General experimental information: Anhydrous grade solvents were purchased from Sigma-Aldrich (St Louis, MO) and used without further drying. Reagents purchased from commercial sources were used as supplied. Deblocking, oxidizing and capping mixtures, 2-OMe phosphoramidites and fluorescein phosphoramidite were purchased from Glen Research (Sterling, VA). Activator 42TM (5-(bis-3.5-trifluoromethylphenyl)-1H-tetrazole) was purchased from SAFC Proligo (St Louis, MO). RNA for thermal melting and biological experiments was purchased from IDT (Coralville, IA). Flash column chromatography was performed using 230 x 400 mesh silica gel (Sorbent Technologies, Atlanta, GA) and thin layer chromatography (tlc) was performed on aluminum-backed silica 60 F254 plates (EMD Biosciences, Gibbstown, NJ). NMR spectra were acquired on a BioSpin 300 MHz spectrometer (Bruker, Billerica, MA). Mass spectra were obtained using a Pulsar QStar Time of Flight spectrometer (AB Sciex, Foster City, CA), equipped with a syringe pump. Phosphinoamidites were analyzed in ESI+ mode in methanol solution at 5.2 kV. Oligoribonucleotides were analyzed in ESI- mode in 1:1 acetonitrile:water at 3.3 kV. Analytical RP-HPLC was performed on an Agilent 1100 series HPLC on a Hypersil ODS column, 4.0 x 250 mm, 5 µm particle size, (Agilent Technologies, Santa Clara, CA) with 0.05M triethylammonium bicarbonate (mobile phase A) and acetonitrile (mobile phase B) at a flow rate of 1.5 mL/min and the following gradient: 0 - 30 minutes, 0-50 % B, 30 – 35 minutes, 50 – 100 % B, 35 – 39 minutes, 100% B. Preparative RP-HPLC was performed on an Agilent 1100 series HPLC on a Zorbax SB-C18 column, 9.4 x 250 mm, 5 µm particle size, (Agilent Technologies, Santa Clara, CA) with the same mobile phases and flow rate and the following gradient: 0 - 50 minutes, 0-30 % B, 50 – 60 minutes, 30 – 50 % B, 60 – 65 minutes, 50 – 100% B. Duplex melting experiments were performed on a Cary 100 Bio UV-visible spectrophotometer (Varian, Santa Clara, CA). The solutions were prepared by dissolving PACE/thioPACE 2'-OMe ORN and complementary RNA in a solution of 0.1 M NaCl/0.01 M Na2HPO4 to a concentration of 1.0 µM of duplex. The duplex solution was placed in a 1 cm quartz cuvette and annealed by heating to 95 °C for 3 minutes followed by cooling to room temperature. Absorbance was then measured at 260 nm over a range of 25 – 95 °C at a heating rate of 1 °C per minute. Melting temperature (Tm) was calculated using the derivative method in the Cary UV Thermal software application.

For biological experiments, unless otherwise specified the fluorescence ratios or cell numbers obtained were normalised to equivalent negative control cells treated with transfection media in the absence of oligonucleotides. The results are presented as average values with standard deviations. Data processing was carried out using Microsoft Excel and GraphPad Prism (version 5.0d).

