# Synthesis of Antimicrobial Natural Products Targeting FtsZ: (+)-Totarol and Related Totarane Diterpenes

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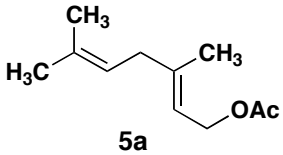
## Supporting Information



**Materials:** Unless otherwise specified, all commercially available reagents were used as received. All reactions using dried solvents were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring. Dry solvent was dispensed from a solvent purification system that passes solvent through two columns of dry neutral alumina.

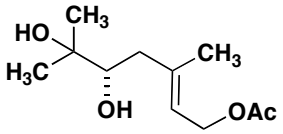
**Instrumentation:** $^{1}$H NMR spectra and proton-decoupled $^{13}$C NMR spectra were obtained on a 300 or 400 MHz Varian NMR spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) relative to residual solvent ($CHCl_3$, s, δ 7.26). Multiplicities are given as: s (singlet), d (doublet), t (triplet), dd (doublet of doublets), m (multiplet), br m (broad multiplet), br s (broad singlet). $^{13}$C NMR chemical shifts are reported relative to $CDCl_3$ (t, δ 77.0) unless otherwise noted. High resonance mass spectra were recorded on positive ESI mode in methanol or acetonitrile. Melting points were taken on an EZ-melting apparatus and were uncorrected. Infrared spectra were taken on a Bruker Tensor 27 spectrometer. Gas chromatography-mass spectrometry data was recorded on a GCMS-QP 2010 Shimadzu spectrometer. Silica gel chromatographic purifications were performed by flash chromatography with silica gel (Silicycle, 40–63 $\mu$m) packed in glass columns. The eluting solvent for each purification was determined by thin layer chromatography (TLC) on glass plates coated with EMD silica gel 50 F254 and visualized by ultraviolet light or by staining $KMnO_4$ stain followed by gentle heating. Optical rotations were obtained on a Rudolph AUTOPOL IV polarimeter at a wavelength of 589 nm using a 1.0 dm cell. Specific rotations are reported in degrees per decimeter at 23 °C and the concentrations are given in grams per 100 mL of solvent. Solvents used for optical rotations were EtOH (100%) and $CHCl_3$ (stabilized with 0.5% - 1% EtOH, then filtered through basic alumina). Chiral HPLC analysis was performed on a Shimadzu LC-20AB system with a Daicel CHIRALPAK® AS-H column (4.6 x 250 mm, 5 μm) with a flow rate of 1.0 mL/min in isopropanol:hexane (97:3) and a Shimadzu SPD-M20A photodiode array detector was used. The following abbreviations are used throughout: ethyl acetate (EtOAc), hexanes (Hex), dichloromethane (DCM), triethylamine (TEA).

**Experimental:**



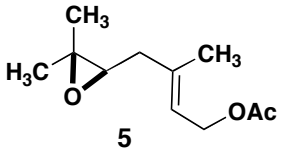

5a

**3,7-Dimethyl-2,6-octadiene acetate (5a).**[1] To a flask containing geraniol (4.0 g, 26 mmol) was added DCM (260 mL). Triethylamine (7.9 g, 78 mmol, 10.9 mL) was added followed by addition of acetic anhydride (6.6 g, 65 mmol, 6.1 mL). A catalytic amount of DMAP was added and the solution was allowed to stir overnight. The clear solution was washed with $H_2O$ (50 x 2 mL) and the organic layer was collected and dried over $MgSO_4$ and the solvent was removed *in vacuo*. Purification was done via flash chromatography in 5 % EtOAc:Hex to give a clear oil (4.4 g, 87%). $^1$H NMR spectrum matches those reported in the literature. $^1$H NMR (300 MHz, $CDCl_3$) 5.31 (t, *J* = 7.2, 1H), 5.04 (t, *J* = 6.3, 1H), 4.55 (d, *J* = 7.2, 2H), 2.02-2.06 (m, 4H), 2.01(s, 3H), 1.67 (s, 3H), 1.57 (s, 3H).



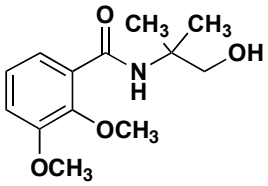

5b

**(S,Z)-6,7-dihydroxy-3,7-dimethyloct-2-enyl acetate (5b)**.[2] To **5a** (0.20 g, 1.0 mmol) was added *t*-BuOH and $H_2O$ (6:6 mL) at 0 °C. To this solution was added AD-mix α (1.0 g) and $MeSO_2NH_2$ (0.1 g, 1.0 mmol). The orange mixture was allowed to stir at 4 °C for 48 h. The reaction was quenched with solid $Na_2SO_3$ and was allowed to stir for 30 min then diluted with DCM (40 mL) and extracted with EtOAc, dried over $MgSO_4$ to give a clear oil. Purification was done via flash chromatography in 50 % EtOAc:Hex to give a clear oil (0.13 g, 57%). $^1$H NMR spectrum matches those reported in the literature.$^1$H NMR (300 MHz, $CDCl_3$) 5.39 (t, *J* = 7, 1H), 4.59 (t, *J* = 6.9, 2H), 3.34 (dd, *J* = 8.4, 1.8, 1H), 2.29 (dd, 1H), 2.10 (m, 1H), 2.04 (s, 3H), 1.71 (s, 3H), 1.59 (m, 1H), 1.45 (m, 1H), 1.23 (s, 3H), 1.14 (s, 3H).



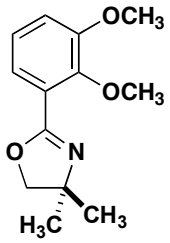

5

**(R,Z)-5-(3,3-dimethyloxiran-2-yl)-3-methylpent-2-enyl acetate (5)**.[2] To a solution of **5b** in DCM (10 mL) at 0 °C, was added TEA and was stirred for 30 min. After 30 min, methanesulfonyl chloride was added and allowed to stir for 35 min. After 35 min, the solution was warmed to 23 °C then a second aliquot of TEA was added and stirred for an additional 30 min. Potassium carbonate (0.23 g, 1.7 mmol) in MeOH (7 mL) was added and stirred overnight. The mixture was filtered and diluted with EtOAc. The solvent was evaporated and dissolved in $H_2O$ (20 mL) and washed with EtOAc (30 mL) then dried over $MgSO_4$ to give a clear oil (40 mg, 63%). $^1$H NMR spectrum matches those reported in the literature. $^1$H NMR (300 MHz, $CDCl_3$) 5.38 (t, *J* = 6.9, 1H), 4.58 (d, *J* = 6.9, 2H), 2.69 (t, *J* = 6.2, 1H), 2.14 (m, 2H), 1.72 (s, 3H), 1.63 (m, 2H), 1.30 (s, 3H), 1.26 (s, 3H).



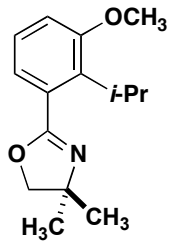
**11**

***N*-(1-hydroxy-2-methylpropan-2-yl)-2,3-dimethoxybenzamide (11)**. In a flame-dried flask, 2,3-dimethoxybenzoic acid (0.2 g, 1.1 mmol) was dissolved in 5 mL of dry THF and the solution was cooled to 0 °C. To the solution was added TEA (0.12 g, 1.2 mmol, 0.16 mL) then isobutylchloroformate (0.16 g, 1.1 mmol, 0.15 mL). Upon the complete formation of the mixed anhydride, a solution of 2-amino-2-methyl-1-propanol (0.11 g, 1.2 mmol, 0.11 mL) in THF (5 mL) was added to the reaction. The reaction was monitored by TLC until completion. The reaction was washed with $H_2O$ then extracted with EtOAc (3 x 30 mL). The combined organic layer was washed with brine, and then dried over $MgSO_4$ and the solvent was removed *in vacuo* to give a white solid. Purification by column chromatography in 50% EtOAc:Hex and recrystallization in 40 % EtOAc afforded white needles (0.27 g, 98%): $^1$H NMR (300 MHz, $CDCl_3$) 8.24 (bs, 1H), 7.63 (dd, $J$ = 5.7, 1.2, 1H), 7.14 (t, $J$ = 2.9, 1H), 7.02 (dd, $J$ = 6.4, 2.0, 1H), 3.88 (d, 6H), 3.67 (s, 2H), 1.38 (s, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) 165.7, 152.8, 147.4, 127.1, 124.6, 122.5, 115.6, 70.8, 61.4, 56.2, 56.1, 24.8; HRMS (ESI) $m$ / $z$ calcd for $C_{13}H_{20}NO_4$ $(M + H)^+$ 254.1392, found 254.1381. Melting Point: 88-90 °C.



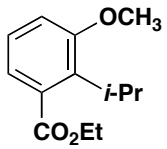
**12**

**2-(2,3-dimethoxyphenyl)-4,4-dimethyl-4,5-dihydrooxazole (12)**. To **11** (0.21 g, 0.80 mmol) was added titanium isopropoxide (0.92 g, 3.2 mmol, 0.95 mL) and heated at 150 °C for 24 h then allowed to cool to 23 °C. To it 3-(dimethylamino)-1,2-propane diol (0.14 g, 0.70 mmol, 0.14 mL) was added and allowed to stir for 30 min to complex with the metal. A solution of EtOAc:$H_2O$ (4 : 4 mL) was added producing a white precipitate that was allowed to stir for 1 h. The reaction mixture was extracted with EtOAc (3 x 20 mL). The collected solvent was filtered through a plug of silica and $MgSO_4$, and the solvent was removed *in vacuo* to give a white solid (0.14 g, 75%): $^1$H NMR (300 MHz, $CDCl_3$) 7.28 (dd, $J$ = 7.7, 1.8 Hz, 1H), 7.04 (t, $J$ = 8.1, 1H), 6.98 (dd, $J$ = 8.1, 1.8, 1H), 4.11 (s, 2H), 3.85 (two s, 6H), 1.38 (s, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) 161.8, 153.5, 148.9, 124.0, 123.4, 122.8, 115.3, 79.5, 67.5, 61.6, 56.4, 28.5, 21.3; IR (thin film) 2968, 1743, 1652, 1581 cm$^{-1}$; HRMS (ESI) $m$ / $z$ calcd for $C_{13}H_{18}NO_3$ $(M + H)^+$ 236.1287, found 236.1292. Melting Point: 48-50 °C.



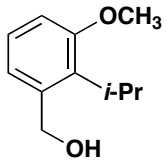

**13**

**2-(2-isopropyl-3-methoxyphenyl)-4,4-dimethyl-4,5-dihydrooxazole (13)**. To a flame-dried flask, **12** (0.24 g, 1.0 mmol) was dissolved in dry ether (10 mL). Isopropyl magnesium chloride (2.0 M in ether, 2.6 mL, 5.2 mmol) was added dropwise, and the orange solution was allowed to stir for 1 h. The reaction was quenched by adding $H_2O$ (8 mL) dropwise followed by 10 % HCl (4 mL). The solution was extracted with DCM (3 x 15 mL), dried over $MgSO_4$, and the solvent was removed *in vacuo* to give a clear oil. (0.24 g, 93%): $^1$H NMR (300 MHz, $CDCl_3$) 7.14 (m, 2H), 6.93 (dd, $J$ = 7.5, 1.8, 1H), 6.98 (dd, $J$ = 8.1, 1.8, 1H), 4.17 (s, 2H), 3.82 (s, 3H), 3.26 (m, 1H), 1.43 (s, 6H) 1.30 (two s, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) 165.9, 159.0, 136.1, 128.1, 126.9, 122.5, 114.2, 80.2, 67.1, 55.6, 30.6, 28.2, 21.0; IR (thin film) 2962, 1654 cm$^{-1}$; HRMS (ESI) *m/z* calcd for $C_{15}H_{22}NO_2$ $(M + H)^+$ 248.1651, found 248.1649.




**14**

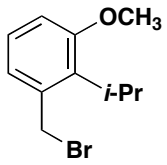
**Ethyl-2-isopropyl-3-methoxybenzoate (14)**. In a microwave tube was added **13** (1.0 g, 4.1 mmol) in 5 mL of 10% $H_2SO_4$ in EtOH. The solution was heated at 160 °C for 1 h. After cooling to 23 °C the ethanol was evaporated from the biphasic solution *in vacuo*. The resulting oil was carefully neutralized with $NaHCO_3$ and extracted with DCM (3 x 15 mL), dried over $MgSO_4$ and the solvent was removed *in vacuo*. Flash chromatography in 10 % EtOAc:Hex gave a light yellow oil. (0.54 g, 60%): $^1$H NMR (400 MHz, $CDCl_3$) 7.17 (m, 2H), 4.33 (q, $J$ = 7.2, 3H), 3.82 (s, 3H), 3.36 (m, 1H), 3.82 (s, 3H), 3.26 (m, 1H), 1.43 (s, 6H) 1.30 (two s, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) 165.9, 159.0, 136.1, 128.1, 127.0, 122.5, 114.2, 80.2, 67.1, 55.6, 30.6, 28.2, 21.0; IR (thin film) 2957, 2916, 1718 cm$^{-1}$; HRMS (ESI) *m / z* calcd for $C_{13}H_{19}O_3$ $(M + H)^+$ 223.1334 found 223.1328.[4]




**15**

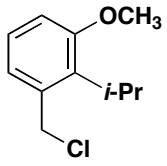
**(2-isopropyl-3-methoxyphenyl)methanol (15)**. In a flame-dried flask was added $LiAlH_4$ (0.17 g, 4.6 mmol) in dry ether (4 mL). To the flask, a solution of **14** (0.25 g, 1.1 mmol) in dry ether (12 mL) was added dropwise at 0 °C. After addition, the mixture was allowed to reach 23 °C and stirred for 1 h. The reaction was quenched slowly with an equal mixture of EtOAc:$H_2O$ (12

mL) and the precipitate was filtered. The resulting solution was extracted with EtOAc, collected, and dried over $MgSO_4$ and concentrated *in vacuo* as a colorless oil (0.19 g, 90%). $^1$H NMR (400 MHz, $CDCl_3$) 7.15 (t, *J* = 8, 1H**),** 6.94 (d, *J* = 7.6, 1H), 6.85 (d, *J* = 8.4, 1H), 4.67 (s, 2H), 3.81 (s, 3H), 3.32 (m, 1H), 1.85 (s, 6H) 1.36 (two s, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) 159.3, 139.2, 126.8, 121.4, 111.9, 64.5, 55.5, 28.5, 21.1; IR (thin film) 3289, 2950, 2832, 1581, 1451 cm$^{-1}$; HRMS (ESI) *m / z* calcd for $C_{11}H_{17}O_2$ $(M + H)^+$ 181.1229 found 181.1237.



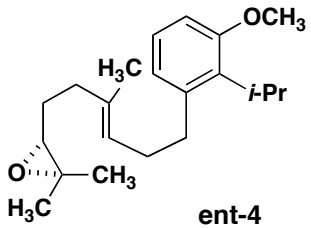

**16a**

**1-(bromomethyl)-2-isopropyl-3-methoxybenzene (16a)**. To a flask containing **15** (90 mg, 50 mmol) was added dry DCM (2 mL). Phosphorus tribromide (49 mg, 18 mmol, 17 μL) was added to the solution dropwise at 0 °C. The solution was allowed to stir for 2 h, and then quenched with $H_2O$ (1 mL). The aqueous layer was extracted with DCM (3 x 15 mL). The organic layer was washed with water, $NaHCO_3$, brine, and dried over $NaSO_4$. The solvent was removed *in vacuo* and the residue was filtered through a small plug of silica with 100 % Hexane. The solvent was removed to give a white solid (0.11 g, 89%). $^1$H NMR (400 MHz, $CDCl_3$) 7.11 (t, *J* = 6, 1H), 6.88 (d, *J* = 6, 1H), 6.84 (d, *J* = 6, 1H), 4.53 (s, 2H), 3.81 (s, 3H), 3.33 (m, 1H), 1.38 (two s, 6H); IR (thin film) 2924, 1579, 1257, 740 cm$^{-1}$; HRMS (ESI) *m / z* calcd for $C_{11}H_{16}BrO$ $(M + H)^+$ 243.0385 found 243.0373.

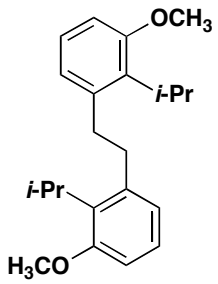



**16b**

**1-(chloromethyl)-2-isopropyl-3-methoxybenzene** (**16b**). To a flask containing **15** (0.21 g, 1.2 mmol) was added dry DCM (5 mL). To it was added thionyl chloride (0.21 g, 1.8 mmol, 1.3 mL) at 0 °C and was allowed to stir for 3 h. The solvent was evaporated *in vacuo*. Purification via flash chromatography in 5 % EtOAc:Hex yielded a white crystals (0.18 g, 78%). $^1$H NMR (300 MHz, $CDCl_3$) 7.13 (t, *J* = 8, 1H), 6.87 (t, *J* = 6.6, 2H), 4.61 (s, 2H), 3.81 (s, 3H), 3.33 (m, 1H), 1.36 (two s, 6H); IR (thin film) 2924, 1581, 1255, 742 cm$^{-1}$; HRMS (ESI) *m / z* calcd for $C_{11}H_{16}ClO$, $(M + H)^+$ 199.0889 found 199.0878.



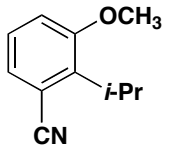

**ent-4**




**18**

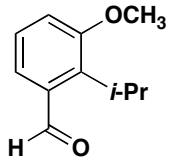
**Ent-(4)**. In a flame-dried flask was added magnesium turnings (11 mg, 0.46 mmol) in dry THF (13 mL). One drop of 1,2-dibromoethane was added and stirred vigorously. Once the magnesium was activated **16** (0.11 g, 0.46 mmol) in dry ether (1 mL) was added dropwise. The enantiomer of epoxyacetate **5** (65 mg, 0.31 mmol) in dry THF (3mL) was added to 10 mol% CuCN (2.7 mg, 0.03 mmol) and cooled to 0 °C. The Grignard **6a** was added to the epoxyacetate dropwise and stirred for 3 h. Sat. $NH_4Cl$ was added (1 mL) and extracted with EtOAc (3 x 10 mL). The solvent was collected and dried over $MgSO_4$, and purified via flash column chromatography 5 % EtOAc:Hex yield a colorless oil (33 mg, 34%). The NMR spectrum of **ent-4** matched exactly with the spectrum of **4**. The Wurtz coupled product **18** was isolated as a white solid. GC-MS (EI) *m / z* calcd for $C_{22}H_{30}O_2$, $(M)^+$ 326 found 326.

**Synthetic Route 2:**



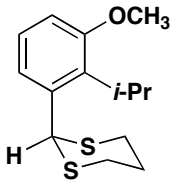

**20a**

**2-isopropyl-3-methoxybenzonitrile (20a)**. To a stirred solution of nitrile **19** (1.8 g, 11 mmol) in dry ether (100 ml), was added *i*-PrMgCl (2.0 M in ether, 22 mL, 43 mmol) dropwise at 0 °C. The orange solution was warmed to 23 °C and allowed to stir for 4 h. The reaction was cooled to 0 °C and quenched carefully with $H_2O$. The solution was extracted with EtOAc (3 x 35 mL) and the organic layer was extracted with 10 % HCl (2 x 25 mL). The solution was dried over $MgSO_4$ and solvent was removed *in vacuo*. The crude material was purified using flash chromatography in 20 % EtOAc:Hex to give a clear yellowish oil. (1.8 g, 94%): $^1$H NMR (300 MHz, $CDCl_3$) 7.20 (t, *J* = 7.8, 1H), 7.15 (dd, *J* = 7.8, 1.5, 1H), 7.04 (dd, *J* = 7.8, 1.5, 1H), 3.82 (s, 3H), 3.54 (m, 1H), 1.37 (s, 3H), 1.35 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) 159.4, 140.3, 127.6, 125.5, 118.9, 115.6, 112.6, 55.8, 31.1, 20.8.



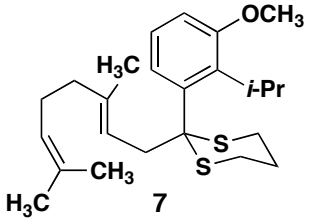

**20b**

**2-isopropyl-3-methoxybenzaldehyde (20b)**. In a flame-dried flask purged with argon was added **20a** (1.3 g, 7.4 mmol) dissolved in dry toluene (30 mL). The solution was cooled to -78 °C, and to it was added DIBALH (1.0 M in Hexane, 8.2 mL, 8.2 mmol) dropwise. After 1 h, the reaction was poured into a slurry of ice and 10 % glacial acetic acid (100 mL) and stirred for 30 min, then filtered through Celite. The mixture was separated and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layer was dried over $MgSO_4$ then the solvent was removed *in vacuo*. The crude product was purified using flash column chromatography in 10 % EtOAc:Hex and isolated as a clear oil. (1.2 g, 87%): $^1$H NMR (300 MHz, $CDCl_3$) 10.45 (s, 1H), 7.41 (dd, *J* = 7.8, 1.2, 1H), 7.27 (t, *J* = 8.0, 1H), 7.07 (d, *J* = 8.4, 1H), 4.03 (m, 1H), 3.85 (s, 3H), 1.40 (s, 3H), 1.37 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) 192.8, 159.1, 139.2, 135.6, 127.1, 122.5, 116.6, 55.8, 26.2, 21.7, 20.8; IR (thin film) 2958, 1695, 1577, 1452, 1253 $cm^{-1}$.



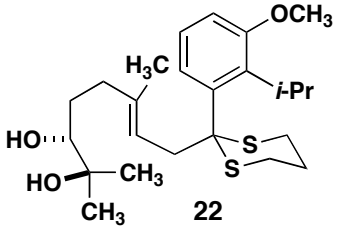

21

**2-(2-isopropyl-3-methoxyphenyl)-1,3-dithiane (21)**. To a slurry of **20b** (1.2 g, 6.5 mmol) in glacial acetic acid (5 mL) at 0 °C was added 1,3-propanedithiol (0.97 mL, 1.1 g, 9.7 mmol) and $BF_3$-$OEt_2$ (2.7 mL, 3.0 g, 21.3 mmol). After 5 min, a white precipitate began to form. The solid was filtered then recrystallized with acetic acid to give a white solid. (1.7 g, 85%): $^1$H NMR (300 MHz, $CDCl_3$) 7.21 (d, *J* = 6.9, 1H), 7.15 (t, *J* = 8.0, 1H), 6.81 (dd, J = 7.8, 1.2, 1H), 5.44 (s, 1H), 3.80 (s, 3H), 3.56 (bs, 1H), 3.09 (td, *J* = 15.3, 12, 2.3, 2H) 2.90 (dt, J = 14.1, 7.5, 4.2, 2H), 2.18 (m, 1H), 1.97, (m, 1H), 1.39 (s, 3H), 1.36 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) 158.9, 137.8, 134.1, 127.6, 127.2, 121.3, 55.6, 49.9, 33.1, 33.7, 28.3, 25.6, 21.5, 20.9; IR (thin film) 2947, 1693, 1577, 1449, 1253 cm$^{-1}$; HRMS (ESI) *m / z* calcd for $C_{14}H_{21}OS_2$, $(M + H)^+$ 269.1034 found 269.1017.




7

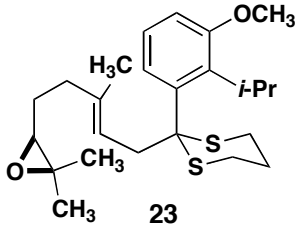
**(*E*)-2-(3,7-dimethylocta-2,6-dienyl)-2-(2-isopropyl-3-methoxyphenyl)-1,3-dithane (7)**. Dithiane **21** (1.3 g, 4.8 mmol) was dissolved in dry THF (30 mL) and cooled to 0 °C and to it was added *n*-BuLi (2.15 mL, 5.3 mmol, 2.5 M THF). The resulting orange solution was stirred for 40 min, and then geranyl bromide **8** (1.4 g, 1.3 mL) was added dropwise. The solution turned light yellow upon addition and was allowed to stir. When the reaction was complete by TLC, the solution was quenched with $NH_4Cl$, and then extracted with EtOAc (3 x 30 mL). The organic layer was collected and dried over $MgSO_4$ and the solvent removed *in vacuo*. Purification using flash chromatography in a gradient of 100 Hex - 5 % EtOAc gave a clear oil (1.5 g, 78%). $^1$H NMR (300 MHz, $CDCl_3$) 7.66 (d, *J* = 8.1, 1H), 7.12 (t, *J* = 8.0, 1H), 6.85 (d, *J* = 8.1, 1H), 5.03 (t, *J* = 7.8, 1H), 4.96 (t, *J* = 7.8, 1H), 4.24 (m, 1H), 3.82 (s, 3H), 3.02 (d, *J* =6.6, 2H), 2.79 (t, *J* =5.6, 4H), 1.95 (m, 6H), 1.65 (s, 6H), 1.55 (s, 3H), 1.31 (s, 3H), 1.29 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) 161.0, 138.7, 137.9, 136.6, 131.4, 125.4, 124.6, 124.5, 119.2, 111.7, 59.6, 55.4, 40.7, 39.9, 29.2, 28.6, 26.7, 25.9, 24.9, 20.2, 17.9, 16.9; IR (thin film) 2912, 1738, 1574, 1431, 1248 cm$^{-1}$; HRMS (ESI) *m / z* calcd for $C_{24}H_{37}OS_2$, $(M + H)^+$ 405.2286 found 405.2277.




22

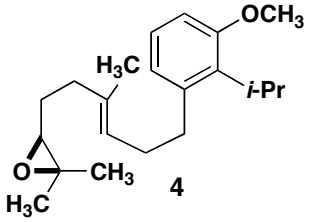
**(*R*,*E*)-8-(2-(2-isopropyl-3-methoxyphenyl)-1,3-dithiane-2-yl)-2,6-dimethyloct-6-ene-2,3-diol (22)**. The coupled product **7** (3.7 g, 9.3 mmol) was taken up in *t*-BuOH: $H_2O$ (125 mL each) and cooled to 0 °C. Admix-β (11.1 g, 2.55 eq.) was added to the solution followed by $MeSO_3NH_2$ (0.88 g, 9.3 mmol). The orange suspension was stirred vigorously at 4 °C for 48 h. The active

oxidizer was quenched with $Na_2SO_3$ (8 g) and stirred for 30 min. The mixture was diluted with water and DCM, and extracted with DCM (3 x 150 mL). The combined extracts were dried over $MgSO_4$ and the solvent removed *in vacuo*. Purification using flash chromatography in 20 % EtOAc:Hex yielded a clear oil (3.44 g, 83%). $^1$H NMR (300 MHz, $CDCl_3$) 7.66 (dd, $J$ = 8.1, 1.2, 1H), 7.13 (t, $J$ = 8.3, 1H), 6.85 (d, $J$ = 7.5, 1H), 5.07 (t, $J$ = 6.5, 1H), 4.20 (m, 1H), 3.81 (s, 3H), 3.29 (m, 1H), 3.00 (m, 2H), 2.78 (m, 4H), 2.32 (d, J = 4.8, 1 H), 2.23 (s, 1H), 2.11 (t, J = 6.8, 2H), 1.93 (m, 2H), 1.67 (s, 3H), 1.55 (m, 1H), 1.36 (m, 1H), 1.30 (s, 3H), 1.28 (s, 3H), 1.14 (s, 3H), 1.11 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) 161.1, 138.6, 137.9, 136.5, 125.6, 124.3, 120.3, 111.8, 77.4, 72.9, 59.9, 55.4, 40.6, 36.9, 29.2, 28.8, 28.7, 28.6, 26.5, 24.9, 23.6, 20.3, 20.2, 16.6; IR (thin film) 3400, 2914, 1573, 1429, 1247 cm$^{-1}$; HRMS (ESI) *m / z* calcd for $C_{24}H_{39}O_3S_2$, $(M + H)^+$ 439.2341 found 439.2328; $[\alpha]^{20}_D$ + 9.96 (c 2.1, $CHCl_3$).




