Supplementary Material (ESI) for Chemical Communications


# Supporting Information

# A Concise Synthesis of the Molecular Framework of Pleuromutilin

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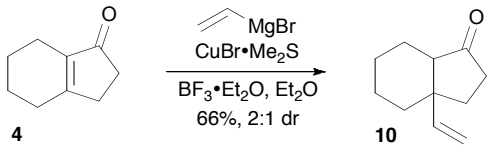
Table of Contents

**General Methods.** All reactions were carried out under an atmosphere of argon with magnetic stirring unless otherwise indicated. Palladium (II) acetate was purchased from Gelest. In other cases, commercial reagents of high purity were purchased from either Aldrich or Acros and used without further purification. Tetrahydrofuran (THF), dichloromethane ($CH_2Cl_2$), toluene, benzene, ether ($Et_2O$), acetonitrile ($CH_3CN$), triethylamine ($NEt_3$), and pyridine were dried by passing through activated alumina columns. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm Whatman silica gel plates Partisil K6F (60 Å) using UV light as a visualizing agent and aqueous potassium permanganate or ethanolic *p*-anisaldehyde solution and heat as developing agents. Silica gel from SiliCycle silicaFlash P60 40-63 μm (230-400 mecsh) or from Dynamic Adsorbent Inc 32-63 μm was used for flash column chromatography.

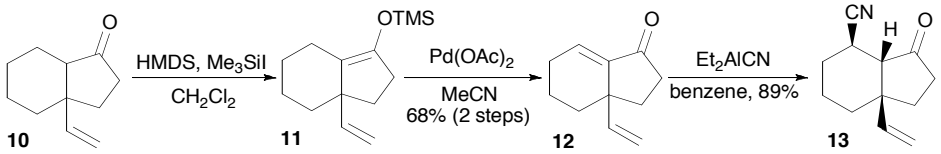
**Instrumentation.** FT-IR spectra were obtained on a Perkin-Elmer Paragon 500. Nuclear magnetic resonance (NMR) spectra were obtained on a 500 MHz Bruker AVANCE spectrometer and calibrated to the residual solvent peak. Coupling constant values were extracted assuming first-order coupling and are given in Hz. The multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad signal. High resolution mass spectra were obtained on a Kratos MS 50 using electrospray ionization (ESI).




4 10

3a-vinyloctahydro-1*H*-inden-1-one (**10**): To a suspension of copper(I) bromide dimethyl sulfide complex ($CuBr•Me_2S$, 10.4 g, 50 mmol, 2 eq.) in 150 mL ether, vinylmagnesium bromide (1.0 M in THF, 100 mL, 100 mmol, 4 eq.) was added dropwise at -40 ºC and the mixture turned dark. After stirring at - 40 ºC for 1.5 hours, the mixture was cooled to -78 ºC and $BF_3•$ $Et_2O$ (7.7 mL, 7.1 g, 50 mmol, 2 eq.) was added dropwise. 10 minutes later, enone **4**[1] (3.4 g, 25 mmol, 1 eq.) in 50 mL ether was added dropwise at -78 ºC. The mixture was stirred at -78 ºC for 5 hours, and then was slowly warmed to room temperature. 200 mL of saturated aqueous $NH_4Cl$ was added, and the mixture was extracted with ether (4 x 100 mL). The combined organic layers were washed with saturated aqueous $NH_4Cl$ twice and brine once, then dried over $MgSO_4$ and filtered through Celite before removal of the solvent under reduced pressure. The residue was purified by chromatography on silica gel (ether/pentane: 1/19) to give ketone **10** (2.7 g, 66%) as an oil and as a 2:1 mixture of diastereomers. Major diastereomer: $^1$H-NMR (500 MHz, $CDCl_3$): δ 5.92 (1H, dd, *J* = 17.5, 10.8), 5.13 (1H, d, *J* = 10.8), 5.08 (1H, d, *J* = 17.5), 2.37 - 2.23 (2H, m), 2.17 (1H, s), 2.01 (1H, dd, *J* = 13.5, 2.8), 1.84 - 1.69 (2H, m), 1.60 (1H, t, *J* = 14.2), 1.52 - 1.42 (3H, m), 1.40 - 1.29 (1H, m), 1.28 - 1.20 (1H, m), 1.11 - 1.00 (1H, m). $^{13}$C-NMR (500 MHz, $CDCl_3$): δ 219.7, 145.0, 112.9, 53.8, 44.8, 34.9,

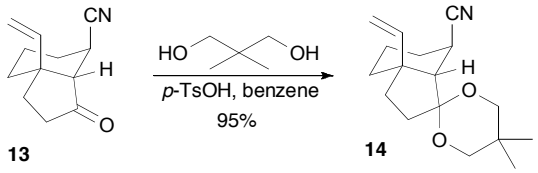
32.9, 32.1, 22.7, 21.7, 21.3. IR (neat): ν 2932, 2859, 1741, 1638, 1448 $cm^{-1}$. HRMS (ESI+): calculated for $C_{11}H_{17}O$ ($[M+H]^+$) 165.12794, found 165.12746.




3a-vinyl-2,3,3a,4,5,6-hexahydro-1*H*-inden-1-one (**13**): Hexamethyldisilazane (HMDS, 26 mL, 20 g, 125 mmol, 7.6 eq.) was added dropwise to a solution of ketone **10** (2.7 g, 16.5 mmol, 1 eq.) in 50 mL dichloromethane at -20 ºC, followed by dropwise addition of trimethylsilyl iodide (TMSI, 8.8 mL, 13 g, 63 mmol, 3.8 eq.). The mixture was slowly warmed to room temperature and stirred for 4 hours. The dark greenish mixture was cooled back to -20 ºC, and another portion of HMDS (10 mL, 8.0 g, 50 mmol, 3 eq.) and TMSI (3.5 mL, 5.1 g, 25 mmol, 1.5 eq.) was added dropwise. The system was allowed to warm to room temperature and stirred overnight. 300 mL of saturated aqueous $NaHCO_3$ was added to the orange mixture at 0 ºC before extraction with ether. The combined organic layers were washed with brine and then dried over $MgSO_4$ before removal of the solvent under reduced pressure to give crude silyl enol ether **11**. Palladium (II) acetate ($Pd(OAc)_2$, 3.7 g, 16.5 mmol, 1 eq.) was added to a solution of the crude **11** in 50 mL acetonitrile in one portion at room temperature. After the solution was stirred for 2.5 hours, $Pd(OAc)_2$ (1.9 g, 8.5 mmol, 0.5 eq.) was added in three portions during the next 2 hours. Ether, saturated aqueous $Na_2S_2O_3$ and an excess of $Na_2S_2O_3$ solid were added after the mixture was filtered through Celite, and the resultant two-phase solution was stirred overnight until the organic layer turned colorless. After filtration through Celite, the mixture was extracted with ether, and the combined organic layers were washed with brine twice, and dried over $MgSO_4$ before removal of the solvent under reduced pressure. The residue was purified by chromatography on silica gel (ether/pentane: 1/10) to give enone **12** (1.8 g, 68%) as a volatile oil. Due to this compound's volatility, not all the ether could be removed, and the yield was calculated by integration of the $^1$H-NMR spectrum; the mixture was used directly in the next step. $^1$H-NMR (500 MHz, $CDCl_3$): δ 6.80 (1H, d, *J* = 3.2), 5.74 (1H, dd, *J* = 17.2, 10.3), 5.15 (1H, d, *J* = 10.3), 4.75 (1H, dd, *J* = 17.3, 1.0), 2.36 - 2.05 (5H, m), 1.91 (1H, dd, *J* = 12.6, 3.1), 1.68 - 1.53 (3H, m), 1.34 - 1.23 (1H, m). $^{13}$C-NMR (500 MHz, $CDCl_3$): δ 207.0, 143.8, 141.4, 134.2, 117.0, 46.6, 35.2, 34.4, 33.9, 25.5, 17.9.

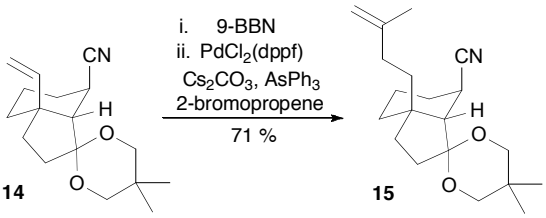
(3a*S*,4*R*,7a*S*)-3-oxo-7a-vinyloctahydro-1*H*-indene-4-carbonitrile (**13**): To a solution of enone **12** (160mg, 1.0 mmol, 1 eq.) in 5 mL of benzene was added diethylaluminum cyanide (1.0 M in toluene, 3.0 mL, 3.0 mmol, 3 eq.) dropwise at -10 ºC. The solution was slowly warmed to room temperature over 3 hours, and the reacion mixture turned red. Saturated aqueous sodium potassium tartrate (Rochelle's salt) was added, and the reaction was stirred at room temperature for 30 minutes. The mixture was extracted with ether, and the combined organic layers were dried over $MgSO_4$ before removal of the solvent under reduced pressure. The residue was purified by chromatography on silica gel (ether/pentane: 1/3) to give ketone **13** (166 mg, 89%, >95:5 dr) as a solid. $^1$H-NMR (500

MHz, $CDCl_3$): δ 6.14 (1H, dd, *J* = 17.4, 10.9), 5.27 (1H, d, *J* = 10.8), 5.26 (1H, d, *J* = 17.6), 3.42 (1H, dd, *J* = 3.6, 0.9), 2.46 - 2.25 (3H, m), 1.94 - 1.71 (5H, m), 1.60 - 1.52 (1H, m), 1.28 (1H, dddd, *J* = 8.1, 4.8, 4.0, 1.6), 1.21 - 1.13 (1H, m). $^{13}$C-NMR (500 MHz, $CDCl_3$): δ 214.5, 142.8, 121.8, 114.5, 55.4, 44.1, 33.9, 33.0, 30.3, 25.4, 23.9, 18.2. M.P.: 41-42 ºC. IR (neat): ν 3084, 2940, 2868, 2237, 1745, 1452 $cm^{-1}$. HRMS (ESI+): calculated for $C_{12}H_{16}NO$ ($[M+H]^+$) 190.12319, found 190.12271.




13 14

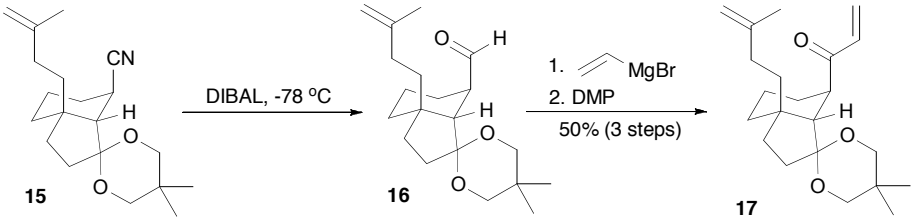
(3a'*S*,7'*R*,7a'*S*)-5,5-dimethyl-3a'-vinyloctahydrospiro[[1,3]dioxane-2,1'-indene]-7'-carbonitrile (**14**): A solution of **13** (0.51 g, 2.7 mmol, 1 eq.), 2,2-dimethylpropane-1,3-diol (1.4 g, 13.5 mmol, 5 eq.), and *p*-toluenesulfonic acid (0.26 g, 1.35 mmol, 0.5 eq.) in 25 mL benzene was stirred at reflux using a Dean-Stark trap for removal of water. Upon consumption of **13** by TLC, saturated aqueous $NaHCO_3$ (50 ml) was added at 0 ºC, and the aqueous layer was separated and extracted with ether. The combined organic layers were dried over $MgSO_4$ before removal of the solvent under reduced pressure. The residue was purified by chromatography on silica gel (ether/hexane: 1/9) to give ketal **14** (0.71 g, 95%). $^1$H-NMR (500 MHz, $CDCl_3$): δ 5.99 (1H, dd, *J* = 17.5, 10.8), 5.13 (1H, d, *J* = 17.6), 5.11 (1H, d, *J* = 10.8), 3.54 (2H, t, *J* = 11.6), 3.45 - 3.34 (2H, m), 3.23 - 3.14 (1H, m), 2.19 (1H, s), 2.05 (1H, ddd, *J* = 13.2, 9.0, 4.0), 2.00 - 1.86 (2H, m), 1.75 - 1.61 (4H, m), 1.55 - 1.42 (3H, m), 1.19 (3H, s), 0.72 (3H, s). $^{13}$C-NMR (500 MHz, $CDCl_3$): δ 145.4, 123.8, 112.8, 109.0, 72.5, 71.4, 54.7, 44.2, 36.7, 30.1, 30.0, 28.6, 25.9, 23.9, 22.8, 22.2, 18.4. IR (neat): ν 3083, 2951, 2868, 2237, 1638, 1471, 1396 $cm^{-1}$. HRMS (ESI+): calculated for $C_{17}H_{26}NO_2$ ($[M+H]^+$) 276.19635, found 276.19539.



