

Electronic Supporting Information

Design, synthesis and P-gp induction activity of aryl phosphonate esters: Identification of tetraethyl-2-phenylethene-1,1-diyldiphosphonate as an orally bioavailable P-gp inducer[‡]

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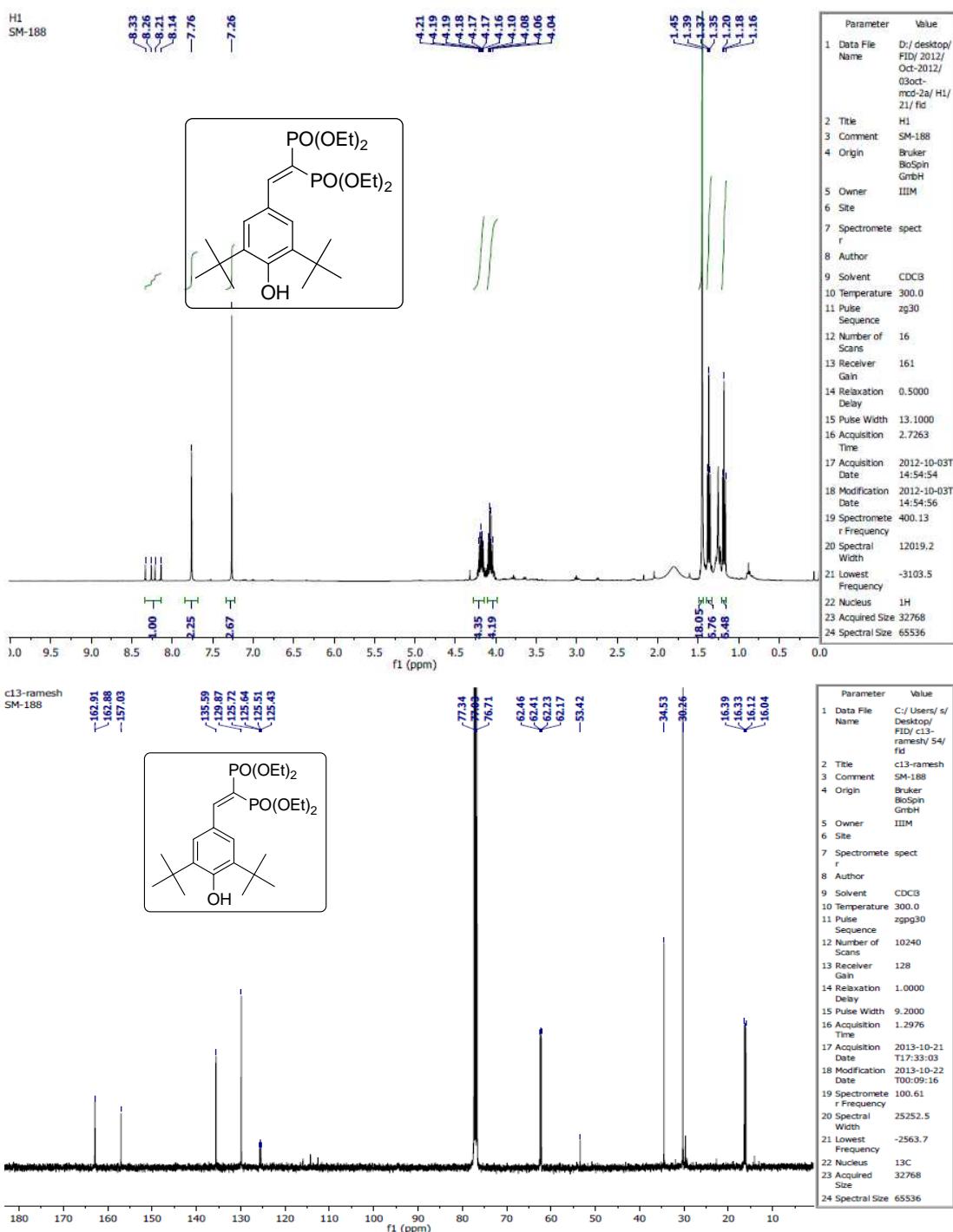
*Corresponding Author E-mail: sbharate@iiim.ac.in (SBB); ajaykmahajan@hotmail.com (AK),
Fax: +91-191-2586333; Tel: +91-191-2585006.

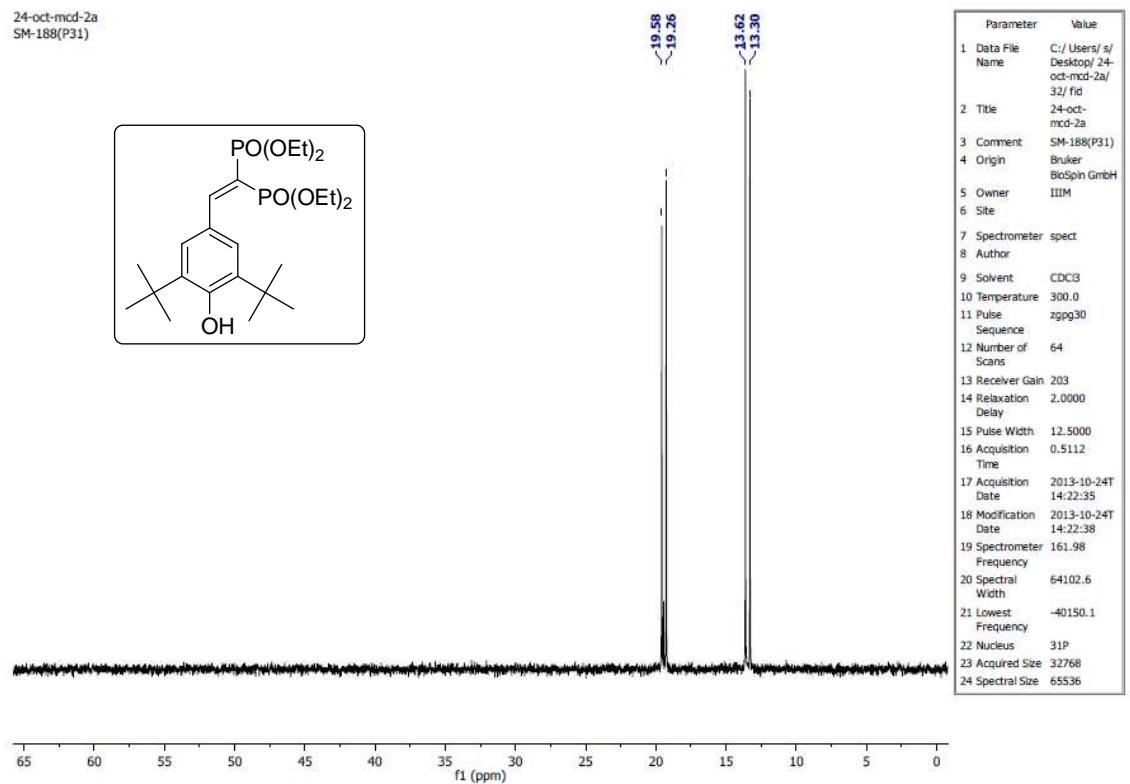
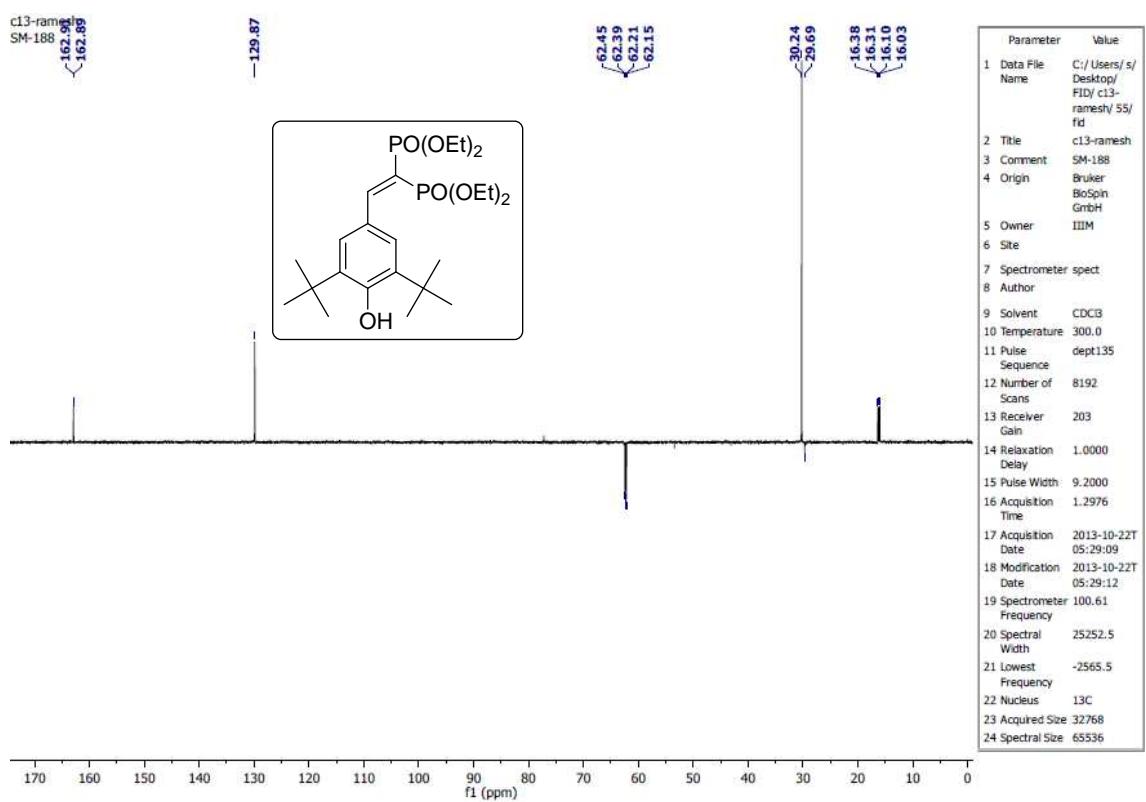
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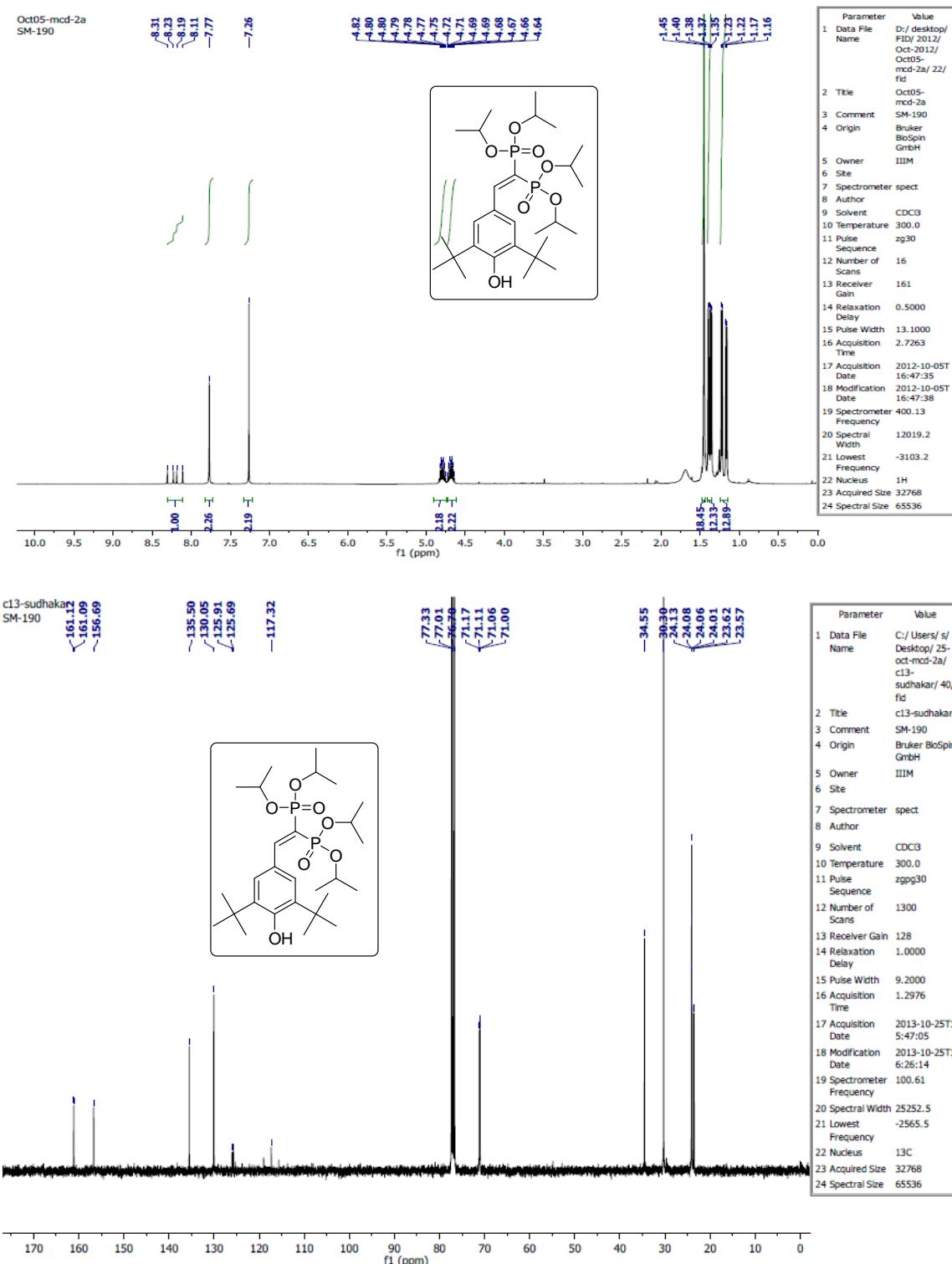
S1. NMR SPECTRA SCANS

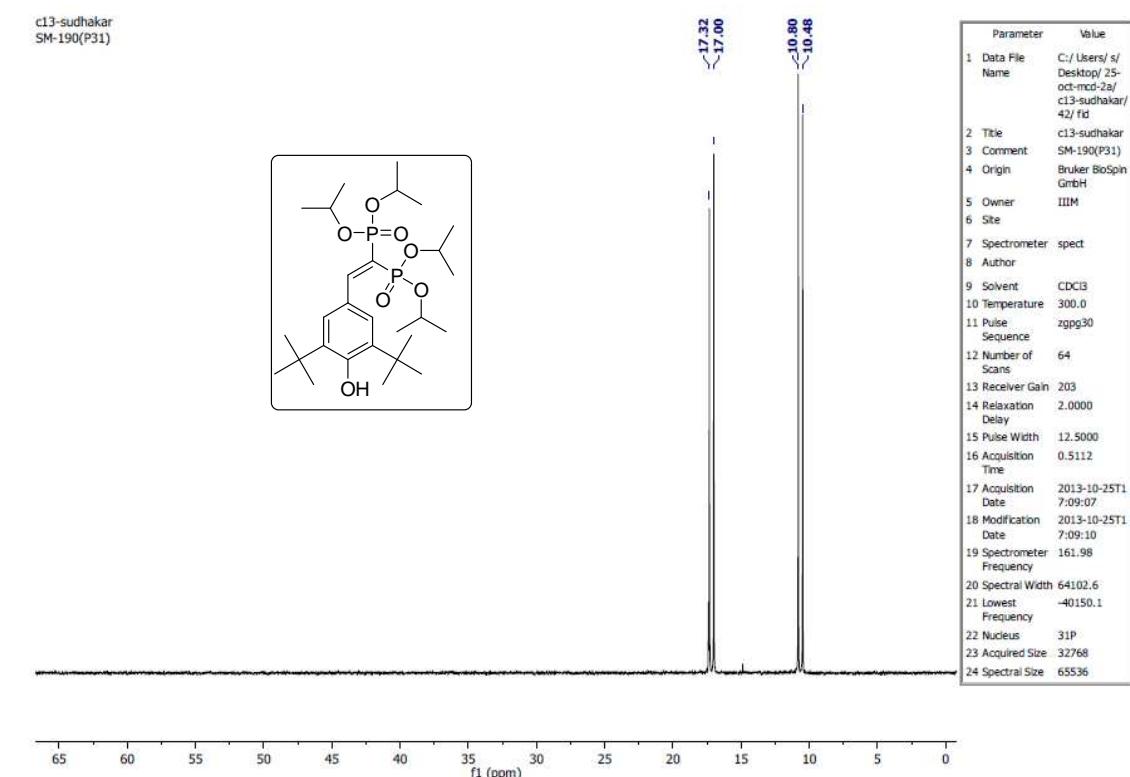
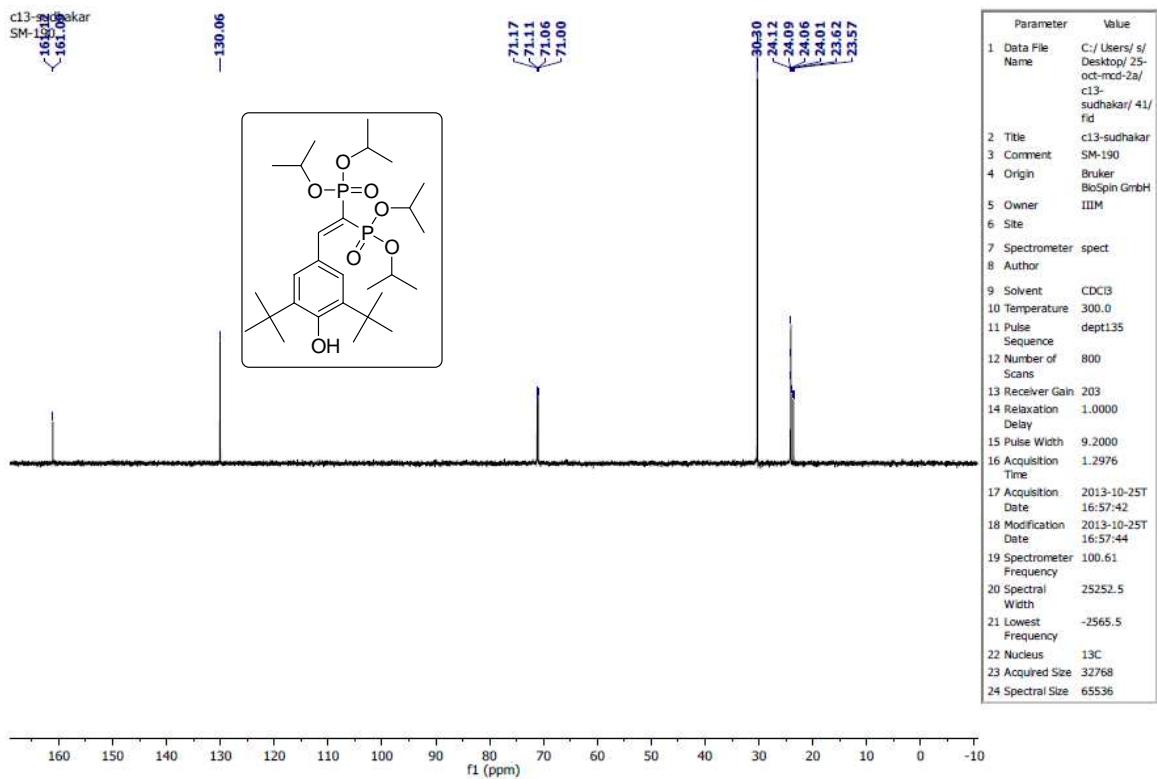
1. ^1H , ^{13}C , DEPT135 and ^{31}P NMR spectra of Tetraethyl 2-(3, 5-di-t-butyl-4-hydroxyphenyl)ethene-1,1 diyldiphosphonate (6a)



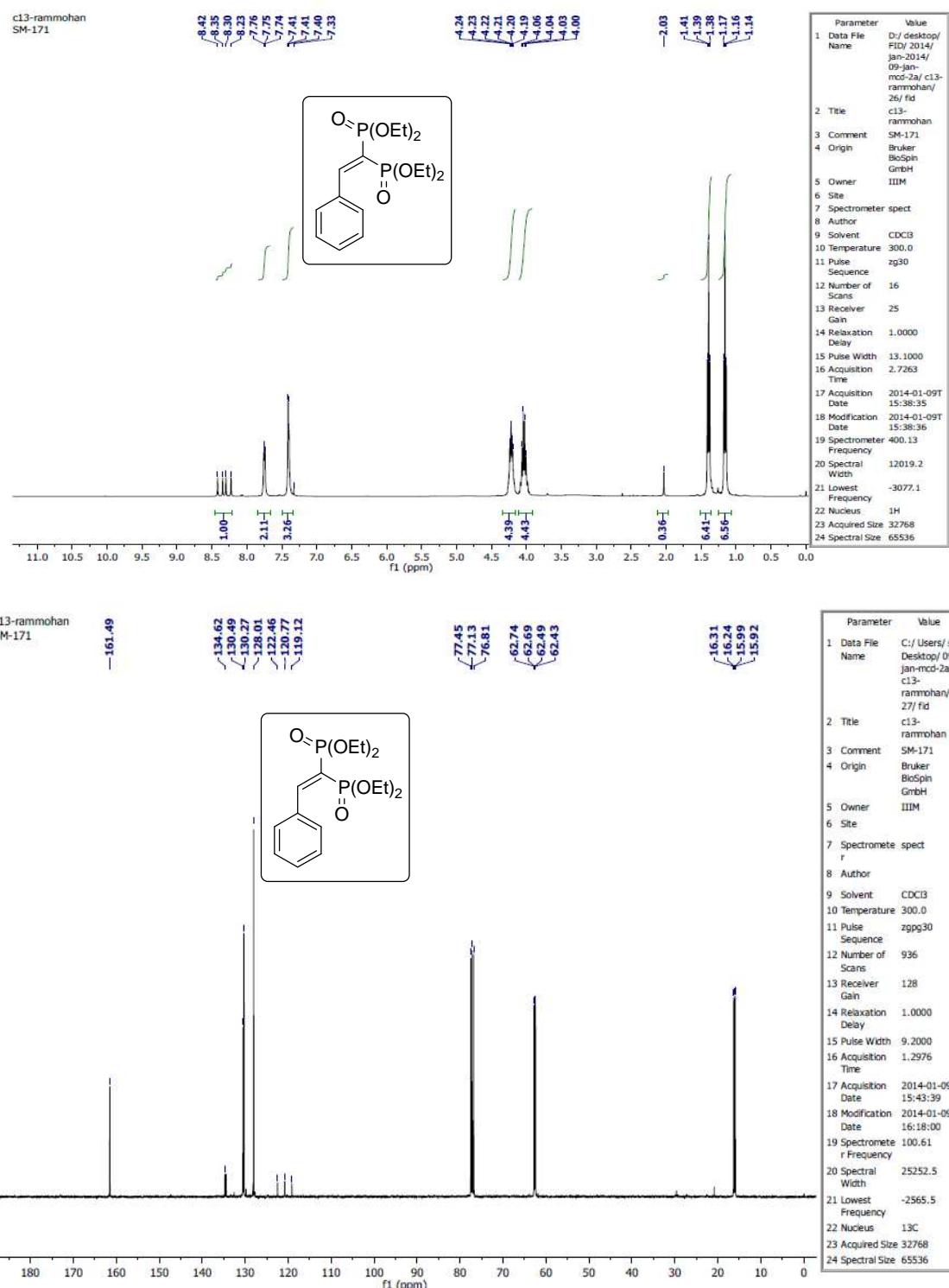


2. ^1H , ^{13}C , DEPT135 and ^{31}P NMR spectra of Tetraisopropyl 2-(3, 5-di-t-Butyl 4-hydroxy phenyl)ethene-1,1-diyldiphosphonate (6b)

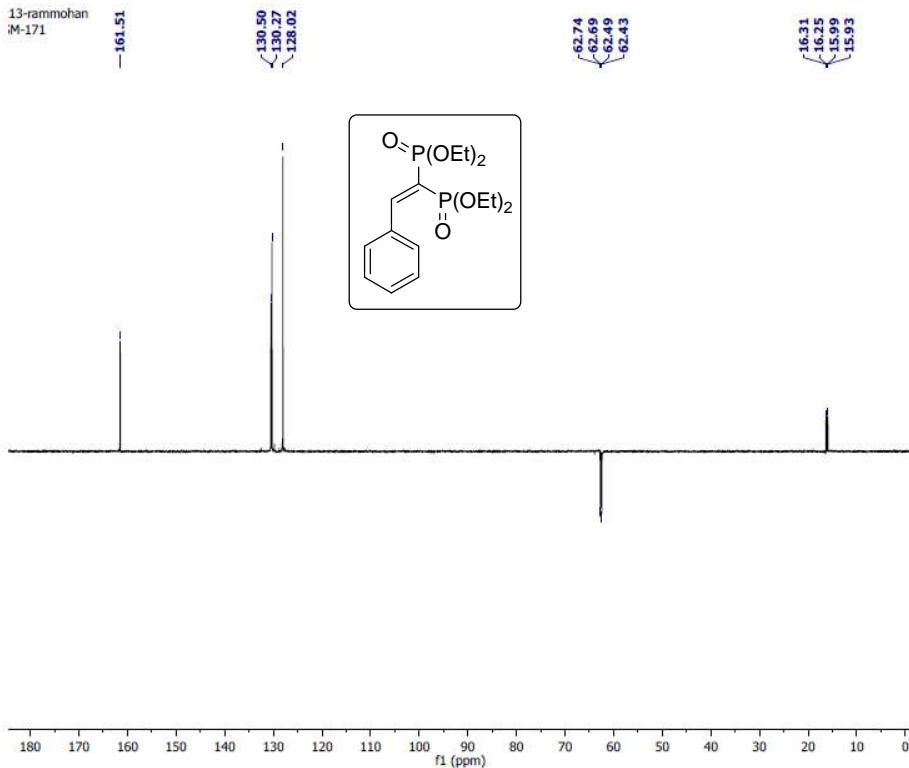




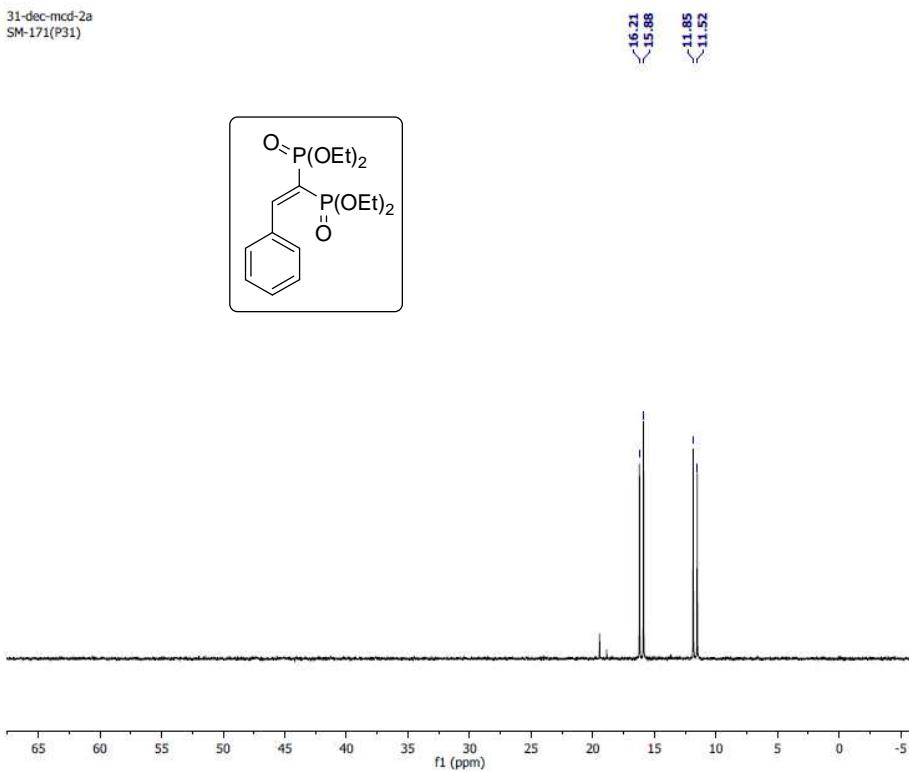
3. ^1H , ^{13}C , DEPT135 and ^{31}P NMR spectra of Tetraethyl 2-phenylethene-1,1-diyldiphosphonate (6c)



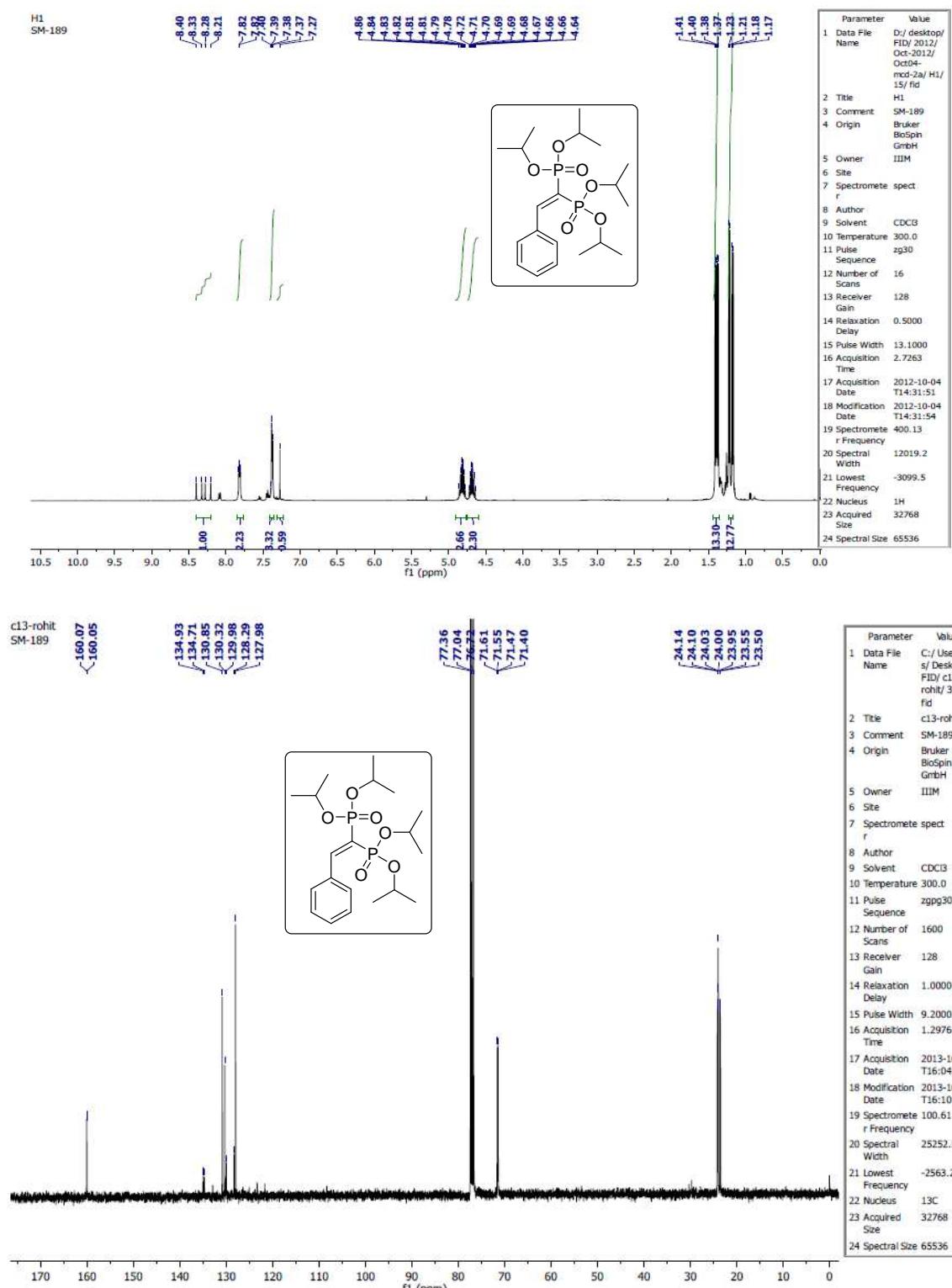
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M-171

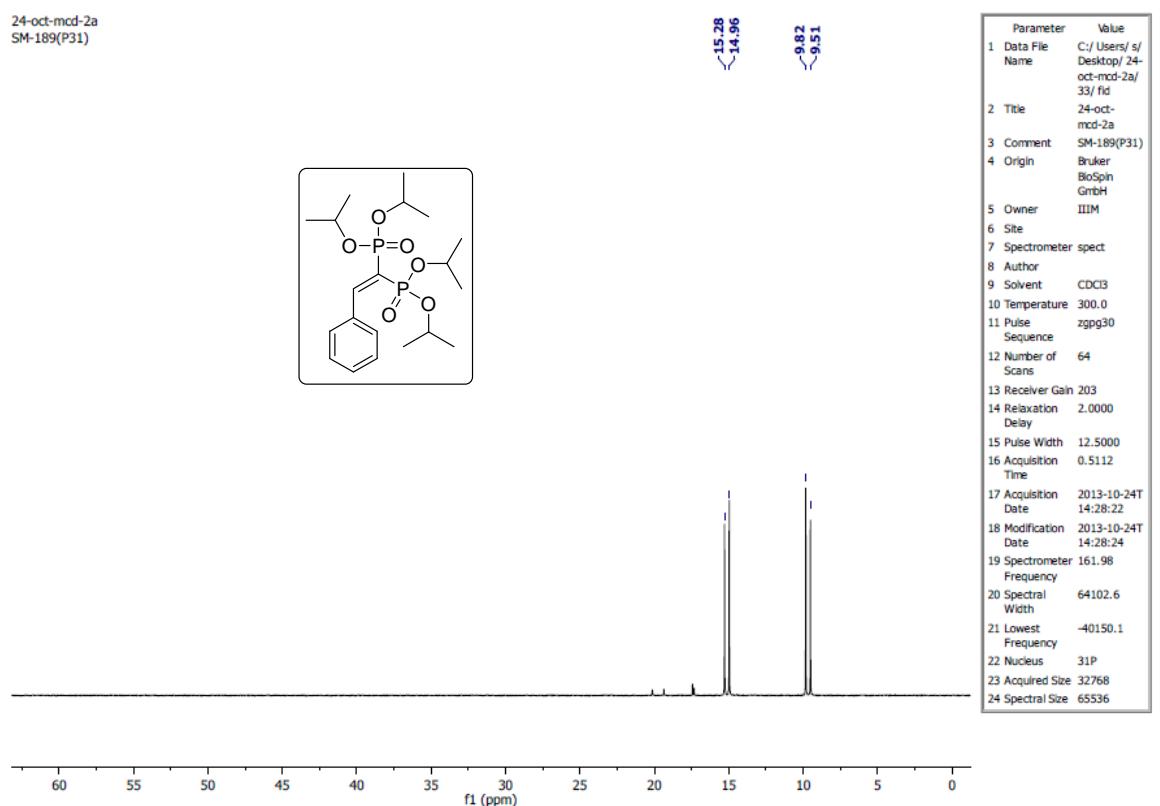
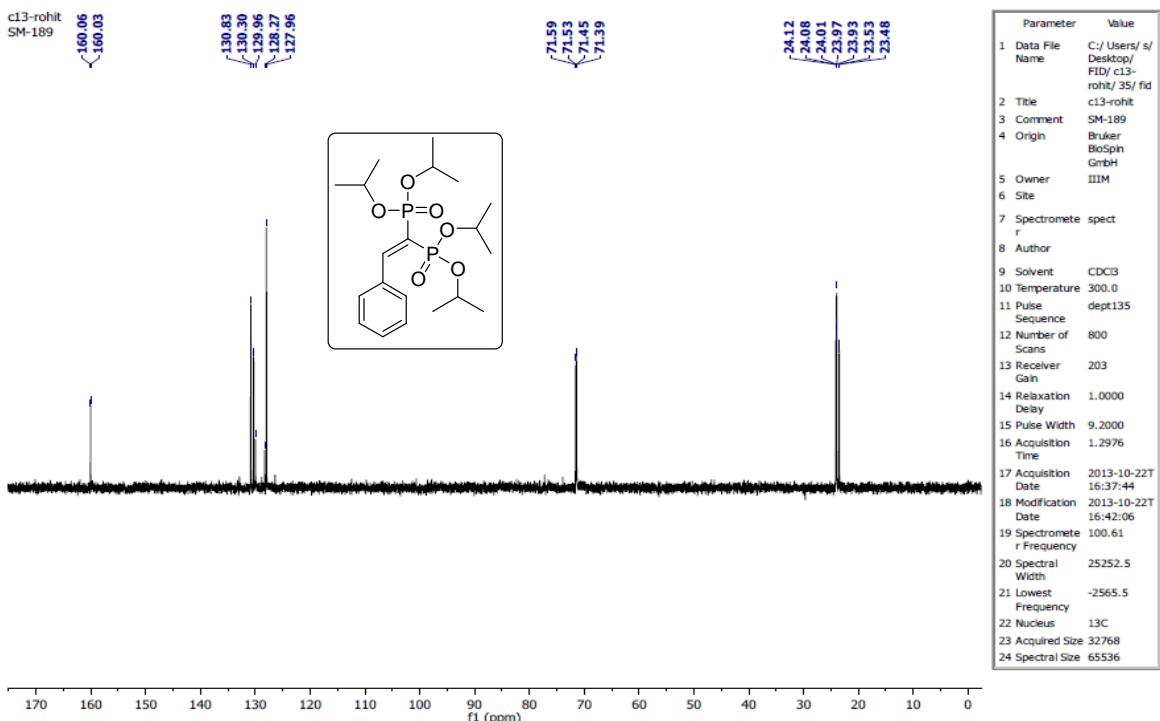


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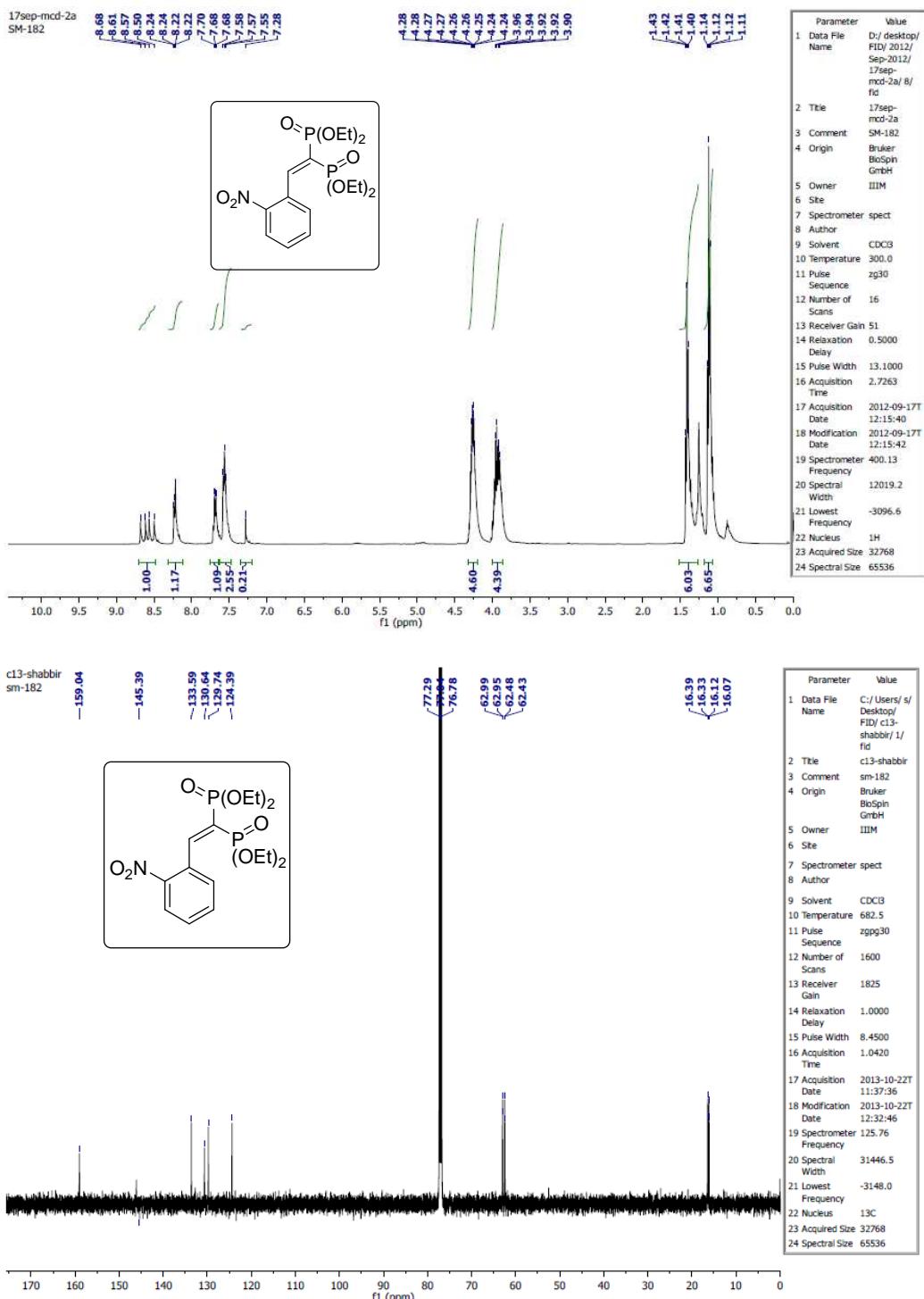


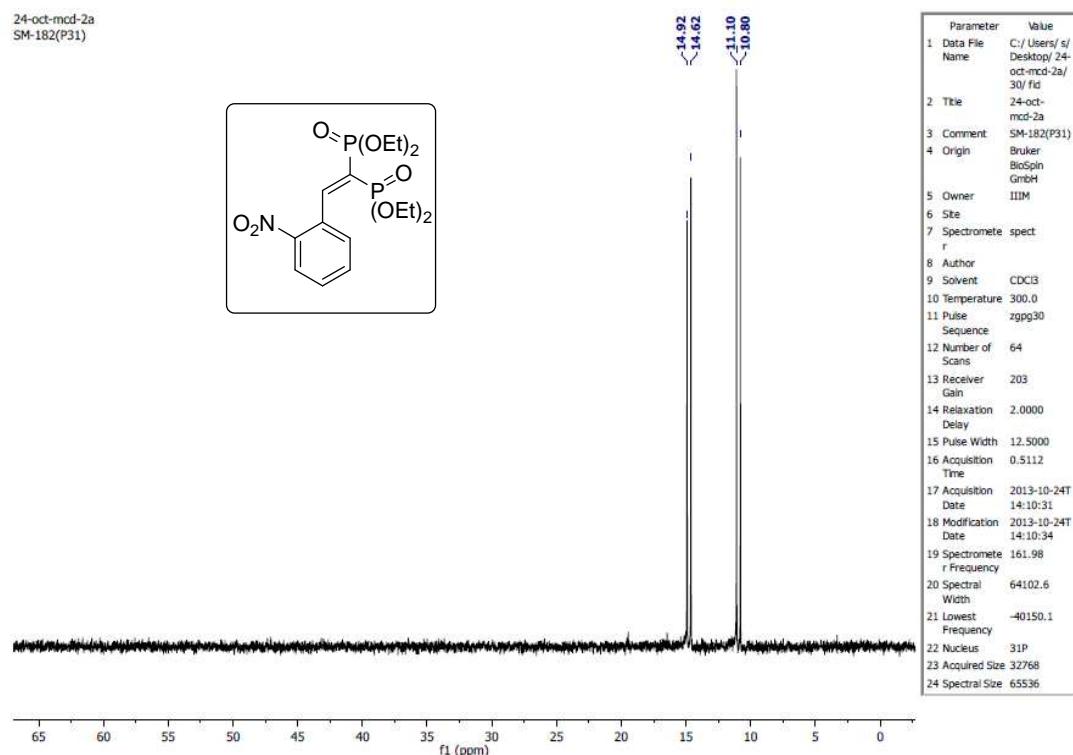
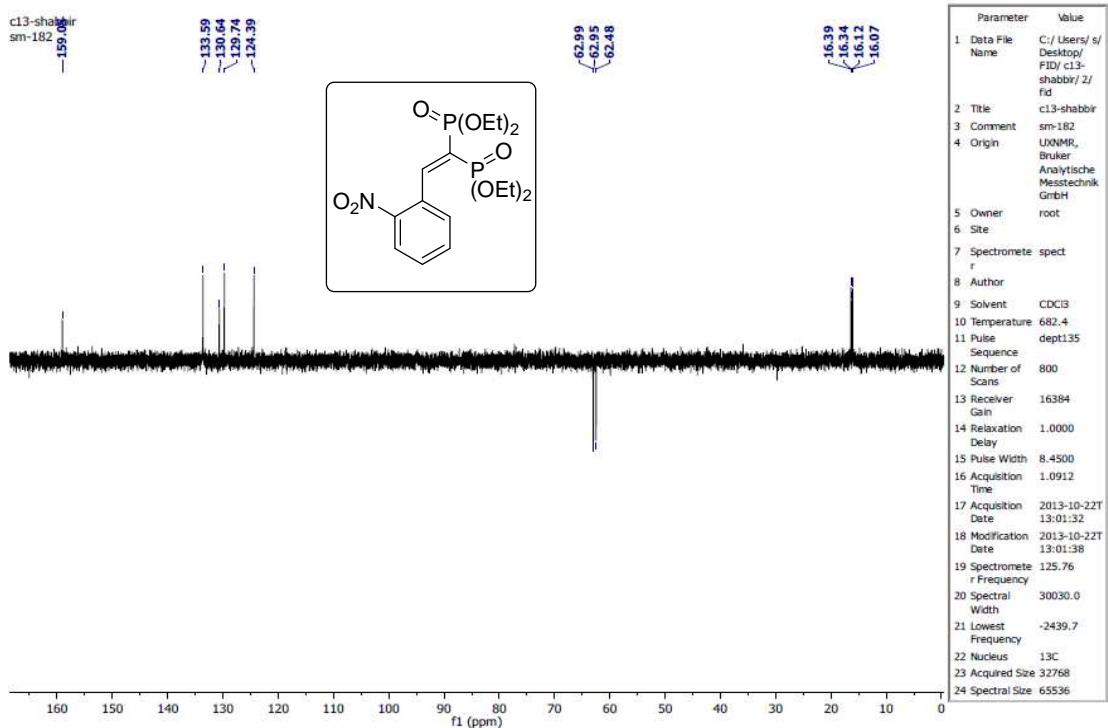
4. ^1H , ^{13}C , DEPT135 and ^{31}P NMR spectra of Tetraisopropyl-2-phenylethene-1,1-diyldiphosphonate (6d)



