Enantiospecific Total Synthesis of the Highly Strained (–)-Presilphiperfolan-8-ol via a Pd-Catalyzed Tandem Cyclization

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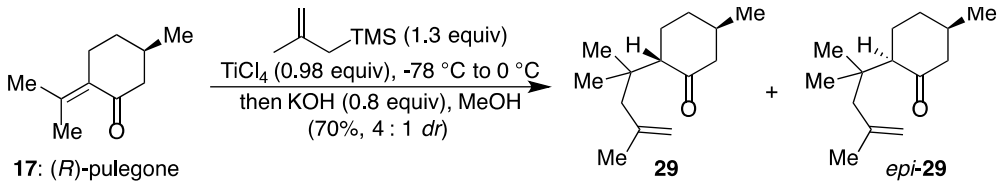
Supporting Information

Experimental Data for Compounds

General Procedures. All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), toluene, diethyl ether (Et_2O), dichloromethane (CH_2Cl_2), and acetonitrile (CH_3CN) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent, and an ethanolic solution of phosphomolybdic acid and cerium sulfate, and heat as developing agents. SiliCycle silica gel (60, academic grade, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography separations were carried out on 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Bruker 400 and 500 MHz instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, br = broad, app = apparent. IR spectra were recorded on a Perkin-Elmer 1000 series FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded on Agilent 6244 Tof-MS using ESI (Electrospray Ionization) at the University of Chicago Mass Spectroscopy Core Facility.

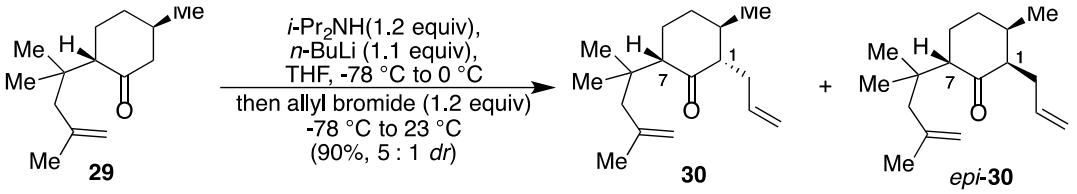
Abbreviations. EtOAc = ethyl acetate, THF = tetrahydrofuran, *n*-BuLi = *n*-butyllithium, KHMDS = potassium bis(trimethylsilyl)amide, Comins' reagent = *N*-(5-chloro-2-pyridyl)bis(trifluoromethanesulfonimide), $Pd(OAc)_2$ = palladium acetate, DPEphos = (oxydi-2,1-phenylene)bis(diphenylphosphine), Et_3N = triethylamine, NMO = 4-methylmorpholine *N*-oxide, *m*CPBA = *m*-chloroperoxybenzoic acid, LiHMDS = lithium bis(trimethylsilyl)amide, Stryker's reagent = $[(Ph_3P)_3CuH]_6$ = (triphenylphosphine)copper hydride hexamer, TMSOTf = trimethylsilyl trifluoromethanesulfonate, *p*-ABSA = 4-acetamidobenzenesulfonyl azide, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DIBAL-H = diisobutylaluminum hydride, *t*-BuOH = *tert*-butanol, DMP = Dess–Martin periodinane = 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1H)-one, TBAF = tetra-*n*-butylammonium fluoride, MeOH = methanol.



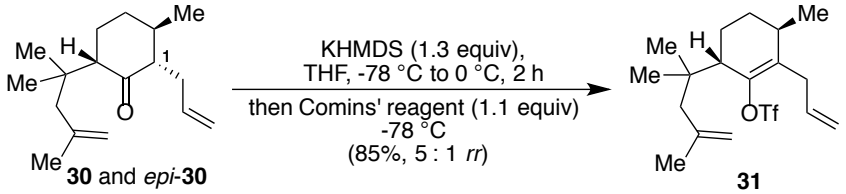
17: (*R*)-pulegone **29** *epi*-**29**

(2*S*,5*R*)-2-(2,4-dimethylpent-4-en-2-yl)-5-methylcyclohexanone (29).[1] To a solution of (*R*)-pulegone (**17**, 9.13 g, 60 mmol, 1.0 equiv) in CH_2Cl_2 (270 mL) at –78 °C was added $TiCl_4$ (6.45 mL, 58.8 mmol, 0.98 equiv) dropwise over the course of 10 min. After stirring the resultant brown solution at –78 °C for another 10 min, a solution of methallyltrimethylsilane (13.7 mL, 78 mmol, 1.3 equiv) in CH_2Cl_2 (60 mL) was then added via syringe pump over 30 min. The color of the reaction solution turned blue during the addition. Once the addition was complete, the reaction contents were stirred at –78 °C for a further 10 min and then warmed to 0 °C. Upon completion, typically 10 to 15 min after the reaction solution reached 0 °C, the contents were quenched by slowly adding a mixture of Et_3N (42 mL) and MeOH (12 mL). Et_2O (500 mL) was then added and the resultant white precipitate was removed by filtration. The filtrate was washed with 1 N HCl (2 × 300 mL), saturated aqueous $NaHCO_3$ (100 mL), H_2O (200 mL) and brine (100 mL), and then the resultant organic layer was dried ($MgSO_4$), filtered, and concentrated. The resultant yellow oil was then dissolved in MeOH (60 mL) and treated with solid KOH (2.69 g, 48 mmol, 0.8 equiv) at 23 °C. After stirring the resultant mixture at 23 °C for 4 h, the reaction contents were quenched by the addition of 1 N HCl (100 mL), Et_2O (300 mL) was added, and the contents were poured into a separatory funnel. After separating the layers, the organic phase was washed with saturated aqueous $NaHCO_3$ (100 mL), H_2O (100 mL), and brine (100 mL), dried ($MgSO_4$), filtered, and concentrated. A small portion of the resultant crude product was purified by a quick filtration through a short pad of silica gel using hexanes/Et_2O (50/1) as the eluent; these studies revealed that **29** and *epi*-**29** had been generated as a 4:1 mixture of diastereomers. The entire crude product mixture was then purified via very careful column chromatography (silica gel, hexanes/Et_2O = 100/1→50/1) to give pure (2*S*,5*R*)-2-(2,4-dimethylpent-4-en-2-yl)-5-methylcyclohexanone (**29**, 4.46 g, 36% yield) as a colorless oil along with an additional sample that was a mixture of the diastereomers (**29** and *epi*-**29**, 4.28 g, 34% yield) as a colorless oil. The latter mixture was redissolved in MeOH (20.5 mL) and retreated with KOH (0.92 g, 16.4 mmol, 0.8 equiv) at 23 °C followed by the same work-up and column chromatography purification to afford an additional sample of **29** (2.01 g, 16% yield) and a mixed sample of **29** and *epi*-**29** (2.12 g, 17% yield). Thus, pure **29** (6.47 g, 52% yield) was isolated from two runs of thermodynamic isomerization along with some additional mixed fractions. [Note: The purity of the reagents is crucial in this reaction. Commercial methallyltrimethylsilane should be dried over the course of 24 h using 4Å molecular sieves before use and $TiCl_4$ needs to be properly stored with a SureSeal™ cap; efforts using either technical grade (*R*)-pulegone (Aldrich) gave a very messy reaction and a low yield of the desired product. In addition, using slightly less than one equivalent of $TiCl_4$ is important to obtain a reproducible yield of **29**, especially at large scale]. **29**: R_f = 0.27 (silica gel, hexanes/Et_2O, 100/3); $[\alpha]_D^{23}$ = +20.0° (*c* = 1.0, $CHCl_3$); IR (film) ν_{max} 2955, 2871, 1709, 1640, 1456, 1374, 1319, 1266, 1121, 1050, 984, 891 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.86–4.80 (m, 1 H), 4.61–4.58 (m, 1 H), 2.41–2.35 (m, 1 H), 2.30–2.20 (m, 2 H), 2.17–2.10 (m, 1 H), 2.06–1.96 (m, 2 H), 1.94–1.81 (m, 2 H), 1.76 (s, 3 H), 1.46 (qd, *J* = 12.9, 3.1 Hz, 1 H), 1.38–1.27 (m, 1 H), 1.04 (s, 3 H), 1.00 (d, *J* = 6.2 Hz, 3 H), 0.97 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.3, 143.7, 114.3, 57.4, 52.6, 47.5, 36.6, 35.2, 34.8, 28.5, 26.4, 25.5, 24.8, 22.3; HRMS (ESI) calcd for

$C_{14}H_{25}O^+$ [M + H$^+$] 209.1900, found 209.1897.

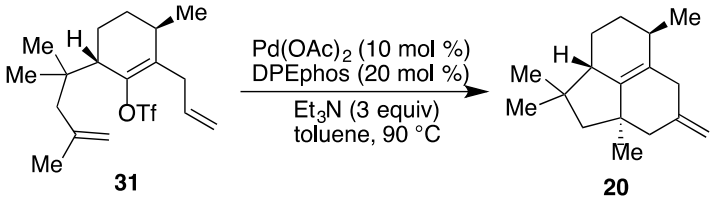


(2*S*,3*R*,6*R*)-2-allyl-6-(2,4-dimethylpent-4-en-2-yl)-3-methylcyclohexanone (30)[2] and (2*R*,3*R*,6*S*)-2-allyl-6-(2,4-dimethylpent-4-en-2-yl)-3-methylcyclohexanone (*epi*-30). To a solution of *i*-Pr$_2$NH (5.21 mL, 37.2 mmol, 1.2 equiv) in THF (80 mL) at 0 °C was added *n*-BuLi (2.5 M in hexane, 13.6 mL, 34.1 mmol, 1.1 equiv). The resultant solution was then stirred at 0 °C for 30 min. The solution was then cooled to –78 °C and a solution of **29** (6.47 g, 31.0 mmol, 1.0 equiv) in THF (70 mL) was added dropwise over the course of 30 min. Once the addition was complete, the reaction contents were then warmed to 0 °C and kept at that temperature for 1.5 h before being cooled to –78 °C again. Allyl bromide (3.22 mL, 37.2 mmol, 1.2 equiv) was added at –78 °C and the resultant reaction mixture was then slowly warmed to 23 °C and stirred overnight for 12 h. Upon completion, the reaction contents were quenched by the addition of H_2O (100 mL) and EtOAc (100 mL) and poured into a separatory funnel. After separating the layers, the aqueous phase was extracted with EtOAc (100 mL) and the combined organic layers were washed with H_2O (200 mL) and brine (100 mL) before being dried ($MgSO_4$), filtered, and concentrated. The resultant residue was purified by column chromatography (silica gel, hexanes/Et_2O, 100/1→50/1) to give a 5:1 mixture of **30** and *epi*-**30** (6.94 g, 90% yield combined) as a colorless oil. A small portion of the material was purified further in order to characterize the major diastereomer **30**. **30**: R_f = 0.60 (silica gel, hexanes/Et_2O, 100/3); $[\alpha]_D^{23}$ = +21.0° (*c* = 1.0, $CHCl_3$); IR (film) ν_{max} 3074, 2954, 2927, 2873, 1711, 1638, 1473, 1457, 1374, 1066, 909, 894 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.90–5.75 (m, 1 H), 5.03–4.96 (m, 1 H), 4.95–4.90 (m, 1 H), 4.83–4.79 (m, 1 H), 4.59–4.54 (m, 1 H), 2.38 (d, *J* = 13.0 Hz, 1 H), 2.40–2.30 (m, 1 H), 2.27 (dd, *J* = 12.2, 4.7 Hz, 1 H), 2.23–2.16 (m, 1 H), 2.15–2.03 (m, 2 H), 1.97 (d, *J* = 13.0 Hz, 1 H), 1.90−1.83 (m, 1 H), 1.75 (s, 3 H), 1.65–1.54 (m, 1 H), 1.52–1.39 (m, 2 H), 1.05 (s, 3 H), 1.04 (d, *J* = 6.9 Hz, 3 H), 0.97 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.0, 143.7, 137.4, 115.3, 114.4, 58.8, 58.3, 47.6, 41.2, 35.4, 35.3, 30.6, 29.1, 26.5, 25.5, 24.9, 20.5; HRMS (ESI) calcd for $C_{17}H_{29}O^+$ [M + H$^+$] 249.2213, found 249.2211.

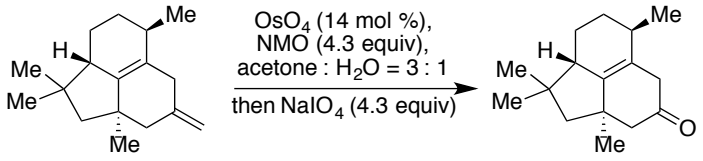


Alkenyl trifluoromethanesulfonate 31. A mixture of **30** and *epi*-**30** (7.33 g, 29.5 mmol, 1.0 equiv) was dissolved in THF (250 mL) and the resultant solution was cooled to –78 °C. Next, KHMDS (1.0 M in THF, 38.4 mL, 38.4 mmol, 1.3 equiv) was added slowly over the course of 30 min at –78 °C. Once the addition was complete, the reaction contents were warmed to 0 °C and kept at that temperature for 2 h before being cooled again to –78 °C. A solution of Comins' reagent (12.7 g, 32.5 mmol, 1.1 equiv) in THF (50 mL) was then added slowly over the course of 30 min at –78 °C and the resultant mixture was stirred for a further 20 min at –78 °C.

Upon completion, the reaction contents were quenched by the addition of saturated aqueous $NaHCO_3$ (100 mL) and then warmed to 23 °C. H_2O (100 mL) was added to dissolve any remaining solids, and the mixture was poured into a separatory funnel and the layers were separated. The aqueous layer was then extracted with hexanes (2 × 100 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (100 mL), H_2O (100 mL) and brine (100 mL) before being dried ($MgSO_4$), filtered, and concentrated. The resultant residue was purified by column chromatography (Et_3N-buffered silica gel, hexanes) to give a 5:1 mixture of **31** and its alkene regioisomer (9.54 g, 85% yield) as a colorless oil. These two isomers were not separable by chromatography and thus were characterized as a mixture. [Note: the product was found to be unstable on standard silica gel and Et_3N-buffering proved necessary for successful purification]. **31**: R_f = 0.43 (silica gel, hexanes); $[\alpha]_D^{23}$ = +129.1° (*c* = 1.1, $CHCl_3$); IR (film) ν_{max} 2969, 1641, 1457, 1412, 1244, 1209, 1143, 1039, 981, 876, 810, 608, 513 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, major product only) δ 5.76–5.66 (m, 1 H), 5.16–5.10 (m, 1 H), 5.10–5.05 (m, 1 H), 4.90–4.86 (m, 1 H), 4.69–4.65 (m, 1 H), 3.40–3.30 (m, 1 H), 2.74–2.66 (m, 1 H), 2.46–2.43 (m, 1 H), 2.41–2.35 (m, 1 H), 2.32–2.17 (m, 1 H), 2.13 (d, *J* = 13.1 Hz, 1 H), 1.98 (d, *J* = 13.1 Hz, 1 H), 1.94–1.75 (m, 2 H), 1.78 (s, 3 H), 1.32−1.23 (m, 1 H), 1.09 (d, *J* = 7.0 Hz, 3 H), 1.02 (s, 3 H), 1.00 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$, major product only) δ 145.4, 143.0, 137.2, 134.5, 118.3, 117.0, 114.9, 47.9, 46.4, 38.4, 33.3, 32.0, 28.1, 27.5, 26.7, 25.5, 23.0, 19.7; HRMS (ESI) calcd for $C_{18}H_{28}F_3O_3S^+$ [M + H^+] 381.1706, found 381.1702.

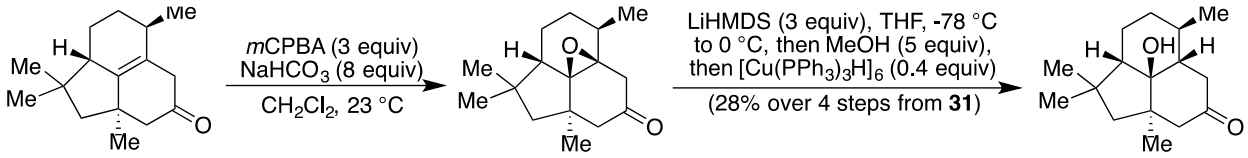


Cyclized Diene 20. To a flame-dried sealed tube was added alkenyl triflate **31** its alkene regioisomer (3.80 g total, 10.0 mmol, 1.0 equiv; corresponds to 3.17 g or 8.33 mmol of **31** and 0.63 g or 1.67 mmol of its alkene isomer), $Pd(OAc)_2$ (0.225 g, 1.0 mmol, 0.1 equiv), DPEphos (1.08 g, 2.00 mmol, 0.2 equiv), Et_3N (2.80 mL, 20.0 mmol, 2.0 equiv) and toluene (100 mL). The reaction tube was then sealed and heated at 90 °C until consumption of the starting material was indicated by TLC analysis (typically 10 to 12 h). Upon completion, the reaction contents were cooled to 23 °C and the solvent was removed in vacuo. The resultant residue was purified by column chromatography (silica gel, hexanes) to give cyclized diene **20** (2.06 g) as a colorless oil, which contained some inseparable by-products which were carried forward into the next step without further purification. The yield of the reaction (75% yield) was determined via ^1H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [Note: A pure sample of the desired product could be obtained from reactions conducted at 0.2 mmol scale using the same procedure described above]. **20**: R_f = 0.90 (silica gel, hexanes); $[\alpha]_D^{23}$ = –6.0° (*c* = 1.0, $CHCl_3$); IR (film) ν_{max} 2926, 1718, 1695, 1684, 1670, 1456, 1374, 1185, 1009, 879 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.90–4.87 (m, 1 H), 4.86–4.83 (m, 1 H), 2.98–2.91 (m, 1 H), 2.70–2.60 (m, 1 H), 2.31 (d, *J* = 13.1 Hz, 1 H), 2.26–2.17 (m, 1 H), 2.09–1.94 (m, 3 H), 1.72–1.65 (m, 1 H), 1.54 (d, *J* = 12.4 Hz, 1 H), 1.46 (d, *J* = 12.4 Hz, 1 H), 1.36–1.22 (m, 2 H), 1.01 (s, 3 H), 0.99 (s, 3 H), 0.97 (d, *J* = 6.4 Hz, 3 H), 0.96 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.3, 146.9, 127.8, 110.1, 55.5, 52.2, 48.4, 40.4, 40.2, 34.9, 32.1, 30.6, 30.2, 26.4, 24.1, 24.0, 19.7; HRMS (ESI) was attempted, but no molecular ion peak was observed under various conditions.



