Supplementary information

Synthesis of new alendronate analogs for bone-targeted drug delivery strategies

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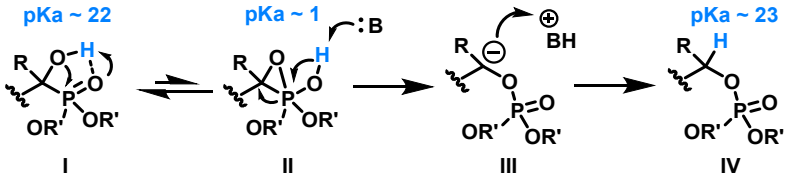
Table of contents

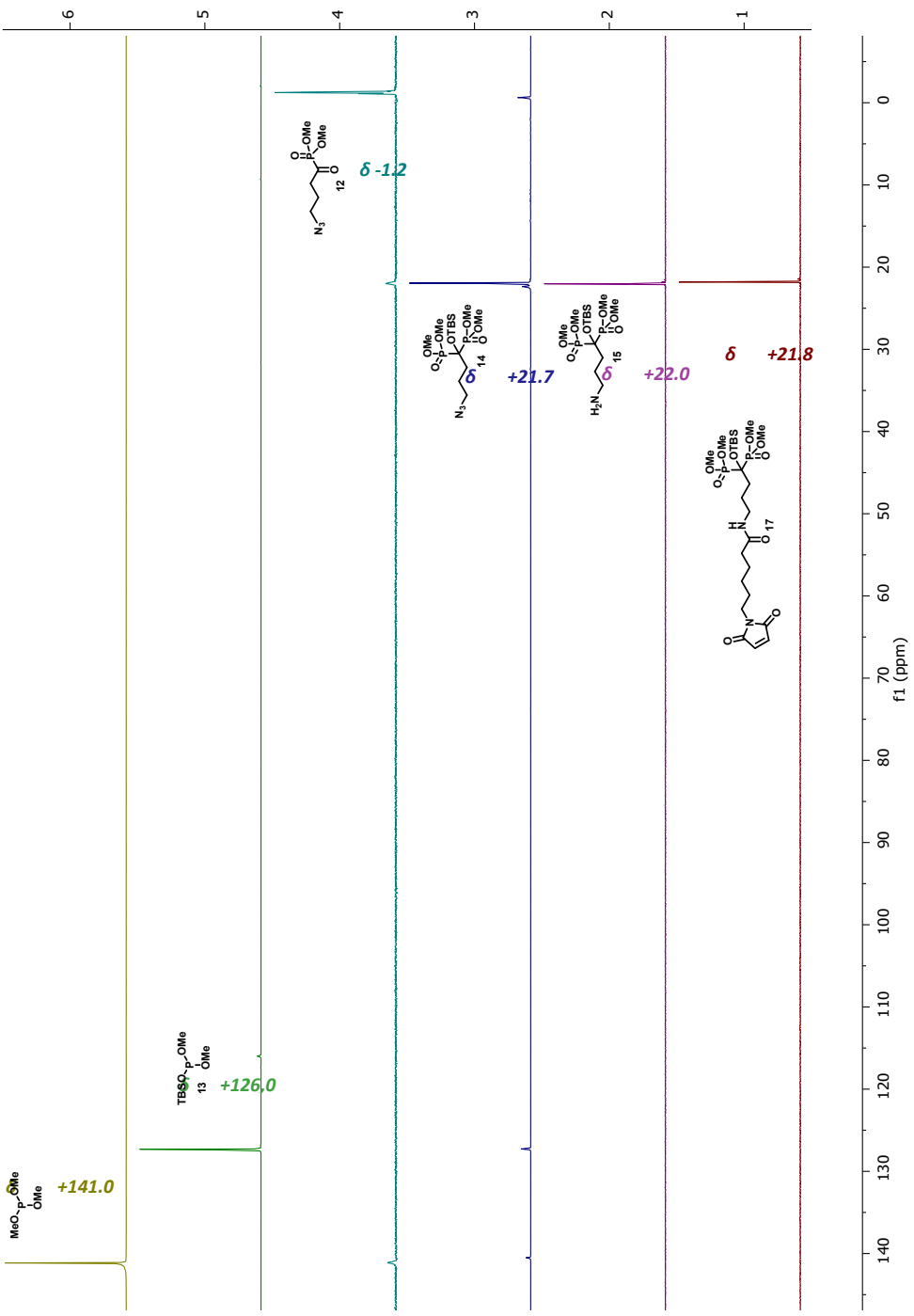
I. Mechanism of tetraester bisphosphonate isomerization



Scheme S1: Mechanism of tetraester bisphosphonate isomerization (from Niemi *et al*., 2000).

The pKa of the central alcohol is ~22, where the proton is typically not easily captured from the structure. Through intramolecular hydrogen bonding (**I**) and structure rearrangement, the intermediate product **II** is formed, for which pKa is ~1. The base is able to capture the proton to produce **III**, which takes the proton back from the base, and forms **IV**.

II. $^{31}P\{^{1}H\}$ NMR monitoring



Scheme S2: $^{31}P\{^{1}H\}$ NMR monitoring of phosphorus derivatives **12** to **17** synthesis (in CDCl3; full spectra)

III. Experimental procedures and characterization data of compounds

General remarks

Chemicals were purchased from common commercial suppliers (Sigma-Aldrich, Alfa Aesar, Acros Organics) and used as delivered. All solvents were extra-dried grade or distillated prior to use. Reactions requiring inert conditions were carried out in flame-dried glassware under an argon atmosphere.

NMR spectra were recorded at room temperature on a Bruker Avance-III-400 spectrometer (^{1}H, 400 MHz; ^{13}C, 101 MHz; ^{31}P, 162 MHz). Chemical shifts (δ) were given in ppm and coupling constants *J* in Hz. ^{1}H NMR (400 MHZ) spectra were calibrated based on the nondeuterated solvent residual peak ($CDCl_3$: 7.26 ppm), while H_3PO_4 (85% in water) was used as an external standard for ^{31}P NMR (162 MHz) notably for the monitoring of the reaction. The following abbreviations were used for ^{1}H, ^{13}C and ^{31}P NMR (162 MHz) spectra to indicate the signal multiplicity: *s* (singlet), *bs* (broad singlet), *d* (doublet), *dt* (doublet of triplets), *dm* (doublet of mutiplets), *t* (triplet), *td* (triplet of doublets), and *m* (multiplet). All ^{13}C NMR (101 MHz) spectra were measured with ^{1}H decoupling while ^{31}P NMR (162 MHz) spectra were measured with ^{1}H coupling (zoom on the spectrum) and ^{1}H decoupling. The reactions were followed by ^{31}P and ^{31}P{^{1}H} NMR experiments (the spectra were recorded without lock and shims).

High-resolution mass spectra (HRMS) were performed on a Bruker maXis mass spectrometer in positive (ESI+) mode by the "Fédération de Recherche" ICOA/CBM (FR2708) platform. Analyses were performed using a Q-TOF Impact HD mass spectrometer equipped with the electrospray (ESI) ion source (Bruker Daltonics). The instrument was operated in the positive mode with an ESI source on a Q-TOF mass spectrometer with an accuracy tolerance of 2 ppm. Samples were diluted with acetonitrile and water (15:85) and were analyzed by mass spectrometry in continuous infusion using a syringe pump at 200 µL/min. The mass profiles obtained by ESI-MS were analyzed using DataAnalysis software (Bruker Daltonics).

Infrared spectra were recorded on a ThermoFisher scientific Nicolet 380 FT-IR spectrometer. The Smart OMNI-Sampler Germanium ATR Sampling Accessory was used. The Smart OMNI-Sampler used an extremely rugged germanium ATR crystal. The wave numbers were expressed in cm^{-1} and comprised between 4000 and 675 cm^{-1}. The samples were analyzed neat. The following abbreviations were used for IR spectra to indicate the signal intensities: *w* (weak), *m* (medium), *s* (strong), *br* (broad).

Methyl 4-azidobutanoate **9**[1]

Methyl 4-bromobutanoate (1.26 mL, 10 mmol, 1 equiv.) was added to a sodium azide (780 mg, 12 mmol, 1.2 equiv.) suspension in anhydrous dimethylformamide (10 mL) at room temperature under argon. The reaction mixture was heated to 80°C for 16 h. Water (50 mL) was then added to the reaction mixture and the aqueous layer was extracted with Et_2O (3 x 100 mL). The organic layers were combined, washed with water (3 x 50 mL), brine (20 mL), dried over $MgSO_4$ and concentrated under vacuum to afford the product **9** (1.43 g,

quantitative) as a yellow oil. **NMR ^{1}H (400 MHz, $CDCl_3$)**: δ = 3.69 (s, 3H, OCH_3), 3.35 (t, ^{3}J = 6.7 Hz, 2H, CH_2N_3), 2.42 (t, ^{3}J = 7.2 Hz, 2H, C(O)CH_2), 1.95-1.87 (m, 2H, CH_2); **NMR ^{13}C {^{1}H} (101 MHz, $CDCl_3$)**: δ = 173.3 (*C*(O)CH_3), 51.9 (O*C*H_3), 50.7 (*C*H_2N_3), 31.0 (C(O)*C*H_2), 24.4 (*C*H_2).

4-Azidobutanoic acid <u>10</u>[1]

A solution of ester **<u>9</u>** (1.42 g, 9.9 mmol, 1 equiv.) in a 1:1 H_2O/MeOH mixture (20 mL) and sodium hydroxide (596 mg, 14.9 mmol, 1.5 equiv.) was heated to reflux for 3 h. After concentration of the reaction mixture under vacuum, the residue was dissolved in water (10 mL) and the pH was adjusted to 1 with HCl 37%. The reaction mixture was cooled to room temperature. The aqueous layer was extracted with Et_2O (3 x 30 mL). The organic layers were combined, washed with brine (30 mL), dried over $MgSO_4$ and concentrated under vacuum to afford the acid **<u>10</u>** (1.28 g, quantitative) as a yellow oil. **Rf**: 0.26 (PE/EtOAc 80:20); **NMR ^{1}H (400 MHz, $CDCl_3$)**: δ = 3.38 (t, ^{3}J = 6.7 Hz, 2H, CH_2N_3), 2.47 (t, ^{3}J = 7.2 Hz, 2H, C(O)CH_2), 1.96-1.87 (m, 2H, CH_2); **NMR ^{13}C {^{1}H} (101 MHz, $CDCl_3$)**: δ = 179.0 (*C*(O)OH), 50.6 (*C*H_2N_3), 31.0 (C(O)*C*H_2), 24.1 (*C*H_2).

4-Azidobutanoyl chloride <u>11</u>[1]

Oxalyl chloride (0.67 mL, 7.8 mmol, 1.5 equiv.) was added dropwise to a solution of carboxylic acid **<u>10</u>** (671 mg, 5.2 mmol, 1 equiv.) in anhydrous CH_2Cl_2 (10 mL), under argon, cooled to 0°C, followed by one drop of dry dimethylformamide. After stirring for 2 h at room temperature, the reaction mixture was concentrated under vacuum at 5°C. After several co-evaporations with dry CH_2Cl_2 and Et_2O, the crude product **<u>11</u>** (760 mg, quantitative) was obtained as a thick yellow oil. The crude oil was used immediately without further purification. **NMR ^{1}H (400 MHz, $CDCl_3$)**: δ = 3.40 (t, ^{3}J = 6.5 Hz, 2H, CH_2N_3), 3.02 (t, ^{3}J = 7.1 Hz, 2H, C(O)CH_2), 2.04-1.87 (m, 2H, CH_2); **NMR ^{13}C {^{1}H} (101 MHz, $CDCl_3$)**: δ = 173.4 (*C*(O)Cl), 49.9 (*C*H_2N_3), 44.1 (C(O)*C*H_2), 24.6 (*C*H_2).

