Supporting Information

Acyloxybenzyl and alkoxyalkyl prodrugs of a fosmidomycin surrogate as antimalarial and antitubercular agents.

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General experimental information

All reactions were performed using oven dried round-bottomed flasks sealed with rubber septa, unless otherwise stated. Reactions were magnetically stirred using teflon-coated stir bars. Where appropriate, reactions were carried out in dry solvents and under an inert nitrogen atmosphere. Dropwise addition of reagents or solutions was carried out using a syringe pump. Yields refer to chromatographically and spectroscopically (^{1}H NMR) pure homogeneous materials. Reagents were purchased at the highest commercial quality and used without additional purification, unless otherwise stated. Hexanes for flash column chromatography were distilled prior to use. Reactions were monitored by thin layer chromatography (TLC) carried out on precoated Macherey-Nagel® SIL G/UV254 plates using ultraviolet light (254 nm wave length) as visualizing agent and either potassium permanganate or ceric ammonium molybdate (CAM) as developing agents. Flash column chromatography was performed manually using Grace Davisil® silica gel (40-60 µm particle size) or automatically using a Grace Reveleris X2 purification system with flash cartridges. NMR spectra were recorded at 25 °C on a Varian Mercury-300 spectrometer. ^{1}H NMR spectra were calibrated using TMS as a reference (TMS: ^{1}H NMR = 0.00) and ^{13}C NMR spectra were calibrated using residual undeuterated solvent as an internal reference ($CDCl_3$: ^{13}C NMR = 77.16, METHANOL-*d4*: ^{13}C NMR = 49.00). In ^{31}P NMR, signals are referenced to the $CDCl_3$ lock resonance frequency according to IUPAC referencing, with H_3PO_4 set to 0.00 ppm. The following abbreviations or combinations thereof were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad signal. Chemical shifts are expressed in ppm and coupling constants are given in Hertz (Hz). Weak carbon signals were assigned using HSQC experiments. High resolution mass spectra (HRMS) were recorded on a Waters LCT Premier XE TOF equipped with an electrospray ionization (ESI-MS) interface and a modular Lockspray TM interface. Samples were infused in an acetonitrile/water (1:1) + 0.1% formic acid mixture at a rate of 100 µL/min. LC-MS analyses were carried out on a Waters AutoPurification System equipped with PDA and ESI-MS detection and using a Waters CORTECS C18 Column (4.6×100 mm, 2.7 µm) and a water/acetonitrile/formic acid linear gradient system at a flow rate of 1.44 mL/min. Preparative HPLC purifications were carried out on a Waters AutoPurification System equipped with PDA and ESI-MS detection and using a Waters Xbridge C18 column (19×250 mm, 5µm) and a water/acetonitrile/formic acid linear gradient system at a flow rate of 20 mL/min.

Experimental procedures

General procedure 1: phosphonate ester formation.
A solution of crude phosphonic dichloride **9** (1 eq) in DCM (0.2M) was cooled to 0°C in an ice bath. DIPEA (6 eq) was added to a solution of the corresponding acyloxybenzyl alcohol or alkoxyalkyl alcohol (2.5 eq) in DCM (0.3M). Anhydrous pyridine (1 eq) was added to the first solution, followed by addition of the second to the first solution. The reaction mixture was stirred overnight, slowly warming to room temperature. After overnight stirring, the reaction mixture was further diluted with DCM and washed with 0.1M HCl (aq. soln.) and $NaHCO_3$ (sat. aq. soln.). The organic layer was dried over

Na_2SO_4, filtered and concentrated *in vacuo*. The products were purified by column chromatography with appropriate eluents.

General procedure 2: cross metathesis reaction.
Phosphonate esters **10** or **15** and respectively silyl-protected acryl hydroxamate **11** or benzyl-protected hydroxamate **16** (4 eq) were dissolved in toluene (0.1M). This solution was heated to 70°C. Hoveyda-Grubbs 2nd generation catalyst (0.05 eq) was dissolved in a small amount of toluene and a volume corresponding to 0.01 eq of catalyst was added to the reaction mixture every hour. After overnight stirring at 70°C, all volatiles were removed *in vacuo* and the resulting crude was purified by flash column chromatography with appropriate eluents.

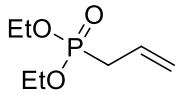
General procedure 3: nickel boride reduction.
Compounds **12** or **17** (1 eq) were dissolved in THF (0.1M).The resulting solution was cooled to 0°C in an ice bath and $NiCl_2.6H_2O$ (2 eq) and $NaBH_4$(4 eq) were subsequently added. After 1 hour, HRMS confirmed complete conversion of the starting material. The reaction was quenched with NH_4Cl (sat. aq. soln.) and was vigorously stirred at room temperature for 2 hours until a clear blue solution was obtained. The reaction mixture was extracted three times with DCM. The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The products were purified by column chromatography with appropriate eluents.

General procedure 4: HF.pyridine deprotection.
TBDPS protected compounds **13** (1 eq) were dissolved in dry THF (0.1M) in a plastic vessel and cooled to 0°C in an ice bath. A stock solution of HF.pyridine was prepared as follows: 1 volume of HF.pyridine was added to 1.15 volumes of pyridine and 1.85 volumes of dry THF. 1mL/mmol of the stock solution was added to the reaction mixture. After 2 hours at 0°C, TLC confirmed complete conversion of the starting material. The reaction was carefully quenched with $NaHCO_3$ (sat. aq. soln.). The reaction was extracted with EtOAc and the organic layer was subsequently washed with H_2O. The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The products were purified by column chromatography with appropriate eluents.

General procedure 5: hydrogenation.
Benzyl protected compounds **18d** and **19** (1 eq) were dissolved in MeOH (0.05M). A catalytic amount of Pd/C was added to the reaction mixture. The reaction was stirred for 30 minutes under a hydrogen atmosphere, after which TLC confirmed complete conversion of the starting material. The reaction mixture was filtered and all volatiles were removed *in vacuo*. The products were purified by column chromatography with appropriate eluents.

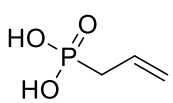
General procedure 6: monoester formation.
Compounds **18** (1 eq) were dissolved in DMF (0.1M). Sodium azide (20 eq) was added to the resulting solution and the reaction was heated to 130°C. After 24 hours at 130°C, HRMS confirmed complete conversion of the starting material. All volatiles were removed *in vacuo* and the resulting crude material was purified by column chromatography with appropriate eluents.

Diethyl allylphosphonate (7)



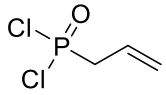
Allyl bromide (20.0mL, 231mmol) and triethyl phosphite (19.9mL, 116mmol) were refluxed under neat conditions for 24 hours. ^{31}P nmr confirmed completion of the reaction, after which all volatiles were removed *in vacuo* and pure **7** was obtained as a yellow oil (97%). Spectral data are in accordance with those reported in the literature[1].

Allyl phosphonic acid (8)



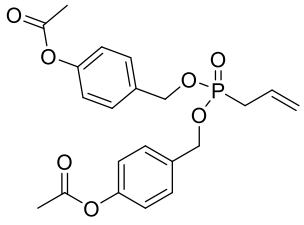
7 (0.89g, 5.0mmol) was dissolved in DCM (40mL) and cooled to 0°C in an ice bath. TMSBr (6.6mL, 25mmol) was added and the solution was subsequently stirred for 10' at 0°C and 2 hours at room temperature. ^{31}P nmr confirmed completion of the reaction, after which all volatiles were removed *in vacuo*. The crude oil was dissolved in THF (17mL) and treated with H_2O (0.17mL). The reaction was stirred for 1 hour at room temperature, after which all volatiles were removed *in vacuo*. The residue was coevaporated three times with toluene in order to remove all traces of water. The resulting crude material was dried overnight at high vacuum and immediately used in the next reaction without further purification or characterization.

Allyl phosphonic dichloride (9)



A solution of crude **8** (0.61g, 5.0mmol) in DCM (12.5mL) was heated to 50°C. After addition of a catalytic amount of DMF, oxalyl chloride (1.7mL, 20mmol) was added dropwise over 30 minutes. After 3 hours at 50°C, ^{31}P nmr confirmed completion of the reaction, after which all volatiles were removed *in vacuo*. The resulting crude material was immediately used in the next reaction without further purification or characterization.

{[(Allylphosphoryl)bis(oxy)]bis(methylene)}bis(4,1-phenylene) diacetate (10a)



Following general procedure **1**, crude **9** (0.64g, 4.0mmol) afforded **10a** (51%) as a pale yellow oil after purification by column chromatography (toluene → 1Tol/1EtOAc).

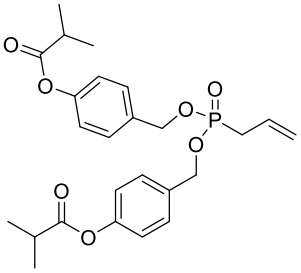
^{1}H NMR (300 MHz, $CDCl_3$) δppm 2.29 (s, 6 H) 2.56 - 2.70 (m, 2 H) 4.92 - 5.07 (m, 4 H) 5.11 - 5.21 (m, 2 H) 5.67 - 5.84 (m, 1 H) 7.04 - 7.10 (m, 4 H) 7.31 - 7.38 (m, 4 H)

^{13}C NMR (75 MHz, $CDCl_3$) δppm 21.14, 32.08 (d, $^1J_{C\text{-}P}$ = 139.4 Hz) 66.88 (d, $^2J_{C\text{-}P}$ = 6.9 Hz) 120.50 (d, $^3J_{C\text{-}P}$ = 15.0 Hz) 121.80, 126.89 (d, $^2J_{C\text{-}P}$ = 12.7 Hz) 129.16, 133.93 (d, $^3J_{C\text{-}P}$ = 5.8 Hz) 150.70, 169.35

^{31}P NMR (121.5 MHz, $CDCl_3$): δ_P ppm = 28.26.

HRMS (ESI-MS): calculated for $C_{21}H_{24}O_7P$ $[M+H]^+$: 419.1254, found: 419.1271.

{[(Allylphosphoryl)bis(oxy)]bis(methylene)}bis(4,1-phenylene) bis(2-methylpropanoate) (10b)



Following general procedure **1**, crude **9** (0.64g, 4.0mmol) afforded **10b** (53%) as a yellow oil after purification by column chromatography (toluene → 1Tol/1EtOAc).

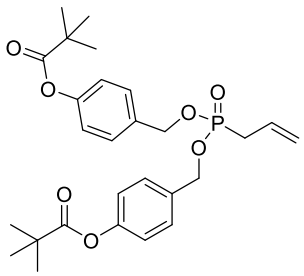
^{1}H NMR (300 MHz, $CDCl_3$) δppm 1.31 (d, *J* = 7.0 Hz, 12 H) 2.56 - 2.68 (m, 2 H) 2.80 (spt, *J* = 7.0 Hz, 2 H) 4.92 - 5.08 (m, 4 H) 5.11 - 5.20 (m, 2 H) 5.66 - 5.83 (m, 1 H) 7.03 - 7.08 (m, 4 H) 7.32 - 7.37 (m, 4 H)

^{13}C NMR (75 MHz, $CDCl_3$) δppm 18.89, 32.08 (d, $^1J_{C\text{-}P}$ = 139.4 Hz) 34.16, 66.88 (d, $^2J_{C\text{-}P}$ = 5.8 Hz) 120.44 (d, $^3J_{C\text{-}P}$ = 13.8 Hz) 121.70, 126.87 (d, $^2J_{C\text{-}P}$ = 12.7 Hz) 129.11, 133.71 (d, $^3J_{C\text{-}P}$ = 5.8 Hz) 150.91, 175.45

^{31}P NMR (121.5 MHz, $CDCl_3$): δ_P ppm = 28.23

HRMS (ESI-MS): calculated for $C_{25}H_{32}O_7P$ $[M+H]^+$: 475.1880, found: 475.1894

{[(Allylphosphoryl)bis(oxy)]bis(methylene)}bis(4,1-phenylene) bis(2,2-dimethylpropanoate) (10c)



Following general procedure **1**, crude **9** (0.64g, 4.0mmol) afforded **10c** (60%) as a yellow solid after purification by column chromatography (toluene → 1Tol/1EtOAc).

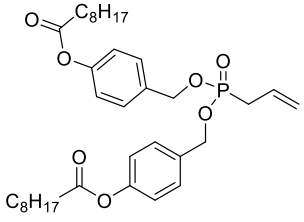
^{1}H NMR (300 MHz, $CDCl_3$) δppm 1.35 (s, 18 H) 2.56 - 2.68 (m, 2 H) 4.88 - 5.11 (m, 4 H) 5.11 - 5.21 (m, 2 H) 5.66 - 5.83 (m, 1 H) 7.01 - 7.06 (m, 4 H) 7.32 - 7.37 (m, 4 H)

^{13}C NMR (75 MHz, $CDCl_3$) δppm 27.16, 32.14 (d, $^1J_{C\text{-}P}$ = 139.4 Hz) 39.14, 66.95 (d, *J* = 5.8 Hz) 120.47 (d, $^3J_{C\text{-}P}$ = 13.8 Hz) 121.74, 126.94 (d, $^2J_{C\text{-}P}$ = 10.4 Hz) 129.14, 133.66 (d, *J* = 5.8 Hz) 151.19, 176.91 - 177.04 (m)

^{31}P NMR (121.5 MHz, $CDCl_3$): δ_P ppm = 28.22

HRMS (ESI-MS): calculated for $C_{27}H_{36}O_7P$ $[M+H]^+$: 503.2193, found: 503.2202

{[(Allylphosphoryl)bis(oxy)]bis(methylene)}bis(4,1-phenylene) dinonanoate (10d)



Following general procedure **1**, crude **9** (0.64g, 4.0mmol) afforded **10d** (60%) as a yellow solid after purification by column chromatography (toluene → 3Tol/1EtOAc).

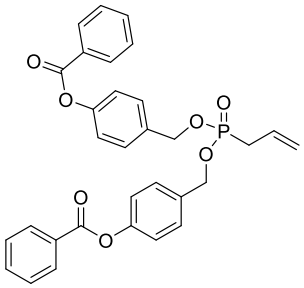
^{1}H NMR (300 MHz, $CDCl_3$) δppm 0.84 - 0.94 (m, 6 H) 1.20 - 1.46 (m, 20 H) 1.74 (quintet, *J* = 7.4 Hz, 4 H) 2.50 - 2.68 (m, 6 H) 4.91 - 5.08 (m, 4 H) 5.11 - 5.20 (m, 2 H) 5.65 - 5.86 (m, 1 H) 7.03 - 7.09 (m, 4 H) 7.32 - 7.37 (m, 4 H)

^{13}C NMR (75 MHz, $CDCl_3$) δppm 14.11, 22.66, 24.93, 29.13, 29.22, 32.08 (d, $^1J_{C\text{-}P}$ = 139.4 Hz) 31.81, 34.39, 66.89 (d, $^2J_{C\text{-}P}$ = 5.8 Hz) 120.45 (d, $^3J_{C\text{-}P}$ = 15.0 Hz) 121.80, 126.90 (d, $^2J_{C\text{-}P}$ = 11.5 Hz) 129.13, 133.78 (d, $^3J_{C\text{-}P}$ = 5.8 Hz) 150.79, 172.18

^{31}P NMR (121.5 MHz, $CDCl_3$): δ_P ppm = 28.22

HRMS (ESI-MS): calculated for $C_{35}H_{52}O_7P$ $[M+H]^+$: 615.3445, found: 615.3450

{[(Allylphosphoryl)bis(oxy)]bis(methylene)}bis(4,1-phenylene) dibenzoate (10d)



Following general procedure **1**, crude **9** (0.64g, 4.0mmol) afforded **10d** (56%) as a pale yellow solid after purification by column chromatography (toluene → 4Tol/6EtOAc).

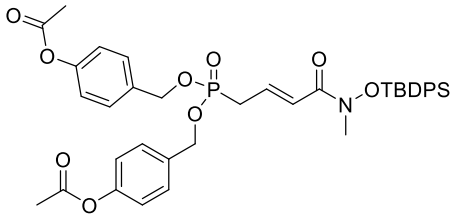
^{1}H NMR (300 MHz, $CDCl_3$) δppm 2.60 - 2.73 (m, 2 H) 4.97 - 5.15 (m, 4 H) 5.15 - 5.25 (m, 2 H) 5.70 - 5.88 (m, 1 H) 7.17 - 7.28 (m, 4 H) 7.38 - 7.55 (m, 8 H) 7.59 - 7.66 (m, 2 H) 8.16 - 8.24 (m, 4 H)

^{13}C NMR (75 MHz, $CDCl_3$) δppm 32.13 (d, $^1J_{C\text{-}P}$ = 139.4 Hz) 66.95 (d, $^2J_{C\text{-}P}$ = 5.8 Hz) 120.53 (d, $^3J_{C\text{-}P}$ = 15.0 Hz) 121.97, 126.93 (d, $^2J_{C\text{-}P}$ = 11.5 Hz) 128.61, 129.24, 129.42, 130.21, 133.68, 134.01 (d, $^3J_{C\text{-}P}$ = 5.8 Hz) 151.00, 165.06

^{31}P NMR (121.5 MHz, $CDCl_3$): δ_P ppm = 28.31

HRMS (ESI-MS): calculated for $C_{31}H_{28}O_7P$ $[M+H]^+$: 543.1567, found: 543.1588

(*E*)-({[(4-{[(Tert-butyldiphenylsilyl)oxy](methyl)amino}-4-oxobut-2-en-1-yl)phosphoryl]bis(oxy)}bis (methylene))bis(4,1-phenylene)diacetate (12a)



Following general procedure **2**, **10a** (0.21g, 0.50mmol) afforded **12a** (54% E-isomer) as a black oil after purification by column chromatography (toluene → 35Tol/65EtOAc).

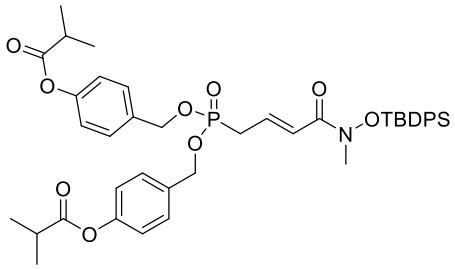
^{1}H NMR (300 MHz, $CDCl_3$) δppm 1.15 (s, 9 H) 2.30 (s, 6 H) 2.54 - 2.69 (m, 2 H) 3.10 (s, 3 H) 4.85 - 5.03 (m, 4 H) 6.43 - 6.65 (m, 2 H) 7.01 – 7.10 (m, 4 H) 7.24 - 7.47 (m, 10 H) 7.62 – 7.71 (m, 4 H)

^{13}C NMR (75 MHz, $CDCl_3$) δppm 19.5, 21.3, 27.1, 31.3 (d, $^1J_{C\text{-}P}$ = 139.4 Hz), 38.0 (w), 67.2 (d, $^2J_{C\text{-}P}$ = 6.9 Hz) 122.0, 125.0 (d, $^3J_{C\text{-}P}$ = 15.0 Hz) 127.9, 129.4, 130.6, 131.5, 133.7, 133.8, 134.0 (d, $^2J_{C\text{-}P}$ = 11.5 Hz) 136.2, 150.9, 166.7 (w), 169.4

^{31}P NMR (121.5 MHz, $CDCl_3$): δ_P ppm = 26.06

HRMS (ESI-MS): calculated for $C_{39}H_{45}NO_9PSi$ $[M+H]^+$: 730.2596, found: 730.2592

(*E*)-({[(4-{[(Tert-butyldiphenylsilyl)oxy](methyl)amino}-4-oxobut-2-en-1-yl)phosphoryl]bis(oxy)}bis (methylene))bis(4,1-phenylene) bis(2-methylpropanoate) (12b)



Following general procedure **2**, **10b** (0.24g, 0.50mmol) afforded **12b** (54% E-isomer) as a black oil after purification by column chromatography (toluene → 35Tol/65EtOAc).

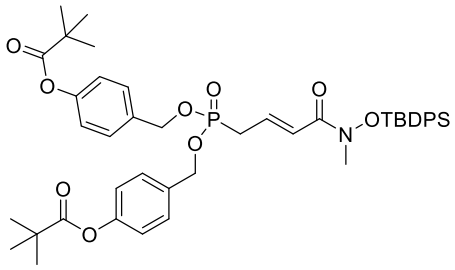
^{1}H NMR (300 MHz, $CDCl_3$) δppm 1.15 (s, 9 H) 1.31 (d, *J* = 7.0 Hz, 12 H) 2.55 - 2.67 (m, 2 H) 2.80 (spt, *J* = 7.0 Hz, 2 H)) 3.10 (s, 3 H) 4.92 - 5.08 (m, 4 H) 6.36 - 6.68 (m, 2 H) 7.01 - 7.08 (m, 4 H) 7.29 - 7.46 (m, 10 H) 7.64 - 7.69 (m, 4 H)

^{13}C NMR (75 MHz, $CDCl_3$) δppm 19.1, 27.1, 31.4 (d, $^1J_{C\text{-}P}$ = 131.7 Hz), 34.3, 38.0, 67.3, 122.0, 128.0, 129.4, 130.7, 136.3

^{31}P NMR (121.5 MHz, $CDCl_3$): δ_P ppm = 26.00

HRMS (ESI-MS): calculated for $C_{43}H_{53}NO_9PSi$ $[M+H]^+$: 786.3222, found: 786.3198

(*E*)-({[(4-{[(Tert-butyldiphenylsilyl)oxy](methyl)amino}-4-oxobut-2-en-1-yl)phosphoryl]bis(oxy)}bis (methylene))bis(4,1-phenylene) bis(2,2-dimethylpropanoate) (12c)



Following general procedure **2**, **10c** (0.25g, 0.50mmol) afforded **12c** (60% E-isomer) as a black oil after purification by column chromatography (toluene → 1Tol/1EtOAc).

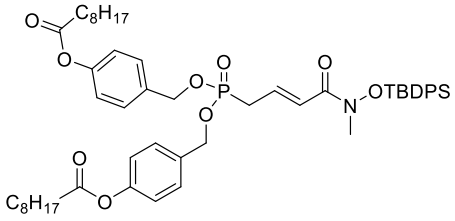
^{1}H NMR (300 MHz, $CDCl_3$) δppm 1.14 (s, 9 H) 1.35 (s, 18 H) 2.55 - 2.67 (m, 2 H) 3.10 (s, 3 H) 4.87 – 5.01 (m, 4 H) 6.42 - 6.67 (m, 2 H) 7.00 - 7.06 (m, 4 H) 7.29 - 7.48 (m, 10 H) 7.64 - 7.70 (m, 4 H)

^{13}C NMR (75 MHz, $CDCl_3$) δppm 27.0, 27.1, 31.2 (d, $^1J_{C-P}$ = 131.1 Hz), 37.9 (w), 67.1 (d, $^2J_{C-P}$ = 6.9 Hz), 121.8, doublet 127.8, 129.4, 130.5, 131.4 (w), 136.1

^{31}P NMR (121.5 MHz, $CDCl_3$): δ_P ppm = 25.98

HRMS (ESI-MS): calculated for $C_{45}H_{57}NO_9PSi$ $[M+H]^+$: 814.3535, found: 814.3565

(*E*)-({[(4-{[(Tert-butyldiphenylsilyl)oxy](methyl)amino}-4-oxobut-2-en-1-yl)phosphoryl]bis(oxy)}bis (methylene))bis(4,1-phenylene) dinonanoate (12d)



Following general procedure **2**, **10d** (0.18g, 0.30mmol) afforded **12d** (64% E-isomer) as a black oil after purification by column chromatography (toluene → 1Tol/1EtOAc).

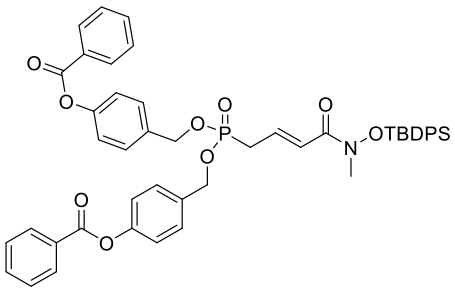
^{1}H NMR (300 MHz, $CDCl_3$) δppm 0.84 - 0.92 (m, 6 H) 1.11 - 1.17 (m, 9 H) 1.21 - 1.45 (m, 20 H) 1.75 (quintet, *J* = 7.4 Hz, 4 H) 2.45 - 2.67 (m, 6 H) 3.10 (s, 3 H) 4.86 - 5.01 (m, 4 H) 6.37 - 6.67 (m, 2 H) 7.02 - 7.09 (m, 4 H) 7.28 - 7.46 (m, 10 H) 7.64 - 7.70 (m, 4 H)

^{13}C NMR (75 MHz, $CDCl_3$) δppm 14.1, 19.4, 22.7, 24.9, 27.0, 29.1, 29.2, 31.2 (d, $^1J_{C-P}$ = 138.2 Hz) 31.8, 34.4, 37.9, 67.1 (d, $^2J_{C-P}$ = 5.8 Hz) 121.8, 124.8 (d, $^3J_{C-P}$ = 15.0 Hz) 127.8, 129.2, 130.5, 131.4, 133.5, 133.6, 133.9 (d, $^2J_{C-P}$ = 11.5 Hz) 136.1, 150.9, 166.6, 172.1

^{31}P NMR (121.5 MHz, $CDCl_3$): δ_P ppm = 26.01

HRMS (ESI-MS): calculated for $C_{53}H_{73}NO_9PSi$ $[M+H]^+$: 926.4787, found: 926.4821

(*E*)-({[(4-{[(Tert-butyldiphenylsilyl)oxy](methyl)amino}-4-oxobut-2-en-1-yl)phosphoryl]bis(oxy)}bis (methylene))bis(4,1-phenylene) dibenzoate (12e)



Following general procedure **2**, **10e** (0.27g, 0.50mmol) afforded **12e** (51% E-isomer) as a black oil after purification by column chromatography (toluene → 1Tol/1EtOAc).

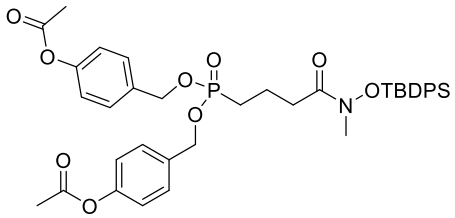
^{1}H NMR (300 MHz, $CDCl_3$) δppm 1.16 (s, 9 H) 2.59 - 2.72 (m, 2 H) 3.11 (s, 3 H) 4.96 - 5.04 (m, 4 H) 6.44 - 6.71 (m, 2 H) 7.18 - 7.24 (m, 4 H) 7.32 - 7.54 (m, 14 H) 7.60 - 7.71 (m, 6 H) 8.16 - 8.23 (m, 4 H)

^{13}C NMR (75 MHz, $CDCl_3$) δppm 19.4, 27.0, 31.3 (d, $^1J_{C-P}$ = 138.2 Hz) 37.9, 67.2 (d, $^2J_{C-P}$ = 6.9 Hz) 122.0, 124.9 (d, $^3J_{C-P}$ = 13.8 Hz) 127.8, 128.6, 129.36, 129.43, 130.2, 130.5, 131.4, 133.7 - 134.0 (m) 136.1, 151.06, 165.0, 166.63

^{31}P NMR (121.5 MHz, $CDCl_3$): δ_P ppm = 26.09

HRMS (ESI-MS): calculated for $C_{49}H_{49}NO_9PSi$ $[M+H]^+$: 854.2909, found: 854.2942

({[(4-{[(Tert-butyldiphenylsilyl)oxy](methyl)amino}-4-oxobutyl)phosphoryl]bis(oxy)}bis(methylene)) bis(4,1-phenylene) diacetate (13a)



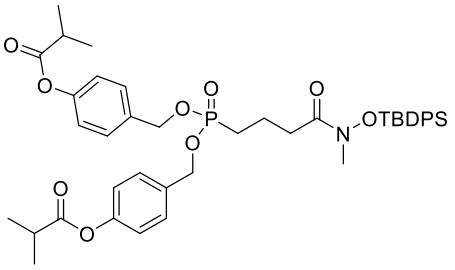
Following general procedure **3**, **12a** (0.14g, 0.19mmol) afforded **13a** (61%) as a transparent oil after purification by column chromatography (toluene → 35Tol/65EtOAc).

^{1}**H NMR** (300 MHz, $CDCl_3$) δppm 1.15 (s, 9 H) 1.48 - 1.78 (m, 4 H) 2.24 (br t, *J* = 5.3 Hz, 2 H) 2.30 (s, 6 H) 3.11 (s, 3 H) 4.86 - 5.01 (m, 4 H) 7.03 - 7.10 (m, 4 H) 7.29 - 7.47 (m, 10 H) 7.57 - 7.68 (m, 4 H)

^{31}**P NMR** (121.5 MHz, $CDCl_3$): δ_P ppm = 32.89

HRMS (ESI-MS): calculated for $C_{39}H_{47}NO_9PSi$ $[M+H]^+$: 732.2752, found: 732.2782

({[(4-{[(Tert-butyldiphenylsilyl)oxy](methyl)amino}-4-oxobutyl)phosphoryl]bis(oxy)}bis(methylene)) bis(4,1-phenylene) bis(2-methylpropanoate) (13b)



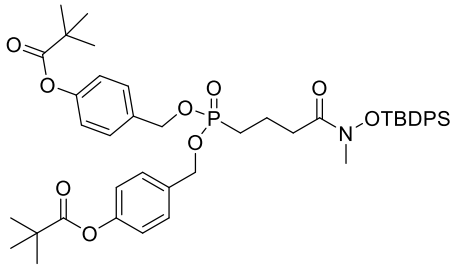
Following general procedure **3**, **12b** (0.15g, 0.19mmol) afforded **13b** (51%) as a transparent oil after purification by column chromatography (toluene → 35Tol/65EtOAc).

^{1}**H NMR** (300 MHz, $CDCl_3$) δppm 1.15 (s, 9 H) 1.31 (d, *J* = 7.0 Hz, 12 H) 1.48 - 1.72 (m, 4 H) 2.18 - 2.29 (m, 2 H) 2.80 (spt, *J* = 7.0 Hz, 2 H) 3.11 (s, 3 H) 4.85 - 5.03 (m, 4 H) 7.02 - 7.08 (m, 4 H) 7.30 - 7.47 (m, 10 H) 7.62 - 7.68 (m, 4 H)

^{31}**P NMR** (121.5 MHz, $CDCl_3$): δ_P ppm = 32.86

HRMS (ESI-MS): calculated for $C_{43}H_{55}NO_9PSi$ $[M+H]^+$: 788.3378, found: 788.3388

({[(4-{[(Tert-butyldiphenylsilyl)oxy](methyl)amino}-4-oxobutyl)phosphoryl]bis(oxy)}bis(methylene)) bis(4,1-phenylene) bis(2,2-dimethylpropanoate) (13c)



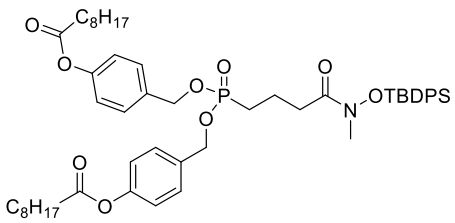
Following general procedure **3**, **12c** (0.21g, 0.26mmol) afforded **13c** (60%) as a transparent oil after purification by column chromatography (toluene → 1Tol/1EtOAc).

