Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Identification of noreremophilane-based inhibitors of angiogenesis using zebrafish assays†

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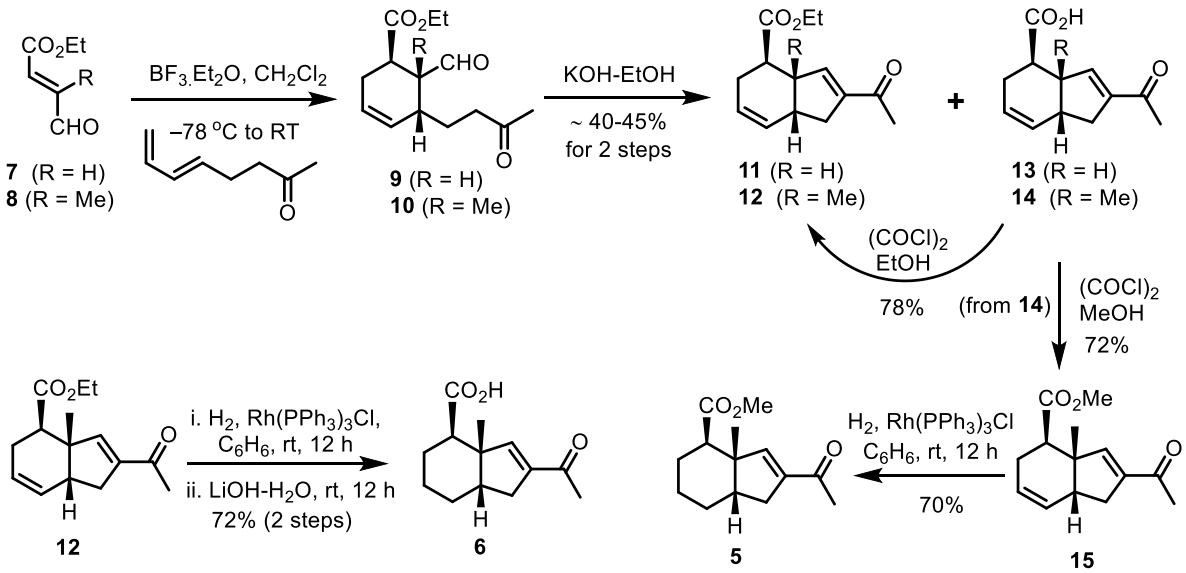
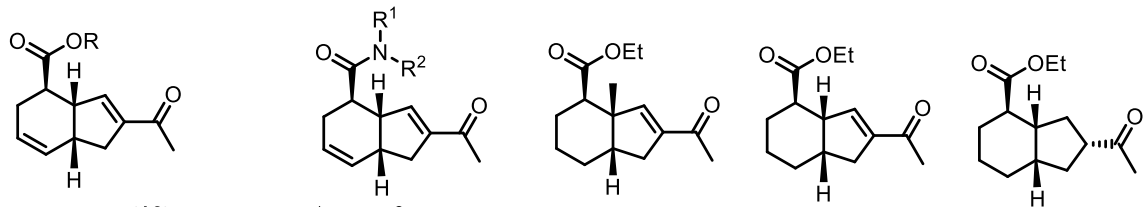
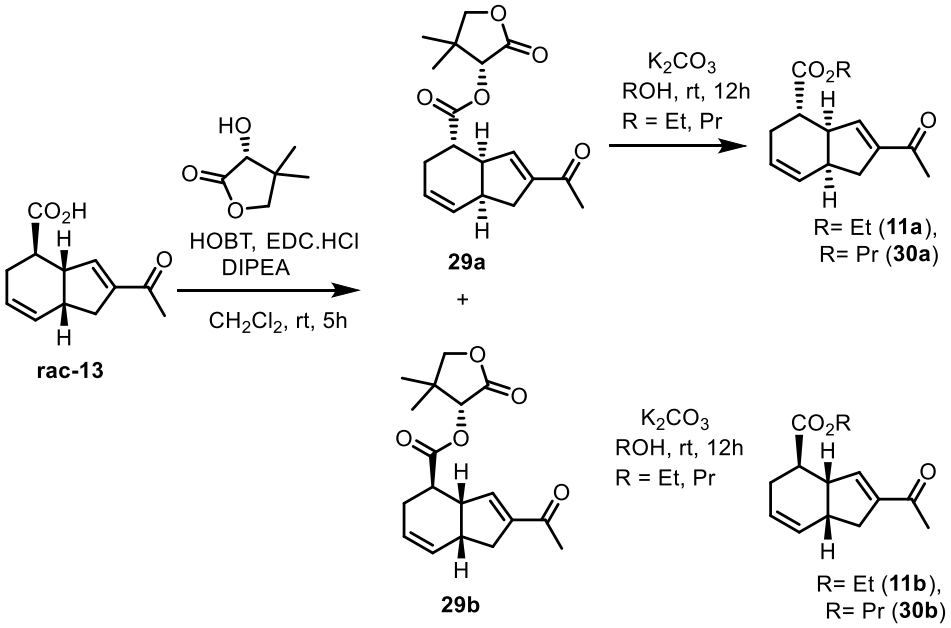
Synthesis of *cis*-hydrindanes and 11

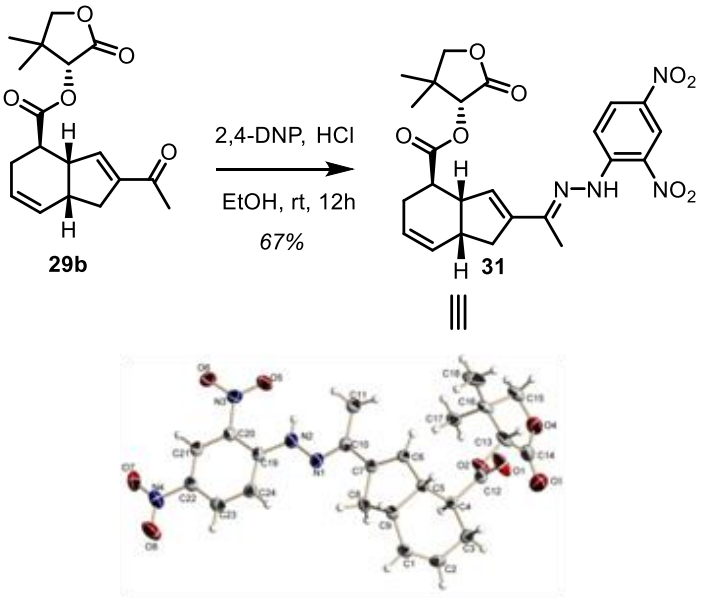




Scheme S1

Synthesis of enantiopure *cis*-hydrindanes





ORTEP of **31**

Scheme S2

Single X-ray Crystal Structure of 31

(*R*)-4,4-dimethyl-2-oxotetrahydrofuran-3-yl(3a*S*,4*R*,7a*R*)-2-((E)-1-(2-(2,4-dinitrophenyl)hydrazono)ethyl)-3a,4,5,7a-tetrahydro-1H-indene-4-carboxylate (31): To a solution of **29b**(20 mg, 0.062 mmol) in EtOH (3.0 mL) was added 2,4-dinitrophenylhydrazine (21 mg, 0.106 mmol) followed by 1 drops of conc. HCl at room temperature. The mixture was allowed to stir at room temperature for overnight. Solvent was removed *in vacuo*. Ether (5 mL) was added followed by 10% $NaHCO_3$ (2 mL). The aqueous layer was extracted by ether (2 x 5 mL) and dried over anhydrous Na_2SO_4. Purification by flash chromatography (2.0:8.0% EtOAc: Petroleum Ether) to afford **31** (21 mg, 67%) as orange colored solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.2 (s, 1H), 9.11 (d, *J* = 2.4 Hz, 1H), 8.30 (dd, *J* = 9.5, 2.4 Hz, 1H), 7.95 (d, *J* = 9.5 Hz, 1H), 6.54 (s, 1H), 5.88–5.78 (m, 2H), 5.45 (s, 1H), 4.07 (s, 2H), 3.16–3.01 (m, 3H), 2.56–2.52 (m, 1H), 2.47–2.41 (m, 1H), 2.34–2.32 (m , 2H), 2.23 (s, 3H), 1.22 (s, 3H), 1.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 172.5, 151.0, 144.9, 143.6, 138.2, 137.5, 130.1, 130.0, 129.7, 124.3, 123.6, 116.8, 76.4, 75.2, 46.4, 42.5, 40.3, 37.9, 37.5, 27.0, 23.1, 20.1, 12.9.

Single crystals of compounds **31** (KLH-E-23) were obtained from ethyl acetate-hexane mixture. X-ray intensity data were collected on a Bruker SMART APEX II CCD diffractometer with graphite-monochromatized (Mo Kα=0.71073 Å) radiation at room temperature 296(2) K. The X-ray generator was operated at 50 kV and 30 mA. Diffraction data were collected with a ω scan width of 0.5° and at different settings of φ and 2θ. The sample-to-detector distance was fixed at 5.00 cm. The X-ray data acquisition was monitored by APEX II program suite.[1] All the data were corrected for Lorentz-polarization and absorption effects using SAINT and SADABS programs integrated in APEX II program package.[1] The structures were solved by direct method and refined by full matrix least squares, based on F^2, using SHELX-97[2]. Molecular diagrams were generated using XSHELL program integrated in SHELXTL package. All the H-atoms (except H-atom bound to N atom) were placed in geometrically idealized position (C-H = 0.93 Å for the phenyl H-atom, C-H = 0.97 Å for the methylene H-atom, C-H = 0.98 Å for the methine H-atom and C-H = 0.96 Å for the methyl H-atom) and constrained to ride on their parent atoms [U_{iso}(H) = 1.2U_{eq}(C) for the phenyl, methylene and methine group and U_{iso}(H) = 1.5 U_{eq}(C) for the methyl group]. The H-atom attached to N-atom in **31** (KLH-E-23) is located in difference Fourier and refined isotropically.

Crystallographic data for 31 (KLH-E-23)**.** ($C_{24}H_{26}N_4O_8$): *M* = 498.49, Crystal dimensions 0.53 x 0.49 x 0.30 mm^3, monoclinic, space group *P* 2_1,*a* = 5.9435(4), *b* = 12.4041(8), *c* = 16.5108(11) Å, β= 92.519(4)°, *V* = 1216.06(14) Å^3, *Z* = 2, ρ_{calcd} = 1.361 gcm^{-3}, μ (Mo-K$_\alpha$) = 0.104 mm^{-1}, *F(000)* = 524, $2\theta_{max}$ = 56.64°, *T* = 296(2) K, 23510 reflections collected, 5326 unique, 4403 observed ($I > 2\sigma(I)$) reflections, 332 refined parameters, *R* value 0.0545, *wR*2 = 0.1114, (all data *R* = 0.0702, *wR*2 = 0.1181), *S* = 1.123, minimum and maximum

transmission 0.947 and 0.970; maximum and minimum residual electron densities +0.20 and –0.21 e $Å^{-3}$.

Figures:

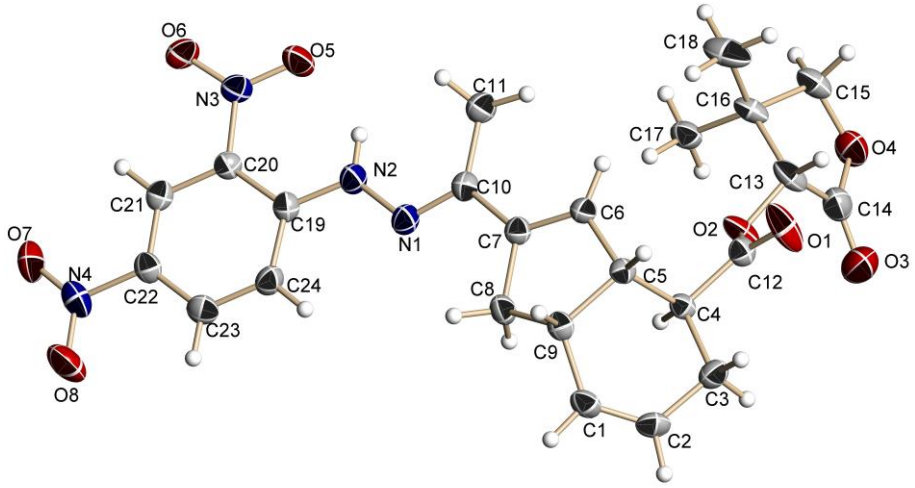


Figure S1. ORTEP of Compound **31** (KLH-E-23)

Crystallographic data for compound**31** (KLH-E-23)deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. **CCDC 1009597.**

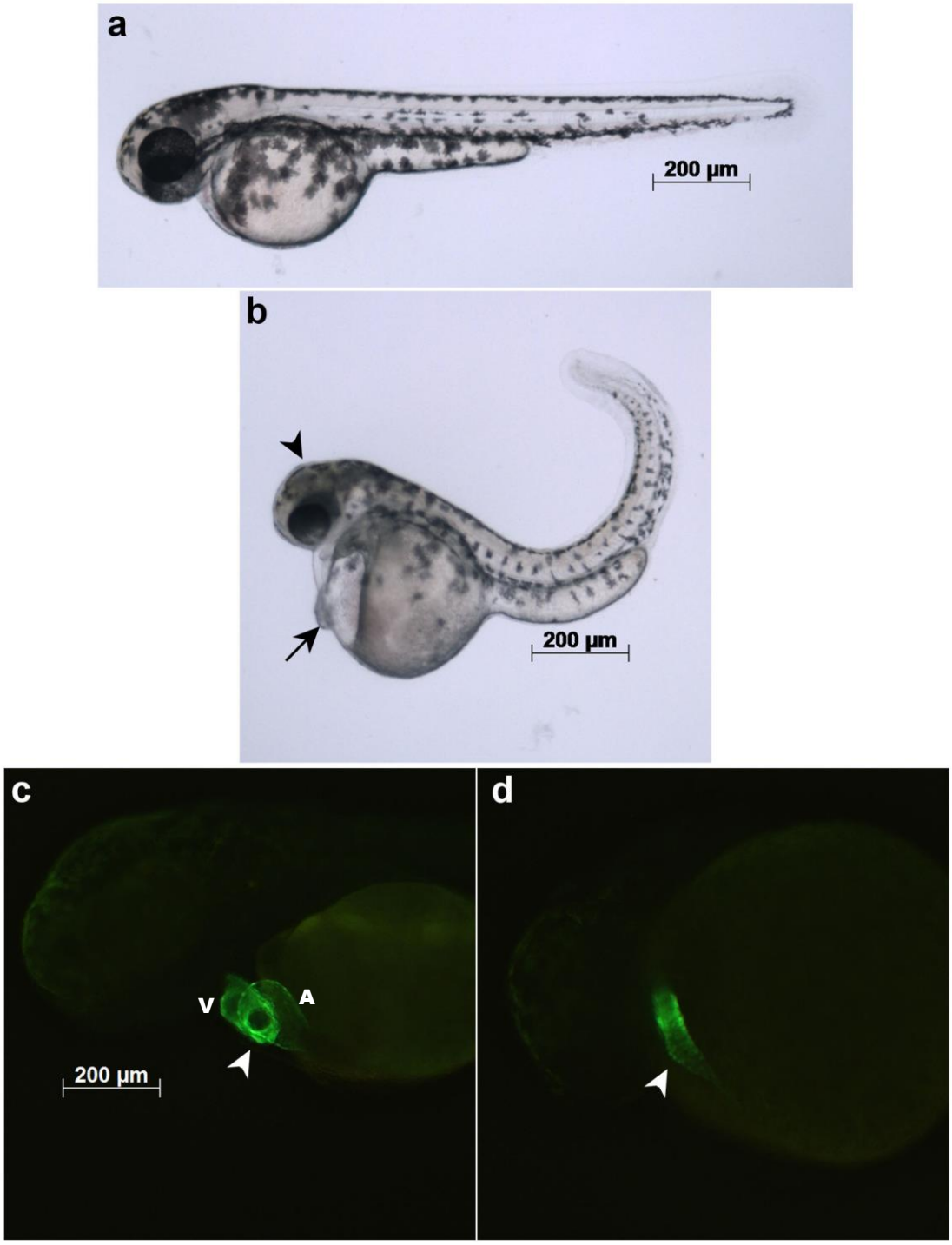


Figure S2. Noreremophilane scaffold elicits pleiotropic effects in zebrafish embryos. Compared to a vehicle treated 2-day old control embryo (a) embryos treated with 25µMNER**11** (b) has curved tail, necrosis in the brain (arrowhead) and pericardial edema (arrow). Two day old control transgenic *Tg(myl7:GAL4-VP16*) embryos show looped heart with two chambers, atrium (A) and ventricle (V) in green (c, arrowhead) while compound treated embryos show a tube shaped heart (d, arrowhead).

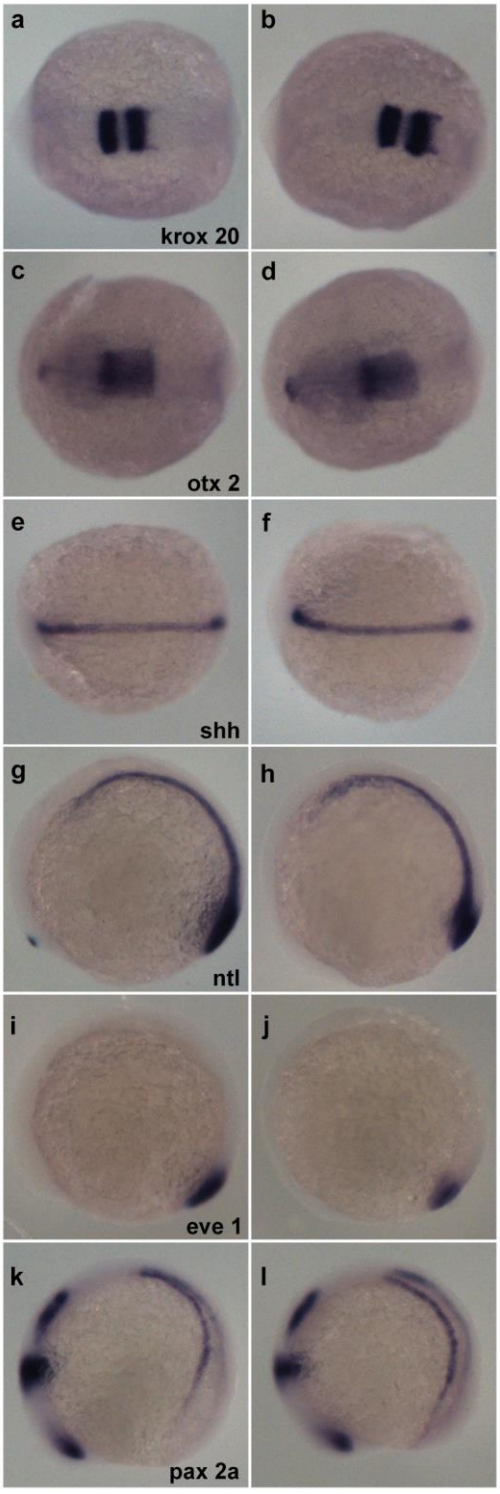
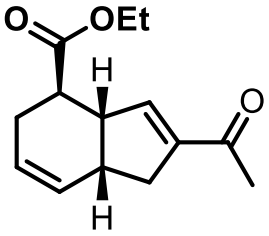


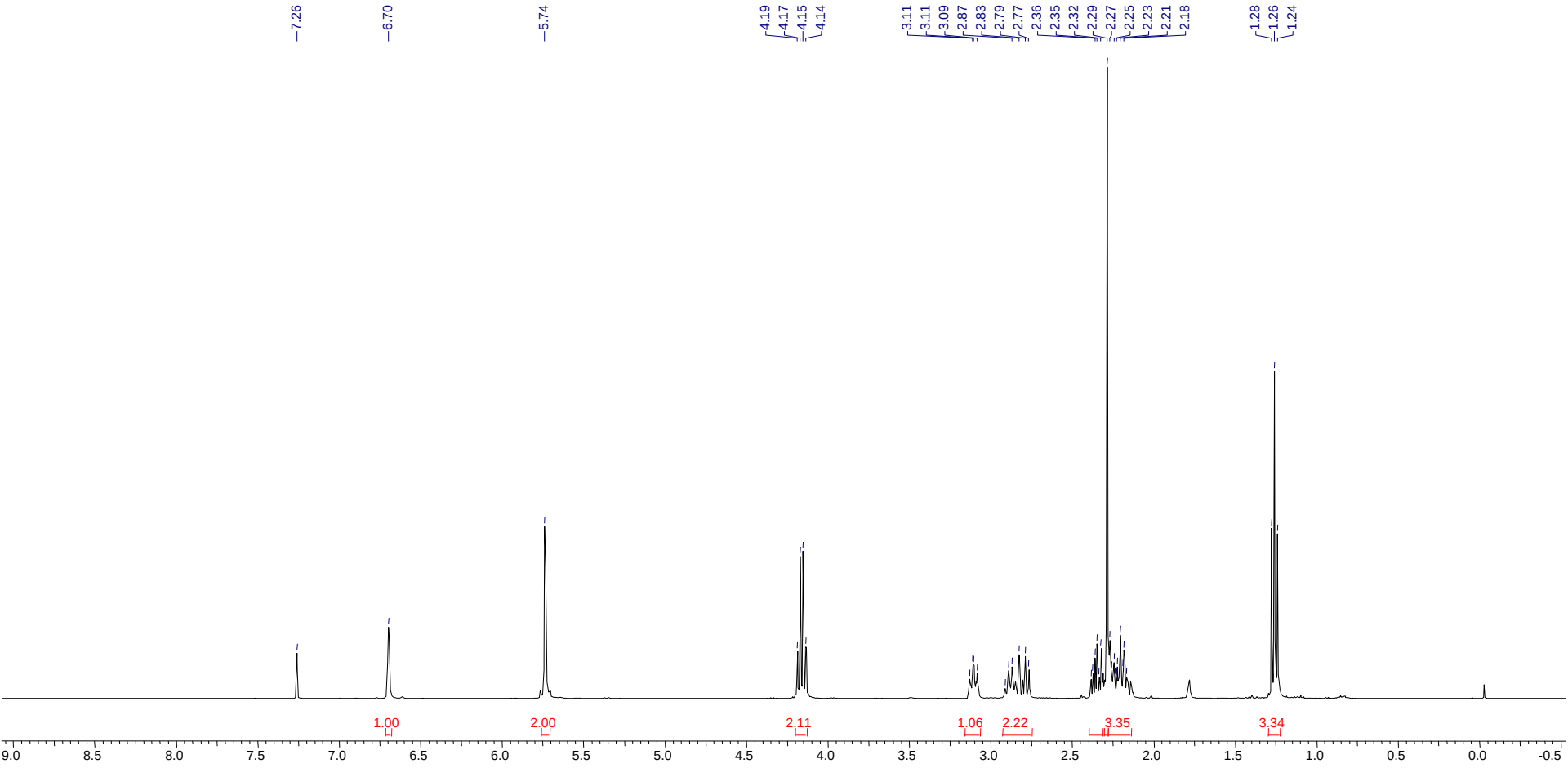
Figure S3. Early markers of development are unaffected by treatment with NER**11**. RNA in situ hybridization was performed on 10 somite stage embryos treated with DMSO (a,c,e,g,i,k) or **11**(25µM) (b, d, f, h, j, l). (a-f) dorsal views with anterior to the left. (g-l) are lateral views with anterior to the left and dorsal to the top.