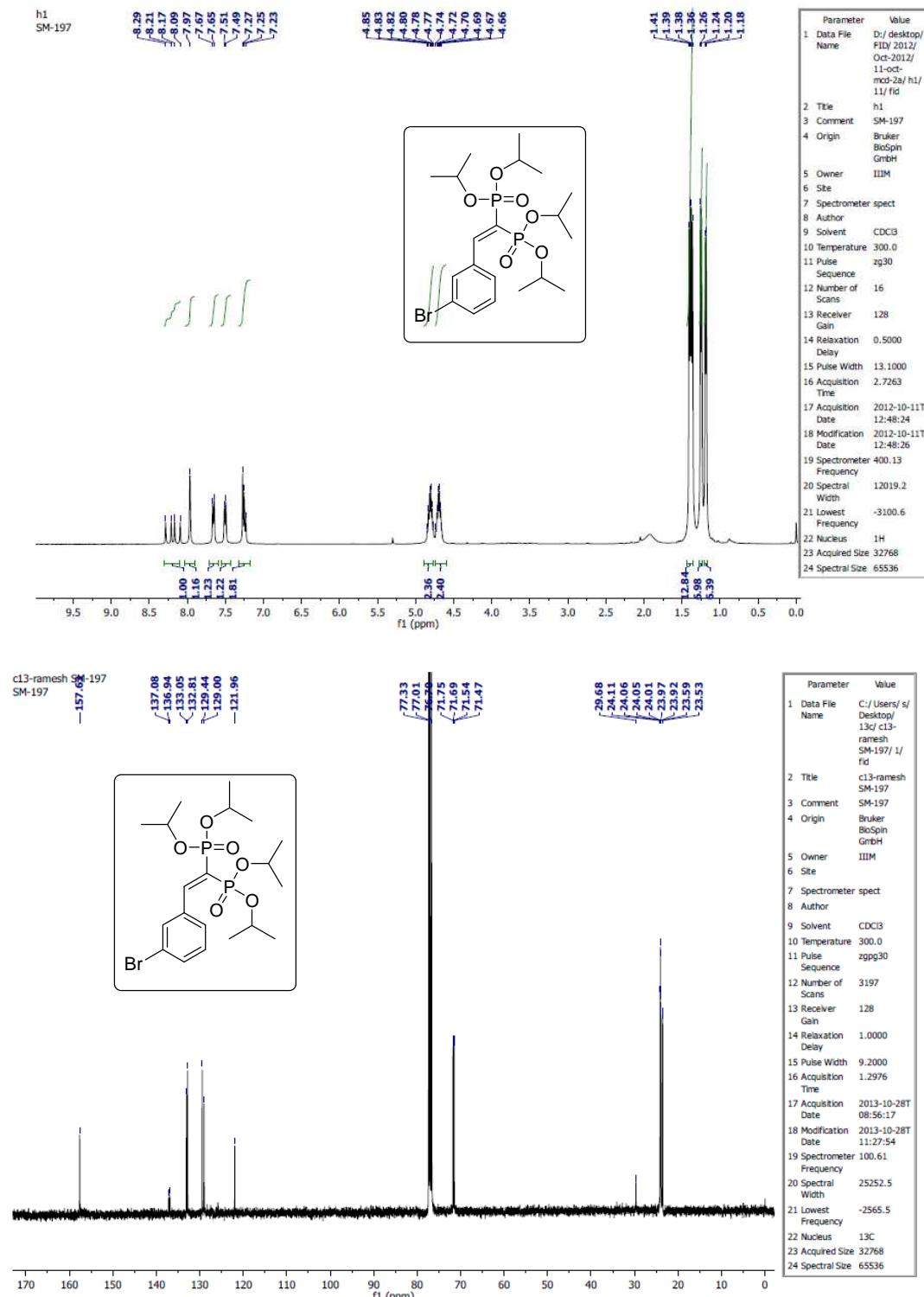


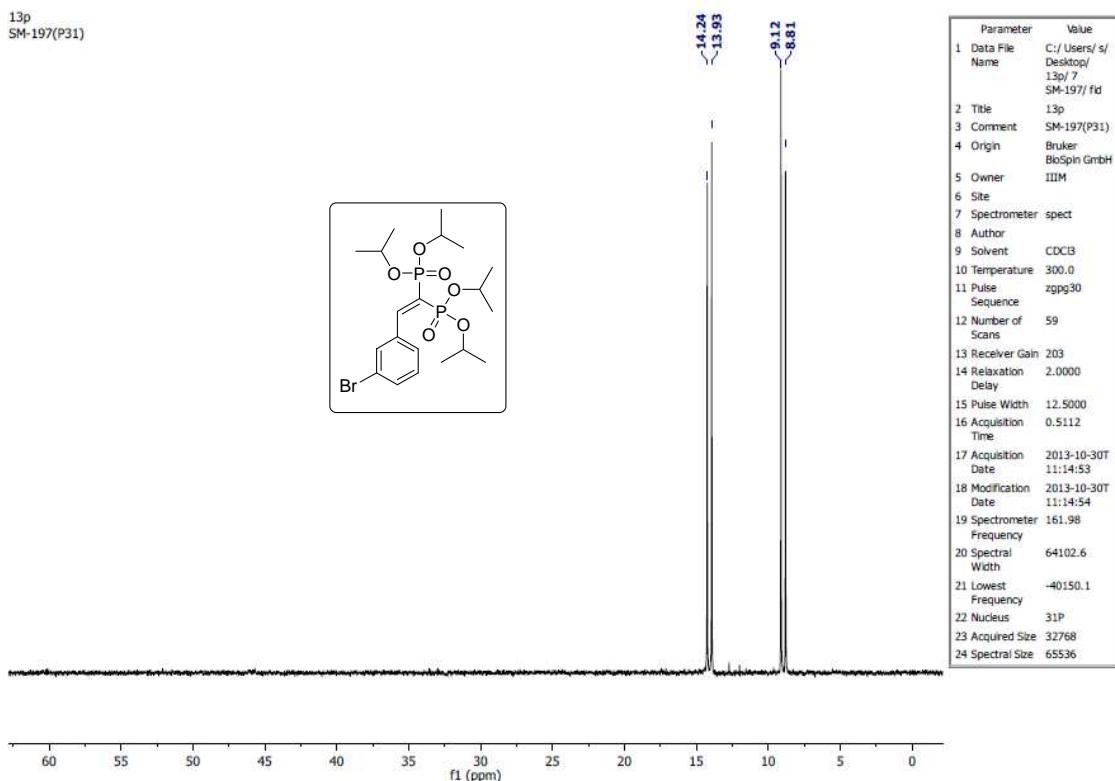
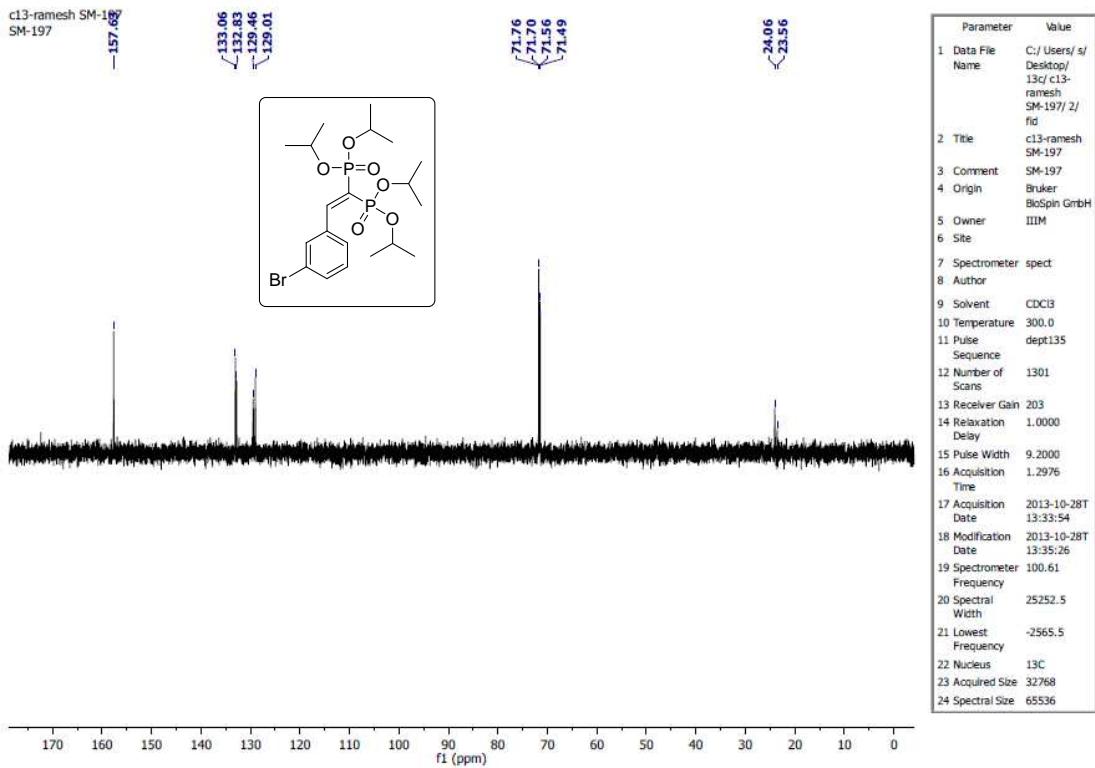
5. ^1H , ^{13}C , DEPT135 and ^{31}P NMR spectra of Tetraethyl 2-(2-nitrophenyl)ethene-1,1-diyldiphosphonate (6e)



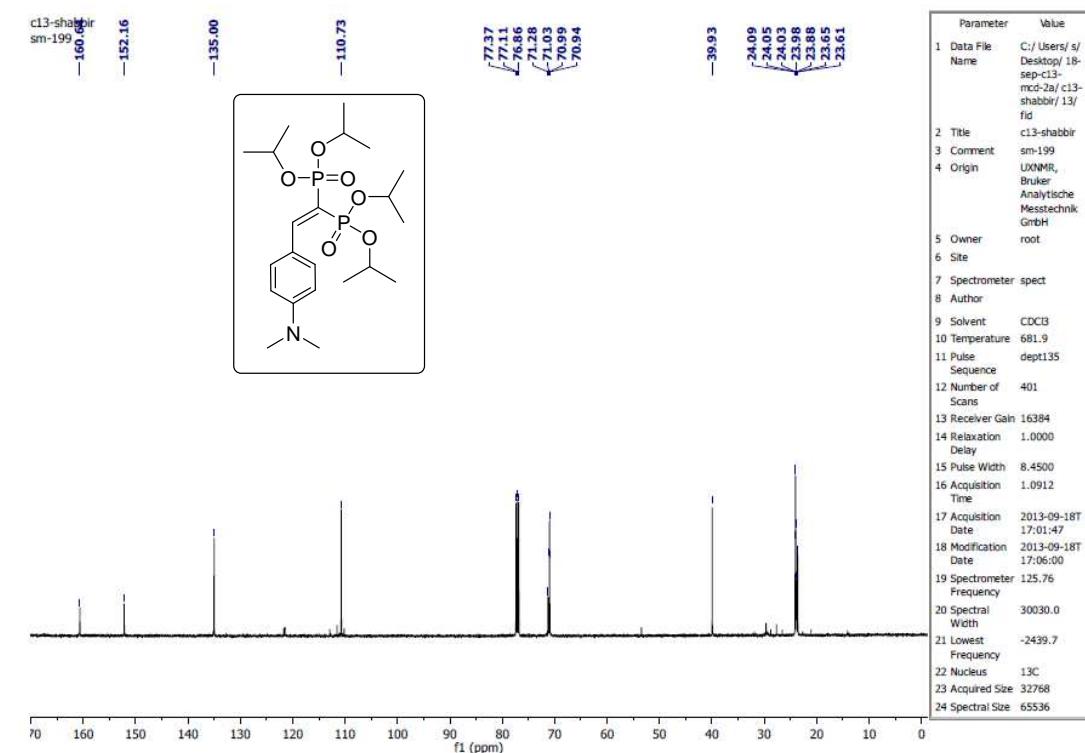
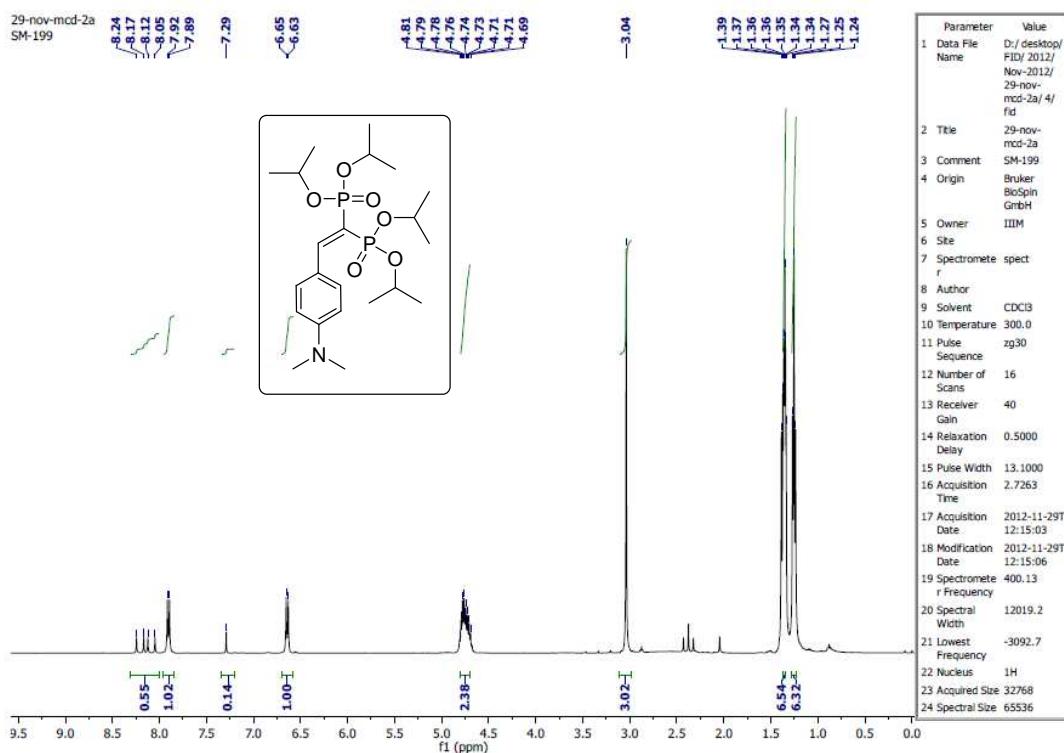


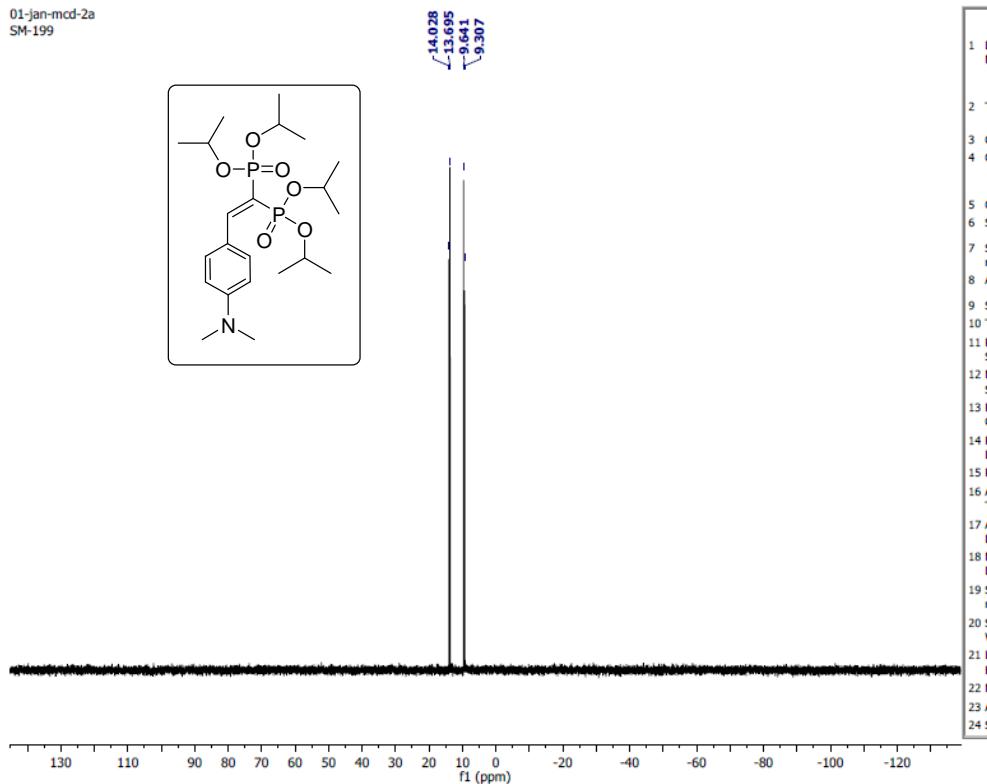
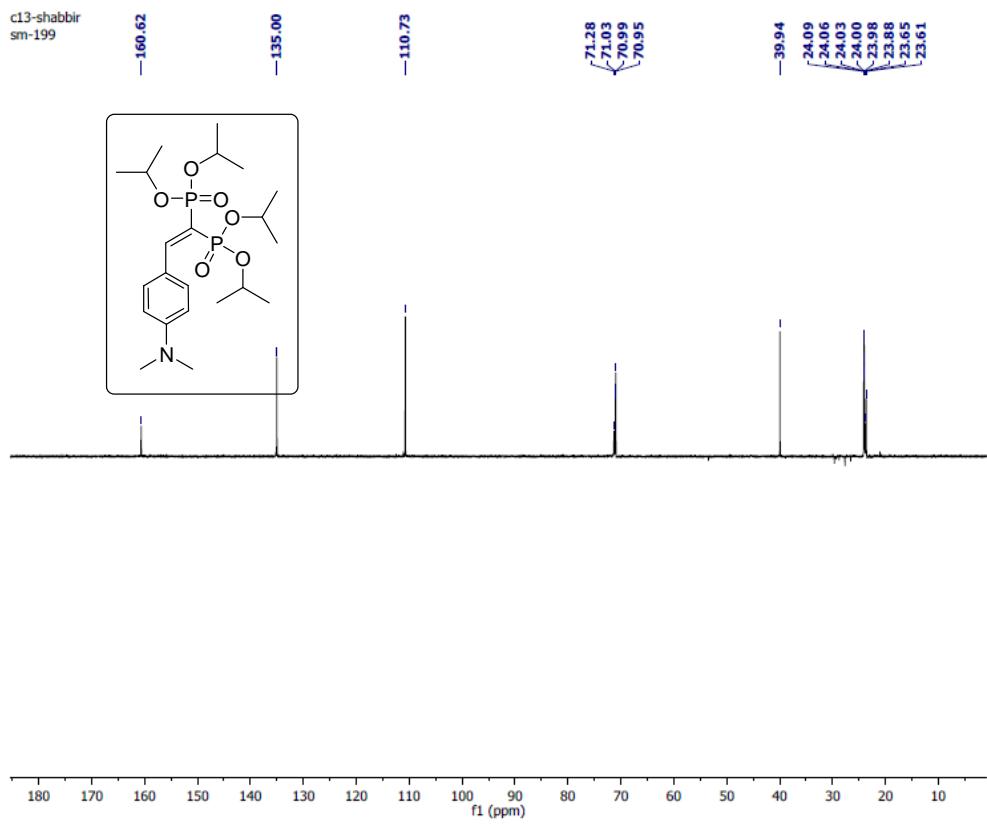
6. ^1H , ^{13}C , DEPT135 and ^{31}P NMR spectra of Tetraisopropyl,2-(3-bromophenyl)ethane-1,1-diylidiphosphonate (6f)



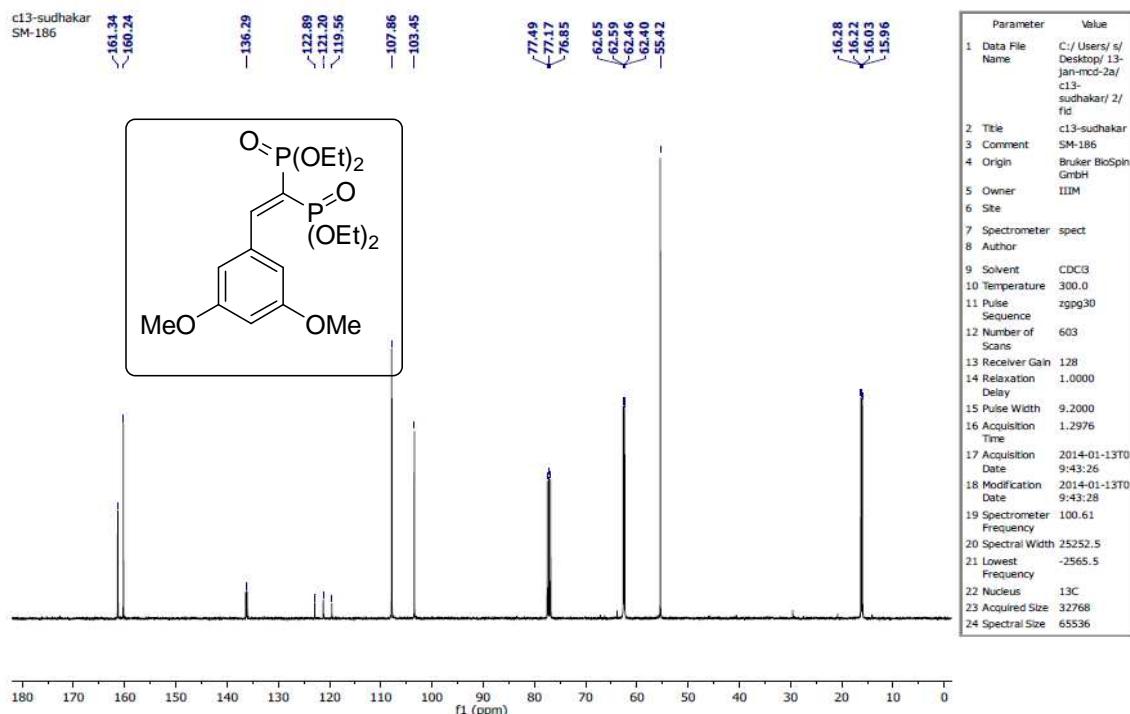
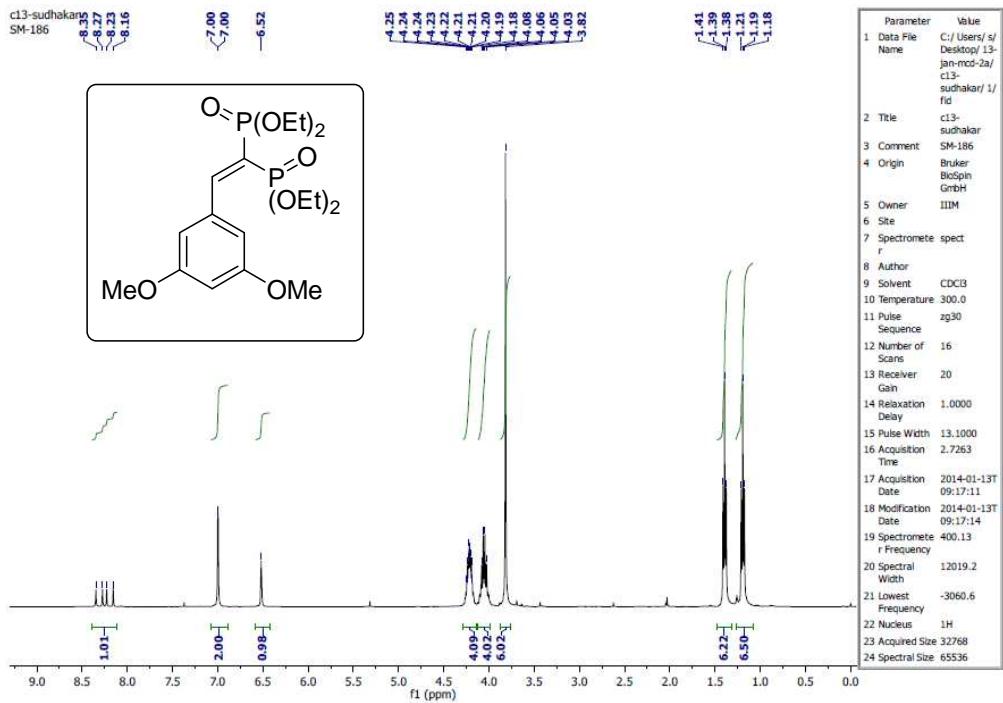


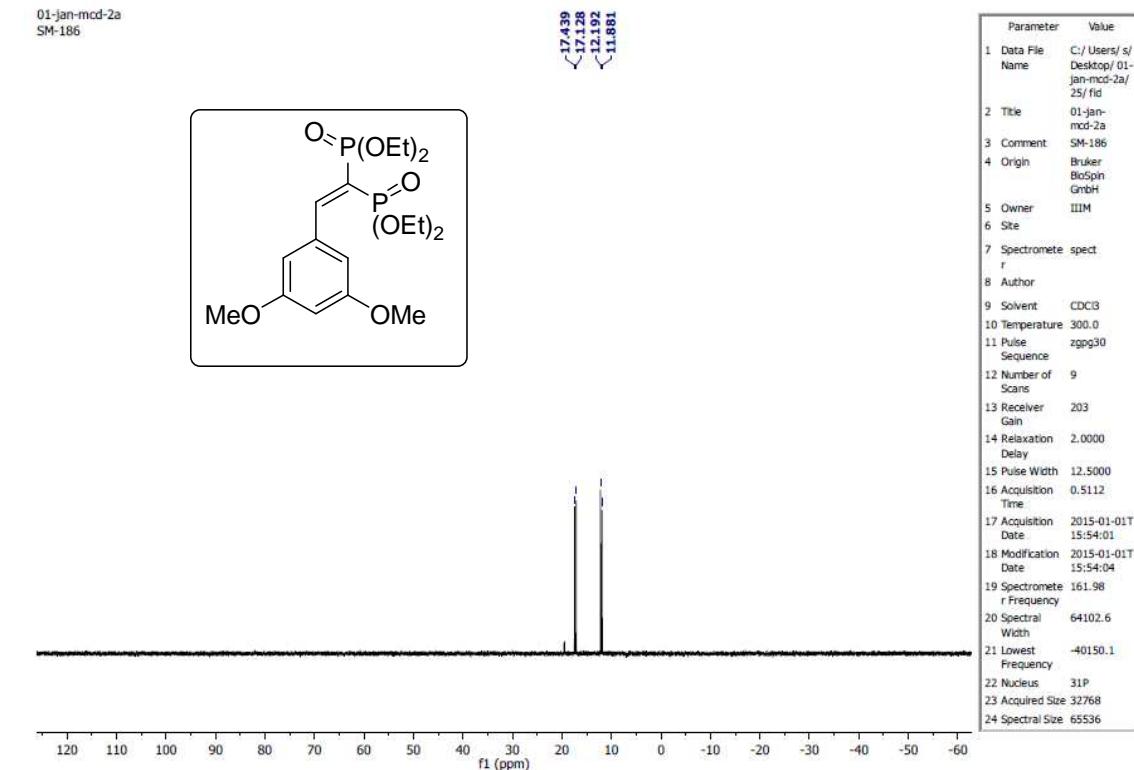
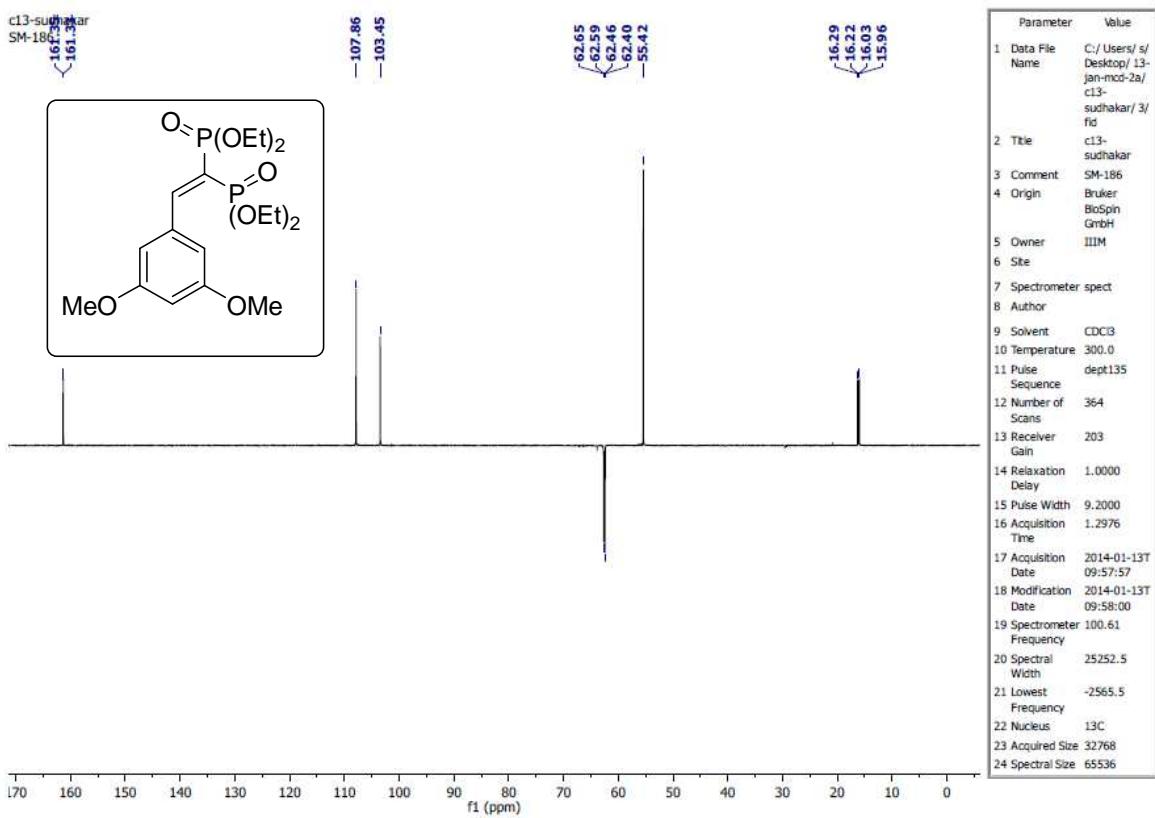
7. ^1H , ^{13}C , DEPT135 and ^{31}P NMR spectra of Tetraisopropyl2-(4-N,N-dimethylaminophenyl)ethene-1,1-diylidiphosphonate (6g)



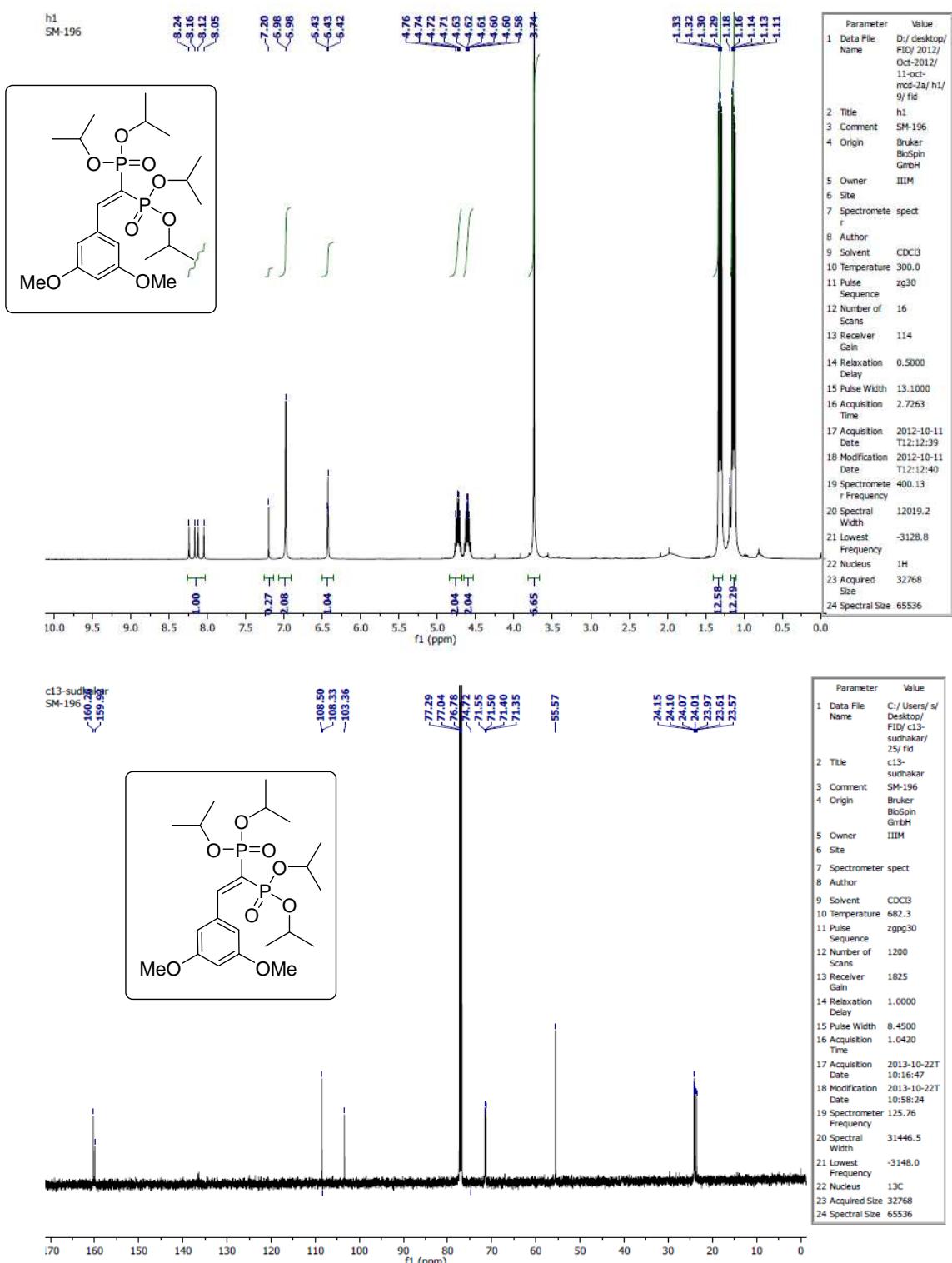


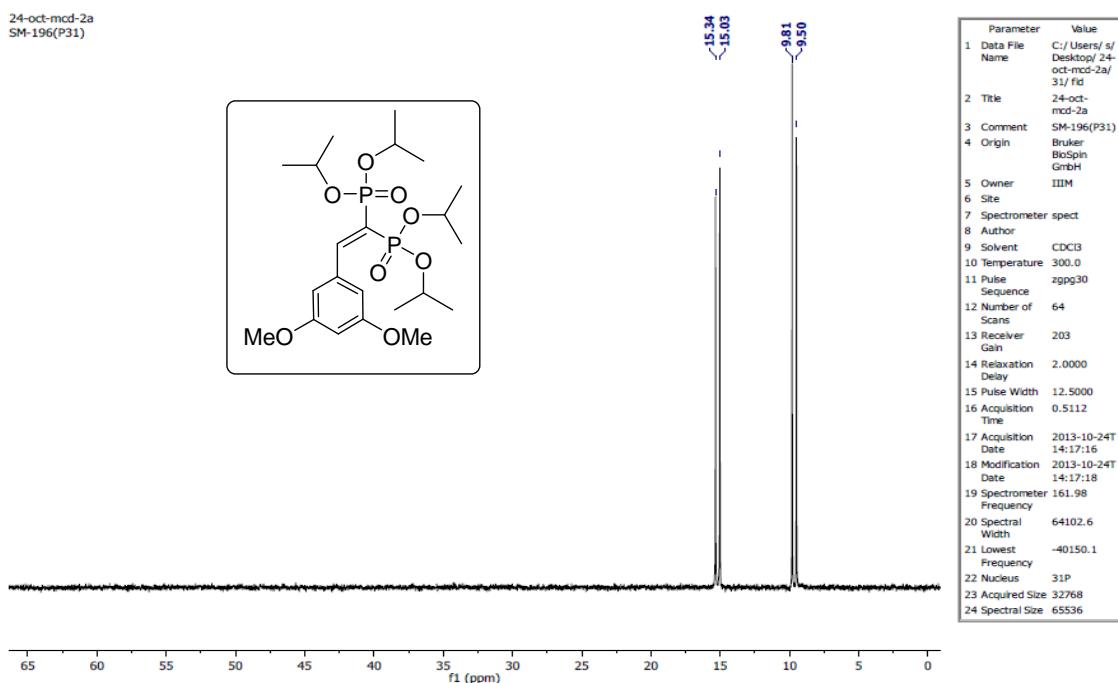
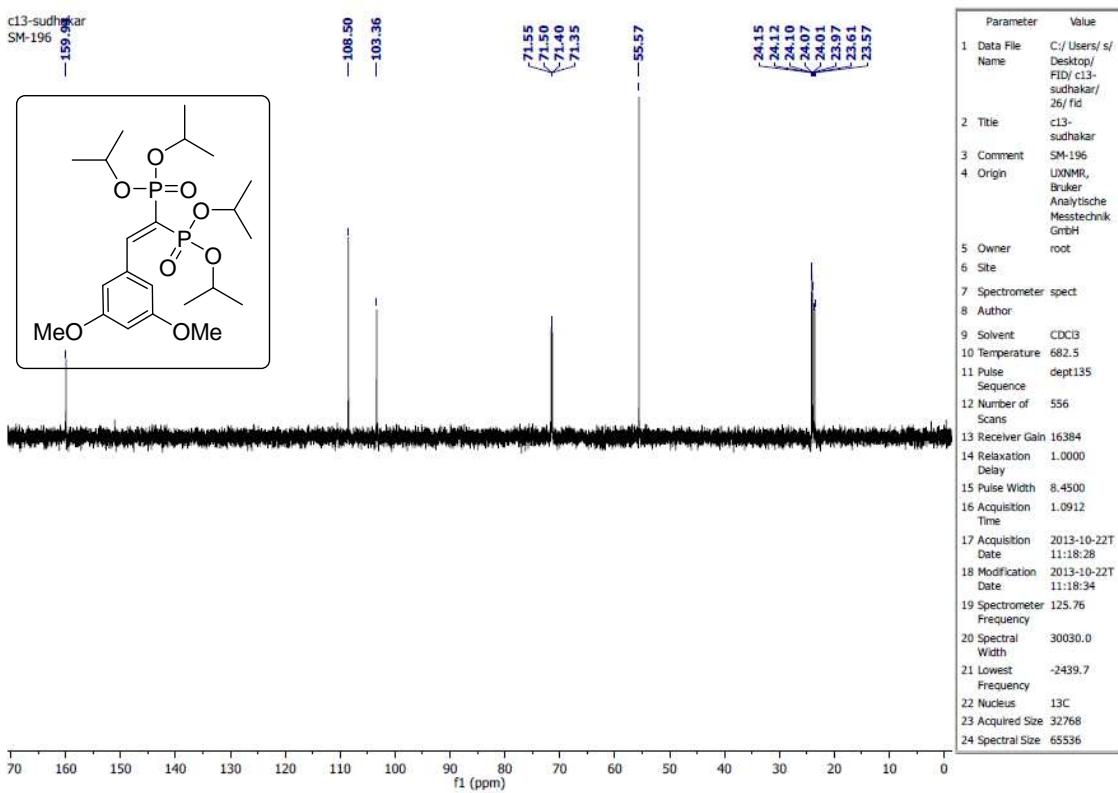
8. ^1H , ^{13}C , DEPT135 and ^{31}P NMR spectra of Tetraethyl2-(3,5dimethoxyphenyl)ethene-1,1-diyldiphosphonate (6h)



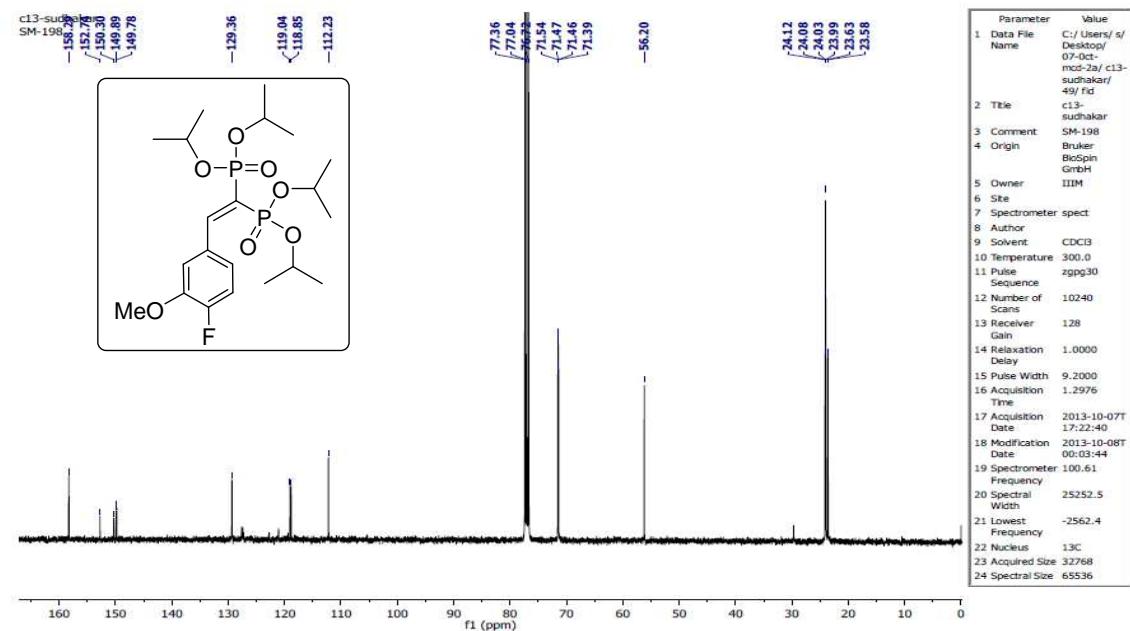
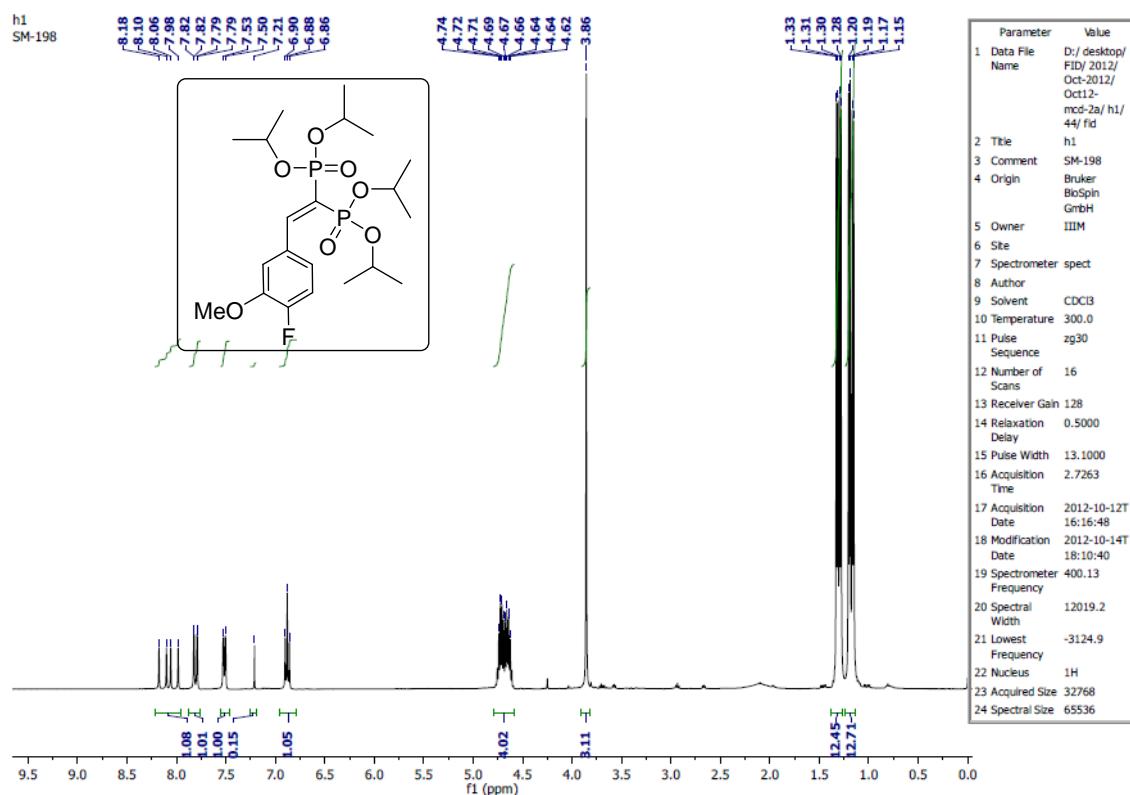