^{1}**H NMR** (300 MHz, $CDCl_3$) δppm 1.15 (s, 9 H) 1.35 (s, 18 H) 1.46 - 1.75 (m, 4 H) 2.17 - 2.28 (m, 2 H) 3.11 (s, 3 H) 4.86 - 5.01 (m, 4 H) 6.99 - 7.06 (m, 4 H) 7.29 - 7.47 (m, 10 H) 7.66 (dd, *J* = 7.9, 1.5 Hz, 4 H)

^{31}**P NMR** (121.5 MHz, $CDCl_3$): δ_P ppm = 32.85

HRMS (ESI-MS): calculated for $C_{45}H_{59}NO_9PSi$ $[M+H]^+$: 816.3691, found: 816.3727

({[(4-{[(Tert-butyldiphenylsilyl)oxy](methyl)amino}-4-oxobutyl)phosphoryl]bis(oxy)}bis(methylene)) bis(4,1-phenylene) dinonanoate (13d)



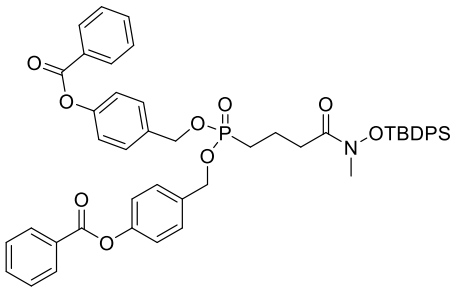
Following general procedure **3**, **12d** (95mg, 0.10mmol) afforded **13d** (75%) as a faint yellow oil after purification by column chromatography (toluene → 1Tol/1EtOAc).

^{1}**H NMR** (300 MHz, $CDCl_3$) δppm 0.84 - 0.94 (m, 6 H) 1.15 (s, 9 H) 1.25 - 1.44 (m, 20 H) 1.66 - 1.80 (m, 8 H) 2.19 - 2.29 (m, 2 H) 2.55 (t, *J* = 7.5 Hz, 4 H) 3.11 (s, 3 H) 4.85 - 5.03 (m, 4 H) 7.01 - 7.10 (m, 4 H) 7.30 - 7.47 (m, 10 H) 7.66 (dd, *J* = 7.9, 1.4 Hz, 4 H)

^{31}**P NMR** (121.5 MHz, $CDCl_3$): δ_P ppm = 32.85

HRMS (ESI-MS): calculated for $C_{53}H_{75}NO_9PSi$ $[M+H]^+$: 928.4943, found: 928.4983

({[(4-{[(Tert-butyldiphenylsilyl)oxy](methyl)amino}-4-oxobutyl)phosphoryl]bis(oxy)}bis(methylene)) bis(4,1-phenylene) dibenzoate (13e)



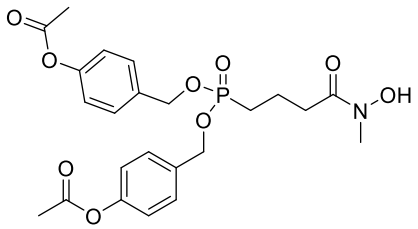
Following general procedure **3**, **12e** (95mg, 0.10mmol) afforded **13e** (53%) as a transparent oil after purification by column chromatography (toluene → 1Tol/1EtOAc).

^{1}H NMR (300 MHz, $CDCl_3$) δppm 1.16 (s, 9 H) 1.52 - 1.81 (m, 4 H) 2.21 - 2.31 (m, 2 H) 3.13 (s, 3 H) 4.91 - 5.08 (m, 4 H) 7.13 - 7.24 (m, 4 H) 7.32 - 7.54 (m, 14 H) 7.60 - 7.70 (m, 6 H) 8.16 - 8.23 (m, 4 H)

^{31}P NMR (121.5 MHz, $CDCl_3$): δ_P ppm = 32.94

HRMS (ESI-MS): calculated for $C_{49}H_{51}NO_9PSi$ $[M+H]^+$: 856.3065, found: 856.3043

{[({4-[Hydroxy(methyl)amino]-4-oxobutyl}phosphoryl)bis(oxy)]bis(methylene)}bis(4,1-phenylene) diacetate (14a)



Following general procedure **4**, **13a** (94mg, 0.13mmol) afforded **14a** (74%) as a transparent oil after purification by column chromatography (DCM → 5%MeOH in DCM).

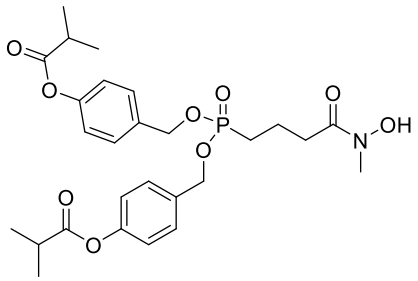
^{1}H NMR (300 MHz, $CDCl_3$) δppm 1.75 - 2.04 (m, 4 H) 2.30 (s, 6 H) 2.50 - 2.62 (m, 2 H) 3.23 (s, 3 H) 4.85 - 5.07 (m, 4 H) 7.04 - 7.11 (m, 4 H) 7.34 (br d, *J* = 8.4 Hz, 4 H)

^{13}C NMR (75 MHz, $CDCl_3$) δppm 18.3 (d, $^2J_{C\text{-}P}$ = 4.6 Hz), 21.2, 24.5 (d, $^1J_{C\text{-}P}$ = 135.9 Hz), 30.4 (d, $^3J_{C\text{-}P}$ = 6.9 Hz), 36.0 (w), 67.0, 122.0, 129.4, 133.8 (w), 150.9, 169.6, 173.0

^{31}P NMR (121.5 MHz, $CDCl_3$): δ_P ppm rotamers at 32.45, 33.86

HRMS (ESI-MS): calculated for $C_{23}H_{29}NO_9P$ $[M+H]^+$: 494.1574, found: 494.1579

{[({4-[Hydroxy(methyl)amino]-4-oxobutyl}phosphoryl)bis(oxy)]bis(methylene)}bis(4,1-phenylene) bis(2-methylpropanoate) (14b)



Following general procedure **4**, **13b** (76mg, 0.10mmol) afforded **14b** (73%) as a transparent oil after purification by column chromatography (DCM → 5%MeOH in DCM).

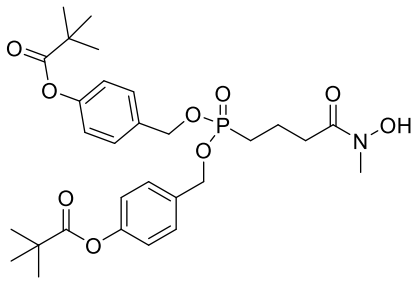
^{1}H NMR (300 MHz, $CDCl_3$) δppm 1.32 (d, *J* = 7.0 Hz, 12 H) 1.73 - 2.02 (m, 4 H) 2.45 – 2.63 (m, 2 H) 2.80 (septet, *J* = 7.0 Hz, 2 H) 3.24 (s, 3 H) 4.86 - 5.07 (m, 4 H) 7.03 - 7.10 (m, 4 H) 7.35 (d, *J* = 8.5 Hz, 4 H)

^{13}C NMR (75 MHz, $CDCl_3$) δppm 18.3, 19.1, 24.3 (d, $^1J_{C\text{-}P}$ = 128.8 Hz), 30.1, 34.3, 35.9, 67.0, 122.0, 129.4, 151.2

^{31}P NMR (121 MHz, $CDCl_3$) δppm rotamers at 32.42, 33.94

HRMS (ESI-MS): calculated for $C_{27}H_{37}NO_9P$ $[M+H]^+$: 550.2200, found: 550.2209

{[({4-[Hydroxy(methyl)amino]-4-oxobutyl}phosphoryl)bis(oxy)]bis(methylene)}bis(4,1-phenylene) bis(2,2-dimethylpropanoate) (14c)



Following general procedure **4**, **13c** (0.16g, 0.19mmol) afforded **14c** (63%) as a transparent oil after purification by column chromatography (DCM → 3%MeOH in DCM).

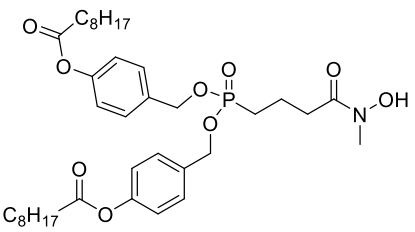
^{1}H NMR (300 MHz, $CDCl_3$) δppm 1.35 (s, 18 H) 1.73 - 2.01 (m, 4 H) 2.53 (br t, *J* = 5.0 Hz, 2 H) 3.23 (s, 3 H) 4.85 - 5.07 (m, 4 H) 7.01 - 7.07 (m, 4 H) 7.34 (d, *J* = 8.5 Hz, 4 H)

^{13}C NMR (75 MHz, $CDCl_3$) δppm 18.2 (d, $^2J_{C\text{-}P}$ = 5.8 Hz) 25.1 (d, $^1J_{C\text{-}P}$ = 144.8 Hz) 27.2, 30.5 (w), 35.9 (w), 39.2, 67.1, 122.0, 129.4, 133.6, 151.4, 173.0 (w), 177.4 (w)

^{31}P NMR (121 MHz, $CDCl_3$) δppm rotamers at 32.44, 33.83

HRMS (ESI-MS): calculated for $C_{29}H_{41}NO_9P$ $[M+H]^+$: 578.2513, found: 578.2494

{[({4-[Hydroxy(methyl)amino]-4-oxobutyl}phosphoryl)bis(oxy)]bis(methylene)}bis(4,1-phenylene) dinonanoate (14d)



Following general procedure **4**, **13d** (70mg, 0.080mmol) afforded **14d** (80%) as a white solid after purification by column chromatography (DCM → 3.5%MeOH in DCM).

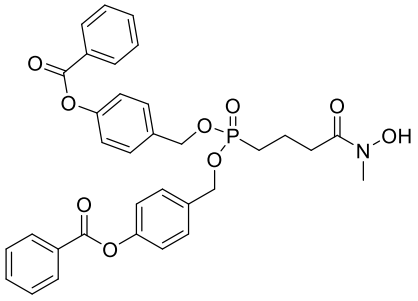
^{1}H NMR (300 MHz, $CDCl_3$) δppm 0.81 - 0.97 (m, 6 H) 1.23 - 1.46 (m, 20 H) 1.65 – 2.02 (m, 10 H) 2.55 (t, *J* = 7.5 Hz, 4 H) 3.24 (s, 3 H) 4.84 - 5.08 (m, 4 H) 7.03 - 7.10 (m, 4 H) 7.35 (d, *J* = 8.6 Hz, 4 H)

^{13}C NMR (75 MHz, $CDCl_3$) δppm 14.2, 18.4 (w), 22.8, 23.4, 25.1, 29.3 (d, $^{3}J_{C-P}$ = 6.9 Hz), 31.9, 34.6, 35.9, 67.0, 122.1, 129.4, 133.6 (w), 151.0 (w), 172.5 (w)

^{31}P NMR (121 MHz, $CDCl_3$) δppm rotamers at 32.44, 34.01

HRMS (ESI-MS): calculated for $C_{37}H_{57}NO_9P$ $[M+H]^+$: 690.3765, found: 690.3734

{[({4-[Hydroxy(methyl)amino]-4-oxobutyl}phosphoryl)bis(oxy)]bis(methylene)}bis(4,1-phenylene) dibenzoate (14e)



Following general procedure **4**, **13e** (0.10g, 0.12mmol) afforded **14e** (78%) as a white solid after purification by column chromatography (DCM → 3%MeOH in DCM).

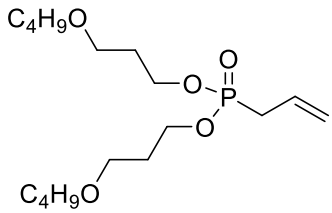
^{1}H NMR (300 MHz, $CDCl_3$) δppm 1.79 - 2.07 (m, 4 H) 2.55 - 2.65 (m, 2 H) 3.26 (s, 3 H) 4.92 - 5.12 (m, 4 H) 7.19 - 7.28 (m, 4 H) 7.38 - 7.55 (m, 8 H) 7.60 - 7.68 (m, 2 H) 8.15 - 8.23 (m, 4 H)

^{13}C NMR (75 MHz, $CDCl_3$) δppm 18.4, 24.6 (d, $^{1}J_{C-P}$ = 136.7 Hz), 30.2, 30.4, 35.9, 67.1, 122.1, 122.2, 128.8, 129.5, 129.6, 130.3, 133.9, 151.2

^{31}P NMR (121 MHz, $CDCl_3$) δppm rotamers at 32.52, 33.98

HRMS (ESI-MS): calculated for $C_{33}H_{33}NO_9P$ $[M+H]^+$: 618.1887, found: 618.1857

Bis(3-butoxypropyl) allylphosphonate (15a)



Following general procedure **1**, crude **9** (400mg, 2.50mmol) afforded **15a** (30%) as a yellow oil after purification by column chromatography (toluene → EtOAc).

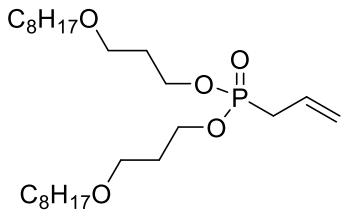
^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm 0.92 (t, *J* = 7.3 Hz, 6 H), 1.23 - 1.43 (m, 4 H), 1.44 -1.61 (m, 4 H), 1.92 (quintet, *J* = 6.2 Hz, 4 H), 2.63 (dd, *J* = 21.9, 7.3 Hz, 2 H), 3.41 (t, *J* = 6.6 Hz, 4 H), 3.49 (t, *J* = 6.2 Hz, 4 H), 4.05 - 4.22 (m, 4 H), 5.05 - 5.32 (m, 2 H), 5.64 - 5.87 (m, 1 H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ ppm 13.9, 19.3, 30.9 (d, $^{3}J_{C-P}$ = 5.8 Hz), 31.5 (d, $^{1}J_{C-P}$ = 139.4 Hz), 31.8, 63.2 (d, $^{2}J_{C-P}$ = 6.9 Hz), 66.5, 70.8, 119.8 (d, $^{3}J_{C-P}$ = 13.8 Hz), 127.4 (d, $^{2}J_{C-P}$ = 11.5 Hz)

^{31}P-NMR (121 MHz, $CDCl_3$) δ ppm 27.10

HRMS (ESI-MS): calculated for $C_{17}H_{36}O_5P$ $[M+H]^+$: 351.2295, found: 351.2301

Bis[3-(octyloxy)propyl] allylphosphonate (15b)



Following general procedure **1**, crude **9** (0.80g, 5.0mmol) afforded **15b** (32%) as a yellow oil after purification by column chromatography (toluene → EtOAc).

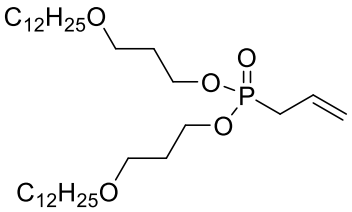
^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm 0.82 - 0.93 (m, 6 H), 1.21 - 1.38 (m, 20 H), 1.49-1.61 (m, 4 H), 1.92 (quintet, *J* = 6.3 Hz, 4 H), 2.56 - 2.69 (m, 2 H), 3.39 (t, *J* = 6.7 Hz, 4 H), 3.49 (t, *J* = 6.2 Hz, 4 H), 4.03 - 4.23 (m, 4 H), 5.09 - 5.29 (m, 2 H), 5.71 - 5.89 (m, 1 H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ ppm 14.2, 22.8, 26.3, 29.4, 29.6, 29.9, 31.1 (d, $^{3}J_{C-P}$ = 6.9 Hz), 32.0, 31.6 (d, $^{1}J_{C-P}$ = 139.4 Hz), 63.4 (d, $^{2}J_{C-P}$ = 6.9 Hz), 66.7, 71.4, 120.1 (d, $^{3}J_{C-P}$ = 13.8 Hz), 255.2 (d, $^{2}J_{C-P}$ = 10.4 Hz)

^{31}P-NMR (121 MHz, $CDCl_3$) δ ppm 27.14

HRMS (ESI-MS): calculated for $C_{25}H_{52}O_5P$ $[M+H]^+$: 463.3547, found: 463.3540

Bis[3-(dodecyloxy)propyl] allylphosphonate (15c)



Following general procedure **1**, crude **9** (0.80g, 5.0mmol) afforded **15c** (29%) as a yellow oil after purification by column chromatography (toluene → Et_2O).

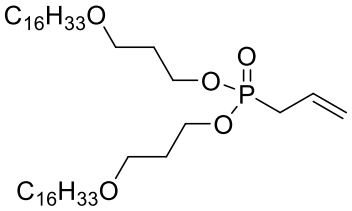
^{1}**H-NMR** (300 MHz, $CDCl_3$) δppm 0.82 - 0.97 (m, 6 H), 1.26 (br s, 36 H), 1.50-1.61 (m, 4H), 1.92 (quintet, *J* = 6.3 Hz, 4 H), 2.55 - 2.69 (m, 2 H), 3.39 (t, *J* = 6.7 Hz, 4 H), 3.49 (t, *J* = 6.2 Hz, 4 H), 4.00 - 4.21 (m, 4 H), 5.16 - 5.27 (m, 2 H), 5.71 - 5.89 (m, 1 H)

^{13}**C-NMR** (75 MHz, $CDCl_3$) δppm 14.3, 22.8, 26.3, 29.5, 29.7, 29.7 - 29.9 (m), 31.1 (d, $^3J_{C\text{-}P}$ = 5.8 Hz), 31.6 (d, $^1J_{C\text{-}P}$ = 139.4 Hz), 32.1, 63.3 (d, $^2J_{C\text{-}P}$ = 6.9 Hz), 66.7, 71.4, 120.1 (d, $^3J_{C\text{-}P}$ = 15.0 Hz); 127.6 (d, $^2J_{C\text{-}P}$ = 11.5 Hz)

^{31}**P-NMR** (121 MHz, $CDCl_3$) δppm 27.13

HRMS (ESI-MS): calculated for $C_{33}H_{68}O_5P$ $[M+H]^+$: 575.4799, found: 575.4801

Bis[3-(hexadecyloxy)propyl] allylphosphonate (15d)



Following general procedure **1**, crude **9** (0.80g, 5.0mmol) afforded **15d** (52%) as a white solid after purification by column chromatography (toluene → 6Tol/4EtOAc).

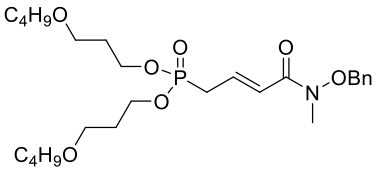
^{1}**H NMR** (300 MHz, $CDCl_3$) δppm 0.82 - 0.94 (m, 6 H) 1.19 - 1.36 (m, 52 H) 1.49 - 1.60 (m, 4 H) 1.92 (quintet, *J* = 6.3 Hz, 4 H) 2.54 - 2.69 (m, 2 H) 3.39 (t, *J* = 6.7 Hz, 4 H) 3.49 (t, *J* = 6.2 Hz, 4 H) 4.05 – 4.21 (m, 4 H) 5.16 – 5.27 (m, 2 H) 5.71 – 5.88 (m, 1 H)

^{13}**C NMR** (75 MHz, $CDCl_3$) δppm 14.3, 22.8, 26.3, 29.5, 29.6 - 29.9 (m) 31.1 (d, $^3J_{C\text{-}P}$ = 5.8 Hz) 31.6 (d, $^1J_{C\text{-}P}$ = 139.4 Hz) 32.1, 63.3 (d, $^2J_{C\text{-}P}$ = 6.9 Hz) 66.7, 71.4, 119.9 (d, $^3J_{C\text{-}P}$ = 13.8 Hz) 127.4 (d, $^2J_{C\text{-}P}$ = 11.5 Hz)

^{31}**P NMR** (121 MHz, $CDCl_3$) δppm 27.14

HRMS (ESI-MS): calculated for $C_{41}H_{83}O_5PNa$ $[M+Na]^+$: 709.5870, found: 709.5895

Bis(3-butoxypropyl) (*E*)-{4-[(benzyloxy)(methyl)amino]-4-oxobut-2-en-1-yl}phosphonate (17a)



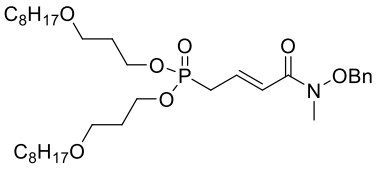
Following general procedure **2**, **15a** (621mg, 1.77mmol) afforded **17a** (67%) as a black oil after purification by column chromatography (toluene → EtOAc).

^{1}**H-NMR** (300 MHz, $CDCl_3$) δ ppm 0.91 (t, *J* = 7.4 Hz, 6 H), 1.22 - 1.44 (m, 4 H), 1.44 - 1.60 (m, 4 H), 1.90 (quintet, *J* = 6.3 Hz, 4 H), 2.69 - 2.82 (m, 2 H), 3.24 (s, 3 H), 3.39 (t, *J* =6.6 Hz, 4 H), 3.43 - 3.51 (m, 4 H), 4.07 - 4.21 (m, 4 H), 4.84 (s, 2 H), 6.51 - 6.61 (m, 1 H), 6.84 (app sextet, *J* = 7.7 Hz, 1 H), 7.34 - 7.41 (m, 5 H)

^{31}**P-NMR** (121 MHz, $CDCl_3$) δ ppm 24.96

HRMS (ESI-MS): calculated for $C_{26}H_{45}NO_7P$ $[M+H]^+$: 514.2928, found: 514.2951

Bis(3-(octyloxy)propyl) (*E*)-{4-[(benzyloxy)(methyl)amino]-4-oxobut-2-en-1-yl}phosphonate (17b)



Following general procedure **2**, **15b** (740mg, 1.60mmol) afforded **17b** (76%) as a black oil after purification by column chromatography (toluene → EtOAc).

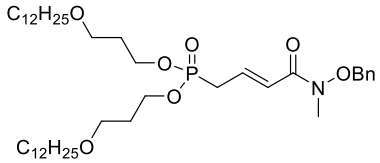
^{1}**H-NMR** (300 MHz, $CDCl_3$) δ ppm 0.88 (t, *J* = 6.5 Hz, 6 H), 1.18 - 1.35 (m, 20 H), 1.47 -1.59 (m, 4 H), 1.91 (quintet, *J* = 6.2 Hz, 4 H), 2.75 (dd, *J* = 22.6, 7.6 Hz, 2 H), 3.24 (s, 3 H), 3.34 - 3.41 (m, 4 H), 3.43 - 3.51 (m, 4 H), 4.09 – 4.19 (m, 4 H), 4.84 (s, 2 H), 6.51 – 6.61 (m, 1 H), 6.77 - 6.92 (m, 1 H), 7.39 (s, 5 H)

^{13}**C-NMR** (75 MHz, $CDCl_3$) δ ppm 14.2, 22.8, 26.3, 29.4, 29.6, 29.9, 30.6 (d, $^1J_{C\text{-}P}$ = 139.4 Hz), 31.1 (d, $^3J_{C\text{-}P}$ = 6.9 Hz), 32.0, 34.0, 77.4, 127.3 (d, $^2J_{C\text{-}P}$ = 6.9 Hz), 66.7, 71.4, 123.8 (d, $^3J_{C\text{-}P}$ = 13.8 Hz), 128.9, 129.2, 129.4, 134.5, 135.7 (d, ^2JC_P = 11.5 Hz), 166.5

^{31}**P-NMR** (121 MHz, $CDCl_3$) δ ppm 24.99

HRMS (ESI-MS): calculated for $C_{34}H_{61}NO_7P$ $[M+H]^+$: 626.4180, found: 626.4194

Bis(3-(dodecyloxy)propyl) (*E*)-{4-[(benzyloxy)(methyl)amino]-4-oxobut-2-en-1-yl}phosphonate (17c)



Following general procedure **2**, **15c** (1.65g, 2.87mmol) afforded **17c** (59%) as a black oil after purification by column chromatography (toluene → 1Tol/1EtOAc).

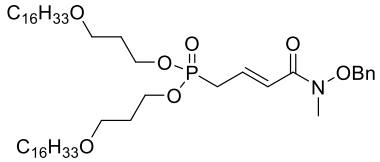
^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm 0.80 - 0.98 (m, 6 H), 1.26 (br s, 36 H), 1.32 - 1.66 (m, 4 H), 1.91 (quintet, *J* = 6.2 Hz, 4 H), 2.57 - 2.94 (m, 2 H), 3.24 (s, 3 H), 3.37 (t, *J* = 6.7 Hz, 4 H), 3.41 - 3.57 (m, 4 H), 4.01 - 4.22 (m, 4 H), 4.84 (s, 2 H), 6.50 - 6.61 (m, 1 H), 6.83 (app sextet, *J* = 7.8 Hz, 1 H), 7.35 - 7.42 (m, 5 H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ ppm 14.2, 22.8, 26.3, 29.4, 29.6, 29.7, 29.8, 30.6 (d, $^{1}J_{C\text{-}P}$ = 131.3 Hz), 31.0 (d, $^{3}J_{C\text{-}P}$ = 6.9 Hz), 31.5, 32.0, 33.9, 63.6 (d, $^{2}J_{C\text{-}P}$ = 5.8 Hz), 66.6, 71.3, 77.1, 123.8 (d, $^{3}J_{C\text{-}P}$ = 13.8 Hz), 128.8, 129.1, 129.4, 134.4, 135.6 (d, $^{2}J_{C\text{-}P}$ = 11.5 Hz), 166.4

^{31}P-NMR (121 MHz, $CDCl_3$) δ ppm 24.97

HRMS (ESI-MS): calculated for $C_{42}H_{77}NO_7P$ $[M+H]^+$: 738.5432, found: 738.5427

Bis(3-(hexadecyloxy)propyl) (*E*)-{4-[(benzyloxy)(methyl)amino]-4-oxobut-2-en-1-yl}phosphonate (17d)



Following general procedure **2**, **15d** (0.21g, 0.30mmol) afforded **17d** (55%) as a black oil after purification by column chromatography (toluene → 1Tol/3EtOAc).

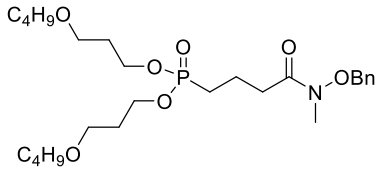
^{1}H NMR (300 MHz, $CDCl_3$) δppm 0.80 - 0.94 (m, 6 H) 1.16 - 1.36 (br s, 52 H) 1.47 - 1.60 (m, 4 H) 1.90 (quintet, *J* = 6.3 Hz, 4 H) 2.65 - 2.84 (m, 2 H) 3.24 (s, 3 H) 3.37 (t, *J* = 6.7 Hz, 4 H) 3.46 (t, *J* = 6.2 Hz, 4 H) 4.06 - 4.21 (m, 4 H) 4.84 (s, 2 H) 6.51 – 6.60 (m, 1 H) 6.84 (app sxt, *J* = 7.7 Hz, 1 H) 7.39 (s, 5 H)

^{13}C NMR (75 MHz, $CDCl_3$) δppm 14.3, 22.9, 26.3, 29.6 – 30.0 (m) 31.1 (d, $^{3}J_{C\text{-}P}$ = 5.8 Hz), 31.6, 32.1, 33.8, 63.6 (d, $^{2}J_{C\text{-}P}$ = 6.9 Hz), 66.7, 71.4, 77.2, 123.8 (d, $^{3}J_{C\text{-}P}$ = 13.8 Hz), 128.9, 129.2, 129.4, 135.7 (d, $^{2}JC_{\text{-}P}$ = 11.5 Hz)

^{31}P NMR (121 MHz, $CDCl_3$) δppm 24.97

HRMS (ESI-MS): calculated for $C_{50}H_{93}NO_7P$ $[M+H]^+$: 850.6684, found: 850.6647

Bis(3-butoxypropyl) {4-[(benzyloxy)(methyl)amino]-4-oxobutyl}phosphonate (18a)



Following general procedure **3**, **17a** (607mg, 1.18mmol) afforded **18a** (58%) as a transparent oil after purification by column chromatography (DCM → 3%MeOH in DCM).

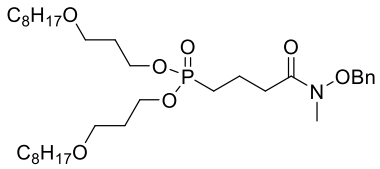
^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm 0.91 (t, *J* = 7.3 Hz, 6 H), 1.28 - 1.43 (m, 4 H), 1.45 - 1.61 (m, 4 H), 1.69 - 1.85 (m, 4 H), 1.91 (quintet, *J* = 6.3 Hz, 4 H), 2.49 (t, *J* = 6.9 Hz, 2 H), 3.19 (s, 3 H), 3.40 (t, *J* = 6.6 Hz, 4 H), 3.48 (t, *J* = 6.2 Hz, 4 H), 4.02 - 4.19 (m, 4 H), 4.83 (s, 2 H), 7.38 (s, 5 H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ ppm 14.0, 17.6 (d, $^{2}J_{C\text{-}P}$ = 4.6 Hz), 19.4, 24.7 (d, $^{1}J_{C\text{-}P}$ = 140.5 Hz), 31.0 (d, $^{3}J_{C\text{-}P}$ = 5.8 Hz), 31.8, 32.3 (d, $^{3}J_{C\text{-}P}$ = 15.0 Hz), 33.5, 62.8 (d, $^{2}J_{C\text{-}P}$ = 6.9 Hz), 66.6, 70.9, 76.2, 128.8, 129.0, 129.3, 134.5

^{31}P-NMR (121 MHz, $CDCl_3$) δ ppm 31.74

HRMS (ESI-MS): calculated for $C_{26}H_{47}NO_7P$ $[M+H]^+$: 516.3085, found: 516.3089

Bis[3-(octyloxy)propyl] {4-[(benzyloxy)(methyl)amino]-4-oxobutyl}phosphonate (18b)



Following general procedure **3**, **17b** (760mg, 1.21mmol) afforded **18b** (27%) as a transparent oil after purification by column chromatography (toluene → 1Tol/3EtOAc).

