Electronic Supplementary Material (ESI) for Chemical Communications

Supporting Information for:

Discovery of a multi-bond forming, four-step tandem process: construction of drug-like polycyclic scaffolds

Mark W. Grafton, Louis J. Farrugia, Hans Martin Senn and Andrew Sutherland*

WestCHEM, School of Chemistry, The Joseph Black Building, University of Glasgow, Glasgow G12 8QQ, UK. Email: Andrew.Sutherland@glasgow.ac.uk;
Fax: 0141 330 4888; Tel: 0141 330 5936.

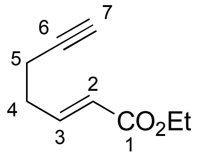
Table of Contents

1. General Experimental

All reagents and starting materials were obtained from commercial sources and used as received. All dry solvents were purified using a PureSolv 500 MD solvent purification system. All reactions were performed under an atmosphere of argon unless otherwise mentioned. Brine refers to a saturated solution of sodium chloride. Flash column chromatography was carried out using Fisher matrix silica 60. Macherey-Nagel aluminium-backed plates pre-coated with silica gel 60 (UV_{254}) were used for thin layer chromatography and were visualised by staining with $KMnO_4$. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX 400 spectrometer with chemical shift values in ppm relative to TMS (δ_H 0.00 and δ_C 0.0) or residual chloroform (δ_H 7.28 and δ_C 77.2) as standard. Proton and carbon assignments are based on two-dimensional COSY and DEPT experiments, respectively. Mass spectra were obtained using a JEOL JMS-700 spectrometer. Infrared spectra were obtained neat using a Shimadzu IRPrestige-21 spectrometer. Melting points were determined on a Reichert platform melting point apparatus.

2. Experimental Procedures and Spectroscopic Data for All Compounds

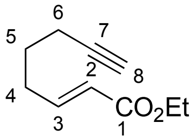
Ethyl (2*E*)-hept-2-en-6-ynoate (7)[1]



Dimethyl sulfoxide (3.60 mL, 50.8 mmol) was added to a stirred solution of oxalyl chloride (2.49 mL, 28.4 mmol) in dichloromethane (100 mL) at −78 °C. The mixture was stirred for 0.3 h before 4-pentyn-1-ol (**5**) (1.70 g, 20.3 mmol) in dichloromethane (25 mL) was slowly added. The mixture was stirred for a further 0.3 h before triethylamine (14.1 mL, 102 mmol) was added. This reaction mixture was stirred for 0.5 h at −78 °C and then allowed to warm to room temperature and stirred for a further 3 h. A solution of lithium chloride (1.55 g, 36.5 mmol), triethyl phosphonoacetate (7.24 mL, 36.5 mmol) and 1,8-diazabicyclo[5,4,0]undec-7-ene (5.14 mL, 36.5 mmol) in acetonitrile (70 mL) was then prepared and stirred for 1 h. The Swern solution was concentrated *in vacuo*, then the Horner Wadsworth Emmons solution was added and the reaction mixture was stirred at room temperature overnight. The reaction was quenched with a saturated solution of ammonium chloride (50 mL) and concentrated to give an orange residue, which was then extracted with diethyl ether (4 × 75 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated to give an orange oil. Purification by flash column chromatography (diethyl ether/petroleum ether, 1:9) gave ethyl

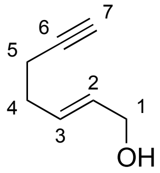
(2*E*)-hept-2-en-6-ynoate (**7**) (2.93 g, 95%) as a yellow oil. Spectroscopic data consistent with literature.[1] R$_f$ (25% diethyl ether/petroleum ether) 0.63; ν_{max}/cm^{-1} (neat) 3302 (C≡C−H), 2984 (CH), 1715 (CO), 1657 (C=C), 1445, 1368, 1267, 1155, 1038, 756; δ_H (400 MHz, $CDCl_3$) 1.30 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 2.01 (1H, t, *J* 2.5 Hz, 7-H), 2.34–2.39 (2H, m, 5-H_2), 2.41–2.48 (2H, m, 4-H_2), 4.20 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 5.90 (1H, dt, *J* 15.7, 1.5 Hz, 2-H), 6.97 (1H, dt, *J* 15.7, 6.7 Hz, 3-H); δ_C (126 MHz, $CDCl_3$) 14.3 (CH_3), 17.4 (CH_2), 31.0 (CH_2), 60.3 (CH_2), 69.4 (CH), 82.7 (C), 122.6 (CH), 146.3 (CH), 166.4 (C); *m/z* (CI) 153 (MH^+, 100%), 139 (5), 113 (10), 97 (5), 81 (15), 69 (15).

Ethyl (2*E*)-octa-2-en-7-ynoate (8)[2]



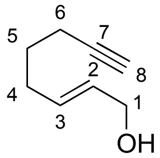
Dimethyl sulfoxide (5.42 mL, 76.5 mmol) was added to a stirred solution of oxalyl chloride (29.5 mL, 42.8 mmol) in dichloromethane (150 mL) at −78 °C. The mixture was stirred for 0.3 h before 5-hexyn-1-ol (**6**) (3.00 g, 30.6 mmol) in dichloromethane (25 mL) was slowly added. The mixture was stirred for a further 0.3 h before triethylamine (21.3 mL, 153 mmol) was added. This reaction mixture was stirred for 0.5 h at −78 °C and then allowed to warm to room temperature and stirred for a further 2 h. A solution of lithium chloride (2.34 g, 55.1 mmol), triethyl phosphonoacetate (10.9 mL, 55.1 mmol) and 1,8-diazabicyclo[5,4,0]undec-7-ene (7.75 g, 55.1 mmol) in acetonitrile (150 mL) was then prepared and stirred for 1 h. The Swern solution was concentrated *in vacuo*, then the Horner Wadsworth Emmons solution was added and the reaction mixture was stirred at room temperature overnight. The reaction was quenched with a saturated solution of ammonium chloride (50 mL) and concentrated to give an orange residue, which was then extracted with diethyl ether (4 × 75 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated to give an orange oil. Purification by flash column chromatography (diethyl ether/petroleum ether, 1:9) gave ethyl (2*E*)-octa-2-en-7-ynoate (**8**) (4.99 g, 99%) as a yellow oil. Spectroscopic data consistent with literature.[2] R$_f$ (50% diethyl ether/petroleum ether) 0.74; ν_{max}/cm^{-1} (neat) 3295 (C≡C−H), 2940 (CH), 1713 (CO), 1651 (C=C), 1265, 1188, 1150, 1042, 979, 756, 633; δ_H (400 MHz, $CDCl_3$) 1.29 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 1.70 (2H, quin, *J* 6.9 Hz, 5-H_2), 1.98 (1H, s, 8-H), 2.23 (2H, t, *J* 6.9 Hz, 6-H_2), 2.33 (2H, q, *J* 6.9 Hz, 4-H_2), 4.18 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 5.86 (1H, d, *J* 15.6 Hz, 2-H), 6.94 (1H, dt, *J* 15.6, 6.9 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 14.3 (CH_3), 17.9 (CH_2), 26.7 (CH_2), 30.9 (CH_2), 60.2 (CH_2), 69.0 (CH), 83.5 (C), 122.1 (CH), 147.8 (CH), 166.6 (C); *m/z* (CI) 167 (MH^+, 100%), 139 (42), 113 (10), 97 (12), 81 (25), 71 (30).

(2*E*)-Hept-2-en-6-yn-1-ol (9)[3]



Ethyl (2*E*)-hept-2-en-6-ynoate (**7**) (1.50 g, 9.87 mmol) was dissolved in diethyl ether (50 mL) and cooled to −78 °C. DIBAL-H (1 M in hexane) (21.7 mL, 21.7 mmol) was added dropwise and the reaction mixture was stirred at −78 °C for 3 h, before warming to room temperature overnight. The solution was cooled to 0 °C and quenched by the addition of a saturated solution of ammonium chloride (10 mL) and warmed to room temperature with vigorous stirring over 1 h, producing a white precipitate. The precipitate was filtered through a pad of Celite® and washed with diethyl ether (3 × 50 mL). The filtrate was then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (diethyl ether/petroleum ether, 1:1) gave (2*E*)-hept-2-en-6-yn-1-ol (**9**) (1.01 g, 93%) as a yellow oil. Spectroscopic data consistent with literature.[3] R_f (50% diethyl ether/petroleum ether) 0.33; ν_{max} /cm^{-1} (neat) 3360 (OH), 3295 (C≡C−H), 2915 (CH), 1670 (C=C), 1433, 1084, 997, 968; δ_H (500 MHz, $CDCl_3$) 1.42 (1H, br s, OH), 1.99 (1H, t, *J* 2.5 Hz, 7-H), 2.28–2.33 (4H, m, 4-H_2 and 5-H_2), 4.14 (2H, d, *J* 4.0 Hz, 1-H_2), 5.70–5.81 (2H, m, 2-H and 3-H); δ_C (126 MHz, $CDCl_3$) 18.5 (CH_2), 31.1 (CH_2), 63.5 (CH_2), 68.8 (CH), 83.7 (C), 130.5 (CH), 130.6 (CH); *m/z* (CI) 111 (MH^+, 3%), 107 (15), 93 (100), 81 (10), 69 (10).

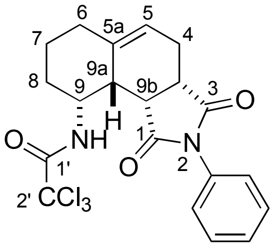
(2*E*)-Octa-2-en-7-yn-1-ol (10)[4]



Ethyl (2*E*)-octa-2-en-7-ynoate (**8**) (4.10 g, 24.7 mmol) was dissolved in diethyl ether (50 mL) and cooled to −78 °C. DIBAL-H (1 M in hexane) (54.3 mL, 54.3 mmol) was added dropwise and the reaction mixture was stirred at −78 °C for 3 h, before warming to room temperature overnight. The solution was cooled to 0 °C and quenched by the addition of a saturated solution of ammonium chloride (10 mL) and warmed to room temperature with vigorous stirring over 1 h, producing a white precipitate. The precipitate was filtered through a pad of Celite® and washed with diethyl ether (3 × 50 mL). The filtrate was then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (diethyl ether/petroleum ether, 1:1) gave (2*E*)-octa-2-en-7-yn-1-ol (**10**) (2.95 g, 97% yield) as a yellow oil. Spectroscopic data consistent with literature.[4] R_f (50% petroleum ether/diethyl ether) 0.29; ν_{max}/cm^{-1} (neat) 3361 (OH), 3302 (C≡C−H), 2932 (CH), 1674

(C=C), 1435, 1219, 1088, 972; δ_H (400 MHz, $CDCl_3$) 1.29 (1H, br s, OH), 1.63 (2H, quin, *J* 6.9 Hz, 5-H_2), 1.96 (1H, t, *J* 2.6 Hz, 8-H), 2.15–2.25 (4H, m, 4-H_2 and 6-H_2), 4.09–4.15 (2H, m, 1-H_2), 5.63–5.74 (2H, m, 2-H and 3-H); δ_C (101 MHz, $CDCl_3$) 17.8 (CH_2), 27.8 (CH_2), 31.1 (CH_2), 63.7 (CH_2), 68.5 (CH), 84.2 (C), 129.9 (CH), 131.9 (CH); *m/z* (CI) 125 (MH^+, 20%), 107 (95), 97 (40), 81 (80), 71 (100).

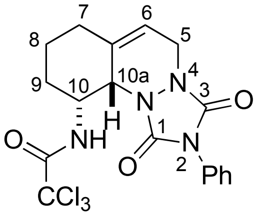
(3a*S**,9*R**,9a*R**,9b*R**)-9-(2',2',2'-Trichloromethylcarbonylamino)-3a,4,6,7,8,9,9a,9b-octahydro-2-phenyl-1*H*-benz[*e*]isoindole-1,3(2*H*)-dione (14)



(2*E*)-Octa-2-en-7-yn-1-ol (**10**) (0.050 g, 0.40 mmol) was dissolved in dichloromethane (15 ml) and cooled to 0 °C. To the solution, 1,8-diazabicyclo[5.4.0]undec-7-ene (0.011 mL, 0.08 mmol) and trichloroacetonitrile (0.060 mL, 0.60 mmol) was added. The reaction mixture was allowed to warm to room temperature before stirring for 3 h. The reaction mixture was filtered through a short pad of silica gel and the filtrate concentrated *in vacuo* to give the allylic trichloroacetimidate, which was used without further purification. The allylic trichloroacetimidate was dissolved in toluene (10 mL) and transferred to a Schlenk tube containing potassium carbonate (0.050 g) and purged with Ar and sealed. The reaction mixture was then heated to 140 °C and stirred for 24 h. Grubbs 1st generation catalyst (0.025 g, 0.030 mmol) was added and the reaction mixture was heated for 24 h at 75 °C. A further portion of Grubbs 1st generation catalyst (0.0082 g, 0.010 mmol) was added and the reaction mixture was stirred at 75 °C for 24 h. *N*-Phenyl maleimide (0.10 g, 0.60 mmol) was added with hydroquinone[5] (0.013 g, 0.12 mmol). The reaction mixture was stirred for 48 h at 111 °C. Flash column chromatography (petroleum ether/diethyl ether, 2:3) gave (3a*S**,9*R**,9a*R**,9b*R**)-9-(2',2',2'-trichloromethylcarbonylamino)-3a,4,6,7,8,9,9a,9b-octahydro-2-phenyl-1*H*-benz[*e*]isoindole-1,3(2*H*)-dione (**14**) (0.13 g, 72%) as a white solid. R_f(70% diethyl ether/petroleum ether) 0.33; Mp 152–154 °C; ν_{max}/cm^{-1} (neat) 3567 (NH), 3056 (ArH), 2944 (CH), 1712 (CO), 1501, 1385, 1265, 1188; δ_H (500 MHz, $CDCl_3$) 1.57–1.62 (1H, m, 7-*H*H), 1.68–1.73 (1H, m, 7-H*H*), 1.86 (2H, q, *J* 7.6 Hz, 8-H_2), 2.24–2.47 (3H, m, 6-H_2 and 4-*H*H), 2.75 (1H, dt, *J* 16.5, 4.4 Hz, 4-H*H*), 3.08 (1H, t, *J* 7.6 Hz, 9a-H), 3.29 (1H, ddd, *J* 9.4, 8.1, 4.4 Hz, 3a-H), 3.47 (1H, dd, *J* 9.4, 7.6 Hz, 9b-H), 4.72 (1H, dq, *J* 9.3, 7.6 Hz, 9-H), 5.84–5.89 (1H, m, 5-H), 7.20–7.24 (2H, m, 2 ×

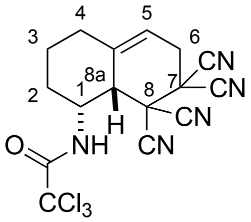
ArH), 7.40 (1H, t, *J* 7.5 Hz, ArH), 7.46 (2H, t, *J* 7.5 Hz, 2 × ArH), 7.63 (1H, d, *J* 9.3 Hz, NH); δ_C (126 MHz, $CDCl_3$) 22.7 (CH_2), 23.4 (CH_2), 29.5 (CH_2), 32.4 (CH_2), 38.1 (CH), 38.9 (CH), 40.3 (CH), 48.8 (CH), 91.8 (C), 121.1 (CH), 126.4 (2 × CH), 128.8 (CH), 129.2 (2 × CH), 131.5 (C), 138.1 (C), 161.1 (C), 178.1 (C), 178.3 (C); *m/z* (EI) 440.0450 (M^+. $C_{20}H_{19}{}^{35}Cl_3N_2O_3$ requires 440.0461), 403 (5%), 323 (5), 279 (100), 241 (10), 132 (65), 91 (32), 77 (11).

(10*R,10a*S**)-5,7,8,9,10,10a-Hexahydro-10-(2’,2’,2’-trichloromethylcarbonylamino)-1*H*-[1,2,4]-triazolo[1,2-*a*]cinnoline-1,3(2*H*)-dione (15)**



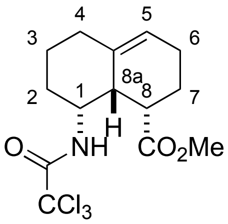
(10*R**,10a*S**)-5,7,8,9,10,10a-Hexahydro-10-(2’,2’,2’-trichloromethylcarbonylamino)-1*H*-[1,2,4]-triazolo[1,2-*a*]cinnoline-1,3(2*H*)-dione (**15**) was synthesised according to above procedure using (2*E*)-octa-2-en-7-yn-1-ol (**10**) (0.050 g, 0.40 mmol). The reaction mixture was stirred with Grubbs 1st generation catalyst (0.033 g, 0.040 mmol) for 48 h at 75 °C before 4-phenyl-1,2,4-triazole-3,5-dione (0.11 g, 0.60 mmol) was added. The reaction mixture was stirred for 24 h at 111 °C. Flash column chromatography (petroleum ether/ethyl acetate, 1:3) gave (10*R**,10a*S**)-5,7,8,9,10,10a-hexahydro-10-(2’,2’,2’-trichloromethylcarbonylamino)-1*H*-[1,2,4]-triazolo[1,2-*a*]cinnoline-1,3(2*H*)-dione (**15**) (0.13 g, 75%) as a black oil. R_f (75% ethyl acetate/petroleum ether) 0.46; ν_{max} /cm^{-1} (neat) 3418 (NH), 3055 (ArH), 2940 (CH), 2361, 1775, 1705 (CO), 1505, 1420, 819, 733; δ_H (500 MHz, $CDCl_3$) 1.45–1.55 (1H, m, 8-*H*H), 1.89–1.99 (2H, m, 9-*H*H and 8-H*H*), 2.04–2.11 (1H, m, 9-H*H*), 2.22–2.31 (1H, m, 7-*H*H), 2.59 (1H, dtd, *J* 13.5, 4.2, 2.1 Hz, 7-H*H*), 3.96 (1H, ddd, *J* 16.3, 5.6, 2.7 Hz, 5-*H*H), 4.30 (1H, dd, *J* 16.3, 4.9 Hz, 5-H*H*), 4.59–4.63 (1H, m, 10a-H), 5.04 (1H, dq, *J* 8.5, 3.3 Hz, 10-H), 5.93–5.97 (1H, m, 6-H), 6.85 (1H, d, *J* 8.5 Hz, NH), 7.36–7.41 (1H, m, ArH), 7.45–7.53 (4H, m, 4 × ArH); δ_C (126 MHz, $CDCl_3$) 22.4 (CH_2), 28.7 (CH_2), 33.8 (CH_2), 43.0 (CH_2), 49.4 (CH), 56.3 (CH), 92.7 (C), 116.6 (CH), 126.2 (CH), 128.4 (2 × CH), 129.2 (2 × CH), 131.0 (C), 132.0 (C), 150.8 (C), 152.5 (C), 161.3 (C); *m/z* (EI) 442.0358 (M^+. $C_{18}H_{17}{}^{35}Cl_3N_4O_3$ requires 442.0366), 408 (10%), 325 (5), 281 (100), 253 (10), 162 (5), 119 (20), 91 (20).

(1*R**, 8a*R**)-1-(2’,2’,2’-Trichloromethylcarbonylamino)-1,2,3,4,6,7,8,8a-octahydro-7,7,8,8-tetracyanonaphthalene (16)



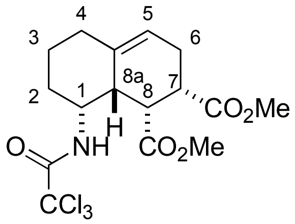
(1*R**,8a*R**)-1-(2’,2’,2’-Trichloromethylcarbonylamino)-1,2,3,4,6,7,8,8a-octahydro-7,7,8,8-tetracyanonaphthalene (**16**) was synthesised according to above procedure using (2*E*)-octa-2-en-7-yn-1-ol (**10**) (0.060 g, 0.48 mmol). The reaction mixture was stirred with Grubbs 1st generation catalyst (0.040 g, 0.048 mmol) for 48 h at 75 °C before tetracyanoethylene (0.37 g, 2.88 mmol) was added. The reaction mixture was stirred for 24 h at 111 °C. Flash column chromatography (petroleum ether/ethyl acetate, 3:1) gave (1*R**,8a*R**)-1-(2’,2’,2’-trichloromethylcarbonylamino)-1,2,3,4,6,7,8,8a-octahydro-7,7,8,8-tetracyanonaphthalene (**16**) (0.13 g, 66%) as an orange oil. R_f (50% ethyl acetate/petroleum ether) 0.56; ν_{max}/cm^{-1} (neat) 3313 (NH), 2945 (CH), 2359 (CN), 2342 (CN), 1699 (CO), 1514, 1275, 910, 733; δ_H (500 MHz, $CDCl_3$) 1.53 (1H, qt, *J* 12.7, 3.9 Hz, 3-*H*H), 1.82 (1H, qd, *J* 12.7, 3.9 Hz, 2-*H*H), 1.92–1.99 (1H, m, 3-H*H*), 2.13–2.25 (2H, m, 2-H*H* and 4-*H*H), 2.49–2.56 (1H, m, 4-H*H*), 3.06 (1H, ddt, *J* 18.1, 6.2, 2.1 Hz, 6-*H*H), 3.15 (1-H, ddd, *J* 18.1, 5.3, 2.1 Hz, 6-H*H*), 3.37 (1H, dd, *J* 11.5, 1.3 Hz, 8a-H), 4.11–4.20 (1H, m, 1-H), 5.70–5.74 (1H, m, 5-H), 7.11 (1H, d, *J* 9.6 Hz, NH); δ_C (125 MHz, $CDCl_3$) 23.4 (CH_2), 31.4 (CH_2), 32.3 (CH_2), 34.1 (CH_2), 39.7 (C), 42.6 (C), 47.1 (CH), 54.4 (CH), 91.9 (C), 108.5 (C), 110.3 (C), 110.9 (C), 112.1 (C), 115.8 (CH), 135.0 (C), 161.9 (C); *m/z* (CI) 396.0197 (MH^+. $C_{16}H_{13}{}^{35}Cl_3N_5O$ requires 396.0186), 362 (100%), 328 (20), 292 (25), 264 (30), 237 (25), 183 (42), 167 (50), 147 (25), 107 (65), 69 (74).