***Tert*-butyldimethylsilyl dimethyl phosphite <u>13</u>**[2]

Dimethyl phosphite (2.76 mL, 30 mmol, 1 equiv.) was added dropwise to a sodium hydride (1.08 g, 45 mmol, 1.5 equiv.) suspension in anhydrous THF (55 mL), under argon, cooled down to 0°C. The reaction mixture was heated to reflux for 2.5 h until the complete disappearance of dimethyl phosphite was confirmed by ^{31}P{^{1}H} NMR analysis. After cooling to room temperature, *tert*-butyldimethylsilyl chloride (4.07 g, 27 mmol, 0.9 equiv.) was added and the reaction mixture was heated to reflux for 16 h. Insoluble salts were filtered on celite and the filtrate was concentrated under vacuum. After distillation under reduced pressure, product **<u>13</u>** (4.37 g, 65%) was obtained as a colorless oil. **NMR ^{31}P {^{1}H} (162 MHz, $CDCl_3$)**: δ = 127.3 (s); **NMR ^{31}P (162 MHz, $CDCl_3$)**: δ = 127.5-127.2 (m); **NMR ^{1}H (400 MHz, $CDCl_3$)**: δ = 3.82-3.68 (m, 6H, OCH_3), 0.94 (s, 9H, SiC(CH_3)$_3$), 0.28 (s, 6H, Si(CH_3)$_2$);

Tetramethyl (4-azido-1-((*tert*-butyldimethylsilyl)oxy)-butylidene)-1,1-bisphosphonate 14

Distillated trimethyl phosphite (614 μL, 5.2 mmol, 1 equiv.) was added dropwise to a solution of acyl chloride **11** (767 mg, 5.2 mmol, 1 equiv.) in anhydrous THF (1 mL) and cooled to -15°C under argon. After stirring 30 min at -15°C, the reaction mixture was heated to room temperature and stirred for 45 min more. The disappearance of trimethyl phosphite and formation of dimethyl α—ketophosphonate intermediate **12** were monitored by $^{31}P\{^{1}H\}$ NMR analysis. After cooling back to 0°C, *tert*-butyldimethylsilyl dimethyl phosphite **13** (1,17 g, 5.2 mmol, 1 equiv.) was added dropwise to the reaction mixture. After stirring at room temperature for 1 h, the reaction mixture was concentrated under vacuum. Purification by silica gel column chromatography (CH_2Cl_2/MeOH gradient 100:0 to 96:4) afforded the bisphosphonate product **14** (1.39 g, 60%) as a colorless oil. **Rf**: 0.45 (CH_2Cl_2/MeOH 96:4); **IR (KBr, cm^{-1})**: ν (cm^{-1}) = 2957 (m, C-H), 2856 (m, C-H), 2098 (s, N_3), 1254 (m, P-O-CH_3), 1143 (m, P=O), 1034 (s, C-O), 839 (m, P-O), 780 (m, P-C); **NMR ^{31}P {^{1}H} (162 MHz, $CDCl_3$)**: δ = 21.7 (s); **NMR ^{31}P (162 MHz, $CDCl_3$)**: δ = 22.0-21.3 (m); **NMR ^{1}H (400 MHz, $CDCl_3$)**: δ = 3.88-3.78 (m, 12H, OC*H*$_3$), 3.28 (t, ^{3}J = 6.5 Hz, 2H, C*H*$_2$N$_3$), 2.20-2.01 (m, 2H, C*H*$_2$), 2.01-1.86 (m, 2H, C*H*$_2$), 0.90 (s, 9H, SiC(C*H*$_3$)$_3$), 0.19 (s, 6H, Si(C*H*$_3$)$_2$); **NMR ^{13}C {^{1}H} (101 MHz, $CDCl_3$)**: δ = 77.9 (t, $^{1}J_{CP}$ = 157.2 Hz, P*C*P), 53.6 (dt, $^{2}J_{CP}$ = 23.5 Hz, $^{5}J_{CP}$ = 3.3 Hz, O*C*H$_3$), 51.7 (*C*H$_2$N$_3$), 33.1 (*C*H$_2$), 25.8 (SiC(*C*H$_3$)$_3$), 23.7 (t, $^{3}J_{CP}$ = 5.7 Hz, *C*H$_2$), 19.0 (Si*C*(CH$_3$)$_3$), -2.8 (Si(*C*H$_3$)$_2$); **MS (ESI+)** m/z : 446.16 $[M+H]^+$, 468.15 $[M+Na]^+$; **HRMS (ESI+)** calculated for [$C_{14}H_{34}N_3O_7P_2Si$] : 446.1636 ; measured : 446.1640.

2,5-Dioxopyrrolidin-1-yl 6-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl) hexanoate 16

N-(3-dimethylaminopropyl)-*N'*-ethyl carbodiimide hydrochloride (2.88 g, 15 mmol, 1.5 equiv.) and *N*-hydroxysuccinimide (1.38 g, 12 mmol, 1.2 equiv.) were sequentially added to a solution of 6-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl) hexanoic acid (2.11 g, 10 mmol, 1 equiv.) in dry dimethylformamide (10 mL), cooled down to 0°C, under argon. The reaction mixture was heated to 35°C for 12 h. After cooling to room temperature, dichloromethane (200 mL) was added and the organic layer was successively washed with 5% aqueous $NaHCO_3$ (50 mL), water (50 mL), brine (50 mL), dried over $MgSO_4$ and concentrated under vacuum. Purification by silica gel column chromatography (PE/EtOAc 40:60) afforded the NHS-activated ester **16** (2.74 g, 83%) as a white solid. **Rf**: 0.47 (PE/EtOAc 40:60); **NMR ^{1}H (400 MHz, $CDCl_3$)**: δ = 6.68 (s, 2H, C*H*=C*H*), 3.52 (t, ^{3}J = 7.2 Hz, 2H, NC*H*$_2$), 2.82 (s, 4H, NC(O)C*H*$_2$), 2.59 (t, ^{3}J = 7.4 Hz, 2H, C*H*$_2$C(O)), 1.76 (q, ^{3}J = 7.5 Hz, 2H, C*H*$_2$), 1.62 (q, ^{3}J = 7.5 Hz, 2H, C*H*$_2$), 1.47-1.34 (m, 2H, C*H*$_2$); **NMR ^{13}C {^{1}H} (101 MHz, $CDCl_3$)**: δ = 171.0 (2C, N*C*(O)CH=CH), 169.3 (2C, N*C*(O)CH$_2$), 169.0 (*C*(O)O), 134.2 (2C, *C*H=*C*H), 37.6 (N*C*H$_2$), 30.9 (CH$_2$*C*(O)), 28.2 (*C*H$_2$), 25.9 (*C*H$_2$), 25.7 (NC(O)*C*H$_2$), 24.2 (*C*H$_2$); **Mp (°C)**: 75°C.

Tetramethyl (4-(6-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)hexanamido)-1-((*tert*-butyldimethylsilyl) oxy)-butylidene)-1,1-bisphosphonate 17

10% Pd/C (81 mg, 50% w/w) was added to a stirred solution of azide **14** (162 mg, 0.36 mmol, 1 equiv.) in ethyl acetate (6 mL) under argon. After three vacuum/H_2 cycles to remove argon from the reaction flask, **14** was hydrogenated (balloon) at room temperature for 1 h. The reaction was monitored by TLC ninhydrin assay (CH_2Cl_2/MeOH 96:4) and ^{31}P NMR (162 MHz) (for **15**: ^{31}P {^1H}: δ = 22.0 (s)) until the complete disappearance of the starting material. The reaction mixture was then filtered on a celite pad. To the crude organic layer containing the amine intermediate **15**, NHS-activated ester **16** (111 mg, 0.36 mmol, 1 equiv.) and triethylamine (50 μL, 0.36 mmol, 1 equiv.) were sequentially added. The reaction mixture was stirred to room temperature for 2 h, until the complete disappearance of the amine **15**. The organic layer was then washed with water (3 x 10 mL), brine (10 mL), dried over $MgSO_4$ and concentrated under vacuum. Purification by silica gel column chromatography (CH_2Cl_2/MeOH gradient 100:0 to 96:4) afforded the bisphosphonate product **17** (206 mg, 94%) as a pale-yellow oil. **Rf**: 0.48 (CH_2Cl_2/MeOH 95:5); **IR (KBr, cm^{-1})**: ν (cm^{-1}) = 3309 (br, NH), 3087 (w, =C-H), 2957 (m, C-H), 2856 (m, C-H), 1708 (s, NC=O), 1655 (m, NC=O), 1250 (s, P-O-CH_3), 1143 (w, P=O), 1038 (s, C-O), 837 (m, P-O), 781 (m, P-C); **NMR ^{31}P {^{1}H} (162 MHz, $CDCl_3$):** δ = 21.8 (s); **NMR ^{31}P (162 MHz, $CDCl_3$) $_3$):** δ = 22.1-21.6 (m); **NMR ^{1}H (400 MHz, $CDCl_3$) $_3$):** δ = 6.67 (s, 2H, C*H*=C*H*), 5.75 (t, ^3J = 4.8 Hz, 1H, C(O)N*H*), 3.88-3.69 (m, 12H, OCH_3), 3.49 (t, ^3J = 7.2 Hz, 2H, NCH_2), 3.28-3.14 (m, 2H, C(O)NHCH_2) 2.13 (t, ^3J = 7.6 Hz, 2H, CH_2C(O)), 2.10-1.95 (m, 2H, CH_2), 1.89-1.74 (m, 2H, CH_2), 1.71-1.51 (m, 4H, CH_2), 1.40-1.18 (m, 2H, CH_2), 0.87 (s, 9H, SiC(CH_3)$_3$), 0.15 (s, 6H, Si(CH_3)$_2$); **NMR ^{13}C {^{1}H} (101 MHz, $CDCl_3$) $_3$):** δ = 172.9 (*C*(O)NH), 171.0 (2C, N*C*(O)CH=CH), 134.2 (*C*H=*C*H), 78.2 (t, $^1J_{CP}$ = 157.6 Hz, P*C*P), 53.7 (dt, $^2J_{CP}$ = 18.6 Hz, $^5J_{CP}$ = 3.5 Hz, O*C*H$_3$), 39.7 (C(O)NH*C*H$_2$), 37.7 (N*C*H$_2$), 36.6 (CH$_2$*C*(O)), 33.2 (*C*H$_2$), 28.4 (*C*H$_2$), 26.5 (*C*H$_2$), 25.9 (SiC(*C*H$_3$)$_3$), 25.2 (*C*H$_2$), 24.0 (t, $^3J_{CP}$ = 5.0 Hz, *C*H$_2$), 19.1 (Si*C*(CH$_3$)$_3$), -2.57 (Si(*C*H$_3$)$_2$); **MS (ESI+)** m/z: 613.25 [M+H]$^+$, 635.23 [M+Na]$^+$, 326.10 [M+Ca]$^{2+}$, 335.11 [M+Ca+H_2O]$^{2+}$; **HRMS (ESI+)** calculated for [$C_{24}H_{47}N_2O_{10}P_2Si$] : 613.2470 ; measured: 613,2461.

3-((1-(6-((4-((*Tert*-butyldimethylsilyl)oxy)-4,4-bis(dimethoxyphosphoryl)butyl)amino)-6-oxohexyl)-2,5-dioxopyrrolidin-3-yl)thio)propanoic acid 18

3-Mercaptopropanoic acid (31 µL, 0.35 mmol, 1.2 equiv.) and triethylamine (48 µL, 0.35 mmol, 1.2 equiv.) were added to a solution of maleimide-bisphosphonate **17** (180 mg, 0.30 mmol, 1 equiv.) in dry dichloromethane (4 mL), under argon. After stirring at room temperature for 2 h, the reaction mixture was washed with water (3 x 5 mL), brine (5 mL), dried over $MgSO_4$ and concentrated under vacuum to afford the pure thia-Michael addition product **18** (220 mg, quantitative) as a yellow oil.

