Synthesis and biological evaluation of palmyrolide A macrocycles as sodium channel blockers towards neuroprotection

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Electronic Supplementary Information

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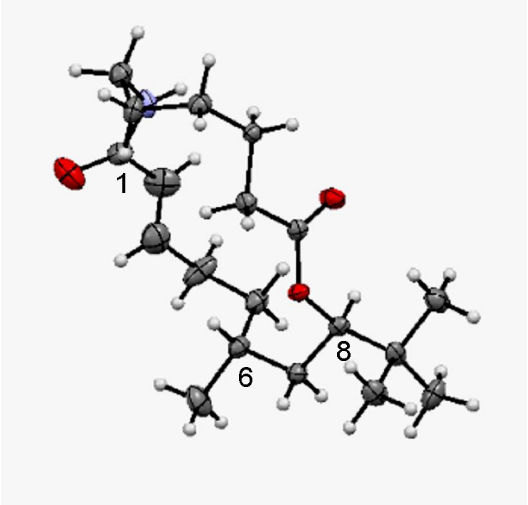
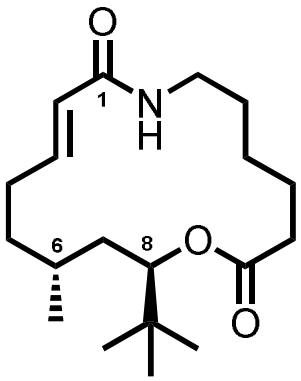
Single X-ray Crystal Structures of 18 and 30

Single crystals of compound **18** and **30** were obtained from Ethyl acetate/ Hexanes solvent system. X-ray intensity data were collected on a SMART APEX II DUO diffractometer with graphite-monochromatized (Mo KŬ=0.71073 Å) radiation at 296 K. ORTEPs were generated using Mercury program. All the H-atoms were located in the difference Fourier and refined isotropically.

Compound 18:





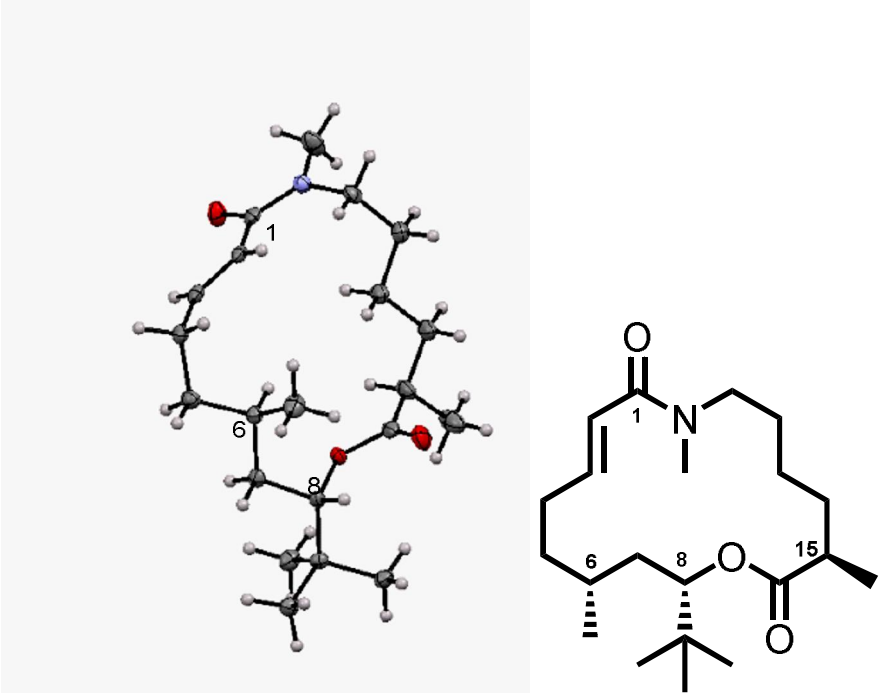
ORTEP of Compound **18 (**50% probability for the thermal ellipsoids)

Crystallographic data for compound **18** deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. **CCDC1454803**.

Crystallographic data for 18 ($C_{19}H_{33}O_3N$): M =323.2, Crystal dimensions 0.450 x 0.360 x 0.180 mm^3, monoclinic, space group $P\,2_1$,a = 11.998(3), b = 8.740(2), c = 18.751(5) Å, α = 90.00°,β= 104.393(6)°, γ =90.00°, V = 1904.6 (8) $Å^3$, Z = 4, ρ_{calcd} = 1.128gcm^{-3}, μ (Mo-K$_\alpha$) = 0.075mm^{-1}, *F(000)* = 712.0, $2\theta_{max}$ = 56.68°, T = 296 K, 36143 reflections collected, 9449unique, 5015 observed ($I > 2\sigma(I)$) reflections, 424 refined parameters, R value 0.0701,

*wR*2 = 0.0.1336, (all data *R* = 0.1626, *wR*2 = 0.1757), *S* = 0.987, minimum and maximum transmission 0.967 and 0.987; maximum and minimum residual electron densities 0.674 and -0.316 eÅ^{-3}.

Compound 30:



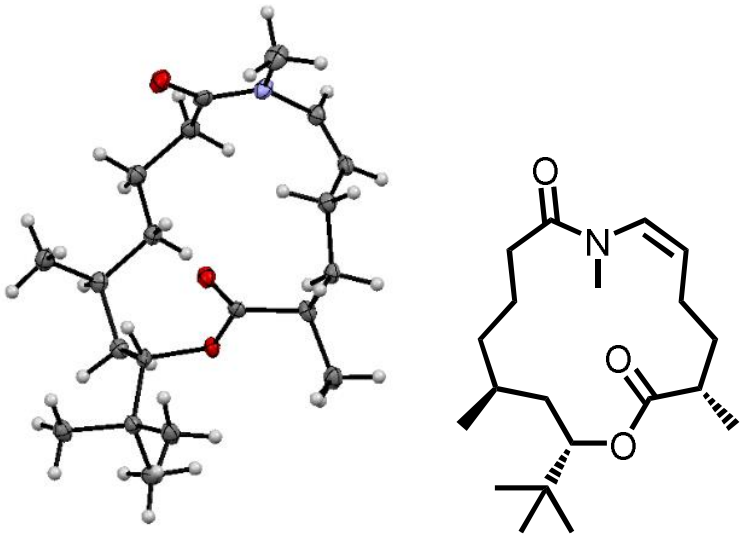
ORTEP of Compound **30 (**50% probability for the thermal ellipsoids)

Crystallographic data for compound **30** deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. **CCDC1454804**.

Crystallographic data for 30 ($C_{21}H_{37}O_3N$): *M* = 337.2, Crystal dimensions 0.460 x 0.320 x 0.110 mm^3, Orthorhombic, space group *P* $2_12_12_1$,*a* = 5.615 (3), *b* = 10.654 (5), *c* = 35.955(17) Å, α = 90.00°, β= 90.00°, γ = 90.00°, *V* = 2151.0 (18) Å^3, *Z* = 4, ρ_{calcd} = 1.085gcm^{-3}, μ (Mo-K$_\alpha$) = 0.071 mm^{-1}, *F(000)* = 776.0, $2\theta_{max}$ = 52°, *T* = 296 K, 19159 reflections collected, 4182 unique, 3406 observed ($I > 2\sigma(I)$) reflections, 232 refined parameters, *R* value 0.0445, *wR*2 = 0.0607, (all data *R* = 0.0617, *wR*2 = 0.0628), *S* = 1.618,

minimum and maximum transmission 0.968 and 0.992; maximum and minimum residual electron densities 0.166 and -0.201 e.Å^{-3}

Compound 7:

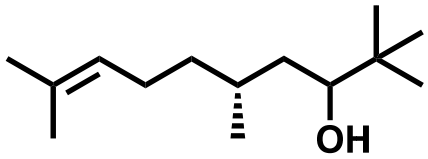


ORTEP of Compound **7** (50% probability for the thermal ellipsoids)

Crystallographic data for compound **7** deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. **CCDC920726.**

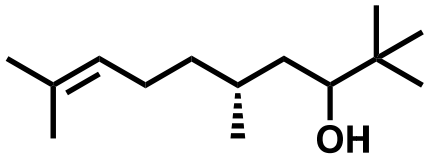
Copies of ^{1}H & ^{13}C NMR of all compounds

^{1}H NMR of Compound **2'** at 400 MHz in $CDCl_3$



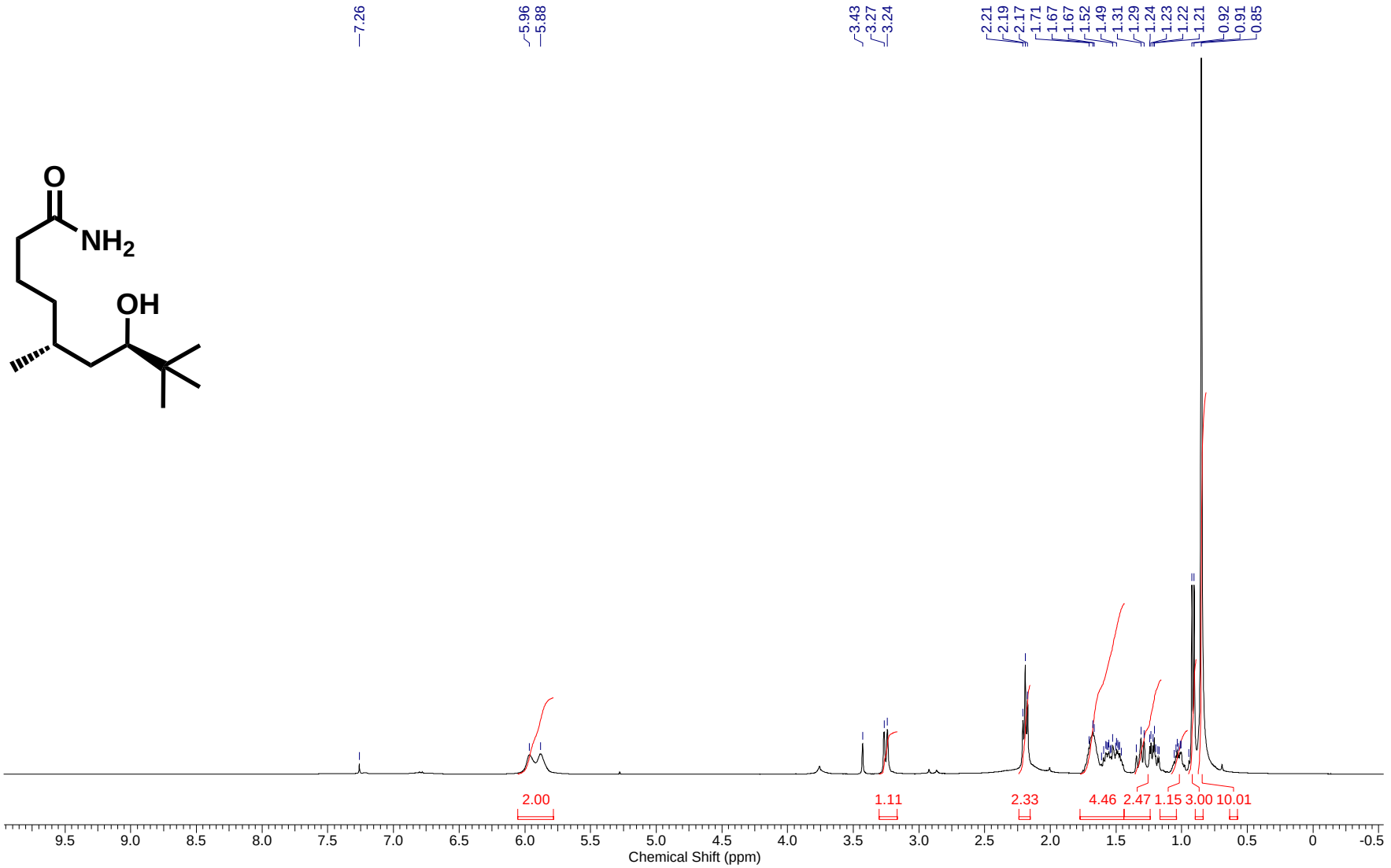
Diastereomeric mixture

^{13}C NMR of Compound **2'** at 100 MHz in $CDCl_3$

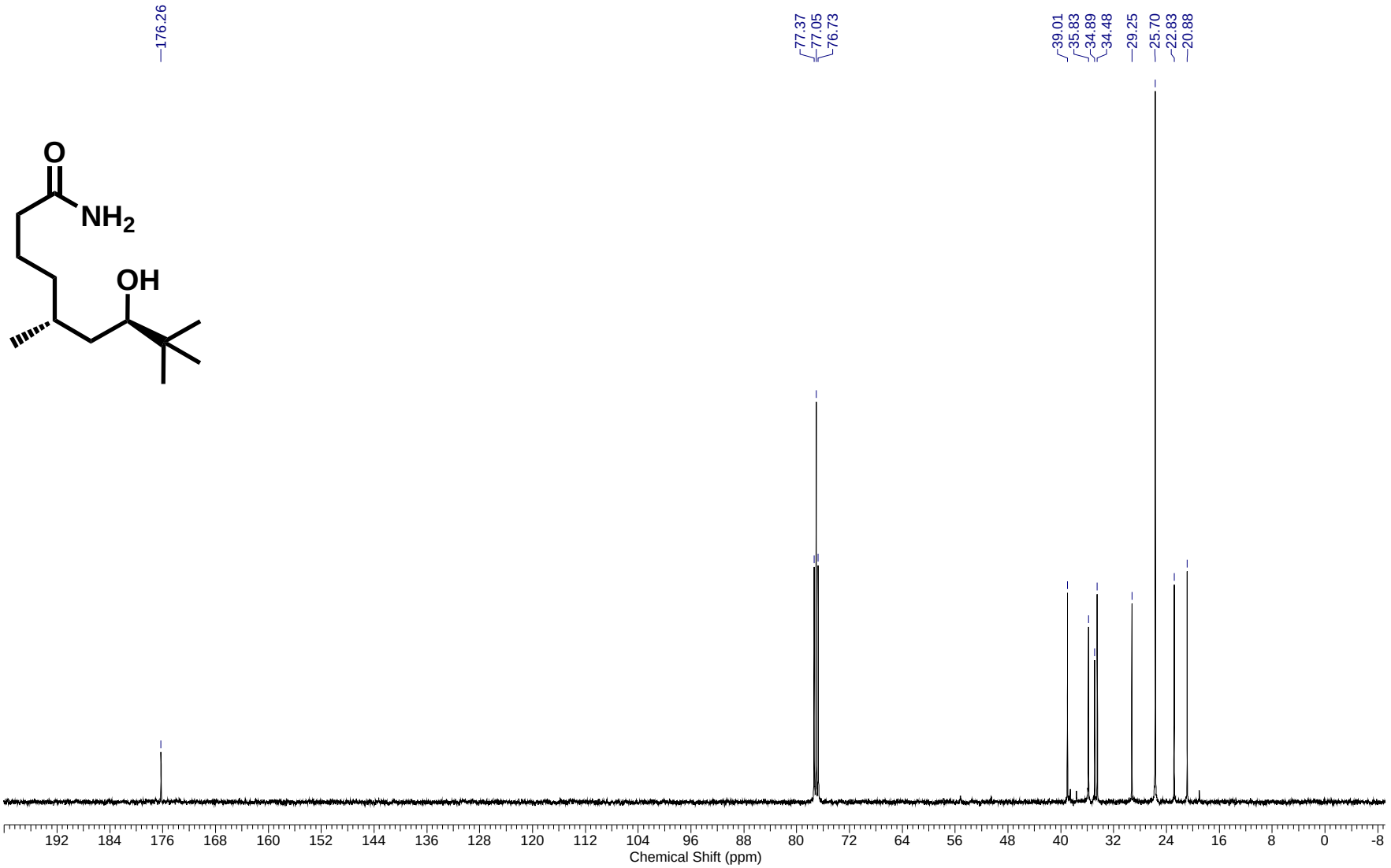


Diastereomeric mixture

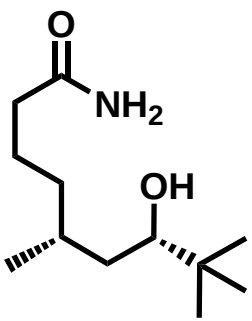
^{1}H NMR of Compound (+)-**4'** at 400 MHz in $CDCl_3$



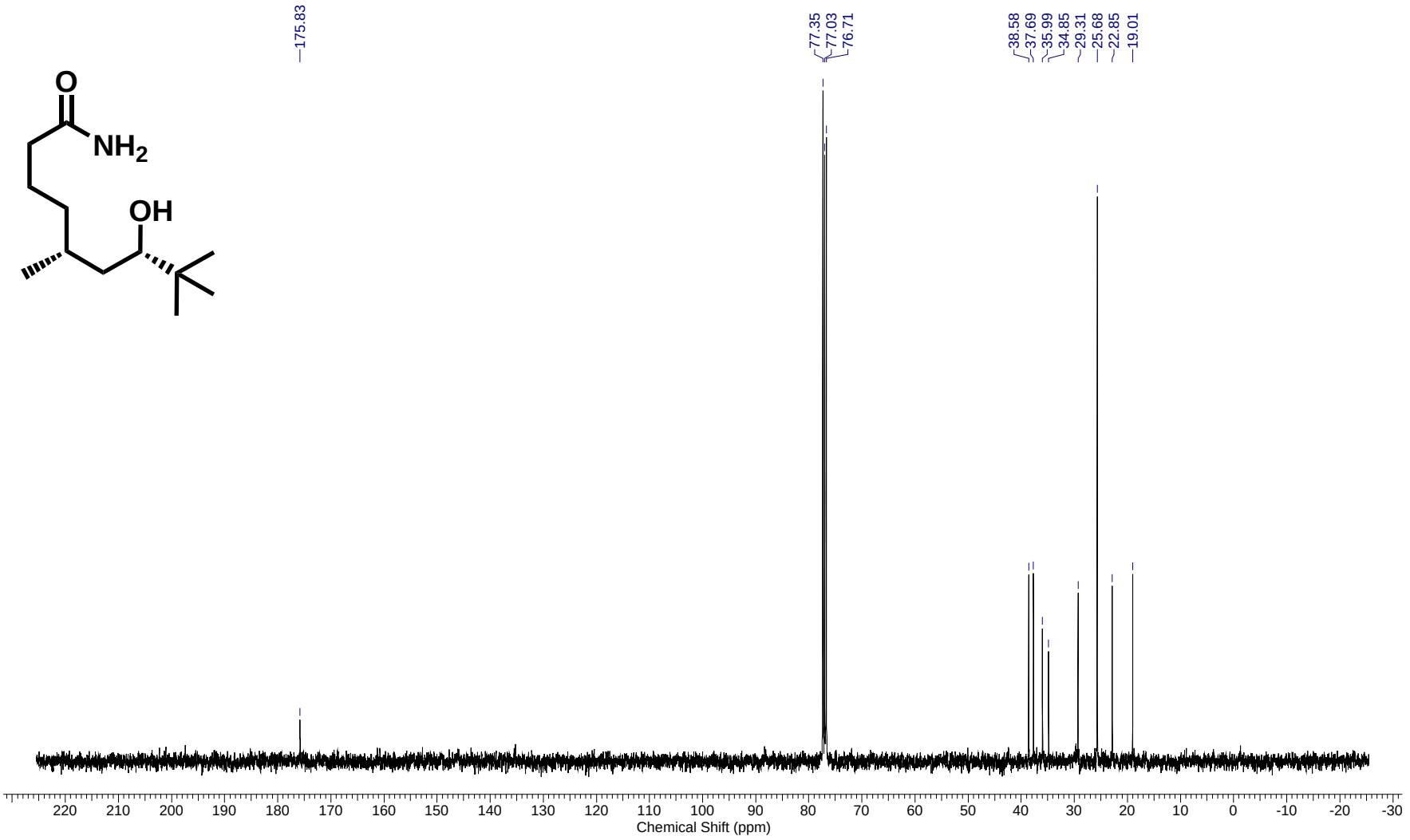
^{13}C NMR of Compound (+)-**4'** at 100 MHz in $CDCl_3$



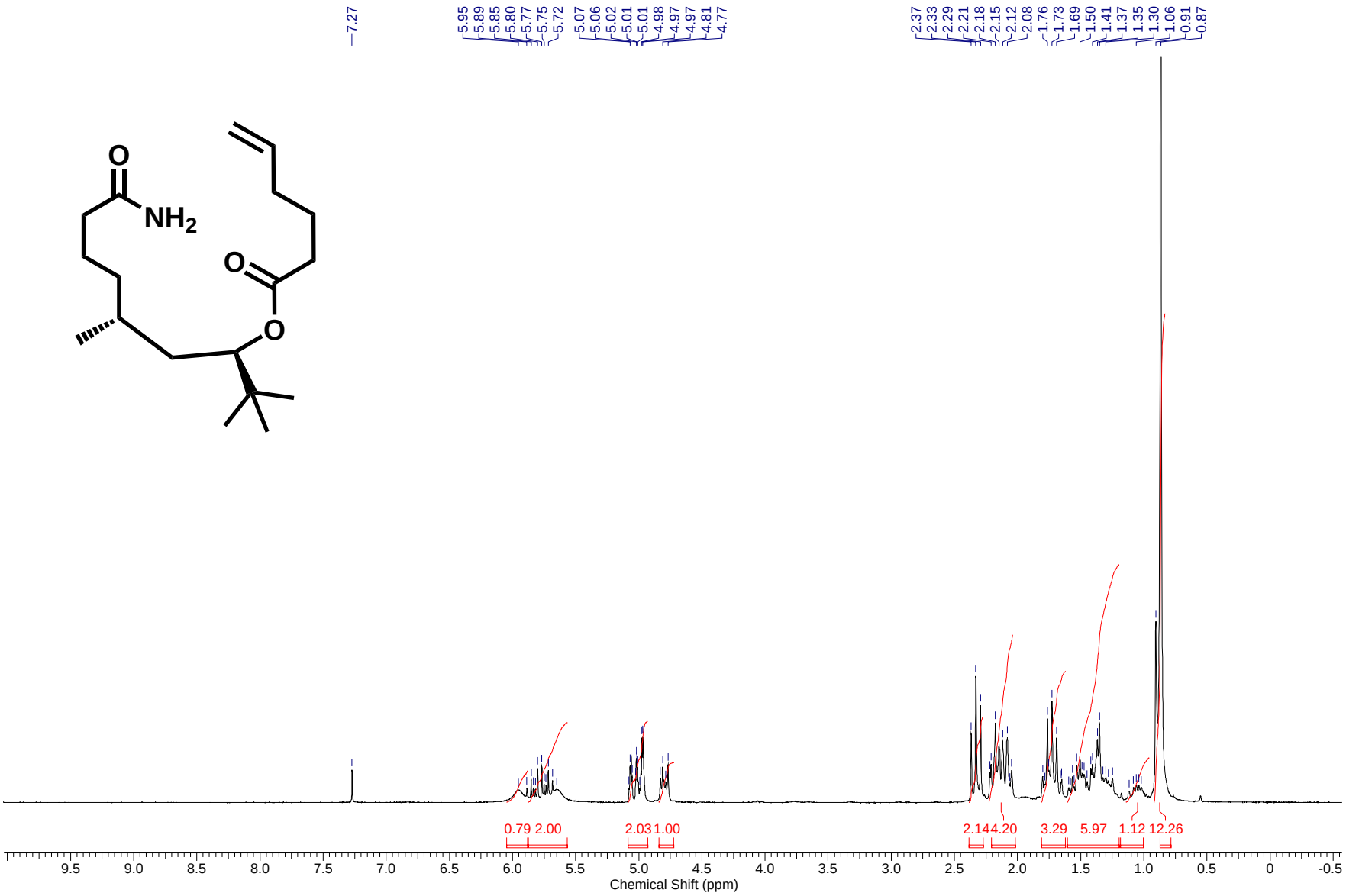
^{1}H NMR of Compound (-)-**4 a'** at 400 MHz in $CDCl_3$



