Supporting info

General experimental and full experimental for compounds 18-20, 33 & 34

NMR spectra of compounds 13-16, 18-20, 29, 30, 32 & 33
Electrospray MS of compounds 13, 14, 33 and 34

Diagnostic NMR spectra for mixture of compounds 22 & 23

HPLC analysis of peptides 33 and 34

General experimental

Unless otherwise stated, all reagents were purchased from Sigma Aldrich, Alfa Aesar, Merck, Iris Biochem or Fisher Scientific and were used without further purification. LCMS data were attained using a Bruker Ion Trap Mass Spectrometer. NMR data were collected using a Bruker Avance 500, Bruker DRX500, or Bruker DPX300 and analysed using MestReNova software. IR spectra were recorded using a PerkinElmer spectrum one FTIR spectrometer. Optical rotations were measured using an AA-5 automatic polarimeter, $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1} High resolution mass spectrometry (HRMS) was carried out on a Bruker Daltonics micrOTOF by Mrs Tanya Marinko-Covell in accordance with University guidelines. Mixtures of solvents, such as those used in column chromatography, are v/v and all column chromatography was carried out using silica gel.

Diethyl(2,2-dibenzoxy)ethylphosphonate (18)

Diethyl ethynylphosphonate (prepared as in ref 21, (98 mg, 0.617 mmol) was dissolved in BnOH (1 mL), potassium carbonate (10 mg, 0.062 mmol) added and the mixture stirred at 120°C for 3 h, then cooled to rt and diluted with water (10 mL). The resultant solution was concentrated in vacuo to an oily solution, which was dissolved in toluene (5 mL) and concentrated twice to yield a pale yellow oil. The title compound was obtained via column chromatography (hexane:EtOAc 2:1 – 1:1) as a yellow oil (74 mg, 32%). R_f (Hex:EtOAc 1:1) = 0.18; ν_{max} (film)/cm^{-1} 3462, 2929 (C-H acetal) 1742, 1497, 1454, 1254 (P=O), 1119 (O-C-O), 1027 (P-O); δ_H (500MHz, $CDCl_3$): 7.41-7.27 (10H, m, Ph-*H*), 5.19 (1H, q*, *J* 5.6, CC*H*$(OBn)_2$), 4.69 (2H, d, $^2J_{H\text{-}H}$ 11.5, CCH(OC*H*HPh)$_2$), 4.50 (2H, d, $^2J_{H\text{-}H}$ 11.5, CCH(OCH*H*Ph)$_2$), 4.02 (4H, p†, *J* 7.3, PO(OC$H_2$$CH_3$)$_2$), 2.35 (2H, dd, $^2J_{H\text{-}P}$ 18.7, $^3J_{H\text{-}H}$ 5.7, PCH_2C), 1.25 (6H, t, $^3J_{H\text{-}H}$ 7.0, PO(OCH_2CH_3)$_2$; δ_C(125MHz, $CDCl_3$): 138.0 (s, Ph-C_1), 128.8, 128.3, 128.2 (Ph-$C_{2,3,4}$), 98.4 (app s, C*C*H$(OBn)_2$), 68.2 (s, CH(O*C*H_2Ph)$_2$), 62.2 (d, $^2J_{C\text{-}P}$ 6.3, PO(O*C*$H_2$$CH_3$)$_2$), 32.1 (d, $^1J_{C\text{-}P}$ 140.3, P*C*H_2C), 16.8 (d, $^2J_{C\text{-}P}$ 6.3, PO(OCH_2*C*H_3)$_2$); δ_P(121MHz, $CDCl_3$): 26.4 (m -dtp pred‡: $^3J_{H\text{-}P}$ 5.6, $^2J_{H\text{-}P}$ 18.7, $^3J_{H\text{-}P}$ 7.2)); HRMS: Found MH^+*:* found 379.1684; $C_{20}H_{28}O_5P$ requires 379.1669; Found MNa^+: found 401.1502; $C_{20}H_{27}NaO_5P$ requires 401.1488.

*actually dt, $^3J_{H\text{-}H}$ 5.6, $^3J_{H\text{-}P}$ 5.6; found by comparison with ^{31}P decoupled ^{1}H NMR spectrum

†actually dp, $^3J_{H\text{-}H}$ 7.2, $^3J_{H\text{-}P}$ 7.2; found by comparison with ^{31}P decoupled ^{1}H NMR spectrum

Dibenzyl(2,2-dibenzoxy)ethynylphosphonate (19)

Yellow oil (3 mg, 1%). R_f (Hex:EtOAc 1:1) = 0.36; δ_H (500MHz, $CDCl_3$): 7.30-7.17 (20H, m, Ph-*H*), 5.12 (1H, q*, *J* 5.7, CC*H*$(OBn)_2$), 4.91 (2H, dd, $^2J_{H\text{-}H}$ 14.2, $^3J_{H\text{-}P}$ 8.2, PO(OC*H*HPh)$_2$), 4.88 (2H, dd, $^2J_{H\text{-}H}$ 14.2, $^3J_{H\text{-}P}$ 8.2, PO(OCH*H*Ph)$_2$), 4.58 (2H, d, $^2J_{H\text{-}H}$ 11.5, CCH(OC*H*HPh)$_2$) , 4.48 (2H, d, $^2J_{H\text{-}H}$ 11.5, CCH(OCH*H*Ph)$_2$), 2.33 (2H, dd, $^2J_{H\text{-}P}$ 18.9, $^3J_{H\text{-}H}$ 5.7, PCH_2C); δ_C (125MHz, $CDCl_3$): 137.9 (s, Ph-C_1), 128.9, 128.8, 128.7, 128.3, 128.2 (Ph-$C_{2,3,4}$), 98.3 (app s, C*C*H$(OBn)_2$), 68.3 (s, CH(O*C*H_2Ph)$_2$), 67.7 (d, $^2J_{C\text{-}P}$ 6.25, PO(O*C*H_2Ph)$_2$), 32.3 (d, $^1J_{C\text{-}P}$ 149.9, P*C*H_2C); δ_P(121MHz, $CDCl_3$): 26.9 (app m (dtp pred†: $^3J_{H\text{-}P}$ 5.7, $^2J_{H\text{-}P}$ 18.9, $^3J_{H\text{-}P}$ 8.2)); HRMS: Found MH^+*:* found 503.1980; $C_{30}H_{32}O_5P$ requires 503.1980; Found MNa^+: found 525.1795; $C_{30}H_{31}NaO_5P$ requires 525.1801.

*actually dt, $^3J_{H\text{-}H}$ 5.7, $^3J_{H\text{-}P}$ 5.7; found by comparison with ^{31}P decoupled ^{1}H NMR spectrum

Benzylethyl(2,2-dibenzoxy)ethylphosphonate (20)

Yellow oil (17 mg, 6%). R_f (Hex:EtOAc 1:1) = 0.25; ν_{max} (film)/cm^{-1} 3444, 2928 (C-H acetal) 1716, 1497, 1455, 1255 (P=O), 1118 (O-C-O), 1024 (P-O); δ_H (300MHz, $CDCl_3$): 7.36-7.27 (15H, m, Ph-*H*), 5.19 (1H, q*, *J* 5.7, CC*H*$(OBn)_2$), 5.05 (1H, dd, $^2J_{H\text{-}H}$ 11.5, $^3J_{H\text{-}P}$ 7.8, PO(OC*H*HPh)(OEt)), 5.05 (1H, dd, $^2J_{H\text{-}H}$ 11.5, $^3J_{H\text{-}P}$ 7.8, PO(OCH*H*Ph)(OEt)), 4.67 (2H, d, $^2J_{H\text{-}H}$ 11.5, CCH(OC*H*HPh)$_2$) , 4.57

(2H, d, $^{2}J_{H\text{-}H}$ 11.5, CCH(OCH*H*Ph)$_2$), 4.02 (2H, m, PO(OC*H*$_2$CH$_3$)(OBn)), 2.33 (2H, dd, $^{2}J_{H\text{-}P}$ 18.9, $^{3}J_{H\text{-}H}$ 5.7, PC*H*$_2$C), 1.21 (3H, t, $^{3}J_{H\text{-}H}$ 7.1, PO(OCH$_2$C*H*$_3$)(OBn)); δ_C (125MHz, $CDCl_3$): 137.9 (s, Ph-*C*$_1$), 128.9, 128.8, 128.7, 128.4, 128.3, 128.2 (Ph-*C*$_{2,3,4}$), 98.3 (app s, C*C*H(OBn)$_2$), 68.3 (s, CH(O*C*H$_2$Ph)$_2$), 67.7 (d, $^{2}J_{C\text{-}P}$ 6.1, PO(O*C*H$_2$Ph)(OEt)), 62.3 (d, $^{2}J_{C\text{-}P}$ 6.5, PO(O*C*H$_2$CH$_3$)(OBn)), 32.3 (d, $^{1}J_{C\text{-}P}$ 140.2, P*C*H$_2$C), 16.7 (d, $^{2}J_{C\text{-}P}$ 6.4, PO(OCH$_2$*C*H$_3$)(OBn)); δ_P(121MHz, $CDCl_3$): 26.4 (app m (dtp or dttt pred[†])); HRMS: Found *MH*$^+$*:* found 441.1834; $C_{25}H_{30}O_5P$ requires 441.1825; Found *MNa*$^+$: found 463.1663; $C_{25}H_{29}NaO_5P$ requires 463.1645.
*actually dt, $^{3}J_{H\text{-}H}$ *5.7,* $^{3}J_{H\text{-}P}$ 5.7; found by comparison with ^{31}P decoupled ^{1}H NMR spectrum

H-CGAGAG(pTz)GAGAG-OH (33)