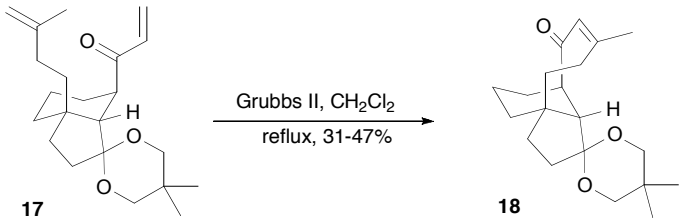

14 15

(3a'*R*,7'*R*,7a'*S*)-5,5-dimethyl-3a'-(3-methylbut-3-enyl)octahydrospiro[[1,3]dioxane-2,1'-indene]-7'-carbonitrile (**15**): 9-borabicyclo(3.3.1)nonane (9-BBN, 0.5 M in THF, 2.67 mL, 1.33 mmol, 2 eq.) was added to ketal **14** (183 mg, 0.67 mmol, 1 eq.) at room temperature under argon. The solution was stirred for 3.5 hours until **14** was consumed by TLC. In a separate flask, a solution of 2-bromopropene (0.29 mL, 0.40 g, 3.3 mmol, 5 eq.) in 10 mL DMF was stirred, and cesium carbonate ($Cs_2CO_3$, 0.54 g, 1.67 mmol, 2.5 eq.), triphenylarsine ($AsPh_3$, 41 mg, 0.13 mmol, 0.2 eq.), [1,1-bis(diphenylphosphino) ferrocene]dichloropalladium(II) ($PdCl_2$(dppf), 97 mg, 0.13 mmol, 0.2 eq.), and $H_2O$ (0.5

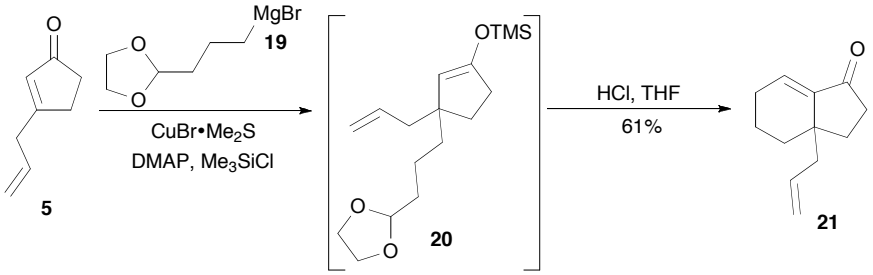
mL) were added successively at room temperature. The mixture was stirred for 5 minutes, and the crude alkyl borane from **14** was added dropwise. The mixture was stirred overnight and then quenched with saturated aqueous $NH_4Cl$. The mixture was extracted with ethyl acetate. The combined organic layers were washed with water and dried over $MgSO_4$ before removal of the solvent under reduced pressure. The residue was purified by chromatography on silica gel (ethyl acetate/hexane: 1/20) to give **13** (150 mg, 71%). $^1$H-NMR (500 MHz, $CDCl_3$): δ 4.70 (1H, s), 4.68 (1H, s), 3.53 (2H, t, *J* = 11.1), 3.43 - 3.33 (2H, m), 3.21 - 3.13 (1H, m), 2.04 - 1.85 (7H, m), 1.76 - 1.44 (10H, m), 1.35 (1H, td, *J* = 13.8, 4.2), 1.17 (3H, s), 0.71 (3H, s). $^{13}$C-NMR (500 MHz, $CDCl_3$): δ 146.2, 124.1, 109.9, 109.2, 72.5, 71.3, 54.7, 41.2, 36.7, 34.7, 32.8, 30.1, 29.7, 28.2, 26.1, 23.6, 22.8, 22.8, 22.2, 18.0. IR (neat): ν 2941, 2867, 2235, 1648, 1457, 1133, 1100 cm$^{-1}$. HRMS (ESI+): calculated for $C_{20}H_{32}NO_2$ ([M+H]$^+$) 318.24330, found 318.24323.




1-((3a'*R*,7'*R*,7a'*S*)-5,5-dimethyl-3a'-(3-methylbut-3-enyl)octahydrospiro[[1,3]dioxane-2,1'-indene]-7'-yl)prop-2-en-1-one (**17**): To a solution of nitrile **15** (13 mg, 0.041 mmol, 1 eq.) in 1.5 mL toluene was added diisobutylaluminum hydride (DIBAL, 1.0 M in toluene, 0.05 mL, 0.05 mmol, 1.2 eq.) dropwise at -78 °C. Upon completion by TLC, 0.3 mL methanol was added at -78 °C. The bath was removed, and 0.5 mL aqueous citric acid (1.0 M) was then added. The reaction was stirred for 15 minutes at room temperature. The organic layer was washed with saturated $NaHCO_3$ and brine and dried over $MgSO_4$ before removal of the solvent under reduced pressure, giving crude aldehyde **16** in quantative yield without purification. To a solution of crude **16** in 2 mL THF was added vinylmagnesium bromide (1.0 M in THF, 0.045 mL, 0.045 mmol, 1.1 eq.) at -78 °C. Upon consumption of **16**, saturated aqueous $NH_4Cl$ was added at -78 °C. After extraction with ether, drying, and removal of the solvent, the crude allylic alcohol mixture was subjected to a solution of Dess-Martin periodinane (DMP, 52 mg, 0.12 mmol, 3 eq.) and pyridine (0.1 mL) in 2 mL dichloromethane. After quenching with $NaHCO_3$ and extraction with dichloromethane, the mixture was dried over $Na_2SO_4$ before removal of the solvent under reduced pressure. The residue was purified by chromatography on silica gel (ethyl acetate/hexane: 1/19) to give **17** (7 mg, 50% over 3 steps). $^1$H-NMR (500 MHz, $CDCl_3$): δ 6.42 (1H, dd, *J* = 17.4, 10.6), 6.22 (1H, d, *J* = 17.4), 5.65 (1H, d, *J* = 10.5), 4.64 (2H, s), 3.48 (1H, d, *J* = 11.2), 3.44 (1H, d, *J* = 11.1), 3.33 (1H, d, *J* = 11.2), 3.25 (1H, d, *J* = 11.0), 2.97 (1H, m), 2.33 (1H, d, *J* = 7.9), 2.03 - 1.80 (4H, m), 1.75 - 1.31 (13H, m), 1.03 (3H, s), 0.67 (3H, s). $^{13}$C-NMR (500 MHz, $CDCl_3$): δ 203.5, 146.9, 136.1, 126.7, 109.8, 109.4, 71.7, 71.7, 55.1, 43.8, 41.7, 38.0, 33.1, 32.6, 30.8, 30.3, 28.9, 25.8, 22.9, 22.8, 22.3, 19.7. IR (neat): ν 2935, 2865, 1698, 1456, 1397, 1133, 1110 cm$^{-1}$. HRMS (ESI+): calculated for $C_{22}H_{35}O_3$ ([M+H]$^+$) 347.25862, found 347.25838.

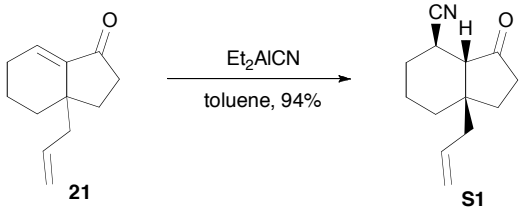



tricyclic pleuromutilin derivative **18:** To a solution of enone **17** (7 mg, 0.02 mmol) in 10 mL dichloromethane was added Grubbs' second generation olefin metathesis catalyst (Grubbs II, 2 mg, 0.002 mmol, 0.1 eq.) at room temperature. The solution was refluxed for 24 hours, and additional Grubbs II was added during this period (2 x 2 mg). Saturated aqueous $NaHCO_3$ was added, and the solution was extracted with dichloromethane. The organic layers were dried over $MgSO_4$ before removal of the solvent under reduced pressure. The residue was purified by chromatography on silica gel (ethyl acetate/hexane: 1/9) to give **18** (2-3 mg, 31-47%). $^1$H-NMR (500 MHz, $CDCl_3$): δ 5.66 (1H, s), 3.57 (1H, d, *J* =10.9), 3.55 (1H, d, *J* = 10.9), 3.42 (1H, dd, *J* = 11.1, 2.8), 3.38 (1H, dd, J 11.1, 2.8), 2.65 (1H, s), 2.61 - 2.56 (1H, m), 2.26 - 2.05 (5H, m), 1.94 (1H, tt, *J* = 13.3, 5.1), 1.85 - 1.72 (5H, m), 1.65 (1H, td, *J* = 13.3, 4.6), 1.45 (1H, qd, *J* = 13.7, 9.5), 1.37 - 1.30 (1H, m), 1.26 - 1.21 (2H, m), 1.15 (3H, s), 1.04 (1H, d, *J* = 13.7), 0.71 (3H, s). $^{13}$C-NMR (500 MHz, $CDCl_3$): δ 210.4, 148.5, 124.4, 110.1, 72.8, 71.0, 49.9, 45.9, 41.0, 33.2, 32.0, 31.9, 31.0, 30.1, 29.2, 27.1, 22.6, 22.2, 20.9, 17.7. IR (neat): ν 2944, 2867, 2360, 1666, 1457 cm$^{-1}$. HRMS (ESI+): calculated for $C_{20}H_{31}O_3$ ([M+H]$^+$) 319.22732, found 319.22691.



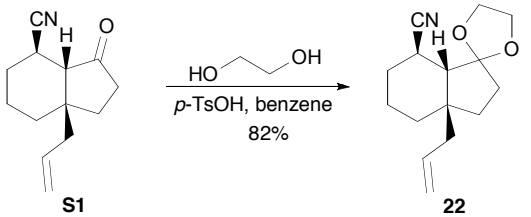

3a-allyl-2,3,3a,4,5,6-hexahydro-1*H*-inden-1-one (**21**): To a suspension of CuBr•$Me_2S$ (5.06 g, 24.6 mmol, 1.5 eq.) in THF (100 ml) was added 4-dimethylaminopyridine (DMAP, 4.00 g, 32.8 mmol, 2.0 eq.) at -78 ºC. The green suspension was stirred for 5 minutes at -78 ºC before dropwise addition of Grignard reagent **19**[2] (2.5 M solution in THF, 20 ml, 50 mmol, 3.0 eq.). After 30 minutes of stirring, a solution of **5**[3] (2.00 g, 16.4 mmol, 1 eq.) in THF (20 ml) and trimethylsilyl chloride (4.10 ml, 32.78 mmol, 2.0 eq.) were added successively at -78 ºC. The reaction was stirred for 1 hour at -78 ºC and was allowed to warm to room temperature overnight. Upon consumption of **5** by TLC, aqueous HCl (5 M, 100 ml) was added, and the mixture was refluxed for 6 hours until the reaction was complete. Upon cooling to room temperature, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (200 ml), followed by addition of ether (200 ml). The aqueous layer was separated and extracted with ether (2 x 100 ml). The combined organic layers were dried over $MgSO_4$ before removal of the solvent under reduced pressure. The residue was purified by chromatography on silica gel

(ether/pentane: 1/9) to give **21** (1.77 g, 61% from **5**) as a pale orange oil. $^{1}$H-NMR (500 MHz, $CDCl_3$): δ 6.64 (1H, t, *J* = 3.7), 5.78 (1H, ddt, *J* = 17.4, 10.2, 7.4), 5.11 – 5.05 (2H, m), 2.43 - 2.26 (2H, m), 2.24 - 2.07 (5H, m), 2.04 (1H, dt, *J* = 13.0, 3.4), 1.74 – 1.68 (2H, m), 1.38 (1H, ddd, *J* = 12.6, 9.6, 0.7), 1.11 (1H, td, *J* = 12.6, 5.4). $^{13}$C-NMR (500 MHz, $CDCl_3$): δ 207.4, 145.4, 134.4, 132.7, 118.1, 41.6, 40.2, 35.2, 32.5, 32.0, 25.1, 17.7. IR (neat): ν 2935, 2870, 1718, 1651, 1458, 1419 cm$^{-1}$. HRMS (ESI+): calculated for $C_{12}H_{17}O$ ($[M+H]^+$) 177.12794, found 177.1266.




