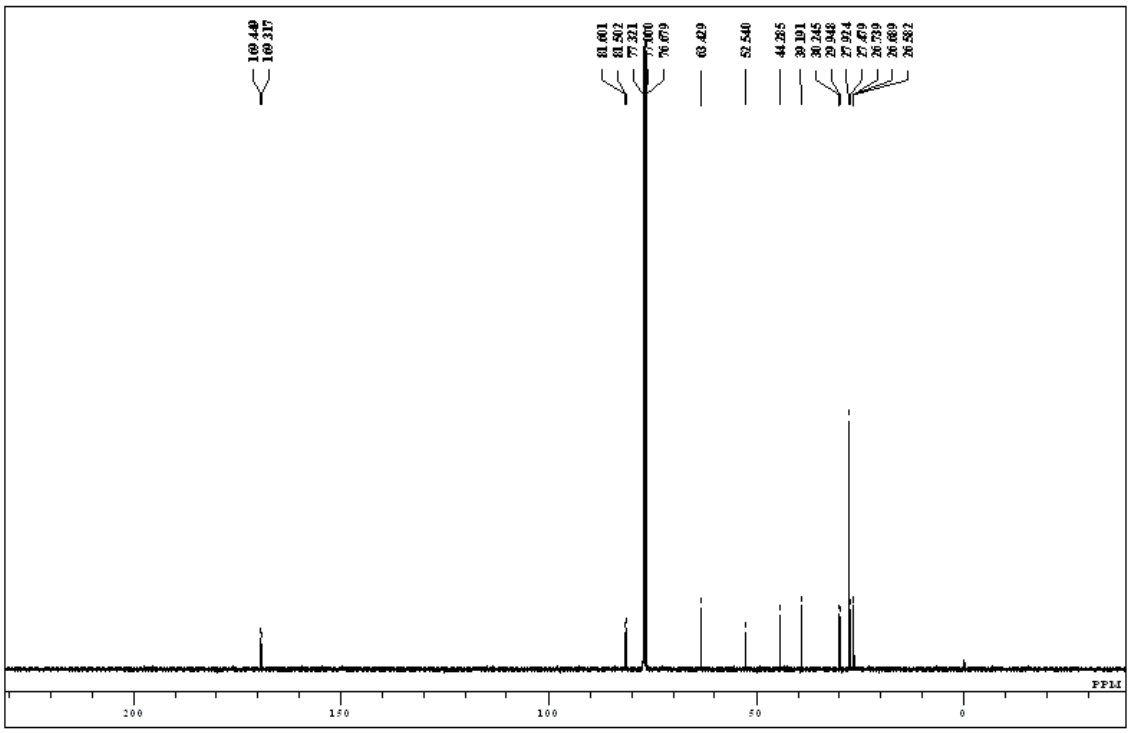
Di-*t*-butyl (*R*)-2-(2-(hydroxymethyl)-3-methylbutyl)malonate (7k)



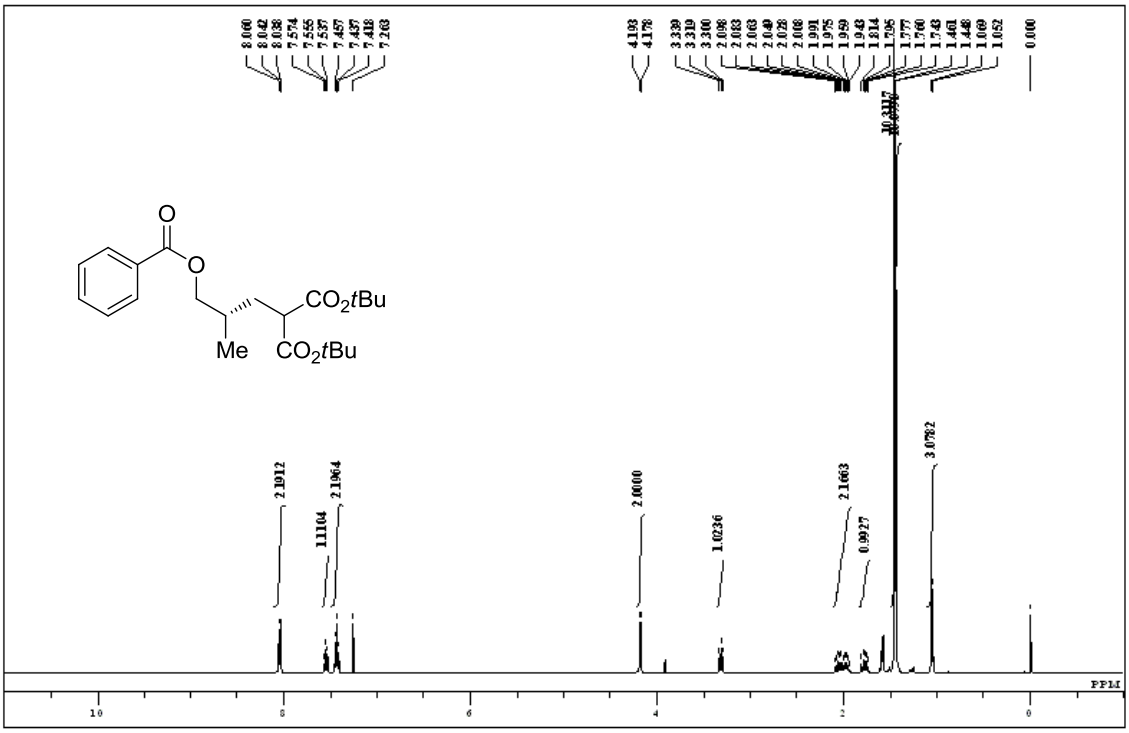


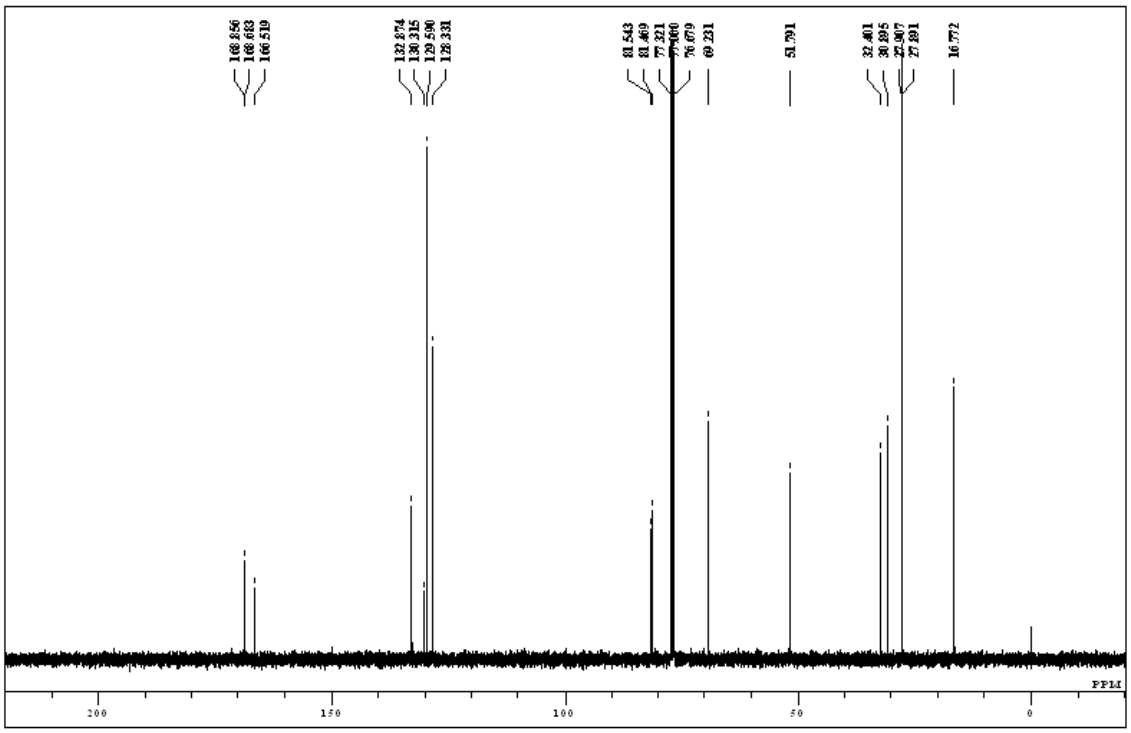
Di-*t*-butyl (*R*)-2-(2-cyclohexyl-3-hydroxypropyl)malonate (7l)