**23**

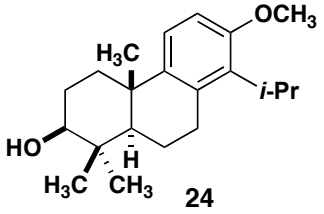
**(*S,E*)-3-(5-(2-(2-isopropyl-3-methoxyphenyl)-1,3-dithian-2-yl)-3-methylpent-3-enyl)-2,2-dimethyloxirane (23)**. A solution of **22** (3.4 g, 7.85 mmol) in dry DCM (90 mL) was cooled to 0 °C and to it was added TEA (1.9 g, 2.6 mL). The solution was allowed to stir for 5 min, and then methanesulfonyl chloride (1.8 g, 0.73 mL) was added dropwise. The solution was warmed to 23 °C and stirred for 1.5 h and then a second portion of TEA (0.95 g, 1.3 mL) was added. The solution was stirred for another 2 h, and then the solvent was evaporated. The resulting solid was taken up in MeOH (150 mL) and $K_2CO_3$ (3.3 g, 23 mmol) and allowed to stir overnight. The suspension was filtered through celite and the solvent was evaporated. The residue was taken was diluted with water and DCM, and extracted with DCM (3 x 150 mL). The combined extracts were dried over $MgSO_4$ and the solvent removed *in vacuo*. Purification using flash column chromatography in 20 % EtOAc gave a pale yellow oil (2.62 g, 79 %)
%). $^1$H NMR (300 MHz, $CDCl_3$) 7.64 (d, $J$ = 8.1, 1H), 7.11 (t, $J$ = 8.1, 1H), 6.85 (d, $J$ = 8.1, 1H), 5.02 (t, $J$ = 6.9, 1H), 4.22 (m, 1H), 3.02 (s, 3H), 3.01 (d, $J$ = 6.6, 2H), 2.78 (t, $J$ = 5.1, 4 H), 2.68 (t, $J$ = 6.3, 1H), 2.06 (m, 2H), 1.91 (m, 2H), 1.67 (s, 3H), 1.54 (m, 2H), 1,30 (s, 3H), 1.28 (s, 3H), 1.26 (s, 3H), 1.21 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) 161.0, 138.6, 137.1, 136.5, 125.5, 124.5, 119.8, 111.7, 64.2, 59.5, 58.5, 55.4, 40.7, 36.6, 29.2, 28.6, 27.5, 25.2, 24.9, 20.2, 18.9, 16.9; IR (thin film) 2952, 2924, 1738, 1573, 1462 cm$^{-1}$; HRMS (ESI) *m / z* calcd for $C_{24}H_{37}O_2S_2$, $(M + H)^+$ 421.2235 found 421.2235; $[\alpha]^{20}_D$ +4.12 (c 0.9, $CHCl_3$).




**4**

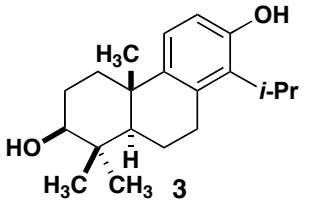
**(*S,E*)-3-(6-(2-isopropyl-3-methoxyphenyl)-3-methylhex-3-enyl)-2,2-dimethyloxirane (4)**. To a stirred solution of **23** (0.88 g, 2.1 mmol) in dry toluene (12 mL) was added $SnBu_3H$ (1.8 g, 1.7 mL) and a catalytic amount of AIBN. The solution was heated to 90 °C for 2 h. The solvent was evaporated and the crude material was immediately purified using flash column chromatography in a gradient of 100 % Hex – 5 % EtOAc to give a clear oil (0.52 g, 77%). $^1$H NMR (300 MHz,

$CDCl_3$) 7.07 (t, *J* = 7.8, 1H), 6.74 (d, *J* = 7.8, 2H), 5.29 (t, *J* = 6.8, 1H), 3.79 (s, 3H), 3.25 (m, 1H), 2.70 (m, 3H), 2.20 (m, 4H), 1.68 (m, 2H), 1.62 (s, 3H), 1.36 (s, 3H), 1.35 (s, 3H), 1.32 (s, 3H), 1.28 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) 159.3, 140.9, 134.9, 134.2, 126.4, 124.6, 122.7, 109.8, 64.4, 58.5, 55.3, 36.5, 34.9, 30.6, 28.5, 27.7, 25.1, 21.1, 18.9, 16.2; IR (thin film) 2956, 2868, 1577, 1465, 1251 $cm^{-1}$; HRMS (ESI) *m / z* calcd for $C_{21}H_{33}O_2$, $(M + H)^+$ 317.2481 found 317.2492; $[\alpha]^{20}_D$ -3.23 (c 1.6, $CHCl_3$).



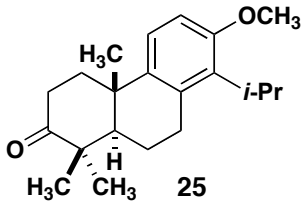
**24**

**(2*S*,4a*S*,10a*R*)-8-isopropyl-7-methoxy-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2ol (24)**. In a flame-dried flask containing the dethiolated epoxide **4** (1.4 g, 2.5 mmol) dissolved in dry DCM (50 mL) was added $InBr_3$ (3.2, 8.9 mmol). The solution was allowed to stir for 2 h, and then quenched with a sat. $NH_4Cl$ (20 mL). The two layers were separated and the aqueous layer was extracted with DCM (3 x 40 mL). The combined organic layers were washed with brine and dried over MgSO4. The solvent was removed *in vacuo* and the crude material was purified by flash column chromatography in 20 % EtOAc:Hex to yield a white solid (0.82 g, 58 %). $^1H$ NMR (400 MHz, $CDCl_3$) 7.10 (d, *J* = 8.8, 1H), 6.74 (d, *J* = 8.8, 1H), 3.78 (s, 3H), 3.31 (bm, 2H), 3.00 (dd, *J* = 17, 6.8, 1H), 2.78 (m, 1H), 2.30 (dt, *J* = 13.2, 6.8, 3.2, 1H), 1.92 (m, 1H), 1.82-1.68 (m, 4H), 1.67 (bs, 1H), 1.54 (ddd, *J* = 17.6, 12.8, 4.8, 1H), 1.31 (t, *J* = 7.2 , 6H), 1.22 (s, 3H), 1.09 (s, 3H), 0.91 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) 156.7, 142.5, 133.6, 123.0, 109.8, 78.9, 55.3, 49.3, 39.0, 38.0, 37.7, 29.3, 28.4, 28.3, 27.9, 25.5, 20.6, 19.4, 15.6; IR (thin film) 3331, 2939, 1589, 1477, 1259, 1031 $cm^{-1}$; HRMS (ESI) *m / z* calcd for $C_{21}H_{33}O_2$, $(M + H)^+$ 317.2481 found 317.2476; $[\alpha]^{20}_D$ +26.2 (c 0.95, $CHCl_3$).



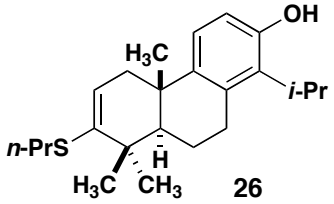
**3**

**(2*S*,4a*S*,10a*R*)-8-isopropyl-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-2,7-diol (3)**. Into a flame-dried flask containing dry DCM (5 mL) was added $AlBr_3$ (0.46 g, 1.7 mmol) and PrSH (1 mL). The protected totarodiol **24** (0.18 g, 0.58 mmol) was dissolved in dry DCM (5 mL) and added to the solution. The reaction was stirred for 2 h and then MeOH was added until the solution was clear of precipitates. A 10% HCl solution (10 mL) was added then extracted with DCM (3 x 15 mL). The combined organic layers was collected and dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude material was purified using flash column chromatography in 10% EtOAc:Hex to give a white solid (0.13 g, 75%). $^1H$ NMR (300 MHz, $CDCl_3$) 6.97 (d, *J* = 8.4, 1H), 6.53 (d, *J* = 8.7, 1H), 5.17 (s, OH), 3.33 (m, 2H), 3.00 (dd, *J* = 6.0, 1H), 2.79 (m, 1H), 2.27 (d, *J* = 12.9, 1H), 1.97-1.68 (m, 6 H), 1.53 (ddd, J = 17.1, 12.3, 4.8, 1H), 1.36 (q, J = 7.2, 2.7, 6H), 1.20 (s, 3H), 1.09 (s, 3H), 0.91 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) 152.6, 142.3, 134.0, 131.3, 123.2, 114.6, 79.2, 49.3, 39.0, 37.9, 37.7, 29.3, 28.4, 28.3, 27.6, 25.4, 20.5, 19.4, 15.6; $[\alpha]^{20}_D$ +25.9 (c 0.38, EtOH).



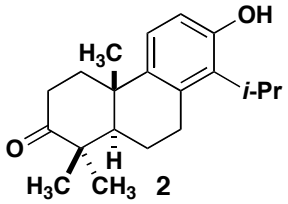

25

**(4a*S*,10a*R*)-8-isopropyl-7-methoxy-1,1,4a-trimethyl-3,4,4a,9,10,10a-hexahydrophenanthren-2(1*H*)-one (25)**. Fresh Jones reagent was prepared by the addition of $CrO_3$ (0.28 g, 2.8 mmol) and $H_2SO_4$ (0.18 g, 1.8 mmol) in $H_2O$ (1.8 mL). In a separate flask, protected totarodiol **24** (0.44 g, 1.4 mmol) was dissolved in acetone (10 mL) and cooled to 0 °C. The Jones reagent was added dropwise to **24**, and was allowed to stir for 30 min. The reaction was quenched with 2-propanol (10 mL) and then extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed *in vacuo* to give a white solid (0.33 g, 74%). The solid was taken to the next step without purification; $^1$H NMR (300 MHz, $CDCl_3$) 7.13 (d, $J$ = 8.7, 1H), 6.78 (d, $J$ = 8.7, 1H), 3.79 (s, 3H), 3.29 (m, 1H), 3.06 (dd, $J$ = 16.8, 5.1, 1H), 2.84-2.46 (m, 4H), 1.90 (m, 4H), 1.34 (s, 9H), 1.19 (s, 3H), 1.16 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) 217.5, 156.9, 140.5, 133.6, 124.0, 110.1, 55.3, 50.1, 47.4, 38.6, 37.5, 35.1, 29.3, 27.9, 27.0, 25.1, 21.4, 20.8, 20.7, 20.6; IR (thin film) 2950, 1705, 1590, 1480, 1260 cm$^{-1}$; HRMS (ESI) $m$ / $z$ calcd for $C_{21}H_{31}O_2$, $(M + H)^+$ 315.2324 found 315.2319; $[\alpha]^{20}_D$ +74.2 (c 0.58, EtOH).




26

**(4b*S*,8a*R*)-1-isopropyl-4b,8,8-trimethyl-7-(propylthio)-4b,5,8,8a,9,10-hexahydrophenanthre-2-ol (26)**. To a flame-dried flask was added protected totarolone **25** (0.33 g, 1.0 mmol) in dry DCM (10 mL). PrSH (1.5 mL) was added to the solution followed by $AlBr_3$ (0.83 g, 3.1 mmol). After 30 min, MeOH was added and the solution was washed with 10 % HCl. The reaction was extracted with DCM and the combined organic layers were washed with brine, and then dried over $MgSO_4$. The solvent was removed *in vacuo* and material was purified by flash column chromatography in 5 % EtOAc:Hex, to yield a light yellow oil (0.22 g, 72%); $^1$H NMR (300 MHz, $CDCl_3$) 7.00 (d, $J$ = 6.9, 1H), 6.58 (d, $J$ = 8.1, 1H), 5.61 (d, $J$ = 22, 1H), 4.91 (s, 1H), 3.34 (m, 1H), 3.02 (d, $J$ =16.2, 1H), 2.72 (m, 3H), 2.58 (dd, $J$ = 18.3, 6.6, 1H), 2.21 (d, $J$ = 1.8, 1H), 1.93 (m, 1H), 1.73-1.64 (m, 4H), 1.37 (d, $J$ = 7.2, 6H), 1.26 (s, 3H), 1.23 (s, 3H), 1.15 (s, 3H), 1.04 (t, $J$ = 7.2, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) 152.4, 142.6, 140.5, 134.6, 130.9, 124.7, 121.8, 115.1, 49.2, 42.5, 39.9, 36.9, 35.9, 30.6, 29.6, 27.6, 25.4, 22.4, 21.2, 21.1, 20.6, 20.5, 14.0;

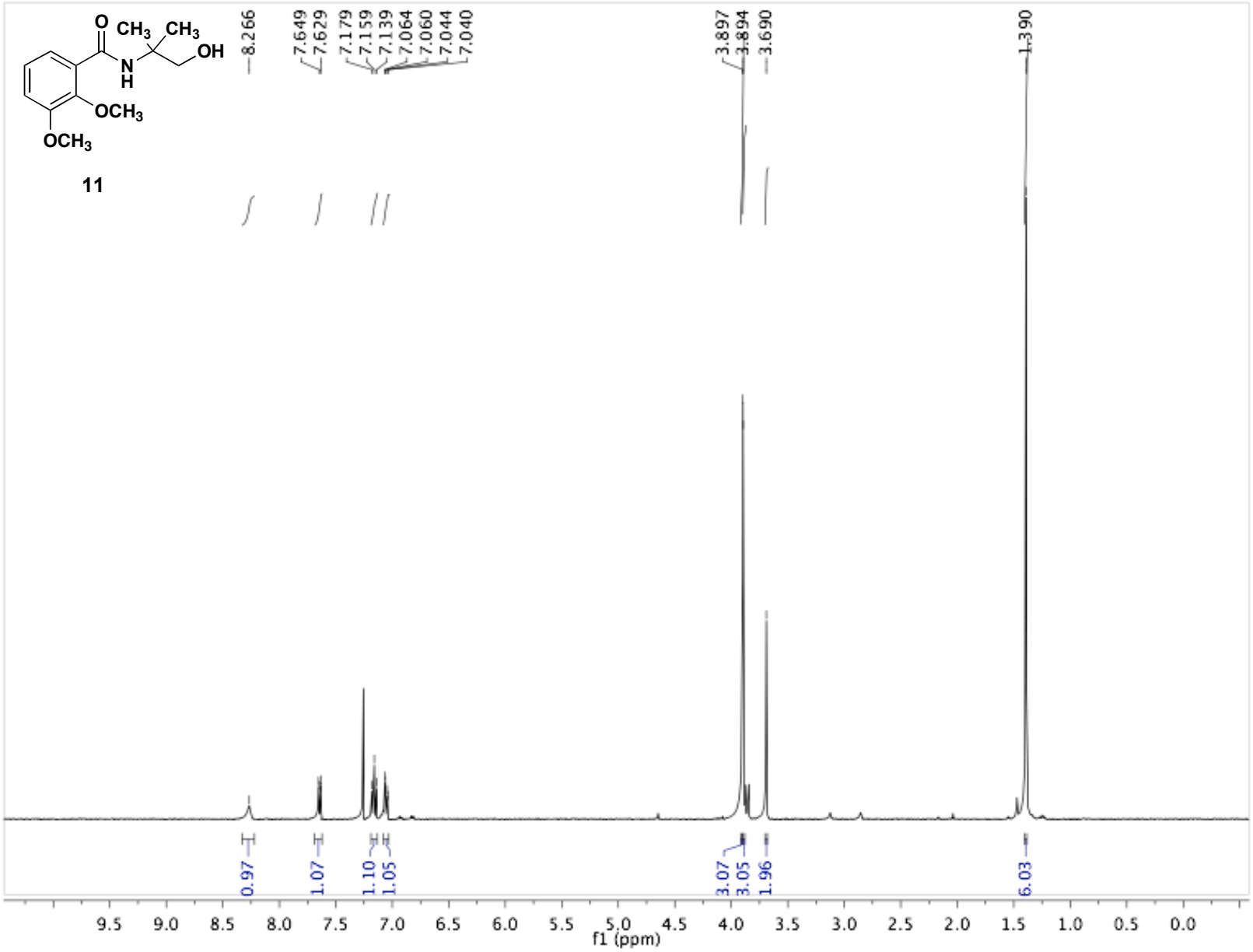


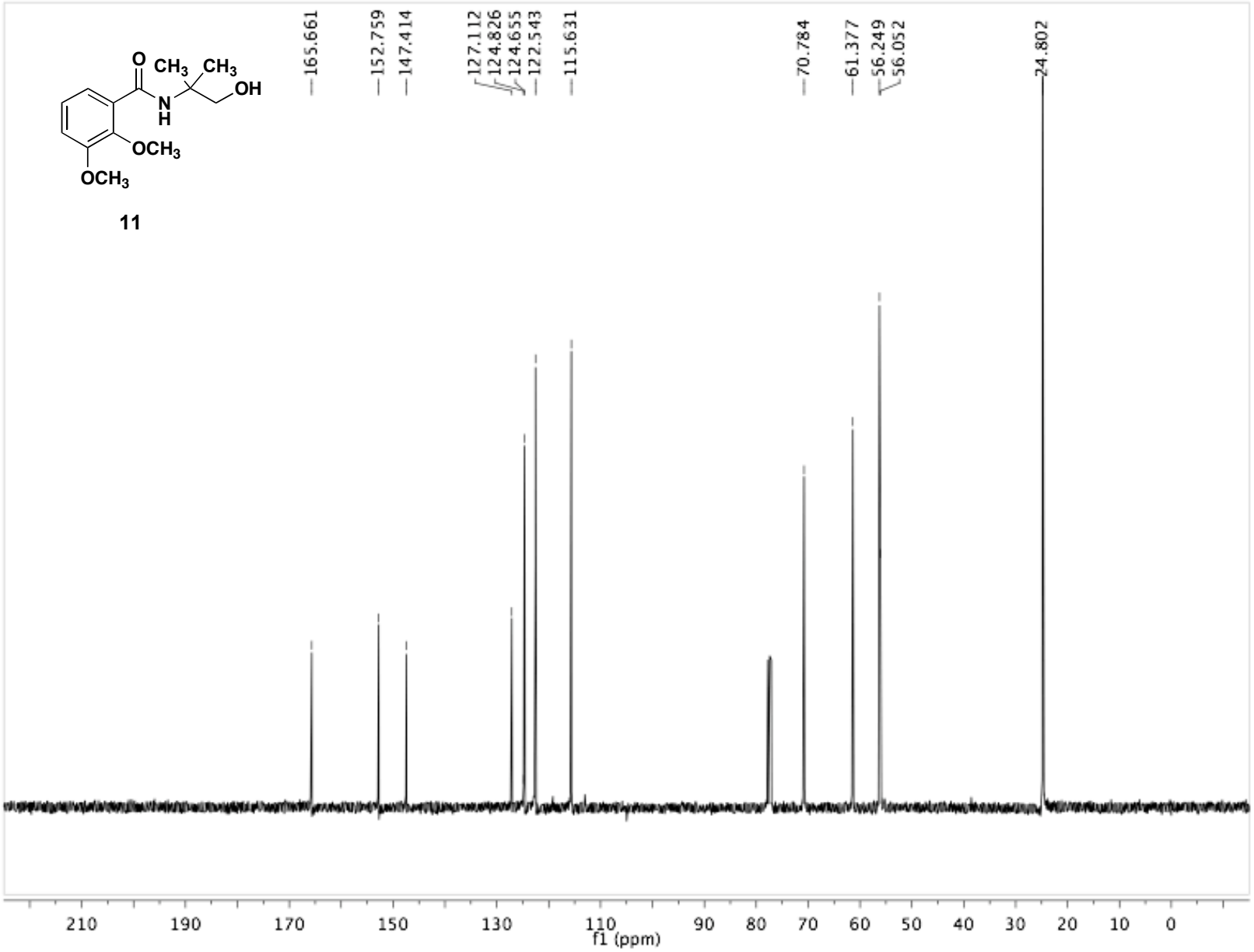

2

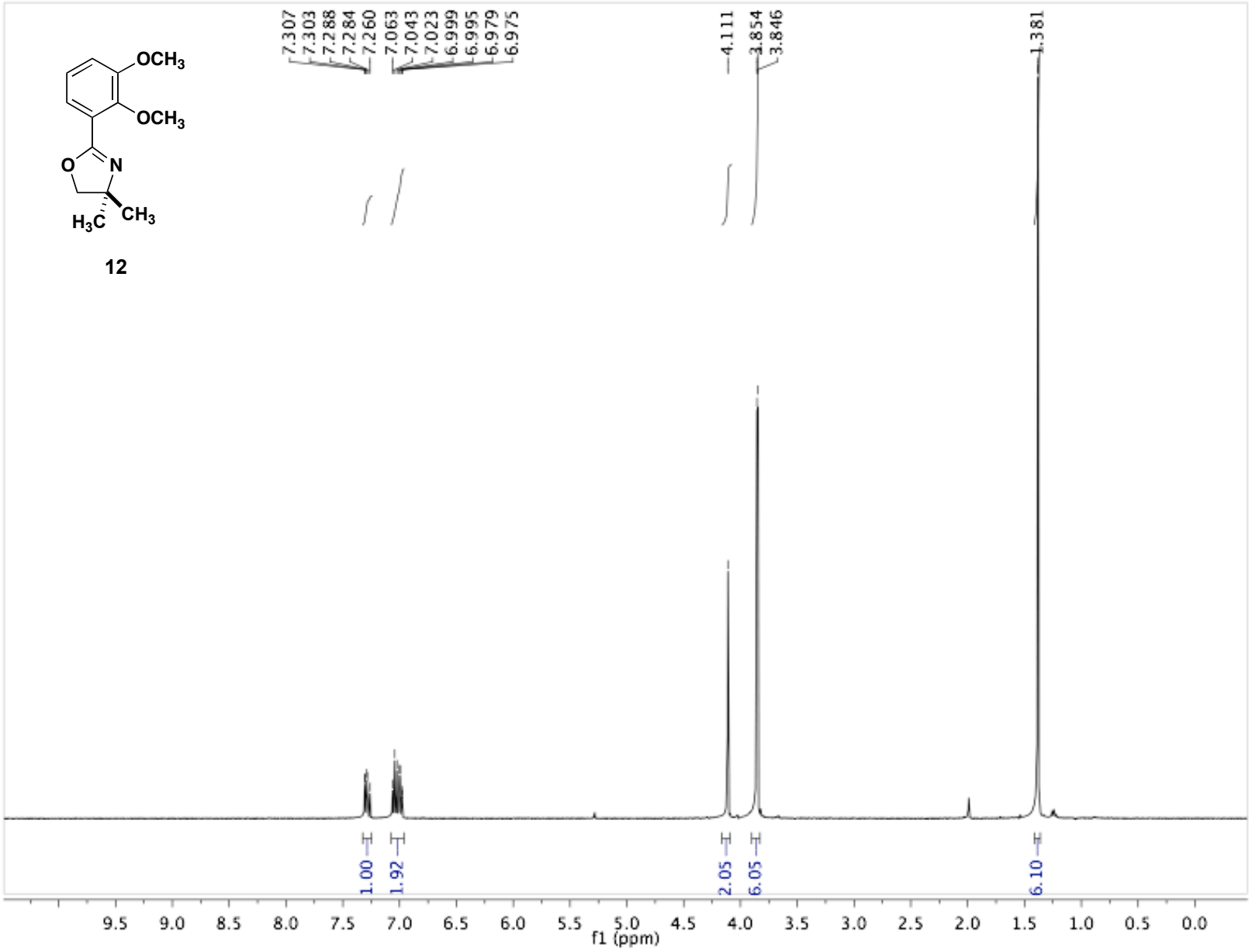
**(4aS,10aR)-7-hydroxy-8-isopropyl-1,1,4a-trimethyl-3,4,4a,9,10,10a-hexahydrophenanthren-2(1H)-one (2)**.

