Supporting information for

A potent triazole bisphosphonate inhibitor of geranylgeranyl diphosphate synthase

Veronica S. Wills,[a] Cheryl Allen,[b] Sarah A. Holstein,[b]

and David F. Wiemer[a,c]*

[a] *Department of Chemistry, University of Iowa, Iowa City, IA 52242-1294, USA*

[b] *Department of Medicine, Roswell Park Cancer Institute, Buffalo, NY 14263, USA*

[c] *Department of Pharmacology, University of Iowa, Iowa City, IA 52242-1109, USA*

david-wiemer@uiowa.edu

General experimental procedures.

Tetrahydrofuran (THF) and ether were freshly distilled from sodium and benzophenone, while methylene chloride (CH_2Cl_2) was distilled from calcium hydride prior to use. All other reagents and solvents were purchased from commercial sources and used without further purification. Acetonitrile (CH_3CN) and H_2O for UHPLC were LC-MS grade. All reactions in nonaqueous solvents were conducted in flame-dried glassware under a positive pressure of argon and with magnetic stirring. The NMR spectra were obtained at 300 or 500 MHz for ^1H, and 75 or 125 MHz for ^{13}C, with internal standards of $Si(CH_3)_4$ (^1H, 0.00 ppm) or $CDCl_3$ (^1H, 7.27 ppm; ^{13}C, 77.2 ppm) for non–aqueous samples or D_2O (^1H, 4.80 ppm) and 1,4-dioxane (^{13}C, 66.6 ppm) for aqueous samples. The ratio of olefin isomers for the tetraethyl ester **14** and sodium salt **8** was determined by integration of the resonances at approximately 39 ppm and 32 ppm in the ^{13}C NMR spectra, representing the *E*- and *Z*-isomers respectively. These resonances correspond to the methylene group adjacent to the more substituted carbon of the olefin. The peak at 168.0 ppm in the ^{13}C NMR spectrum of some bisphosphonate sodium salts corresponds to carbonate that formed during the reaction. An independent experiment was done to confirm the identity of this contaminant. The ^{31}P chemical shifts were reported in ppm relative to 85% H_3PO_4 (external standard). UHPLC and high resolution mass spectra were obtained at the University of Iowa Mass Spectrometry Facility. A Waters Q-TOF Premier with an Acquity UHPLC was used to collect LC-UV-MS data. Silica gel (60 Å, 0.040–0.063 mm) was used for flash chromatography. Purity of assayed compounds was ≥95% based on analytical UHPLC and/or NMR analysis.

Cyclopropyl alcohol 10.[1,2] This reaction is analogous to a published procedure,[3] with some modifications as described below. To a commercial solution of cyclopropylmagnesium bromide (0.5 M in THF, 27.2 mL, 13.6 mmol) at 0 °C, 6–methyl–5–hepten–2–one (**9**, 1.0 mL,

6.8 mmol) in THF (21 mL) was added dropwise over 13 minutes. The reaction was allowed to stir for 7 hours while it warmed to room temperature, and then it was quenched by addition of water and the mixture was extracted with Et_2O (3x). The combined organic extracts were washed with water, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Final purification by flash column chromatography (1% EtOAc in hexanes) afforded alcohol **10** (841 mg, 74%) as a light yellow oil. The ^{1}H NMR data was consistent with literature data,[2] except it was reported that the multiplet at 2.18–2.10 ppm was 1H rather than 2H: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.18–5.12 (m, 1H), 2.18–2.10 (m, 2H), 1.70 (br s, 3H), 1.64 (br s, 3H), 1.60–1.54 (m, 2H), 1.11 (s, 3H), 1.10 (br s, 1H), 0.94–0.86 (m, 1H), 0.41–0.26 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.7, 124.6, 71.1, 42.9, 25.9, 25.7, 22.7, 21.0, 17.7, 0.5, 0.4; HRMS (EI^+) *m/z* calcd for $C_{11}H_{18}$ $(M - H_2O)^+$ 150.1409, found 150.1417.

(6*E/Z*)–9–bromo–2,6–dimethyl–2,6–nonadiene (**11**).[1] This reaction is analogous to a published procedure.[4] To a stirred solution of $MgBr_2$ (958 mg, 5.20 mmol) in Et_2O (20 mL) at reflux, a solution of cyclopropyl alcohol **10** (672 mg, 3.99 mmol) in Et_2O (20 mL) was added dropwise. The resulting mixture was heated at reflux for 3 hours and then allowed to cool to room temperature. The reaction mixture was washed with water (2x) and brine. The organic extract was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Final purification by flash column chromatography (100% hexanes) afforded homoallylic bromide **11** (619 mg, 67%) as a clear oil. The ^{1}H NMR spectrum shows a 3:1 mixture of *E* and *Z* olefin isomers at C7. The ratio was determined by integration of the unique portions of the two overlapping triplets at 3.35 and 3.33ppm. The triplet corresponds to the methylene group adjacent to the bromide. Both ^{1}H and ^{13}C NMR data were consistent with literature data.[5]

Tetraethyl (3*E/Z*)–(2–(1–(4,8–dimethylnon–3,7-dien–1–yl)–1*H*–1,2,3–triazol–4–yl)ethane–1,1–diyl)bis–(phosphonate) (14). This reaction is analogous to a published procedure.[6] To a stirred solution of homoallylic bromide **11** (309 mg, 1.34 mmol) in DMF (5.2 mL) at room temperature, sodium azide (132 mg, 2.03 mmol) was added. The round bottom flask was covered with foil and allowed to stir overnight. The reaction then was diluted with EtOAc, washed with water (5x) and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Homoallylic azide **12** was afforded as a clear oil (180 mg, 70%) and was used immediately in the next reaction without further purification.

To a stirred solution of tetraethyl but–3–yne–1,1–diyldiphosphonate[7] (**13**, 202 mg, 0.62 mmol) and the homoallylic azide **12** (180 mg, 0.93 mmol) in *t*-BuOH/H_2O (4:1, 6.2 mL total), saturated $CuSO_4$ (0.01 mL) and sodium ascorbate (38 mg, 0.19 mmol) were added in sequence. The resulting reaction mixture was allowed to stir overnight at room temperature, and the solvent then was removed *in vacuo*. The resulting residue was dissolved in brine and extracted with EtOAc (5x). The combined organic extracts were washed with 5% NH_4OH, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Final purification by flash column chromatography (10% EtOH in hexanes) afforded triazole **14** (179 mg, 56%) as an oil that is a ~3:1 *E:Z* mixture of olefin isomers: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (s, 1H), 5.15–5.02 (m, 2H), 4.30 (t, J = 7.3 Hz, 2H), 4.21–4.06 (m, 10H), 3.33 (td, J_{HP} = 16.1 Hz, J = 6.5 Hz, 3H), 2.99 (tt, J_{HP} = 23.4 Hz, J = 6.6 Hz, 1H), 2.63–2.53 (m, 3H), 2.11–1.95 (m, 5H), 1.70 (s, 1H), 1.68 (s, 4H), 1.60 (s, 4H), 1.55 (s, 3H), 1.30 (t, J = 7.2 Hz, 8H), 1.29 (t, J = 7.2 Hz, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.7 (t, J_{CP} = 8.1 Hz), 144.7 (t, J_{CP} = 8.8 Hz), 139.2, 139.2, 131.8, 131.5, 123.8, 123.7, 122.1, 122.1, 119.4 118.6, 62.7 (d, J_{CP} = 6.4 Hz, 2C), 62.4 (d, J_{CP} = 6.7 Hz, 2C), 50.1 49.9, 39.3, 36.5 (t, J_{CP} = 132.5 Hz), 31.8, 29.6, 29.0, 28.9, 26.4, 26.2 25.6, 23.3, 22.0 (t, J_{CP} = 5.0 Hz), 17.5, 17.5

16.3–16.1 (m, 4C), 15.9; ^{31}P NMR: δ 22.4; HRMS (ES$^+$) *m/z* calcd for $C_{23}H_{44}N_3O_6P_2$ $(M + H)^+$ 520.2705, found 520.2709.