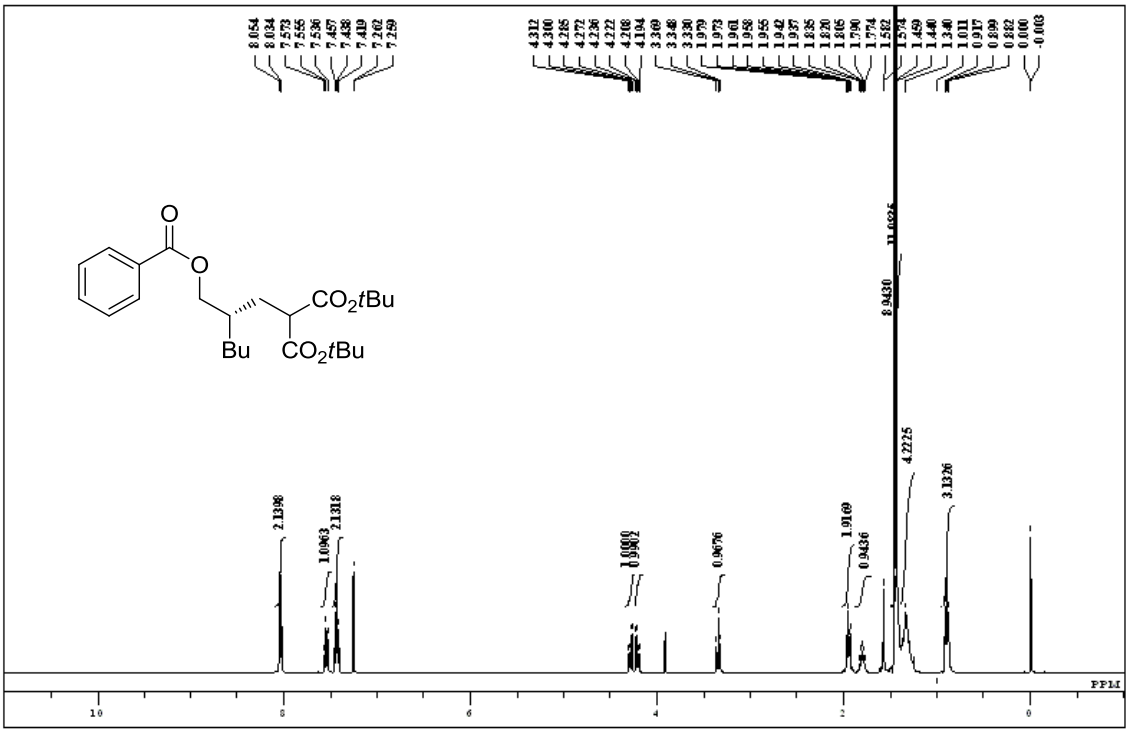


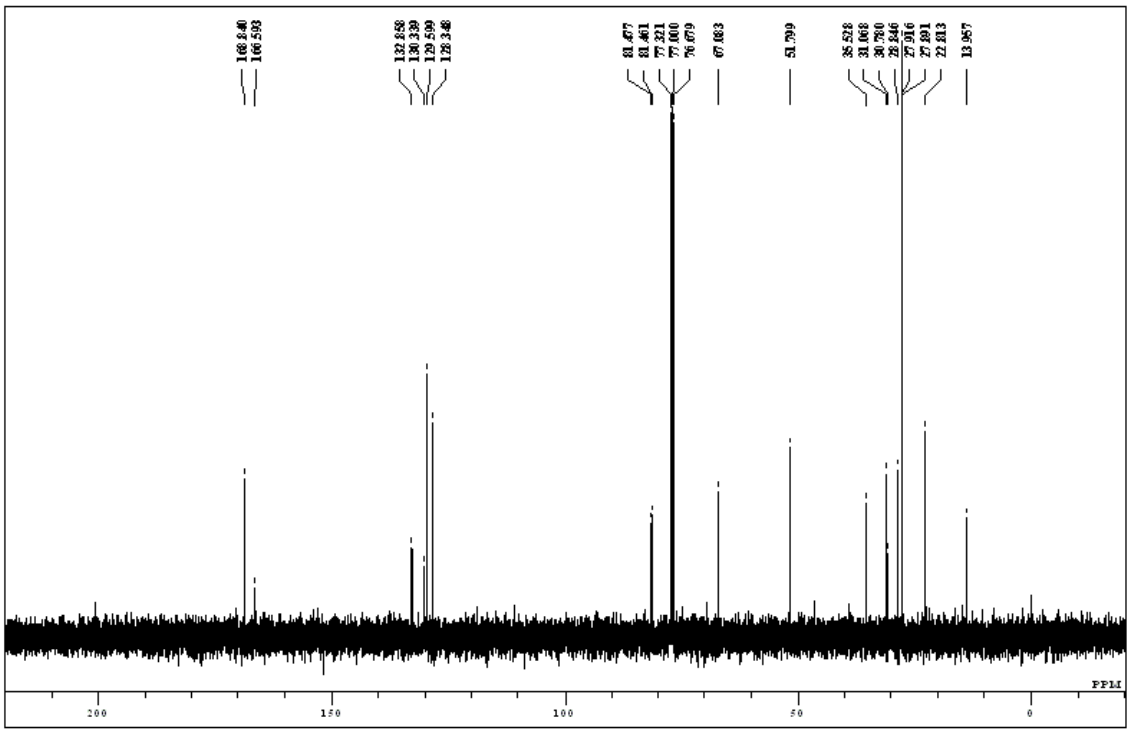
Di-*t*-butyl (*S*)-2-(3-(benzoyloxy)-2-methylpropyl)malonate



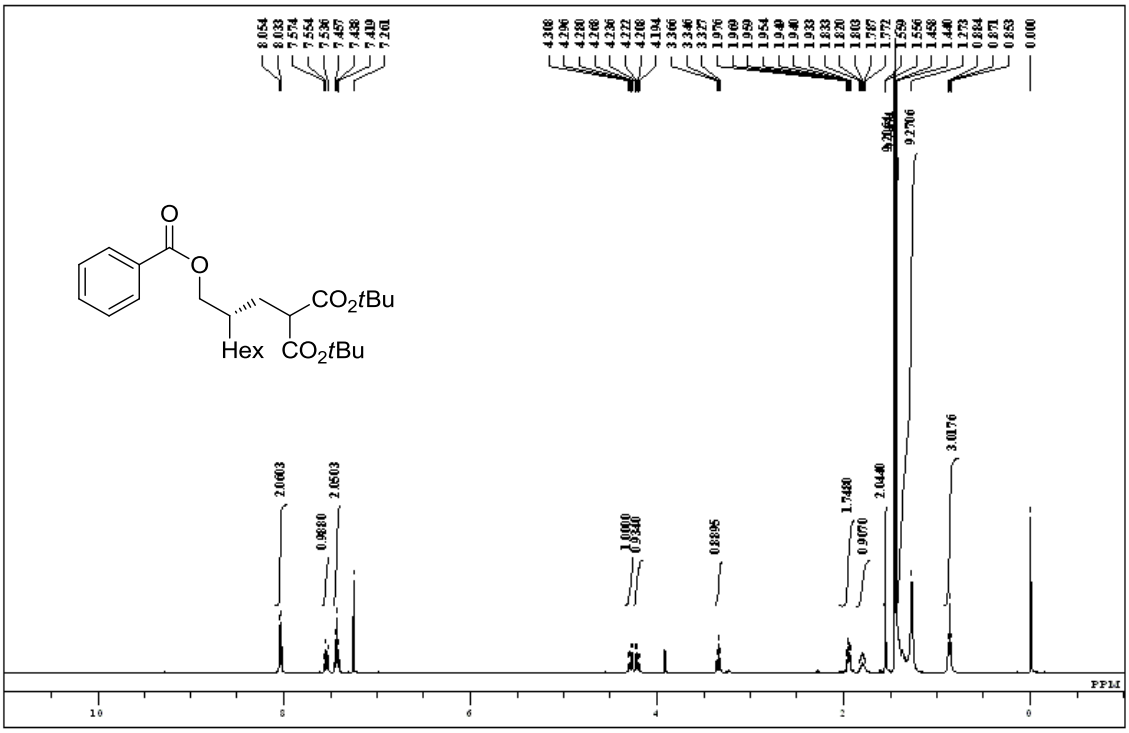


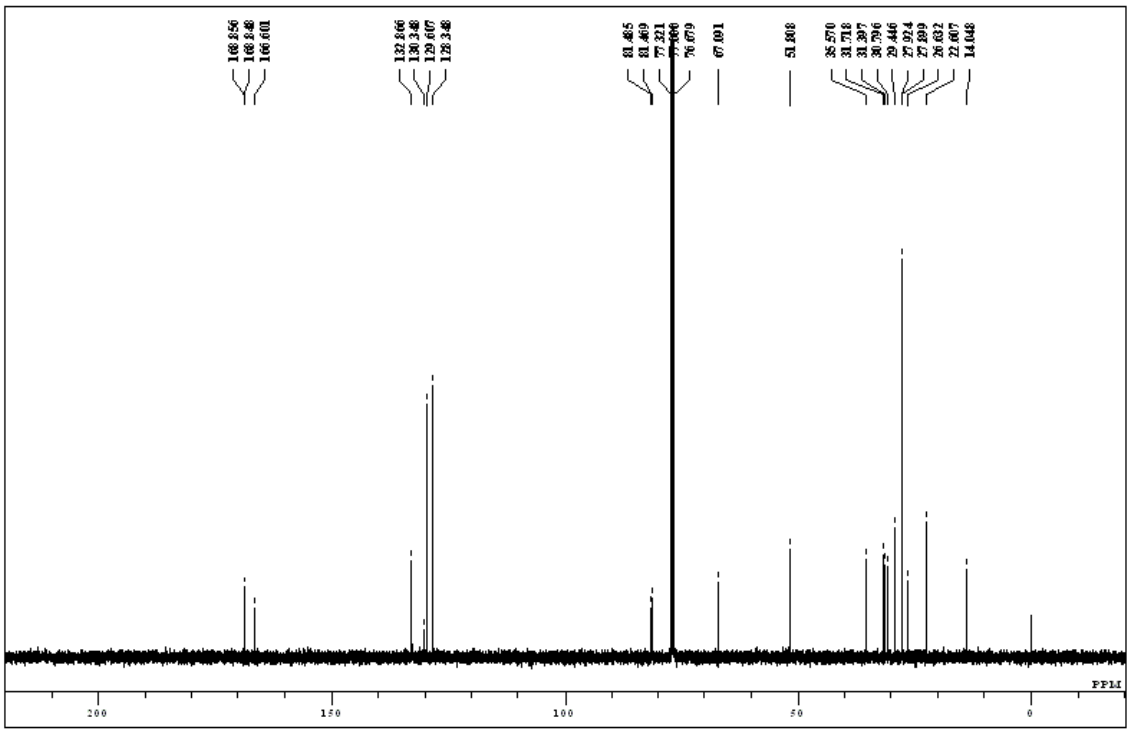
Di-*t*-butyl (*S*)-2-(2-((benzoyloxy)methyl)hexyl)malonate