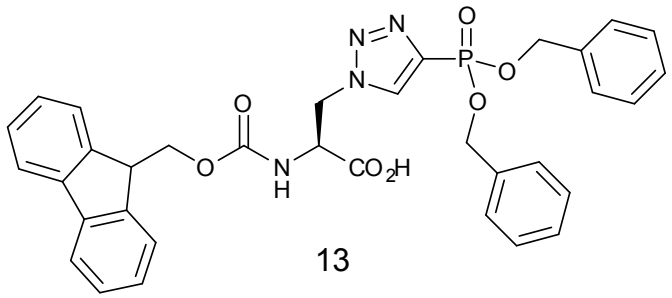
Chlorotrityl resin prelodaded with glycine (0.64 mmol/g loading, 200 mg, 0.128 mmol) was swollen in DMF (6 mL) for 30 min. The DMF was then removed by filtration and a solution of Fmoc-Ala-OH (199 mg, 0.64 mmol, 5 equiv), HCTU (259 mg, 0.627 mmol, 4.9 equiv) and DIPEA (236 µL, 1.28 mmol, 10 equiv) in DMF (6 mL) added to the resin and mixed for 1 h. The solution was removed by filtration and the resin was washed with DMF (3 × 6 ml, 2 min), 20% piperidine in DMF (5 × 6 ml, 2 min) and DMF (5 × 6 ml, 2 min). Subsequent couplings of Fmoc-Gly-OH (190 mg, 0.64 mmol, 5 equiv), Fmoc-Ala-OH (199 mg, 0.64 mmol, 5 equiv) and Fmoc-Cys(Trt)-OH (375 mg, 0.64 mmol, 5 equiv) followed the same procedure and used the same quantities of HCTU (259 mg, 0.627 mmol, 4.9 equiv) and DIPEA (236 µL, 1.28 mmol, 10 equiv). An alternative procedure was used for coupling Fmoc-pTz (OBn)$_2$-OH: a solution of the amino acid (82 mg, 0.128 mmol, 1 equiv), HATU (42mg, 0.128 mmol, 1 equiv) and DIPEA (47 µL, 0.256 mmol, 2 equiv) in DMF (4 mL) was mixed with the resin for 1h. The solution was removed by filtration, the resin washed with DMF (3 × 6 ml, 2 min) and a further solution of the amino acid (140 mg, 0.22 mmol, 1.7 equiv), HATU (71 mg, 0.22 mmol, 1.7 equiv) and DIPEA (80 µL, 0.44 mmol, 3.4 equiv) in DMF (4 mL) mixed with the resin for 1 h. The resin was then washed, as previously - DMF (3 × 6 mL, 2 min), 20% piperidine in DMF (5 × 6 mL, 2 min) and DMF (5 × 6 mL, 2 min) – and the subsequent couplings carried out as normal. Following the final coupling the resin was washed with DMF (3 × 6 ml, 2 min), DCM (3 × 6 ml, 2min) and MeOH (3 × 6 ml, 2 min) before drying overnight under a stream of air.
The peptide was cleaved from the resin by mixing with a cleavage cocktail (4 mL) consisting of TFA (94%), EDT (2.5%), H_2O (2.5%) and TIS (1%) for 2 h.. The solution was dripped into cold ether (40 ml) and the precipitate collected by centrifugation. The etheral supernatant was decanted off, and the peptide pellet resuspened in cold ether (40 ml). The resin was mixed again with TFA (4 mL, 10 min) which was then dripped into the ether containing the peptide precipitate. The peptide was collected by centrifugation, the ether decanted and the peptide resuspended in ether (40 mL) a further 4 times. Residual ether was removed under a stream of nitrogen and the resultant amorphous yellow solid was dissolved in the minimum volume H_2O and lyophilised to leave a flocculent yellow solid (63 mg, 51% yield),. δ_H (300MHz, D_2O): 8.09 (1H, s, pTz-Tz*H*$_5$), 5.02-4.85 (2H, m, pTz-C*H*$_2$), 4.84-4.72 (1H, m, pTz- C*H*), 4.39-4.19 (5H, m, 4 × Ala- C*H*CH$_3$ + Cys- C*H*CH$_2$SH), 4.00-3.76 (12H, 6 × Gly- C*H*$_2$), 3.02 (2H, d, *J* 5.6, Cys- CHC*H*$_2$SH), 1.39-1.25 (12H, m, 4 × Ala- CHC*H*$_3$); δ_P(121MHz, D_2O): 0.81 (s); HRMS Found *MH*$^-$: Found 964.3080, $C_{32}H_{51}N_{15}O_{16}PS$ requires 964.3102.

H-GMTS(pTz)AA-NH$_2$ (34)

Rink amide Novagel™ resin (0.64 mmol/g loading, 50 mg, 0.032 mmol) was swollen in DMF (0.8 mL) for 30 min. The DMF was then removed by filtration and a solution of Fmoc-Ala-OH (50 mg, 0.16 mmol, 5 equiv), HCTU (65 mg, 0.15 mmol, 4.9 equiv) and DIPEA (59 µL, 0.32 mmol, 10 equiv) in DMF (0.8 mL) added to the resin and mixed for 1 h. The solution was removed by filtration and the resin was washed with DMF (3 × 0.8 mL, 2 min), 20% piperidine in DMF (5 × 0.8 mL, 2 min) and DMF (5 × 0.8 mL, 2 min). Subsequent couplings of Fmoc-Ala-OH (30 mg, 0.096 mmol, 5

equiv), Fmoc-Ser(*t*Bu)-OH (37 mg, 0.096 mmol, 5 equiv), Fmoc-Thr(*t*Bu)-OH (38 mg, 0.096 mmol, 5 equiv), Fmoc-Met-OH (36 mg, 0.096 mmol, 5 equiv) and Fmoc-Gly-OH (29 mg, 0.096 mmol, 5 equiv) followed the same procedure and used the same quantities of HCTU (40 mg, 0.094 mmol, 4.9 equiv) and DIPEA (35 µL, 0.192 mmol, 10 equiv). An alternative procedure was used for coupling Fmoc-pTz $(OBn)_2$-OH: a solution of **13** (20 mg, 0.032 mmol, 1 equiv), HATU (12mg, 0.030 mmol, 0.95 equiv) and DIPEA (12 µL, 0.064 mmol, 2 equiv) in DMF (0.6 mL) was mixed with the resin for 1h. The solution was removed by filtration and the resin washed with DMF (3 × 0.8 mL, 2 min) and a second solution of **13** (40 mg, 0.064 mmol, 2 equiv), HATU (24 mg, 0.060 mmol, 1.95 equiv) and DIPEA (24 µL, 0.128 mmol, 4 equiv) in DMF (0.6 mL) was mixed with the resin for 1h. The solution was removed by filtration and the resin washed, as previously - DMF (3 × 0.8 ml, 2 min), 20% piperidine in DMF (5 × 0.8 ml, 2 min) and DMF (5 × 0.8 ml, 2 min) – and the subsequent couplings carried out as normal. Following the final coupling the resin was washed with DMF (3 × 0.8 ml, 2 min), DCM (3 × 0.8 ml, 2min) and MeOH (3 × 0.8 ml, 2 min) before drying overnight under a stream of air.

The peptide was cleaved from the resin by mixing with a cleavage cocktail (0.8 mL) consisting of TFA (94%), EDT (2.5%), H_2O (2.5%) and TIS (1%) for 1h 30. The solution was dripped into cold ether (10 ml) and the precipitate collected by centrifugation. The etheral supernatant was decanted off, and the peptide pellet resuspened in more cold ether (10 ml). The resin was mixed again with the cleavage cocktail (0.8 mL, 1h 30 min) which was then dripped into the ether containing the peptide precipitate. The peptide was collected by centrifugation, the ether decanted and the peptide resuspended in ether (10 mL) a further 4 times. Residual ether was removed under a stream of nitrogen and the resultant colourless solid was dissolved in H_2O and lyophilised to leave an amorphous colourless solid (11.4 mg, 47%). This crude product was purified by anion exchange on Q-sepharose resin (1 mL): the peptide was dissolved in water (adjusted to pH 11.2 by addition of $NH_4OH_{(aq)}$) and passed through the resin under gravity. The flow-through was collected and passed through the column again. The peptide was eluted with a stepwise gradient of $NH_4HCO_{3(aq)}$ (0 - 500 mM, adjusted to pH 10.4 by addition of $NH_4OH_{(aq)}$). LCMS analysis of the fractions showed the elution at 20mM contained only **34**. This fraction was lyophilised to give **34** (4.7 mg, 0.0062 mmol, 19% yield – based upon initial resin loading).



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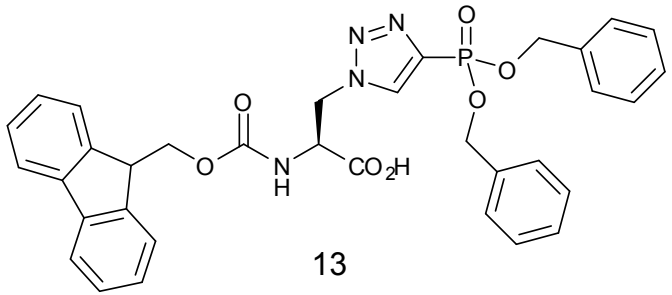

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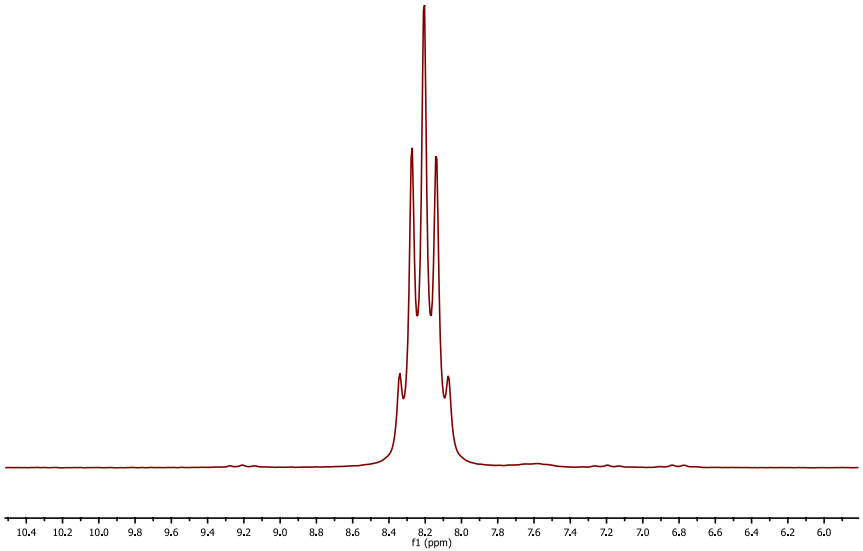