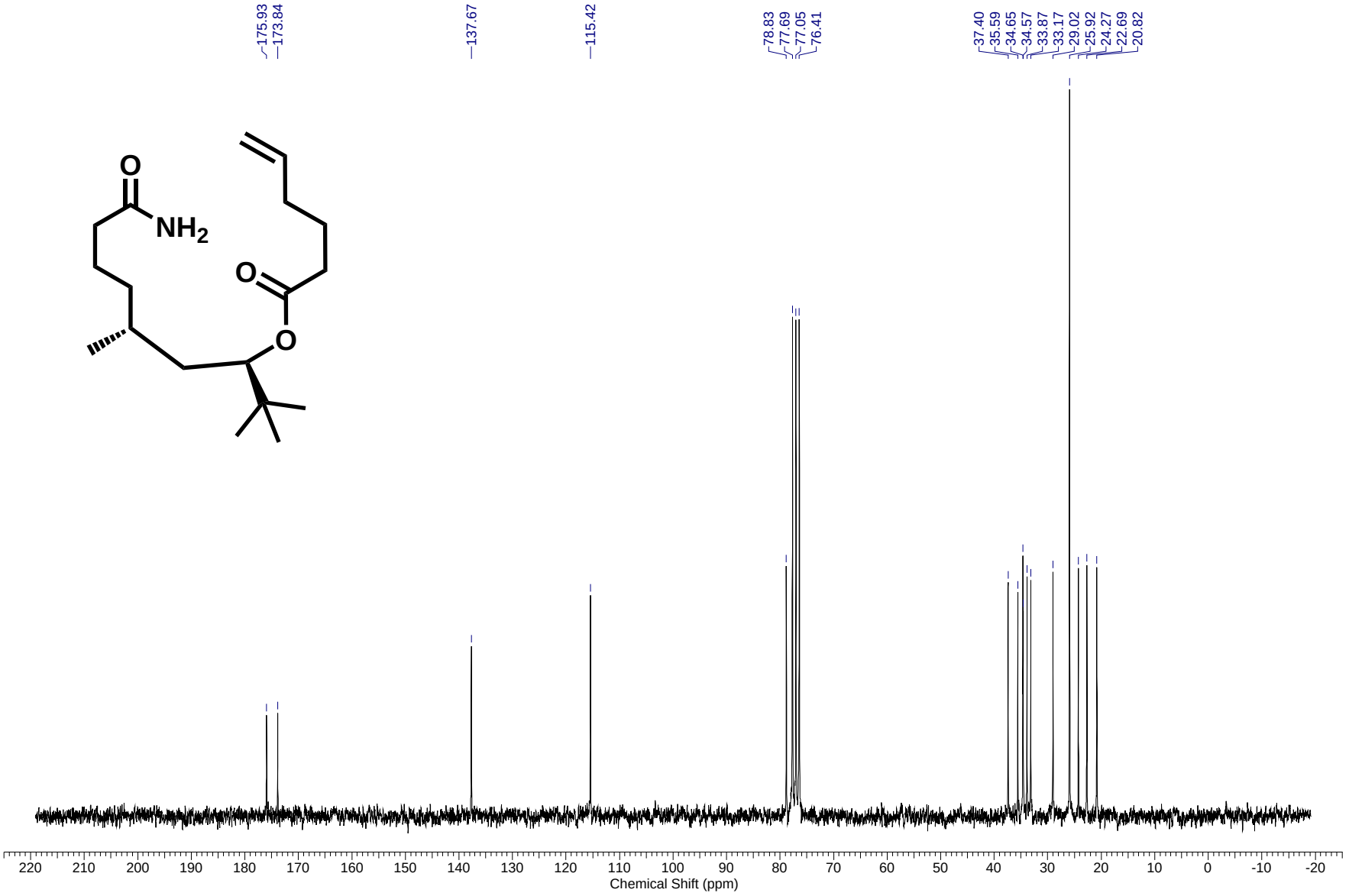
^{13}C NMR of Compound (-)-**4 a'** at 100 MHz in $CDCl_3$



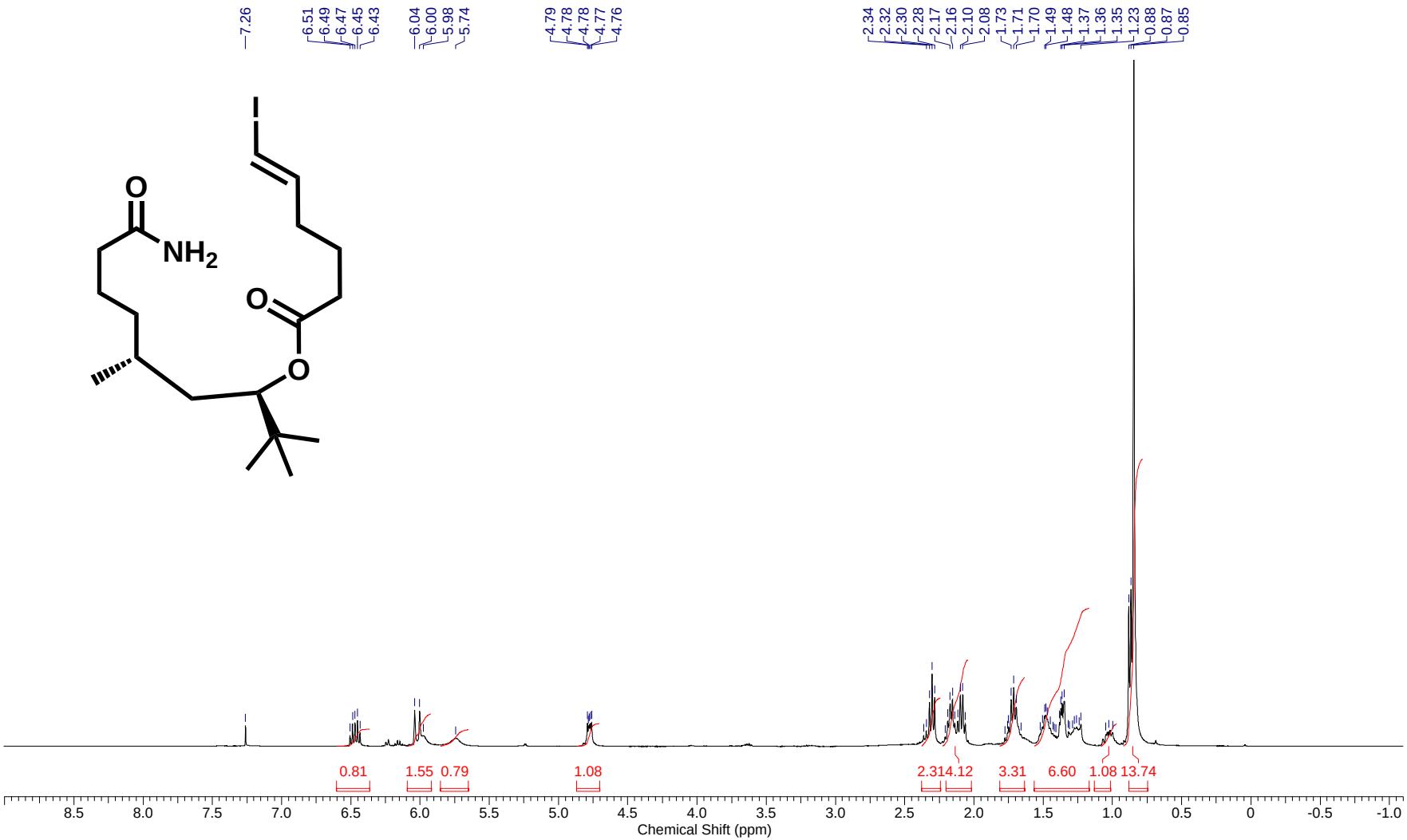
^{1}H NMR of Compound **10** at 200 MHz in $CDCl_3$



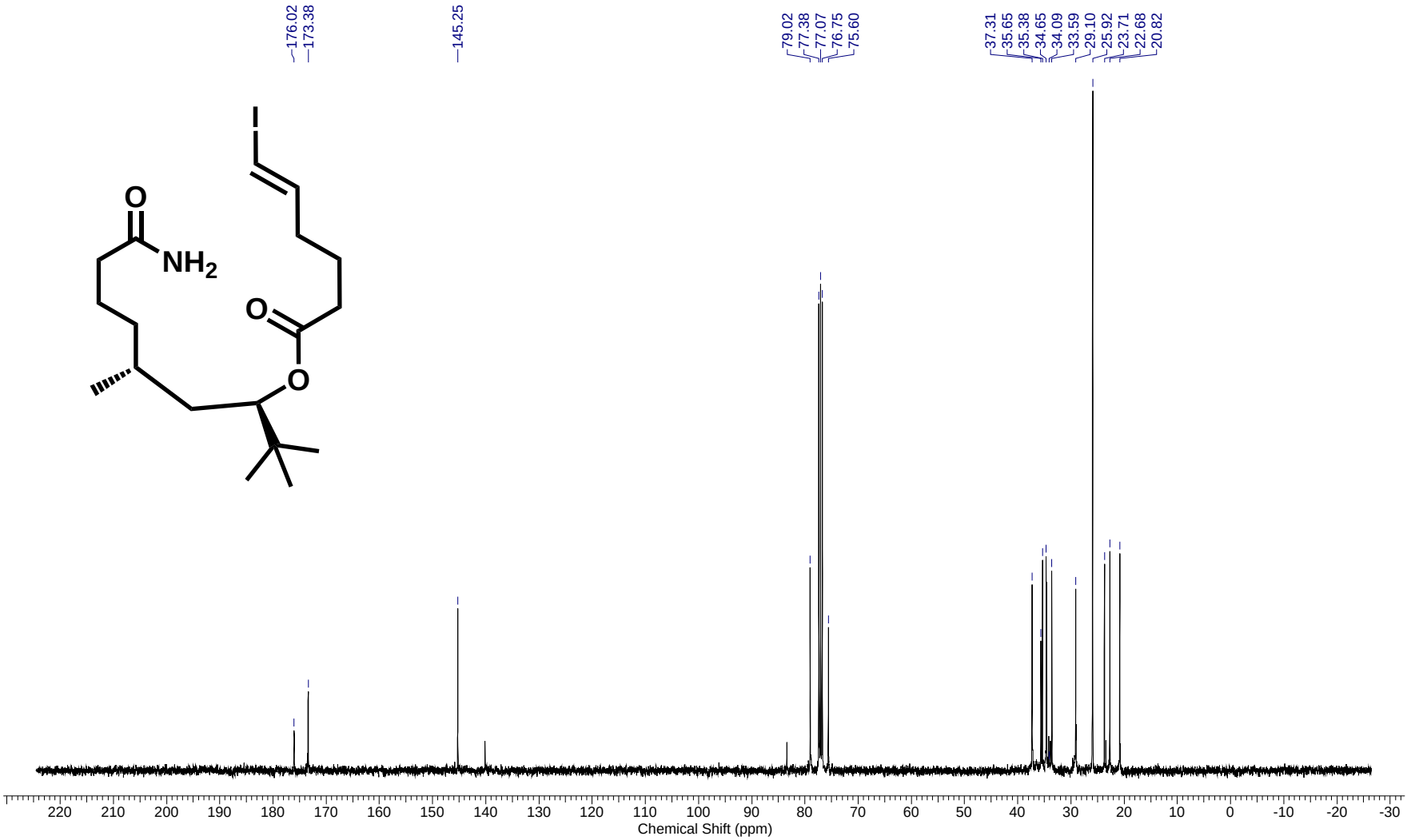
^{13}C NMR of Compound **10** at 50 MHz in $CDCl_3$



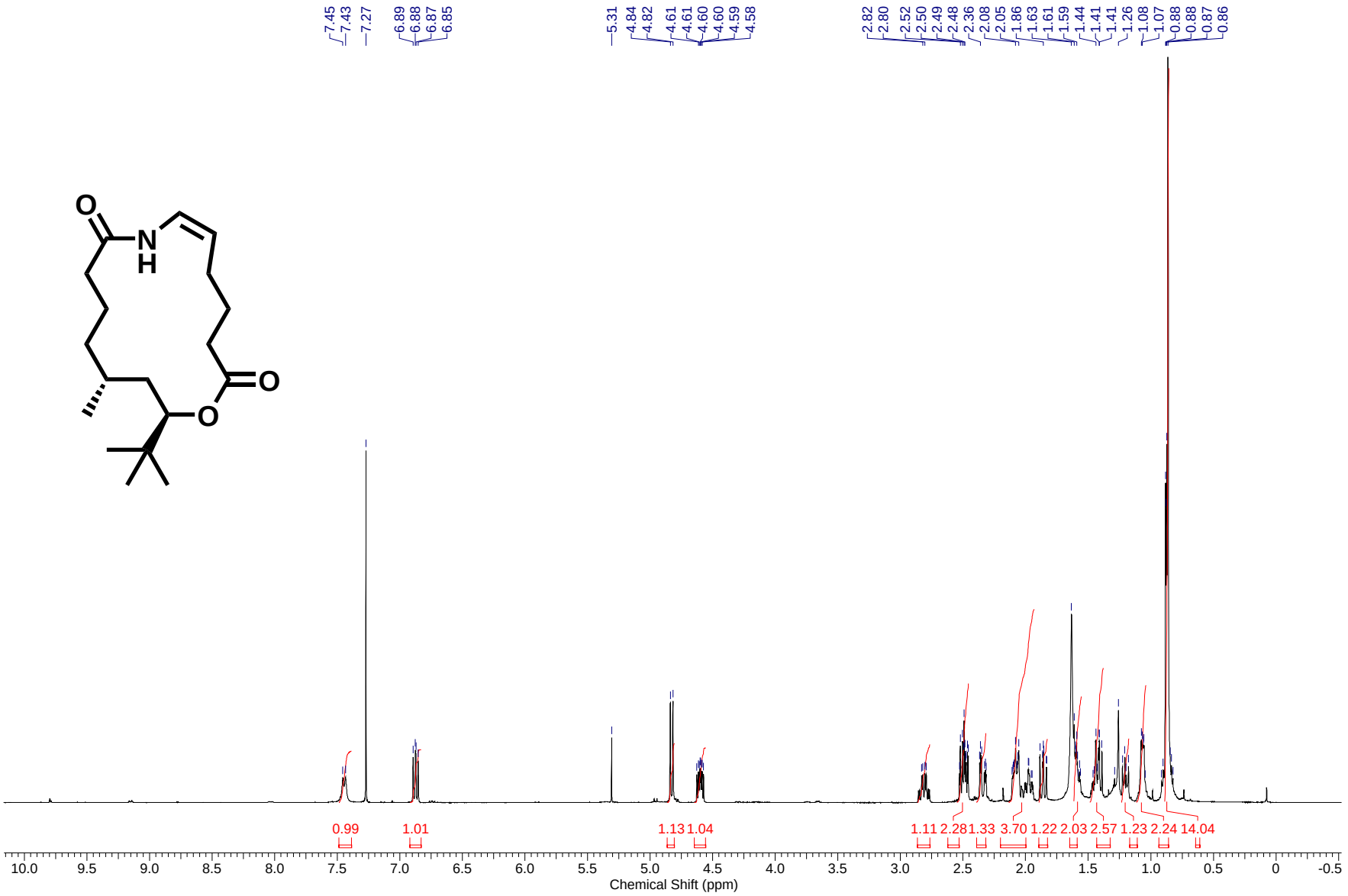
^{1}H NMR of Compound **11** at 400 MHz in $CDCl_3$



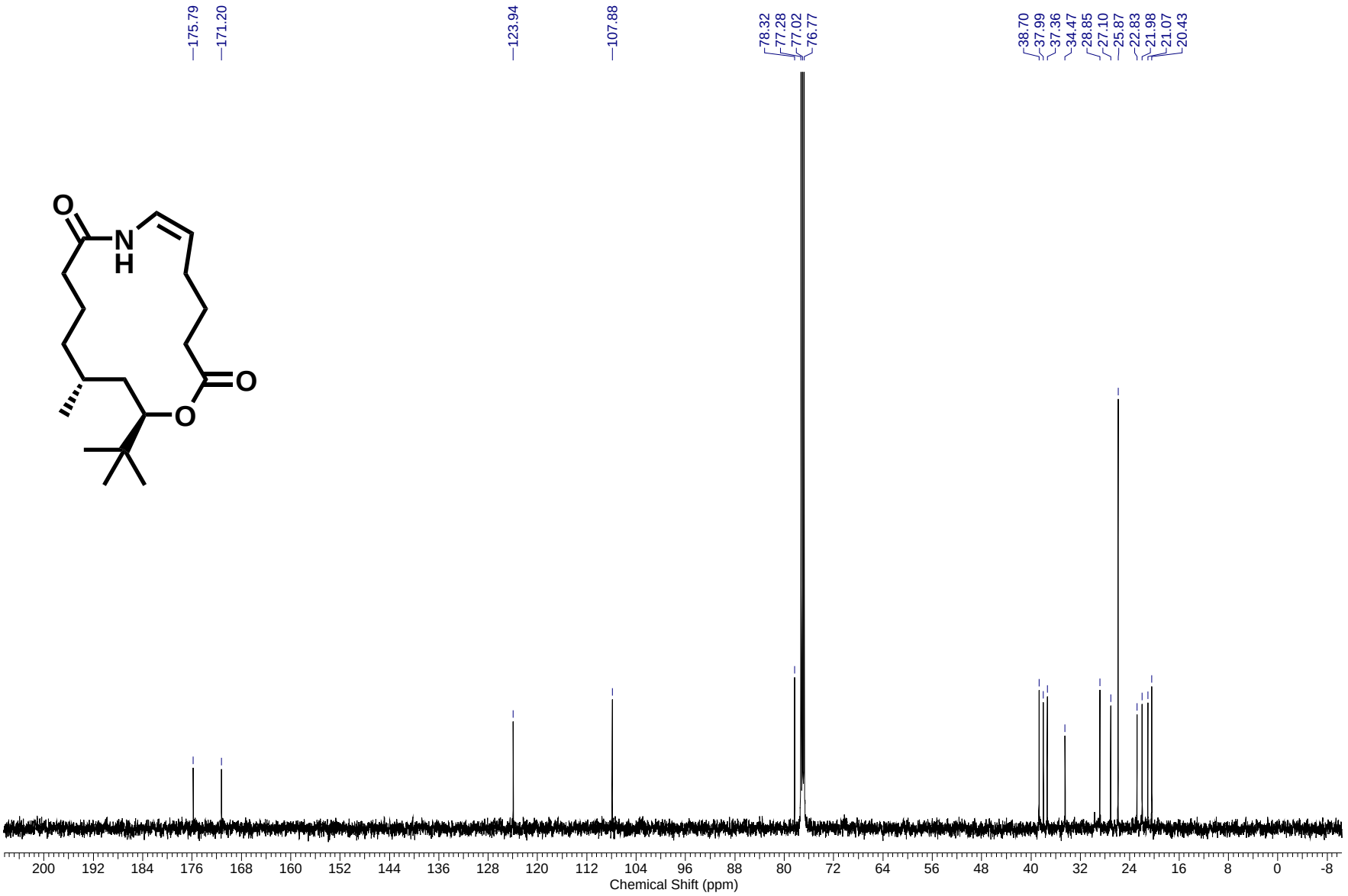
^{13}C NMR of Compound **11** at 100 MHz in $CDCl_3$



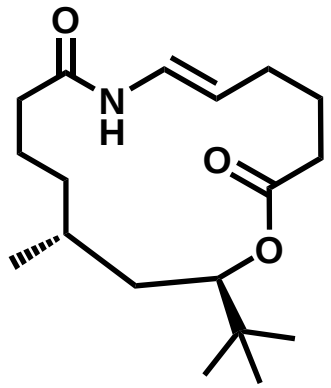
^{1}H NMR of Compound **12** at 500 MHz in $CDCl_3$



