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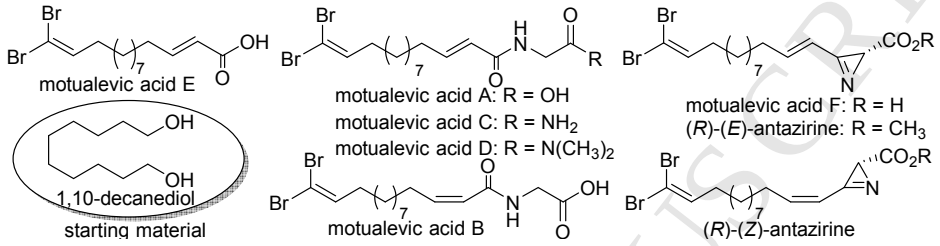

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Total synthesis of motualevic acids A-F, (*E*) and (*Z*)-antazirines

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ABSTRACT

Total synthesis of motualevic acids A-F and (*E*) & (*Z*) geometrical isomers of antazirines has been achieved from a commercially available starting material, 1,10-decanediol. The synthesis of motualevic acid E served as a common key intermediate for the synthesis of most of these natural products. The key steps involved in this synthesis were Wittig-olefination, Corey-Fuchs reaction, Neber reaction, amide coupling.

1. Introduction

The 2*H*-Azirine ring system contains highly strained azacyclopropene ring and corresponds to the smallest of the nitrogen-unsaturated heterocycles. Because of high reactivity, it became a key intermediate in the synthesis of various acyclic functionalized amino derivatives and heterocycles.[1] Additionally, it also represents a very important class of bioactive natural products (Figure 1).[1] Azirinomycine (**1**), a naturally occurring antibiotic and the first example of this class, was isolated from a strain of the soil bacterium *Streptomyces aureus*.[2] The first long chain 2*H*-azirine carboxylic acid methyl ester, (2*R*)-(*E*)-dysidazirine (**2**), isolated from the marine sponge *Dysidea fragilis*, is cytotoxic to L1210 cells and found to exhibit potent antifungal activity against *Candida albicans* and *Saccharomyces cerevisiae* at minimum concentration of 4μg per disk in a standard paper disk assay.[3] Later on Faulkner and co-workers isolated (2*S*)-(4*E*)-dysidazirine (*ent*-**2**) and its geometrical isomer, (*Z*)-dysidazirine (**3**) along with the (*E*) and (*Z*) geometrical isomers of brominated analogues, antazirines (**4**) and (**5**) from the same *D. fragilis* sponge.[4] Molinski et al. isolated another three heterogenous terminal halogenated antazirine analogs **6-8** along with antazirines (**4**) and (**5**) from *D. fragilis* and these are found to exhibit moderate cytotoxicity against HCT-116 cells.[5]

Recently, Bewley and co-workers isolated motualevic acids A-F (**9**-**14**), a new class of *ω*-dibrominated unsaturated fatty acids, along with an enantiomer of **4**, (2*R*)-(4*E*)-antazirine (*ent*-**4**) from *Siliquariaspongia sp.* (Figure 1).[6] Motualevic acid F (**14**) represents the first example of a long chain 2*H*-azirine containing a C-2 carboxylic acid. The crude extracts from *Siliquariaspongia sp.* are found to inhibit the growth of *Staphalococcus aureus* (SA) and methecilline-resistant *Staphalococcus aureus* (MRSA) in the disk diffusion assay. Antimicrobial disk diffusion assays performed with pure motualevic acids A-F (**9**-**14**) and (4*E*)-(*R*)-antazirine (*ent*-**4**) traced the MRSA-inhibitory activity to acids **9** and **14**, which inhibited the growth of MRSA at loadings of 10 and 5 μg/disk, respectively. The same assay performed with SA showed compounds **9**, **10**, **13**, and **14** to be active at respective loadings of 10, 10, 50, and 2 μg/disk. According to the observations made by Bewley, the presence of a free carboxylic acid is important for antimicrobial activity, which is supported by the fact that the esters bearing antazirines and azirinomycine lack the antimicrobial activity while motualevic acid F (**14**) and azirinomycine (**1**) showed the significant antimicrobial activity in its naturally occurring form.

Important biological profile along with interesting structural features, the synthesis of this class of molecules have been reported in a reasonable number. The first enantioselective synthesis of (*R*)-(*E*)-dysidazirine (**2**) was reported by Davis et. al. in 1995.[7] The methyl ester of azirinomycine (**1a**) was reported by Zwanenburg and co-workers in 1996.[8] Recently, Molinski et al. reported the synthesis of (*R*)-(*Z*)-dysidazirine (*ent*-**3**) and (*R*)-(*E*)-dysidazirine (**2**) and their analogs.[9] Very recently, the synthesis of (*S*)-(*E*)-dysidazirine (*ent*-**2**) was reported by Takemoto et al. using organocatalytic asymmetric Neber reaction.[10]

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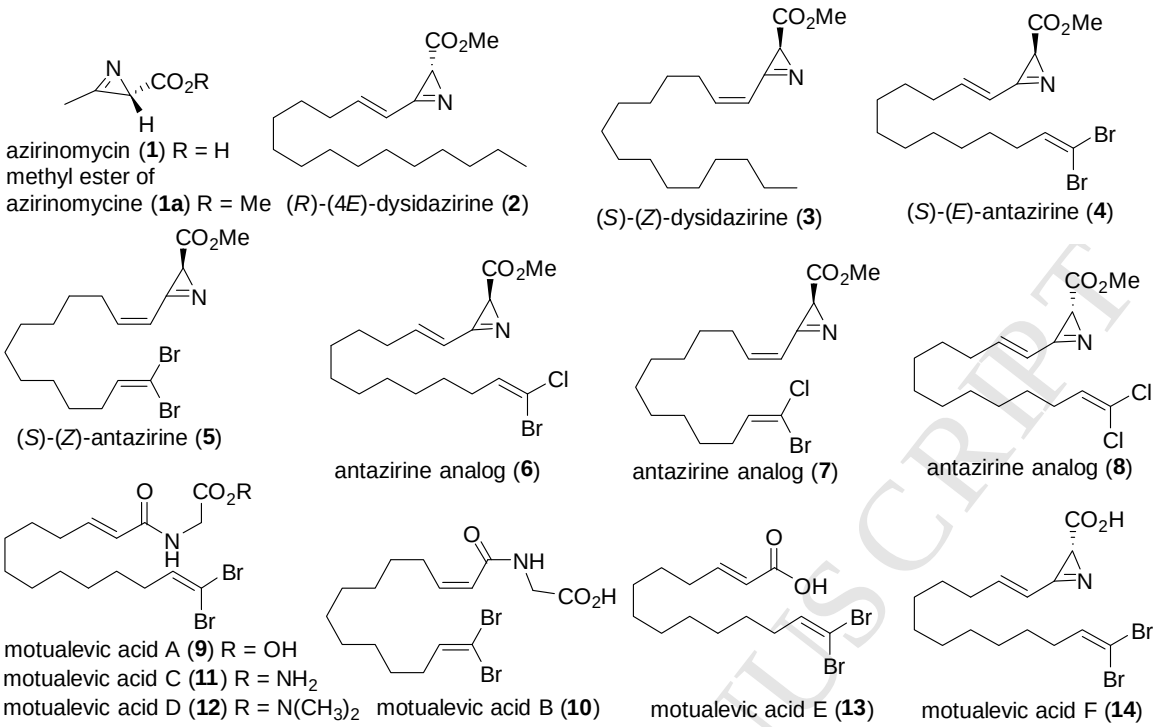
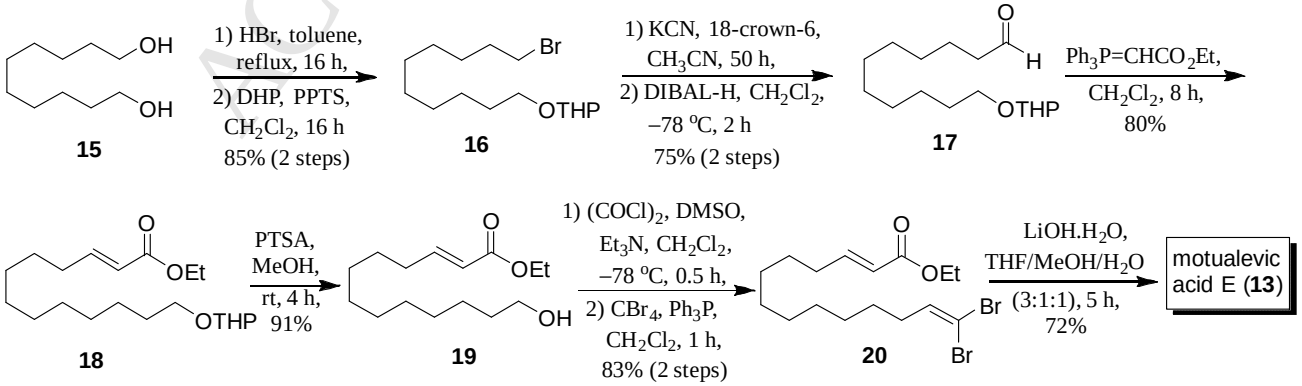


Figure 1. 2*H*-Azirine containing natural products and motualevic acids.

We communicated the first total synthesis of motualevic acids A-E (**9**-**13**),[11] and after our report, Bewley and co-workers reported the synthesis of motualevic acids A (**9**), E (**13**), and their analogs along with structure-activity relationships.[12] However, to the best of our knowledge the synthesis of *ω*-dibromovinylidene azirine-2-carboxylic acid (motualevic acid F) or its methyl ester, (*E*)-antazirine, and geometrical isomer of a latter one, (*Z*)-antazirin, have not been reported. We report here full details of total synthesis of motualevic acids A-E (**9**-**13**), and the first total synthesis of motualevic acid F (**14**), and (*E*) & (*Z*)-antazirines (*ent*-**4** and *ent*-**5**).

2. Result and Discussion

We envisioned that the synthesis of motualevic acid E (**13**) could serve as a key common intermediate in the synthesis of several of these natural products such as motualevic acids A (**9**), C (**11**), D (**12**), and F (**14**), and (*E*)-antazirine (**4**) by using appropriate reactions. Then, we focused our attention on the synthesis of motualevic acid E (**13**), which was commenced from the commercially available 1,10-decanediol (**15**) as shown in Scheme 1. The diol **15** was, easily, converted to bromo-functionality intermediate **16**[13] (in 85% yield over 2 steps) by bromination followed by THP ether protection. Treatment of **16** with KCN in the presence of catalytic amount of 18-crown-6 in CH_3CN at room temperature gave nitrile,[14] which on reduction with DIBAL-H at −78 °C afforded aldehyde **17**[15] in 75% yield over two steps. Two carbon Wittig olefination of **17** in CH_2Cl_2 at room temperature furnished α,β-unsaturated ester **18** in 80% yield and with complete *E* selectivity.[16] Deprotection of THP ether moiety in **18** with a catalytic amount of PTSA in MeOH resulted in a primary hydroxyl group **19** in excellent yield. Swern oxidation was performed on **19** to give the corresponding aldehyde, which was subjected to Corey-Fuchs reaction[17] to furnish 1,1-dibromoalkene **20** in 83% yield over two steps. Hydrolysis of ester **20** using LiOH in THF/MeOH/H_2O system resulted the desired motualevic acid E (**13**) in a yield of 72%. The spectral data of synthetic motualevic acid E (**13**) has well coincided with that of the natural material.[6]



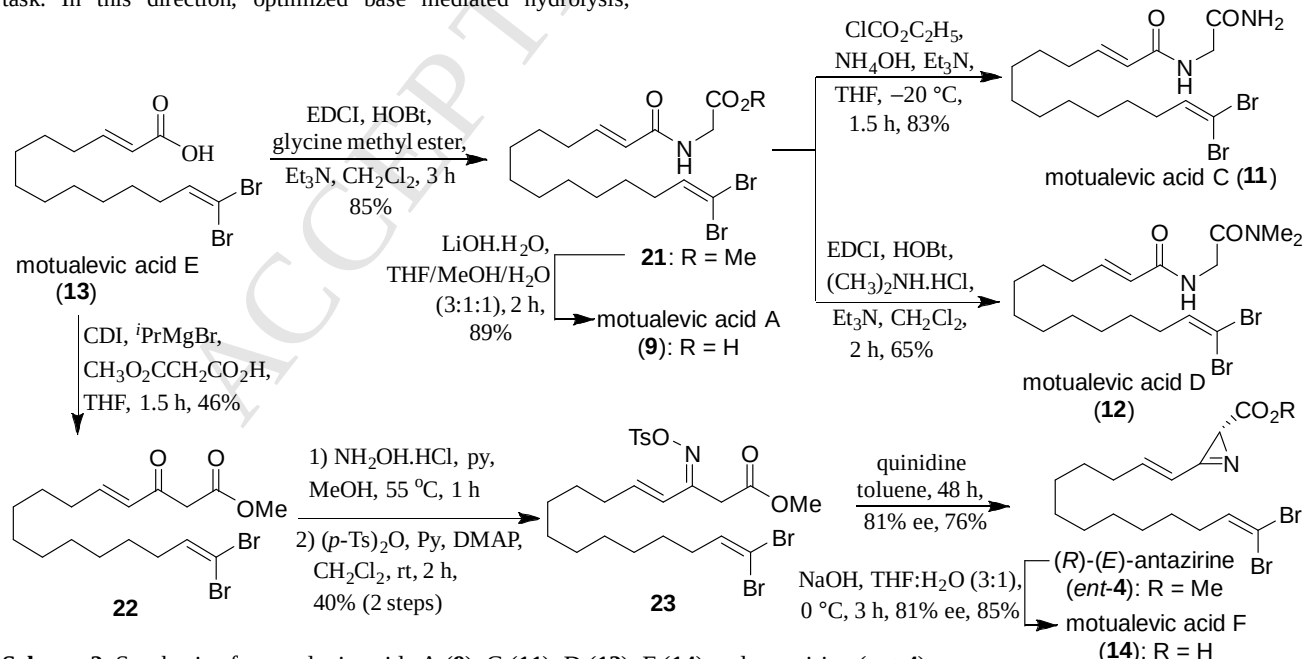
Scheme 1. Synthesis of motualevic acid E (**13**).

Having achieved the synthesis of motualevic acid E (**13**), we turned our attention to the synthesis of other motualevic acids. In this direction, motualevic acid E (**13**) was coupled with glycine methyl ester hydrochloride using EDCI, HOBt as a coupling reagents in the presence of Et_3N in CH_2Cl_2 to give methyl ester of motualevic acid A **21**, which upon hydrolysis with LiOH in THF/MeOH/H_2O system afforded motualevic acid A (**9**) in 75% yield over two steps (Scheme 2). Motualevic acid A (**9**) on treatment with ethyl chloroformate in the presence of Et_3N in THF at −20 °C yielded motualevic acid C (**11**) in 83% yield, whereas with *N*,*N*'-dimethylamine hydrochloride using EDCI, HOBt in the presence of Et_3N in CH_2Cl_2 afforded motualevic acid D (**12**) in 65% yield. The spectral data of synthesized motualevic acids A (**9**), C (**11**) and D (**12**) were in good agreement with those of the natural products.[6]

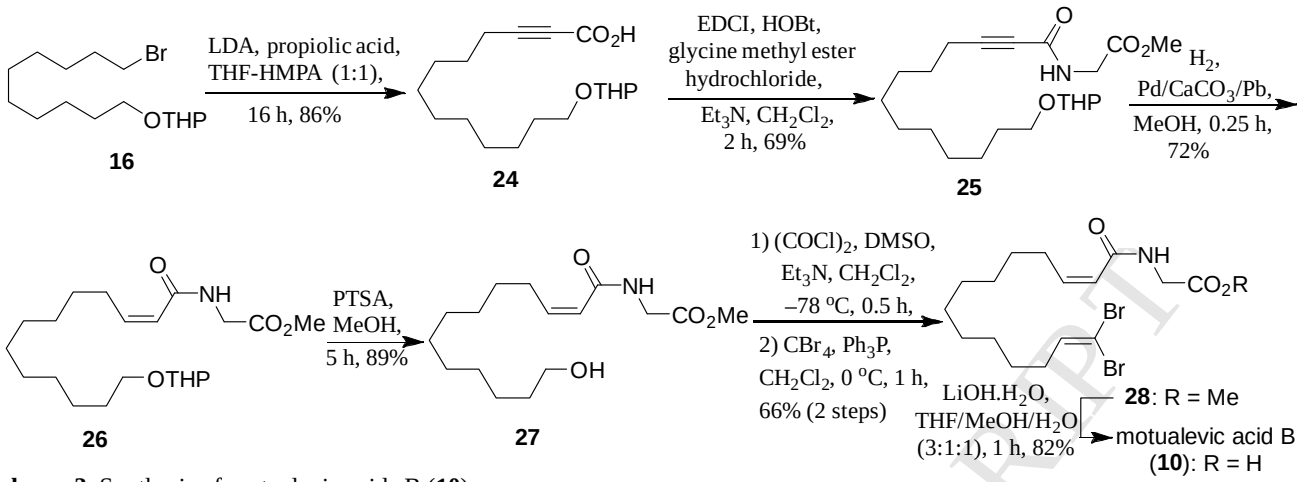
Further, (*E*)-antazirine (*ent*-**4**) and motualevic acid F (**14**) could be accessed from motualevic acid E (**13**) as shown in Scheme 2. Hence, motualevic acid E (**13**) was reacted with carbonyldiimidazole (CDI) to give the corresponding imidazolide, which on treatment with the magnesium salt of monomethyl malonic acid[18] afforded *β*-ketoester[19] **22** in moderate yield. *β*-Keto-ester **22** was converted to oxime using hydroxylamine hydrochloride in the presence of pyridine in MeOH at 55 °C. Subsequently, oxime was treated with Ts_2O, pyridine and catalytic amount of DMAP in CH_2Cl_2 to furnish oxime-tosylate **23** in 40% yield over 2 steps.[9a] To induce the chirality present in (*E*)-antazirine, we have selected a cinchona alkaloid, quinidine, to catalyze the asymmetric Neber reation.[9a,10] The reaction of tosylated compound **23** with quinidine in toluene at 0 °C went smoothly to give the desired (*R*)-(*E*)-antazirine (*ent*-**4**) in very good yield and 81% ee. The data of synthetic (*R*)-(*E*)-antazirine (*ent*-**4**) was identical with the data reported for the natural product, but the specific rotation of synthetic compound: $[\alpha]^{24}_D$ = −85.1 (*c* 0.63, MeOH), is the same sign but higher value than the natural compound: $[\alpha]_D$ = −7.3 (*c* 0.1, MeOH). This more magnitude is attributed to a higher optical purity of synthetic compound than the natural compound.[6]

To achieve the synthesis of motualevic acid F (**14**), hydrolysis of the methyl ester present in antazirine (*ent*-**4**), became the next task. In this direction, optimized base mediated hydrolysis, NaOH and THF/H_2O (3:1) system at 0 °C was used to accomplish the first total synthesis of motualevic acid F (**14**) in 85% yield. In spite of several reports for the synthesis of azirine esters, this is the first report for the hydrolysis of azirine ester to the corresponding carboxylic acid. Notably, hydrolysis of some model azirine esters having saturated side chain, led to only some unidentified mixture of compounds. This is supported by the fact that the azirinomycin (**1**) is unstable in its naturally occurring form (carboxylic acid), and it was characterized by spectral measurements of its methyl ester **1a** and other derivative.[2] But, whereas motualevic acid F with an unsaturated side chain, was reported no issue with the stability in its naturally occurring form (carboxylic acid).[6] The data of synthetic motualevic acid F agree well with the natural product and the optical purity is also comparable with the natural product based on the specific rotation (synthetic: $[\alpha]^{26}_D$ = −78.8 (*c* 0.48, MeOH); natural: $[\alpha]_D$ = −74.0 (*c* 0.1, MeOH))[6] and 81% ee.

Having accomplished most of motualevic acids A (**9**), C-F (**11**-**14**) and (*R*)-(*E*)-antazirine (*ent*-**4**)), we thought that the bromo-functionality intermediate **16** encountered during the synthesis of motualevic acid E (**13**) could serve as a starting material for the synthesis of motualevic acid B (**10**) and (*Z*)-antazirine (*ent*-**5**). Accordingly, intermediate **16** was treated with dianion of propiolic acid, generated *in situ* by reacting propiolic acid in HMPA:THF (1:1) with LDA at −40 °C and at −15 °C for 2 h, to give the acetylenic acid **24** in an improved yield of 86% (Scheme 3).[11,20] The acid **24** was reacted with glycine methyl ester hydrochloride using EDCI and HOBt in the presence of Et_3N in CH_2Cl_2 to give a glycine residue coupled product **25** in 69% yield. Partial hydrogenation of acetylenic moiety in **25** using Lindlar's catalyst in MeOH furnished the *Z*-olefin **26** in 72% yield. Deprotection of the THP group of **26** using a catalytic amount of PTSA in MeOH resulted in a primary hydroxyl group **27** in 89% yield. Oxidation of the hydroxyl group in **27** using Swern oxidation reaction conditions resulted in aldehyde, which was converted to terminal dibromide[17] **28** in 66% yield over 2 steps. Subsequent hydrolysis of the methyl ester with LiOH in THF/MeOH/H_2O solvent system furnished the motualevic acid B (**10**) in a yield of 82%. The spectral data of motualevic acid B is in accordance with the natural product.[6]



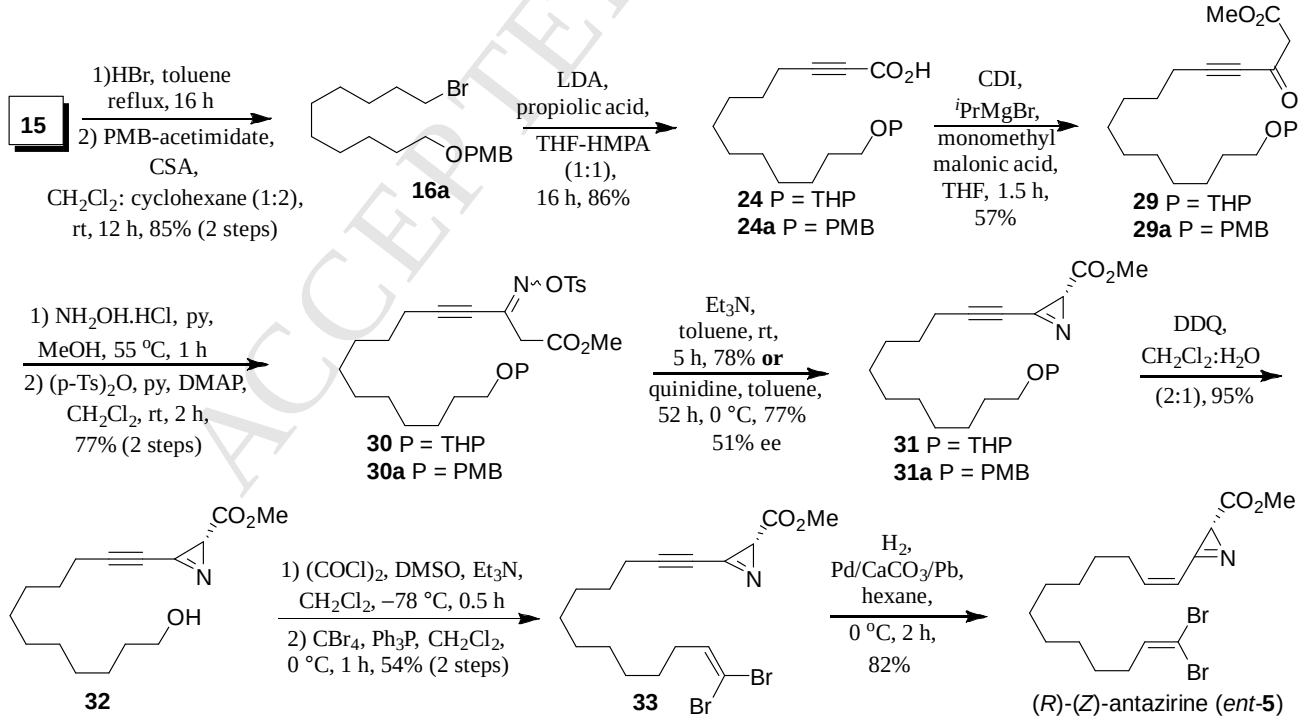
Scheme 2. Synthesis of motualevic acids A (**9**), C (**11**), D (**12**), F (**14**) and antazirine (*ent*-**4**).



Scheme 3. Synthesis of motualevic acids B (**10**).

The synthesis of (*Z*)-antazirine was attempted from the intermediate **24** as shown in Scheme 4. Reaction of **24** with CDI in THF provided corresponding imidazolide, which on treatment with the magnesium salt of monomethyl malonic acid in THF gave *β*-ketoester **29**[19] in moderate yield. Treatment of **29** with hydroxylamine hydrochloride and pyridine in MeOH led to oxime, which was tosylated immediately with TS_2O, pyridine, DMAP in CH_2Cl_2 to give oxime-tosylate **30** in 77% yield (2 steps).[9a] Treatment of **30** with Et_3N in toluene provided azirine **31** in 78% yield. Disappointingly, attempts to deprotect the THP ethereal moiety of **31** using PTSA or CSA in MeOH or CH_2Cl_2 found problematic due to the disturbances in azirine ring. To overcome this difficulty, we had to switch over the primary hydroxyl protecting group in **31** (P = THP) to **31a** (P = PMB). Here, the synthesis of **31a** was achieved from **15** which was converted to **16a** in two steps: bromination followed by PMB protection with *p*-methoxybenzyltrichloroacetimidate, and CSA in 1:2 mixture of CH_2Cl_2-cyclohexane (85% yield in 2 steps).[21]

As before, the compound **16a** was converted to acetylenic acid **24a**,[20] which was reacted with CDI, the magnesium salt of monomethyl malonic acid in THF to give *β*-keto ester **29a** (57%).[19] The ketoester **29a** was converted to corresponding oxime-tosylate **30a**[9a] (77%, 2 steps), which underwent quinidine-mediated cyclization to give the desired **31a** in 77% yield, but only with low enantiomeric excess (51% ee) was observed in alkynyl ketoxime tosylate **30a** comparatively alkenyl ketoxime tosylate **23**. Then, deprotection of PMB group of **31a** with DDQ in CH_2Cl_2/H_2O solvent system provided primary hydroxyl compound **32** in excellent yield without any problem. Oxidation of **32** under Swern oxidation reaction conditions furnished aldehyde, which was immediately and without further purification treated with PPh_3/CBr_4 in CH_2Cl_2 at 0 °C to give dibromoalkene **33** in 54% yield over two steps.[17] The acetylenic compound **33** was selectively reduced with Lindlar catalyst at lower temperature in hexane under a hydrogen atmosphere to afford exclusively desired (*Z*)-antazirine (*ent*-**5**) in 82% yield.



Scheme 4. Synthesis of (*Z*)-antazirine (*ent*-**5**).

The data of synthesised (*Z*)-antazirine (*ent*-**5**) is identical in all respects with the natural product data.[4,5] The specific rotation of synthetic (*R*)-(*Z*)-antazirine: $[\alpha]^{24}_{D}$ = −63.6 (*c* 0.64, *n*-hexane) shown the opposite sign and lower magnitude to the natural (*S*)-(*Z*)-antazirine (**5**): $[\alpha]^{24}_{D}$ +98.9 (*c* 3.33, *n*-hexane),[5] indicates low enantiopurity (51% ee), which was retained from **31a**, indicates that no racemization and this is in accordance with the earlier report.[9]

3. Conclusions

In summary, we have accomplished the total synthesis of motualevic acids A-F, and (*E*) and (*Z*) antazirines from a single starting material, commercially available 1,10-decanediol. Notably, motualevic acid F and (*E*) and (*Z*)-antazirines were achieved for the first time. Motualevic acid E was used as a common intermediate for the synthesis of several of this class of molecules. The synthesis and biological activity of motualevic acid and antazirine analogs are under progress in our laboratory and will be reported in due course.

4. Experimental section

4.1. General methods

Anhydrous solvents were dried and distilled by standard methods prior to use. Commercially available reagents were used without further purification unless otherwise specified. All the reactions were performed under an atmosphere of nitrogen or argon in oven-dried glassware under magnetic stirring. Column chromatography was carried out using silica gel (60-120 or 100-200 or 230-400 mesh) and the column was eluted with EtOAc-hexanes, EtOAc-MeOH or EtOAc. Analytical thin layer chromatography (TLC) was performed on precoated silica gel-60 F254 (0.5 mm) glass plates. Visualization of the spots on TLC plates was achieved either by UV light or by staining the plates in methanolic anisaldehyde-sulphuric acid-acetic acid or in methanolphosphomolybdic acid-sulphuric acid solution and charring on hot plate. Optical rotation values were measured on Digipol 781 M6U NOVA high sensitive polarimeter using a 2 mL cell with a 10 mm path length. FTIR spectra were recorded on Bruker (alpha) spectrometer. Mass spectra were recorded on Micro Mass VG-7070H Mass spectrometer for ESI and are given in mass units (m/z). High resolution mass spectra (HRMS) [ESI+] were obtained using either a TOF or a double focusing spectrometer.

4.2. *2-((10-Bromodecyl)oxy)tetrahydro-2H-pyran* ***(16)****:* 1,10-Decanediol **15** (10 g, 57.47 mmol) in toluene (600 mL) was taken in a 1 L two neck round bottom flask equipped with a Dean Stark apparatus, to which HBr (48%, 7.15 mL, 63.21 mmol) was added and refluxed for 16 h. After cooling, the reaction mixture was washed with 1N HCl, 2M aq NaOH, H_2O and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (15% EtOAc/hexanes) to give bromo-alcohol as a clear oil (12.7 g, 93%). R_f = 0.45 (20% EtOAc/hexanes) ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.63 (t, *J* = 5.8 Hz, 2H), 3.39 (t, *J* = 6.8 Hz, 2H), 1.85 (m, 2H), 1.56 (m, 2H), 1.42 (m, 2H), 1.38-1.27 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 62.9, 33.9, 32.7, 32.6, 29.3, 29.2, 29.2, 28.6, 28.0, 25.6; IR (neat): ν_{max} 2927, 2856, 1738, 1593, 1449, 1367, 1241 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{22}BrO$ $[M+H]^+$ 237.0854, found 237.0845.

DHP (6 mL, 65.82 mmol) and PPTS (127 mg, 0.50 mmol) were added to a solution of bromo-alcohol (12 g, 50.63 mmol) in 100 mL of CH_2Cl_2 and the mixture was stirred for 16 h. The reaction mixture was quenched with 2M Na_2CO_3 solution and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, concentrated under reduced pressure. Purification by flash column (6% EtOAc/hexanes) yielded **16** (14.9 g, 92%) as a colorless oil. R_f = 0.65 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.54 (dd, *J* = 3.9, 2.9 Hz, 1H), 3.83 (ddd, *J* = 11.7, 8.7, 2.9 Hz, 1H), 3.69 (dt, *J* = 9.7, 6.8 Hz, 1H), 3.47 (m, 1H), 3.36 (m, 3H), 1.81 (m, 3H), 1.67 (m, 1H), 1.53 (m, 6H), 1.39 (m, 2H), 1.28 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 98.7, 67.5, 62.2, 33.9, 32.7, 30.6, 29.6, 29.3, 29.2, 28.6, 28.0, 26.1, 25.4, 19.5; IR (neat): ν_{max} 2924, 2855, 1454, 1354, 1126, 1072, 1028 cm^{-1}; HRMS (ESI): calcd for $C_{15}H_{29}O_2NaBr$ $[M+Na]^+$ 343.1248; found 343.1251.

4.3. *1-((10-Bromodecyl)oxy)methyl)-4-methoxybenzene* ***(16a)****:* To a suspension of NaH (60% dispersion in oil, 80 mg, 2.41 mmol) in ether (30 mL) was added 4-methoxybenzyl alcohol (3 mL, 24.16 mmol) drop wise at 0 °C. After being stirred at 0 °C for 5 min, trichloroacetonitrile (2.5 mL, 25.37 mmol) was added and then the reaction mixture was warmed to rt. The reaction mixture was again cooled to 0 °C and stirred for another 15 min and concentrated under reduced pressure. The resulting residue was diluted with hexane and filtered through celite bed. The filtrate was concentrated under reduced pressure to give crude *p*-methoxybenzyltrichloroacetimidate (6.5 g), which was immediately used for the reaction.

To a solution of bromoalcohol (5 g, 21.09 mmol) and the *p*-methoxybenzyltrichloroacetimidate (6.5 g, 23.20 mmol) in CH_2Cl_2: cyclohexane (80 mL, 1:2) was added catalytic amount of CSA (49 mg, 2.11 mmol) at 0 °C. The reaction mixture was warmed to rt and stirred for 12 h while a white precipitate was formed. The solution was filtered with celite bed and the solids were washed with 1:2 CH_2Cl_2: cyclohexane (50 mL). The filterate was washed with saturated aq $NaHCO_3$, brine and dried over Na_2SO_4. The organic layer was concentrated under reduced pressure to give a crude which was purified by flash column (6% EtOAc/hexanes) to give compound **16a** as a clear oil (6.9 g, 92%). R_f = 0.6 (10% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19 (d, *J* = 8.6 Hz, 2H), 6.81 (d, *J* = 8.6, 2H), 4.38 (s, 2H), 3.78 (s, 3H), 3.37 (m, 4H), 1.84 (m, 2H), 1.56 (m, 2H), 1.45-1.25 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.8, 130.5, 129.4, 128.8, 113.5, 113.4, 72.2, 69.9, 54.9, 33.6, 32.6, 29.5, 29.2, 29.2, 29.1, 28.5, 27.9, 25.9; IR (neat): ν_{max} 2925, 2853, 1608, 1511, 1456, 1246, 1098, 1036 cm^{-1}; HRMS (ESI): calcd for $C_{18}H_{28}BrO_2$ $[M-H]^+$ 355.1267, found 355.1269.

4.4. *11-((Tetrahydro-2H-pyran-2-yl)oxy)undecanal* ***(17)****:* To a solution of compound **16** (6 g, 18.69 mmol) in dry CH_3CN (75 mL) were added KCN (1.46 g, 22.42 mmol) and 18-crown-6 (0.4 mL, 1.87 mmol) and stirred at rt for 50 h. The reaction mixture was diluted with H_2O, extracted with EtOAc, dried over Na_2SO_4 and concentrated in *vacuo*. The residue was purified (10% EtOAc/hexanes) to give nitrile compound as a colorless oil (4.44 g, 89%). R_f = 0.4 (10% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.54 (dd, *J* = 3.7, 3.0 Hz, 1H), 3.81 (ddd, *J* = 11.3, 8.3, 3.7 Hz, 1H), 3.68 (dt, *J* = 9.8, 6.7 Hz, 1H), 3.46 (m, 1H), 3.32 (dt, *J* = 9.8, 6.7 Hz, 1H), 2.32 (t, *J* = 6.7 Hz, 2H), 1.81 (m, 1H), 1.74-1.39 (m, 11H), 1.32 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 119.7, 98.7, 67.5, 62.2, 30.6, 29.6, 29.3, 29.1, 28.6, 28.5, 26.1, 25.4, 25.2, 19.6, 17.0; IR (neat): ν_{max} 2926, 2856, 2246, 1728, 1455, 1355, 1265, 1127, 1072, 1028 cm^{-1}; HRMS (ESI): calcd for $C_{16}H_{29}O_2NNa$ $[M+Na]^+$ 290.2090, found 290.2088.

To a solution of nitrile compound (4 g, 14.98 mmol) in dry CH_2Cl_2 (60 mL) was added 1M solution of DIBAL-H in toluene (16.5 mL, 16.47 mmol) drop wise at −78 °C and stirred at −78 °C for 2 h under argon. The reaction mixture was quenched with MeOH, poured into saturated Rochelle's salt solution and extracted with EtOAc. The organic layer was washed with brine,

dried over Na_2SO_4 and concentrated in *vacuo*. The residue was purified (8% EtOAc/hexanes) to give aldehyde **17** as a clear oil (3.4 g, 84%). R_f = 0.55 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.75 (s, 1H), 4.54 (dd, *J* = 3.9, 2.9 Hz, 1H), 3.81 (ddd, *J* = 11.7, 8.7, 3.9 Hz, 1H), 3.68 (dt, *J* = 9.7, 6.8 Hz, 1H), 3.46 (m, 1H), 3.32 (dt *J* = 9.7, 6.8 Hz, 1H), 2.4 (t, *J* = 8.7 Hz, 2H), 1.83 (m, 1H), 1.75-1.46 (m, 10H), 1.30 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.8, 98.7, 67.5, 62.2, 43.8, 30.7, 29.6, 29.4, 29.3, 29.2, 29.2, 29.0, 26.1, 25.4, 21.9, 19.6; IR (neat): ν_{max} 2925, 2856, 2715, 1727, 1456, 1355, 1127, 1029 cm^{-1}; HRMS (ESI): calcd for $C_{16}H_{30}O_3Na$ $[M+Na]^+$ 293.2087, found 293.2086.

4.5. *(E)-Ethyl 13-((tetrahydro-2H-pyran-2-yl)oxy)tridec-2-enoate* ***(18):*** (Carbethoxymethylene)triphenylphospharane (4.6 g, 13.33 mmol) was added to a solution of aldehyed **17** (3 g, 11.11 mmol) in dry CH_2Cl_2 (50 mL) and stirred at rt for 8 h. The reaction mixture was concentrated under reduced pressure and purified (5% EtOAc/hexanes) to give **18** as colorless oil (3.05 g, 80%). R_f = 0.4 (5% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.91 (dt, *J* = 15.6, 6.8 Hz, 1H), 5.77 (d, *J* = 15.6, 1H), 4.54 (dd, *J* = 3.9, 2.9 Hz, 1H), 4.16 (q, *J* = 6.8, 2H), 3.82 (ddd, *J* = 11.7, 8.7, 3.9 Hz, 1H), 3.69 (dt, *J* = 9.7, 6.8 Hz, 1H), 3.47 (m, 1H), 3.33 (dt *J* = 9.7, 6.8 Hz, 1H), 2.19 (q, *J* = 6.8 Hz, 2H), 1.83 (m, 1H), 1.67 (m, 1H), 1.62-1.41 (m, 10H), 1.29 (m, 13H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.5, 149.2, 121.1, 98.6, 67.5, 62.1, 59.9, 32.0, 30.6, 29.6, 29.3, 29.3, 29.3, 29.2, 28.9, 27.8, 26.1, 25.4, 19.5, 14.1; IR (neat): ν_{max} 2926, 2857, 1721, 1655, 1454, 1362, 1266, 1180, 1033 cm^{-1}; HRMS (ESI): calcd for $C_{20}H_{36}O_4Na$ $[M+Na]^+$ 363.2505, found 363.2504.

4.6. *(E)-Ethyl 13-hydroxytridec-2-enoate* ***(19):*** To a solution of **18** (2.9 g, 8.53 mmol) in dry MeOH (30 mL) was added catalytic amount of PTSA (81 mg, 0.43 mmol) at 0 °C and stirred at rt for 4 h. The reaction mixture was quenched by the addition of saturated aq $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified (15% EtOAc/hexanes) to give alcohol **19** as colorless oil (1.98 g, 91%). R_f = 0.5 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.92 (dt, *J* = 15.6, 6.8 Hz, 1H), 5.77 (d, *J* = 15.6 Hz, 1H), 4.17 (q, *J* = 6.8 Hz, 2H), 3.61 (t, *J* = 6.8 Hz, 2H), 2.2 (q, *J* = 7.8 Hz, 2H), 1.53 (m, 2H), 1.46 (m, 1H), 1.31-1.25 (m, 16H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.8, 149.5, 121.1, 62.8, 60.1, 32.7, 32.1, 29.5, 29.3, 29.3, 29.0, 27.9, 25.7, 14.2; IR (neat): ν_{max} 3424, 2923, 2854, 1715, 1652, 1458, 1369, 1269, 1181, 1042 cm^{-1}; HRMS (ESI): calcd for $C_{15}H_{28}O_3Na$ $[M+Na]^+$ 279.1930, found 279.1927.

4.7. *(E)-Ethyl 14,14-dibromotetradeca-2,13-dienoate* ***(20):*** Oxalyl chloride (0.9 mL, 10.54 mmol) was dissolved in CH_2Cl_2 (25 mL) and cooled to −78 °C. Then, DMSO (1.5 mL, 21.09 mmol) was added and the solution was stirred for 20 min at −78 °C. The alcohol **19** (1.8 g, 7.03 mmol) dissolved in CH_2Cl_2 (15 mL) was cannulated drop wise at −78 °C and stirred for 20 min. Triethylamine (3.9 mL, 28.12 mmol) was added and the reaction was stirred for 5 min at −78 °C. The mixture was allowed to warm to 0 °C before quenching by the addition of H_2O and CH_2Cl_2. The organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified (8% EtOAc/hexanes) to give aldehyde as a colorless oil (1.71 g, 96%). R_f = 0.6 (15% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.75 (t, *J* = 1.5 Hz, 1H), 6.91 (dt, *J* = 15.8, 6.7 Hz, 1H), 5.77 (dt, *J* = 15.8, 1.5 Hz, 1H), 4.16 (q, *J* = 6.7 Hz, 2H), 2.40 (dt, *J* = 9.0, 1.5 Hz, 2H), 2.19 (m, 2H), 1.62 (m, 2H), 1.46 (m, 2H), 1.29 (m, 13H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.7, 166.6, 149.2, 121.1, 59.9, 43.7, 32.0, 29.1, 28.9, 28.9, 27.8, 21.9, 14.1; IR (neat): ν_{max} 2926, 2854, 2717, 1719, 1654, 1456, 1368, 1267, 1180, 1043 cm^{-1}; HRMS (ESI): calcd for $C_{15}H_{27}O_3$ $[M+H]^+$ 255.1954, found 255.1953.

To a stirred solution of PPh_3 (6.6 g, 25.19 mmol) in CH_2Cl_2 (10 mL) was added CBr_4 (4.18 g, 12.59 mmol) at 0 °C. After being stirred for 15 min, a solution of aldehyde (1.6 g, 6.29 mmol) in CH_2Cl_2 (8 mL) was added at 0 °C. The mixture was stirred at 0 °C for 10 min and quenched with cold hexane. The suspension was filtered through a pad of celite. The filtrate was concentrated and purified (4% EtOAc/hexanes) to give dibromoalkene **20** as colorless oil (2.21 g, 86%). R_f = 0.4 (5% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.94 (dt, *J* = 15.6, 6.9 Hz, 1H), 6.36 (t, *J* = 7.3 Hz, 1H), 5.78 (dt, *J* = 15.6, 1.3 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 2.17 (q, *J* = 6.9 Hz, 2H), 2.06 (q, *J* = 7.3 Hz, 2H), 1.55-1.22 (m, 17H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.7, 149.3, 138.8, 121.1, 88.4, 60.0, 32.9, 32.1, 29.3, 29.2, 29.2, 29.0, 28.9, 27.9, 27.7, 14.2; IR (neat): ν_{max} 2922, 2854, 1720, 1654, 1456, 1367, 1266, 1179, 1043 cm^{-1}; HRMS (ESI): calcd for $C_{16}H_{27}Br_2O_2$ $[M+H]^+$ 409.0534, found 409.0546.

4.8. *Motualevic acid E* ***(13):*** To a solution of ester **20** (2 g, 4.87 mmol) in 3:1:1 of THF: MeOH: H_2O (20 mL) at 0 °C, $LiOH.H_2O$ (82 mg, 19.51 mmol) was added and stirred at rt for 5 h. The reaction mixture was then acidified to PH 2 with 1N HCl and extracted with EtOAc, washed with brine, dried over Na_2SO_4, filtered and concentrated in *vacuo*. The crude was purified by flash column (25% EtOAc/hexanes) to give motualevic acid E (**13**) as colorless amorphous solid (1.34 g, 72%). R_f = 0.4 (30% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.04 (dt, *J* = 15.9, 6.7 Hz, 1H), 6.36 (t, *J* = 7.5 Hz, 1H), 5.81 (d, *J* = 15.9 Hz, 1H), 2.24 (q, *J* = 6.7 Hz, 2H), 2.10 (dt, *J* = 7.5, 6.7 Hz, 2H), 1.53-1.40 (m, 4H), 1.37-1.20 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.1, 152.1, 138.6, 120.5, 88.4, 32.8, 32.1, 29.2, 29.1, 29.0, 28.9, 28.8, 27.7, 27.6; IR (neat): ν_{max} 2927, 2854, 1696, 1649, 1222 cm^{-1}; HRMS (ESI): calcd for $C_{14}H_{22}Br_2O_2Na$ $[M+Na]^+$ 402.9884, found 402.9897.

4.9. *(E)-Methyl 2-(14,14-dibromotetradeca-2,13-dienamido)acetate* ***(21):*** To a solution of motualevic acid E (**13**) (300 mg, 0.78 mmol) in 8 mL of CH_2Cl_2 was added sequentially HOBt (212 mg, 1.57 mmol), EDCI (301 mg, 1.57 mmol) and glycine methyl ester hydrochloride (148 mg, 1.17 mmol) at 0 °C. Then, Et_3N (0.65 mL, 4.71 mmol) was added at 0 °C and the reaction mixture was stirred for 3 h at rt. After completion of the reaction, diluted with CH_2Cl_2 (100 mL), sequencially, washed with 1N HCl, saturated aq $NaHCO_3$ and brine. The organic layer was dried with Na_2SO_4, concentrated and purified (30% EtOAc/hexanes) to give amide compound **21** as colorless oil (300 mg, 85%). R_f = 0.3 (30% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.87 (dt, *J* = 15.1, 6.7 Hz, 1H), 6.37 (t, *J* = 7.5 Hz, 1H), 6.01 (bs, 1H), 5.83 (dt, *J* = 15.1, 1.5 Hz, 1H), 4.11 (d, *J* = 5.2 Hz, 2H), 3.76 (s, 3H), 2.17 (q, *J* = 6.7 Hz, 2H), 2.07 (q, *J* = 7.5 Hz, 2H), 1.41 (m, 3H), 1.27 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.2, 166.1, 145.2, 138.5, 122.6, 88.1, 51.8, 40.8, 32.6, 31.7, 29.0, 28.9, 28.8, 28.6, 27.8, 27.4; IR (neat): ν_{max} 3292, 2923, 2853, 1747, 1666, 1627, 1538, 1441, 1364, 1202 cm^{-1}; HRMS (ESI): calcd for $C_{17}H_{28}Br_2NO_3$ $[M+H]^+$ 452.0430, found 452.0435.

4.10. *Motualevic acid A* ***(9):*** Motualevic acid A (**9**) was prepared from amide compound **21** using the method described for the preparation of motualevic acid E (**13**) from ester **20**. The crude product was purified (20% MeOH/EtOAc) to give motualevic acid A (**9**), as colorless amorphous solid (258 mg, 89%). R_f = 0.3 (20% MeOH/EtOAc); ^{1}H NMR (300 MHz, CD_3OD): δ 6.82 (dt, *J* = 15.8, 6.8 Hz, 1H), 6.50 (t, *J* = 7.5 Hz, 1H), 6.02 (d, *J* = 15.8 Hz, 1H), 3.92 (s, 2H), 2.24 (q, *J* = 6.8 Hz, 2H), 2.14 (dt, *J* = 7.5, 6.7 Hz, 2H), 1.56-1.30 (m, 14H); ^{13}C NMR (75 MHz, CD_3OD): δ 174.7, 168.6, 145.9, 140.3, 124.5, 89.1, 43.2, 33.9, 33.0, 30.5, 30.5, 30.4, 30.2, 30.1, 29.4, 28.8; IR (neat): ν_{max} 2919, 2849, 1733, 1661, 1557, 1262 cm^{-1}; HRMS (ESI): calcd for $C_{16}H_{26}Br_2NO_3$ $[M+H]^+$ 438.0274, found 438.0280.