Rf: 0.57 (CH_2Cl_2/MeOH 95:5); **IR (KBr, cm^{-1})**: ν (cm^{-1}) = 3373 (br, OH), 2956 (m, C-H), 2856 (m, C-H), 1775 (m, OC=O), 1703 (s, NC=O), 1650 (m, NC=O), 1248 (s, P-O-CH_3), 1148 (m, P=O), 1041

(s, C-O), 839 (m, P-O), 781 (m, P-C); **NMR ^{31}P {^{1}H} (162 MHz, $CDCl_3$)**: δ = 21.2 (s); **NMR ^{31}P (162 MHz, $CDCl_3$)**: δ = 21.5-20.9 (m); **NMR ^{1}H (400 MHz, $CDCl_3$)**: δ = 6.52-6.46 (m, 1H, C(O)N*H*), 3.87-3.79 (m, 12H, OCH_3), 3.76 (dd, ^{3}J = 9.0 Hz, ^{3}J = 3.3 Hz, 1H, SC*H*), 3.57 (t, ^{3}J = 5.9 Hz, 2H, NCH_2), 3.32-3.19 (m, 2H, C(O)NHCH_2), 3.13 (dd, ^{2}J = 18.8 Hz, ^{3}J = 9.0 Hz, 1H, SCH-CH_2-C(O)), 2.96 (t, ^{3}J = 7.3 Hz, 2H, CH_2S), 2.77-2.61 (m, 2H, HOC(O)CH_2), 2.57 (dd, ^{2}J = 18.8 Hz, ^{3}J = 3.3 Hz, 1H, SCH-CH_2-C(O)), 2.22-2.15 (m, 2H, CH_2C(O)), 2.14-2.02 (m, 2H, CH_2), 1.90-1.79 (m, 2H, CH_2), 1.76-1.54 (m, 4H, CH_2), 1.39-1.28 (m, 2H, CH_2), 0.88 (s, 9H, SiC(CH_3)$_3$), 0.16 (s, 6H, Si(CH_3)$_2$); **NMR ^{13}C {^{1}H} (101 MHz, $CDCl_3$):** δ = 176,5 (*C*(O)N), 174.8 (*C*(O)N), 173.8 (*C*(O)NH), 173.6 (*C*(O)OH), 78.1 (t, $^{1}J_{CP}$ = 159.1 Hz, P*C*P), 53.9 (dt, $^{2}J_{CP}$ = 21.1 Hz, $^{5}J_{CP}$ = 3.5 Hz, O*C*H$_3$), 40.0 (S*C*H), 39.6 (C(O)NH*C*H$_2$), 38.5 (N*C*H$_2$), 36.6 (*C*H$_2$C(O)), 36.0 (SCH-*C*H$_2$-C(O)), 34.1 (HOC(O)*C*H$_2$), 33.1 (*C*H$_2$), 27.1 (*C*H$_2$), 26.0 (*C*H$_2$), 25.9 (*C*H$_2$S) 25.8 (SiC(*C*H$_3$)$_3$), 25.4 (*C*H$_2$), 23.7 (t, $^{3}J_{CP}$ = 4.8 Hz, *C*H$_2$), 19.0 (Si*C*(CH$_3$)$_3$), -2.5 (Si(*C*H$_3$)$_2$).

MS (ESI+) m/z: 719.25 $[M+H]^+$, 741.24 $[M+Na]^+$, 379.10 $[M+Ca]^{2+}$; **HRMS (ESI+)** calculated for $[C_{27}H_{53}N_2O_{12}P_2SSi]$: 719.2558; measured: 719.2547.

Reference:

1 J. Dussart, N. Guedeney, J. Deschamp, M. Monteil, O. Gager, T. Legigan, E. Migianu-Griffoni and M. Lecouvey, *Org. Biomol. Chem.*, 2018, **16**, 6969–6979.