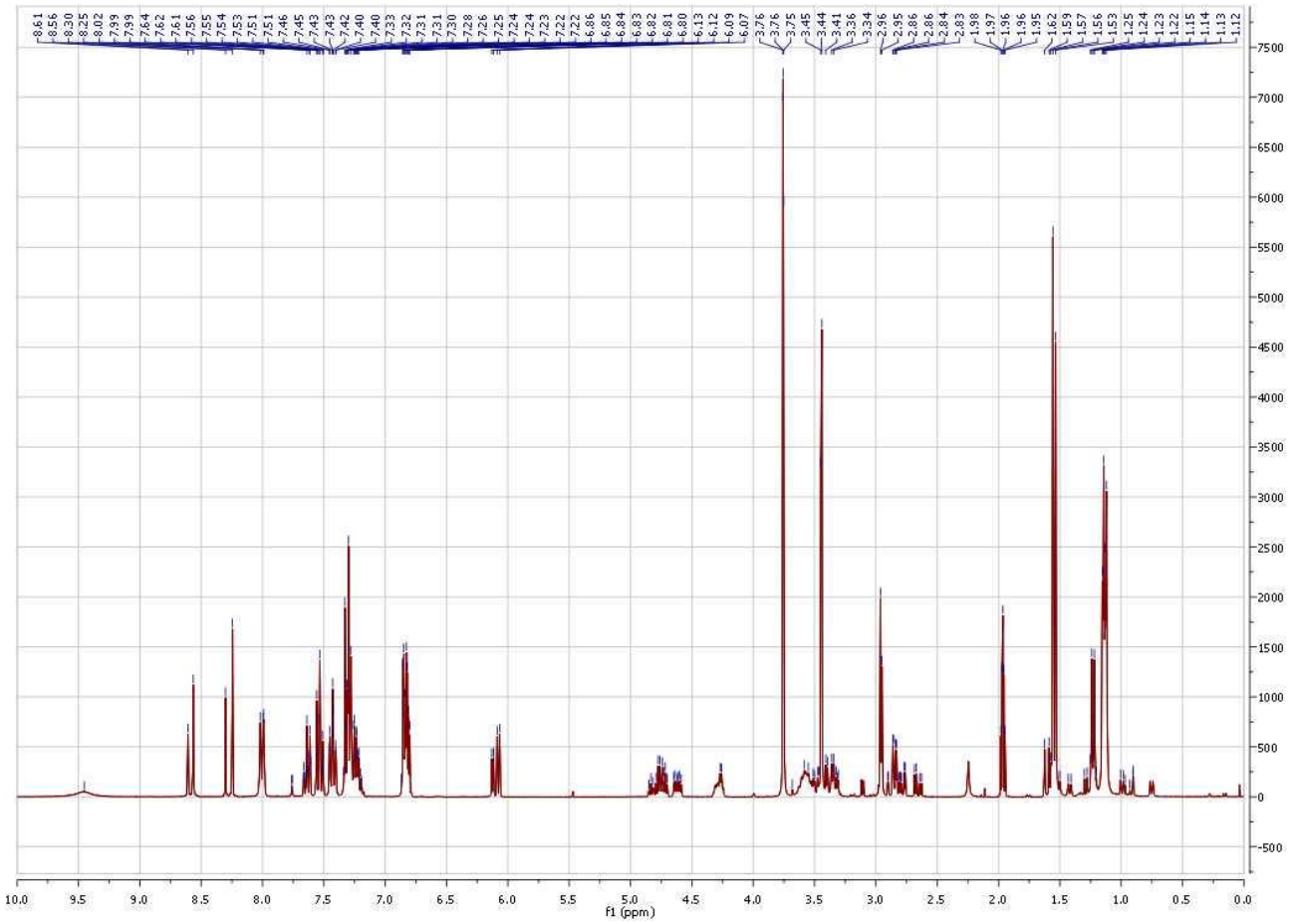

Figure S1 ^{1}H NMR (300 MHz, $CDCl_3$) of **2a**

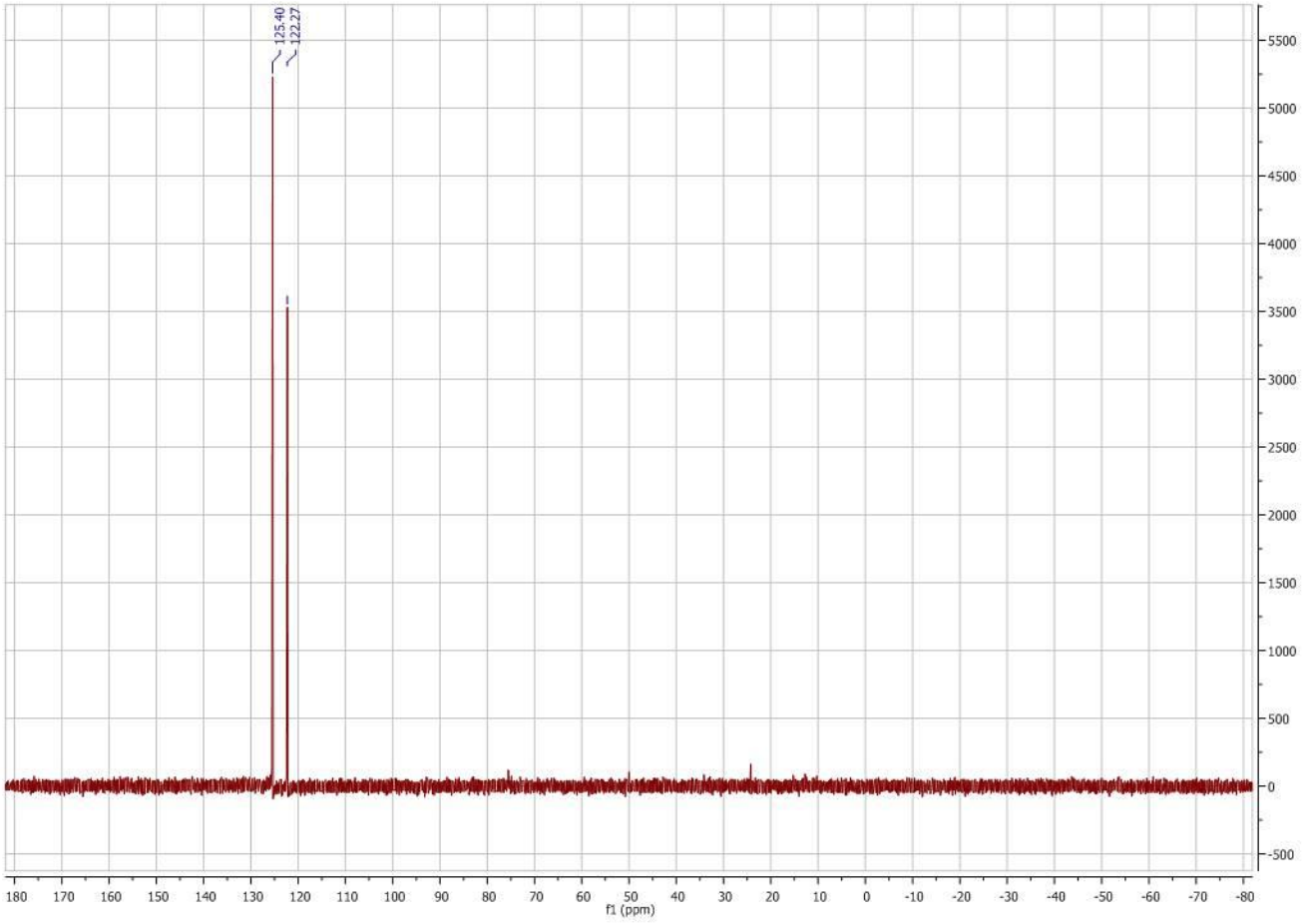

Figure S2 ^{31}P NMR (121 MHz, $CDCl_3$) of **2a**

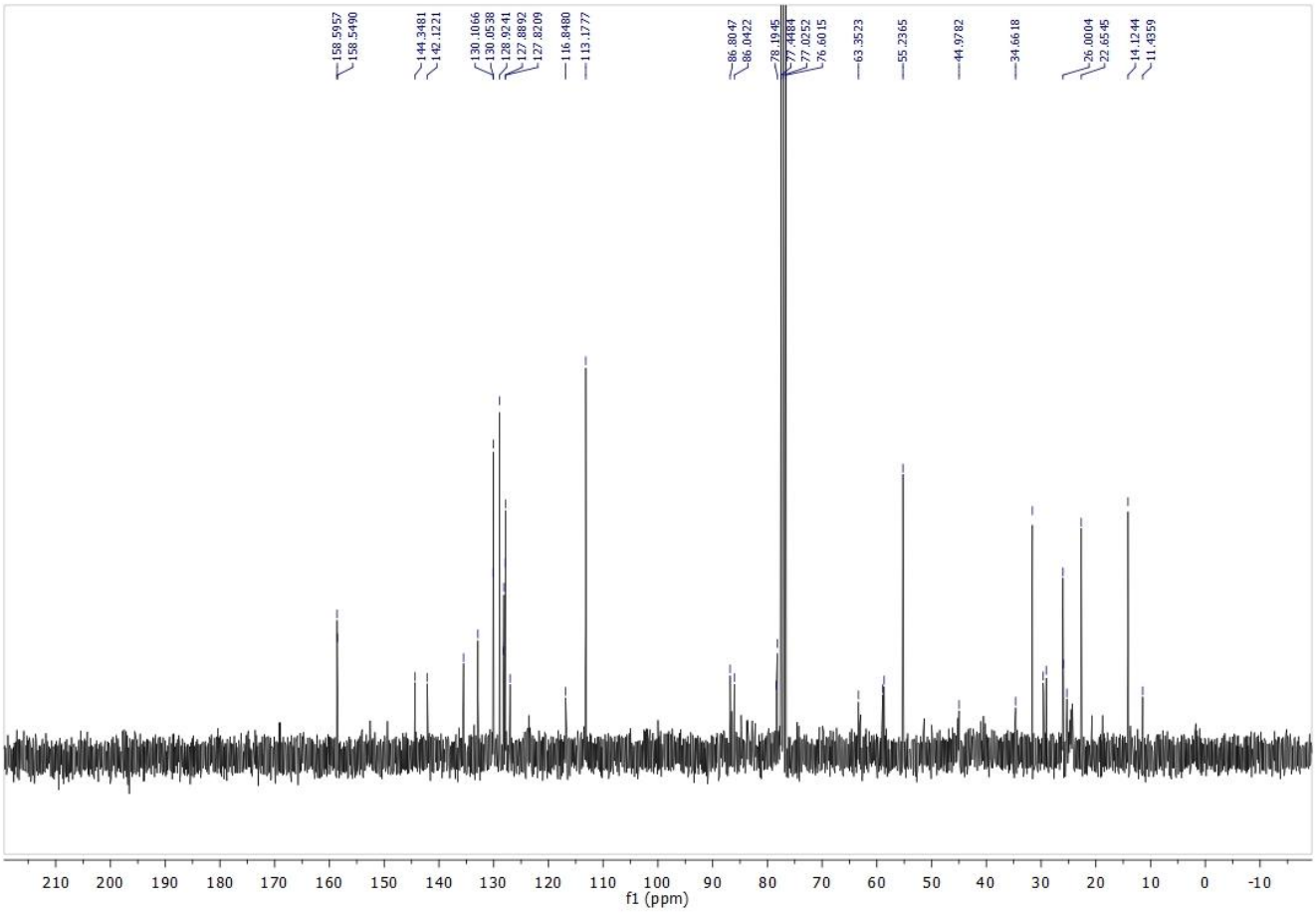

Figure S3 ^{13}C NMR (100 MHz, $CDCl_3$) of **2a**

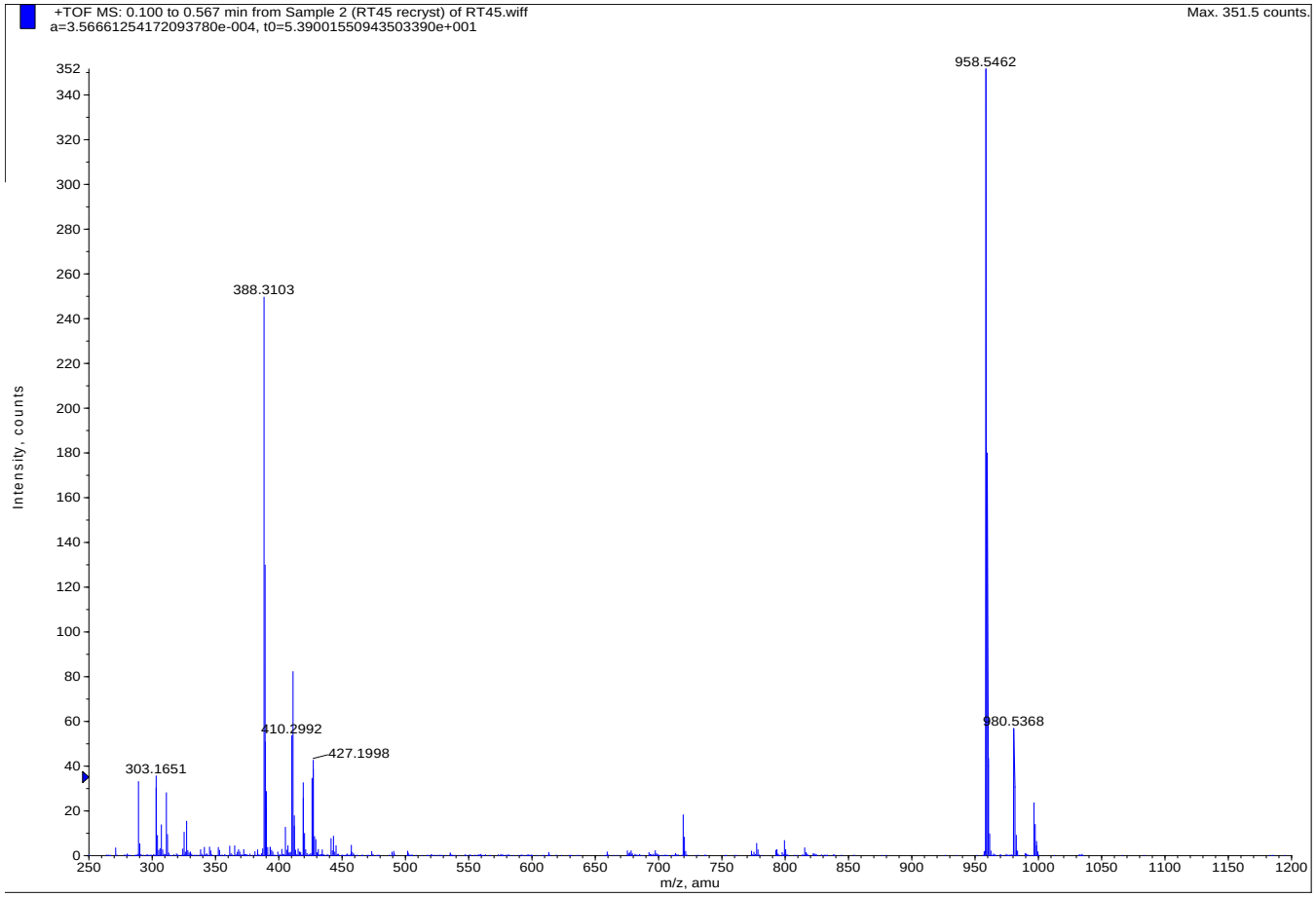

Figure S4 ESI$^+$ mass spectrum of **2a**

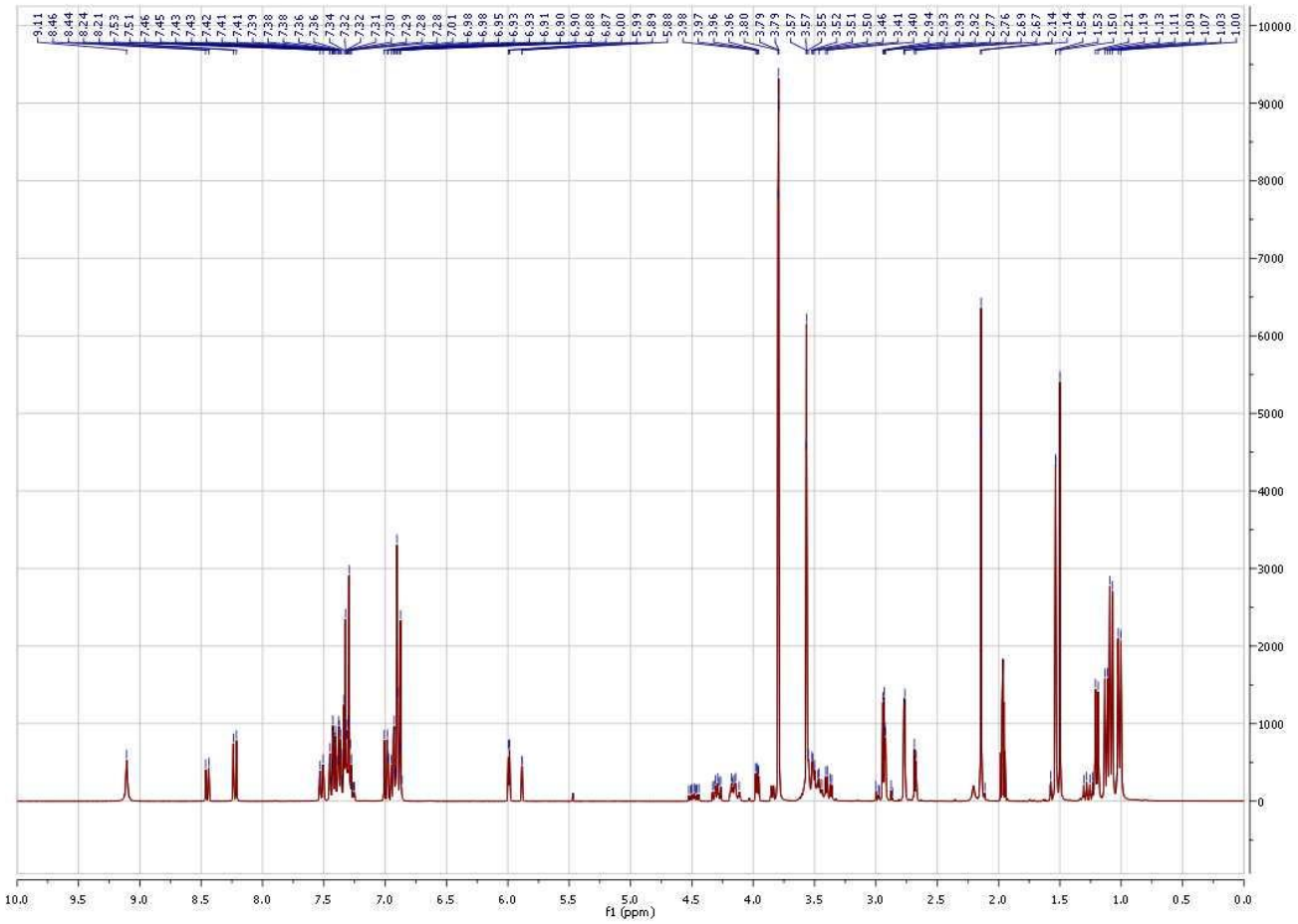

Figure S5 ^{1}H NMR (300 MHz, $CDCl_3$) of **2b**

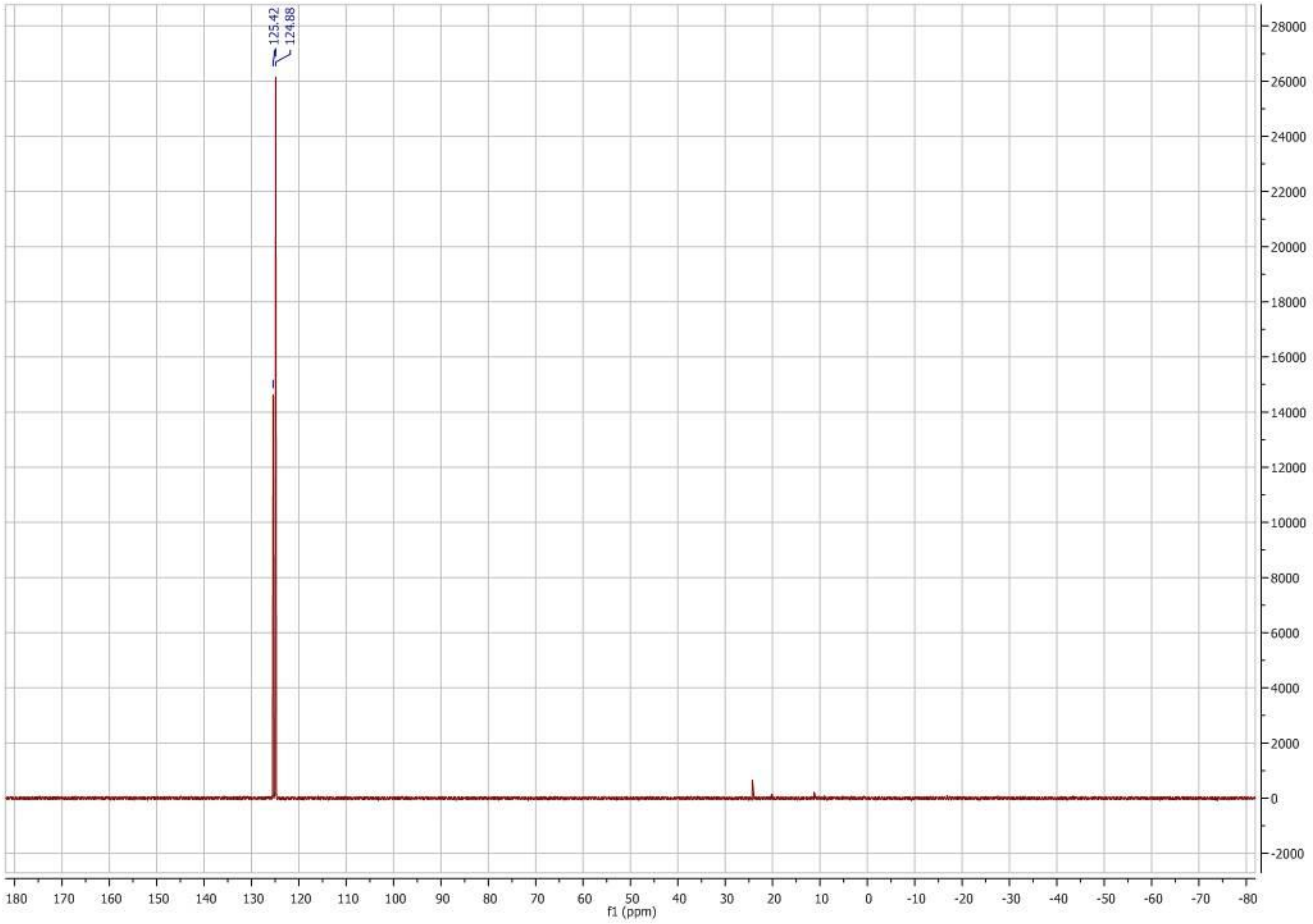

Figure S6 ^{31}P NMR (121 MHz, $CDCl_3$) of **2b**

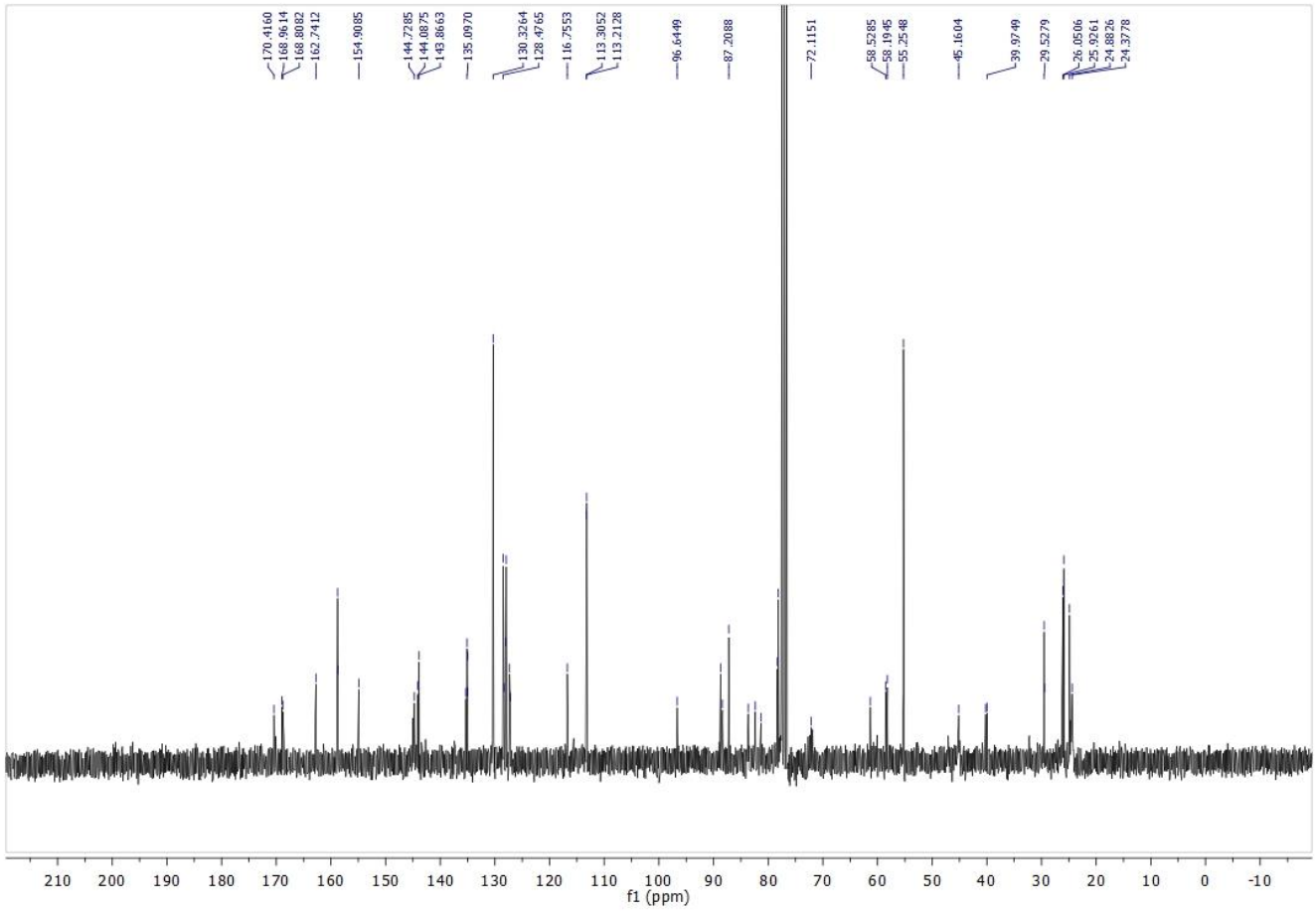

Figure S7 ^{13}C NMR (100 MHz, $CDCl_3$) of **2b**

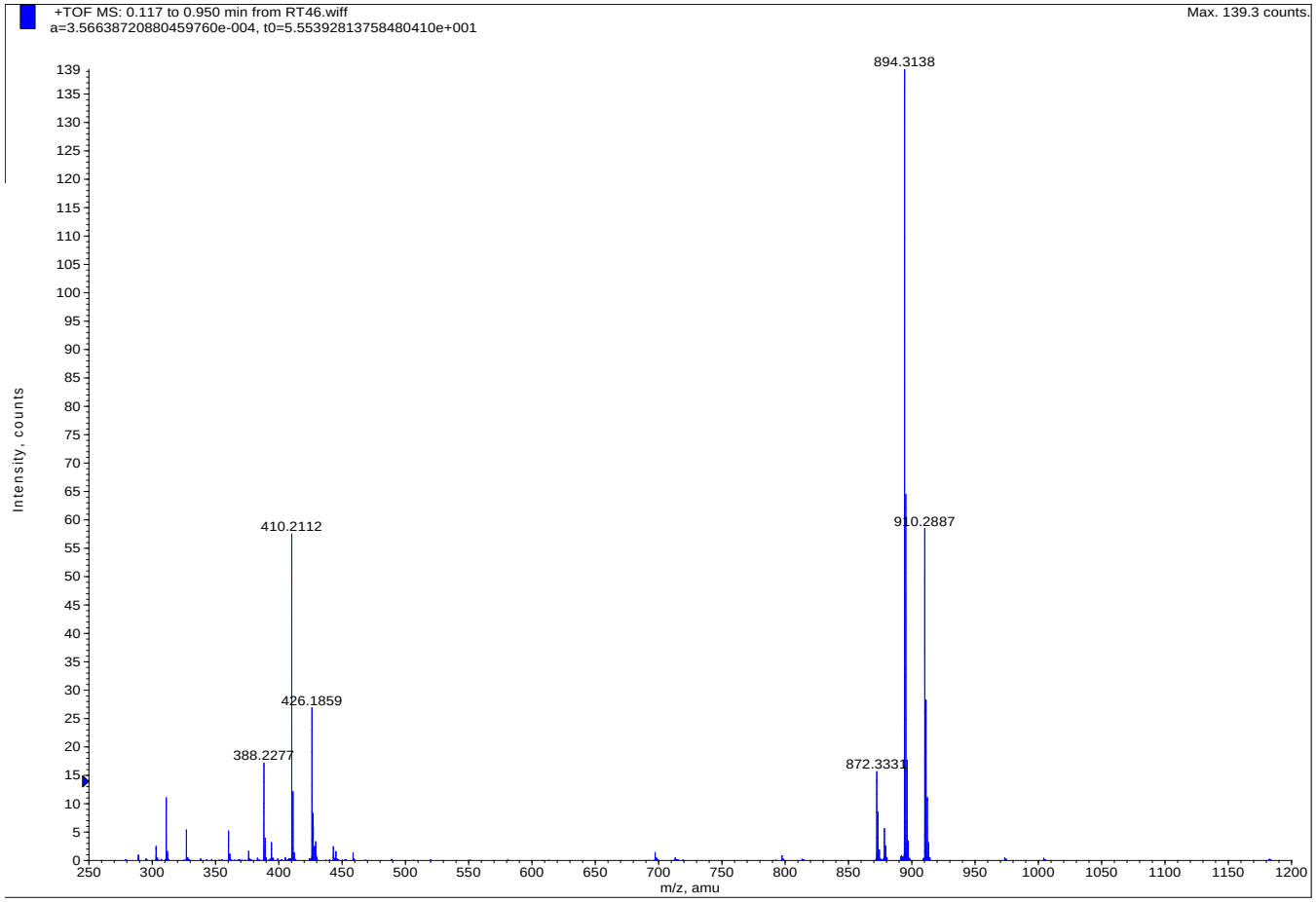

Figure S8 ESI$^+$ mass spectrum of **2b**

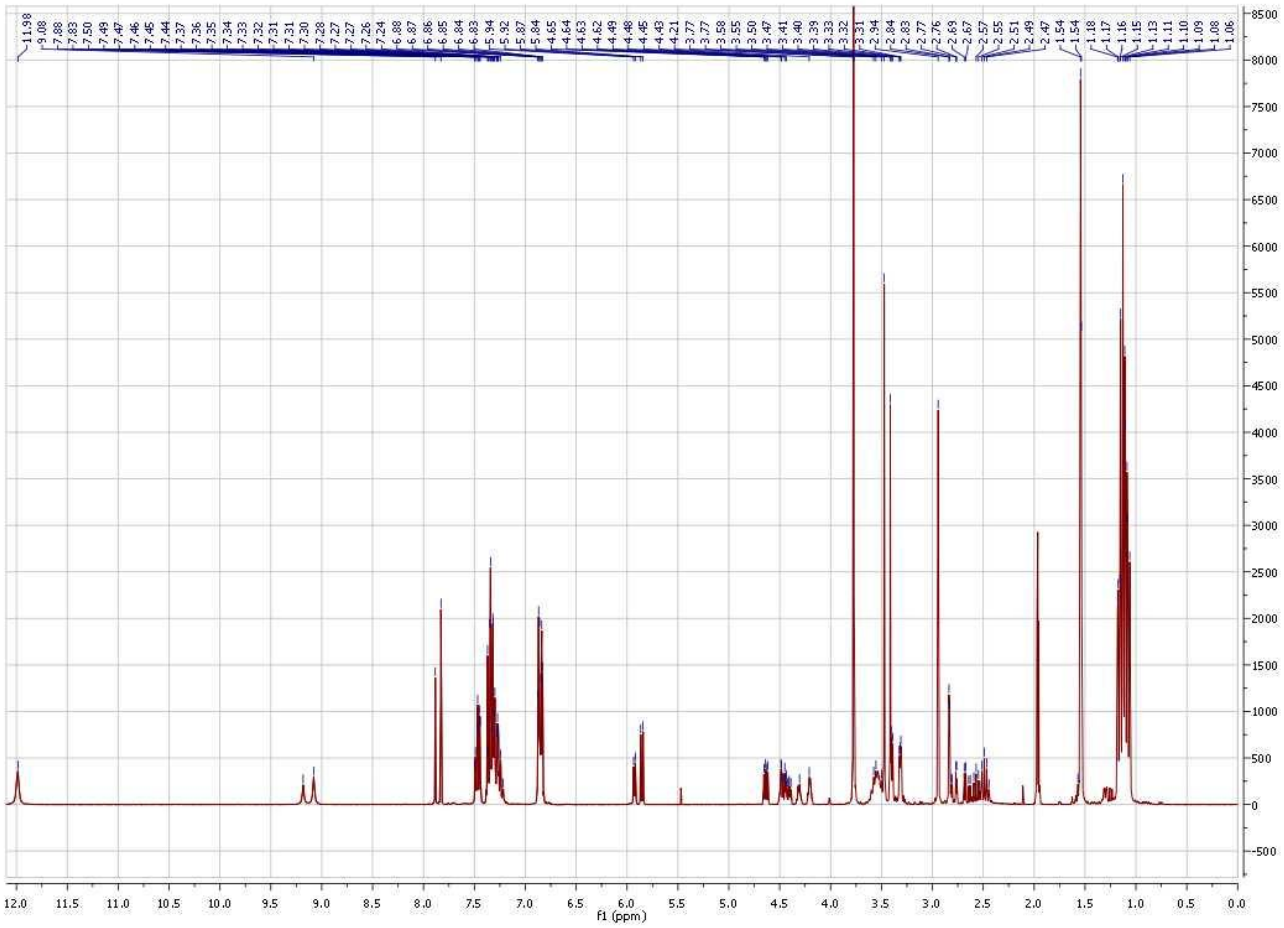

Figure S9 ^{1}H NMR (300 MHz, $CDCl_3$) of **2c**

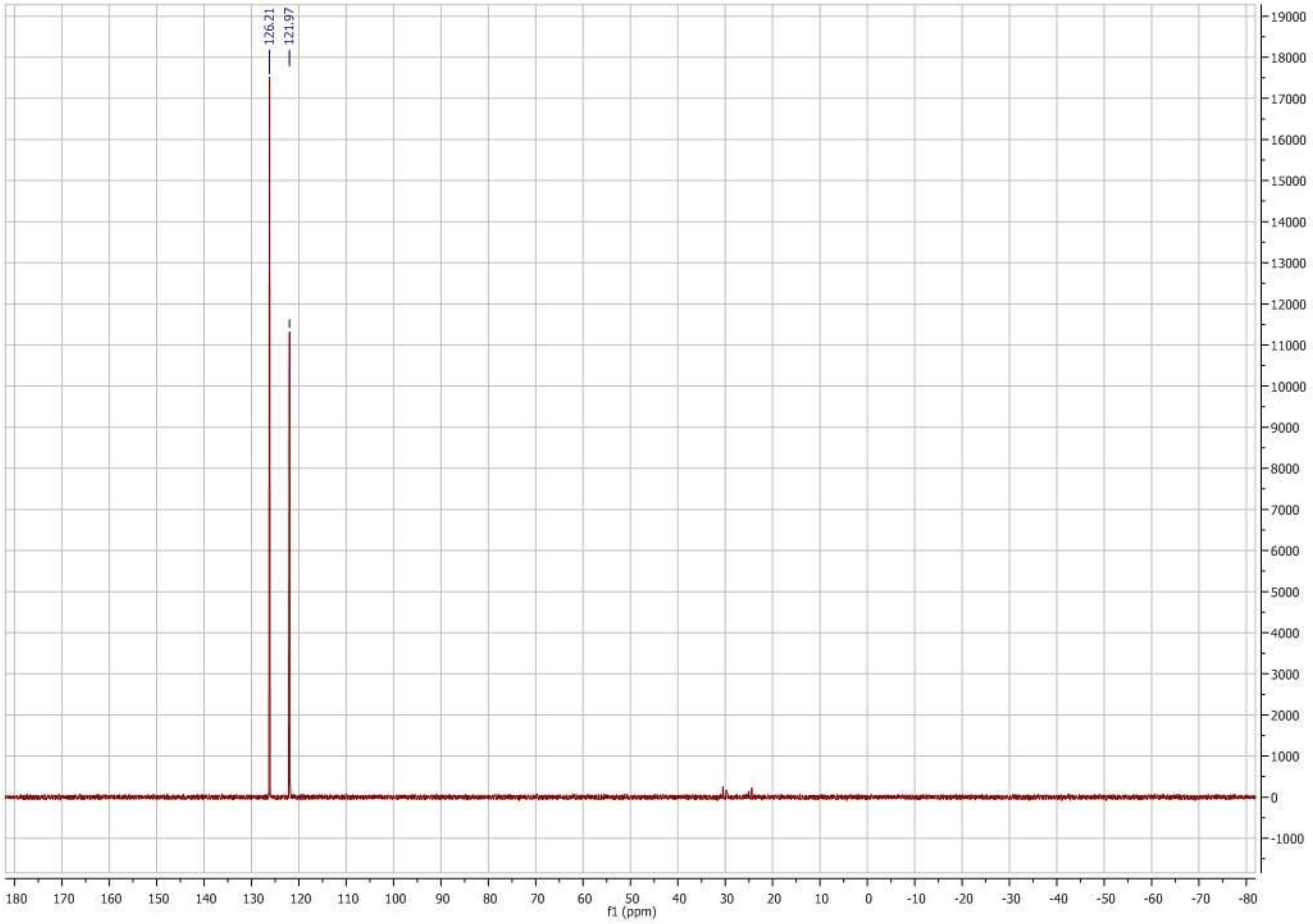

Figure S10 ^{31}P NMR (121 MHz, $CDCl_3$) of **2c**

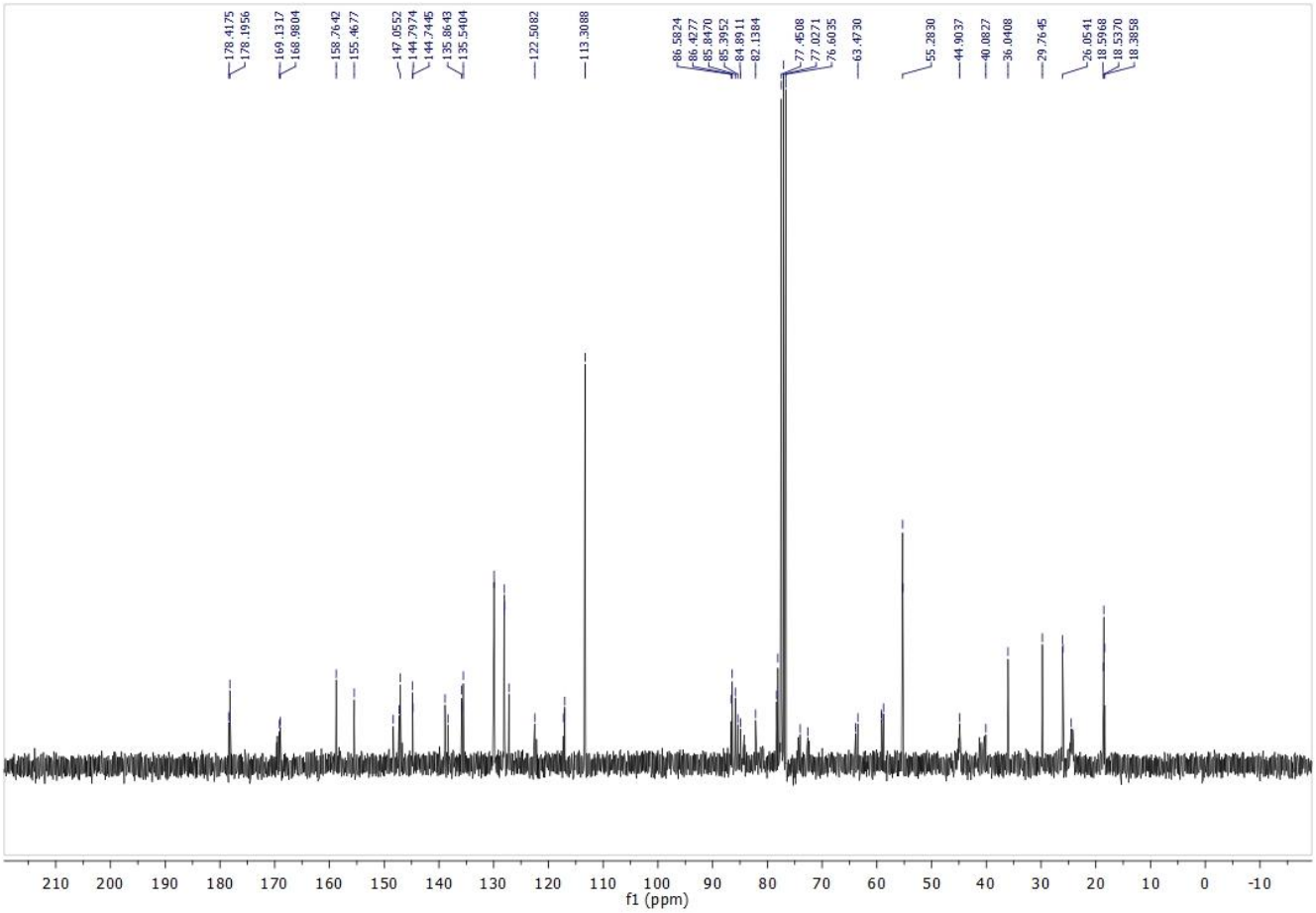

Figure S11 ^{13}C NMR (100 MHz, $CDCl_3$) of **2c**

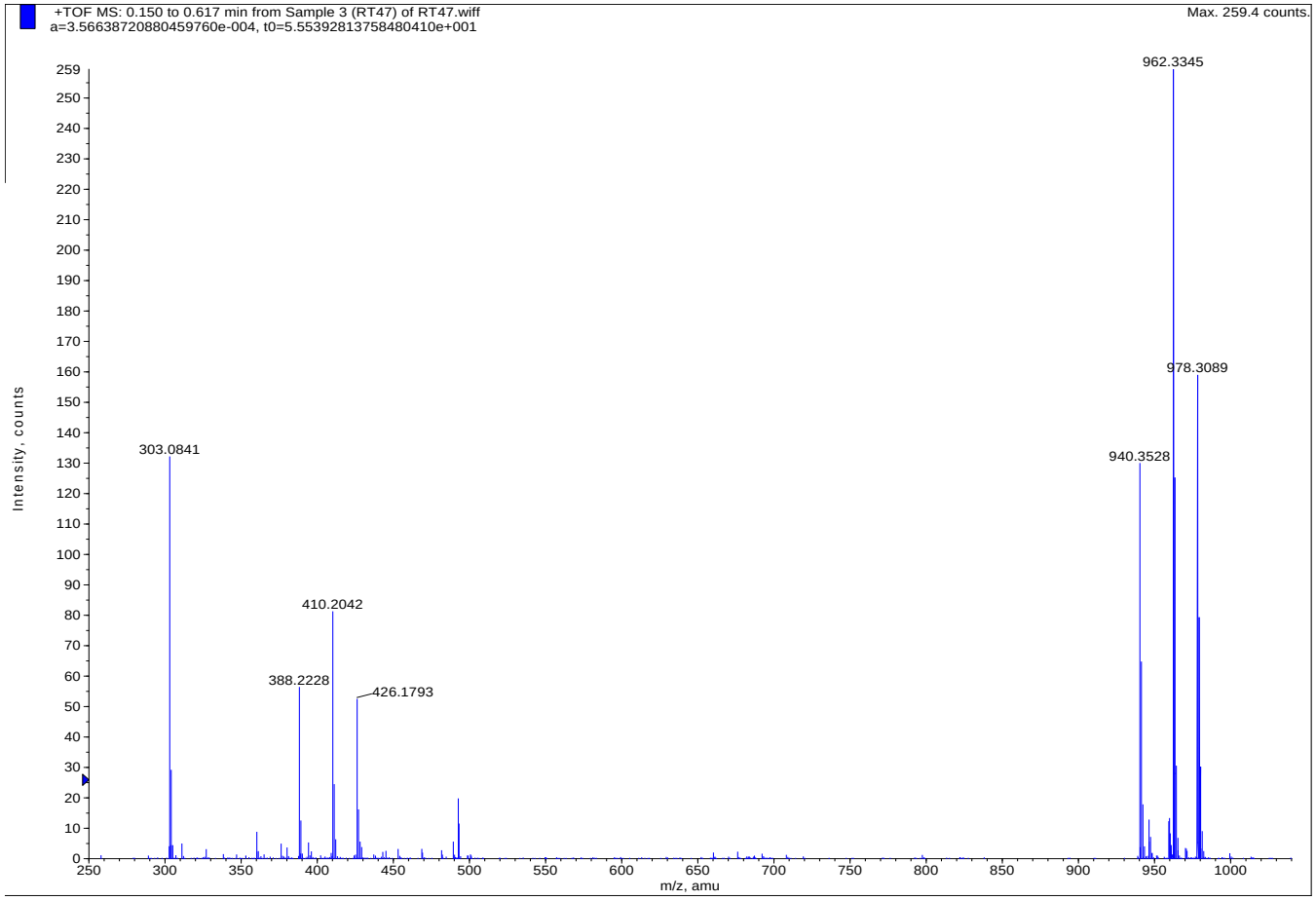

Figure S12 ESI$^+$ mass spectrum of **2c**

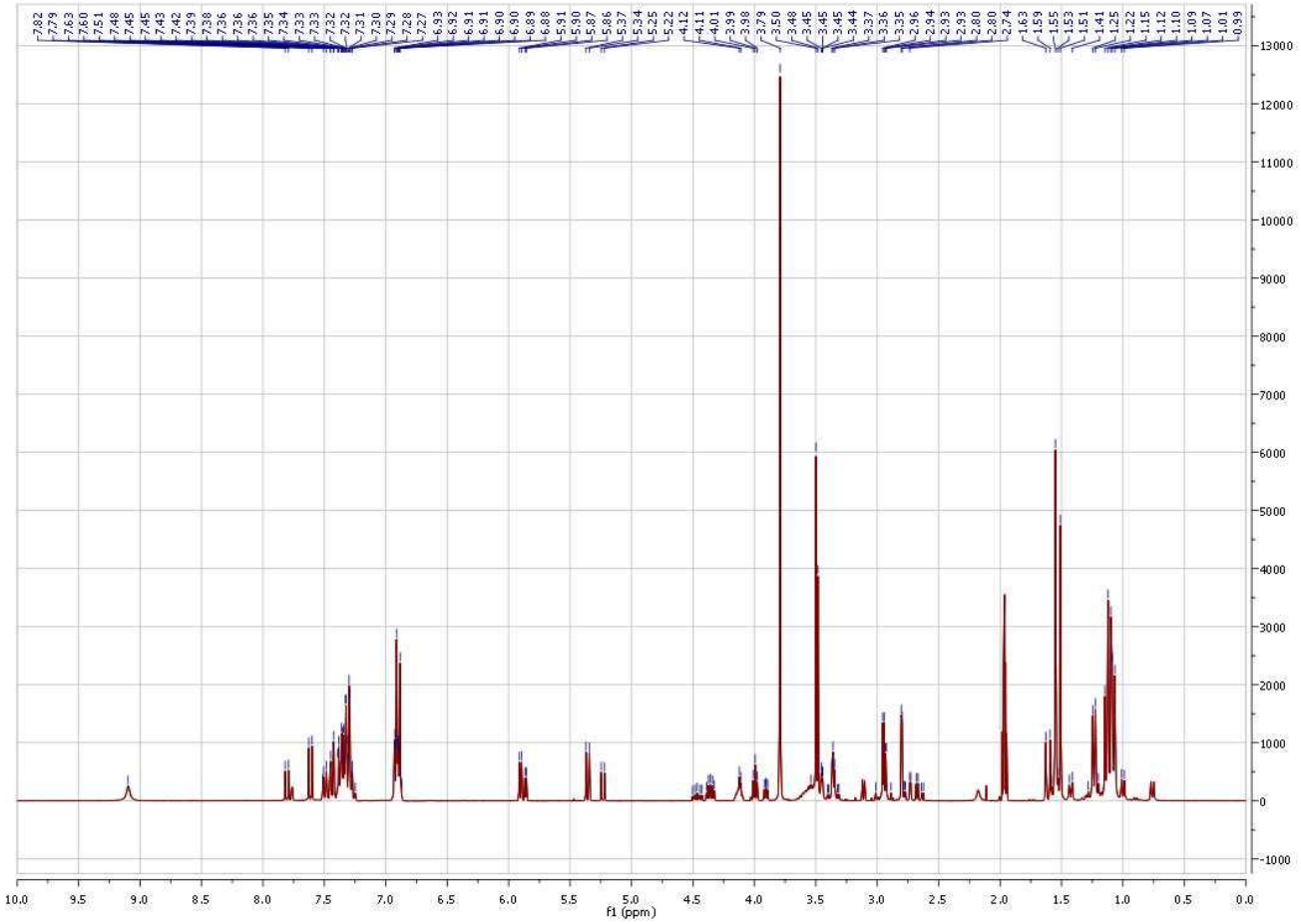

Figure S13 ^{1}H NMR (300 MHz, $CDCl_3$) of **2c**