Sodium (3*E/Z*)–(2–(1–(4,8–dimethylnon–3,7-dien–1–yl)–1*H*–1,2,3–triazol–4–yl)ethane–1,1–diyl)bis–(phosphonate) (8). This reaction is analogous to a published procedure.[8,9] To a stirred solution of compound **14** (177 mg, 0.34 mmol) in CH_2Cl_2 (11.0 mL) at 0 °C, collidine (0.46 mL, 3.43 mmol) and TMSBr (97%, 0.55 mL, 4.13 mmol) were each added dropwise in succession. The reaction was allowed to stir overnight while it warmed to room temperature. Once the reaction was complete, which was determined by analysis of the ^{31}P NMR spectrum of the reaction mixture, the solvent was removed *in vacuo*. The residue then was diluted with toluene (10 mL) and concentrated *in vacuo* to remove excess TMSBr (3x). The resulting residue was dried on a vacuum line (30 minutes). It then was treated with 1.8 N NaOH (1.26 mL, 2.3 mmol) and allowed to stir at room temperature overnight. An additional aliquot of 3 N NaOH (0.17 mL, 0.51 mmol) was added to remove residual collidine observed in the ^{1}H NMR spectrum and the reaction was allowed to stir over the weekend. Anhydrous acetone then was added to the mixture, and it was placed in the freezer for 20 minutes. The resulting solid was removed by filtration, dissolved in water, and dried on a lyophilizer to provide the desired sodium salt **8** as a white powder that was a ~3:1 *E:Z* mixture of olefin isomers. A portion of the salt was dried in an Abderhalden overnight to calculate the yield (114 mg, 68%). For the 3:1 *E:Z* mixture of olefin isomers: ^{1}H NMR (300 MHz, D_2O) δ 7.85 (s, 1H), 5.21–5.09 (m, 2H), 4.38 (t, J = 6.6 Hz, 2H), 3.17 (td, J_{HP} = 20.7 Hz, J = 7.2 Hz, 2H), 2.65–2.54 (m, 2H), 2.18 (tt, J_{HP} = 20.7 Hz, J = 6.6 Hz, 1H), 2.10–1.92 (m, 4H), 1.68 (s, 3H), 1.61 (s, 3H), 1.46 (s, 3H); ^{13}C NMR (125 MHz, D_2O) δ 167.2, 148.7, 139.7, 139.3, 133.2, 132.9, 124.2, 124.1, 124.0, 123.9, 120.0, 119.2, 50.2, 50.0, 40.6 (t, J_{CP} = 112.4 Hz), 39.0, 31.1, 28.4, 28.3, 25.9, 25.9, 25.0, 22.8, 22.6, 17.1, 17.1,

15.2; ^{31}P NMR δ 19.3; LC-UV-MS: (95% H_2O/5% CH_3CN for 5 minutes, then increased to 100% CH_3CN over 10 minutes); Acquity UHPLC BEH C_{18} column (2.1 x 100 mm, 1.7 um); 0.3 mL/min; 15 min run; HRMS (ES^-) *m/z* calcd for $C_{15}H_{26}N_3O_6P_2$ $(M - H)^-$ 406.1297, found 406.1291.

Tetraethyl (2-(1-(4-methylpent-3-en-1-yl)-1*H*-1,2,3-triazol-4-yl)ethane-1,1-diyl)bis-(phosphonate) (**17**). According to the general procedure for preparation of triazole **14**, commercial 5–bromo–2–methyl–2–pentene (**15**, 97%, 0.42 mL, 3.04 mmol) was treated with NaN_3 (299 mg, 4.60 mmol), and the resulting azide (**16**, 195 mg, 1.56 mmol, 51%) then was isolated and treated with tetraethyl but–3–yne–1,1–diyldiphosphonate[7] (**13**, 391 mg, 1.20 mmol). A parallel work-up and purification afforded triazole **17** (284 mg, 52%) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (s, 1H), 5.12–5.05 (m, 1H), 4.28 (t, J = 7.2 Hz, 2H), 4.24–4.06 (m, 8H), 3.33 (td, J_{HP} = 16.1 Hz, J = 6.5 Hz, 2H), 2.96 (tt, J_{HP} = 23.4 Hz, J = 6.3 Hz, 1H), 2.61–2.51 (m, 2H), 1.70 (s, 3H), 1.56 (s, 3H), 1.30 (t, J = 7.1 Hz, 6H), 1.29 (t, J = 7.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.1 (t, J_{CP} = 8.5 Hz), 136.0, 122.4, 119.0, 63.0 (d, J_{CP} = 6.6 Hz, 2C), 62.7 (d, J_{CP} = 6.7 Hz, 2C), 50.2, 36.8 (t, J_{CP} = 132.9 Hz), 29.4, 25.9, 22.3 (t, J_{CP} = 4.7 Hz), 17.9, 16.5 (d, J_{CP} = 5.7 Hz, 2C), 16.5 (d, J_{CP} = 6.0 Hz, 2C); ^{31}P NMR: δ 22.5; HRMS (ES^+) *m/z* calcd for $C_{18}H_{36}N_3O_6P_2$ $(M + H)^+$ 452.2079, found 452.2081.

Sodium (2-(1-(4-methylpent-3-en-1-yl)-1*H*-1,2,3-triazol-4-yl)ethane-1,1-diyl)bis-(phosphonate) (**18**). According to the general procedure for preparation of sodium salt **8**, triazole **17** (142 mg, 0.31 mmol) in CH_2Cl_2 (8.5 mL) was treated with collidine (0.42 mL, 3.14 mmol) and TMSBr (97%, 0.50 mL, 3.75 mmol), and then 1N NaOH (1.60 mL, 1.60 mmol) under Ar. A parallel work-up, precipitation, and removal of water on a lyophilizer afforded the initial salt. The salt then was dissolved in water/D_2O and allowed to stir in 1N NaOH (0.065 mL)

under Ar over the weekend to remove residual collidine observed in the ^{1}H NMR spectrum. The salt then was precipitated by the addition of acetone, filtered, and lyophilized to remove water and provide the desired salt **18** (64 mg, 48%) as a white powder: ^{1}H NMR (500 MHz, D_2O) δ 7.83 (s, 1H), 5.14 (t, *J* = 6.7 Hz, 1H), 4.37 (t, *J* = 6.7 Hz, 2H), 3.16 (td, J_{HP} = 15.3 Hz, *J* = 6.8 Hz, 2H), 2.59–2.53 (m, 2H), 2.18 (tt, J_{HP} = 20.8 Hz, *J* = 6.3 Hz, 1H), 1.65 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (125 MHz, D_2O) δ 148.0 (br), 137.1, 124.3, 119.1, 50.2, 40.0 (t, J_{CP} = 112.3 Hz), 28.5, 24.9, 22.1, 16.8; ^{31}P NMR δ 18.7; LC-UV-MS: 1.07 min (95% H_2O/5% CH_3CN for 5 minutes, then increased to 100% CH_3CN over 10 minutes); Acquity UHPLC BEH C_{18} column (2.1 x 100 mm, 1.7 um); 0.3 mL/min; 15 min run (>99% total peak area at 210 and 254 nm); HRMS (ES^-) *m/z* calcd for $C_{10}H_{18}N_3O_6P_2$ $(M - H)^-$ 338.0671, found 338.0682.

Geranyl–homoprenyl triazole bisphosphonate (**19**). According to the published protocol,[10] to a stirred solution of bisphosphonate **17** (122 mg, 0.27 mmol) in THF (2.1 mL) at 0 °C were added solid NaH (60% dispersion in mineral oil, 19 mg, 0.48 mmol) and 15–crown–5 (0.01 mL, 0.05 mmol). After the reaction was allowed to stir at 0 °C for 30 minutes, geranyl bromide (101 mg, 0.47 mmol) was added dropwise. The resulting mixture was allowed to stir for 4.5 hours, while slowly warming to room temperature, then was quenched by addition of saturated NH_4Cl, and extracted with EtOAc (4x). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Final purification by flash column chromatography (10% EtOH in hexanes) afforded the bisphosphonate **19** (124 mg, 78%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (s, 1H), 5.54 (t, *J* = 6.9 Hz, 1H), 5.14–5.05 (m, 2H), 4.28 (t, *J* = 7.2 Hz, 2H), 4.21–4.05 (m, 8H), 3.38 (t, J_{HP} = 15.0 Hz, 2H), 2.70 (td, J_{HP} = 16.8 Hz, *J* = 6.9 Hz, 2H), 2.56 (td, *J* = 7.2 Hz, *J* = 7.2 Hz, 2H), 2.13–1.98 (m, 4H), 1.69 (s, 3H), 1.67 (s, 3H), 1.62 (s, 3H), 1.60 (s, 3H), 1.56 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 6H), 1.28 (t, *J* = 7.2 Hz, 6H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 142.9, 137.4, 135.8, 131.5, 124.6, 124.1, 119.2, 119.1, 62.9 (d, J_{CP} = 3.3 Hz), 62.8 (d, J_{CP} = 3.5 Hz), 62.6 (d, J_{CP} = 3.1 Hz), 62.6 (d, J_{CP} = 3.3 Hz), 50.2, 46.6 (t, J_{CP} = 130.6 Hz), 40.3, 29.8, 29.5, 27.7, 26.9, 25.9 (2C), 17.9 (2C), 16.7–16.5 (m, 5C); ^{31}P NMR δ 25.5; HRMS (ES^+) *m/z* calcd for $C_{28}H_{52}N_3O_6P_2$ $(M + H)^+$ 588.3331, found 588.3343.