Methyl (1*R**,8*S**,8a*S**)-1-(2’,2’,2’-trichloromethylcarbonylamino)-1,2,3,4,6,7,8,8a-octahydronaphthalene-8-carboxylate (17)



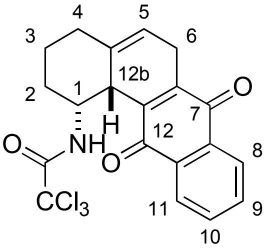
Methyl (1*R**,8*S**,8a*S**)-1-(2’,2’,2’-trichloromethylcarbonylamino)-1,2,3,4,6,7,8,8a-octahydronaphthalene-8-carboxylate (**17**) was synthesised according to above procedure using (2*E*)-octa-2-en-7-yn-1-ol (**10**) (0.050 g, 0.40 mmol). The reaction mixture was stirred with Grubbs 1st generation catalyst (0.033 g, 0.040 mmol) for 48 h at 75 °C before methyl acrylate (0.22 mL, 2.41 mmol) was added. The reaction mixture was stirred for 6 days at 111 °C. Flash column chromatography (petroleum ether/diethyl ether, 5:2) gave methyl (1*R**,8*S**,8a*S**)-1-(2',2',2'-trichloromethylcarbonylamino)-1,2,3,4,6,7,8,8a-octahydronaphthalene-8-carboxylate (**17**) (0.068 g, 48%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3416 (NH), 2938 (CH), 1713 (CO), 1501, 1435, 1265, 1152, 1020, 952, 816; δ_H (500 MHz, $CDCl_3$) 1.35 (1H, qt, *J* 13.3, 4.4 Hz, 3-*H*H), 1.59 (1H, tdd, *J* 13.3, 4.4, 3.0 Hz, 2-*H*H), 1.65–1.72 (1H, m, 3-H*H*), 1.74–1.88 (3H, m, 2-H*H* and 7-H_2), 1.93–2.04 (2H, m, 4-*H*H and 6-*H*H), 2.05–2.13 (1H, m, 6-H*H*), 2.24 (1H, ddt, *J* 13.3, 4.4, 2.2 Hz, 4-H*H*), 2.63–2.67 (1H, m, 8a-H), 2.72 (1H, ddd, *J* 12.8, 7.1, 4.4 Hz, 8-H), 3.66 (3H, s, OCH_3), 4.11 (1H, dq, *J* 9.2, 3.0 Hz, 1-H), 5.69–5.72 (1H, m, 5-H), 6.76 (1H, br d, *J* 9.2 Hz, NH); δ_C (126 MHz, $CDCl_3$) 20.7 (CH_2), 22.9 (CH_2), 23.5 (CH_2), 31.5 (CH_2), 35.5 (CH_2), 40.9 (CH), 42.8 (CH), 50.2 (CH), 52.1 (CH_3), 93.0 (C), 123.8 (CH), 134.4 (C), 160.1 (C), 173.7 (C); *m/z* (CI) 354.0431 (MH^+. $C_{14}H_{19}{}^{35}Cl_3NO_3$ requires 354.0431), 320 (60%), 291 (20), 257 (15), 193 (15), 107 (23), 69 (53).

Dimethyl (1*R**,7*R**,8*S**,8a*S**)-1-(2',2',2'-trichloromethylcarbonylamino)-1,2,3,4,6,7,8,8a-octohydronaphthalenene-7,8-dicarboxylate (18)



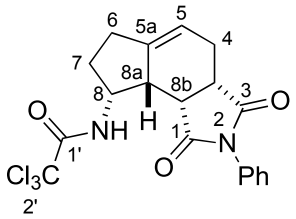
Dimethyl (1*R**,7*R**,8*S**,8a*S**)-1-(2',2',2'-trichloromethylcarbonylamino)-1,2,3,4,6,7,8,8a-octohydronaphthalenene-7,8-dicarboxylate (**18**) was synthesised according to above procedure using (2*E*)-octa-2-en-7-yn-1-ol (**10**) (0.050 g, 0.40 mmol). The reaction mixture was stirred with Grubbs 1st generation catalyst (0.033 g, 0.040 mmol) for 48 h at 75 °C before dimethyl maleate (0.15 mL, 1.20 mmol) was added. The reaction mixture was stirred for 120 h at 111 °C. Flash column chromatography (petroleum ether/diethyl ether, 1:1) afforded dimethyl (1*R**,7*R**,8*S**,8a*S**)-1-(2',2',2'-trichloromethylcarbonylamino)-1,2,3,4,6,7,8,8a-octohydronaphthalenene-7,8-dicarboxylate (**18**) (0.065 g, 39%) as a colourless oil. R_f (50% diethyl ether/petroleum ether) 0.37; ν_{max} /cm^{-1} (neat) 3395 (NH), 2951 (CH), 2939 (CH), 1730 (CO), 1710 (CO), 1502, 1436, 1201, 1173, 1162, 819, 734; δ_H (500 MHz, $CDCl_3$) 1.46–1.57 (2H, m, 2-*H*H and 3-*H*H), 1.60–1.67 (1H, m, 3-H*H*), 2.05–2.17 (2H, m, 2-H*H* and 4-*H*H), 2.33–2.42 (2H, m, 4-H*H* and 6-*H*H), 2.65 (1H, dt, *J* 11.3, 4.6 Hz, 7-H), 2.85–2.95 (2H, m, 6-H*H* and 8a-H), 3.43 (1H, dd, *J* 8.6, 4.6 Hz, 8-H), 3.64 (3H, s, OCH_3), 3.68 (3H, s, OCH_3), 4.41–4.47 (1H, m, 1-H), 5.80–5.85 (1H, m, 5-H), 6.88 (1H, d, *J* 7.5 Hz, NH); δ_C (126 MHz, $CDCl_3$) 20.3 (CH_2), 23.9 (CH_2), 29.5 (CH_2), 33.5 (CH_2), 41.3 (CH), 41.6 (CH), 41.8 (CH), 50.1 (CH), 52.0 (CH_3), 52.1 (CH_3), 92.5 (C), 124.2 (CH), 132.8 (C), 160.7 (C), 173.3 (C), 173.5 (C); *m/z* (CI) 412.0475 (MH^+. $C_{16}H_{21}{}^{35}Cl_3NO_5$ requires 412.0485), 378 (100%), 344 (40), 310 (10), 235 (55), 193 (10), 113 (12), 69 (42).

(1*R,12b*R**)-1-(2',2',2'-Trichloromethylcarbonylamino)-1,2,3,4,6,12b-hexahydrobenz[*a*]anthracene-7,12-dione (19)**



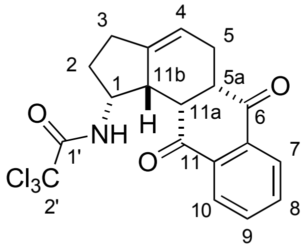
(1*R**,12b*R**)-1-(2',2',2'-Trichloromethylcarbonylamino)-1,2,3,4,6,12b-hexahydrobenz[*a*]anthracene-7,12-dione (**19**) was synthesised according to above procedure using (2*E*)-octa-2-en-7-yn-1-ol (**10**) (0.060 g, 0.48 mmol). The reaction mixture was stirred with Grubbs 1st generation catalyst (0.040 g, 0.048 mmol) for 48 h at 75 °C, before 1,4-naphthoquinone (0.15 g, 1.0 mmol) was added. The reaction mixture was stirred for 48 h at 111 °C. Flash column chromatography (petroleum ether/diethyl ether 7:3) gave (1*R**,12b*R**)-1-(2',2',2'-trichloromethylcarbonylamino)-1,2,3,4,6,12b-hexahydrobenz[*a*]anthracene-7,12-dione (**19**) (0.12 g, 61%) as a yellow solid. R_f (50% diethyl ether/petroleum ether) 0.51; Mp 176–178 °C; ν_{max} /cm^{-1} (neat) 3418, 3333 (NH), 3073 (ArH), 2935 (CH), 1705 (CO), 1661 (CO), 1591, 1506, 1330, 1293, 821; δ_H (500 MHz, $CDCl_3$) 1.43 (1H, qt, *J* 13.6, 3.6 Hz, 3-*H*H), 1.84–1.94 (2H, m, 2-*H*H and 3-H*H*), 1.99 (1H, qt, *J* 13.6, 3.6 Hz, 2-H*H*), 2.12 (1H, m, 4-*H*H), 2.34–2.40 (1H, m, 4-H*H*), 3.15 (1H, dddd, *J* 24.9, 6.4, 2.6, 1.9 Hz, 6-*H*H), 3.24 (1H, dddd, *J* 24.9, 6.4, 3.6, 2.6 Hz, 6-H*H*), 3.78 (1H, td, *J* 6.4, 3.6 Hz, 12b-H), 4.62 (1H, dq, *J* 9.3, 3.6 Hz, 1-H), 5.78–5.82 (1H, m, 5-H), 6.83 (1H, br d, *J* 9.3 Hz, NH), 7.62 (1H, td, *J* 7.4, 1.3 Hz, ArH), 7.66 (1H, td, *J* 7.4, 1.3 Hz, ArH), 7.96 (1H, dd, *J* 7.4, 1.3 Hz, ArH), 8.07 (1H, dd, *J* 7.4, 1.3 Hz, ArH); δ_C (126 MHz, $CDCl_3$) 23.6 (CH_2), 25.3 (CH_2), 30.3 (CH_2), 34.7 (CH_2), 41.5 (CH), 51.1 (CH), 92.6 (C), 118.5 (CH), 126.1 (CH), 126.7 (CH), 131.7 (C), 132.2 (C), 133.5 (CH and C), 133.9 (CH), 140.4 (C), 142.7 (C), 161.4 (C), 183.7 (C), 184.3 (C); *m/z* (Cl) 426.0245 (MH^+. $C_{20}H_{17}{}^{35}Cl_2{}^{37}ClNO_3$ requires 426.0247), 390 (85%), 356 (30), 279 (35), 261 (30), 162 (10), 130 (7), 85 (33), 69 (48).

(3a*S**,8*R**,8a*R**,8b*R**)-8-(2’,2’,2’-Trichloromethylcarbonylamino)-4,6,7,8,8a,8b-hexahydro-2-phenylcyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (20)



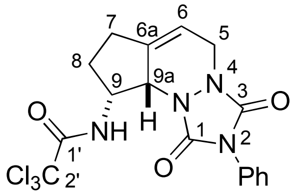
(3a*S**,8*R**,8a*R**,8b*R**)-8-(2’,2’,2’-Trichloromethylcarbonylamino)-4,6,7,8,8a,8b-hexahydro-2-phenylcyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**20**) was synthesised according to above procedure using (2*E*)-hept-2-en-6-yn-1-ol (**9**) (0.050 g, 0.48 mmol). The reaction mixture was stirred with Grubbs 1st generation catalyst (0.040 g, 0.048 mmol) for 48 h at 75 °C before *N*-phenyl maleimide (0.13 g, 0.73 mmol) was added. The reaction mixture was stirred for 72 h at 75 °C. Flash column chromatography (petroleum ether/diethyl ether, 3:7) gave (3a*S**,8*R**,8a*R**,8b*R**)-8-(2’,2’,2’-trichloromethylcarbonylamino)-4,6,7,8,8a,8b-hexahydro-2-phenylcyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**20**) (0.13 g, 62%) as white solid. R_f (70% diethyl ether/petroleum ether) 0.44; Mp 174–176 °C; ν_{max}/cm^{-1} (neat) 3304 (NH), 2955 (CH), 2924 (CH), 1695 (CO), 1516, 1388, 1288, 1202, 1182, 822, 750; δ_H (500 MHz, CDCl$_3$) 1.81 (1H, qd, *J* 12.5, 7.6 Hz, 7-*H*H), 2.10–2.18 (1H, m, 7-H*H*), 2.19–2.38 (2H, m, 6-*H*H and 4-*H*H), 2.47 (1H, dd, *J* 16.2, 7.6 Hz, 6-H*H*), 2.85 (1H, ddd, *J* 15.1, 7.2, 1.1 Hz, 4-H*H*), 2.89–2.96 (1H, m, 8a-H), 3.33 (1H, ddd, *J* 8.7, 7.2, 1.1 Hz, 3a-H), 3.43 (1H, dd, *J* 8.7, 6.4 Hz, 8b-H), 4.80–4.91 (1H, m, 8-H), 5.75–5.81 (1H, m, 5-H), 7.15–7.20 (2H, m, 2 × ArH), 7.39–7.51 (3H, m, 3 × ArH), 8.95 (1H, d, *J* 9.2 Hz, NH); δ_C (126 MHz, CDCl$_3$) 26.1 (CH$_2$), 28.6 (CH$_2$), 31.7 (CH$_2$), 39.4 (CH), 41.2 (CH), 41.5 (CH), 52.9 (CH), 92.9 (C), 117.1 (CH), 126.5 (2 × CH), 129.2 (CH), 129.3 (2 × CH), 131.5 (C), 145.8 (C), 162.3 (C), 178.6 (C), 179.7 (C); *m*/*z* (CI) 427.0373 (MH$^+$. $C_{19}H_{18}{}^{35}Cl_3N_2O_3$ requires 427.0383), 393 (65%), 359 (100), 325 (65), 311 (20), 266 (25), 174 (25), 113 (25), 71 (73).

(1*R**,5a*S**,11a*R**,11b*S**)-1-(2',2',2'-Trichloromethylcarbonylamino)-1,2,3,5,11a,11b-hexahydrocyclopent[*a*]anthracene-6,11(5a*H*)-dione (21)



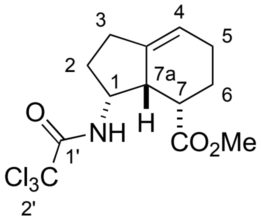
(1*R**,5a*S**,11a*R**,11b*S**)-1-(2',2',2'-Trichloromethylcarbonylamino)-1,2,3,5,11a,11b-hexahydrocyclopent[*a*]anthracene-6,11(5a*H*)-dione (**21**) was synthesised according to above procedure using (2*E*)-hept-2-en-6-yn-1-ol (**9**) (0.055 g, 0.50 mmol). The reaction mixture was stirred with Grubbs 1st generation catalyst (0.041 g, 0.050 mmol) for 48 h at 75 °C, before 1,4-naphthoquinone (0.12 g, 0.75 mmol) was added. The reaction mixture was stirred for 24 h at 75 °C. Flash column chromatography (petroleum ether/ diethyl ether, 1:1) gave (1*R**,5a*S**,11a*R**,11b*S**)-1-(2',2',2'-Trichloromethylcarbonylamino)-1,2,3,5,11a,11b-hexahydrocyclopent[*a*]anthracene-6,11(5a*H*)-dione (**21**) (0.097 g, 47%) as white solid. R_f (50% diethyl ether/petroleum ether) 0.40; Mp 153–155 °C; ν_{max} /cm^{-1} (neat) 3364 (NH), 2940 (CH), 2847 (CH), 2338, 1682 (CO), 1589, 1512, 1281, 1247, 810, 741; δ_H (500 MHz, CDCl$_3$) 1.95–2.15 (2H, m, 2-*H*H and 5-*H*H), 2.15–2.30 (2H, m, 2-H*H* and 3-*H*H), 2.35–2.48 (2H, m, 3-H*H* and 5-H*H*), 2.91–2.97 (1H, m, 11b-H), 3.33 (1H, ddd, *J* 11.3, 7.2, 4.4 Hz, 5a-H), 3.51 (1H, t, *J* 4.4 Hz, 11a-H), 4.65 (1H, m, 1-H), 5.31–5.36 (1H, m, 4-H), 7.44 (1H, d, *J* 8.8 Hz, NH), 7.60–7.72 (2H, m, 2 × ArH), 7.84 (1H, dd, *J* 7.3, 1.6 Hz, ArH), 7.99 (1H, dd, *J* 7.3, 1.6 Hz, ArH); δ_C (126 MHz, CDCl$_3$) 26.9 (CH$_2$), 31.4 (CH$_2$), 32.0 (CH$_2$), 41.5 (CH), 48.6 (CH), 49.5 (CH), 52.9 (CH), 93.0 (C), 114.2 (CH), 126.4 (CH) 127.4 (CH), 132.6 (C), 134.6 (CH), 134.8 (CH), 135.0 (C), 141.7 (C), 161.8 (C), 198.2 (C), 199.9 (C); *m/z* (EI) 413.0159 (M$^+$. $C_{19}H_{16}{}^{35}Cl_2{}^{37}ClNO_3$ requires 413.0169), 376 (5%), 324 (5) 294 (5), 250 (100), 232 (40), 205 (25), 165 (18), 117 (70), 91 (32), 77 (22).

(9*R**,9a*S**)-7,8,9,9a-Tetrahydro-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*,5*H*-cyclopent[*c*][1,2,4]-triazolo[1,2-*a*]pyridazine-1,3(2*H*)-dione (22)



(9*R**,9a*S**)-7,8,9,9a-Tetrahydro-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*,5*H*-cyclopent[*c*][1,2,4]-triazolo[1,2-*a*]pyridazine-1,3(2*H*)-dione (**22**) was synthesised according to above procedure using (2*E*)-hept-2-en-6-yn-1-ol (**9**) (0.054 g, 0.48 mmol). The reaction mixture was stirred with Grubbs 1st generation catalyst (0.040 g, 0.048 mmol) for 48 h at 75 °C, before 4-phenyl-1,2,4-triazole-3,5-dione (0.13 g, 0.73 mmol) was added. The reaction mixture was stirred for 24 h at 75 °C. Flash column chromatography (dichloromethane/methanol, 19:1) gave (9*R**,9a*S**)-7,8,9,9a-tetrahydro-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*,5*H*-cyclopent[*c*][1,2,4]-triazolo[1,2-*a*]pyridazine-1,3(2*H*)-dione (**22**) (0.095 g, 46%) as a white solid. R_f (10% methanol/dichloromethane) 0.58; Mp 55–57 °C; ν_{max} /cm^{-1} (neat) 3396 (NH), 3057 (ArH), 2359, 2342, 1773 (CO), 1699 (CO), 1516, 1503, 1419, 1265, 1140, 820, 731; δ_H (500 MHz, $CDCl_3$) 2.13–2.22 (1H, m, 8-*H*H), 2.31 (1H, dt, *J* 15.0, 5.6 Hz, 8-H*H*), 2.53–2.61 (1H, m, 7-H_2), 4.11 (1H, dquin, *J* 16.4, 2.8 Hz, 5-*H*H), 4.32–4.41 (2H, m, 5-H*H* and 9a-H), 4.89 (1H, q, *J* 5.6 Hz, 9-H), 5.93–5.98 (1H, m, 6-H), 6.75 (1H, d, *J* 5.6 Hz, NH), 7.38–7.53 (5H, m, 5 × ArH); δ_C (126 MHz, $CDCl_3$) 24.9 (CH_2), 27.8 (CH_2), 42.5 (CH_2), 53.3 (CH), 59.9 (CH), 92.6 (C), 115.6 (CH), 125.4 (2 × CH), 128.4 (CH), 129.2 (2 × CH), 130.9 (C), 137.0 (C), 151.5 (C), 153.2 (C), 161.4 (C); *m/z* (EI) 428.0208 (M^+. $C_{17}H_{15}{}^{35}Cl_3N_4O_3$ requires 428.0210), 393 (5%), 343 (10), 311 (20), 267 (100), 241 (5), 192 (8), 148 (23), 119 (83), 91 (70), 66 (29).