20 **S1**

Ketone S1. To a solution of the crude diene **20** (2.06 g, 6.25 mmol assumed, 1.0 equiv) in acetone (67 mL) at 23 °C was sequentially added NMO (3.14 g, 26.9 mmol, 4.3 equiv) and H_2O (22 mL). After all of the solids had dissolved, OsO_4 (2.5 wt % in *t*-BuOH, 9.103 g, 0.90 mmol, 0.14 equiv) was added. The reaction contents were then stirred at 23 °C for 12 h before solid $NaIO_4$ (5.74 g, 26.9 mmol, 4.3 equiv) was added in a single portion. After stirring the resultant mixture at 23 °C for 30 min, the reaction contents were then filtered to remove any solids and the filtrate was diluted with EtOAc (100 mL) and H_2O (100 mL) and then poured into a separatory funnel. After separating the layers, the aqueous phase was extracted with EtOAc (2 × 100 mL). The combined organic layers were then washed with H_2O (2 × 100 mL) and brine (100 mL) before being dried ($MgSO_4$), filtered, and concentrated. The resultant residue was purified via column chromatography (silica gel, hexanes/EtOAc, 30/1→20/1) to afford ketone **S1** (0.753 g) as white solid containing a small amount of an unidentified contaminant. A small portion of **S1** was further purified by three additional column chromatographies (silica gel, hexanes/EtOAc, 30/1→20/1) to give a pure sample for characterization. Repetition of the reaction using another batch of crude diene **20** (2.30 g, 6.98 mmol assumed, prepared from 9.30 mmol of **31**) using the same procedure resulted in an additional sample of **S1** (0.840 g) with the same purity. This material was combined with the batch above and used in further experiments. Thus, in total, crude **S1** (1.59 g, 6.84 mmol assumed) were prepared from **31** (15.6 mmol). **S1**: R_f = 0.47 (silica gel, hexanes/EtOAc = 10/1); $[\alpha]_D^{23}$ = –127.3 (*c* = 1.5, $CHCl_3$); IR (film) ν_{max} 2945, 2923, 1716, 1653, 1559, 1457, 1380, 1275, 1222, 1180 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.86 (dd, *J* = 22.5 Hz, 2.5 Hz, 1 H), 2.75 (ddd, *J* = 22.5, 5.0, 1.9 Hz, 1 H), 2.46 (d, *J* = 15.2 Hz, 1 H), 2.28–2.20 (m, 1 H), 2.14 (d, *J* = 15.2 Hz, 1 H), 2.12–2.06 (m, 2 H), 1.79–1.71 (m, 1 H), 1.60 (d, *J* = 12.6 Hz, 1 H), 1.56 (d, *J* = 12.6 Hz, 1 H), 1.41–1.27 (m, 2 H), 1.11 (s, 3 H), 1.05 (s, 3 H), 0.98 (s, 3 H), 0.97 (d, *J* = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.9, 148.2, 126.1, 55.0, 54.9, 52.0, 40.6, 40.3, 38.9, 34.4, 31.7, 29.9, 26.4, 24.0, 23.7, 19.4; HRMS (ESI) calcd for $C_{16}H_{25}O^+$ [M + H^+] 233.1900, found 233.1898.

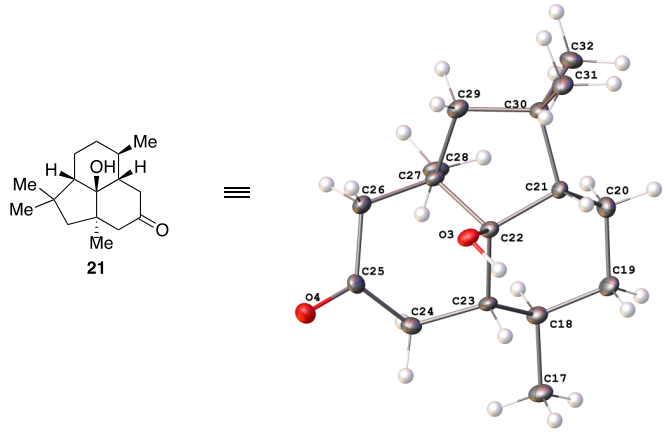


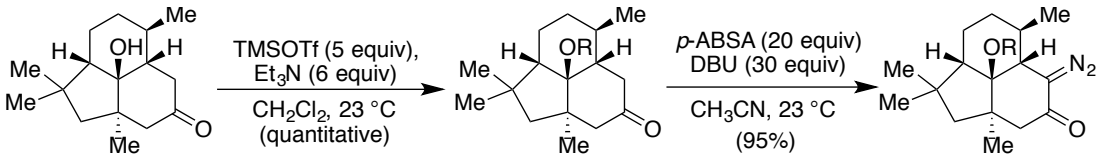
S1 **32** **21**

Hydroxyketone 21. To a solution of ketone **S1** (1.23 g, 5.3 mmol assumed, 1.0 equiv, 77% of the 1.59 g of **S1** described above) in CH_2Cl_2 (53 mL) at 23 °C was added solid $NaHCO_3$ (3.52 g, 42.4 mmol, 8.0 equiv) in a single portion followed by solid *m*CPBA (77%, 3.56 g, 15.9 mmol, 3.0 equiv) in ten batches added over the course of 10 min. The resultant mixture was then stirred at 23 °C for 15 min. Upon completion, the reaction contents were quenched by the addition of a mixed solution of saturated aqueous NaS_2O_3 (50 mL) and saturated aqueous $NaHCO_3$ (50 mL) and the resultant slurry was stirred vigorously at 23 °C for 30 min. The

reaction contents were then poured into a separatory funnel, the layers were separated, and the aqueous phase was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (100 mL), H_2O (100 mL) and brine (50 mL) before being dried ($MgSO_4$), filtered, and concentrated. The resultant crude yellow oil was found to be unstable and thus was used immediately in the next step without further purification; characterization was similarly performed in crude form. **32**: R_f = 0.31 (silica gel, hexanes/EtOAc = 10/1); ^{1}H NMR (500 MHz, C_6D_6) δ 2.95 (d, *J* = 18.6 Hz, 1 H), 2.41 (d, *J* = 16.6 Hz, 1 H), 2.19 (d, *J* = 16.6 Hz, 1 H), 2.11 (dd, *J* = 18.6, 0.8 Hz, 1 H), 1.74 (dd, *J* = 13.7, 4.7 Hz, 1 H), 1.52 (d, *J* = 12.6 Hz, 1 H), 1.45–1.36 (m, 2 H), 1.32–1.22 (m, 3 H), 1.20 (d, *J* = 12.6 Hz, 1 H), 0.99 (s, 3 H), 0.90 (s, 3 H), 0.84 (s, 3 H), 0.83 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 206.1, 76.9, 60.6, 54.0, 52.6, 50.4, 43.2, 39.8, 38.4, 34.6, 32.3, 31.7, 26.6, 25.0, 24.2, 15.3. Thus, pressing forward, crude epoxide **32** (5.0 mmol assumed, 1.0 equiv) was dissolved in THF (50 mL), cooled to –78 °C, and LiHMDS (1.0 M in hexane, 15 mL, 15 mmol, 3.0 equiv) was added dropwise over the course of 10 min. Once the addition was complete, the reaction contents were warmed to 0 °C and stirred at this temperature for 1.5 h before being cooled back to –78 °C. The reaction contents were then quenched with MeOH (1.14 mL, 25 mmol, 5.0 equiv) and the resultant mixture was warmed to 23 °C and stirred at that temperature for 1 h. In a separate flask in a glove-box, commercial Strycker's reagent (3.92 g, 2.0 mmol, 0.4 equiv) was dissolved in benzene (25 mL) and the entire volume was transferred into a syringe. That syringe was then removed from the glove-box and its contents were immediately added to the reaction flask. Once TLC analysis indicated reaction completion (typically in 5 h), the contents were quenched by the addition of H_2O (100 mL) and poured into a separatory funnel. The layers were then separated and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were then washed with H_2O (3 × 100 mL) and brine (100 mL) before being dried ($MgSO_4$), filtered, and concentrated. The resultant residue was purified via column chromatography (silica gel, toluene/EtOAc, 10/1→3/1) to afford hydroxyketone **21** (0.828 g, 28% yield over 4 steps from **31**) as a white solid. **21**: R_f = 0.64 (silica gel, hexanes/EtOAc = 2/1); $[\alpha]_D^{23}$ = +93.0° (*c* = 1.0, $CHCl_3$); IR (film) ν_{max} 3445, 2968, 2886, 1694, 1459, 1372, 1272, 1172, 994, 920, 738, 703 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.71–2.63 (m, 2 H), 2.24 (dd, *J* = 16.5, 6.3 Hz, 1 H), 2.01 (d, *J* = 17.4 Hz, 1 H), 1.92 (d, *J* = 12.5 Hz, 1 H), 1.79–1.70 (m, 2 H), 1.65–1.58 (m, 2 H), 1.57–1.53 (m, 1 H), 1.53–1.47 (m, 1 H), 1.47 (d, *J* = 12.6 Hz, 1 H), 1.31 (s, 3 H), 1.22 (s, 3 H), 1.09 (s, 3 H), 1.07–0.96 (m, 2 H), 0.88 (d, *J* = 6.3 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.4, 84.0, 58.1, 56.0, 51.8, 51.7, 47.5, 41.0, 39.5, 37.1, 36.3, 34.1, 27.9, 27.6, 27.3, 20.5; HRMS (ESI) calcd for $C_{16}H_{25}O^+$ [M + H^+ – H_2O] 233.1900, found 233.1908.

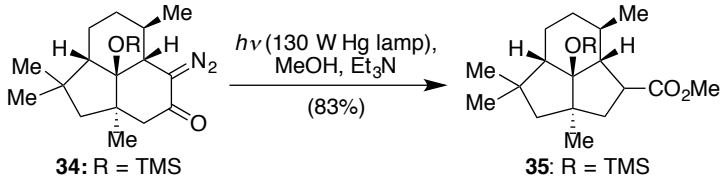
Scheme S1. X-ray crystal structure of **21**.





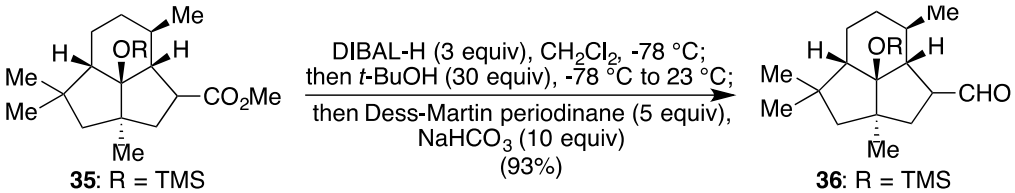
Diazoketone 34. To a solution of **21** (1.00 g, 4.0 mmol, 1.0 equiv) in CH_2Cl_2 (40 mL) at 23 °C was added Et_3N (3.34 mL, 12 mmol, 6.0 equiv) in a single portion followed by the slow addition of TMSOTf (3.62 mL, 20 mmol, 5.0 equiv) over the course of 10 min at 23 °C. Upon completion, 2 N HCl (50 mL) was added and the resultant mixture was vigorously stirred until TLC analysis indicated that all of the enol silyl ether had been hydrolyzed (typically 30 min). Et_2O (100 mL) was then added, the reaction contents were transferred to a separatory funnel, and the aqueous layer was separated. The organic layer was then washed with saturated aqueous $NaHCO_3$ (50 mL), H_2O (50 mL), and brine (50 mL) before being dried ($MgSO_4$), filtered, and concentrated. The resultant residue was purified by column chromatography (silica gel, hexanes/EtOAc, 50/1) to give protected ketone **S2** (1.29 g, 100% yield) as a colorless oil which turned into a solid upon freezer storage. **S2**: R_f = 0.21 (silica gel, hexanes/EtOAc = 20/1); $[\alpha]_D^{23}$ = –56.0° (*c* = 1.0, $CHCl_3$); IR (film) ν_{max} 2957, 2868, 1701, 1470, 1253, 1163, 1078, 1043, 948, 875, 837, 753 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 2.69 (d, *J* = 17.6 Hz, 1 H), 2.64–2.55 (m, 1 H), 1.93–1.87 (m, 2 H), 1.84 (d, *J* = 12.2 Hz, 1 H), 1.80–1.72 (m, 2 H), 1.46–1.38 (m, 5 H), 1.22 (d, *J* = 12.2 Hz, 1 H), 1.20 (s, 3 H), 1.18–1.10 (m, 1 H), 0.97 (s, 3 H), 0.93 (s, 3 H), 0.91–0.80 (m, 1 H), 0.68 (d, *J* = 6.4 Hz, 3 H), 0.16 (s, 9 H); ^{13}C NMR (125 MHz, C_6D_6) δ 210.2, 88.3, 56.7, 55.8, 52.4, 50.4, 49.0, 41.8, 39.5, 37.9, 36.0, 34.3, 28.3, 27.8, 27.0, 20.8, 2.5; HRMS (ESI) calcd for $C_{19}H_{35}O_2Si^+$ [M + H^+] 323.2401, found 323.2402. Next, to a solution of ketone **S2** (1.00 g, 3.1 mmol, 1.0 equiv) in CH_3CN (31 mL) at 23 °C was sequentially added *p*-ABSA (14.9 g, 62 mmol, 20 equiv) and DBU (13.9 mL, 93 mmol, 30 equiv). The reaction contents were then stirred at 23 °C overnight for 12 h before being quenched by the addition of H_2O (100 mL). The reaction contents were then poured into a separatory funnel, the layers were separated, and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with H_2O (3 × 50 mL) and brine (50 mL) before being dried ($MgSO_4$), filtered, and concentrated. The resultant residue was purified by column chromatography (silica gel, hexanes/EtOAc, 30/1→10/1) to gave the desired diazoketone **34** (1.03 g, 95% yield) as a yellow solid. **34**: R_f =

0.30 (silica gel, hexanes/EtOAc, 20/1); $[\alpha]_D^{23}$ = –125.0° (*c* = 1.3, $CHCl_3$); IR (film) ν_{max} 3048, 2960, 2082, 1623, 1456, 1380, 1316, 1264, 1222, 1174, 1093, 1051, 946, 839, 739, 650 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.70–2.60 (m, 2 H), 2.08 (d, *J* = 17.0 Hz, 1 H), 2.05–1.97 (m, 1 H), 1.96–1.90 (m, 1 H), 1.85 (d, *J* = 12.2 Hz, 1 H), 1.82–1.68 (m, 2 H), 1.58–1.45 (m, 1 H), 1.31 (d, *J* = 12.2 Hz, 1 H), 1.26–1.12 (m, 4 H), 1.20 (s, 3 H), 1.06 (s, 3 H), 1.05 (d, *J* = 6.4 Hz, 3 H), 0.14 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.4, 85.1, 66.2, 56.2, 54.7, 50.8, 49.0, 47.5, 39.1, 37.0, 35.7, 34.2, 27.8, 27.6, 26.5, 21.5, 2.3; HRMS (ESI) calcd for $C_{19}H_{32}N_2NaO_2Si^+$ [M + Na^+] 371.2125, found 371.2118.



34: R = TMS **35**: R = TMS

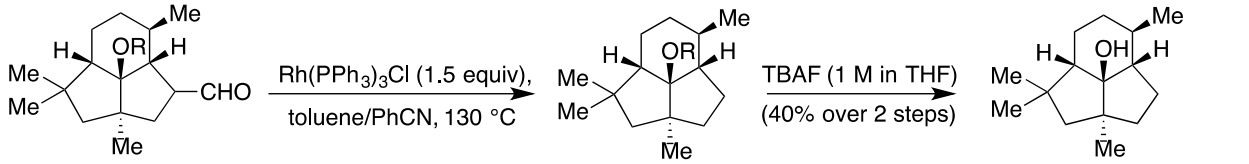
Ester 35. To a 100 mL quartz reaction flask was added diazoketone **34** (1.00 g, 2.87 mmol, 1.0 equiv), MeOH (80 mL), and Et_3N (0.54 mL). The resultant yellow solution was then degassed at 23 °C by bubbling argon directly through the mixture for 30 min, and then the contents were irradiated at 23 °C using a 125 W medium pressure UV lamp. Once TLC analysis indicated that the starting material was fully consumed (typically following 30 min of irradiation), the reaction contents were concentrated directly and purified by column chromatography (silica gel, hexanes/EtOAc, 30/1→20/1) to afford the desired ring-contracted ester **35** (0.837 g, 83% yield) as an colorless oil which solidified under freezer storage. **35**: R_f = 0.51 (silica gel, hexanes/EtOAc, 20/1); $[\alpha]_D^{23}$ = +12.2° (*c* = 1.5, $CHCl_3$); IR (film) ν_{max} 2951, 1734, 1458, 1380, 1250, 1224, 1196, 1078, 1037, 939, 839 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 3.41 (s, 3 H), 2.95 (ddd, *J* = 9.1, 7.6, 4.3 Hz, 1 H), 2.54 (t, *J* = 10.5 Hz, 1 H), 2.15–2.10 (m, 1 H), 2.04 (dd, *J* = 10.5, 4.4 Hz, 1 H), 1.68 (dd, *J* = 12.5, 8.0 Hz, 1 H), 1.54 (dd, *J* = 11.0, 7.6 Hz, 1 H), 1.52–1.40 (m, 2 H), 1.32 (s, 3 H), 1.25–1.15 (m, 1 H), 1.14–1.12 (m, 1 H), 1.13 (s, 3 H), 1.12–1.05 (m, 5 H), 1.04 (s, 3 H), 0.26−0.20 (m, 9 H); ^{13}C NMR (125 MHz, C_6D_6) δ 175.6, 99.5, 58.0, 53.8, 52.6, 52.1, 51.2, 49.5, 47.6, 38.5, 38.3, 36.3, 34.7, 28.2, 27.2, 22.0, 3.1; HRMS (ESI) calcd for $C_{20}H_{37}O_3Si^+$ [M + H^+] 353.2505, found 353.2507.



35: R = TMS **36**: R = TMS

Aldehyde 36. To a solution of **35** (0.320 g, 0.91 mmol, 1.0 equiv) in CH_2Cl_2 (9 mL) at –78 °C was added DIBAL-H (1.0 M in CH_2Cl_2, 2.73 mL, 2.73 mmol, 3.0 equiv) dropwise over the course of 10 min. The reaction contents were then stirred at –78 °C until TLC analysis indicated that the starting material was fully consumed (typically 1 h). Upon completion, the reaction contents were quenched at –78 °C by a slow addition of *t*-BuOH (2.02 g, 27.3 mmol, 30 equiv) and then warmed to 23 °C and stirred at that temperature for 1 h. Next, solid $NaHCO_3$ (0.755 g, 9.1 mmol, 10 equiv) was added in a single portion and then Dess-Martin periodinane (1.93 g,

4.55 mmol, 5 equiv) was added in 10 batches over the course of 10 min. The reaction contents were then stirred vigorously at 23 °C for 2 h before being quenched by the addition of a mixed solution of saturated aqueous $NaHCO_3$ (20 mL) and saturated aqueous $Na_2S_2O_3$ (20 mL). After stirring the resultant slurry at 23 °C for 1 h, the reaction mixture was diluted with Et_2O (50 mL) and H_2O (50 mL) and transferred to a separatory funnel. The layers were separated and the aqueous phase was extracted with Et_2O (2 × 30 mL). The combined organic layers were then washed with $NaHCO_3$ (50 mL), H_2O (3 × 50 mL), and brine (50 mL) before being dried ($MgSO_4$), filtered, and concentrated. The resultant residue was purified by column chromatography (silica gel, hexanes/EtOAc, 30/1→10/1) to gave the desired aldehyde **36** (0.274 g, 93% yield) as a colorless oil, which solidified under freezer storage. [Note: aldehyde **36** was found to be unstable for storage and thus should be used immediately]. **36**: $R_f = 0.50$ (silica gel, hexanes/EtOAc, 20/1); $[\alpha]_D^{23} = +20.8°$ ($c = 2.5$, $CHCl_3$); IR (film) ν_{max} 2952, 1723, 1457, 1379, 1264, 1251, 1040, 940, 876, 838, 754 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 9.66 (s, 1 H), 2.65–2.58 (m, 1 H), 2.31–2.25 (m, 1 H), 2.07 (d, $J = 10.0$ Hz, 1 H), 1.83 (dd, $J = 10.0$, 5.0 Hz, 1 H), 1.67–1.61 (m, 1 H), 1.48–1.37 (m, 3 H), 1.30–1.23 (m, 1 H), 1.29 (s, 3 H), 1.19–1.13 (m, 1 H), 1.11 (s, 3 H), 1.03–0.96 (m, 2 H), 0.99 (s, 3H), 0.90 (d, $J = 10.0$ Hz, 1 H), 0.16 (s, 9 H); ^{13}C NMR (125 MHz, C_6D_6) δ 202.3, 99.4, 62.7, 57.8, 51.6, 50.4, 49.3, 47.7, 37.8, 36.3, 35.8, 34.4, 28.2, 28.1, 27.2, 21.8, 3.5; HRMS (ESI) calcd for $C_{19}H_{35}O_2Si^+$ [M + H^+] 323.2401, found 323.2404.