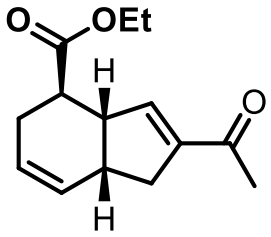
^{1}H and ^{13}C NMR Spectra



11

^{1}H NMR of Compound 11 ($CDCl_3$; 400MHz)





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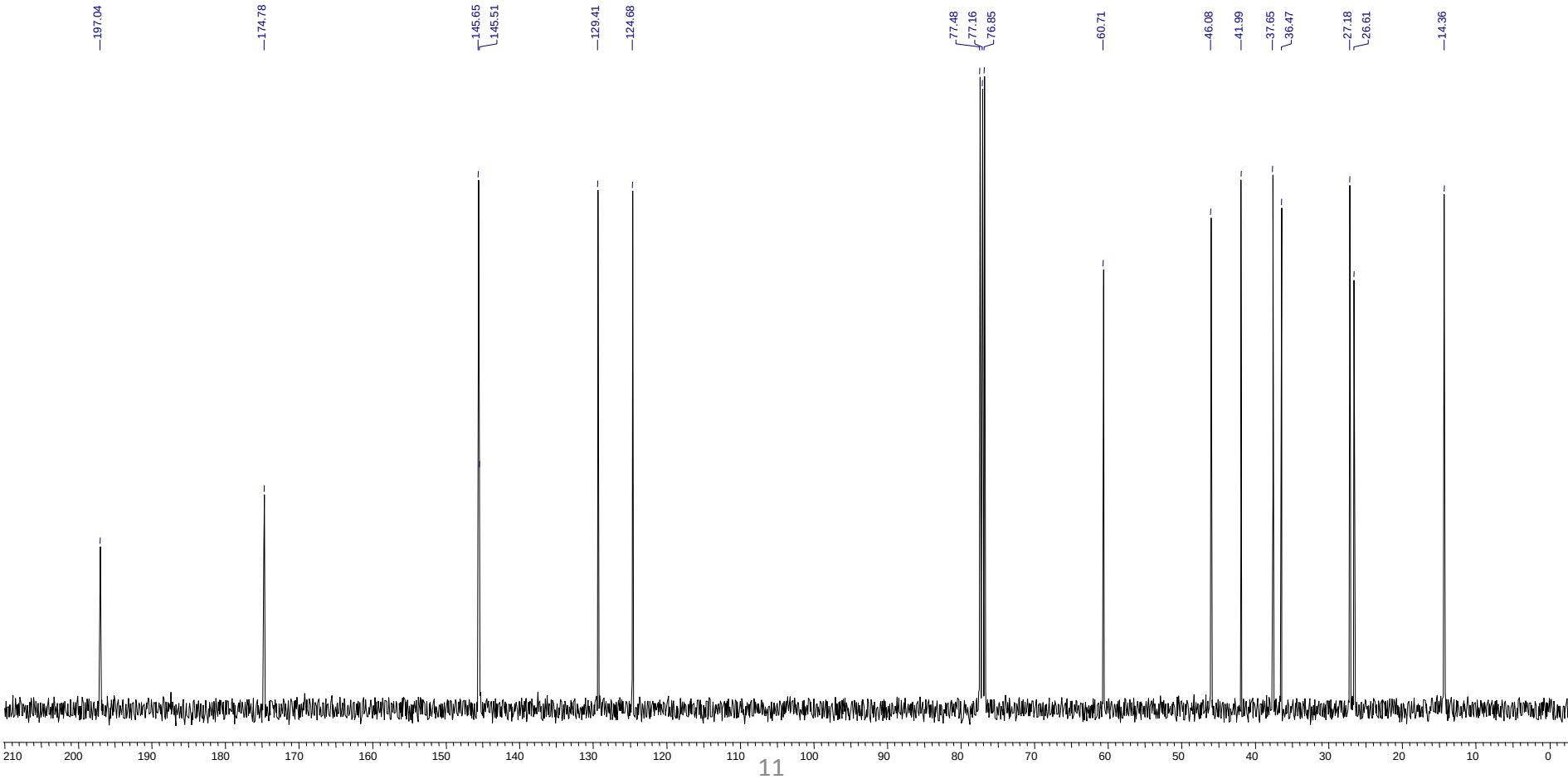
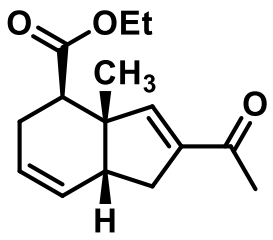
^{13}C NMR of Compound 11 ($CDCl_3$; 100MHz)





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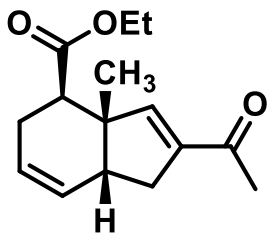
^{1}H NMR of Compound 12 ($CDCl_3$; 400MHz)



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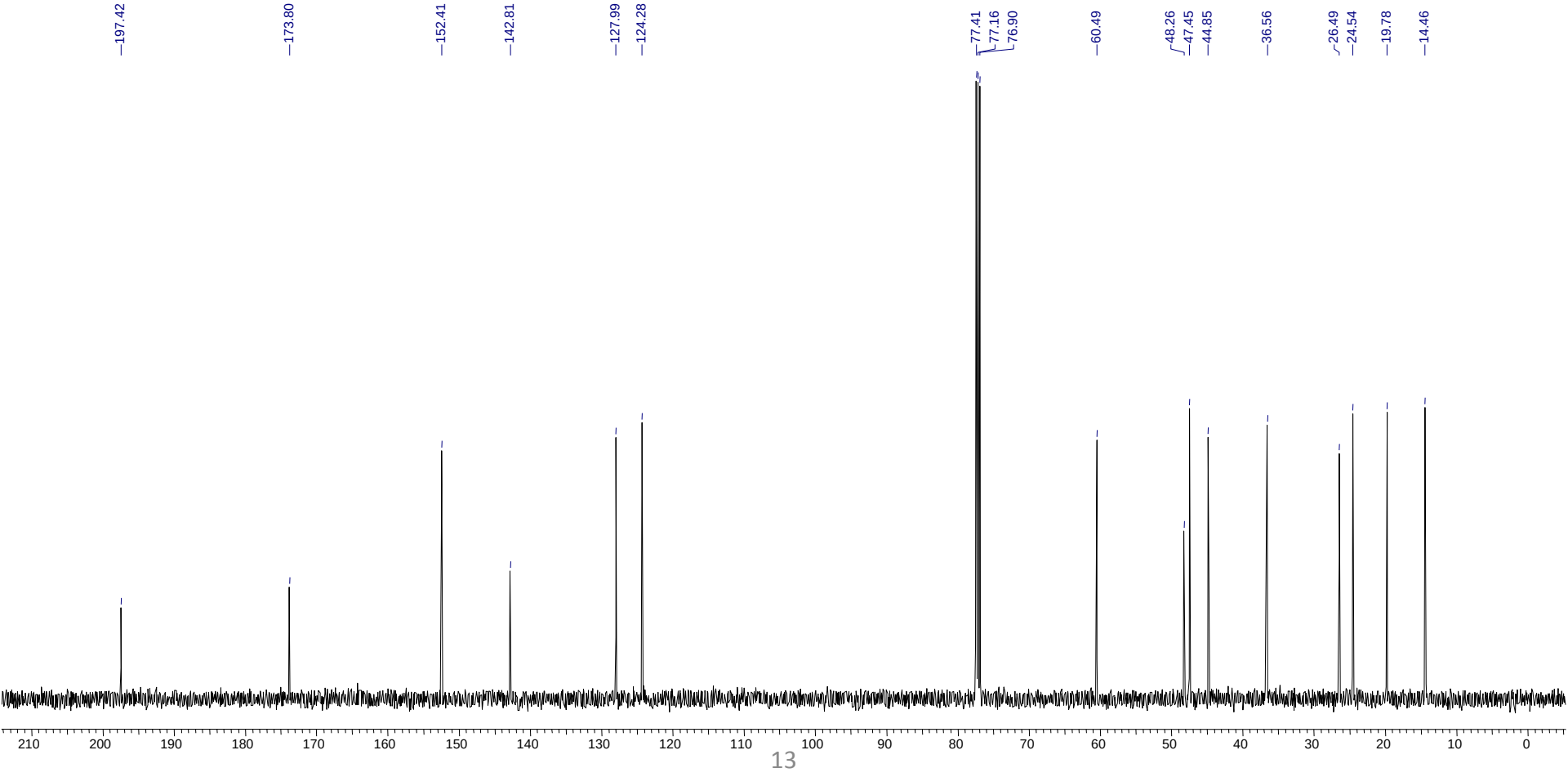
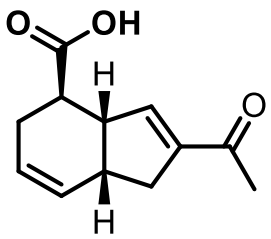
^{13}C NMR of Compound 12 ($CDCl_3$; 100MHz)





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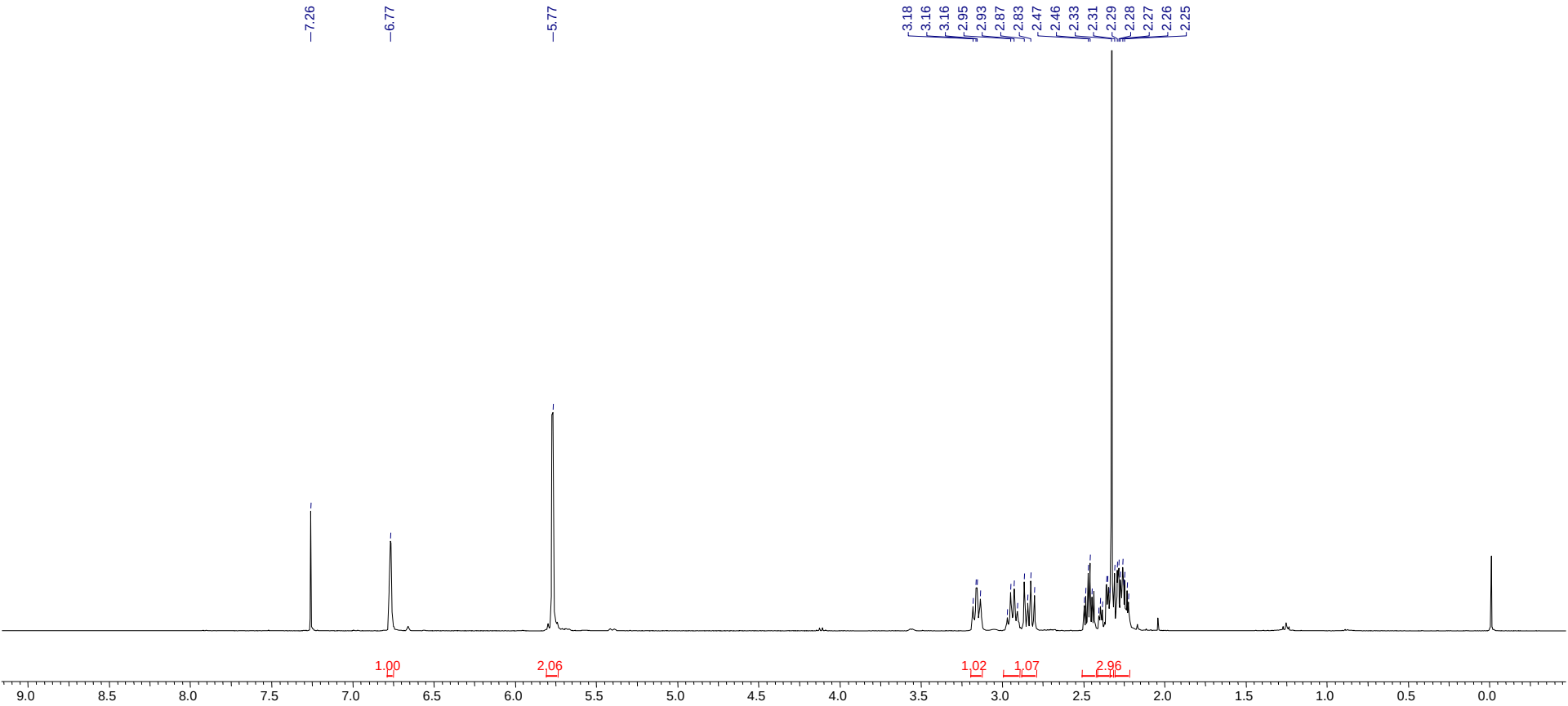
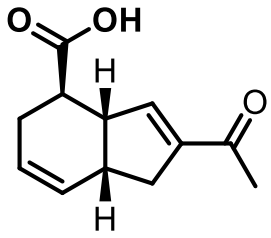
^{1}H NMR of Compound 13 ($CDCl_3$; 400MHz)





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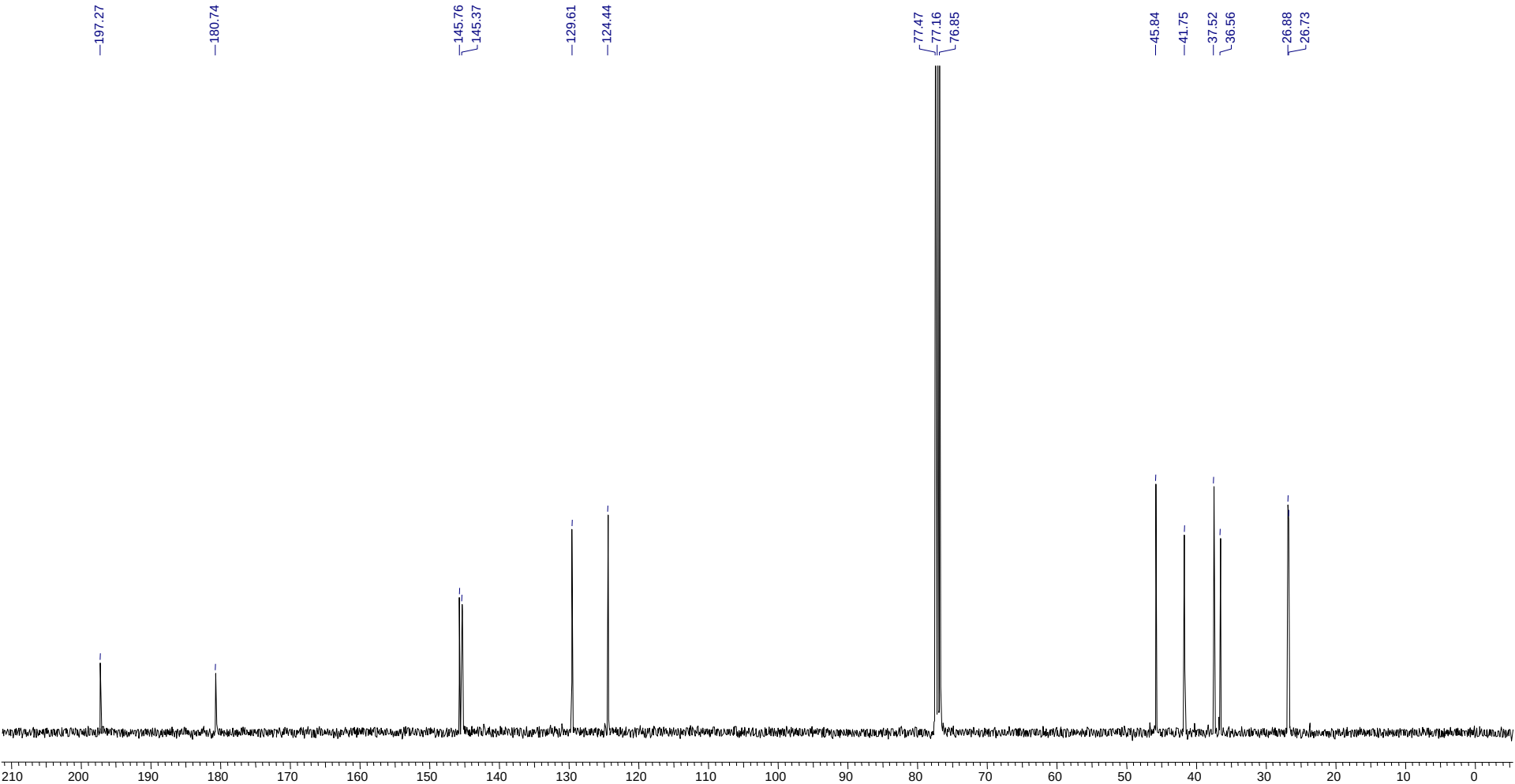

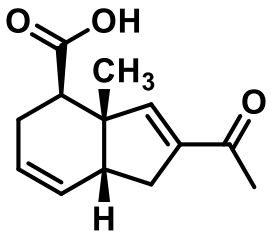

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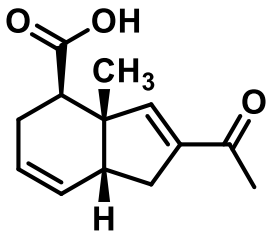
^{1}H NMR of Compound 14 ($CDCl_3$; 400MHz)



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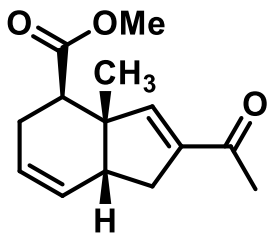
^{13}C NMR of Compound 14 ($CDCl_3$; 100MHz)



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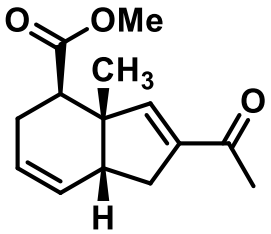
^{1}H NMR of Compound 15 ($CDCl_3$; 400MHz)



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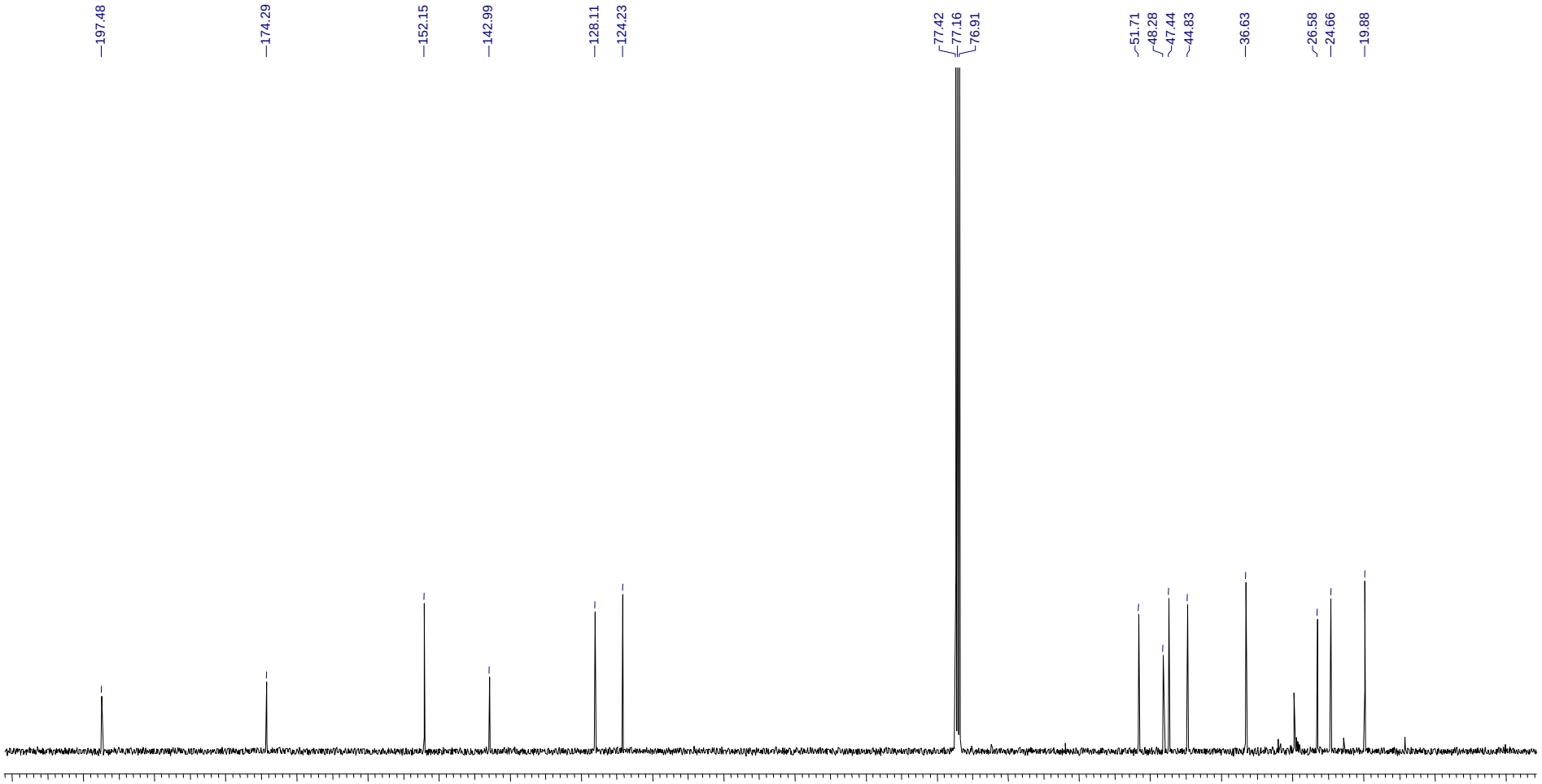

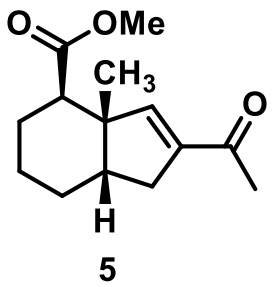

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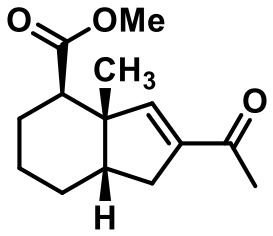
^{1}H NMR of Compound 5 ($CDCl_3$; 400MHz)



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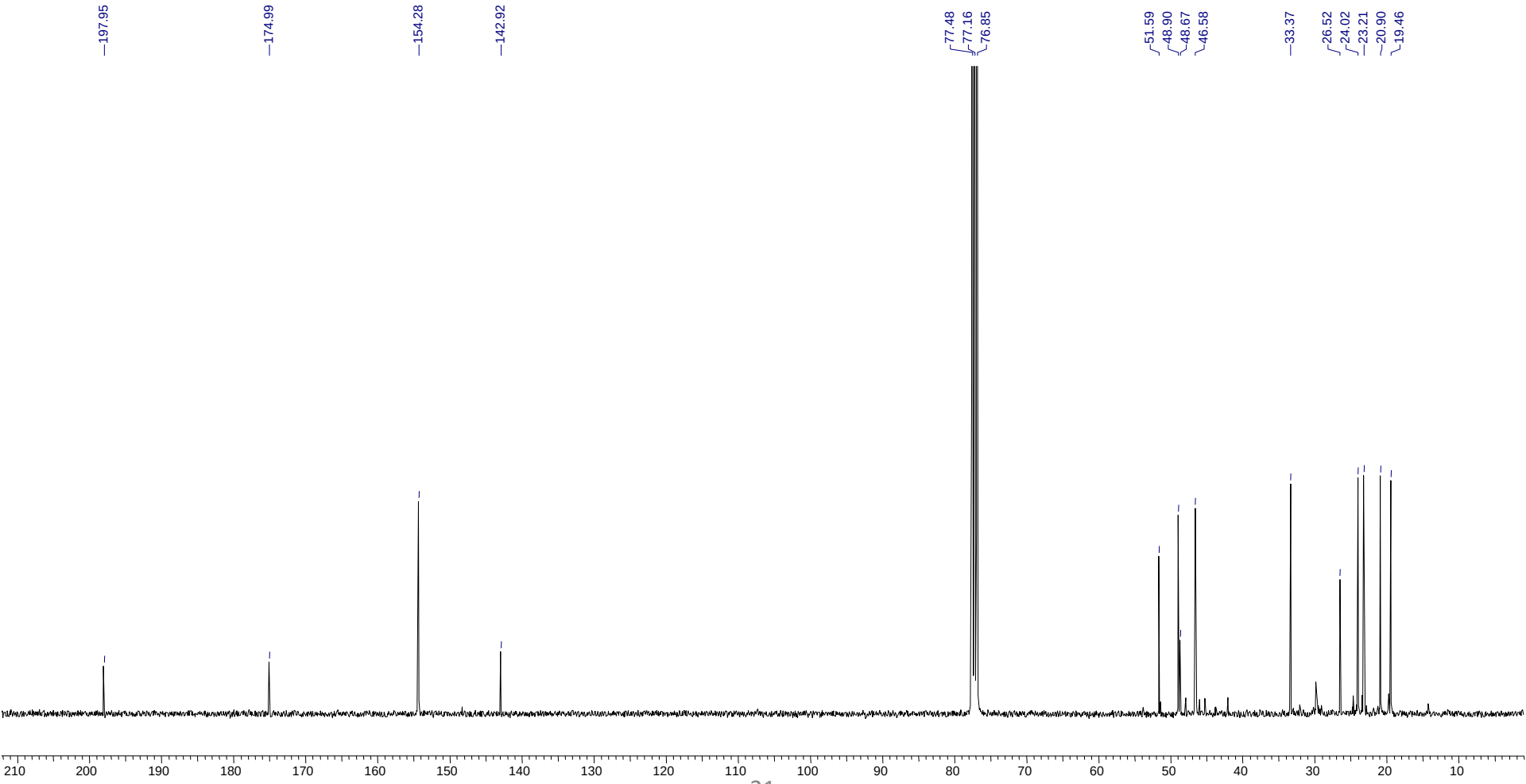

