A Bicyclo[3.2.0]hept-3-en-6-one Approach to Prostaglandin Intermediates.

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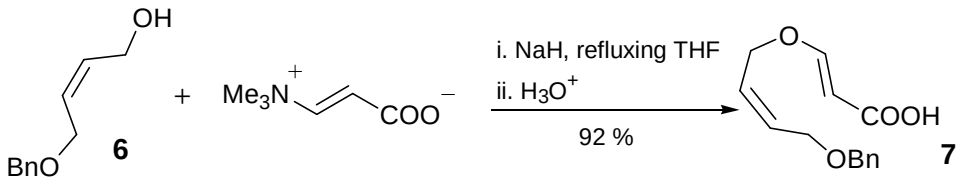
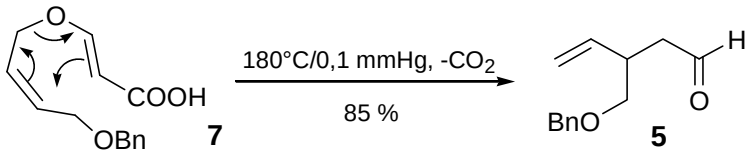
Supplementary material.

General Procedures. All commercial available reagents were used without further purification. Diethyl ether, THF and dichloromethane were dried by being passed through a column of neutral alumina under nitrogen immediately prior to use. All air and water sensitive reactions were performed in flasks flame dried under a positive flow of nitrogen and conducted under a nitrogen atmosphere. NMR (^{1}H, ^{13}C) spectra were recorded on 200 or 300 MHz spectrometers in $CDCl_3$, and DEPT experiments were performed routinely. R_f values indicated refer to Analytical TLC performed using pre-coated silica gel 60 F_{254} plates and developed in the solvent system indicated. Compounds were visualized by use of UV light, I_2 vapor, 1% $Ce(SO_4)_2$-2.5% phosphomolibdic acid in 6% H_2SO_4 and warming. Flash column chromatography[i] was performed in the usual way using Merck 60 (40-60 μm) silica gel. GC analyses were performed on a Hewlett-Packard HP-5 column (crosslinked 5% phenylmethylsiloxane; silica fused, 25 m; id 0.32 mm; film thickness 0.25 μm); carrier Nitrogen, 75 kPa) Program: 100°C (2 min)-275°C (15 °C/min). Retention times (t_R) are quoted in minutes. Melting points are uncorrected.

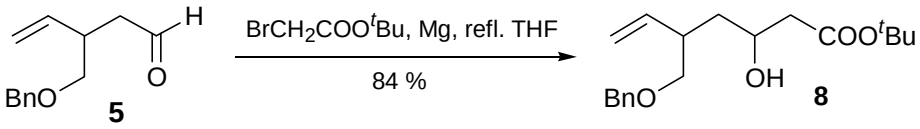


(*E*)-3-[(*Z*)-4-Benzyloxy-2-buteneoxy]acrylic Acid (7). An oven dried, 1 L, three necked, round bottom flask equipped with mechanical stirrer, reflux condenser and dropping funnel was purged with argon and charged with 8.20 g (0.171 mol) of a 50% suspension of NaH in oil and 90 mL of anhydrous THF. To this well stirred suspension was added a solution of compound **6** (23.76 g, 0.143 mol) in 180 mL of dry THF. The mixture was stirred for 30 min at room temperature and then (E)-carboxyvinyl)trimethylammonium betaine (25.05 g, 0.194 mol) was added and the reaction mixture was heated at gentle reflux for 12 hr. The cooled reaction mixture was then added to a mixture of water (600

mL) and a saturated aqueous solution of NaCl (220 mL). The aqueous solution was washed three times with wet ether (100 mL) and acidified with conc HCl to pH 1. This mixture was extracted with diethyl ether (3x200 mL). The combined ether layers were dried (Na_2SO_4). Solvent was removed at reduced pressure to give an oily brown residue which was used without further purification: yield 32.66 g (92 %); **^{1}H-NMR** ($CDCl_3$): δ 11.05 (bs, 1H), 7.68 (d, *J* = 12.6 Hz, 1H), 7.40 (m, 5H), 5.81 (m, 2H), 5.19 (d, *J* = 12.6 Hz, 1H), 4.52 (s, 2H), 4.47 (m, 2H), 4.09 (d, *J* = 5.5, 2H); **^{13}C-NMR** ($CDCl_3$): δ 174.20 (C), 164.50 (CH), 138.20 (C), 131.58 (CH), 129.05 (CH), 128.92 (CH), 128.84 (CH), 128.41 (CH), 126.78 (CH), 96.81 (CH), 72.91 (CH_2), 67.41 (CH_2), 66.00 (CH_2) ppm.

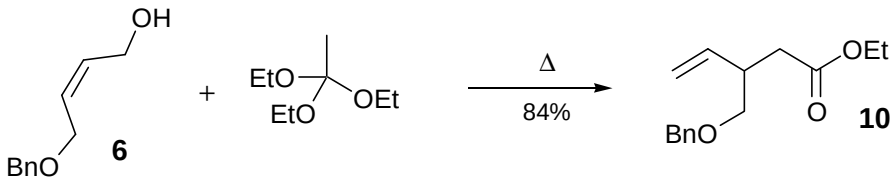


3-[(Benzyloxy)methyl]-4-pentenal (5). Compound **7** (20 g, 120 mmol) was placed in a 100 mL round bottom flask equipped with a magnetic stirrer and then fitted with a distillation head for vacuum distillation. Under a 0.1 mm pressure the mixture was heated and the external bath was maintained at nearly 165°C over a period of 10 min and then the temperature was slowly heated to 180°C. With the bath at this temperature an yellow oily product was collected and was further purified by flash column chromatography. Elution of the column (petroleum ether-Et_2O, 7:3) gave the pure product as a clear oil: yield 20.83 g (85%); **GC**: t_R 8.26; **TLC:** R_f 0.70 (petroleum ether-Et_2O, 7:3); **^{1}H-NMR** ($CDCl_3$): δ 9.73 (t, *J* = 2.2 Hz, 1H), 7.31 (m, 5H), 5.75 (m, 1H), 5.10 (m, 2H), 4.48 (s, 2H), 3.51 (dd, *J* = 5.2 Hz, *J* = 9.2 Hz, 1H), 3.34 (dd, *J* = 7.6 Hz, *J* = 9.2 Hz, 1H), 2.99 (m, 1H), 2.62 (ddd, *J* = 2.0 Hz, *J* = 15.7 Hz, *J* = 6.3 Hz, 1H), 2.45 (ddd, *J* = 2.0 Hz, *J* = 15.7 Hz, *J* = 7.3 Hz, 1H); **^{13}C-NMR** ($CDCl_3$): δ 202.41 (CHO), 138.63 (C), 138.16 (CH), 128.97- 128.18 (CH), 117.01 (CH_2), 73.69 (CH_2), 73.40 (CH_2), 46.23 (CH_2), 39.08 (CH) ppm. ***Anal.***: Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.53; H, 7.94.

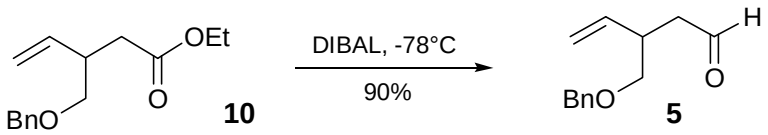


***t* –Butyl 5-[(Benzyloxy)methyl]-3-hydroxy-6-heptenoate** (**8**). A solution of compound **5** (10.21 g, 50 mmol) and *t*-butyl α-bromoacetate (8.5 mL, 57 mmol) in dry THF (40 mL) was slowly added at room temperature to a well stirred dispersion of magnesium turnings (2.0 g, 80 mmol) in THF (30 mL) activated by the addition of 700 μL of methyl iodide. The reaction mixture was heated to reflux for approximately 3 h. The cooled reaction mixture was slowly added with 10% aqueous H_2SO_4 and ice. The deep green color turns to pale yellow. Reaction mixture was diluted with diethyl ether (100 mL) and

poured in a separatory funnel. The aqueous layer was further extracted with diethyl ether (2x50 mL. The combined organic layers were washed with a saturated aqueous sodium bicarbonate (2x20 mL) and dried (Na_2SO_4). Solvent was removed under reduced pressure to give the hydroxy ester **8** (mixture of diastereoisomers) as colorless oil: yield 84%; **GC**: t_R 12.82; **TLC:** R_f 0.21 (petroleum ether-Et_2O, 7:3); **^{1}H-NMR** ($CDCl_3$): δ 7.29 (m, 5H), 5.71 (m, 1H), 5.10 (m, 2H), 4.51 (s, 2H), 4.05 (m, 1H), 3.52-3.24 (m, 3H), 2.79-2.30 (m, 3H), 1.64 (m, 2H), 1.43 (s, 9H); **^{13}C-NMR** ($CDCl_3$): δ 172.75 (C), 140.45 (CH), 139.97 (CH), 138.72 (C), 128.95-128.13 (CH), 117.08 (CH_2), 116.23 (CH_2), 81.67 (C), 74.68 (CH_2), 73.90 (CH_2), 73.70 (CH_2), 73.50 (CH_2), 66.85 (CH), 66.49 (CH), 43.61 (CH_2) 42.90 (CH_2), 41.37 (CH), 41.14 (CH), 39.08 (CH_2), 39.00 (CH_2), 28.69 (CH_3) ppm. ***Anal.***: Calcd for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 71.32; 8.75.

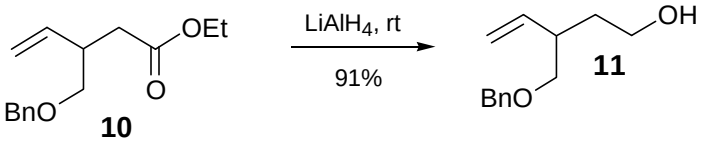


Ethyl 3-[(Benzyloxy)methyl]-4-pentenoate (**10**). The monoprotected alcohol **6** (24.93 g, 150 mmol), ethyl orthoacetate (56 mL, 300 mmol) and hydroquinone (1.65 g, 15 mmol) were placed in a 100 mL round bottom flask equipped with a distillation head with a condenser. The reaction mixture was heated to 140-145°C and the ethanol was continuously collected during the reaction. After 5 h the excess of orthoacetate was distilled and the residue was purified by a further distillation to obtain essentially pure compound **10** as an oil (bp 140°C/1.5 mmHg): yield 31.28 g (84%): **GC**: t_R 9.63; **TLC:** R_f 0.30 (petroleum ether-EtOAc, 9:1); **^{1}H-NMR** ($CDCl_3$): δ 7.30 (m, 5H), 5.78 (m, 1H), 5.10 (m, 2H), 4.50 (d, *J* = 12.4 Hz, 1H), 4.40 (d, *J* = 12.4 Hz, 1H), 4.08 (q, *J* = 7.1 Hz, 2H), 3.48 (dd, *J* = 5.7 Hz, *J* = 9.2 Hz, 1H), 3.38 (dd, *J* = 6.9 Hz, *J* = 9.2 Hz, 1H), 2.91 (m, 1H), 2.56 (dd, *J* = 6.1 Hz, *J* = 15.3 Hz, 1H), 2.34 (dd, *J* = 8.1 Hz, *J* = 15.3 Hz, 1H), 1.20 (t, *J* = 7.1 Hz, 3H); **^{13}C-NMR** ($CDCl_3$): δ 172.88 (C), 138.87 (C), 138.56 (CH), 128.84-128.06 (CH), 116.63 (CH_2), 73.50 (CH_2), 73.26 (CH_2), 60.74 (CH_2), 40.85 (CH), 37.10 (CH_2), 14.75 (CH_3) ppm. ***Anal***: Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.37; H, 8.03.