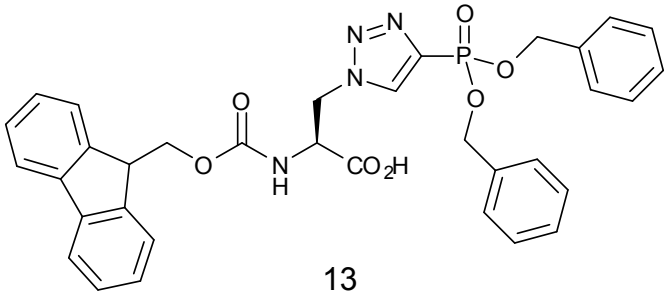

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School of Chemistry Mass Spectrometry Service

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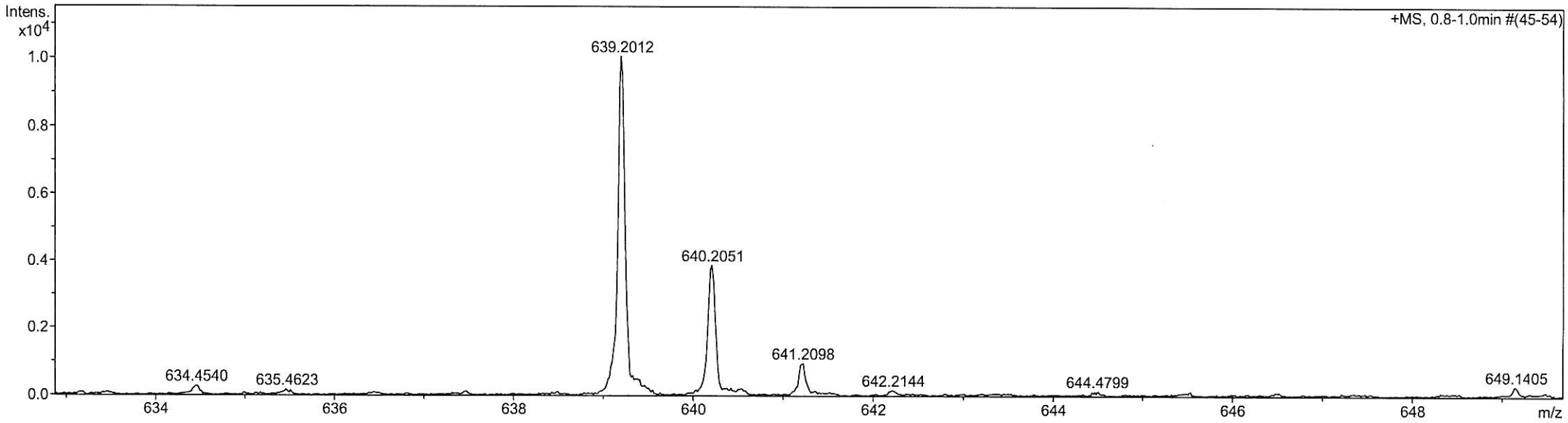

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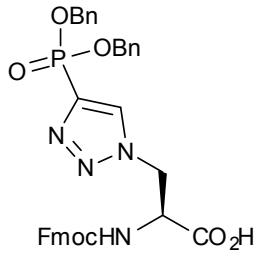
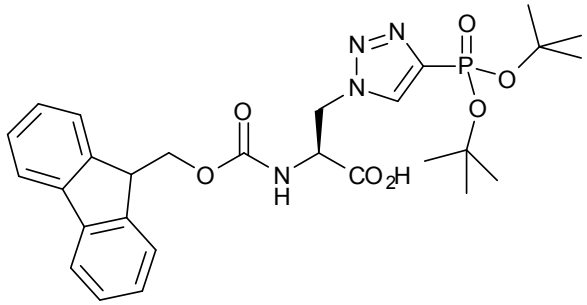
C 34 H 35 N 1 Na 1 O 8 P 1	0.006	639.1992	-3.02	-3.54	-1.93	18.00	ok	odd
C 33 H 29 N 8 Na 1 O 3 P 1	0.009	639.1992	-3.03	-3.78	-1.94	23.50	ok	even
C 35 H 31 N 5 Na 1 O 4 P 1	0.010	639.2006	-0.93	-1.61	-0.60	23.00	ok	odd
C 33 H 26 N 11 O 2 P 1	0.011	639.2003	-1.37	-2.24	-0.88	27.00	ok	odd
C 33 H 36 O 11 P 1	0.011	639.1990	-3.45	-3.94	-2.21	16.50	ok	even
C 35 H 28 N 8 O 3 P 1	0.014	639.2016	0.73	-0.07	0.47	26.50	ok	even





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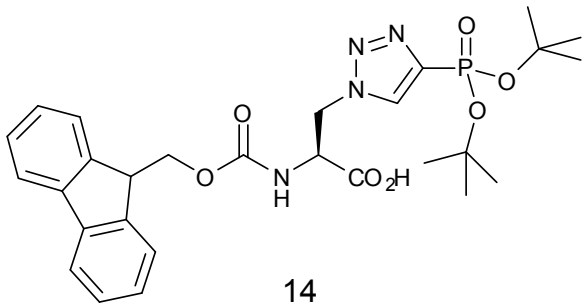

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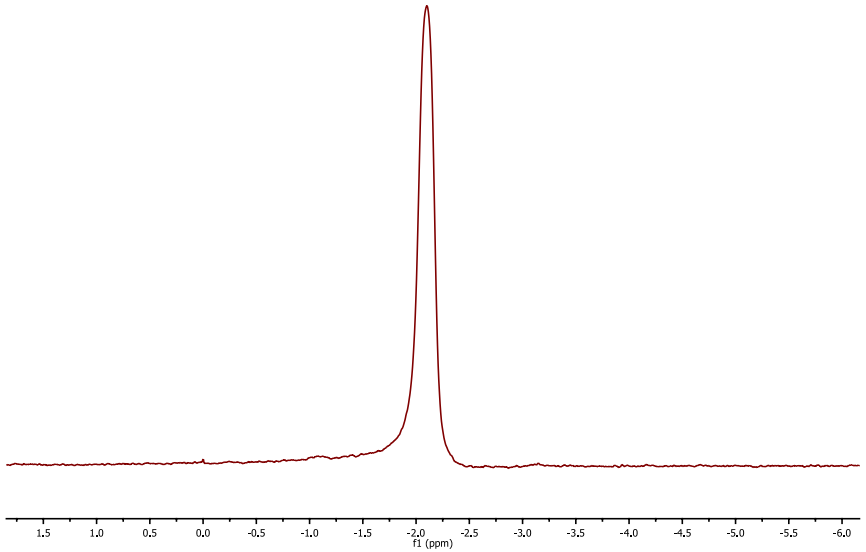

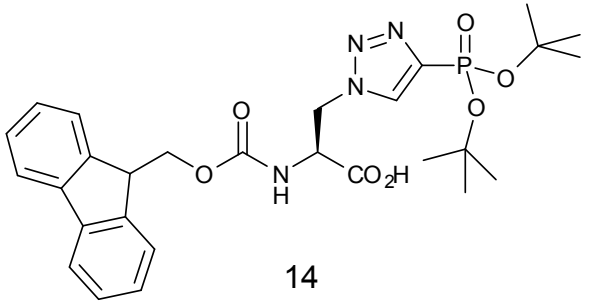

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School of Chemistry Mass Spectrometry Service

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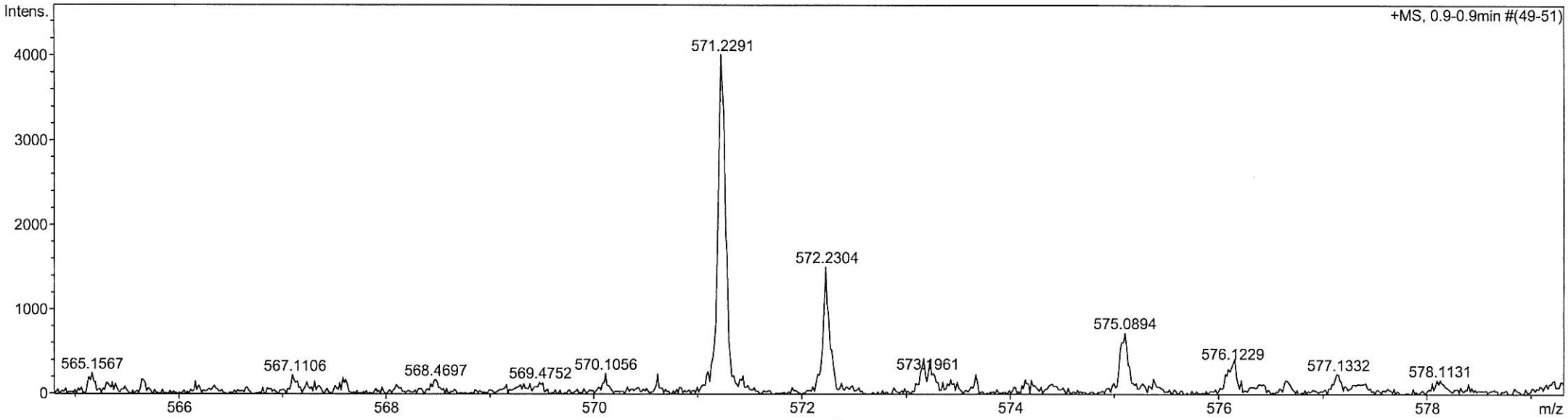