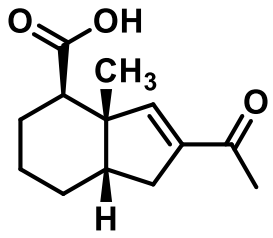

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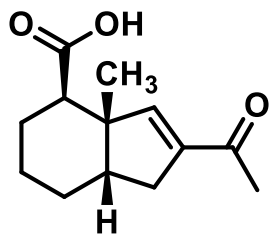
^{1}H NMR of Compound 6 ($CDCl_3$; 400MHz)

^{13}C NMR of Compound 6 ($CDCl_3$; 100MHz)



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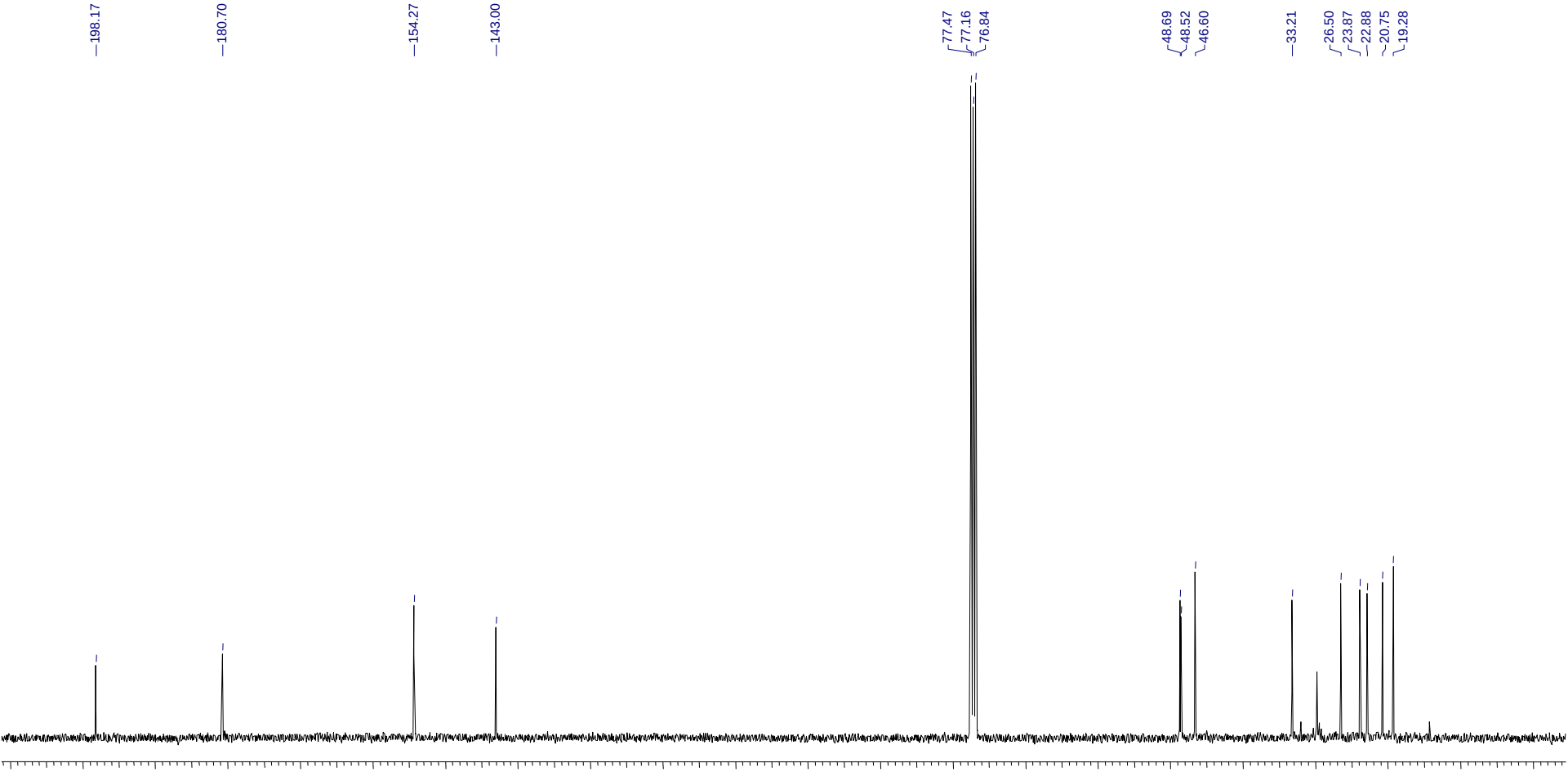

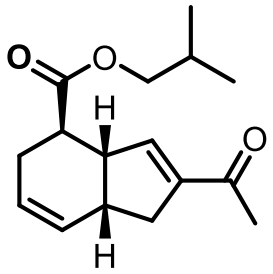

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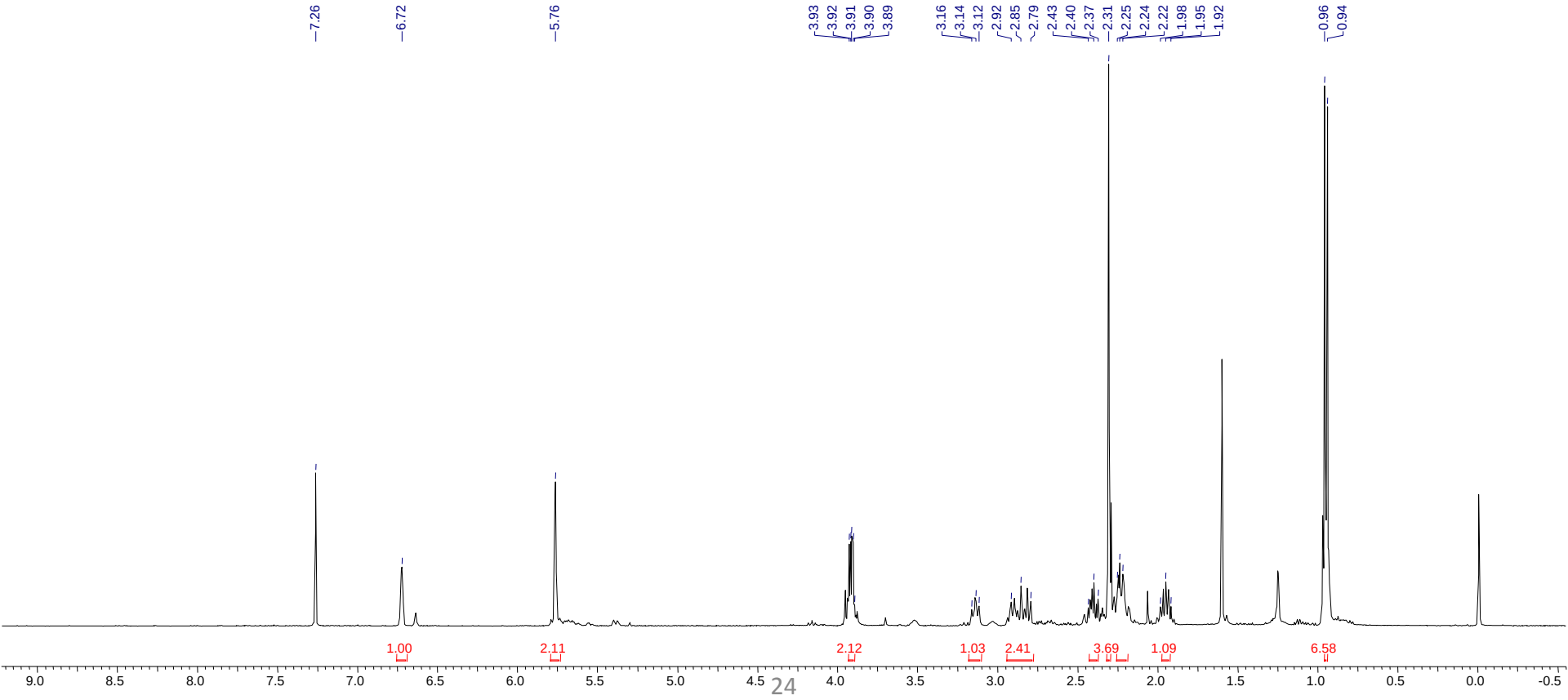
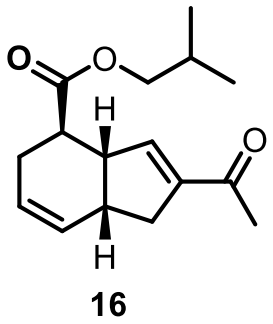
^{1}H NMR of Compound 16 ($CDCl_3$; 400MHz)





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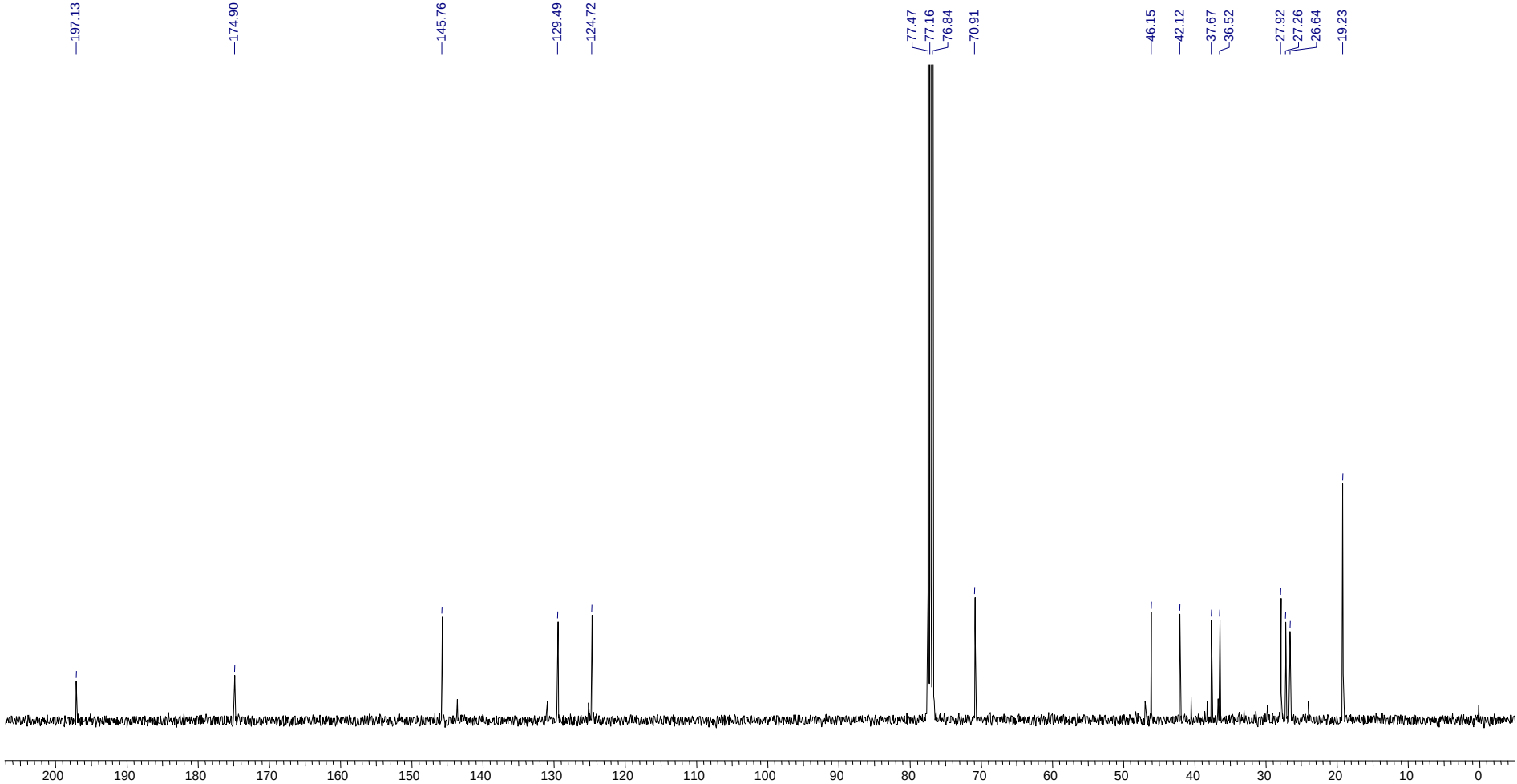
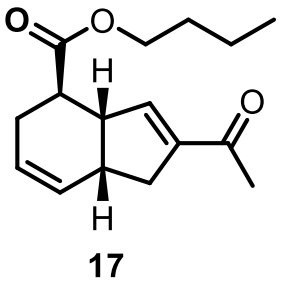
^{13}C NMR of Compound 16 ($CDCl_3$; 100MHz)





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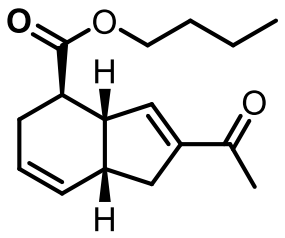
^{1}H NMR of Compound 17 ($CDCl_3$; 400MHz)



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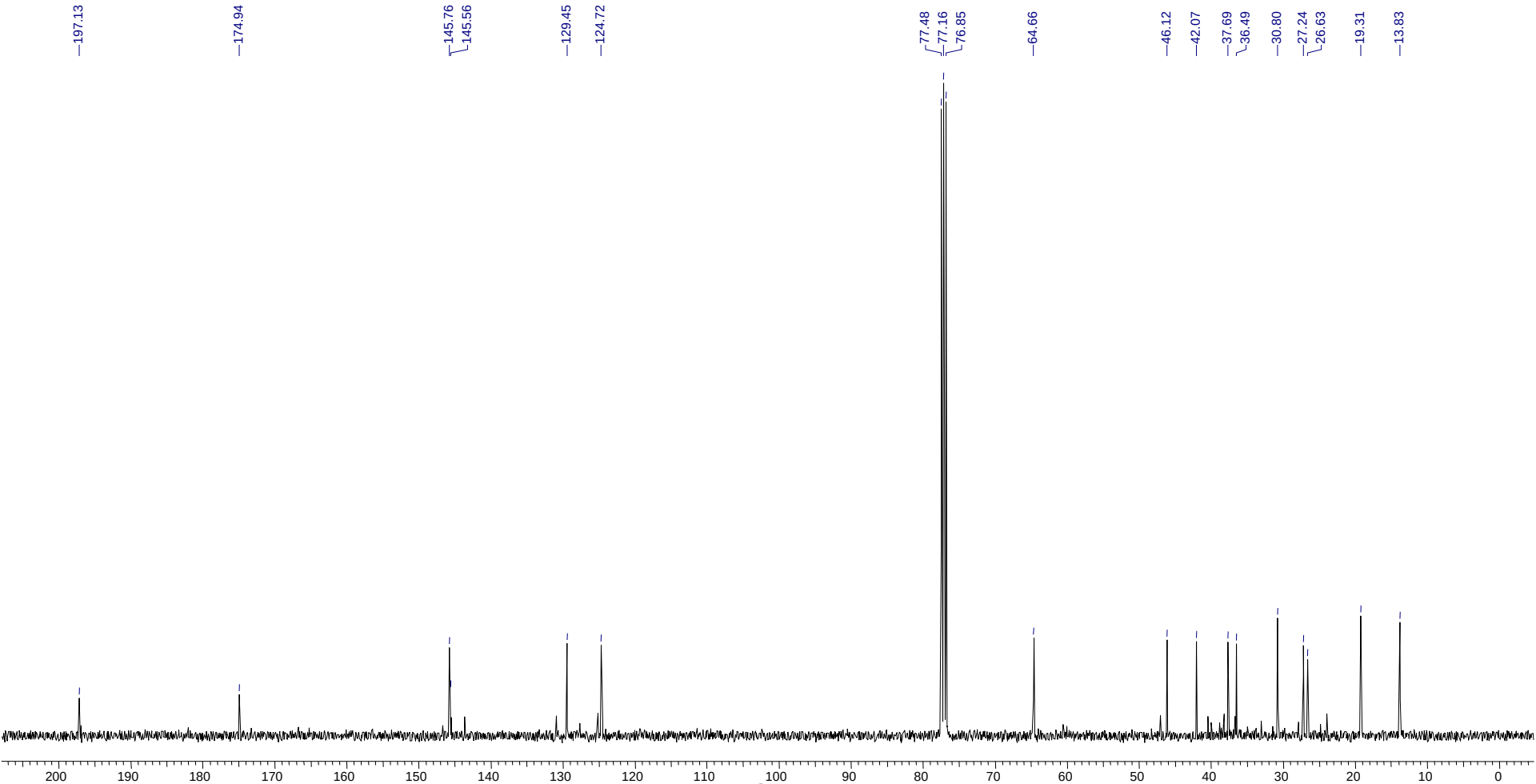
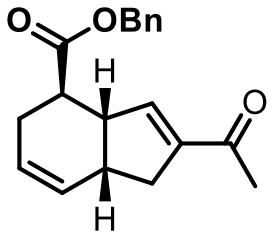
^{13}C NMR of Compound 17 ($CDCl_3$; 100MHz)





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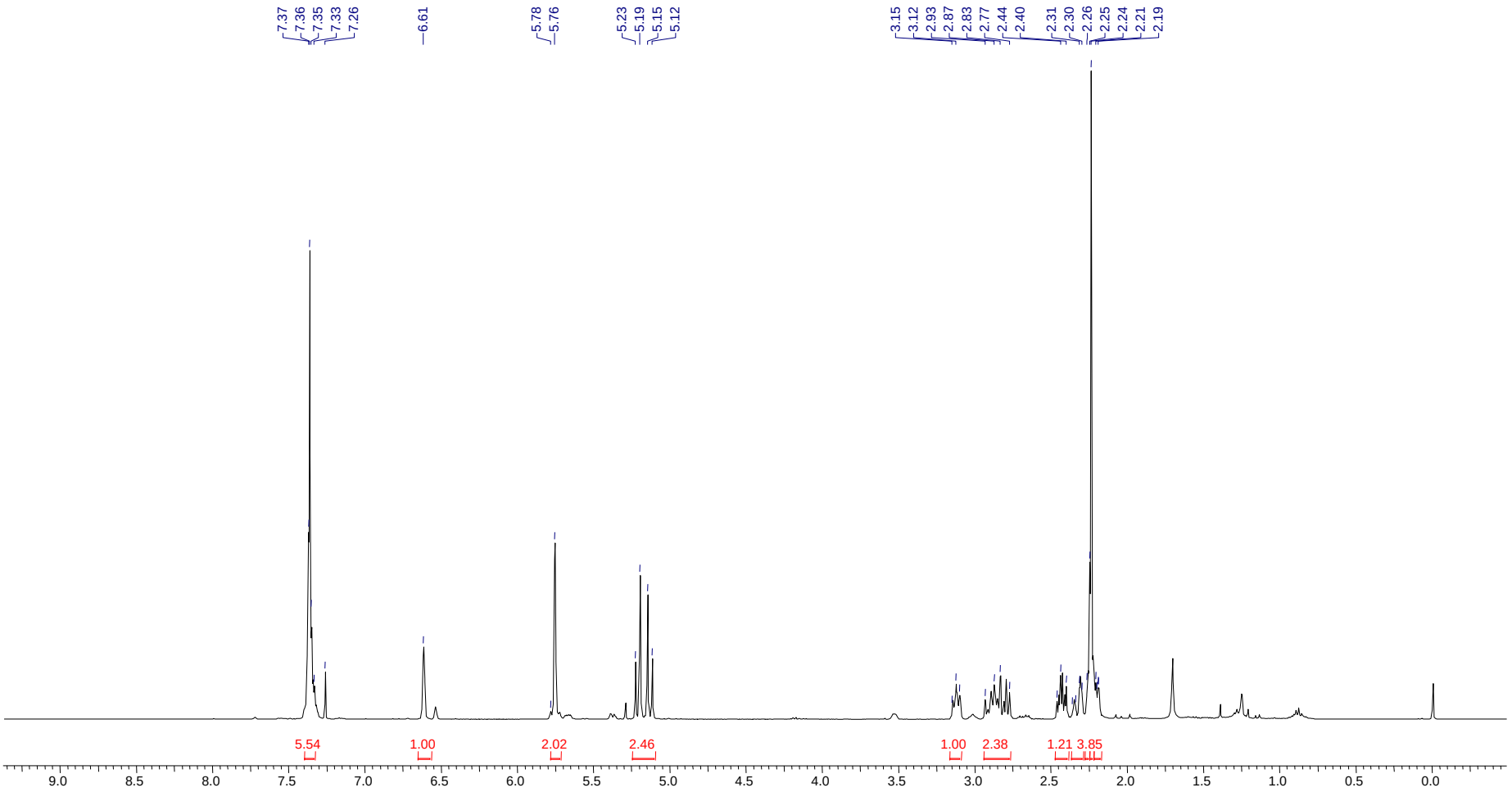
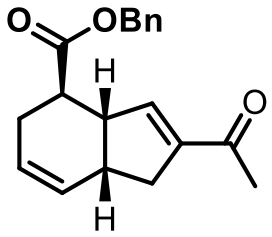
^{1}H NMR of Compound 18 ($CDCl_3$; 400MHz)





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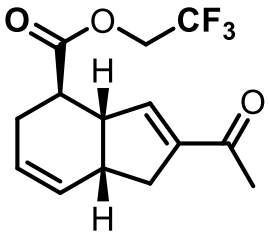
^{13}C NMR of Compound 18 ($CDCl_3$; 100MHz)