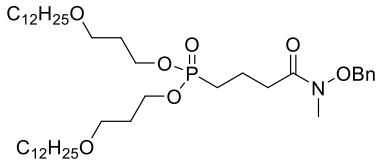
^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm 0.83 - 0.92 (m, 6 H), 1.28 (br s, 20 H), 1.48 - 1.61 (m, 4 H), 1.69 - 1.83 (m, 4 H), 1.91 (t, *J* = 6.3 Hz, 4 H), 2.49 (t, *J* = 6.9 Hz, 2 H), 3.19 (s, 3 H), 3.38 (t, *J* = 6.7 Hz, 4 H), 3.48 (t, *J* = 6.2 Hz, 4 H), 4.03 – 4.18 (m, 4 H), 4.83 (s, 2 H) 7.32 - 7.45 (m, 5 H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ ppm 14.1, 17.6 (d, $^2J_{C\text{-}P}$ = 4.6 Hz), 22.7, 49.4 (d, $^1J_{C\text{-}P}$ = 140.5 Hz), 26.2, 29.2, 29.5, 29.8, 31.0 (d, $^3J_{C\text{-}P}$ = 5.8 Hz), 31.8, 32.3 (d, $^3J_{C\text{-}P}$ = 16.1 Hz), 33.5, 62.8 (d, $^2J_{C\text{-}P}$ = 6.9 Hz), 66.6, 71.2, 76.2, 128.7, 129.0, 129.3, 134.5

^{31}P-NMR (121 MHz, $CDCl_3$) δ ppm 31.75

HRMS (ESI-MS): calculated for $C_{34}H_{63}NO_7P$ $[M+H]^+$: 628.4337, found: 628.4357

Bis[3-(dodecyloxy)propyl] {4-[(benzyloxy)(methyl)amino]-4-oxobutyl}phosphonate (18c)



Following general procedure **3**, **17c** (1.16g, 1.57mmol) afforded **18c** (45%) as a transparent oil after purification by column chromatography (toluene → 3Tol/7EtOAc).

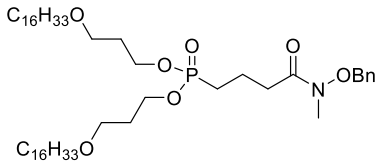
^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm 0.80 - 0.96 (m, 6 H), 1.26 (br s, 36 H), 1.37 - 1.61 (m, 4 H), 1.69 - 1.85 (m, 4 H), 1.89 (quintet, *J* = 6.2 Hz, 4 H), 2.35 - 2.57 (m, 2 H), 3.19 (s, 3 H), 3.41 (t, *J* = 6.6 Hz, 4 H), 3.50 (t, *J* = 6.1 Hz, 4 H), 4.01 - 4.18 (m, 4 H), 4.83 (s, 2 H), 7.31 - 7.45 (m, 5 H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ ppm 14.3, 17.7 (d, $^2J_{C\text{-}P}$ = 5.8 Hz), 22.8, 24.9 (d, $^1J_{C\text{-}P}$ = 140.5 Hz), 26.3, 29.5, 29.7-29.9 (m), 31.1 (d, $^3J_{C\text{-}P}$ = 6.9 Hz), 32.1, 32.5 (d, $^3J_{C\text{-}P}$ = 15.0 Hz), 33.7, 62.9 (d, $^2J_{C\text{-}P}$ = 5.8 Hz), 66.8, 71.4, 76.4, 128.9, 129.1, 129.4, 134.6, 174.3

^{31}P-NMR (121 MHz, $CDCl_3$) δ ppm 31.75

HRMS (ESI-MS): calculated for $C_{42}H_{79}NO_7P$ $[M+H]^+$: 740.5589, found: 740.5605

Bis[3-(hexadecyloxy)propyl] {4-[(benzyloxy)(methyl)amino]-4-oxobutyl}phosphonate (18d)



Following general procedure **3**, **17d** (0.15g, 0.15mmol) afforded **18d** (91%) as a white solid after purification by column chromatography (toluene → 1Tol/3EtOAc).

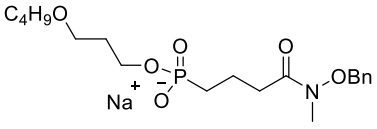
^{1}H NMR (300 MHz, $CDCl_3$) δppm 0.79 - 0.96 (m, 6 H) 1.19 - 1.36 (m, 52 H) 1.44 - 1.60 (m, 4 H) 1.69 – 1.85 (m, 4 H) 1.91 (quintet, *J* = 6.3 Hz, 4H) 2.44 - 2.54 (m, 2 H) 3.19 (s, 3 H) 3.38 (t, *J* = 6.7 Hz, 4 H) 3.48 (t, *J* = 6.2 Hz, 4 H) 4.05 – 4.17 (m, 4 H) 4.82 (s, 2 H) 7.38 (s, 5 H)

^{13}C NMR (75 MHz, $CDCl_3$) δppm 14.2, 17.7 (d, $^2J_{C\text{-}P}$ = 4.6 Hz), 22.8, 24.8 (d, $^1J_{C\text{-}P}$ = 141.7 Hz), 26.3, 29.5, 29.7, 29.8, 31.1 (d, $^3J_{C\text{-}P}$ = 5.8 Hz) 32.0, , 32.4 (d, $^3J_{C\text{-}P}$ = 15.0 Hz), 62.9 (d, $^2J_{C\text{-}P}$ = 5.8 Hz) 66.8, 71.3, 76.3, 128.8, 129.1, 129.4, 134.6 (w)

^{31}P-NMR (121 MHz, $CDCl_3$) δppm 31.75

HRMS (ESI-MS): calculated for $C_{50}H_{95}NO_7P$ $[M+H]^+$: 852.6841, found: 852.6807

3-Butoxypropyl {4-[(benzyloxy)(methyl)amino]-4-oxobutyl}phosphonate (19a)



Following general procedure **6**, **18a** (0.20g, 0.39mmol) afforded **19a** (48%) as a white solid after purification by column chromatography (EtOAc → 40%MeOH in EtOAc) and HPLC.

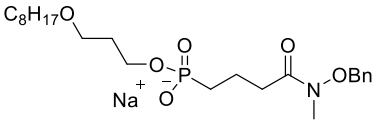
^{1}**H-NMR** (300 MHz, METHANOL-*d*4) δ ppm 0.92 (t, *J* = 7.3 Hz, 3 H), 1.28 - 1.44 (m, 2H), 1.45 - 1.62 (m, 2 H), 1.72 - 1.93 (m, 6 H), 2.47 (t, *J* = 7.4 Hz, 2 H), 3.21 (s, 3 H), 3.42 (t, *J* = 6.4 Hz, 2 H), 3.50 (t, *J* = 6.2 Hz, 2 H), 3.89 (app q, *J* = 6.4 Hz, 2 H),4.91 (s, 2 H), 7.32 - 7.49 (m, 5 H)

^{13}**C-NMR** (75 MHz, METHANOL-*d*4) δ ppm 14.3, 19.1 (d, $^{2}J_{C\text{-}P}$ = 4.6 Hz), 20.4, 26.2 (d, $^{1}J_{C\text{-}P}$ = 139.4 Hz), 32.0 (d, $^{3}J_{C\text{-}P}$ = 5.8 Hz), 32.5, 32.9, 33.5 (d, $^{3}J_{C\text{-}P}$ = 16.1 Hz), 63.3 (d, $^{2}J_{C\text{-}P}$ = 6.9 Hz), 67.8, 71.8, 77.1, 129.7, 130.0, 130.8, 136.1

^{31}**P-NMR** (121 MHz, METHANOL-*d*4) δ ppm 25.31

HRMS (ESI-MS): calculated for $C_{19}H_{33}NO_6P$ $[M+H]^+$: 402.2040, found: 402.2050

3-(Octyloxy)propyl {4-[(benzyloxy)(methyl)amino]-4-oxobutyl}phosphonate (19b)



Following general procedure **6**, **18b** (0.21g, 0.33mmol) afforded **19b** (78%) as a faint yellow solid after purification by column chromatography (EtOAc → 40%MeOH in EtOAc and DCM → 1DCM/1MeOH).

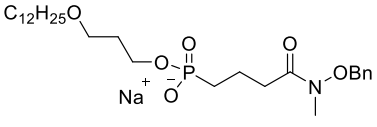
^{1}**H-NMR** (300 MHz, METHANOL-*d*4) δ ppm 0.84 - 0.94 (m, 3 H), 1.29 (br s, 10 H), 1.46 - 1.62 (m, 4 H), 1.75 - 1.91 (m, 4 H), 2.48 (t, *J* = 7.4 Hz, 2 H), 3.19 (s, 3 H), 3.40 (t, *J* = 6.6 Hz, 2 H), 3.51 (t, *J* = 6.3 Hz, 2 H), 3.89 (app q, *J* = 6.3 Hz, 2 H), 4.90 (s, 2 H), 7.27 - 7.54(m, 5 H)

^{13}**C-NMR** (75 MHz, METHANOL-*d*4) δ ppm 14.6, 20.5 (d, $^{2}J_{C\text{-}P}$ = 3.5 Hz), 23.9, 27.4, 27.7 (d, $^{1}J_{C\text{-}P}$ = 135.9 Hz), 30.6, 30.8, 31.0, 32.6 (d, $^{2}J_{C\text{-}P}$ = 6.9 Hz), 33.2, 62.2 (d, $^{2}J_{C\text{-}P}$ = 5.8 Hz), 68.7, 72.2, 77.3, 129.8, 130.1, 130.9, 136.4

^{31}**P-NMR** (121 MHz, METHANOL-*d*4) δ ppm 25.14

HRMS (ESI-MS): calculated for $C_{23}H_{41}NO_6P$ $[M+H]^+$: 458.2666, found: 458.2666

3-(Dodecyloxy)propyl {4-[(benzyloxy)(methyl)amino]-4-oxobutyl}phosphonate (19c)



Following general procedure **6**, **18c** (0.50g, 0.68mmol) afforded **19c** (84%) as a white solid after purification by column chromatography (EtOAc → 40%MeOH in EtOAc and DCM → 30%MeOH in DCM).

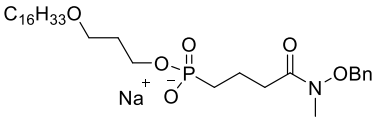
^{1}**H-NMR** (300 MHz, $CDCl_3$) δ ppm 0.89 (t, *J* = 6.3 Hz, 3 H), 1.23 (br s, 18 H), 1.34 - 1.63(m, 4 H), 1.63 - 1.93 (m, 4 H), 2.48 (br t, *J* = 7.4 Hz, 2 H), 3.13 (s, 3 H), 3.40 (br t, *J* = 6.5 Hz, 2 H), 3.51 (br t, *J* = 6.3 Hz, 2 H), 3.84 (app q, *J* = 6.2 Hz, 2 H), 4.78 (s, 2 H), 7.30 -7.47 (m, 5 H)

^{13}**C-NMR** (75 MHz, $CDCl_3$) δ ppm 14.2, 22.8, 26.3, 29.4, 29.6, 29.7, 29.75, 29.81, 31.0 (d, $^{3}J_{C\text{-}P}$ = 6.9 Hz), 31.5, 32.0, 33.9, 63.3 (d, $^{3}J_{C\text{-}P}$ = 5.8 Hz), 63.6 (d, $^{2}J_{C\text{-}P}$ = 6.9 Hz), 66.6, 66.7, 71.3, 123.6, 123.8, 129.1, 129.4, 134.4, 135.6, 135.7, 166.4

^{31}**P-NMR** (121 MHz, $CDCl_3$) δ ppm 26.38

HRMS (ESI-MS): calculated for $C_{27}H_{49}NO_6P$ $[M+H]^+$: 514.3292, found: 514.3290

3-(Hexadecyloxy)propyl {4-[(benzyloxy)(methyl)amino]-4-oxobutyl}phosphonate (19d)



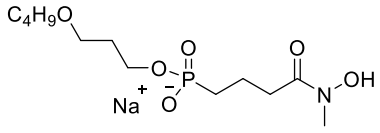
Following general procedure **6**, **18d** (0.12g, 0.14mmol) afforded **19d** (77%) as a white solid after purification by column chromatography (DCM → 50%MeOH in DCM).

^{1}**H NMR** (300 MHz, METHANOL-d_4) δppm 0.89 (t, *J* = 6.7 Hz, 3 H) 1.28 (br s, 26 H) 1.44 - 1.66 (m, 4 H) 1.70 - 1.95 (m, 4 H) 2.48 (br t, *J* = 7.3 Hz, 2 H) 3.21 (s, 3 H) 3.39 (br t, *J* = 6.6 Hz, 2 H) 3.51 (t, *J* = 6.4 Hz, 2 H) 3.90 (app q, *J* = 6.3 Hz, 2 H) 4.84 (s, 2 H) 7.35 - 7.47 (m, 5 H)

^{31}**P NMR** (121 MHz, METHANOL-d_4) δppm 25.01

HRMS (ESI-MS): calculated for $C_{31}H_{55}NO_6P$ $[M-H]^-$: 568.3772, found: 568.3745

3-Butoxypropyl {4-[hydroxy(methyl)amino]-4-oxobutyl}phosphonate (20a)



Following general procedure **5**, **19a** (67mg, 0.16mmol) afforded **20a** (67%) as a white solid after purification by column chromatography (DCM → 40%MeOH in DCM).

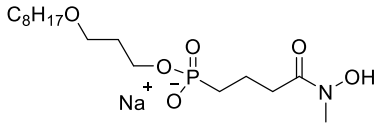
^{1}H NMR (300 MHz, METHANOL-*d*4) δ ppm 0.92 (t, *J* = 7.3 Hz, 3 H), 1.32 - 1.43 (m, 4 H), 1.47 - 1.60 (m, 2 H), 1.86 (quintet, *J* = 6.3 Hz, 4 H), 2.56 (br t, *J* = 7.1 Hz, 2 H), 3.15 - 3.22 (m, 3 H), 3.43 (t, *J* = 6.5 Hz, 2 H), 3.52 (t, *J* = 6.3 Hz, 2 H), 3.95 (app q, *J* = 6.3 Hz, 2 H), 4.88 (br s, 2 H)

^{13}C-NMR (75 MHz, METHANOL-*d*4) δ ppm 9.1, 14.3, 20.2 – 20.3 (m), 20.4, 27.1 (d, $^1J_{C\text{-}P}$ = 137.1 Hz), 32.3 (d, $^3J_{C\text{-}P}$ = 6.9 Hz), 32.9, 33.8 (d, $^3J_{C\text{-}P}$ = 15.0 Hz), 36.2, 62.4 (d, $^2J_{C\text{-}P}$ = 5.8 Hz), 68.3, 71.8, 175.5

^{31}P-NMR (121 MHz, METHANOL-*d*4) δ ppm 26.49

HRMS (ESI-MS): calculated for $C_{12}H_{27}NO_6P$ $[M+H]^+$: 312.1571, found: 312.1582

3-(Octyloxy)propyl {4-[hydroxy(methyl)amino]-4-oxobutyl}phosphonate (20b)



Following general procedure **5**, **19b** (0.12g, 0.26mmol) afforded **20b** (30%) as a white solid after purification by column chromatography (DCM → 35%MeOH in DCM).

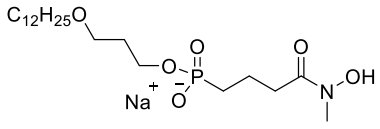
^{1}H-NMR (300 MHz, METHANOL-*d*4) δ ppm 0.85 - 0.94 (m, 3 H), 1.30 (br s, 10 H), 1.45 - 1.66 (m, 4 H), 1.80 - 1.94 (m, 4 H), 2.56 (br t, *J* = 7.3 Hz, 2 H), 3.19 (s, 3 H), 3.42 (t, *J* = 6.6 Hz, 2 H), 3.53 (t, *J* = 6.4 Hz, 2 H), 3.93 (app q, *J* = 6.4 Hz, 2 H), 4.86 (br s, 2 H)

^{13}C-NMR (75 MHz, METHANOL-*d*4) δ ppm 14.4, 20.3 (d, $^2J_{C\text{-}P}$ = 4.6 Hz), 23.7, 27.26 (d, $^1J_{C\text{-}P}$ = 137.1 Hz), 27.29, 30.4, 30.6, 30.8, 32.4 (d, $^3J_{C\text{-}P}$ = 5.8 Hz), 33.0, 33.9 (d, $^3J_{C\text{-}P}$ = 15.0 Hz), 36.2, 61.7 (d, $^2J_{C\text{-}P}$ = 5.8 Hz) 68.4, 72.1, 175.5

^{31}P-NMR (121 MHz, METHANOL-*d*4) δ ppm 26.00

HRMS (ESI-MS): calculated for $C_{16}H_{35}NO_6P$ $[M+H]^+$: 368.2197, found: 368.2206

3-(Dodecyloxy)propyl {4-[hydroxy(methyl)amino]-4-oxobutyl}phosphonate (20c)



Following general procedure **5**, **19c** (0.31g, 0.57mmol) afforded 20**c** (24%) as a white solid after purification by column chromatography (DCM → 40%MeOH in DCM).

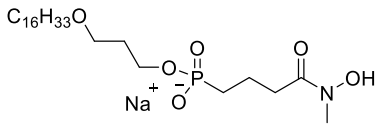
^{1}H NMR (300 MHz, METHANOL-*d*4) δ ppm 0.73 - 1.05 (m, 3 H), 1.29 (br s, 18 H), 1.36 - 1.69 (m, 4 H), 1.69 - 2.04 (m, 4 H), 2.56 (br t, *J* = 7.0 Hz, 2 H), 3.20 (s, 3 H), 3.42 (t, *J* = 6.6 Hz, 2 H), 3.53 (t, *J* = 6.4 Hz, 2 H), 3.91 (app q, *J* = 6.2 Hz, 2 H), 8.53 (br s, 1H)

^{13}C-NMR (75 MHz, METHANOL-*d*4) δ ppm 14.5, 20.6 (d, $^2J_{C\text{-}P}$ = 4.6 Hz), 23.8, 27.41, 27.42 (d, $^1J_{C\text{-}P}$ = 135.9 Hz), 30.6, 30.8, 30.86, 30.93, 32.5 (d, $^3J_{C\text{-}P}$ = 5.8 Hz), 33.2, 34.0 (d, $^3J_{C\text{-}P}$ = 15.0 Hz) 36.4, 62.2 (d, $^2J_{C\text{-}P}$ = 5.8 Hz), 68.6, 72.2, 175.8

^{31}P-NMR (121 MHz, METHANOL-*d*4) δ ppm 24.55

HRMS (ESI-MS): calculated for $C_{20}H_{43}NO_6P$ $[M+H]^+$: 424.2823, found: 424.2834

3-(Hexadecyloxy)propyl {4-[hydroxy(methyl)amino]-4-oxobutyl}phosphonate (20d)



Following general procedure **5**, **19d** (62mg, 0.11mmol) afforded **20d** (73%) as a white solid after purification by column chromatography (DCM → 50%MeOH in DCM).

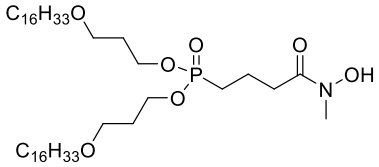
^{1}H NMR (300 MHz, METHANOL-d_4) δppm 0.85 - 0.94 (m, 3 H) 1.28 (br s, 26 H) 1.48 - 1.69 (m, 4 H) 1.76 - 1.95 (m, 4 H) 2.58 (t, *J* = 7.7 Hz, 2 H) 3.23 (s, 3 H) 3.41 (t, *J* = 6.6 Hz, 2 H) 3.49 - 3.56 (m, 2 H) 3.85 - 3.97 (m, 2 H) 8.54 (s, 1 H)

^{13}C-NMR (75 MHz, METHANOL-*d*4) δ ppm 14.4, 23.7, 27.3, 30.8, 33.1, 62.0, 68.6, 72.1

^{31}P NMR (121 MHz, METHANOL-d_4) δppm rotamers at 25.58, 26.17

HRMS (ESI-MS): calculated for $C_{24}H_{49}NO_6P$ $[M-H]^-$: 478.3303, found: 478.3324

Bis[3-(hexadecyloxy)propyl] {4-[hydroxy(methyl)amino]-4-oxobutyl}phosphonate (21d)



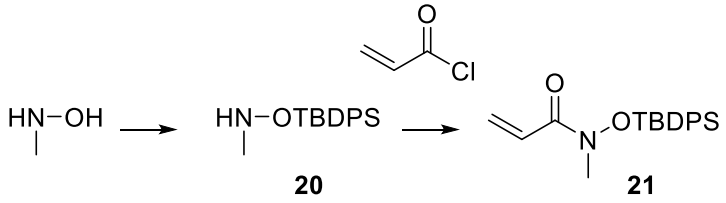
Following general procedure **5**, **18d** (0.13g, 0.15mmol) afforded **21d** (75%) as a white solid after purification by column chromatography (toluene → 7.5%MeOH in Tol).

^{1}H NMR (300 MHz, $CDCl_3$) δppm 0.84 - 0.92 (m, 6 H) 1.16 - 1.37 (br s, 52 H) 1.48 - 1.60 (m, 4 H) 1.75 - 2.04 (m, 8 H) 2.64 (t, *J* = 6.5 Hz, 2 H) 3.24 (s, 3 H) 3.39 (t, *J*=6.7 Hz, 4 H) 3.49 (t, *J* = 6.1 Hz, 4 H) 4.00 - 4.20 (m, 4 H)

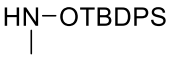
^{13}C NMR (75 MHz, $CDCl_3$) δppm 14.2, 18.3 (d, $^2J_{C\text{-}P}$ = 5.8 Hz), 22.8, 23.9 (d, $^1J_{C\text{-}P}$ = 140.5 Hz), 26.3, 29.6 – 30.0 (m), 31.0 (d, $^3J_{C\text{-}P}$ = 8.1 Hz) 32.0, 36.0, 63.3 (d, $^2J_{C\text{-}P}$ = 6.9 Hz) 66.5, 71.4, 173.0 (w)

^{31}P NMR (121 MHz, $CDCl_3$) δppm 32.56

HRMS (ESI-MS): calculated for $C_{43}H_{89}NO_7P$ $[M+H]^+$: 762.6371, found: 762.6406



***O*-(Tert-butyldiphenylsilyl)-*N*-methylhydroxylamine (22)**



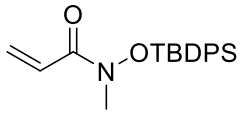
N-methyl hydroxylamine hydrochloride (1.93g, 23.1mmol) was dissolved in DCM (36mL). DIPEA (9.15mL, 52.5mmol) was added, followed by addition of TBDPSCl (5.5mL, 21mmol) and DMF (3.6mL). After 40 hours at room temperature, the reaction mixture was further diluted with DCM and washed with H_2O. The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. Column chromatography (hexanes → 5%Et_2O in hexanes) yielded pure **22** as a transparent liquid (79%).

^{1}H NMR (300 MHz, $CDCl_3$) δppm 1.09 (s, 9 H) 2.68 (s, 3 H) 7.31 - 7.46 (m, 6 H) 7.65 - 7.77 (m, 4 H)

^{13}C NMR (75 MHz, $CDCl_3$) δppm 27.5, 41.6, 127.7, 129.7, 134.0, 135.8

HRMS (ESI-MS): calculated for $C_{17}H_{24}NOSi$ $[M+H]^+$: 286.1622, found: 286.1621

***N*-[(Tert-butyldiphenylsilyl)oxy]-*N*-methylacrylamide (11)**

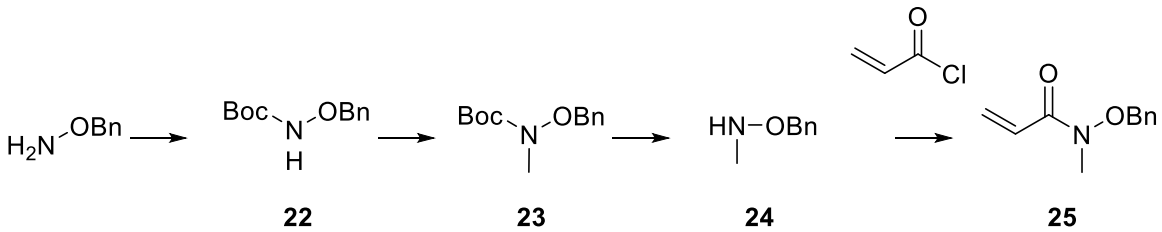


Acryloyl chloride (2.0mL, 25mmol) and protected hydroxylamine **22** (7.85g, 27.5mmol) were dissolved in DCM (50mL) and cooled to 0°C in an ice bath. Dry pyridine (4.0mL, 50mmol) was added dropwise and the resulting solution was allowed to warm to room temperature. Upon completion of the reaction, as confirmed by TLC, the reaction mixture was further diluted with DCM and washed with 1M HCl (aq. soln.). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. Column chromatography (toluene → 2Tol/1EtOAc) yielded pure **11** as pale yellow oil (88%).

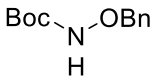
^{1}H NMR (300 MHz, $CDCl_3$) δppm 1.17 (s, 9 H) 3.13 (s, 3 H) 5.54 (dd, *J* = 10.4, 2.0 Hz, 1 H) 6.17 (dd, *J* = 17.1, 2.0 Hz, 1 H) 7.34 - 7.50 (m, 6 H) 7.66 - 7.74 (m, 4 H)

^{13}C-NMR (75 MHz, $CDCl_3$) δppm 27.2, 39.0 (w) 126.9, 128.0, 128.1, 130.6, 136.2

HRMS (ESI-MS): calculated for $C_{20}H_{26}NO_2Si$ $[M+H]^+$: 340.1727, found: 340.1728

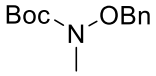


Tert-butyl (benzyloxy)carbamate (23)



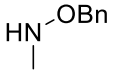
O-benzylhydroxylamine hydrochloride (26.5g, 166mmol), di-tert-butyl dicarbonate (36.2g, 166mmol) and $NaHCO_3$(14.0g, 166mmol) were dissolved in dioxane (169mL) and H_2O (166mL). The reaction was allowed to stir overnight at room temperature, after which TLC confirmed complete conversion of starting materials. The reaction mixture was partially evaporated *in vacuo* in order to remove dioxane. The pH of the reaction was lowered to pH4 with 1M citric acid (aq. soln.) and the reaction mixture was extracted three times with DCM. The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Column chromatography (hexanes → Et_2O) yielded pure **23** as colourless crystals (93%). Spectral data are in accordance with those reported in the literature[2].

Tert-butyl (benzyloxy)(methyl)carbamate (24)



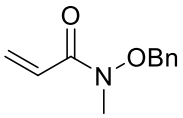
To a solution of **23** (4.53g, 20.3mmol) in DMF (40mL), NaH (60% dispersion in mineral oil, 893mg, 22.3mmol) was added gradually. The reaction was stirred for 30 minutes at room temperature, after which iodomethane (1.40mL, 22.3mmol) was added. After overnight stirring, TLC confirmed completion of the reaction. The reaction was quenched by the addition of H_2O and extracted three times with hexanes. The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Column chromatography (hexanes → 10%Et_2O in hexanes) yielded pure **24** as a pale yellow oil (97%). Spectral data are in accordance with those reported in the literature[2].

***O*-Benzyl-*N*-methylhydroxylamine (25)**



To a solution of **24** (11.9g, 37.2 mmol) in DCM (190mL), TFA (30.0mL, 391 mmol) was added. After 2 hours at room temperature, TLC confirmed completion of the reaction. Toluene was added to the reaction mixture all volatiles were removed *in vacuo*. H_2O was added and the pH was adjusted up to pH 9 with KOH (aq. soln.), followed by extraction with DCM. The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was used without further purification or characterization.

***N*-(Benzyloxy)-*N*-methylacrylamide (16)**



Acryloyl chloride (1.1mL, 13mmol) and protected hydroxylamine **25** (1.96g, 14.3mmol) were dissolved in DCM (30mL) and cooled to 0°C in an ice bath. Dry pyridine (2.1mL, 26mmol) was added dropwise and the resulting solution was allowed to warm to room temperature. Upon completion of the reaction, as confirmed by TLC, the reaction mixture was further diluted with DCM and washed with 1M HCL (aq. soln.). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. Column chromatography (toluene → 8Tol/2EtOAc) yielded pure **16** as pale yellow oil (75%). Spectral data are in accordance with those reported in the literature[3].

Plasma stability assay

The plasma stability assay was carried out in duplicate by incubating 40 µl of the test compounds (1 mM -100% DMSO) in 360 µL plasma at 37°C. After respectively 0, 30 and 60 minutes, 20 µl was withdrawn and 80 µl cold acetonitrile, containing the internal standard tolbutamide, was added to precipitate the proteins. The mixture was vortexed for 30 sec and centrifuged at 4°C for 5 min at 15,000 rpm. The loss of parent compound over a 30 and 60 minute time interval was determined using liquid chromatography (UPLC) (Waters Aquity™) coupled with tandem quadrupole mass spectrometry (MS^2) (Waters Xevo™), equipped with an electrospray ionization (ESI) interface and operated in multiple reaction monitoring (MRM) mode.

Table S1: Stability in human serum (37°C)

Compound	T (min)	% remaining compound (n = 2)	st dev
	0	100	-
4	30	2.55	0.32
	60	2.89	0.30
	0	100	-
5	30	0.50	0.08
	60	0.57	0.11
	0	100	-
14a	30	5.95	0.37
	60	5.74	0.14
	0	100	-
14b	30	42.02	0.26
	60	17.46	0.15
	0	100	-
14c	30	88	4.5
	60	81	3.9
	0	100	-
14d	30	62	0.9
	60	42	3.8
	0	100	-
14e	30	77	4.8
	60	61	3.0

Biological Details

Antiplasmodial susceptibility testing[4]

Chloroquine resistant *P. falciparum*-K1 parasites were cultured in human erythrocytes (O+) at 37 °C under a low oxygen atmosphere (3% O2, 4% CO2, and 93% N2) in RPMI-1640, supplemented with 10% human serum. Infected human red blood cells (200 µL, 1% parasitaemia, 2% haematocrit) were added to each well and incubated for 72 h. After incubation, test plates were frozen at -20°C. Parasite multiplication was measured by the Malstat method. One hundred microliters of Malstat™ reagent was transferred in a new plate and mixed with 20 µL of the hemolysed parasite suspension for 15 min at room temperature. Then, 20 µL of nitro blue tetrazolium chloride (NBT) at 2 mg/mL/PES at 0.1 mg/mL solution was added and the plate was incubated again for 2 h at room temperature in the dark. Absorbance was read at 655 nm in a Biorad 3550-UV microplate reader. As a positive control, chloroquine was included (IC_{50} = 0.13 µM).