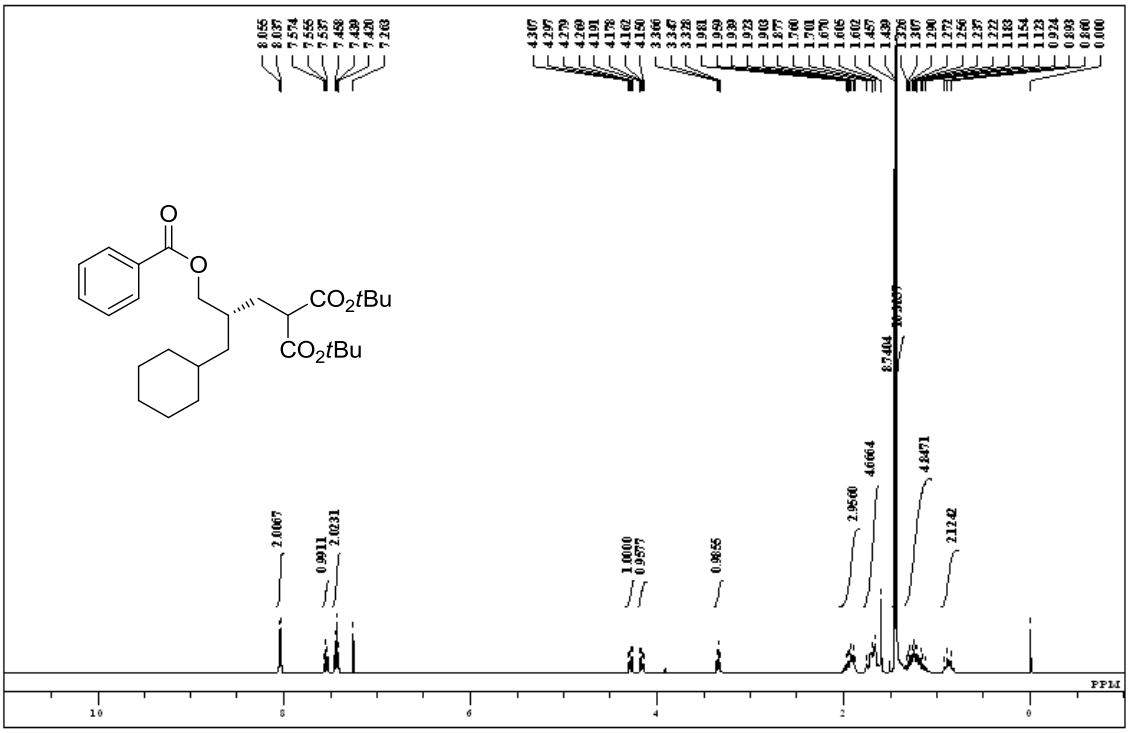


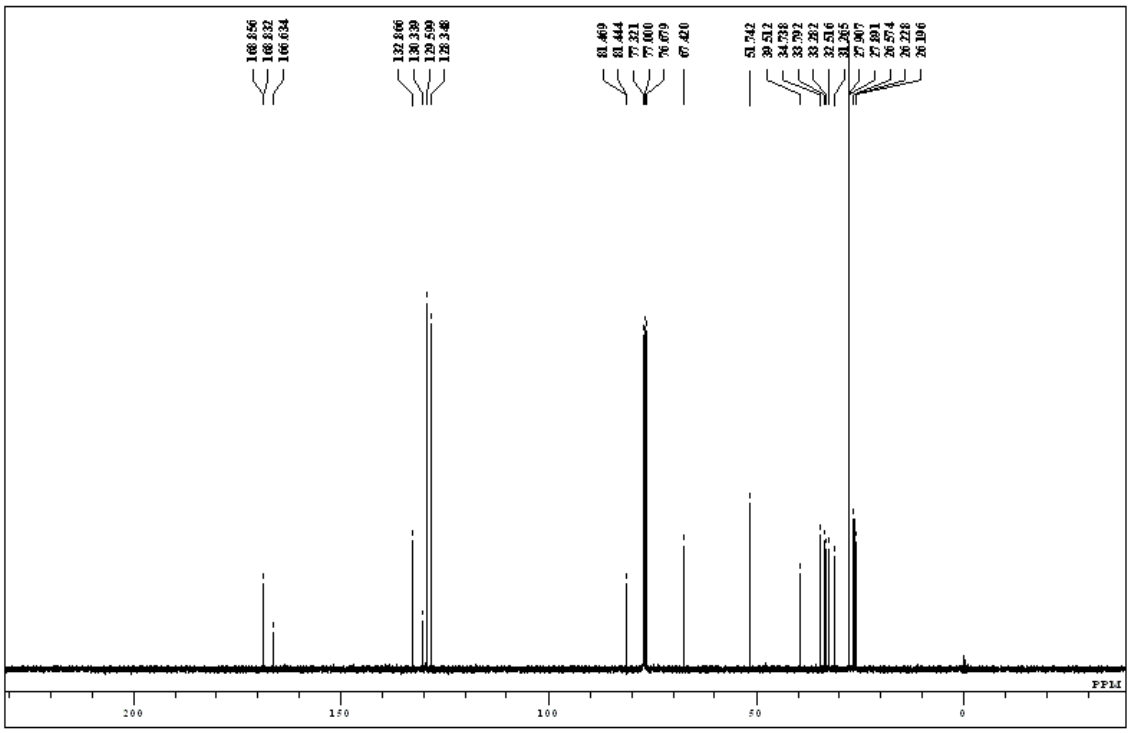
Di-*t*-butyl (*S*)-2-(2-((benzoyloxy)methyl)octyl)malonate



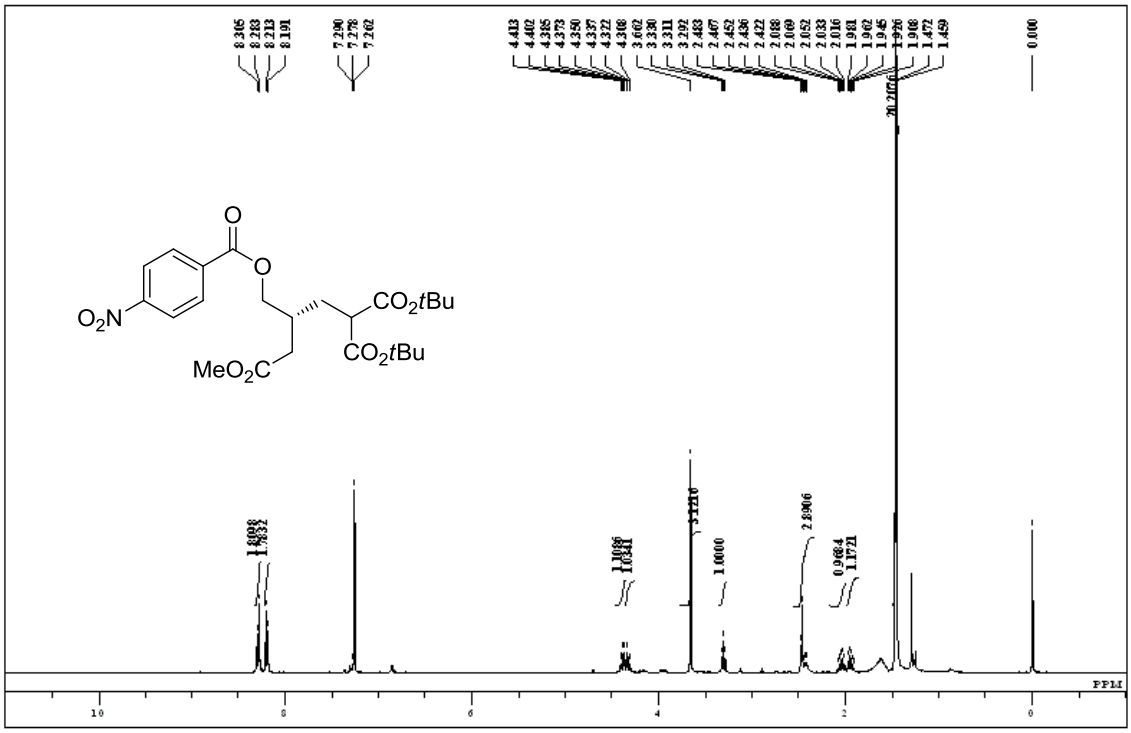


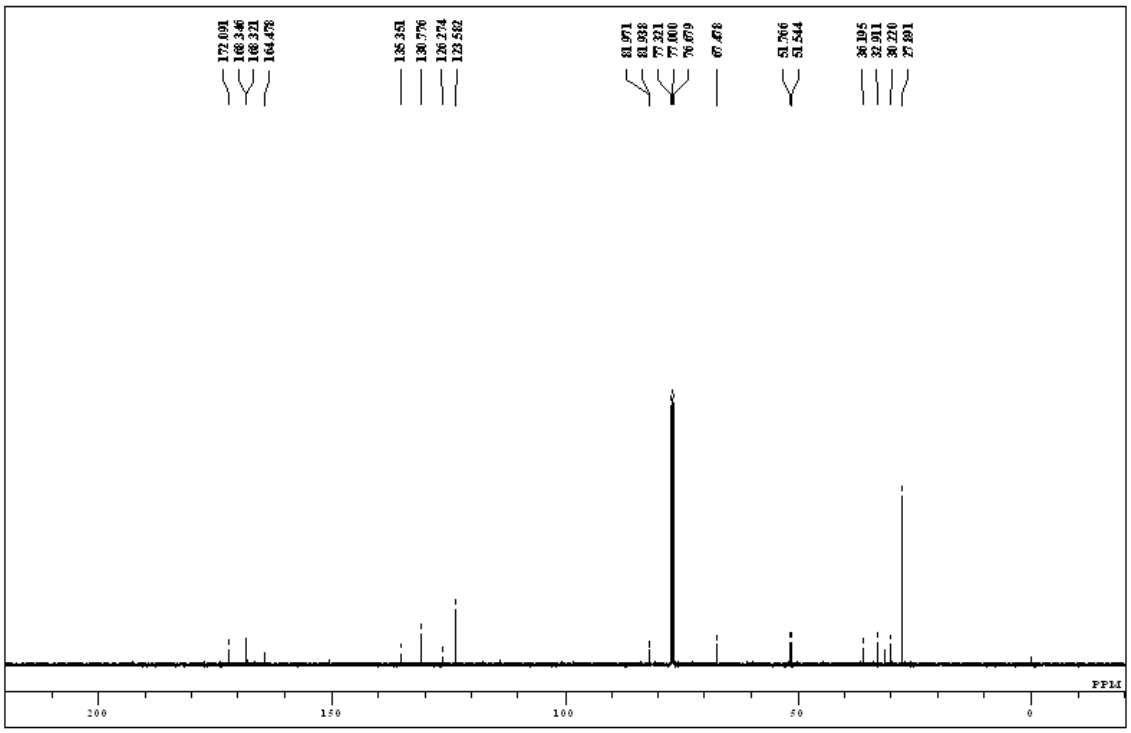
Di-*t*-butyl (*R*)-2-(3-(benzoyloxy)-2-(cyclohexylmethyl)propyl)malonate