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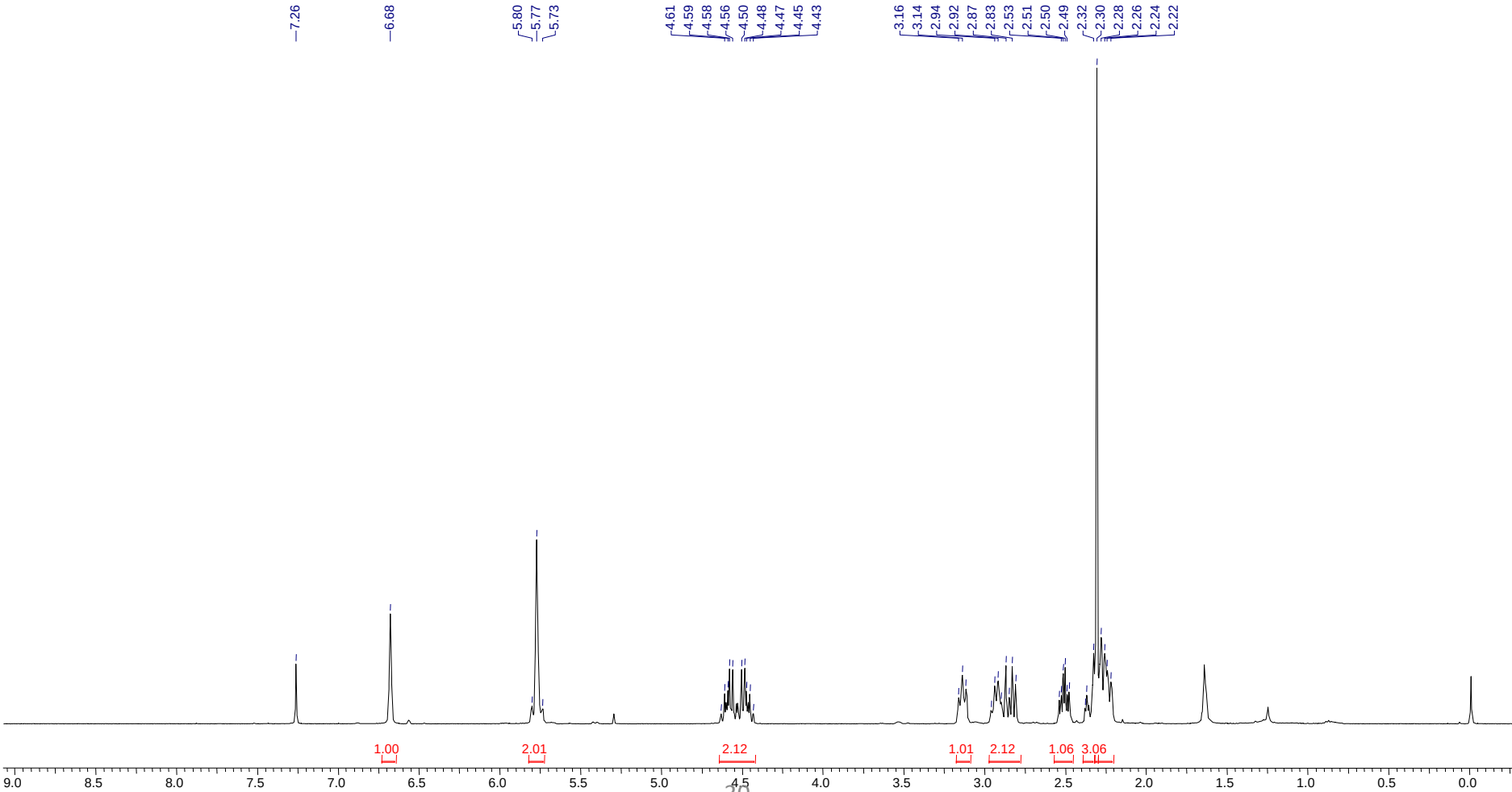
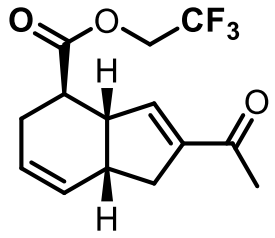
^{1}H NMR of Compound 19 ($CDCl_3$; 400MHz)





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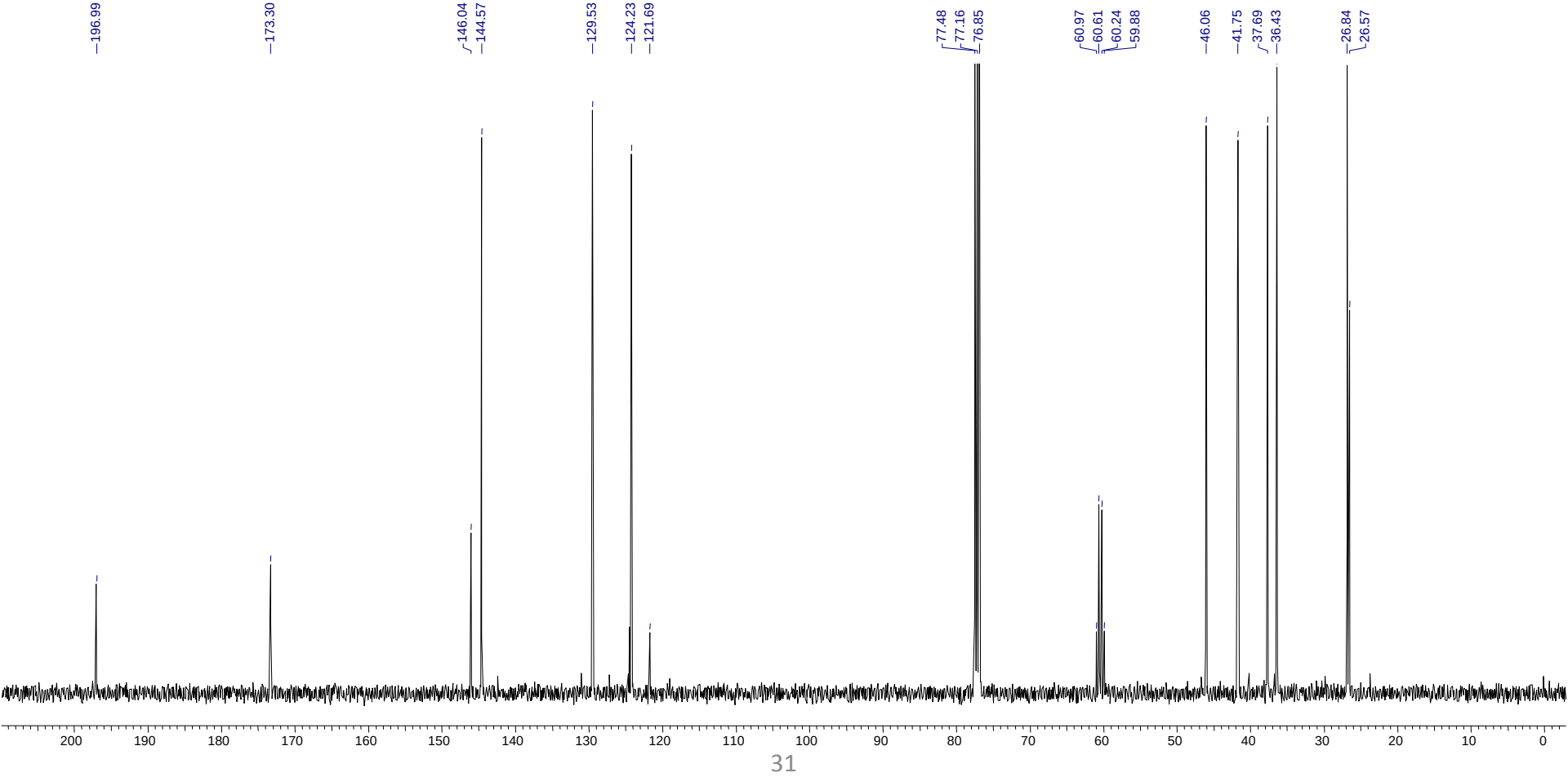
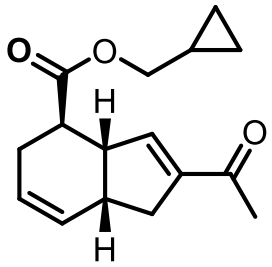
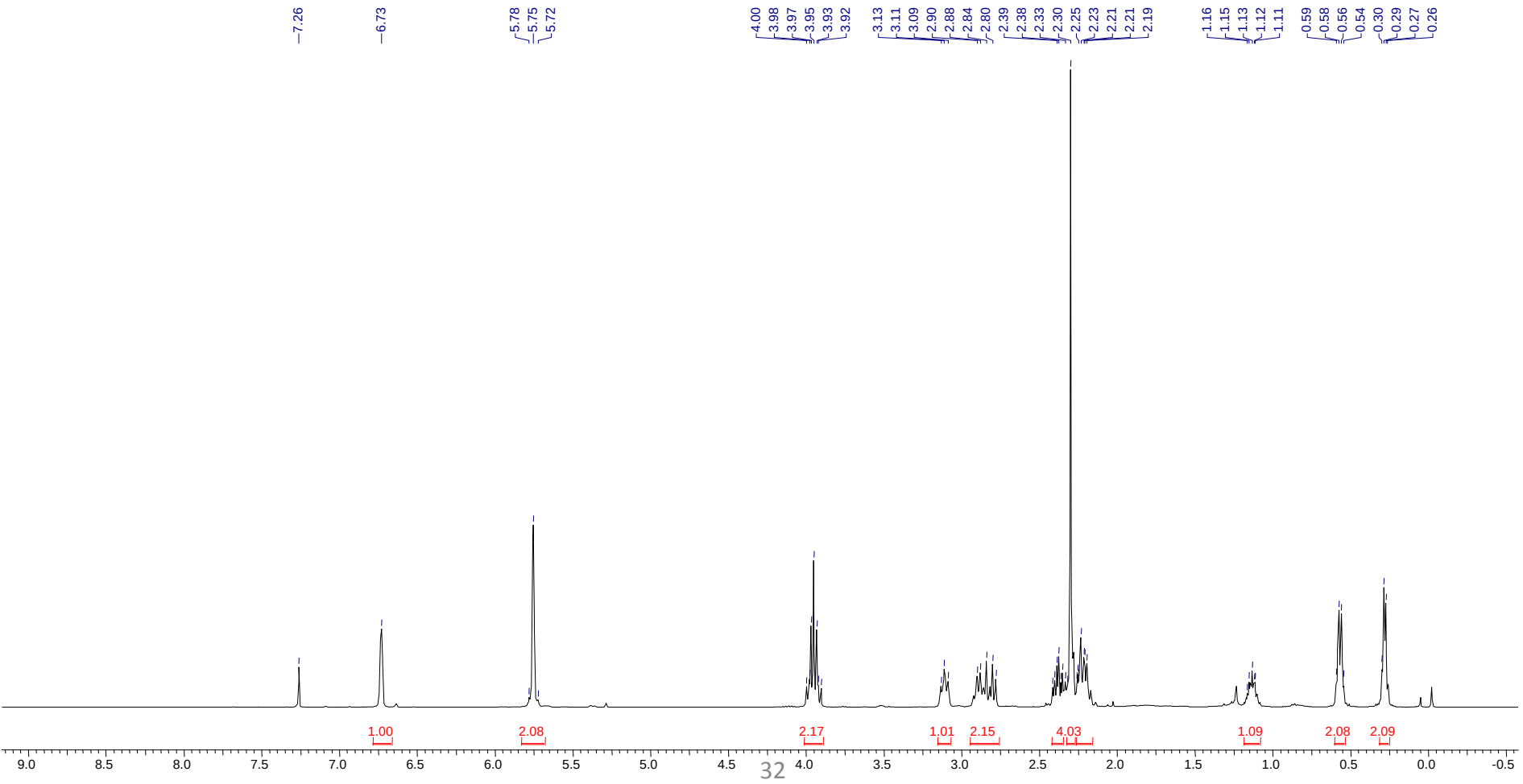
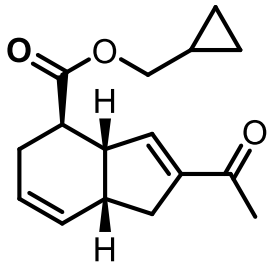




20

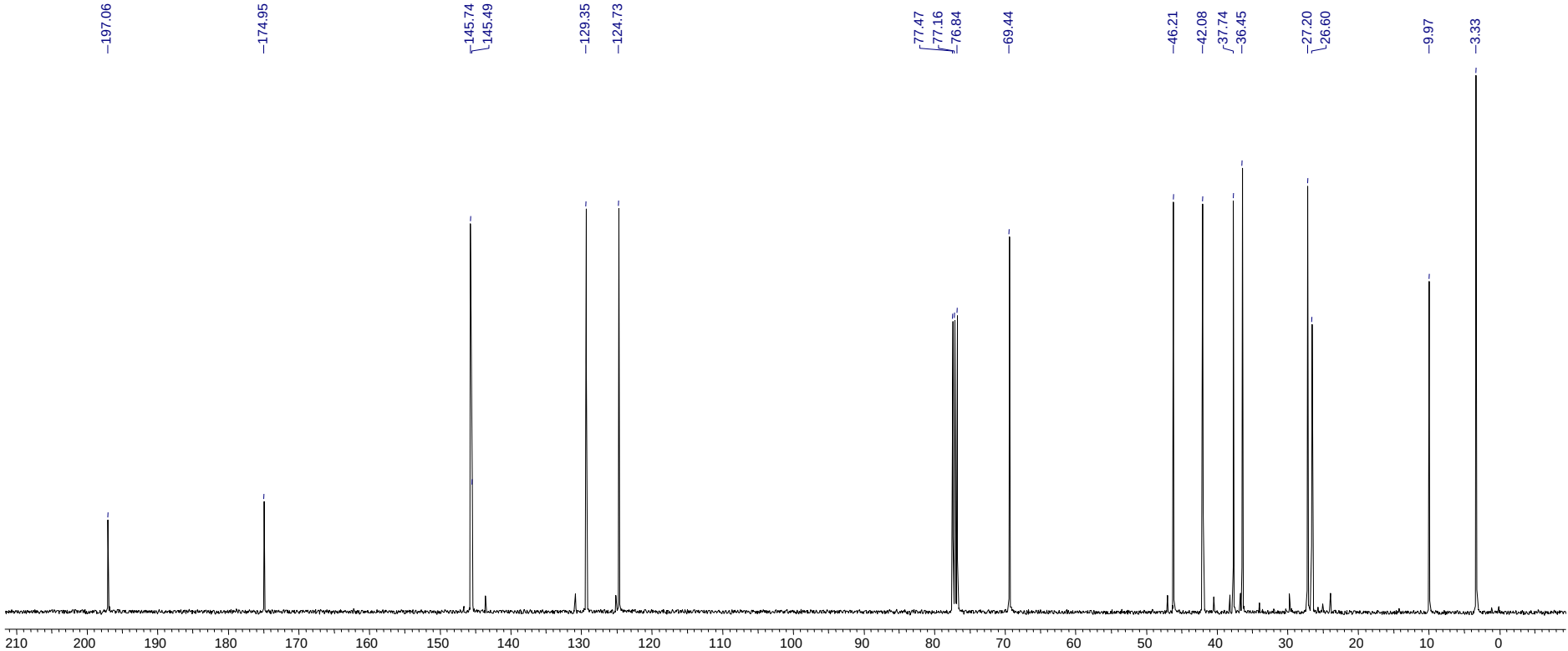
^{1}H NMR of Compound 20 ($CDCl_3$; 400MHz)

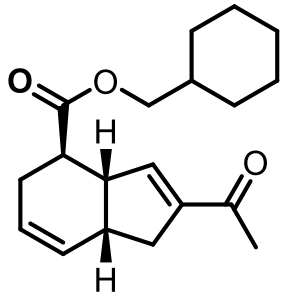




20

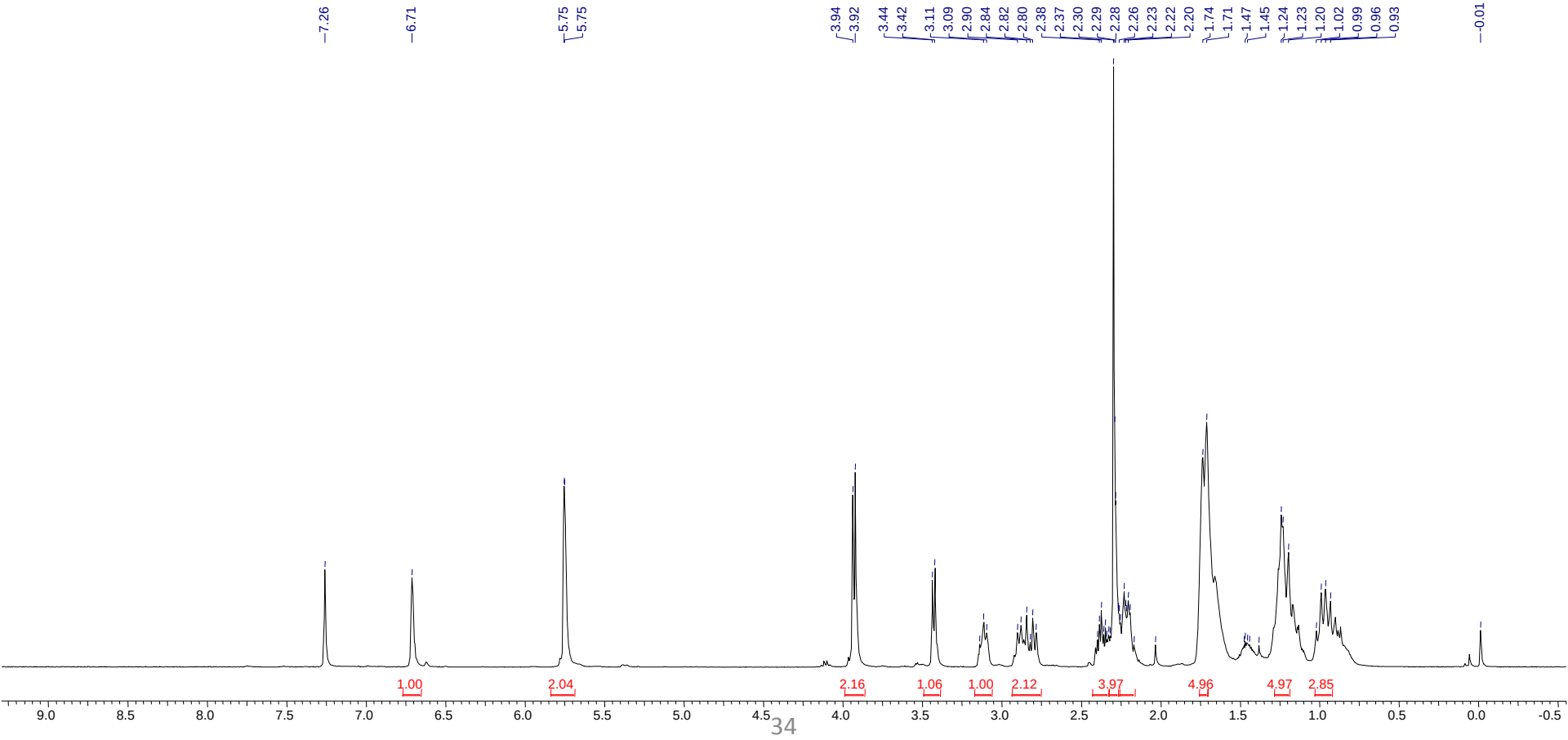
^{13}C NMR of Compound 20 ($CDCl_3$; 100MHz)

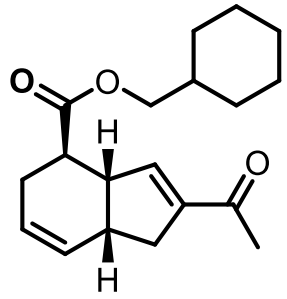




21

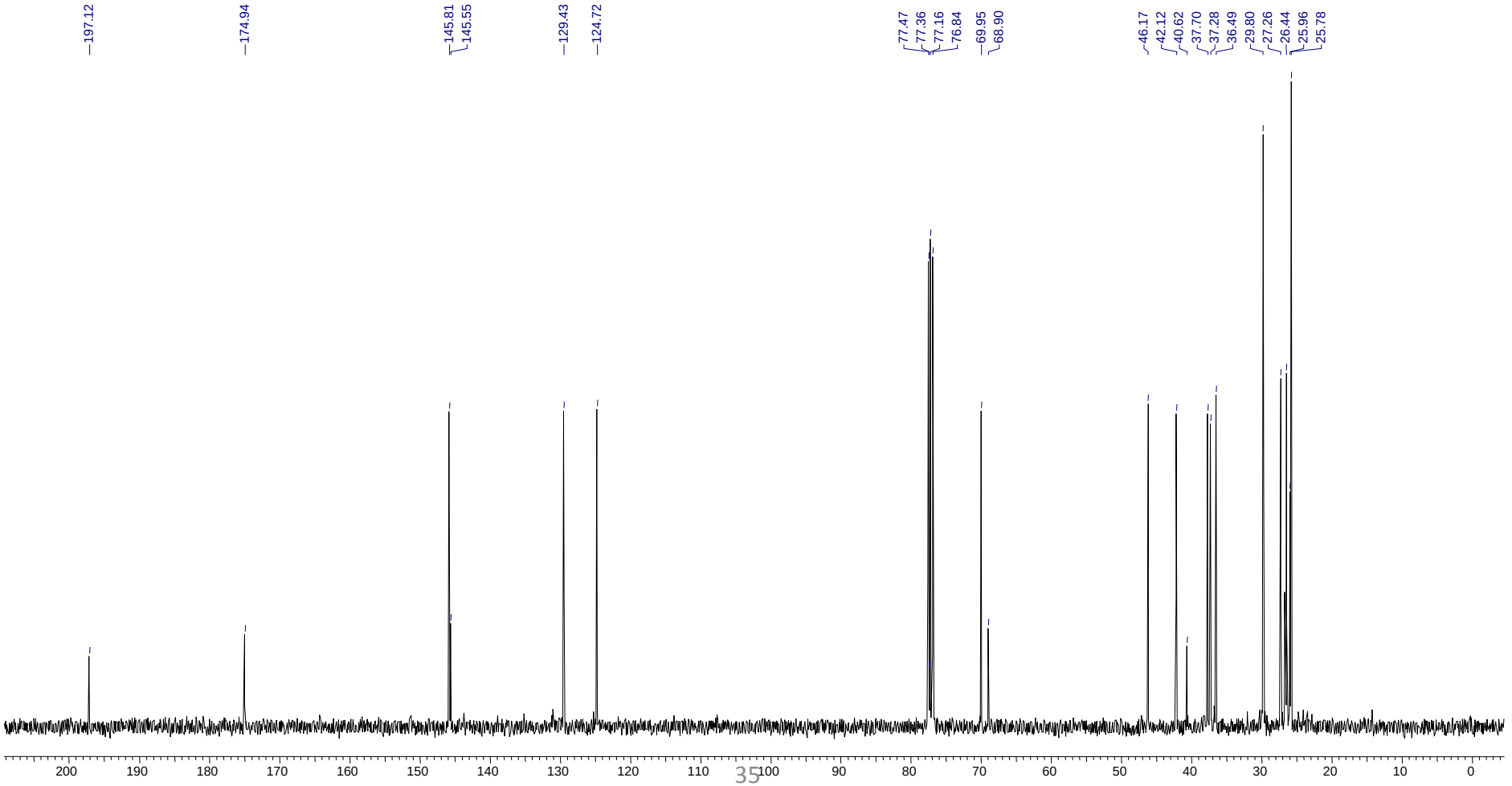
^{1}H NMR of Compound 21 ($CDCl_3$; 400MHz)

