Determining a Synthetic Approach to Pierisformoside C

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Supporting Information

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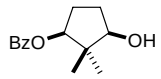
Materials and Methods

^{1}H and ^{13}C NMR spectra were recorded on Bruker AV300, AMX400 and/or DRX500 instruments using $CDCl_3$ (99.8 atom % D) as solvent. Coupling constants are given in Hz and chemical shifts are expressed as δ values in ppm. The residue solvent peaks were used as internal references (δ_H 7.24; δ_C 77.0). High resolution ESI mass spectral data were obtained on a Finnigan MAT 900XL or Bruker micrOTOF$_Q$ spectrometer. Column chromatography was undertaken on silica gel (flash silica gel 230–400 mesh), with distilled solvents. Anhydrous solvents were prepared according to Perin and Armarego, 'Purification of laboratory solvents', 3rd Ed. Fine chemicals were purchased from the Aldrich Chem. Co. Petroleum spirit constitutes the fraction boiling between 40-60°C. Melting points were measured on a Buchi Dr Tottoli apparatus and are uncorrected.

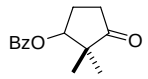
3-Hydroxy-2,2-dimethylcyclopentyl benzoate 21



To 2,2-dimethyl-1,3-cyclopentadione **13** (0.50 g, 4.0 mmol) in tetrahydrofuran (10 mL) was added $NaBH_4$ (0.18 g, 4.8 mmol) in water (1.5 mL). After stirring for 2.5 h water (2.5 mL) was added and the solution was acidified to pH ~2 with hydrochloric acid (2 M solution). The mixture was extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), and evaporated. 2,2-Dimethyl-1,3-cyclopentadiol was purified by column chromatography (EtOAc/petroleum spirit, 3:7), with the *cis*-isomer eluting first and then the *trans*-isomer in a 1:1 ratio. Both diols were obtained as a white solid (0.47 g, 90%). *cis-diol:* ^{1}H NMR (400 MHz, DMSO) δ 0.65 (s, 3H), 0.85 (s, 3H), 1.37-1.41 (m, 2H), 1.69-1.73 (m, 2H), 3.38-3.45 (m, 2H), 4.38 (d, *J* 4.1, 2H). ^{13}C NMR (100 MHz, DMSO) δ 13.3, 24.3, 28.4, 43.4, 76.5. M.p. 128-130°C. *trans-diol:* ^{1}H NMR (400 MHz, DMSO) δ 0.78 (s, 6H), 1.26-1.38 (m, 2H), 1.85-1.98 (m, 2H), 3.59-3.64 (m, 2H), 4.31 (bd, 2H). ^{13}C NMR (100 MHz, DMSO) δ 20.3, 29.7, 44.8, 77.5. M.p. 88-89°C.

C*is*-2,2-dimethylcyclopentane-1,3-diol[1] (0.10 g, 0.77 mmol) was dissolved in dry anhydrous pyridine (2 mL) and stirred under an argon atmosphere. Benzoyl chloride (89 μL, 0.77 mmol) was added dropwise. After 3 h of stirring at room temperature the reaction mixture was diluted with water (10 mL), followed by extraction with dichloromethane (3 × 5 mL). The combined organic phases were dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (EtOAc /petroleum spirit 1:3) to afford the desired alcohol **21** (0.12 g, 64%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (s, 3H), 1.09 (s, 3H), 1.75-1.91 (m, 2H), 2.09-2.28 (m, 2H), 3.80 (dd, *J* 6.7, 5.0, 1H), 5.02 (dd, *J* 6.9, 4.6, 1H), 7.42 (m, 2H), 7.53 (m, 1H), 8.01 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.0, 25.1, 28.1, 30.8, 45.7, 79.7, 82.0, 128.4 (2C), 129.5 (2C), 130.1, 132.9, 171.1. HRESIMS *m/z* 257.1148 (calcd for $C_{14}H_{18}O_3Na$, 257.1154).

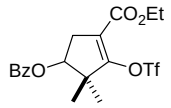
2,2-Dimethyl-3-oxocyclopentyl benzoate 22



[1] Herein we report the mono-protection of the *cis*-diol **13**. On other occasions, a mixture of the *cis*- and *trans*-diols **13** was protected and then oxidised directly, under the same conditions, to give the same benzoate **22**.

3-Hydroxy-2,2-dimethylcyclopentyl benzoate **21** (0.12 g, 0.49 mmol) was dissolved in anhydrous dichloromethane (2 mL) under an argon atmosphere and a few pre-dried 4Å molecular sieves was added. *N*-Methyl morpholine *N*-oxide (0.097 g, 0.83 mmol) and tetrapropylammonium perruthenate (TPAP, 7.4 mg, 4 mol%) were then added. The mixture was stirred for 80 min and then eluted (EtOAc) through silica. The residue was purified by column chromatography (EtOAc /petroleum spirit 1:4) affording the title ketone **22** (0.11 g, 95%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (s, 3H), 1.11 (s, 3H), 2.07-2.12 (m, 1H), 2.34-2.51 (m, 3H), 5.34 (m, 1H), 7.41 (m, 2H), 7.53 (m, 1H), 7.97 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.7, 22.5, 25.4, 34.0, 49.3, 80.2, 128.4 (2C), 129.5 (2C), 129.9, 133.1, 165.7, 219.5. HRESIMS *m/z* 255.0992 (calcd for $C_{14}H_{16}O_3Na$, 255.0997).

4-(Ethoxycarbonyl)-2,2-dimethyl-3-(trifluoromethylsulfonyloxy)cyclopent-3-enyl benzoate 23

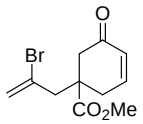


Mander's reaction. 2,2-Dimethyl-3-oxocyclopentyl benzoate **22** (0.10 g, 0.43 mmol) was dissolved in anhydrous THF (2 mL) under an argon atmosphere. To this was added hexamethylphosphoramide (HMPA, 0.12 mL, 0.69 mmol) followed by cooling to –78 °C. Diisopropylamine (0.072 mL, 0.51 mmol) was added to THF (1 mL) under an argon atmosphere. Upon cooling to 0 °C, ^{n}BuLi solution (1.3 M in THF, 0.36 mL) was added and the solution was stirred for 10 min before addition to the above solution. After 1 h of stirring, ethyl cyanoformate (0.047 mL, 0.47 mmol) was added and the reaction was allowed to warm to room temperature over 18 h. The reaction was quenched with saturated NH_4Cl solution. The mixture was diluted with water (10 mL) and extracted with Et_2O (3 × 5 mL). The combined organic phases were dried ($MgSO_4$), concentrated and the residue was purified by column chromatography (Et_2O/petroleum spirit 1:1) to afford a diastereomeric mixture of 4-(ethoxycarbonyl)-2,2-dimethyl-3-oxocyclopentyl benzoate (95 mg, 73%) as a pale yellow oil, which was used in the next reaction directly.

Triflate formation. 4-(Ethoxycarbonyl)-2,2-dimethyl-3-oxocyclopentyl benzoate (95 mg, 0.31 mmol) was dissolved in THF (2 mL) and cooled to –78 °C. Diisopropylamine (0.052 mL, 0.37 mmol) was added to THF (1 mL) under an argon atmosphere and cooled to 0 °C, ^{n}BuLi solution (1.3 M in THF, 0.26 mL) was added and the mixture was stirred at 0 °C for 10 min before adding to the above solution. After 1 h of stirring, trifluoromethanesulfonic anhydride (0.11 mL, 0.63 mmol) was added and the reaction was stirred at –78 °C for 3h. The reaction was quenched with saturated NH_4Cl solution, then diluted with water (10 mL) and extracted with Et_2O (3 × 5 mL). The

combined organic phases were dried ($MgSO_4$), concentrated and the residue was purified by column chromatography (EtOAc/petroleum spirit 1:1) to give triflate **23** (0.13 g, 92%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (s, 3H), 1.29 (s, 3H), 1.31 (t, *J* 7.2, 3H), 2.75 (dd, *J* 16.9, 3.8, 1H), 3.23 (dd, *J* 17.0, 6.9, 1H), 4.28 (q, *J* 7.4, 2H), 5.26 (dd, *J* 6.7, 3.8, 1H), 7.44 (m, 2H), 7.58 (m, 1H), 8.02 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 18.1, 23.4, 34.3, 48.6, 61.5, 76.9, 118.5 (q, $J_{C\text{-}F}$ 320.4), 118.7, 128.5 (2C), 129.5, 129.6 (2C), 133.4, 156.3, 162.1, 165.8. HRESIMS *m/z* 459.0696 (calcd for $C_{18}H_{19}F_3O_7SNa$, 459.0701).

Methyl 1-(2-bromoallyl)-5-oxocyclohex-3-enecarboxylate 16



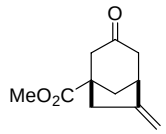
Birch reduction. Following the combined methods of Marinovic and Smith,[2] to liquid ammonia (180 mL) at –78 °C was added a solution of 3-methoxybenzoic acid 15 (5.41 g, 35.5 mmol) in anhydrous THF (35 mL) followed by lithium metal (0.74 g, 0.11 mmol) until the blue colour persisted. The blue solution was stirred for 1 h before rapid dropwise addition of 2,3-dibromopropene (5.14 mL, 49.8 mmol). After a further 1 h at –78 °C solid ammonium chloride (9.50 g, 178 mmol) was added and the ammonia was allowed to evaporate overnight. Hydrochloric acid (3 N, 180 mL) was added to the residue and refluxed for 20 min. On cooling the reaction mixture was extracted with Et_2O (3 × 60 mL). The combined organic layers were extracted with $NaHCO_3$ solution (10%, 2 × 90 mL). The aqueous phase was acidified with conc. hydrochloric acid to pH 2 and then reextracted with Et_2O (5 × 60 mL) and dried ($MgSO_4$). Upon solvent evaporation, 1-(2-bromoprop-2-en-1-yl)-5-oxocyclohex-3-ene-1-carboxylic acid (6.9 g, 76%) was obtained and used in the next step without further purification.

Esterification. 1-(2-Bromoallyl)-5-oxocyclohex-3-enecarboxylic acid (6.5 g, 25 mmol) was suspended in Et_2O (200 mL) and diazomethane in Et_2O was added in portions at 5 °C, until all solid was dissolved. The reaction was allowed to warm to room temperature. After 2 h the ethereal solution was washed with saturated $NaHCO_3$ solution (75 mL), dried ($NaSO_4$), filtrated and concentrated under vacuo. The residue was subjected to column chromatography (EtOAc/petroleum spirit, 1:1), to give compound **18** (6.2 g, 90%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.47 (d, *J* 16.5, 1H), 2.49 (ddd, *J* 18.4, 3.4, 2.8, 1H), 2.82 (d, *J* 14.6, 1H), 2.89 (ddd, *J* 18.5, 5.2, 1.6, 1H), 2.90 (d, *J* 14.6, 1H), 2.94 (dd, *J* 16.4, 1.4, 1H), 3.67 (s, 3H), 5.56 (s, 2H), 6.02 (m, 1H), 6.85

[2] a) Marinovic, N.N.; Ramanathan, H. *Tetrahedron Lett.*, **1983**, *24*, 1871; b) Smith, A.B., III; Richmond, R.E. *J. Am. Chem. Soc.* **1983**, *105*, 575.

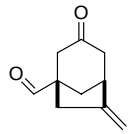
(ddd, *J* 10.1, 5.0, 3.4, 1H).[13]C NMR (100 MHz, $CDCl_3$) δ 33.9, 44.8, 48.3, 48.5, 52.6, 121.9, 126.6, 129.8, 146.7, 174.2, 196.3.