^{13}C NMR of Compound **12** at 125 MHz in $CDCl_3$

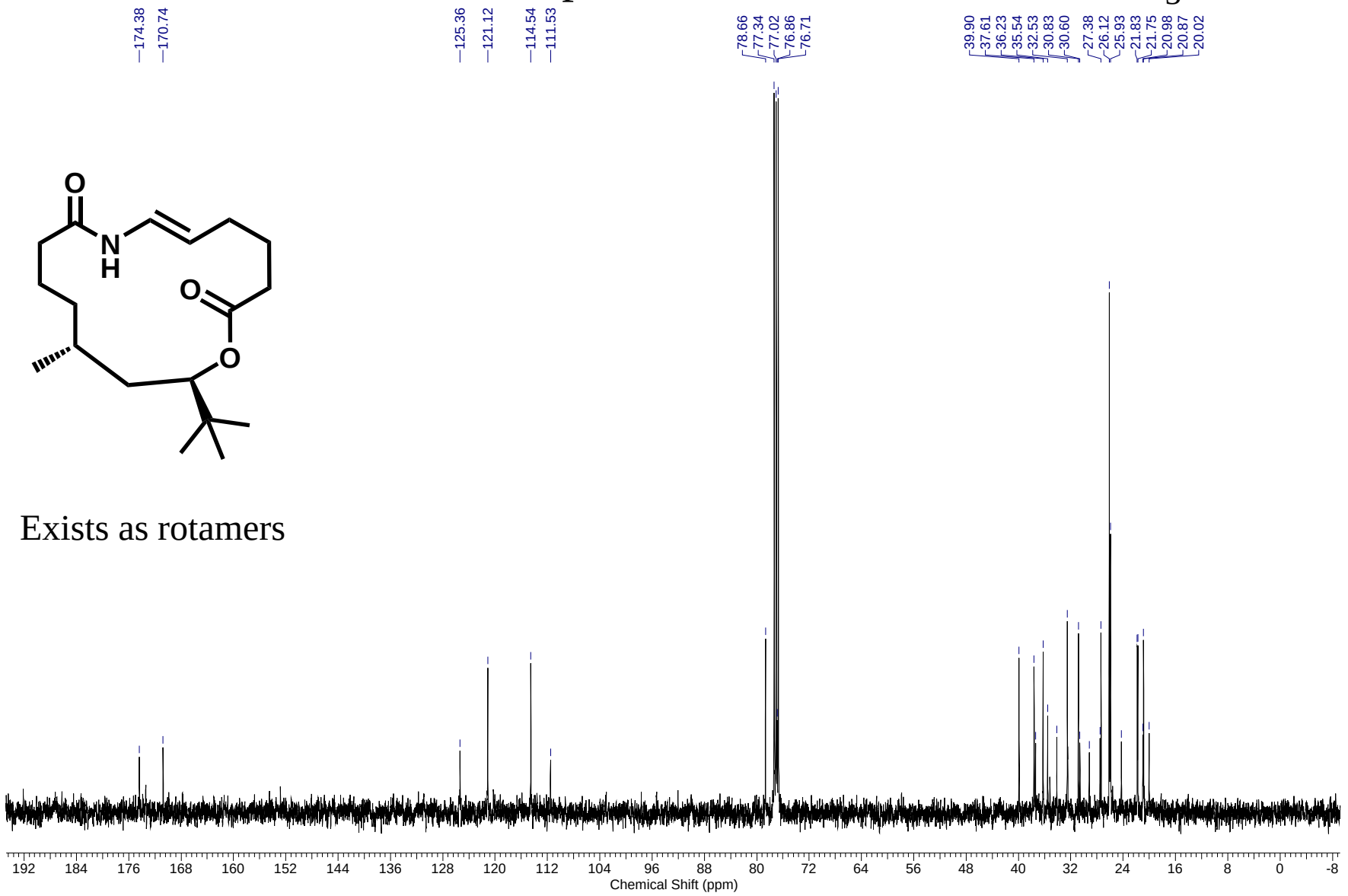


^{1}H NMR of Compound **13** at 400 MHz in $CDCl_3$



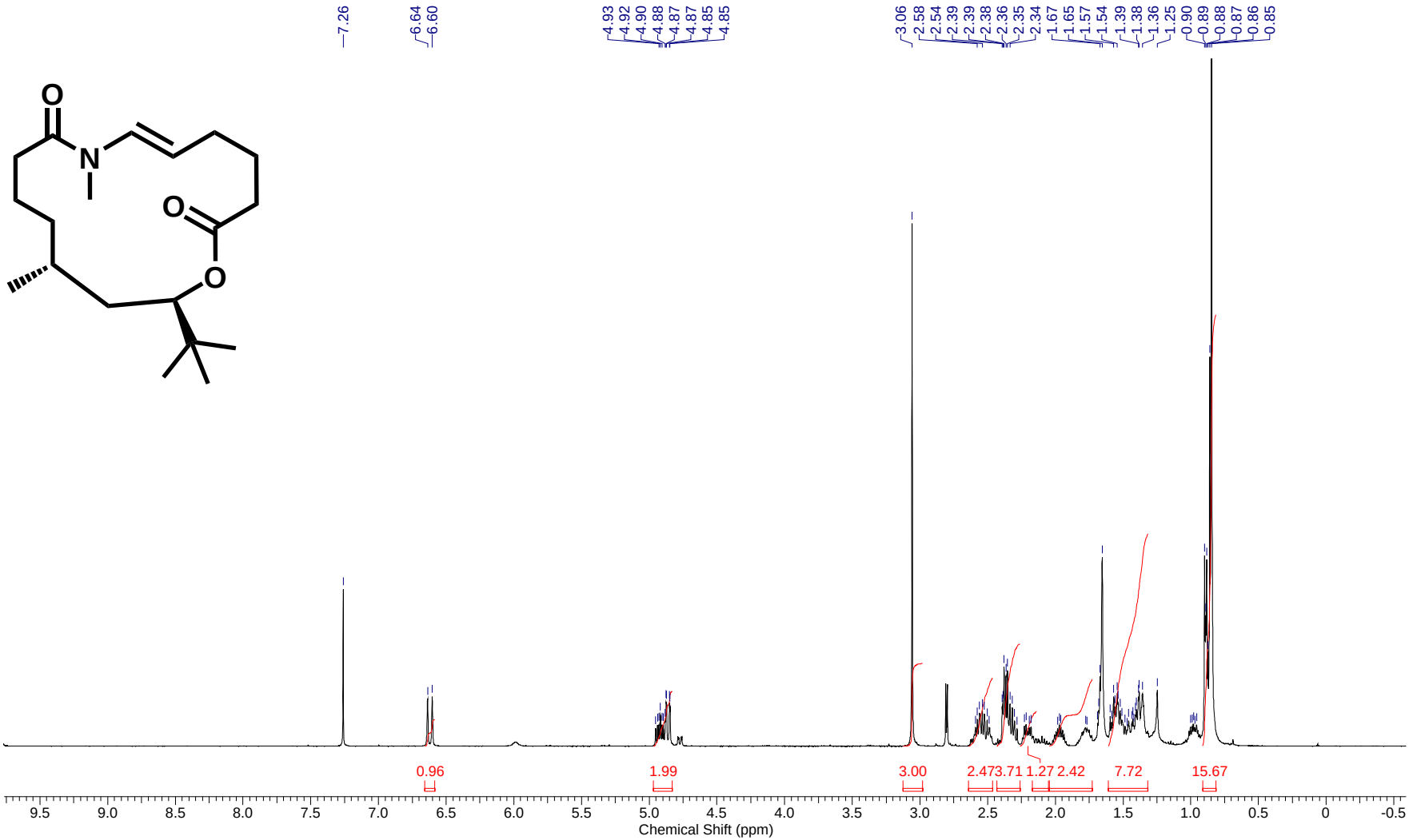
Exist as rotamers

^{13}C NMR of Compound **13** at 100 MHz in $CDCl_3$

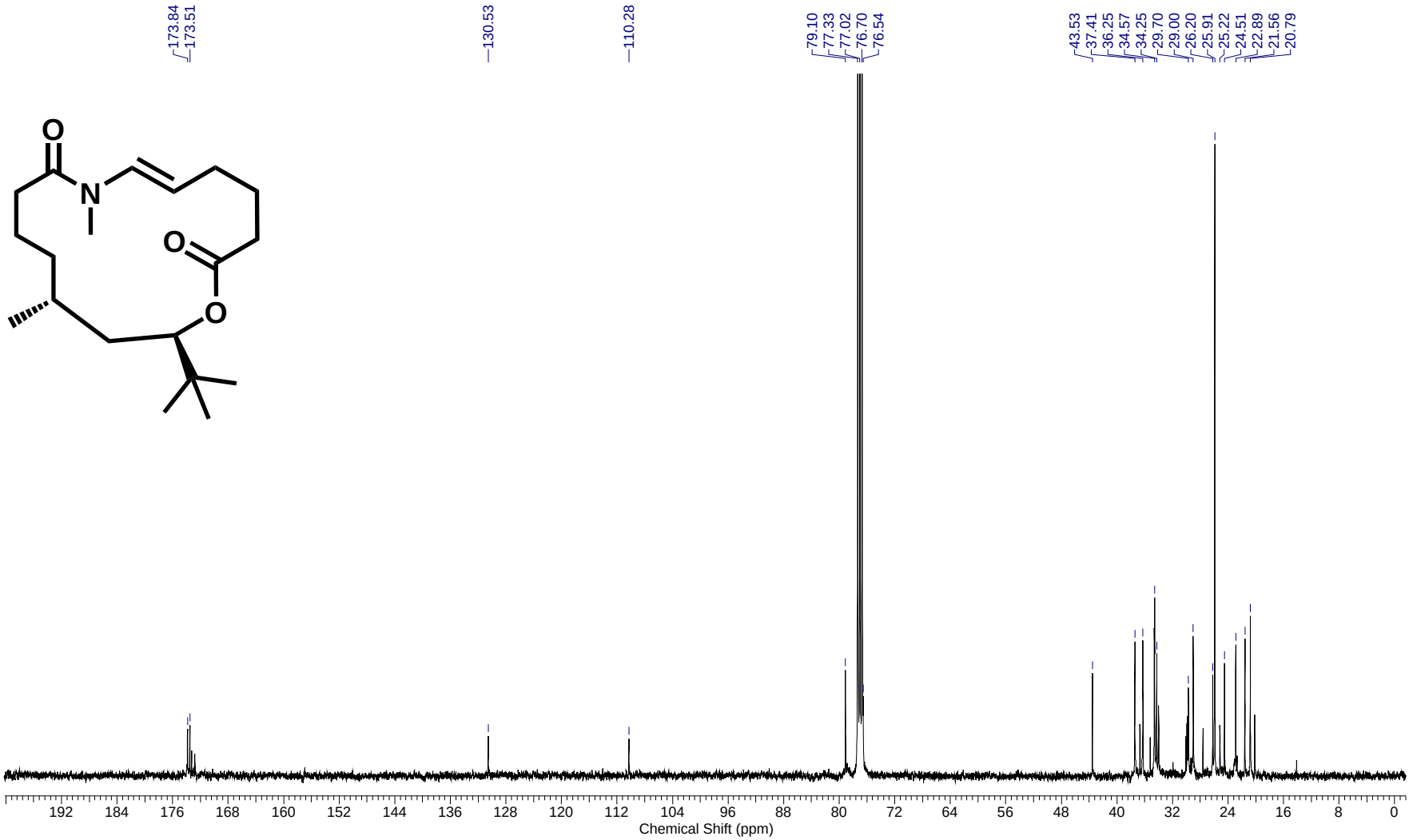


Exists as rotamers

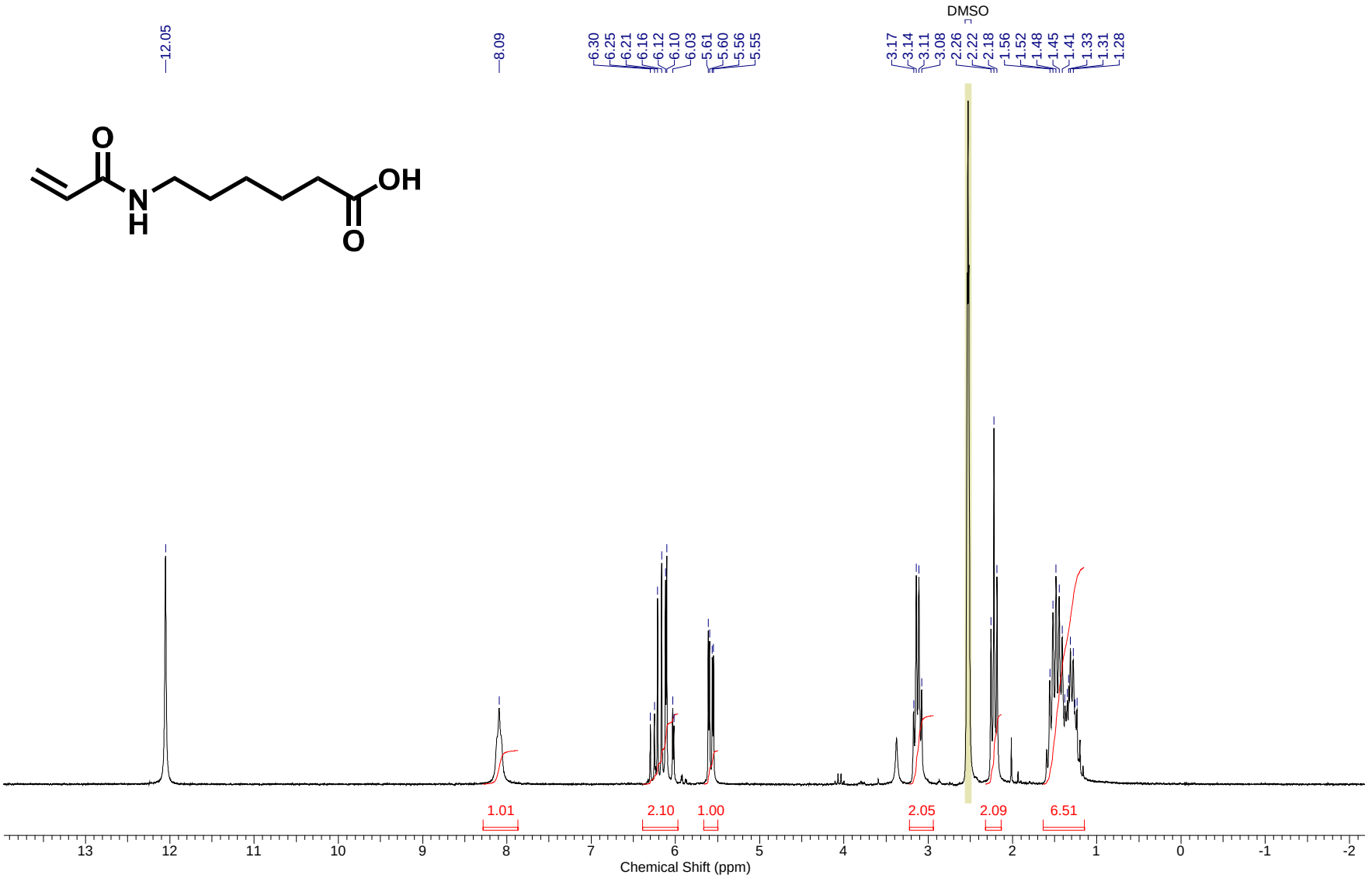
^{1}H NMR of Compound **14** at 400 MHz in $CDCl_3$



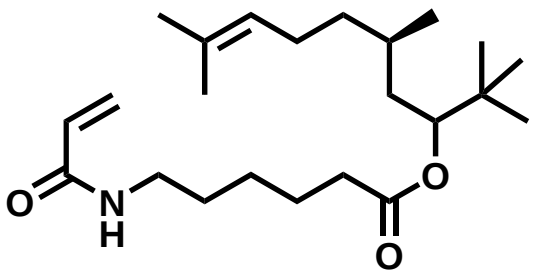
^{13}C NMR of Compound **14** at 100 MHz in $CDCl_3$



^{1}H NMR of Compound **16** at 200 MHz in DMSO-d6

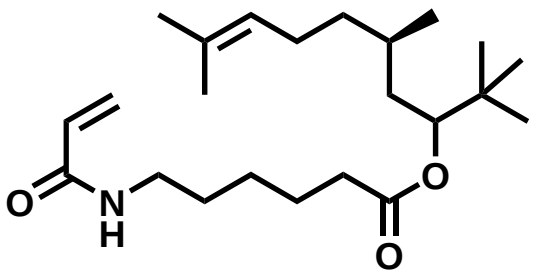


^{1}H NMR of Compound **17** at 200 MHz in $CDCl_3$



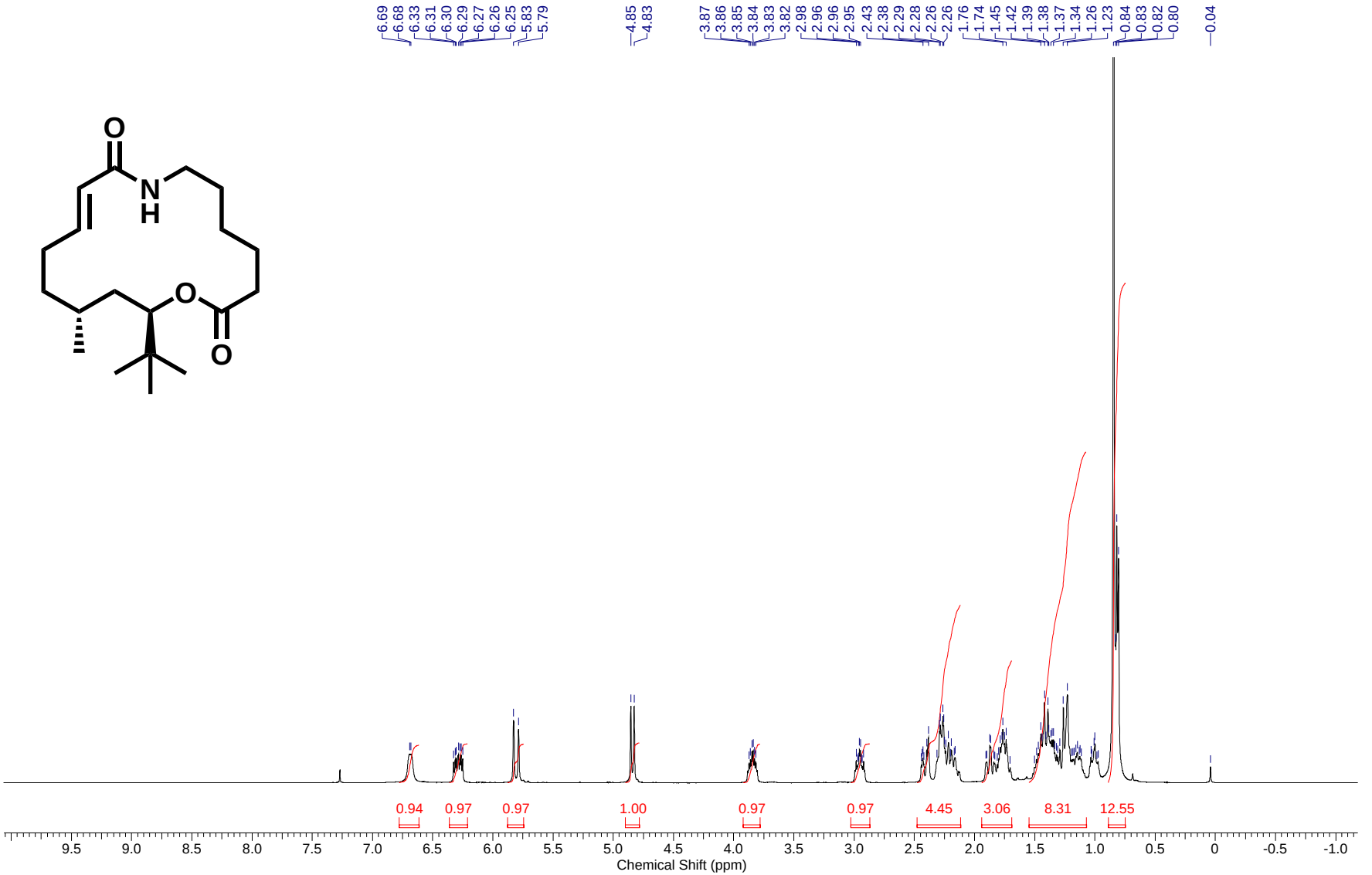
Diastereomeric mixture

^{13}C NMR of Compound **17** at 50 MHz in $CDCl_3$

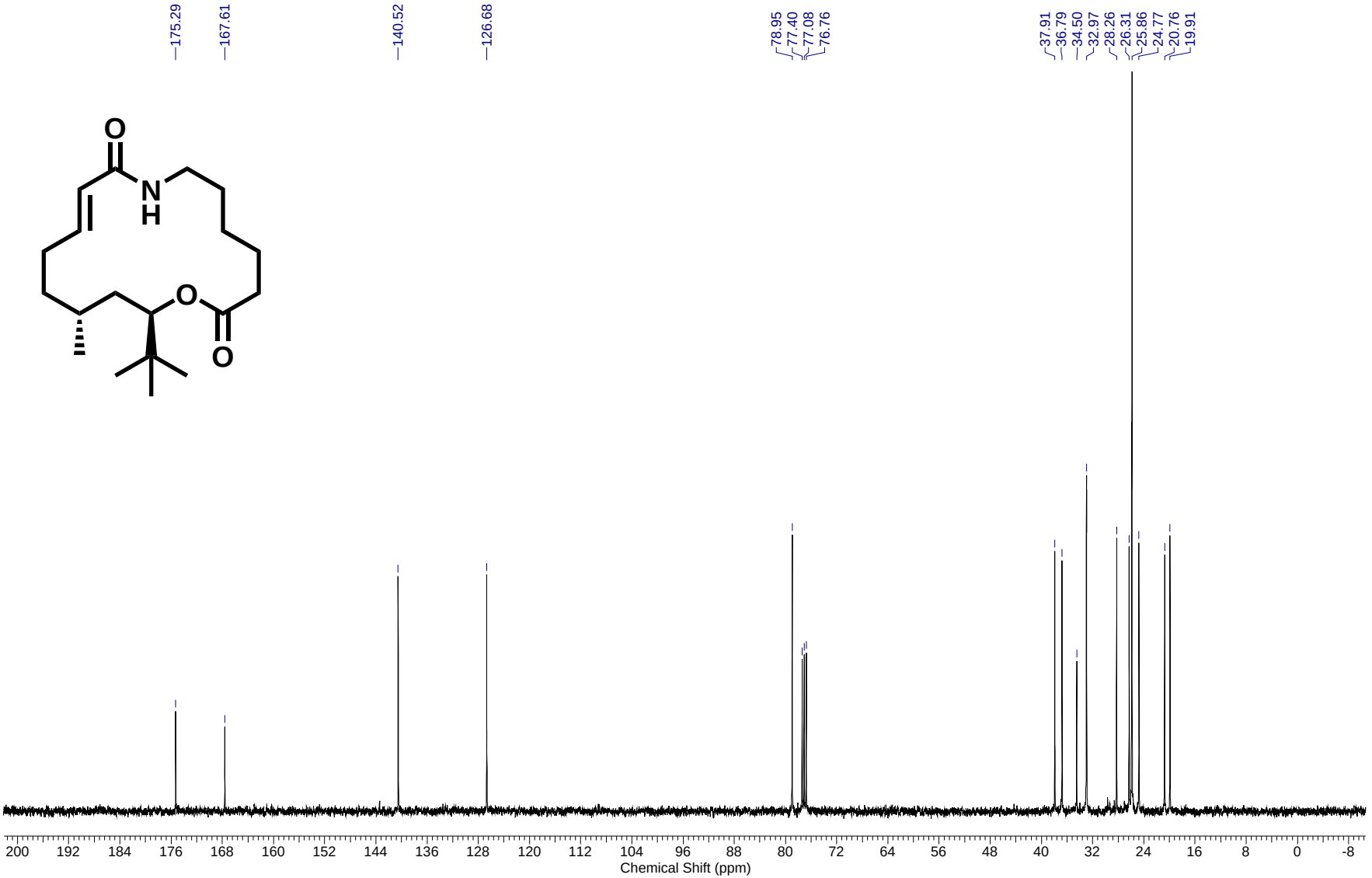


Diastereomeric mixture

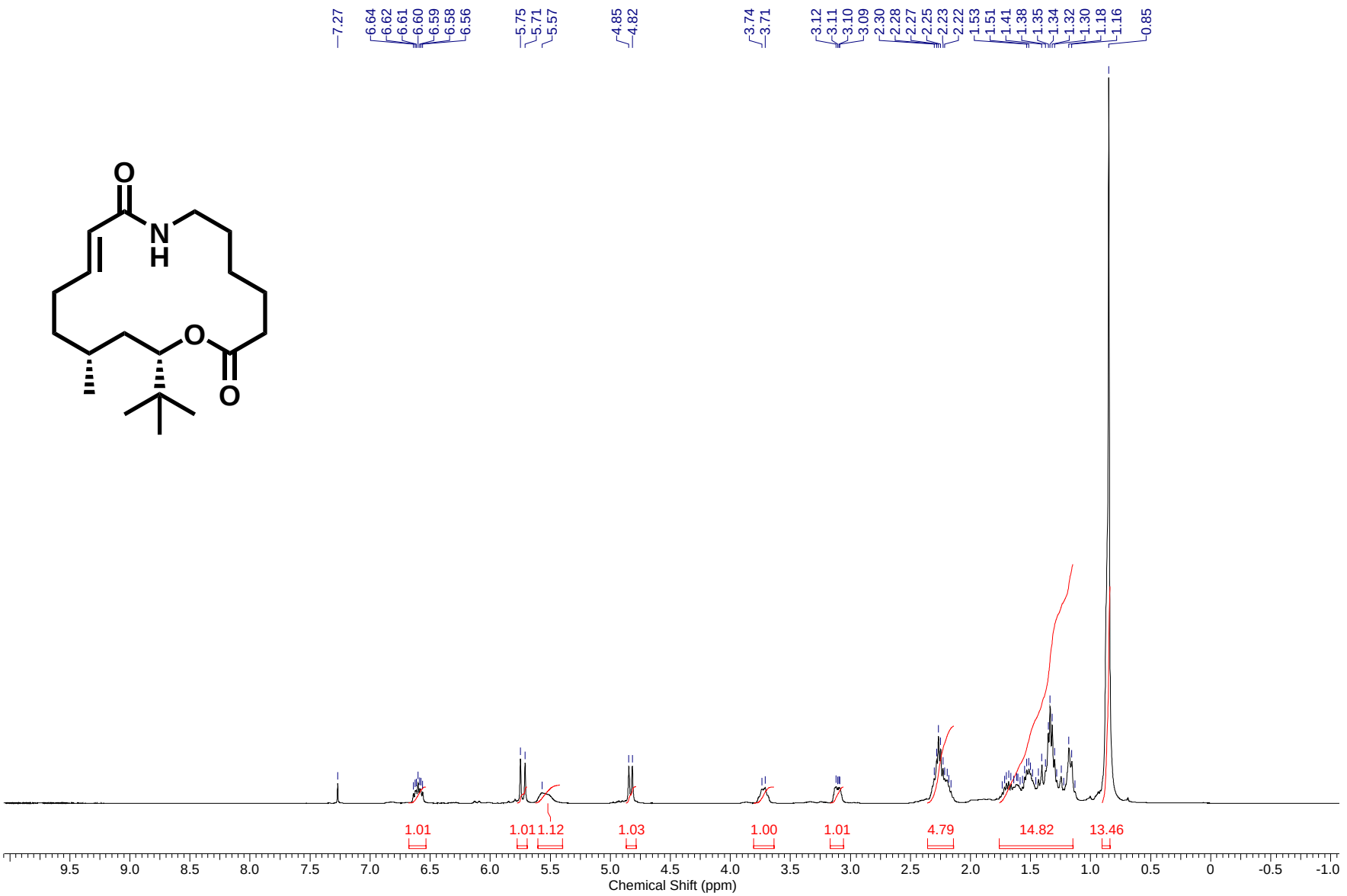
^{1}H NMR of Compound **18** at 400 MHz in $CDCl_3$



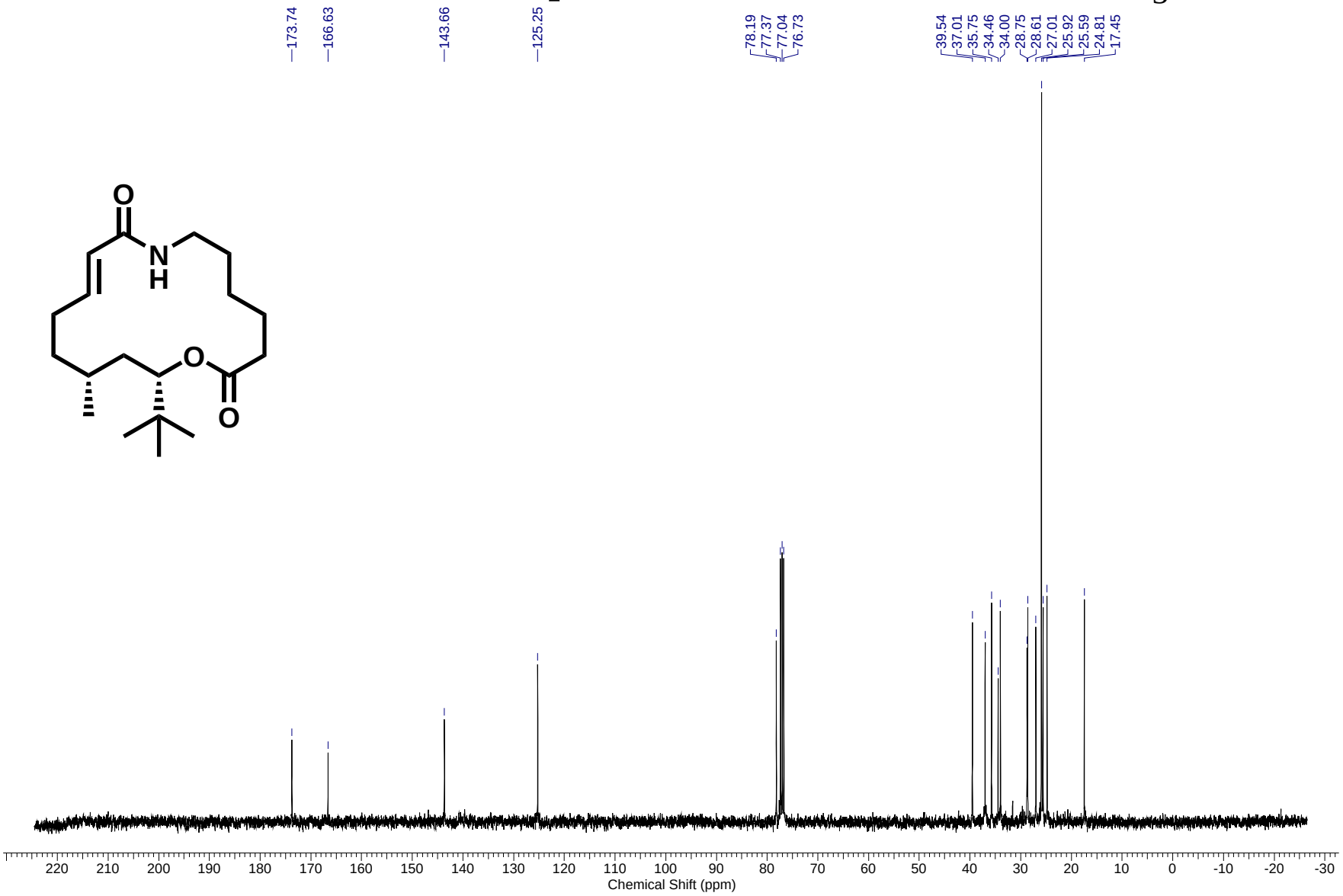
^{13}C NMR of Compound **18** at 100 MHz in $CDCl_3$



