Impact of α-modifications on the activity of triazole bisphosphonates as geranylgeranyl diphosphate synthase inhibitors

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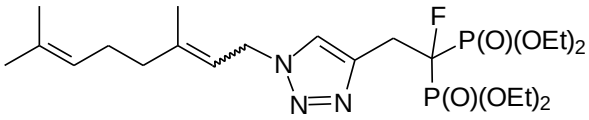
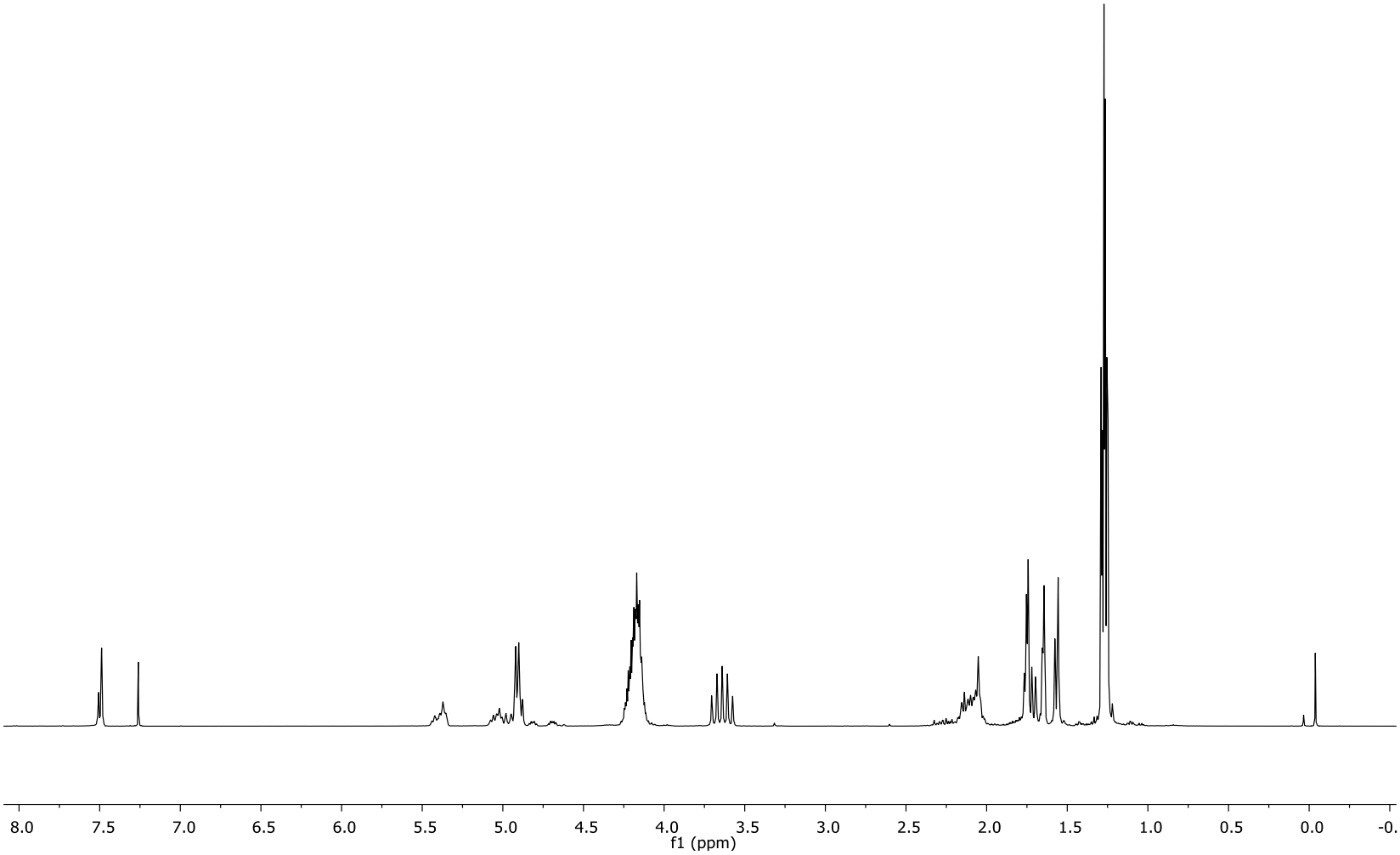
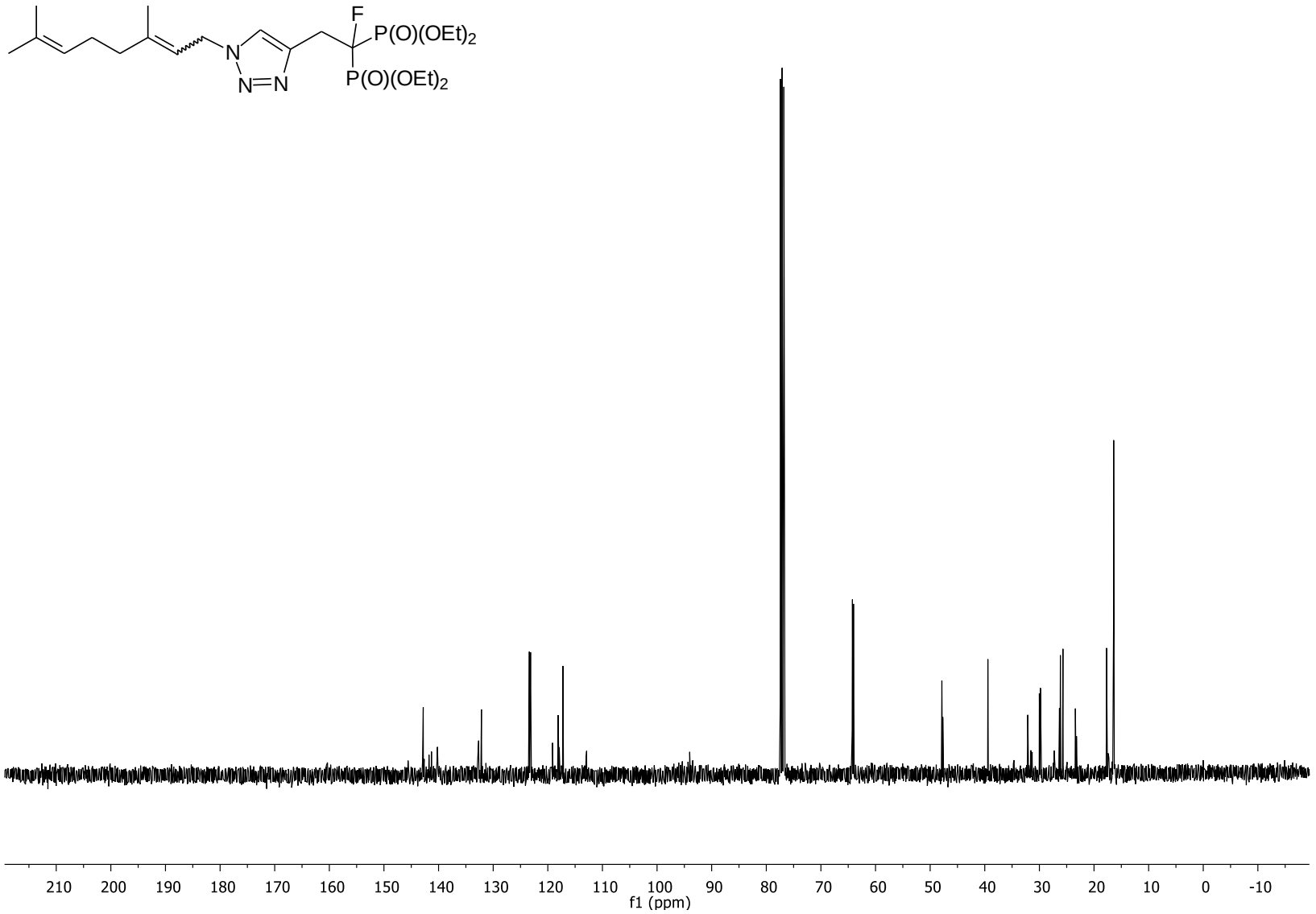
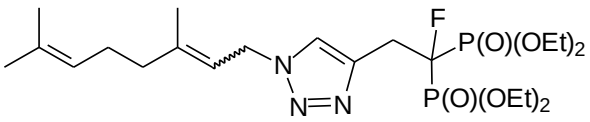


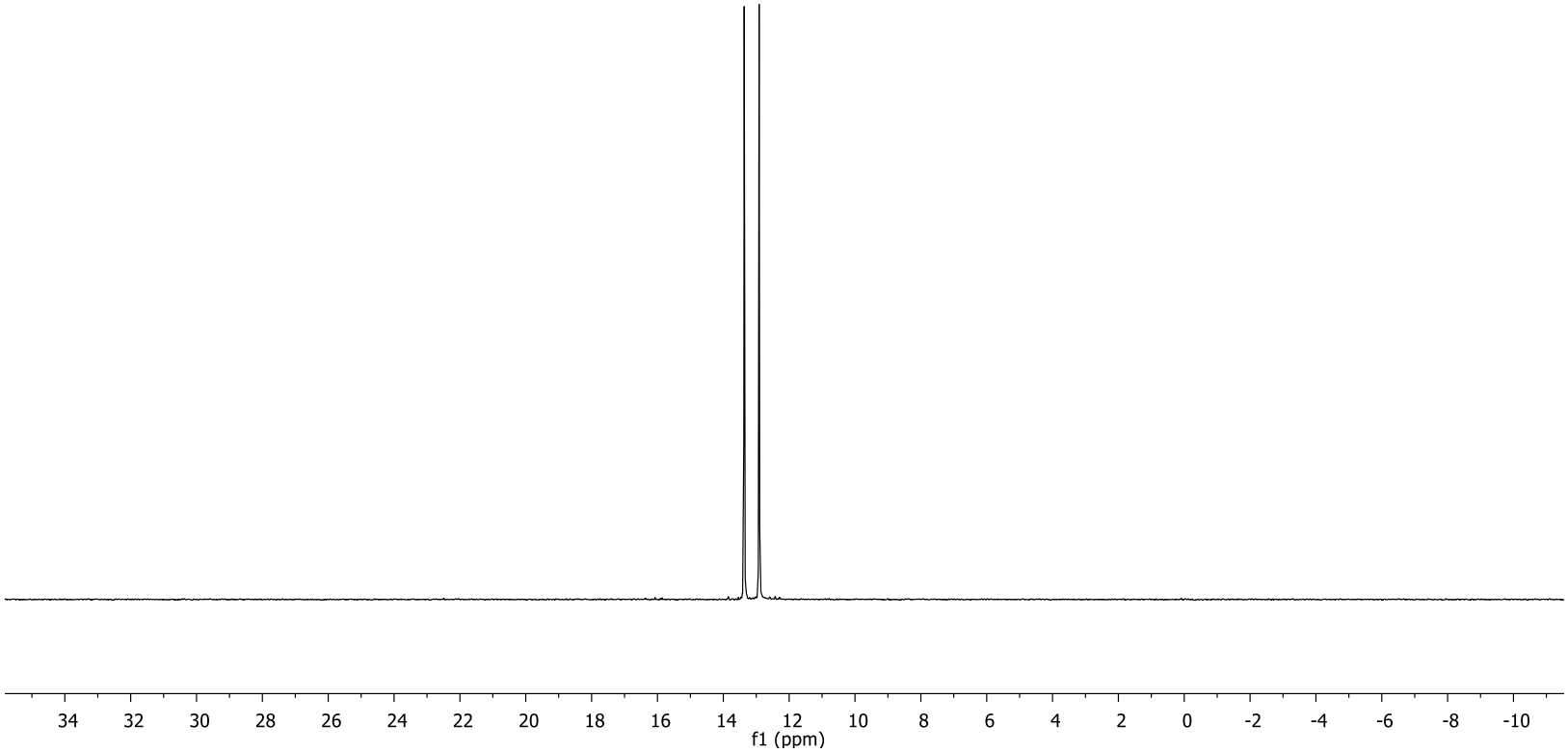


^{1}H NMR Spectrum of Compound **6** ($CDCl_3$, 400 MHz)

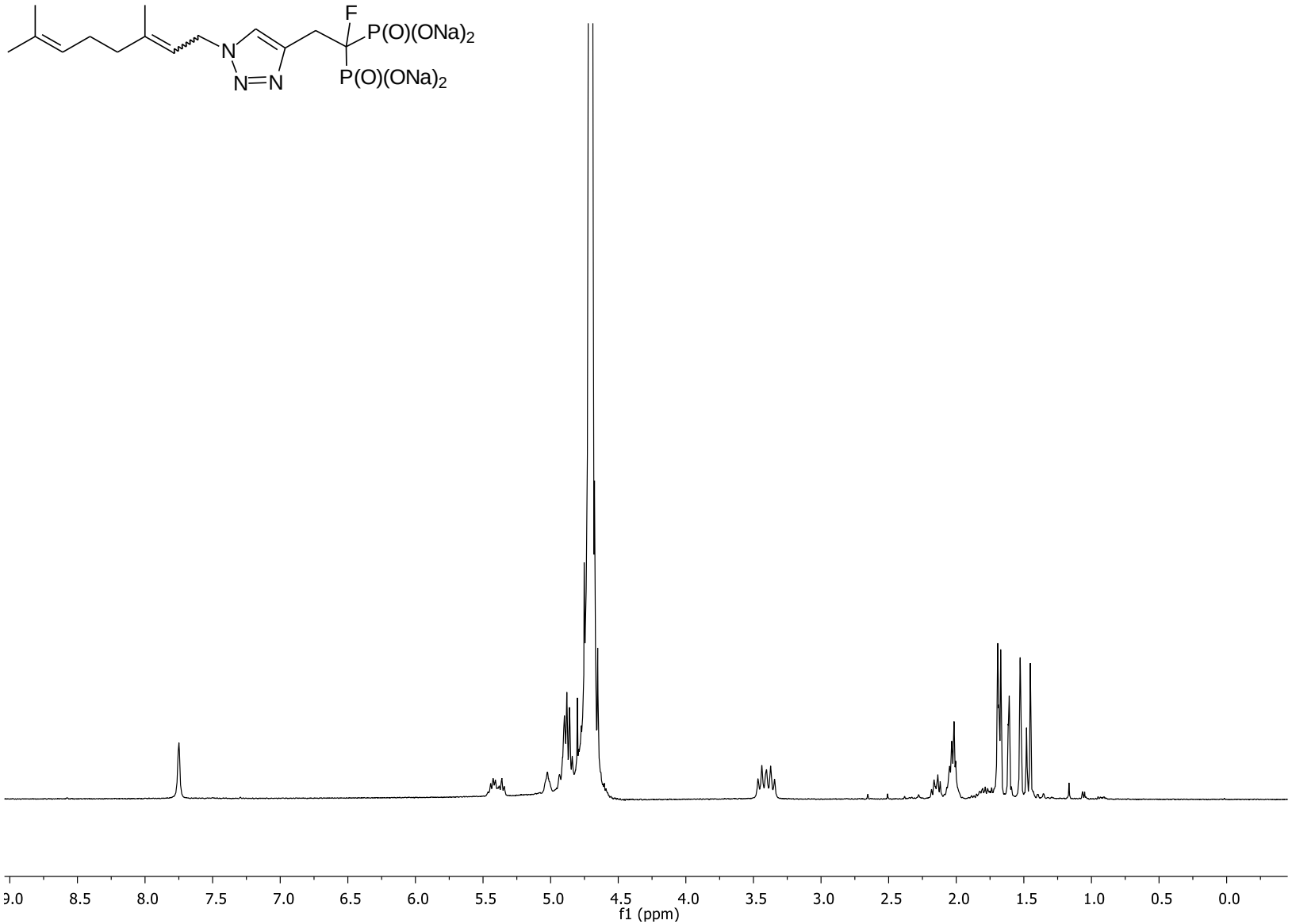


^{13}C NMR Spectrum of Compound **6** ($CDCl_3$, 100 MHz)

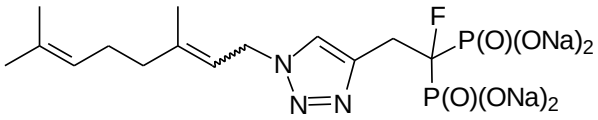


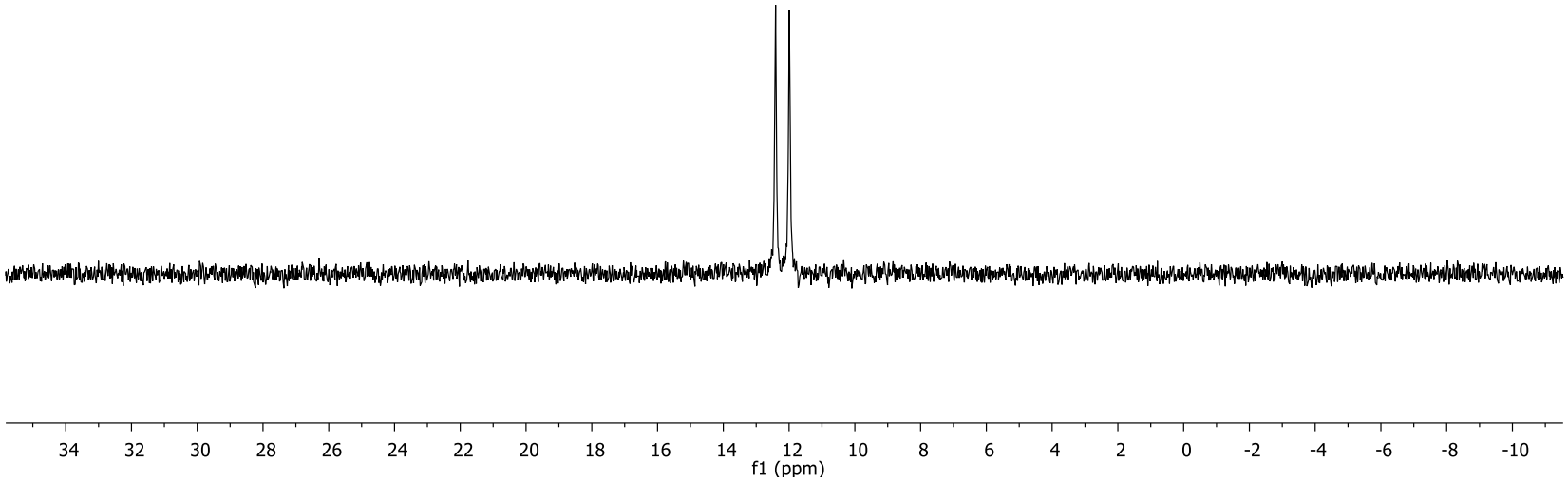


^{31}P NMR Spectrum of Compound **6** ($CDCl_3$, 162 MHz)

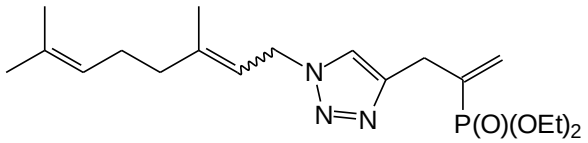


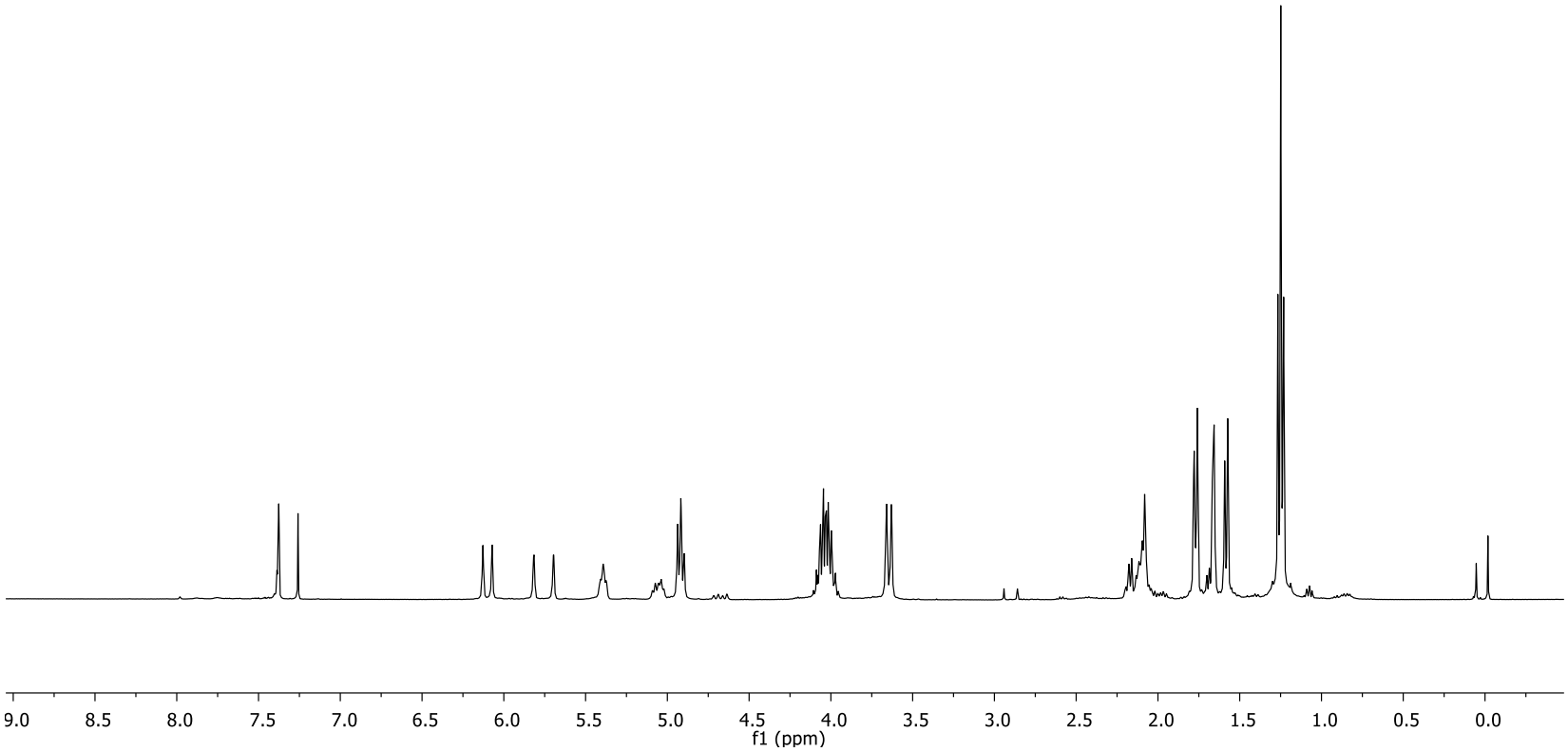
^{1}H NMR Spectrum of Compound **7** (D_2O, 400 MHz)



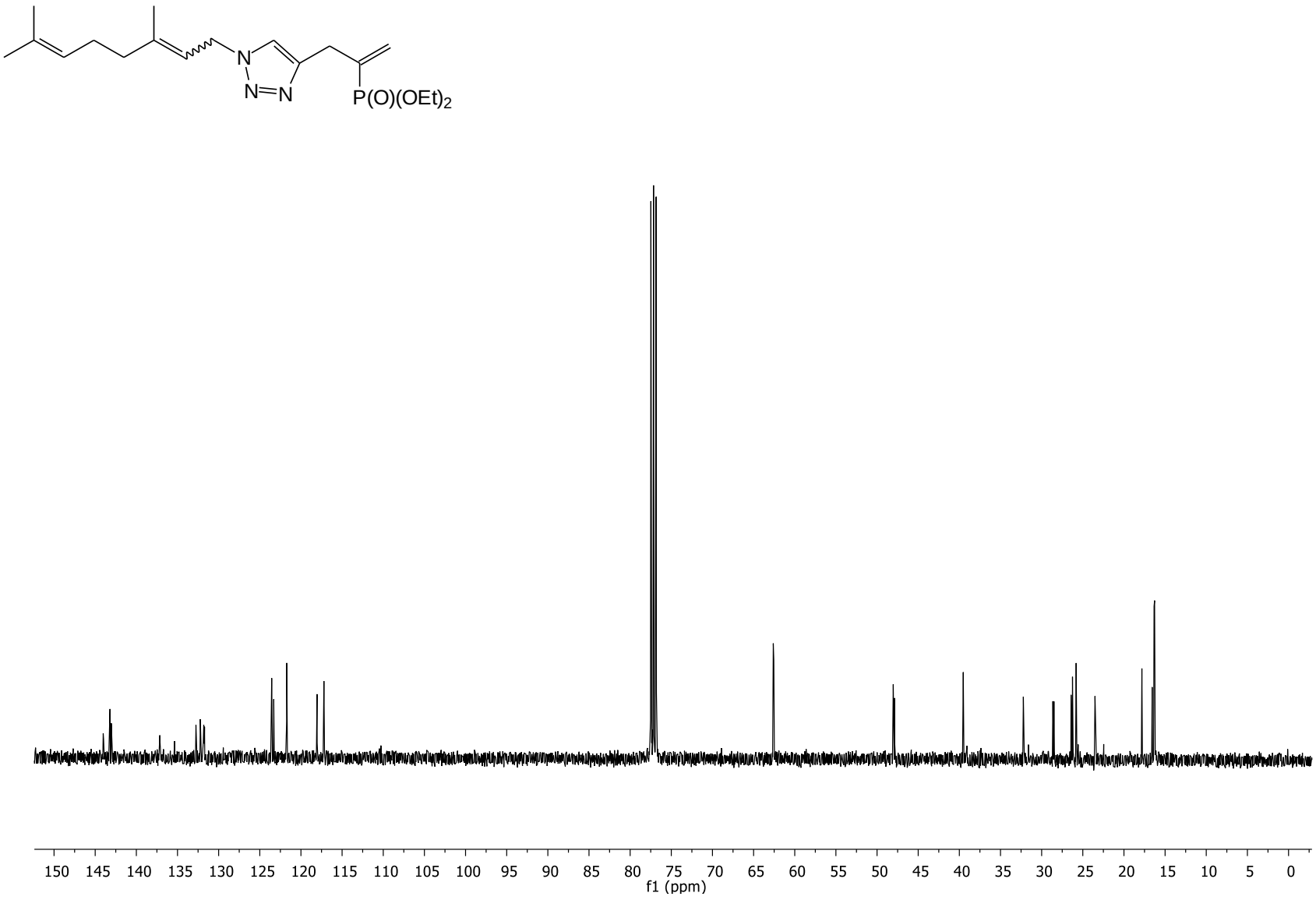


^{31}P NMR Spectrum of Compound **7** (D_2O, 400 MHz)