36: R = TMS **S3**: R = TMS **5**: (-)-presilphiperfolan-8-ol

(–)-Presilphiperfolan-8-ol (5). To a flame-dried flask at 23 °C was sequentially added freshely prepared aldehyde **36** (16.1 mg, 0.05 mmol, 1 equiv), $Rh(PPh_3)_3Cl$ (69.4 mg, 0.075 mmol, 1.5 equiv), toluene (0.9 mL) and benzonitrile (0.15 mL). The reaction contents were then degassed at 23 °C by bubbling argon directly through the mixture for 30 min and then were heated at 130 °C for 12 h. Upon completion, the reaction contents were cooled to 23 °C, the solvent was removed under vacuum, and the resultant residue was purified directly by filtration through a short pad of silica gel using hexanes as eluent to remove any metal salts. The filtrate was concentrated to afford a crude sample of TMS-protected presilphiperfolan-8-ol **S3**. Pressing forward, that material (0.05 mmol assumed, 1.0 equiv) was treated with TBAF (1.0 M in THF, 0.5 mmol, 0.5 mL) at 23 °C and the resultant solution was then warmed to 30 °C and stirred overnight for 12 h. Upon completion, the reaction contents were diluted with Et_2O (10 mL) and H_2O (10 mL), transferred to a separatory funnel, and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic layers were then washed with H_2O (20 mL) before being dried ($MgSO_4$), filtered, and concentrated. The resultant residue was purified by column chromatography (silica gel, hexanes/Et_2O, 50/1→30/1) to give presilphiperfolan-8-ol (**5**, 4.5 mg, 40% yield over 2 steps) as a white solid. Reactions with similar scale were repeated two additional times to generate in total ~15 mg of the natural product. **5**: $R_f = 0.42$ (silica gel, hexanes/Et_2O, 6/1); $[\alpha]_D^{23} = –18.0°$ ($c = 0.5$, $CHCl_3$); IR (film) ν_{max} 3375 (OH), 3024, 1456, 1375, 1160, 1117, 977, 894, 869 cm^{-1}; ^1H NMR (500 MHz, C_6D_6)

δ 2.30 (ddt, *J* = 13.6, 8.8, 0.8 Hz, 1 H), 2.15 (d, *J* = 11.3 Hz, 1 H), 2.07 (ddd, *J* = 19.0, 9.0, 1.3, 1 H), 1.78 (dddd, *J* = 13.4, 9.2, 7.7, 4.0 Hz, 1 H), 1.53–1.43 (m, 2 H), 1.40–1.37 (m, 1 H), 1.37 (s, 3 H), 1.31–1.22 (m, 3 H), 1.22–1.19 (m, 1 H), 1.19–1.16 (m, 1 H), 1.16 (s, 3 H), 1.16–1.14 (m, 1 H), 1.11 (s, 3 H), 0.99 (ddd, J = 10.7, 9.0, 3.9 Hz, 1 H), 0.84 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 96.3, 56.4, 52.3, 50.3, 49.5, 48.1, 37.5, 36.5, 34.6, 34.1, 33.3, 28.1, 28.0, 27.2, 21.8; HRMS (ESI) calcd for $C_{15}H_{25}^+$ [M + H^+ − H_2O] 205.1951, found 205.1946. All spectral data matched that reported by Coates and co-workers[3] for natural (–)-presilphiperfolan-8-ol, with a comparison table provided below in Table S1.

Table S1. Comparison of NMR data between our synthetic material and that obtained from Nature by Coates and co-workers

^{1}H NMR (C_6D_6)		^{13}C NMR (C_6D_6)	
Synthetic	Natural	Synthetic	Natural
2.30 (ddt, *J* = 13.6, 8.8, 0.8 Hz, 1 H)	2.29 (dddd, *J* = 14, 9, 8, 0.5 Hz, 1H)	96.30	96.22
2.15 (d, *J* = 11.3 Hz, 1 H)	2.14 (d, *J* = 11 Hz, 1 H)	56.45	56.29
2.07 (ddd, *J* = 19.0, 9.0, 1.3, 1 H)	2.06 (ddd, *J* = 14, 9, 8 Hz, 1 H)	52.34	52.48
1.78 (dddd, *J* = 13.4, 9.2, 7.7, 4.0 Hz, 1 H)	1.77 (dddd, *J* = 14, 9, 8, 4 Hz, 1 H)	50.27	50.17
1.53–1.43 (m, 2 H)	1.48 (ddd, *J* = 12, 6, 3 Hz, 1 H)	49.47	49.37
	1.46 (ddd, *J* = 12, 6, 3 Hz, 1 H)	48.06	48.01
1.40–1.37 (m, 1 H)	1.44 (ddd, *J* = 12, 6, 3 Hz, 1 H)	37.53	37.47
1.37 (s, 3 H)	1.36 (s, 3 H)	36.51	36.46
	1.26 (m, 1 H)	34.59	34.53
1.31–1.22 (m, 3 H)	1.23 (s, 1 H, OH)	34.09	34.02
	1.22 (m, 1 H)	33.33	33.28
1.22–1.19 (m, 1 H)	1.21 (m, 1 H)	28.13	28.09
1.19–1.16 (m, 1 H)	1.16 (ddd, *J* = 15, 9, 4 Hz, 1 H)	27.99	27.95
1.16 (s, 3 H)	1.15 (s, 3 H)	27.16	27.09
1.16–1.14 (m, 1 H)	1.14 (d, *J* = 11 Hz, 1 H)	21.81	21.80
1.11 (s, 3 H)	1.10 (s, 3 H)		
0.99 (ddd, J = 10.7, 9.0, 3.9 Hz, 1 H)	0.98 (m, 1 H)		
0.84 (d, *J* = 6.4 Hz, 3 H)	0.83 (d, *J* = 6 Hz, 3 H)		

References

1. (a) Davis, C. E.; Coates, R. M. *Angew. Chem. Int. Ed.* **2002**, *41*, 491; (b) Miles, R. B.; Davis, C. E.; Coates, R. M. *J. Org. Chem.* **2006**, *71*, 1493.
2. Kobayashi, T.; Shiroi, H.; Abe, H.; Ito, H. *Chem. Lett.* **2013**, *42*, 975.
3. Coates, R. M.; Ho, Z.; Klobus, M.; Wilson, S. R. *J. Am. Chem. Soc.* **1996**, *118*, 9249.

Enantiospecific Total Synthesis of the Highly Strained (–)-Presilphiperfolan-8-ol via a Pd-Catalyzed Tandem Cyclization

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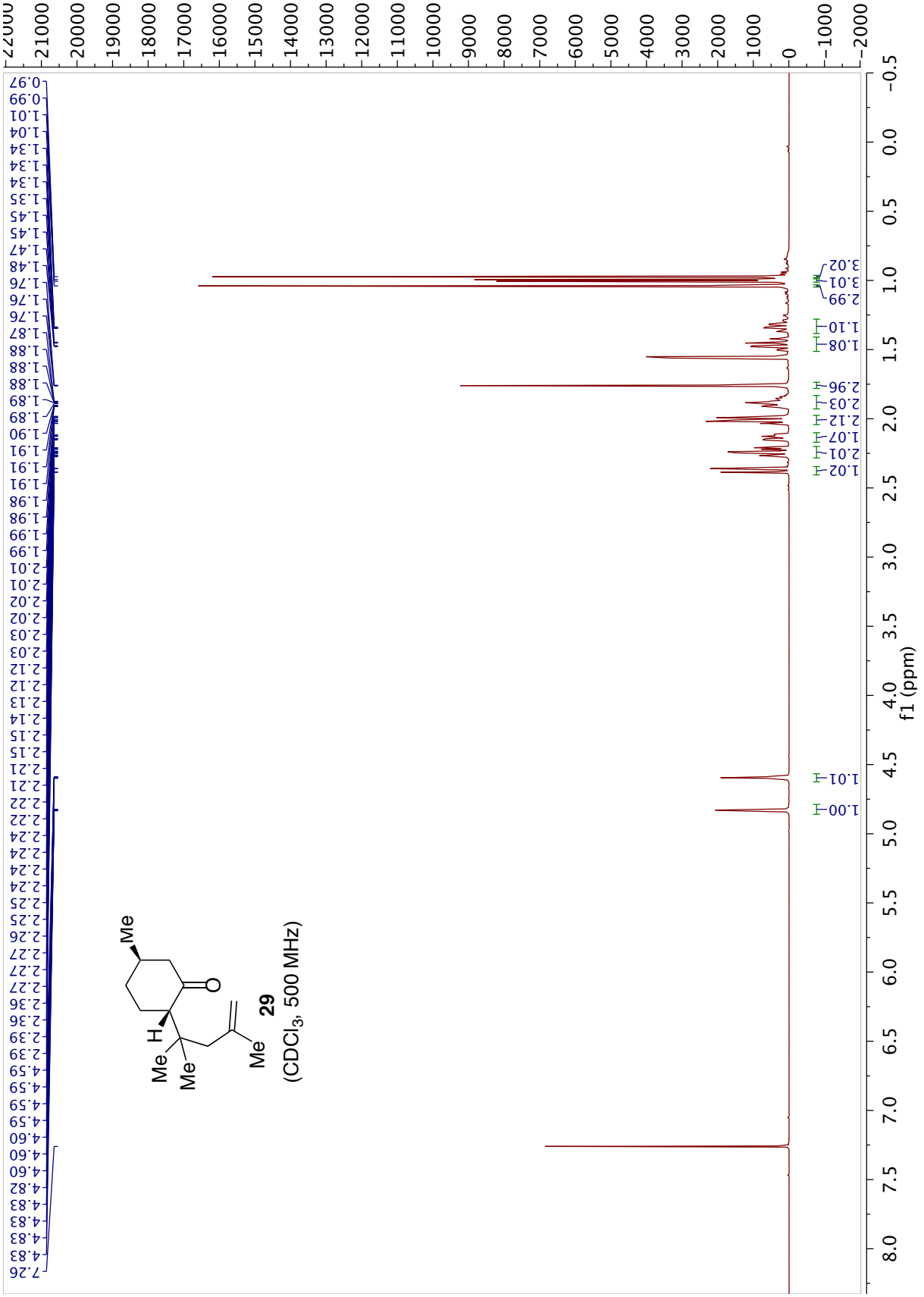
Supporting Information