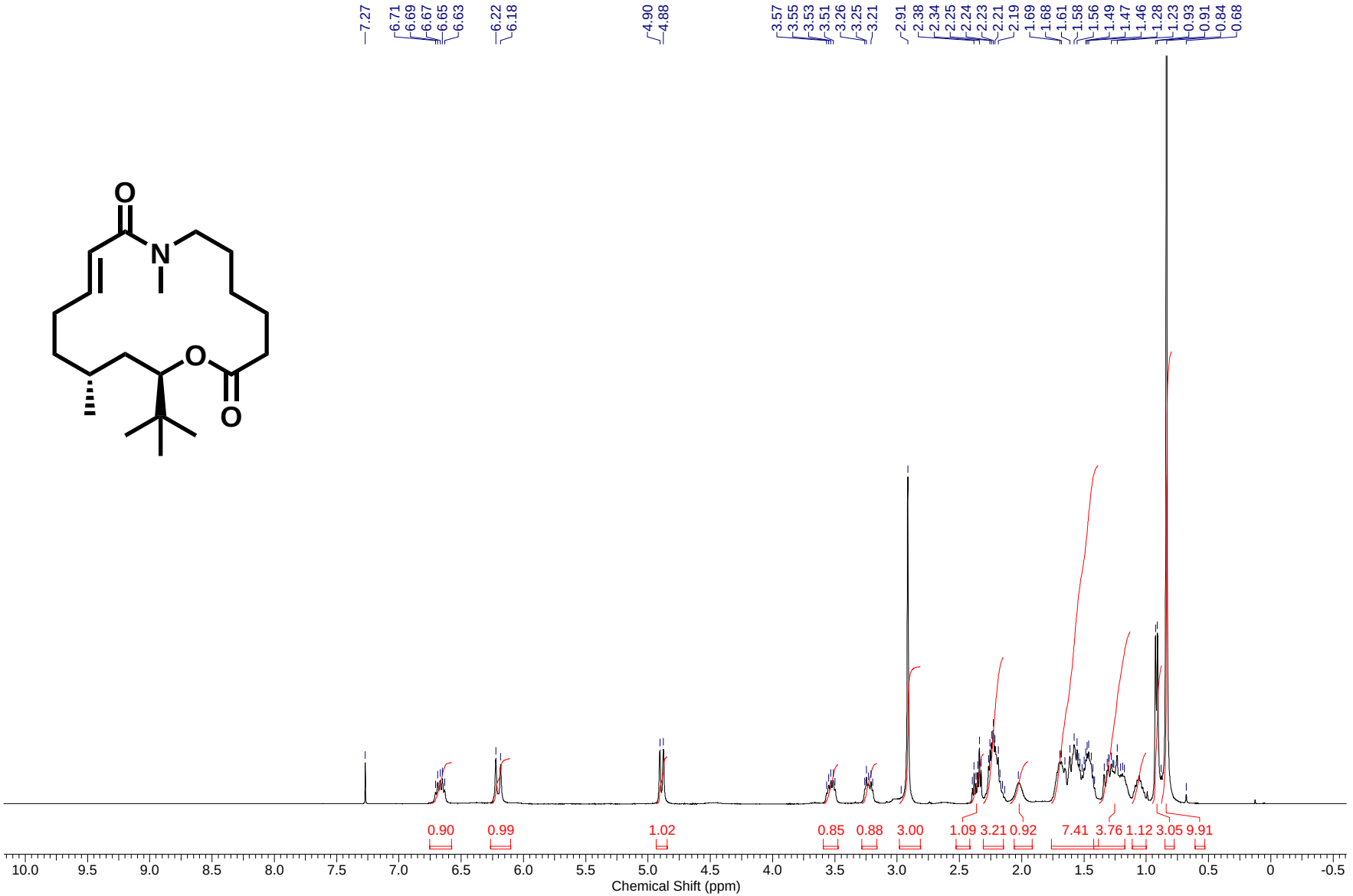
^{1}H NMR of Compound **19** at 400 MHz in $CDCl_3$



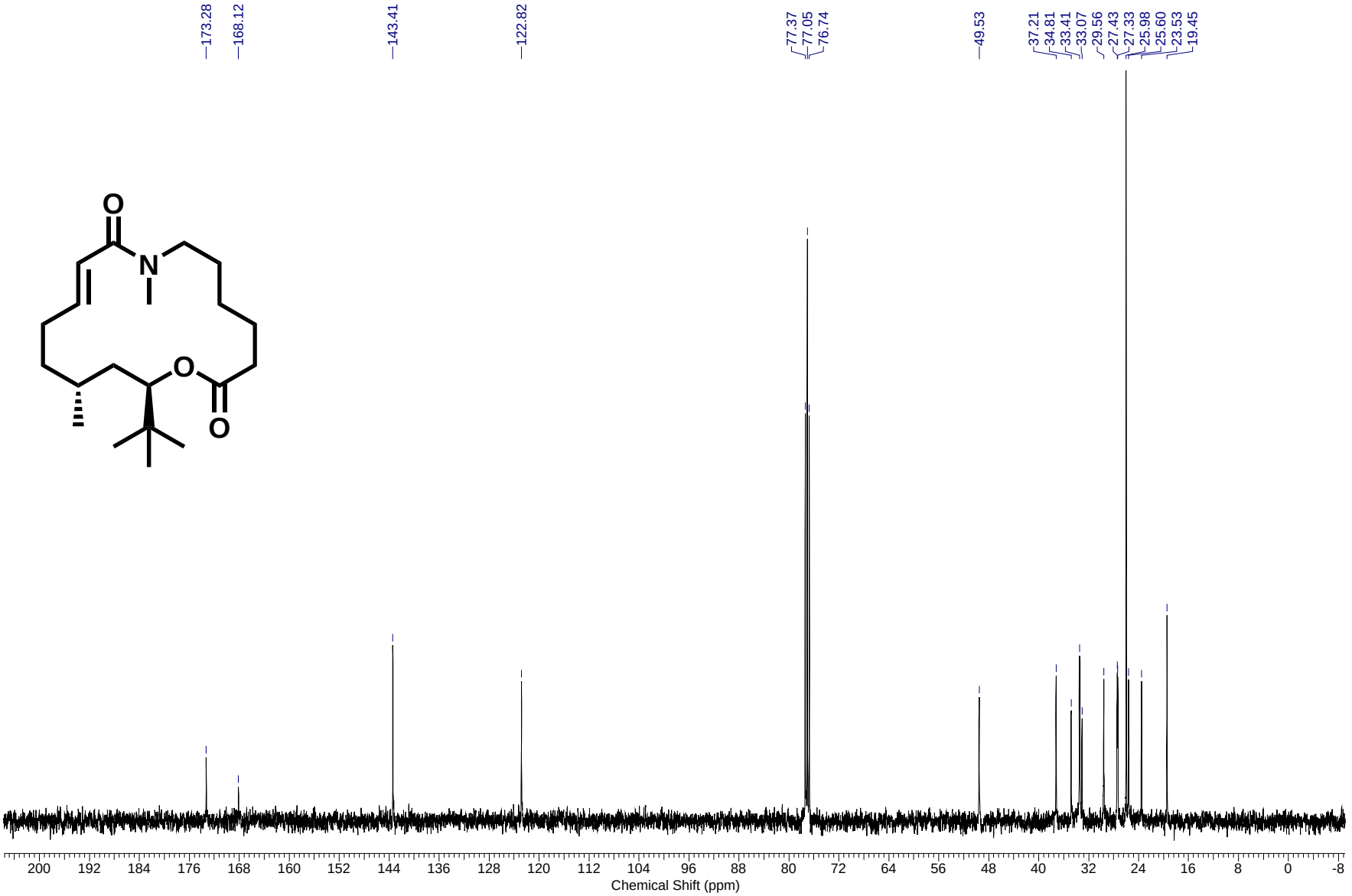
^{13}C NMR of Compound **19** at 100 MHz in $CDCl_3$



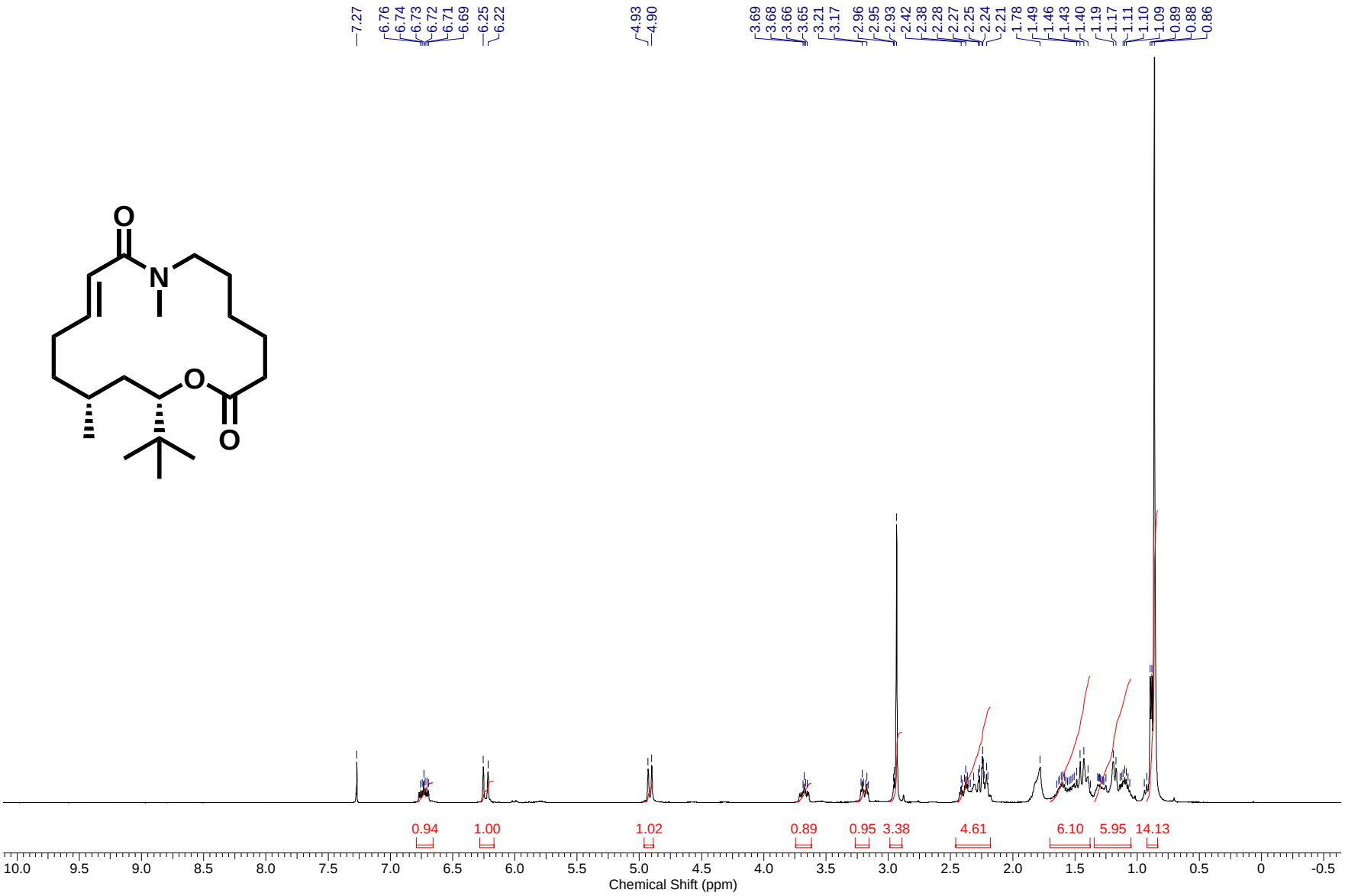
^{1}H NMR of Compound **20** at 400 MHz in $CDCl_3$



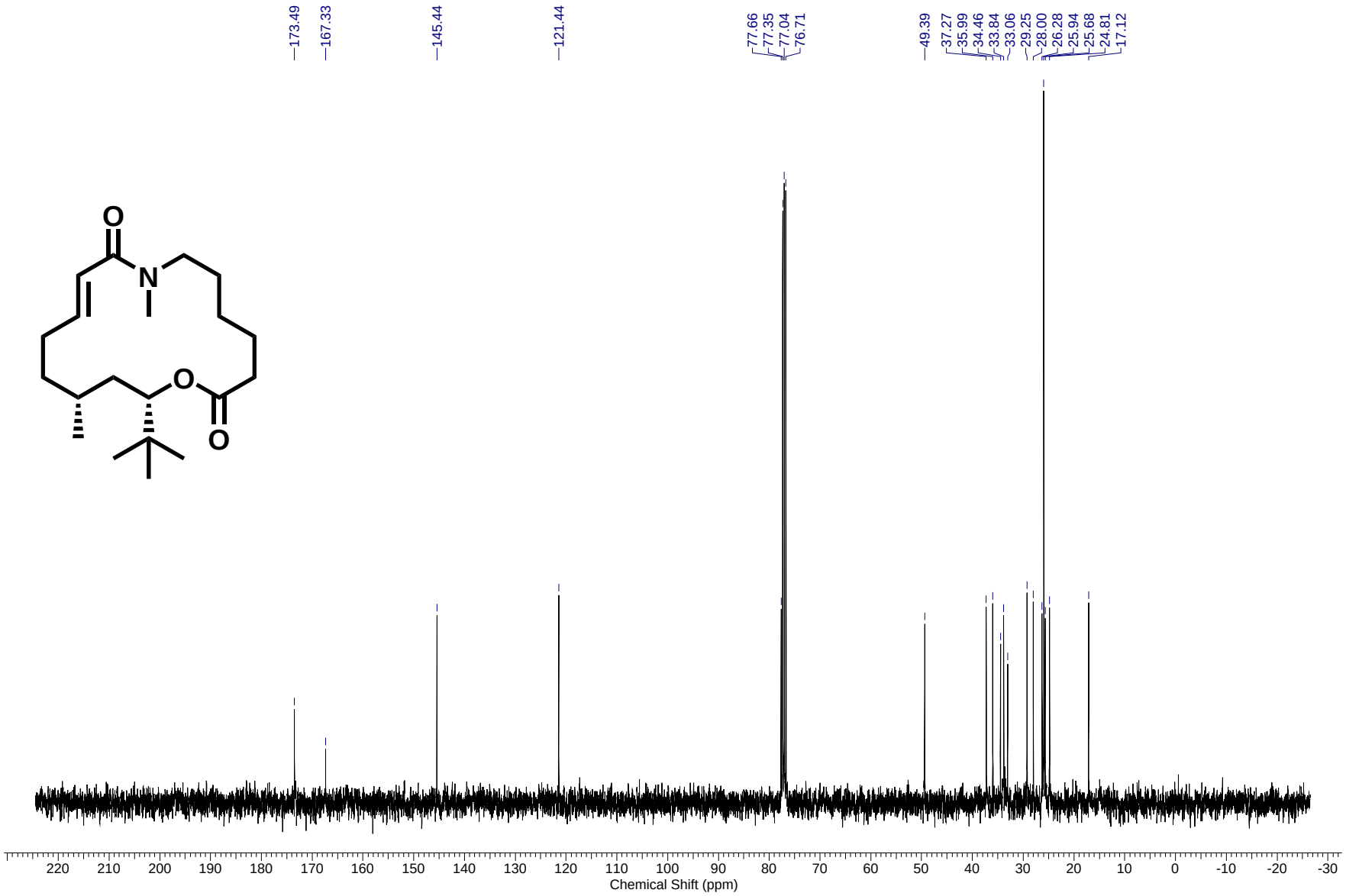
^{13}C NMR of Compound **20** at 100 MHz in $CDCl_3$



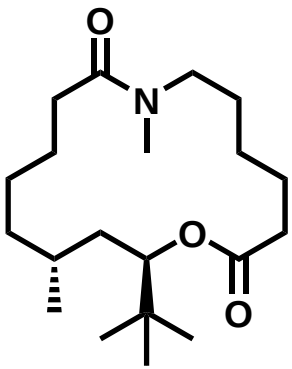
^{1}H NMR of Compound **21** at 400 MHz in $CDCl_3$