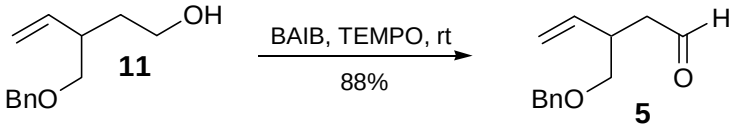


3-[(Benzyloxy)methyl]-4-pentenal (5) by Reduction of Compound 10. To a well stirred solution of the unsaturated ester **10** (28.80 g, 116 mmol) in CH_2Cl_2 (260 mL) at –78°C, was slowly added DIBALH

(1M in *n*-hexane, 128 mL, 128 mmol) with a careful control of the temperature. At the end of the addition the reduction revealed to be complete. Reaction mixture was quenched at –78°C by slow addition of cold methanol (64 mL) and then with an aqueous solution of sodium tartrate (20%, 320 mL) allowing the temperature of mixture to raise to 0°C. Diethyl ether (240 mL) was added and the mixture was stirred (20 min) at room temperature, filtered through a short path of celite to remove the aluminum salts. The filtrate cake was washed with ether (3x 20 mL). The filtrate was transferred into a separatory funnel and the organic phase was separated, washed with brine (3x100 mL) and dried (K_2CO_3). The solvent was removed at reduced pressure to obtain pure aldehyde **5**: yield 21.32 g (90 %).

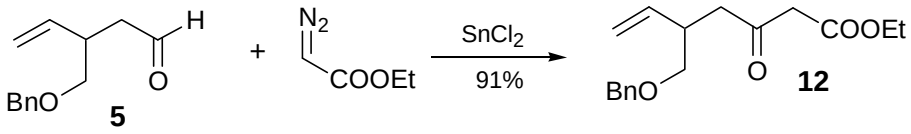


3-[(Benzyloxy)methyl]-4-penten-1-ol (**11**). Unsaturated ester **10** (2.98 g, 12 mmol) was slowly added at room temperature to a well stirred suspension of $LiAlH_4$ (0.412 g, 10.8 mmol) in dry THF (10 mL). The reaction was protracted for an additional one h and then was cooled with an ice bath and carefully treated with wet THF until the effervescence was no longer observed. A saturated NH_4Cl (1 mL) was added and generated a white precipitate that during the time turned to brown green. When the effervescence ceased the reaction mixture was filtered through a celite pad. The celite cake was washed with diethyl ether (3x30 mL), the organic layers were combined and dried (Na_2SO_4) and the solvent was removed under reduced pressure to give the alcohol **11** as brown oil: yield 2.25 g (91 %); **GC**: t_R 8.96; **TLC:** R_f 0.15 (petroleum ether-Et_2O, 7:3); **^{1}H-NMR** ($CDCl_3$): δ 7.29 (m, 5H), 5.71 (m, 1H), 5.10 (m, 2H), 4.51 (s, 2H), 3.61 (m, 2H), 3.45 (dd, *J* = 5.8 Hz, *J* = 9.1 Hz, 1H), 3.38 (dd, *J* = 6.7 Hz, *J* = 9.1 Hz, 1H), 2.54 (m, 2H), 1.70-1.50 (m, 2H); **^{13}C-NMR** ($CDCl_3$): δ 140.01 (CH), 138.60 (C), 128.90 (CH), 128.17 (CH), 116.41 (CH_2), 74.35 (CH_2), 73.63 (CH_2), 61.23 (CH_2), 41.80 (CH), 35.31 (CH_2) ppm. ***Anal***: Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.78; H, 7.72.

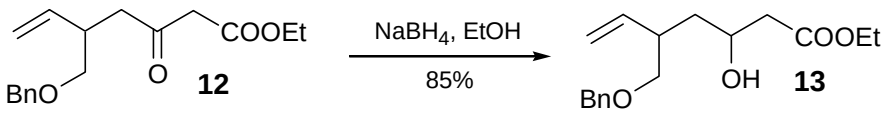


3-[(Benzyloxy)methyl]-4-pentenal (5) by Oxidation of Compound 11. TEMPO (0.182 g, 11.6 mmol), and BAIB (4.13 g, 0.128 mmol) were added at room temperature to a well stirred solution of the unsaturated alcohol **11** (2.39 g, 11.6 mmol) dissolved in CH_2Cl_2 (14 mL) according to the protocol developed by Piancatelli. After 10 min the reaction was complete (TLC, GC). The reaction mixture was diluted with CH_2Cl_2 (55 mL) and washed with saturated aqueous sodium bisulfite (2x20 mL). Aqueous

phase was back extracted with CH_2Cl_2 (2x30 mL). Combined organic layers were treated with brine and dried (Na_2SO_4). Solvent was removed under reduced pressure and the crude residue was purified by flash column chromatography. Elution of the column with petroleum ether-diethyl ether (9:1) allowed to obtain a first fraction consisting of phenyl iodide (1.76 g, R_f = 0.8, UV) and pure aldehyde **5**, yield 2.09 g (88%).

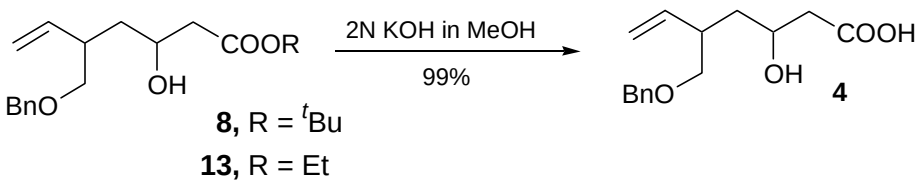


Ethyl 5-(Benzyloxy)methyl-3-oxo-6-heptenoate (12). Anhydrous $SnCl_2$ (0.35 g, 1.86 mmol) was added to a well stirred solution of ethyl diazoacetate (2.03 mL, 19.5 mmol) in CH_2Cl_2 (38 mL). After 15 min a solution of aldehyde **5** (3.79 g, 18.6 mmol) in CH_2Cl_2 (10 mL) was slowly added and evolution of nitrogen was observed during the reaction. The reaction was continued for additional 30 min after the TLC showed the disappearance of the aldehyde **5**, then the reaction mixture was diluted with CH_2Cl_2 and washed with water. The combined organic layers were dried ($MgSO_4$), filtered and evaporated at reduced pressure giving the β-ketoester **12** as a colorless oil: yield 4.91 (91 %); **TLC:** R_f 0.32 (petroleum ether-Et_2O, 4:1); **^{1}H-NMR** ($CDCl_3$): δ 7.32 (m, 5H), 5.74 (m, 1H), 5.09 (m, 2H), 4.48 (s, 2H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.48 (dd, *J* = 5.4 Hz, *J* = 9.2,Hz, 1H), 3.42 (s, 2H), 3.36 (dd, *J* = 7.2 Hz, *J* = 9.2 Hz, 1H), 2.98 (m, 1H), 2.79 (dd, *J* = 6.00, *J* = 16.7 Hz, 1H), 2.58 (dd, *J* = 7.4 Hz, *J* = 16.7 Hz, 1H), 1.25 (t, *J* = 7.2, 3H); **^{13}C-NMR** ($CDCl_3$): δ 201.26 (C), 167.73 (C), 138.74 (C), 138.43 (CH), 128.95 (CH), 128.18 (CH), 116.76 (CH_2), 73.57 (CH_2), 73.15 (CH_2), 61.85 (CH_2), 50.33 (CH_2), 45.29 (CH_2), 39.65 (CH), 14.66 (CH_3) ppm; . ***Anal***: Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.58; H, 7.71.



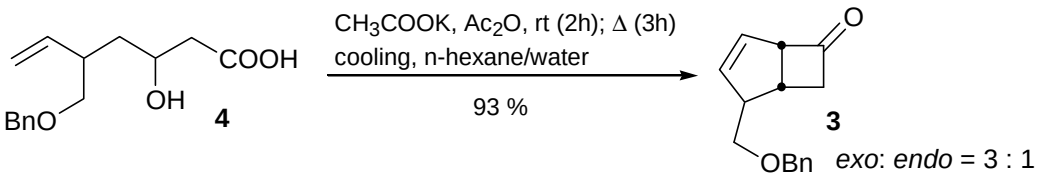
Ethyl 5-(Benzyloxy)methyl-3-hydroxy-6-heptenoate (**13**). A well stirred solution of β-ketoester **12** (4.97 g, 17.1 mmol) in ethanol (60 mL) was cooled at 2-5°C and $NaBH_4$ (0.840 g, 22.2 mmol) was added in small doses. The reaction progress was monitored by TLC and the reaction was continued until the starting material was disappeared. The reaction mixture was concentrated at reduced pressure. Water was added and the mixture was stirred for further 20 min and then extracted with diethyl ether (5x40 mL). Combined organic layers were dried (Na_2SO_4) and when the solvent was evaporated at reduced pressure gave 3-hydroxyester **13** (mixture of diastereoisomers) as a pale yellow oil: Yield 4.24 g (85%);

TLC: R_f 0.32 (Et_2O- petroleum ether 3:2);**^{1}H-NMR** ($CDCl_3$): δ, 7.31 (m, 5H), 5.79 (m, 1H), 5.11 (m, 2H), 4.52 (s, 2H), 4.14 (q, *J* = 7.2 Hz, 2H), 4.10 (m, 2H), 3.41 (m, 2H), 2.67 (m, 1H), 2.42 (m, 2H), 1.64 (m, 2H), 1.22 (t, *J* = 7.2 Hz, 3H); **^{13}C-NMR** ($CDCl_3$): δ 173.59 (C), 140.20 (CH), 139.64 (CH), 139.22 (C), 128.90-128.15 (CH), 117.13 (CH_2), 116.30 (CH_2), 74.55 (CH_2), 74.13 (CH_2), 73.62 (CH_2), 73.44 (CH_2), 66.65 (CH), 66.34 (CH), 61.15 (CH_2), 42.64 (CH_2), 41.85 (CH_2), 41.36 (CH), 41.10 (CH), 39.13 (CH_2), 39.05 (CH_2), 14.70 (CH_3) ppm. ***Anal***: Calcd for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27. Found: C, 69.75; H, 8.42.



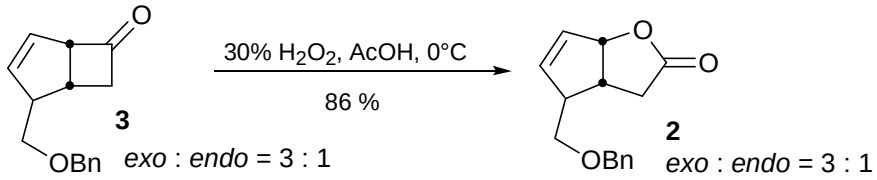
8, R = ^{t}Bu
13, R = Et

5-(Benzyloxy)methyl-3-hydroxy-6-heptenoic Acid (**4**). β-Hydroxyester **8** or **13** (38.8 mmol) was dissolved in a 2N KOH methanol solution (25 mL) and maintained at room temperature with occasional stirring for 12 h. Methanol was evaporated at reduced pressure, the residue was diluted with water (90 mL) and extracted with diethyl ether (3x 20 mL). The aqueous phase was acidified with 6N HCl to pH 2 and extracted with diethyl ether (3x50 mL). The combined organic layers were washed with water, brine and finally dried (Na_2SO_4). Evaporation of solvent at reduced pressure gave 3-hydroxy acid **4** (mixture of diastereoisomers) as an oil: yield 10.20 g (99%); **TLC:** R_f 0.39 (Et_2O-petroleum ether-acetic acid, 9:1: 0.01); **^{1}H-NMR** ($CDCl_3$): δ 7.30 (m, 5H), 5.69 (m, 1H), 5.53 (m, 2H), 5.11 (m, 2H), 4.51 (s, 2H), 4.09 (m, 1H), 3.42 (m, 2H), 2.64 (m, 1H), 2.49 (m, 2H), 1.70-1.50 (m, 2H); **^{13}C-NMR** ($CDCl_3$): δ 177.02 (C), 139.91 (CH), 139.46 (CH), 137.84 (C), 137.87 (C), 129.10 (CH), 128.41 (CH), 117.29 (CH_2), 116.68 (CH_2), 74.67 (CH_2), 74.04 (CH_2), 73.93 (CH_2), 73.78 (CH_2), 66.79 (CH), 42.51 (CH_2), 41.68 (CH_2), 41.16 (CH), 39.58 (CH_2), 39.42 (CH_2) ppm. ***Anal***: Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: 68.35; H, 7.53.

