Supporting Information

"De Novo Synthesis of (–)-virginiamycin M_2 via an Asymmetric Hydration Sequence"

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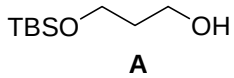
CONTENTS

General Methods and Materials. ^{1}H and ^{13}C NMR spectra were recorded on a 600 MHz spectrometer. Chemical shifts are reported relative to internal tetramethylsilane (δ 0.00 ppm) or $CDCl_3$ (δ 7.26 ppm) for ^{1}H and $CDCl_3$ (δ 77.0 ppm) for ^{13}C. Infrared (IR) spectra were obtained on a FT-IR spectrometer. Optical rotations were measured with a digital polarimeter in the solvent specified. Melting points were determined with a standard melting point apparatus and are uncorrected. Flash column chromatography was performed on 60-200 mesh silica gel. Analytical thin-layer chromatography was performed with precoated glass-backed plates and visualized by quenching of fluorescence and by charring after treatment with *p*-anisaldehyde or phosphomolybdic acid or potassium permanganate stain. R_f values are obtained by elution in the stated solvent ratios (v/v). Ether, THF, Methylene chloride and triethylamine were dried by passing through activated alumina column with argon gas pressure. Commercial reagents were used without purification unless otherwise noted. Air and/ or moisture- sensitive reactions were carried out under an atmosphere of argon/nitrogen using oven-dried glassware and standard syringe/septa techniques. HPLC analyses were run with either Chiralcell OD or AD columns, using HPLC grade solvents purchased from Aldrich.

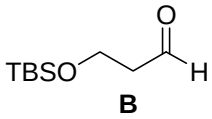
For spectra which contain mixtures of amide rotamers, the signals that can be assigned as specific to a particular rotamer are designated with a '*' for the major and '**' for the minor; signals that have contributions from both rotamers are not denoted with a special character.



A

3-(*tert*-butyldimethylsilyloxy)propan-1-ol (A). To an RBF under argon containing NaH-60% dispersion in mineral oil (21.0 g) was added THF (1000 mL). The reaction was stirred vigorously and addition of propanediol (40.0 g, neat, obtained from Aldrich® chemical company in 98% purity) was started using an addition funnel. After dropwise addition was complete the funnel was rinsed with a minimal amount of THF and removed from the flask. The reaction was allowed to stir for 45 min at RT over which time the initial grey suspension became white. Next, TBSCl (79.0 g) was added in several portions to the flask being careful to avoid overflow by the vigorous release of gases. The reaction was then allowed to stir for another 45 min. The reaction was then quenched SLOWLY with 100 mL of 10% aqueous Na_2CO_3 solution, this addition caused the cloudy reaction mixture to become clear and, when stirring was ceased, two layers formed. The bottom aqueous layer was cloudy and both layers were yellow in color. The two layers were separated and the aqueous layer was extracted with Et_2O. The combined organics were washed with brine and dried over $MgSO_4$ (Na_2SO_4 was a far inferior drying agent for this mixture). After concentration the crude **A** (100.4 g, 99%) was of sufficient purity for next reaction. Spectral data agreed with previous report.[1]

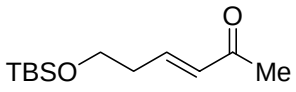
[1] Procedure used and spectral data are from: McDougal, P. G.; Rico, J. G.; Oh, Y.-I.; Condon, B. *J. Org. Chem.* **1986**, *51*, 3388-3390.



B

3-(*tert*-butyldimethylsilyloxy)propanal (B). Into a 2-necked 3L RBF equipped with an overhead mechanical stirrer an argon inlet adapter (14/20 – 24/40) and containing CH_2Cl_2 (750 mL) was added oxalyl chloride (19.2 mL) via syringe. A second equal portion of CH_2Cl_2 was then added and the mixture was cooled to –78^oC. The rubber septum on top of the argon adapter was then exchanged for a 60 mL addition funnel which was subsequently loaded with DMSO (26.7 mL) and dropwise addition began and lasted for 40 min. After addition was complete the reaction was allowed to stir for 10 min and the argon adapter was replaced with a Claisen head with argon inlet in the vertical shaft and a 250 mL pressure-equalizing addition funnel on the sidearm. The addition funnel was connected by tubing *via* the top to a bleach scrubber which was open to the atmosphere and served as a bubbler to monitor argon flow. Next, the addition funnel was loaded with mono TBS alcohol **A** (32.3 g) in 200 mL CH_2Cl_2. Slow addition was started and lasted for 2.5 hours. Immediately after addition of alcohol was complete, dropwise addition of Et_3N (118 mL) was started and lasted 40 min. The reaction was allowed to stir at –78^oC for 2 h. After this time the reaction was warmed to 0^oC by switching the dry ice bath with an ice/water bath. The reaction was quenched by slow addition of 250 mL water through the addition funnel. A two phase mixture formed and was allowed to sit overnight (not necessary). The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 75 mL) and the organics were then divided into two flasks to accommodate a 2 L separatory funnel. Each portion was washed with brine (100 mL).

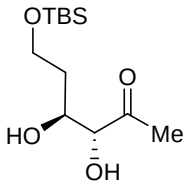
The combined aqueous layers were then extracted with Et_2O (100 mL) to remove any remaining product. The organics were then dried over Na_2SO_4 and concentrated by rotovap. Crude ^1H NMR of crude product showed product of sufficient purity for next step, the yield was 31.8 g (99%). Previous attempts at column chromatography indicated that this compound was unstable on silica gel. Spectral data agreed with previous report.[2]



15

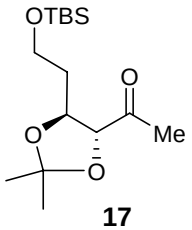
(*E*)-6-(*tert*-butyldimethylsilyloxy)hex-3-en-2-one (15). To crude aldehyde **B** (19.3 g, 0.103 mol) in CH_2Cl_2 (100 ml) was added (acetylmethylene)triphenylphosphorane (34.3 g, 0.108 mol) and the mixture was refluxed for 3 hours. The reaction mixture was cooled and then concentrated en vacuo. Halfway through concentration Et_2O (100 ml) was added so that a more easily-handled solid would result.[3] The resulting yellow solid mixture was dissolved in Et_2O and filtered over a plug of silica gel and washed with Et_2O. The filtrate was concentrated en vacuo (rotovap then high vacuum) and resulted in 65% yield (11.0 g) of enone **15** as a yellow oil. Spectral data agreed satisfactorily with previous report.[4]

[2] Trost, B. M.; Verhoeven, T. R. *J. Am. Soc. Chem*. **1980**, *102*, 4743-4745.
[3] Concentrating the sample from CH_2Cl_2 resulted in a gum-like solid that would not dry even after 24 h of high vacuum pumping and was thus more difficult to handle.
[4] Vijn, R. J.; Hiemstra, H.; Kok, J. J.; Knotter, M.; Speckamp, W. N. *Tetrahedron* **1987**, *43*, 5019-5021



16

(–)-(3*R*,4*S*)-6-(*tert*-butyldimethylsilyloxy)-3,4-dihydroxyhexan-2-one (16). Into a round bottom flask containing $K_3Fe(CN)_6$ (61.5 g, 187 mmol), K_2CO_3 (25.8 g, 187 mmol), $MeSO_2NH_2$ (17.7 g, 187 mmol), $NaHCO_3$ (15.7 mg, 187 mmol) and $(DHQ)_2PHAL$ (728 mg, 0.933 mmol) was added 270 mL of *t*-BuOH and 270 mL of water. The mixture was stirred at 0°C for 5 minutes and then to this solution was added OsO_4 (15.7 mg, 0.622 mmol) immediately followed by addition of enone **15** (14.2 g, 62.2 mmol). The reaction was stirred vigorously at 0°C for 5 hours. Ethyl acetate (250 mL) was added to the reaction mixture followed by quenching with solid sodium sulfite. The layers were separated and the aqueous layer was extracted with EtOAc (2 x 150 mL). The combined organic layers were washed with 200 mL of brine and then dried over Na_2SO_4. After concentration the crude mixture was purified by silica gel column chromatography (10-50% EtOAc/hexanes) to yield 11.5 mg (71%) of diol **16**. R_f = 0.10 (20% EtOAc:hexanes), $[\alpha]_D^{24}$ –46.9 (*c* 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 3452(br), 2954, 2929, 2857, 1717, 1472, 1463, 1389, 1360, 1253, 1086, 833, 812, 776, 663; ^1H NMR ($CDCl_3$, 600 MHz) δ 4.25 (m, 1H), 4.05 (dd, *J* = 5.4, 1.8 Hz, 1H), 3.89 (m, 1H), 3.81 (m, 1H), 3.71 (d, *J* = 5.4 Hz, 1H), 3.17 (d, *J* = 5.4 Hz, 1H), 2.27 (s, 3H), 1.85 (m, 1H), 1.73 (m, 1H), 0.88 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 208.6, 79.5, 71.5, 61.6, 35.1, 25.8, 25.7, 18.0, -5.5, -5.5; HRMS (ESI) calcd for $[C_{12}H_{26}NaO_4Si]^+$: 285.14926, Found: 285.14917.

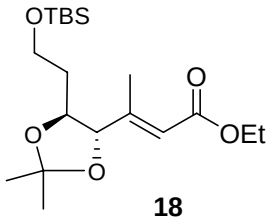


17

(+)-1-((4*R*,5*S*)-5-(2-(*tert*-butyldimethylsilyloxy)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethanone (17). To an RBF containing diol **16** (132 mg, 0.504 mmol) in acetone (500 μL) was added 2,2-dimethoxypropane (625 μL, 5.04 mmol) and camphorsulfonic acid (1 mg) and this mixture was placed in a warm sand bath[5] such that reflux began almost instantly. The reaction was allowed to reflux for 30 minutes, at which time TLC (PMA stain) indicated all starting material was consumed. The reaction mixture was then cooled to rt followed by addition of EtOAc (2 mL) then sat. aq. $NaHCO_3$ (0.5 mL). The mixture was stirred for 5 min and then the two layers were separated. The aqueous layer was then extracted (2 x 1 mL) with EtOAc and the organic layers were combined and washed with brine (1 x 1 mL) and dried over Na_2SO_4. After concentration the crude mixture was purified by silica gel column chromatography (10% EtOAc/hexanes) to yield 110 mg (72%) of acetonide **17**. R_f = 0.70 (20% EtOAc:hexanes), $[\alpha]_D^{24}$ +3.3 (*c* 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 2988, 2954, 2930, 2857, 1719, 1472, 1463, 1381, 1357, 1251, 1166, 1091, 939, 872, 832, 812, 774, 664; ^1H NMR ($CDCl_3$, 600 MHz) δ 4.12 (dt, *J* = 7.8, 3.6 Hz, 1H), 4.04 (d, *J* = 7.8 Hz, 1H), 3.75 (m, 2H), 2.25 (s, 3H), 1.96 (m, 1H), 1.82 (m, 1H), 1.44 (s, 3H), 1.42 (s, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 150

[5] It is crucial that the bath be preheated to ca. 50 °C as bringing the reaction slowly to reflux results in the formation of at least two other minor ketals resulting from reaction of the ketone moiety.

MHz) δ 207.9, 110.2, 85.3, 74.8, 59.4, 36.4, 27.2, 26.2, 26.2, 25.8, 18.2, -5.3, -5.4; HRMS (ESI) calcd for $[C_{15}H_{31}O_4Si]^+$: 303.19861, Found: 303.19878.



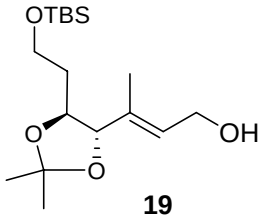
18

(–)-(*E*)-ethyl 3-((4*S*,5*S*)-5-(2-(*tert*-butyldimethylsilyloxy)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-enoate (18). To an RBF containing potassium tert-butoxide (8.0 mg, 0.073 mmol) in THF (100 μL) at 0°C was added phosphonate (18 mg, 0.079 mmol) in THF (200 μL) slowly via syringe. The mixture was allowed to stir for 10 min and then acetonide **17** (20 mg, 0.0622 mmol) in THF (150 μL) was added dropwise via syringe. The reaction was allowed to stir at 0°C for 1.5 h at which time TLC (UV, $KMnO_4$) indicated all starting material was consumed. The reaction was then quenched by the addition of 200 μL of pH 7.0 buffer solution followed by 500 μL brine. This mixture is extracted with ether (3 x 2 mL) and the combined organics are dried over Na_2SO_4. After concentration the crude mixture (10:1 *E:Z*) was purified by silica gel column chromatography (20% EtOAc/hexanes) to yield 20 mg (84%) of pure *E*-enoate **18**.

Alternatively from diol F[6]: To an RBF containing diol **E** (480 mg, 1.45 mmol) in acetone:CH_2Cl_2 (1:1, 9.6 mL) was added 2,2-dimethoxypropane (1.78 mL, 14.4 mmol) and camphorsulfonic acid (6 mg). The mixture was allowed to stir for 25 min and was then quenched by addition of ether (10 mL) and sat. aq. $NaHCO_3$ (3 mL). The layers were separated and the organic layer was washed with brine (1 x 5 mL). After concentration the crude mixture was purified by silica gel column chromatography (10%

[6] This diol is mentioned at end of this document.

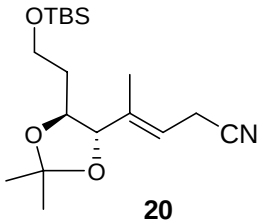
EtOAc/hexanes) to yield 462 mg (80%) of acetonide **18**. R_f = 0.60 (20% EtOAc:hexanes), $[\alpha]_D^{24}$ –19.6 (*c* 1.2, CH_2Cl_2); IR (neat, cm^{-1}) 2985, 2954, 2930, 2858, 1718, 1654, 1472, 1463, 1379, 1369, 1251, 1221, 1153, 1088, 1040, 939, 871, 774, 664; ^1H NMR ($CDCl_3$, 600 MHz) δ 5.96 (s, 1H), 4.17 (dq, *J* = 7.2, 1.8 Hz, 2H), 4.08 (d, *J* = 8.4 Hz, 1H), 3.92 (dt, *J* = 8.4, 3.0 Hz, 1H), 3.75 (m, 2H), 2.16 (d, *J* = 1.2 Hz, 3H), 1.84 (m, 1H), 1.75 (m, 1H), 1.43 (s, 6H), 1.28 (t, *J* = 7.2 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 166.2, 154.1, 117.6, 109.2, 85.2, 76.4, 59.8, 59.6, 35.7, 27.4, 26.6, 25.8, 18.2, 14.3, 14.2, -5.3, -5.4; HRMS (ESI) calcd for $[C_{19}H_{36}O_5SiNa]^+$: 395.22242, Found: 395.22271.