Antitubercular susceptibility testing[5]

In vitro antimycobacterial activity was evaluated by a luminometric assay based on a *M. tuberculosis* H37Ra laboratory strain (ATCC 25177) transformed with a pSMT1 luciferase reporter plasmid (H37Ra-lux). A 2-fold serial dilution of each compound was made in Middlebrook 7H9 broth and 10% OADC (complete 7H9 broth) with final concentrations ranging from 128 µM to 0.5 µM. Volumes of 100 µL of the serial dilutions were added in triplicate to black, flat-bottomed 96-well plates. As a positive control, isoniazid, a first-line antimycobacterial drug, was included (IC_{50} = 0.21 µM). The mycobacterial suspension was made by thawing a frozen glycerol stock of H37Ra-lux and, subsequently, diluting it in complete 7H9 broth to obtain a suspension with 10.000 relative light units (RLU)/mL. A volume of 100 µL of bacteria was added to each well. All of the outer-perimeter wells were filled with 200 µL of sterile deionized water to minimize evaporation of the medium in the test wells during incubation. After 7 days, the bacterial replication was analyzed by luminometry. To evoke a luminescent signal, 25 µL of 1% n-decanal in ethanol was added to each well, where after light emission was measured using a luminometer (Promega Discover).

In vitro cytotoxicity assay[4]

The *in vitro* cytotoxicity on the MRC-5 *Homo sapiens* long fibroblast cell line (ATCC® CCL-171™) was assessed for each analogue by a resazurin-based cytotoxicity assay. Briefly, the MRC-5 cells were cultured in 75 cm^2 sterile Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% heat-inactivated fetal calf serum in a 5% CO_2 atmosphere at 37°C. When a semi-confluent layer of cells was formed, the cells were trypsinized, washed with sterile PBS, seeded into a transparent, flat-bottomed 96-well plate at a density of 4 x 10^4 cells per well and left for recovery at 37°C, 5% CO_2 for at least 24 hours. For each compound, a two-fold serial dilution was made in complete DMEM with final concentrations ranging from 128 µM to 0.5 µM. Subsequently, the MRC-5 cells were exposed to the compounds by adding 100 µL of the serial dilutions to the wells. Test plates were incubated for 24 hours in an atmosphere of 5% CO_2 at 37°C. For the resazurin assay, the cells were washed 2 times with 200 µL PBS and 100 µL resazurin working solution was added per well. Subsequently, the plates were left for incubation at 37°C, 5% CO_2 for 3 hours. The irreversible reduction of resazurin to resorufin is proportional to aerobic respiration and the quantity of resorufin produced is proportional to the number of viable cells. To monitor the viable cell number after compound exposure, each well was analyzed using a microplate fluorometer equipped with a 560 nm excitation / 590 nm emission filter set. Tamoxifen was included as positive control (IC_{50} = 11.09 µM).

References

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(2) Grigg, R.; Rankovic, Z.; Thoroughgood, M. Acyclic Oxyiminium Ions. Mannich Reactions and Addition of Grignard Reagents. *Tetrahedron* **2000**, *56* (40), 8025–8032.

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(4) Cos, P.; Vlietinck, A. J.; Berghe, D. V.; Maes, L. Anti-Infective Potential of Natural Products: How to Develop a Stronger in Vitro 'Proof-of-Concept.' *J. Ethnopharmacol.* **2006**, *106* (3), 290–302.

(5) de Macedo, M. B.; Kimmel, R.; Urankar, D.; Gazvoda, M.; Peixoto, A.; Cools, F.; Torfs, E.; Verschaeve, L.; Lima, E. S.; Lyčka, A.; et al. Design, Synthesis and Antitubercular Potency of 4-Hydroxyquinolin-2(1H)-Ones. *Eur. J. Med. Chem.* **2017**, *138*, 491–500.

Purity confirmation of final compounds

For the final compounds described in this letter (**14b-e** and **20a-c**), LC-MS analyses are provided to confirm purity. LC-MS analyses were carried out on a Waters AutoPurification System equipped with PDA and ESI-MS detection and using a Waters CORTECS C18 Column (4.6×100 mm, 2.7 μm) and a water/acetonitrile/formic acid linear gradient system at a flow rate of 1.44 mL/min. For compound **14a**, LC-MS analysis was not used to confirm purity, since the lack of stability of this compound in aqueous medium results in breakdown during analysis. For compounds **20d** and **21d**, LC-MS analysis was not used to confirm purity, since the long C_{16} alkyl chains are not compatible with the LC-MS analysis test conditions.

18-Apr-2018

MeOH

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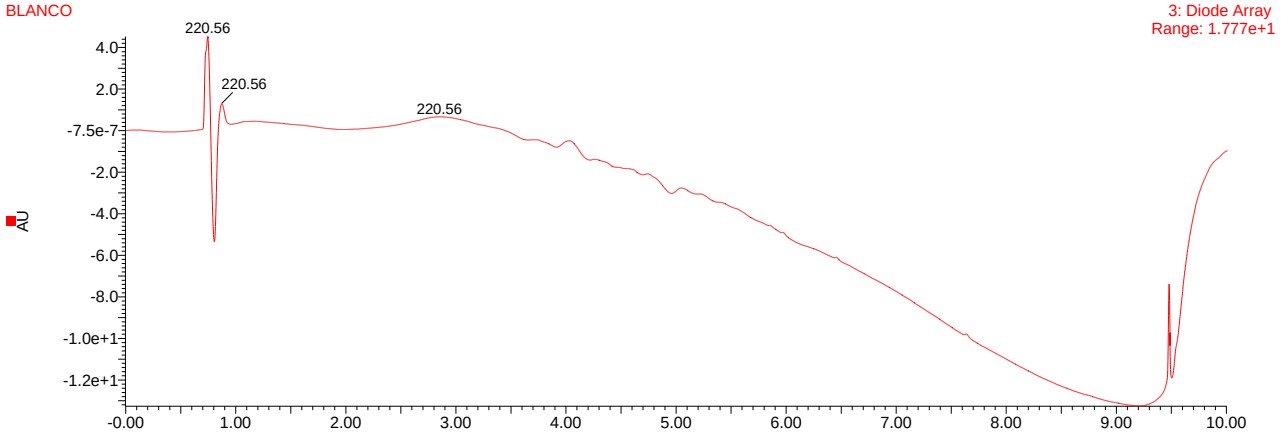

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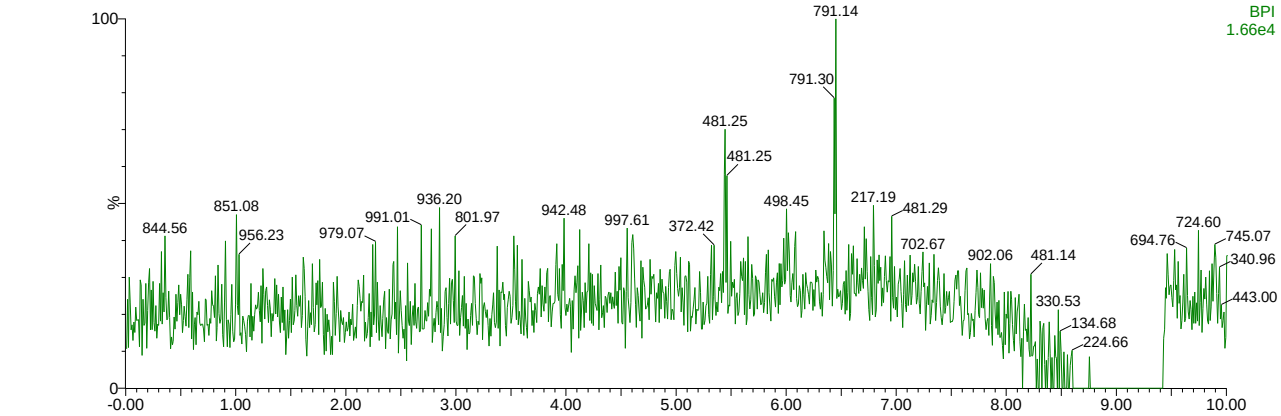

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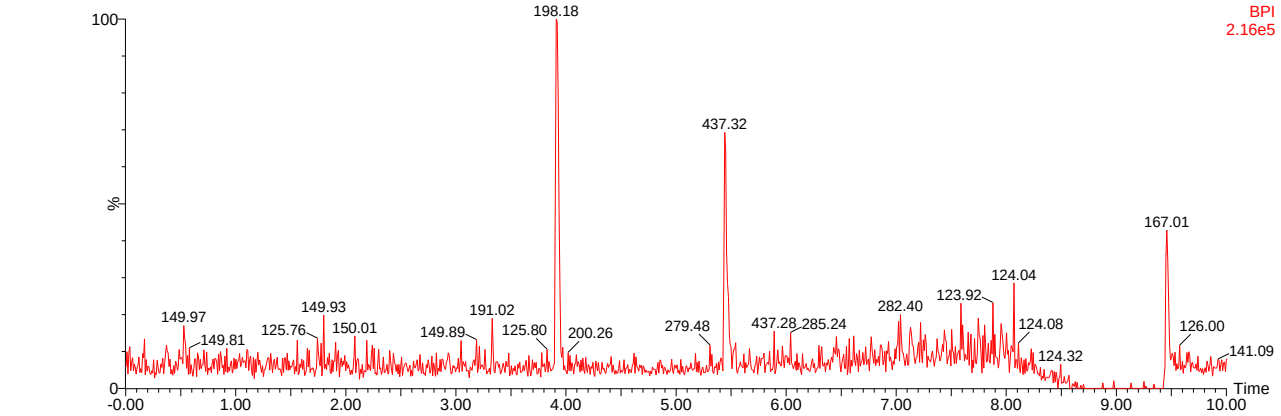
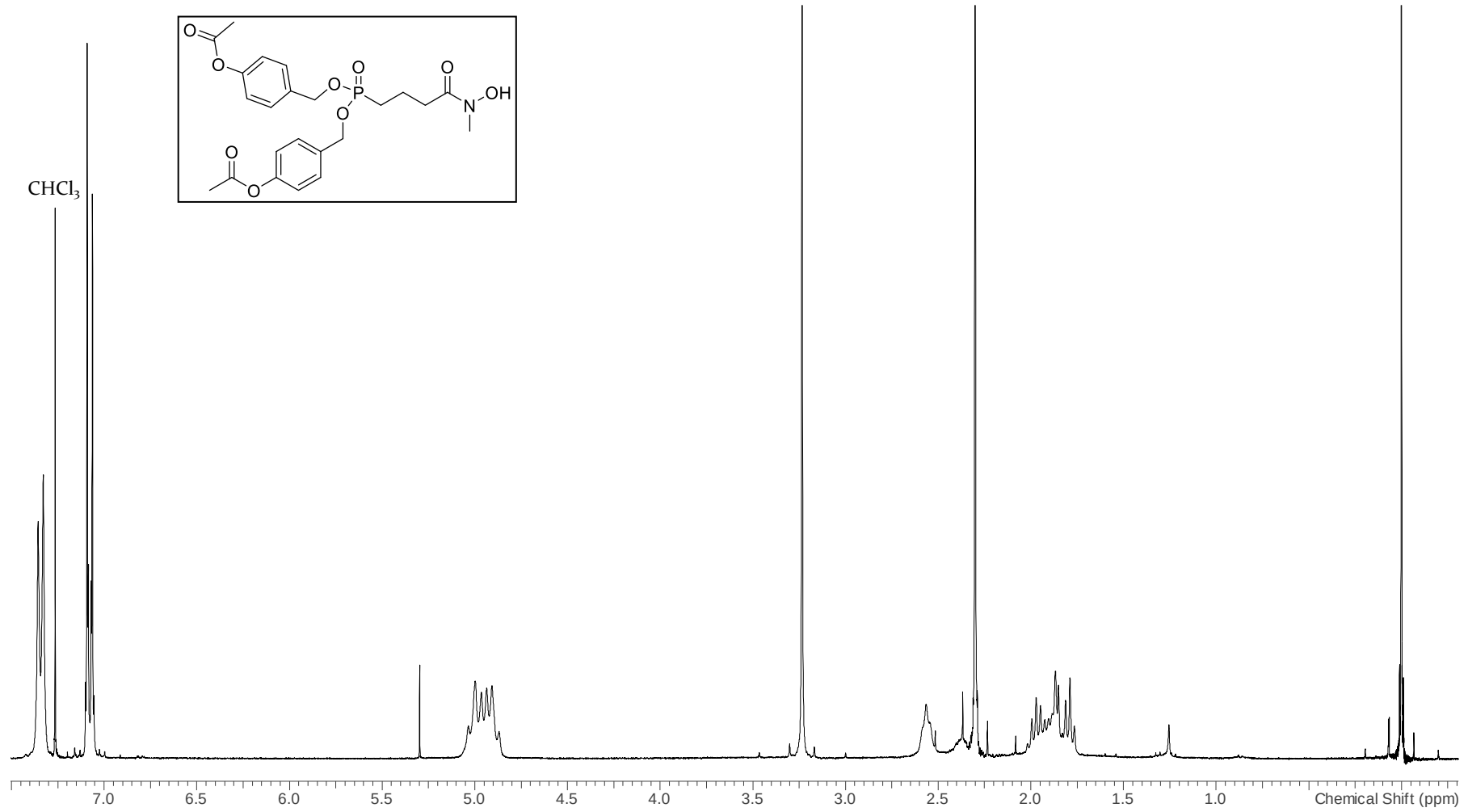
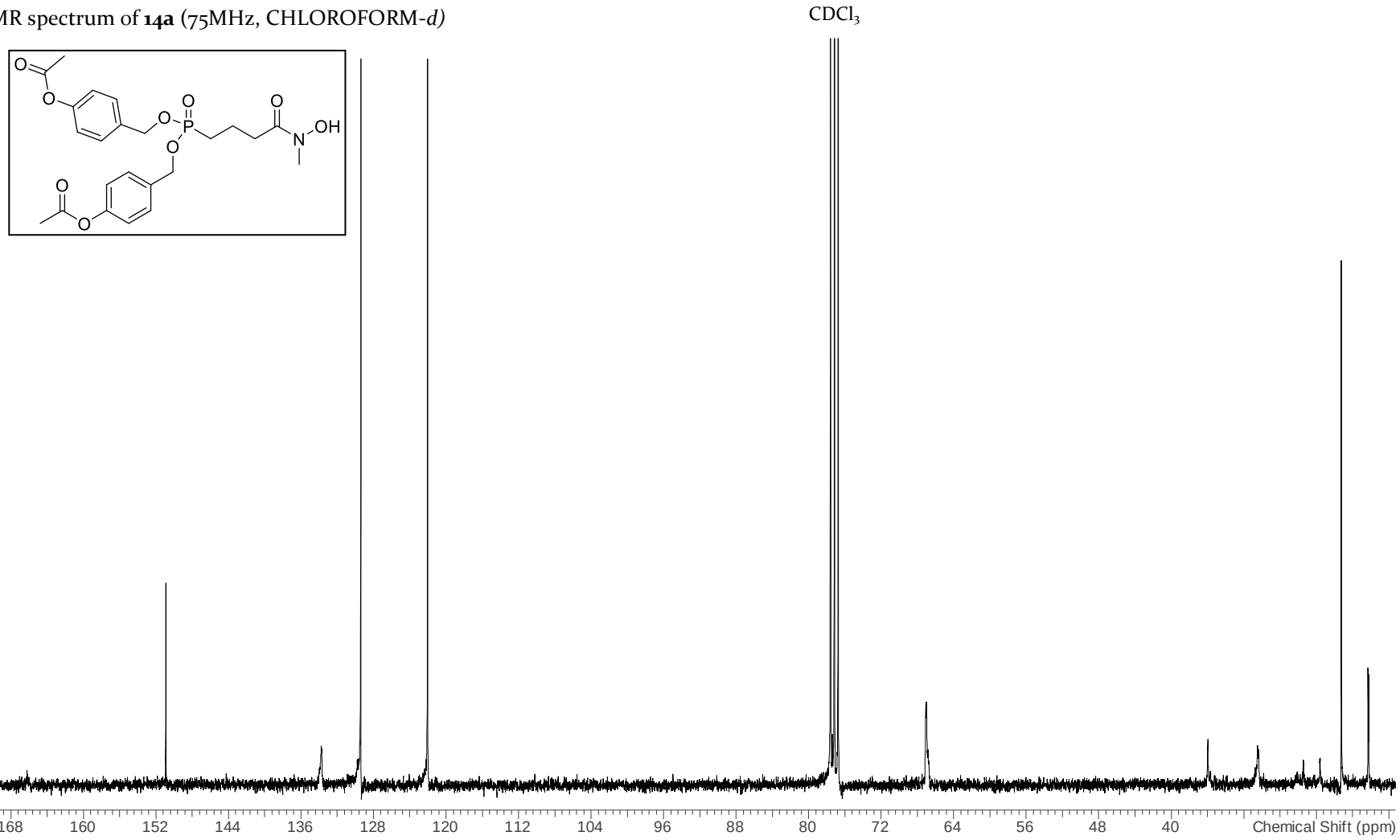


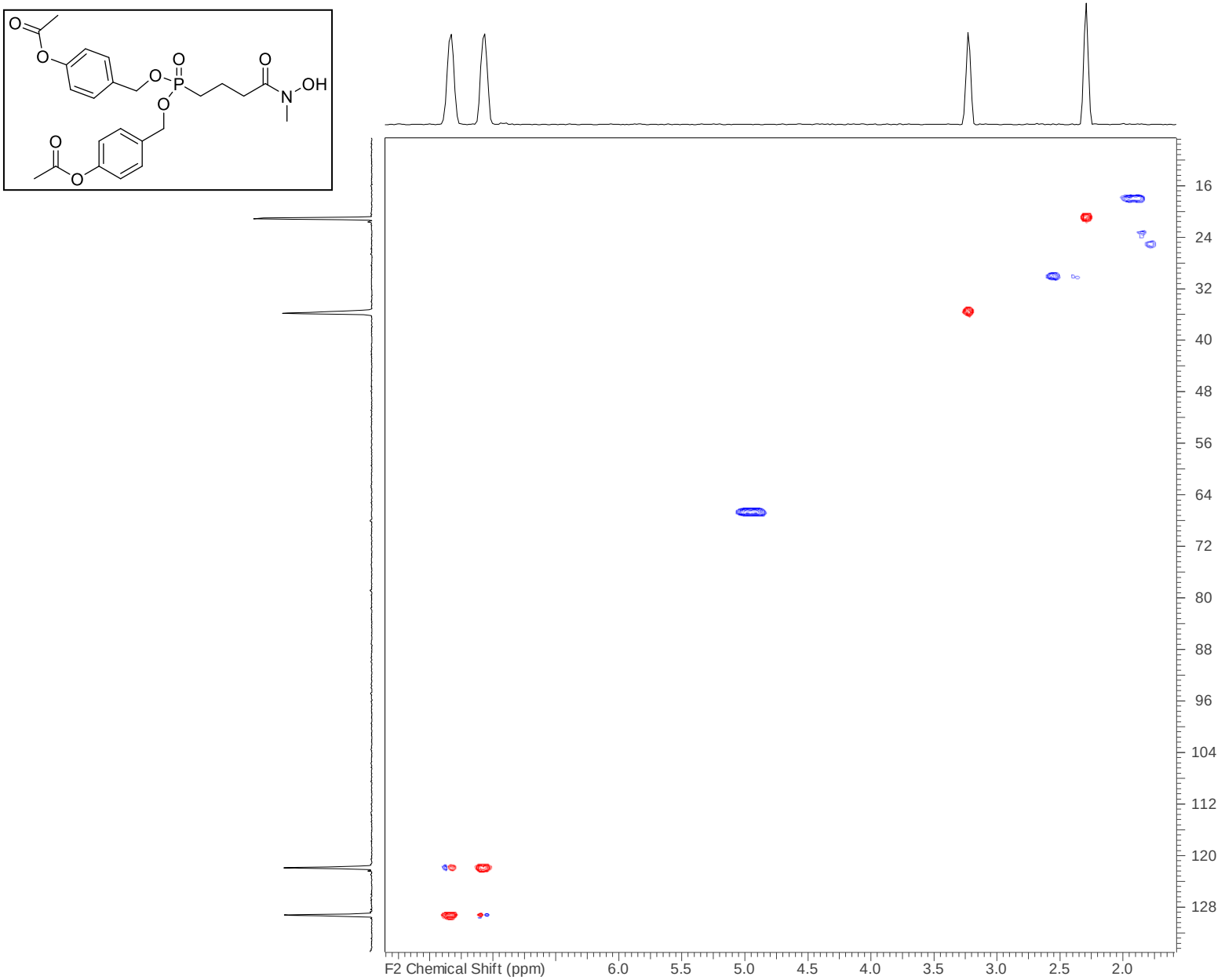
^{1}H NMR spectrum of **14a** (300MHz, CHLOROFORM-*d)*



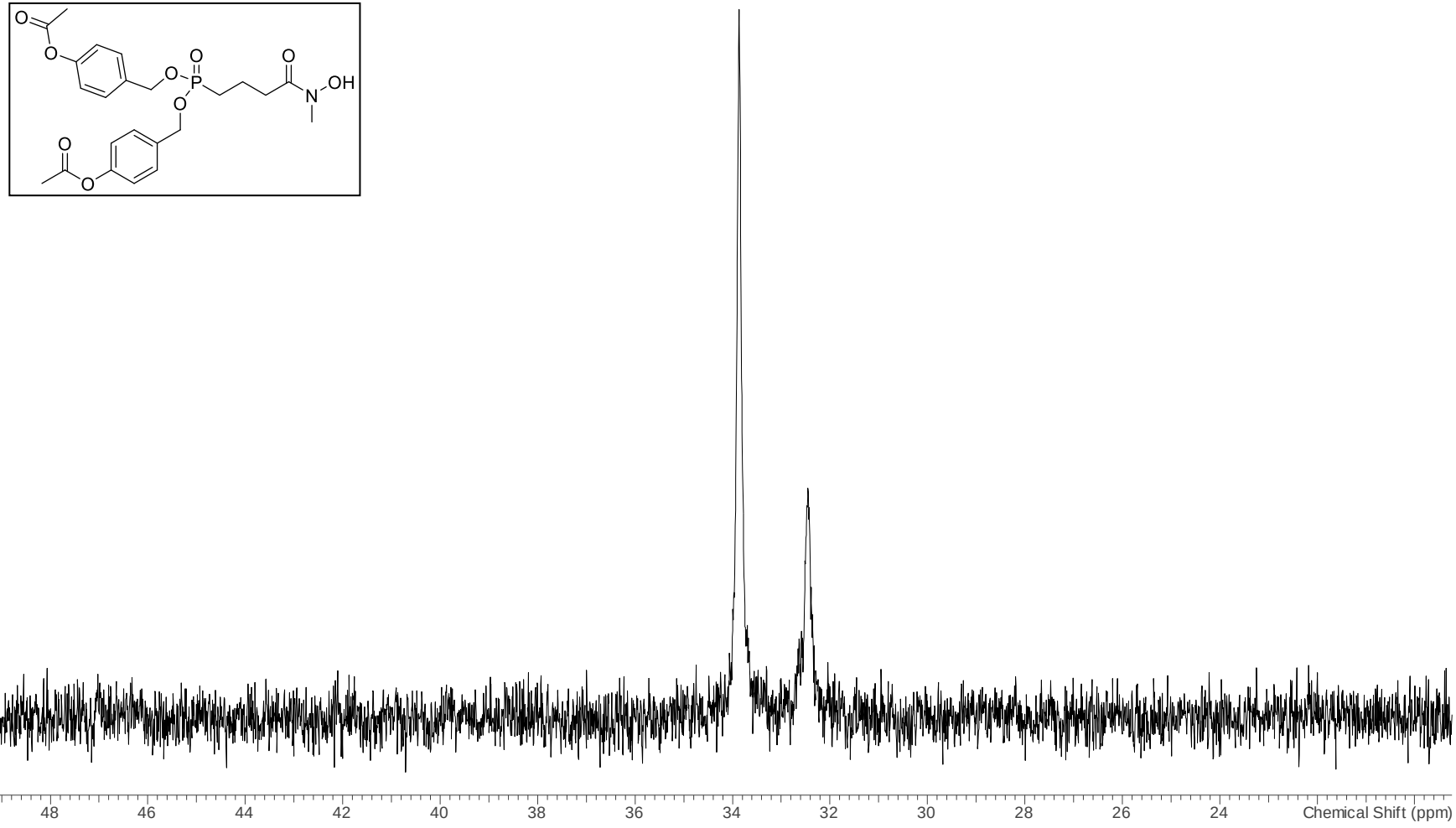
^{13}C NMR spectrum of **14a** (75MHz, CHLOROFORM-*d)*



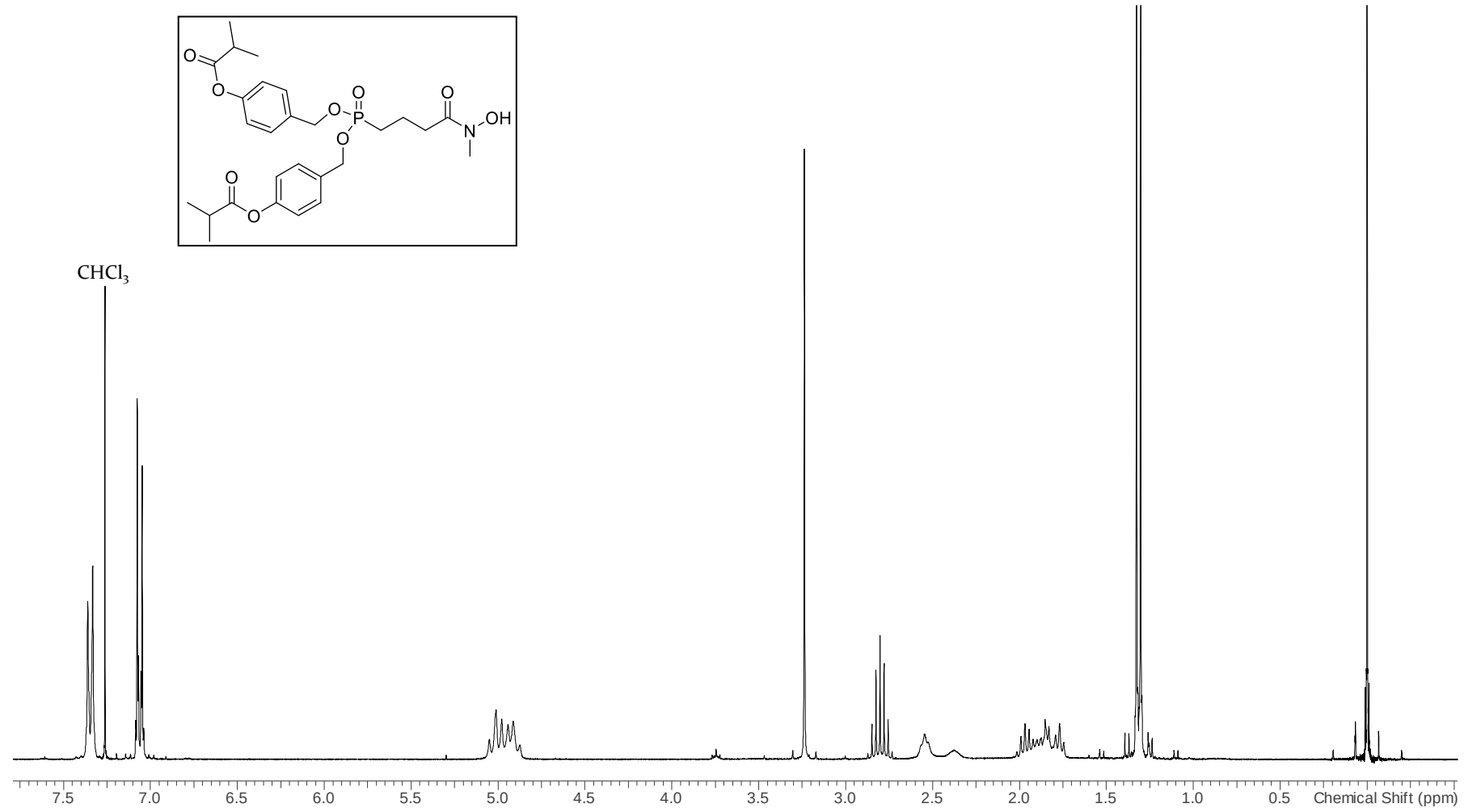
HSQC of **14a** (75MHz, CHLOROFORM-*d)*



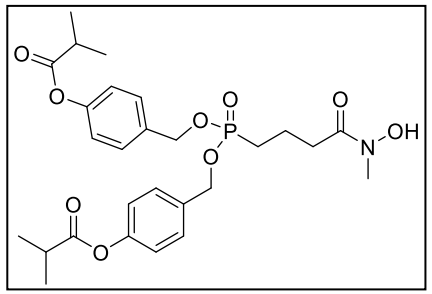
^{31}P NMR spectrum of **14a** (121MHz, CHLOROFORM-*d)*



