Supporting Information

syn-Selective asymmetric cross-aldol reactions between aldehydes and glyoxylic acid derivatives catalyzed by an axially chiral amino sulfonamide

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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 a Daicel CHIRALPAK AD-H and AS-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). *tert*-Butyl glyoxylate and *N*-glyoxyloylmorpholine were prepared by a similar method described in literature.[1] Aldehydes were distilled and stored under argon atmosphere at –17 °C. Amino sulfonamide (*S*)-**1** was synthesized according to the literature procedure. [2] Other simple chemicals were purchased and used as such.

General Procedure for the Catalytic Asymmetric Cross-Aldol Reaction between Aldehydes and *tert*-Butyl Glyoxylate: To a stirred solution of chiral amino sulfonamide (*S*)-**1** (2.2 mg, 0.005 mmol) in CH_3CN (250 μL) were added *tert*-butyl glyoxylate (32.5 mg, 0.25 mmol) and a donor aldehyde (0.75 mmol) in this sequence at room temperature. The mixture was stirred for the time indicated in Table 2, and then quenched with water. After extraction 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.

***tert*-Butyl (2*R*,3*R*)-3-Formyl-2-hydroxyheptanoate (Table 2, entry 2):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (1H, d, J = 2.2 Hz, CHO), 4.46 (1H, t, J = 3.9 Hz, C<u>H</u>OH), 2.99 (1H, d, J = 4.4 Hz, OH), 2.63-2.55 (1H, m, C<u>H</u>CHO), 1.89-1.76 (1H, m, C<u>H</u>H), 1.76-1.52 (1H, m, CH<u>H</u>), 1.50 (9H, s, $C(CH_3)_3$), 1.50-1.20 (4H, m, CH_2), 0.90 (3H, t, J = 7.0 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.3, 172.7, 83.6, 69.6, 55.1, 29.6, 27.9, 23.6, 22.6, 13.7; IR (neat) 3499, 2959, 1724, 1256, 1159, 845 cm^{-1}; HRMS (ESI-TOF) Calcd. for

$C_{12}H_{22}NaO_4$: 253.1410 ([M + Na]$^+$), Found: 253.1403 ([M + Na]$^+$). The title compound was reduced for determining the enantiomeric excess. The enantiomeric excess was determined by the method described below.

***tert*-Butyl (2*R*,3*R*)-3-Benzyl-2-hydroxy-4-oxobutanoate (Table 2, entry 3):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73 (1H, d, *J* = 1.5 Hz, CHO), 7.36-7.13 (5H, m, ArH), 4.49 (1H, d, *J* = 3.1 Hz, C<u>H</u>OH), 3.19 (1H, dd, *J* = 14.1, 8.6 Hz, $C_6H_5C\underline{H}H$), 3.10 (1H, br, OH), 3.08-3.00 (1H, m, C<u>H</u>CHO), 2.80 (1H, dd, *J* = 14.1, 5.7 Hz, $C_6H_5CH\underline{H}$), 1.45 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.4, 172.4, 138.3, 129.1, 128.7, 126.6, 83.8, 69.2, 56.6, 30.2, 27.9; IR (neat) 3493, 2978, 1724, 1252, 1155, 700 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{15}H_{20}NaO_4$: 287.1254 ([M + Na]$^+$), Found: 287.1267 ([M + Na]$^+$). Daicel Chiralpak AS-H, hexane/2-propanol = 40/1, flow rate 1.0 mL/min, λ = 210 nm, retention time: 16.4 min (major) and 18.3 min (minor).

***tert*-Butyl (2*R*,3*R*)-3-Formyl-2-hydroxy-4-methylpentanoate (Table 2, entry 5):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (1H, d, *J* = 3.4 Hz, CHO), 4.43 (1H, d, *J* = 5.1 Hz, C<u>H</u>OH), 2.97 (1H, br, OH), 2.46-2.40 (1H, m, C<u>H</u>CHO), 2.35-2.24 (1H, m, CH), 1.48 (9H, s, $C(CH_3)_3$), 1.08 (3H, d, *J* = 6.8 Hz, CH_3), 1.05 (3H, d, *J* = 6.8 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.9, 173.1, 83.7, 68.9, 60.9, 27.9, 26.4, 21.1, 19.6; IR (neat) 3499, 2967, 1721, 1252, 1142, 845 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{11}H_{20}NaO_4$: 239.1254 ([M + Na]$^+$), Found: 239.1265 ([M + Na]$^+$). The title compound was reduced for determining the enantiomeric excess. The enantiomeric excess was determined by the method described below.

Typical Procedure for the Catalytic Asymmetric Cross-Aldol Reaction between Aldehydes and *tert*-Butyl Glyoxylate (Table 2, entries 1 and 4): To a stirred solution of chiral amino sulfonamide (*S*)-**1** (2.2 mg, 0.005 mmol) in CH_3CN (250 μL) were added *tert*-butyl glyoxylate (32.5 mg, 0.25 mmol) and a donor aldehyde (0.75 mmol) in this sequence at room temperature and stirred for 1 h. To the reaction mixture were added MeOH (500 μL) and $NaBH_4$ (28 mg, 0.75 mmol) at 0 °C. The reaction mixture was stirred for 30 min at same temperature, then 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. The enantiomeric excess was determined by the method described below.

***tert*-Butyl (2*R*,3*S*)-2,4-Dihydroxy-3-methylbutanoate (Table 2, entry 1):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.31 (1H, d, *J* = 2.4 Hz, C<u>H</u>OH), 3.75-3.59 (2H, m, C<u>H</u>$_2$OH), 2.96 (1H, br, OH), 2.20-2.08 (1H, m, CH), 1.50 (9H, s, $C(CH_3)_3$), 0.85 (3H, d, *J* = 7.0 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 82.7, 71.8, 65.6, 38.4, 28.0, 9.6; IR (neat) 3383, 2970, 1728, 1121, 1043, 853 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_9H_{18}NaO_4$: 213.1097 ([M + Na]$^+$), Found: 213.1089 ([M + Na]$^+$).

***tert*-Butyl (2*R*,3*R*)-4-(Benzyloxy)-2-hydroxy-3-(hydroxymethyl)butanoate (Table 2, entry 4):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.26 (5H, m, ArH), 4.47 (2H, d, *J* = 2.9 Hz, OC<u>H</u>$_2$C$_6$H$_5$), 4.26 (1H, d, *J* = 2.7 Hz, C<u>H</u>OH), 3.90-3.75 (2H, m, C<u>H</u>$_2$OH), 3.56 (2H, d, *J* = 6.5 Hz, CHC<u>H</u>$_2$O), 3.16 (1H, br, OH),

2.41-2.30 (1H, m, CH), 1.44 (9H, s, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 137.9, 128.4, 127.8, 127.7, 82.7, 73.5, 70.7, 67.6, 63.0, 44.2, 27.9; IR (neat) 3441, 2932, 1722, 1254, 1161, 741 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{16}H_{24}NaO_5$: 319.1516 ($[M + Na]^+$), Found: 319.1504 ($[M + Na]^+$).

General Procedure for the Catalytic Asymmetric Cross-Aldol Reaction between Aldehydes and *N*-Glyoxyloylmorpholine: To a stirred solution of chiral amino sulfonamide (*S*)-**1** (2.2 mg, 0.005 mmol) in CH_3CN (250 μL) were added *N*-glyoxyloylmorpholine (36.0 mg, 0.25 mmol) and a donor aldehyde (0.75 mmol) in this sequence at room temperature. After stirring for the time indicated in Table 3, to the reaction mixture were added MeOH (500 μL) and $NaBH_4$ (28 mg, 0.75 mmol) slowly at 0 °C. The reaction mixture were stirred for 30 min at same temperature, then 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 adducts. The enantiomeric excess was determined by the method described below.

(2*R*,3*S*)-2-Hydroxy-3-(hydroxymethyl)-1-morpholinoheptan-1-one (Table 3, entry 1): $[\alpha]_D^{21}$ = +10.4 (*c* 2.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 4.72 (1H, d, *J* = 1.9 Hz, C<u>H</u>OH), 3.81-3.40 (10H, m, NC<u>H</u>$_2$C<u>H</u>$_2$O, C<u>H</u>$_2$OH), 2.18 (1H, br, OH), 1.73-1.62 (1H, m, CH), 1.40-1.10 (6H, m, CH_2), 0.87 (3H, t, *J* = 7.0 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 68.2, 66.8, 66.5, 63.1, 45.5, 43.3, 42.9, 29.7, 23.4, 22.8, 13.9; IR (neat) 3416, 2928, 1639, 1271, 1115, 1030, 860 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{12}H_{23}NNaO_4$: 268.1519 ($[M + Na]^+$), Found: 268.1507 ($[M + Na]^+$).

(2*R*,3*S*)-3-Benzyl-2,4-dihydroxy-1-morpholinobutan-1-one (Table 3, entry 2): $[\alpha]_D^{21}$ = -6.7 (*c* 2.3, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.31-7.25 (2H, m, ArH), 7.19 (1H, d, *J* = 7.3 Hz, ArH), 7.12 (2H, d, *J* = 7.3 Hz, ArH), 4.75 (1H, app s, C<u>H</u>OH), 3.78-3.36 (10H, m, NC<u>H</u>$_2$C<u>H</u>$_2$O, C<u>H</u>$_2$OH), 2.62-2.47 (2H, m, C<u>H</u>$_2$$C_6H_5$), 2.09 (1H, br, OH), 2.09-1.98 (1H, m, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 140.0, 129.0, 128.4, 126.2, 67.8, 66.7, 66.3, 63.1, 45.6, 45.4, 42.8, 30.5; IR (neat) 3418, 2924, 1636, 1113, 1032, 525 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{15}H_{21}NNaO_4$: 302.1363 ($[M + Na]^+$), Found: 302.1358 ($[M + Na]^+$).

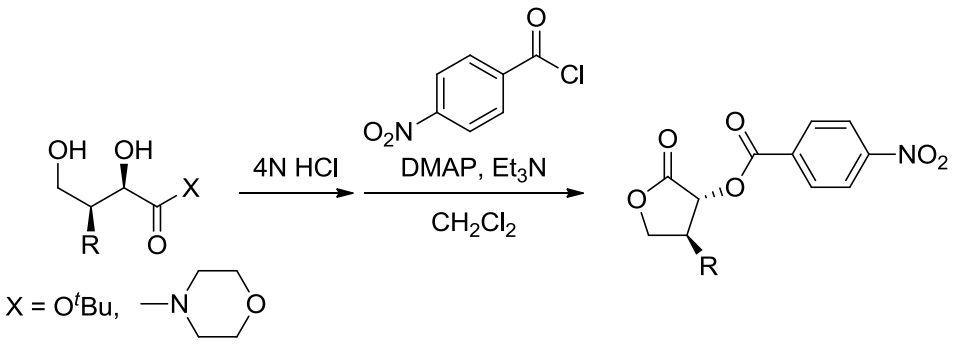
(2*R*,3*S*)-2-Hydroxy-3-(hydroxymethyl)-1-morpholinononan-1-one (Table 3, entry 3): ^1H NMR (400 MHz, $CDCl_3$) δ 4.71 (1H, d, *J* = 1.7 Hz, C<u>H</u>OH), 3.91-3.38 (10H, m, NC<u>H</u>$_2$C<u>H</u>$_2$O, C<u>H</u>$_2$OH), 1.66 (1H, m, CH), 1.38-1.07 (10H, m, CH_2), 0.87 (3H, t, *J* = 6.8 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 68.2, 66.8, 66.5, 63.1, 45.5, 43.3, 42.9, 31.6, 29.4, 27.5, 23.7, 22.6, 14.0; IR (neat) 3420, 2926, 1639, 1271, 1115, 1032 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{14}H_{27}NNaO_4$: 296.1832 ($[M + Na]^+$), Found: 296.1820 ($[M + Na]^+$).

(2*R*,3*R*)-4-(Benzyloxy)-2-hydroxy-3-(hydroxymethyl)-1-morphoinobutan-1-one (Table 3, entry 4): ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.21 (5H, m, ArH), 4.65 (1H, dd, *J* = 6.2, 3.8 Hz, C<u>H</u>OH), 4.42 (2H, s, OC<u>H</u>$_2$$C_6H_5$), 3.93 (1H, d, *J* = 6.5 Hz, CHC<u>H</u>HO), 3.89-3.75 (2H, m, CH_2OH), 3.75-3.37 (10H, m, CHCH<u>H</u>O, NC<u>H</u>$_2$C<u>H</u>$_2$O, OH), 2.64 (1H, br, OH), 2.15-2.03 (1H, m, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 137.9, 128.4, 127.9, 127.8, 73.6, 67.5, 67.1, 66.5, 66.3, 62.7, 45.5, 44.6, 42.9; IR (neat) 3414, 2860,

1636, 1111, 1036, 742 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{16}H_{23}NNaO_5$: 332.1468 ($[M + Na]^+$), Found: 332.1458 ($[M + Na]^+$).

(2*R*,3*S*)-2-Hydroxy-3-(hydroxymethyl)-4-methyl-1-morpholinopentan-1-one (Table 3, entry 5): ^1H NMR (400 MHz, $CDCl_3$) δ 4.75 (1H, d, J = 2.7 Hz, C<u>H</u>OH), 3.90-3.79 (2H, m, C<u>H</u>$_2$OH), 3.76-3.40 (8H, m, NC<u>H</u>$_2$C<u>H</u>$_2$O), 1.90-1.78 (1H, m, C<u>H</u>$(CH_3)_2$), 1.65-1.58 (1H, m, CH), 0.95 (3H, d, J = 4.4 Hz, CH_3) 0.93 (3H, d, J = 4.4 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 68.4, 66.8, 66.5, 60.7, 49.1, 45.7, 42.9, 25.3, 23.0, 19.5; IR (neat) 3420, 2924, 1632, 1269, 1113, 1040 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{11}H_{21}NNaO_4$: 254.1363 ($[M + Na]^+$), Found: 254.1354 ($[M + Na]^+$).

Typical Procedure for Determining the Enantiomeric Excess of Aldol Product:



The reduced aldol product was dissolved in 4N HCl (2 mL). After stirring for 3 h at 80 °C, the reaction mixture was quenched with $NaHCO_3$ aq and extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was used for the next step directly.

To a solution of the residue in CH_2Cl_2 (1 mL) were added triethylamine (1.2 equiv), 4-nitrobenzoyl chloride (1.1 equiv) and 4-dimethylaminopyridine (0.5 equiv) in this sequence at room temperature. After 12 h of stirring, 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 product.

(3*R*,4*S*)-4-Methyl-2-oxotetrahydrofuran-3-yl 4-Nitrobenzoate (Table 2 entry 1): ^1H NMR (400 MHz, $CDCl_3$) δ 8.32 (2H, app d, J = 9.2 Hz, ArH), 8.26 (2H, app d, J = 9.2 Hz, ArH), 5.49 (1H, d, J = 10.4 Hz, C<u>H</u>OCOAr), 4.57 (1H, app t, J = 8.6 Hz, C<u>H</u>HO), 3.97 (1H , app t, J = 9.7 Hz, CH<u>H</u>O), 2.95-2.80 (1H, m, OCH$_2$C<u>H</u>), 1.31 (3H, d, J = 6.5 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 163.7, 151.0, 134.1, 131.2, 123.7, 74.6, 70.6, 37.0, 14.5; IR (neat) 2922, 1790, 1732, 1526, 1269, 1119, 716 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{12}H_{11}NNaO_6$: 288.0479 ($[M + Na]^+$), Found: 288.0476 ($[M + Na]^+$). Daicel Chiralpak AS-H, hexane/2-propanol = 4/1, flow rate 0.5 mL/min, λ = 254 nm, retention time: 89 min (major) and 99 min (minor).

(3*R*,4*S*)-4-Butyl-2-oxotetrahydrofuran-3-yl 4-Nitrobenzoate (Table 2, entry 2 and Table 3, entry 1): Spectral dates of the title compound were in accordance with those previously reported.[3] Daicel Chiralpak AS-H, hexane/2-propanol = 9/1, flow rate 0.5 mL/min, λ = 254 nm, retention time: 60 min (major) and 75

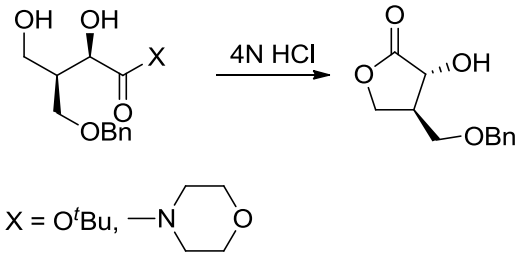
min (minor).

