A General Approach to the Synthesis of 19-*nor*-Vitamin D_3 and its Cyclic Phosphate Analogs Prepared from Cyclohexadienyl Sulfone.

Vikas Sikervar, James C. Fleet*, Philip L. Fuchs*

Department of Chemistry, Purdue University, West Lafayette, Indiana 47907.

Department of Foods and Nutrition Chemistry, Purdue University, West Lafayette, Indiana 47907.

Email: pfuchs@purdue.edu

Supporting Information

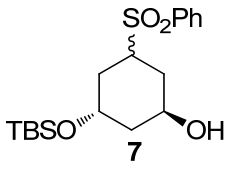
GENERAL PROCEDURES

Tetrahydrofuran (THF) was distilled from benzophenone ketyl. Sodium sulfate (Na_2SO_4) was anhydrous. Unless otherwise indicated, all reactions were carried out under in a positive pressure of Argon in anhydrous solvents and the reaction flasks were fitted with rubber septa for the introduction of substrates and reagents via syringe. Progress of reactions was monitored by thin layer chromatography (TLC) using silica gel plates. The TLC plates were visualized with a UV lamp (254 nm) and/or with TLC visualizing solutions activated with heat. The two commonly employed TLC visualizing solutions were: (i) *p*-anisaldehyde solution (1350mL absolute ethanol, 50mL concentrated H_2SO_4, 37mL *p*-anisaldehyde), and (ii) permanganate solution (weight percents of 1% $KMnO_4$ and 2% Na_2CO_3 in water).

^{1}H NMR and ^{13}C NMR spectra were recorded on 300-500 MHz. The NMR spectra were determined in CDCl3 solution. Peak multiplicities in ^{1}H-NMR spectra, when reported, are abbreviated as s (singlet), d (doublet), t (triplet), m (multiplet), and/or quint (quintet). Mass spectra were run by the Purdue University campus wide mass spectrometry facility.

EXPERIMENTALS

Preparation of **7**:



7

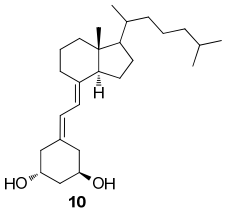
To a -78 °C solution of epoxyvinyl sulfone **6** (200 mg, 0.55 mmol) in THF (6 mL) was added $LiBH_4$ (3.0 equiv, 1.65 mmol, 1.65 mL of 1.0 M THF solution). The reaction mixture was slowly allowed to warm to room temperature and stirred for 8 h and then quenched with water and extracted with diethyl ether. The combined extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The residues were purified on silica gel using 1:3 Ethyl Acetate/Hexane to give the desired alcohol **7** in 81 % yield and 2.8:1 dr. (164 mg).

^{1}H NMR ($CDCl_3$, 300 MHz): 7.86 (1H, d, J= 9 Hz), 7.65 (1H, t, J= 9Hz), 7.55 (2H, t, J= 9 Hz), 4.32 (1H, s), 3.96 (1H, m), 3.37 (1H, m), 2.35 – 1.23 (6H, m), 0.85 (9H, s), 0.02 (6H, s).

^{13}C NMR ($CDCl_3$, 75 MHz): 136.9, 136.7, 133.7, 129.1, 129.0, 128.8, 66.4, 67.0, 66.4, 66.2, 57.4, 41.5, 41.3, 34.4, 33.8, 32.2, 31.6, 25.7, 25.6, 18.0, 17.8, -4.8, -5.1, -5.3.

HRMS (CI) calculated for $C_{18}H_{30}O_4SSi$ (M+H), 371.1712 found 371.1717.

Preparation of **10**:



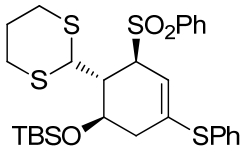
10

To a -78 °C solution of alcohol **7** (40 mg, 0.11 mmol) in THF (0.5 mL) was added BuLi (2.0 equiv, 0.22 mmol, 88 µL of 2.5M hexane solution). The reaction mixture was slowly allowed to warm to 0 ^oC over a period of 1 h and then cooled back to -78 ^oC. Allyl chloride **8** (1.1 equiv) dissolved in 0.2 mL HMPA was added drop wise to the reaction mixture. The reaction mixture was slowly allowed to warm to room temperature over a period of 3 h and then quenched by adding water (10 µL). TBAF (10 equiv, 1.1 mmol, 1M in THF) was added and

the reaction mixture heated at 65 ^{o}C for 8 h after which it is quenched with 5 mL of water and extracted with diethyl ether (10 mL). The combined extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was purified on silica gel using 1:1 Ethyl Acetate/Hexane to give the diol **10** in 70 % yield (29 mg).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.31 (1H, d, J= 10 Hz), 5.85 (1H, d, J= 10Hz), 4.11 (1H, m), 4.03 (1H, m), 2.73 (2H, m), 2.47 (1H, d, J= 10 Hz), 2.19 (2H, m), 2.01 – 1.01 (21H, m), 0.92 (3H, d, J= 5Hz), 0.88 (3H, d, J= 2.5 Hz), 0.87 (3H, d, J= 2.5 Hz), 0.55 (3H, s).
^{13}C NMR ($CDCl_3$, 500 MHz) δ 143.2, 131.0, 123.9, 115.2, 67.4, 67.2, 56.6, 56.3, 45.8, 44.6, 42.2, 40.5, 39.5, 37.2, 36.1, 29.0, 28.0, 27.6, 23.8, 23.5, 22.8, 22.6, 22.3, 18.8, 12.1 HRMS (CI) calculated for $C_{26}H_{44}O_2$ (M+) 388.3341, found 388.3347

Preparation of **14:**



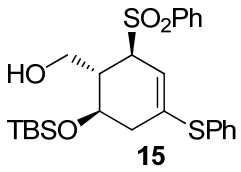
14

1,3-dithaine (223 mg, 1.86 mmol) was dissolved in THF (5 mL) and cooled to – 10 ^{o}C. BuLi (0.74 mL, 2.5 M solution in hexane, 1.86 mmol) was added and reaction mixture left stirring for 30 minutes at -10 ^{o}C and then further cooled to – 78 ^{o}C. Dienyl sulfone **12** (500 mg, 1.43 mmol) was dissolved in THF (3 mL) and added dropwise to the above solution and reaction mixture left stirring at the same temperature for 1 h. Diphenyl disulfide (218 mg, 2.79 mmol) dissolved in THF (1 mL) was added to the above reaction mixture and the reaction mixture gradually warmed to room temperature over 5 h and then quenched by adding water and extracted with ether (50 mL). The combined extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was purified on silica gel using 1:4 Ethyl Acetate/Hexane to give the vinyl sulfide **14** in 80% yield (661 mg).

^{1}H NMR ($CDCl_3$, 400 MHz): 7.83(2H, d, J = 4.0 Hz), 7.61 (1H, t, J= 8 Hz), 7.50(2H, t, J= 8Hz), 7.40- 7.31 (5H, m), 5.26 (1H, d, J= 4 Hz), 4.40 (1H, d, J = 4.0 Hz), 4.18 (1H, dd, J= 4 Hz, 8 Hz), 3.99 (1H, dd, J= 8 Hz, 16 Hz), 2.88- 2.75 (6H, m), 2.06 (2H, d, J= 8 Hz), 1.87- 1.76 (1H, M), 0.87 (9H, s), 0.10 (3H, s), -0.06 (3H, s).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 141.7, 137.9, 133.6, 133.5, 131.1, 129.3, 129.2, 128.9, 128.4, 114.7, 68.7, 66.4, 51.6, 45.5, 36.5, 31.0, 25.8, 17.9, -4.3, -4.5. HRMS (CI) calculated for $C_{28}H_{38}O_3S_4Si$ (M+Na) 601.1371 found 601.1366.

Preparation of **15:**



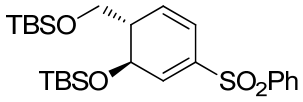
15

To a suspension of HgO (300 mg, 1.38 mmol) in THF/ H_2O (5 mL, 5:1) was added $BF_3.OEt_2$ (196 mg, 0.17 mL, 1.38 mmol) and reaction mixture stirred for 10 min. Vinyl sulfide **14** (400 mg, 0.69 mmol) dissolved in THF (3 mL) was added to the above suspension and reaction mixture heated to 75 ^oC for 30 min. and then diluted with H_2O (20 mL) and extracted with ether (50 mL). The combined extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was dissolved in MeOH (10mL) and reaction mixture cooled to 0 ^oC and $NaBH_4$ (78.7 mg, 2.07 mmol) was added in small portions over 30 minutes and reaction mixture stirred for an additional 2.5 h. The reaction mixture was then quenched by adding NH_4Cl and extracted with ether (50 mL). The combined extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was purified on silica gel using 1:2 Ethyl Acetate/Hexane to give the alcohol **15** in 72% yield (243 mg).

^{1}H NMR ($CDCl_3$, 400 MHz): 7.80 (2H, d, J = 8.0 Hz), 7.67 (2H, t, J= 8 Hz), 7.54 (3H, t, J= 8 Hz), 7.38 (5H, s), 5.38 (1H, d, J= 4 Hz), 4.18 (1H, d, J= 8 Hz), 4.08 (1H, d, J=8 Hz), 3.99 (1H, d, J= 12 Hz), 3.77 (1H, t, J= 4 Hz, 12 Hz), 2.06 (2H, m), 1.84 (1H, m), 0.87 (9H s), 0.07 (3H, s), 0.02 (3H, s)

^{13}C NMR ($CDCl_3$, 100 MHz): δ 140.3, 136.4, 133.7, 133.6, 130.9, 129.3, 129.2, 128.9, 128.9, 128.6, 115.3, 68.1, 64.8, 60.3, 43.1, 37.7, 25.6, 17.8, -4.4, -5. HRMS (ESI) calculated for $C_{25}H_{34}O_4S_2Si$ (M+Na), 513.1566, found 513.1561.

Preparation of **16:**

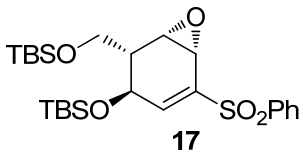


16

Alcohol **15** (200 mg, 0.41 mmol) was dissolved in DCM (20 mL) and Et_3N (373 mg, 0.51 mL, 3.69 mmol) followed by TBSOTf (130 mg, 0.11 mL, 0.492 mmol) was added at 0 ^oC and solution left stirring for 1 h. TMSOTf (456 mg, 0.37 mL, 2.05 mmol) was added drop wise and then solution refluxed for 8 h and finally quenched by adding H_2O (200 mL). The organic phase is separated and cooled to 0 ^oC and MCPBA (460 mg, 2.05 mmol) is added portion wise over 3 h and reaction mixture stirred for another 8 h and then quenched by adding saturated aq. $NaHSO_3$ (10 mL). The organic phase is separated and washed with saturated aq. $NaHCO_3$ (20 mL). The combined extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was purified on silica gel using 1:4 Ethyl Acetate/Hexane to give the dienyl sulfone **16** in 74% yield (202 mg).

^1H NMR ($CDCl_3$, 300 MHz): 7.87 (1H, d, J= 9 Hz), 7.49 (3H, m), 6.76 (1H, s), 6.08 (1H, d, J= 12 Hz), 5.94 (1H, dd, J= 6 Hz, 9 Hz), 4.63 (1H, dd, J= 3 Hz, 9 Hz), 3.53 (1H, m), 3.43 (1H, m), 2.57 (1H, brs), 0.89 (9H, s), 0.87 (9H, s), 0.12 (3H, s), 0.09 (3H, s), 0.02 (6H, s)
^{13}C NMR ($CDCl_3$, 75 MHz): δ 139.4, 137.9, 136.6, 133.4, 132.7, 129.2, 127.8, 118.1, 66.7, 61.7, 45.2, 25.8, 25.7, 18.2, 17.9, - 4.36, - 4.85, -5.46, -5.56.
HRMS (ESI) calculated for $C_{25}H_{42}O_4S_2Si$ (M+Na), 517.2240 found 517.2248.

Preparation of **17:**



17

Dienyl sulfone **16** (510 mg, 1.03 mmol) was dissolved in MeCN/H_2O (10 mL, 10:1) and $NaHCO_3$ (519 mg, 6.18 mmol) was added to it and the reaction mixture cooled to 0 ^oC. 1,1,1 - trifluoroacetone (346 mg, 0.28 mL, 3.09 mmol) was added and Oxone (1.90 g, 3.09 mmol) added over 1 hr and reaction mixture stirred for another 2 h and then diluted by adding water (20 mL) and DCM (50 mL). The organic phase was separated and combined

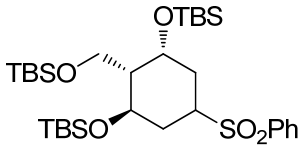
extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was purified on silica gel using 1:4 Ethyl Acetate/Hexane to give the epoxide **17** in 6:1 dr and in 75% yield (394 mg).

^{1}H NMR ($CDCl_3$, 300 MHz): 7.89(2H, d, J = 9.0 Hz), 7.64-7.48 (3H, m), 6.92 (1H, s), 4.10 (1H, d, J= 12 Hz), 3.99 (1H, dd, J= 3 Hz, 9 Hz), 3.75 (1H, dd, J= 6 Hz, 3.68 (1H, dd, J= 2 Hz, 4 Hz), 3.61 (1H, d, J= 6 Hz), 1.82 (1H, m), 0.89 (9H, s), 0.87 (9H, s), 0.10 (3H, s), 0.06 (6H, s)

^{13}C NMR ($CDCl_3$, 75 MHz): δ 145.3, 139.1, 137.8, 133.7, 129.4, 127.9, 66.2, 61.9, 53.6, 45.7, 43.0, 25.7, 25.5, 18.1, 17.7, 4.6, 5.1, 5.6.

HRMS (ESI) calculated for $C_{25}H_{42}O_5SSi_2$ (M+Na) 533.2189 found 533.2192.

Preparation of sulfone **4:**



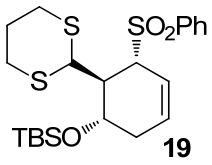
4

Epoxide **17** (300 mg, 0.59 mmol) was dissolved in THF (10 mL) and cooled to -78 ^{o}C. $LiBH_4$ (1.8 mL, 1M solution in THF, 1.77 mmol) was added dropwise and reaction mixture gradually allowed to warm to room temperature over a period of 10 h and then quenched by adding NH_4Cl. The reaction mixture was diluted with ether (30 mL), organic phase separated and combined extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was dissolved in DCM (10 mL) and cooled to 0 ^{o}C and Et_3N (119 mg, 0.16 mL, 1.18 mmol) followed by TBSOTf (156 mg, 0.14 mL, 0.59 mmol) was added and reaction mixture quenched by adding water after 1 h. The organic phase was separated and combined extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was purified on silica gel using 1:5 Ethyl Acetate/Hexane to give the sulfone **4** with >90% purity and in 56% yield (208 mg).

^{1}H NMR ($CDCl_3$, 400 MHz): 7.86 (2H, d, J= 8.0 Hz), 7.64 (1H, t, J= 8 Hz), 7.54(2H, t, J=8 Hz), 5.82 (1H, s), 5.22 (1H, s), 4.36 (1H, d, J = 2.4Hz), 4.10 (1H, s), 1.81 (1H, m), 1.06(1H, d, J = 6.9 Hz), 0.693(9H, s,), -0.452(3H, s), -0.044(3H, s). ^{13}C NMR ($CDCl_3$, 300 MHz): δ 137.2,

133.6, 129.0, 128.8, 67.0, 66.2, 60.1, 57.4, 52.1, 33.2, 33.1, 25.8, 25.6, 18.1, 17.8, 17.7, - 4.2, - 5.1, - 5.2, -5.4, -5.5 HRMS (ESI) calculated for $C_{31}H_{60}O_5SSi_3$ (M+Na) 651.3367 found 651.3359.

Preparation of allyl sulfone **19:**



19

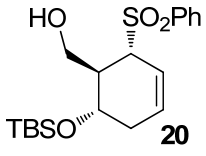
1,3-dithaine (223 mg, 1.86 mmol) was dissolved in THF (5 mL) and cooled to – 10 °C. n-BuLi (0.74 mL, 2.5 M solution in hexane, 1.86 mmol) was added and reaction mixture left stirring for 30 minutes at -10 °C and then further cooled to – 78 °C. Dienyl sulfone **18** (500 mg, 1.43 mmol) was dissolved in THF (3 mL) and added dropwise to the above solution and reaction mixture left stirring at the same temperature for 1 h and then quenched by adding water and extracted with ether (50 mL). The combined extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was purified on silica gel using 1:4 Ethyl Acetate/Hexane to give the allyl sulfone **19** in 83% yield (558 mg).

^{1}H NMR ($CDCl_3$, 300 MHz): 7.89 (2H, d, J= 9.0 Hz), 7.61 (1H, t, J= 9 Hz), 7.51 (2H, t, J=9 Hz), 5.96 (1H, m), 5.57 (1H, m), 4.32 (1H, d, J= 3 Hz), 4.18 (1H, t, J=3 Hz), 3.98 (1H, m), 2.75 (6H, m), 2.04 (1H, m), 1.8 (2H, m), 0.90 (9H, s), 0.15 (3H, s), 0.06 (3H, s)

^{13}C NMR ($CDCl_3$, 75 MHz): δ 137.9, 133.6, 133.2, 129.4, 128.8, 119.7, 67.7, 64.6, 51.6, 45.5, 32.0, 31.0, 30.8, 25.9, 18.0, -4.3.

HRMS (ESI) calculated for $C_{22}H_{34}O_3S_3Si$ (M+Na), 493.1337 found 493.1344. .

Preparation of allyl sulfone **20:**



20

To a suspension of HgO (300 mg, 1.38 mmol) in THF/ H_2O (5 mL, 5:1) was added $BF_3.OEt_2$ (196 mg, 0.17 mL, 1.38 mmol) and reaction mixture stirred for 10 min. Allyl sulfone **19** (324 mg, 0.69 mmol) dissolved in THF (3 mL) was added to the above suspension and reaction mixture heated to 75 °C for 30 min. and then diluted with H_2O (20 mL) and extracted with ether (50 mL). The combined extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was dissolved in MeOH (10 mL)

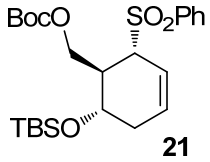
and reaction mixture cooled to 0 ^{o}C and $NaBH_4$ (78.7 mg, 2.07 mmol) was added in small portions over 30 minutes and reaction mixture stirred for an additional 2.5 h. The reaction mixture was then quenched by adding NH_4Cl and extracted with ether (50 mL). The combined extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was purified on silica gel using 1:2 Ethyl Acetate/Hexane to give the alcohol **20** in 77% yield (264 mg).

^{1}H NMR ($CDCl_3$, 400 MHz): 7.85 (2H, d, J= 8.0 Hz), 7.63 (1H, t, J=8.0 Hz), 7.52 (2H, d, J= 8Hz), 5.84 (1H, t, J= 8 Hz), 5.64 (1H, d, J= 12 Hz), 4.13 (1H, d, J= 8 Hz), 4.02 (2H, d, J= 4 Hz), 3.72 (1H, dt, J= 8 Hz, 12 Hz), 2.13 (1H, td, J= 8 Hz, 16 Hz), 1.91 (1H, t, J= 12 Hz), 1.68 (1H, t, J= 12 Hz), 0.86 (9H, s), 0.07 (3H, s), 0.03 (3H, s).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 136.4, 133.8, 131.9, 129.4, 128.8, 120.4, 67.8, 64.3, 60.1, 43.6, 33.8, 25.7, 17.8, -4.3, -5.1.

HRMS (ESI) calculated for $C_{19}H_{30}O_4SSi$ (M+H) 383.1712 found 383.1708.

Preparation of allyl sulfone **21:**



21

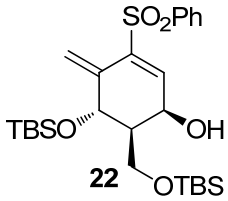
Alcohol **20** (50 mg, 0.13 mmol) was dissolved in DCM (1mL) and DMAP (3 mg, 0.03 mmol) followed by Pyridine (31 mg, 31 µl, 0.39 mmol) was added to it. The reaction mixture was cooled to 0 ^{o}C and $(Boc)_2O$ (57 mg, 0.26 mmol) was added and the reaction mixture warmed to room temperature and left stirring for 3 h. The reaction mixture was directly loaded on the silica gel column and purified by using Ethyl Acetate/Hexane (1:4) to give the allyl sulfone **21** in 90% yield (56 mg).

^{1}H NMR ($CDCl_3$, 400 MHz): 7.86 (2H, d, J= 8 Hz), 7.65 (1H, t, J= 8 Hz), 7.54 (2H, t, J= 8 Hz), 5.86 (1H, t, J= 8 Hz), 5.65 (1H, d, J= 8Hz), 4.47 (2H, s), 4.18 (1H, d, J= 8 Hz), 3.78 (1H, dt, J= 4 Hz, 12 Hz), 2.16 (1H, td, J= 8 Hz, 16 Hz), 2.06 (1H, t, J= 8 Hz), 1.69 (1H, t, J=12 Hz), 1.48 (3H, s), 0.86 (9H, s), - 0.02 (3H, s), -0.01 (3H, s)

^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.1, 136.6, 133.8, 131.8, 129.5, 128.9, 120.4, 82.0, 66.2, 63.9, 63.8, 41.3 33.8, 27.8, 25.7, 17.9, -4.4, -5.3.

HRMS (ESI) calculated for $C_{24}H_{38}O_6SSi$ (M+Na) 505.2056 found 505.2063.

Preparation of alcohol **22:**



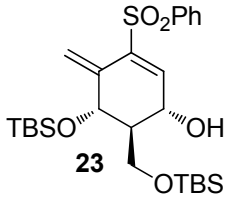
To a -10 °C suspension of trimethylsulfonium iodide (82 mg, 0.40 mmol) in THF (0.6 mL) was added *n*-BuLi (0.15 mL of 2.5 M hexane solution, 0.37 mmol). After 30 min, the solution was cooled to -78 ^{0}C and epoxide **17** (50 mg, 0.10 mmol) in THF (0.6 mL) was introduced. The reaction was left stirring for 1 h and then quenched with water and extracted with diethyl ether (10 mL). The combined extracts were washed with brine, dried over magnesium sulfate, filtered, and concentrated under vacuum. The residues were purified on silica gel using Ethyl Acetate/Hexane (1:3) to give the desired alcohol **22** in 52 % yield (27 mg).

^{1}H NMR ($CDCl_3$, 300 MHz): 7.84 (2H, d, J= 9.0 Hz), 7.55 (1H, t, J= 9 Hz), 7.46 (2H, t, J= 9 Hz), 7.25 (1H, s), 5.91 (1H, s), 5.22 (1H, s), 4.93 (1H, s), 4.06 (1H, d, J= 3 Hz), 3.79 (1H, d, J= 6 Hz), 3.57 (1H, t, J= 9 Hz), 2.36 (1H, m), 0.89 (9H, s), 0.74 (9H, s), 0.08 (3H, s), 0.06 (3H, s), -0.03 (3H, s), - 0.33 (3H, s).

^{13}C NMR ($CDCl_3$, 125 MHz): δ142.0, 139.9, 136.2, 136.3, 133.1, 128.9, 127.8, 117.6, 73.9, 68.0, 61.7, 46.3, 25.7, 25.5, 18.0, 17.8, 1.0, -4.8, -5.1, -5.7.

HRMS (ESI) calculated for $C_{26}H_{44}O_5SSi_2$ (M+Na), 547.2346 found 547.2343.

Preparation of allyl sulfone **23:**



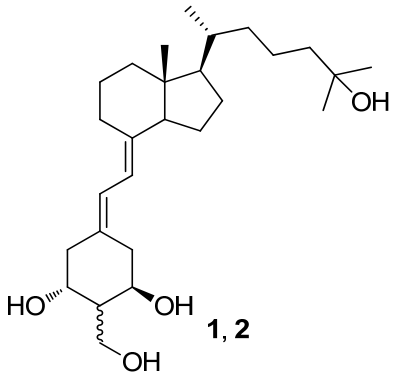
To a 0 °C solution of alcohol **22** (25 mg, 0.05 mmol) in THF (1 mL) was added DEAD (26 mg, 24µl, 0.15 mmol) and PPh_3 (40 mg, 0.15 mmol) followed by HCOOH (3.5 mg, 3µl, 0.075 mmol). The reaction mixture was left stirring for 5 h and then quenched by adding 5 mL of saturated solution of Na_2CO_3. The solution was left stirring for an additional 2 h and then extracted with diethyl ether (10 mL). The combined extracts were washed with brine, dried over magnesium sulfate, filtered, and concentrated under vacuum. The residues were purified on silica gel column using Ethyl Acetate/Hexane (1:3) to give the desired allylic alcohol **23** in 65 % yield (16 mg).

^{1}H NMR ($CDCl_3$, 500 MHz): 7.88 (2H, d, J= 7.0 Hz), 7.58 (1H, t, J= 7 Hz), 7.49 (2H, t, 7 Hz), 7.20 (1H, d, J= 5 Hz), 6.05 (1H, s), 5.28 (1H, s), 4.28 (1H, d, J = 5 Hz), 4.24 (1H, t, J= 3.5 Hz), 3.42 (1H, d, J= 10 Hz), 2.36 (1H, m), 0.88 (9H, s), 0.75 (9H, s), 0.04 (3H, s), 0.02 (3H, s), -0.06 (3H, s), -0.33 (3H, s).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 139.6, 138.5, 137.0 134.8, 133.3, 129.0, 128.1, 119.1, 73.7, 67.4, 62.4, 48.8, 25.8, 25.6, 18.1, 17.9, -4.9, -5.4, -5.6.

HRMS (ESI) calculated for $C_{26}H_{44}O_5SSi_2$ (M+Na), 547.2346 found 547.2343.

Preparation of tetrol **1,2**:



1, 2

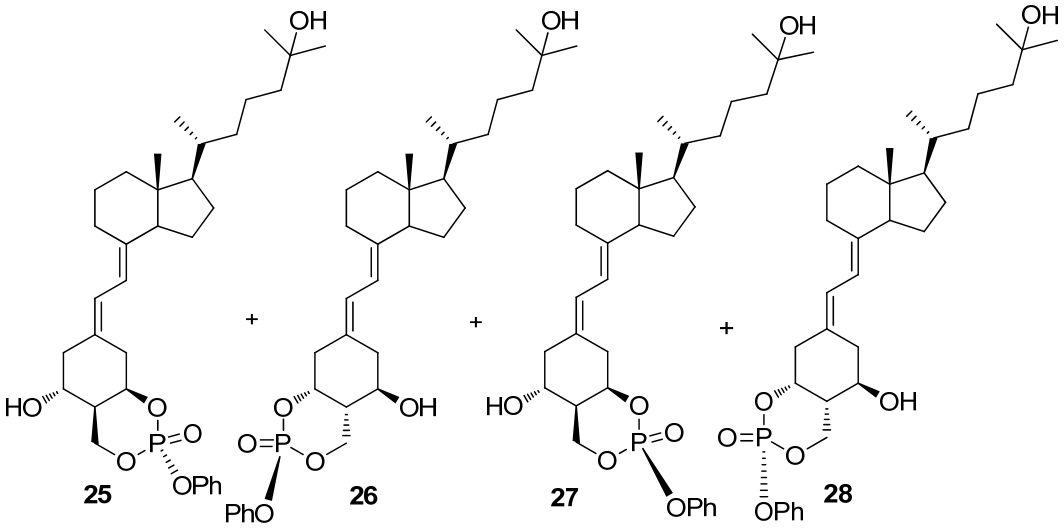
To a -78 °C solution of sulfone **4** (60 mg, 0.10 mmol) in THF (0.3 mL) was added *n*-BuLi (44 µL of 2.5M hexane solution, 0.11 mmol) and yellow solution left stirring for 30 min. Allyl Chloride (48 mg, 0.11 mmol) dissolved in HMPA (0.1 mL) was added drop wise to the reaction mixture. The reaction mixture was slowly allowed to warm to room temperature over a period of 6h. TBAF (1 mL, 1M solution in THF, 1.0 mmol) was added and the reaction mixture heated at 65 ^{o}C for 8 h after which it is quenched with 5 mL of water and extracted with diethyl ether (10 mL). The combined extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was purified on silica gel using 4:1 Ethyl Acetate/Hexane to give the tetrol **1** and **2** in 76 % yield and 2:1 dr (32 mg).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.39 (1Ha, d, J= 10 Hz), 6.24 (1Hb, d, J= 10Hz), 5.88 (1Hb, d, J= 10 Hz), 5.79 (1Ha, d, J= 10 Hz), 4.24 (1Ha, s), 4.16 (1Hb, s), 4.02 (3Ha, m), 3.92 (3Hb, m), 3.17 – 0.90 (64 H), 0.53 (3Ha + 3Hb, d, J= 6 Hz).