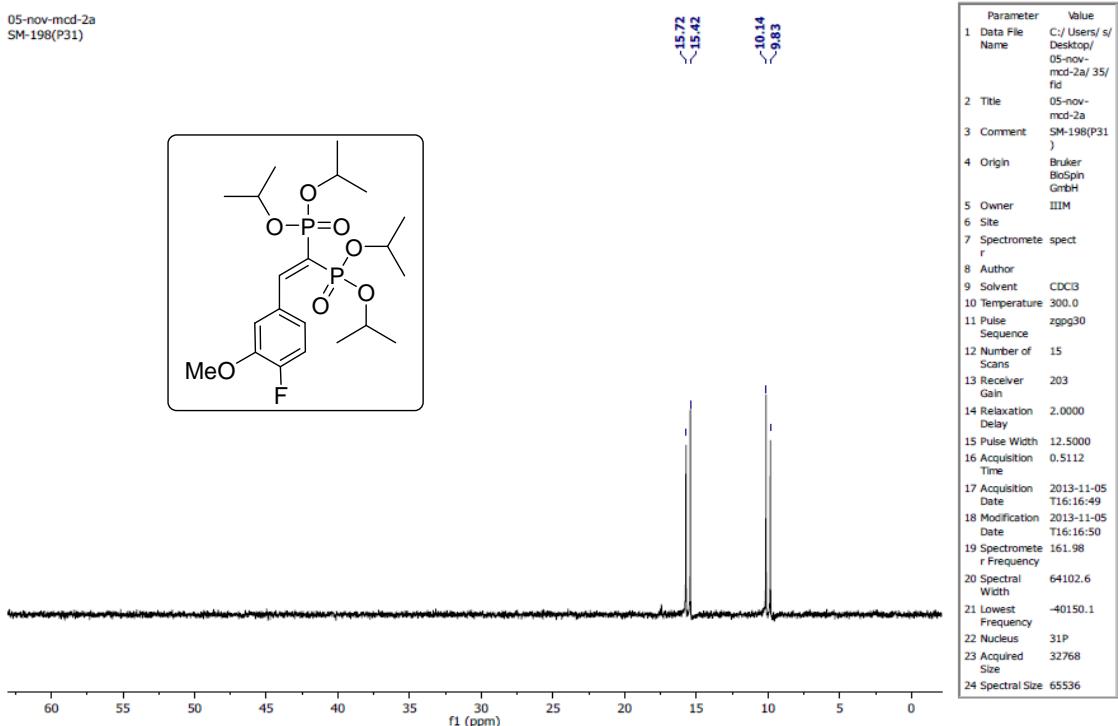
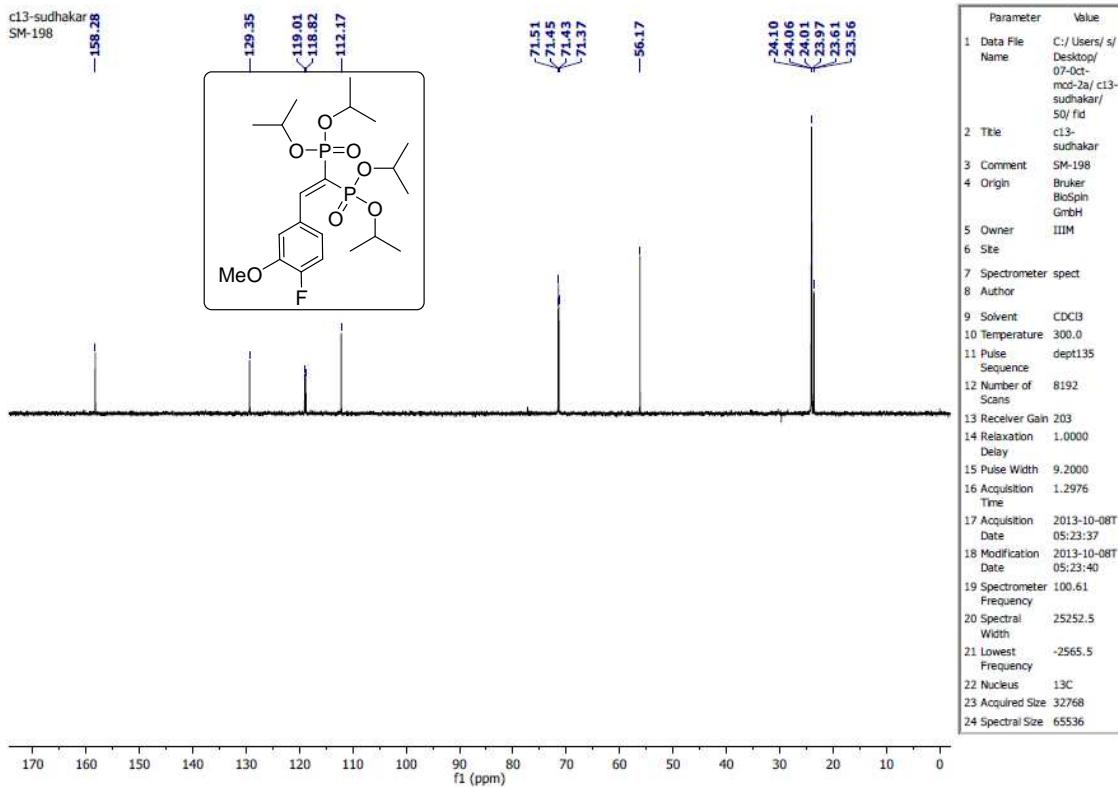
9. ^1H , ^{13}C , DEPT135 and ^{31}P NMR spectra of Tetraisopropyl2-(3,5-dimethoxyphenyl)ethene-1,1 diyldiphosphonate (6i)



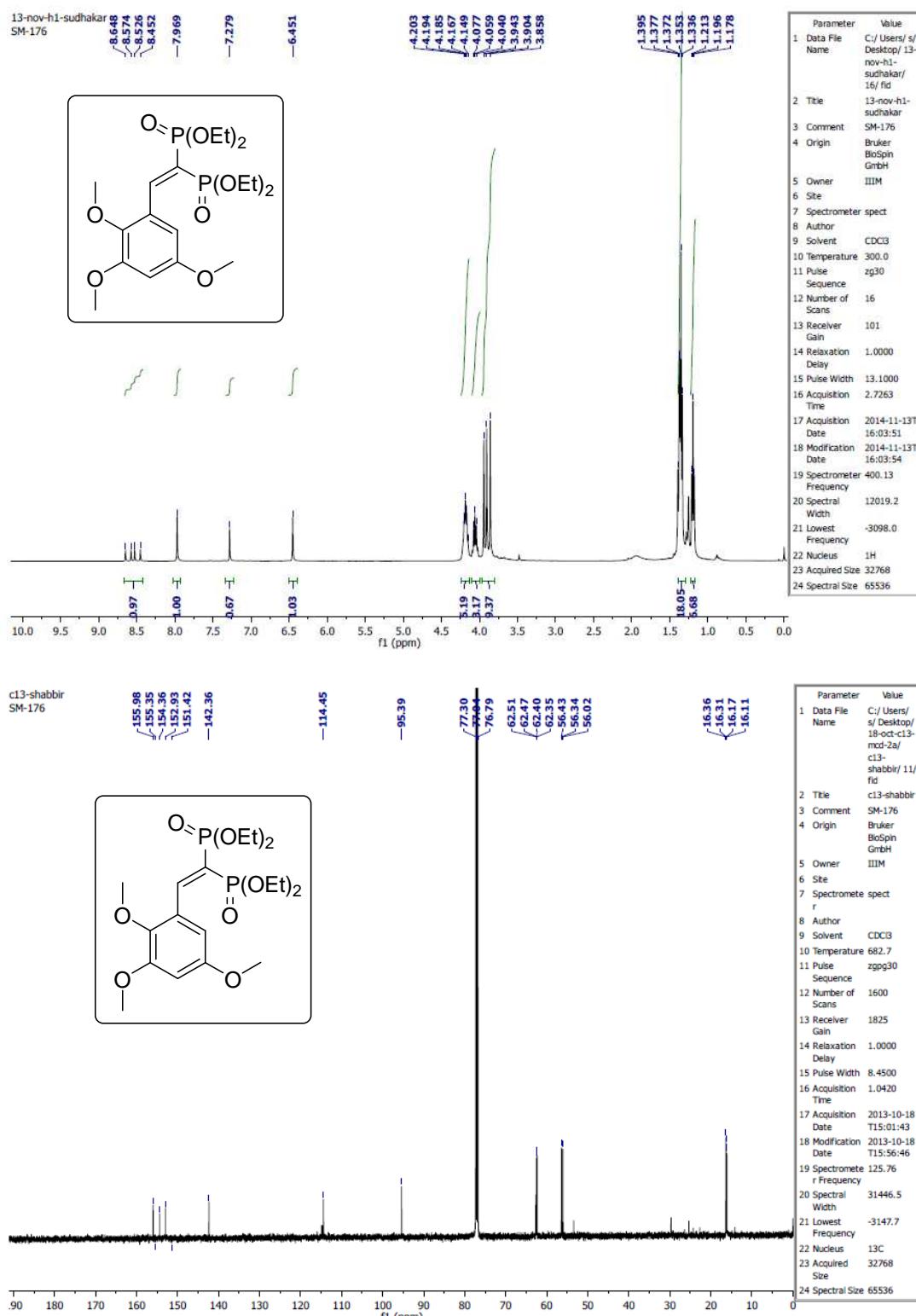


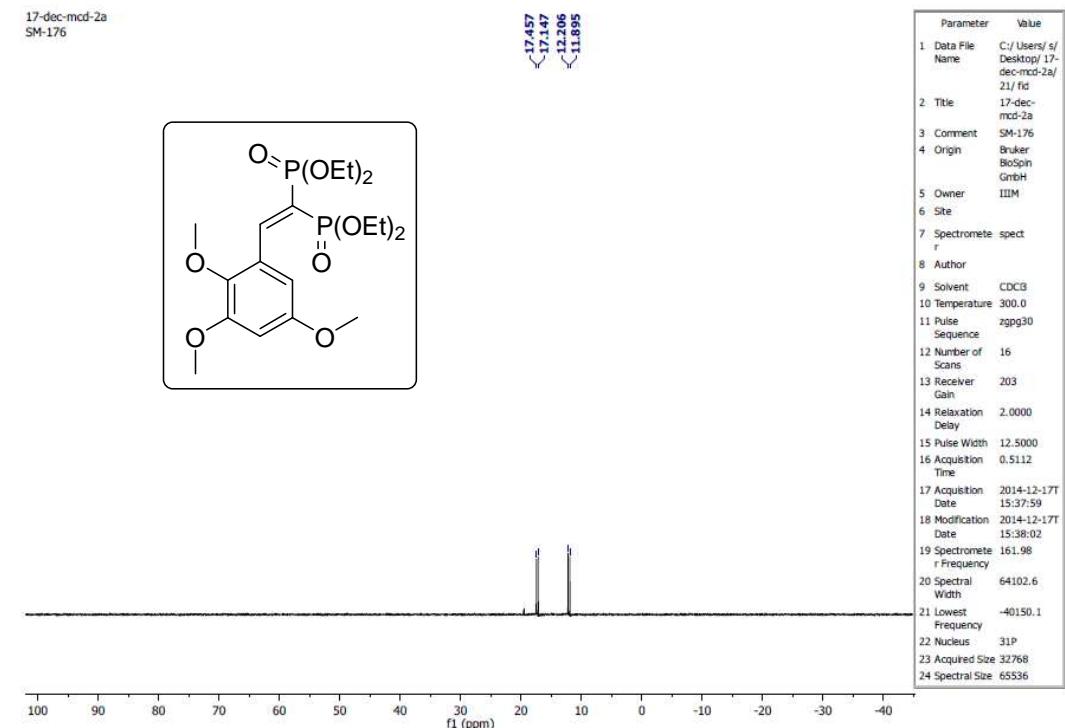
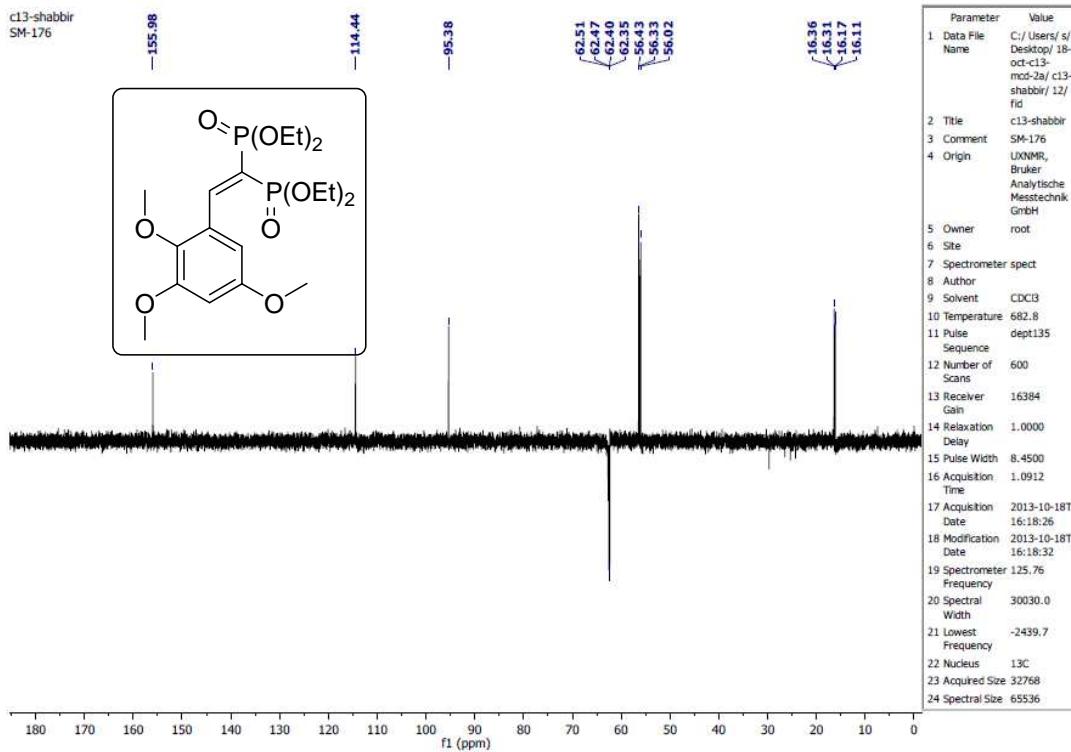
10. ^1H , ^{13}C , DEPT135 and ^{31}P NMR spectra of tetraisopropyl-2-(3-methoxy4-fluorophenyl)ethene-1,1diyldiphosphonate (6j)



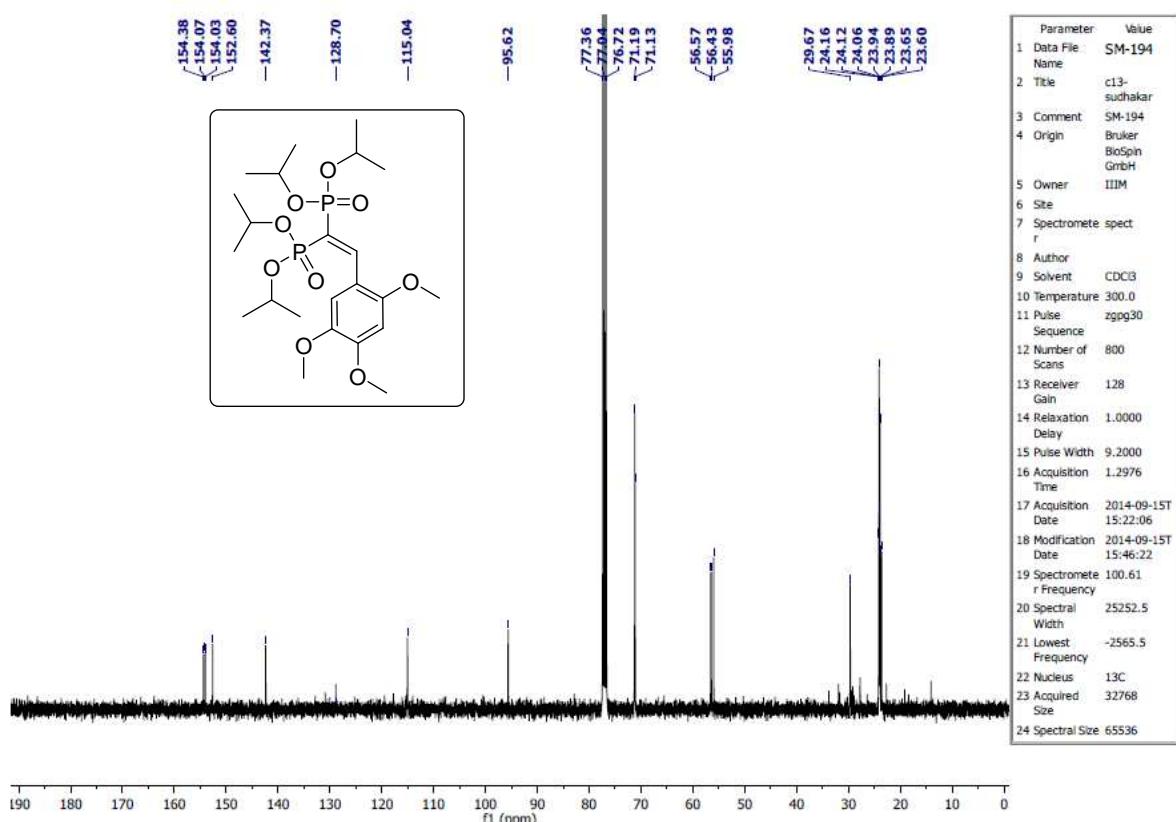
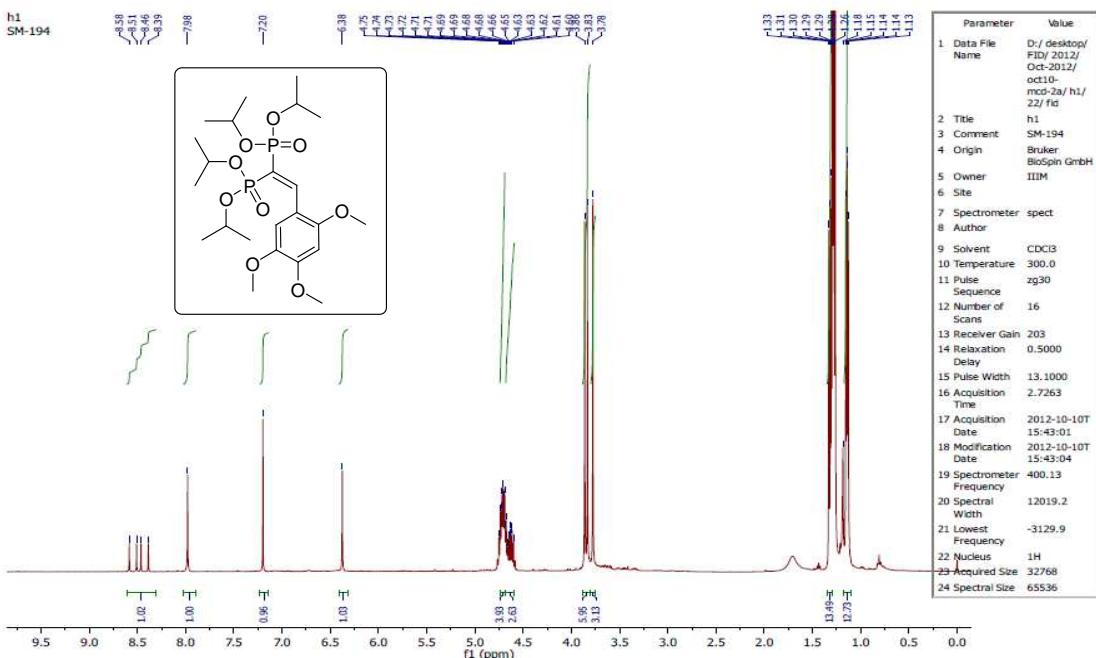


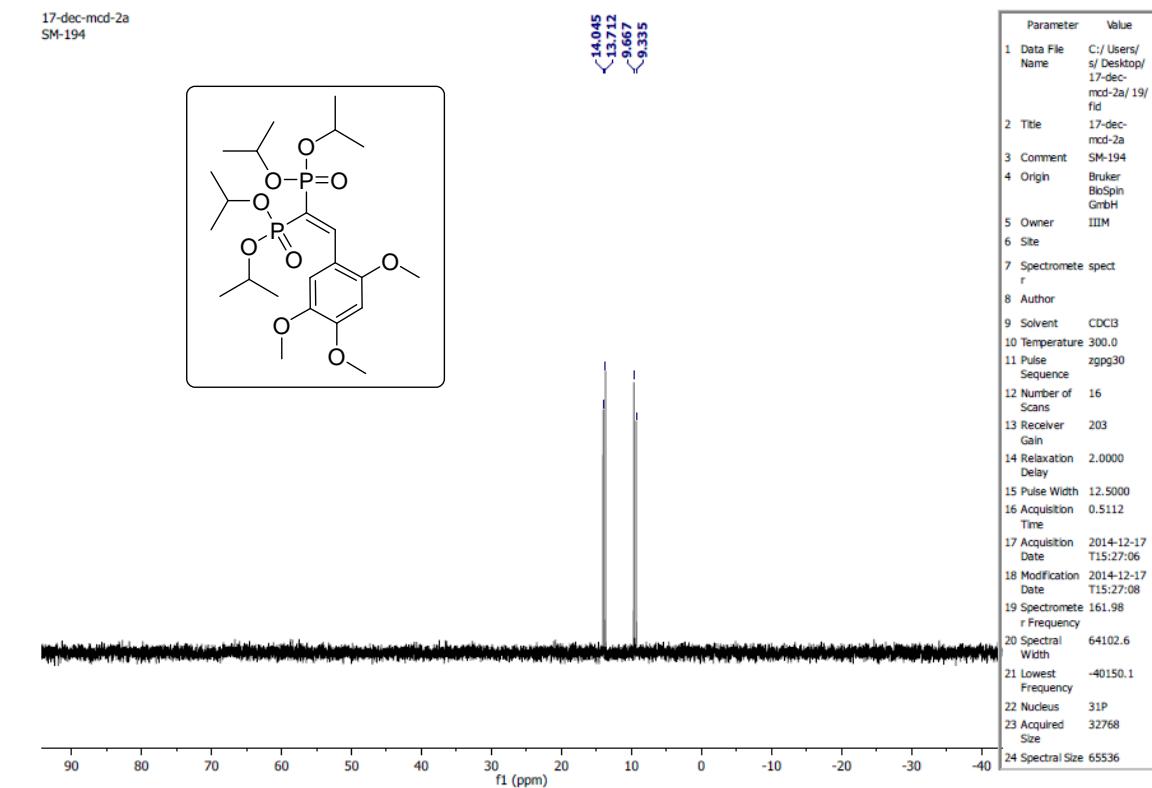
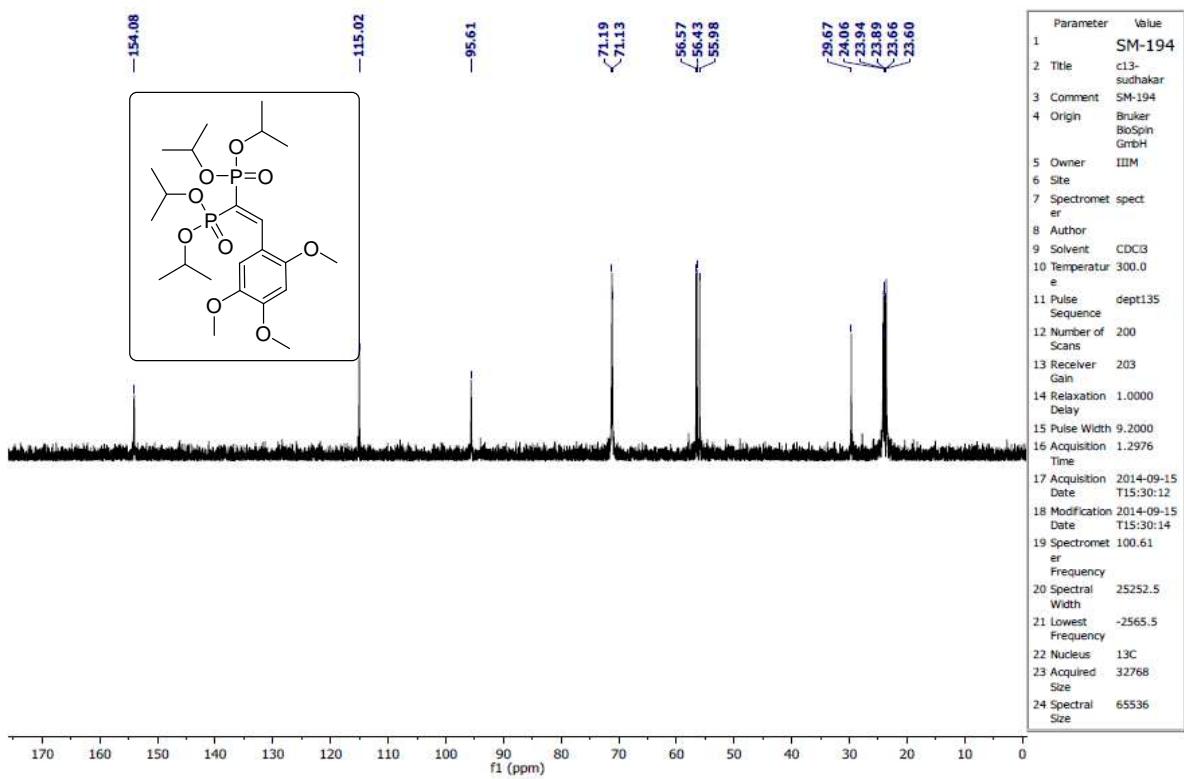
11. ^1H , ^{13}C , DEPT135 and ^{31}P NMR spectra of tetraethyl- 2(2,3,5-trimethoxyphenyl)ethane-1,1 diydiphosphonate (6k)



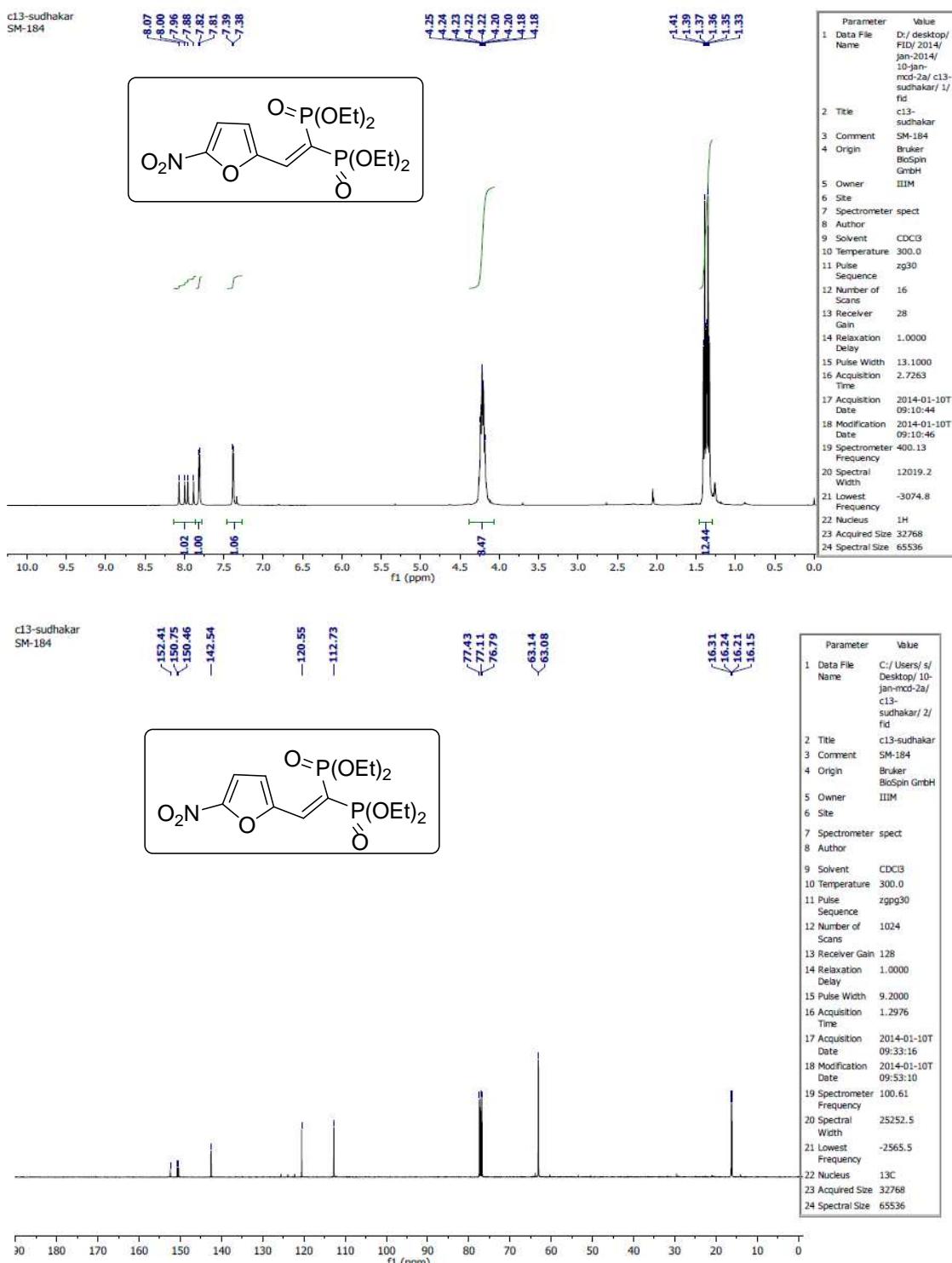


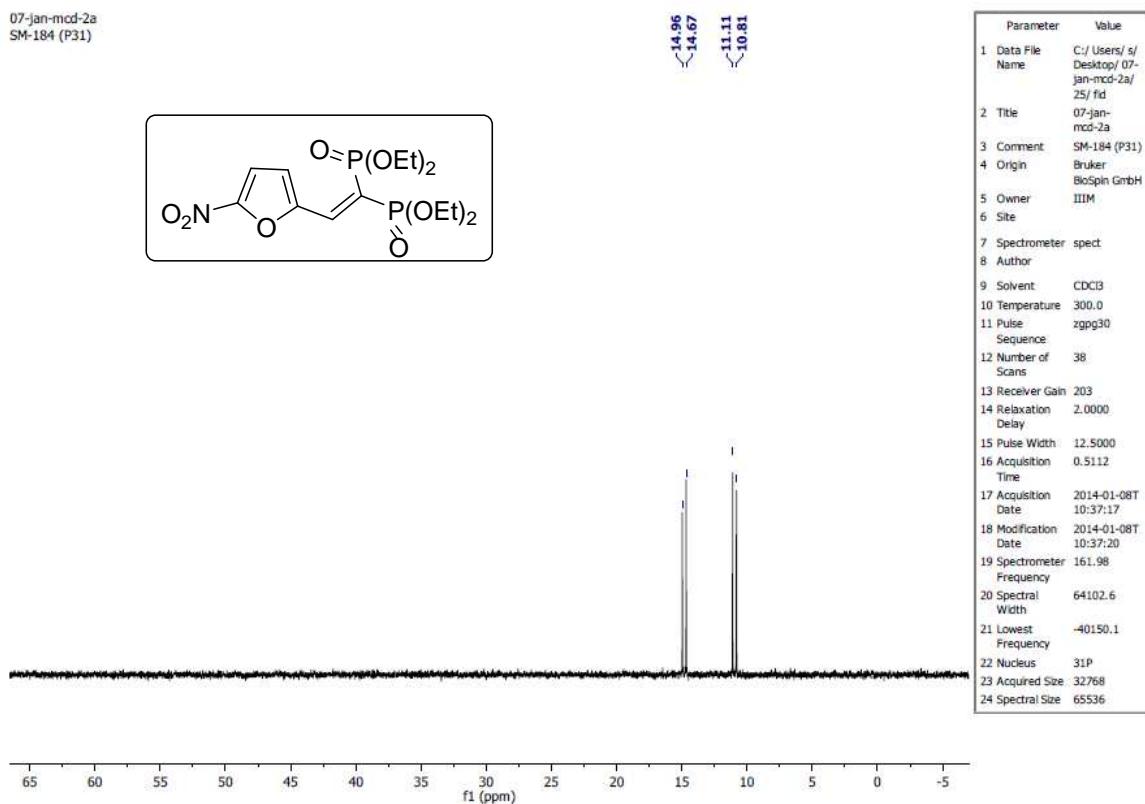
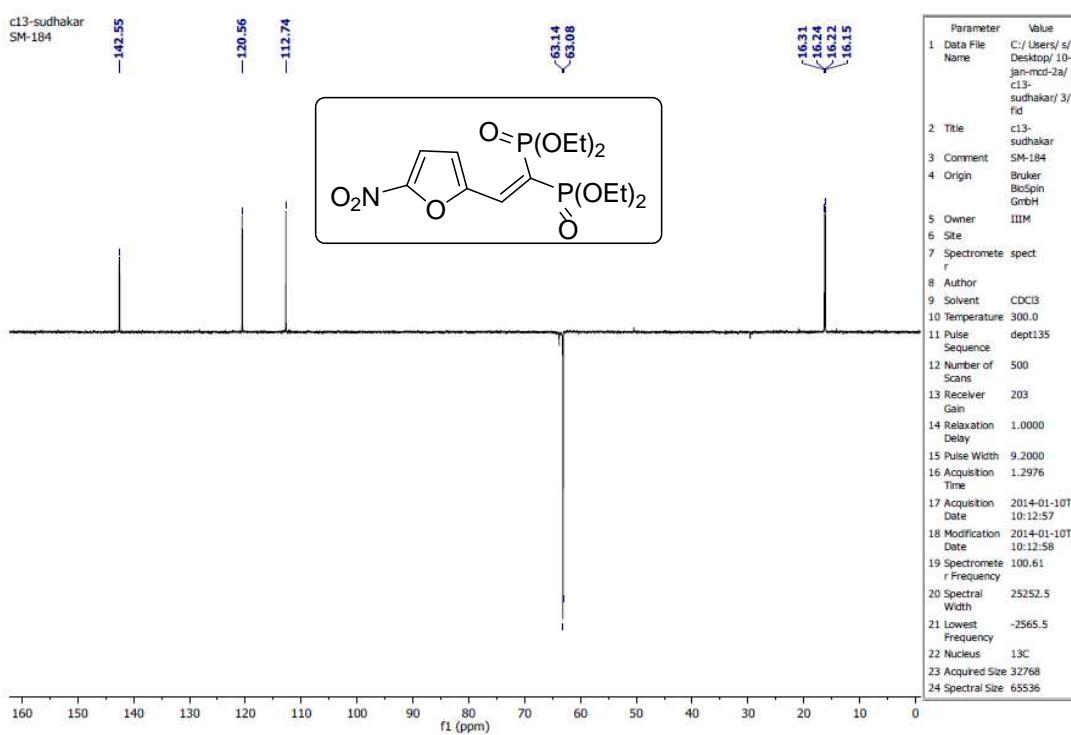
12. ^1H , ^{13}C , DEPT135 and ^{31}P NMR spectra of tetraisopropyl 2-(2,4,5-trimethoxyphenyl)ethene-1,1 diyldiphosphonate (6l)



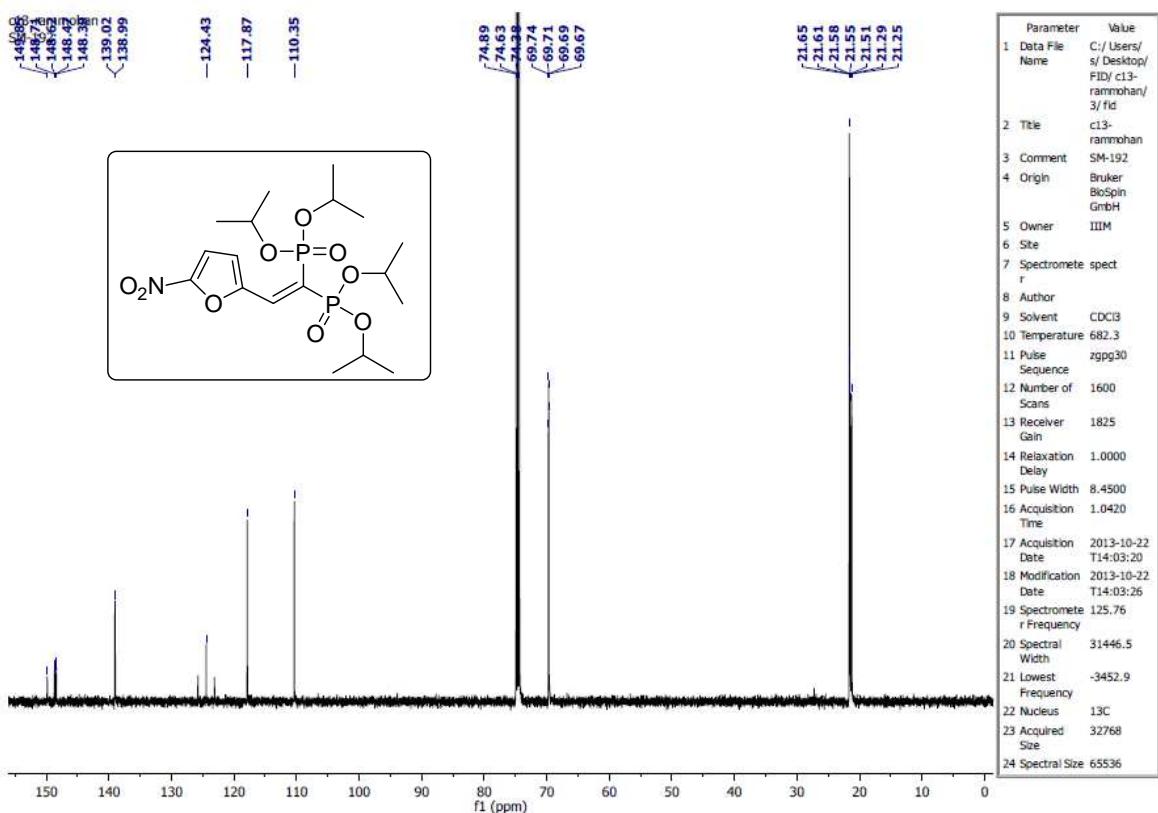
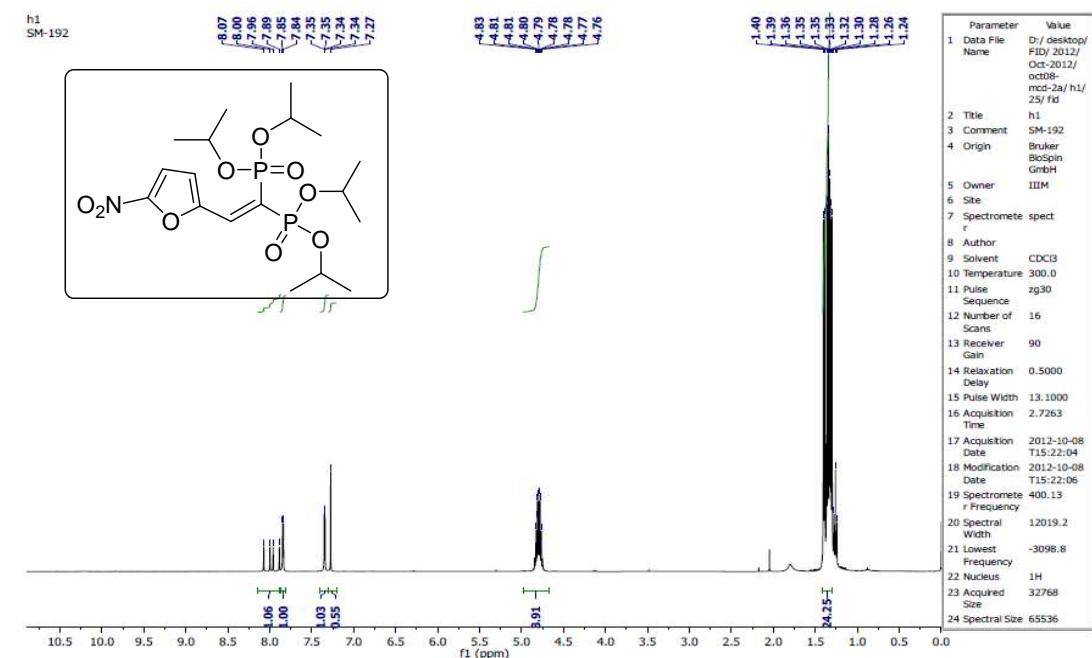