Methyl (1*R**,7*S**,7a*S**)-1-(2',2',2'-trichloromethylcarbonylamino)-2,3,5,6,7,7a-hexahydroindene-7-carboxylate (23)



Methyl (1*R**,7*S**,7a*S**)-1-(2',2',2'-trichloromethylcarbonylamino)-2,3,5,6,7,7a-hexahydroindene-7-carboxylate (**23**) was synthesised according to above procedure, using (2*E*)-hept-2-en-6-yn-1-ol (**9**) (0.050 g, 0.48 mmol). The reaction mixture was stirred with Grubbs 1st generation catalyst

(0.041 g, 0.050 mmol) for 48 h at 75 °C, before methyl acrylate (0.13 mL, 1.44 mmol) was added. The reaction mixture was stirred for 13 days at 75 °C. Flash column chromatography (petroleum ether/diethyl ether, 20:7) gave methyl (1*R**,7*S**,7a*S**)-1-(2',2',2'-trichloromethylcarbonylamino)-2,3,5,6,7,7a-hexahydroindene-7-carboxylate (**23**) (0.074 g, 45%) as a colourless oil. R_f (50% petroleum ether/diethyl ether) 0.66; ν_{max}/cm^{-1} 3410 (NH), 2953 (CH), 1709 (CO), 1508, 1198, 1171, 818, 735; δ_H (500 MHz, $CDCl_3$) 1.69–1.83 (2H, m, 2-*H*H and 3-*H*H), 1.95–2.11 (4H, m, 2-H*H*, 5-*H*H and 6-H_2), 2.15–2.25 (1H, m, 3-H*H*), 2.32 (1H, dd, *J* 15.2, 6.3 Hz, 5-H*H*), 2.79–2.89 (2H, m, 7-H and 7a-H), 3.60 (1H, s, OCH_3), 4.51 (1H, dq, *J* 8.7, 7.2 Hz, 1-H), 5.45 (1H, br s, 4-H), 7.51 (1H, d, *J* 7.2 Hz, NH); δ_c (126 MHz, $CDCl_3$) 22.6 (CH_2), 26.0 (CH_2), 30.2 (CH_2), 31.7 (CH_2), 39.3 (CH), 42.5 (CH), 52.0 (CH), 53.3 (CH_3), 92.9 (C), 117.7 (CH), 140.1 (C), 161.7 (C), 175.7 (C); *m/z* (CI) 342.0247 (MH^+. $C_{13}H_{17}{}^{35}Cl_2{}^{37}ClNO_3$ requires 342.0246), 324 (60%), 306 (29), 257 (8), 230 (11), 195 (49), 179 (28), 157 (50), 141 (16), 73 (24).

3. Experimental for Molecular Modeling

All calculations were done with the program Gaussian 09[6] using the M06-2X exchange-correlation functional,[7] which has been shown[7,8] to provide accurate results for main-group thermochemistry, including reaction barriers. For the reaction at hand, where two relatively large molecules are brought together, it is particularly important to use a method that accounts for dispersive interactions, such as the functionals of the M06 family. The def2-TZVP basis set[9] was used, which affords results close to the basis-set limit for density-functional theory. All calculations included the effects of the toluene solvent at the level of the IEF-PCM polarizable continuum model as implemented in Gaussian 09. Default parameters for SCF and geometry convergence were used. The characters of stationary points were verified by the appropriate number of imaginary frequencies, which were obtained from analytical second derivatives. Thermochemical data were calculated within the standard rigid-rotor/harmonic-oscillator framework at 384 K (boiling point of toluene), 100 kPa; vibrational frequencies were not scaled.

Different rotamers of the diene were explored by structure optimisations starting from a series of initial structures with different exocyclic torsions θ and ϕ (Figure S1). The cyclohexene ring was maintained in a pseudo-chair conformation with (pseudo-) equatorial amide.

In the lowest-energy conformer of the diene, which was used in all subsequent calculations, the diene moiety is non-planar, with the vinyl substituent on the same side of the ring as the amide ($\theta =$

38°). It should be noted, however, that the energy differences between different rotamers are insignificant (~0.1 kJ mol^{-1}). With respect to ϕ, only one rotamer was found, with $\phi = 139°$.

Structures of products and pre-reaction complexes were determined by displacing the optimised TS structures slightly along the imaginary mode in either direction and optimising. Interestingly, the pre-reaction complexes are bound only on the potential-energy surfaces (irrespective of zero-point vibrational or thermal corrections), but not on the free-energy surface; see Table S1.

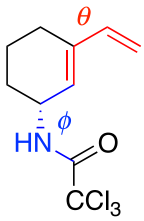


Figure S1.

Table S1. Thermochemical data (384 K, 100 kPa, relative to free reactants) for the formation of pre-reaction complexes, transition states, and products.

		ΔE kJ mol^{-1}	ΔU(0 K) kJ mol^{-1}	ΔH kJ mol^{-1}	ΔS J mol^{-1} K^{-1}	ΔG kJ mol^{-1}
pre-reaction complex	*syn*	–42.5	–38.6	–36.1	–183.2	34.2
	anti	–40.0	–37.1	–37.0	–207.3	42.6
TS	*syn*	20.9	29.6	25.7	–231.1	114.5
	anti	23.7	31.0	24.4	–261.5	124.8
product	*syn*	–195.9	–174.2	–180.0	–227.3	–92.8
	anti	–188.1	–168.0	–173.4	–231.6	–84.5