(3*R*,4*S*)-4-Benzyl-2-oxotetrahydrofuran-3-yl 4-Nitrobenzoate (Table 3, entry 2): $[\alpha]_D^{21}$ = +39.6 (*c* 2.8, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (2H, app d, *J* = 8.9 Hz, ArH), 8.06 (2H, app d, *J* = 8.9 Hz, ArH), 7.22 (2H, d, *J* = 7.5 Hz, ArH), 7.18-7.09 (3H, m, ArH), 5.67 (1H, d, *J* = 10.4 Hz, C<u>H</u>OCOAr), 4.49 (1H, app t, *J* = 8.6 Hz, C<u>H</u>HO), 4.09 (1H, app t, *J* = 9.8 Hz, CH<u>H</u>O), 3.23-3.10 (1H, m, $OCH_2C\underline{H}$), 3.04-2.89 (2H, m, $C\underline{H}_2C_6H_5$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 163.4, 150.9, 136.6, 134.0, 131.0, 128.9, 128.5, 127.1, 123.5, 73.0, 69.1, 43.1, 36.3; IR (neat) 1790, 1732, 1524, 1346, 1265, 1130, 1011, 702 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{18}H_{15}NNaO_6$: 364.0792 ([M + Na]$^+$), Found: 364.0778 ([M + Na]$^+$). Daicel Chiralpak AD-H, hexane/2-propanol = 9/1, flow rate 0.5 mL/min, λ = 254 nm, retention time: 99.3 min (major) and 161.0 min (minor).

(3*R*,4*S*)-4-Isopropyl-2-oxotetrahydrofuran-3-yl 4-Nitrobenzoate (Table 2, entry 5 and Table 3, entry 5): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (2H, app d, *J* = 8.9 Hz, ArH), 8.25 (2H, app d, *J* = 8.9 Hz, ArH), 5.63 (1H, d, *J* = 10.4 Hz, C<u>H</u>OCOAr), 4.57 (1H, app t, *J* = 8.8 Hz, C<u>H</u>HO), 4.05 (1H, app t, *J* = 9.7 Hz, CH<u>H</u>O), 2.74-2.60 (1H, m, $OCH_2C\underline{H}$), 1.96-1.84 (1H, m, $C\underline{H}(CH_3)_2$), 1.01 (3H, t, *J* = 4.4 Hz, CH_3), 0.99 (3H, t, *J* = 4.4 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 163.5, 151.0, 134.2, 131.1, 123.7, 72.4, 68.4, 47.4, 30.0, 20.2, 19.8; IR (neat) 2963, 1790, 1732, 1528, 1267, 1121, 1009, 716 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{14}H_{15}NNaO_6$: 316.0792 ([M + Na]$^+$), Found: 316.0787 ([M + Na]$^+$). Daicel Chiralpak AD-H, hexane/2-propanol = 9/1, flow rate 0.5 mL/min, λ = 254 nm, retention time: 84.2 min (major) and 118.0 min (minor).

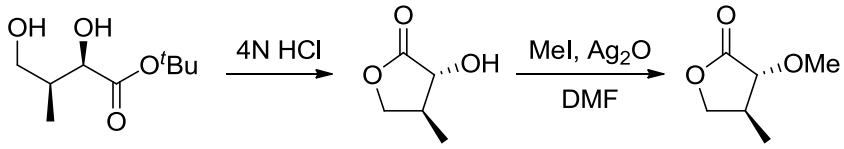
(3*R*,4*S*)-4-Hexyl-2-oxotetrahydrofuran-3-yl 4-Nitrobenzoate (Table 3, entry 3): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (2H, app d, *J* = 8.9 Hz, ArH), 8.25 (2H, app d, *J* = 8.9 Hz, ArH), 5.56 (1H, d, *J* = 10.2 Hz, C<u>H</u>OCOAr), 4.58 (1H, app t, *J* = 8.6 Hz, C<u>H</u>HO), 4.01 (1H, app t, *J* = 9.6 Hz, CH<u>H</u>O), 2.93-2.74 (1H, m, $OCH_2C\underline{H}$), 1.80-1.67 (1H, m, C<u>H</u>H), 1.65-1.50 (1H, m, CH<u>H</u>), 1.42-1.15 (8H, m, CH_2), 0.85 (3H, t, *J* = 6.7 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 163.6, 151.0, 134.2, 131.2, 123.7, 73.7, 69.8, 41.5, 31.5, 30.6, 29.1, 26.8, 22.5, 14.0; IR (neat) 2926, 1791, 1734, 1528, 1265, 1099, 1013, 716 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{17}H_{21}NNaO_6$: 358.1261 ([M + Na]$^+$), Found: 358.1248 ([M + Na]$^+$). Daicel Chiralpak AD-H, hexane/2-propanol = 9/1, flow rate 0.5 mL/min, λ = 254 nm, retention time: 64.3 min (major) and 72.8 min (minor).

Determination of the Enantiomeric Excess of *tert*-Butyl (2*R*,3*R*)-4-(Benzyloxy)-2-hydroxy-3-(hydroxymethyl)butanoate and (2*R*,3*R*)-4-(Benzyloxy)-2-hydroxy-3-(hydroxymethyl)-1-morphoinobutan-1-one (Table 2, entry 4 and Table 3, entry 4):

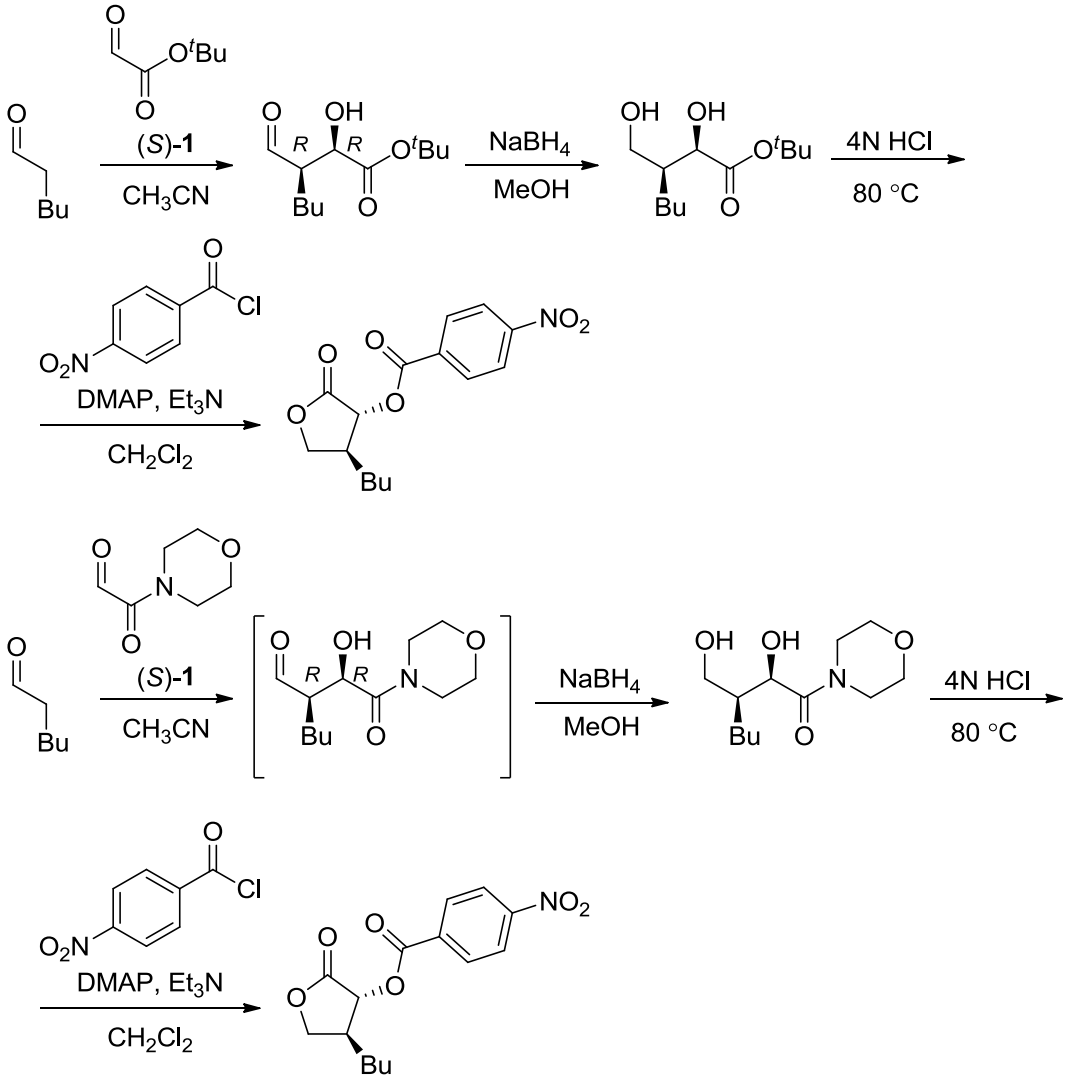


The title compound was dissolved in 4N HCl (2 mL). After stirring for 3 h at 80 °C, the reaction mixture was quenched with $NaHCO_3$ aq and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate = 2/1) to afford (2*R*,3*S*)-3-benzyloxymethyl-2-hydroxy-4-butanolide.[4] Daicel Chiralpak AD-H, hexane/2-propanol = 4/1, flow rate 0.5 mL/min, λ = 210 nm, retention time: 65.7 min (major) and 82.3 min (minor).

Determination of Relative and Absolute Configuration of Aldol Product:

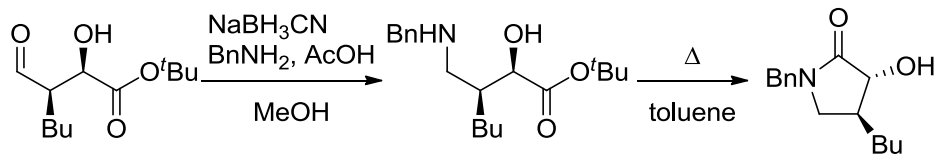


(3*R*,4*S*)-3-Hydroxy-4-methyldihydrofuran-2(3H)-one was prepared by a similar method described above. A mixture of (3*R*,4*S*)-3-hydroxy-4-methyldihydrofuran-2(3H)-one (14 mg, 0.121 mmol), MeI (36 mg, 0.25 mmol) and Ag_2O (58 mg, 0.25 mmol) in *N*,*N*-dimethylformamide (DMF) (65 μL) was stirred for 5 h at room temperature. The resulting precipitate was filtered off with the aid of Celite and the filtrate was diluted with H_2O and extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate = 5/1) to afford a (2*S*,3*R*)-2-methyl-3-methoxy-1-butanolide[5] (43% yield). $[\alpha]_D^{21}$ = +77.8 (*c* 0.7, $CHCl_3$). The relative and absolute configuration was determined by comparison with ^{1}H NMR spectrum and optical rotation of the literature.[5] (lit $[\alpha]_D^{21}$ = +124.7 (*c* 4.6, $CHCl_3$)).



The absolute configuration of the *syn*-aldol product obtained in the reaction between *tert*-butyl glyoxylate and hexanal catalyzed by (*S*)-**1** was determined to be (2*R*,3*R*). Based on this information, the absolute configuration of the *syn*-aldol product obtained in the reaction between *N*-glyoxyloylmorpholine and hexanal catalyzed by (*S*)-**1** was determined to be (2*R*,3*R*) by converted to (3*R*,4*S*)-4-butyl-2-oxotetrahydrofuran-3-yl 4-nitrobenzoate and comparison of the HPLC analysis retention time of (3*R*,4*S*)-4-butyl-2-oxotetrahydrofuran-3-yl 4-nitrobenzoate.

Synthesis of (3*R*,4*S*)-1-Benzyl-4-butyl-3-hydroxypyrrolidin-2-one 4:[6,7]



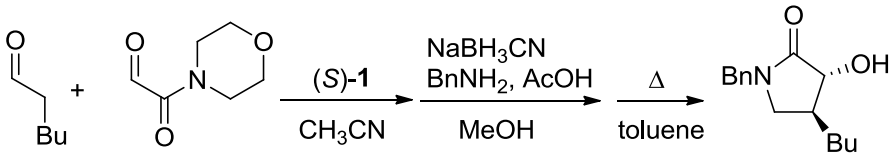
4

To a solution of *tert*-butyl (2*R*,3*R*)-3-formyl-2-hydroxyheptanoate (45.6 mg, 0.195 mmol) in MeOH(2 mL) were added benzylamine (2 equiv), an $NaBH_3CN$ solution in THF (1M, 2 equiv) and acetic acid (2.5 equiv). The mixture was stirred overnight at room temperature, after which MeOH was evaporated, and the crude was dissolved in ethyl acetate. The organic phase was washed with a $NaHCO_3$ aq and brine, dried over

Na_2SO_4 and concentrated to afford *tert*-butyl (2*S*,3*S*)-3-((benzylamino)methyl)-2-hydroxyheptanoate which was roughly purified by flash column chromatography on silica gel (77% yield).

tert-Butyl (2*S*,3*S*)-3-((benzylamino)methyl)-2-hydroxyheptanoate was refluxed in toluene for 16 h. After removal of toluene, the residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate = 1/1) afforded (3*R*,4*S*)-1-benzyl-4-butyl-3-hydroxypyrrolidin-2-one (84% yield, 94% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.16 (5H, m, ArH), 4.48 (1H, d, *J* = 14.8 Hz, NC<u>H</u>HC_6H_5), 4.42 (1H, d, *J* = 14.8 Hz, NCH<u>H</u>C_6H_5), 4.15 (1H, br, OH), 4.03 (1H, d, *J* = 9.2 Hz, C<u>H</u>OH), 3.27 (1H, app t, *J* = 9.1 Hz, NC<u>H</u>HCH), 2.80 (1H, app t, *J* = 9.4 Hz, NCH<u>H</u>CH), 2.24-2.12 (1H, m, NCH_2C<u>H</u>), 1.80-1.65 (1H, m, C<u>H</u>H), 1.45-1.13 (5H, m, CH_2), 0.87 (3H, t, *J* = 7.0 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 135.7, 128.7, 128.1, 127.7, 75.4, 48.7, 46.9, 41.7, 31.9, 29.4, 22.7, 13.9; IR (neat) 3337, 2926, 1676, 1452, 1263, 700 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{15}H_{21}NNaO_2$: 270.1465 ([M + Na]$^+$), Found: 270.1460 ([M + Na]$^+$). Daicel Chiralpak AD-H, hexane/2-propanol = 9/1, flow rate 0.5 mL/min, λ = 210 nm, retention time: 27.8 min (major) and 40.0 min (minor).

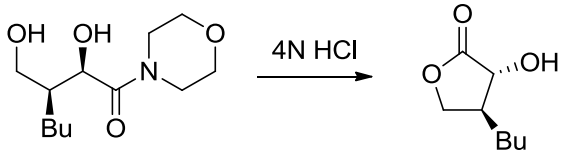
One-Pot Synthesis of (3*R*,4*S*)-1-Benzyl-4-butyl-3-hydroxypyrrolidin-2-one 4:



4

To a stirred solution of chiral amino sulfonamide (*S*)-**1** (2.2 mg, 0.005 mmol) in CH_3CN (250 μL) were added *N*-glyoxyloylmorpholine (36.0 mg, 0.25 mmol) and a donor aldehyde (0.75 mmol) in this sequence at room temperature. After stirring for 48 h, the reaction mixture was quenched with water and extracted with ethyl acetate, dried over Na_2SO_4 and concentrated. To a stirred solution of the reaction mixture in MeOH (2.3 mL) were added benzylamine (68 μL, 3 equiv), an $NaBH_3CN$ solution in THF (1M, 3 equiv) and acetic acid (2.5 equiv). The mixture was stirred overnight at room temperature, after which MeOH was evaporated, and the crude was dissolved in ethyl acetate. The organic phase was washed with a $NaHCO_3$ aq and brine, dried over Na_2SO_4 and concentrated. The residue was refluxed in toluene for 16 h. After removal of toluene, the residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate = 1/1) afforded (3*R*,4*S*)-1-benzyl-4-butyl-3-hydroxypyrrolidin-2-one (56% yield for 3 steps, 94% ee). $[\alpha]_D^{21}$ = +78.0 (*c* 0.79, $CHCl_3$).

(3*R*,4*S*)-4-Butyl-3-hydroxydihydrofuran-2(3H)-one 6:



5 **6**

(2*R*,3*S*)-2-Hydroxy-3-(hydroxymethyl)-1-morphorinoheptan-1-one **5** (50.8 mg, 0.207 mmol) was dissolved in 4N HCl (2 mL). After stirring for 3 h at 80 °C, the reaction mixture was quenched with $NaHCO_3$ aq and

extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate = 2/1) to afford (3*R*,4*S*)-4-butyl-3-hydroxydihydrofuran-2(3H)-one (51% yield). $[\alpha]_D^{21}$ = +65.2 (*c* 0.77, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.44 (1H, app t, *J* = 8.5 Hz, C<u>H</u>HOCO), 4.08 (1H, d, *J* = 10.4 Hz, C<u>H</u>OH), 3.83 (1H, dd, *J* = 10.4, 9.2 Hz, CH<u>H</u>OCO), 2.54-2.40 (1H, m, CH), 1.81-1.61 (1H, m, C<u>H</u>H), 1.56-1.29 (5H, m, CH), 0.92 (3H, t, *J* = 7.0 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9, 72.9, 69.9, 43.7, 30.5, 29.1, 22.7, 13.8; IR (neat) 3441, 2928, 1784, 1143, 1096, 1005 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_8H_{14}NaO_3$: 181.0835 ($[M + Na]^+$), Found: 181.0836 ($[M + Na]^+$). The enantiomeric excess was determined by the method described above.