19

(–)-(*E*)-3-((4*S*,5*S*)-5-(2-(*tert*-butyldimethylsilyloxy)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-en-1-ol (19). To an RBF containing ester **18** (1.20 g, 3.23 mmol) in THF (8 mL) at -78oC was added DIBAL (9.70 mL of 1.0 M hexane solution) slowly via syringe. The reaction was allowed to stir for 10 min and was then quenched with acetone pre-cooled to -78^{o}C and then warmed to rt. Once at rt 20% sodium, potassium tartrate solution (2 mL) was added and vigorously stirred for 30 minutes. The layers were separated and the organic layer was washed with brine (1 x 3 mL) and dried over Na_2SO_4. After concentration the crude mixture was purified by silica gel column chromatography (30% EtOAc/hexanes) to yield 995 mg (94%) of allylic alcohol **19**. R_f = 0.25 (20% EtOAc:hexanes), $[\alpha]_D^{24}$ –20.0 (*c* 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 3410(br), 2985, 2954, 2929, 2857, 1472, 1463, 1369, 1250, 1168, 1085, 1005, 878, 774, 665; ^1H NMR

($CDCl_3$, 600 MHz) δ 5.73 (t, J = 6.6 Hz, 1H), 4.21 (m, 2H), 3.99 (d, J = 9.0 Hz, 1H), 3.90 (dt, J = 9.0, 3.0 Hz, 1H), 3.74 (m, 2H), 1.72 (m, 2H), 1.69 (s, 3H), 1.41 (s, 3H), 1.41 (s, 3H), 0.88 (s, 9H), 0.04 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 134.4, 128.7, 108.4, 86.2, 75.1, 59.8, 59.1, 35.4, 27.4, 26.8, 25.8, 18.2, 11.7, -5.3, -5.3; HRMS (ESI) calcd for $[C_{17}H_{34}O_4SiNa]^+$: 353.21186, Found: 353.21187.



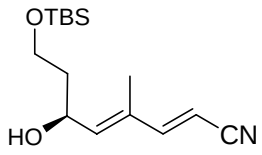
20

(–)-(*E*)-4-((4*S*,5*S*)-5-(2-(*tert*-butyldimethylsilyloxy)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-3-enenitrile (20). To a flask containing CH_3CN (2.0 mL) was added first PPh_3 (160 mg, 0.606 mmol) and then I_2 (150 mg, 0.606 mmol) and yellow solution was allowed to stir for 5 min. Imidazole (50 mg, 0.757 mmol) was then added and after 30 s the mixture became cloudy white with black particles[7] at bottom of flask. Alcohol **19** (100 mg, 0.303 mmol) in CH_3CN (0.50 mL) was then added and over the course of 2 min the reaction became dark orange signaling the complete consumption of alcohol as evidenced by TLC (UV, $KMnO_4$). At this point the reaction mixture was filtered through a plug of silica gel[8] with the aid of 50 mL of 20% ether:hexanes to remove colored polar impurities. The filtrate was then concentrated *en vacuo* and redissolved in CH_3CN (2.5 mL). NaCN (50 mg, 0.909 mmol) was added and the mixture was brought to reflux.

[7] An orange color can be seen leaching off this solid as the reaction progresses and when only 1 equiv of I_2/PPh3 is used the black particles are not present and no desired product is observed

[8] Although the iodo-intermediate is clearly detectable by TLC, without this intermediate filtration no cyanide product is formed. This is likely due to the formation of ICN with CN^- and excess I_2 which causes oxidative destruction of the reaction mixture. TLC plates of crude mixture before and after filtration are identical (UV, anisaldehyde), ruling out the possibility that a different intermediate is taken into the next step.

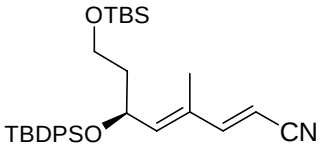
After 3.5 h of reflux the mixture was cooled to rt and diluted with ether (15 mL) followed by sat. aq. $Na_2S_2O_3$ (2 mL), which caused the cloudy white solution to become a clear yellow. After concentration the crude mixture was purified by silica gel column chromatography (20% Et_2O/hexanes) to yield 50 mg (50%) of nitrile **20**. R_f = 0.80 (40% EtOAc:hexanes), $[\alpha]_D^{24}$ –36.4 (*c* 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 2987, 2930, 2857, 1472, 1379, 1369, 1251, 1168, 1090, 1037, 878, 835, 776; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 5.56 (t, *J* = 7.2 Hz, 1H), 4.01 (d, *J* = 8.4 Hz, 1H), 3.90 (dt, *J* = 8.4, 3.0 Hz, 1H), 3.72 (m, 2H), 3.11 (d, *J* = 7.2 Hz, 2H), 1.72 (m, 2H), 1.72 (s, 3H), 1.41 (s, 6H), 0.88 (s, 9H), 0.05 (s, 3H), 0.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 138.6, 117.5, 116.4, 108.7, 85.3, 75.3, 59.6, 35.4, 27.4, 26.7, 25.8, 18.2, 16.1, 12.0, -5.3(2C); HRMS (ESI) calcd for $[C_{18}H_{33}NO_3SiNa]^+$: 362.21219, Found: 362.21227.



21

(+)-(*S*,2*E*,4*E*)-8-(*tert*-butyldimethylsilyloxy)-6-hydroxy-4-methylocta-2,4-dienenitrile (21). To a flask containing allylic nitrile **20** (45 mg, 0.133 mmol) in MeOH (550 μL) was added K_2CO_3 (21 mg, 0.152 mg) and stirred at rt for 3.5 h, at which time the reaction was determined complete by TLC (UV, anisaldehyde). The reaction was quenched by the addition of ether and water, the layers were separated and the aqueous layer was extracted with ether (2 x 2 mL). The combined organic layers were washed with brine (1 x 1 mL) and dried over Na_2SO_4. After concentration the crude mixture was purified by silica gel column chromatography (10-20% EtOAc/hexanes) to yield 30 mg (81%) of alcohol **21**. R_f = 0.70 (40% EtOAc:hexanes), $[\alpha]_D^{24}$ +26.8 (*c* 1.0, CH_2Cl_2); IR (neat, cm^-

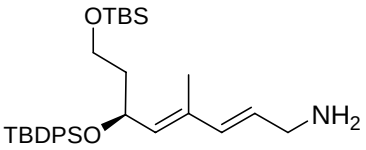
[1]) 3467(br), 2929, 2857, 2218, 1628, 1600, 1472, 1256, 1095, 966, 836, 776; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.02 (d, J = 16.2 Hz, 1H), 5.88 (d, J = 8.4 Hz, 1H), 5.31 (d, J = 16.2 Hz, 1H), 4.75 (m, 1H), 3.90 (ddd, J = 10.8, 6.0, 4.2 Hz, 1H), 3.82 (ddd, J = 10.8, 8.4, 3.6 Hz, 1H), 3.39 (d, J = 2.4 Hz, 1H), 1.83 (m, 1H), 1.79 (d, J = 1.2 Hz, 3H), 1.69 (m, 1H), 0.90 (s, 9H), 0.09 (s, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 154.4, 143.6, 132.3, 118.3, 95.4, 68.4, 61.7, 38.0, 25.8, 18.0, 11.9, -5.5(2C); HRMS (ESI) calcd for $[C_{15}H_{27}NO_2SiNa]^+$: 304.17033, Found: 304.17038.



C

(–)-(*S*,2*E*,4*E*)-8-(*tert*-butyldimethylsilyloxy)-6-(*tert*-butyldiphenylsilyloxy)-4-methylocta-2,4-dienenitrile (C). To a flask containing alcohol **21** (25 mg, 0.089 mmol) in CH_2Cl_2 (175 μL) at 0^{o}C was added imidazole (12 mg, 0.18 mmol) followed by TBDPSCl (25 μL, 0.090). The reaction was stirred at 0^{o}C for 1 h, at which time it was determined complete by TLC (UV, anisaldehyde). The reaction was diluted with ether and filtered through a plug of silica gel. After concentration the crude mixture was purified by silica gel column chromatography (0-5% EtOAc/hexanes) to yield 41 mg (89%) of TBDPS ether **C**. Spectral data agreed with previous report.[9] $[\alpha]_D^{24}$ –94.4 (*c* 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.65-7.59 (m, 4H), 7.42-7.31 (m, 6H), 6.79 (d, J = 16.2 Hz, 1H), 5.70 (d, J = 8.4 Hz, 1H), 5.07 (d, J = 16.2 Hz, 1H), 4.73 (ddd, J = 8.4, 6.6, 6.0 Hz, 1H), 3.70 (m, 1H), 3.56 (m, 1H), 1.90 (m, 1H), 1.63 (m, 1H), 1.22 (s, 3H), 1.05 (s, 9H), 0.84 (s, 9H), 0.00 (s, 3H), -0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz)

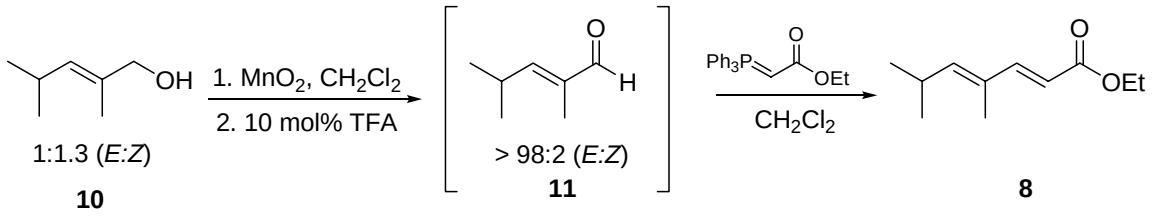
δ 154.5, 144.3, 135.8, 135.8, 134.0, 133.6, 131.2, 129.6, 129.6, 127.5, 127.4, 118.4, 94.7, 67.4, 58.9, 40.8, 26.9, 25.8, 19.2, 18.1, 11.3, -5.4, -5.4.



5

(S,2E,4E)-8-(*tert*-butyldimethylsilyloxy)-6-(*tert*-butyldiphenylsilyloxy)-4-methylocta-2,4-dien-1-amine (5). Primary amine **5** was synthesized using the procedure of Schlessinger[9]: Alane[10] (150 μL of a 0.50 M solution in THF) was added to nitrile **C** in THF (75 μL) at 0°C. The reaction was allowed to stir for 1 h at which time the reaction was determined complete by TLC (UV, anisaldehyde). The reaction mixture was then diluted with diethyl ether (1 mL) and 1 M NaOH solution was dripped in until white precipitate stops forming (ca. 200 μL). The layers are separated and the aqueous is extracted with more ether (2 x 0.500 mL) and the combined organics are washed with brine and dried over Na_2SO_4. After concentration the crude mixture was purified by silica gel column chromatography (5% MeOH/EtOAc) to yield 7 mg (70%) of allylic amine **5**. The product matched the spectral data previously reported.[9] $[\alpha]_D^{24}$ –23.3 (*c* 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.66-7.61 (m. 4H), 7.39-7.29 (m, 6H), 5.98 (d, *J* = 15.6 Hz, 1H), 5.57 (dt, 15.6, 6.0 Hx, 1H), 5.37 (d, *J* = 8.4 Hz, 1H), 4.69 (ddd, *J* = 9.0, 6.6, 6.0 Hz, 1H), 3.64-3.60 (m, 1H), 3.55-3.51 (m, 1H), 3.32 (d, *J* = 6.0 Hz, 2H), 1.90-1.84 (m, 1H), 1.65-1.59 (m, 1H), 1.52-1.40 (bs, 2H), 1.26 (s, 3H), 1.03 (s, 9H), 0.82 (s, 9H), -0.03 (s, 3H), -0.03 (s, 3H)

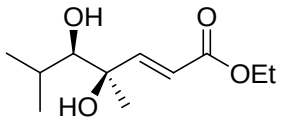
[9] Schlessinger, R. H.; Li, Y.-J. *J. Am. Chem. Soc.* **1996**, *118*, 3301-3302
[10] AlH_3 solution prepared from lithium aluminum hydride and sulfuric acid as described in: Brown, H. C.; Yoon, N. M. *J. Am. Chem. Soc.* **1966**, *88*, 1464-1472



(2*E*,4*E*)-Ethyl 4,6-dimethylhepta-2,4-dienoate (8). Allylic alcohol **10** (7.0 g, 61 mmol) was added to a RBF in CH_2Cl_2 (120 mL) followed by addition of 10 mass equivalents of activated MnO_2 (70 g). The reaction was allowed to stir for 24 hours at RT when determined complete by TLC (UV, $KMnO_4$). The reaction mixture was then filtered through celite and concentrated to approximately 100 mL. The reaction mixture was again placed under an inert atmosphere and 10 mol% trifluoroacetic acid (528 μl, 6.1 mmol) was added via syringe. This isomerization was allowed to take place for 18 hours when determined complete (^{1}H NMR). The TFA in the flask was quenched using sat. aqueous $NaHCO_3$ and the mixture was washed with brine and dried over Na_2SO_4. The crude mixture was then concentrated to approximately 100 mL[11] and 1.1 equivalents of (carboethoxymethylene)triphenylphosphorane (22.7 g, 67 mmol) was added to the flask in one portion. The mixture was allowed to stir at RT for 2 days until determined complete by TLC (UV, anisaldehyde stain). The crude mixture was concentrated *en vacuo* and immediately subjected to flash column chromatography on silica gel (10% EtOAc/hexanes) to yield 7.9 g (72%, 3 steps) of dienoate **8** as a clear, colorless oil. R_f = 0.59 (4:1 hexanes:EtOAc); IR (neat, cm^{-1}) 2962, 2870, 1710, 1623, 1465, 1393, 1365, 1305, 1283, 1265, 1249, 1145, 1120, 1096, 1029, 981, 844, 748; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.28 (d, J = 15.6 Hz, 1H), 5.77 (d, J = 15.6 Hz, 1H), 5.70 (d, J = 9.0 Hz, 1H), 4.19 (q, J = 7.2 Hz, 2H), 2.66 (m, 1H), 1.77 (d, J = 1.2 Hz, 3H), 1.29 (t, J = 7.2 Hz, 3H),

[11] When intermediate aldehyde **11** is fully concentrated, the combined yield for the first two steps falls to 65%; therefore, we found it best to carry the crude material forward.

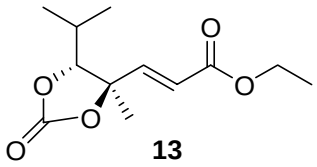
0.99 (d, J = 6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 167.7, 150.0, 149.3, 130.7, 115.8, 60.2, 28.0, 22.5 (2C), 14.5, 12.2; HRMS (ESI) calcd for $[C_{11}H_{19}O_2]^+$: 183.1379, Found: 183.1385.