Geranyl–homoprenyl triazole bisphosphonate sodium salt (**20**). According to the general procedure described for formation of sodium salt **8**, triazole **19** (114 mg, 0.19 mmol) in CH_2Cl_2 (5.4 mL) was treated with collidine (0.26 mL, 1.9 mmol) and TMSBr (97%, 0.31 mL, 2.3 mmol). The resulting residue was washed with toluene (10 mL, 3x) and then treated with 1N NaOH (1.0 mL, 1.0 mmol) under Ar for 30 minutes. A parallel work-up, precipitation, and removal of water on a lyophilizer afforded the initial salt. The salt then was dissolved in H_2O/D_2O and allowed to stir in 1N NaOH (0.2 mL, 0.2 mmol) under Ar for 1 hour to remove residual collidine observed in the ^{1}H NMR spectrum. The salt then was precipitated by addition of acetone, filtered, and lyophilized to remove water to provide the desired salt **20** (70 mg, 64%) as a white powder: ^{1}H NMR (500 MHz, D_2O) δ 8.07 (s, 1H), 5.59 (t, J = 6.5 Hz, 1H), 5.19–5.11 (m, 2H), 4.33 (t, J = 6.5 Hz, 2H), 3.26 (t, J_{HP} = 14.0 Hz, 2H), 2.57 (td, J = 7.0 Hz, J = 7.0 Hz, 2H), 2.50 (td, J_{HP} = 14.3 Hz, J = 6.5 Hz, 2H), 2.04–1.97 (m, 2H), 1.95–1.90 (m, 2H), 1.69 (s, 3H), 1.66 (s, 3H), 1.61 (s, 3H), 1.49 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (125 MHz, D_2O) δ 146.4, 136.9, 134.6, 133.3, 125.7, 124.9, 123.6, 119.1, 50.0, 43.6 (t, J_{CP} = 118.8 Hz), 39.4, 30.3, 28.5, 28.4, 26.2, 25.1, 24.9, 17.0, 16.9, 15.0; ^{31}P NMR δ 22.9; LC-UV-MS: 8.75 min (95% H_2O/5% CH_3CN for 5 minutes, then increased to 100% CH_3CN over 10 minutes); Acquity UHPLC BEH C_{18} column (2.1 x 100 mm, 1.7 um); 0.3 mL/min; 15 min run; HRMS (ES^-) *m/z* calcd for $C_{20}H_{34}N_3O_6P_2$ $(M - H)^-$ 474.1923, found 474.1918.

Immunoblot analysis. RPMI-8226 (ATCC, Manassas, VA) cells were incubated at 37 ºC and 5% CO_2 with test compounds for 48 hrs in RPMI-1640 media containing 10% fetal bovine serum and penicillin-streptomycin. Whole cell lysate was obtained using RIPA buffer (0.15 M NaCl, 1% sodium deoxycholate, 0.1% SDS, 1% Triton (v/v) X-100, 0.05 M Tris HCl) containing protease and phosphatase inhibitors. Protein content was determined using the bicinchoninic acid (BCA) method (Pierce Chemical, Rockford, IL). Equivalent amounts of cell lysate were resolved by SDS-PAGE, transferred to polyvinylidene difluoride membrane, probed with the appropriate primary antibodies, and detected using HRP-linked secondary antibodies and Amersham Pharmacia Biotech ECL Western blotting reagents per manufacturer's protocols.

FDPS and GGDPS enzyme assays. Recombinant FDPS and GGDPS were kindly provided by Dr. Raymond Hohl, Penn State Cancer Center. Recombinant enzyme (10 nM FDPS, 20 nM GGDPS) was incubated with assay buffer (50 mM Tris-HCl, pH 7.7, 20 mM $MgCl_2$, 5 mM TCEP, 5 μg/mL BSA) and test compounds for 10 minutes at room temperature. The reaction was initiated by the addition of 10 μM GPP (for FDPS) or 10 μM FPP (for GGDPS) and 10 μM [^{14}C]-IPP and was carried out at 37 °C for 30 minutes. The reaction was stopped by the addition of saturated NaCl. Radiolabeled FPP (for FDPS) or GGPP (for GGDPS) was extracted with *n*-butanol and counted via liquid scintillation counting. Compounds were tested in duplicate and 3-5 independent experiments were performed.

Lambda light chain ELISA. Cells were incubated in the presence or absence of test compounds for 48 hrs. The cells were lysed in RIPA buffer containing protease and phosphatase inhibitors. Protein content was determined using the BCA method. Human lambda light chain kit (Bethyl Laboratories, Montgomery, TX) was used to quantify intracellular monoclonal protein levels.

MTT cytotoxicity assay. RPMI-8226 cells incubated in phenol red-free media were plated (2.5 $x10^4$ cells/100 μL/well) in 96-well plates in the presence or absence of the novel compounds. After 48 hrs, 35 μL of a MTT solution (5 mg/mL PBS) was added to each well and cells were incubated for an additional 4 hrs. MTT solubilizing solution (0.01 M HCl/10% SDS) was added (100 μL/well). After overnight incubation at 37 °C, plates were analyzed on a microplate spectrophotometer at 540 nm. Compounds were tested in quadruplicate and two independent experiments were performed. The absorbance for control cells was defined as an MTT activity of 100%.

Statistics. Two-tailed *t*-testing was used to calculate statistical significance. An α of 0.05 was set as the level of significance. CalcuSyn software (Biosoft, Cambridge, UK) was used to analyze the concentration response curves and determine the IC_{50} values for the enzyme assays and the EC_{50} for the MTT cytotoxicity assays.

References

(1) Julia, M.; Julia, S.; Guegan, R. Terpenes and related compounds from methyl cyclopropyl ketone. *Bull. Soc. Chim. Fr.* **1960**, 1072-1079.

(2) Li, W. D. Z.; Peng, Y. An effective and highly stereoselective Julia olefination of cyclopropyl carbinol mediated by $CeCl_3 \cdot 7H_2O$/NaI. *Org. Lett.* **2005**, *7*, 3069-3072.

(3) Mothe, S. R.; Chang, P. W. H. Highly Efficient synthesis of tri- and tetrasubstituted conjugated enynes from Brønsted acid catalyzed alkoxylation of 1-cyclopropylprop-2-yn-1-ols with alcohols. *J. Org. Chem.* **2009**, *74*, 5887-5893.

(4) McCormick, J. P.; Barton, D. L. Synthetic applications of metal halides. conversion of cyclopropylmethanols into homoallylic halides. *J. Org. Chem.* **1980**, *45*, 2566-2570.

(5) Smitt, O.; Högberg, H. E. Syntheses of a prenylbisabolane diterpene, a natural insecticide from Croton linearis, and of the bisabolane sesquiterpenes (−)-delobanone and (−)-epi-delobanone. *Tetrahedron* **2002**, *58*, 7691-7700.

(6) Skapos, H.; Osipov, S. N.; Vorob'eva, D. V.; Odinets, I. L.; Lork, E.; Roeschenthaler, G. Synthesis of functionalized bisphosphonates via click chemistry. *Org. Biomol. Chem.* **2007**, *5*, 2361-2367.

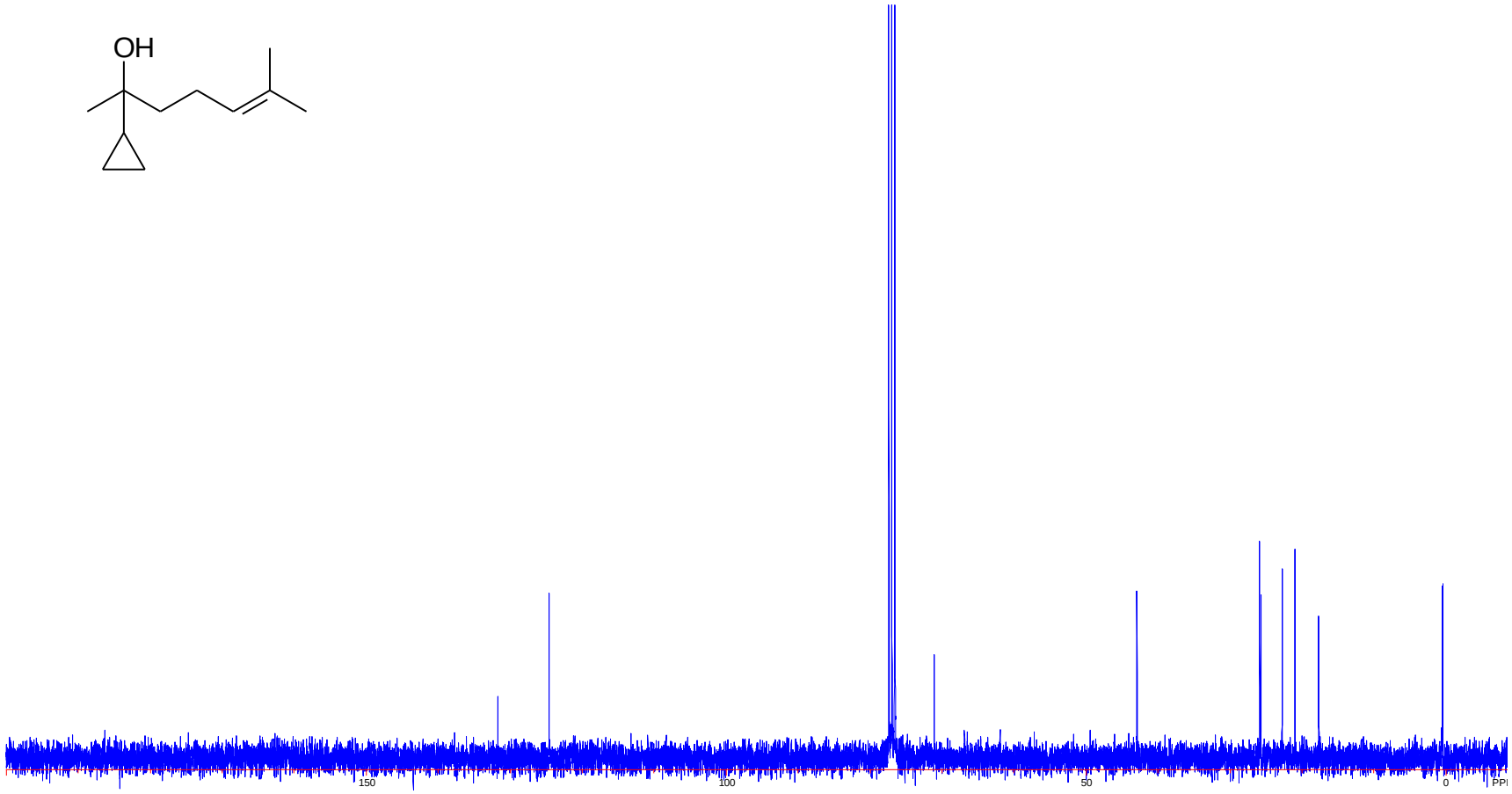
(7) Weinhart, M.; GroÌˆger, D.; Enders, S.; Dernedde, J.; Haag, R. Synthesis of dendritic polyglycerol anions and their efficiency toward L-selectin inhibition. *Biomacromolecules* **2011**, *12*, 2502-2511.