^{13}C NMR ($CDCl_3$, 125 MHz) δ 143.2, 143.1, 130.9, 130.8, 124.2, 123.6, 115.3, 115.2, 71.4, 71.1, 68.6, 68.3, 64.4, 64.1, 56.5, 56.3, 53.7, 49.7, 45.7, 45.4, 44.4, 44.1, 40.4, 37.5, 36.3, 36.1, 35.7, 29.3, 29.1, 29.0, 28.7, 27.7, 23.5, 23.4, 22.3, 20.8, 18.8, 14.1, 12.1, 12.0.

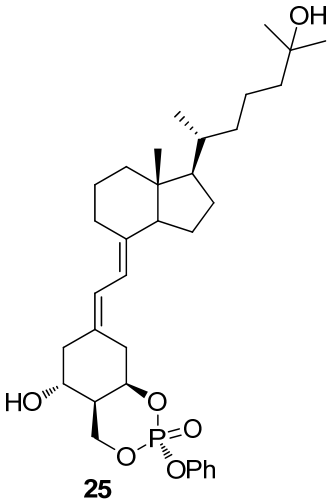
HRMS (ESI) calculated for $C_{27}H_{46}O_4$ (M+Na) 457.3294, found 457.3298.

Preparation of cyclic phosphates **25**, **26**, **27**, **28**:



To a -20 °C solution of 1:1 mixture of tetrol **1, 2** (50 mg, 0.12 mmol) in DCM (1.0 mL) was added Pyridine (57 mg, 58 µL, 0.72 mmol) followed by Phenyl dichlorophosphate (25mg, 18 µL, 0.12 mmol). The solution was left stirring for 1 h at -20 ^{o}C and at room temperature for 6 h and then directly loaded on silica gel column and purified using CH_3CN/DCM (1:5) to give the mixture of phosphate **25** and **26** (which were separated on HPLC column to give **25** (9 mg) and **26** (15.5 mg) and **27** (6.4 mg), **28** (10 mg) in 60 % yield.

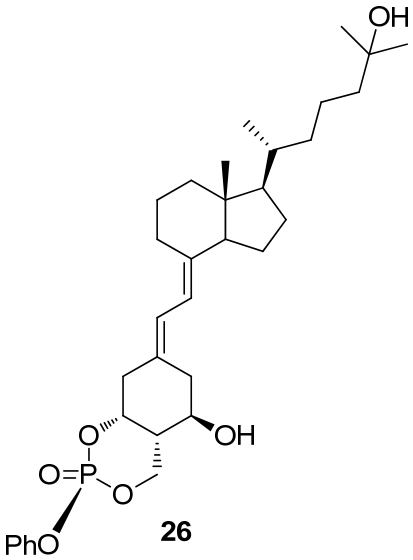
Phosphonate **25**:



25

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34 (2H, t, J= 8 Hz), 7.27 (1H, m), 7.17 (2H, m, 7 Hz), 6.34 (1H, d, J= 11 Hz), 5.85 (1H, d, J= 11 Hz), 4.57 (2H, m), 4.34 (1H, m), 4.07 (1H, m), 3.29 (1H, dd, J= 5 Hz, 14 Hz), 2.78 (1H, dd, J= 5 Hz, 13 Hz), 2.54 (1H, d, J= 14 Hz), 2.38 (1H, d, J= 13 Hz), 2.15 (1H, t, J= 12 Hz), 2.02 (2H, d, J= J= 11 Hz), 1.90 (2H, m), 1.68 (2H, m), 1.49 – 1.27 (10 H, m), 1.23 (6H, s), 1.06 (2H, m), 0.96 (3H, d, J= 6 Hz), 0.83 (2H, m), 0.56 (3H, s). 31P (200 MHz): δ -13.05. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 143.7, 129.9, 127.6, 125.0, 124.3, 119.5, 115.2, 79.6 (d, J (P, H) = 7 Hz), 71.1, 68.4 (d, J (P, H) = 6 Hz), 64.5, 56.5, 56.2, 45.7, 44.4, 43.7 (d, J (P, H) = 4 Hz), 41.5 (d, J (P, H) = 9 Hz), 40.4, 37.4, 36.4, 36.1, 29.7, 29.3, 29.2, 29.0, 27.7, 23.5, 22.3, 20.8, 18.8, 12.0. HRMS (ESI) calculated for $C_{33}H_{49}O_6P$ (M+Na) 595.3168, found 595.3168.

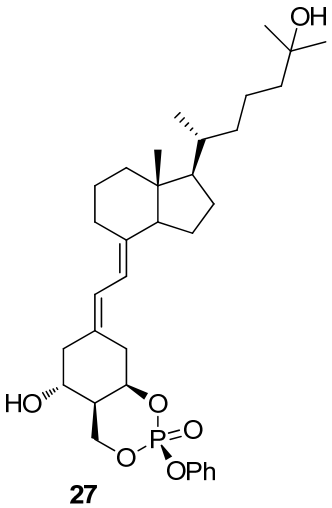
Phosphonate **26**:



26

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34 (2H, t, J= 8 Hz), 7.18 (3H, m), 6.50 (1H, d, J= 11Hz), 5.75 (1H, d, J= 11 Hz), 4.69 (2H, m), 4.36 (1H, m), 4.04 (1H, s), 3.67 (1H, m), 2.98 (1H, d, J= 14 Hz), 2.79 (1H, dd, J= 5 Hz, 14 Hz), 2.33 (1H, t, J= 13 Hz), 2.10 (1H, d, J= 14 Hz), 2.02 (1H, d, J= 10 Hz), 1.87 (1H, m), 1.68 – 1.26 (12 H, m), 1.23 (6H, s), 1.06 (1H, m), 0.94 (3H, d, J= 6 Hz), 0.83 (1H, m), 0.54 (3H, s). 31P (200 MHz): δ -10.61. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 150.5, 145.1, 129.7, 126.8, 126.1, 125.4, 120.3, 114.8, 77.9 (d, J (P, H) = 6 Hz), 71.1, 70.6 (d, J (P, H) = 7 Hz), 66.5, 56.5, 56.3, 45.9, 44.8 (d, J (P, H) = 7 Hz), 44.4, 43.8, 40.4, 36.3 (d, J (P, H) = 7 Hz), 36.1, 35.3, 29.7, 29.3, 29.2, 29.0, 27.7, 23.6, 22.2, 20.8, 18.8, 12.0. HRMS (ESI) calculated for $C_{33}H_{49}O_6P$ (M+Na) 595.3168, found 595.3168.

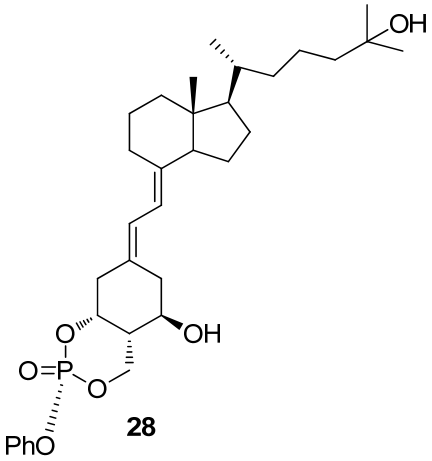
Phosphonate **27**:



27

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34 (2H, t, J= 10 Hz), 7.19 (3H, m), 6.32 (1H, d, J= 11 Hz), 5.83 (1H, d, J= 11 Hz), 4.68 (1H, dt, J= 6 Hz, 12 Hz), 4.62 (1H, dt, J= 6 Hz, 11 Hz), 4.35 (1H, m), 3.99 (1H, s), 3.33 (1H, dd, J= 5 Hz, 12 Hz), 2.76 (1H, d, J= 12 Hz), 2.46 (1H, d, J= 15 Hz), 2.35 (1H, d, J= 14 Hz), 2.12 – 1.91 (4H, m), 1.68 (2H, m), 1.51 – 1.27 (10H, m), 1.23 (6H, s), 1.06 (2H, m), 0.95 (3H, d, J= 6 Hz), 0.82 (2H, m), 0.55 (3H, s). 31P (200 MHz): δ -10.40. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 150.4, 145.0, 129.8, 127.1, 126.0, 125.0, 119.6, 114.9, 78.8 (d, J(P, H) = 7 Hz), 71.2 (d, J (P, H) = 7 Hz), 71.1, 66.8, 56.5, 56.3, 46.0, 45.1 (d, J(P, H) = 7 Hz), 44.4, 44.0, 40.4, 36.3, 36.0, 35.0 (d, J (P, H) = 9 Hz), 29.7, 29.4, 29.2, 29.1, 27.6, 23.6, 22.2, 20.7, 18.8, 12.0. HRMS (ESI) calculated for $C_{33}H_{49}O_6P$ (M+Na) 595.3168, found 595.3168.

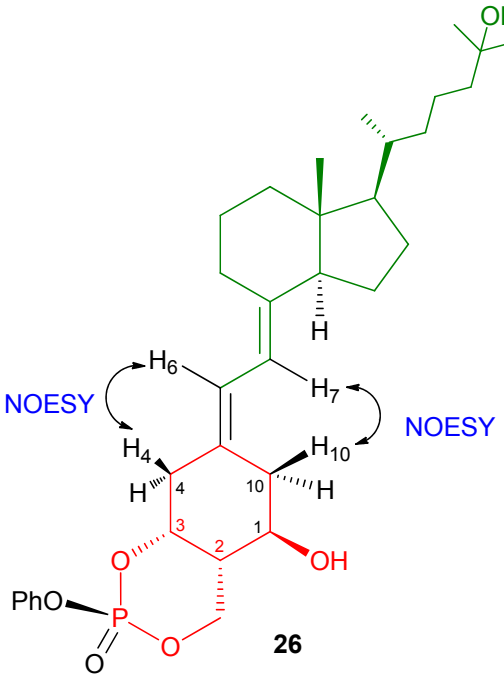
Phosphonate **28**:



28

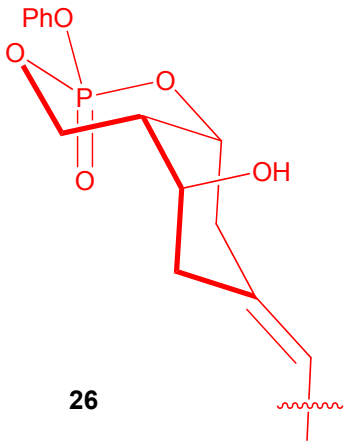
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.34 (2H, t, J= 8 Hz), 7.27 (1H, m), 7.17 (2H, t, J= 8 Hz), 6.50 (1H, d, J= 12 Hz), 5.76 (1H, d, J= 12 Hz), 4.66 (1H, dt, J= 5 Hz, 11 Hz), 4.61 (1H, t, J= 11 Hz), 4.37 (1H, m), 4.15 (1H, s), 3.66 (1H, m), 2.99 (1H, d, J= 15 Hz), 2.77 (1H, m), 2.45 (1H, t, J= 12 Hz), 2.17 (1H, d, J= 14 Hz), 2.01 (1H, d, J= 11 Hz), 1.90 (1H, m), 1.68 (1H, d, J= 11 Hz), 1.49 - 1.26 (10H, m), 1.23 (6H, s), 1.06 (2H, m), 0.94 (3H, d, J= 6 Hz), 0.82 (2H, m), 0.54 (3H, s). 31P (200 MHz): δ -13.04. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 150.5, 145.2, 129.8, 126.8, 125.1, 119.5, 114.6, 79.1 (d, J (P, H) = 8 Hz), 71.3 (d, J (P, H) = 7 Hz), 71.1, 67.1, 56.5, 56.3, 45.9, 45.1 (d, J (P, H) = 6 Hz), 44.4, 42.9 (d, J (P, H) = 9 Hz), 40.3, 36.3, 36.1, 35.8, 29.7, 29.4, 29.2, 29.0, 27.6, 23.4, 22.2, 20.8, 18.8, 12.1. HRMS (ESI) calculated for $C_{33}H_{49}O_6P$ (M+Na) 595.3168, found 595.3168

Structural assignments for cyclic phosphate analogs of 19-*nor*-Vitamin D_3:

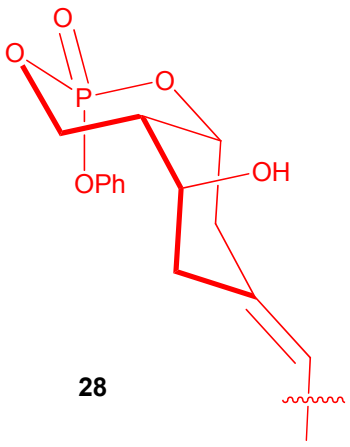


26

COSY spectra of all the four compounds **25**, **26**, **27** and **28** were recorded which helped identify the protons at C-1, C-2, C-3, C-4 and C-10. NOESY spectra of the compounds showed the correlation between H_7 and H_{10}. Correlation was also seen between H_4 and H_6 in the NOESY spectra. These NMR results confirmed the ring structures in the respective molecules. To confirm the stereochemistry at the phosphorus stereo-center, 31P spectra were recorded for all the four compounds. As already reported in literature,[1] the axial P-O bond results in an upfield shift in the 31P spectra, this lead to the assignment for the cyclic phosphate analogs **25**, **26**, **27** and **28**. (Figure 1)



26



28

[1] (a) Riley, A. M.; Guedat, P.; Schlewer, G.; Spiess, B.; Potter, B. V. L. *J. Org. Chem.* **1998**, *63*, 295. (b) Xu, H.; Zhang, J.; Liu, H.; Wang, J. *Synthetic communications*, **2006**, *36*, 407. (c) Hoeve, W. T.; Wynberg, H. *J. Org. Chem.*, **1985**, *23*, 4508.

Figure 1: Axial P-O vs. equatorial P-O bond (CD rings not shown).

Cell culture experiment:

Cells were seeded in 12 well dishes (100,000 cells/well for Caco-2; 50,000 cells/well for SW480-ADH) and studied when they reached 70-80% confluence (3 days in culture). Cells were treated with 1,25 dihydroxyvitamin D or analogs in high glucose DMEM supplemented with Pen/Strep but without fetal bovine serum (FBS). Cell culture conditions have been previously described by our group.[2] Vitamin D compounds were diluted in ethanol and used at three concentrations: 1 nM, 10 nM, and 100 nM. Ethanol control groups were included for all of the three treatments but total ethanol levels in the medium were 0.001, 0.01, and 0.1% for the three treatment groups, respectively. Four replicate wells were used for each of the vitamin D compounds. Six hours after the treatment started, medium was removed and cells were harvested directly into TriReagent (Molecular Research Center, Inc., Cincinnati, OH). RNA was isolated, converted to cDNA, and analyzed by real-time PCR for mRNA levels for the two target genes using methods previously described.[3] Data were normalized to the expression level of the control gene RPLP0. Primers for human CYP24 and RPLPO have been described previously[4] and the primers for E-Cadherin are: Forward $^{5'}$GATTGCAAATTCCTGCCATT$^{3'}$; Reverse: $^{5'}$GCTGGCTCAAGTCAAAGTCC$^{3'}$.

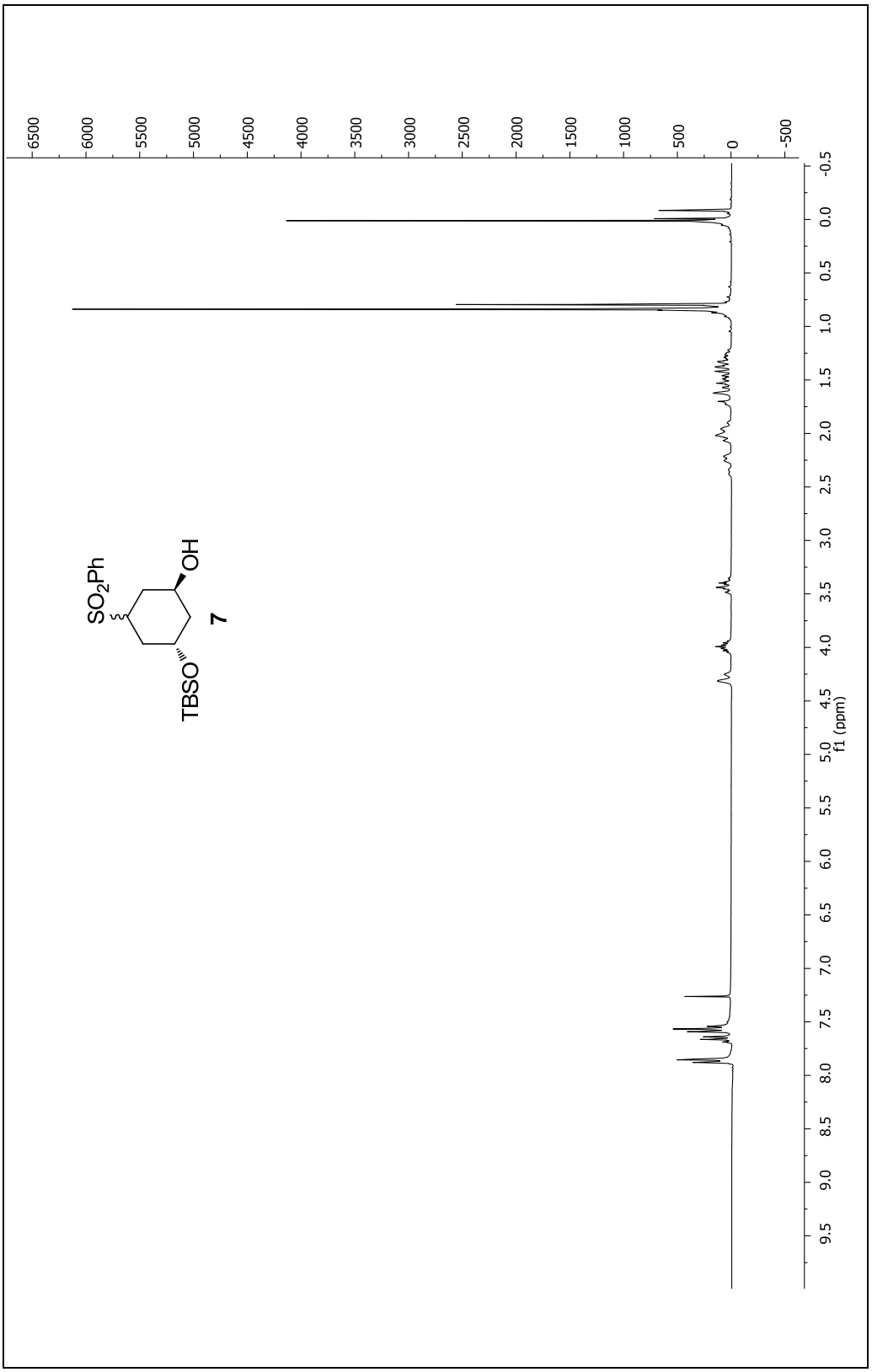
Table 1: Caco-2 Summary:

Treatment	1 nM	SEM	10 nM	SEM	100 nM	SEM
Ethanol	1.00	0.08	0.92	0.10	1.19	0.20
1,25D	233.31	57.10	1479.96	305.84	1417.24	216.53
33	1.25	0.27	1.28	0.21	1.32	0.16
32	0.85	0.26	1.21	0.10	1.60	0.37
34	1.26	0.18	1.38	0.50	5.04	0.36
35	2.00	0.17	1.82	0.20	3.31	0.36

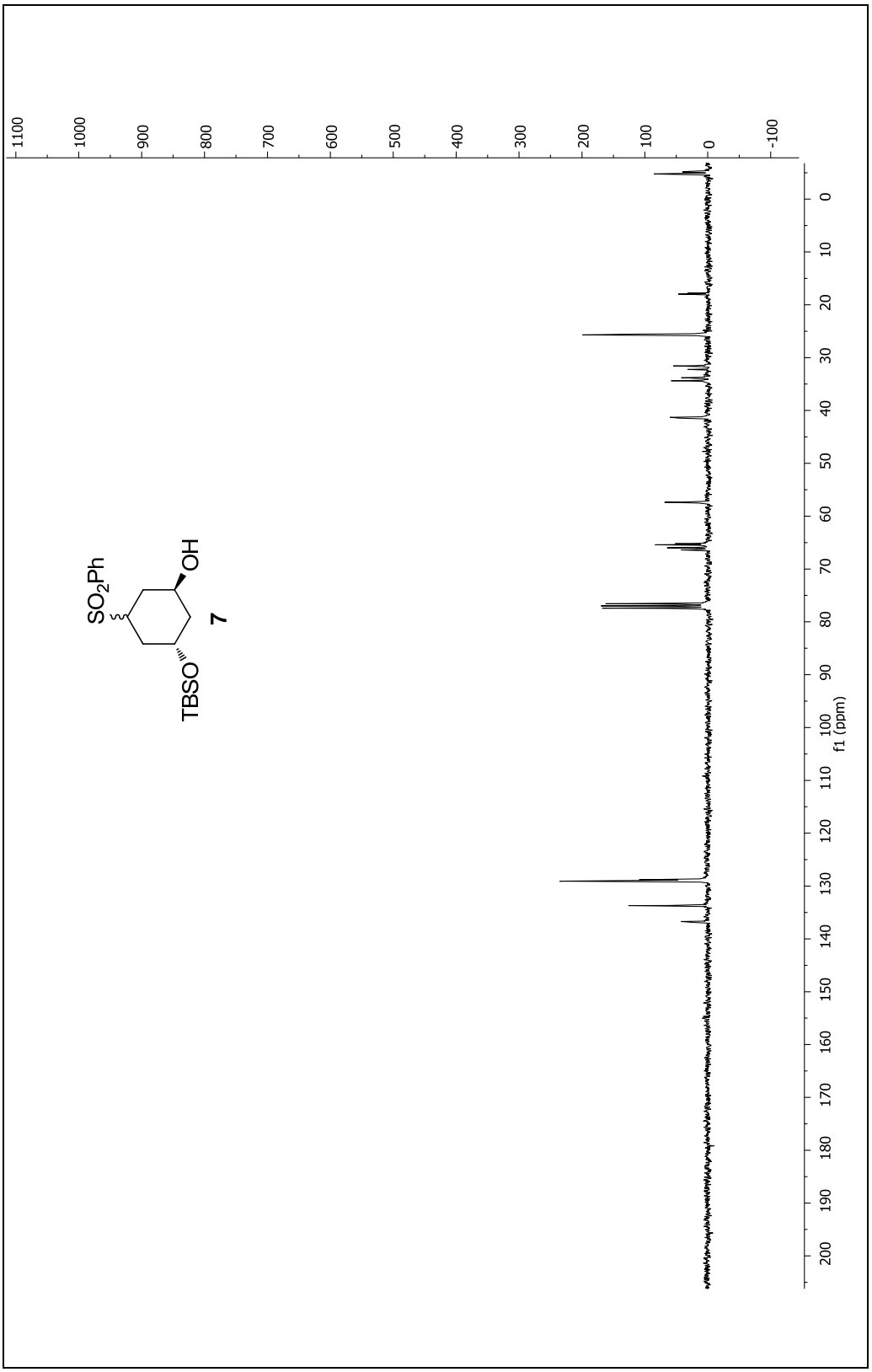
Table 2: SW480 ADH Summary:

[2] Fleet, J.C., DeSmet, M., Johnson, R., Li, Y. *Biochemical Journal*, **2012**, 61-76.
[3] Cui, M., Klopot, A., Jiang, Y. and Fleet, J.C. *J. Cell Physiol.*, **2009**, 113.
[4] Kovalenko, P.L., Zhang, Z., Cui, M., Clinton, S.K., Fleet, J.C. *BMC Genomics*, **2009**, *11*, 26.

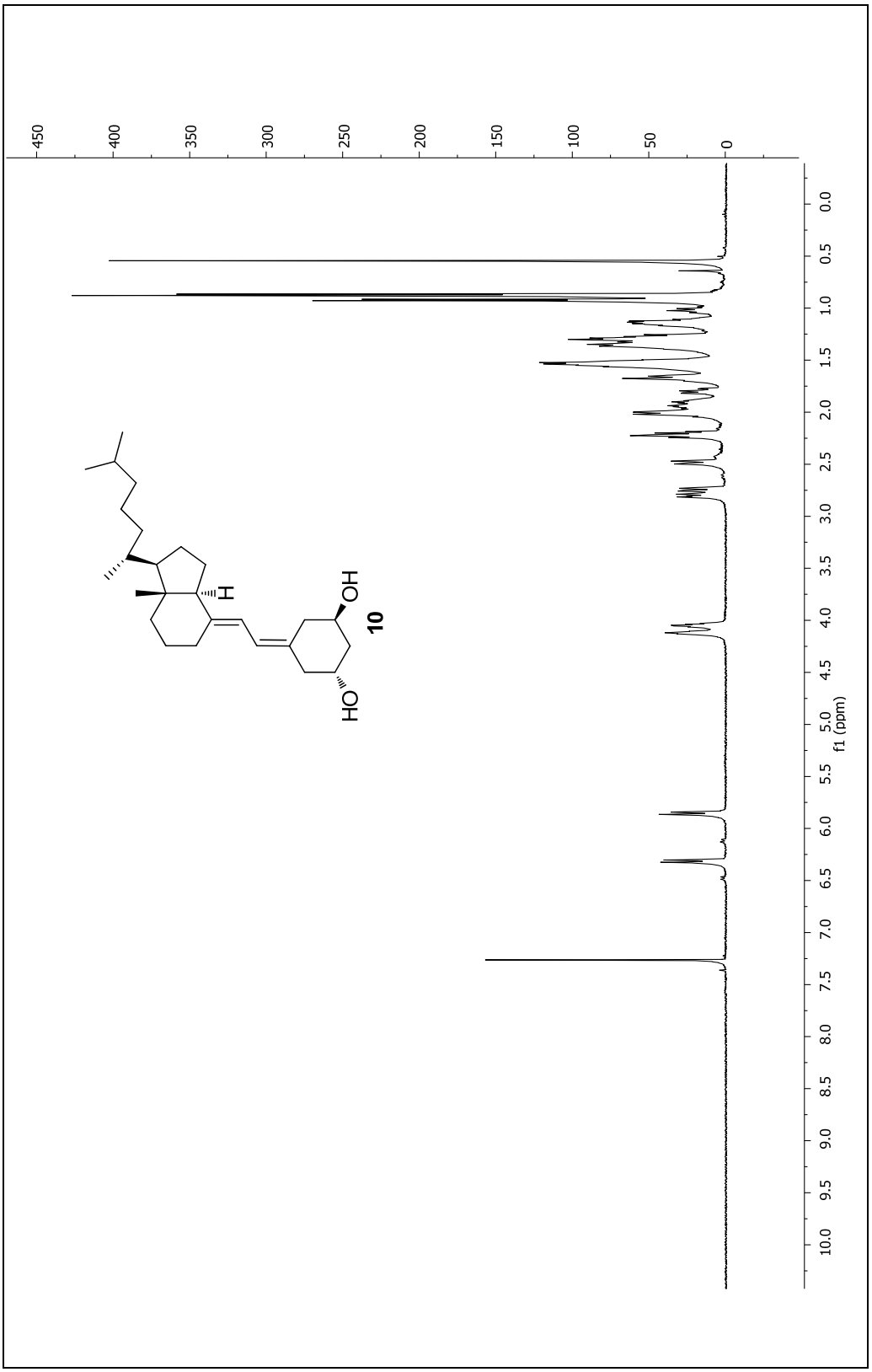
SW480 ADH Summary Table		CYP24			E-Cadherin		
Compound	Dose (nM)	Mean	SD	SEM	Mean	SD	SEM
ethanol	1	1.00	0.15	0.08	1.00	0.07	0.03
	10	1.03	0.19	0.09	1.07	0.43	0.22
	100	1.12	0.71	0.35	1.07	0.37	0.18
1,25(OH)2 D	1	653.35	92.18	46.09	6.57	0.99	0.50
	10	1380.02	211.28	105.64	11.36	2.65	1.32
	100	634.80	257.35	128.68	4.97	1.16	0.58
33	1	0.79	0.22	0.11	1.05	0.31	0.15
	10	1.45	0.34	0.17	1.09	0.33	0.16
	100	23.54	6.37	3.68	1.92	0.59	0.34
32	1	0.89	0.18	0.09	0.87	0.32	0.16
	10	1.10	0.22	0.11	0.94	0.07	0.04
	100	3.95	0.50	0.25	1.06	0.30	0.15
34	1	1.07	0.22	0.11	0.73	0.39	0.19
	10	23.51	1.79	0.89	1.17	0.23	0.11
	100	650.31	119.53	59.77	6.11	2.89	1.45
35	1	1.19	0.47	0.24	1.36	0.77	0.38
	10	6.55	1.43	0.72	1.42	0.24	0.12
	100	429.01	42.71	24.66	5.89	0.46	0.26