12

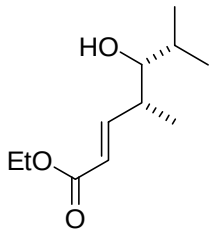
(+)-(*E*,4*R*,5*R*)-Ethyl 4,5-dihydroxy-4,6-dimethylhept-2-enoate (12). Into a round bottom flask containing $K_3Fe(CN)_6$ (49.8 g, 151 mmol), K_2CO_3 (20.7 g, 151 mmol), $MeSO_2NH_2$ (14.4 g, 151 mmol), $NaHCO_3$ (12.7 g, 151 mmol) and hydroquinidine-4-methyl-2-quinolyl ether (1.18 g, 2.52 mmol) was added 130 mL of *t*-BuOH and 130 mL of water. The mixture was stirred at 0°C for 5 minutes and then to this solution was added OsO_4 (128 mg, 0.505 mmol) immediately followed by addition of dienoate **8** (9.19 mg, 50.5 mmol). The reaction was stirred vigorously at 0°C for 24 hours. Ethyl acetate (50 mL) was added to the reaction mixture followed by quenching with solid sodium sulfite. The layers were separated and the aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with 100 mL of brine and then dried over Na_2SO_4. After concentration the crude mixture was purified by silica gel column chromatography (30% EtOAc/hexanes) to yield 8.17 g (75%) of diol **12**. R_f = 0.11 (4:1 hexanes:EtOAc), $[\alpha]_D^{24}$+ 3.4 (*c* 0.5, CH_2Cl_2); IR (neat, cm^{-1}) 3448, 2962, 2874, 1698, 1655, 1467, 1368, 1303, 1279, 1179, 1096, 1031, 984, 869, 725, 679; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 6.89 (d, J = 15.6 Hz, 1H), 5.99 (d, J = 15.6 Hz, 1H), 4.10 (q, J = 7.2 Hz, 2H), 3.27 (dd, J = 4.8, 3.6 Hz, 1H), 2.32 (s, 1H), 1.95 (d, J = 4.8 Hz, 1H), 1.86 (m, 1H), 1.22 (s, 3H), 1.19 (t, J = 7.2 Hz, 3H), 0.90 (d, J = 6.6 Hz, 3H), 0.89 (d, J =

6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 166.8, 153.4, 120.2, 80.1, 75.6, 60.7, 29.0, 23.1, 22.0, 16.6, 14.4; HRMS (ESI) calcd for $[C_{11}H_{20}O_4 + Na]^+$: 239.1253, Found: 239.1249.



13

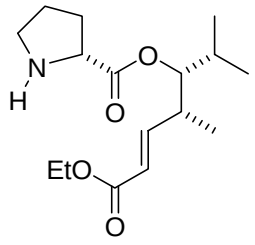
(–)-(*E*)-Ethyl 3-((4*R*,5*R*)-5-isopropyl-4-methyl-2-oxo-1,3-dioxolan-4-yl)acrylate (13). To diol **12** (1.04 g, 4.81 mmol) in CH_2Cl_2 (14 mL) in an ice bath was added pyridine (1.96 mL, 24.0 mmol). Triphosgene (1.57 g, 5.29 mmol) in CH_2Cl_2 (14 mL) was added via syringe and the reaction was allowed to stir for 5 min when determined complete by TLC (UV, PMA stain). The reaction was diluted with ether (40 mL) and was placed in a separatory funnel. The crude mixture, including salts, was washed vigorously with a saturated $CuSO_4$ solution until all salts dissolved. The layers were then separated and the organic layer was washed with brine. After separation the organic layer was dried over Na_2SO_4 and concentrated. The crude mixture was then purified by flash column chromatography (20% EtOAc/hexanes) to yield 1.05 g (90%) of carbonate **13**. R_f = 0.22 (4:1 hexanes:EtOAc), $[\alpha]_D^{24}$ –19.4 (*c* 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 2973, 1801, 1720, 1663, 1472, 1368, 1281, 1245, 1175, 1109, 1062, 1027, 982, 839, 774; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 6.84 (d, *J* = 15.6 Hz, 1H), 6.20 (d, *J* = 15.6 Hz, 1H), 4.23 (q, *J* = 7.2 Hz, 2H), 3.98 (d, *J* = 9.6 Hz, 1H), 2.04 (m, 1H), 1.54 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.11 (d, *J* = 6.6 Hz, 3H), 0.95 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 165.6, 153.1, 144.5, 123.0, 89.1, 84.5, 61.2, 28.2, 19.8, 19.1, 18.7, 14.3; HRMS (ESI) calcd for $[C_{12}H_{18}O_5 + Na]^+$: 265.1046, Found: 265.1050.



6

(+)-(*E*,4*R*,5*R*)-ethyl 5-hydroxy-4,6-dimethylhept-2-enoate (6). To a flask containing carbonate **13** (1.12 g, 4.63 mmol) in THF (22 mL) was added $Pd_2(dba)_3{\cdot}CHCl_3$ (47 mg, 0.046 mmol), PPh_3 (12 mg, 0.046 mmol), Et_3N (3.19 mL, 23.1 mmol) and finally formic acid (875 μL, 23.1 mmol). The reaction was then refluxed for 35 min when determined complete by TLC (UV, anisaldehyde). The reaction was then allowed to cool to RT then diluted with ether and filtered through a large plug of silica gel to remove Pd(0) before concentration. After concentration the crude mixture was purified by silica gel column chromatography (20% EtOAc/hexanes) to yield 908 mg (98%) of alcohol **6**. R_f = 0.24 (4:1 hexanes:EtOAc), $[\alpha]_D^{24}$ +31.9 (*c* 1.0, CH_2Cl_2); IR (neat) 3480(br), 2963, 2874, 1701, 1651, 1464, 1368, 1332, 1268, 1227, 1178, 1150, 1096, 1033, 970, 926, 864, 727 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 6.90 (dd, *J* = 15.6, 7.8 Hz, 1H), 5.84 (dd, *J* = 15.6, 1.2 Hz, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 3.25 (dd, *J* = 6.0, 5.4 Hz, 1H), 2.50 (m, 1H), 1.72 (m, 1H), 1.53 (d, *J* = 5.4 Hz, 1H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.08 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 5.4 Hz, 3H), 0.90 (d, *J* = 5.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 166.6, 151.6, 121.1, 79.1, 60.2, 39.8, 30.9, 19.7, 16.5, 14.2, 13.9; HRMS (ESI) calcd for $[C_{11}H_{20}NaO_3]^+$: 223.1304 Found: 223.1292.[12]

[12] Spectral data agreed satisfactorily with the literature, see: Schlessinger, R. H.; Iwanowicz, E. J.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 3070-3073

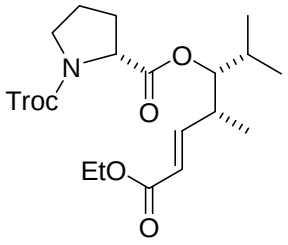


23

(+)-(2*R*)-(*E*,3*R*,4*R*)-6-(ethoxycarbonyl)-2,4-dimethylhex-5-en-3-yl pyrrolidine-2-carboxylate (23). To an RBF containing alcohol **6** (80 mg, 0.40 mmol) in CH_2Cl_2 at 0^oC is added Boc-D-Proline[13] **22** (172 mg, 0.80 mmol) followed by DCC (180 mg, 0.88 mmol) and then DMAP (1 mg). The reaction is allowed to warm to rt and stirred for 24 h, at which time careful TLC in 5% MeOH/20% EtOAc/hexanes (UV, anisaldehyde) indicated the starting material had been consumed.[14] This crude material was placed in a flask with straight TFA at 0 ^oC for 10 min. The reaction was then diluted with EtOAc (6 mL) and sat. aq. $NaHCO_3$ was added until gases stopped evolving. The layers were separated and the aqueous layer was extracted with EtOAc (2 x 10 mL) and dried over Na_2SO_4. After concentration the crude mixture was purified by silica gel column chromatography (10% MeOH/EtOAc) to yield 105 mg (88%, 2 steps) of amine **23**. R_f = 0.40 (10% MeOH/EtOAc), $[\alpha]_D^{24}$ +2.6 (*c* 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 2968, 2876, 1718, 1653, 1463, 1368, 1333, 1267, 1179, 1131, 1036, 989, 908, 864, 726; ^1H NMR ($CDCl_3$, 600 MHz) δ 6.83 (dd, *J* = 15.6, 7.8 Hz, 1H), 5.85 (d, *J* = 15.6 Hz, 1H), 4.38 (dd, 6.6, 5.4 Hz, 1H), 4.18 (dq, *J* = 7.2, 1.2 Hz, 2H), 3.77 (dd, *J* = 8.4, 5.4 Hz, 1H), 3.08 (m, 1H), 2.90 (m, 1H), 2.67 (m, 1H), 2.13 (m, 1H), 1.86 (m, 2H), 1.75 (m, 2H), 1.28 (t, *J* = 7.2 Hz, 3H);

[13] Boc protected D-proline was synthesized using the procedure from: Bartoli, G.; Bosco, M.; Dalpozzo, R.; Giuliani, A.; Marcantoni, E.; Mecozzi, T.; Sambri, L.; Torregiani, E. *J. Org. Chem.* **2002**, *67*, 9111-9114.
[14] This product was not separated without great difficulty from trace urea byproduct so the reaction was diluted with ether, filtered through a plug of silica gel, concentrated and subjected directly to the subsequent step.

^{13}C NMR ($CDCl_3$, 150 MHz) δ 175.2, 166.2, 149.7, 121.6, 80.0, 60.3, 59.9, 46.9, 38.4, 30.5, 29.9, 25.4, 19.5, 16.8, 14.4, 14.2; HRMS (ESI) calcd for $[C_{16}H_{28}NO_4]^+$: 298.20128, Found: 298.20120.

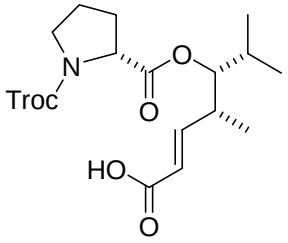


24

(+)-(2*R*)-(*E*,3*R*,4*R*)-6-(ethoxycarbonyl)-2,4-dimethylhex-5-en-3-yl 2,2,2-trichloroethyl pyrrolidine-1,2-dicarboxylate (24). To an RBF containing free amine **23** (27 mg, 0.091 mmol) in DMF/pyr (1/1, 600 μL) at 0^{o}C was added TrocCl (65 μL, 0.45 mmol) dropwise. The reaction was allowed to warm to rt and stirred for 6.5 h. The reaction was diluted with ether (2 mL) and quenched with sat. aq. NH_4Cl. The layers were separated and the aqueous layer was extracted with ether (3 x 1 mL) and the combined organics were washed with brine (1 x 2 mL) and dried over Na_2SO_4. After concentration the crude mixture was purified by silica gel column chromatography (40% EtOAc/hexanes) to yield 29 mg (71%) of Troc-protected amine **24**.[15] R_f = 0.80 (40% EtOAc/hexanes), $[\alpha]_D^{24}$ +6.0 (*c* 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 2967, 2332, 1720, 1654, 1413, 1336, 1274, 1192, 1127, 1094, 1050, 951, 866, 818, 760, 668; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 6.81 (dd, *J* = 15.6, 7.6 Hz, 1H), 5.84 (d, *J* = 15.6 Hz, 1H), 5.09-4.39 (m, 2H), 4.83 (m, 1H), 4.54-4.43 (m, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 3.72-3.53 (m, 2H), 2.75-2.60 (m, 1H), 2.38-2.20 (m, 1H), 2.15-1.85 (m, 4H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.08 (d, *J* =

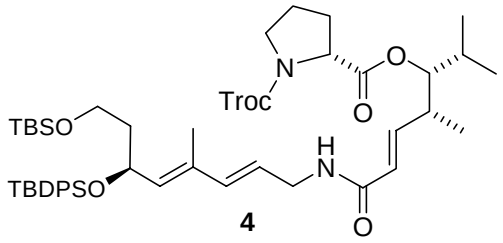
[15] The complex ^{1}H NMR and ^{13}C NMR of such compounds has been previously noted: Breuilles, P.; Uguen, D. *Tetrahedron Lett.* **1998,** 39, 3149.

6.6 Hz, 3H), 0.97-0.85 (m, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 171.8*, 171.6**, 166.2*, 166.2**, 152.9**, 152.4*, 149.6*, 149.3**, 121.7**, 121.7*, 95.6, 80.6*, 80.5**, 77.3**, 76.3*, 74.9*, 74.7**, 60.4*, 60.3**, 59.4*, 59.0**, 47.0*, 46.5**, 38.4*, 38.3**, 30.9*, 30.1**, 29.9, 24.1**, 23.0*, 19.5, 16.9*, 16.7**, 14.4*, 14.3**, 14.2; HRMS (ESI) calcd for $[C_{19}H_{28}Cl_3NNaO_6]^+$: 494.08744, Found: 494.08799.



25

(+)-(*E*,4*R*,5*R*)-5-((*R*)-1-((2,2,2-trichloroethoxy)carbonyl)pyrrolidine-2-carboxyloyloxy)-4,6-dimethylhept-2-enoic acid (25). To an RBF containing ester **24** (17 mg, 0.036 mmol) in THF (425 μL) was added pH 7.0 buffer solution (210 μL), followed by 1N aq. NaOH (210 μL). This biphasic mixture was stirred rapidly for 24 h over which time the reaction had gone from cloudy white to clear and colorless. TLC (UV, $KMnO_4$) at this time indicated that all starting material had been consumed. The mixture was extracted with ether (3 x 2 mL) and dried over Na_2SO_4. After concentration the crude mixture was purified by silica gel column chromatography (25-40% EtOAc/hexanes) to yield 9 mg (56%) of acid **25**. Spectral data agreed with previous report. $[\alpha]_D^{24}$ +26.4 (*c* 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.00-6.92 (dd, *J* = 15.6, 7.6 Hz, 1H), 5.86 (d, *J* = 15.6 Hz, 1H), 5.12-4.39 (m, 2H), 4.85 (m, 1H), 4.58-4.41 (m, 1H), 3.76-3.58 (m, 2H), 2.78-2.69 (m, 1H), 2.40-2.22 (m, 1H), 2.11-1.84 (m, 4H), 1.08 (d, *J* = 6.6 Hz, 3H), 0.99-0.80 (m, 6H); HRMS (ESI) calcd for $[C_{19}H_{28}Cl_3NO_6Na]^+$: 466.05614, Found: 466.05669

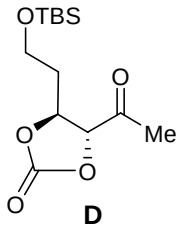


4

(–)-(2*R*)-(3*R*,4*R*,5*E*)-6-((*S*,2*E*,4*E*)-8-(*tert*-butyldimethylsilyloxy)-6-(*tert*-butyldiphenylsilyloxy)-4-methylocta-2,4-dienylcarbamoyl)-2,4-dimethylhex-5-en-3-yl 2,2,2-trichloroethyl pyrrolidine-1,2-dicarboxylate (4). To a flask containing acid **25** (5.0 mg, 0.011 mmol) in CHCl2 (100 μL) at 0°C was added amine **5** (6.0 mg, 0.012 mmol) followed by solid dicyclohexylcarbodiimide (5.0 mg, 0.024 mmol) and DMAP (0.1 mg). The reaction was allowed to warm to rt and was quenched after 2 h total stirring time by dilution with ether followed by filtration through a plug of silica gel. The filtrate was concentrated and the crude adduct was purified by silica gel column chromatography (20% acetone/hexanes) to yield 9 mg (82%) of amide **4**. Spectral data agreed with previous report. $[\alpha]_D^{24}$ –6.1 (*c* 0.2, $CHCl_3$); IR (neat, cm^{-1}) 3295, 2976, 2929, 2856, 1724, 1670, 1630, 1535, 1413, 1389, 1036, 1343, 1255, 1195,1127, 1093, 1005, 947, 912, 835, 775, 734, 702; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.63 (m, 4H), 7.33 (m, 6H), 6.70** (dd, *J* = 15.0, 7.8 Hz, 1H), 6.65* (dd, *J* = 15.0, 7.8 Hz, 1H), 6.01 (d, *J* = 15.6 Hz, 1H), 5.80 *(d, *J* = 15.6 Hz, 1H), 5.78** (d, *J* = 15.6 Hz, 1H), 5.60 (m, 1H), 5.48-5.42 (m, 1H), 5.39 (d, *J* = 9.0 Hz, 1H), 5.10-4.38 (m, 2H), 4.81 (m, 1H), 4.69 (m, 1H), 4.55-4.42 (m, 1H), 3.94 (m, 2H), 3.70-3.50 (m, 4H), 2.64 (m, 1H), 2.26 (m, 1H), 2.12-1.80 (m, 6H), 1.61 (m, 1H), 1.25 (s, 3H), 1.03 (s, 9H), 0.93-0.88 (m, 9H), 0.83 (s, 9H), -0.03 (s, 3H), -0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz)[16] δ 171.9, 171.7, 165.4,

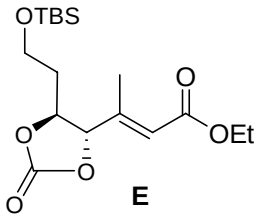
[16] The signal at 95.5 ppm corresponding to Troc CH_2 was not seen in CDCl3; but was detected in toluene-d8 at 96.8 ppm.