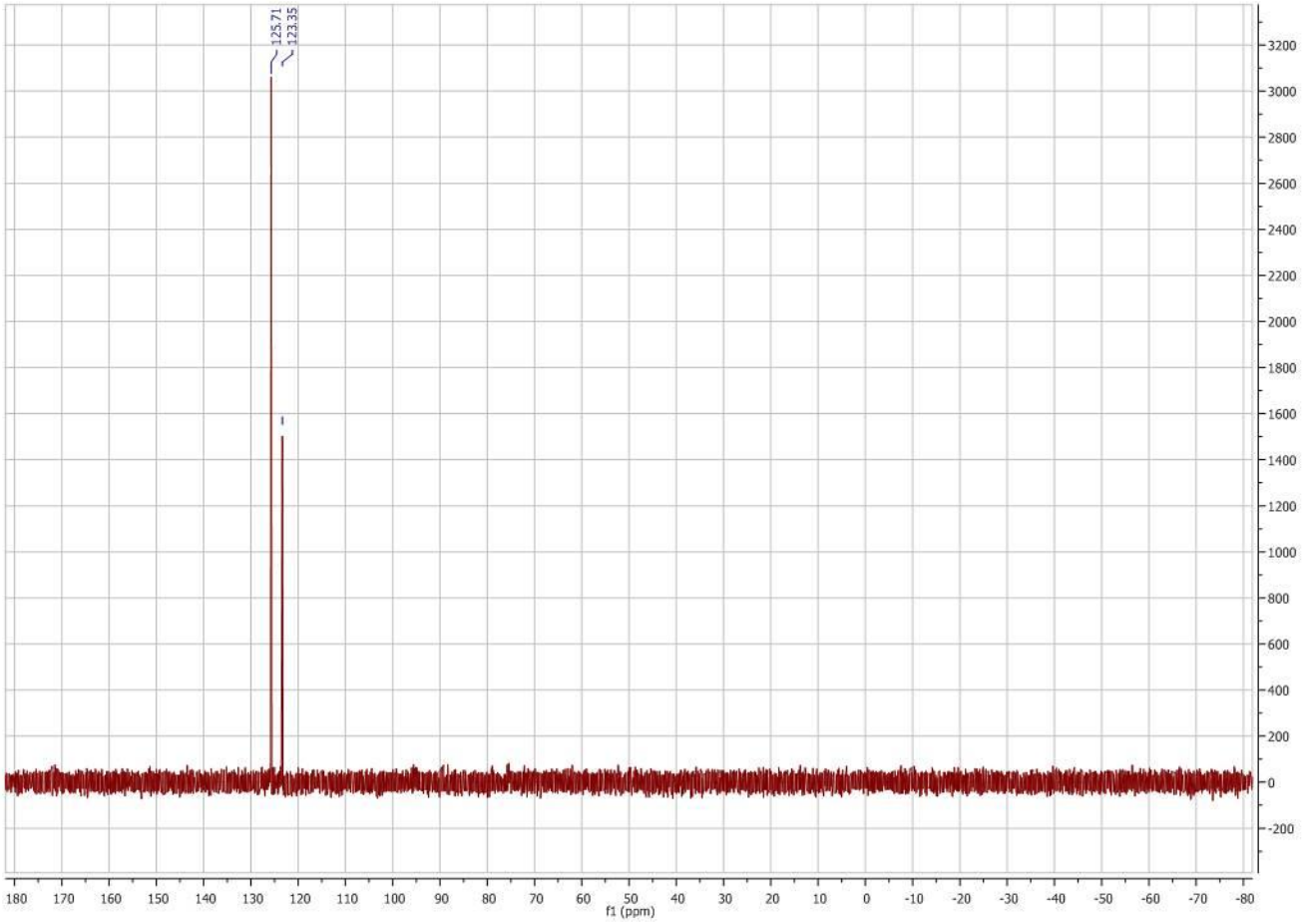

Figure S14 ^{31}P NMR (121 MHz, $CDCl_3$) of **2d**

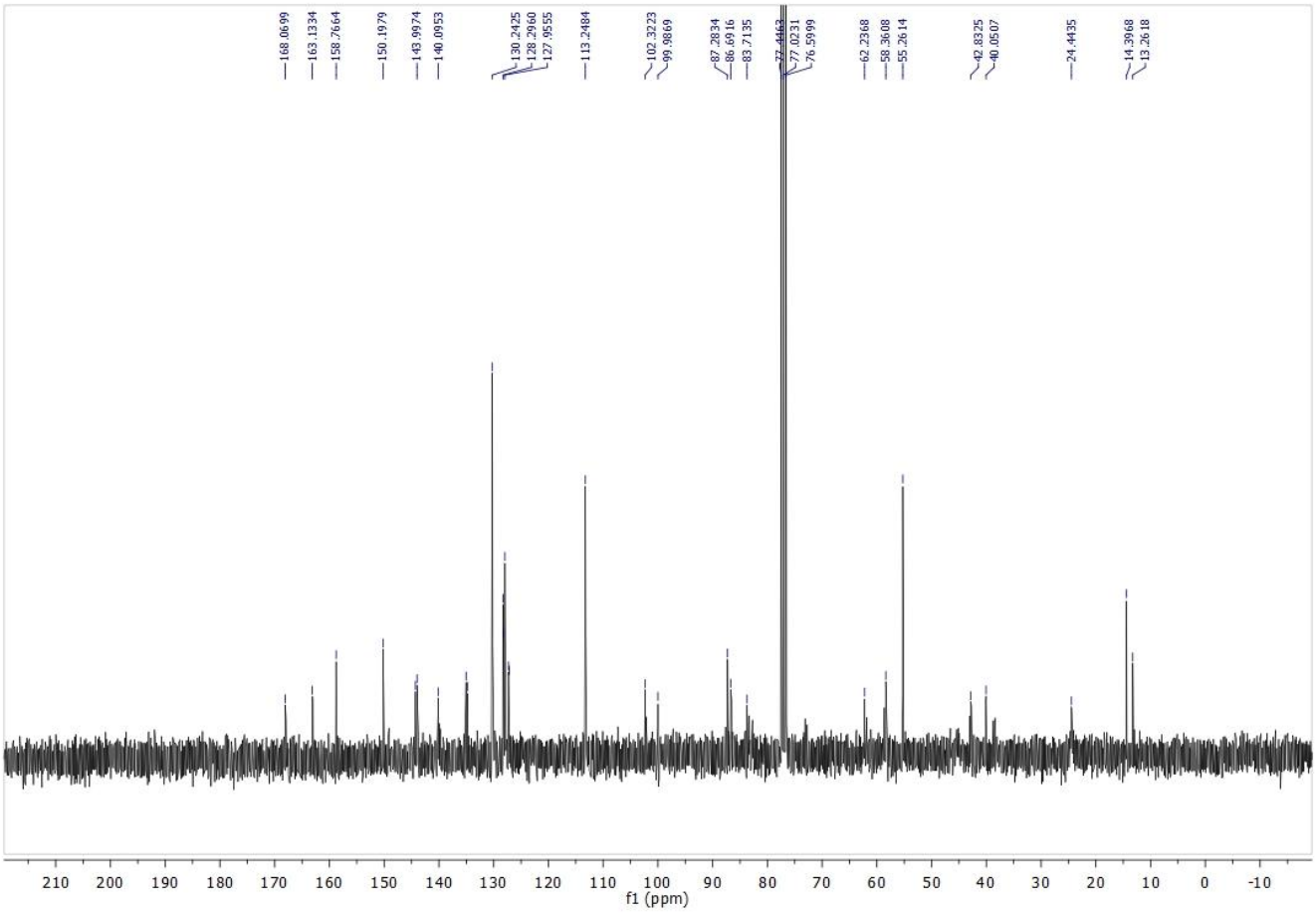

Figure S15 ^{13}C NMR (100 MHz, $CDCl_3$) of **2d**

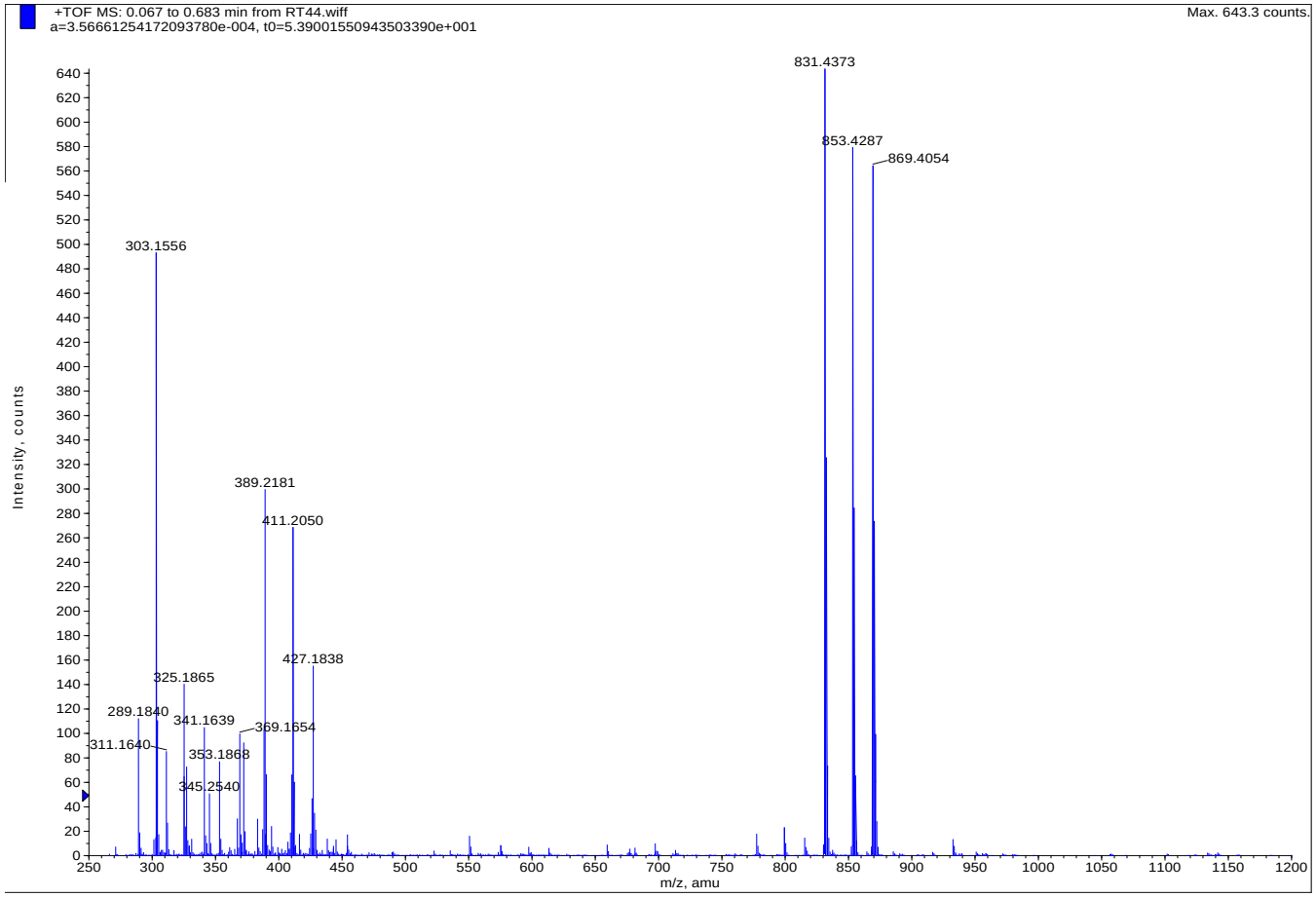

Figure S16 ESI$^+$ mass spectrum of **2d**

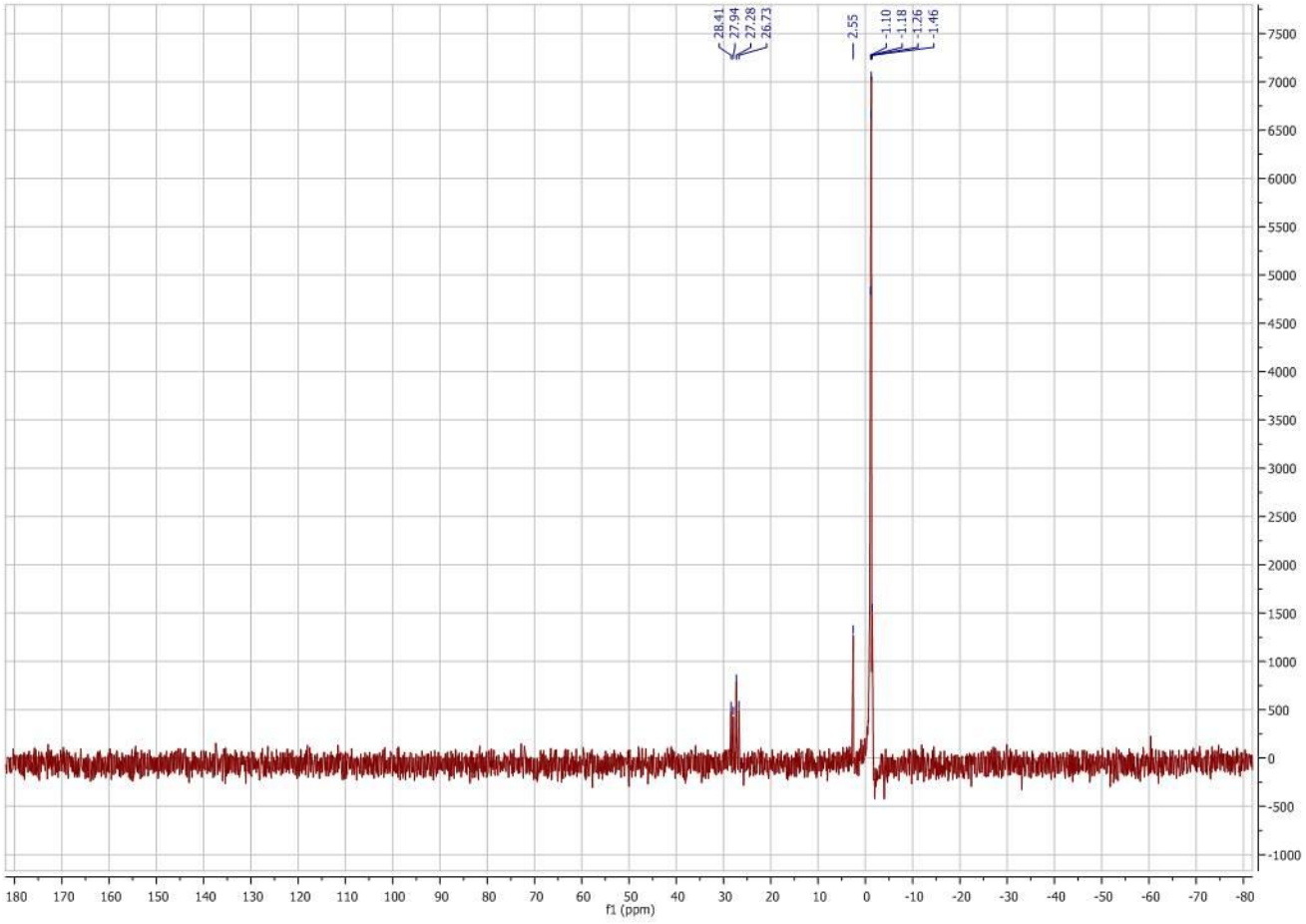

Figure S17 ^{31}P NMR (121 MHz, D_2O) of ORN **4**

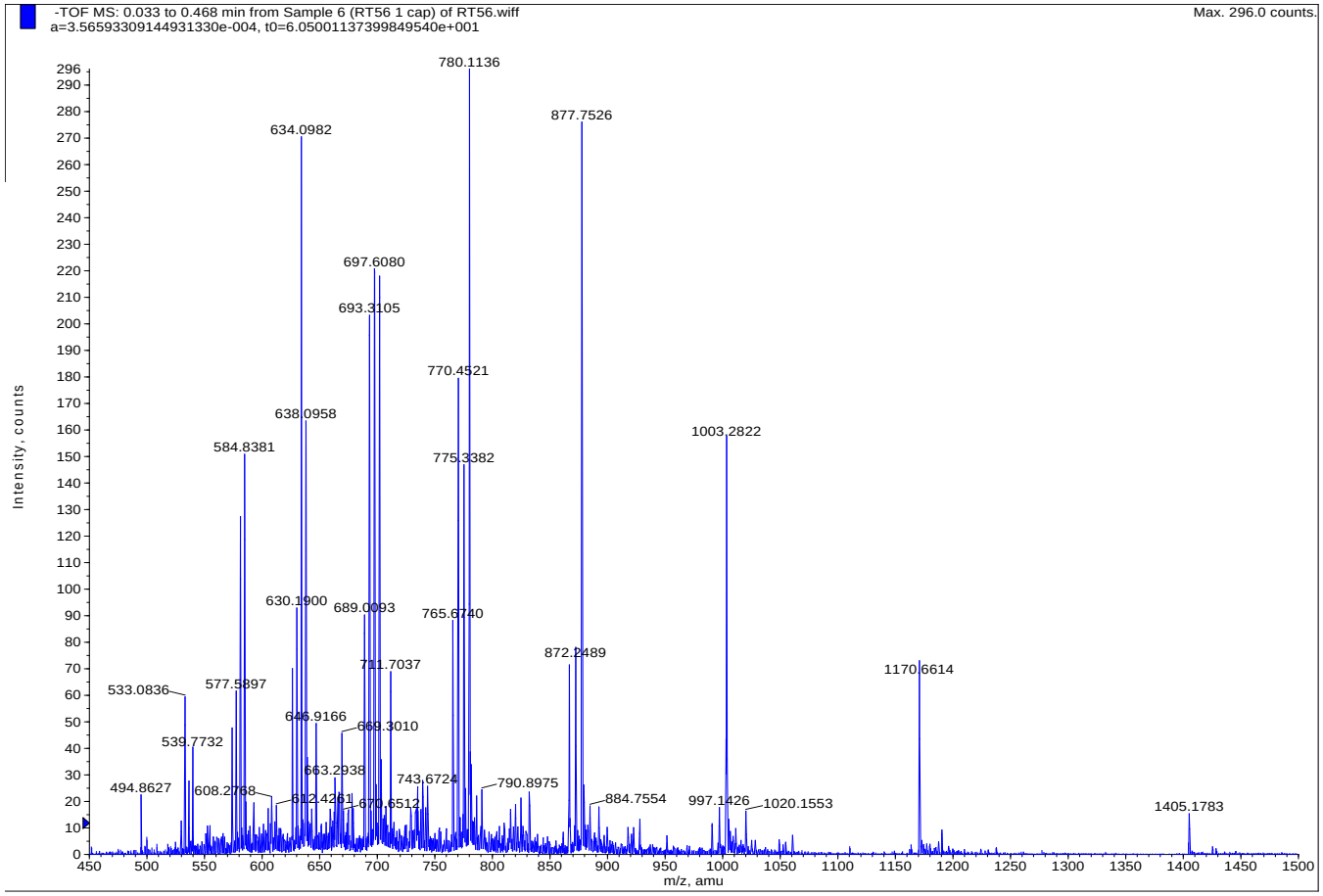

Figure S18 ESI$^-$ mass spectrum of ORN **4**

Data File C:\HPCHEM\1\DATA\RICHARD\03241002.D Sample Name: RT56 1cap DMToff

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Sample Name     : RT56 1cap DMToff               Location : Vial 1
Acq. Operator   : richard                            Inj :   1
                                                Inj Volume : 100 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 10 µl
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Method          : C:\HPCHEM\1\METHODS\A-50B.M
Last changed    : 2/24/2010 2:46:50 PM by richard
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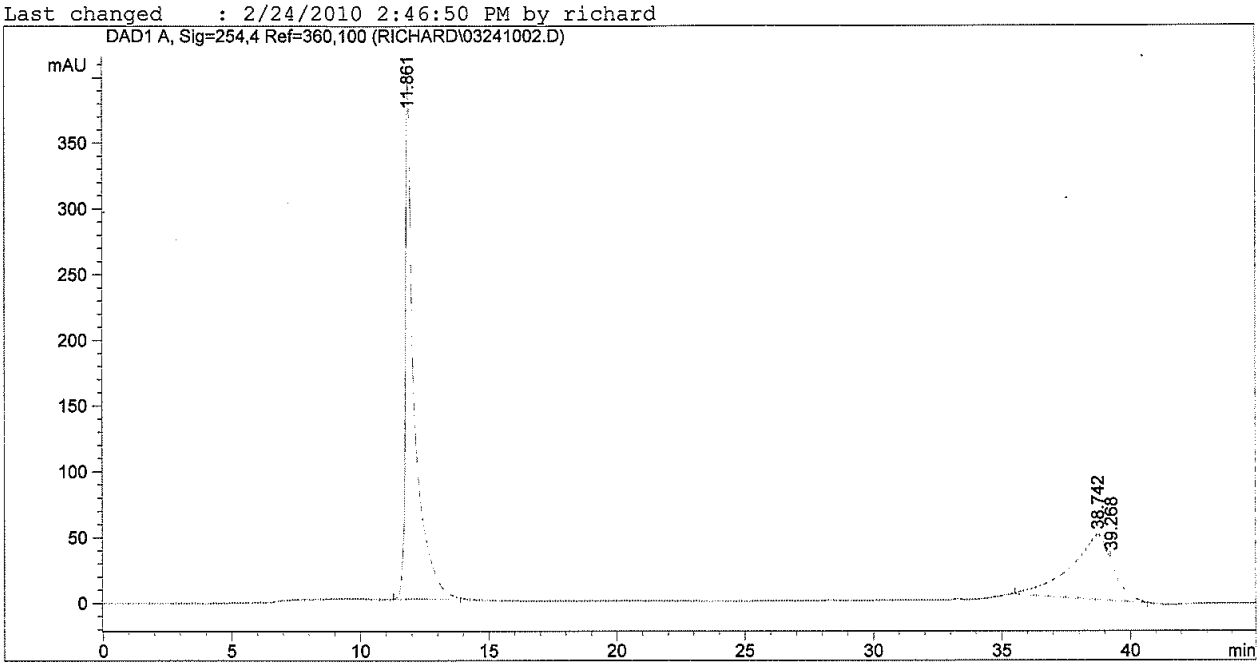


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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