**21** **S1**

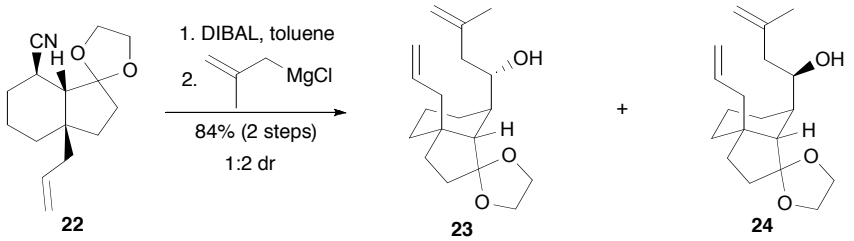
(3a*S*,4*R*,7a*S*)-7a-allyl-3-oxooctahydro-1*H*-indene-4-carbonitrile (**S1**): To a solution of **21** (1.77 g, 10 mmol, 1.0 eq.) in 50 mL toluene was added $Et_2AlCN$ (1.0 M solution in toluene, 20 mL, 20 mmol, 2.0 eq.) dropwise at -10 ºC. The reaction was stirred at 0 ºC and was monitored by TLC. Upon complete consumption of **21** by TLC (~3 hours), the solution was cooled to -20 ºC, and saturated aqueous Rochelle's salt (125 ml) was added. The bath was removed, and the reaction was stirred for 1 hour at room temperature. The aqueous layer was separated and extracted with ether (2 x 25 ml). The combined organic layers were dried over $MgSO_4$ before removal of the solvent under reduced pressure. The residue was purified by chromatography on silica gel (ethyl acetate/hexane: 1/10) to give **S1** (1.93 g, 94%, >95:5 dr). $^{1}$H-NMR (500 MHz, $CDCl_3$): δ 5.91 - 5.77 (1H, m), 5.27 - 5.16 (2H, m), 3.39 (1H, d, *J* = 2.3), 2.61 (1H, dd, *J* = 14.0, 7.9), 2.49 (1H, dd, *J* = 14.0, 6.9), 2.37 - 2.17 (3H, m), 1.91 - 1.48 (6H, m), 1.30 - 1.16 (1H, m), 1.07 (1H, td, *J* = 13.8, 3.1). $^{13}$C-NMR (500 MHz, $CDCl_3$): δ 215.4, 133.2, 122.2, 119.8, 54.0, 41.4, 41.2, 33.6, 30.6, 25.5, 23.6, 17.6. IR (neat): ν 3076, 2938, 2067, 2236, 1744, 1639, 1453, 1409 cm$^{-1}$. HRMS (ESI+): calculated for $C_{13}H_{18}NO$ ($[M+H]^+$) 204.13884, found 204.13864.




**S1** **22**

(3a'*S*,7'*R*,7a'*S*)-3a'-allyloctahydrospiro[[1,3]dioxolane-2,1'-indene]-7'-carbonitrile (**22**): A solution of **S1** (1.93 g, 9.5 mmol, 1.0 eq.), ethylene glycol (5.30 ml, 95 mmol, 10 eq.), and *p*-toluenesulfonic acid (900 mg, 4.75 mmol, 0.5 eq.) in benzene (150 ml) was refluxed using a Dean-Stark trap for removal of water. Upon consumption of **S1** by TLC, saturated aqueous $NaHCO_3$ (50 ml) was added at 0 ºC, and the aqueous layer was separated and extracted with ether (50 ml). The combined organic layers were dried over

$MgSO_4$ before removal of the solvent under reduced pressure. The residue was purified by chromatography on silica gel (ethyl acetate/hexane: 7.5/92.5) to give **22** (1.93 g, 82%). $^1$H-NMR (500 MHz, $CDCl_3$): δ 5.84 - 5.71 (1H, m), 5.14 - 5.07 (2H, m), 4.00 - 3.83 (4H, m), 2.65 (1H, td, *J* = 7.2, 4.7), 2.42 (1H, dd, *J* = 13.9, 7.6), 2.24 (1H, dd, *J* = 13.8, 7.3), 2.02 - 1.95 (2H, m), 1.92 (2H, dd, *J* = 8.6, 7.1), 1.71 - 1.56 (2H, m), 1.56 - 1.36 (5H, m). $^{13}$C-NMR (500 MHz, $CDCl_3$): δ 134.4, 123.8, 118.6, 118.2, 65.1, 64.3, 51.5, 43.5, 42.7, 34.6, 32.0, 30.8, 27.2, 25.5, 18.7. IR (neat): ν 3075, 2236, 1638, 1455 cm$^{-1}$. HRMS (ESI+): calculated for $C_{15}H_{22}NO_2$ ($[M+H]^+$) 248.16505, found 248.1652.



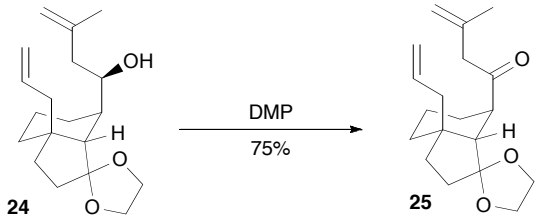

**22** **23** **24**

(*S*)-1-((3a'*S*,7'*R*,7a'*S*)-3a'-allyloctahydrospiro[[1,3]dioxolane-2,1'-indene]-7'-yl)-3-methylbut-3-en-1-ol (**23**) & (*R*)-1-((3a'*S*,7'*R*,7a'*S*)-3a'-allyloctahydrospiro[[1,3]dioxolane-2,1'-indene]-7'-yl)-3-methylbut-3-en-1-ol (**24**): To a solution of **22** (200 mg, 0.81 mmol, 1 eq.) in 15 mL toluene was added DIBAL (1.0 M in toluene, 2.45 mL, 2.45 mmol, 3 eq.) at -78 ºC. The solution was stirred for three hours at - 78 ºC before addition of 5 mL methanol and 10 mL 10% aqueous citric acid at -78 ºC. The mixture was slowly warmed to room temperature before extraction with ether. The combined organic layers were dried over $MgSO_4$ before removal of the solvent under reduced pressure to give the crude aldehyde. To a solution of the resultant aldehyde in 15 mL THF was added (2-methylallyl)magnesium chloride (0.5 M in THF, 1.7 mL, 0.85 mmol, 1.05 eq.) dropwise at –78 ºC. The solution was stirred for 10 minutes at -78 ºC, and saturated aqueous $NH_4Cl$ was added at this temperature. The mixture was slowly warmed to room temperature and extracted with ether. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine successively and dried over $MgSO_4$ before removal of the solvent under reduced pressure. The residue was purified by chromatography on silica gel (ethyl acetate/hexane: 3/17) to give a mixture of **23** and **24** (206 mg, 84%, 1:2 dr). These two diastereomers were further separated by repeated chromatography (ethyl acetate/hexane: 1/19).

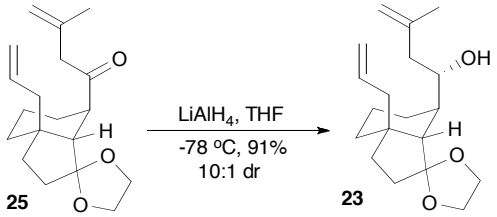
(**23**): $^1$H-NMR (500 MHz, $CDCl_3$): δ 5.86 (1H, td, *J* = 17.0, 7.4), 5.09 - 5.00 (2H, m), 4.88 (1H, s), 4.81 (1H, s), 3.96 - 3.89 (3H, m), 3.78 (2H, dt, *J* = 17.4, 10.5), 2.36 (1H, d, *J* = 13.5), 2.26 (1H, dd, *J* = 13.7, 7.6), 2.17 (1H, dd, *J* = 13.6, 7.2), 2.10 (2H, s), 1.93 (1H, dd, *J* = 13.1, 10.8), 1.82 - 1.60 (8H, m), 1.51 - 1.37 (4H, m), 1.37 - 1.23 (2H, m). $^{13}$C-NMR (500 MHz, $CDCl_3$): δ 143.8, 136.0, 119.4, 117.4, 113.6, 69.5, 64.7, 63.7, 49.1, 44.9, 43.4, 41.6, 37.9, 34.5, 34.3, 31.6, 22.7, 22.4, 18.0. IR (neat): ν 3555, 3073, 2934, 1640, 1455 cm$^{-1}$. HRMS (ESI+): calculated for $C_{19}H_{30}NaO_3$ ($[M+Na]^+$) 329.20926, found 329.20896.

(**24**): $^1$H-NMR (500 MHz, $CDCl_3$): δ 5.87 - 5.75 (1H, m), 5.09 - 5.01 (2H, m), 4.85 (1H, s), 4.79 (1H, s), 3.95 - 3.80 (5H, m), 2.27 - 2.19 (2H, m), 2.13 (2H, ddd, *J* = 13.9, 8.4,

5.8), 1.89 (2H, dd, *J* = 12.5, 5.9), 1.81 - 1.72 (5H, m), 1.70 - 1.29 (9H, m). $^{13}$C-NMR (500 MHz, $CDCl_3$): δ 143.7, 135.8, 119.4, 117.5, 113.1, 69.3, 64.5, 63.8, 50.1, 45.2, 43.9, 41.8, 37.5, 34.1, 34.1, 31.6, 22.5, 20.7, 18.0. IR (neat): ν 3478, 3073, 2939, 1639, 1455 cm$^{-1}$. HRMS (ESI+): calculated for $C_{19}H_{30}NaO_3$ ([M+Na]$^+$) 329.20926, found 329.20887.

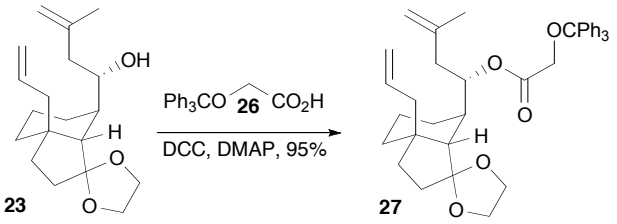



1-((3a'*S*,7'*R*,7a'*S*)-3a'-allyloctahydrospiro[[1,3]dioxolane-2,1'-indene]-7'-yl)-3-methylbut-3-en-1-one (**25**): To a solution of **24** (0.43 g, 1.4 mmol, 1.0 eq.) in 20 mL dichloromethane was added $NaHCO_3$ (1.2 g, 14 mmol, 10 eq.) and Dess-Martin periodinane (DMP, 0.78 g, 1.8 mmol, 1.3 eq.) at room temperature. The mixture was stirred for 1.5 hours and then saturated aqueous $NaHCO_3$ was added. After the organic layer turned transparent, the mixture was extracted with dichloromethane. The combined organic layers were dried over $Na_2SO_4$ before removal of the solvent under reduced pressure. The residue was purified by chromatography on silica gel (ethyl acetate/hexane: 1/9) to give **25** (0.32 g, 75%). $^1$H-NMR (500 MHz, $CDCl_3$): δ 5.89 - 5.71 (1H, m), 5.08 - 5.00 (2H, m), 4.95 - 4.92 (1H, m), 4.78 (1H, d, *J* = 0.8), 3.92 (1H, ddd, *J* = 8.2, 6.4, 3.4), 3.73 (1H, td, *J* = 8.3, 6.7), 3.57 (1H, dt, *J* = 8.5, 6.6), 3.40 (1H, td, *J* = 6.7, 3.4), 3.31 (1H, d, *J* = 16.6), 3.20 (1H, dd, *J* = 16.6), 2.50 - 2.42 (1H, m), 2.25 (2H, qd, *J* = 13.7, 7.4), 2.15 (1H, d, *J* = 11.3), 2.06 - 2.01 (2H, m), 1.83 - 1.68 (5H, m), 1.66 - 1.60 (1H, m), 1.46 - 1.31 (4H, m), 0.96 (1H, tdd, *J* = 12.4, 5.7, 3.5). $^{13}$C-NMR (500 MHz, $CDCl_3$): δ 210.9, 140.0, 135.4, 119.7, 117.7, 114.8, 64.7, 64.3, 51.8, 51.1, 48.2, 45.0, 43.6, 34.7, 32.0, 29.6, 28.4, 23.0, 21.1. IR (neat): ν 3075, 2928, 2857, 1714 cm$^{-1}$. HRMS (ESI+): calculated for $C_{19}H_{29}O_3$ ([M+H]$^+$) 305.21167, found 305.2113.

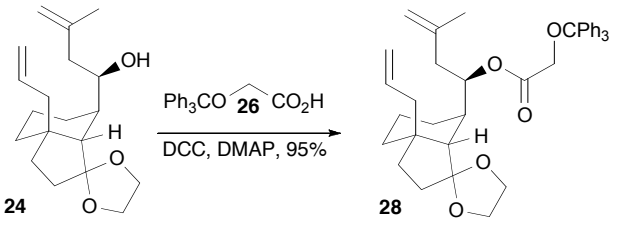



(*S*)-1-((3a'*S*,7'*R*,7a'*S*)-3a'-allyloctahydrospiro[[1,3]dioxolane-2,1'-indene]-7'-yl)-3-methylbut-3-en-1-ol (**23**): To a solution of **25** (80 mg, 0.27 mmol, 1 eq.) in 5 mL THF was added lithium aluminum hydride (LAH, 1.0 M in ether, 8 mL, 8 mmol, 30 eq.) at -78 °C, and the solution was stirred at -78 °C for 2 hours. The reaction was carefully quenched with Rochelle's salt at -78 °C and slowly warmed to room temperature. The mixture was extracted with ether, and the combined organic layers were washed with saturated $NaHCO_3$ and brine, then dried over $MgSO_4$ before removal of the solvent under

reduced pressure. The residue was purified by chromatography on silica gel (ethyl acetate/hexane: 1/7) to give **23** (73 mg, 91%, 10:1 dr).