165.0, 152.9, 152.4, 145.1, 144.9, 137.0, 136.8, 135.8, 135.8, 135.5, 135.3, 134.4, 134.2, 132.3, 132.3, 129.4, 129.3, 127.4, 127.3, 124.1, 123.9, 123.6, 123.4, 80.9, 80.9, 75.0, 74.7, 67.6, 59.6, 59.3, 59.0, 47.0, 46.5, 41.5, 41.4, 38.2, 38.0, 30.9, 30.1, 29.8, 29.7, 27.0, 25.8, 24.2, 23.1, 19.6, 19.4, 19.3, 18.1, 16.9, 16.8, 14.8, 14.5, 12.4. -5.3.



D

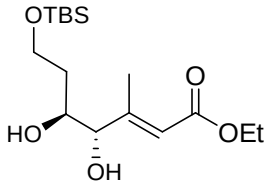
(–)-(4*R*,5*S*)-4-acetyl-5-(2-(*tert*-butyldimethylsilyloxy)ethyl)-1,3-dioxolan-2-one (D). To diol in CH_2Cl_2 (0.4 M) in an ice bath was added pyridine (10 equiv.). Triphosgene (1.1 equiv.) in CH_2Cl_2 (0.4 M based on diol) was added via syringe and the reaction was immediately diluted with ether and was placed in a separatory funnel. The crude mixture, including salts, was washed vigorously with a saturated NH_4Cl solution until all salts dissolved. . The layers were then separated and the organic layer was washed with brine. After separation the organic layer was examined by TLC (UV, PMA stain) and dried over Na_2SO_4 and concentrated. The crude mixture was then purified by flash column chromatography. R_f = 0.40 (20% EtOAc/hexanes), $[\alpha]_D^{24}$ –38.2 (*c* 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 2954, 2930, 2885, 2857, 1807, 1727, 1472, 1464, 1418, 1361, 1254, 1210, 1161, 1088, 1005, 939, 813, 774, 732, 663; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 4.85 (dt, *J* = 6.6, 6.0 Hz, 1H), 4.76 (d, *J* = 6.0 Hz, 1H), 3.80 (m, 2H), 2.34 (s, 3H), 2.01 (m, 2H), 0.87 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 203.1, 153.2, 82.7, 76.4, 58.0, 36.6, 26.4, 25.7, 18.1, -5.6, -5.6.



E

(–)-(*E*)-ethyl 3-((4*S*,5*S*)-5-(2-((*tert*-butyldimethylsilyloxy)ethyl)ethyl)-2-oxo-1,3-dioxolan-4-yl)but-2-enoate (E). To an RBF containing potassium tert-butoxide (2.18 g, 19.5 mmol) in THF (32 mL) at 0^{o}C was added triethyl phosphonoacetate (4.76 g, 21.3 mmol) in THF (32 mL) slowly via syringe. This mixture was allowed to stir for 10 min and was then cooled to -40^{o}C (bath temp, dry ice/CH_3CN). To the reaction was then added ketone **D** (5.1 g, 17.7 mmol) in THF (100 mL) dropwise via syringe. Upon completion of addition the reaction was allowed to stir for 25 min at -40^{o}C and at this time TLC (UV, KMnO4) indicated the starting material was entirely consumed. The mixture was then warmed to rt and was quenched with pH 7.0 buffer solution (50 mL). The layers were separated and the aqueous layer was extracted with ether (3 x 25 mL). The combined organics were washed with brine (1 x 100 mL), dried over Na_2SO_4 and concentrated to yield a 4:1 (*E:Z*) mixture of isomers. After concentration the crude mixture was purified by silica gel column chromatography (10% EtOAc/hexanes) to yield 4.2 g (67%) of *E*-enoate (and 1.1 g (17%) of *Z*-enoate). R_f = 0.75 (20% EtOAc:hexanes), $[\alpha]_D^{24}$ –62.0 (*c* 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 2955, 2930, 2884, 2857, 1808, 1662, 1472, 1444, 1388, 1367, 1294, 1253, 1225, 1153, 1086, 1036, 939, 884, 808, 774, 663; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 5.97 (s, 1H), 4.81 (d, *J* = 6.6 Hz, 1H), 4.59 (ddd, *J* = 7.2, 6.6, 4.8 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 3.80 (m, 2H), 2.16 (d, *J* = 1.2 Hz, 3H), 1.98 (m, 2H), 1.29 (t, *J* = 7.2 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 165.4, 153.8, 149.6, 118.5, 83.6, 77.8, 60.3, 58.0, 36.8, 25.8, 18.1,

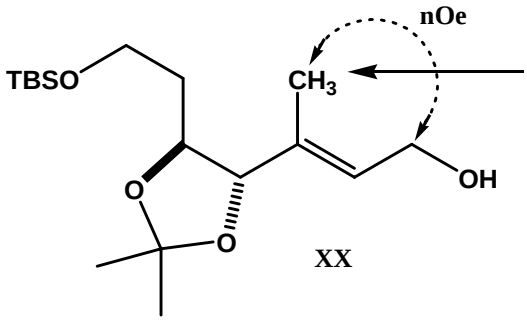
14.1, 13.4, -5.5, -5.5; HRMS (ESI) calcd for $[C_{17}H_{30}NaO_6Si]^+$: 381.17039, Found: 381.17038.



F

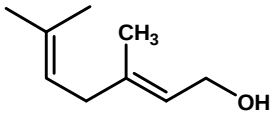
(+)-(*E*,4*S*,5*S*)-ethyl 7-(*tert*-butyldimethylsilyloxy)-4,5-dihydroxy-3-methylhept-2-enoate (F). To an RBF containing carbonate **E** (40.0 mg, 0.112 mmol) in THF/H_2O (9:1, 200 μL) was added LiOH (4.6 mg, 0.112 mmol) and the mixture was heated to 45°C. After 3 h another equal portion of LiOH was added to the hot mixture. After stirring for another 3 h the reaction was allowed to cool to rt and was quenched by the addition of sat. aq. NH_4Cl. The layers were separated and the organic layer was washed with brine and dried over Na_2SO_4. After concentration the crude mixture was purified by silica gel column chromatography (40% EtOAc/hexanes) to yield 36 mg (95%) of diol **F**. R_f = 0.10 (20% EtOAc:hexanes), $[\alpha]_D^{24}$ +4.8 (*c* 1.0, CH_2Cl_2); IR (neat, cm^{-1}) 3421(br), 2955, 2929, 2858, 1718, 1653, 1472, 1389, 1255, 1220, 1153, 1095, 1038, 939, 836, 777, 662; ^1H NMR ($CDCl_3$, 600 MHz) δ 5.96 (s, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 3.90 (m, 2H), 3.86 (m, 2H), 3.55 (bs, 1H), 3.12 (bs, 1H), 2.15 (d, *J* = 1.2 Hz, 3H), 1.81 (m, 1H), 1.68 (m, 1H0 1.27 (t, *J* = 7.2 Hz, 3H), 0.89 (s, 9H), 0.08 (s, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 166.4, 157.0, 117.0, 78.9, 71.8, 61.7, 59.7, 35.3, 25.7, 18.0, 15.3, 14.2, -5.5, -5.5; HRMS (ESI) calcd for $[C_{16}H_{33}O_5Si]^+$: 333.20918, Found: 333.20939.

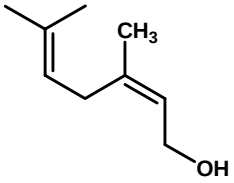
The double-bond geometry of alcohol X was assigned by nOe and further confirmed by comparing the ^{13}C NMR chemical shift of the vinyl Me group with that of geraniol and nerol, as well as with (*E*)- and (*Z*)-3-methyl-3-hexene.

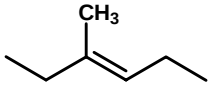


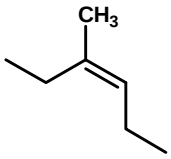
XX

^{13}C NMR (150 MHz, CDCl3)
δ : 11.7 ppm



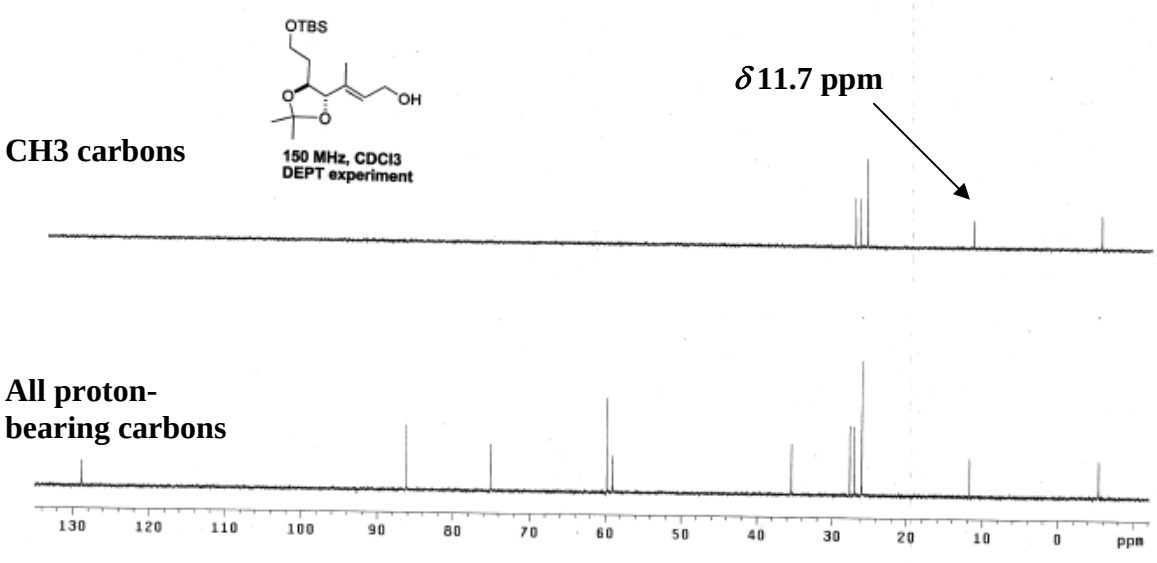




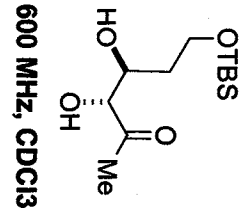


	E (geraniol)	*Z (nerol)*	*(E)-3-methyl-3-hexene*	*(Z)-3-methyl-3-hexene*
^{13}C NMR δ[a]	16.2 ppm[b]	23.4 ppm[c]	14.4 ppm[d]	22.8 ppm[e]

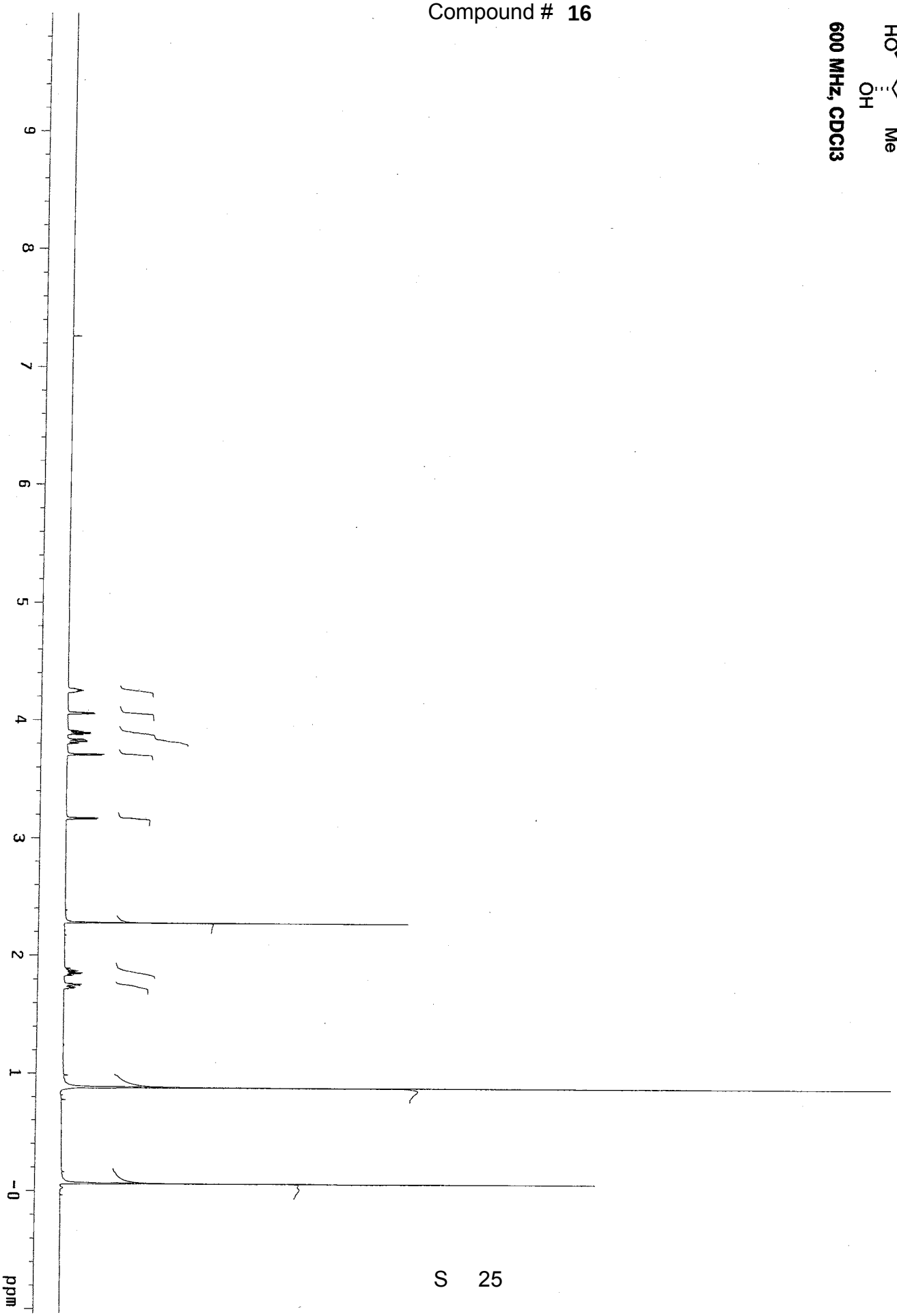
a) all data taken from the Spectral Database for Organic Compounds(C) National Institute of Advanced Industrial Science and Technology. b) SDBS No. 2200CDS-03-602; 25 MHz, CDCl3. c) SDBS No. 10622CDS-03-491; 25 MHz, CDCl3. d) SDBS No. 16403CDS-10-226; 50 MHz, CDCl3. e) SDBS No. 16404CDS-10-225; 50 MHz, CDCl3.