4.11. *Motualevic acid C* ***(11)****:* To a solution of motualevic acid A (**9**) (50 mg, 0.11 mmol) in dry THF (1 mL) at –20 °C, Et_3N (0.02 mL, 0.14 mmol) was added drop wise and stirred for 5 min. Then ethyl chloroformate (0.013 mL, 0.14 mmol) was added and stirring was continued at –20 °C for 30 min. Then 25% NH_4OH (0.013 mL, 0.68 mmol) was added at the same temperature and stirred for another 1.5 h. The reaction mixture was quenched by adding saturated aq NH_4Cl solution and extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Column purification (8% MeOH/EtOAc) gave motualevic acid C (**11**) as a colorless amorphous solid (40 mg, 83%). R_f = 0.43 (10% MeOH/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.87 (dt, *J* = 15.1, 6.8 Hz, 1H), 6.42-6.32 (m, 3H), 5.84 (d, *J* = 15.1 Hz, 1H), 5.57 (bs, 1H), 4.05 (d, *J* = 5.2 Hz, 2H), 2.18 (dt, *J* = 7.5, 6.8 Hz, 2H), 2.08 (dt, *J* = 7.5, 6.8 Hz, 2H), 1.50-1.37 (m, 4H), 1.35-1.24 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.5, 166.7, 146.4, 139.0, 122.8, 88.6, 43.1, 33.1, 32.2, 29.9, 29.5, 29.4, 29.3, 29.2, 28.3, 27.9; IR (neat): ν_{max} 2917, 2848, 1660, 1625, 1551, 1461, 1274, 1133 cm^{-1}; HRMS (ESI): calcd for $C_{16}H_{27}Br_2N_2O_2$ $[M+H]^+$ 437.0433, found 437.0403.

4.12. *Motualevic acid D* ***(12)***: Motualevic acid D (**12**) was prepared from motualevic acid A (**9**) using the same method described for the preparation of amide compound **21** from motualevic acid E (**13**). The crude product was purified (6% MeOH/EtOAc) to give motualevic acid D (**12**) as colorless amorphous solid (34 mg, 65%). R_f = 0.6 (10% MeOH/EtOAc); ^{1}H NMR (300 MHz, CD_3OD): δ 6.81 (dt, *J* = 15.3, 6.8 Hz, 1H), 6.47 (t, *J* = 7.1 Hz, 1H), 6.02 (d, *J* = 15.3 Hz, 1H), 4.11 (s, 2H), 3.05 (s, 3H), 2.95 (s, 3H), 2.21 (q, *J* = 6.9 Hz, 2H), 2.11 (q, *J* = 7.1 Hz, 2H), 1.53-1.35 (m, 2H), 1.35-1.25 (m, 12H); ^{13}C NMR (125 MHz, CD_3OD): δ 170.5, 168.9, 146.4, 140.4, 124.5, 89.2, 42.0, 36.7, 36.1, 34.1, 33.1, 30.6, 30.6, 30.5, 30.3, 30.2, 29.5, 28.9; IR (neat): ν_{max} 2919, 2850, 1672, 1617, 1507, 1461, 1407, 1216 cm^{-1}; HRMS (ESI): calcd for $C_{18}H_{31}N_2O_2$ $[M+H]^+$ 465.0746, found 465.0734.

4.13. *(E)-Methyl 16,16-dibromo-3-oxohexadeca-4,15-dienoate* ***(22)****:* To a solution of motualevic acid E (**13**) (1 g, 2.61 mmol) in dry THF (10 mL) at 0 °C was added CDI (509 mg, 3.14 mmol) and stirred for 1 h at 0 °C. Parallelly in another round bottom flask, monomethylmalonic acid (618 mg, 5.23 mmol) in dry THF (10 mL) was taken and a solution of isopropylmagnesium bromide (1M, 10.47 mL, 10.47 mmol) was added drop wise at 0 °C and stirred for 30 min. The reaction mixture was cooled to –20 °C and previously prepared imidazolide solution was added drop wise and the resulting mixture was stirred at –20 °C for 20 min at rt for 1.5 h. The reaction mixture was quenched by the addition of 1N HCl and extracted with EtOAc (2 times). The combined organic layers were washed with saturated aq $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified (10% EtOAc/hexanes) to give *β*-ketoester **22** as a colorless oil (525 mg, 46%, the ratio of keto:enol is 1:0.3). R_f = 0.5 (10% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.81 (s, 0.3H), 6.88 (dt, *J* = 15.8, 6.9 Hz, 1H), 6.66 (dt, *J* = 15.8, 6.9 Hz, 0.3H), 6.38 (t, *J* = 7.3 Hz, 1.3H), 6.15 (d, *J* = 15.8 Hz, 1H), 5.78 (d, *J* = 15.8 Hz, 0.3H), 4.98 (s, 0.3H), 3.74 (s, 3.9H), 3.59 (s, 2H), 2.24 (q, *J* = 6.7 Hz, 2.6H), 2.08 (q, *J* = 6.9 Hz, 2.6H), 1.43 (m, 4H), 1.36-1.23 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.0, 167.8, 150.2, 141.2, 138.7, 129.4, 124.1, 89.5, 88.3, 52.2, 51.1, 46.4, 32.8, 32.4, 29.2, 29.1, 29.0, 28.8, 28.5, 28.3, 27.7, 27.6, 25.2, 17.0; IR (neat): ν_{max} 2924, 2854, 1726, 1659, 1447, 1236, 1161, 1025 cm^{-1}; HRMS (ESI): calcd for $C_{17}H_{26}Br_2O_3Na$ $[M+Na]^+$ 459.0146, found 459.0135.

4.14. *(4E)-Methyl 16,16-dibromo-3-((tosyloxy)imino)hexadeca-4,15-dienoate* ***(23)****:* To a solution of *β*-keto ester **22** (700 mg, 1.59 mmol) in methanol (10 mL) was added hydroxylamine hydrochloride (122 mg, 1.75 mmol) and pyridine (0.14 mL, 1.75 mmol). The reaction mixture was stirred at 55 °C for 1 h and then concentrated under reduced pressure. The residue was taken up in H_2O and extracted with EtOAc, washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure.

The crude oxime was dissolved in dry CH_2Cl_2 (10 mL) and *p*-toluenesulfonic anhydride (778 mg, 2.38 mmol), pyridine (0.21 mL, 2.38 mmol) and catalytic amount of DMAP (9.7 mg, 0.08 mmol) were added at 0 °C. The reaction mixture was stirred at 0 °C for 2 h and quenched with aq NH_4Cl. The layers were separated and aq layer was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography (20% EtOAc/hexanes) afforded tosylated compound **23** as a clear oil (386 mg, 40%). R_f = 0.4 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.86 (d, *J* = 7.7 Hz, 2H), 7.32 (d, *J* = 7.7, 2H), 6.67 (d, *J* = 15.4 Hz, 1H), 6.39 (t, *J* = 7.7 Hz, 1H), 6.29 (dt, *J* = 15.4, 6.6 Hz, 1H), 3.64 (s, 3H), 3.39 (s, 2H), 2.44 (s, 3H), 2.21 (q, *J* = 6.6 Hz, 2H), 2.09 (q, *J* = 7.7 Hz, 2H), 1.42 (m, 4H), 1.36-1.24 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.7, 157.6, 146.4, 144.9, 138.8, 132.5, 129.5, 128.8, 118.1, 88.4, 52.4, 36.8, 33.2, 32.9, 29.6, 29.3, 29.2, 29.0, 28.9, 28.2, 27.7, 21.7; IR (neat): ν_{max} 2921, 2854, 2355, 1742, 1594, 1453, 1218 cm^{-1}; HRMS (ESI): calcd for $C_{24}H_{34}Br_2NO_5S$ $[M+H]^+$ 606.0519, found 606.0521.

4.15. *(R)-(E)-Antazirine (ent-****4****):* To an oven dried round bottom flask, quinidine (534 mg, 1.64 mmol) was taken and dissolved in dry toluene (35 mL) and cooled to 0 °C. A solution of compound **23** (200 mg, 0.33 mmol) in toluene was cannulated and the resulting mixture was stirred for 48 h at 0 °C. The reaction mixture was quenched with 0.05 M HCl and extracted with EtOAc. Organic layer was washed with brine, dried over Na_2SO_4 and concentrated in *vacuo*. The crude was purified (5% EtOAc/hexanes) to give (*R*)-(*E*)-antazirine (*ent*-**4**) as a light yellowish foam (109 mg, 76% yield, 81% ee, (determined by chiral HPLC, ciralpack-IC3, MeOH/CH_3CN 90:10)). R_f = 0.6 (10% EtOAc/hexanes); $[\alpha]_D^{24}$ = –85.1 (*c* 0.63, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.68 (dt, *J* = 15.9, 7.0 Hz, 1H), 6.53 (d, *J* = 15.9 Hz, 1H), 6.37 (t, *J* = 7.0 Hz, 1H), 3.71 (s, 3H), 2.55 (s, 1H), 2.35 (dd, *J* = 14.0, 7.0 Hz, 2H), 2.07 (dd, *J* = 14.9, 7.0 Hz, 2H), 1.50 (m, 2H), 1.40 (m, 2H), 1.35-1.24 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.6, 156.9, 156.1, 139.2, 113.2, 88.8, 52.6, 33.5, 33.3, 29.7, 29.6, 29.6, 29.5, 29.3, 28.6, 28.1, 28.1; IR (neat): ν_{max} 2921, 2854, 1760, 1733, 1453, 1342, 1268, 1195, 1028 cm^{-1}; HRMS (ESI): calcd for $C_{17}H_{26}Br_2NO_2$ $[M+H]^+$ 434.0330, found 434.0321.

4.16. *Motualevic acid F****(14)****:* To a solution of (*R*)-(*E*)-antazirine (*ent*-**4**) (50 mg, 0.11 mmol) in 3:1 of THF:H_2O (4.4 mL) at 0 °C was added NaOH (18.4 mg, 0.46 mmol). The reaction mixture was stirred at 0 °C for 3 h and neutralized with 0.05 M HCl. The mixture was extracted with EtOAc (3 times), the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in *vacuo*. It was purified by flash column chromatography (80% EtOAc/hexanes) to give motualevic acid F (**14**) as light yellow foam (39.5 mg, 85% yield, 81% ee (determined by chiral HPLC, ciral column-ODH, hexane/isopropanol 80:20)). R_f = 0.4 (EtOAc); $[\alpha]_D^{26}$ = –78.8 (*c* 0.48, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.72 (dt, *J* = 15.5, 7.7 Hz, 1H), 6.53 (d, *J* = 15.5 Hz, 1H), 6.37 (t, *J* = 7.7 Hz, 1H), 2.55 (s, 1H), 2.36 (dd, *J* = 15.4, 7.7 Hz, 2H), 2.07 (dd, *J* = 15.4, 7.7 Hz, 2H), 1.51 (m, 2H), 1.40 (m, 2H), 1.35-1.21 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.6, 156.5, 156.2, 139.1, 112.8, 88.7, 33.5, 33.2, 29.6, 29.5, 29.5, 29.4, 29.2, 28.2, 28.0, 28.0; IR (neat): ν_{max} 3424, 2925, 2853, 1771, 1698, 1458, 1213, 771 cm^{-1}; HRMS (ESI): calcd for $C_{16}H_{23}Br_2NO_2Na$ $[M+Na]^+$ 441.9993, found 441.9981.

4.17. *13-((Tetrahydro-2H-pyran-2-yl)oxy)tridec-2-ynoic acid (**24**):* A 250 mL round bottom flask equipped with a stirring bar was flame dried under vacuum and filled with an argon. After cooling, diisopropylamine (3.5 mL, 24.92 mmol) and 6 mL of THF was added and cooled to 0 °C, while a solution of *n*-BuLi (1.6M in hexanes, 14.3 mL, 22.92 mmol) was added dropwise. After 20 min, the reaction mixture was cooled to −40 °C and the solution of propiolic acid (0.77 mL, 12.46 mmol) in 10 mL of HMPA was cannulated. The resulting mixture was allowed to warm to −15 °C and stirred for 2 h at the same temp. Then bromo compound **16** (2 g, 6.2 mmol) was cannulated using THF (4 mL) and warmed to rt. The reaction mixture was stirred at rt for 16 h and then quenched by the addition of H_2O. The reaction mixture was acidified to PH 2 using 1N HCl. The aq phase was extracted with EtOAc, washed with brine, dried over Na_2SO_4 and concentrated in *vacuo*. The residue was purified by flash column chromatography (60% EtOAc/hexanes) to give acid **24** as pale yellow oil (1.66 g, 86%). R_f = 0.2 (60% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.24 (bs, 1H), 4.58 (dd, *J* = 3.7, 3.0 Hz, 1H), 3.84 (ddd, *J* = 11.3, 8.3, 3.7 Hz, 1H), 3.68 (dt, *J* = 9.8, 6.7 Hz, 1H), 3.50 (m, 1H), 3.34 (dt *J* = 9.8, 6.7 Hz, 1H), 2.35 (t, *J* = 6.7 Hz, 2H), 1.90-1.49 (m, 9H), 1.48-1.21 (m, 13H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.2, 98.6, 90.6, 73.0, 67.6, 62.0, 30.5, 29.5, 29.3, 29.2, 29.1, 28.8, 28.6, 27.3, 26.0, 25.2, 19.3, 18.5; IR (neat): ν_{max} 2925, 2856, 2235, 1711, 1455, 1364, 1247, 1071, 1029 cm^{-1}; HRMS (ESI): calcd for $C_{18}H_{30}O_4Na$ $[M+Na]^+$ 333.2036, found 333.2035.

4.18. *13-((4-Methoxybenzyl)oxy)tridec-2-ynoic acid (**24a**):* Acid **24a** was prepared from compound **16a** using the same method described for the preparation of compound **24**. The residue was purified by flash column chromatography (60% EtOAc/hexane) to give acid **24a** as pale yellow oil (3.3 g, 86%). R_f = 0.2 (60% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21 (d, *J* = 8.0 Hz, 2H), 6.82 (d, *J* = 8.0, 2H), 5.44 (bs, 1H), 4.41 (s, 2H), 3.80 (s, 3H), 3.40 (t, *J* = 7.0 Hz, 2H), 2.34 (t, *J* = 7.0 Hz, 2H), 1.58 (m, 4H), 1.45-1.25 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.0, 156.9, 130.4, 129.2, 113.7, 91.6, 72.8, 72.3, 70.0, 55.2, 29.5, 29.3, 29.3, 29.2, 28.8, 28.7, 27.3, 26.0, 18.6; IR (neat): ν_{max} 2924, 2854, 2234, 1707, 1512, 1244, 1086, 1035 cm^{-1}; HRMS (ESI): calcd for $C_{21}H_{30}O_4Na$ $[M+Na]^+$ 369.2036, found 369.2038.

4.19. *Methyl 2-(13-((tetrahydro-2H-pyran-2-yl)oxy)tridec-2-ynamido)acetate (**25**):* Amide **25** was prepared from the compound **24** using the same method described for the preparation of amide compound **21** from motualevic acid E (**13**). The crude product was purified (25% EtOAc/hexanes) to give amide compound **25** as pale yellow oil (1.05 g, 69%). R_f = 0.4 (30% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.14 (bs, 1H), 4.55 (dd, *J* = 3.9, 2.9 Hz, 1H), 4.05 (d, *J* = 4.8 Hz, 2H), 3.82 (ddd, *J* = 11.7, 8.7, 3.9 Hz, 1H), 3.79 (s, 3H), 3.69 (dt, *J* = 9.7, 6.8 Hz, 1H), 3.47 (m, 1H), 3.33 (dt *J* = 9.7, 6.8 Hz, 1H), 2.31 (t, *J* = 6.8 Hz, 2H), 1.83 (m, 1H), 1.67 (m, 1H), 1.57 (m, 6H), 1.45-1.25 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.6, 153.3, 98.7, 88.6, 74.8, 67.6, 62.2, 52.4, 41.2, 30.7, 29.6, 29.4, 29.3, 29.2, 28.9, 28.7, 27.6, 26.1, 25.4, 19.6, 18.5; IR (neat): ν_{max} 3325, 2923, 2854, 2232, 1751, 1651, 1526, 1449, 1364, 1279, 1203, 1129 cm^{-1}; HRMS (ESI): calcd for $C_{21}H_{35}NO_5Na$ $[M+Na]^+$ 404.2407, found 404.2402.

4.20. *(Z)-Methyl 2-(13-((tetrahydro-2H-pyran-2-yl)oxy)tridec-2-enamido) acetate (**26**):* To a solution of amide **25** (900 mg, 2.36 mmol) in MeOH (30 mL) was added catalytic amount of Lindlar catalyst (225 mg) and the resulting mixture was stirred vigorously under a hydrogen atmosphere for 15 min at rt. The mixture was filtered through celite and washed with EtOAc. The filtrate was concentrated in *vacuo*. Purification of the residue with flash column chromatography (25% EtOAc/hexanes) gave compound **26** as pale yellow oil (650 mg, 72%). R_f = 0.4 (30% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.03 (dt, *J* = 11.3, 7.5 Hz, 1H), 5.94 (bs, 1H), 5.71 (dt, *J* = 11.3, 1.5 Hz, 1H), 4.54 (dd, *J* = 3.7, 3.0 Hz, 1H), 4.05 (d, *J* = 5.2 Hz, 2H), 3.82 (ddd, *J* = 11.3, 8.3, 3.7 Hz, 1H), 3.77 (s, 3H), 3.67 (dt, *J* = 9.8, 6.7 Hz, 1H), 3.46 (m, 1H), 3.31 (dt *J* = 9.8, 6.7 Hz, 1H), 2.64 (m, 2H), 1.88-1.47 (m, 7H), 1.45-1.22 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4, 166.3, 147.1, 121.1, 98.7, 67.6, 62.2, 52.2, 40.8, 30.6, 29.6, 29.4, 29.3, 29.3, 29.2, 28.7, 26.1, 25.3, 19.5; IR(neat): ν_{max} 3320, 2923, 2854, 1750, 1665, 1530, 1448, 1361, 1202, 1028 cm^{-1}; HRMS (ESI): calcd for $C_{21}H_{37}NO_5Na$ $[M+Na]^+$ 406.2569, found 406.2560.

4.21. *(Z)-Methyl 2-(13-hydroxytridec-2-enamido)acetate (**27**):* Alcohol **27** was prepared from compound **26** using the same method described for the preparation of alcohol **19** from compound **18**. The crude product was purified (35% EtOAc/hexanes) to give alcohol **27** as pale yellow oil (277 mg, 89%). R_f = 0.4 (50% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.04 (dt, *J* = 11.3, 7.5 Hz, 1H), 5.88 (bs, 1H), 5.72 (dt, *J* = 11.3, 1.5 Hz, 1H), 4.06 (d, *J* = 4.5 Hz, 2H), 3.78 (s, 3H), 3.61 (t, *J* = 6.7 Hz, 2H), 2.65 (m, 2H), 1.61-1.48 (m, 2H), 1.46-1.23 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.5, 166.4, 147.1, 121.1, 62.9, 52.3, 40.9, 32.7, 29.4, 29.3, 29.3, 29.2, 28.7, 25.6; IR(neat): ν_{max} 3383, 3309, 2921, 2853, 1744, 1660, 1535, 1445, 1207 cm^{-1}; HRMS (ESI): calcd for $C_{16}H_{29}NO_4Na$ $[M+Na]^+$ 322.1988, found 322.1984.

4.22. *(Z)-Methyl 2-(14,14-dibromotetradeca-2,13-dienamido)acetate (**28**):* Compound **28** was synthesized from **27** using the same procedure described for **20** from **19**.

Data for oxidation product of **27** (aldehyde): Yield 94% (186 mg); pale yellow oil; R_f = 0.6 (50% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.74 (t, *J* = 1.7 Hz, 1H), 6.03 (dt, *J* = 11.5, 7.5 Hz, 1H), 5.88 (bs, 1H), 5.72 (dt, *J* = 11.3, 1.5 Hz, 1H), 4.06 (d, *J* = 5.0 Hz, 2H), 3.78 (s, 3H), 2.65 (m, 2H), 2.40 (dt, *J* = 7.3, 1.7 Hz, 2H), 1.69-1.54 (m, 2H), 1.49-1.24 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.0, 170.5, 166.4, 147.1, 121.1, 52.3, 43.8, 40.9, 33.7, 29.1, 29.0, 28.8, 28.7, 24.6, 21.9; IR (neat): ν_{max} 3361, 2921, 2854, 1734, 1720, 1659, 1531, 1443, 1365, 1209 cm^{-1}; HRMS (ESI): calcd for $C_{16}H_{26}NO_4$ $[M-H]^+$ 296.1856, found 296.1854.

Data of **28**: Yield 70% (198 mg); as colorless oil; R_f = 0.4 (30% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.38 (t, *J* = 7.7 Hz, 1H), 6.06 (dt, *J* = 11.2, 6.9 Hz, 1H), 5.91 (bs, 1H), 5.74 (d, *J* = 11.2, Hz, 1H), 4.09 (d, *J* = 5.1 Hz, 2H), 3.77 (s, 3H), 2.65 (q, *J* = 6.9 Hz, 2H), 2.08 (dd, *J* = 14.7, 7.7 Hz, 2H), 1.41 (m, 4H), 1.36-1.24 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 166.4, 147.2, 138.9, 121.1, 88.3, 52.3, 40.9, 32.9, 29.6, 29.3, 29.2, 28.9, 28.8, 27.7; IR (neat): ν_{max} 3312, 2920, 2853, 1748, 1664, 1530, 1454, 1364, 1207 cm^{-1}; HRMS (ESI): calcd for $C_{17}H_{28}Br_2NO_3$ $[M+H]^+$ 452.0432, found 452.0421.

4.23. *Motualevic acid B (**10**):* Motualevic acid B (**10**) was prepared from ester **28** using the same method described for the preparation of motualevic acid E (**13**) from ester **20**. Yield: 82% (79 mg); as colorless amorphous solid; R_f = 0.4 (20% MeOH/EtOAc); ^{1}H NMR (300 MHz, CD_3OD): δ 6.49 (t, *J* = 7.5 Hz, 1H), 6.07 (dt, *J* = 11.3, 7.5 Hz, 1H), 5.87 (d, *J* = 11.3 Hz, 1H), 3.94 (s, 2H), 2.64 (q, *J* = 7.5 Hz, 2H), 2.12 (q, *J* = 7.5 Hz, 2H), 1.54-1.26 (m, 14H); ^{13}C NMR (75 MHz, CD_3OD): δ 173.0, 169.0, 146.8, 140.0, 122.4, 88.7, 41.4, 33.6, 30.4, 30.2, 30.1, 30.0, 30.0, 29.7, 29.4, 28.4; IR (neat); ν_{max} 2925, 2855, 1705, 1670, 1607, 1460, 1218 cm^{-1}; HRMS (ESI): calcd for $C_{16}H_{26}Br_2NO_3$ $[M+H]^+$ 438.0273, found 438.0268.

4.24. *Methyl 3-oxo-15-((tetrahydro-2H-pyran-2-yl)oxy)pentadec-4-ynoate (**29**):* Ketoester **29** was prepared from compound **24** using the same method described for the preparation of

compound **22** from motualevic acid E (**13**). The residue was purified by flash column chromatography (15% EtOAc/hexanes) to give *β*-ketoester **29** as a pale yellow oil (471 mg, 57%; the ratio of keto-enol is 1:0.3). R_f = 0.6 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.75 (s, 0.3H), 5.23 (s, 0.3H), 4.54 (t, *J* = 3.8 Hz, 1.3H), 3.81 (ddd, *J* = 10.7, 8.4, 3.8 Hz, 1.3H), 3.75 (s, 3.6H), 3.74 (s, 0.9H), 3.69 (dt, *J* = 9.2, 6.9 Hz, 1.3H), 3.51 (s, 2H), 3.47 (m, 1.3H), 3.32 (dt, *J* = 9.2, 6.9 Hz, 1.3H), 2.37 (t, *J* = 6.9 Hz, 2.6H), 2.37 (t, *J* = 6.9 Hz, 0.6H), 1.83 (m, 1H), 1.72-1.49 (m, 13.3H), 1.40-1.26 (m, 14.4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.6, 172.5, 166.5, 155.7, 98.7, 97.0, 96.3, 95.7, 94.5, 80.2, 75.3, 67.5, 62.8, 62.2, 52.4, 52.3, 51.3, 51.0, 30.7, 30.6, 29.6, 29.4, 29.3, 29.2, 28.8, 28.7, 27.7, 27.4, 26.1, 25.4, 25.3, 19.6, 19.1, 18.9; IR (neat): ν_{max} 2926, 2856, 2215, 1748, 1676, 1609, 1445, 1252, 1028 cm^{-1}; HRMS (ESI): calcd for $C_{21}H_{34}O_5Na$ $[M+Na]^+$ 389.2298, found 389.2297.

4.25. *Methyl 15-((4-methoxybenzyl)oxy)-3-oxopentadec-4-ynoate (**29a**):* Ketoester **29a** was prepared from **24a** using the same method described for the preparation of compound **22** from motualevic acid E (**13**). The residue was purified by flash column chromatography (15% EtOAc/hexanes) to give *β*-ketoester **29a** as a pale yellow oil (662 mg, 57%; the ratio of keto:enol is 1:0.3). R_f = 0.6 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 11.75 (s, 0.3H), 7.20 (d, *J* = 9.0 Hz, 2.6H), 6.82 (d, *J* = 9.0 Hz, 2.6H), 5.23 (s, 0.3H), 4.39 (s, 2.6H), 3.79 (s, 3.9H), 3.75 (s, 3H), 3.74 (s, 0.6H), 3.51 (s, 2H), 3.39 (t, *J* = 7.0 Hz, 2.6H), 2.37 (m, 2.6H), 1.58 (m, 7H), 1.44-1.24 (m, 13H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.6, 166.5, 158.9, 155.7, 130.6, 129.0, 113.6, 97.0, 95.7, 80.2, 72.4, 70.0, 67.7, 55.1, 52.3, 51.3, 51.0, 29.6, 29.4, 29.3, 29.2, 28.8, 28.7, 27.7, 27.4, 26.0, 19.1, 18.9; IR (neat): ν_{max} 2927, 2855, 2215, 1744, 1609, 1448, 1248, 1099 cm^{-1}; HRMS (ESI): calcd for $C_{24}H_{34}O_5Na$ $[M+Na]^+$ 425.2298, found 425.2297.

4.26. *(Z)-Methyl 15-((tetrahydro-2H-pyran-2-yl)oxy)-3-(tosylimino)pentadec-4-ynoate (**30**):* Oxime-tosylate **30** was prepared from ketoester **29** using the same method described for the preparation of compound **23** from *β*-ketoester **22**. The residue was purified (20% EtOAc/hexanes) to give tosylated compound **30** as a pale yellow oil (449 mg, 77%). R_f = 0.4 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85 (d, *J* = 7.9 Hz, 2H), 7.33 (d, *J* = 7.9 Hz, 2H), 4.57 (t, *J* = 3.9 Hz, 1H), 3.87 (ddd, *J* = 10.9, 8.9, 3.9 Hz, 1H), 3.72 (dt, *J* = 8.9, 6.9 Hz, 1H), 3.68 (s, 3H), 3.50 (m, 1H), 3.38 (dt, *J* = 8.9, 6.9 Hz, 1H), 3.35 (s, 2H), 2.44 (s, 3H), 2.42 (t, *J* = 6.9 Hz, 2H), 1.82 (m, 1H), 1.76 (m, 1H), 1.64-1.47 (m, 8H), 1.41-1.23 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.5, 145.0, 144.5, 132.2, 129.6, 129.5, 128.8, 128.7, 107.8, 98.7, 70.6, 67.5, 62.2, 52.3, 39.9, 30.6, 29.6, 29.4, 29.3, 29.2, 28.8, 28.6, 27.5, 26.1, 25.3, 21.5, 19.6; IR (neat): ν_{max} 2930, 2856, 2223, 1746, 1597, 1379, 1186 cm^{-1}; HRMS (ESI): calcd for $C_{28}H_{41}NO_7SNa$ $[M+Na]^+$ 558.2495, found 558.2491.

4.27. *(E, Z)-Methyl 15-((4-methoxybenzyl)oxy)-3-(tosylimino)pentadec-4-ynoate (**30a**):* Compound **30a** was prepared from *β*-ketoester **29a** using the same method described for the preparation of compound **23** from *β*-ketoester **22**. The crude product was purified (20% EtOAc/hexanes) to give tosylated compound **30a** as a pale yellow oil (656 mg, 77%). R_f = 0.4 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85 (d, *J* = 7.6 Hz, 2H), 7.33 (d, *J* = 7.6 Hz, 2H), 7.25 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 4.43 (s, 2H), 3.80 (s, 3H), 3.68 (s, 3H), 3.43 (t, *J* = 6.7 Hz, 2H), 3.35 (s, 2H), 2.44 (s, 3H), 2.42 (t, *J* = 7.6 Hz, 2H), 1.63-1.52 (m, 6H), 1.42-1.25 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.6, 159.0, 145.1, 144.5, 132.3, 130.7, 129.6, 129.5, 129.1, 128.9, 128.8, 113.6, 107.8, 72.4, 70.6, 70.1, 55.2, 52.3, 40.0, 29.7, 29.4, 29.3, 29.3, 28.9, 28.6, 27.6, 26.1, 21.6, 19.7; IR (neat): ν_{max} 2930, 2856, 2223, 1746, 1598, 1379, 1186, 818 cm^{-1}; HRMS (ESI): calcd for $C_{31}H_{41}NO_7SNa$ $[M+Na]^+$ 594.2495, found 594.2488.

4.28. *Methyl 3-(12-((tetrahydro-2H-pyran-2-yl)oxy)dodec-1-yn-1-yl)-2H-azirine-2-carboxylate ((±)-**31**):* To a solution of **30** (300 mg, 0.56 mmol) in dry toluene (10 mL) at 0 °C was added Et_3N (0.39 mL, 2.80 mmol). The reaction mixture was stirred at rt for 5 h and then H_2O was added and extracted with EtOAc, washed with brine and dried over Na_2SO_4. The organic layer was concentrated in *vacuo* to give a crude compound which was purified (15% EtOAc/hexanes) to give compound **31** as a pale yellow oil (159 mg, 78%). R_f = 0.55 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.53 (t, *J* = 4.4, Hz, 1H), 3.82 (ddd, *J* = 11.0, 8.8, 3.3 Hz, 1H), 3.70 (s, 3H), 3.68 (m, 1H), 3.45 (m, 1H), 3.34 (dt, *J* = 8.8, 6.6 Hz, 1H), 2.67 (s, 1H), 2.54 (t, *J* = 7.7 Hz, 2H), 1.79 (m, 1H), 1.70-1.44 (m, 9H), 1.42-1.21 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.7, 149.2, 118.1, 98.7, 67.5, 64.5, 62.2, 52.3, 31.4, 30.6, 29.6, 29.3, 29.3, 29.2, 28.8, 28.7, 27.3, 26.0, 25.3, 20.2, 19.5; IR (neat): ν_{max} 2930, 2855, 2227, 1766, 1745, 1345, 1202, 1058 cm^{-1}; HRMS (ESI): calcd for $C_{21}H_{33}NO_4Na$ $[M+Na]^+$ 386.2307, found 386.2319.

4.29. *(R)-Methyl 3-(12-((4-methoxybenzyl)oxy)dodec-1-yn-1-yl)-2H-azirine-2-carboxylate (**31a**):* To an oven dried round bottom flask, quinidine (1.02 g, 3.15 mmol) was taken and dry toluene (120 mL) was added and cooled to 0 °C. A solution of compound **30a** (600 mg, 1.05 mmol) in toluene was cannulated at 0 °C. The resulting mixture was stirred for 52 h at 0 °C. The reaction mixture was quenched with 0.05 M HCl and extracted with EtOAc. Organic layer was washed with brine, dried over Na_2SO_4 and concentrated in *vacuo*. The crude was purified (15% EtOAc/hexanes) to give compound **31a** as pale yellow oil (323 mg, 77% yield, 51% ee (chiral HPLC, ciral column-ODH, hexane/isopropanol 80:20)). R_f = 0.55 (20% EtOAc/hexanes); $[\alpha]_D^{24}$ = –58.1 (*c* 0.58, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 4.43 (s, 2H), 3.80 (s, 3H), 3.75 (s, 3H), 3.43 (t, *J* = 7.6 Hz, 2H), 2.71 (s, 1H), 2.58 (t, *J* = 7.6 Hz, 2H), 1.69-1.54 (m, 6H), 1.47-1.38 (m, 2H), 1.38-1.25 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.9, 159.0, 149.3, 129.2, 118.2, 113.7, 72.5, 70.1, 64.6, 55.2, 52.4, 31.5, 29.7, 29.4, 29.4, 29.3, 28.9, 28.8, 27.4, 26.1, 20.3; IR (neat): ν_{max} 2921, 2852, 2223, 1753, 1735, 1602, 1446, 1344, 1196, 1094 cm^{-1}; HRMS (ESI): calcd for $C_{24}H_{34}NO_4$ $[M+H]^+$ 400.2487, found 400.2490.

4.30. *(R)-Methyl 3-(12-hydroxydodec-1-yn-1-yl)-2H-azirine-2-carboxylate (**32**):* To a solution of compound **31a** (200 mg, 0.50 mmol) in CH_2Cl_2: H_2O (2:1, 2 mL) was added DDQ (156 mg, 0.68 mmol) at 0 °C. The reaction mixture was stirred at rt for 50 min and quenched by adding saturated aq $NaHCO_3$. The reaction mixture was extracted with EtOAc and washed with aq $NaHCO_3$ (2 times). The organic layer was separated, dried over Na_2SO_4, filtered and concentrated in *vacuo*. The residue was purified (30% EtOAc/hexanes) to give compound **32** as clear oil (133 mg, 95%). R_f = 0.4 (30% EtOAc/hexanes); $[\alpha]_D^{25}$ = –106.4 (*c* 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.75 (s, 3H), 3.64 (t, *J* = 6.8 Hz, 2H), 2.71 (s, 1H), 2.58 (t, *J* = 7.8 Hz, 2H), 1.65 (m, 2H), 1.56 (m, 2H), 1.43 (m, 2H), 1.38-1.28 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.8, 149.2, 118.2, 64.5, 62.8, 52.4, 32.6, 31.4, 29.3, 29.2, 29.2, 28.8, 28.7, 27.3, 25.6, 20.2; IR (neat): ν_{max} 3432, 2927, 2855, 2227, 1768, 1747, 1438, 1345, 1204 cm^{-1}; HRMS (ESI): calcd for $C_{16}H_{26}NO_3$ $[M+H]^+$ 280.1907, found 280.1907.

4.31. *(R)-Methyl 3-(13,13-dibromotridec-12-en-1-yn-1-yl)-2H-azirine-2-carboxylate (**33**):* Compound **33** was prepared from **32** following the same procedure described for the synthesis of **20** from **19**. *Dibromo* alkene **33** was obtained as a clear oil (94 mg, 54% over two steps). R_f = 0.4 (5% EtOAc/hexanes); $[\alpha]_D^{24}$ = –60.2 (*c* 0.16, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.39 (t, *J* = 7.8 Hz, 1H), 3.75 (s, 3H), 2.72 (s, 1H), 2.59 (t, *J* = 7.8 Hz, 2H), 2.09 (q, *J* = 7.8 Hz, 2H), 1.66 (m, 2H), 1.43 (m, 4H), 1.35-1.28 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.8, 149.3, 138.8, 118.1, 88.4, 64.7, 52.4, 32.9, 31.5, 29.2, 29.2, 28.9, 28.9, 28.7,

27.7, 27.4, 20.3; IR (neat): ν_{max} 2925, 2854, 2227, 1744, 1731, 1437, 1272, 1202 cm^{-1}; HRMS (ESI): calcd for $C_{17}H_{24}Br_2NO_2$ $[M+H]^+$ 432.0168, found 432.0176.

4.32. *(R)-(Z)-Antazirine (ent-**5**):* To a solution of compound **33** (60 mg, 0.14 mmol) in dry hexane (6 mL) was added catalytic amount of Lindlar catalyst (24 mg) and evacuated and purged with H_2 and cooled to 0 °C. The reaction mixture was stirred at 0 °C for 2 h under hydrogen atmosphere. The reaction mixture was then filtered through a pad of celite using hexane. The solvent was concentrated under reduced pressure to afford crude which was purified by column chromatography (10% EtOAc/hexanes) to give (*R*)-(*Z*)-antazirine (*ent*-**5**) as a pale yellow foam (50 mg, 82% yield, 51% ee (chiral HPLC, ciral column-ODH, hexane/isopropanol 80:20)). R_f = 0.4 (5% EtOAc/hexane); $[\alpha]_D^{24}$ = –63.6 (*c* 0.64, *n*-hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.57 (dt, *J* = 10.7, 7.7 Hz, 1H), 6.42 (d, *J* = 10.7 Hz, 1H), 6.38 (t, *J* = 7.3 Hz, 1H), 3.73 (s, 3H), 2.62 (s, 1H), 2.50 (m, 2H), 2.08 (q, *J* = 7.3 Hz, 2H), 1.48-1.37 (m, 4H), 1.33-1.24 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.2, 154.2, 152.5, 138.8, 111.2, 88.5, 52.2, 33.0, 29.7, 29.3, 29.2, 29.2, 29.2, 29.1, 28.9, 28.8, 27.7; IR (neat): ν_{max} 2926, 2853, 1762, 1730, 1618, 1436, 1269, 1196, 1030 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{26}Br_2NO_2$ $[M+H]^+$ 434.0324, found 434.0333.

Acknowledgments

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References and notes

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Supplementary Material

Supplementary data associated with this article can be found, in the online version, at

Supporting Information for

Total synthesis of motualevic acids A-F, (*E*) and (*Z*)-antazirines

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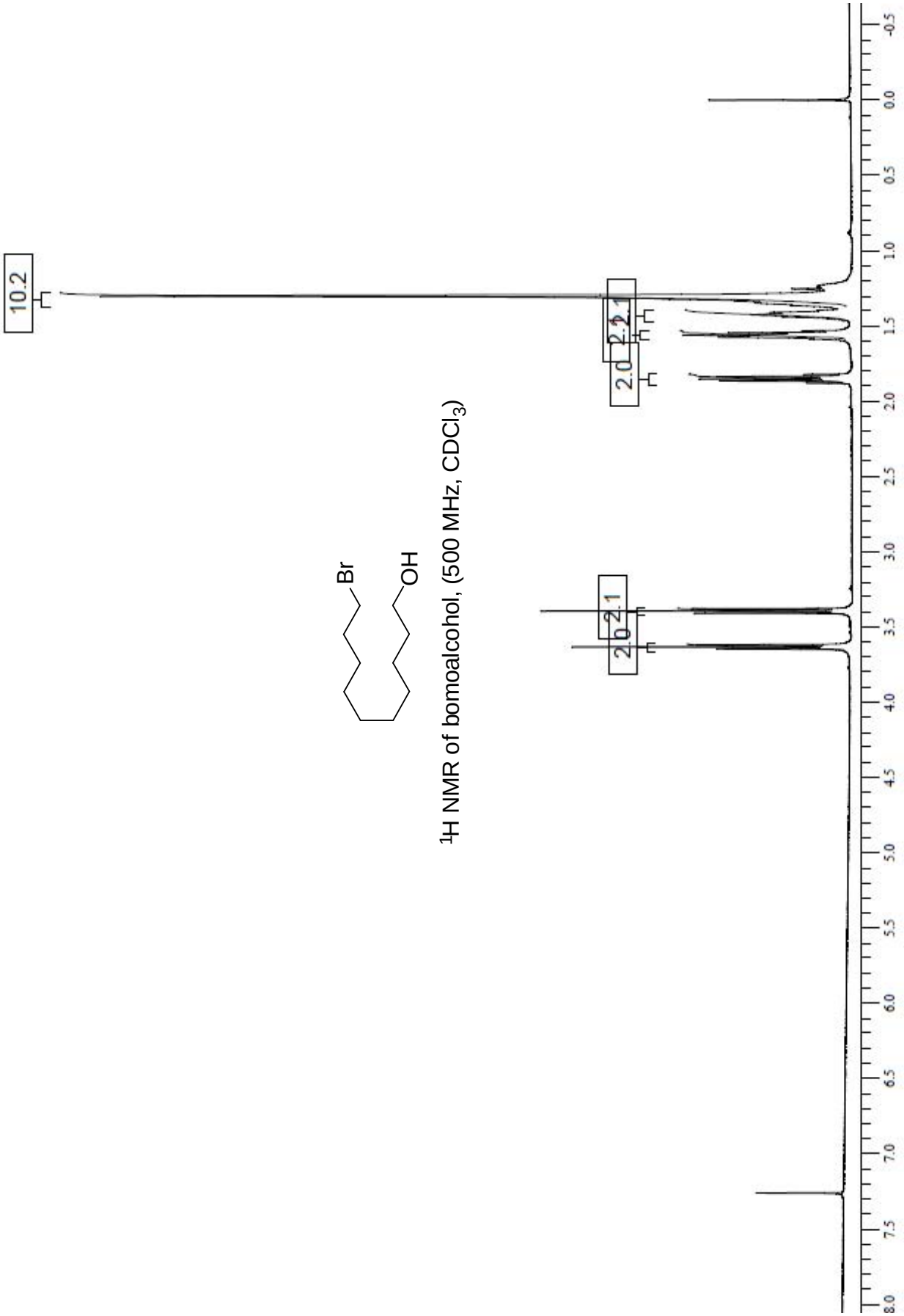

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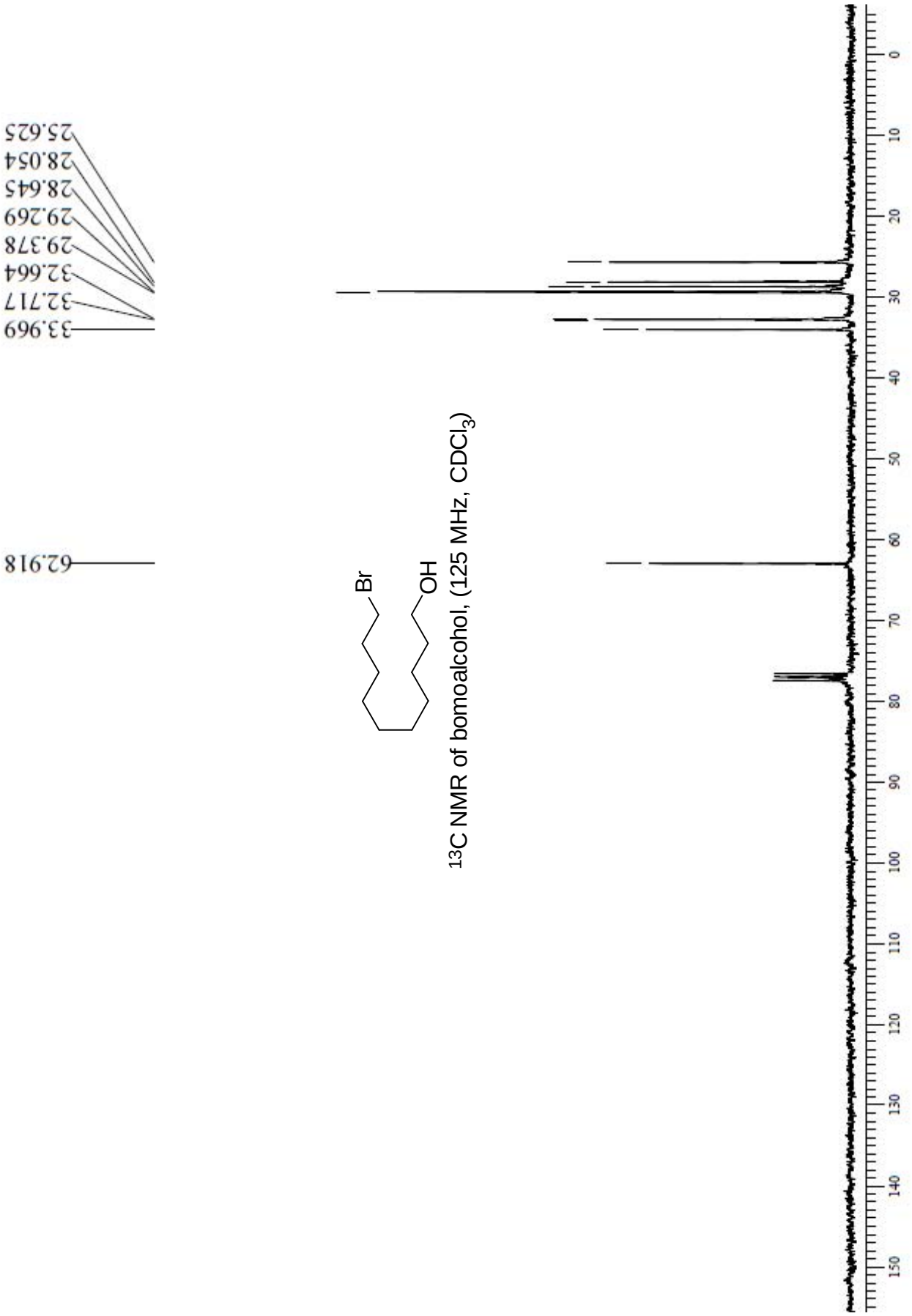
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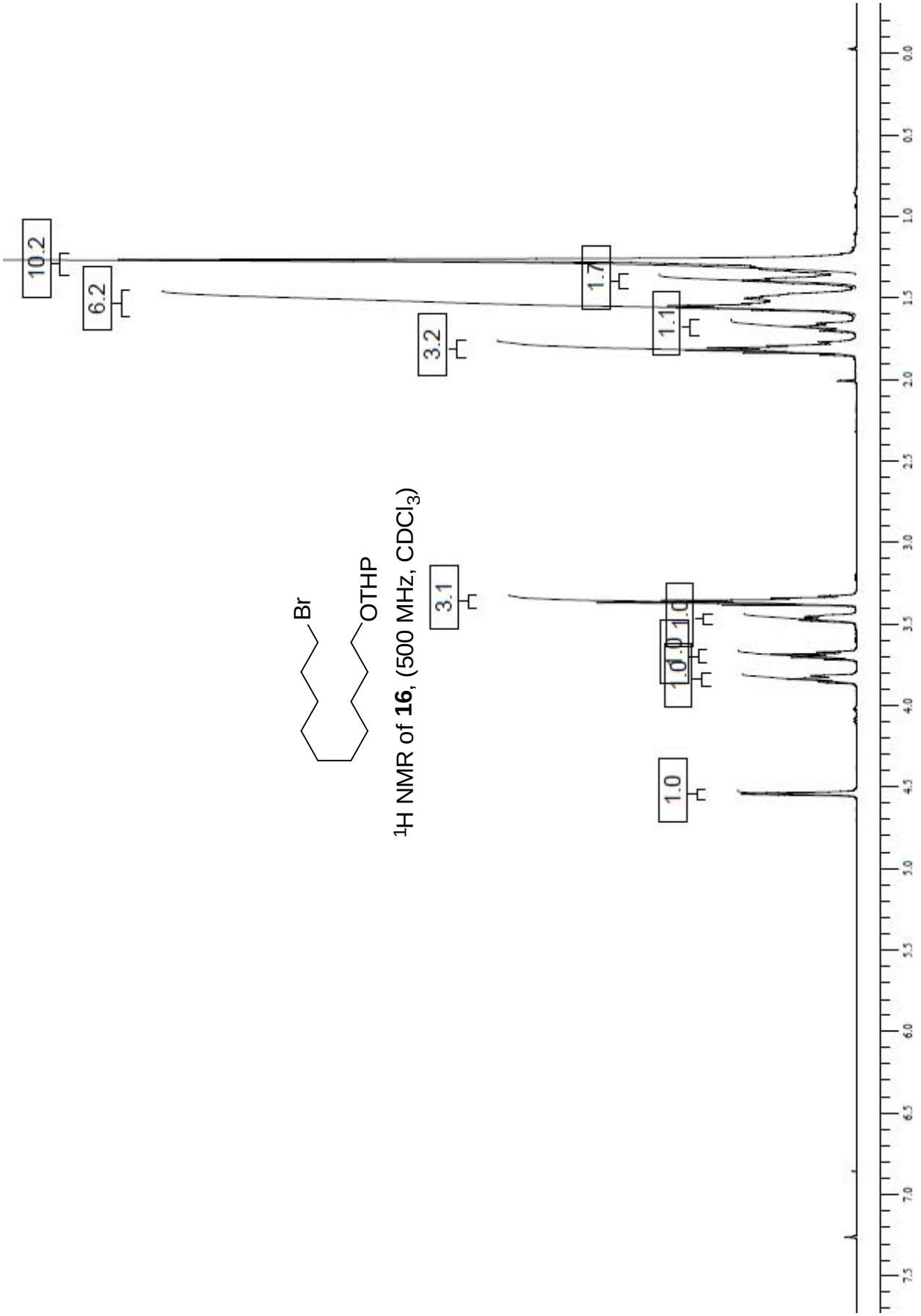