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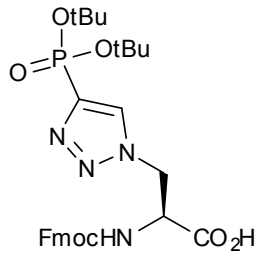
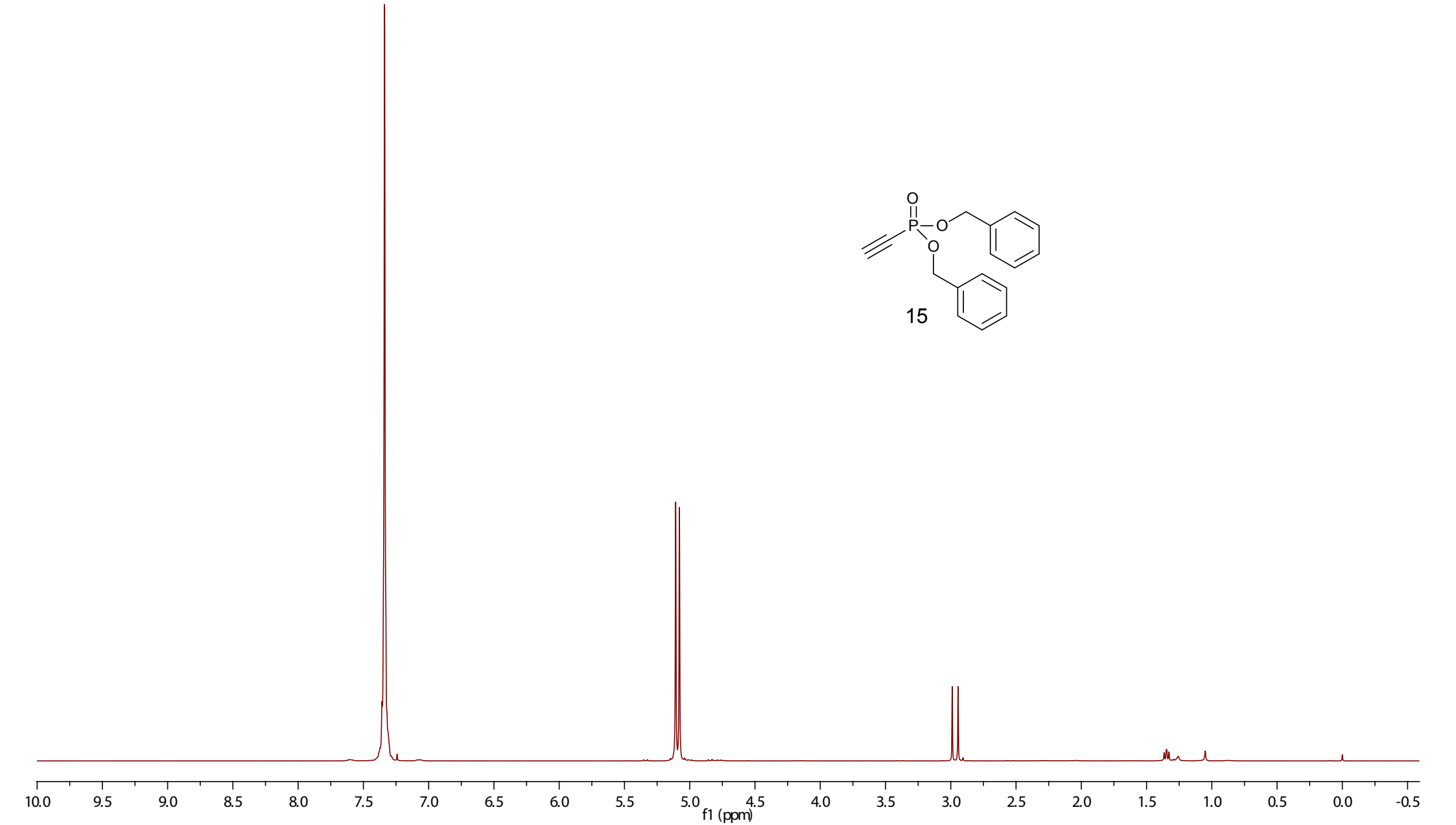
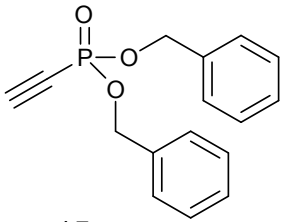
C 29 H 32 N 8 O 3 P 1	0.015	571.2329	6.75	10.16	3.86	18.50	ok	even
C 29 H 35 N 5 Na 1 O 4 P 1	0.019	571.2319	4.89	8.29	2.79	15.00	ok	odd
C 30 H 38 N 1 O 8 P 1	0.021	571.2330	6.76	10.41	3.86	13.00	ok	odd
C 27 H 30 N 11 O 2 P 1	0.022	571.2316	4.40	7.06	2.51	19.00	ok	odd
C 28 H 36 N 4 O 7 P 1	0.026	571.2316	4.41	7.73	2.52	13.50	ok	even
C 27 H 33 N 8 Na 1 O 3 P 1	0.028	571.2305	2.54	5.06	1.45	15.50	ok	even
C 28 H 39 N 1 Na 1 O 8 P 1	0.031	571.2305	2.55	5.86	1.46	10.00	ok	odd
C 27 H 40 O 11 P 1	0.038	571.2303	2.07	5.31	1.18	8.50	ok	even







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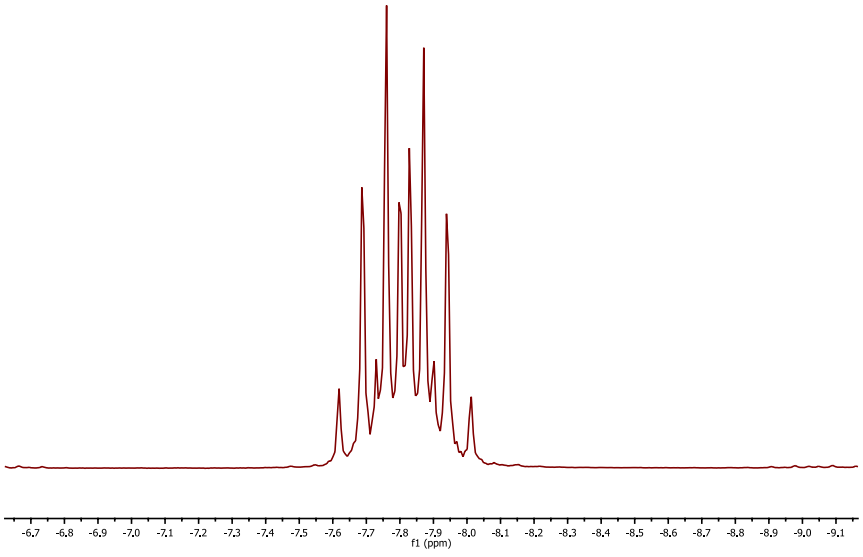

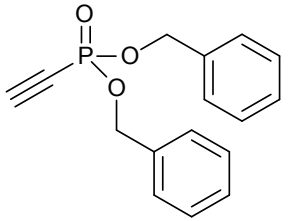

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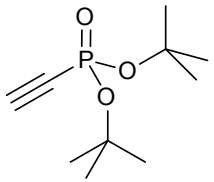

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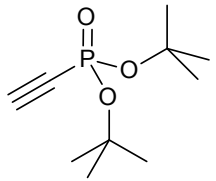

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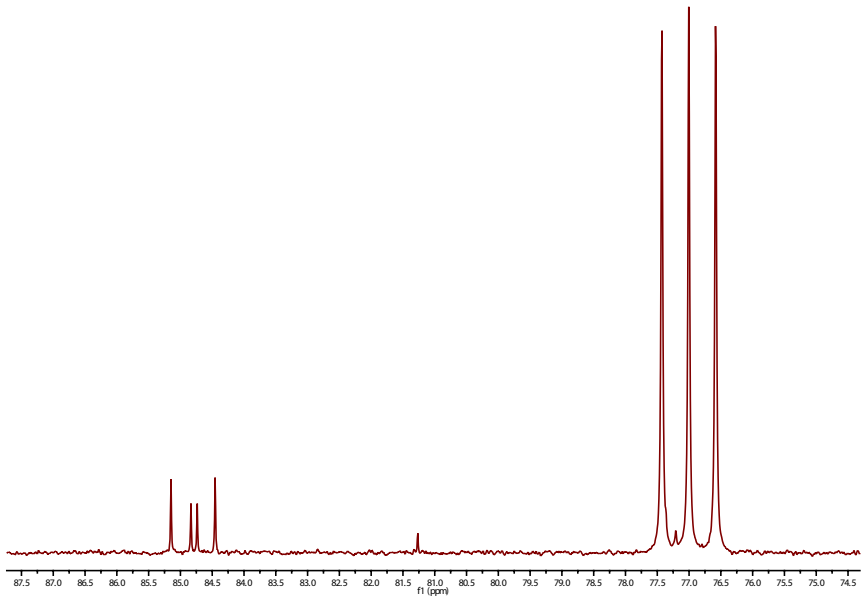

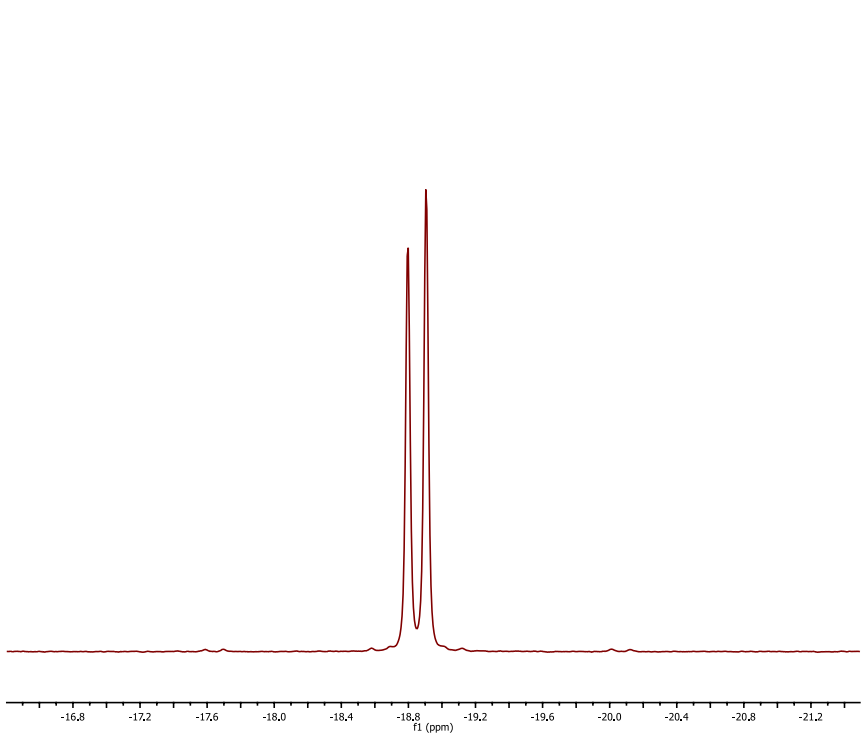

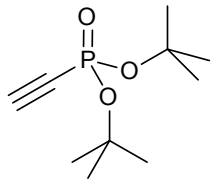

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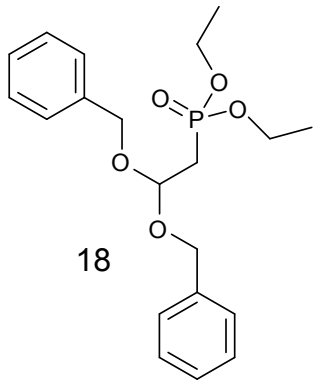