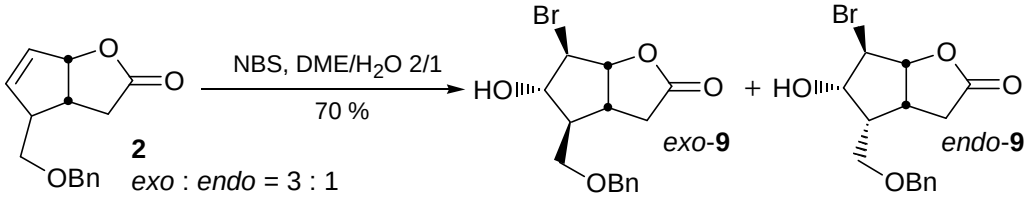


(1*S,2*S**,5*R**)-2-[(Benzyloxy)methyl]-bicyclo[3.2.0]hept-3-en-6-one** (***exo*-3**) **Contaminated by the endo-3 Isomer**. 3-Hydroxy acid **4** (12.0 g, 45.5 mmol) was dissolved in Ac_2O (50 mL) and KOAc (10.7 g, 109 mmol) was added at room temperature under an efficient stirring protracted for 2 h. During this time the temperature rose at nearly 40°C and then slowly went back at room temperature. The reaction

mixture was stirred at refluxing conditions for further 3 h, cooled at nearly 40°C and then transferred into a flask containing ice (120 g) and water (30 mL) and petroleum ether (150 mL) under magnetic stirring.. Under these conditions the complete hydrolysis of the anhydride in excess occurred after 12 h at rt. The reaction mixture was transferred into a separatory funnel and the aqueous phase was extracted again with petroleum ether (5x50 mL). The combined organic layers were washed with water (2x50 mL), with a saturated aqueous $NaHCO_3$ and finally with a brine, dried (Na_2SO_4), filtered and evaporated at reduced pressure to give the bicyclic heptenone ***exo*-3** contaminated by the ***endo***-isomer (3:1 ratio by GLC analysis) as a colorless oil: yield 9.66 g (93%); %). **GC**: t_R 10.88 (***exo*-3**), t_R 11.13 (***endo*-3**); **IR** (film): í 3020, 2890, 1780, 1607 cm^{-1}; **TLC:** R_f 0.42 (petroleum ether-Et_2O, 7:3). **^{1}H-NMR** ($CDCl_3$): δ 7.32 (m, 5H), 5.88- 5.70 (m, 2H), 4.54 and 4.51 (2s, 3H), 4.22 (m, 1H), 3.72-2.66 (m, 6H); **^{13}C-NMR** ($CDCl_3$): δ 206.51 (C), 138.70 (C), 134.96 (CH), 134.86 (CH), 127.84 (CH), 128.94 (CH), 127.35 (CH), 127.33 (CH), 74.10 (CH), 73.81 (CH_2), 73.70 (CH_2), 73.60 (CH_2), 73.47 (CH), 69.29 (CH_2), 54.59 (CH), 52.83 (CH_2), 48.78 (CH), 46.74 (CH_2), 29.81 (CH), 28.83 (CH) ppm. ***Anal***: Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 79.08; H, 7.12.



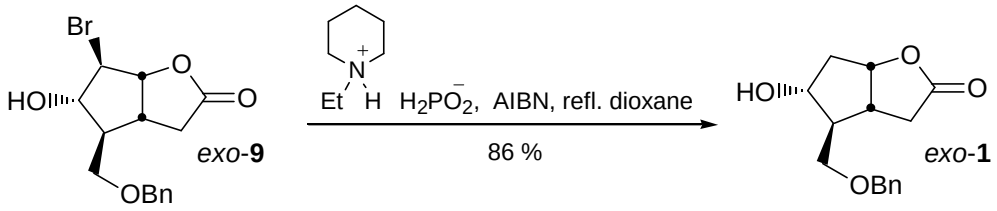
6-*exo*-[(Benzyloxy)methyl]-2-oxabicyclo[3.3.0]oct-7-en-3-one (*endo*-2) Contaminated by the *exo*-2 Isomer. A well stirred solution of bicyclic ketones **3** (6.87 g, 30.1 mmol) in 90 % acetic acid (45 mL) was cooled to –10°C and then a solution of 30% hydrogen peroxide (8.2 g, 72.3 mmol) in 90 % acetic acid (19 mL) was slowly added. The reaction was continued for 10 h at 0°C and monitored by TLC and by GC. The reaction mixture was transferred into a separatory funnel, diluted with water (40 mL) and extracted with diethyl ether (3x150 mL). The ethereal layers were combined and washed with 10% aqueous $Na_2S_2O_6$ (2x50 mL) and then with $NaHCO_3$ (3x50 mL), water and brine. The solution was dried (Na_2SO_4), filtered and when the solvent was evaporated at reduced pressure gave a mixture of bicyclic lactones **2** (3:1 ratio in favor of the ***exo*-2** isomer by GC) as a colorless oil: yield 6.32 g (86%). **GC**: t_R 12.76 (***exo*-2**), t_R 12.88 (***endo*-2**); **TLC:** R_f 0.32 (petroleum ether-Et_2O, 4:6).); **IR** (film): í 3017, 1615, 1360, 1770, 1258 cm^{-1}; **^{1}H-NMR** ($CDCl_3$): δ 7.30 (m, 5H), 6.05 and 5.90 (2m, 2H), 5.49 and 5.40 (2m, 1H), 4.49 and 4.46 (2s, 3H), 3.52-3.30 (m, 2H), 3.01-2.23 (m, 4H); **^{13}C-NMR** ($CDCl_3$): d 177.70 (C), 177.58(C), 138.92 (CH), 138.59 (C), 138.87 (CH), 130.85 (CH), 130.07 (CH), 128.94-128.03 (CH), 89.60 (CH), 89.21 (CH), 73.78 (CH_2), 73.64 (CH_2), 72.87 (CH_2), 69.97 (CH_2), 54.27 (CH), 47.59 (CH), 38.97 (CH), 38.60 (CH), 35.72 (CH_2), 30.10 (CH_2) ppm. ***Anal***: Calcd for $C_{15}H_{16}O_3$: C, 73.75; H,6.60. Found: C,73.81; H, 6.47.



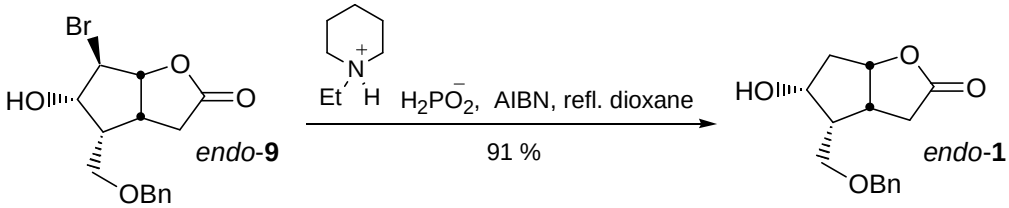
(1*S,5*R**,6*S**,7*S**,8*S**)-6-[(Benzyloxy)methyl]-8-bromo-7-hydroxy-2-oxabicyclo[3.2.0]octan-3-one** (***exo*-9**) and **(1*S**,5*R**,6*R**,7*S**,8*S**)-6-[(Benzyloxy)methyl]-8-bromo-7-hydroxy-2-oxabicyclo-[3.2.0]octan-3-one** (***endo*-9**). The mixture of bicyclic lactones 2 (3.00 g, 12.3 mmol) was dissolved in 250 mL of a solution of DME-water (2:1). The reaction mixture was cooled to –10°C and then NBS (3.28 g, 18.4 mmol) was added at a rate adequate to maintain this low temperature. The reaction mixture was allowed to reach the rt and reaction was stirred until TLC showed that there was no more starting material (approx 12h) and two new spots appeared. The reaction mixture was estracted with diethyl ether (300 mL). The combined layers were washed with brine (2x50 mL), dried (Na_2SO_4) and the solvent was evaporated at reduced pressure to give a residue that was purified by flash column chromatography. Elution of the column with a mixture of diethyl ether/ petroleum ether (4:1) gave the pure bromohydrins (3:1 mixture, ***exo*-9**: ***endo*-9**); yield: 2.93 g (**70** %).

For bromohydrin ***exo*-9**: **mp** 95-96°C; **TLC:** R_f 0.35 (Et_2O-petroleum ether, 8 : 2); **IR** (KBr): í 3416, 2874, 1762, 1496, 1474, 1452, 1414, 1364, 1289, 1185, 1118, 1075, 963 cm^{-1}; **^{1}H-NMR** ($CDCl_3$): δ 7.31 (m, 5H), 4.85 (dd, J = 3.9 Hz, J = 8.1 Hz, 1H), 4.51 (s, 2H), 4.05 (m, 2H), 3.60 (m, 2H), 3.48 (bs, 1H), 2.84 (m, 1H), 2.81 (dd, J = 1.6 Hz, J = 17.8 Hz, 1H), 2.43 (dd, J = 2.4 Hz, J = 17.8 Hz, 1H), 1.96 (m, 1H); **^{13}C-NMR** ($CDCl_3$): δ 176.63 (C), 138.24 (C), 129.08-128.19 (CH), 88.64 (CH), 80.08 CH), 73.91 (CH_2), 69.76 (CH_2), 57.35 (CH), 50.94 (CH), 37.99 (CH), 34.65 (CH_2) ppm. ***Anal***: Calcd for $C_{15}H_{17}BrO_4$: C, 52.80; H, 5.02. Found: C, 52.87; H, 4.98.

For bromohydrin ***endo*-9**: **mp** 98-100°C; **TLC:** R_f 0.12 (Et_2O-petroleum ether, 8 : 2); **IR** (KBr): í 3489, 2856, 1769, 1497, 1453, 1412, 1366, 1302, 1163, 1099, 1057, 944 cm^{-1}; **^{1}H-NMR** ($CDCl_3$): δ 7.32 (m, 5H), 4.85 (dd, J = 4.6 Hz, J = 6.2 Hz, 1H), 4.70 (bs, 1H), 4.55 (d, J = 11.8 Hz, 1H), 4.48 (d, J = 11.8 Hz, 1H), 4.12 (ddd, J = 3.5 Hz, J = 9.9 Hz, J = 9.9 Hz, 1H), 3.96 (dd, J = 4.6 Hz, J = 9.9 Hz, 1H), 3.64 (dd, J = 5.0 Hz, J = 9.6 Hz, 1H), 3.56 (dd, J = 7.3 Hz, J = 9.6 Hz, 1H), 3.15 (m, 1H), 2.68 (m, 2H), 2.24 (m, 1H);); **^{13}C-NMR** ($CDCl_3$): δ 176.29 (C), 137.95 (C), 129.25 (CH), 128.72 (CH), 128.78 (CH), 82.73 (CH), 78.12 (CH), 74.25 (CH_2), 68.32 (CH_2), 54.87 (CH), 45.21 (CH), 37.41 (CH), 31.54 (CH_2) ppm. ***Anal***: Calcd for $C_{15}H_{17}BrO_4$: C, 52.80; H, 5.02. Found: C, 52.93; H, 4.96