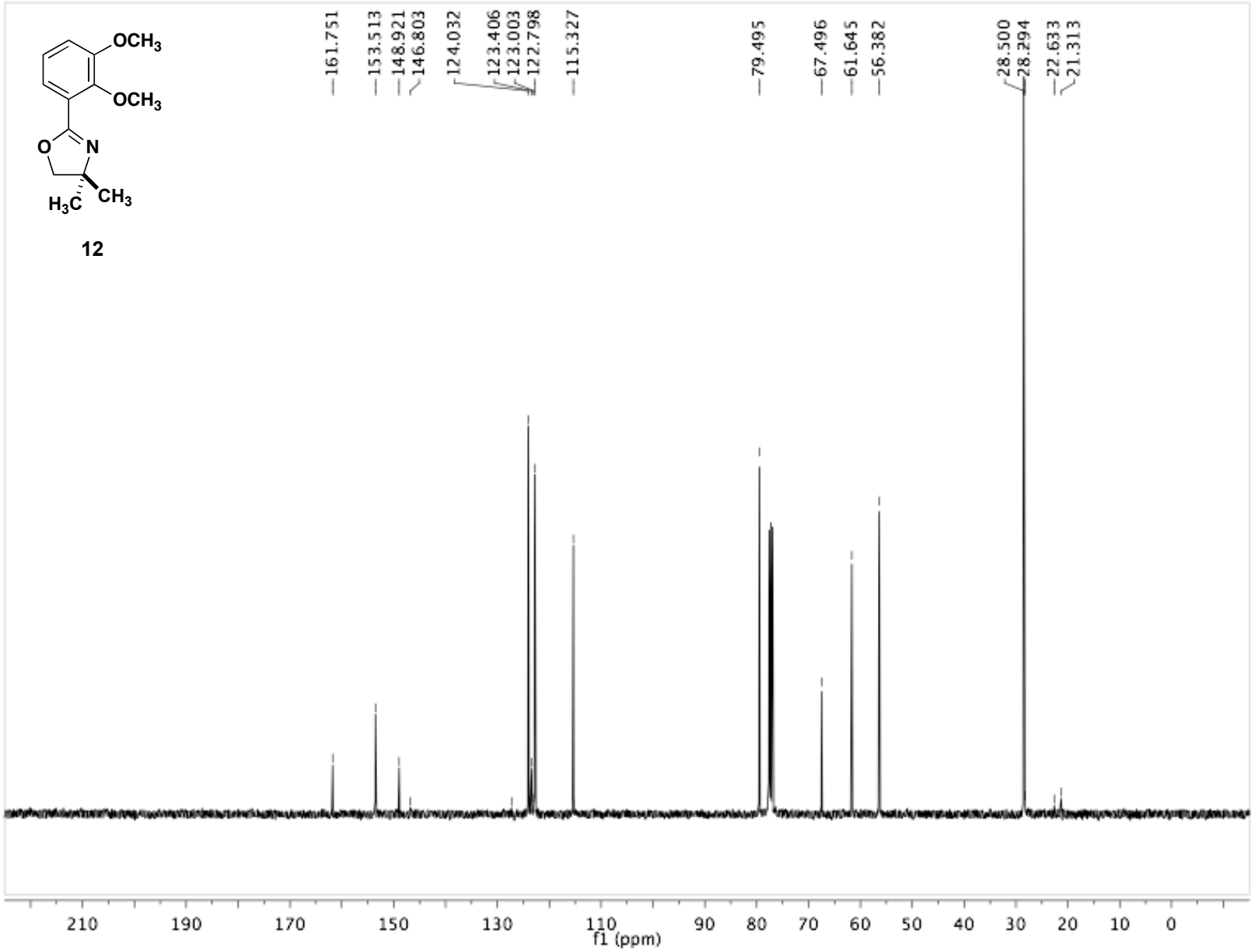
**Method 1:** Totarathiol **26** (0.22 g, 0.623 mmol) was dissolved in MeOH (17.3 mL) and 5% HCl (8.7 mL). The solution was heated at 70 °C for 24 h. The light yellow solution was cooled to 23 °C then the MeOH was removed *in vacuo*. The aqueous layer was washed with $NaHCO_3$ and then extracted with ether. The solvent was removed and the crude material was purified using flash column chromatography (5% EtOAc:Hex) to give totarolone as a white solid (0.14 g, 75%).
**Method 2:** In dry toluene (20 mL) was dissolved totarodiol **3** (0.13 g, 0.43 mmol). To the flask was added aluminum isopropoxide (0.45 g, 2.2 mmol) followed by cyclohexanone (1.7 g, 17.3 mmol, 1.8 mL). The solution was heated to 150 °C for 3 h then cooled to 23 °C. The lemon yellow solution was concentrated and the crude material was purified by flash column chromatography in 20 % EtOAc:Hex to give totarolone as a white solid (43 mg, 33%).
$^1$H NMR (300 MHz, $CDCl_3$) 6.98 (d, *J* = 8.4, 1H), 6.57 (d, *J* = 8.4, 1H), 4.97 (s, 1H), 3.28 (m, 1H), 3.04 (dd, *J* = 16.8, 5.1, 1H), 2.69 (m, 3H), 2.42 (m, 1H), 1.87 (m, 3H) 1.72 (m, 1H), 1.37 (s, 3H), 1.34 (s, 3H), 1.30 (s, 3H), 1.17 (s, 3H), 1.14 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) 218.3, 152.7, 140.4, 134.0, 131.3, 124.2, 115.0, 50.0, 47.5, 38.5, 37.5, 53.0, 29.2, 27.6, 27.0, 25.1, 21.3, 20.7, 20.6, 20.5; $[\alpha]^{20}_D$ +93.2 (c 0.42, EtOH).
**Totarol (1)**. Ketone **2** (9.8 mg, 0.03 mmol) was dissolved in diethylene glycol (1 mL) and to it was added KOH (0.02 g, 0.36 mmol) and $H_2NNH_2 \bullet H_2O$ (0.2 mL, 4.3 mmol, 64%). The reaction was heated at 200 °C overnight. The dark yellow solution was then cooled and then water (10 mL) was added. The solution was then extracted with EtOAc (3 x 15 mL) and the combined organic layers were washed with brine then dried over $MgSO_4$. The solvent was evaporated *in vacuo* and purified using flash column chromatography (5 % EtOAc:Hex) to yield a white solid (4.3 mg, 50%); $^1$H NMR (300 MHz, $CDCl_3$) 6.99 (d, *J* = 8.7, 1H), 6.51 (d, J = 8.4, 1H), 4.41 (s, 1H), 3.29 (m, 1H), 2.93 (dd, J = 16.5, 6.3, 1H), 2.78 (m, 1H), 2.23 (d, *J* =12.6, 1H), 1.91 (m, 1H), 1.74-1.56 (m, 4H), 1.46 (d, 1H), 1.34 (q, *J* = 6.6, 2.7, 6H), 1.27 (d, *J* = 9.6 Hz, 2H), 1.17 (s, 3H), 0.94 (s, 3H), 0.91 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) 143.4, 134.2, 131.2, 123.2, 114.5, 104.9, 49.8, 41.8, 39.8, 37.9, 33.5, 33.48, 33.46, 28.9, 27.3, 25.4, 21.8, 20.6, 19.7, 19.6; $[\alpha]^{20}_D$ +36 (c 0.11, EtOH).

**References:**
1) Felpin, F. X.; Lory, C.; Sow, H.; Acherar, S. *Tetrahedron* **2007**, *63*, 3010-3016.
2) Corey, E. J.; Noe, M. C.; Shieh, W. C. *Tetrahedron Lett.* **1993**, *34*, 5995-5998.

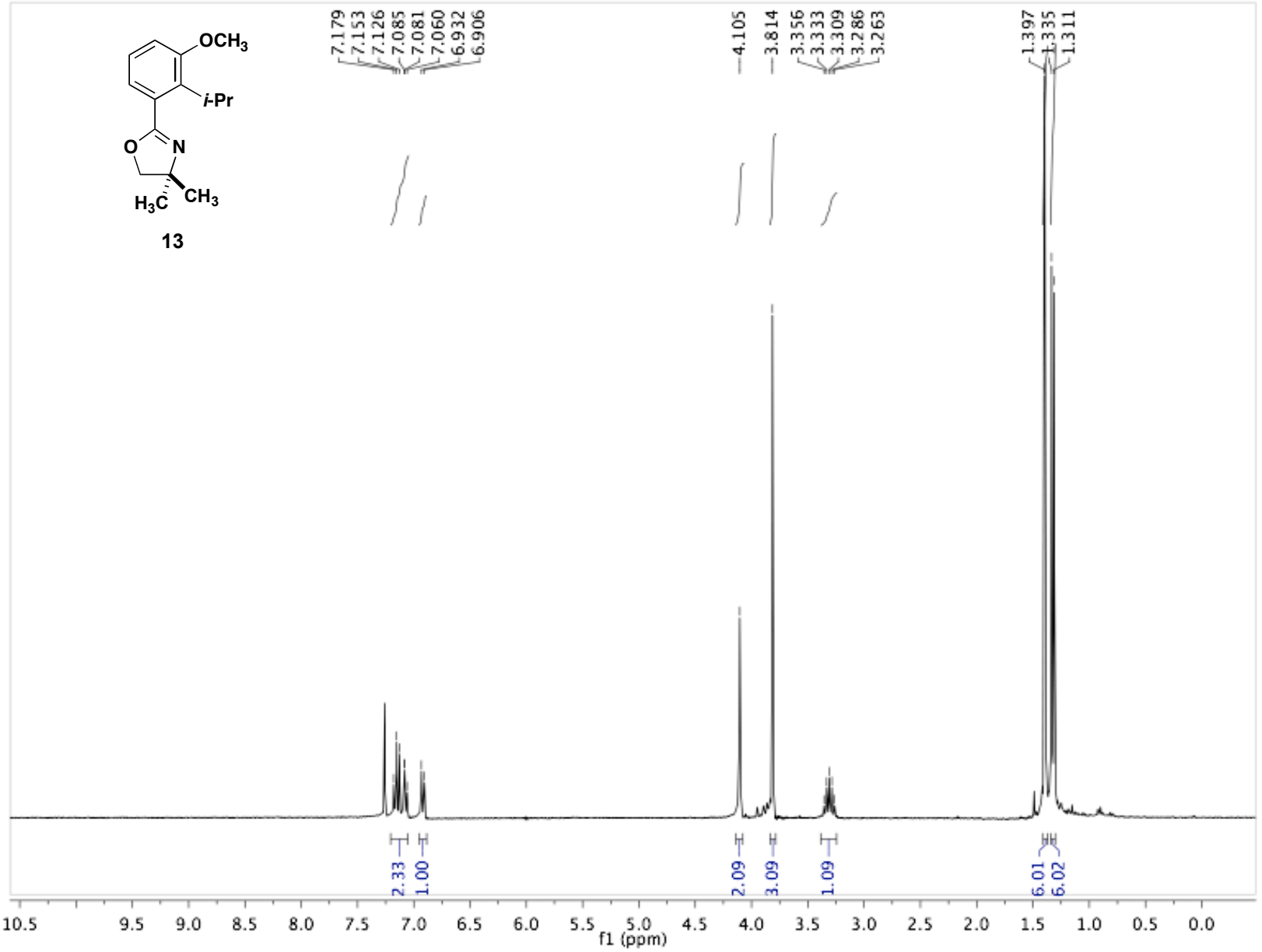

O
CH3
CH3
OH
N
H
OCH3
OCH3
11
8.266
7.649
7.629
7.179
7.159
7.139
7.064
7.060
7.044
7.040
3.897
3.894
3.690
1.390
0.97
1.07
1.10
1.05
3.07
3.05
1.96
6.03
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

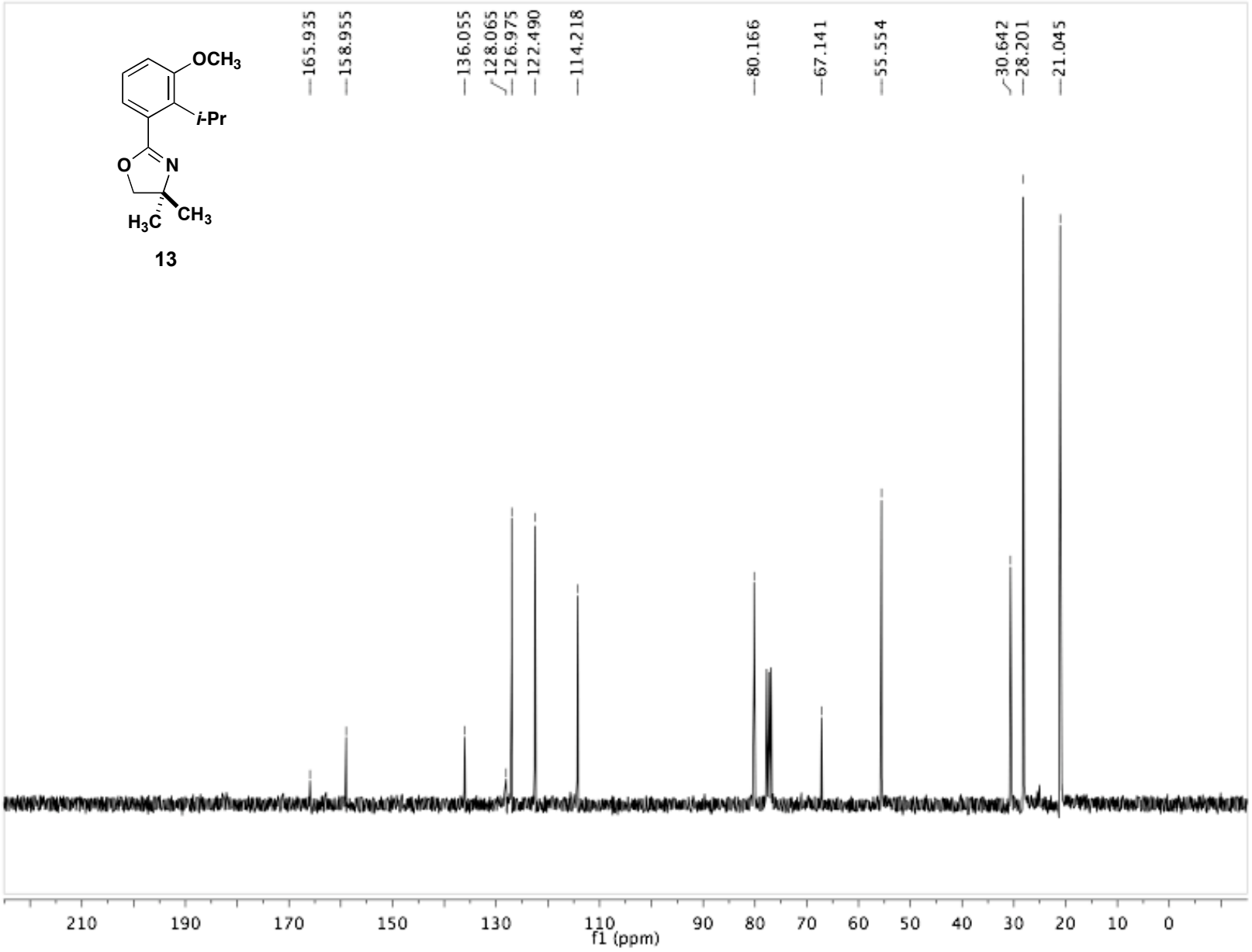

O
CH3
CH3
OH
N
H
OCH3
OCH3
11
165.661
152.759
147.414
127.112
124.826
124.655
122.543
115.631
70.784
61.377
56.249
56.052
24.802
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

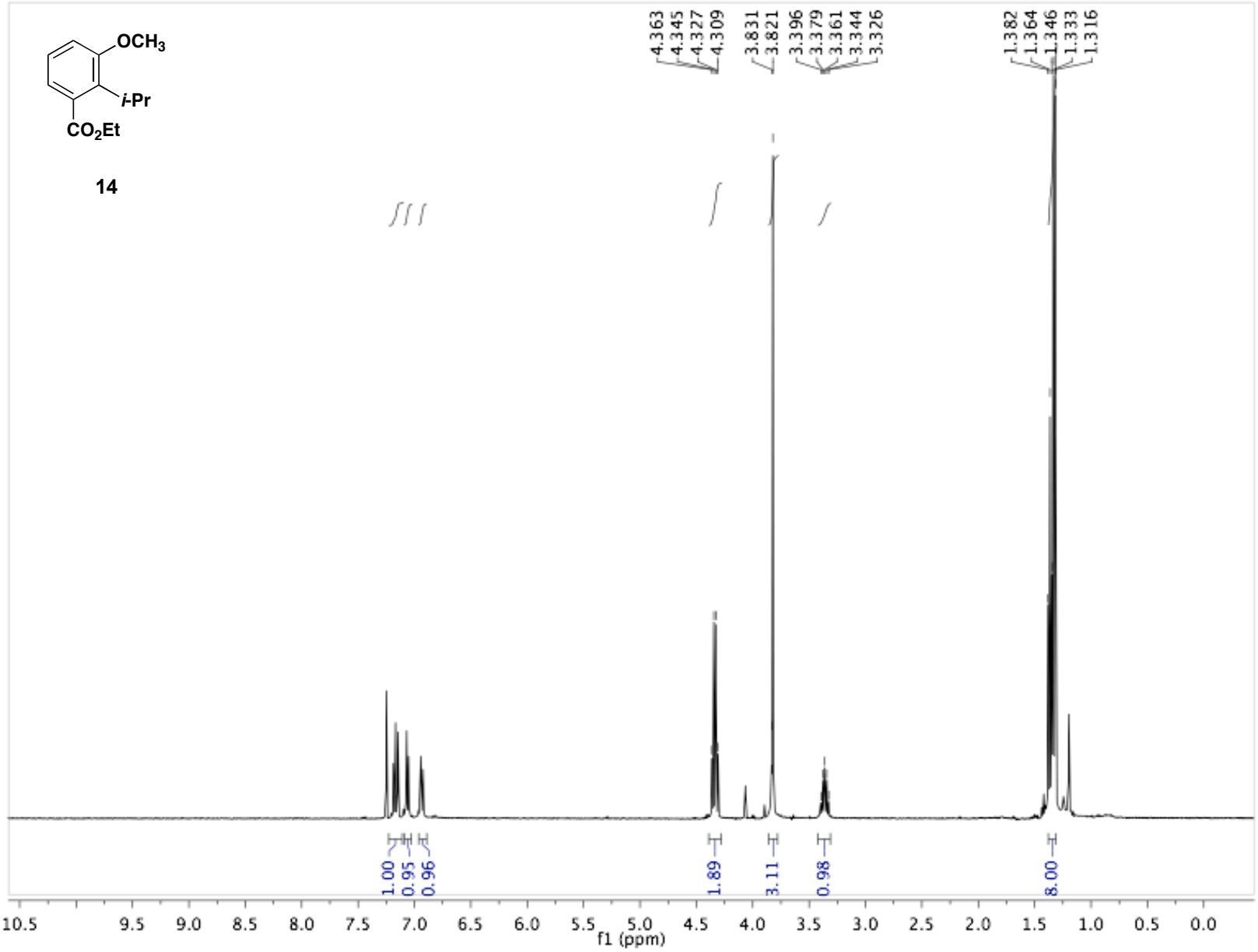

OCH3
OCH3
O
N
H3C
CH3
12
7.307
7.303
7.288
7.284
7.260
7.063
7.043
7.023
6.999
6.995
6.979
6.975
4.111
3.854
3.846
1.381
1.00
1.92
2.05
6.05
6.10
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

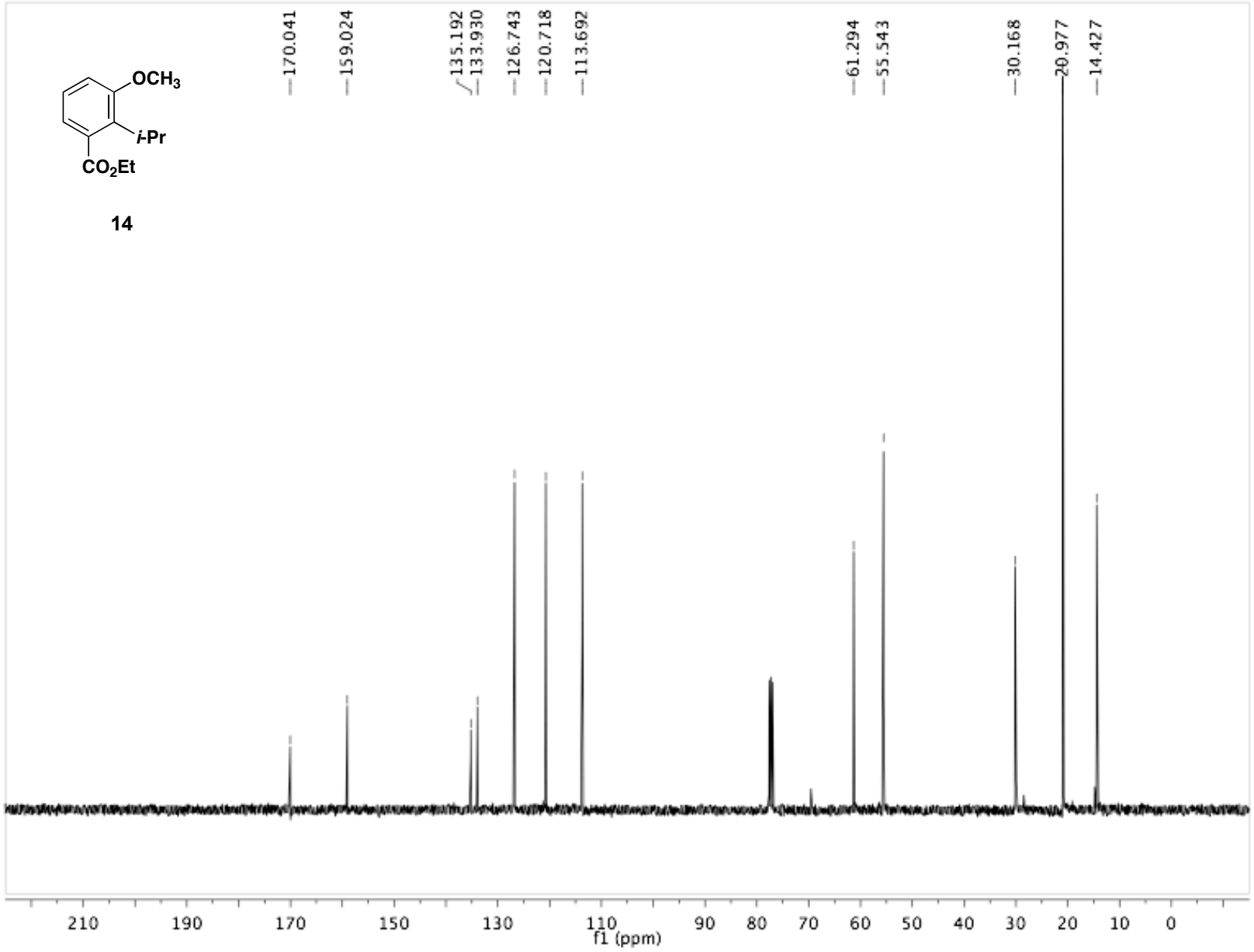

OCH3
OCH3
O
N
H3C
CH3
161.751
153.513
148.921
146.803
124.032
123.406
123.003
122.798
115.327
79.495
67.496
61.645
56.382
28.500
28.294
22.633
21.313
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

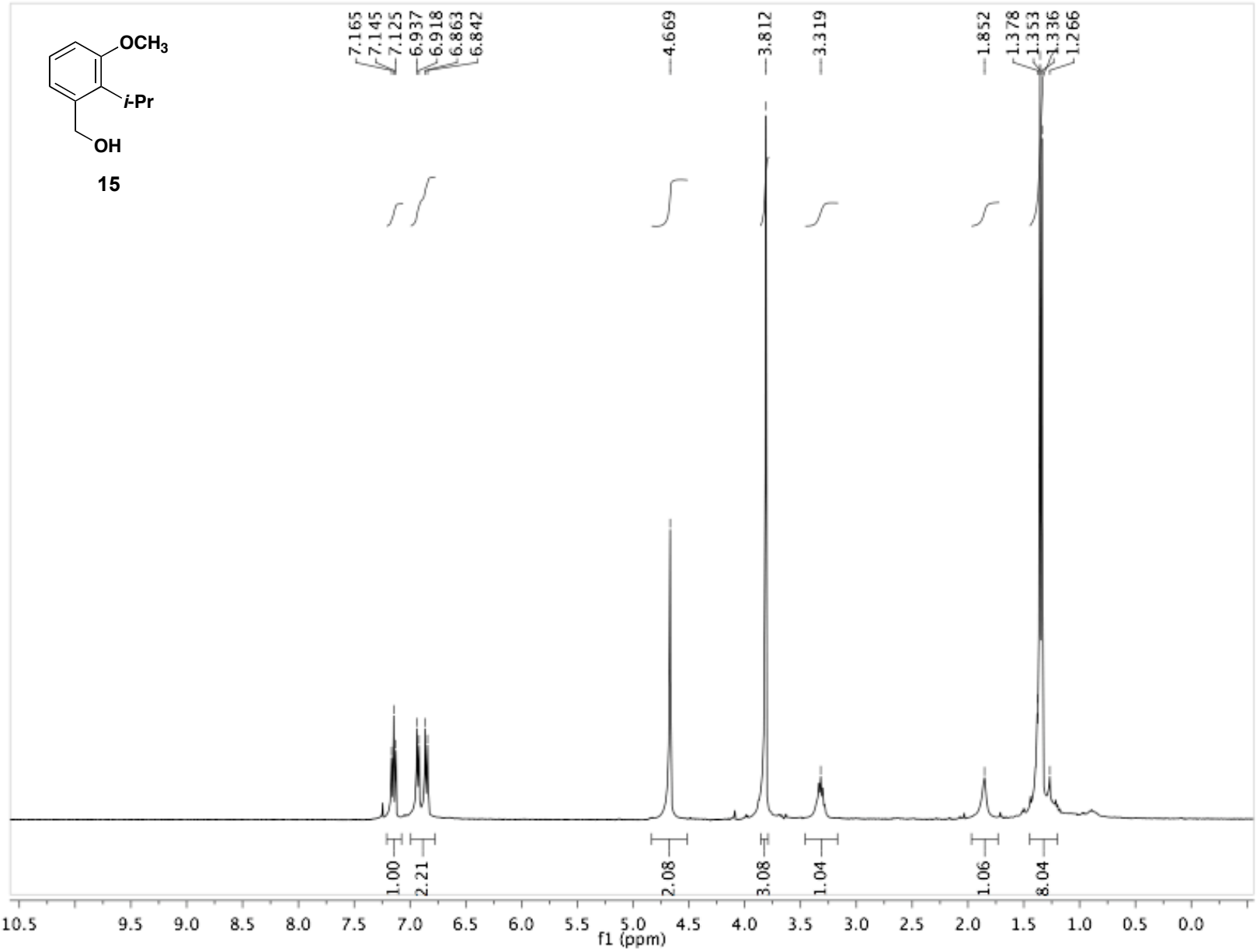
**12**

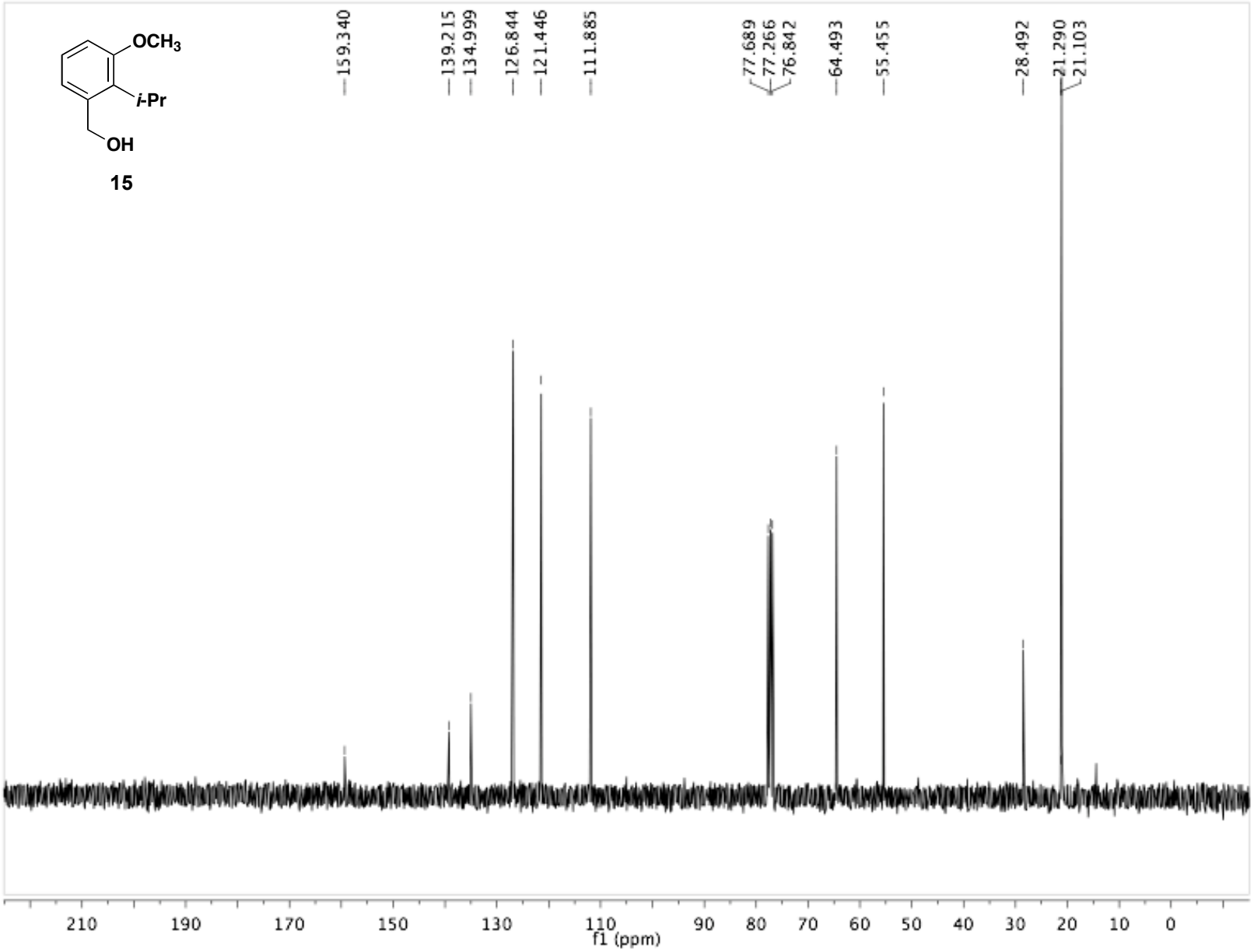

OCH3
i-Pr
O
N
H3C
CH3
13
7.179
7.153
7.126
7.085
7.081
7.060
6.932
6.906
4.105
3.814
3.356
3.333
3.309
3.286
3.263
1.397
1.335
1.311
2.33
1.00
2.09
3.09
1.09
6.01
6.02
f1 (ppm)