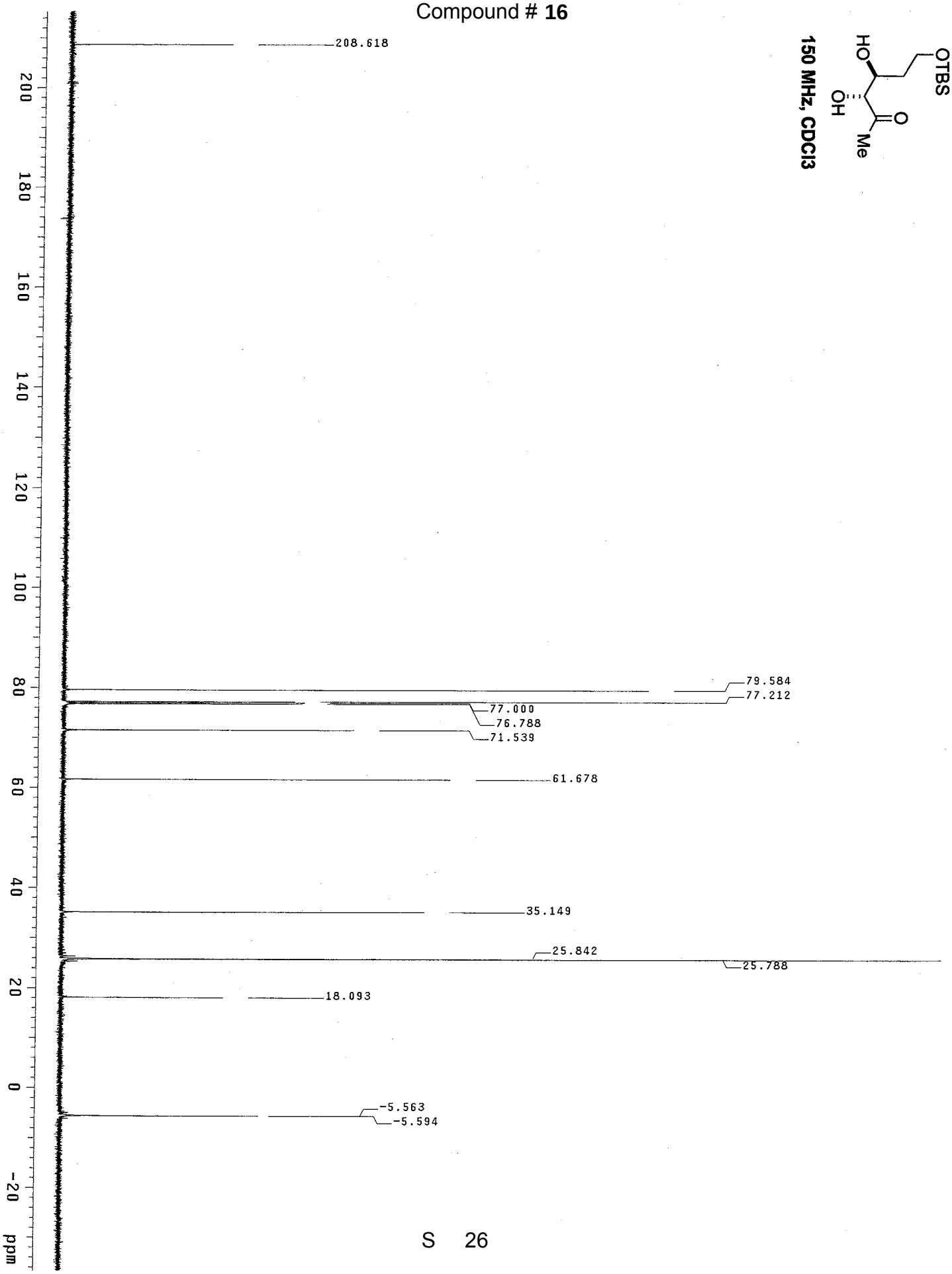
Compound # **16**



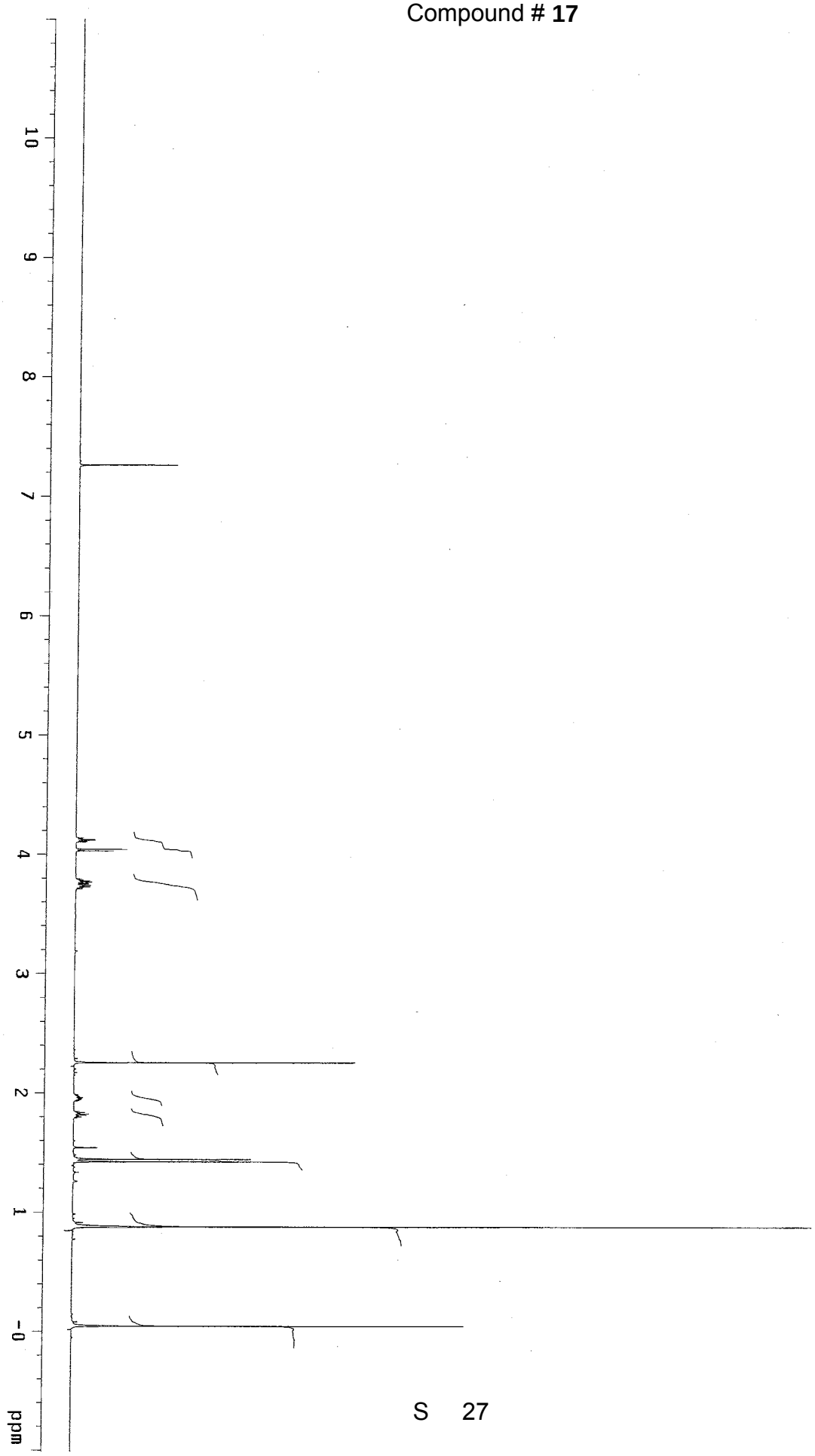
600 MHz, CDCl3



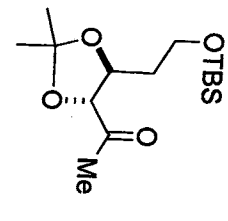
Compound # **16**


208.618
79.584
77.212
77.000
76.788
71.539
61.678
35.149
25.842
25.788
18.093
-5.563
-5.594
200
180
160
140
120
100
80
60
40
20
0
-20
ppm
150 MHz, CDCl3
HO
OTBS
OH
O
Me