Cartesian coordinates of stationary points

20
dienophile

C	-0.249390	-1.448072	0.072591
C	-0.708851	-0.021546	0.080003
N	0.363658	0.740182	-0.396621
O	-1.775947	0.399667	0.427923
C	1.442683	-0.098554	-0.696485
C	0.995014	-1.492629	-0.376675
O	2.506734	0.245173	-1.128696
H	-0.893878	-2.248732	0.399837
H	1.646398	-2.340141	-0.521362
H	2.314181	2.395563	0.290034
C	1.459431	2.894350	-0.144171
C	0.357854	2.152390	-0.552801
C	-0.749328	2.778173	-1.112710
H	-1.599630	2.189658	-1.426645
C	-0.751993	4.157295	-1.255789
H	-1.616020	4.645046	-1.687766
C	0.346570	4.906571	-0.857428
H	0.342164	5.981959	-0.976374

```
C  1.450807  4.271379 -0.305937
H  2.310470  4.848720  0.008236
27
diene
C  0.890052  0.148269 -1.233665
C -0.097423  0.297525 -0.358456
C -1.174359 -0.681396 -0.123911
C -0.937662 -1.994272 -0.115899
C -2.006734 -3.034313  0.073025
H -1.925778 -3.467137  1.074622
N -1.766375 -4.139894 -0.852828
C -2.160304 -5.384968 -0.562220
C -1.763956 -6.473903 -1.614138
Cl -2.887527 -7.819029 -1.522674
Cl -1.744305 -5.845563 -3.275901
Cl -0.130208 -7.017981 -1.178727
O -2.714251 -5.724547  0.455435
C -3.406032 -2.451386 -0.104423
C -3.521437 -1.151646  0.680953
C -2.549760 -0.113268  0.130058
H  1.656449  0.902980 -1.350537
H  0.955159 -0.729363 -1.866126
H -0.157152  1.215404  0.220732
H  0.078694 -2.359887 -0.225444
H -1.382011 -3.932271 -1.761223
H -3.569430 -2.254652 -1.168599
H -4.145517 -3.185411  0.216850
H -4.542280 -0.770820  0.643442
H -3.289921 -1.345362  1.732385
H -2.457764  0.731335  0.818000
H -2.932346  0.304955 -0.807518
47
prereact-syn
C  3.407304  1.719196 -1.642439
C  2.800495  2.095794 -0.520755
C  2.373338  1.212453  0.577048
C  2.060292 -0.070402  0.377603
C  1.521288 -0.986530  1.445290