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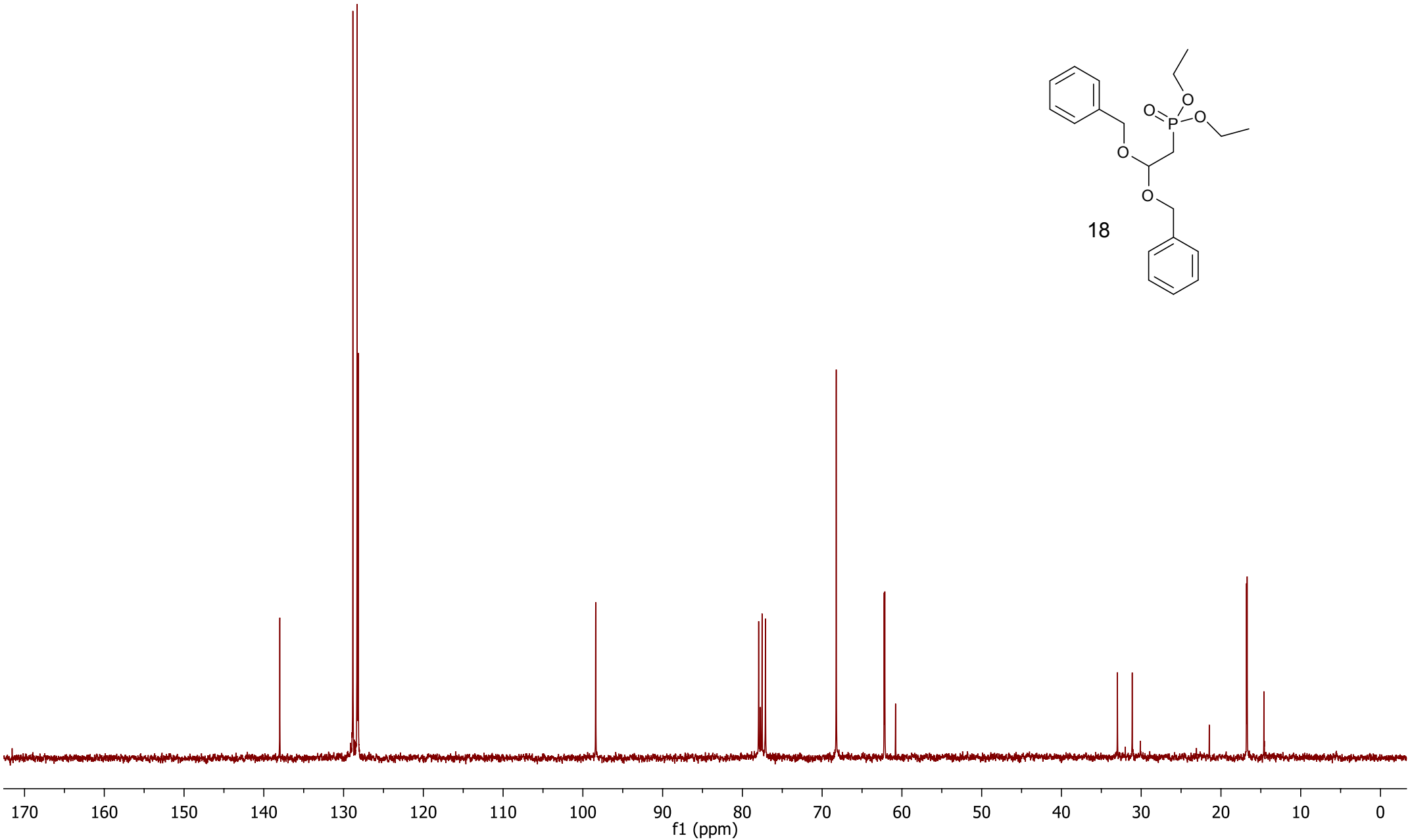

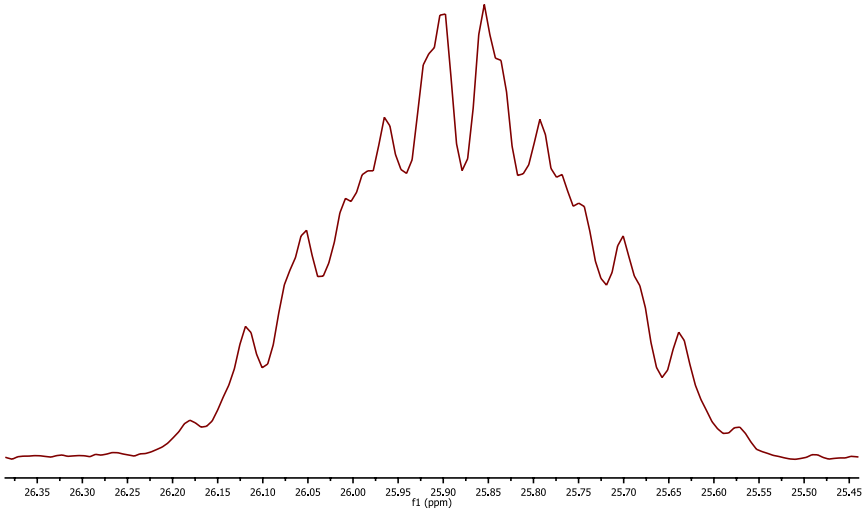

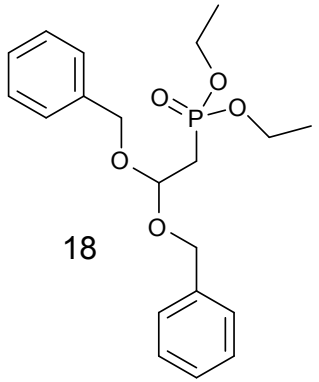

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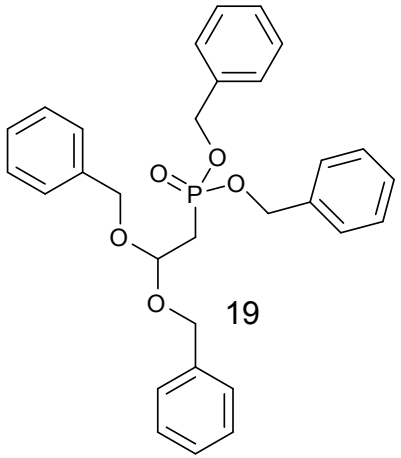

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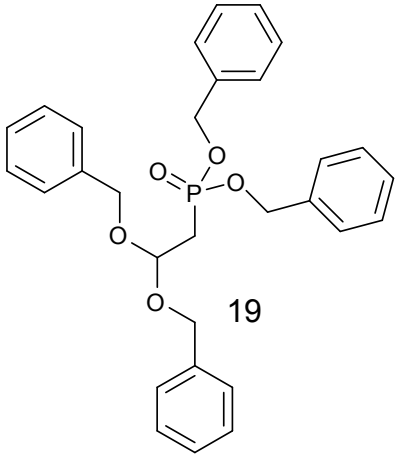

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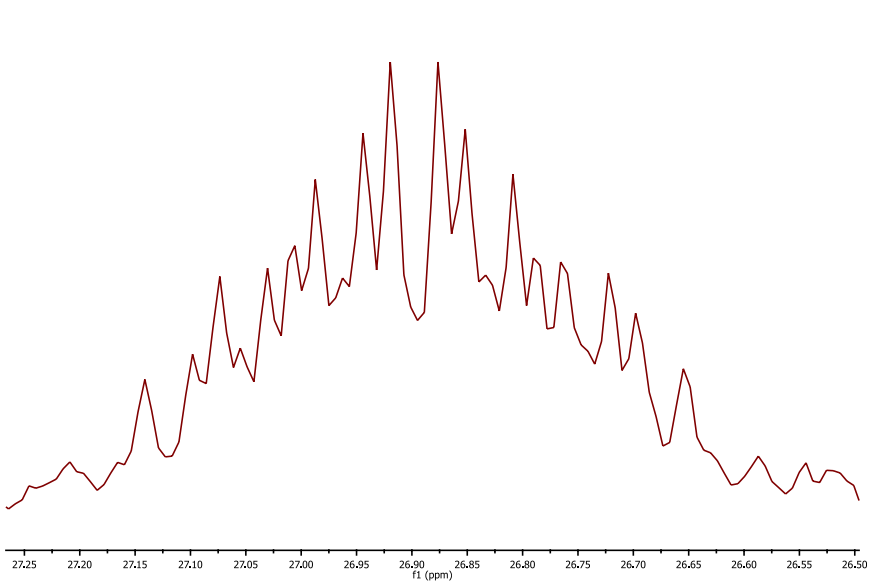

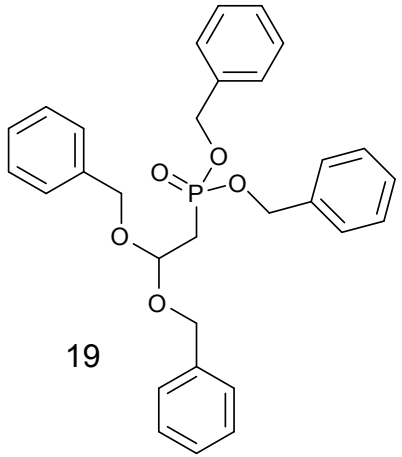

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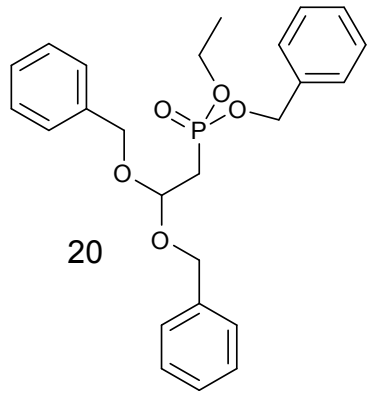