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----|-------|----|-------|----------|----------|-------|
   1  11.861 BB    0.3442 9737.42090  394.15604  63.5044
   2  38.742 BV    1.2629 4761.47510   49.47045  31.0528
   3  39.268 VB    0.3092  834.57184   33.90029   5.4428

Totals :                  1.53335e4   477.52678

 Results obtained with enhanced integrator!
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Instrument 1 3/24/2010 2:55:58 PM richard Page 1 of 1

Figure S19 HPLC chromatogram of ORN **4**

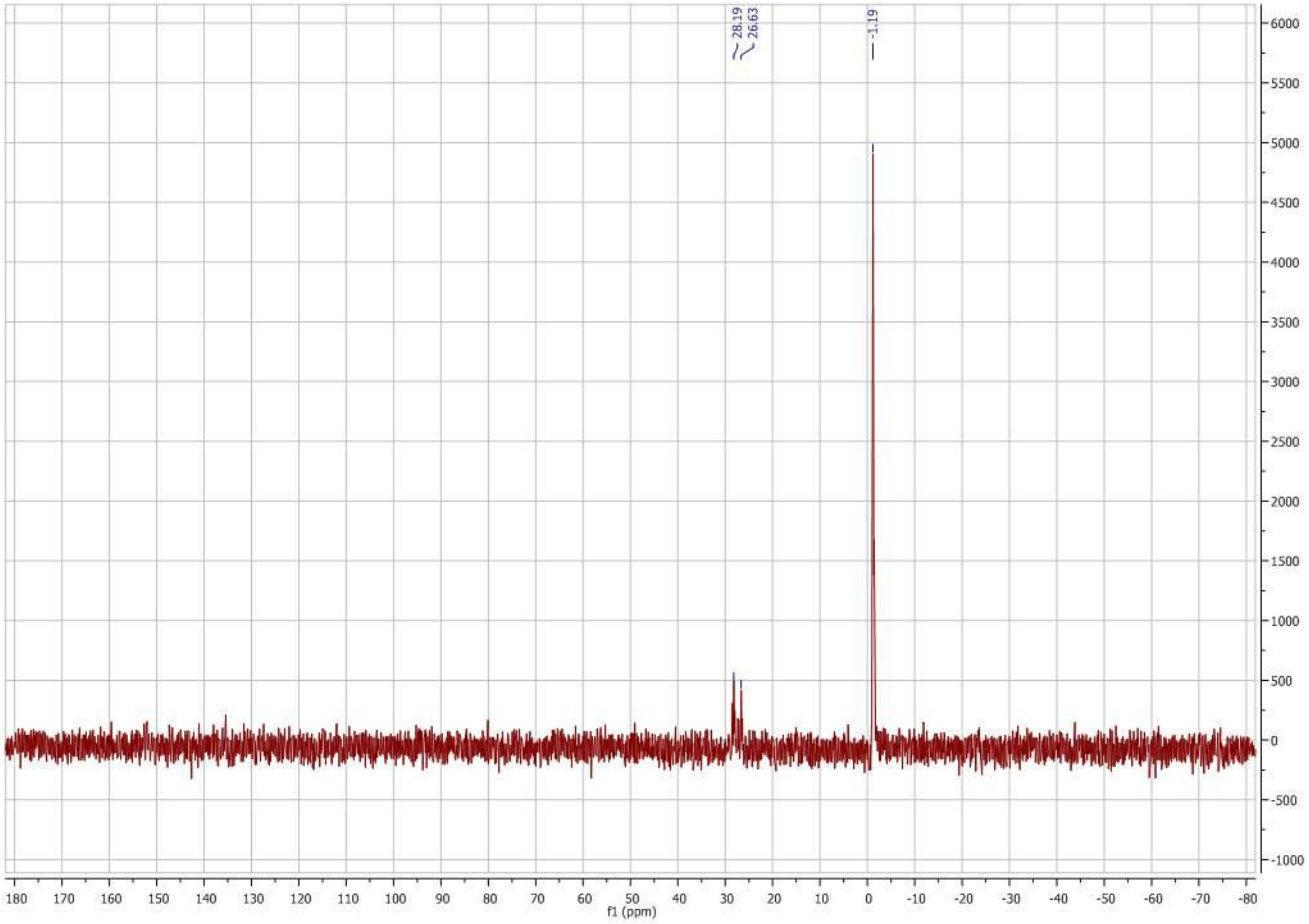

Figure S20 ^{31}P NMR (121 MHz, D_2O) of ORN **5**

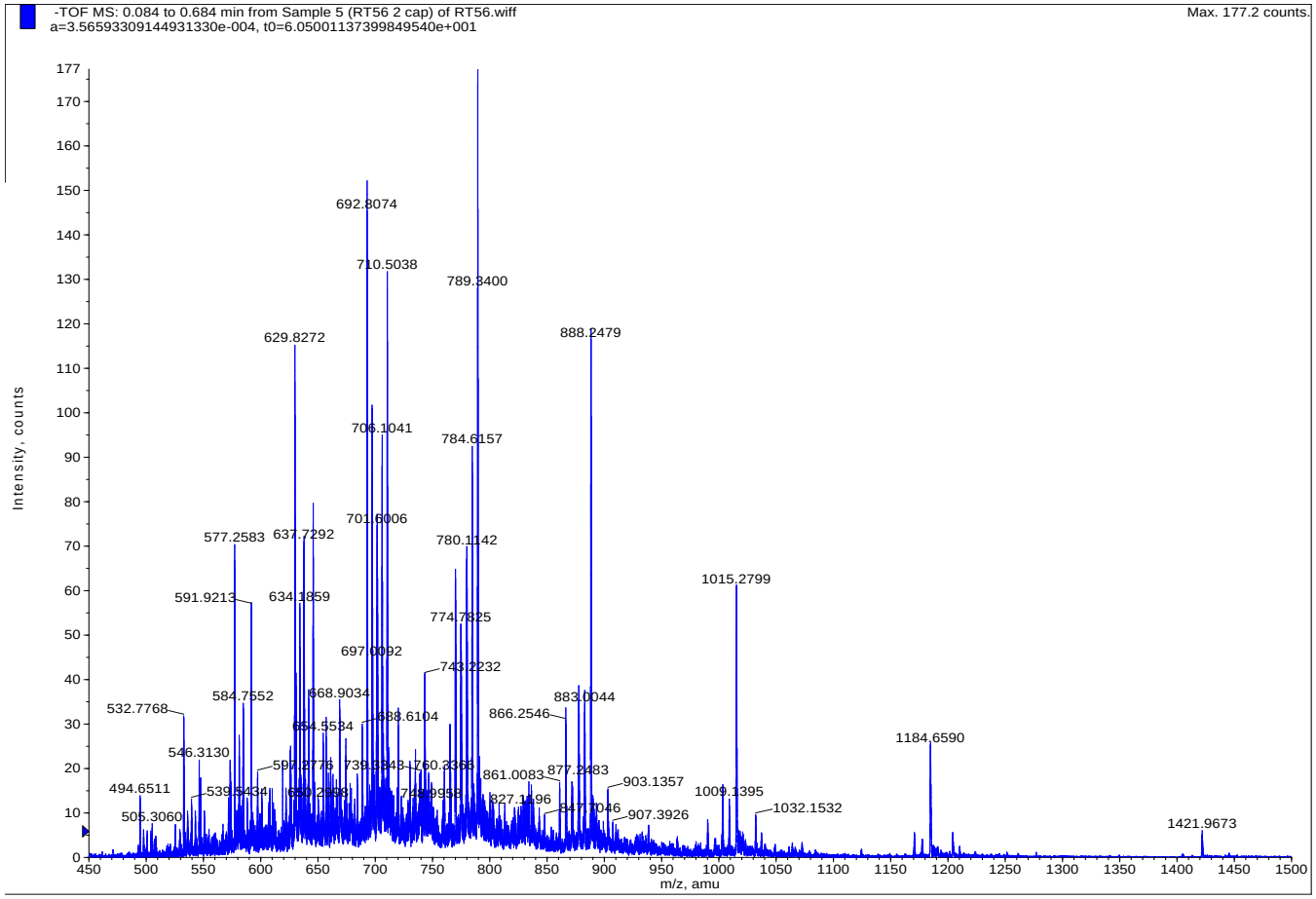

Figure S21 ESI$^-$ mass spectrum of ORN **5**

Data File C:\HPCHEM\1\DATA\RICHARD\03241003.D Sample Name: RT56 2cap DMToff

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                                                 Inj Volume : 100 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 10 µl
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Method          : C:\HPCHEM\1\METHODS\A-50B.M
Last changed    : 2/24/2010 2:46:50 PM by richard
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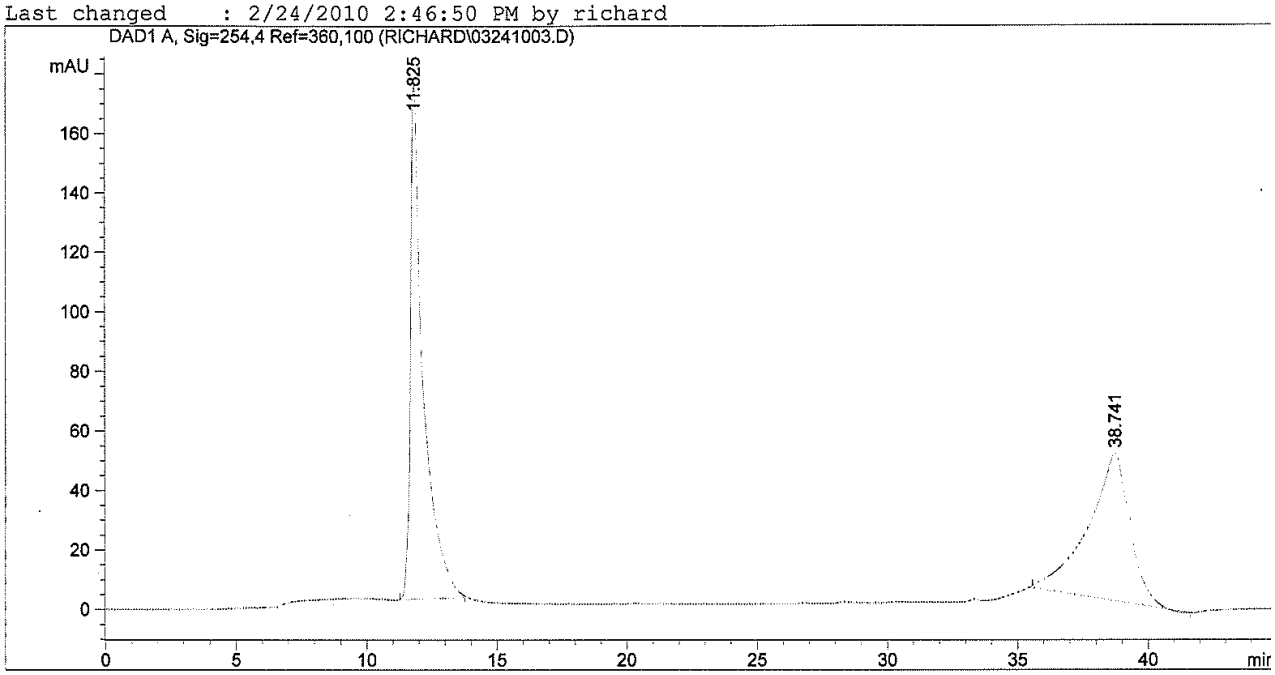