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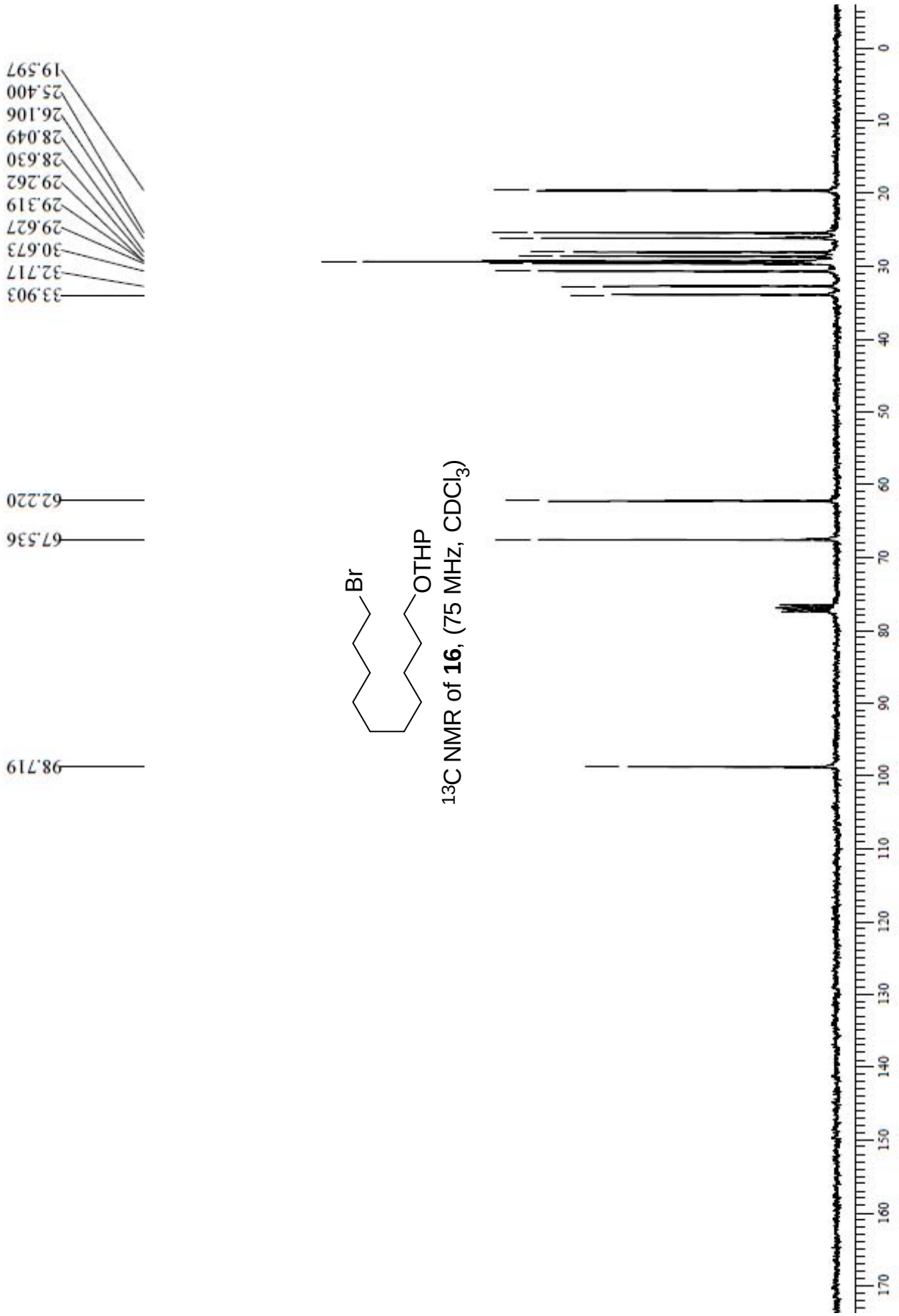
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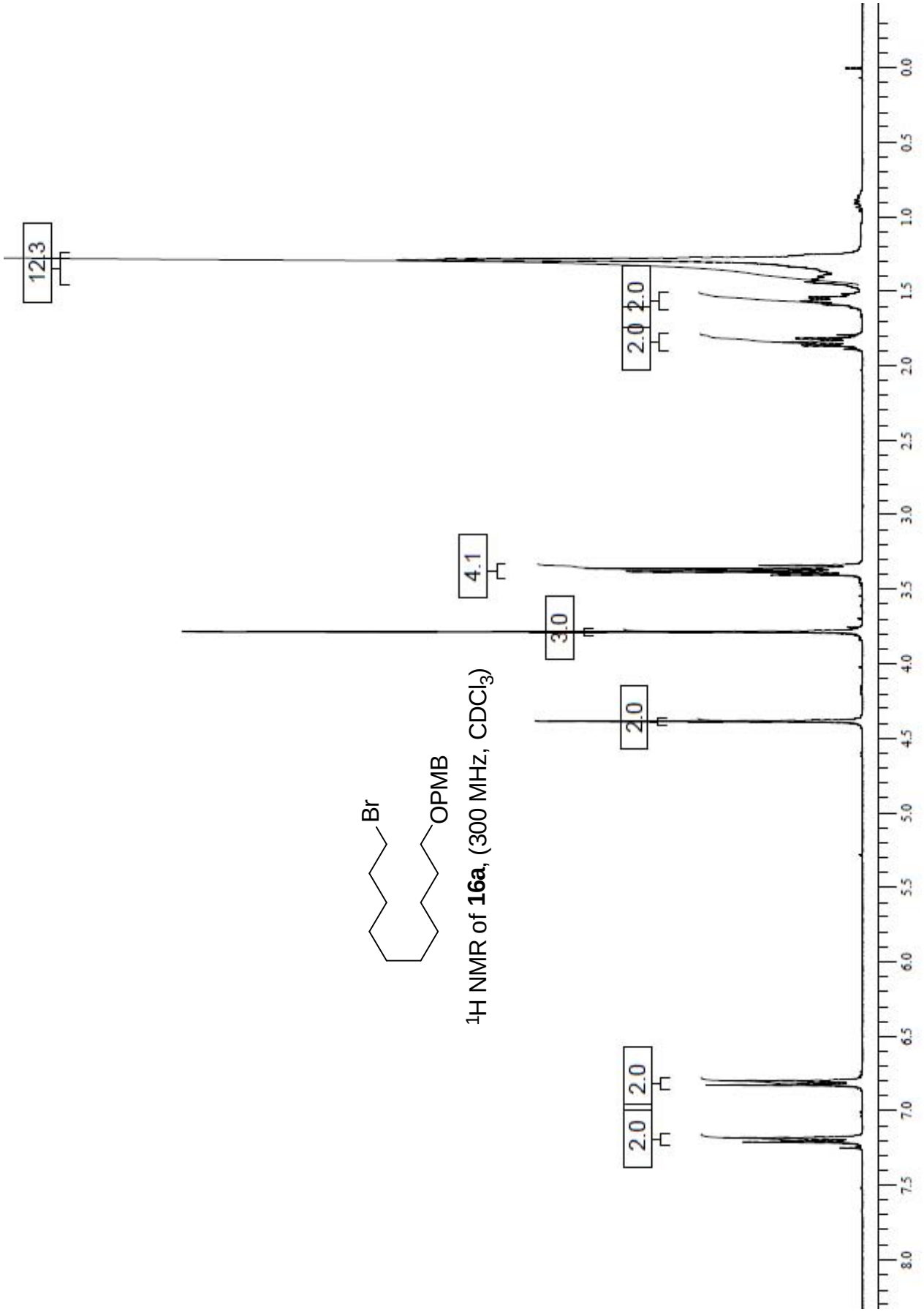

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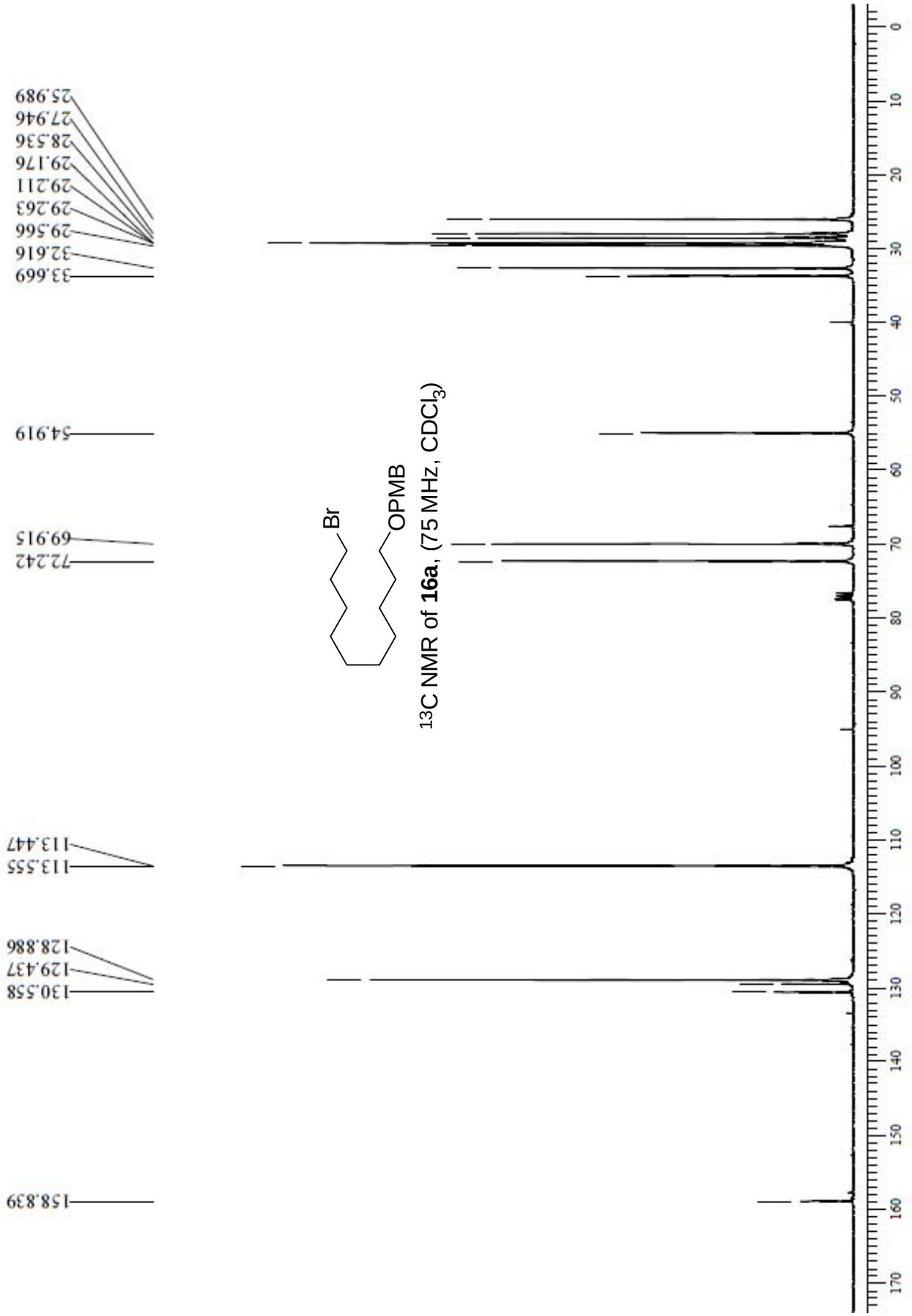
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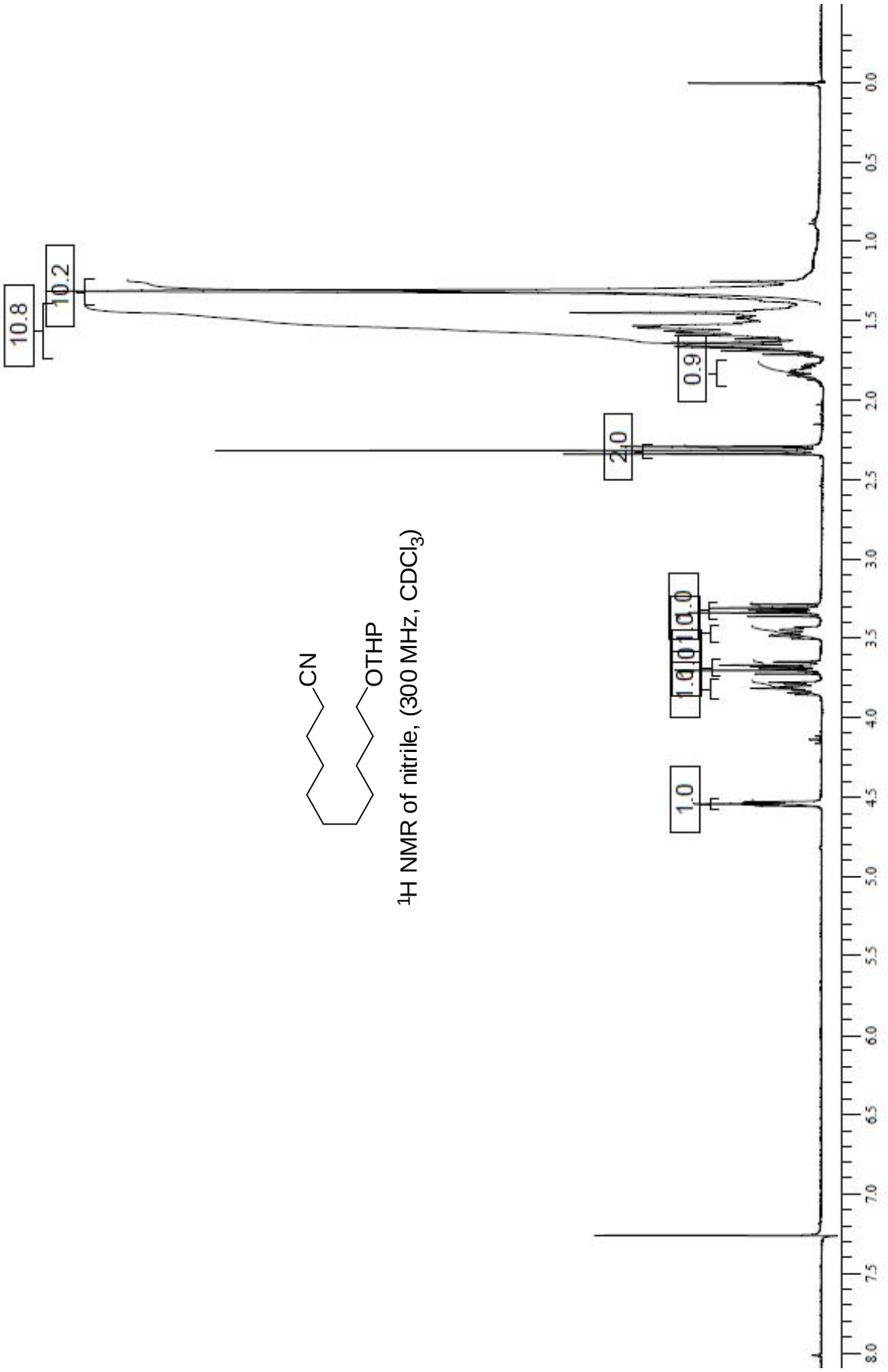

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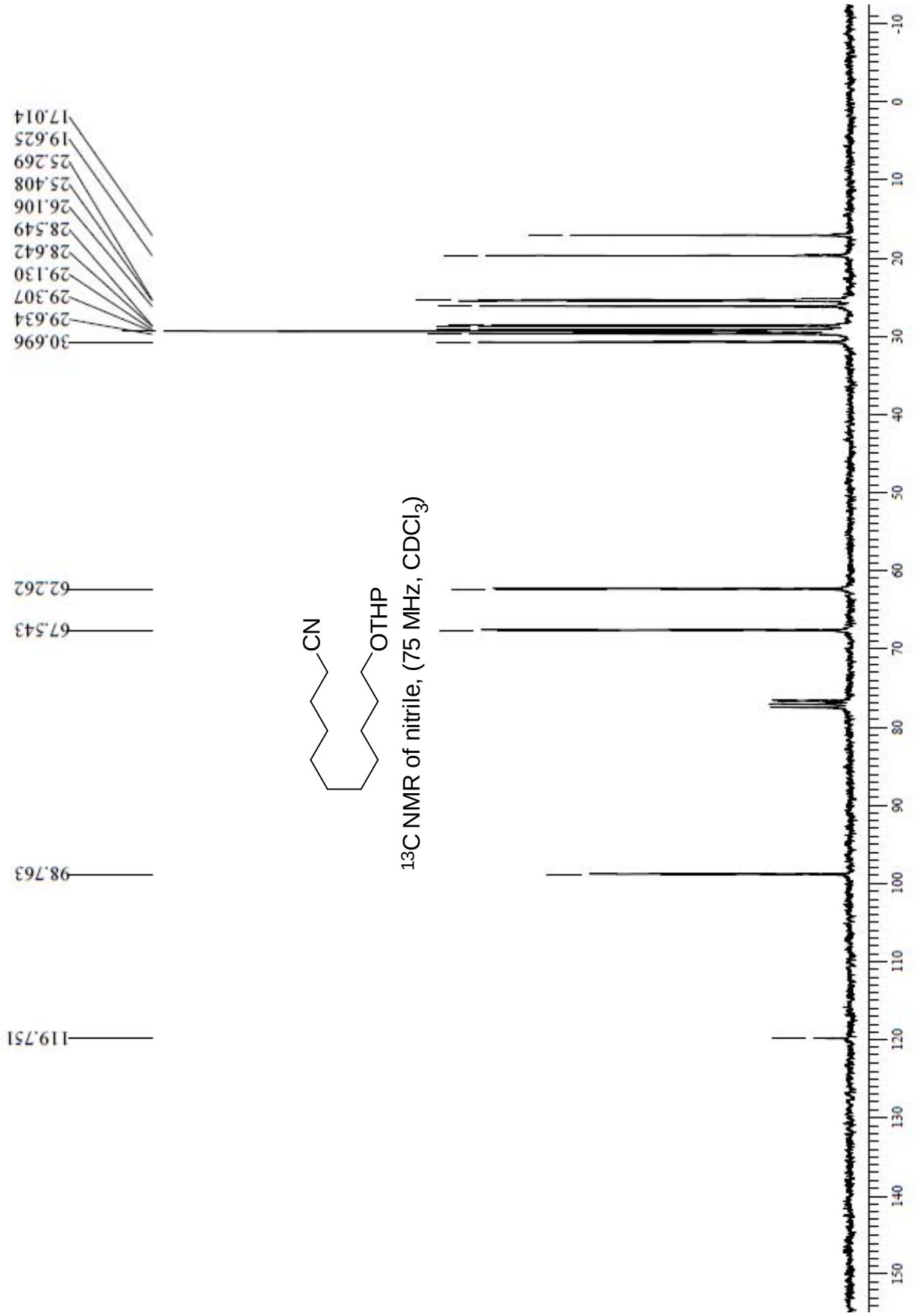
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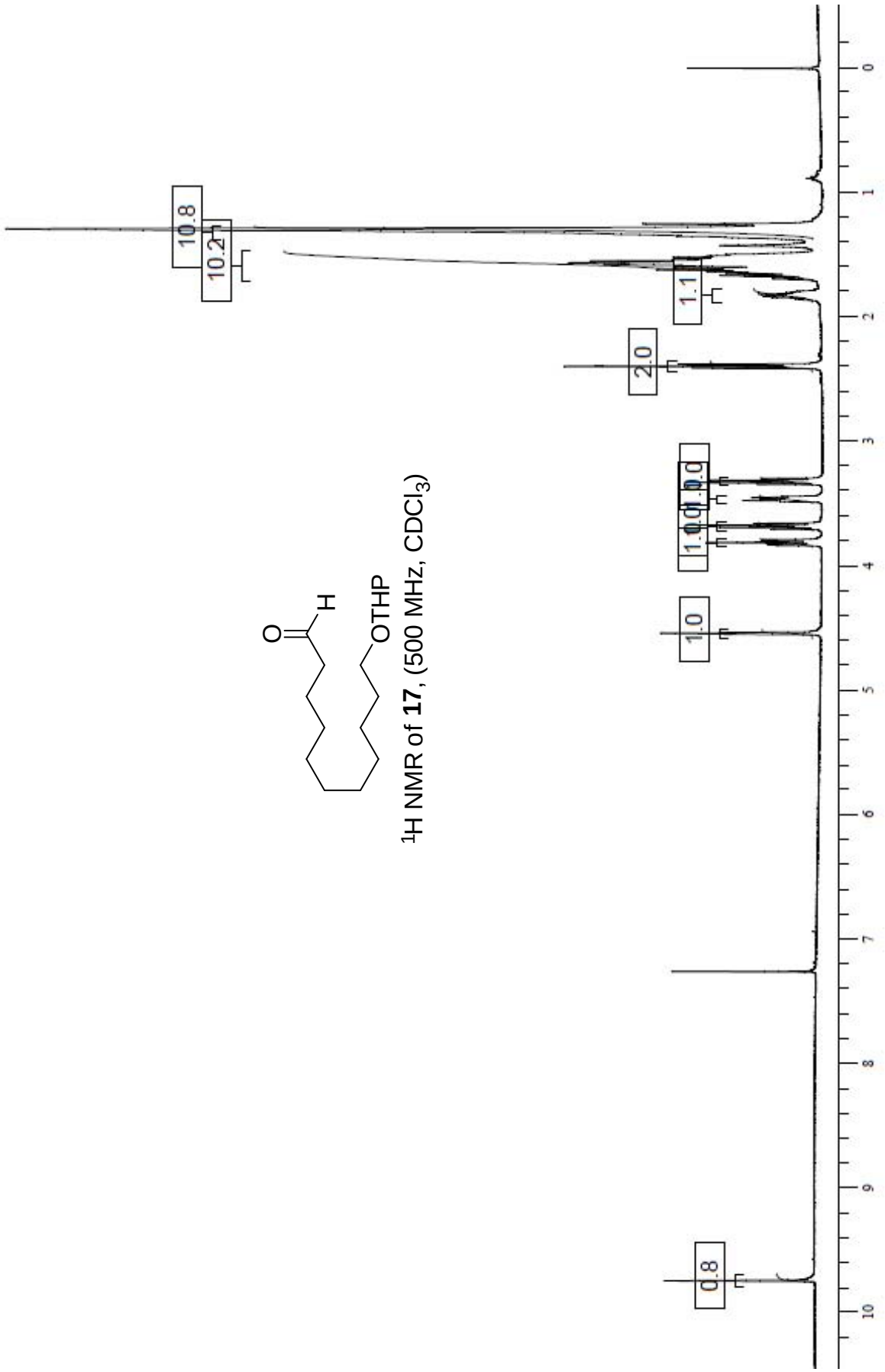

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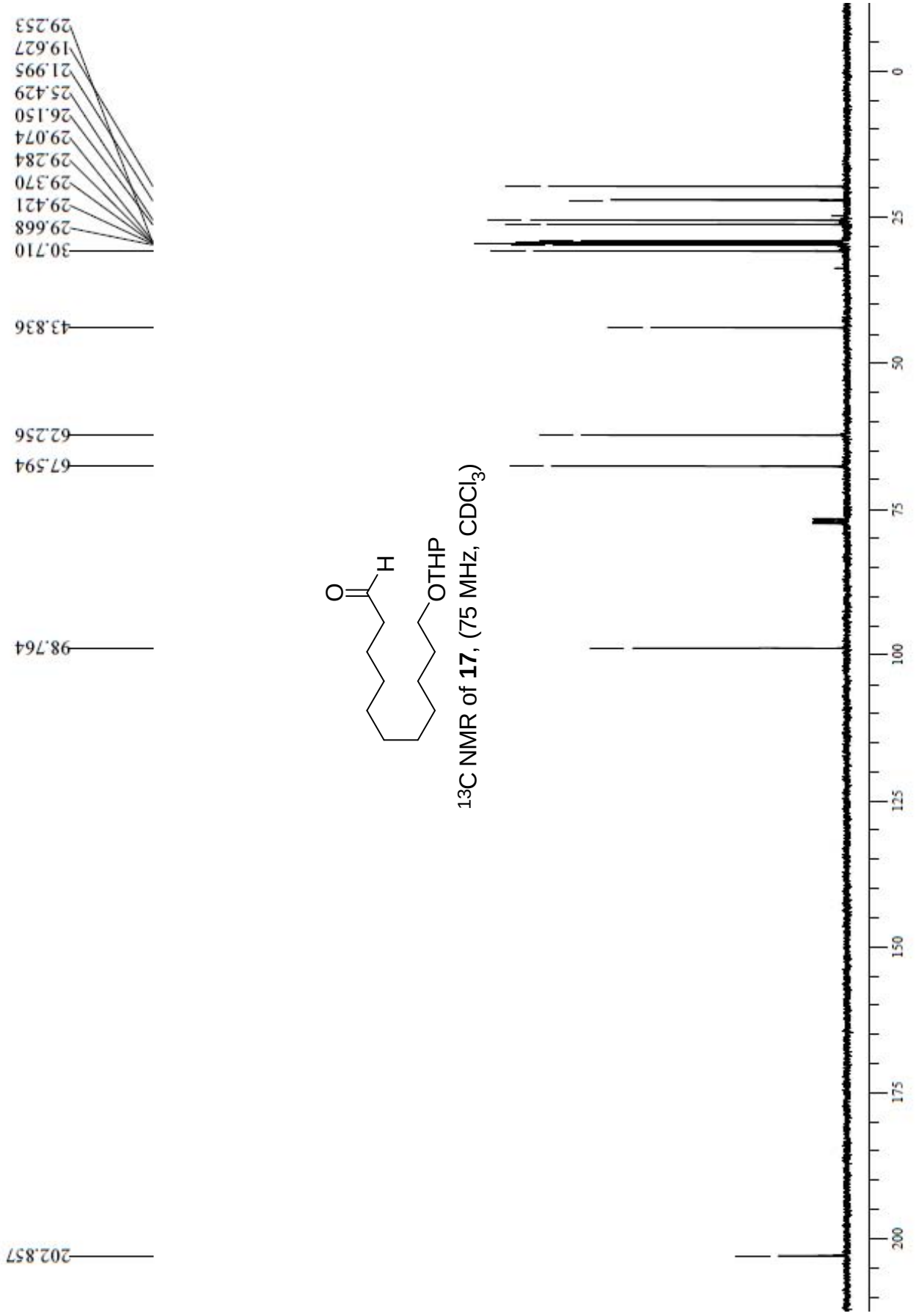

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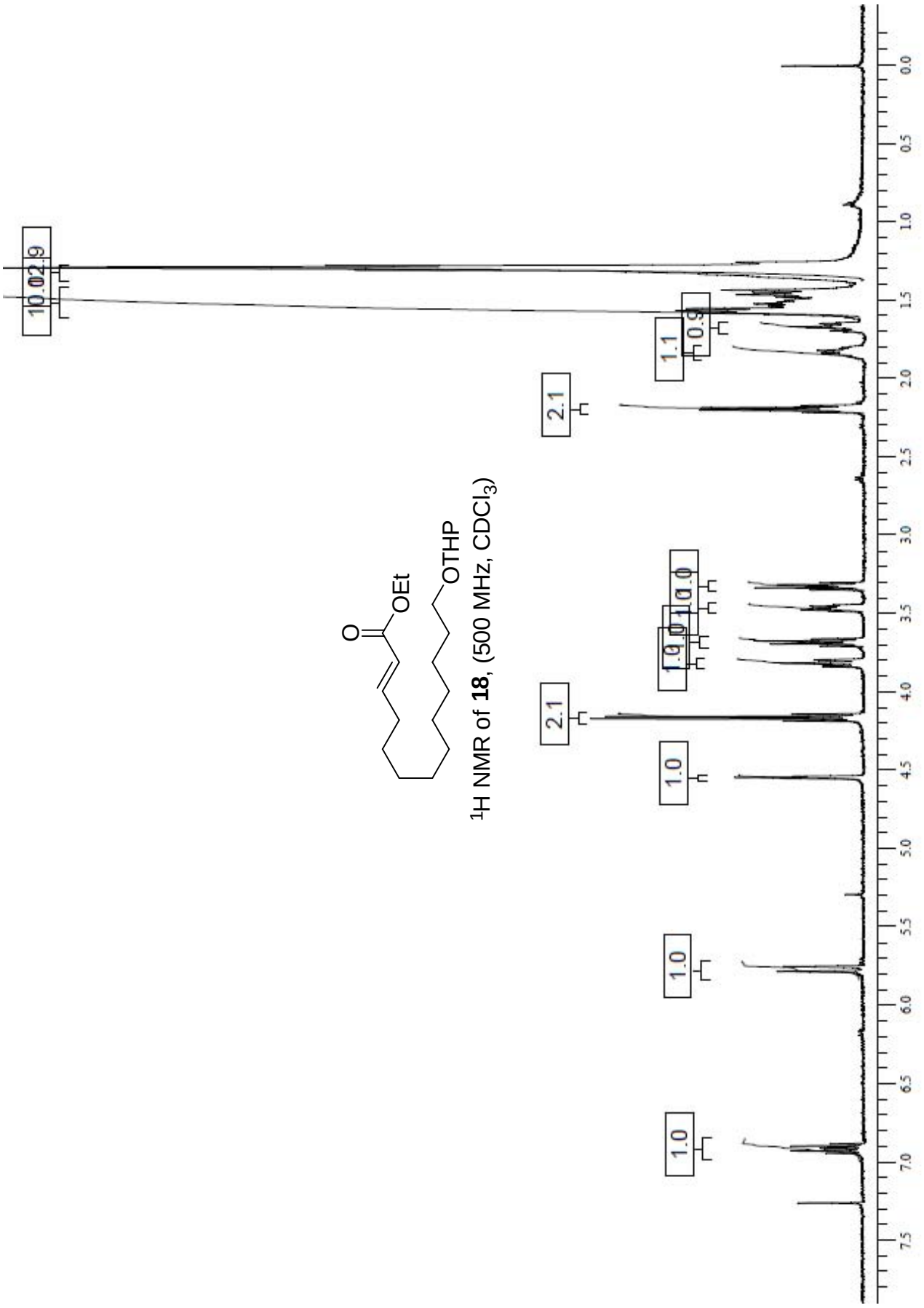

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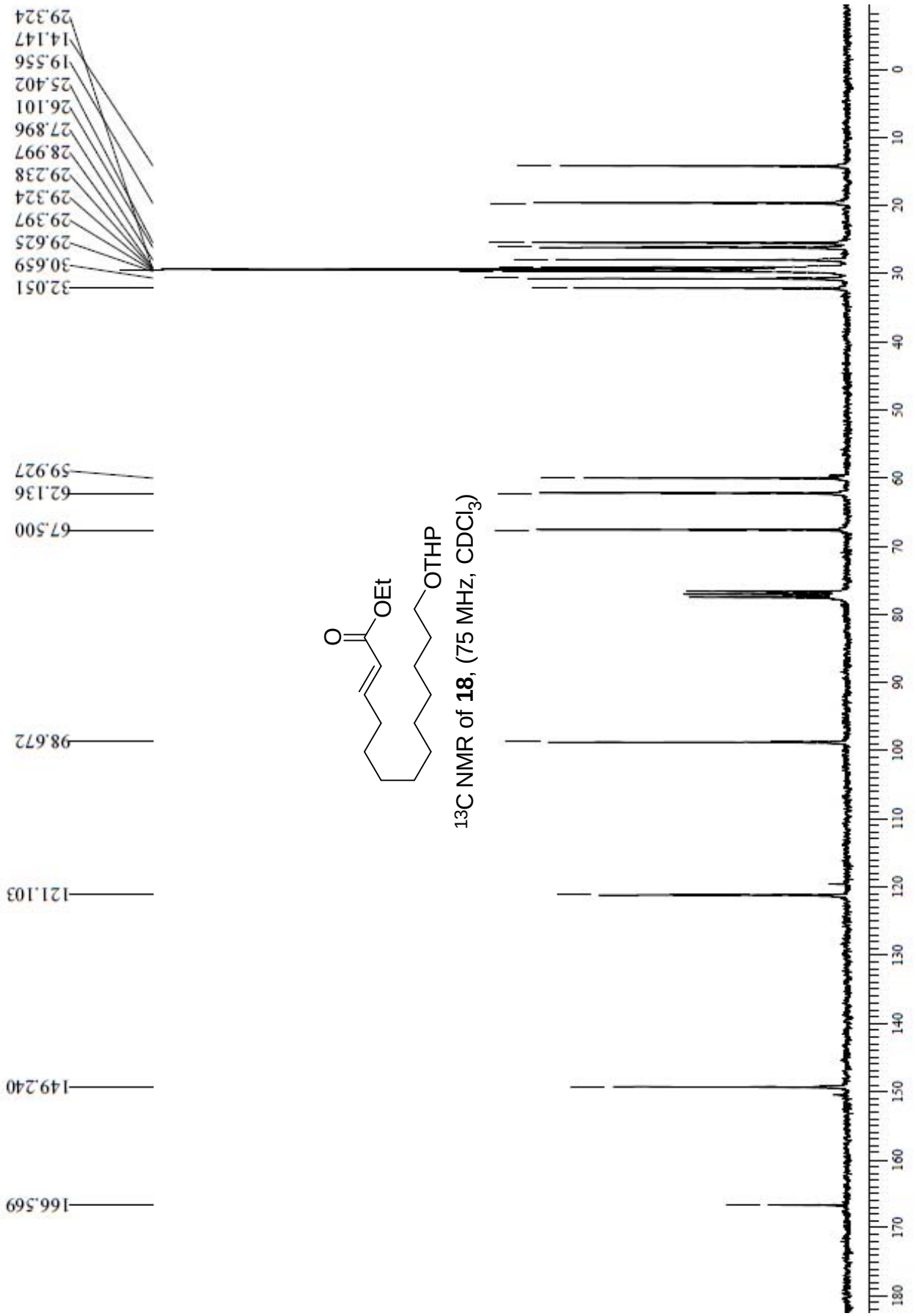
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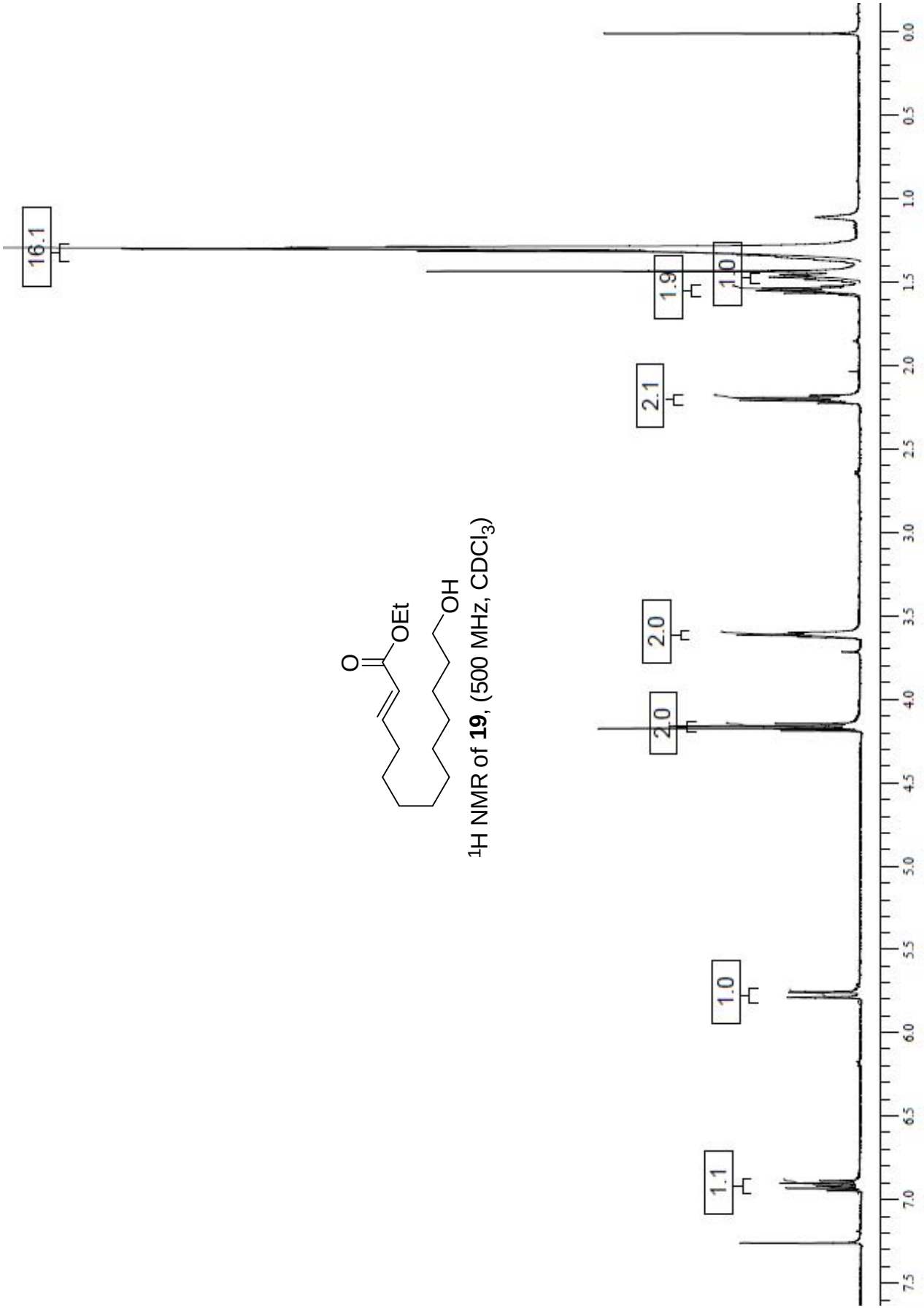

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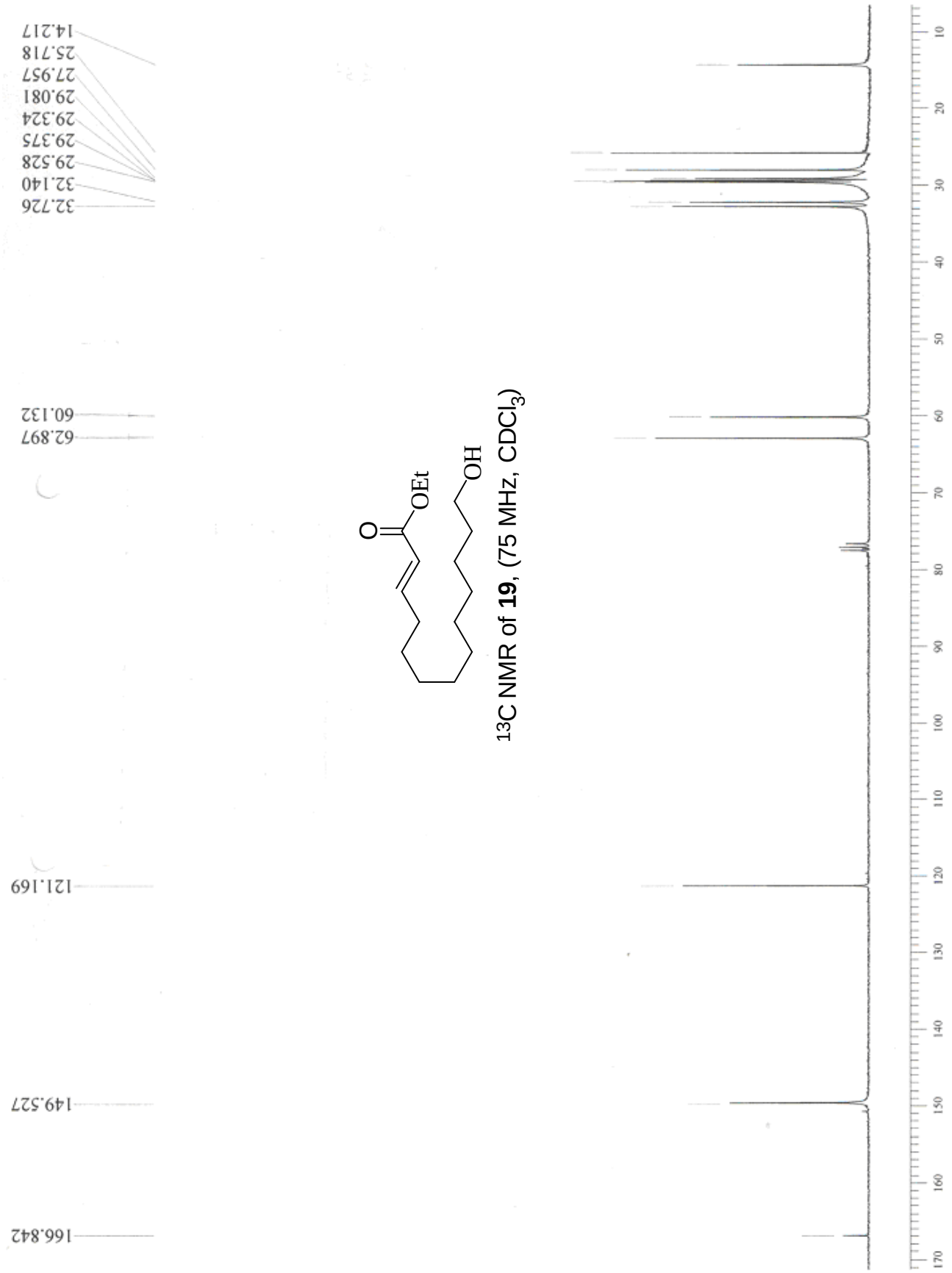

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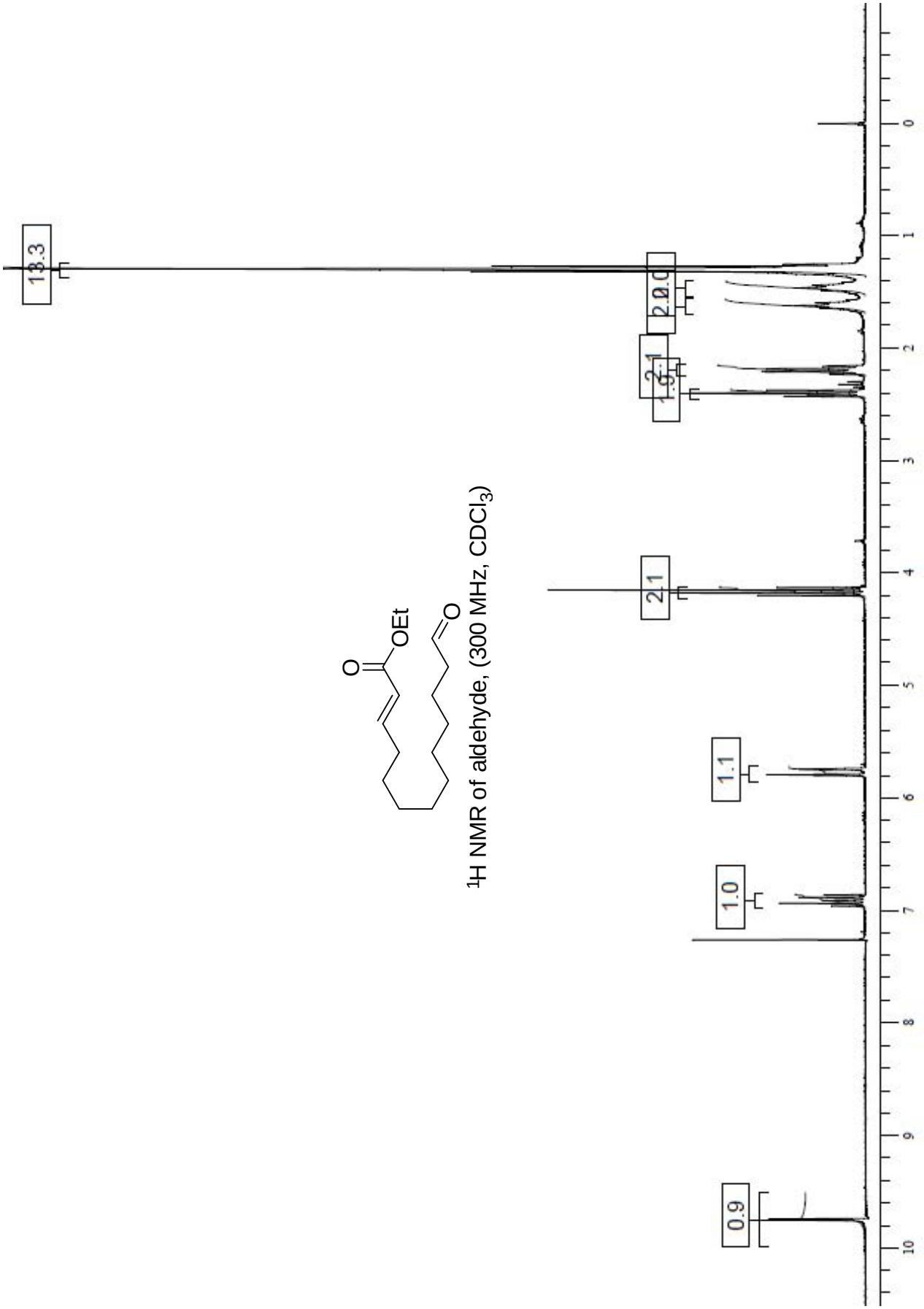