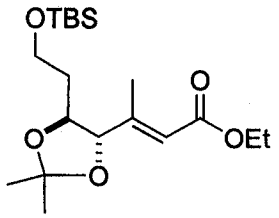
Compound # **17**



Compound # **17**



150 MHz, CDCl3

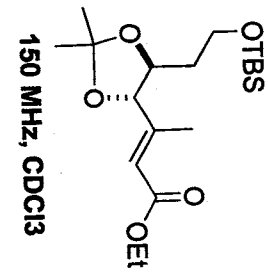


600 MHz, CDCl3

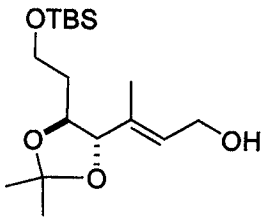
Compound # **18**

S 29

Compound # **18**



150 MHz, CDCl3

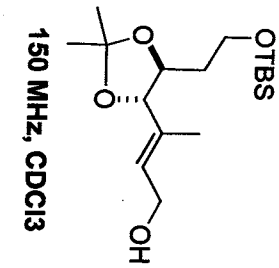


600 MHz, CDCl3

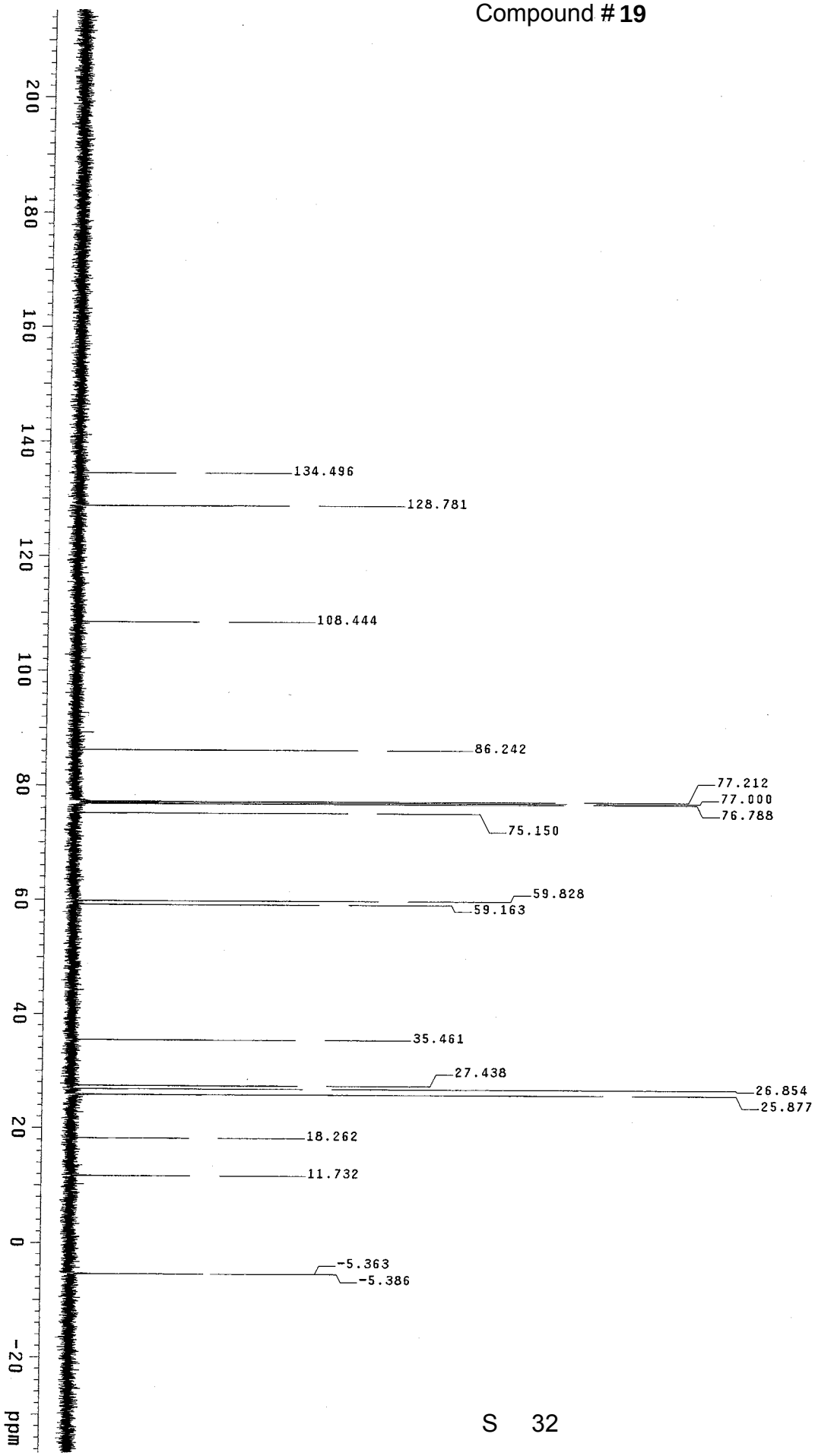
Compound # **19**

S 31

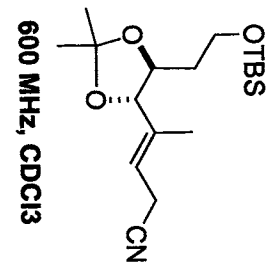
Compound # **19**



150 MHz, CDCl3

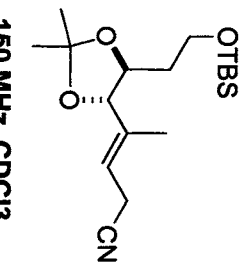


Compound # **20**



600 MHz, CDCl3

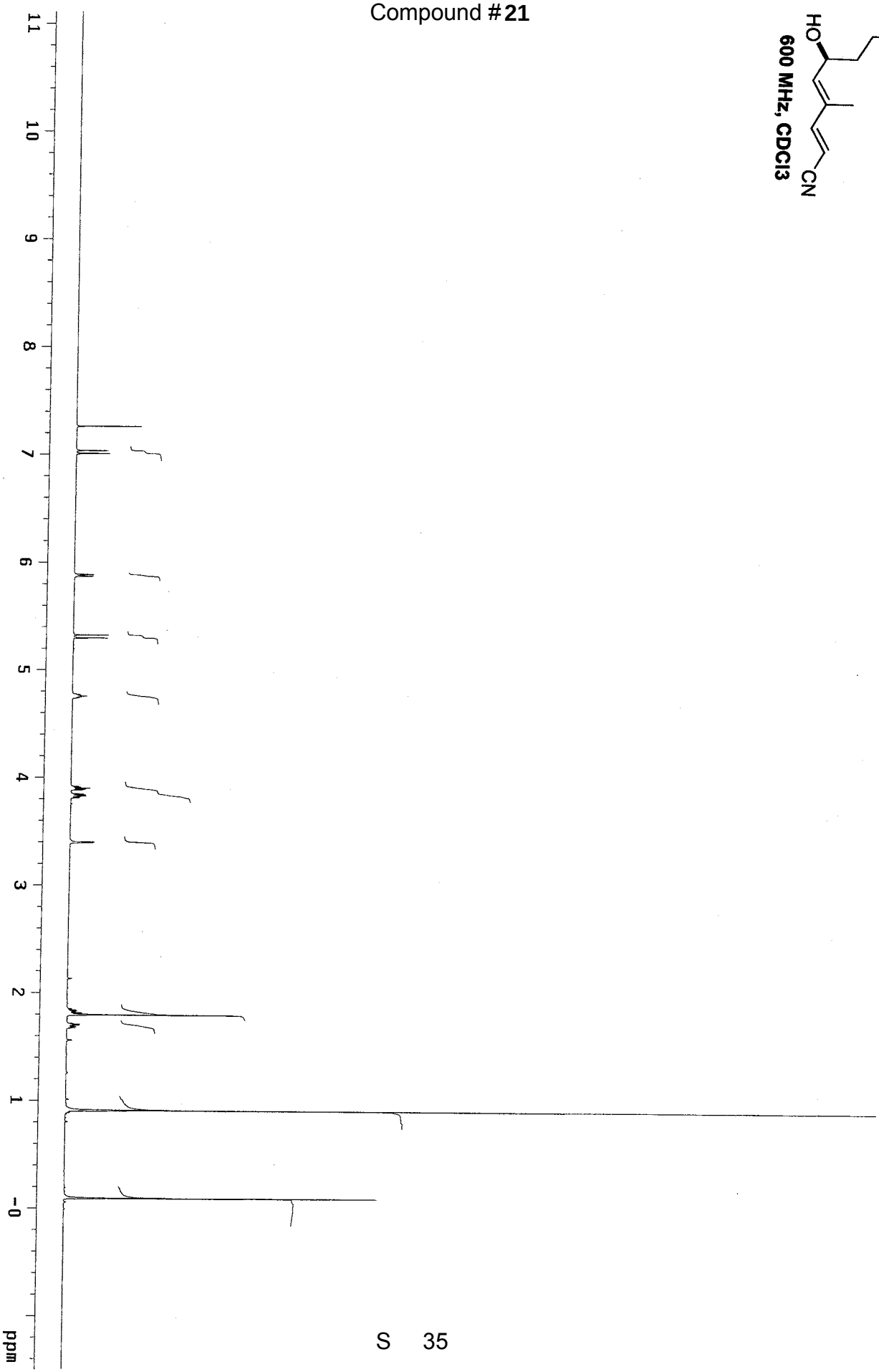
Compound #**20**



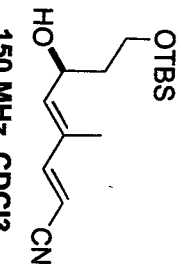
150 MHz, CDCl3

E

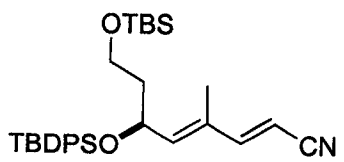
Compound #**21**



Compound # **21**



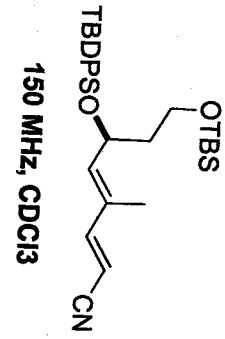
150 MHz, CDCl3