H  2.297131 -1.691251  1.753507
N  0.442965 -1.803187  0.889851
C  0.641522 -3.074737  0.531000
C -0.549779 -3.768961 -0.209159
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47
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H   6.033692 -2.377189  2.220551
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product-syn
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C   2.670090  1.185500  0.642810
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C   1.497479 -1.056053  1.251051
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H  -2.289803  4.958517  2.674192
47
product-anti (final structure)
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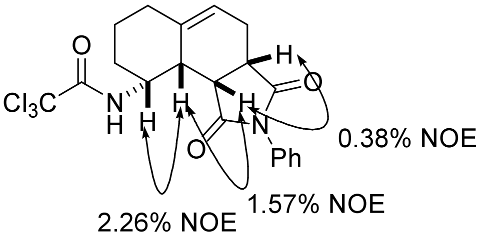
4. NOE Enhancements for compounds 14–23



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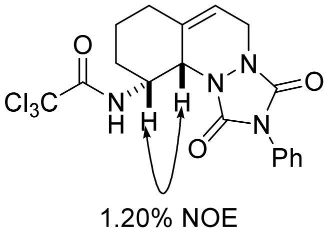

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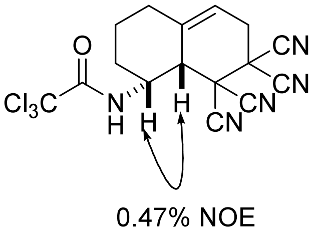

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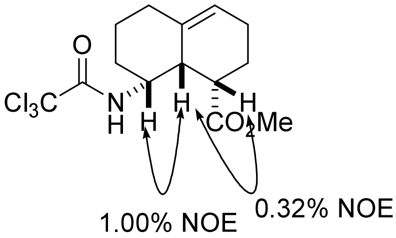

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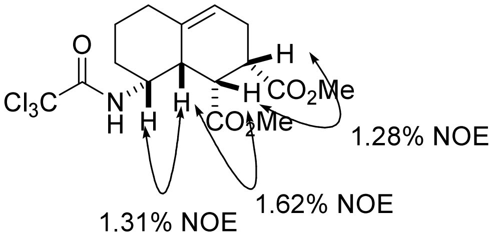

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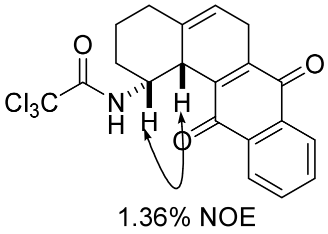

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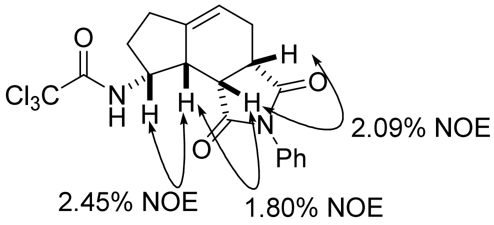

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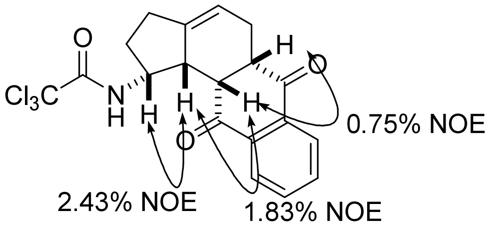

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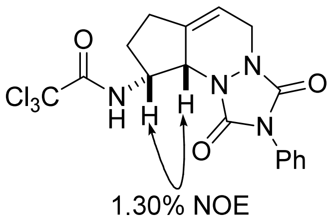

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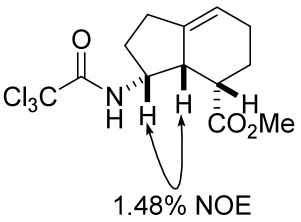

23

5. References

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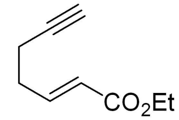