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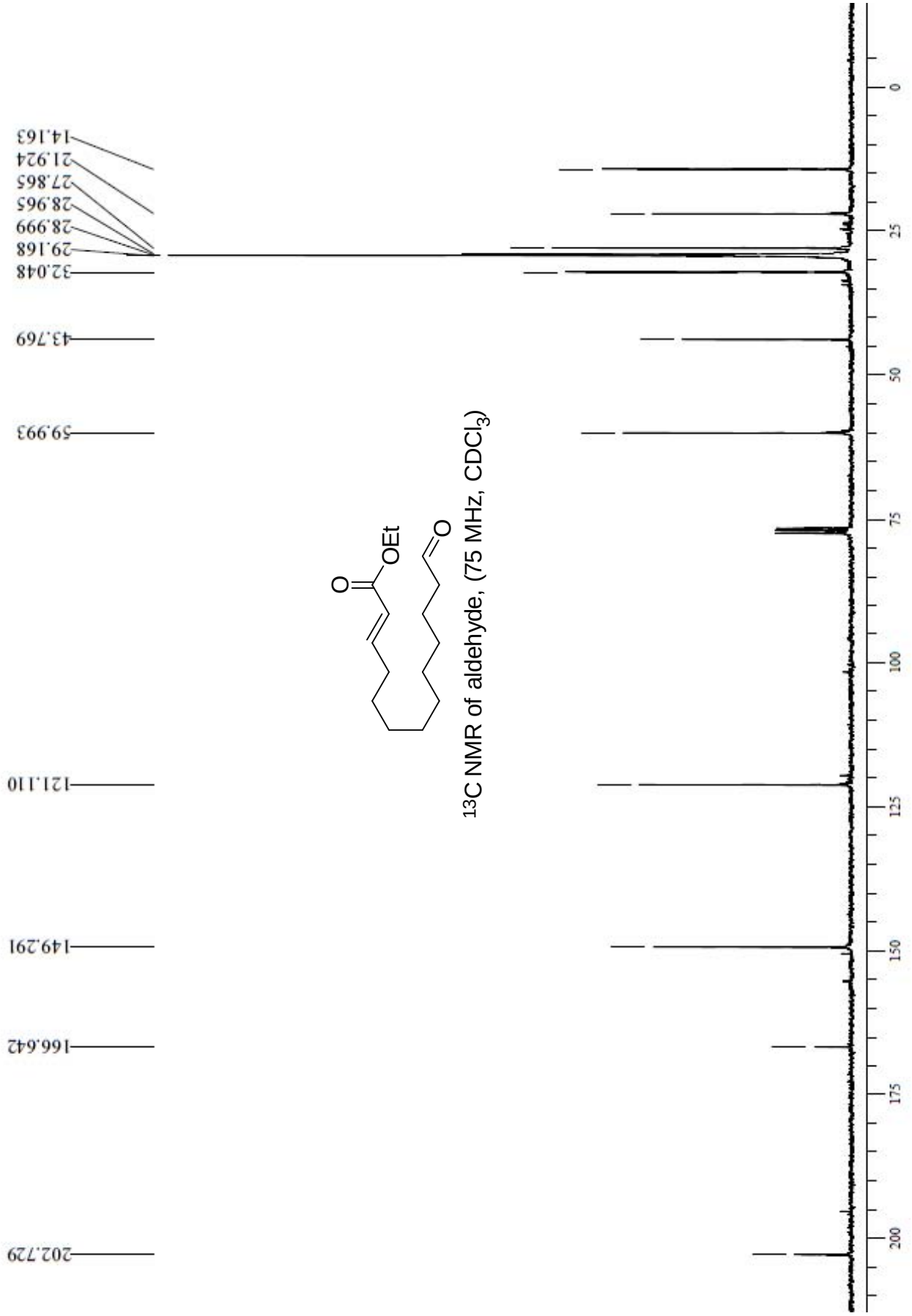
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100
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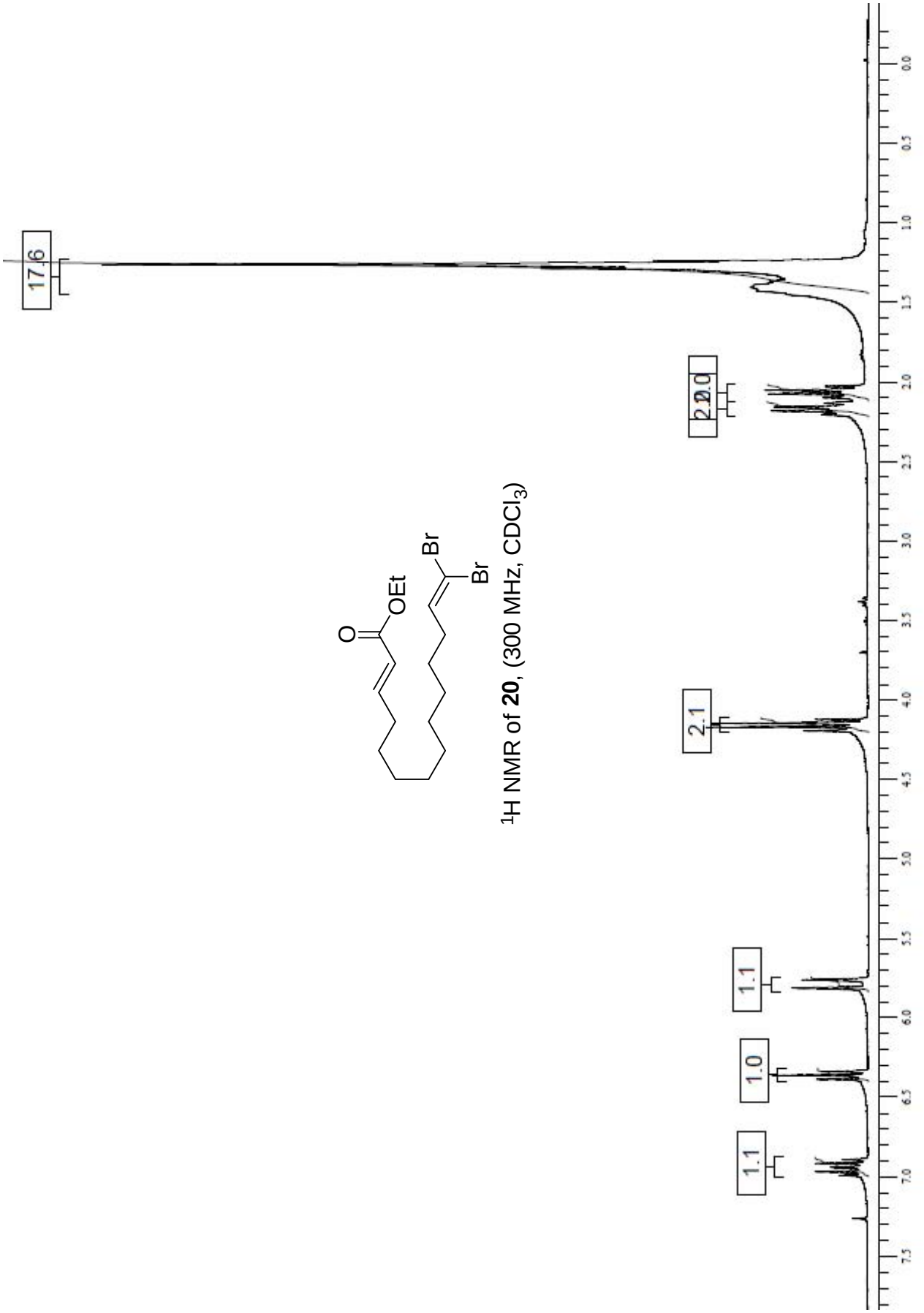
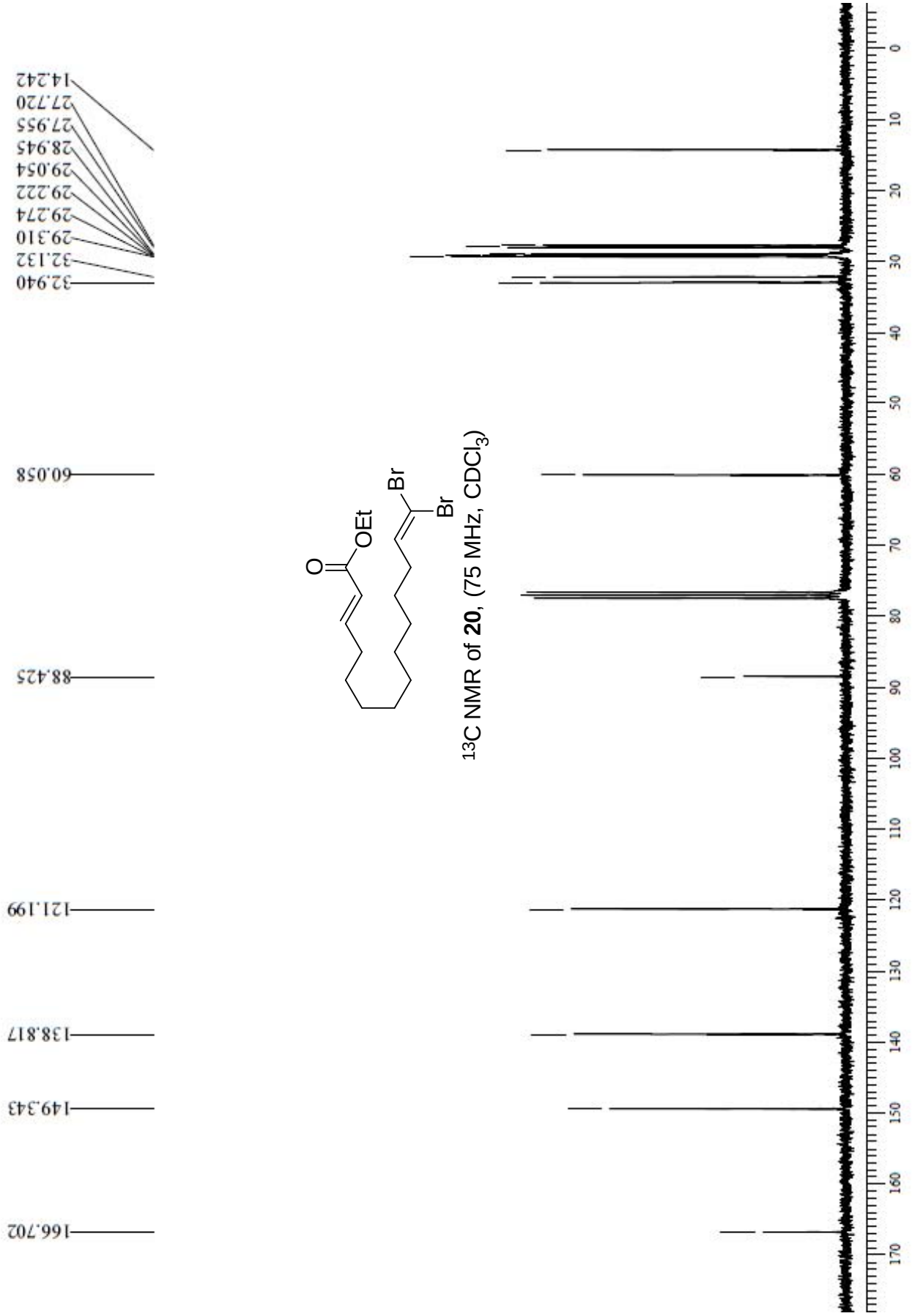
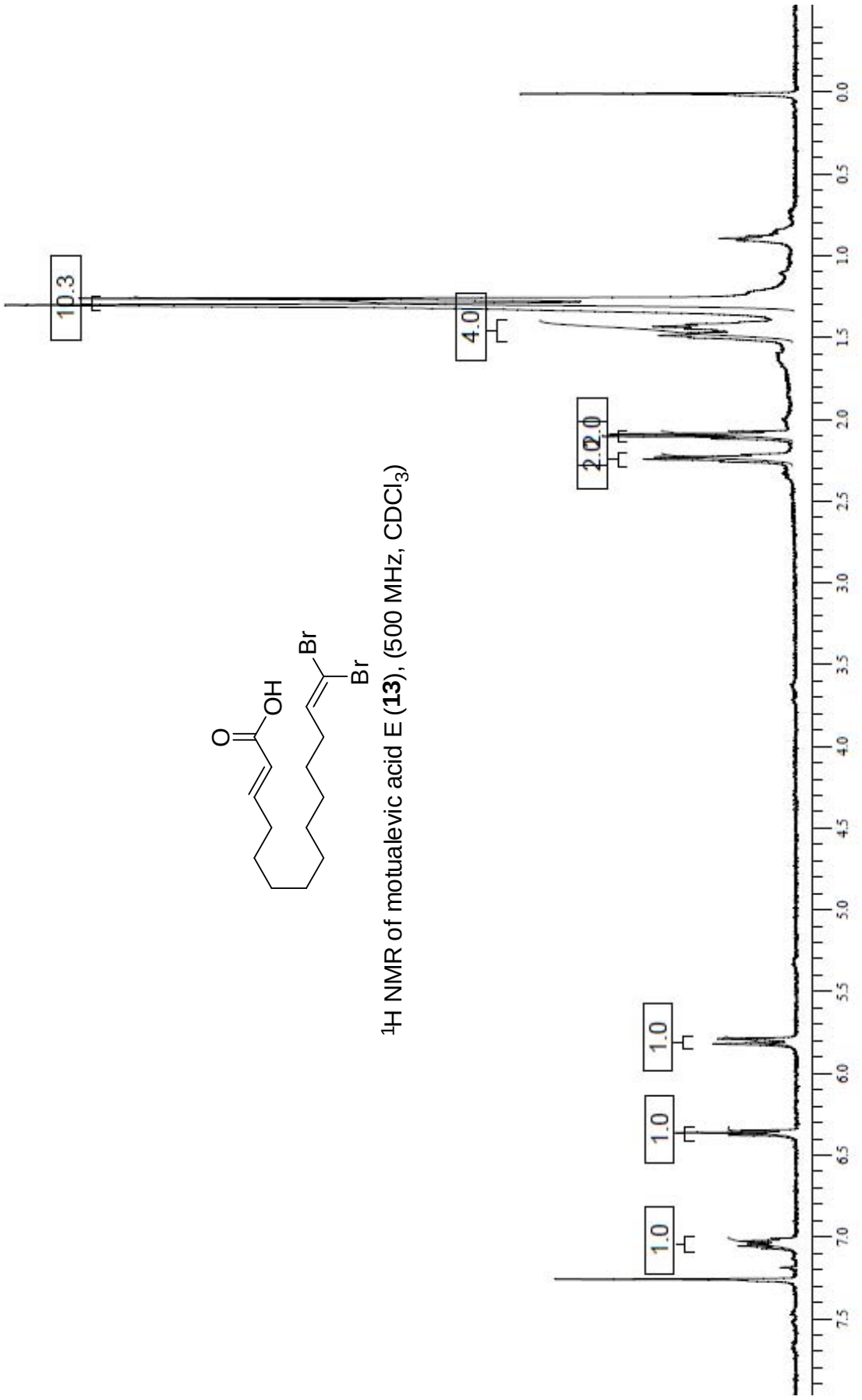
175
200

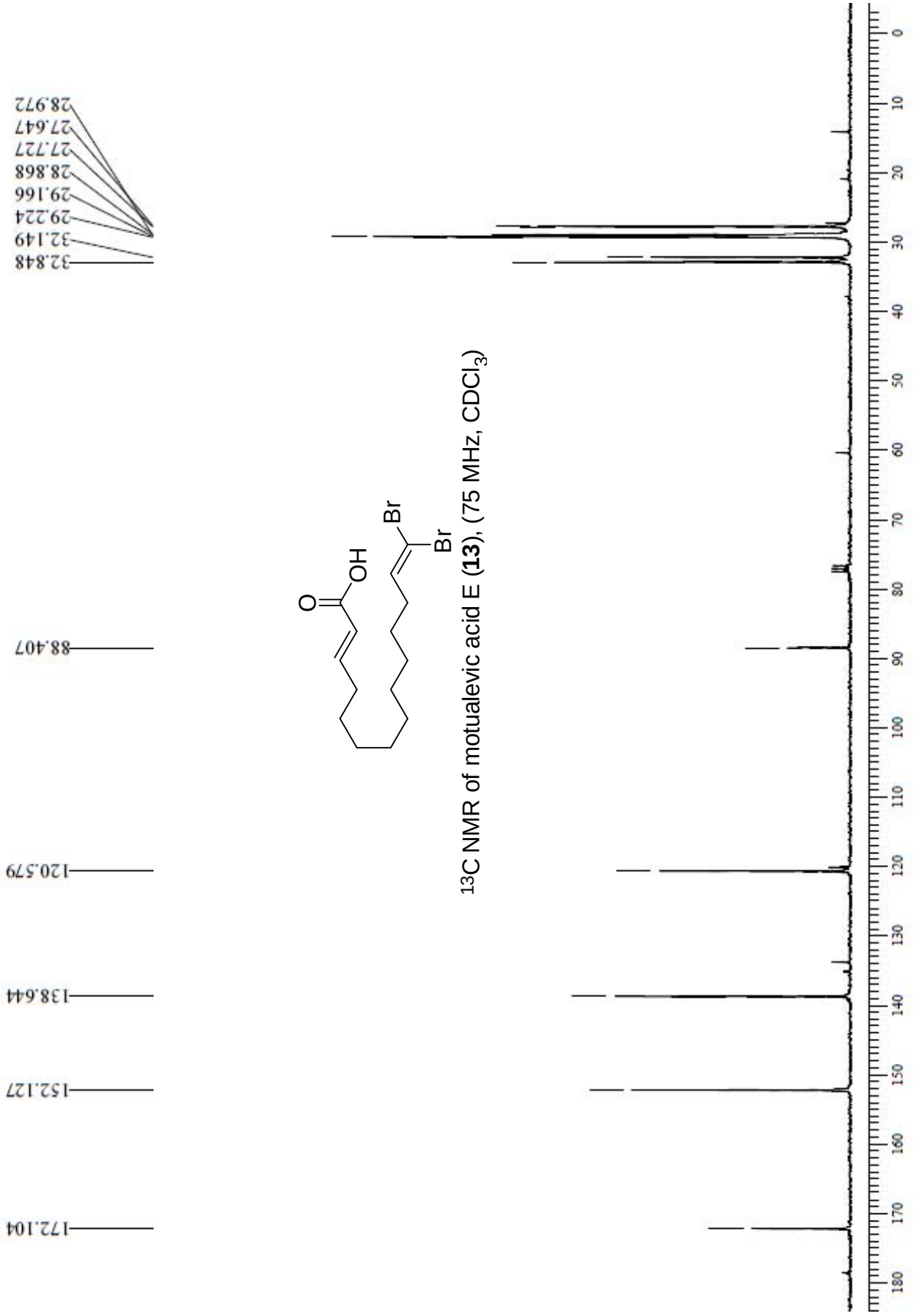


^{1}H NMR of **20**, (300 MHz, $CDCl_3$)

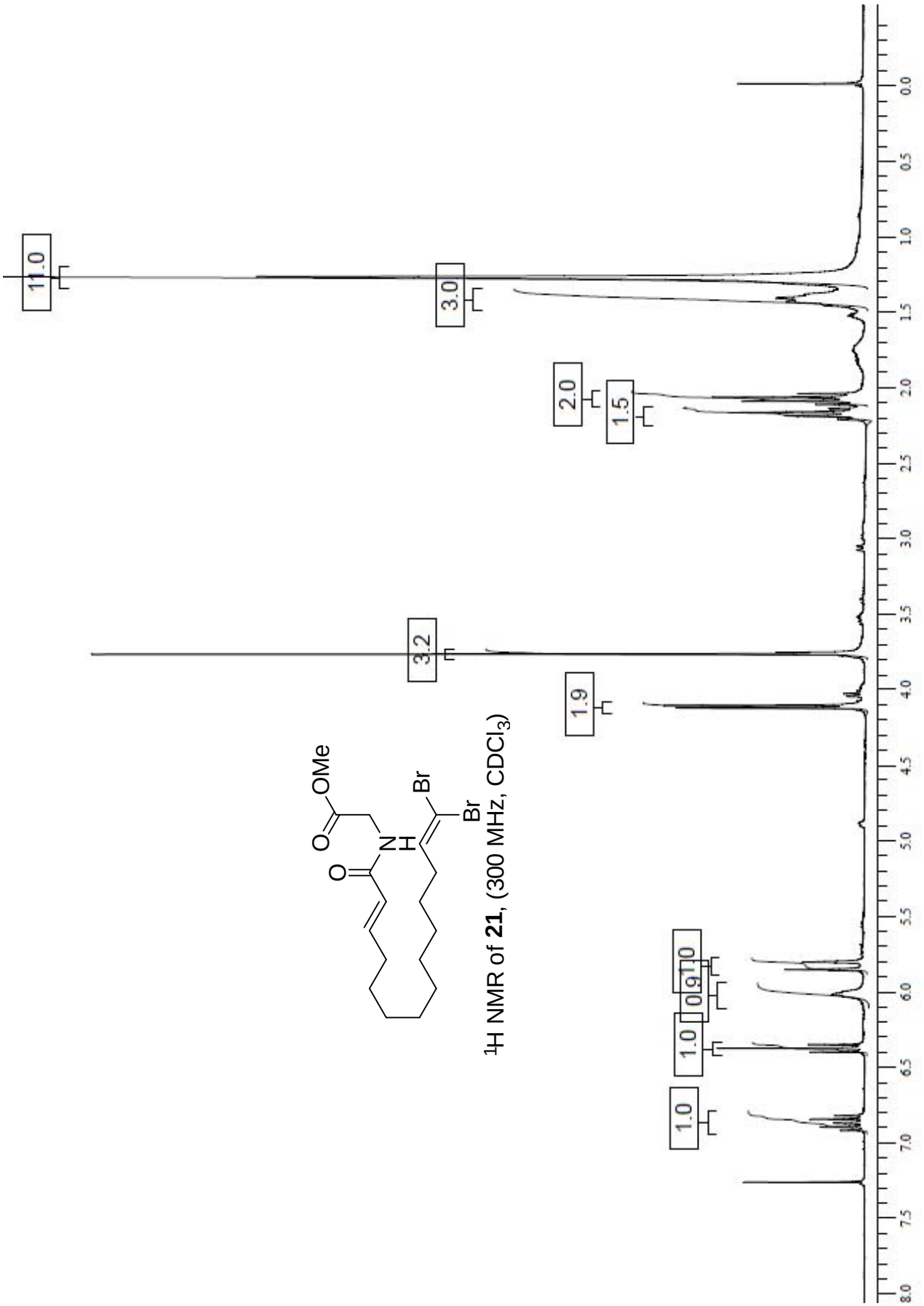

14.242
27.720
27.955
28.945
29.054
29.222
29.274
29.310
32.132
32.940
60.058
88.425
121.199
138.817
149.343
166.702
O
OEt
Br
Br
^{13}C NMR of **20**, (75 MHz, $CDCl_3$)



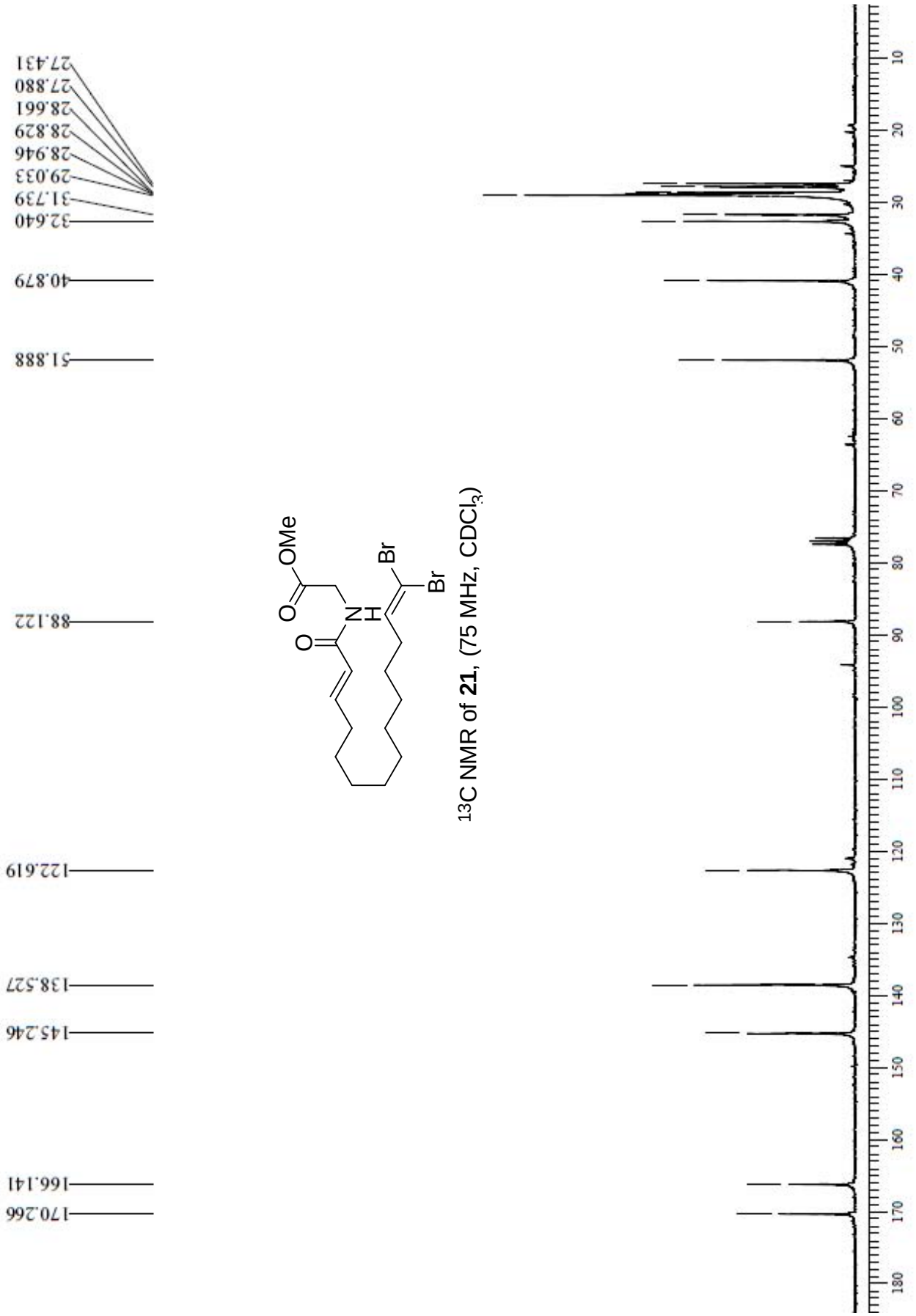
^{1}H NMR of motualevic acid E (**13**), (500 MHz, $CDCl_3$)



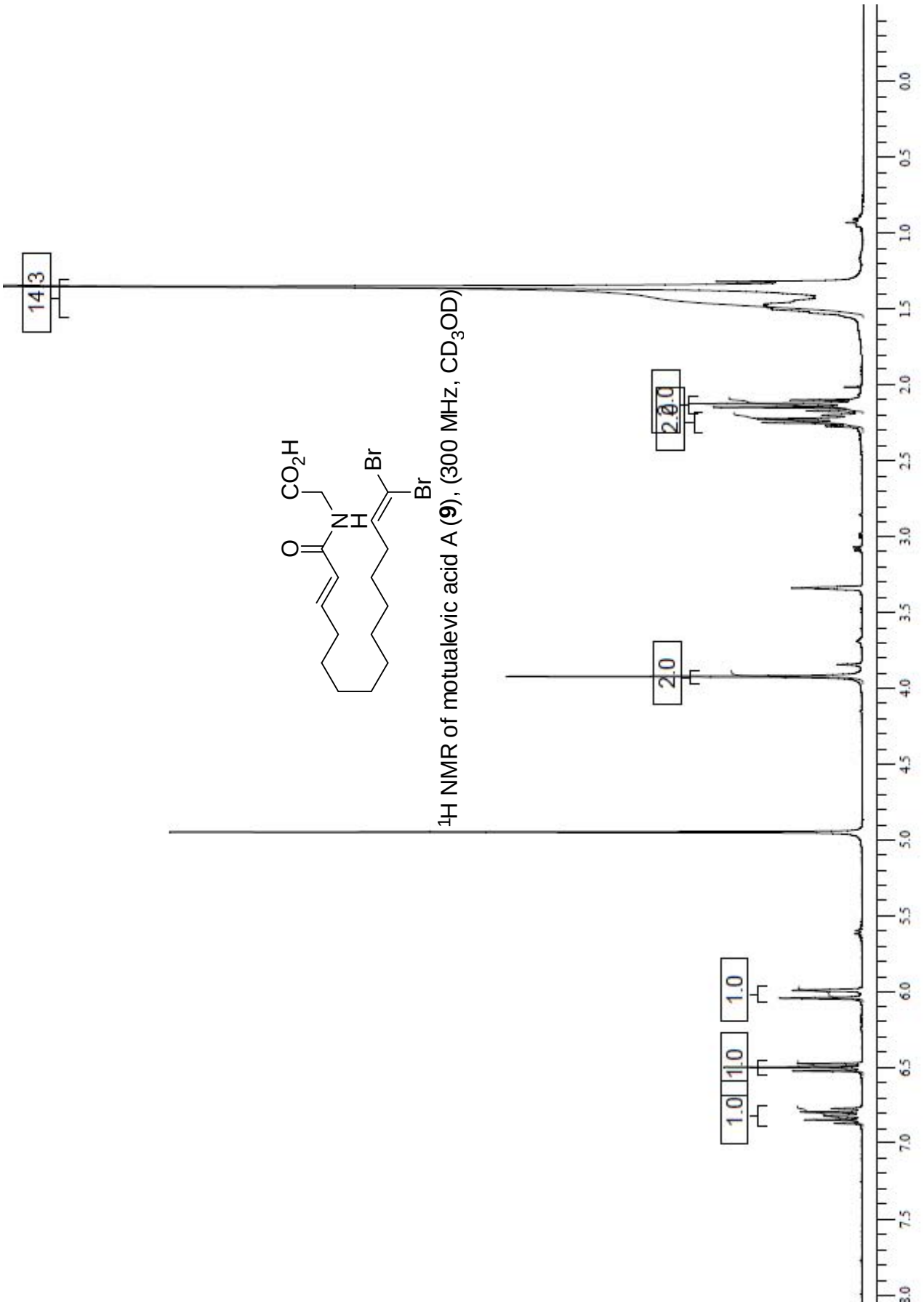
^{13}C NMR of motualevic acid E (**13**), (75 MHz, $CDCl_3$)



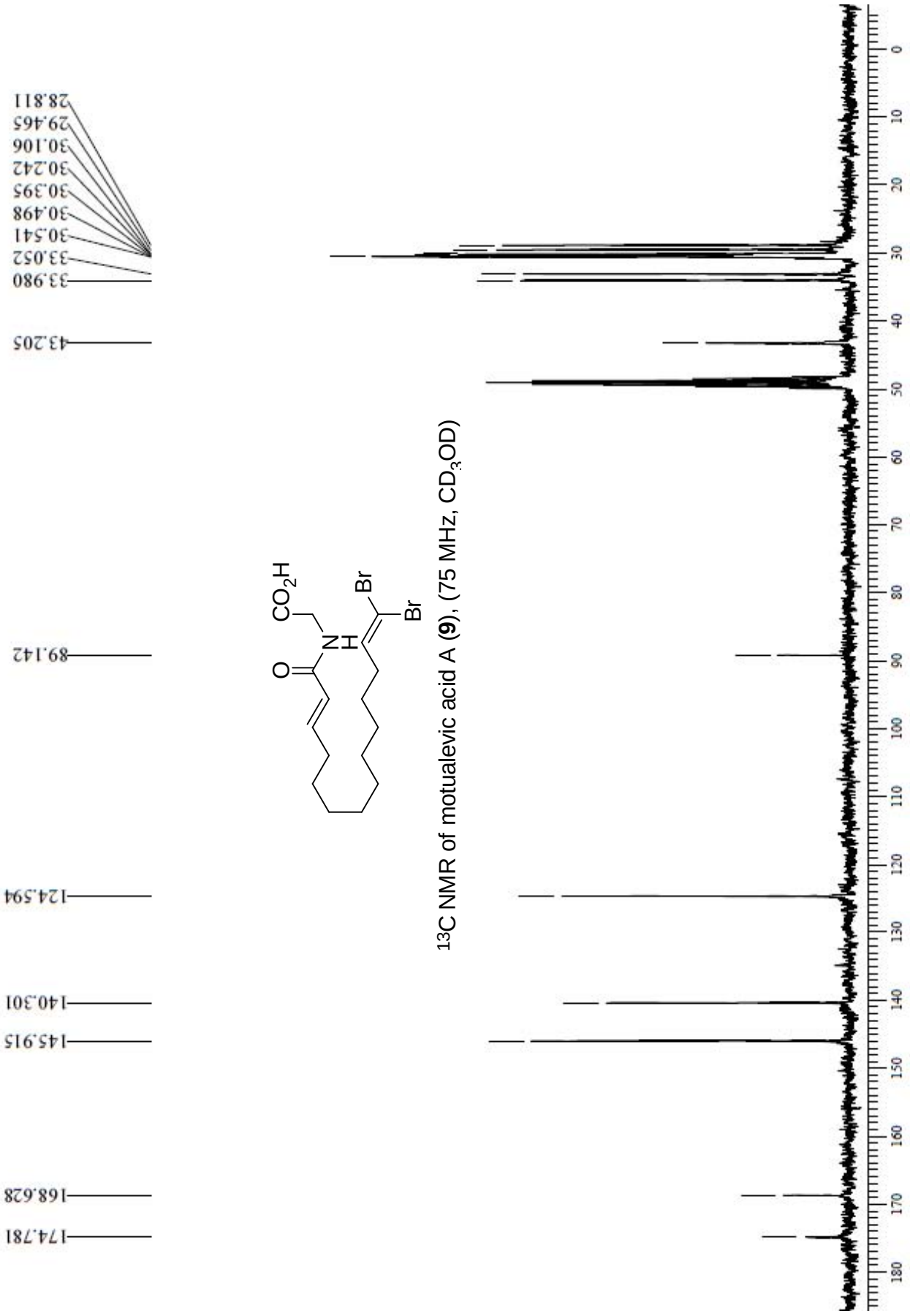
^{1}H NMR of **21**, (300 MHz, $CDCl_3$)



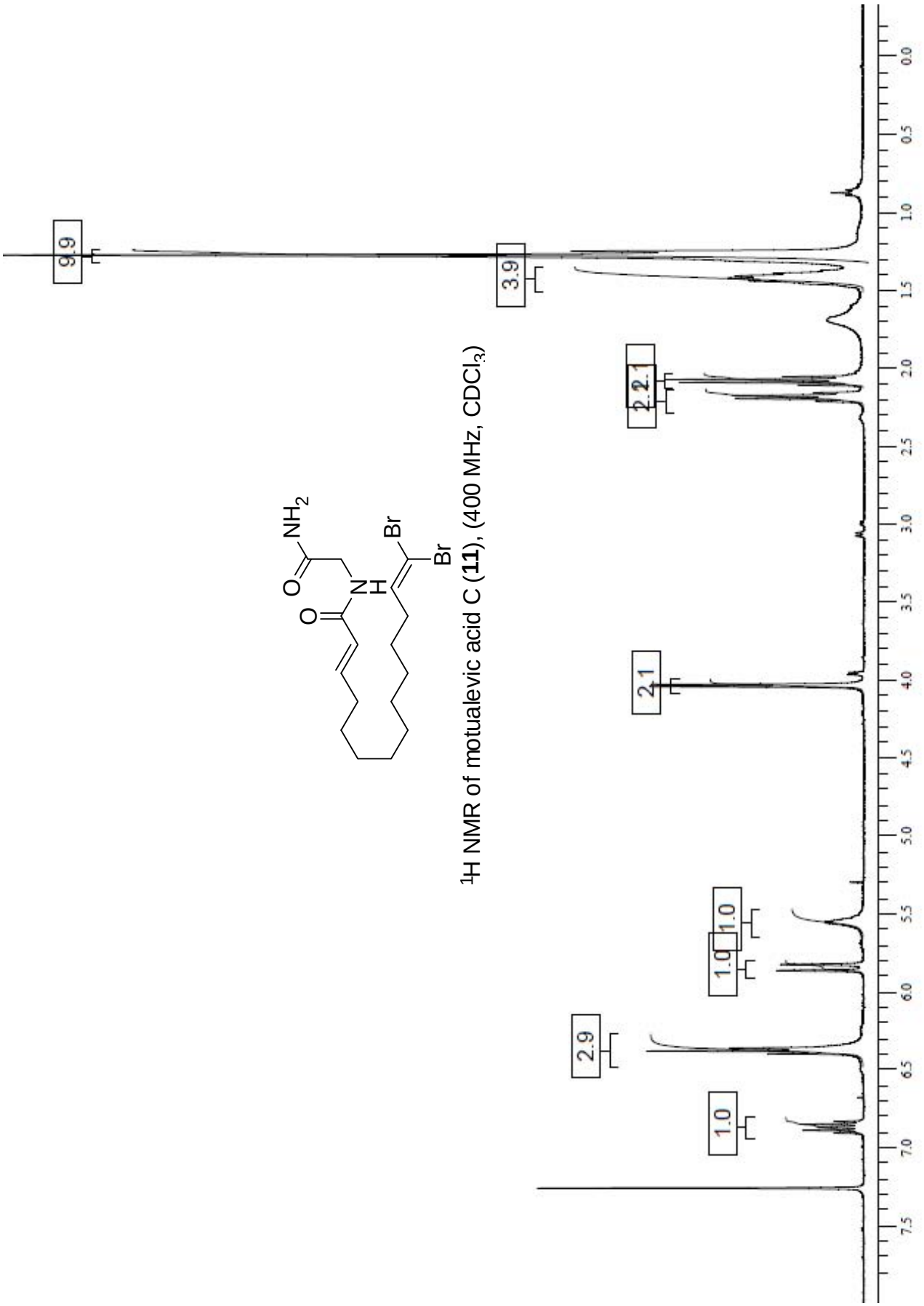
^{13}C NMR of **21**, (75 MHz, $CDCl_3$)



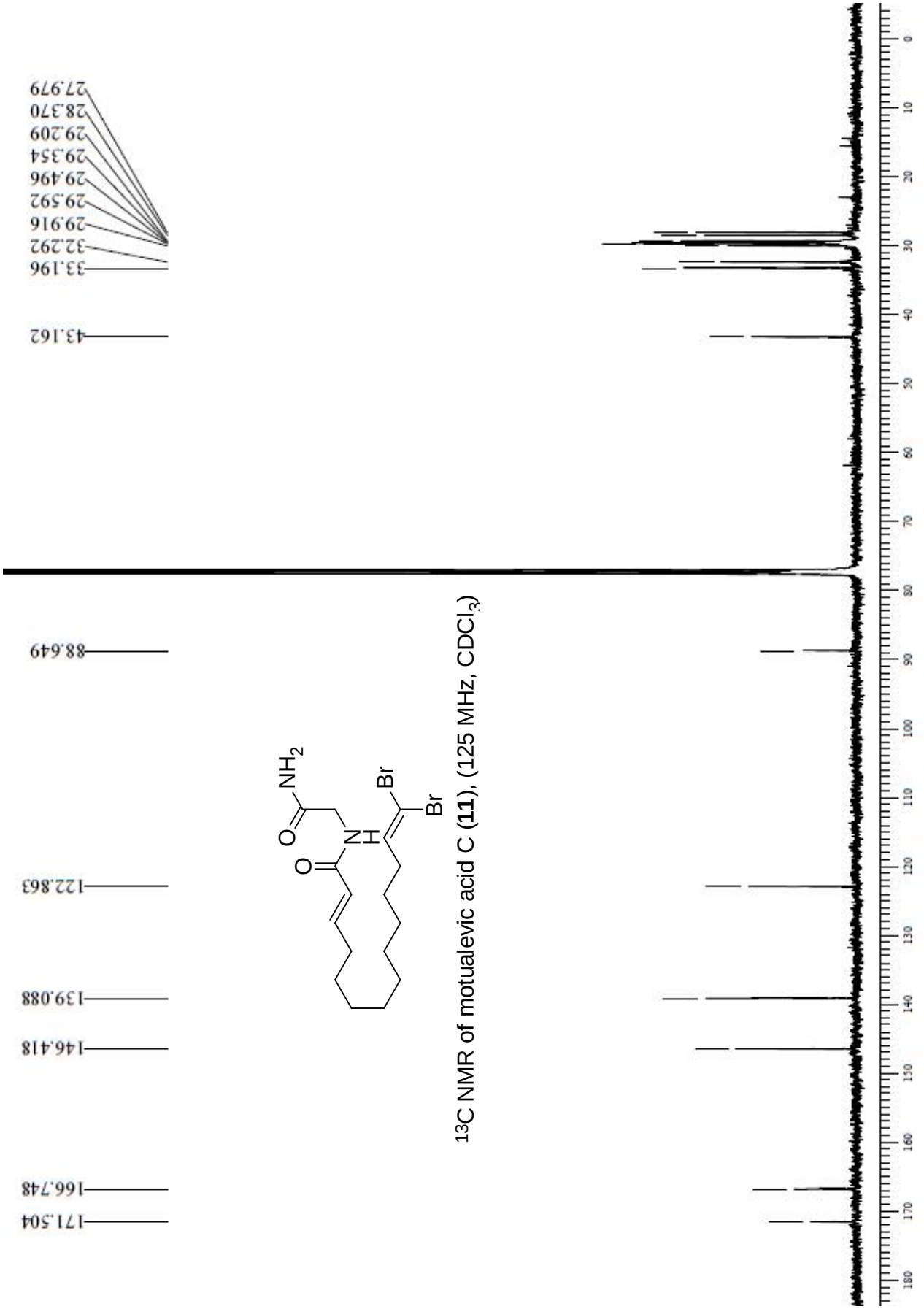
^{1}H NMR of motualevic acid A (**9**), (300 MHz, CD_3OD)



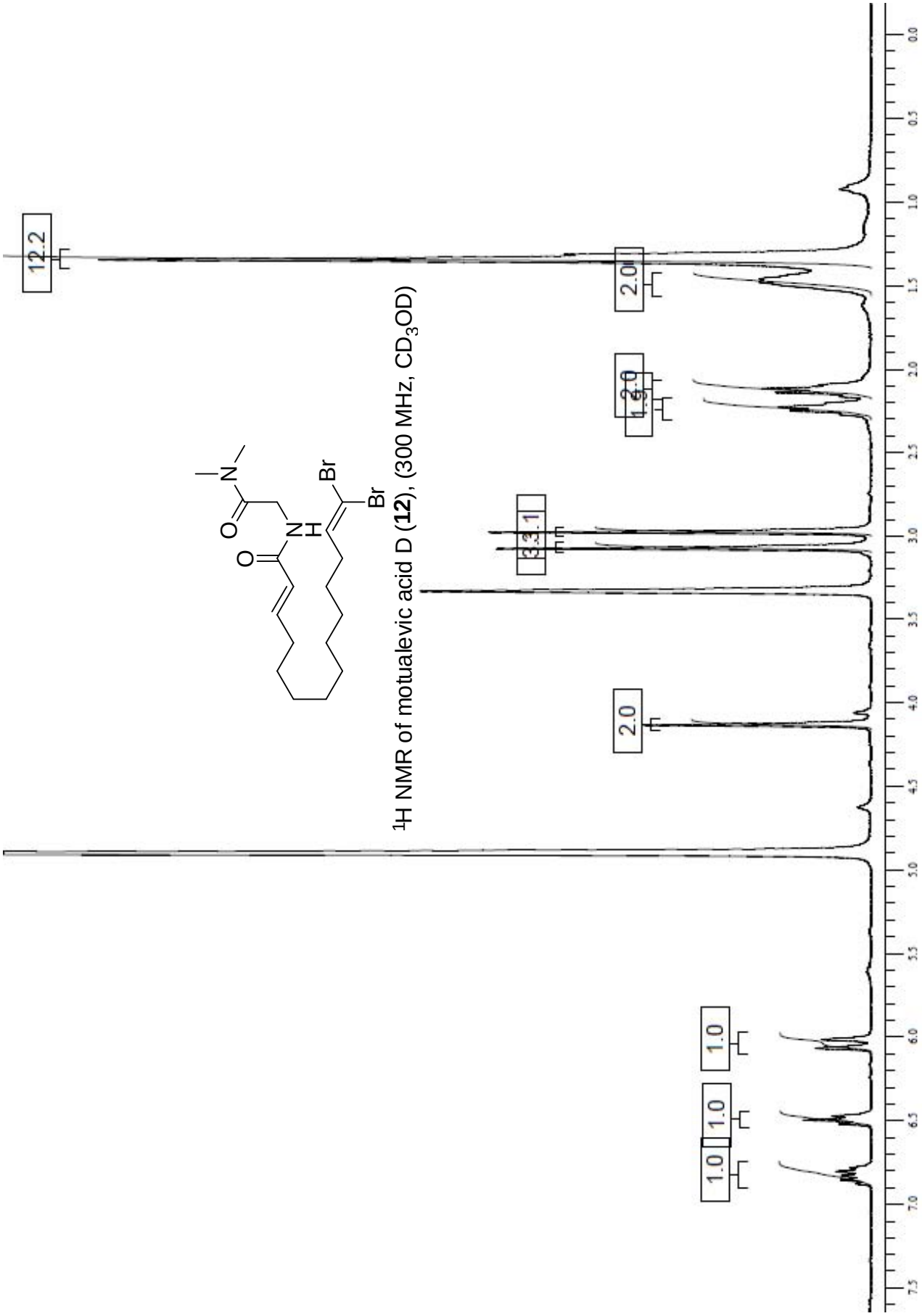
^{13}C NMR of motualevic acid A (**9**), (75 MHz, CD_3OD)



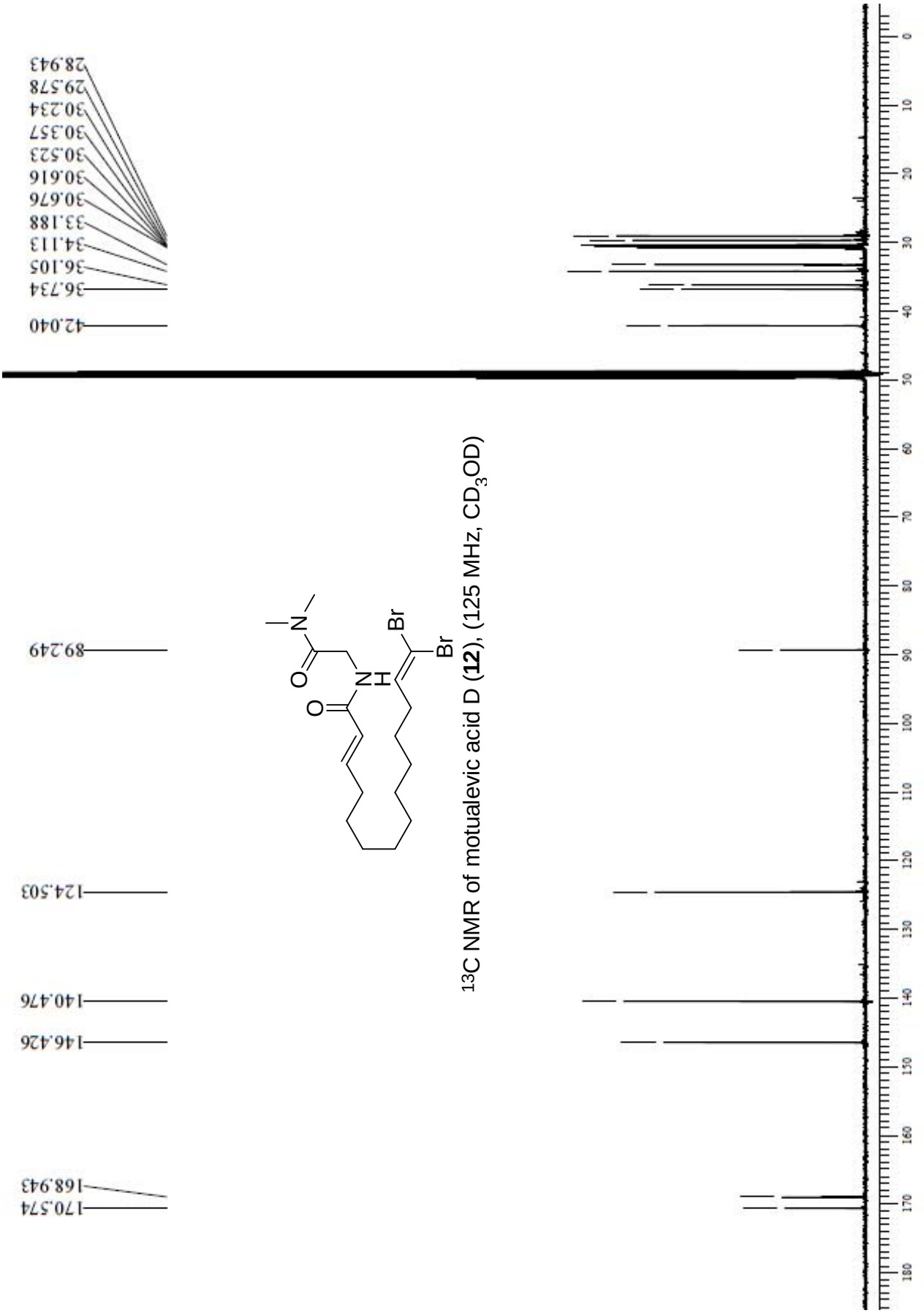
^{1}H NMR of motualevic acid C (**11**), (400 MHz, $CDCl_3$)