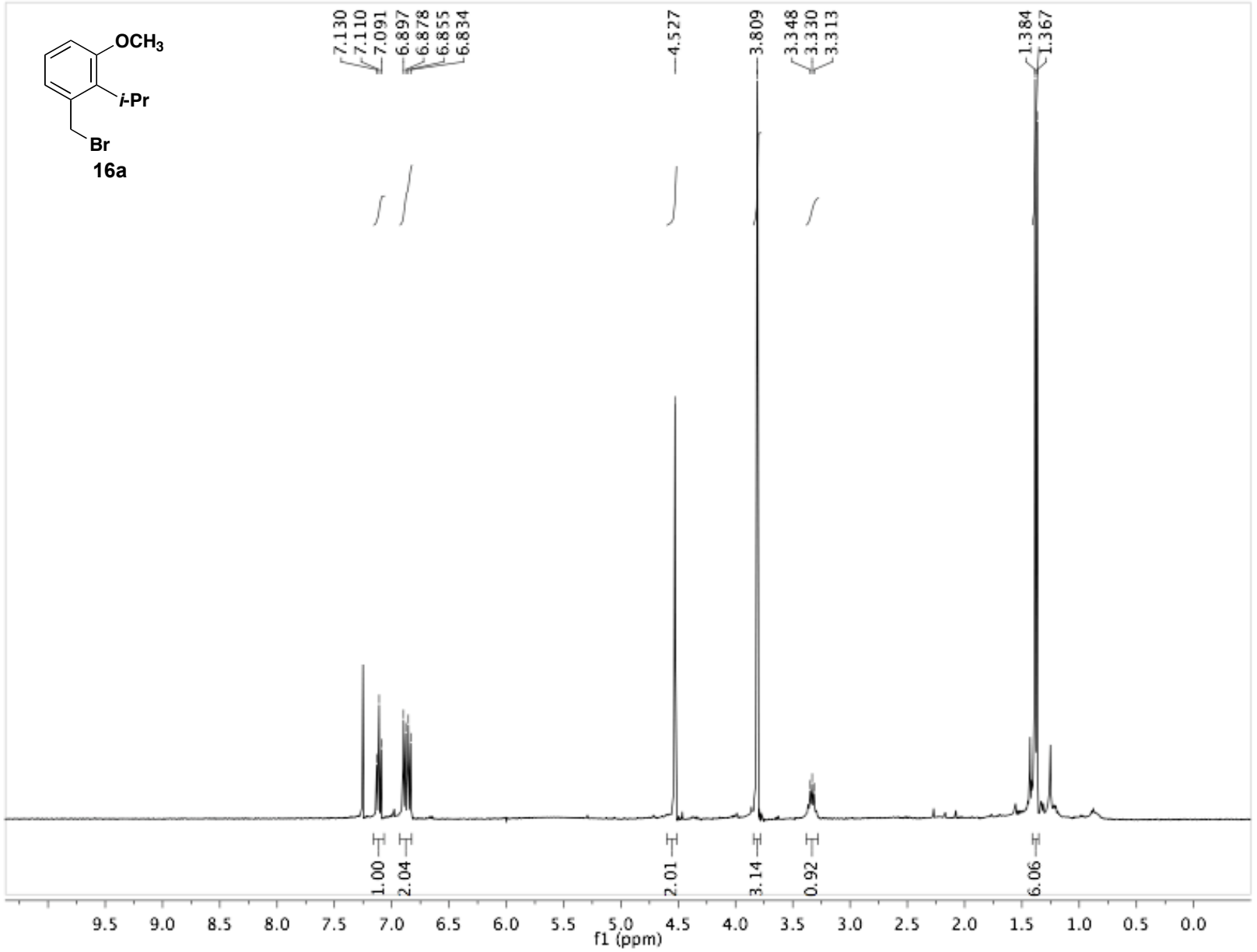

OCH3
i-Pr
O
N
H3C
CH3
13
165.935
158.955
136.055
128.065
126.975
122.490
114.218
80.166
67.141
55.554
30.642
28.201
21.045
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

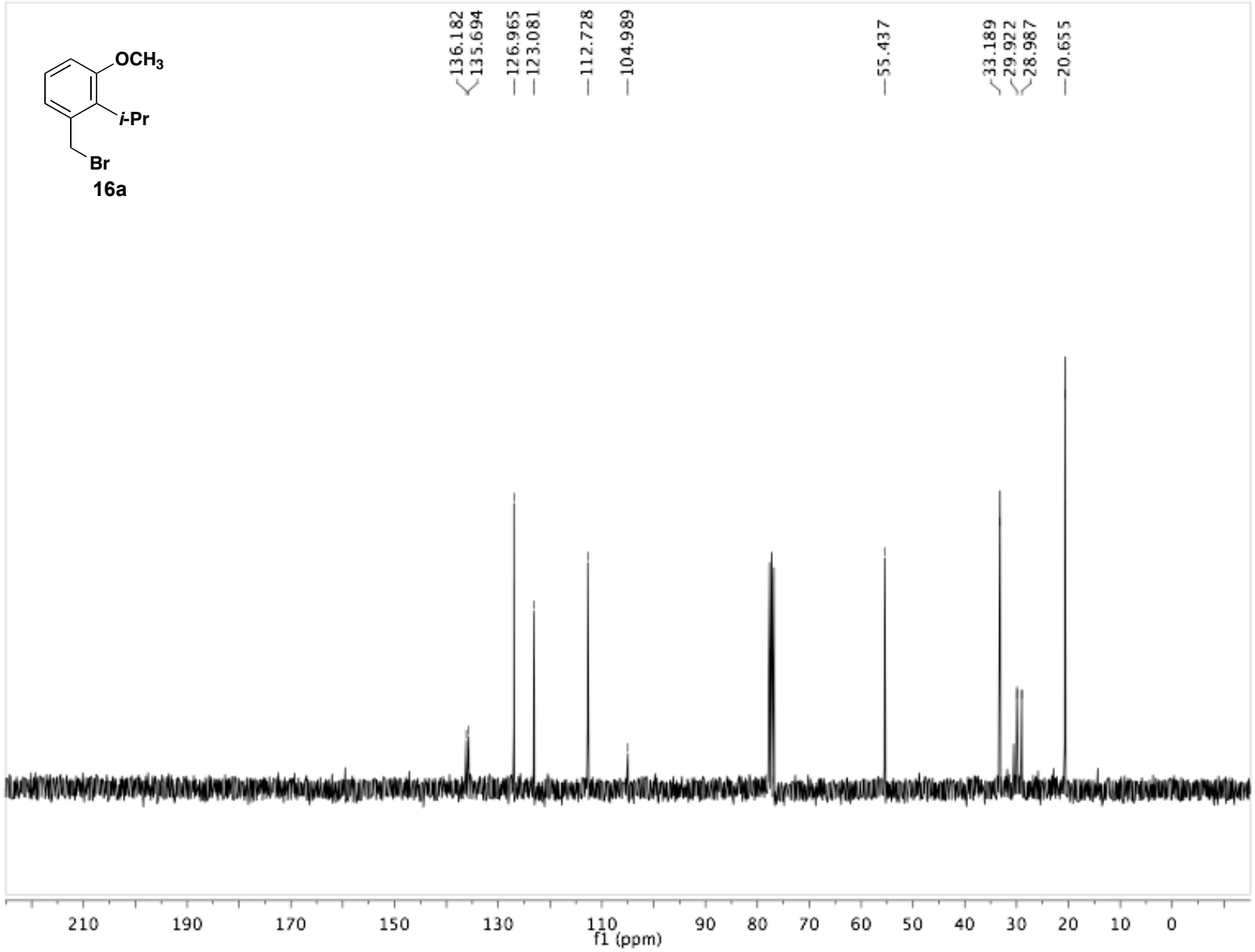

OCH3
i-Pr
CO2Et
14
4.363
4.345
4.327
4.309
3.831
3.821
3.396
3.379
3.361
3.344
3.326
1.382
1.364
1.346
1.333
1.316
1.00
0.95
0.96
1.89
3.11
0.98
8.00
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

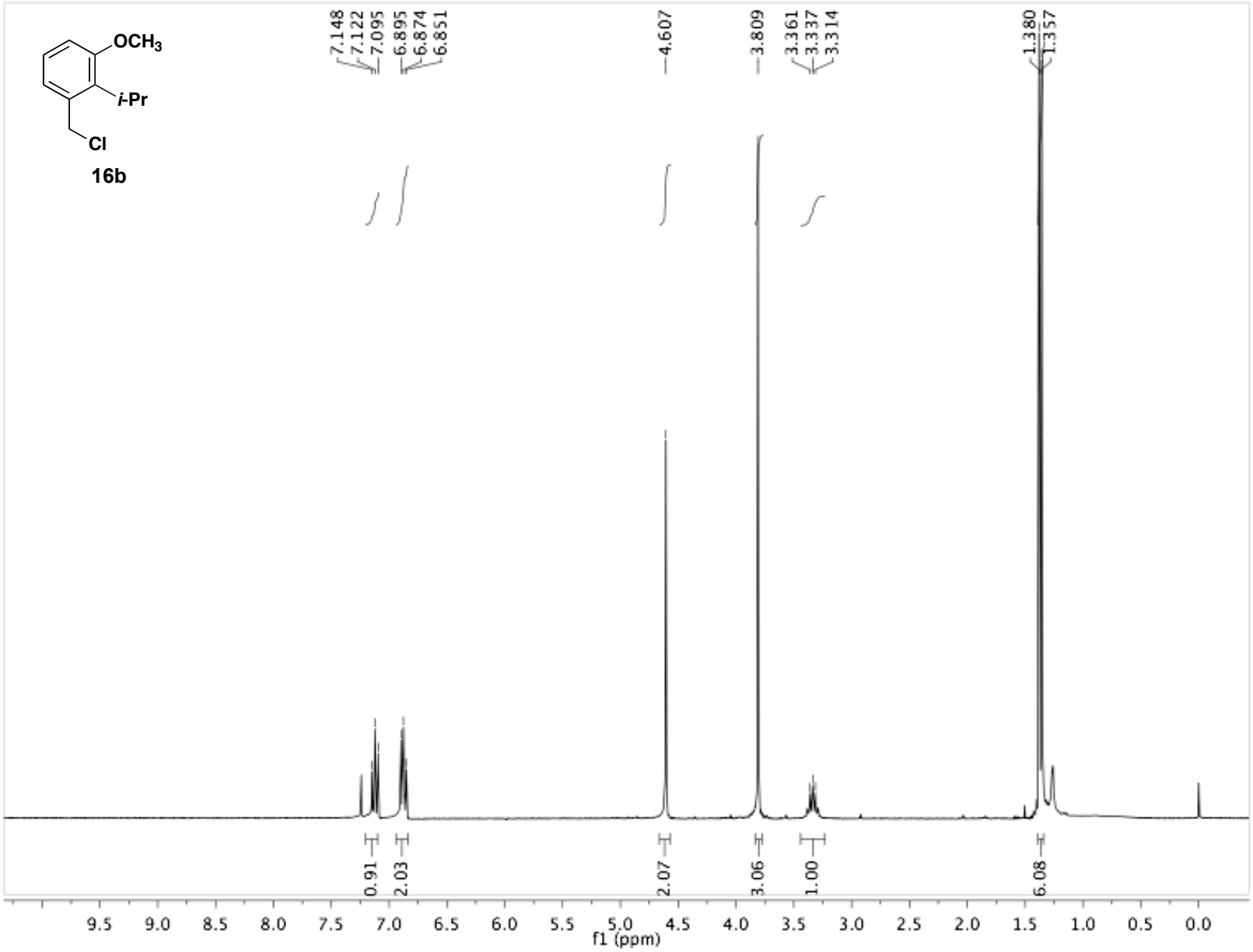

OCH3
i-Pr
CO2Et
14
170.041
159.024
135.192
133.930
126.743
120.718
113.692
61.294
55.543
30.168
20.977
14.427
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

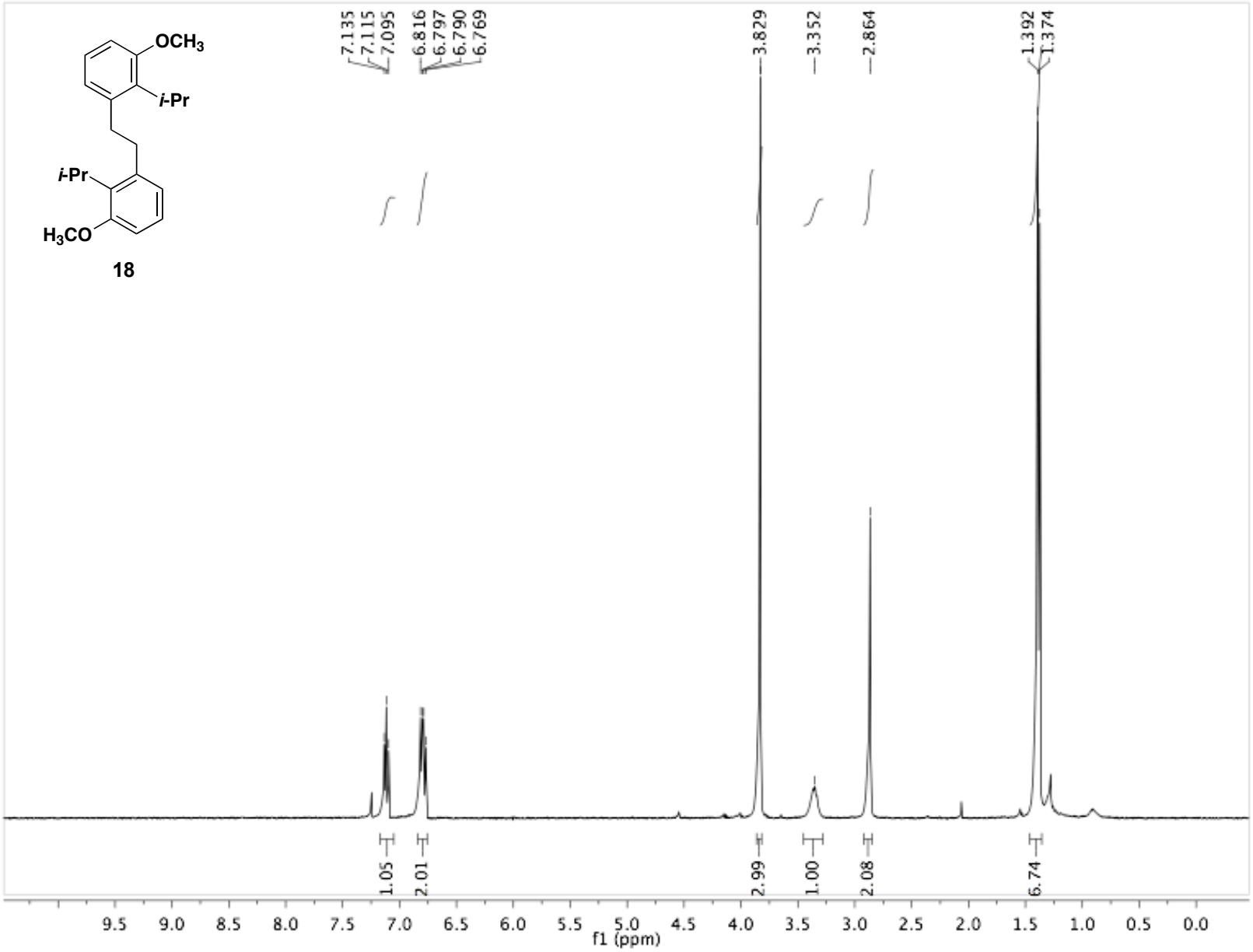

OCH3
i-Pr
OH
15
7.165
7.145
7.125
6.937
6.918
6.863
6.842
4.669
3.812
3.319
1.852
1.378
1.353
1.336
1.266
1.00
2.21
2.08
3.08
1.04
1.06
8.04
f1 (ppm)

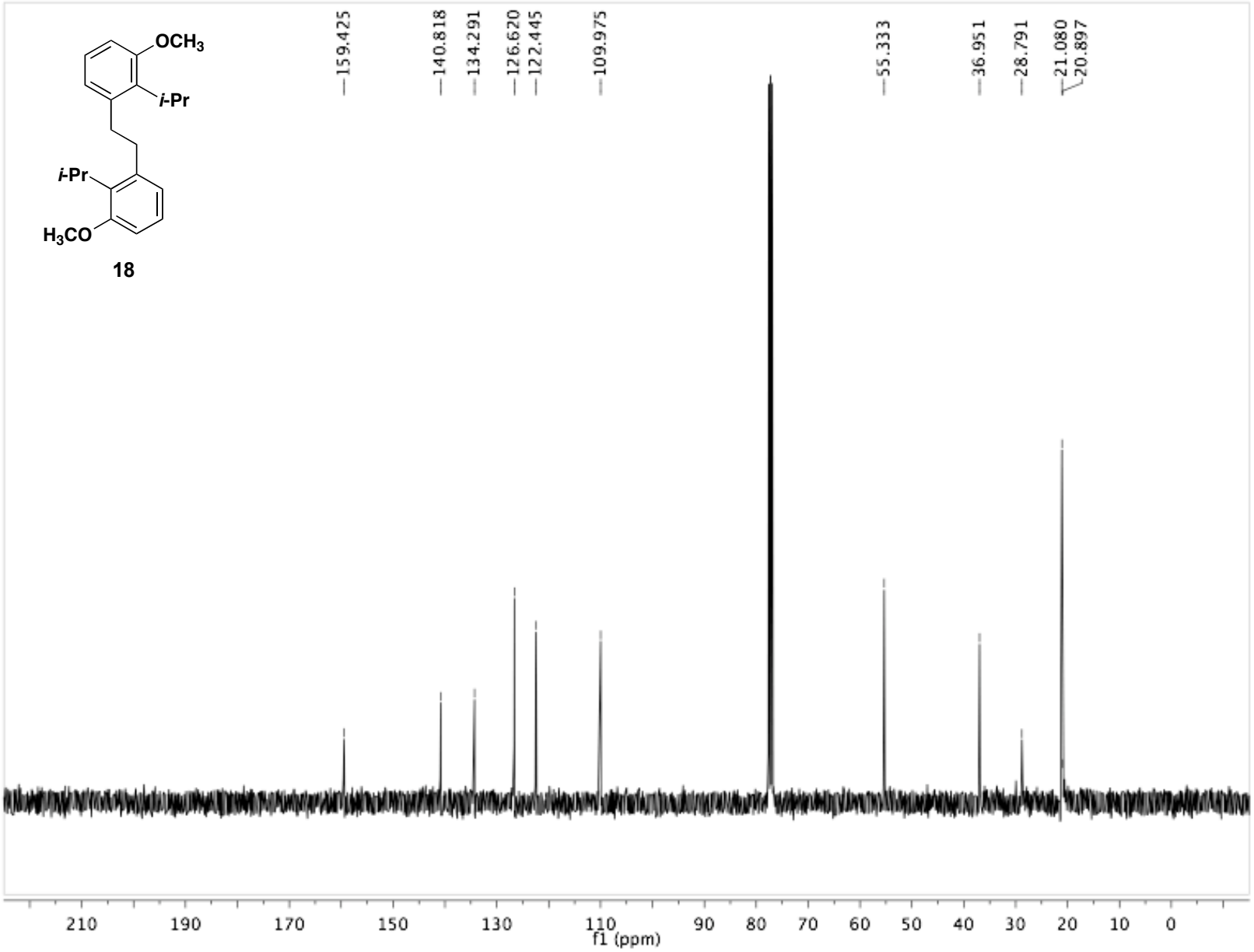

OCH3
i-Pr
OH
15
159.340
139.215
134.999
126.844
121.446
111.885
77.689
77.266
76.842
64.493
55.455
28.492
21.290
21.103
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


OCH3
i-Pr
Br
16a
7.130
7.110
7.091
6.897
6.878
6.855
6.834
4.527
3.809
3.348
3.330
3.313
1.384
1.367
1.00
2.04
2.01
3.14
0.92
6.06
f1 (ppm)

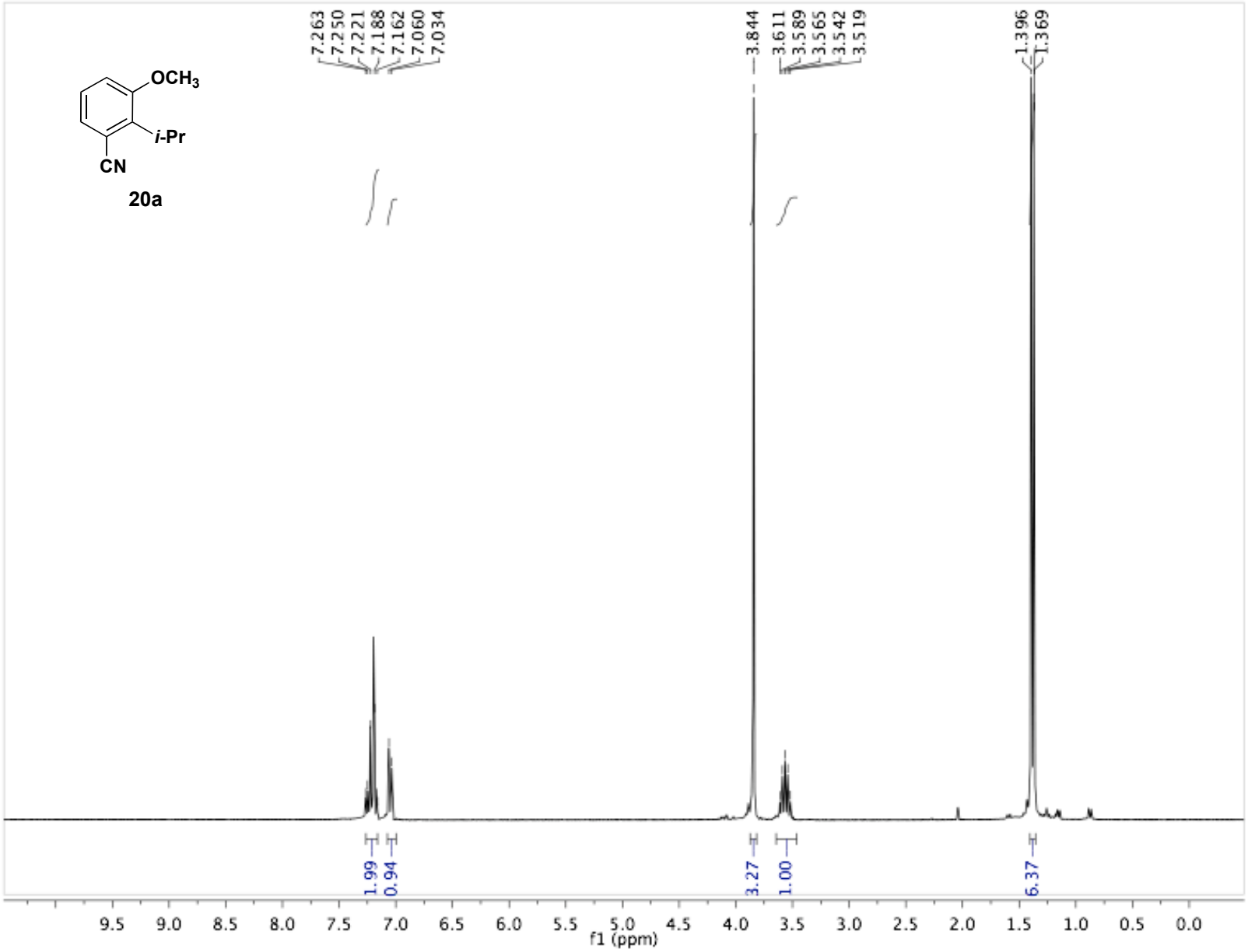

OCH3
i-Pr
Br
16a
136.182
135.694
126.965
123.081
112.728
104.989
55.437
33.189
29.922
28.987
20.655
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