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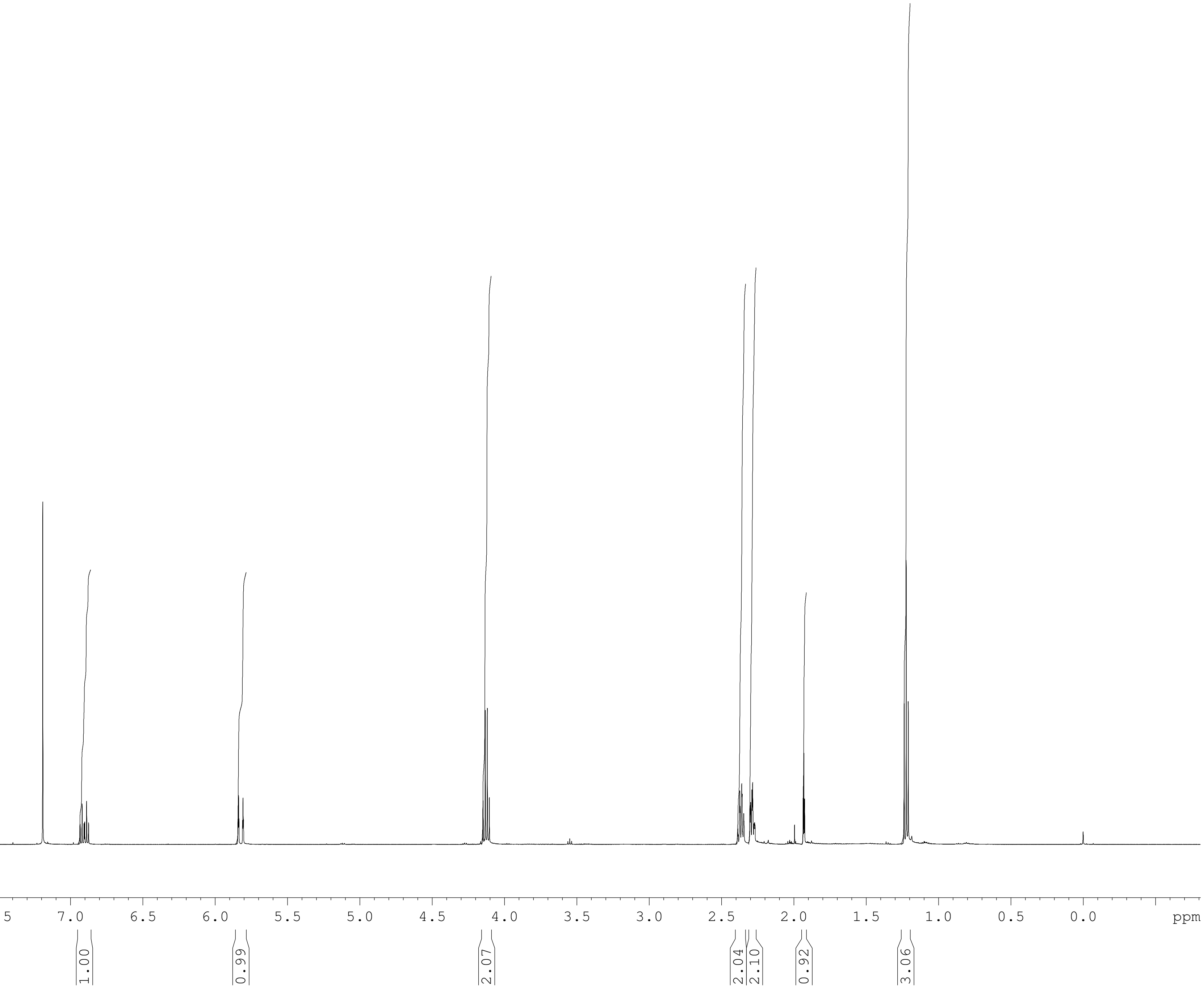
7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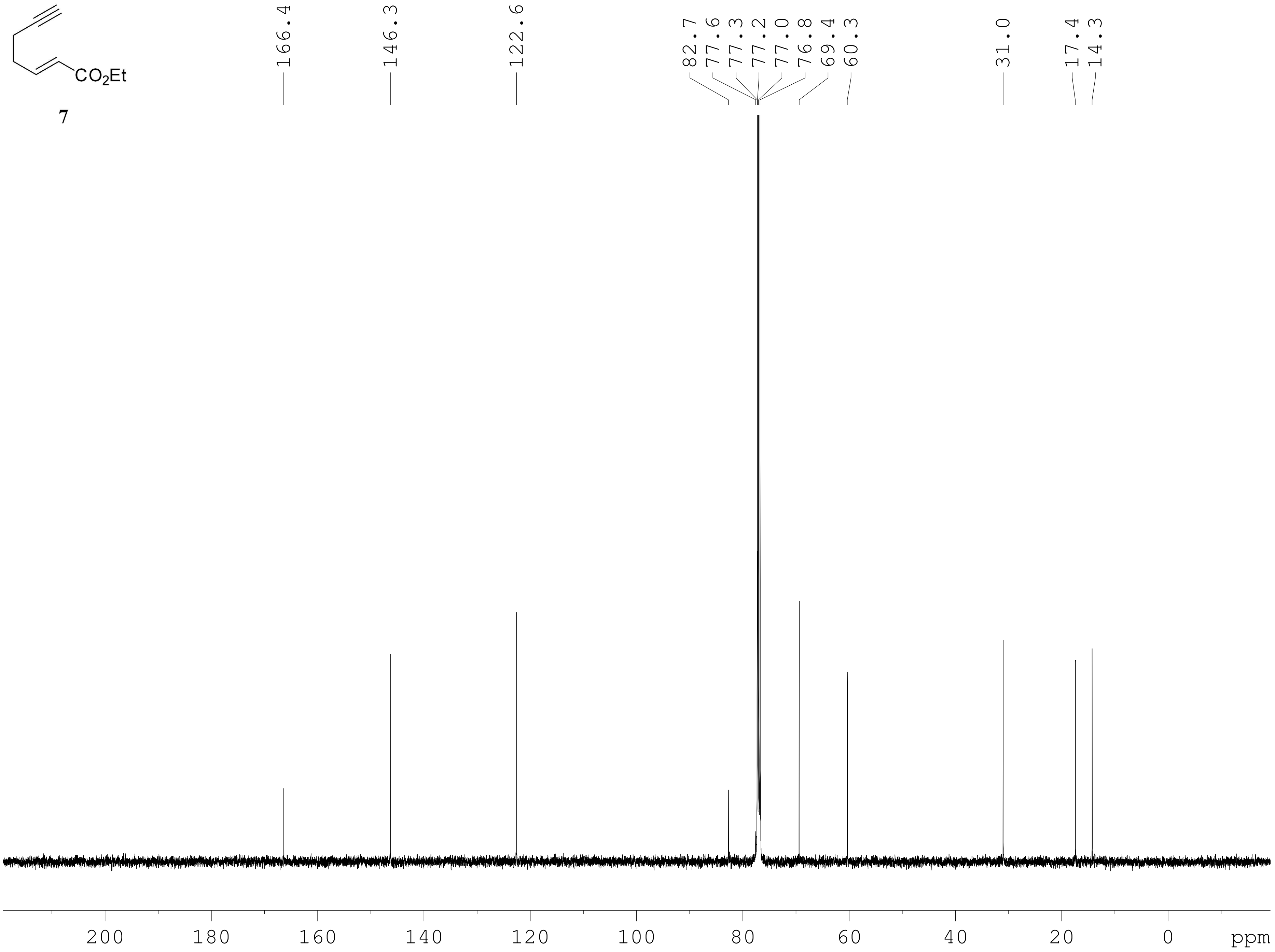
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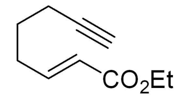
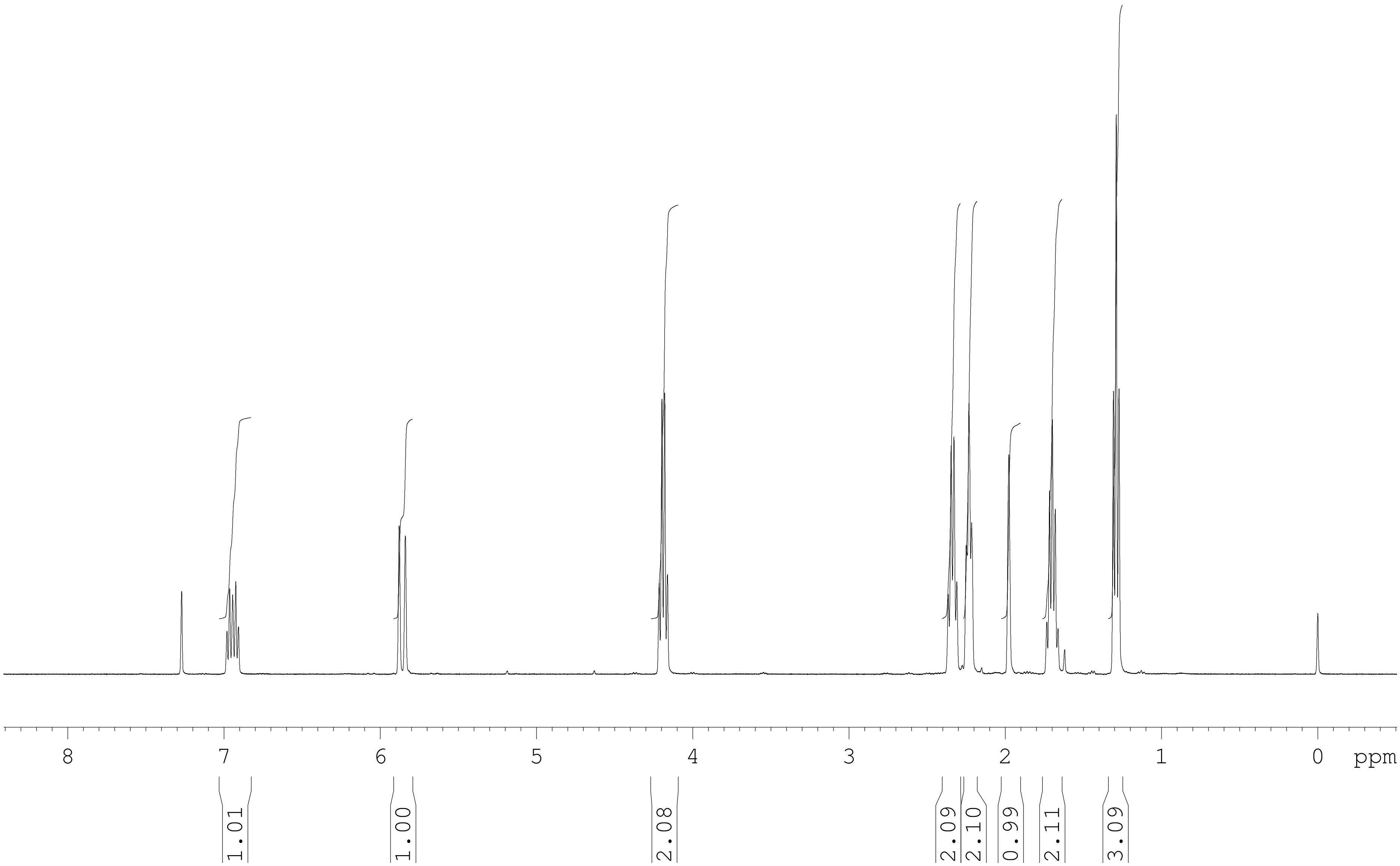
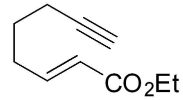
17.4
14.3
200
180
160
140
120
100
80
60
40
20
0
ppm

7

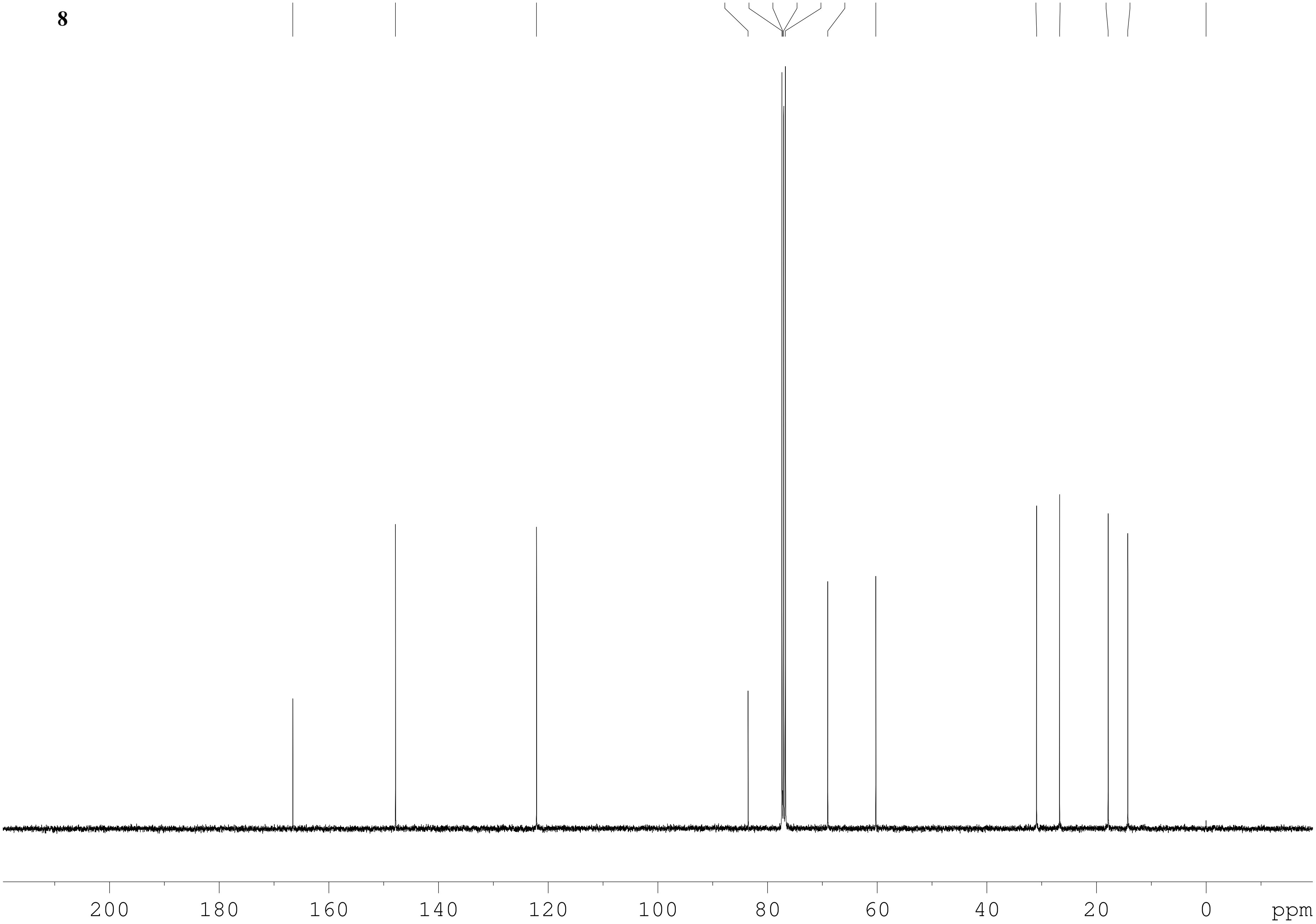


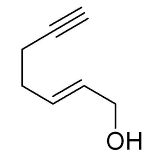
8



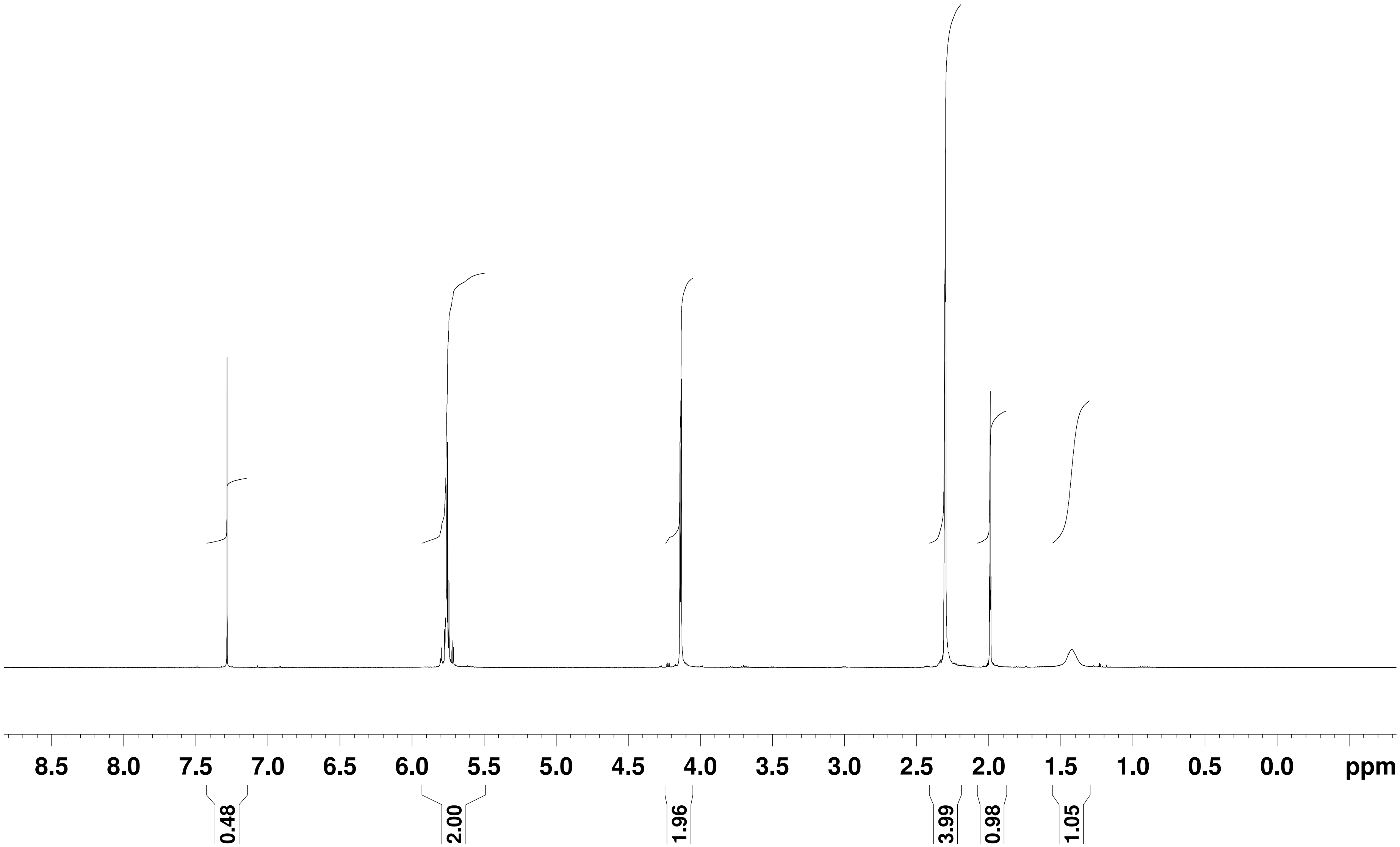

CO$_2$Et

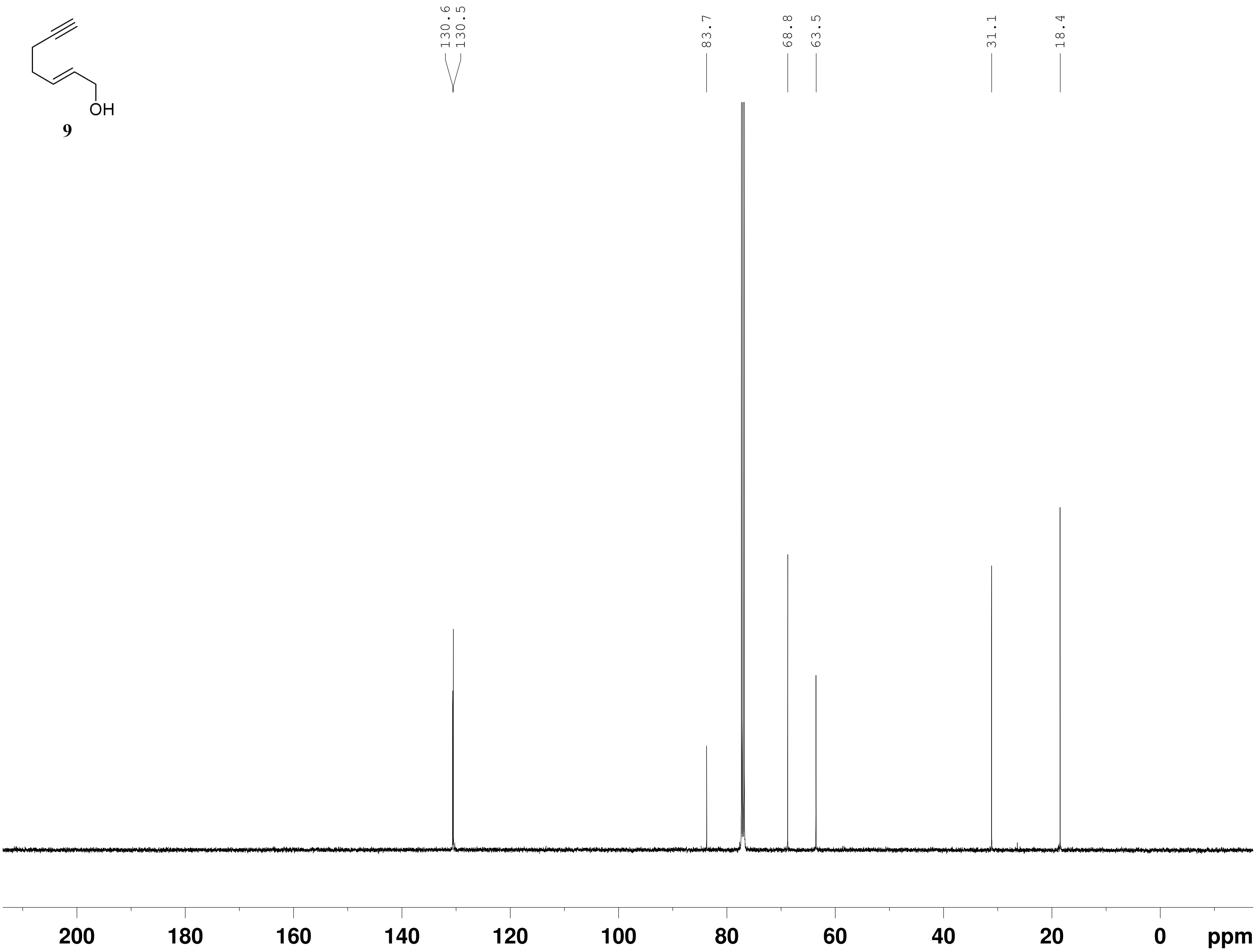
8


166.6
147.8
122.1
83.5
77.4
77.2
77.0
76.7
69.0
60.2
30.9
26.7
17.9
14.3
0.0
200
180
160
140
120
100
80
60
40
20
0
ppm


OH

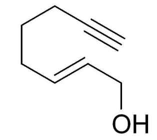
9


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
0.48
2.00
1.96
3.99
0.98
1.05

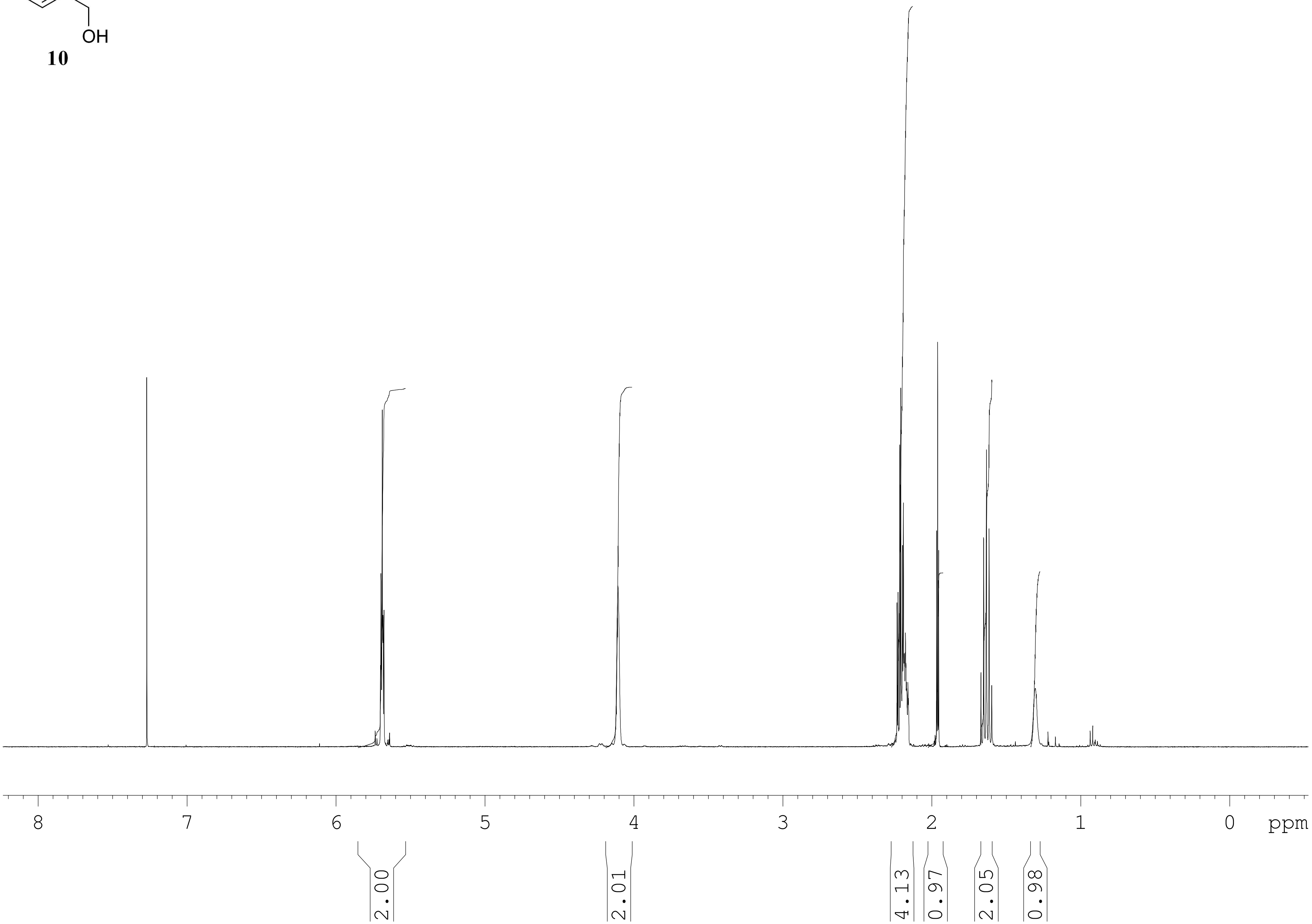


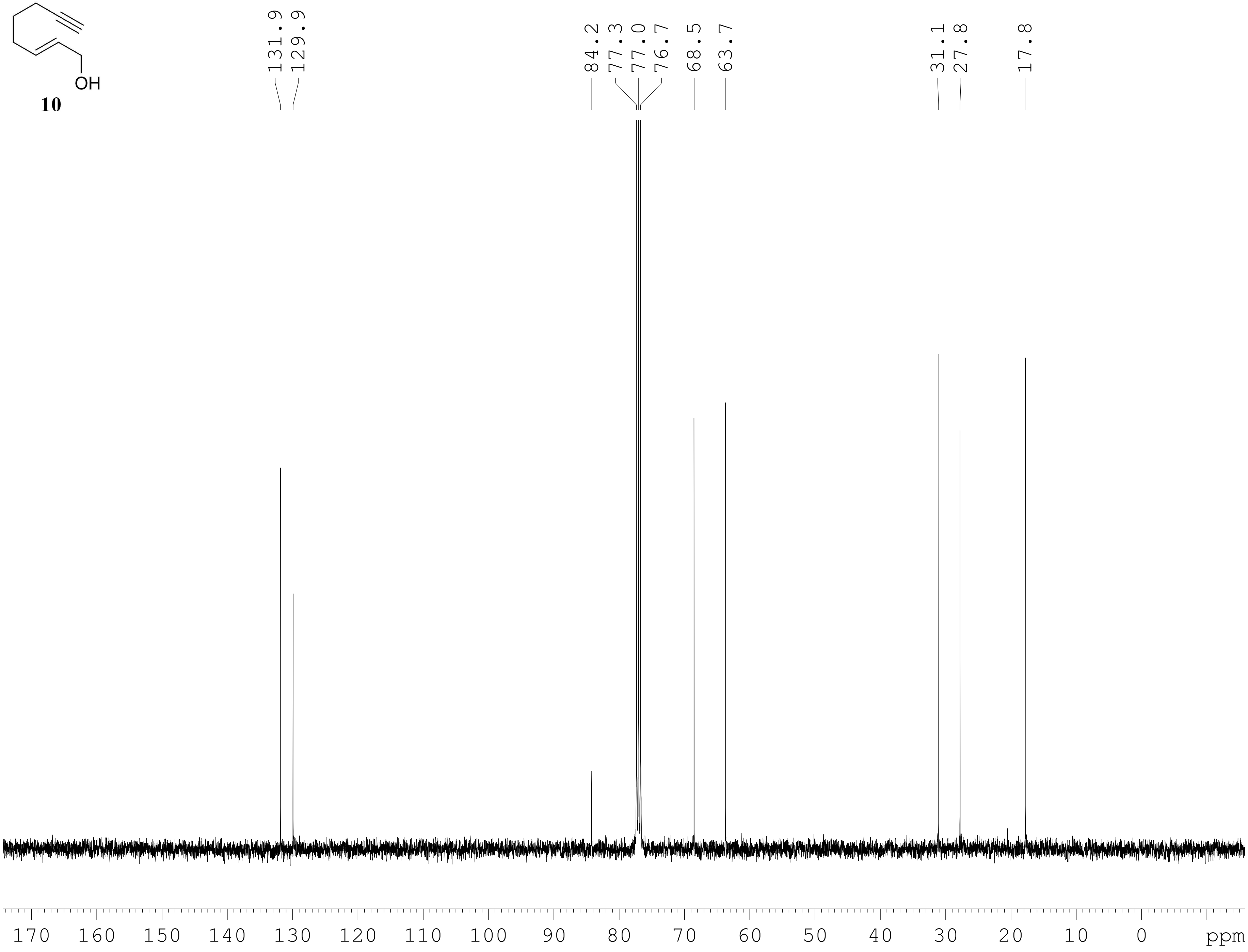
9

OH
130.6
130.5
83.7
68.8
63.5
31.1
18.4
200
180
160
140
120
100
80
60
40
20
0
ppm



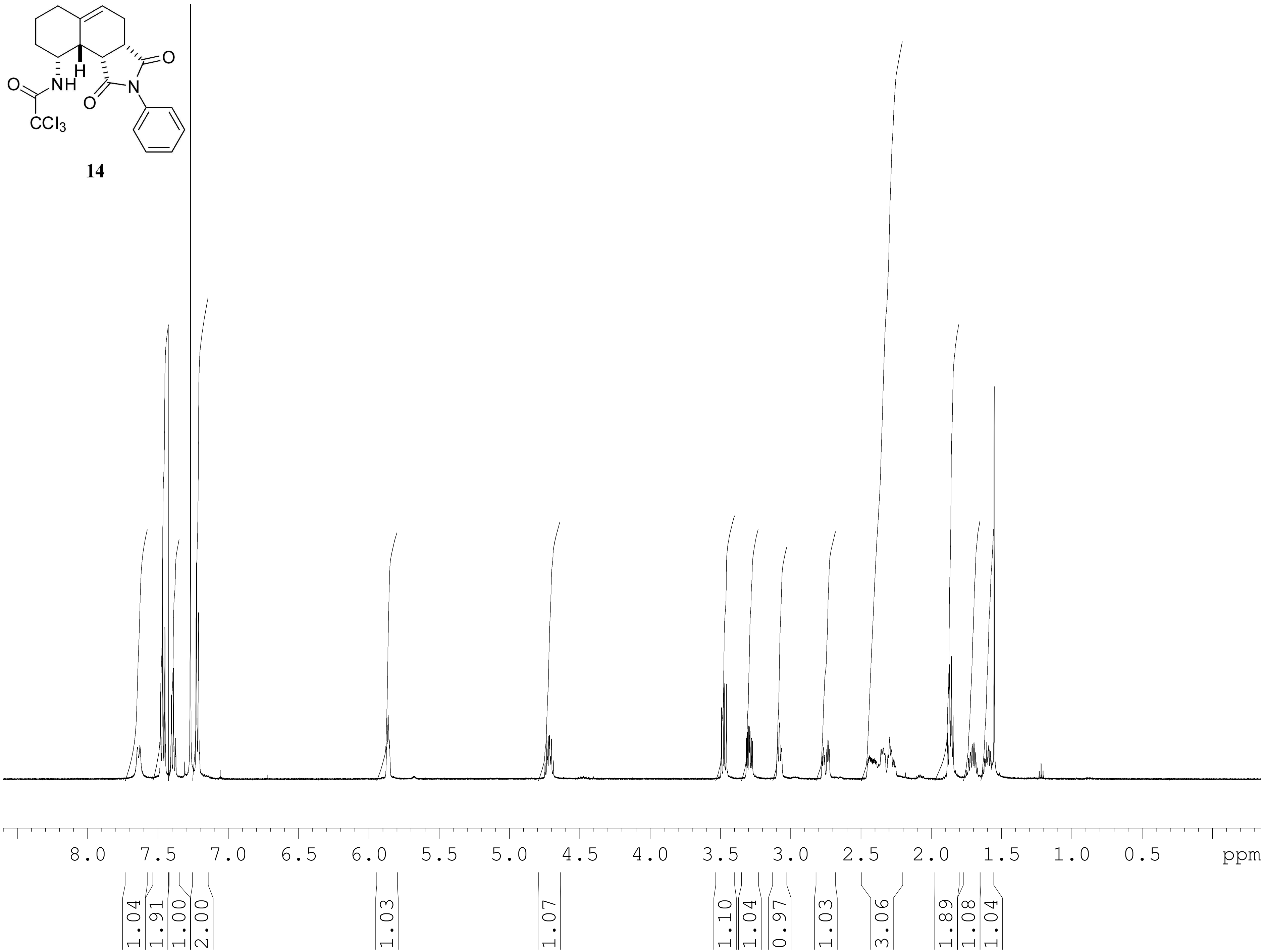
10




OH

10

131.9
129.9
84.2
77.3
77.0
76.7
68.5
63.7
31.1
27.8
17.8
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

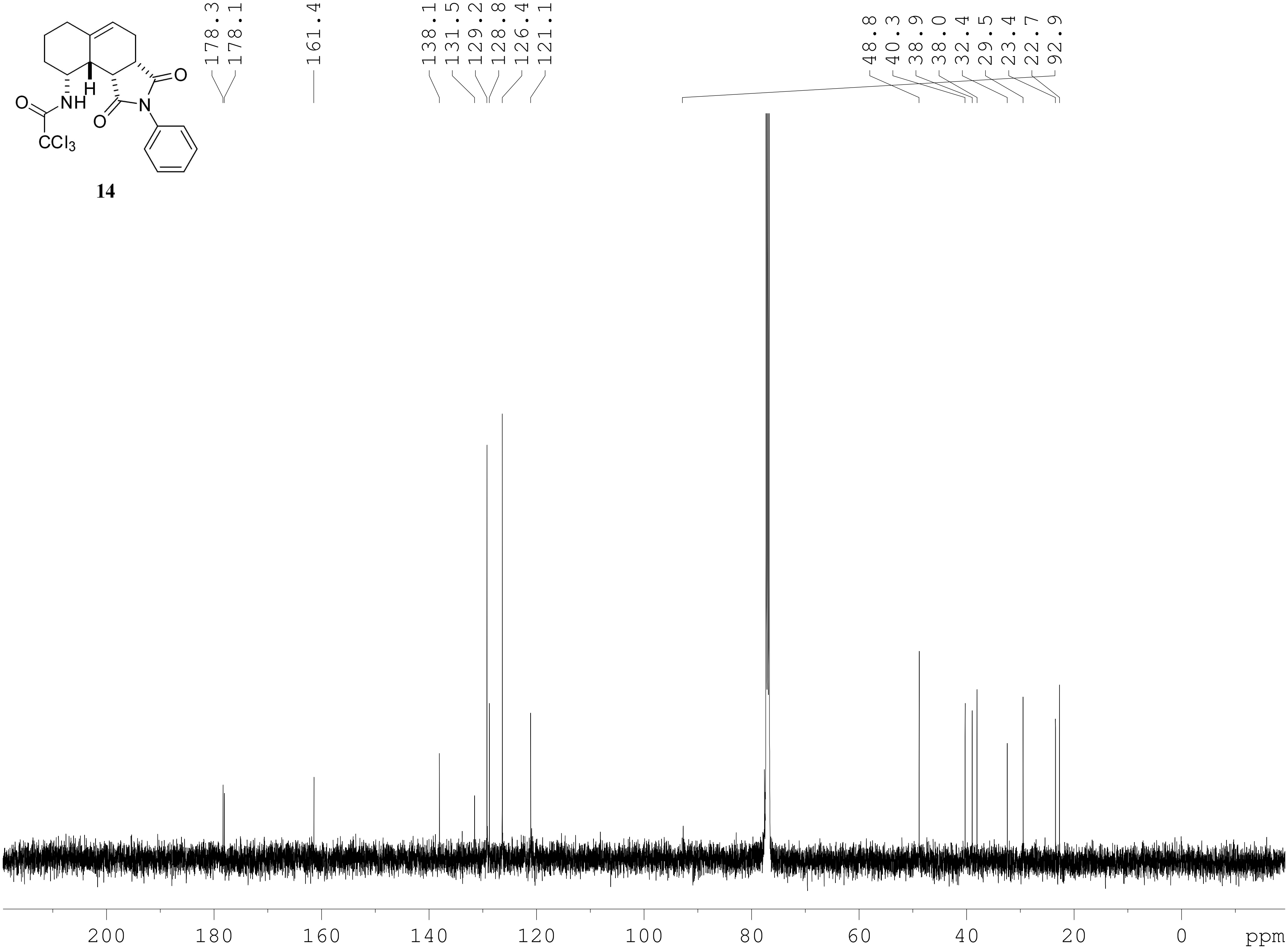


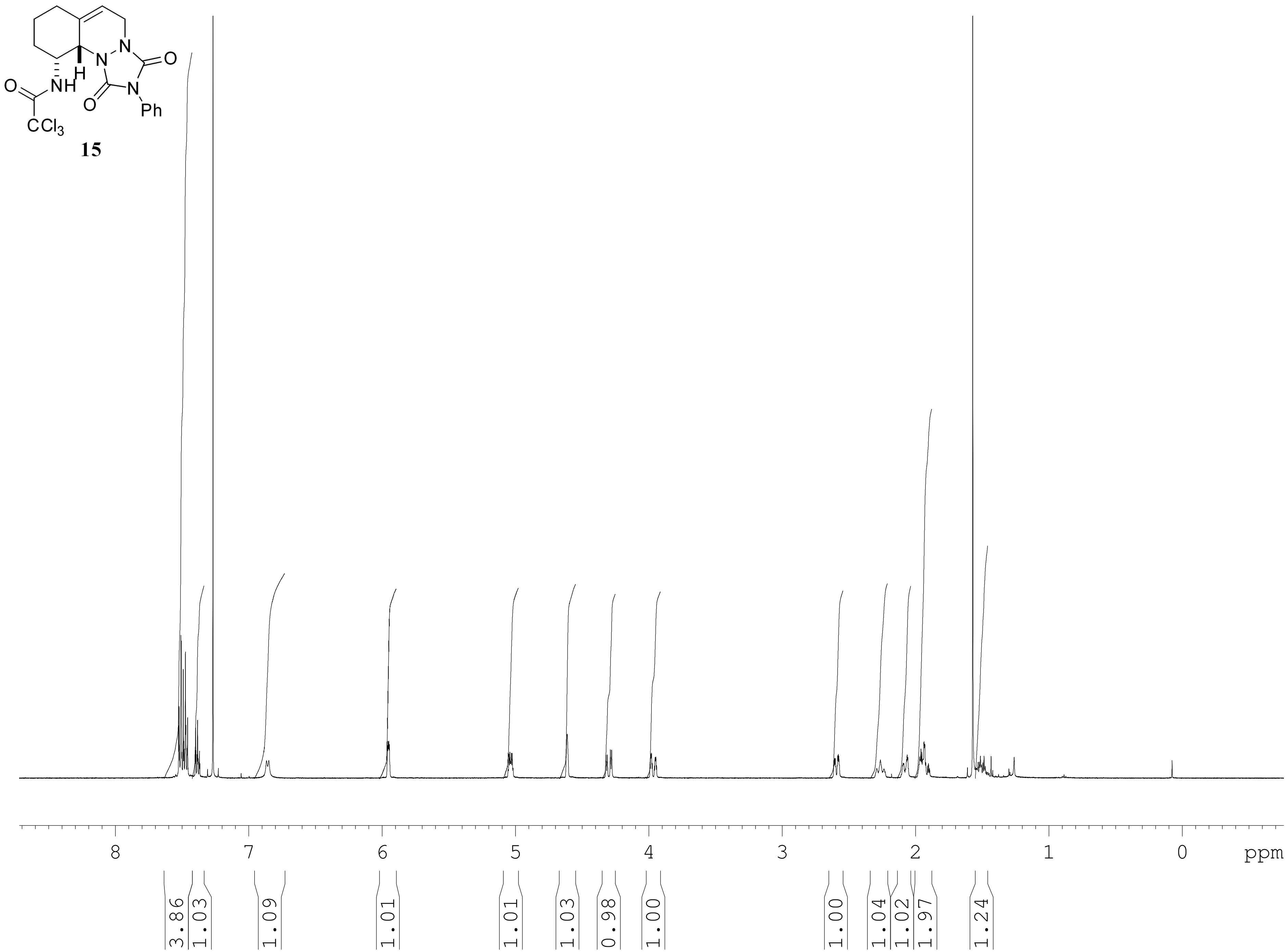
14

O
NH
H
O
O
N
CCl3
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.04
1.91
1.00
2.00
1.03
1.07
1.10
1.04
0.97
1.03
3.06
1.89
1.08
1.04

O
NH
H
CCl3
N
O
O

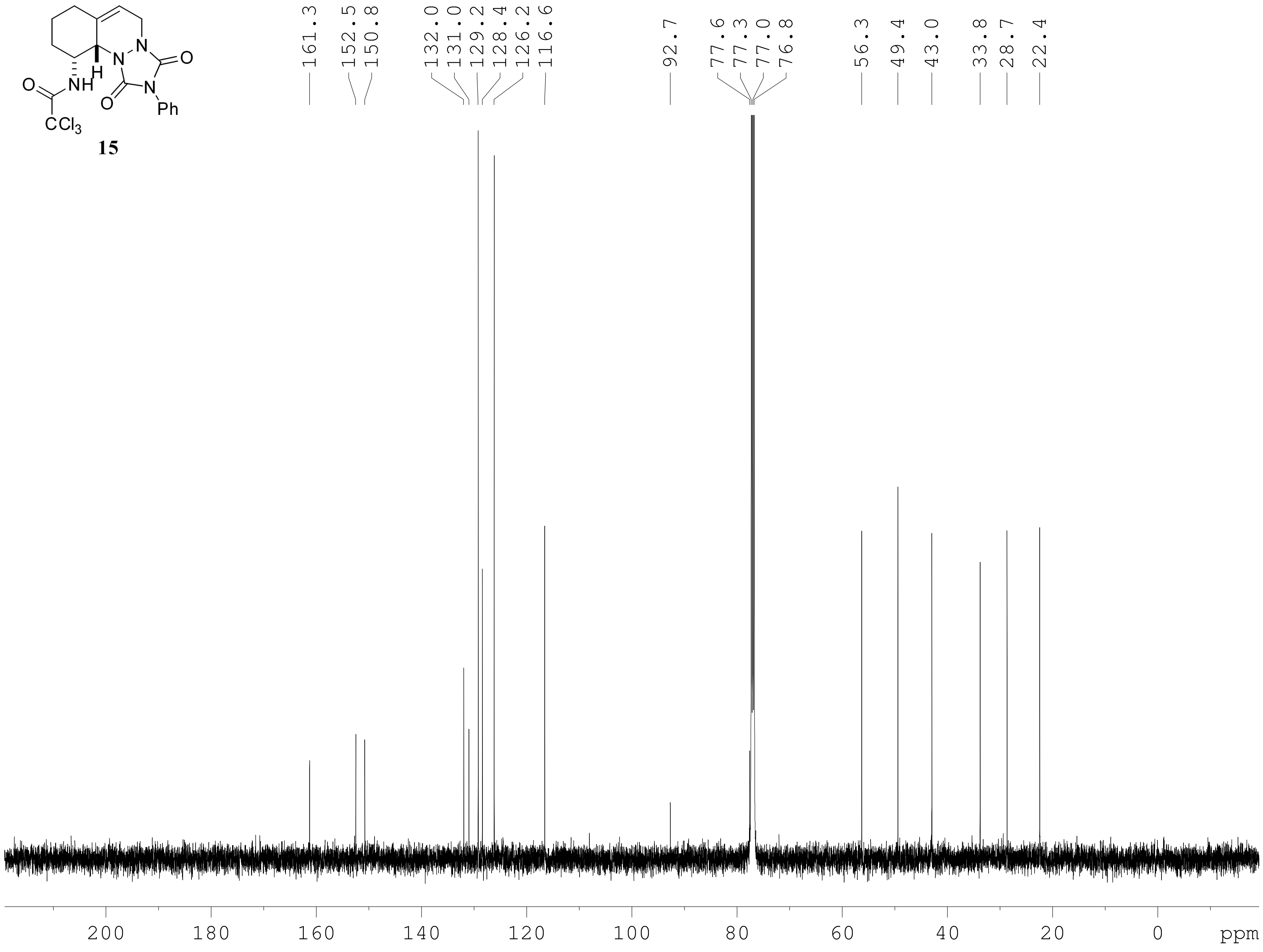
14


178.3
178.1
161.4
138.1
131.5
129.2
128.8
126.4
121.1
48.8
40.3
38.9
38.0
32.4
29.5
23.4
22.7
92.9
200
180
160
140
120
100
80
60
40
20
0
ppm

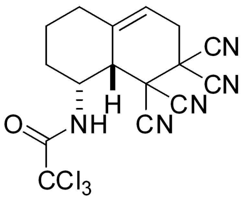


15