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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  11.825 BB    0.4866 6021.92773  173.64264  52.2251
   2  38.741 BP    1.4233 5508.79004   49.61862  47.7749

Totals :                  1.15307e4   223.26126

 Results obtained with enhanced integrator!
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Instrument 1 3/24/2010 3:42:54 PM richard Page 1 of 1

Figure S22 HPLC chromatogram of ORN **5**

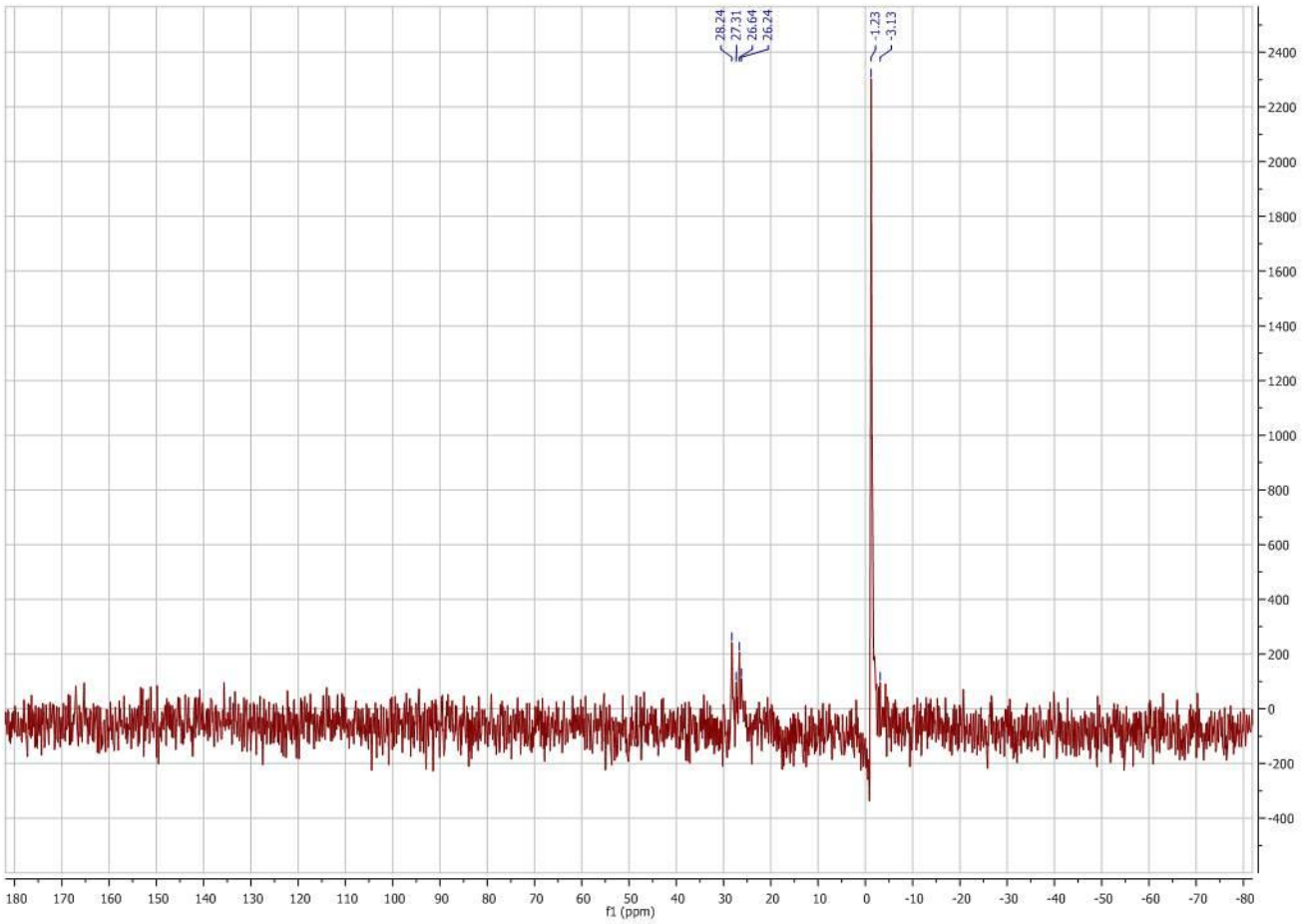

Figure S23 ^{31}P NMR (121 MHz, D_2O) of ORN **6**

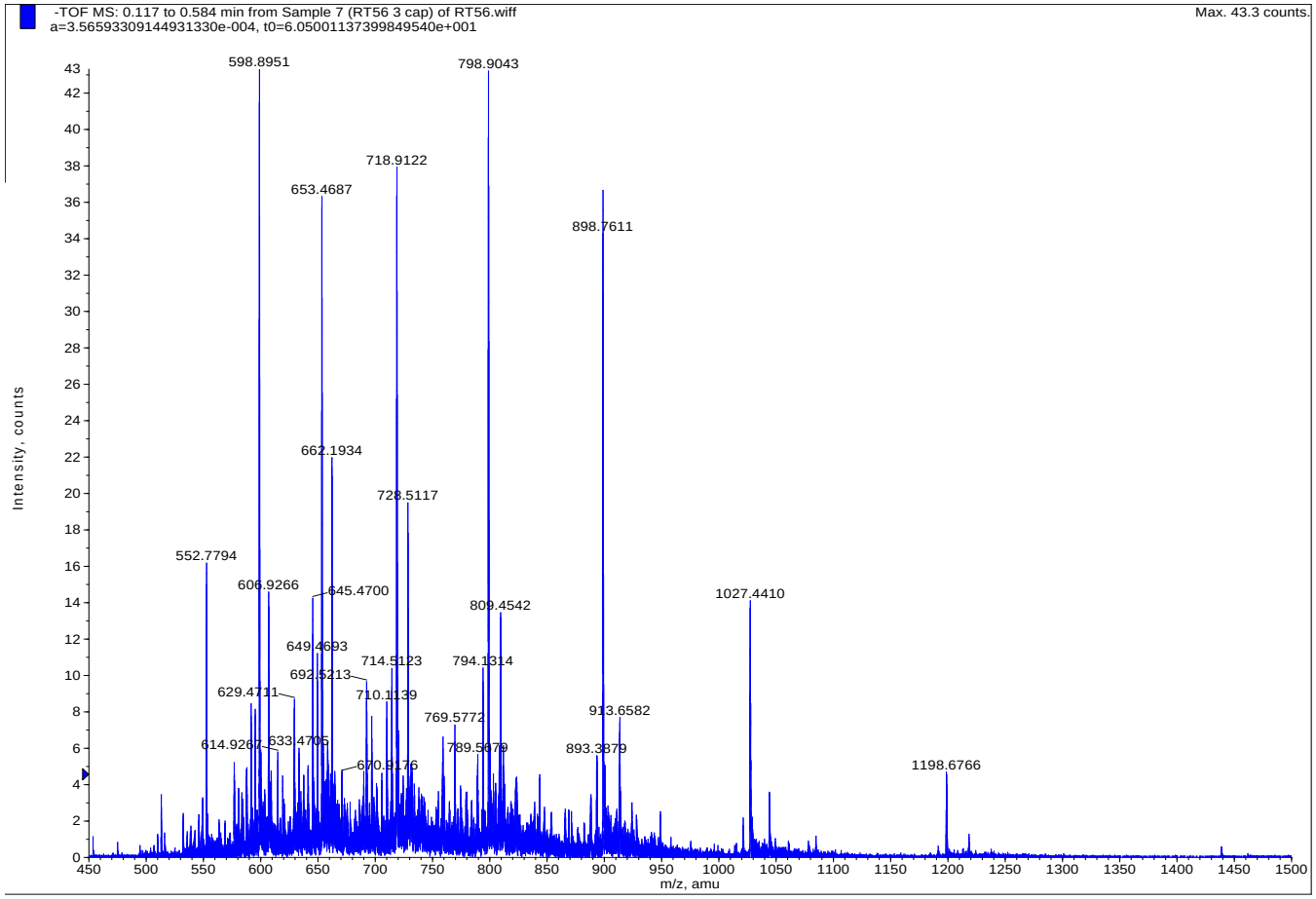

Figure S24 ESI$^-$ mass spectrum of ORN **6**

Data File C:\HPCHEM\1\DATA\RICHARD\03241004.D Sample Name: RT56 3cap DMToff

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Injection Date  : 3/24/2010 3:44:38 PM          Seq. Line :   4
Sample Name     : RT56 3cap DMToff               Location : Vial 3
Acq. Operator   : richard                            Inj :   1
                                                 Inj Volume : 100 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 10 µl
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Method          : C:\HPCHEM\1\METHODS\A-50B.M
Last changed    : 2/24/2010 2:46:50 PM by richard
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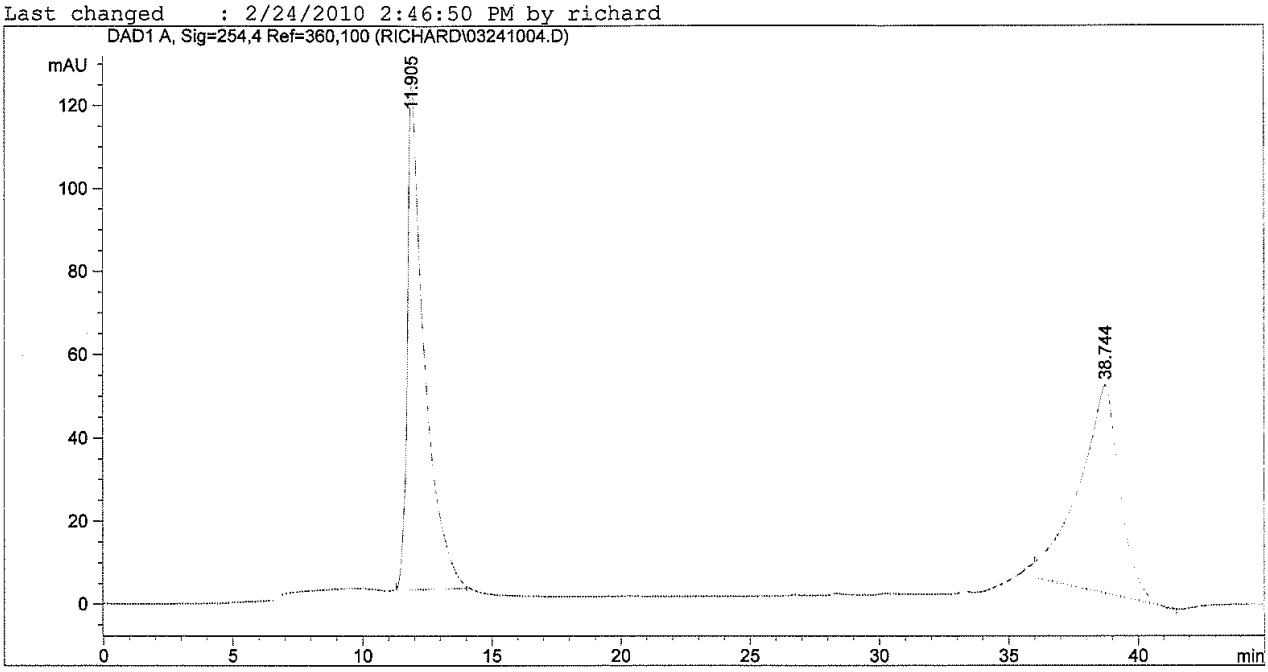


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Sorted By             :      Signal
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Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]    [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  11.905 BB    0.6175 5567.13525  122.19295  50.0254
   2  38.744 BP    1.4283 5561.47266   50.05218  49.9746

Totals :                  1.11286e4   172.24512

 Results obtained with enhanced integrator!
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Instrument 1 3/24/2010 4:29:55 PM richard Page 1 of 1

Figure S25 HPLC chromatogram of ORN **6**

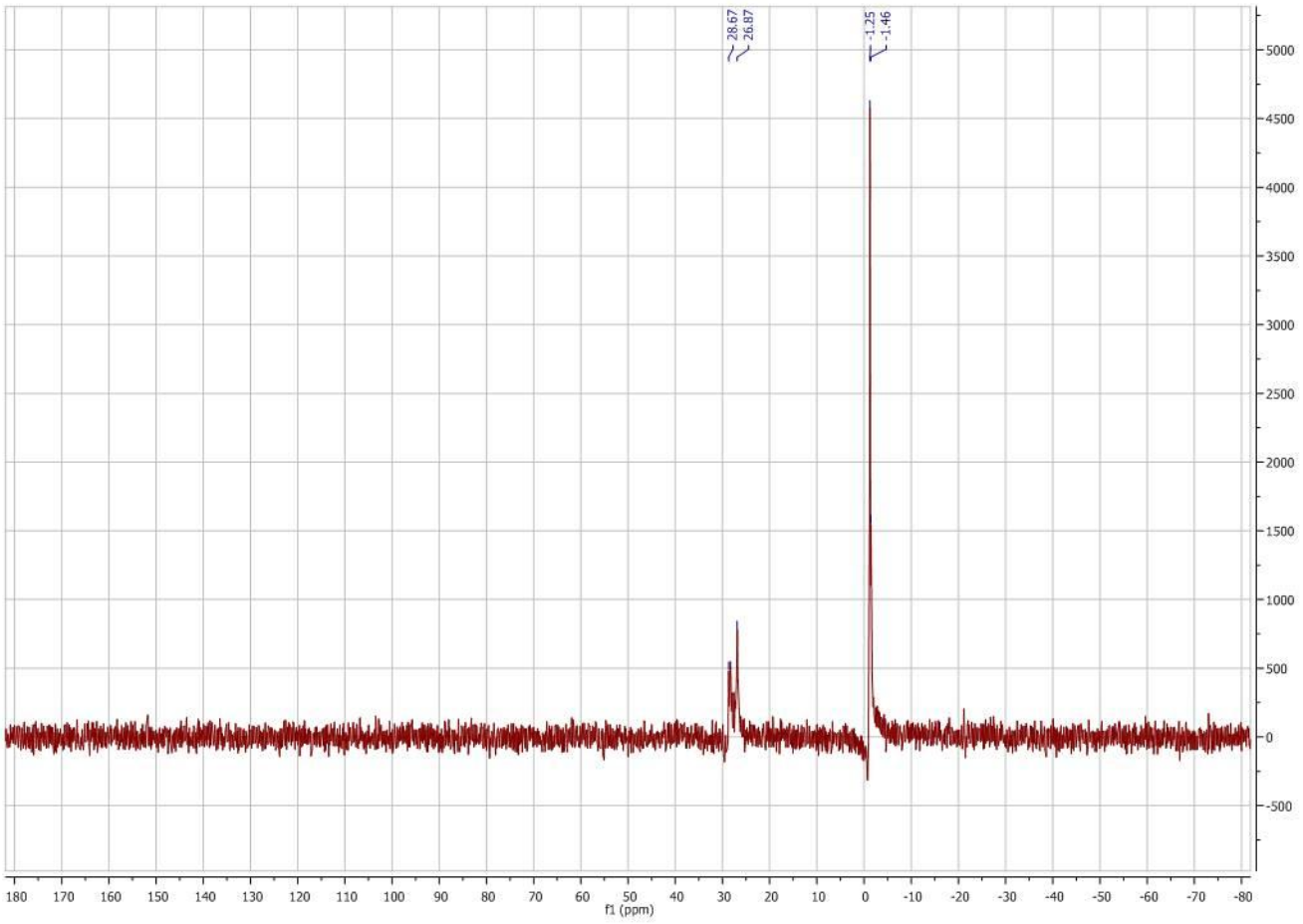

Figure S26 ^{31}P NMR (121 MHz, D_2O) of ORN **7**

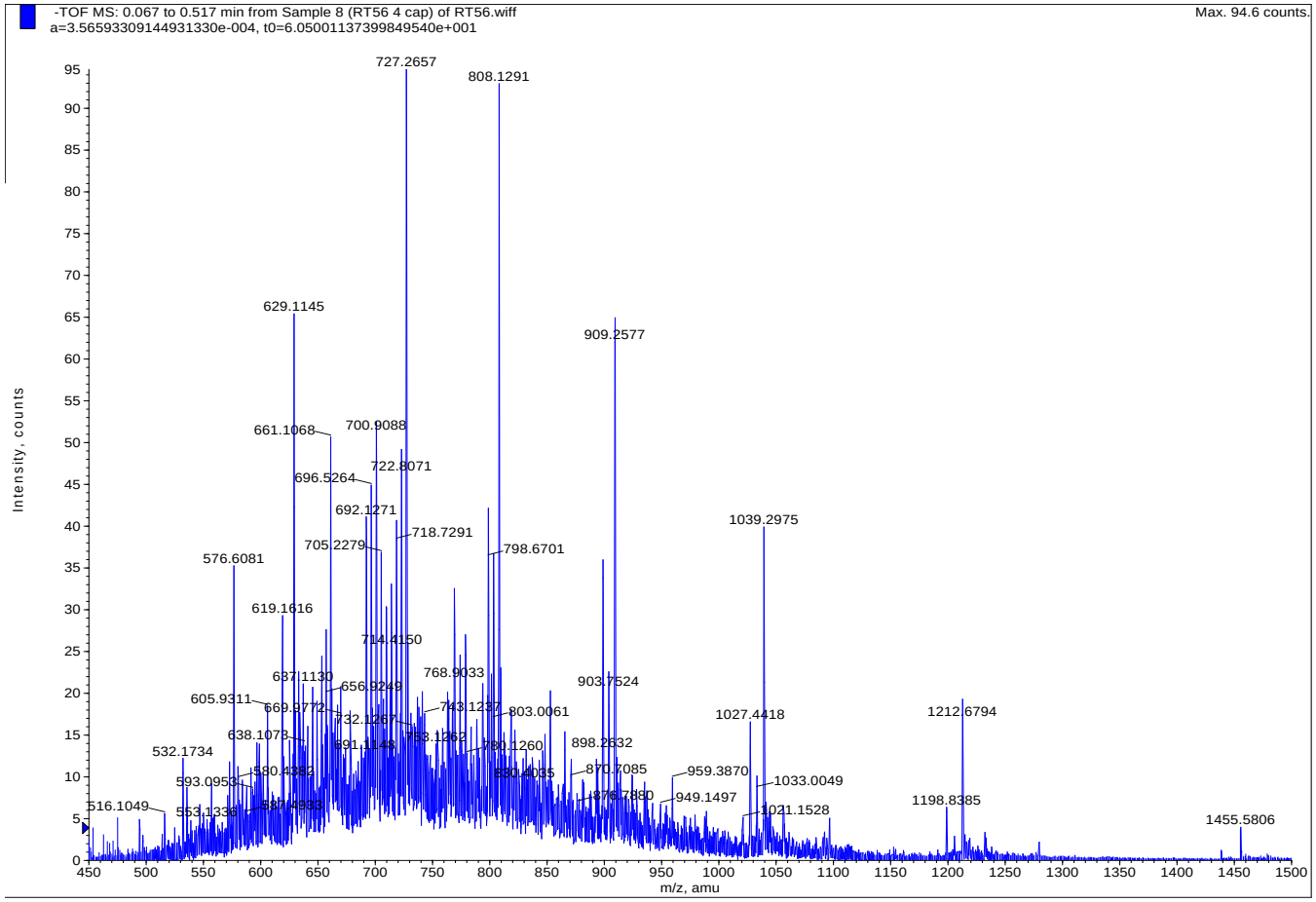

Figure S27 ESI$^-$ mass spectrum of ORN **7**

Data File C:\HPCHEM\1\DATA\RICHARD\03241005.D Sample Name: RT56 4cap DMToff

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Injection Date  : 3/24/2010 4:31:37 PM          Seq. Line :   5
Sample Name     : RT56 4cap DMToff               Location : Vial 4
Acq. Operator   : richard                            Inj :   1
                                                 Inj Volume : 100 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 10 µl
Sequence File   : C:\HPCHEM\1\SEQUENCE\RICHARD1.S
Method          : C:\HPCHEM\1\METHODS\A-50B.M
Last changed    : 2/24/2010 2:46:50 PM by richard
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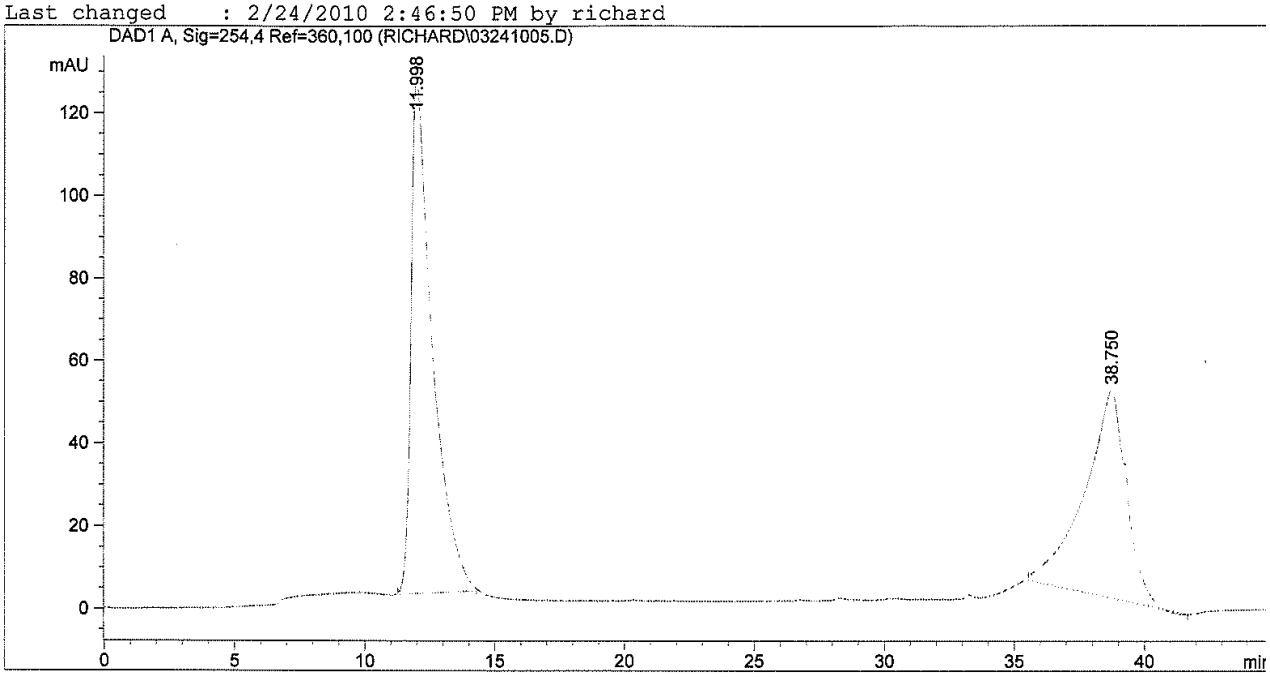