^{1}H and ^{13}C NMR Spectra of Selected Intermediates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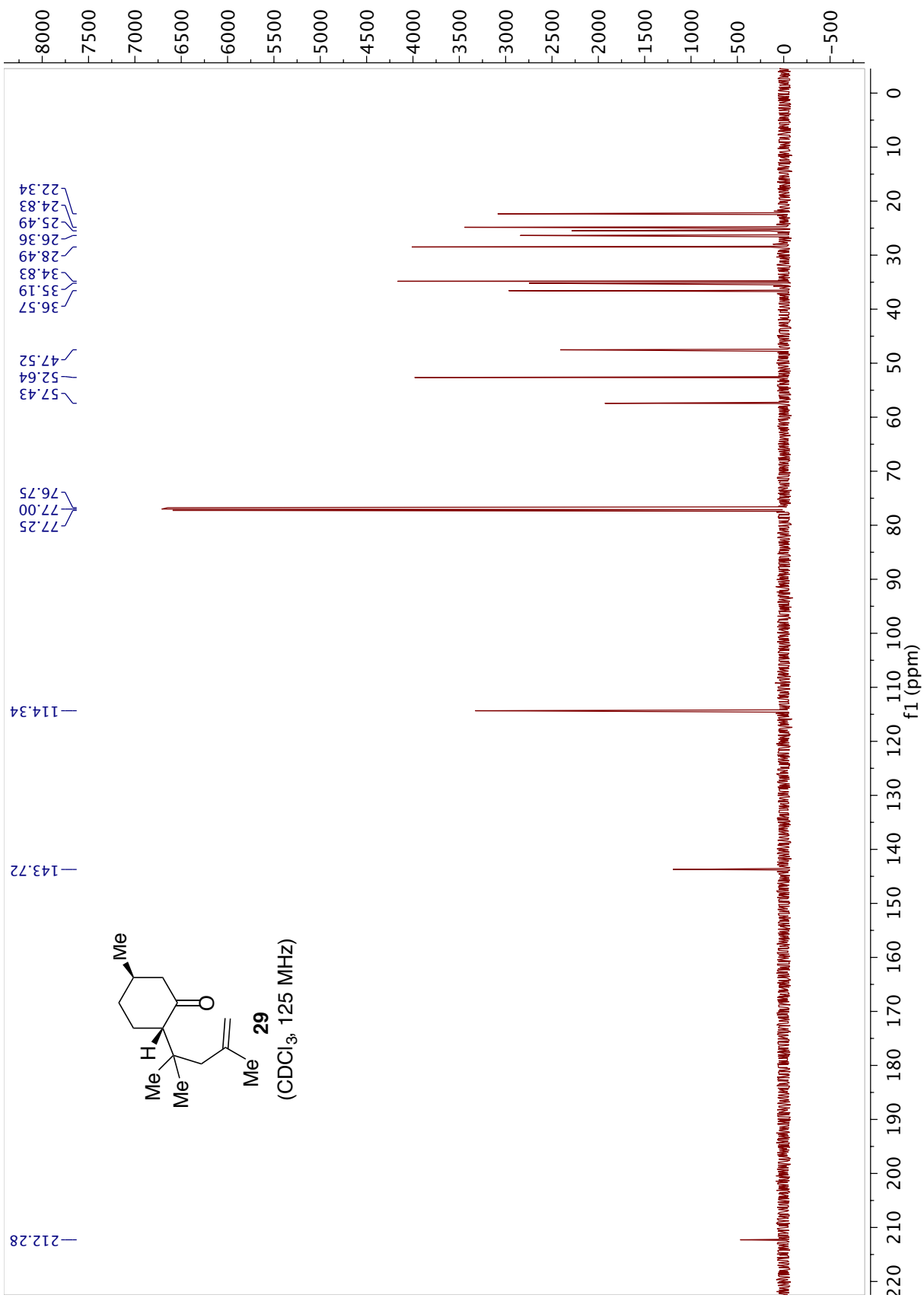
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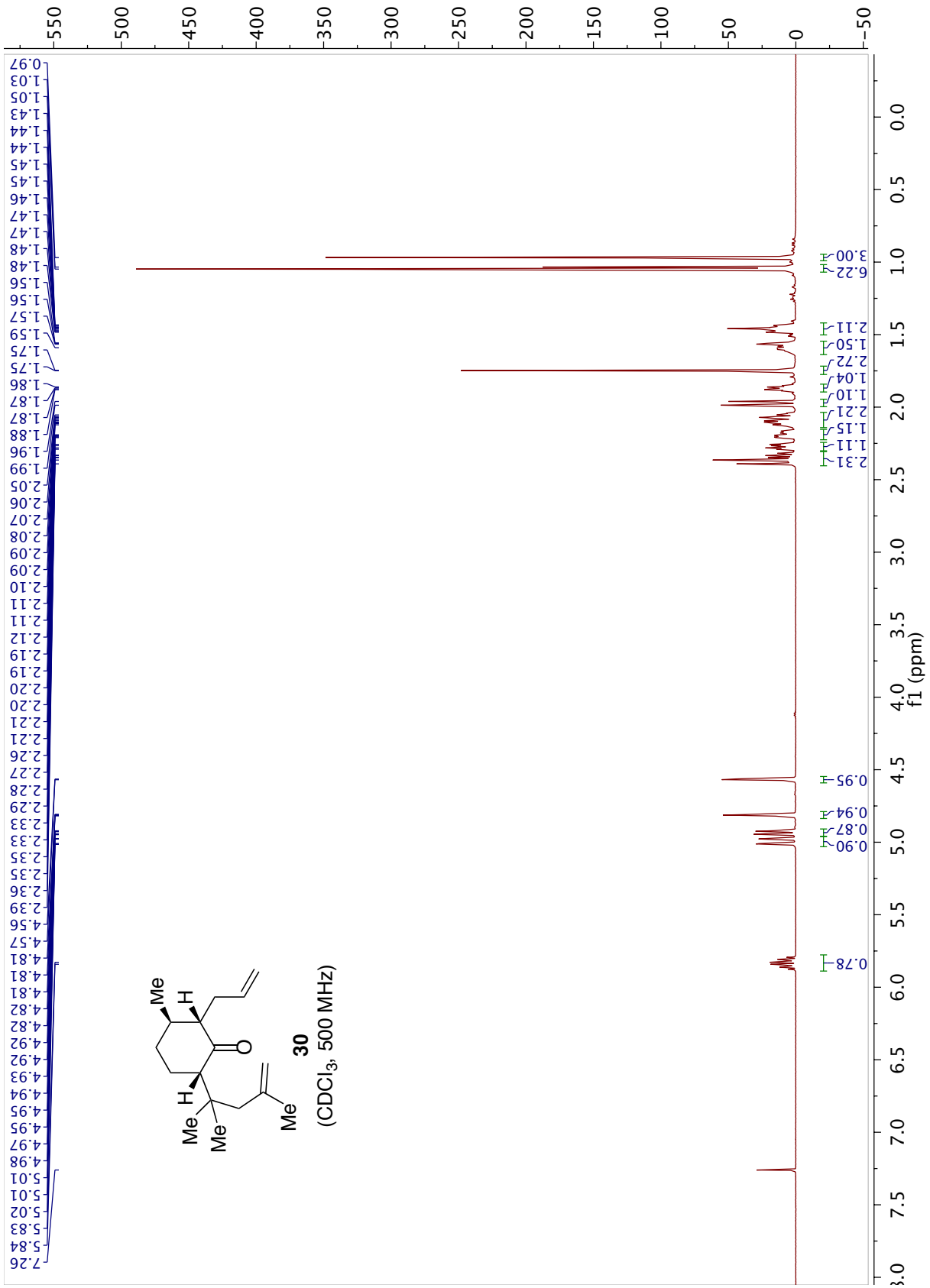
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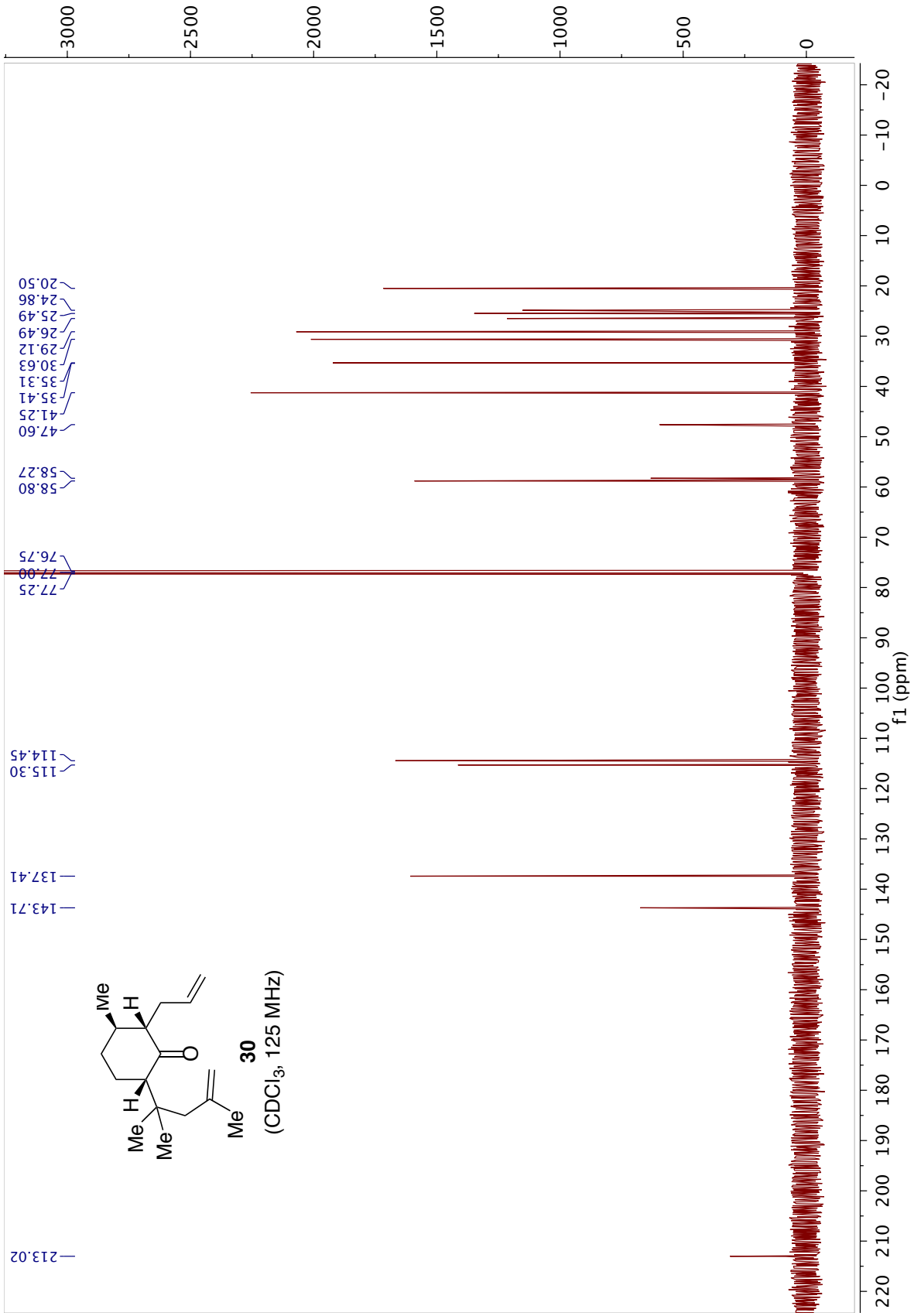
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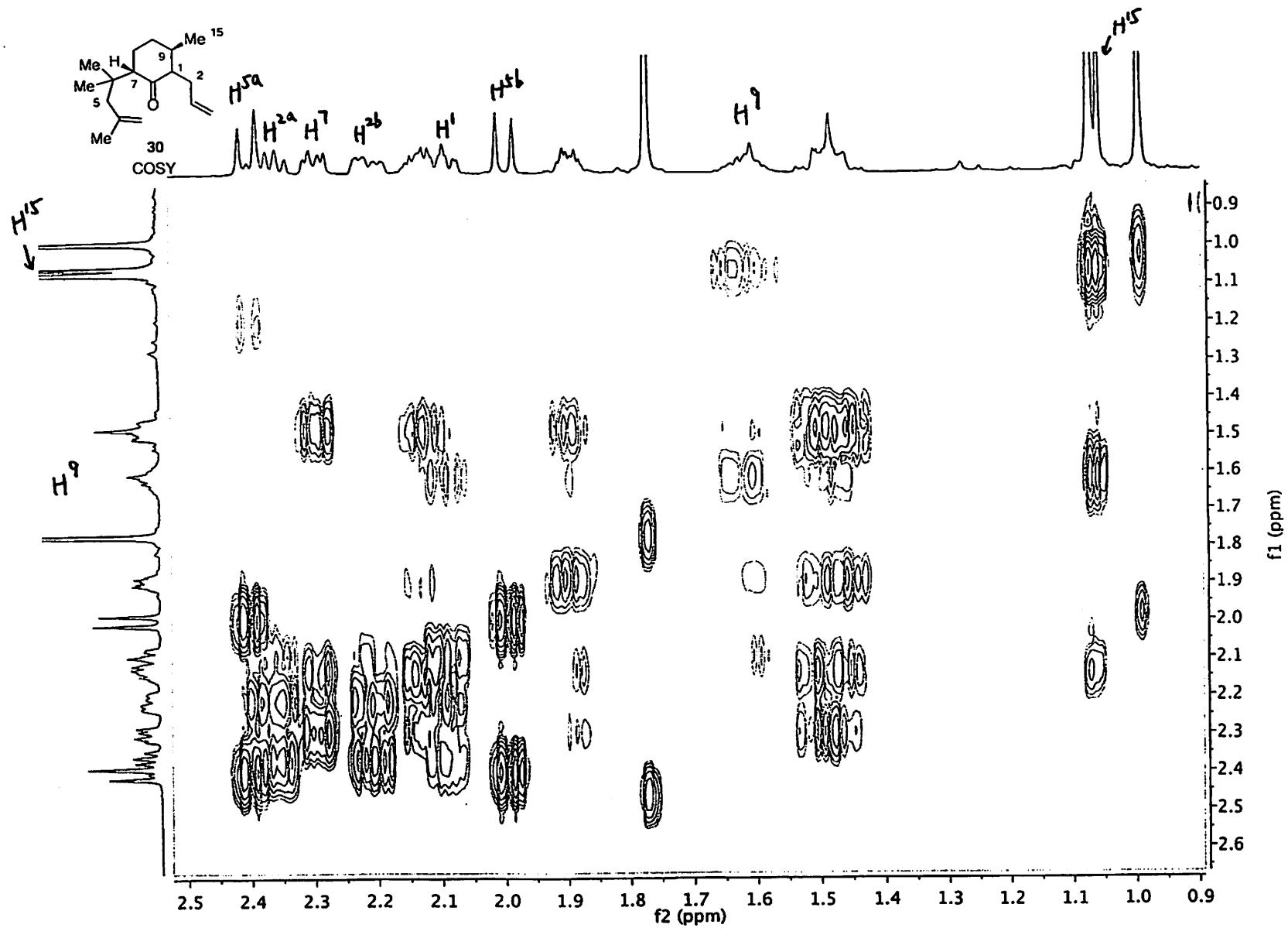
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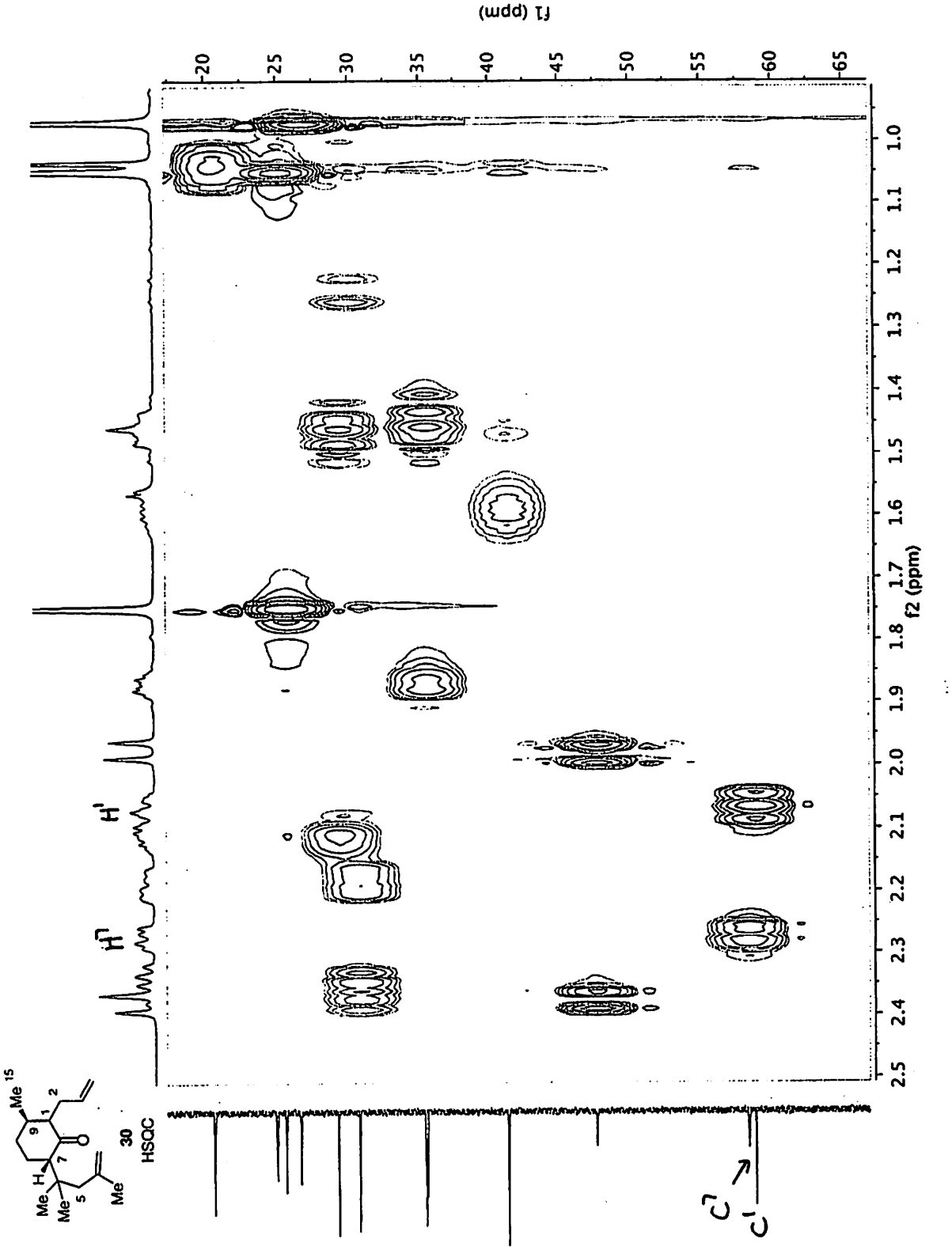
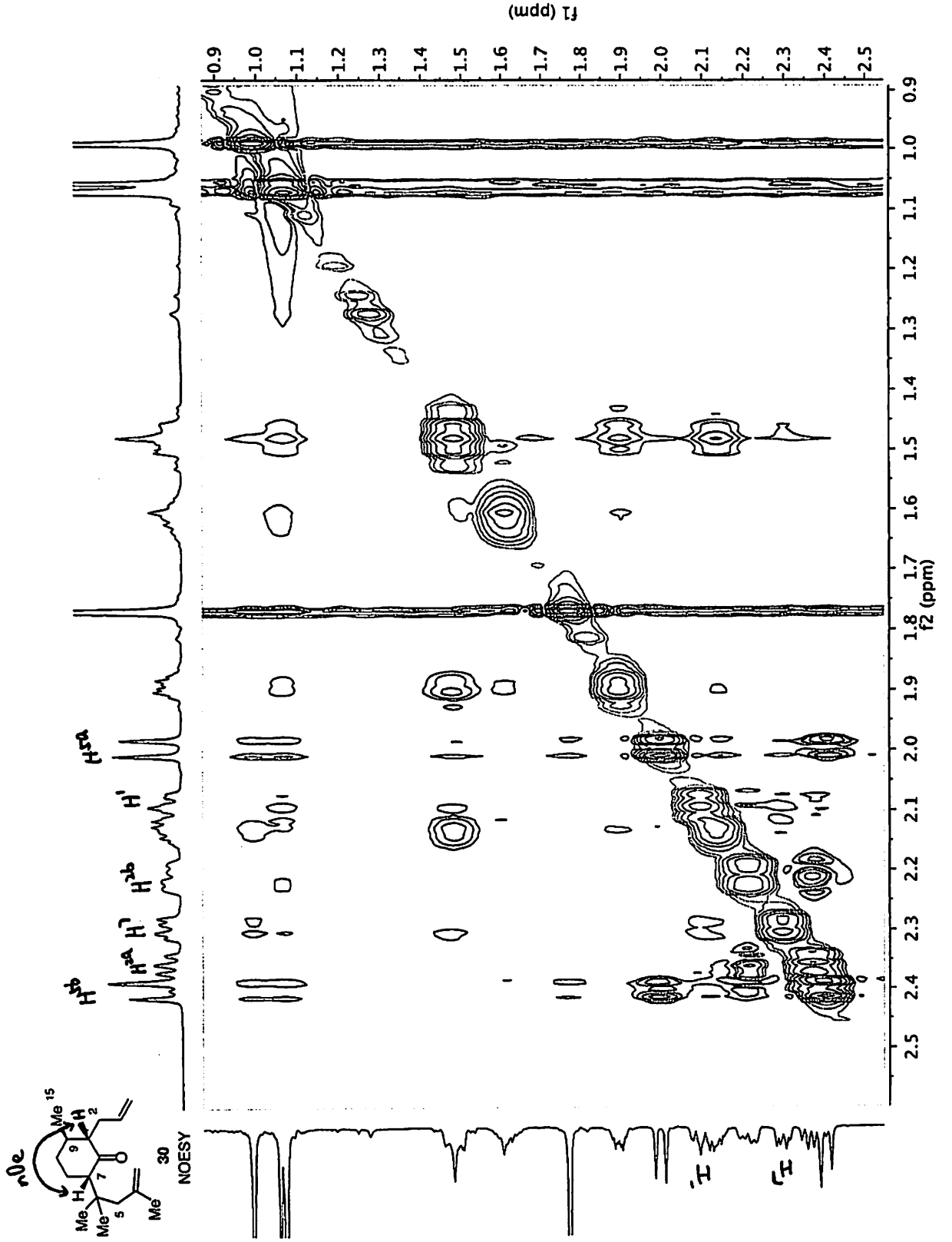
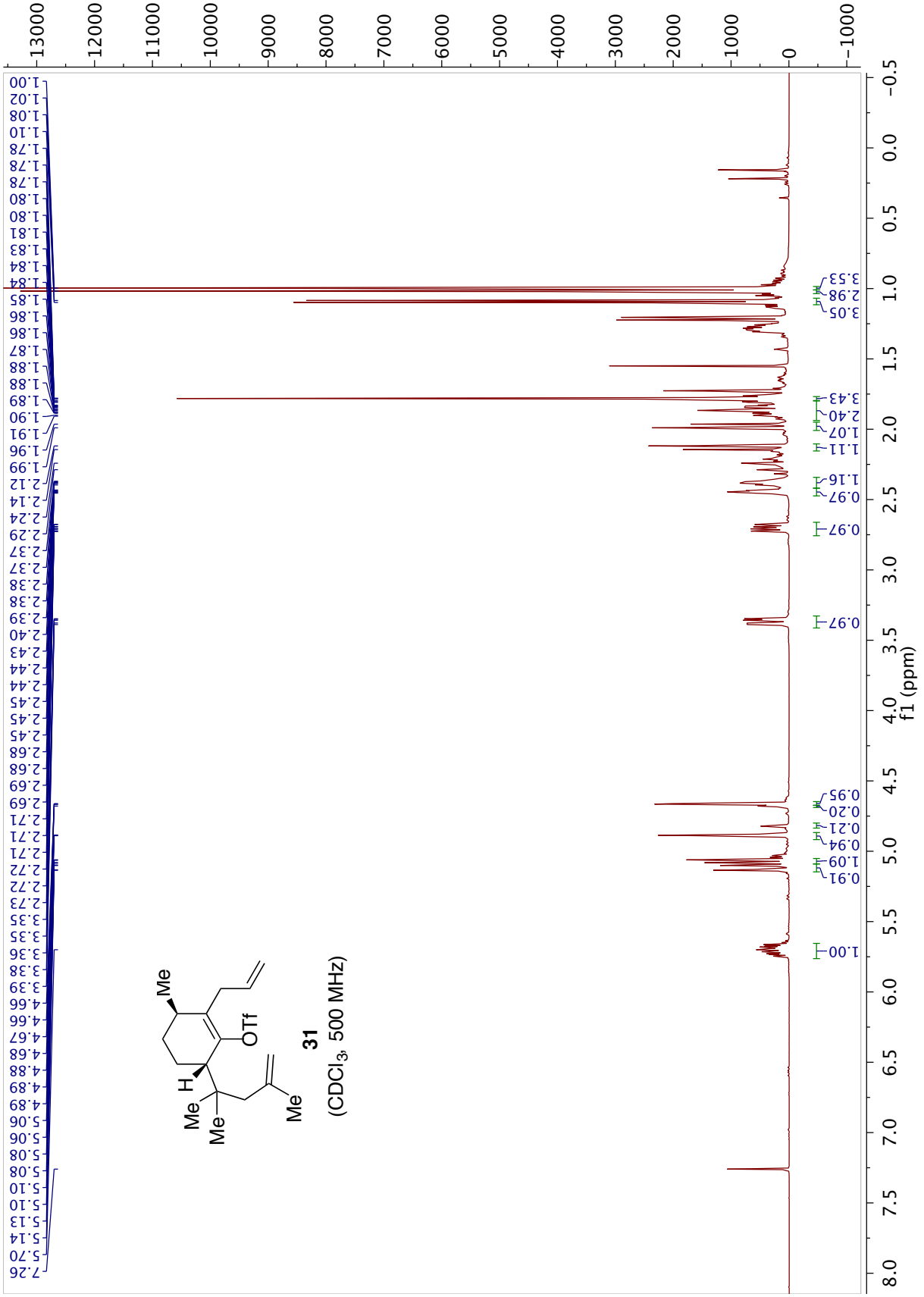
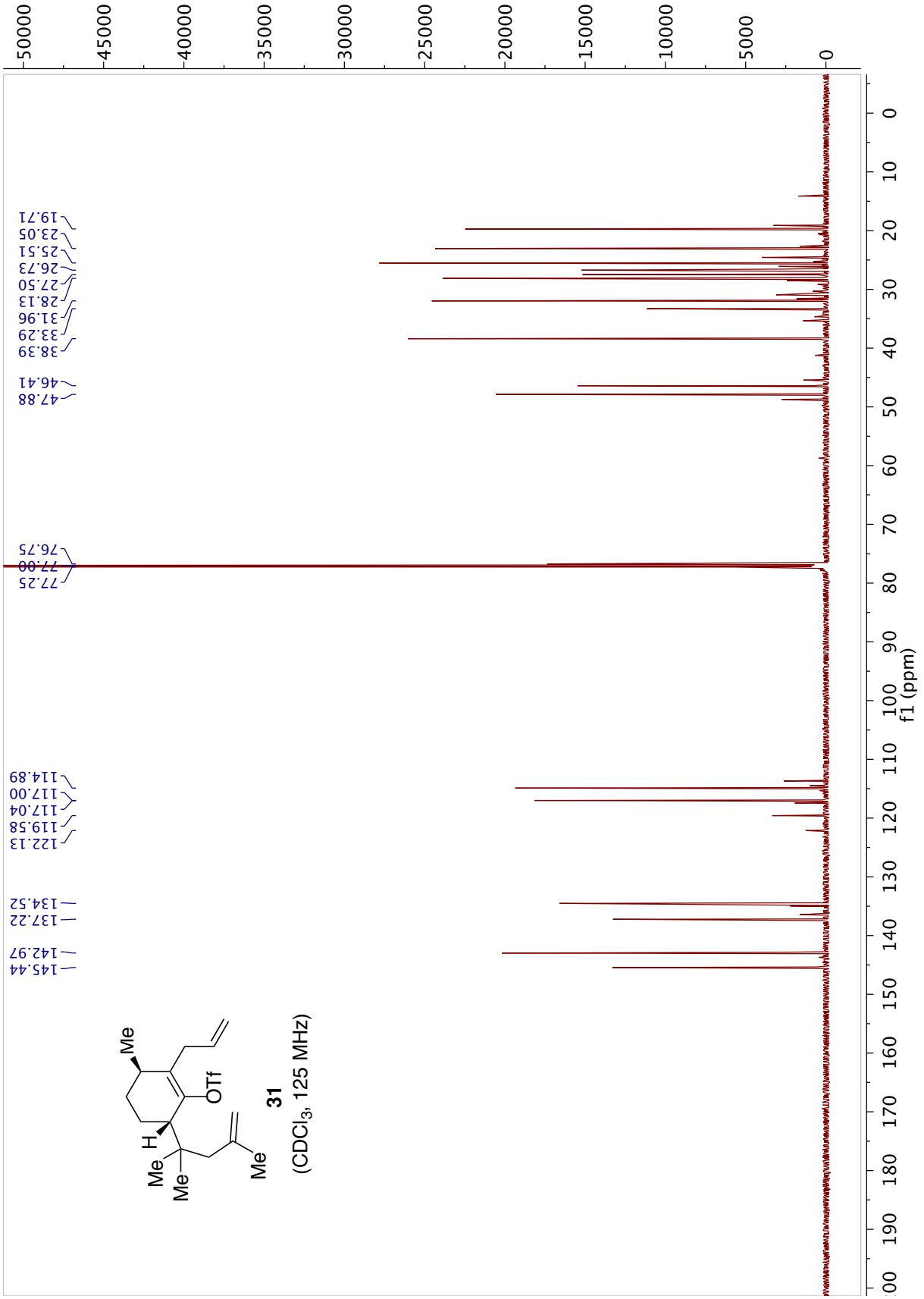
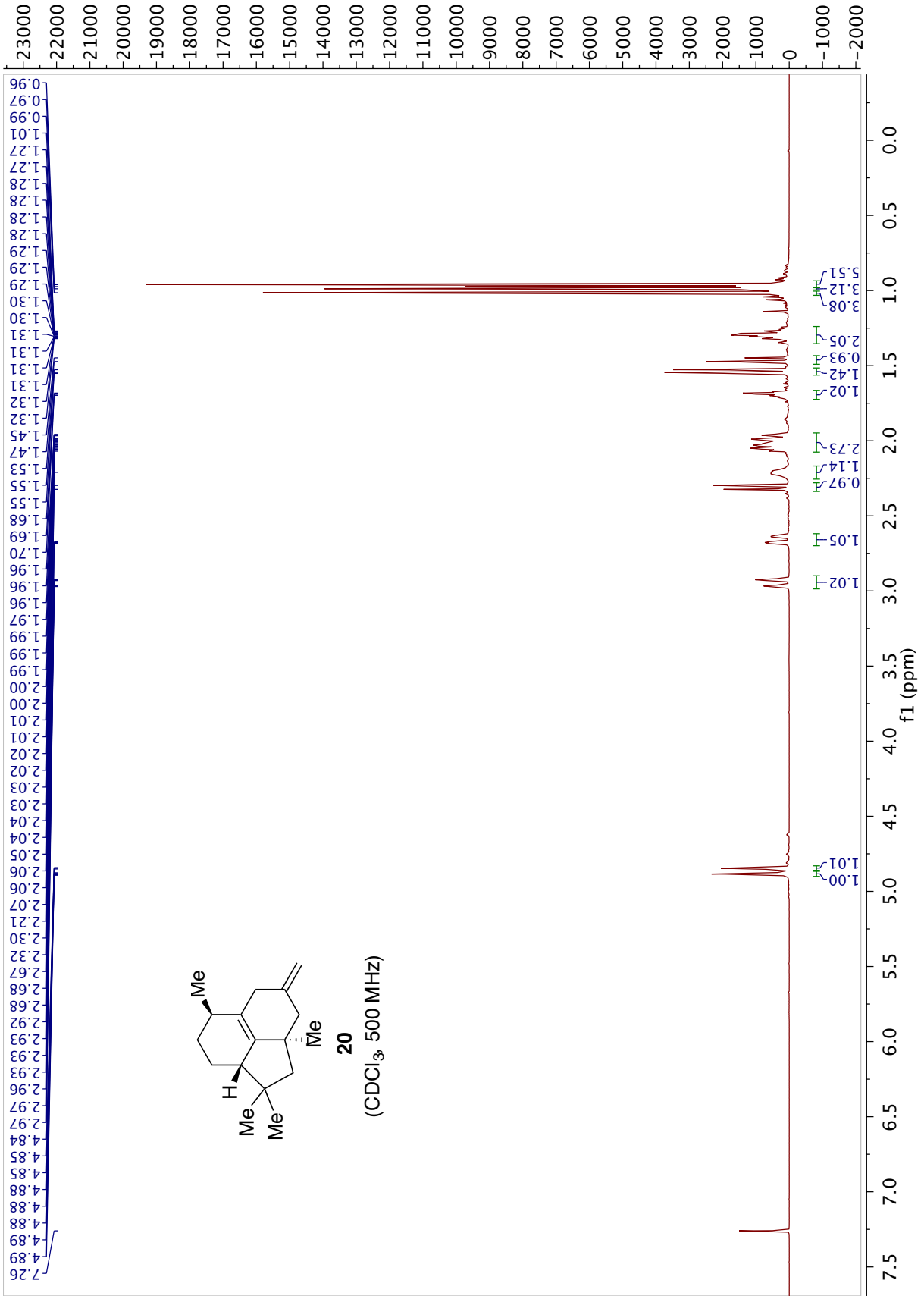
COSY
H5a
H2a
H7
H2b
H1
H5b
H9
H15
H15
H9
0.9
1.0
1.1
1.2
1.3
1.4
1.5
1.6
1.7
1.8
1.9
2.0
2.1
2.2
2.3
2.4
2.5
2.6
f1 (ppm)
2.5
2.4
2.3
2.2
2.1
2.0
1.9
1.8
1.7
1.6
1.5
1.4
1.3
1.2
1.1
1.0
0.9
f2 (ppm)