(1*S,5*R**,6*S**,7*S**)-6-[(Benzyloxy)methyl]-7-hydroxy-2-oxabicyclo[3.2.0]octan-3-one (*exo*-1)**. A solution of ***exo*-9** (1.37 g, 40 mmol) and 1-ethylpiperidine hypophosphite (7.16 g, 400 mmol) in dioxane (30 mL) was warmed at refluxing conditions and a dioxane solution of AIBN (500 mg in 7.5 mL) was added in 5 portions (1.50 mL) every 10 min. The reaction was continued until TLC showed the complete disappearance of the starting material. The reaction mixture was diluted with water (40 mL) and extracted with ethyl acetate (4x50 mL). The combined organic layers were washed with brine (3x50 mL), dried (Na_2SO_4) and the solvent was removed at reduced pressure to give a residue that was purified by flash column chromatography by eluting with a mixture of Et_2O-petroleum ether (1:1). The wanted bicyclic lactone ***exo*-1** was obtained as a pale yellow oil; yield: 0.902 g (86%); **TLC**: R_f 0.23 (petroleum ether-EtOAc, 1 : 1); **IR** (film): í 3446, 2933, 2863, 1767, 1646, 1454, 1362, 1181, 1093 cm^{-1}; **^{1}H-NMR** ($CDCl_3$): δ 7.30 (m, 5H), 4.91 (dt, *J* = 2.5 Hz, *J* = 6.9 Hz, 1H), 4.52 (d, *J* = 12.1 Hz, 1H), 4.48 (d, *J* = 12.1 Hz, 1H), 4.12 (m, 1H), 3.50 (dd, *J* = 5.8 Hz, *J* = 9.3 Hz, 1H), 3.45 (dd, *J* = 6.6 Hz, *J* = 9.3 Hz, 1H), 2.77 (dd, *J* = 10.2 Hz, *J* = 17.6 Hz, 1H), 2.64 (m, 2H), 2.51 (dd, *J* = 2.2 Hz, *J* = 17.6 Hz, 1H), 2.36 (ddd, *J* = 6.4 Hz, *J* = 6.4 Hz, *J* = 14.8 Hz, 1H), 2.10 (m, 1H), 1.99 (ddd, *J* = 2.8 Hz, *J* = 5.8 Hz, *J* = 14.8 Hz, 1H); **^{13}C-NMR** ($CDCl_3$): δ 177.97 (C), 138.44 (C), 129.09 (CH), 128.41 (CH), 128.15 (CH), 84.57 (CH), 76.06 (CH). 73.94 (CH_2), 71.53 (CH_2), 54.25 (CH), 41.26 (CH_2), 40.71 (CH), 36.08 (CH_2) ppm. . ***Anal***: Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.75; H, 7.02.



(1*S,5*R**,6*R**,7*S**)-6-[(Benzyloxy)methyl]-7-hydroxy-2-oxabicyclo[3.2.0]octan-3-one (*endo*-1)**. The conversion of the bromohydrin *endo*-**9** into the isomer ***endo*-1** was accomplished by following the same hydrodebromination reaction. The product ***endo*-1** was obtained in 91% yield as a pale yellow oil after flash column chromatography eluting with a mixture of EtOAc-petroleum ether (7:3). **TLC**: R_f 0.31 (EtOAc-petroleum ether, 7 : 3); **IR** (film): í 3434, 2862, 1767, 1454, 1413, 1367, 1303, 1179, 1078, 1027 cm^{-1}; **^{1}H-NMR** ($CDCl_3$): δ 7.30 (m, 5H), 4.96 (m, 1H), 4.52 (d, *J* = 11.8 Hz, 1H), 4.46 (d, *J* = 11.8 Hz, 1H), 4.12 (m, 1H), 3.60 (dd, *J* = 6.3 Hz, *J* = 9.6 Hz, 1H), 3.54 (dd, *J* = 7.1 Hz, *J* = 9.6 Hz, 1H), 3.10

(m, 1H), 3.00 (bs, 1H), 2.68-2.28 (m, 3H), 2.20 (m, 1H), 1.80 (ddd, *J* = 6.0 Hz, *J* = 9.6 Hz, *J* = 14.3 Hz, 1H); **^{13}C-NMR** ($CDCl_3$): δ 178.07 (C), 138.16 (C), 129.08 (CH), 128.48 (CH), 128.31 (CH), 83.73 (CH), 74.09 (CH_2), 73.61 (CH), 69.72 (CH_2), 48.61 (CH), 41.07 (CH_2), 38.71 (CH), 30.59 (CH_2) ppm. ***Anal***: Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.78; H, 6.85.

[i] . Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem*. **1978**, *43*, 2923.

Acquisition Time (sec)	3.6405	***Comment***				***Date***	4-20-00	***Frequency (MHz)***	300.08	***Nucleus***	1H
Number of Transients	16	***Original Points Count***	12000	***Points Count***	16384	***Solvent***	cdcl3	***Sweep Width (Hz)***	4500.45		
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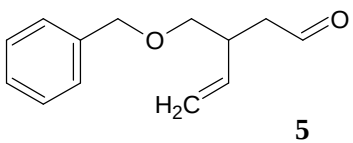

5

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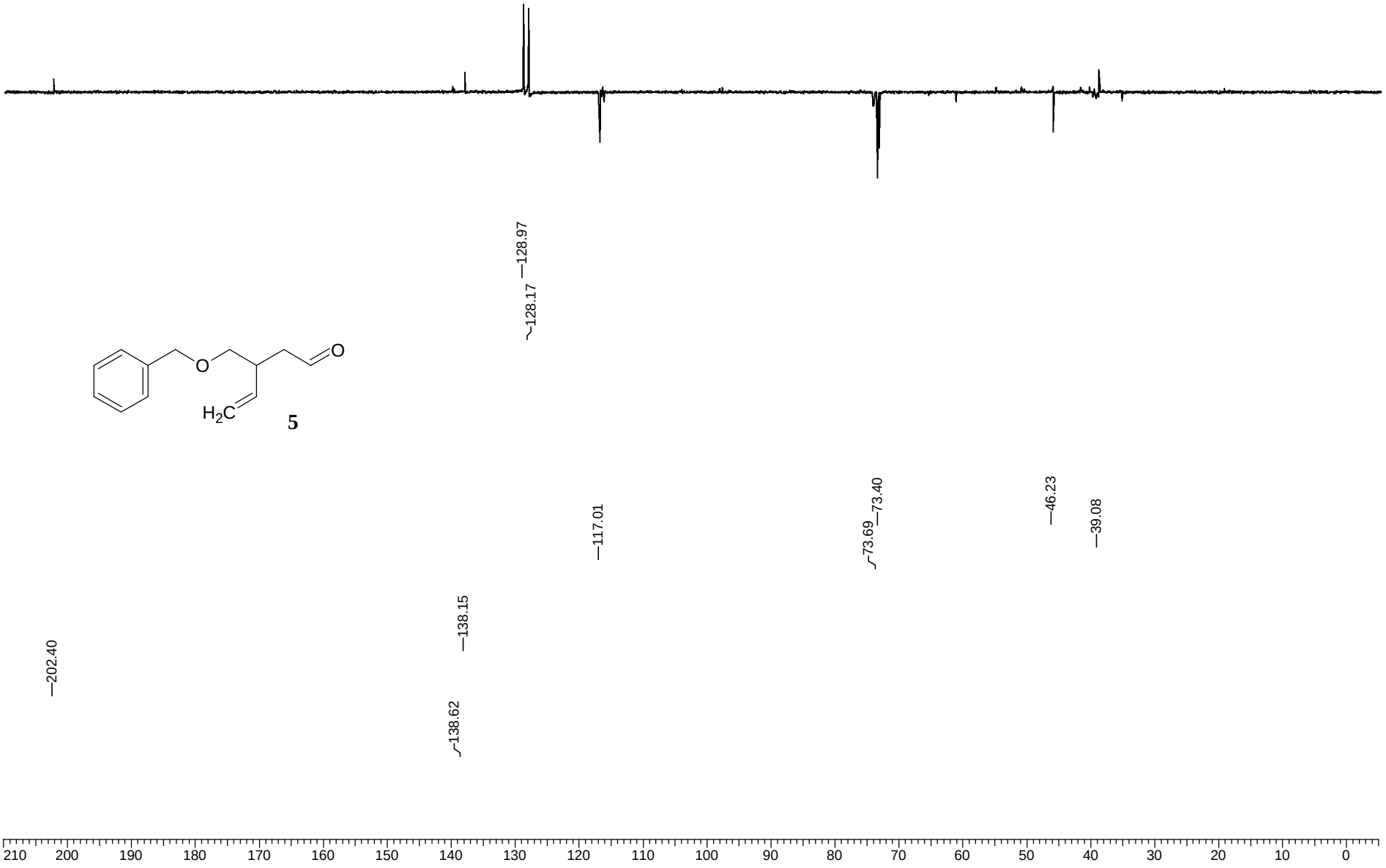
Temperature (grad C)	29.000						



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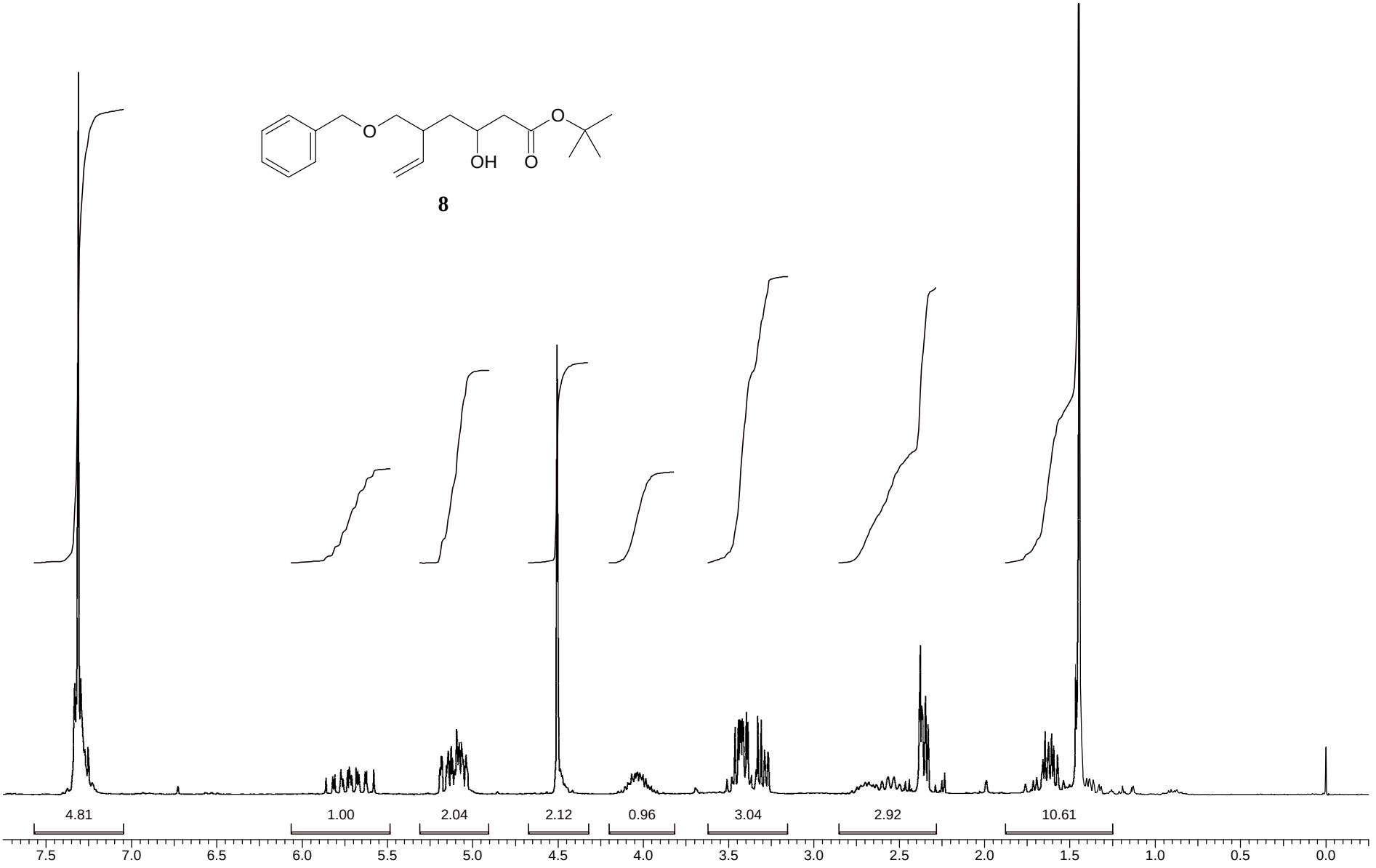