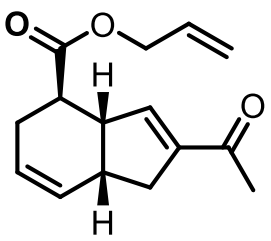




21

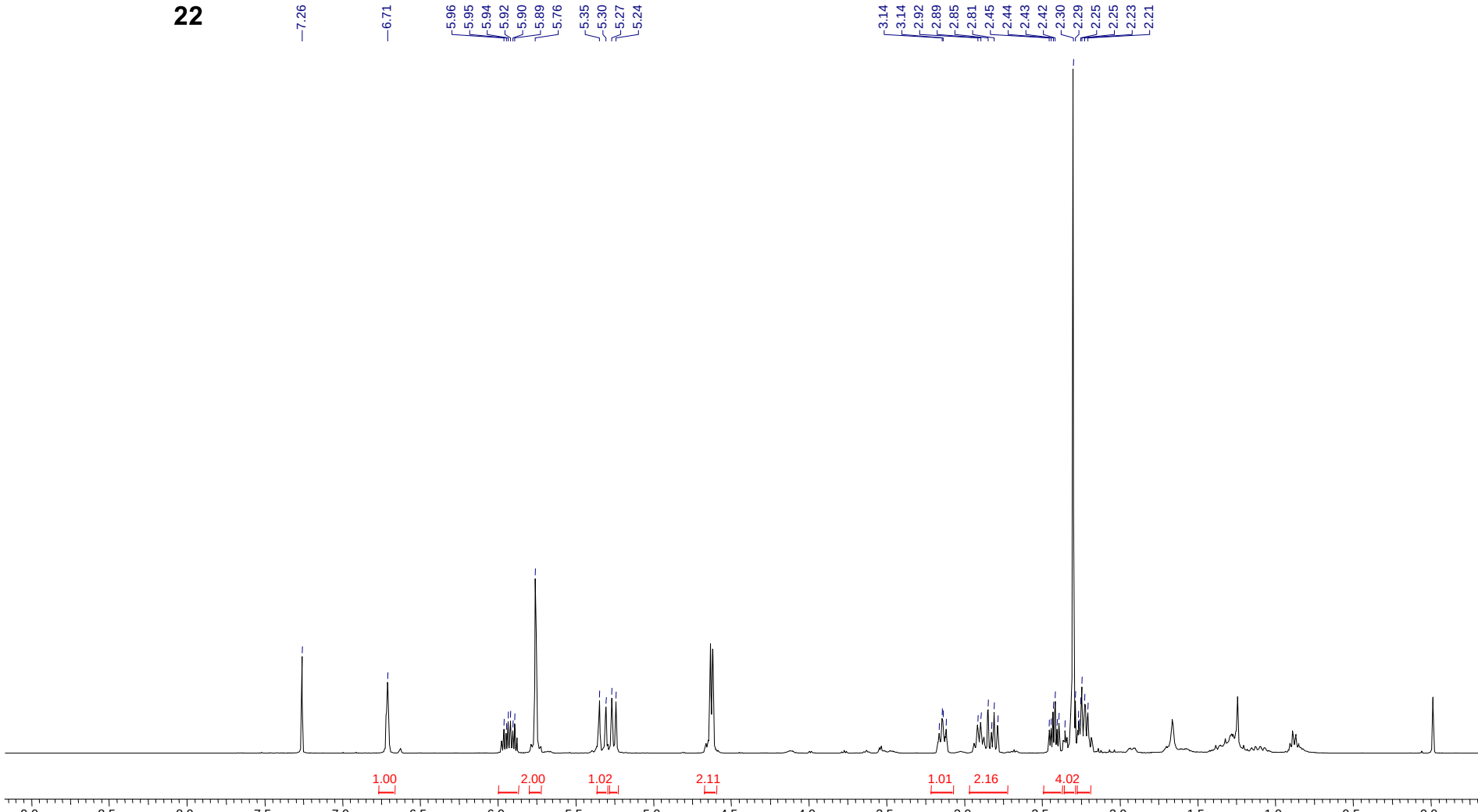
^{13}C NMR of Compound 21 ($CDCl_3$; 100MHz)

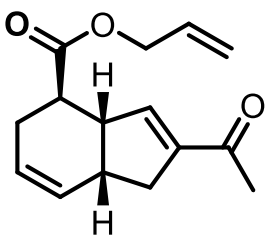




22

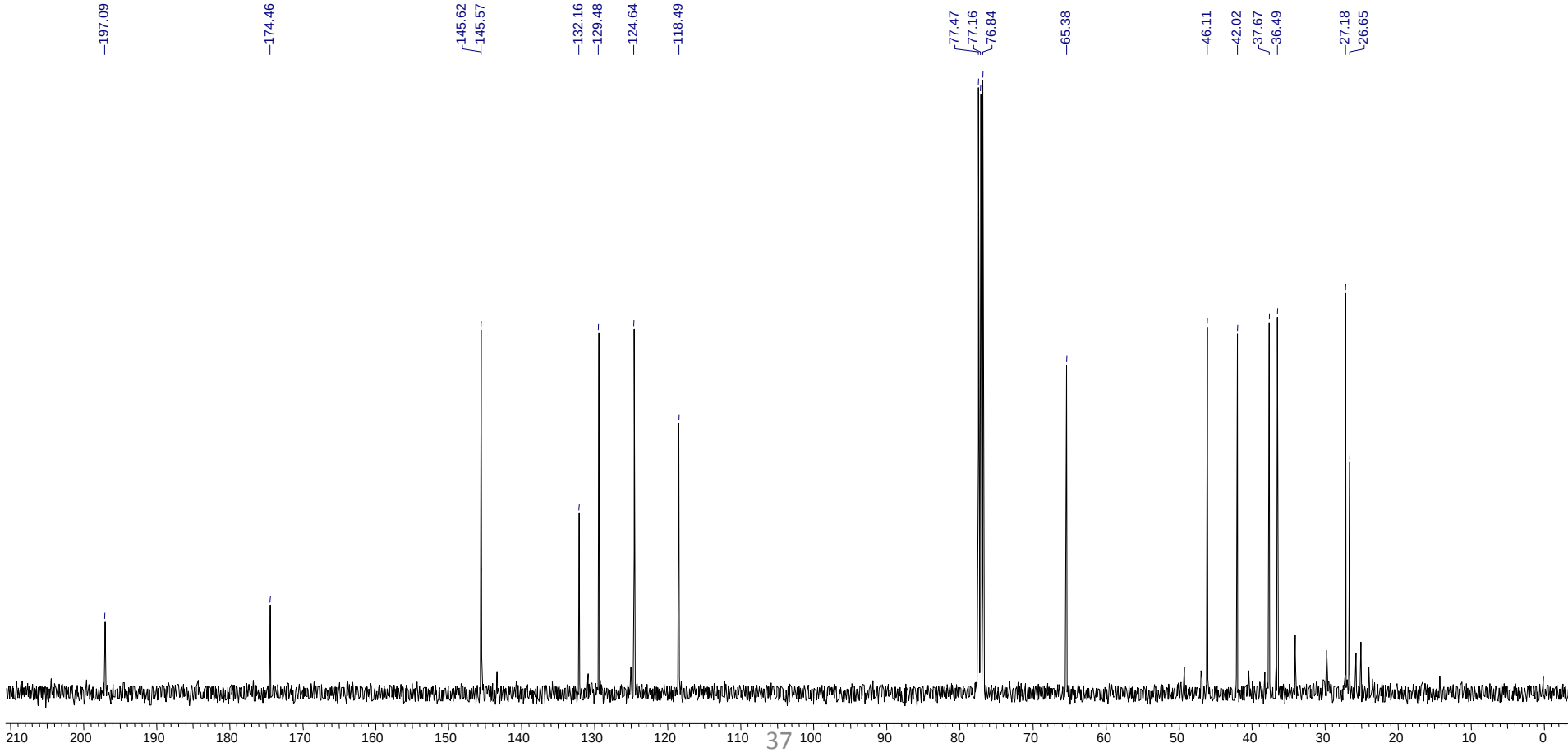
^{1}H NMR of Compound 22 ($CDCl_3$; 400MHz)

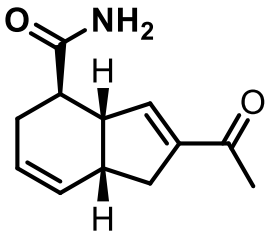




22

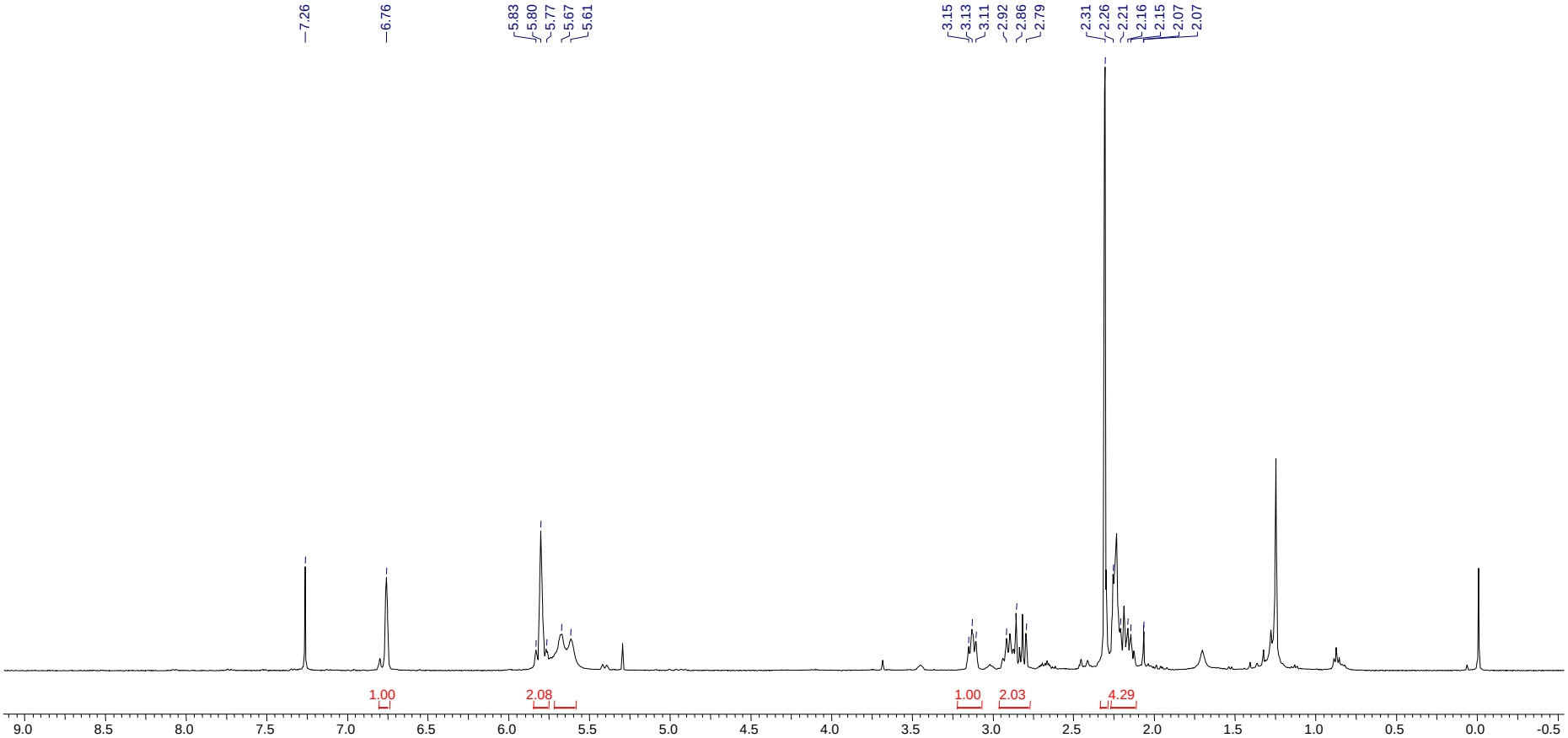
^{13}C NMR of Compound 22 ($CDCl_3$; 100MHz)

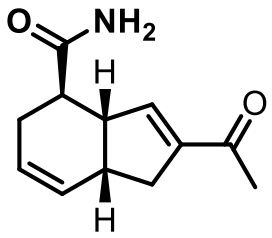




23

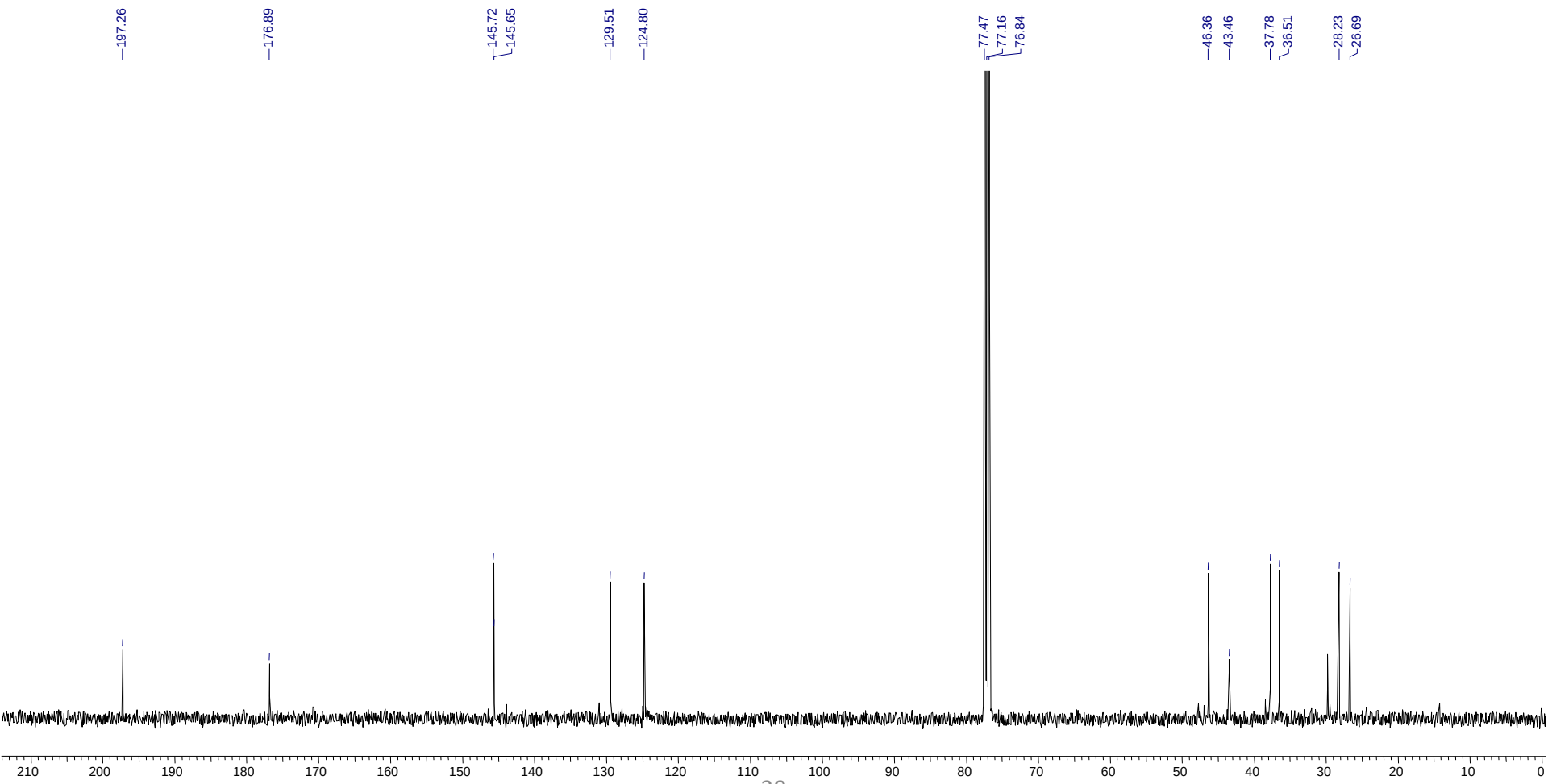
^{1}H NMR of Compound 23 ($CDCl_3$; 400MHz)



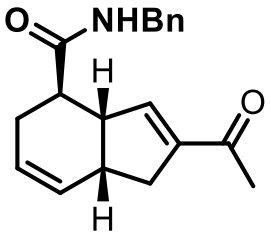


23

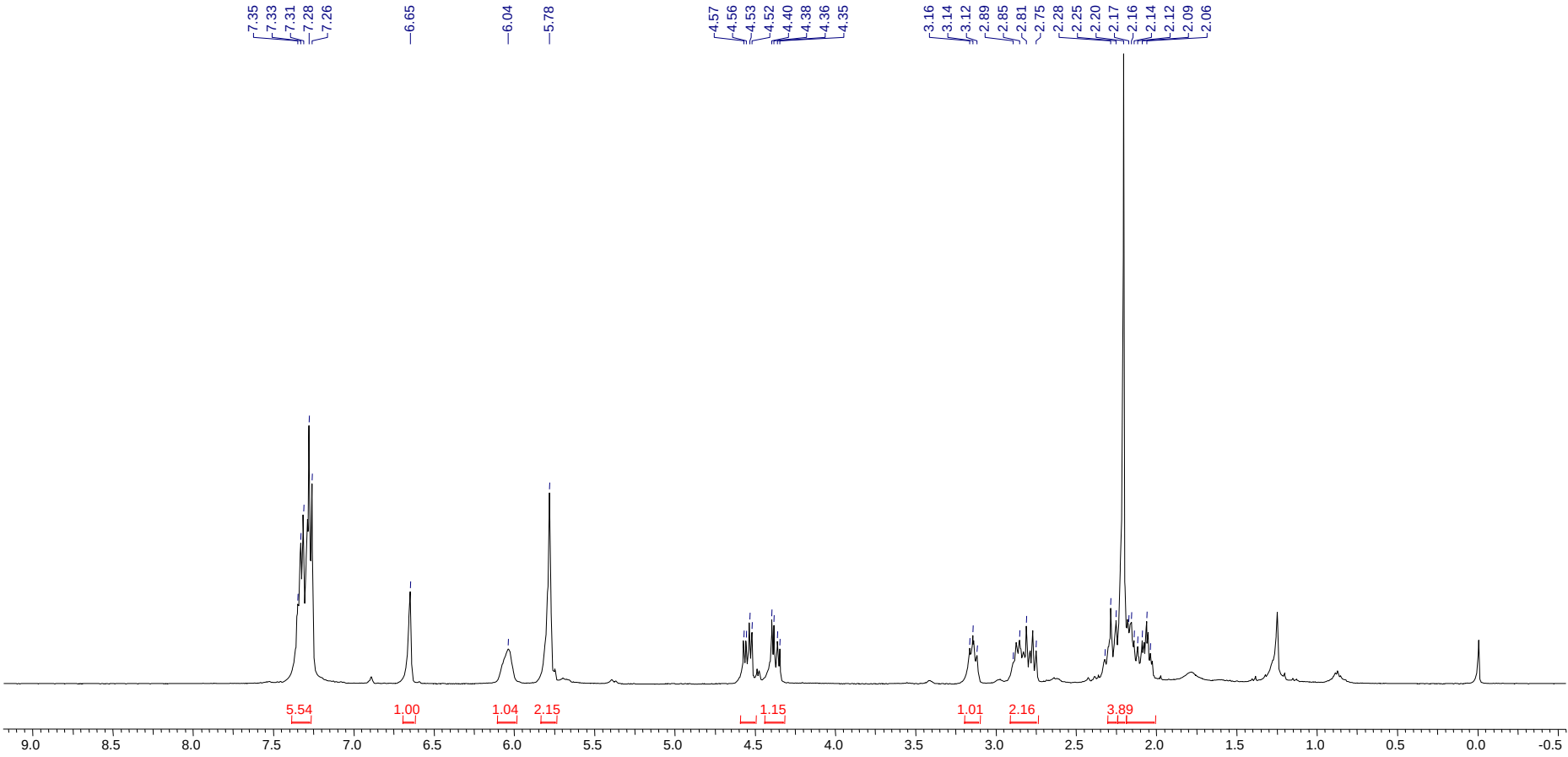
^{13}C NMR of Compound 23 ($CDCl_3$; 100MHz)



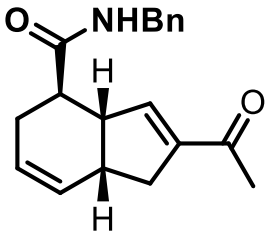
^{1}H NMR of Compound 24 ($CDCl_3$; 400MHz)



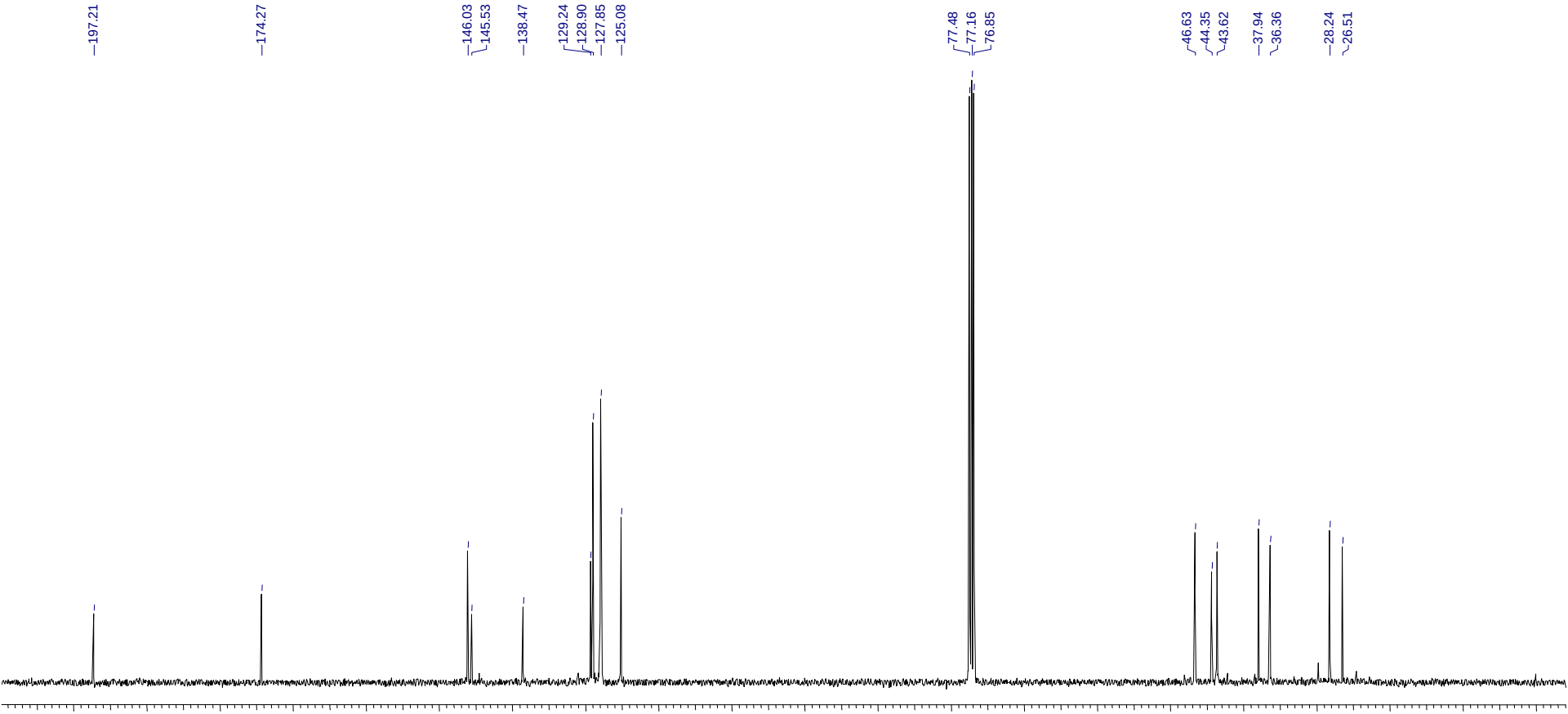
24

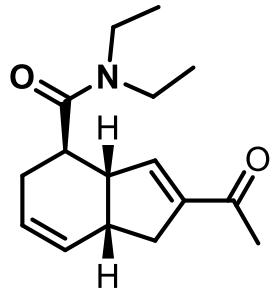


^{13}C NMR of Compound 24 ($CDCl_3$; 100MHz)