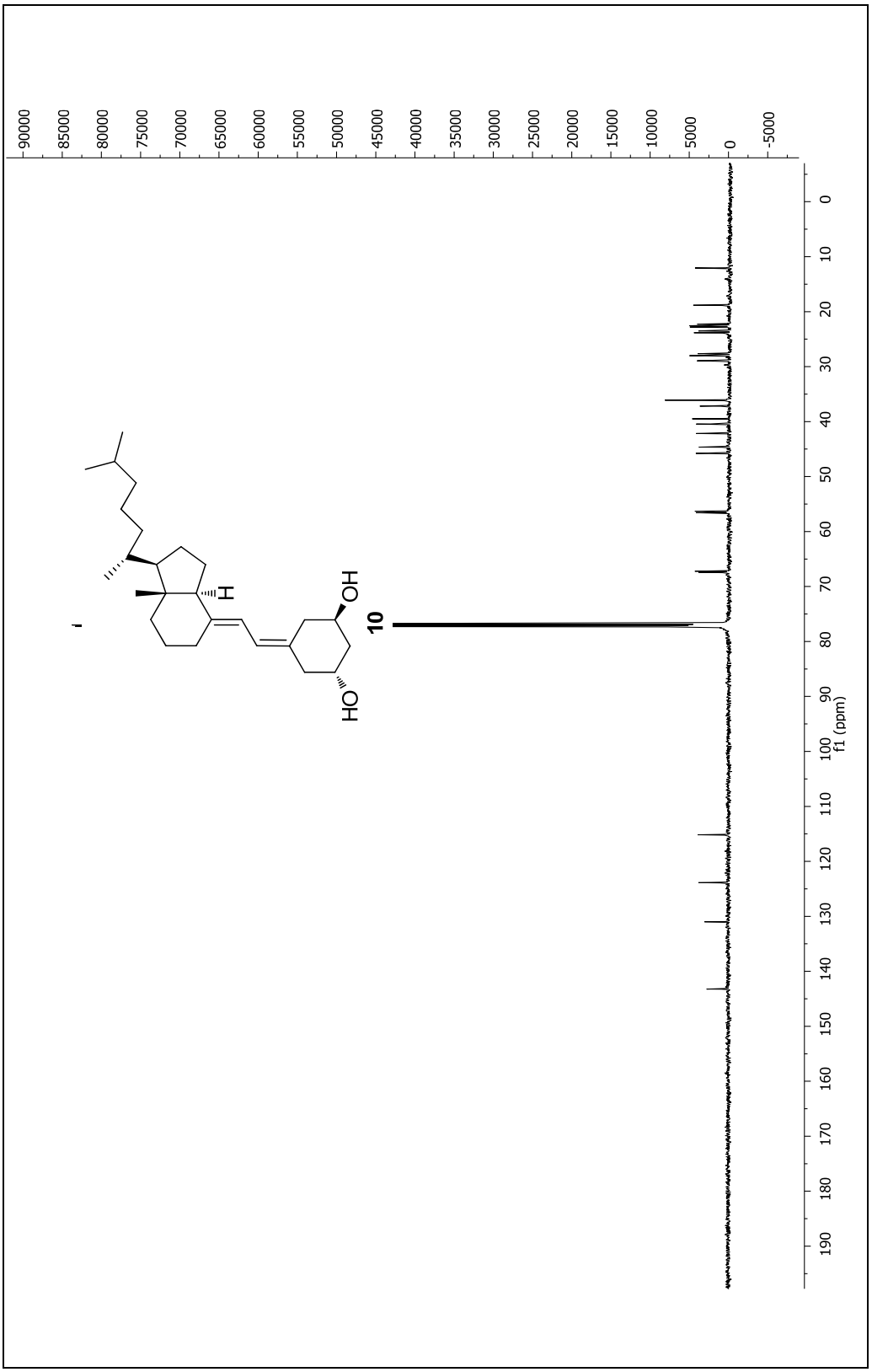
300 MHz ^{1}H NMR of compound **7** in $CDCl_3$



75 MHz ^{13}C NMR of compound **7** in $CDCl_3$

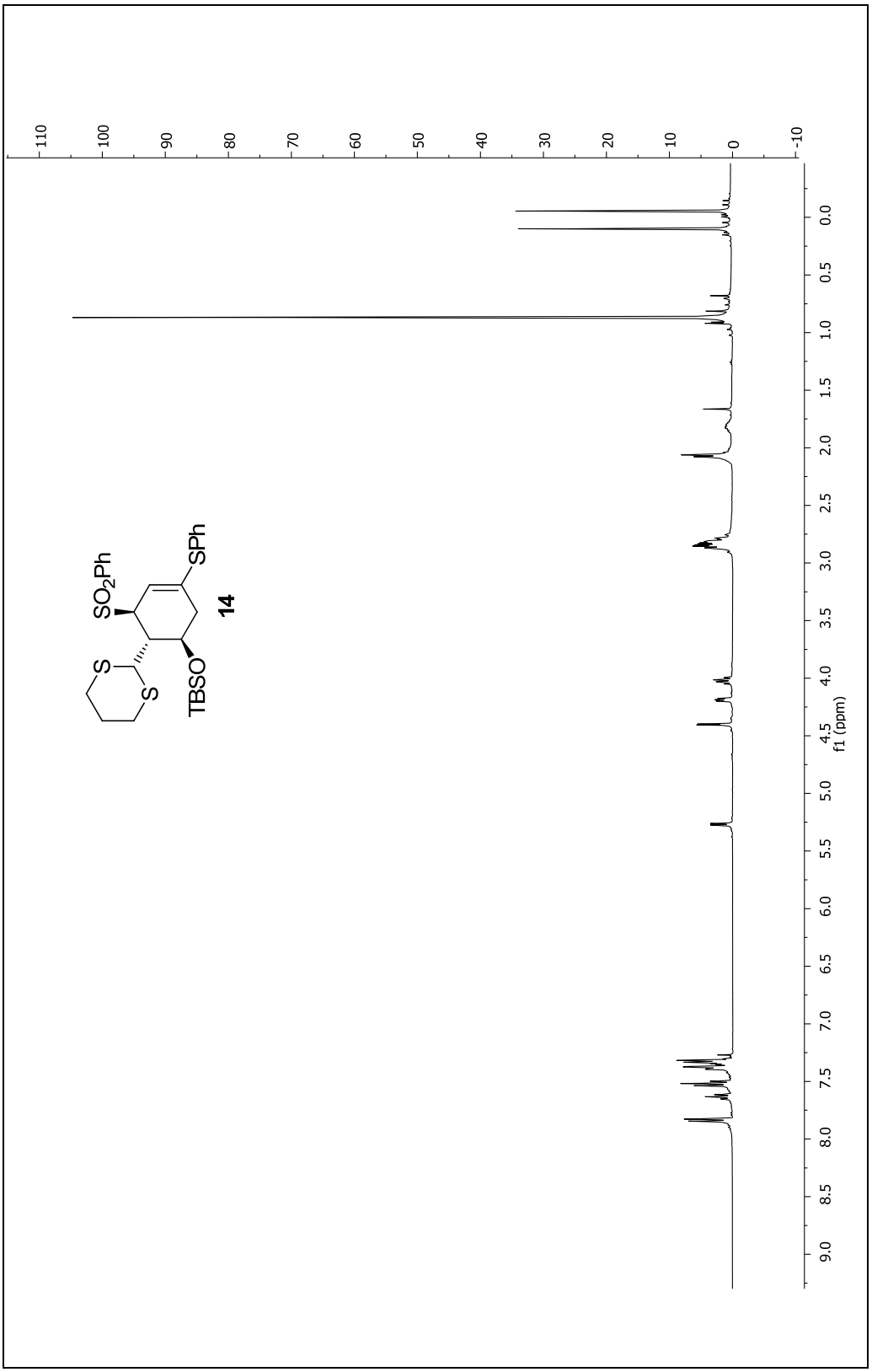


500 MHz ^{1}H NMR of compound **10** in $CDCl_3$

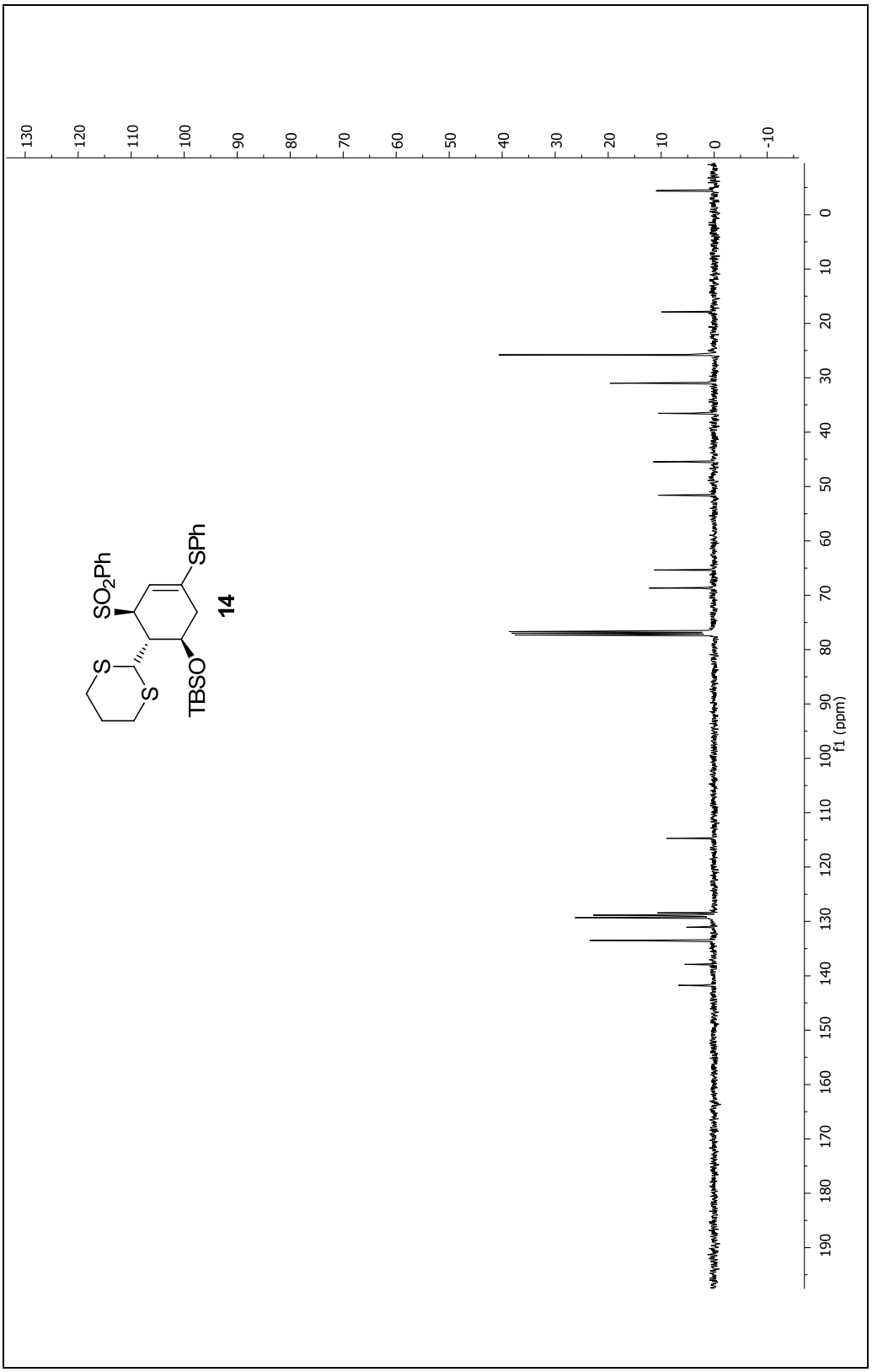


21

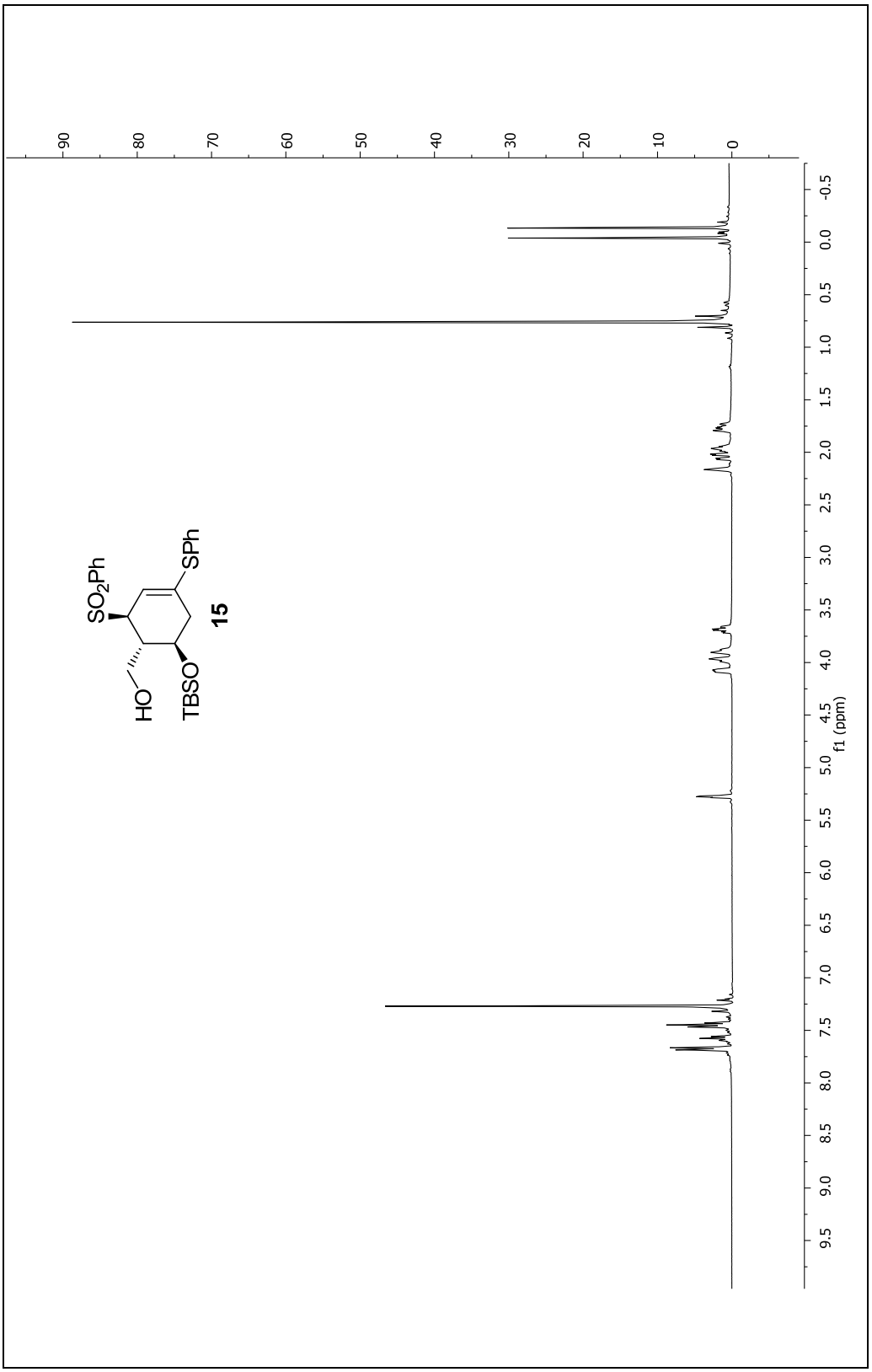
125 MHz ^{13}C NMR of compound **10** in $CDCl_3$



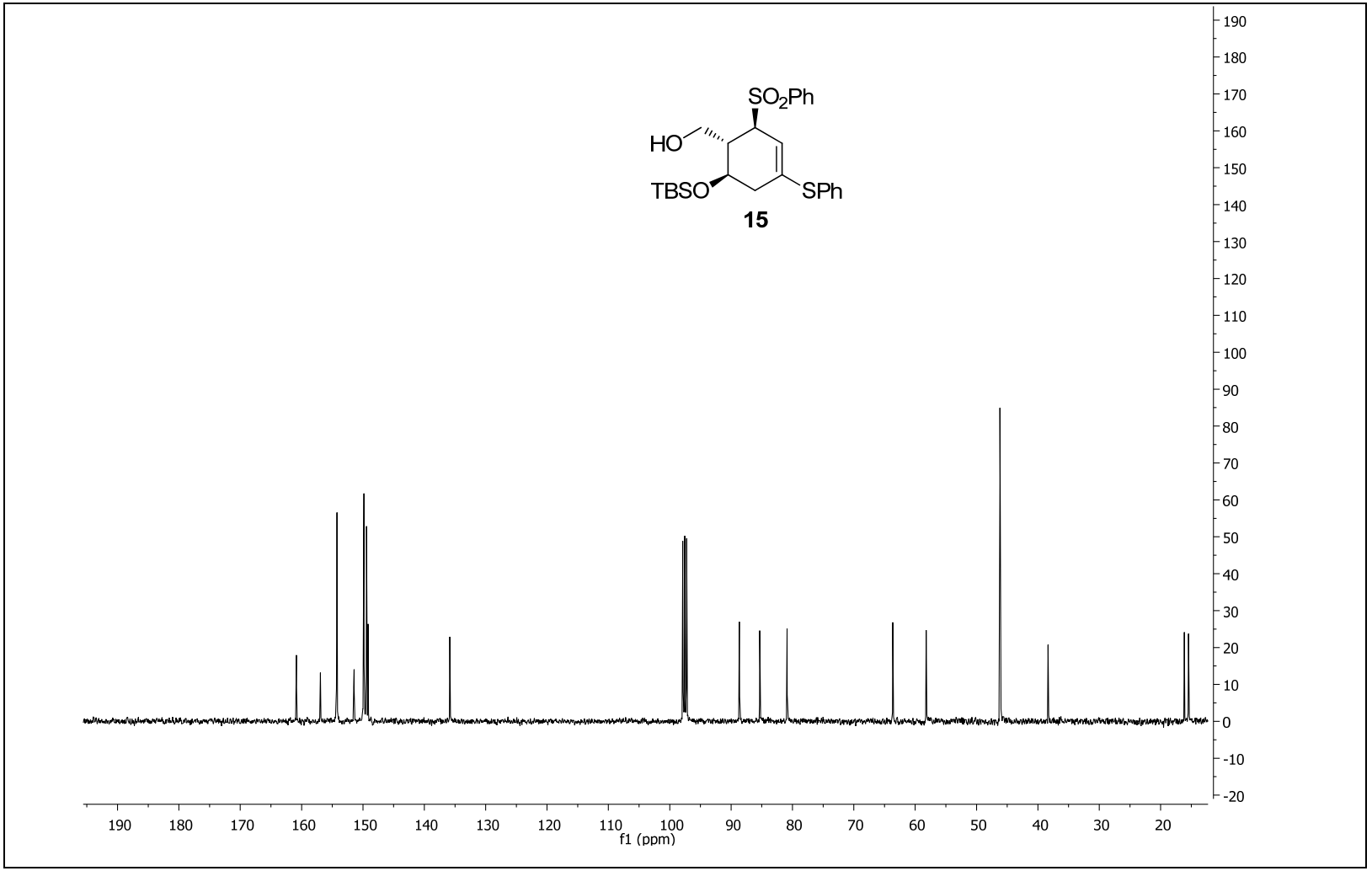
400 MHz ^{1}H NMR of compound **14** in $CDCl_3$



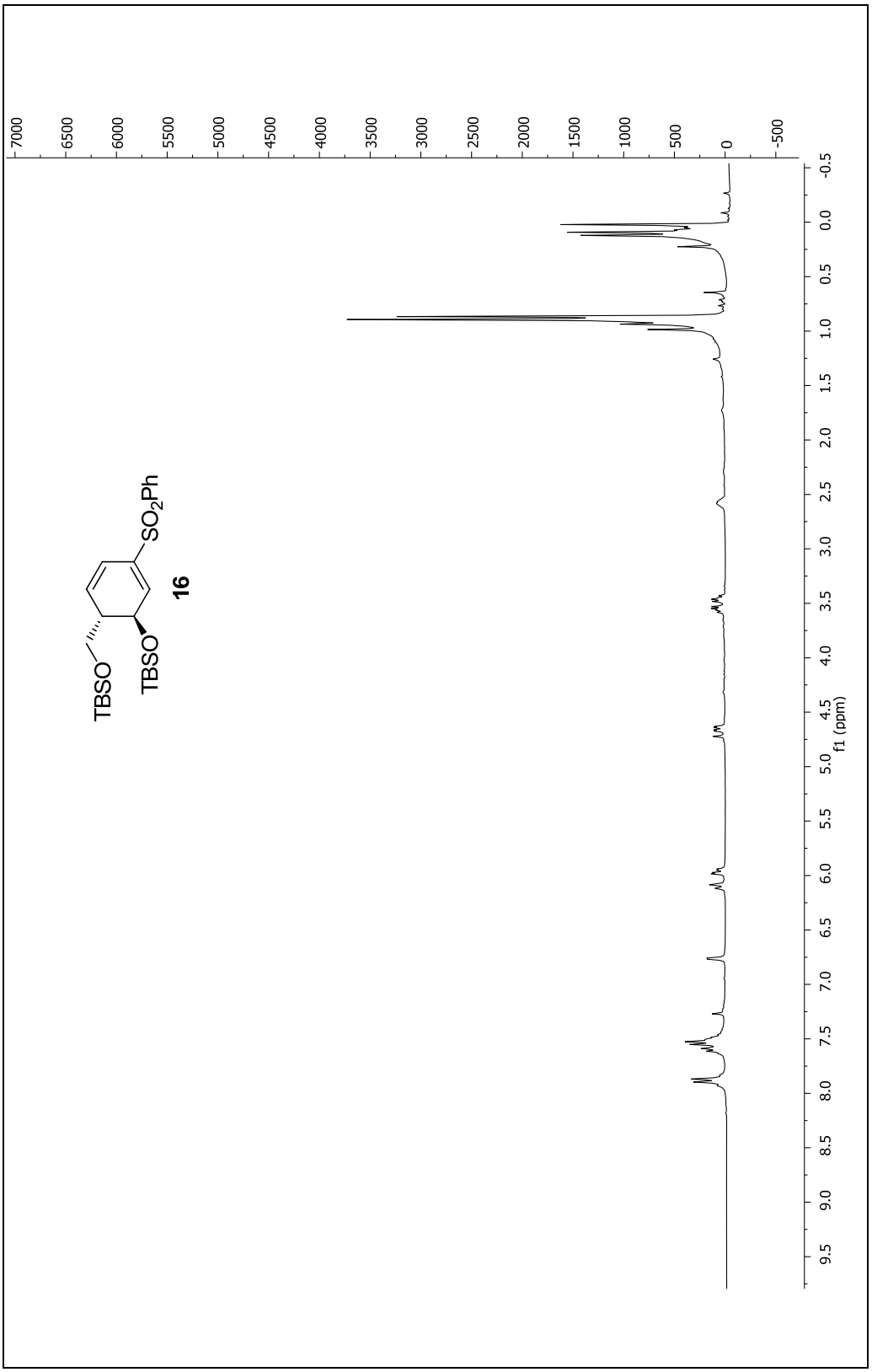
100 MHz ^{13}C NMR of compound **14** in $CDCl_3$



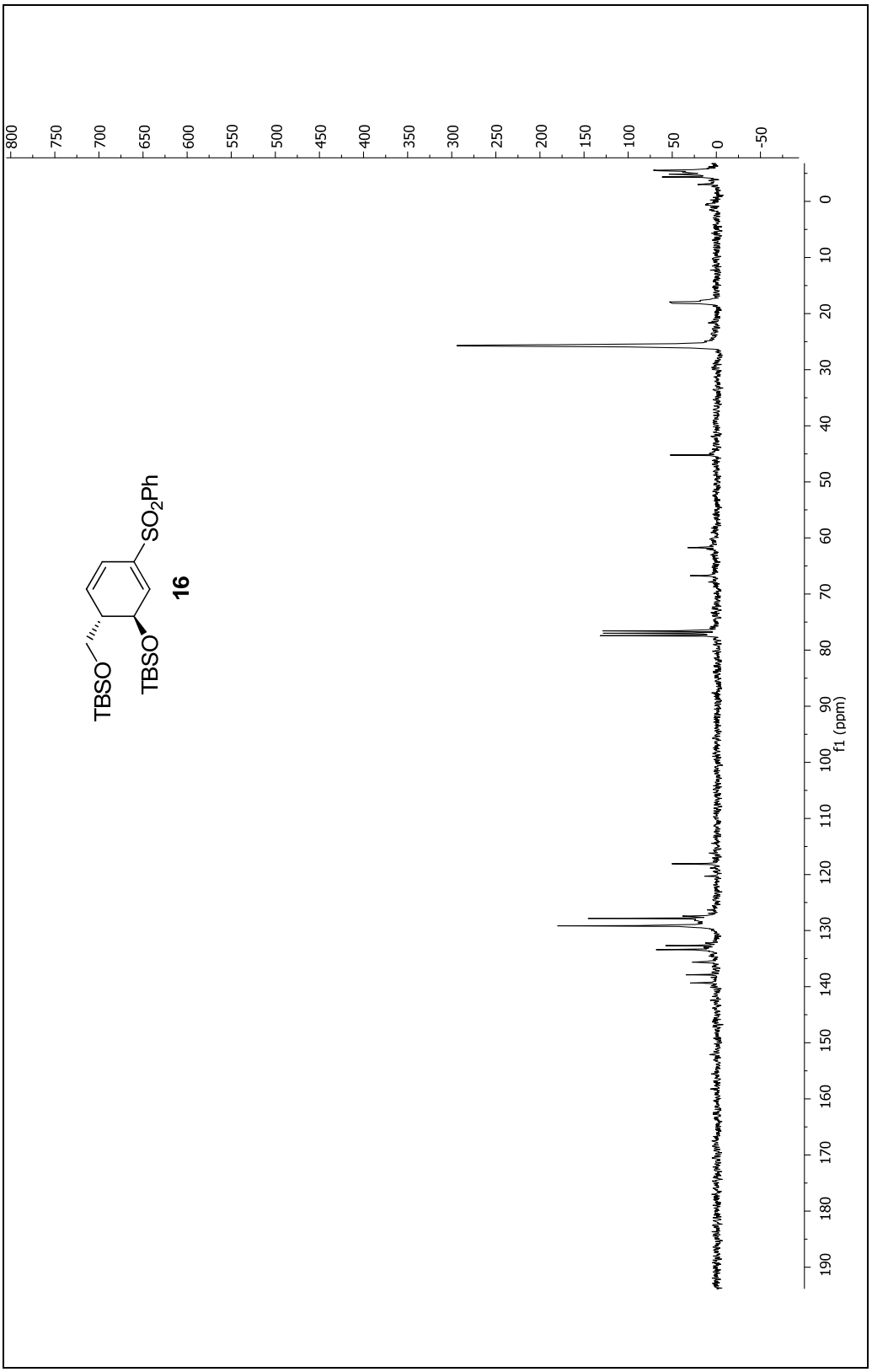
400 MHz ^{1}H NMR of compound **15** in $CDCl_3$



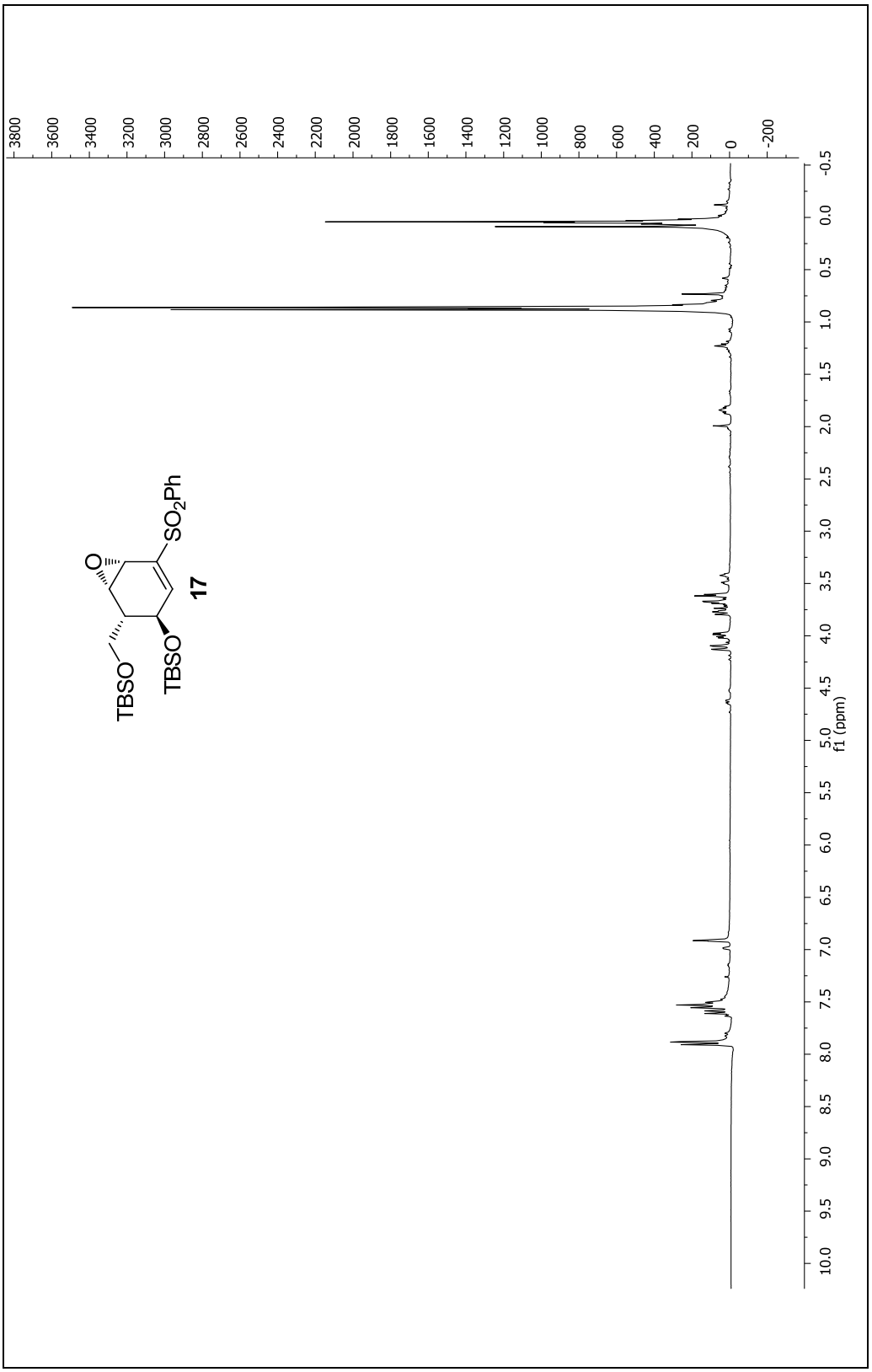
100 MHz ^{13}C NMR of compound **15** in $CDCl_3$