2 T. Yokomatsu, Y. Yoshida and S. Shibuya, *J. Org. Chem.*, 1994, **59**, 7930–7933.

III. NMR Spectra of compounds

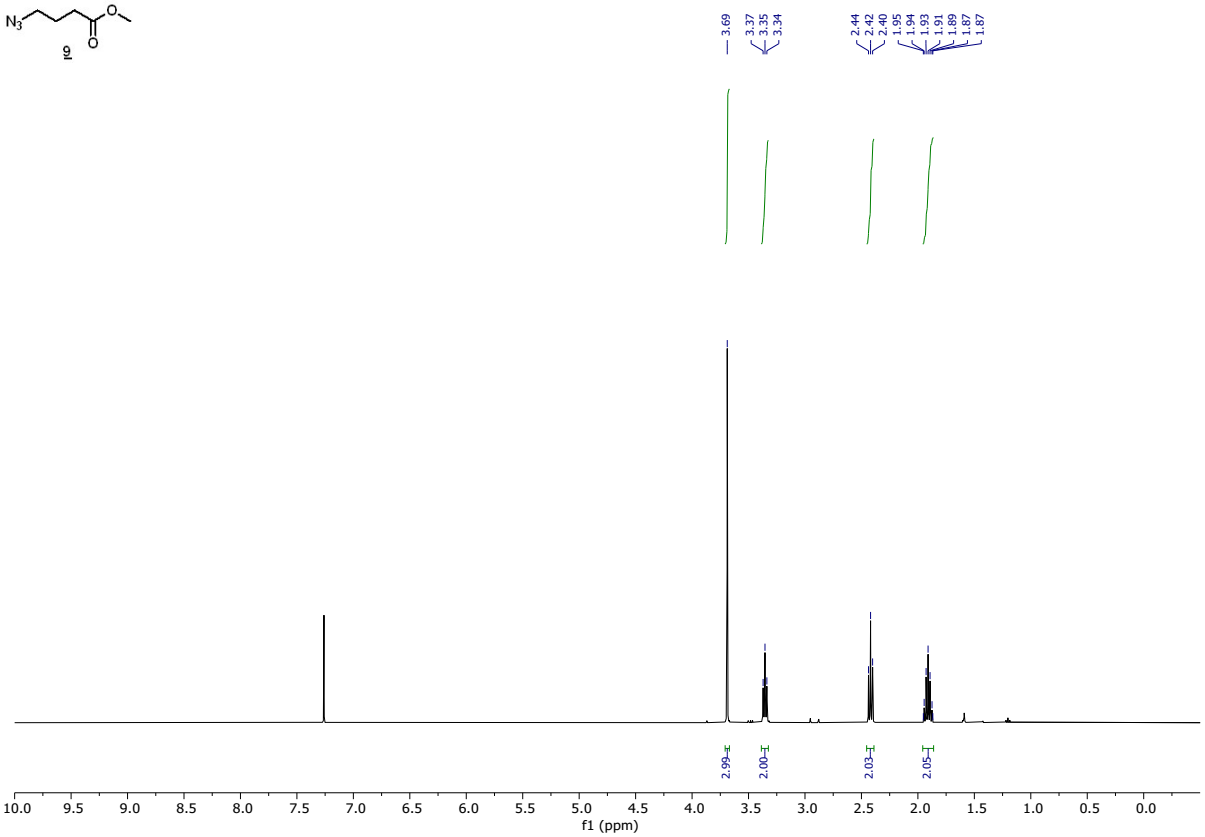


Figure S1: Full ^{1}H NMR (400 MHZ) spectrum for **9**

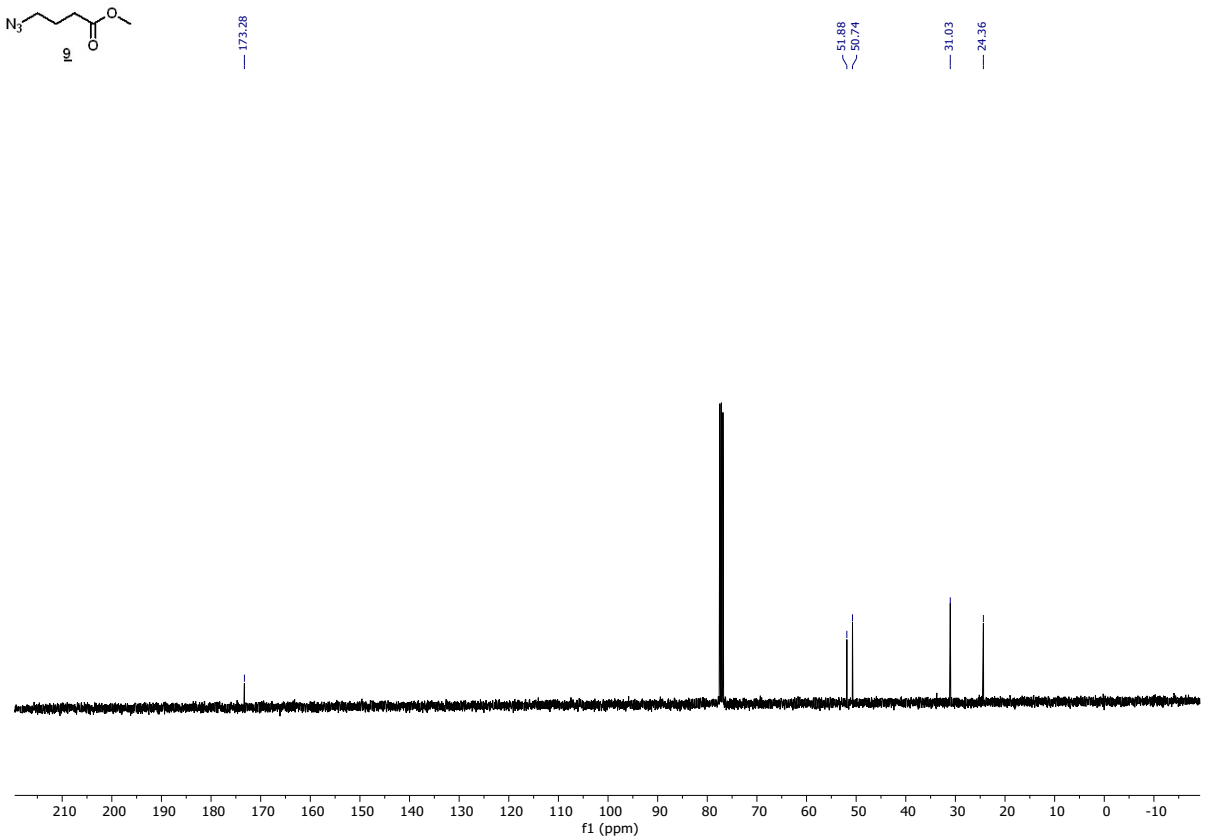


Figure S2: Full ^{13}C NMR (101 MHZ) spectrum for **9**

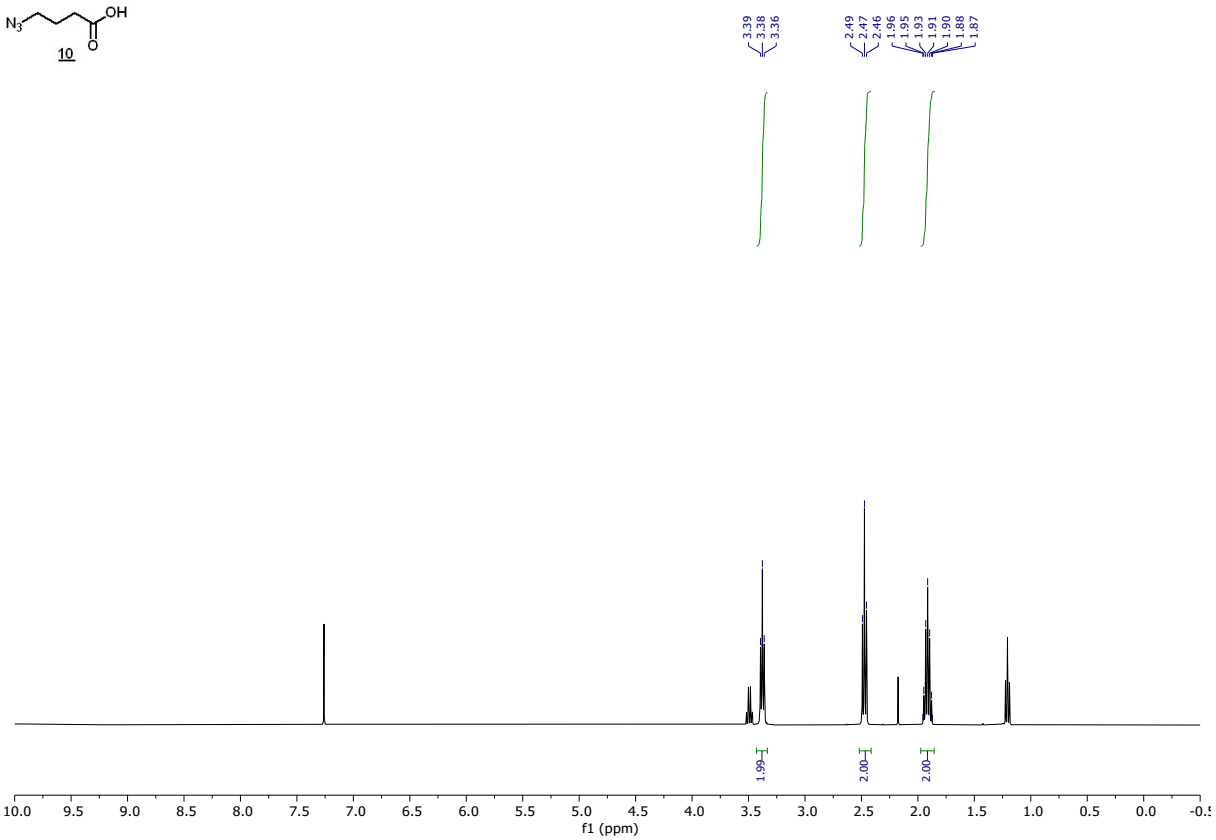


Figure S3: Full ^{1}H NMR (400 MHZ) spectrum for **<u>10</u>**

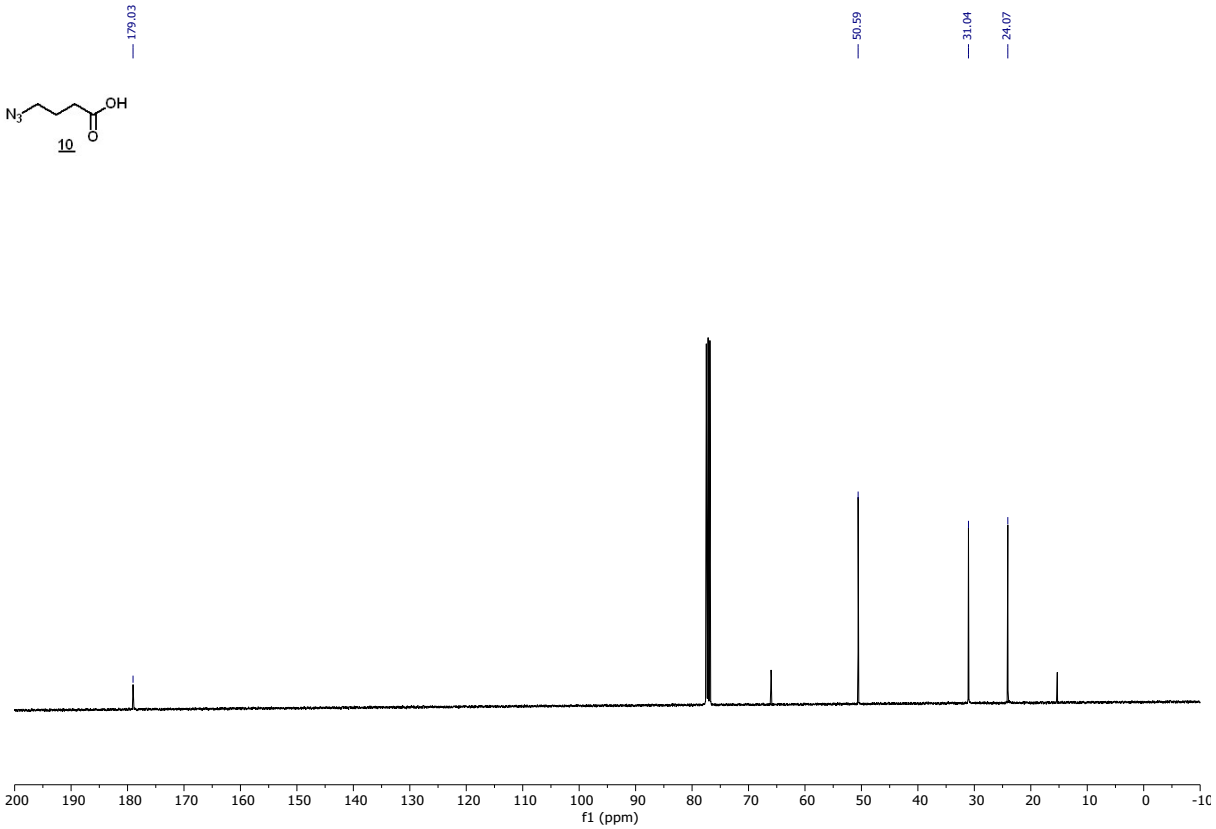


Figure S4: Full ^{13}C NMR (101 MHZ) spectrum for **<u>10</u>**

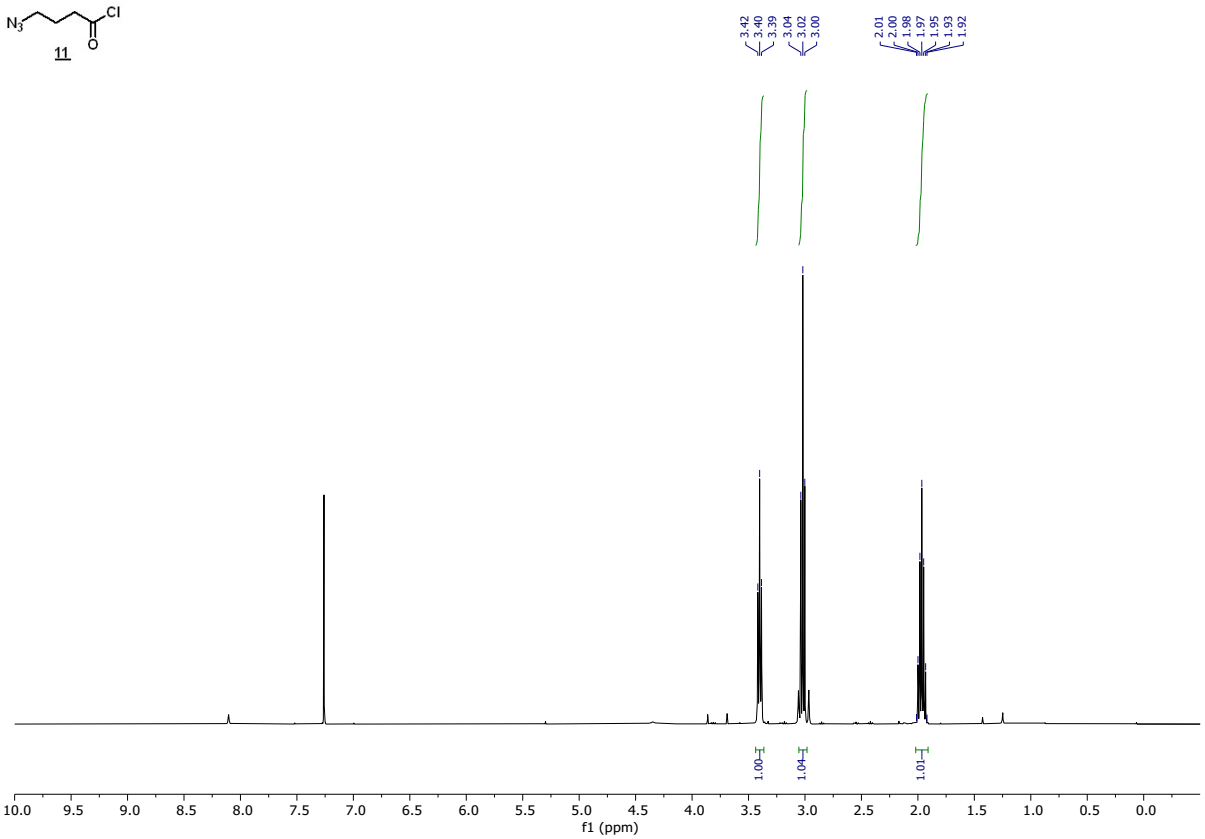