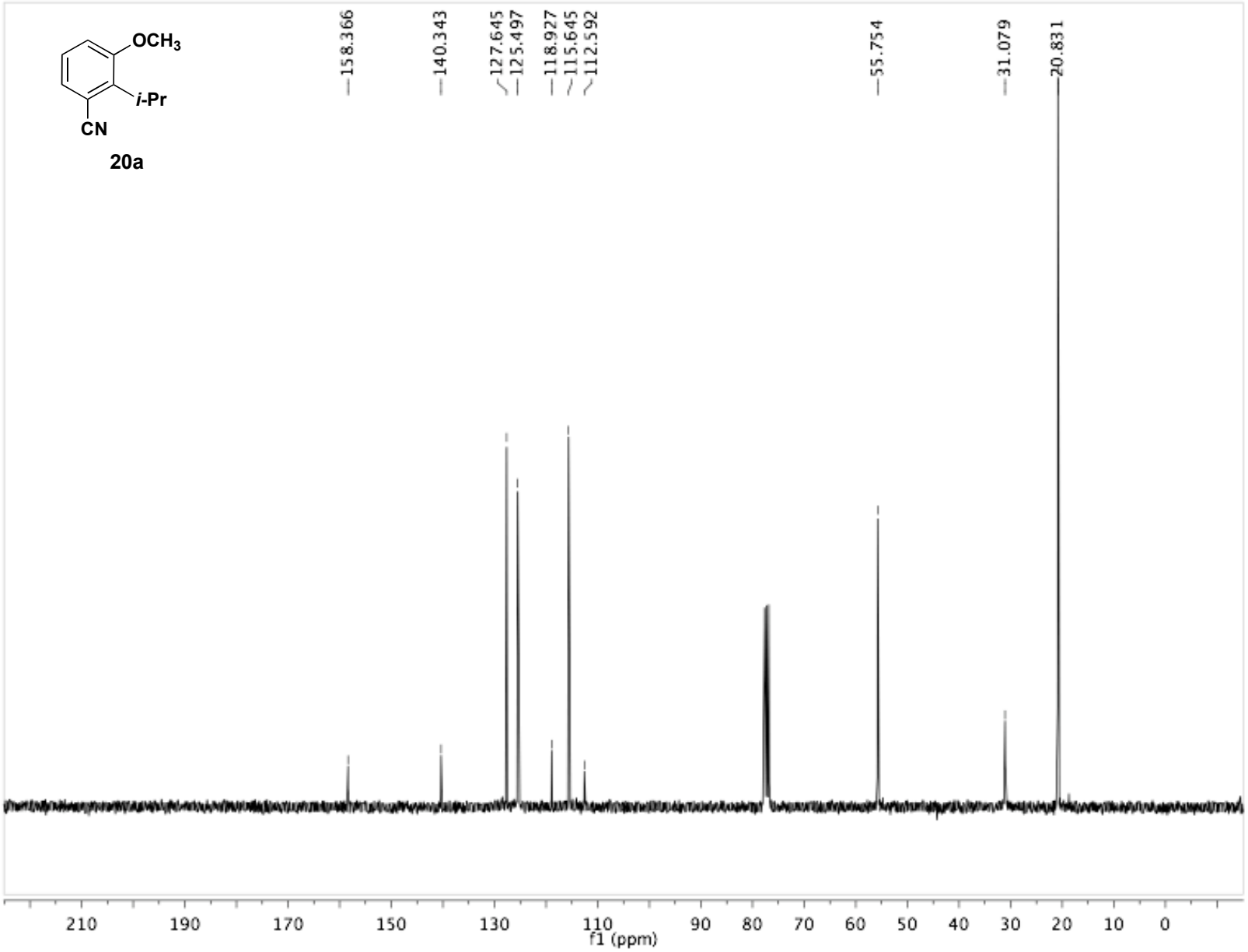

OCH3
i-Pr
Cl
16b
7.148
7.122
7.095
6.895
6.874
6.851
4.607
3.809
3.361
3.337
3.314
1.380
1.357
0.91
2.03
2.07
3.06
1.00
6.08
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

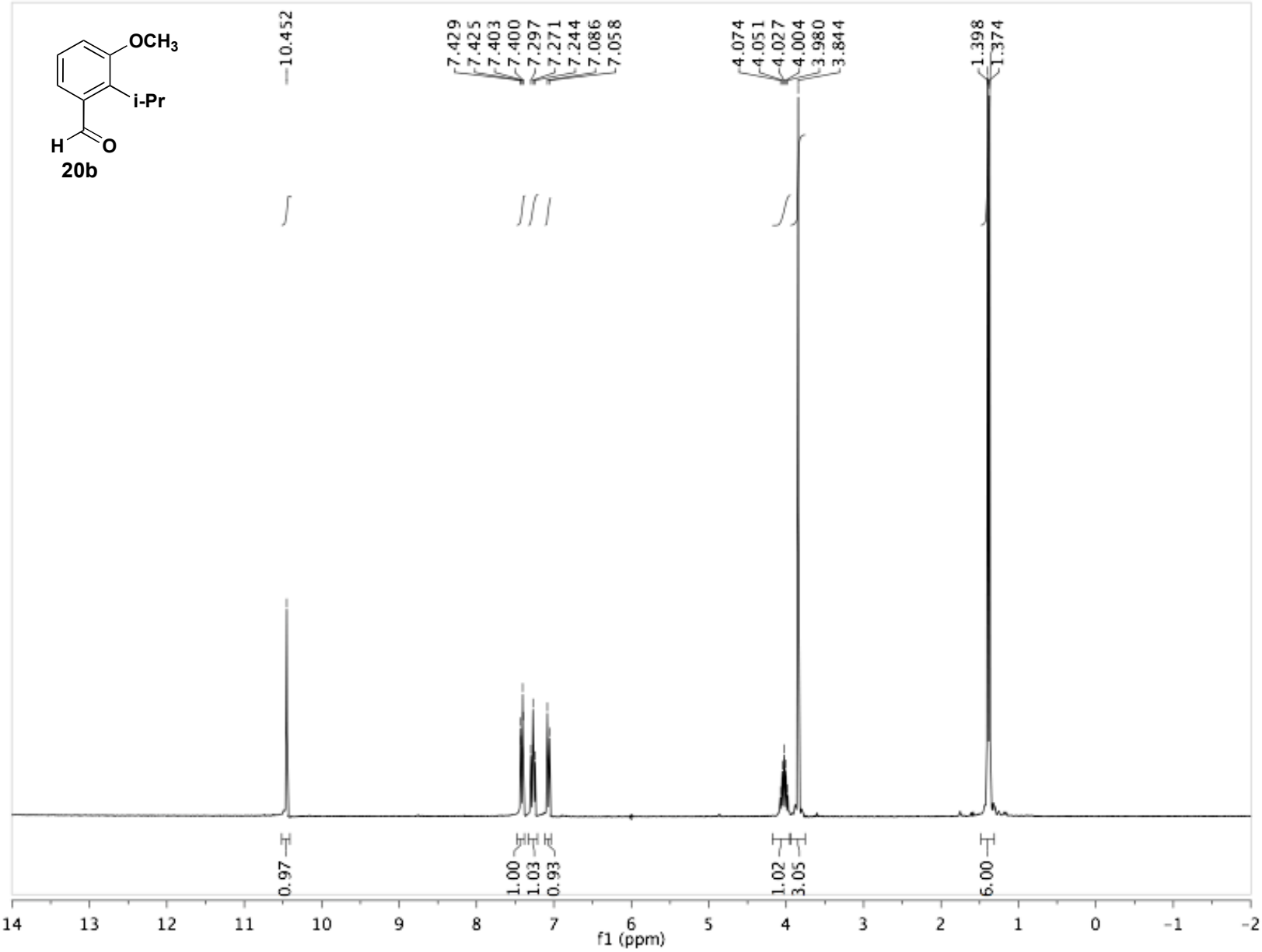

OCH3
i-Pr
i-Pr
H3CO
18
7.135
7.115
7.095
6.816
6.797
6.790
6.769
3.829
3.352
2.864
1.392
1.374
1.05
2.01
2.99
1.00
2.08
6.74
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

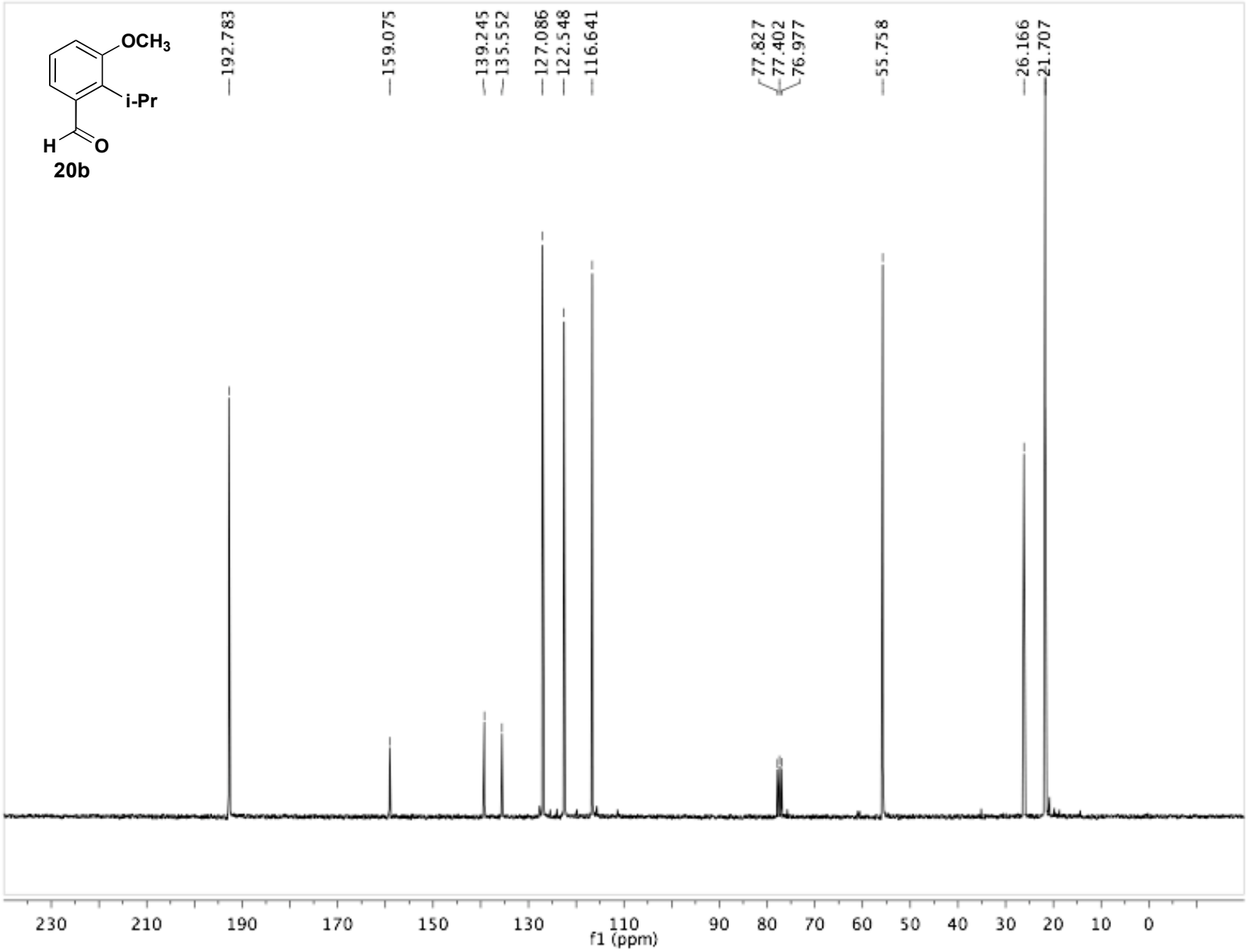

OCH3
i-Pr
i-Pr
H3CO
159.425
140.818
134.291
126.620
122.445
109.975
55.333
36.951
28.791
21.080
20.897
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

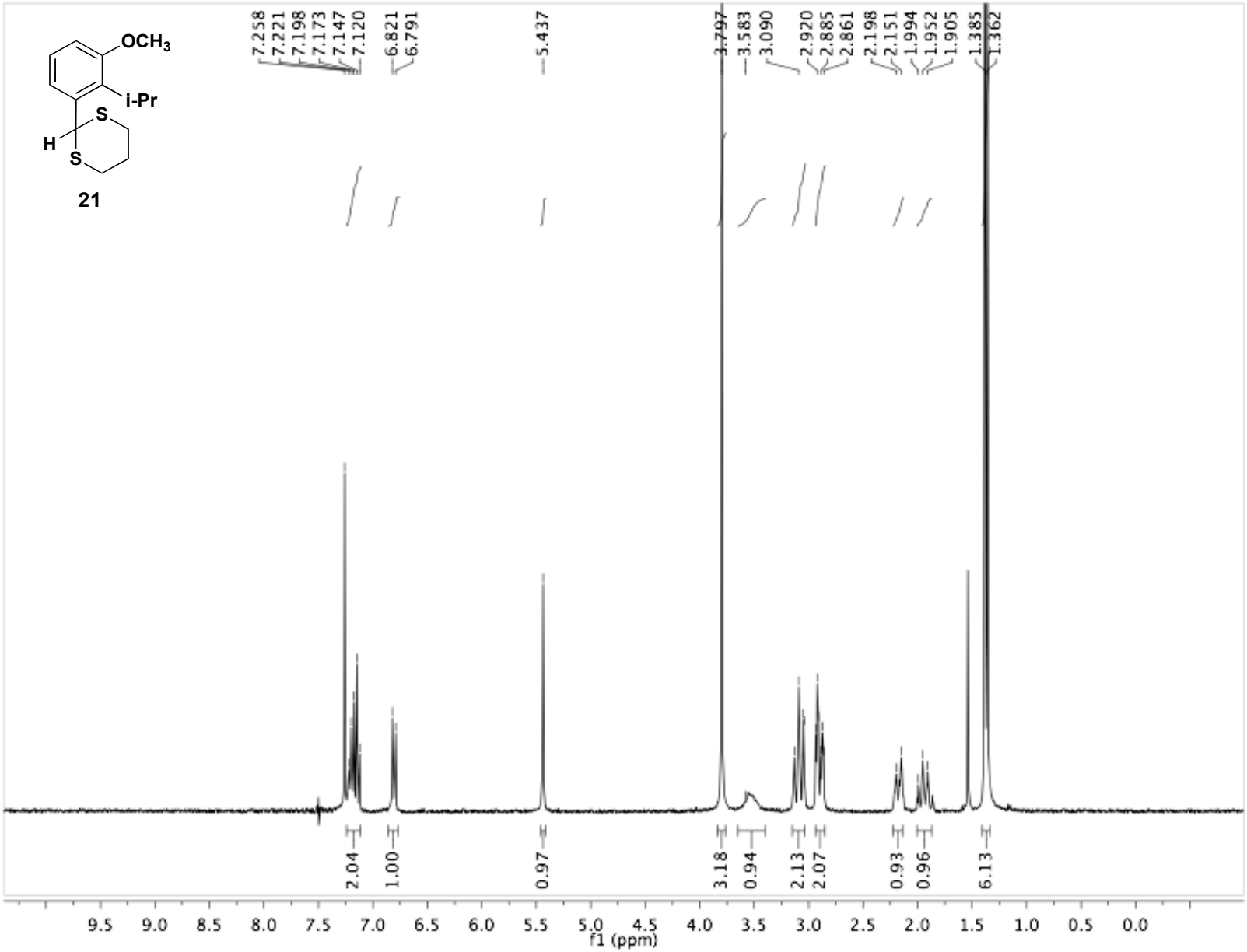
**18**

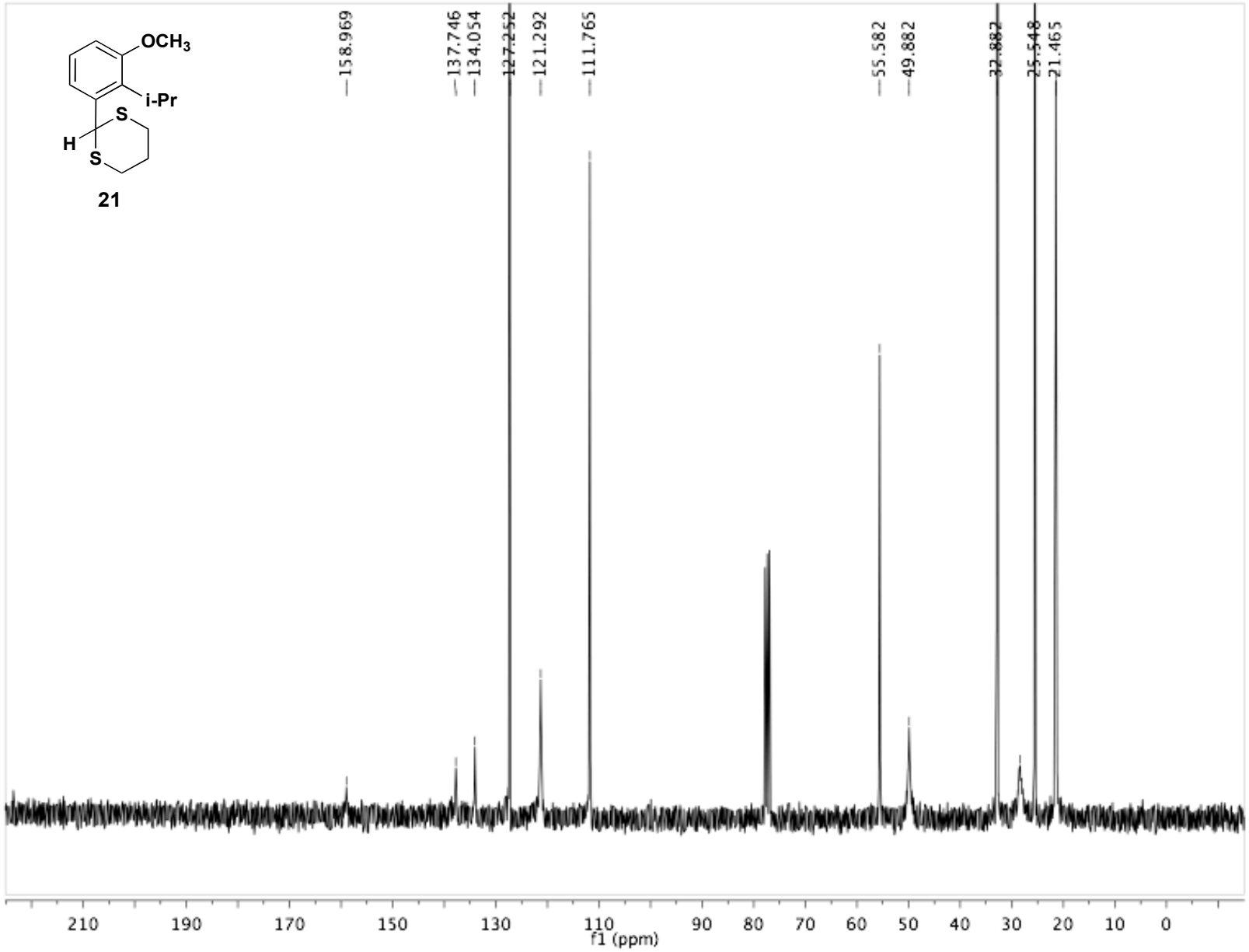

7.263
7.250
7.221
7.188
7.162
7.060
7.034
3.844
3.611
3.589
3.565
3.542
3.519
1.396
1.369
OCH3
i-Pr
CN
20a
1.99
0.94
3.27
1.00
6.37
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

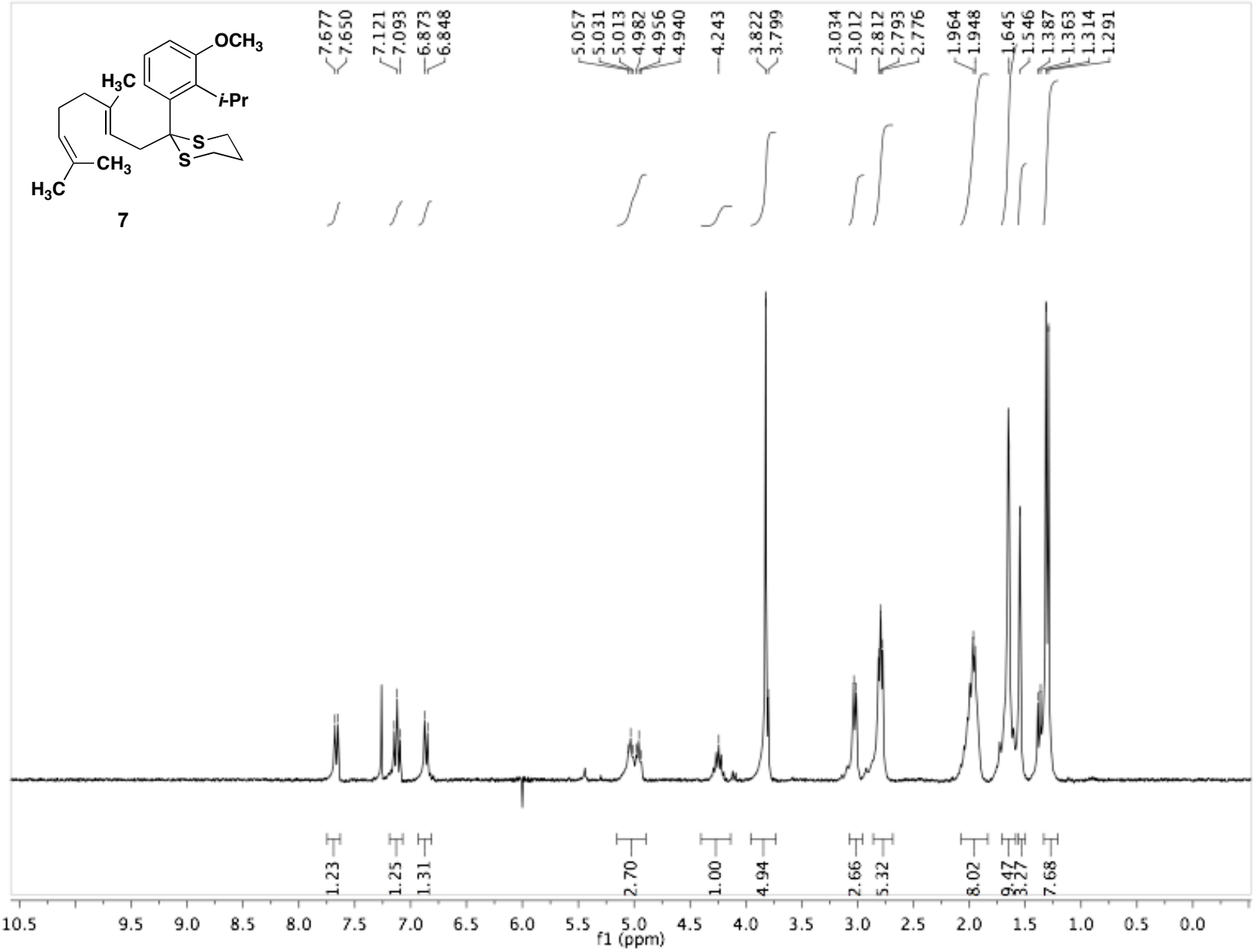

OCH3
i-Pr
CN
20a
158.366
140.343
127.645
125.497
118.927
115.645
112.592
55.754
31.079
20.831
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

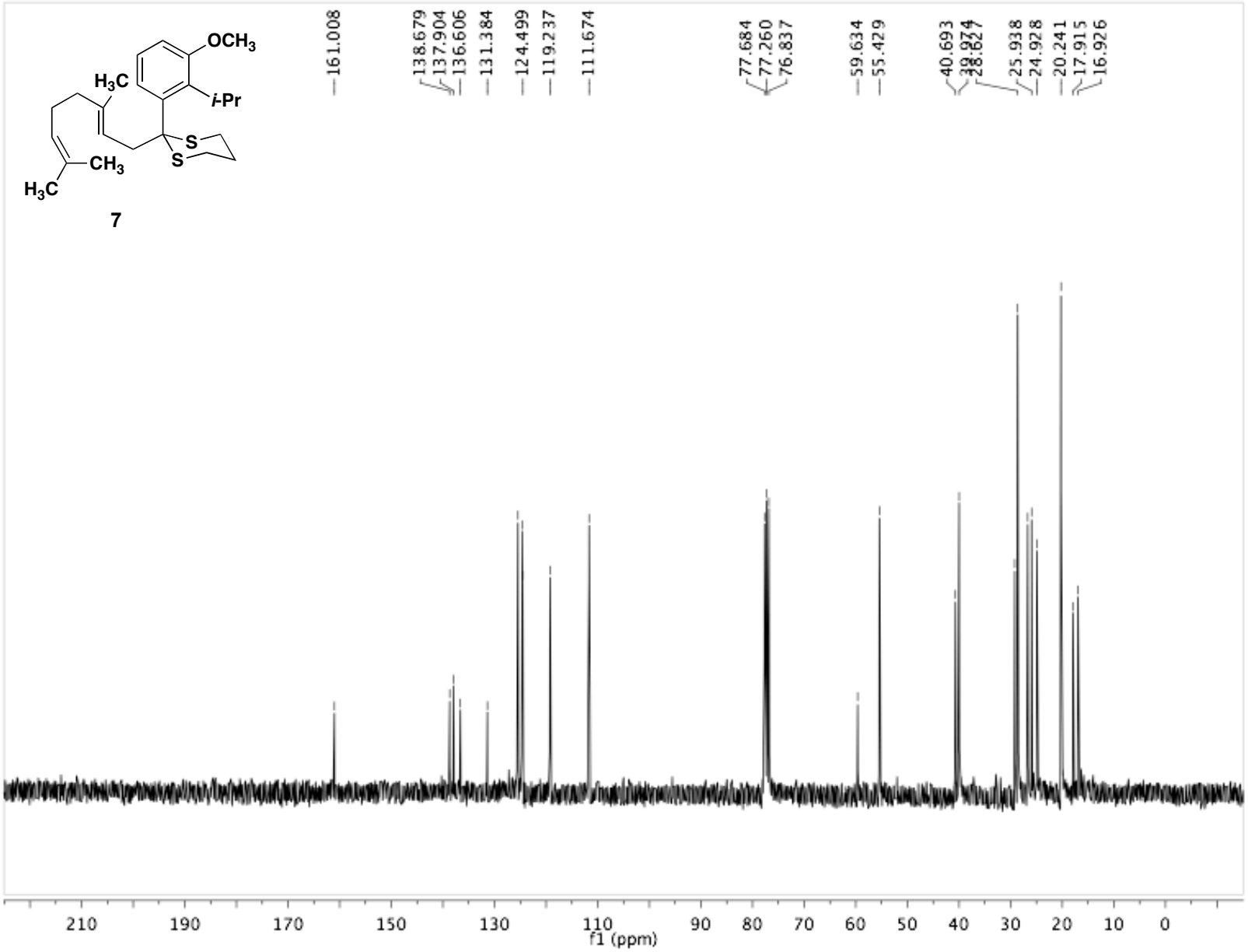

OCH3
i-Pr
H
O
20b
10.452
7.429
7.425
7.403
7.400
7.297
7.271
7.244
7.086
7.058
4.074
4.051
4.027
4.004
3.980
3.844
1.398
1.374
0.97
1.00
1.03
0.93
1.02
3.05
6.00
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f1 (ppm)