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

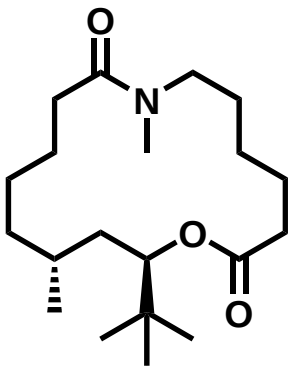


^{1}H NMR of Compound **22** at 400 MHz in $CDCl_3$



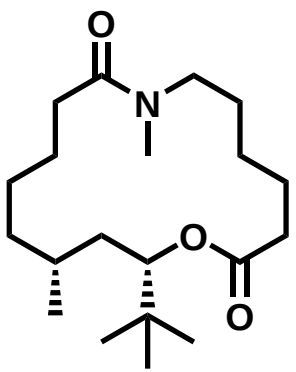
Exists as rotamers

^{13}C NMR of Compound **22** at 100 MHz in $CDCl_3$



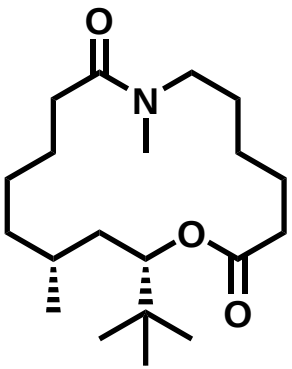
Exists as rotamers

^{1}H NMR of Compound **23** at 400 MHz in $CDCl_3$



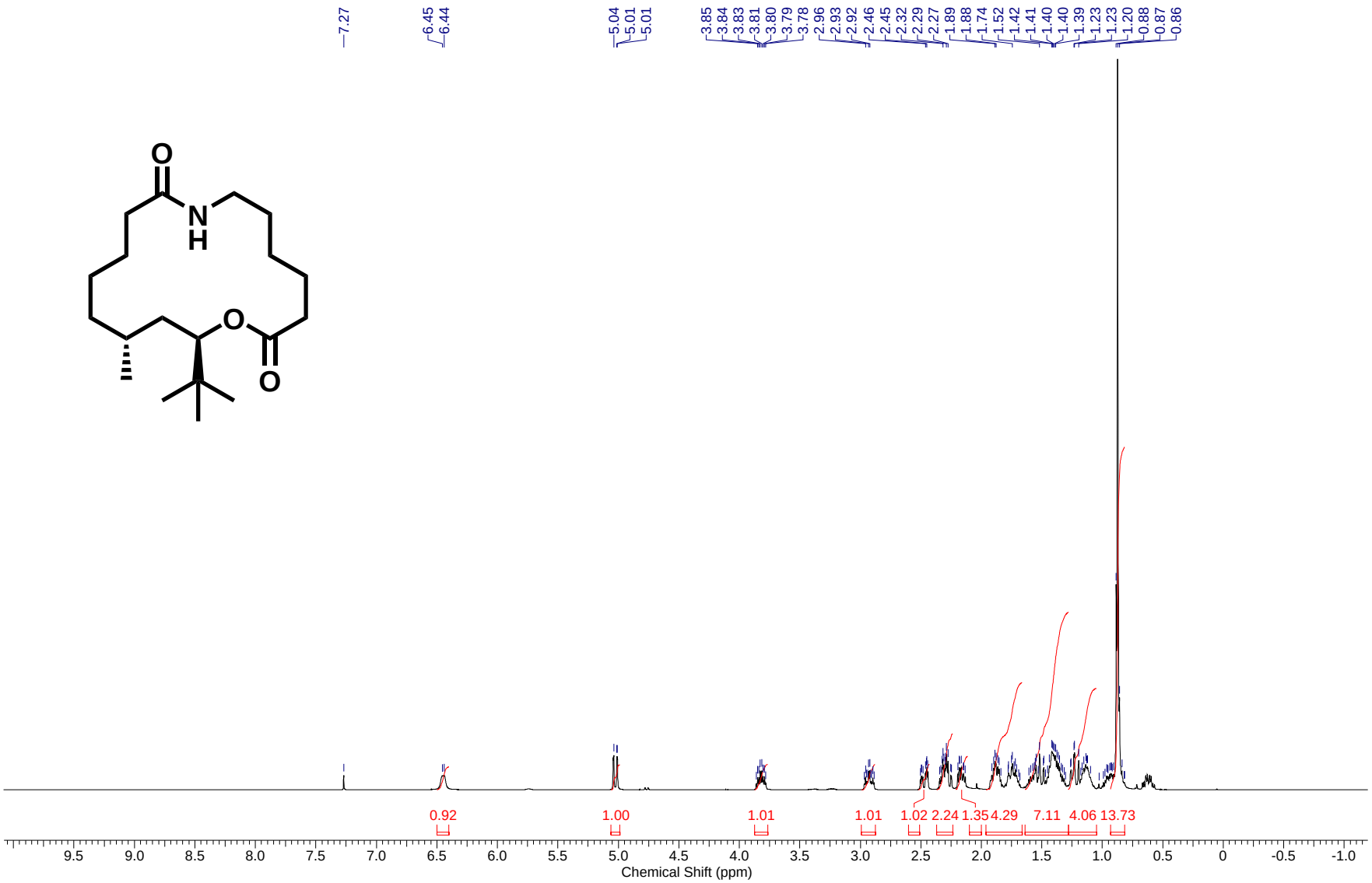
Exists as rotamers

^{13}C NMR of Compound **23** at 100 MHz in $CDCl_3$

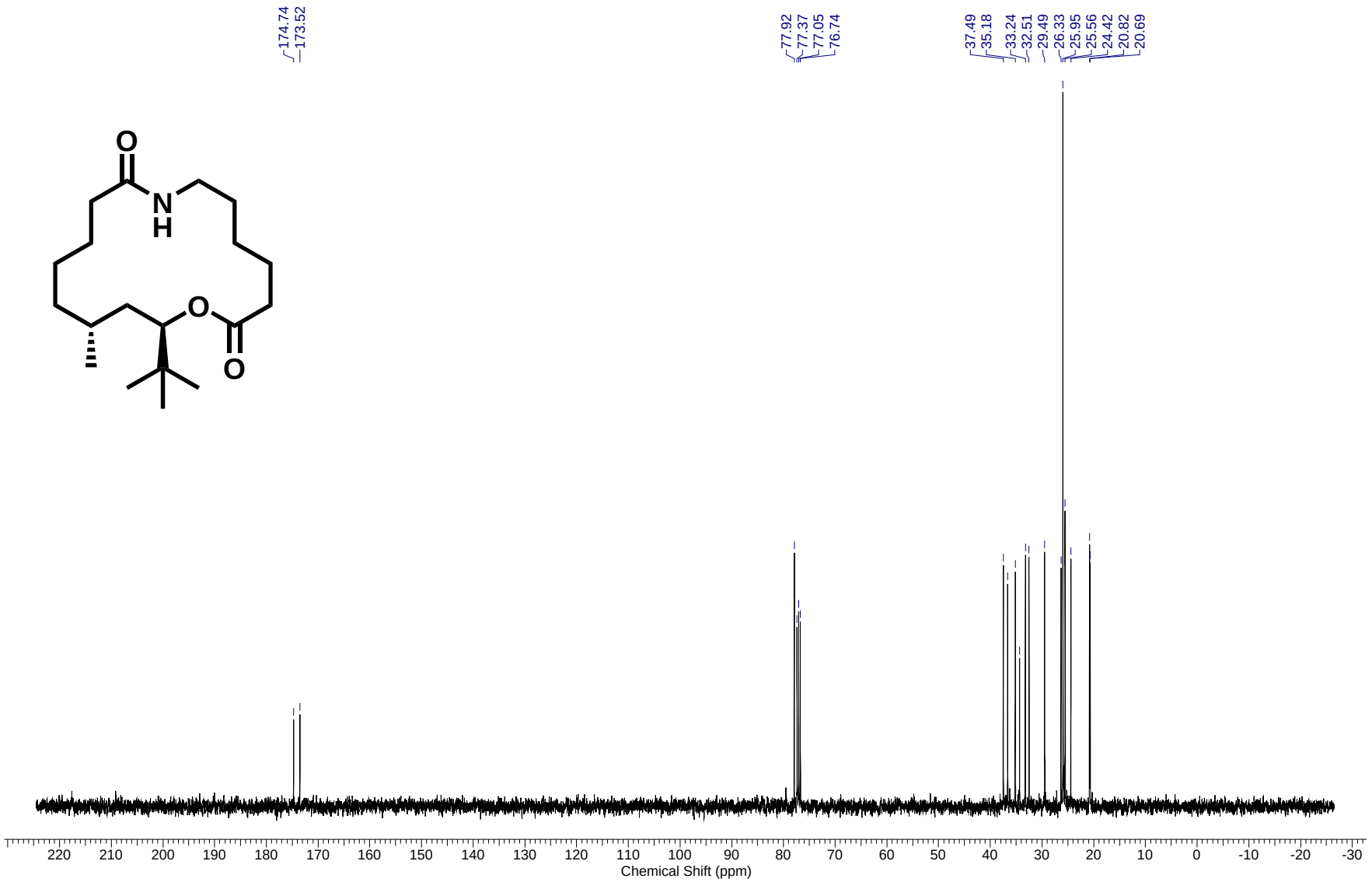


Exists as rotamers

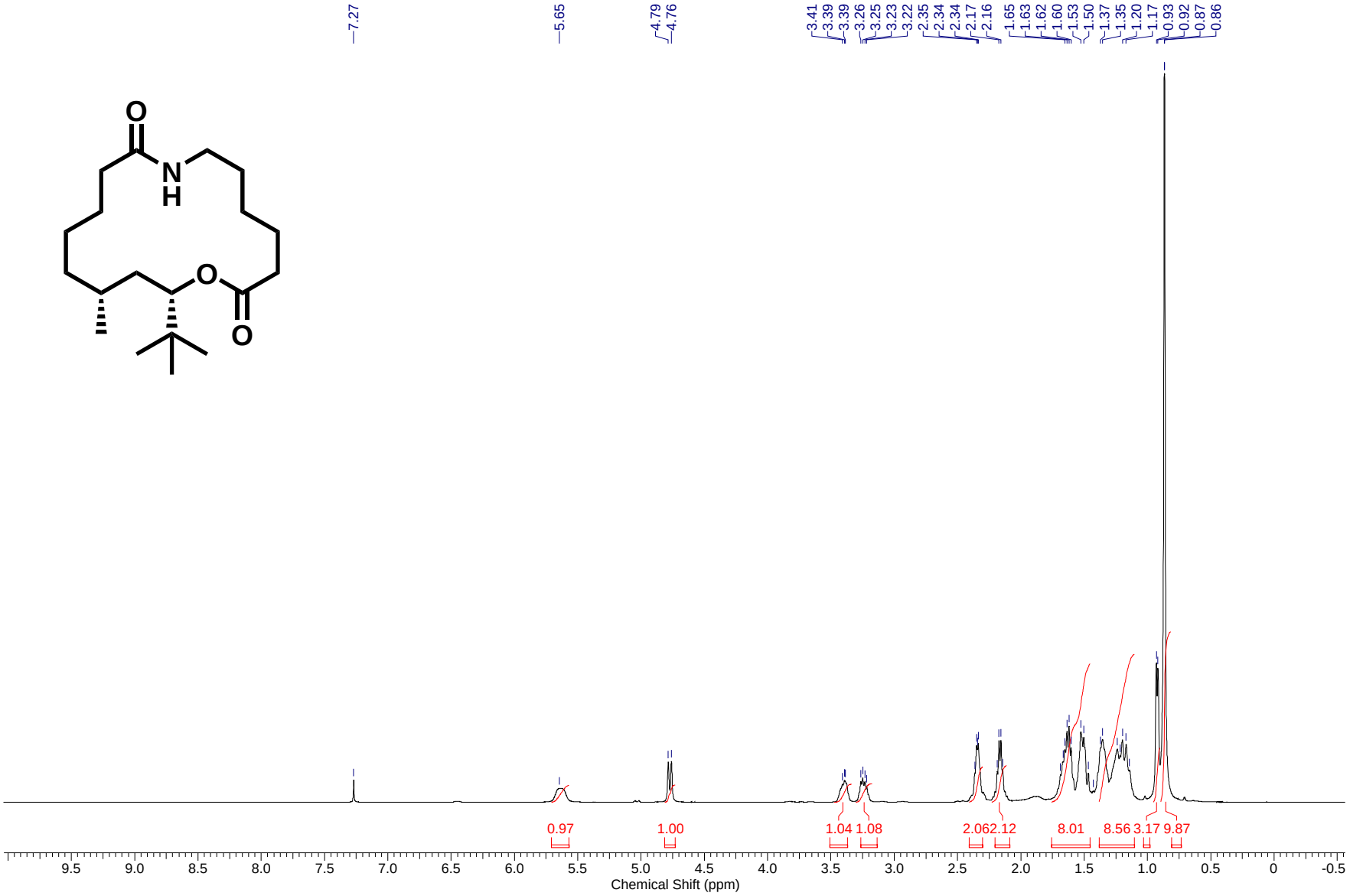
^{1}H NMR of Compound **24** at 400 MHz in $CDCl_3$



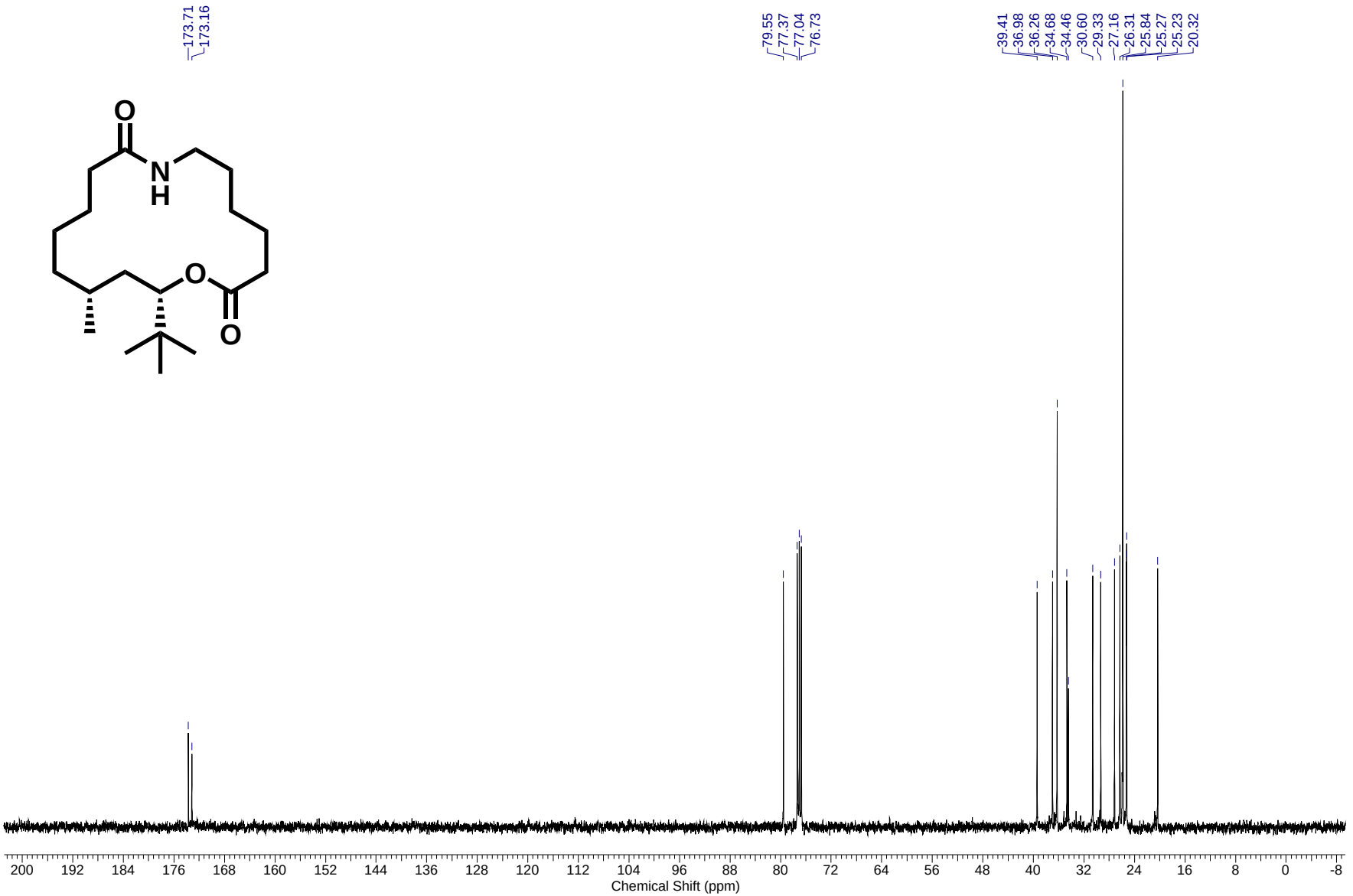
^{13}C NMR of Compound **24** at 100 MHz in $CDCl_3$



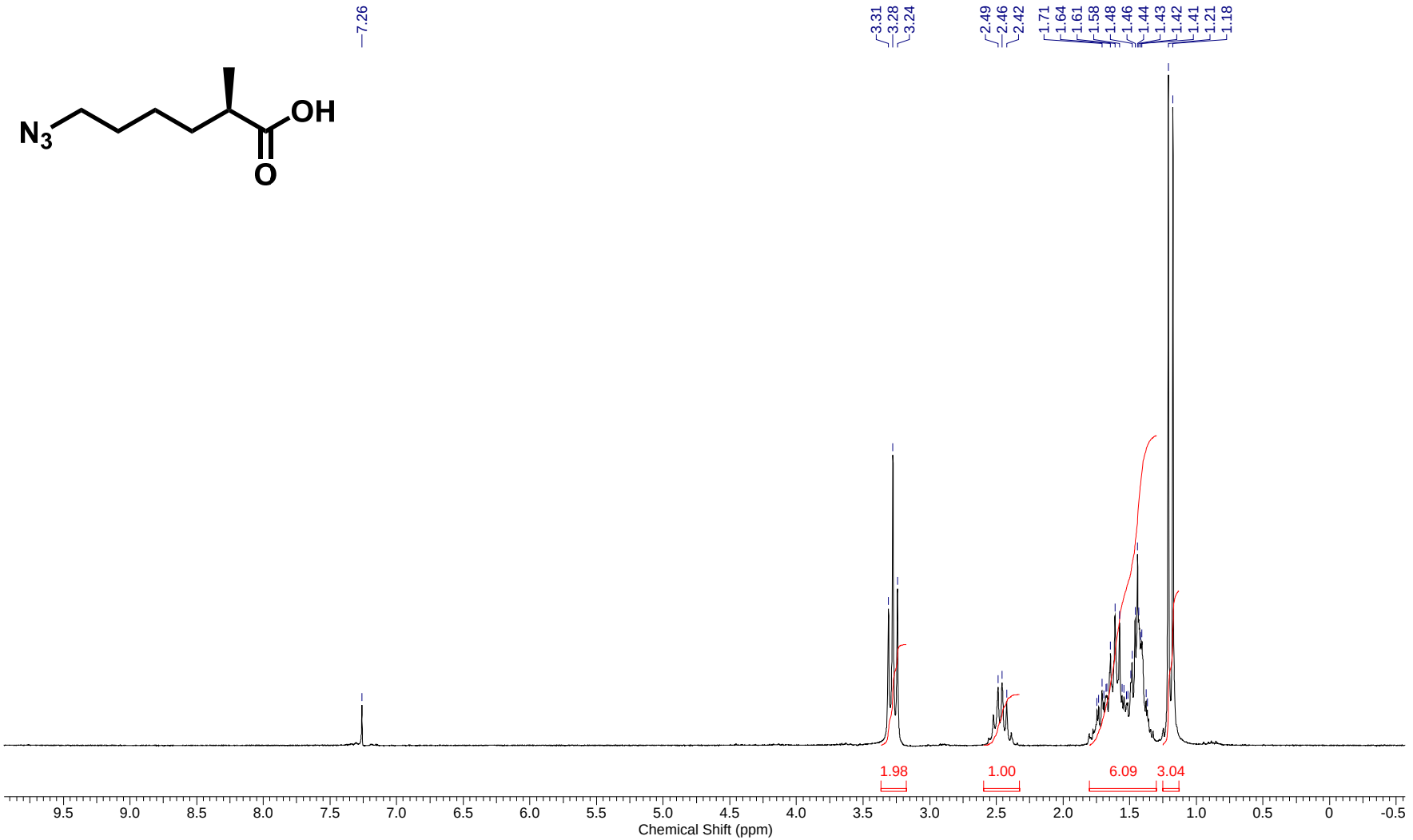
^{1}H NMR of Compound **25** at 400 MHz in $CDCl_3$



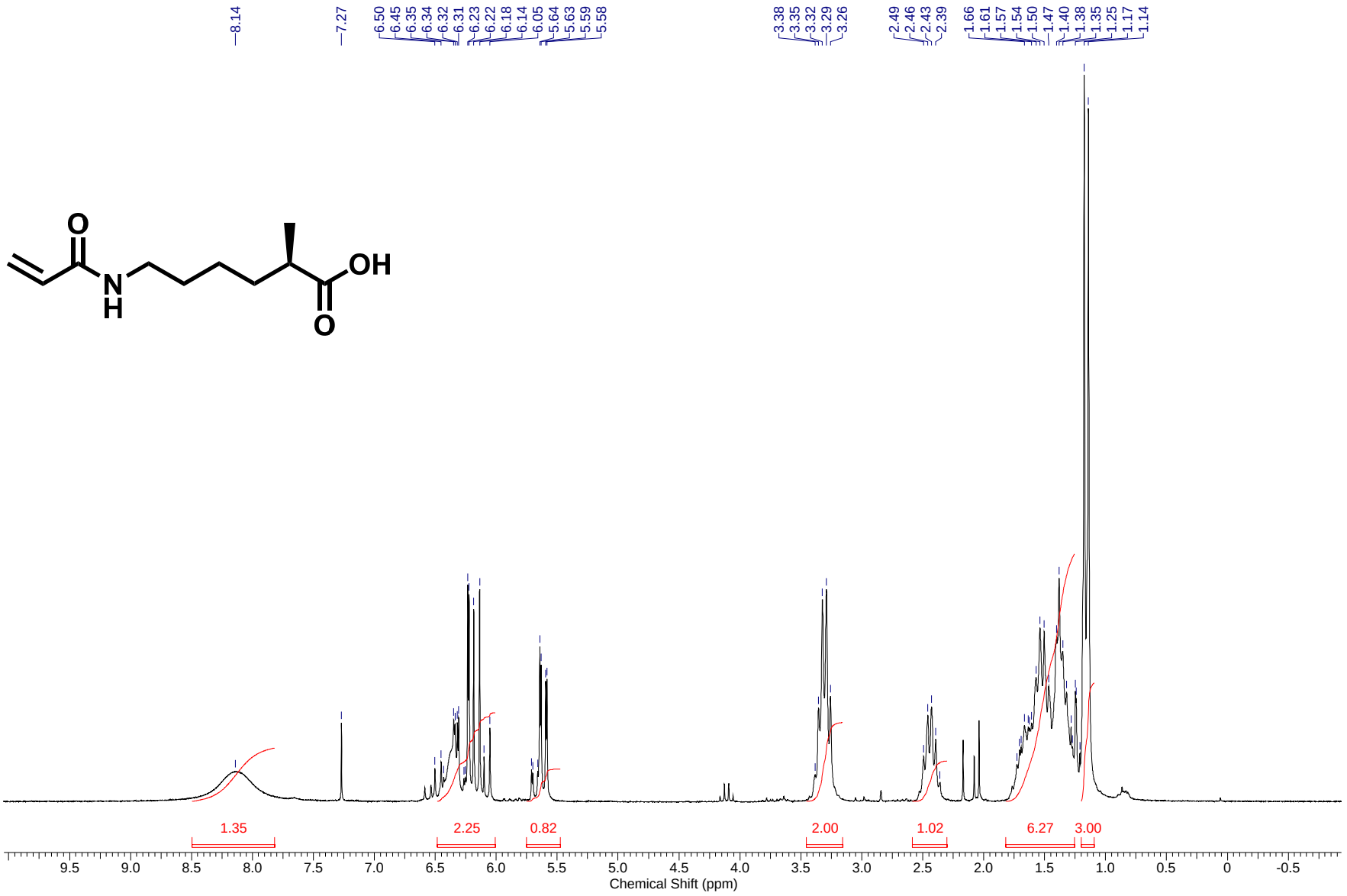
^{13}C NMR of Compound **25** at 100 MHz in $CDCl_3$



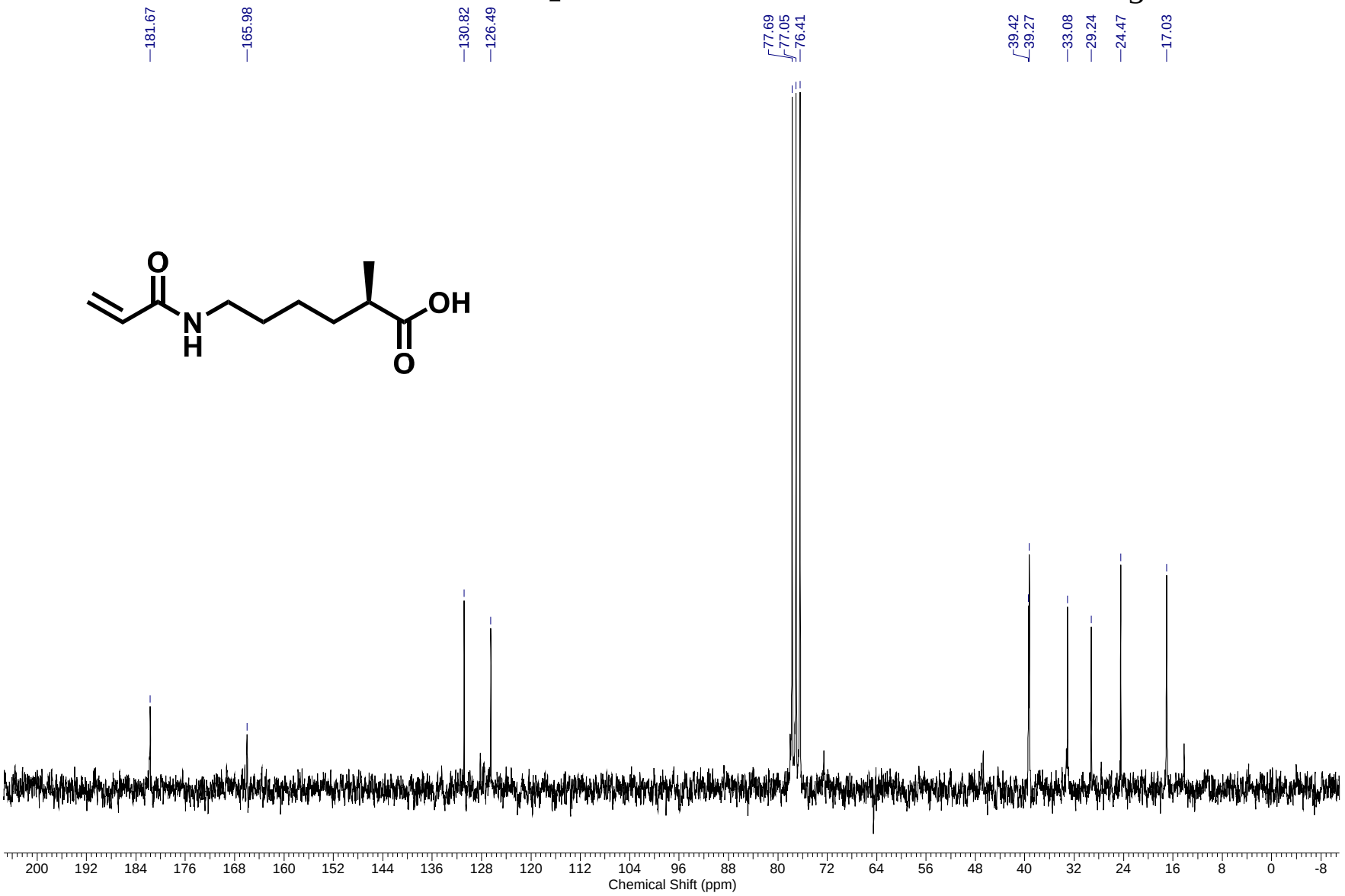
^{1}H NMR of Compound **26** at 200 MHz in $CDCl_3$



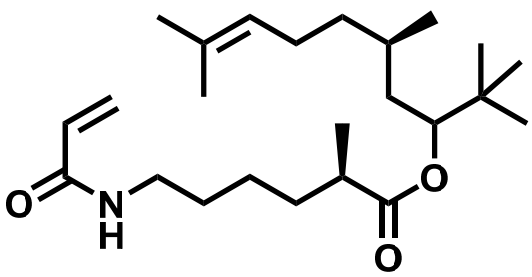
^{1}H NMR of Compound **27** at 200 MHz in $CDCl_3$