Figure S5: Full ^{1}H NMR (400 MHZ) spectrum for **<u>11</u>**

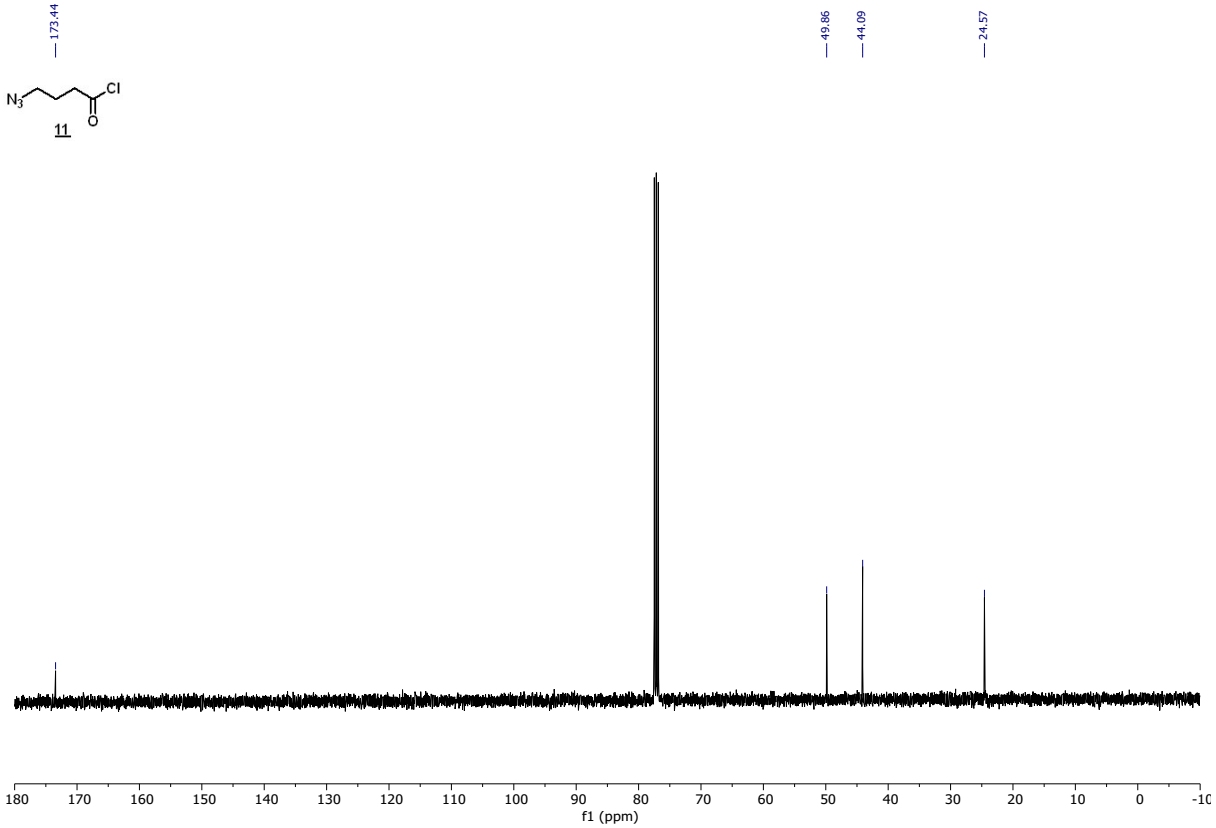


Figure S6: Full ^{13}C NMR (101 MHz) spectrum for **<u>11</u>**

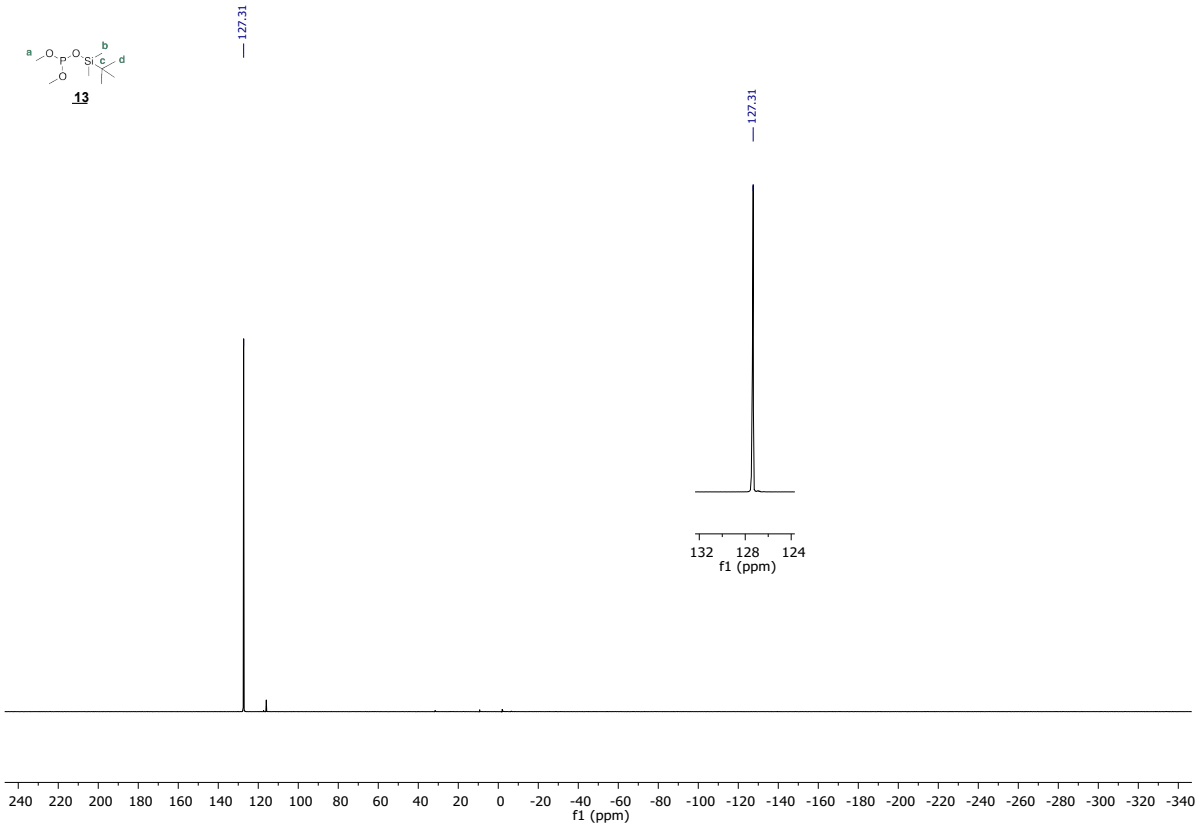


Figure S7: Full ^{31}P {^{1}H} NMR spectrum, and zoomed ^{31}P NMR (162 MHz) spectrum for **13**

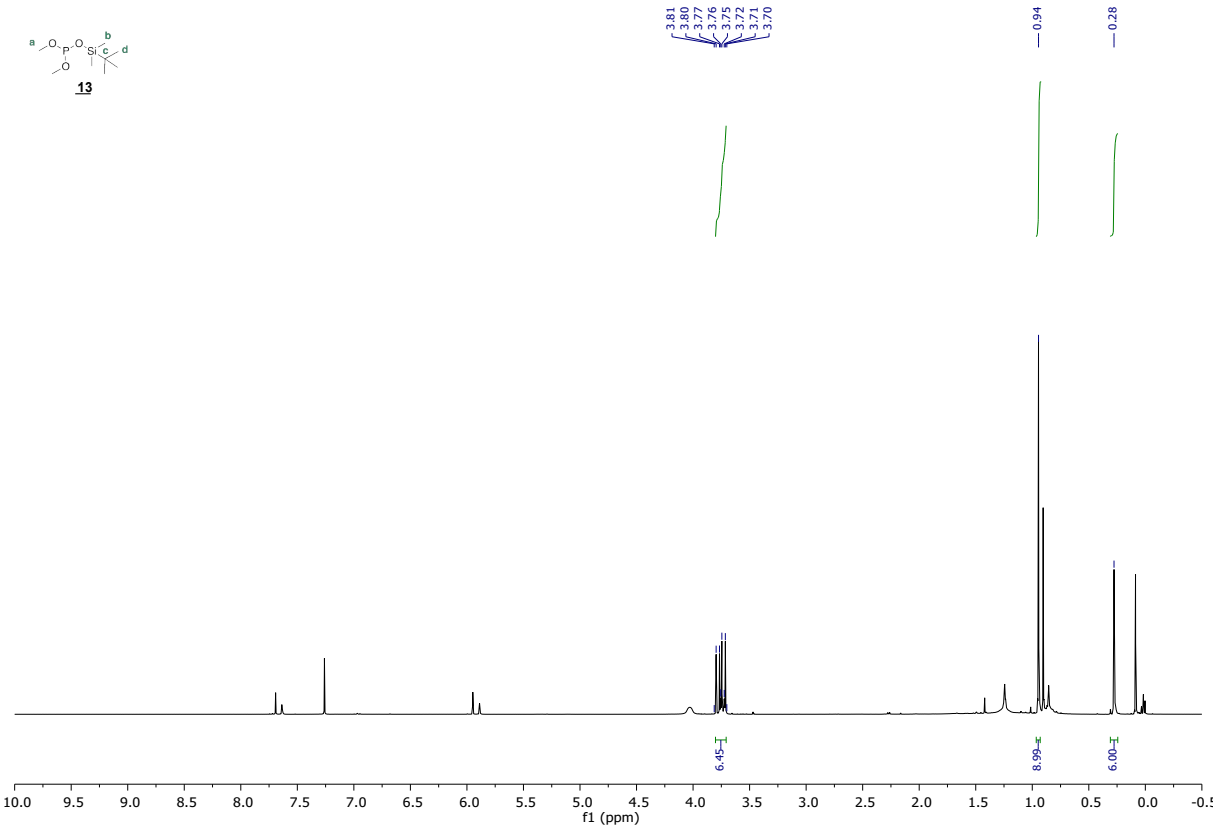


Figure S8: Full ^{1}H NMR (400 MHZ) spectrum for **13**

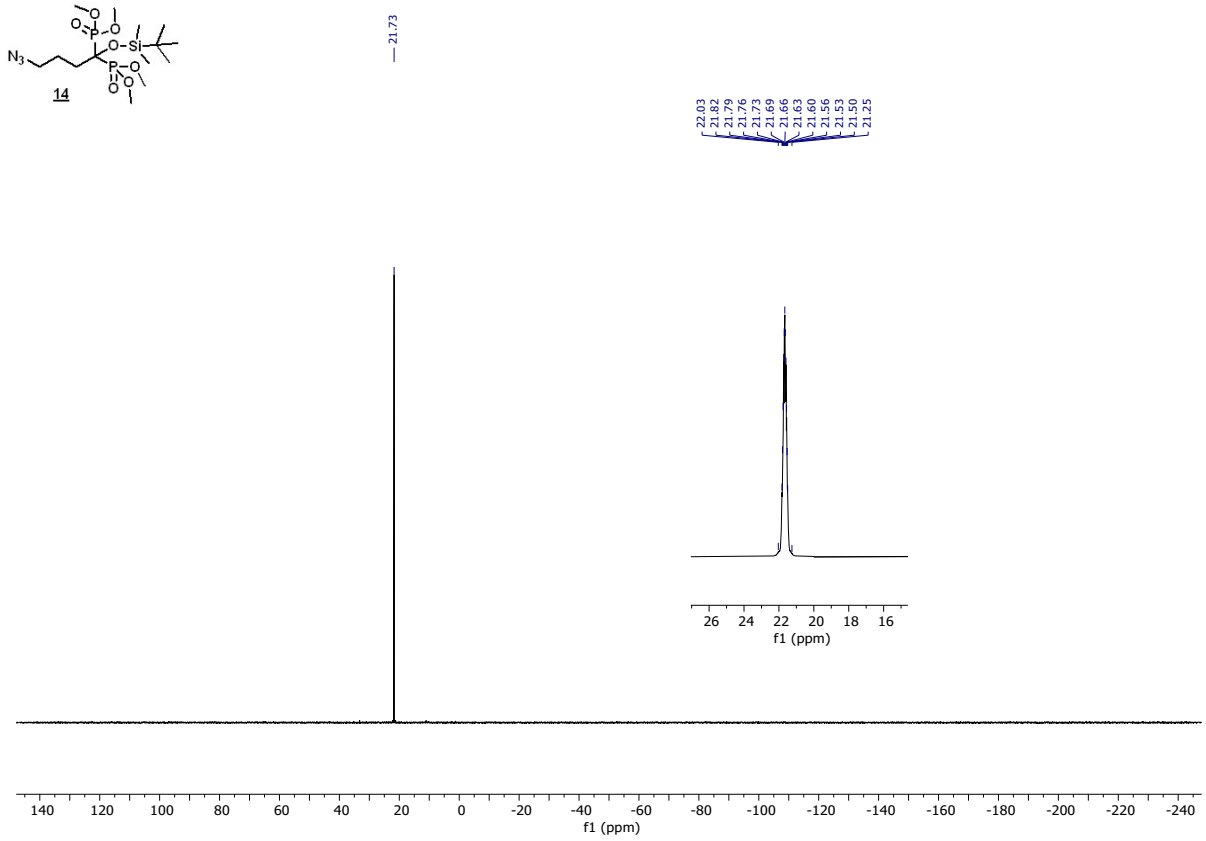


Figure S9: Full ^{31}P {^{1}H} NMR spectrum, and zoomed ^{31}P NMR (162 MHZ) spectrum for **<u>14</u>**