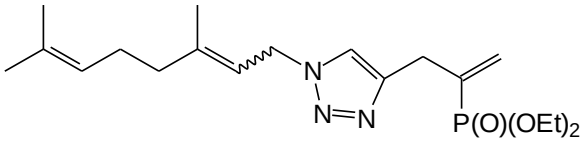


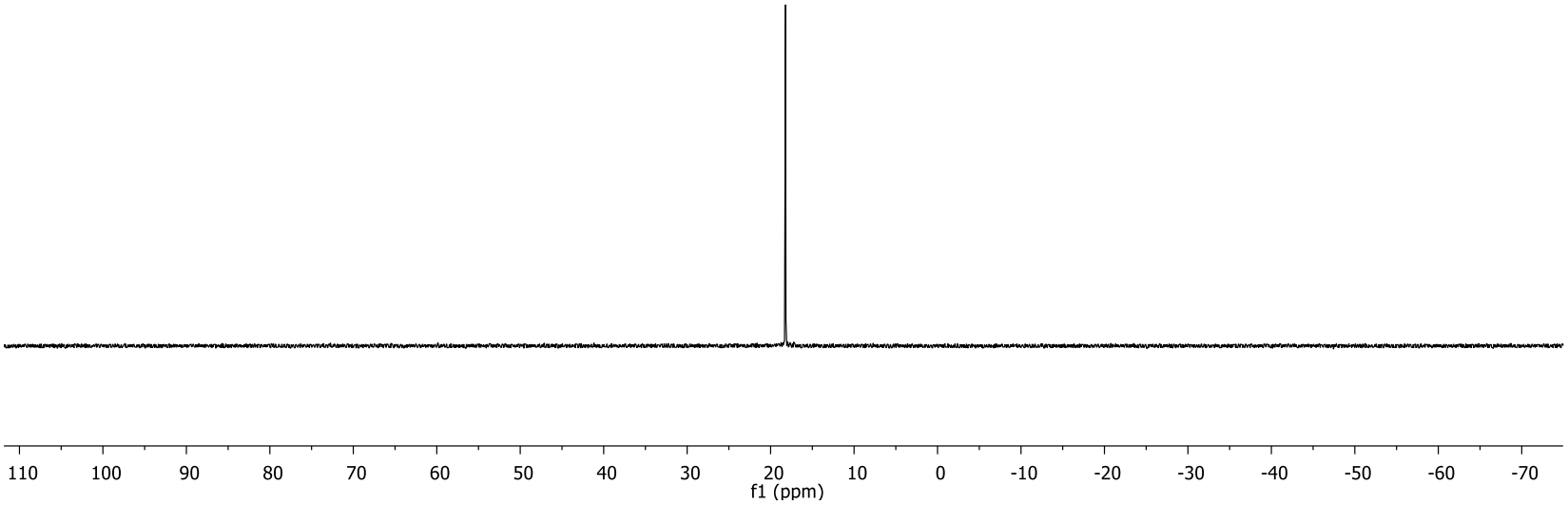


^{1}H NMR Spectrum of Compound **10** ($CDCl_3$, 400 MHz)



^{13}C NMR Spectrum of Compound **10** ($CDCl_3$, 100 MHz)





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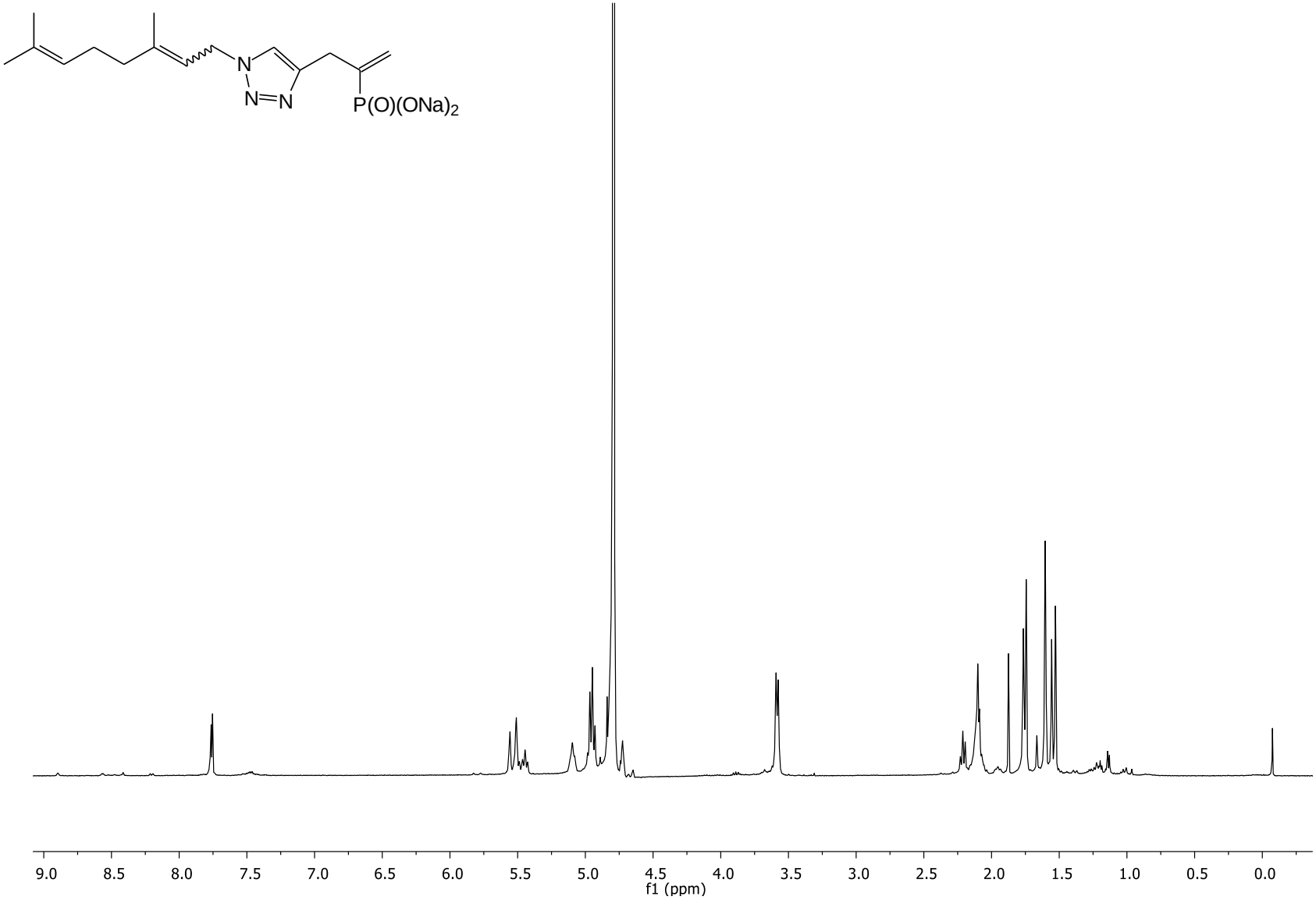
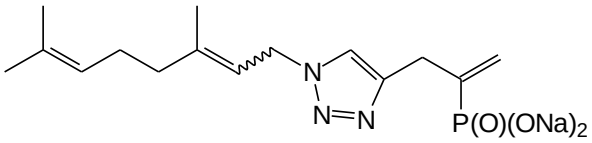
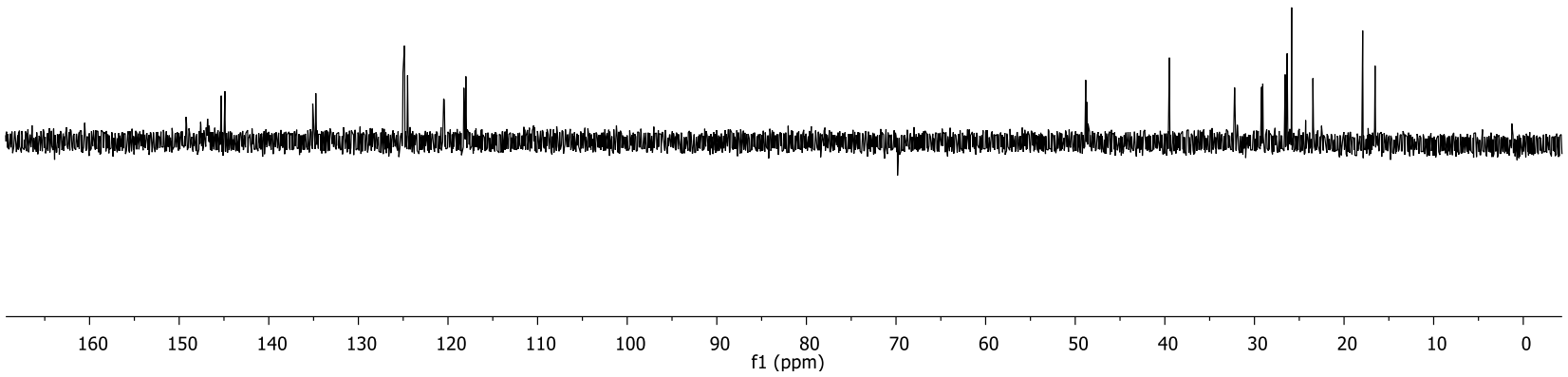
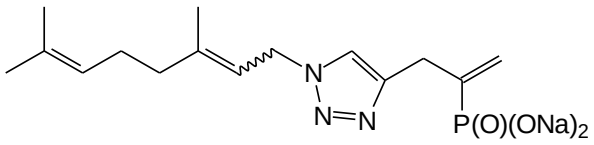


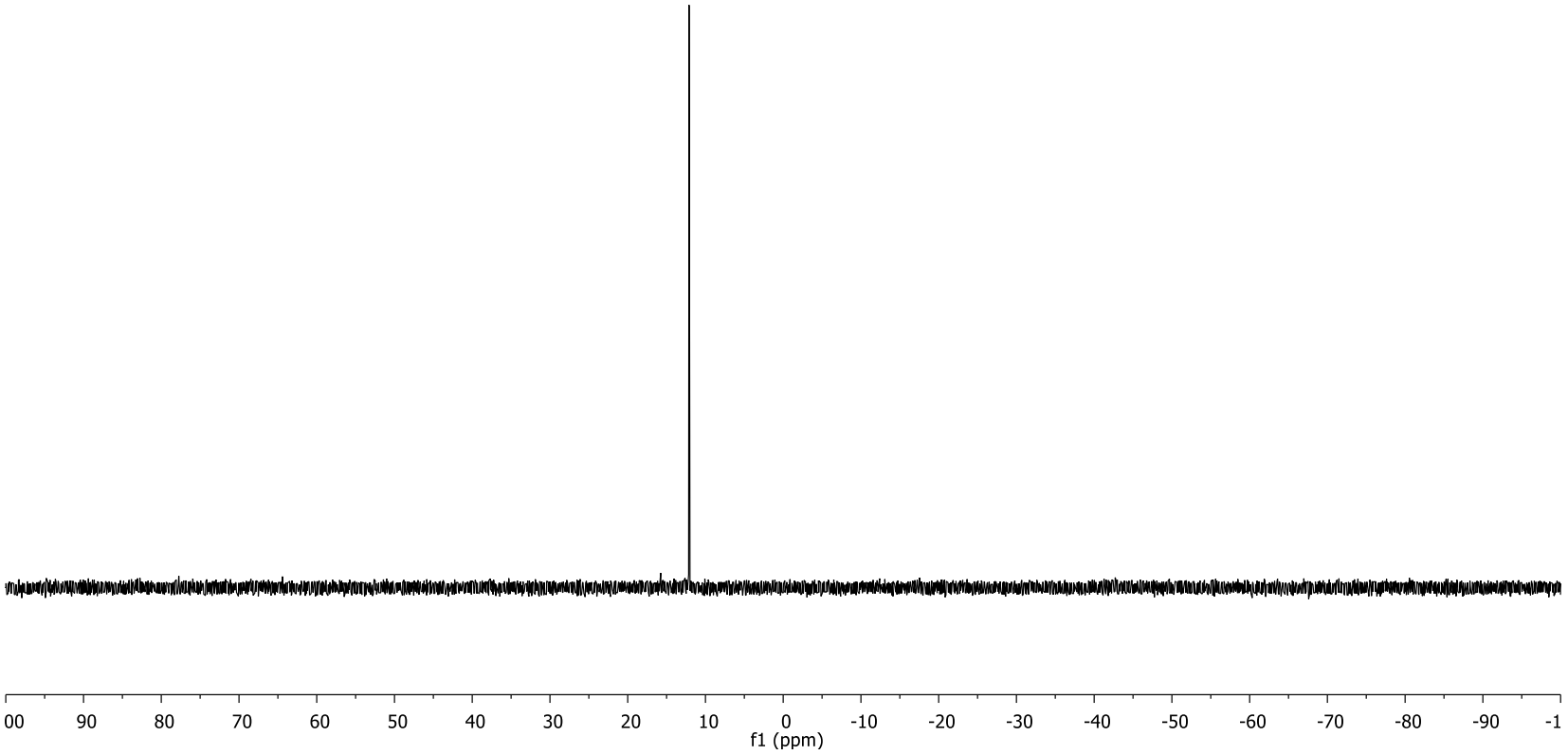
^{1}H NMR Spectrum of Compound **11** (D_2O, 400 MHz)



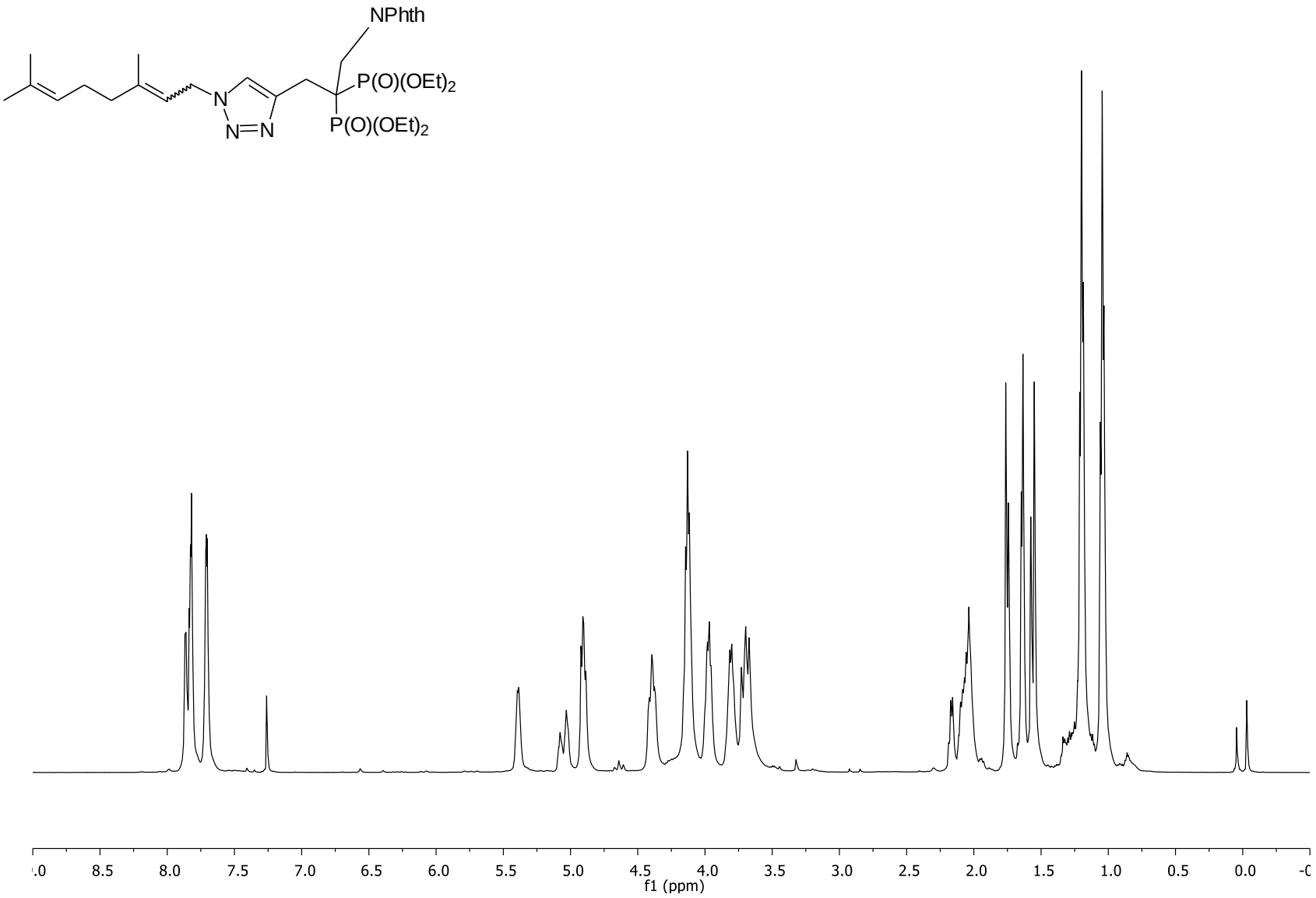


^{13}C NMR Spectrum of Compound **11** (D_2O, 100 MHz)

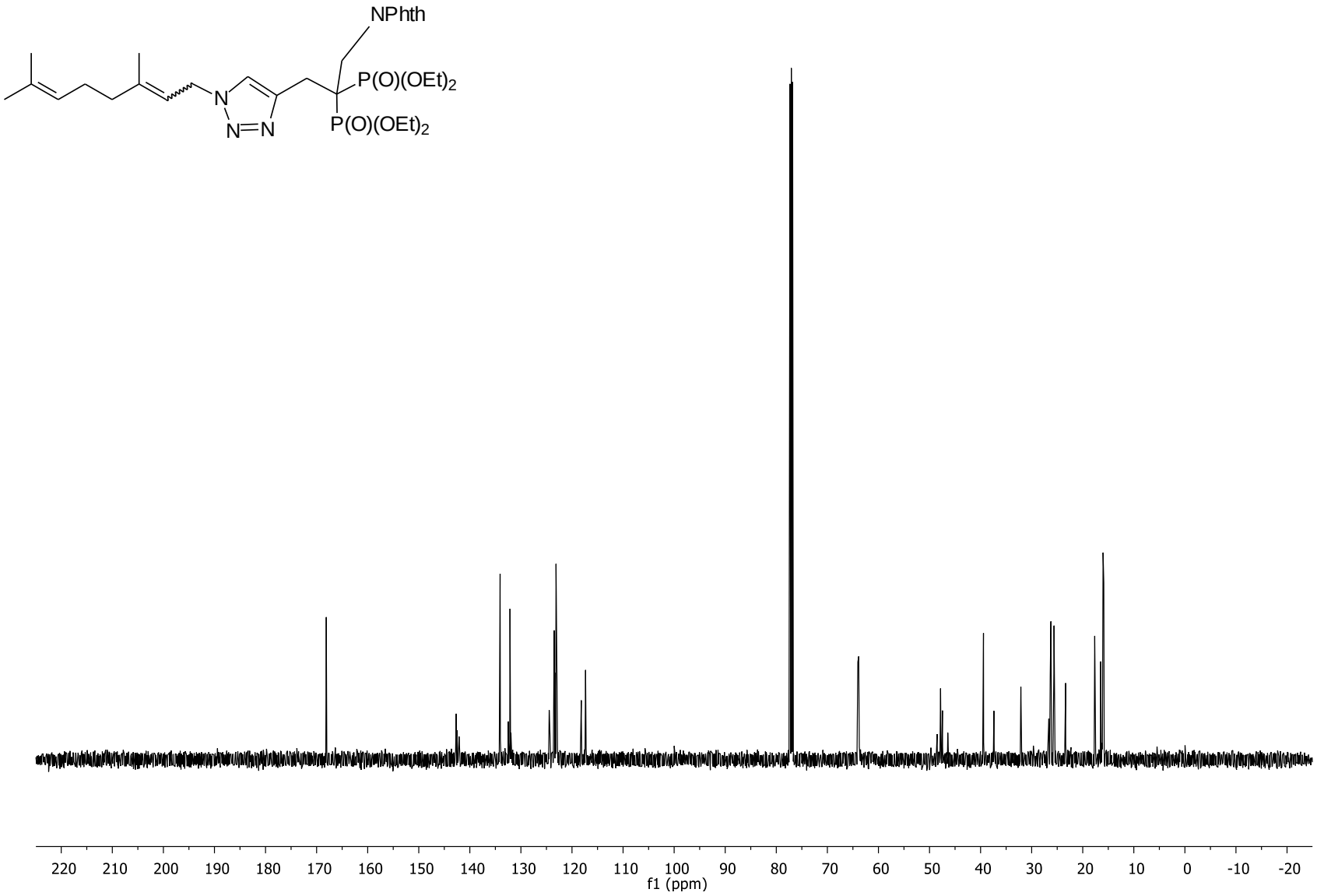




^{31}P NMR Spectrum of Compound **11** (D_2O, 162 MHz)



^{1}H NMR Spectrum of Compound **9** ($CDCl_3$, 500 MHz)



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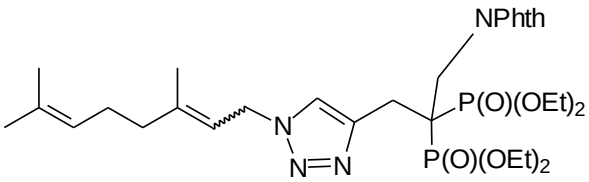

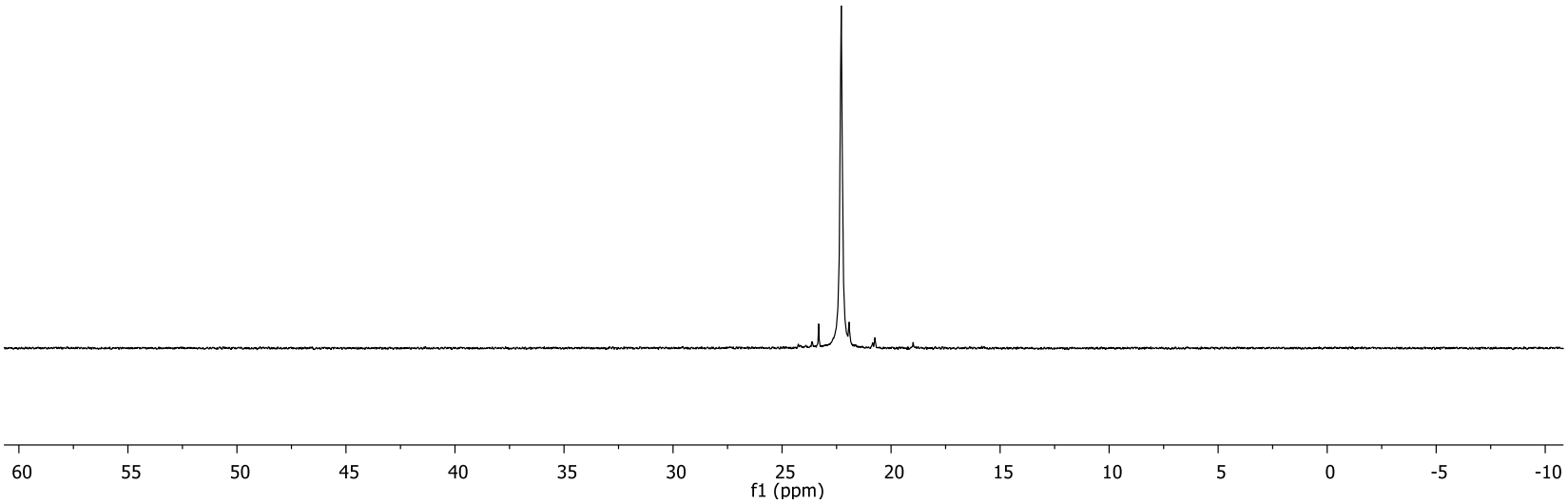

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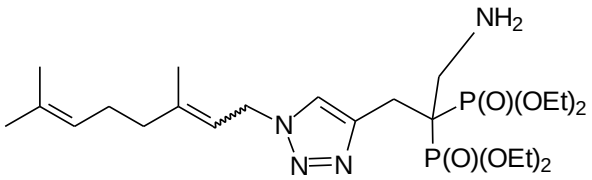
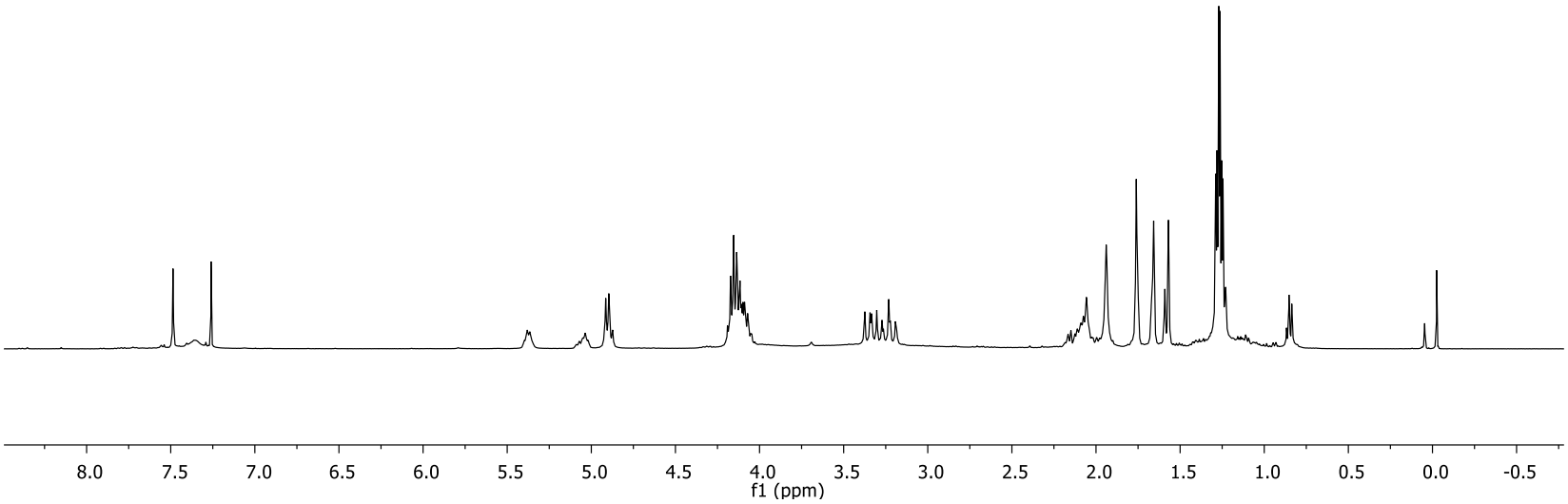
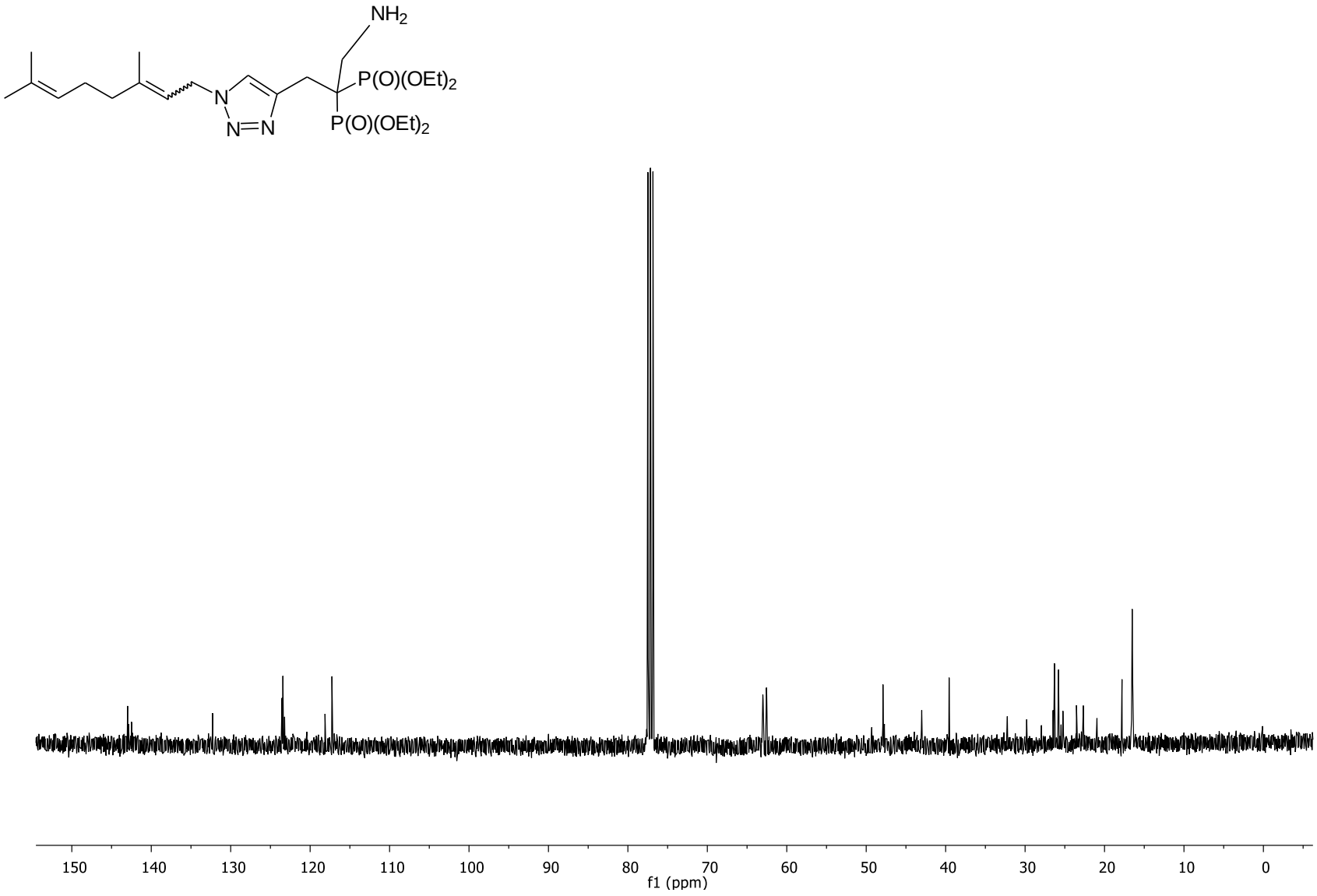
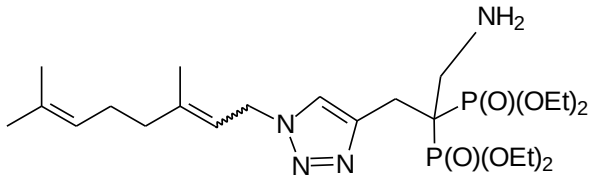