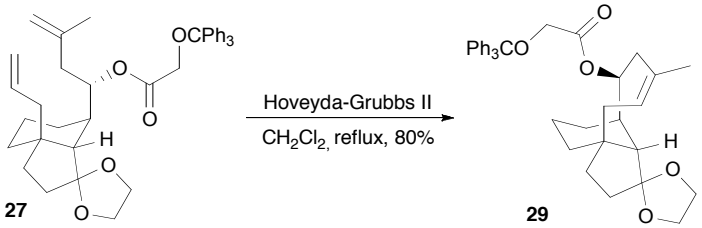



(*S*)-1-((3a'*S*,7'*R*,7a'*S*)-3a'-allyloctahydrospiro[[1,3]dioxolane-2,1'-indene]-7'-yl)-3-methylbut-3-enyl 2-(trityloxy)acetate (**27**): To a solution of **23** (53 mg, 0.17 mmol, 1 eq.) in 5 mL dichloromethane was added 4-dimethylaminopyridine (DMAP, 0.10 g, 0.85 mmol, 5 eq), N,N'-dicyclohexylcarbodiimide (DCC, 0.10 g, 0.50 mmol, 3 eq), and acid **26**[4] (0.11 g, 0.35 mmol, 2 eq.) successively at room temperature. The mixture was stirred for 5 hours before quenching with 10 mL saturated aqueous $NaHCO_3$. The mixture was filtered through Celite and then extracted with ether. The combined organic layers were dried over $MgSO_4$ before removal of the solvent under reduced pressure. The residue was purified by chromatography on silica gel (ethyl acetate/hexane: 7/93) to give **27** (100 mg, 95%). $^1$H-NMR (500 MHz, $CDCl_3$): δ 7.48 (6H, d, *J* = 7.4), 7.33 - 7.22 (9H, m), 5.80 (1H, td, *J* = 17.5, 7.4), 5.46 (1H, ddd, *J* = 10.3, 4.3, 2.0), 5.08 - 5.00 (2H, m), 4.71 (1H, s), 4.63 (1H, s), 4.12 (1H, dd, *J* = 13.5, 6.7), 4.05 (1H, dd, *J* = 12.5, 6.9), 3.92 (1H, dd, *J* = 12.6, 7.1), 3.84 (1H, dd, *J* = 13.7, 6.9), 3.70 (2H, q, *J* = 15.4), 2.25 - 1.99 (5H, m), 1.76 - 1.62 (7H, m), 1.61 - 1.15 (7H, m). $^{13}$C-NMR (500 MHz, $CDCl_3$): δ 169.4, 143.6, 142.6, 135.6, 128.7, 128.1, 127.3, 118.7, 117.7, 113.1, 87.3, 72.9, 64.8, 64.0, 62.9, 50.0, 45.3, 41.3, 38.1, 35.5, 34.6, 33.8, 30.8, 22.2, 20.0, 17.6. IR (neat): ν 3060, 3024, 2929, 2870, 1754, 1730, 1491, 1448 $cm^{-1}$. HRMS (ESI+): calculated for $C_{40}H_{46}NaO_5$ ($[M+Na]^+$) 629.32429, found 629.32415.

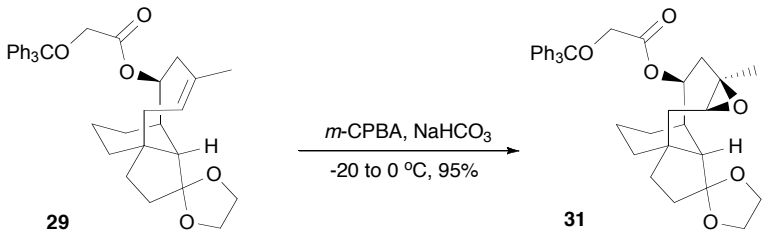



(*R*)-1-((3a'*S*,7'*R*,7a'*S*)-3a'-allyloctahydrospiro[[1,3]dioxolane-2,1'-indene]-7'-yl)-3-methylbut-3-enyl 2-(trityloxy)acetate (**28**): To a solution of **24** (50 mg, 0.16 mmol, 1 eq.) in 5 mL dichloromethane was added 4-dimethylaminopyridine (DMAP, 0.10 g, 0.80 mmol, 5 eq), N,N'-dicyclohexylcarbodiimide (DCC, 0.10 g, 0.50 mmol, 3 eq), and acid **26**[4] (0.11 g, 0.35 mmol, 2 eq.) successively at room temperature. The mixture was stirred for 5 hours before quenching with 10 mL saturated aqueous $NaHCO_3$. The mixture was filtered through Celite and then extracted with ether. The combined organic layers were dried over $MgSO_4$ before removal of the solvent under reduced pressure. The residue was

purified by chromatography on silica gel (ethyl acetate/hexane: 7/93) to give **28** (94 mg, 95%). $^{1}$H-NMR (500 MHz, $CDCl_3$): δ 7.51 - 7.47 (6H, m), 7.33 - 7.22 (9H, m), 5.75 (1H, ddt, *J* = 17.3, 10.1, 7.3), 5.42 (1H, td, *J* = 6.9, 4.4), 4.97 (2H, ddd, *J* = 14.7, 12.6, 2.3), 4.75 - 4.73 (1H, m), 4.68 (1H, s), 4.00 - 3.90 (2H, m), 3.86 (2H, dq, *J* = 12.4, 6.9), 3.72 (2H, s), 2.25 (3H, dd, *J* = 12.0, 7.2), 2.13 (1H, dd, *J* = 13.7, 7.3), 1.85 - 1.66 (7H, m), 1.64 (1H, d, *J* = 8.0), 1.56 - 1.49 (2H, m), 1.45 - 1.26 (5H, m). $^{13}$C-NMR (500 MHz, $CDCl_3$): δ 169.9, 143.6, 142.2, 135.6, 128.7, 128.1, 127.3, 119.6, 117.6, 113.4, 87.4, 73.3, 64.7, 63.9, 62.9, 50.3, 45.4, 42.5, 41.5, 36.0, 34.8, 33.2, 31.9, 22.3, 21.6, 18.5. IR (neat): ν 3060, 2935, 1754, 1727, 1492, 1449 cm$^{-1}$. HRMS (ESI+): calculated for $C_{40}H_{46}NaO_5$ ([M+Na]$^+$) 629.32429, found 629.32418.

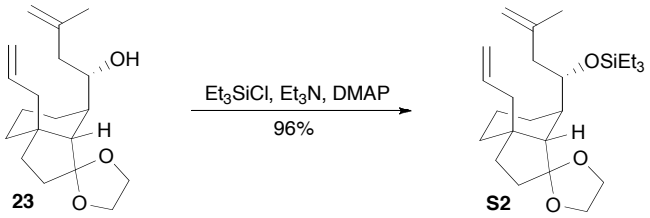



tricyclic pleuromutilin derivative **29:** To a solution of **27** (260 mg, 0.43 mmol, 1 eq.) in 300 mL dichloromethane was added Hoveyda-Grubbs catalyst 2nd Generation (Hoveyda-Grubbs II, 30 mg, 0.05 mmol, 0.11 eq.) at room temperature. The solution was refluxed for 24 hours, and another portion of Hoveyda-Grubbs II (30 mg, 0.11 eq.) was added. The solution was refluxed for one week and monitored by TLC. Upon consumption of **27**, the solvent was removed under reduced pressure, and the residue was purified by chromatography on silica gel (ethyl acetate/hexane: 7/93) to give **29** (200 mg, 80%). $^{1}$H-NMR (500 MHz, $CDCl_3$): δ 7.50 (6H, d, *J* = 7.5), 7.31 (6H, t, *J* = 7.6), 7.24 (3H, t, *J* = 7.3), 5.43 (1H, t, *J* = 7.8), 4.69 (1H, dd, *J* = 10.6, 5.4), 3.94 - 3.66 (6H, m), 2.85 (1H, t, *J* = 12.3), 2.48 (1H, dd, *J* = 14.0, 8.6), 2.09 (1H, t, *J* = 6.3), 1.90 (1H, s), 1.88 (3H, s), 1.85 - 1.61 (7H, m), 1.54 (3H, m), 1.36 - 1.29 (1H, m), 1.17 (1H, d, *J* = 12.6). $^{13}$C-NMR (500 MHz, $CDCl_3$): δ 169.2, 143.5, 137.8, 128.8, 128.1, 127.3, 123.5, 119.4, 87.4, 75.4, 65.1, 63.4, 63.0, 47.3, 42.9, 36.3, 35.4, 35.3, 34.2, 33.4, 31.5, 24.1, 20.0, 19.7. IR (neat): ν 2931, 2869, 1754, 1449, 1203, 1113, 1030 cm$^{-1}$. HRMS (ESI+): calculated for $C_{38}H_{42}NaO_5$ ([M+Na]$^+$) 601.29299, found 601.29247.



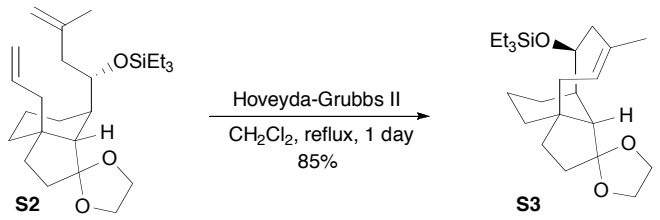

tricyclic pleuromutilin derivative **31**: To a solution of **29** (35 mg, 0.061 mmol, 1 eq.) in 5 mL dichloromethane was added $NaHCO_3$ (20 mg, 0.24 mmol, 4.0 eq.). The suspension

was cooled to -20 ºC and 3-chloroperoxybenzoic acid (77% *m*-CPBA, 21 mg, 0.094 mmol, 1.5 eq.) in 2 mL dichloromethane was added dropwise. The mixture was slowly warmed to 0 ºC and stirred for 1 hour. Then the reaction was cooled back to –20 ºC before addition of another portion of *m*-CPBA (15 mg, 0.087 mmol, 1.4 eq. ) in 1 mL dichloromethane. The mixture was slowly warmed to 0 ºC and stirred for 1 hour before saturated aqueous $NaHCO_3$ was added. The mixture was extracted with ether, and the combined organic layers were washed with saturated aqueous $NaHCO_3$ and dried over $MgSO_4$ before removal of the solvent under reduced pressure. The residue was purified by chromatography on silica gel (ethyl/hexane: 15/85) to give epoxide **31** (34 mg, 95%). $^1$H-NMR (500 MHz, $CDCl_3$): δ 7.50 (6H, d, *J* = 7.5), 7.33 (6H, t, *J* = 7.5), 7.27 (3H, dd, *J* = 8.2, 6.0), 4.95 (1H, s), 3.99 - 3.86 (3H, m), 3.81 (2H, s), 3.79 - 3.72 (1H, m), 2.81 (1H, dd, *J* = 9.8, 4.7), 2.17 (1H, s), 1.96 (1H, dd, *J* = 14.8, 4.6), 1.93 - 1.69 (7H, m), 1.61 - 1.40 (9H, m), 1.11 (1H, d, *J* = 12.6). $^{13}$C-NMR (500 MHz, $CDCl_3$): δ 169.2, 143.3, 128.6, 128.0, 127.3, 119.2, 87.4, 74.5, 65.2, 63.4, 62.8, 60.5, 58.7, 48.0, 40.0, 36.7, 36.4, 36.0, 35.0, 32.1, 31.4, 22.3, 19.4, 19.2. M.P.: 201-202 ºC. IR (neat): ν 2935, 2870, 1754, 1448, 1202, 1112, 1030 cm$^{-1}$. HRMS (ESI+): calculated for $C_{38}H_{42}NaO_6$ ([M+Na]$^+$) 617.28791, found 617.28752.