References

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(5) H. Akita, H. Matsukura, H. Karashima, T. Oishi, *Chem. Pharm. Bull.* **1992**, *40*, 2847.

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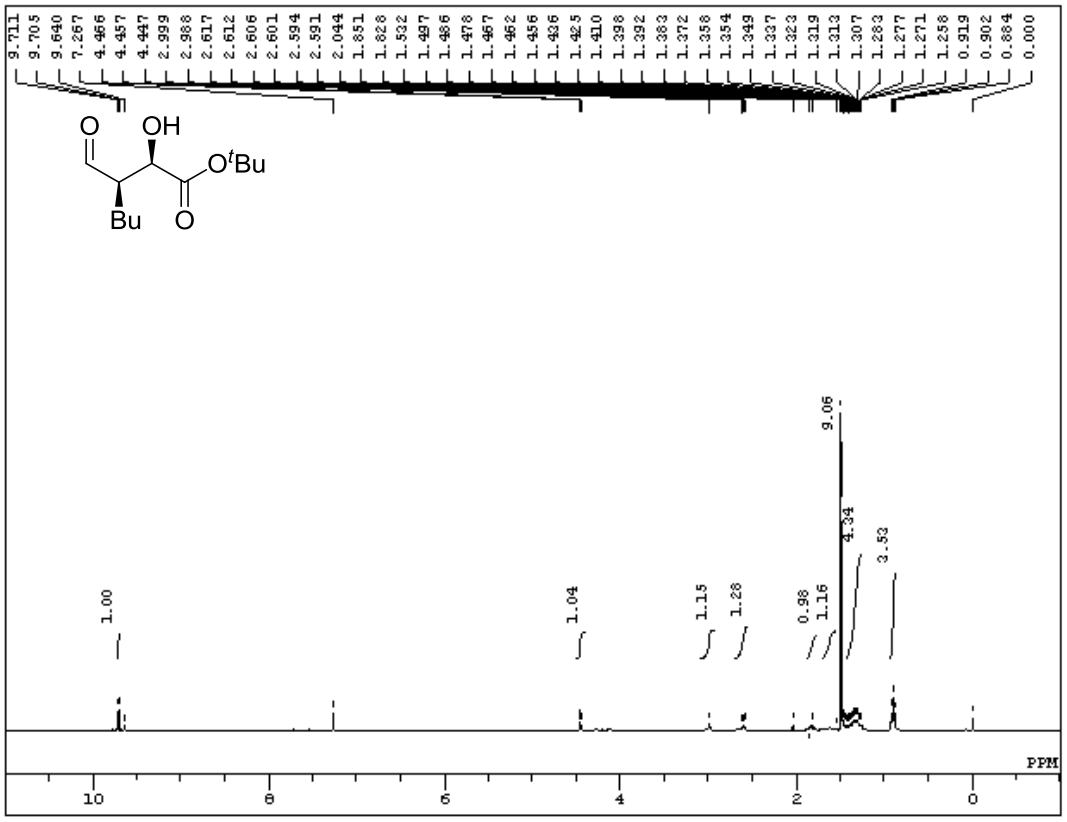
(7) S. G. Davies, D. A. B. Mortimer, A. W. Mulvancy, A. J. Russell, H. Skarphedinsson, A. D. Smith, R. J. Vickers, *Org. Biomol. Chem.* **2008**, *6*, 1625.

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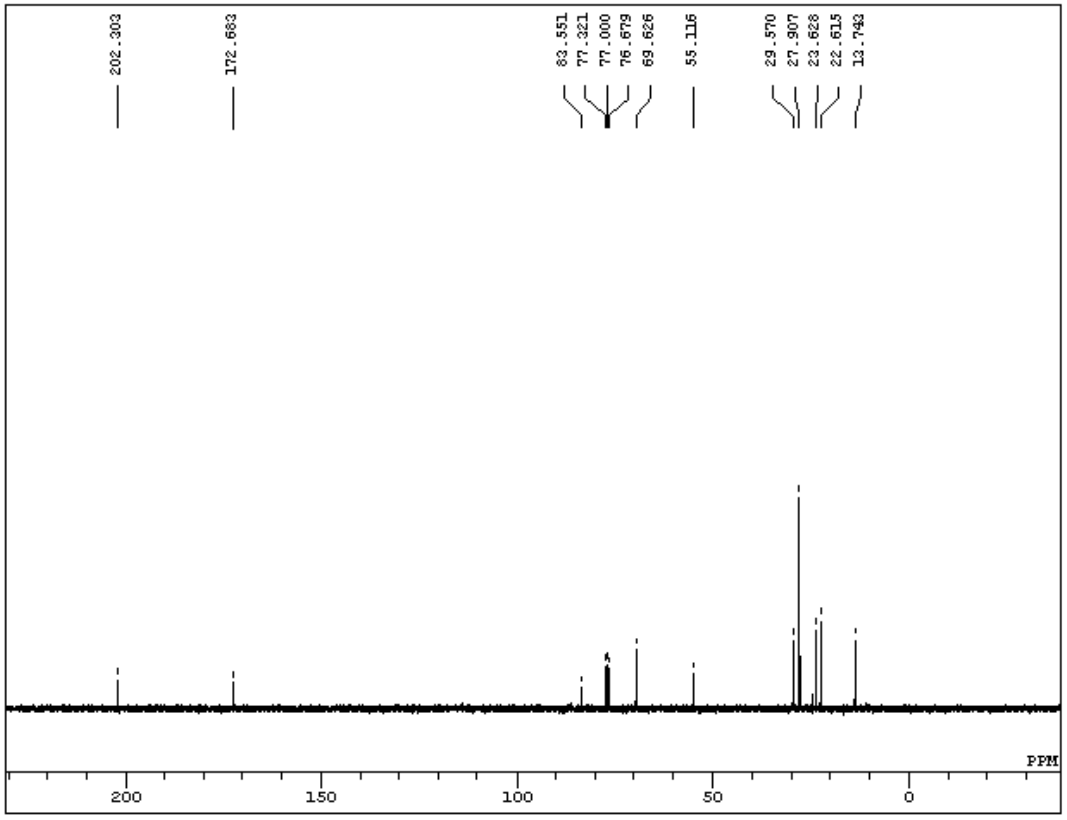


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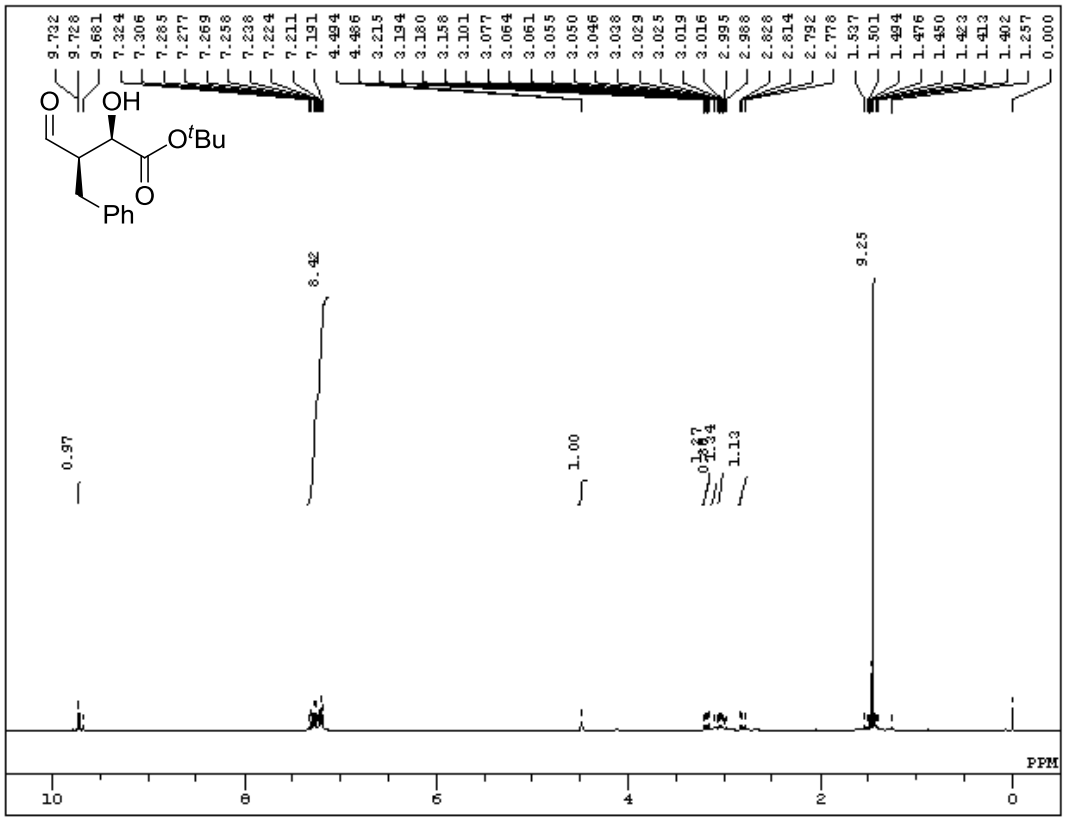


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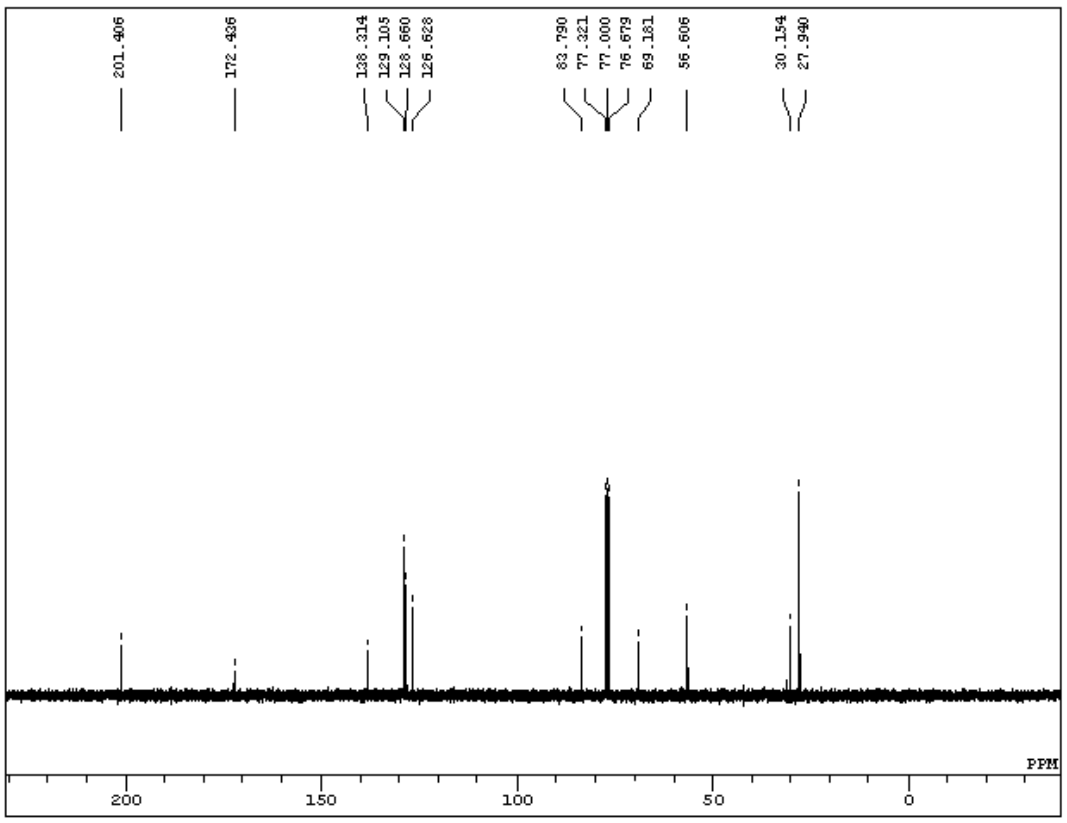


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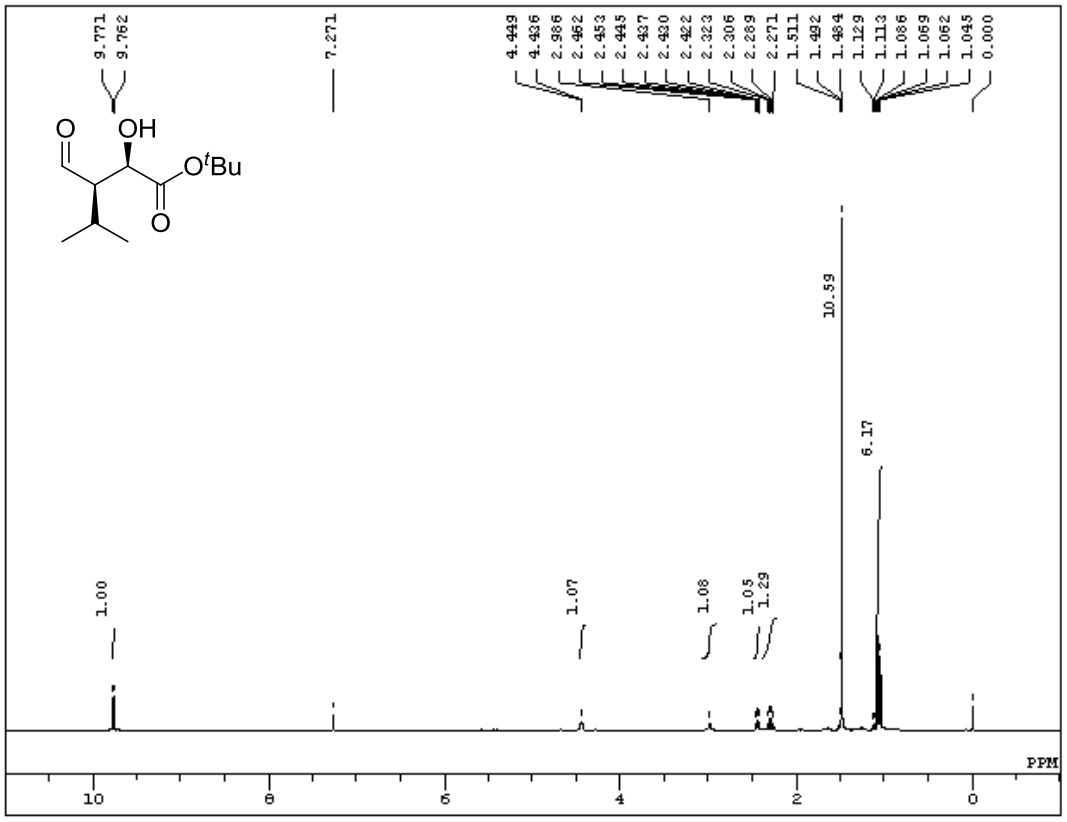


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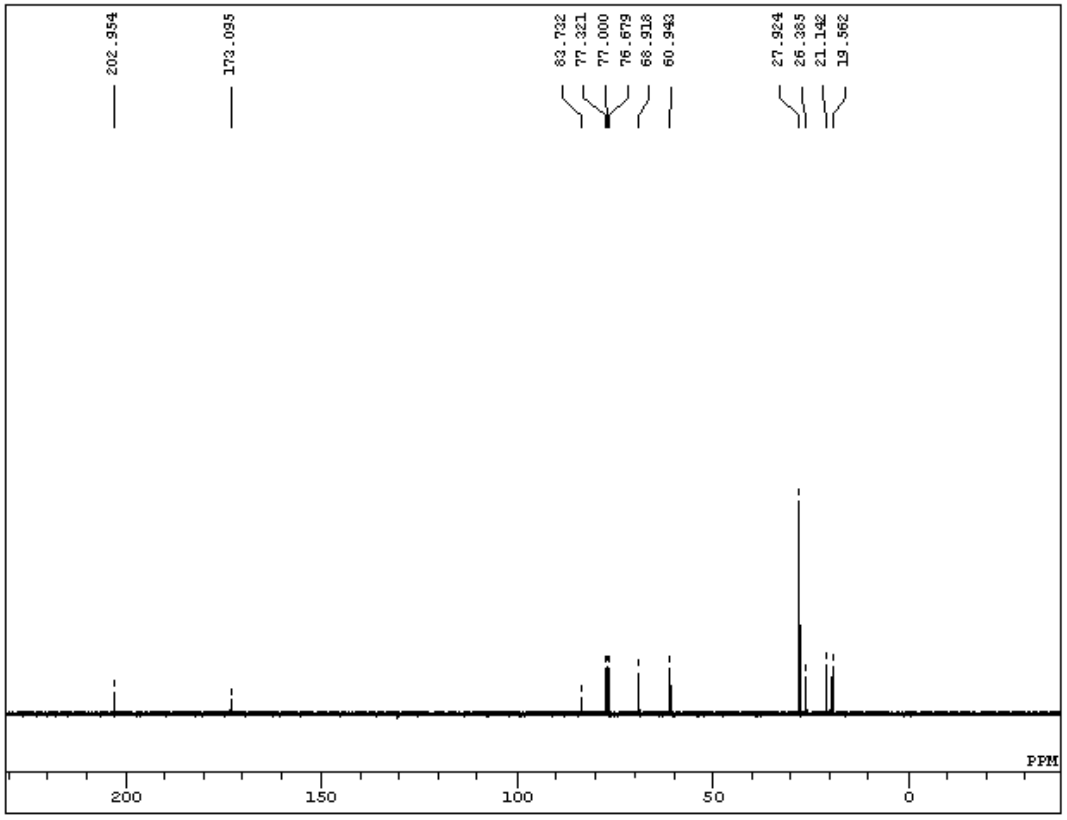