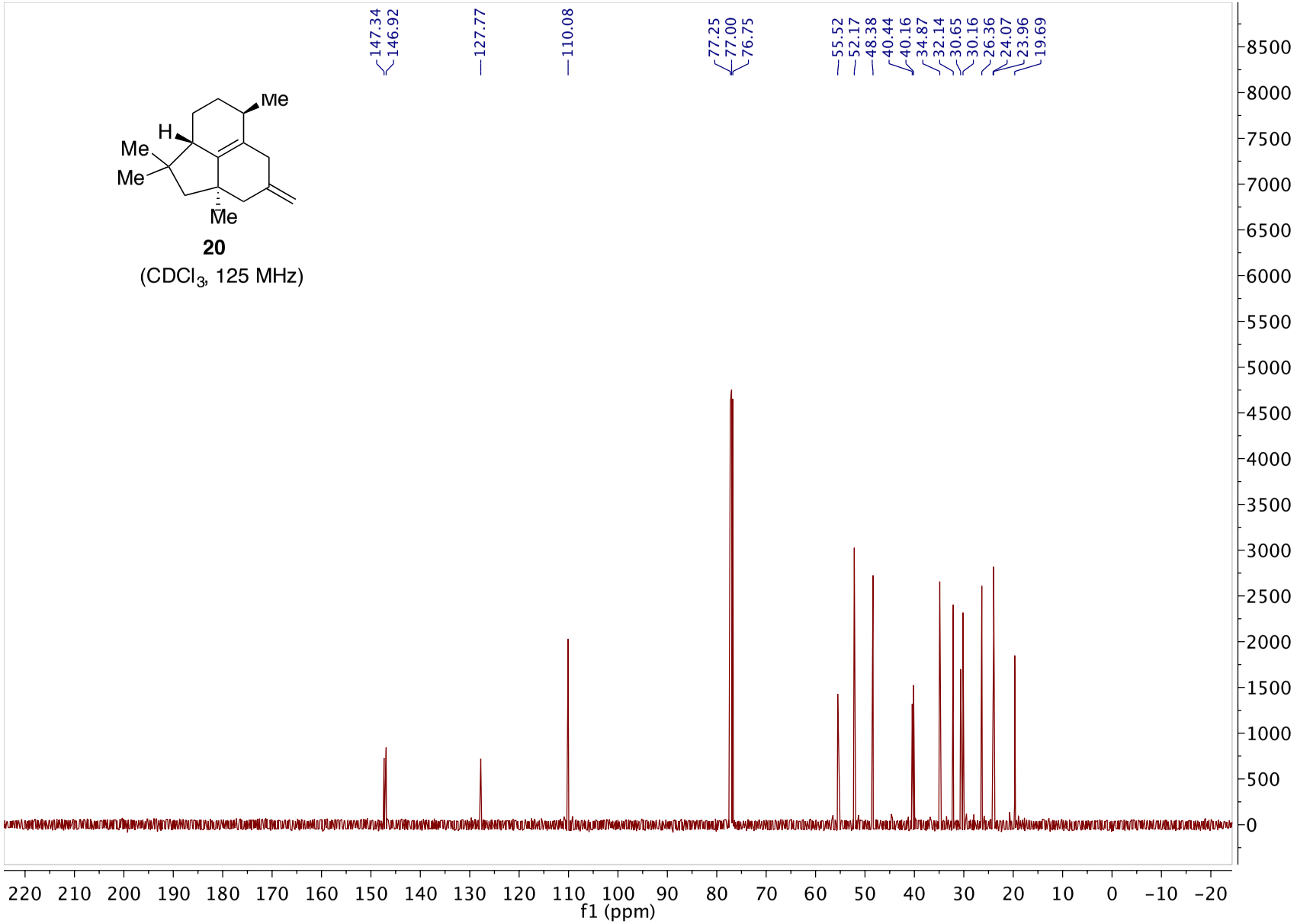

f1 (ppm)
f2 (ppm)
HSQC
30
Me
Me
Me
Me
H
H'
H''
C'
C''

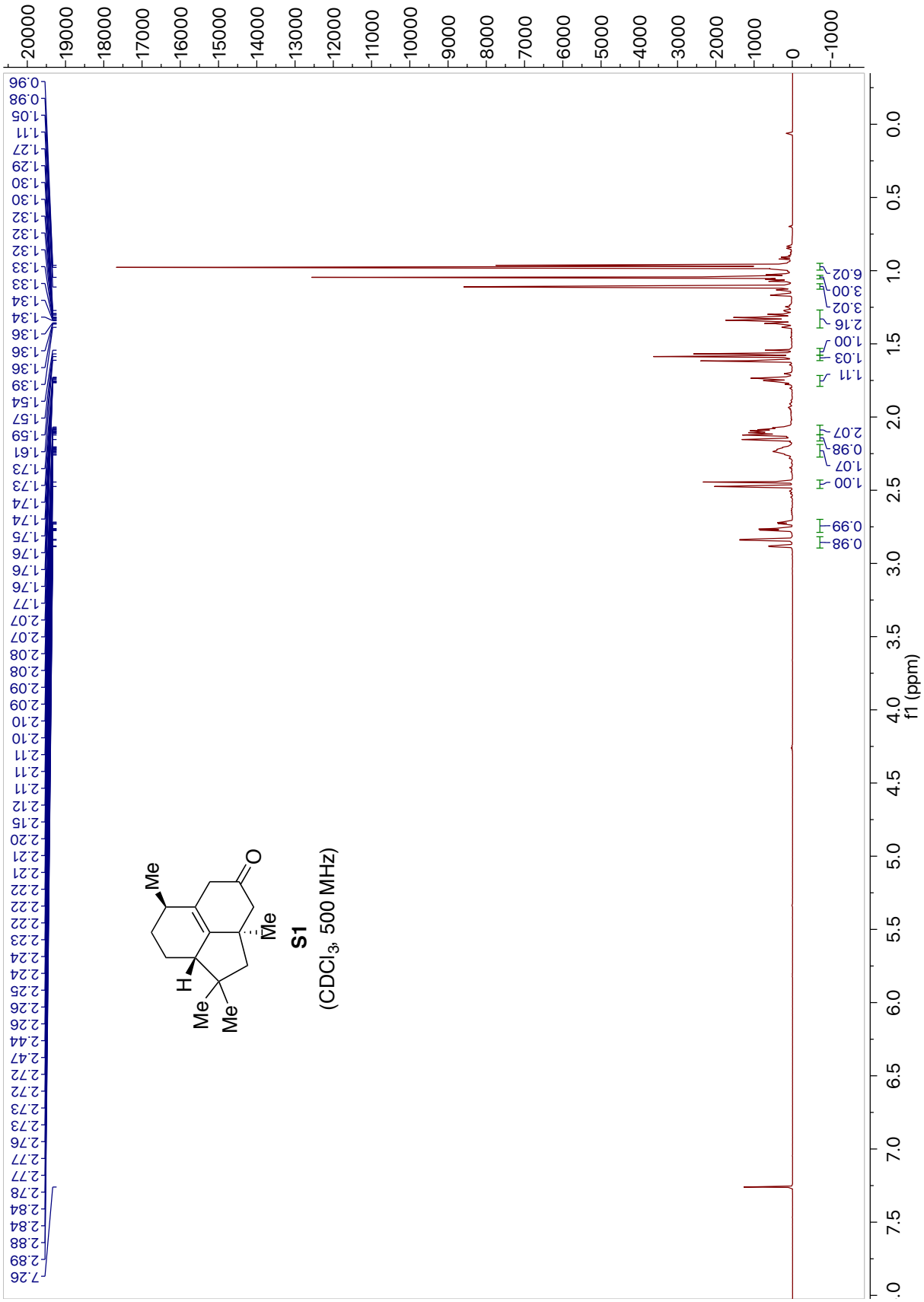

nOe
Me 15
H 2
9
7
O
Me
H
Me
5
Me
30
NOESY
H^4b
H^4a H^7
H^3b
H'
H^5a
f2 (ppm)
f1 (ppm)

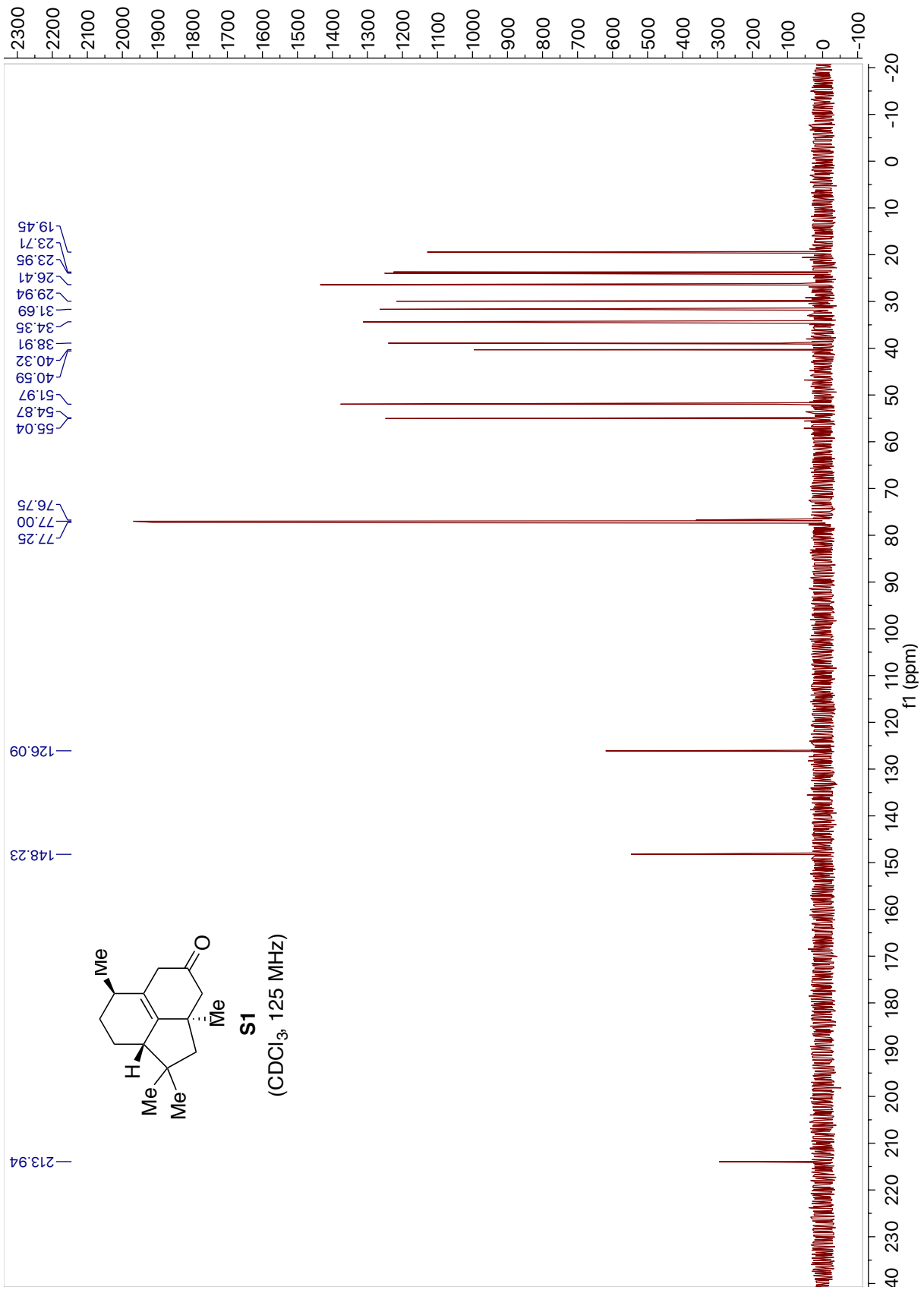

Me
OTf
H
Me
Me
Me
31
(CDCl3, 500 MHz)
f1 (ppm)