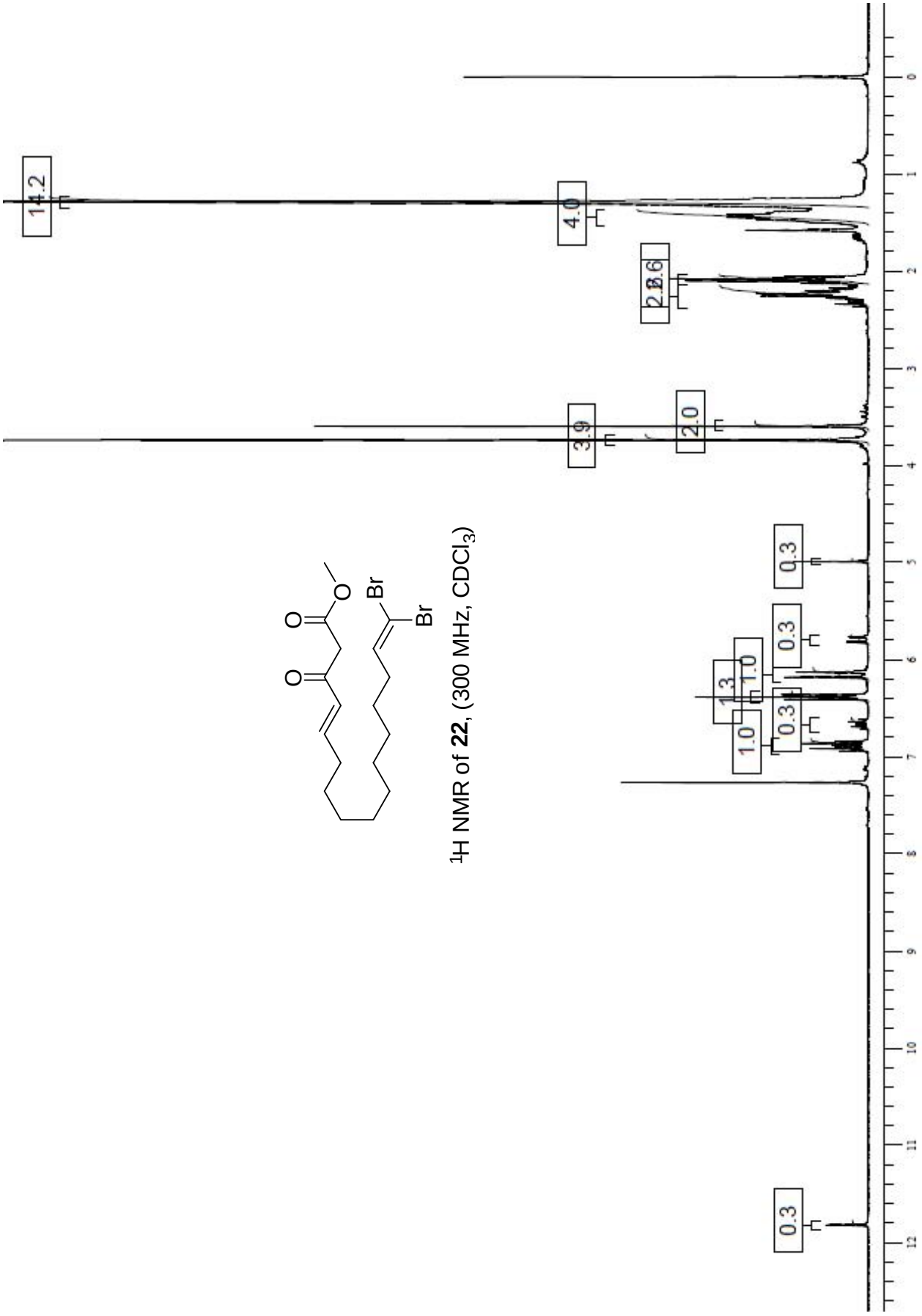
^{13}C NMR of motualevic acid C (**11**), (125 MHz, $CDCl_3$)



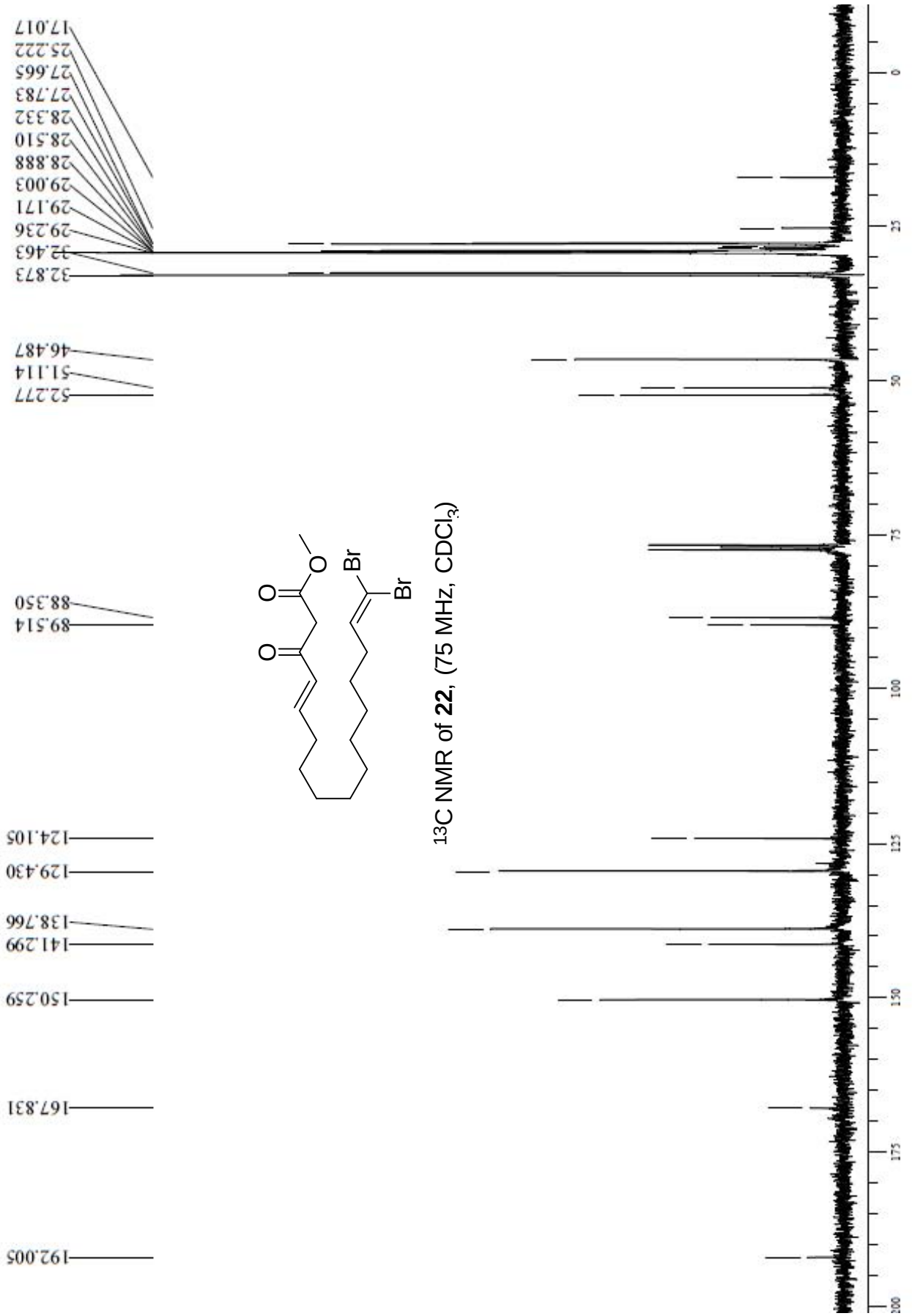
^{1}H NMR of motualevic acid D (**12**), (300 MHz, CD_3OD)



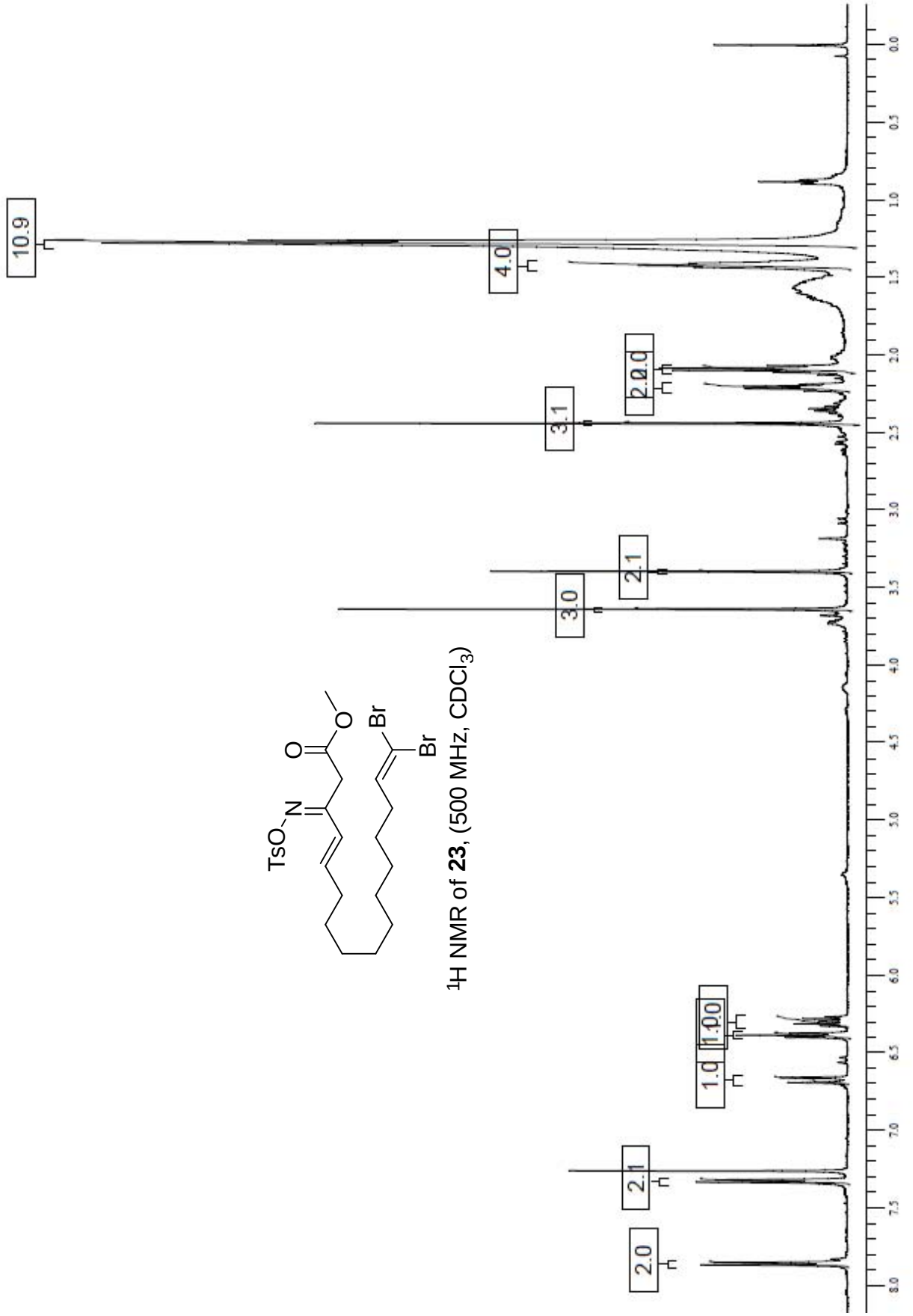
^{13}C NMR of motualevic acid D (**12**), (125 MHz, CD_3OD)



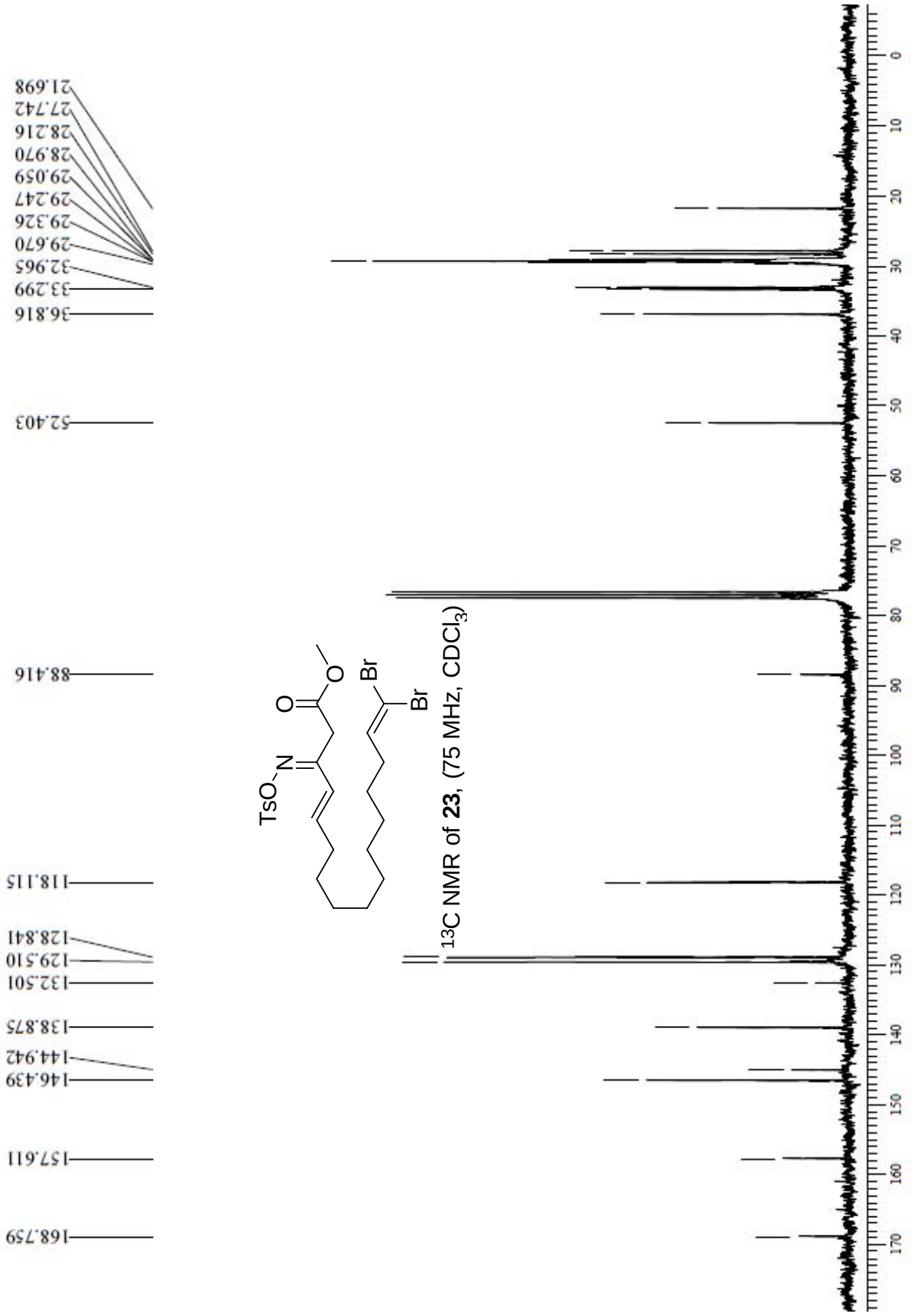
^{1}H NMR of **22**, (300 MHz, $CDCl_3$)

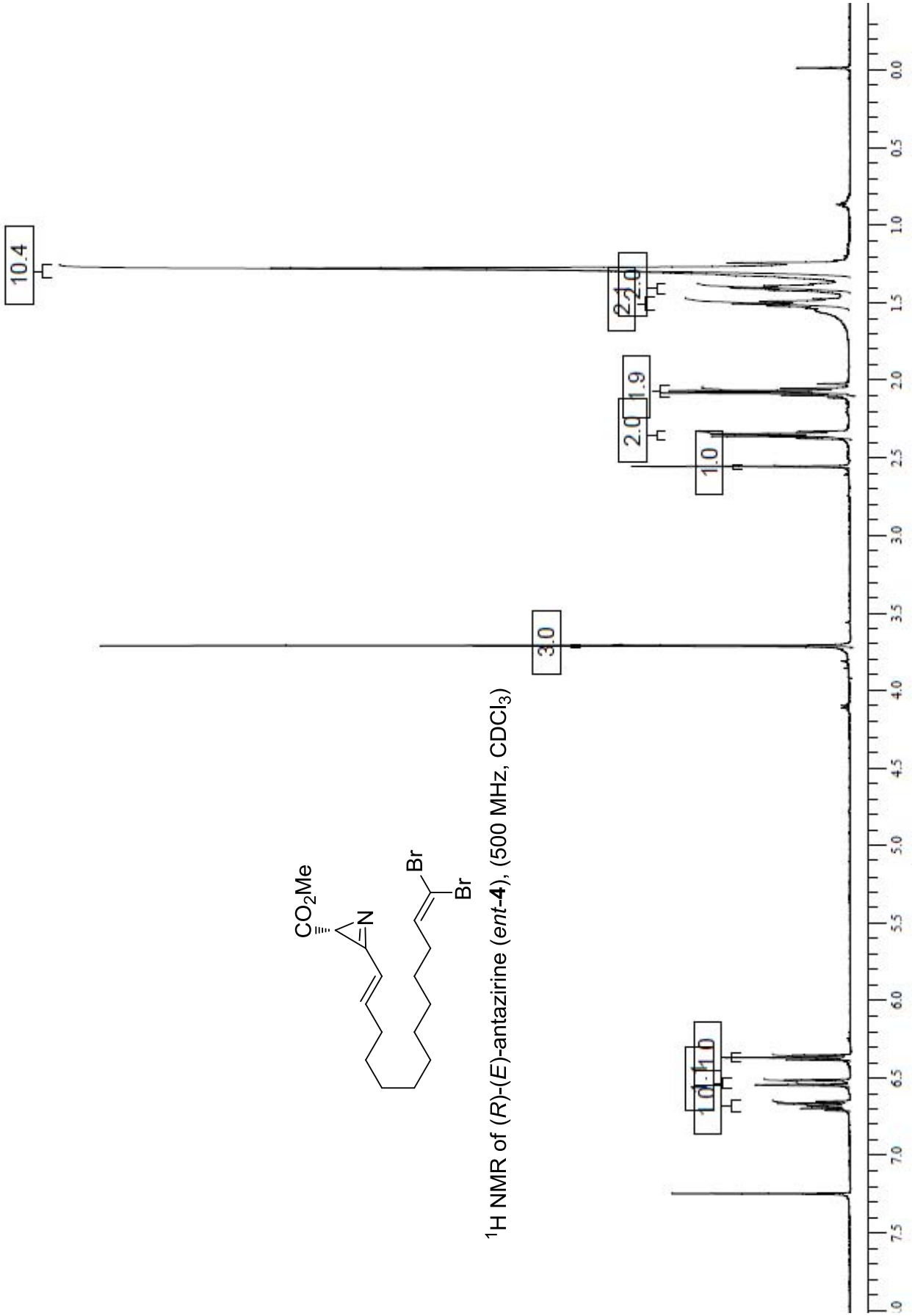


^{13}C NMR of **22**, (75 MHz, $CDCl_3$)

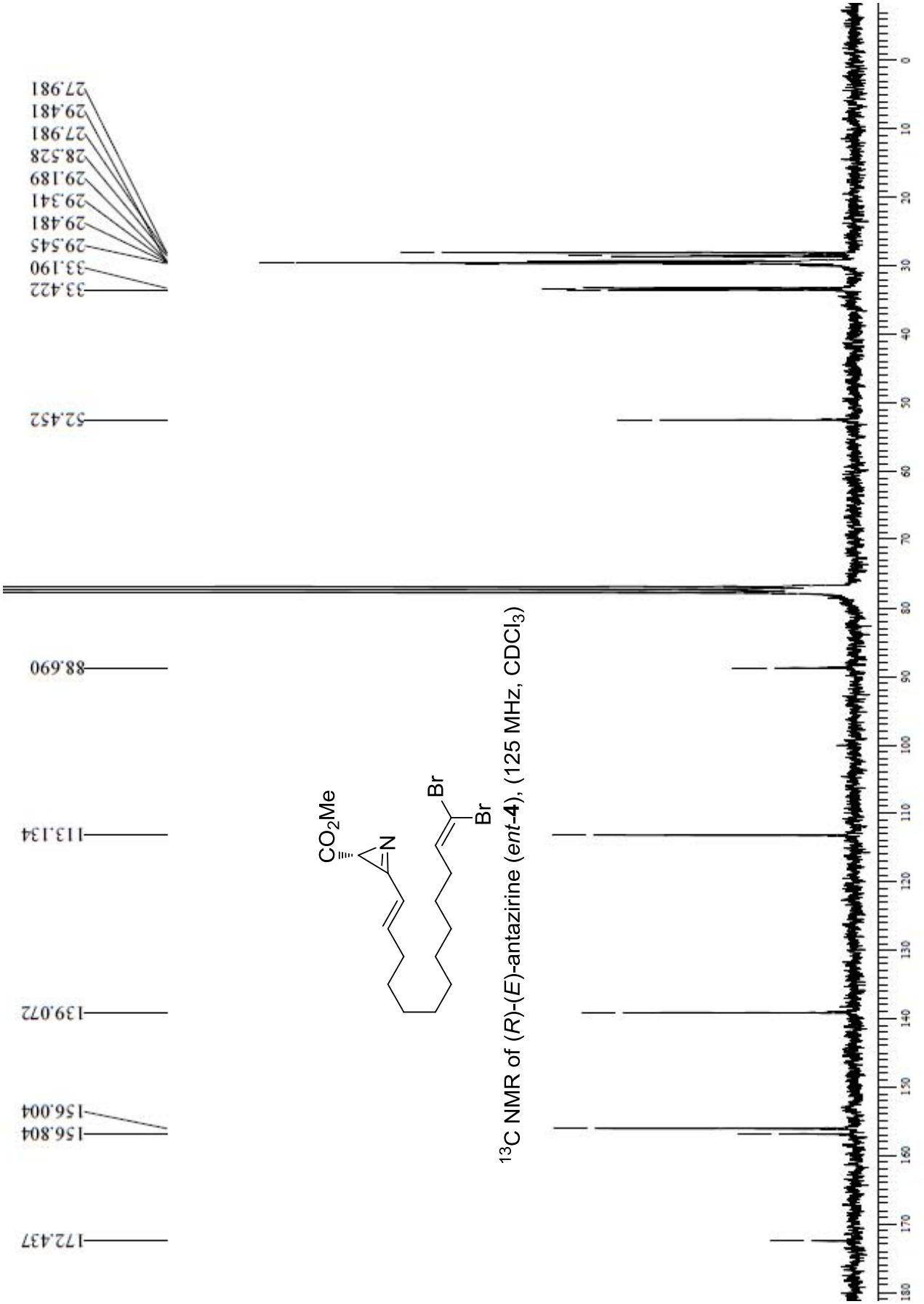


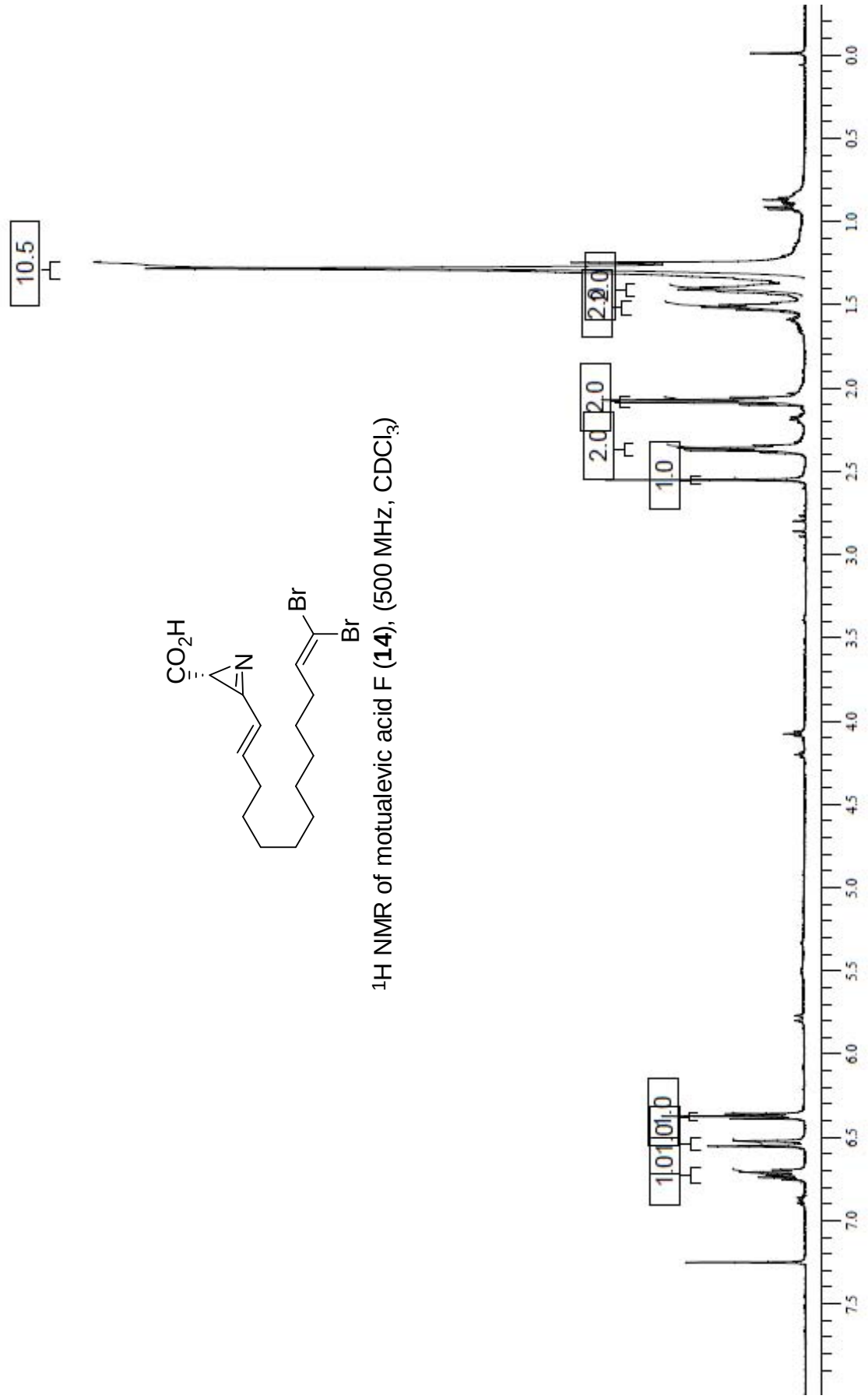
^{1}H NMR of **23**, (500 MHz, $CDCl_3$)


21.698
27.742
28.216
28.970
29.059
29.247
29.326
29.670
32.965
33.299
36.816
52.403
88.416
118.115
128.841
129.510
132.501
138.875
144.942
146.439
157.611
168.759
TsO
N
O
O
Br
Br
^{13}C NMR of **23**, (75 MHz, $CDCl_3$)

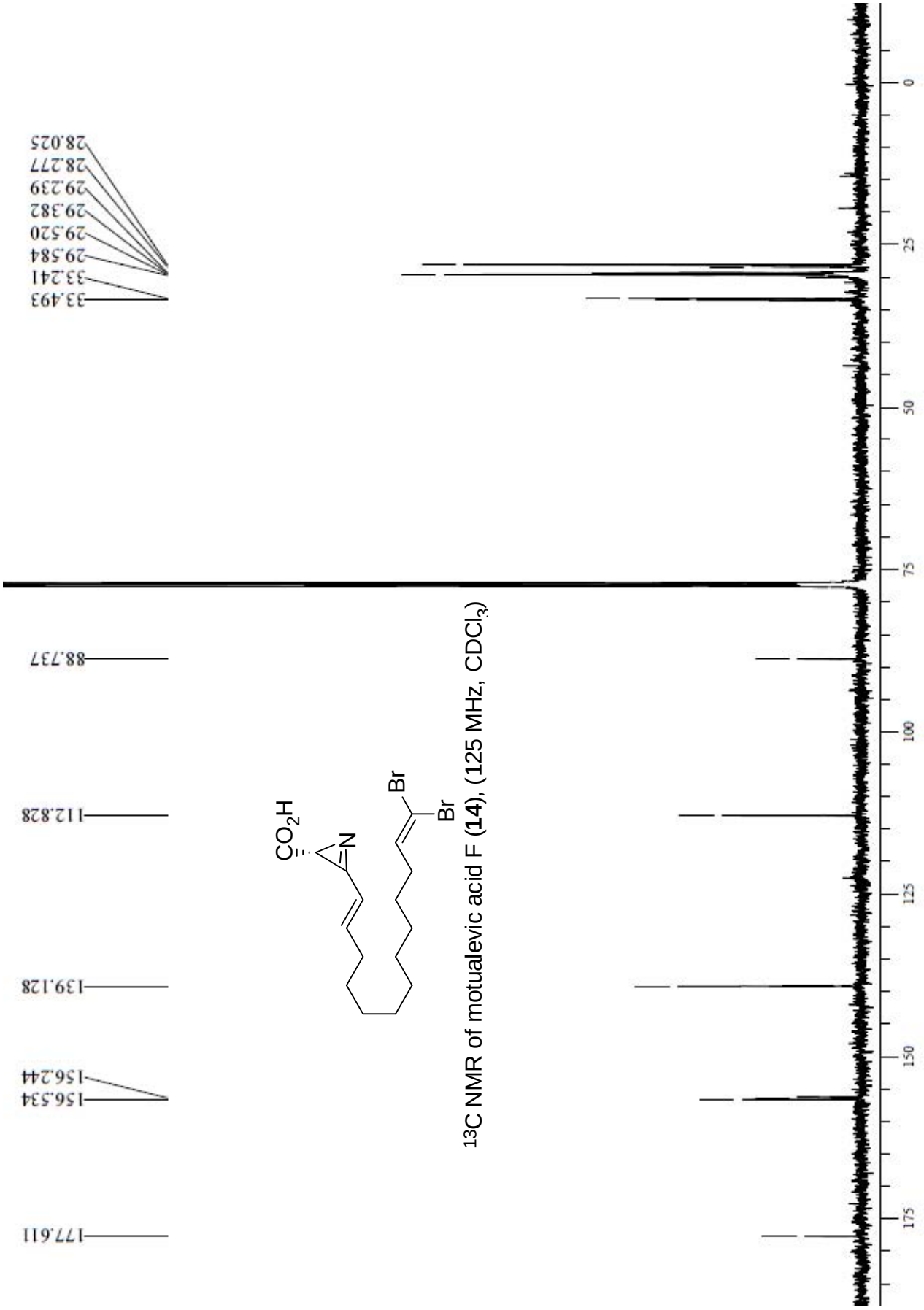


^{1}H NMR of (*R*)-(*E*)-antazirine (*ent*-**4**), (500 MHz, $CDCl_3$)

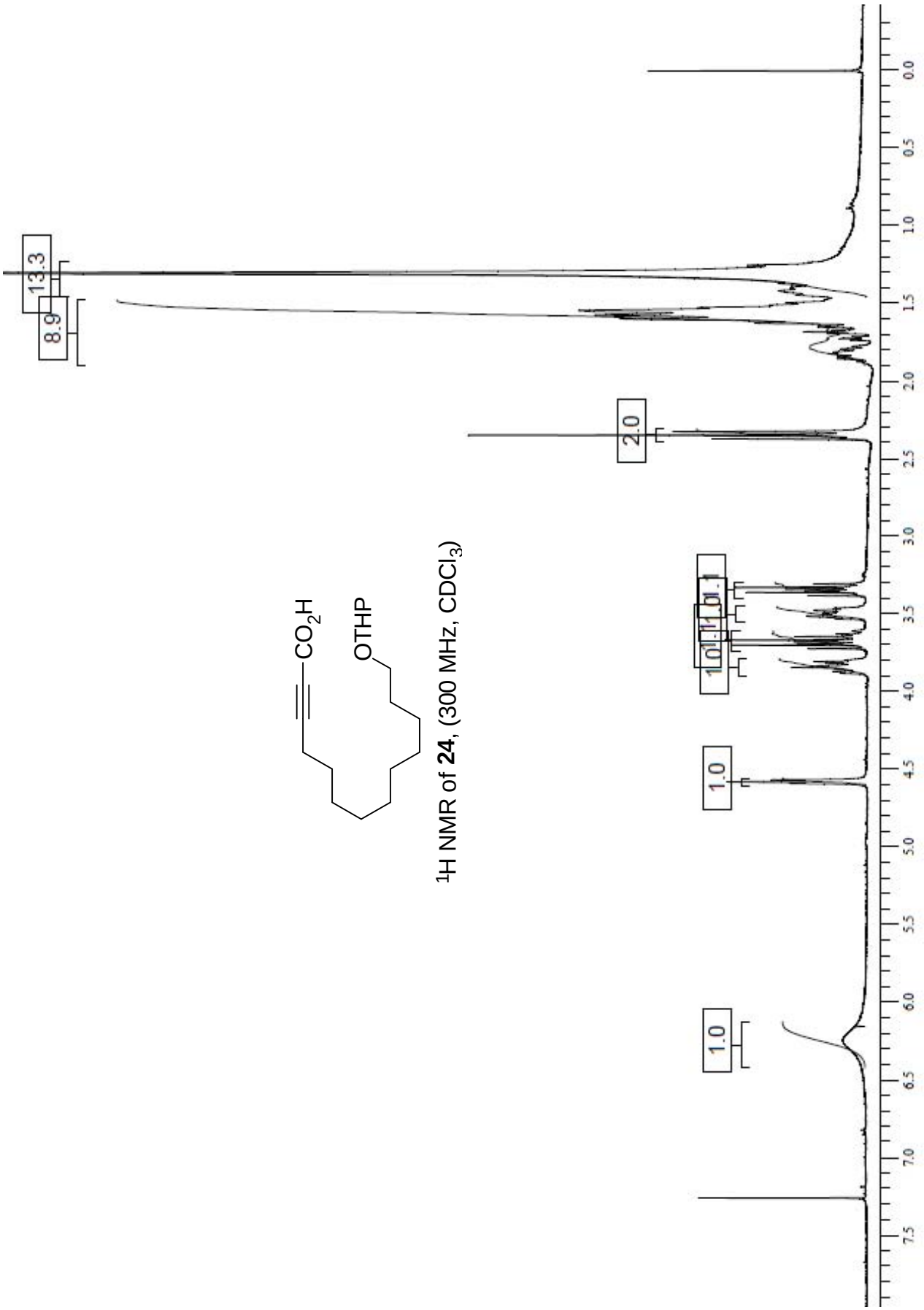

27.981
29.481
27.981
28.528
29.189
29.341
29.481
29.545
33.190
33.422
52.452
88.690
113.134
139.072
156.004
156.804
172.437
CO2Me
N
Br
Br
13C NMR of (R)-(E)-antazirine (ent-4), (125 MHz, CDCl3)



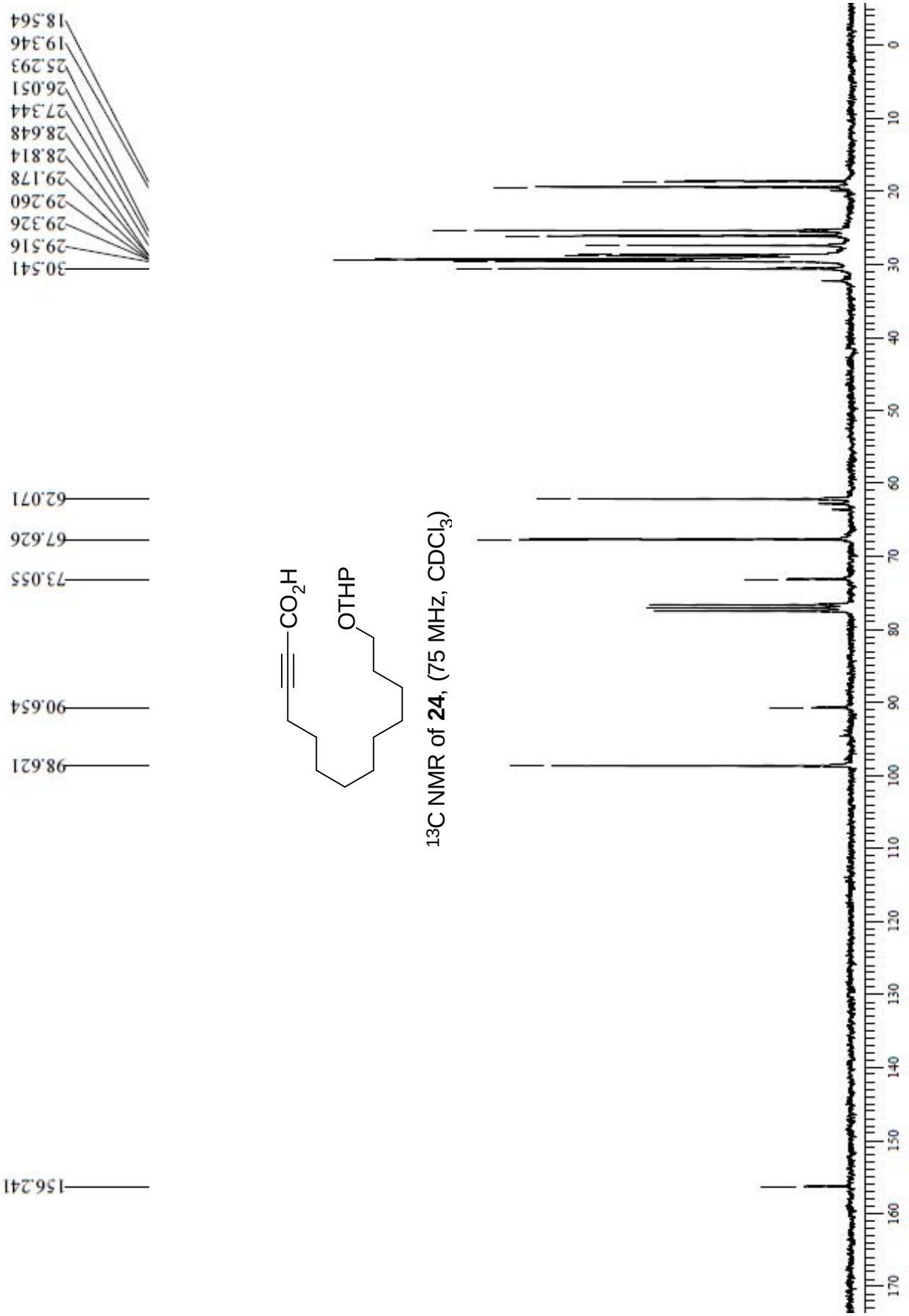
^{1}H NMR of motualevic acid F (**14**), (500 MHz, $CDCl_3$)

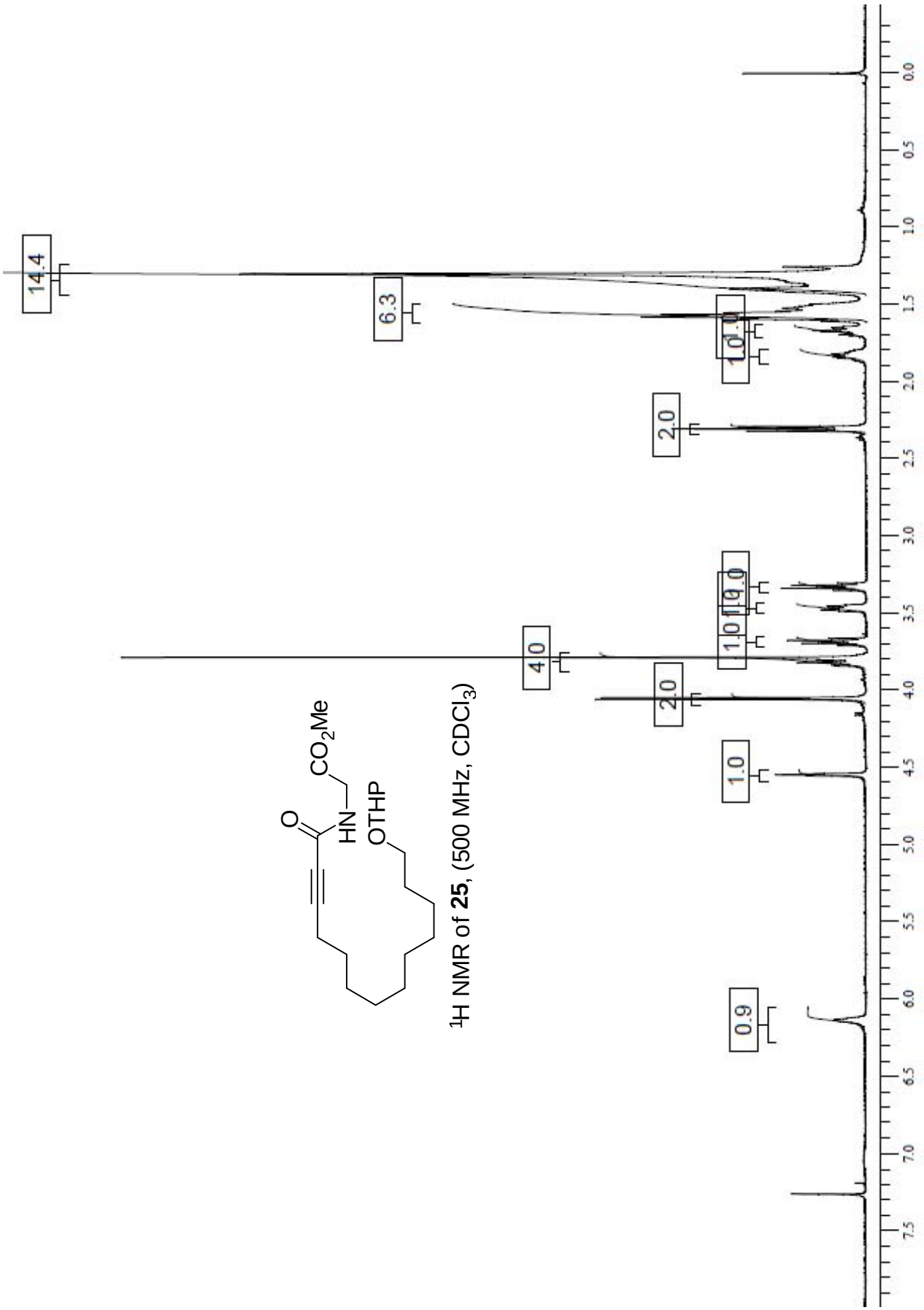


^{13}C NMR of motualevic acid F (**14**), (125 MHz, $CDCl_3$)

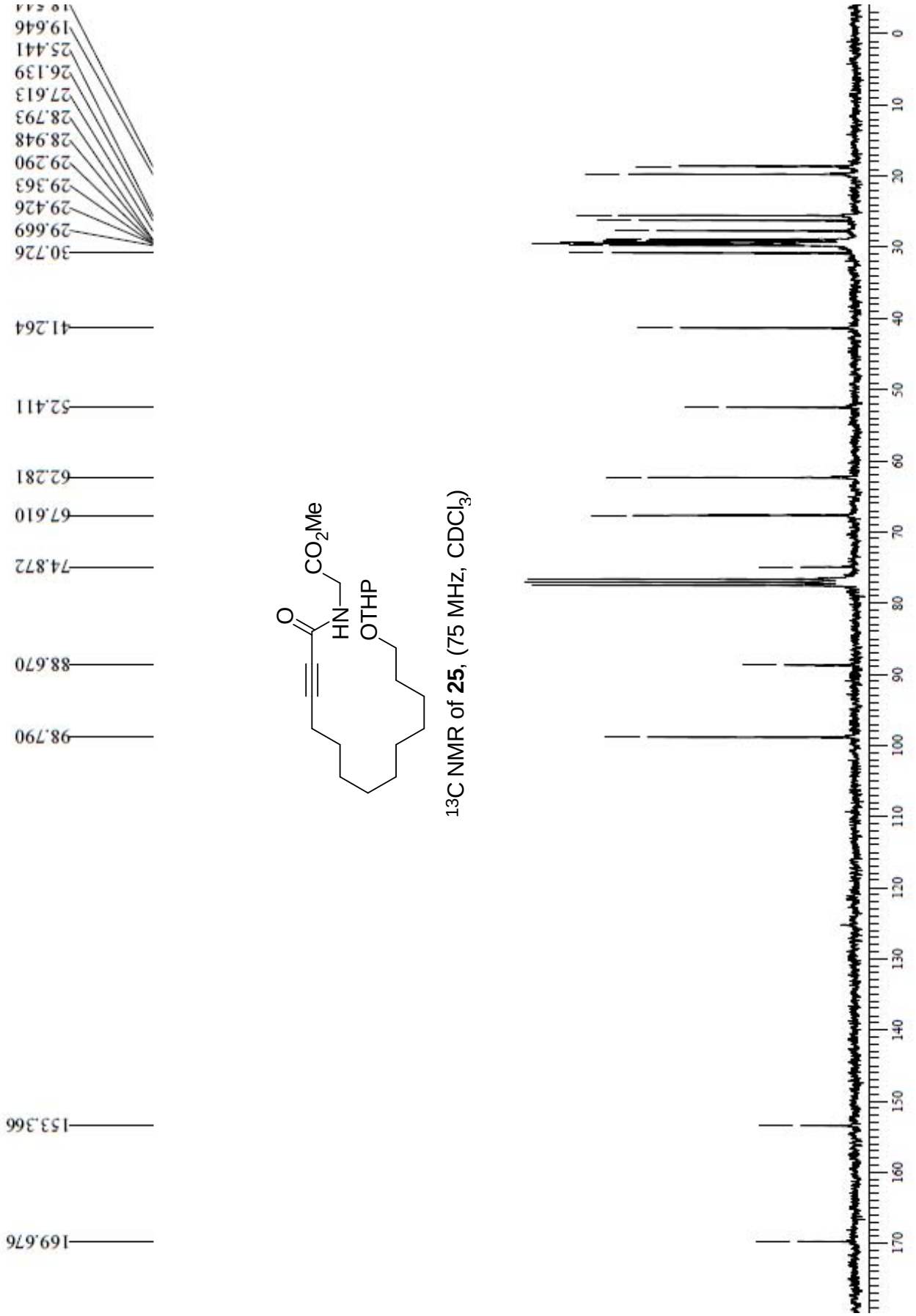


^{1}H NMR of **24**, (300 MHz, $CDCl_3$)