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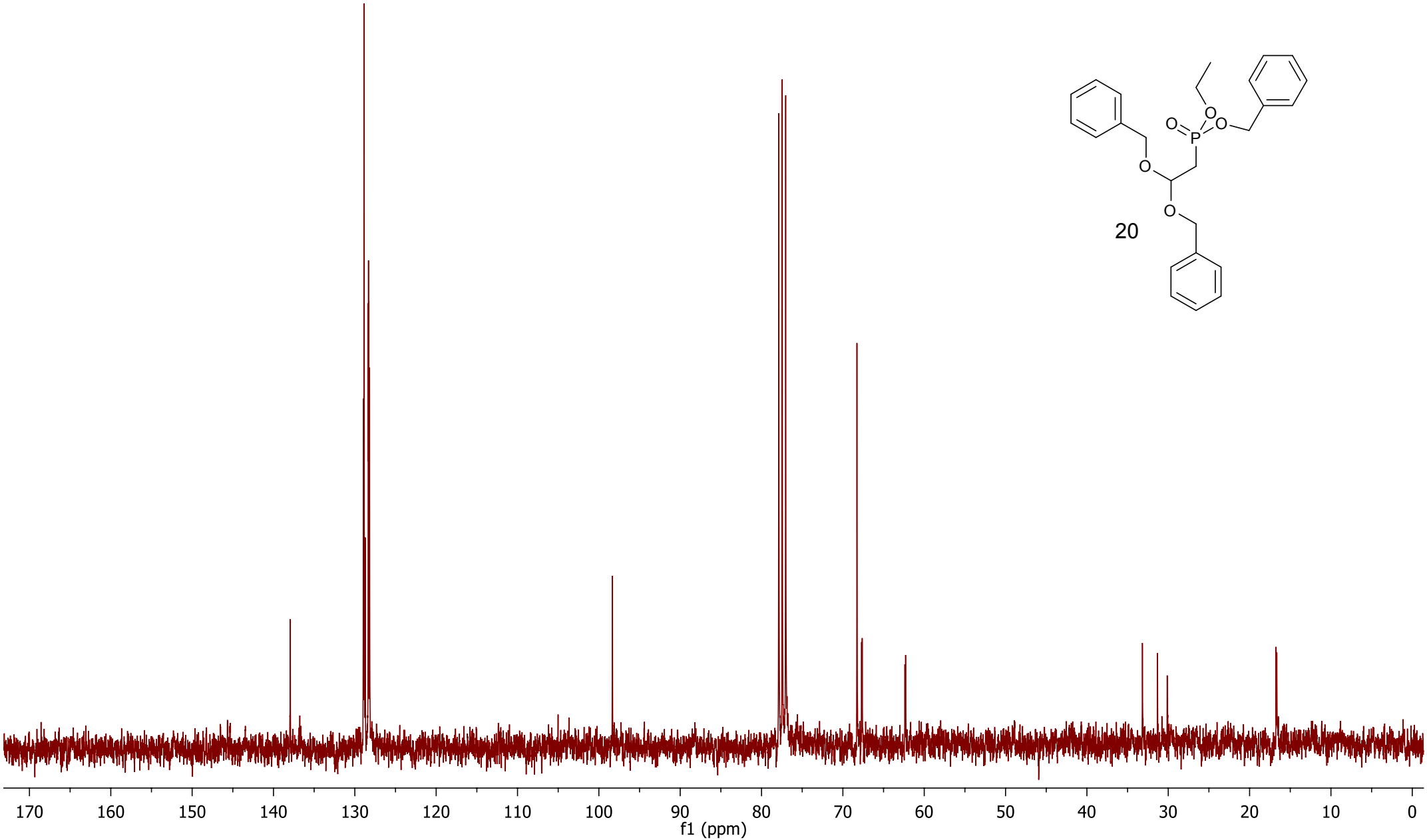

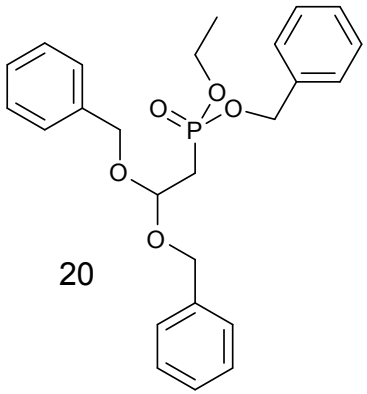

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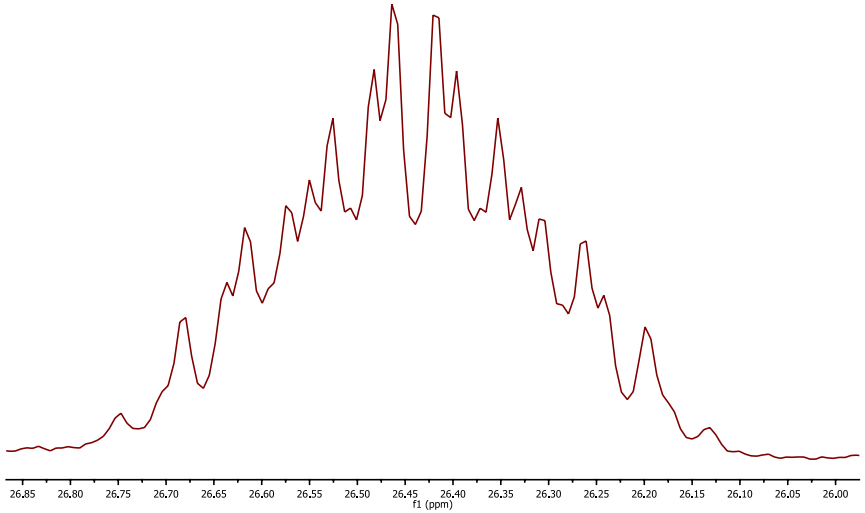

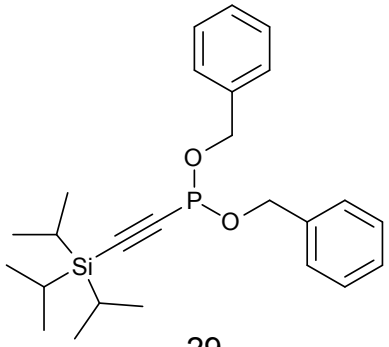

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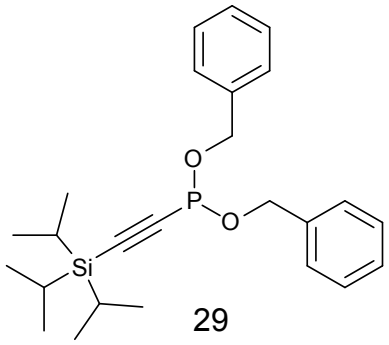

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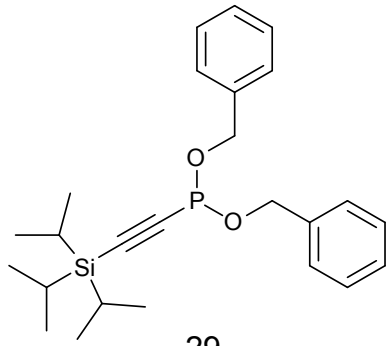

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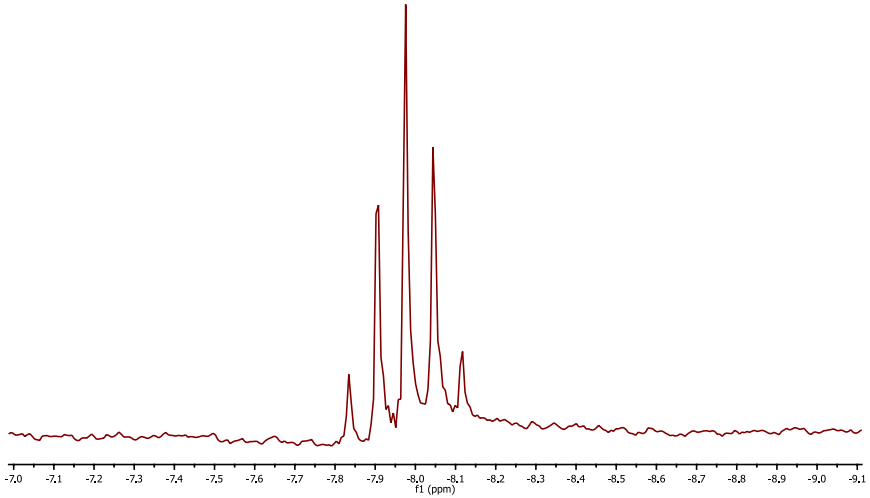

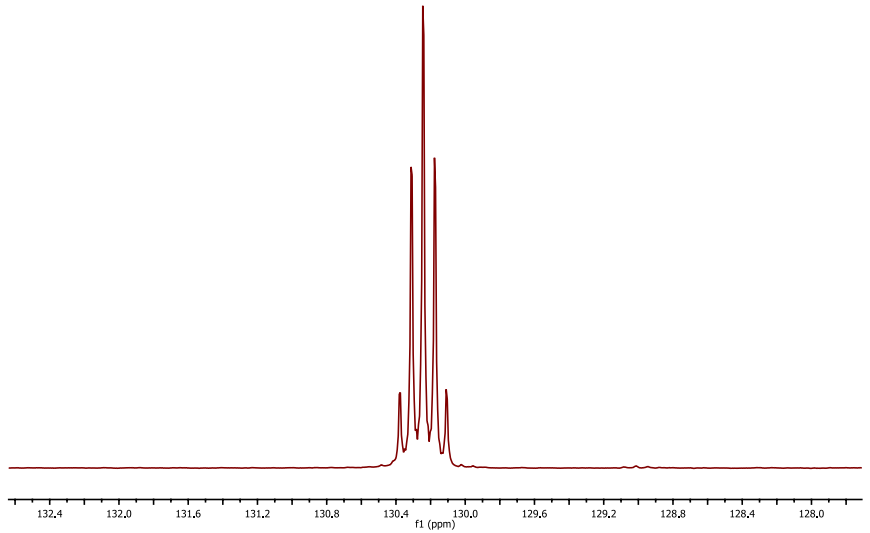

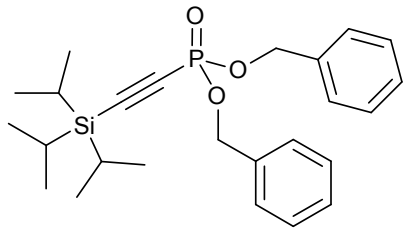

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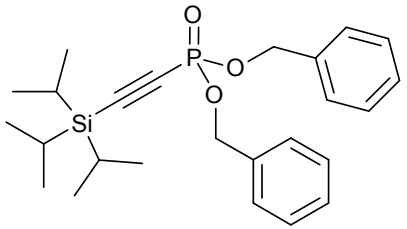