Methyl 6-methylene-3-oxobicyclo[3.2.1]octane-1-carboxylate 17



Following the method of Marinovic,[3] methyl 1-(2-bromoallyl)-5-oxocyclohex-3-enecarboxylate **16** (0.10 g, 0.36 mmol), tributyltinhydride (freshly distilled, 0.10 mL, 0.39 mmol) and recrystallised VAZO-64® (AIBN, 3 mg, 0.02 mmol) were dissolved in anhydrous toluene (2 mL) under an argon atmosphere. The solution was refluxed for 3 h. On cooling the solvent was evaporated and the oily residue was filtered through a pad of potassium fluoride/silica gel (containing 10% K_2CO_3) with dichloromethane. The residue was further purified by column chromatography (EtOAc/petroleum spirit, 1:3) to give the desired bicycle **17** (58 mg, 83%) as a colourless oil containing a trace of inseparable [3.3.1]-bicycle. [1]H NMR (500MHz, $CDCl_3$) δ 1.99 (dd, *J* 11.9, 2.5, 1H), 2.27 (dp, *J* 11.9, 2.7, 1H), 2.37-2.50 (m, 3H), 2.59 (dt, *J* 16.8, 2.5, 1H), 2.69 (dd, *J* 16.8, 2.8, 1H), 2.81 (dt, *J* 17.2, 2.8, 1H), 3.03 (m, 1H), 3.69 (s, 3H), 4.91 (bs, 1H), 4.99 (bt, 1H). [13]C NMR (125MHz, $CDCl_3$) δ 40.8, 41.3, 41.8, 49.7, 50.3, 50.6, 52.2, 108.9, 150.4, 174.9, 208.3.

6-Methylene-3-oxobicyclo[3.2.1]octane-1-carbaldehyde 28



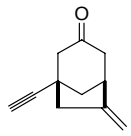
Reduction. Methyl 6-methylene-3-oxobicyclo[3.2.1]octane-1-carboxylate **17** (2.00 g, 10.3 mmol) was dissolved in anhydrous THF (100 mL) under an argon atmosphere. Lithium aluminium hydride ($LiAlH_4$, 1.17 g, 30.9 mmol) was added portion wise at 0 °C, and the suspension was stirred at room temperature for 4 h. The reaction was quenched with $Na_2SO_4 \cdot 10H_2O$ and the mixture was stirred for 30 min. The white solid was filtered off and rinsed with dichloromethane. The combined organic phases were dried ($MgSO_4$) and concentrated under vacuo. After flash chromatography (Et_2O), 1-(hydroxymethyl)-6-methylenebicyclo[3.2.1]octan-3-ol (1.3 g, 75%) was obtained as two column separable diastereomers, both in the form of a colourless oil. *First eluted diol:* [1]H NMR (400 MHz,

[3] Marinovic, N.N.; Ramanathan, H. *Tetrahedron Lett.*, **1983**, *24*, 1871.

$CDCl_3$) δ 1.28 (dd, *J* 10.9, 2.7, 1H), 1.35 (t, *J* 6.0, 1H), 1.63 (m, 1H), 1.80 (ddd, *J* 14.1, 4.7, 1.7, 1H), 1.86 (m, 1H), 1.94 (dt, *J* 3.5, 1.0, 1H), 2.19 (d, *J* 7.5, 1H), 2.23 (ddd, *J* 16.6, 4.7, 2.5, 1H), 2.61 (m, 1H), 2.76 (m, 1H), 3.51 (dd, *J* 5.6, 2.1, 2H), 4.08 (m, 1H), 4.92 (m, 1H), 5.08 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.5, 40.7, 41.5, 41.6, 43.0, 44.6, 67.1, 70.6, 106.7, 155.9. *Second eluted diol:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29-1.42 (m, 5H), 1.54 (m, 1H), 1.95 (ddt, *J* 12.0, 6.0, 2.0, 1H), 2.03 (dddt, *J* 11.9, 6.2, 4.6, 1.8, 1H), 2.16 (m, 1H), 2.74 (bt, *J* 5.3, 1H), 3.50 (d, *J* 5.8, 2H), 3.96 (m, 1H), 4.77 (m, 1H), 4.88 (tt, *J* 2.6, 1.0, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.4, 40.7, 42.5, 43.26, 43.31, 46.0, 66.4, 70.1, 105.1, 153.9. HRESIMS *m/z* 191.1043 (calcd for $C_{10}H_{16}O_2Na$, 191.1048).

Oxidation. 1-(Hydroxymethyl)-6-methylidenebicyclo[3.2.1]octan-3-ol (0.26 g, 1.6 mmol) was dissolved in anhydrous dichloromethane (100 mL) under an argon atmosphere and a few pre-dried 4Å molecular sieves were added. *N*-Methyl morpholine *N*-oxide (0.40 g, 3.4 mmol) and tetrapropylammonium perruthenate (52 mg, 0.15 mmol) were added. The mixture was stirred at room temperature for 3 h and then eluted with EtOAc through a plug of silica. The solvent was evaporated and residue was purified by column chromatography (Et_2O/petroleum spirit 1:8) to afford the title aldehyde **28** (0.86 g, 68%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.83 (dd, *J* 11.7, 2.7, 1H), 2.19 (dddd, *J* 11.7, 5.4, 2.9, 2.1, 1H), 2.32 (m, 1H), 2.46 (m, 2H), 2.53 (dd, *J* 16.6, 3.8, 1H), 2.68 (dd, *J* 16.6, 2.9, 1H), 2.76 (dq, *J* 16.9, 2.9, 1H), 3.12 (m, 1H), 5.00 (m, 1H), 5.09 (ddd, *J* 3.0, 2.1, 0.9, 1H), 9.56 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.65, 38.69, 41.9, 46.9, 50.9, 55.2, 109.7, 149.9, 201.4, 208.1. HRESIMS *m/z* 219.0992 (calcd for $C_{10}H_{12}O_2Na+CH_3OH$, 219.0997).

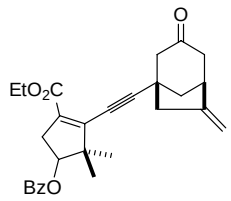
1-Ethynyl-6-methylenebicyclo[3.2.1]octan-3-one 27



6-Methylene-3-oxobicyclo[3.2.1]octane-1-carbaldehyde **28** (0.10 g, 0.58 mmol) was dissolved in anhydrous 1% dichloromethane in methanol (2 mL). To this solution was added diethyl (1-diazo-2-oxopropyl)phosphonate **20** (0.25 g, 1.1 mmol) and potassium carbonate (0.25 g, 1.8 mmol). The mixture was stirred at room temperature for 2 h. The solid was filtered off, washed with Et_2O and solvent was then evaporated. The residue was purified by column chromatography (Et_2O/petroleum spirit 1:9) affording the title acetylene **27** (69 mg, 71%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.07 (dd, *J* 11.9, 2.4, 1H), 2.21 (m, 1H), 2.22 (s, 1H), 2.37 (dddd, *J*

15.9, 3.5, 2.0, 1.2, 1H), 2.47 (dd, *J* 16.2, 3.7, 1H), 2.54 (m, 1H), 2.60 (m, 2H), 2.66 (ddd, *J* 17.2, 5.3, 2.7, 1H), 2.99 (m, 1H), 4.91 (bs, 1H), 4.97 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.7, 41.5, 44.0, 44.9, 50.5, 53.7, 69.7, 87.1,[4] 109.0, 150.5, 207.9. HRESIMS *m/z* 183.0780 (calcd for $C_{11}H_{12}ONa$, 183.0786).

Acetylene 29

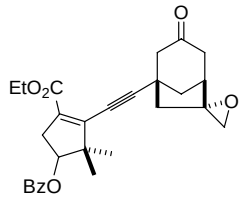


Following the method of Jacobi,[5] to a dry flask was placed CuI (5 mg, 10 μmol) and tetrakis(triphenylphosphine)palladium(0) (15 mg, 13 μmol) under an argon atmosphere. Compound **23** (110 mg, 0.25 mmol) in anhydrous THF (1 mL) and anhydrous triethylamine (0.10 mL, 0.75 mmol) was added to the above mixture. After 10 min, 1-ethynyl-6-methylidenebicyclo[3.2.1]octan-3-one **27** (56 mg, 0.35 mmol) in anhydrous THF (0.5 mL) was added, and the solution darkened after stirring for a minute. The reaction was stirred for 5 h at room temperature, followed by diluting with brine and extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with saturated NH_4Cl solution, dried ($MgSO_4$) and concentrated under vacuo. The residue was purified by column chromatography (EtOAc/petroleum spirit 1:3) affording the title product **29** (81 mg, 72%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (s, 3H), 1.20 (s, 3H), 1.30 (t, *J* 7.1, 3H), 2.15 (dd, *J* 11.9, 2.4, 1H), 2.30 (dtt, *J* 11.9, 5.1, 2.1, 1H), 2.41 (m, 1H), 2.50 (dd, *J* 16.0, 3.6, 1H), 2.60-2.77 (m, 5H), 3.03 (m, 1H), 3.20 (dd, *J* 18.1, 6.6, 1H), 4.21 (q, *J* 7.1, 2H), 4.93 (bs, 1H), 5.00 (bt, *J* 2.2, 1H), 5.24 (dd, *J* 6.7, 4.0, 1H), 7.41 (m, 2H), 7.54 (m, 1H), 8.01 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 20.0, 25.2, 37.4, 39.0, 41.6, 44.0, 45.0, 50.6, 52.1, 53.5, 60.6, 76.4, 79.4, 105.1, 109.1, 128.4 (2C), 129.6 (2C), 130.1, 132.5, 133.1, 141.3, 150.4, 164.1, 166.1, 207.7. HRESIMS *m/z* 469.1991 (calcd for $C_{28}H_{30}O_5Na$, 469.1991).

[4] This ^{13}C NMR data was extracted from 2D NMR HMBC experiment.

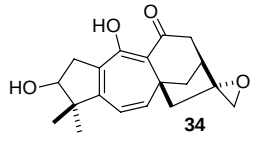
[5] Jacobi, P. A.; DeSimone, R. W.; Ghosh, I.,; Guo, J.; Leung, S. H.; Pippin, D. *J. Org. Chem.*, **2000**, *65*, 8478.

Epoxide 33

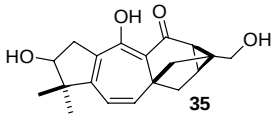


mCPBA (77%, 4.0 mg, 16 μmol) and $NaHCO_3$ (10 mg, 100 μmol) were added respectively to the acetylene **29** (5.7 mg, 13 μmol) in dichloromethane (0.3 mL) at 0°C. The suspension was stirred at the same temperature for 1 h, and then slowly warmed to room temperature. After another 4.5 h of stirring, the reaction was poured into a Na_2SO_3 solution (10%) and extracted with dichloromethane (3 × 2 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution and brine. Upon solvent evaporation, the residue was purified by flash chromatography (EtOAc/petroleum spirit 1:3) to give 3 fractions, with the first being the recovered starting material **29** (1.2 mg, 21%), followed by the major epoxide **33** (2.3 mg, 39%) and the last as a mixture of the major and minor epoxides (1.0 mg, major : minor ≈ 2:3, 17%). ^{1}H NMR (MHz, $CDCl_3$) δ 1.20 (d, *J* 0.7, 3H), 1.21 (d, *J* 1.0, 3H), 1.30 (t, *J* 7.2, 3H), 2.17 (m, 1H), 2.19 (dd, *J* 12.0, 1.6, 1H), 2.25 (dd, *J* 15.0, 1.5, 1H), 2.31 (dd, *J* 14.9, 1.7, 1H), 2.43 (m, 1H), 2.49 (dd, *J* 16.6, 4.1, 1H), 2.59 (m, 1H), 2.74 (m, 3H), 2.79 (d, *J* 4.4, 1H), 2.85 (d, *J* 4.4, 1H), 3.21 (dd, *J* 18.2, 6.6, 1H), 4.22, (q, *J* 7.2, 2H), 5.27 (dd, *J* 6.7, 3.8, 1H), 7.43 (m, 2H), 7.55, (m, 1H), 8.01 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 20.0, 25.2, 37.4, 39.5, 41.8, 42.8, 44.2, 46.1, 50.1, 52.1, 54.3, 60.6, 65.5, 76.5, 79.4, 104.2, 128.4 (2C), 129.6 (2C), 130.1, 132.9, 133.1, 141.0, 164.1, 166.1, 206.9. HRESIMS *m/z* 485.1935 (calcd for $C_{28}H_{30}O_6Na$, 485.1940).