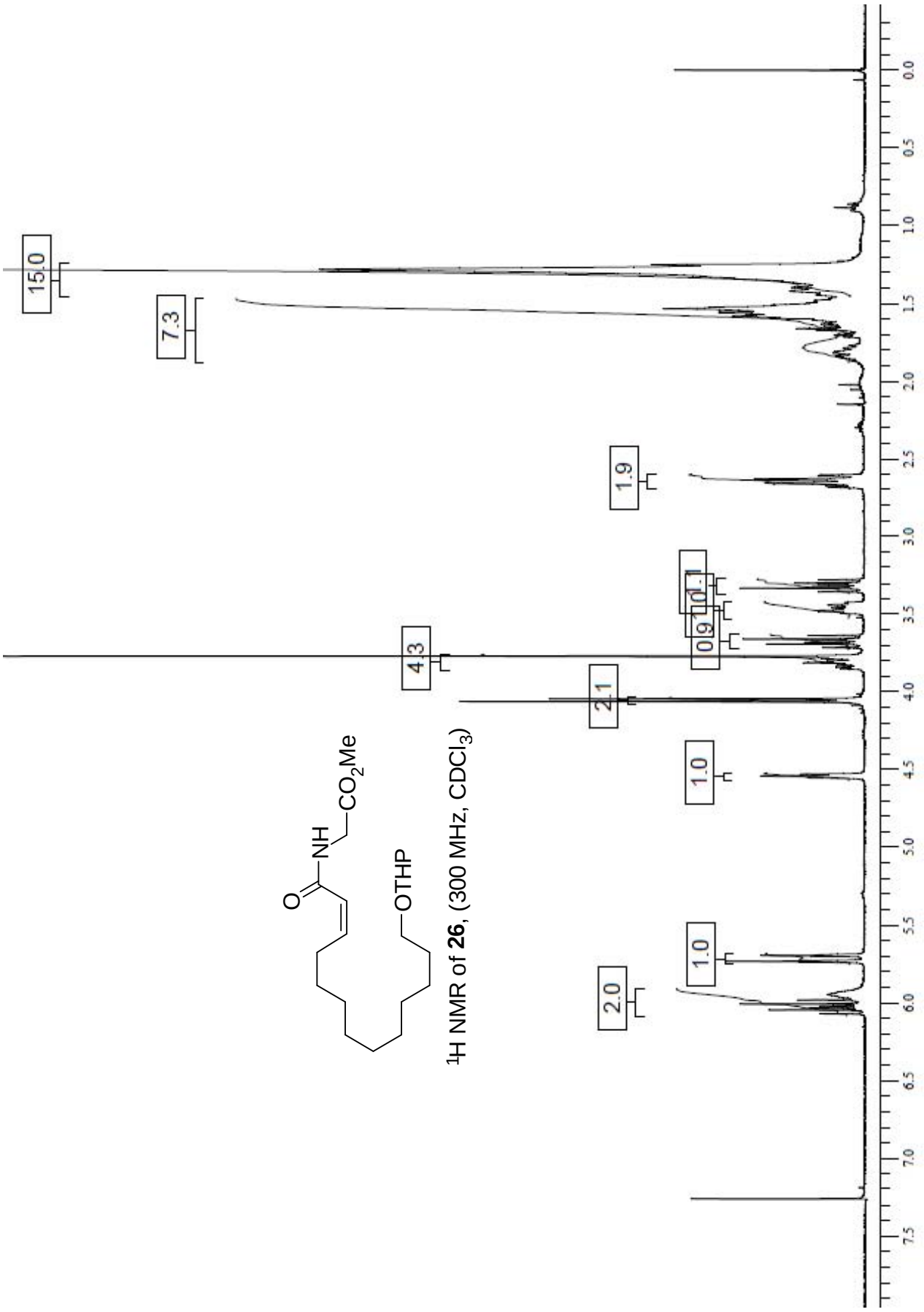

18.564
19.346
25.293
26.051
27.344
28.648
28.814
29.178
29.260
29.326
29.516
30.541
62.071
67.626
73.055
90.654
98.621
156.241
CO2H
OTHP
13C NMR of 24, (75 MHz, CDCl3)



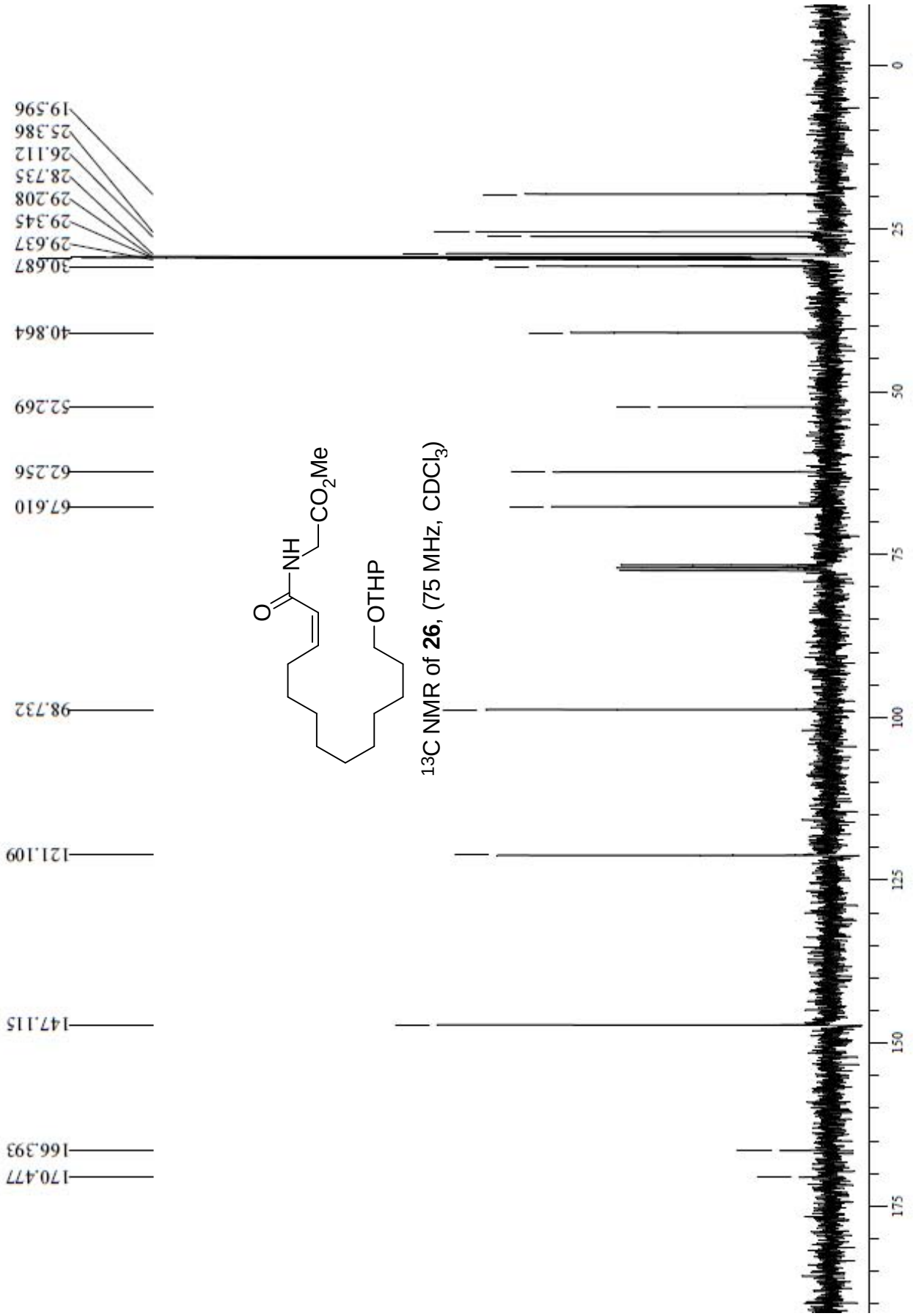
^{1}H NMR of **25**, (500 MHz, $CDCl_3$)

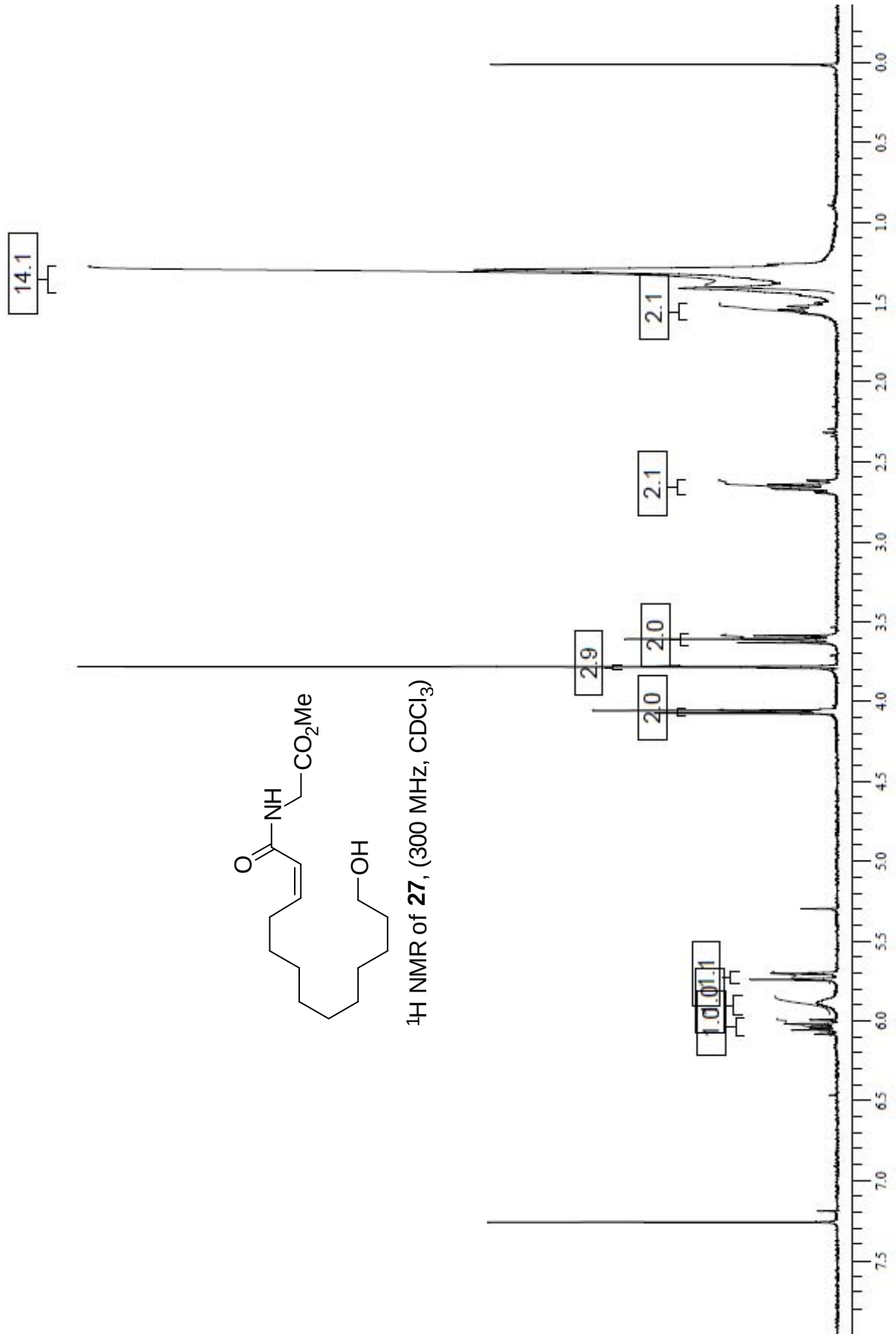


^{13}C NMR of **25**, (75 MHz, $CDCl_3$)

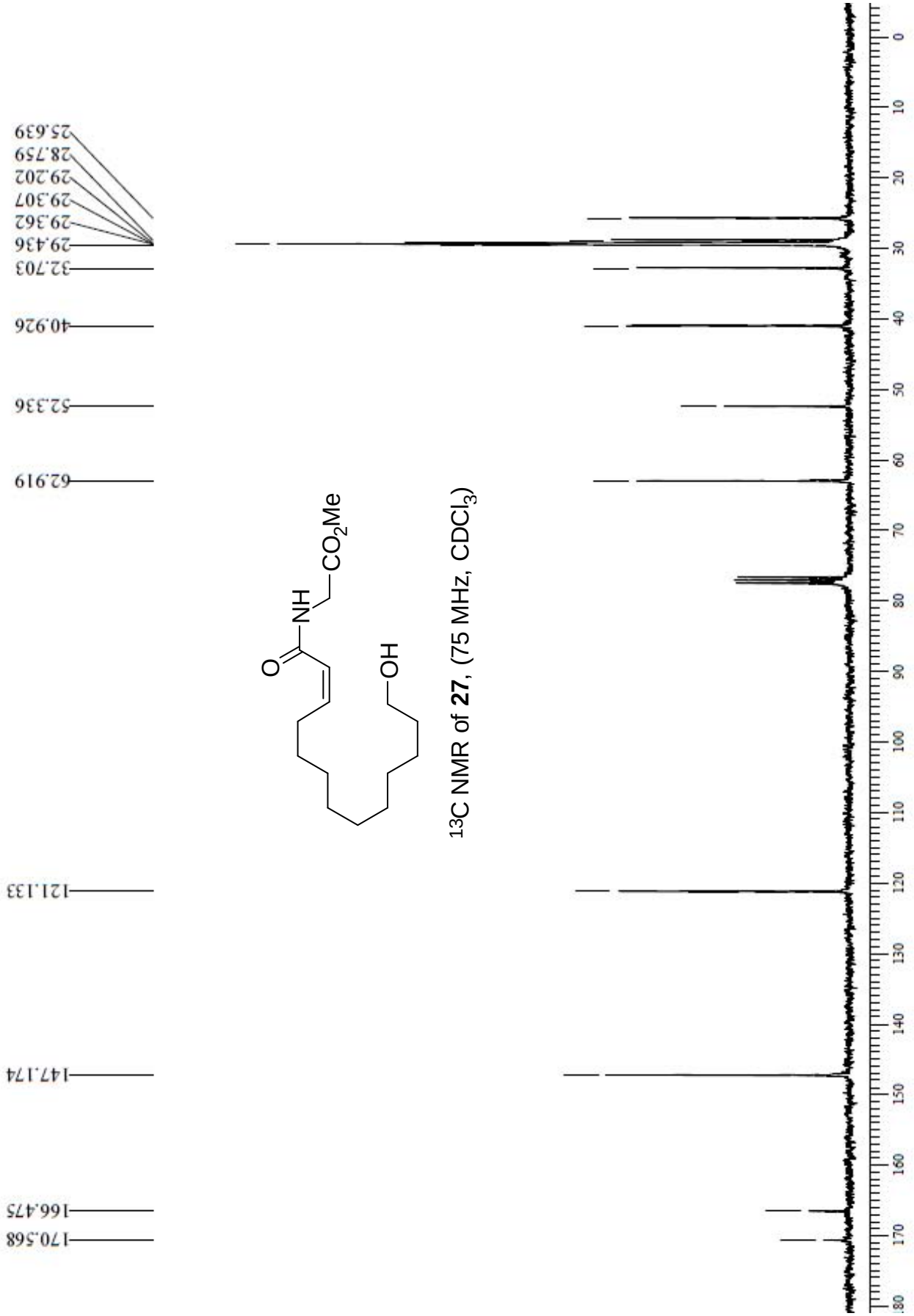


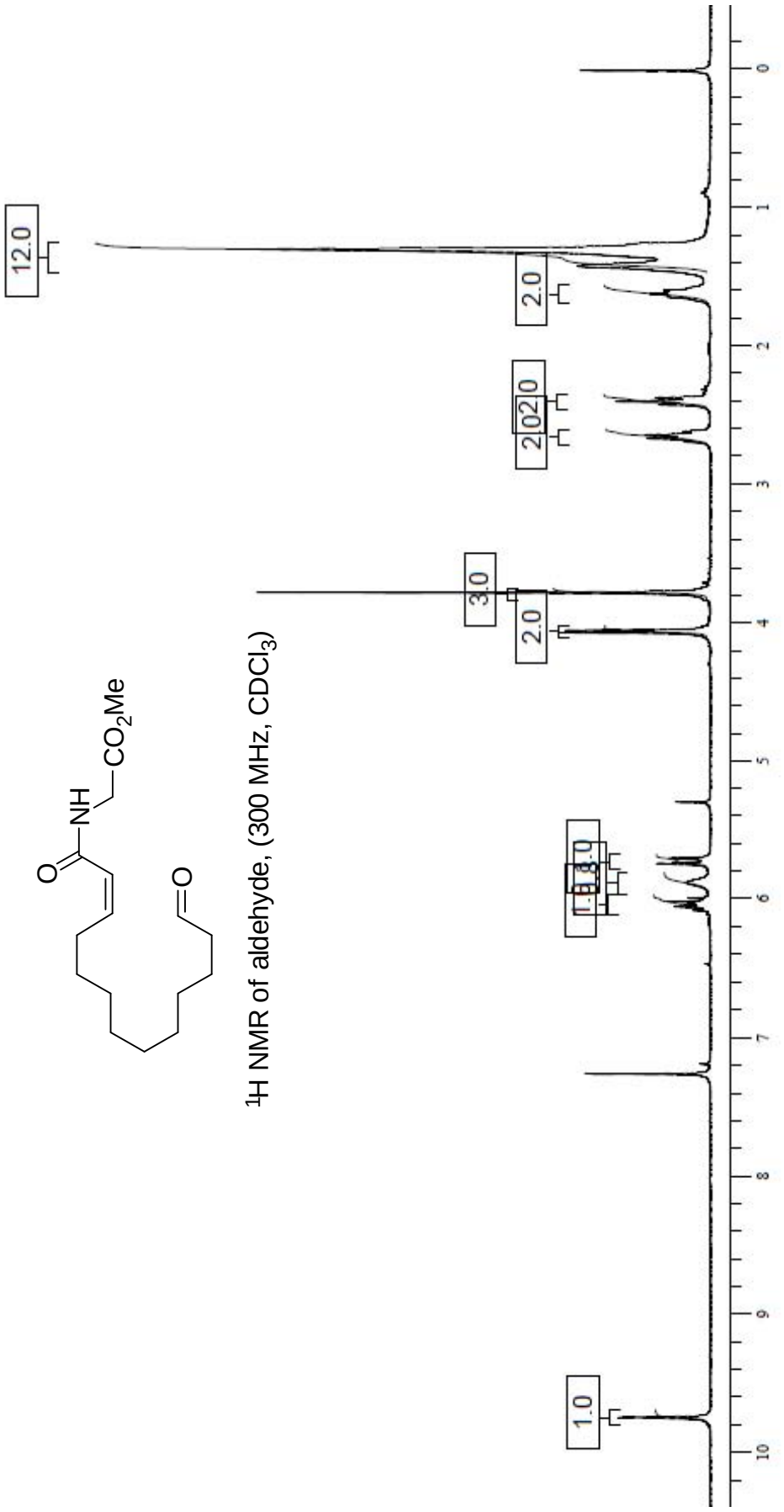
^{1}H NMR of **26**, (300 MHz, $CDCl_3$)


19.596
25.386
26.112
28.735
29.208
29.345
29.637
30.687
40.864
52.269
62.256
67.610
98.732
121.109
147.115
166.393
170.477
NH
CO2Me
O
OTHP
13C NMR of 26, (75 MHz, CDCl3)
0
25
50
75
100
125
150
175

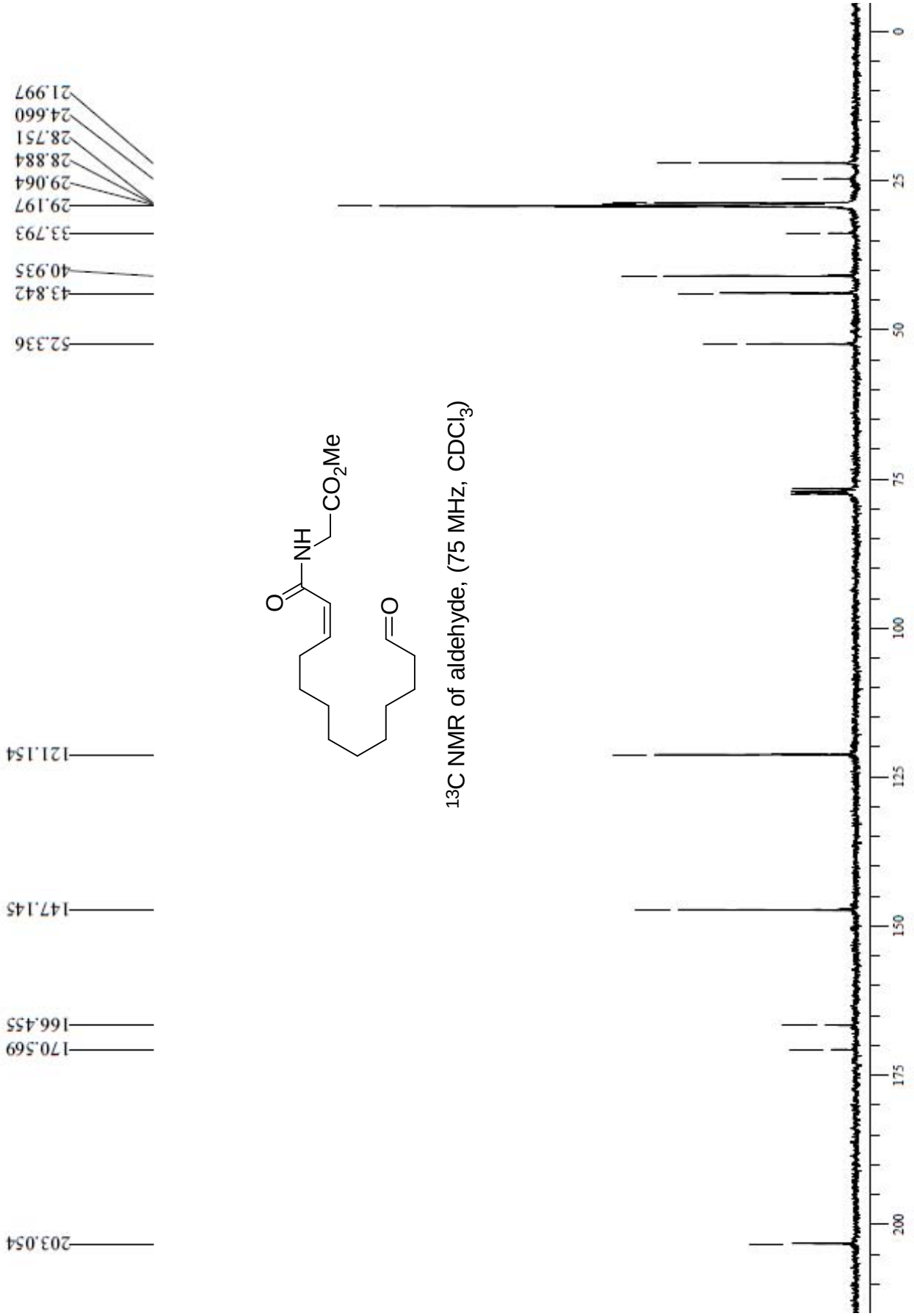


^{1}H NMR of **27**, (300 MHz, $CDCl_3$)

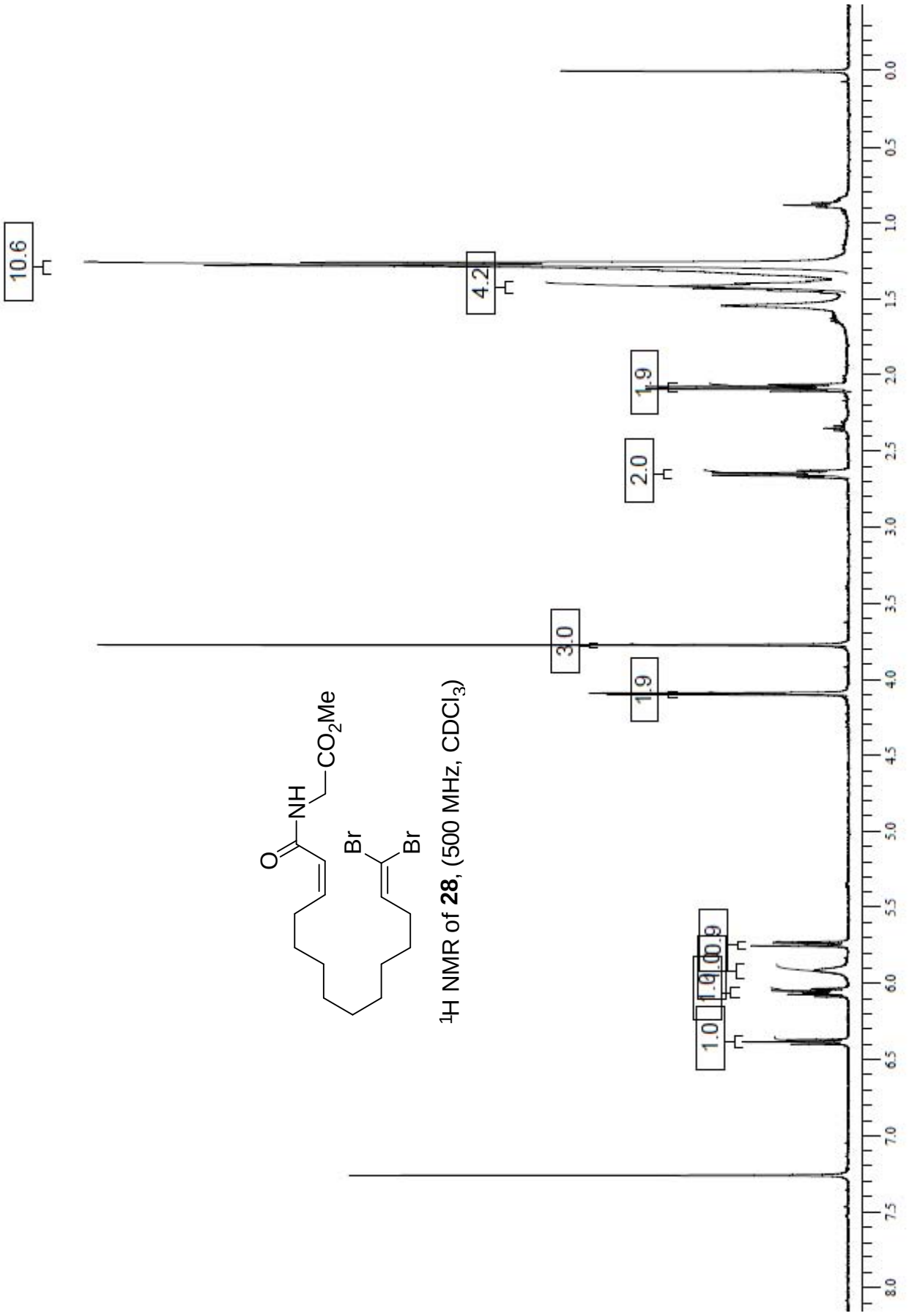

25.639
28.759
29.202
29.307
29.362
29.436
32.703
40.926
52.336
62.919
121.133
147.174
166.475
170.568
NH
CO2Me
O
OH
13C NMR of 27, (75 MHz, CDCl3)



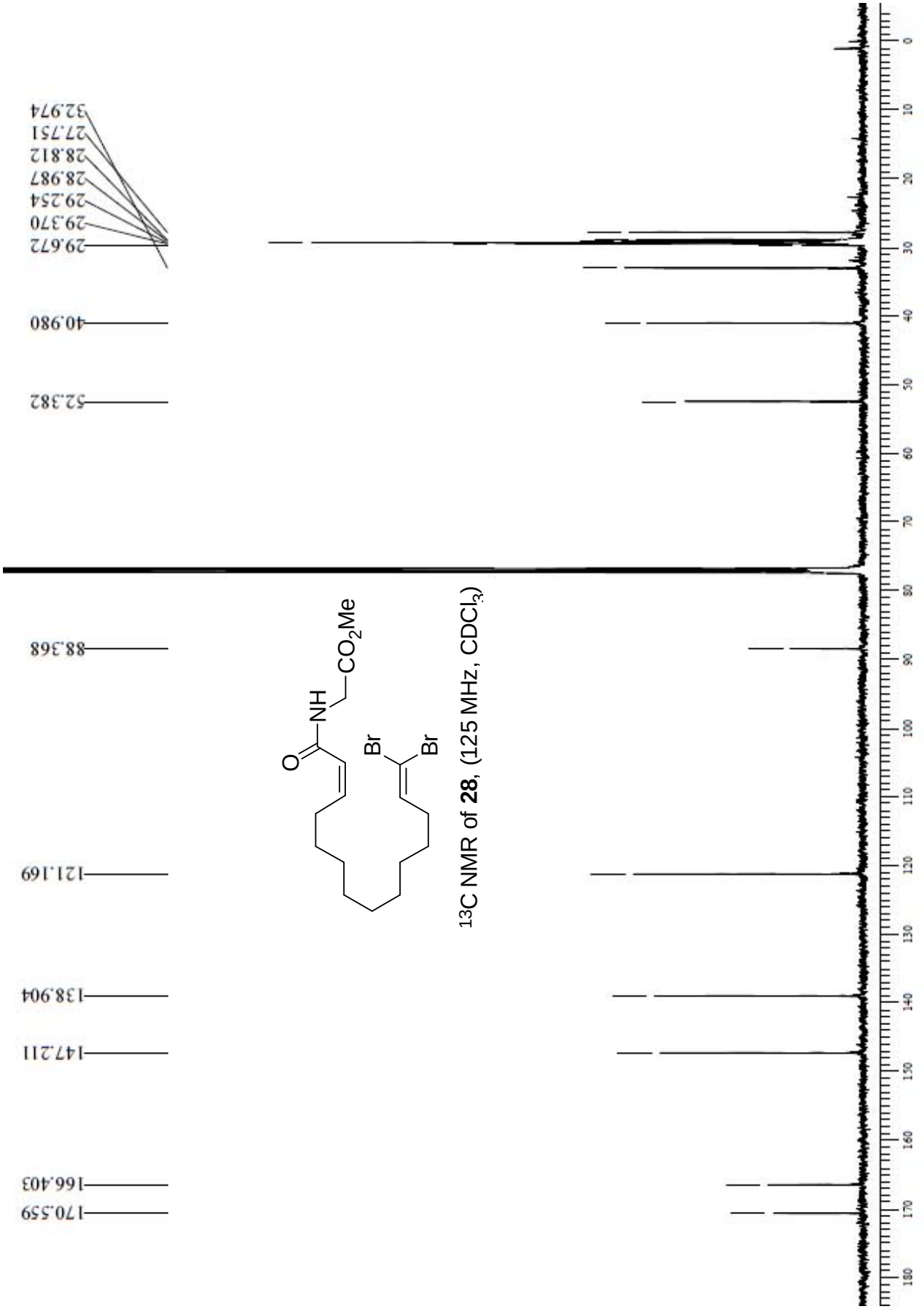
^{1}H NMR of aldehyde, (300 MHz, $CDCl_3$)



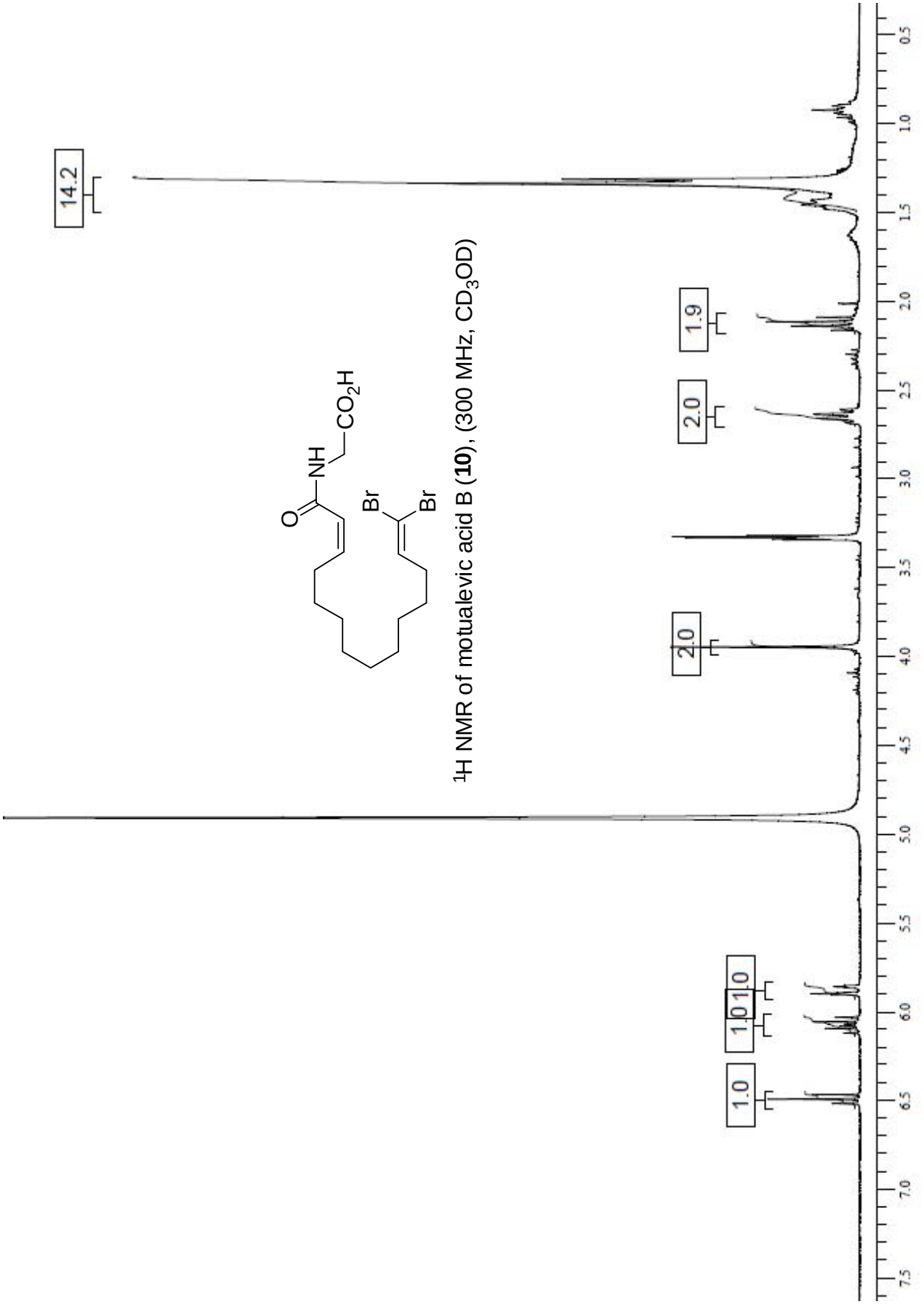
^{13}C NMR of aldehyde, (75 MHz, $CDCl_3$)



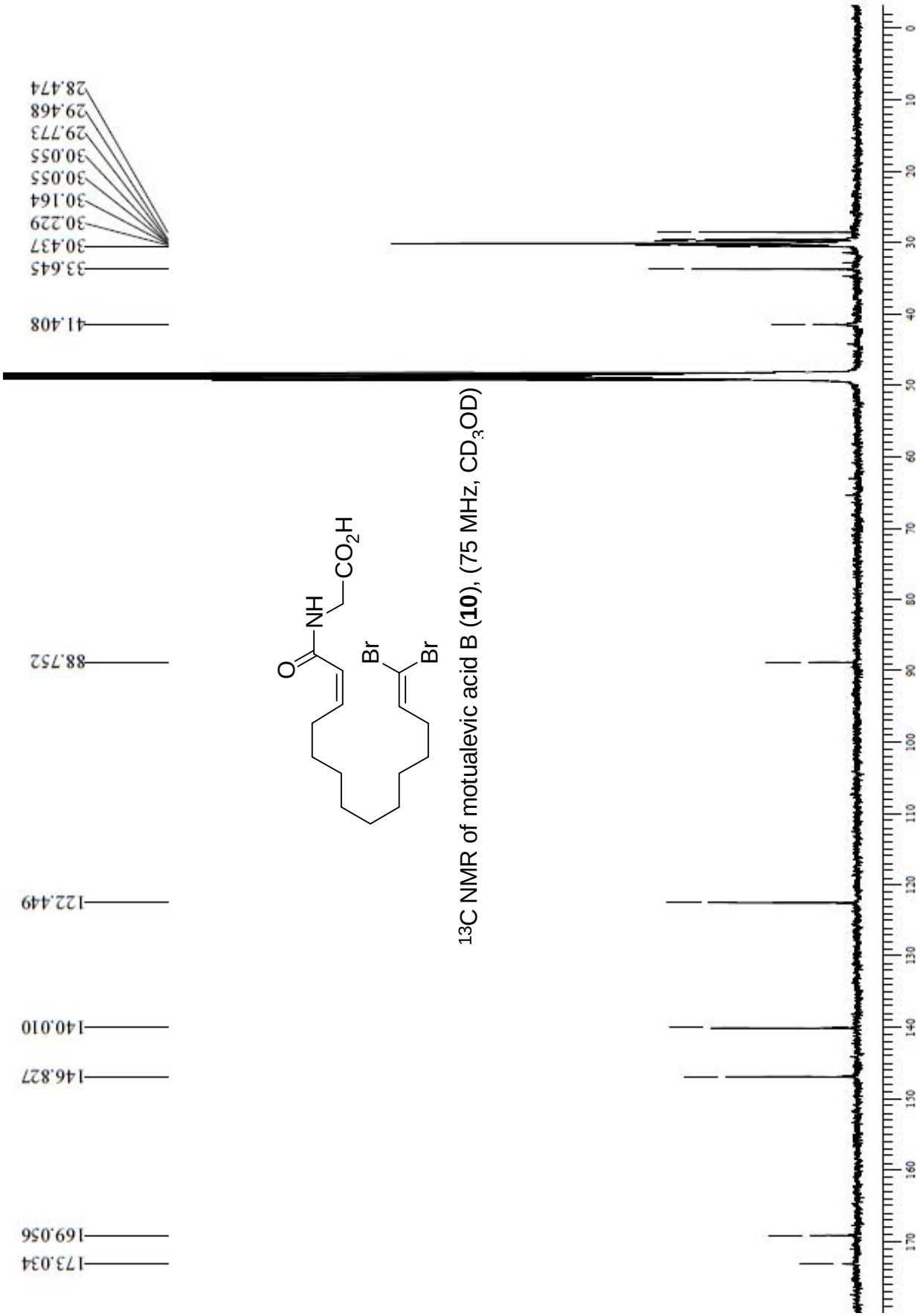
^{1}H NMR of **28**, (500 MHz, $CDCl_3$)



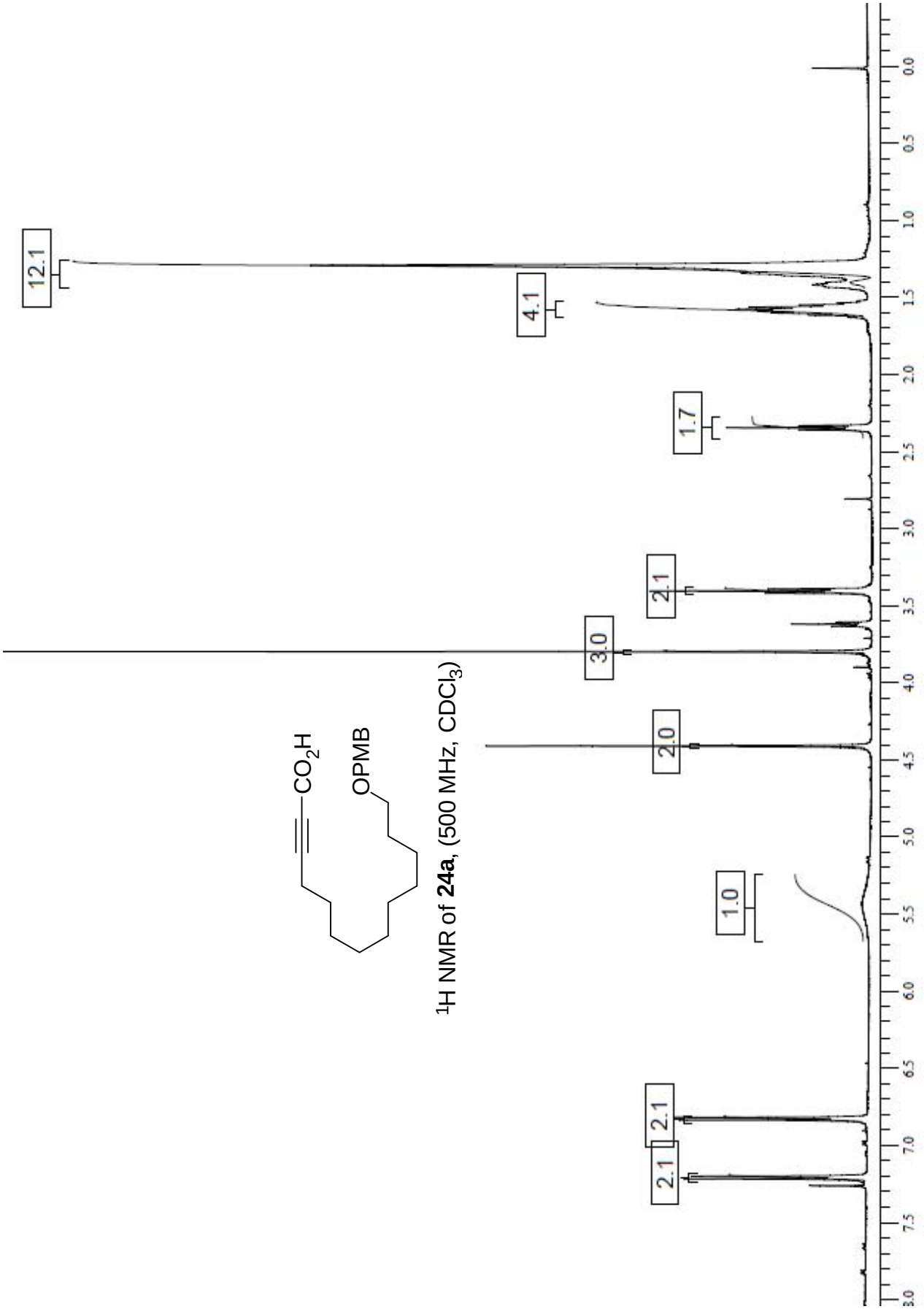
^{13}C NMR of **28**, (125 MHz, $CDCl_3$)



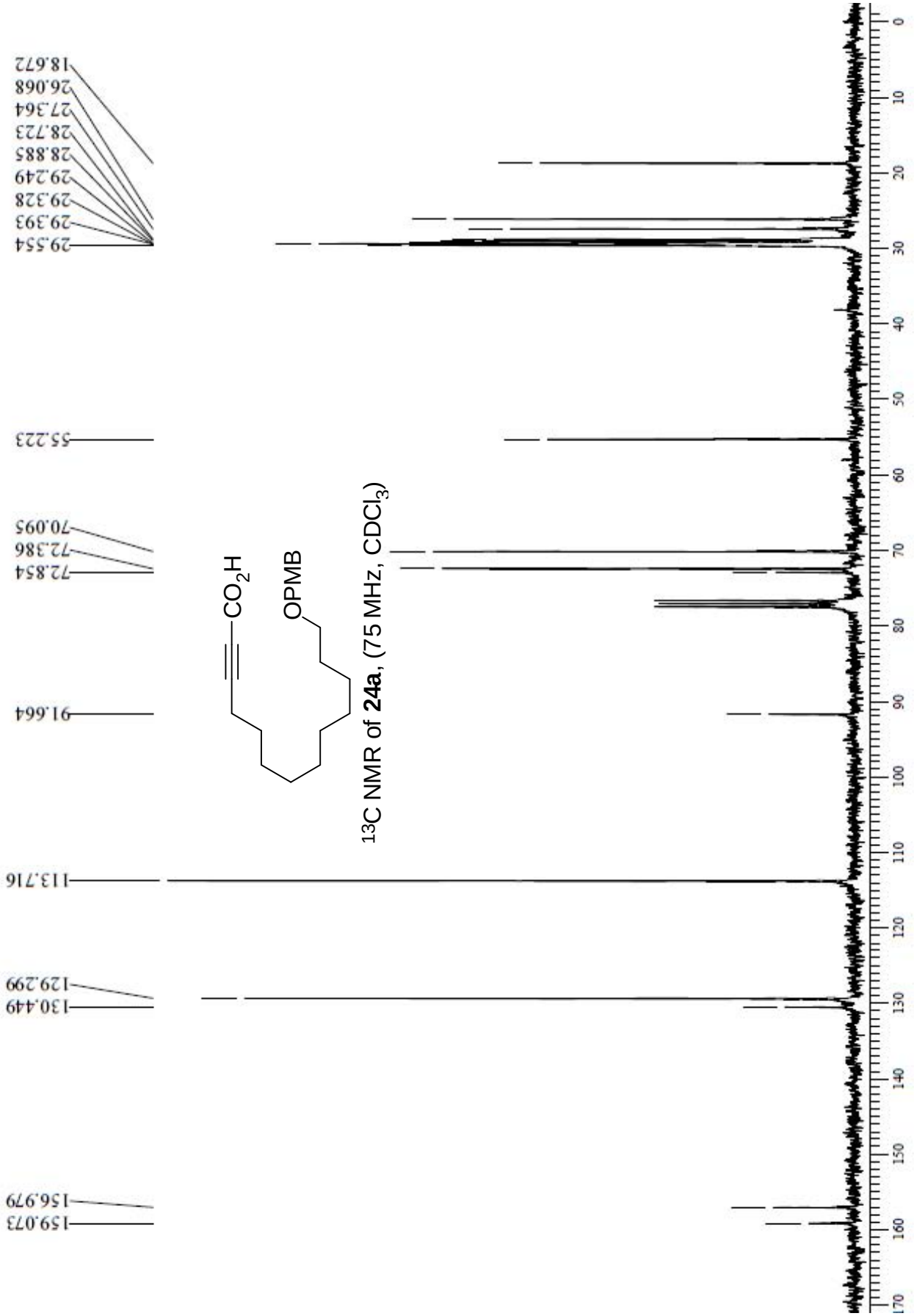
^{1}H NMR of motualevic acid B (**10**), (300 MHz, CD_3OD)