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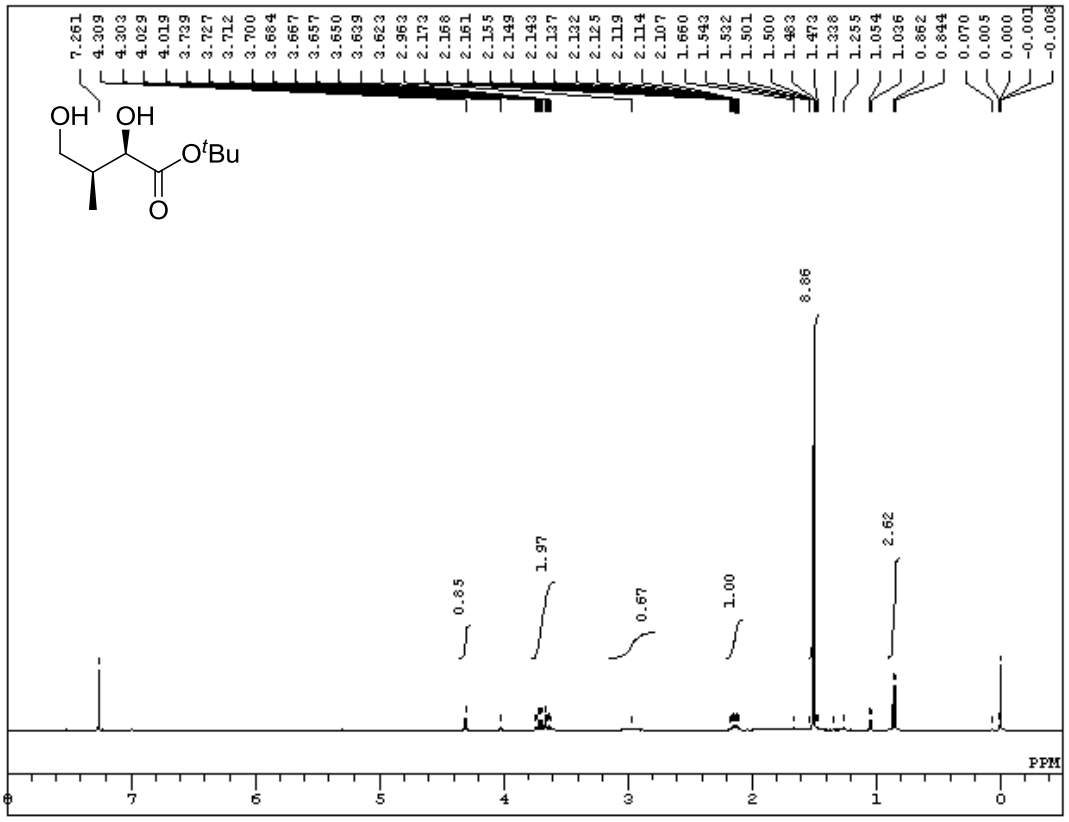


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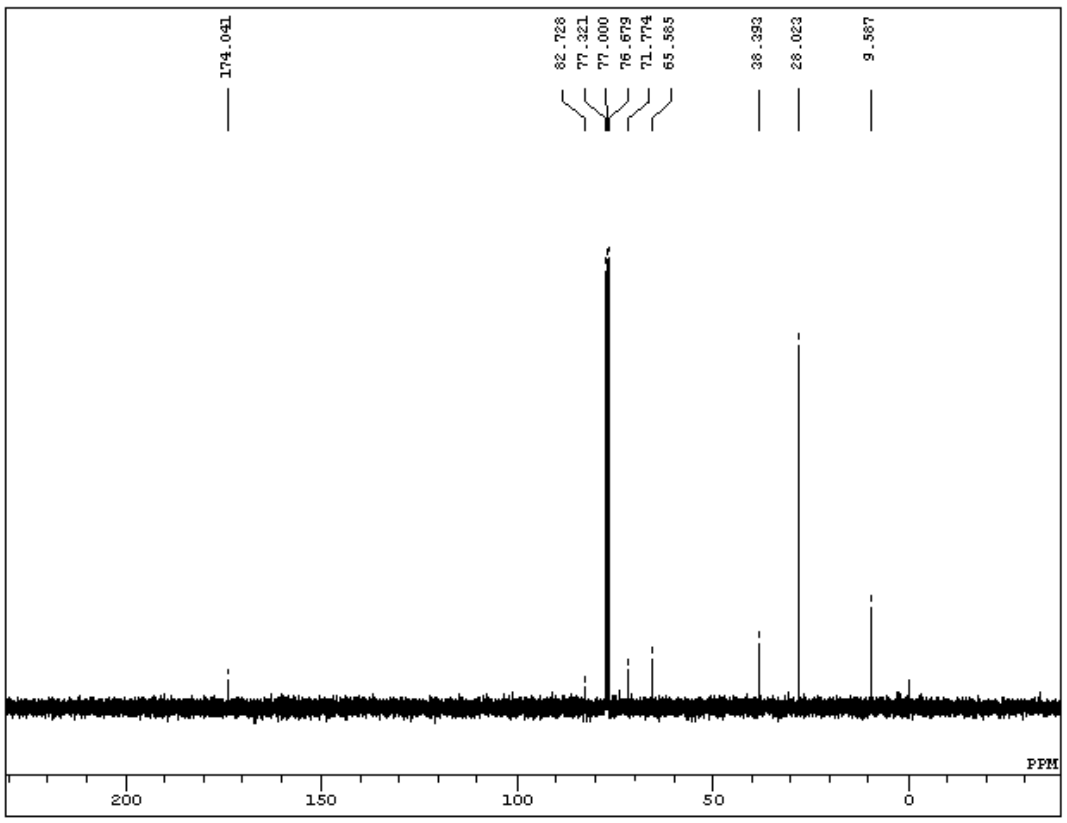


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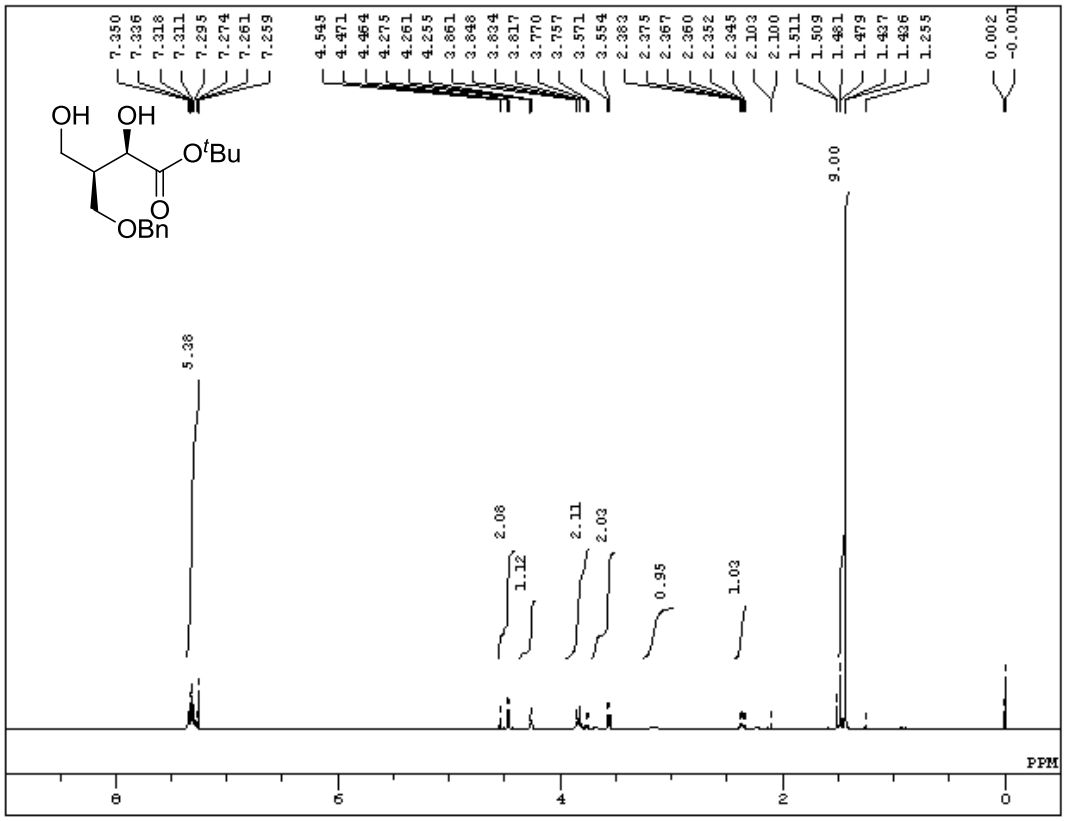


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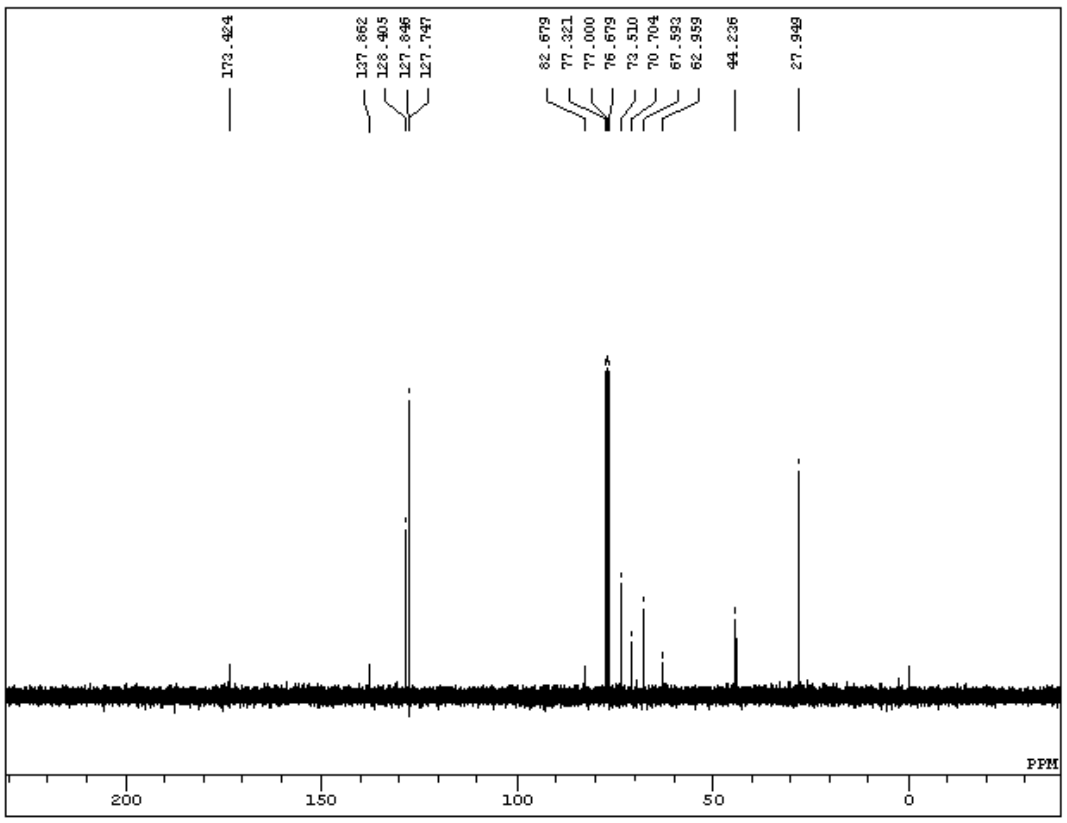


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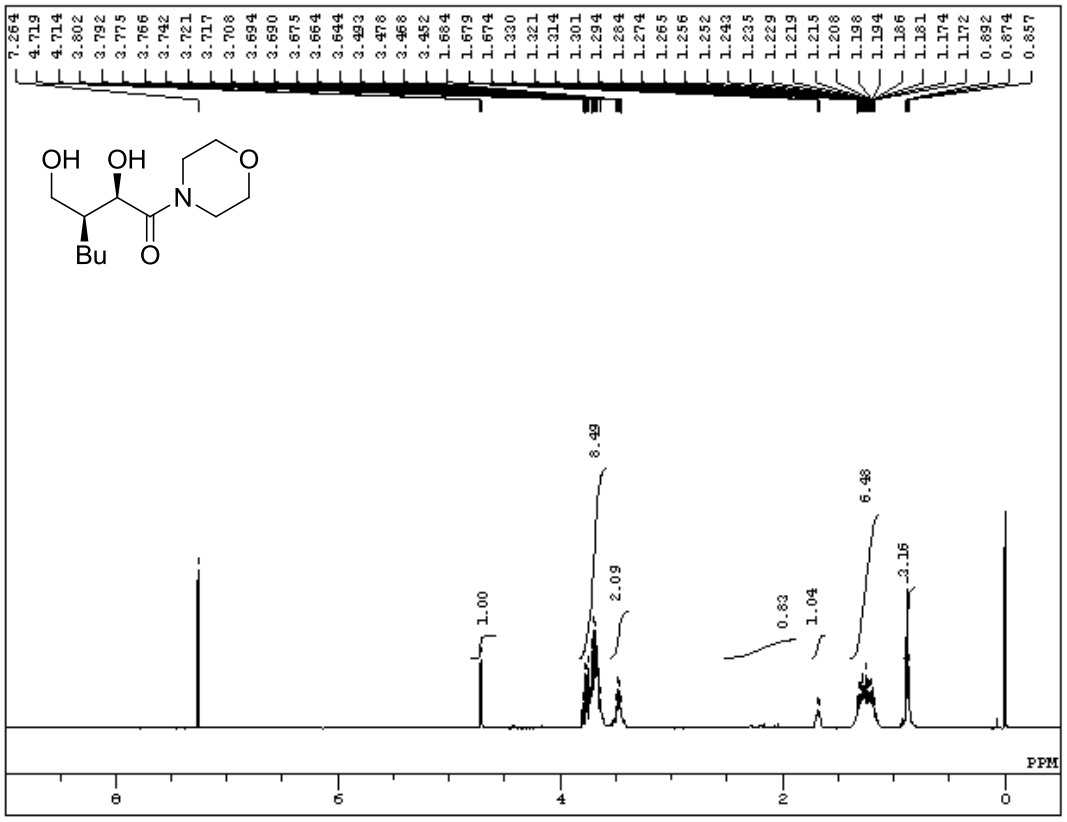


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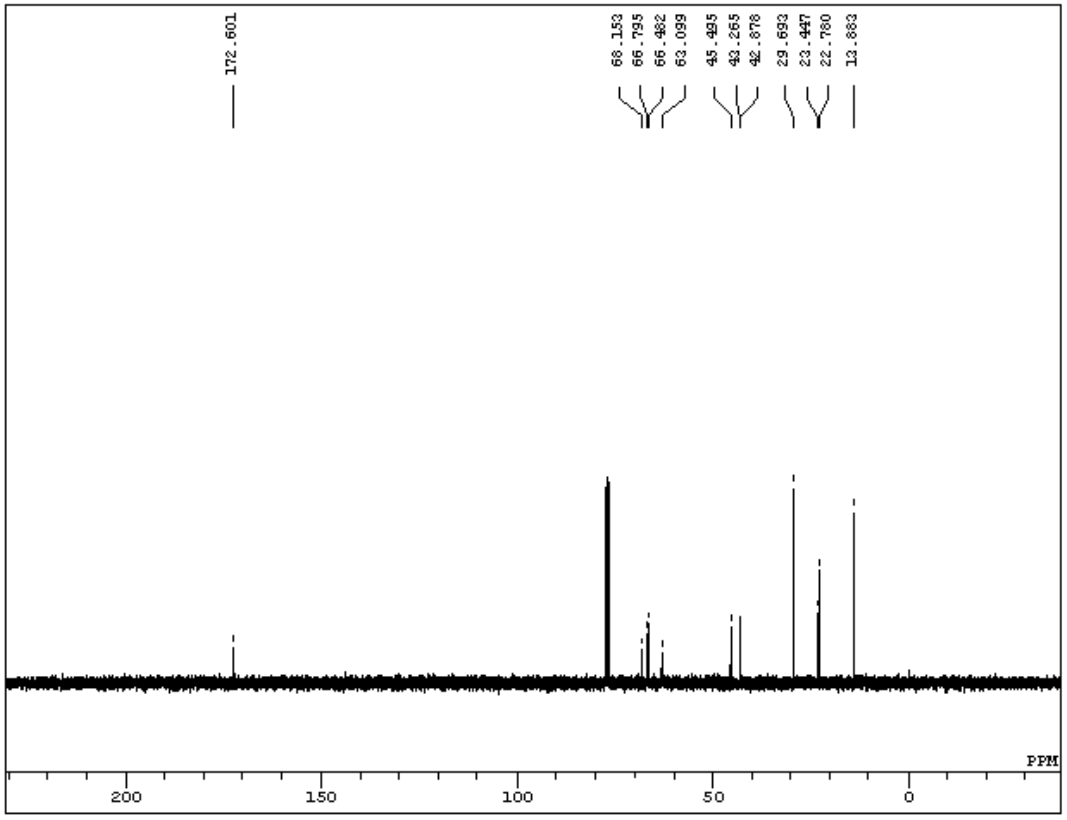