34 and **35**



34



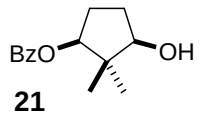
35

To a flask with epoxide **33** (diastereomeric at the benzoate centre, 2.2 mg, 4.8 μmol) and Lindlar catalyst (5% Pd loading, 1 mg) in THF (1.2 mL) was charged with hydrogen. The suspension was stirred at room temperature for 1 h. The reaction was filtered through a pad of celite. After drying thoroughly under vacuum, anhydrous THF (2 mL) was added to the crude *cis*-alkene under an argon

atmosphere. NaOMe in methanol (2 M, 10 μL) was then added dropwise. A pale yellow colour resulted from the addition and the colour slowly intensified over time. The reaction was allowed to stir for 10 h, and then poured into saturated $NaHCO_3$ solution. The aqueous phase was separated and re-extracted with EtOAc (3 × 2 mL). The combined organic layers were washed with brine, dried and concentrated under vacuo. Partial separation of the diastereomers of **34** was achievable by column chromatography (EtOAc/petroleum spirit 1:3). The first and last fractions were mostly a single diastereomer and the middle as a mixture of both (0.7 mg in total, 47%). The doubly cyclised material **35** (0.3 mg, 20%) was eluted last from the column. *First eluted diastereomer of **34:*** ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.04 (s, 3H), 1.06 (s, 3H), 1.50 (d, *J* 6.7, 1H), 1.76 (d, *J* 13.6, 1H), 1.97 (dd, *J* 11.7, 2.6, 1H), 2.05 (dt, *J* 5.8, 1.6, 1H), 2.25 (ddd, *J* 11.7, 6.1, 2.6, 1H), 2.41 (dt, *J* 19.2, 2.2, 1H), 2.46 (dd, *J* 13.5, 2.5, 1H), 2.68 (ddt, *J* 16.6, 7.7, 1.1, 1H), 2.72 (dd, *J* 19.2, 5.5, 1H), 2.81 (d, *J* 4.6, 1H), 2.83 (d, *J* 4.6, 1H), 2.89 (dd, *J* 16.6, 7.1, 1H), 3.97 (q, *J* 7.2, 1H), 5.83 (d, *J* 11.2, 1H), 5.91 (dd, *J* 11.2, 1.7, 1H), 16.67 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.5, 24.9, 38.0, 38.7, 42.4, 44.6, 45.3, 45.5, 49.8, 51.0, 66.8, 78.5, 118.2, 123.6, 132.1, 140.2, 155.5, 174.7, 194.6. HRESIMS *m/z* 337.1410 (calcd for $C_{19}H_{22}O_4Na$, 337.1416). *Second eluted diastereomer of **34:*** ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.07 (s, 6H), 1.41 (d, *J* 5.3, 1H), 1.77 (d, *J* 13.5, 1H), 1.97 (dd, *J* 11.7, 2.6, 1H), 2.05 (m, 1H), 2.26 (ddd, *J* 11.5, 6.0, 2.6, 1H), 2.41 (dt, *J* 19.1, 2.2, 1H), 2.51 (dd, *J* 17.5, 2.7, 1H), 2.52 (d, *J* 13.6, 2.8, 1H), 2.72 (dd, *J* 19.1, 5.5, 1H), 2.83 (s, 2H), 3.19 (m, 1H), 3.97 (dt, *J* 5.4, 2.7, 1H), 5.84 (d, *J* 11.0, 1H), 5.93 (dd, *J* 11.2, 1.4, 1H), 16.62 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.4, 24.5, 38.0, 39.8, 42.4, 44.6, 45.2, 45.6, 51.0, 51.5, 66.8, 77.8, 118.3, 123.4, 132.8, 139.9, 155.1, 175.0, 194.5. ***35:*** ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02 (s, 6H), 1.40 (bs, 1H), 1.44 (bs, 1H), 1.69 (dd, *J* 7.7, 2.8, 1H), 1.76 (d, *J* 12.3, 1H), 1.78 (dd, *J* 12.1, 2.7, 1H), 1.88 (m, 2H), 1.99 (d, *J* 7.8, 1H), 2.50 (dd, *J* 17.4, 5.2, 1H), 2.98 (ddd, *J* 17.5, 6.5, 5.0, 1H), 3.75 (d, *J* 12.2, 1H), 3.80 (d, *J* 12.2, 1H), 3.86 (m, 1H), 5.45 (d, *J* 12.2, 1H), 5.52 (d, *J* 12.2, 1H), 17.1 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.8, 20.7, 24.5, 31.0 (2C), 38.5, 43.6, 44.7, 45.5, 50.8, 63.7, 77.2, 111.1, 118.9, 130.6, 141.2, 151.9, 169.9, 195.8.[6] HRESIMS *m/z* 337.1410 (calcd for $C_{19}H_{22}O_4Na$, 337.1416).

[6] This ^{13}C NMR data was extracted from 2D NMR HMBC experiment.

400 MHz, $CDCl_3$



21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PROCNO                 1
Date_           20100810
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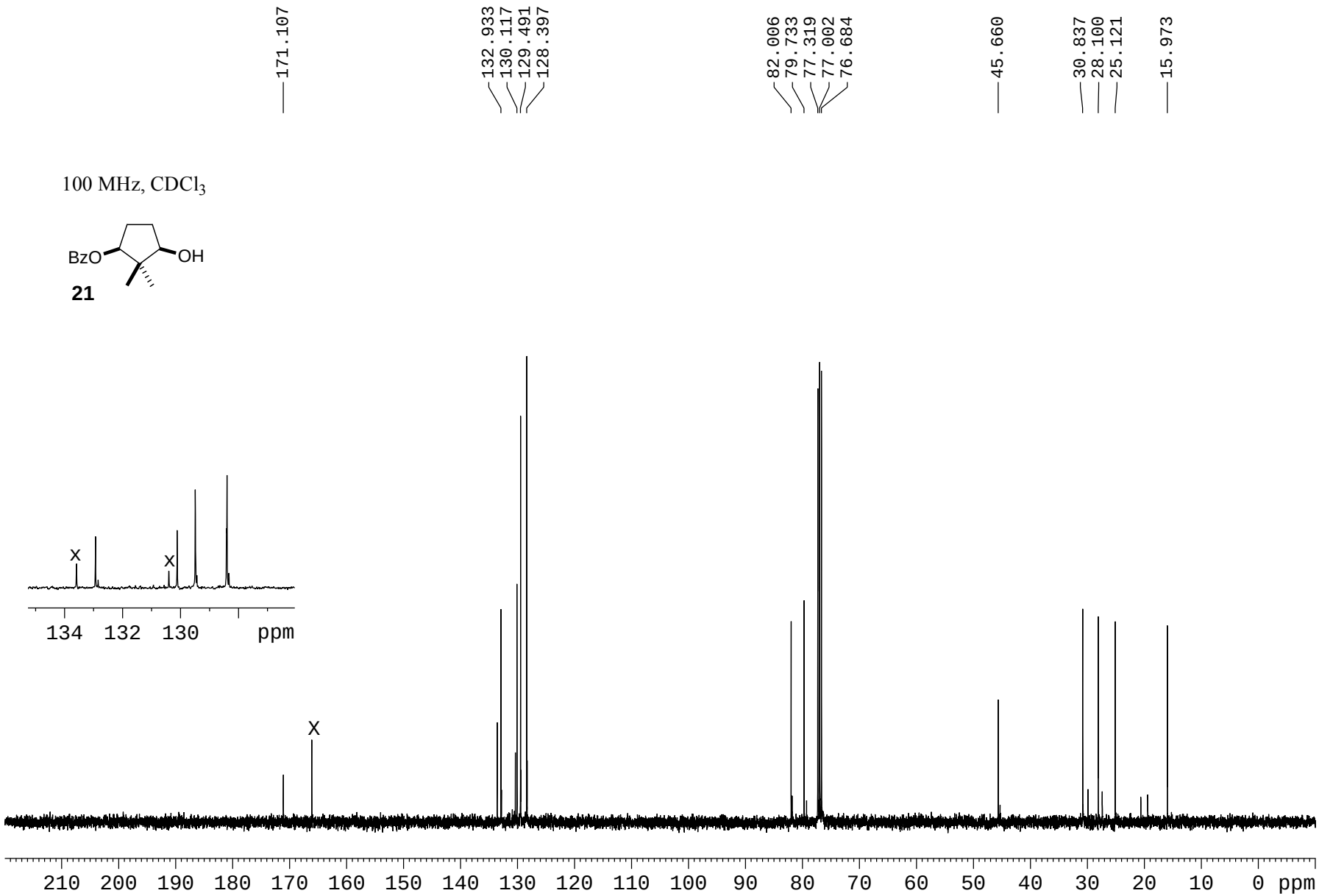
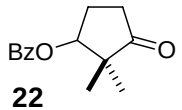
INSTRUM            spect
PROBHD   5 mm Multinucl
PULPROG             zg45
TD                 32768
SOLVENT            CDCl3
NS                    32
DS                     0
SWH             4807.692 Hz
FIDRES          0.146719 Hz
AQ              3.4080260 sec
RG                    57
DW                104.000 usec
DE                 12.00 usec
TE                 298.0 K
D1              2.00000000 sec
TD0                    1