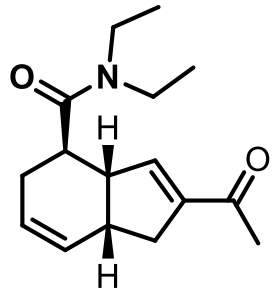
24





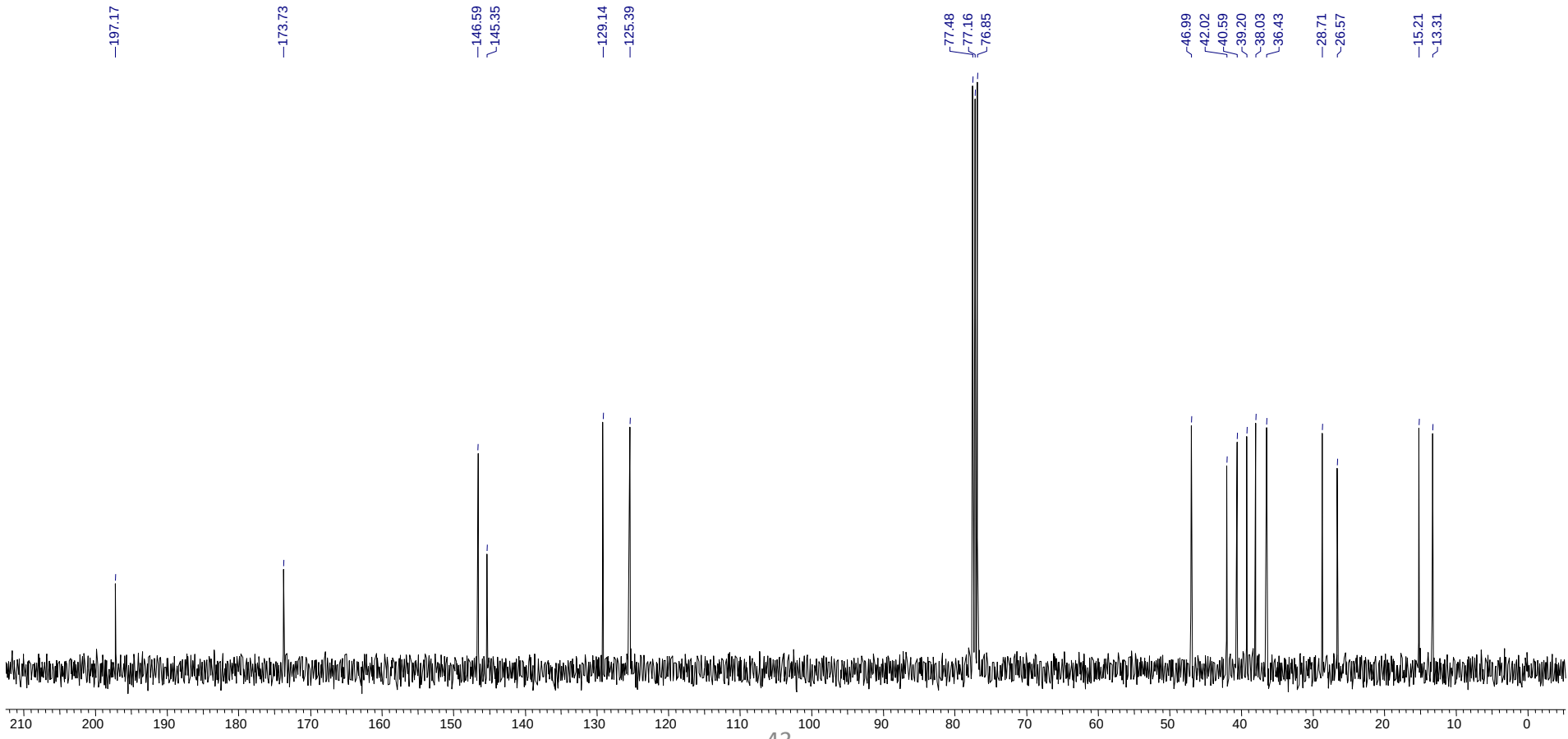
25

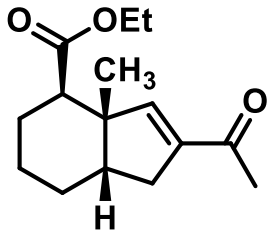
^{1}H NMR of Compound 25 ($CDCl_3$; 400MHz)



25

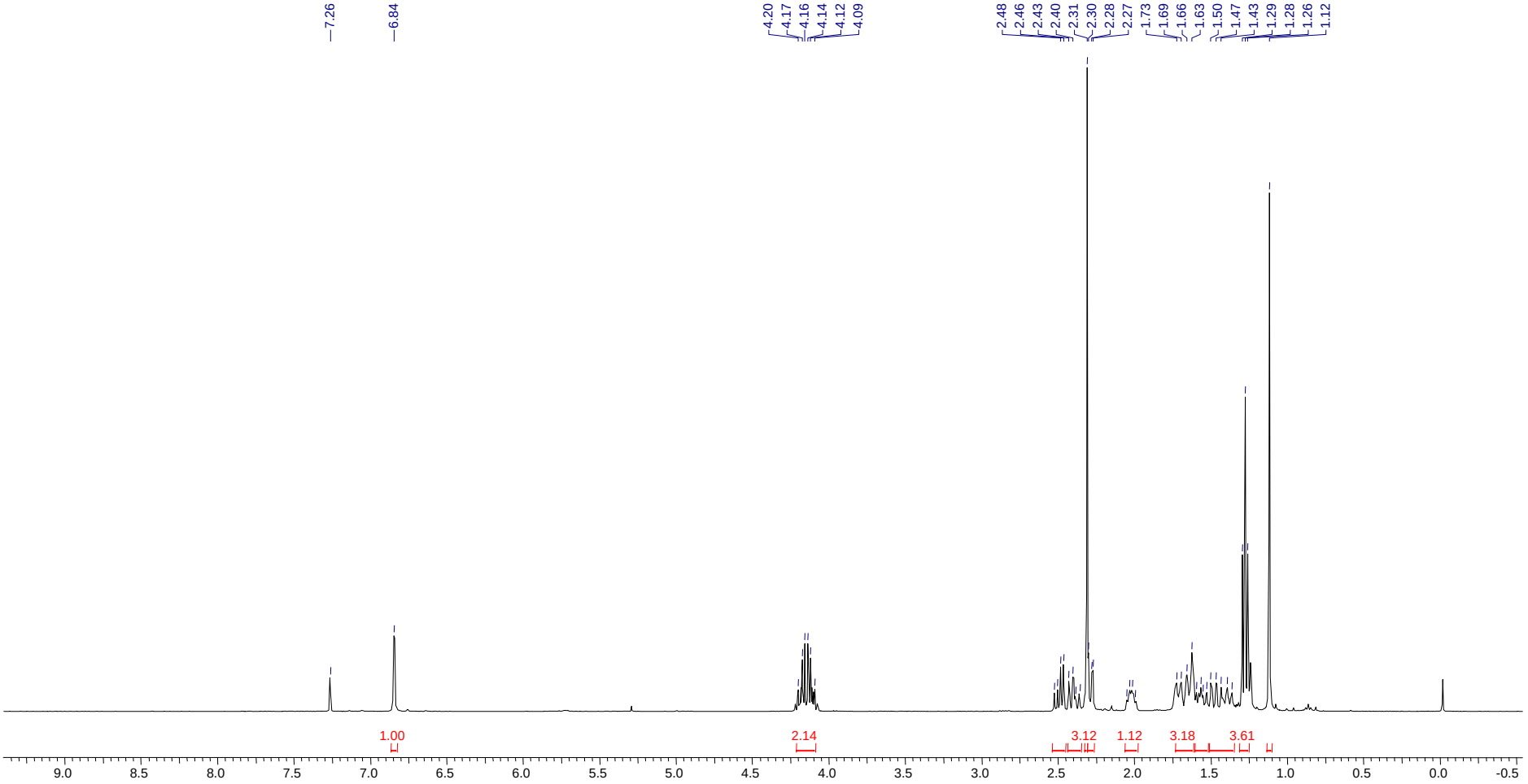
^{13}C NMR of Compound 25 ($CDCl_3$; 100MHz)

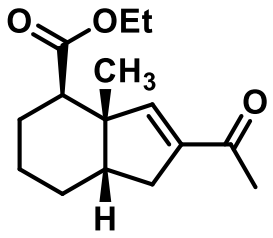




26

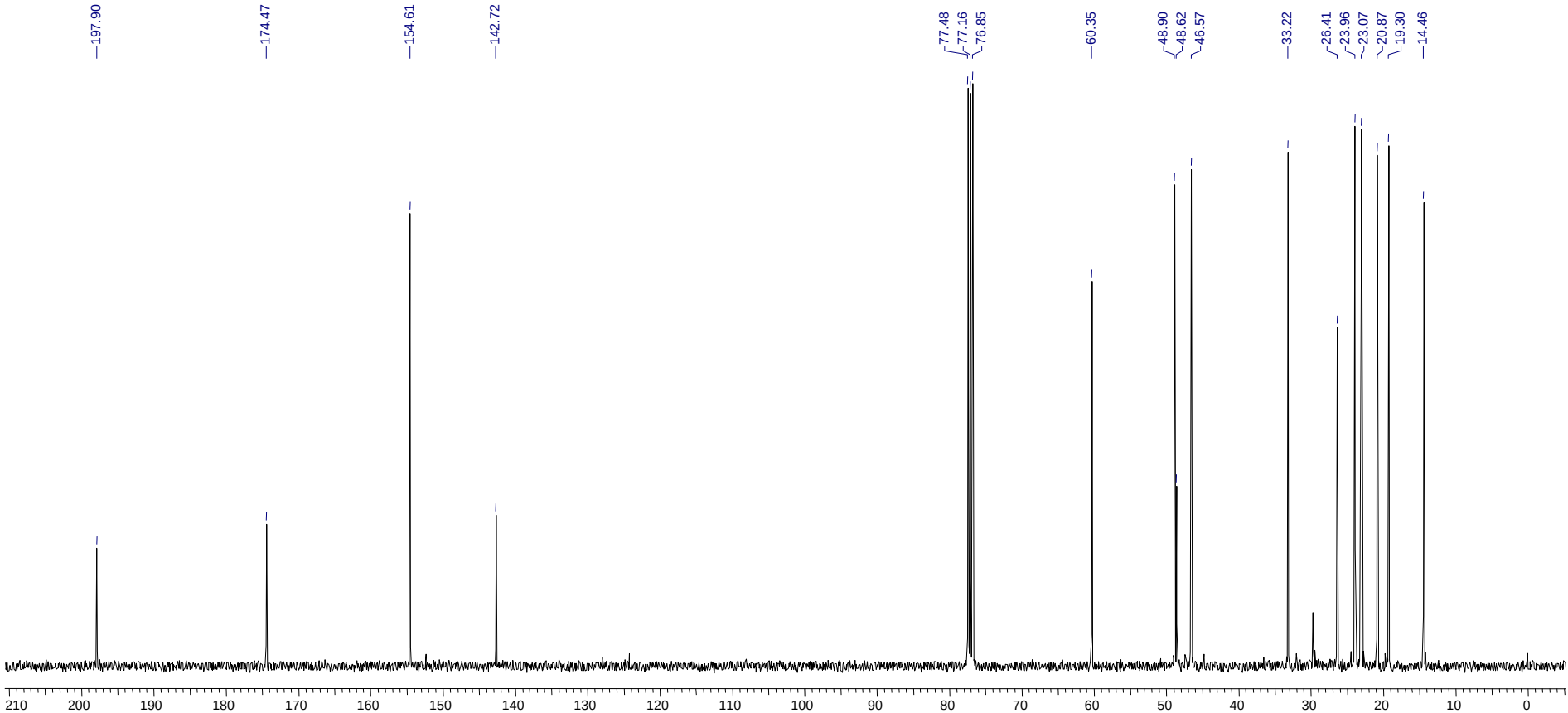
^{1}H NMR of Compound 26 ($CDCl_3$; 400MHz)

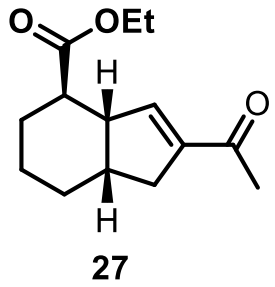




26

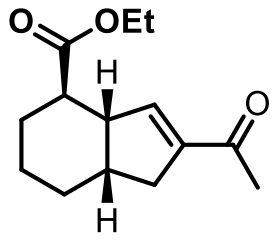
^{13}C NMR of Compound 26 ($CDCl_3$; 100MHz)





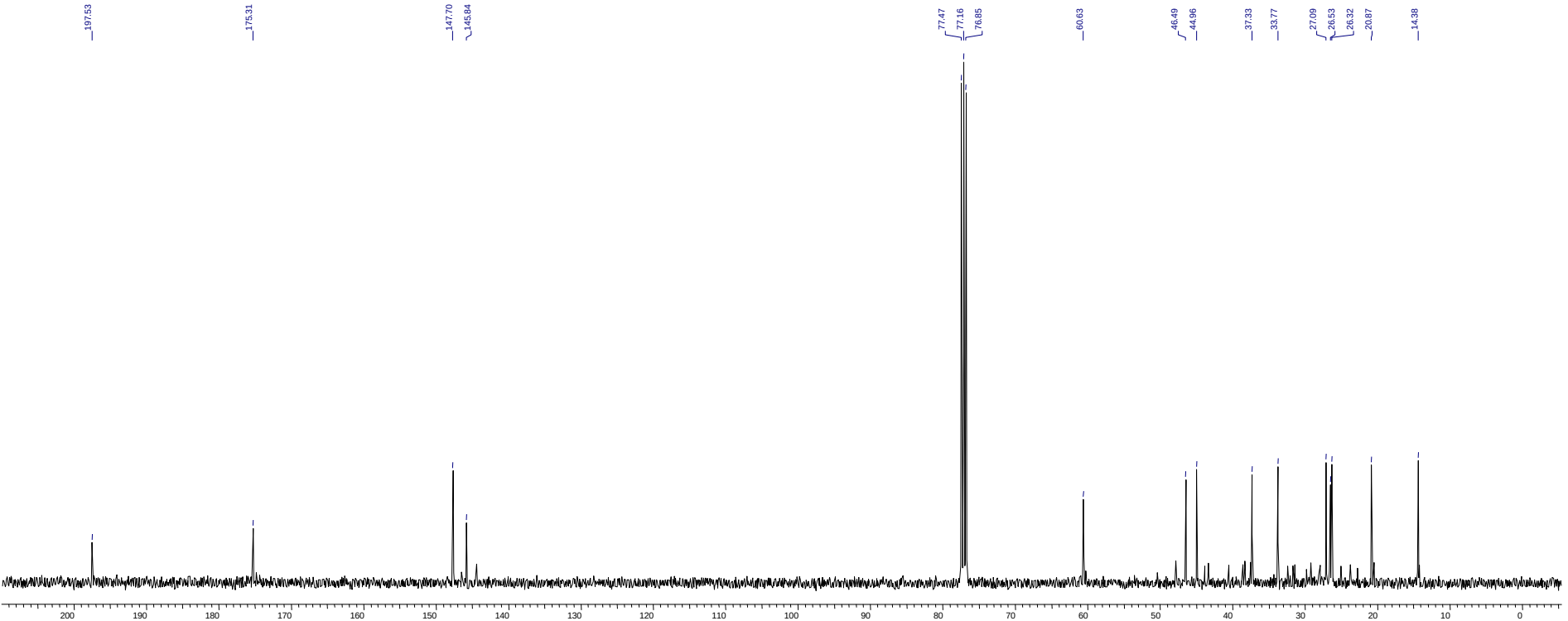
27

^{1}H NMR of Compound 27 ($CDCl_3$; 400MHz)

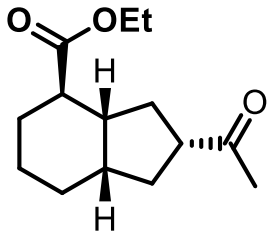


27

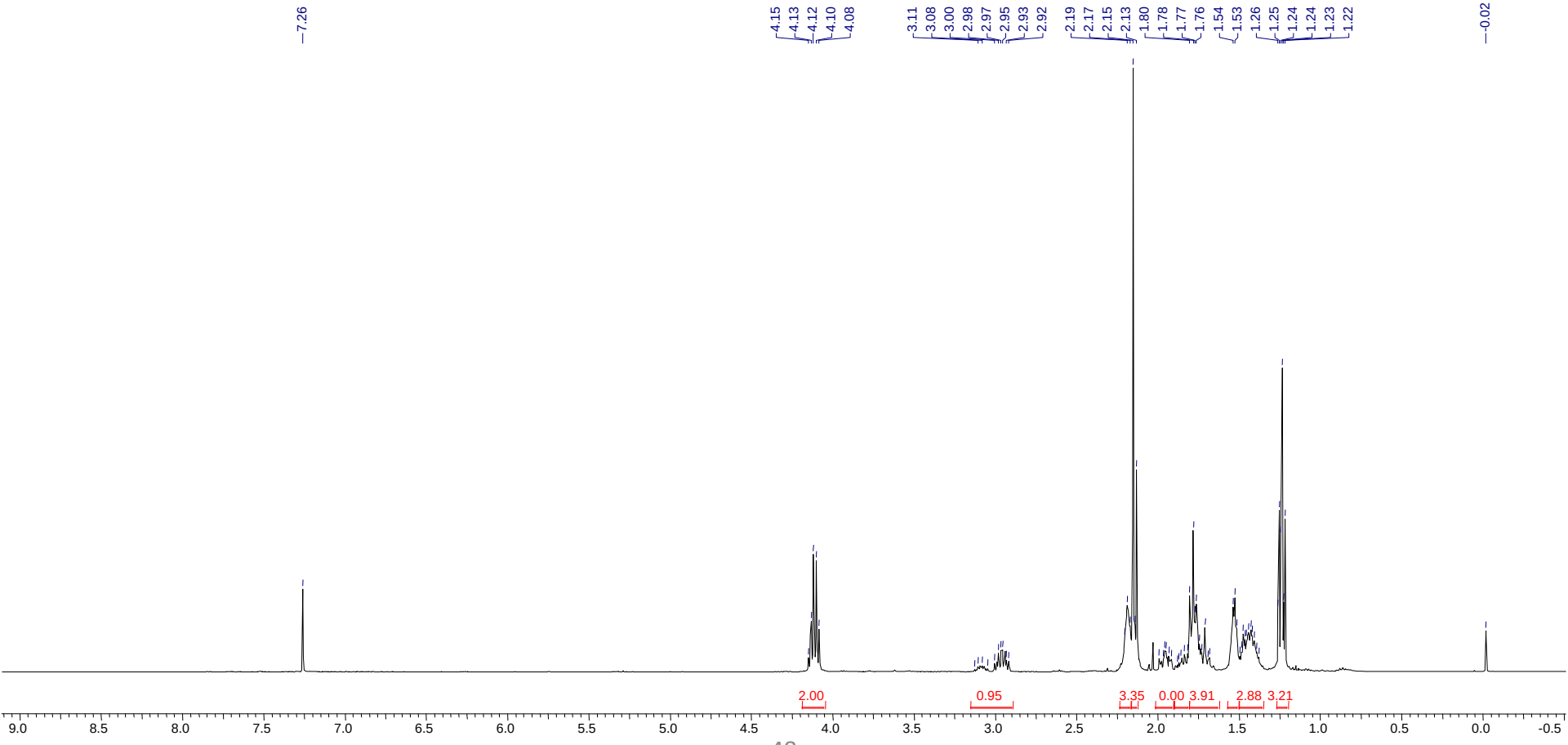
^{13}C NMR of Compound 27 ($CDCl_3$; 100MHz)



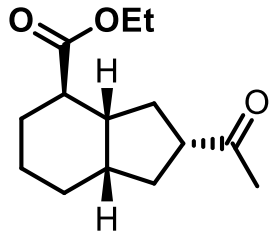
^{1}H NMR of Compound 28 ($CDCl_3$; 400MHz)



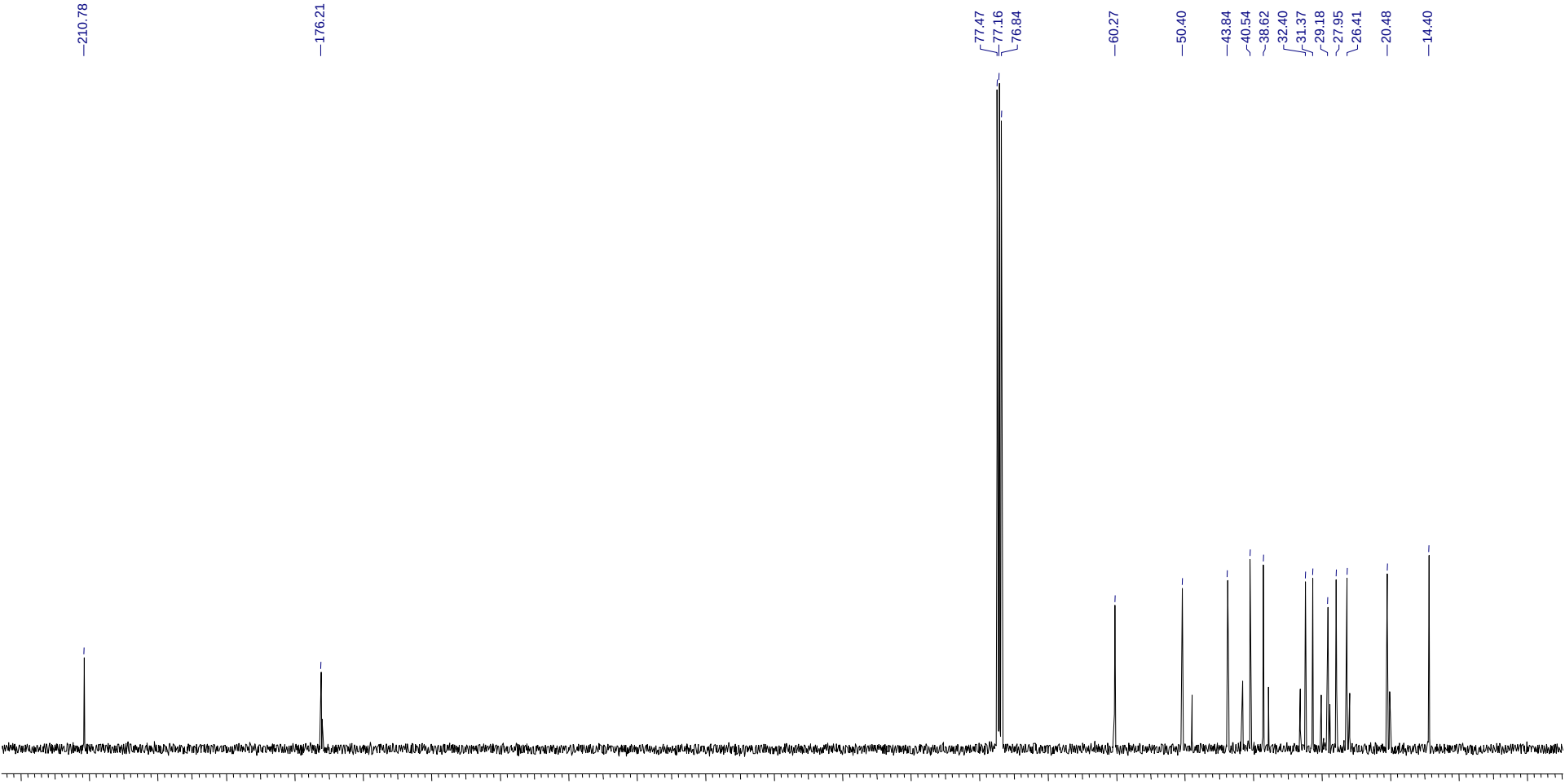
28



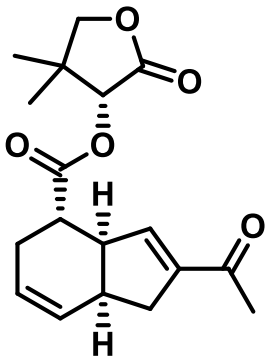
^{13}C NMR of Compound 28 ($CDCl_3$; 100MHz)