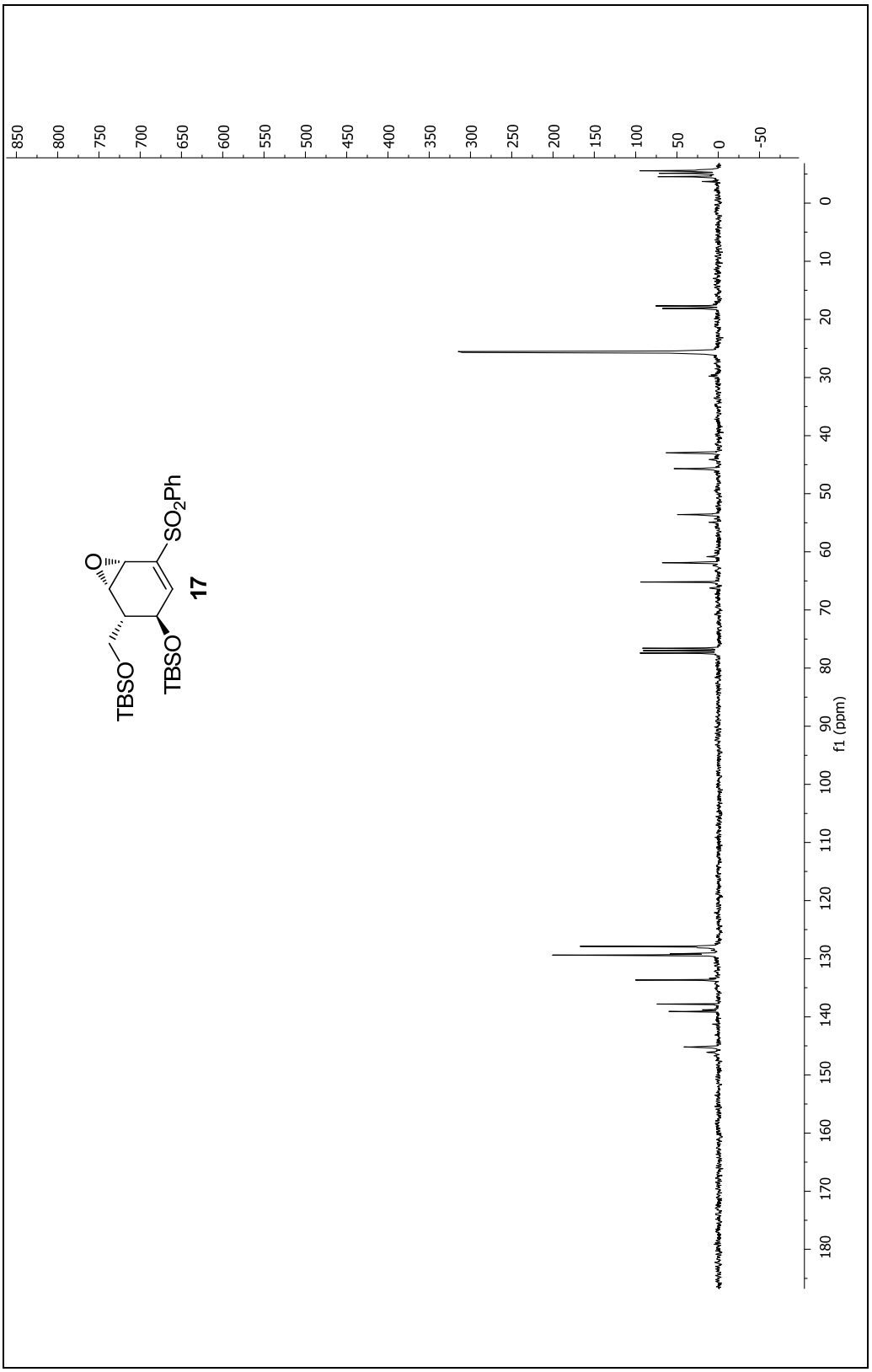
300 MHz ^{1}H NMR of compound **16** in $CDCl_3$



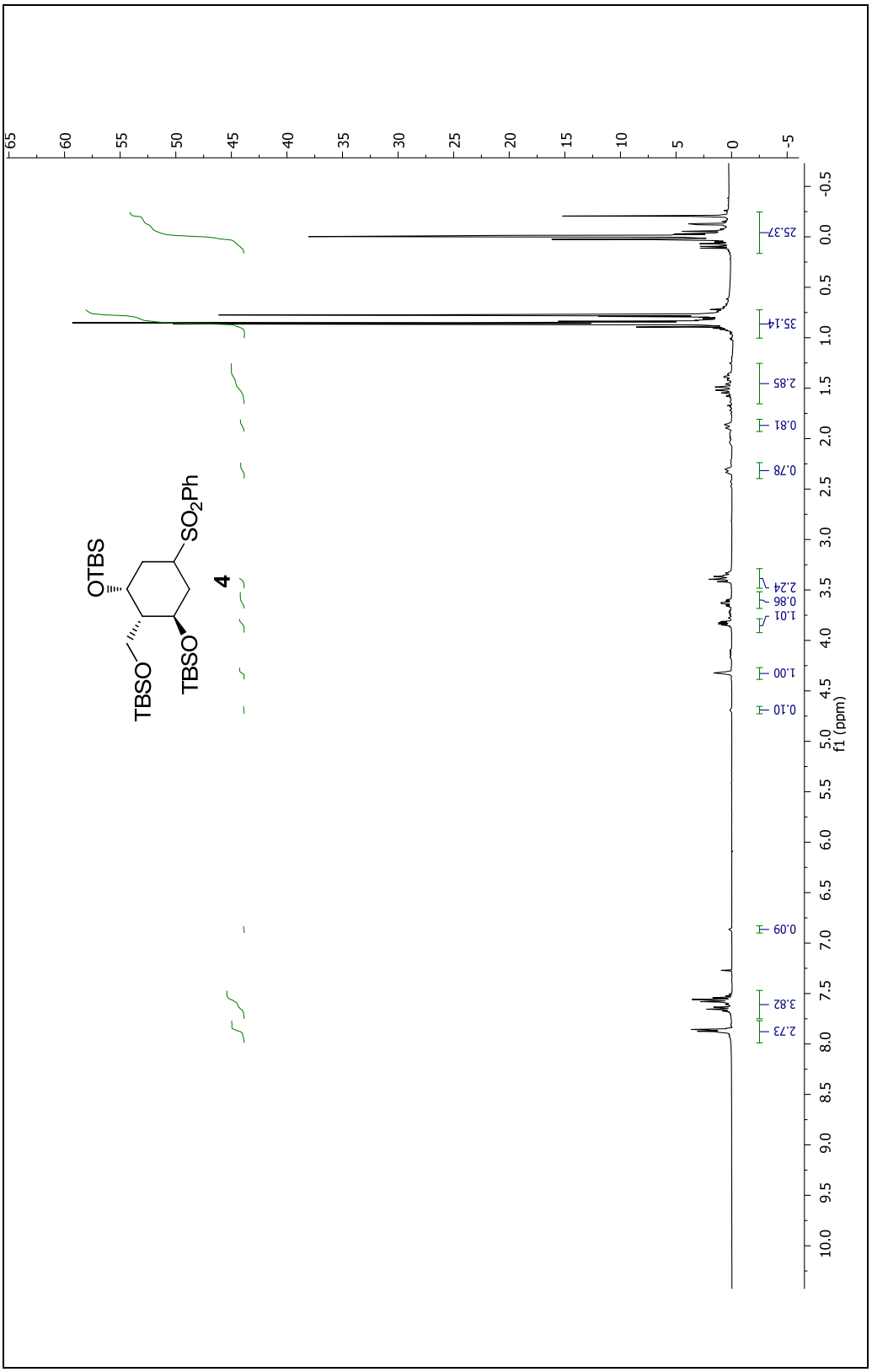
75 MHz ^{13}C NMR of compound **16** in $CDCl_3$



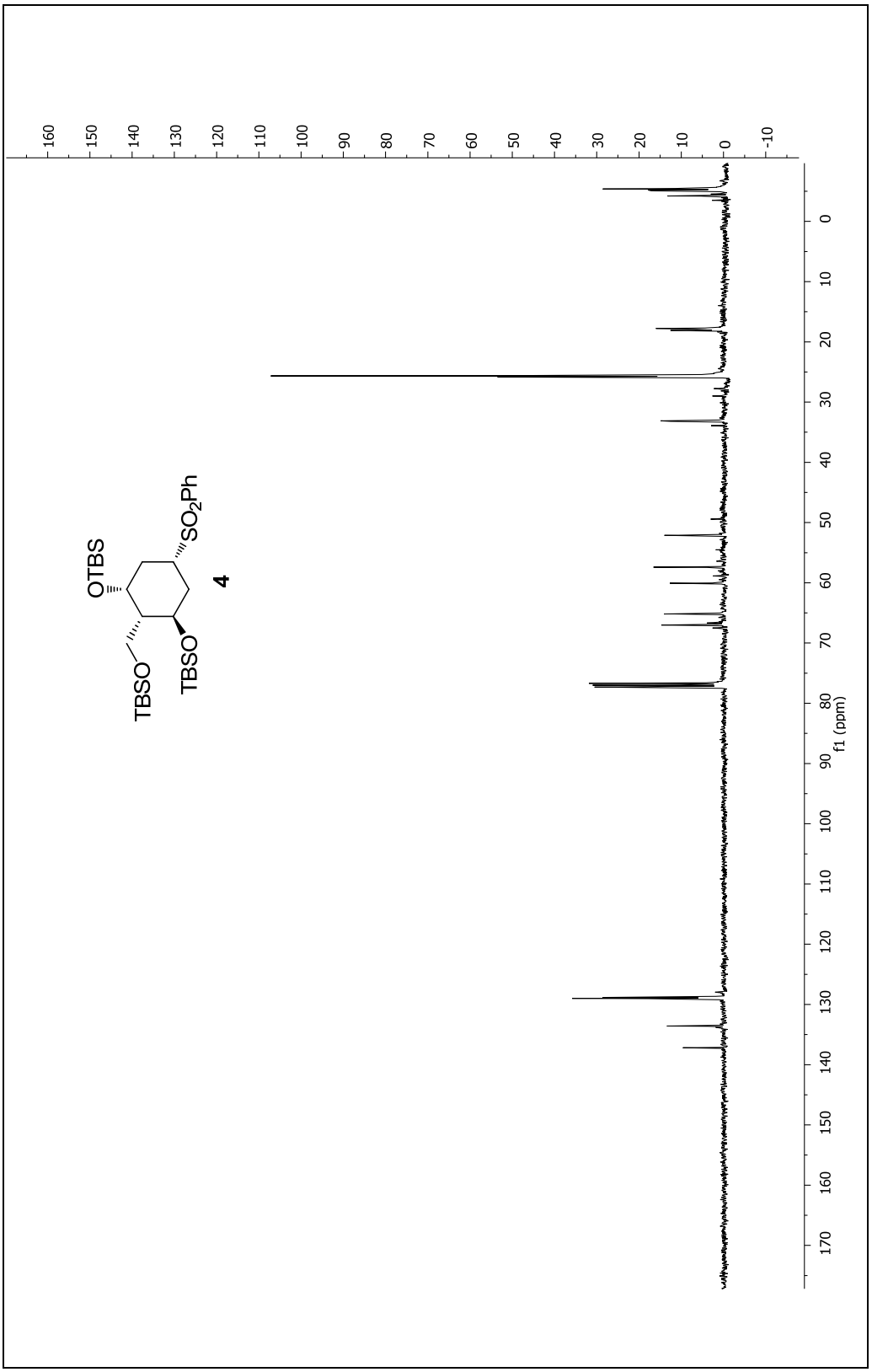
300 MHz ^{1}H NMR of compound **17** in $CDCl_3$



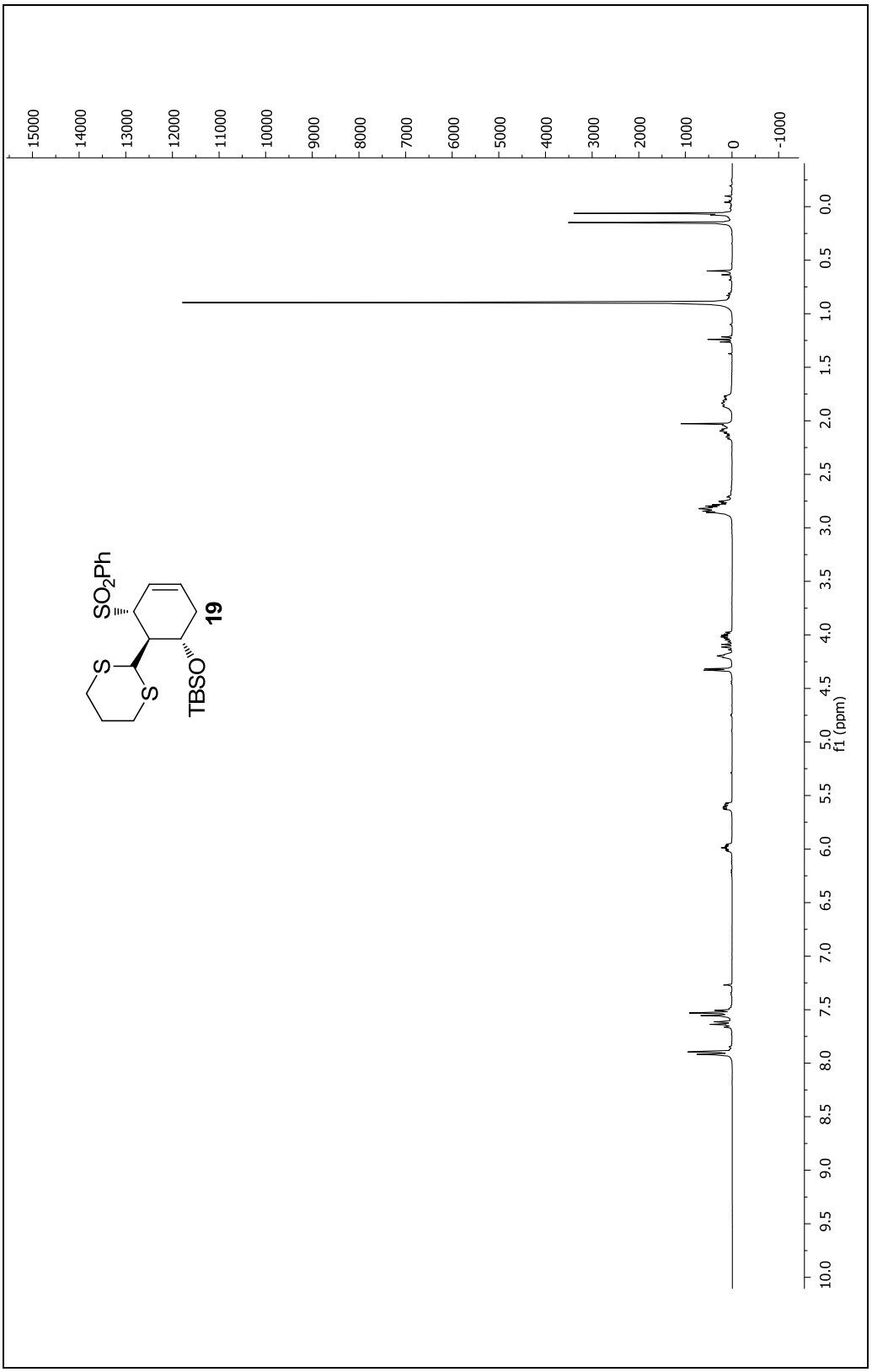
75 MHz ^{13}C NMR of compound **17** in $CDCl_3$



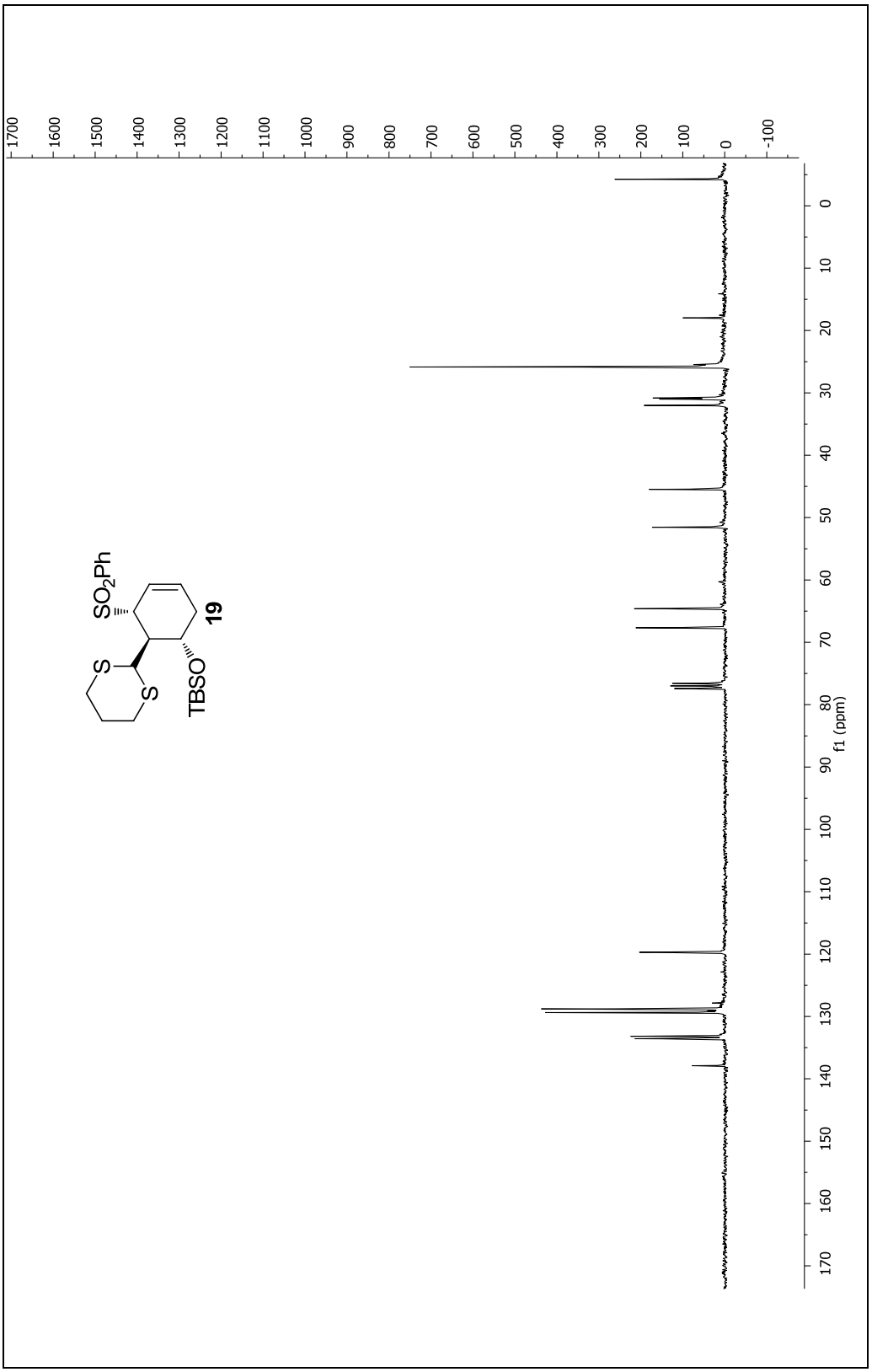
400 MHz ^{1}H NMR of compound **4** in $CDCl_3$



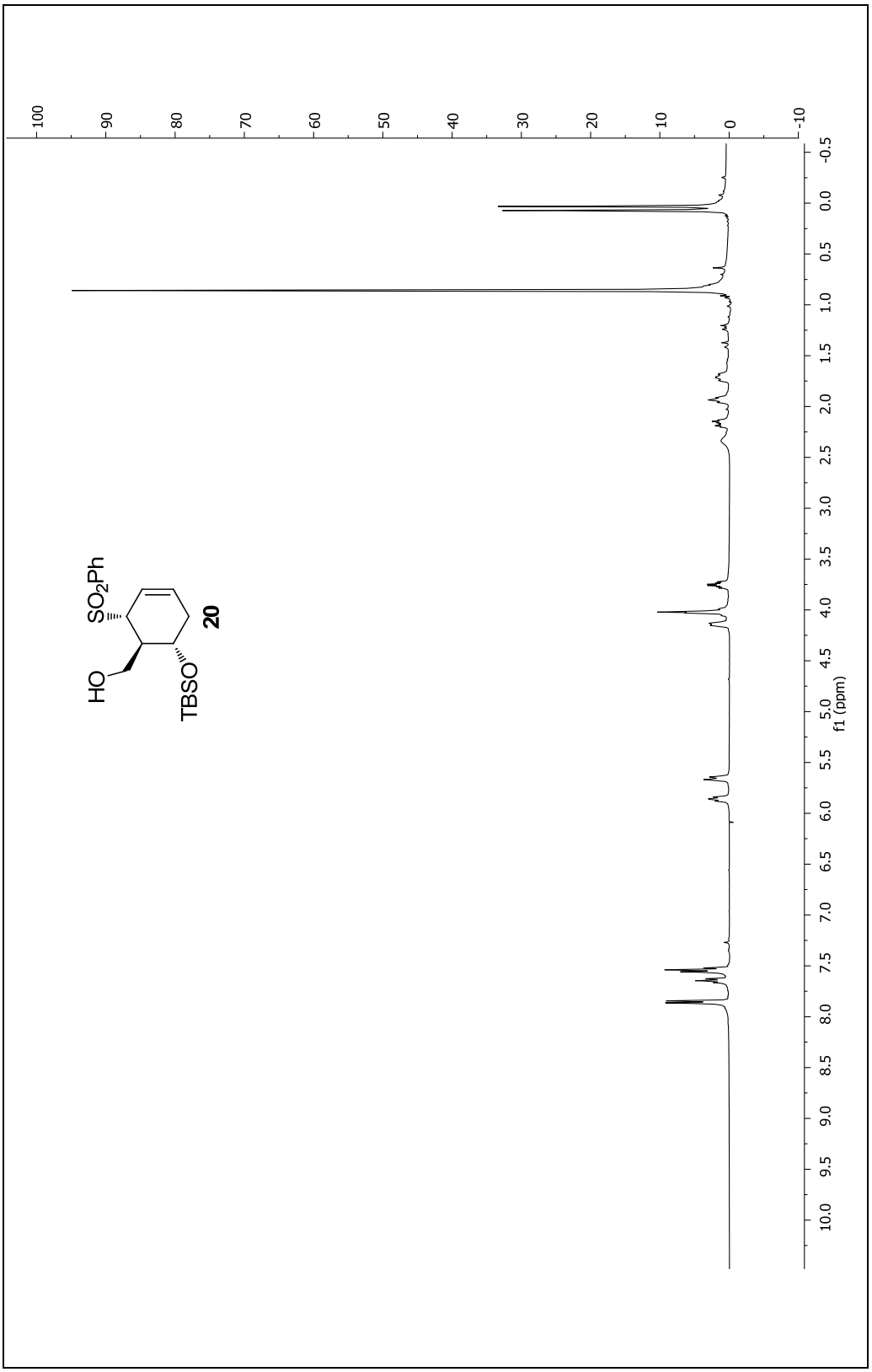
100 MHz ^{13}C NMR of compound **4** in $CDCl_3$



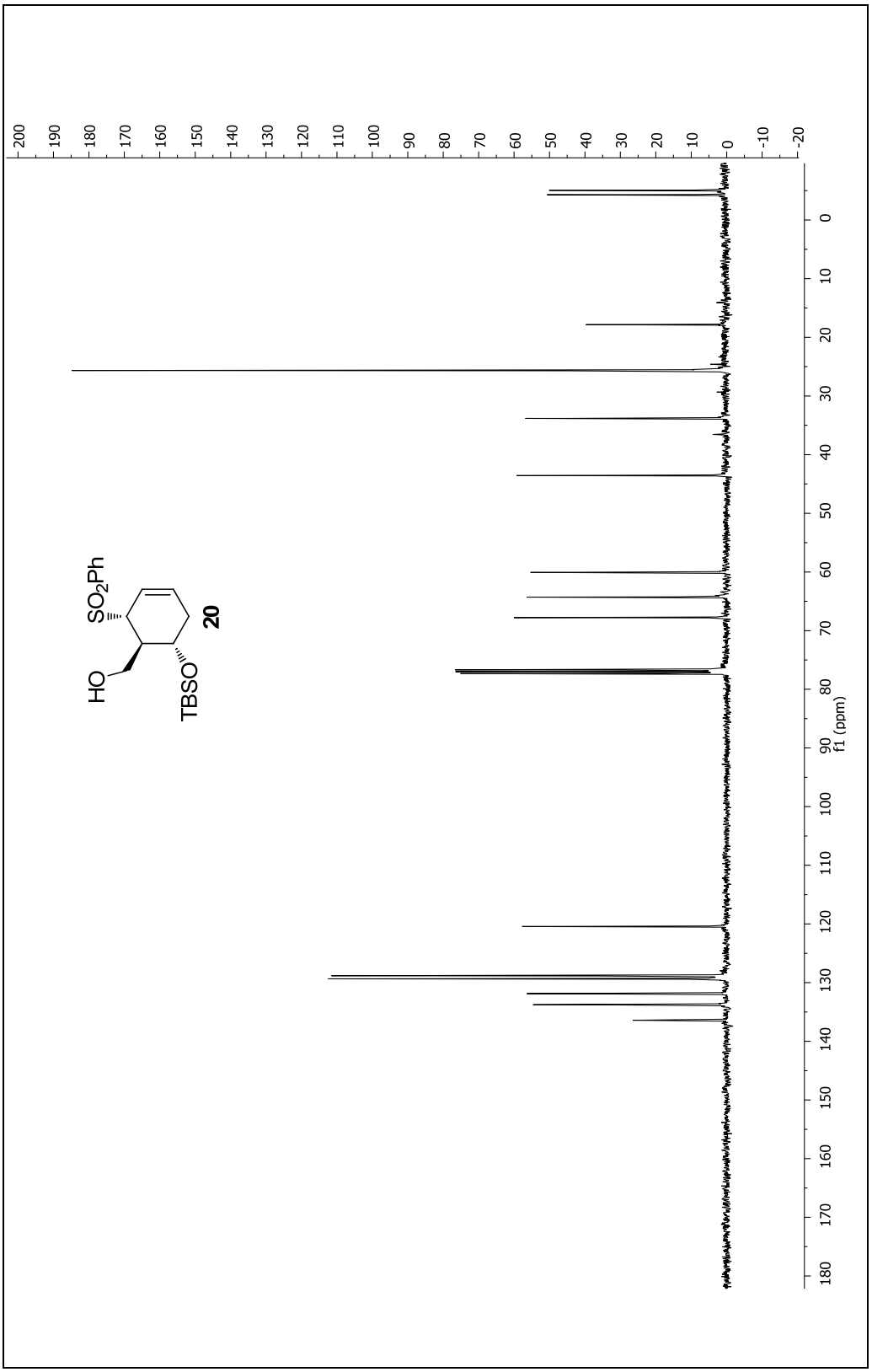
300 MHz ^{1}H NMR of compound **19** in $CDCl_3$