8

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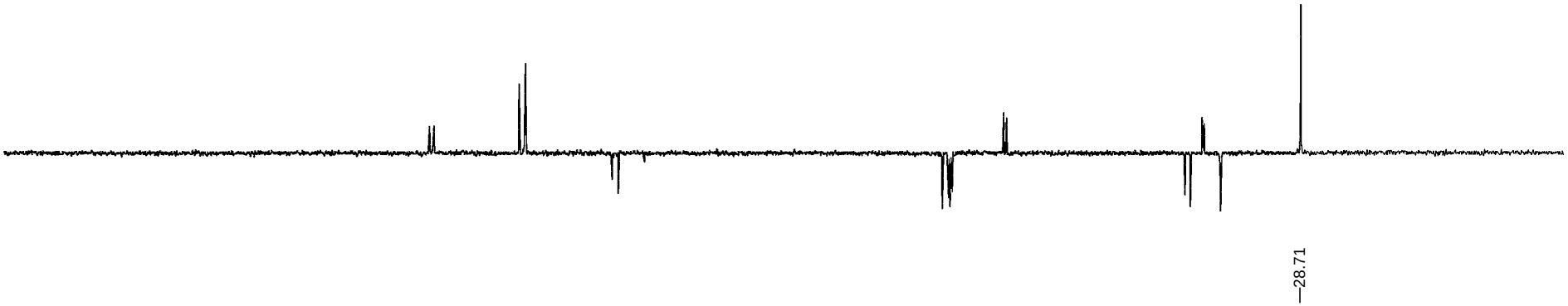
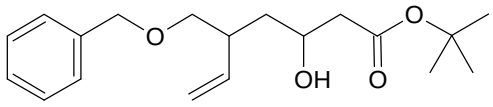
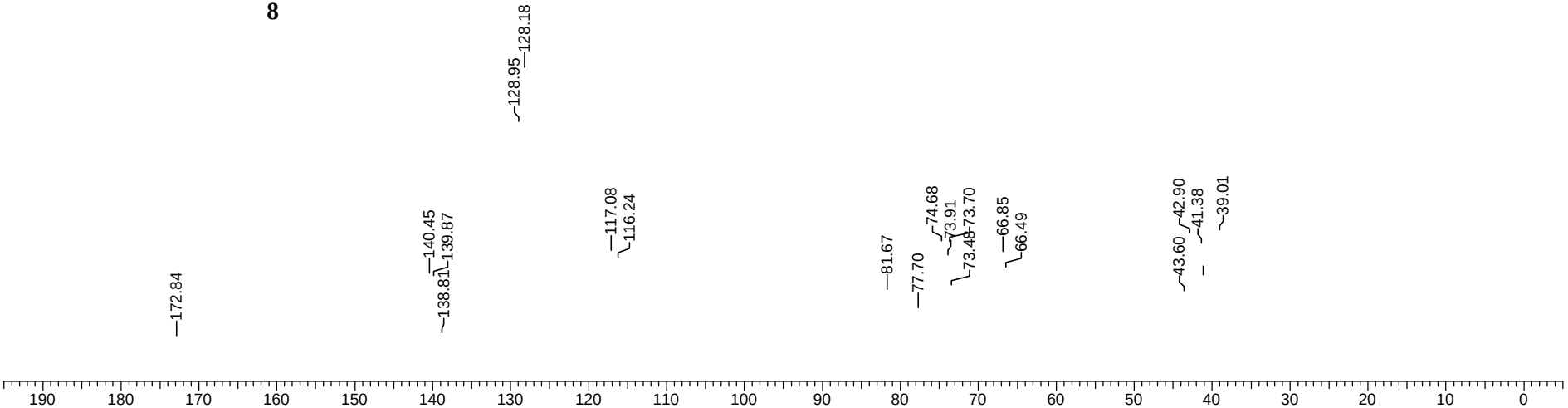
Frequency (MHz)	50.29	***Nucleus***	13C	***Original Points Count***	8000	***Points Count***	8192	***Solvent***	cdcl3	***Sweep Width (Hz)***	14992.51
Temperature (grad C)	29.000										





8



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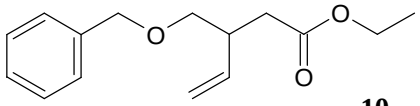
Temperature (grad C)	29.000								



10

Acquisition Time (sec) 0.5464	***Comment***			***Date*** 2-03-00		***Frequency (MHz)*** 50.29	
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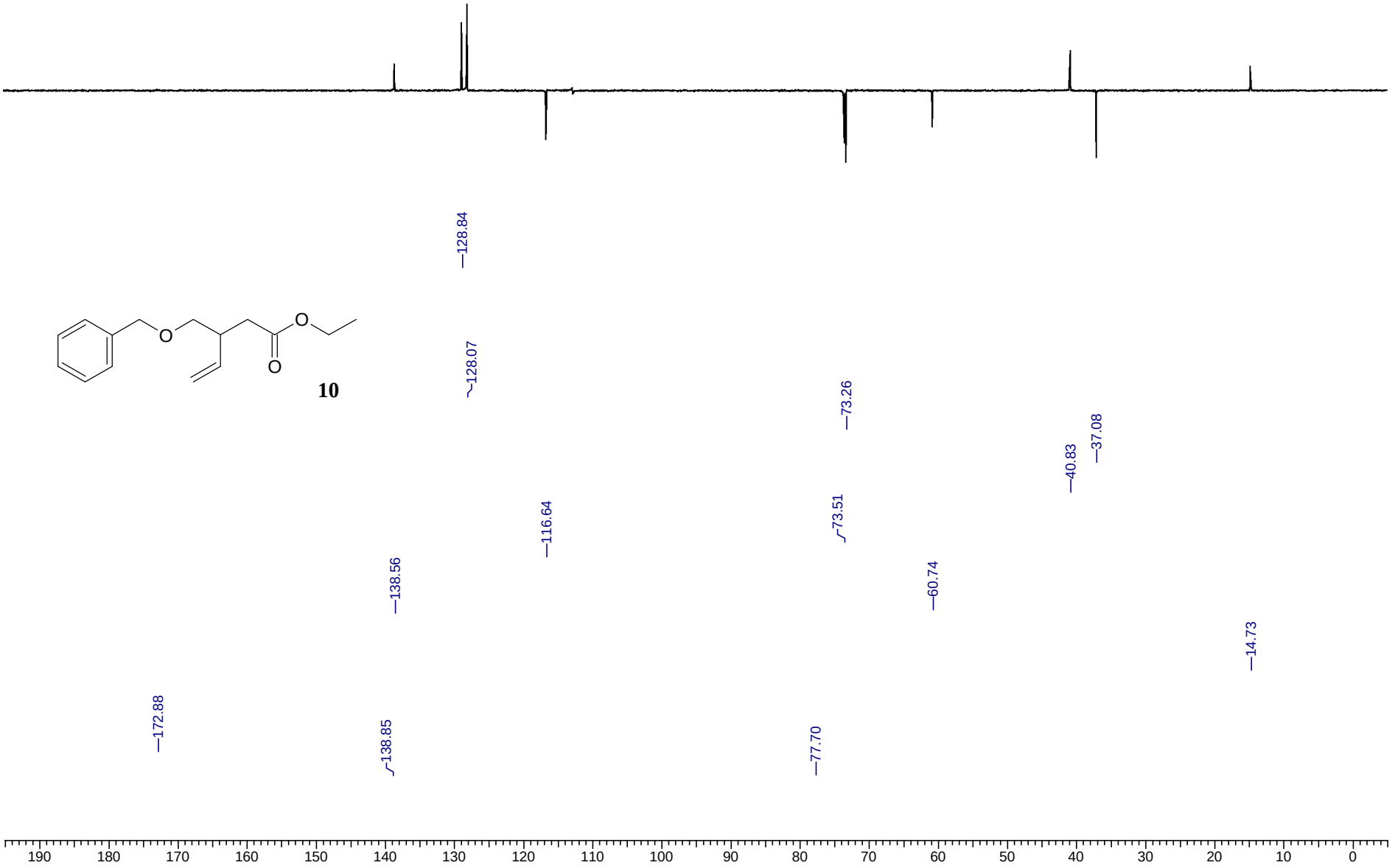
Temperature (grad C) 29.000							



10

Acquisition Time (sec)	2.7304			***Comment***	Fa42	***Date***	3-11-00		
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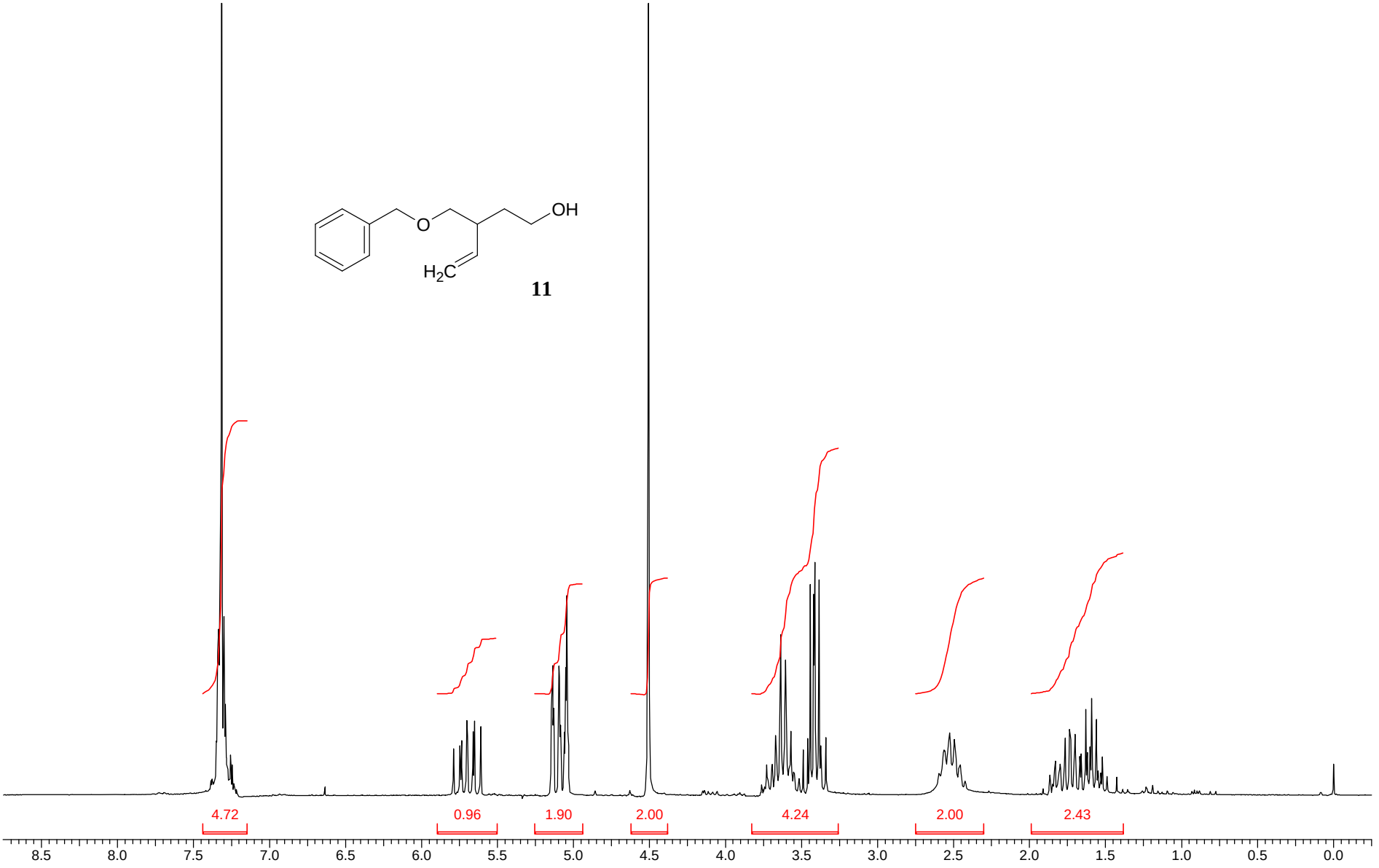
Temperature (grad C)	29.000								