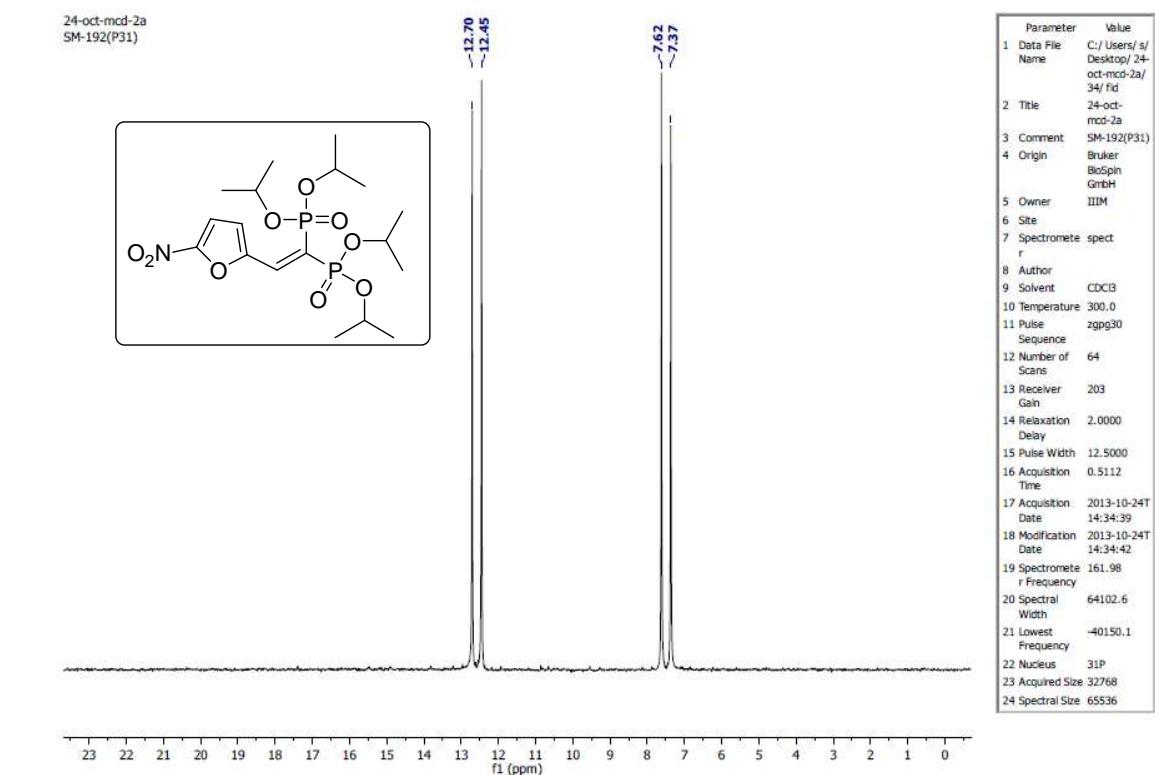
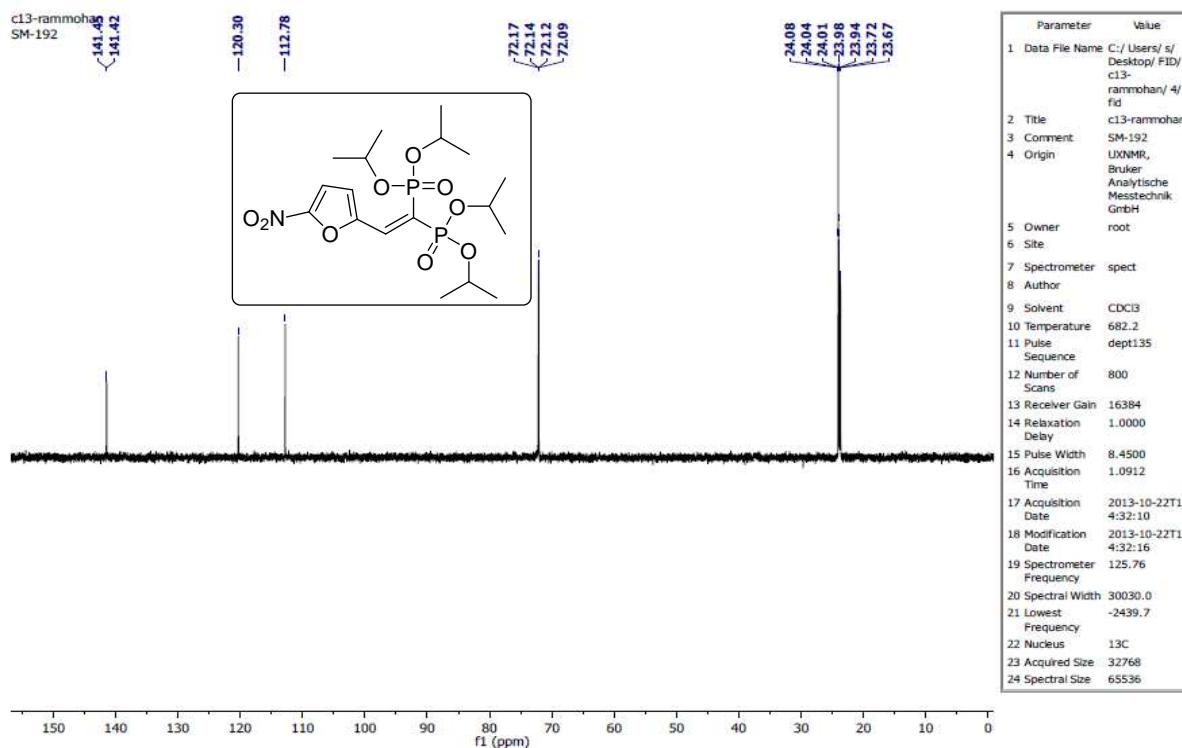
13. ^1H , ^{13}C , DEPT135 and ^{31}P NMR spectra of tetraethyl2-(5-nitrofuran-2-yl)ethene-1,1-diyldiphosphonate (6m)



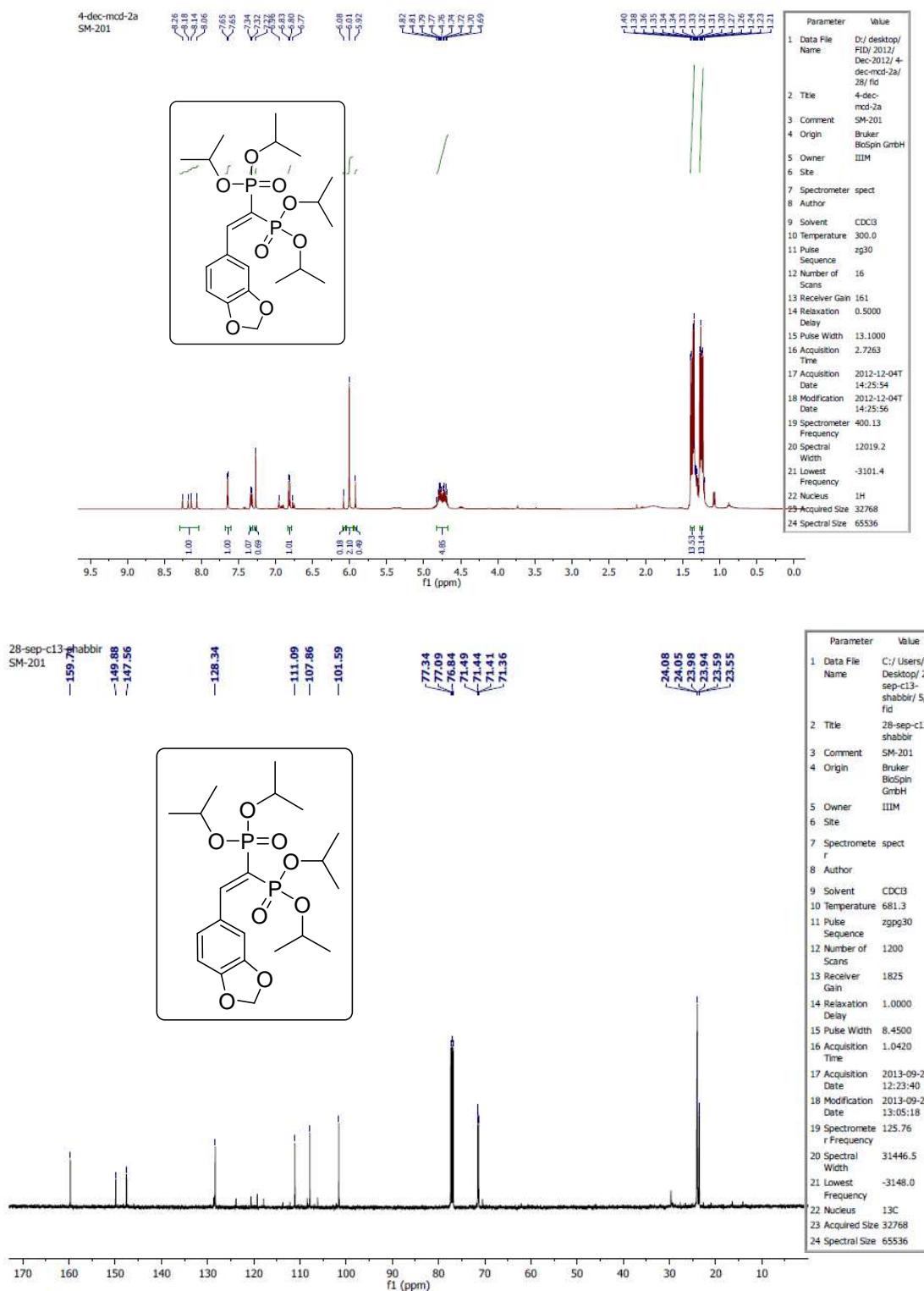


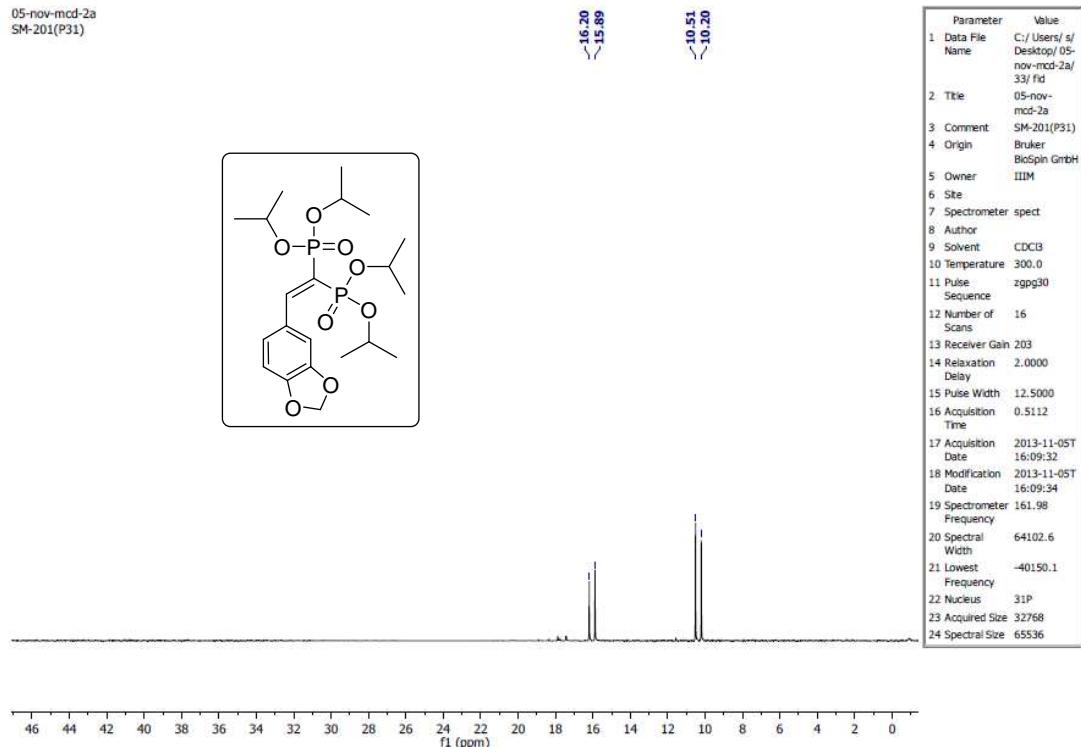
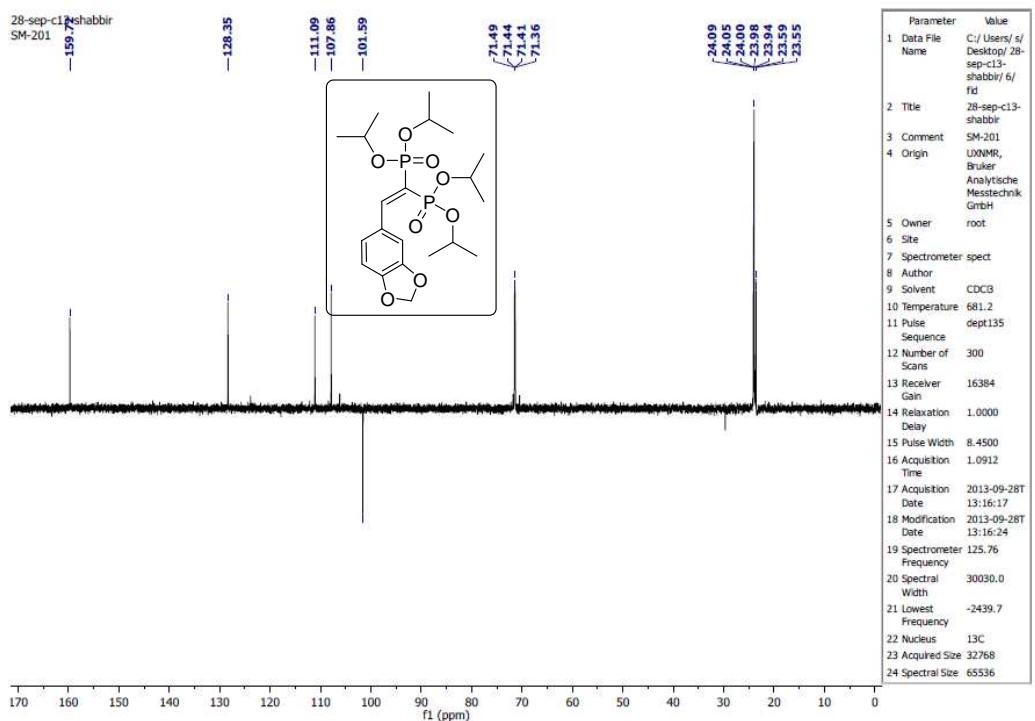
14. ^1H , ^{13}C , DEPT135 and ^{31}P NMR spectra of tetraisoproyl2-(5-nitrofuran-2-yl)ethene-1,1-diyldiphosphonate (6n**)**



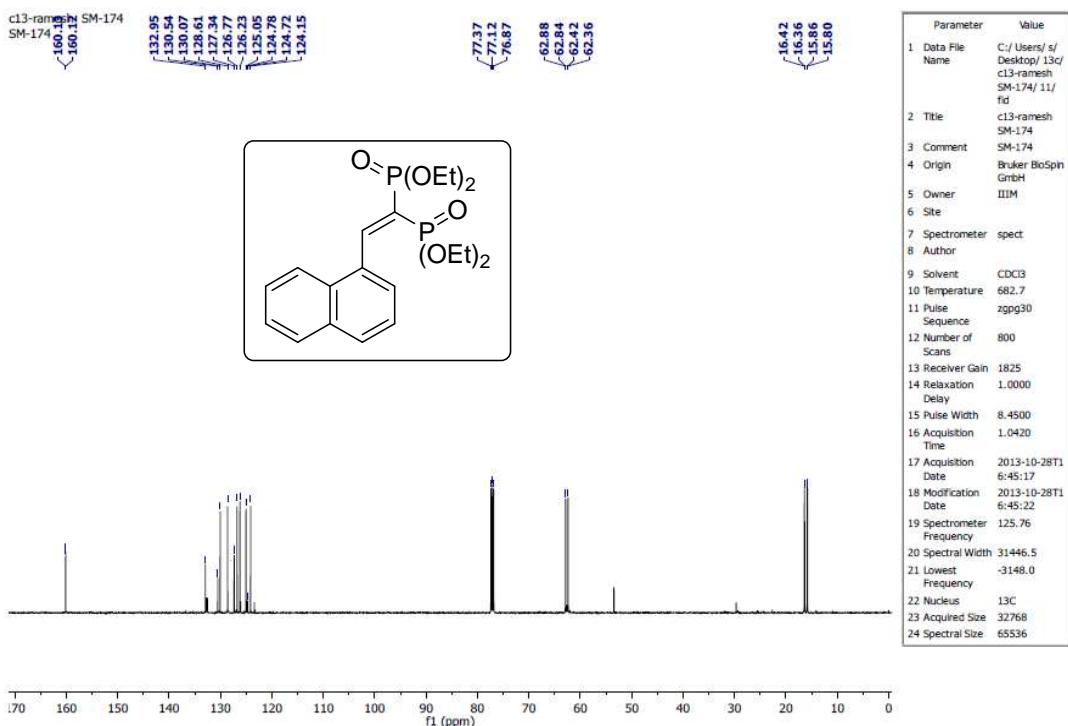
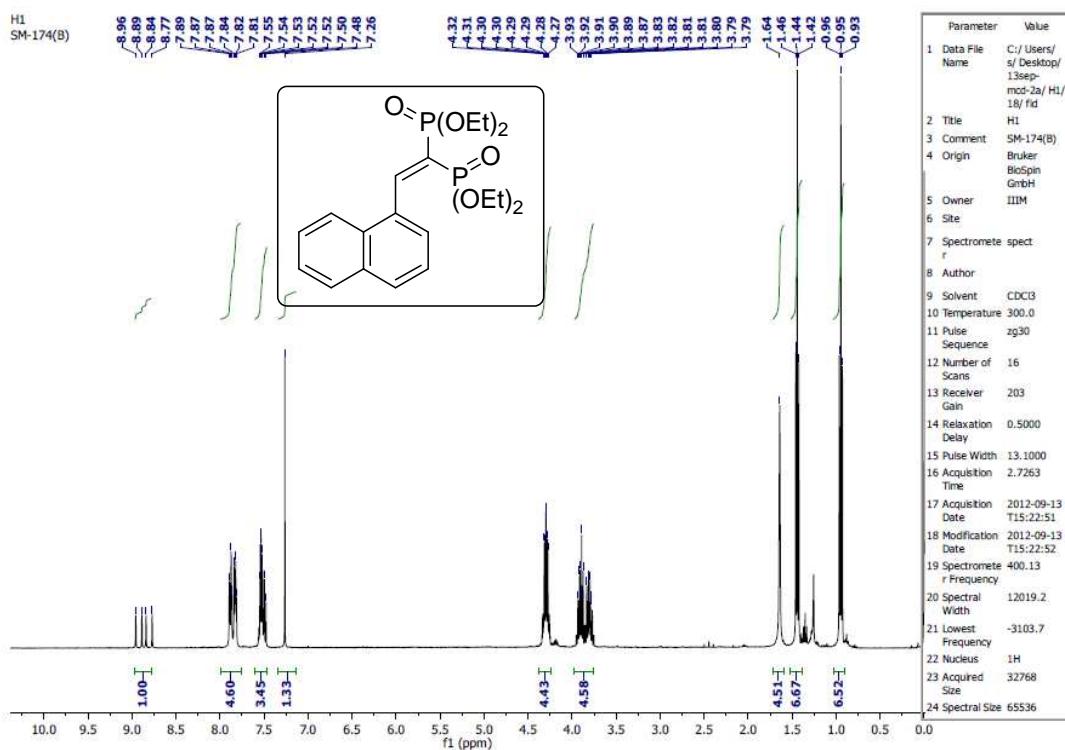


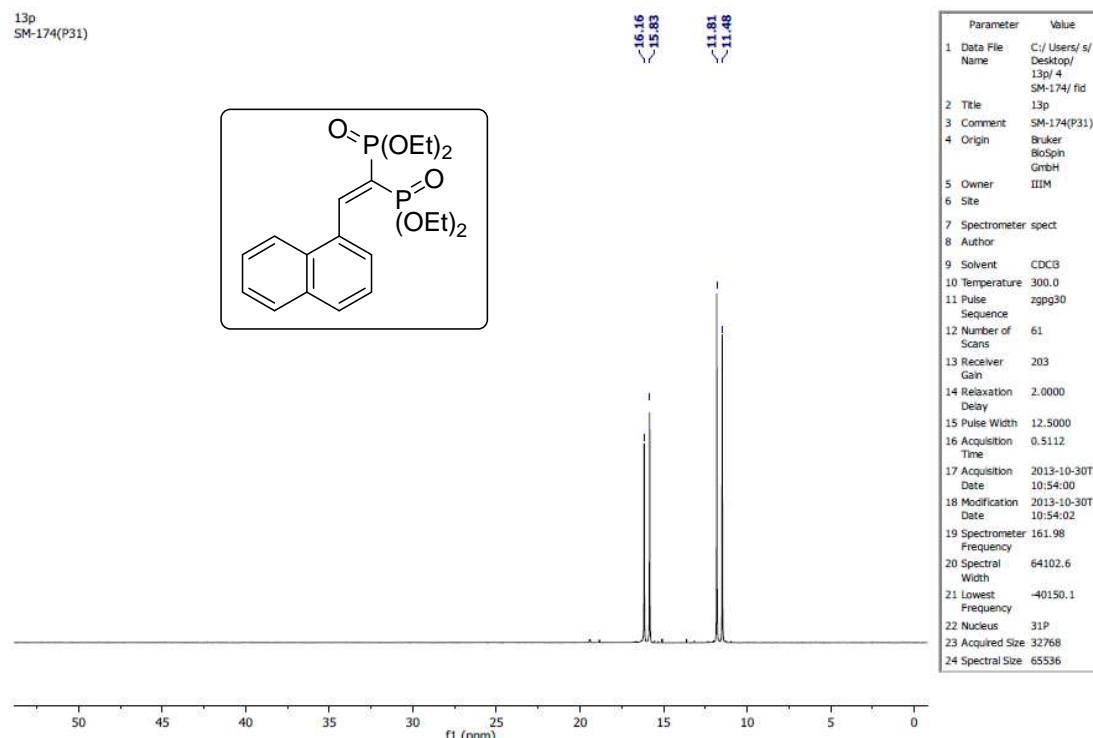
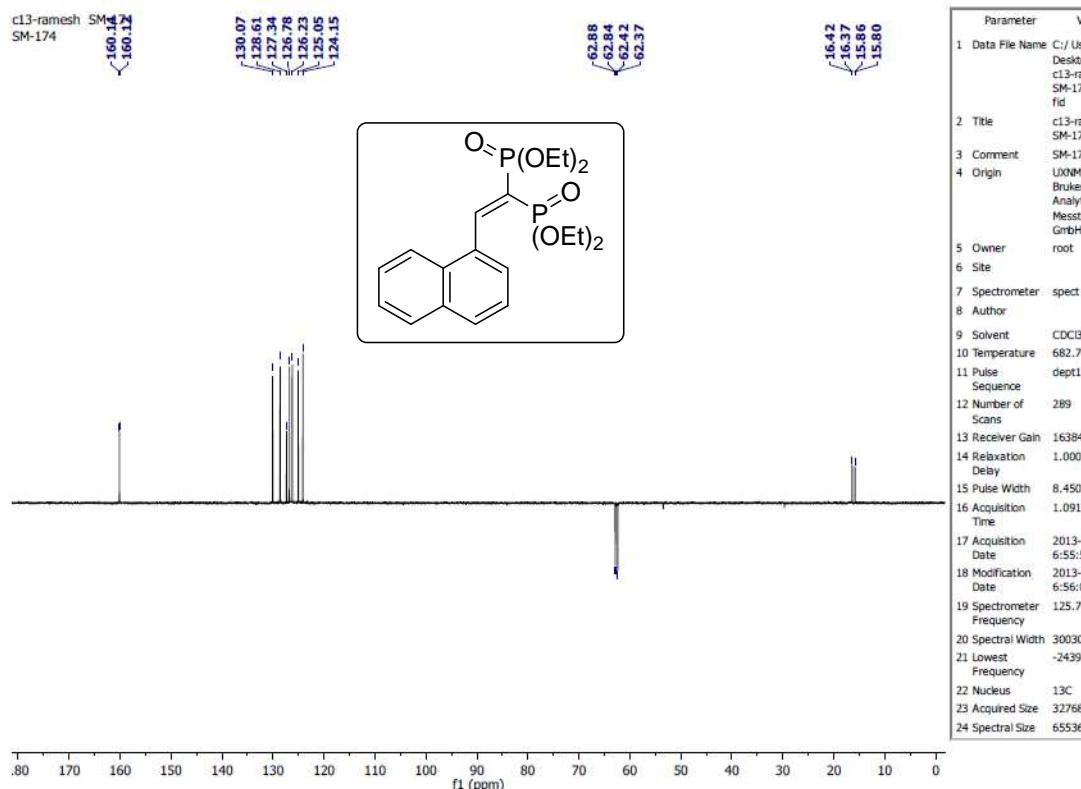
15. ^1H , ^{13}C , DEPT135 and ^{31}P NMR spectra of tetraisopropyl2-(benzo[d][1,3]dioxol-5-yl)ethene-1,1-diyldiphosphonate (6o)



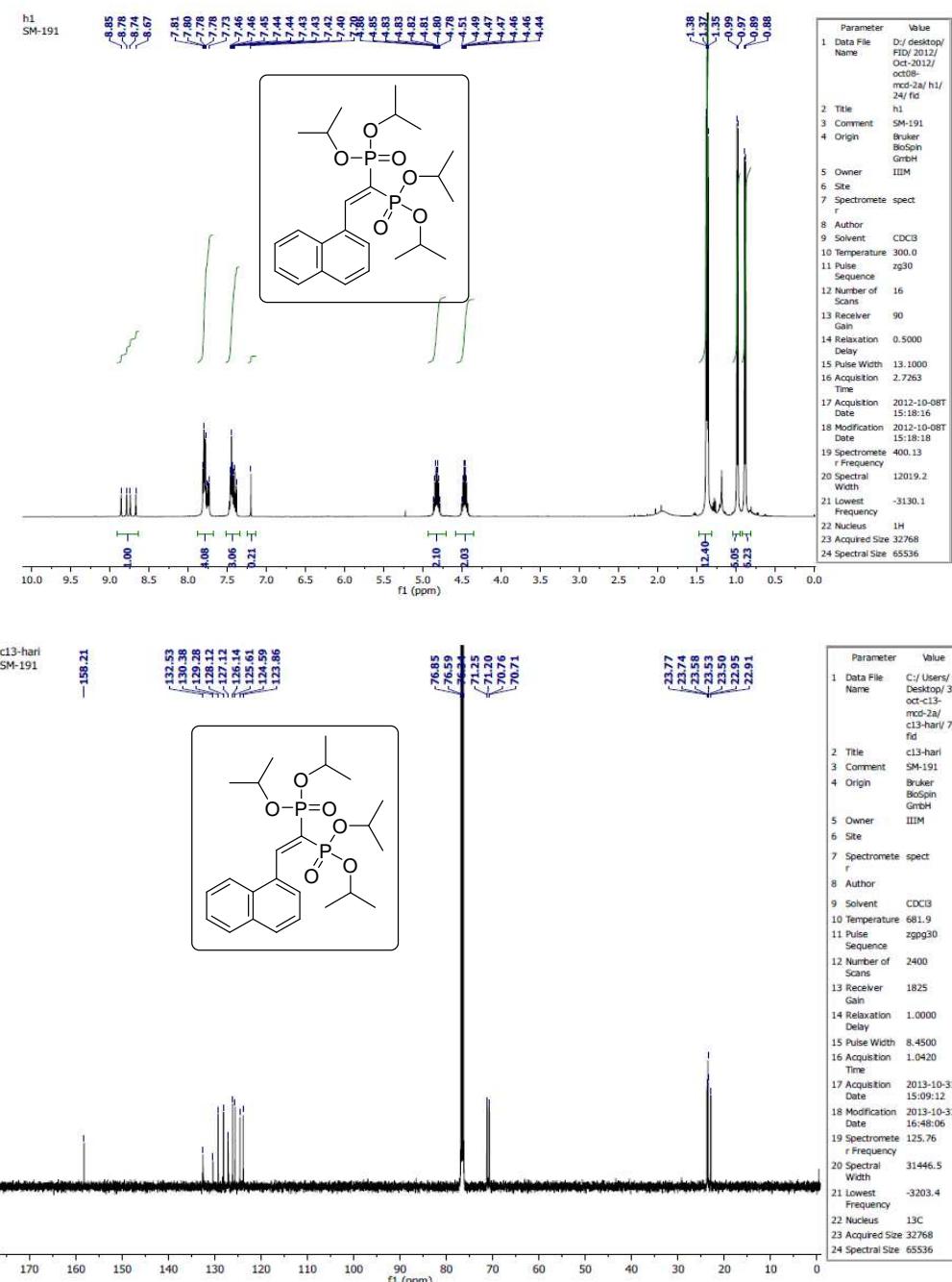


16. ^1H , ^{13}C , DEPT135 and ^{31}P NMR spectra of tetraethyl 2-(naphthalen-1-yl)ethene-1,1-diyldiphosphonate (6p)



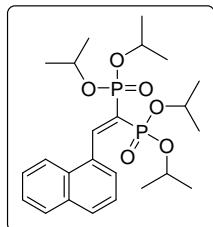


17. ^1H , ^{13}C , DEPT135 and ^{31}P NMR spectra of tetraisopropyl,2-(naphthalen-1-yl)ethene-1,1-diyldiphosphonate (6q)



c13-hari
SM-191

129.77
128.56
127.56
126.58
126.05
125.03
124.30



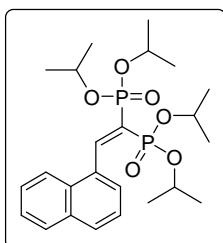
71.70
71.65
71.20
71.15

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8 Author	
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H1
SM-191(P31)

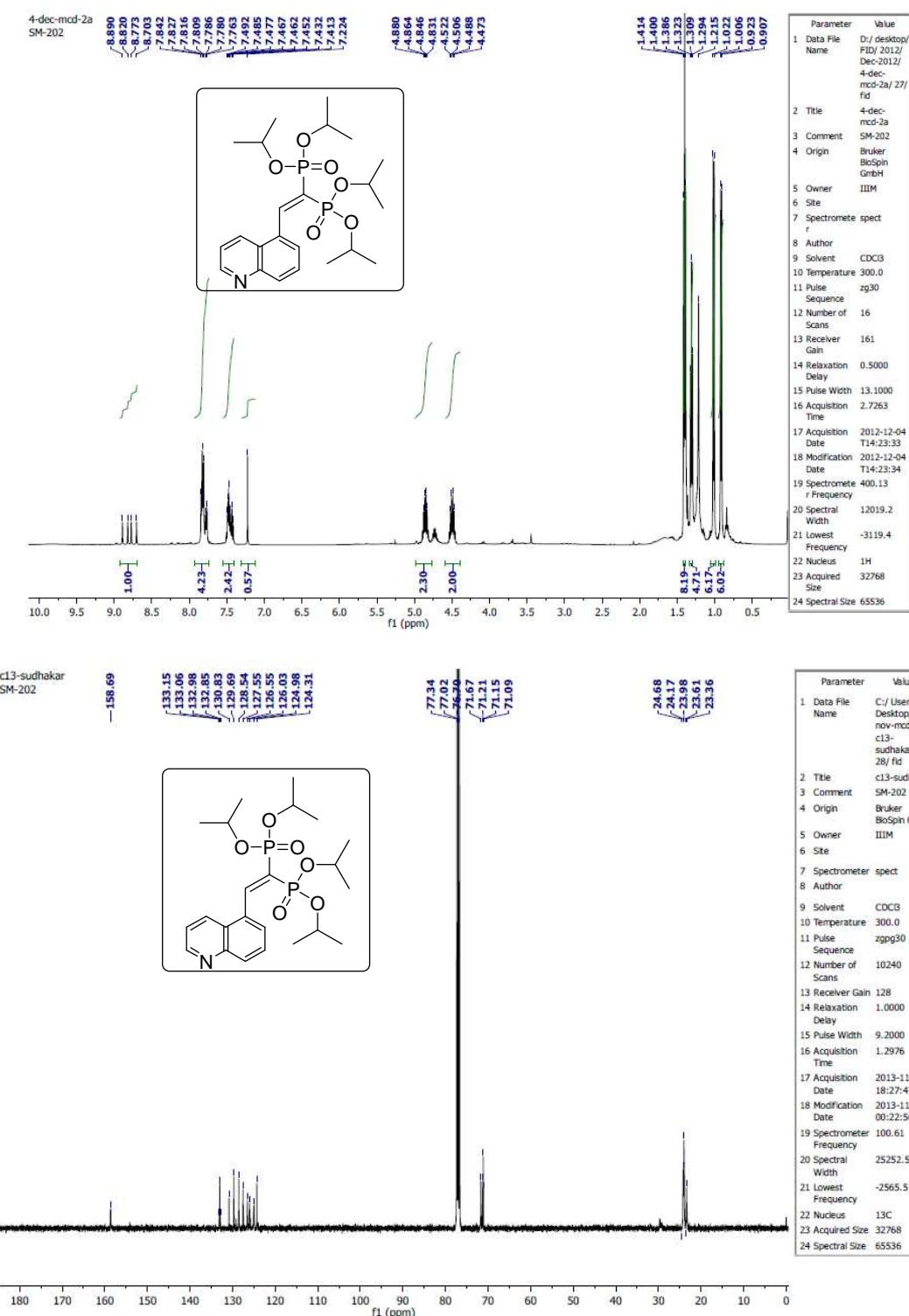
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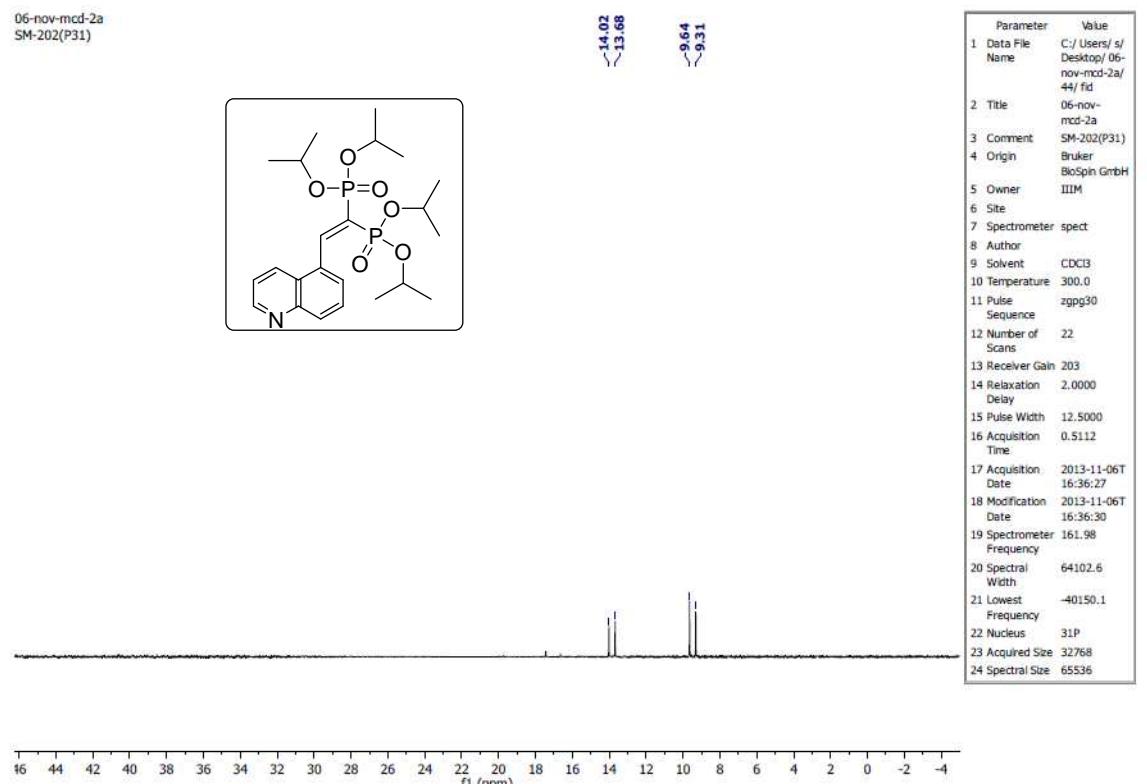
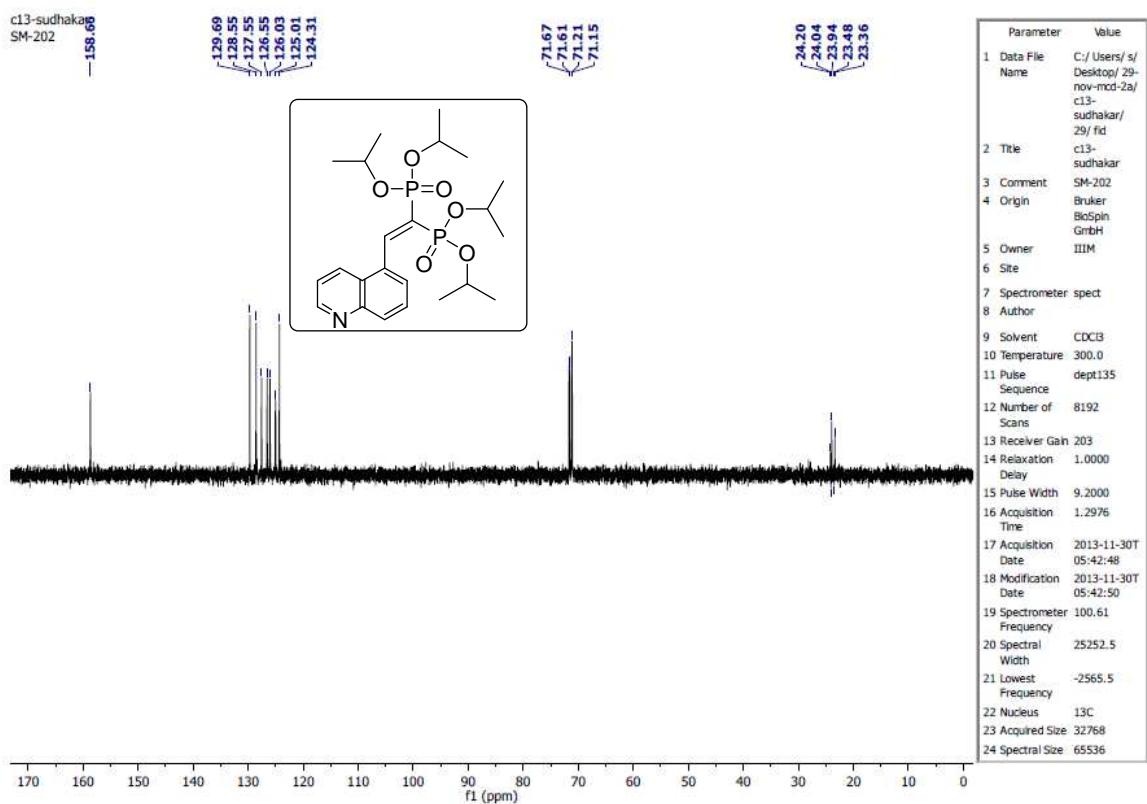


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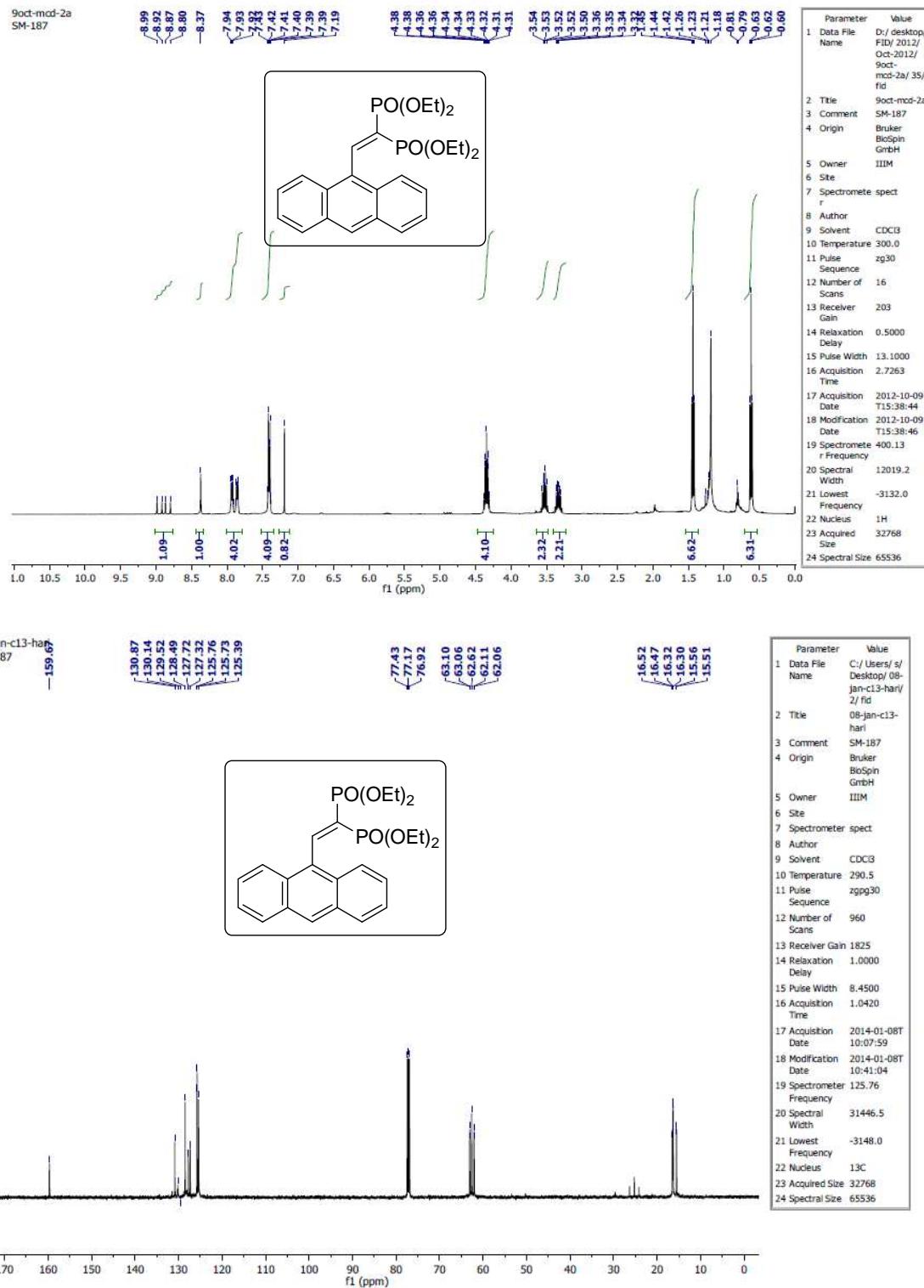
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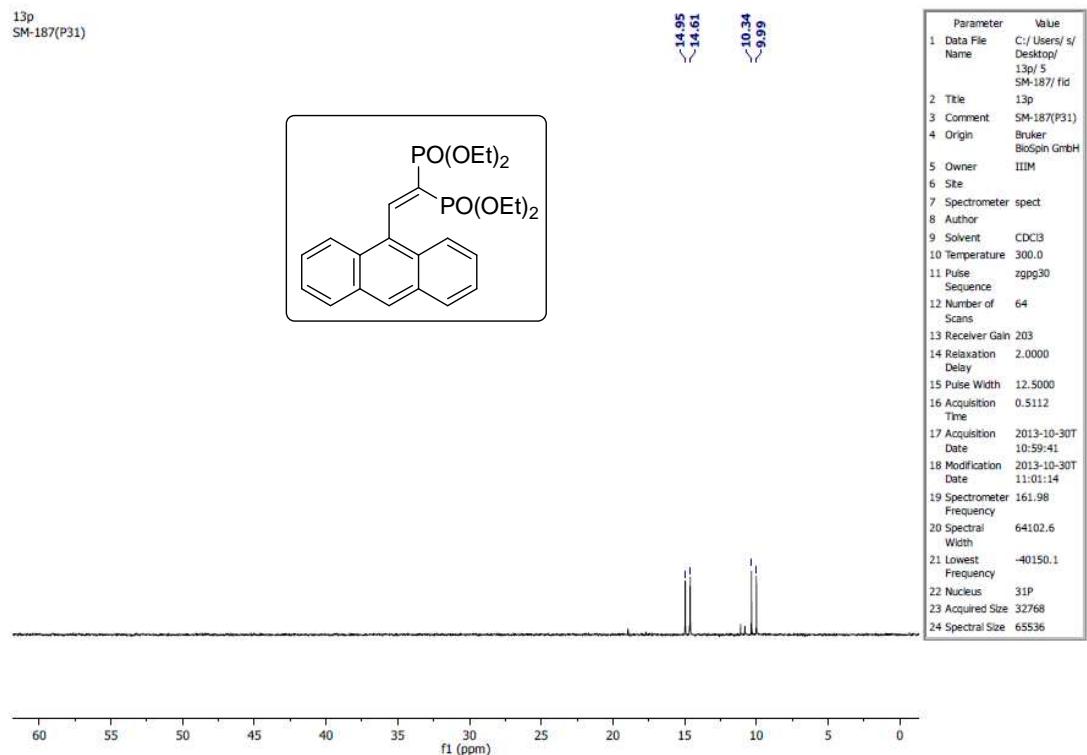
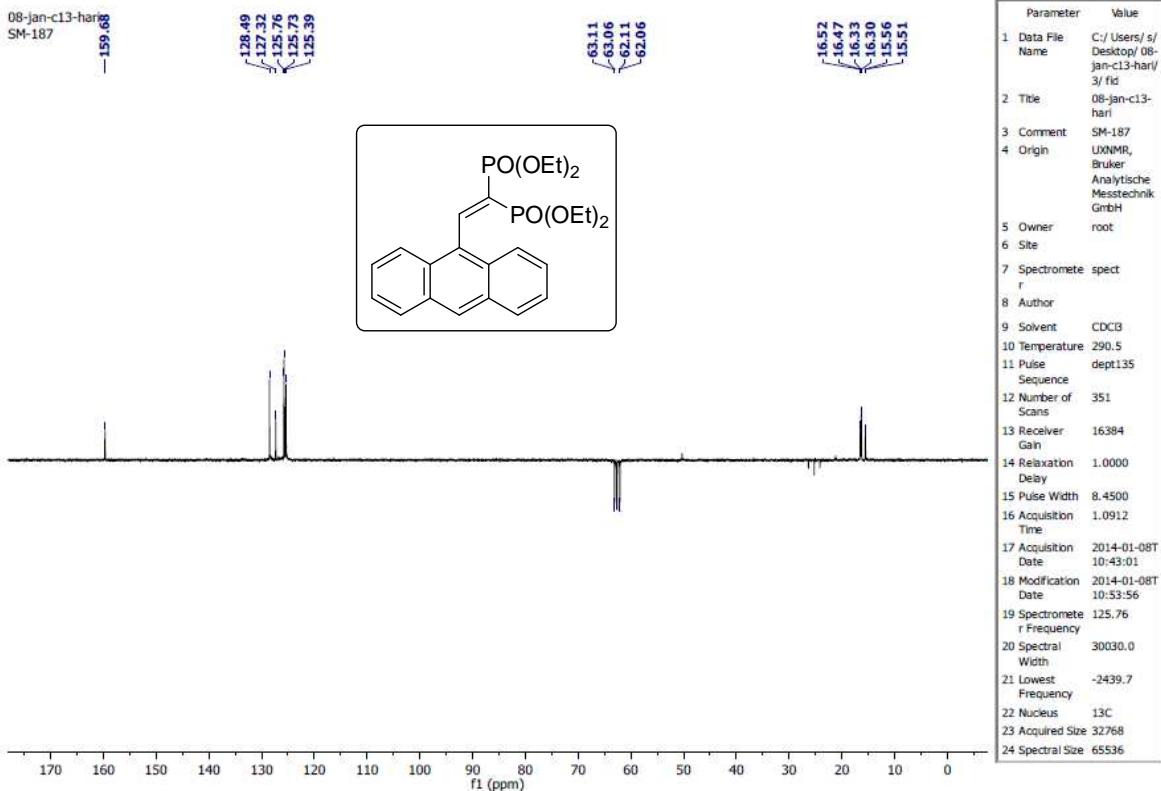
18. ^1H , ^{13}C , DEPT135 and ^{31}P NMR spectra of tetraisopropyl2-(quinol-5-yl)ethene-1,1-diyldiphosphonate (6r)