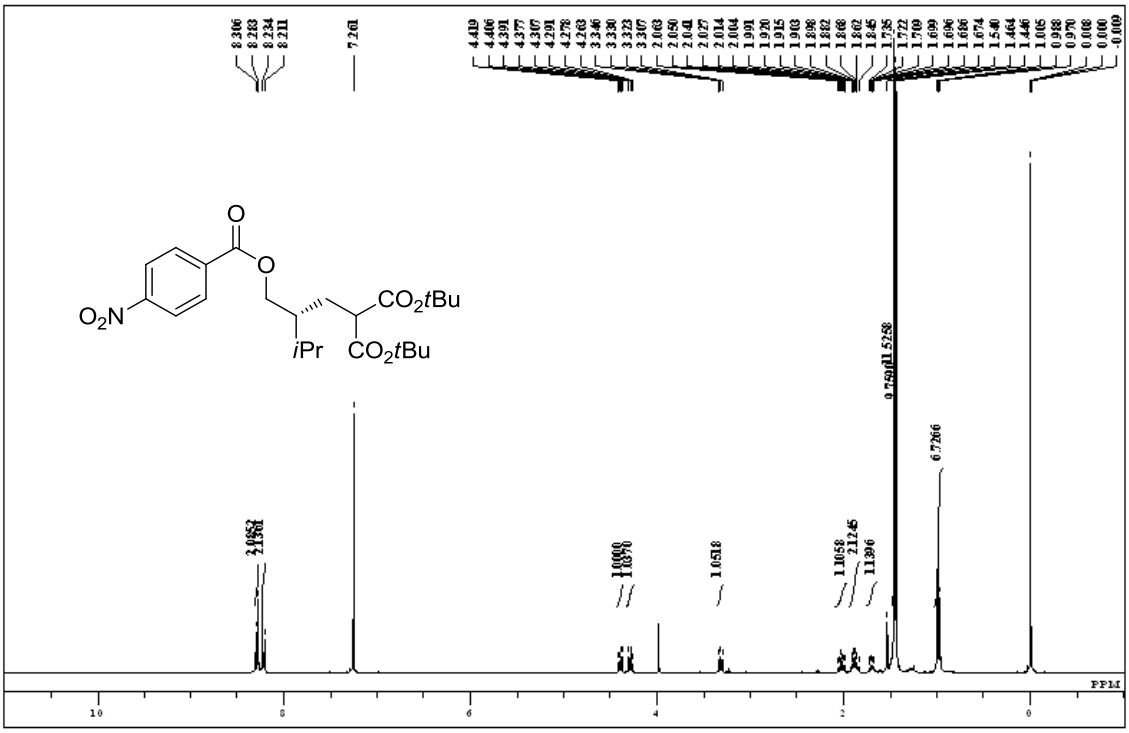


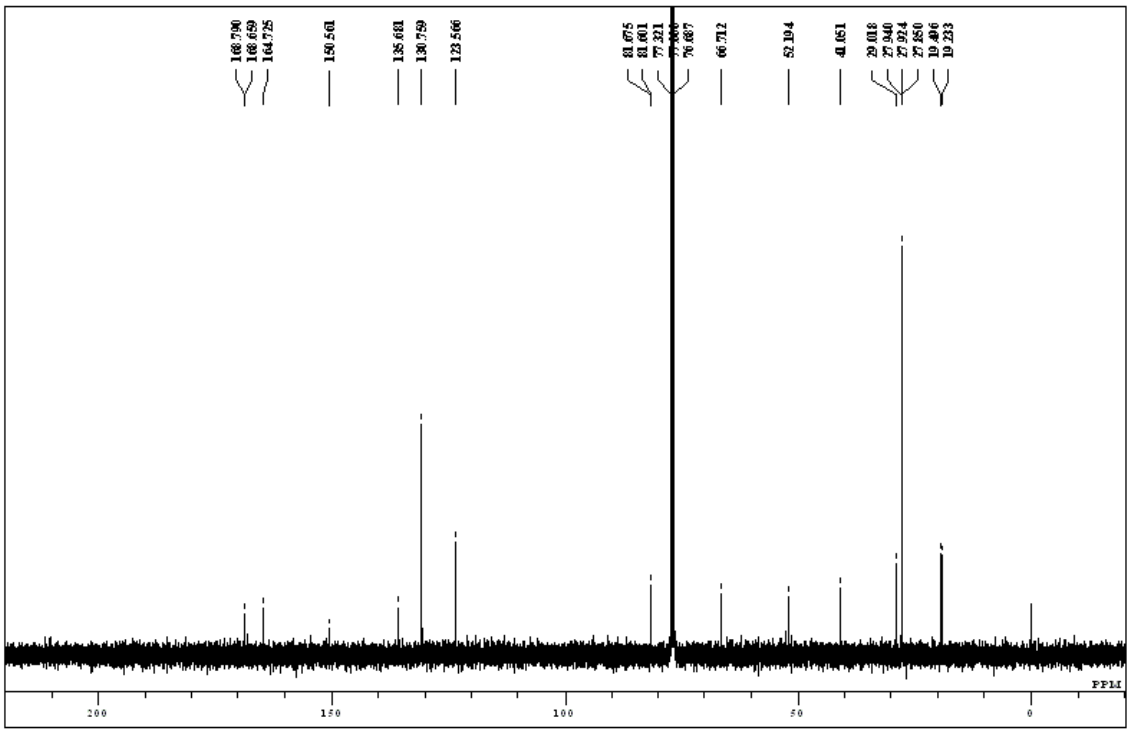
1,1-Di-*t*-butyl 4-methyl (*R*)-3-(((4-nitrobenzoyl)oxy)methyl)butane-1,1,4-tricarboxylate



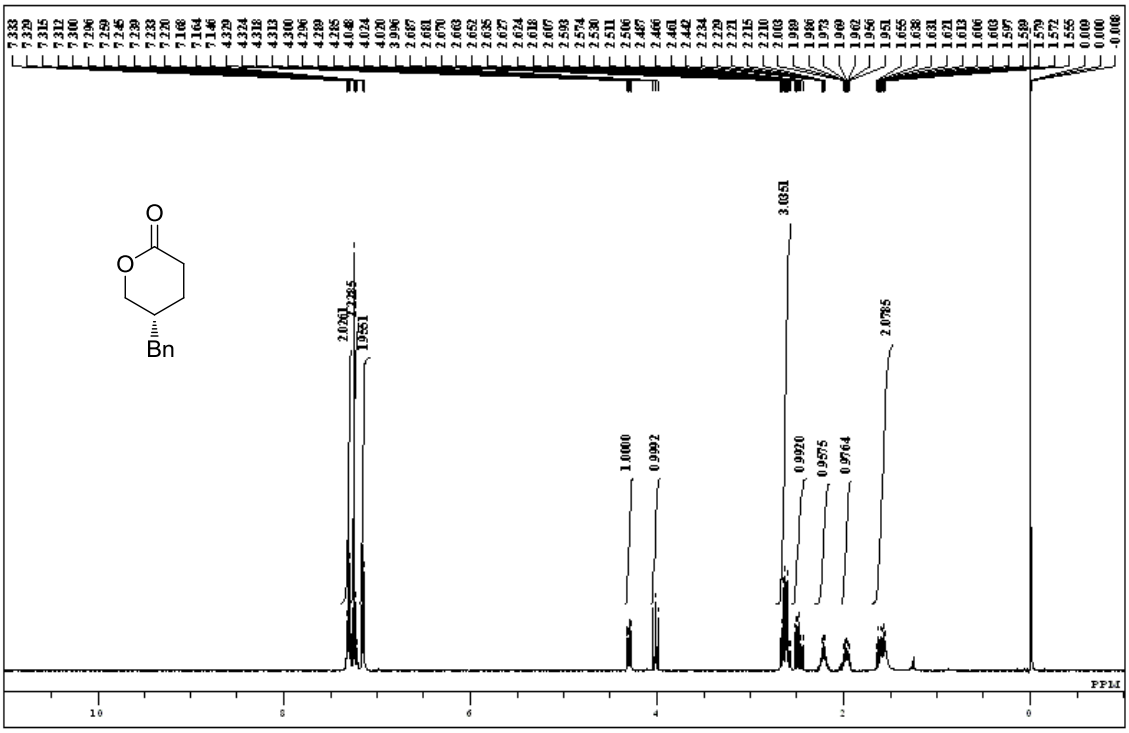


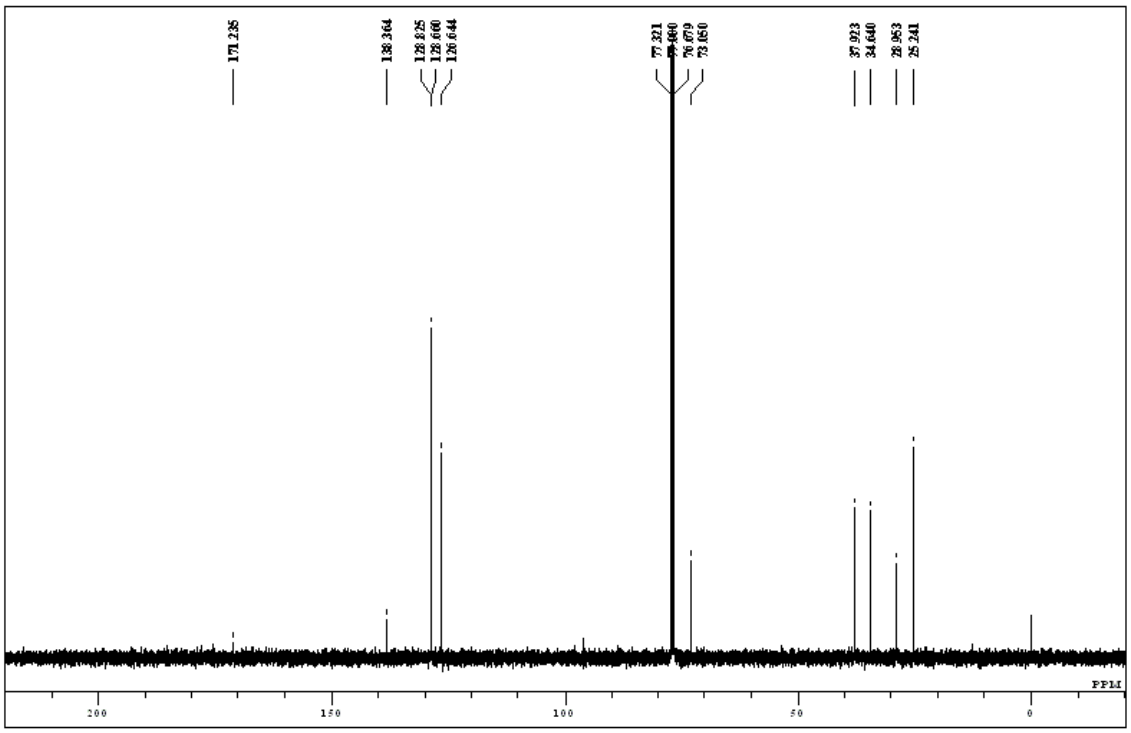
Di-*t*-butyl (*R*)-2-(3-methyl-2-(((4-nitrobenzoyl)oxy)methyl)butyl)malonate