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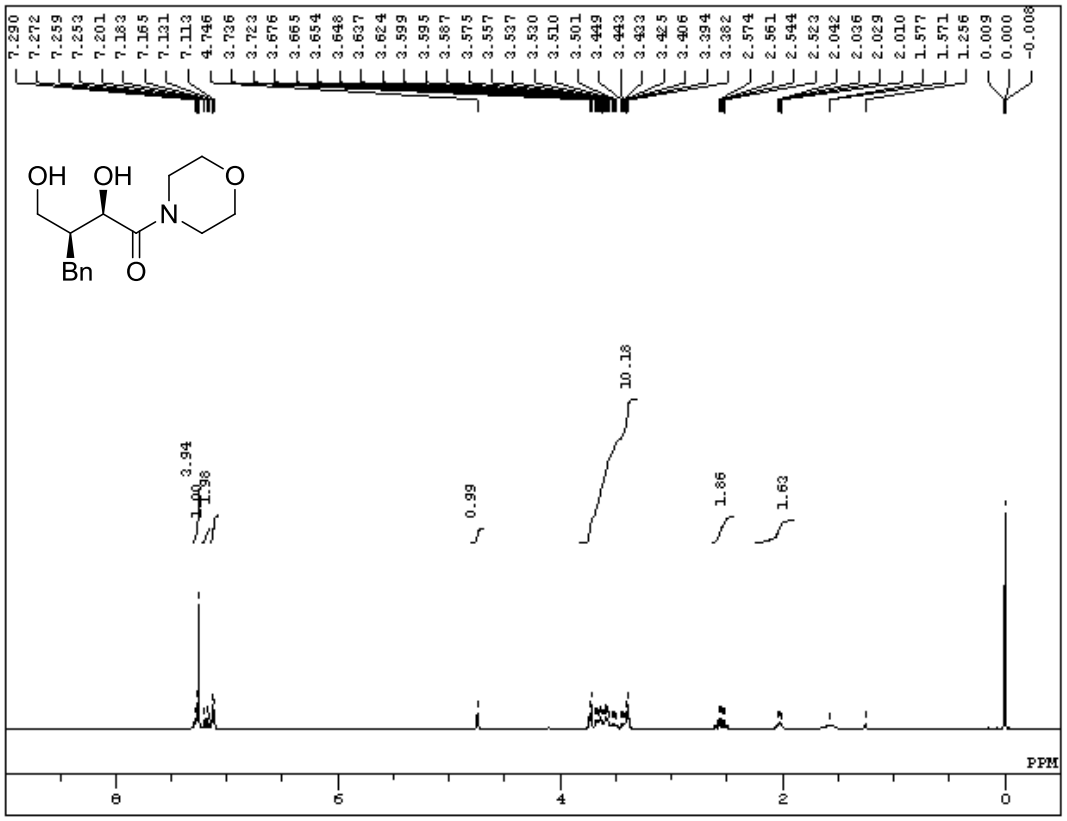


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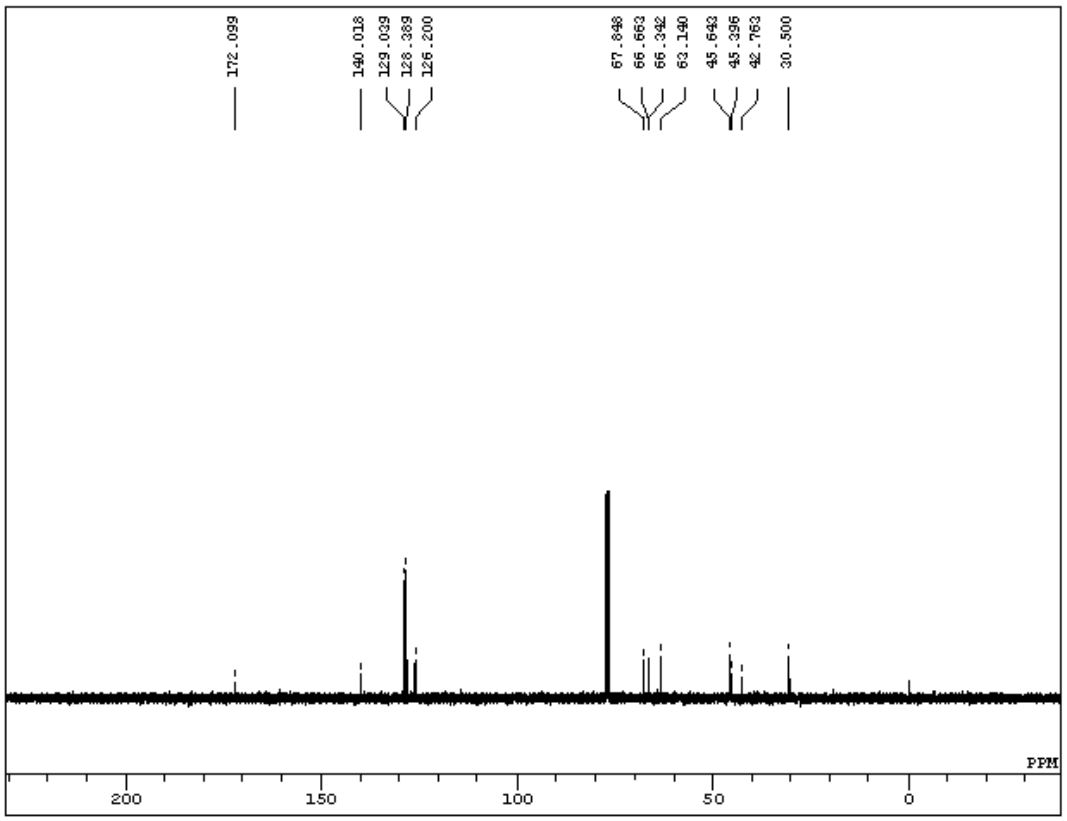


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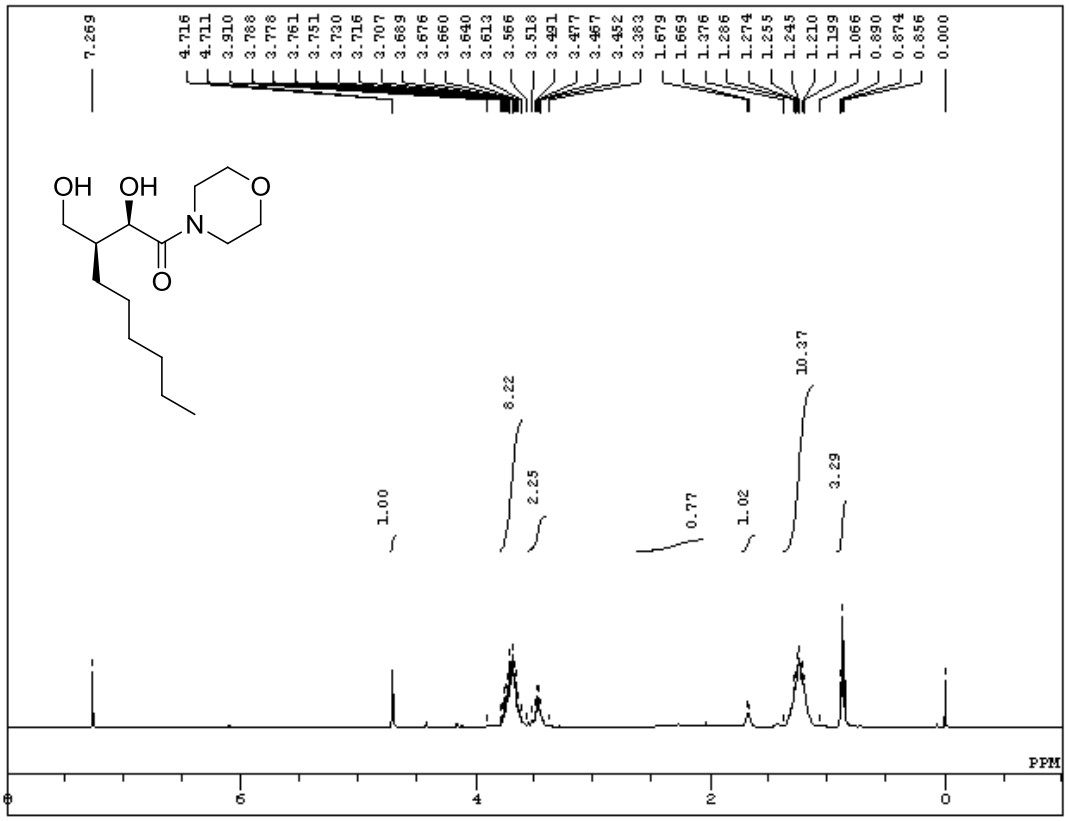

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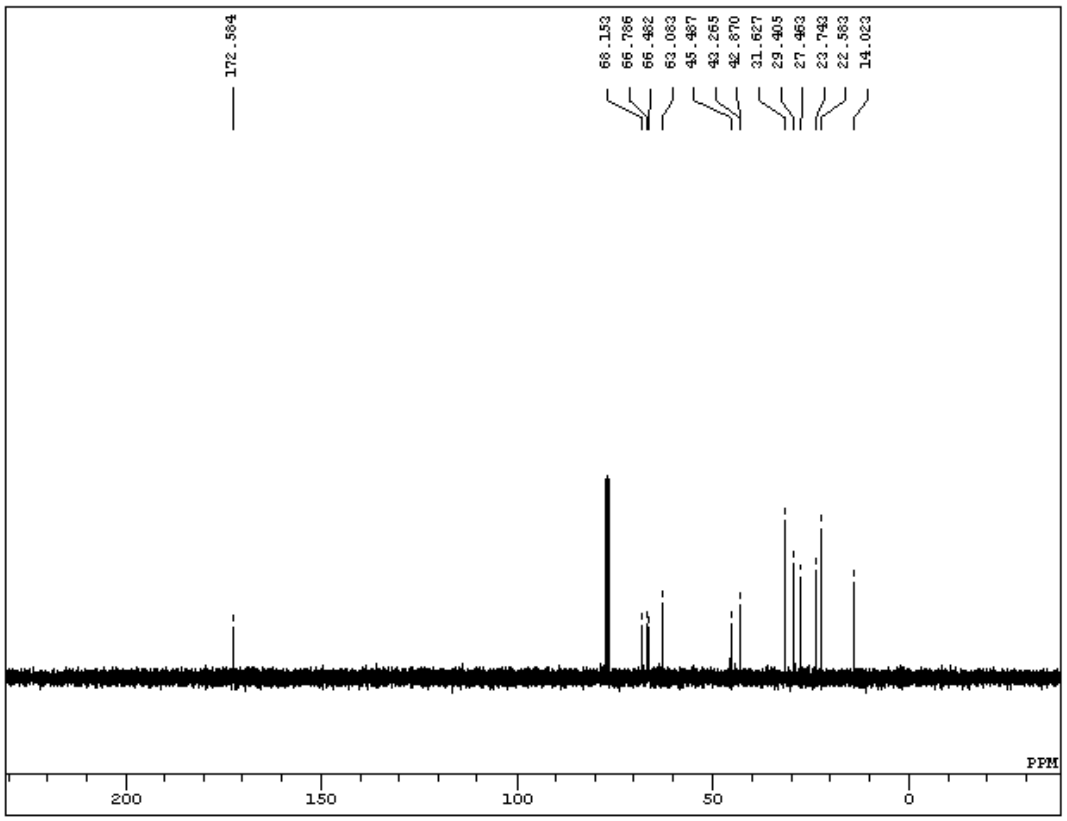
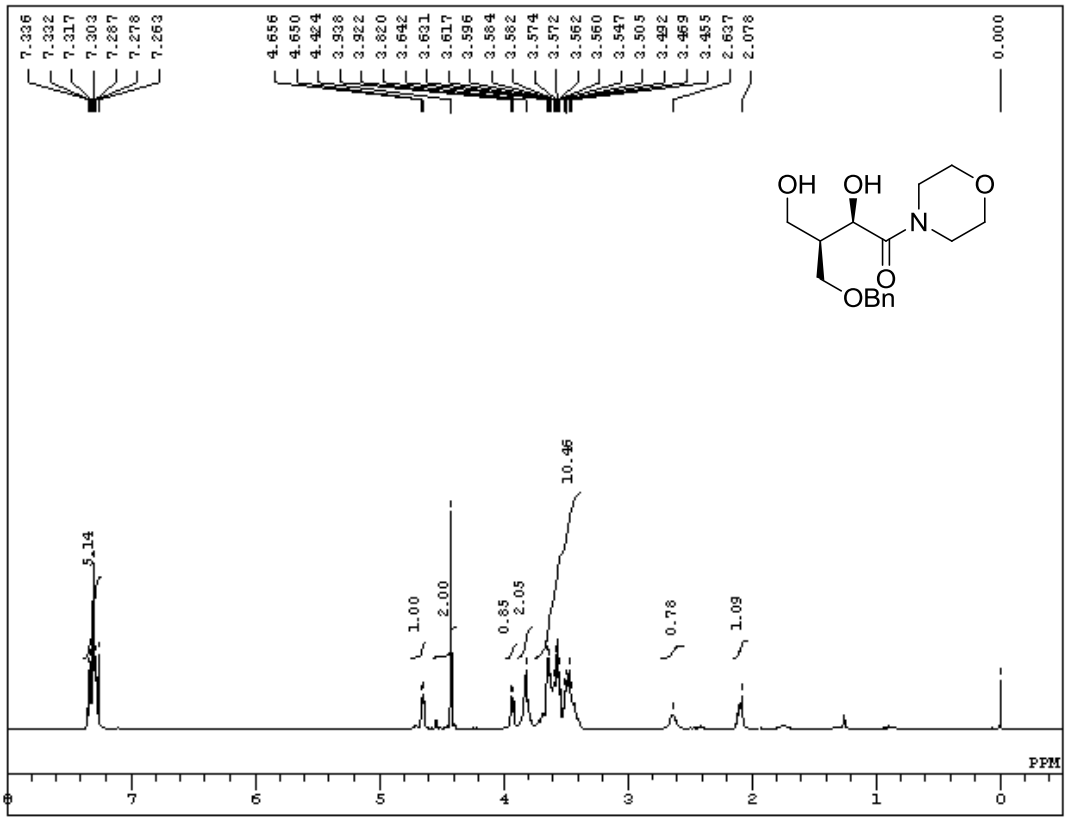
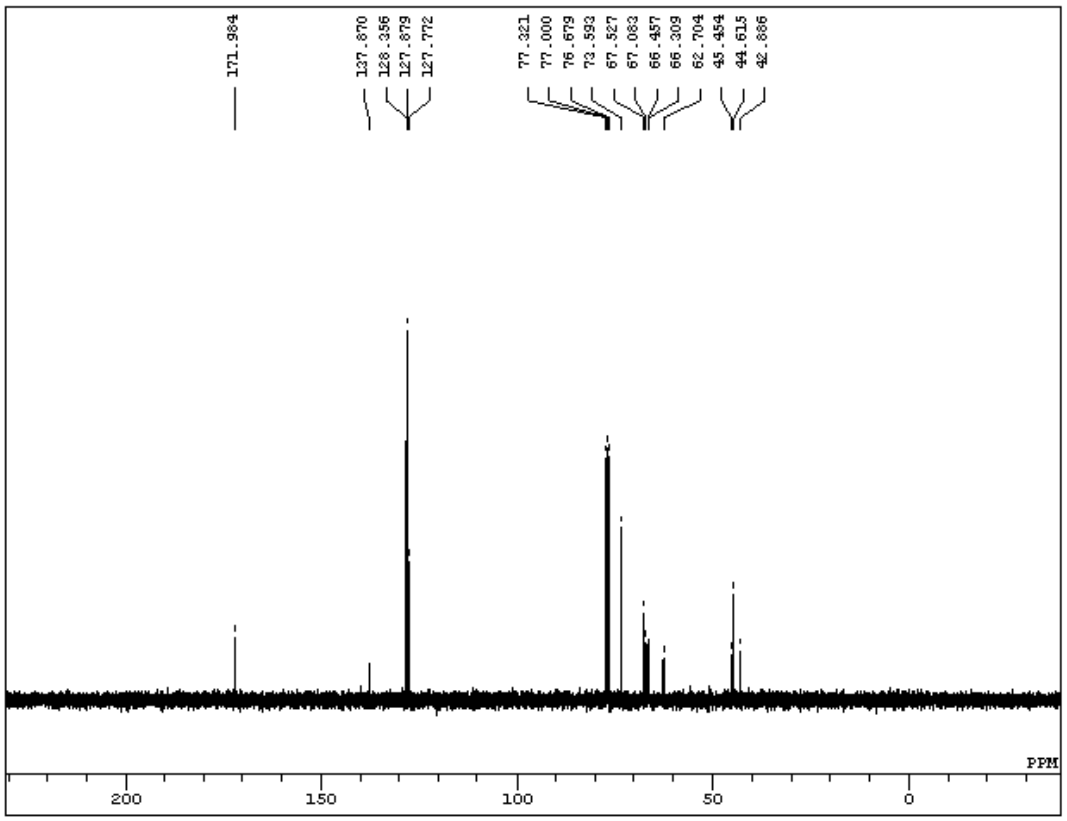
BF 0.12 Hz
RGAIN 13