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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  11.998 BB    0.7957 7148.49951  123.78619  55.8880
   2  38.750 BP    1.4340 5642.26270   50.32434  44.1120

Totals :                  1.27908e4   174.11053

 Results obtained with enhanced integrator!
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                        *** End of Report ***
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Instrument 1 3/24/2010 5:16:54 PM richard Page 1 of 1

Figure S25 HPLC chromatogram of ORN **7**

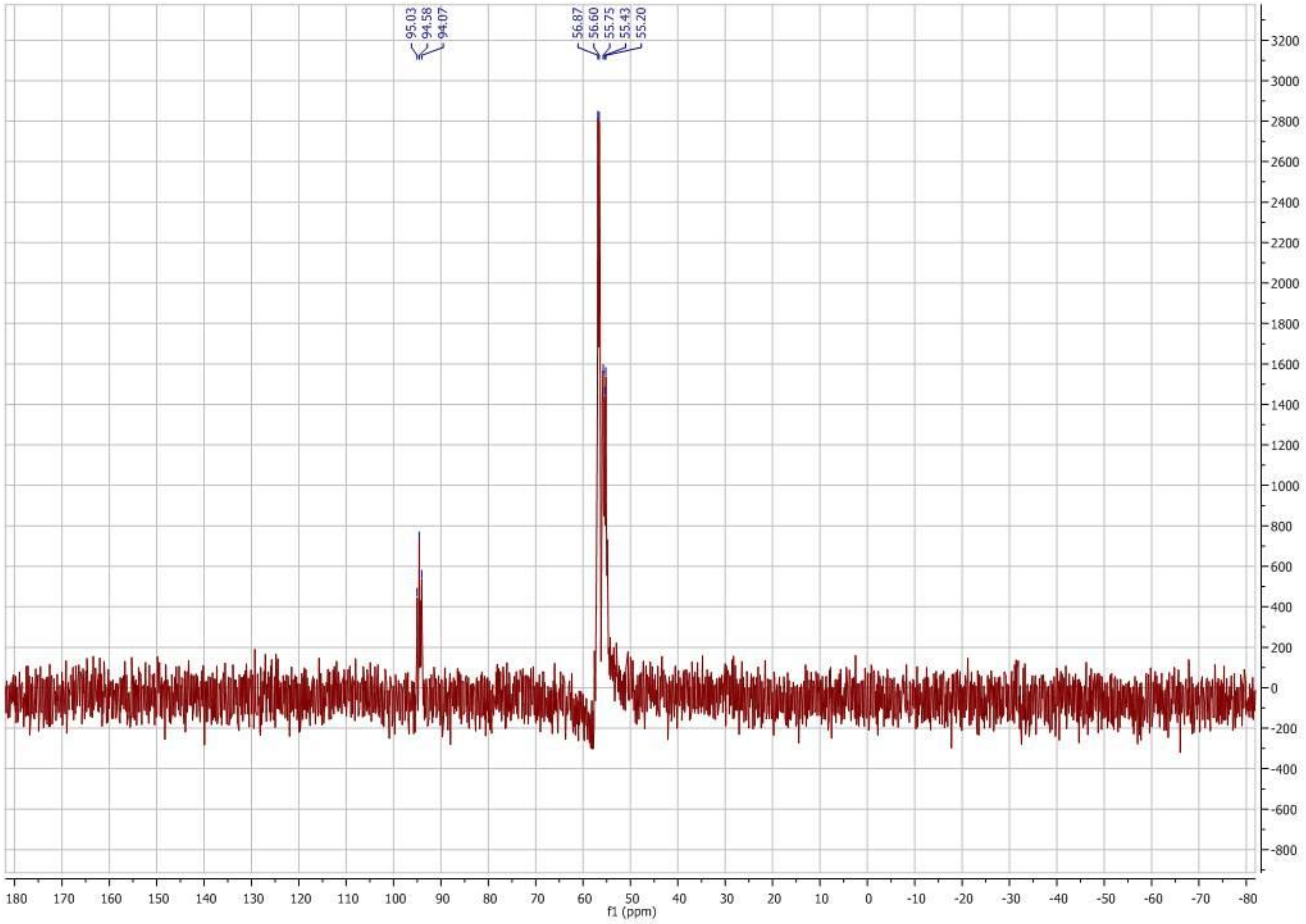

Figure S28 ^{31}P NMR (121 MHz, D_2O) of ORN **9**

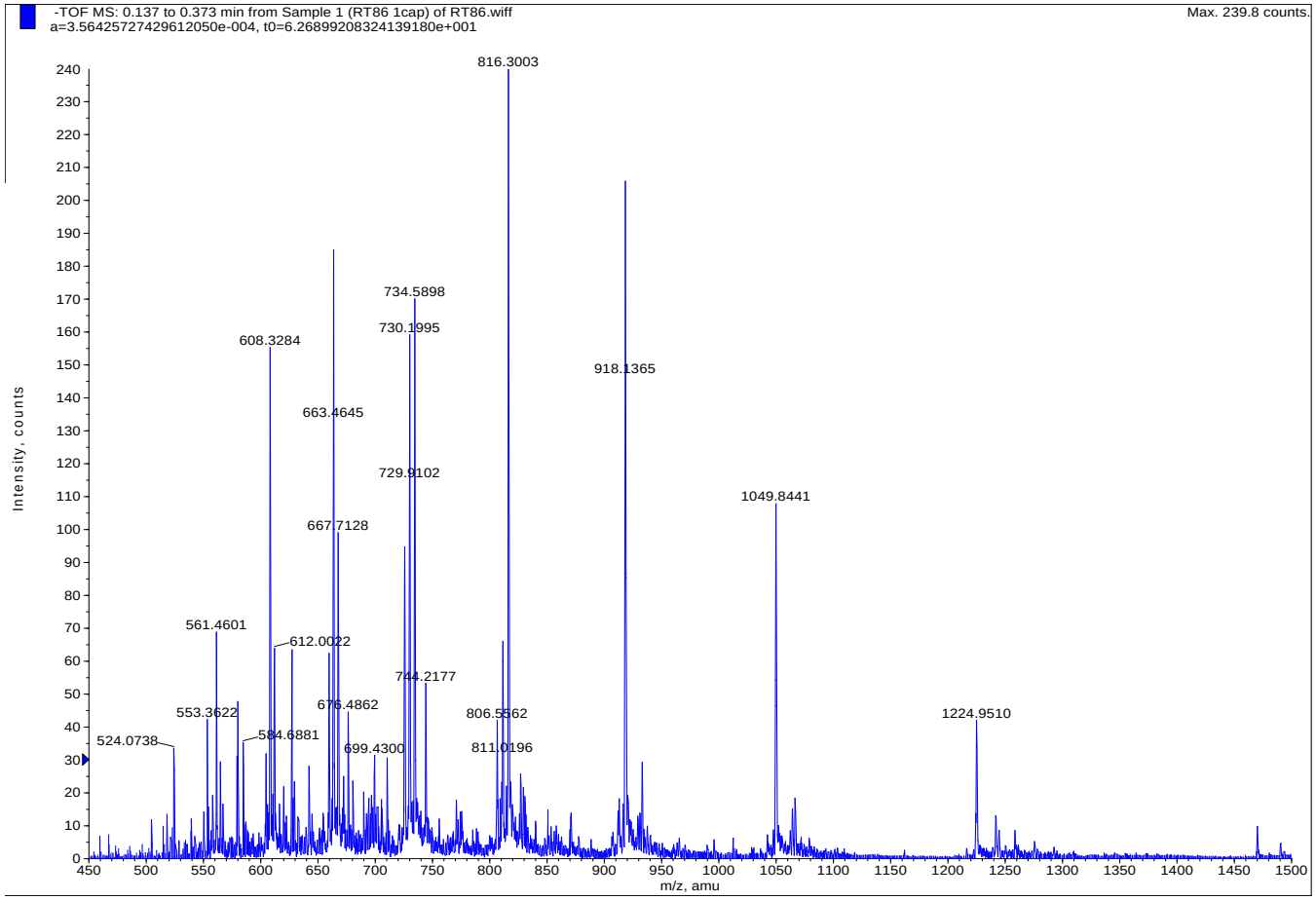

Figure S29 ESI$^-$ mass spectrum of ORN **9**

Data File C:\HPCHEM\1\DATA\RICHARD\07291002.D Sample Name: RT86 1cap DMToff

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Sample Name     : RT86 1cap DMToff                Location : Vial 1
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                                                 Inj Volume : 100 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 10 µl
Sequence File   : C:\HPCHEM\1\SEQUENCE\RICHARD1.S
Method          : C:\HPCHEM\1\METHODS\A-50B.M
Last changed    : 6/10/2010 9:15:59 AM by richard
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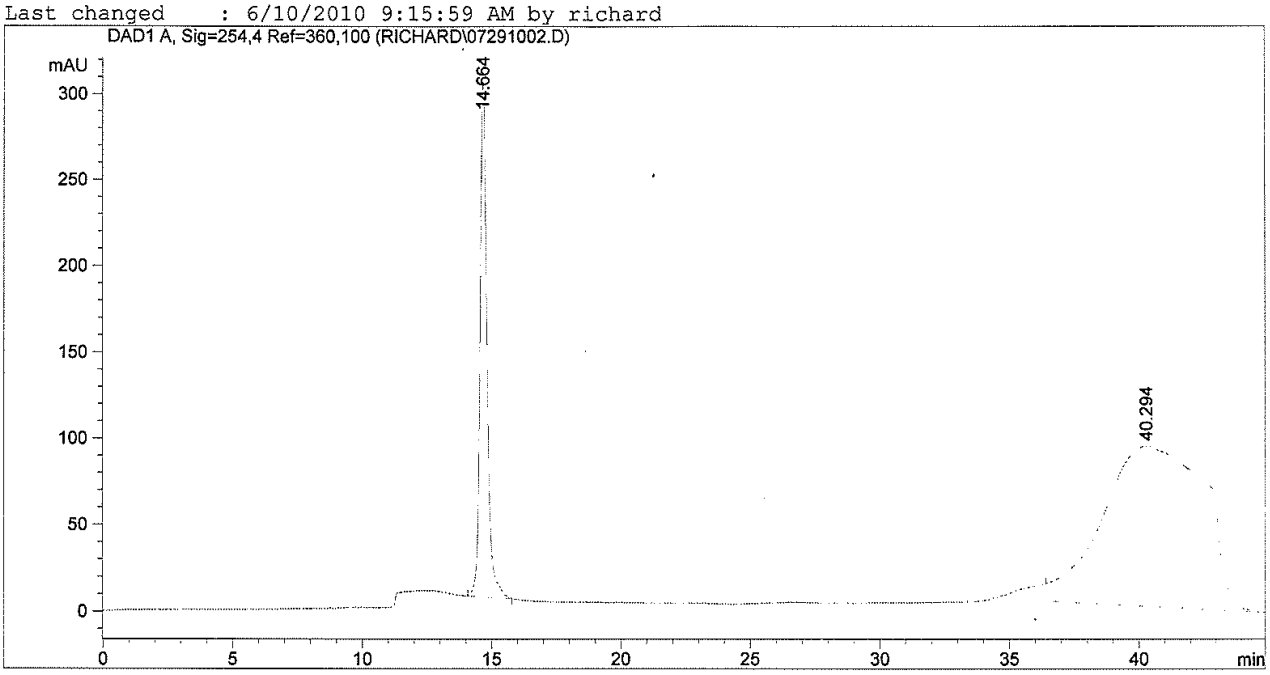


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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  14.664 BB    0.2794 5564.75488  298.58466  17.8568
   2  40.294 BBA   3.2326 2.55985e4    92.78777  82.1432

Totals :                  3.11632e4   391.37243

 Results obtained with enhanced integrator!
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Instrument 1 7/29/2010 12:12:34 PM richard Page 1 of 1

Figure S30 HPLC chromatogram of ORN **9**

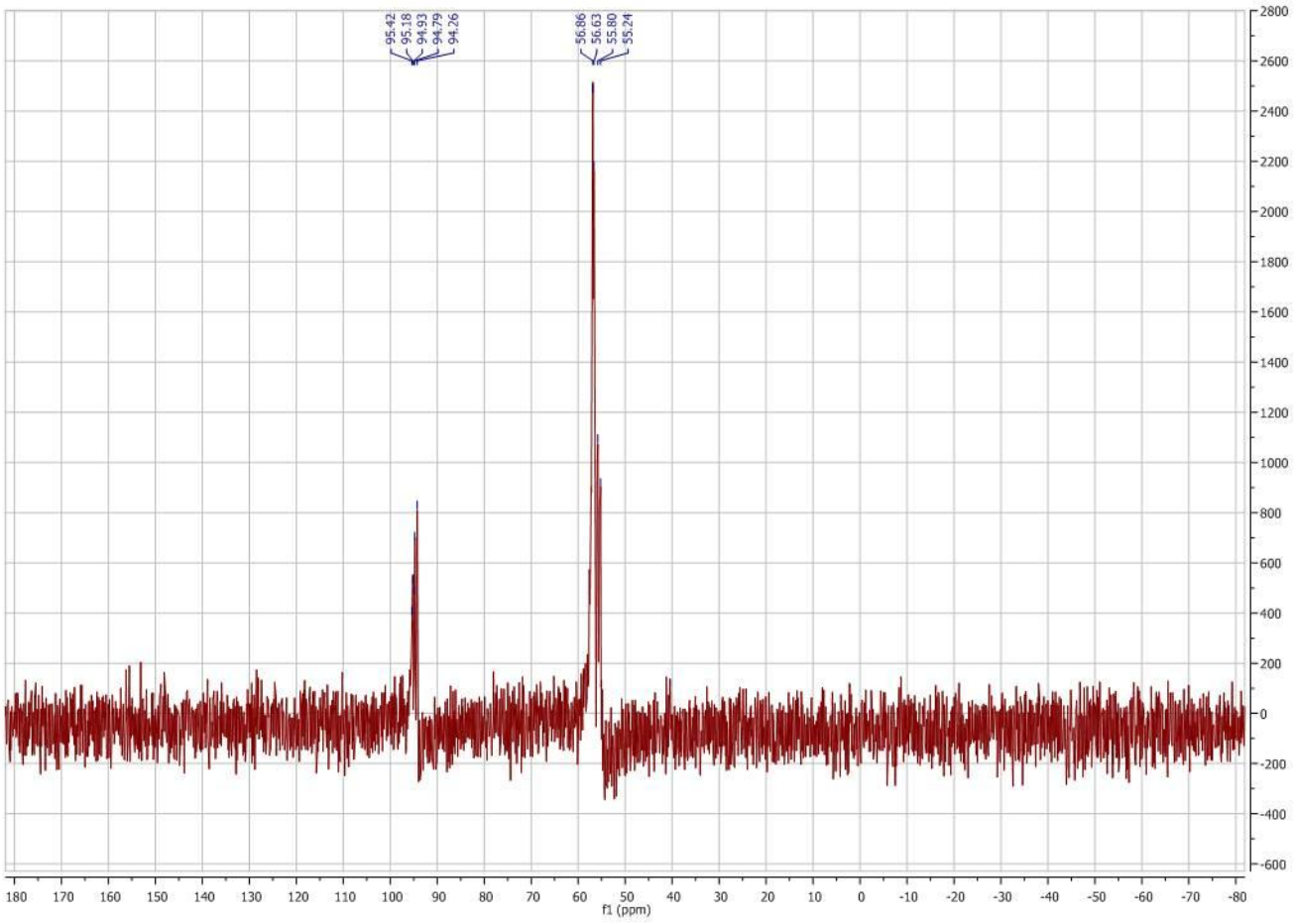

Figure S31 ^{31}P NMR (121 MHz, D_2O) of ORN **10**

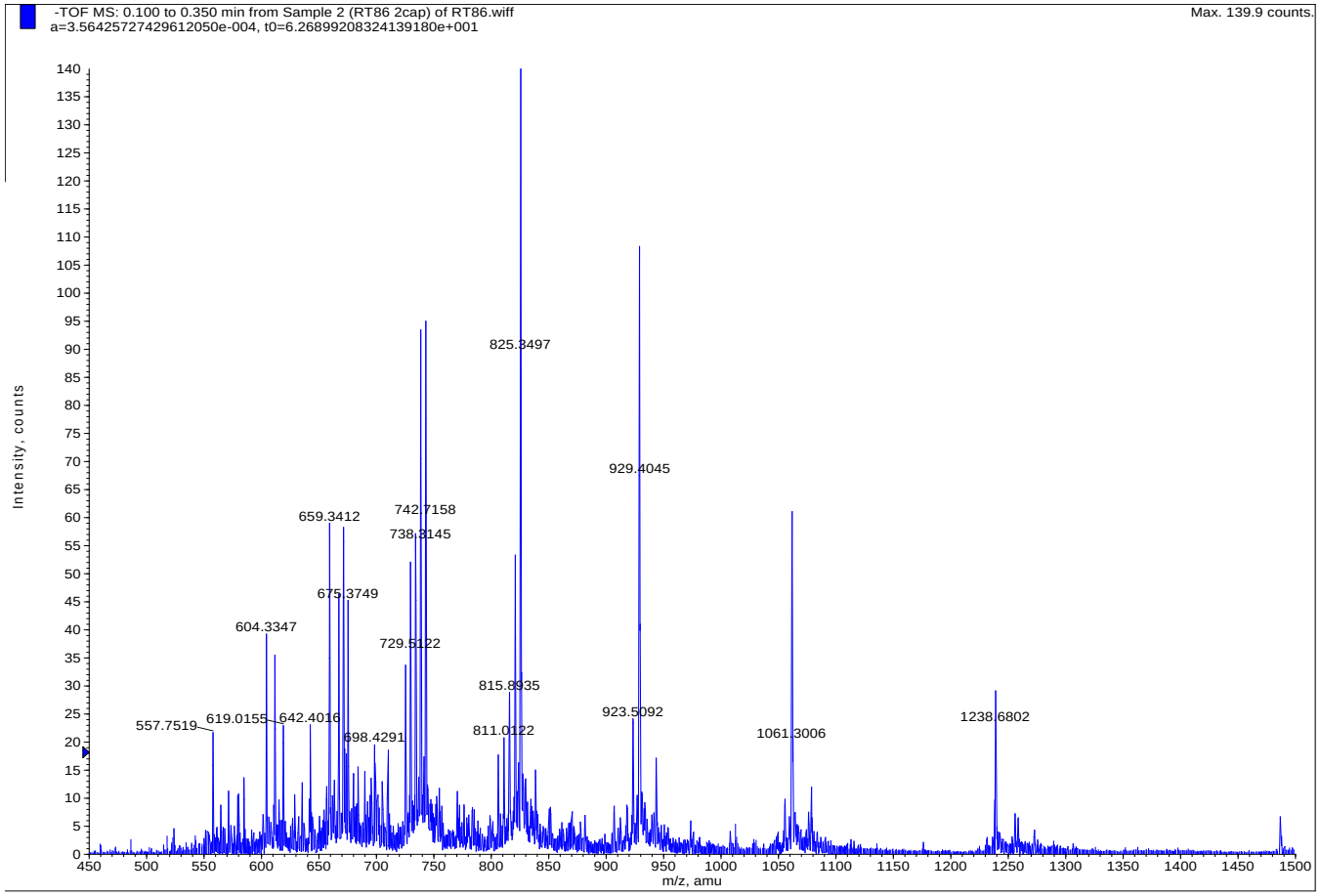

Figure S32 ESI$^-$ mass spectrum of ORN **10**

Data File C:\HPCHEM\1\DATA\RICHARD\07291003.D Sample Name: RT86 2cap DMToff

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                                                 Inj Volume : 100 µl
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Method          : C:\HPCHEM\1\METHODS\A-50B.M
Last changed    : 6/10/2010 9:15:59 AM by richard
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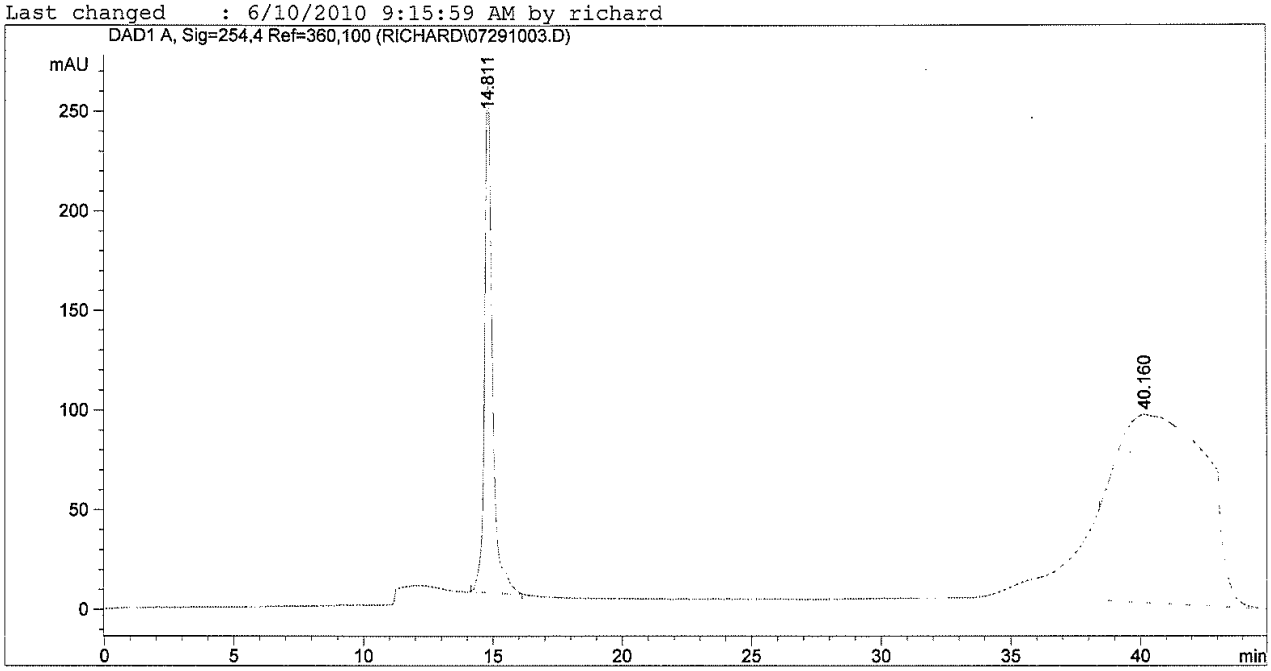


```
==================================================================================
                          Area Percent Report
==================================================================================

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


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  14.811 BB    0.3115 5394.86377  256.40179  18.5915
   2  40.160 BBA   2.9337 2.36230e4    94.39524  81.4085

Totals :                  2.90178e4   350.79704

 Results obtained with enhanced integrator!
==================================================================================
                          *** End of Report ***
```