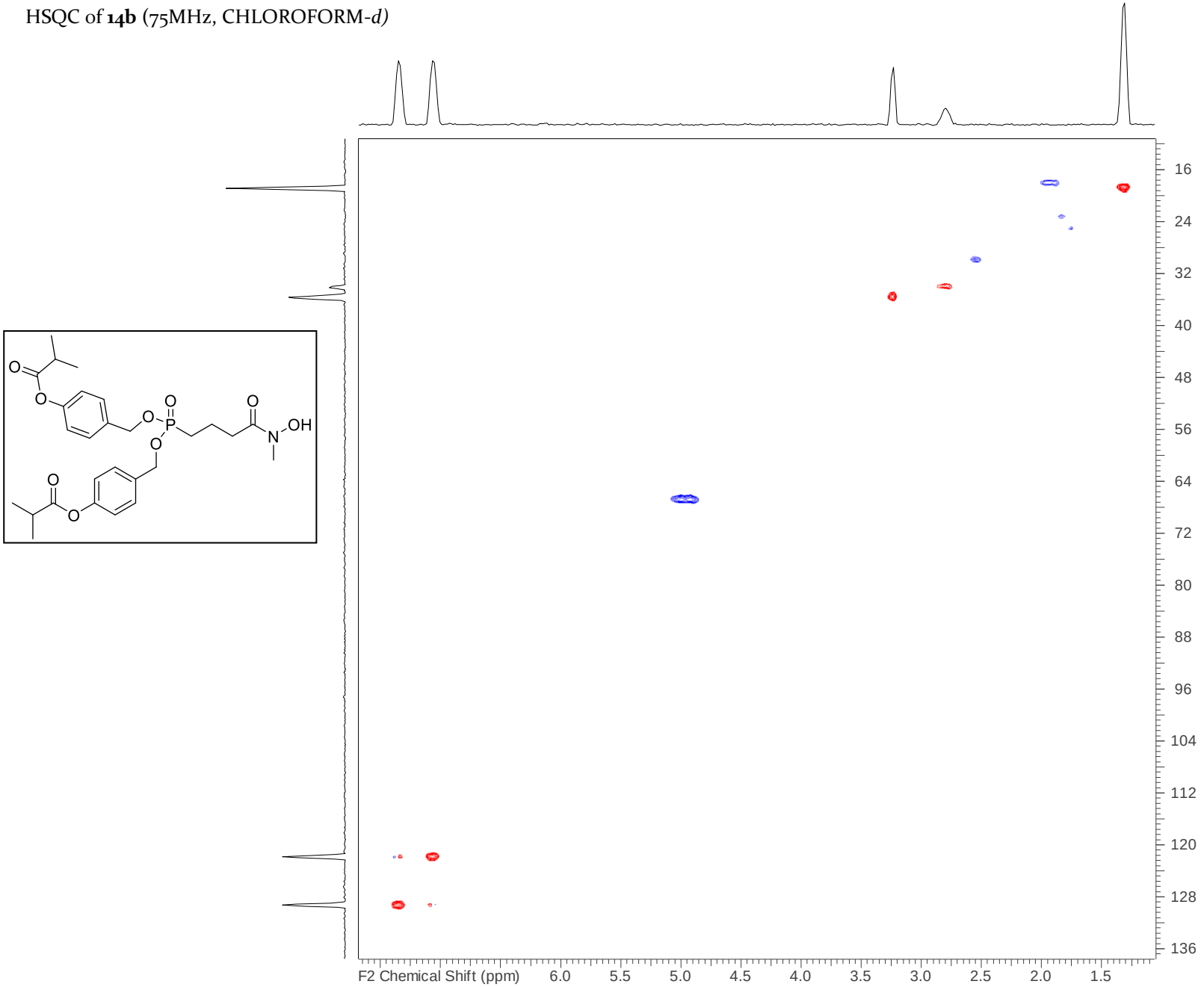
^{1}H NMR spectrum of **14b** (300MHz, CHLOROFORM-*d)*



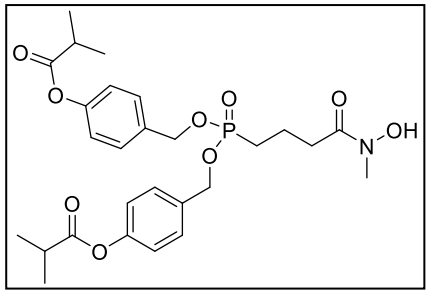
^{13}C NMR spectrum of **14b** (75MHz, CHLOROFORM-*d)*

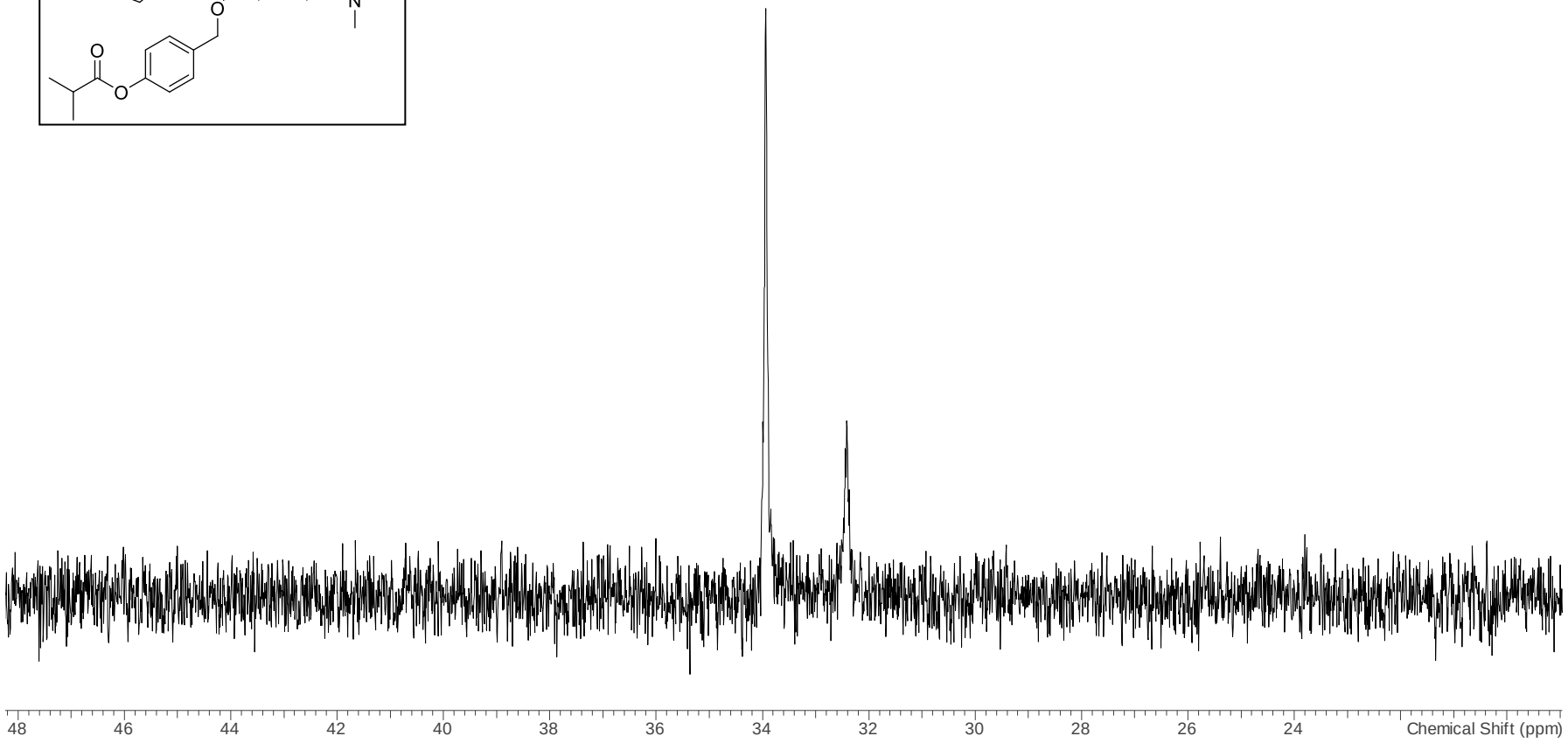


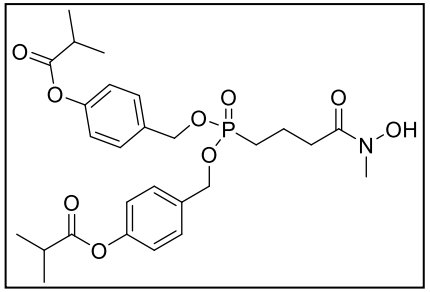
HSQC of **14b** (75MHz, CHLOROFORM-*d)*

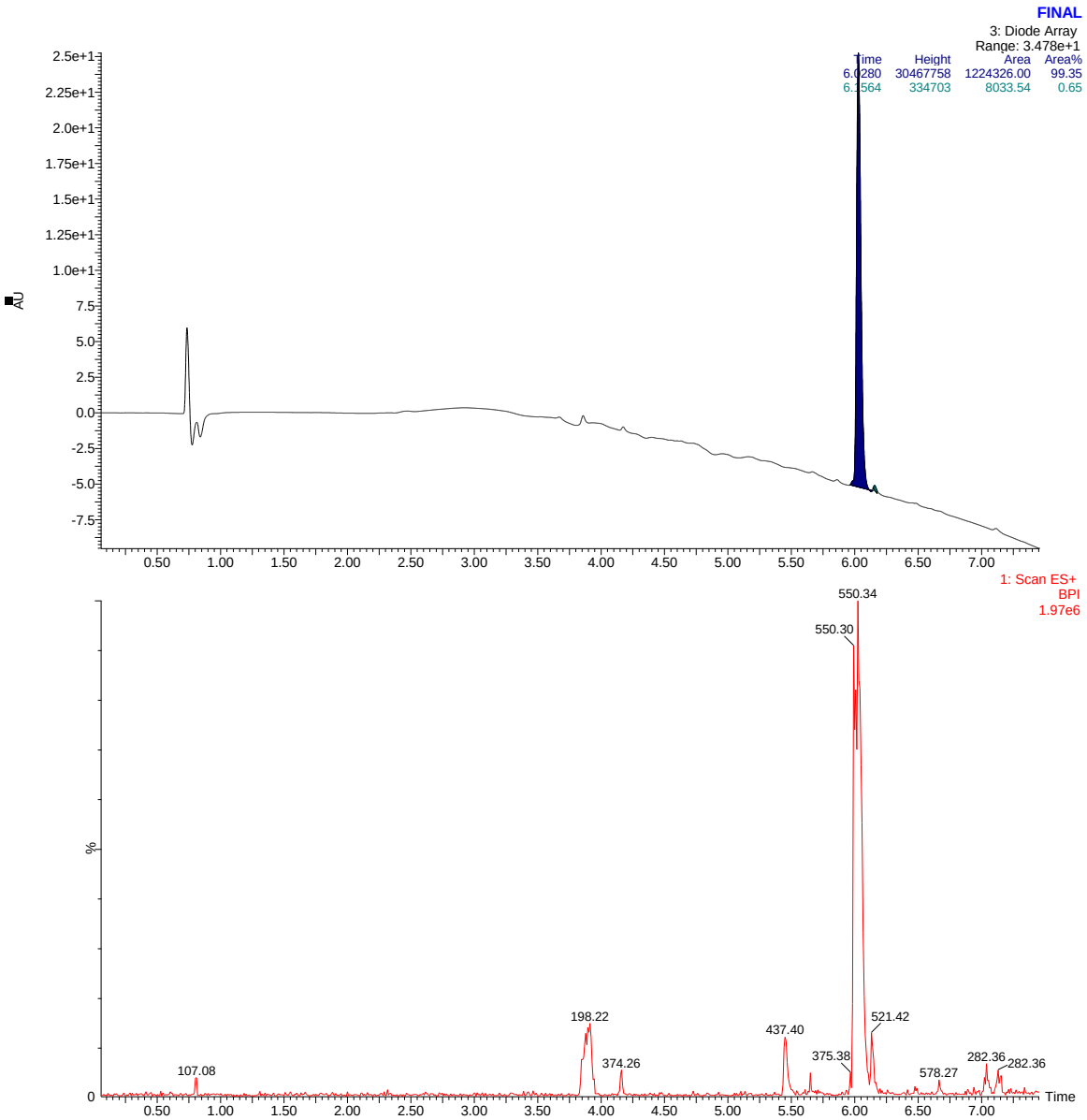


^{31}P NMR spectrum of **14b** (121MHz, CHLOROFORM-*d)*

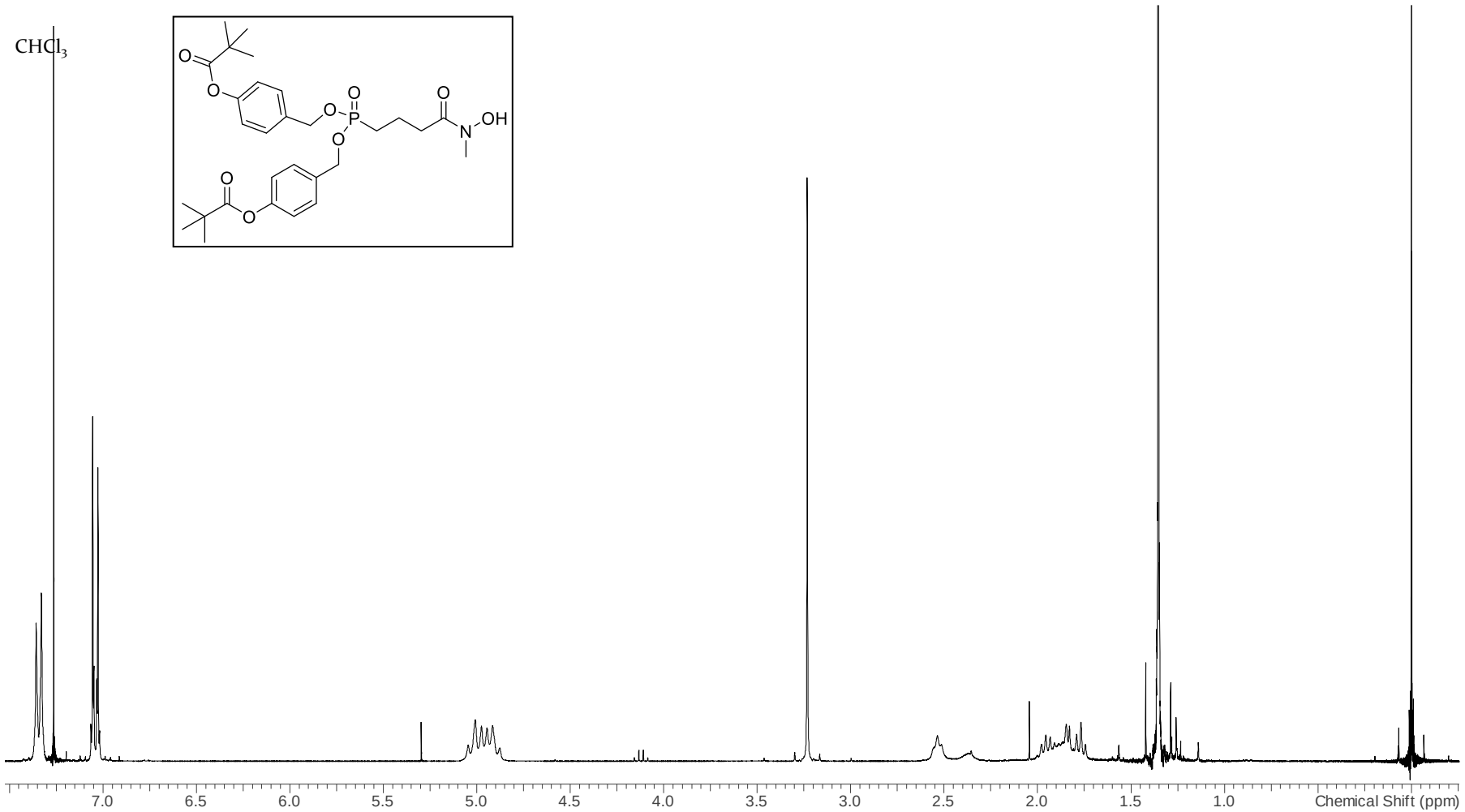




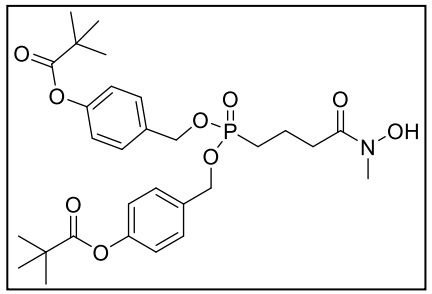



FINAL
3: Diode Array
Range: 3.478e+1
Time Height Area Area%
6.0280 30467758 1224326.00 99.35
6.1564 334703 8033.54 0.65
AU
1: Scan ES+
BPI
1.97e6
%
Time
550.34
550.30
198.22
437.40
521.42
375.38
374.26
107.08
578.27
282.36
282.36

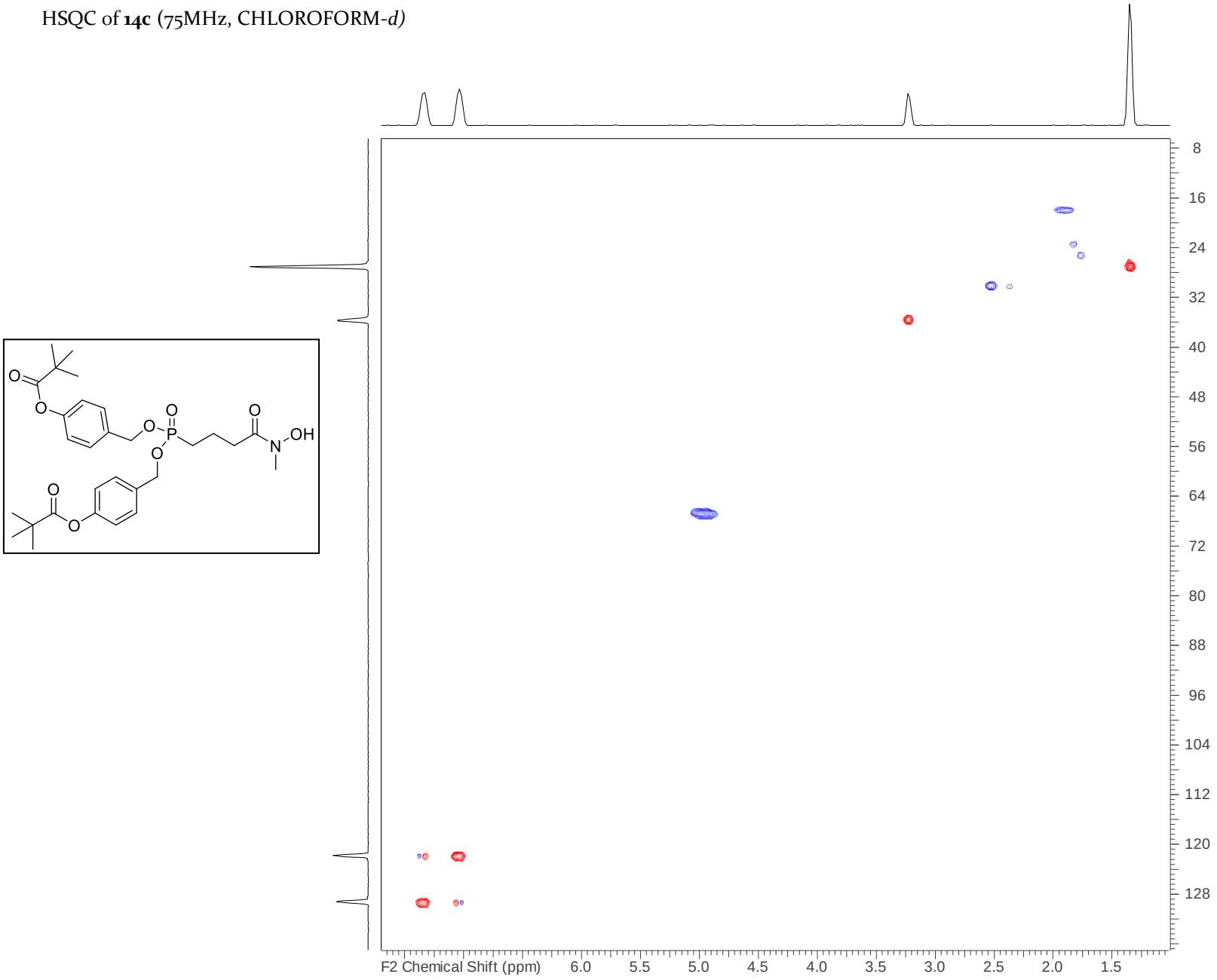
^{1}H NMR spectrum of **14c** (300MHz, CHLOROFORM-*d)*



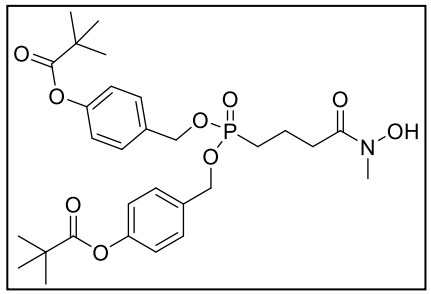
^{13}C NMR spectrum of **14c** (75MHz, CHLOROFORM-*d)*

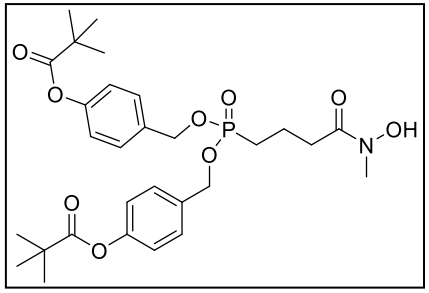


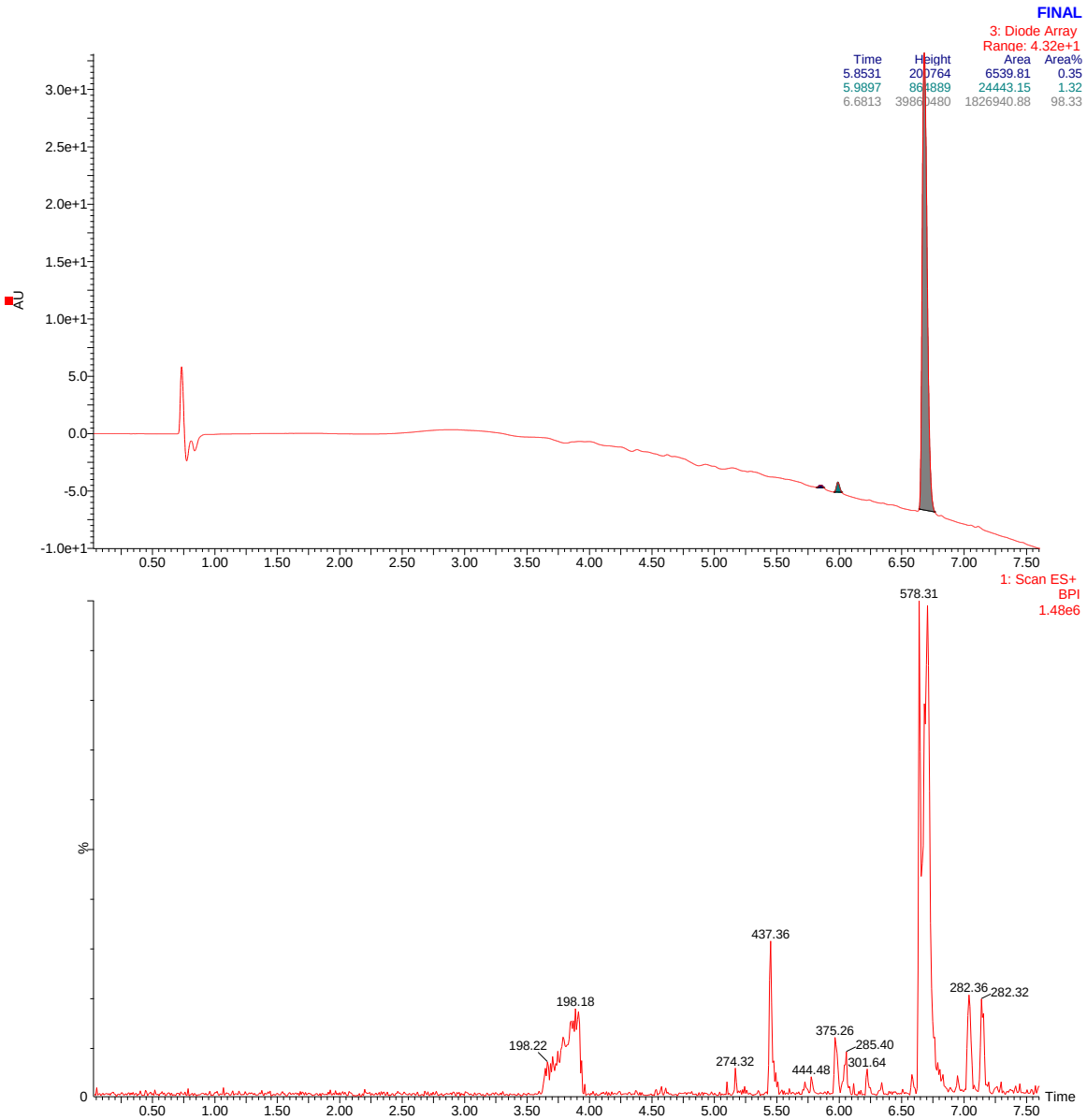
HSQC of **14c** (75MHz, CHLOROFORM-*d)*



^{31}P NMR spectrum of **14c** (121MHz, CHLOROFORM-*d)*



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Time Height Area Area%
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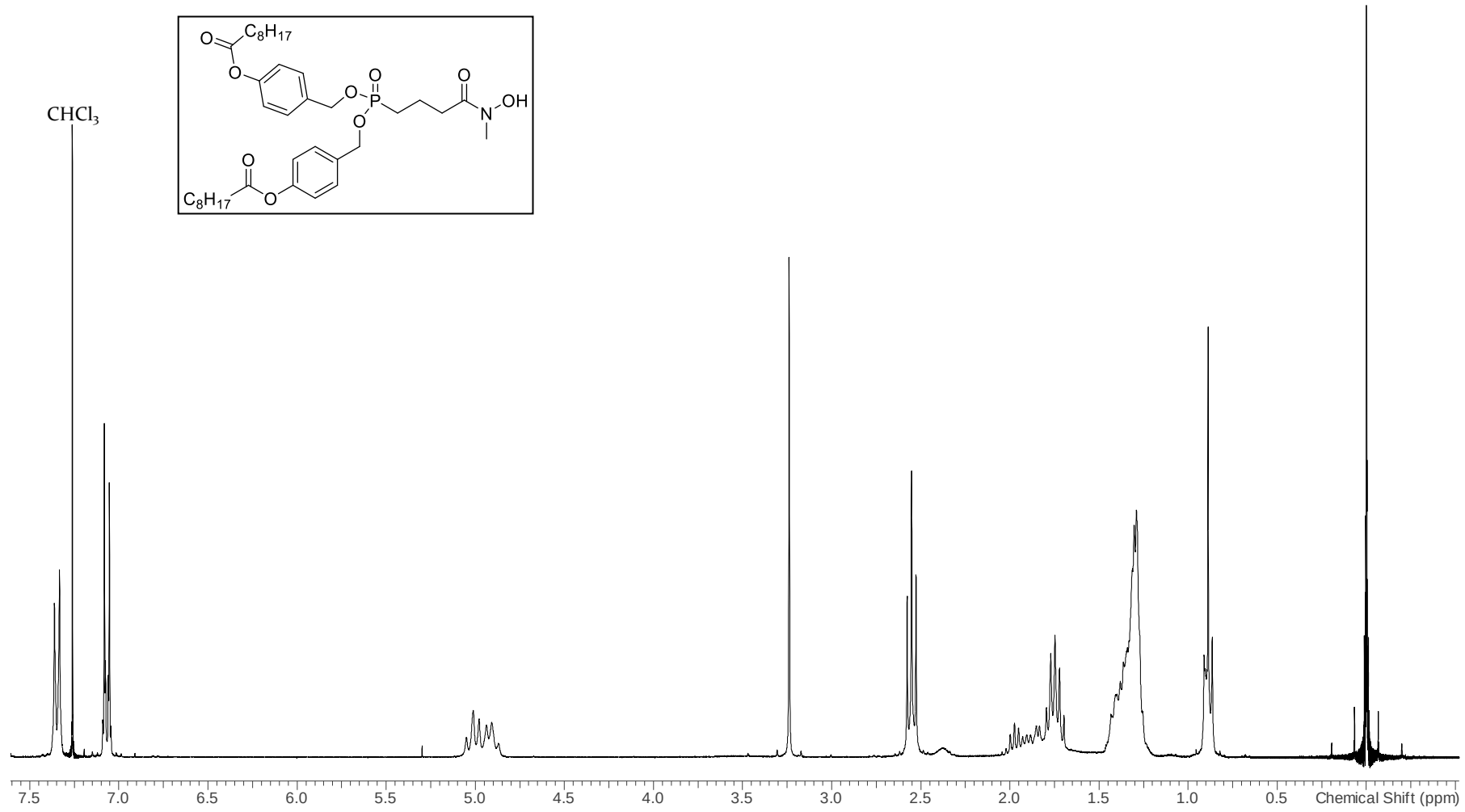
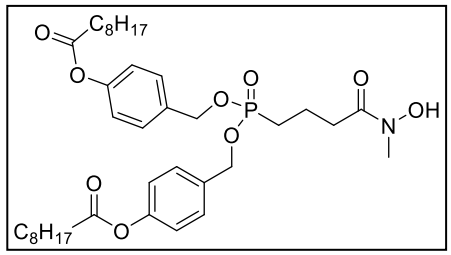
5.9897 864889 24443.15 1.32
6.6813 39860480 1826940.88 98.33
AU
3.0e+1
2.5e+1
2.0e+1
1.5e+1
1.0e+1
5.0
0.0
-5.0
-1.0e+1
0.50 1.00 1.50 2.00 2.50 3.00 3.50 4.00 4.50 5.00 5.50 6.00 6.50 7.00 7.50
1: Scan ES+
BPI
1.48e6
%
0
578.31
437.36
198.18
198.22
282.36
282.32
375.26
285.40
301.64
274.32
444.48
Time
0.50 1.00 1.50 2.00 2.50 3.00 3.50 4.00 4.50 5.00 5.50 6.00 6.50 7.00 7.50

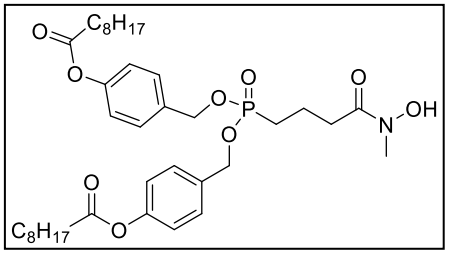
^{1}H NMR spectrum of **14d** (300MHz, CHLOROFORM-*d)*