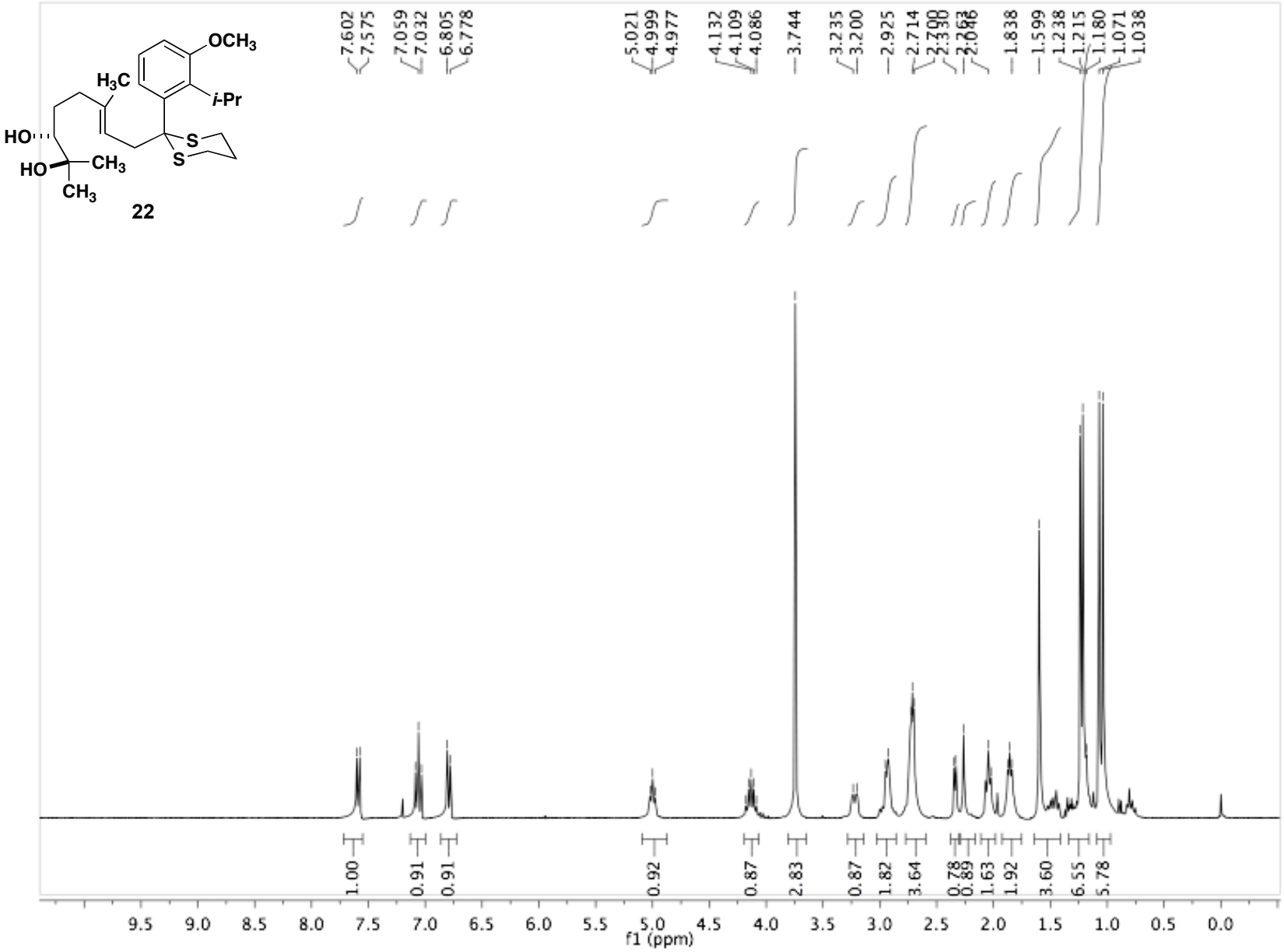

OCH3
i-Pr
H
O
20b
192.783
159.075
139.245
135.552
127.086
122.548
116.641
77.827
77.402
76.977
55.758
26.166
21.707
230
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

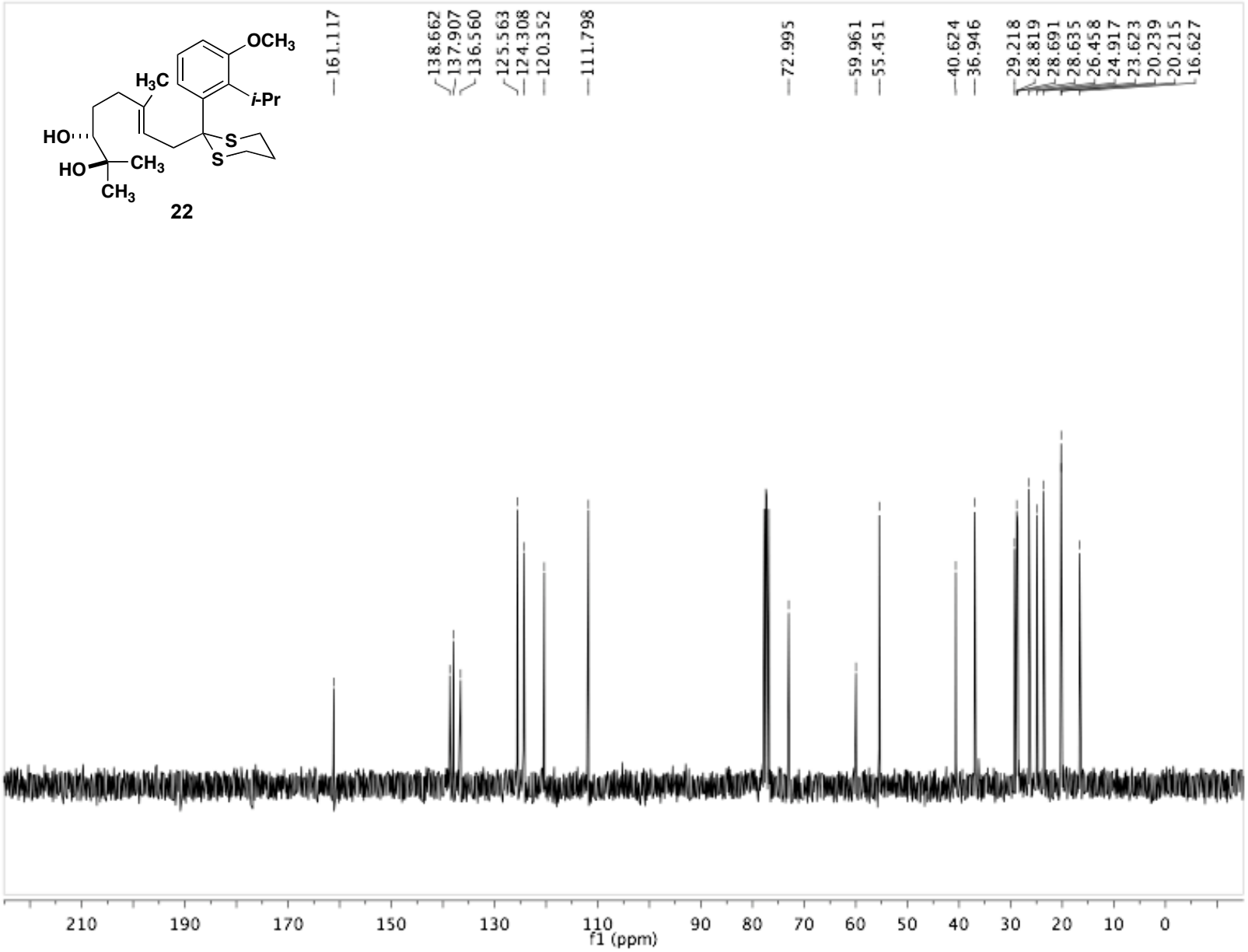

OCH3
i-Pr
S
H
S
21
7.258
7.221
7.198
7.173
7.147
7.120
6.821
6.791
5.437
3.797
3.583
3.090
2.920
2.885
2.861
2.198
2.151
1.994
1.952
1.905
1.385
1.362
2.04
1.00
0.97
3.18
0.94
2.13
2.07
0.93
0.96
6.13
f1 (ppm)

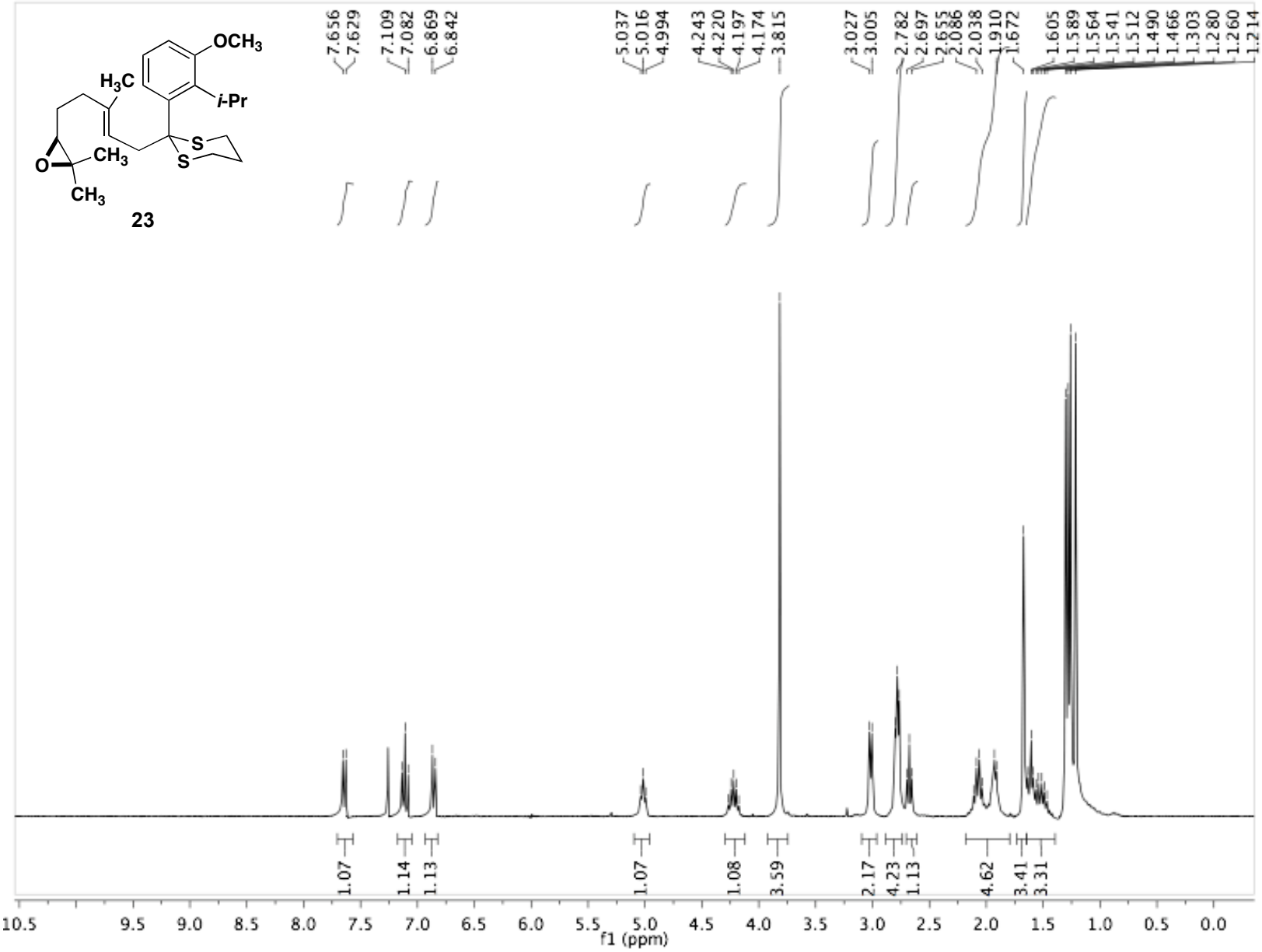

OCH3
i-Pr
S
H
S
21
158.969
137.746
134.054
127.252
121.292
111.765
55.582
49.882
32.882
25.548
21.465
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

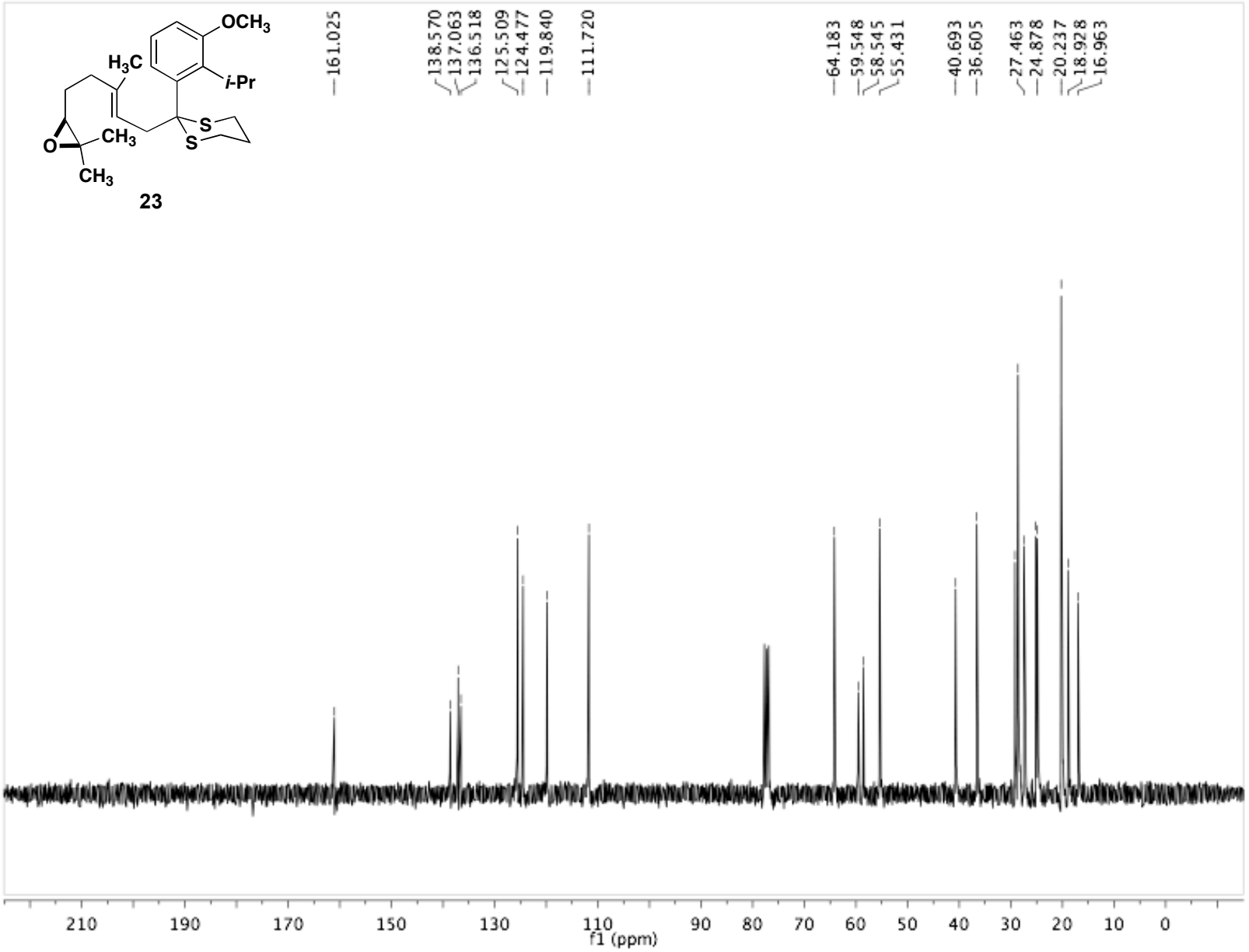

OCH3
H3C
i-Pr
S
S
CH3
H3C
7
7.677
7.650
7.121
7.093
6.873
6.848
5.057
5.031
5.013
4.982
4.956
4.940
4.243
3.822
3.799
3.034
3.012
2.812
2.793
2.776
1.964
1.948
1.645
1.546
1.387
1.363
1.314
1.291
1.23
1.25
1.31
2.70
1.00
4.94
2.66
5.32
8.02
9.47
3.27
7.68
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


OCH3
H3C
i-Pr
S
S
CH3
H3C
7
161.008
138.679
137.904
136.606
131.384
124.499
119.237
111.674
77.684
77.260
76.837
59.634
55.429
40.693
39.974
38.827
25.938
24.928
20.241
17.915
16.926
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

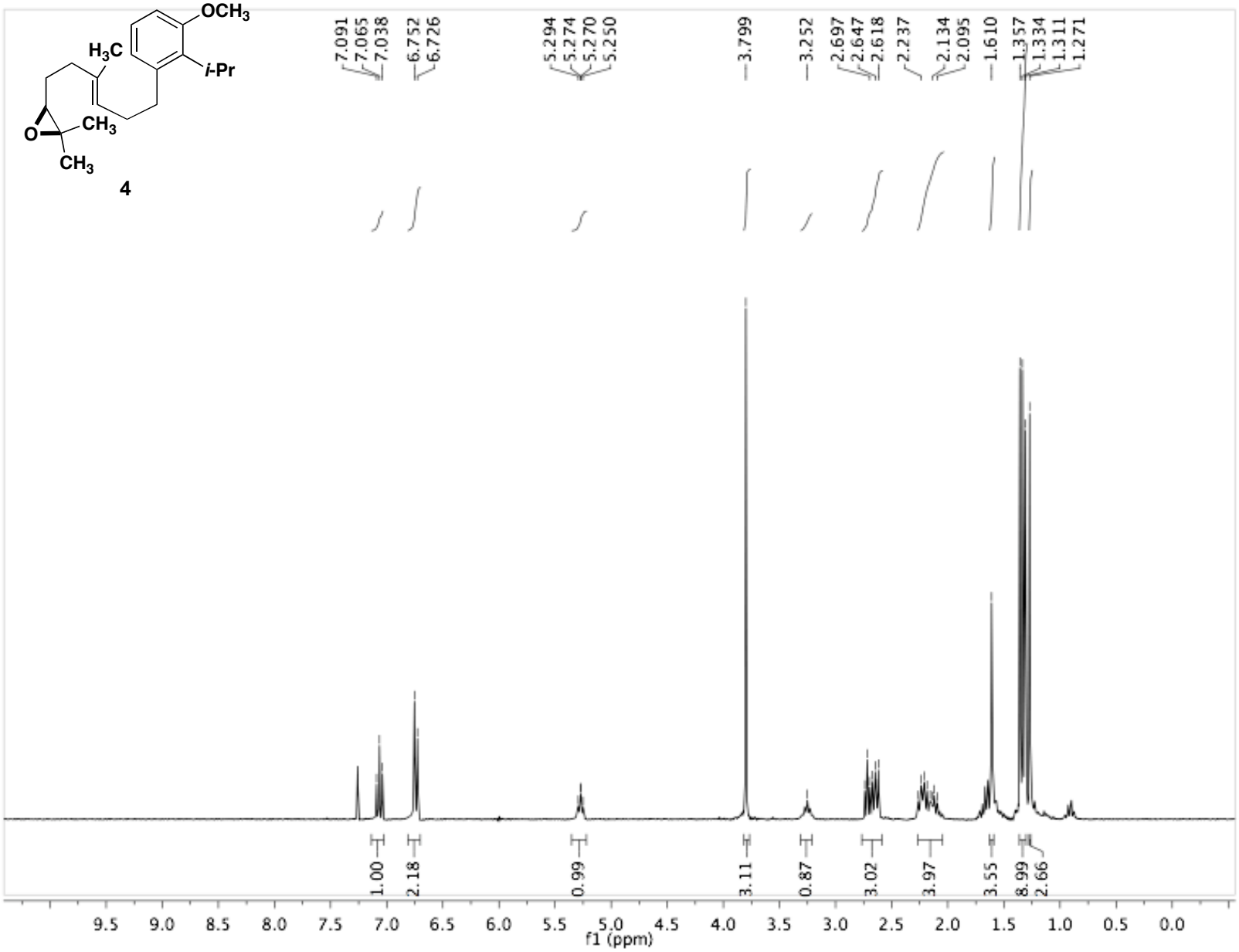

OCH3
H3C
i-Pr
HO
S
S
HO
CH3
CH3
22
7.602
7.575
7.059
7.032
6.805
6.778
5.021
4.999
4.977
4.132
4.109
4.086
3.744
3.235
3.200
2.925
2.714
1.838
1.599
1.238
1.215
1.180
1.071
1.038
1.00
0.91
0.91
0.92
0.87
2.83
0.87
1.82
3.64
0.78
0.89
1.63
1.92
3.60
6.55
5.78
f1 (ppm)

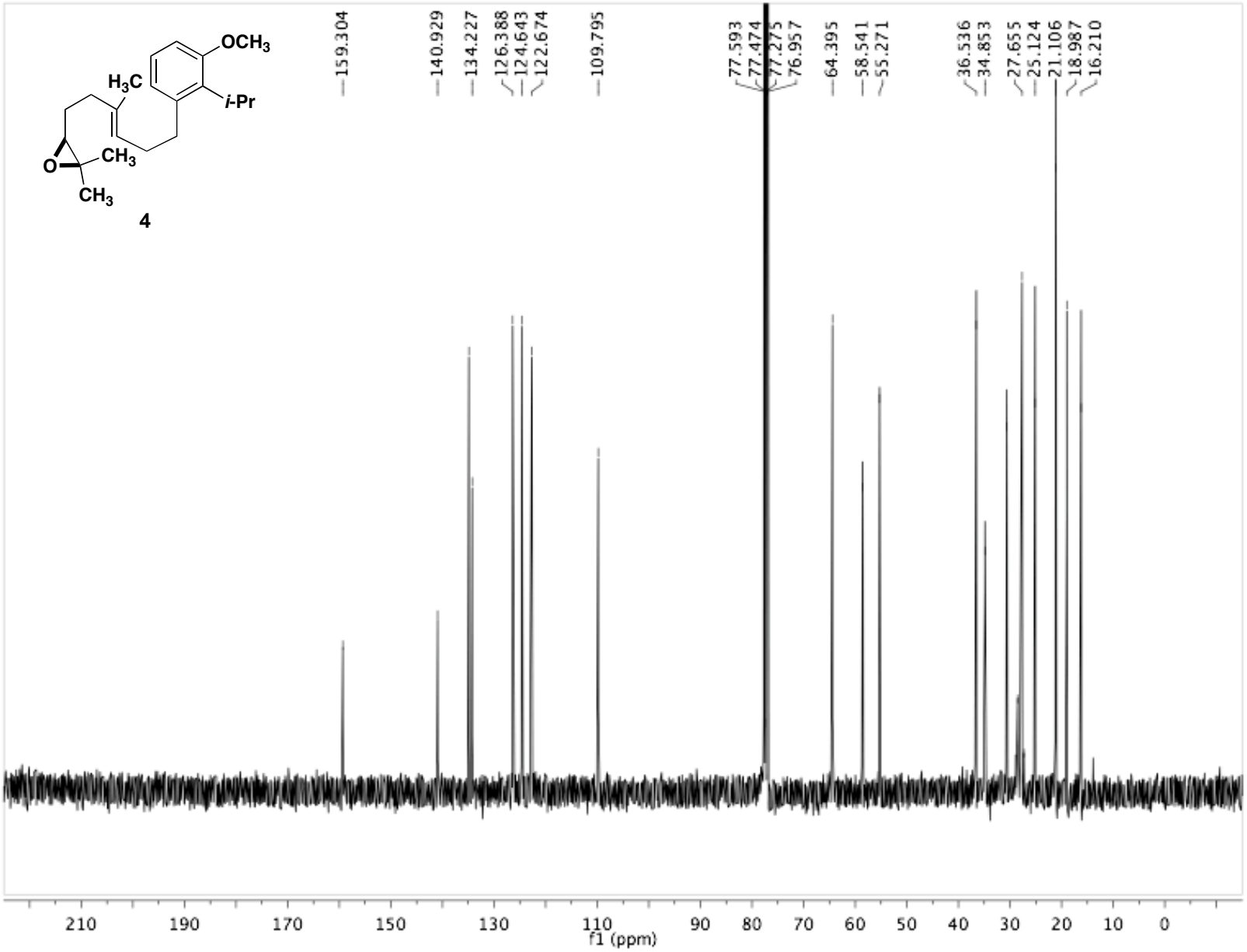

OCH3
H3C
i-Pr
HO
HO
CH3
CH3
S
S
22
161.117
138.662
137.907
136.560
125.563
124.308
120.352
111.798
72.995
59.961
55.451
40.624
36.946
29.218
28.819
28.691
28.635
26.458
24.917
23.623
20.239
20.215
16.627
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


OCH3
H3C
i-Pr
S
S
O
CH3
CH3
23
7.656
7.629
7.109
7.082
6.869
6.842
5.037
5.016
4.994
4.243
4.220
4.197
4.174
3.815
3.027
3.005
2.782
2.697
2.655
2.086
2.038
1.910
1.672
1.605
1.589
1.564
1.541
1.512
1.490
1.466
1.303
1.280
1.260
1.214
1.07
1.14
1.13
1.07
1.08
3.59
2.17
4.23
1.13
4.62
3.41
3.31
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

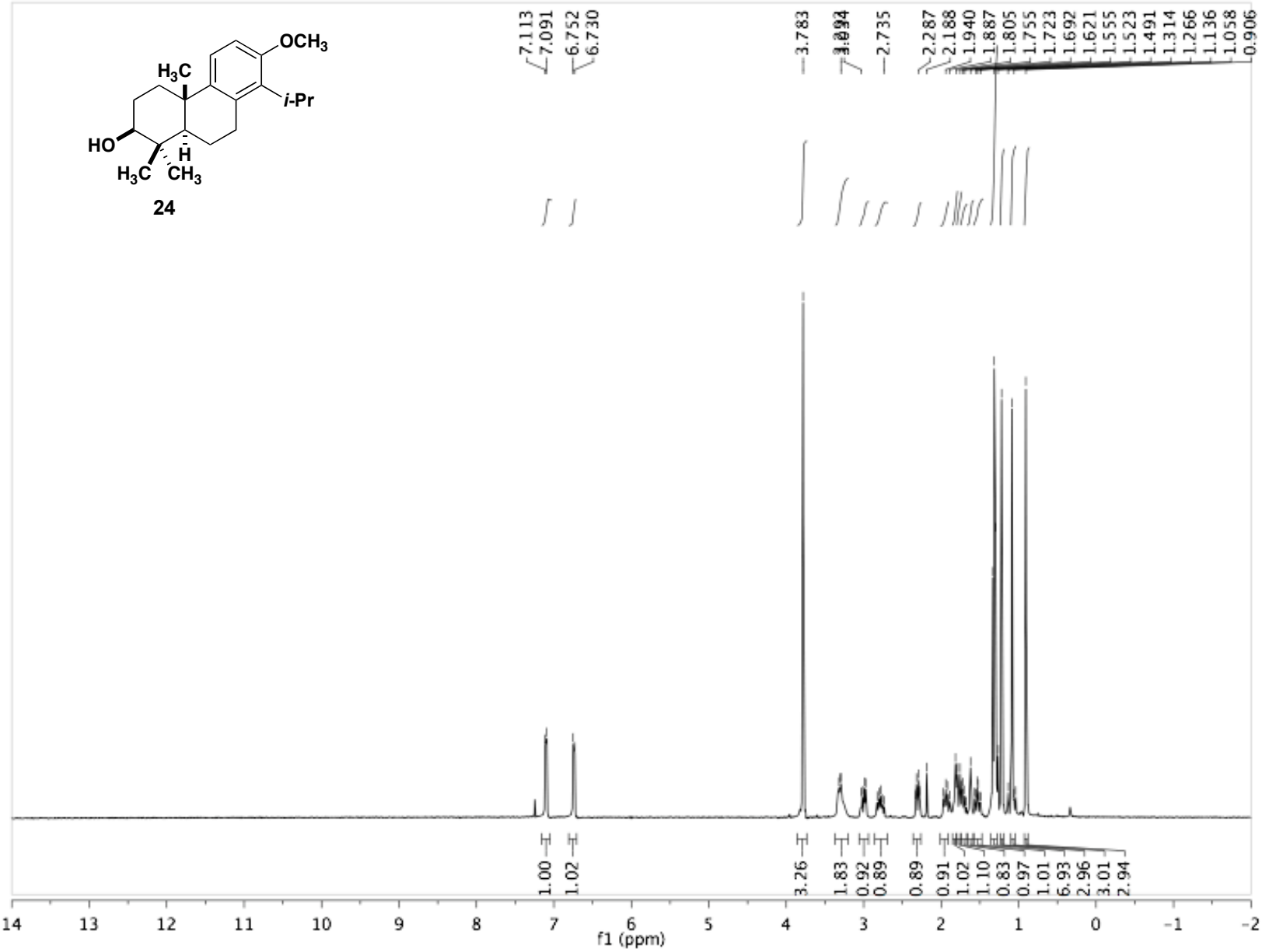

OCH3
H3C
i-Pr
CH3
O
CH3
S
S
161.025
138.570
137.063
136.518
125.509
124.477
119.840
111.720
64.183
59.548
58.545
55.431
40.693
36.605
27.463
24.878
20.237
18.928
16.963
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