^{13}C NMR of Compound **27** at 50 MHz in $CDCl_3$

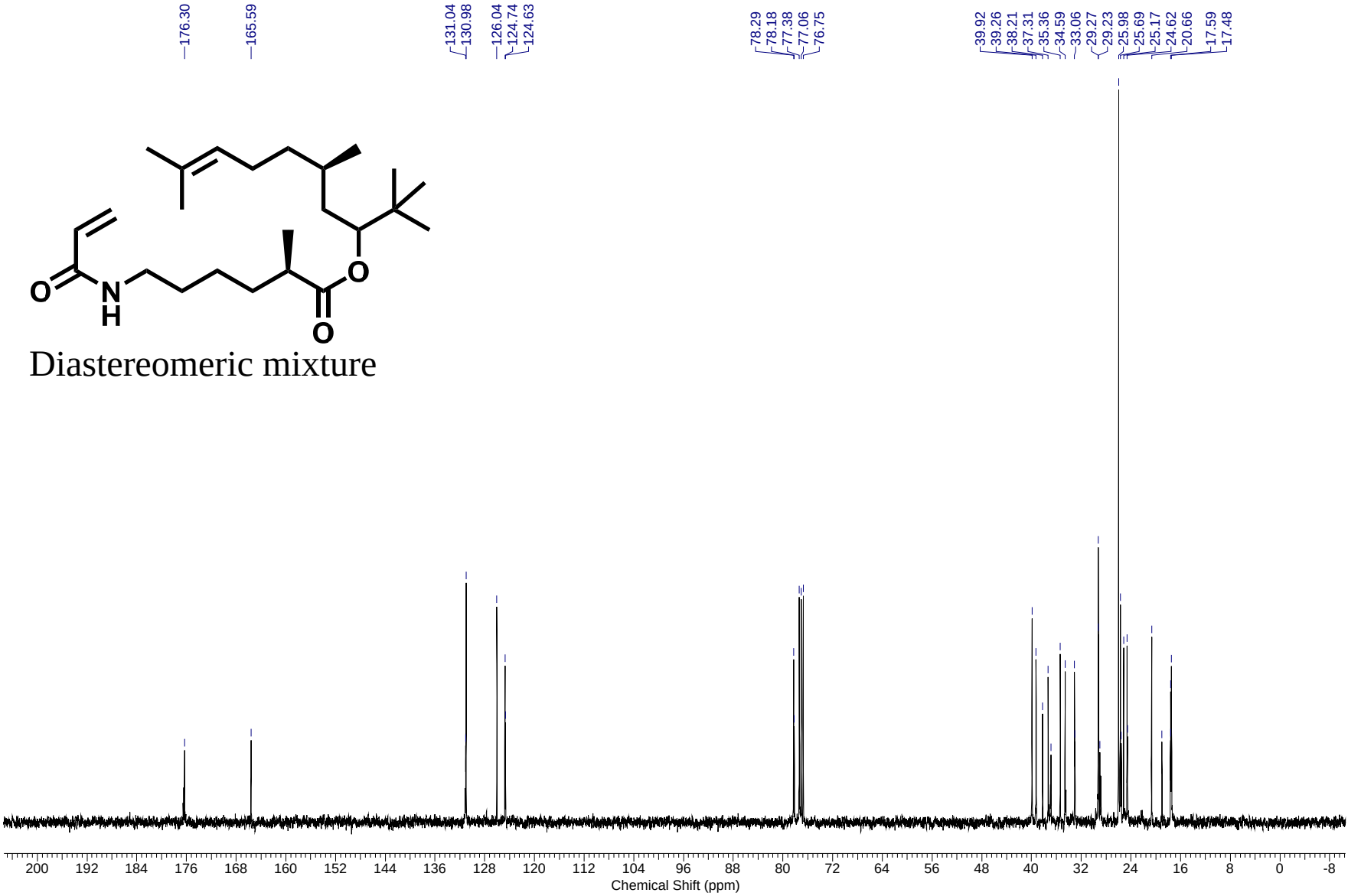


^{1}H NMR of Compound **28** at 200 MHz in $CDCl_3$



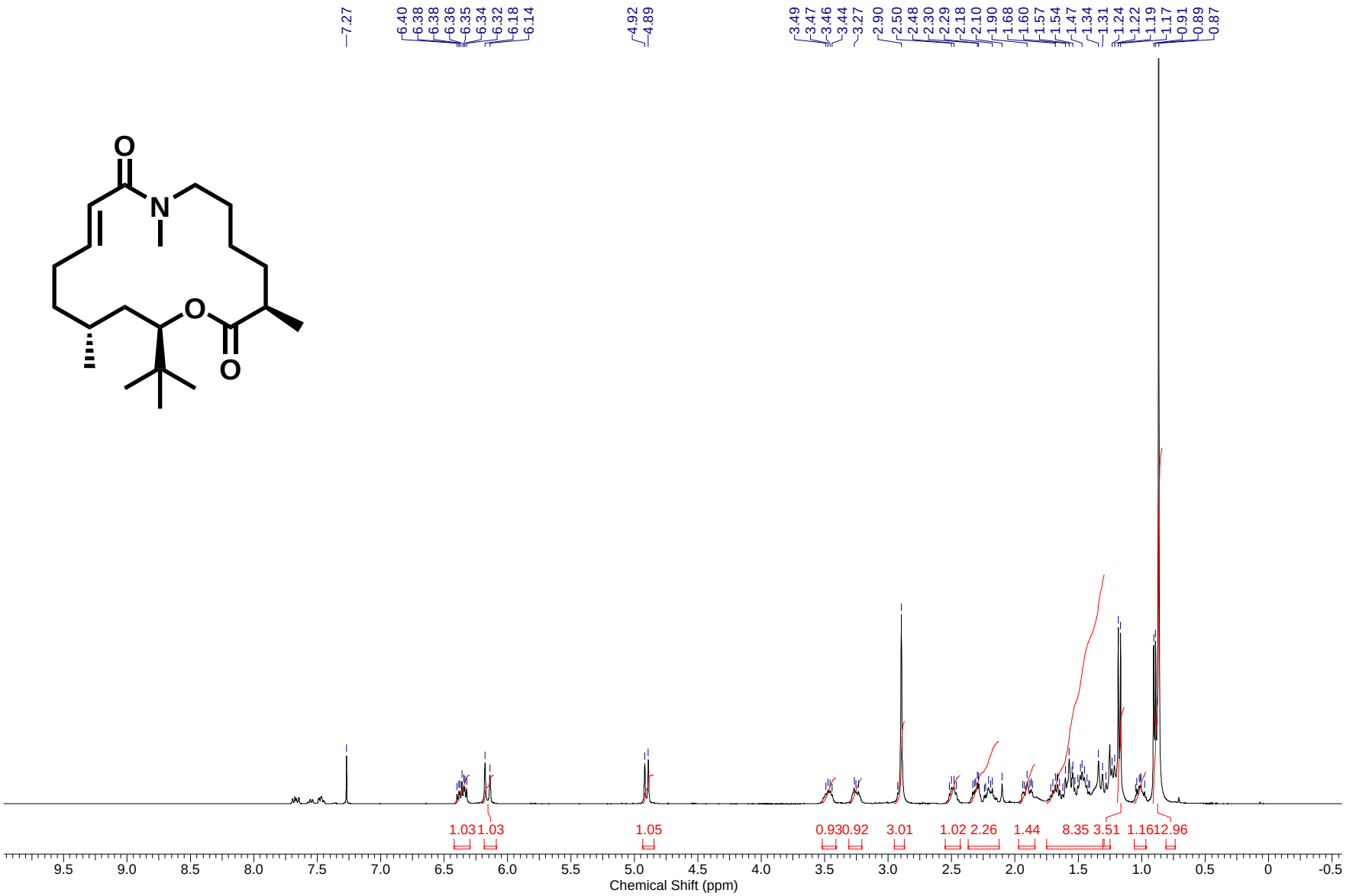
Diastereomeric mixture

^{13}C NMR of Compound **28** at 100 MHz in $CDCl_3$

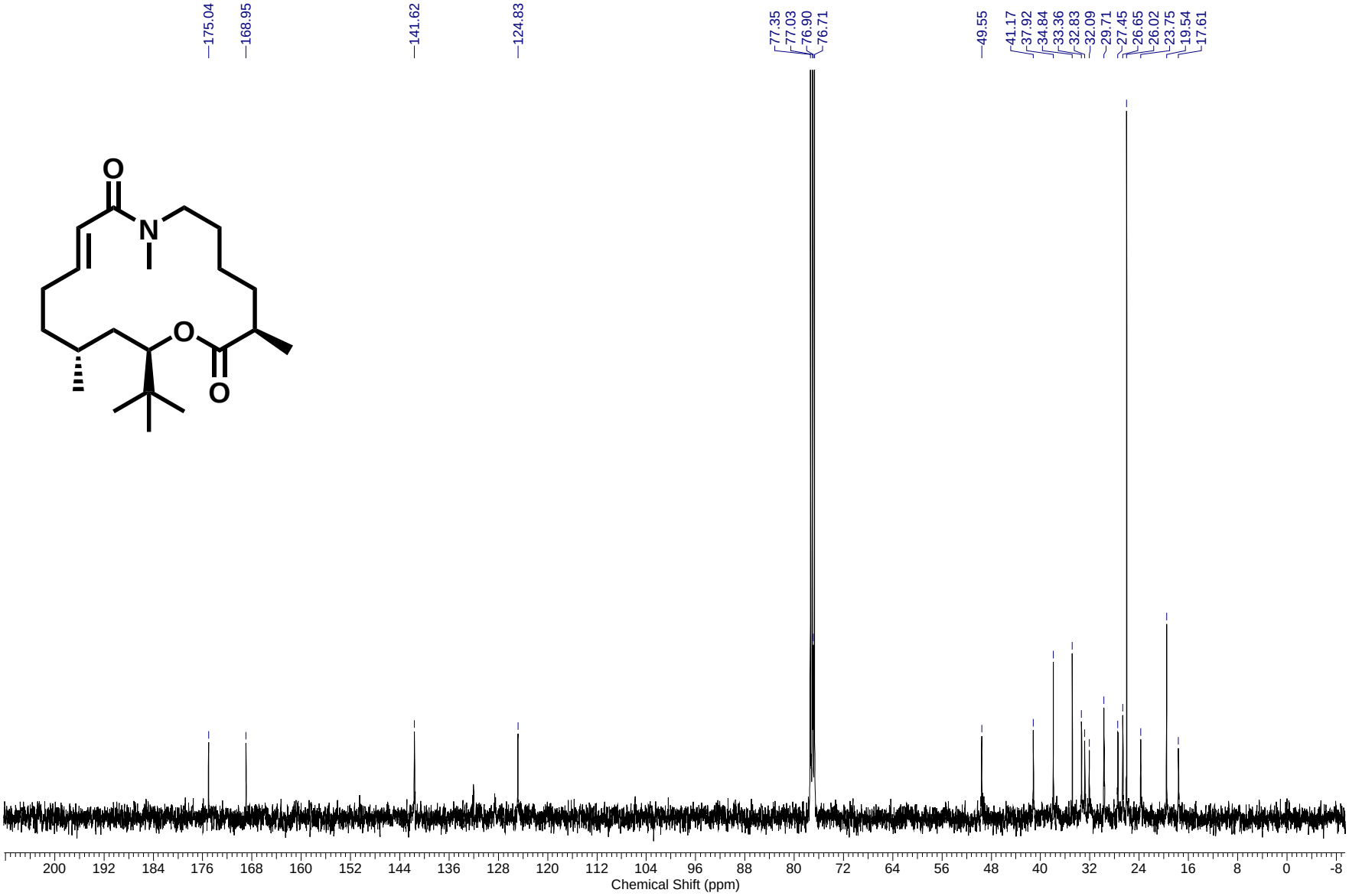


Diastereomeric mixture

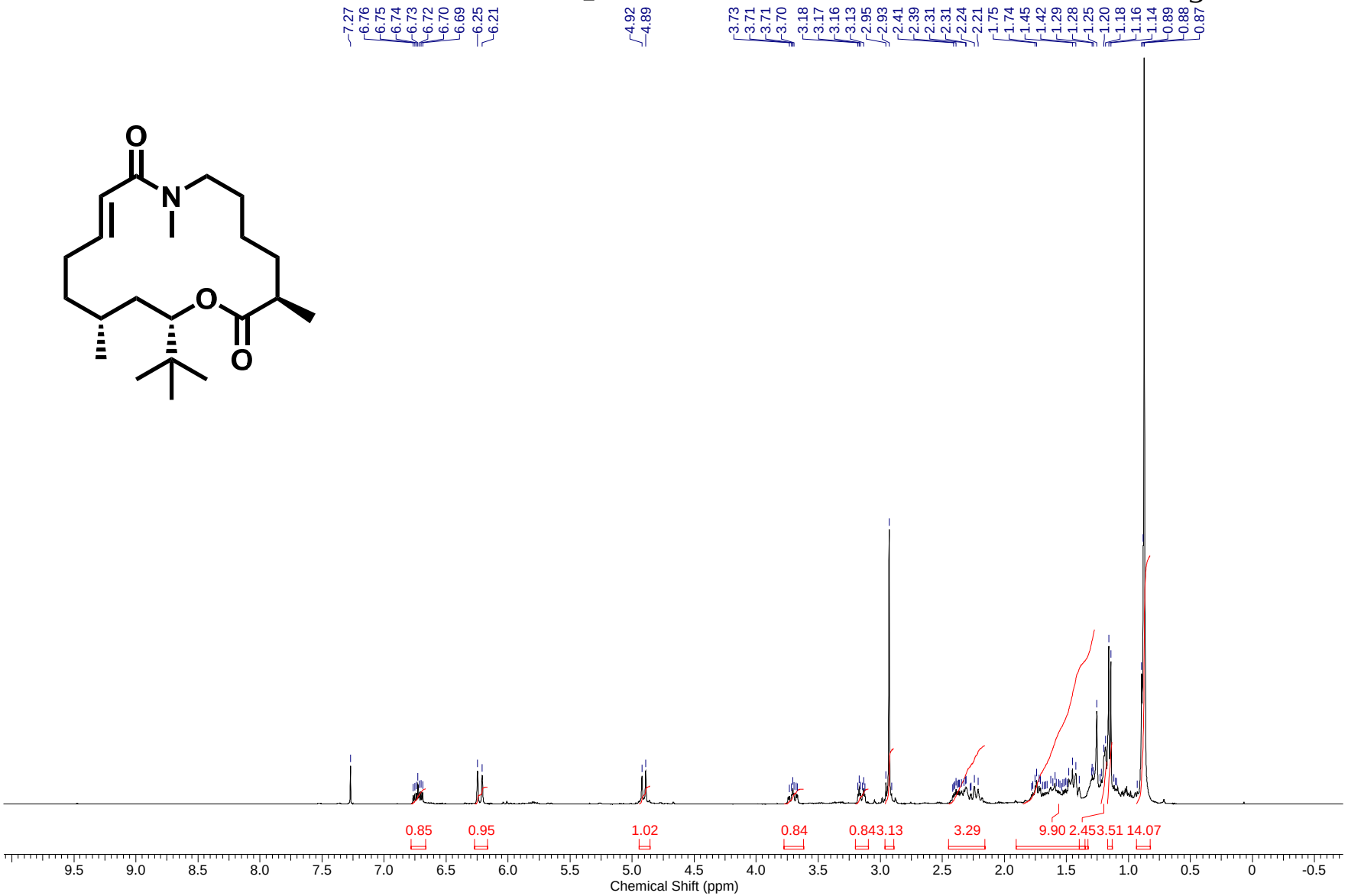
^{1}H NMR of Compound **29** at 400 MHz in $CDCl_3$



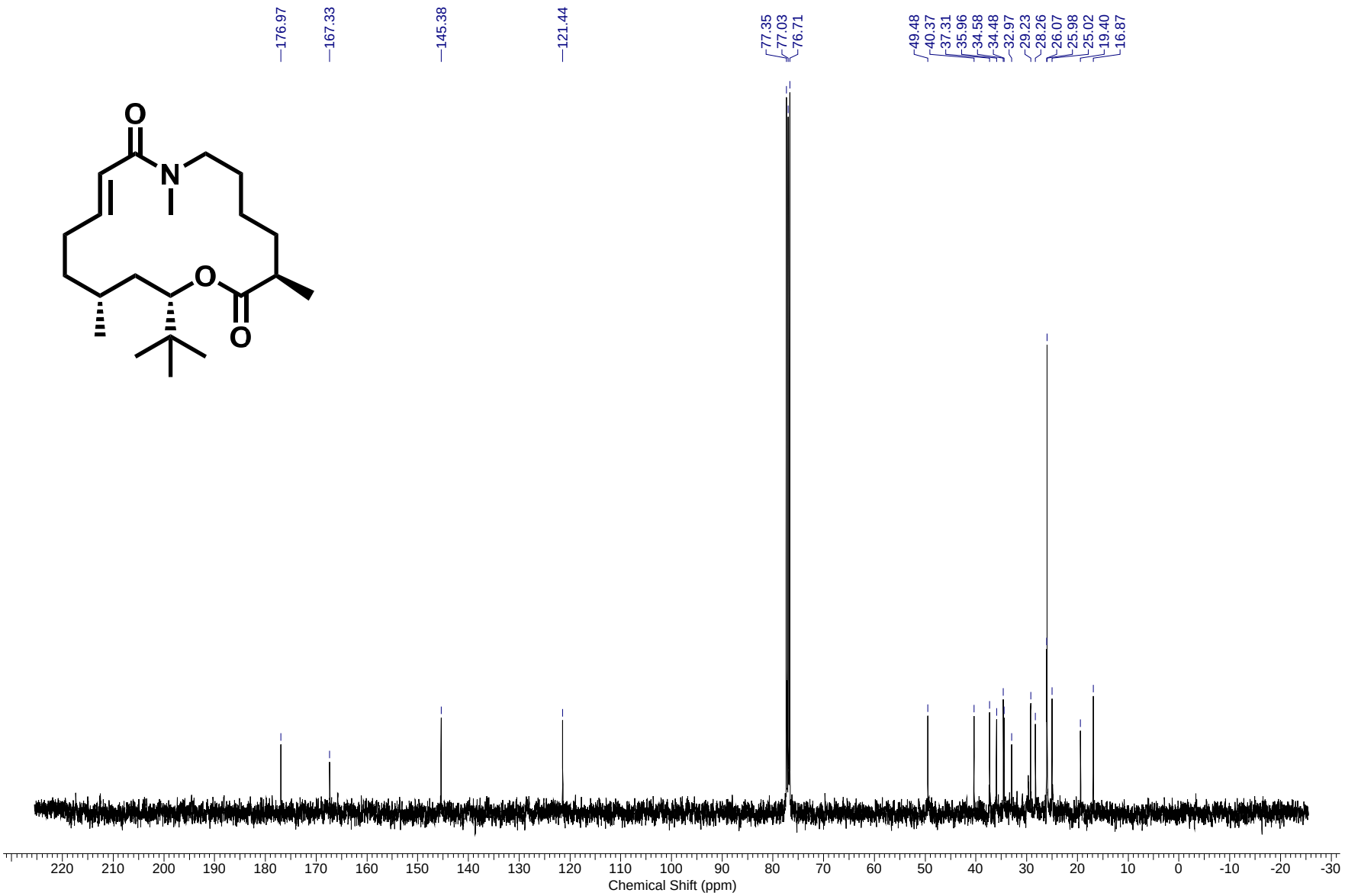
^{13}C NMR of Compound **29** at 100 MHz in $CDCl_3$



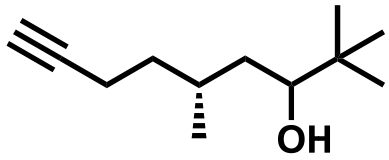
^{1}H NMR of Compound **30** at 400 MHz in $CDCl_3$