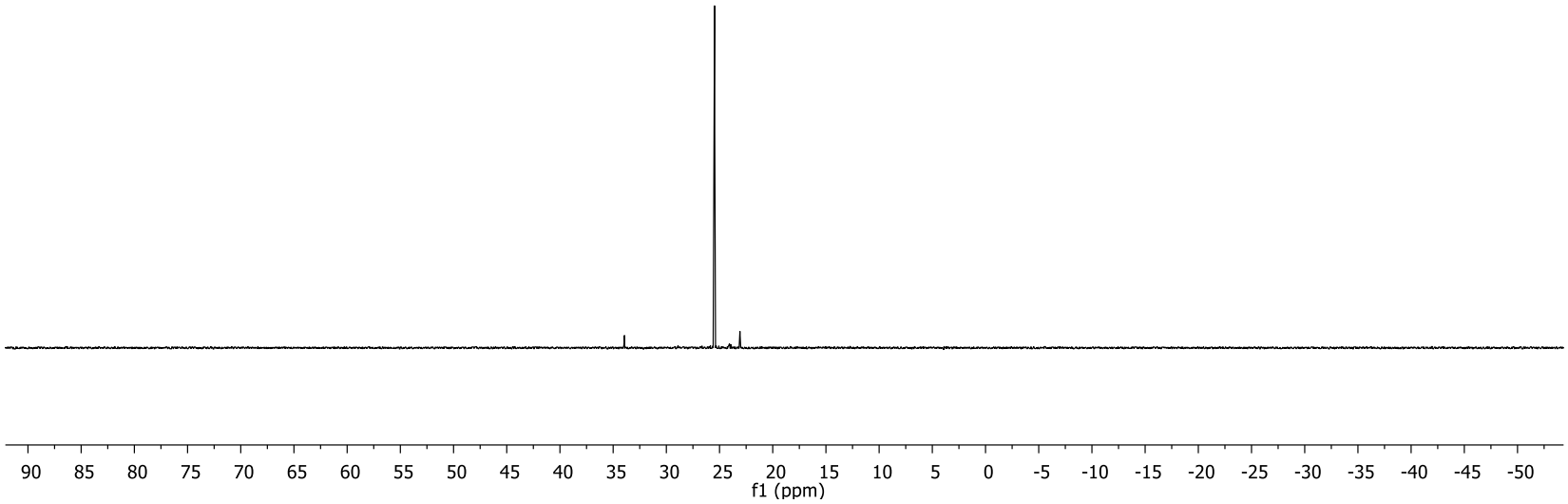


^{1}H NMR Spectrum of Compound **16** ($CDCl_3$, 400 MHz)

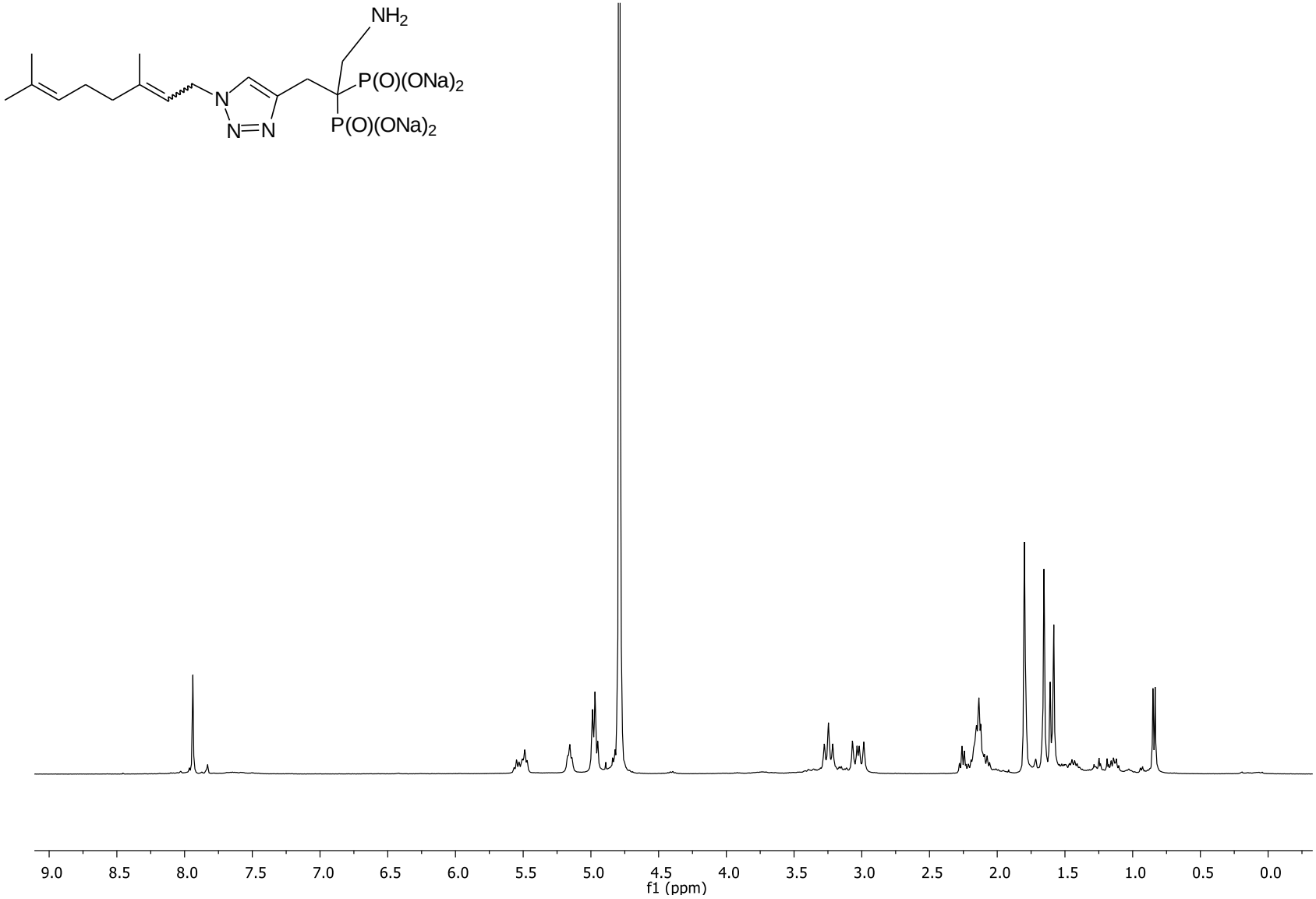


^{13}C NMR Spectrum of Compound **16** ($CDCl_3$, 100 MHz)

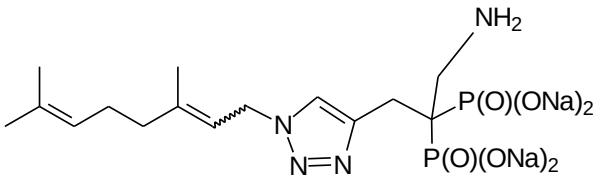


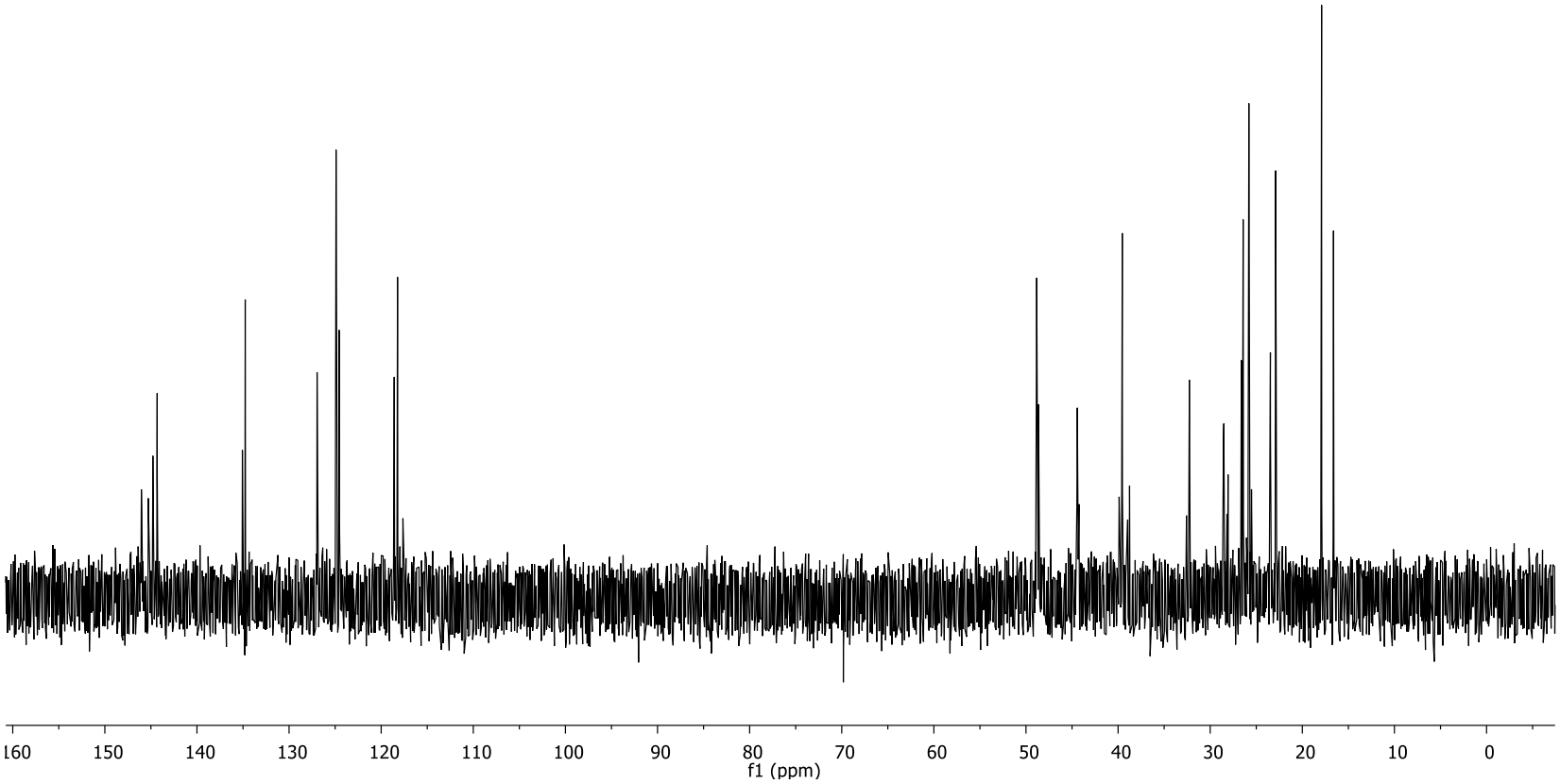


^{31}P NMR Spectrum of Compound **16** ($CDCl_3$,162 MHz)

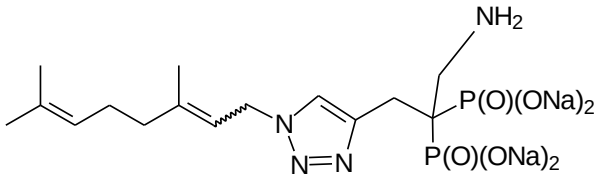


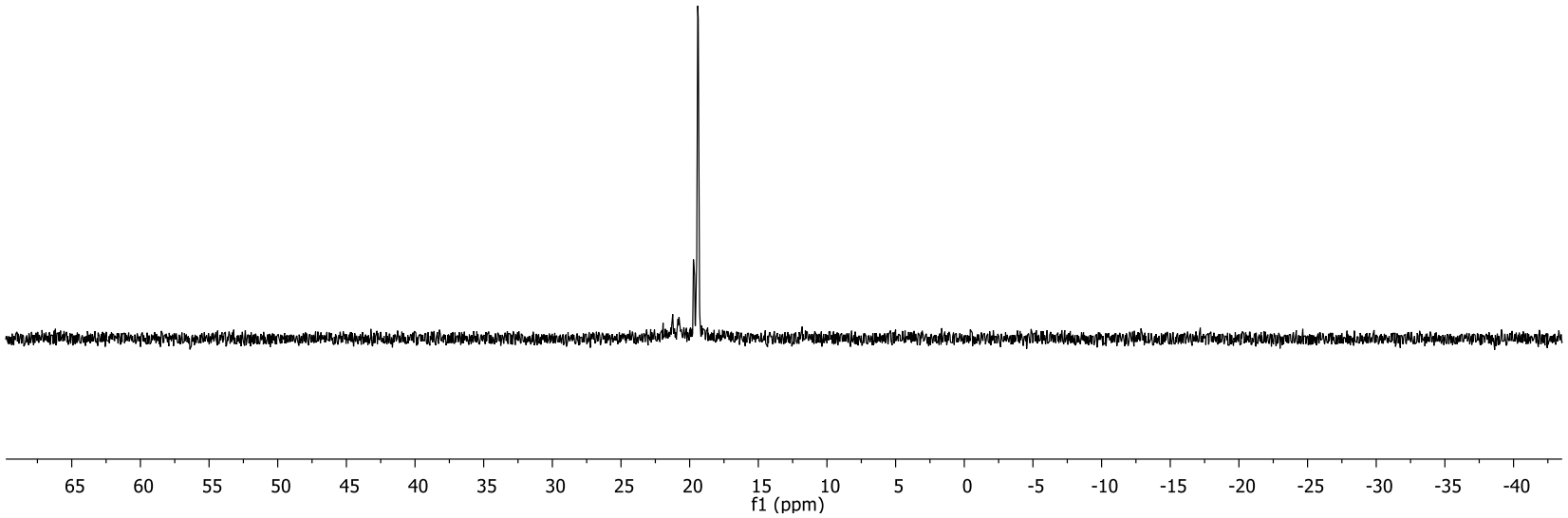
^{1}H NMR Spectrum of Compound **17** (D_2O, 400 MHz)



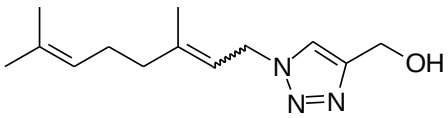


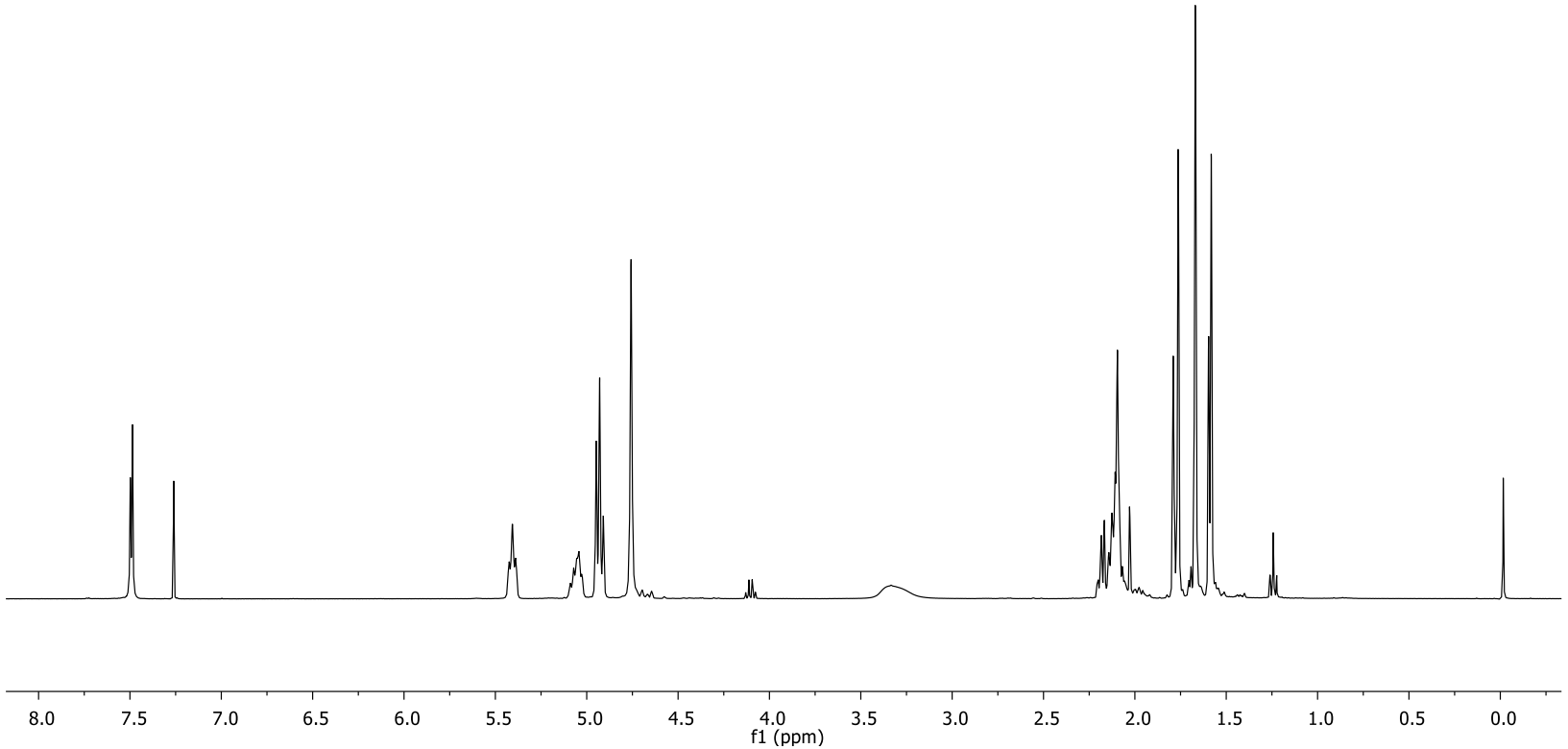
^{13}C NMR Spectrum of Compound **17** (D_2O, 100 MHz)



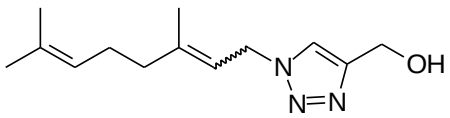


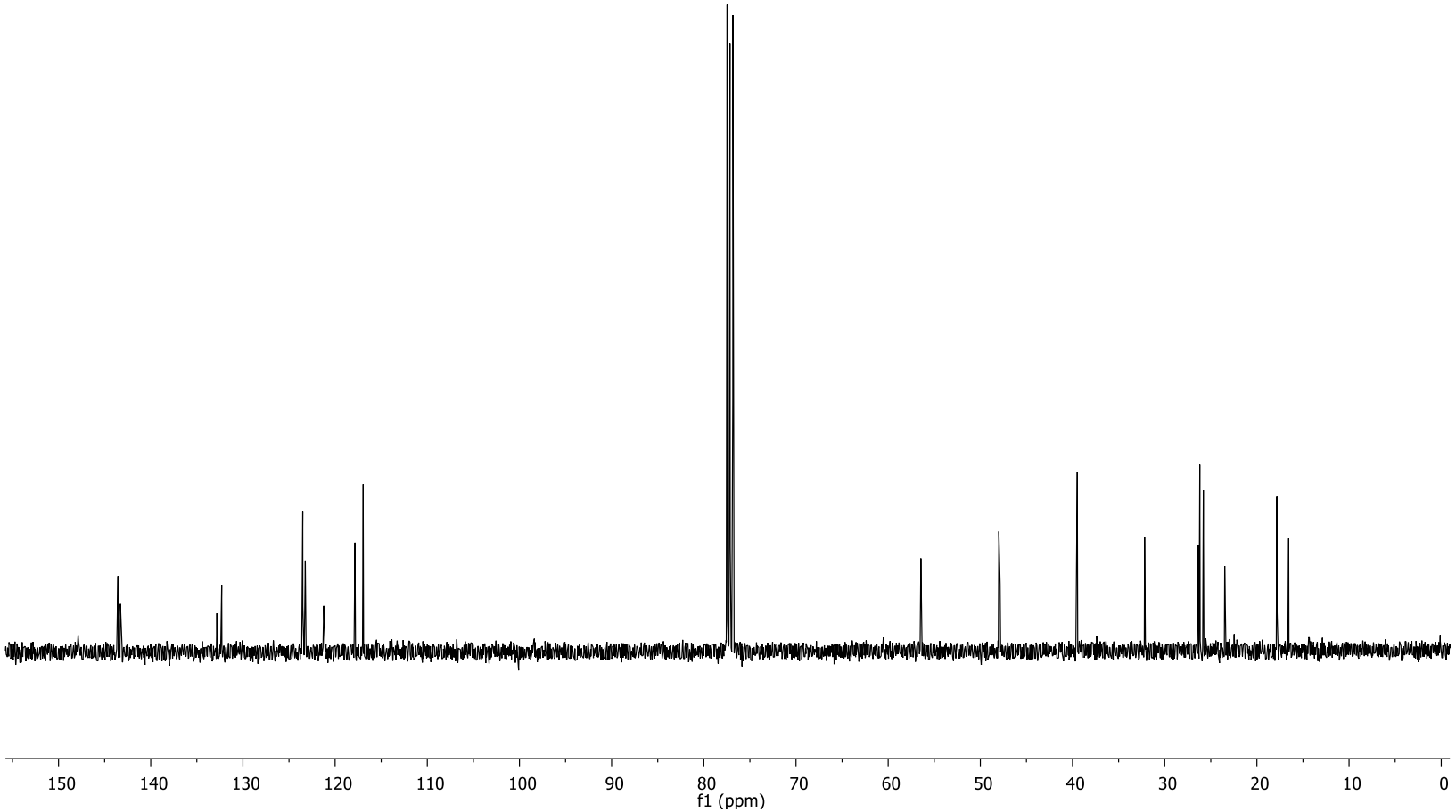
^{31}P NMR Spectrum of Compound **17** (D_2O, 162 MHz)





^{1}H NMR Spectrum of Compound **19** ($CDCl_3$, 400 MHz)





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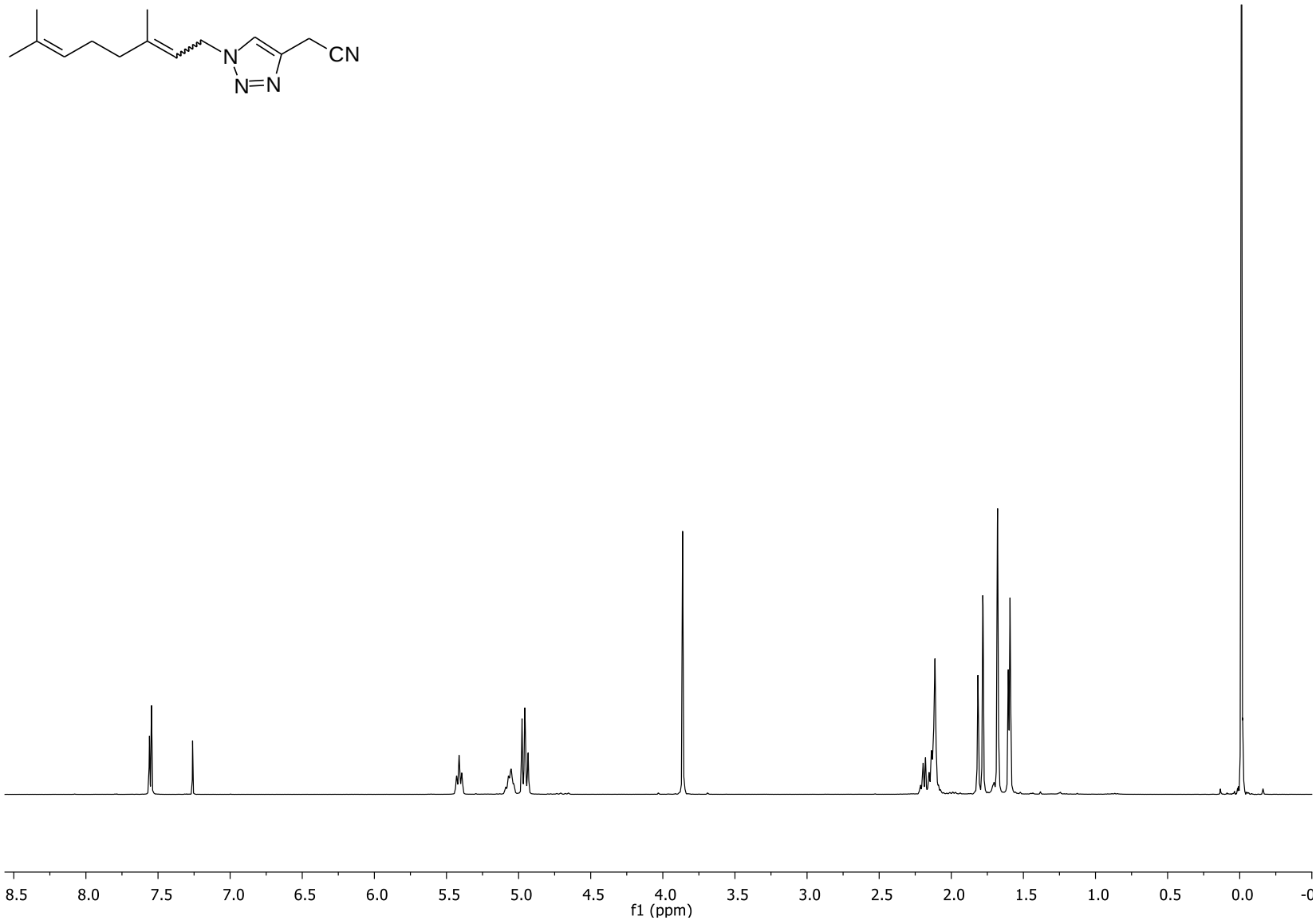