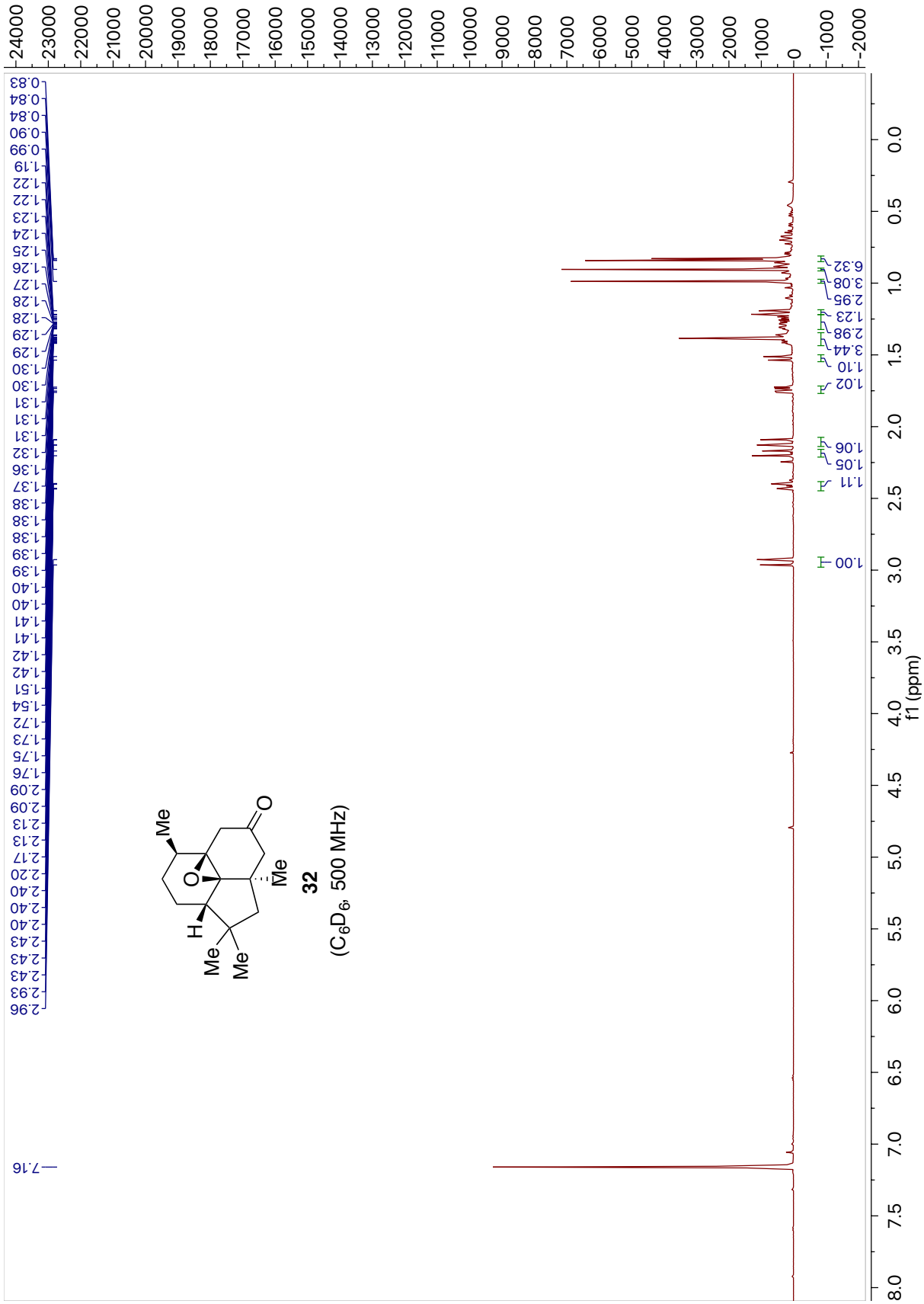

145.44
142.97
137.22
134.52
122.13
119.58
117.04
117.00
114.89
77.25
77.00
76.75
47.88
46.41
38.39
33.29
31.96
28.13
27.50
26.73
25.51
23.05
19.71
f1 (ppm)
Me
OTf
H
Me
Me
Me
31
(CDCl3, 125 MHz)

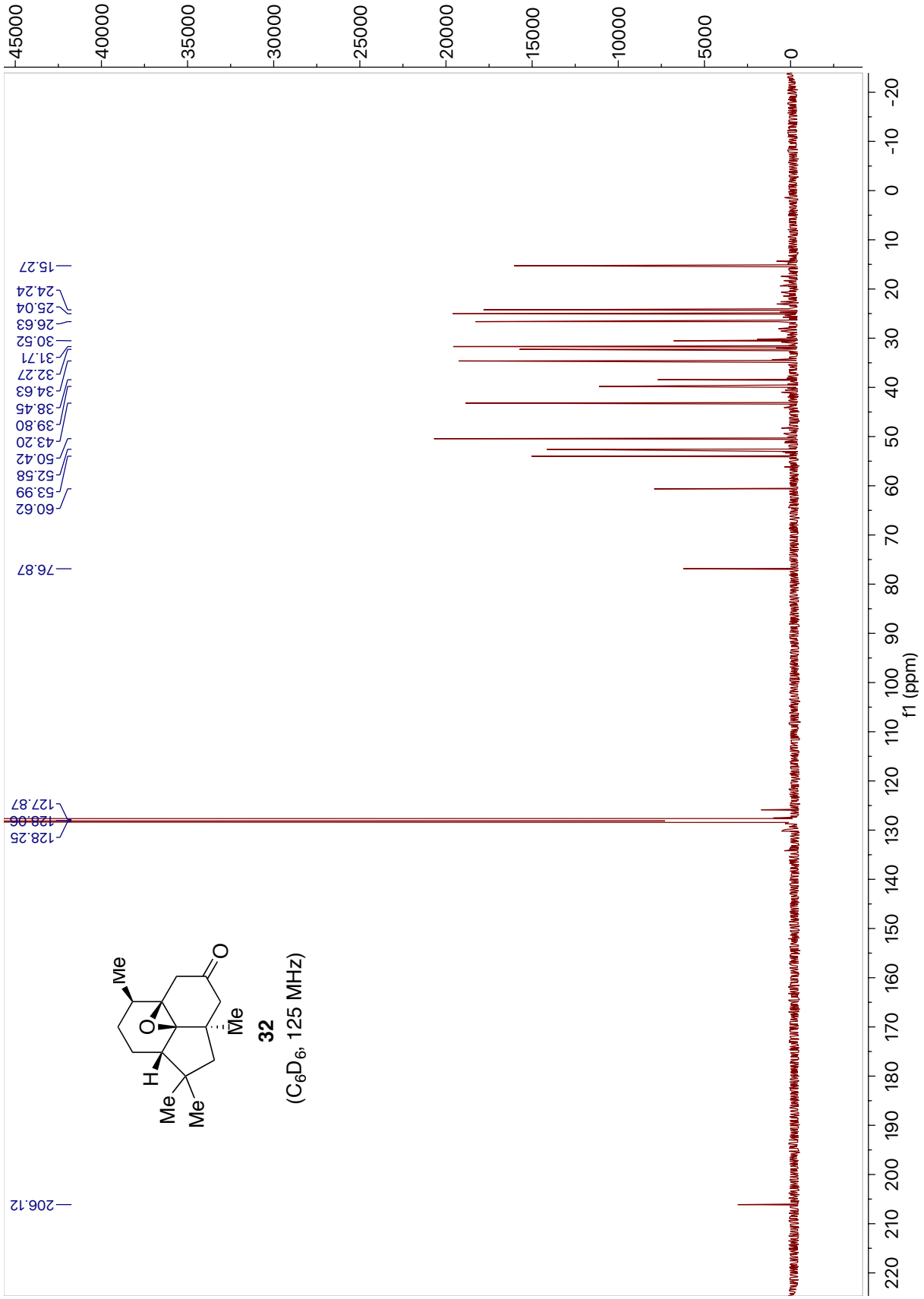

Me
H
Me
Me
Me
20
(CDCl3, 500 MHz)
f1 (ppm)

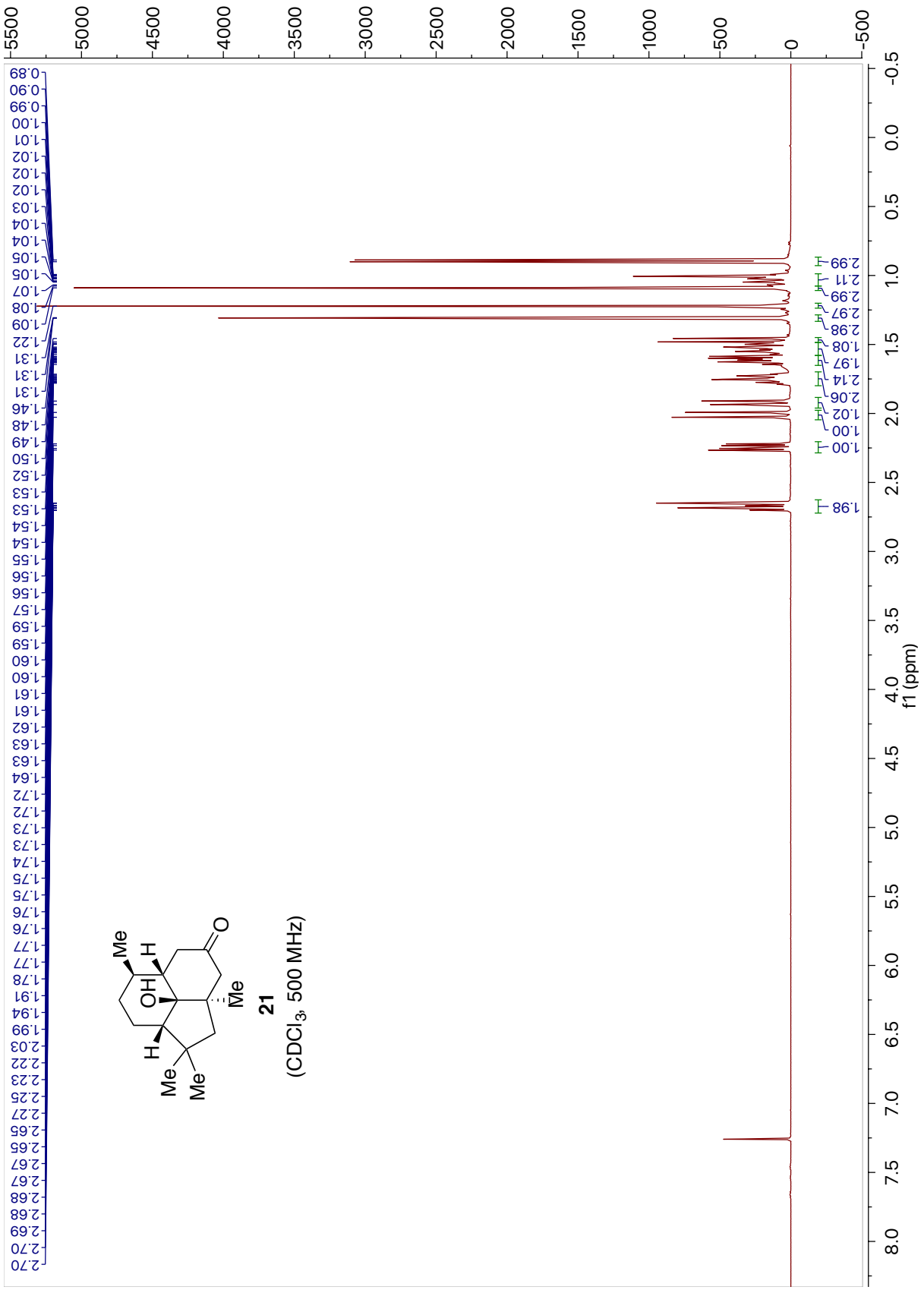

147.34
146.92
127.77
110.08
77.25
77.00
76.75
55.52
52.17
48.38
40.44
40.16
34.87
32.14
30.65
30.16
26.36
24.07
23.96
19.69
Me
H
Me
Me
Me
20
(CDCl3, 125 MHz)
f1 (ppm)

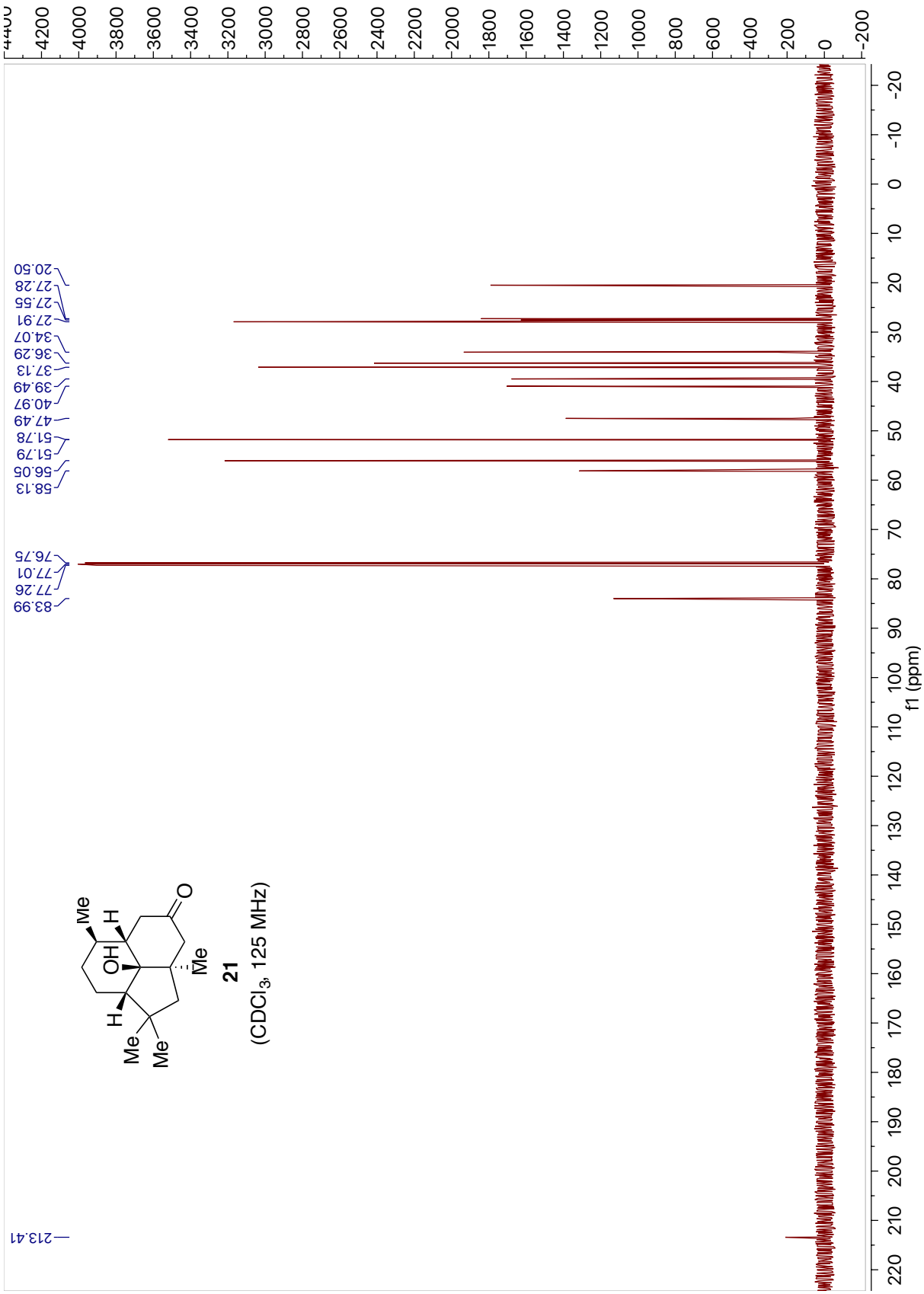

Me
O
Me
H
Me
Me
S1
(CDCl3, 500 MHz)
6.02
3.00
3.02
2.16
1.00
1.03
1.11
2.07
0.98
1.07
1.00
0.99
0.98
f1 (ppm)

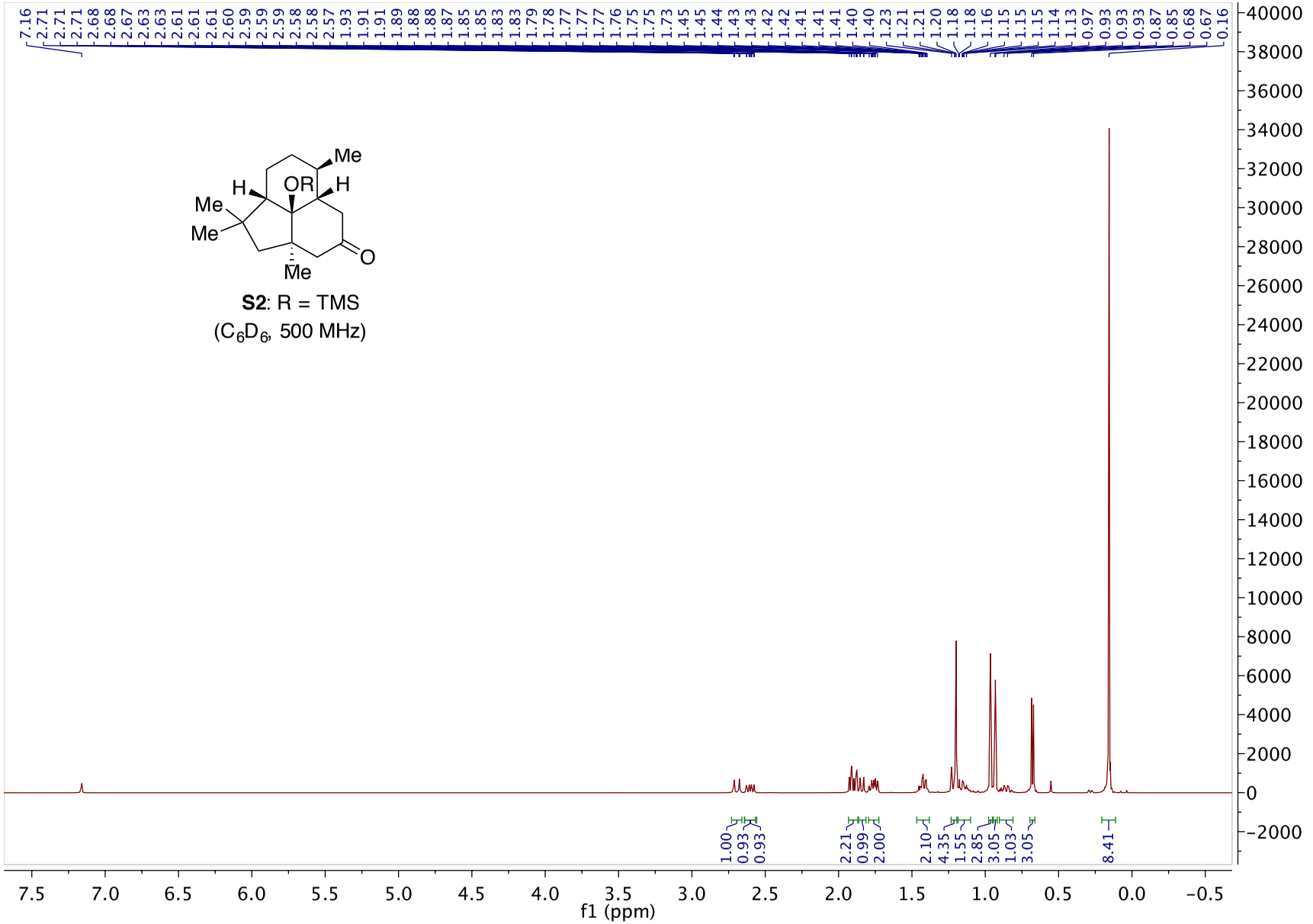

213.94
148.23
126.09
77.25
77.00
76.75
55.04
54.87
51.97
40.59
40.32
38.91
34.35
31.69
29.94
26.41
23.95
23.71
19.45
Me
Me
H
Me
Me
O
S1
(CDCl3, 125 MHz)
f1 (ppm)