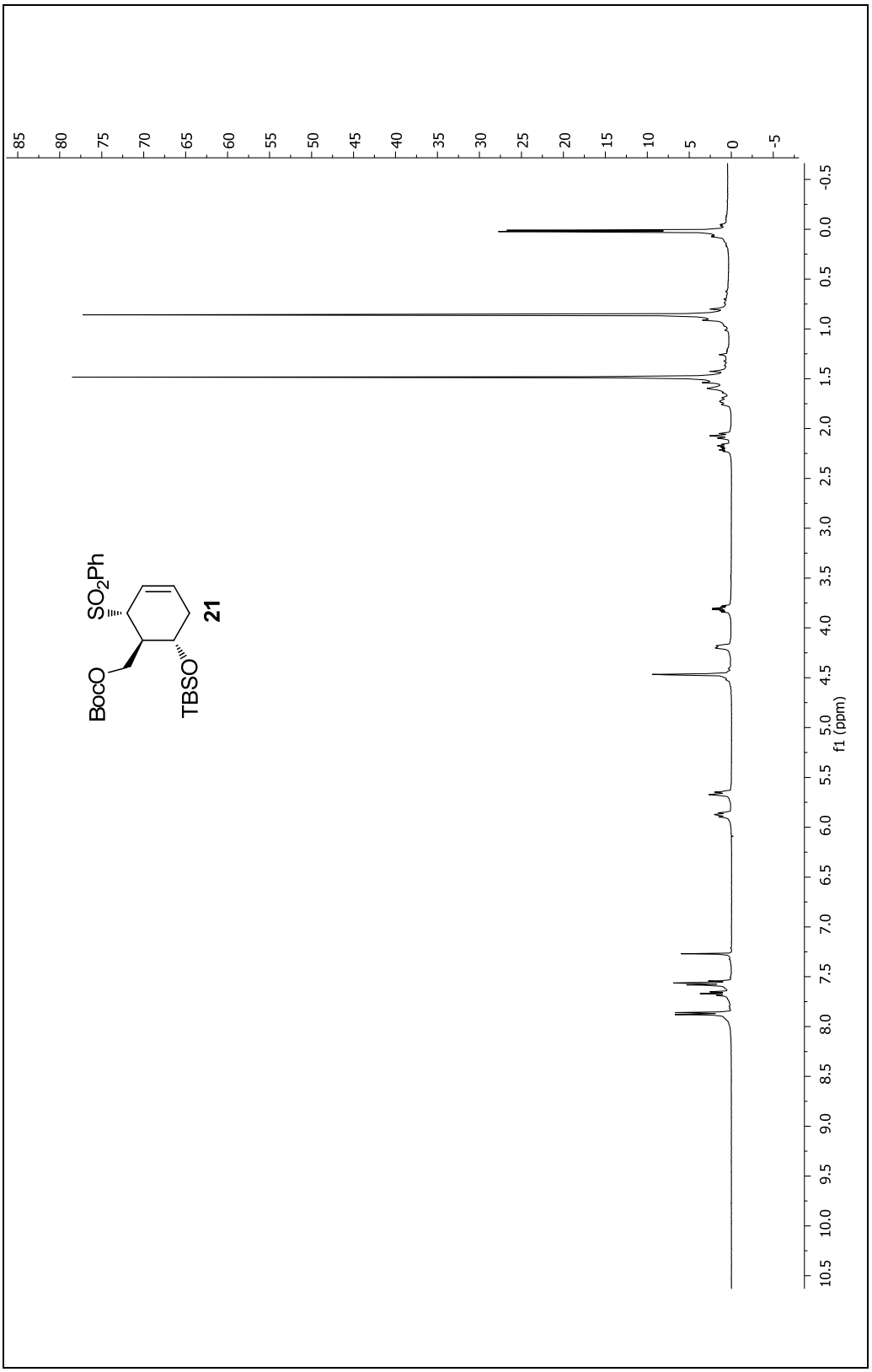
75 MHz ^{13}C NMR of compound **19** in $CDCl_3$



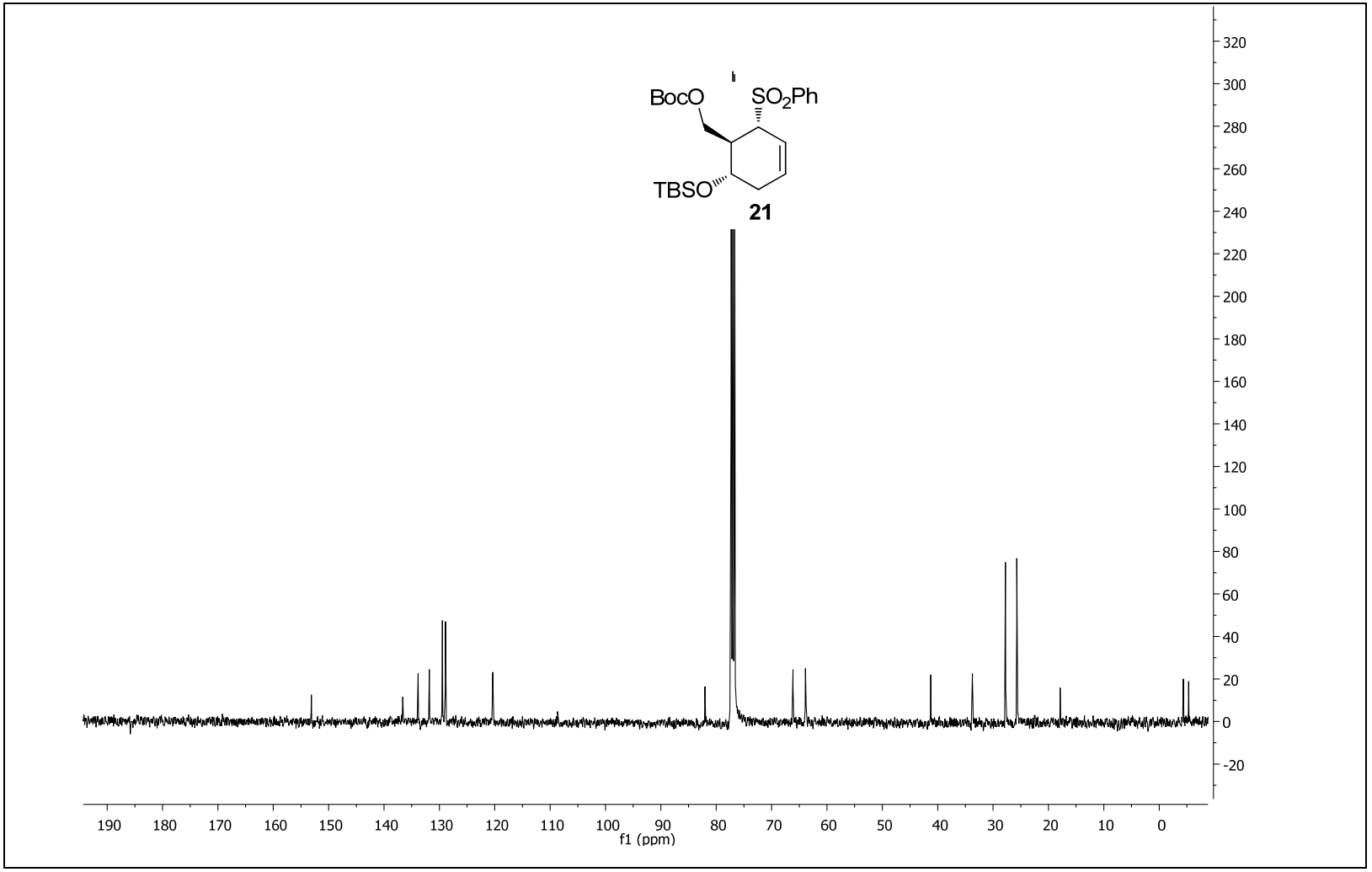
400 MHz ^{1}H NMR of compound **20** in $CDCl_3$



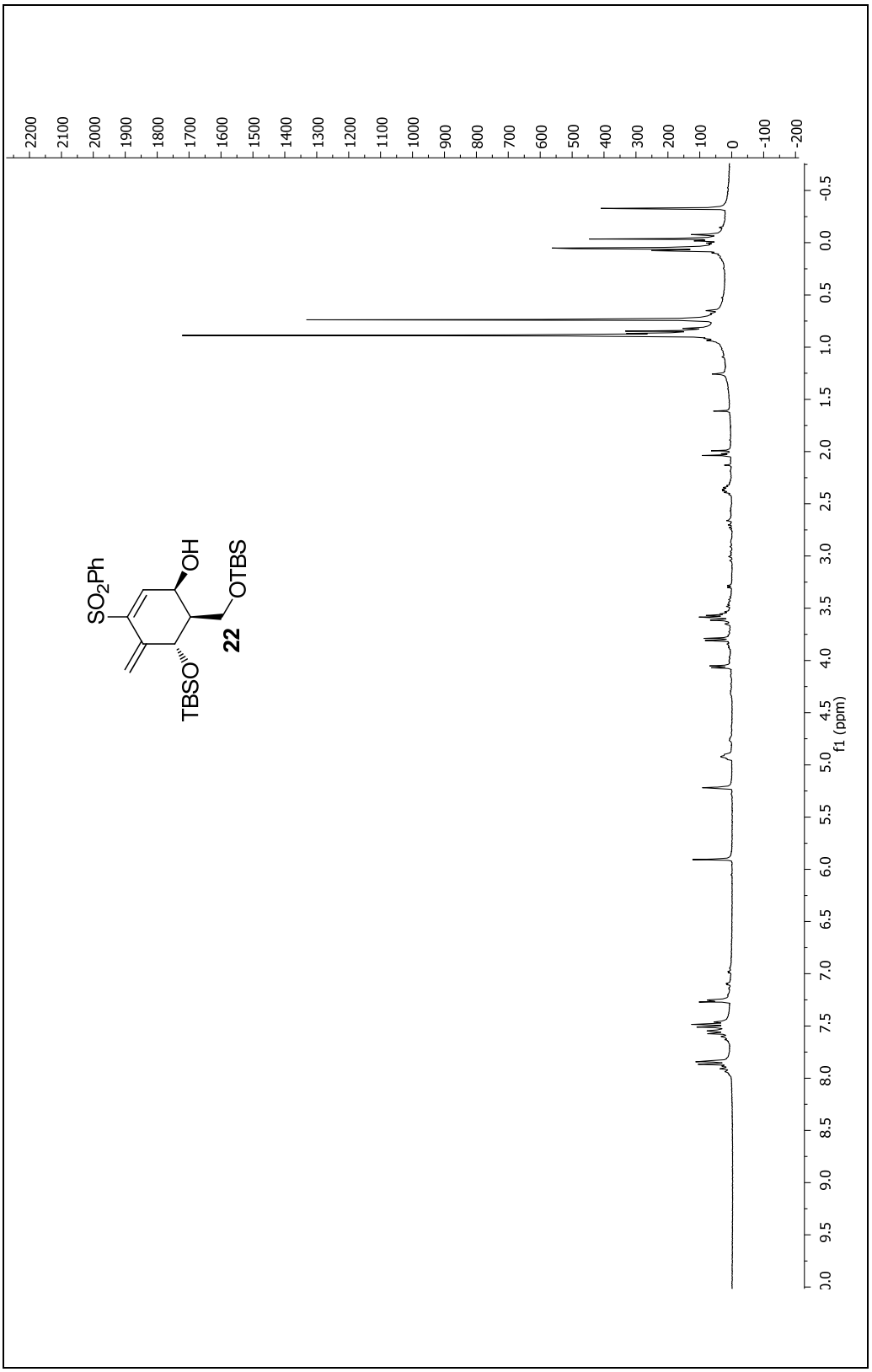
100 MHz ^{13}C NMR of compound **20** in $CDCl_3$



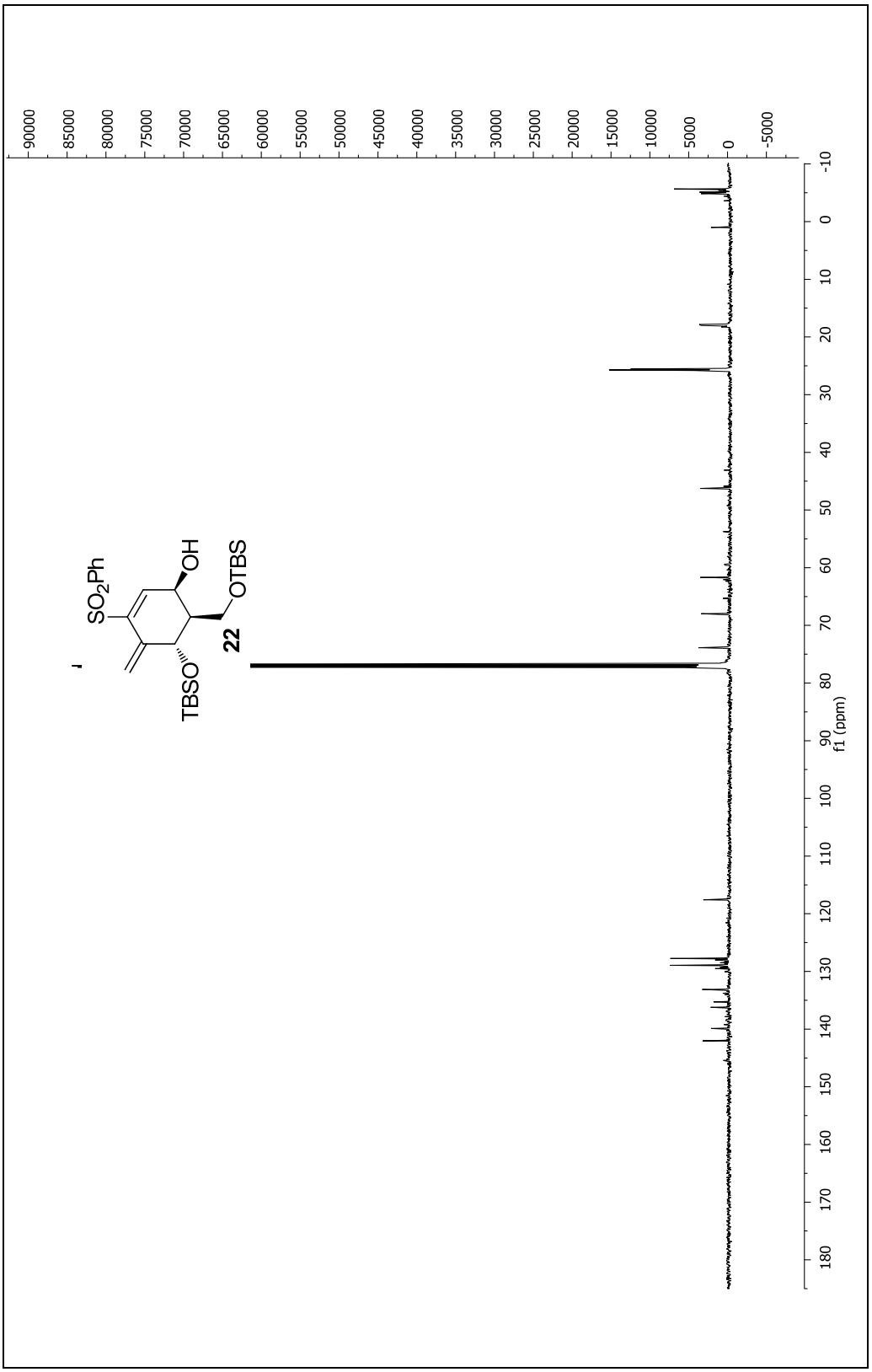
400 MHz ^{1}H NMR of compound **21** in $CDCl_3$



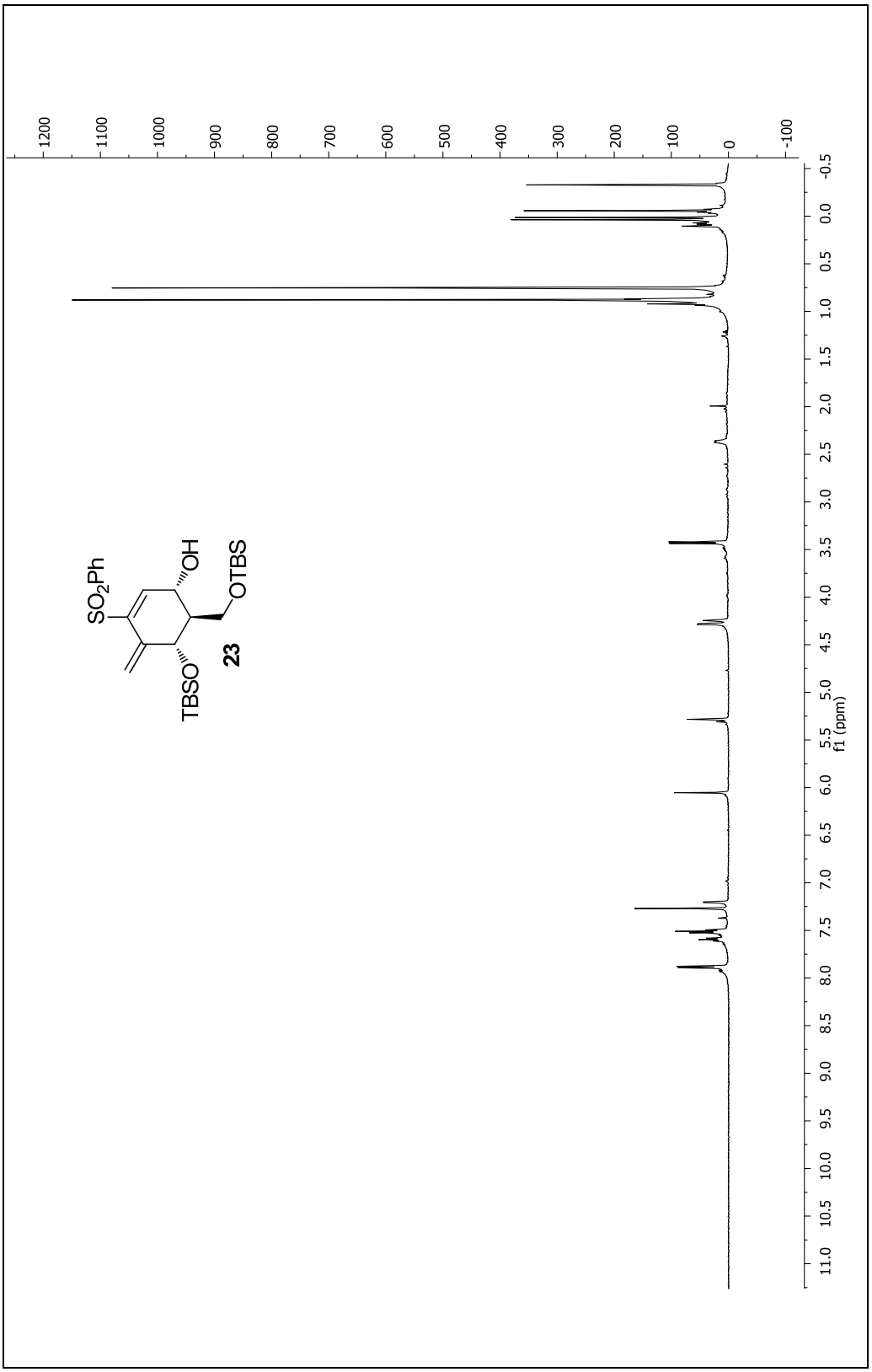
100 MHz ^{13}C NMR of compound **21** in $CDCl_3$



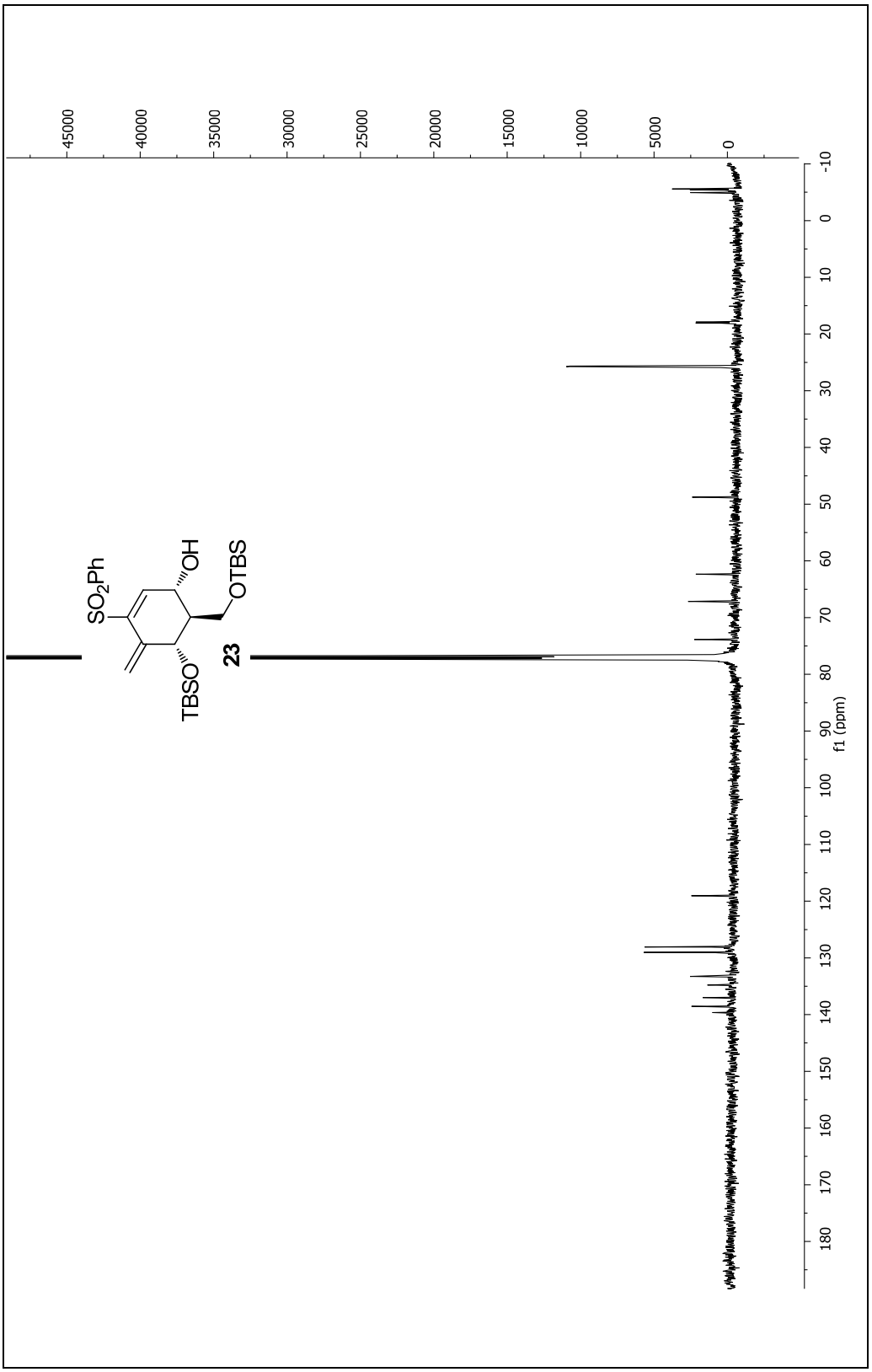
300 MHz ^{1}H NMR of compound **22** in $CDCl_3$



125 MHz ^{13}C NMR of compound **22** in $CDCl_3$



500 MHz ^{1}H NMR of compound **23** in $CDCl_3$



125 MHz ^{13}C NMR of compound **23** in $CDCl_3$

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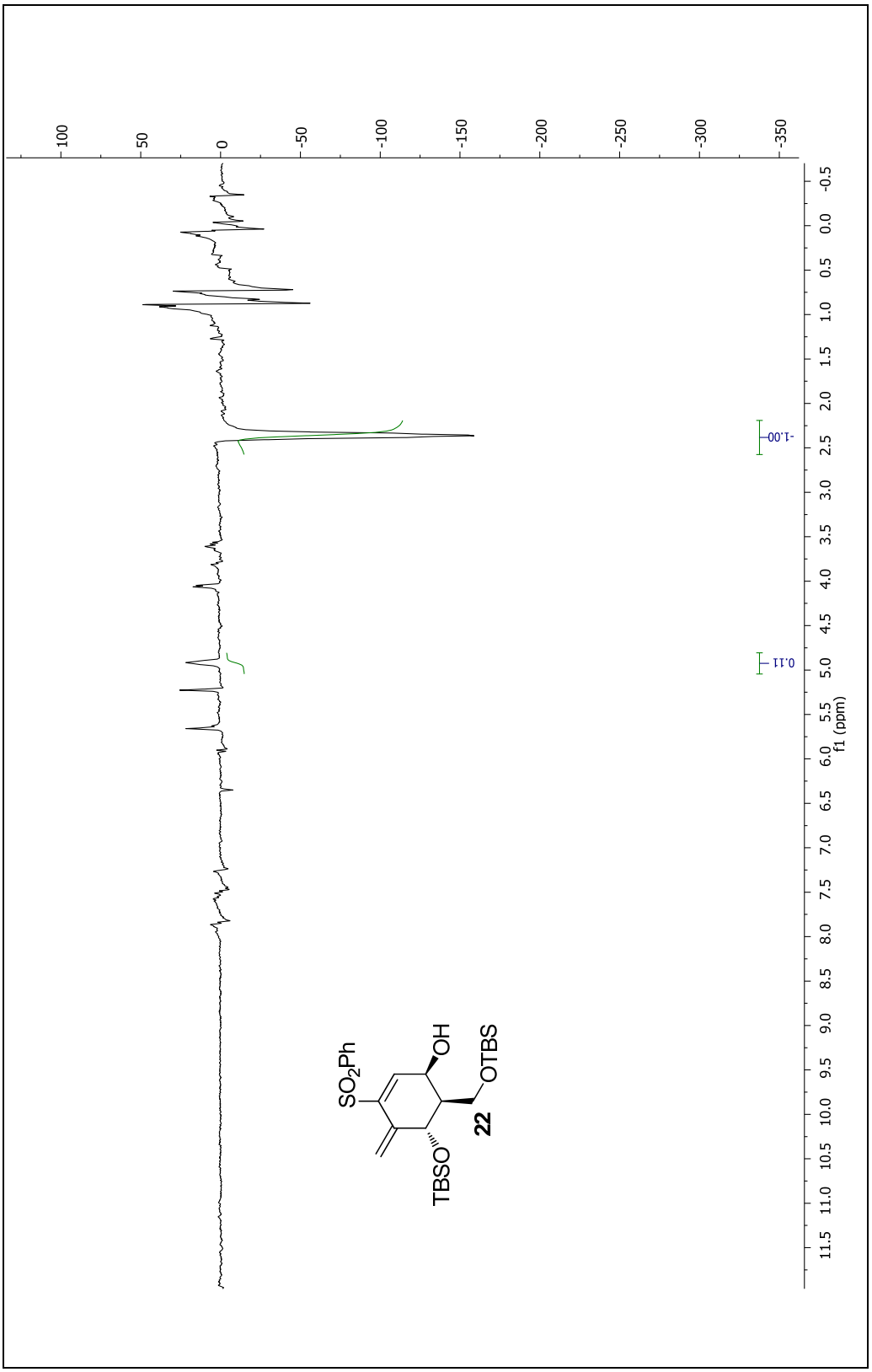