^{13}C NMR of Compound **30** at 100 MHz in $CDCl_3$

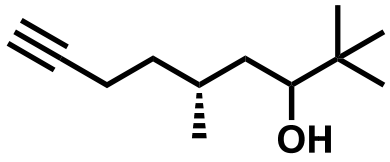


^{1}H NMR of Compound **31** at 500 MHz in $CDCl_3$



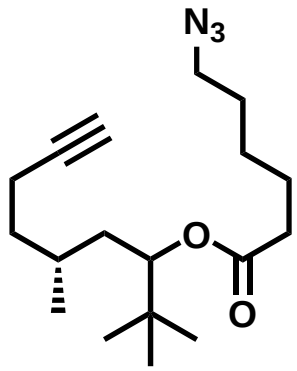
Diastereomeric mixture

^{13}C NMR of Compound **31** at 125 MHz in $CDCl_3$



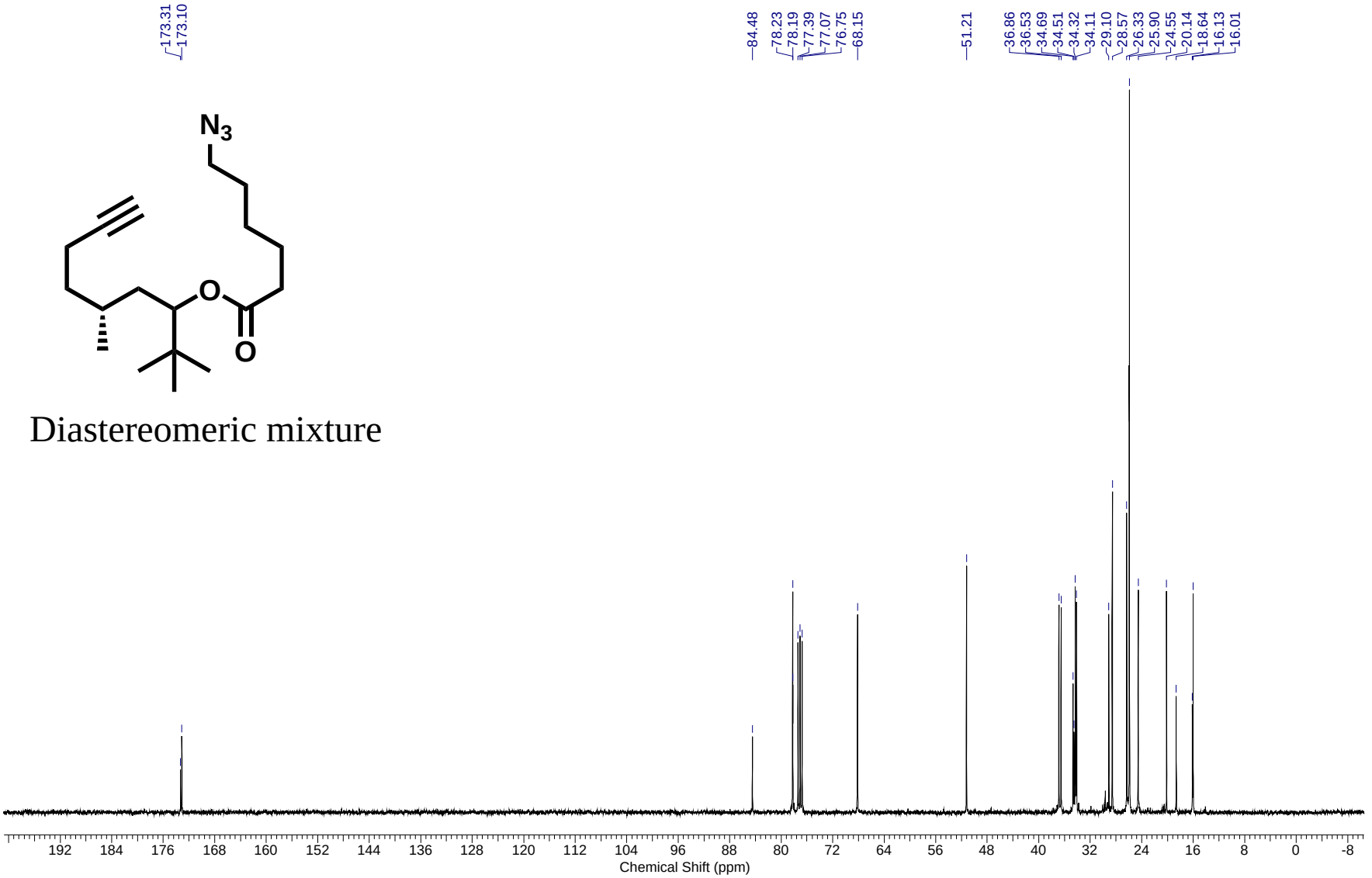
Diastereomeric mixture

^{1}H NMR of Compound **32** at 400 MHz in $CDCl_3$



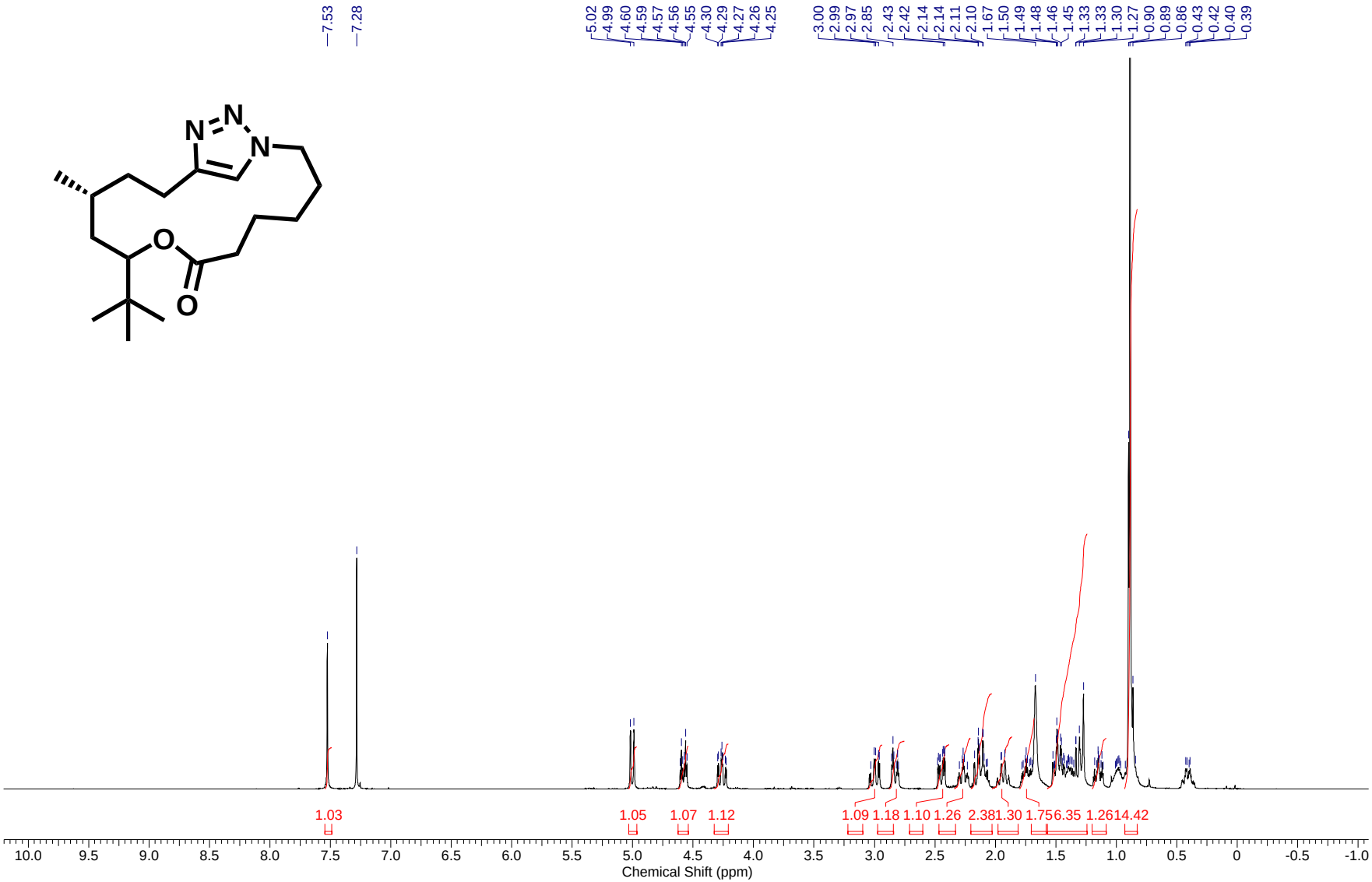
Diastereomeric mixture

^{13}C NMR of Compound **32** at 100 MHz in $CDCl_3$

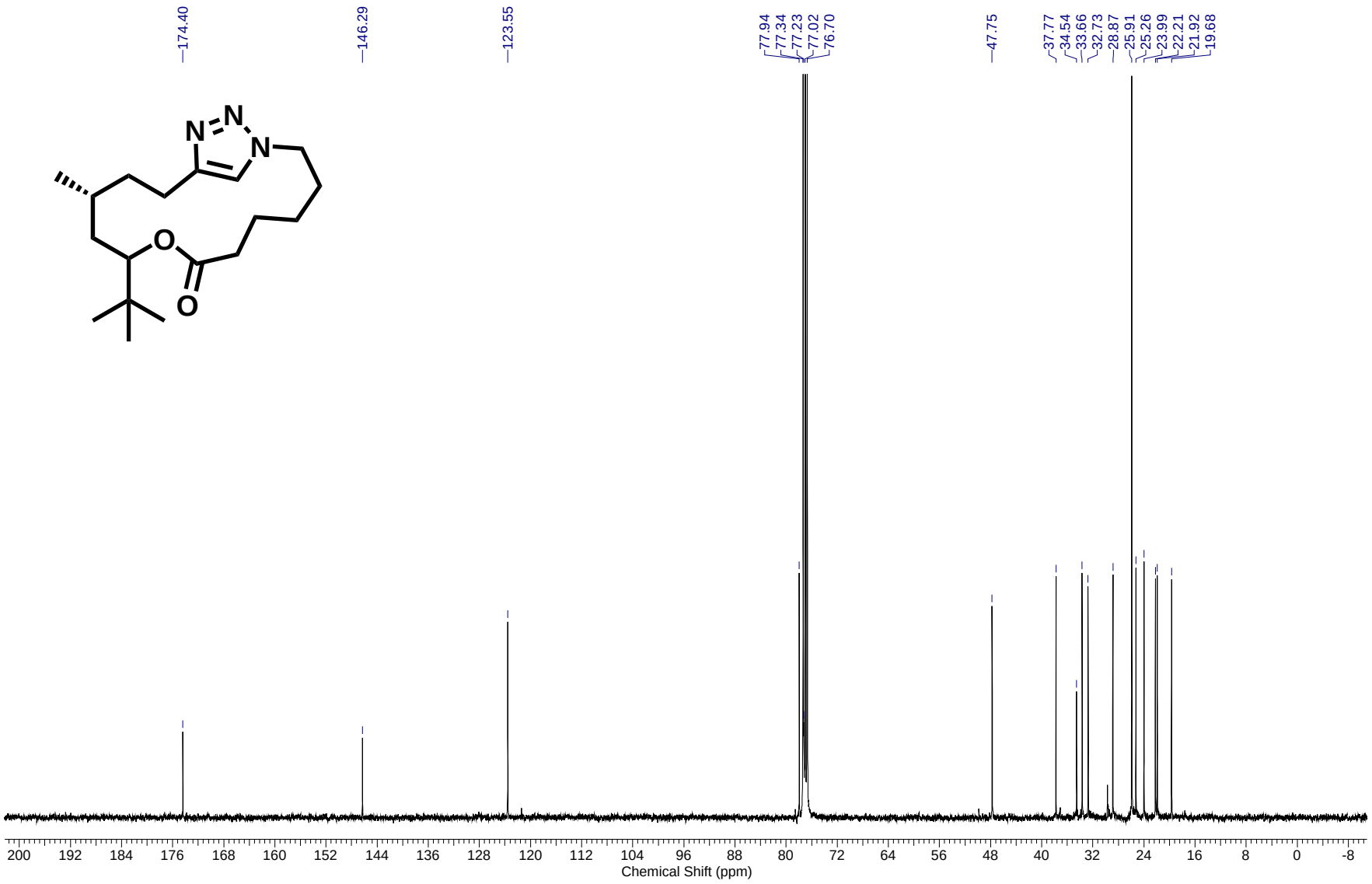


Diastereomeric mixture

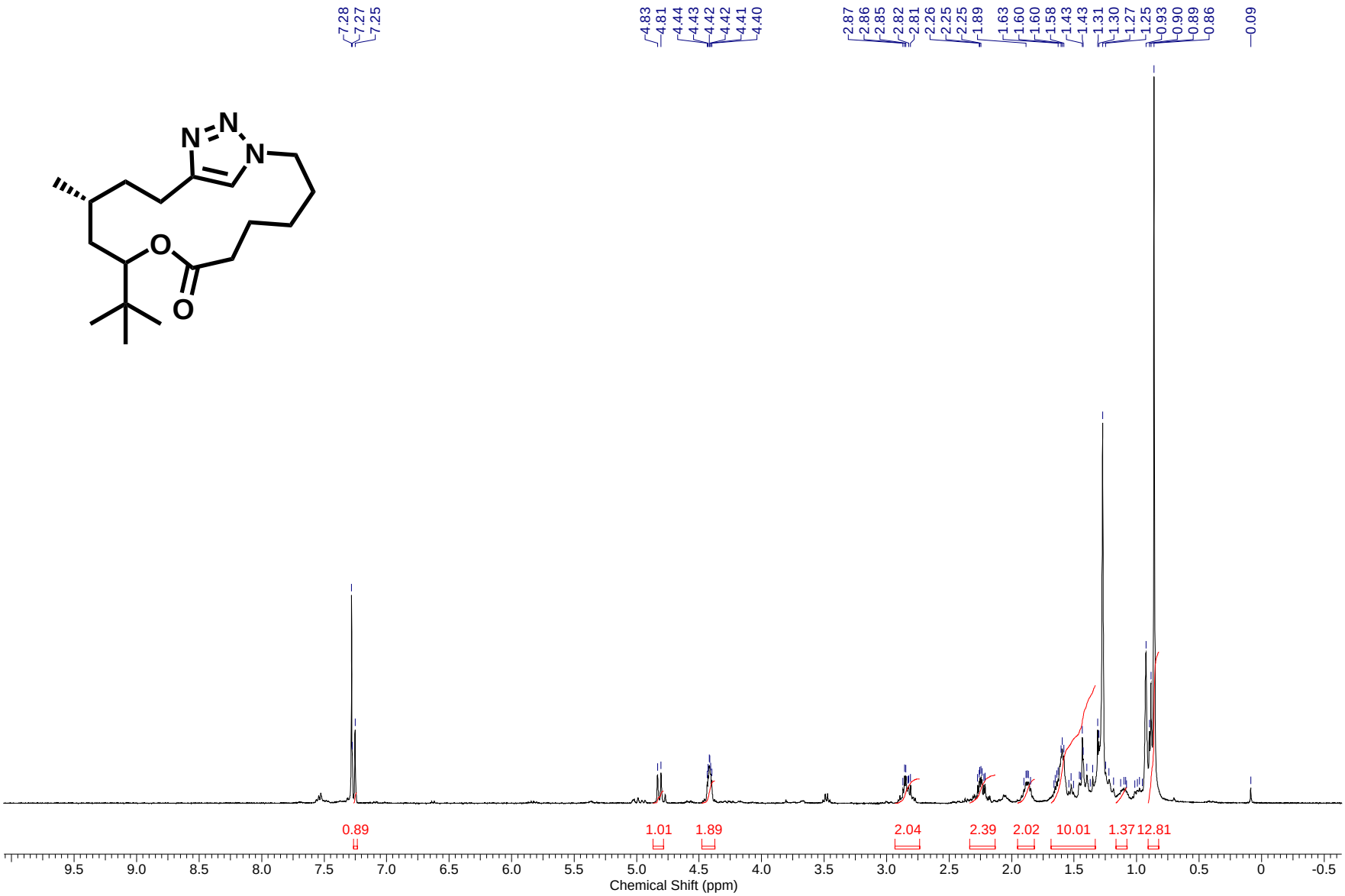
^{1}H NMR of Compound **33** at 400 MHz in $CDCl_3$



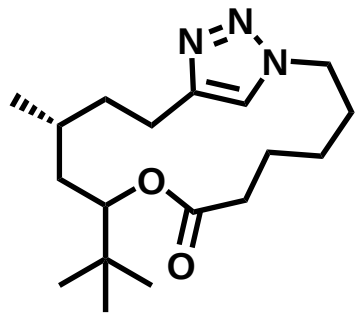
^{13}C NMR of Compound **33** at 100 MHz in $CDCl_3$



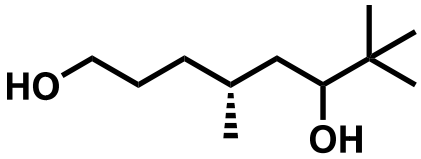
^{1}H NMR of Compound **34** at 400 MHz in $CDCl_3$



^{13}C NMR of Compound **34** at 100 MHz in $CDCl_3$

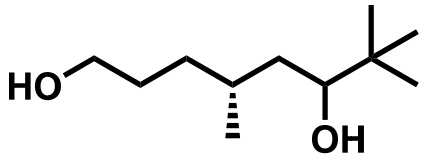


^{1}H NMR of Compound at 400 MHz in $CDCl_3$



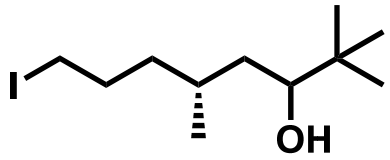
Diastereomeric mixture

^{13}C NMR of Compound at 100 MHz in $CDCl_3$



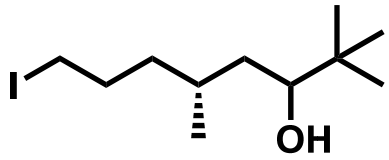
Diastereomeric mixture

^{1}H NMR of Compound **35** at 200 MHz in $CDCl_3$



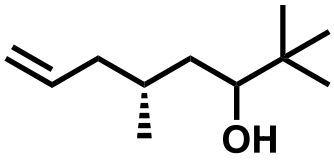
Diastereomeric mixture

^{13}C NMR of Compound **35** at 50 MHz in $CDCl_3$



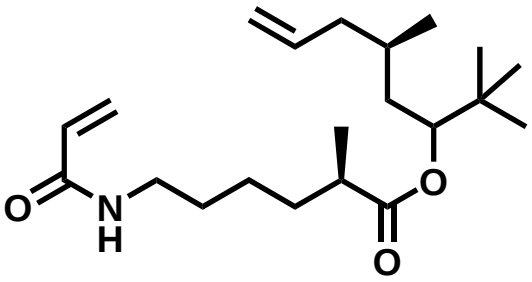
Diastereomeric mixture

^{1}H NMR of Compound **36** at 200 MHz in $CDCl_3$



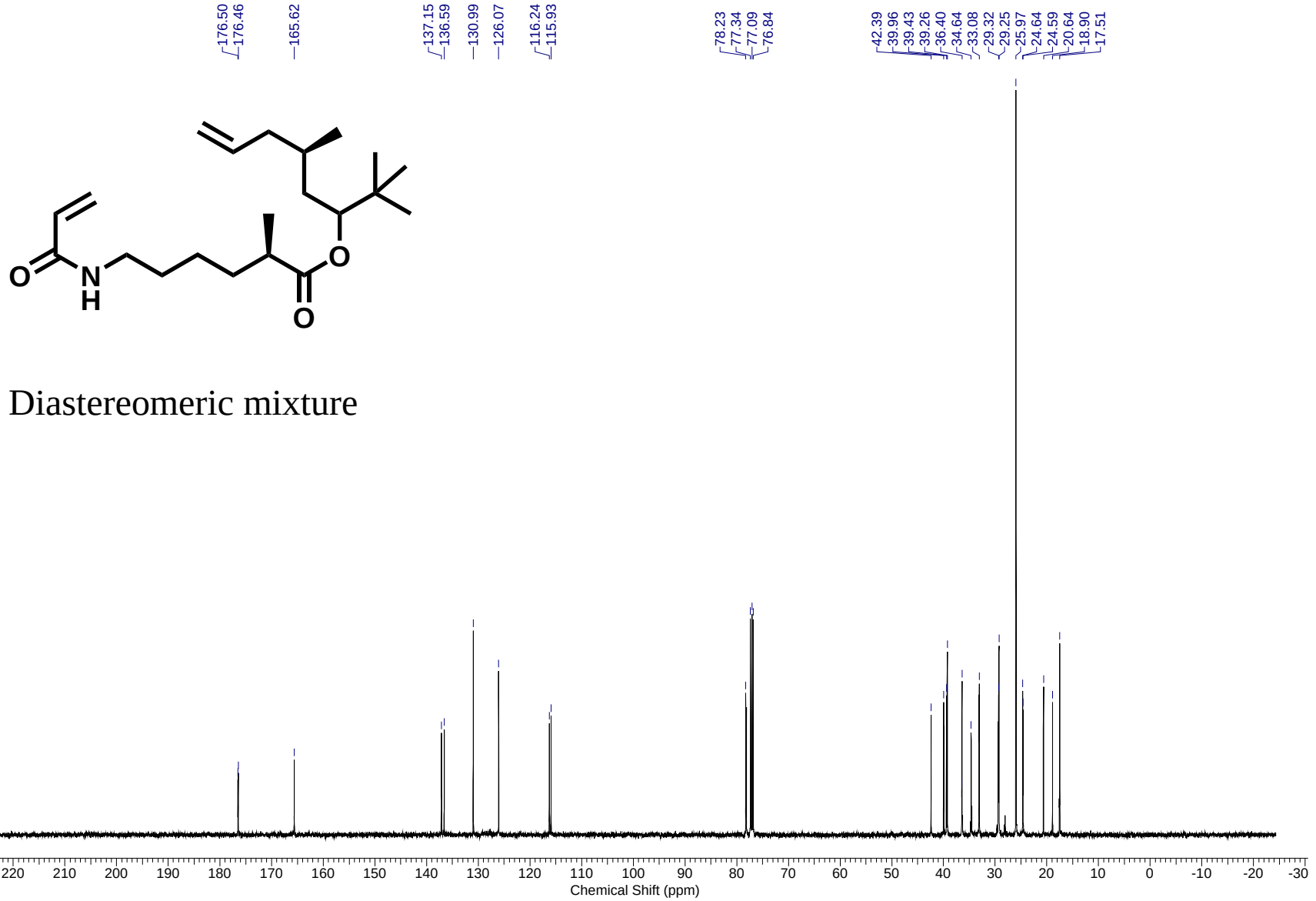
Diastereomeric mixture

^{1}H NMR of Compound **37** at 500 MHz in $CDCl_3$



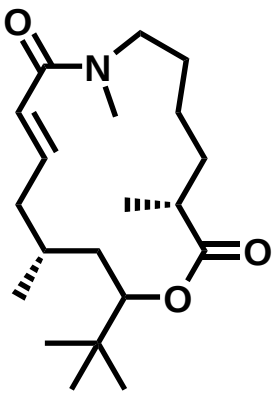
Diastereomeric mixture

^{13}C NMR of Compound **37** at 125 MHz in $CDCl_3$



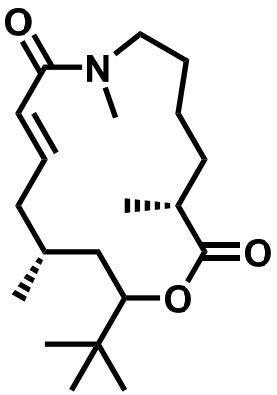
Diastereomeric mixture

^{1}H NMR of Compound **38** at 400 MHz in $CDCl_3$



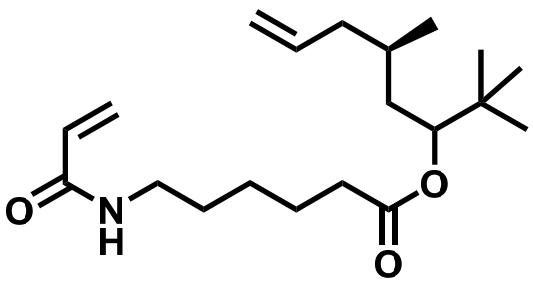
Diastereomeric mixture

^{13}C NMR of Compound **38** at 100 MHz in $CDCl_3$



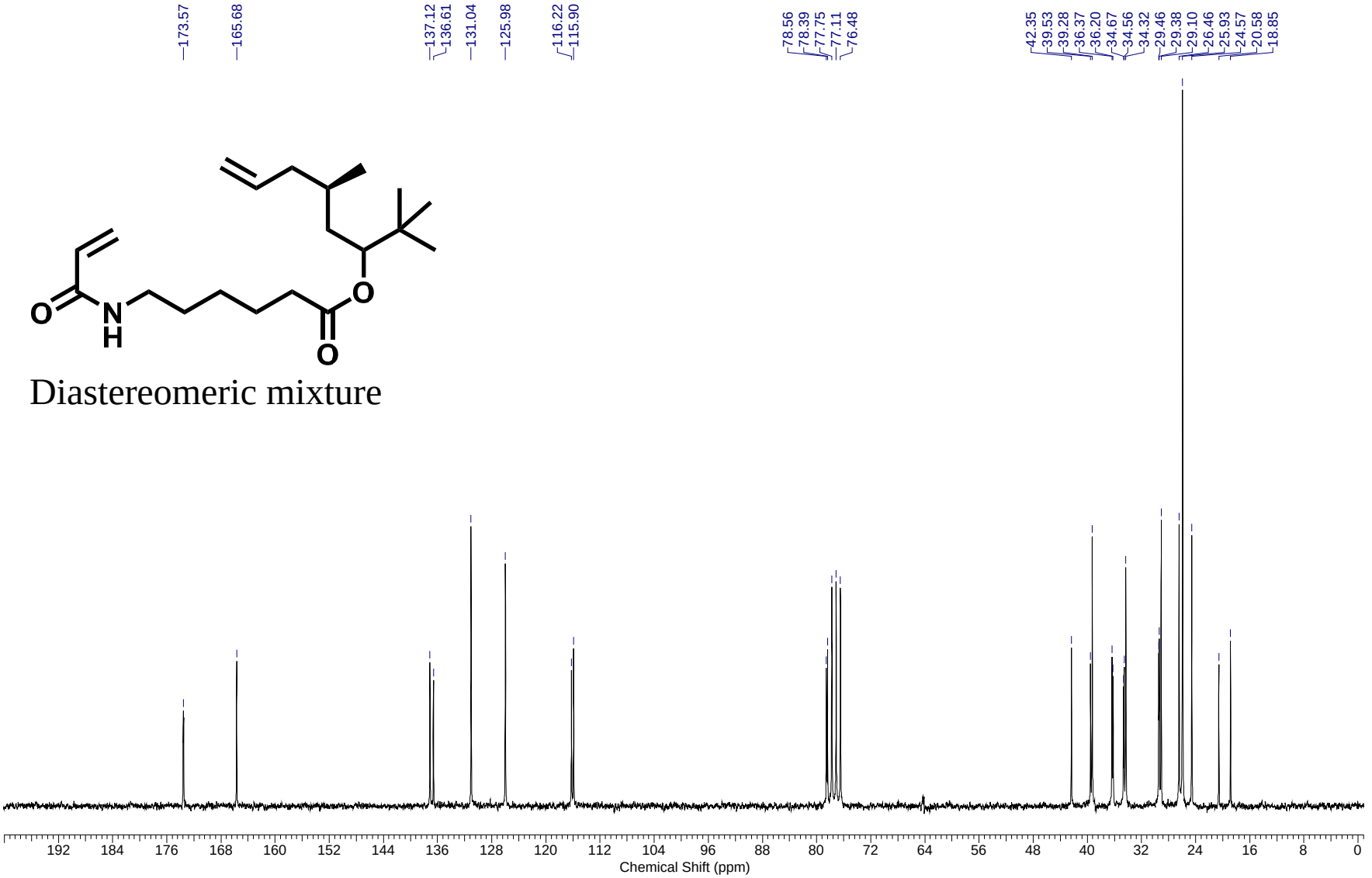
Diastereomeric mixture

^{1}H NMR of Compound **39** at 200 MHz in $CDCl_3$



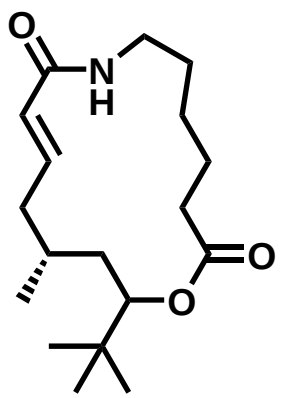
Diastereomeric mixture

^{13}C NMR of Compound **39** at 50 MHz in $CDCl_3$



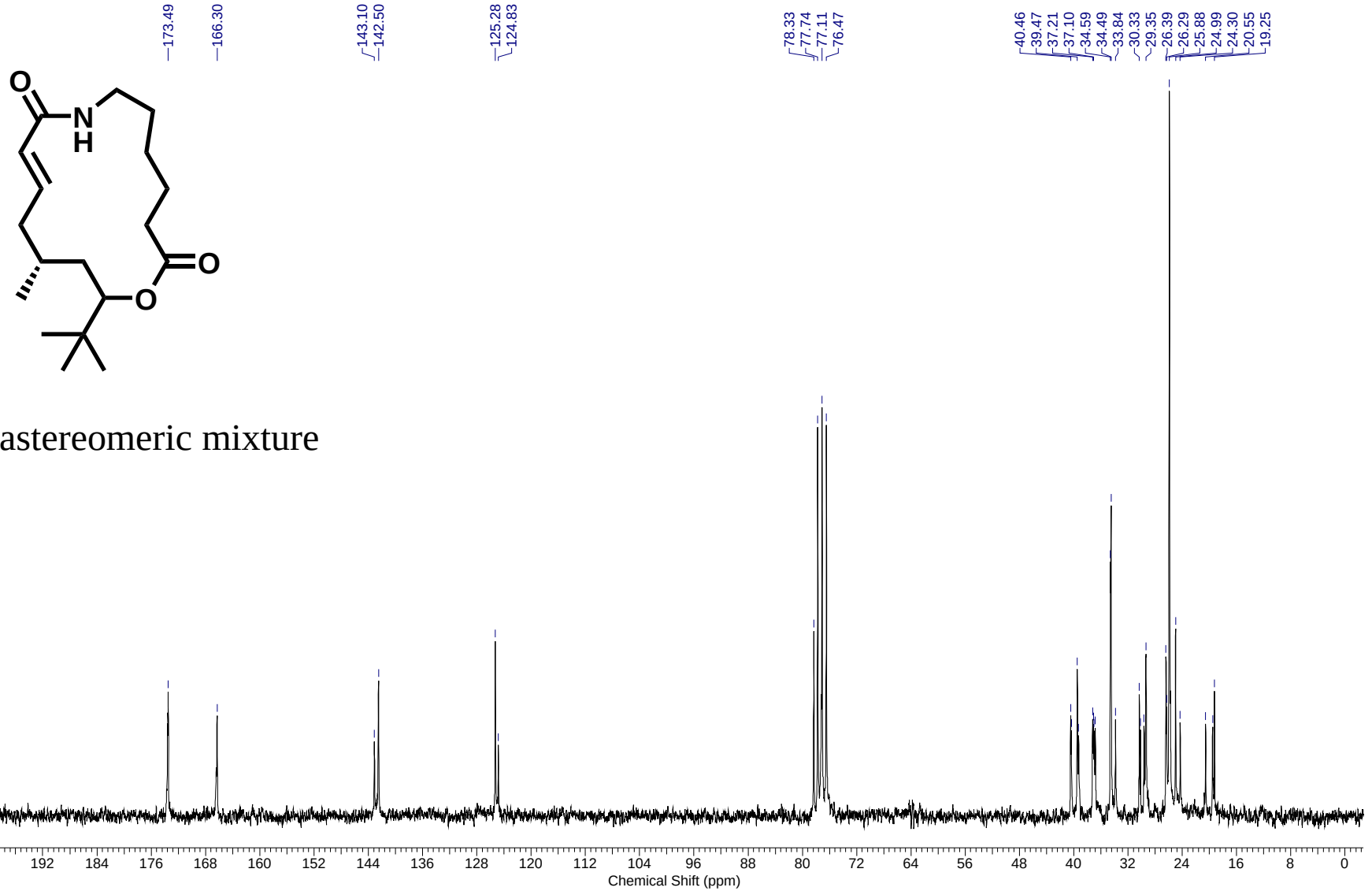
Diastereomeric mixture

^{1}H NMR of Compound **40** at 200 MHz in $CDCl_3$



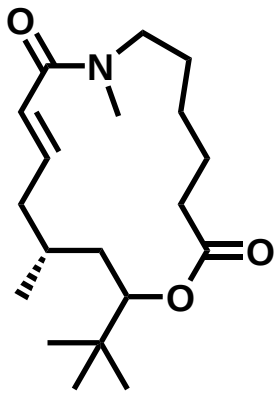
Diastereomeric mixture

^{13}C NMR of Compound **40** at 50 MHz in $CDCl_3$



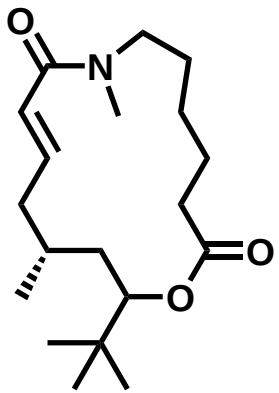
Diastereomeric mixture

^{1}H NMR of Compound **41** at 400 MHz in $CDCl_3$



Diastereomeric mixture

^{13}C NMR of Compound **41** at 50 MHz in $CDCl_3$



Diastereomeric mixture

Graphs showing a 3-parameter logistic fit of the palmyrolide A analogues Time-concentration-response inhibition of veratridine of each compound tested.