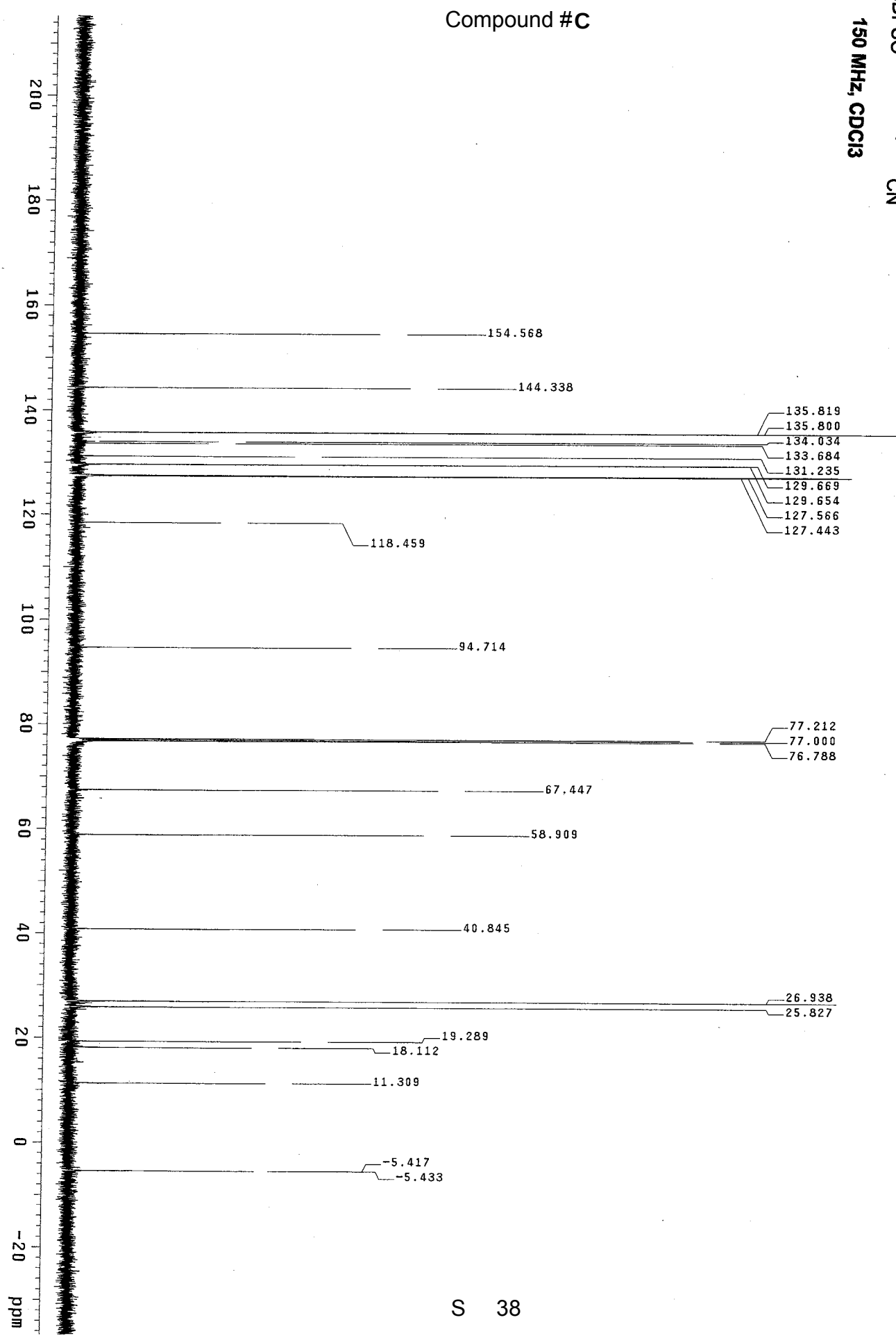
600 MHz, CDCl3

Compound # **C**

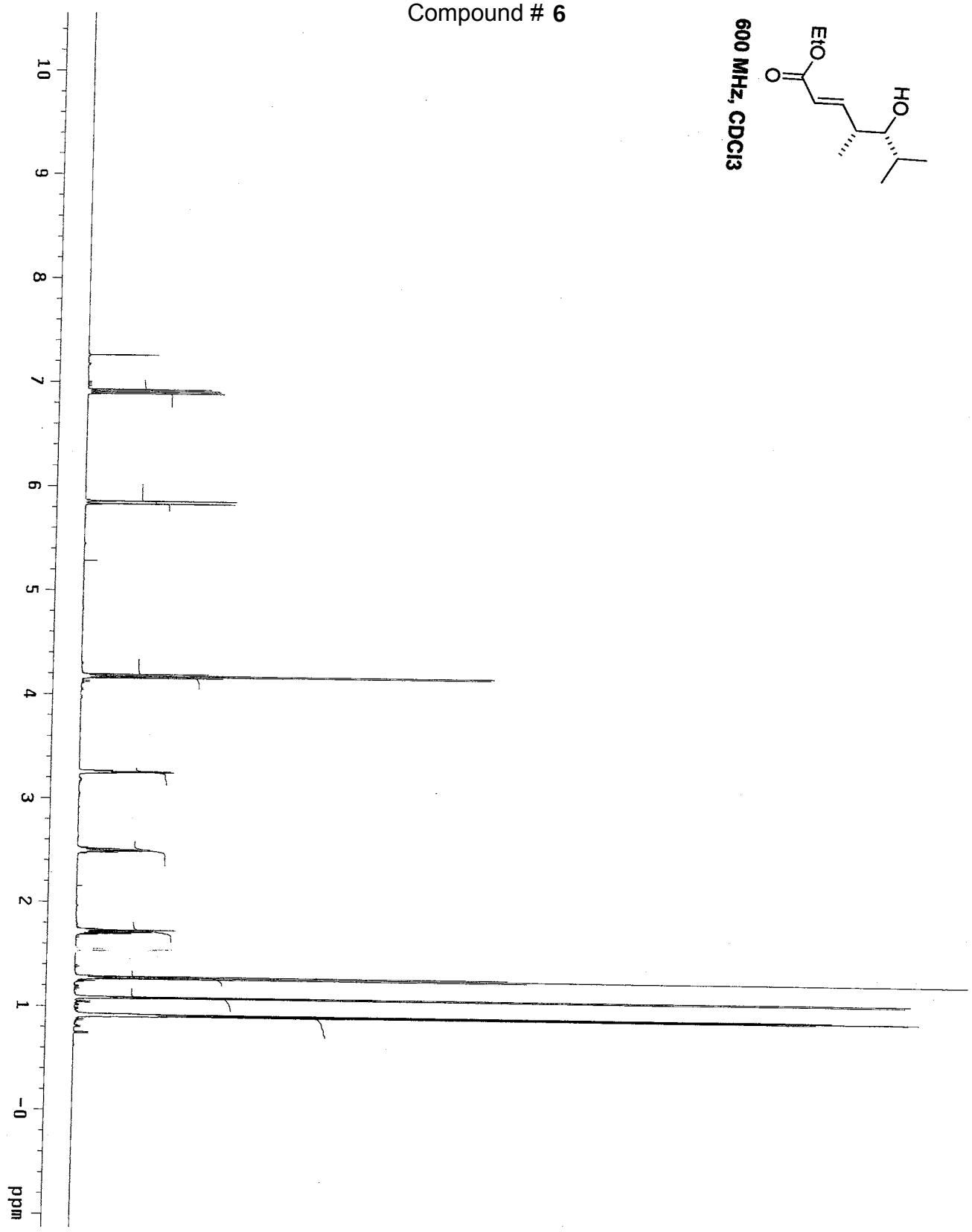
Compound #**C**



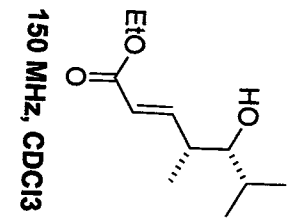
150 MHz, CDCl3



Compound # **6**

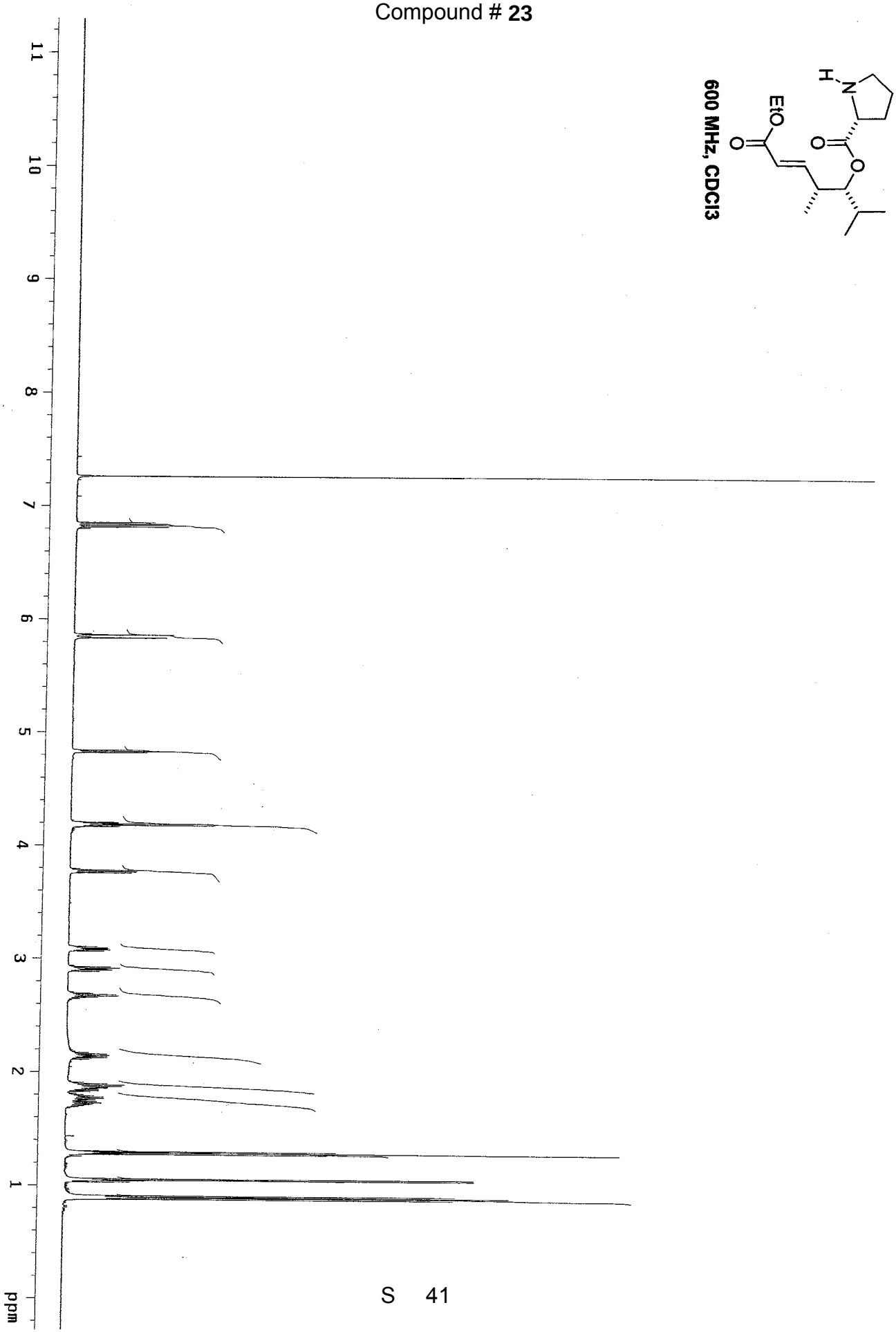


Compound # **6**

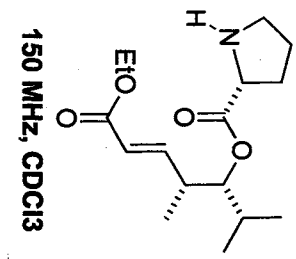


150 MHz, CDCl3

Compound # **23**

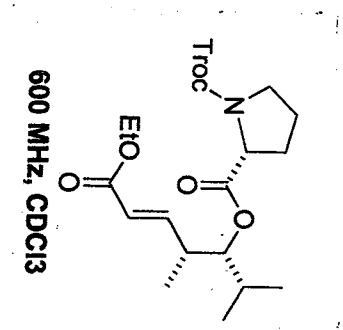


Compound # **23**



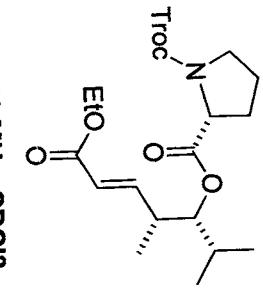
150 MHz, CDCl3

Compound # **24**

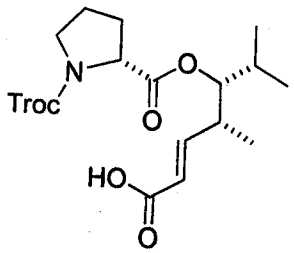


600 MHz, CDCl3

Compound # **24**



150 MHz, CDCl3

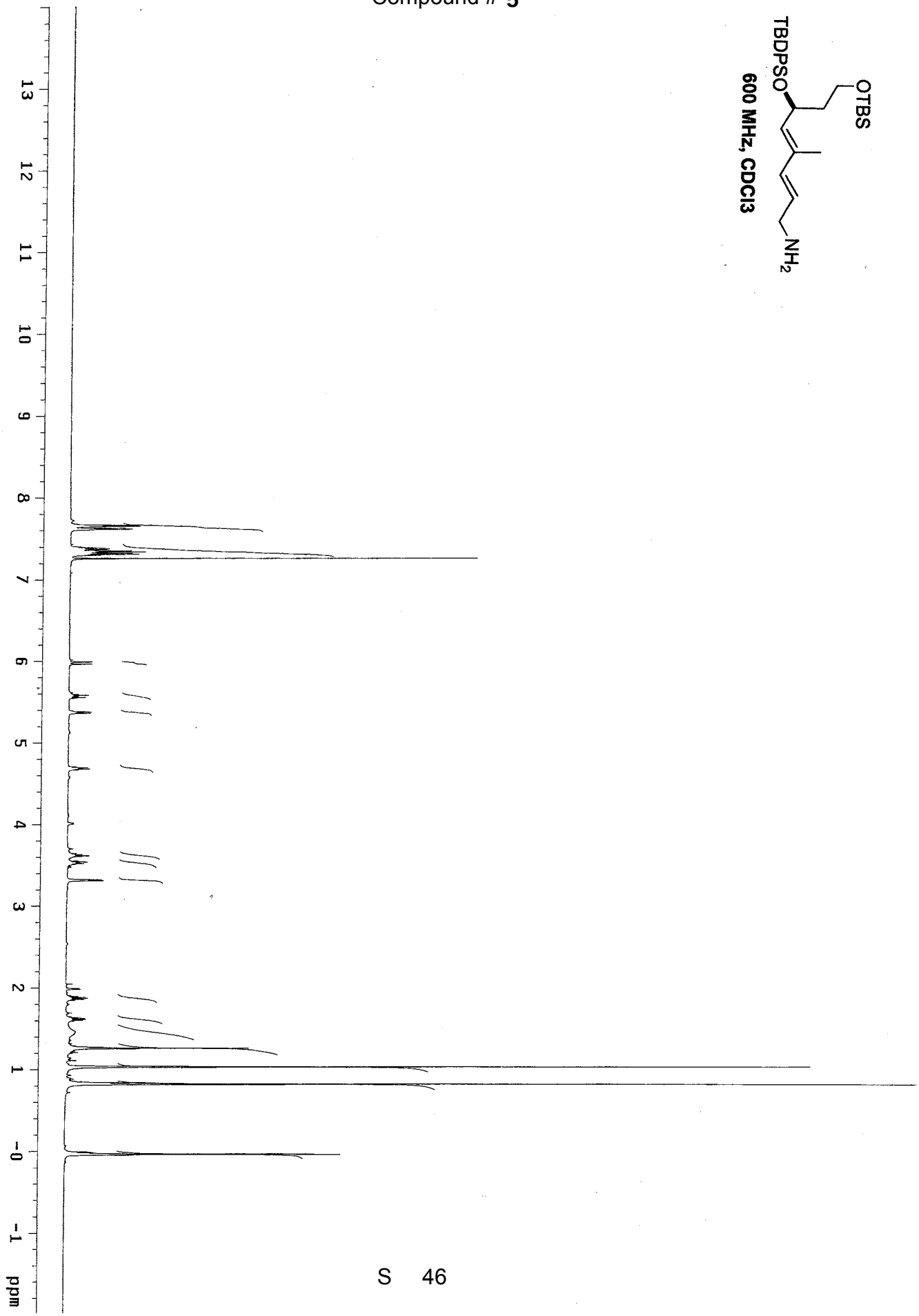


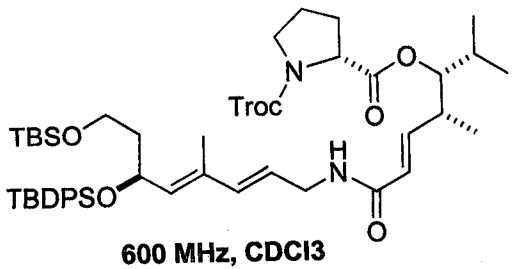
600 MHz, CDCl3

Compound #**25**

S 45

Compound # **5**

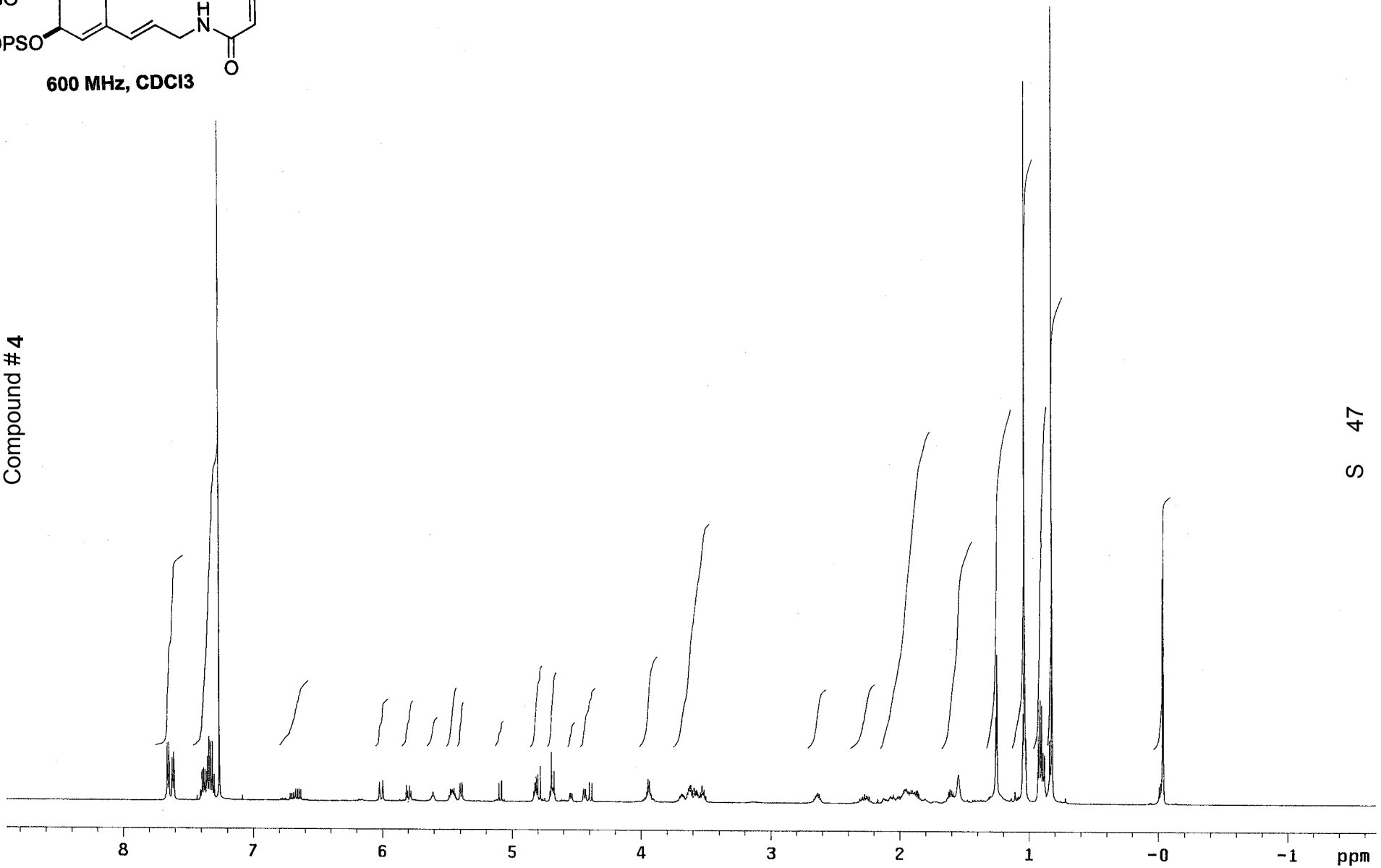




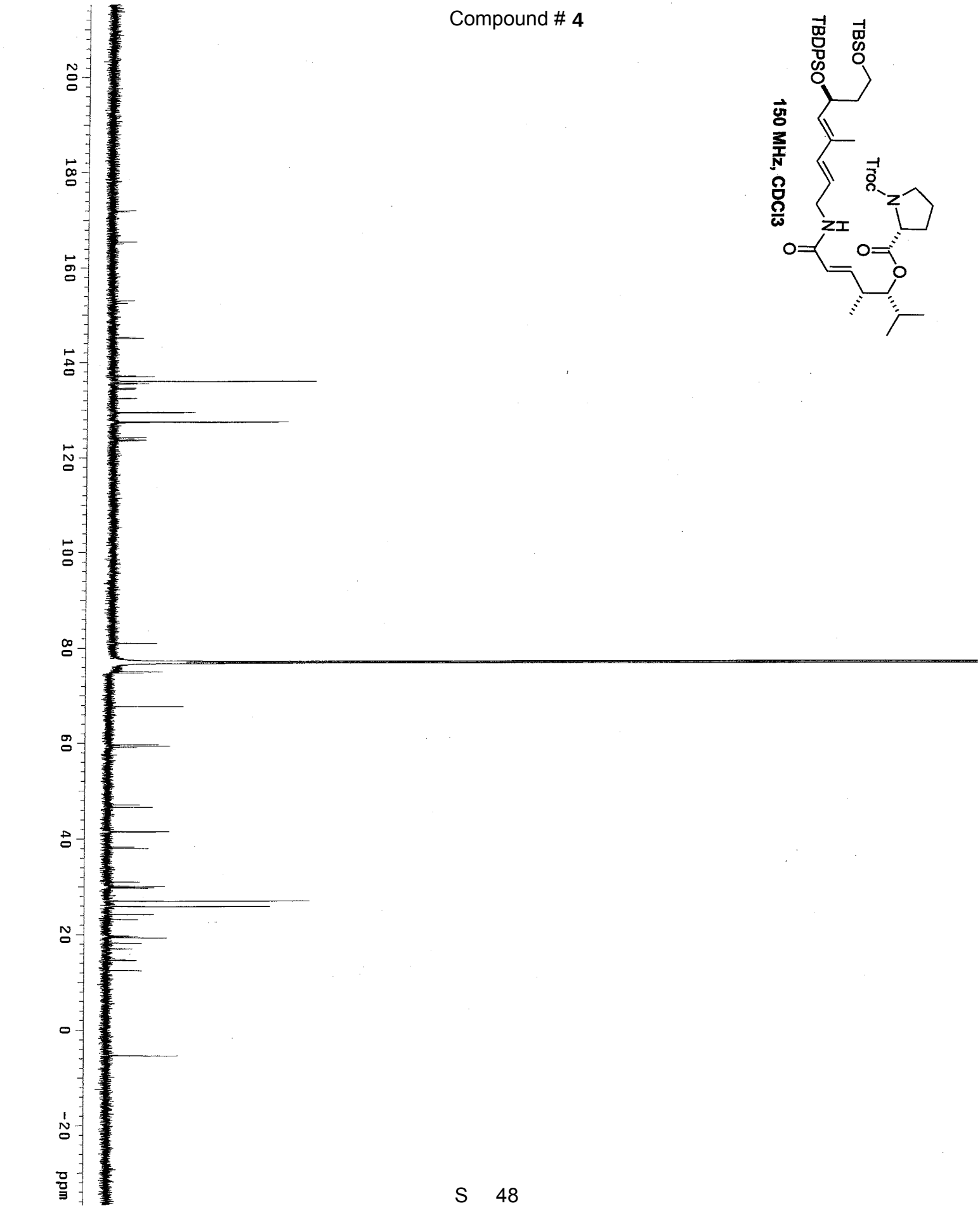
600 MHz, CDCl3