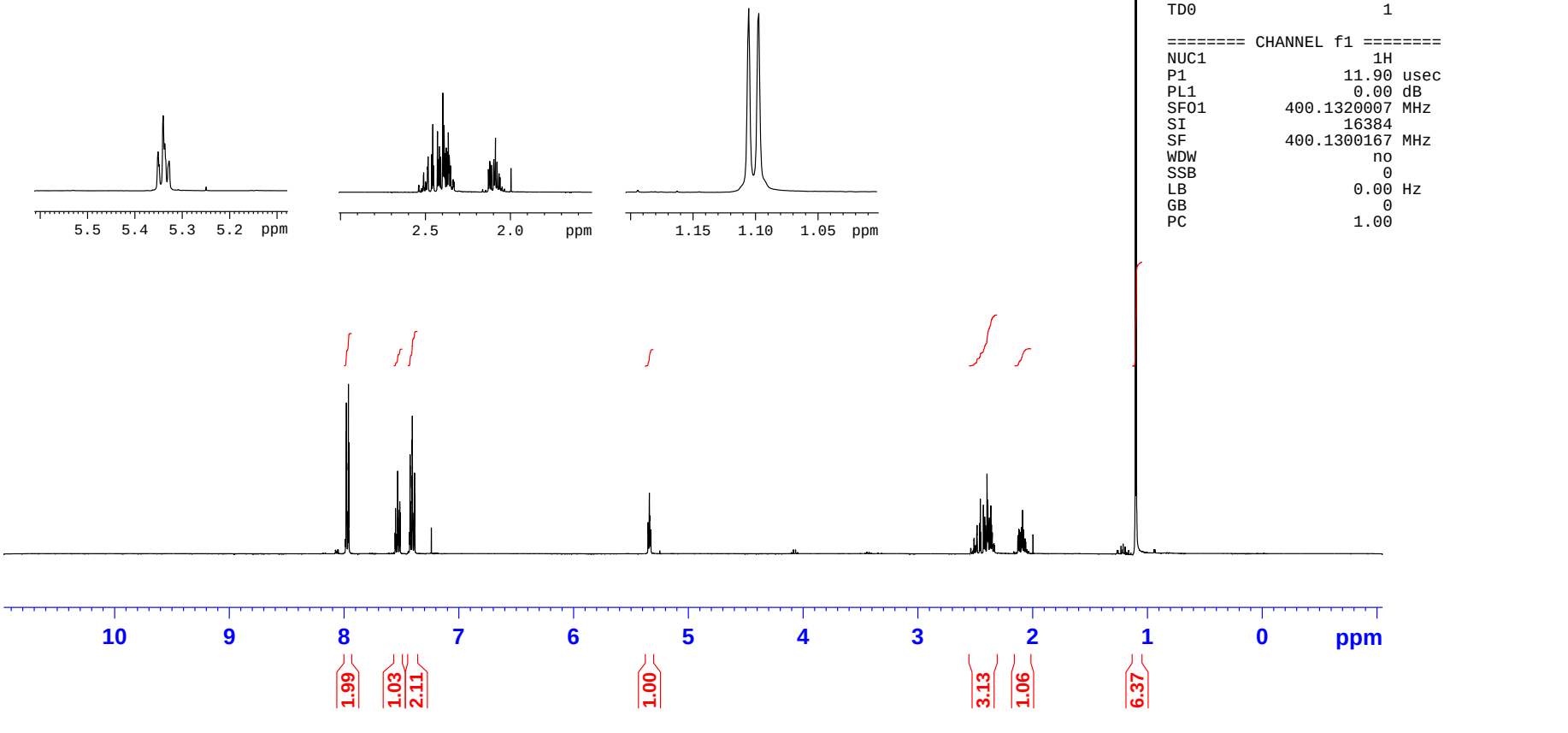
======== CHANNEL f1 ========
NUC1                  1H
P1                 11.90 usec
PL1                 0.00 dB
SFO1          400.1320007 MHz
SI                 16384
SF            400.1300169 MHz
WDW                   no
SSB                    0
LB                  0.00 Hz
GB                     0
PC                  1.00
```


171.107
132.933
130.117
129.491
128.397
82.006
79.733
77.319
77.002
76.684
45.660
30.837
28.100
25.121
15.973
100 MHz, CDCl3
BzO
OH
21
X
X
X
134 132 130 ppm
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

400 MHz, $CDCl_3$



22

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PROCNO                  1
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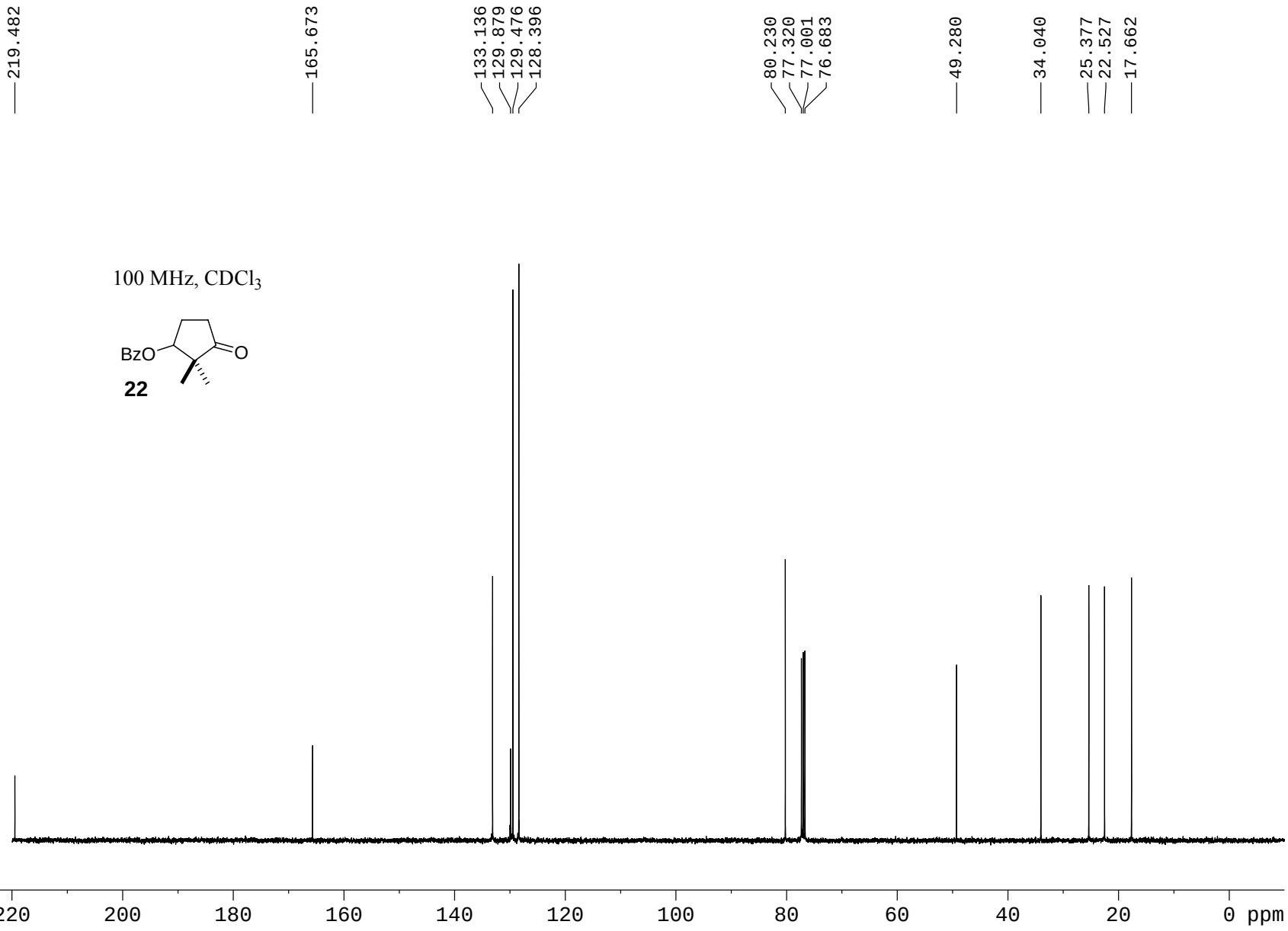
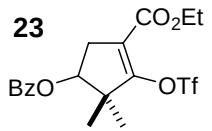
Time                10.29
INSTRUM             spect
PROBHD   5 mm Multinucl
PULPROG              zg45
TD                  32768
SOLVENT             CDCl3
NS                     32
DS                      0
SWH             4807.692 Hz
FIDRES          0.146719 Hz
AQ              3.4080260 sec
RG                   35.9
DW                104.000 usec
DE                 12.00 usec
TE                 298.0 K
D1             2.00000000 sec
TD0                     1

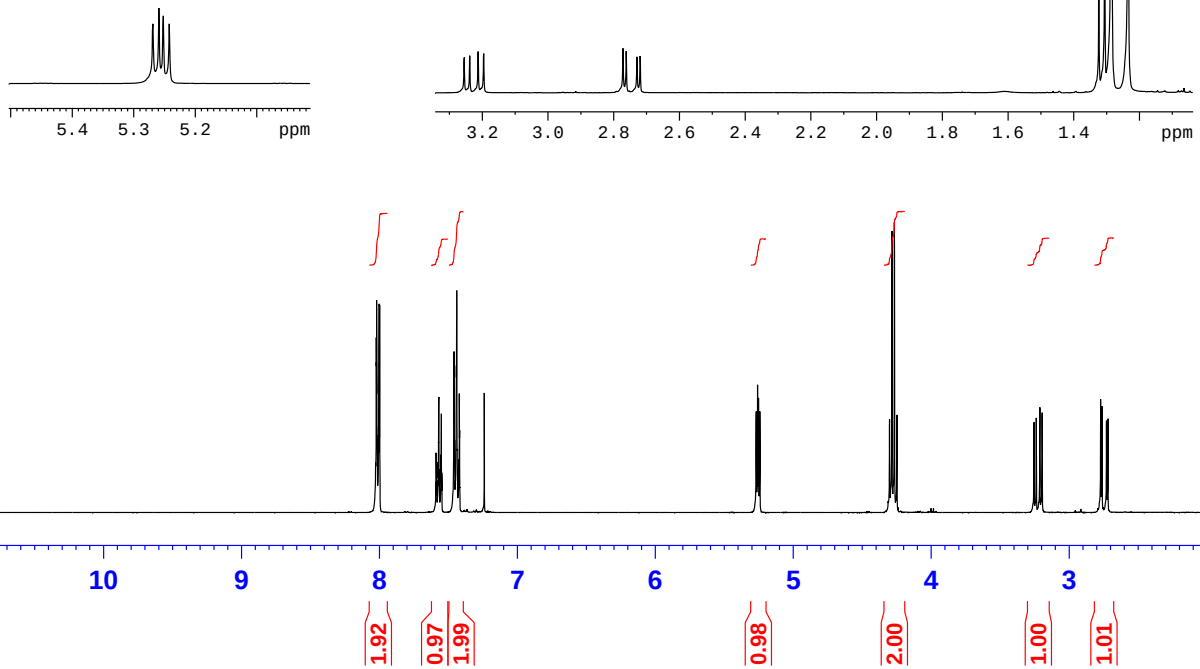
======== CHANNEL f1 ========
NUC1                   1H
P1                  11.90 usec
PL1                  0.00 dB
SFO1          400.1320007 MHz
SI                  16384
SF            400.1300167 MHz
WDW                    no
SSB                     0
LB                   0.00 Hz
GB                      0
PC                   1.00
```


219.482
165.673
133.136
129.879
129.476
128.396
80.230
77.320
77.001
76.683
49.280
34.040
25.377
22.527
17.662
100 MHz, CDCl3
BzO
O
22
220
200
180
160
140
120
100
80
60
40
20
0 ppm

400 MHz, $CDCl_3$

23



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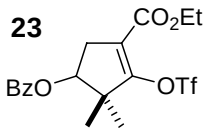
PROCNO                   1
Date_             20100810
Time                 10.51
INSTRUM              spect
PROBHD   5 mm Multinucl
PULPROG               zg45
TD                   32768
SOLVENT              CDCl3
NS                      32
DS                       0
SWH              4807.692 Hz
FIDRES          0.146719 Hz
AQ              3.4080260 sec
RG                      64
DW                104.000 usec
DE                 12.00 usec
TE                 298.0 K
D1            2.00000000 sec
TD0                      1