300 MHz ^{NOE} NMR of compound **22** in $CDCl_3$

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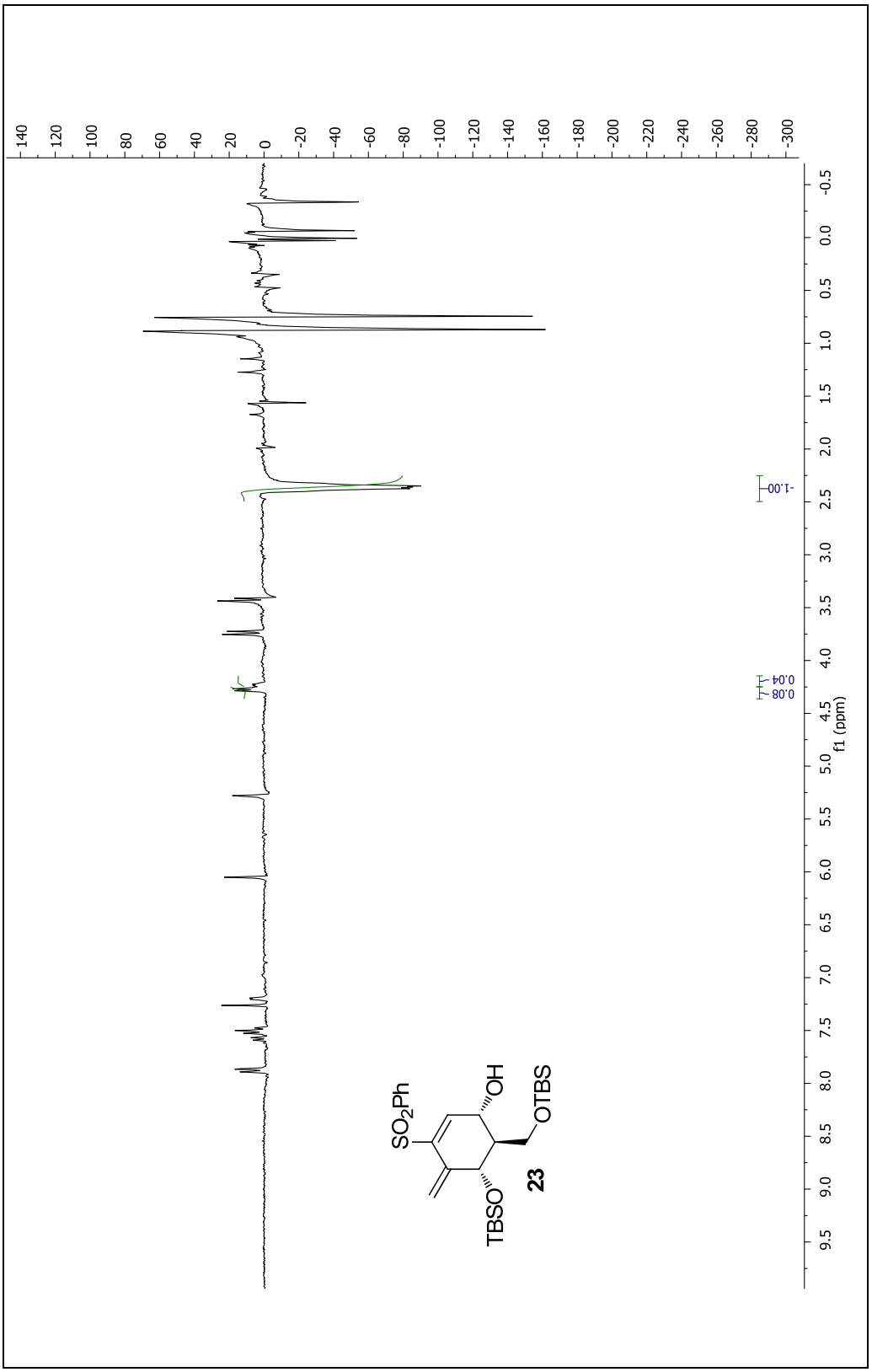
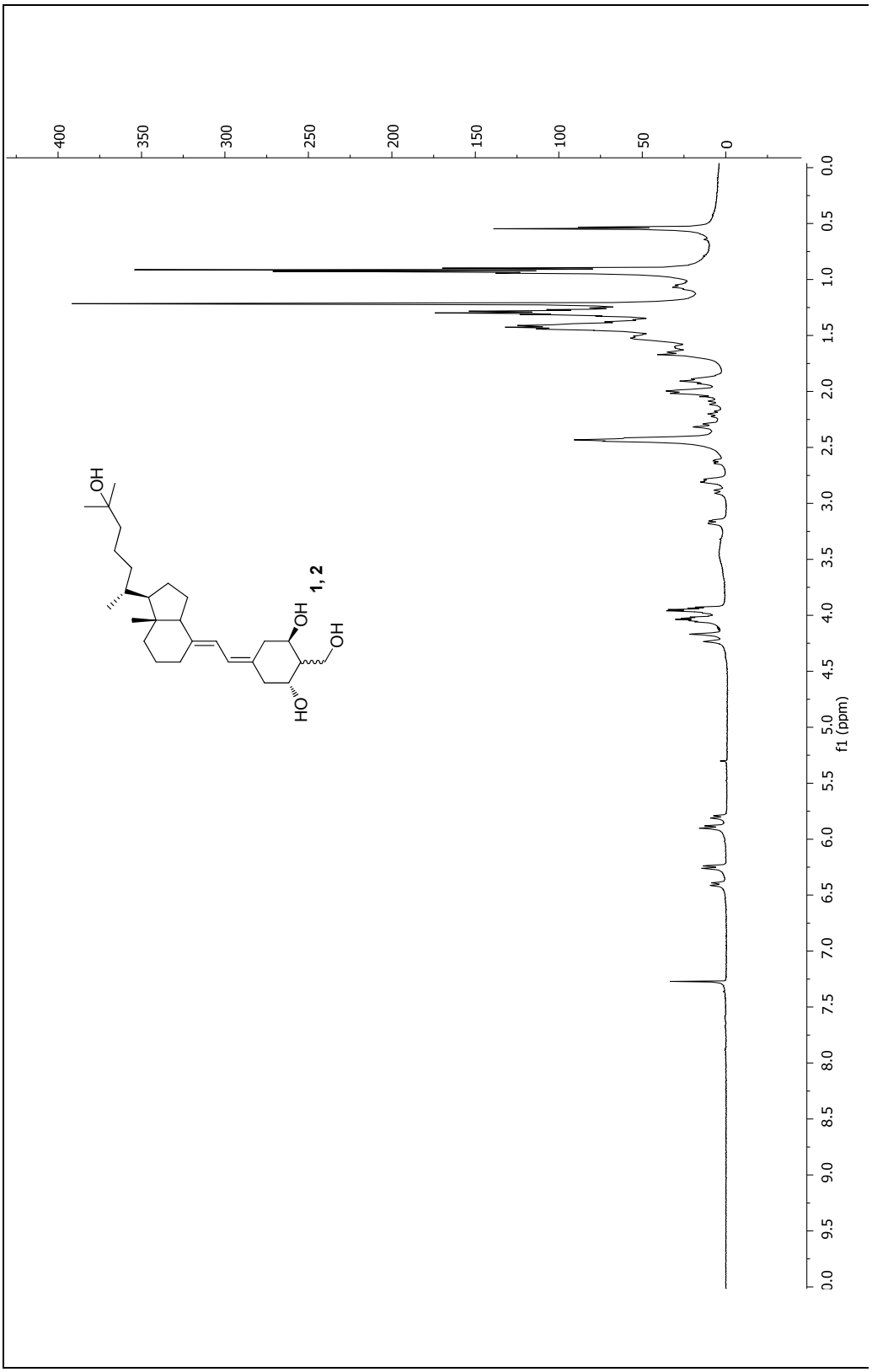
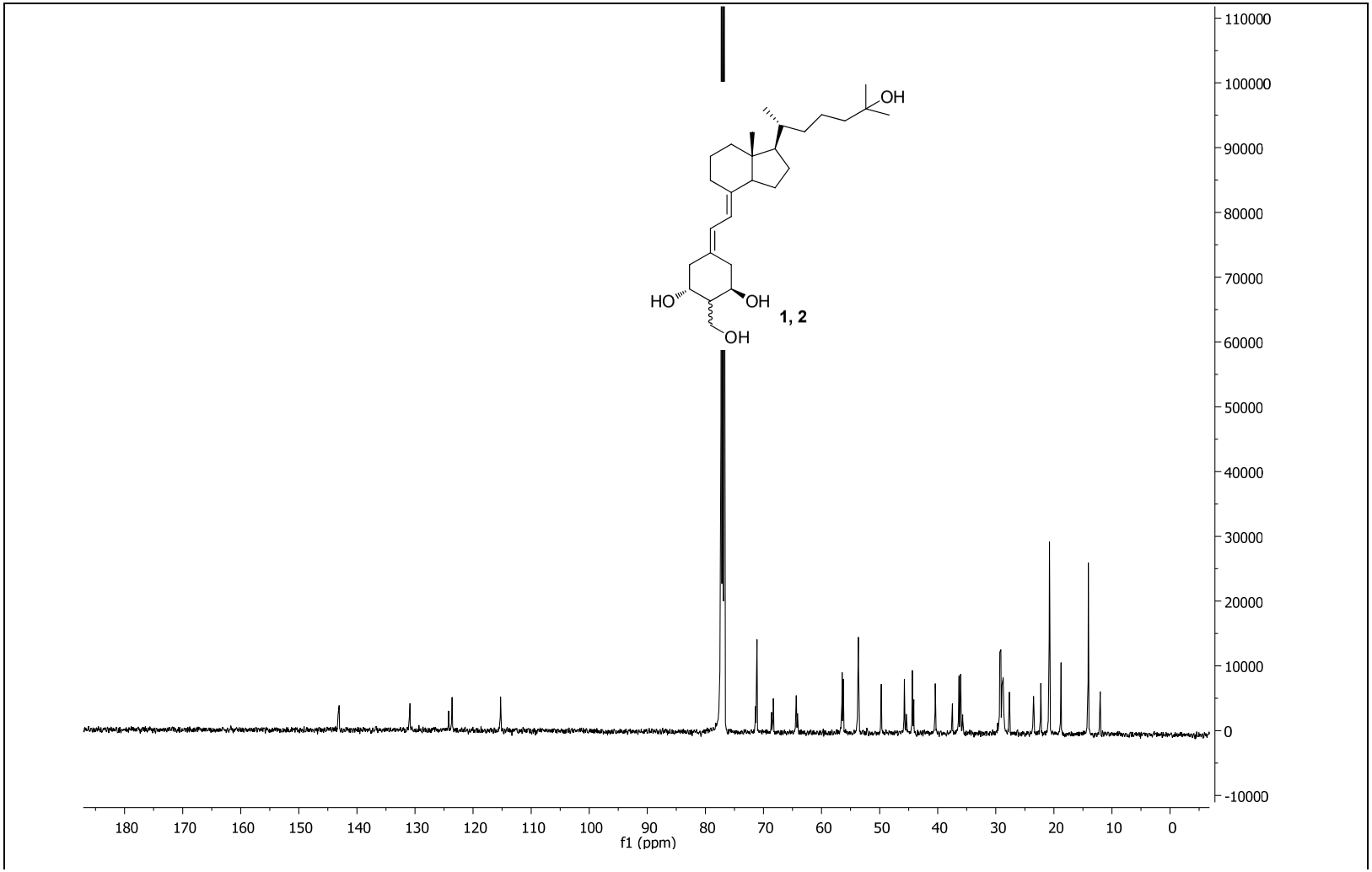


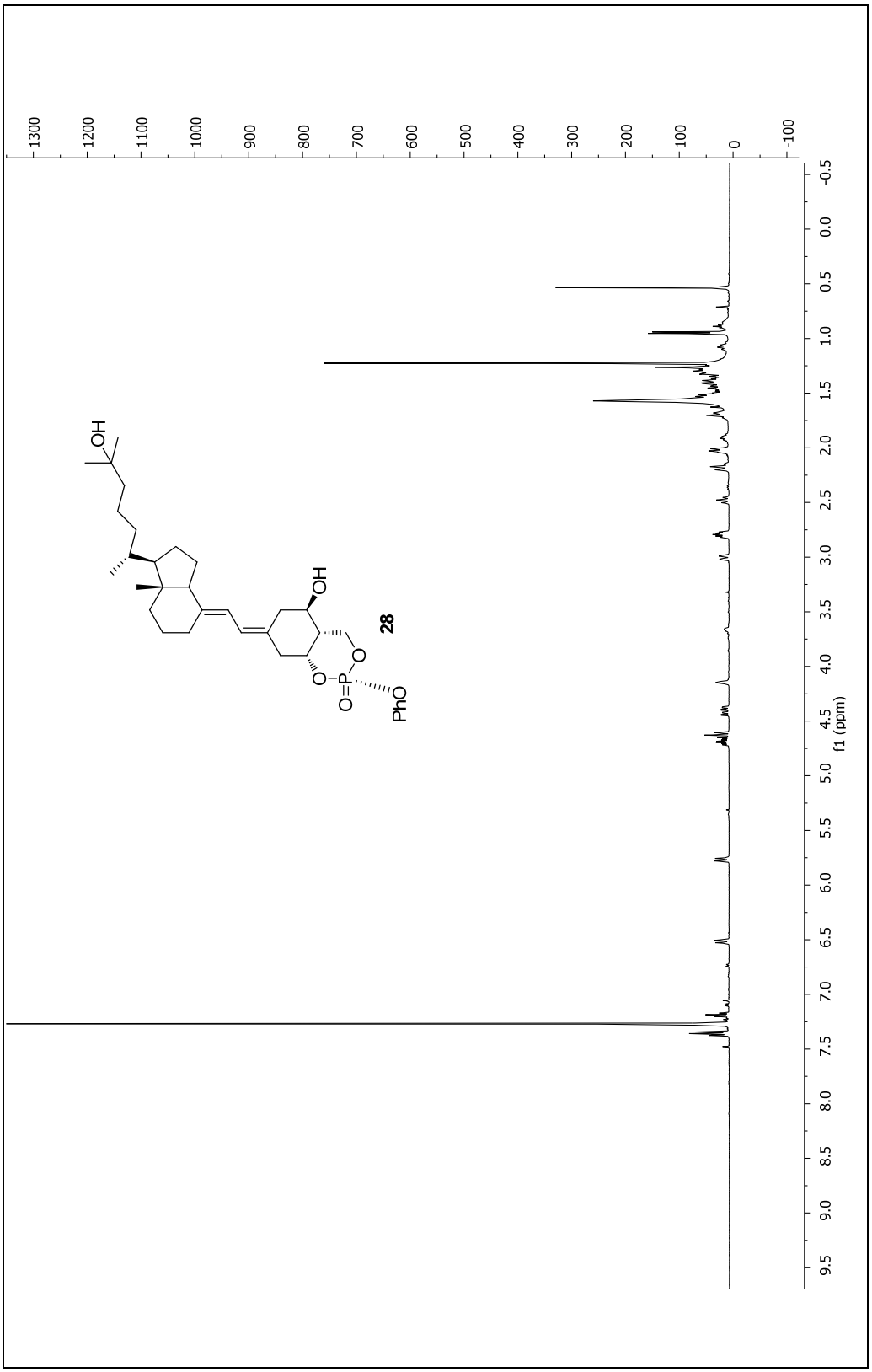
300 MHz ^{NOE} NMR of compound **23** in $CDCl_3$



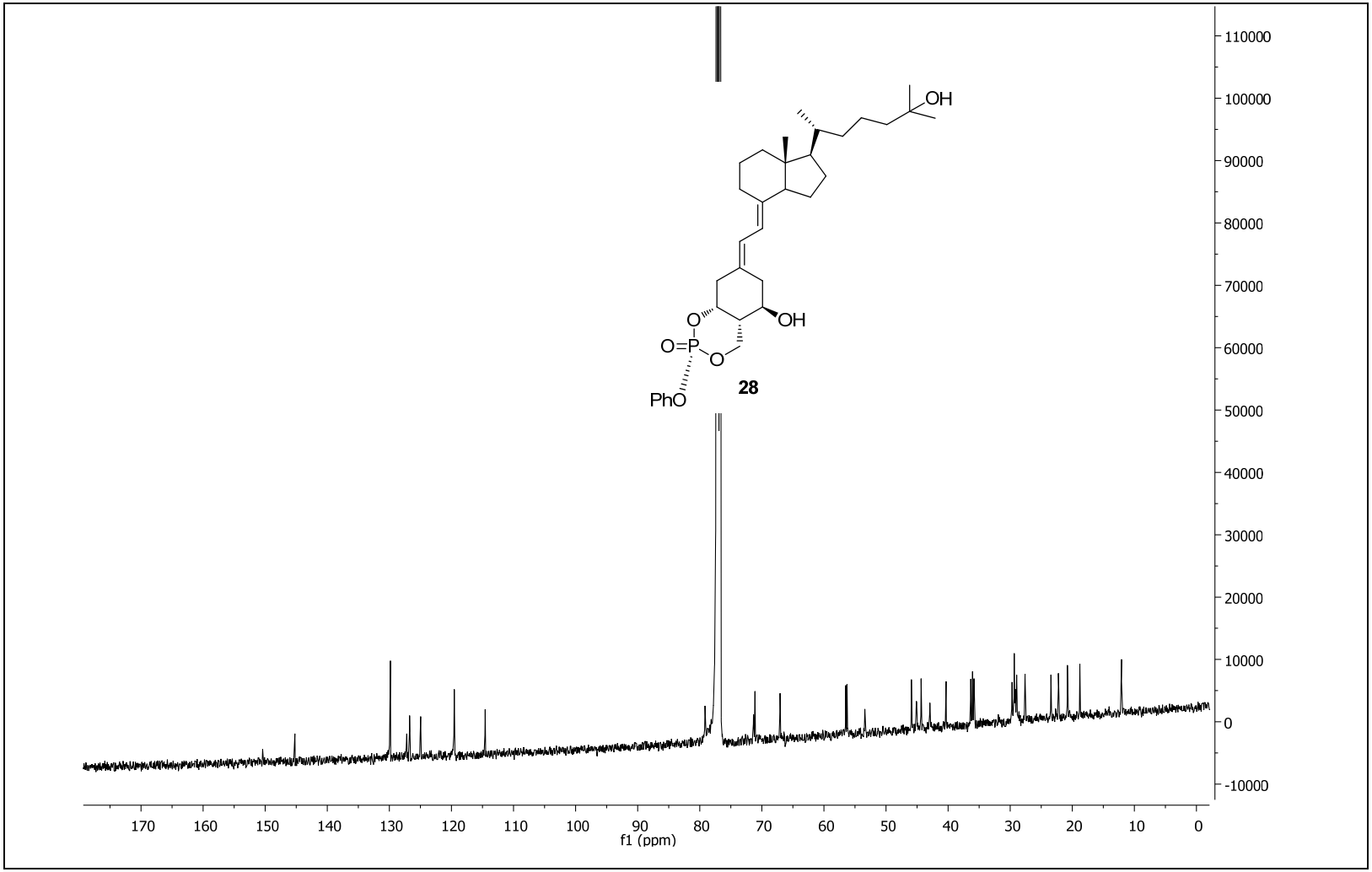
500 MHz ^{1}H NMR of compound **1, 2** in $CDCl_3$



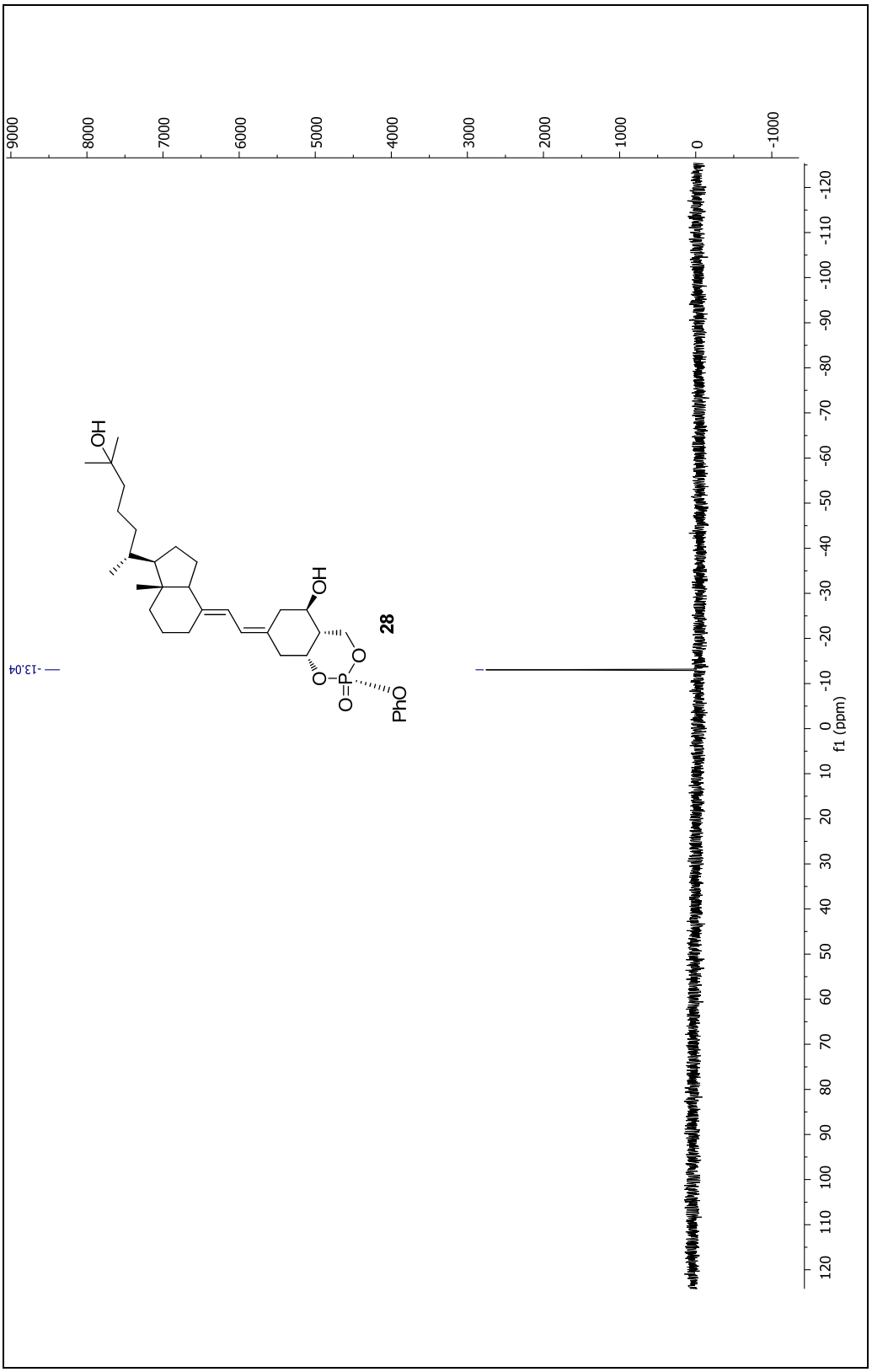
125 MHz ^{13}C NMR of compound **1, 2** in $CDCl_3$



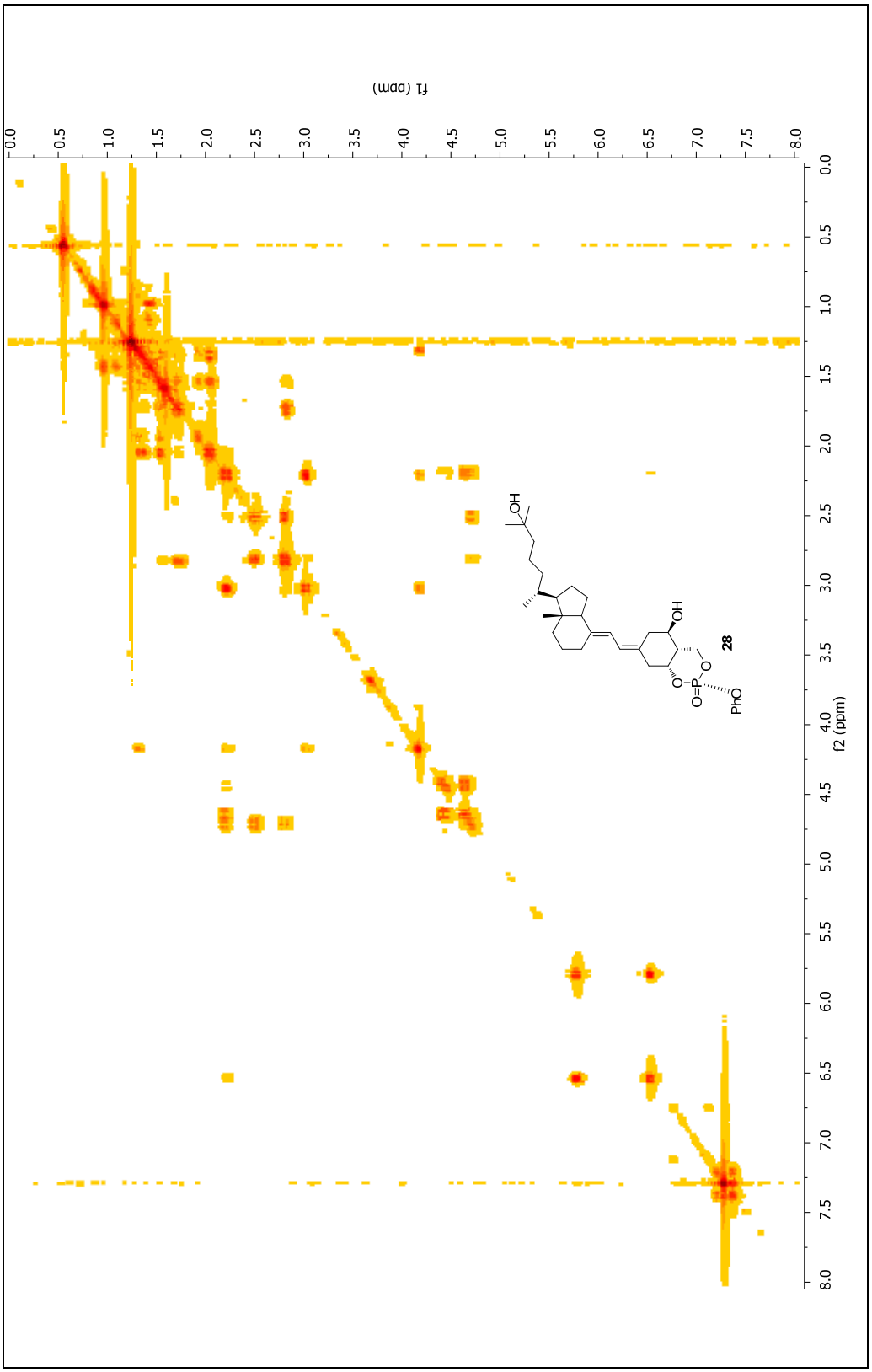
500 MHz ^{1}H NMR of compound **28** in $CDCl_3$



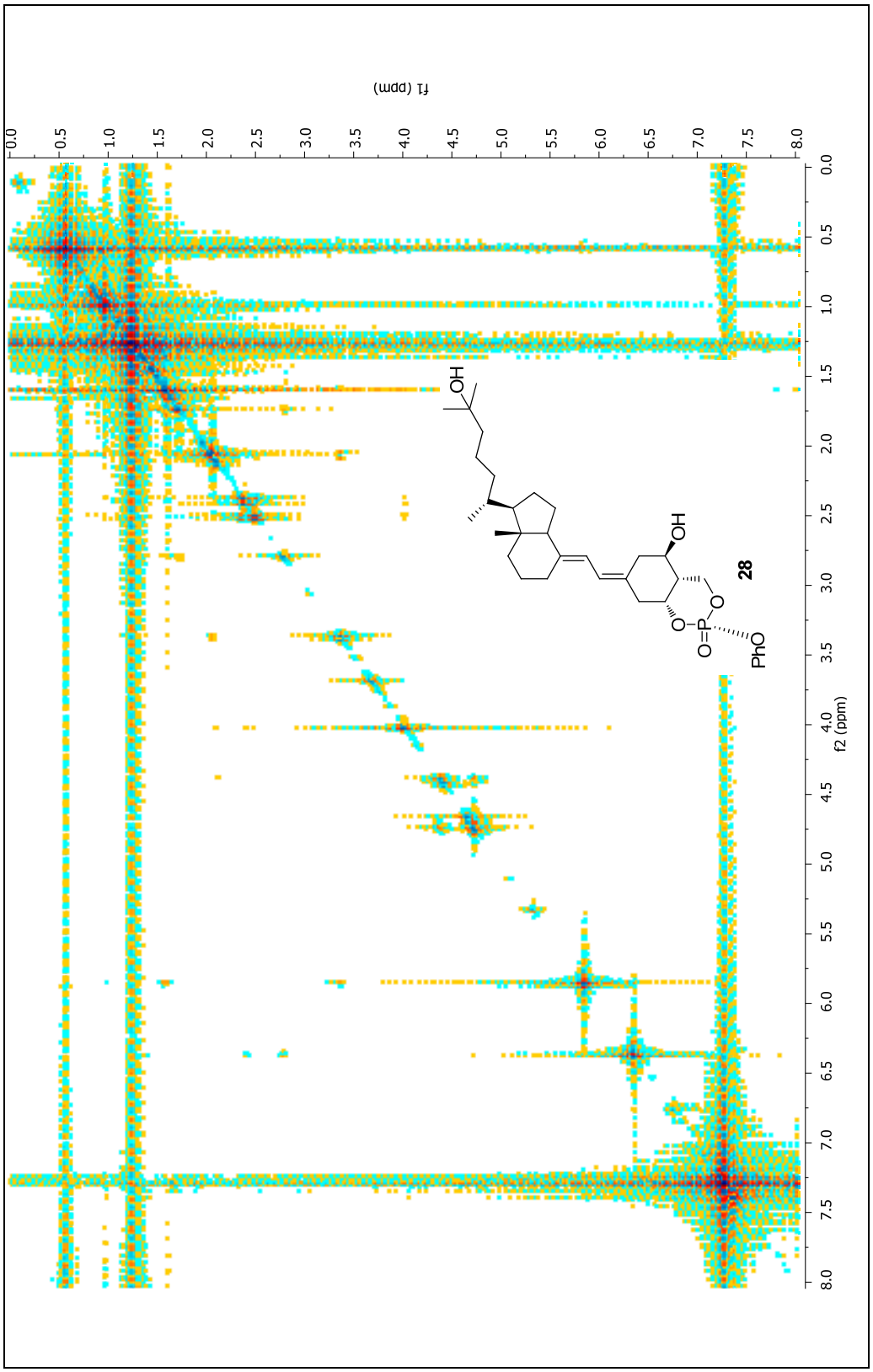
125 MHz ^{13}C NMR of compound **28** in $CDCl_3$