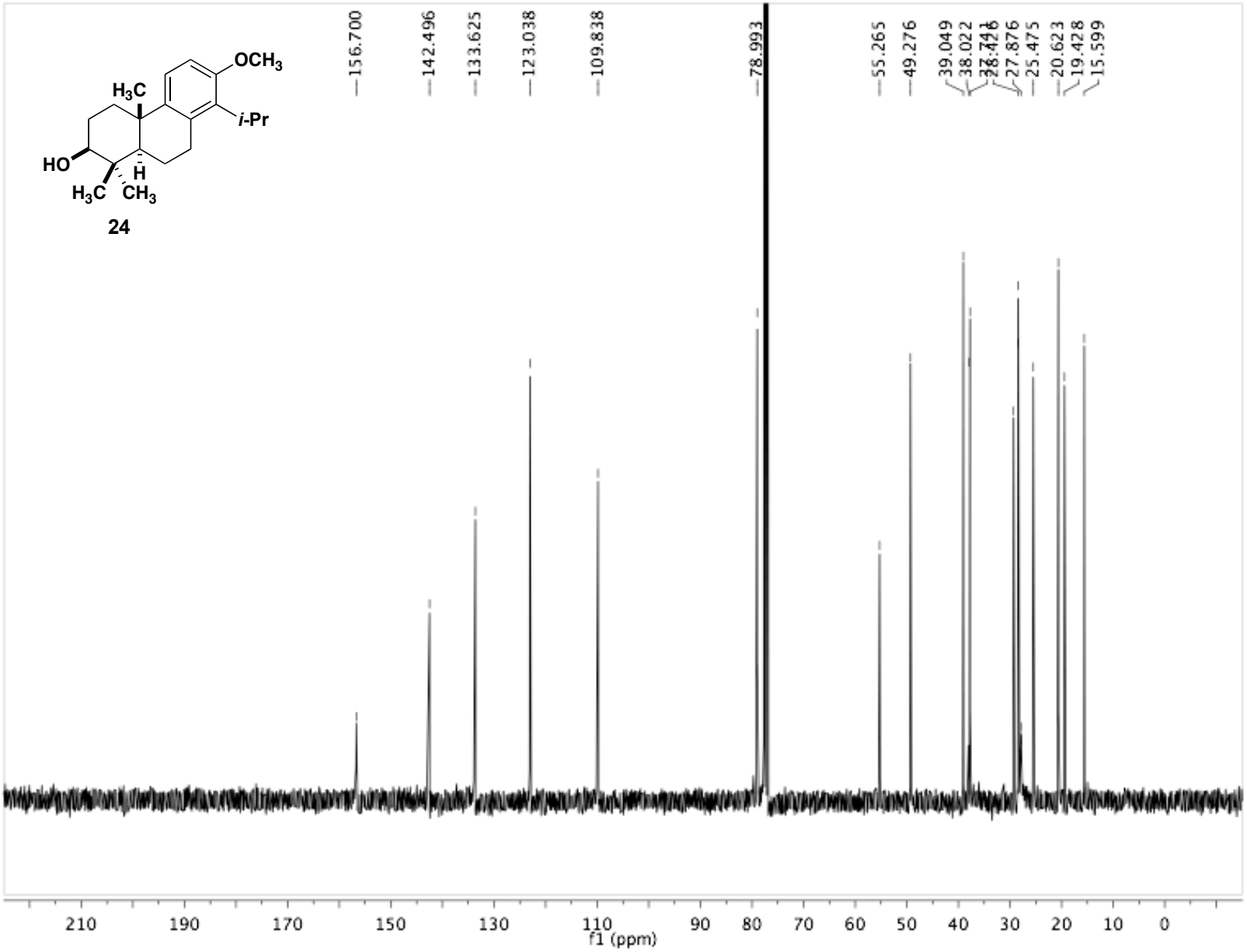
**23**

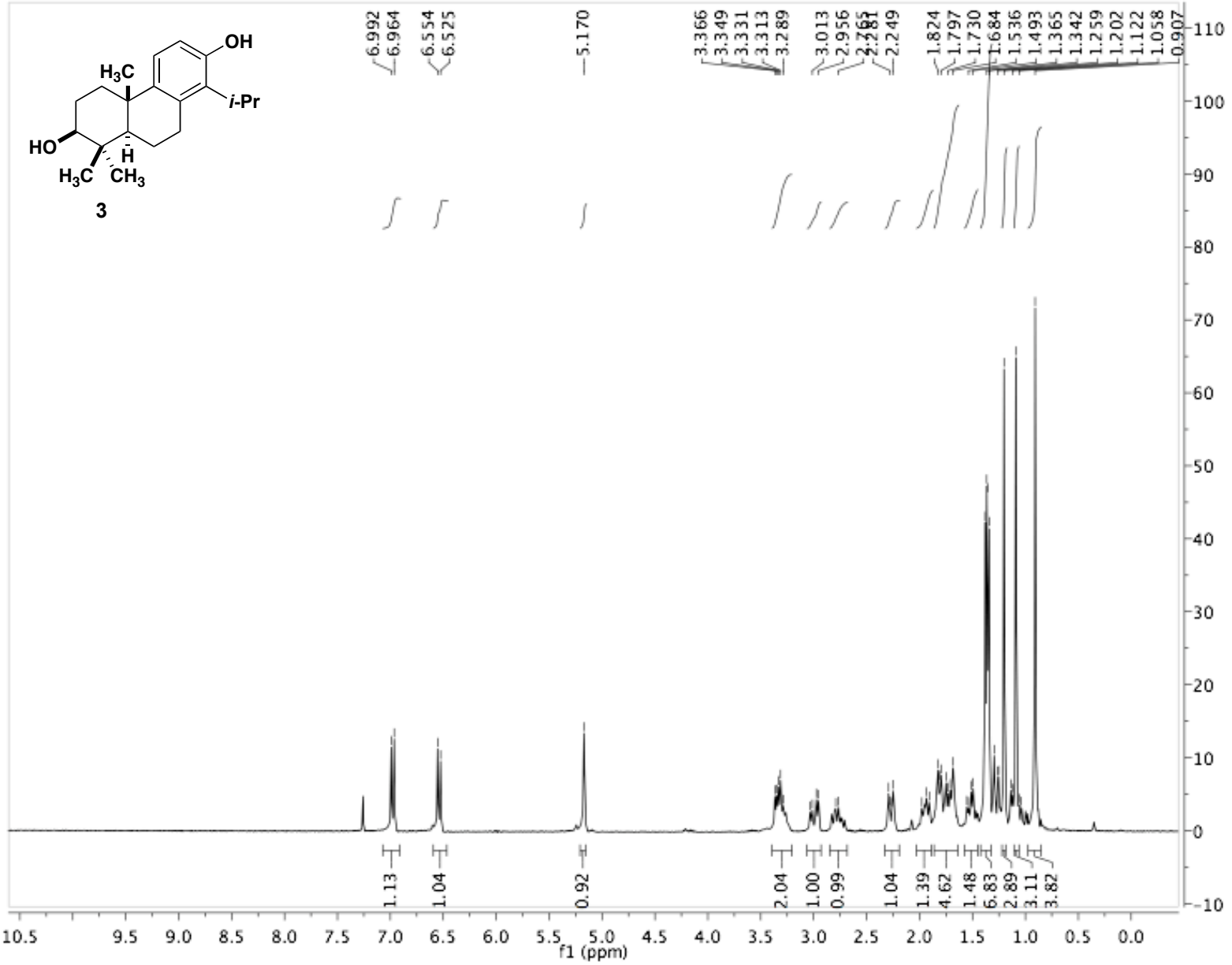

OCH3
H3C
i-Pr
CH3
O
CH3
4
7.091
7.065
7.038
6.752
6.726
5.294
5.274
5.270
5.250
3.799
3.252
2.697
2.647
2.618
2.237
2.134
2.095
1.610
1.357
1.334
1.311
1.271
1.00
2.18
0.99
3.11
0.87
3.02
3.97
3.55
8.99
2.66
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

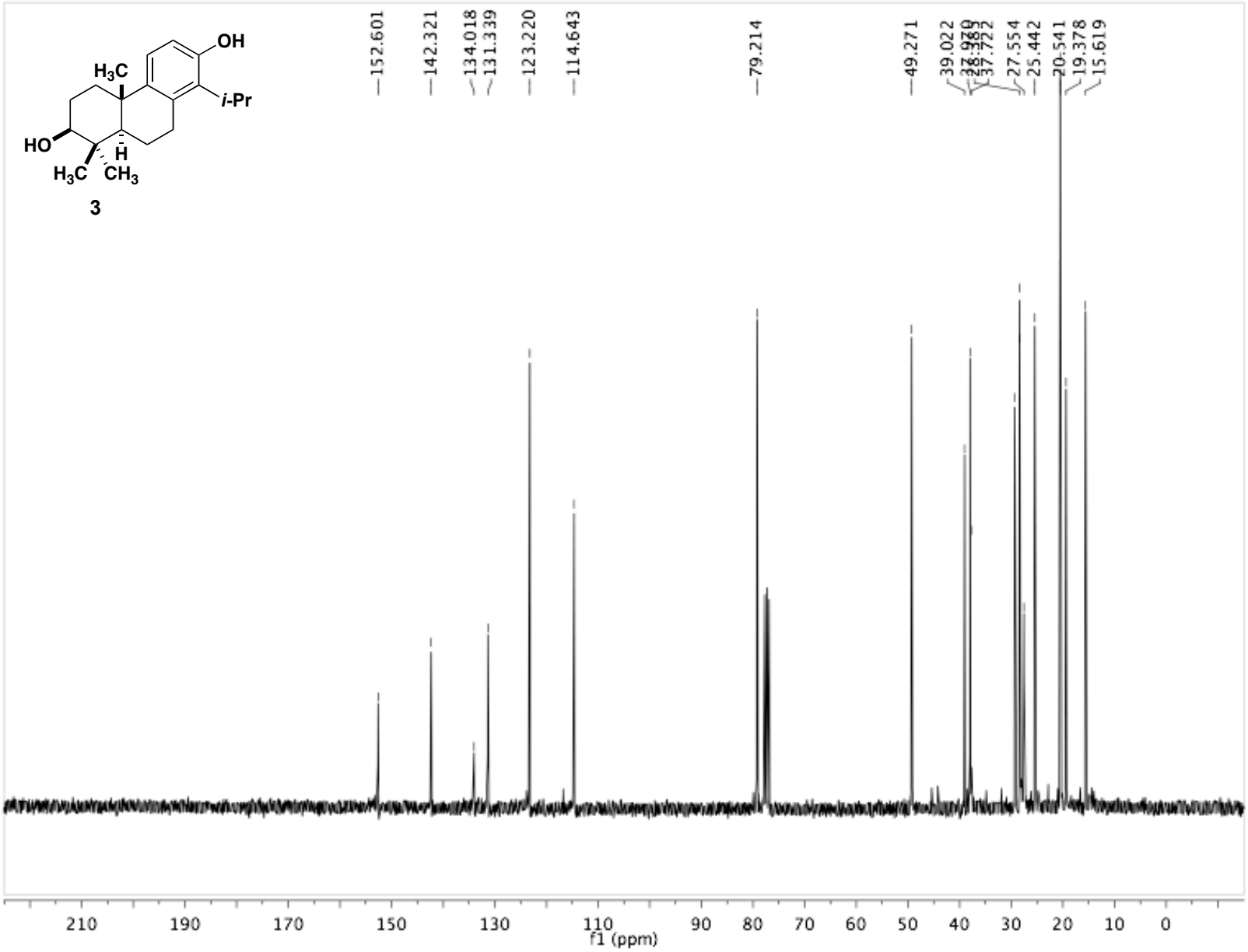

OCH3
H3C
i-Pr
CH3
O
CH3
159.304
140.929
134.227
126.388
124.643
122.674
109.795
77.593
77.474
77.275
76.957
64.395
58.541
55.271
36.536
34.853
27.655
25.124
21.106
18.987
16.210
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

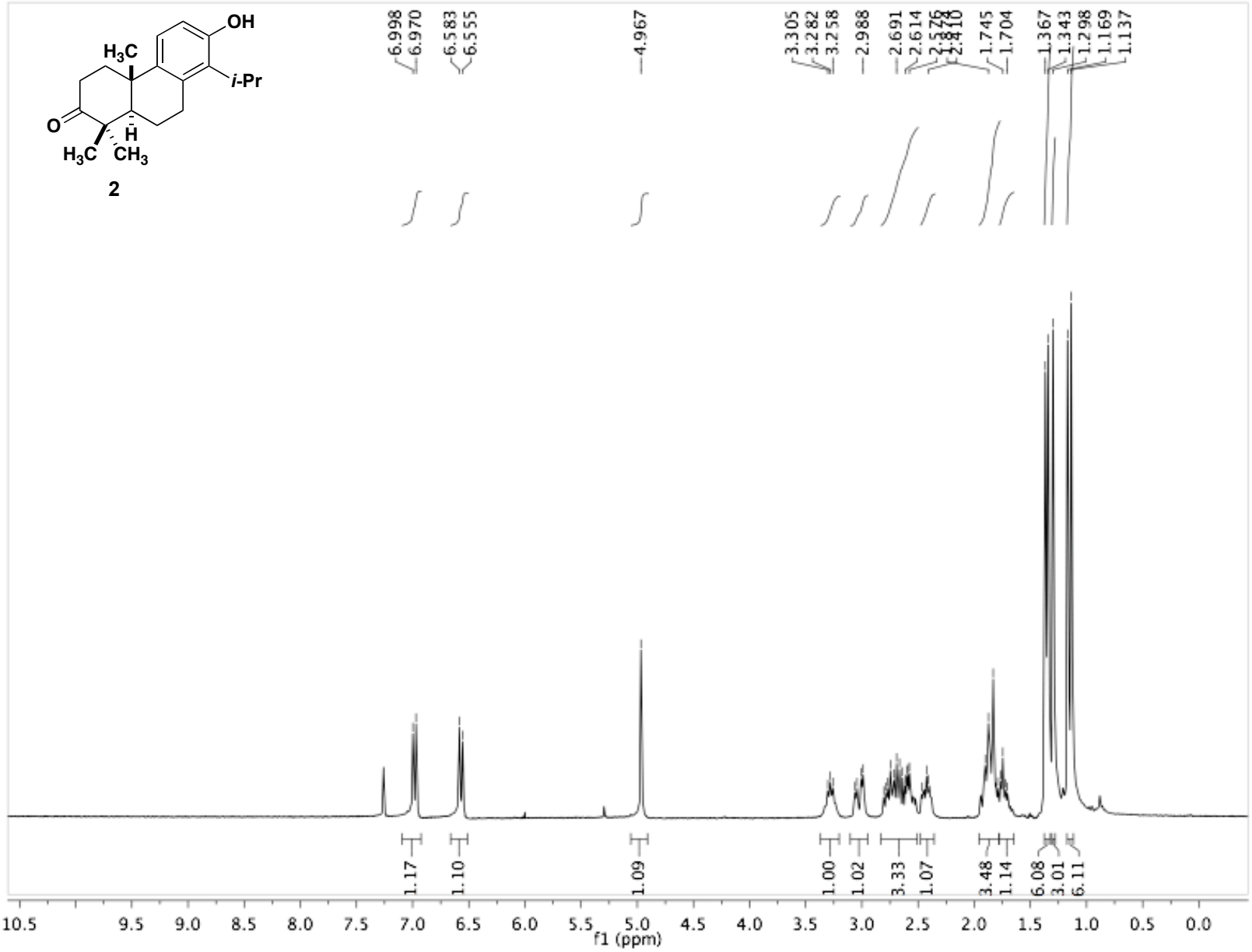
**4**

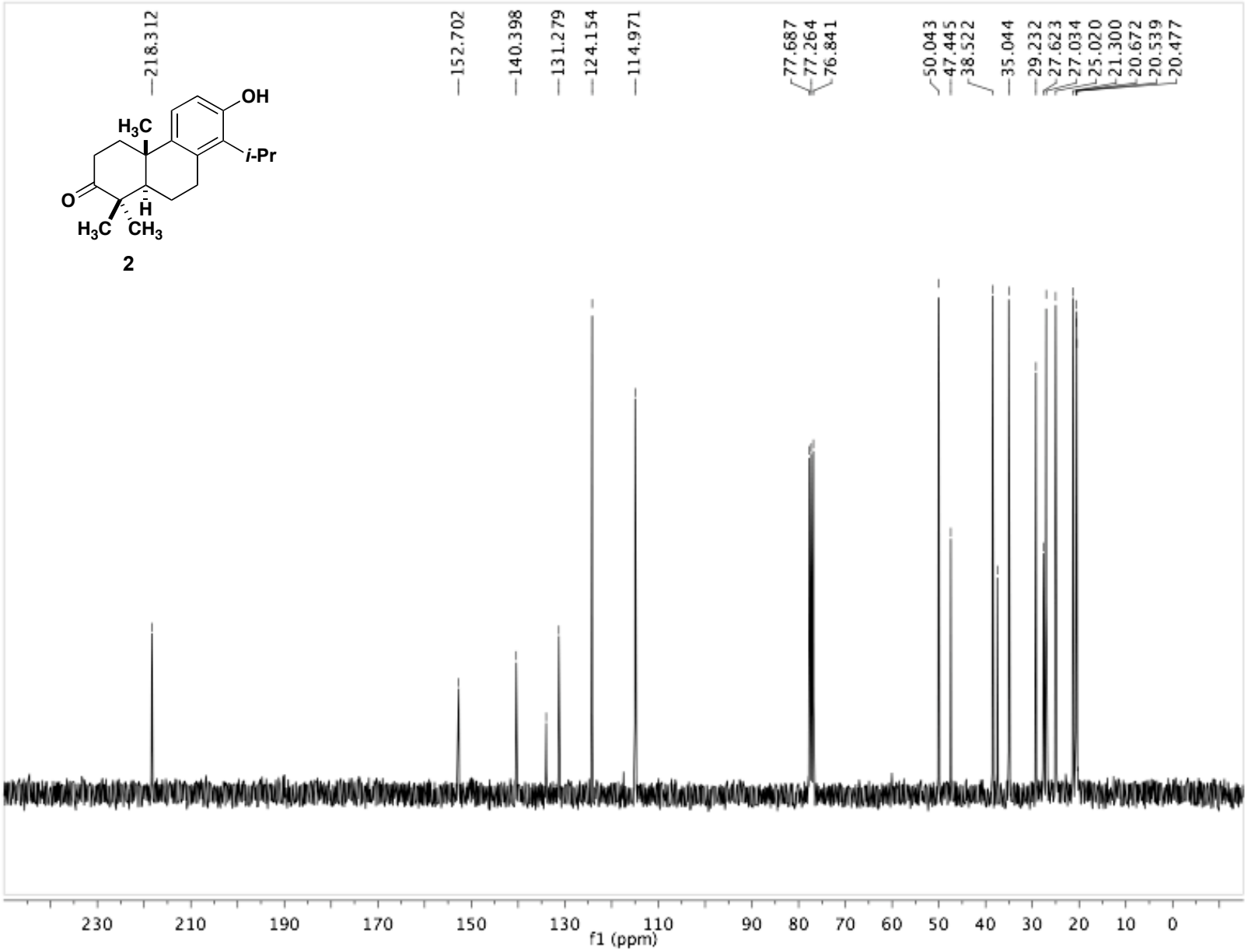

OCH3
H3C
i-Pr
HO
H
H3C
CH3
24
7.113
7.091
6.752
6.730
3.783
2.735
2.287
2.188
1.940
1.887
1.805
1.755
1.723
1.692
1.621
1.555
1.523
1.491
1.314
1.266
1.136
1.058
0.906
1.00
1.02
3.26
1.83
0.92
0.89
0.89
0.91
1.02
1.10
0.83
0.97
1.01
6.93
2.96
3.01
2.94
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f1 (ppm)

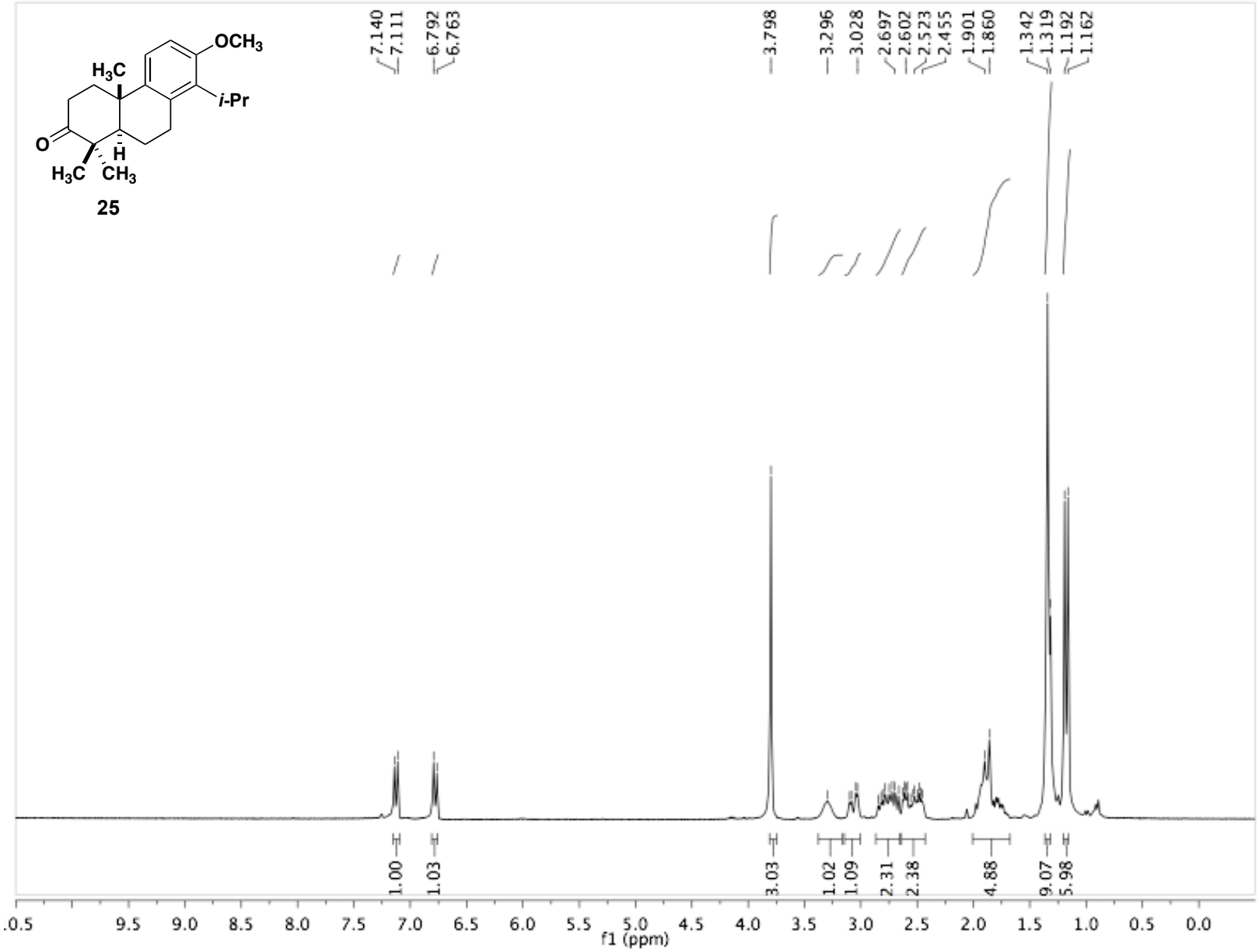

OCH3
H3C
i-Pr
HO
H
H3C
CH3
24
156.700
142.496
133.625
123.038
109.838
78.993
55.265
49.276
39.049
38.022
27.876
25.475
20.623
19.428
15.599
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

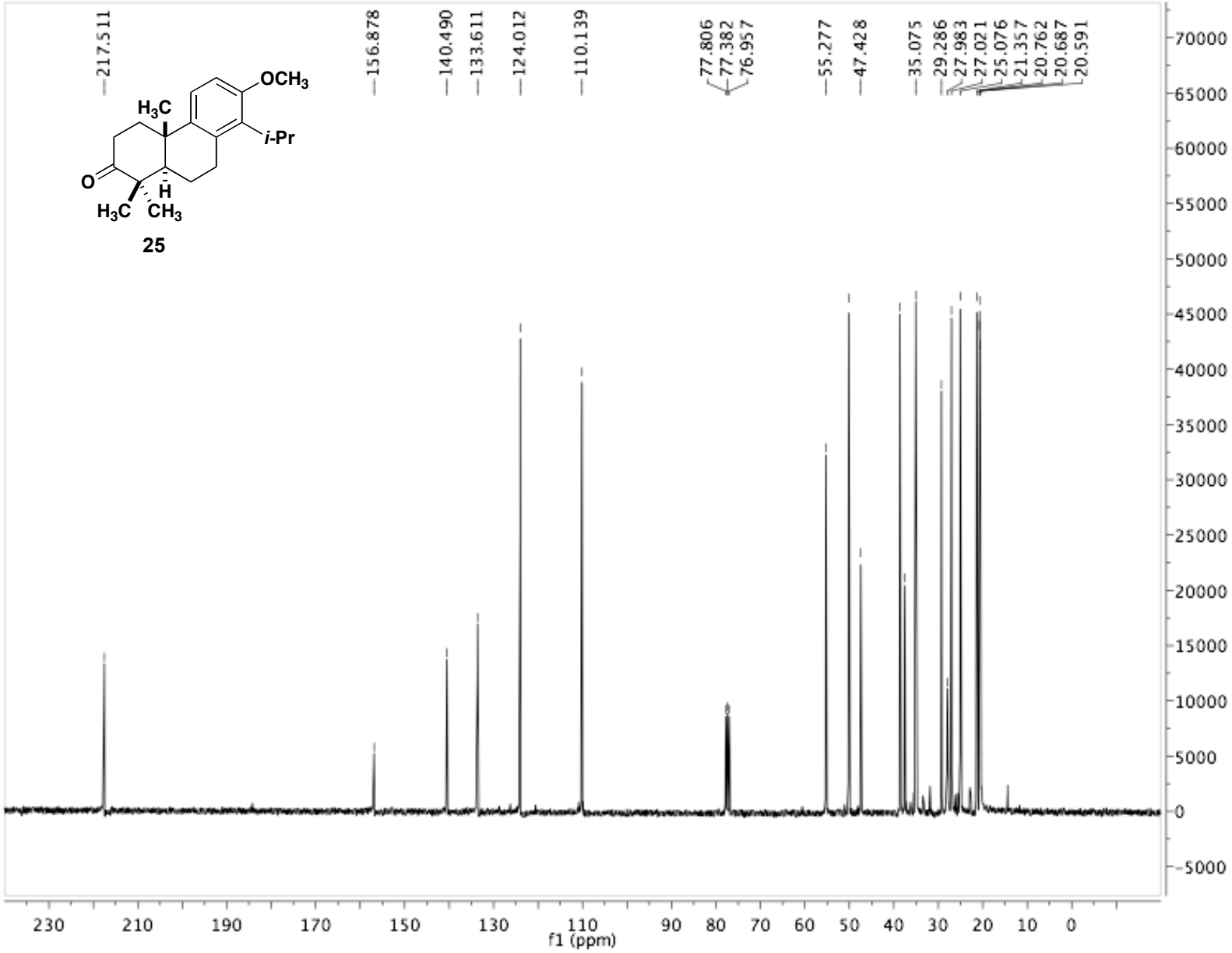

OH
H3C
i-Pr
HO
H
H3C
CH3
3
6.992
6.964
6.554
6.525
5.170
3.366
3.349
3.331
3.313
3.289
3.013
2.956
2.765
2.281
2.249
1.824
1.797
1.730
1.684
1.536
1.493
1.365
1.342
1.259
1.202
1.122
1.058
0.907
1.13
1.04
0.92
2.04
1.00
0.99
1.04
1.39
4.62
1.48
6.83
2.89
3.11
3.82
f1 (ppm)