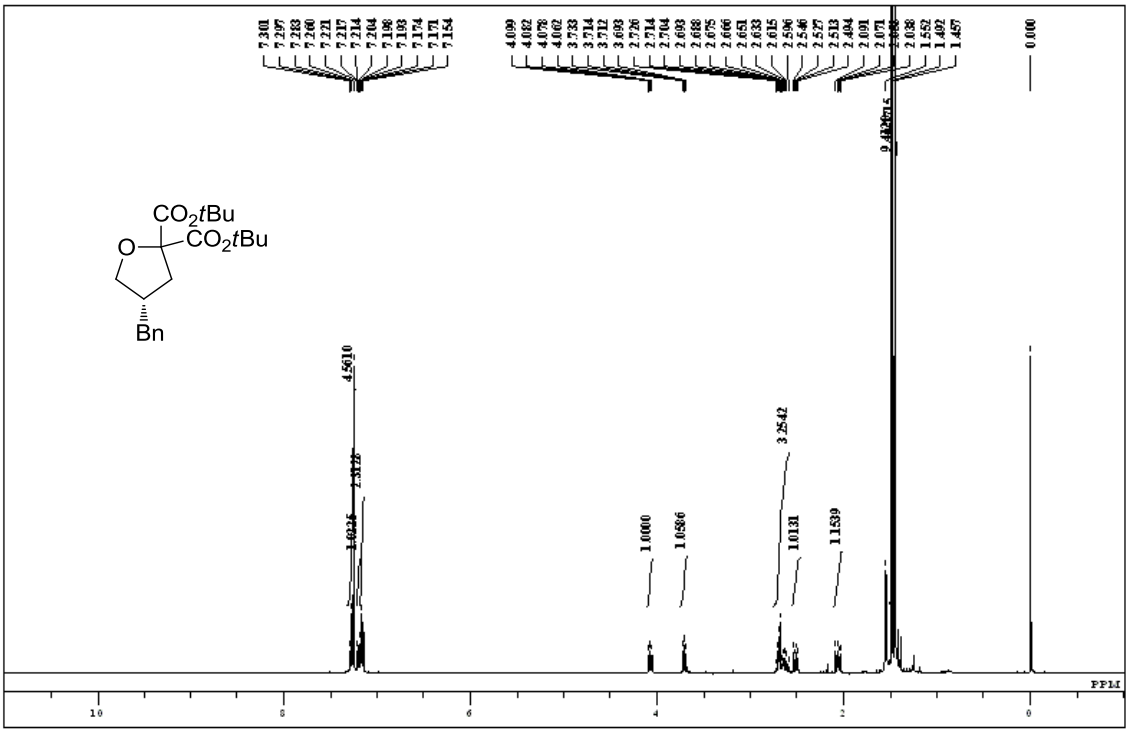


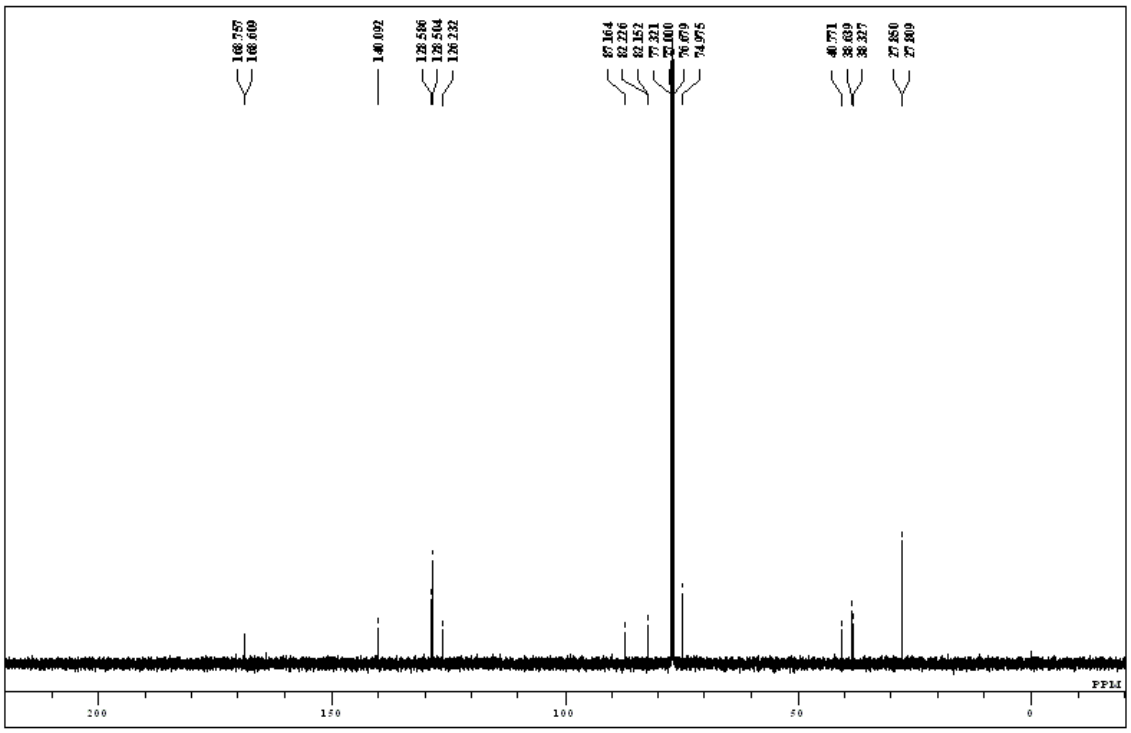
(*R*)-5-Benzyltetrahydro-2*H*-pyran-2-one (9)



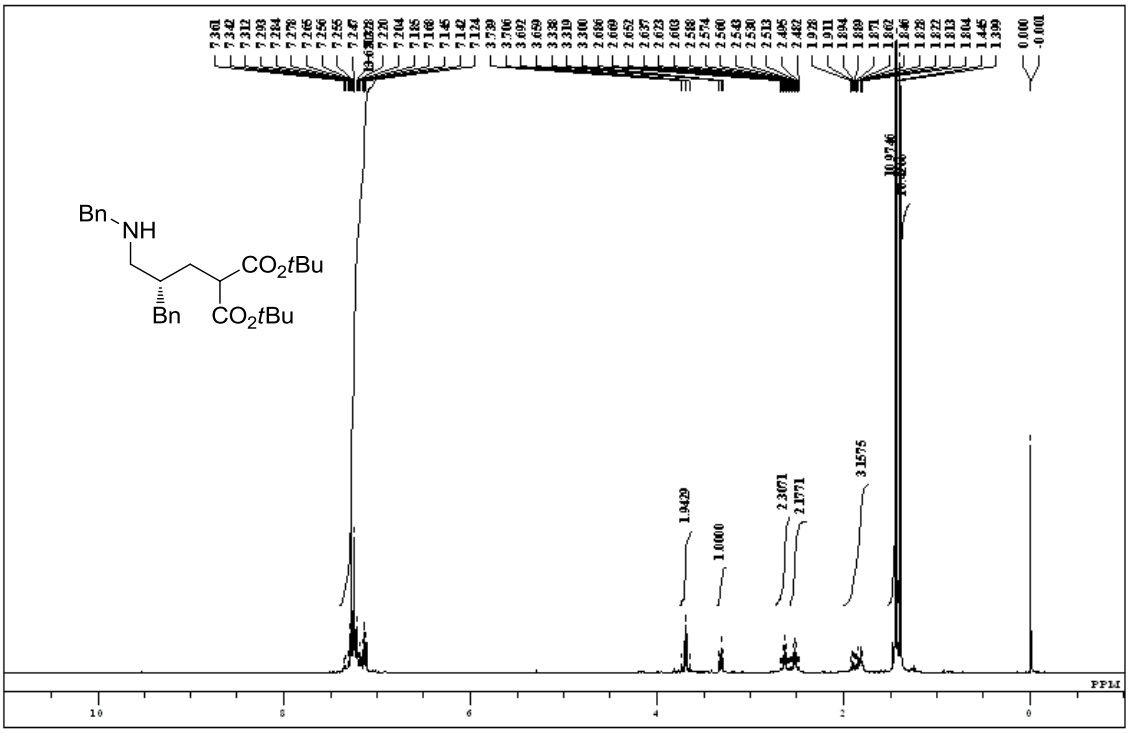


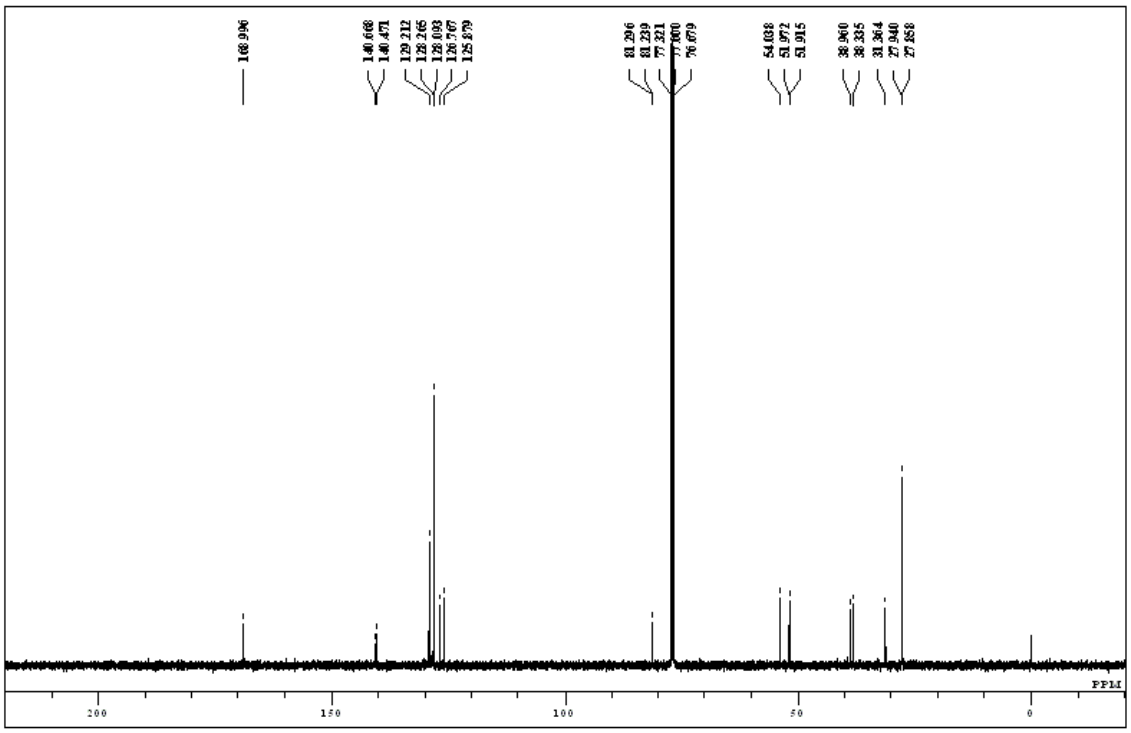
Di-*t*-butyl (*S*)-4-benzyldihydrofuran-2,2(3*H*)-dicarboxylate (10)