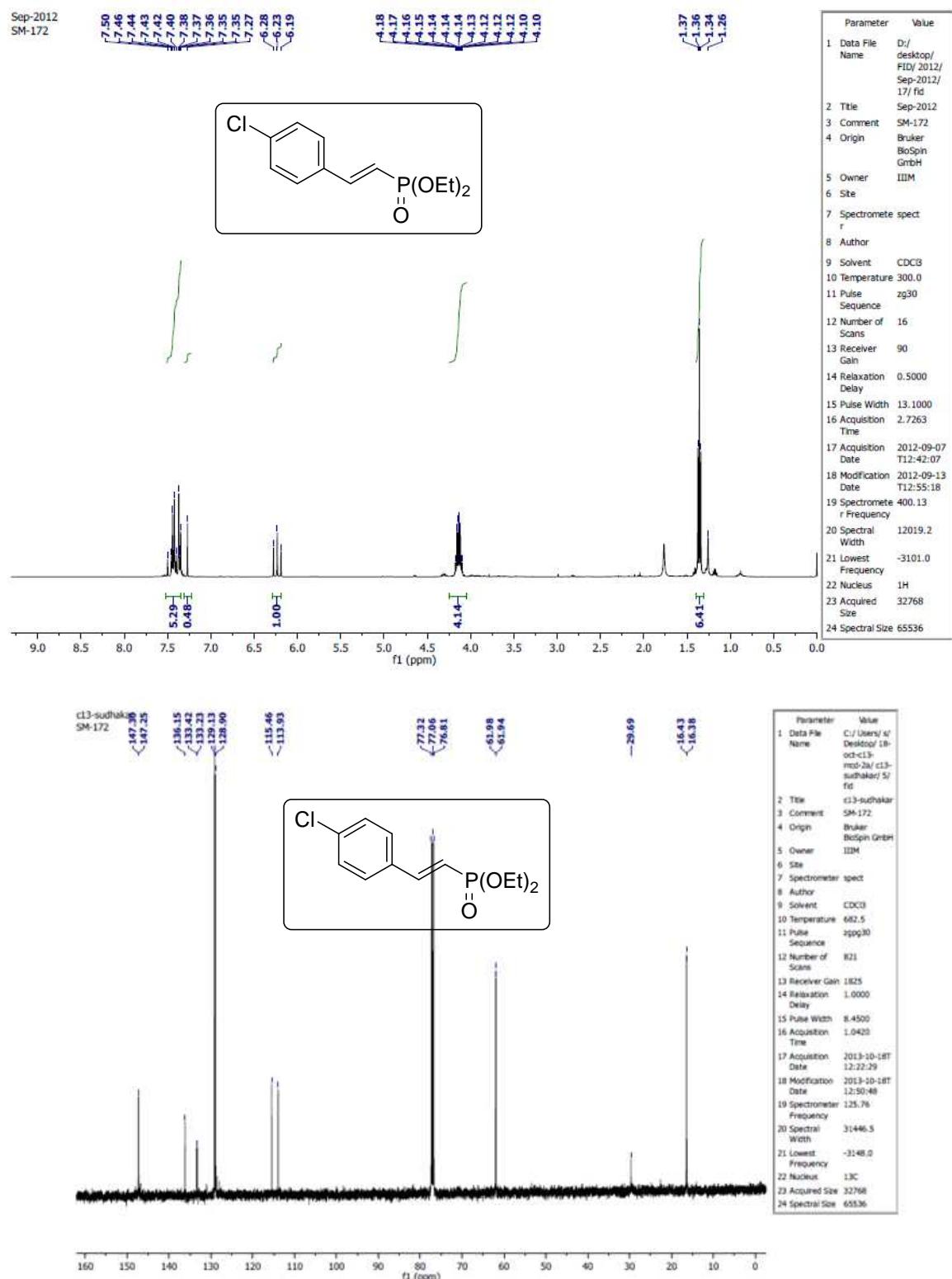


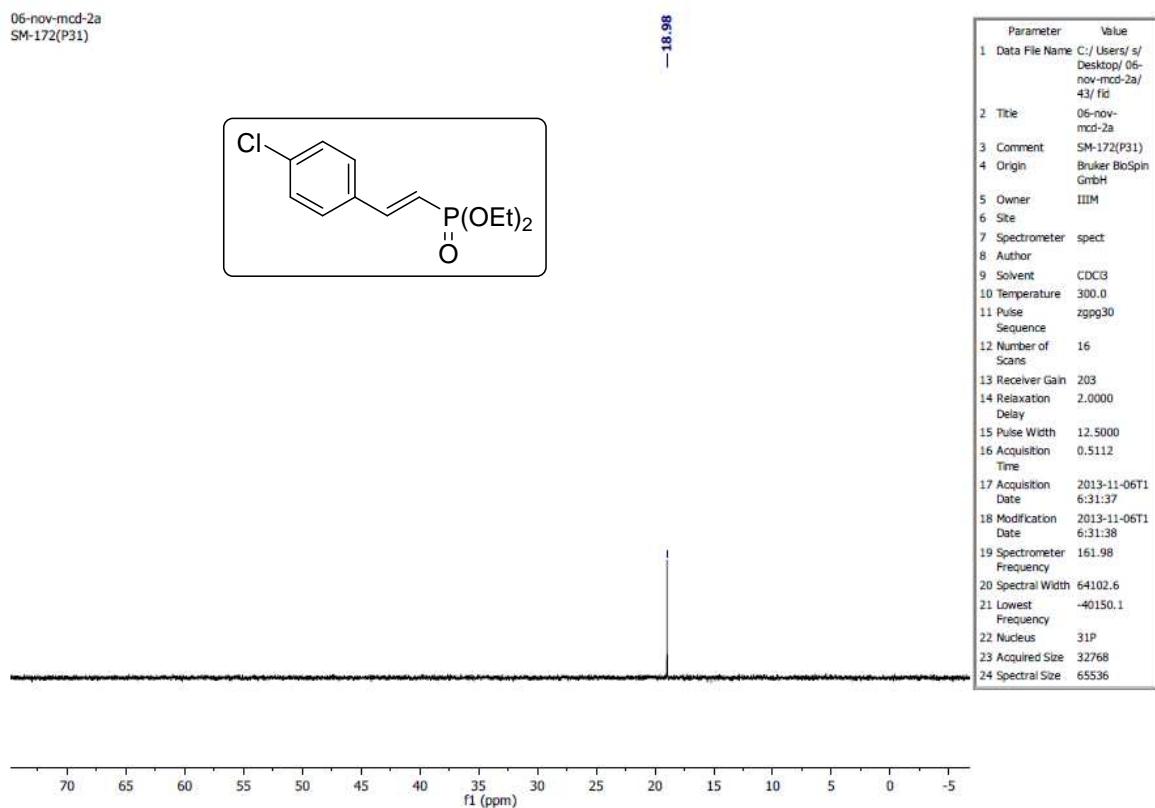
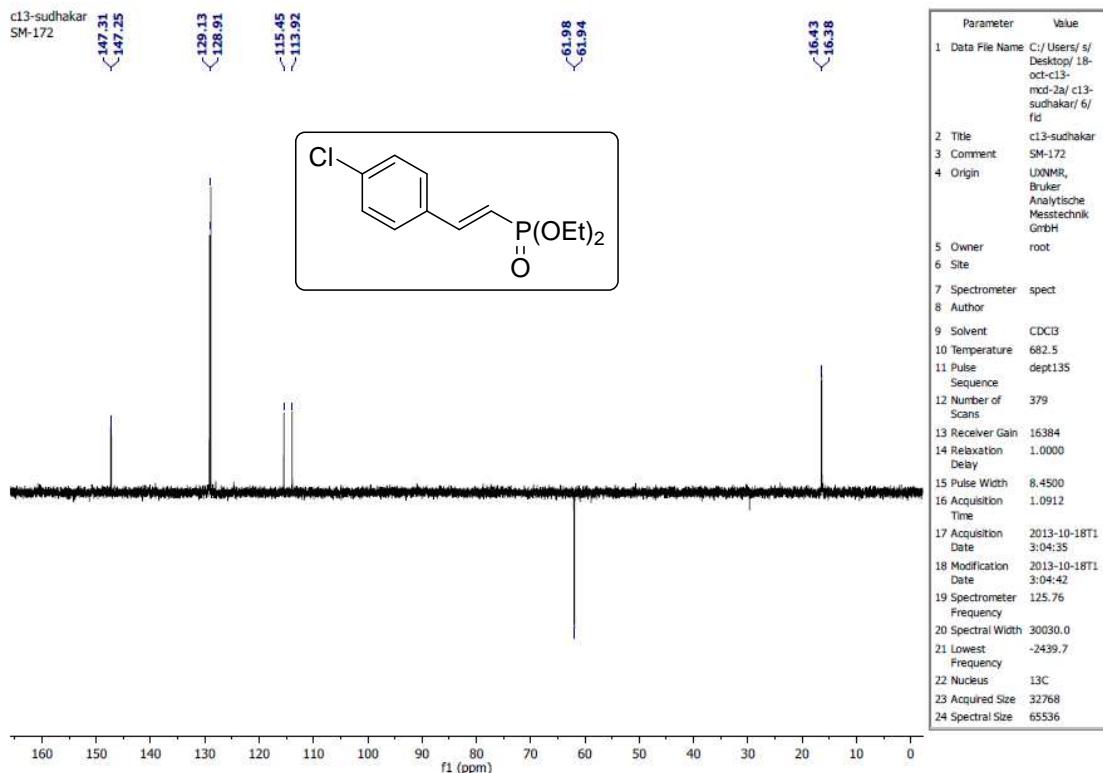
19. ^1H , ^{13}C , DEPT135 and ^{31}P NMR spectra of tetraethyl2-(anthracene-10-yl)ethene-1,1-diyldiphosphonate (6s)



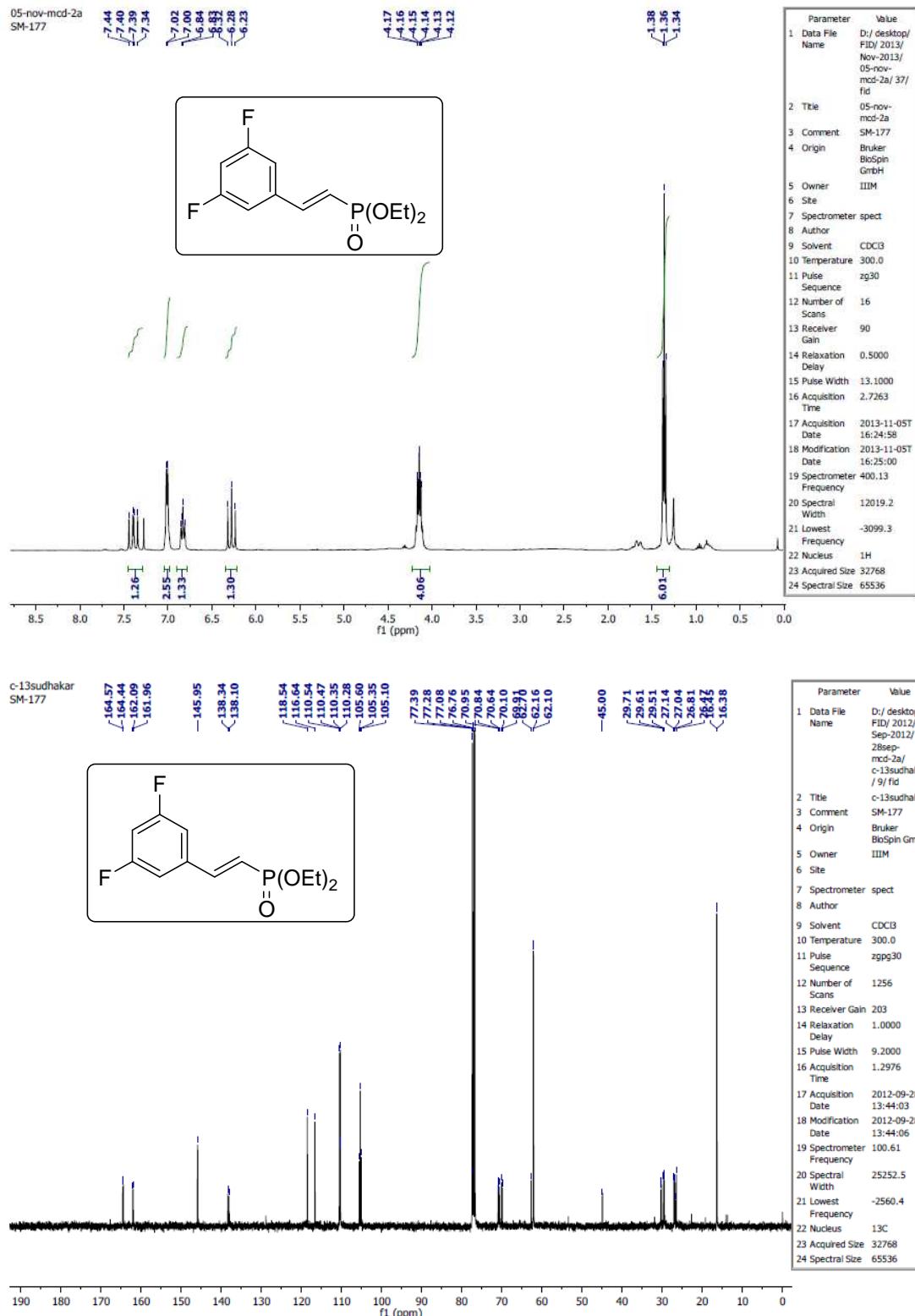


20. ^1H , ^{13}C , DEPT135 and ^{31}P NMR spectra of (E)-diethyl 4-chlorostyrylphosphonate (7a)

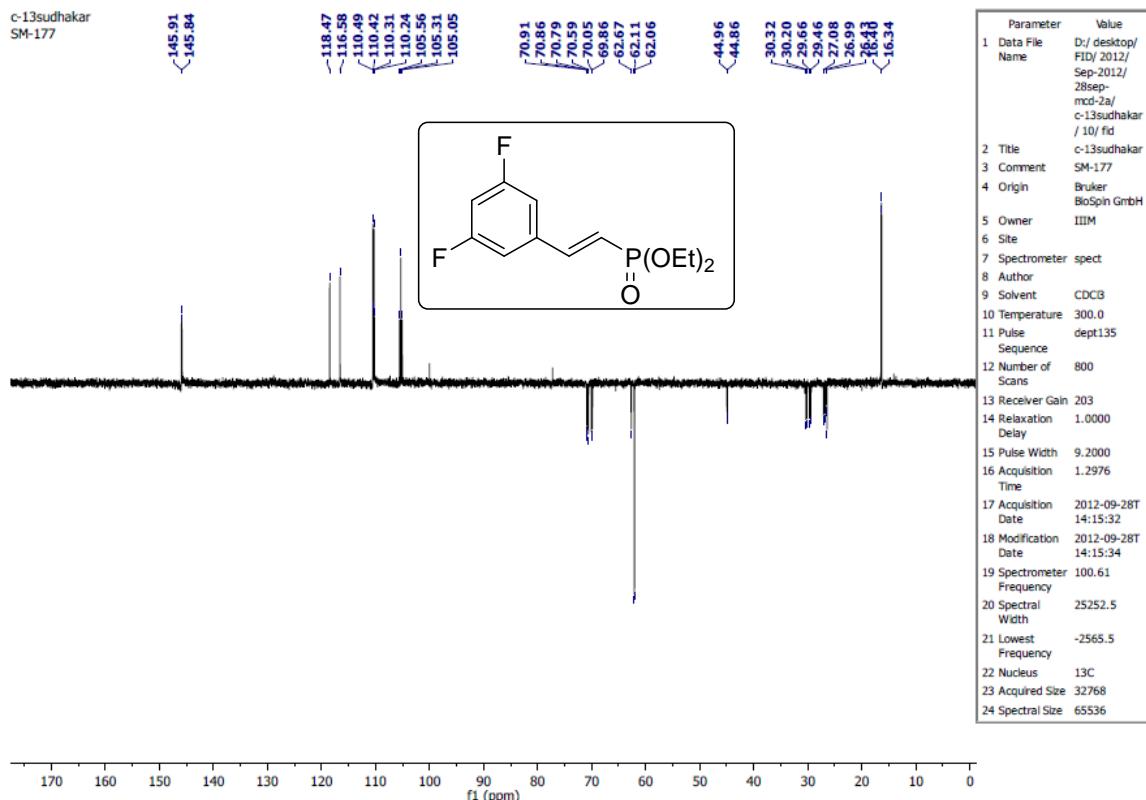




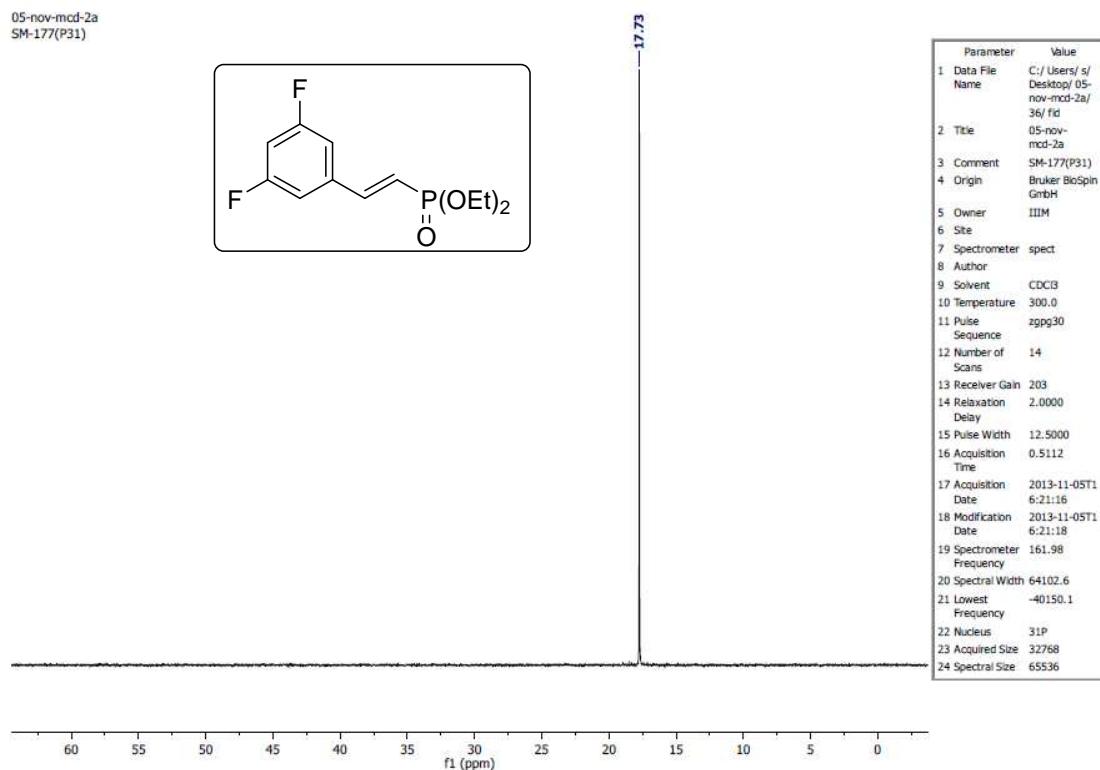
21. ^1H , ^{13}C , DEPT135 and ^{31}P NMR spectra of (E)-diethyl 3, 5-difluoro styrylphosphonate (7b)



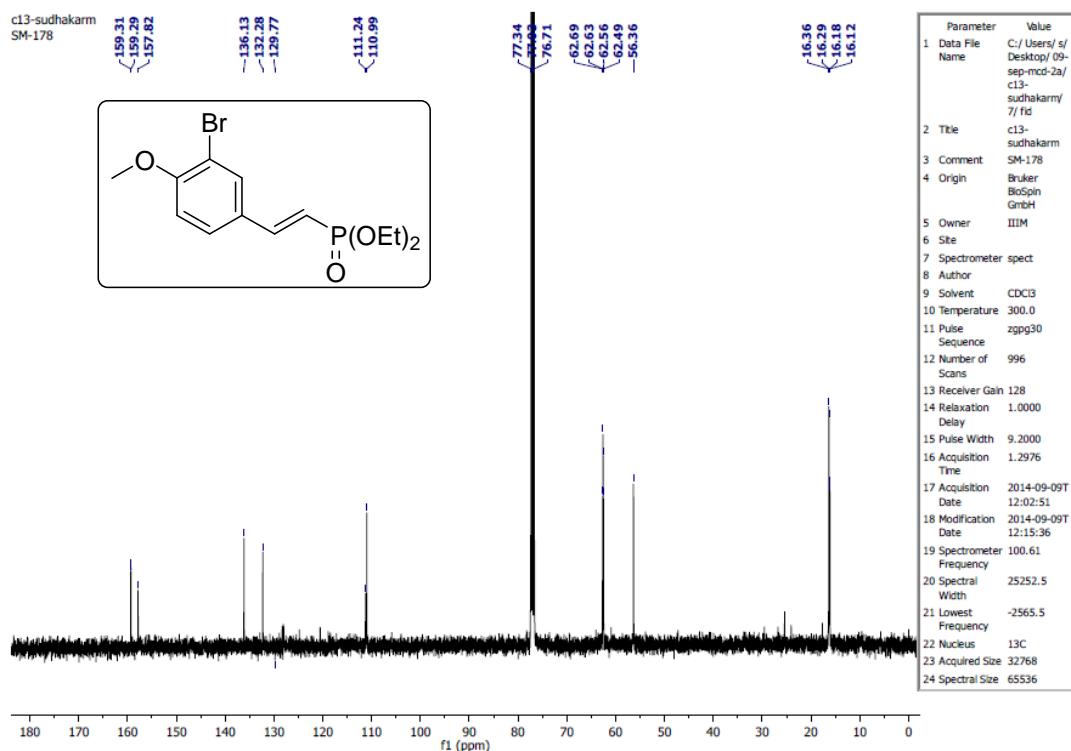
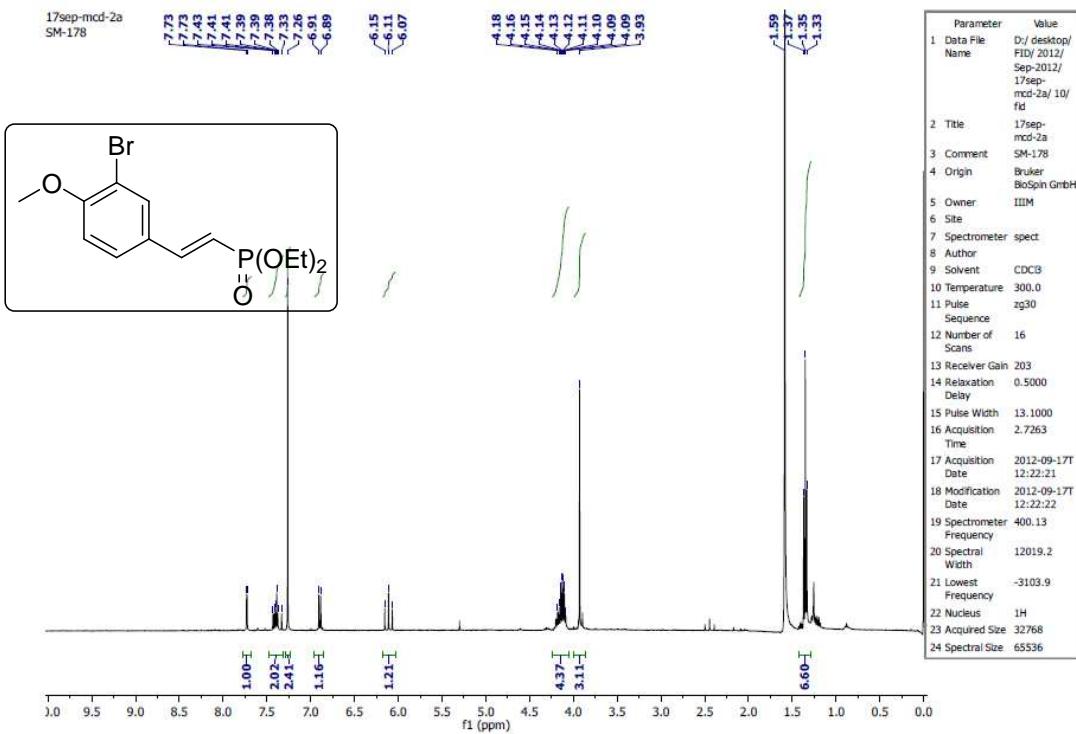
c-13sudhakar
SM-177



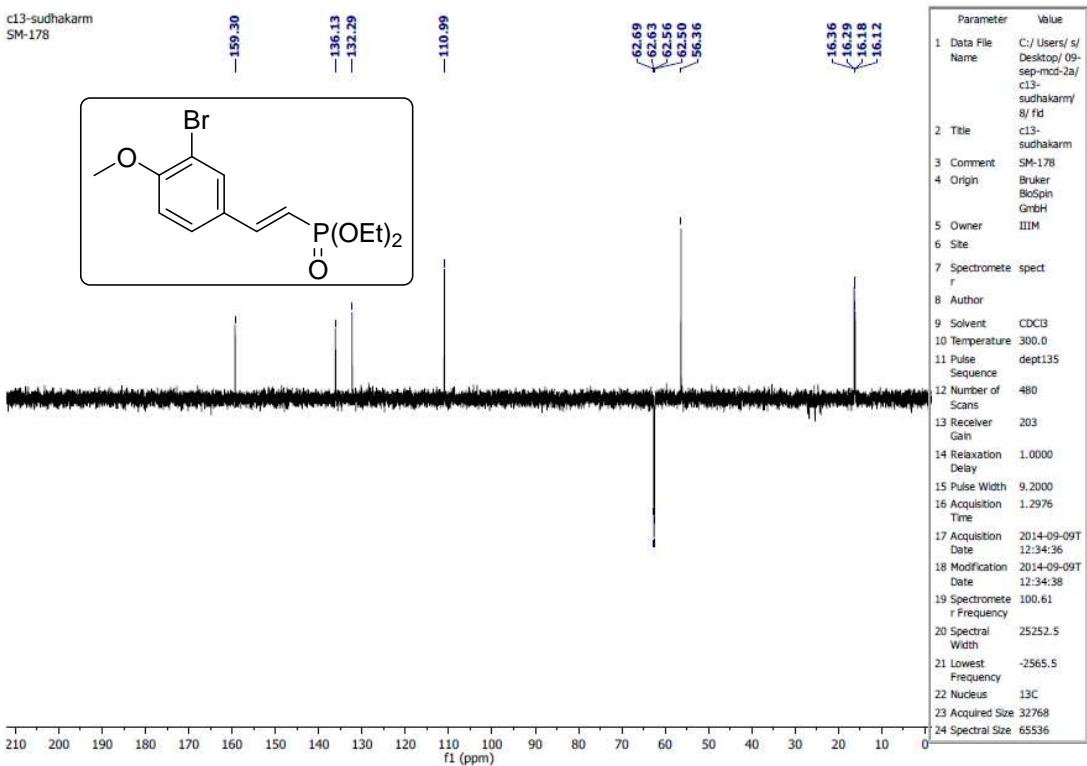
05-nov-mcd-2a
SM-177(P31)



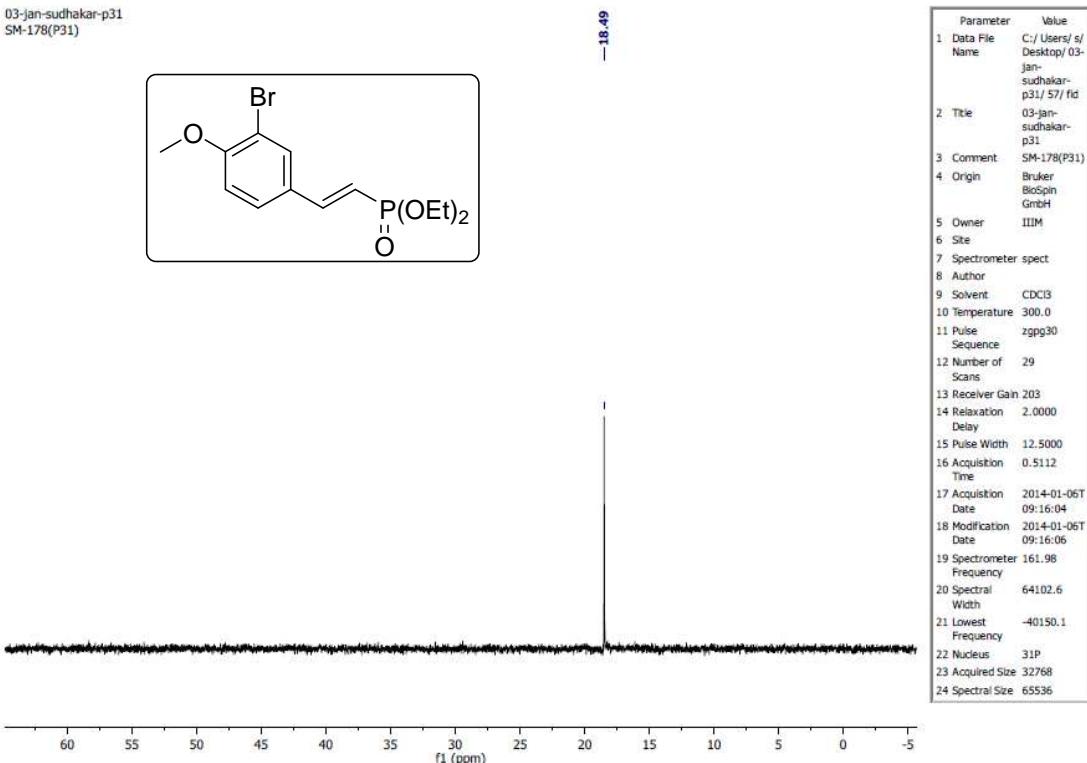
22. ^1H , ^{13}C , DEPT135 and ^{31}P NMR spectra of (E)-diethyl 3-bromo 4-methoxystyrylphosphonate (7c)



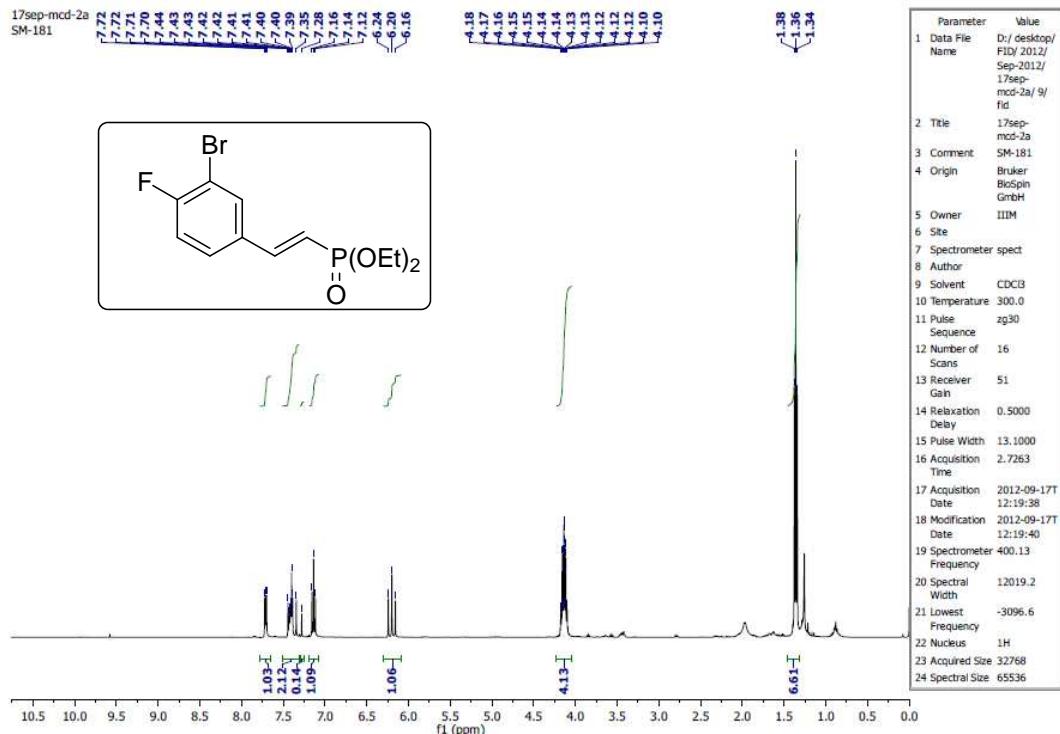
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SM-178



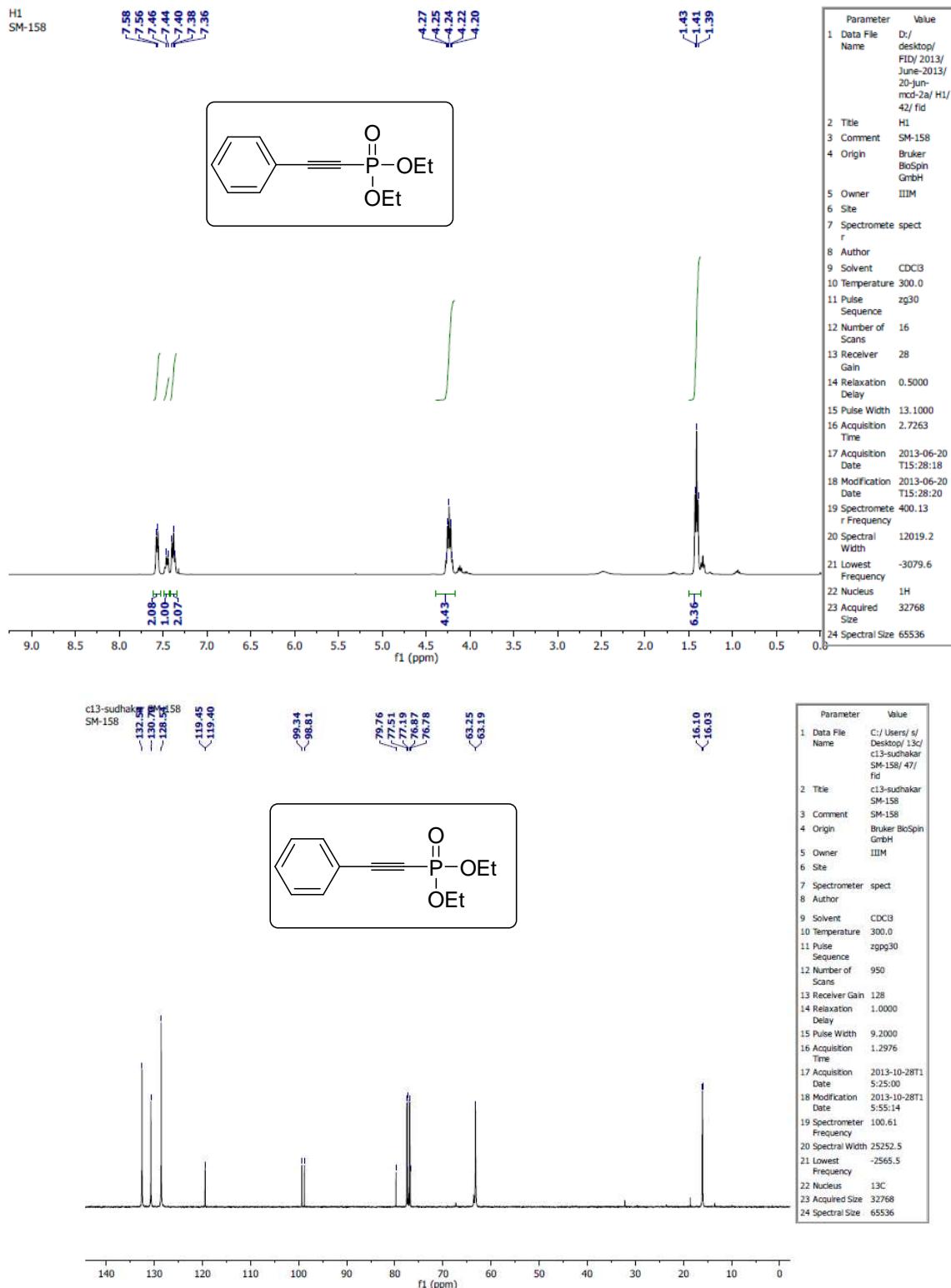
03-jan-sudhakar-p31
SM-178(P31)

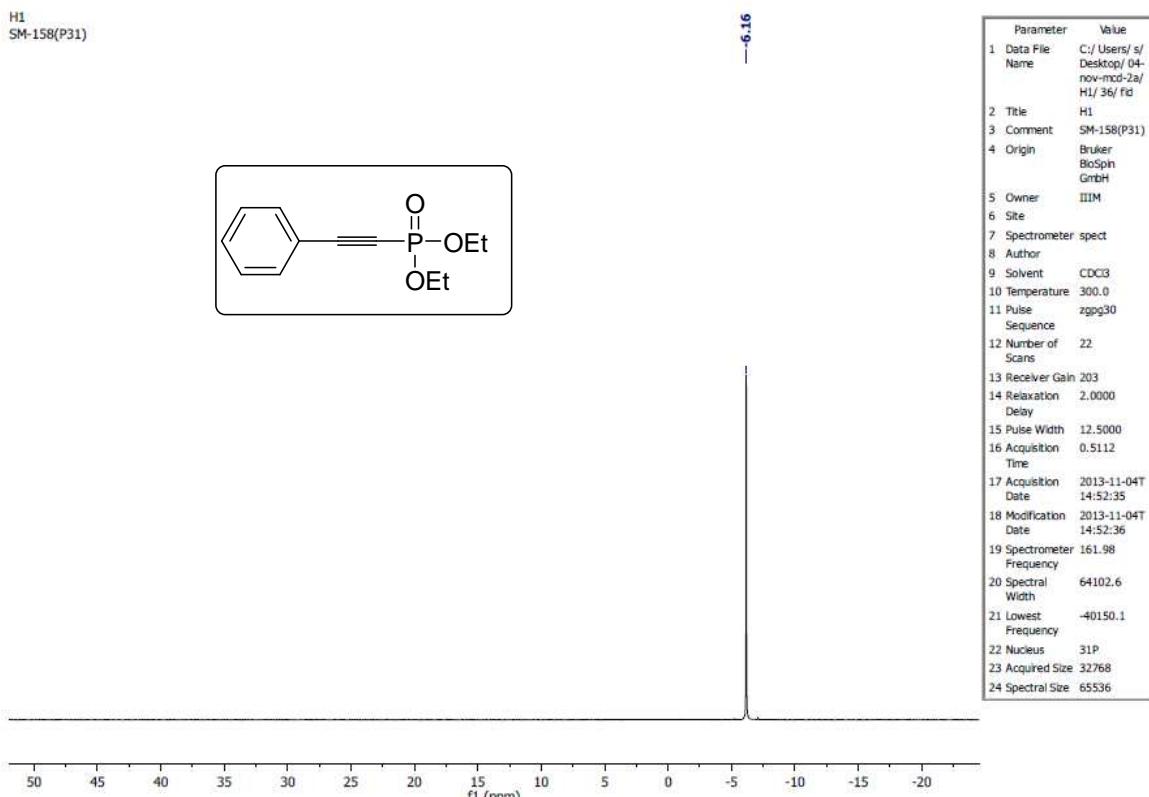
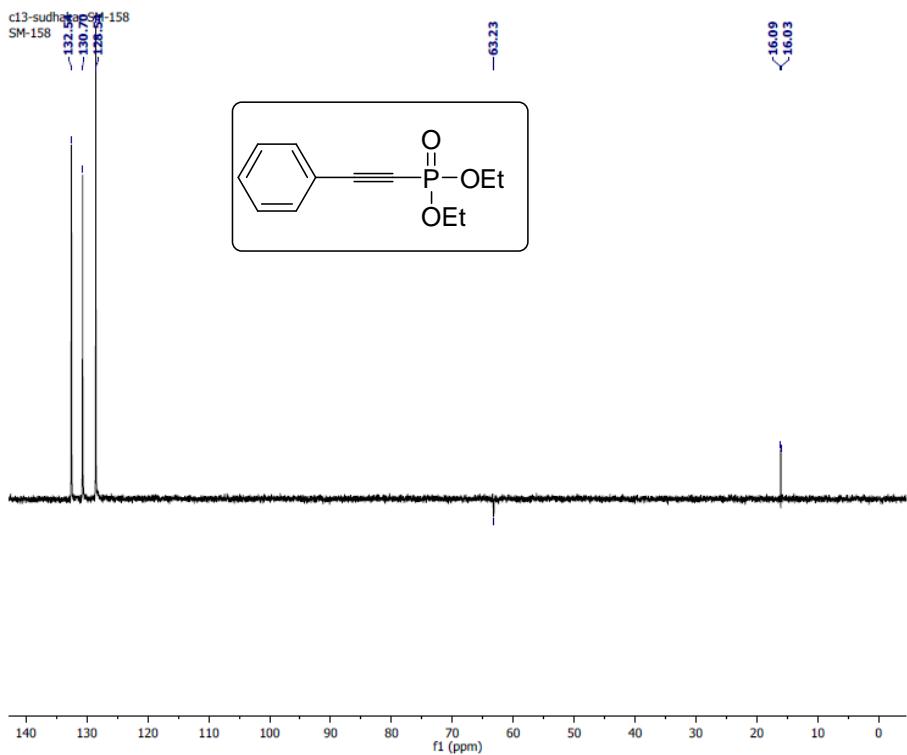


23. ¹H, ¹³C, DEPT135 and ³¹P NMR spectra of (E)-diethyl 3-bromo-4-fluorostyrylphosphonate (7d)