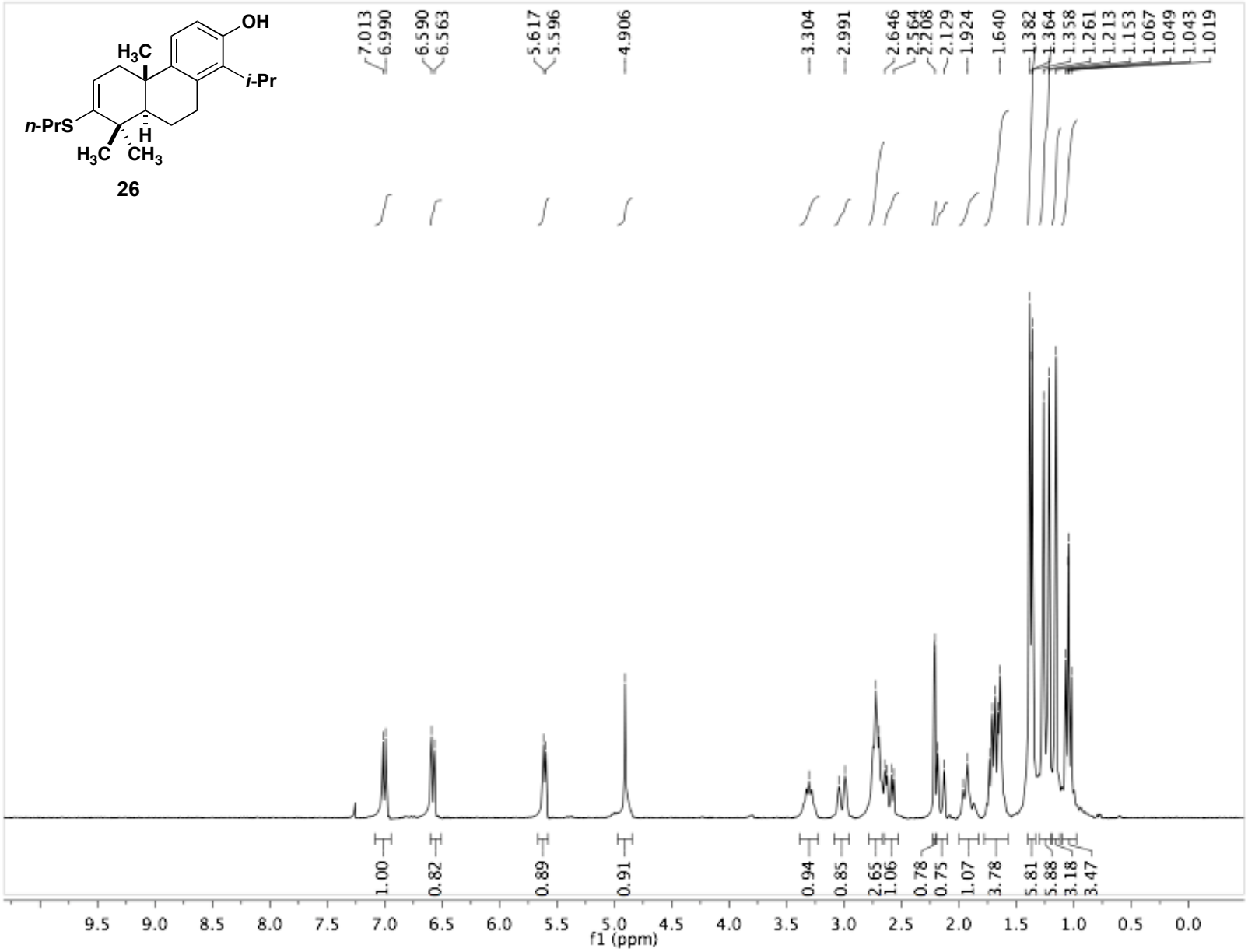

OH
H3C
i-Pr
HO
H
H3C
CH3
3
152.601
142.321
134.018
131.339
123.220
114.643
79.214
49.271
39.022
27.554
25.442
20.541
19.378
15.619
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

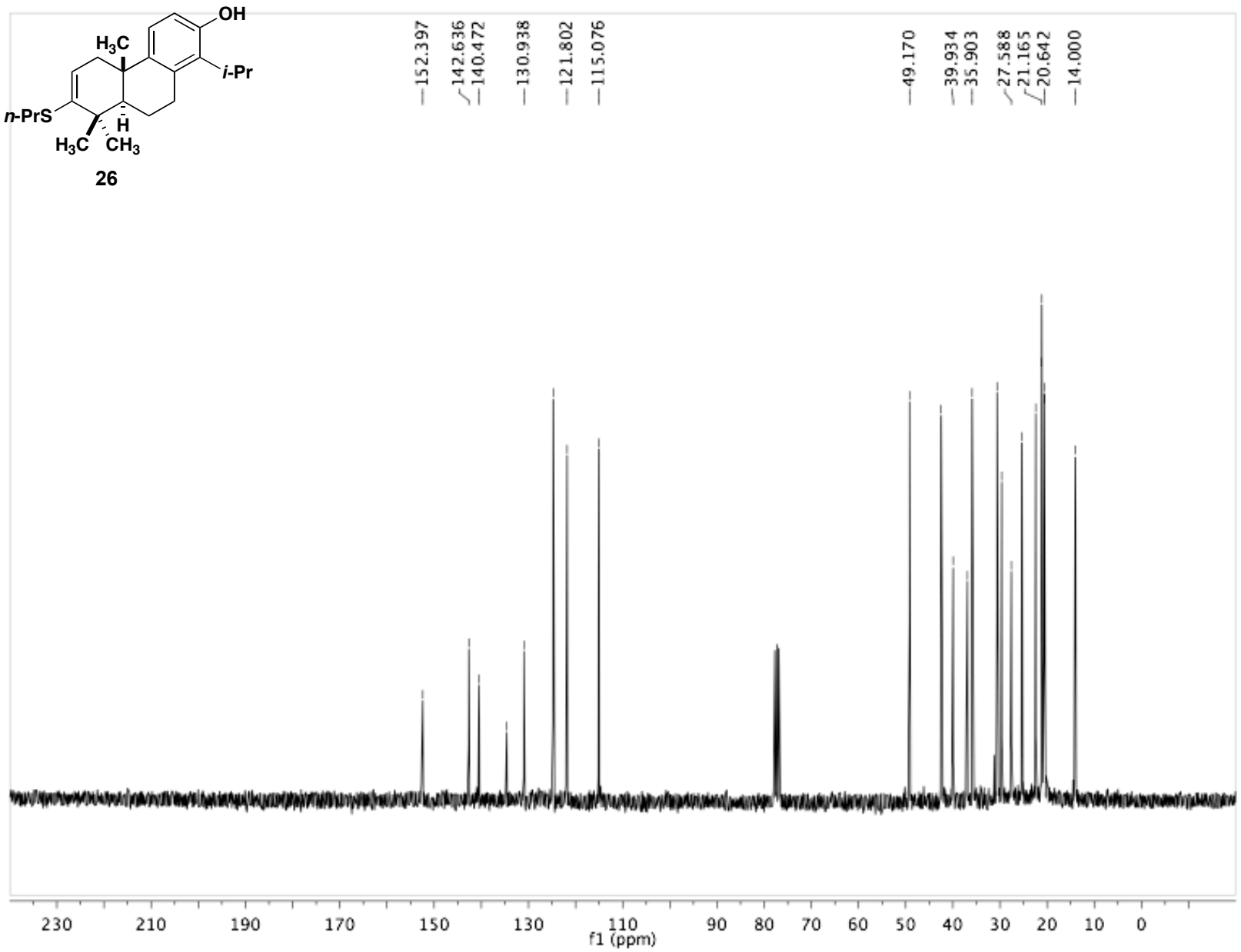

OH
H3C
i-Pr
O
H
H3C
CH3
2
6.998
6.970
6.583
6.555
4.967
3.305
3.282
3.258
2.988
2.691
2.614
1.745
1.704
1.367
1.343
1.298
1.169
1.137
1.17
1.10
1.09
1.00
1.02
3.33
1.07
3.48
1.14
6.08
3.01
6.11
f1 (ppm)

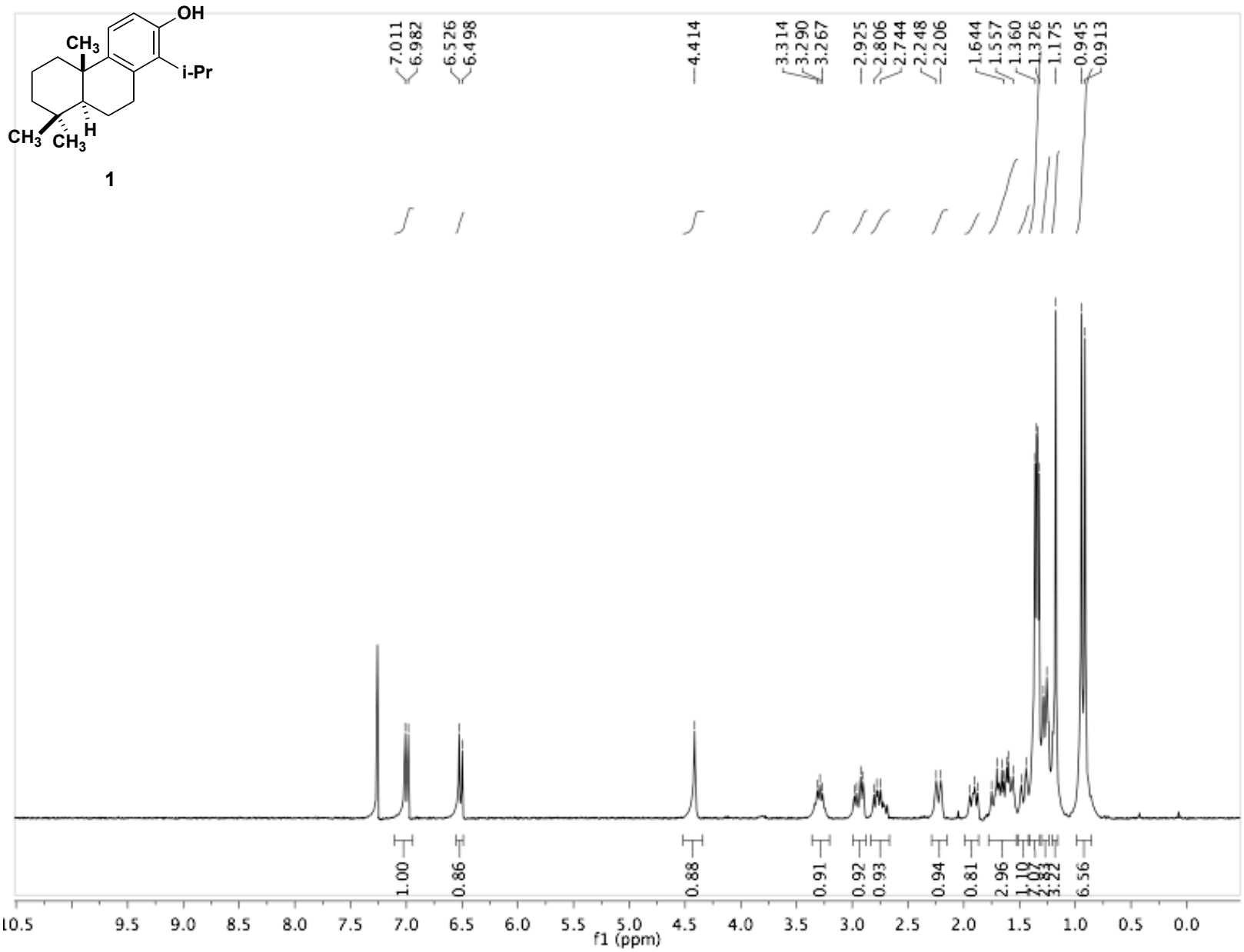

218.312
152.702
140.398
131.279
124.154
114.971
77.687
77.264
76.841
50.043
47.445
38.522
35.044
29.232
27.623
27.034
25.020
21.300
20.672
20.539
20.477
OH
H3C
i-Pr
O
H
H3C
CH3
2
230
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

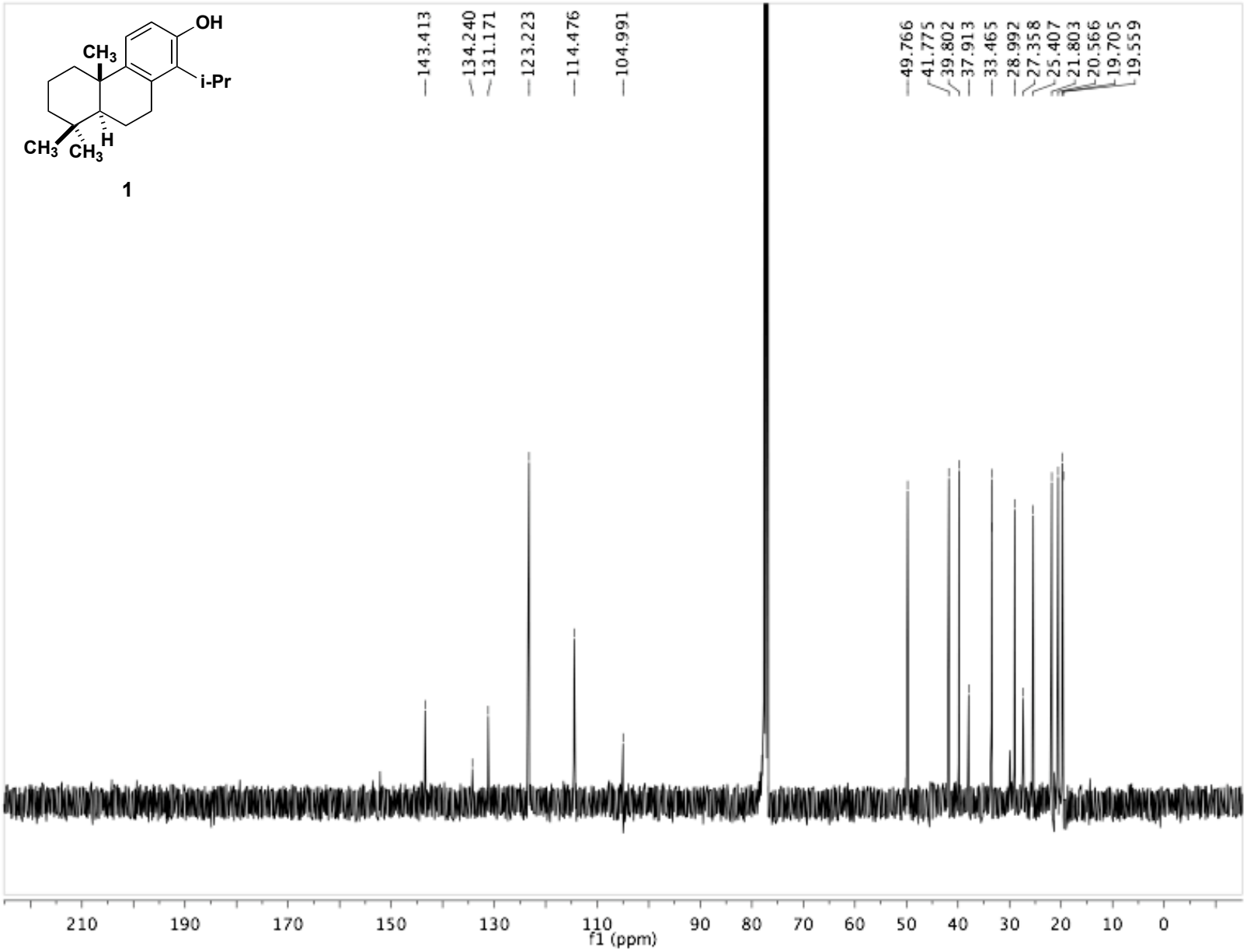

OCH3
H3C
i-Pr
O
H
H3C
CH3
25
7.140
7.111
6.792
6.763
3.798
3.296
3.028
2.697
2.602
2.523
2.455
1.901
1.860
1.342
1.319
1.192
1.162
1.00
1.03
3.03
1.02
1.09
2.31
2.38
4.88
9.07
5.98
f1 (ppm)

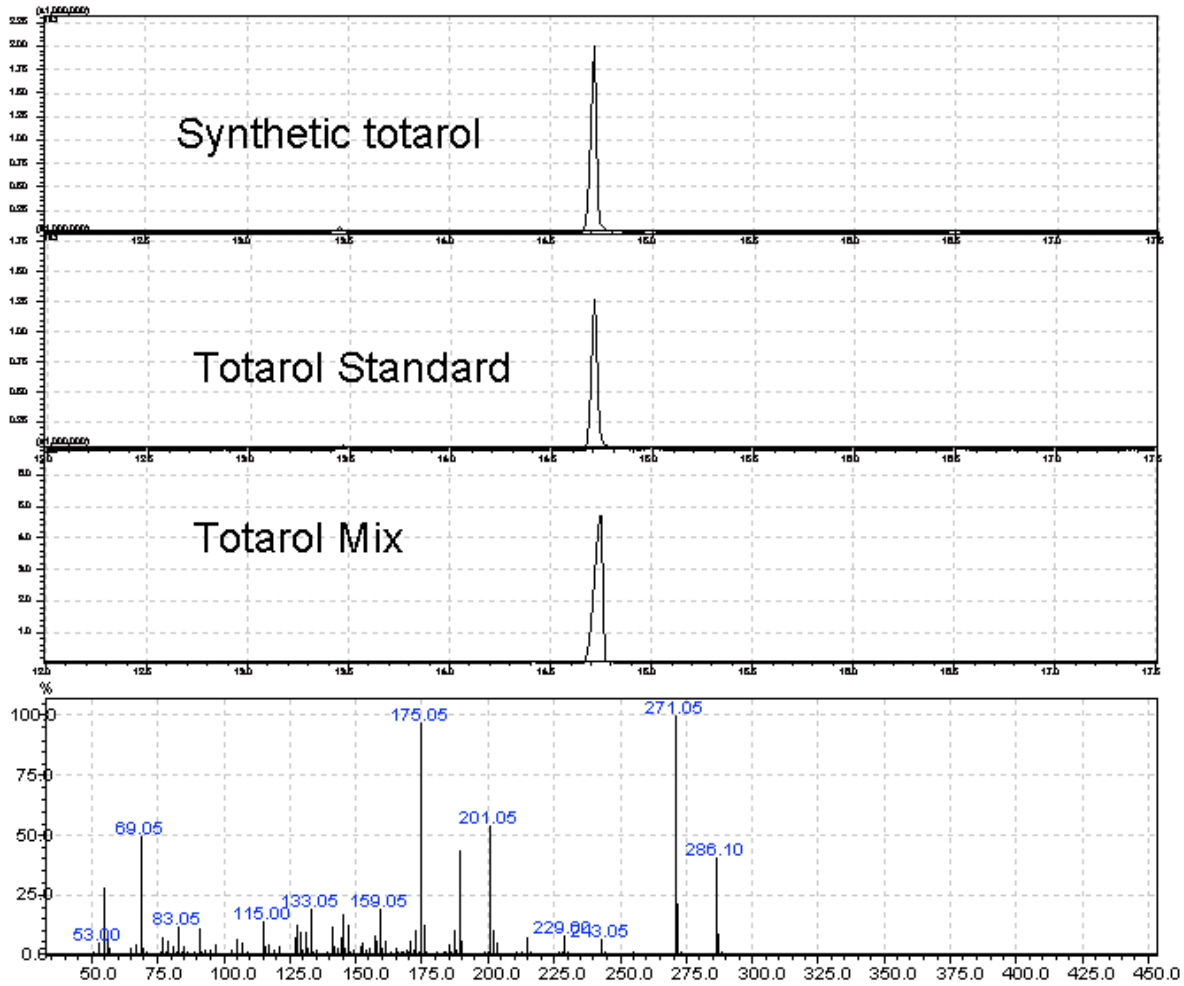

217.511
156.878
140.490
133.611
124.012
110.139
77.806
77.382
76.957
55.277
47.428
35.075
29.286
27.983
27.021
25.076
21.357
20.762
20.687
20.591
OCH3
H3C
i-Pr
O
H
H3C
CH3
25
f1 (ppm)

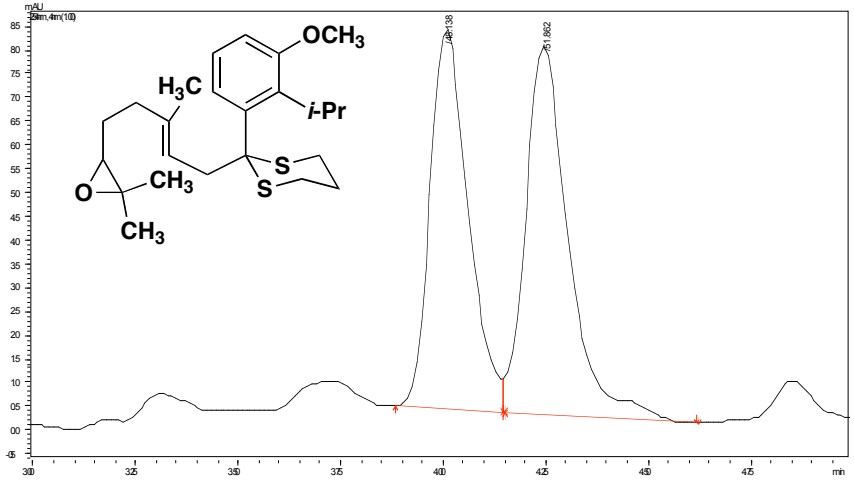

OH
H3C
i-Pr
n-PrS
H
H3C
CH3
26
7.013
6.990
6.590
6.563
5.617
5.596
4.906
3.304
2.991
2.646
2.564
2.208
2.129
1.924
1.640
1.382
1.364
1.358
1.261
1.213
1.153
1.067
1.049
1.043
1.019
1.00
0.82
0.89
0.91
0.94
0.85
2.65
1.06
0.78
0.75
1.07
3.78
5.81
5.88
3.18
3.47
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

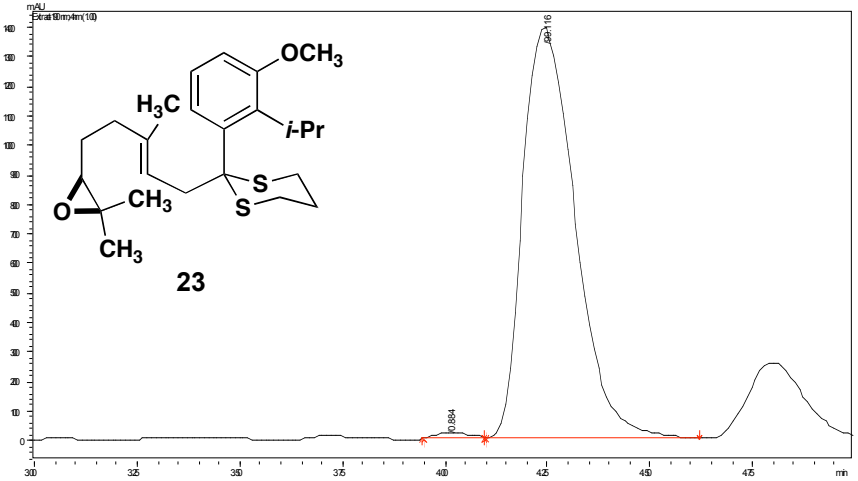

OH
H3C
i-Pr
n-PrS
H
H3C
CH3
26
152.397
142.636
140.472
130.938
121.802
115.076
49.170
39.934
35.903
27.588
21.165
20.642
14.000
230
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


OH
CH3
i-Pr
CH3
CH3
H
1
7.011
6.982
6.526
6.498
4.414
3.314
3.290
3.267
2.925
2.806
2.744
2.248
2.206
1.644
1.557
1.360
1.326
1.175
0.945
0.913
1.00
0.86
0.88
0.91
0.92
0.93
0.94
0.81
2.96
1.10
2.83
3.22
6.56
f1 (ppm)


OH
CH3
i-Pr
CH3
CH3
H
1
143.413
134.240
131.171
123.223
114.476
104.991
49.766
41.775
39.802
37.913
33.465
28.992
27.358
25.407
21.803
20.566
19.705
19.559
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Synthetic totarol
Totarol Standard
Totarol Mix
%
100.0
75.0
50.0
25.0
0.0
175.05
271.05
69.05
201.05
286.10
133.05
159.05
115.00
83.05
53.00
229.00
243.05
50.0
75.0
100.0
125.0
150.0
175.0
200.0
225.0
250.0
275.0
300.0
325.0
350.0
375.0
400.0
425.0
450.0




**23**

HPLC analysis of **23** and the racemic mixture was performed on a Shimadzu LC-20AB system with a Daicel CHIRALPAK® CHIRALPAK® AS-H column (4.6 x 250 mm, 5 μm) with a flow rate of 1.0 mL/min in 97:3 (isopropanol/hexanes isocratic system) using Shimadzu SPD-M20A photodiode array detector.