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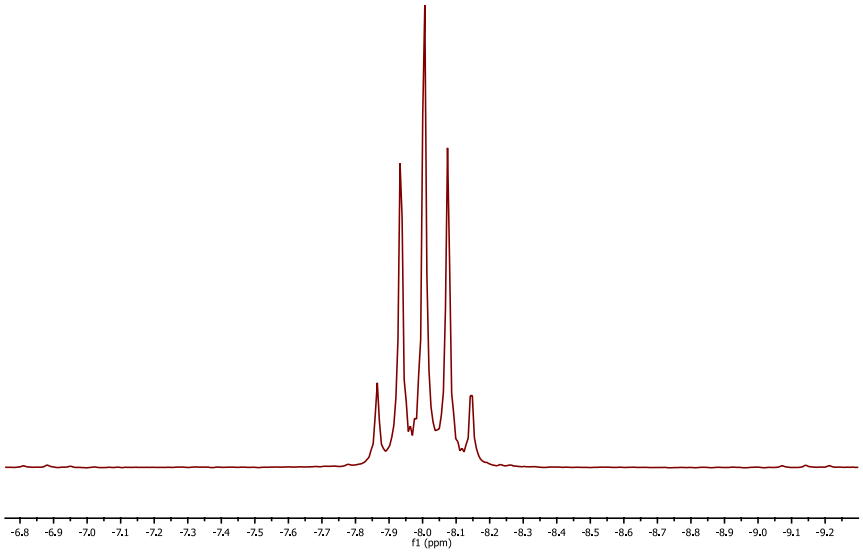

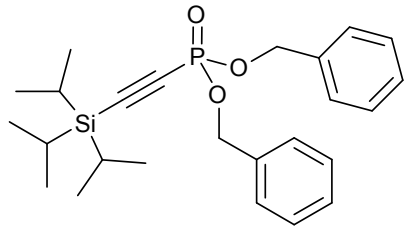

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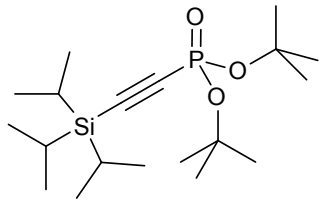

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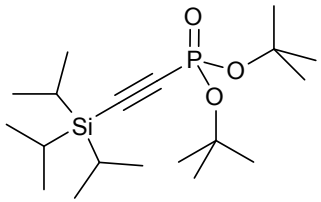

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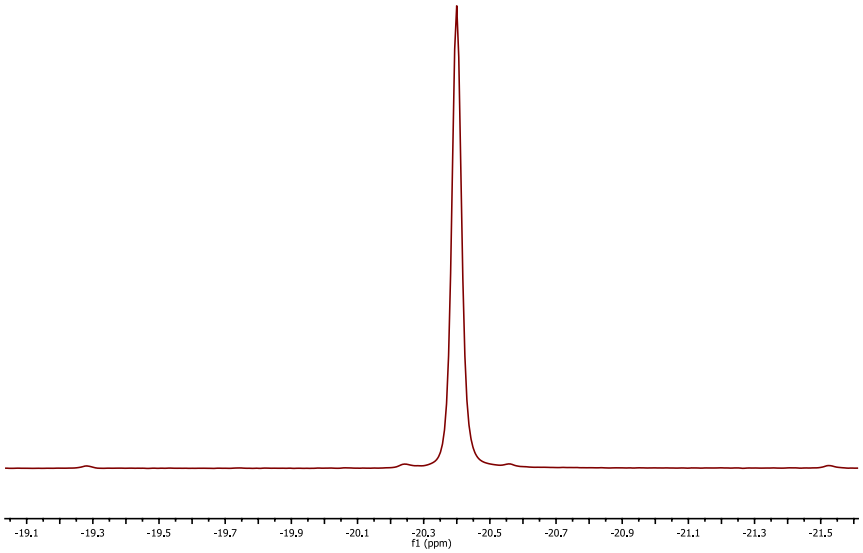

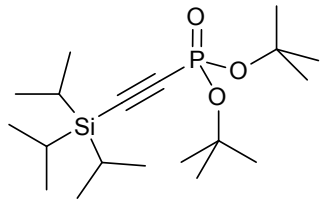

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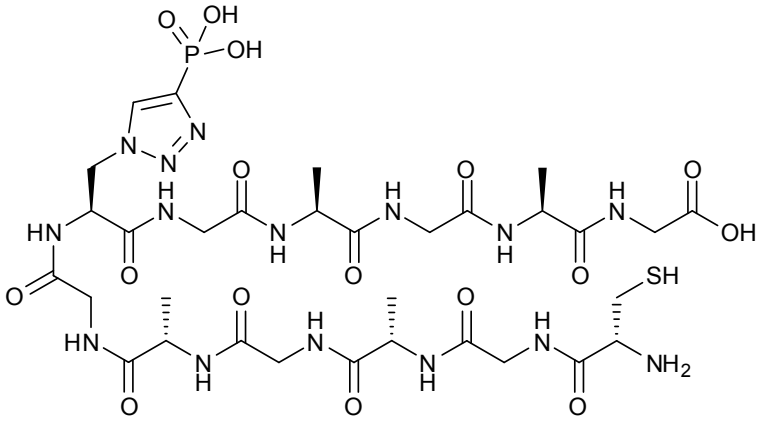

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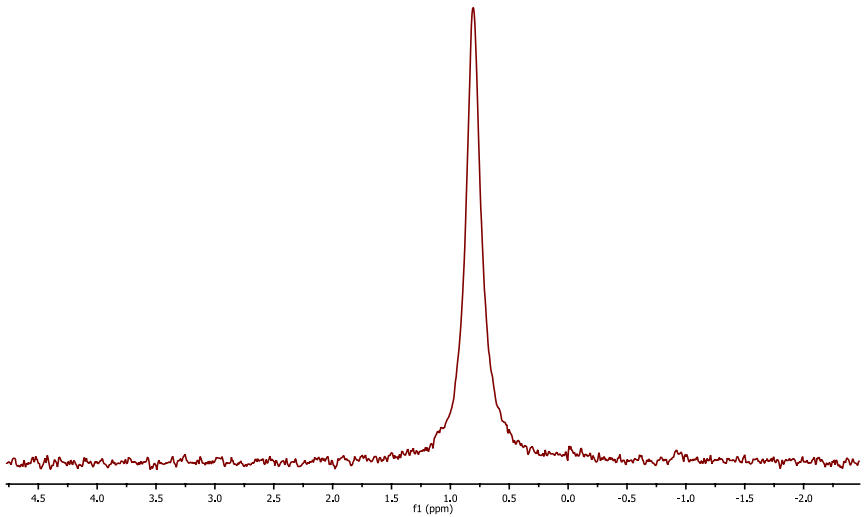

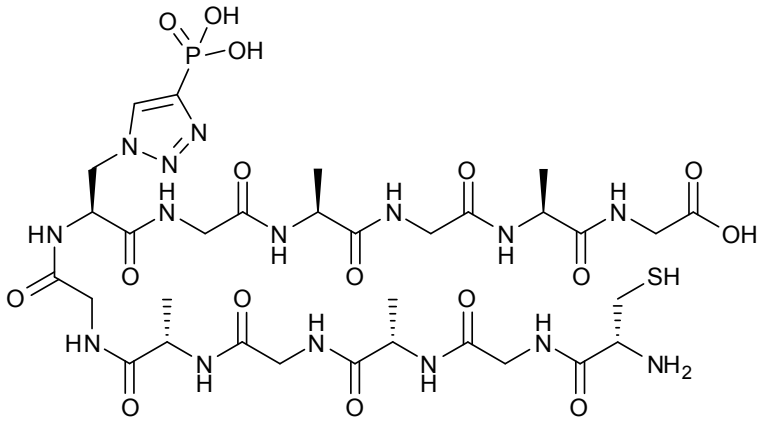

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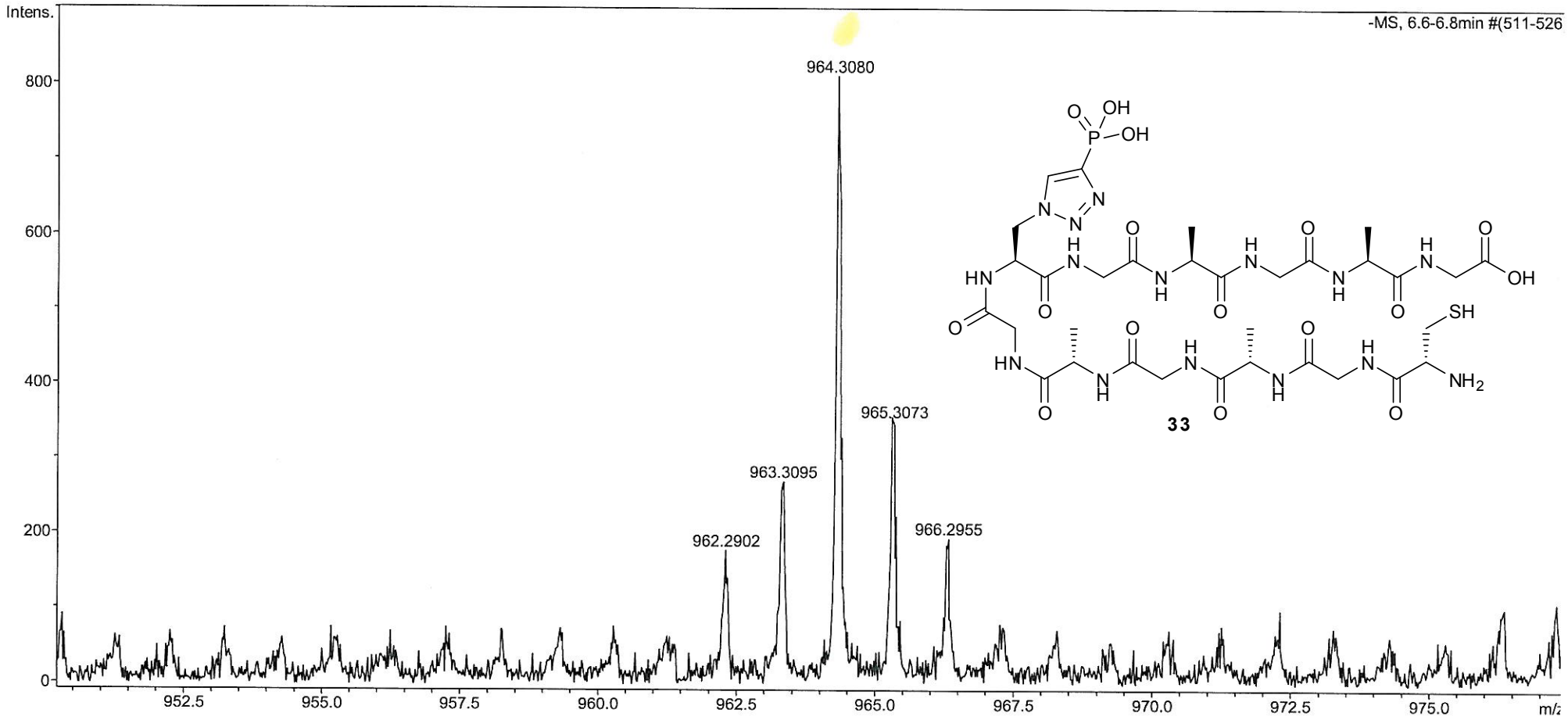
School of Chemistry Mass Spectrometry Service