((*S*)-1-((3a'*S*,7'*R*,7a'*S*)-3a'-allyloctahydrospiro[[1,3]dioxolane-2,1'-indene]-7'-yl)-3-methylbut-3-enyloxy)triethylsilane (**S2**): To a solution of **23** (40 mg, 0.13 mmol, 1.0 eq.) in 5 mL dichloromethane, triethylamine ($Et_3N$, 0.05 mL, 36 mg, 0.36 mmol, 2.8 eq.) and 4-dimethylaminopyridine (DMAP, 1.5 mg, 0.012 mmol, 0.1 eq.) were added before addition of triethylsilyl chloride (TESCl, 0.035 mL, 30 mg, 0.20 mmol, 1.5 eq.) dropwise at room temperature. The solution was stirred overnight before addition of another portion of $Et_3N$ (0.05mL, 36 mg, 0.36 mmol, 2.8 eq.) and TESCl (0.05 mL, 45 mg, 0.30 mmol, 2.3 eq.). The solution was stirred for 3 hours, and $Et_3N$ (0.5 mL, 0.36 g, 3.6 mmol, 28 eq.) was added. Upon consumption of **23**, saturated aqueous $NaHCO_3$ was added. The mixture was extracted with ether, and the combined organic layers were washed with saturated aqueous $NaHCO_3$ and dried over $MgSO_4$ before removal of the solvent under reduced pressure. The residue was purified by chromatography on silica gel (ethyl/hexane: 5/95) to give silyl ether **S2**. (53 mg, 96%) $^1$H-NMR (500 MHz, $CDCl_3$): δ 5.82 (1H, td, *J* = 16.5, 7.5), 5.06 (2H, d, *J* = 12.3), 4.72 (2H, d, *J* = 13.0), 4.01 (2H, dd, *J* = 15.7, 9.7), 3.96 - 3.81 (3H, m), 2.21 - 2.06 (3H, m), 1.98 (1H, t, *J* = 11.6), 1.90 (2H, dd, *J* = 13.0, 9.7), 1.76 - 1.68 (4H, m), 1.67 - 1.59 (2H, m), 1.56 - 1.49 (2H, m), 1.48 - 1.33 (3H, m), 1.33 - 1.24 (1H, m), 1.03 (1H, ddd, *J* = 18.1, 12.7, 9.0), 0.93 (9H, t, *J* = 7.9), 0.57 (6H, q, *J* = 7.7). $^{13}$C-NMR (500 MHz, $CDCl_3$): δ 144.4, 136.0, 119.1, 117.5, 112.3, 72.0, 64.0, 63.4, 50.2, 45.6, 41.9, 39.7, 38.7, 34.3, 33.2, 31.4, 23.0, 19.1, 18.1, 7.1, 5.1. IR

(neat): ν 2954, 2912, 2876, 1639, 1458, 1074, 1005 $cm^{-1}$. HRMS (ESI+): calculated for $C_{25}H_{45}O_3Si$ ($[M+H]^+$) 421.31380, found 421.31331.




tricyclic pleuromutilin derivative **S3:** A solution of diene **S2** (53 mg, 0.13 mmol. 1.0 eq.) and Hoveyda-Grubbs II (12 mg, 0.018 mmol, 0.14 eq.) in 100 mL dichloromethane was refluxed for 24 hours. Saturated aqueous $NaHCO_3$ was added, and the mixture was extracted with ether. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and dried over $MgSO_4$ before removal of the solvent under reduced pressure. The residue was purified by chromatography on silica gel (ethyl/hexane: 5/95) to give **S3** (42mg, 85%). $^1$H-NMR (500 MHz, $CDCl_3$): δ 5.37 (1H, t, *J* = 7.9), 3.97 - 3.89 (1H, m), 3.85 (2H, dq, *J* = 11.9, 6.1), 3.77 - 3.68 (1H, m), 3.55 (1H, dd, *J* = 9.9, 5.4), 2.88 (1H, t, *J* = 12.2), 2.51 (1H, dd, *J* = 14.0, 8.5), 2.05 - 1.91 (2H, m), 1.89 - 1.78 (6H, m), 1.77 - 1.62 (4H, m), 1.55 - 1.39 (3H, m), 1.35 - 1.28 (1H, m), 1.16 (1H, d, *J* = 12.8), 0.96 (9H, t, *J* = 7.9), 0.66 - 0.53 (6H, m). $^{13}$C-NMR (500 MHz, $CDCl_3$): δ 138.7, 122.8, 120.0, 73.1, 65.3, 63.6, 47.9, 42.9, 39.7, 36.8, 36.3, 35.5, 34.4, 32.0, 24.6, 20.4, 18.6, 7.1, 4.9. IR (neat): ν 2934, 2874, 1734, 1474, 1458, 1071, 1034 $cm^{-1}$. HRMS (ESI+): calculated for $C_{23}H_{41}O_3Si$ ($[M+H]^+$) 393.28250, found 393.28175.

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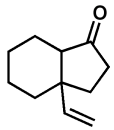

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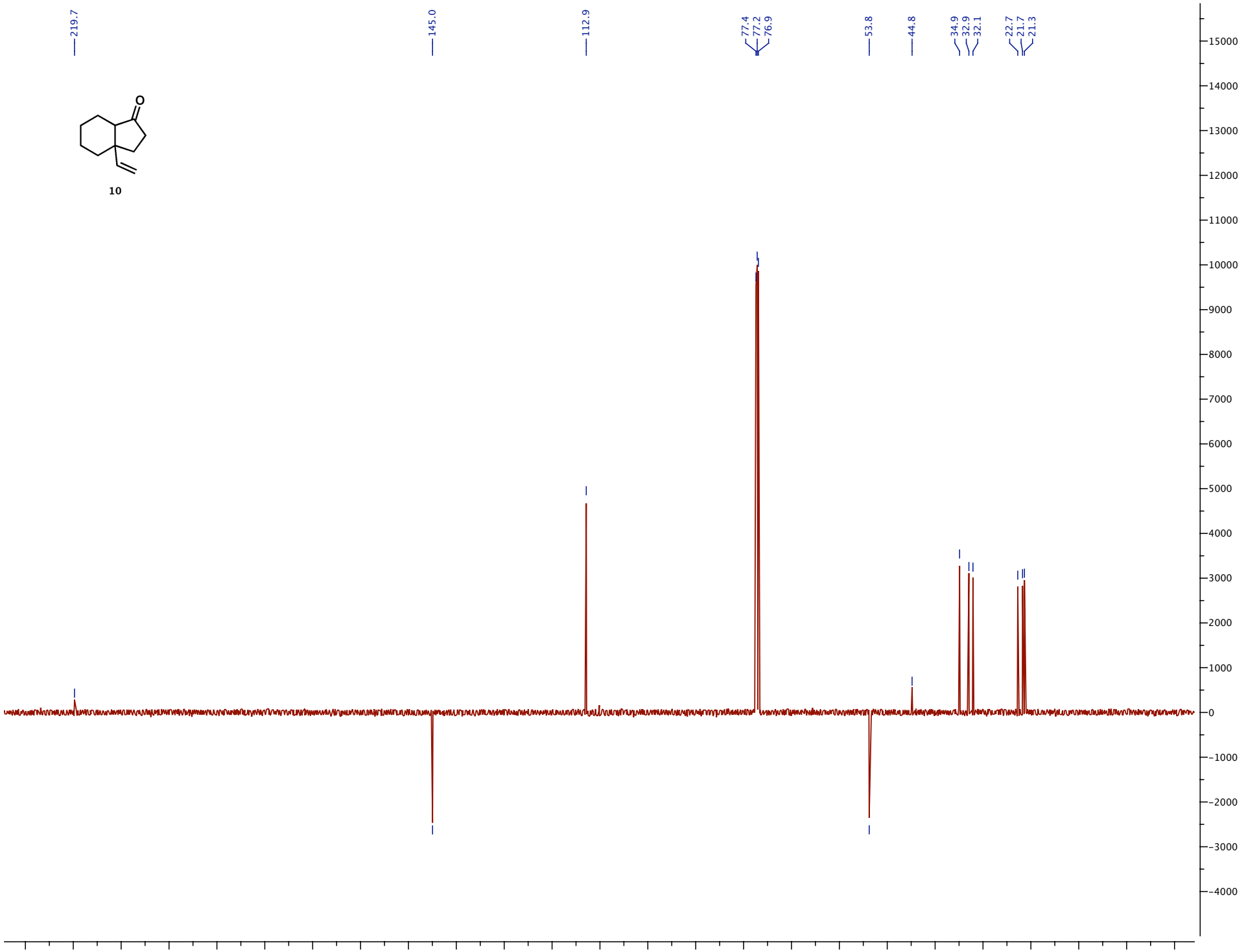

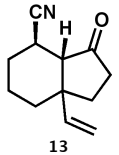


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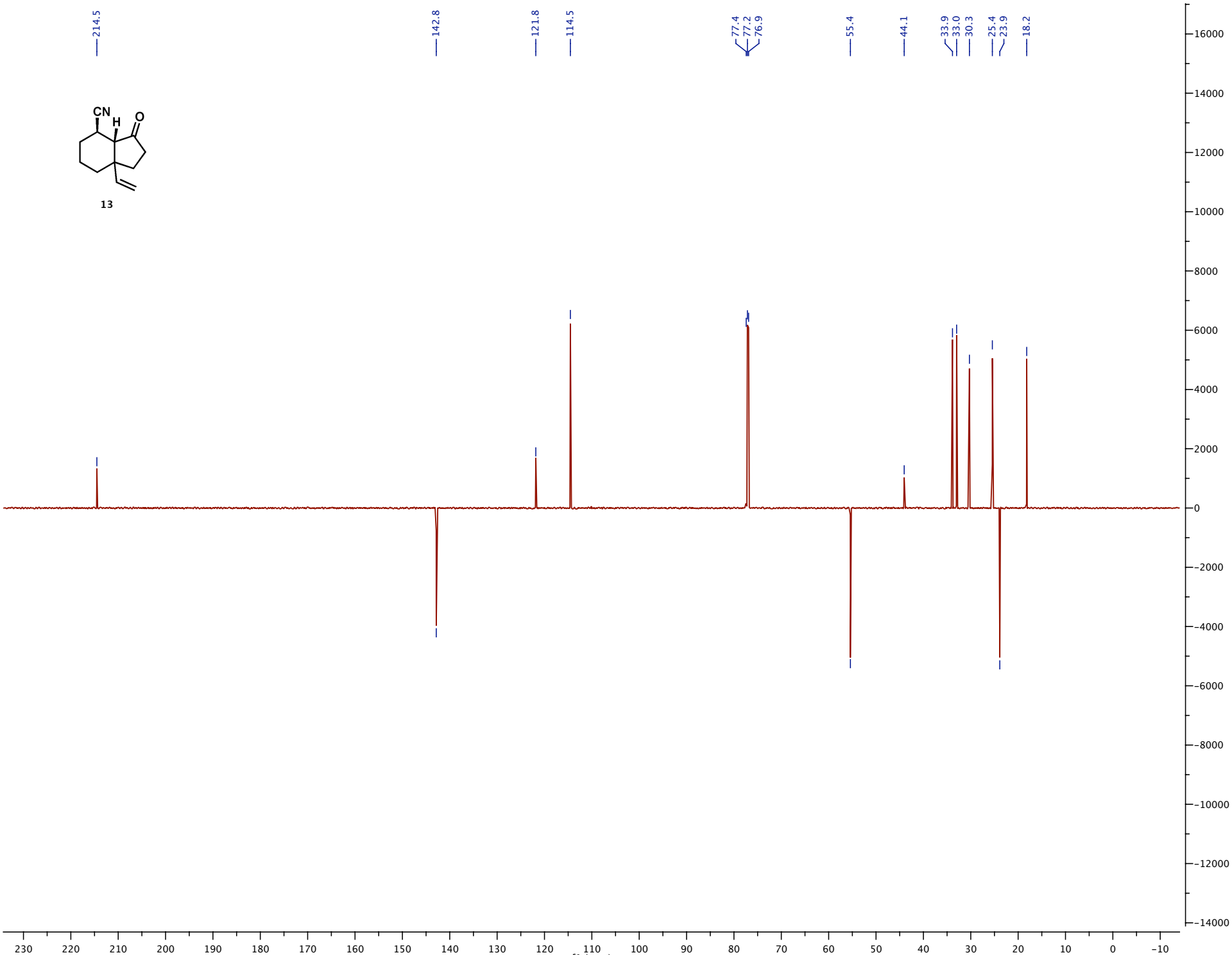

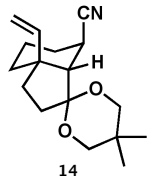


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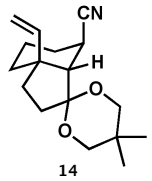


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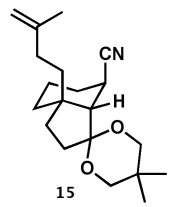


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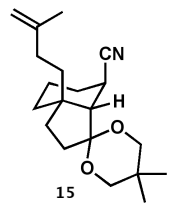


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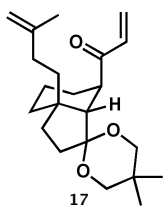

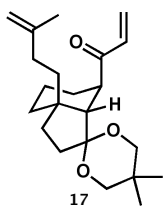


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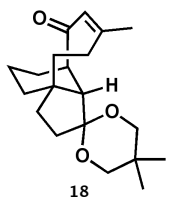