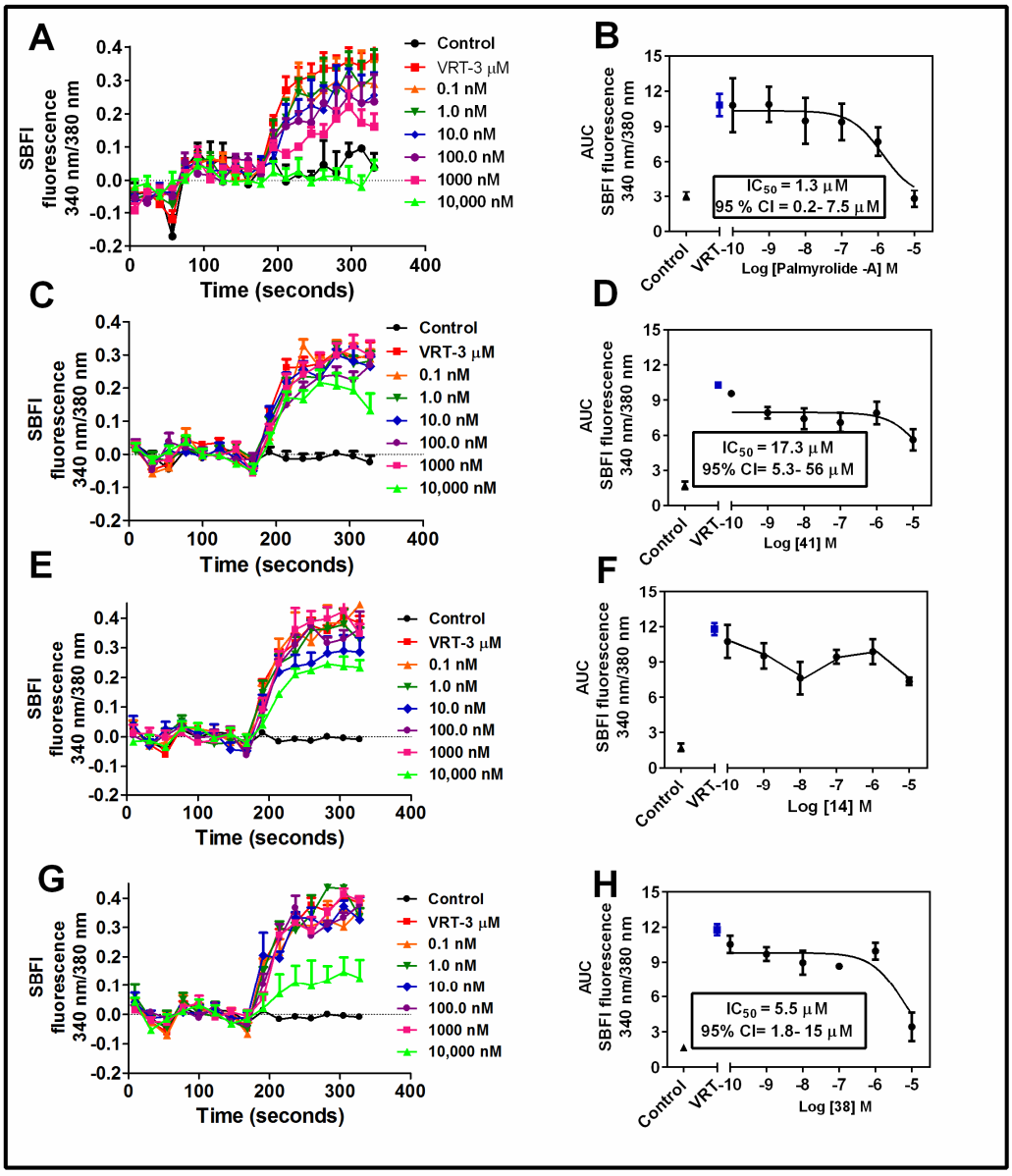


Figure 2: Time and concentration-response analysis of (ī)-palmyrolide A, **(-)-1** and its analogues where sodium influx was monitored with SBFI (340/380) responses to veratridine in the absence and presence of each analogue. The compounds shown are (A & B) (ī)-palmyrolide A **(-)-1**;(C & D)(13*R*,E)-15-(*tert*-butyl)-8,13-dimethyl-1-oxa-8-azacyclopentadec-10-ene-2,9-dione (**41**); (E & F) (13*R*,15*R*,E)-15-(*tert*-butyl)-8,13-dimethyl-

1-oxa-8-azacyclopentadec-6-ene-2,9-dione (**14**); (G & H) (3*R*,13*R*,E)-15-(*tert*-butyl)-3,8,13-trimethyl-1-oxa-8-azacyclopentadec-10-ene-2,9-dione (**38**).

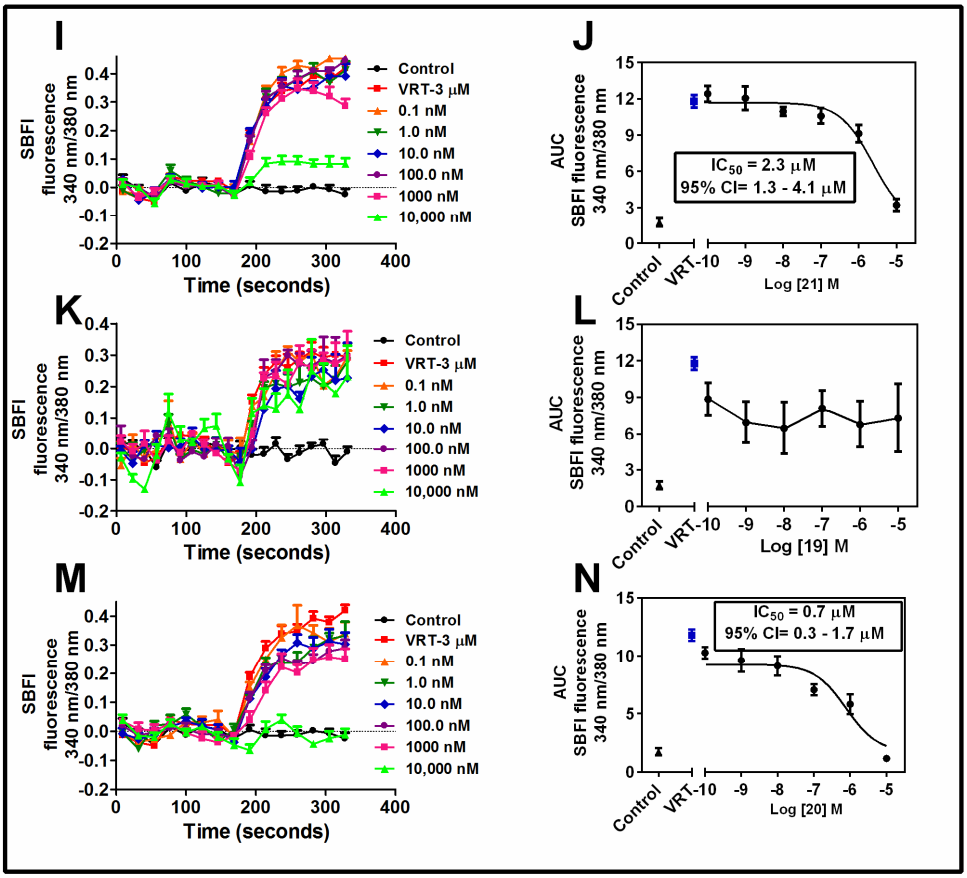


Figure 3: Time and concentration-response analysis of (ī)-palmyrolide A analogues where sodium influx was monitored with SBFI (340/380) responses to veratridine in the absence and presence of (ī)-palmyrolide A analogues. The compounds shown are (I & J)(14*R*,16*S*,E)-16-(*tert*-butyl)-8,14-dimethyl-1-oxa-8-azacyclohexadec-10-ene-2,9-dione (**21**); (K & L) (14*R*,16*S*,E)-16-(*tert*-butyl)-14-methyl-1-oxa-8-azacyclohexadec-10-ene-2,9-dione (**19**); (M & N)(14*R*,16*R*,E)-16-(*tert*-butyl)-8,14-dimethyl-1-oxa-8-azacyclohexadec-10-ene-2,9-dione (**20**).

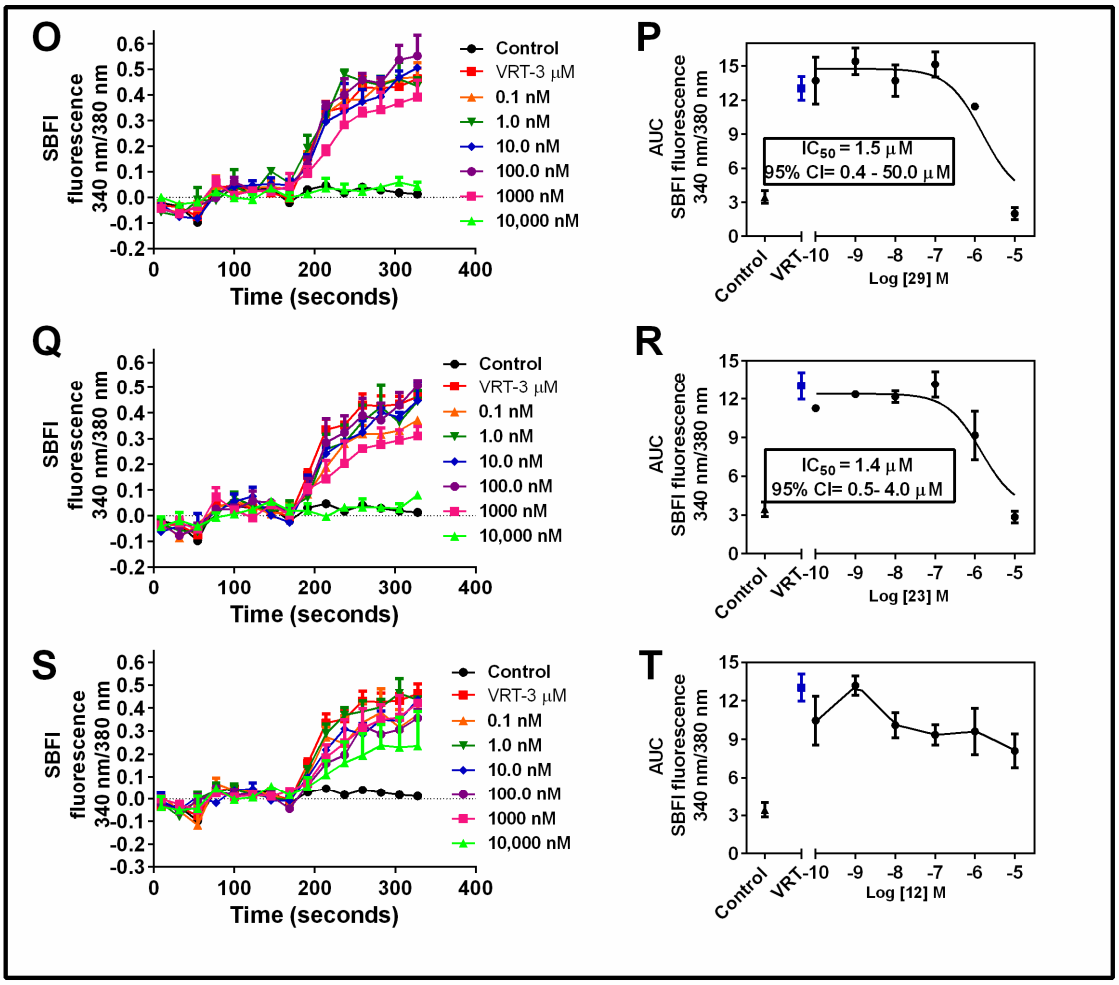


Figure 4: Time and concentration-response analysis of (ī)-palmyrolide A analogues where sodium influx was monitored with SBFI (340/380) responses to veratridine in the absence and presence of (ī)-palmyrolide A analogues. The compounds shown are (O & P)(3*R*,14*R*,16*R*,E)-16-(*tert*-butyl)-3,8,14-trimethyl-1-oxa-8-azacyclohexadec-10-ene-2,9-dione (**29**); (Q & R) (14*R*,16*S*)-16-(*tert*-butyl)-8,14-dimethyl-1-oxa-8-azacyclohexadecane-2,9-dione (**23**); (S & T) (13*R*,15*R*,Z)-15-(*tert*-butyl)-13-methyl-1-oxa-8-azacyclopentadec-6-ene-2,9-dione (**12**).

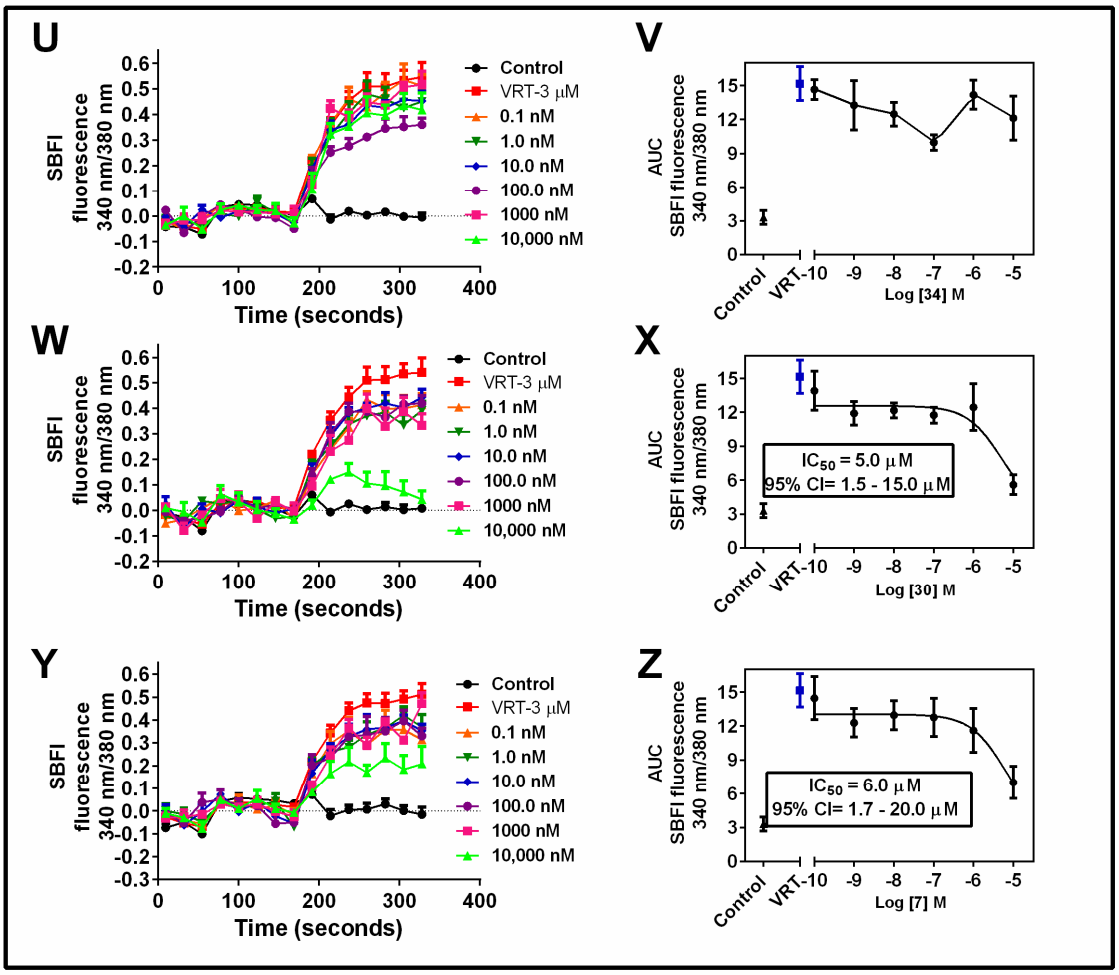


Figure 5: Time and concentration-response analysis of (ī)-palmyrolide A analogues where sodium influx was monitored with SBFI (340/380) responses to veratridine in the absence and presence of (ī)-palmyrolide A analogues. The compounds shown are (U & V) triazole (**34**); (W & X) (3*R*,14*R*,16*S*,E)-16-(*tert*-butyl)-3,8,14-trimethyl-1-oxa-8-azacyclohexadec-10-ene-2,9-dione (**30**); (Y & Z)(3*S*,13*S*,15*S*,Z)-15-(*tert*-butyl)-3,8,13-trimethyl-1-oxa-8-azacyclopentadec-6-ene-2,9-dione (**7**).

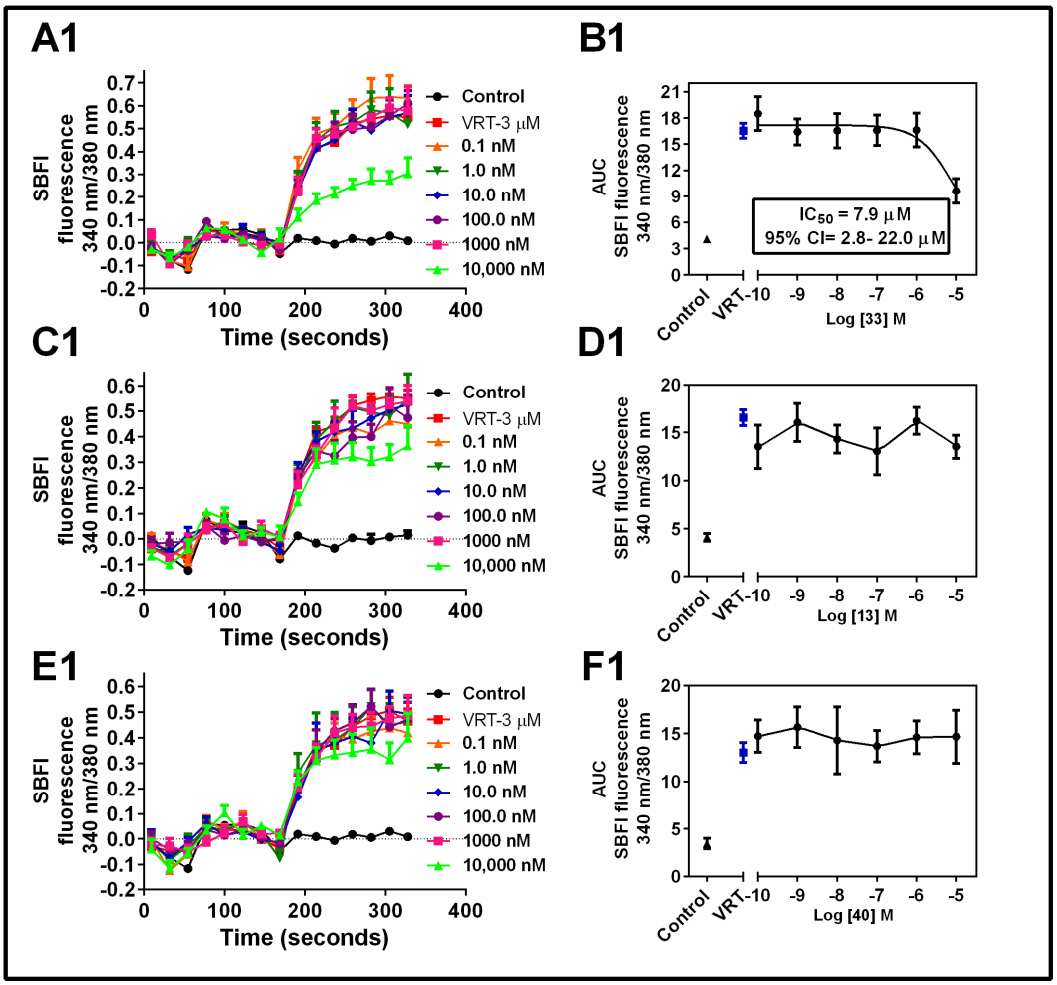


Figure 6: Time and concentration-response analysis of (ī)-palmyrolide A analogues. Sodium influx was monitored with SBFI (340/380) responses to veratridine in the absence and presence of (ī)-palmyrolide A analogues. The compounds shown are (A1 & B1) triazole (**33**); (C1 & D1) (13*R*,15*R*,E)-15-(*tert*-butyl)-13-methyl-1-oxa-8-azacyclopentadec-6-ene-2,9-dione (**13**); (E1 & F1) (13*R*,E)-15-(*tert*-butyl)-13-methyl-1-oxa-8-azacyclopentadec-10-ene-2,9-dione (**40**).

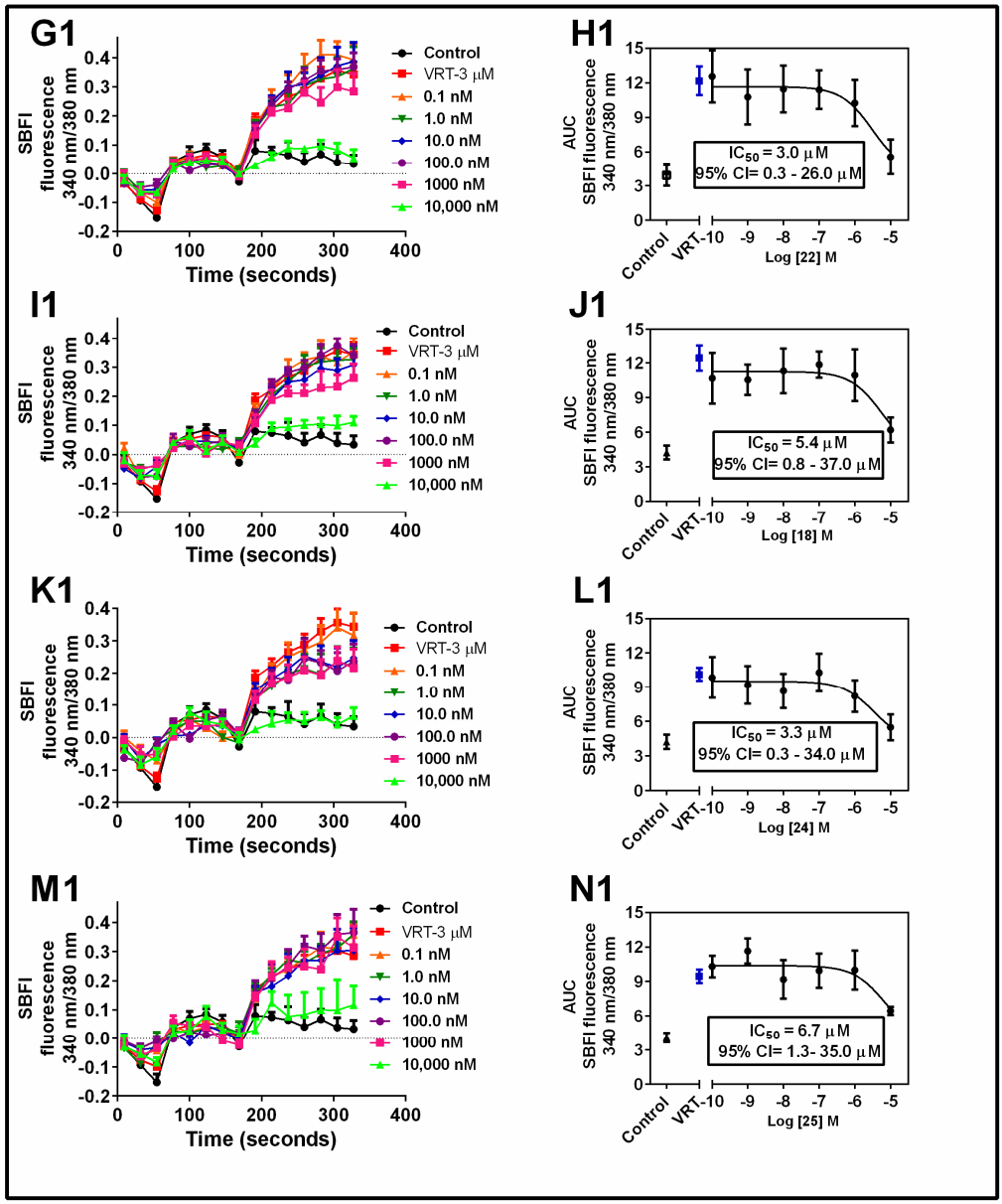


Figure 7: Time and concentration-response analysis of (ī)-palmyrolide A analogues where sodium influx was monitored with SBFI (340/380) responses to veratridine in the absence and presence of (ī)-palmyrolide A analogues. The compounds shown are (G1 & H1) (14*R*,16*R*)-16-(*tert*-butyl)-8,14-dimethyl-1-oxa-8-azacyclohexadecane-2,9-dione (**22**); (I1 & J1)(14*R*,16*R*,E)-16-(*tert*-butyl)-14-methyl-1-oxa-8-azacyclohexadec-10-ene-2,9-dione (**18**); (K1 & L1) (14*R*,16*R*)-16-(*tert*-butyl)-14-methyl-1-oxa-8-azacyclohexadecane-2,9-dione (**24**); (M1 & N1) (14*R*,16*S*)-16-(*tert*-butyl)-14-methyl-1-oxa-8-azacyclohexadecane-2,9-dione (**25**).