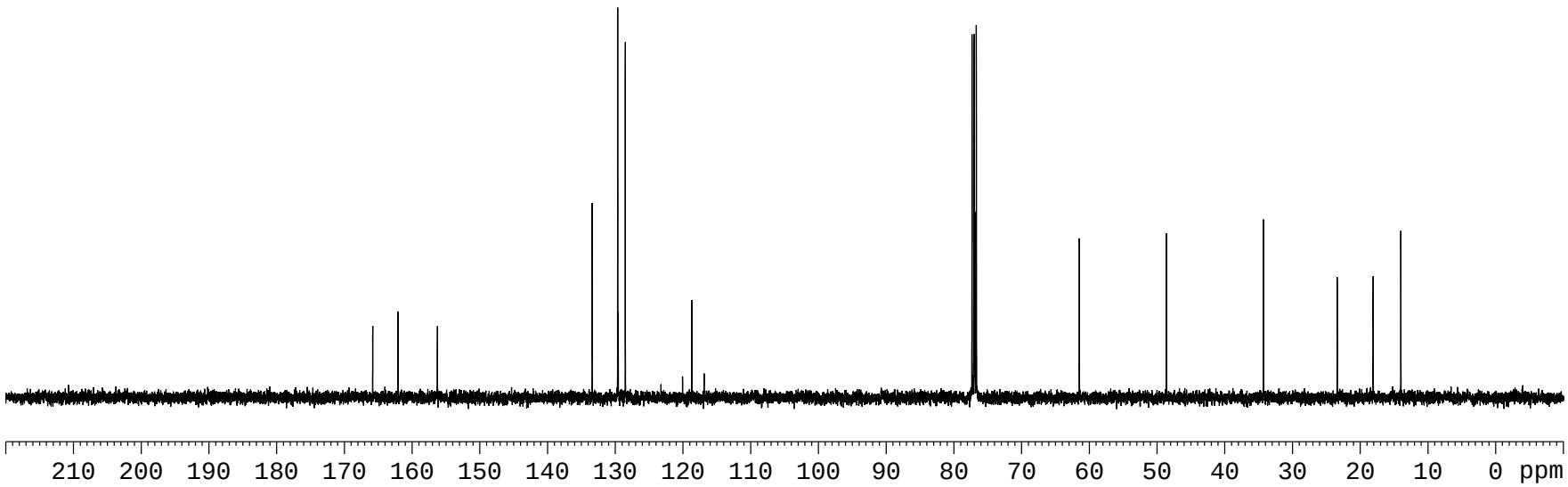
======== CHANNEL f1 ========
NUC1                    1H
P1                   11.90 usec
PL1                   0.00 dB
SFO1          400.1320007 MHz
SI                   16384
SF            400.1300167 MHz
WDW                     no
SSB                      0
LB                    0.00 Hz
GB                       0
PC                    1.00
```

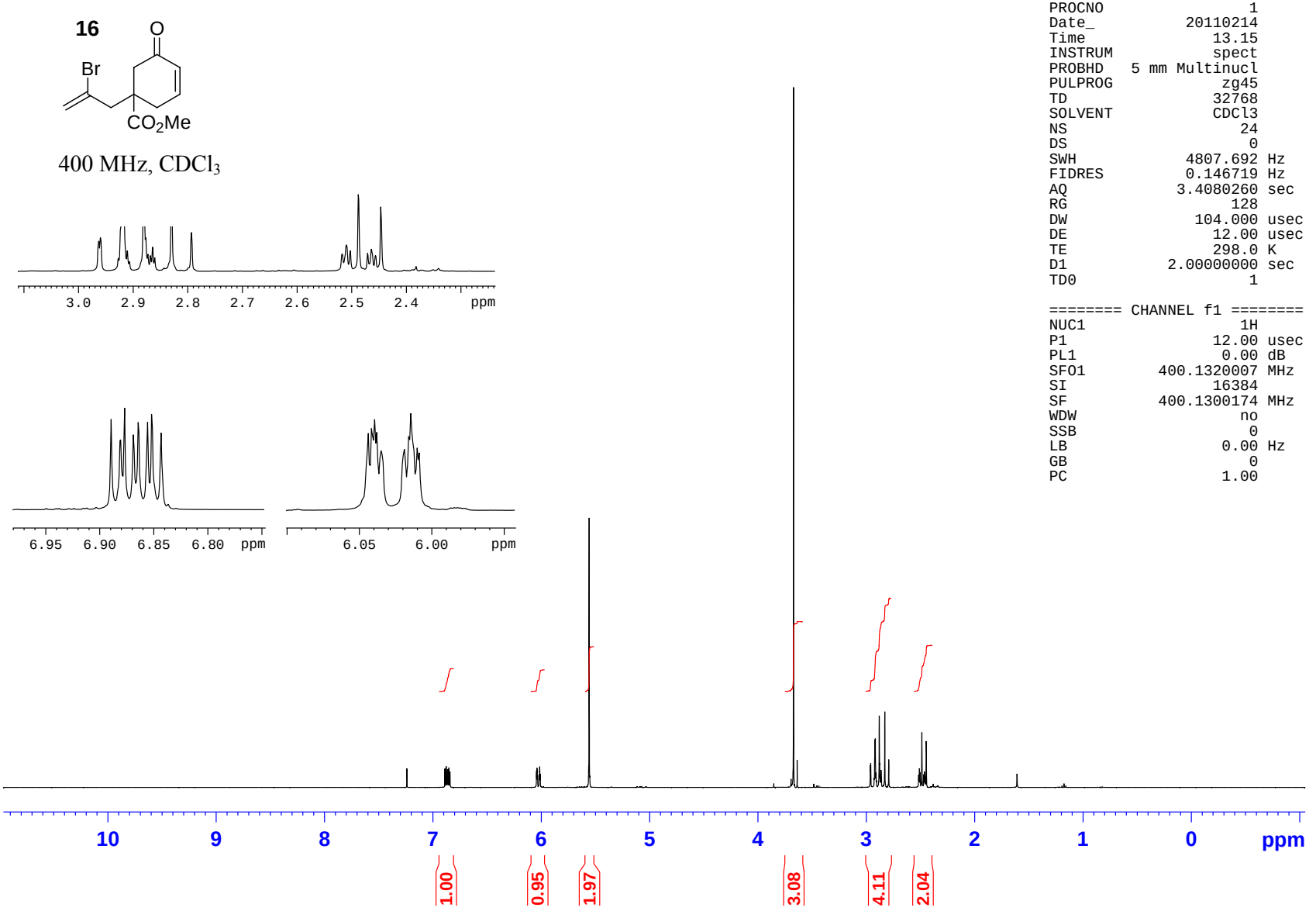
165.818
162.080
156.264
133.398
123.245
120.064
118.682
116.878
77.318
76.999
76.913
76.682
61.477
48.624
34.288
23.396
18.092
13.999

100 MHz, $CDCl_3$

23





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EXPNO                  1
PROCNO                 1
Date_           20110214
Time               13.15
INSTRUM            spect
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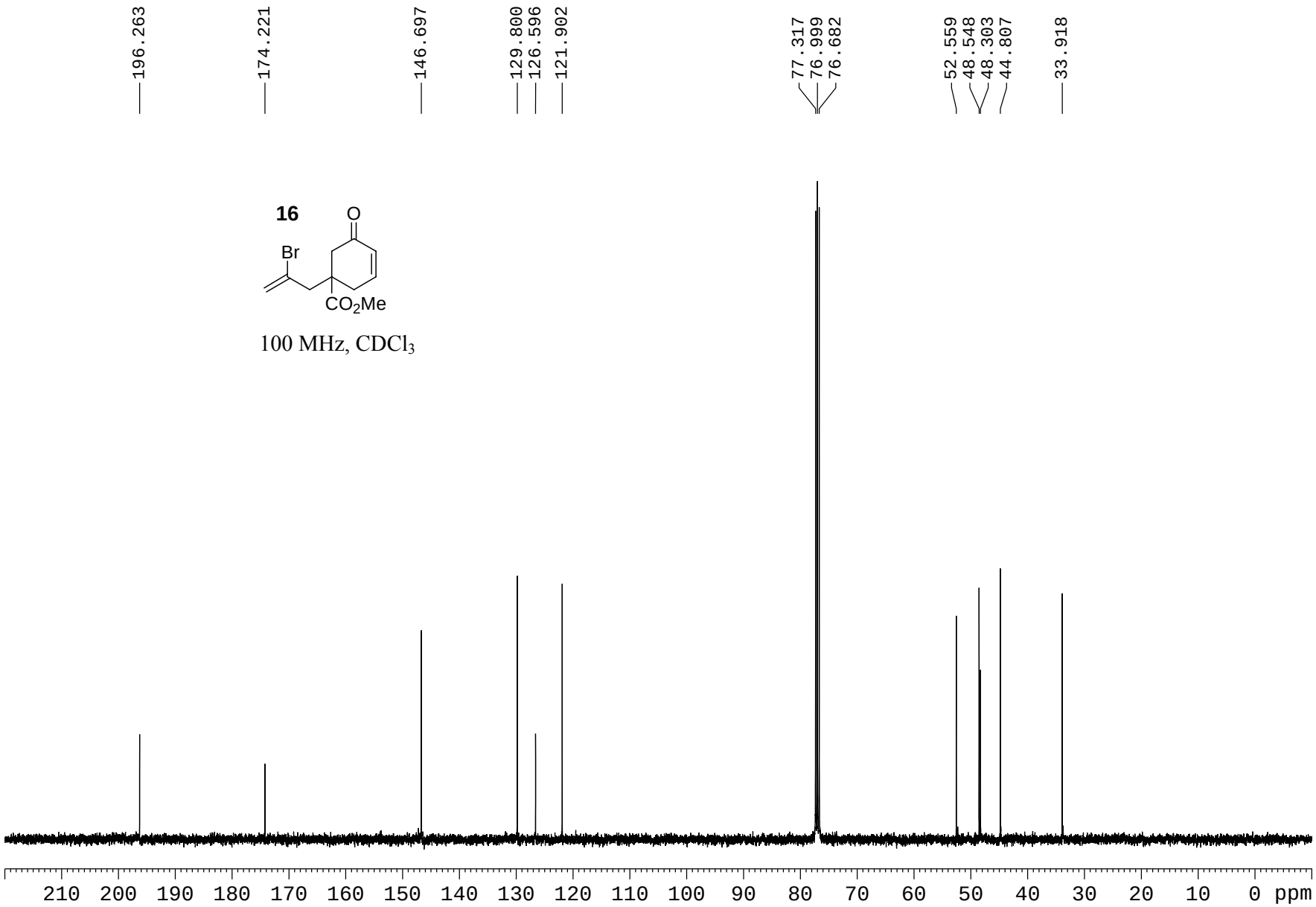
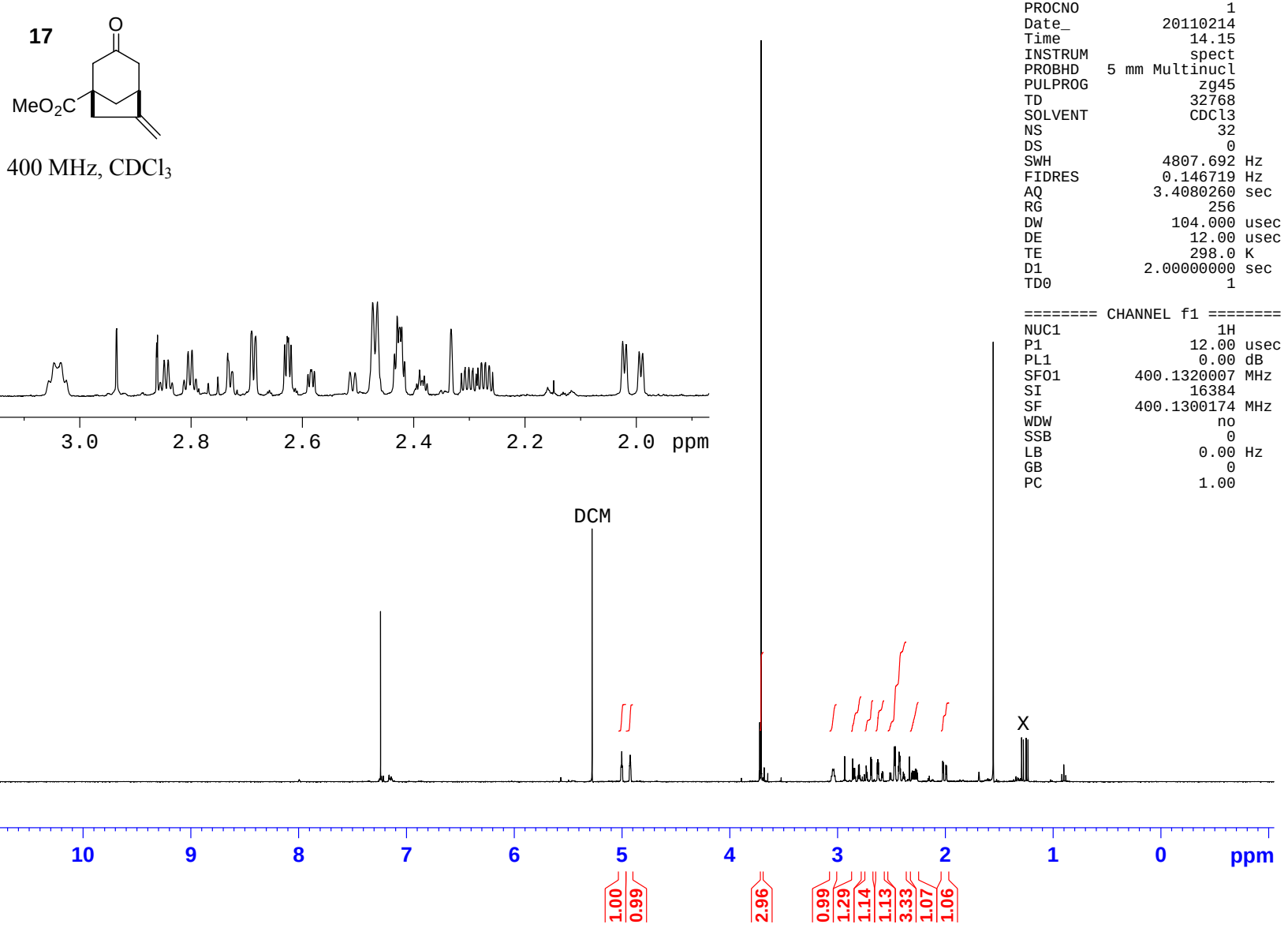
PULPROG             zg45
TD                 32768
SOLVENT            CDCl3
NS                    24
DS                     0
SWH             4807.692 Hz
FIDRES          0.146719 Hz
AQ              3.4080260 sec
RG                   128
DW                104.000 usec
DE                 12.00 usec
TE                 298.0 K
D1           2.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                 12.00 usec
PL1                 0.00 dB
SFO1         400.1320007 MHz
SI                 16384
SF           400.1300174 MHz
WDW                   no
SSB                    0
LB                  0.00 Hz
GB                     0
PC                  1.00
```


196.263
174.221
146.697
129.800
126.596
121.902
77.317
76.999
76.682
52.559
48.548
48.303
44.807
33.918
16
O
Br
CO2Me
100 MHz, CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