(8) Zhou, X.; Ferree, S. D.; Wills, V. S.; Born, E. J.; Tong, H.; Wiemer, D. F.; Holstein, S. A. Geranyl and neryl triazole bisphosphonates as inhibitors of geranylgeranyl diphosphate synthase. *Bioorg. Med. Chem.* **2014**, *22*, 2791-2798.

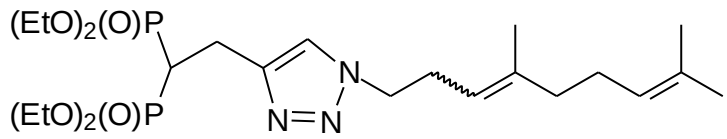
(9) McKenna, C. E.; Higa, M. T.; Cheung, N. H.; McKenna, M. C. The Facile Dealkylation of phosphonic acid dialkyl esters by bromotrimethylsilane. *Tetrahedron Lett.* **1977**, *18*, 155-158.

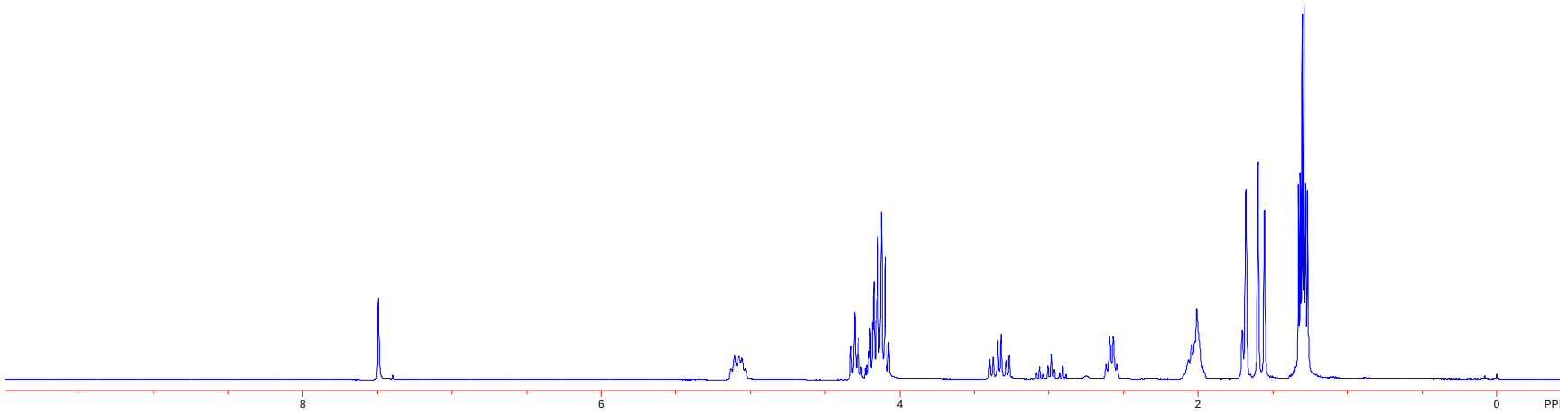
(10) Zhou, X.; Reilly, J. E.; Loerch, K. A.; Hohl, R. J.; Wiemer, D. F. Synthesis of isoprenoid bisphosphonate ethers through C–P bond formations: Potential inhibitors of geranylgeranyl diphosphate synthase. *Beilstein J. Org. Chem.* **2014**, *10*, 1645-1650.

300 MHz ^{1}H NMR spectrum of compound **10**.

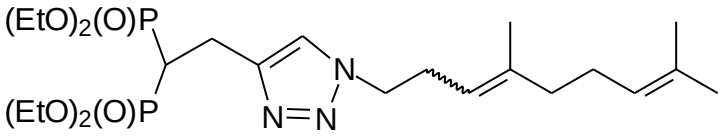


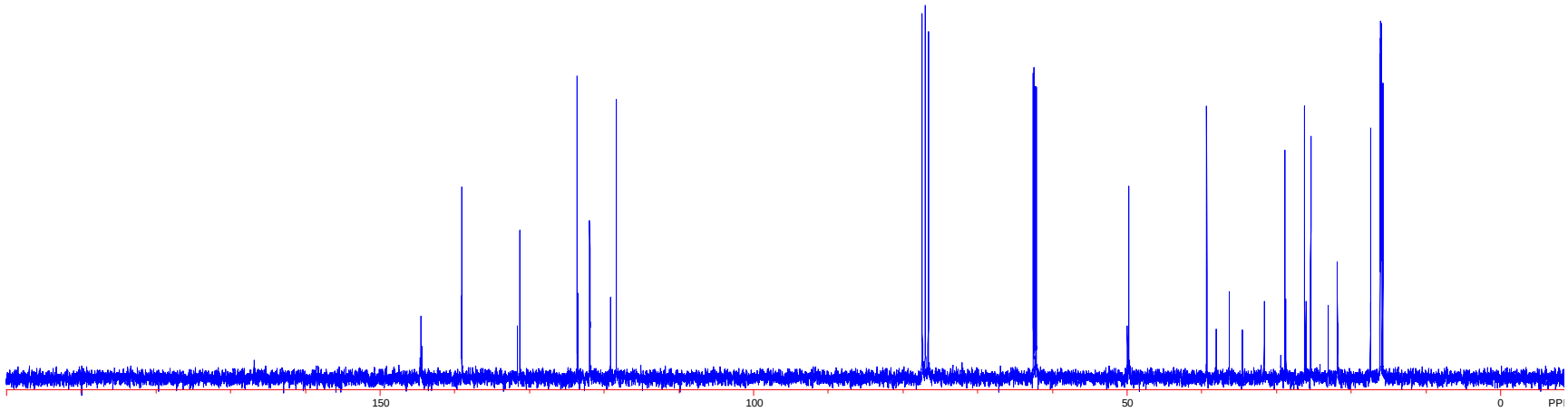
75 MHz ^{13}C NMR spectrum of compound **10**.