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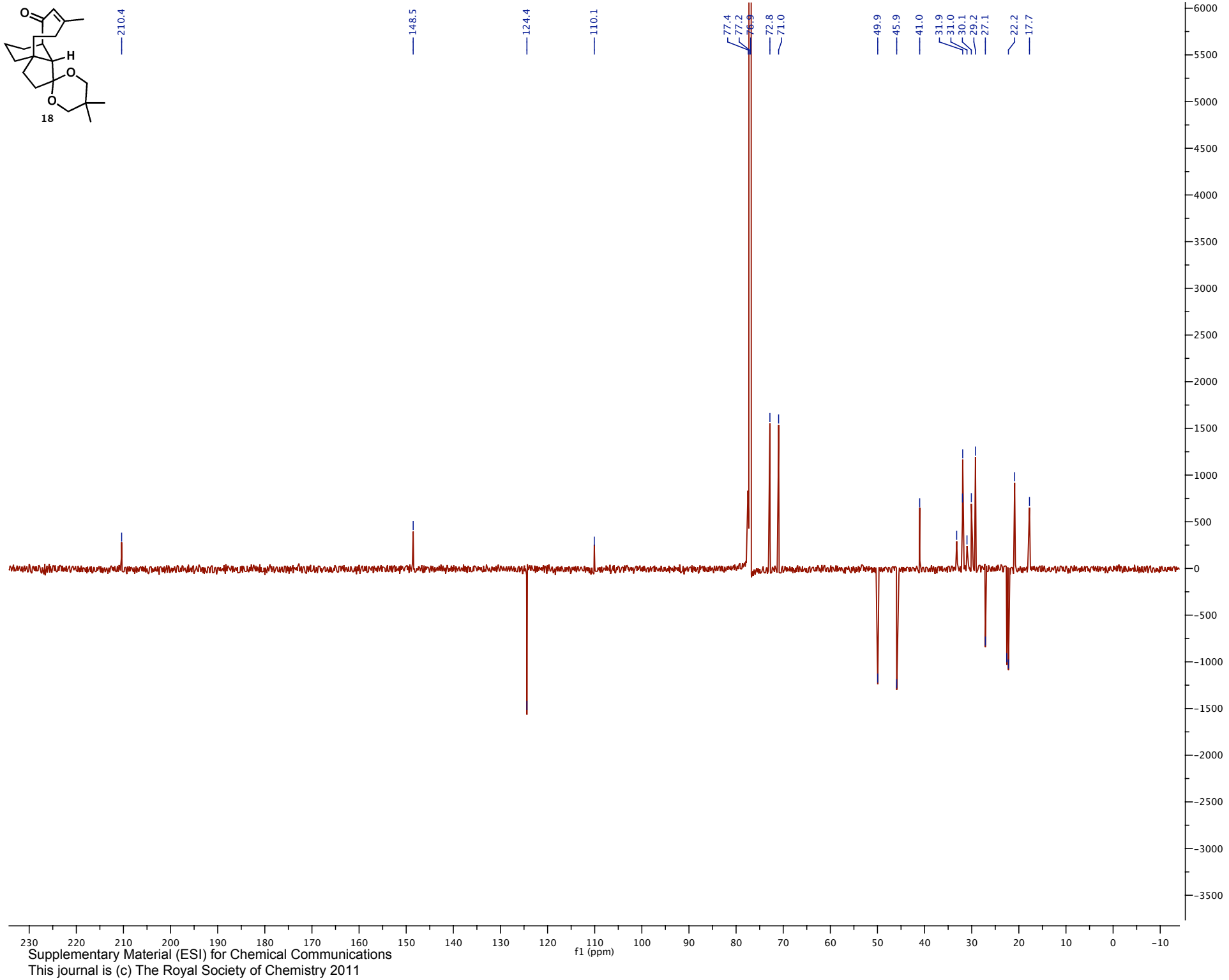