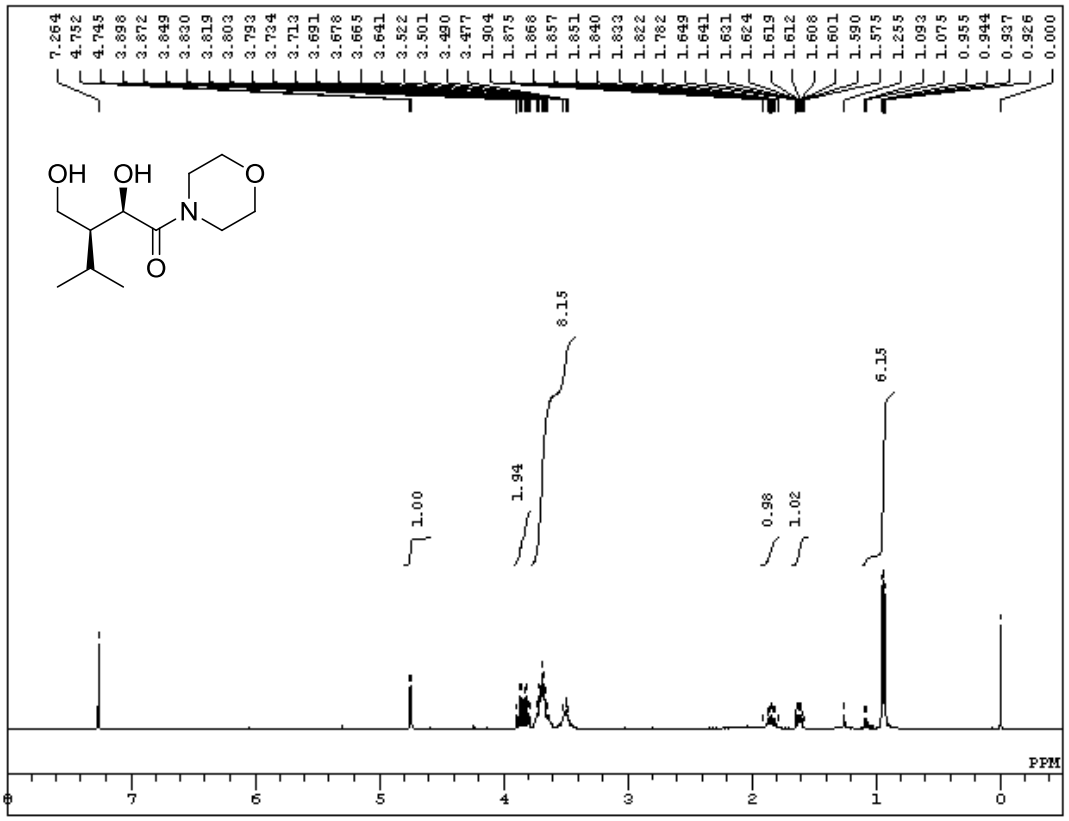
DFILE ocatmal-amide-13
COMNT
DATIM Thu Sep 30 18:56:
OBNUC 13C
EXMOD BCM
OBFRQ 99.45 MHz
OBSET 94.00 KHz
OBFIN 10309.00 Hz
POINT 32768
FREQU 26645.64 Hz
SCANS 76
ACQTM 1.2206 sec
PD 1.7610 sec
PW1 5.70 usec
IRNUC 1H
CTEMP 27.6 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.12 Hz
RGAIN 26



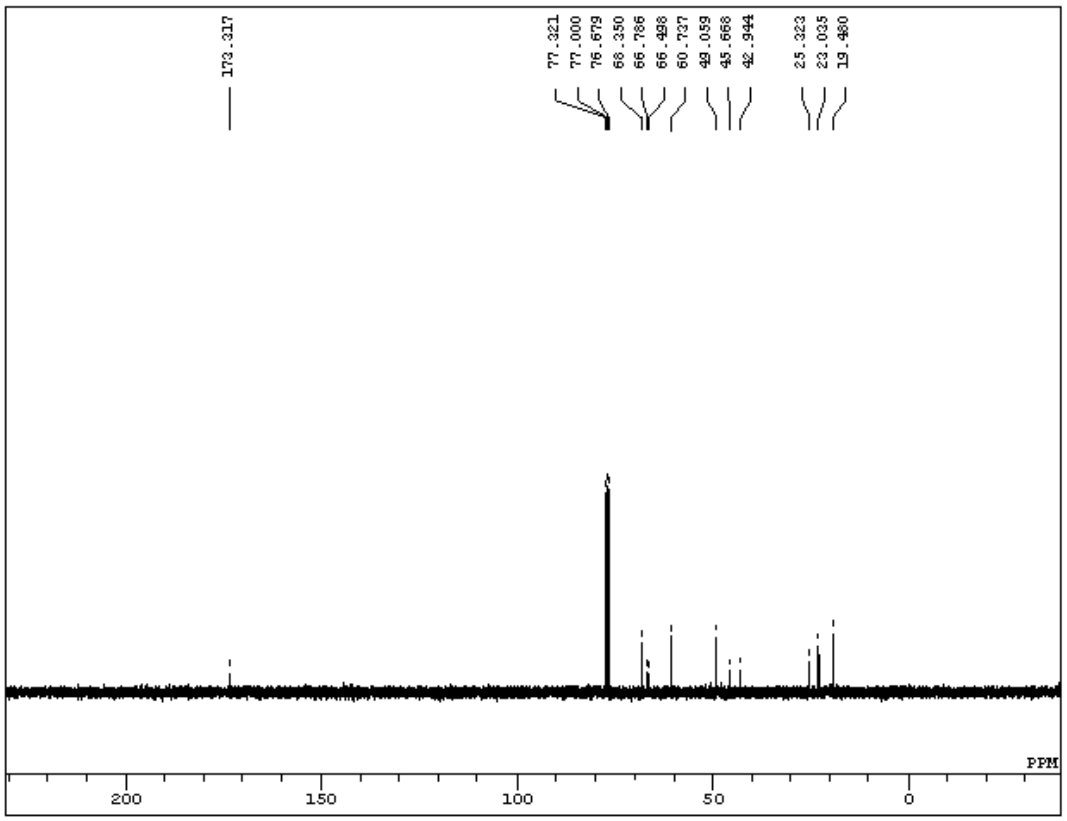

```
DFILE  b-OBn-amide.als
COMNT
DATIM  Tue Nov 30 12:46:
OBNUC  1H
EXMOD  NON
OBFRQ        395.75 MHz
OBSET        124.00 KHz
OBFIN      10277.00 Hz
POINT        32768
FREQU       7920.79 Hz
SCANS            8
ACQTM        4.1370 sec
PD           2.8610 sec
PW1             6.70 usec
IRNUC  1H
CTEMP           27.5 c
SLVNT  CDCL3
EXREF           0.00 ppm
BF              0.12 Hz
RGAIN             14
```



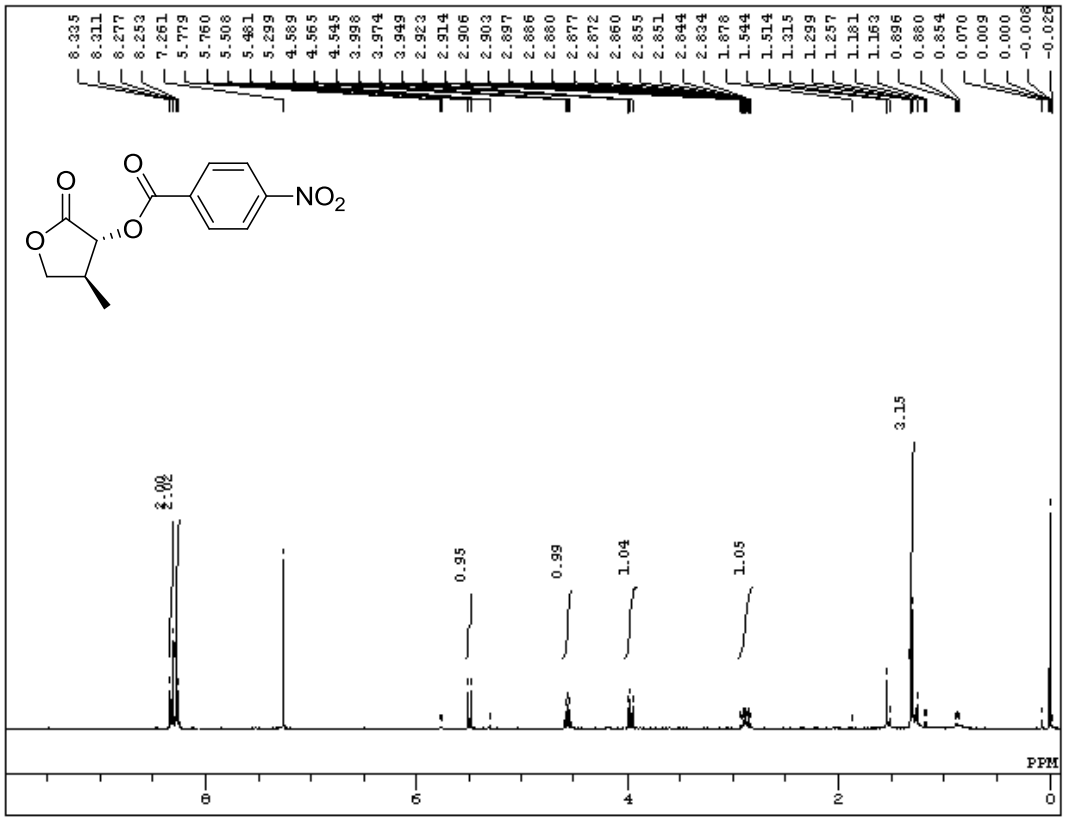

```
DFILE  b-OBn-amide.13C-a
COMNT
DATIM  Tue Nov 30 12:45:(
OBNUC  13C
EXMOD  BCM
OBFRQ         99.45 MHz
OBSET         94.00 KHz
OBFIN      10309.00 Hz
POINT        32768
FREQU      26645.64 Hz
SCANS          142
ACQTM        1.2206 sec
PD           1.7610 sec
PW1             5.70 usec
IRNUC  1H
CTEMP           27.9 c
SLVNT  CDCL3
EXREF          77.00 ppm
BF              0.12 Hz
RGAIN             26
```



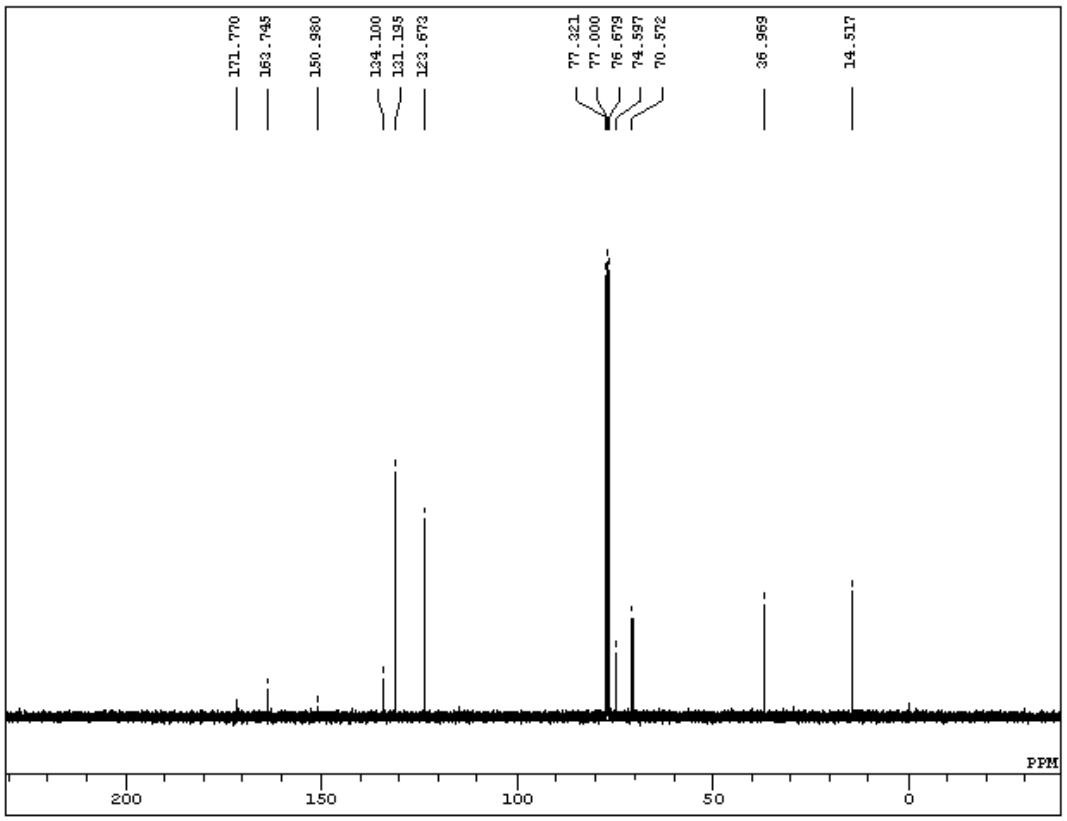
DFILE isoval-amide-.als
COMNT
DATIM Fri Oct 01 12:17:1
OBNUC 1H
EXMOD NON
OBFRQ 395.75 MHz
OBSET 124.00 KHz
OBFIN 10277.00 Hz
POINT 32768
FREQU 7920.79 Hz
SCANS 8
ACQTM 4.1370 sec
PD 2.8610 sec
PW1 6.70 usec
IRNUC 1H
CTEMP 27.7 c
SLVNT CDCL3
EXREF 0.00 ppm
BF 0.12 Hz
RGAIN 17