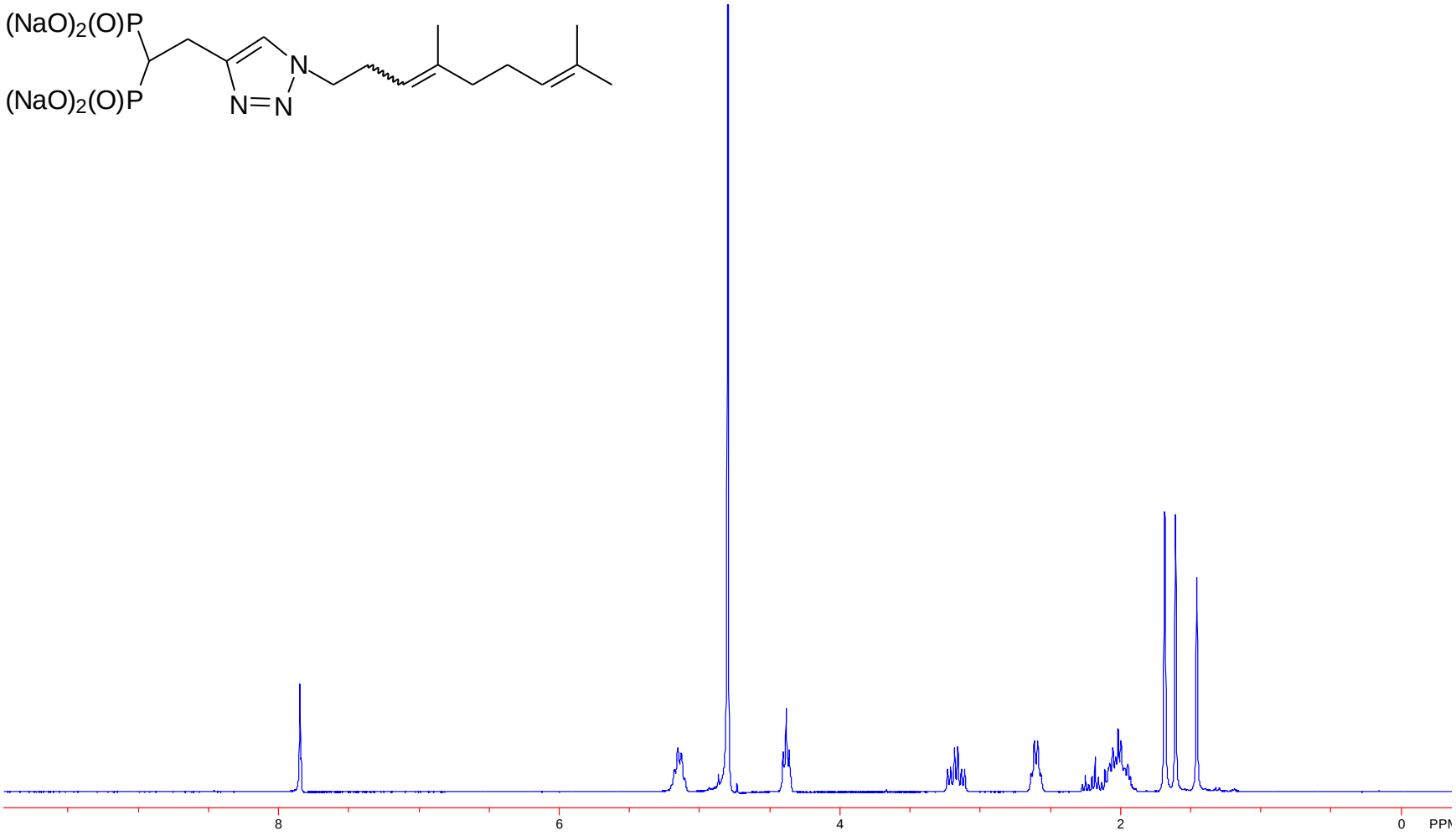


300 MHz ^{1}H NMR spectrum of compound **14**.

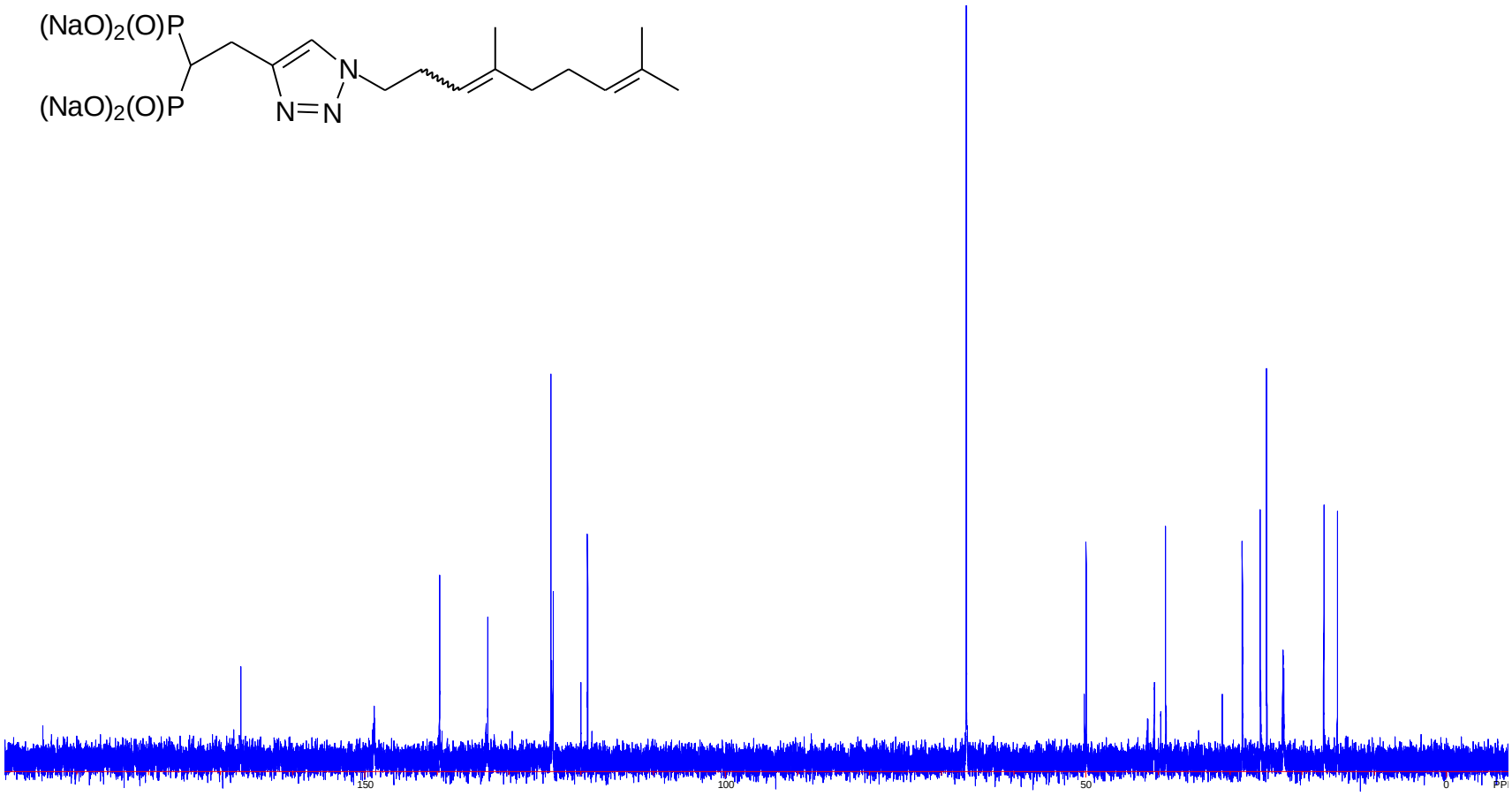




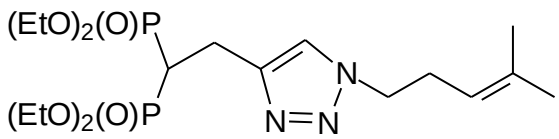
75 MHz ^{13}C NMR spectrum of compound **14**.