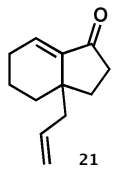

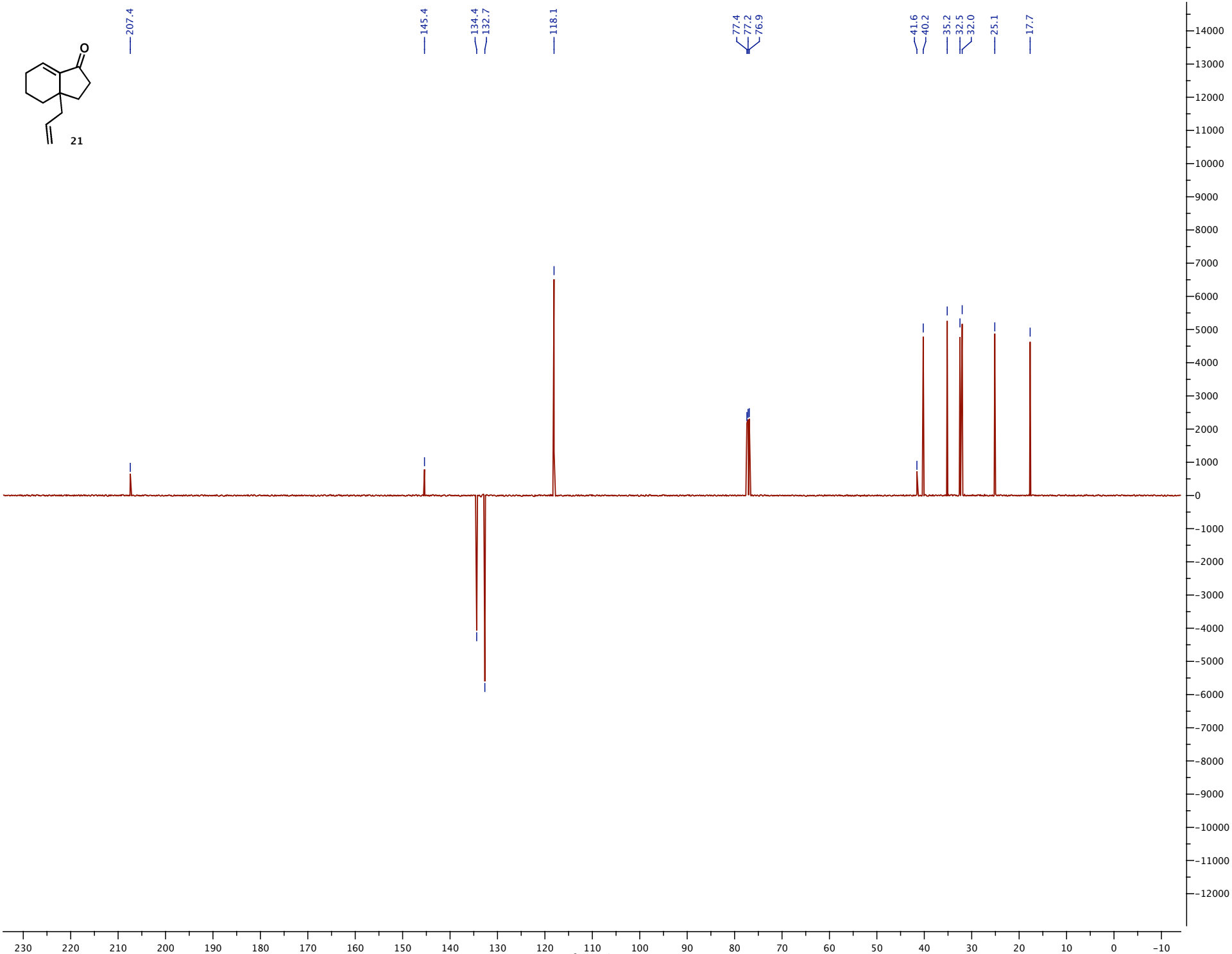

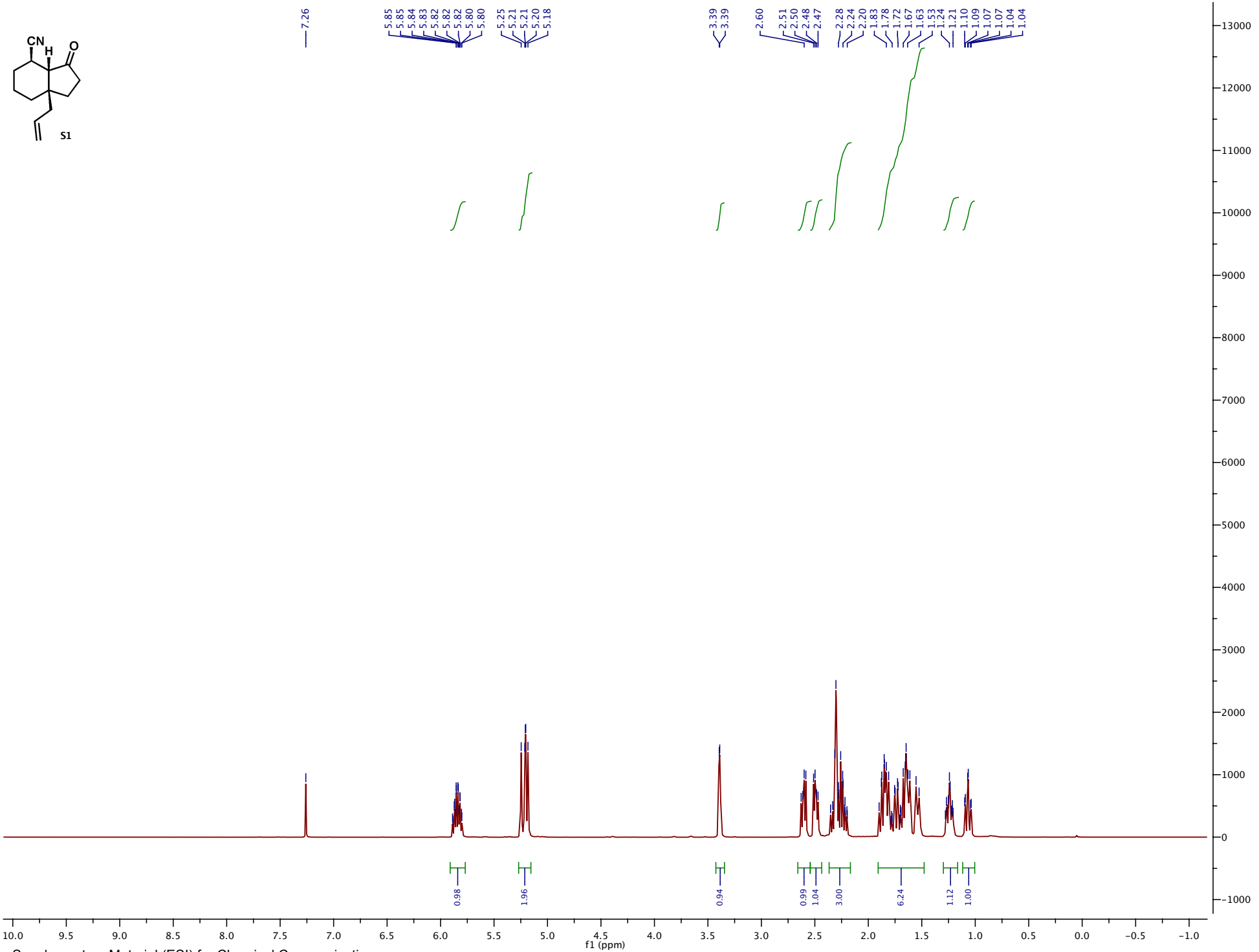

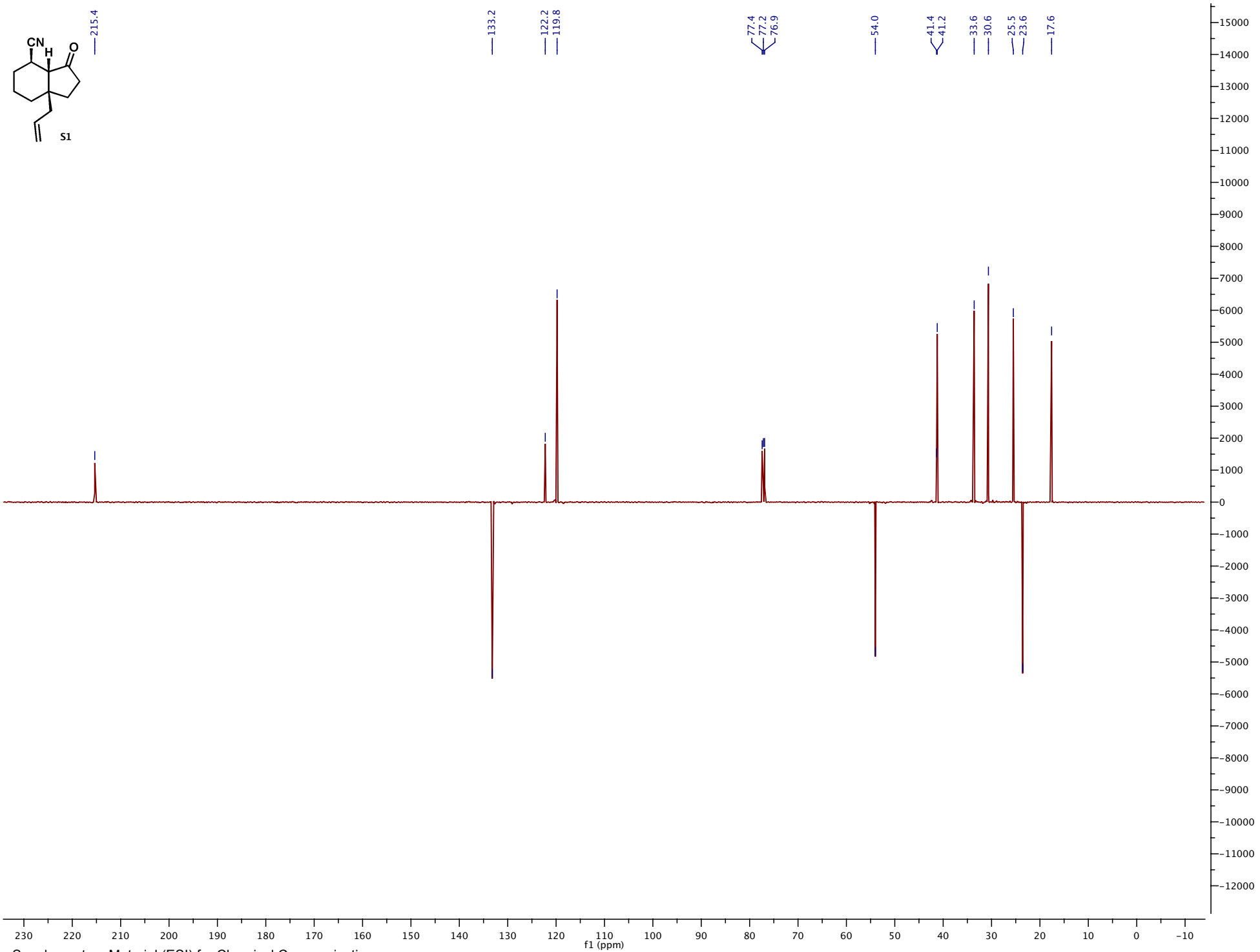

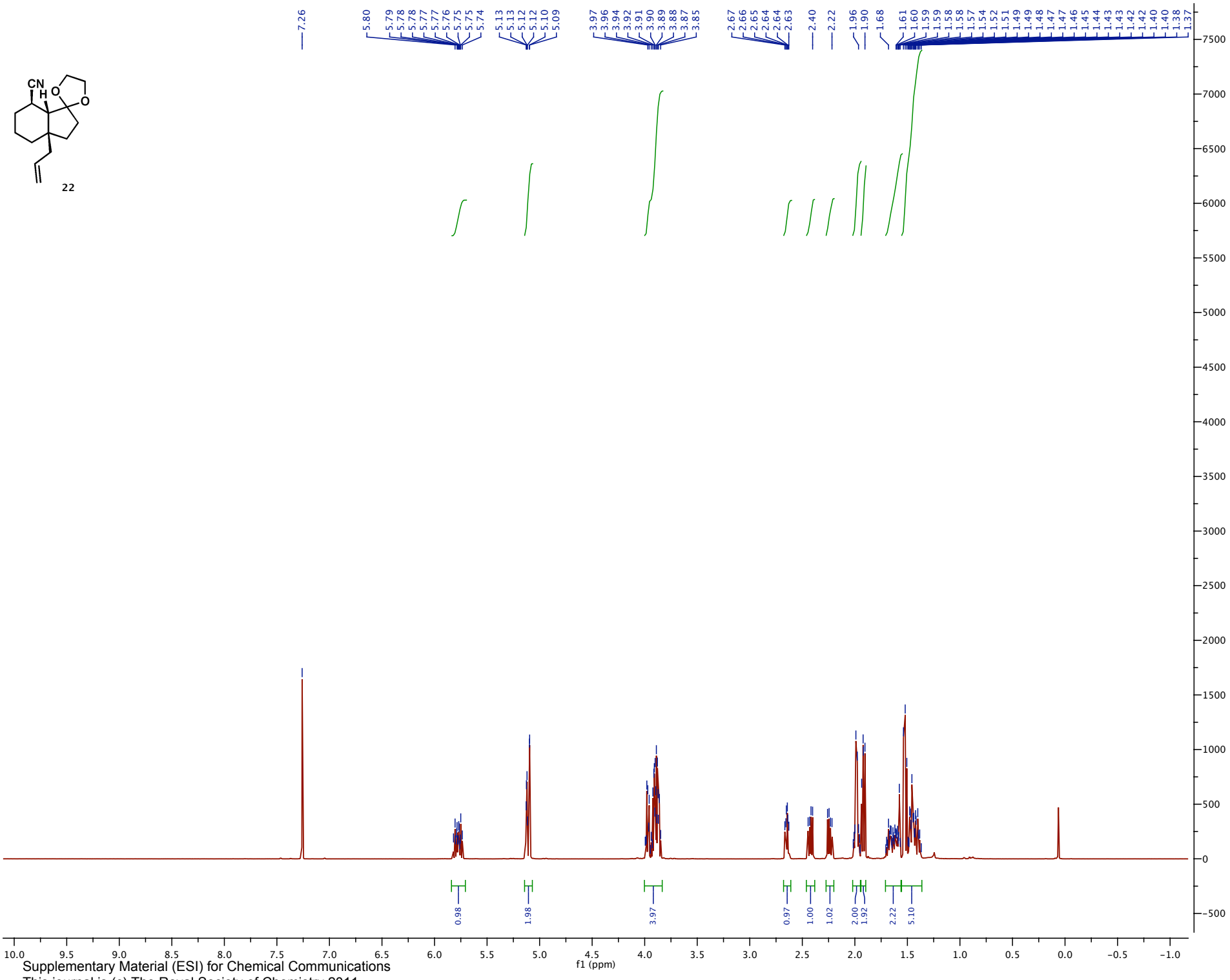

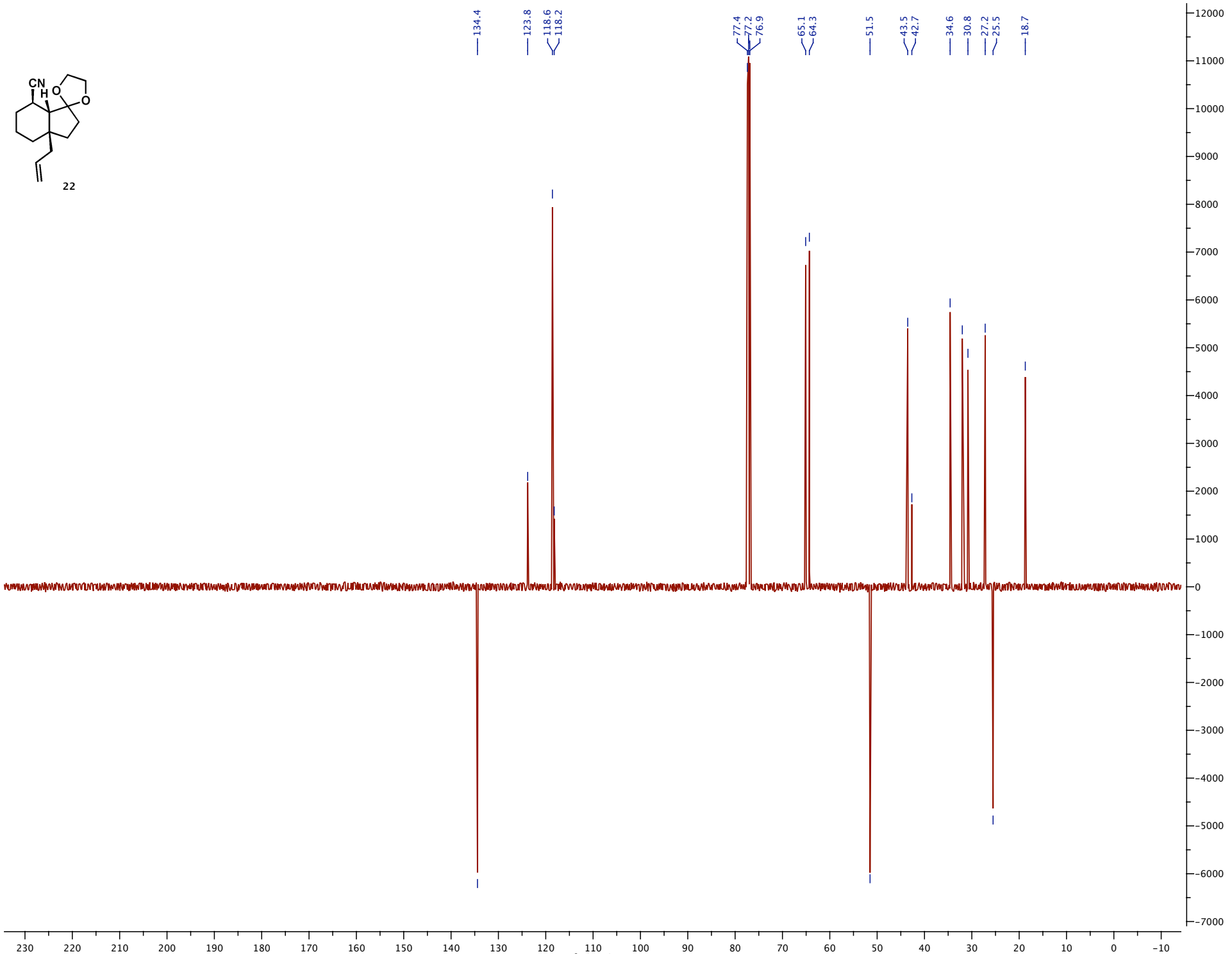

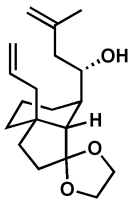


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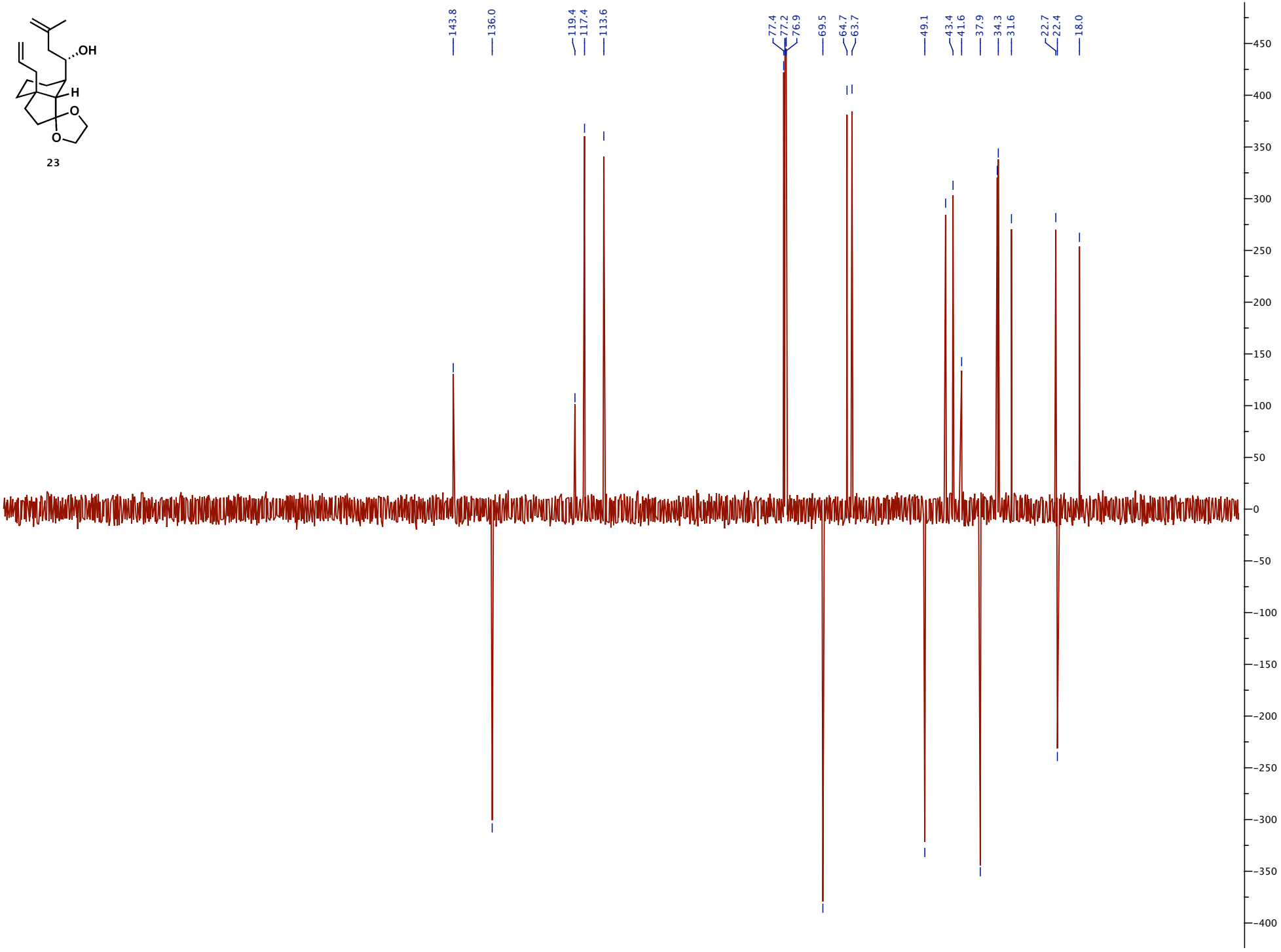

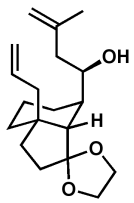


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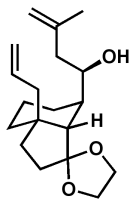


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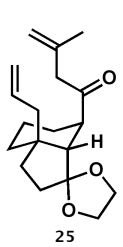