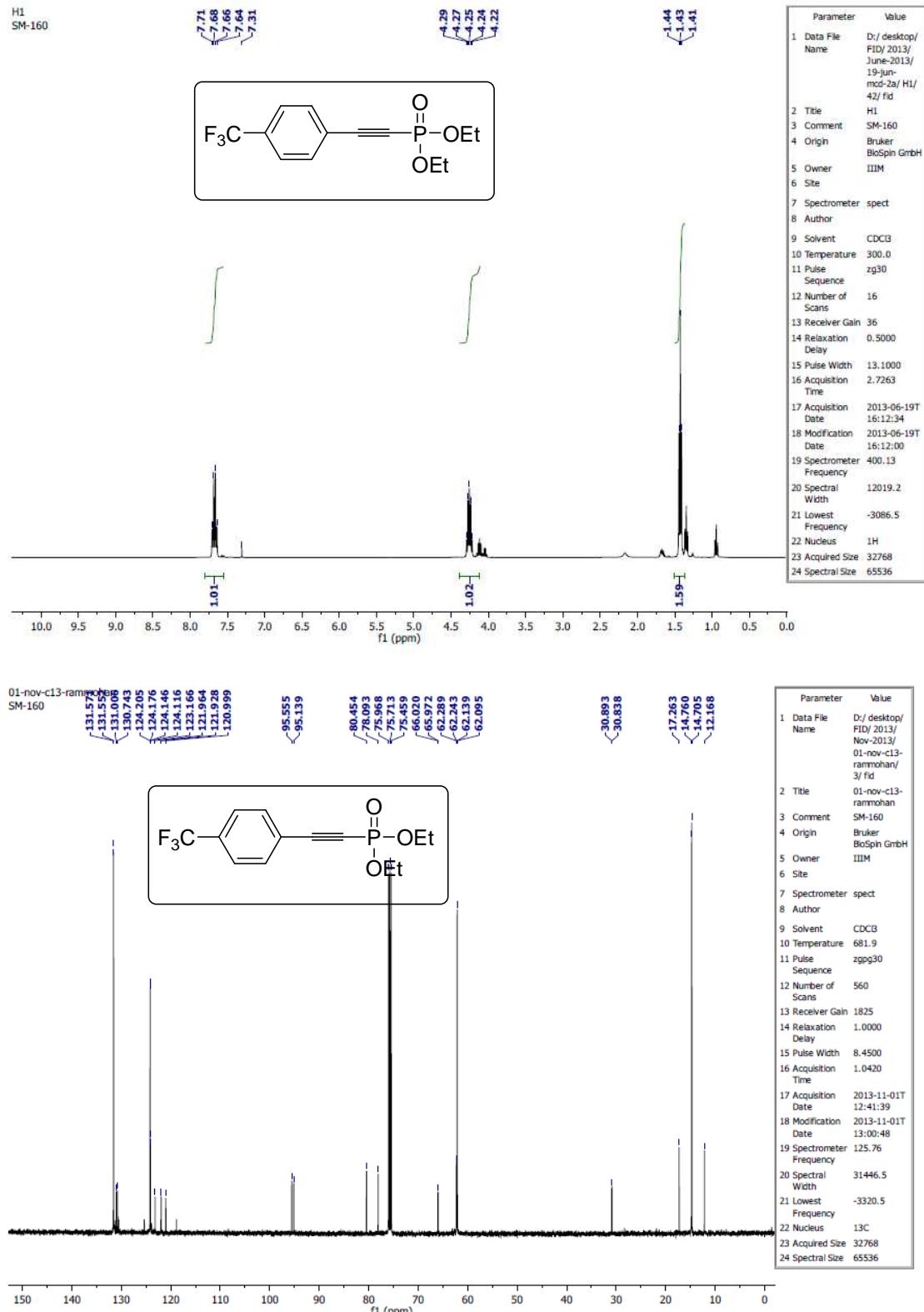


24. ^1H , ^{13}C , DEPT135 and ^{31}P NMR spectra of diethyl 2-phenylethynylphosphonate (8a)





25. ^1H , ^{13}C , DEPT135 and ^{31}P NMR spectra of diethyl-2-(4-(trifluoromethyl)phenyl)ethynylphosphonate (8b)

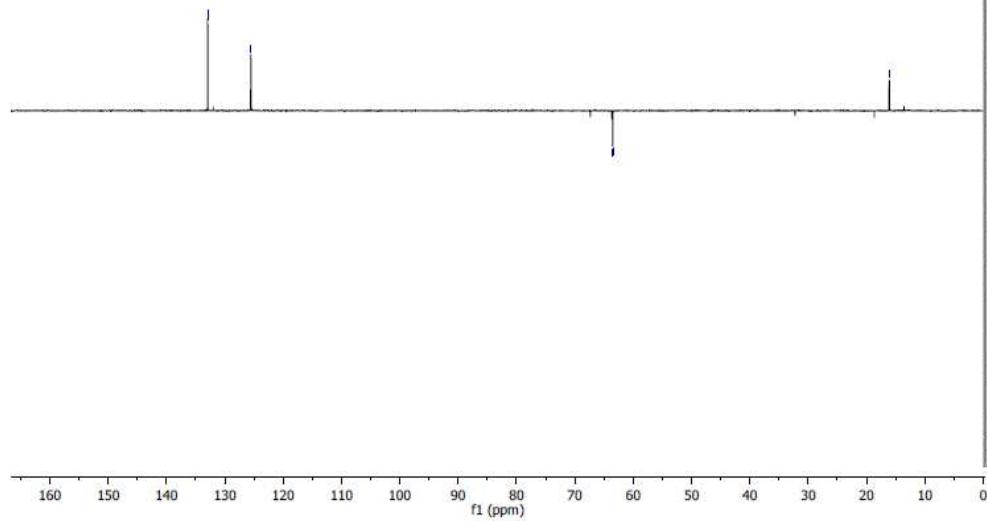
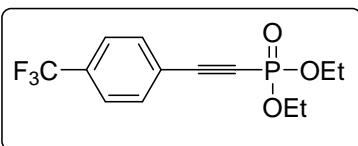


01-nov-c13-rammohan
SM-160

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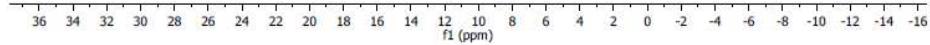
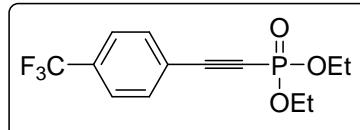
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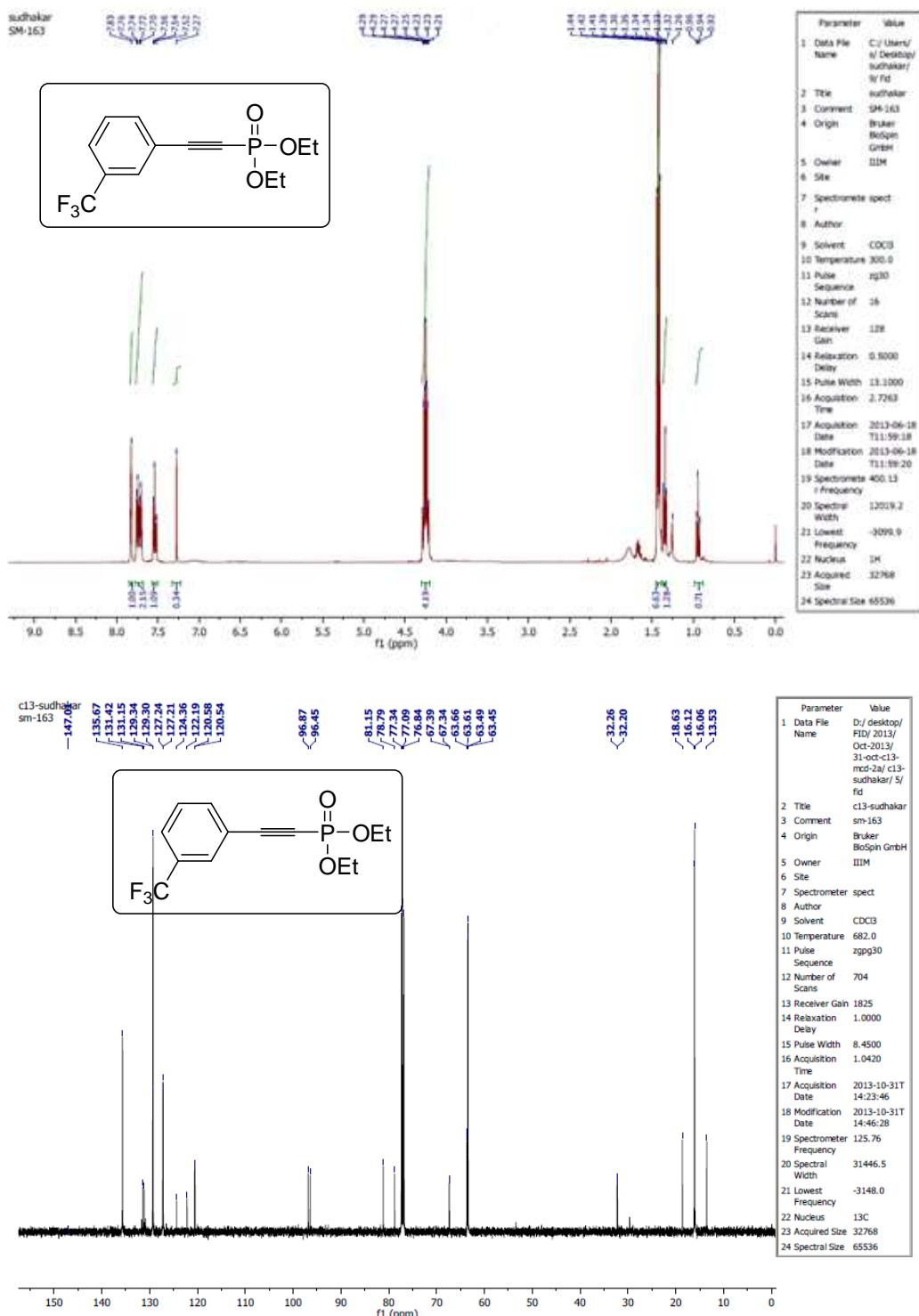
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2 Title	01-nov-c13-rammohan
3 Comment	SM-160
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5 Owner	root
6 Site	
7 Spectrometer	spec
8 Author	
9 Solvent	CDCl ₃
10 Temperature	681.8
11 Pulse Sequence	dept135
12 Number of Scans	325
13 Receiver Gain	16384
14 Relaxation Delay	1.0000
15 Pulse Width	8.4500
16 Acquisition Time	1.0912
17 Acquisition Date	2013-11-01T1 3:12:41
18 Modification Date	2013-11-01T1 3:12:48
19 Spectrometer Frequency	125.76
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22 Nucleus	13C
23 Acquired Size	32768
24 Spectral Size	65536

H1
SM-160(P31)

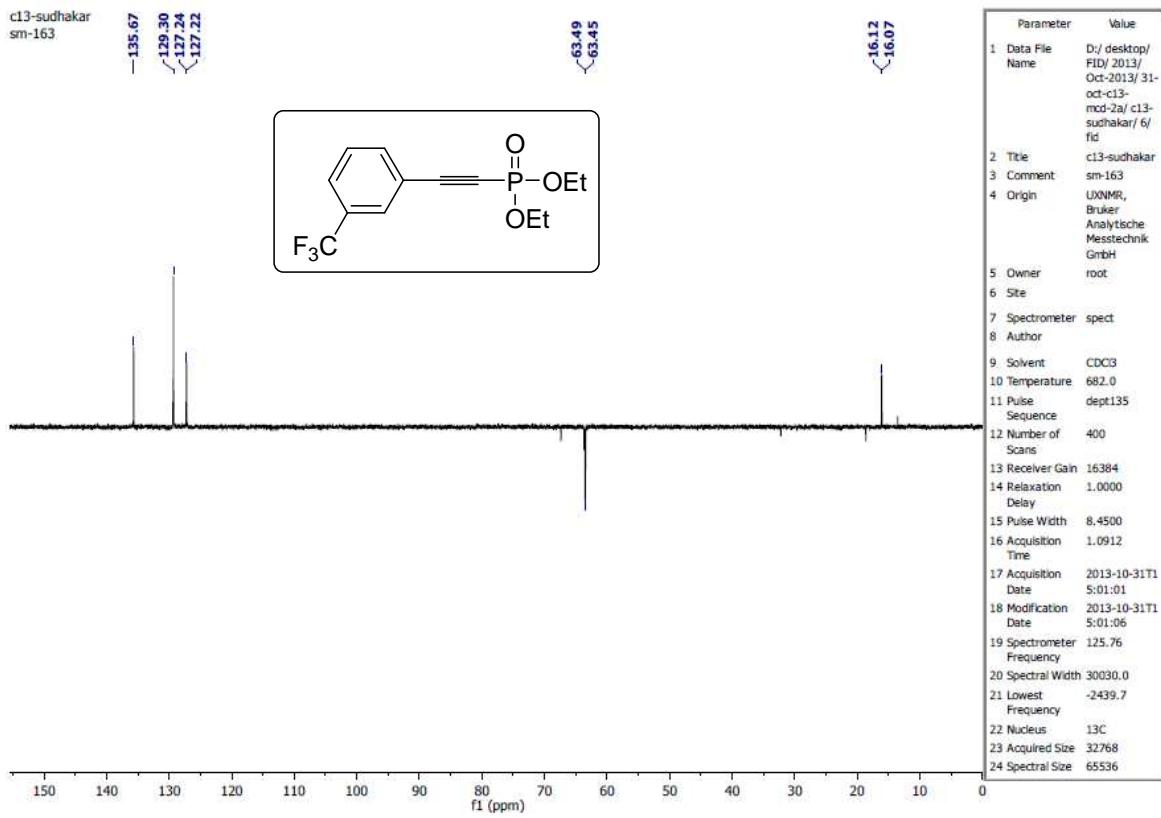


Parameter	Value
1 Data File Name	C:/Users/s/Desktop/04-nov-mcd-2a/H1/37/fid
2 Title	H1
3 Comment	SM-160(P31)
4 Origin	Bruker BioSpin GmbH
5 Owner	IIM
6 Site	
7 Spectrometer	spec
8 Author	
9 Solvent	CDCl ₃
10 Temperature	300.0
11 Pulse Sequence	zgpg30
12 Number of Scans	19
13 Receiver Gain	203
14 Relaxation Delay	2.0000
15 Pulse Width	12.5000
16 Acquisition Time	0.5112
17 Acquisition Date	14:58:26
18 Modification Date	2013-11-04T 14:58:28
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24 Spectral Size	65536

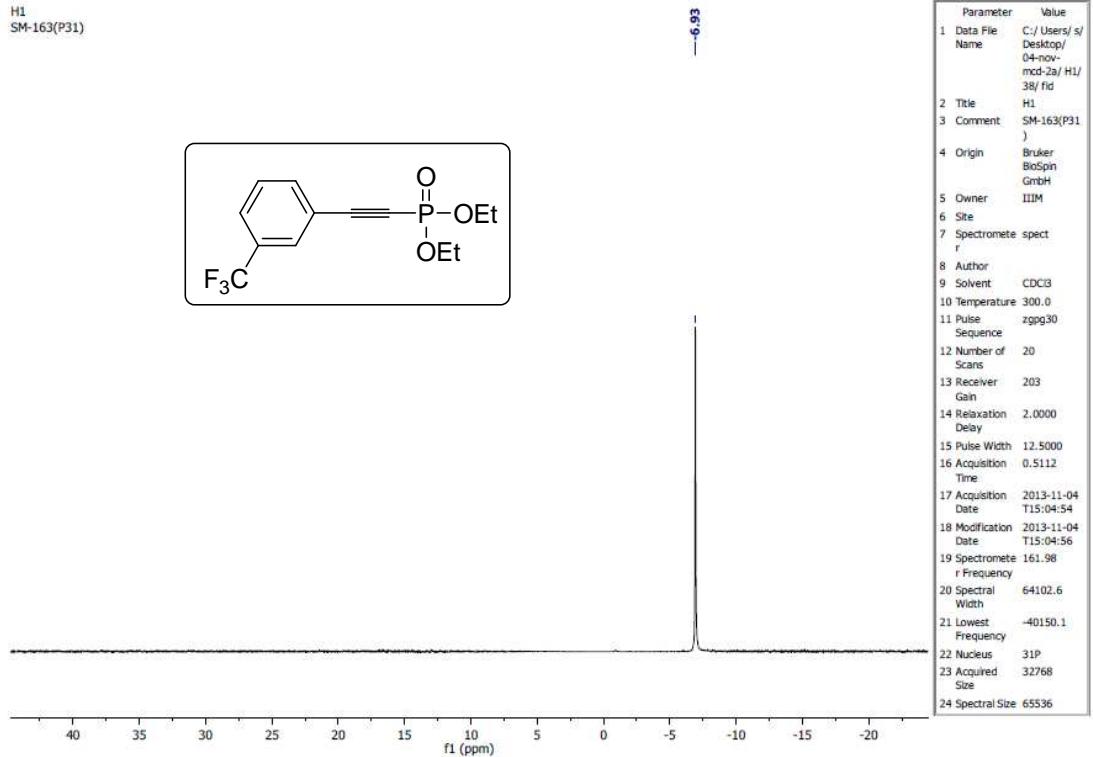
26. ^1H , ^{13}C , DEPT135 and ^{31}P NMR spectra of diethyl 2-(3-(trifluoromethyl)phenyl)ethynylphosphonate (8c)



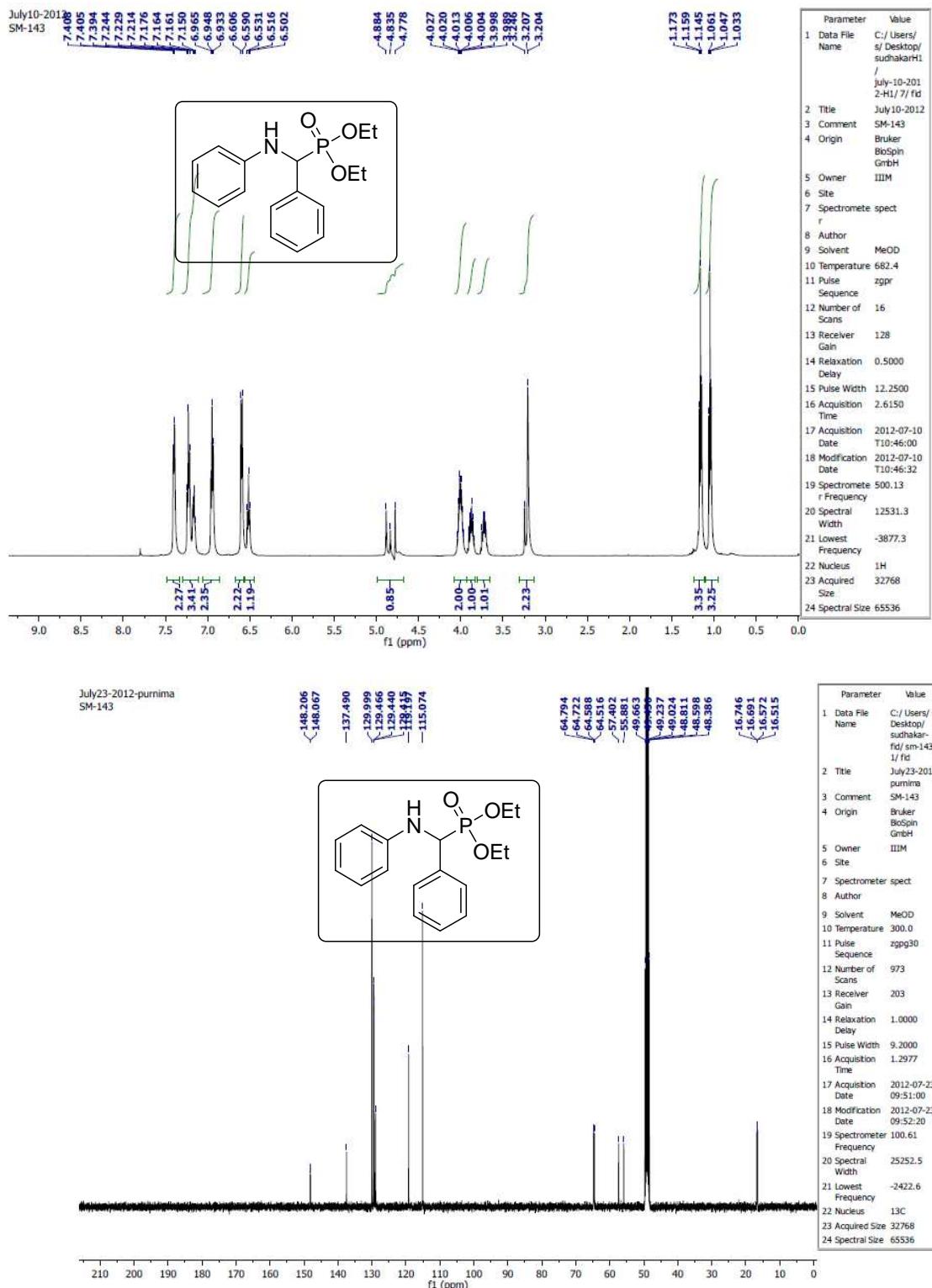
c13-sudhakar
sm-163



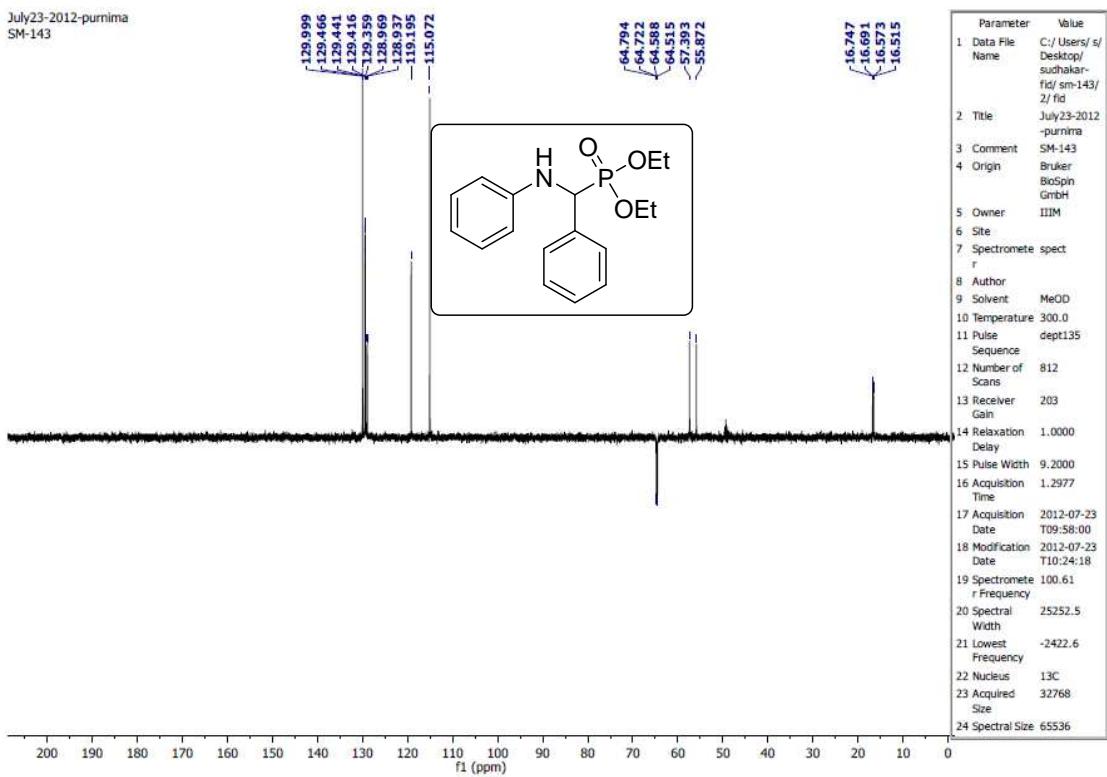
H1
SM-163(P31)



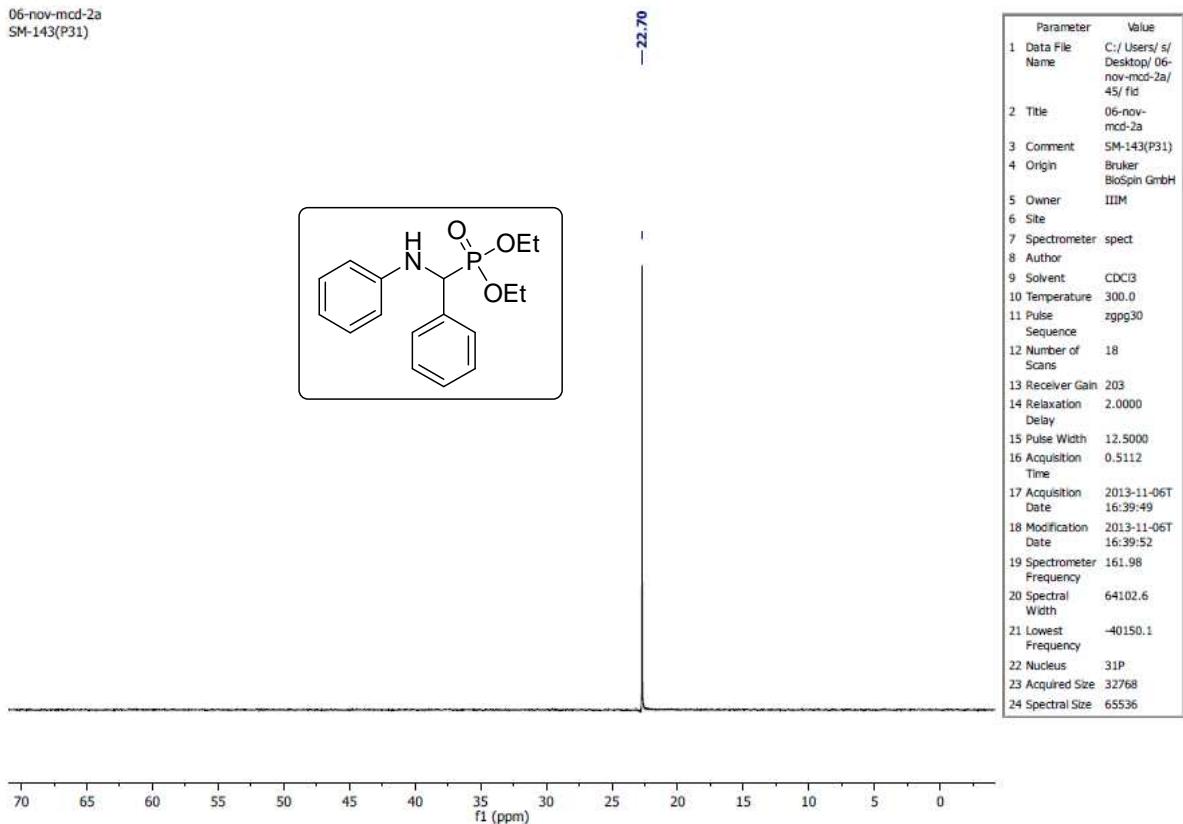
27. ^1H , ^{13}C , DEPT135 and ^{31}P NMR spectra of diethyl phenyl(phenylamino)methylphosphonate (9a)



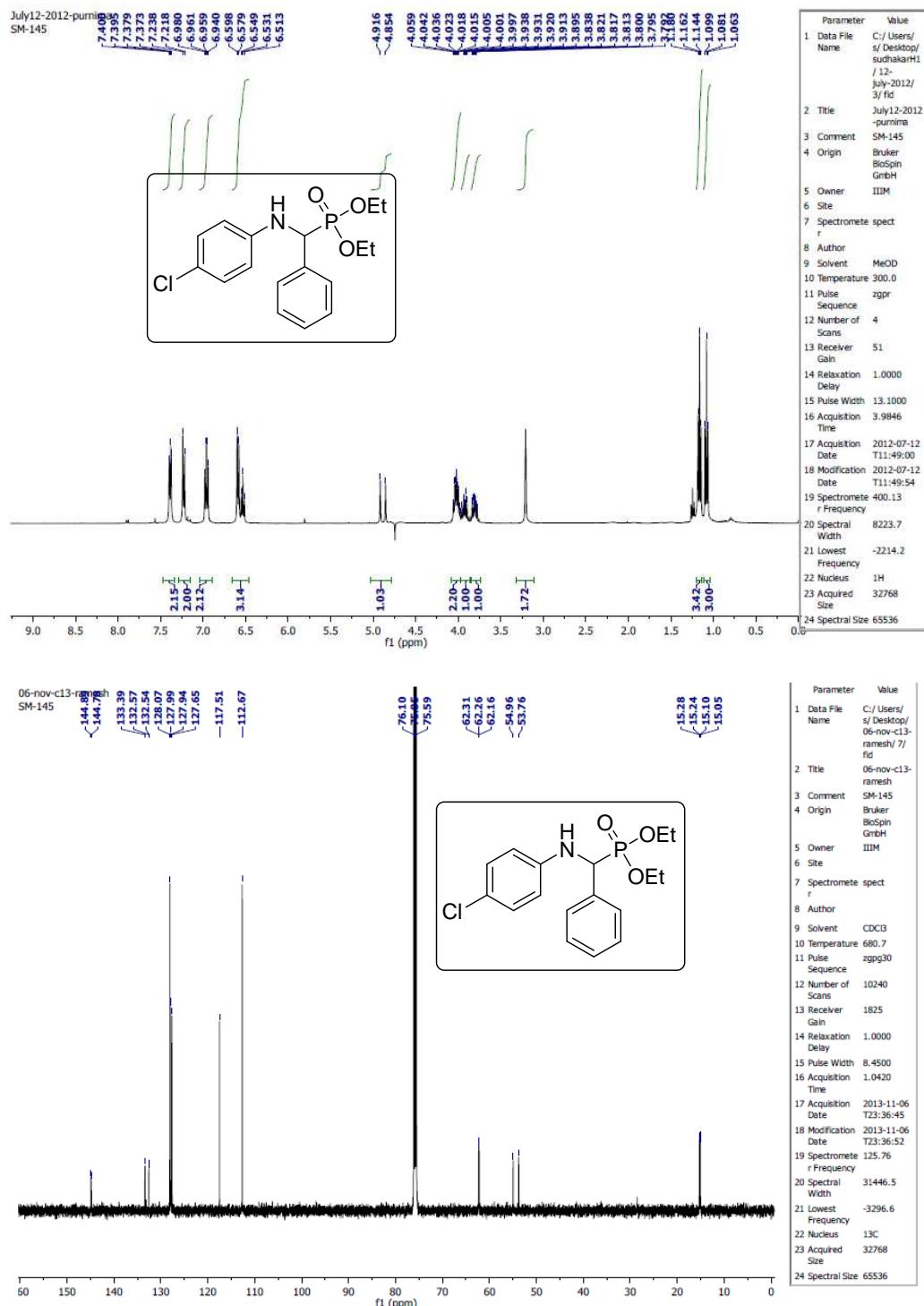
July23-2012-purnima
SM-143

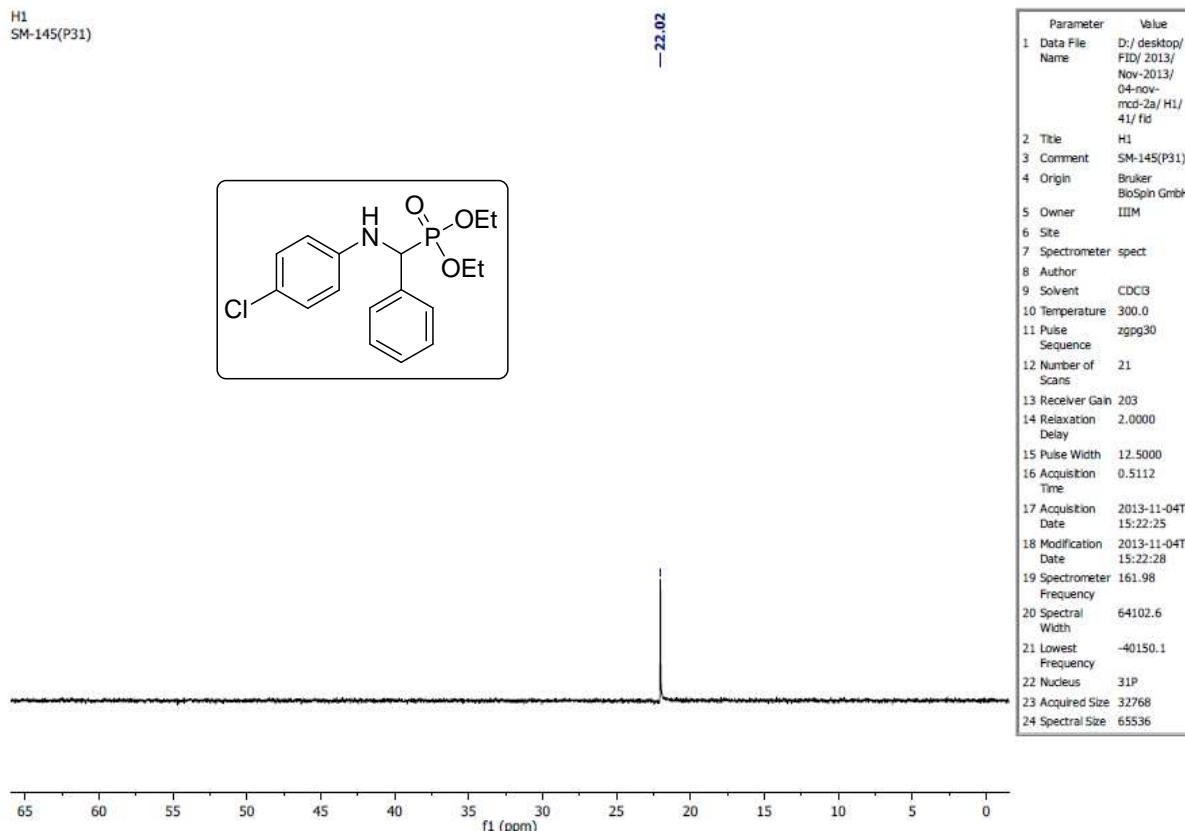
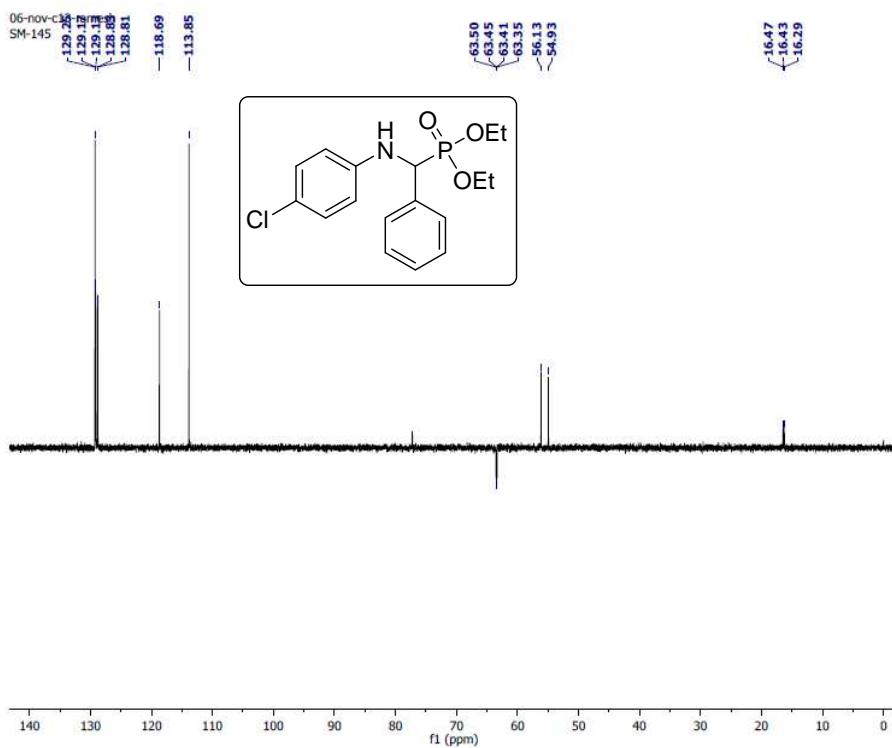


06-nov-mcd-2a
SM-143(P31)



28. ^1H , ^{13}C , DEPT135 and ^{31}P NMR spectra of diethyl (4-chlorophenyl)(phenylamino)methylphosphonate (9b)

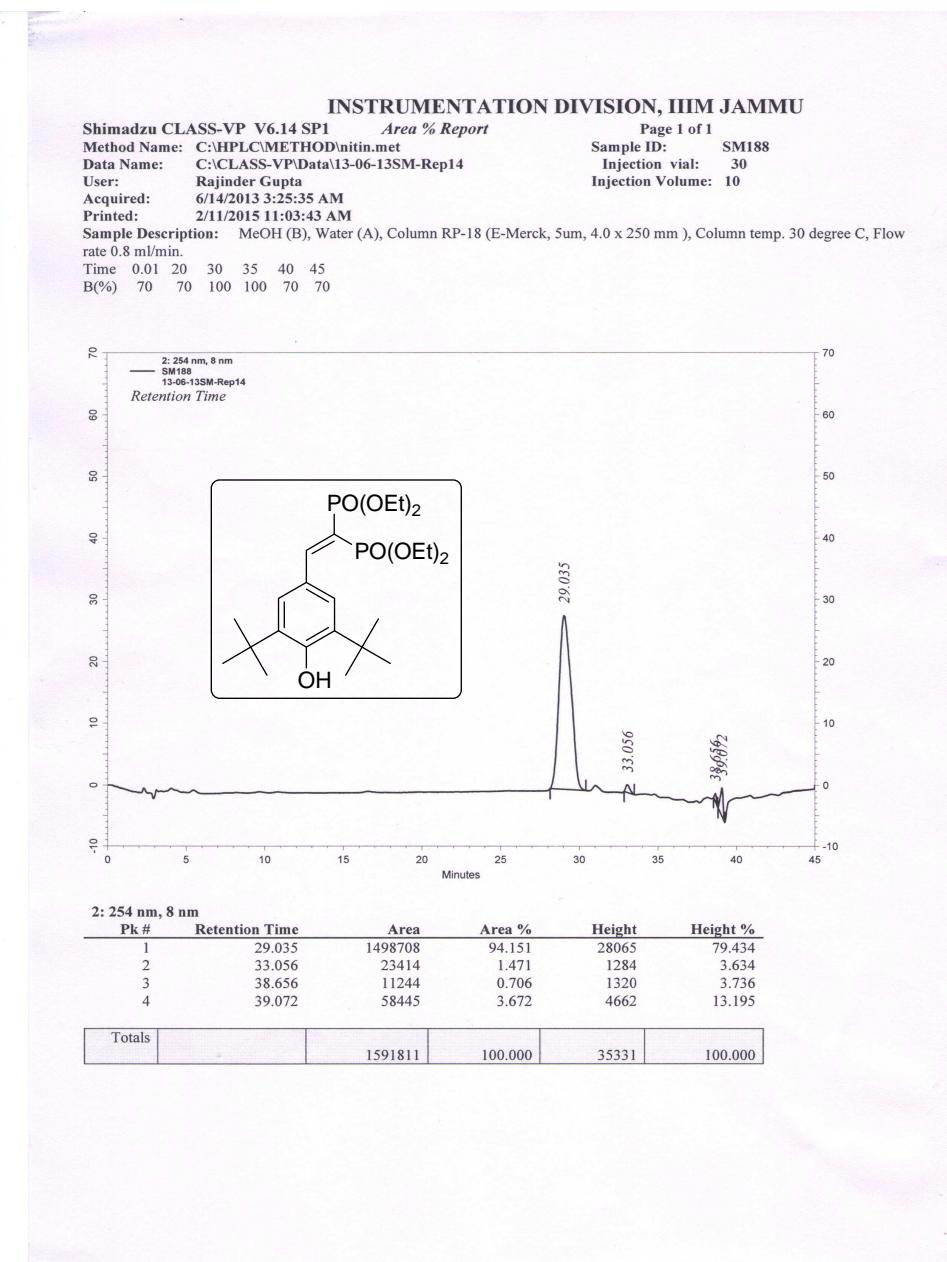




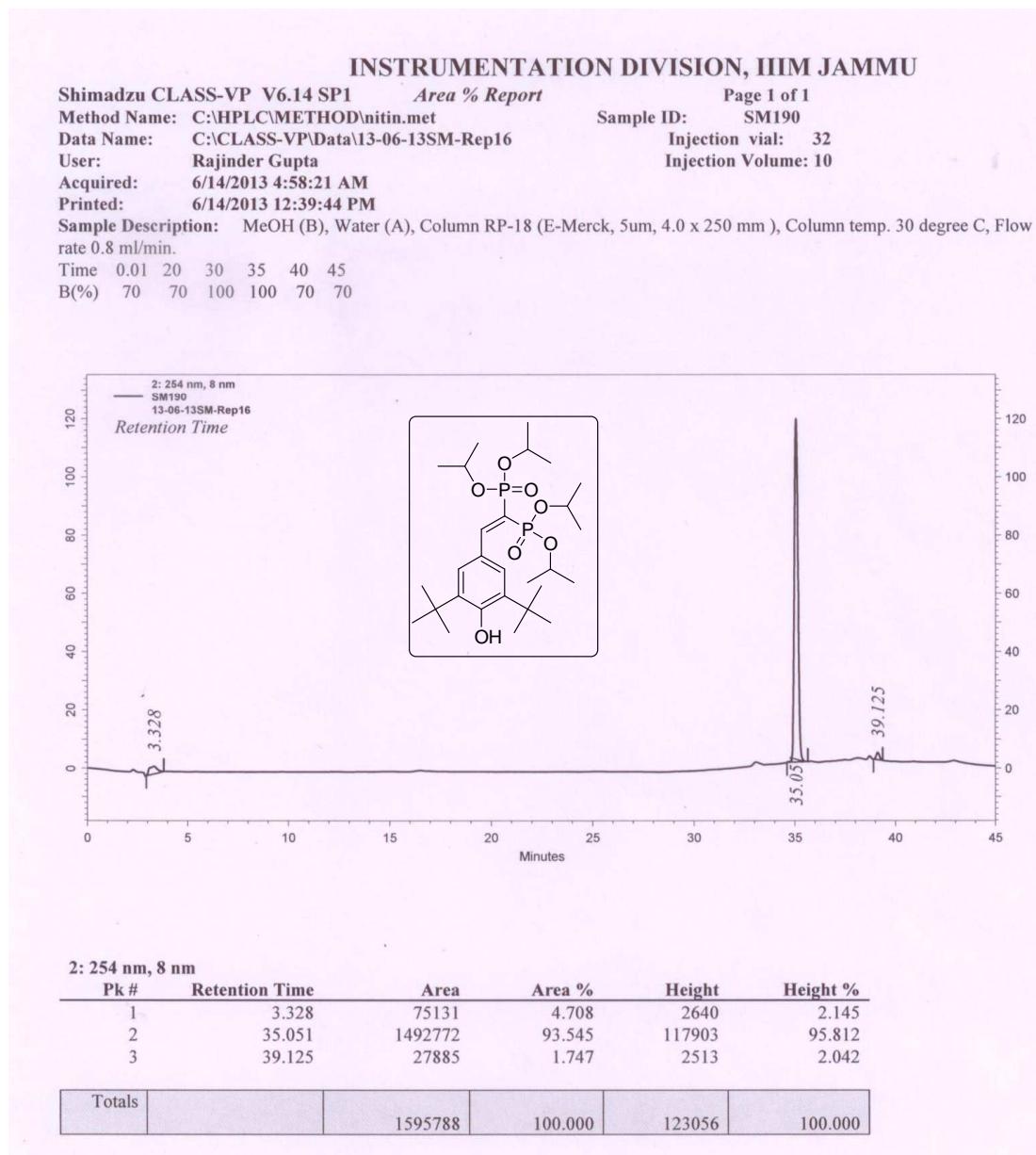
S2. HPLC chromatograms

HPLC analysis was done on Shimadzu HPLC system (model: SCL-10AVP) equipped with a PDA detector (model: RID-10A) using Inertsil RP-18(E-Merck, 5um, 4.0× 250 mm) column. Mobile phase used was Methanol: water (70: 30) isocratic elution at flow rate of 0.8 ml/min.