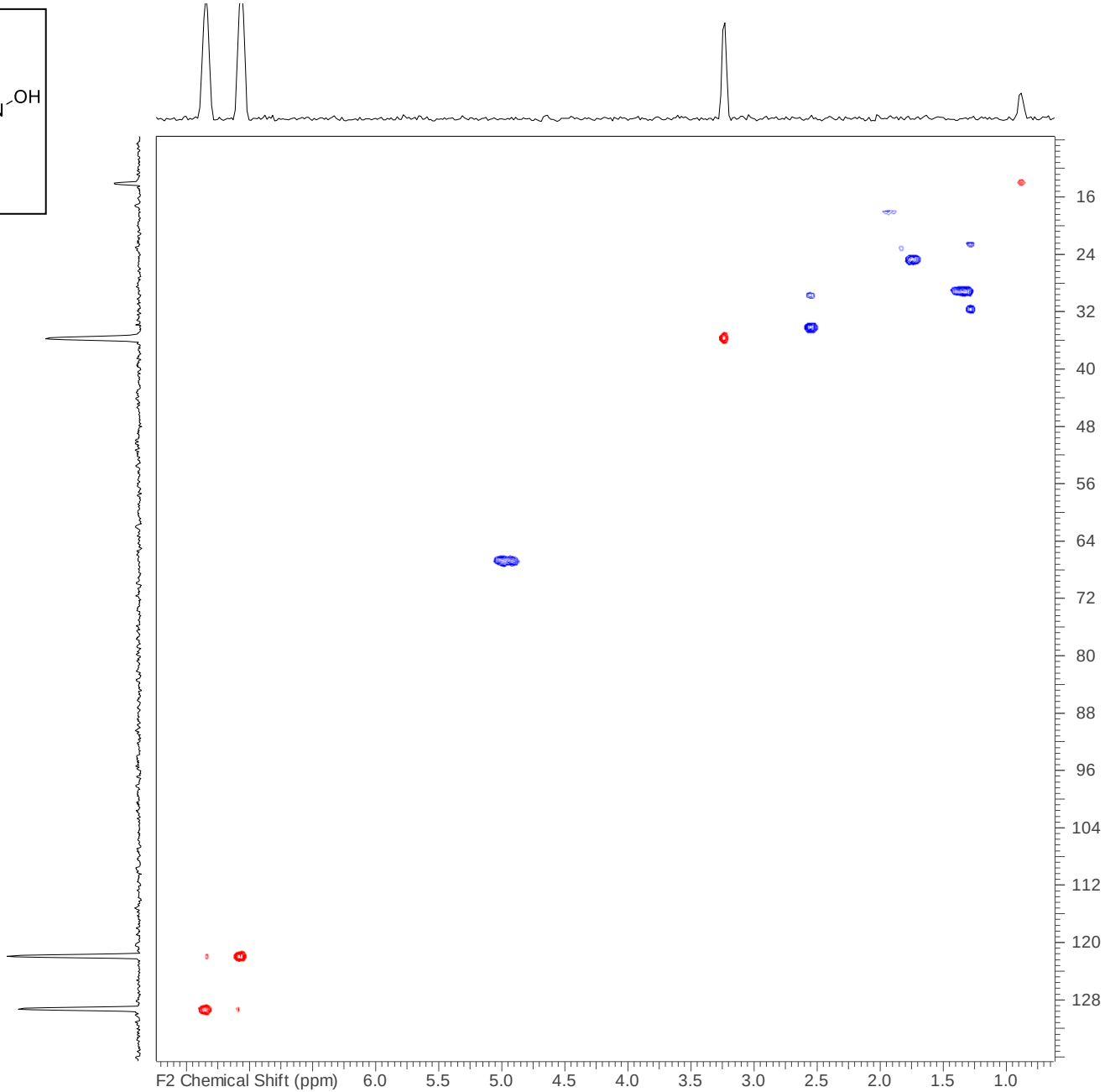


^{13}C NMR spectrum of **14d** (75MHz, CHLOROFORM-*d)*

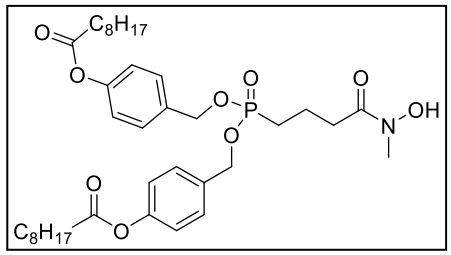


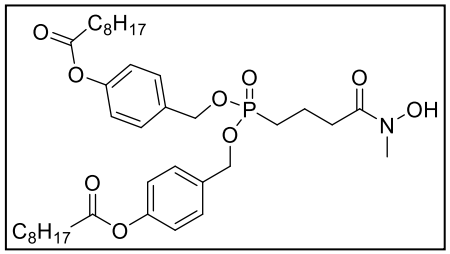
HSQC of **14d** (75MHz, CHLOROFORM-*d)*

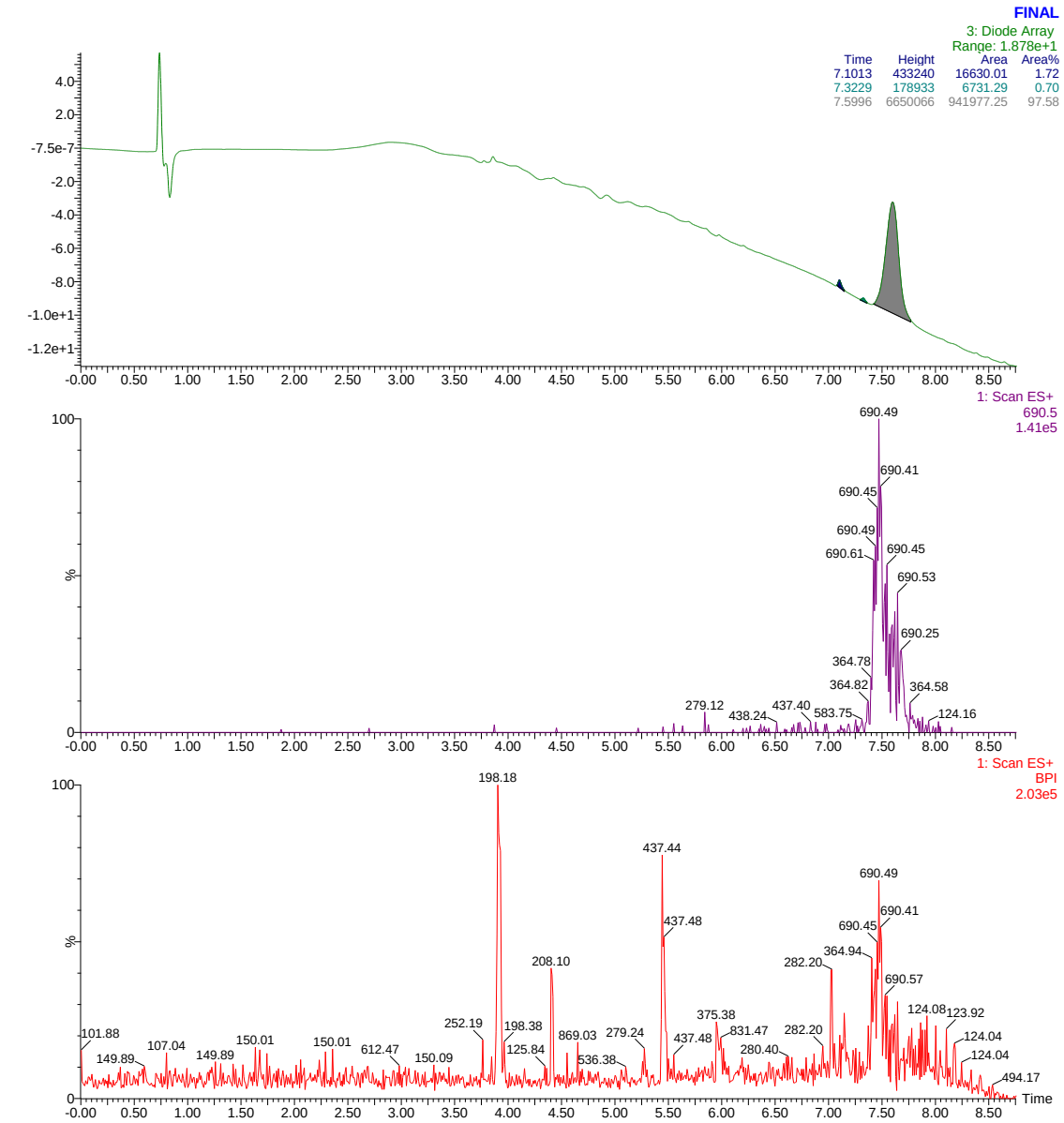




^{31}P NMR spectrum of **14d** (121MHz, CHLOROFORM-*d*)




O
C8H17
O
O
P
O
O
O
N
OH
O
O
C8H17


FINAL
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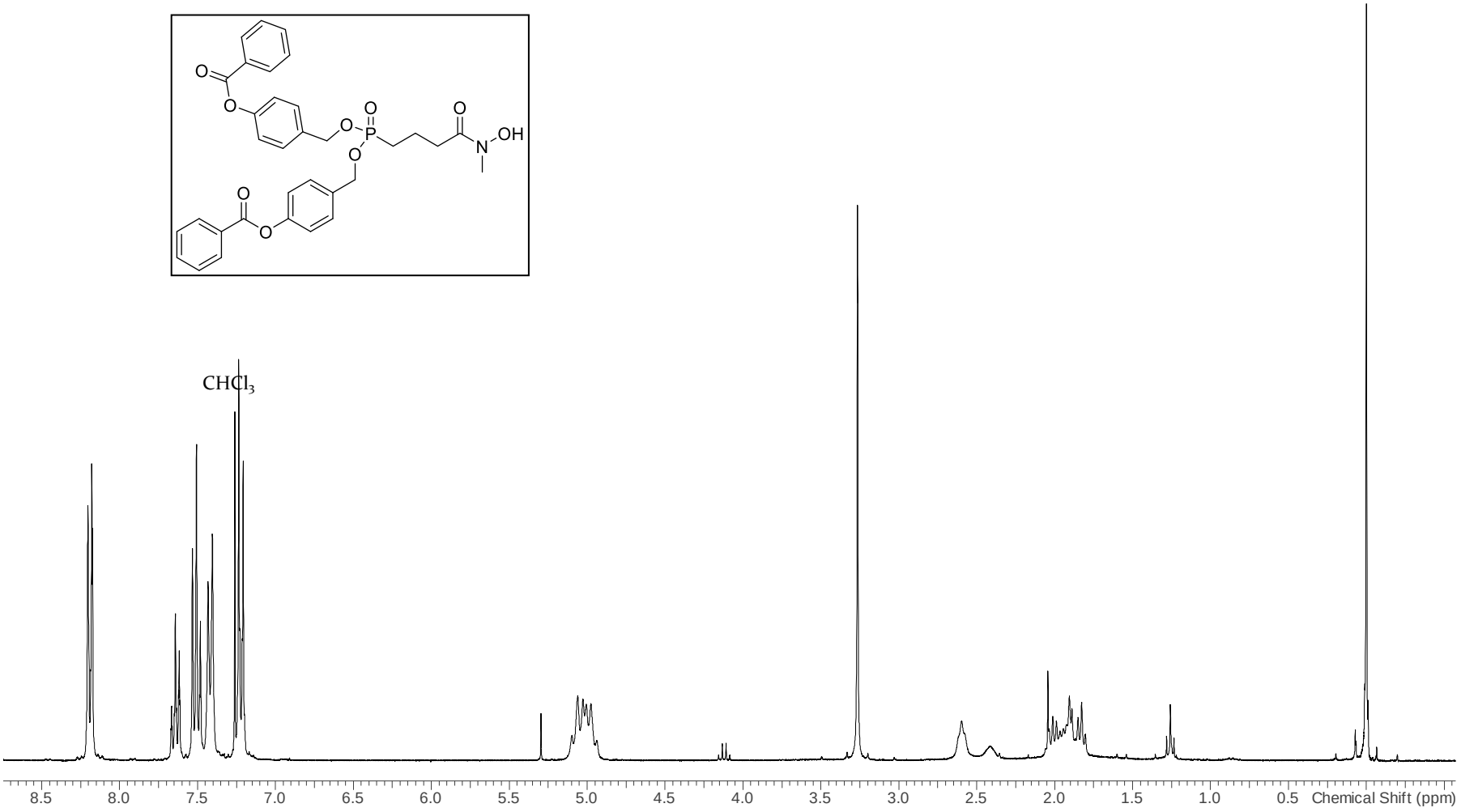
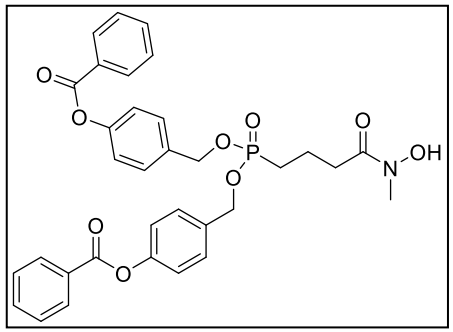
Range: 1.878e+1
Time Height Area Area%
7.1013 433240 16630.01 1.72
7.3229 178933 6731.29 0.70
7.5996 6650066 941977.25 97.58
AU
4.0
2.0
-7.5e-7
-2.0
-4.0
-6.0
-8.0
-1.0e+1
-1.2e+1
1: Scan ES+
690.5
1.41e5
690.49
690.41
690.45
690.49
690.61
690.45
690.53
690.25
364.78
364.82
364.58
279.12
438.24
437.40
583.75
124.16
1: Scan ES+
BPI
2.03e5
198.18
437.44
437.48
690.49
690.41
690.45
208.10
364.94
282.20
690.57
124.08
123.92
375.38
831.47
252.19
198.38
869.03
279.24
437.48
282.20
124.04
101.88
149.89
107.04
149.89
150.01
150.01
612.47
150.09
125.84
536.38
280.40
124.04
494.17
%
Time

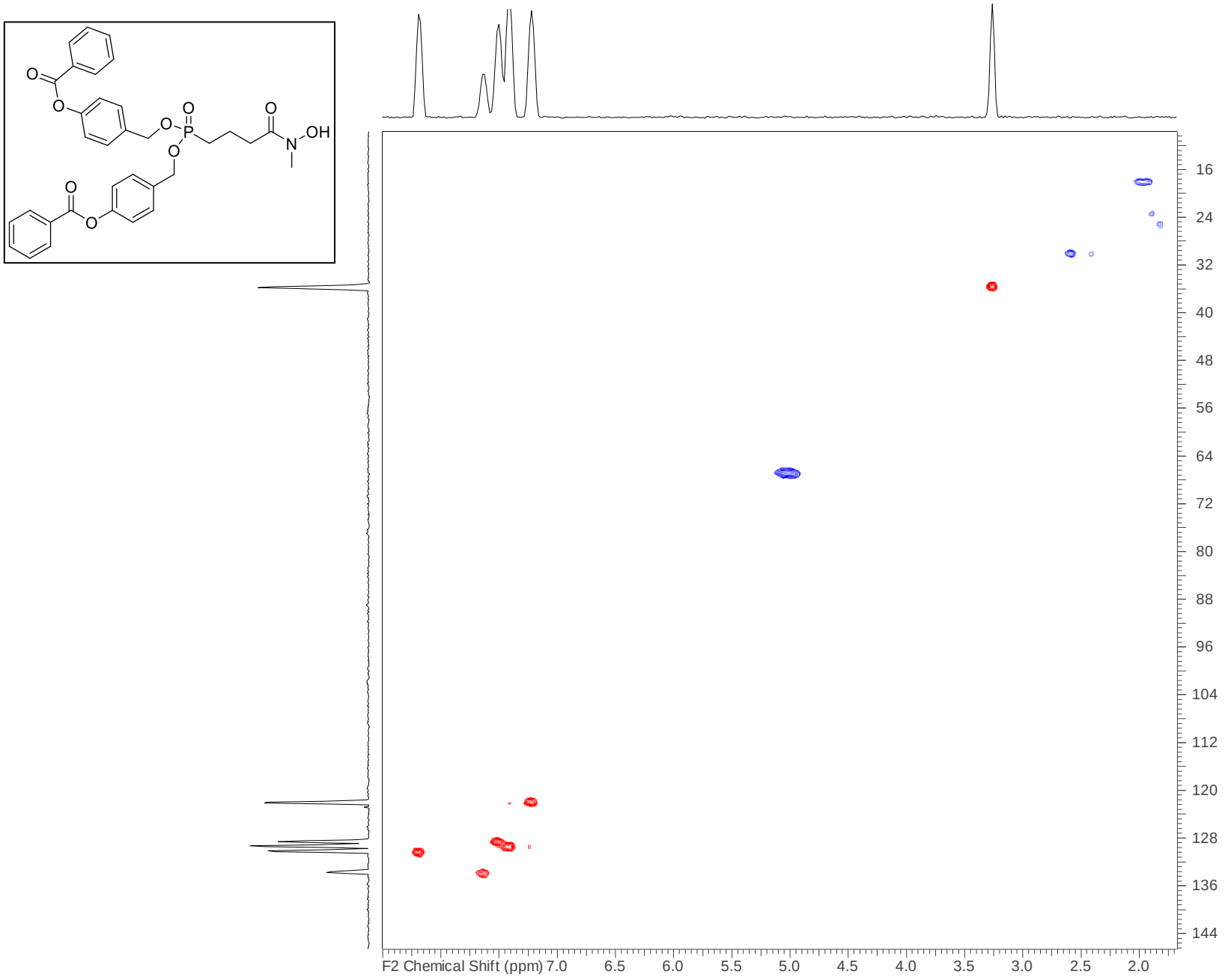
^{1}H NMR spectrum of **14e** (300MHz, CHLOROFORM-*d)*



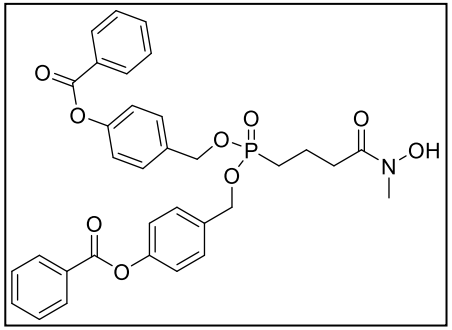
^{13}C NMR spectrum of **14e** (75MHz, CHLOROFORM-*d)*

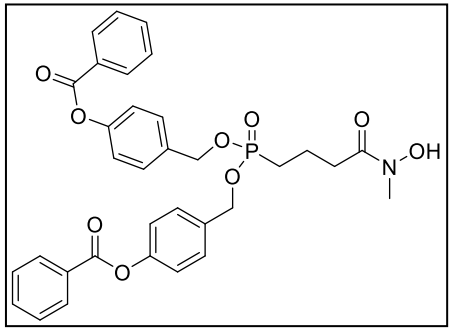


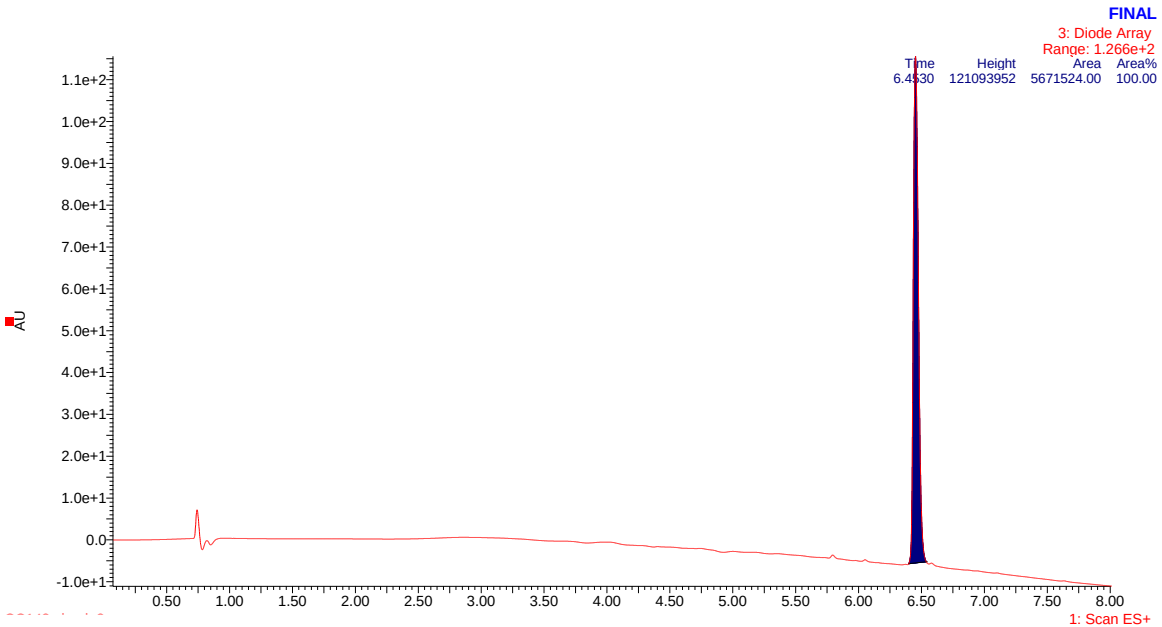
^{13}C NMR spectrum of **14e** (75MHz, CHLOROFORM-*d)*



^{31}P NMR spectrum of **14e** (121MHz, CHLOROFORM-*d)*



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Time Height Area Area%
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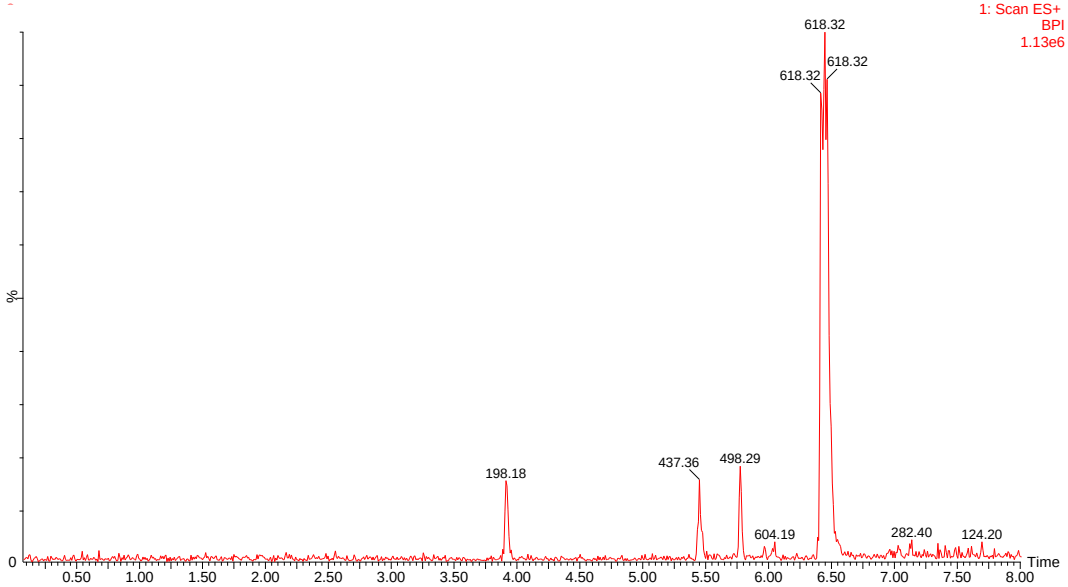
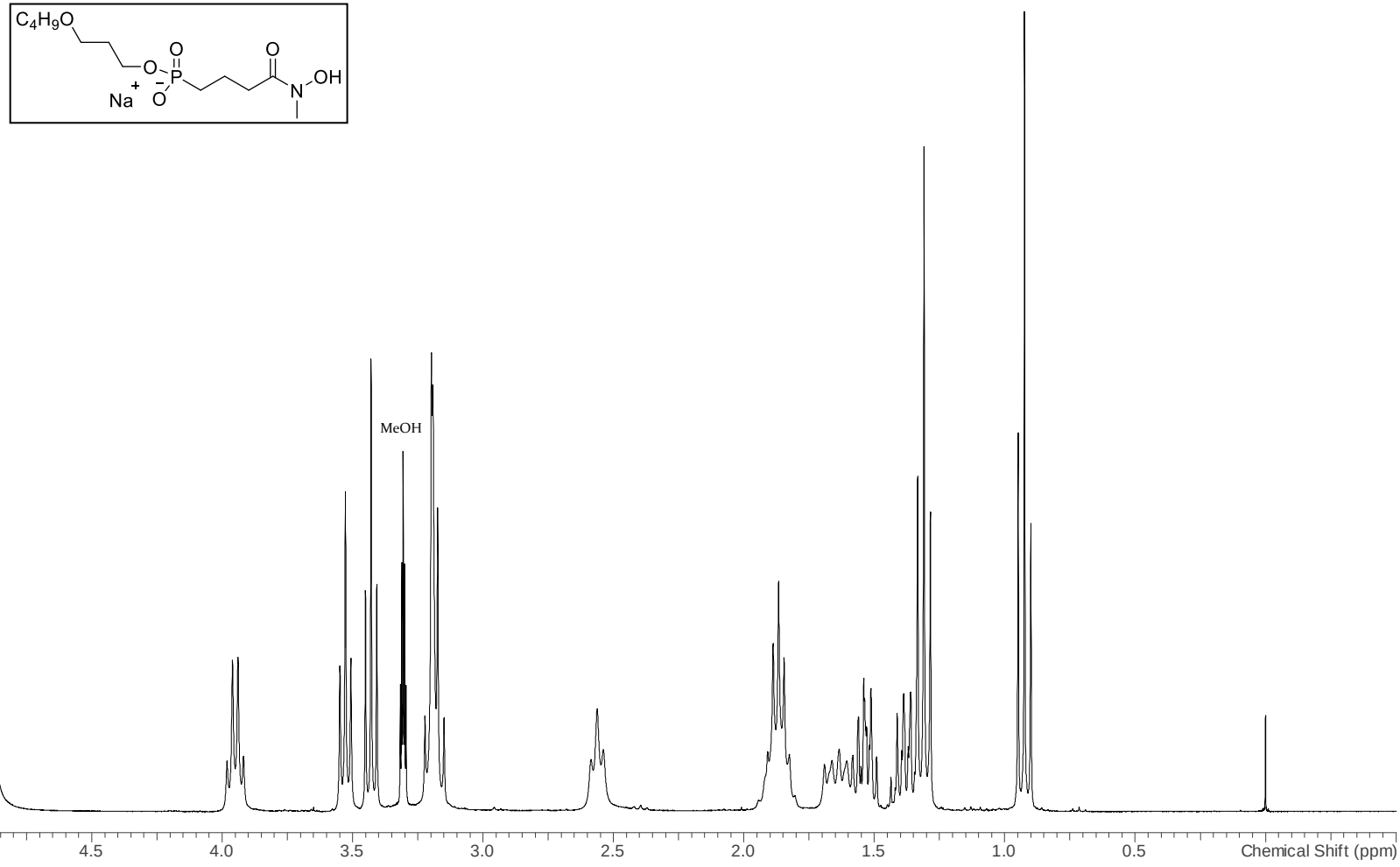
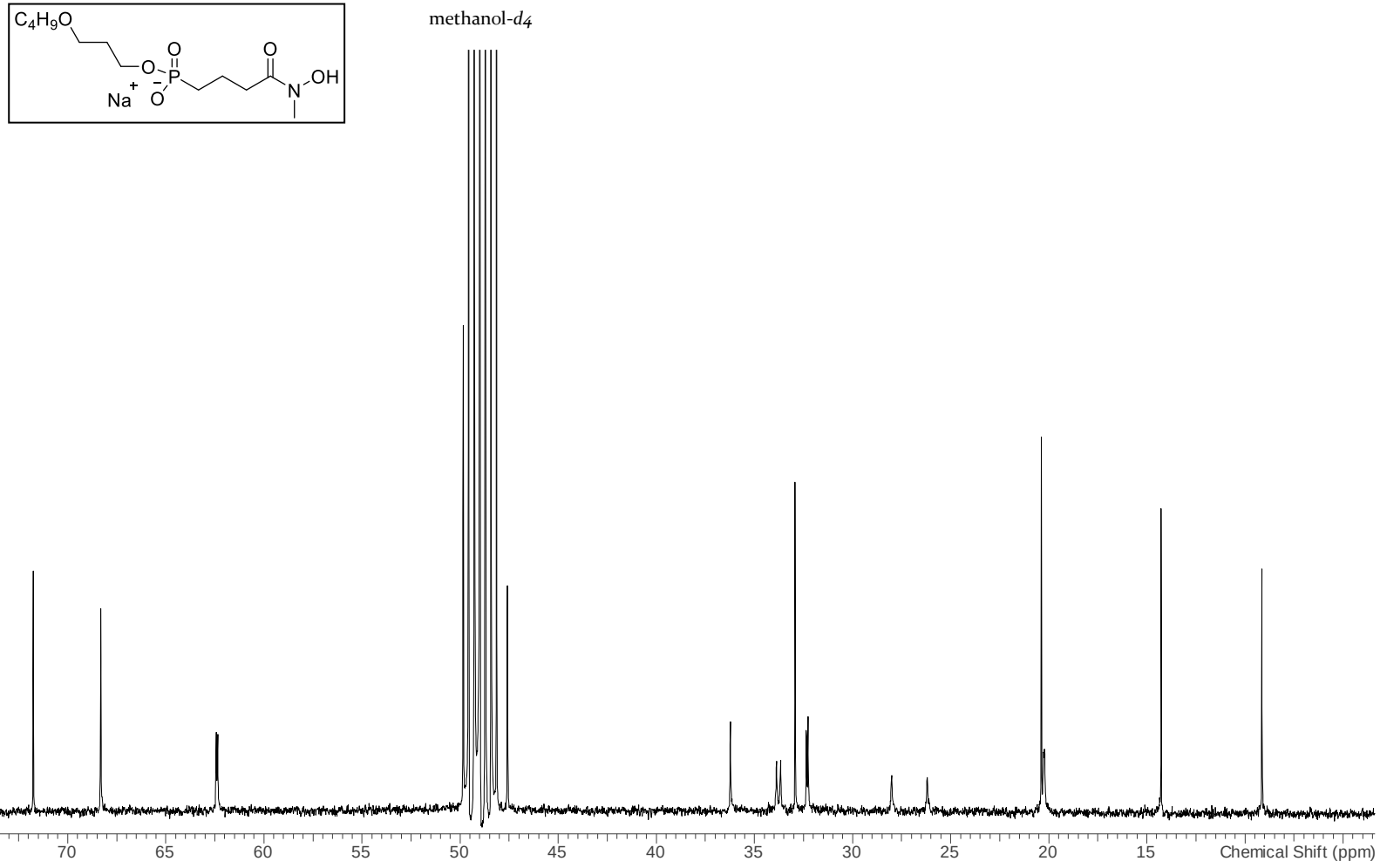
8.0e+1
7.0e+1
6.0e+1
5.0e+1
4.0e+1
3.0e+1
2.0e+1
1.0e+1
0.0
-1.0e+1
0.50 1.00 1.50 2.00 2.50 3.00 3.50 4.00 4.50 5.00 5.50 6.00 6.50 7.00 7.50 8.00


1: Scan ES+
BPI
1.13e6
618.32
618.32
618.32
198.18
437.36
498.29
604.19
282.40
124.20
%
0
Time
0.50 1.00 1.50 2.00 2.50 3.00 3.50 4.00 4.50 5.00 5.50 6.00 6.50 7.00 7.50 8.00