17
O
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400 MHz, CDCl3
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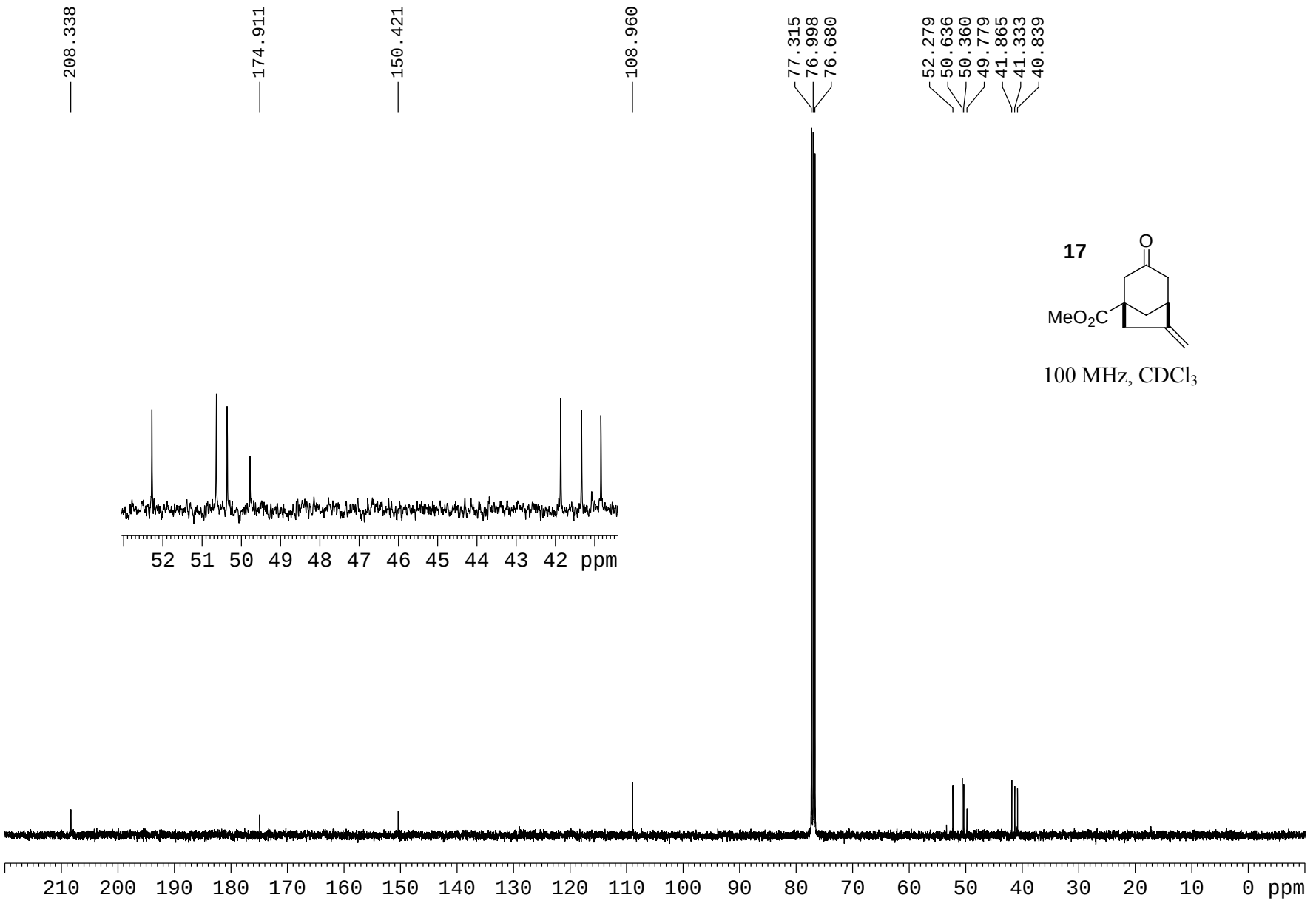
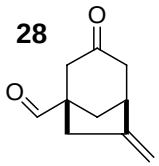
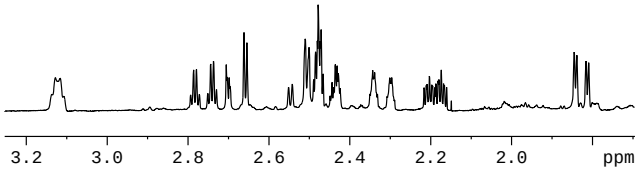
EXPNO 1
PROCNO 1
Date_ 20110214
Time 14.15
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zg45
TD 32768
SOLVENT CDCl3
NS 32
DS 0
SWH 4807.692 Hz
FIDRES 0.146719 Hz
AQ 3.4080260 sec
RG 256
DW 104.000 usec
DE 12.00 usec
TE 298.0 K
D1 2.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 12.00 usec
PL1 0.00 dB
SFO1 400.1320007 MHz
SI 16384
SF 400.1300174 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 1.00
3.0
2.8
2.6
2.4
2.2
2.0 ppm
DCM
X
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
0.99
2.96
0.99
1.29
1.14
1.13
3.33
1.07
1.06

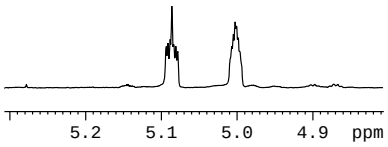

208.338
174.911
150.421
108.960
77.315
76.998
76.680
52.279
50.636
50.360
49.779
41.865
41.333
40.839
17
O
MeO2C
100 MHz, CDCl3
52 51 50 49 48 47 46 45 44 43 42 ppm
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