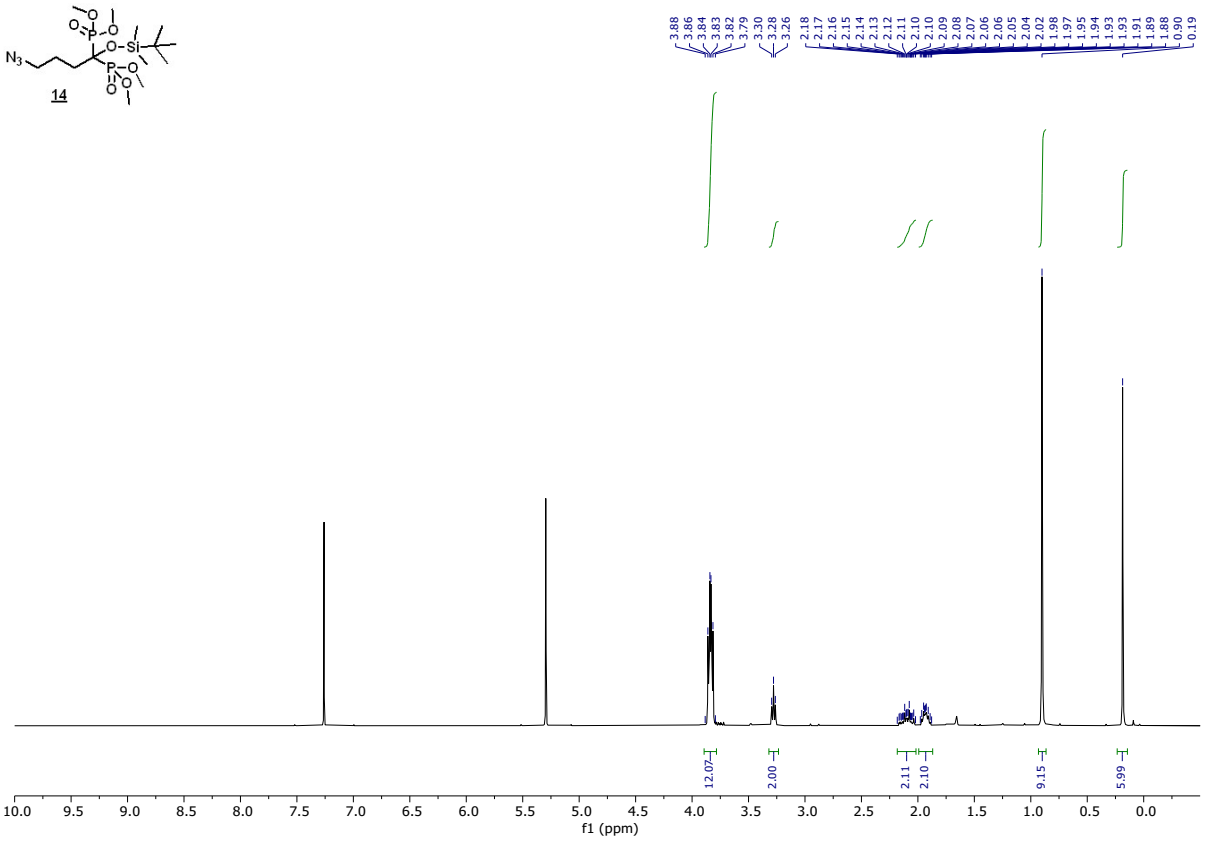


Figure S10: Full ^{1}H NMR (400 MHZ) spectrum for **<u>14</u>**

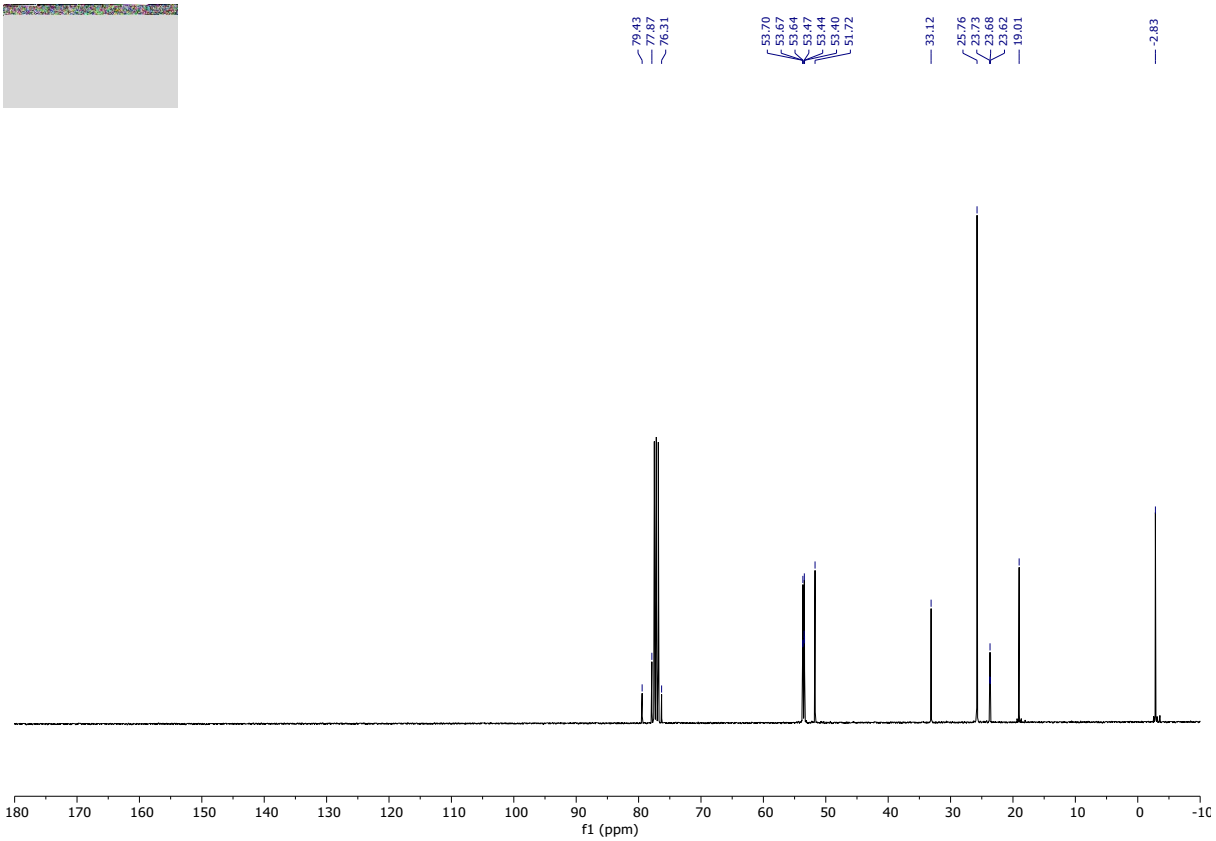
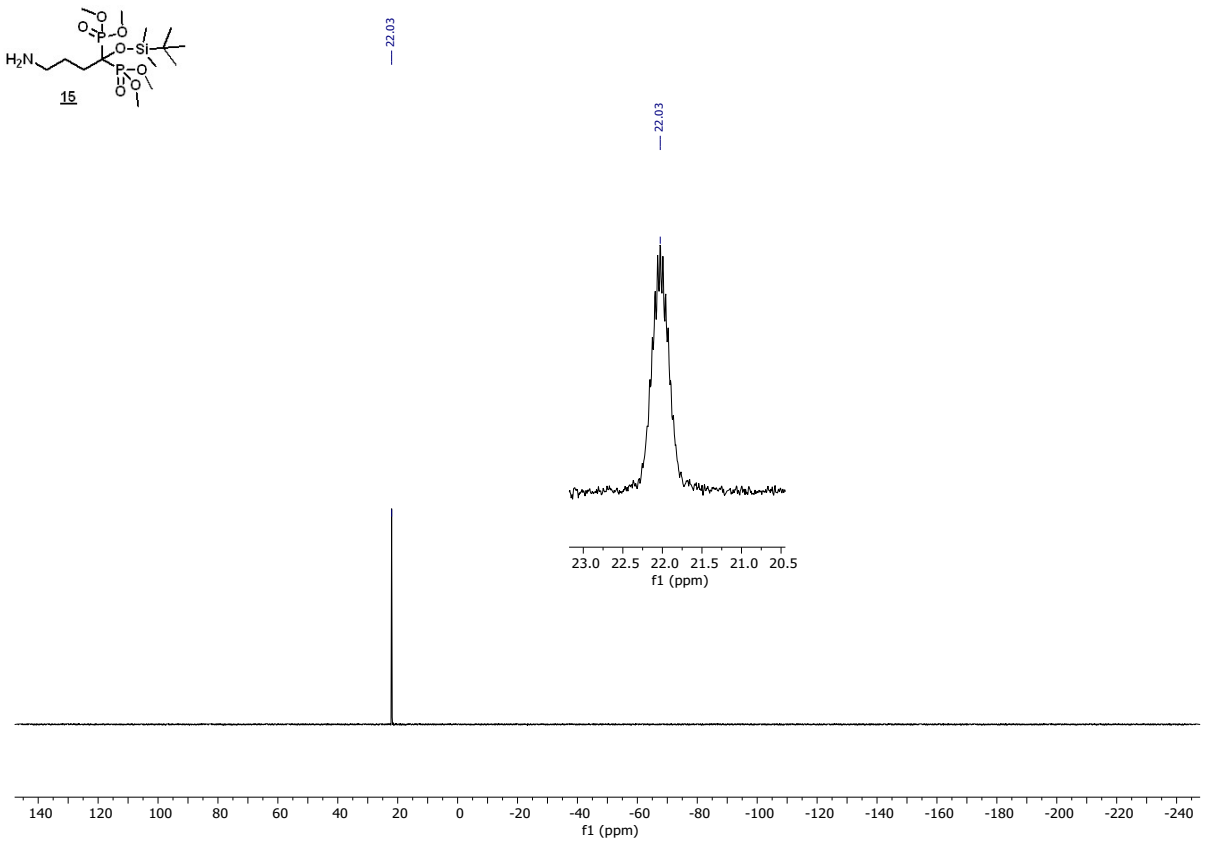


Figure S11: Full ^{13}C NMR (101 MHZ) spectrum for **<u>14</u>**



15

Figure S12: Full ^{31}P {^{1}H} NMR spectrum, and zoomed ^{31}P NMR (162 MHZ) spectrum for **15**