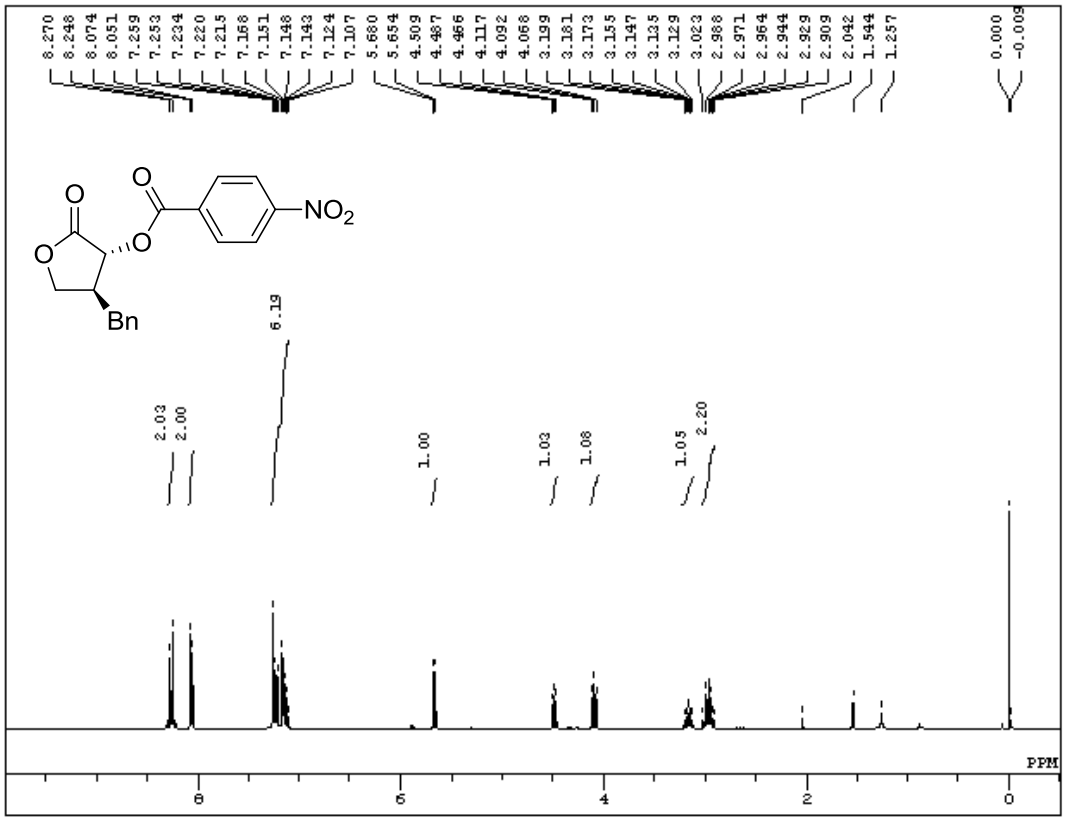
DFILE isoval-amide-13C.
COMNT
DATIM Fri Oct 01 12:35:2
OBNUC 13C
EXMOD BCM
OBFRQ 99.45 MHz
OBSET 94.00 KHz
OBFIN 10309.00 Hz
POINT 32768
FREQU 26845.64 Hz
SCANS 175
ACQTM 1.2206 sec
PD 1.7810 sec
PW1 5.70 usec
IRNUC 1H
CTEMP 28.2 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.12 Hz
RGAIN 26



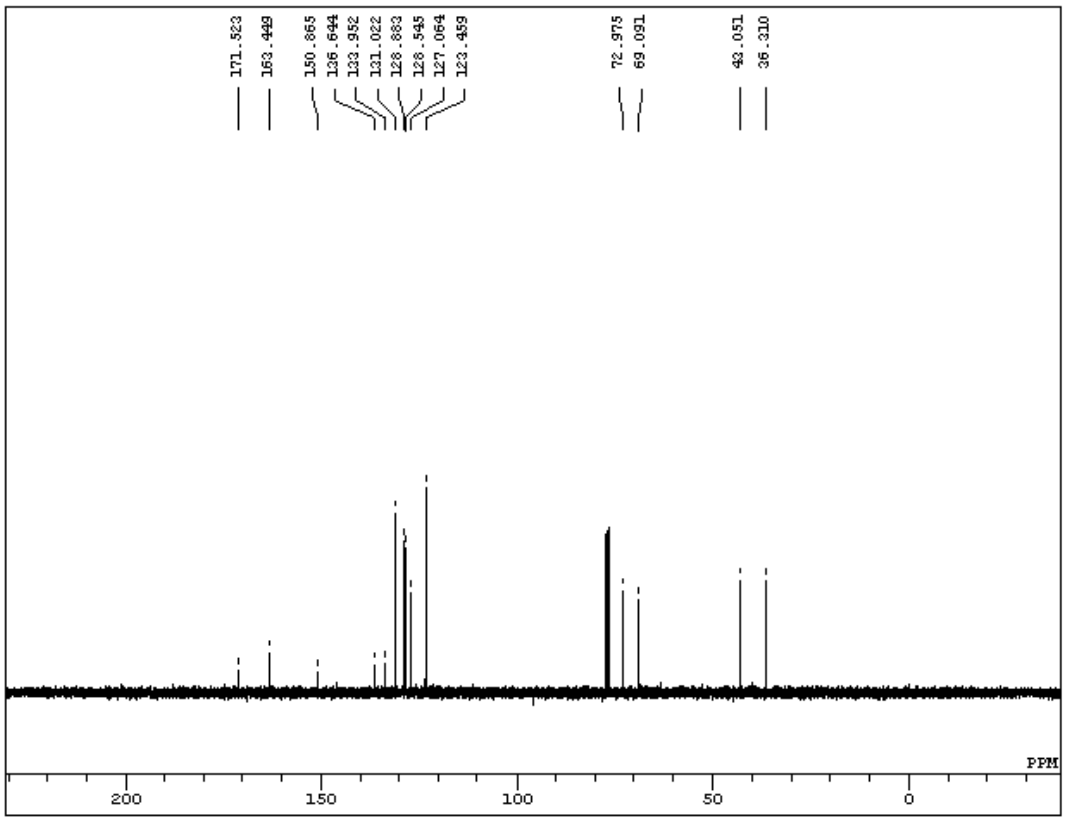
DFILE propanal-lacton-1H
COMNT
DATIM Tue Oct 12 19:27:1
OBNUC 1H
EXMOD NON
OBFRQ 395.75 MHz
OBSET 124.00 KHz
OBFIN 10277.00 Hz
POINT 32768
FREQU 7920.79 Hz
SCANS 8
ACQTM 4.1370 sec
PD 2.8610 sec
PW1 5.50 usec
IRNUC 1H
CTEMP 27.9 c
SLVNT CDCL3
EXREF 0.00 ppm
BF 0.12 Hz
RGAIN 22



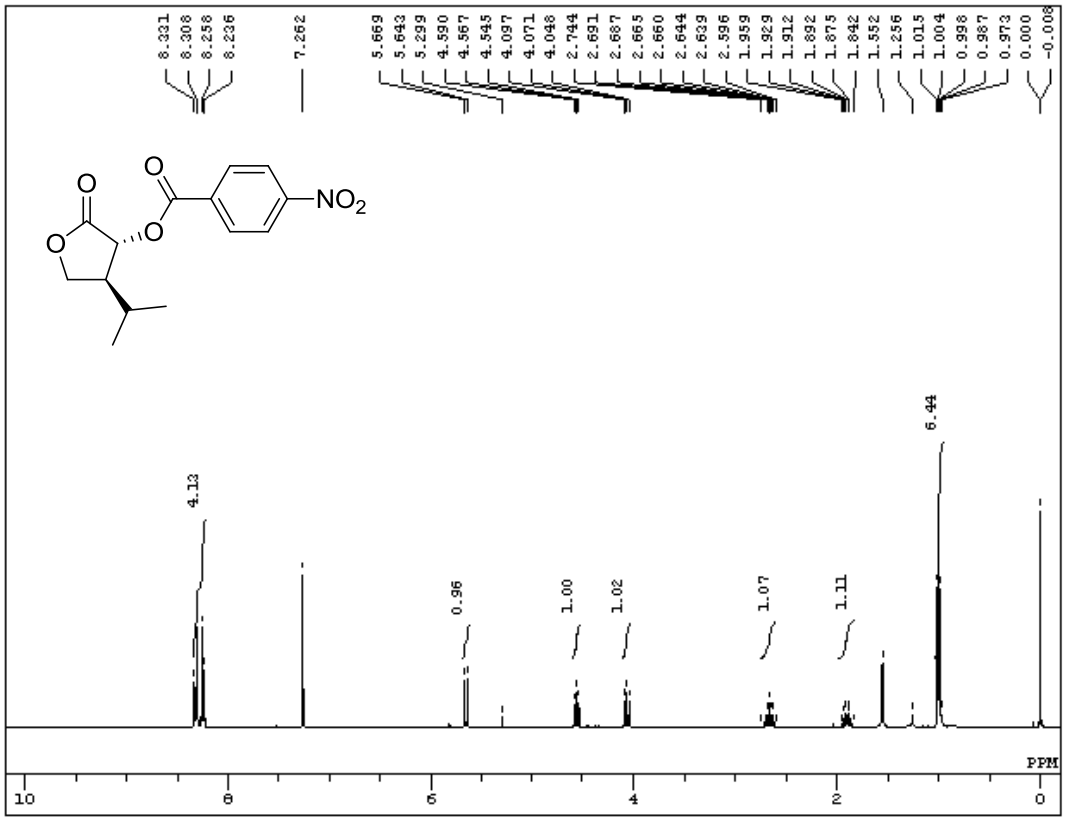
DFILE propanal-lacton-13C
COMNT
DATIM Sat May 14 08:56:4
OBNUC 13C
EXMOD BCM
OBFRQ 99.45 MHz
OBSET 94.00 KHz
OBFIN 10309.00 Hz
POINT 32768
FREQU 26845.64 Hz
SCANS 1069
ACQTM 1.2206 sec
PD 1.7610 sec
PW1 5.70 usec
IRNUC 1H
CTEMP 27.9 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.12 Hz
RGAIN 26



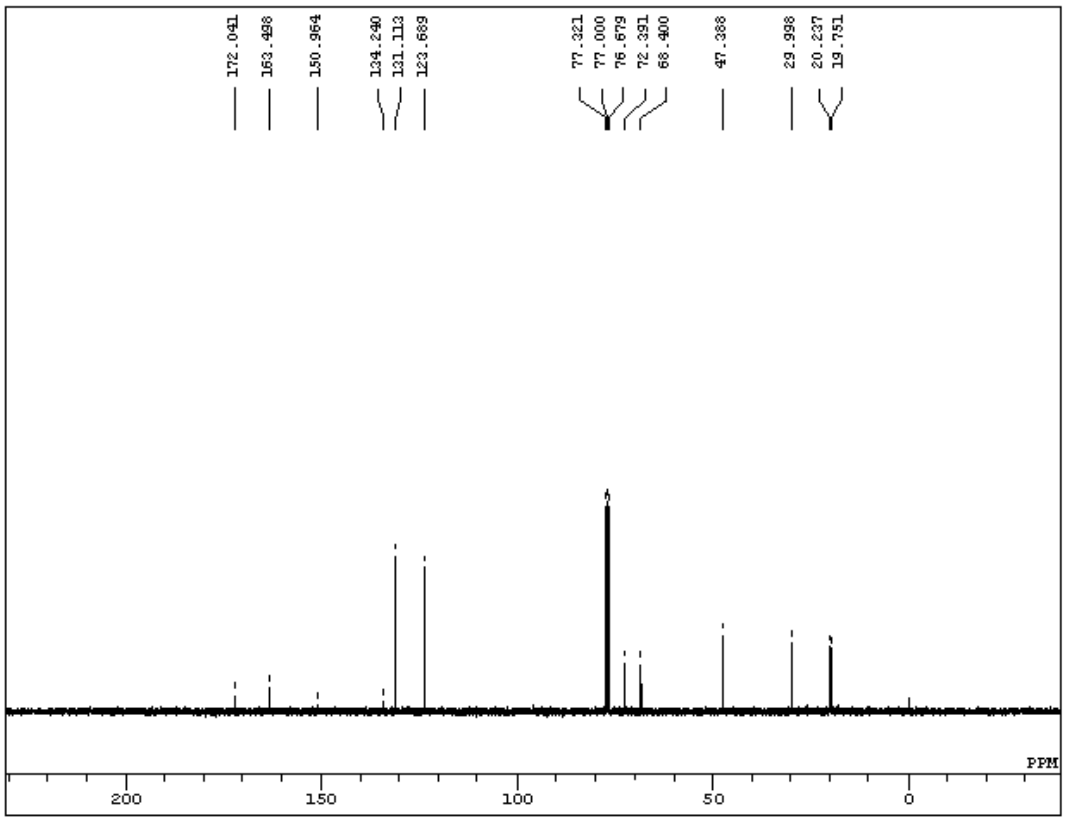

```
DFILE  hydrocynnam-lacto
COMNT
DATIM  Thu Sep 16 17:59:(
OBNUC  1H
EXMOD  NON
OBFRQ        395.75 MHz
OBSET        124.00 KHz
OBFIN      10277.00 Hz
POINT        32768
FREQU       7920.79 Hz
SCANS            8
ACQTM        4.1370 sec
PD           2.8610 sec
PW1             6.70 usec
IRNUC  1H
CTEMP           28.5 c
SLVNT  CDCL3
EXREF           0.00 ppm
BF              0.12 Hz
RGAIN             18
```



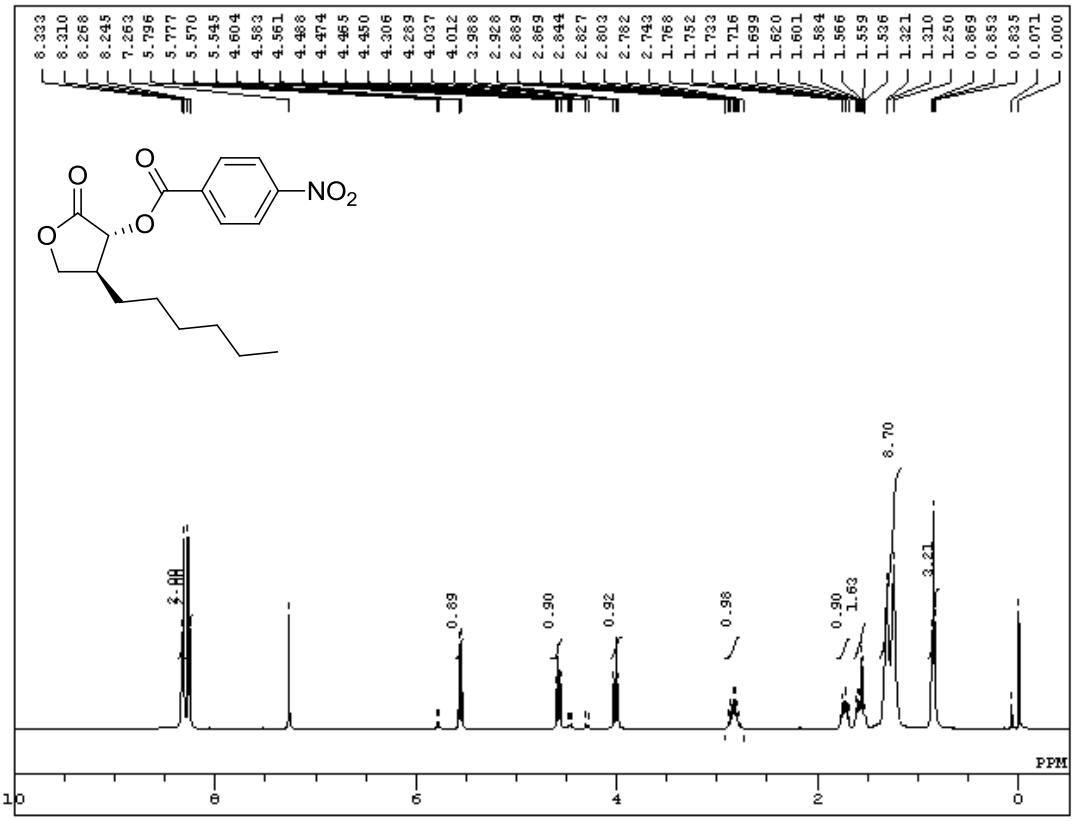

```
DFILE  hydrocynnam-lacto
COMNT
DATIM  Thu Sep 16 22:39:1
OBNUC  13C
EXMOD  BCM
OBFRQ         99.45 MHz
OBSET         94.00 KHz
OBFIN      10309.00 Hz
POINT        32768
FREQU      26845.64 Hz
SCANS          167
ACQTM        1.2206 sec
PD           1.7810 sec
PW1             5.70 usec
IRNUC  1H
CTEMP           28.9 c
SLVNT  CDCL3
EXREF           77.00 ppm
BF              0.12 Hz
RGAIN             26
```