28



400 MHz, $CDCl_3$



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PROCNO                   1
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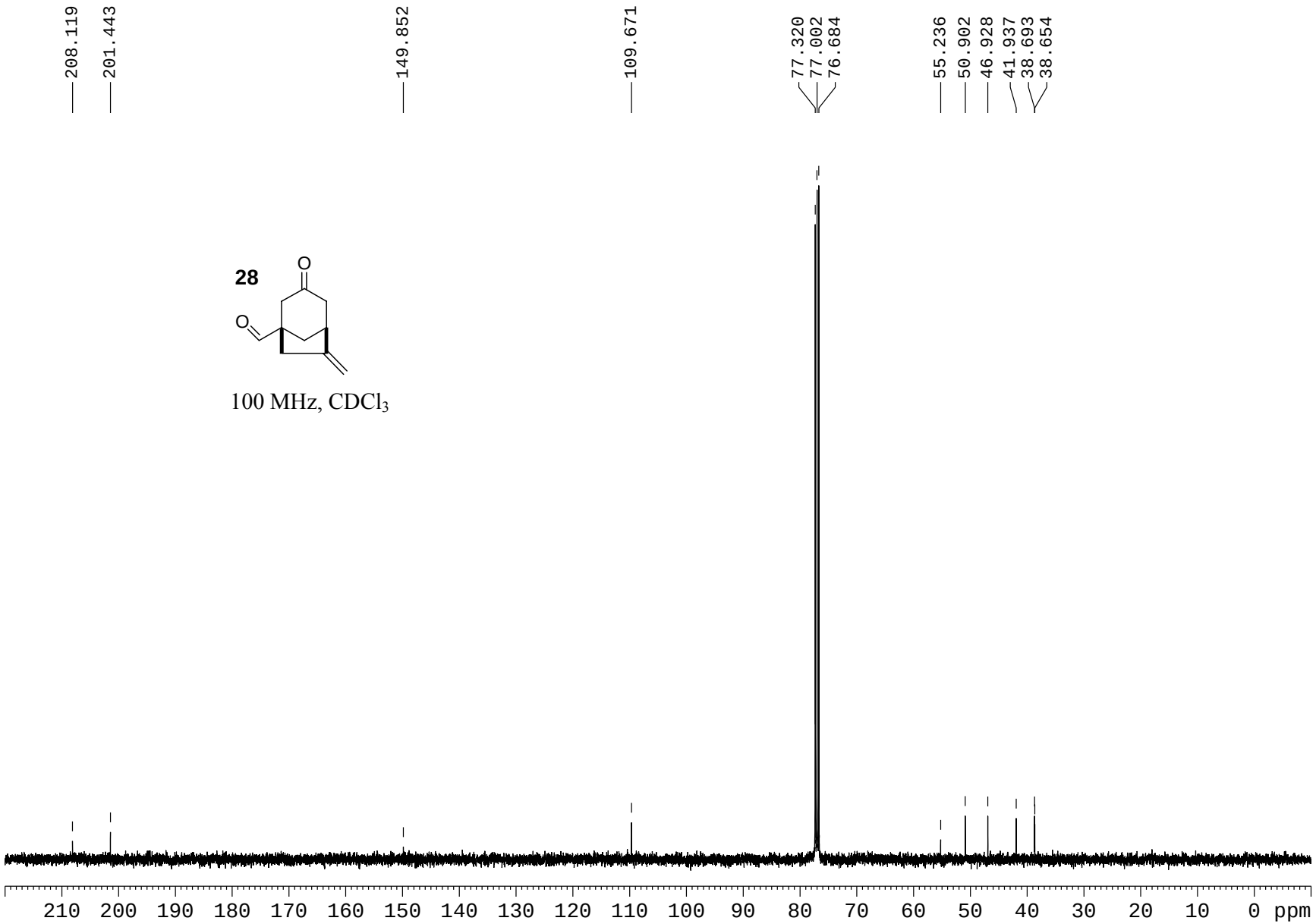
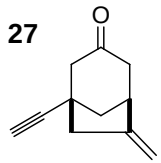
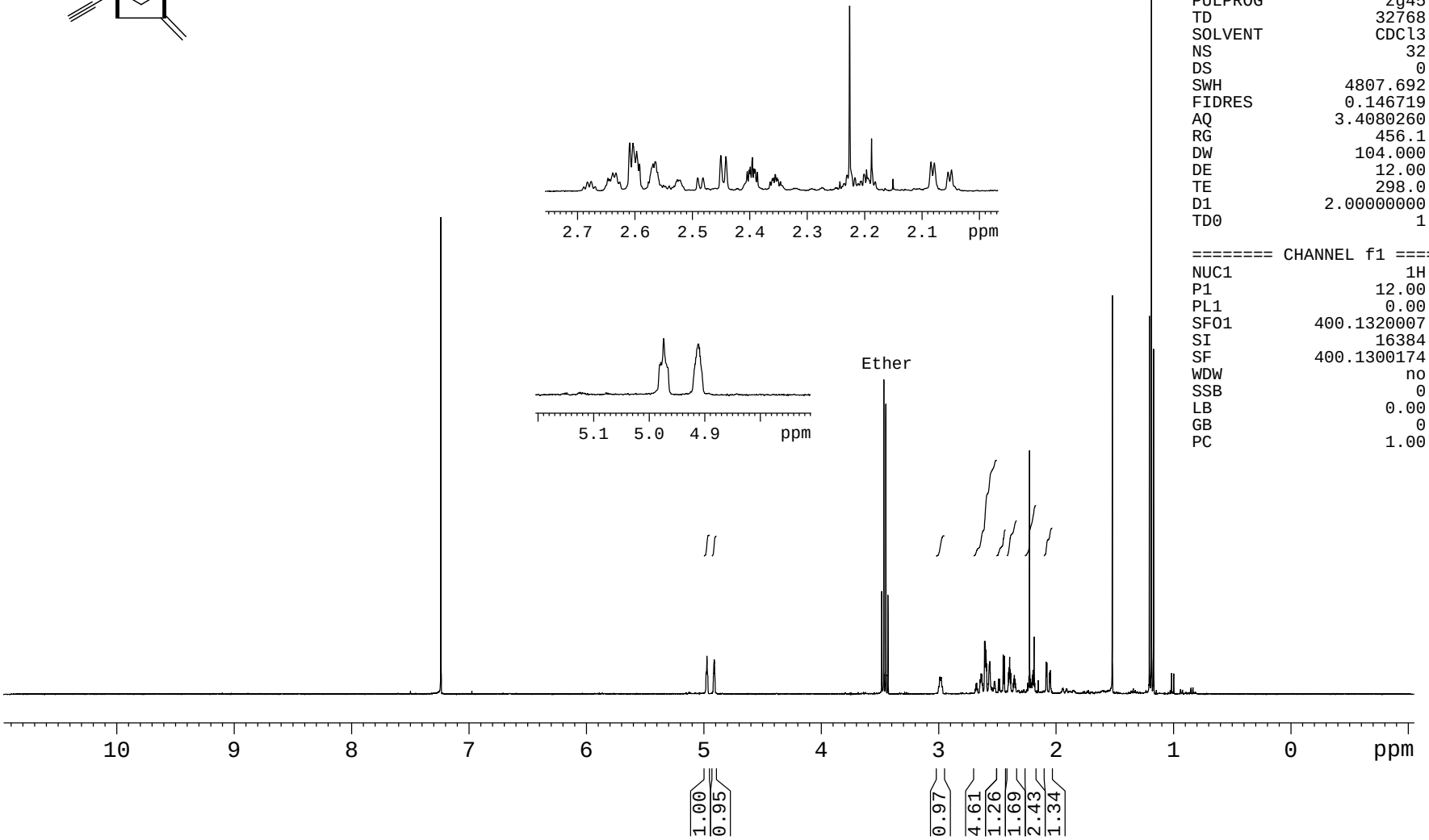
Time                 17.30
INSTRUM              spect
PROBHD   5 mm Multinucl
PULPROG               zg45
TD                   32768
SOLVENT              CDCl3
NS                      16
DS                       0
SWH              4807.692 Hz
FIDRES           0.146719 Hz
AQ               3.4080260 sec
RG                     362
DW                104.000 usec
DE                 12.00 usec
TE                 298.0 K
D1            2.00000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                    1H
P1                   12.00 usec
PL1                   0.00 dB
SFO1          400.1320007 MHz
SI                   16384
SF            400.1300174 MHz
WDW                     no
SSB                      0
LB                    0.00 Hz
GB                       0
PC                    1.00
```


208.119
201.443
149.852
109.671
77.320
77.002
76.684
55.236
50.902
46.928
41.937
38.693
38.654
28
O
O
100 MHz, CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

27





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PROCNO	1	
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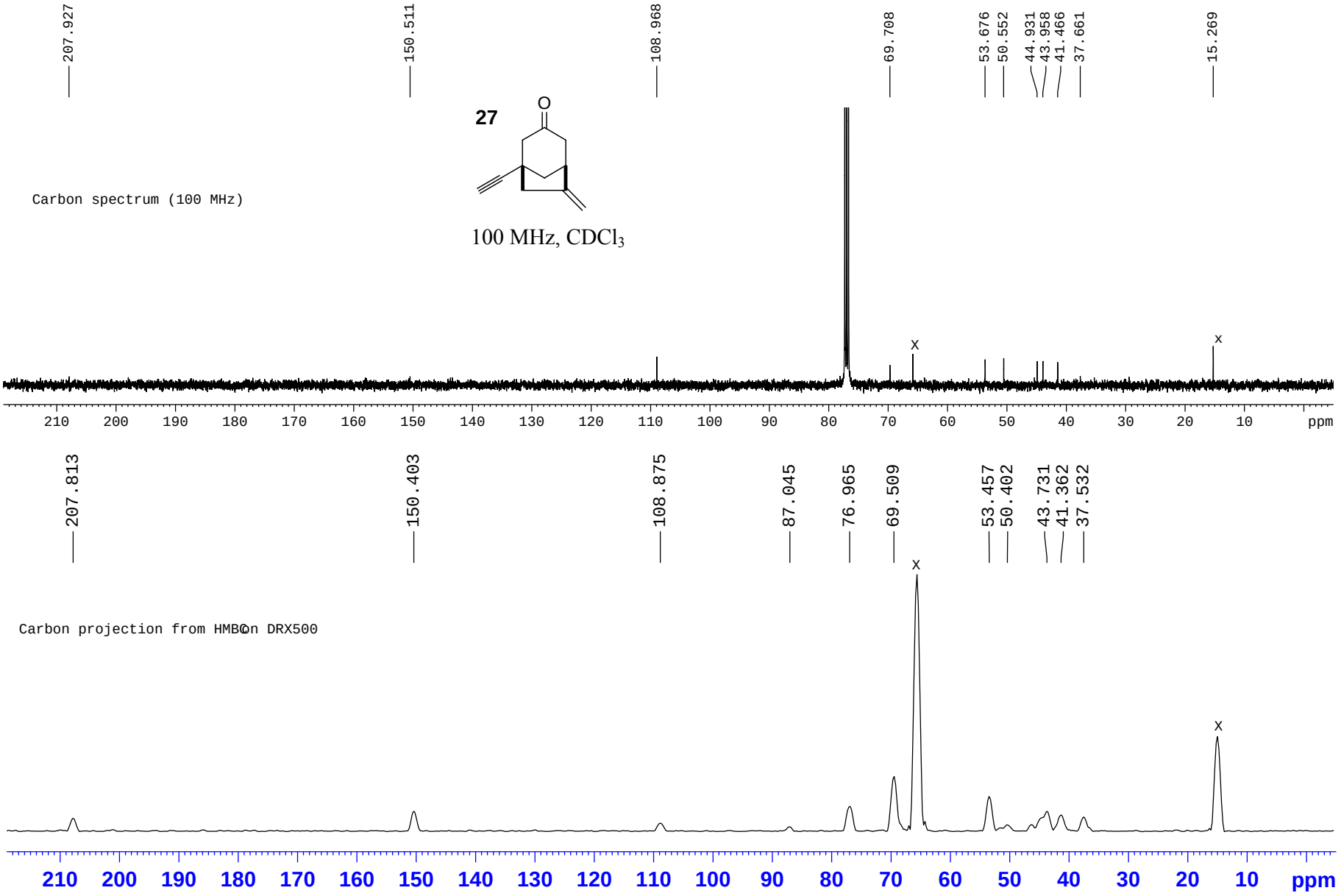
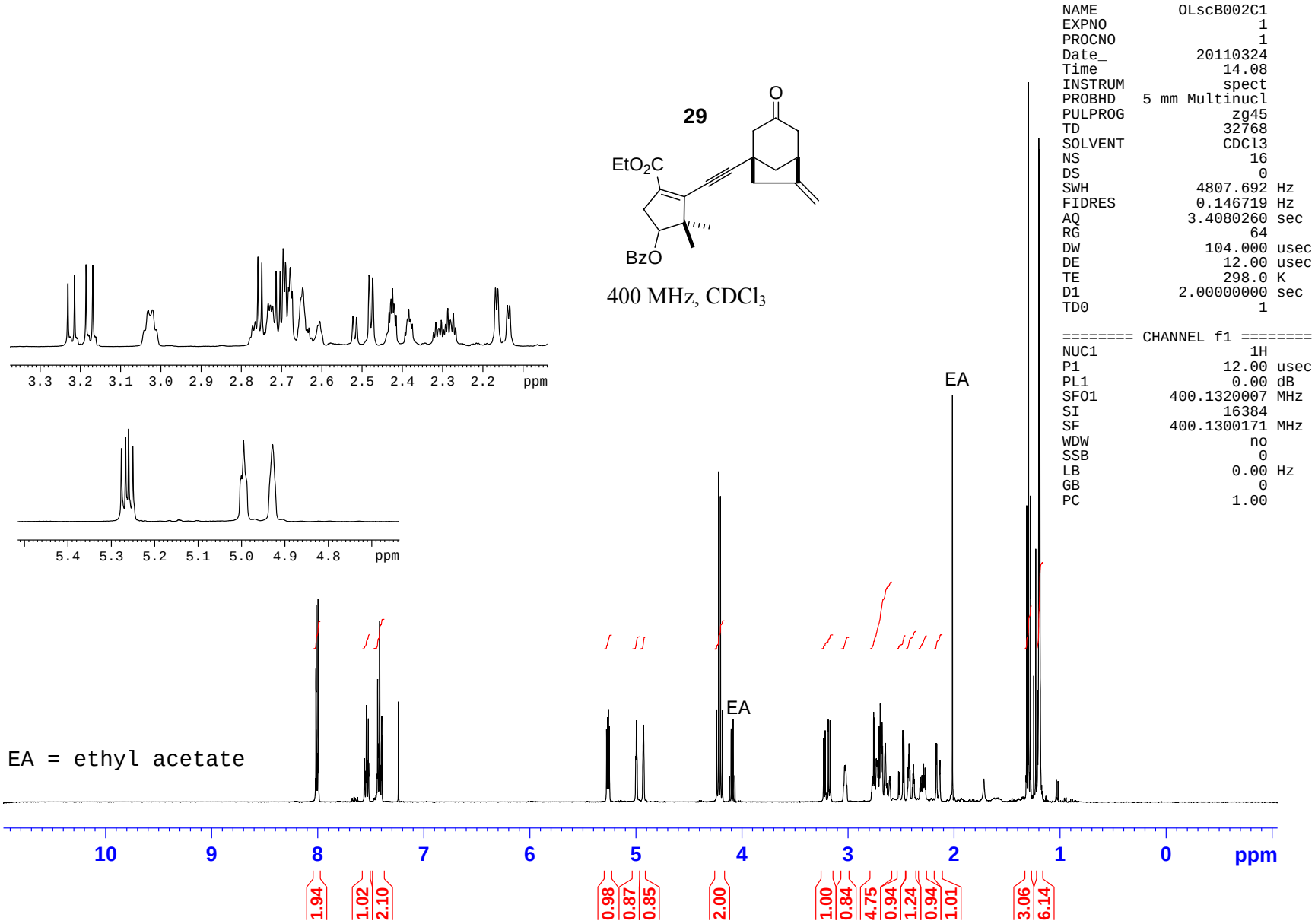
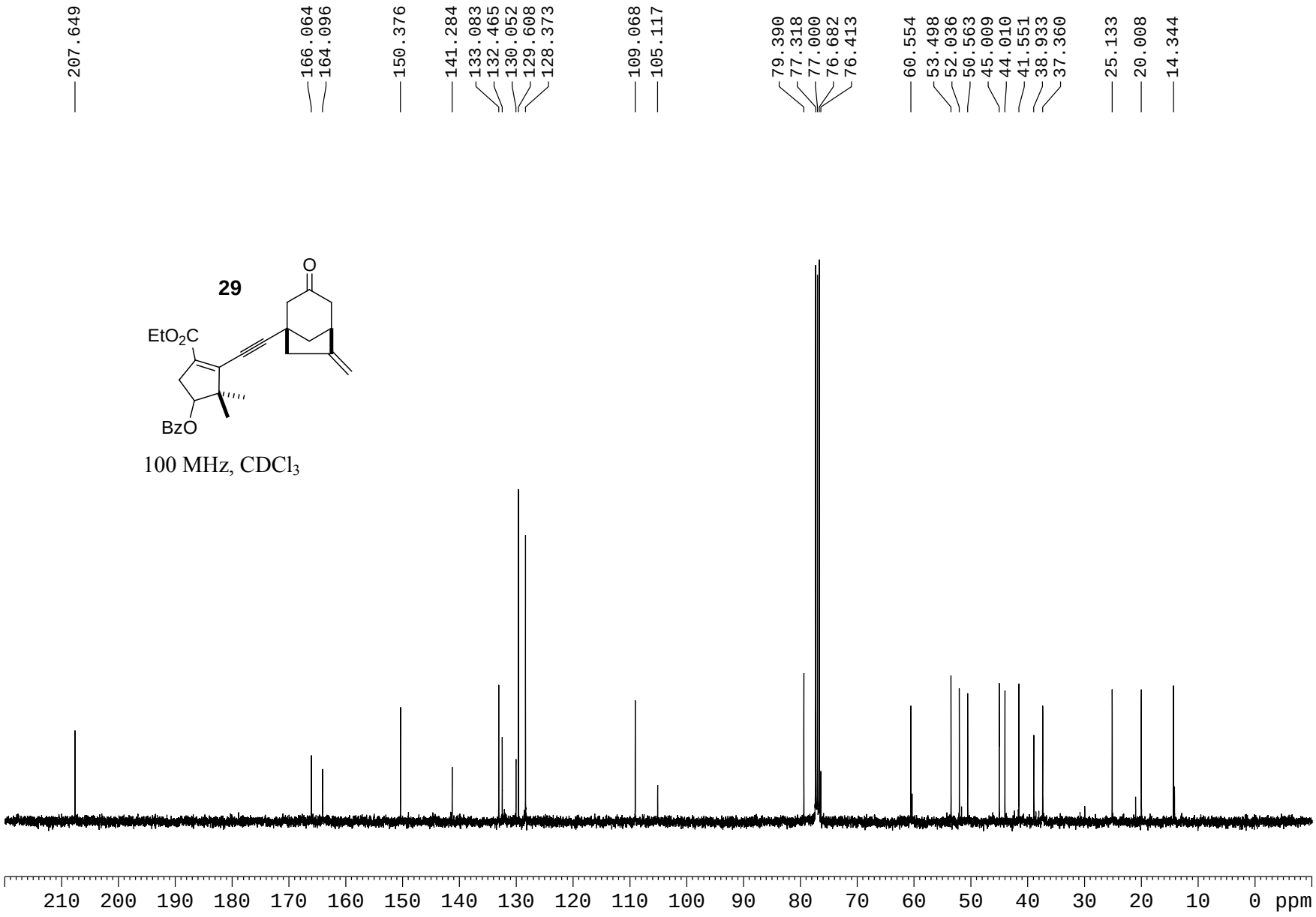
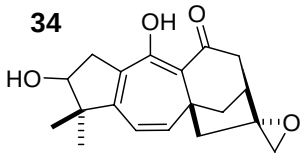
PULPROG	zg45	
TD	32768	
SOLVENT	CDCl3	
NS	32	
DS	0	
SWH	4807.692	Hz
FIDRES	0.146719	Hz
AQ	3.4080260	sec
RG	456.1	
DW	104.000	usec
DE	12.00	usec
TE	298.0	K
D1	2.00000000	sec
TD0	1	
======== CHANNEL f1 ========		
NUC1	1H	
P1	12.00	usec
PL1	0.00	dB
SFO1	400.1320007	MHz
SI	16384	
SF	400.1300174	MHz
WDW	no	
SSB	0	
LB	0.00	Hz
GB	0	
PC	1.00	


207.927
150.511
108.968
69.708
53.676
50.552
44.931
43.958
41.466
37.661
15.269
27
O
Carbon spectrum (100 MHz)
100 MHz, CDCl3
X
X
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm
207.813
150.403
108.875
87.045
76.965
69.509
53.457
50.402
43.731
41.362
37.532
X
X
Carbon projection from HMBC on DRX500
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


29
EtO2C
BzO
O
400 MHz, CDCl3
NAME OLscB002C1
EXPNO 1
PROCNO 1
Date_ 20110324
Time 14.08
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zg45
TD 32768
SOLVENT CDCl3
NS 16
DS 0
SWH 4807.692 Hz
FIDRES 0.146719 Hz
AQ 3.4080260 sec
RG 64
DW 104.000 usec
DE 12.00 usec
TE 298.0 K
D1 2.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 12.00 usec
PL1 0.00 dB
SFO1 400.1320007 MHz
SI 16384
SF 400.1300171 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 1.00
EA
EA
EA = ethyl acetate
ppm
1.94
1.02
2.10
0.98
0.87
0.85
2.00
1.00
0.84
4.75
0.94
1.24
0.94
1.01
3.06
6.14


207.649
166.064
164.096
150.376
141.284
133.083
132.465
130.052
129.608
128.373
109.068
105.117
79.390
77.318
77.000
76.682
76.413
60.554
53.498
52.036
50.563
45.009
44.010
41.551
38.933
37.360
25.133
20.008
14.344
29
O
EtO2C
BzO
100 MHz, CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

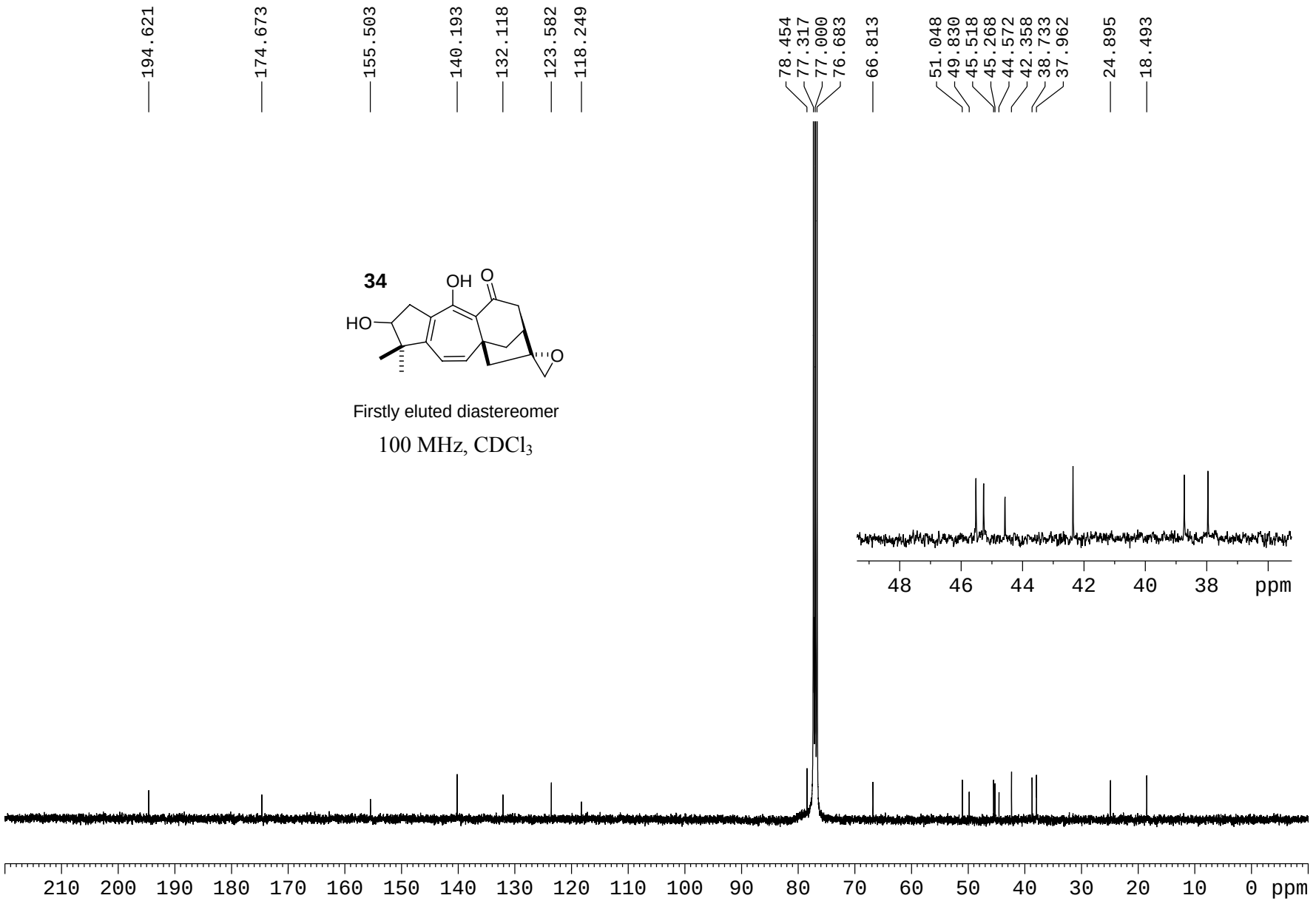


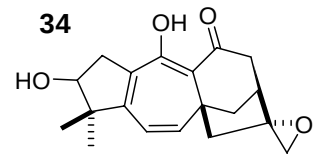
Firstly eluted diastereomer

400 MHz, $CDCl_3$