Frequency (MHz)	199.98				
Sweep Width (Hz)	3000.30				



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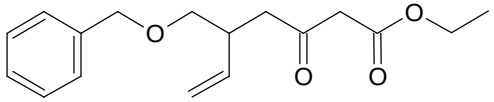
Frequency (MHz)	199.98	***Nucleus***	1H	***Number of Transients***	16	***Original Points Count*** 8000	***Points Count*** 8192
Solvent	cdcl3	***Sweep Width (Hz)***	3000.30	***Temperature (grad C)***	29.000		



12

Acquisition Time (sec)	0.5464			***Comment***	Fa 57	***Date***	2-27-00	***Frequency (MHz)***	50.29
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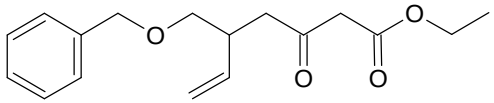
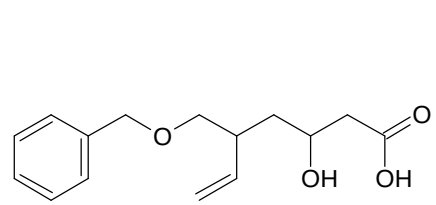
Temperature (grad C)	29.000								



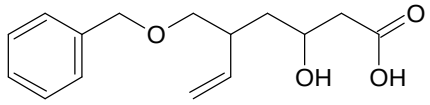
12

Acquisition Time (sec)	3.6405	***Comment***				***Date***	4-26-00
Frequency (MHz)	300.08	***Nucleus***	1H	***Number of Transients*** 16	***Original Points Count*** 12000	***Points Count***	16384
Solvent	cdcl3	***Sweep Width (Hz)***	4500.45	***Temperature (grad C)*** 29.000			



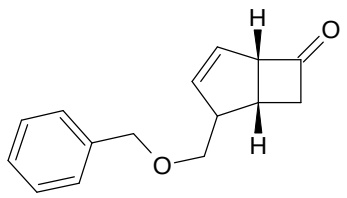
4

Acquisition Time (sec)	0.8192	***Comment***				***Date***	4-26-00
Frequency (MHz)	75.46	***Nucleus***	13C	***Original Points Count*** 12000	***Points Count*** 16384	***Solvent***	cdcl3
Sweep Width (Hz)	20000.00	***Temperature (grad C)***	29.000				



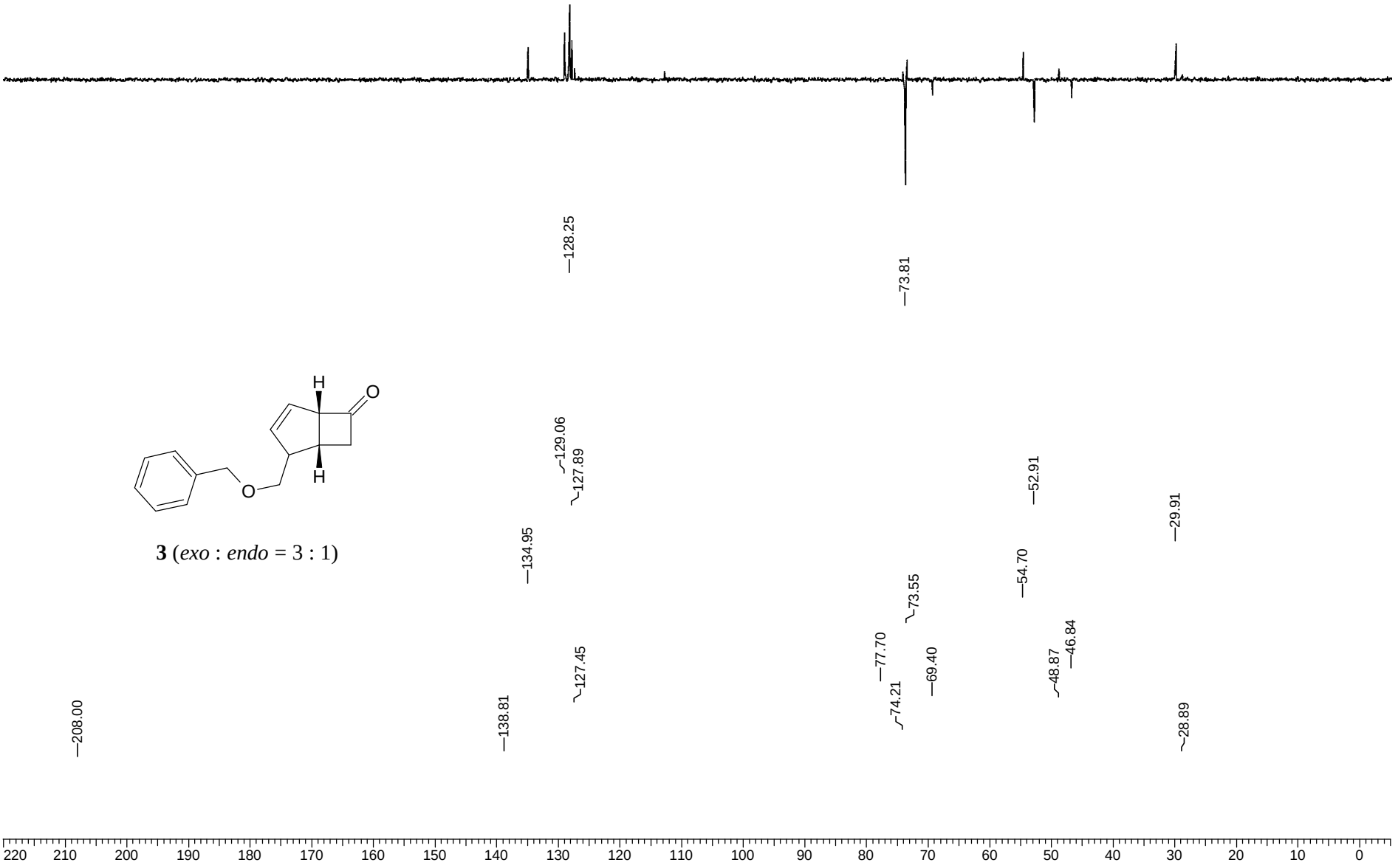
4

Acquisition Time (sec)	2.7304			***Comment***				***Date***	3-24-00
Frequency (MHz)	199.98			***Nucleus***	1H	***Number of Transients***	16	***Original Points Count***	8000
Solvent	cdcl3	***Sweep Width (Hz)***	3000.30			***Temperature (grad C)***	29.000		



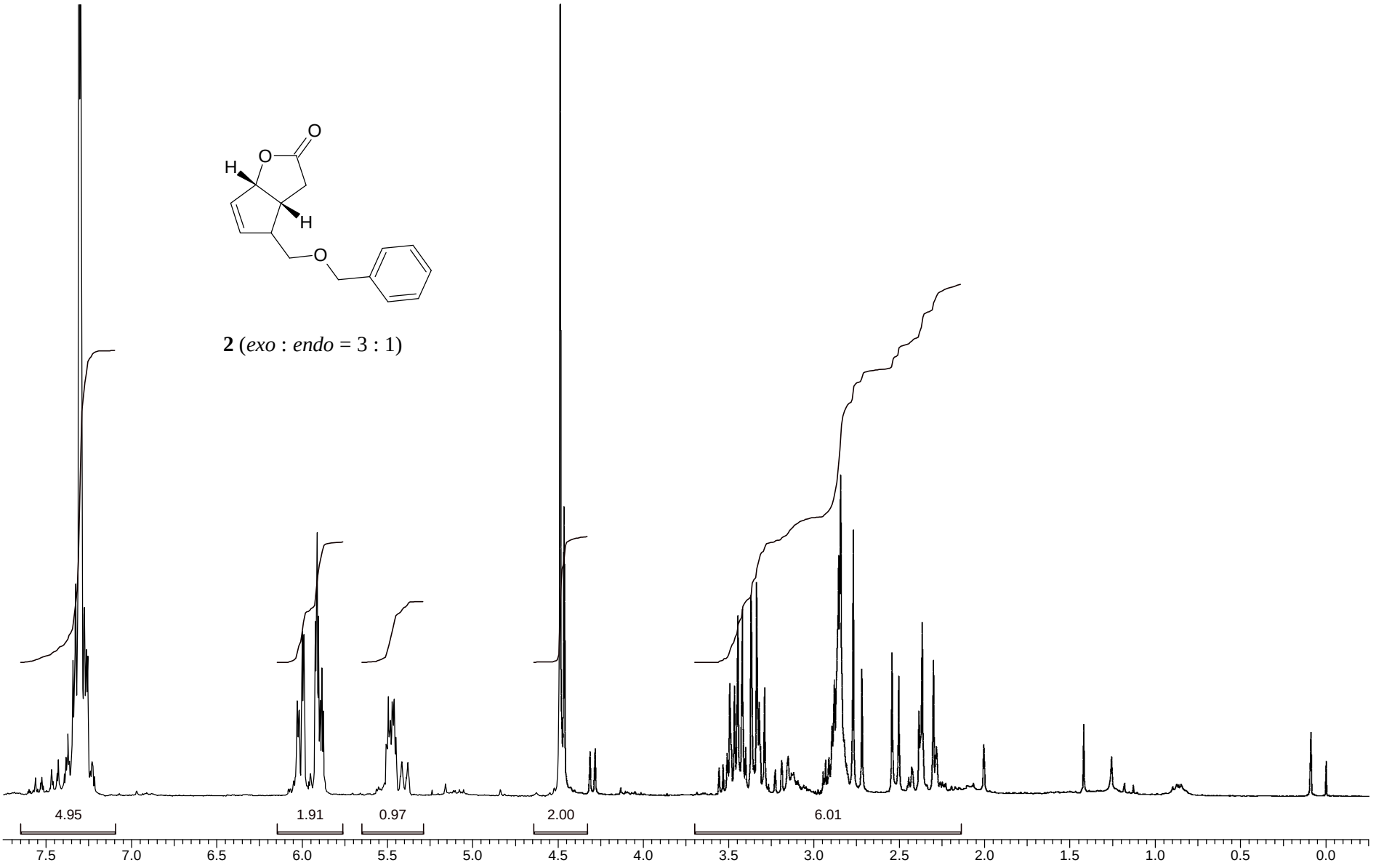
3 (*exo* : *endo* = 3 : 1)

Acquisition Time (sec)	0.5464			***Comment***				***Date***	3-24-00		
Frequency (MHz)	50.29	***Nucleus***	13C	***Original Points Count***	8000	***Points Count***	8192	***Solvent***	cdcl3	***Sweep Width (Hz)***	14992.51
Temperature (grad C)	29.000										