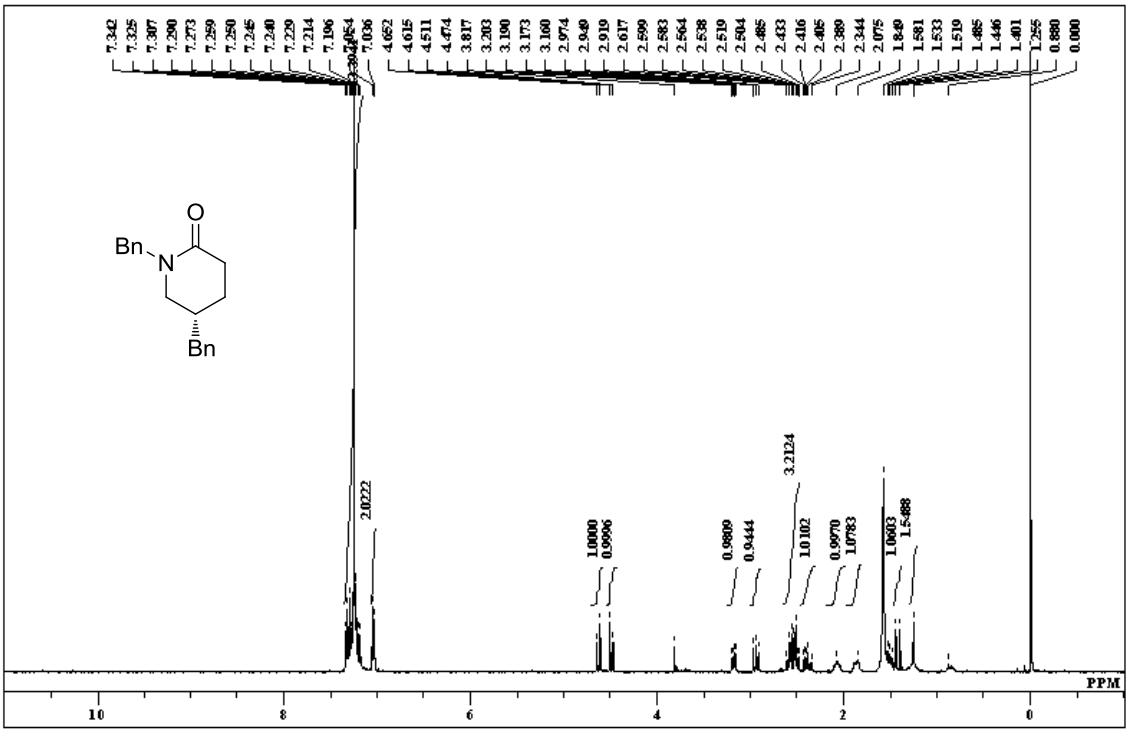


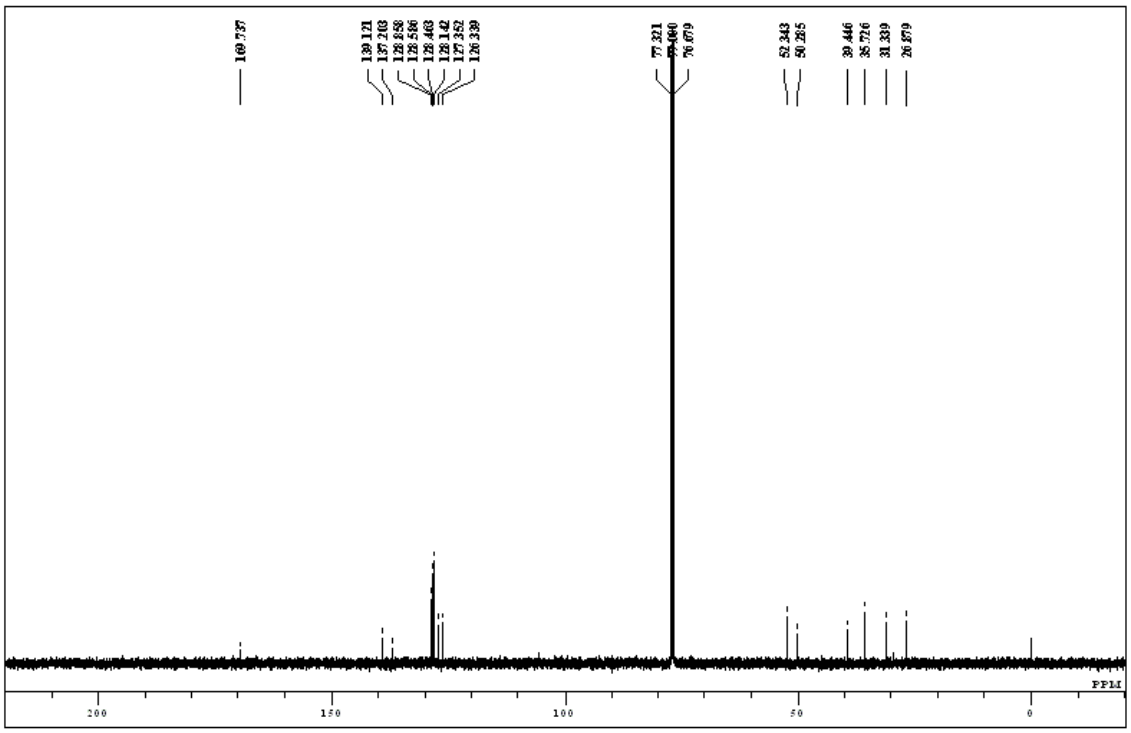
Di-*t*-butyl (*R*)-2-(2-benzyl-3-(benzylamino)propyl)malonate (11)



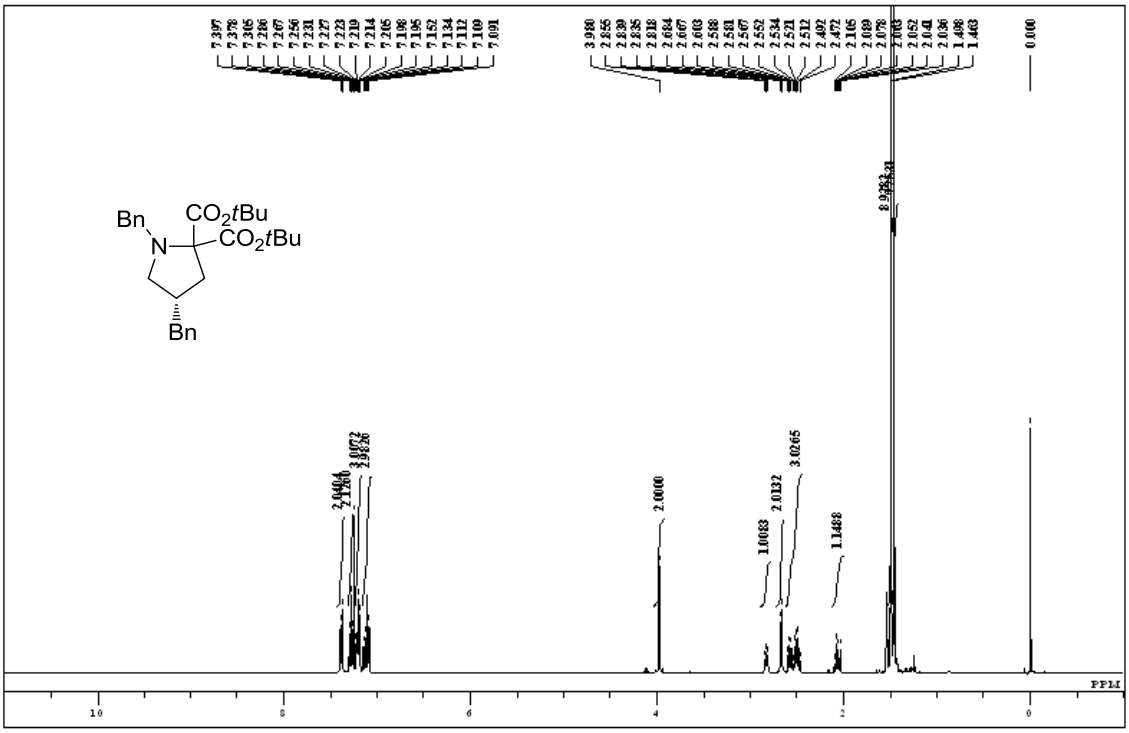


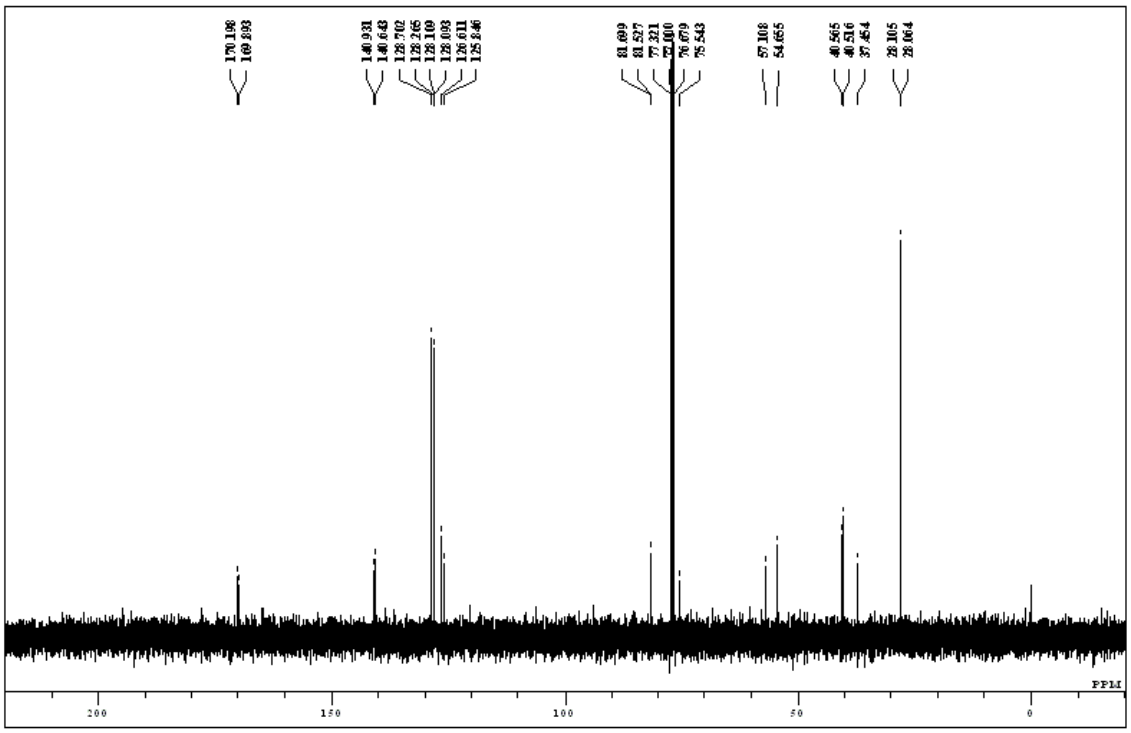
(*R*)-1,5-Dibenzylpiperidin-2-one (12)