```
NAME      OLscB020n031C1
EXPNO                  1
PROCNO                 1
Date_           20110707
Time               14.17
INSTRUM            spect
PROBHD   5 mm Multinucl
PULPROG             zg45
TD                 32768
SOLVENT            CDCl3
NS                    32
DS                     0
SWH             8012.820 Hz
FIDRES          0.244532 Hz
AQ              2.0448356 sec
RG                   512
DW                62.400 usec
DE                12.00 usec
TE                298.0 K
D1           2.00000000 sec
TD0                    1

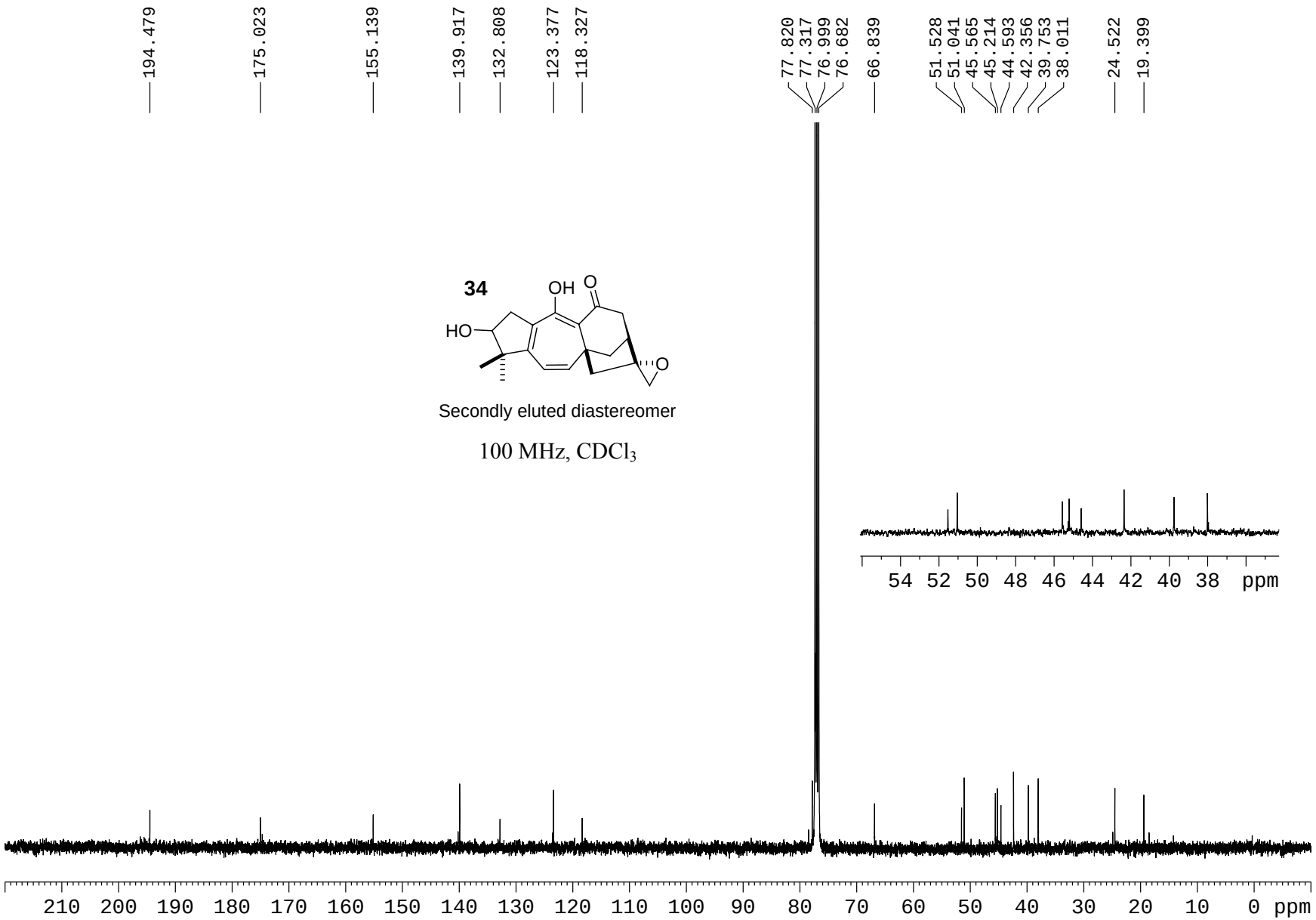
======== CHANNEL f1 ========
NUC1                  1H
P1                 12.00 usec
PL1                 0.00 dB
SFO1         400.1336012 MHz
SI                 16384
SF           400.1300173 MHz
WDW                   no
SSB                    0
LB                  0.00 Hz
GB                     0
PC                  1.00
```

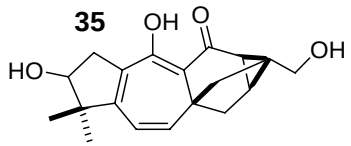

194.621
174.673
155.503
140.193
132.118
123.582
118.249
78.454
77.317
77.000
76.683
66.813
51.048
49.830
45.518
45.268
44.572
42.358
38.733
37.962
24.895
18.493
34
OH
O
HO
O
Firstly eluted diastereomer
100 MHz, CDCl3
48
46
44
42
40
38
ppm
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



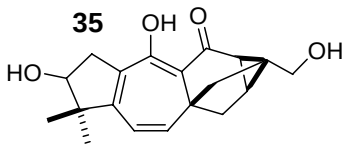
Secondly eluted diastereomer

400 MHz, $CDCl_3$


194.479
175.023
155.139
139.917
132.808
123.377
118.327
77.820
77.317
76.999
76.682
66.839
51.528
51.041
45.565
45.214
44.593
42.356
39.753
38.011
24.522
19.399
34
OH
O
HO
O
Secondly eluted diastereomer
100 MHz, CDCl3
54 52 50 48 46 44 42 40 38 ppm
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



500 MHz, $CDCl_3$



125 MHz, $CDCl_3$