Comment	TEM-PEP35	**Operator**	Tanya
Sample Name	115052	**Acquisition Date**	27/10/2011 11:00:22
Analysis Name	D:\Data\Octber2011\115052.d		
Method	Anneke 50-1000 syringe NEG.m		
Instrument	micrOTOF	**Source Type** ESI	**Ion Polarity** Negative

Scan Begin 50 m/z **Scan End** 1000 m/z



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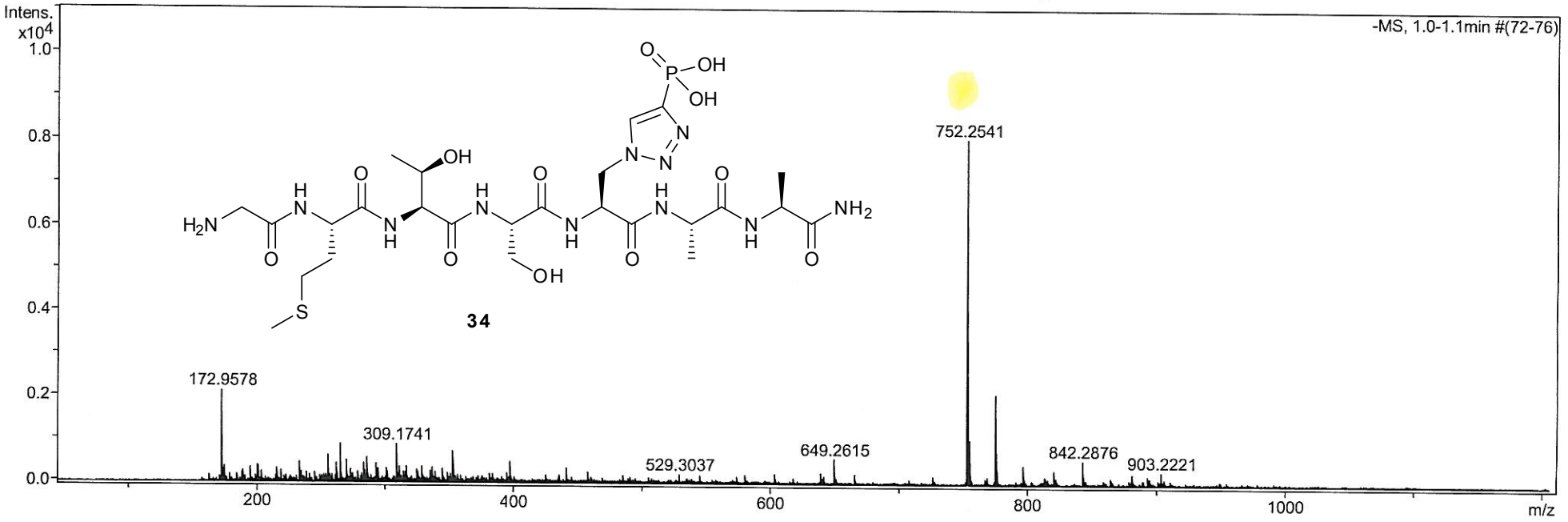
School of Chemistry Mass Spectrometry Service

Comment TEM-pep24/p
Sample Name 115569
Analysis Name D:\Data\March 2012\115569_1-C,6_01_15674.d
Method neg_lowmass_50-1200.m
Instrument micrOTOF **Source Type** ESI **Ion Polarity** Negative **Scan Begin** 50 m/z **Scan End** 1200 m/z

Operator Tanya
Acquisition Date 16/12/2011 15:01:37



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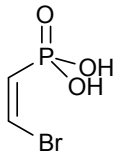
Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
752.2541	1	C 25 H 36 N 19 Na O 4 P S	61.76	752.2559	1.8	2.5	33.3	17.5	even	ok
	2	C 25 H 43 N 11 O 12 P S	55.77	752.2556	1.6	2.1	44.2	10.5	even	ok
	3	C 24 H 40 N 15 Na O 8 P S	100.00	752.2546	0.5	0.7	45.4	12.5	even	ok
	4	C 24 H 47 N 7 O 16 P S	82.10	752.2543	0.2	0.3	55.8	5.5	even	ok
	5	C 24 H 41 N 13 O 11 P S	0.00	750.2512	0.0	0.0	713.7	11.5	even	ok
	6	C 25 H 37 N 17 O 7 P S	0.00	750.2526	0.0	0.0	716.9	16.5	even	ok



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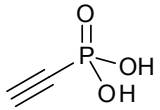

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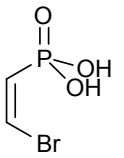

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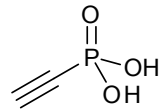

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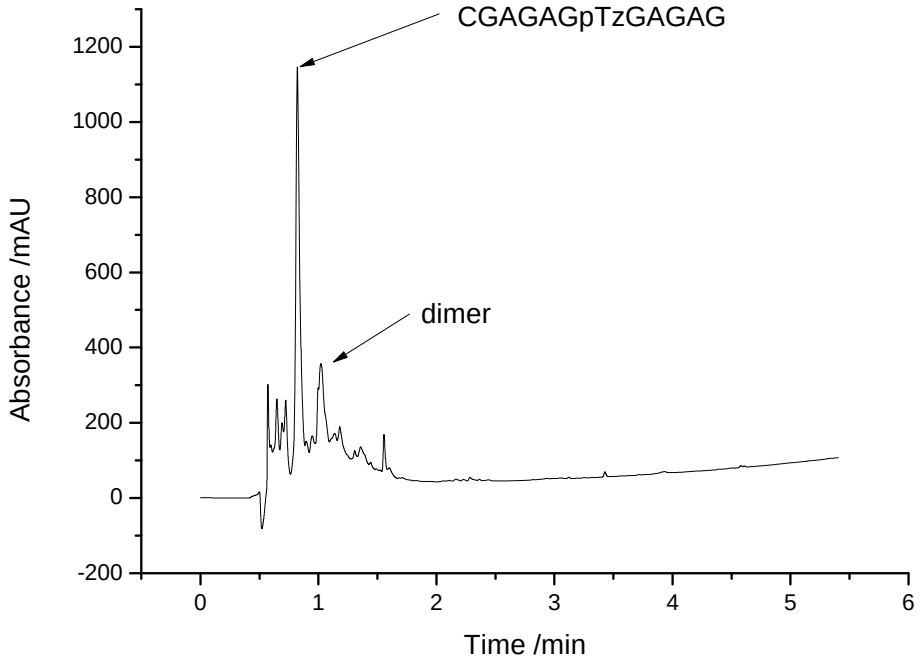
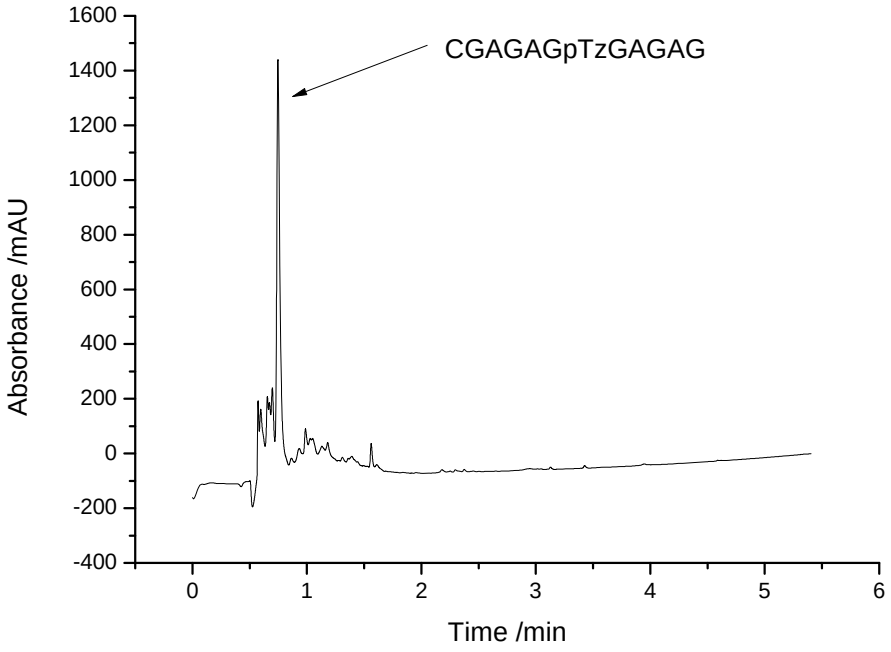
HPLC analysis of peptides

All peptides were analysed by HPLC on an Agilent 1290 infinity LC using an Ascentis® Express Peptide ES-C18 column (10 cm × 2. 1 mm, 2.7 μM particle size) with a flowrate of 0.5 ml min^{-1}. All solvents contain 0.1% TFA.

Crude peptide **33** (5-95% MeCN gradient)



Crude peptide **33** + *tris*(carboxyethyl)phosphine (5-95% MeCN gradient)



Peptide **34** after ion exchange purification (stepped MeCN gradient, 0-20% 1min, 20-50% 4 min)