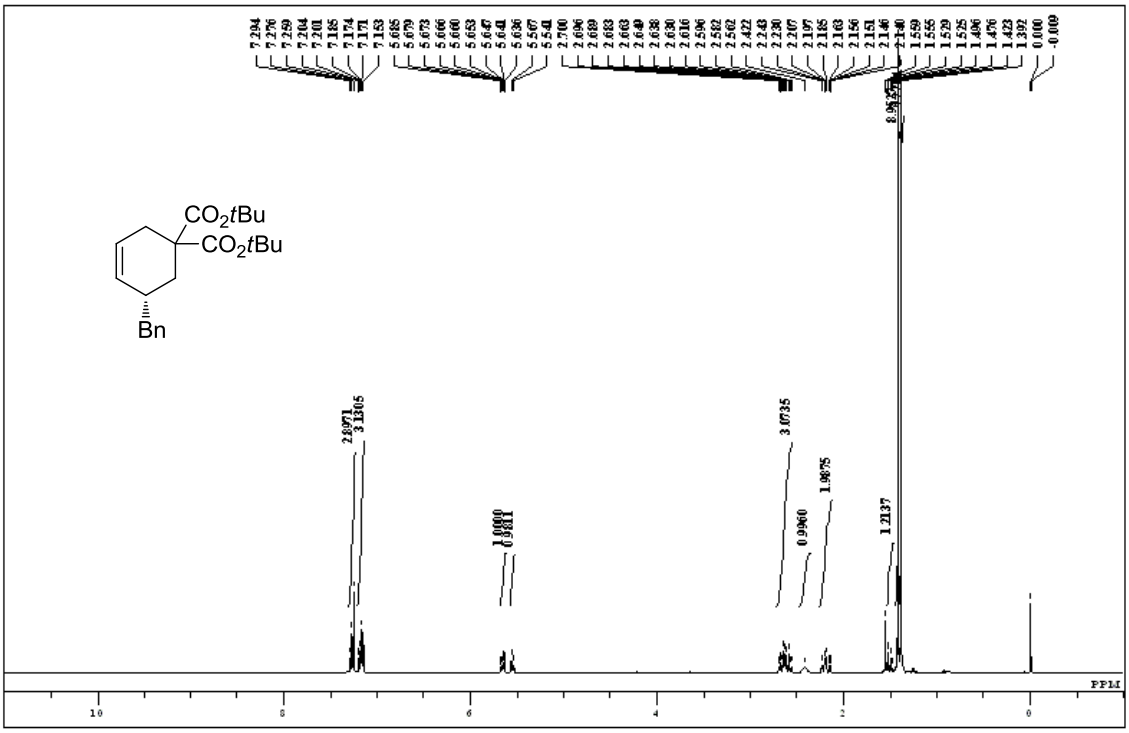


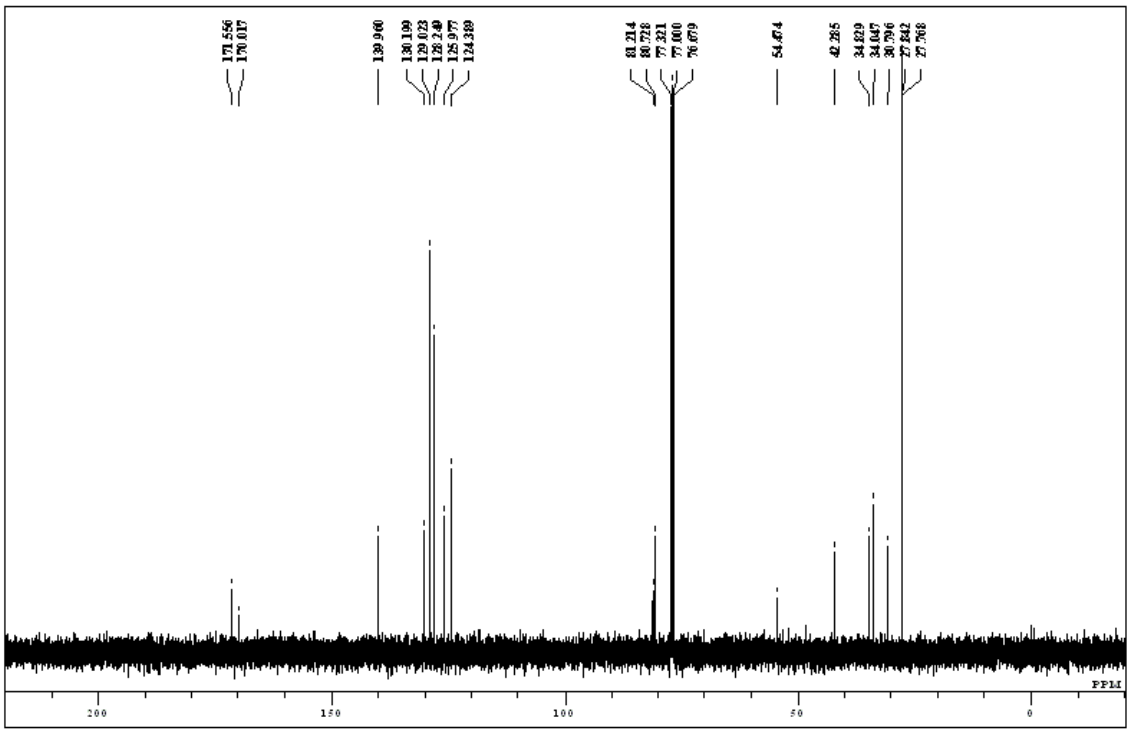
Di-*t*-butyl (*S*)-1,4-dibenzylpyrrolidine-2,2-dicarboxylate (13)



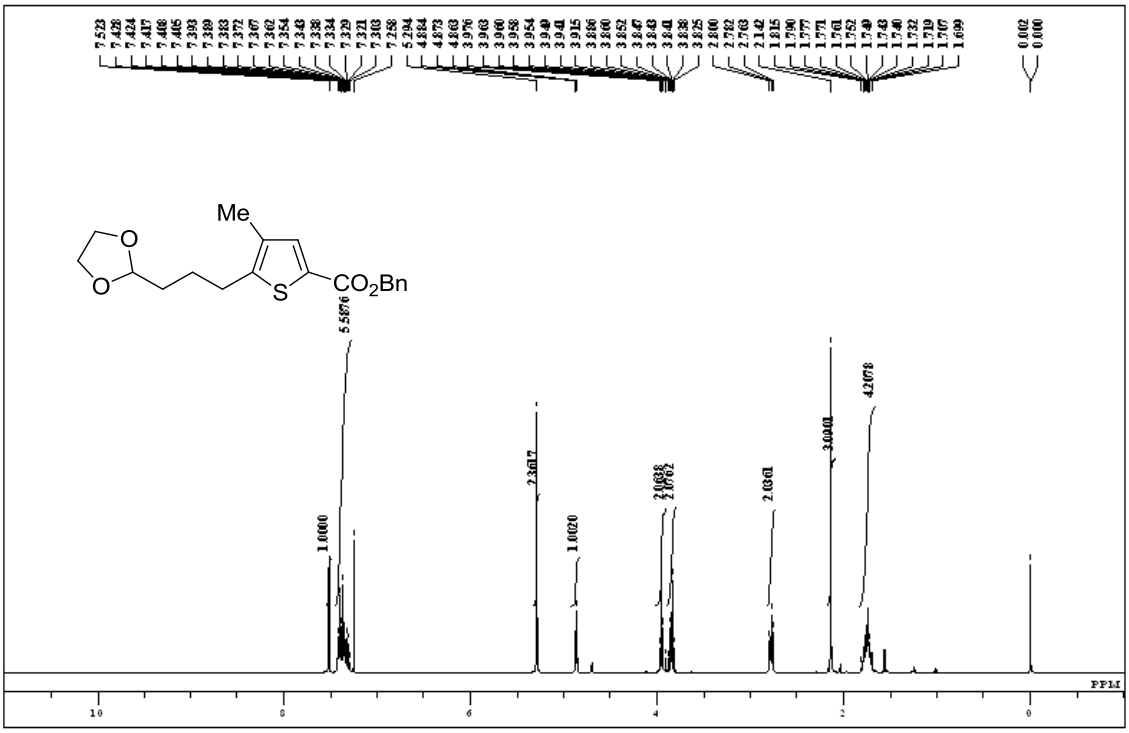


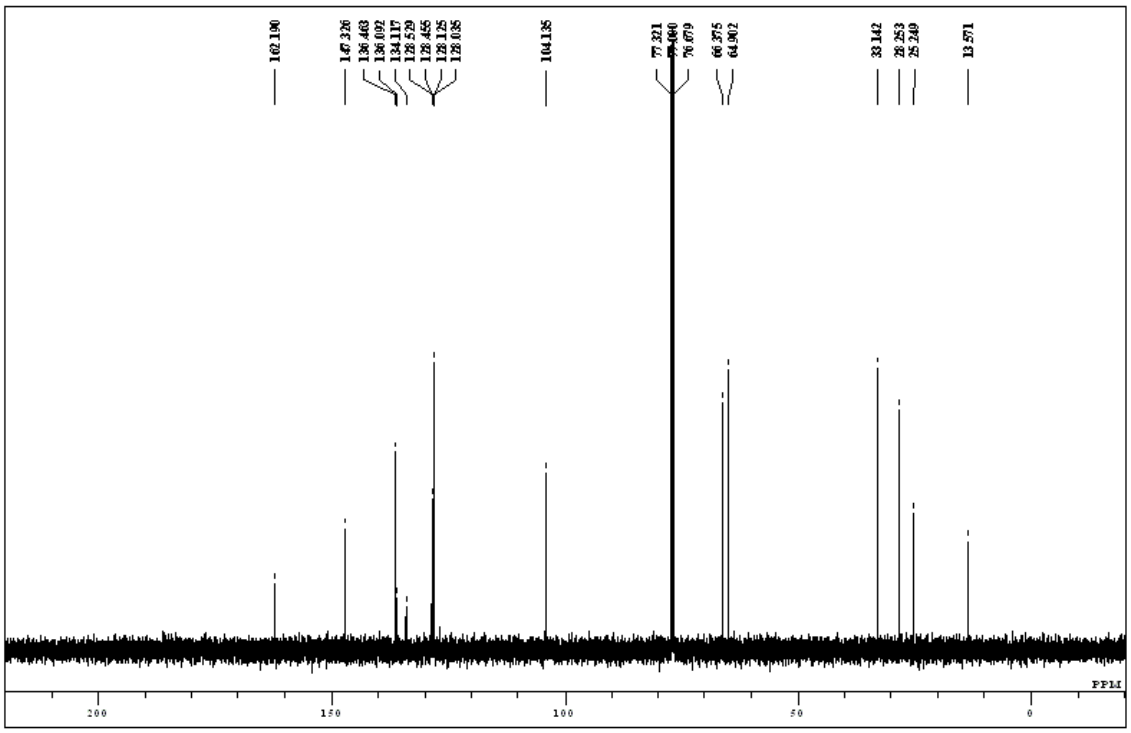
Di-*t*-butyl (*S*)-5-benzylcyclohex-3-ene-1,1-dicarboxylate (14)