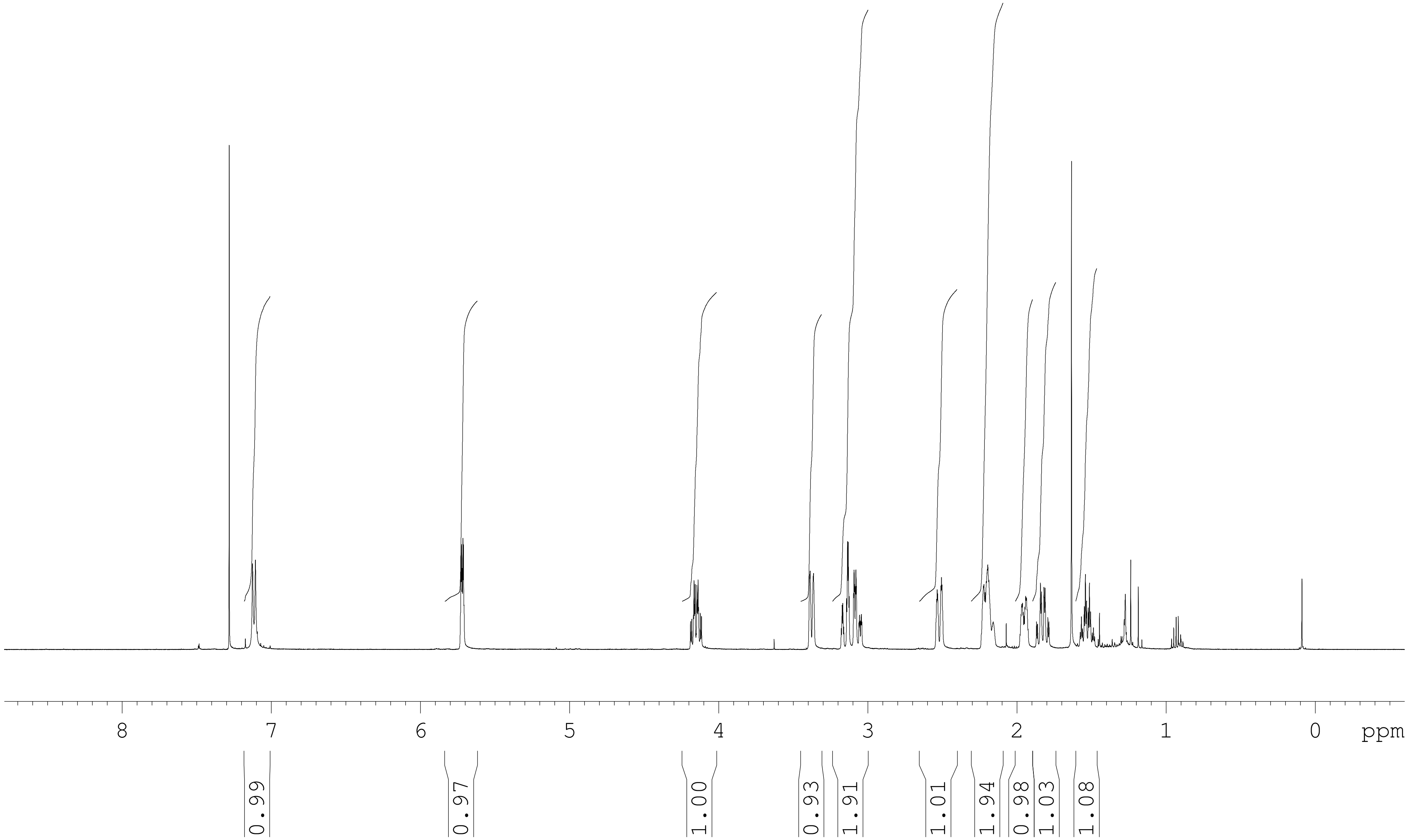
O
NH
H
N
N
O
N
O
Ph
CCl3
8
7
6
5
4
3
2
1
0
ppm
3.86
1.03
1.09
1.01
1.01
1.03
0.98
1.00
1.00
1.04
1.02
1.97
1.24

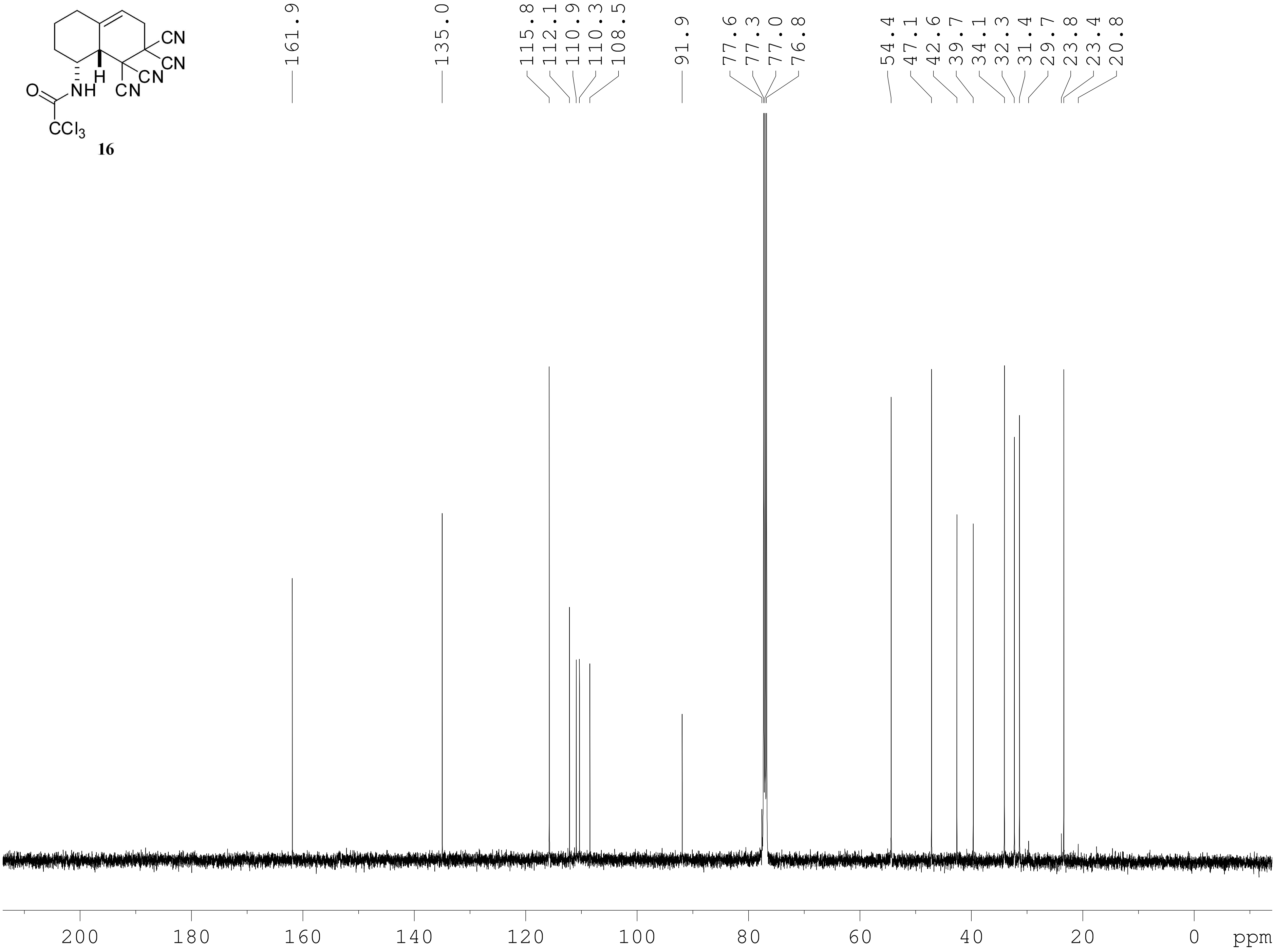

O
NH
H
N
N
O
N
O
Ph
CCl3
161.3
152.5
150.8
132.0
131.0
129.2
128.4
126.2
116.6
92.7
77.6
77.3
77.0
76.8
56.3
49.4
43.0
33.8
28.7
22.4
200
180
160
140
120
100
80
60
40
20
0
ppm

15

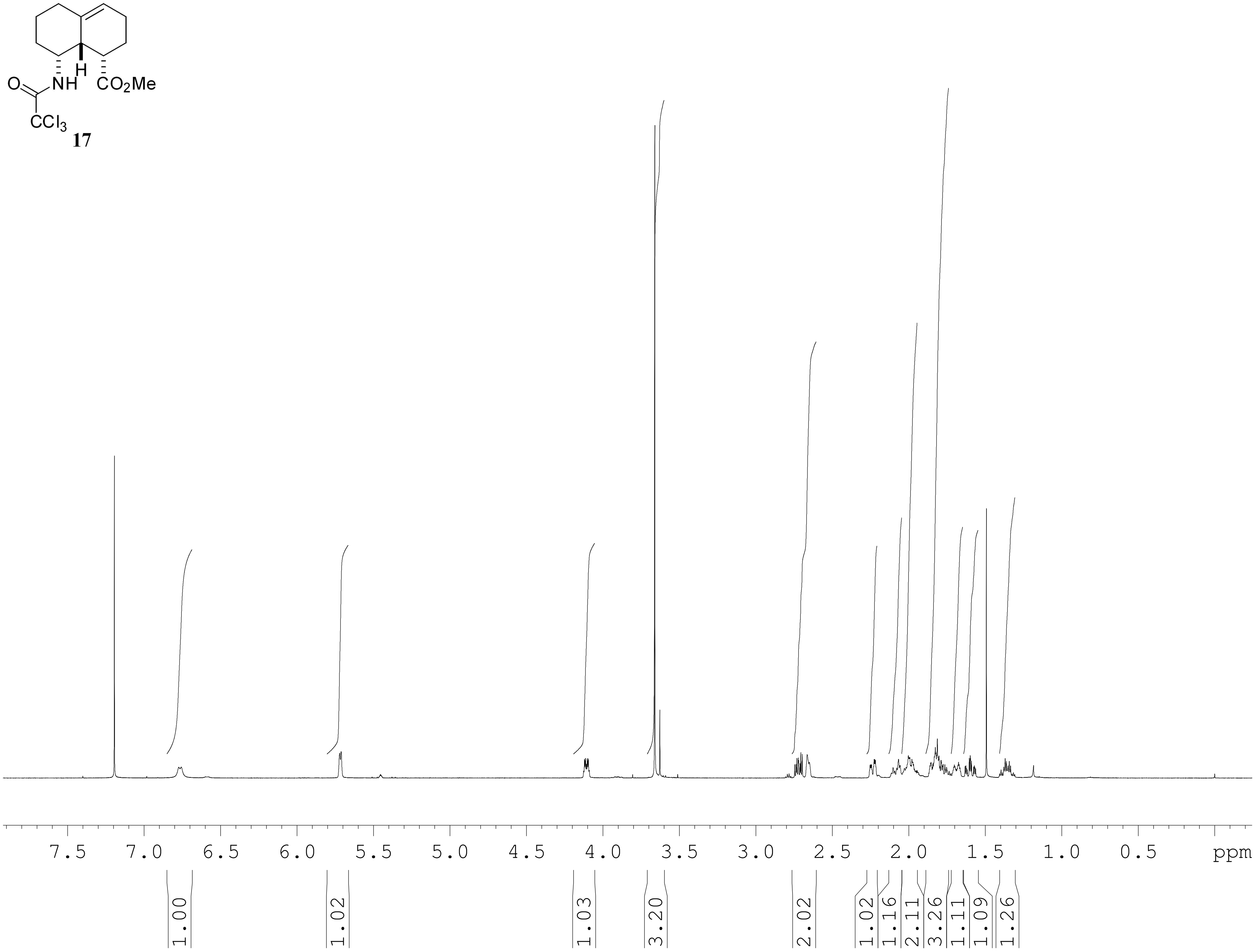

CN
CN
CN
CN
H
O
NH
CCl3

16


8
7
6
5
4
3
2
1
0
ppm
0.99
0.97
1.00
0.93
1.91
1.01
1.94
0.98
1.03
1.08

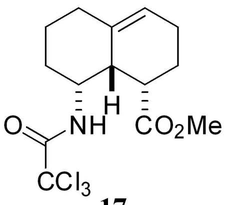

CN
CN
CN
CN
H
O
NH
CCl3
161.9
135.0
115.8
112.1
110.9
110.3
108.5
91.9
77.6
77.3
77.0
76.8
54.4
47.1
42.6
39.7
34.1
32.3
31.4
29.7
23.8
23.4
20.8
200
180
160
140
120
100
80
60
40
20
0
ppm

16

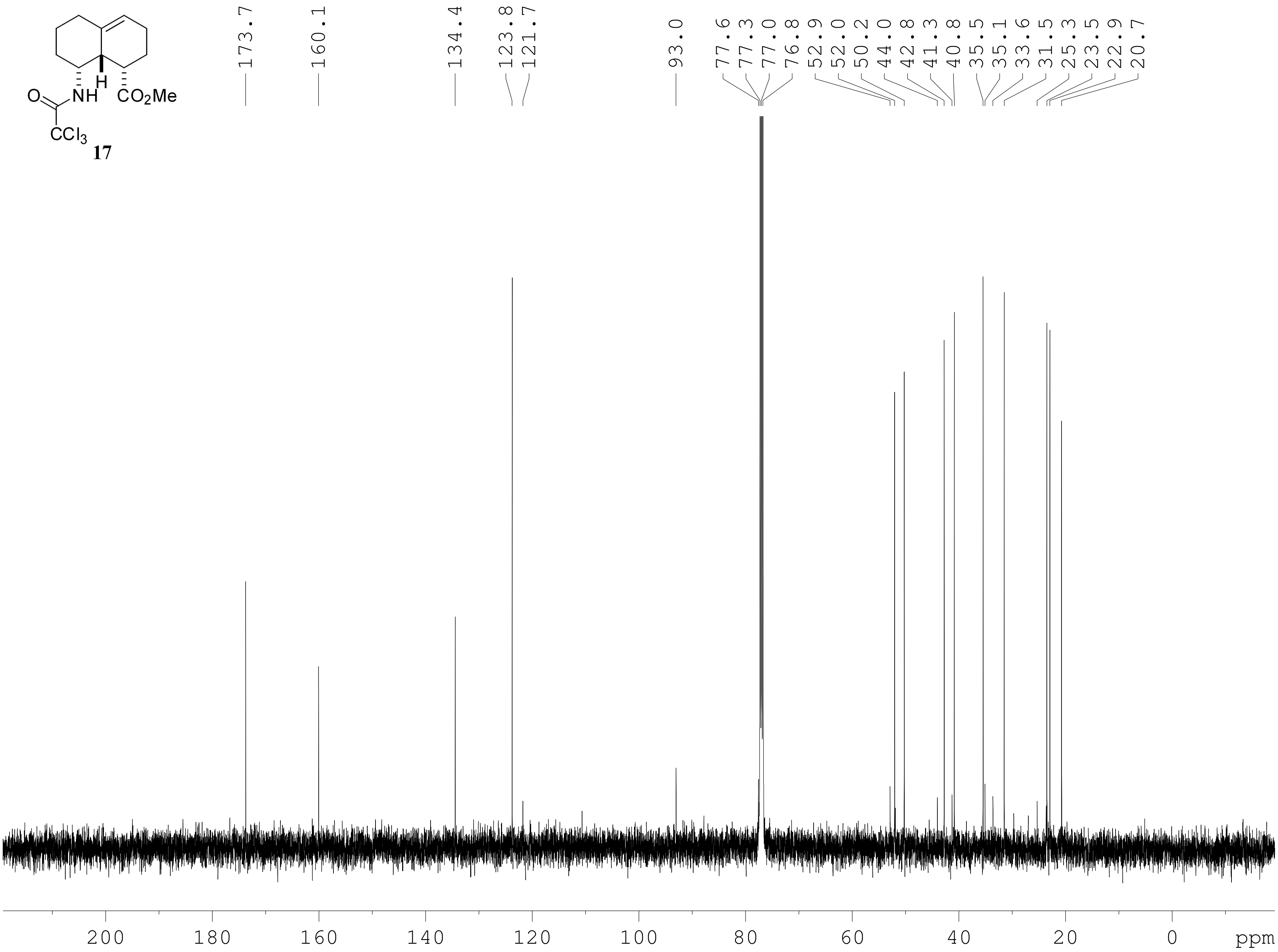


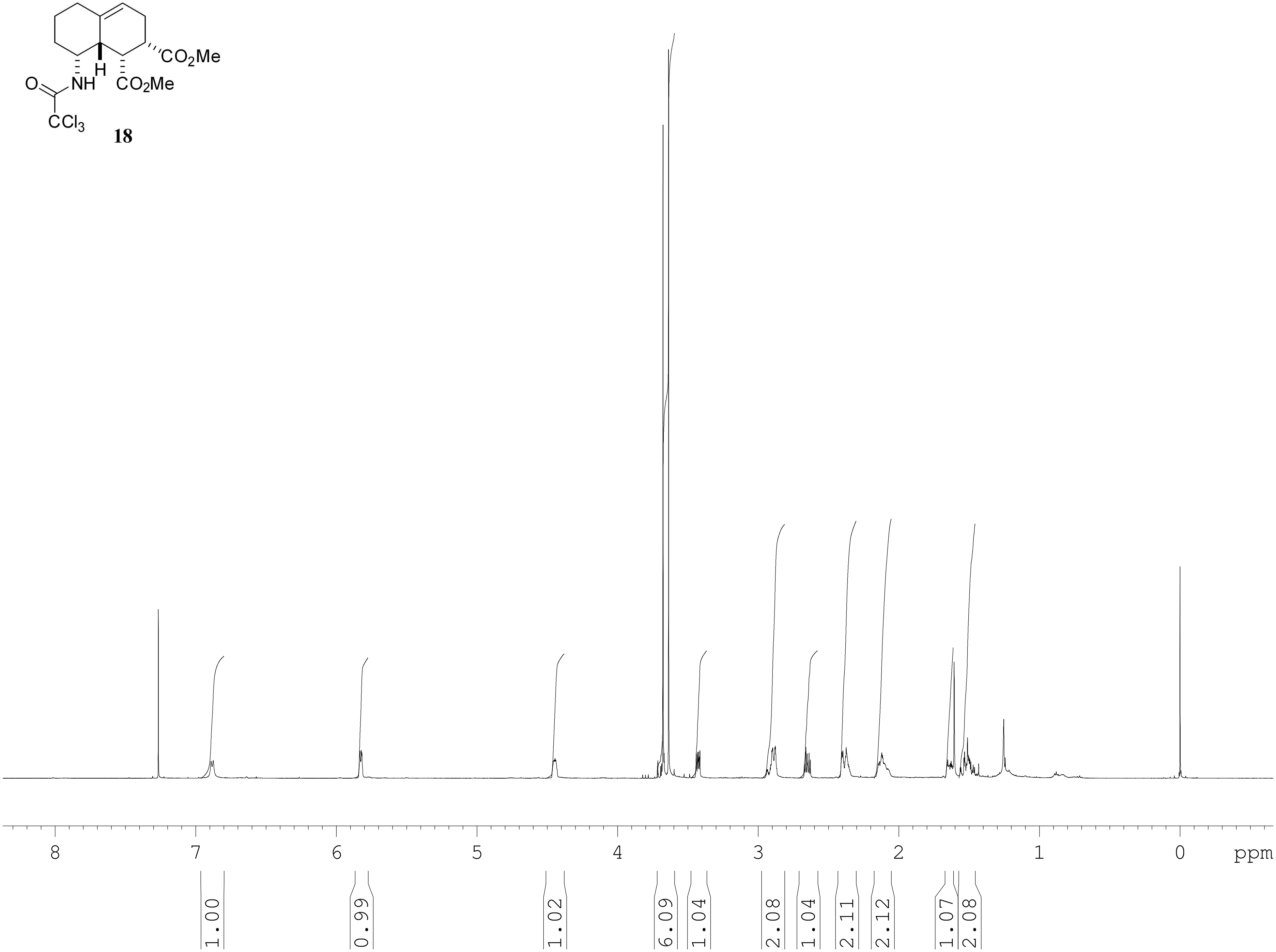
17

O
NH
H
CO$_2$Me
CCl$_3$
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
1.02
1.03
3.20
2.02
1.02
1.16
2.11
3.26
1.11
1.09
1.26


O
NH
H
CO2Me
CCl3

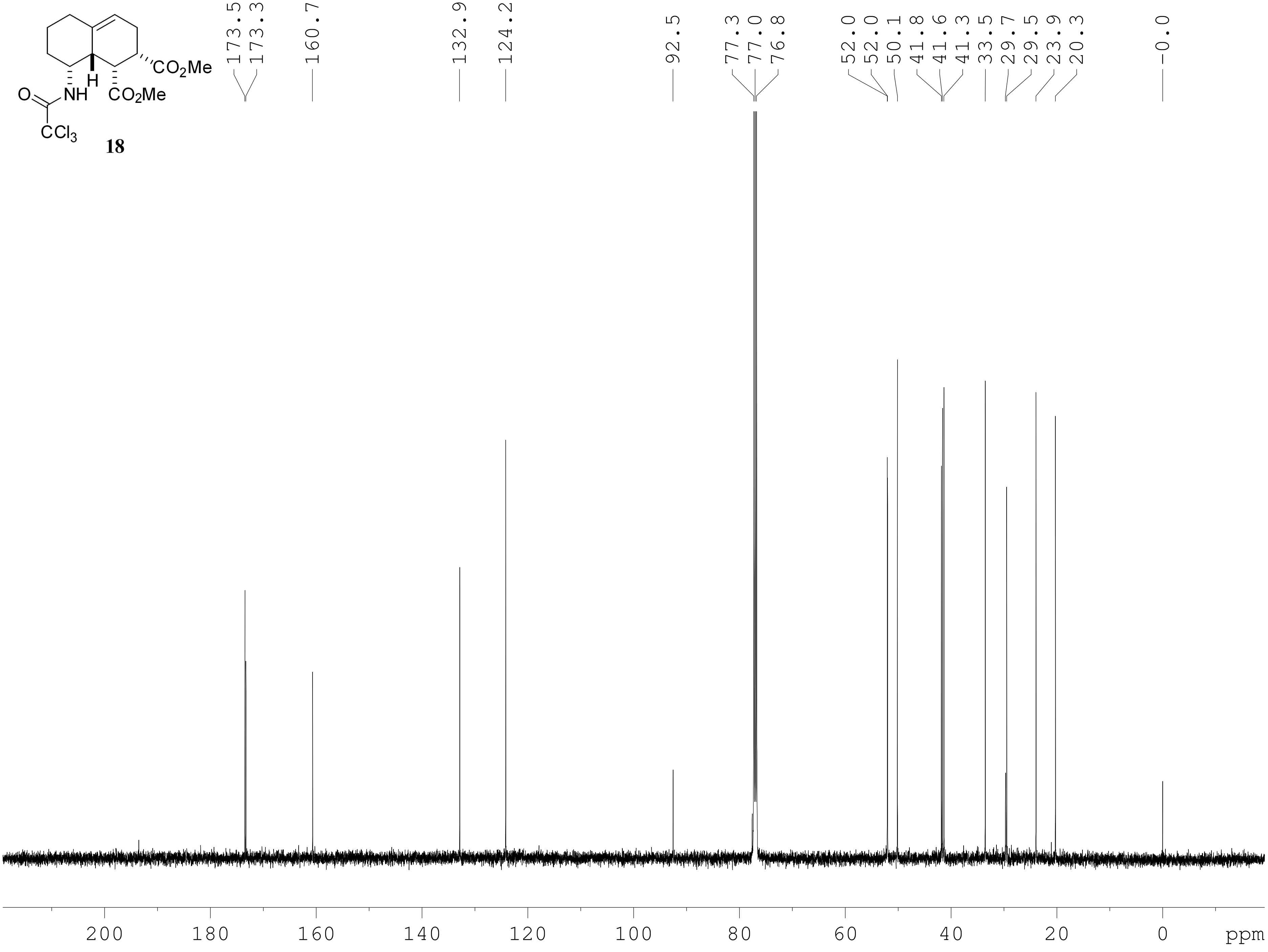
17


173.7
160.1
134.4
123.8
121.7
93.0
77.6
77.3
77.0
76.8
52.9
52.0
50.2
44.0
42.8
41.3
40.8
35.5
35.1
33.6
31.5
25.3
23.5
22.9
20.7
200
180
160
140
120
100
80
60
40
20
0
ppm


CO2Me
H
NH
CO2Me
O
CCl3

18

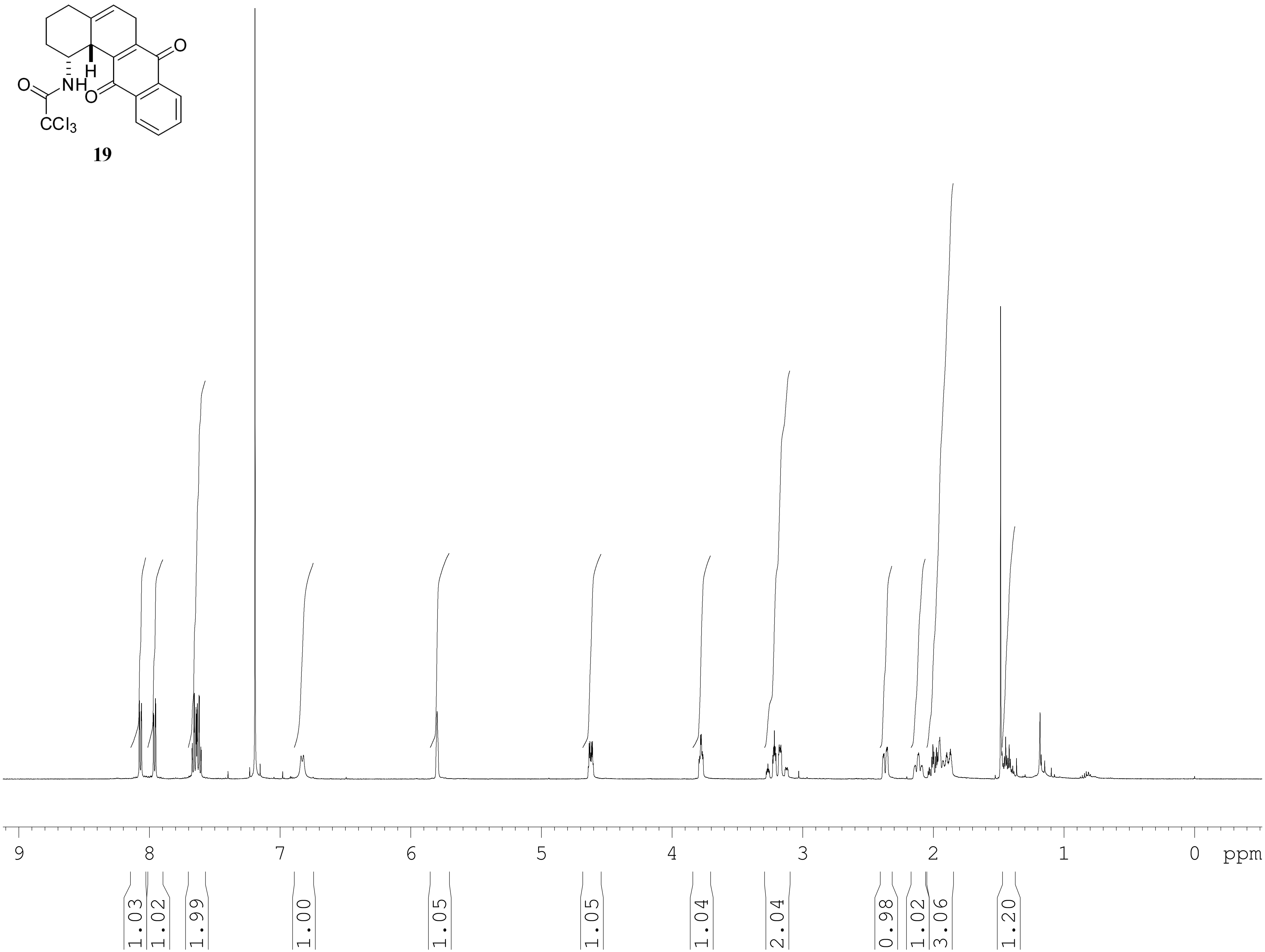
8
7
6
5
4
3
2
1
0
ppm
1.00
0.99
1.02
6.09
1.04
2.08
1.04
2.11
2.12
1.07
2.08

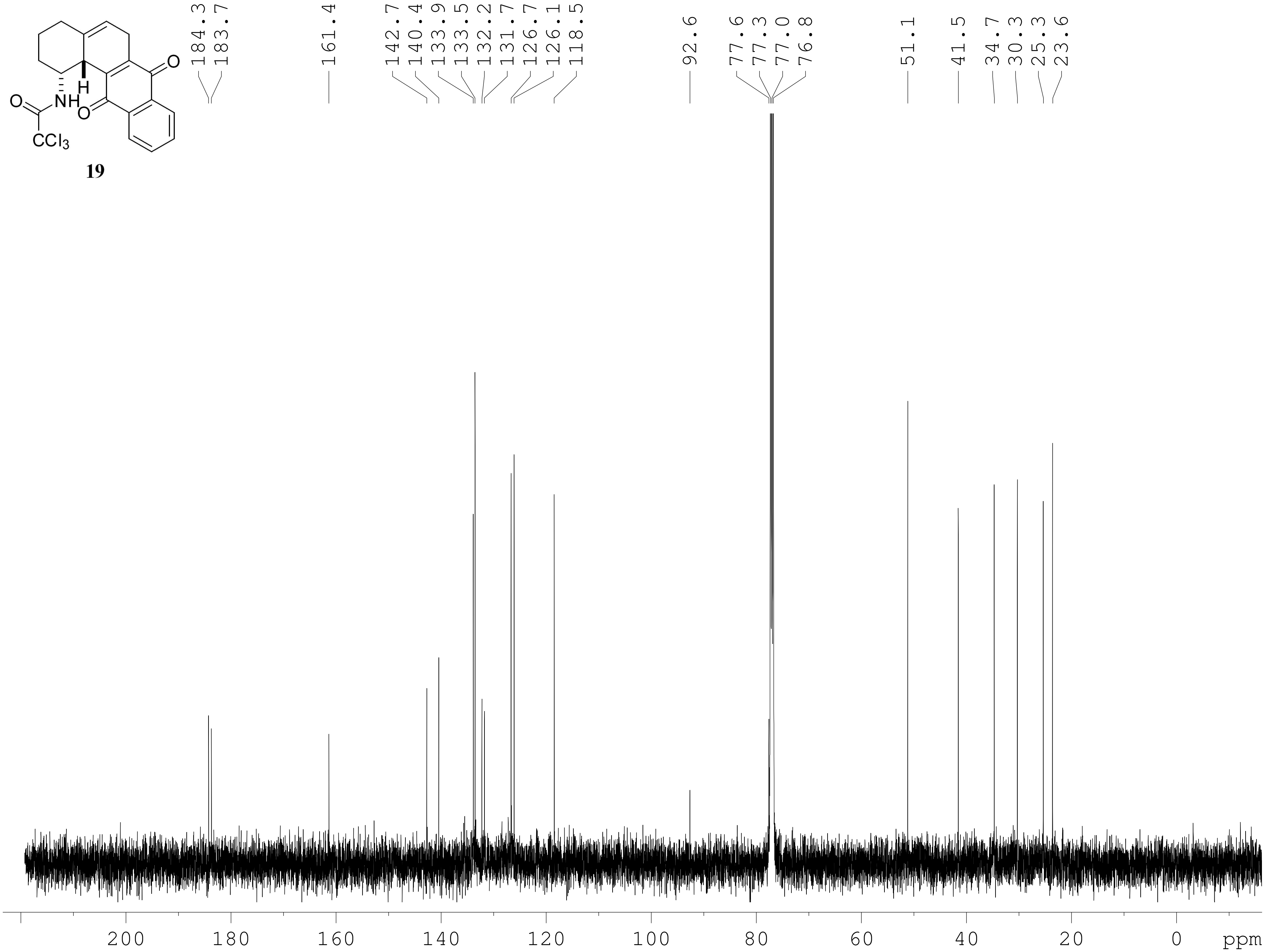

CO2Me
H
NH
CO2Me
O
CCl3
173.5
173.3
160.7
132.9
124.2
92.5
77.3
77.0
76.8
52.0
52.0
50.1
41.8
41.6
41.3
33.5
29.7
29.5
23.9
20.3
-0.0
200
180
160
140
120
100
80
60
40
20
0
ppm

18

O
NH
H
O
O
CCl3

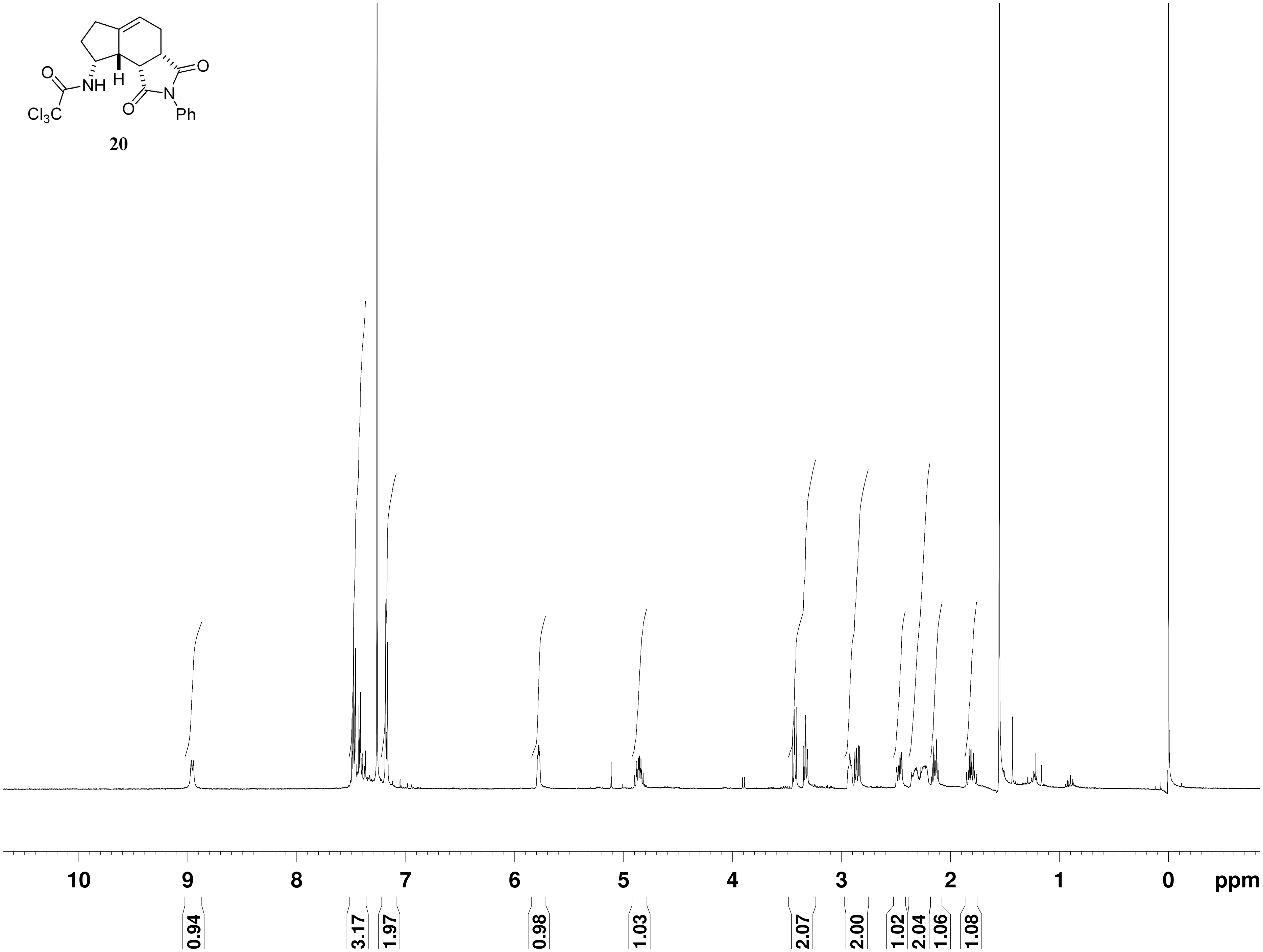
19

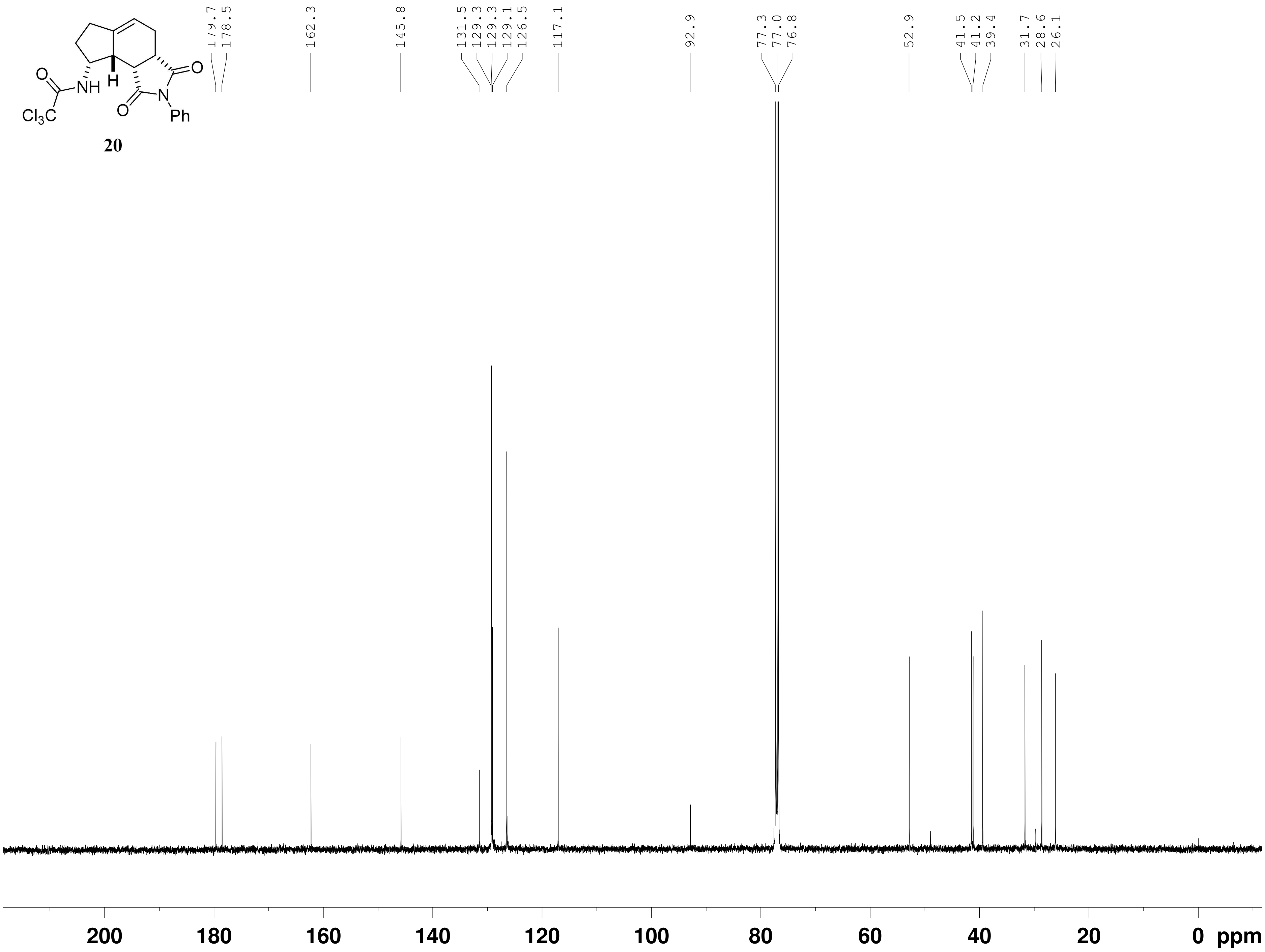

9
8
7
6
5
4
3
2
1
0
ppm
1.03
1.02