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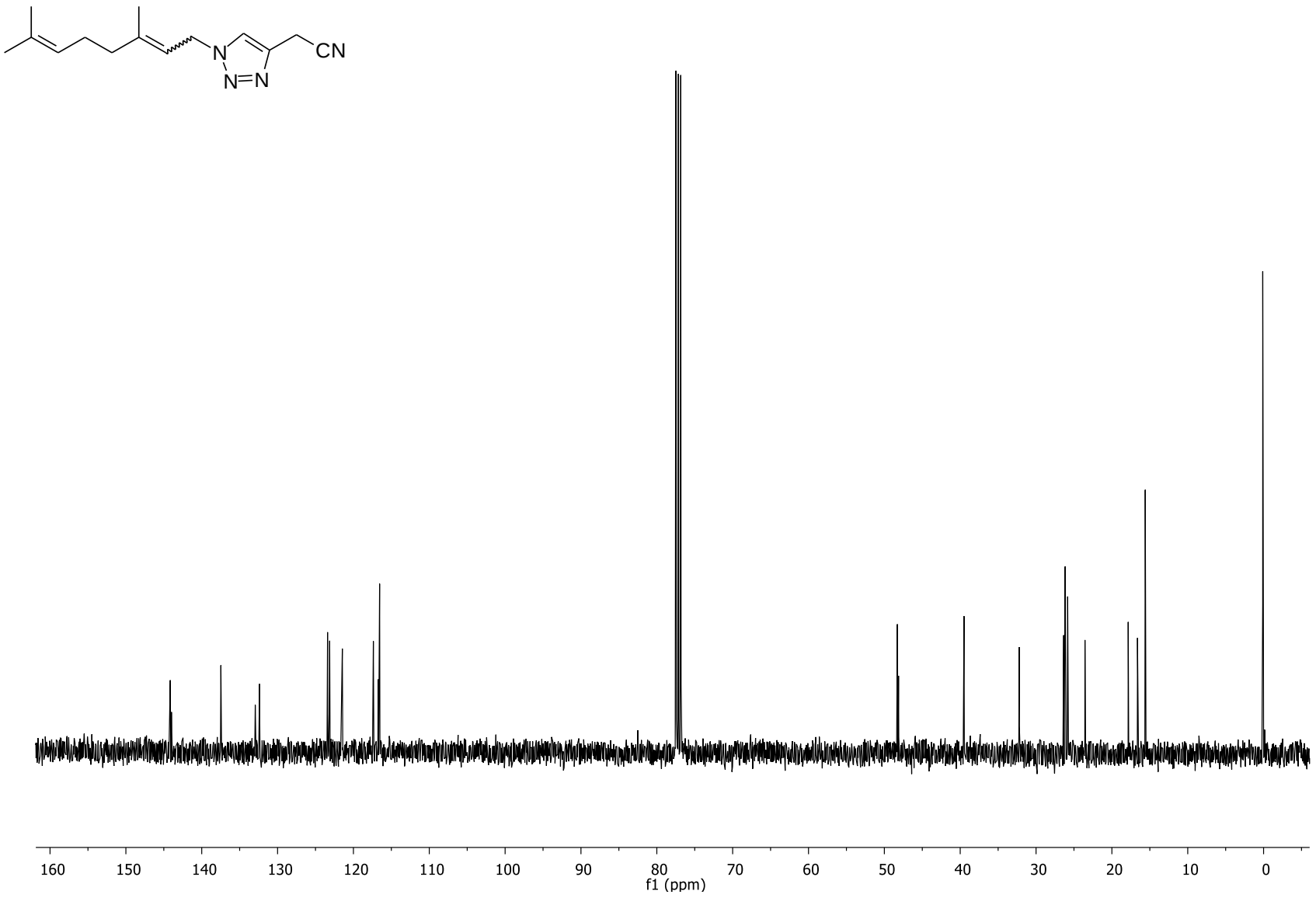
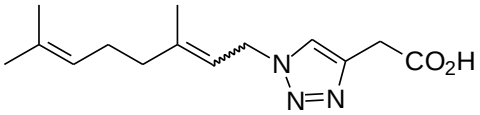
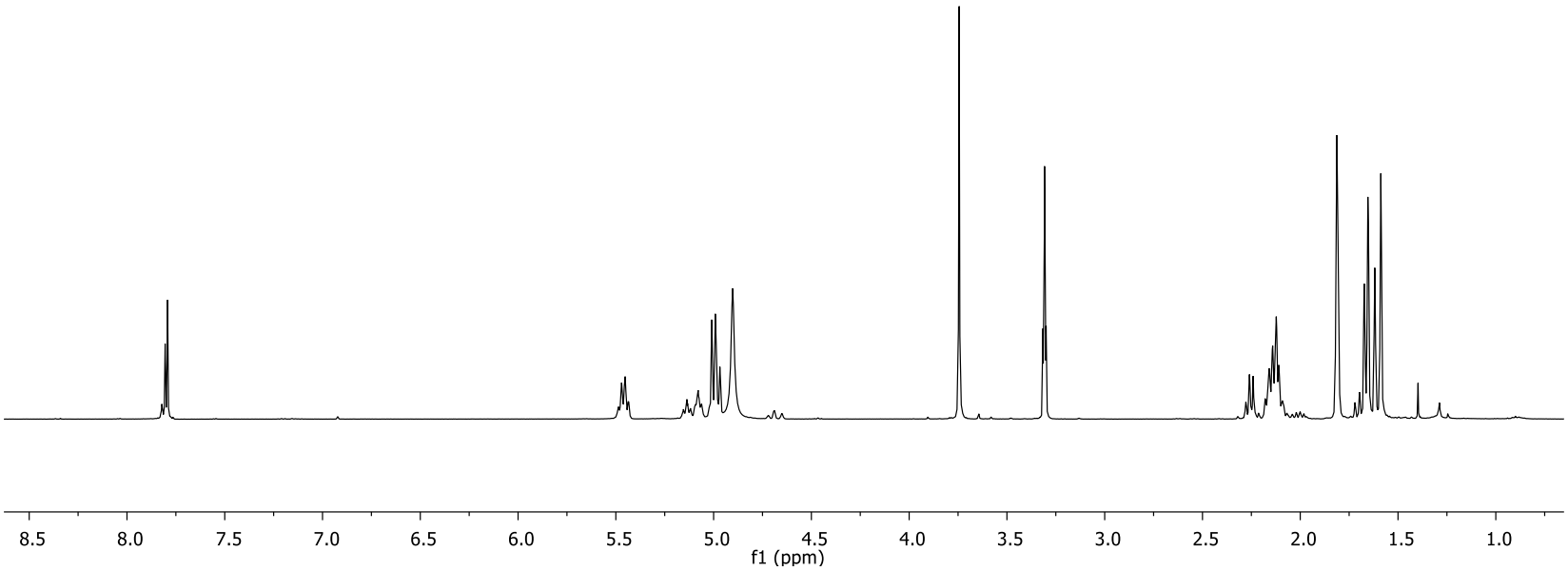
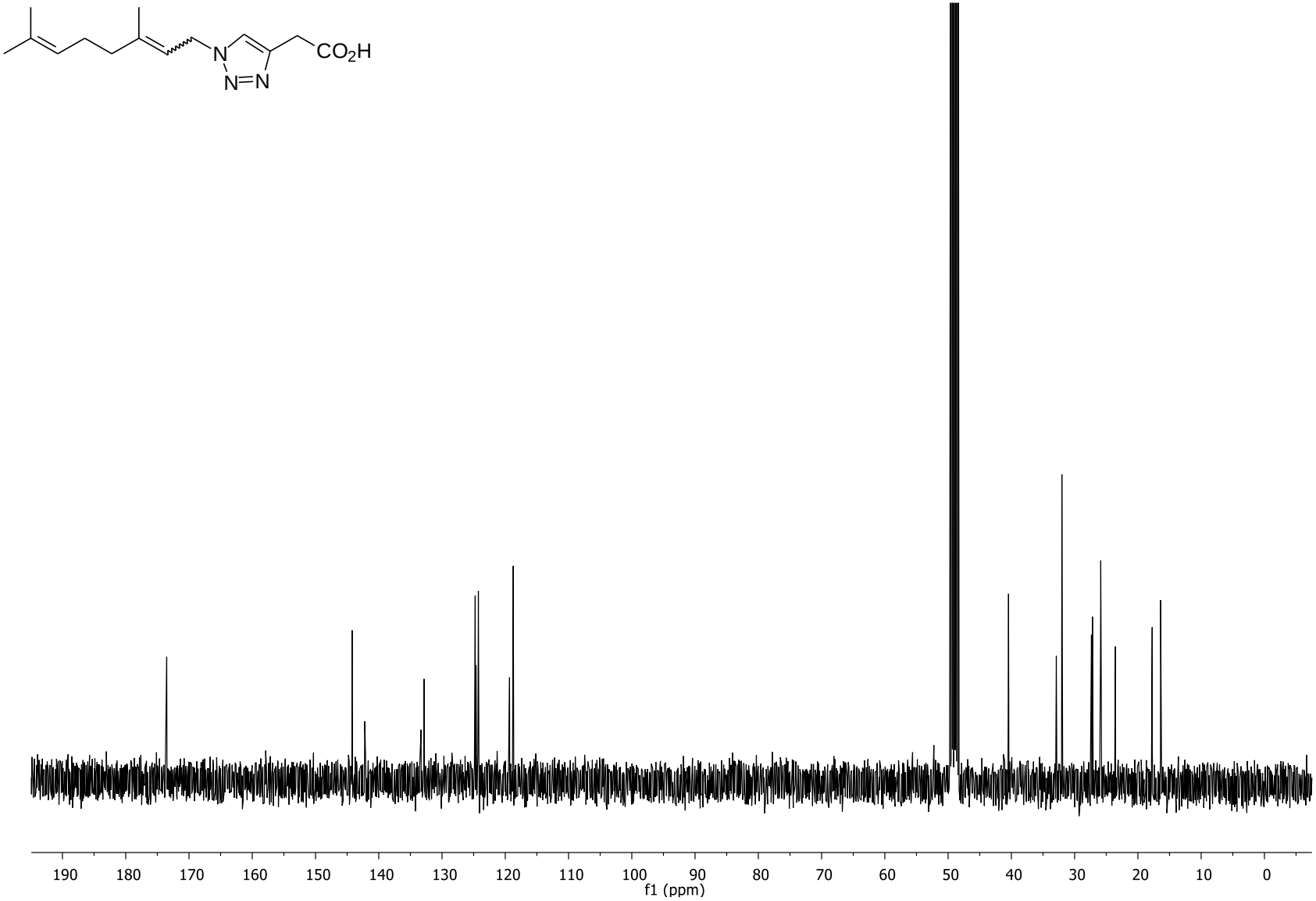


^{13}C NMR Spectrum of Compound **20** ($CDCl_3$, 100 MHz)

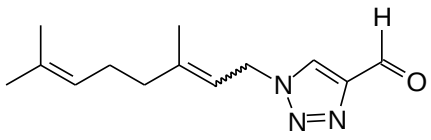


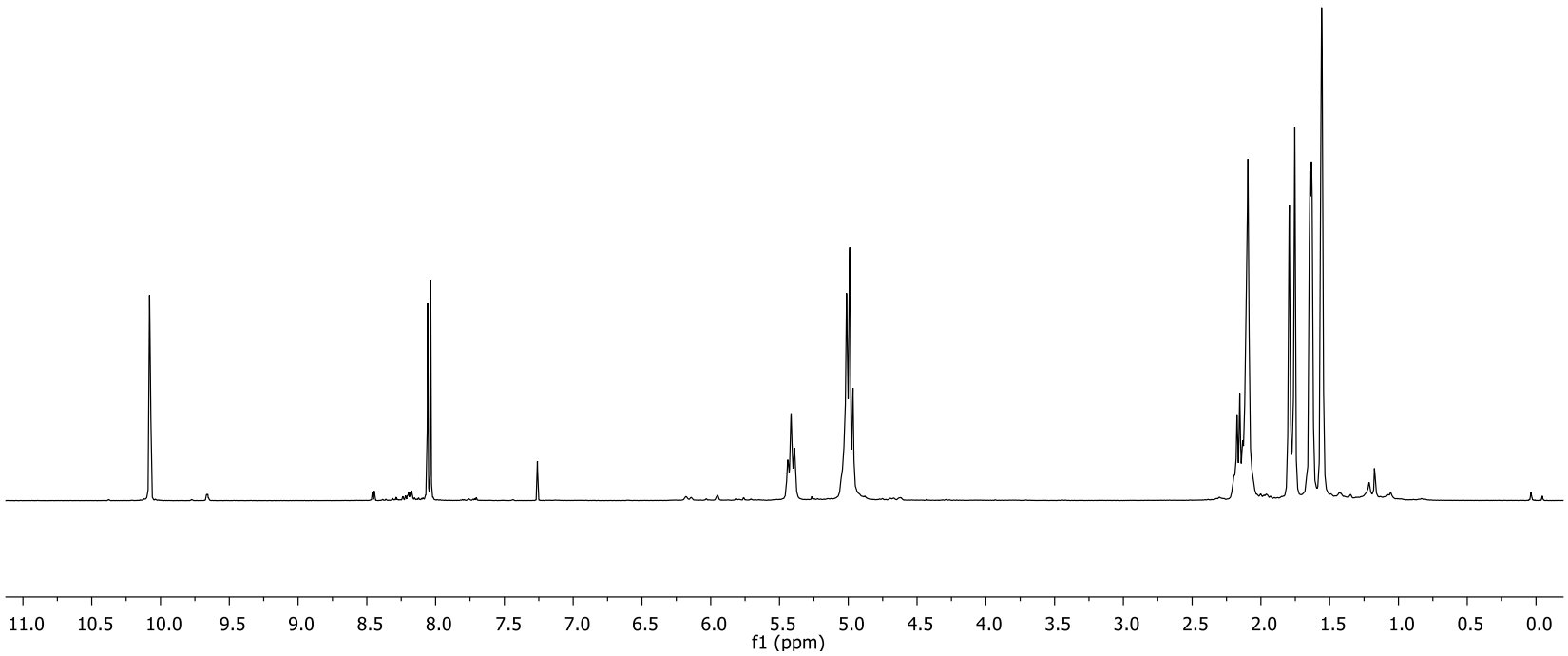


^{1}H NMR Spectrum of Compound **21** (MeOD, 400 MHz)

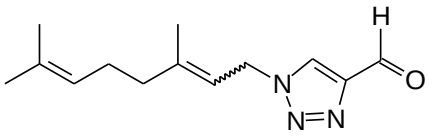


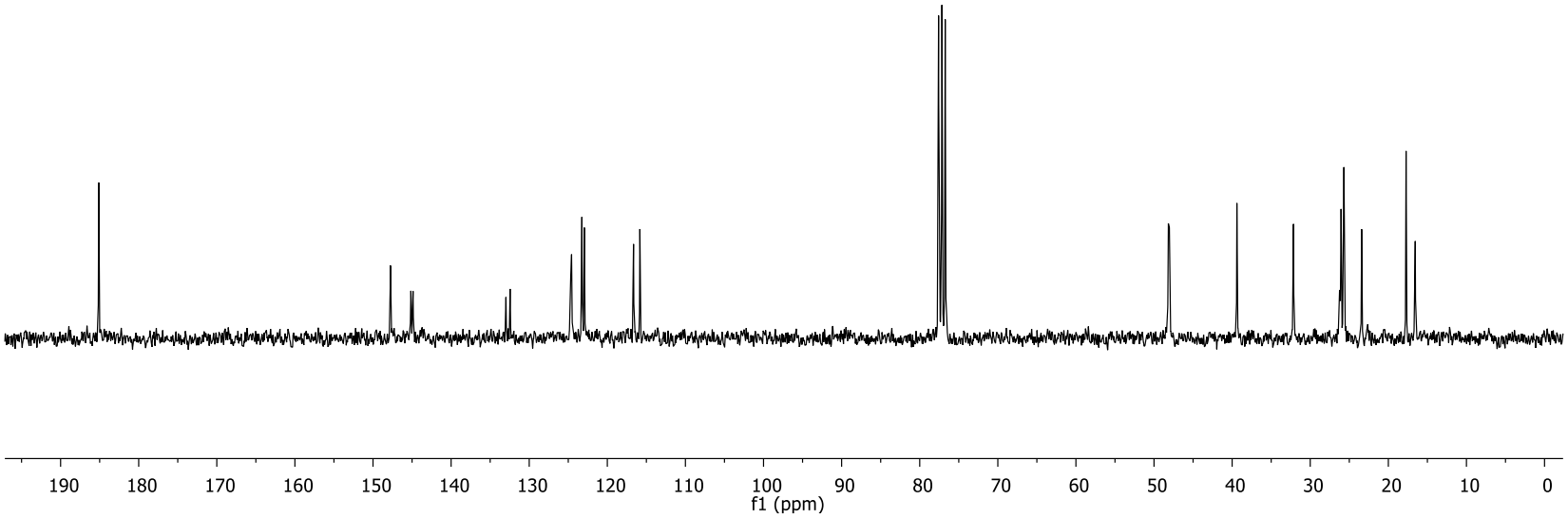
^{13}C NMR Spectrum of Compound **21** (MeOD, 100 MHz)



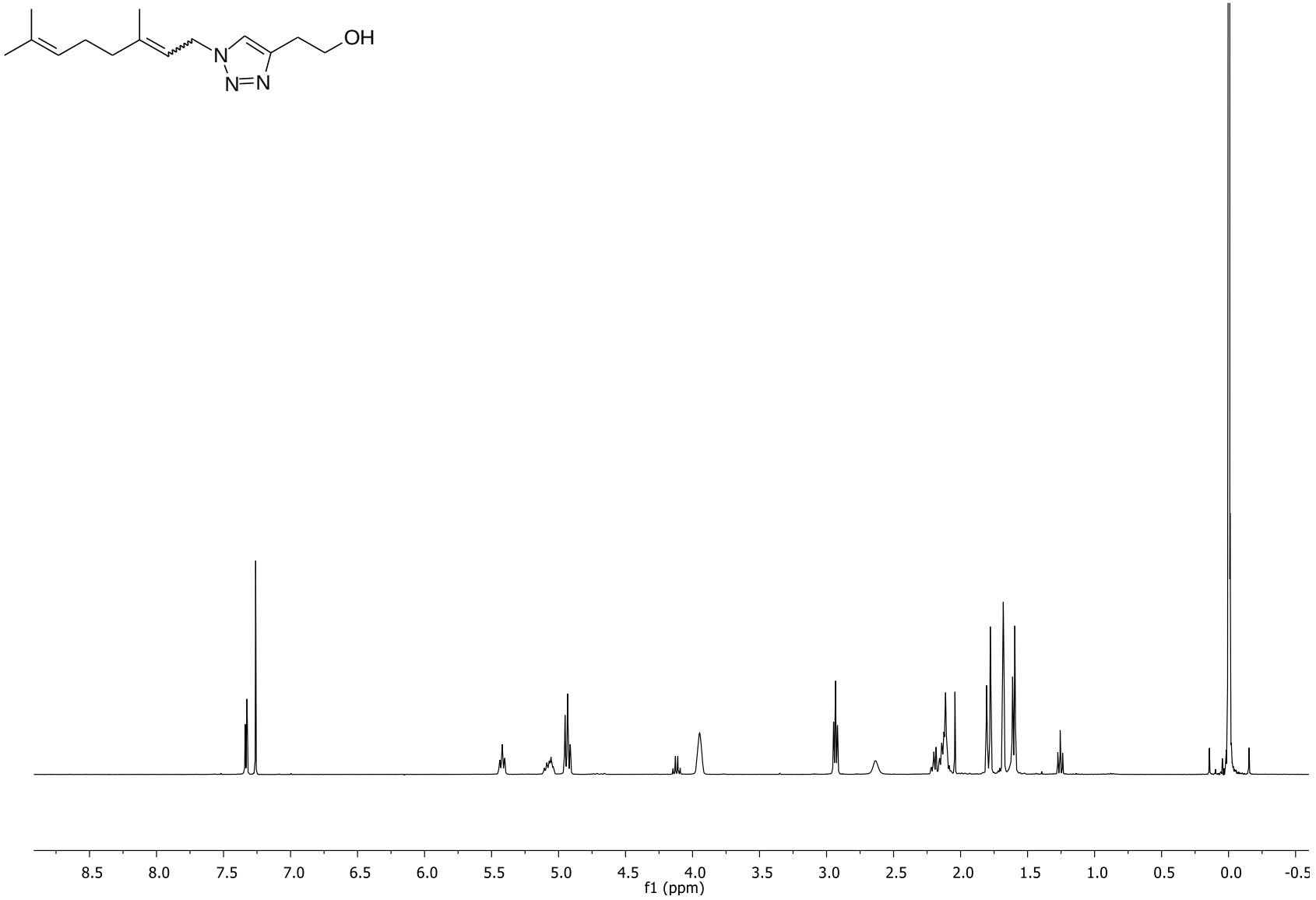


^{1}H NMR Spectrum of Compound **22** ($CDCl_3$, 400 MHz)

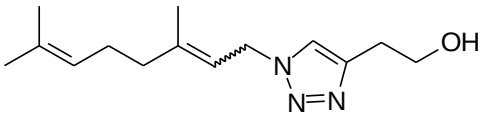


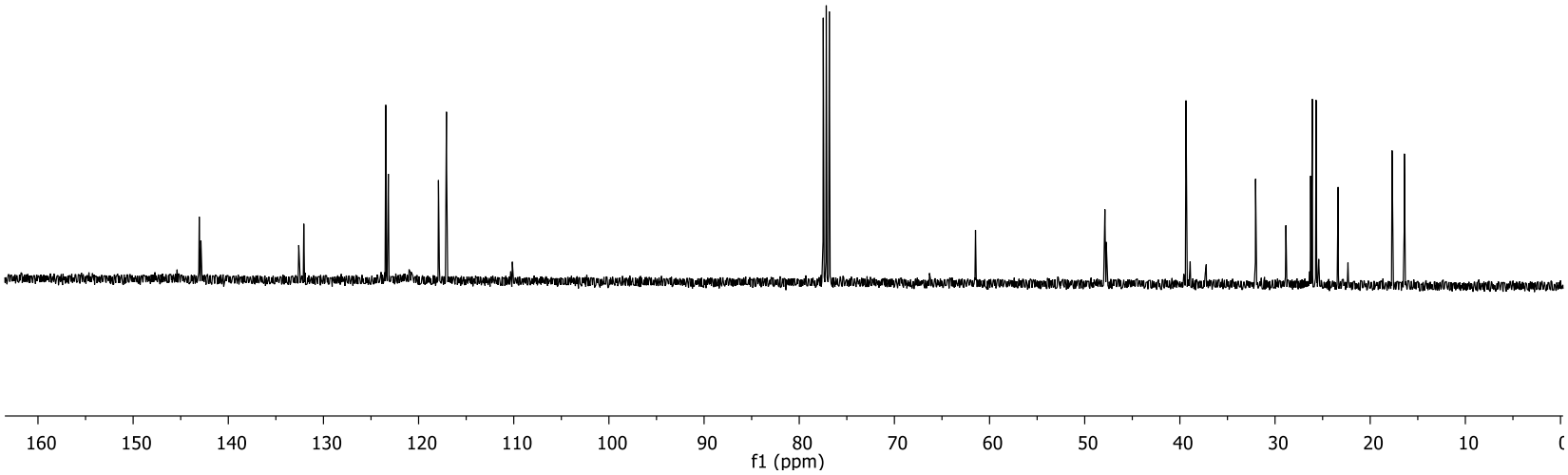


^{13}C NMR Spectrum of Compound **22** ($CDCl_3$, 75.5 MHz)

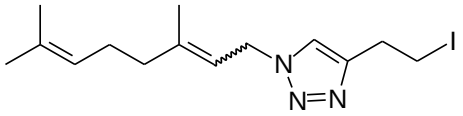


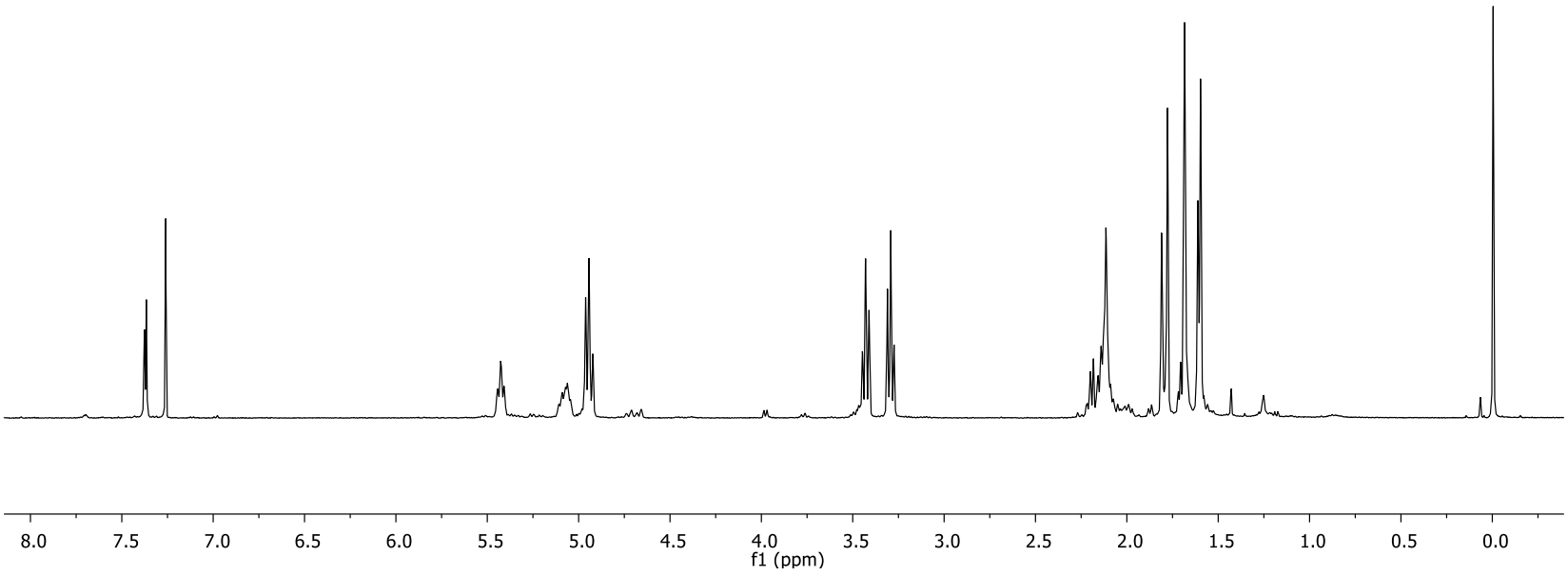
^{1}H NMR Spectrum of Compound **24** ($CDCl_3$, 400 MHz)