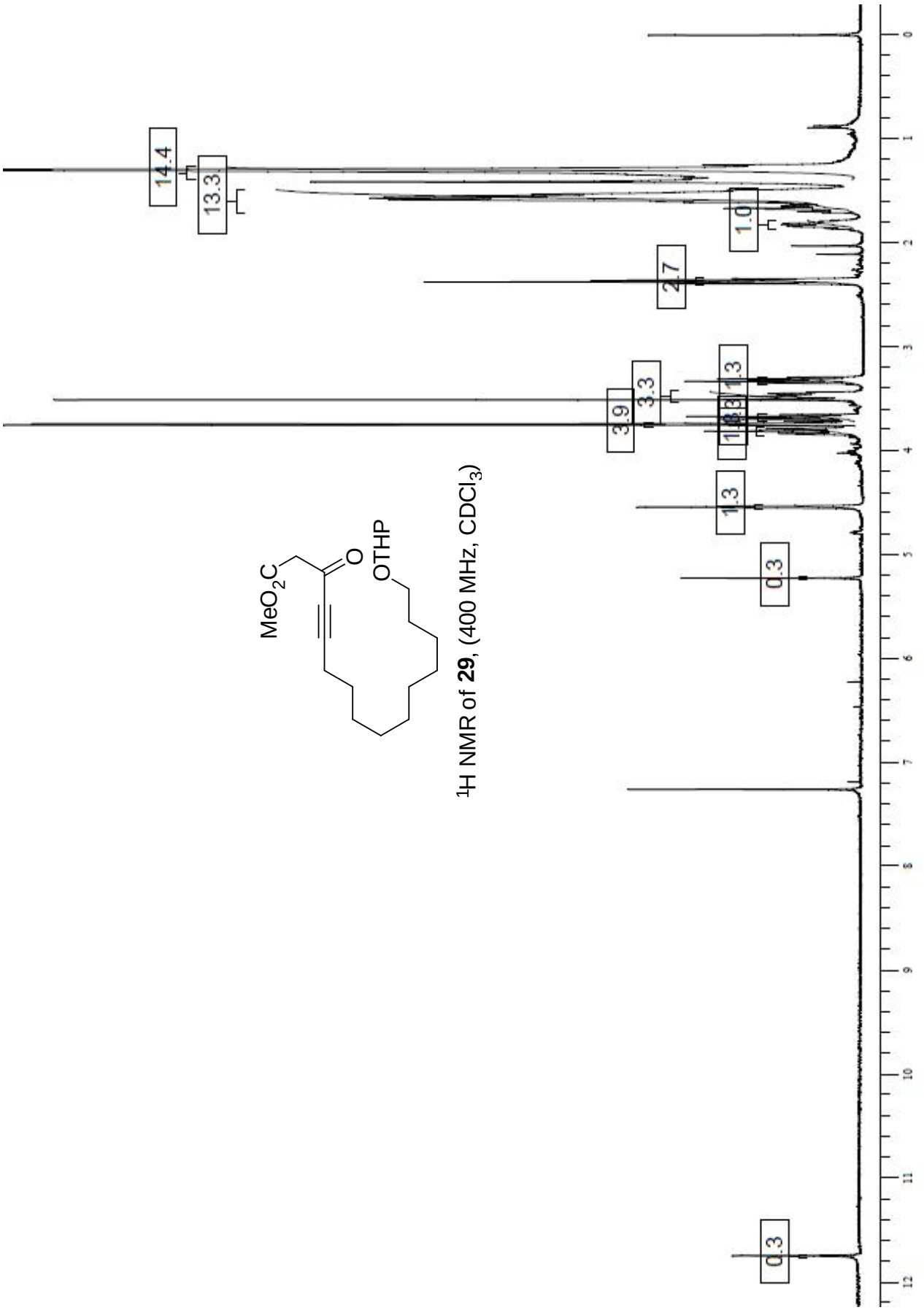


^{13}C NMR of motualevic acid B (**10**), (75 MHz, CD_3OD)

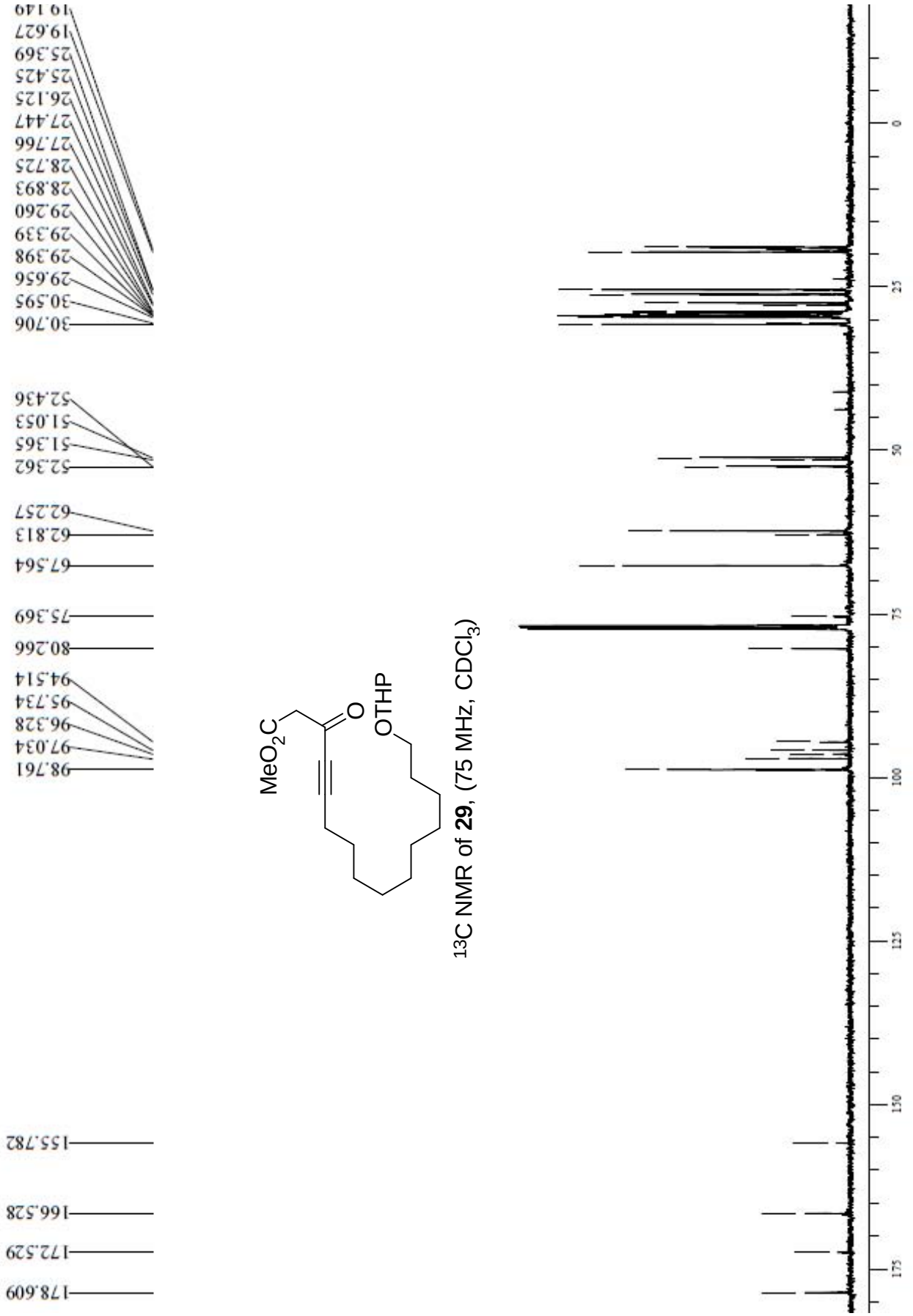


^{1}H NMR of **24a**, (500 MHz, $CDCl_3$)

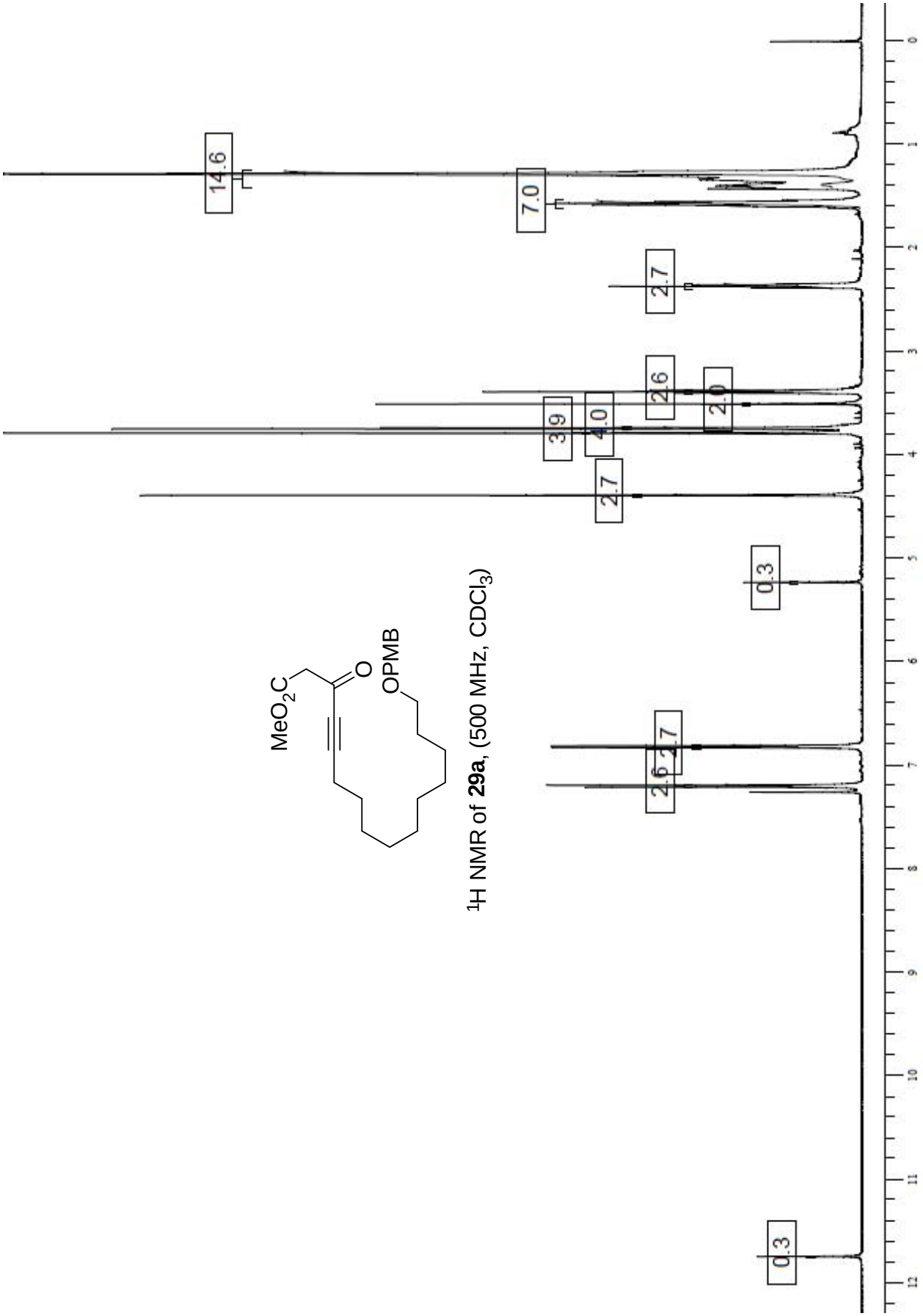

18.672
26.068
27.364
28.723
28.885
29.249
29.328
29.393
29.554
55.223
70.095
72.386
72.854
91.664
113.716
129.299
130.449
156.979
159.073
CO2H
OPMB
13C NMR of 24a, (75 MHz, CDCl3)



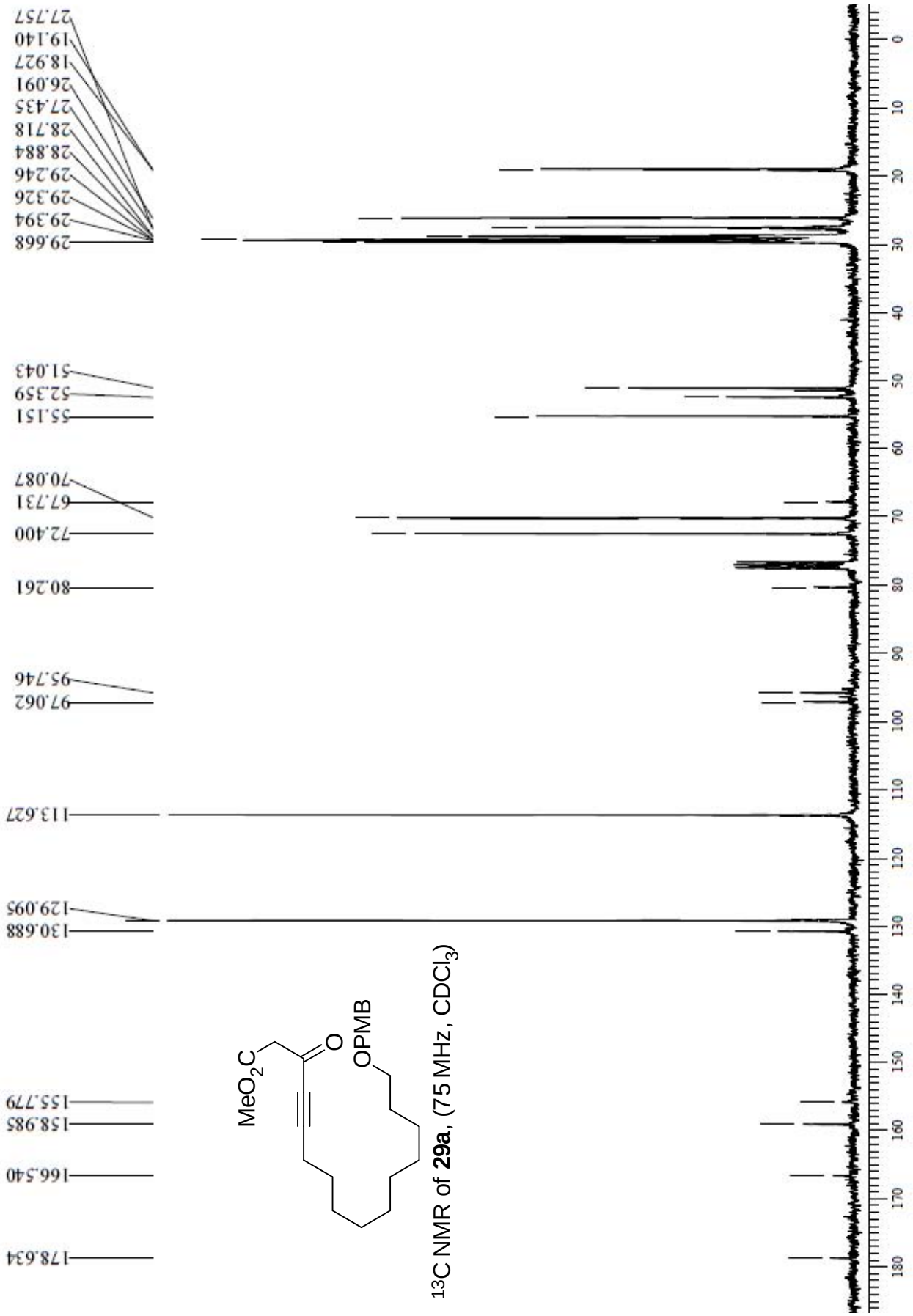
^{1}H NMR of **29**, (400 MHz, $CDCl_3$)

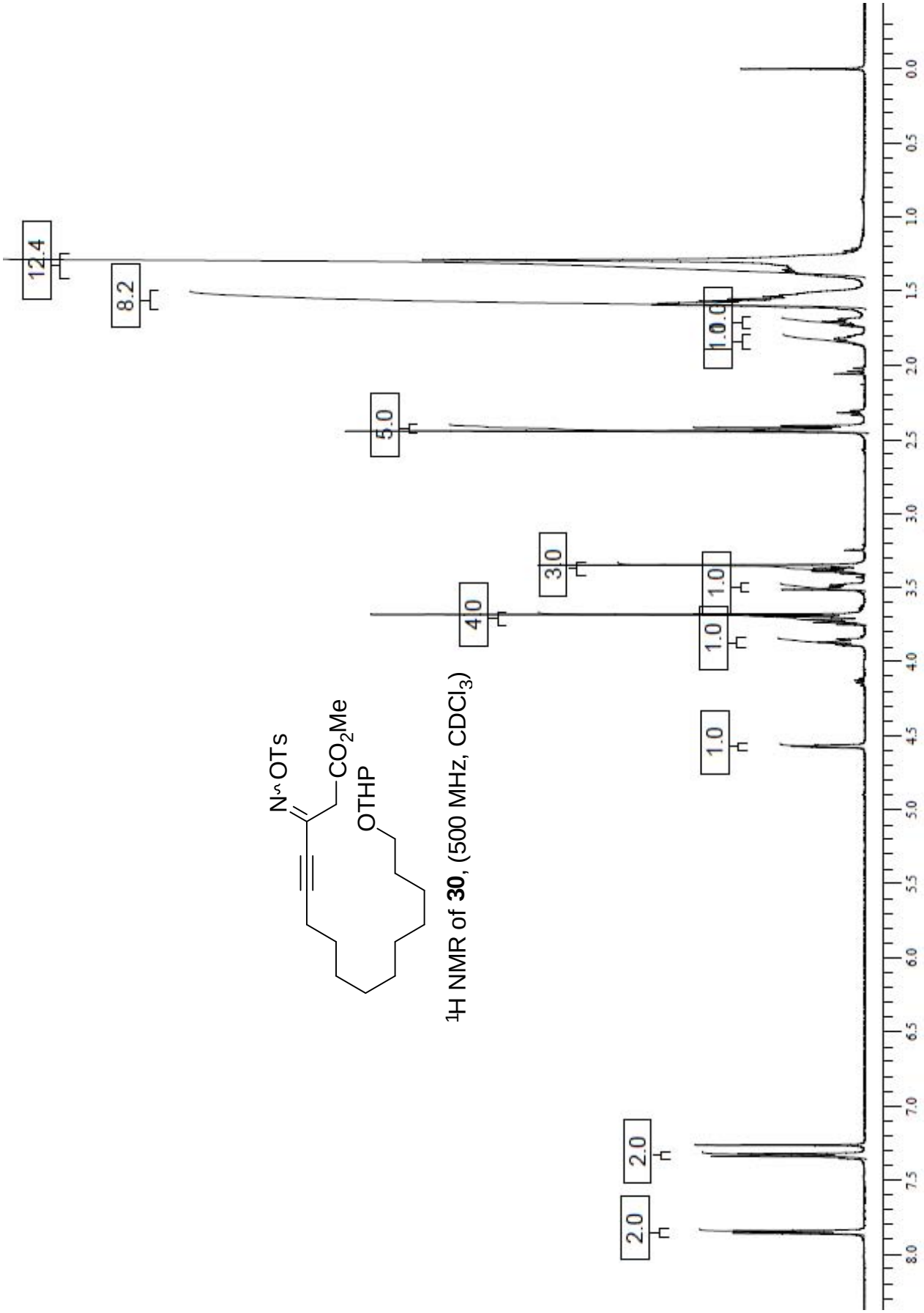


^{13}C NMR of **29**, (75 MHz, $CDCl_3$)

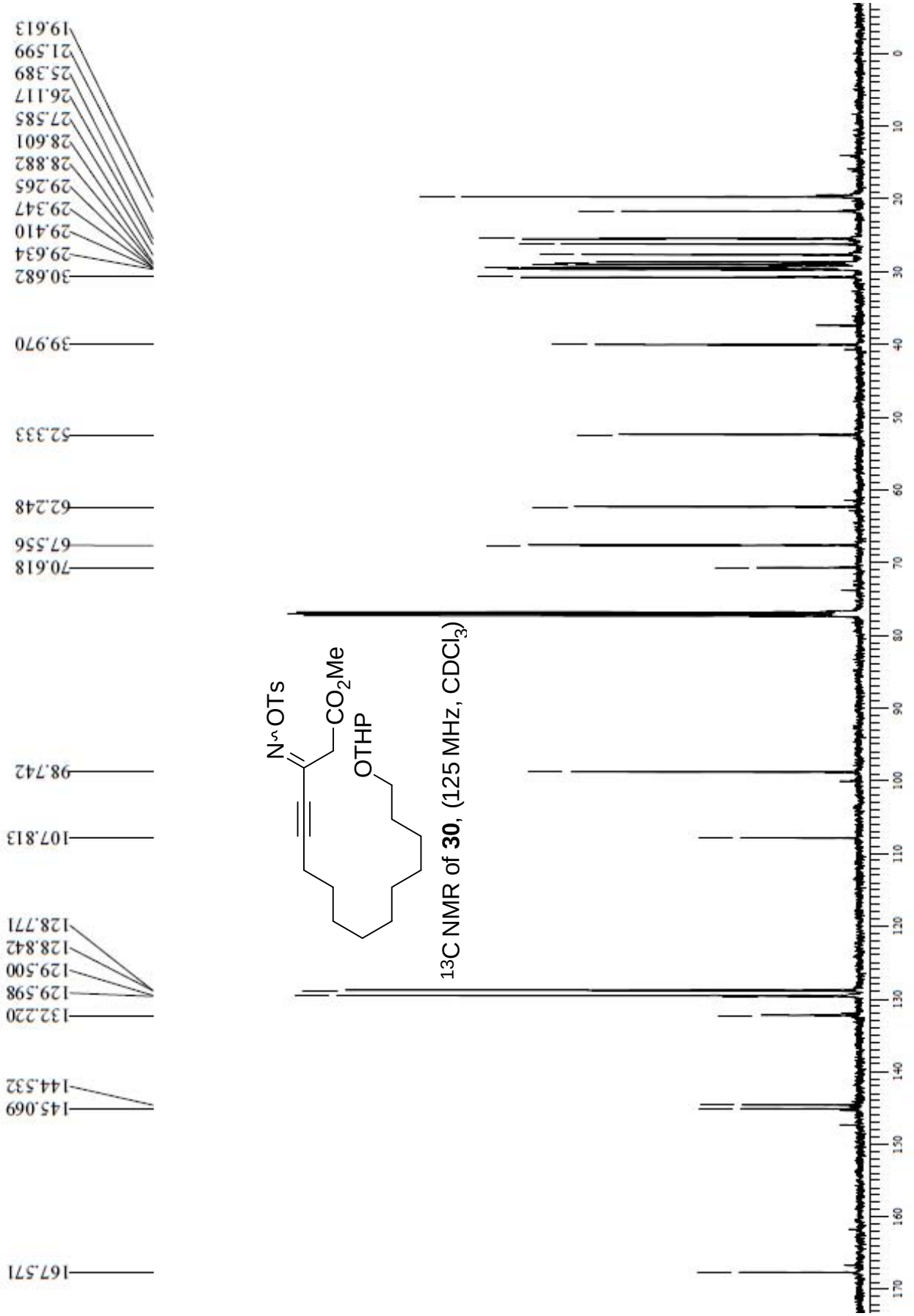


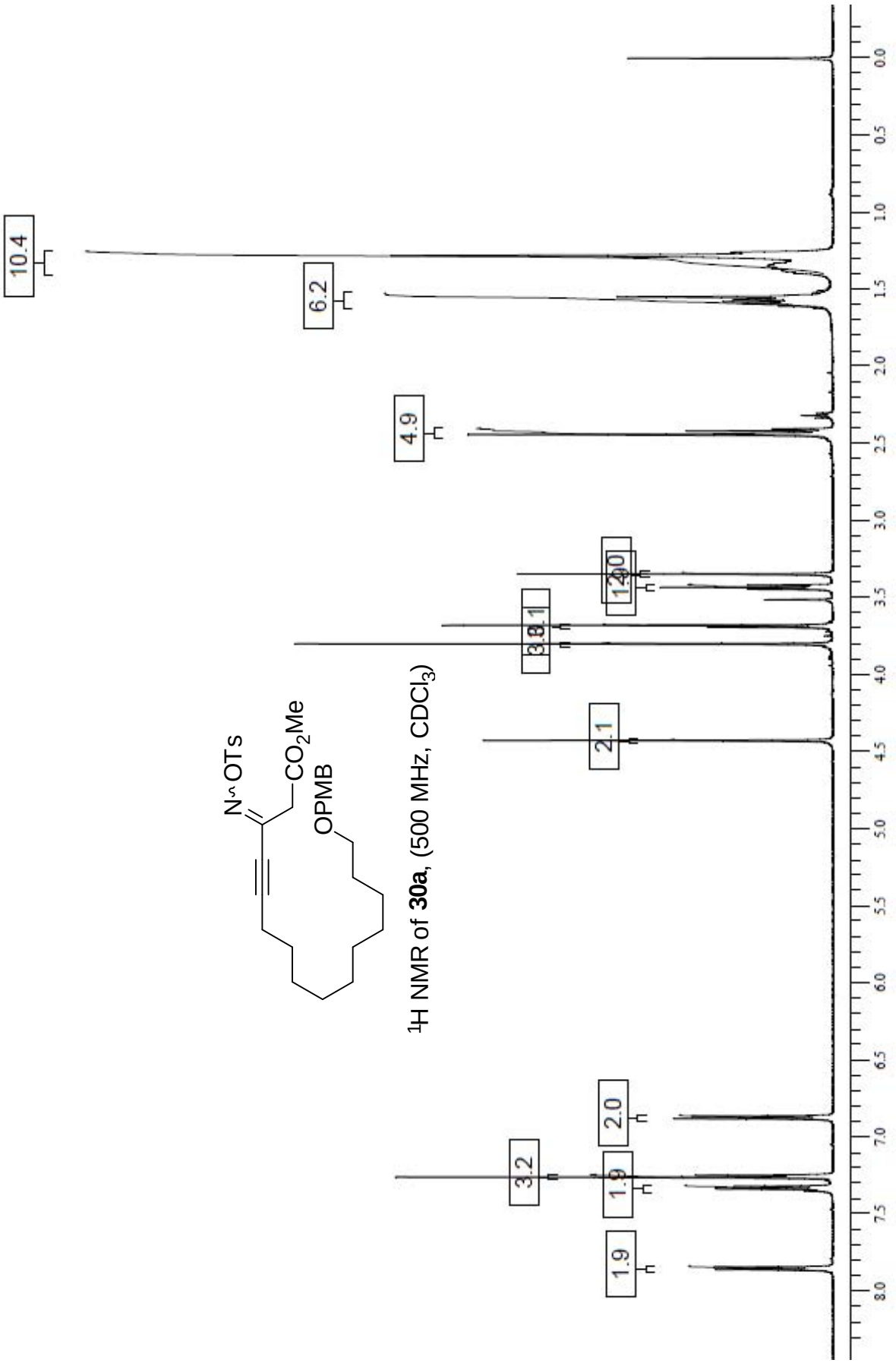
^{1}H NMR of **29a**, (500 MHz, $CDCl_3$)


27.757
19.140
18.927
26.091
27.435
28.718
28.884
29.246
29.326
29.394
29.668
51.043
52.359
55.151
70.087
67.731
72.400
80.261
95.746
97.062
113.627
129.095
130.688
155.779
158.985
166.540
178.634
MeO2C
O
OPMB
13C NMR of 29a, (75 MHz, CDCl3)

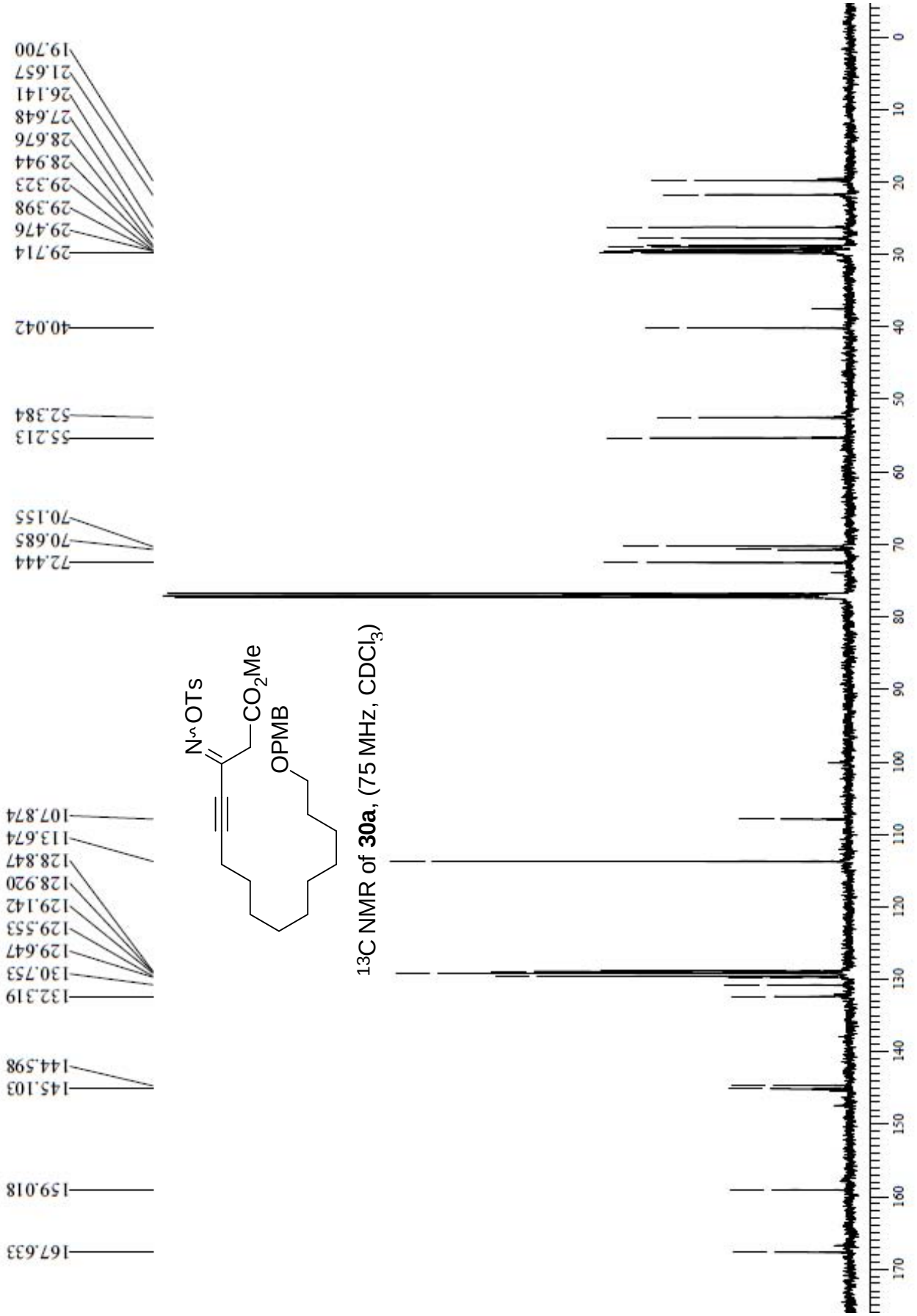


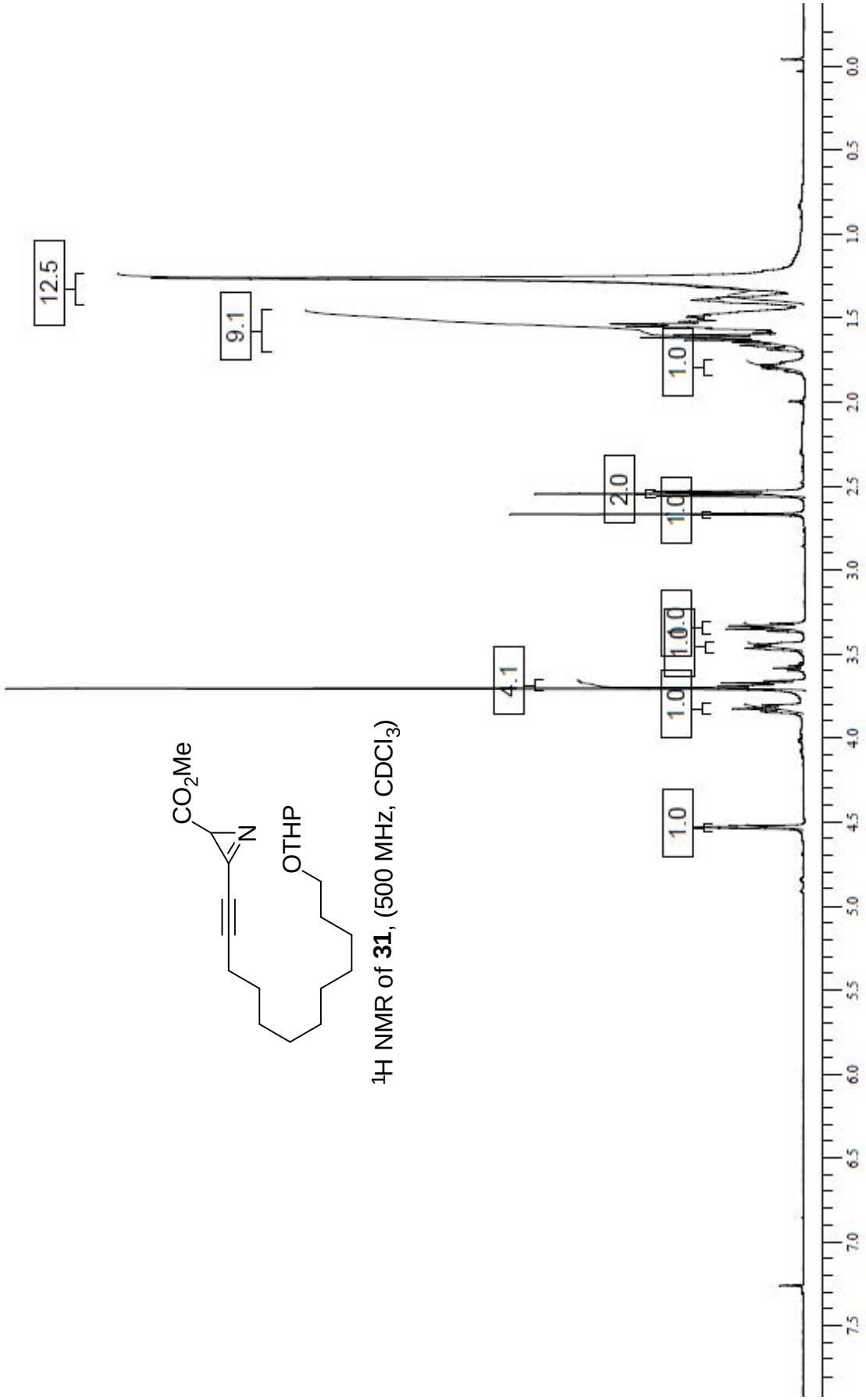
^{1}H NMR of **30**, (500 MHz, $CDCl_3$)


19.613
21.599
25.389
26.117
27.585
28.601
28.882
29.265
29.347
29.410
29.634
30.682
39.970
52.333
62.248
67.556
70.618
98.742
107.813
128.771
128.842
129.500
129.598
132.220
144.532
145.069
167.571
N
OTs
CO2Me
OTHP
13C NMR of 30, (125 MHz, CDCl3)

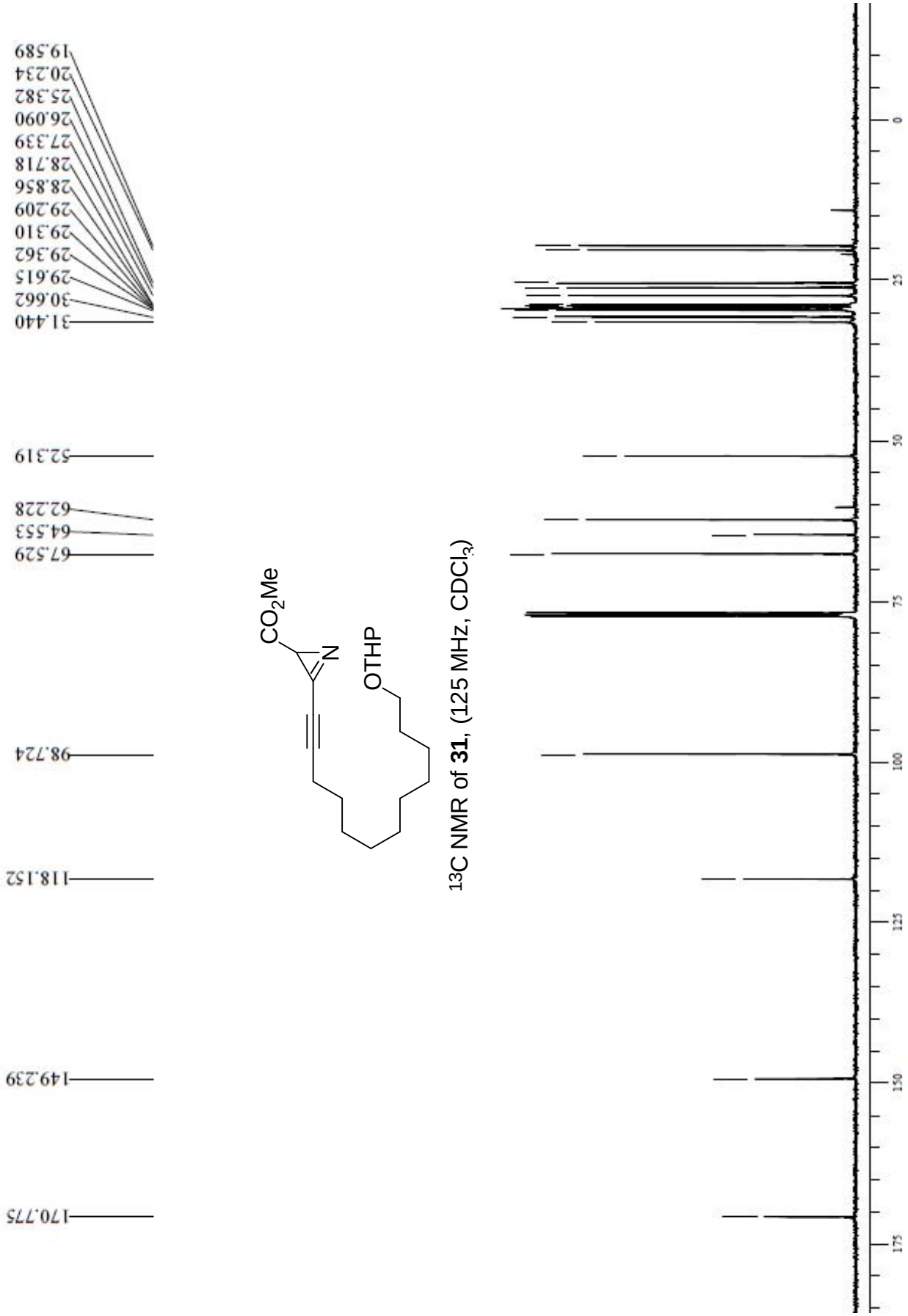


^{1}H NMR of **30a**, (500 MHz, $CDCl_3$)

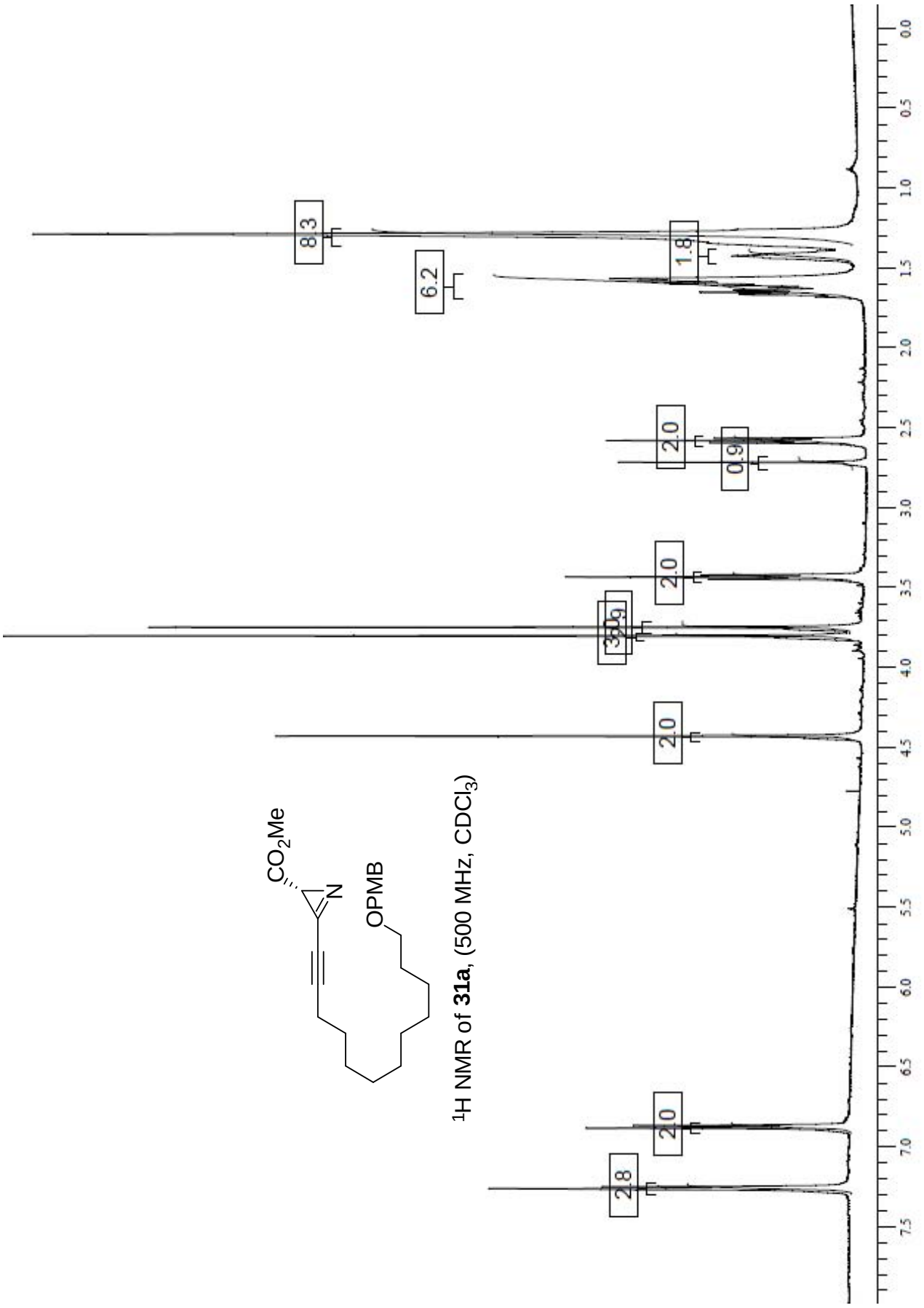

19.700
21.657
26.141
27.648
28.676
28.944
29.323
29.398
29.476
29.714
40.042
52.384
55.213
70.155
70.685
72.444
107.874
113.674
128.847
128.920
129.142
129.553
129.647
130.753
132.319
144.598
145.103
159.018
167.633
NOTs
CO2Me
OPMB
13C NMR of 30a, (75 MHz, CDCl3)



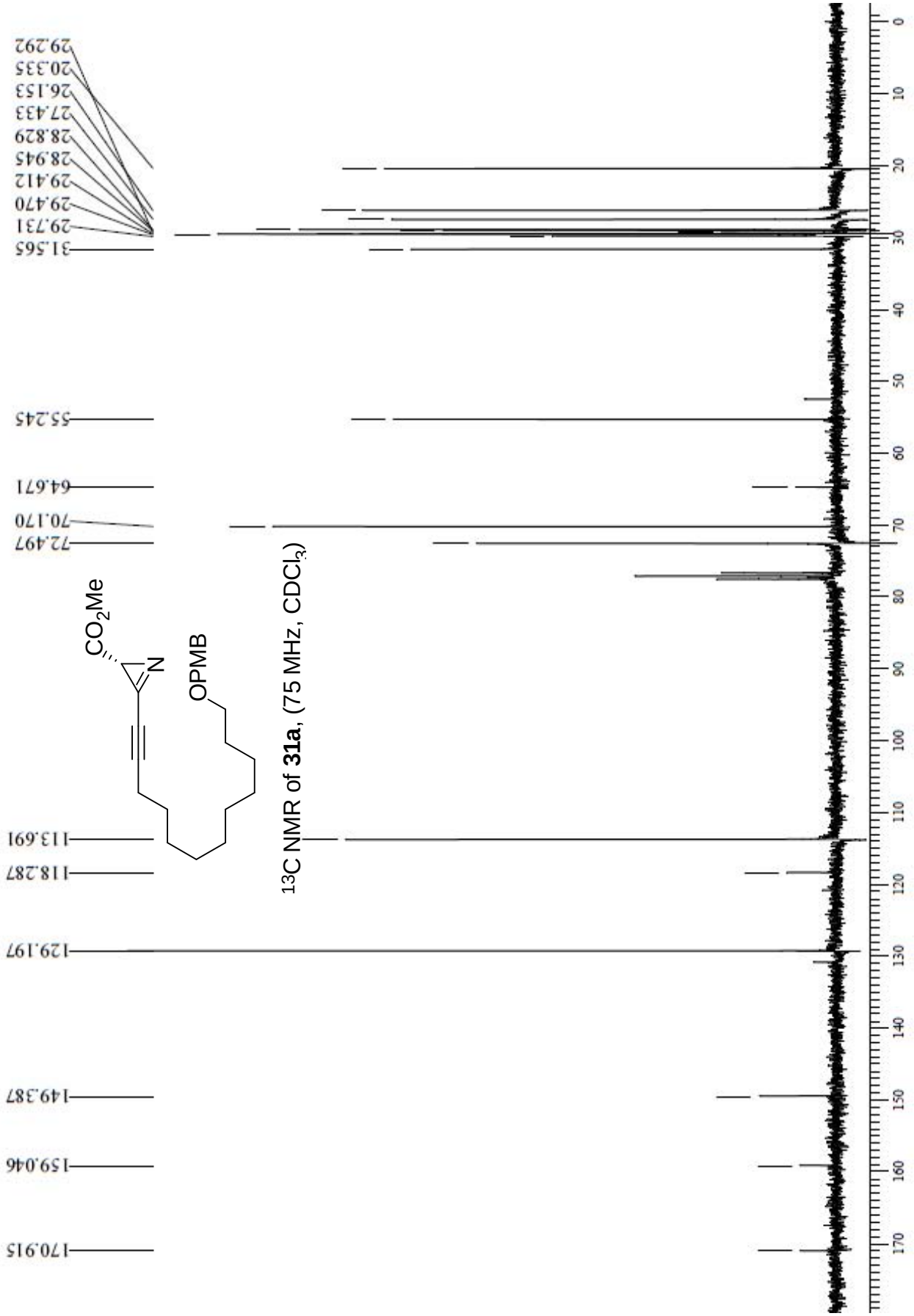
^{1}H NMR of **31**, (500 MHz, $CDCl_3$)

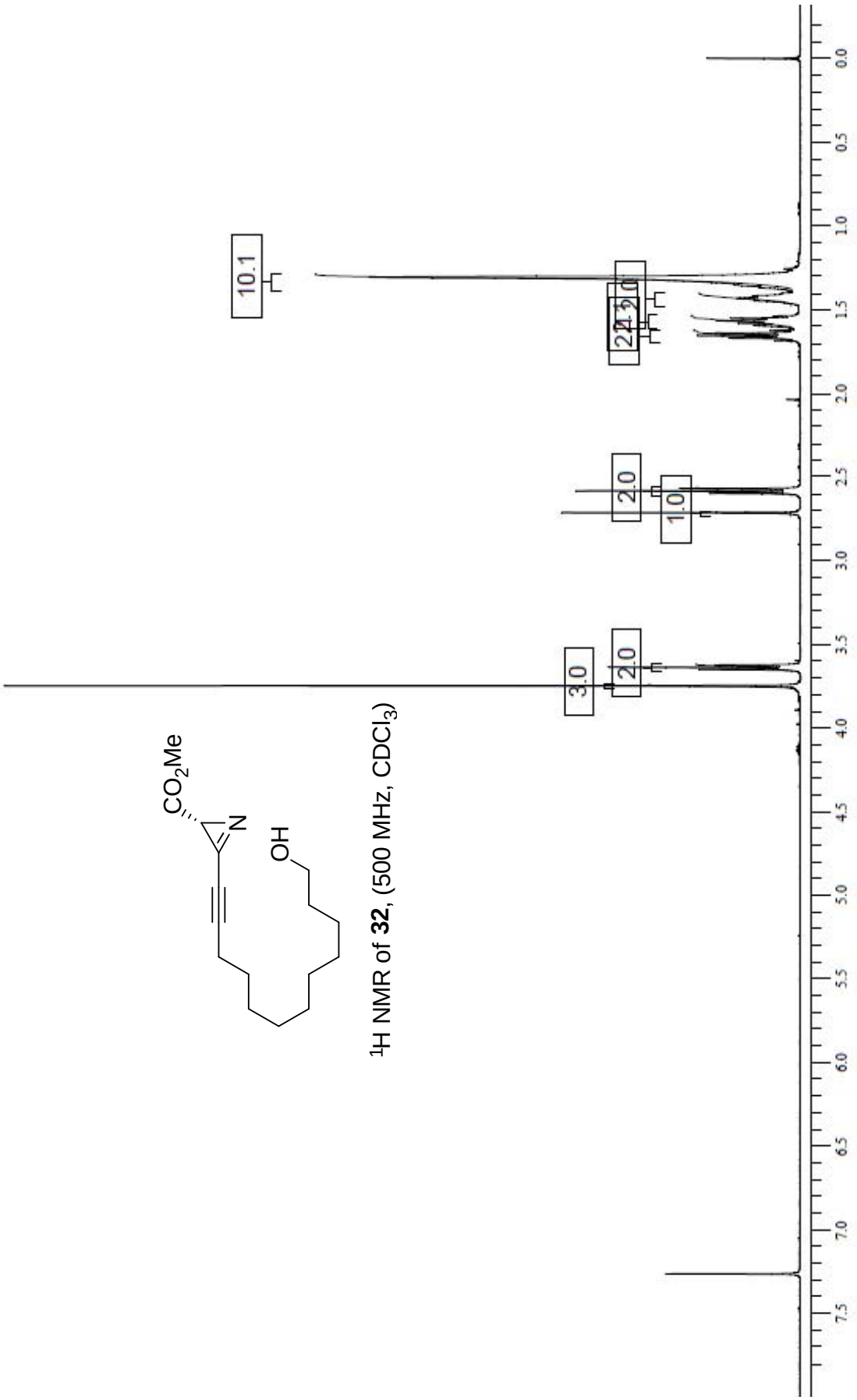


^{13}C NMR of **31**, (125 MHz, $CDCl_3$)