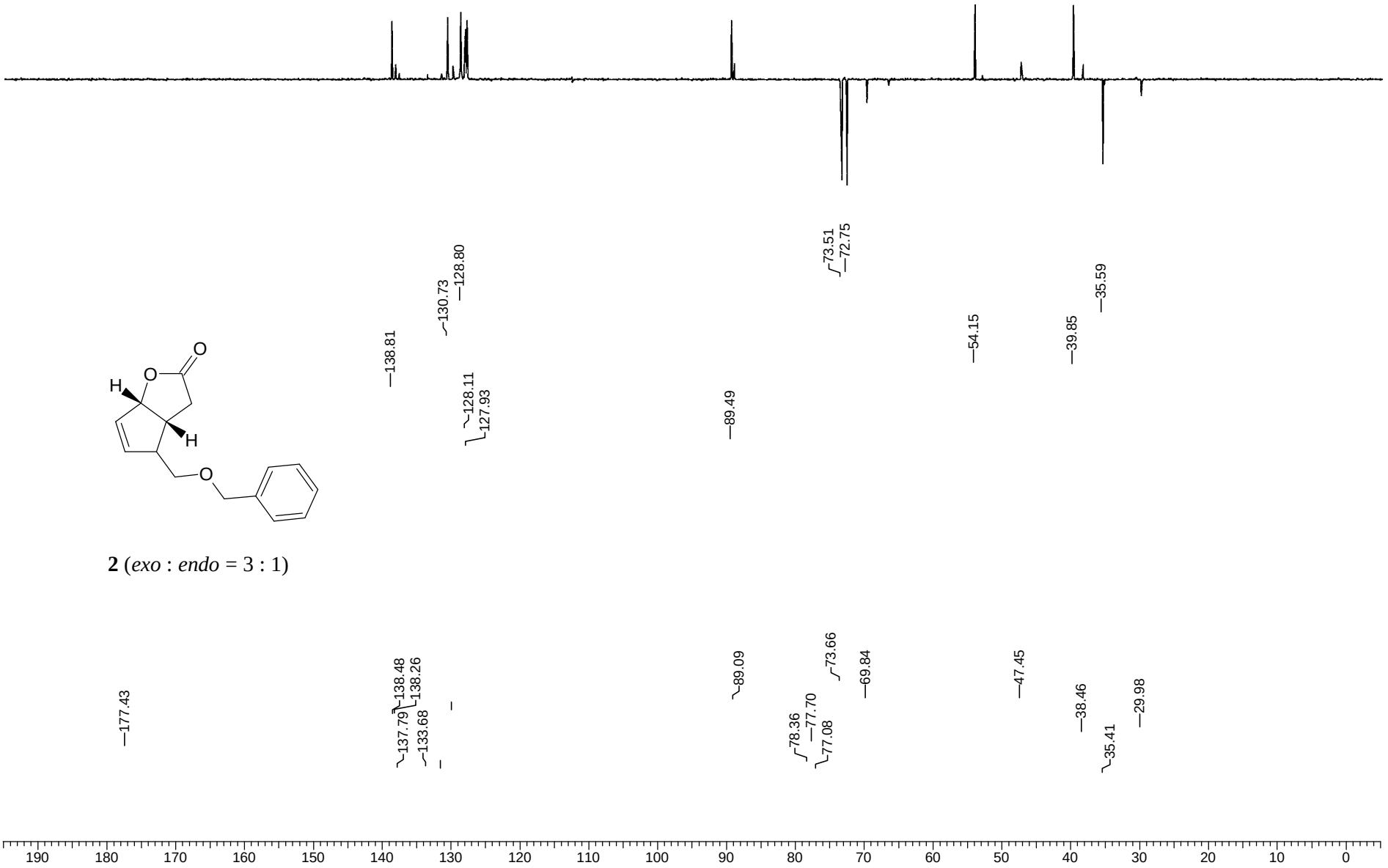
3 (*exo* : *endo* = 3 : 1)

Acquisition Time (sec)	2.7304			***Comment***				***Date***	2-12-00
Frequency (MHz)	199.98			***Nucleus***	1H	***Number of Transients***	16	***Original Points Count***	8000
Solvent	cdcl3	***Sweep Width (Hz)***	3000.30			***Temperature (grad C)***	29.000		



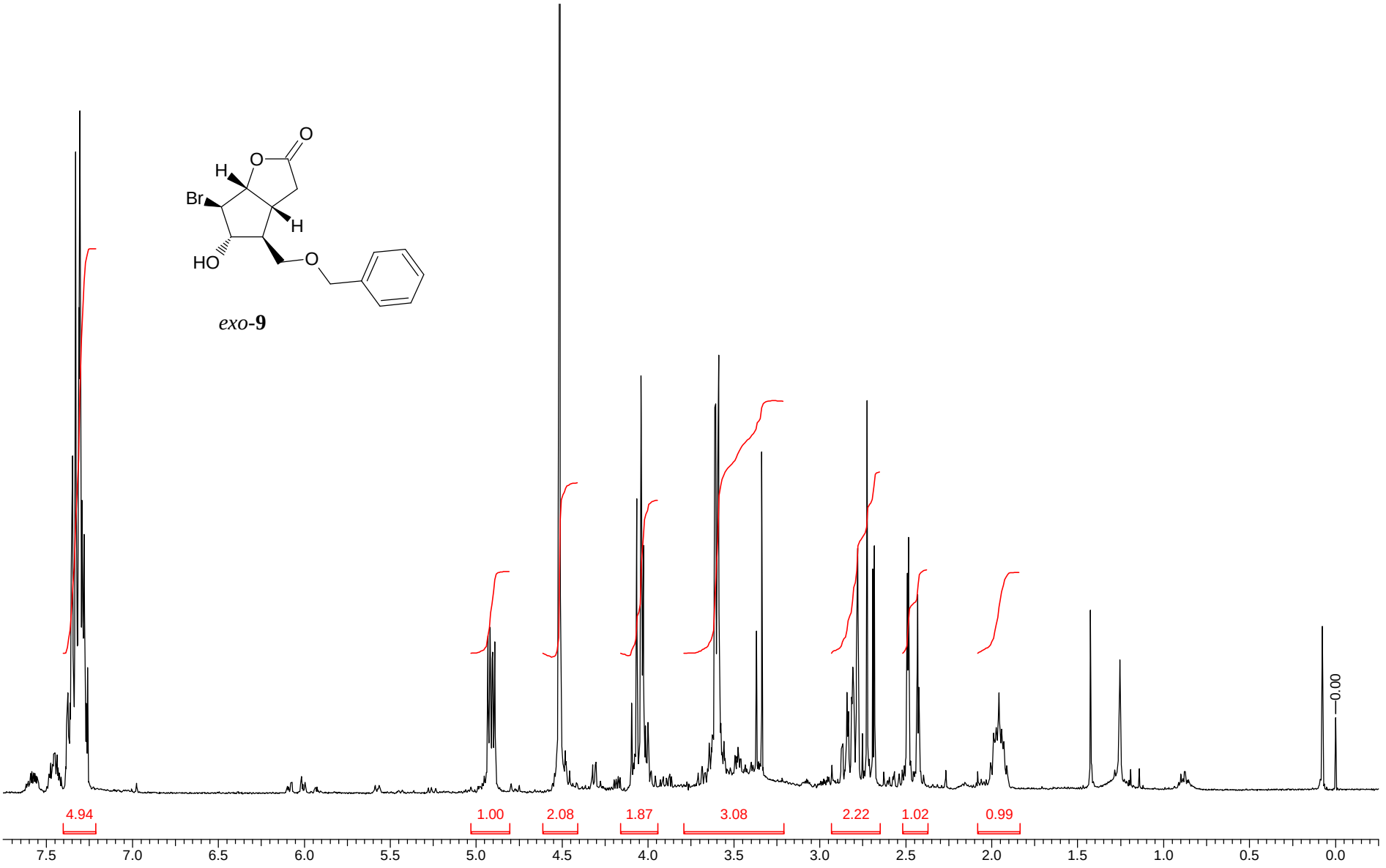
2 (*exo* : *endo* = 3 : 1)

Acquisition Time (sec)	0.5464			***Comment***		***Date***	2-12-00	***Frequency (MHz)***	50.29
Nucleus	13C	***Original Points Count***	8000	***Points Count***	8192	***Solvent***	cdcl3	***Sweep Width (Hz)***	14992.51
Temperature (grad C)	29.000								



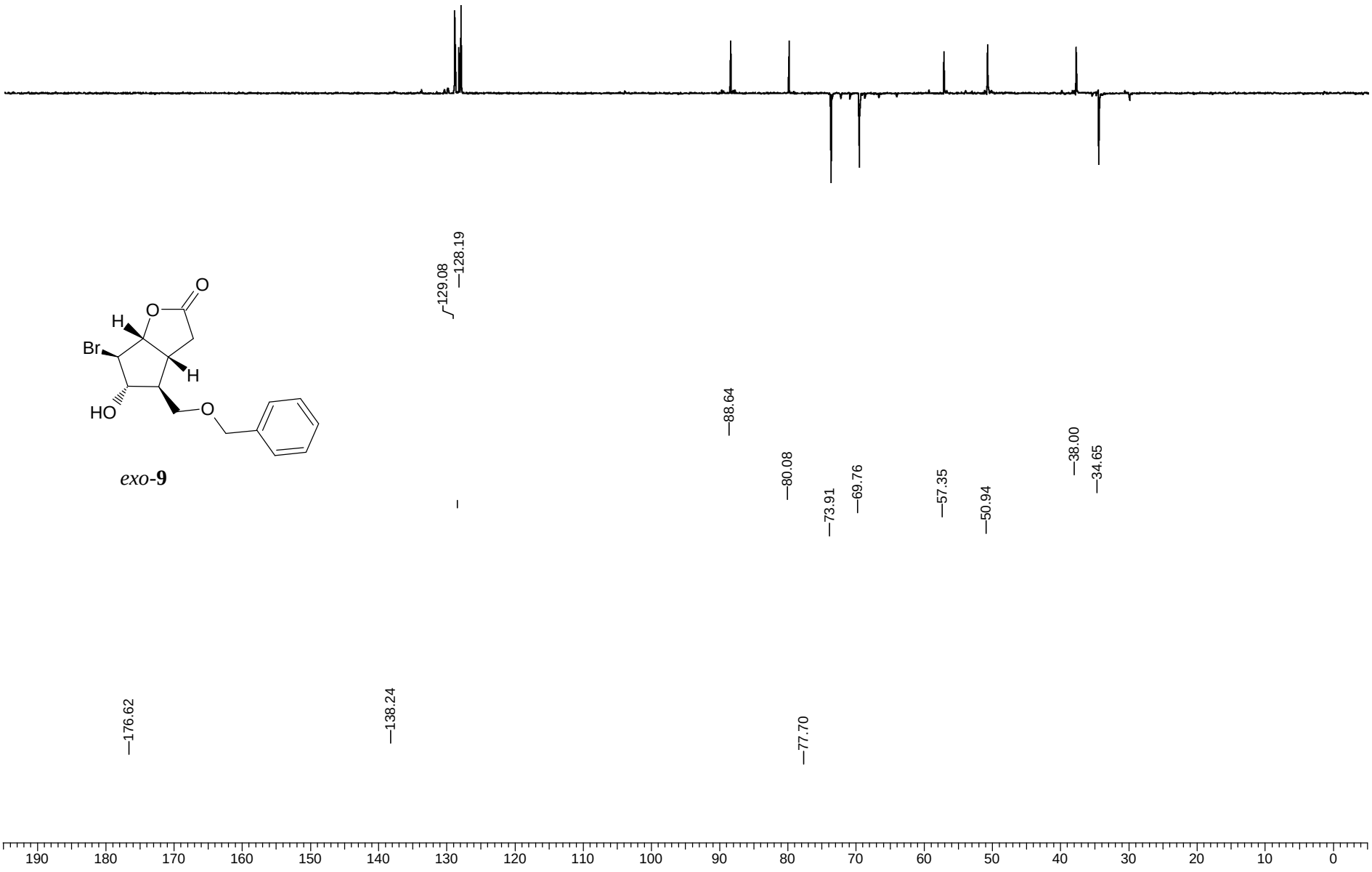
2 (*exo* : *endo* = 3 : 1)