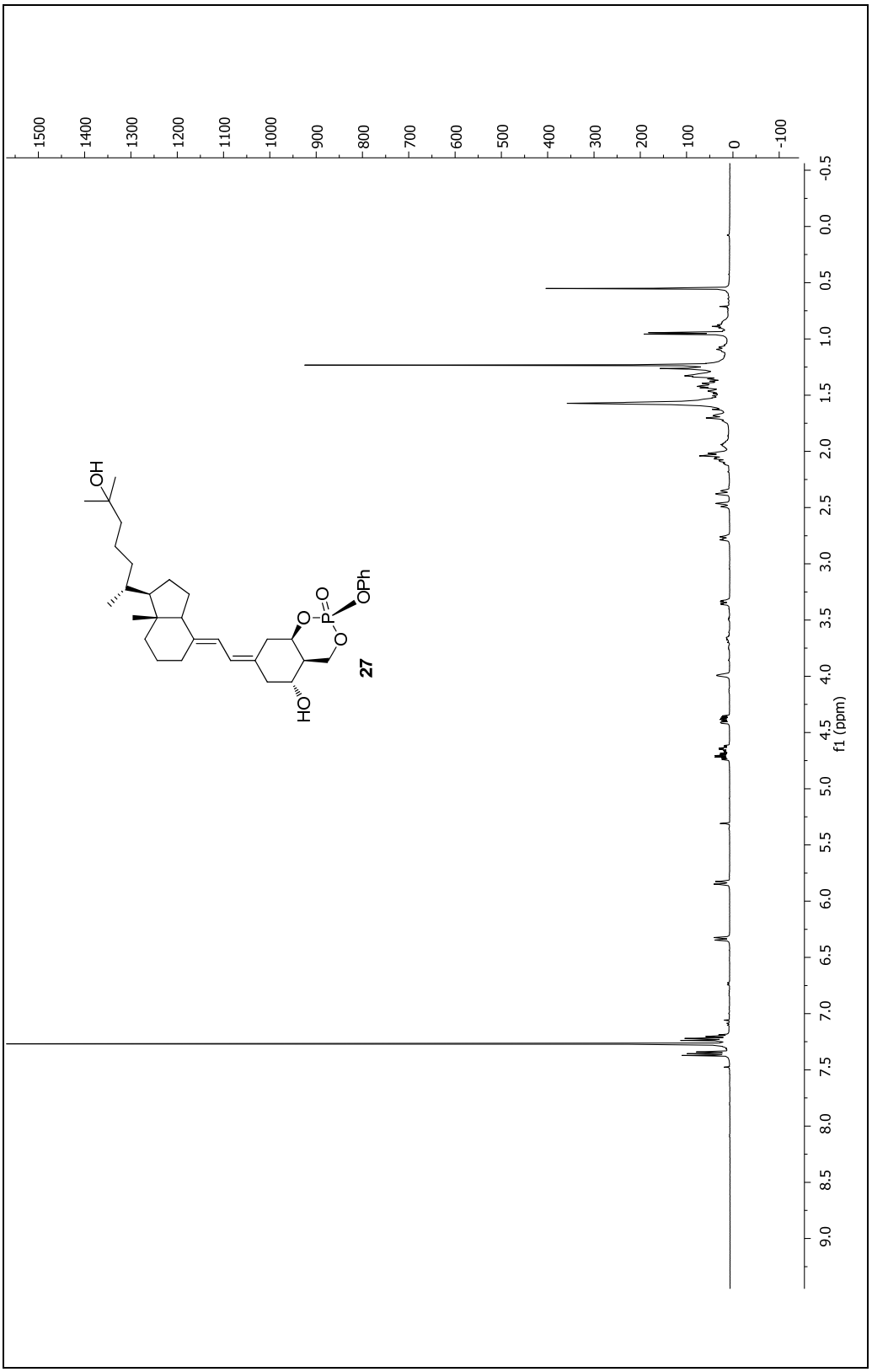
200 MHz ^{31}P NMR of compound **28** in $CDCl_3$



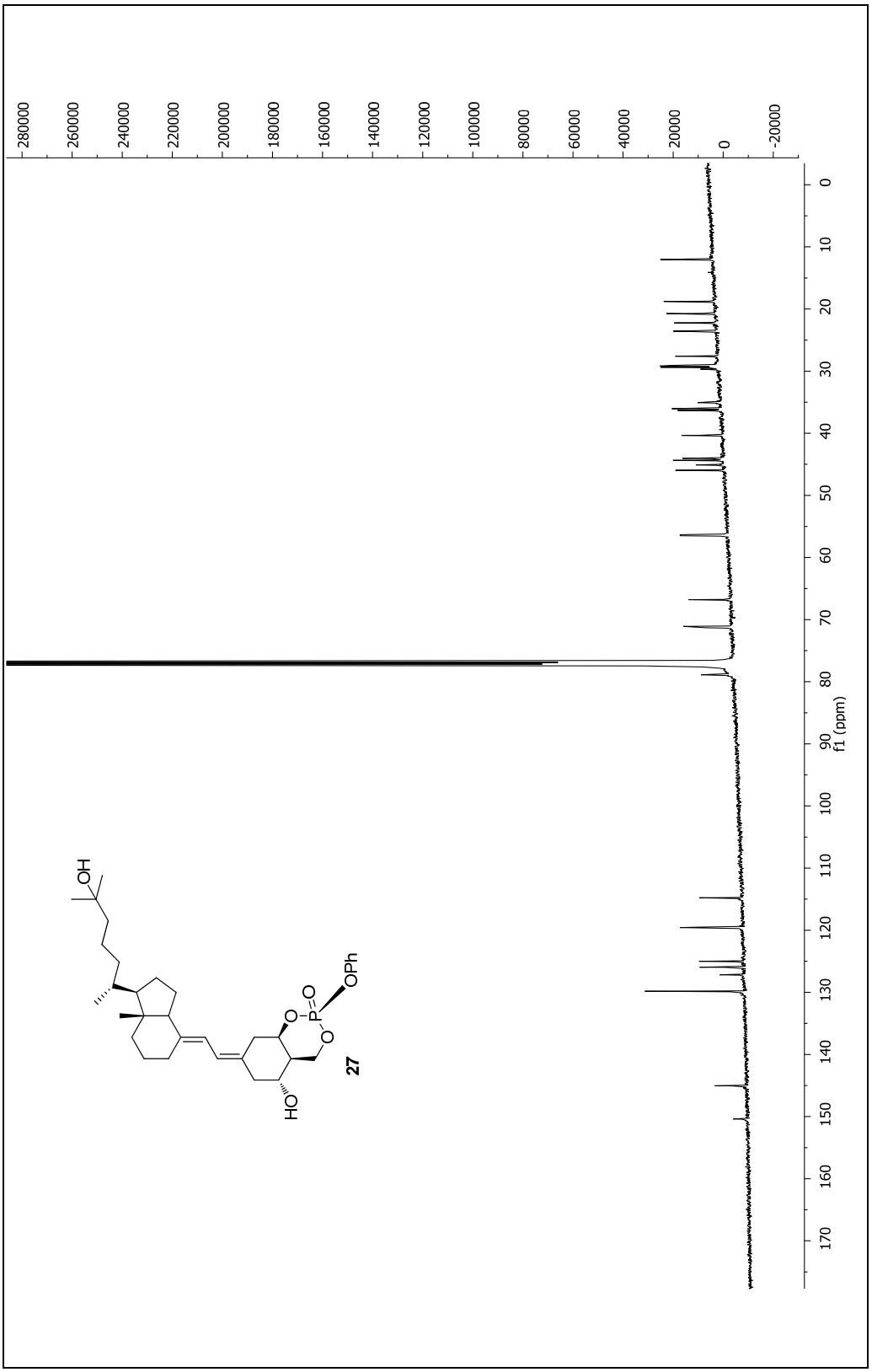
500 MHz ^{COSY} NMR of compound **28** in $CDCl_3$



500 MHz ^{NOESY} NMR of compound **28** in $CDCl_3$



500 MHz ^{1}H NMR of compound **27** in $CDCl_3$



125 MHz ^{1}H NMR of compound **27** in $CDCl_3$

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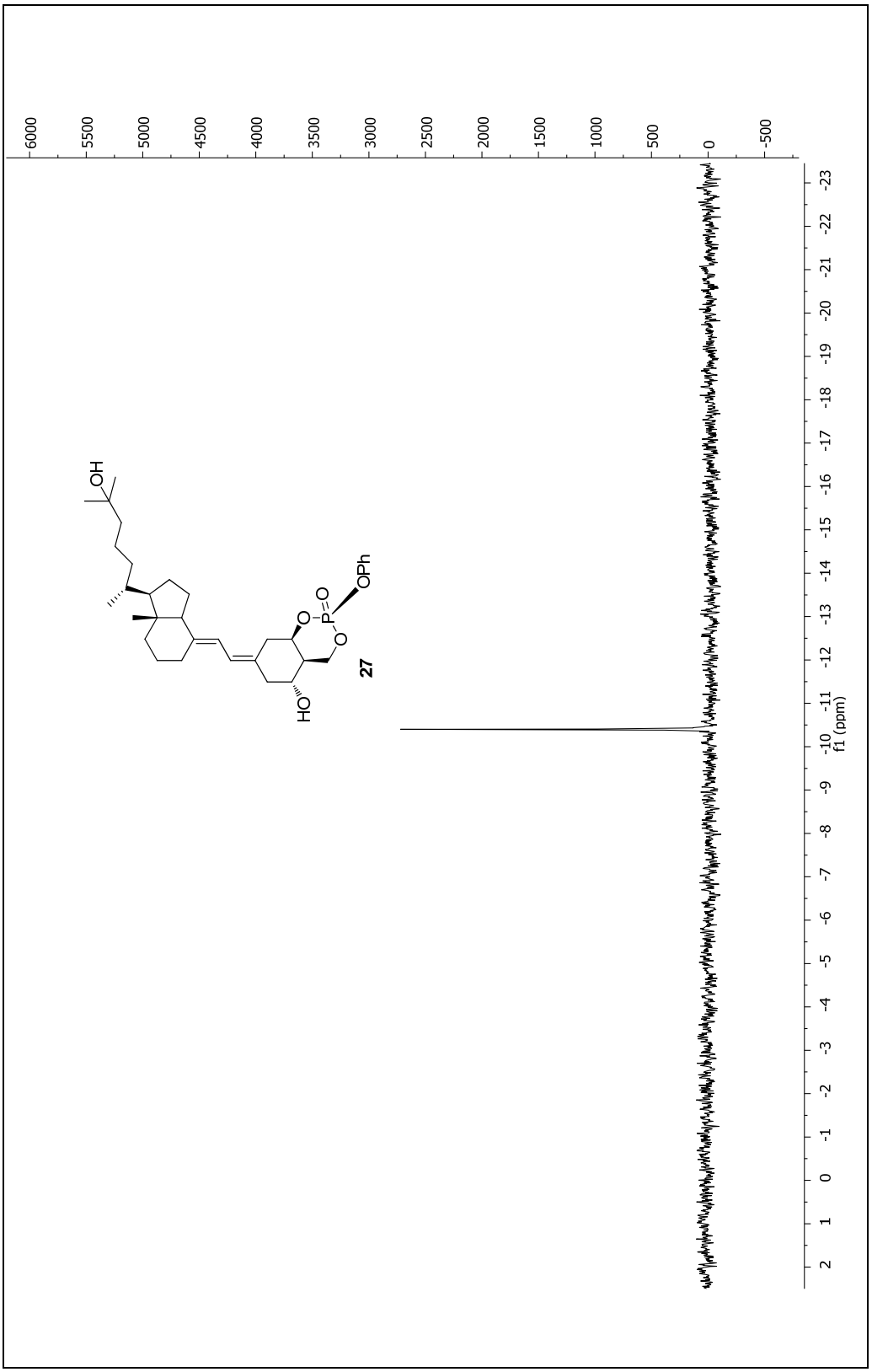
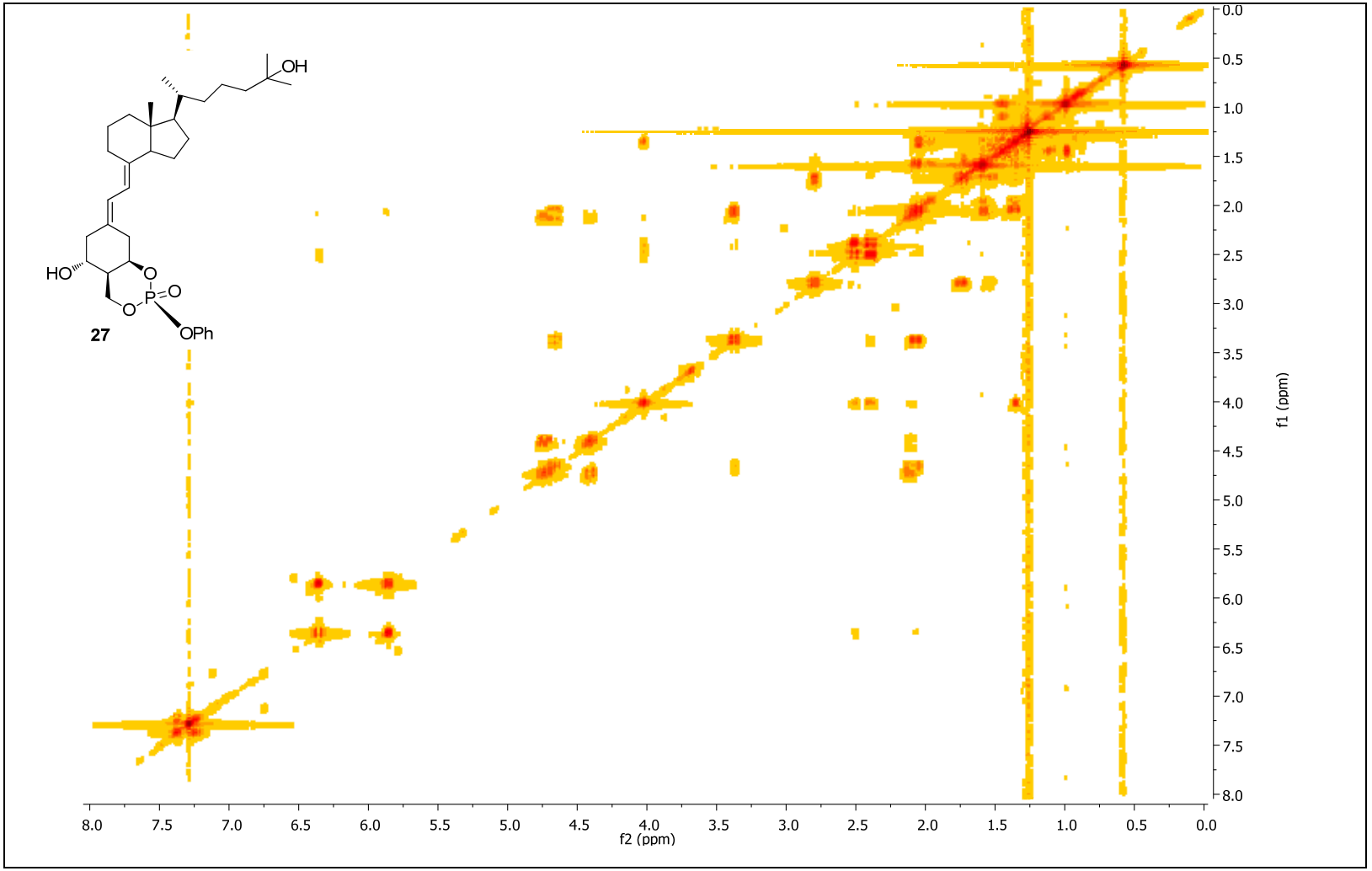
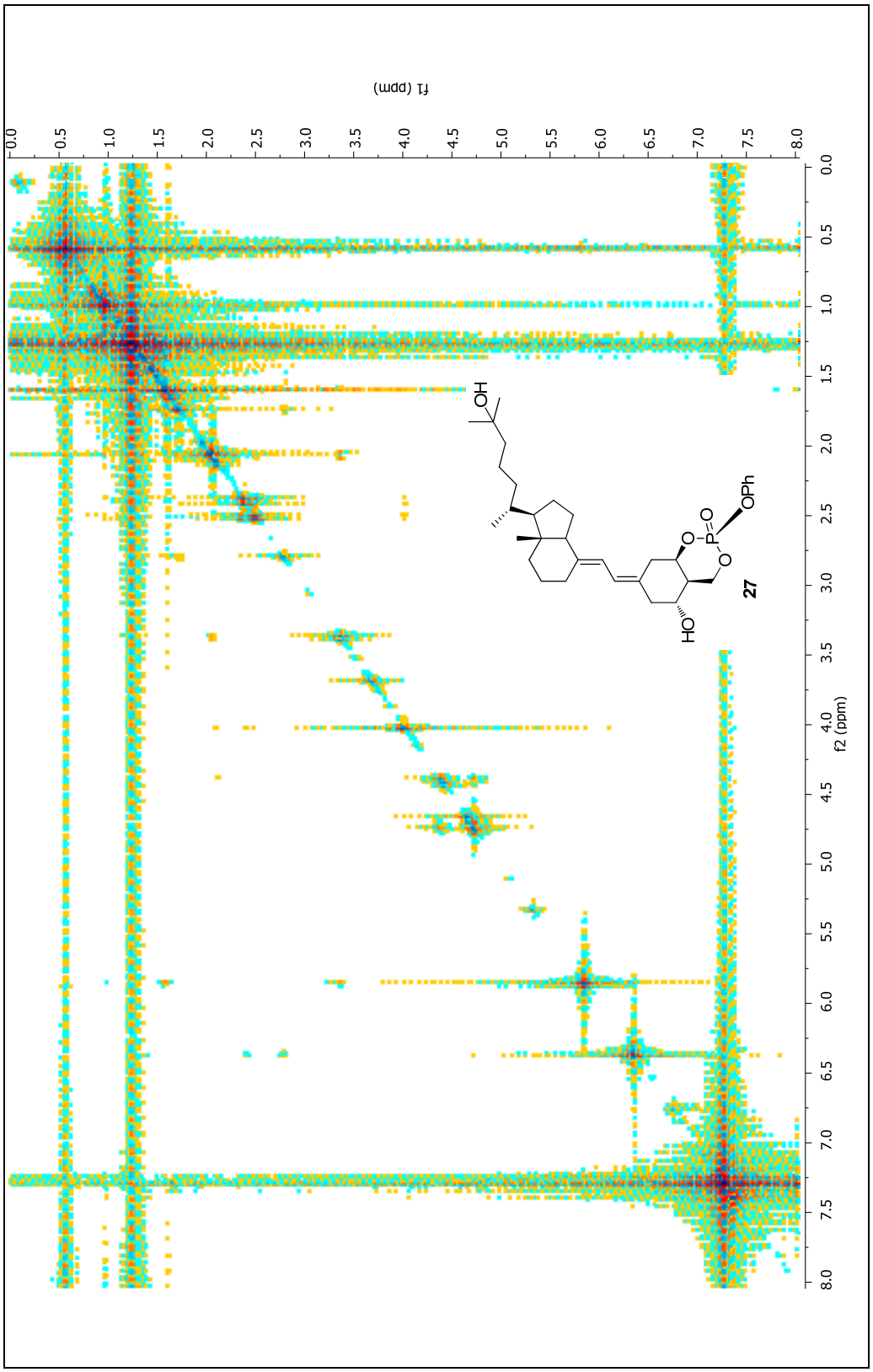


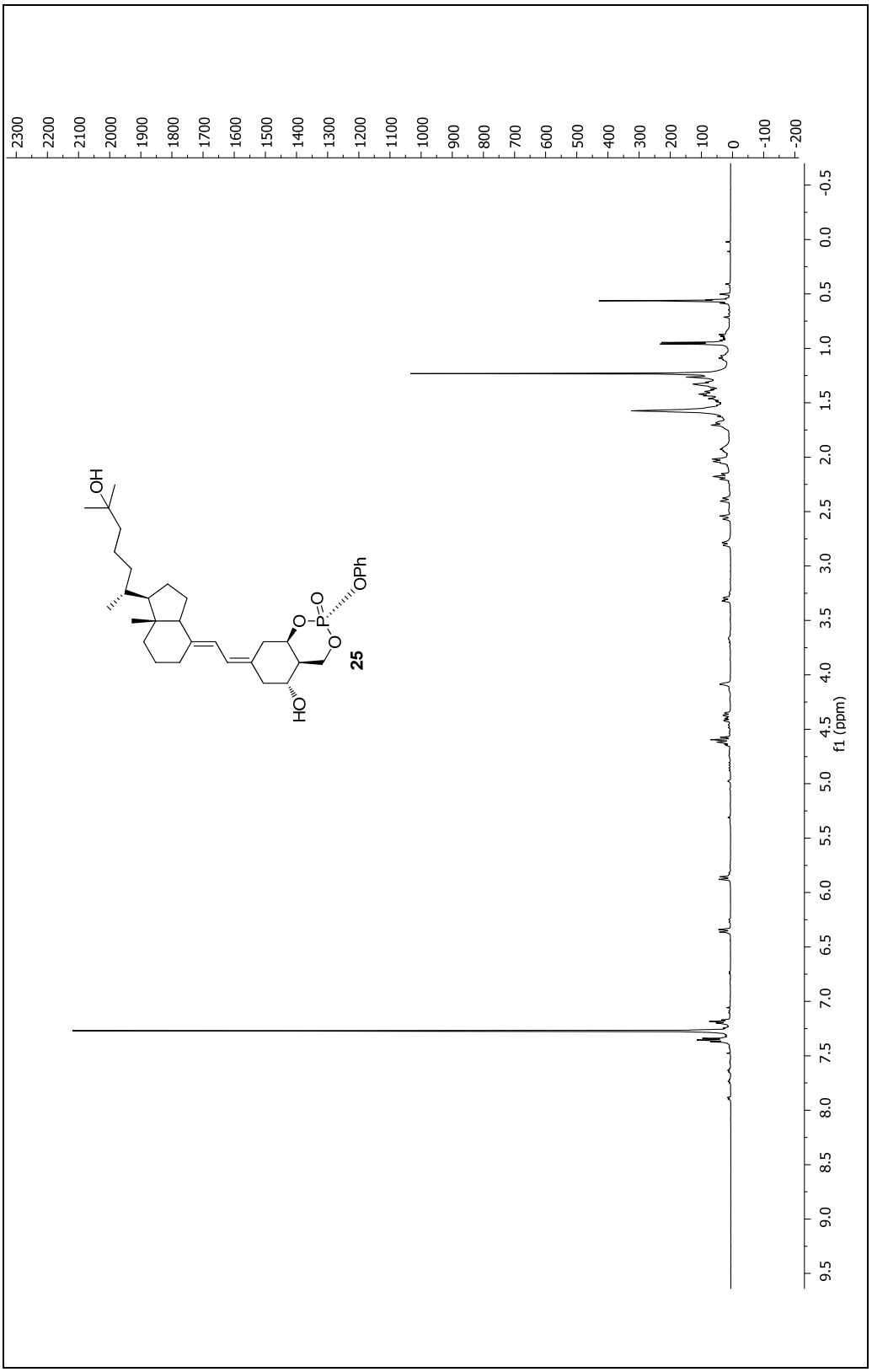
200 MHz ^{31}P NMR of compound **27** in $CDCl_3$



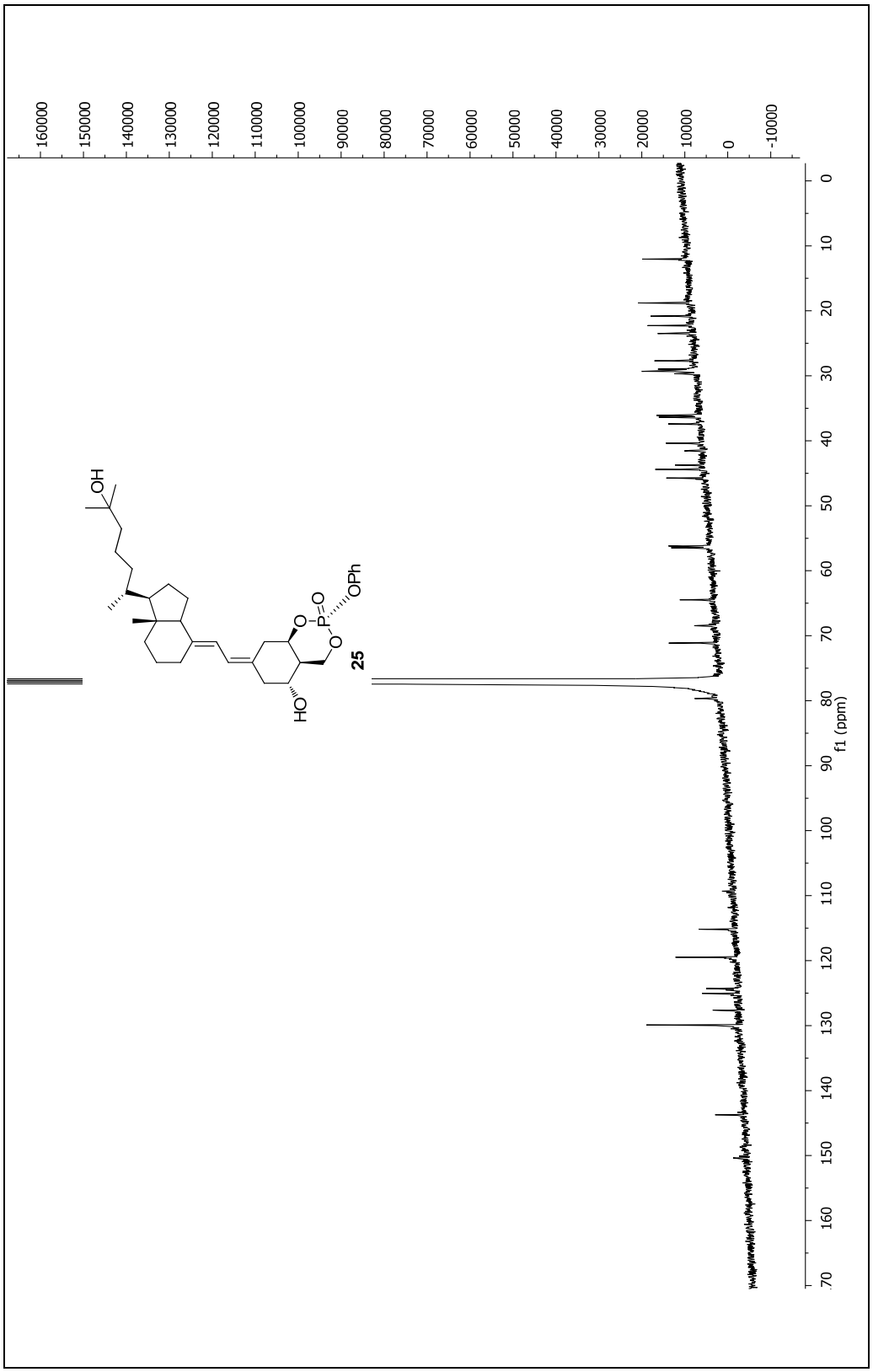
500 MHz ^{COSY} NMR of compound **27** in $CDCl_3$



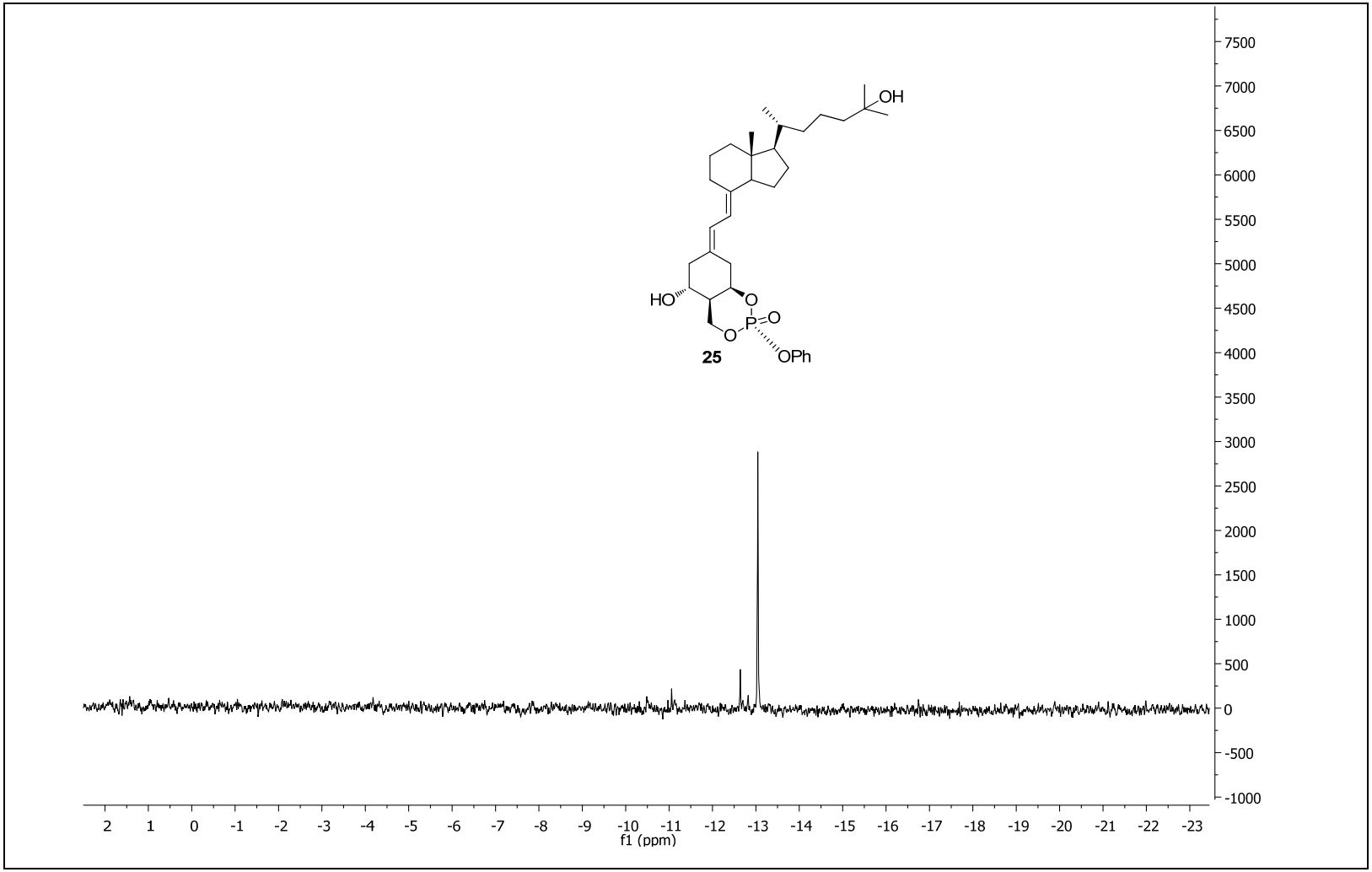
500 MHz ^{NOESY} NMR of compound **27** in $CDCl_3$