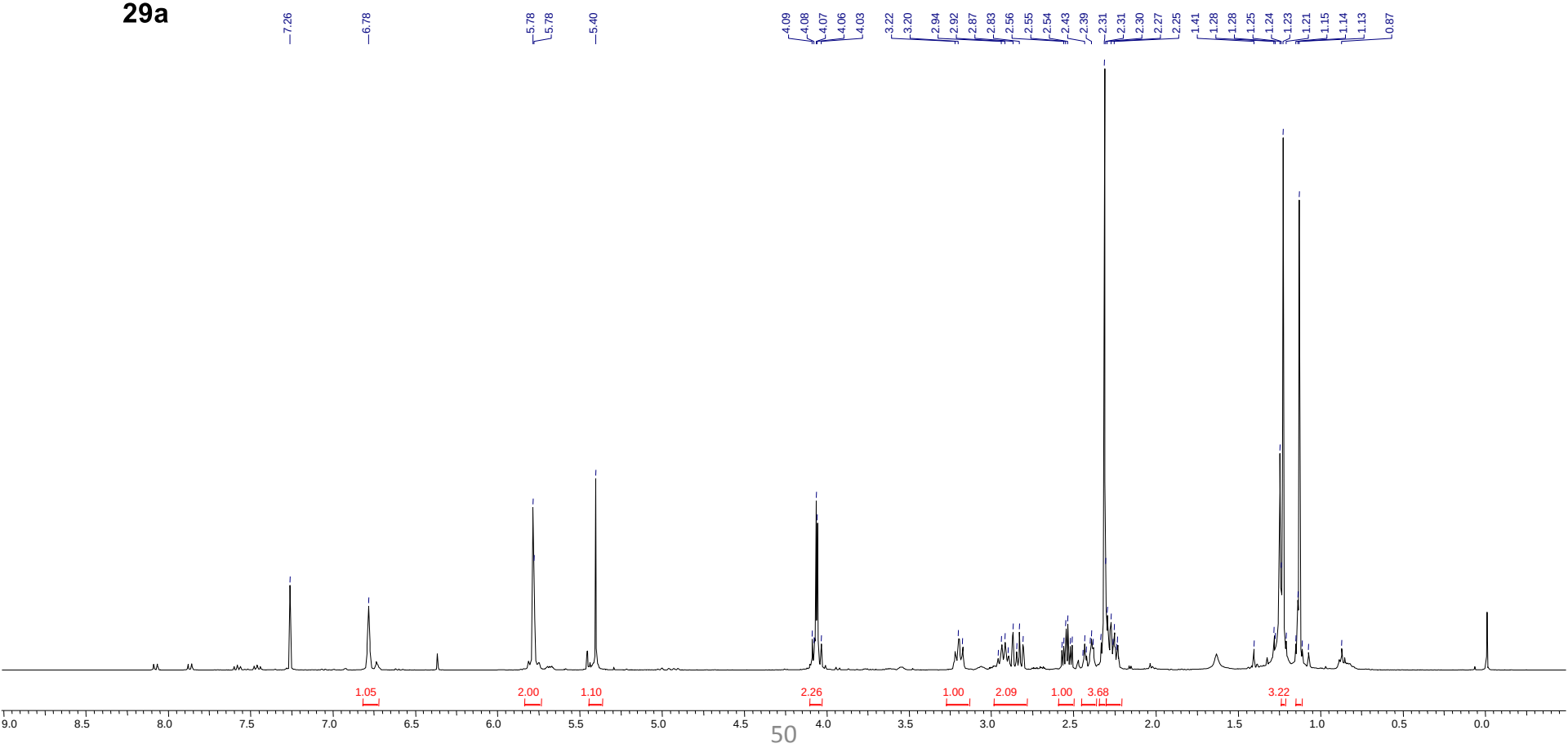
28



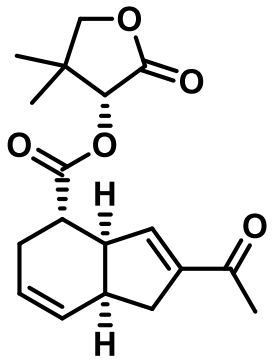
^{1}H NMR of Compound 29a ($CDCl_3$; 400MHz)



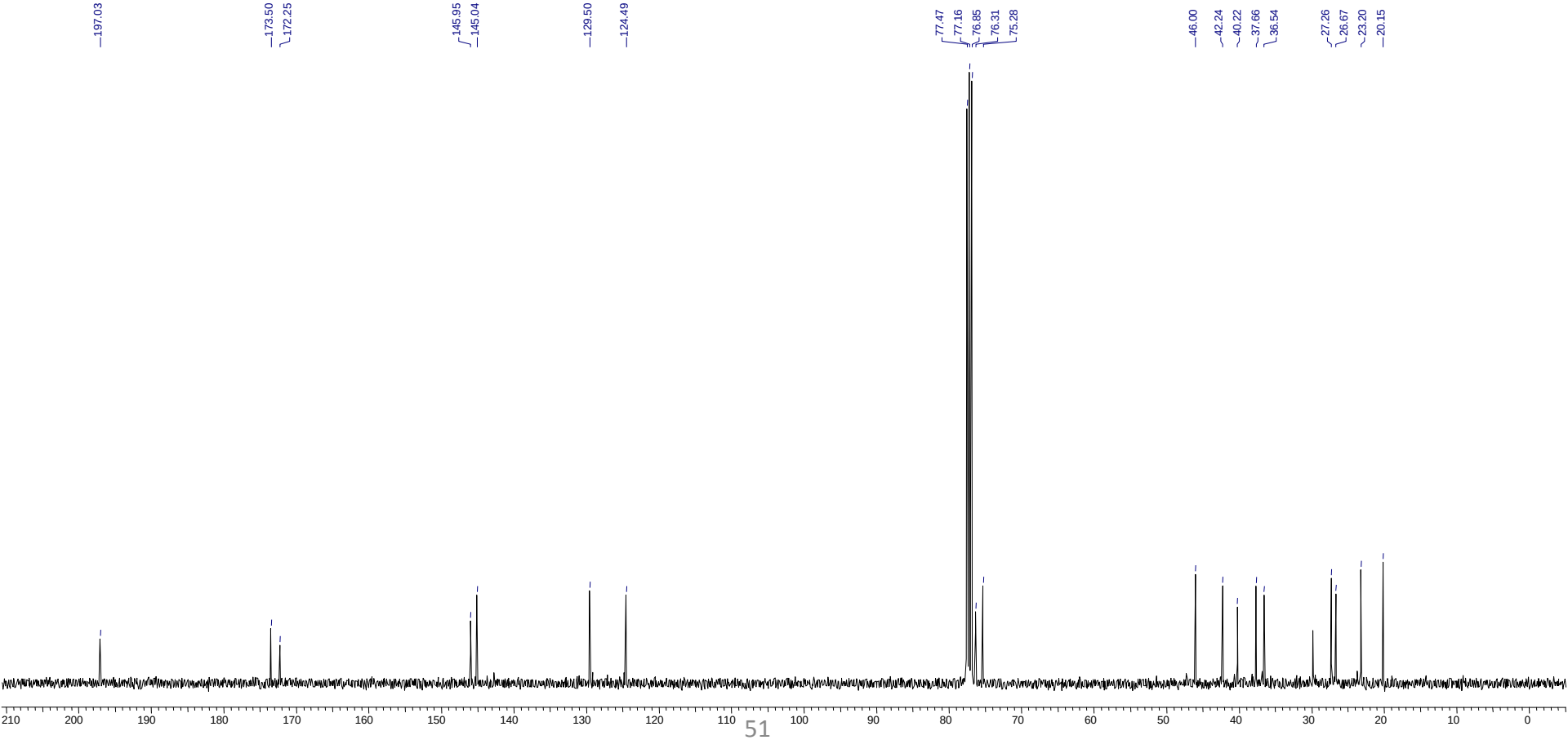
29a



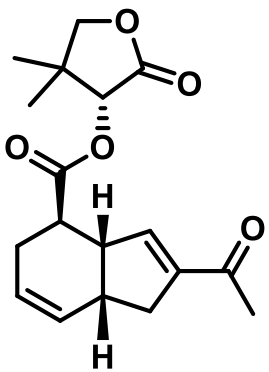
^{13}C NMR of Compound 29a ($CDCl_3$; 100MHz)



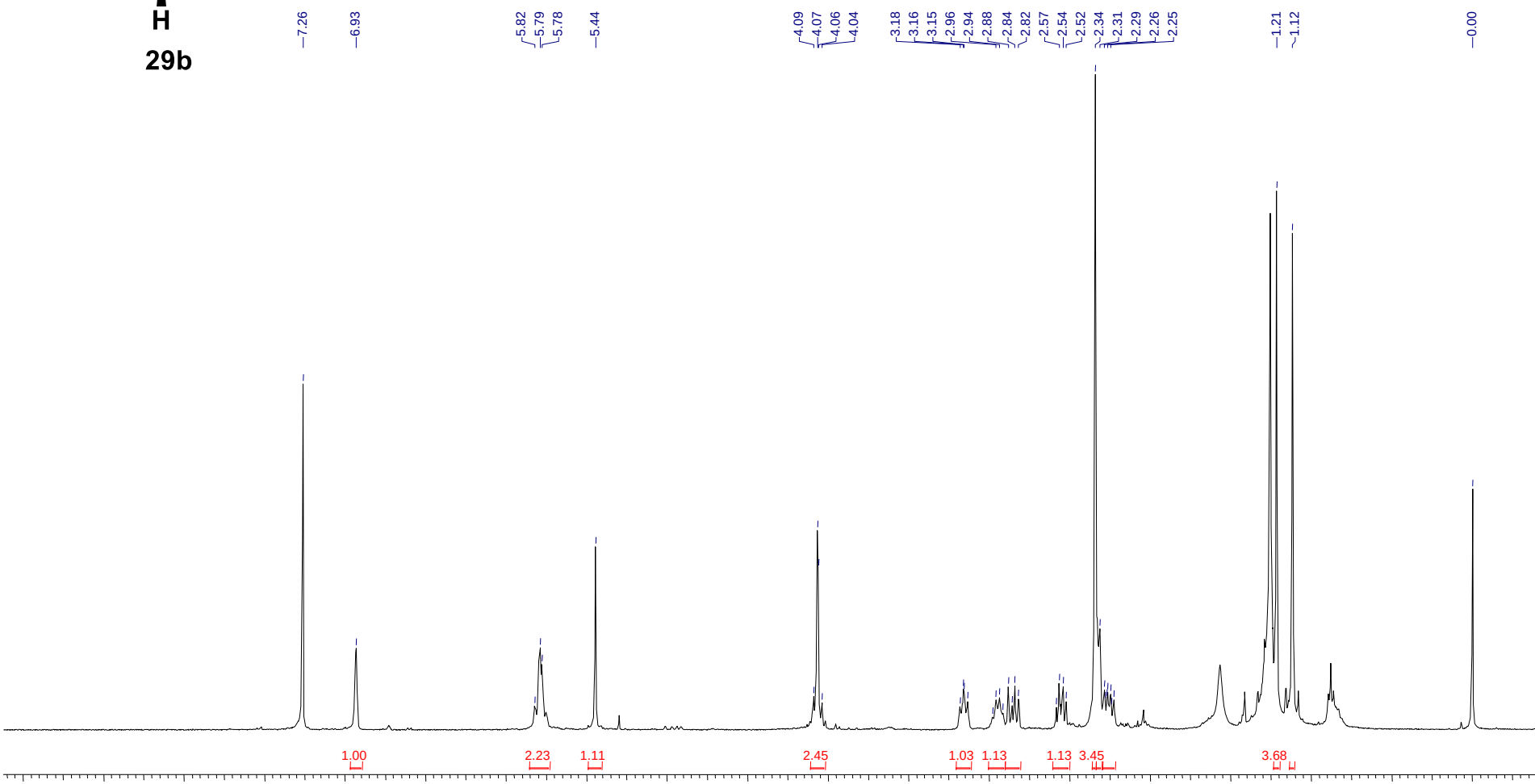
29a



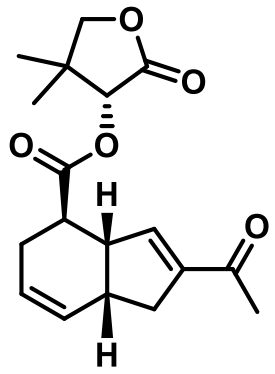
^{1}H NMR of Compound 29b ($CDCl_3$; 400MHz)



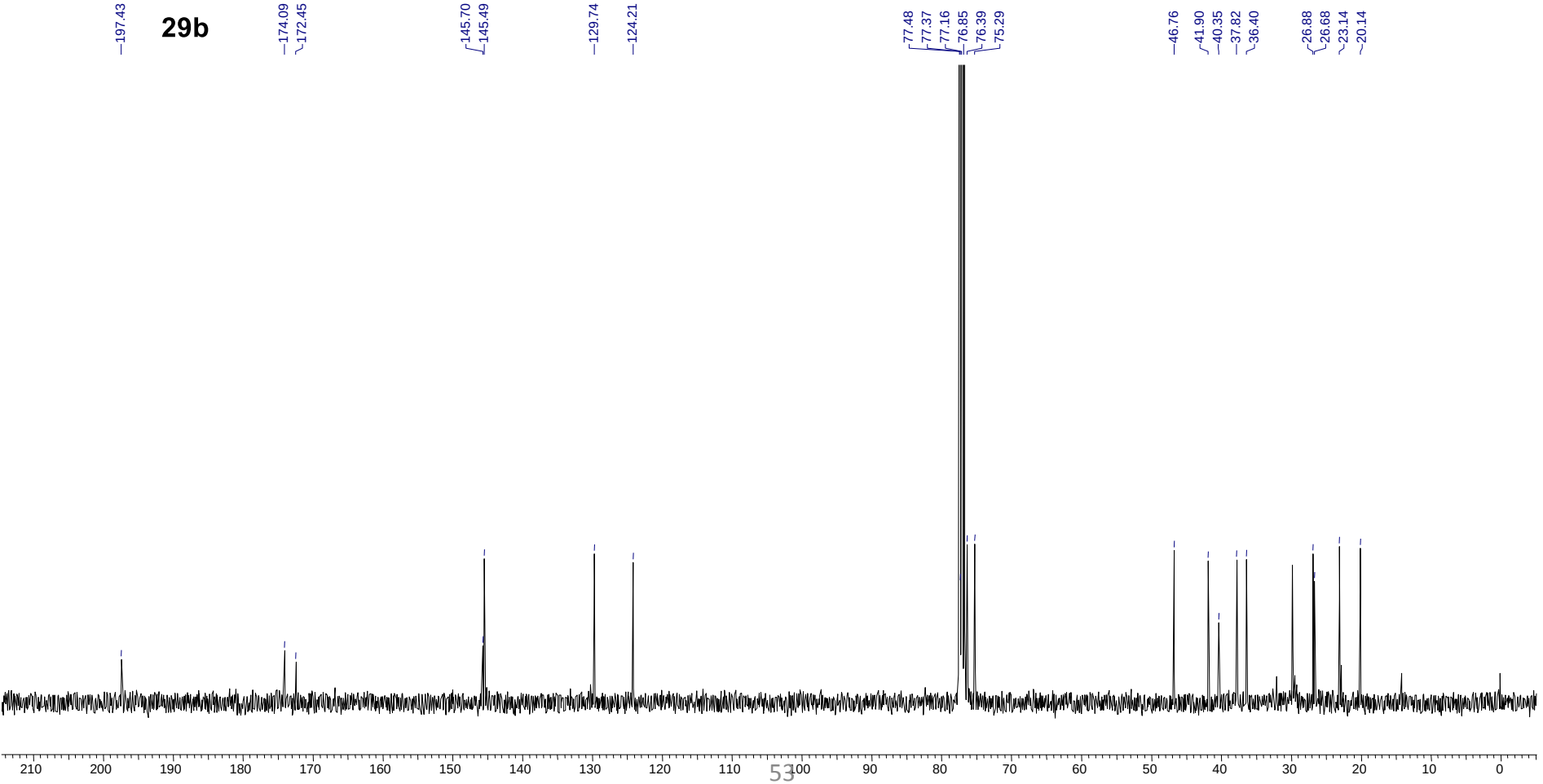
29b

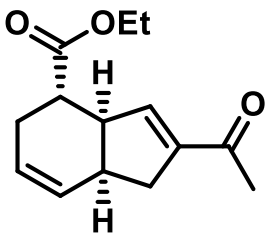


^{13}C NMR of Compound 29b ($CDCl_3$; 100MHz)



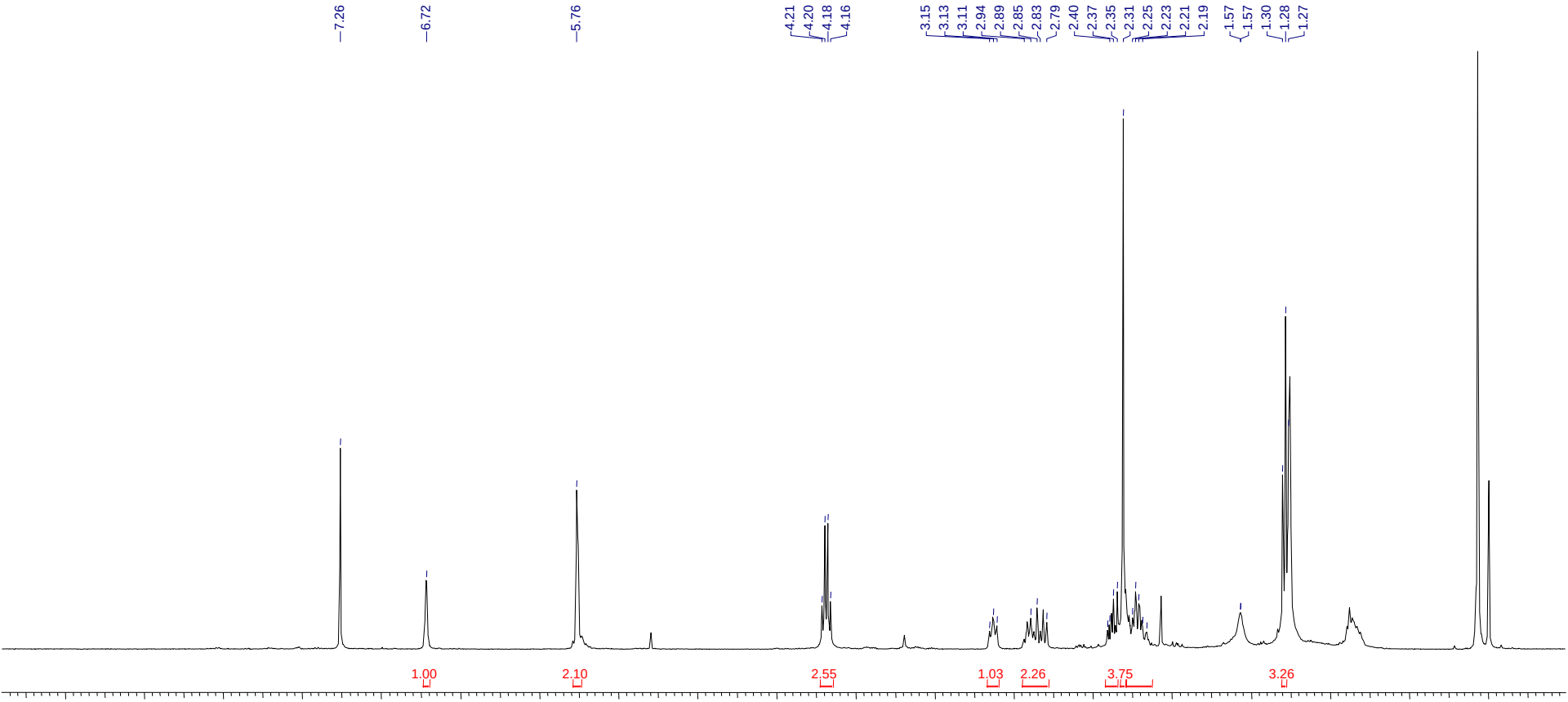
29b

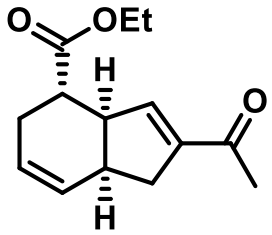




11a

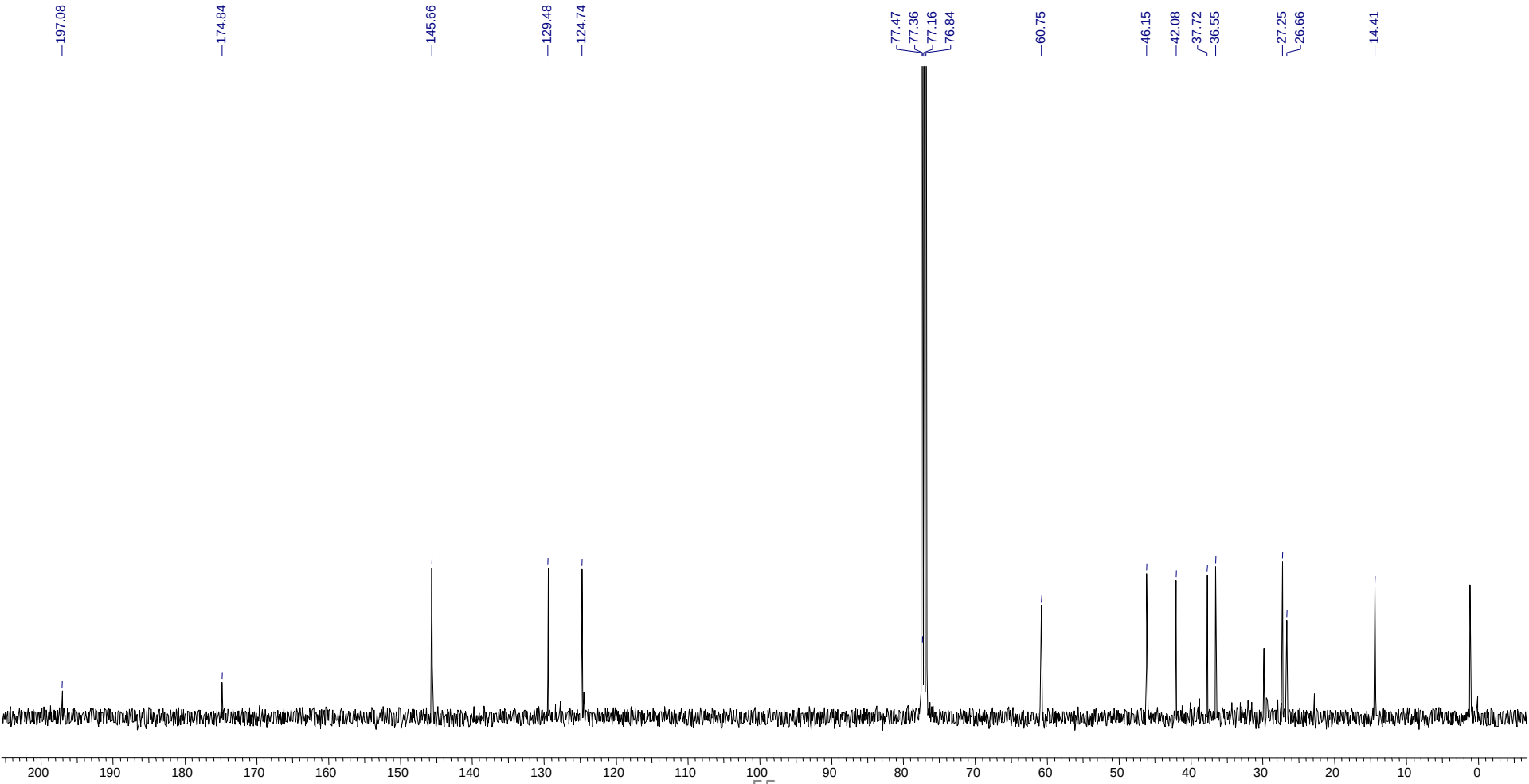
^{1}H NMR of Compound 11a ($CDCl_3$; 400MHz)

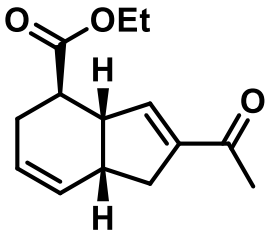




11a

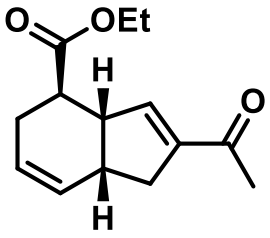
^{13}C NMR of Compound 11a ($CDCl_3$; 100MHz)