Acquisition Time (sec)	3.6405	***Comment***	FA 37b			***Date***	3-04-00
Frequency (MHz)	300.08	***Nucleus***	1H	***Number of Transients***	16	***Original Points Count***	12000
Points Count	16384	***Solvent***	cdcl3	***Sweep Width (Hz)***	4500.45	***Temperature (grad C)***	29.000

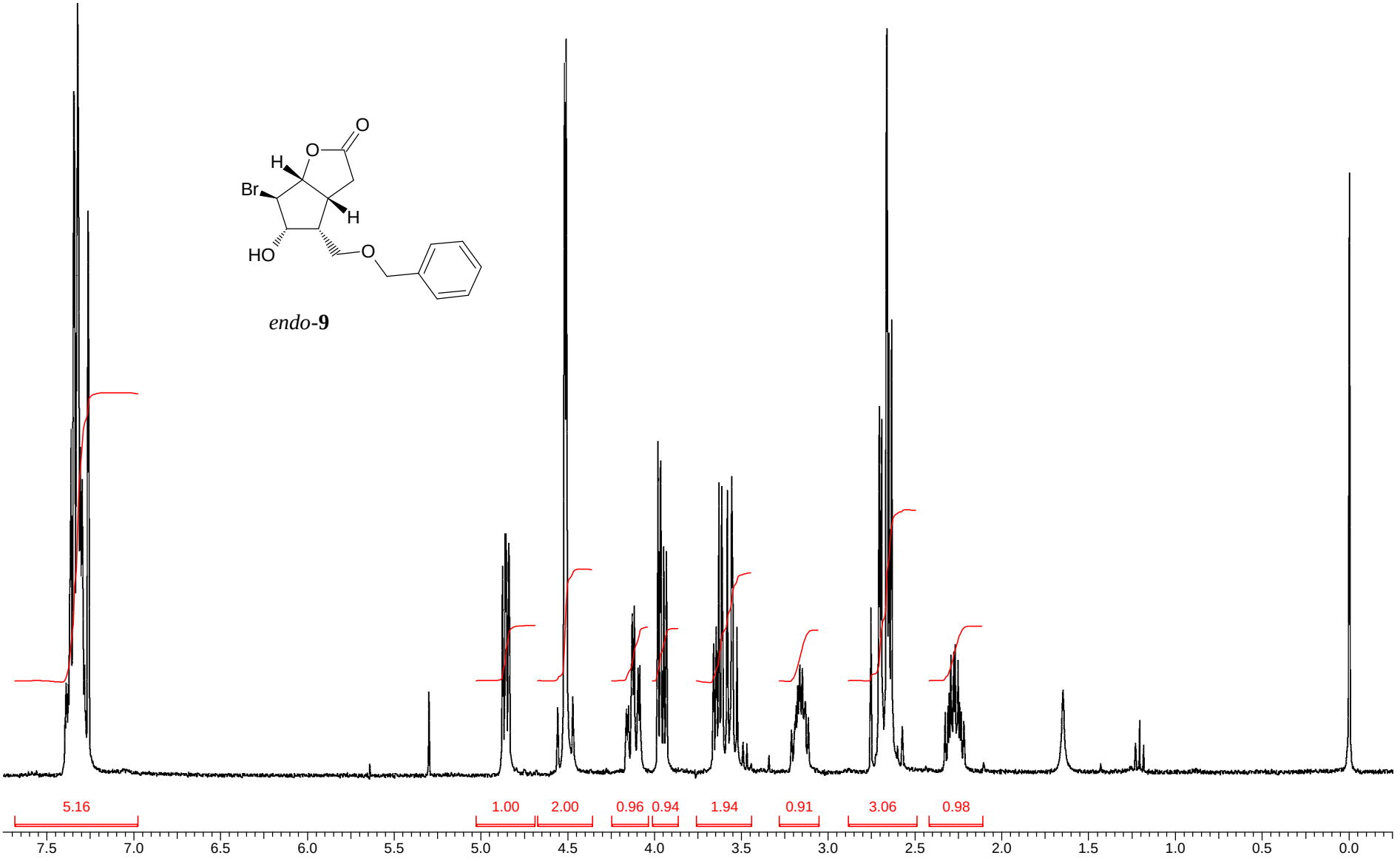


exo-**9**

Acquisition Time (sec)	0.8192	***Comment***				***Date***	3-04-00	***Frequency (MHz)***	75.46	***Nucleus***	13C
Original Points Count	12000	***Points Count***	16384	***Solvent***	cdcl3	***Sweep Width (Hz)***	20000.00			***Temperature (grad C)***	29.000

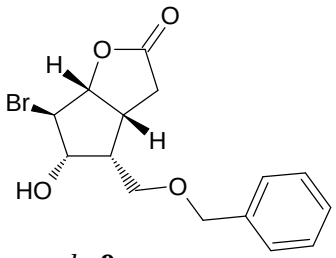


Acquisition Time (sec)	3.6405	***Comment***				***Date***	1-18-00
Frequency (MHz)	300.08	***Nucleus***	1H	***Number of Transients***	16	***Original Points Count***	12000
Points Count	16384	***Solvent***	cdcl3	***Sweep Width (Hz)***	4500.45	***Temperature (grad C)***	29.000



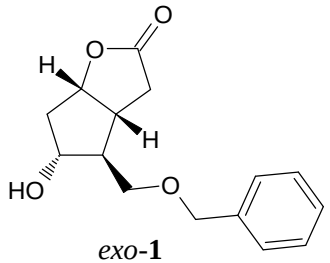
endo-**9**

Acquisition Time (sec)	0.8192			***Comment***	Fa 60bx			***Date***	1-18-99		
Frequency (MHz)	75.46	***Nucleus***	13C	***Original Points Count***	12000	***Points Count***	16384	***Solvent***	cdcl3	***Sweep Width (Hz)***	20000.00
Temperature (grad C)	29.000										



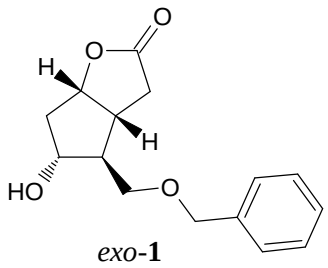
endo-**9**

Acquisition Time (sec)	3.6405	***Comment***				***Date***	7-12-00
Frequency (MHz)	300.08	***Nucleus***	1H	***Number of Transients***	16	***Original Points Count*** 12000	***Points Count*** 16384
Solvent	cdcl3	***Sweep Width (Hz)***	4500.45	***Temperature (grad C)***	29.000		



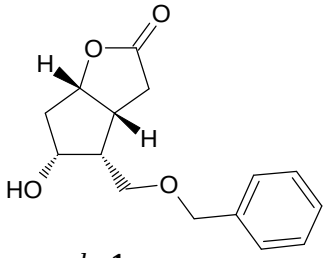
exo-**1**

Acquisition Time (sec)	0.8192	***Comment***				***Date***	7-12-00
Frequency (MHz)	75.46	***Nucleus***	13C	***Original Points Count*** 12000	***Points Count*** 16384	***Solvent***	cdcl3
Sweep Width (Hz)	20000.00	***Temperature (grad C)***	29.000				



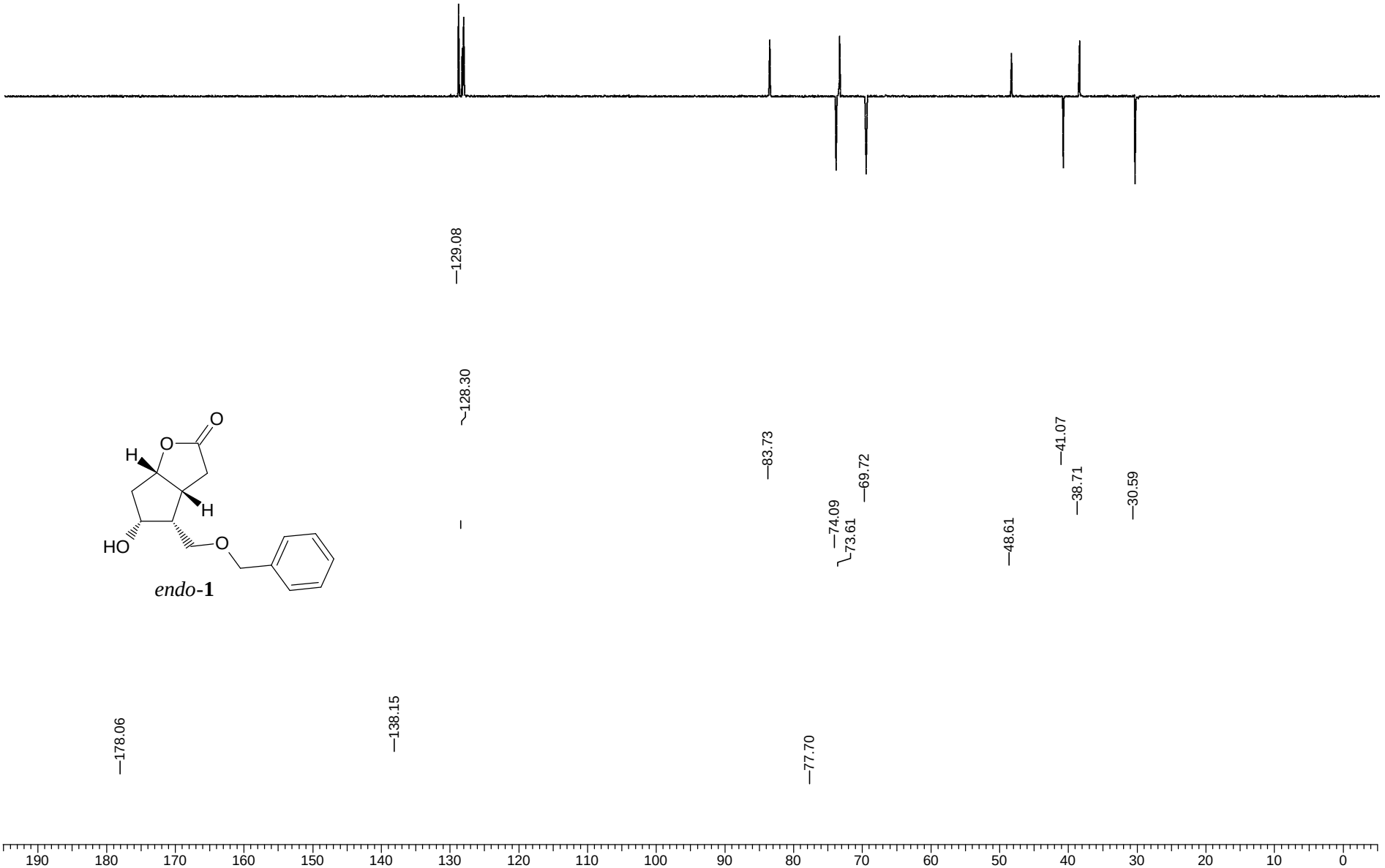
exo-**1**

Acquisition Time (sec)	3.6405			***Comment***		***Date***	7-13-00	***Frequency (MHz)***	300.08
Nucleus	1H	***Number of Transients***	16	***Original Points Count***	12000			***Points Count***	16384
Solvent	cdcl3	***Sweep Width (Hz)***	4500.45			***Temperature (grad C)***	29.000		



endo-**1**

Acquisition Time (sec)	0.8192	***Comment***				***Date***	7-13-00
Frequency (MHz)	75.46	***Nucleus***	13C	***Original Points Count*** 12000	***Points Count*** 16384	***Solvent***	cdcl3
Sweep Width (Hz)	20000.00	***Temperature (grad C)***	29.000				



endo-**1**