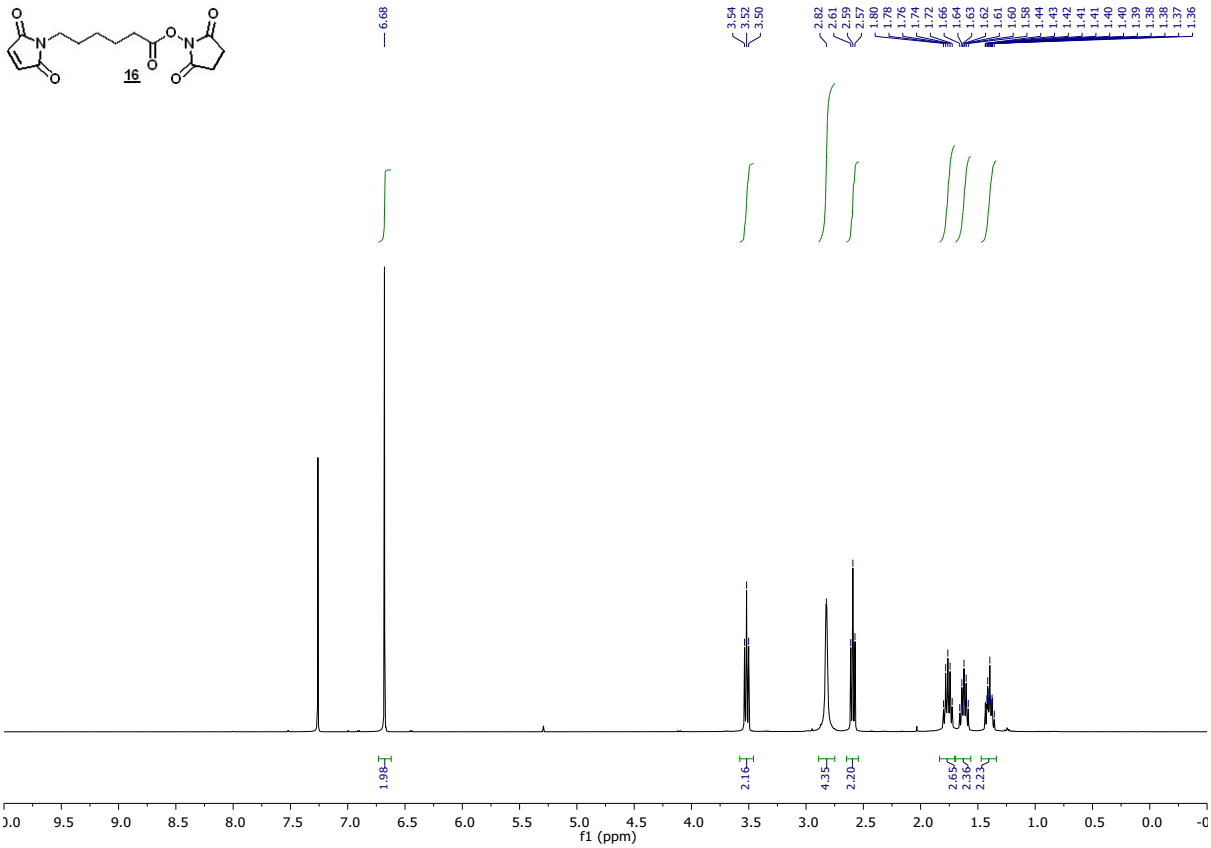


Figure S13: Full ^{1}H NMR (400 MHZ) spectrum for **16**

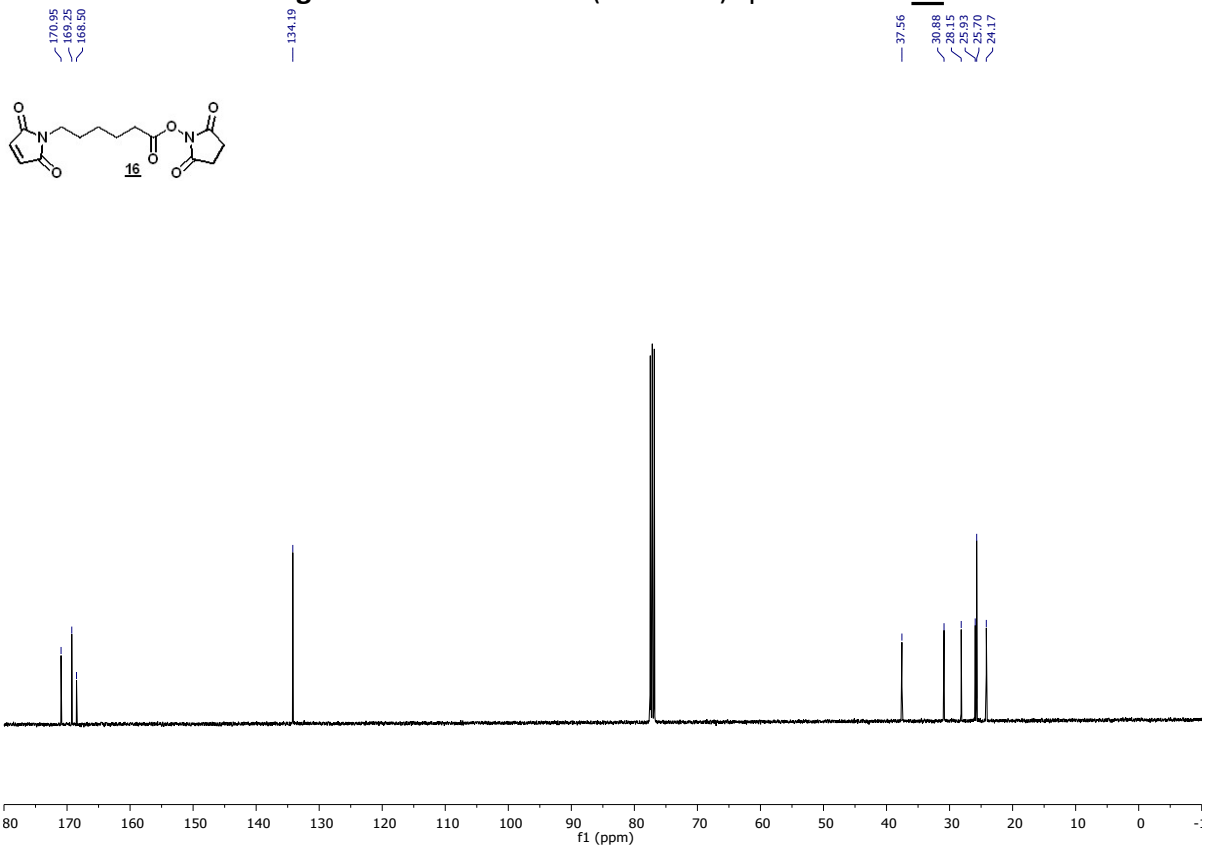


Figure S14: Full ^{13}C NMR (101 MHZ) spectrum for **16**

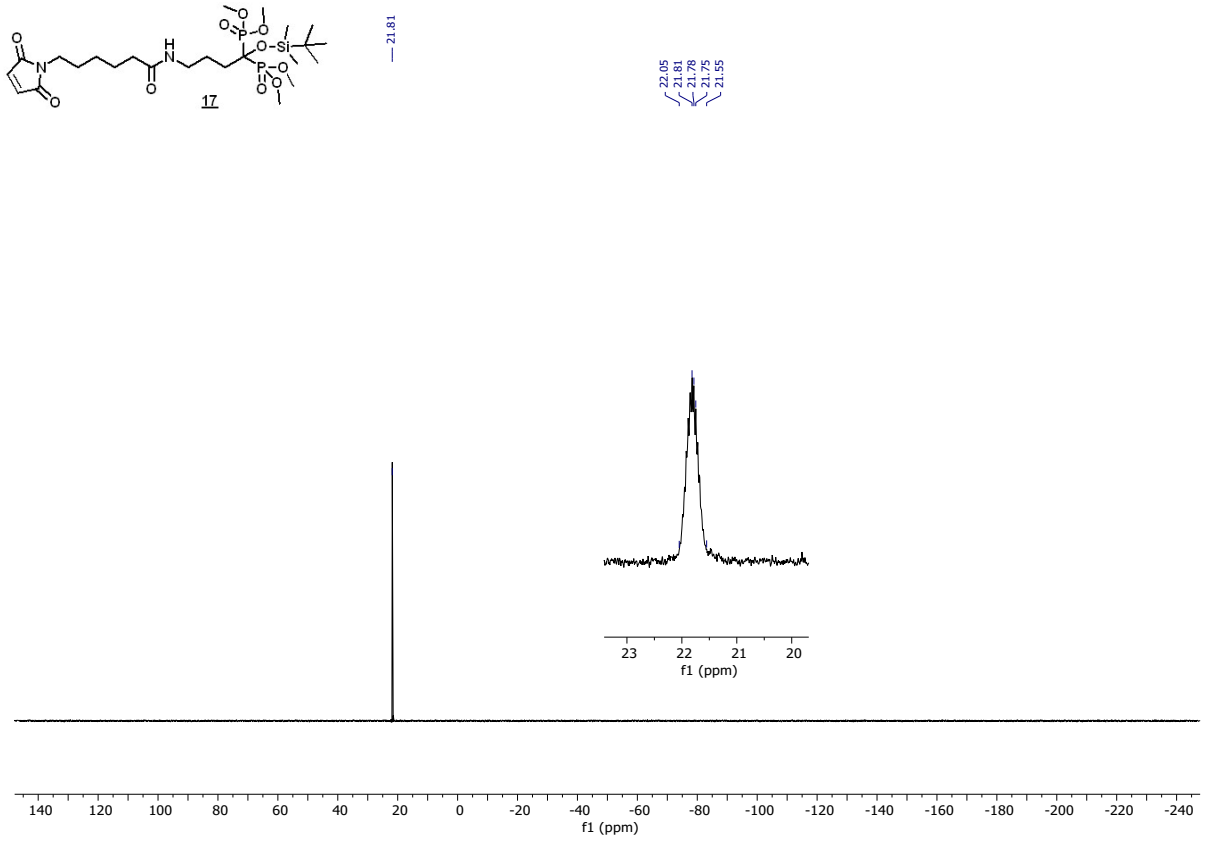


Figure S15: Full ^{31}P {^{1}H} NMR spectrum, and zoomed ^{31}P NMR (162 MHZ) spectrum for **17**