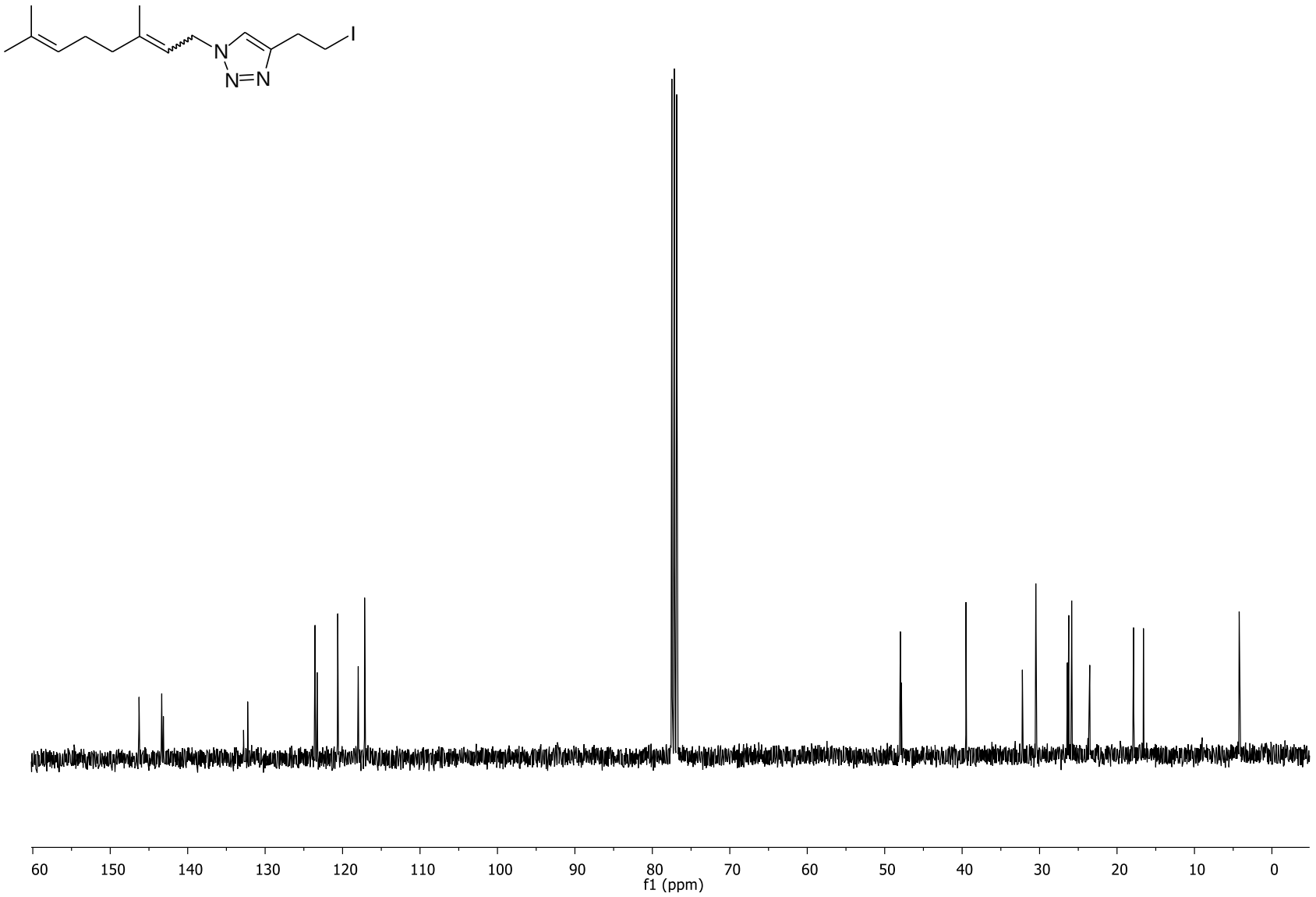


^{13}C NMR Spectrum of Compound **24** ($CDCl_3$, 100 MHz)

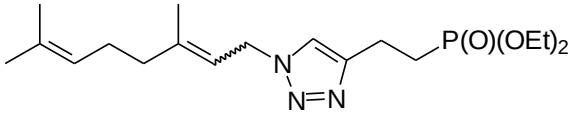


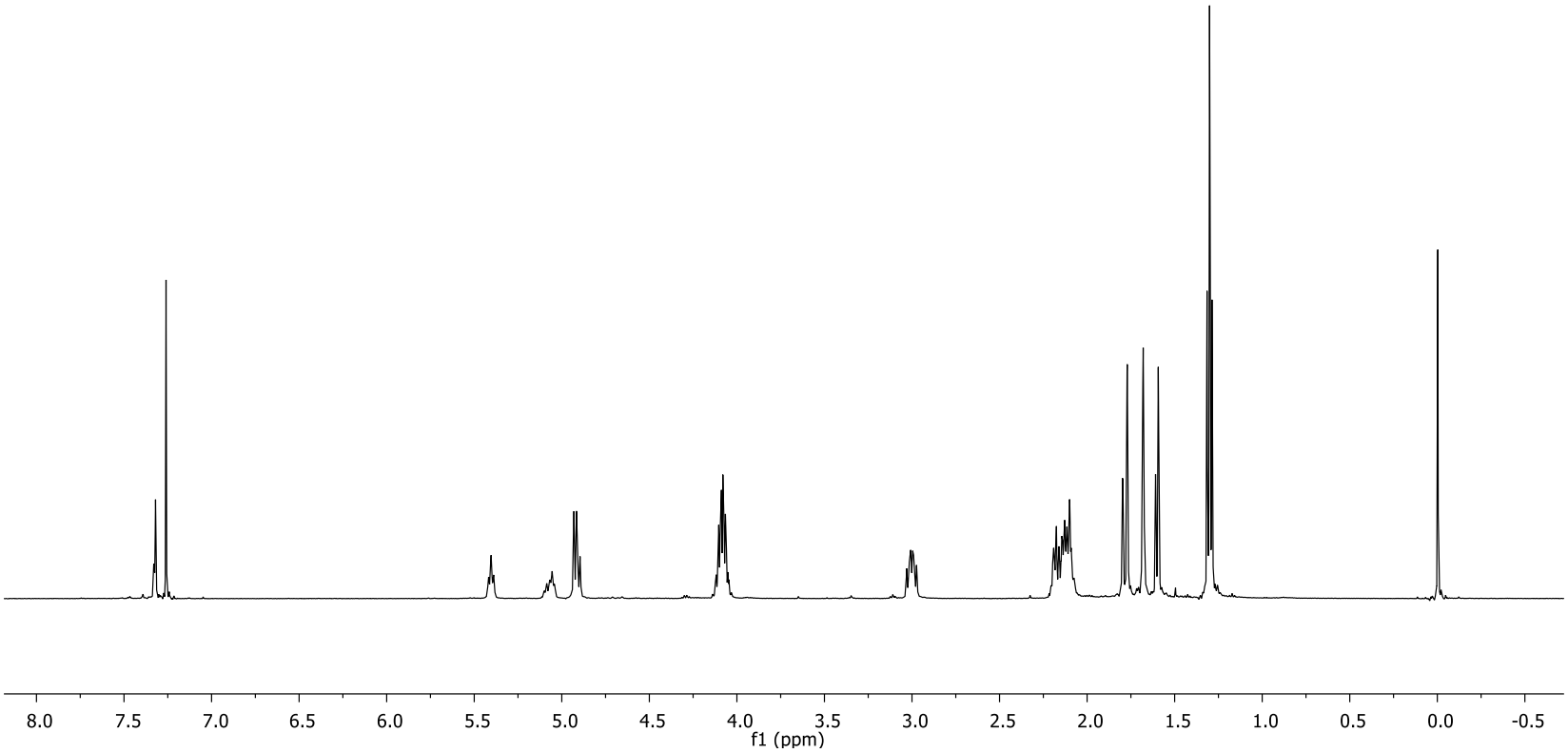


^{1}H NMR Spectrum of Compound **25** ($CDCl_3$, 400 MHz)

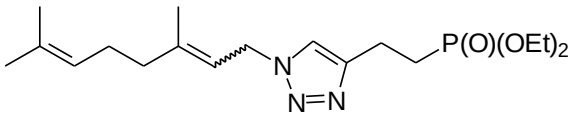


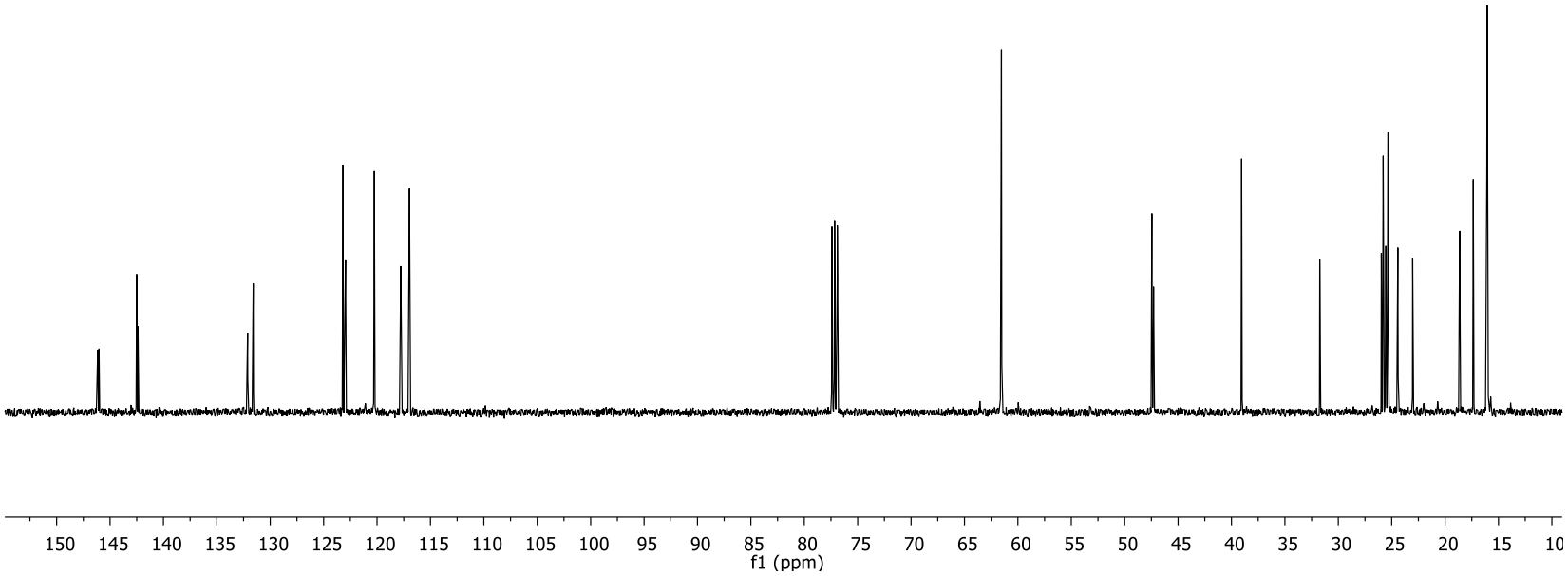
^{13}C NMR Spectrum of Compound **25** ($CDCl_3$, 100 MHz)



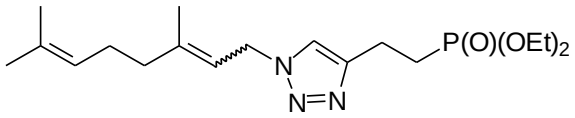


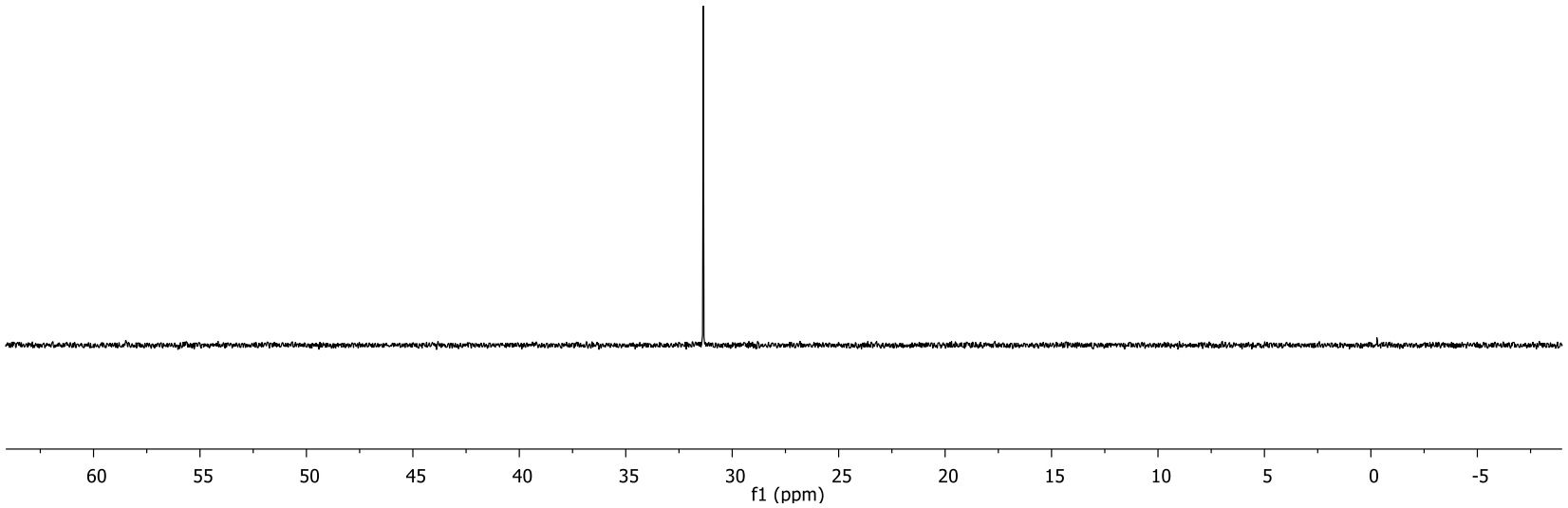
^{1}H NMR Spectrum of Compound **26** ($CDCl_3$, 500 MHz)



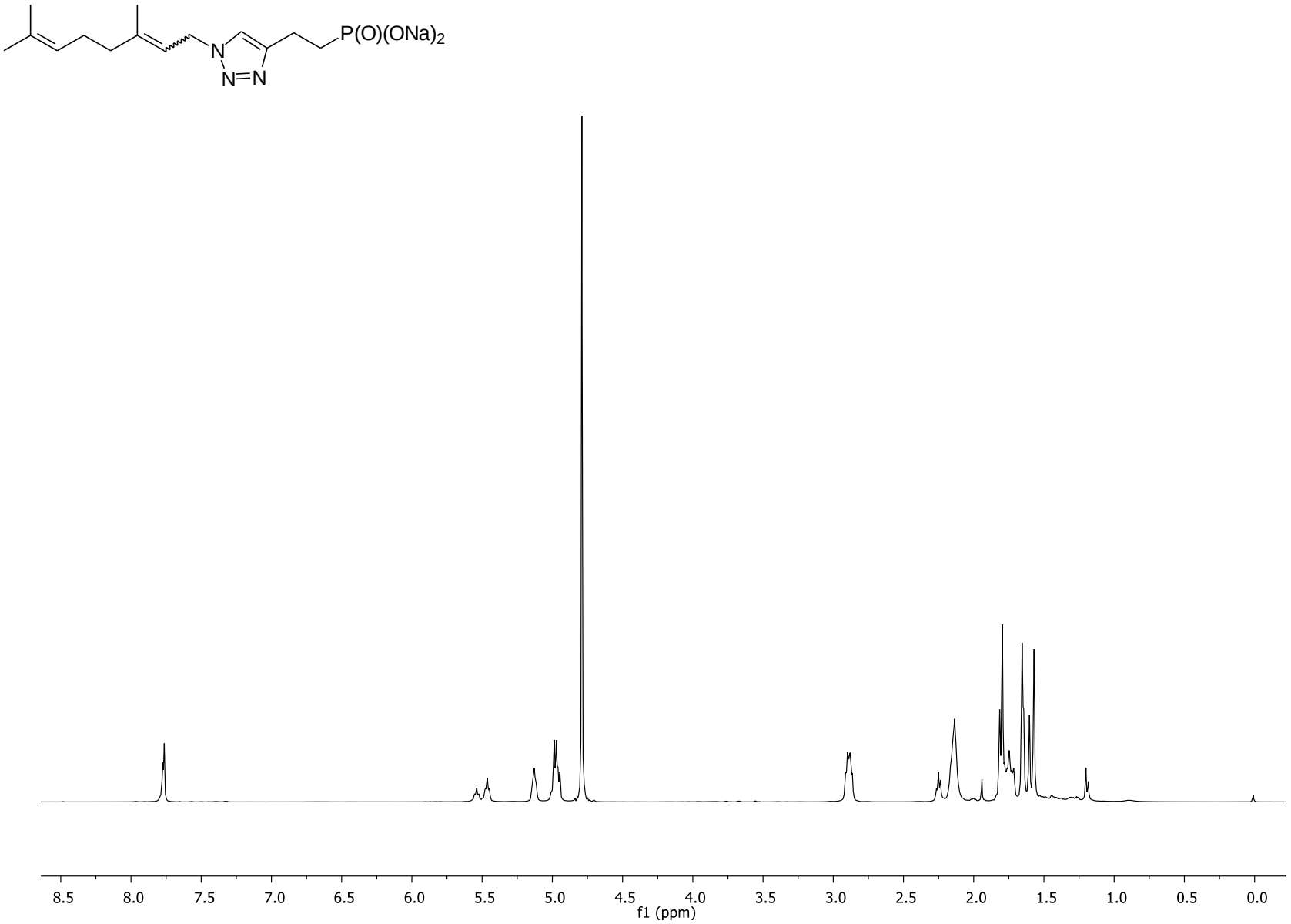


^{13}C NMR Spectrum of Compound **26** ($CDCl_3$, 126 MHz)

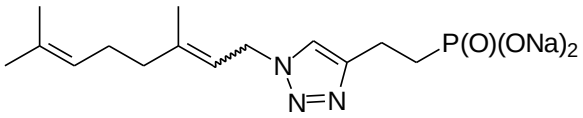


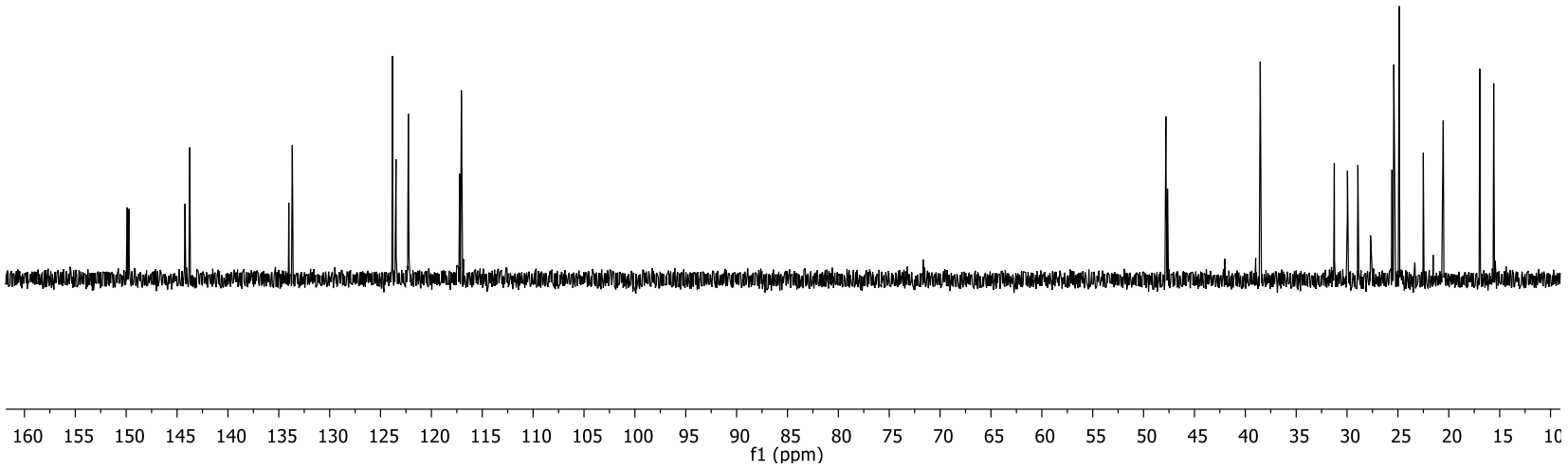


^{31}P NMR Spectrum of Compound **26** ($CDCl_3$, 202 MHz)

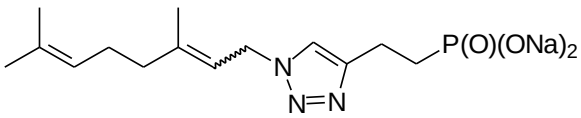


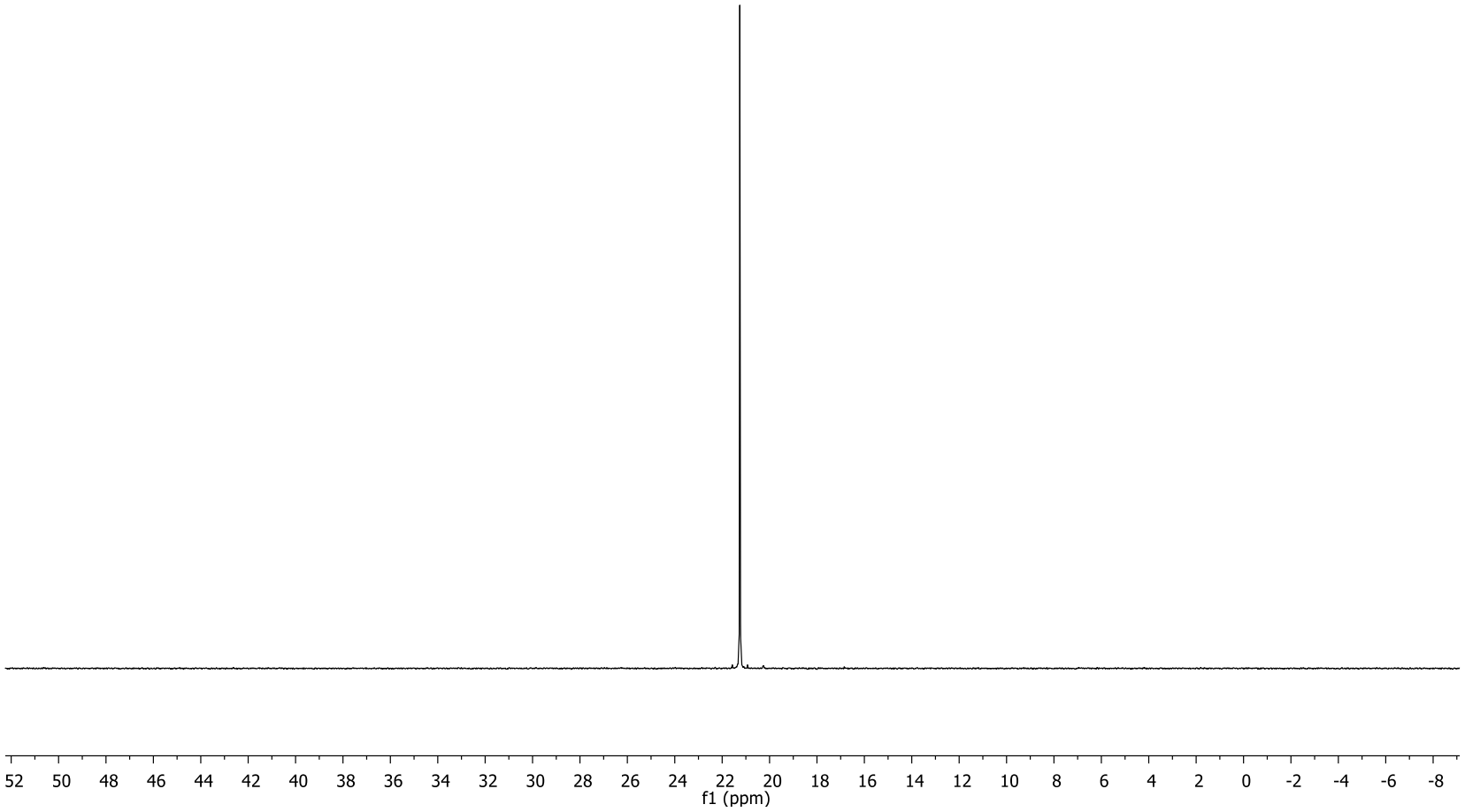
^{1}H NMR Spectrum of Compound **27** (D_2O, 500 MHz)