1. HPLC spectra of tetraethyl 2-(3, 5-di-t-butyl-4-hydroxyphenyl)ethene-1,1-diyldiphosphonate (6a)



2. HPLC spectra of tetraisopropyl 2-(3, 5-di-t-Butyl 4-hydroxy phenyl)ethene-1,1-diyldiphosphonate (6b)



3. HPLC spectra of tetraethyl 2-phenylethene-1,1-diyldiphosphonate (6c)

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Shimadzu CLASS-VP V6.14 SP1 *Area % Report*

Page 1 of 1

Method Name: C:\HPLC\METHOD\nitin.met

Sample ID: SM171

Data Name: C:\CLASS-VP\DATA\13-06-13SM-Rep10

Injection vial: 27

User: Rajinder Gupta

Injection Volume: 10

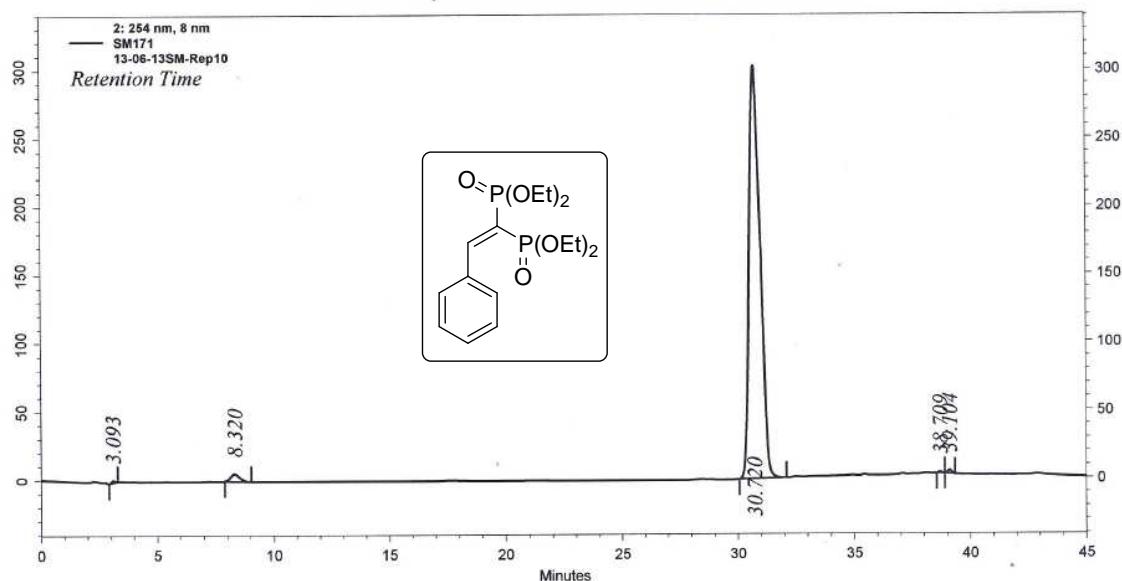
Acquired: 6/14/2013 12:19:58 AM

Printed: 6/14/2013 12:37:57 PM

Sample Description: MeOH (B), Water (A), Column RP-18 (E-Merck, 5um, 4.0 x 250 mm), Column temp. 30 degree C, Flow rate 0.8 ml/min.

Time 0.01 20 30 35 40 45

B(%) 70 70 100 100 70 70



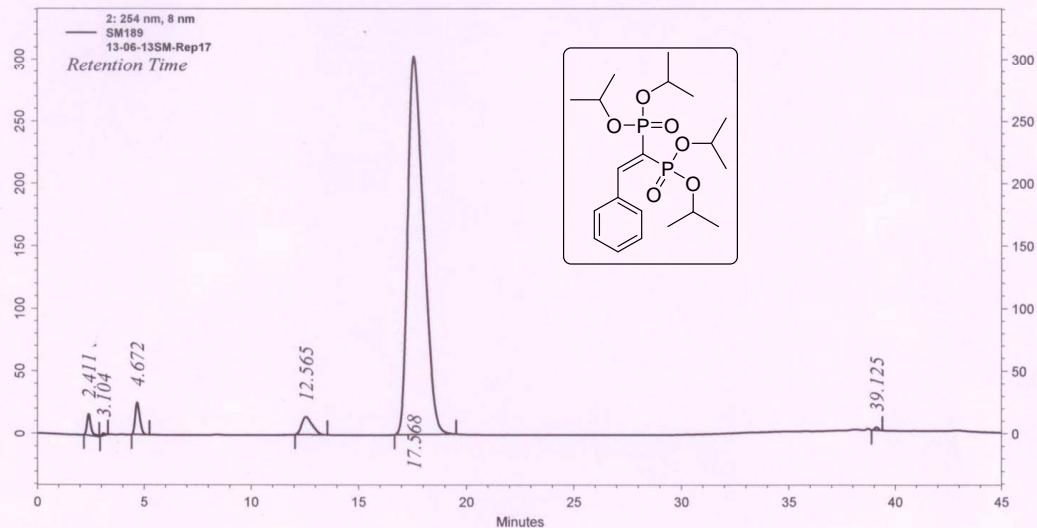
2: 254 nm, 8 nm

Pk #	Retention Time	Area	Area %	Height	Height %
1	3.093	16727	0.166	1638	0.523
2	8.320	144175	1.431	5470	1.746
3	30.720	9875476	98.020	302630	96.574
4	38.709	10800	0.107	1146	0.366
5	39.104	27787	0.276	2483	0.792
Totals		10074965	100.000	313367	100.000

4. HPLC spectra of tetraisopropyl-2-phenylethene-1,1-diyldiphosphonate (6d)

INSTRUMENTATION DIVISION, IIM JAMMU

Shimadzu CLASS-VP V6.14 SP1 *Area % Report* Page 1 of 1
 Method Name: C:\HPLC\METHOD\nitin.met Sample ID: SM189
 Data Name: C:\CLASS-VP\DATA\13-06-13SM-Rep17 Injection vial: 33
 User: Rajinder Gupta Injection Volume: 10
 Acquired: 6/14/2013 5:44:42 AM
 Printed: 6/14/2013 12:39:58 PM
 Sample Description: MeOH (B), Water (A), Column RP-18 (E-Merck, 5um, 4.0 x 250 mm), Column temp. 30 degree C, Flow rate 0.8 ml/min.
 Time 0.01 20 30 35 40 45
 B(%) 70 70 100 100 70 70



2: 254 nm, 8 nm

Pk #	Retention Time	Area	Area %	Height	Height %
1	2.411	222549	1.345	17149	4.695
2	3.104	20372	0.123	1931	0.529
3	4.672	386863	2.338	25898	7.090
4	12.565	491768	2.971	14421	3.948
5	17.568	15399673	93.050	303350	83.042
6	39.125	28586	0.173	2549	0.698
Totals		16549811	100.000	365298	100.000

5. HPLC spectra of tetraethyl 2-(2-nitrophenyl)ethene-1,1-diyldiphosphonate (6e)

INSTRUMENTATION DIVISION, IIIM JAMMU

Shimadzu CLASS-VP V6.14 SP1 *Area % Report*

Page 1 of 1

Method Name: C:\HPLC\METHOD\Nitin.met

Sample ID: SM-182

Data Name: C:\HPLC\DATA\19-12-14 SB-Rep3

Injection vial: 11

User: Rajinder Gupta

Injection Volume: 10

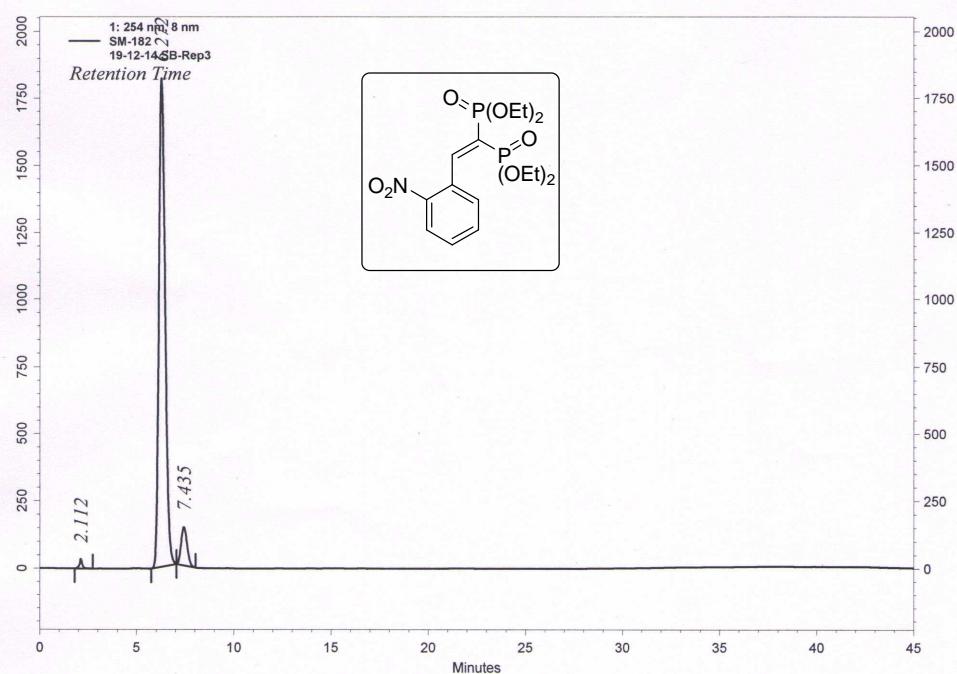
Acquired: 12/19/2014 12:41:01 PM

Printed: 12/19/2014 7:04:21 PM

Sample Description: Methanol (B), Water (A), Column RP-18(E- Merck, 5um, 4.0 x 250 mm), Column temp. 30 deg rare 0.8 ml/min.

Time 0.01 20 30 35 40 45

B(%) 70 70 100 100 70 70



1: 254 nm, 8 nm

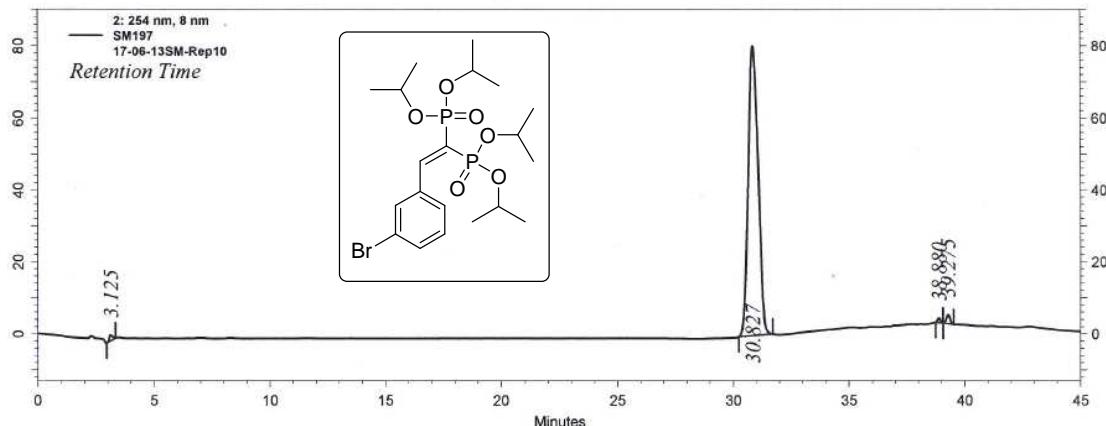
Pk #	Retention Time	Area	Area %	Height	Height %
1	2.112	366181	0.829	35533	1.779
2	6.272	40698084	92.153	1820108	91.101
3	7.435	3099508	7.018	142257	7.120

Totals		44163773	100.000	1997898	100.000
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6. HPLC spectra of tetraisopropyl,2-(3-bromophenyl)ethane-1,1-diyldiphosphonate (6f)

INSTRUMENTATION DIVISION, IIM JAMMU

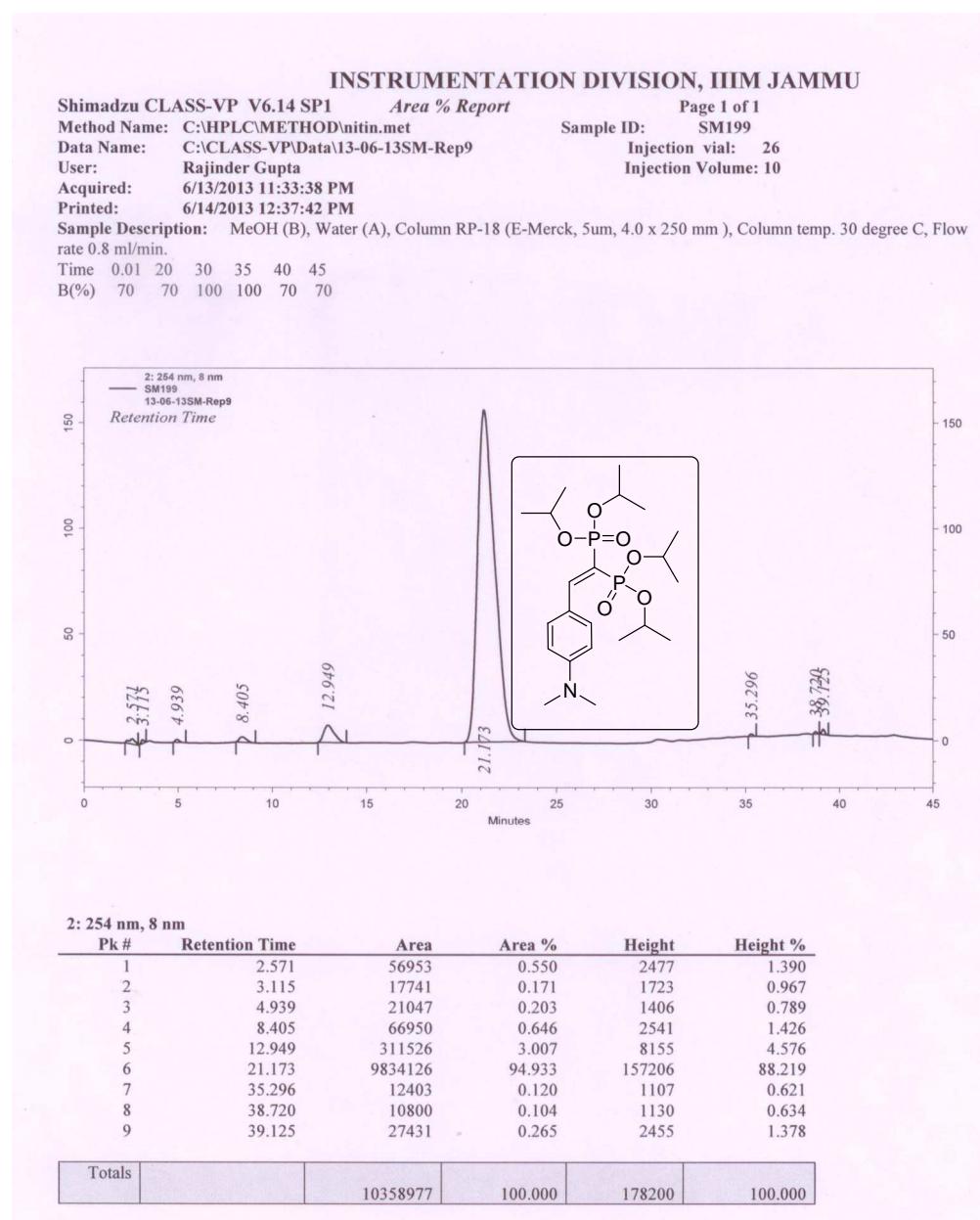
Shimadzu CLASS-VP V6.14 SP1 *Area % Report* Page 1 of 1
 Method Name: C:\HPLC\METHOD\nitin.met Sample ID: SM197
 Data Name: C:\CLASS-VP\DATA\17-06-13SM-Rep10 Injection vial: 7
 User: Niteen Narkhede Injection Volume: 10
 Acquired: 6/18/2013 1:11:36 AM
 Printed: 6/18/2013 10:25:27 AM
 Sample Description: MeOH (B), Water (A), Column RP-18 (E-Merck, 5um, 4.0 x 250 mm), Column temp. 30 degree C, Flow rate 0.8 ml/min.
 Time 0.01 20 30 35 40 45 B(%) 70 70 100 100 70 70



2: 254 nm, 8 nm

Pk #	Retention Time	Area	Area %	Height	Height %
1	3.125	15961	0.649	1555	1.815
2	30.827	2403052	97.784	80405	93.825
3	38.880	11382	0.463	1224	1.428
4	39.275	27108	1.103	2513	2.932
Totals		2457503	100.000	85697	100.000

7. HPLC spectra of tetraisopropyl-2-(4-N,N-dimethylaminophenyl)ethene-1,1-diylidiphosphonate (6g)



8. HPLC spectra of tetraethyl2-(3,5-dimethoxyphenyl)ethene-1,1 diylidiphosphonate (6h)

INSTRUMENTATION DIVISION, IIIM JAMMU

Shimadzu CLASS-VP V6.14 SP1 *Area % Report*

Page 1 of 1

Method Name: C:\HPLC\METHOD\nitin.met

Sample ID: SM-186

Data Name: C:\HPLC\DATA\19-12-14 SB-Rep5

Injection vial: 13

User: Rajinder Gupta

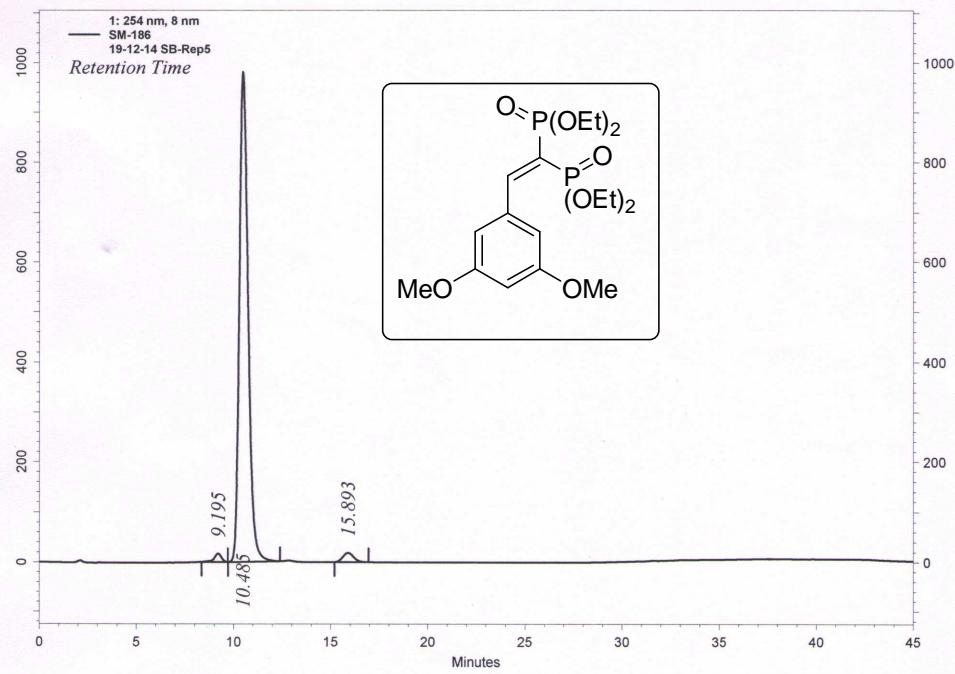
Injection Volume: 10

Acquired: 12/19/2014 2:13:51 PM

Printed: 12/19/2014 7:05:14 PM

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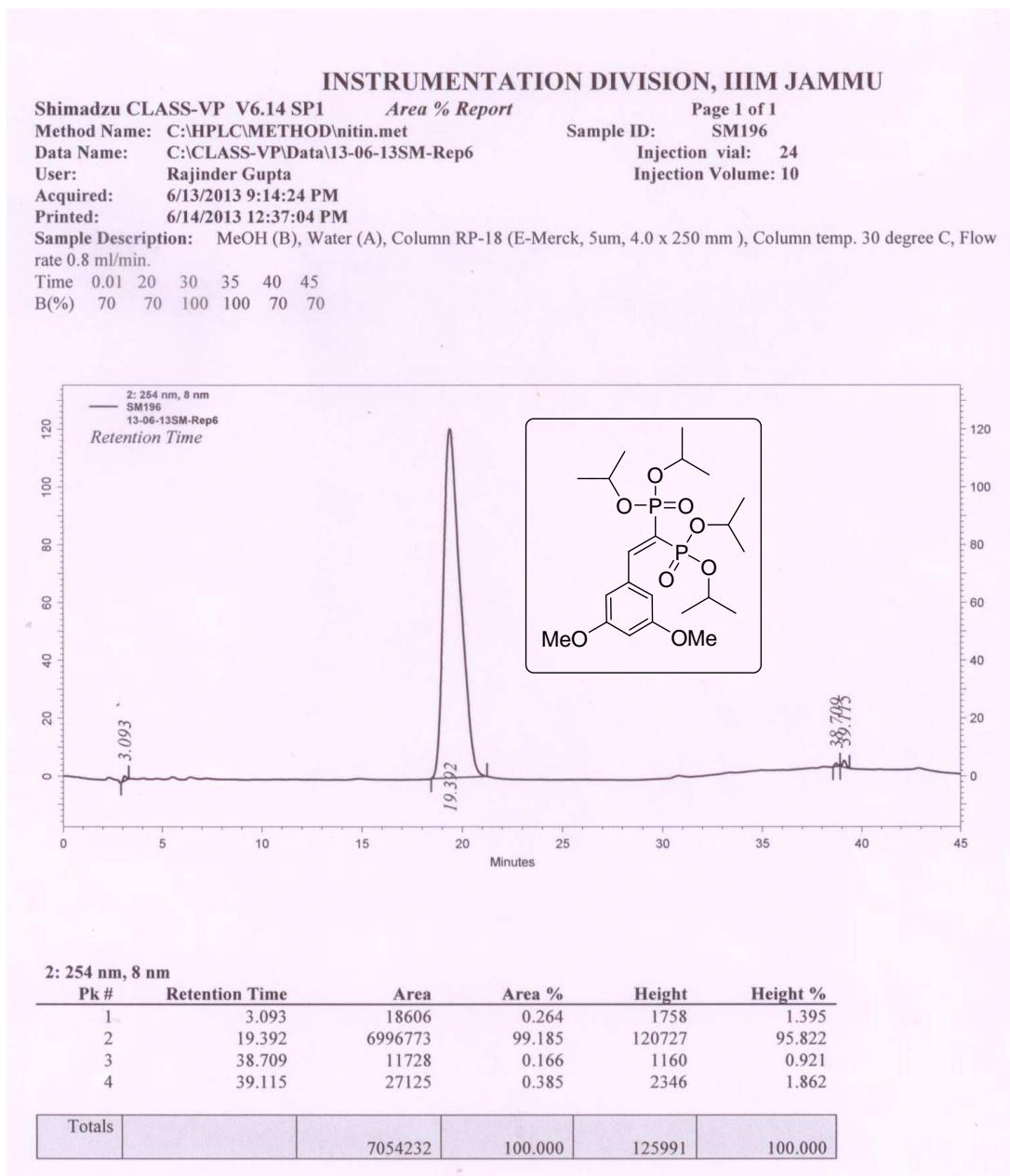
Time	0.01	20	30	35	40	45
B(%)	70	70	100	100	70	70



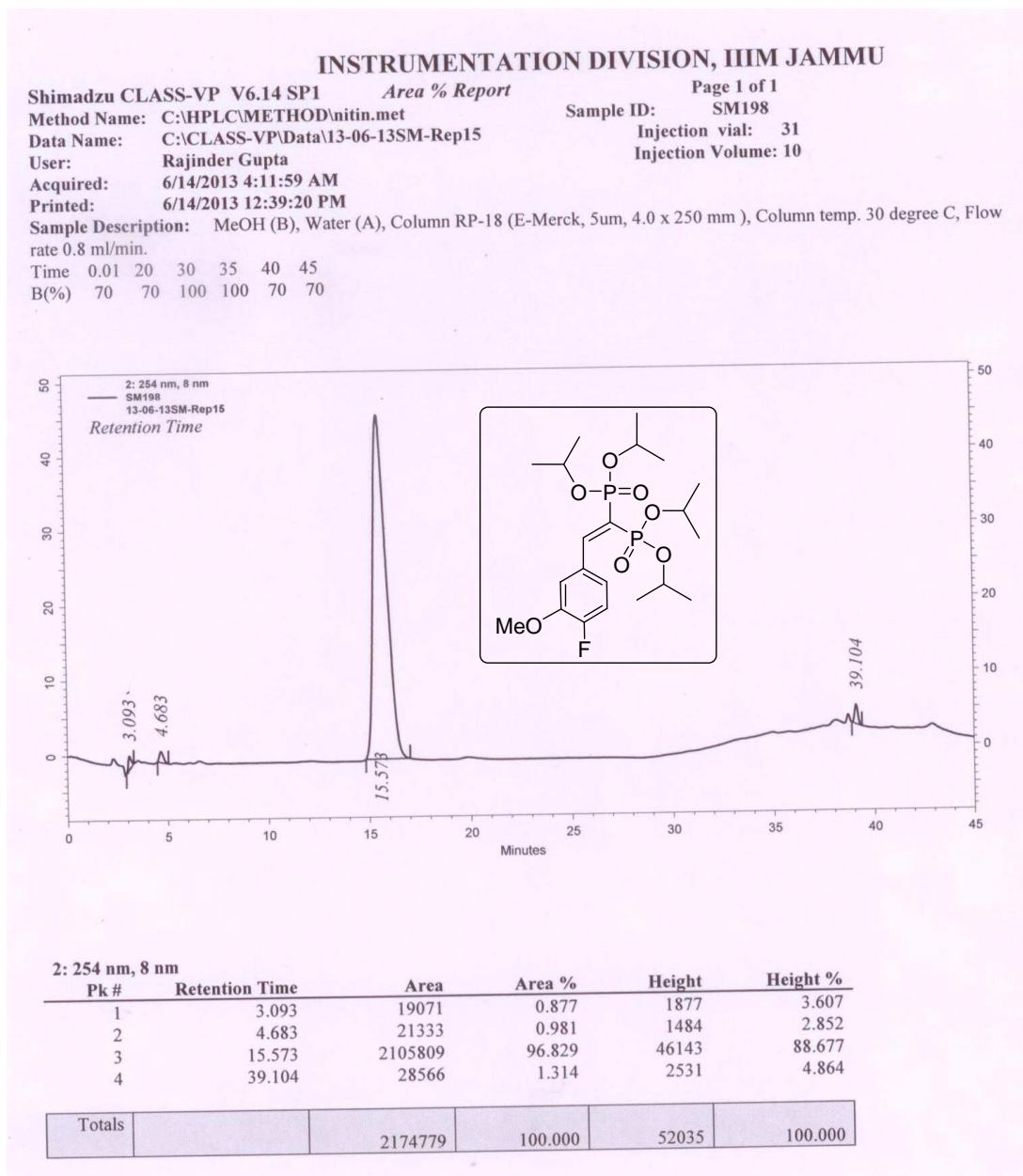
Pk #	Retention Time	Area	Area %	Height	Height %
1	9.195	441281	1.377	17281	1.698
2	10.485	30871857	96.353	981700	96.454
3	15.893	727297	2.270	18815	1.849

Totals		32040435	100.000	1017796	100.000
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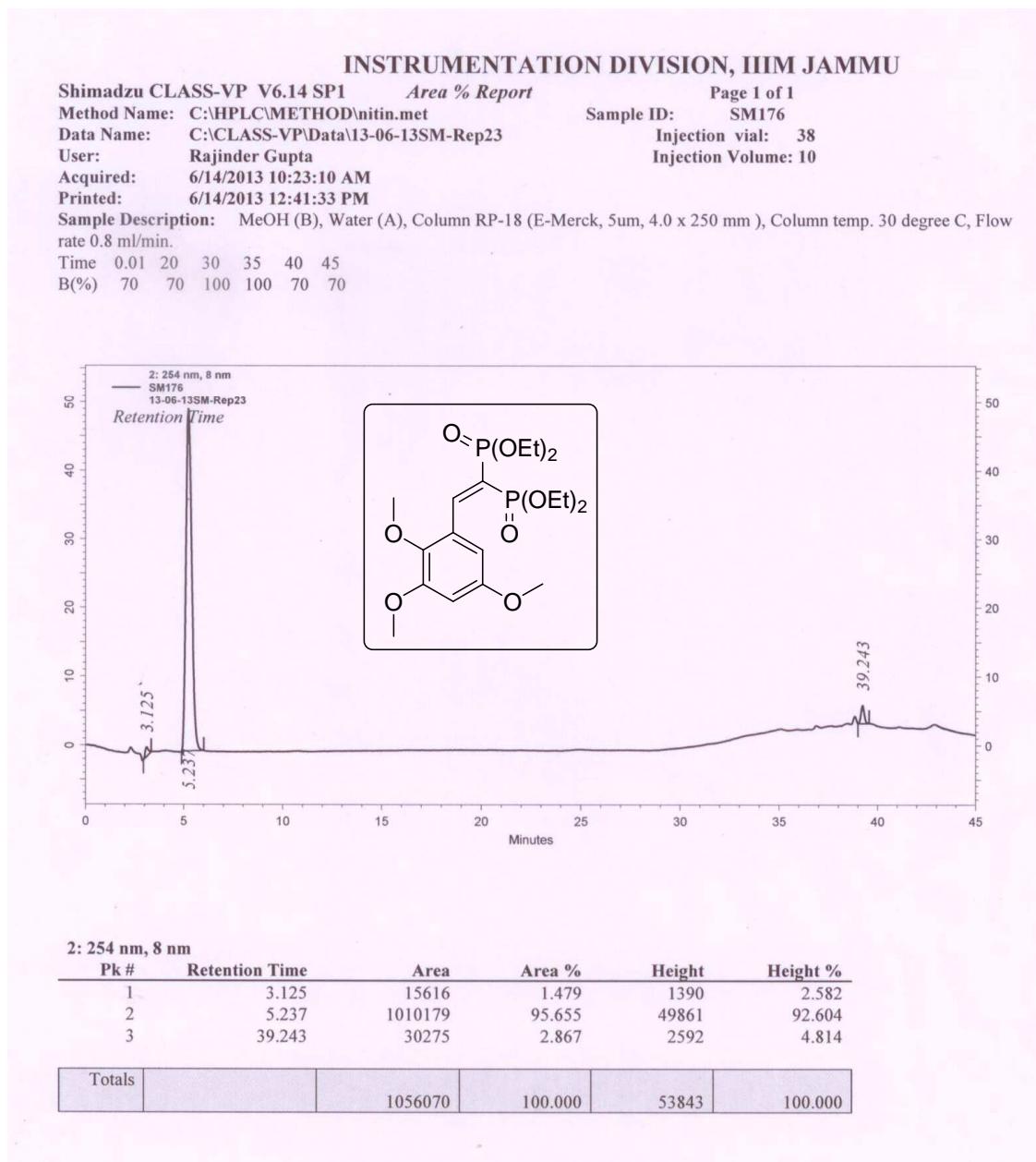
9. HPLC spectra of tetraisopropyl-2-(3,5-dimethoxyphenyl)ethene-1,1-diyldiphosphonate (**6i**)



10. HPLC spectra of tetraisopropyl2-(3-methoxy4-fluorophenyl)ethene-1,1diyldiphosphonate (6j)



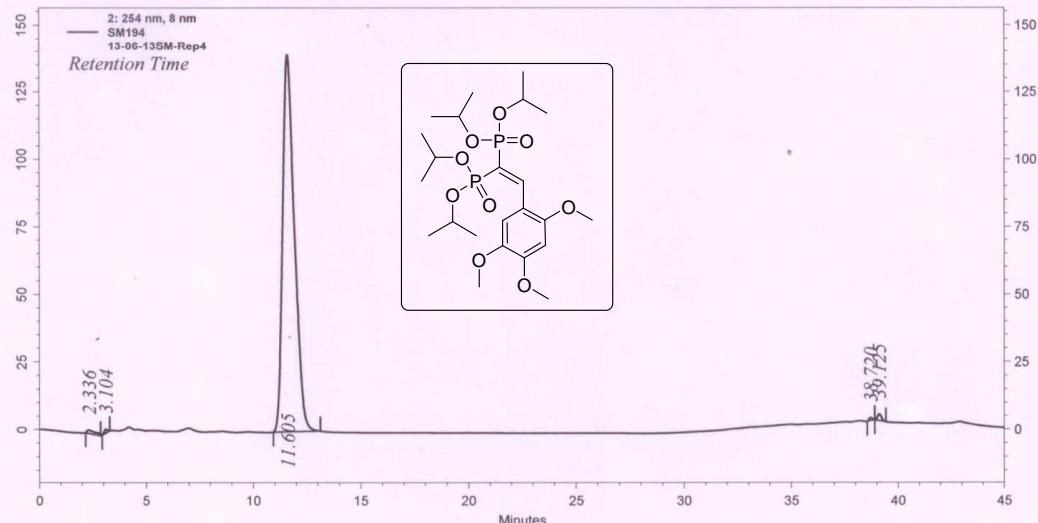
11. HPLC spectra of tetraethyl- 2(2,3,5-trimethoxyphenyl)ethane-1,1-diyldiphosphonate (6k)



12. HPLC spectra of tetraisopropyl 2-(2,4,5-trimethoxyphenyl)ethene-1,1-diyldiphosphonate (6l)

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Shimadzu CLASS-VP V6.14 SP1 Area % Report Page 1 of 1
 Method Name: C:\HPLC\METHOD\nitin.met Sample ID: SM194
 Data Name: C:\CLASS-VP\Data\13-06-13SM-Rep4 Injection vial: 22
 User: Rajinder Gupta Injection Volume: 10
 Acquired: 6/13/2013 7:41:38 PM
 Printed: 6/14/2013 12:36:32 PM
 Sample Description: MeOH (B), Water (A), Column RP-18 (E-Merck, 5um, 4.0 x 250 mm), Column temp. 30 degree C, Flow rate 0.8 ml/min.
 Time 0.01 20 30 35 40 45
 B(%) 70 70 100 100 70 70



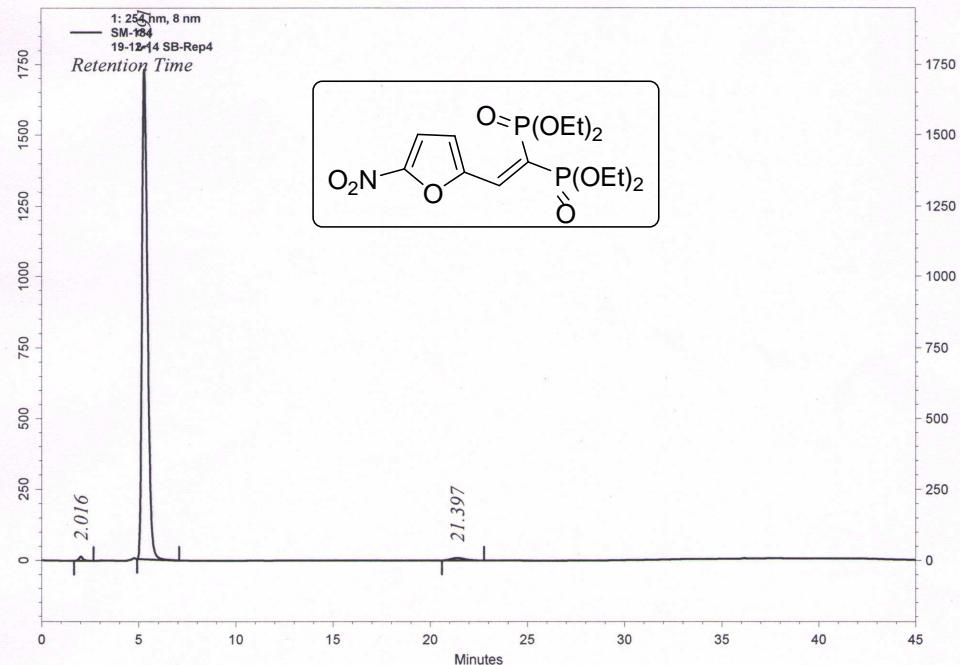
2: 254 nm, 8 nm

Pk #	Retention Time	Area	Area %	Height	Height %
1	2.336	35306	0.657	1261	0.865
2	3.104	14558	0.271	1449	0.994
3	11.605	5284765	98.311	139528	95.739
4	38.720	11065	0.206	1075	0.738
5	39.125	29860	0.555	2425	1.664
Totals		5375554	100.000	145738	100.000

13. HPLC spectra of tetraethyl2-(5-nitrofuran-2-yl)ethene-1,1-diyldiphosphonate (6m)

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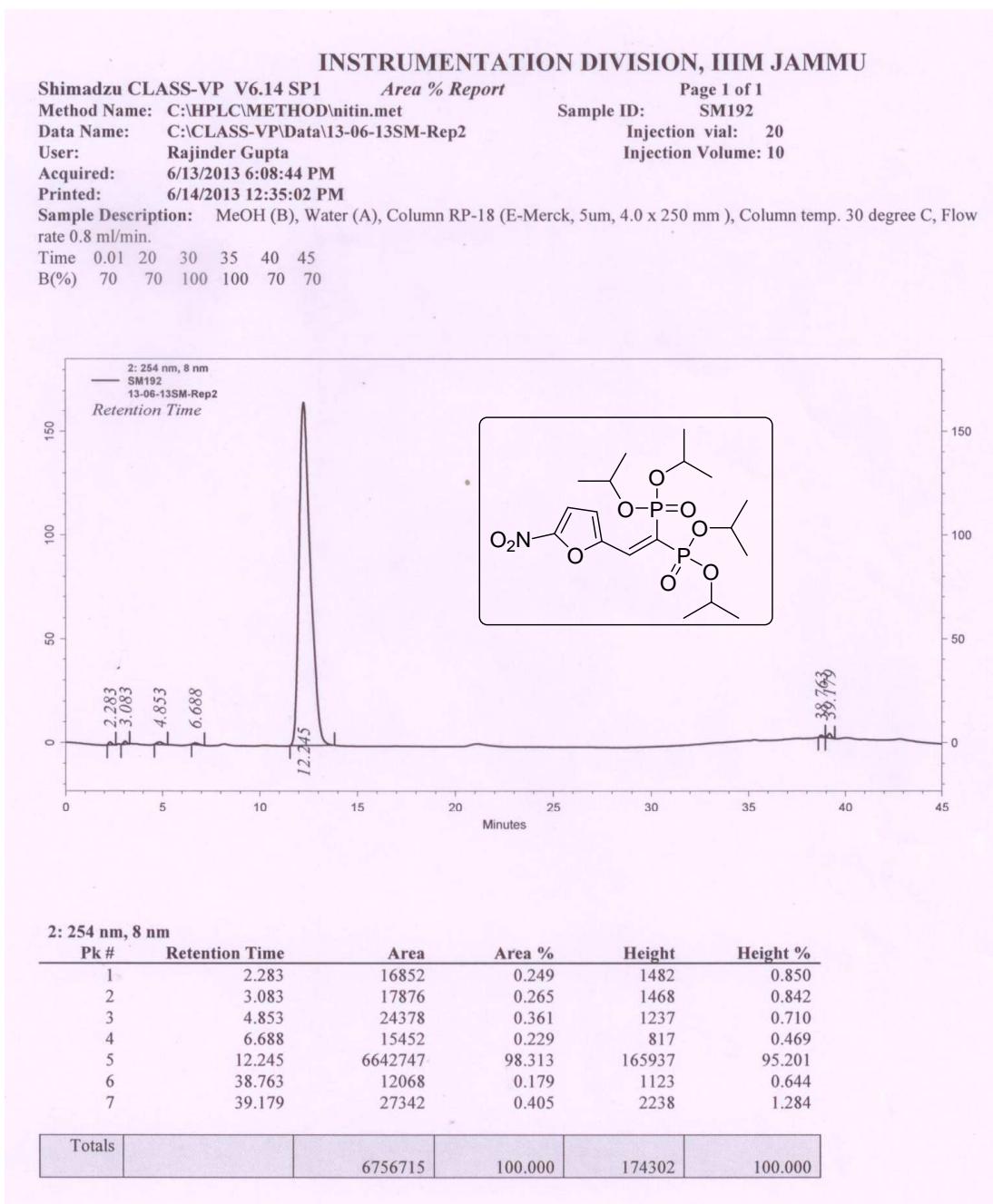
Shimadzu CLASS-VP V6.14 SP1 *Area % Report* Page 1 of 1
 Method Name: C:\HPLC\METHOD\nitin.met Sample ID: SM-184
 Data Name: C:\HPLC\DATA\19-12-14 SB-Rep4 Injection vial: 12
 User: Rajinder Gupta Injection Volume: 10
 Acquired: 12/19/2014 1:27:27 PM
 Printed: 12/19/2014 7:04:46 PM
 Sample Description: Methanol (B), Water (A), Column RP-18(E- Merck, 5um, 4.0 x 250 mm), Column temp. 30 degr rare 0.8 ml/min.
 Time 0.01 20 30 35 40 45
 B(%) 70 70 100 100 70 70



1: 254 nm, 8 nm

Pk #	Retention Time	Area	Area %	Height	Height %
1	2.016	228079	0.656	15812	0.902
2	5.291	34053111	98.015	1727859	98.602
3	21.397	461585	1.329	8686	0.496
Totals		34742775	100.000	1752357	100.000

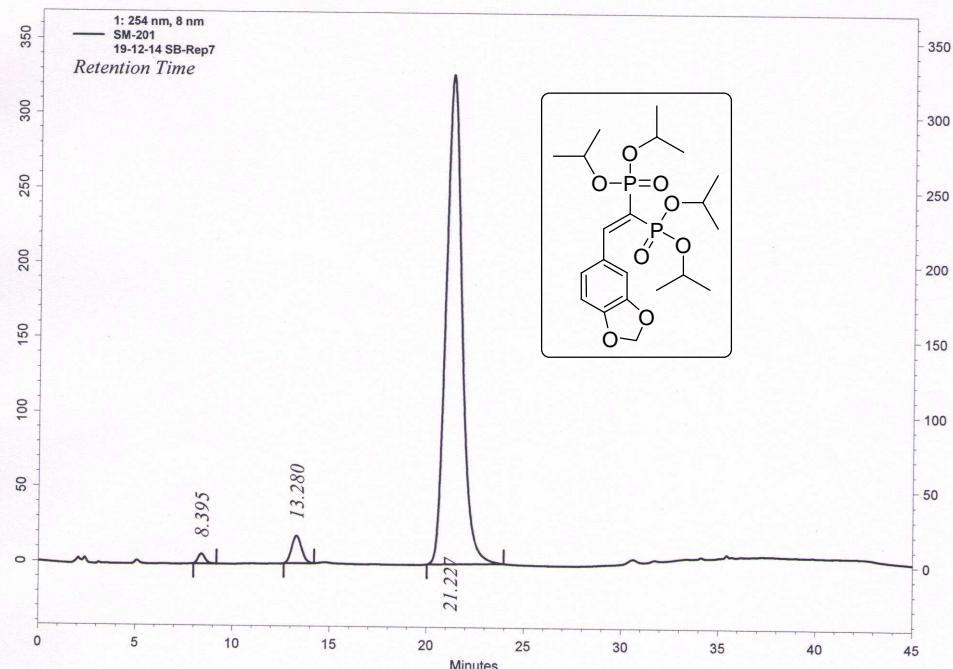
14. HPLC spectra of tetraisopropyl2-(5-nitrofuran-2-yl)ethene-1,1 diyldiphosphonate (6n)



15. HPLC spectra of tetraisopropyl2-(benzo[d][1,3]dioxol-5-yl)ethene-1,1-diyldiphosphonate (6o)

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Shimadzu CLASS-VP V6.14 SP1 *Area % Report* Page 1 of 1
 Method Name: C:\HPLC\METHOD\nitin.met Sample ID: SM-201
 Data Name: C:\HPLC\DATA\19-12-14 SB-Rep7 Injection vial: 15
 User: Rajinder Gupta Injection Volume: 10
 Acquired: 12/19/2014 3:46:40 PM
 Printed: 12/19/2014 7:06:02 PM
 Sample Description: Methanol (B), Water (A), Column RP-18(E- Merck, 5um, 4.0 x 250 mm), Column temp. 30 deg
 re 0.8 ml/min.
 Time 0.01 20 30 35 40 45
 B(%) 70 70 100 100 70 70