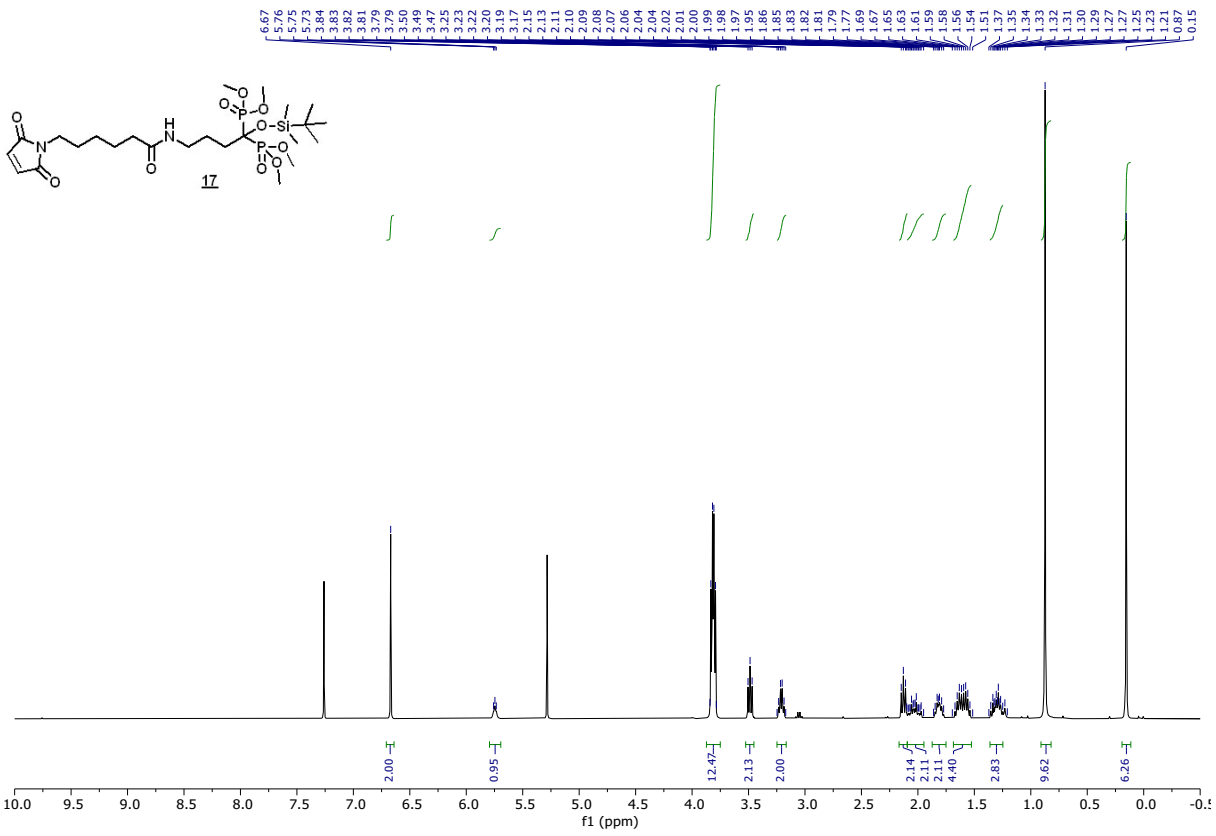


Figure S16: Full ^{1}H NMR (400 MHZ) spectrum for **17**

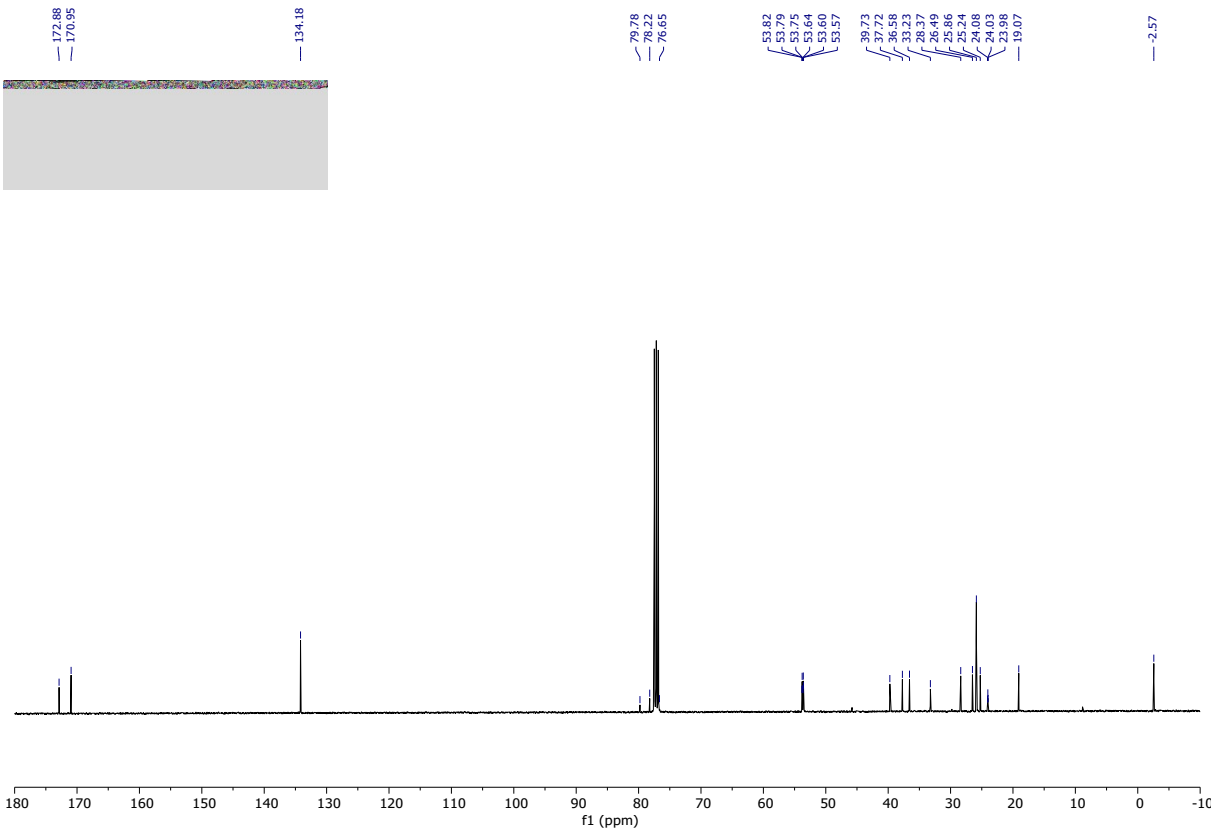


Figure S17: Full ^{13}C NMR (101 MHZ) spectrum for **<u>17</u>**

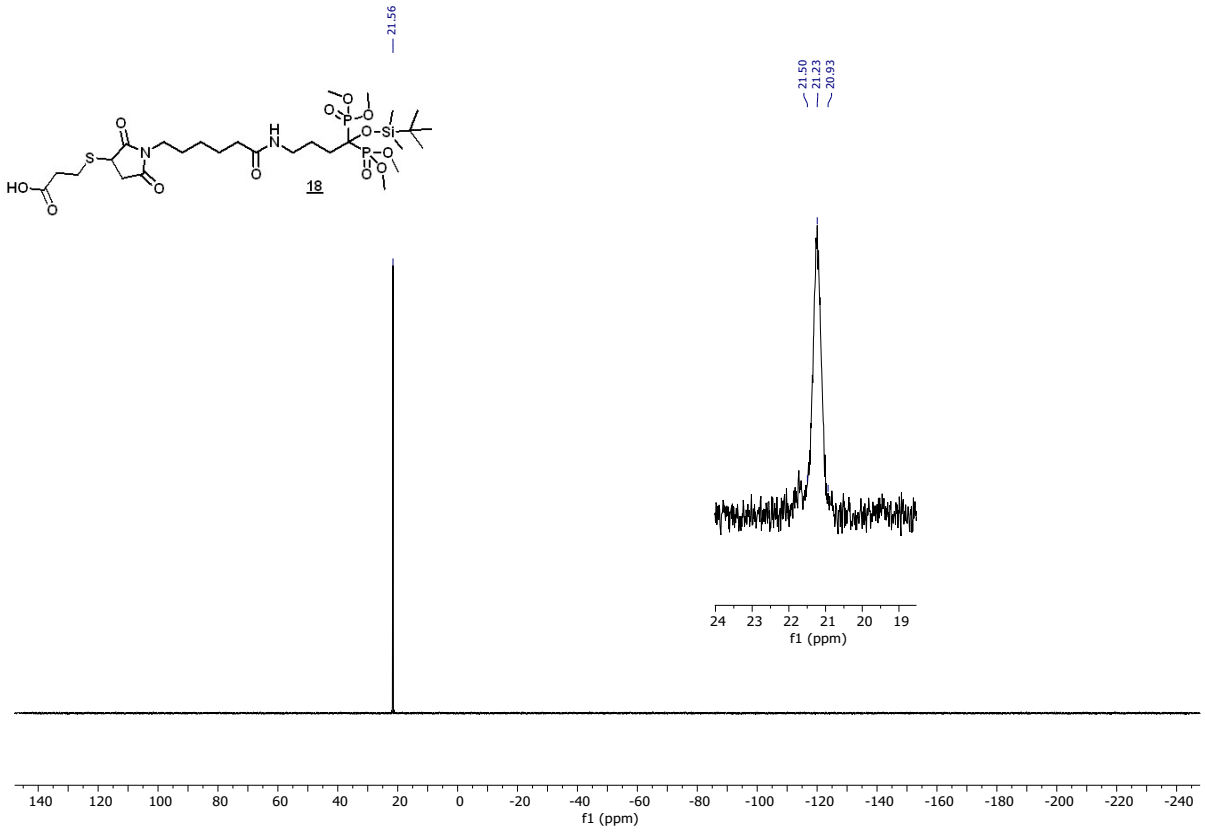


Figure S18: Full ^{31}P {^{1}H} NMR spectrum, and zoomed ^{31}P NMR (162 MHZ) spectrum for **<u>18</u>**

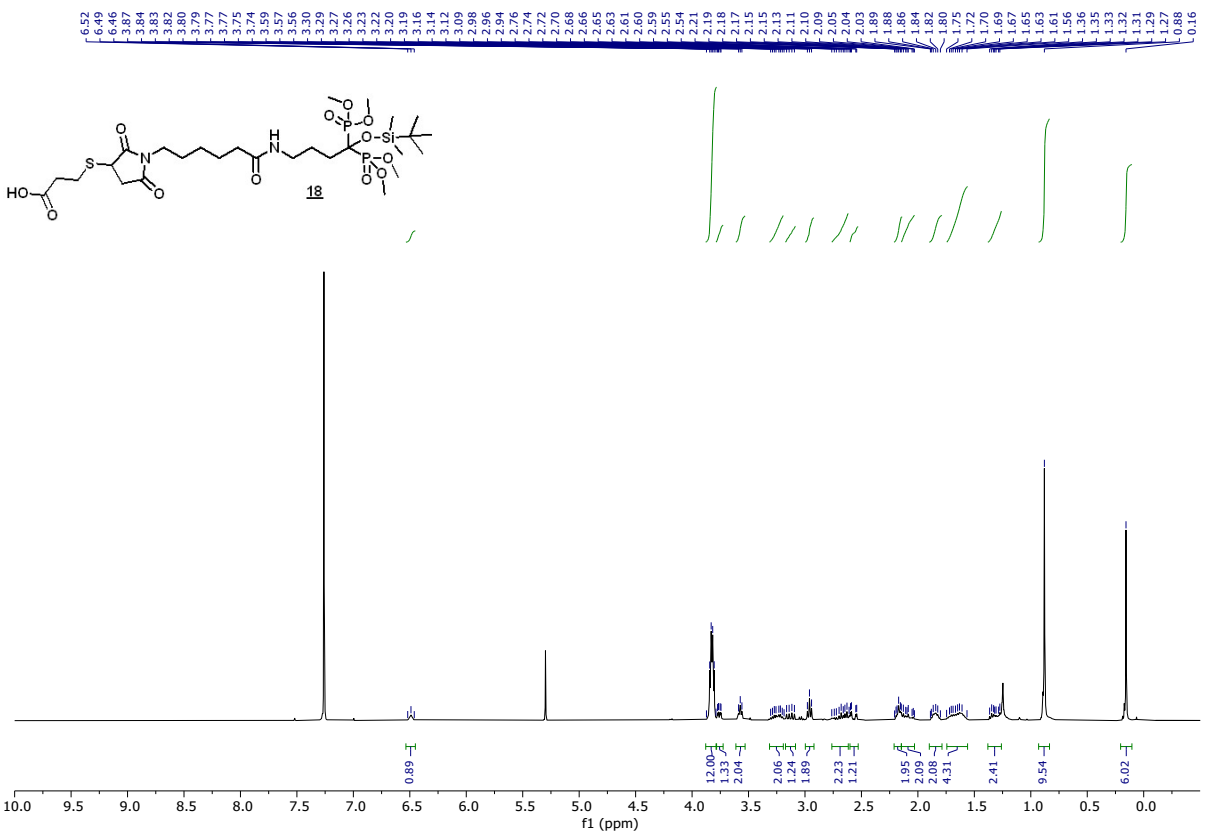


Figure S19: Full ^{1}H NMR (400 MHZ) spectrum for **<u>18</u>**

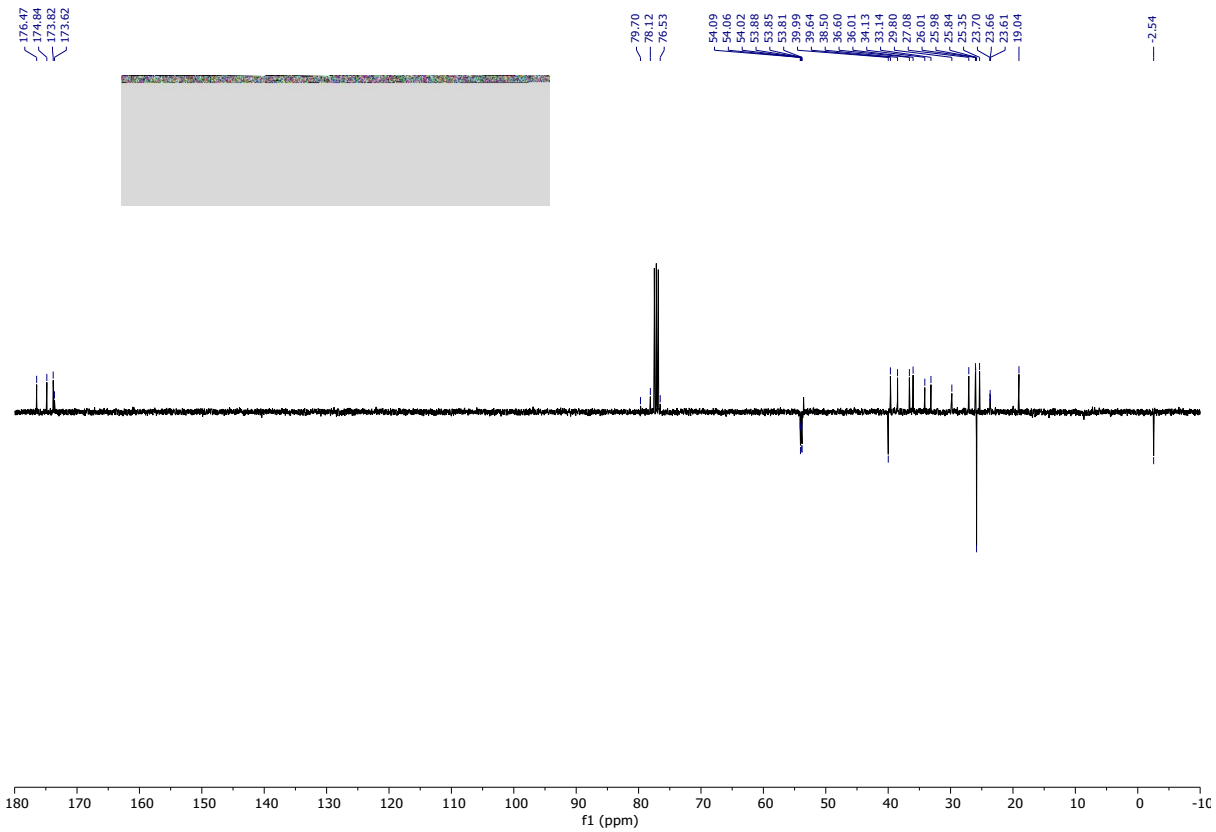


Figure S20: Full ^{13}C NMR (101 MHZ) spectrum for **<u>18</u>**