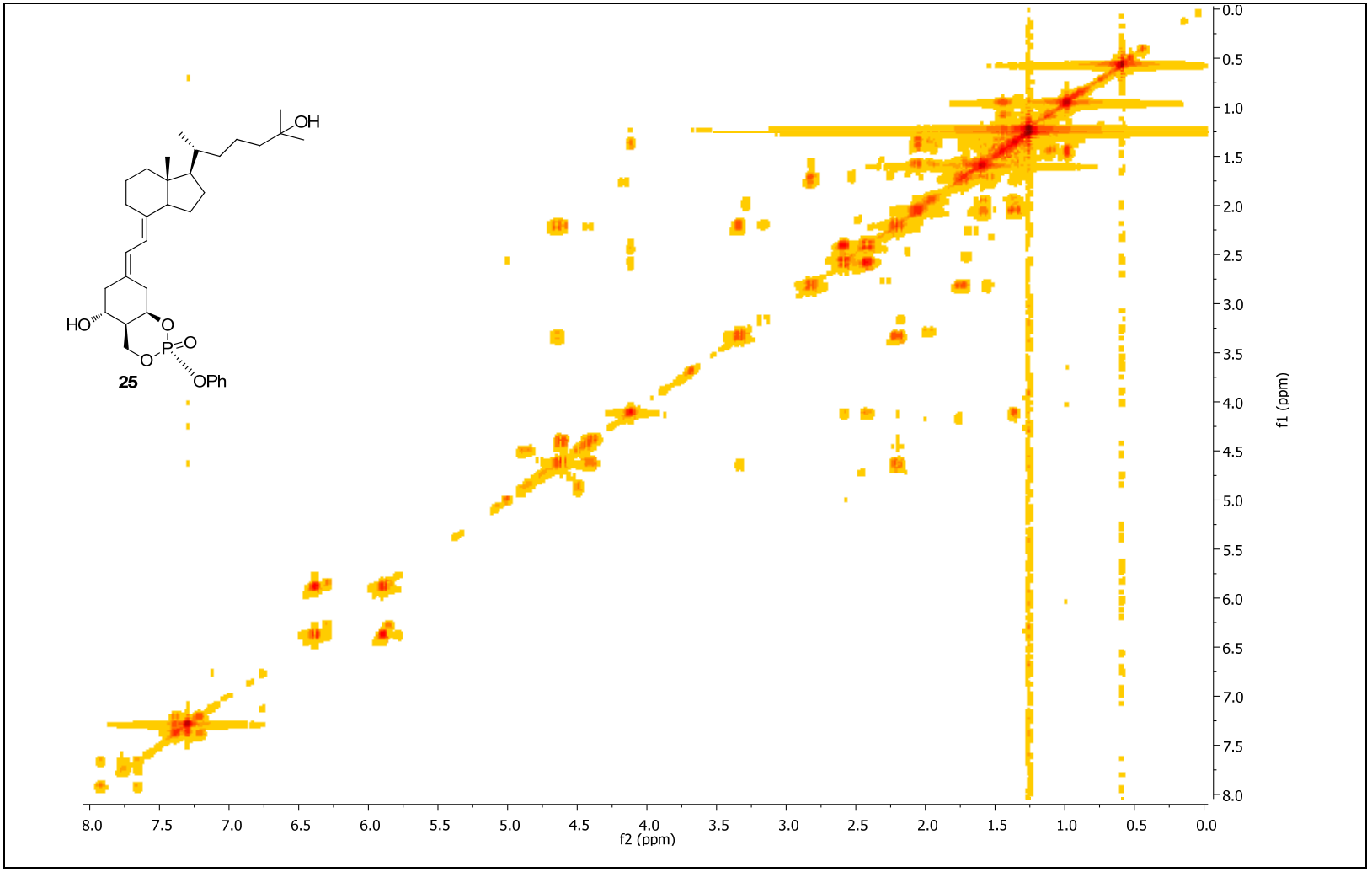
500 MHz ^{1}H NMR of compound **25** in $CDCl_3$



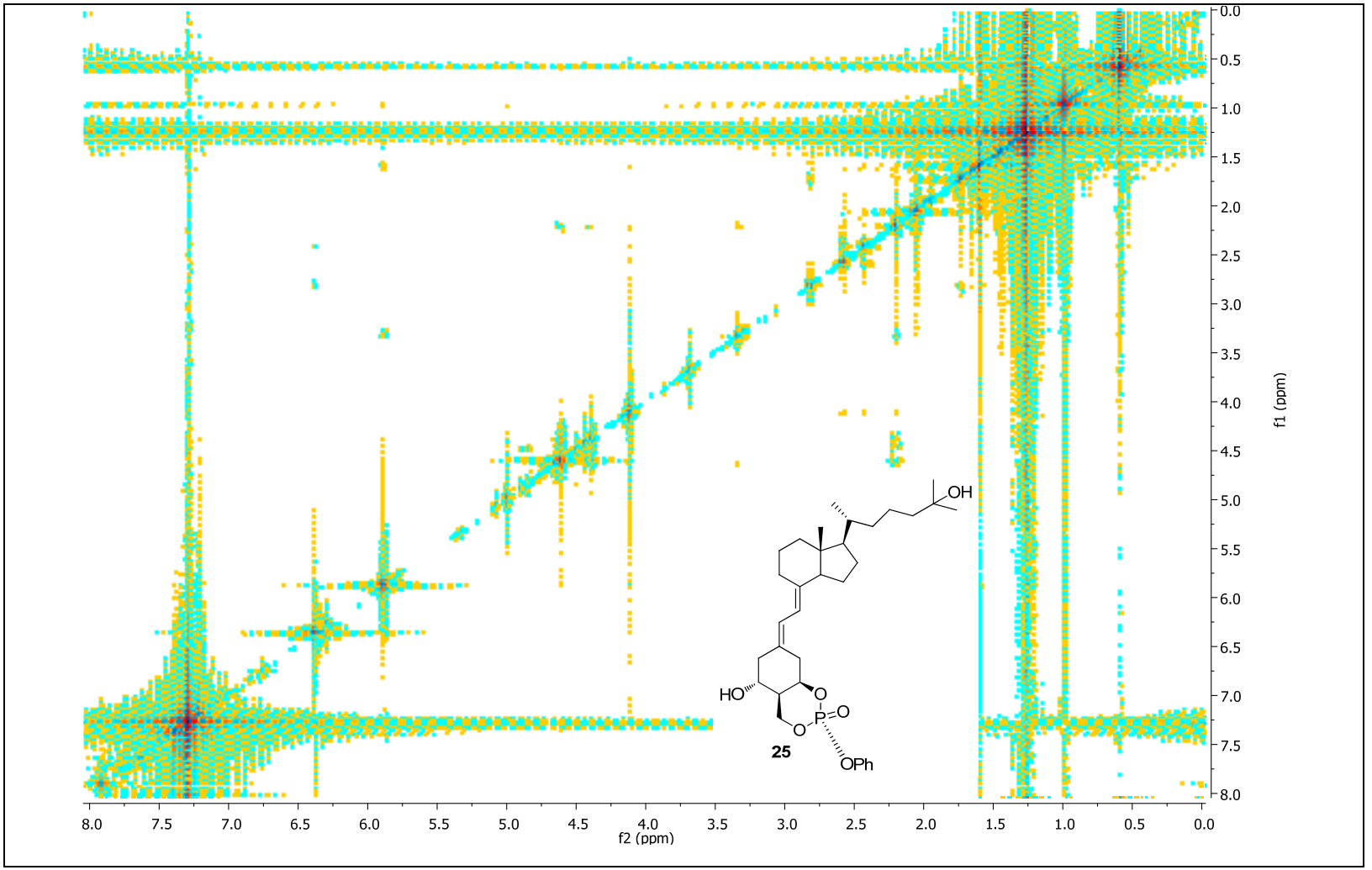
125 MHz ^{13}C NMR of compound **25** in $CDCl_3$



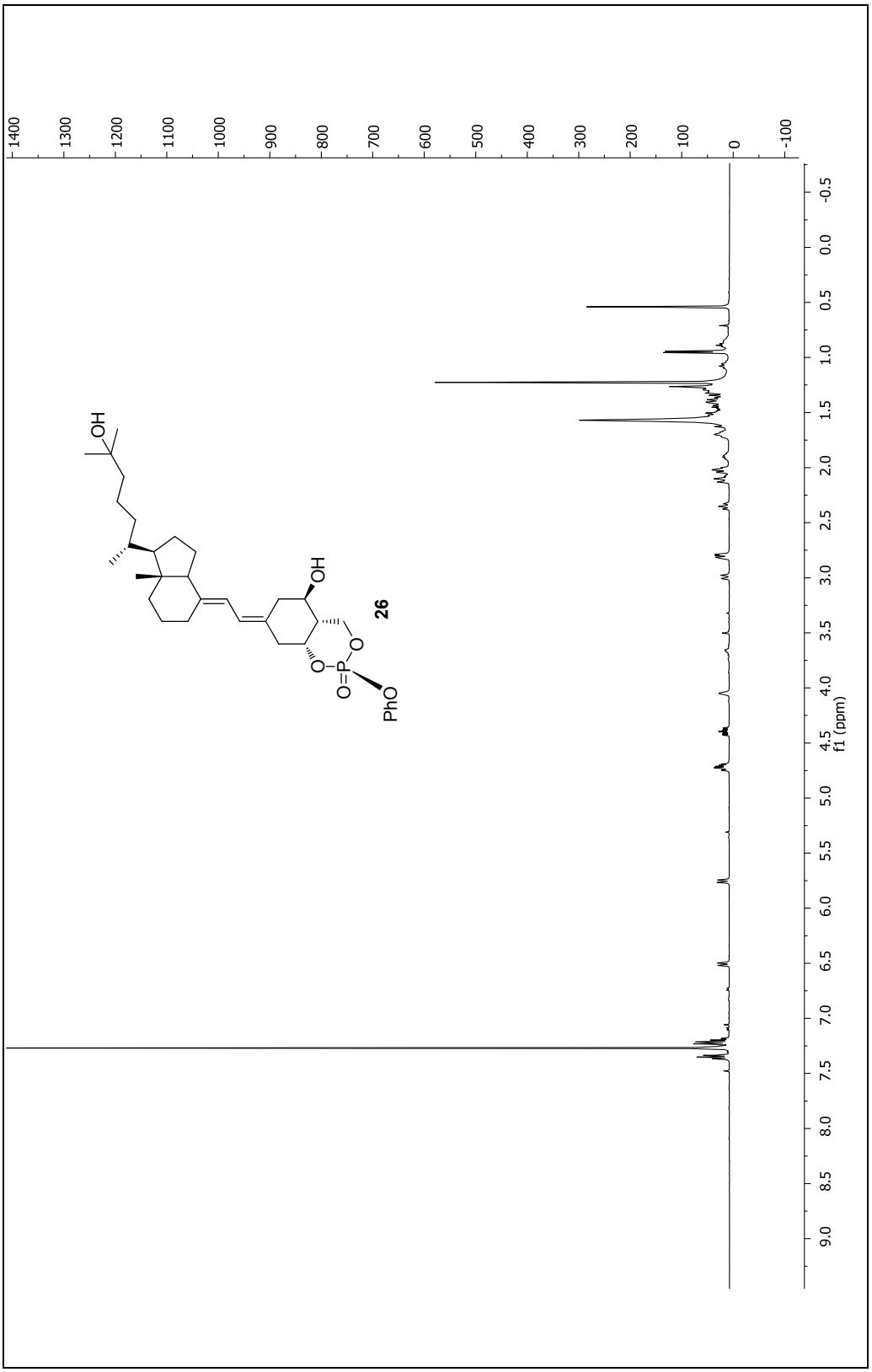
200 MHz ^{31}P NMR of compound **25** in $CDCl_3$



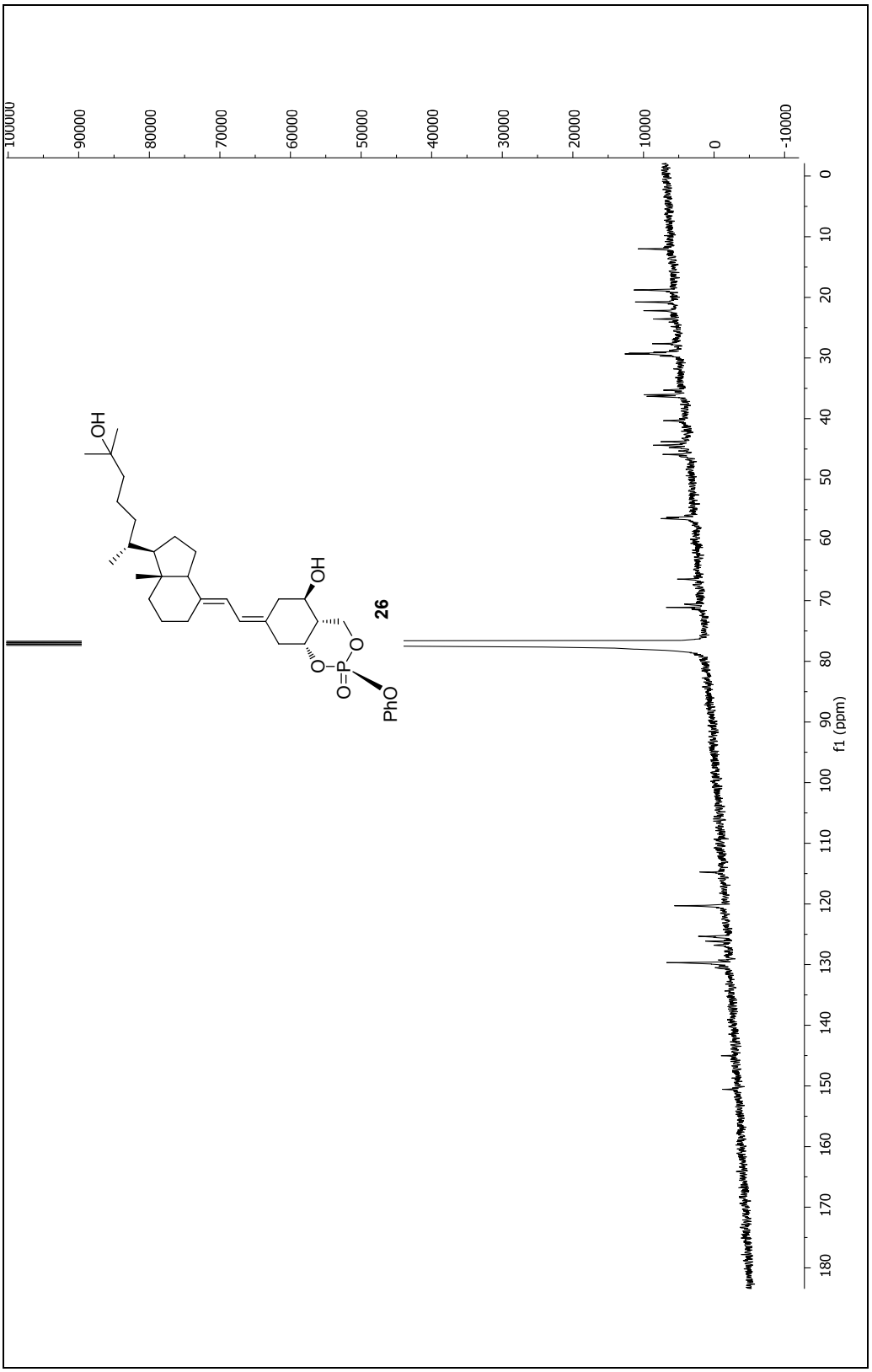
500 MHz ^{COSY} NMR of compound **25** in $CDCl_3$



500 MHz ^{NOESY} NMR of compound **25** in $CDCl_3$

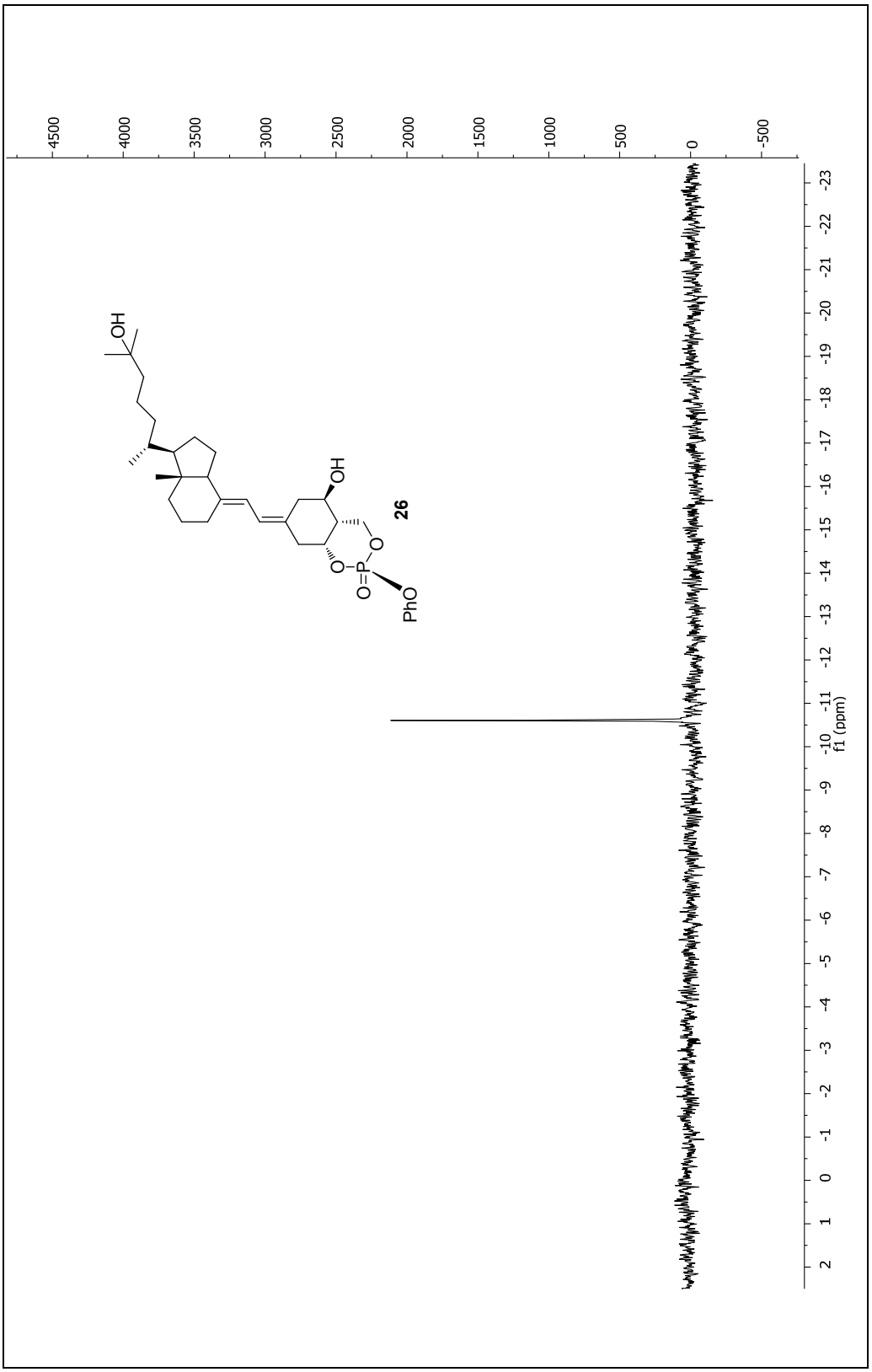


500 MHz ^{1}H NMR of compound **26** in $CDCl_3$

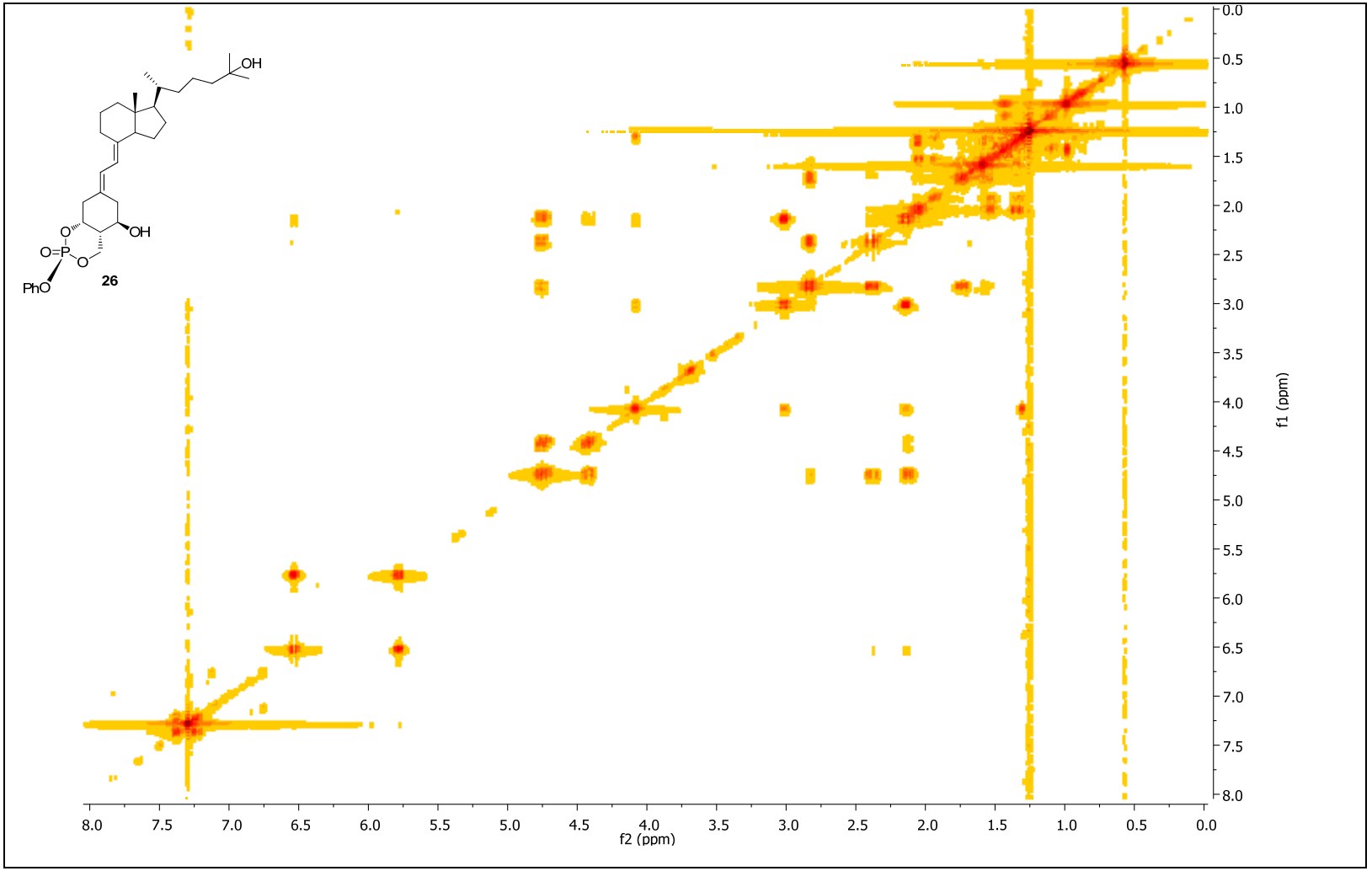


125 MHz ^{13}C NMR of compound **26** in $CDCl_3$

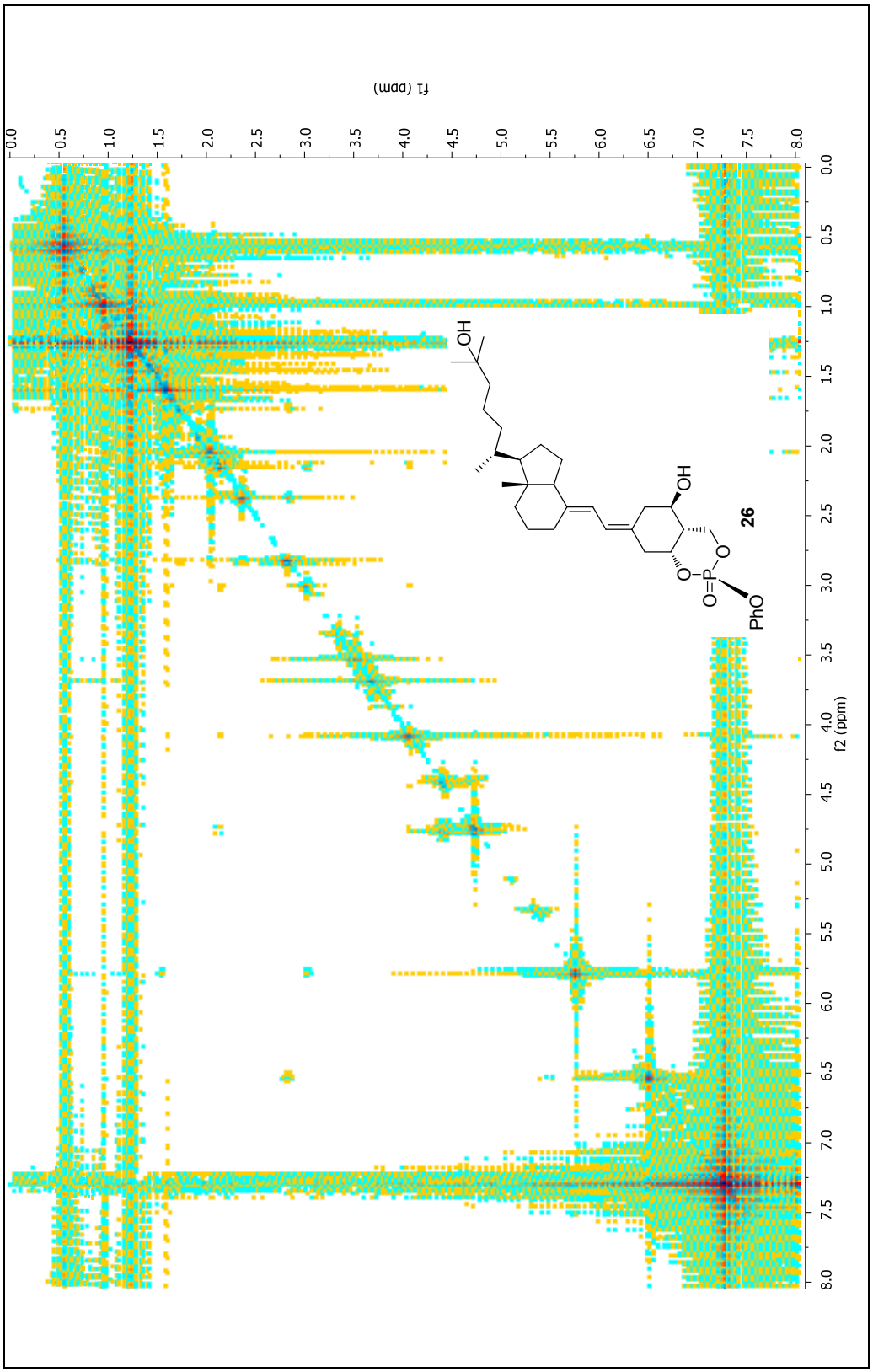
63



200 MHz ^{31}P NMR of compound **26** in $CDCl_3$



500 MHz ^{COSY} NMR of compound **26** in $CDCl_3$



500 MHz NOESY NMR of compound **26** in $CDCl_3$

Electronic Supplementary Material (ESI) for Chemical Communications