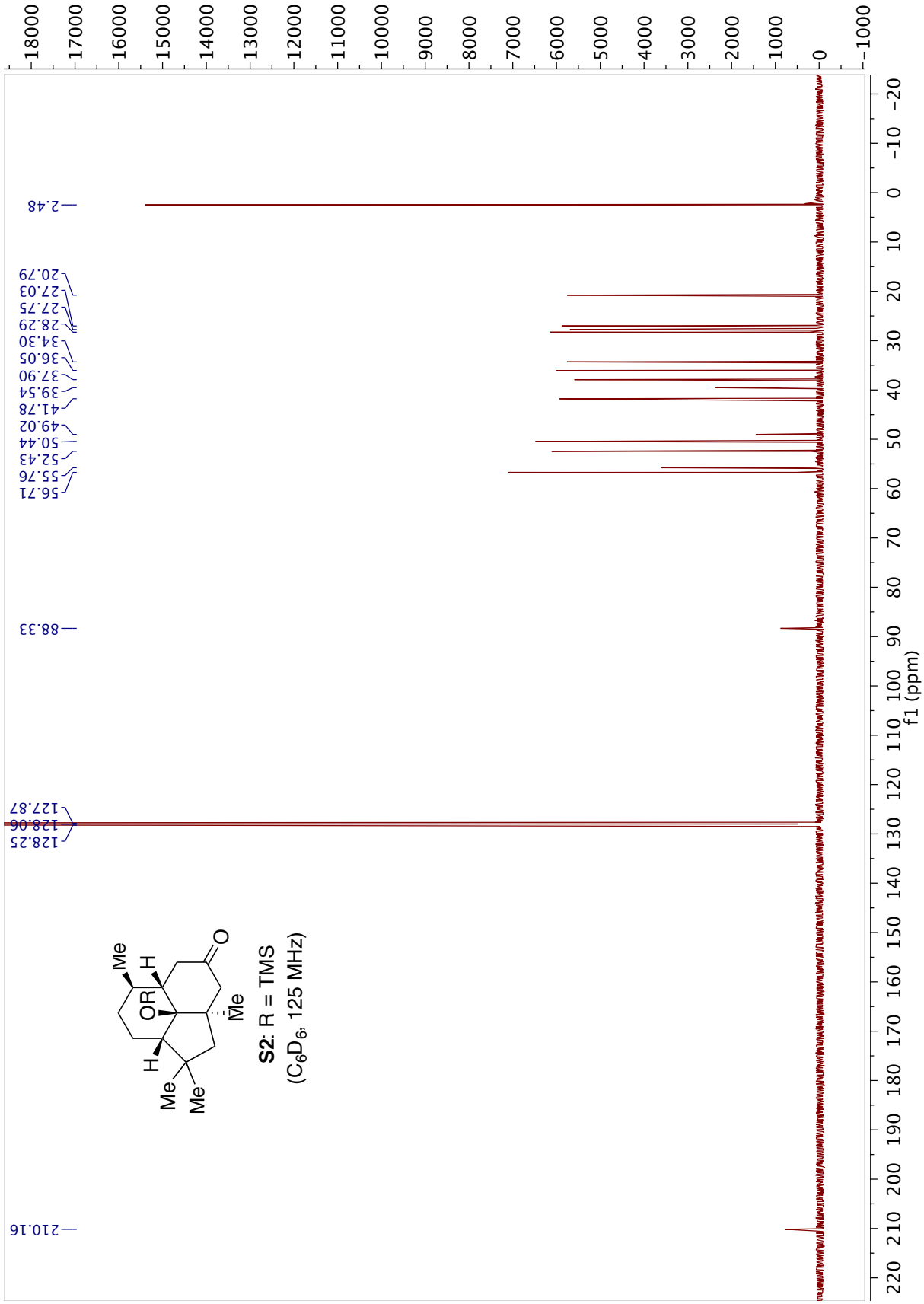

Me
O
H
Me
Me
Me
O
32
(C6D6, 500 MHz)
f1 (ppm)

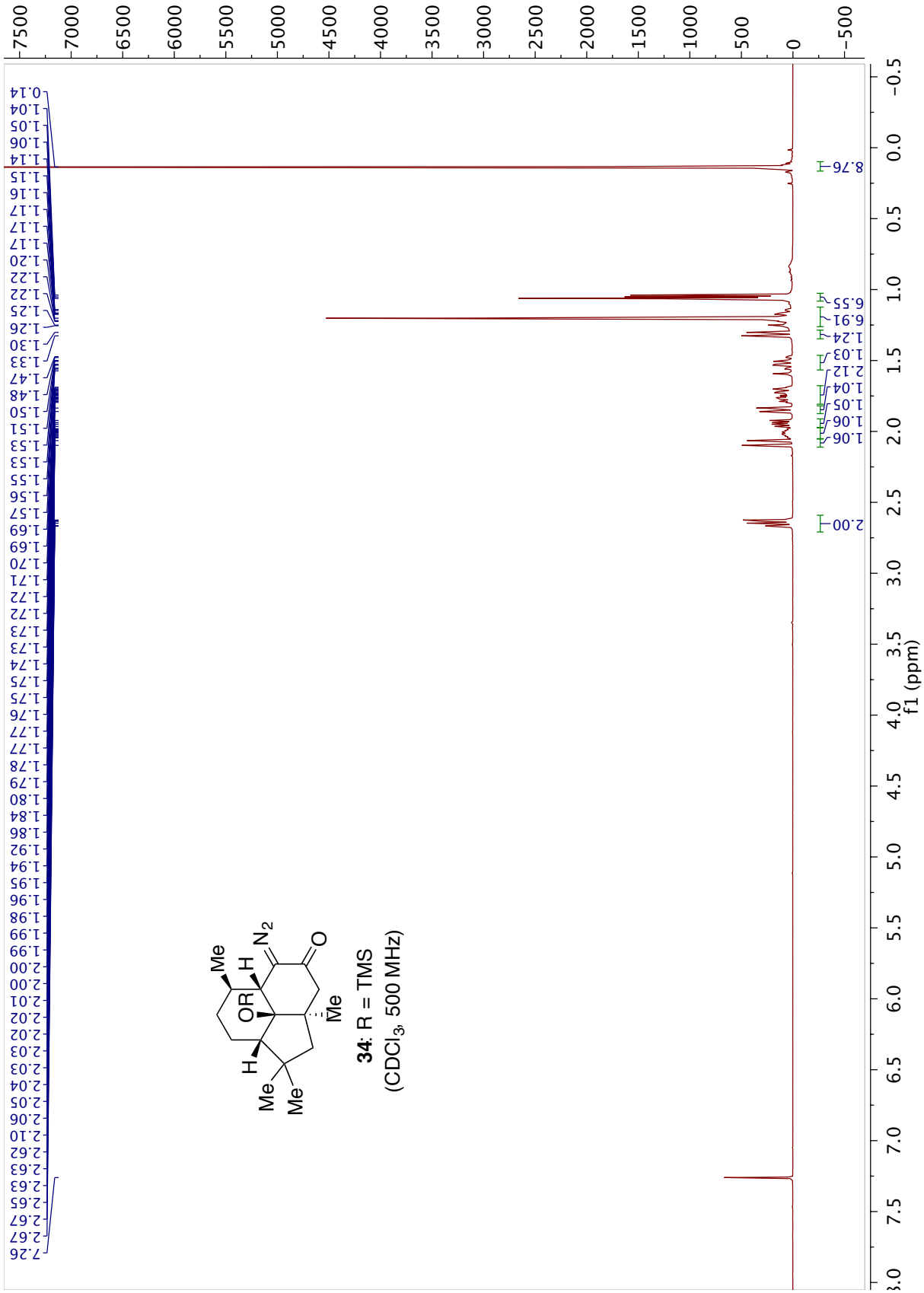

206.12
128.25
128.06
127.87
76.87
60.62
53.99
52.58
50.42
43.20
39.80
38.45
34.63
32.27
31.71
30.52
26.63
25.04
24.24
15.27
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)
Me
O
H
Me
Me
O
Me
32
(C6D6, 125 MHz)

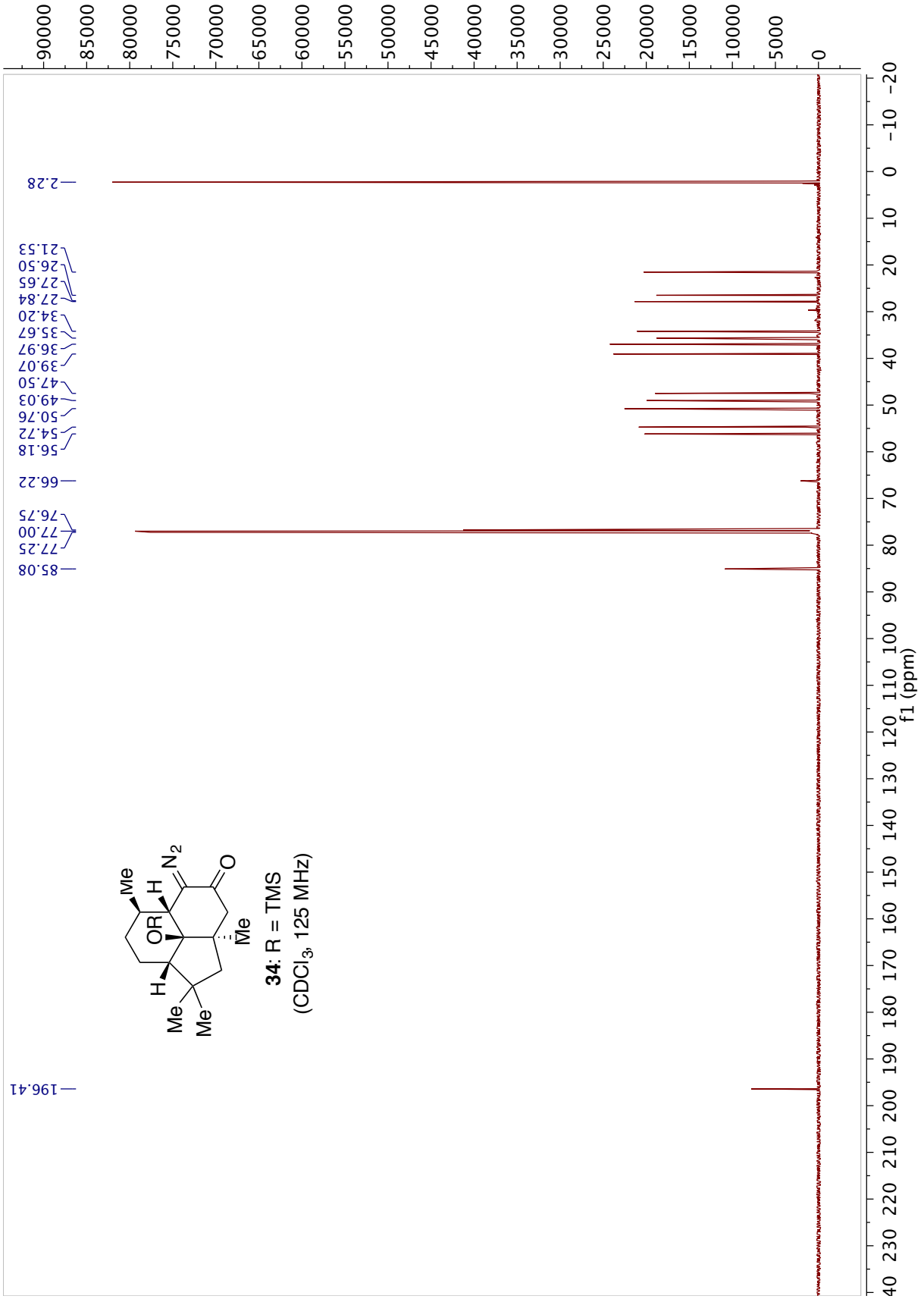

Me
H
OH
H
Me
Me
O
Me
21
(CDCl3, 500 MHz)
f1 (ppm)

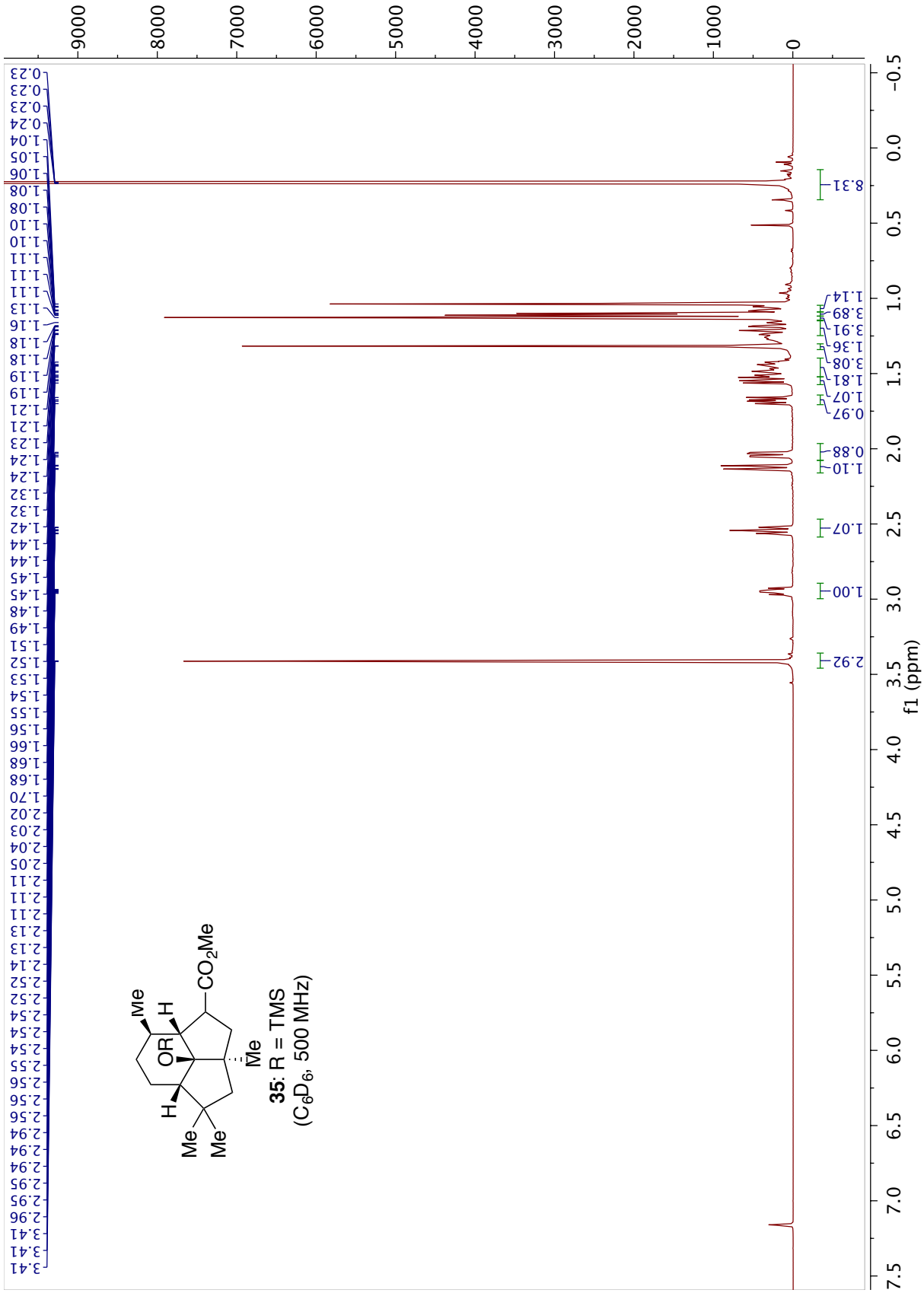

213.41
83.99
77.26
77.01
76.75
58.13
56.05
51.79
51.78
47.49
40.97
39.49
37.13
36.29
34.07
27.91
27.55
27.28
20.50
f1 (ppm)
Me
H
OH
H
Me
Me
Me
O
21
(CDCl3, 125 MHz)

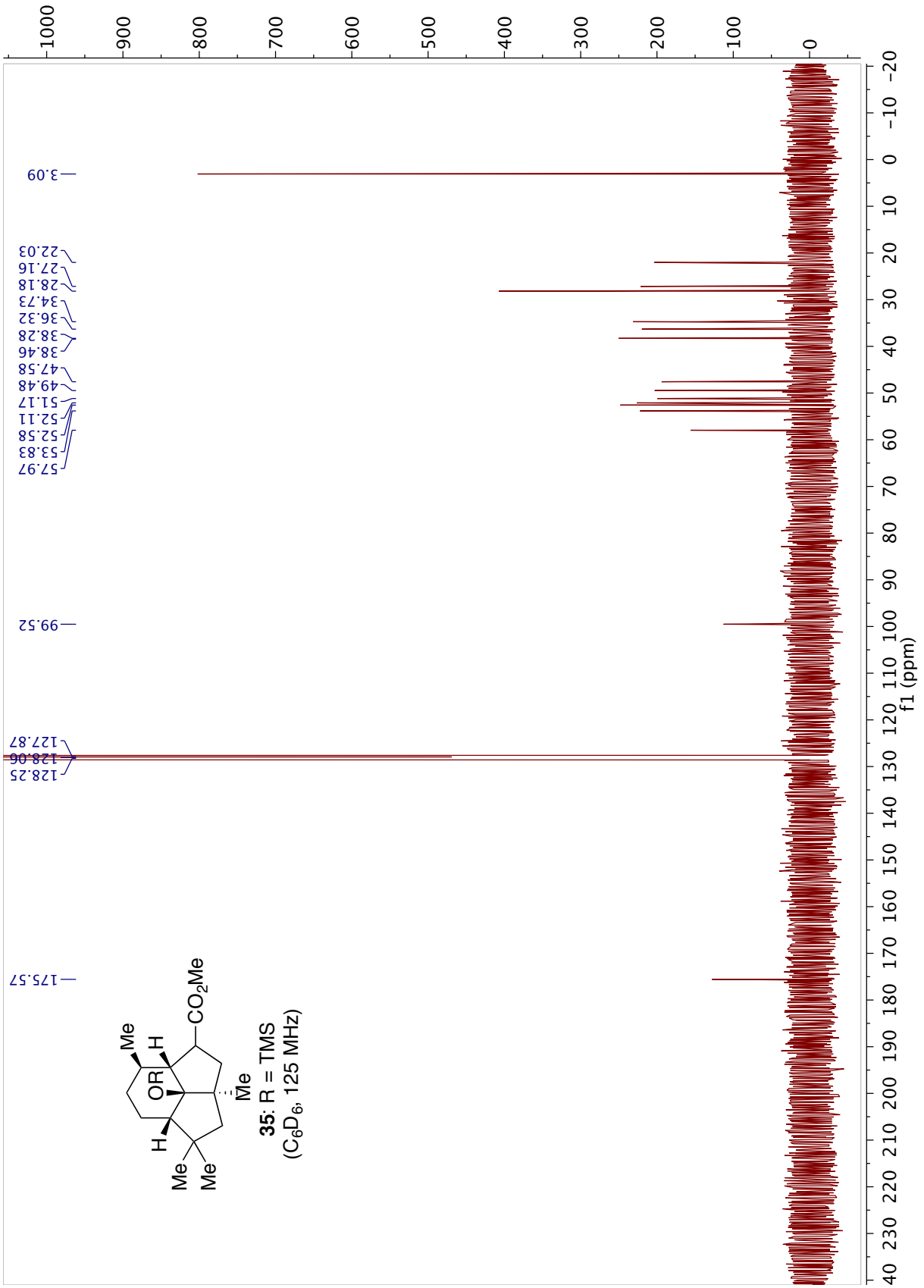

Me
H
OR
H
Me
Me
O
Me
S2: R = TMS
(C6D6, 500 MHz)
f1 (ppm)