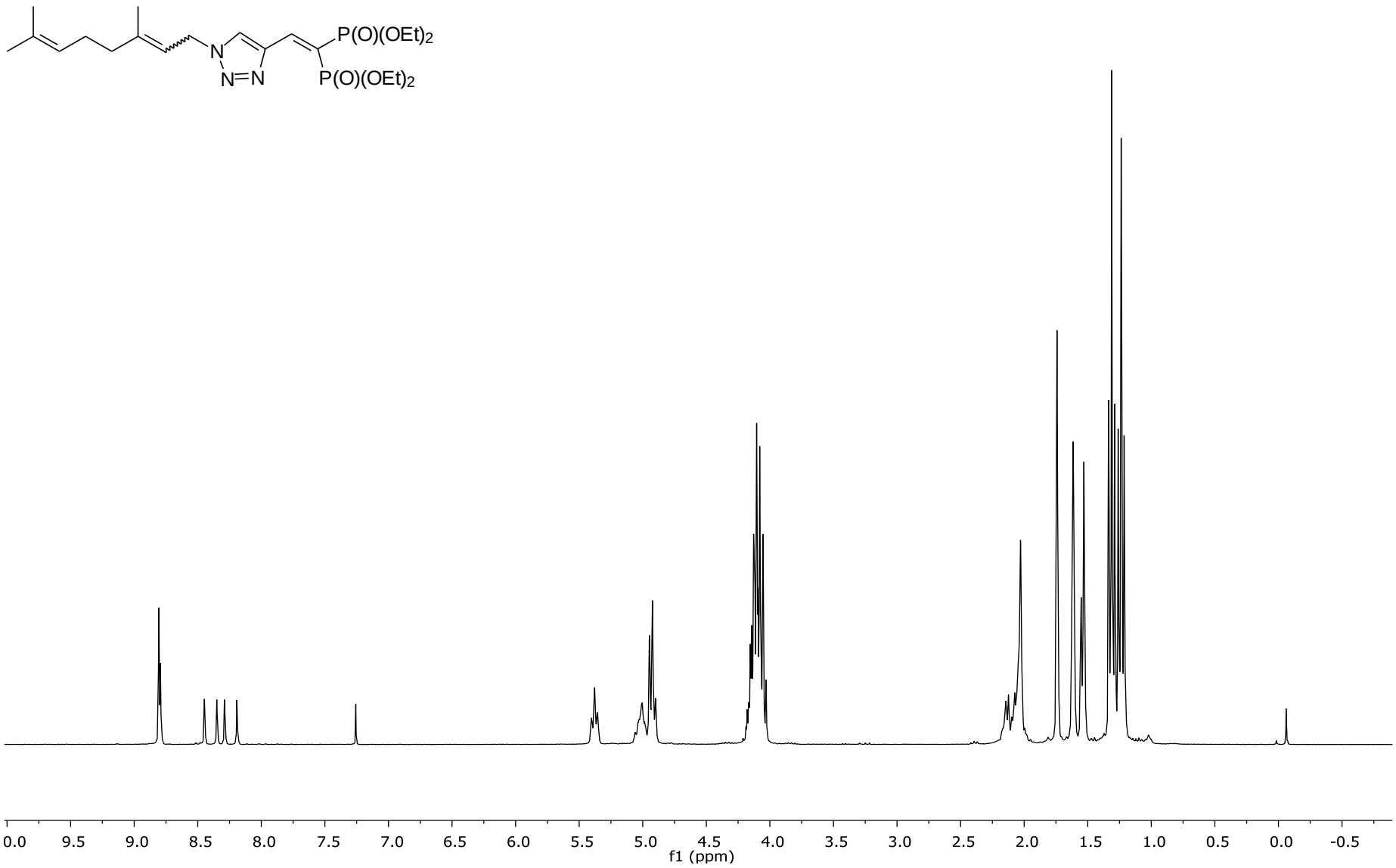


^{13}C NMR Spectrum of Compound **27** (D_2O, 126 MHz)

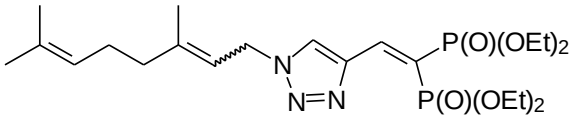


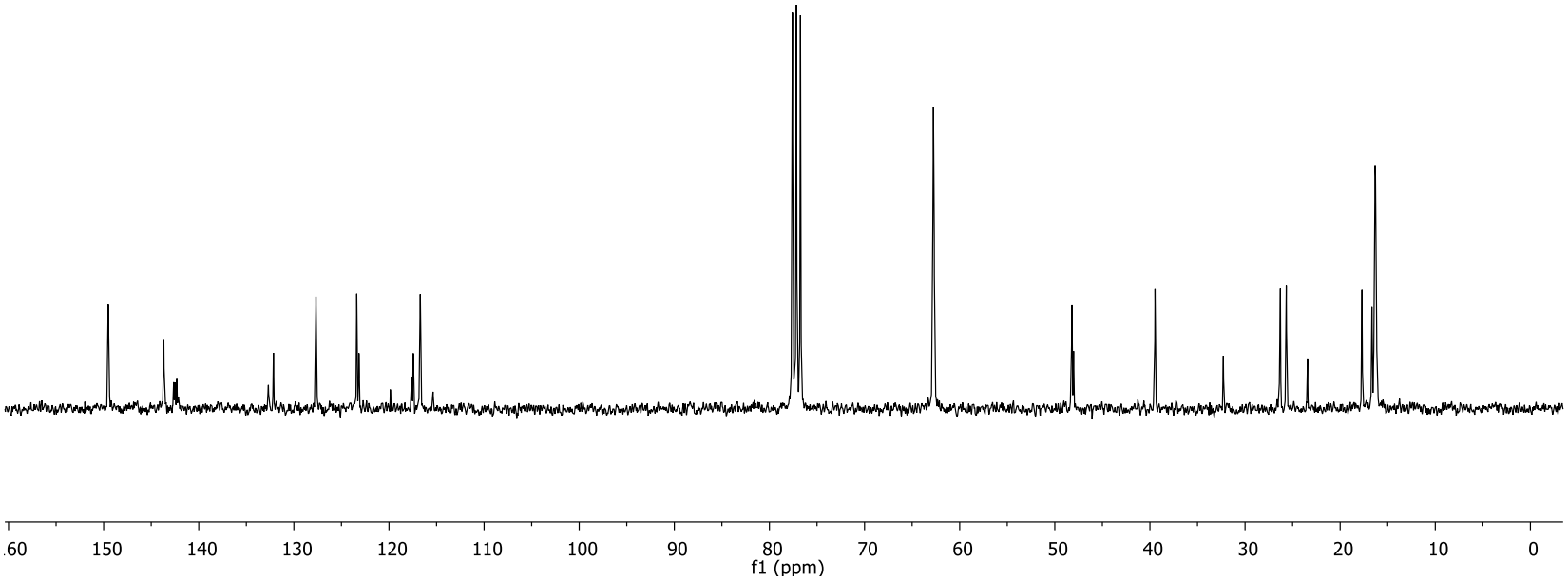


^{31}P NMR Spectrum of Compound **27** D_2O, 202 MHz)

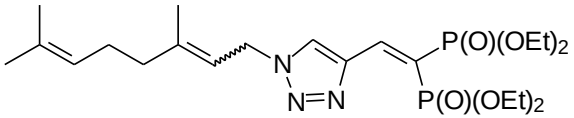


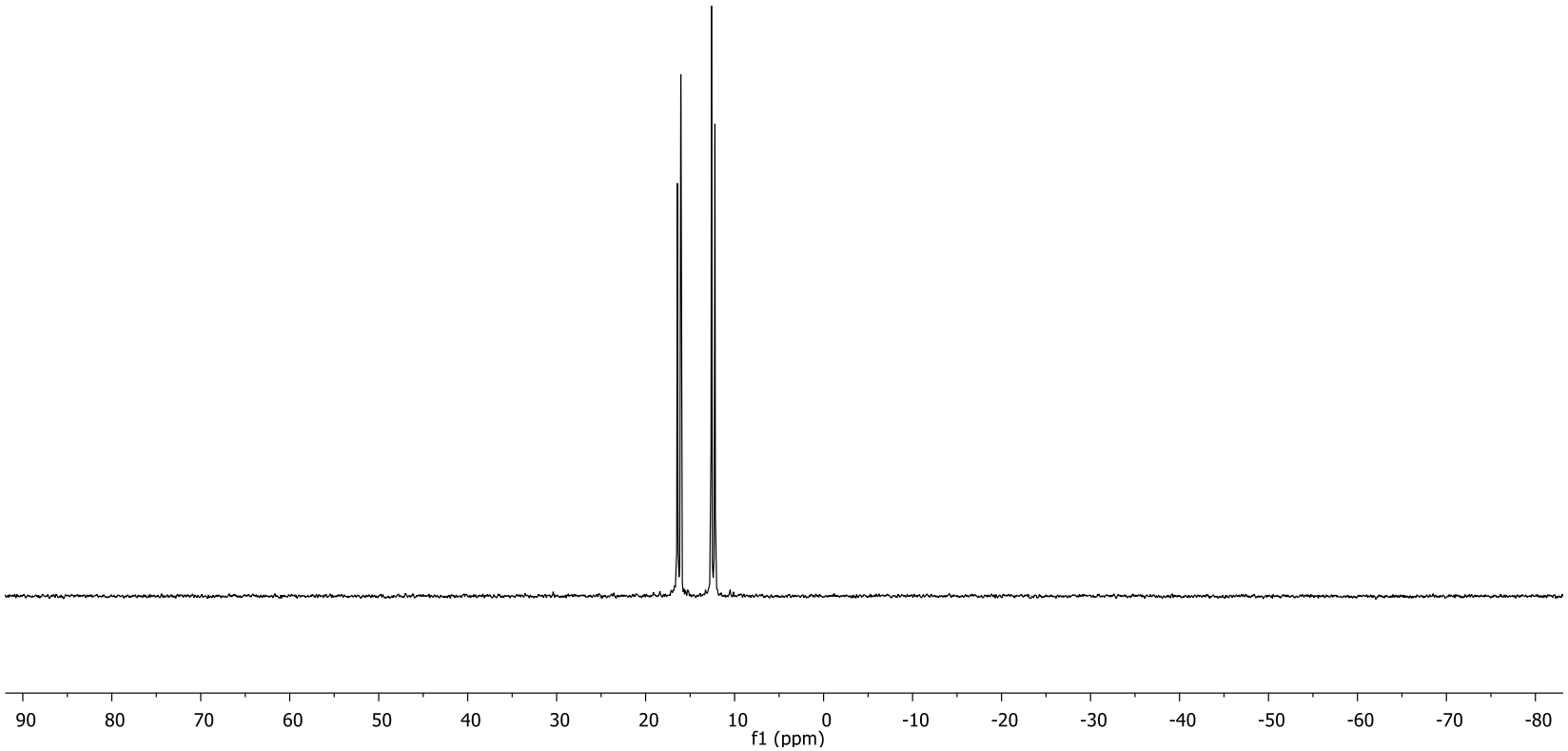
^{1}H NMR Spectrum of Compound **28** ($CDCl_3$, 300 MHz)



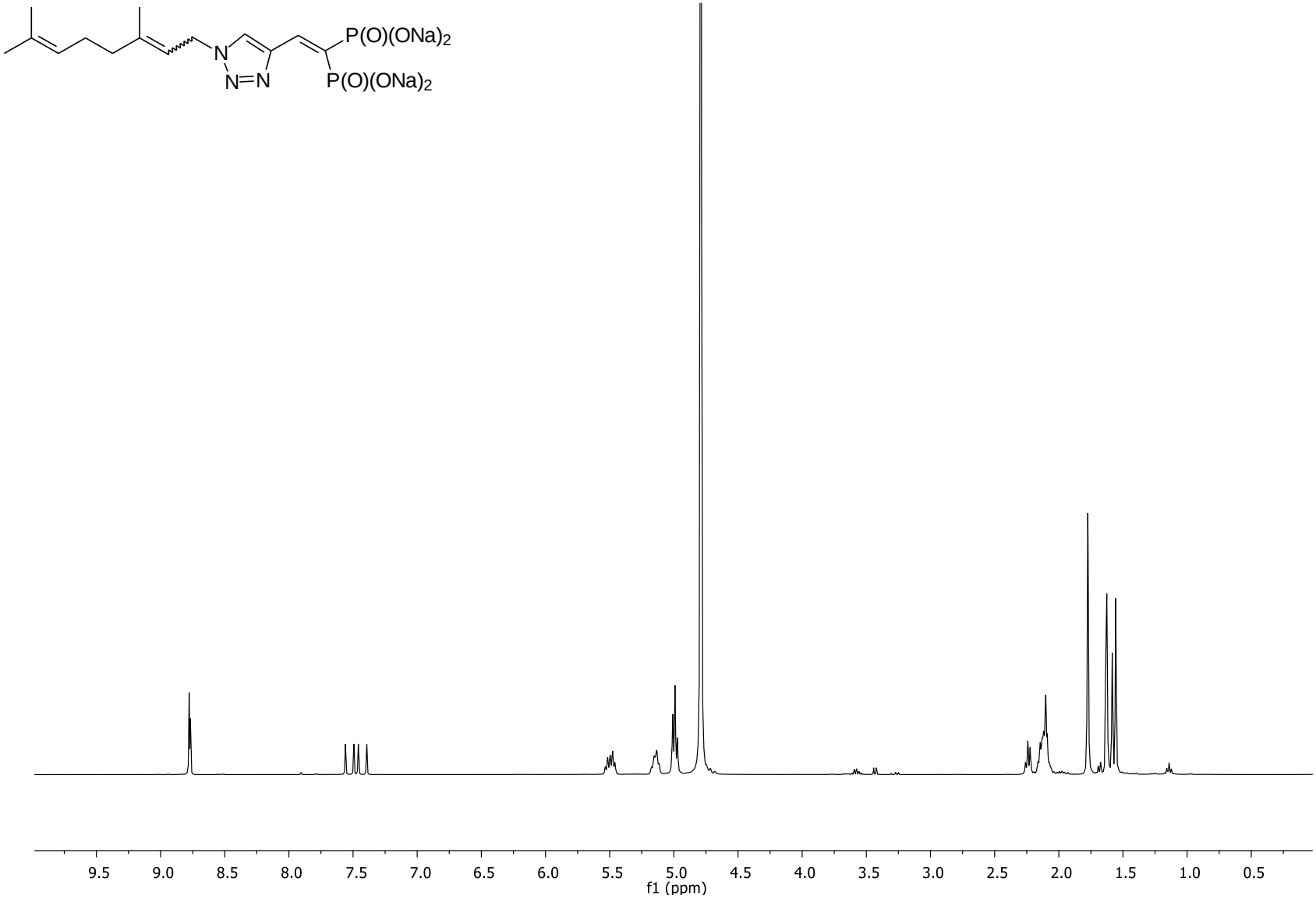


^{13}C NMR Spectrum of Compound **28** ($CDCl_3$, 75.5 MHz)

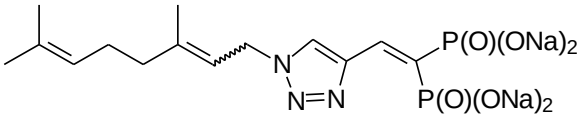


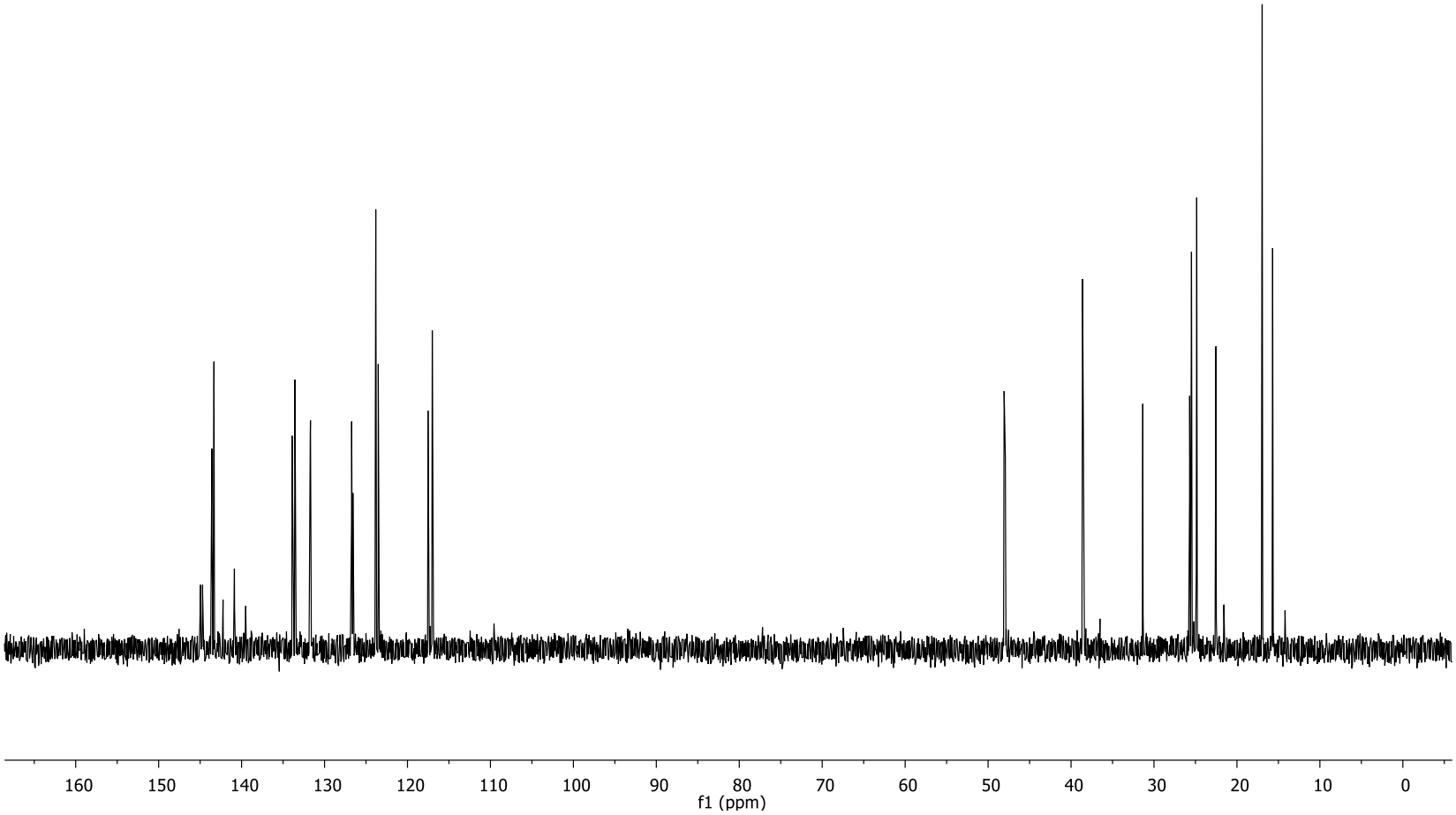


^{31}P NMR Spectrum of Compound **28** ($CDCl_3$, 122 MHz)

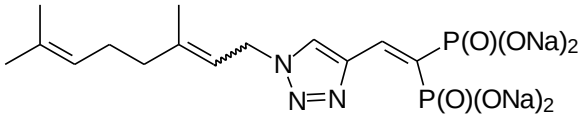


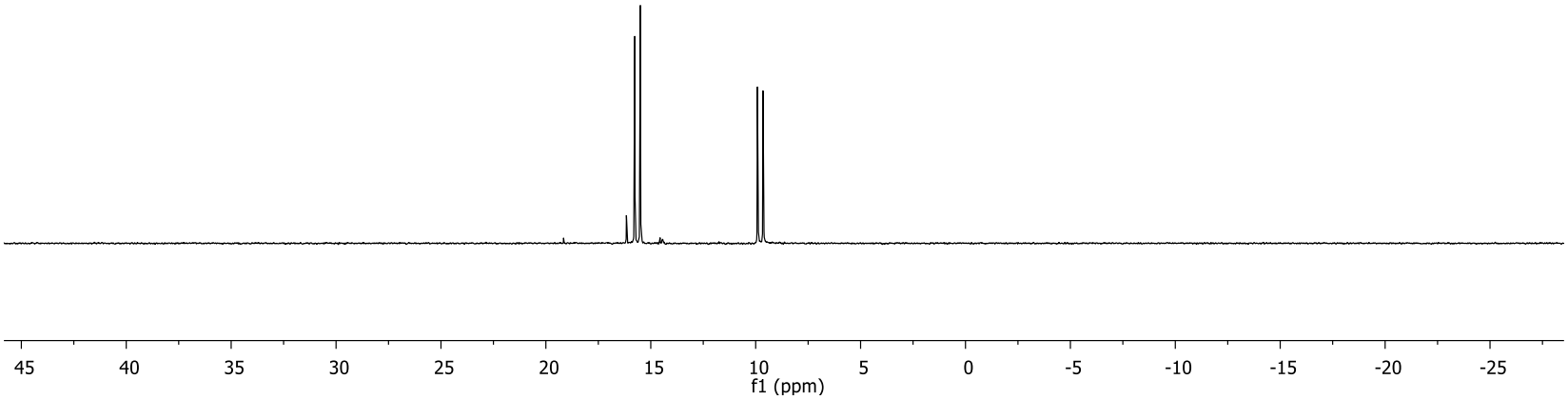
^{1}H NMR Spectrum of Compound **29** (D_2O, 400 MHz)



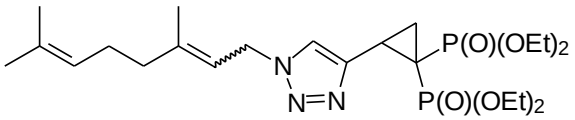


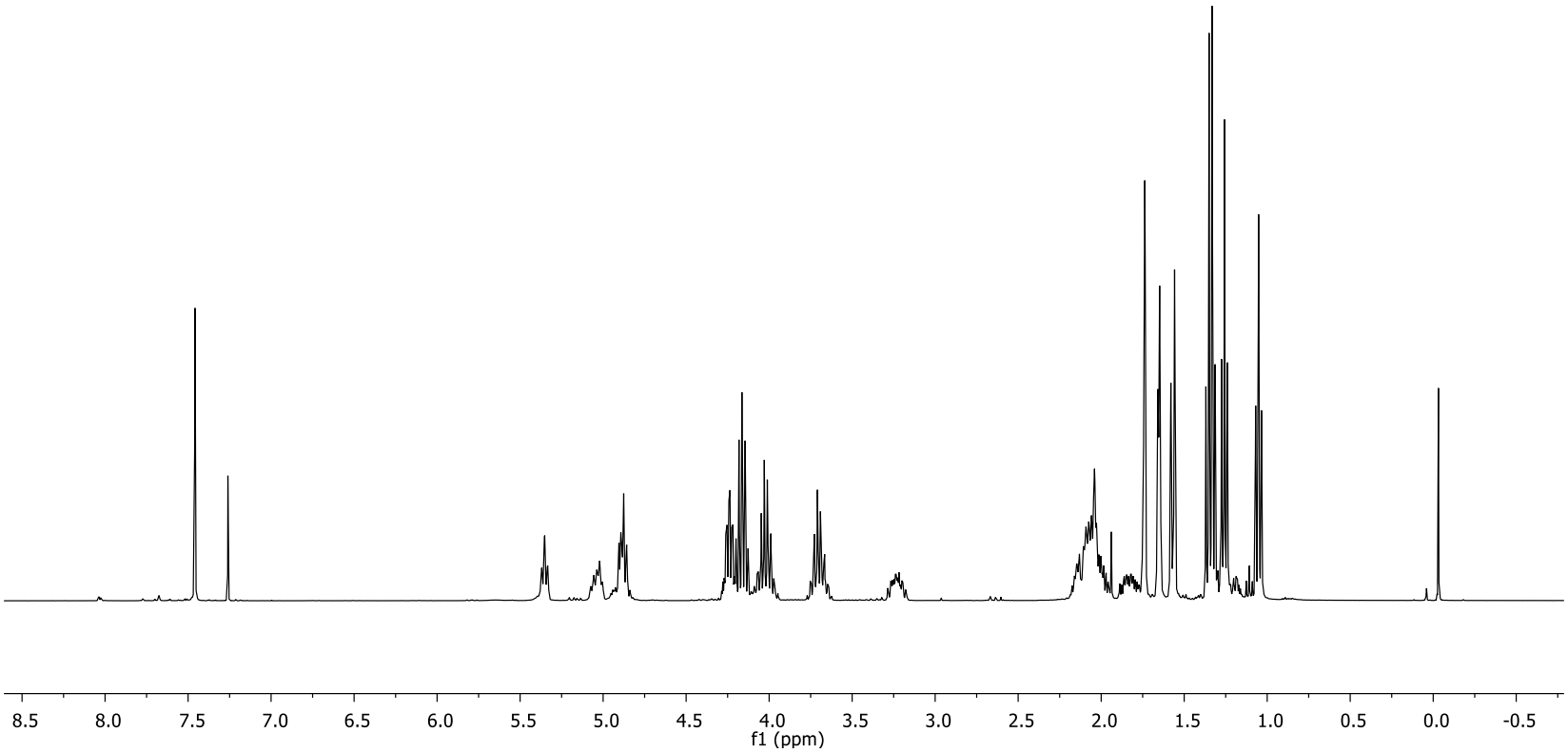
^{13}C NMR Spectrum of Compound **29** (D_2O, 100 MHz)



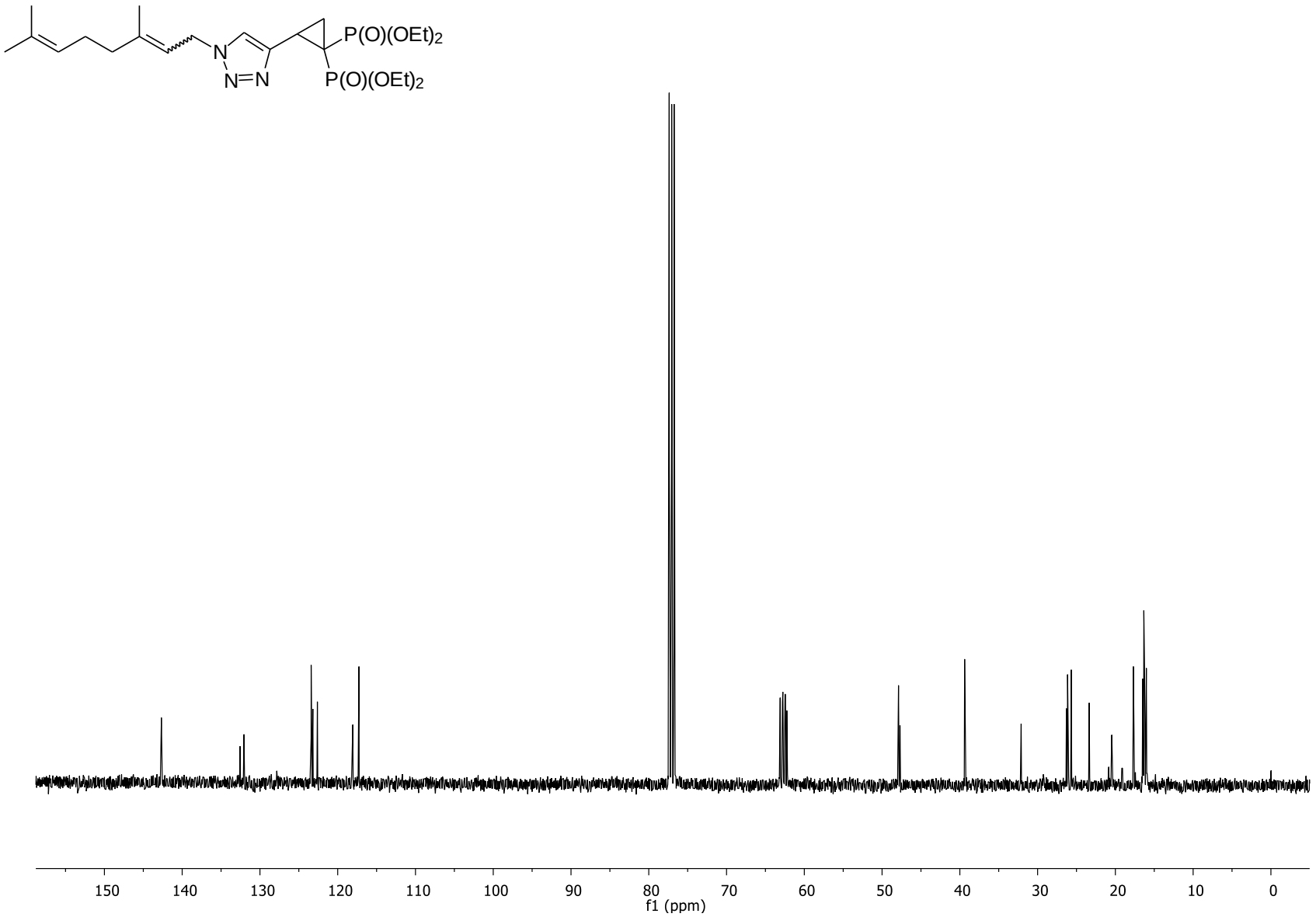


^{31}P NMR Spectrum of Compound **29** (D_2O, 162 MHz)