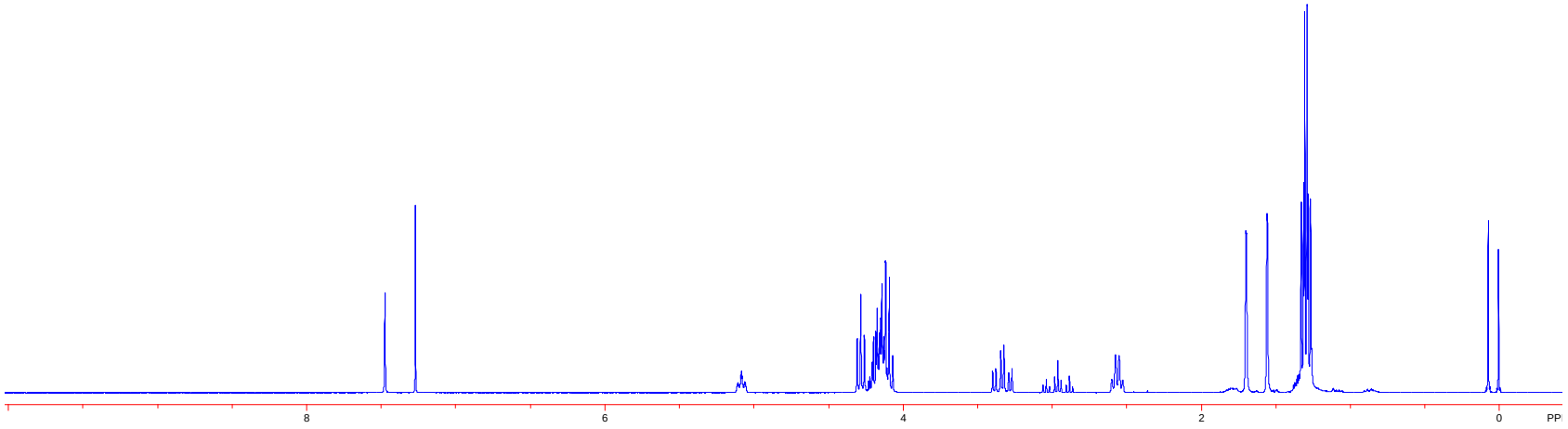


300 MHz ^{1}H NMR spectrum of compound **8**.

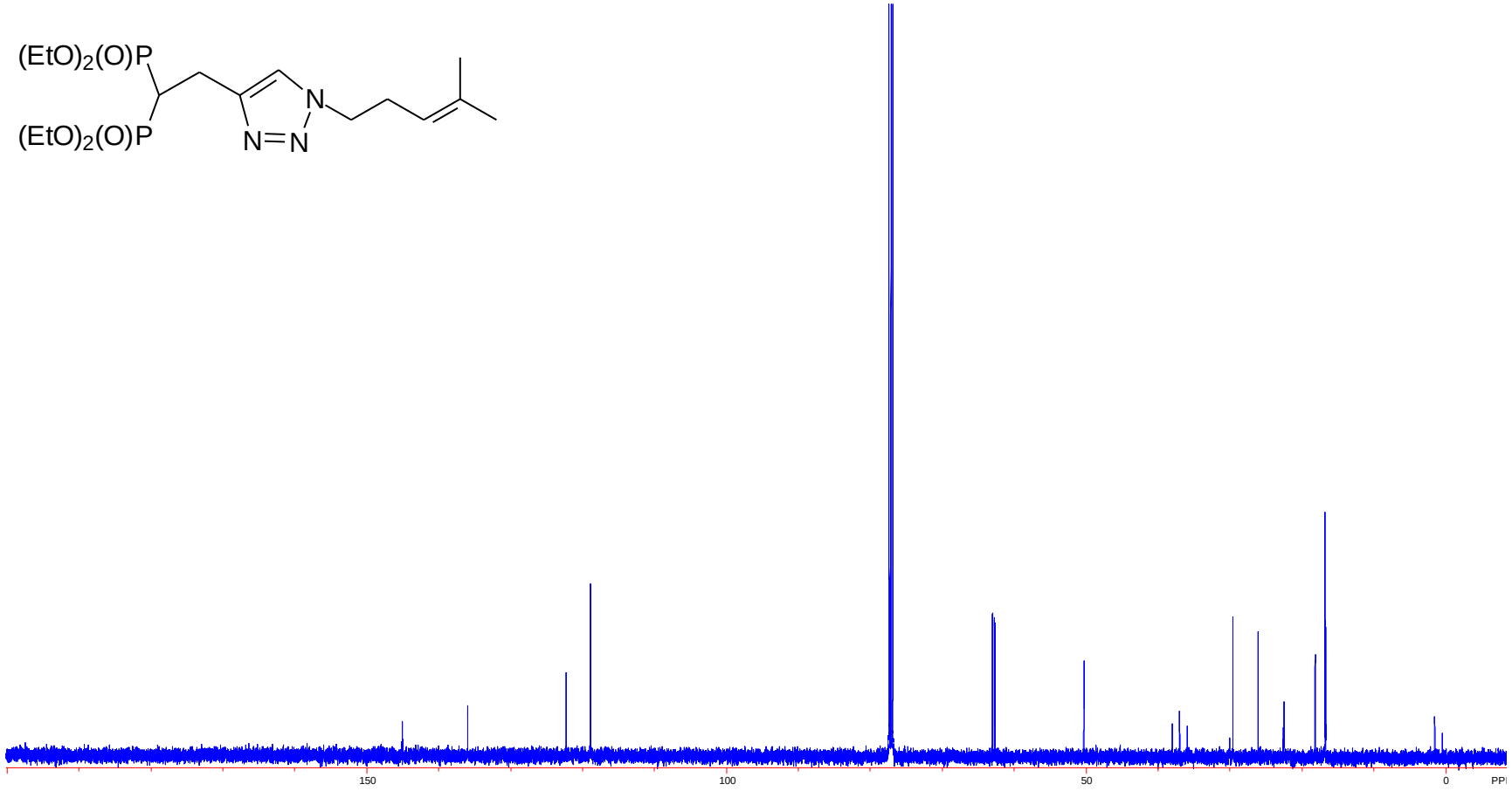


125 MHz ^{13}C NMR spectrum of compound **8.**

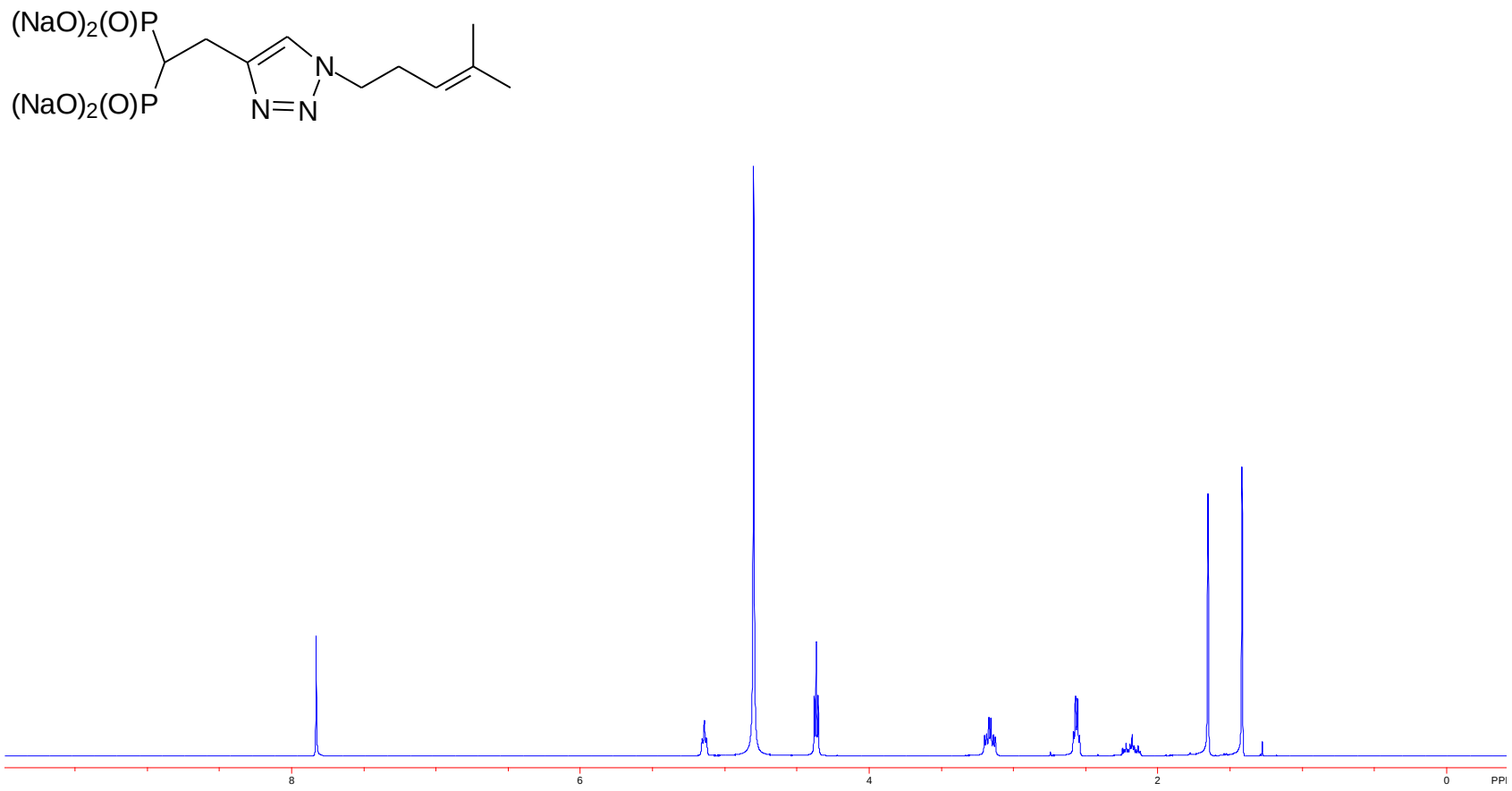




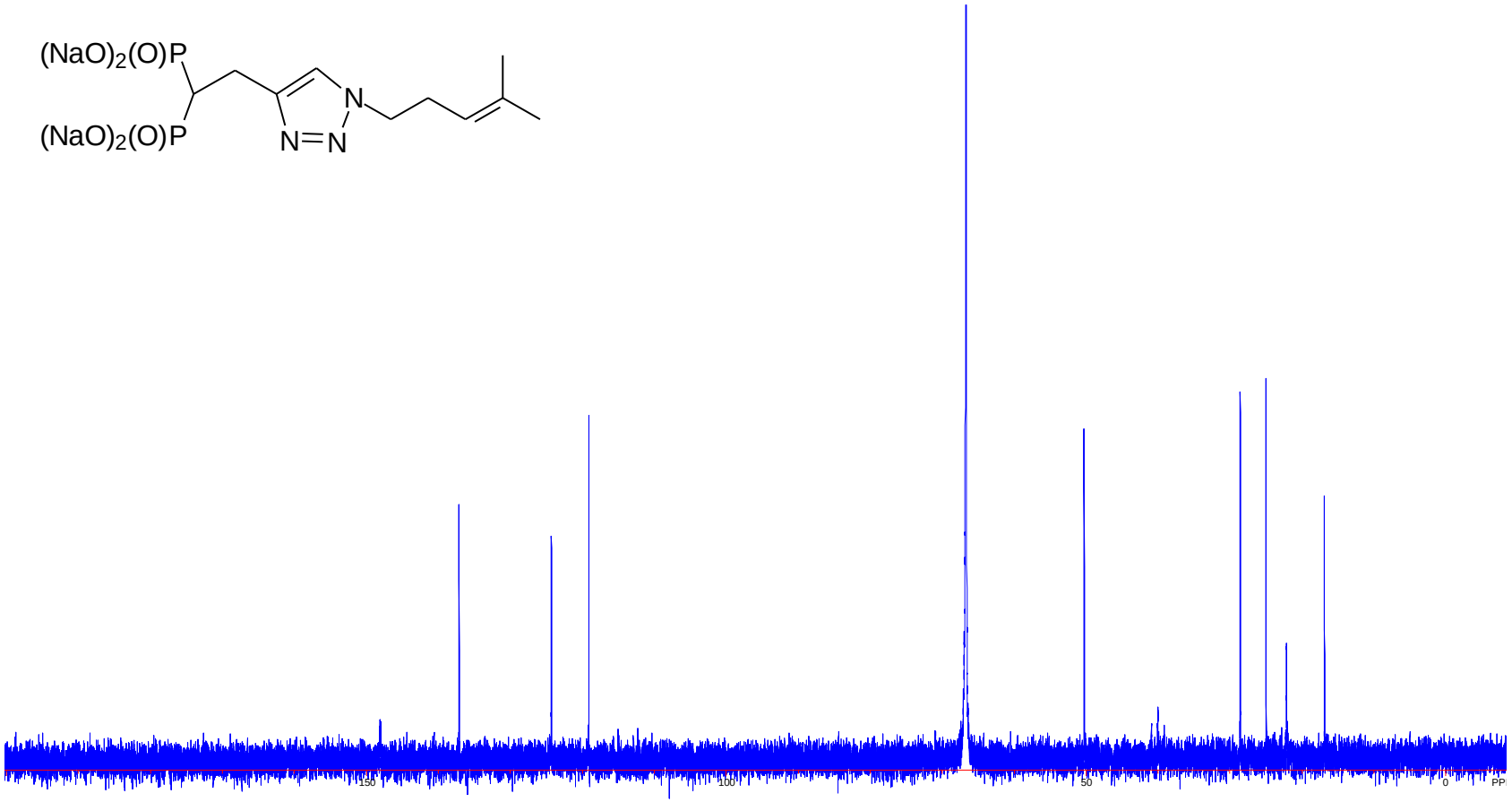