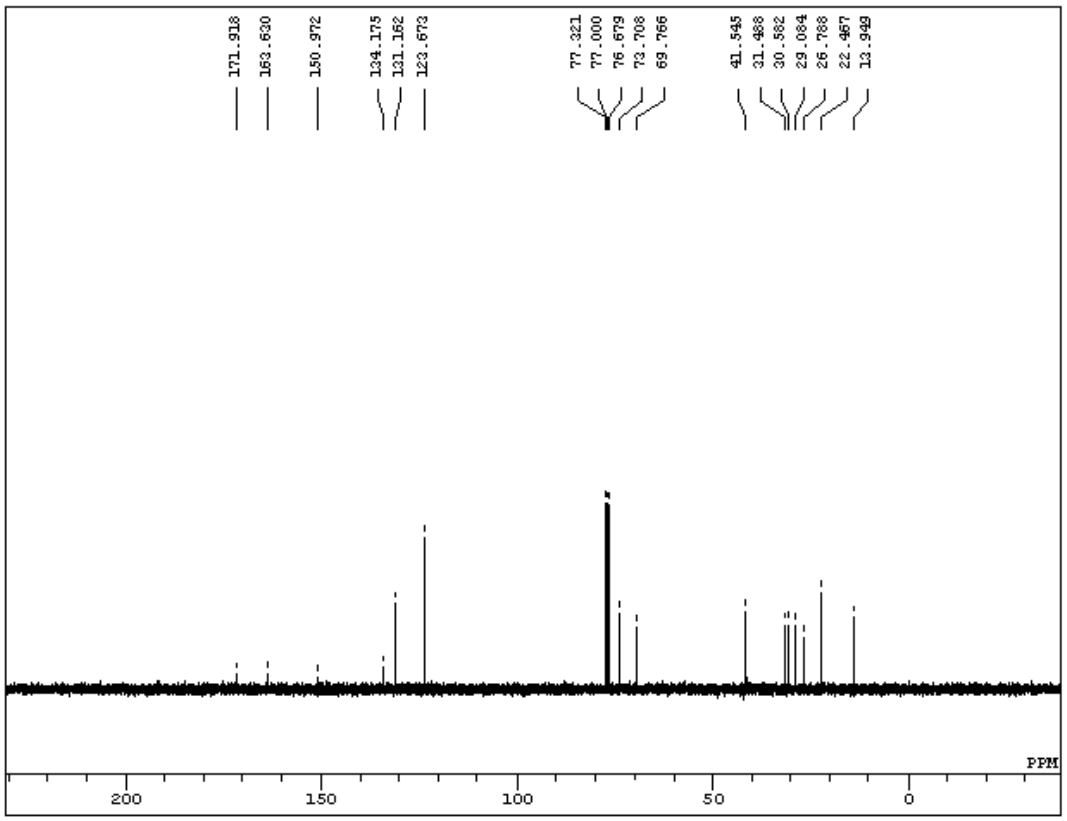
DFILE isoval-lacton.als
COMNT
DATIM Tue Sep 07 16:54:
OBNUC 1H
EXMOD NON
OBFRQ 395.75 MHz
OBSET 124.00 KHz
OBFIN 10277.00 Hz
POINT 32768
FREQU 7920.79 Hz
SCANS 8
ACQTM 4.1370 sec
PD 2.8610 sec
PW1 6.70 usec
IRNUC 1H
CTEMP 27.8 c
SLVNT CDCL3
EXREF 0.00 ppm
BF 0.12 Hz
RGAIN 19



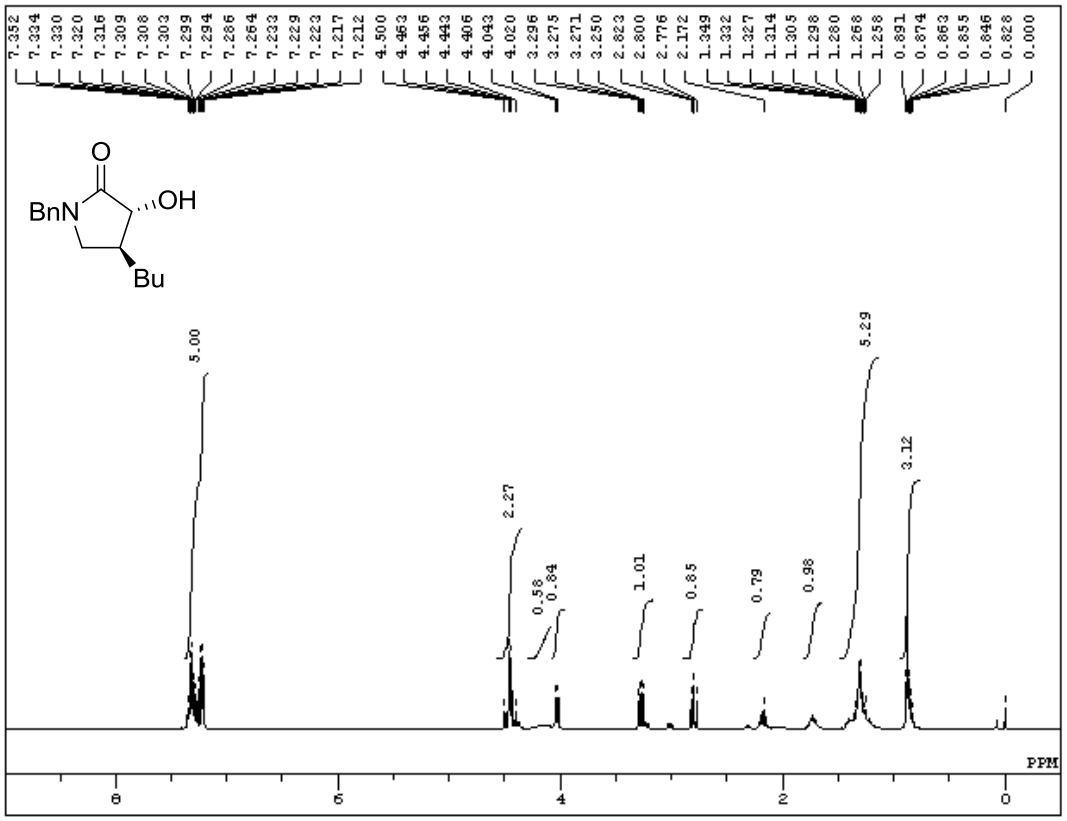
DFILE isoval-lacton13C.
COMNT
DATIM Tue Sep 07 13:32:
OBNUC 13C
EXMOD BCM
OBFRQ 99.45 MHz
OBSET 94.00 KHz
OBFIN 10309.00 Hz
POINT 32768
FREQU 26645.64 Hz
SCANS 586
ACQTM 1.2206 sec
PD 1.7610 sec
PW1 5.70 usec
IRNUC 1H
CTEMP 28.1 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.12 Hz
RGAIN 26



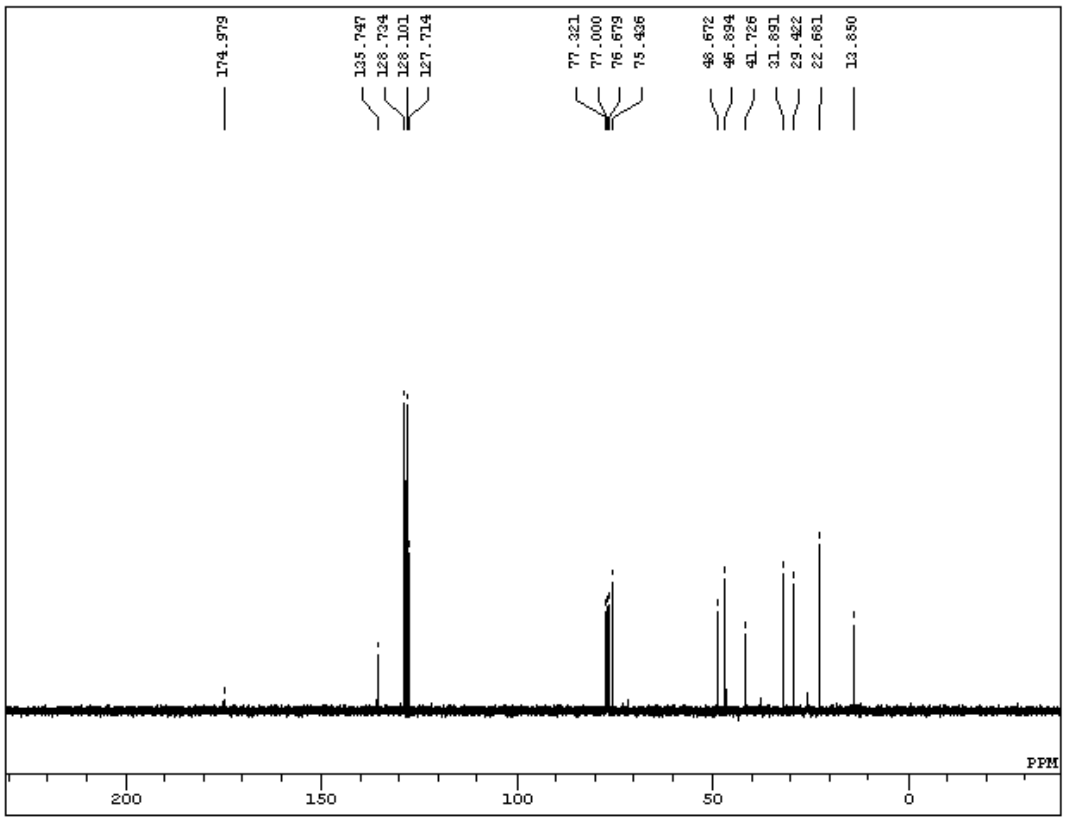

```
DFILE  ocatmal-lactonlH.
COMNT
DATIM  Wed Oct 06 10:05:1
OBNUC  1H
EXMOD  NON
OBFRQ        395.75 MHz
OBSET        124.00 KHz
OBFIN      10277.00 Hz
POINT        32768
FREQU       7920.79 Hz
SCANS            8
ACQTM        4.1370 sec
PD           2.8610 sec
PW1             6.70 usec
IRNUC  1H
CTEMP           27.3 c
SLVNT  CDCL3
EXREF           0.00 ppm
BF              1.20 Hz
RGAIN             16
```



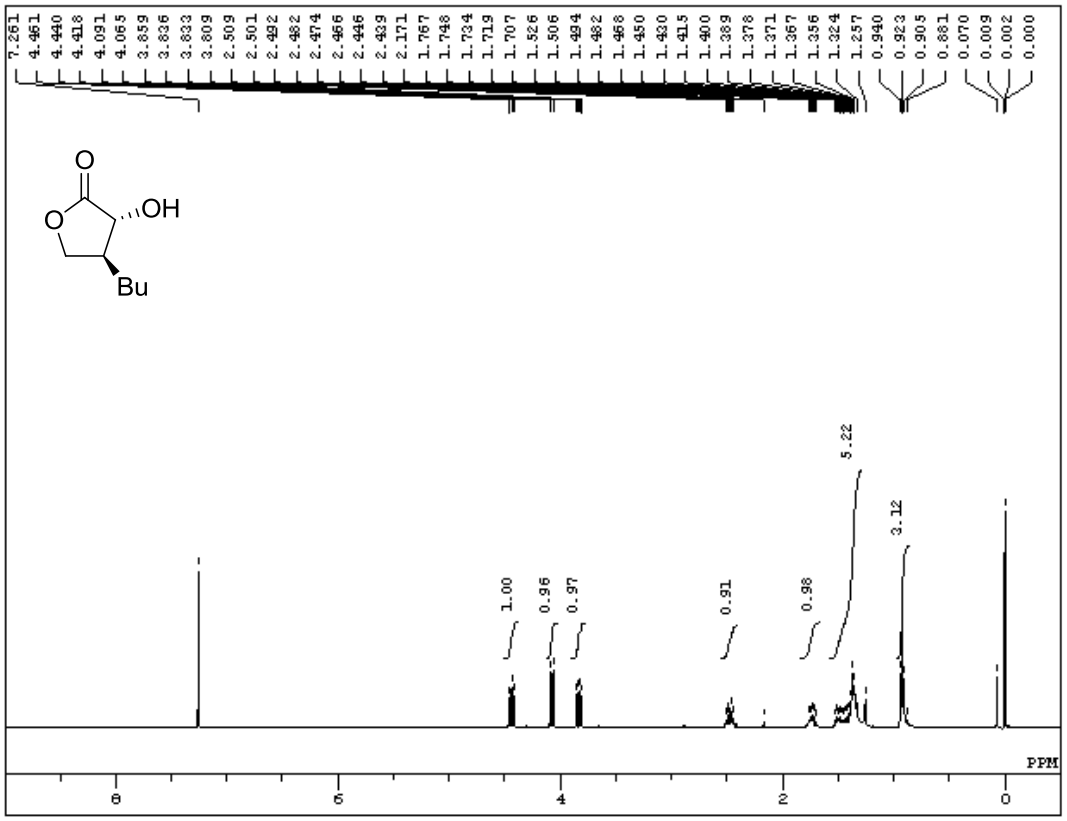

```
DFILE  ocatmal-lacton-1
COMNT
DATIM  Wed Oct 06 13:06:2
OBNUC  13C
EXMOD  BCM
OBFRQ         99.45 MHz
OBSET         94.00 KHz
OBFIN      10309.00 Hz
POINT        32768
FREQU      26645.64 Hz
SCANS          214
ACQTM        1.2206 sec
PD           1.7810 sec
PW1             5.70 usec
IRNUC  1H
CTEMP           28.1 c
SLVNT  CDCL3
EXREF           77.00 ppm
BF               0.12 Hz
RGAIN              26
```



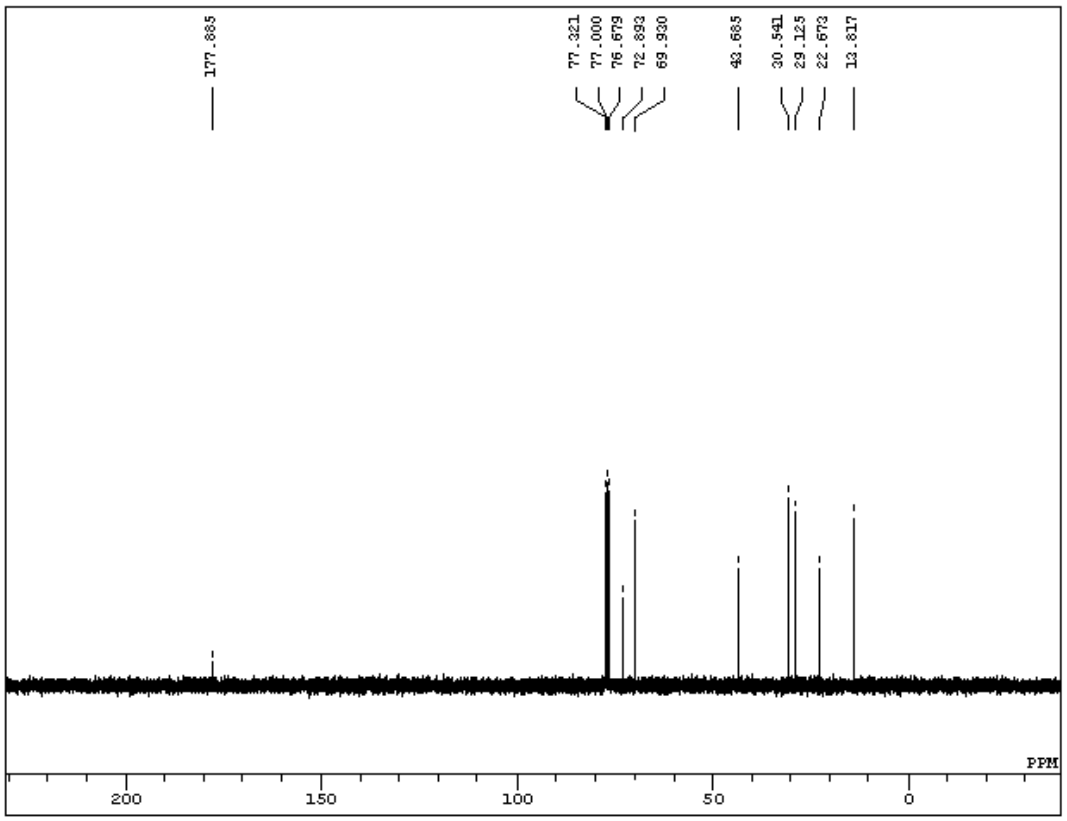
DFILE lactam.als
COMNT
DATIM Wed May 25 10:57:
OBNUC 1H
EXMOD NON
OBFRQ 395.75 MHz
OBSET 124.00 KHz
OBFIN 10277.00 Hz
POINT 32768
FREQU 7920.79 Hz
SCANS 8
ACQTM 4.1370 sec
PD 2.8610 sec
PW1 6.70 usec
IRNUC 1H
CTEMP 28.4 c
SLVNT CDCL3
EXREF 0.00 ppm
BF 0.12 Hz
RGAIN 11



DFILE lactam-13C.als
COMNT
DATIM Wed May 25 10:55:
OBNUC 13C
EXMOD BCM
OBFRQ 99.45 MHz
OBSET 94.00 KHz
OBFIN 10309.00 Hz
POINT 32768
FREQU 26845.64 Hz
SCANS 100
ACQTM 1.2206 sec
PD 1.7810 sec
PW1 5.70 usec
IRNUC 1H
CTEMP 28.7 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.12 Hz
RGAIN 26



DFILE hexanal-lacton.als
COMNT
DATIM Tue Feb 23 14:24:
OBNUC 1H
EXMOD NON
OBFRQ 395.75 MHz
OBSET 124.00 KHz
OBFIN 10277.00 Hz
POINT 32768
FREQU 7920.79 Hz
SCANS 8
ACQTM 4.1370 sec
PD 2.8610 sec
PW1 6.70 usec
IRNUC 1H
CTEMP 26.6 c
SLVNT CDCL3
EXREF 0.00 ppm
BF 0.12 Hz
RGAIN 18



DFILE hexanal-lacton-13
COMNT
DATIM Sat May 28 22:35:
OBNUC 13C
EXMOD BCM
OBFRQ 99.45 MHz
OBSET 94.00 KHz
OBFIN 10309.00 Hz
POINT 32768
FREQU 26645.64 Hz
SCANS 99
ACQTM 1.2206 sec
PD 1.7610 sec
PW1 5.70 usec
IRNUC 1H
CTEMP 27.6 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.12 Hz
RGAIN 26