1.99
1.00
1.05
1.05
1.04
2.04
0.98
1.02
3.06
1.20


O
NH
H
O
O
CCl3
19
184.3
183.7
161.4
142.7
140.4
133.9
133.5
132.2
131.7
126.7
126.1
118.5
92.6
77.6
77.3
77.0
76.8
51.1
41.5
34.7
30.3
25.3
23.6
200
180
160
140
120
100
80
60
40
20
0
ppm

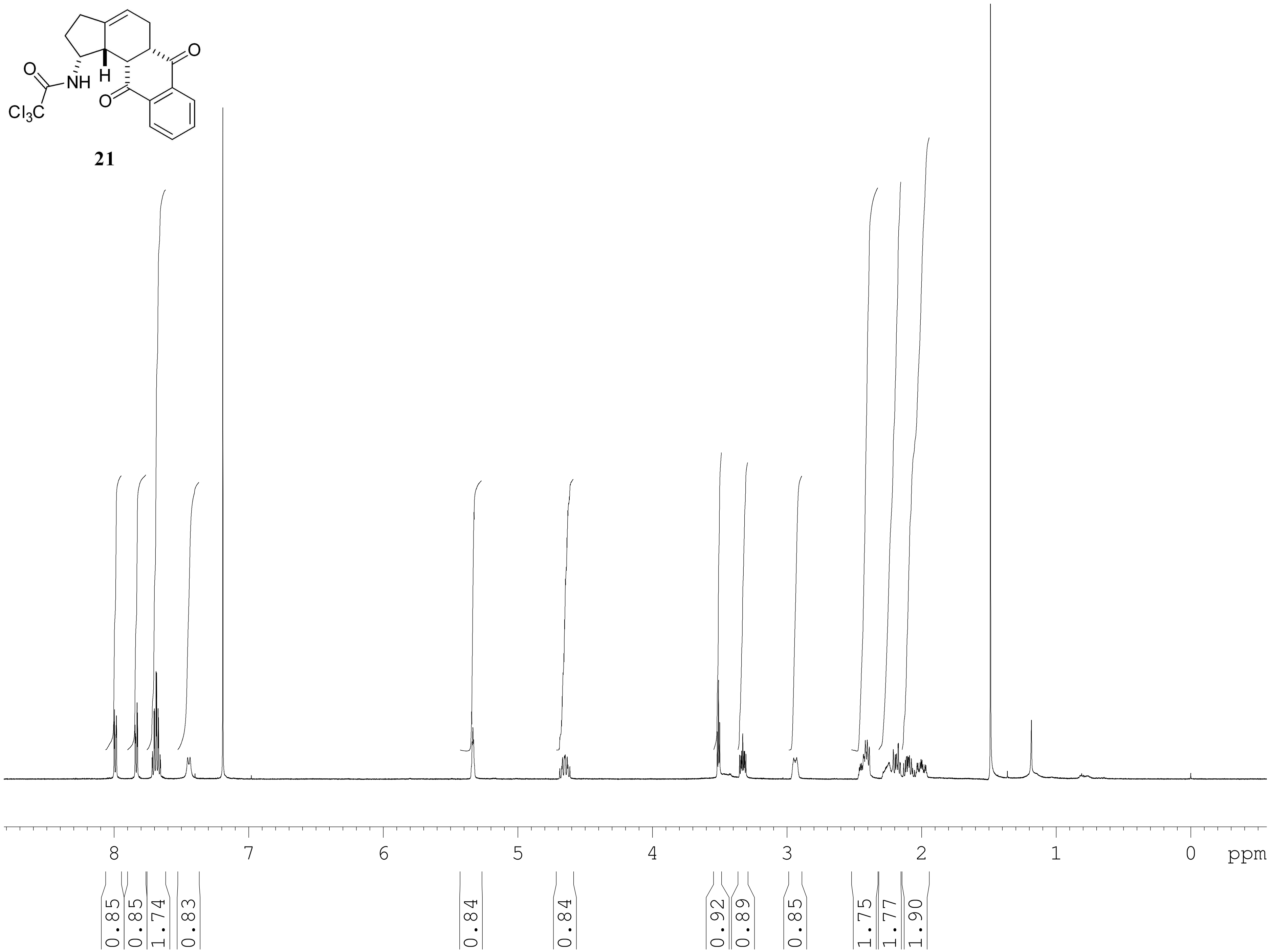
O
NH
H
O
N
O
Cl3C
Ph

20


10
9
8
7
6
5
4
3
2
1
0
ppm
0.94
3.17
1.97
0.98
1.03
2.07
2.00
1.02
2.04
1.06
1.08

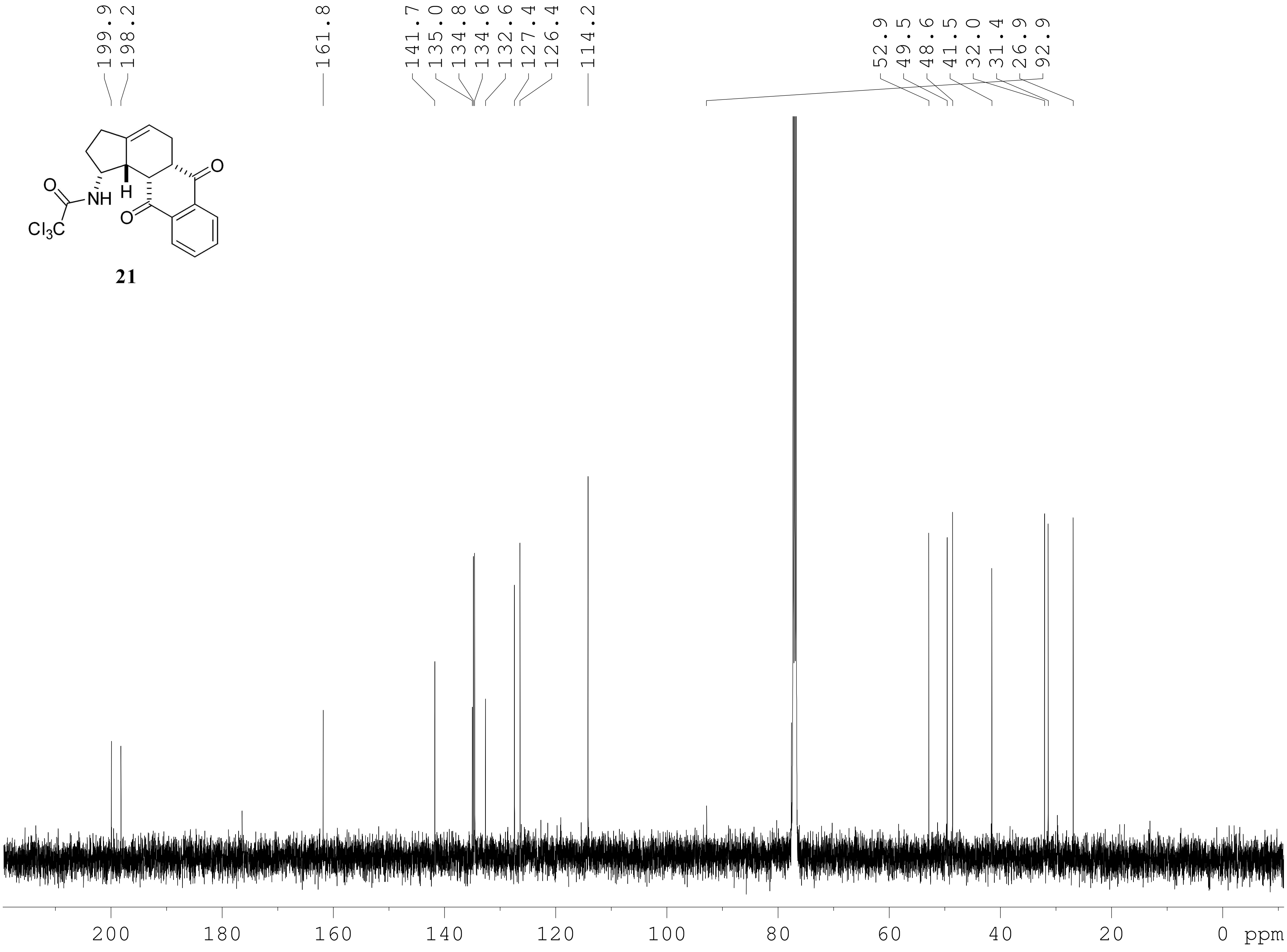

O
NH
H
O
O
N
Ph
Cl_3C
179.7
178.5
162.3
145.8
131.5
129.3
129.3
129.1
126.5
117.1
92.9
77.3
77.0
76.8
52.9
41.5
41.2
39.4
31.7
28.6
26.1
200
180
160
140
120
100
80
60
40
20
0 ppm

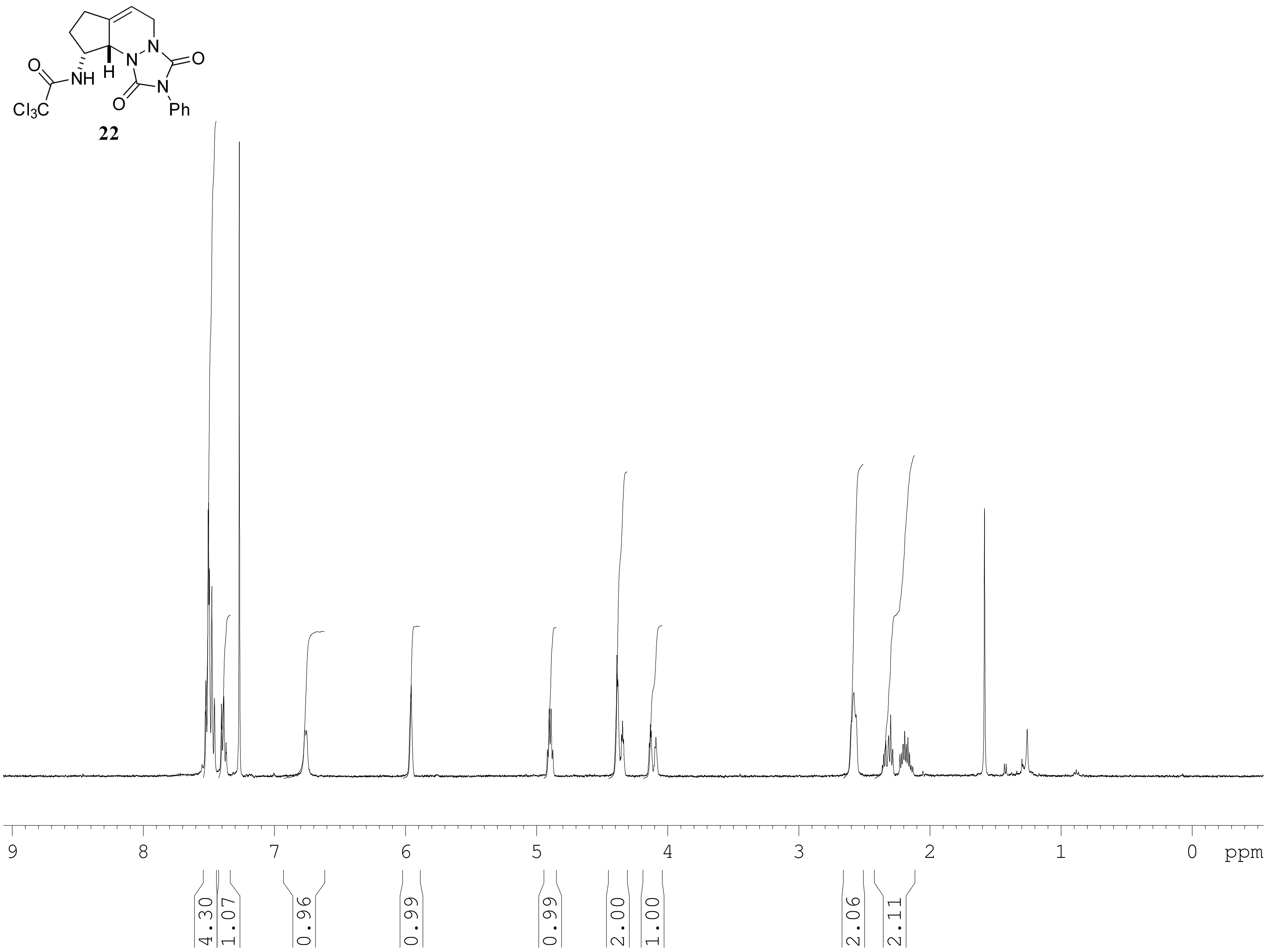
20


O
NH
H
O
O
Cl_3C

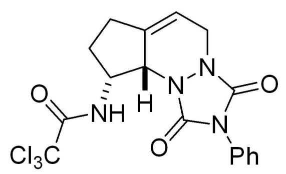
21

8
7
6
5
4
3
2
1
0
ppm
0.85
0.85
1.74
0.83
0.84
0.84
0.92
0.89
0.85
1.75
1.77
1.90

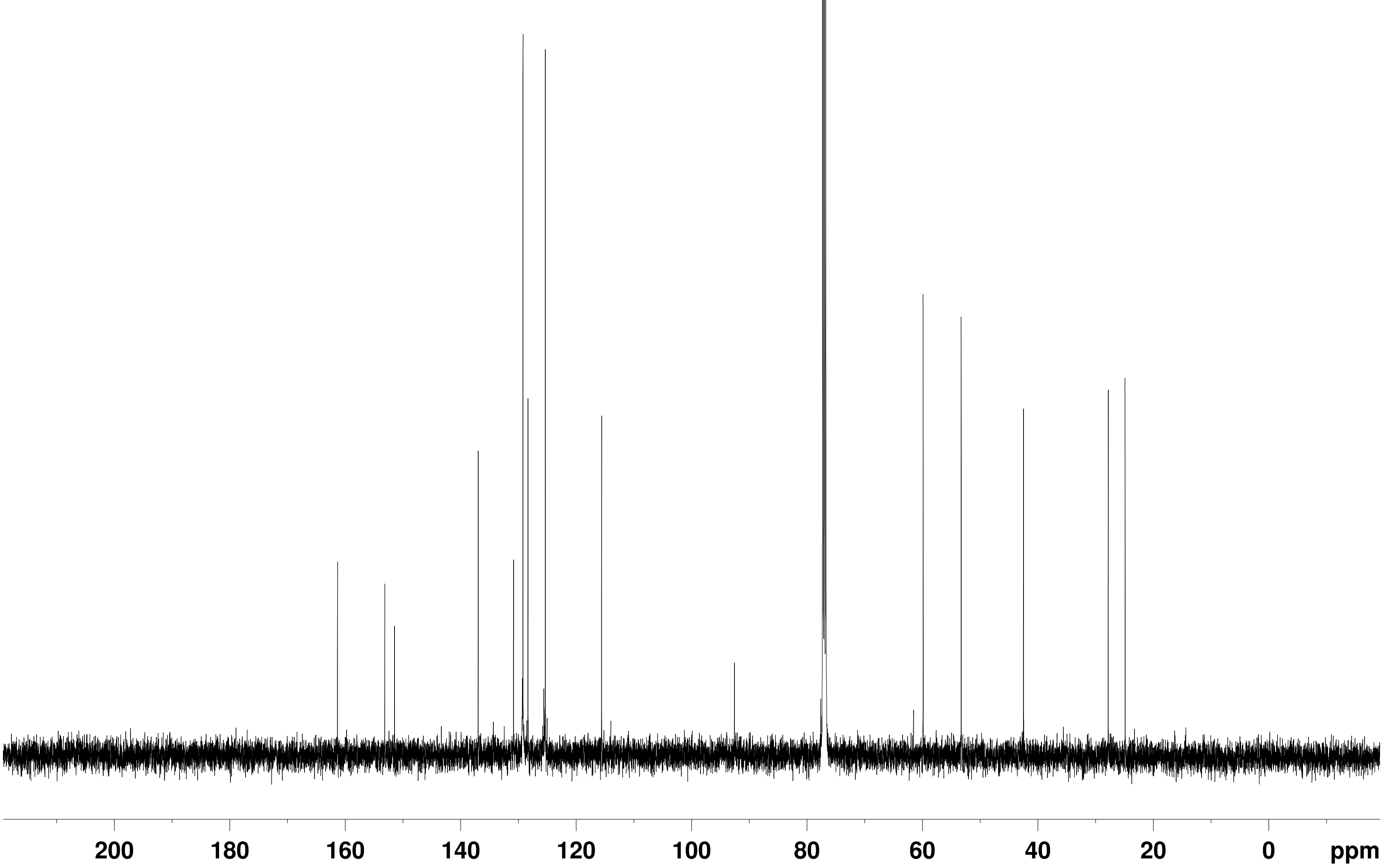

199.9
198.2
161.8
141.7
135.0
134.8
134.6
132.6
127.4
126.4
114.2
52.9
49.5
48.6
41.5
32.0
31.4
26.9
92.9
O
NH
H
O
O
Cl_3C
21
200
180
160
140
120
100
80
60
40
20
0 ppm

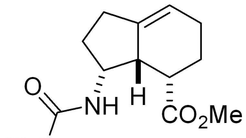

O
NH
H
N
N
O
O
N
Ph
Cl3C
9
8
7
6
5
4
3
2
1
0
ppm
4.30
1.07
0.96
0.99
0.99
2.00
1.00
2.06
2.11

22

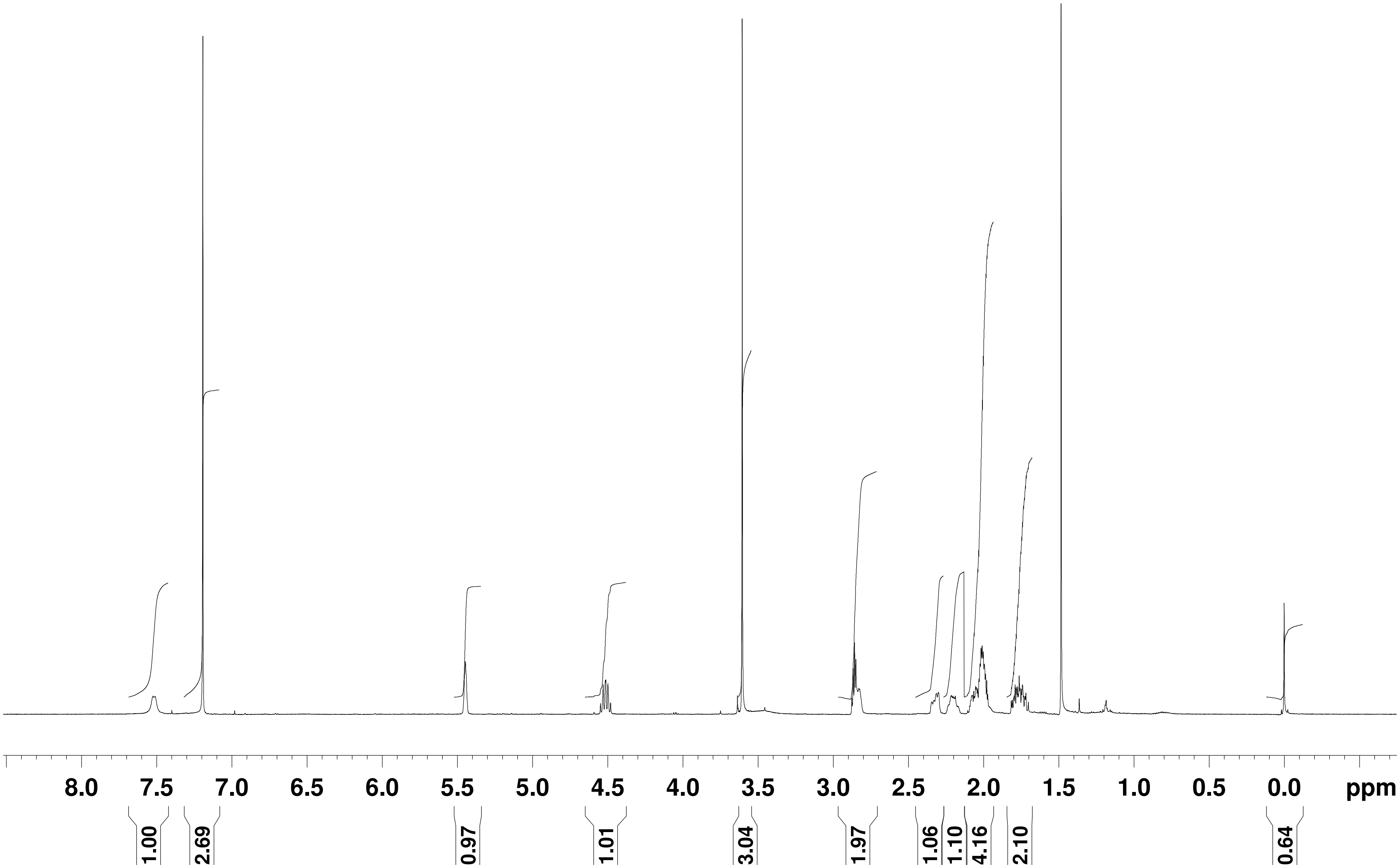

O
NH
H
N
N
O
N
O
Ph
Cl3C

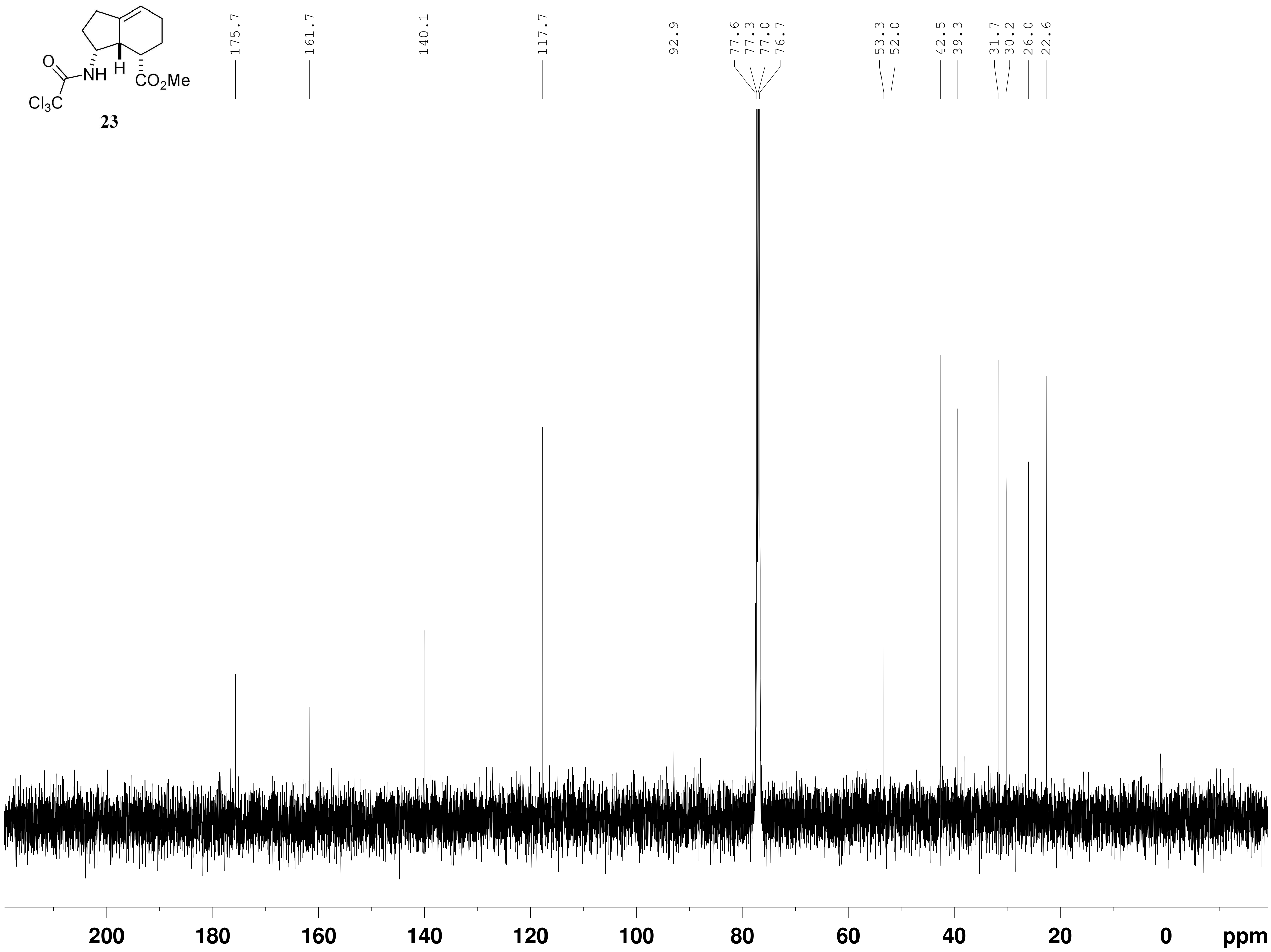
22


161.4
153.2
151.5
137.0
130.9
129.2
128.4
125.6
125.3
115.6
92.6
77.6
77.3
77.0
76.8
61.6
59.9
53.3
42.5
27.8
24.9
200
180
160
140
120
100
80
60
40
20
0
ppm


O
NH
H
CO2Me
Cl3C

23


8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.00
2.69
0.97
1.01
3.04
1.97
1.06
1.10
4.16
2.10
0.64


23

O
NH
H
CO2Me
Cl3C
175.7
161.7
140.1
117.7
92.9
77.6
77.3
77.0
76.7
53.3
52.0
42.5
39.3
31.7
30.2
26.0
22.6
200
180
160
140
120
100
80
60
40
20
0
ppm