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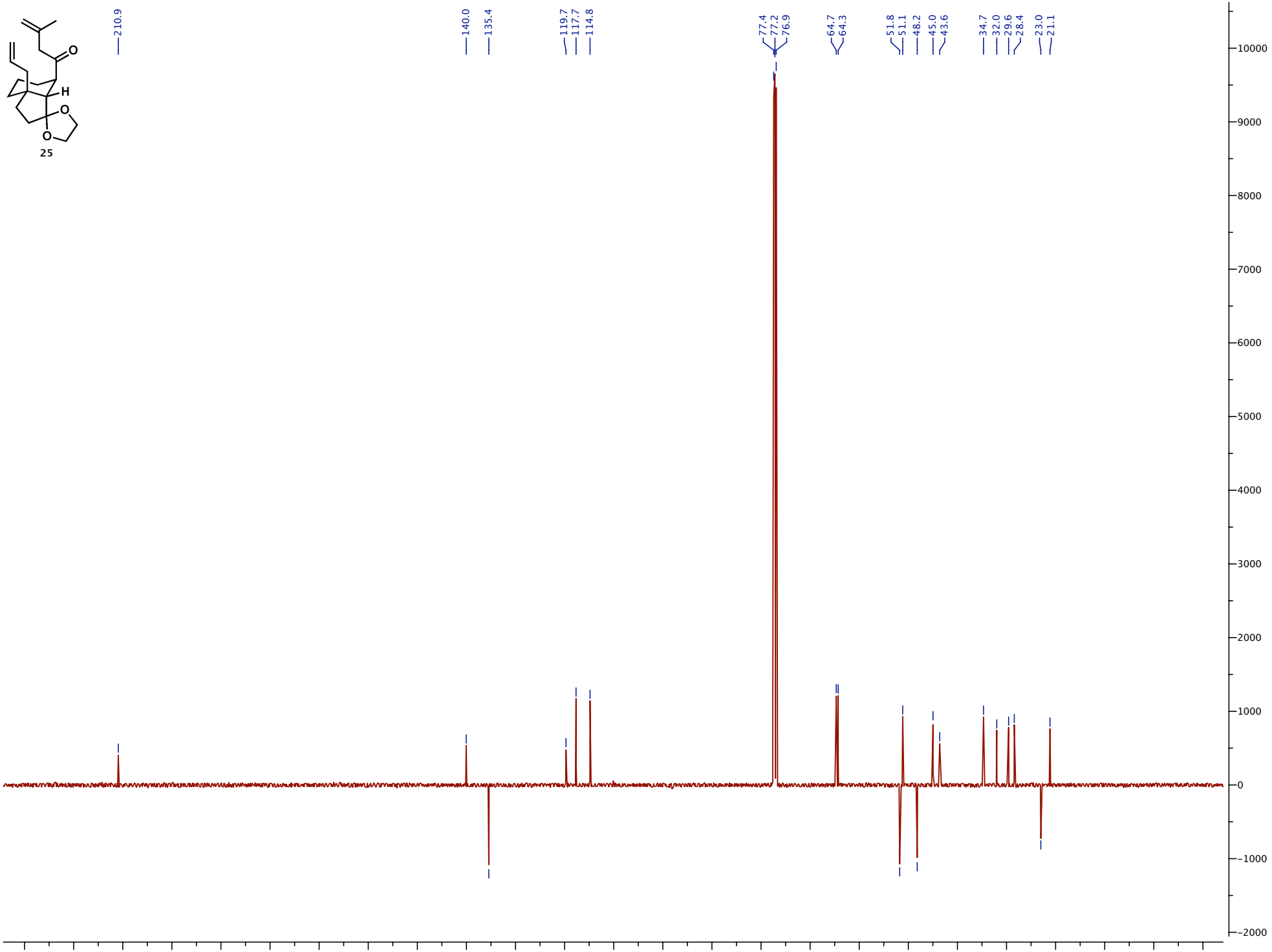

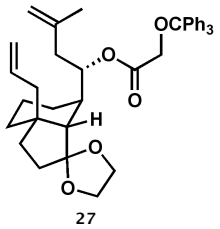


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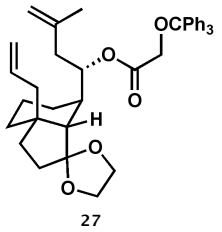


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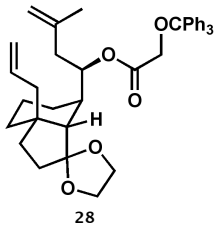


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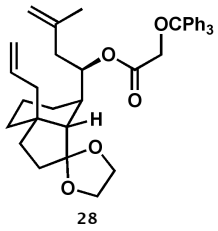


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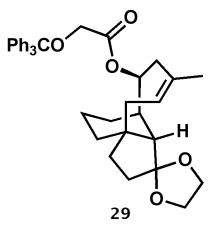


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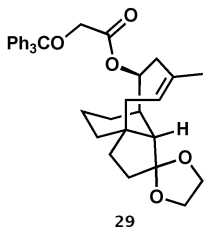


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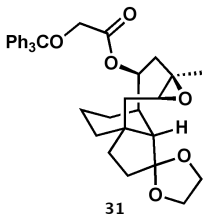
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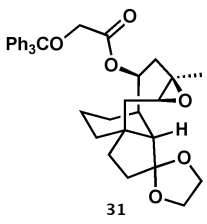

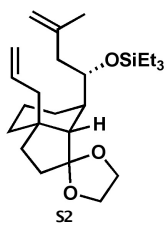


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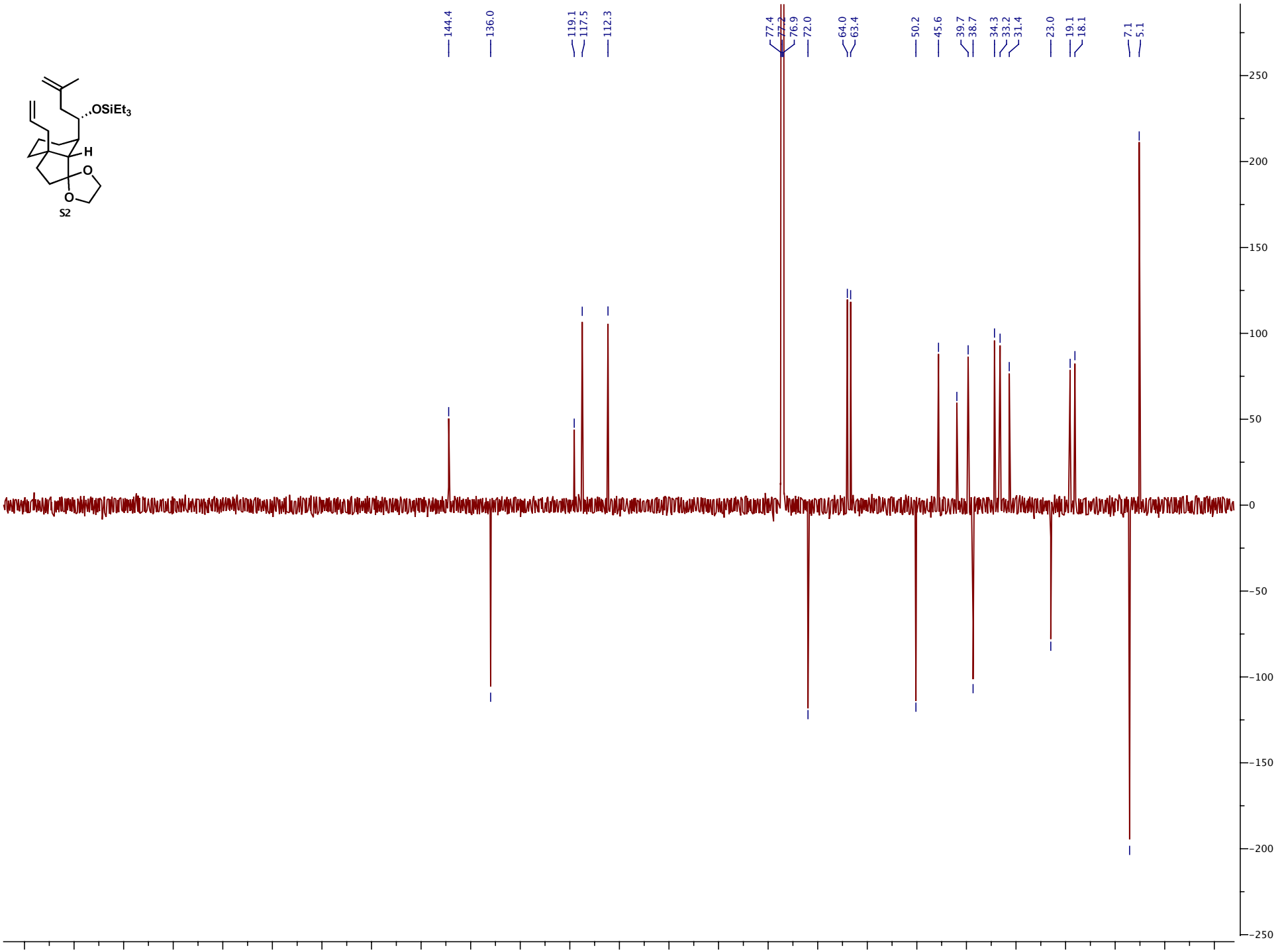

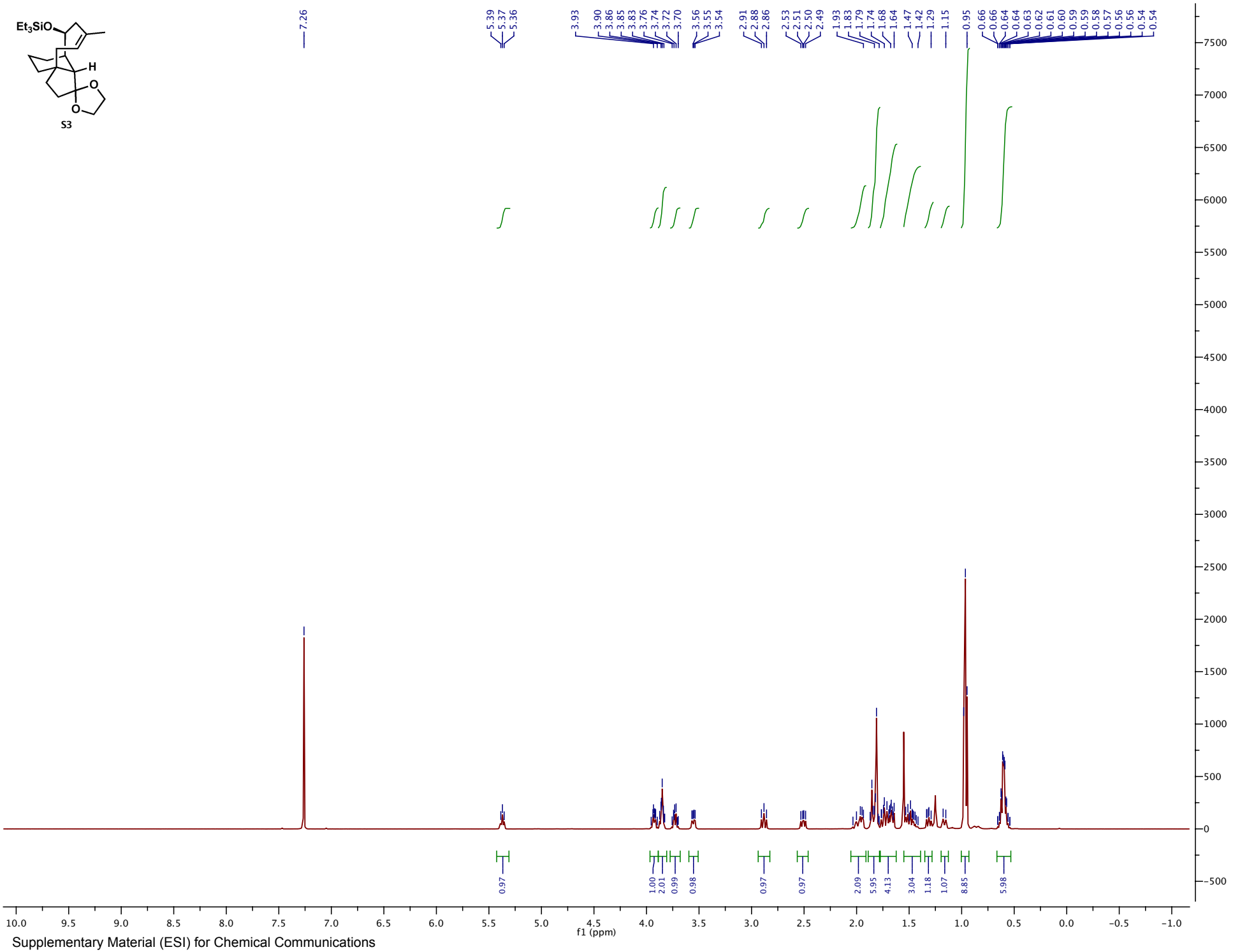

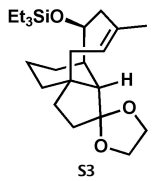


S3