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Figure S33 HPLC chromatogram of ORN **10**

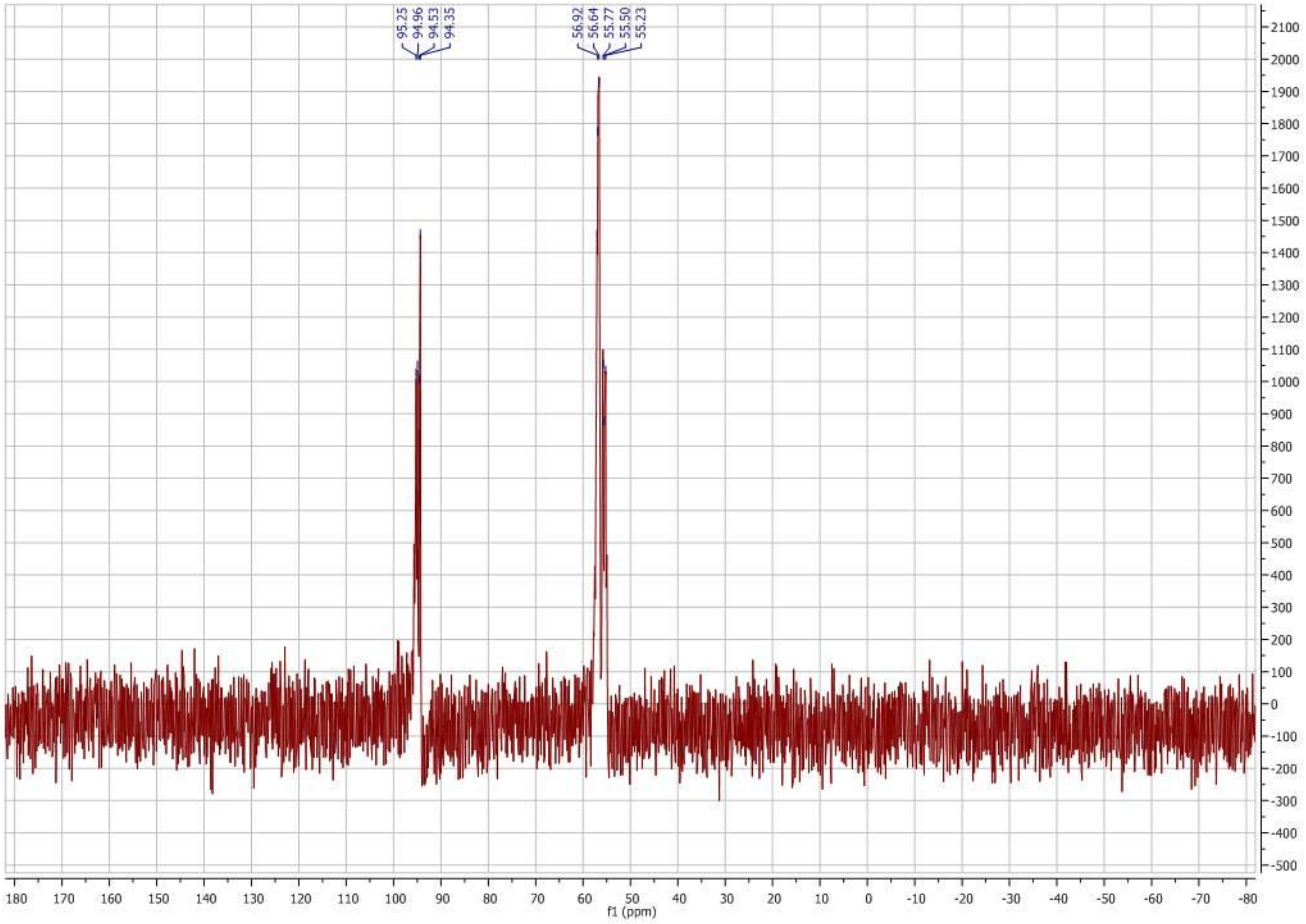


Figure S34 ^{31}P NMR (121 MHz, D_2O) of ORN **11**

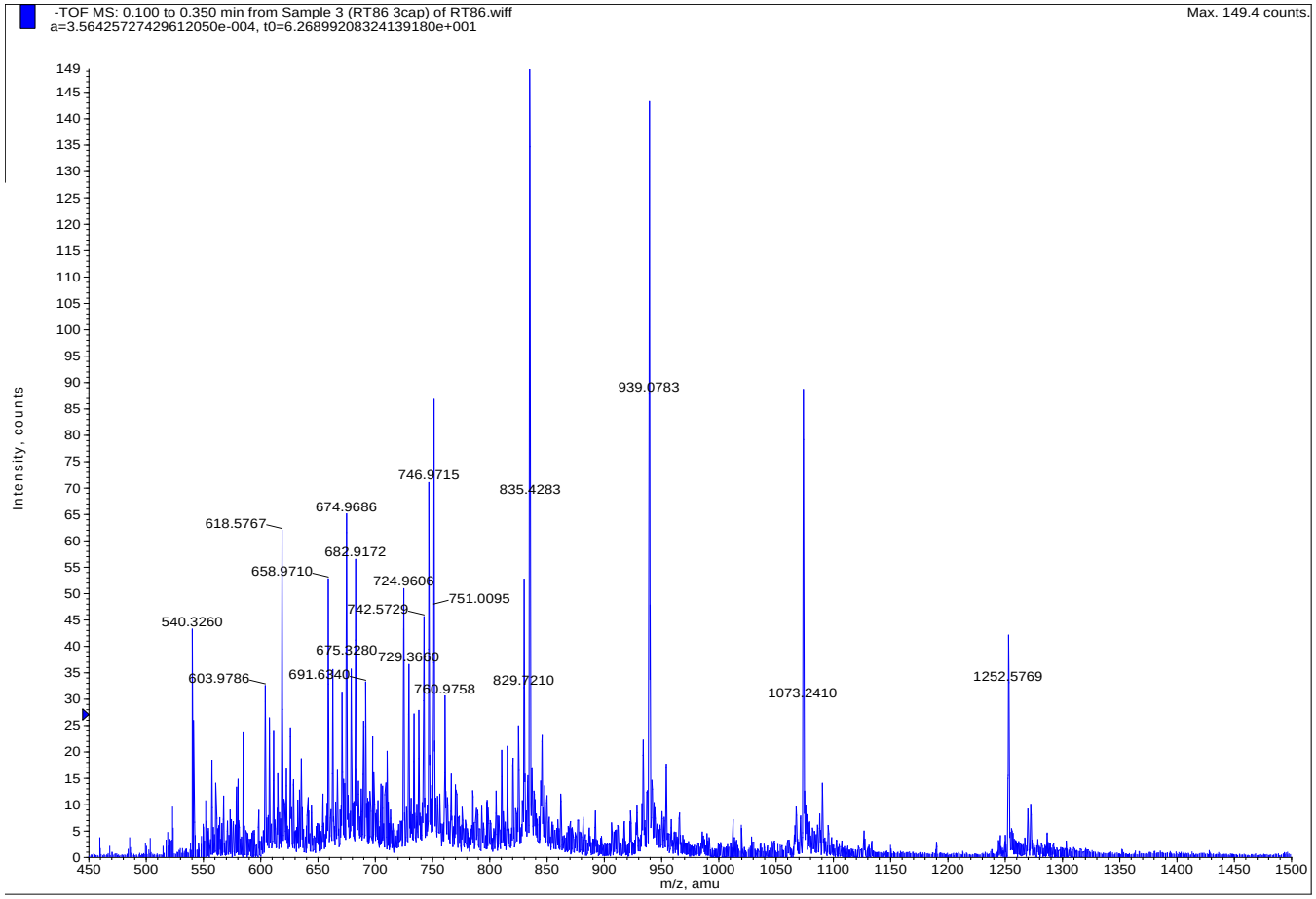
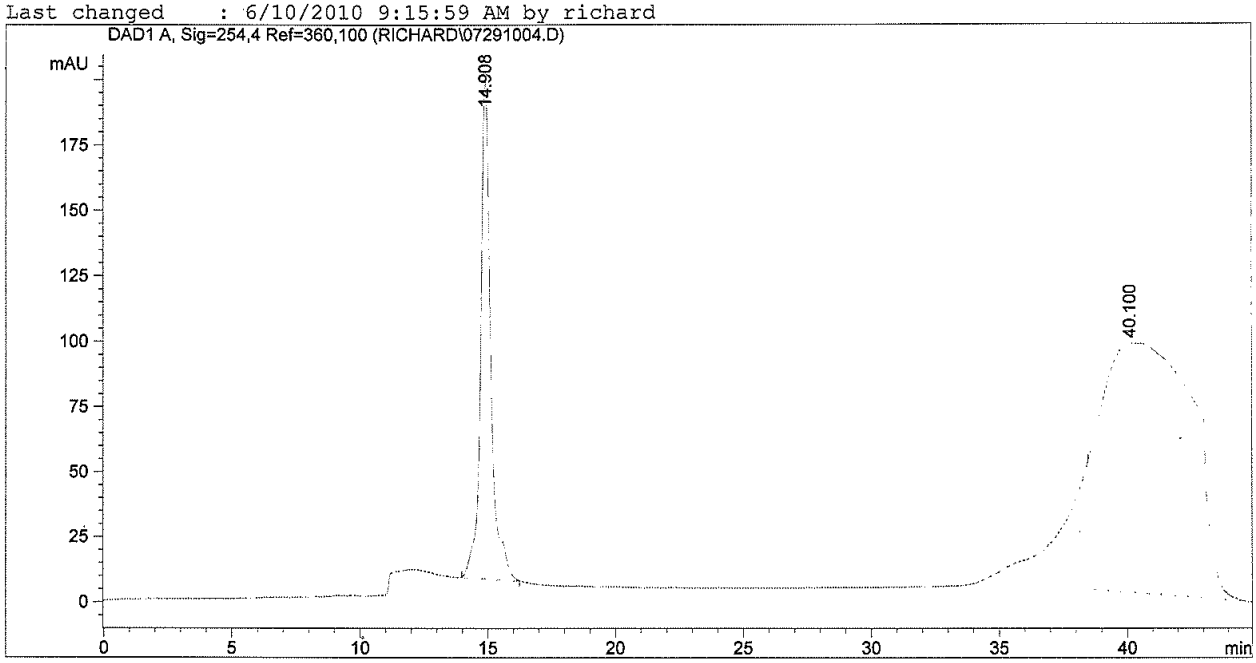


Figure S35 ESI$^-$ mass spectrum of ORN **11**

Data File C:\HPCHEM\1\DATA\RICHARD\07291004.D Sample Name: RT86 3cap DMToff

```
==========================================================================
Injection Date  : 7/29/2010 1:01:18 PM          Seq. Line :   4
Sample Name     : RT86 3cap DMToff               Location : Vial 3
Acq. Operator   : richard                            Inj :   1
                                                 Inj Volume : 100 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 10 µl
Sequence File   : C:\HPCHEM\1\SEQUENCE\RICHARD1.S
Method          : C:\HPCHEM\1\METHODS\A-50B.M
Last changed    : 6/10/2010 9:15:59 AM by richard
```




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

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


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]    [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  14.908 BB    0.4101 5306.27295  190.98944  18.1493
   2  40.100 BBA   2.9346 2.39306e4    95.33340  81.8507

Totals :                  2.92368e4   286.32284

 Results obtained with enhanced integrator!
==========================================================================
                        *** End of Report ***
```

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Figure S36 HPLC chromatogram of ORN **11**

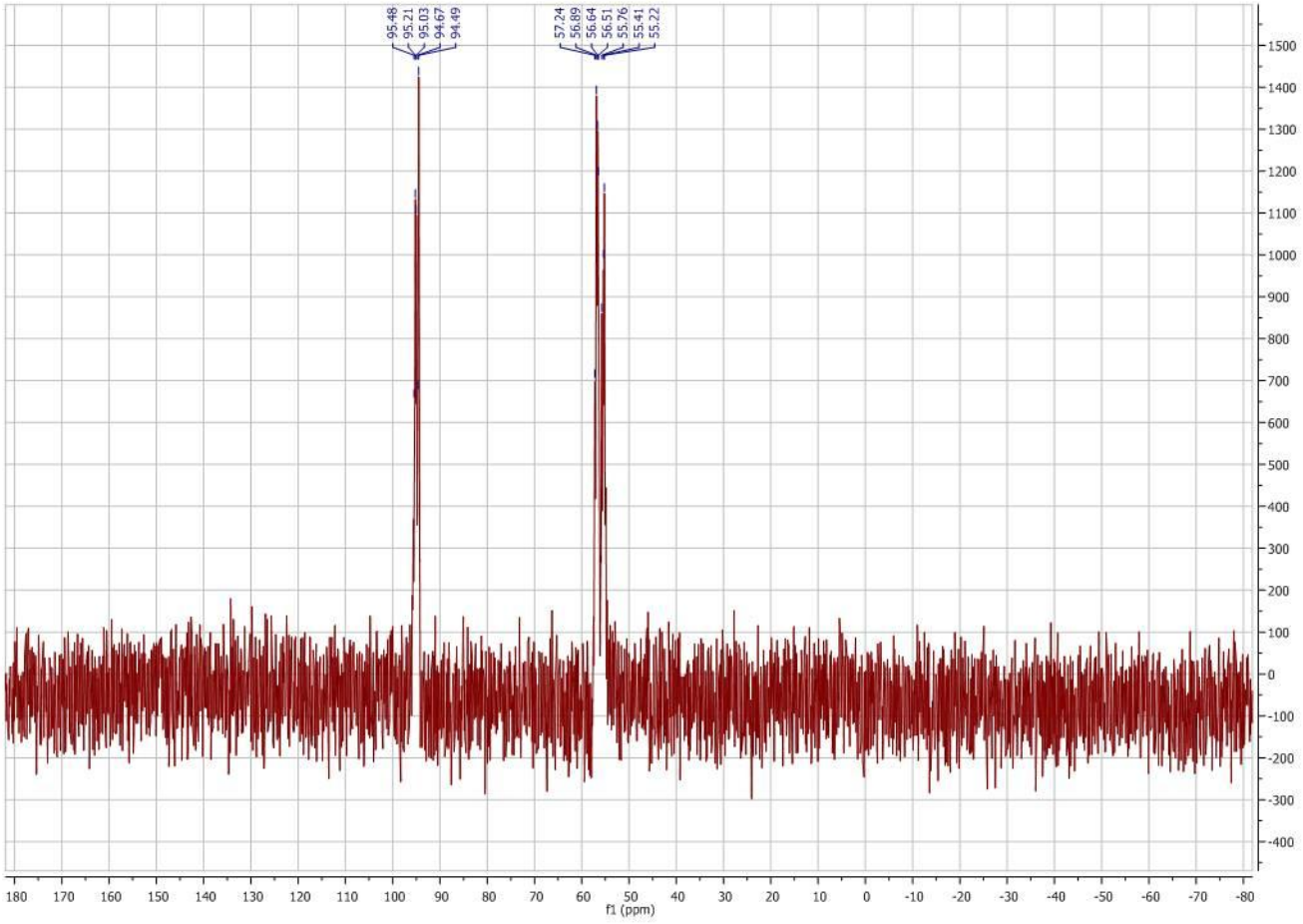


Figure S37 ^{31}P NMR (121 MHz, D_2O) of ORN **12**

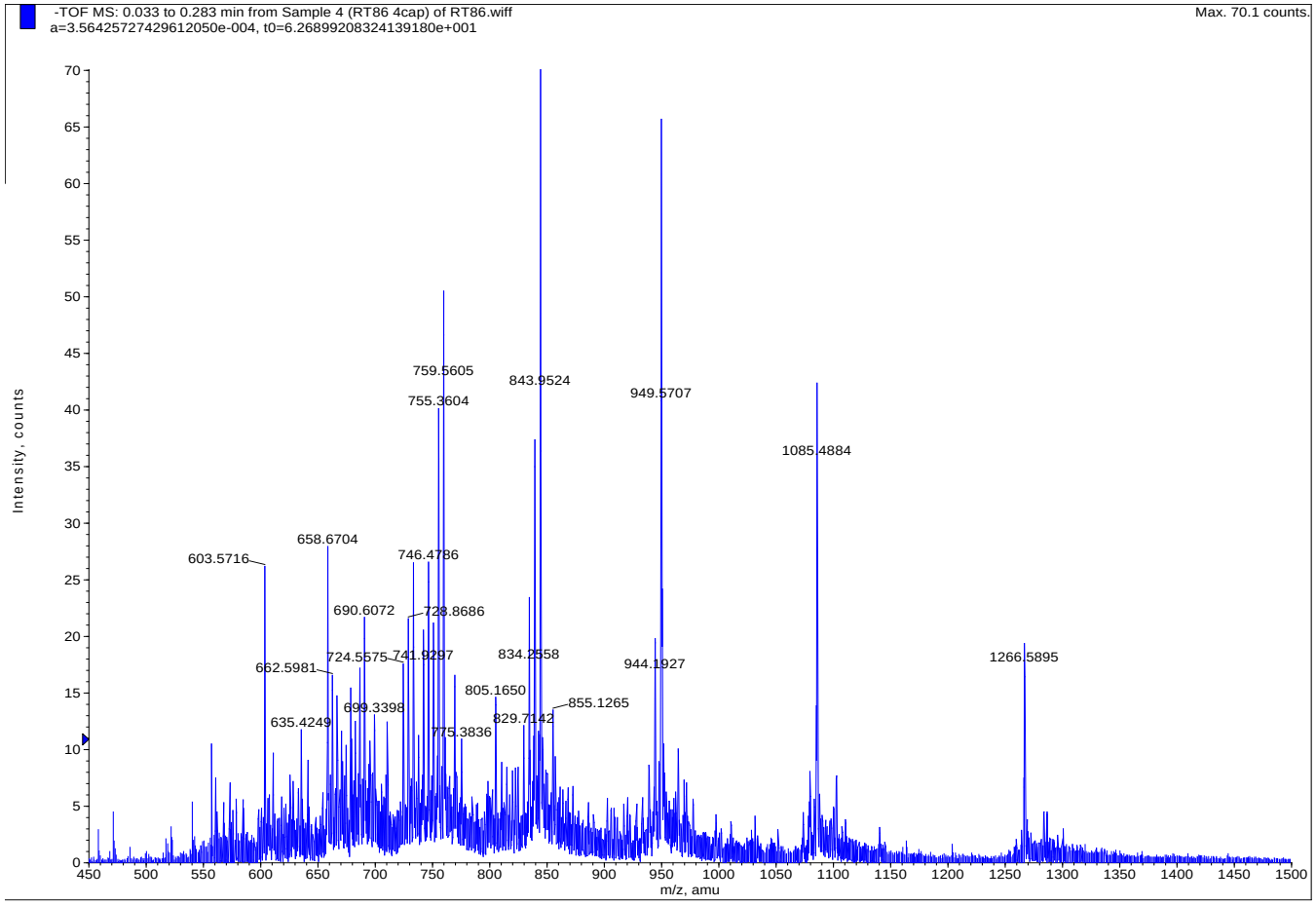
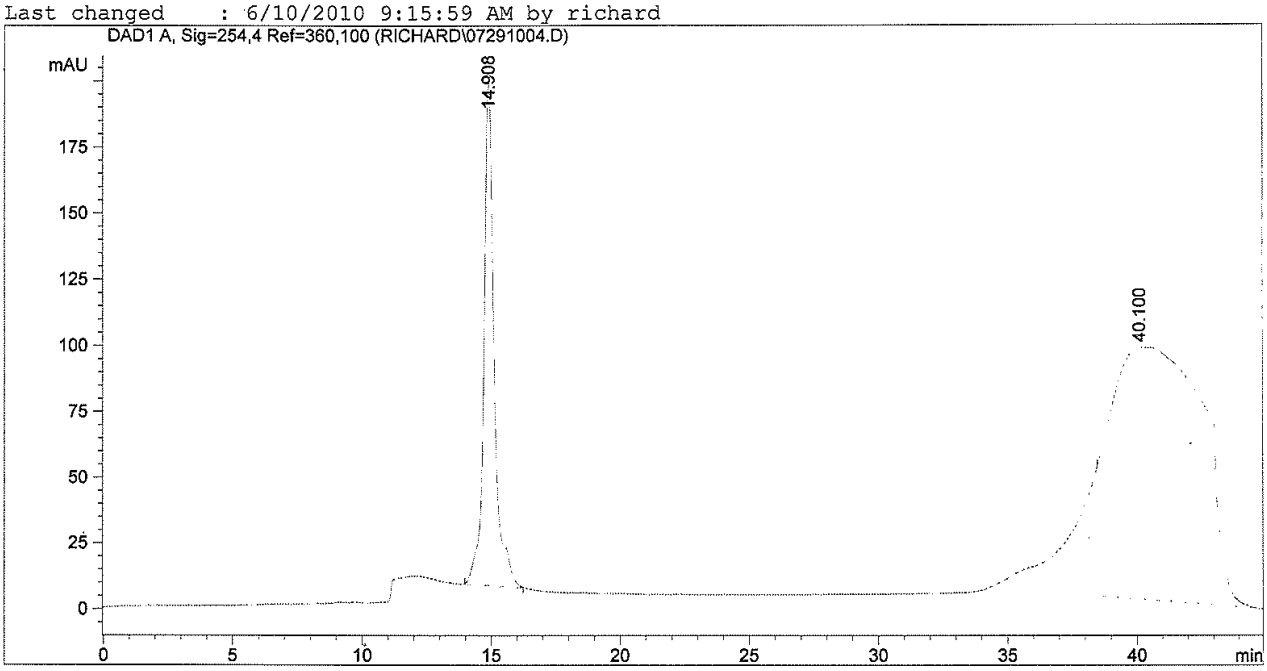


Figure S38 ESI$^-$ mass spectrum of ORN **12**

Data File C:\HPCHEM\1\DATA\RICHARD\07291004.D Sample Name: RT86 3cap DMToff