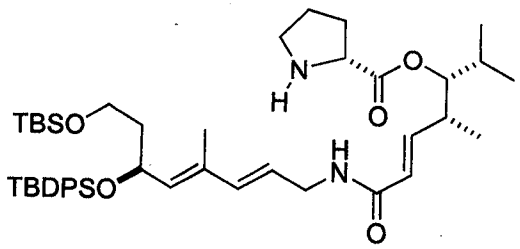
Compound #4

S 47



Compound # **4**

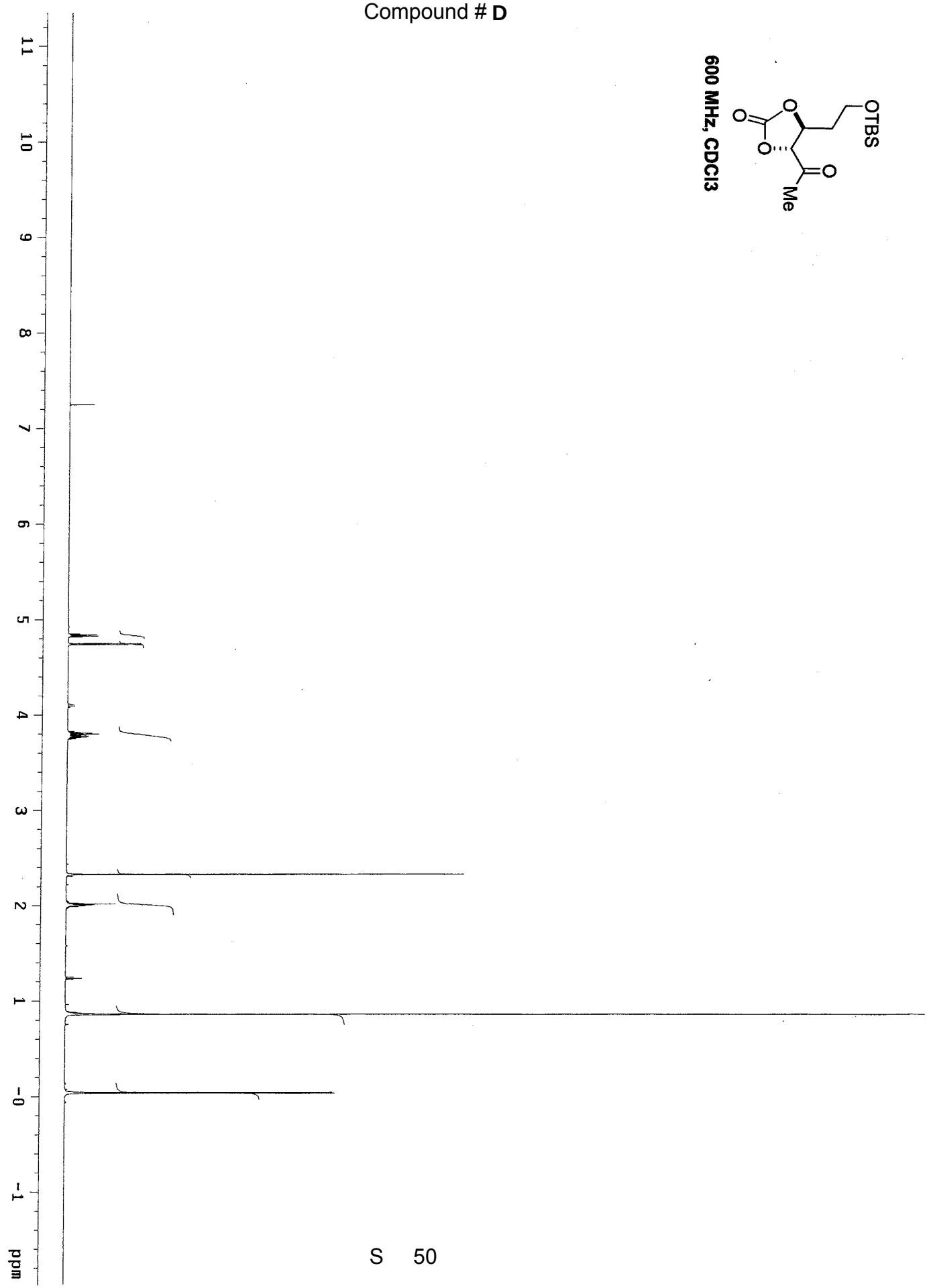

TBSO
TBDPSO
Troc
N
H
N
O
O
O
O
150 MHz, CDCl3
200
180
160
140
120
100
80
60
40
20
0
-20
ppm



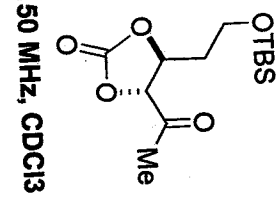
600 MHz, CDCl3
crude (inset signal was complicated by rotamers of Troc precursor)

Compound # 'deprotected 4'

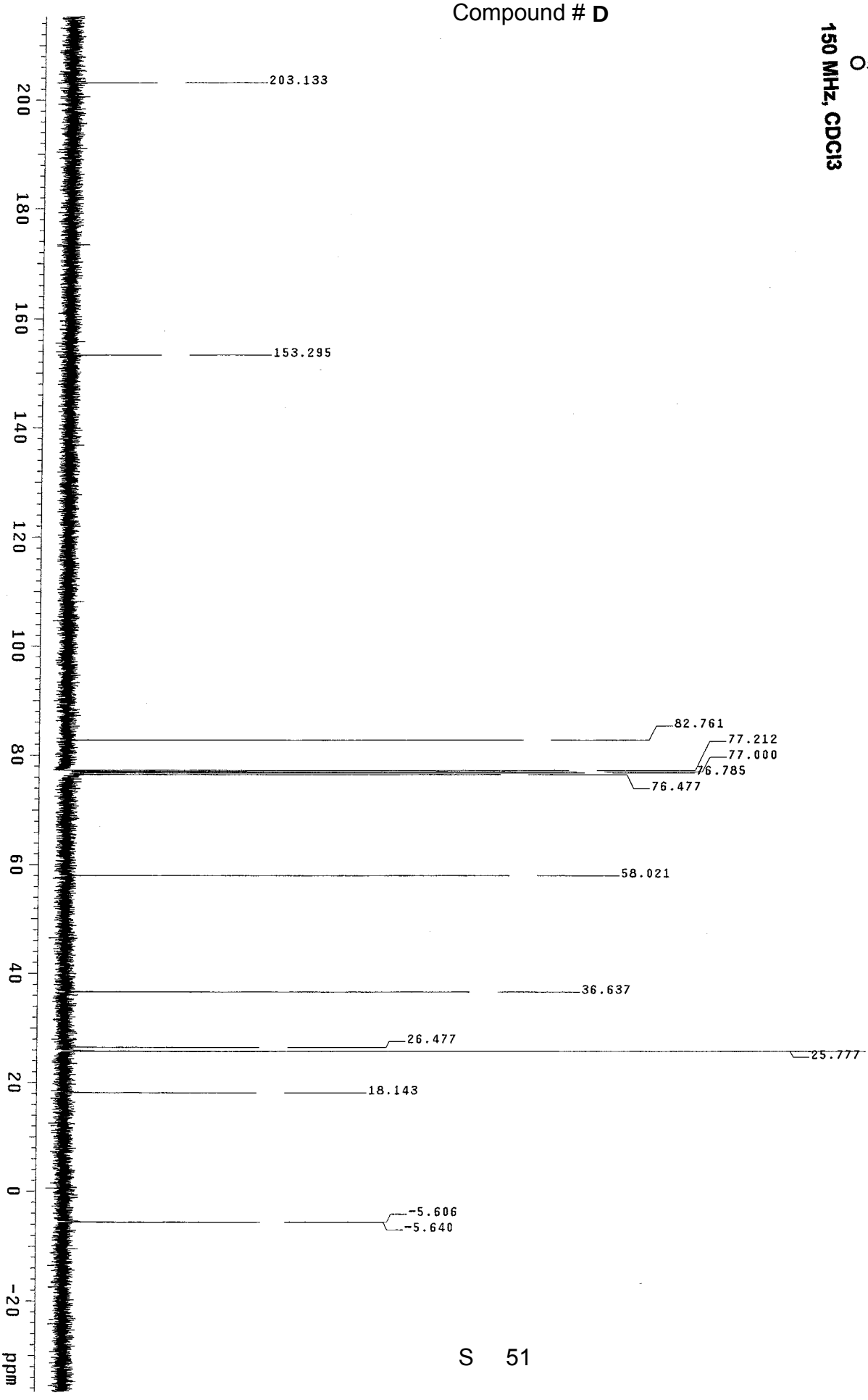
Compound # **D**



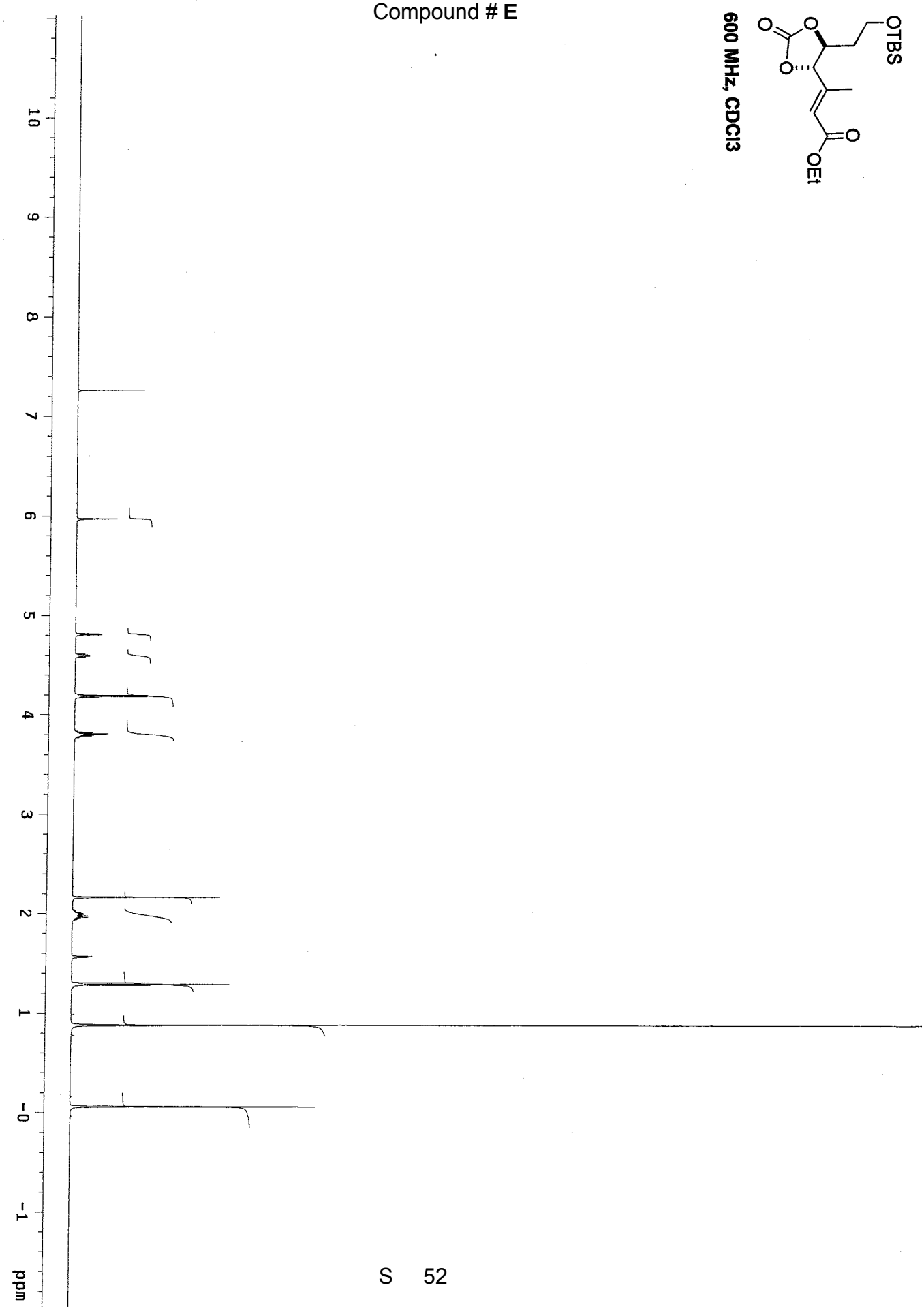
Compound # **D**



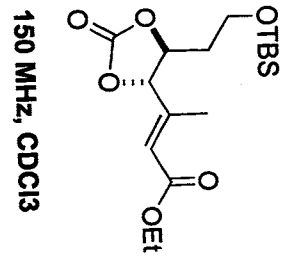
150 MHz, CDCl3



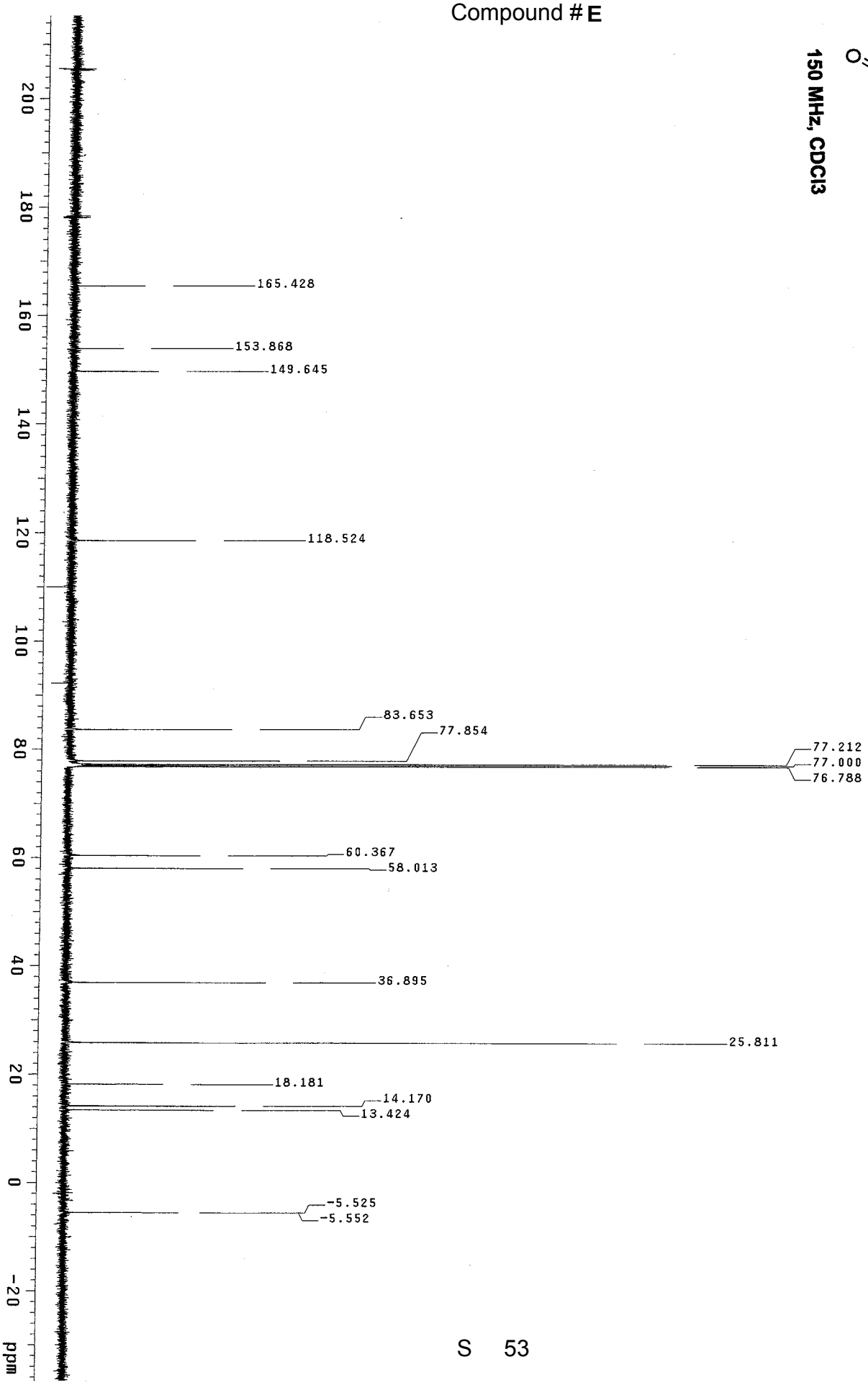
Compound # **E**

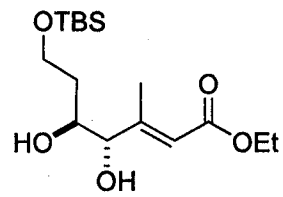


Compound # **E**



150 MHz, CDCl3



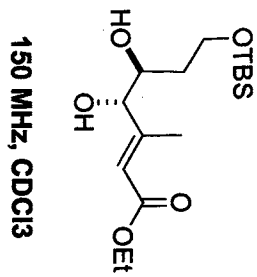


600 MHz, CDCl3

Compound # **F**

S 54

Compound # **F**



150 MHz, CDCl3