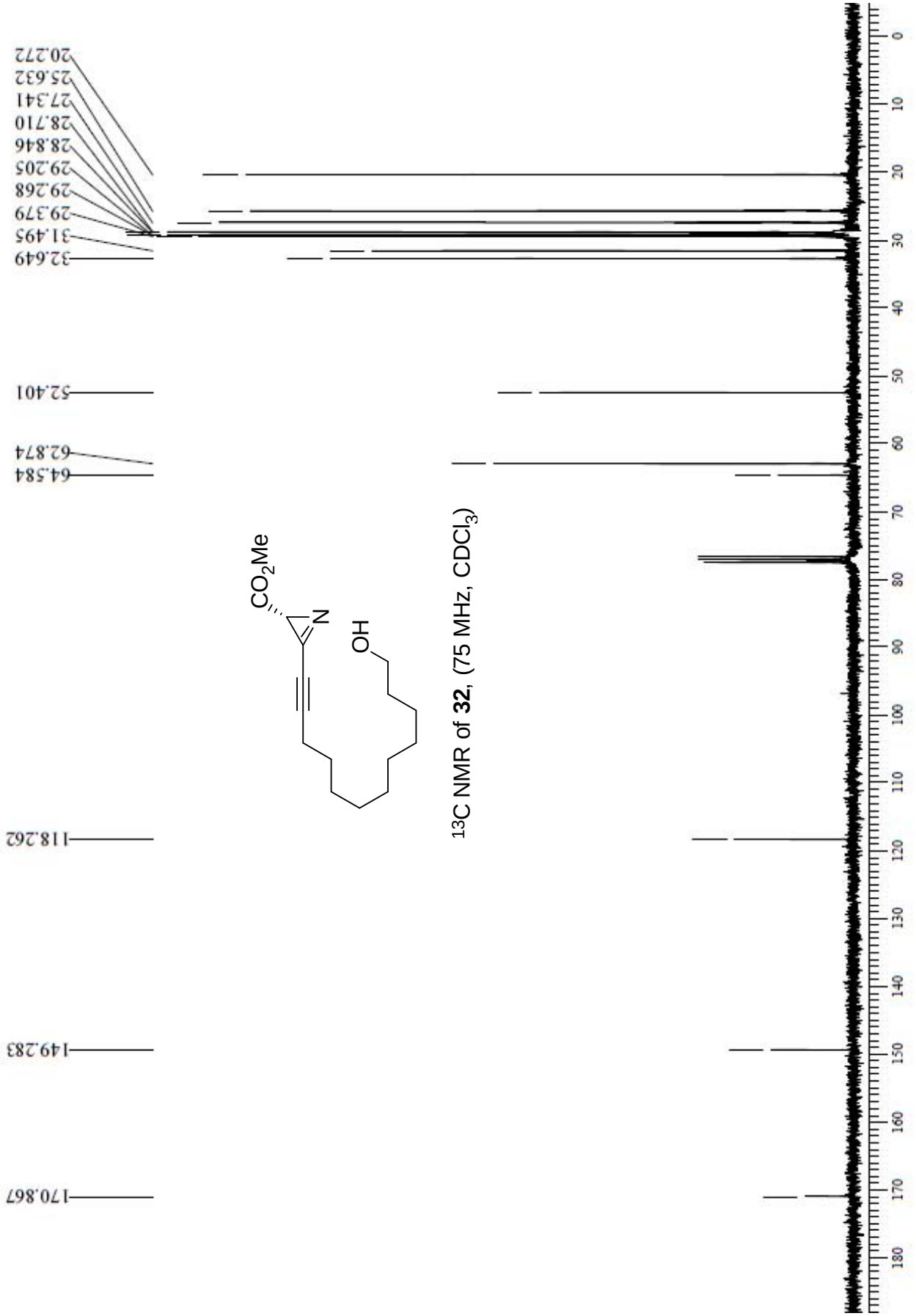


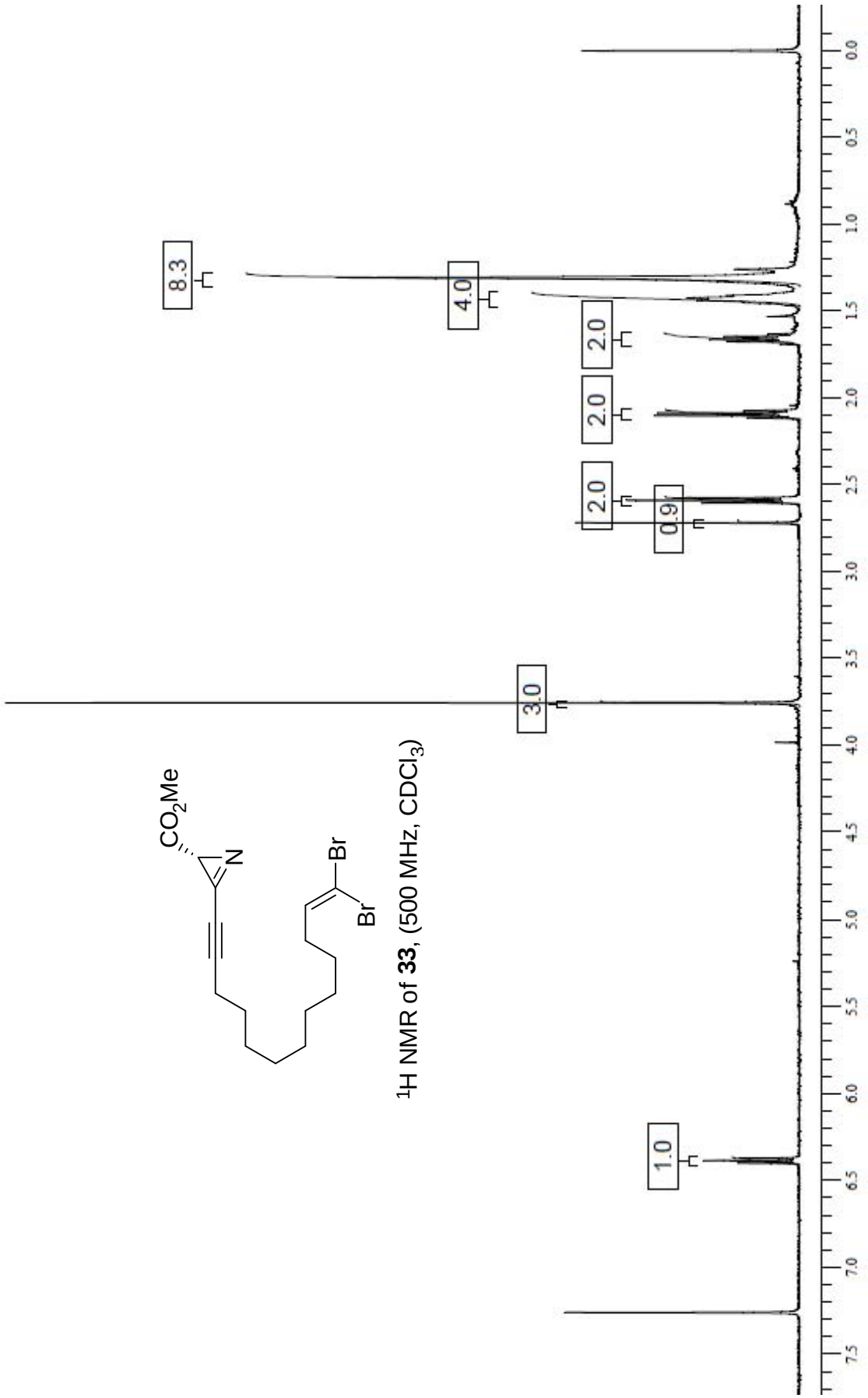
^{1}H NMR of **31a**, (500 MHz, $CDCl_3$)


^{13}C NMR of **31a**, (75 MHz, $CDCl_3$)
CO_2Me
N
OPMB
29.292
20.335
26.153
27.433
28.829
28.945
29.412
29.470
29.731
31.565
55.245
64.671
70.170
72.497
113.691
118.287
129.197
149.387
159.046
170.915

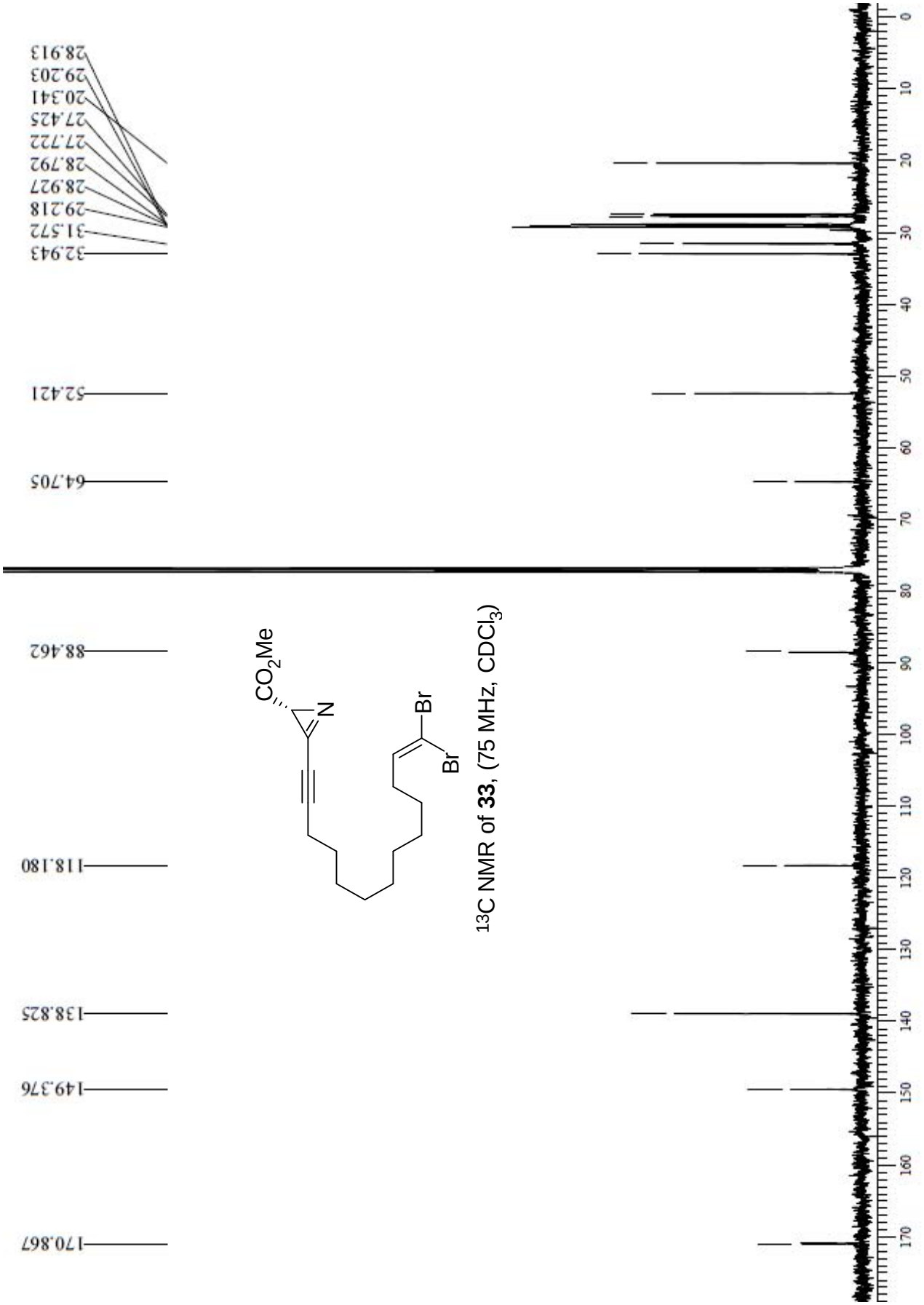


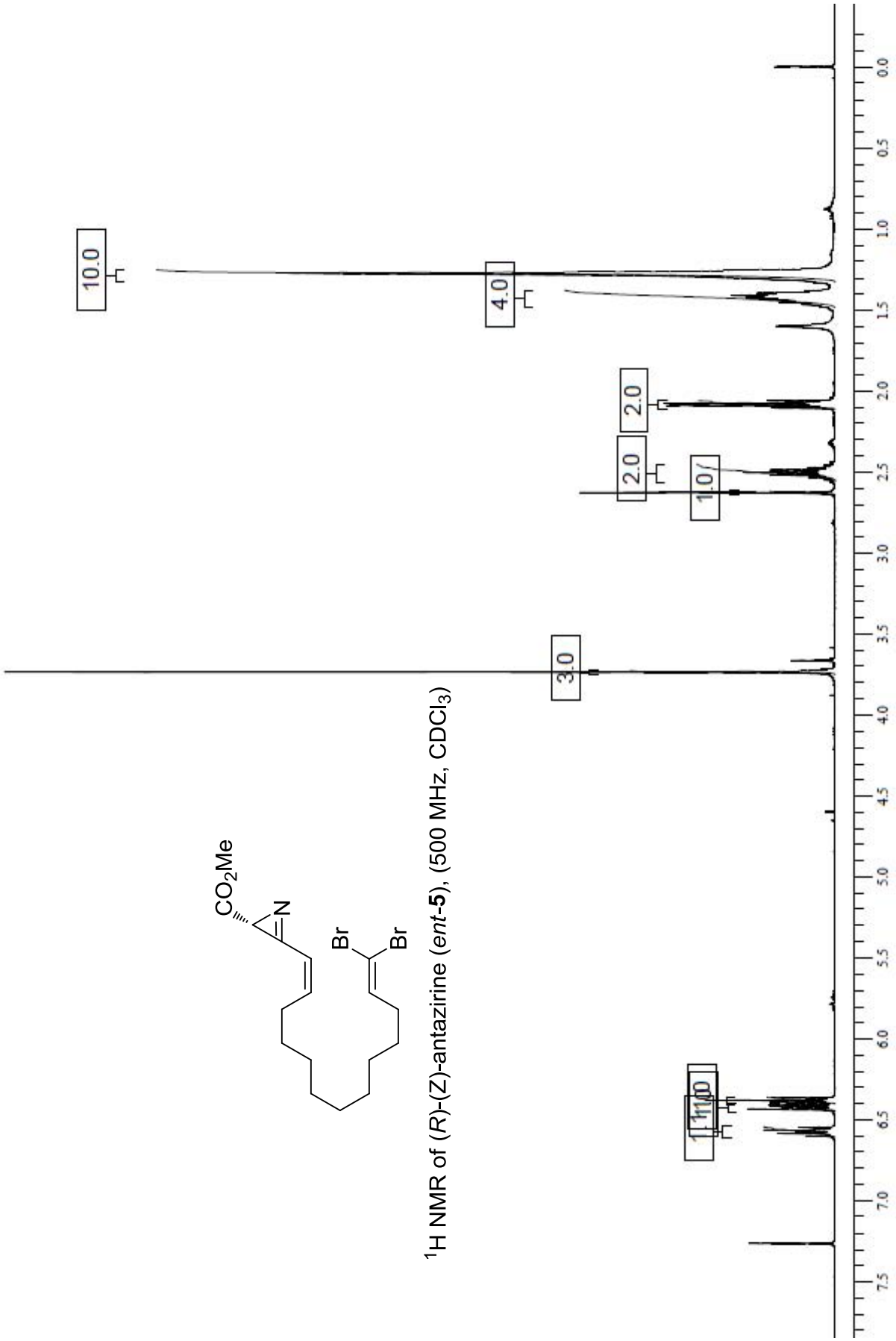
^{1}H NMR of **32**, (500 MHz, $CDCl_3$)


20.272
25.632
27.341
28.710
28.846
29.205
29.268
29.379
31.495
32.649
52.401
62.874
64.584
118.262
149.283
170.867
CO2Me
N
OH
13C NMR of 32, (75 MHz, CDCl3)

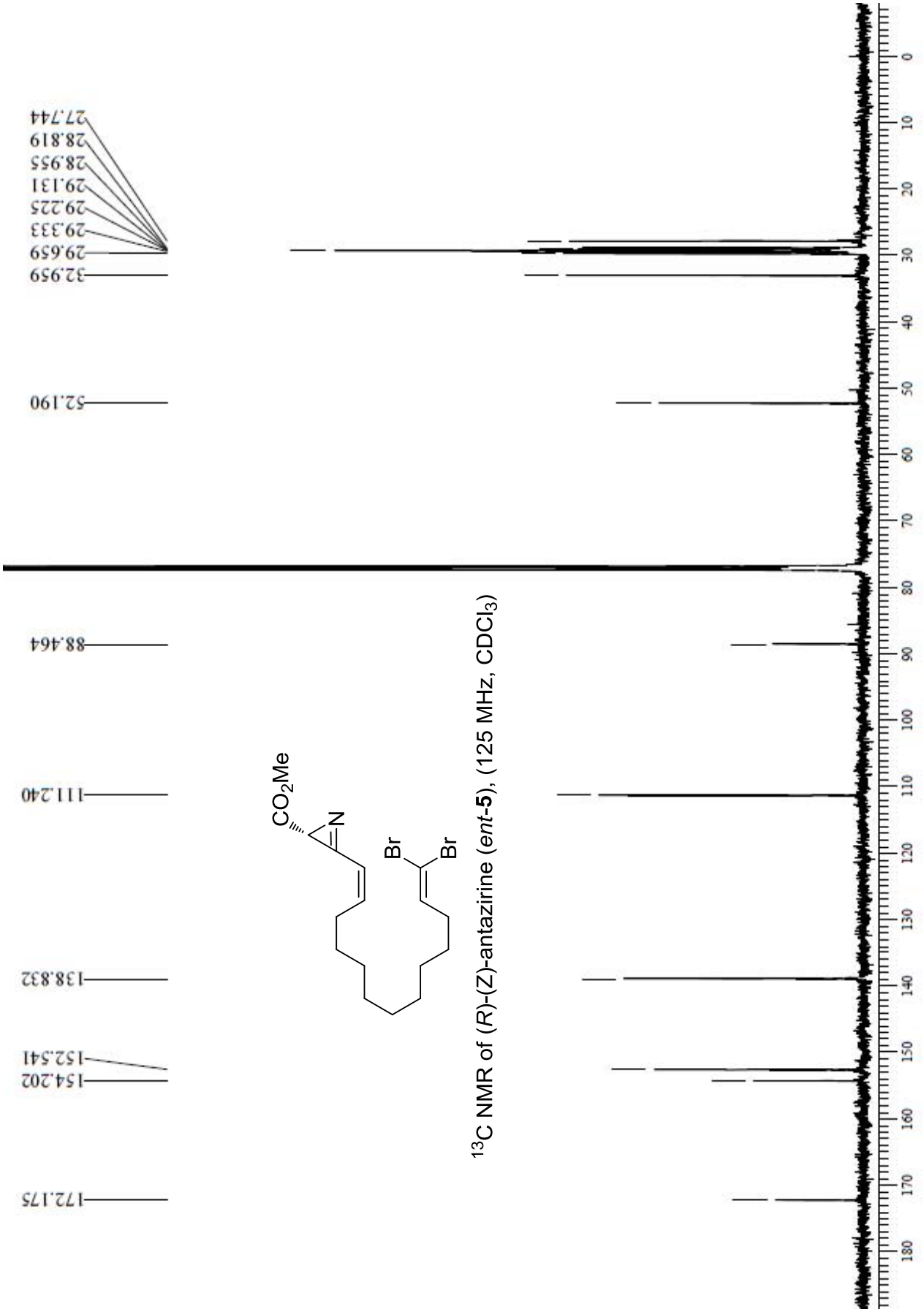


^{1}H NMR of **33**, (500 MHz, $CDCl_3$)

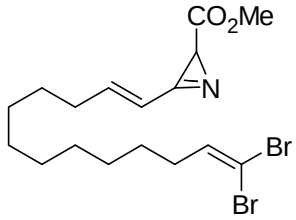

28.913
29.203
20.341
27.425
27.722
28.792
28.927
29.218
31.572
32.943
52.421
64.705
88.462
118.180
138.825
149.376
170.867
CO2Me
N
Br
Br
13C NMR of 33, (75 MHz, CDCl3)



^{1}H NMR of (*R*)-(*Z*)-antazirine (*ent*-**5**), (500 MHz, $CDCl_3$)



^{13}C NMR of (*R*)-(*Z*)-antazirine (*ent*-**5**), (125 MHz, $CDCl_3$)

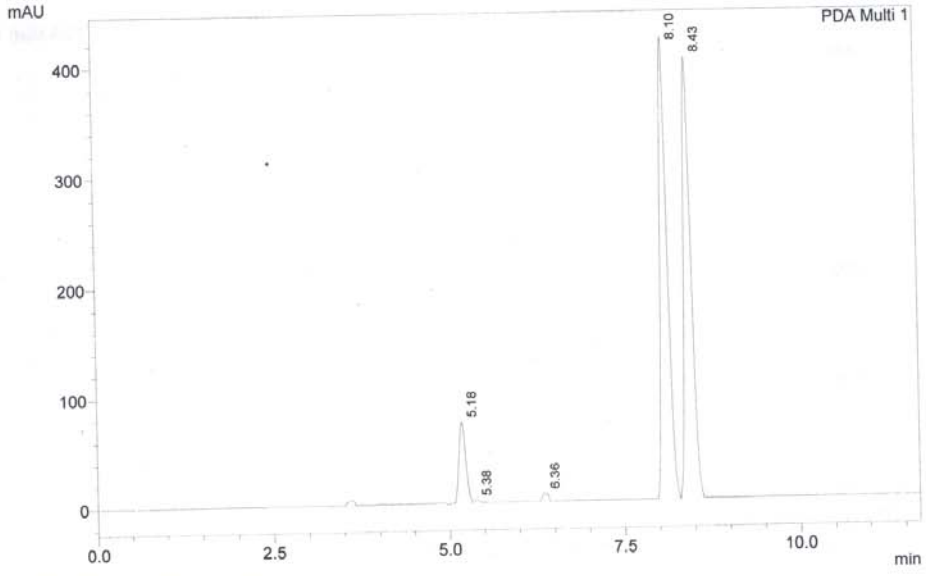


HPLC Chromatogram of (±)-**4**

IICT ORGANIC II DIVISION

D:\vilas\Antazirine Recemic3-3-12.1.lcd

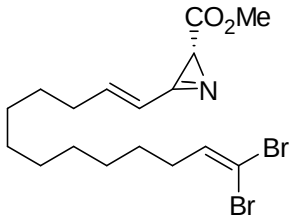
Acquired by : Admin
Sample Name : GS-Vk-279
Sample ID : GS-Vk-279
Data File Name : Antazirine Recemic3-3-12.1.lcd
Method File Name : TRIAL.lcm
Data Acquired : 3/3/2012 11:57:16 AM
Data Processed : 3/3/2012 1:14:10 PM
methanol/acn 90:10
chiralpack
FR:0.6ml/min
racemic
methanol/acn 90:10
chiralpack
FR:0.6ml/min
racemic



1 PDA Multi 1/200nm - 500nm 4nm

PDA Ch1 200nm - 500nm 4nm

Peak#	Ret. Time	Area	Area %
1	5.18	508687	7.80
2	5.38	19750	0.30
3	6.36	41205	0.63
4	8.10	2985853	45.79
5	8.43	2965672	45.48
Total		6521166	100.00

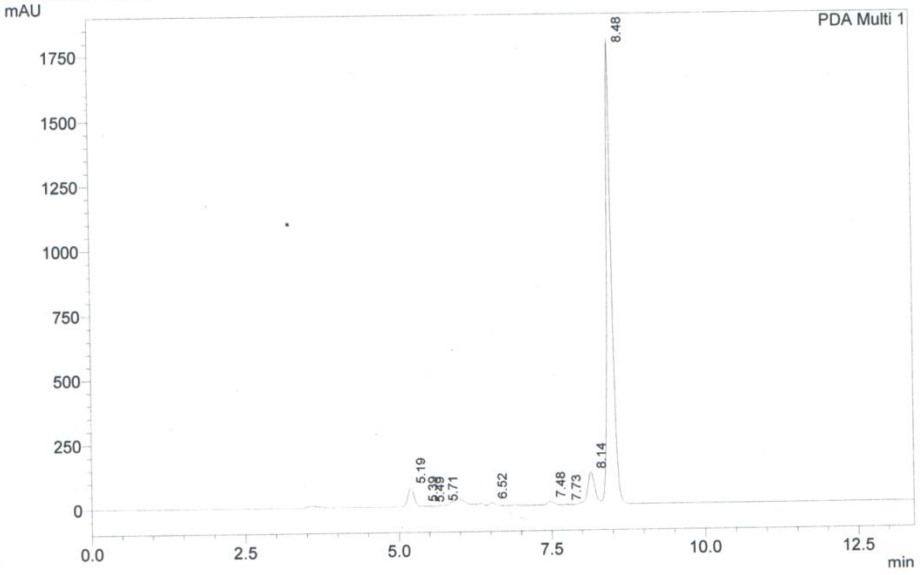


HPLC Chromatogram of (*ent*-**4**)

IICT ORGANIC II DIVISION

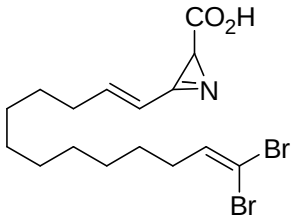
D:\vilas\Antazirine Enantioselective 3-3-13.lcd

Acquired by : Admin
Sample Name : GS-Vk-385
Sample ID : GS-Vk-385
Data File Name : Antazirine Enantioselective 3-3-13.lcd
Method File Name : TRIAL.lcm
Data Acquired : 3/3/2012 12:12:31 PM
Data Processed : 3/3/2012 12:25:58 PM
methanol/acn 90:10
chiralpack
FR:0.6ml/min
enantiomerically pure



PDA Ch1 200nm - 500nm 4nm

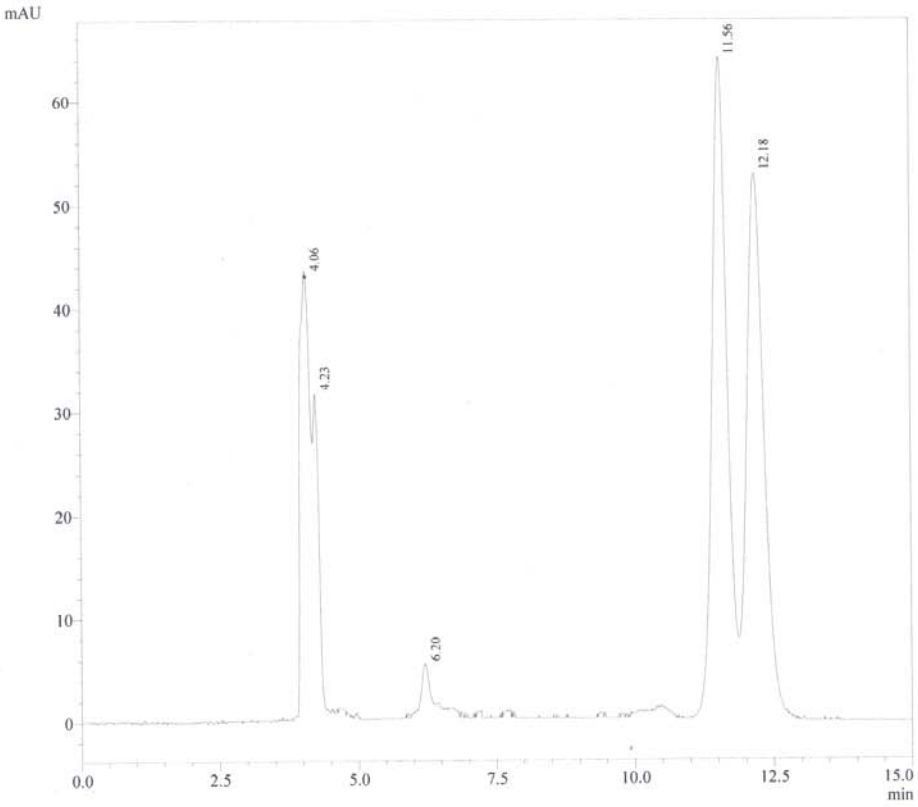
Peak#	Ret. Time	Area	Area %
1	5.19	464911	3.87
2	5.39	6355	0.05
3	5.49	4152	0.03
4	5.71	10667	0.09
5	6.52	62534	0.52
6	7.48	93767	0.78
7	7.73	3158	0.03
8	8.14	1044315	8.69
9	8.48	10330952	85.94
Total		12020810	100.00



HPLC Chromatogram of (±)-**14**

IICT ORGANIC II DIVISION

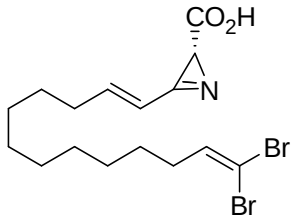
Acquired by : T RAMESH BABU
Sample Name : Ester
Sample ID : GS-VK-420 B
Data Filename : alcohol 104.lcd
Method Filename : rajesh.lcm
Date Acquired : 20/06/2012
D:\SUDHAKAR\alcohol 104.lcd



1 PDA Multi 1 / 200nm - 500nm 2nm

PDA Ch1 200nm - 500nm 2nm

Peak#	Ret. Time	Area	Area %
1	4.06	558855	17.44
2	4.23	230725	7.20
3	6.20	59521	1.86
4	11.56	1206503	37.65
5	12.18	1148970	35.85
Total		3204573	100.00

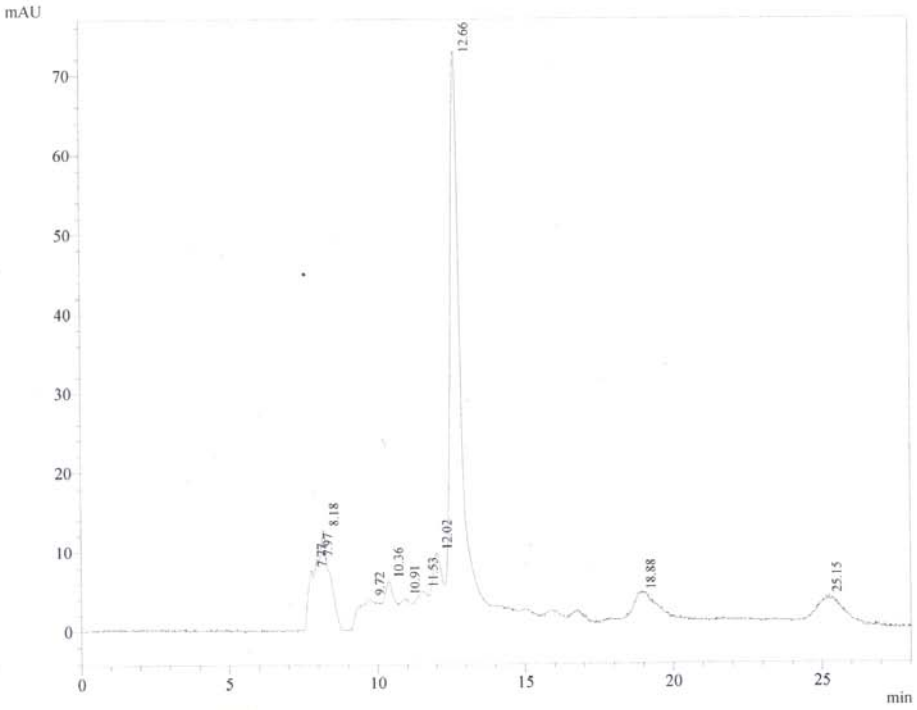


HPLC Chromatogram of (**14**)

INDIAN INSTITUTE OF CHEMICAL TECHNOLOGY
CROP PROTECTION CHEMICALS DIVISION

Acquired by : T RAMESH BABU
Sample Name : GS
Sample ID : VK-482 - Chiral
Data Filename : alcohol 117.lcd
Method Filename : ramesh.lcm
Date Acquired : 04/09/2012

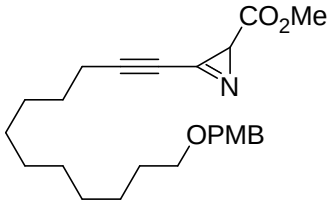
D:\SUDHAKAR\alcohol 117.lcd



1 PDA Multi 1 / 200nm - 500nm 2nm

PDA Ch1 200nm - 500nm 2nm

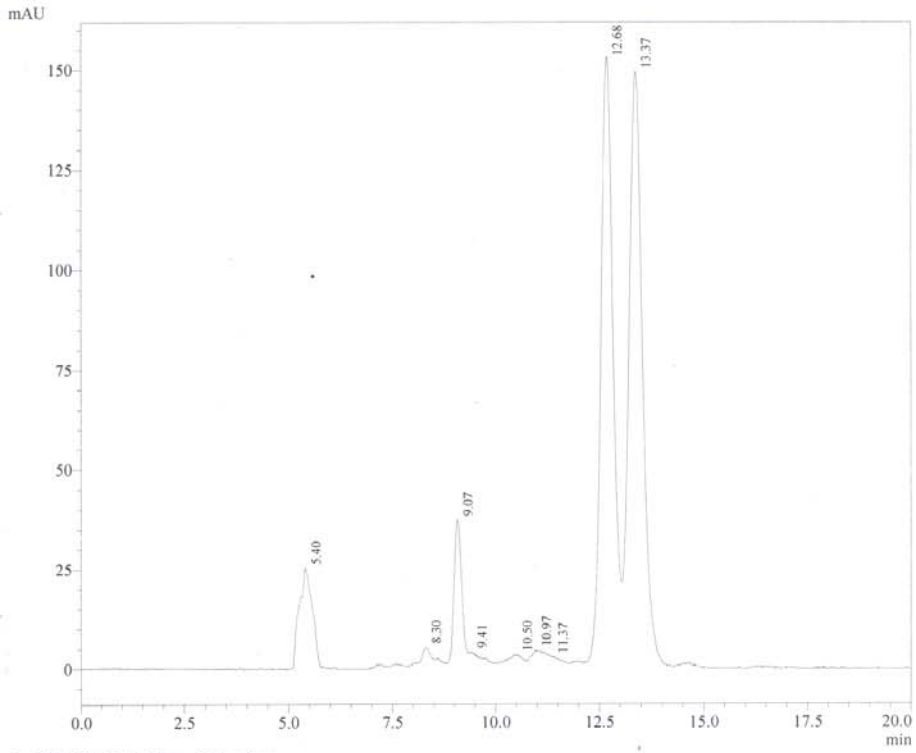
Peak#	Ret. Time	Area	Area %
1	7.77	97862	2.51
2	7.97	86326	2.22
3	8.18	303176	7.79
4	9.72	86978	2.24
5	10.36	170619	4.38
6	10.91	102867	2.64
7	11.53	136687	3.51
8	12.02	254414	6.54
9	12.66	2538455	65.23
10	18.88	67443	1.73
11	25.15	46426	1.19
Total		3891254	100.00



HPLC Chromatogram of (±)-**31a**

IICT ORGANIC II DIVISION

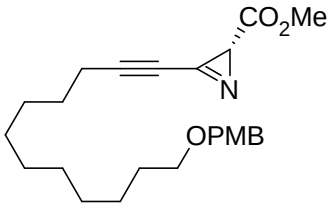
Acquired by : T RAMESH BABU
Sample Name : Ester
Sample ID : GS-VK-420 R
Data Filename : alcohol 102.lcd
Method Filename : rajesh.lcm
Date Acquired : 20/06/2012
D:\SUDHAKAR\alcohol 102.lcd



1 PDA Multi 1 / 200nm - 500nm 2nm

PDA Ch1 200nm - 500nm 2nm

Peak#	Ret. Time	Area	Area %
1	5.40	573146	7.04
2	8.30	86866	1.07
3	9.07	500930	6.16
4	9.41	52559	0.65
5	10.50	98272	1.21
6	10.97	108704	1.34
7	11.37	55293	0.68
8	12.68	3221112	39.58
9	13.37	3440822	42.28
Total		8137704	100.00

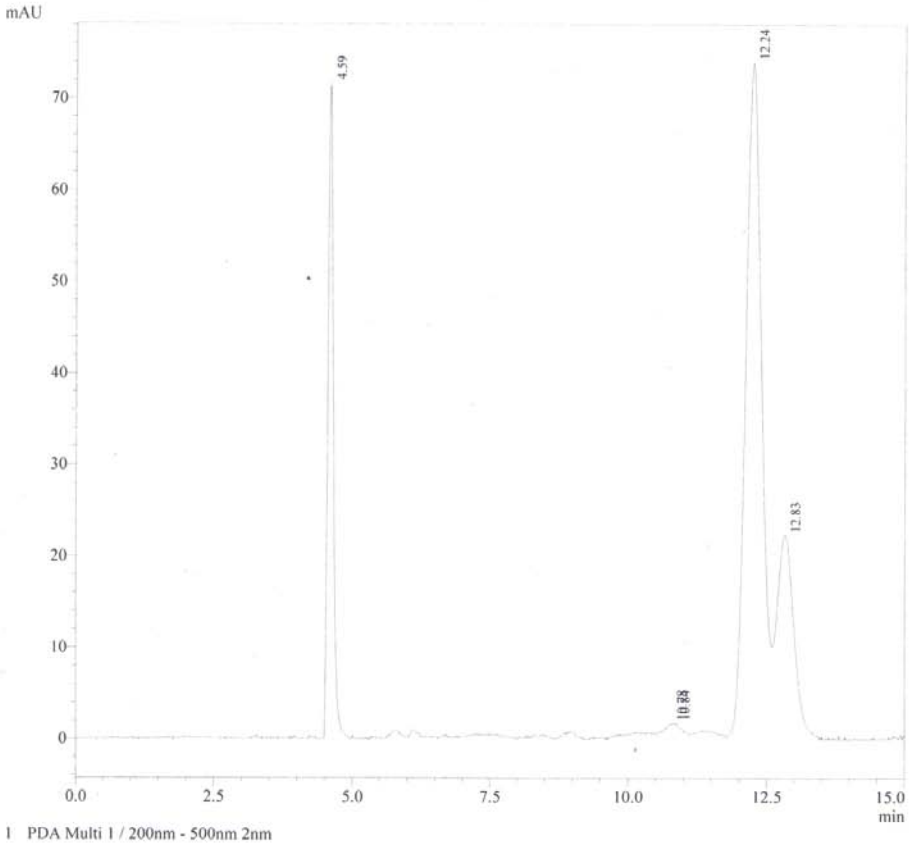


HPLC Chromatogram of **31a**

INDIAN INSTITUTE OF CHEMICAL TECHNOLOGY
CROP PROTECTION CHEMICALS DIVISION

Acquired by : T RAMESH BABU
Sample Name : Ester
Sample ID : GS-VK-478 Chiral
Data Filename : alcohol 111.lcd
Method Filename : ramesh.lcm
Date Acquired : 22/08/2012

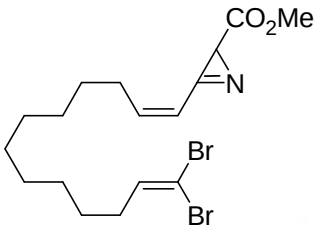
D:\SUDHAKAR\alcohol 111.lcd



1 PDA Multi 1 / 200nm - 500nm 2nm

PDA Ch1 200nm - 500nm 2nm

Peak#	Ret. Time	Area	Area %
1	4.59	491923	19.43
2	10.78	20827	0.82
3	10.84	24354	0.96
4	12.24	1505530	59.46
5	12.83	489462	19.33
Total		2532096	100.00

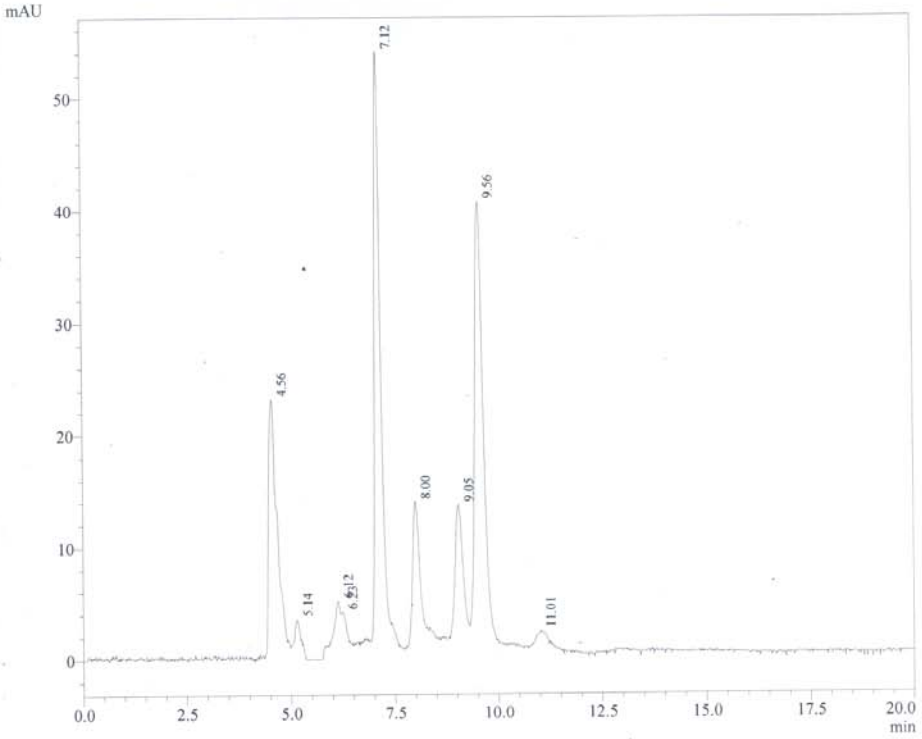


HPLC Chromatogram of (±)-**5**

INDIAN INSTITUTE OF CHEMICAL TECHNOLOGY
CROP PROTECTION CHEMICALS DIVISION

Acquired by : T RAMESH BABU
Sample Name : GS
Sample ID : Vk - 331 - Racemic
Data Filename : alcohol 114.lcd
Method Filename : ramesh.lcm
Date Acquired : 29/08/2012

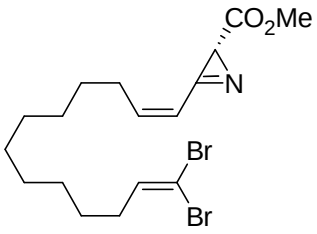
D:\SUDHAKAR\alcohol 114.lcd



1 PDA Multi 1 / 200nm - 500nm 2nm

PDA Ch1 200nm - 500nm 2nm

Peak#	Ret. Time	Area	Area %
1	4.56	347812	16.14
2	5.14	45124	2.09
3	6.12	64270	2.98
4	6.23	42847	1.99
5	7.12	611835	28.38
6	8.00	226558	10.51
7	9.05	218628	10.14
8	9.56	565092	26.22
9	11.01	33415	1.55
Total		2155581	100.00

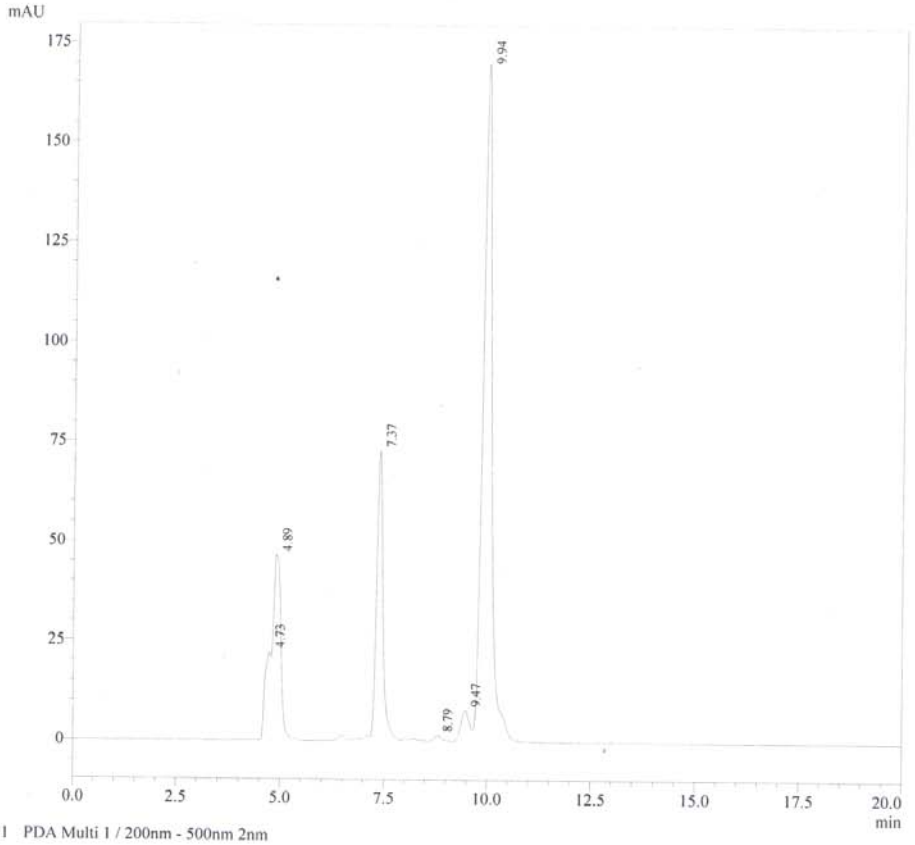


HPLC Chromatogram of (*ent*-**5**)

INDIAN INSTITUTE OF CHEMICAL TECHNOLOGY
CROP PROTECTION CHEMICALS DIVISION

Acquired by : T RAMESH BABU
Sample Name : GS
Sample ID : Vk - 483 - Chiral
Data Filename : alcohol 115.lcd
Method Filename : ramesh.lcm
Date Acquired : 29/08/2012

D:\SUDHAKAR\alcohol 115.lcd



1 PDA Multi 1 / 200nm - 500nm 2nm

PDA Ch1 200nm - 500nm 2nm

Peak#	Ret. Time	Area	Area %
1	4.73	207408	4.71
2	4.89	621150	14.12
3	7.37	795333	18.08
4	8.79	23017	0.52
5	9.47	115454	2.62
6	9.94	2636619	59.94
Total		4398981	100.00