```
==================================================================
Injection Date  : 7/29/2010 1:01:18 PM          Seq. Line :   4
Sample Name     : RT86 3cap DMToff               Location : Vial 3
Acq. Operator   : richard                            Inj :   1
                                                 Inj Volume : 100 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 10 µl
Sequence File   : C:\HPCHEM\1\SEQUENCE\RICHARD1.S
Method          : C:\HPCHEM\1\METHODS\A-50B.M
Last changed    : 6/10/2010 9:15:59 AM by richard
```




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

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


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  14.908 BB    0.4101 5306.27295  190.98944  18.1493
   2  40.100 BBA   2.9346 2.39306e4    95.33340  81.8507

Totals :                  2.92368e4   286.32284

 Results obtained with enhanced integrator!
==================================================================
                        *** End of Report ***
```

Instrument 1 7/29/2010 1:46:31 PM richard Page 1 of 1

Figure S39 HPLC chromatogram of ORN **12**

Figure S40 Cell Viability (No Lipids) 1µM

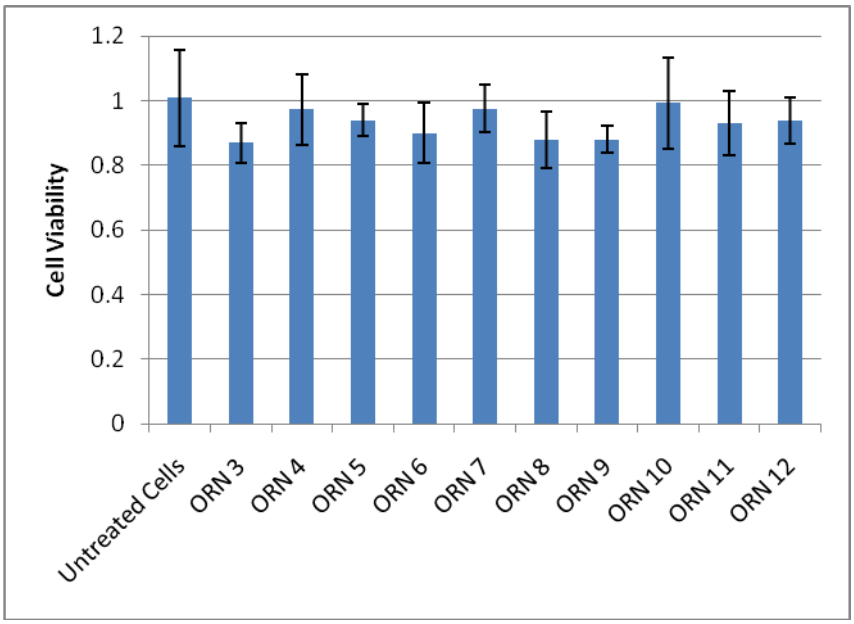
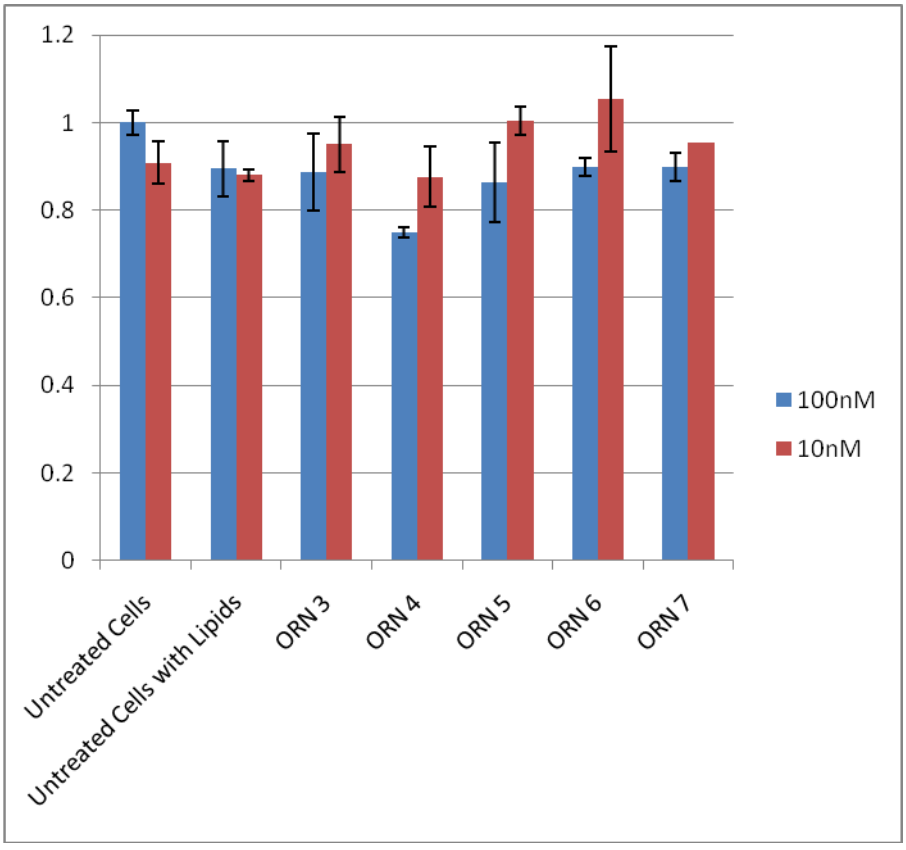
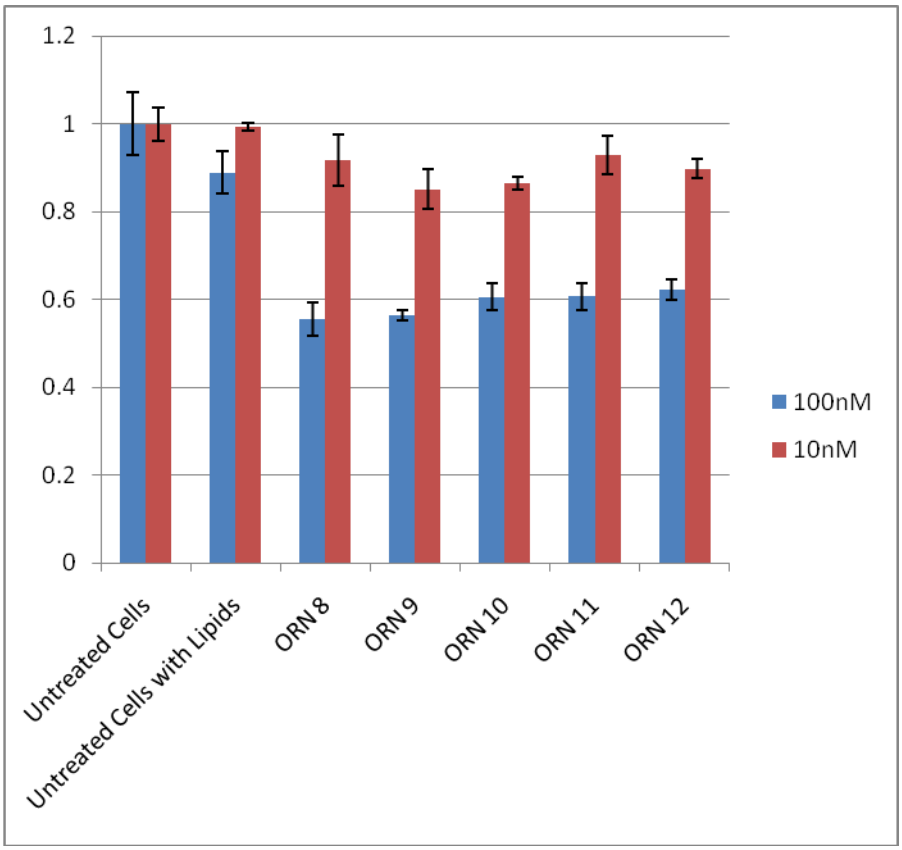


Figure S41 Cell Viability (with Lipids)





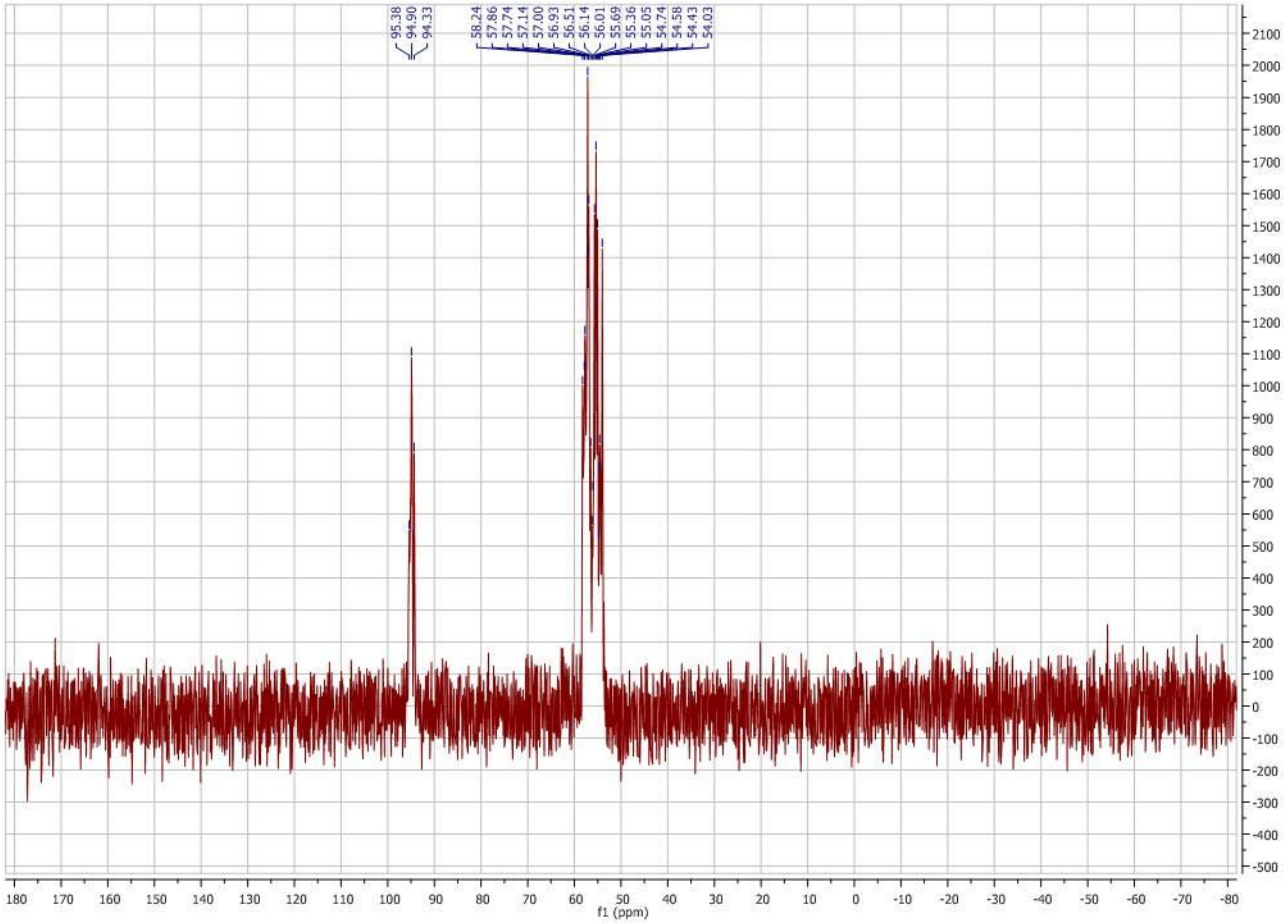


Figure S42 ^{31}P NMR (121 MHz, D_2O) of ORN **13**

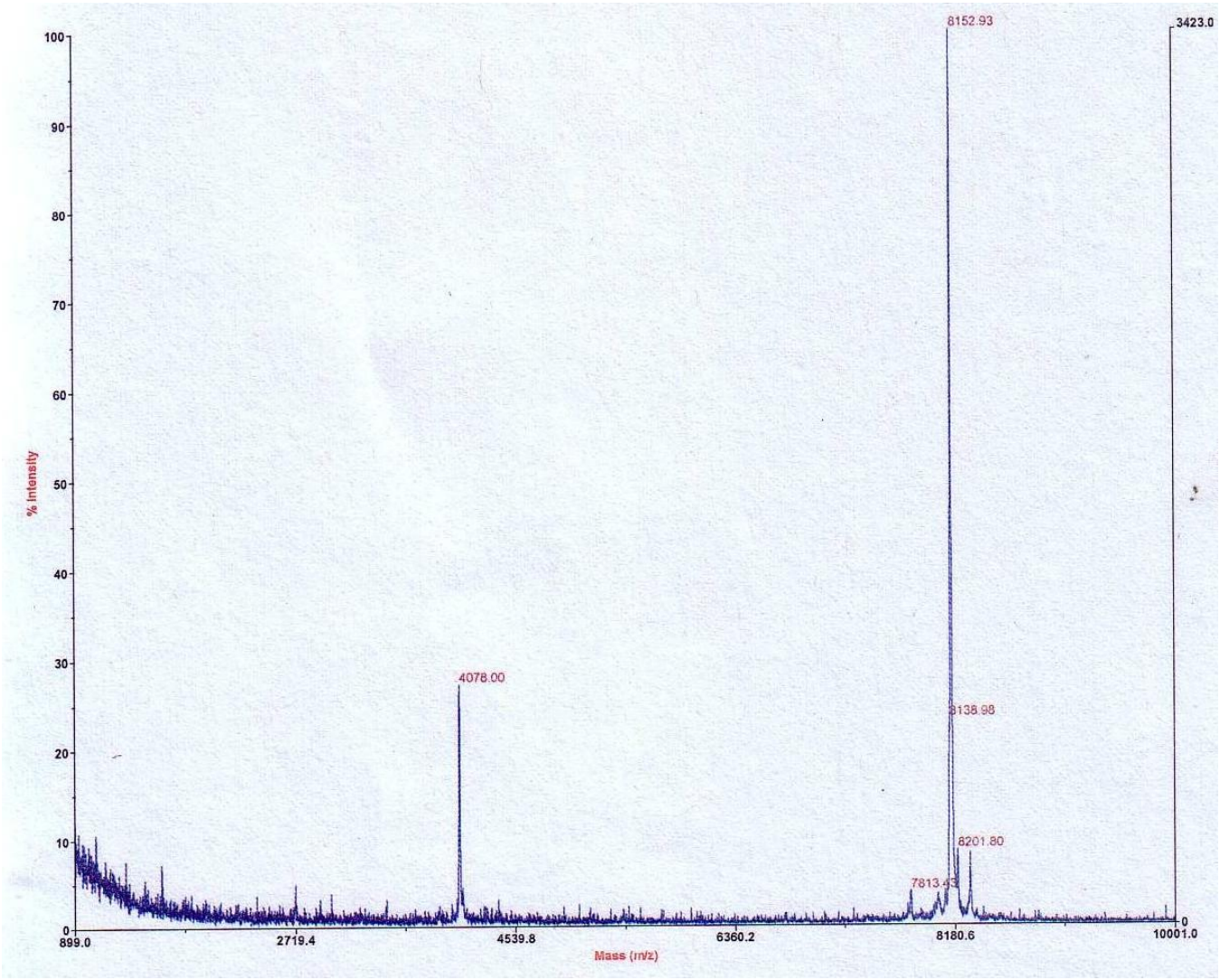
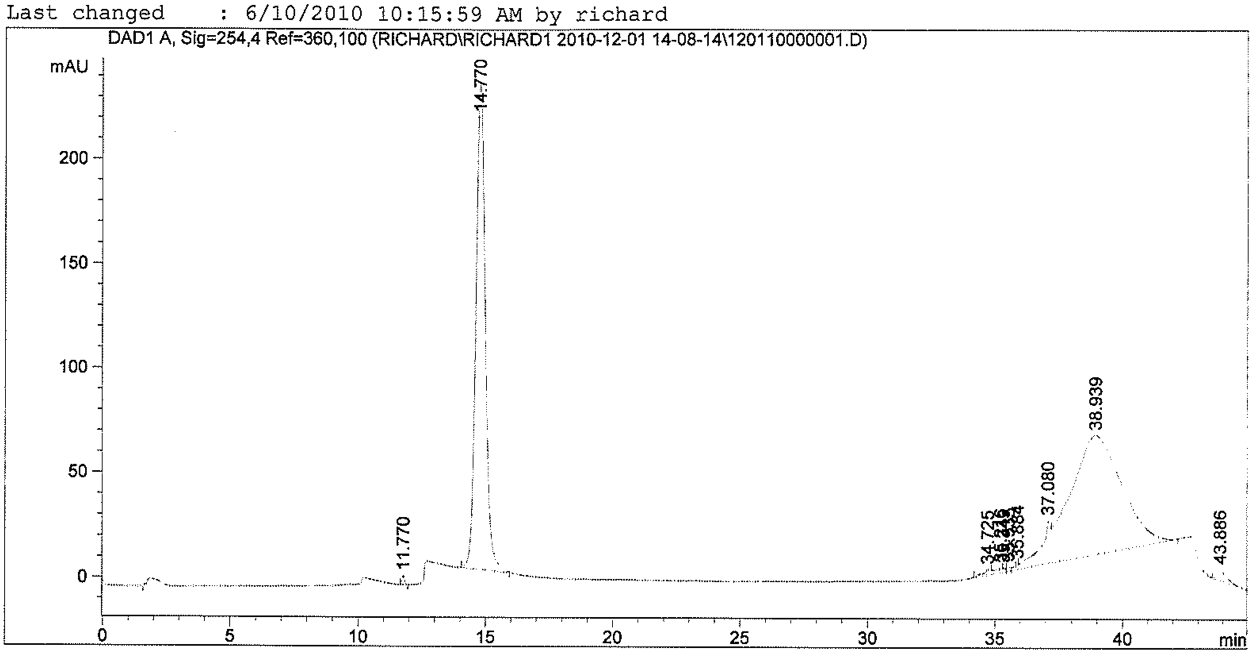


Figure S43 MALDI-TOF mass spectrum of ORN **13**

Data File C:\HPCHEM\1\DATA\RICHARD\RICHARD1 2010-12-01 14-08-14\120110000001.D
Sample Name: RT111 miR122 2'OMe PS 4PACE DMToff

===

Acq. Operator : richard   Seq. Line : 1
Acq. Instrument : Instrument 1   Location : Vial 1
Injection Date : 12/1/2010 2:09:56 PM   Inj : 1
                Inj Volume : 100 µl
Different Inj Volume from Sequence !   Actual Inj Volume : 10 µl
Acq. Method : C:\HPCHEM\1\DATA\RICHARD\RICHARD1 2010-12-01 14-08-14\A-50B.M
Last changed : 6/10/2010 10:15:59 AM by richard
Analysis Method : C:\HPCHEM\1\DATA\RICHARD\RICHARD1 2010-12-01 14-08-14\120110000001.D\DA.M (A-50B.M)
Last changed : 6/10/2010 10:15:59 AM by richard



===
Area Percent Report
===

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

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.770	BB	0.0963	27.23801	4.39394	0.1844
2	14.770	BB	0.4025	6070.83984	232.57483	41.1084
3	34.725	BV	0.2649	55.46663	2.62088	0.3756
4	35.216	VV	0.2456	46.60170	2.36790	0.3156
5	35.349	VB	0.0882	12.35856	1.89311	0.0837
6	35.535	BB	0.1236	18.25552	1.97900	0.1236
7	35.884	BV	0.0813	14.92471	2.58642	0.1011
8	37.080	VV	0.3628	606.84460	20.41373	4.1092

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Figure S44 HPLC chromatogram of ORN **13**