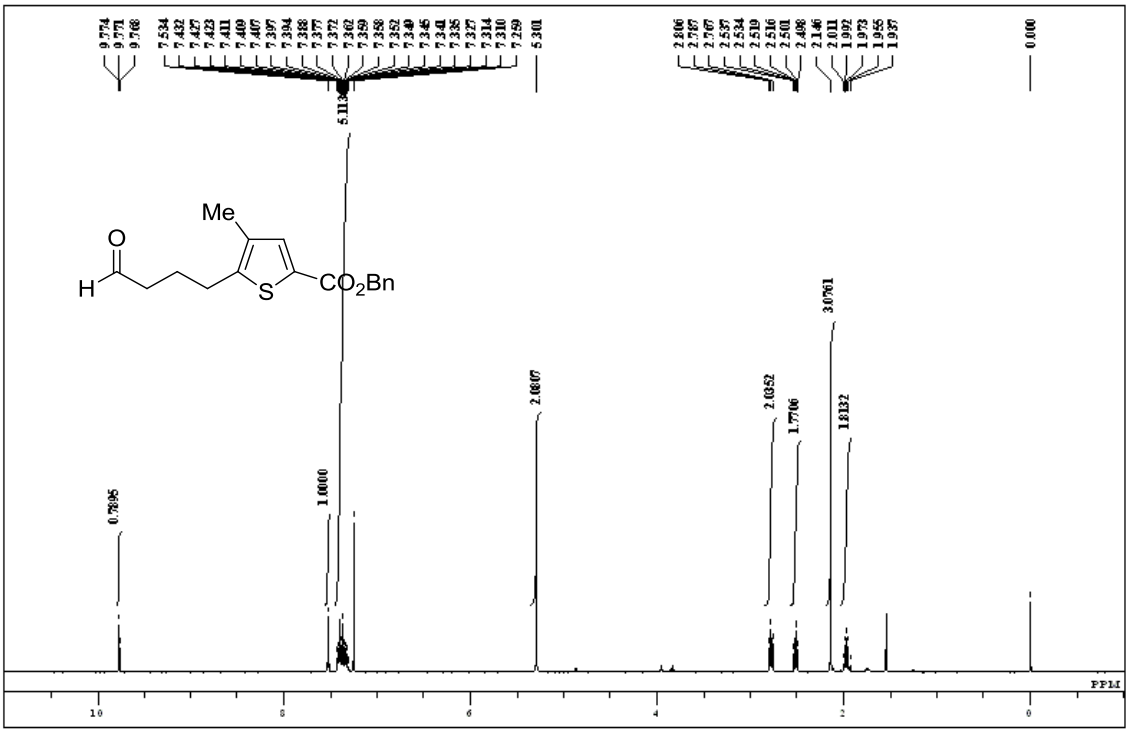


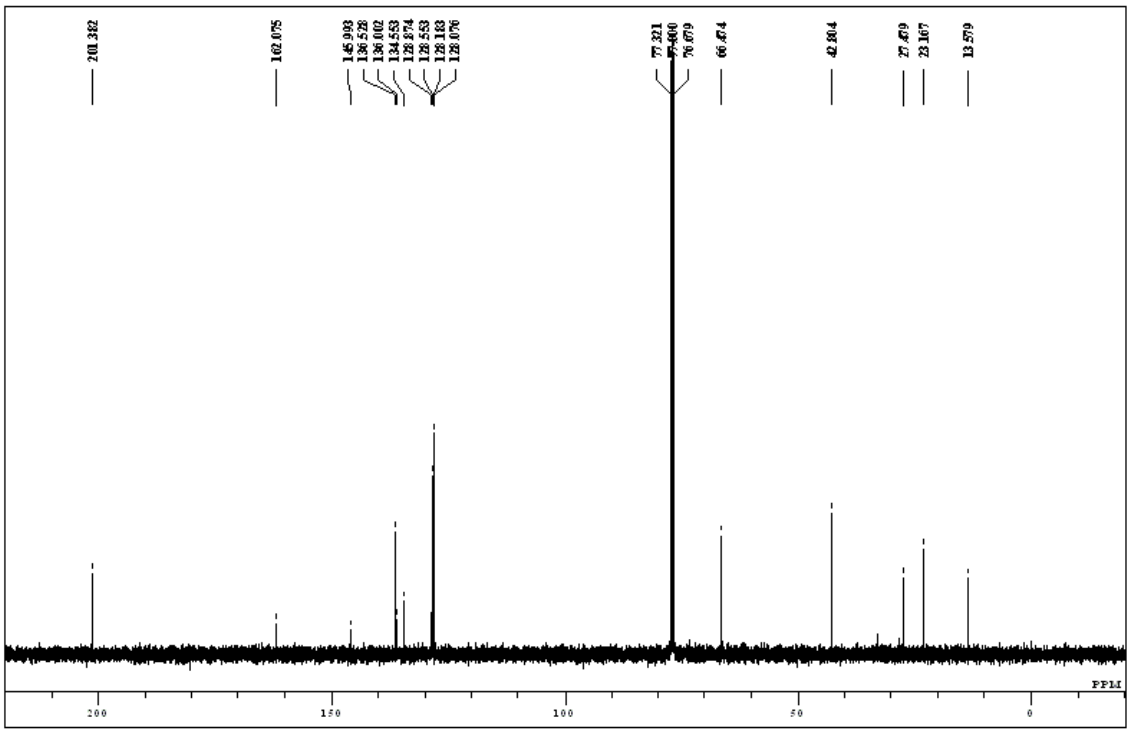
Benzyl 5-(3-(1,3-dioxolan-2-yl)propyl)-4-methylthiophene-2-carboxylate (24)



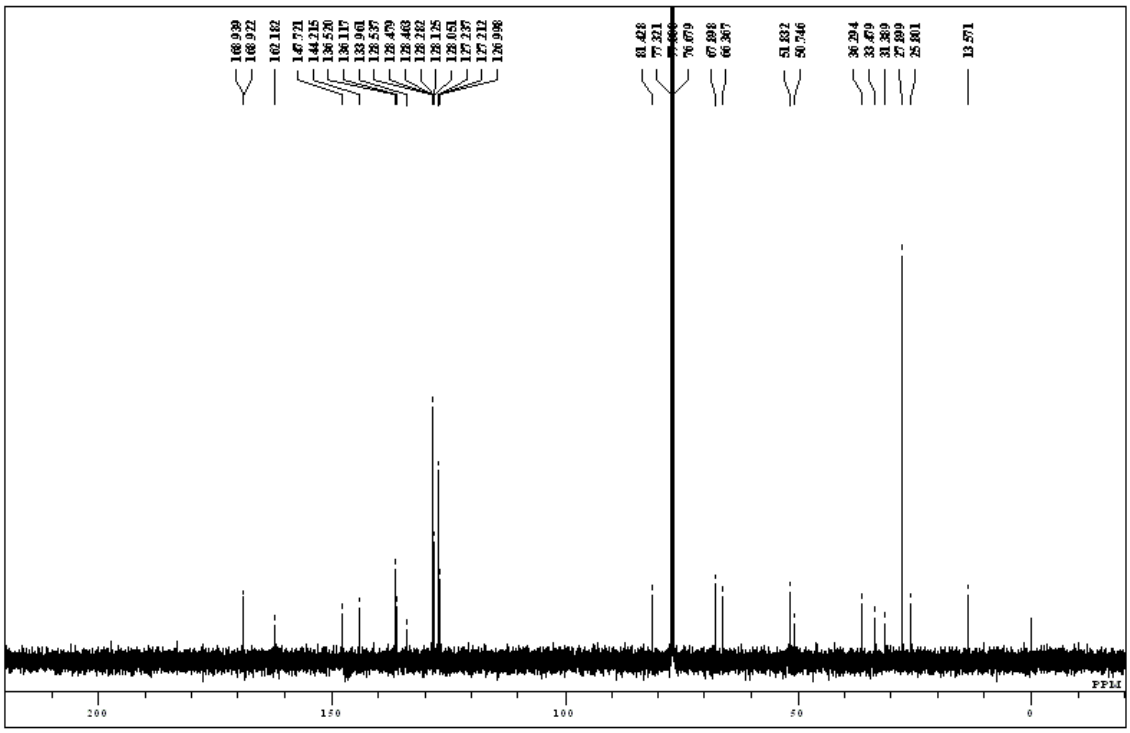


Benzyl 4-methyl-5-(4-oxobutyl)thiophene-2-carboxylate (15)

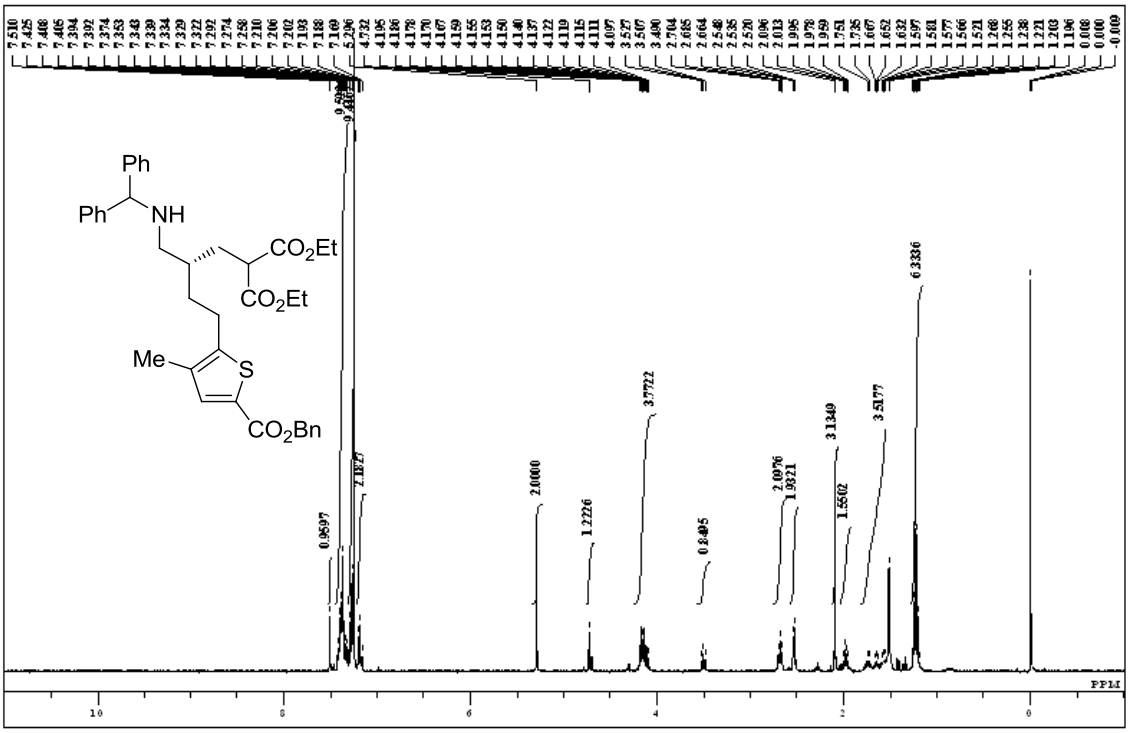


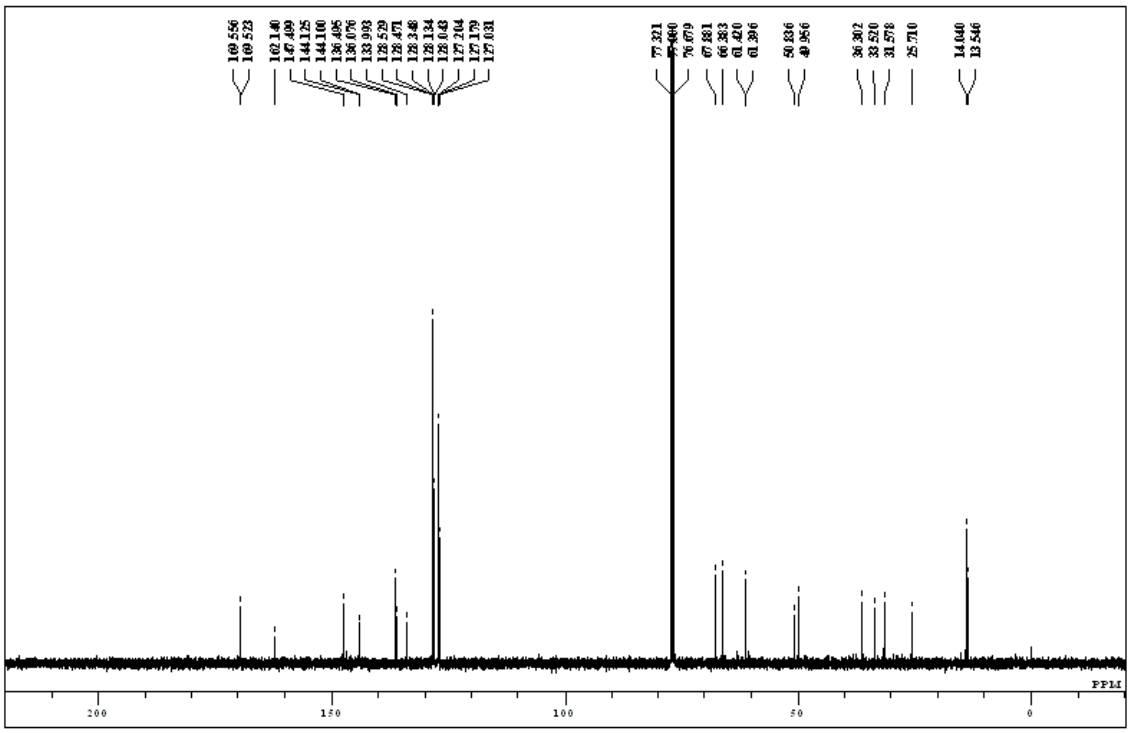


Di-*t*-butyl (*R*)-2-(2-((benzhydrylamino)methyl)-4-(5-((benzyloxy)carbonyl)-3-methylthiophen-2-yl)butyl) malonate (16)



Diethyl (*R*)-2-(2-((benzhydrylamino)methyl)-4-(5-((benzyloxy)carbonyl)-3-methylthiophen-2-yl)butyl) malonate (17)





5-(2-((3*S*)-5-(ethoxycarbonyl)-6-oxopiperidin-3-yl)ethyl)-4-methylthiophene-2-carboxylic acid (18)