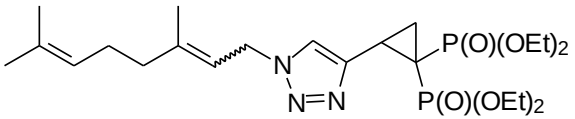


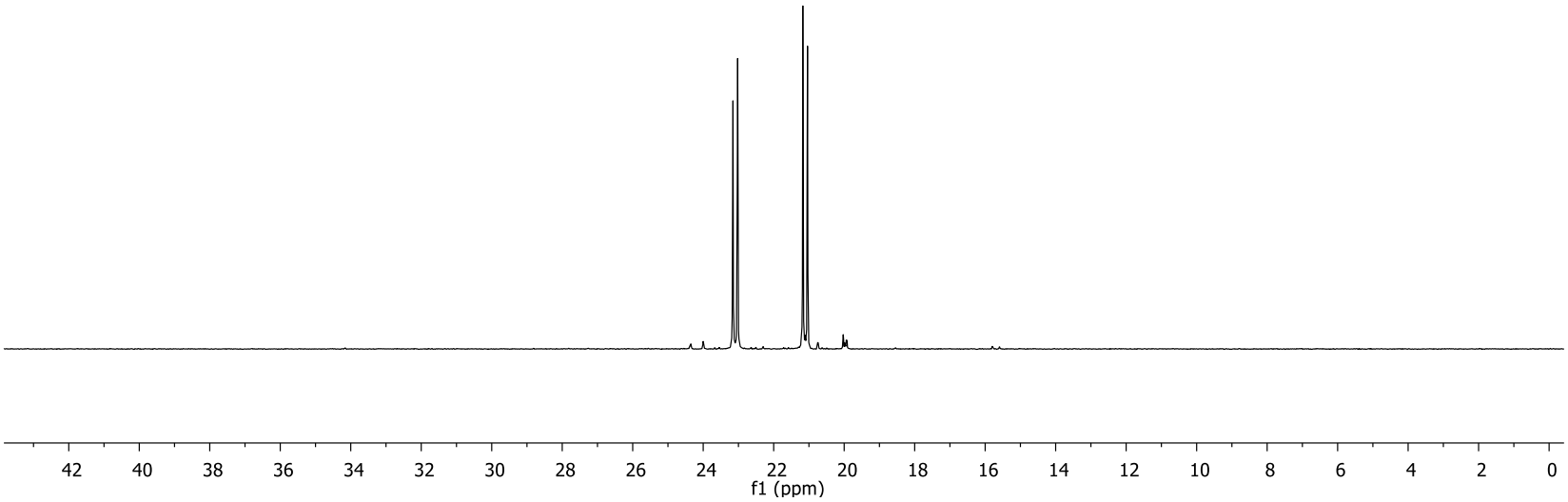


^{1}H NMR Spectrum of Compound **30** ($CDCl_3$, 400 MHz)

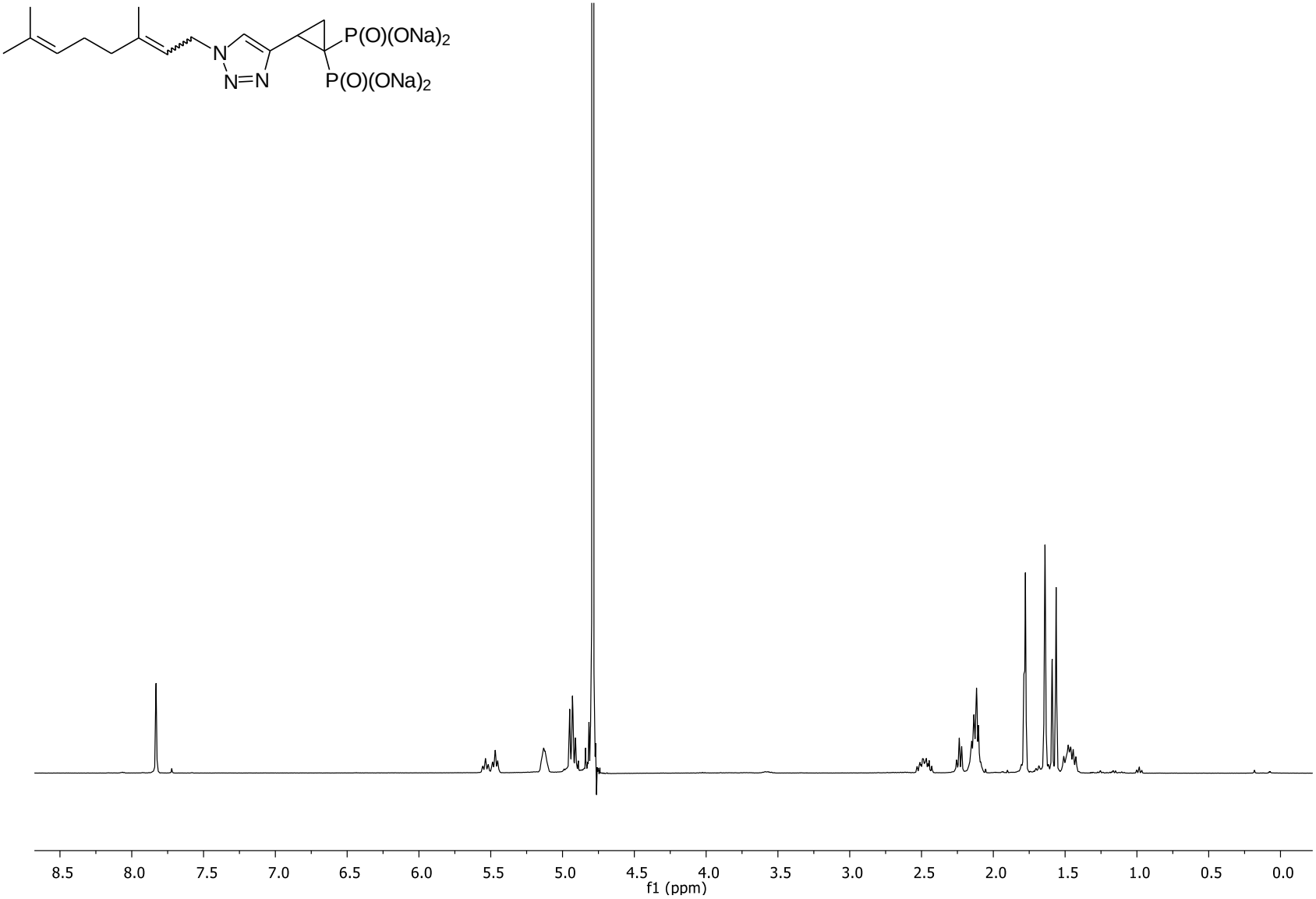


^{13}C NMR Spectrum of Compound **30** ($CDCl_3$, 100 MHz)

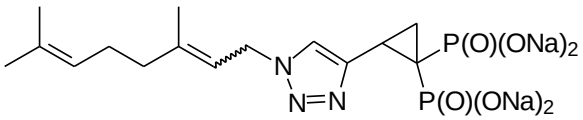


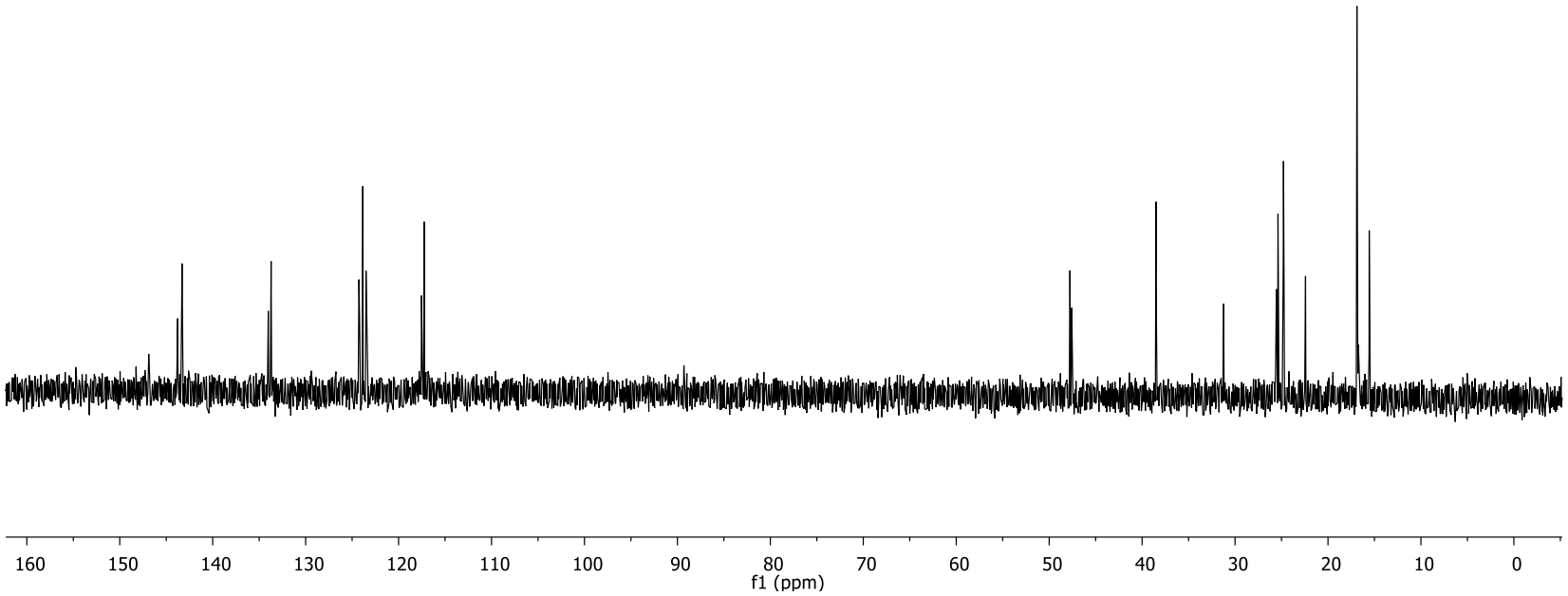


^{31}P NMR Spectrum of Compound **30** ($CDCl_3$, 162 MHz)

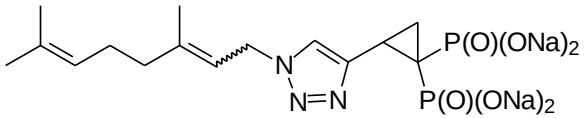


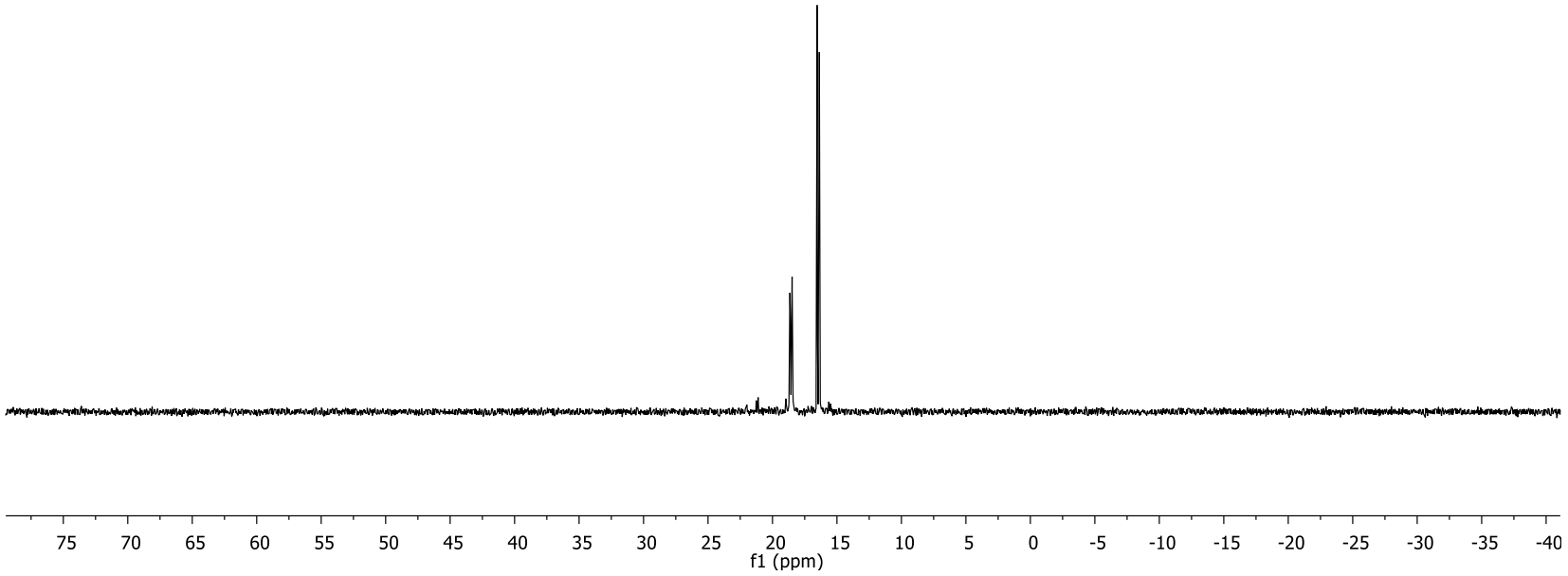
^{1}H NMR Spectrum of Compound **31** (D_2O, 400 MHz)



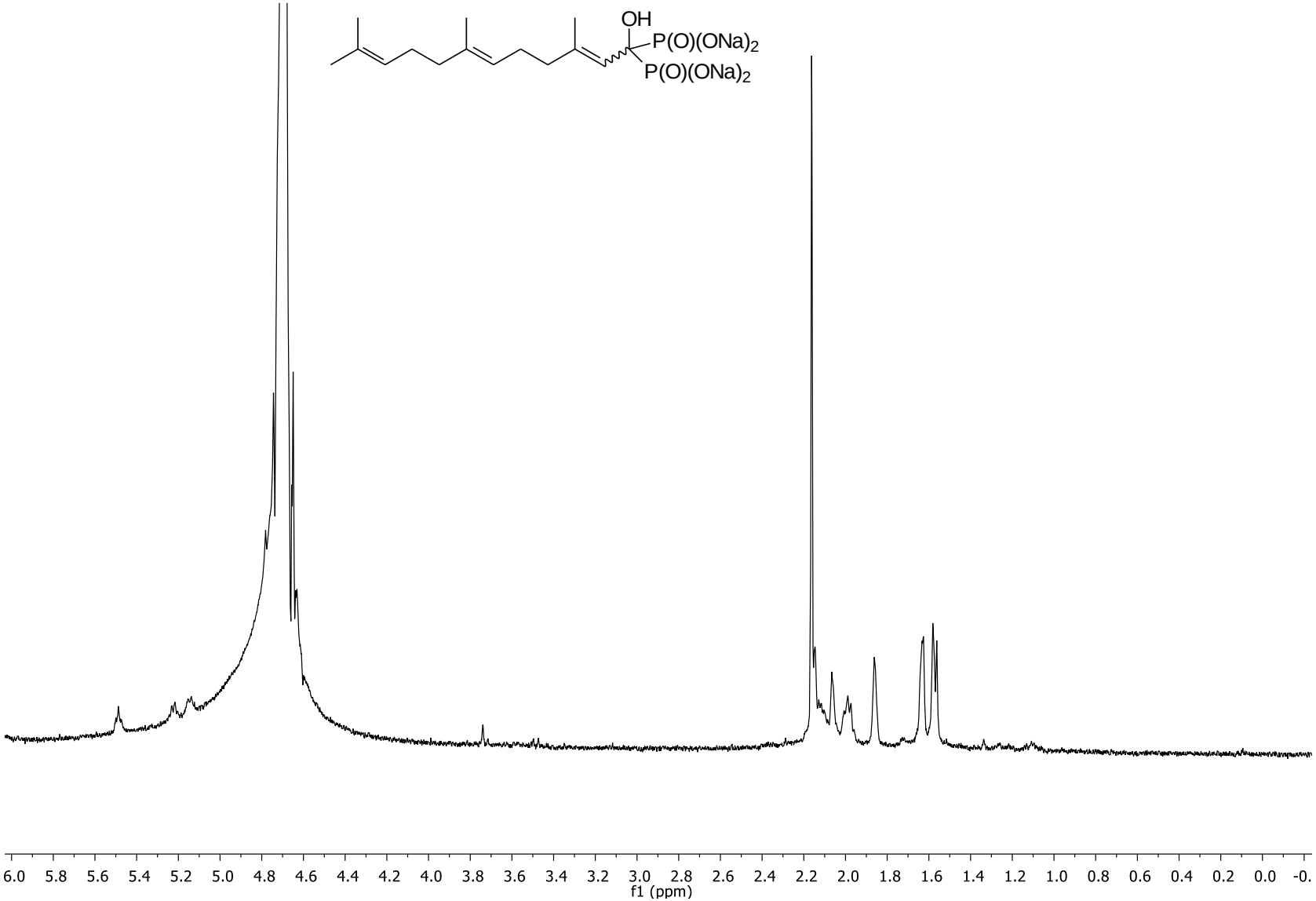


^{13}C NMR Spectrum of Compound **31** (D_2O, 100 MHz)

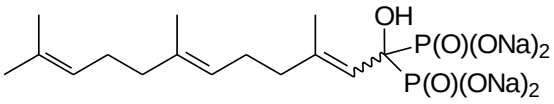


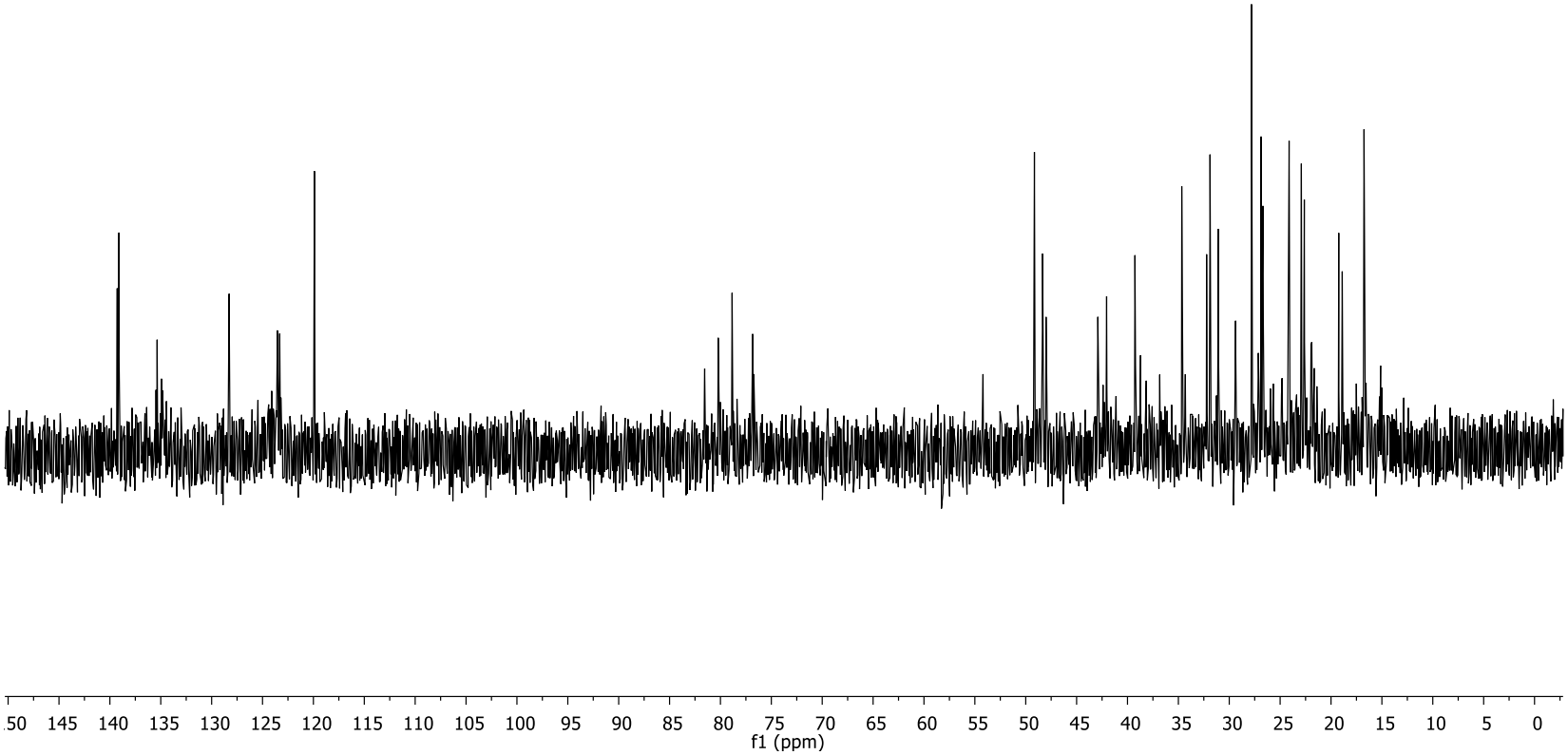


^{31}P NMR Spectrum of Compound **31** (D_2O, 162 MHz)

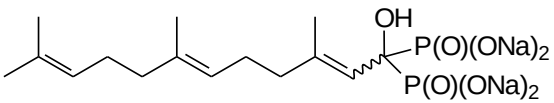


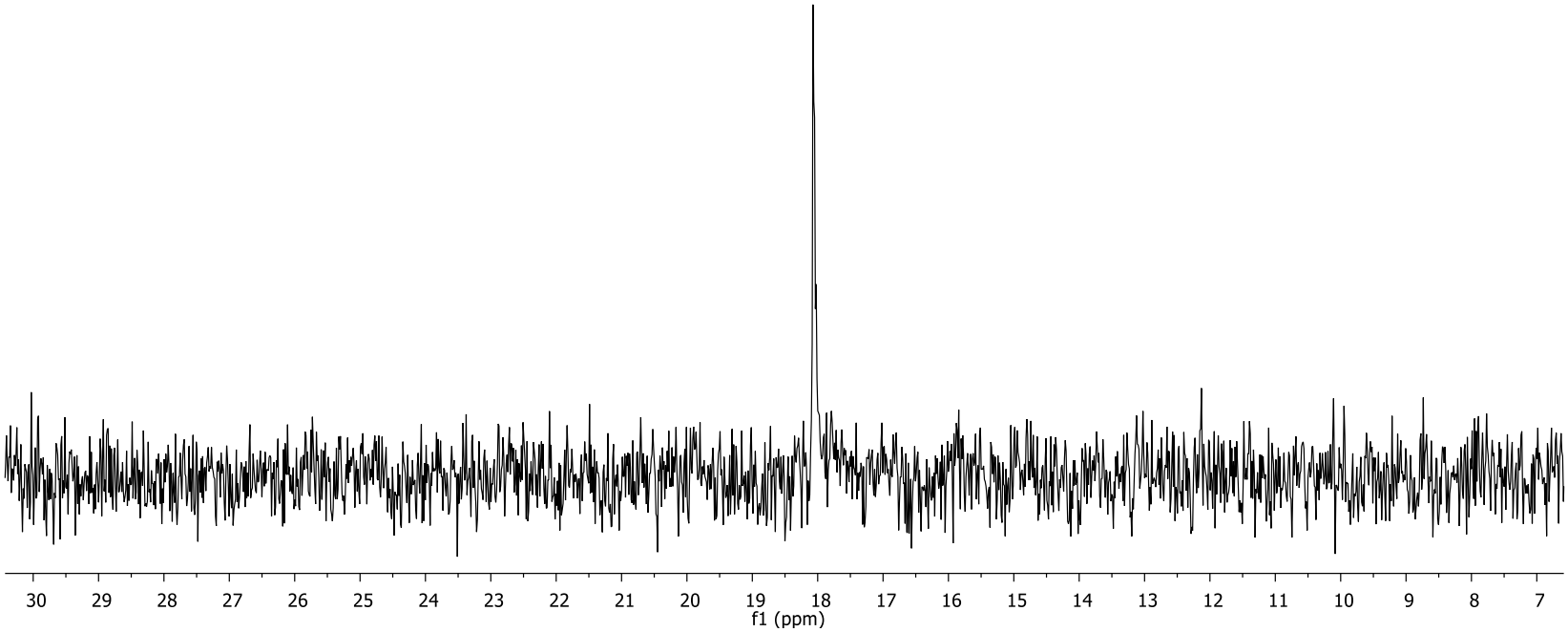
^{1}H NMR Spectrum of Compound **34** (D_2O, 500 MHz)