300 MHz ^{1}H NMR spectrum of compound **17**.



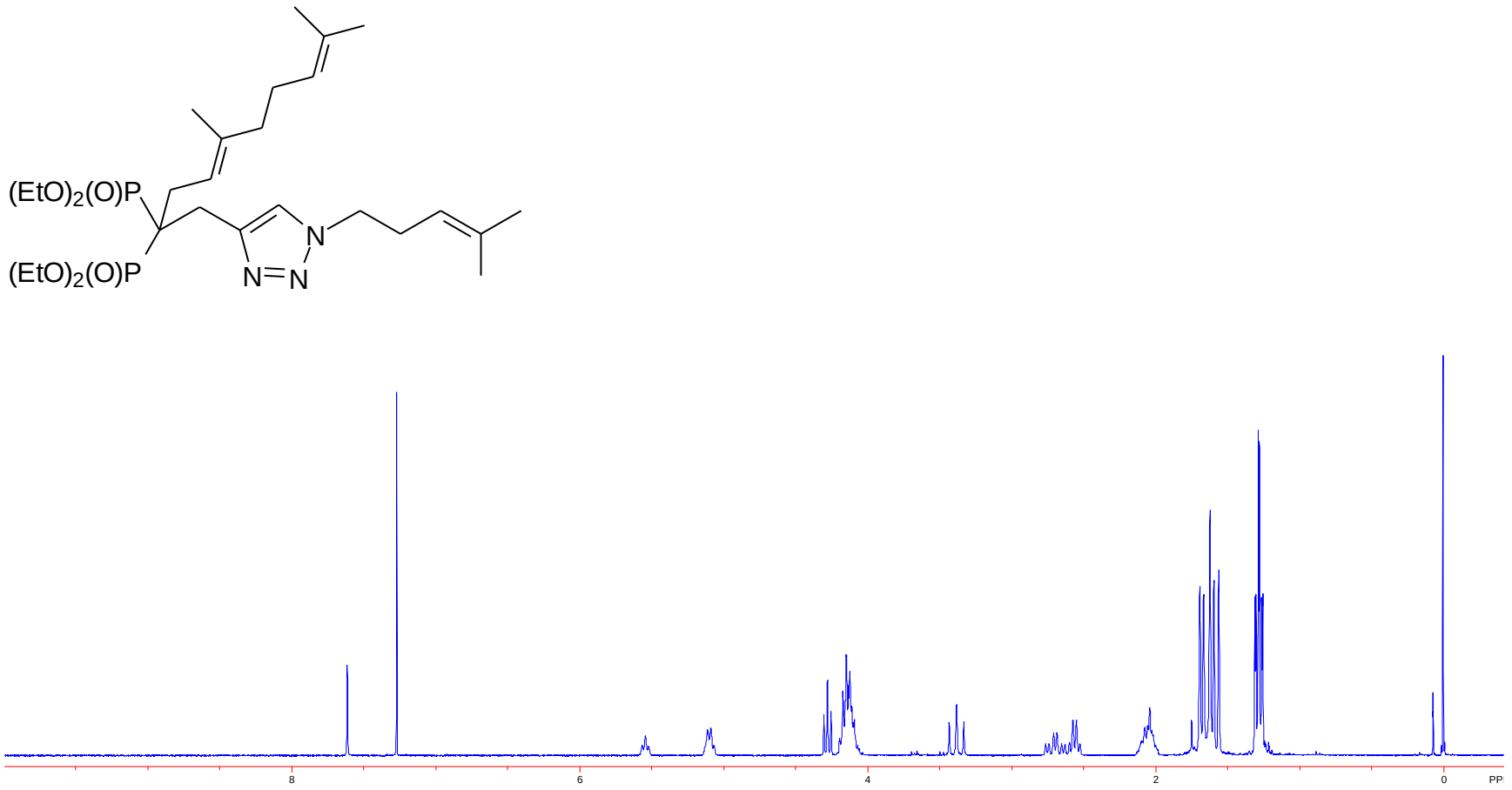
125 MHz ^{13}C NMR spectrum of compound **17**.



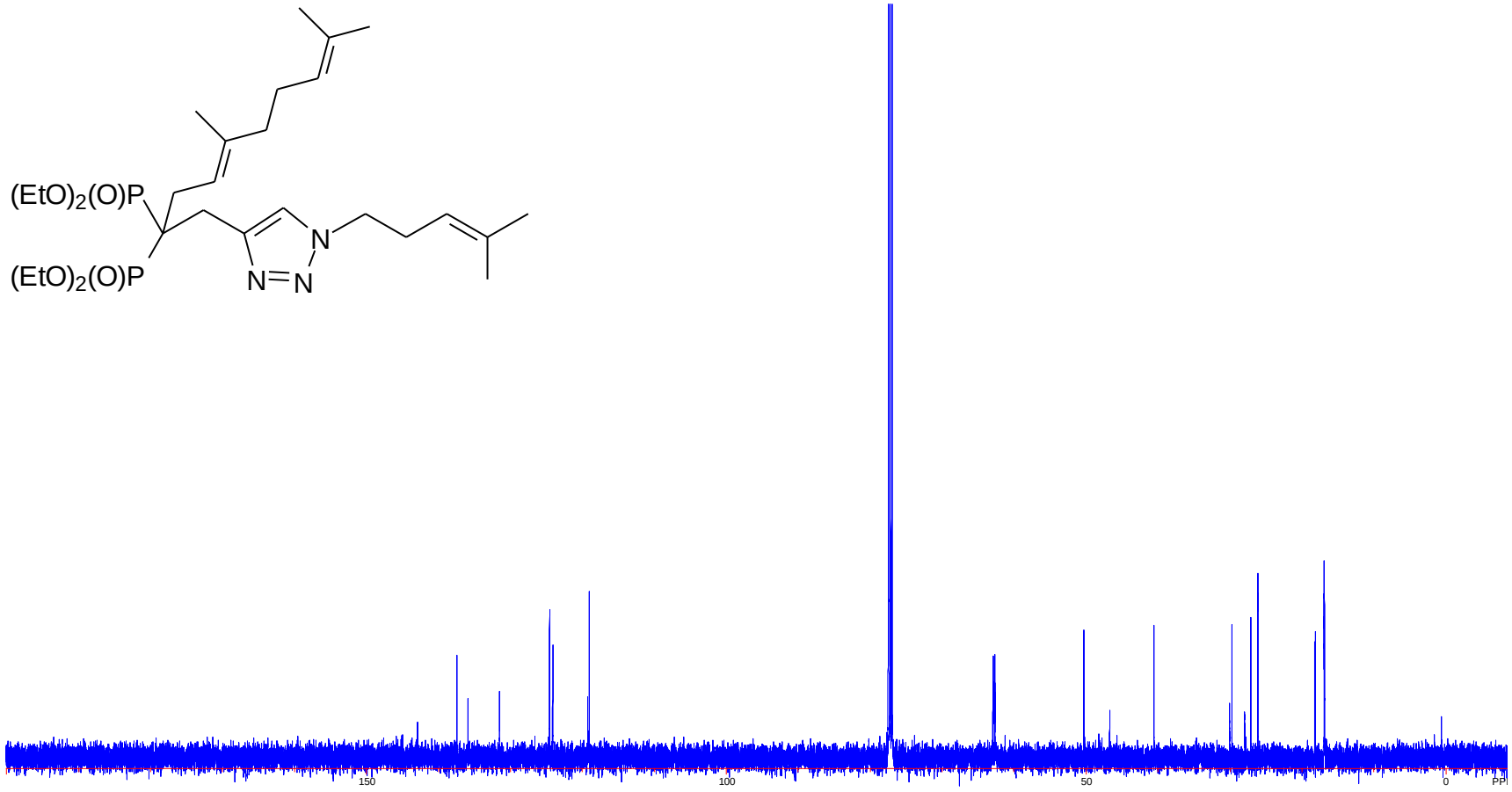
500 MHz ^{1}H NMR spectrum of compound **18**.