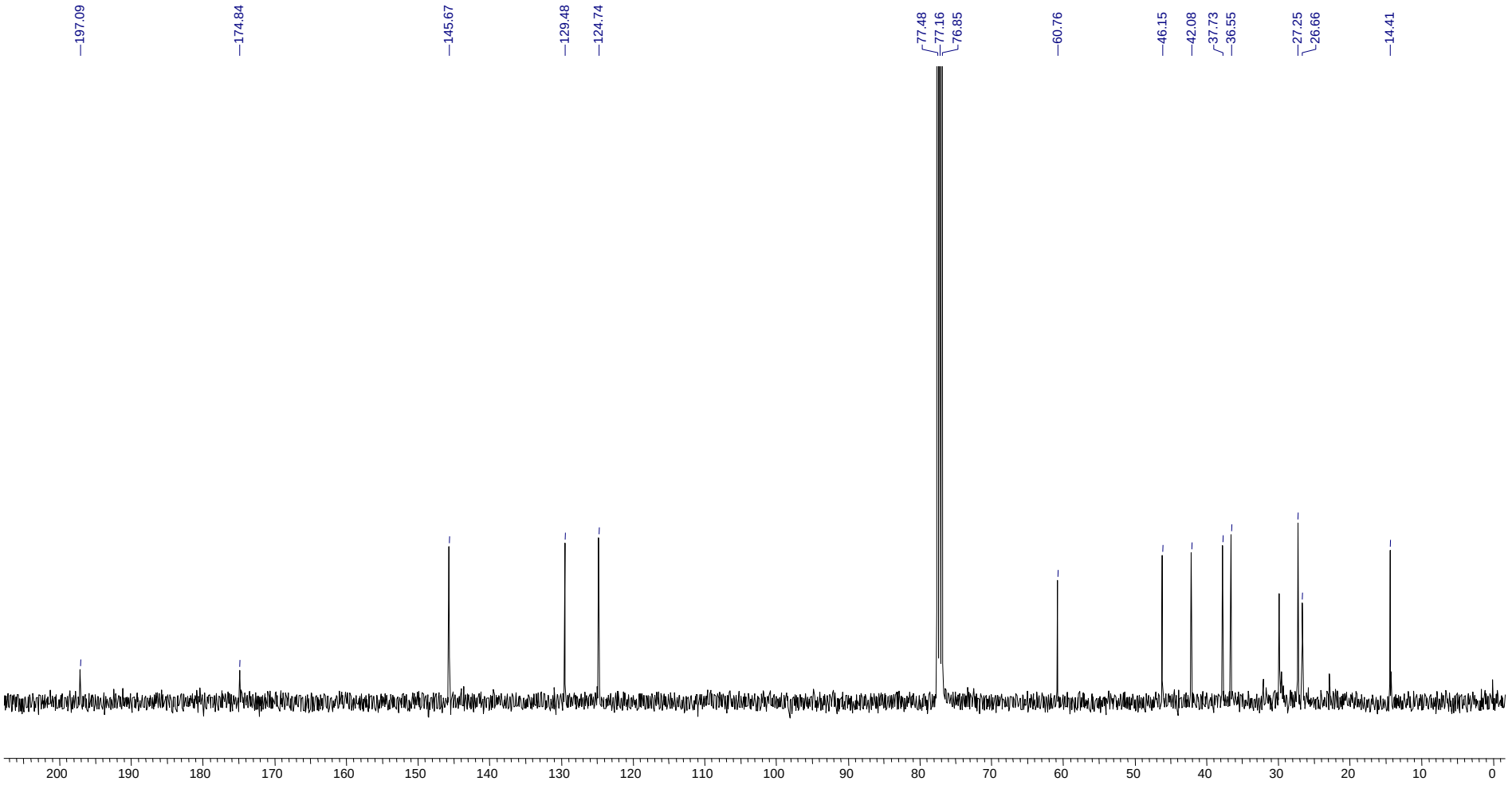
11b

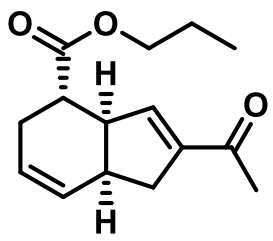
^{1}H NMR of Compound 11b ($CDCl_3$; 400MHz)



11b

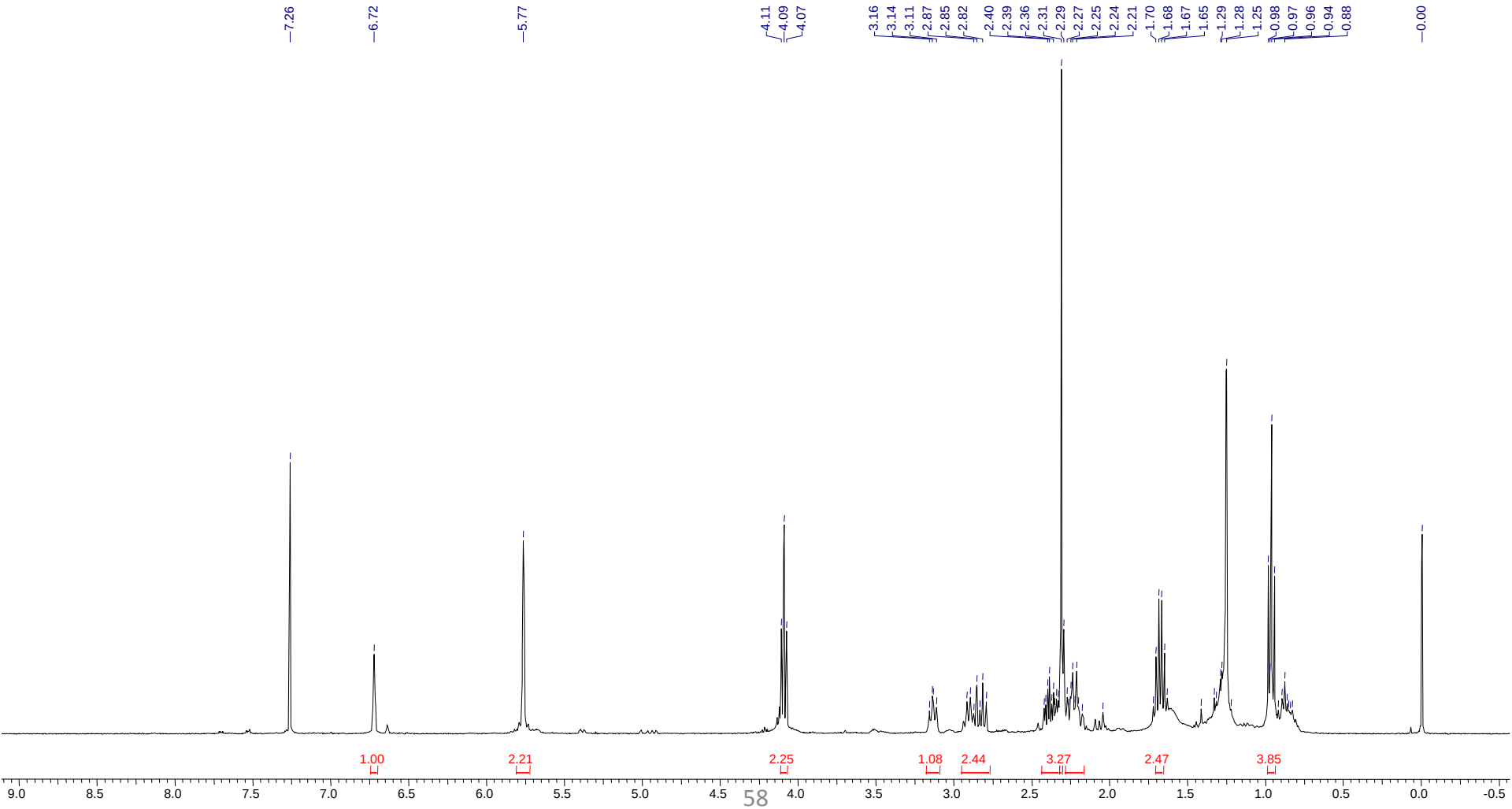
^{13}C NMR of Compound 11b ($CDCl_3$; 100MHz)

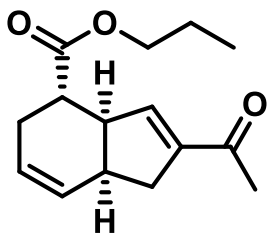




30a

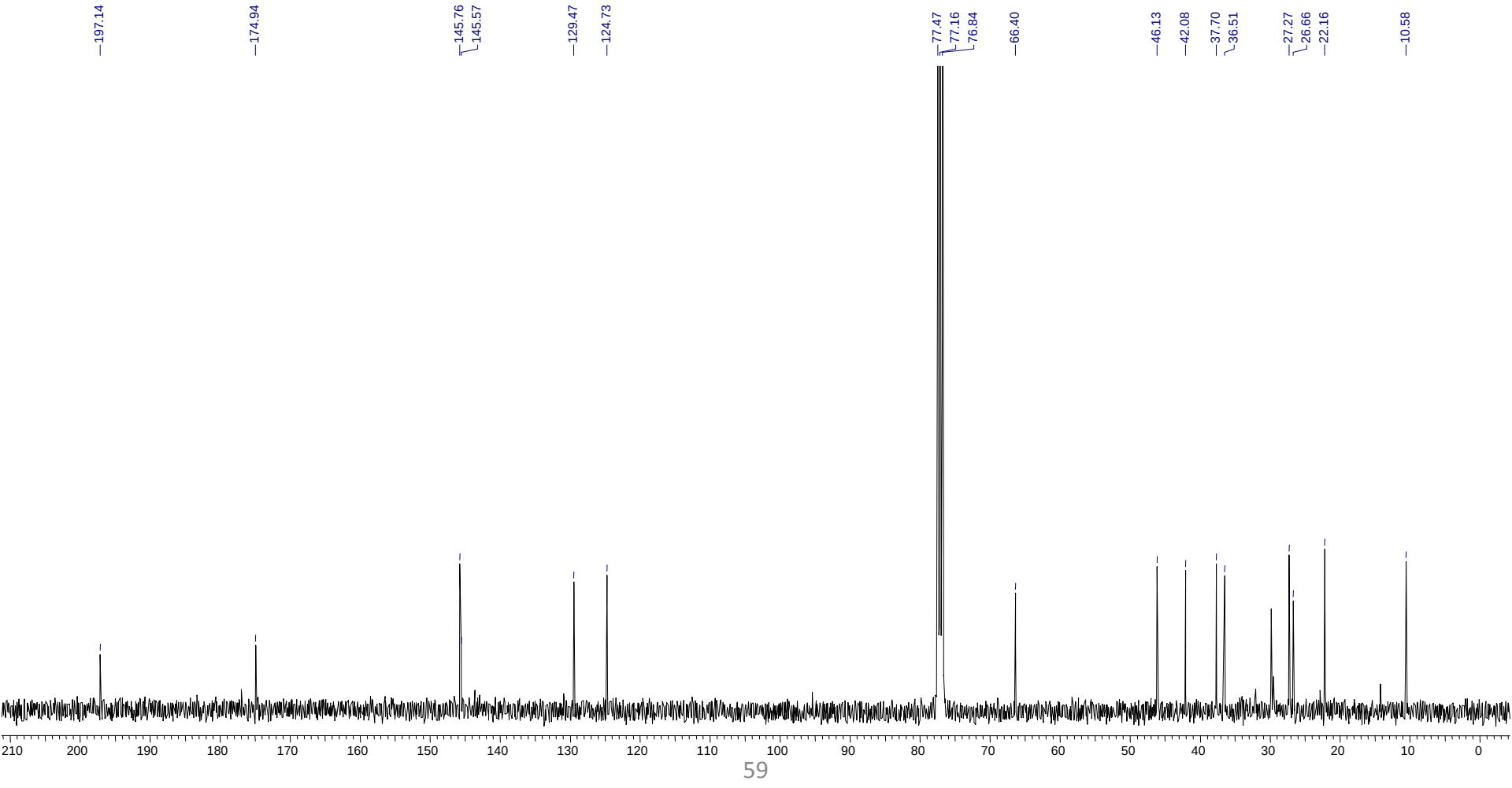
^{1}H NMR of Compound 30a ($CDCl_3$; 400MHz)

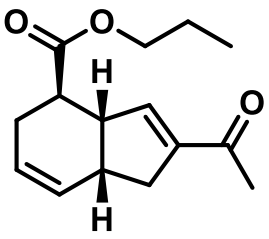




30a

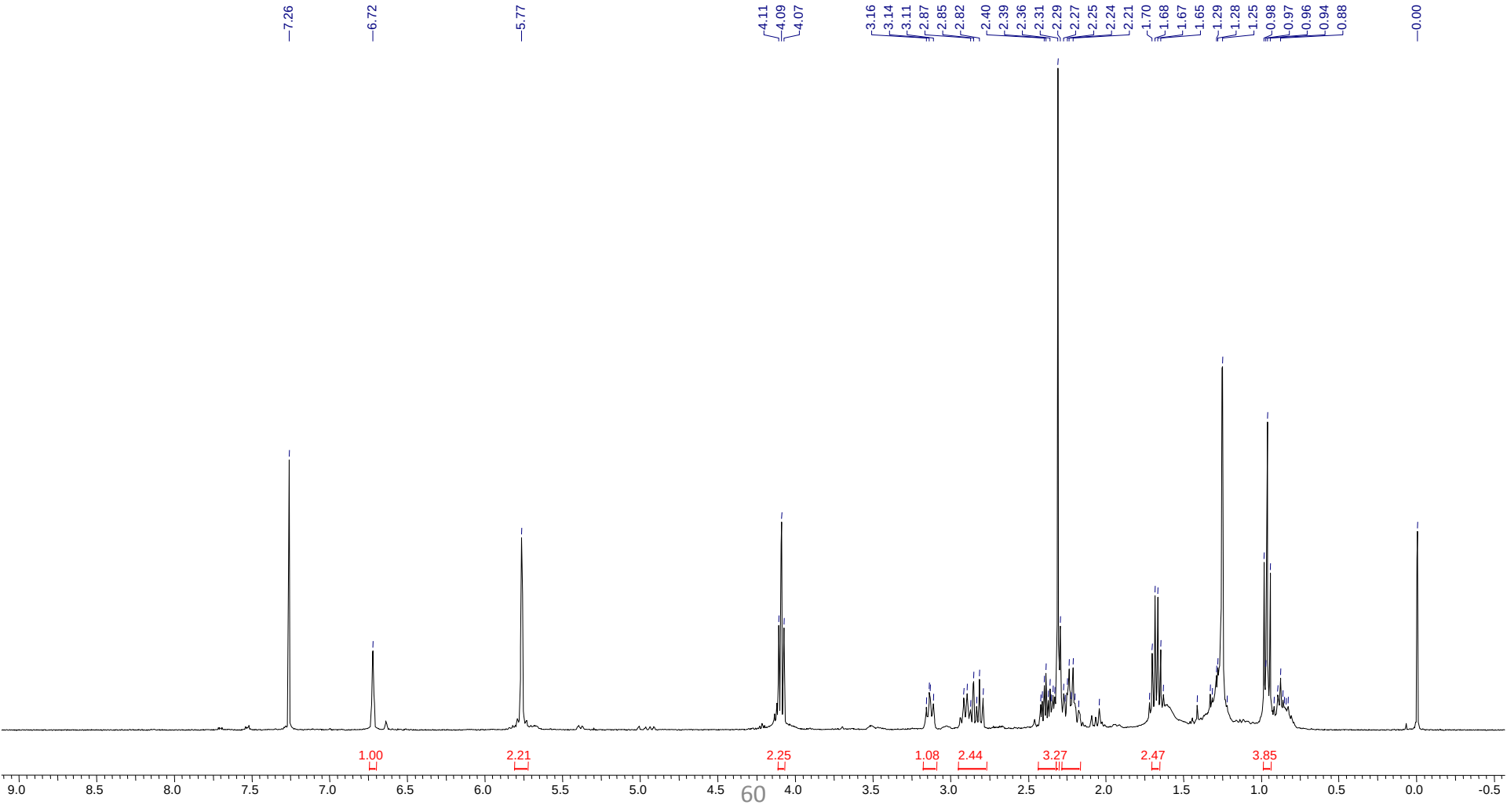
^{13}C NMR of Compound 30a ($CDCl_3$; 100MHz)

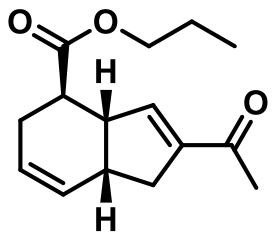




30b

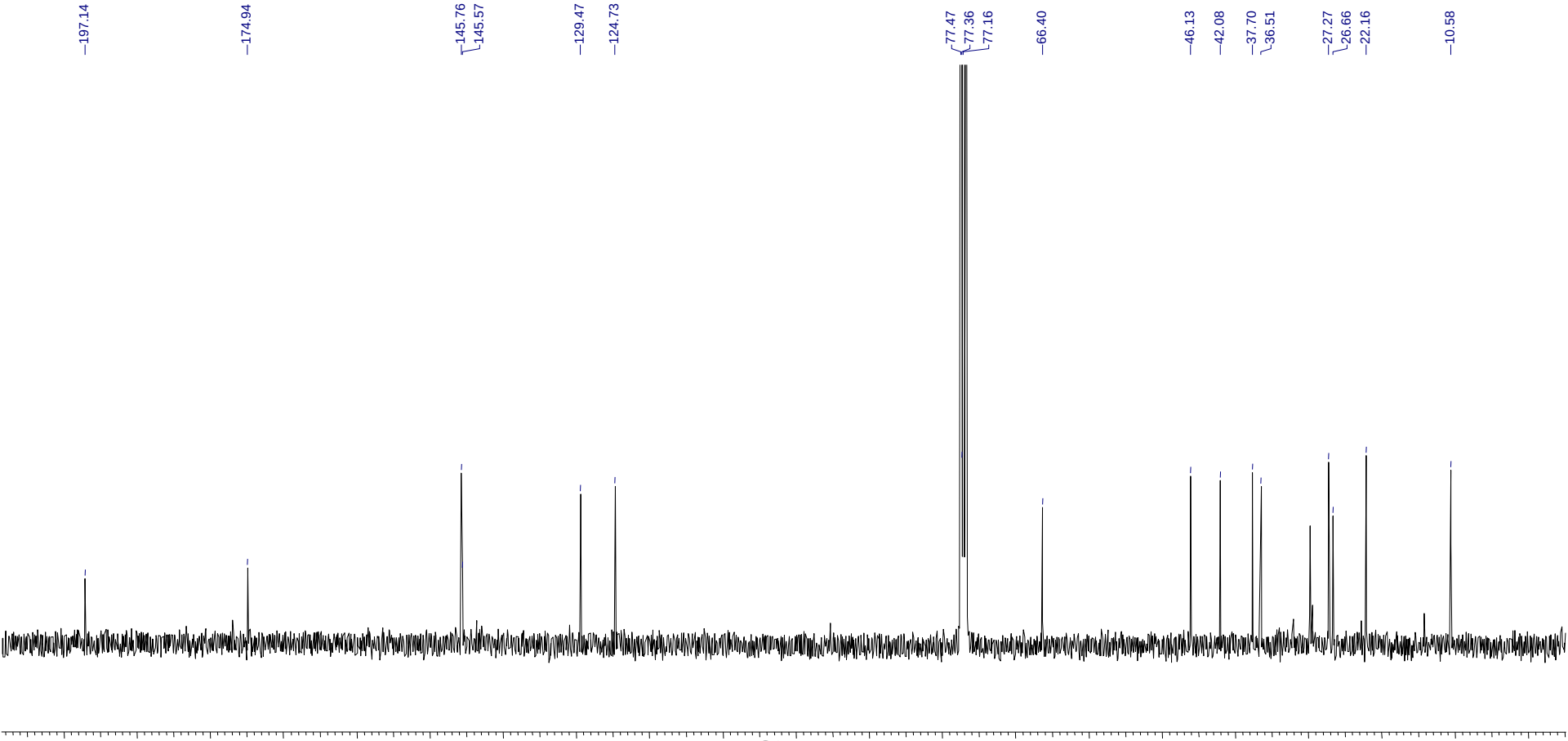
^{1}H NMR of Compound 30b ($CDCl_3$; 400MHz)

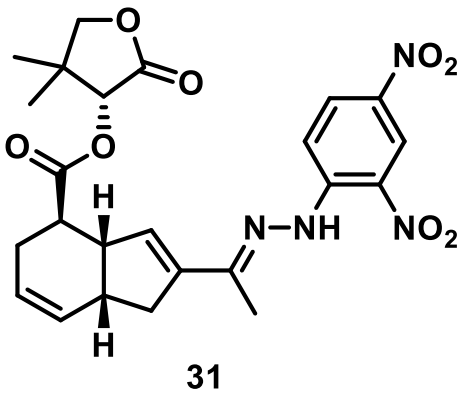




30b

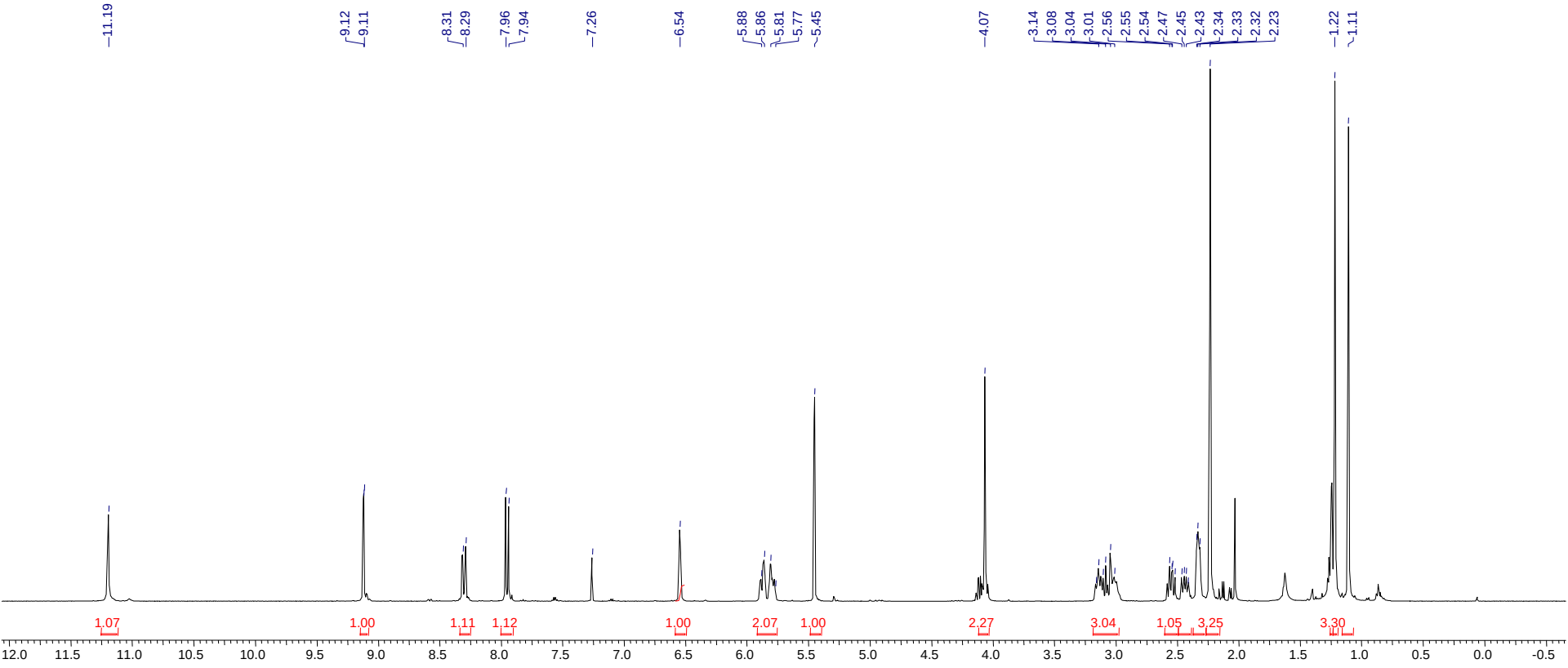
^{13}C NMR of Compound 30b ($CDCl_3$; 100MHz)

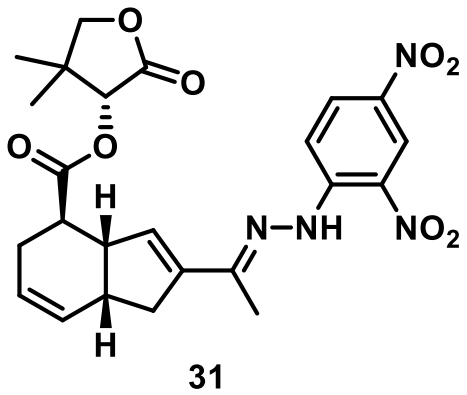




31

^{1}H NMR of Compound 31 ($CDCl_3$; 400MHz)





31

^{13}C NMR of Compound 31 ($CDCl_3$; 100MHz)