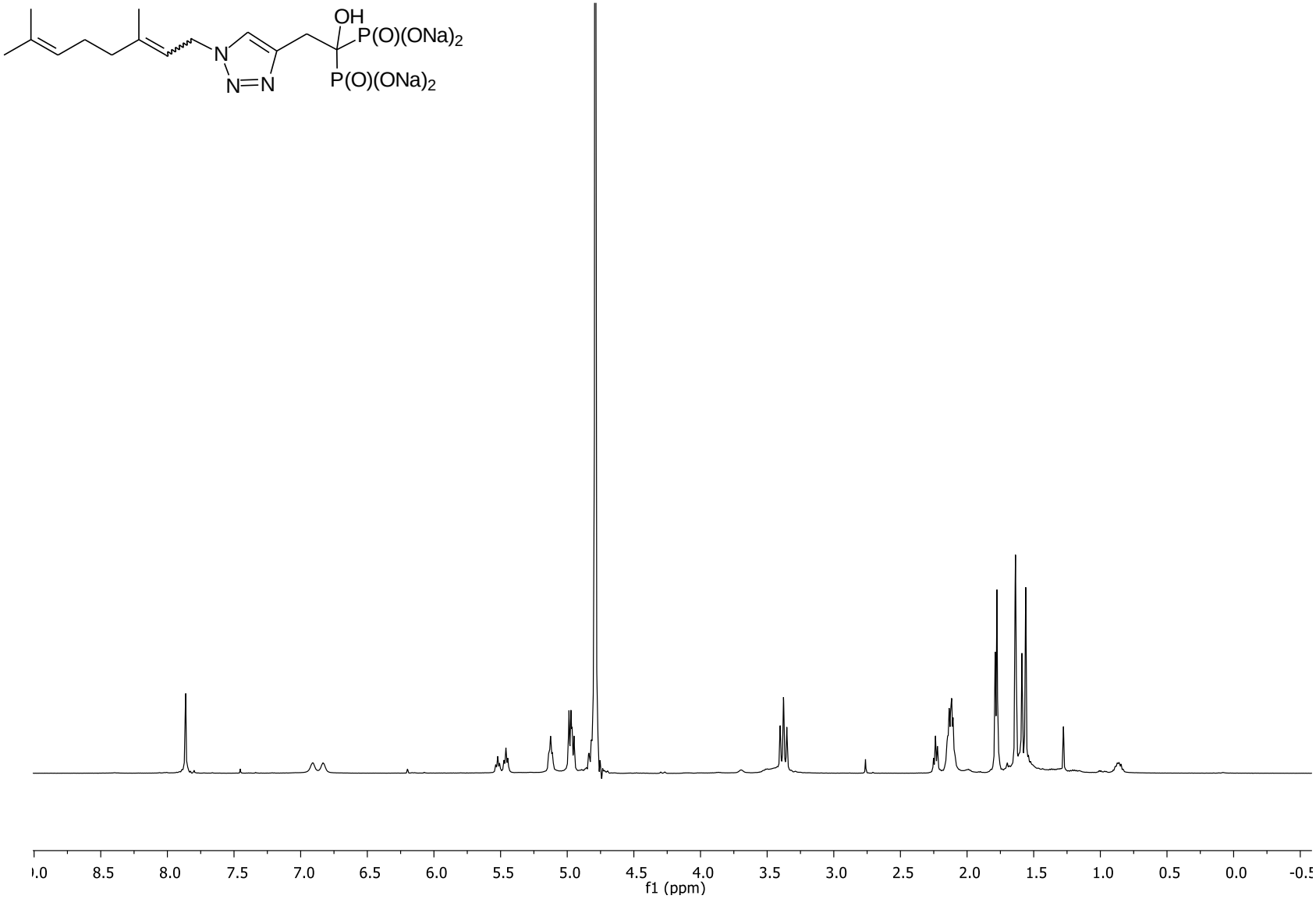


^{13}C NMR Spectrum of Compound **34** (D_2O, 100 MHz)

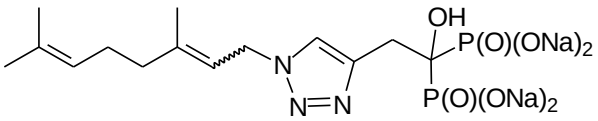


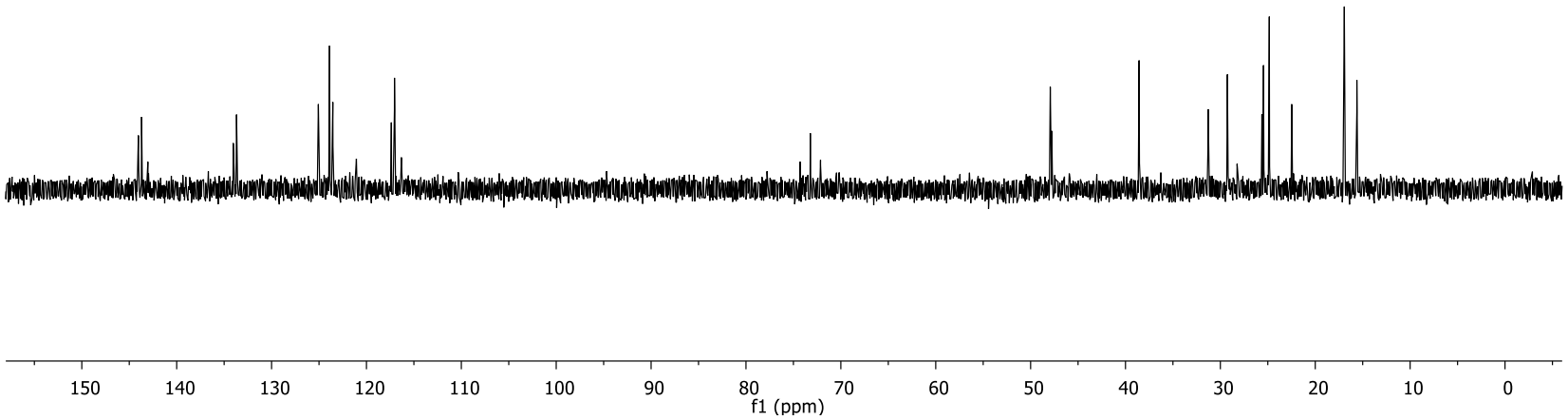


^{31}P NMR Spectrum of Compound **34** (D_2O, 162 MHz)

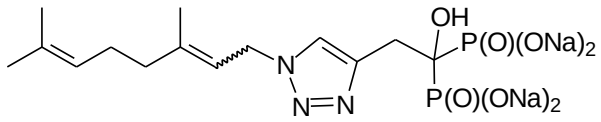


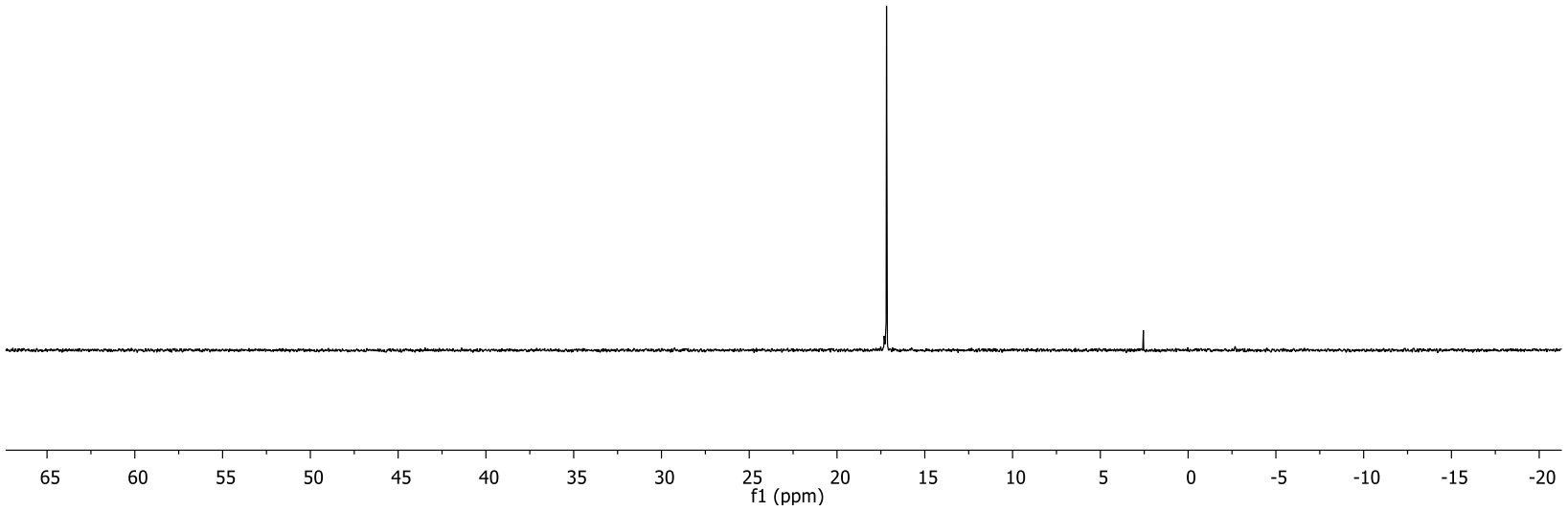
^{1}H NMR Spectrum of Compound **37** (D_2O, 500 MHz)





^{13}C NMR Spectrum of Compound **37** (D_2O, 126 MHz)





^{31}P NMR Spectrum of Compound **37** (D_2O, 202 MHz)

Data File C:\Users\Public\Documents\ChemStation\1\Data\Demo\AERF-03-023.D
Sample Name:

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Acq. Instrument : Shared 1220                    Location :   1
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                                                 Inj Volume : No inj
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Last changed    : 12/2/2020 10:28:53 AM by SYSTEM
                  (modified after loading)
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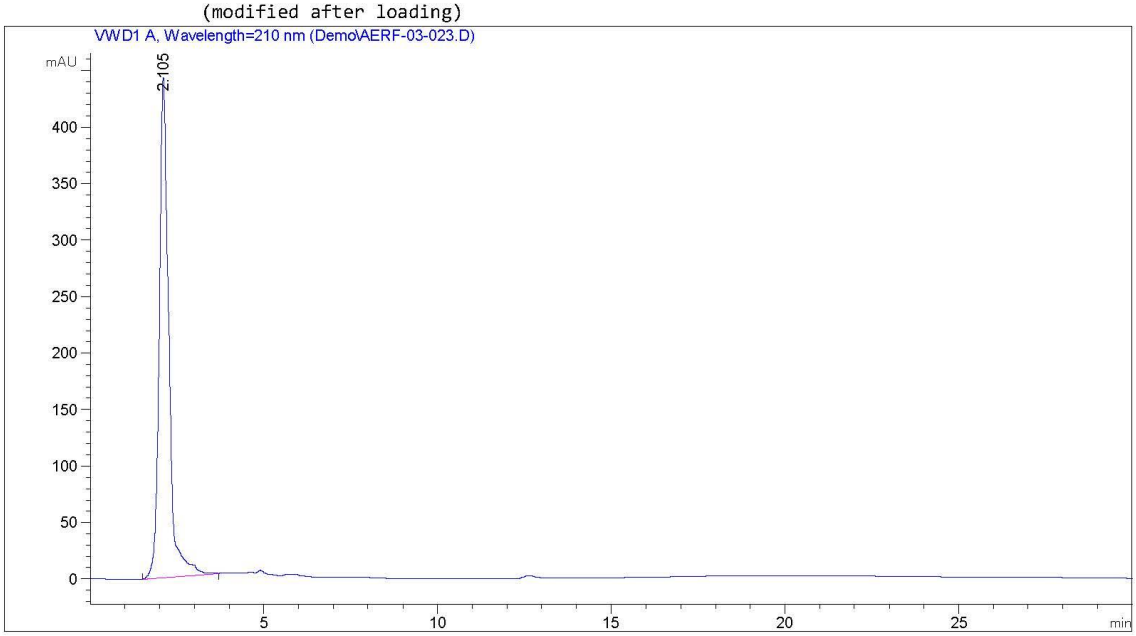


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==========================================================================
                          Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=210 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
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   1   2.105 BV R  0.2686 8444.32617  442.47632 100.0000

Totals :                  8444.32617  442.47632


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HPLC trace of Compound **11**

Data File C:\Users\Public\Documents\ChemStation\1\Data\Demo\AERF-03-046.D
Sample Name:

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Sample Operator : SYSTEM
Acq. Instrument : Shared 1220                    Location :   1
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                                                 Inj Volume : No inj
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Last changed    : 1/5/2021 2:47:56 PM by SYSTEM
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Last changed    : 1/5/2021 2:46:30 PM by SYSTEM
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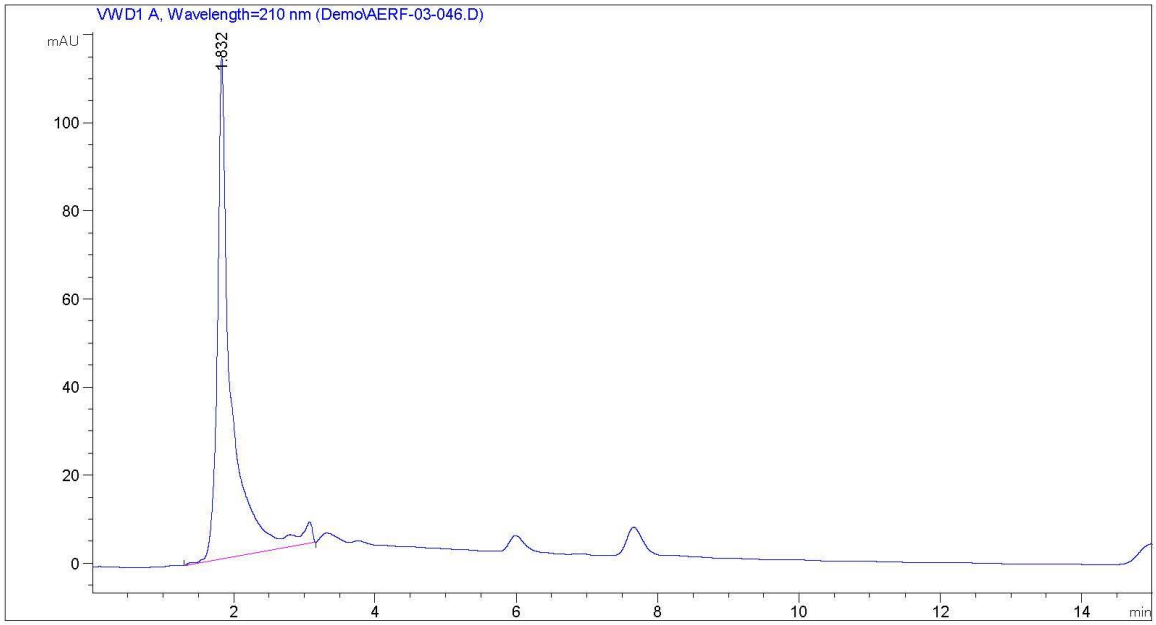


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==========================================================================
                          Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=210 nm

Peak RetTime Type  Width     Area      Height     Area
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Totals :                  1524.75305  113.84121

==========================================================================
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HPLC trace of Compound **17**

Data File C:\Users\P...tion\1\Data\Grant\gns-09-166 Trost Silver (1) 2020-07-27 15-07-02.D
Sample Name: gns-09-166 Trost Silver

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    Sample Operator : SYSTEM
    Acq. Instrument : Shared 1220                    Location :   1
    Injection Date  : 7/27/2020 3:07:03 PM               Inj :   1
                                                   Inj Volume : No inj
    Method          : C:\Users\Public\Documents\ChemStation\1\Methods\DEF_LC.M
    Last changed    : 7/27/2020 3:16:31 PM by SYSTEM
                      (modified after loading)
    Sample Info     : Asymetric Reaction Analysis. Chiracel OJ-H 5:95 IPA:Hex 2mL/min
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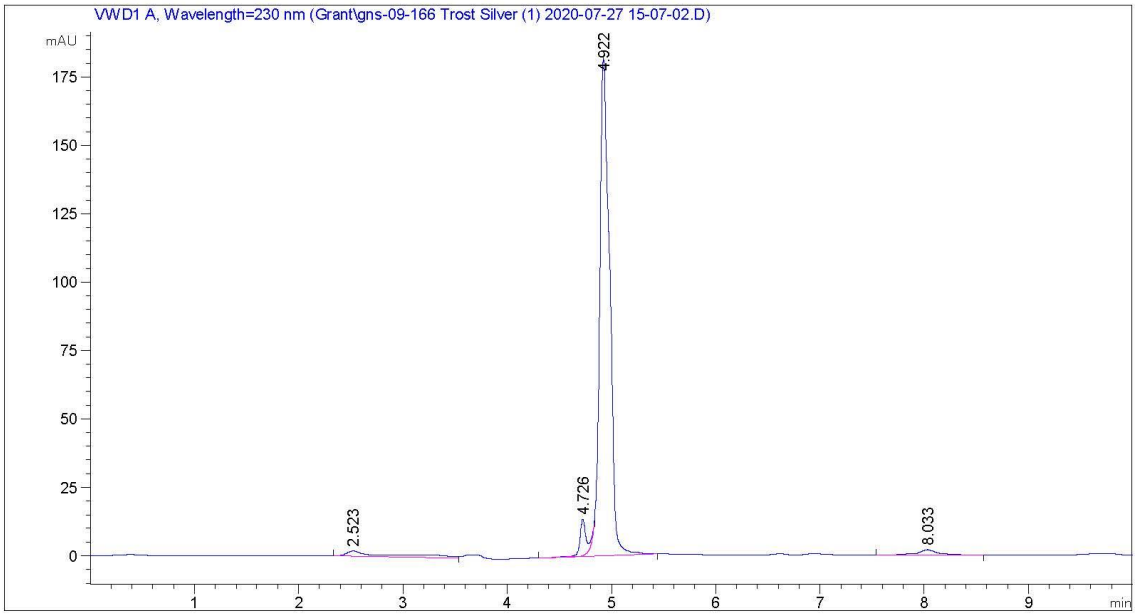


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    ======================================================================
                              Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: VWD1 A, Wavelength=230 nm

    Peak RetTime Type  Width     Area      Height     Area
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    ----|-------|----|-------|----------|----------|--------|
       1   2.523 BV    0.3786   54.47862    1.84451   4.0237
       2   4.726 BV E  0.0599   55.05247   13.41618   4.0661
       3   4.922 VB R  0.0941 1220.58765  182.37109  90.1507
       4   8.033 BB    0.1812   23.82263    1.83874   1.7595

    Totals :                  1353.94137  199.47052
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HPLC trace of Compound **27**

Data File C:\Users\P...cuments\ChemStation\1\Data\no Sample Name (1) 2019-06-04 12-25-36.D
Sample Name:

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Sample Operator : SYSTEM
Acq. Instrument : Shared 1220                    Location :   1
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                                                 Inj Volume : No inj
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Last changed    : 6/4/2019 12:22:13 PM by SYSTEM
                  (modified after loading)
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Last changed    : 6/4/2019 12:57:31 PM by SYSTEM
Additional Info : Peak(s) manually integrated
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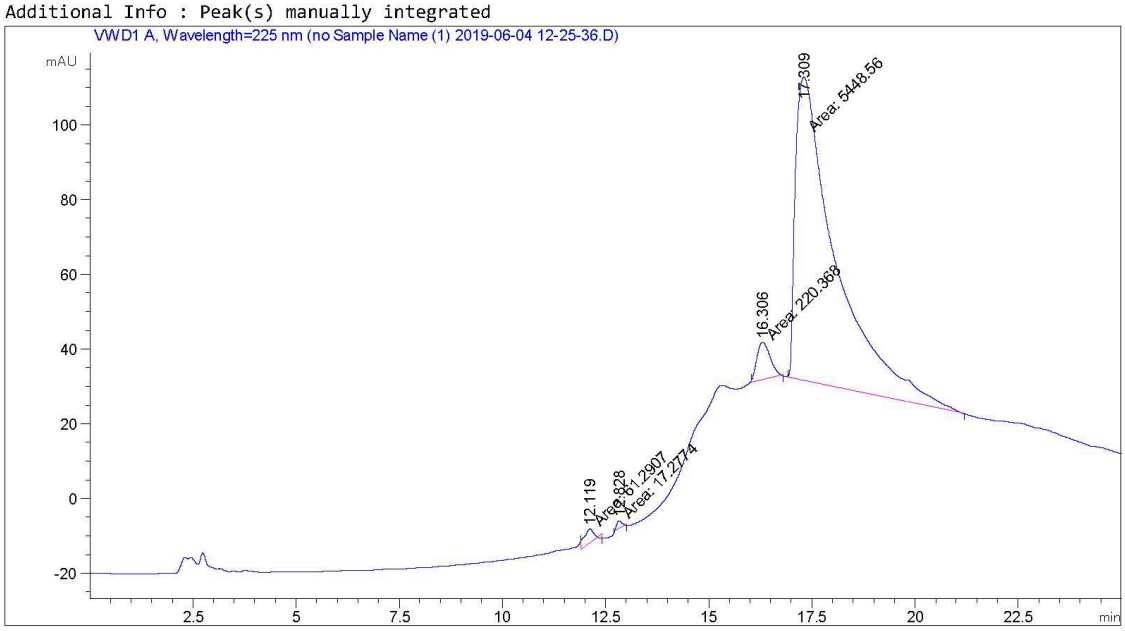


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==================================================================
                        Area Percent Report
==================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=225 nm

Peak RetTime Type  Width     Area      Height     Area
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   2  12.828 MM    0.1398   17.27742    2.05988   0.3006
   3  16.306 MM    0.3701  220.36827    9.92279   3.8342
   4  17.309 MM    1.1195 5448.56006   81.11897  94.7988

Totals :                  5747.49649   96.85090
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HPLC trace of Compound **29**

Data File C:\Users\P...cuments\ChemStation\1\Data\no Sample Name (1) 2019-06-04 12-25-36.D
Sample Name:

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Sample Operator : SYSTEM
Acq. Instrument : Shared 1220                    Location :   1
Injection Date  : 6/4/2019 12:25:37 PM                Inj :   1
                                                 Inj Volume : No inj
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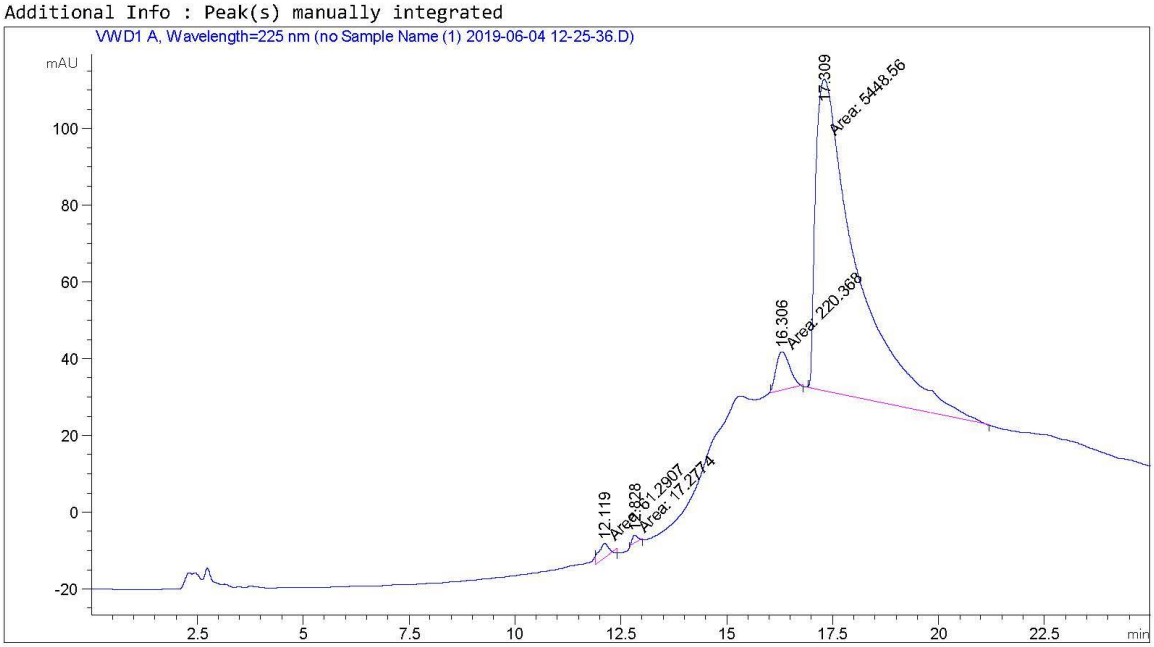
Last changed    : 6/4/2019 12:22:13 PM by SYSTEM
                  (modified after loading)
Analysis Method : C:\Users\Public\Documents\ChemStation\1\Methods\HILIC_analytical_run.M
Last changed    : 6/4/2019 12:57:31 PM by SYSTEM
Additional Info : Peak(s) manually integrated
```




```
=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=225 nm

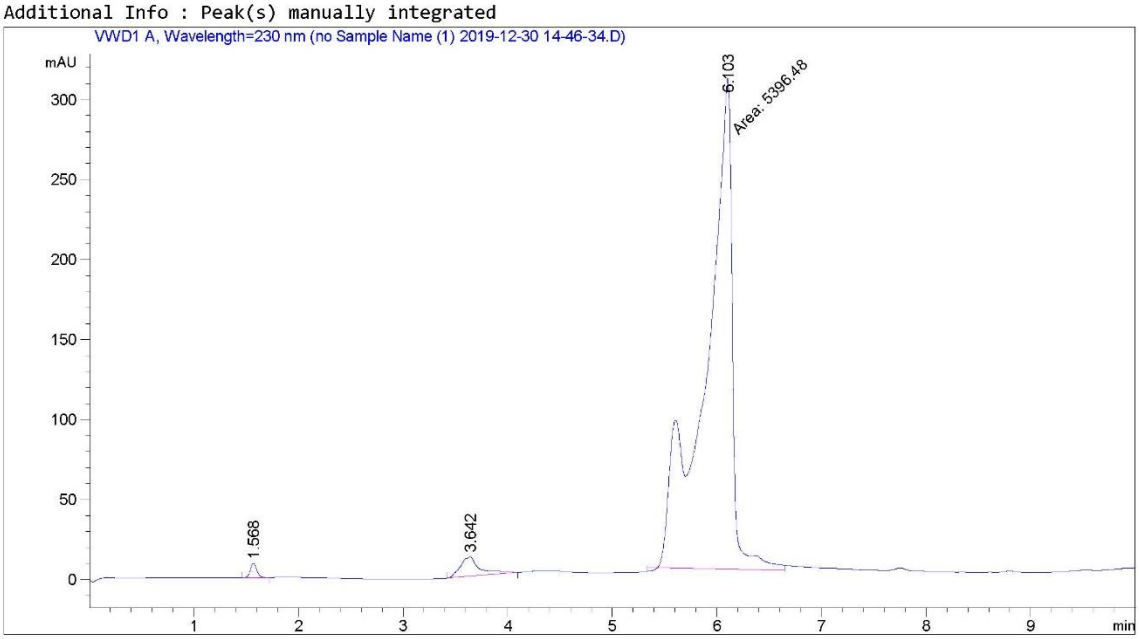
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  12.119 MM    0.2725   61.29074    3.74926   1.0664
   2  12.828 MM    0.1398   17.27742    2.05988   0.3006
   3  16.306 MM    0.3701  220.36827    9.92279   3.8342
   4  17.309 MM    1.1195 5448.56006   81.11897  94.7988

Totals :                  5747.49649   96.85090
```


HPLC trace of Compound **31**

Data File C:\Users\P...cuments\ChemStation\1\Data\no Sample Name (1) 2019-12-30 14-46-34.D
Sample Name:

```
==========================================================================
Acq. Operator   : SYSTEM
Sample Operator : SYSTEM
Acq. Instrument : Shared 1220                    Location :   1
Injection Date  : 12/30/2019 2:46:35 PM               Inj :   1
                                                 Inj Volume : No inj
Acq. Method     : C:\Users\Public\Documents\ChemStation\1\Methods\CMS-C18A.M
Last changed    : 12/30/2019 2:53:18 PM by SYSTEM
                  (modified after loading)
Analysis Method : C:\USERS\PUBLIC\DOCUMENTS\CHEMSTATION\1\METHODS\BMD TTI918.M
Last changed    : 12/30/2019 2:39:49 PM by SYSTEM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=230 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   1.568 BB    0.0629   36.81658    8.96037   0.6590
   2   3.642 BB    0.1597  153.17264   12.18526   2.7418
   3   6.103 MM    0.2932 5396.48389  306.72931  96.5991

Totals :                   5586.47311  327.87493
```


HPLC trace of Compound **37**