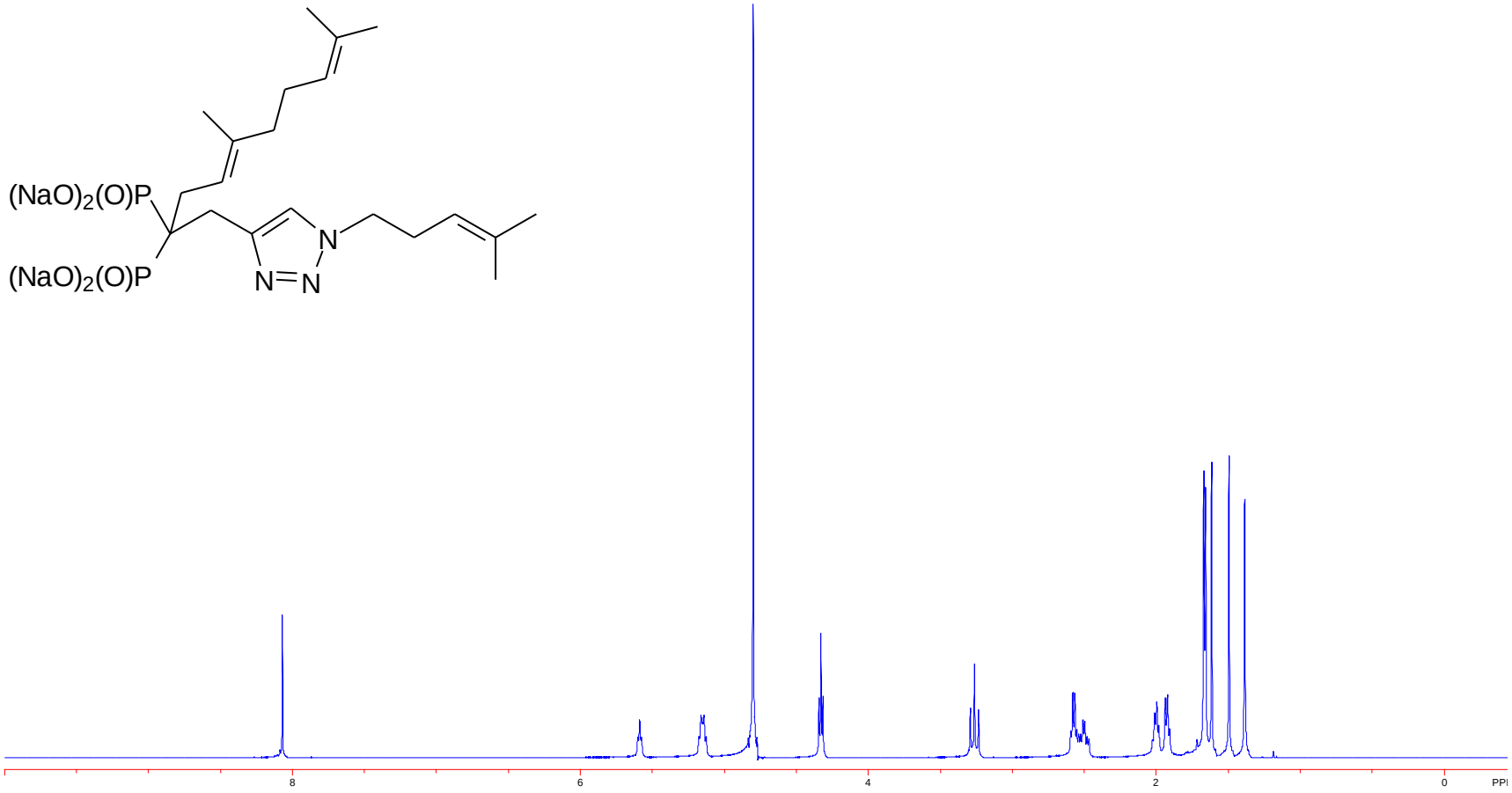
125 MHz ^{13}C NMR spectrum of compound **18**.



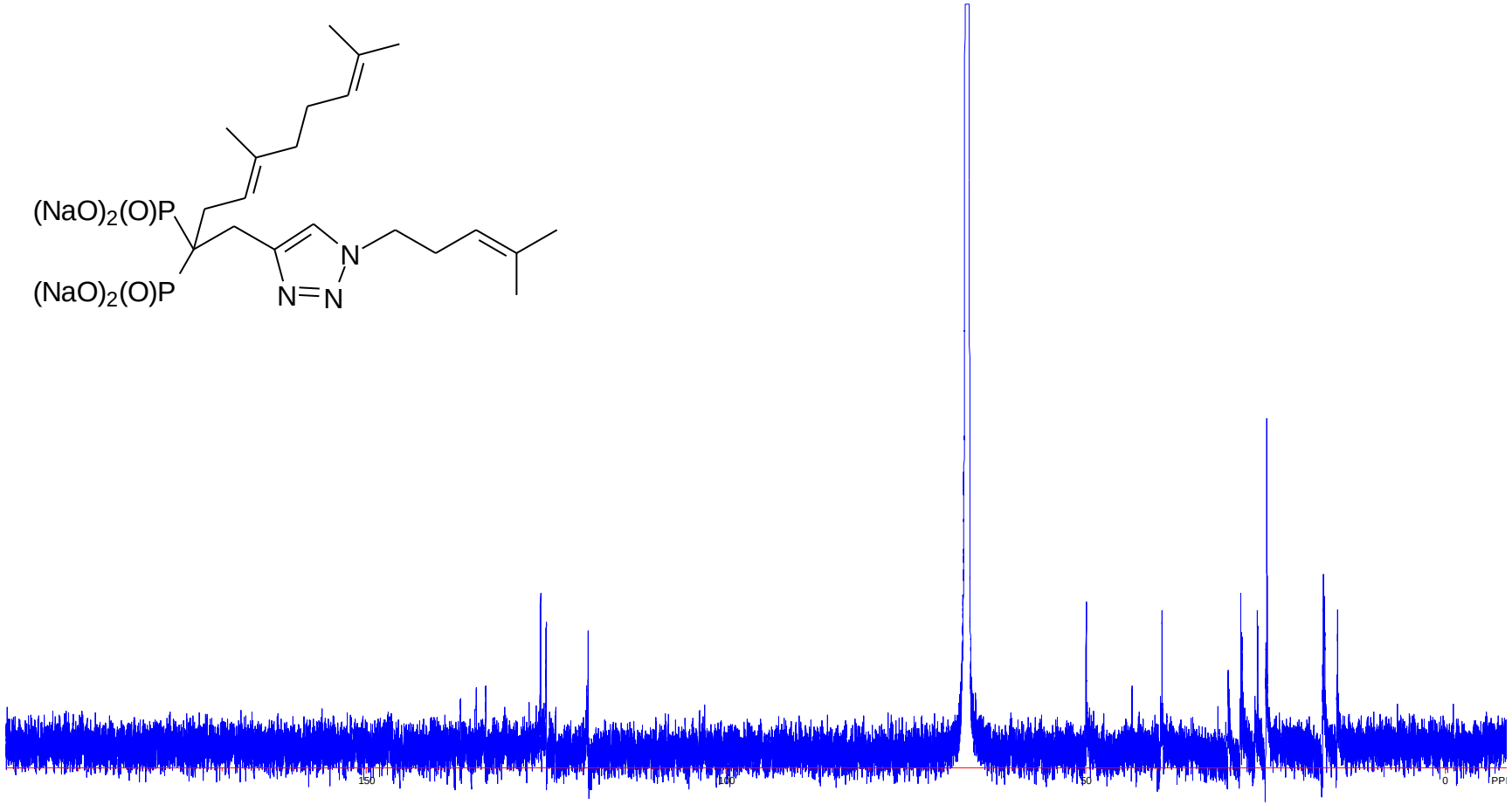
500 MHz ^{1}H NMR spectrum of compound **19**.



125 MHz ^{13}C NMR spectrum of compound **19**.



500 MHz ^{1}H NMR spectrum of compound **20**.



125 MHz ^{13}C NMR spectrum of compound **20**.