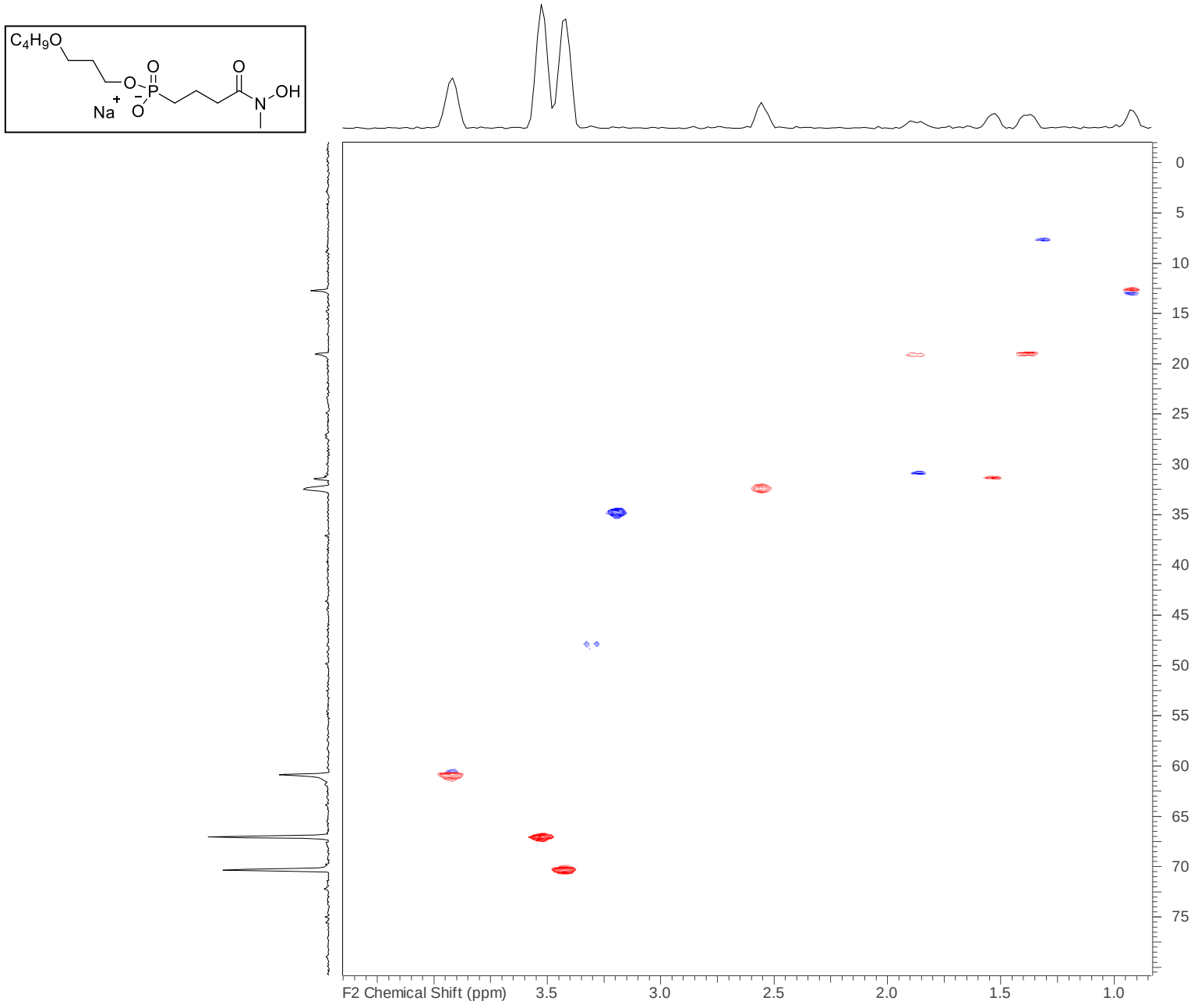
^{1}H NMR spectrum of **20a** (300MHz, METHANOL-*d4)*



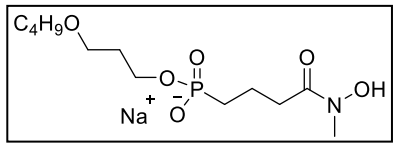
^{13}C NMR spectrum of **20a** (75MHz, METHANOL-*d4)*

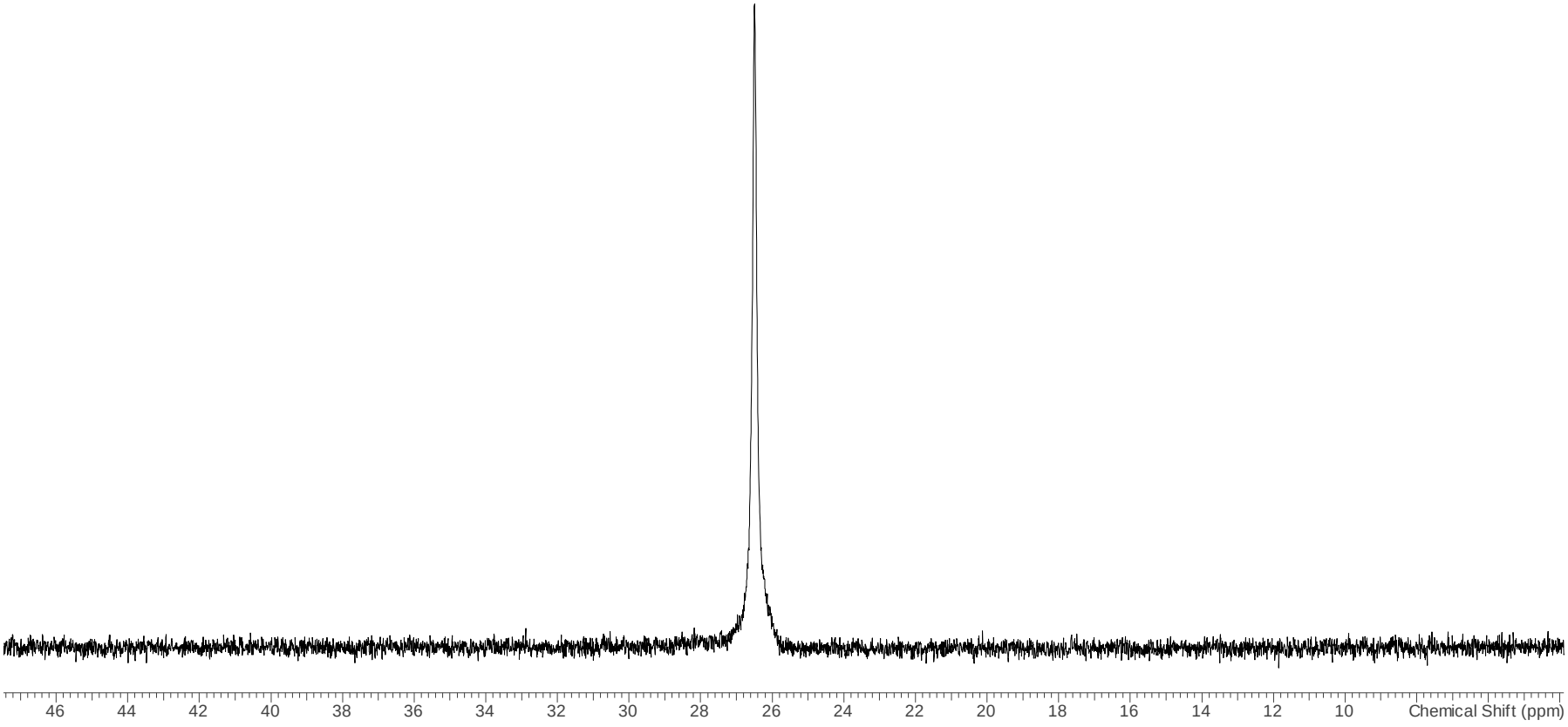


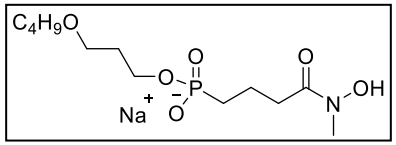
HSQC of **20a** (75MHz, METHANOL-*d4)*

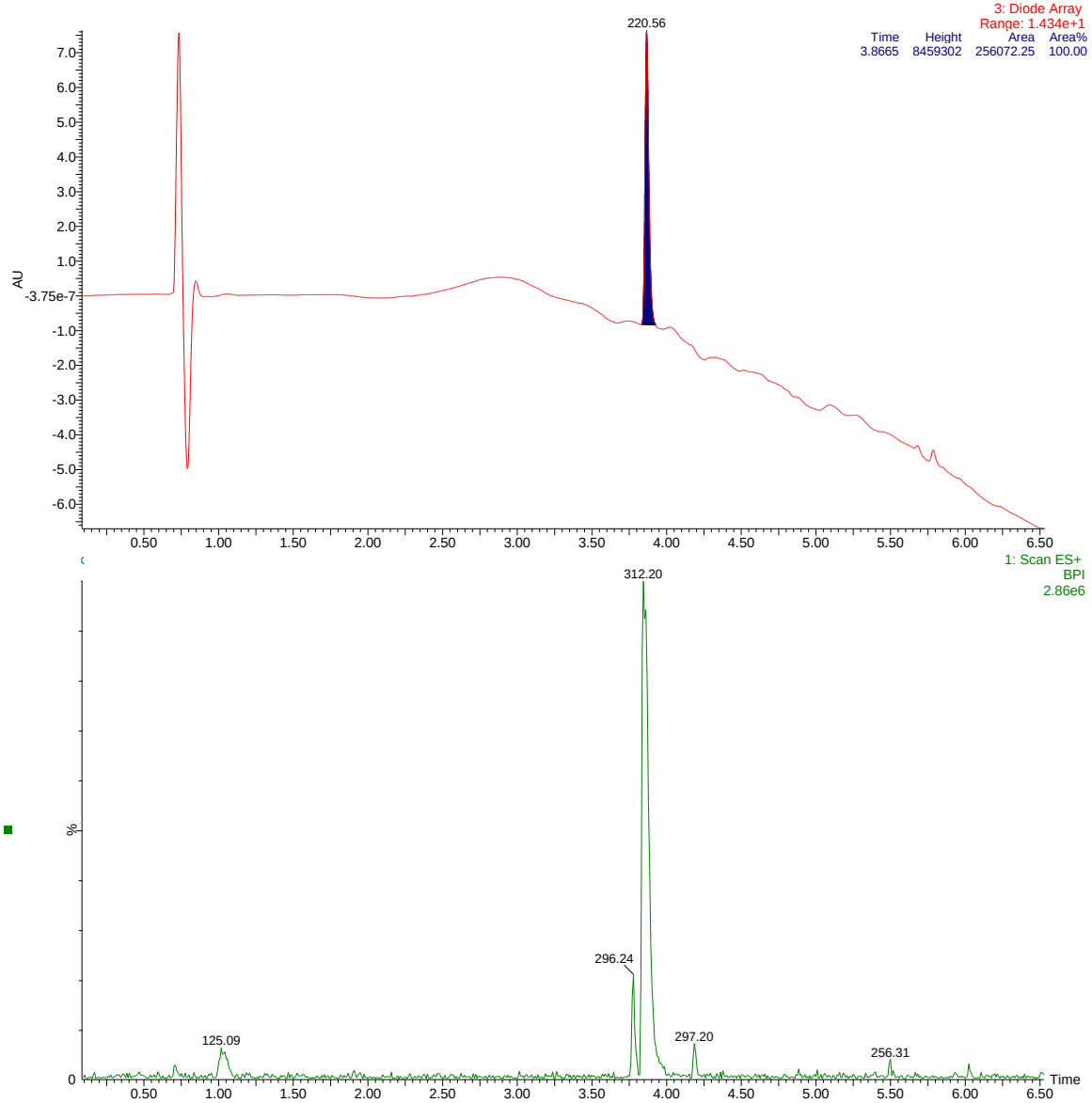


^{31}P NMR spectrum of **20a** (121MHz, METHANOL-*d4)*






C4H9O
O
O
O
P
O
Na
+
−
N
OH


3: Diode Array
Range: 1.434e+1
Time Height Area Area%
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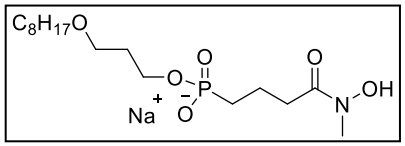
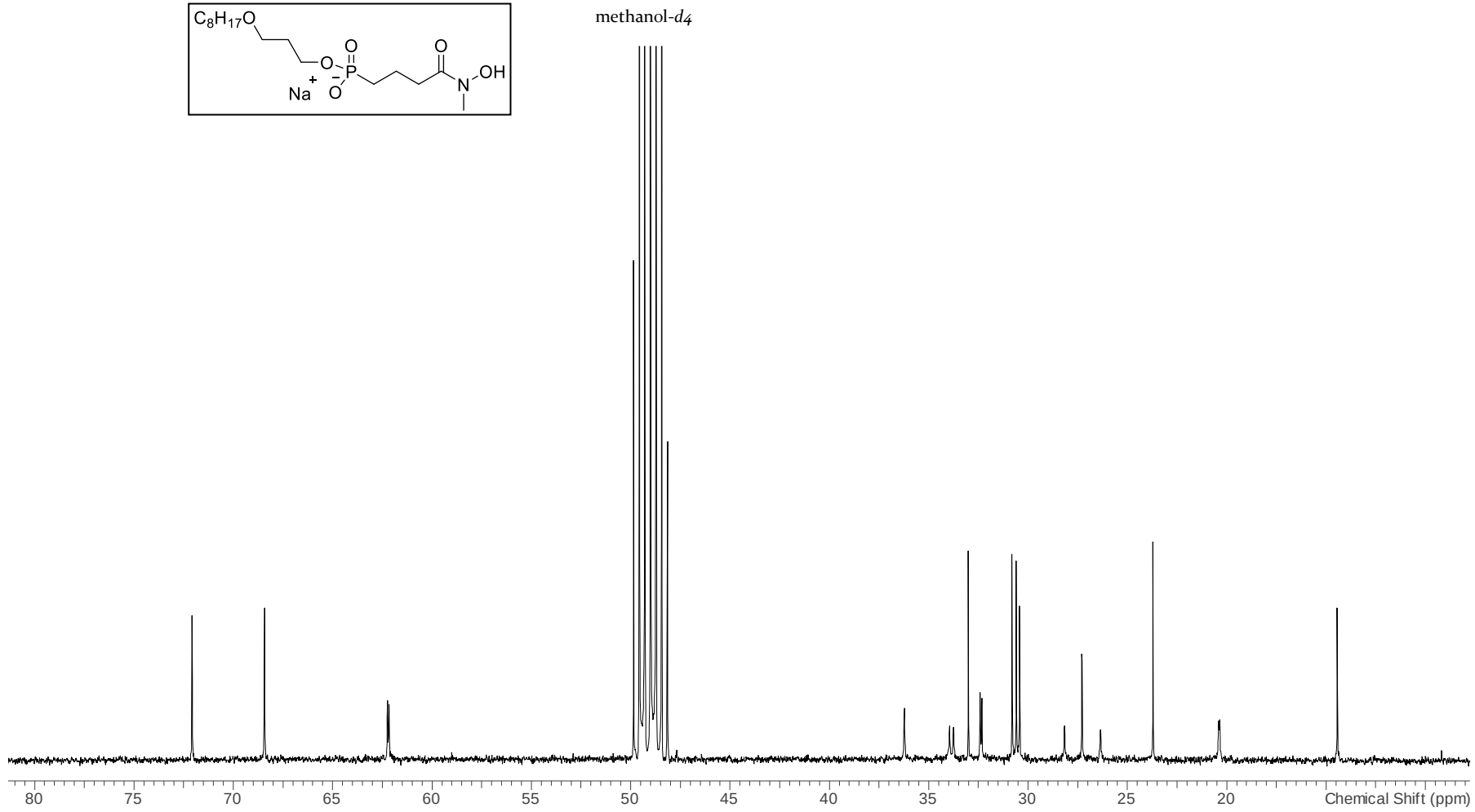
220.56
AU
7.0
6.0
5.0
4.0
3.0
2.0
1.0
-3.75e-7
-1.0
-2.0
-3.0
-4.0
-5.0
-6.0
0.50 1.00 1.50 2.00 2.50 3.00 3.50 4.00 4.50 5.00 5.50 6.00 6.50
1: Scan ES+
BPI
2.86e6
312.20
%
296.24
125.09
297.20
256.31
0
Time
0.50 1.00 1.50 2.00 2.50 3.00 3.50 4.00 4.50 5.00 5.50 6.00 6.50

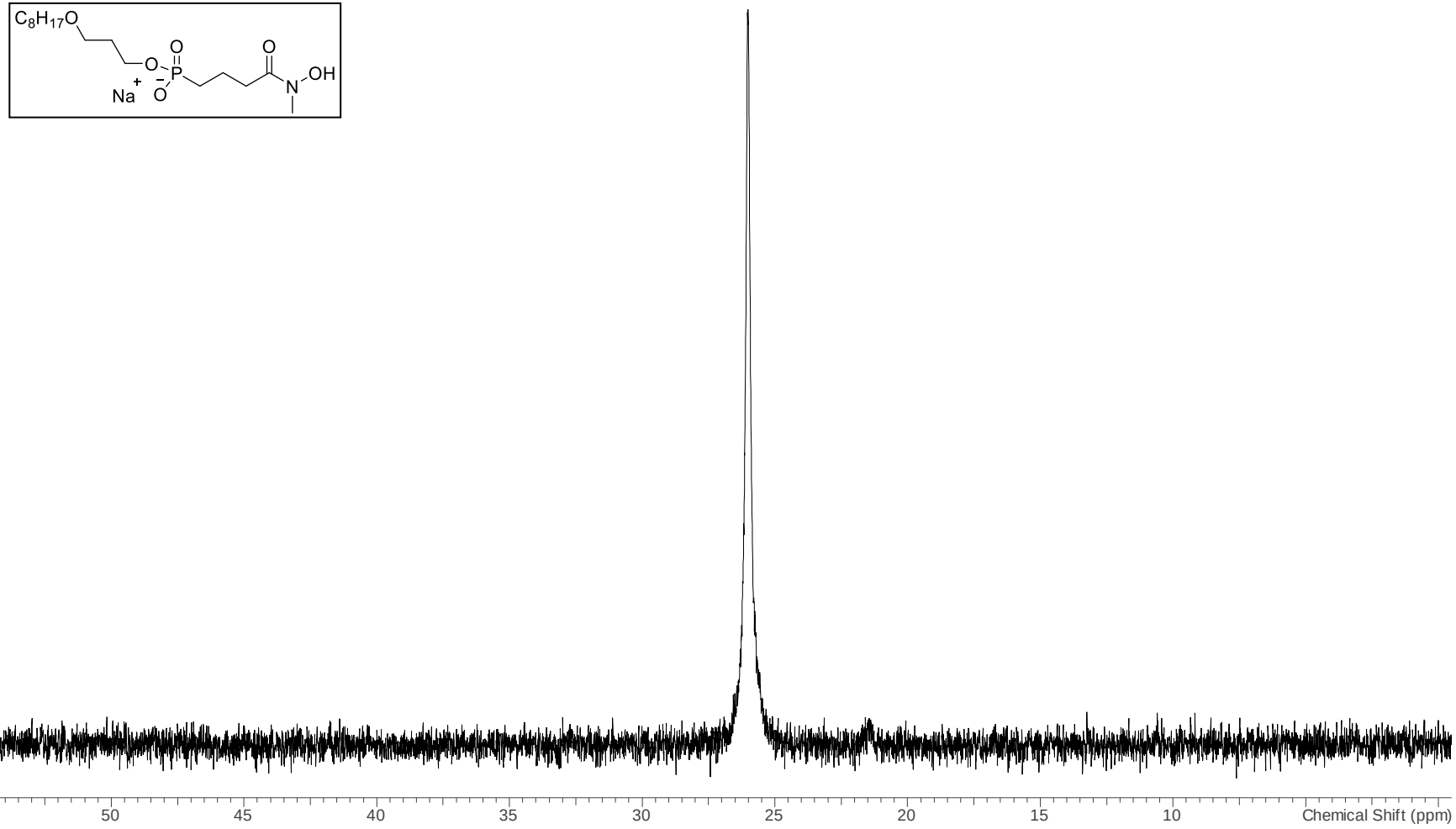
^{1}H NMR spectrum of **20b** (300MHz, METHANOL-*d4)*

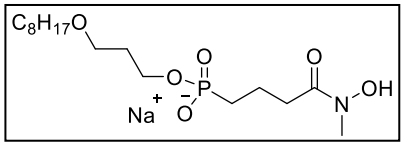


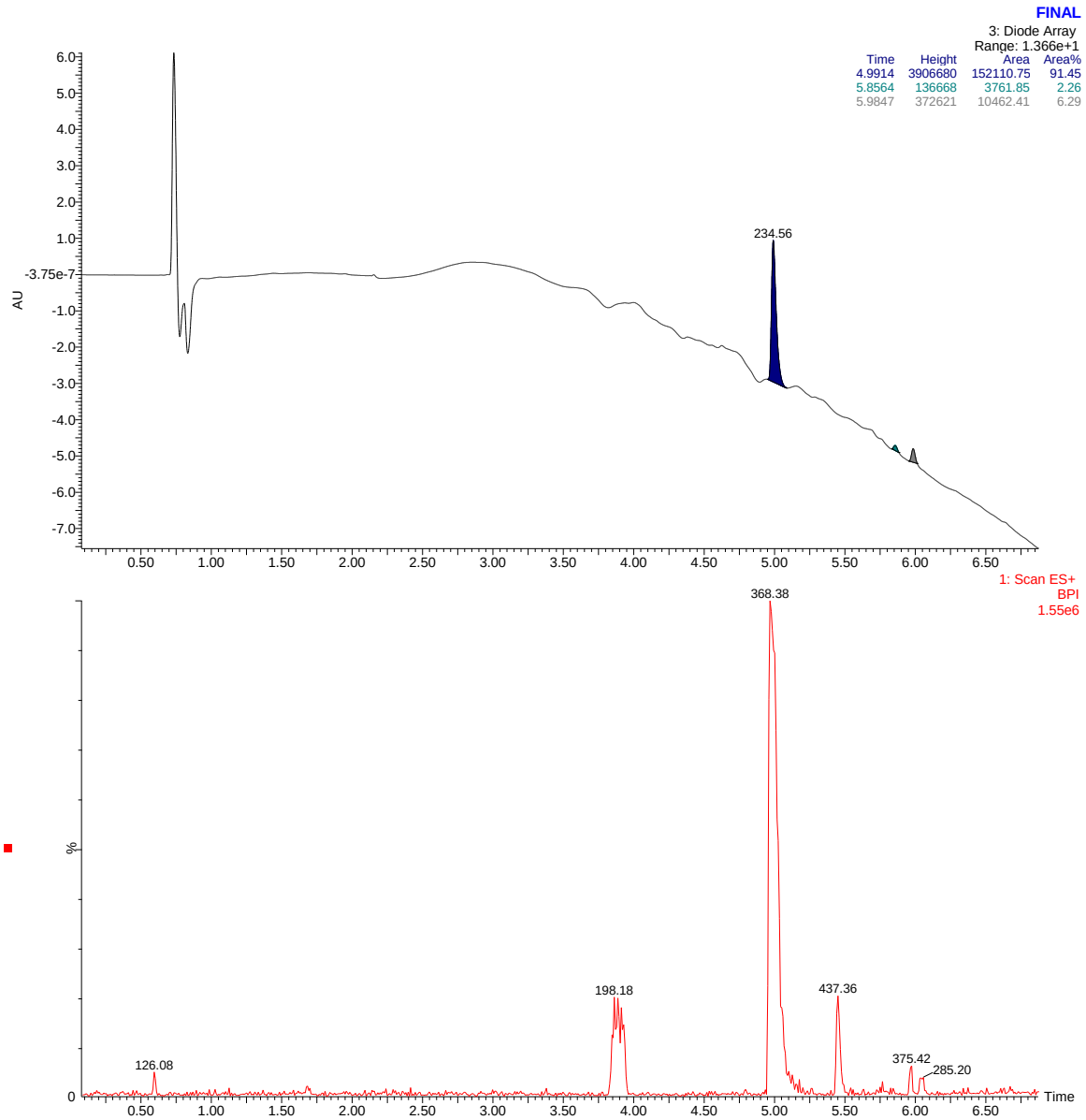
^{13}C NMR spectrum of **20b** (75MHz, METHANOL-*d4)*



^{31}P NMR spectrum of **20b** (121MHz, METHANOL-*d4)*




C8H17O
O
O
P
O
Na
+
O
N
OH


FINAL
3: Diode Array
Range: 1.366e+1
Time Height Area Area%
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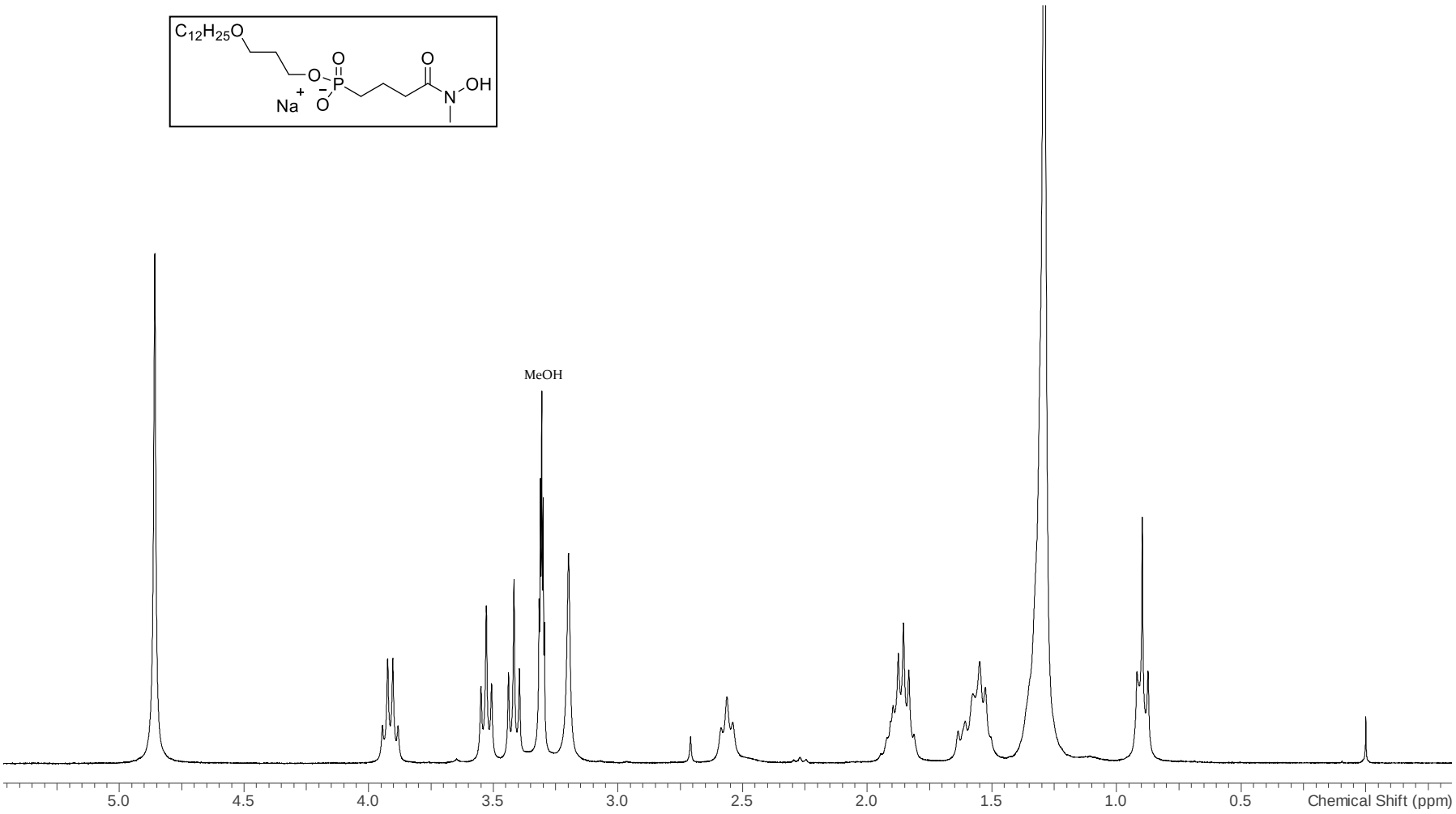
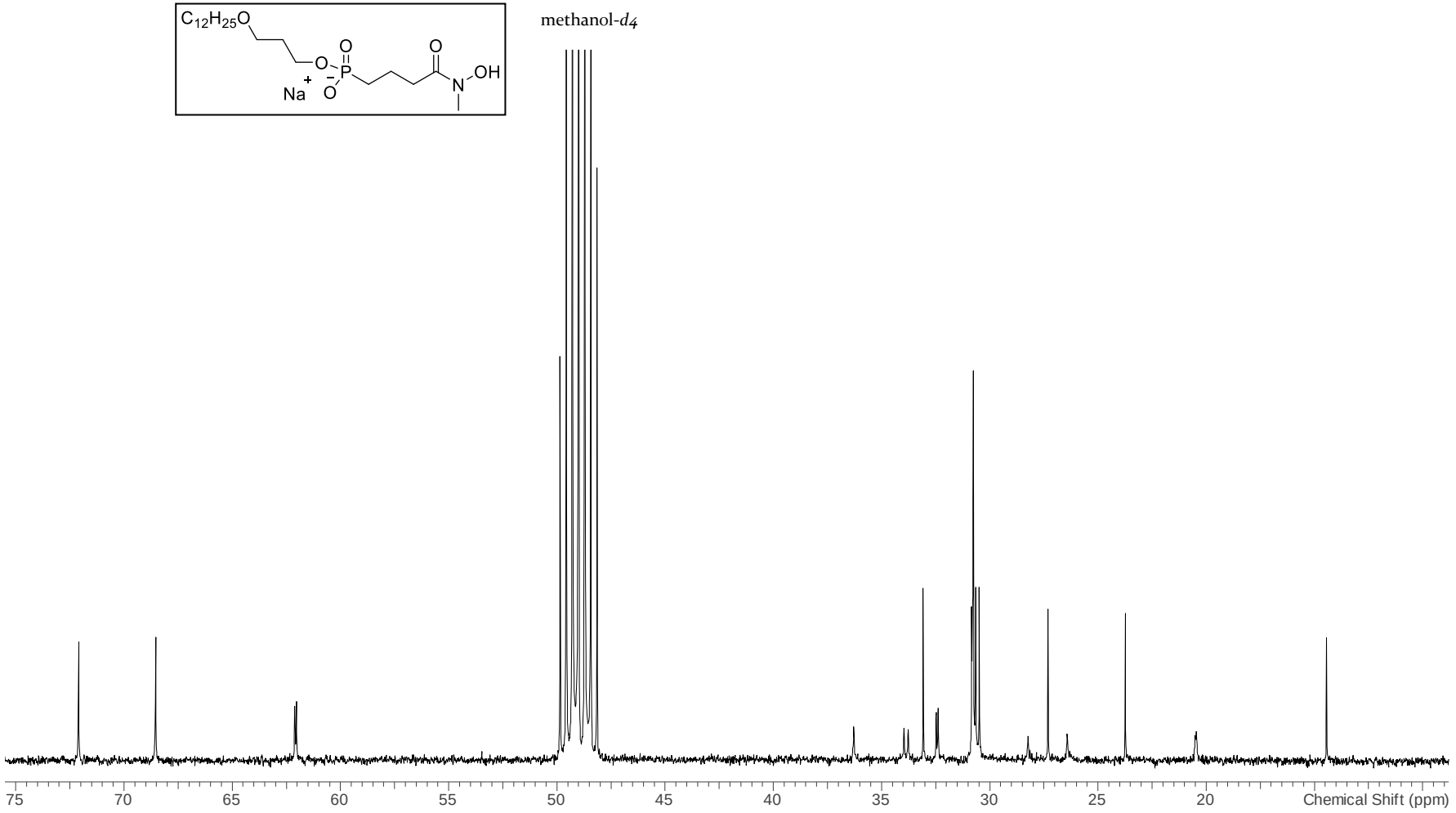
5.9847 372621 10462.41 6.29
AU
6.0
5.0
4.0
3.0
2.0
1.0
-3.75e-7
-1.0
-2.0
-3.0
-4.0
-5.0
-6.0
-7.0
234.56
0.50 1.00 1.50 2.00 2.50 3.00 3.50 4.00 4.50 5.00 5.50 6.00 6.50
1: Scan ES+
BPI
1.55e6
%
0
368.38
198.18
437.36
126.08
375.42
285.20
Time
0.50 1.00 1.50 2.00 2.50 3.00 3.50 4.00 4.50 5.00 5.50 6.00 6.50