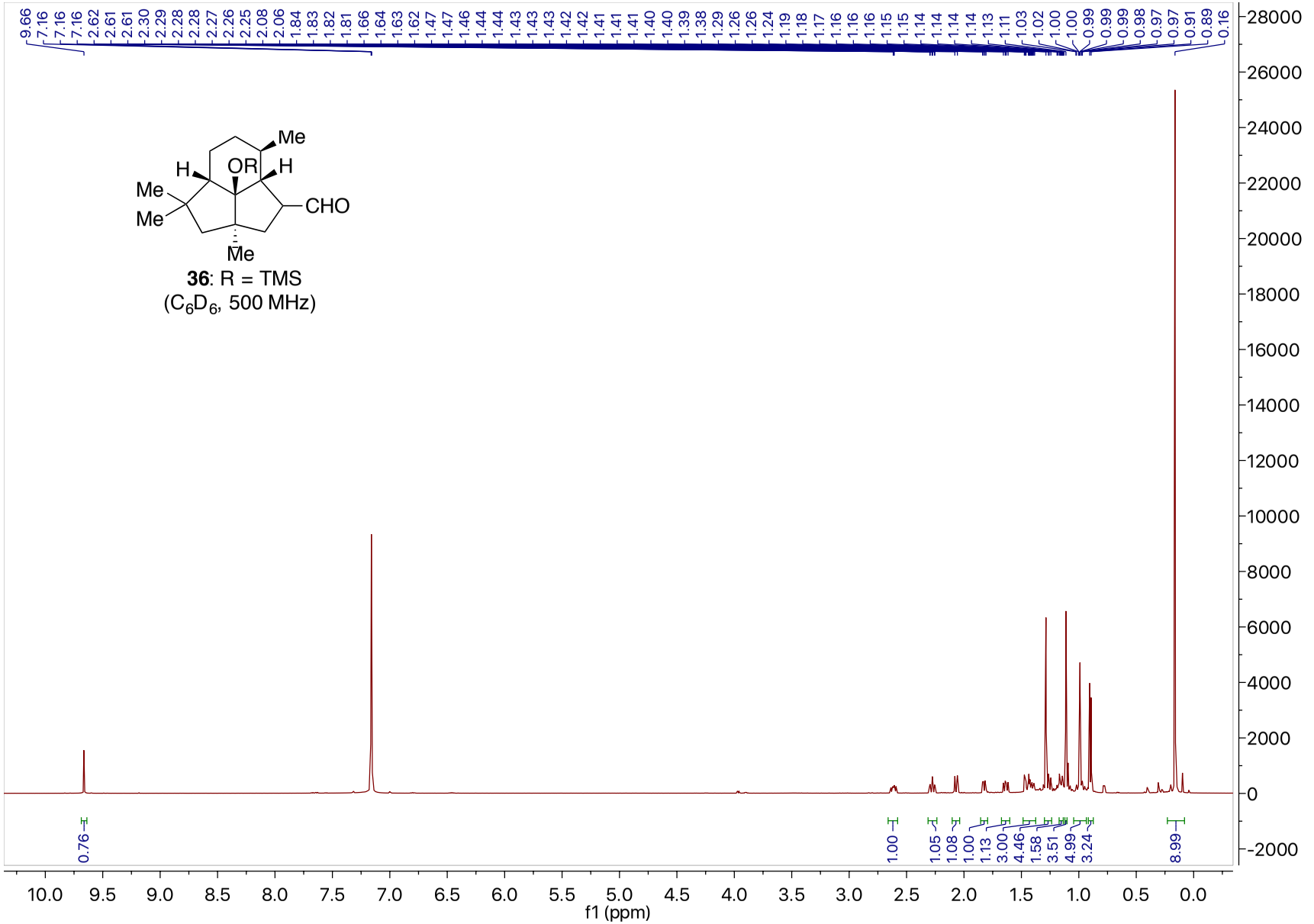

Me
H
OR
H
Me
Me
Me
O
S2: R = TMS
(C6D6, 125 MHz)
210.16
128.25
128.06
127.87
88.33
56.71
55.76
52.43
50.44
49.02
41.78
39.54
37.90
36.05
34.30
28.29
27.75
27.03
20.79
2.48
f1 (ppm)

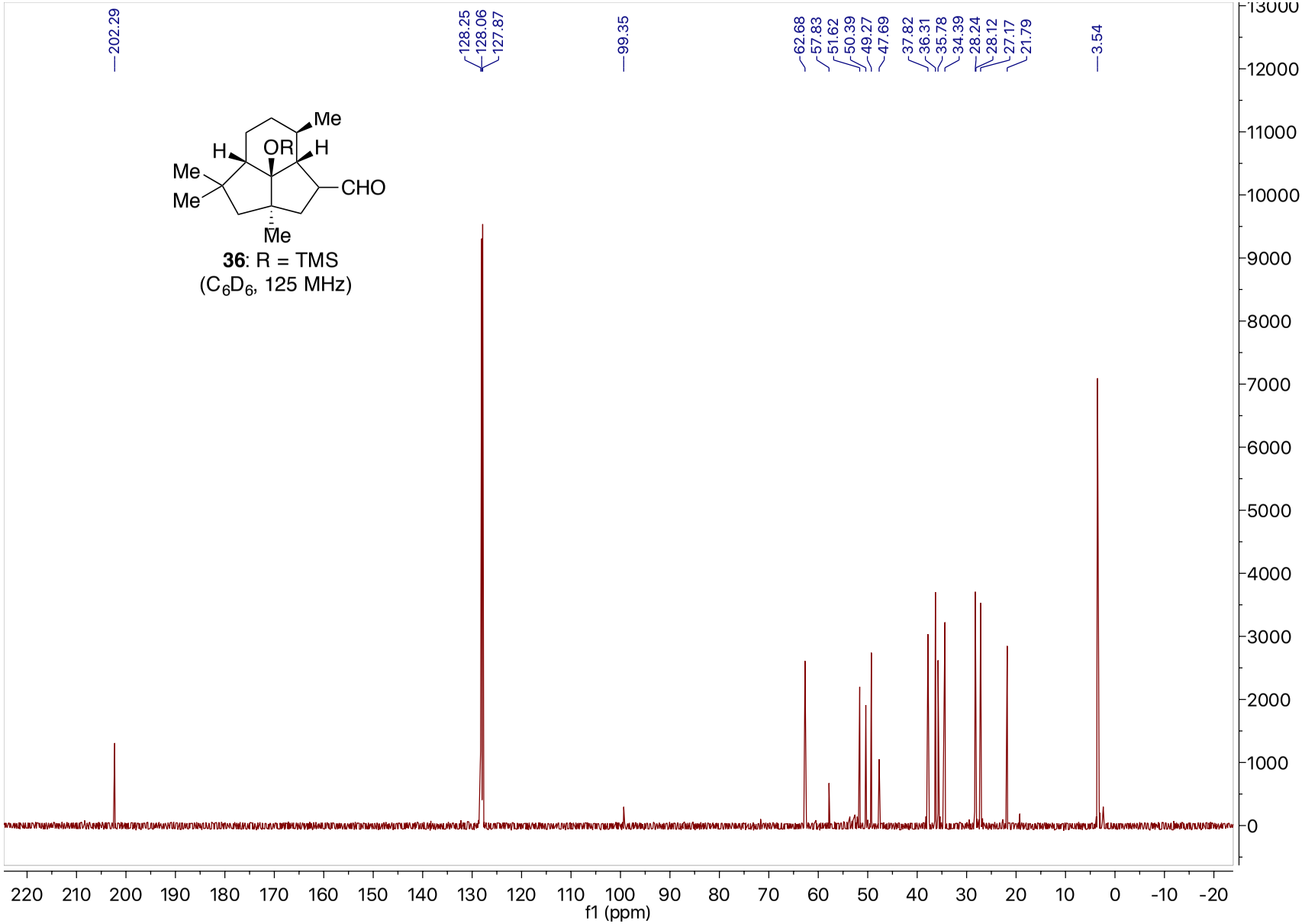

Me
H
N2
O
OR
Me
H
Me
Me
34: R = TMS
(CDCl3, 500 MHz)
f1 (ppm)

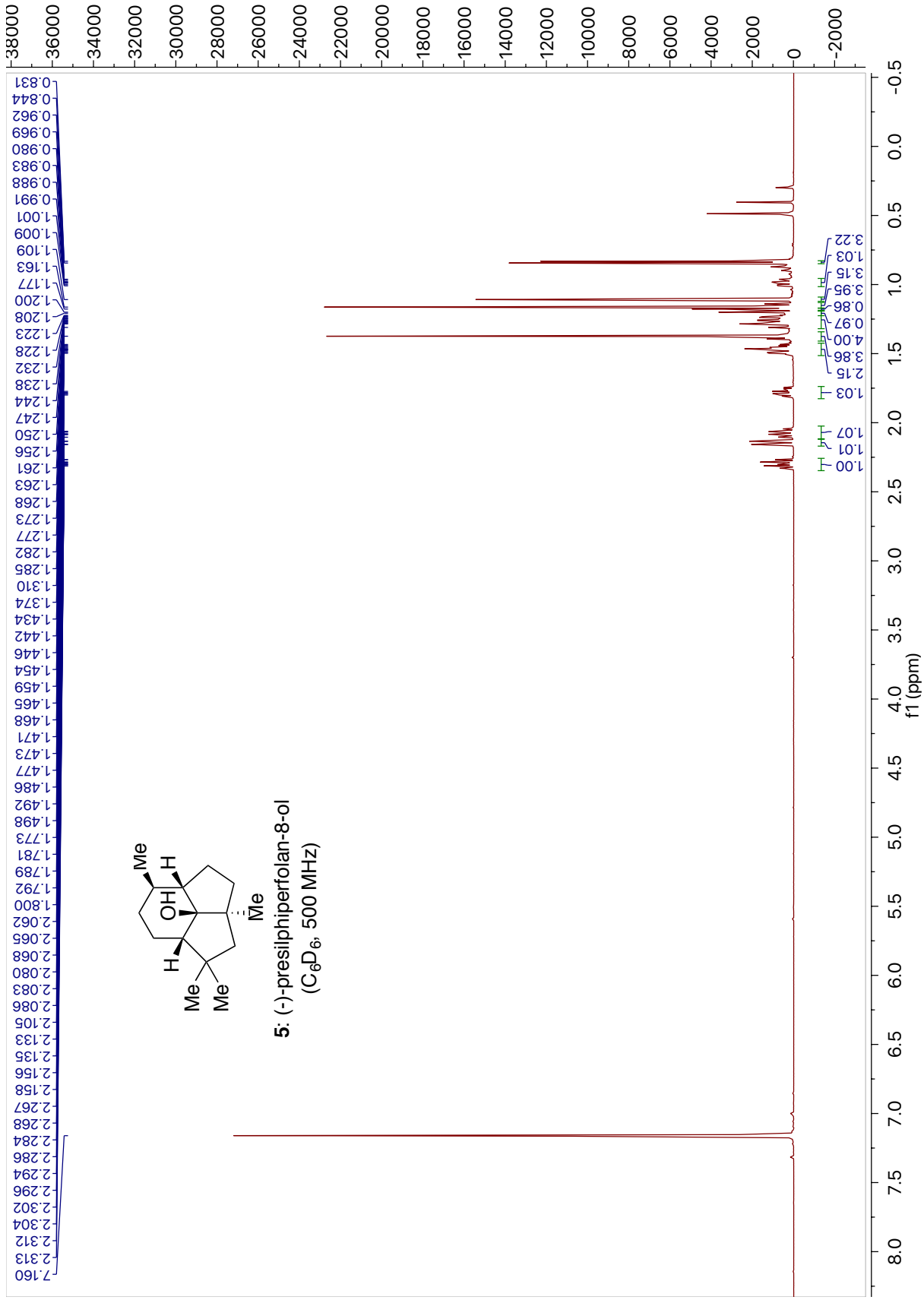

196.41
85.08
77.25
77.00
76.75
66.22
56.18
54.72
50.76
49.03
47.50
39.07
36.97
35.67
34.20
27.84
27.65
26.50
21.53
2.28
f1 (ppm)
Me
H
N2
O
OR
H
Me
Me
Me
34: R = TMS
(CDCl3, 125 MHz)

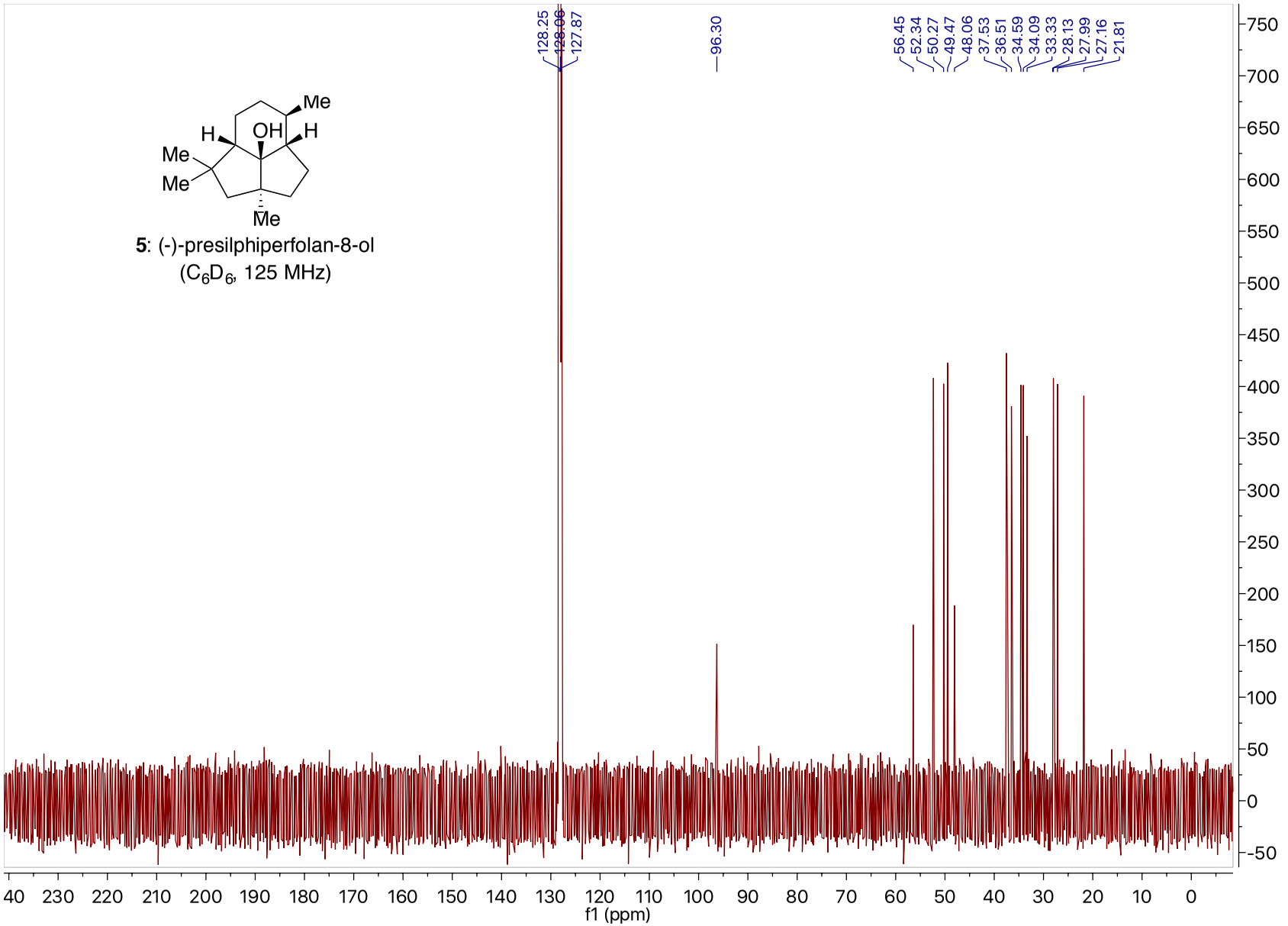

Me
H
OR
H
Me
Me
CO2Me
Me
35: R = TMS
(C6D6, 500 MHz)
f1 (ppm)


175.57
128.25
128.06
127.87
99.52
57.97
53.83
52.58
52.11
51.17
49.48
47.58
38.46
38.28
36.32
34.73
28.18
27.16
22.03
3.09
f1 (ppm)
Me
H
OR
H
Me
Me
CO2Me
Me
35: R = TMS
(C6D6, 125 MHz)


Me
H
OR
H
Me
Me
CHO
Me
36: R = TMS
(C6D6, 500 MHz)
f1 (ppm)


202.29
128.25
128.06
127.87
99.35
62.68
57.83
51.62
50.39
49.27
47.69
37.82
36.31
35.78
34.39
28.24
28.12
27.17
21.79
3.54
Me
H
OR
H
Me
Me
CHO
Me
36: R = TMS
(C6D6, 125 MHz)
f1 (ppm)


Me
H
OH
H
Me
Me
Me
5: (-)-presilphiperfolan-8-ol
(C6D6, 500 MHz)
f1 (ppm)


128.25
128.06
127.87
96.30
56.45
52.34
50.27
49.47
48.06
37.53
36.51
34.59
34.09
33.33
28.13
27.99
27.16
21.81
Me
H
OH
H
Me
Me
Me
5: (-)-presilphiperfolan-8-ol
(C6D6, 125 MHz)
f1 (ppm)