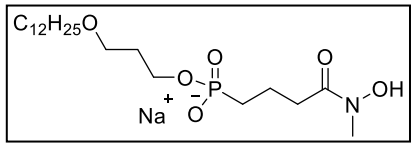
^{1}H NMR spectrum of **20c** (300MHz, METHANOL-*d4*)

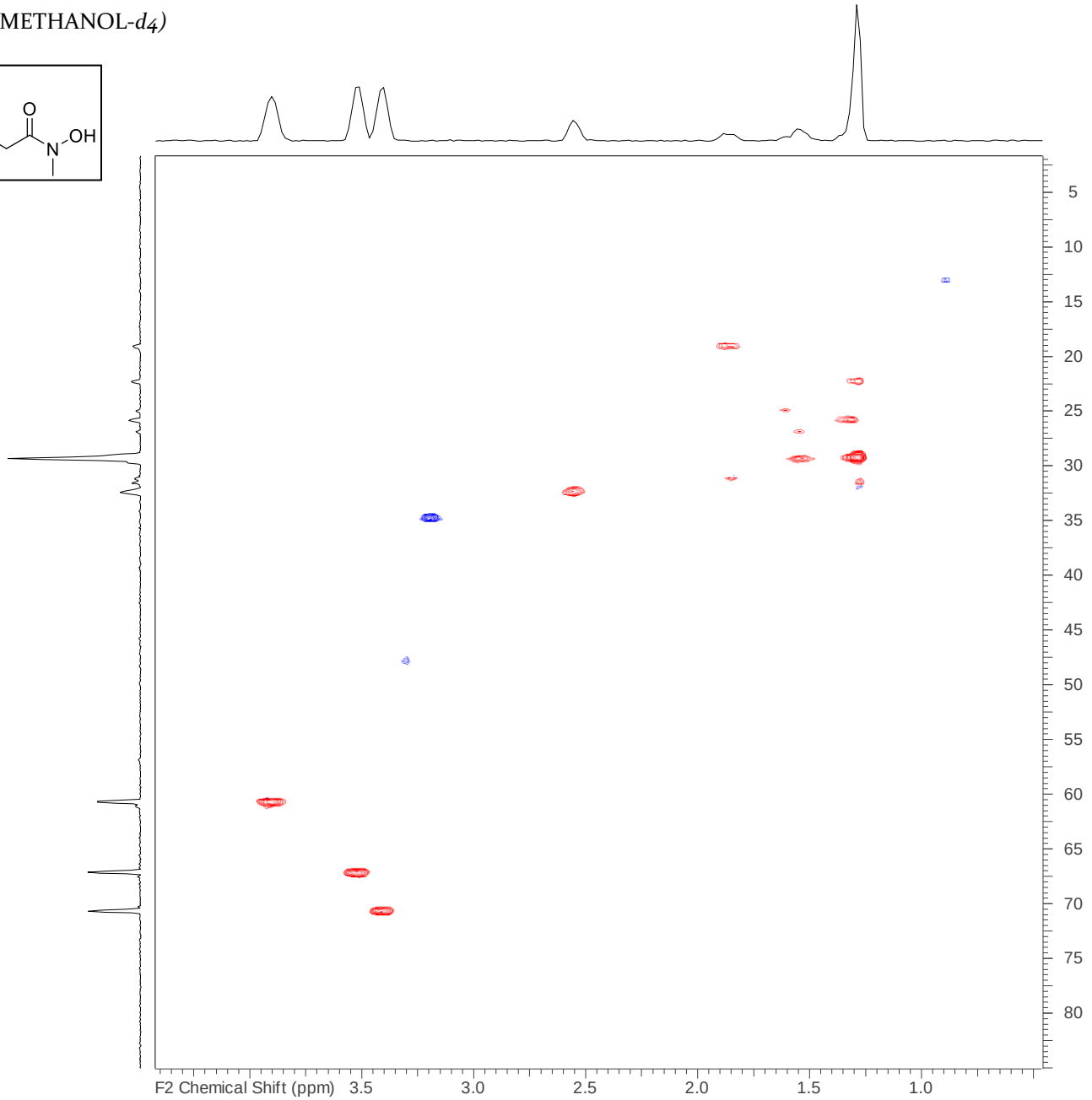


^{13}C NMR spectrum of **20c** (75MHz, METHANOL-*d4)*

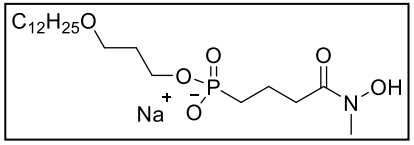


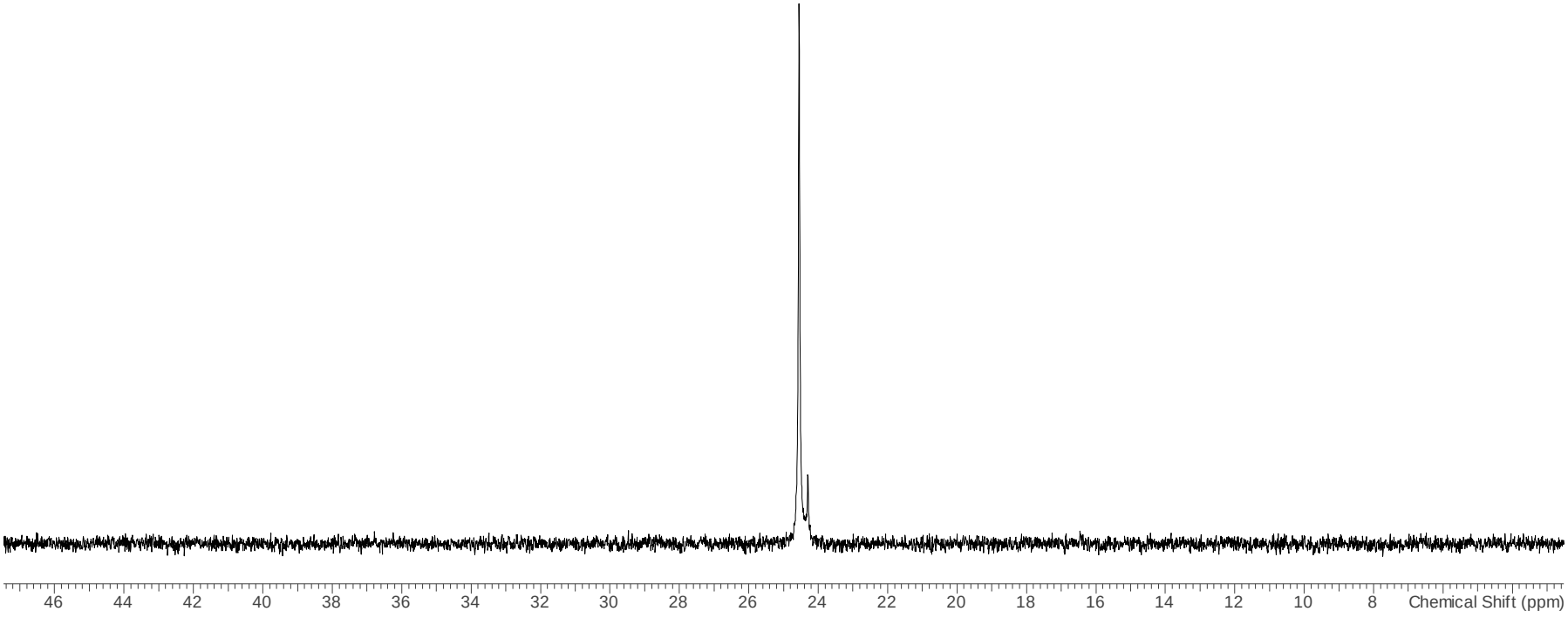
HSQC of **20c** (75MHz, METHANOL-*d4*)

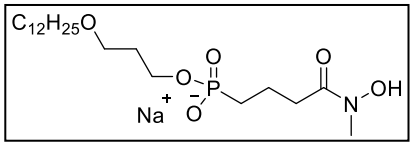




^{31}P NMR spectrum of **20c** (121MHz, METHANOL-*d4)*



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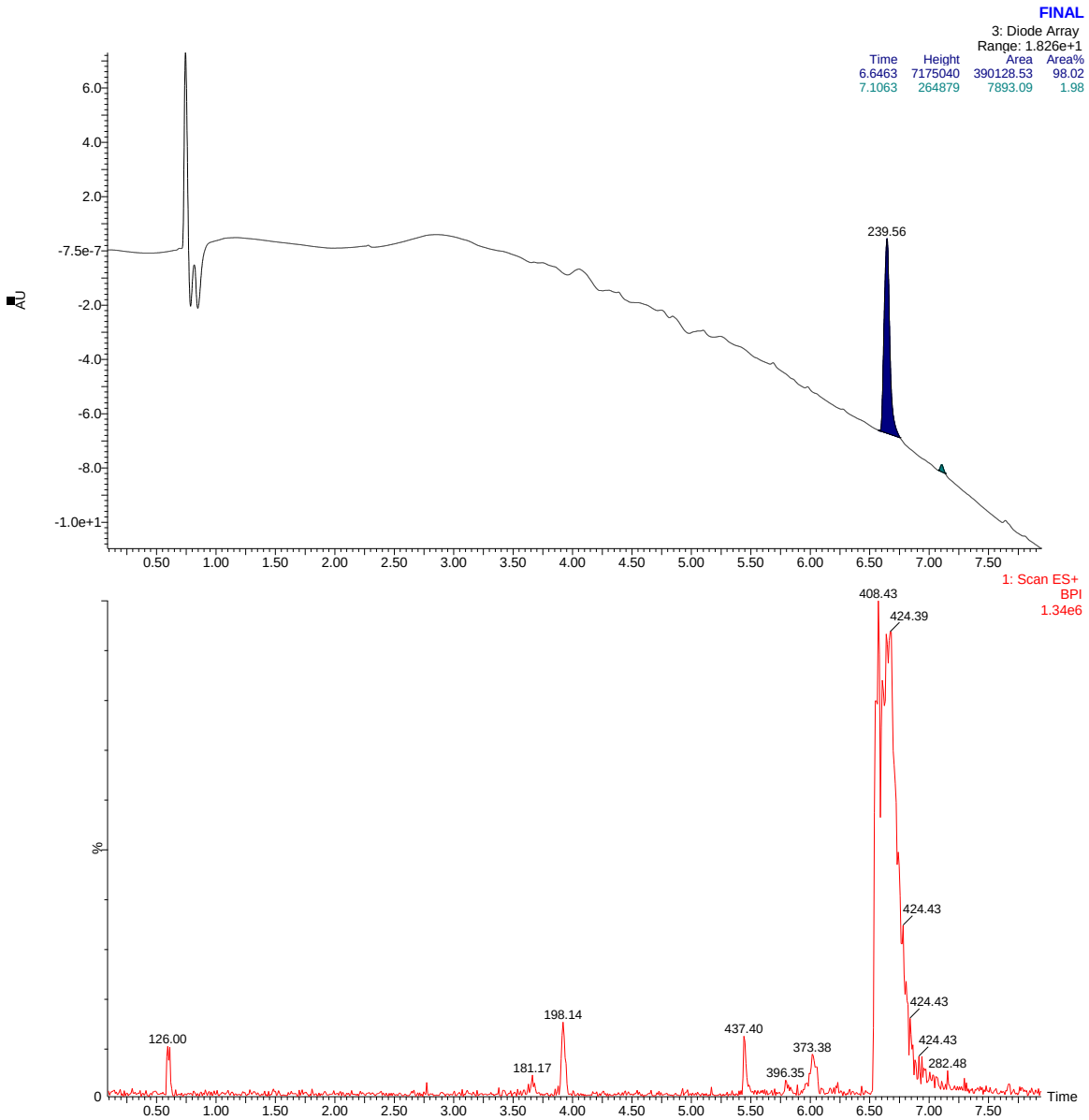
O
O
P
O
Na
+
O
O
N
OH


FINAL
3: Diode Array
Range: 1.826e+1
Time Height Area Area%
6.6463 7175040 390128.53 98.02
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AU
6.0
4.0
2.0
-7.5e-7
-2.0
-4.0
-6.0
-8.0
-1.0e+1
239.56
0.50 1.00 1.50 2.00 2.50 3.00 3.50 4.00 4.50 5.00 5.50 6.00 6.50 7.00 7.50
1: Scan ES+
BPI
1.34e6
%
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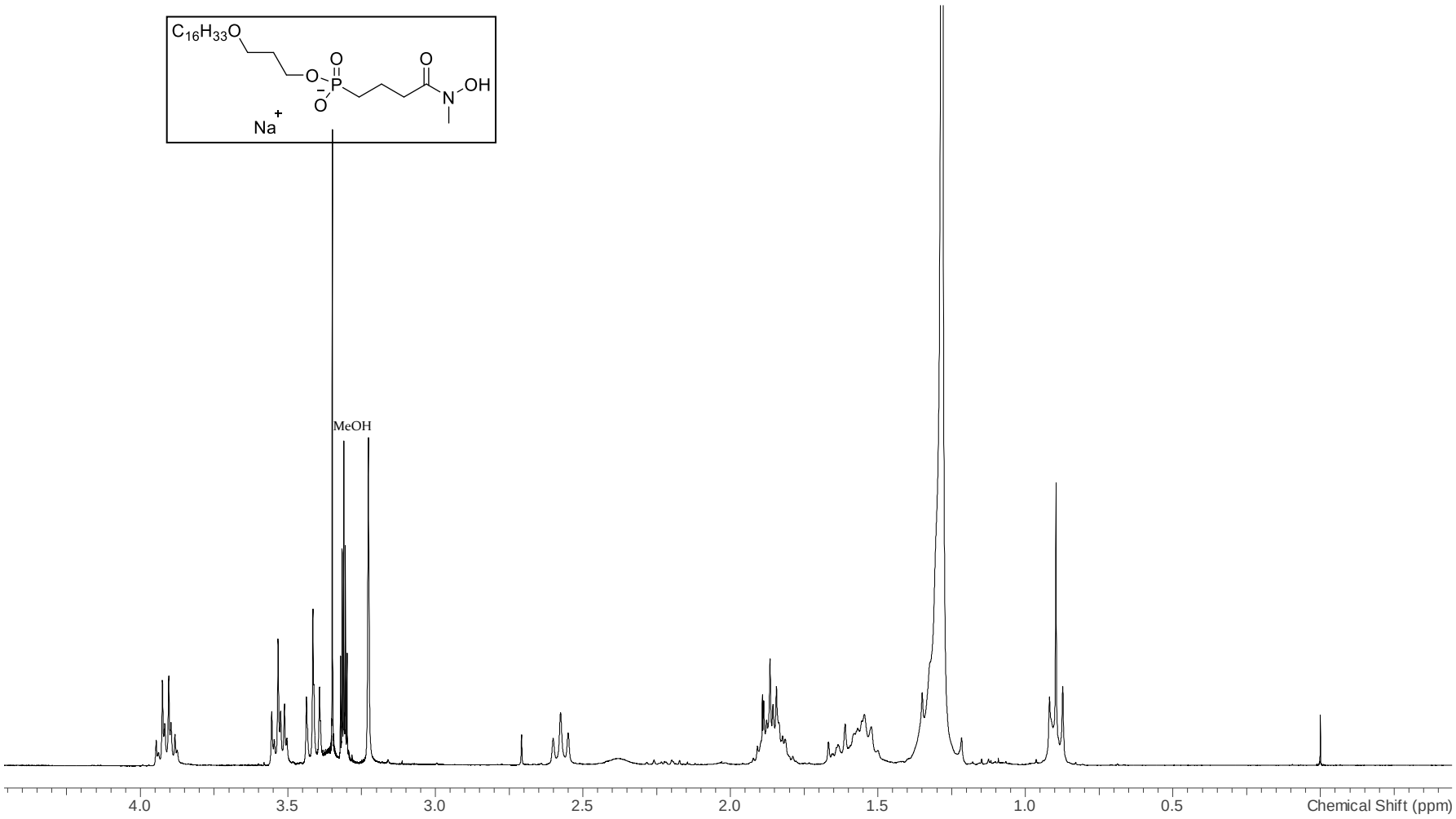
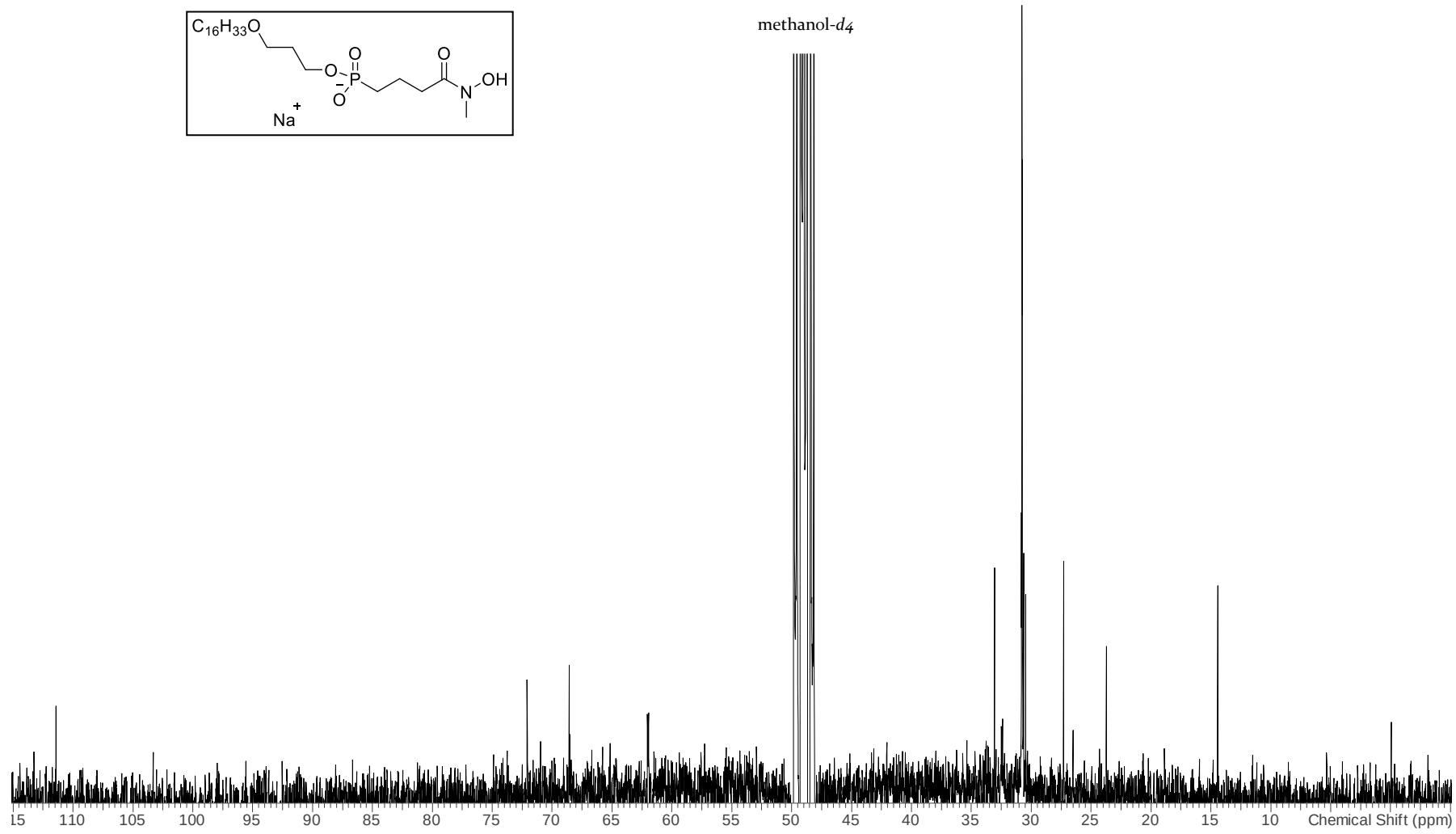
408.43
424.39
424.43
424.43
424.43
282.48
198.14
126.00
181.17
437.40
373.38
396.35
0.50 1.00 1.50 2.00 2.50 3.00 3.50 4.00 4.50 5.00 5.50 6.00 6.50 7.00 7.50
Time

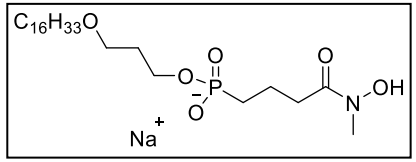
^{1}H NMR spectrum of **20d** (300MHz, CHLOROFORM-*d)*



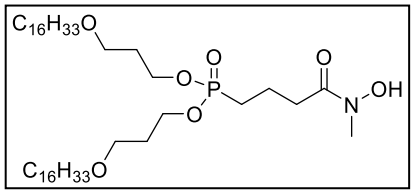
^{13}C NMR spectrum of **20d** (75MHz, CHLOROFORM-*d)*

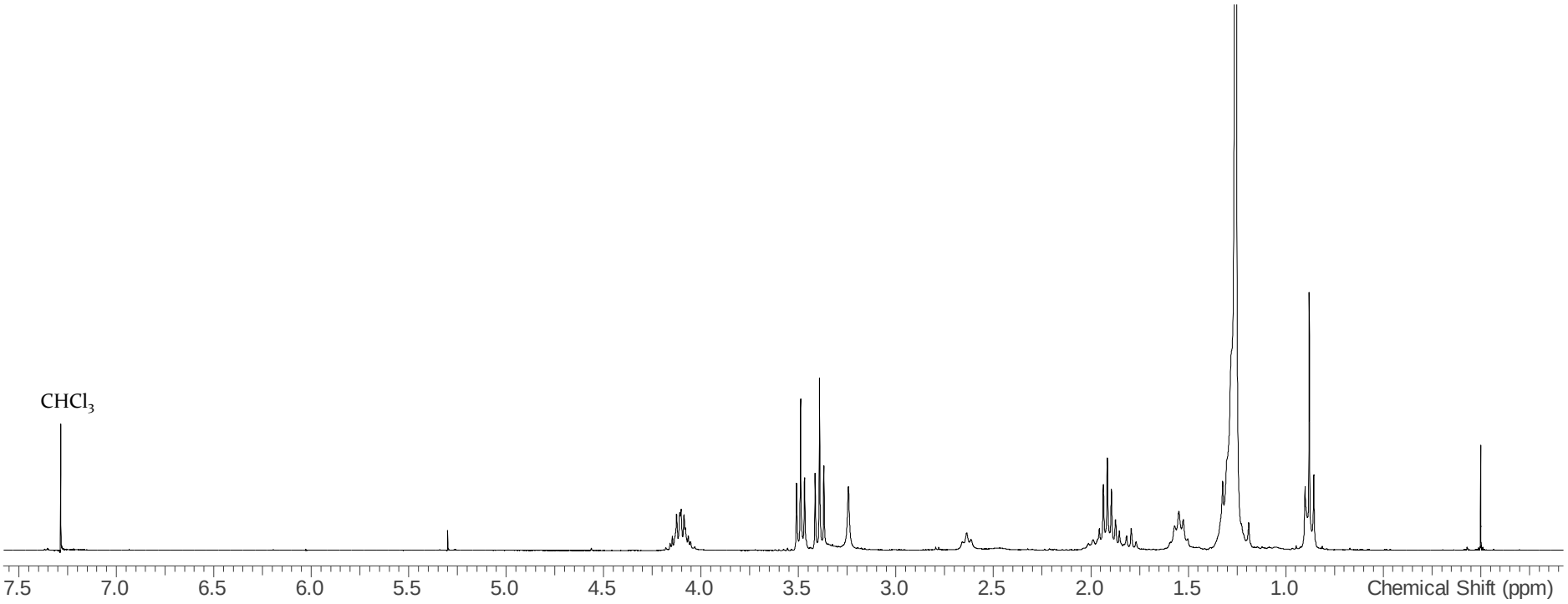


^{31}P NMR spectrum of **20d** (121MHz, CHLOROFORM-*d)*

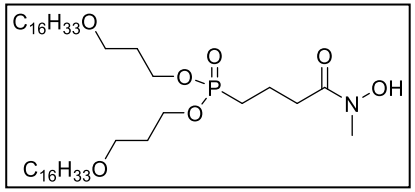


^{1}H NMR spectrum of **21d** (300MHz, CHLOROFORM-*d)*

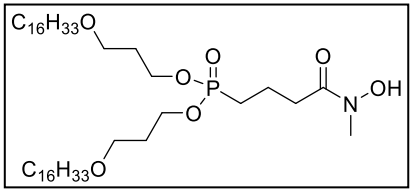


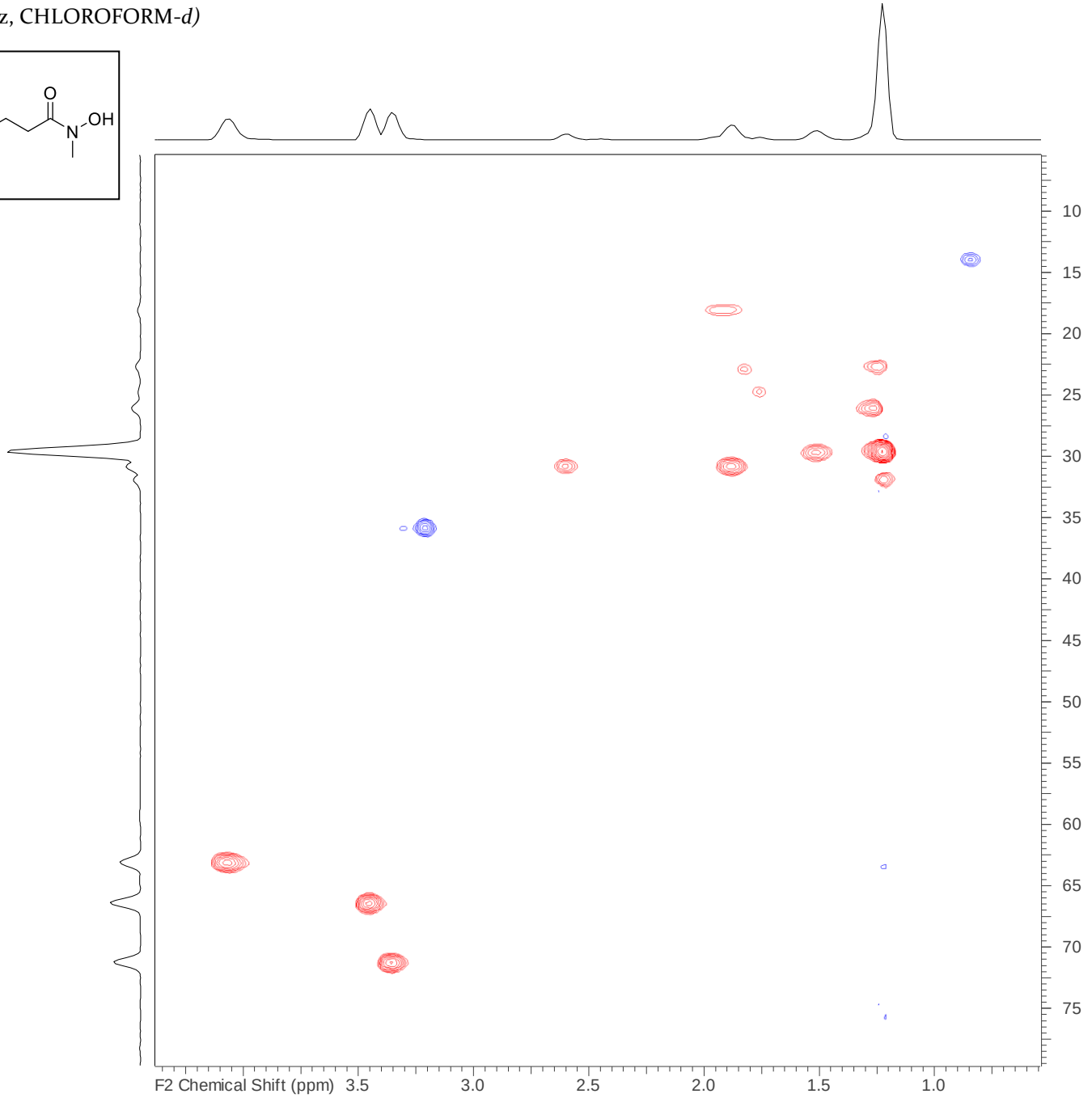


^{13}C NMR spectrum of **21d** (75MHz, CHLOROFORM-*d)*



HSQC of **21d** (75MHz, CHLOROFORM-*d)*





^{31}P NMR spectrum of **21d** (121MHz, CHLOROFORM-*d)*