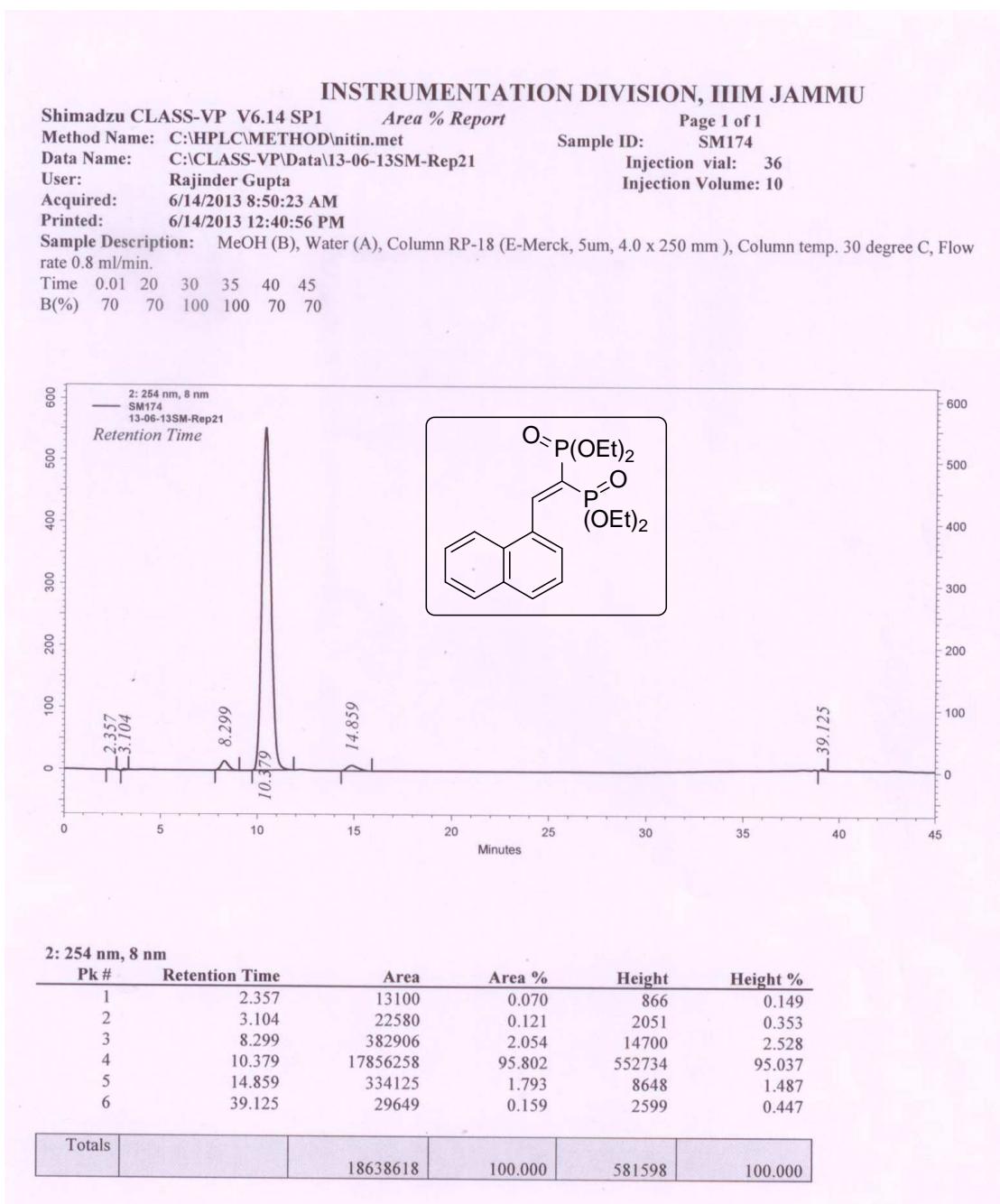


1: 254 nm, 8 nm

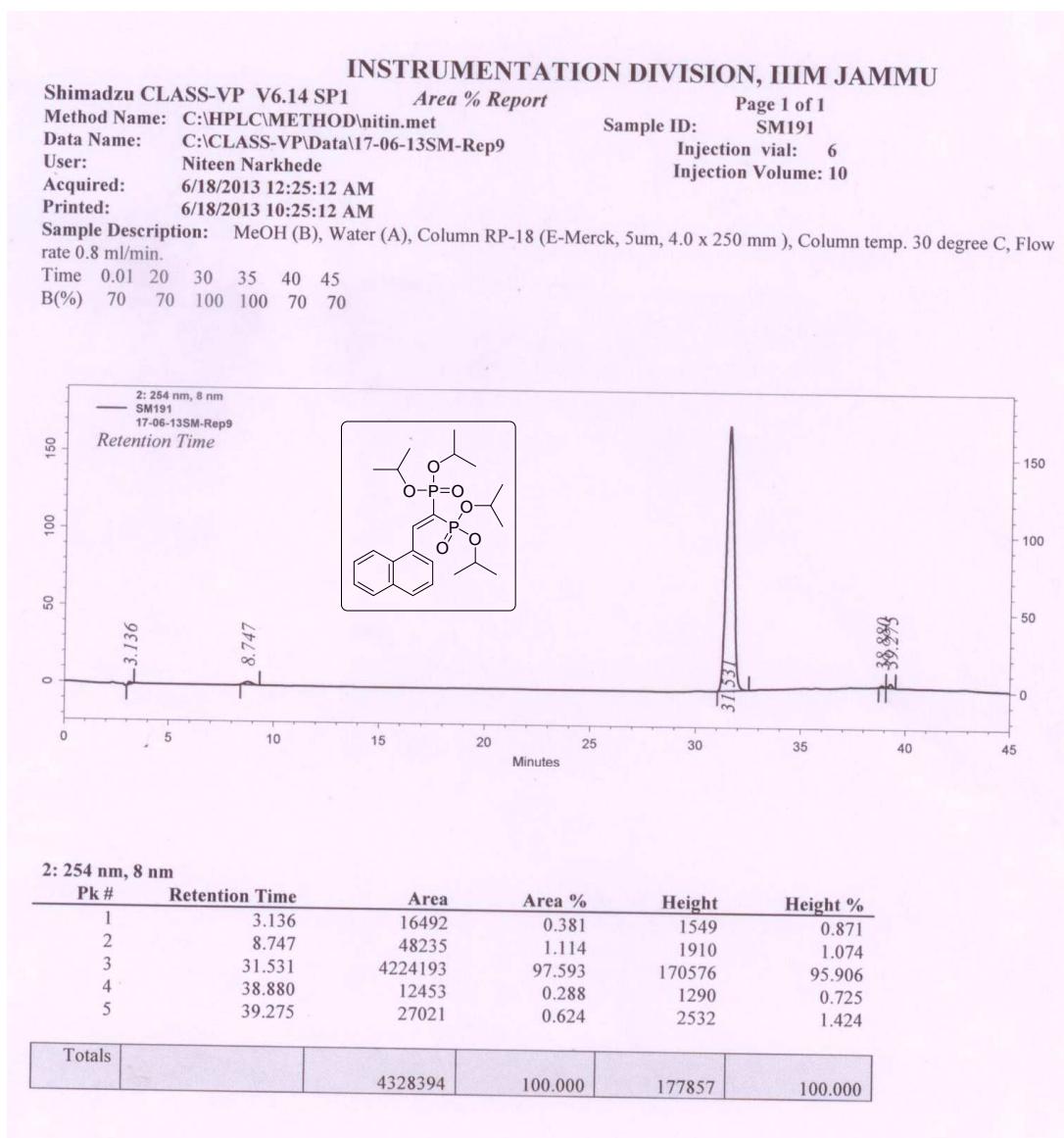
Pk #	Retention Time	Area	Area %	Height	Height %
1	8.395	163078	0.839	6529	1.855
2	13.280	652835	3.359	18333	5.208
3	21.227	18618131	95.802	327165	92.937

Totals		19434044	100.000	352027	100.000
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16. HPLC spectra of tetraethyl 2-(naphthalen-1-yl)ethene-1,1-diylidiphosphonate (6p)



17. HPLC spectra of tetraisopropyl,2-(naphthalen-1-yl)ethene-1,1 diyldiphosphonate (6q)



18. HPLC spectra of tetraisopropyl2-(quinol-5-yl)ethene-1,1-diyldiphosphonate (6r)

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Shimadzu CLASS-VP V6.14 SP1 *Area % Report*

Page 1 of 1

Method Name: C:\HPLC\METHOD\nitin.met

Sample ID: SM-202

Data Name: C:\HPLC\DATA\19-12-14 SB-Rep8

Injection vial: 16

User: Rajinder Gupta

Injection Volume: 10

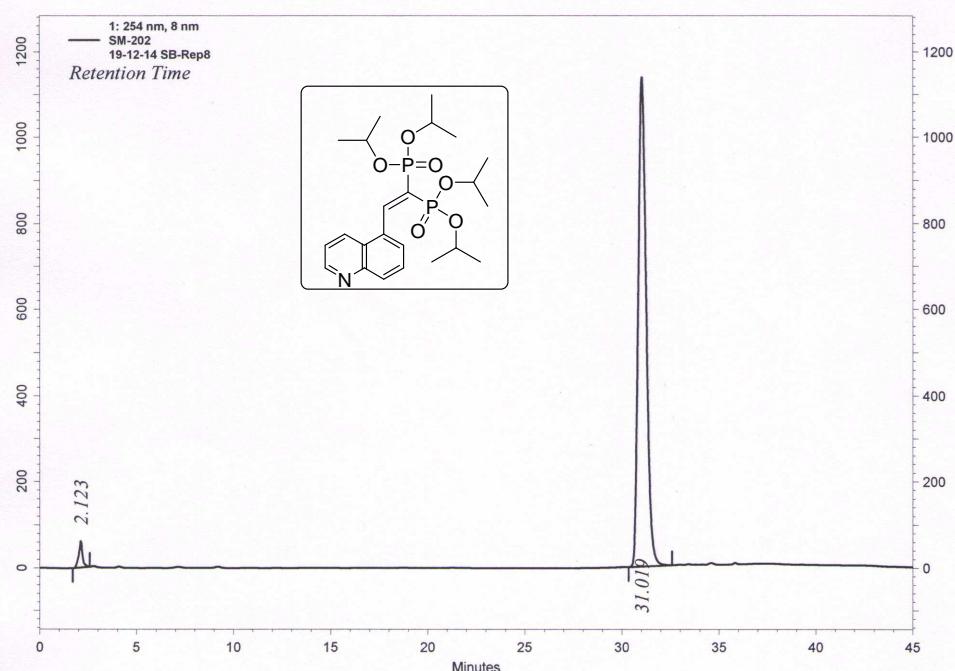
Acquired: 12/19/2014 4:33:07 PM

Printed: 12/19/2014 7:06:31 PM

Sample Description: Methanol (B), Water (A), Column RP-18(E- Merck, 5um, 4.0 x 250 mm), Column temp. 30 degree C, flow rare 0.8 ml/min.

Time 0.01 20 30 35 40 45

B(%) 70 70 100 100 70 70



1: 254 nm, 8 nm

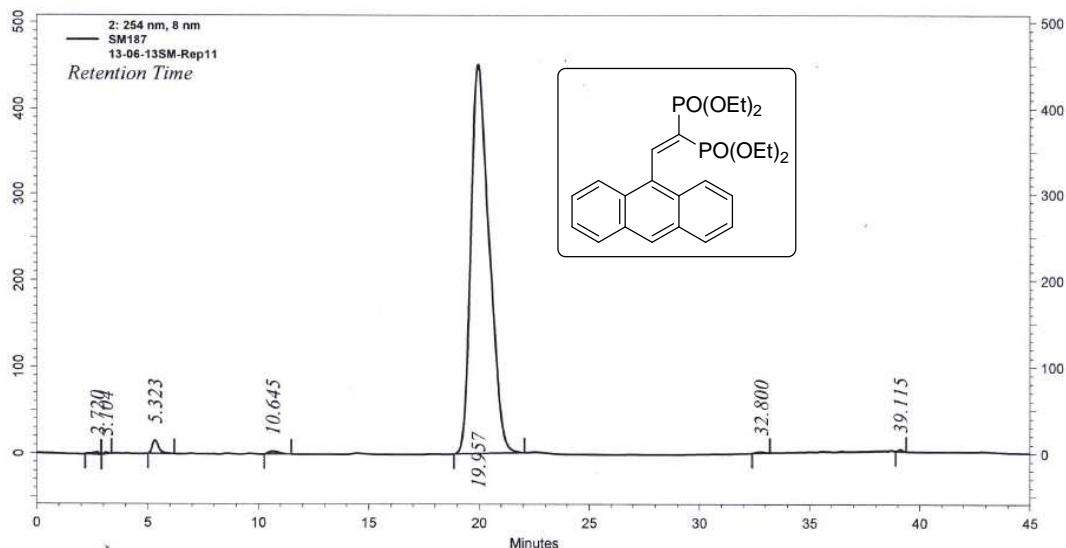
Pk #	Retention Time	Area	Area %	Height	Height %
1	2.123	851554	2.565	61570	5.137
2	31.019	32343942	97.435	1137015	94.863

Totals		33195496	100.000	1198585	100.000
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19. HPLC spectra of tetraethyl2-(anthracene-10-yl)ethene-1,1-diyldiphosphonate (6s)

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Shimadzu CLASS-VP V6.14 SP1 *Area % Report* Page 1 of 1
 Method Name: C:\HPLC\METHOD\nitin.met Sample ID: SM187
 Data Name: C:\CLASS-VP\DATA\13-06-13SM-Rep11 Injection vial: 28
 User: Rajinder Gupta Injection Volume: 10
 Acquired: 6/14/2013 1:06:23 AM
 Printed: 6/14/2013 12:38:13 PM
Sample Description: MeOH (B), Water (A), Column RP-18 (E-Merck, 5um, 4.0 x 250 mm), Column temp. 30 degree C, Flow rate 0.8 ml/min.
 Time 0.01 20 30 35 40 45
 B(%) 70 70 100 100 70 70



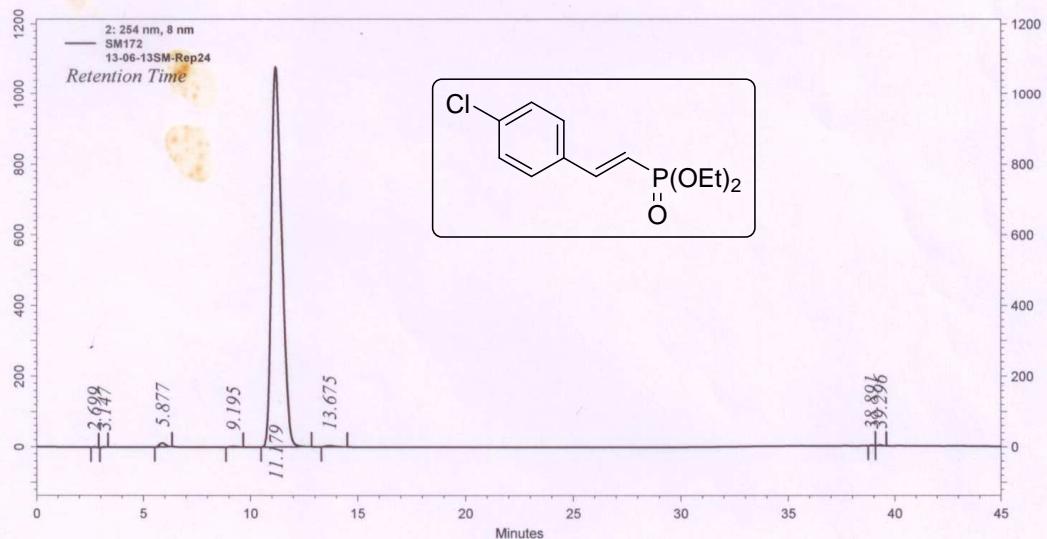
2: 254 nm, 8 nm

Pk #	Retention Time	Area	Area %	Height	Height %
1	2.720	51242	0.194	2334	0.489
2	3.104	19048	0.072	1652	0.346
3	5.323	311208	1.177	15184	3.184
4	10.645	93236	0.353	2942	0.617
5	19.957	25901528	97.994	451345	94.630
6	32.800	28236	0.107	1038	0.218
7	39.115	27227	0.103	2463	0.516
Totals		26431725	100.000	476958	100.000

20. HPLC spectra of (E)-diethyl 4-chlorostyrylphosphonate (7a)

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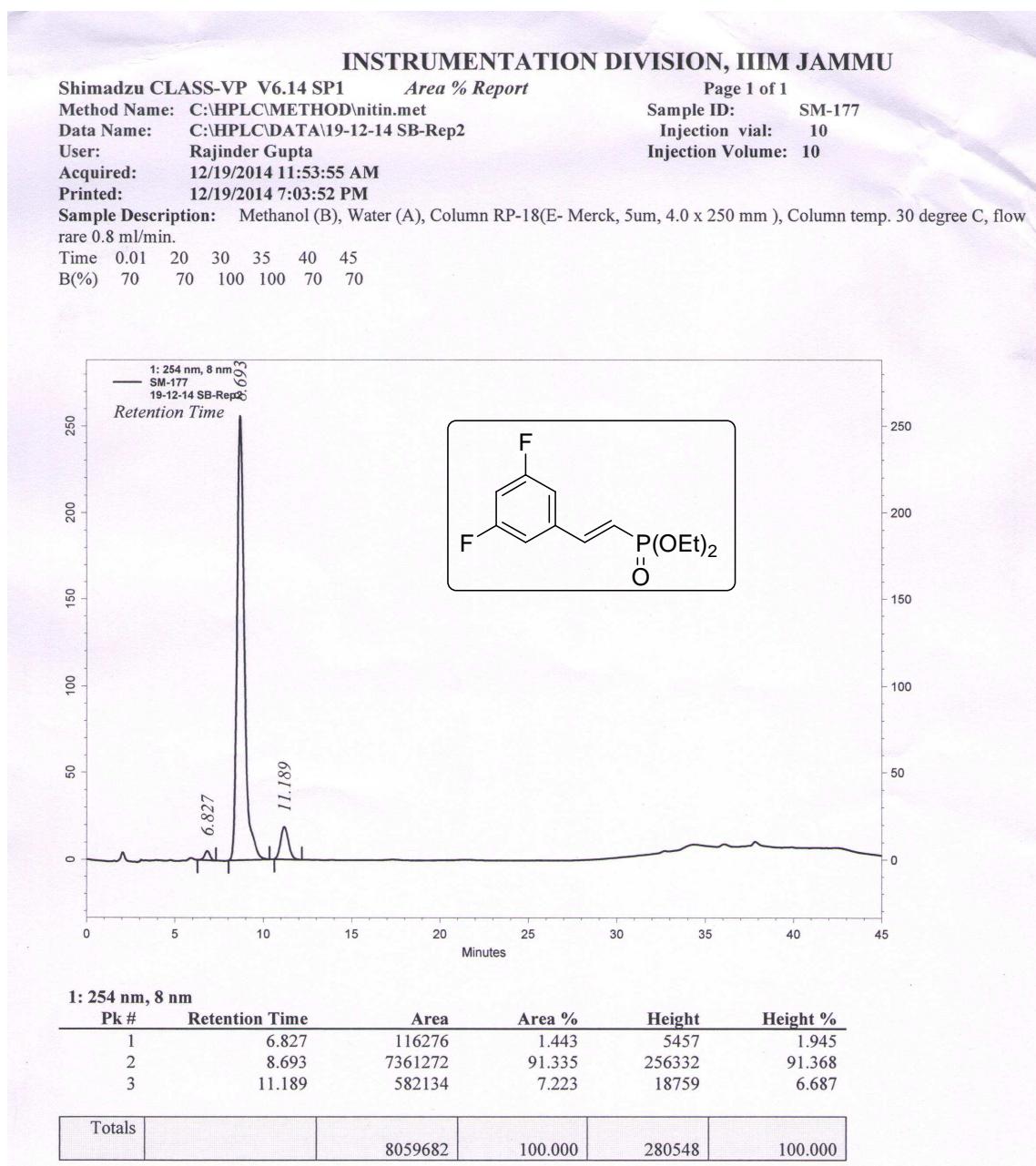
Shimadzu CLASS-VP V6.14 SP1 *Area % Report* Page 1 of 1
 Method Name: C:\HPLC\METHOD\nitin.met Sample ID: SM172
 Data Name: C:\CLASS-VP\DATA\13-06-13SM-Rep24 Injection vial: 39
 User: Rajinder Gupta Injection Volume: 10
 Acquired: 6/14/2013 11:09:33 AM
 Printed: 6/14/2013 12:41:50 PM
 Sample Description: MeOH (B), Water (A), Column RP-18 (E-Merck, 5um, 4.0 x 250 mm), Column temp. 30 degree C, Flow rate 0.8 mL/min.
 Time 0.01 20 30 35 40 45
 B(%) 70 70 100 100 70 70



2: 254 nm, 8 nm

Pk #	Retention Time	Area	Area %	Height	Height %
1	2.699	16112	0.044	1233	0.112
2	3.147	13640	0.038	1194	0.108
3	5.877	212089	0.585	10642	0.967
4	9.195	40883	0.113	1665	0.151
5	11.179	35813808	98.826	1079046	98.042
6	13.675	101552	0.280	3160	0.287
7	38.891	10832	0.030	1087	0.099
8	39.296	30350	0.084	2570	0.234
Totals		36239266	100.000	1100597	100.000

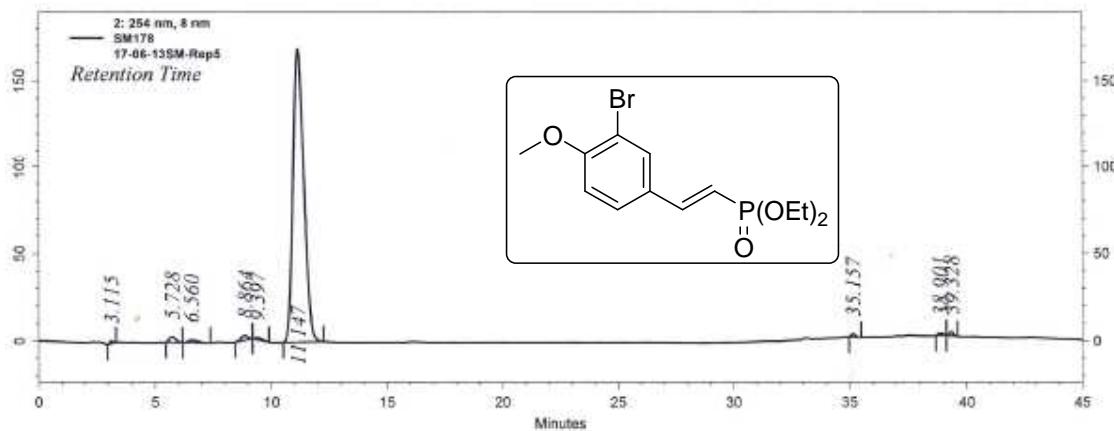
21. HPLC spectra of (E)-diethyl 3, 5-difluoro styrylphosphonate (7b)



22. HPLC spectra of (E)-diethyl 3-bromo 4-methoxystyrylphosphonate (7c)

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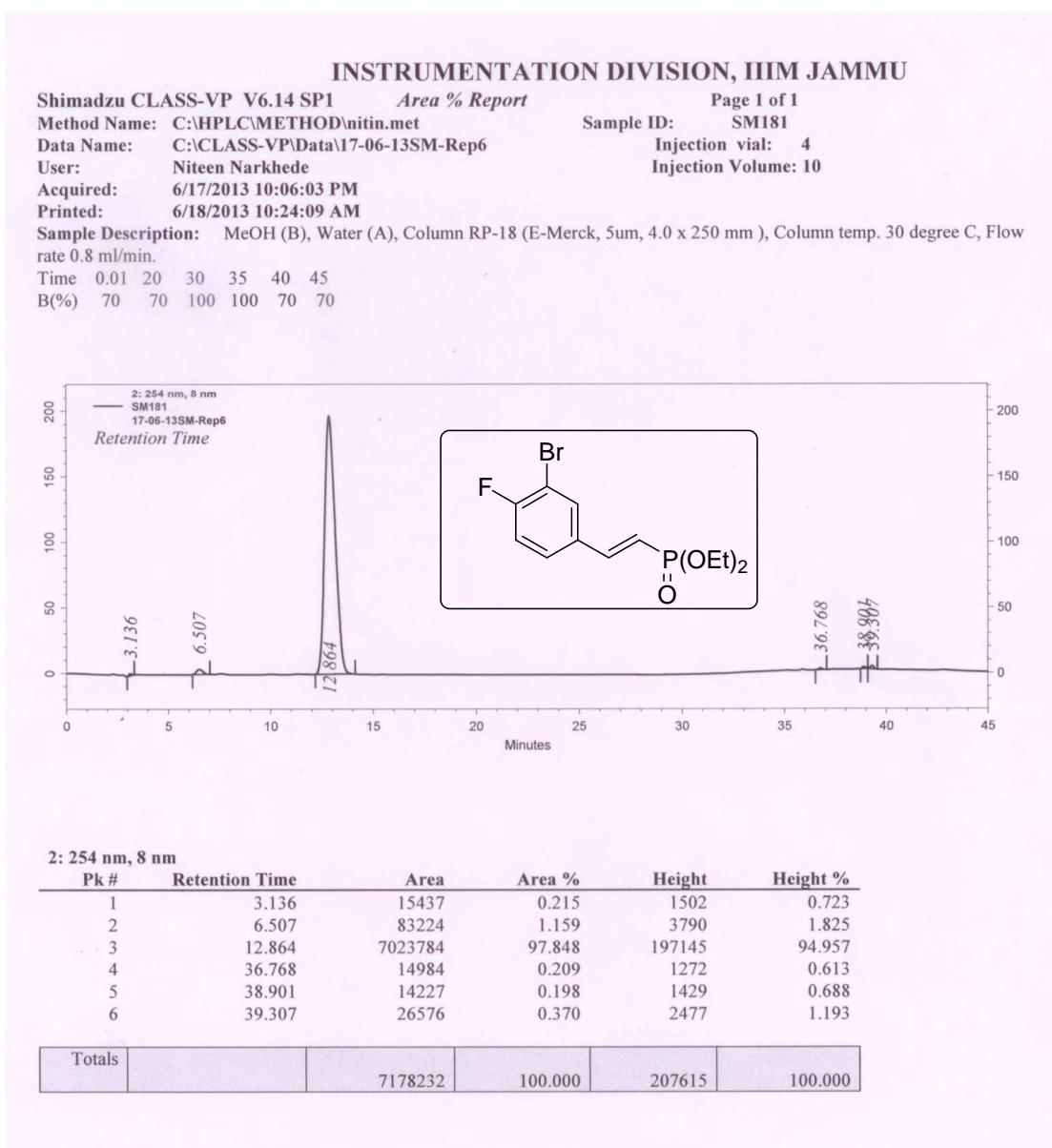
Shimadzu CLASS-VP V6.14 SP1 *Area % Report* Page 1 of 1
 Method Name: C:\HPLC\METHOD\nitin.met Sample ID: SM178
 Data Name: C:\CLASS-VP\Data\17-06-13SM-Rep5 Injection vial: 3
 User: Niteen Narkhede Injection Volume: 10
 Acquired: 6/17/2013 9:19:42 PM
 Printed: 6/18/2013 10:23:55 AM
 Sample Description: MeOH (B), Water (A), Column RP-18 (E-Merck, Sum, 4.0 x 250 mm), Column temp. 30 degree C, Flow rate 0.8 ml/min.
 Time 0.01 20 30 35 40 45
 B(%) 70 70 100 100 70 70



2: 254 nm, 8 nm

Pk #	Retention Time	Area	Area %	Height	Height %
1	3.115	13992	0.243	1464	0.793
2	5.728	60271	1.047	3115	1.686
3	6.560	45848	0.796	1630	0.882
4	8.864	55992	0.972	2633	1.425
5	9.397	28095	0.488	1230	0.666
6	11.147	5491504	95.376	168909	91.442
7	35.157	21333	0.371	1861	1.007
8	38.901	14883	0.258	1449	0.784
9	39.328	25852	0.449	2426	1.313
Totals		5757770	100.000	184717	100.000

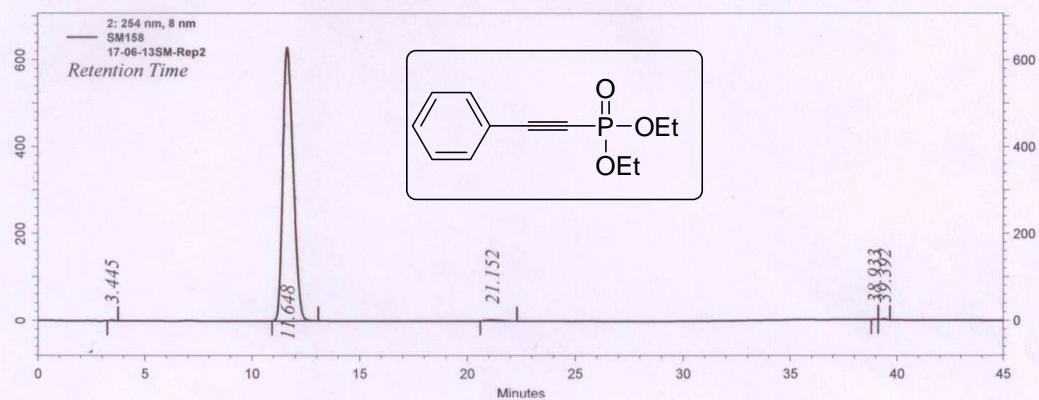
23. HPLC spectra of (E)-diethyl 3-bromo-4-fluorostyrylphosphonate (7d)



24. HPLC spectra of diethyl 2-phenylethylnylphosphonate (8a)

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Shimadzu CLASS-VP V6.14 SP1 Area % Report Page 1 of 1
 Method Name: C:\HPLC\METHOD\nitin.met Sample ID: SM158
 Data Name: C:\CLASS-VP\DATA\17-06-13SM-Rep2 Injection vial: 0
 User: Niteen Narkhede Injection Volume: 10
 Acquired: 6/17/2013 7:00:29 PM
 Printed: 6/18/2013 10:22:05 AM
 Sample Description: MeOH (B), Water (A), Column RP-18 (E-Merck, 5um, 4.0 x 250 mm), Column temp. 30 degree C, Flow rate 0.8 ml/min.
 Time 0.01 20 30 35 40 45
 B(%) 70 70 100 100 70 70



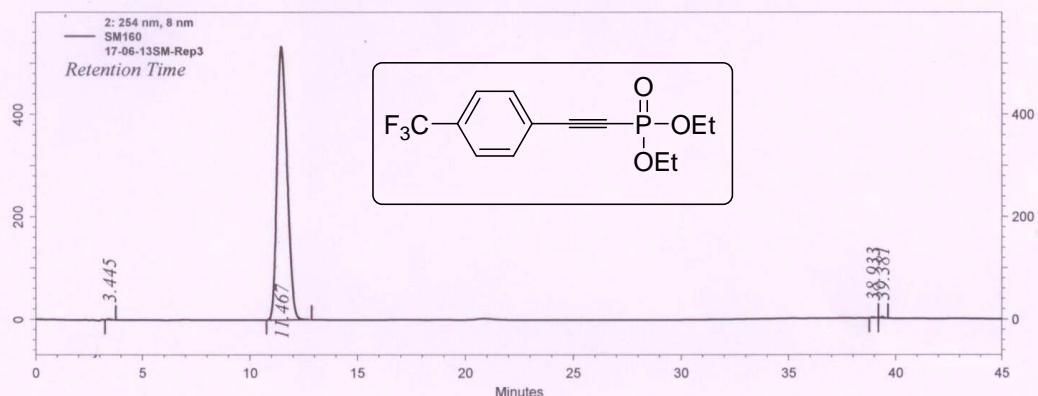
2: 254 nm, 8 nm

Pk #	Retention Time	Area	Area %	Height	Height %
1	3.445	21054	0.099	1693	0.266
2	11.648	21060848	99.138	629510	98.771
3	21.152	123279	0.580	2555	0.401
4	38.933	10284	0.048	1133	0.178
5	39.392	28410	0.134	2454	0.385
Totals		21243875	100.000	637345	100.000

25. HPLC spectra of diethyl-2-(4-(trifluoromethyl)phenyl)lethynylphosphonate (8b)

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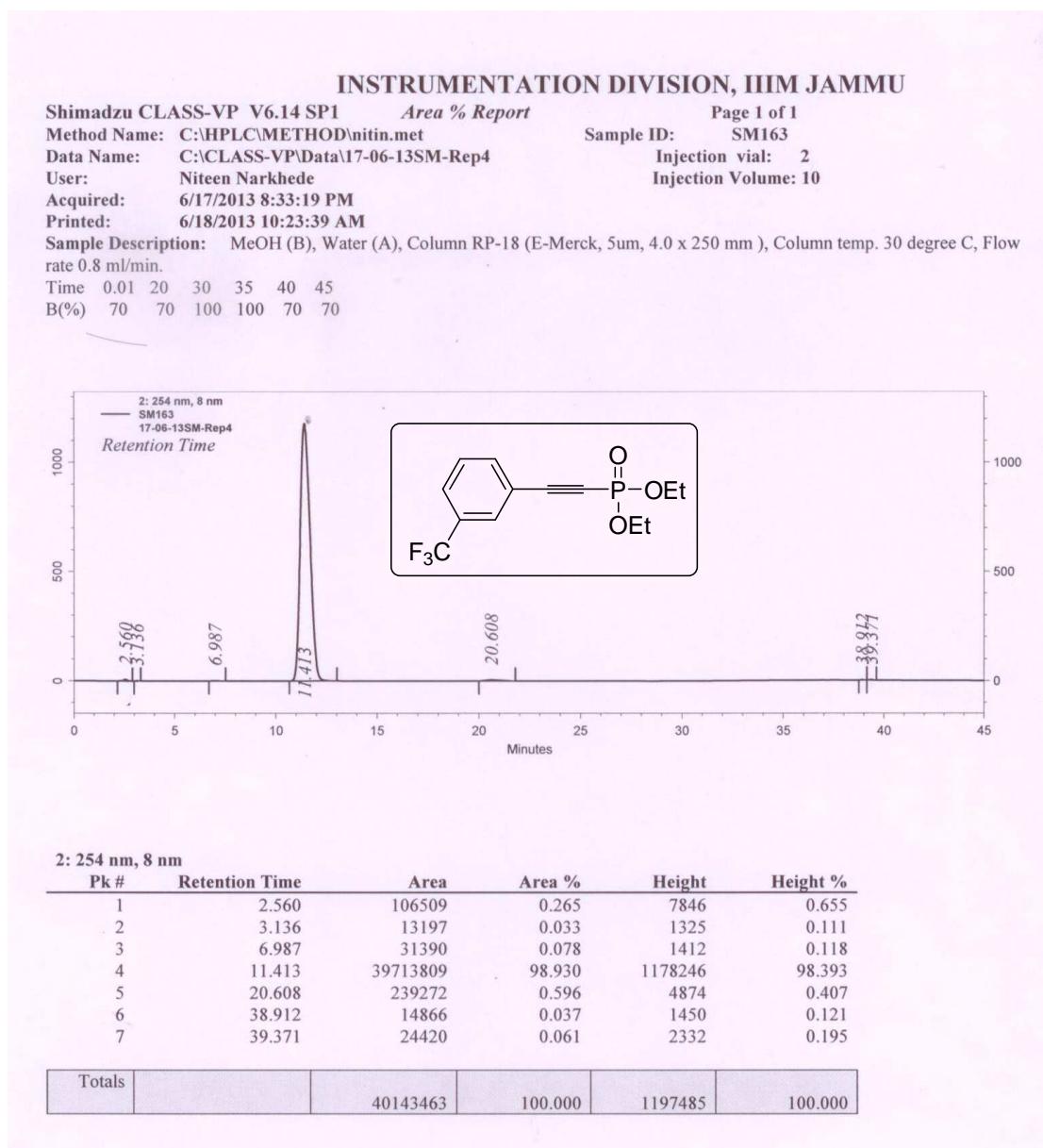
Shimadzu CLASS-VP V6.14 SP1 *Area % Report* Page 1 of 1
 Method Name: C:\HPLC\METHOD\nitin.met Sample ID: SM160
 Data Name: C:\CLASS-VPData\17-06-13SM-Rep3 Injection vial: 1
 User: Niteen Narkhede Injection Volume: 10
 Acquired: 6/17/2013 7:46:53 PM
 Printed: 6/18/2013 10:23:16 AM
 Sample Description: MeOH (B), Water (A), Column RP-18 (E-Merck, 5um, 4.0 x 250 mm), Column temp. 30 degree C, Flow rate 0.8 ml/min.
 Time 0.01 20 30 35 40 45
 B(%) 70 70 100 100 70 70



2: 254 nm, 8 nm

Pk #	Retention Time	Area	Area %	Height	Height %
1	3.445	18202	0.105	1506	0.280
2	11.467	17349485	99.675	533432	99.036
3	38.933	15141	0.087	1423	0.264
4	39.381	23295	0.134	2261	0.420
Totals		17406123	100.000	538622	100.000

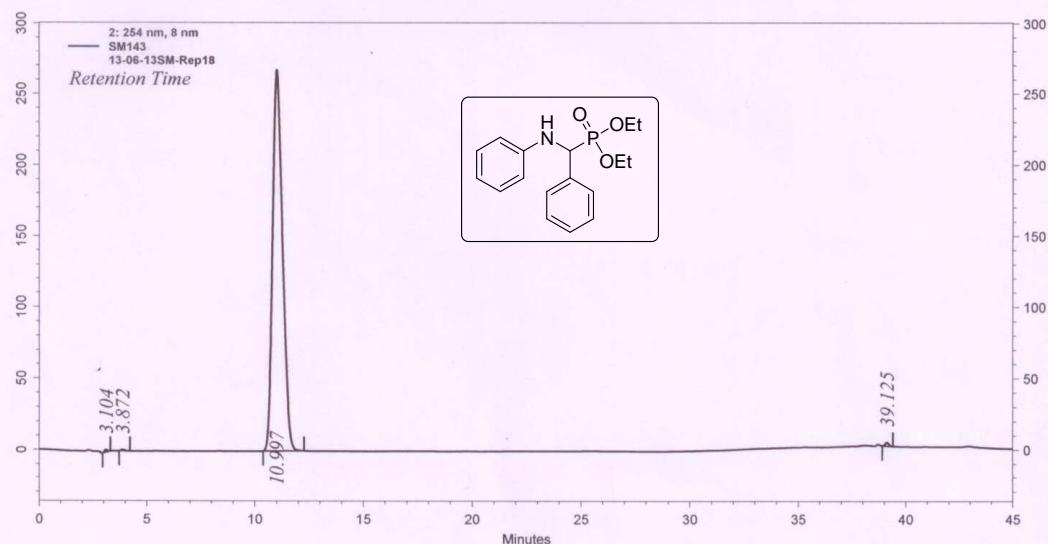
26. HPLC spectra of diethyl 2-(3-(trifluoromethyl)phenyl)ethynylphosphonate (8c)



27. HPLC spectra of diethyl phenyl(phenylamino)methylphosphonate (9a)

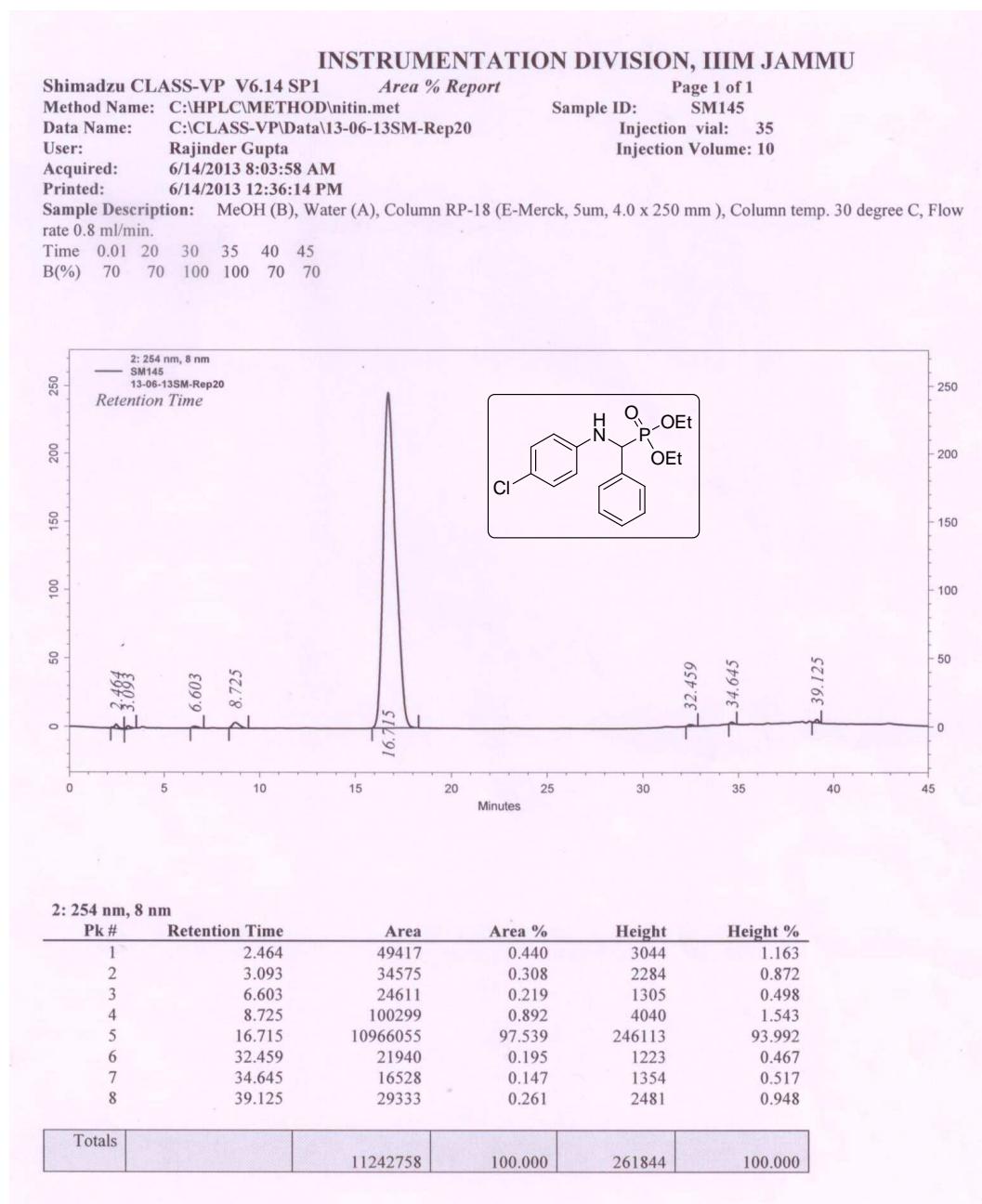
INSTRUMENTATION DIVISION, IIM JAMMU

Shimadzu CLASS-VP V6.14 SP1 *Area % Report* Page 1 of 1
 Method Name: C:\HPLC\METHOD\nitin.met Sample ID: SM143
 Data Name: C:\CLASS-VP\Data\13-06-13SM-Rep18 Injection vial: 34
 User: Rajinder Gupta Injection Volume: 10
 Acquired: 6/14/2013 6:31:08 AM
 Printed: 6/14/2013 12:40:13 PM
 Sample Description: MeOH (B), Water (A), Column RP-18 (E-Merck, 5um, 4.0 x 250 mm), Column temp. 30 degree C, Flow rate 0.8 ml/min.
 Time 0.01 20 30 35 40 45
 B(%) 70 70 100 100 70 70



Pk #	Retention Time	Area	Area %	Height	Height %
1	3.104	19140	0.225	1846	0.676
2	3.872	11556	0.136	902	0.330
3	10.997	8451632	99.304	267867	98.064
4	39.125	28529	0.335	2541	0.930
Totals		8510857	100.000	273156	100.000

28. HPLC spectra of diethyl (4-chlorophenyl)(phenylamino)methylphosphonate (9b)



S3. EXPERIMENTAL PROCEDURES AND SPECTRAL DATA

General. All chemicals were obtained from Sigma-Aldrich Company and used as received. ^1H , ^{13}C and DEPT NMR spectra were recorded on Brucker-Avance DPX FT-NMR 500 and 400 MHz instruments. Chemical data for protons are reported in parts per million (ppm) downfield from tetramethylsilane and are referenced to the residual proton in the NMR solvent (CDCl_3 , 7.26 ppm). Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded at 125 MHz or 100 MHz; chemical data for carbons are reported in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to the carbon resonance of the solvent (CDCl_3 , 77.16 ppm). ESI-MS and HRMS spectra were recorded on Agilent 1100 LC-Q-TOF and HRMS-6540-UHD machines. IR spectra were recorded on Perkin-Elmer IR spectrophotometer. Melting points were recorded on digital melting point apparatus.

General procedure for preparation of alkylidene diphosphonate esters **6a-s and **7a-d**:** A flame-dried 25 ml round bottom flask with magnetic stir bar was charged with TiCl_4 (10 mmol) and 0.5 ml CCl_4 at 0 °C. 5 ml of dry THF was added dropwise to the flask and a bright yellow precipitate formed, and then commercially available different aldehydes **10a-s** (0.1g, 5 mmol) and diphosphonate ester **11a-b** (5 mmol) were added. A solution of 0.5 ml 4-methylmorpholine in 3.0 ml dry THF was then added dropwise to the stirring mixture over 12h. The reaction was allowed to warm to room temperature and stirred over night. The reaction was quenched with water and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4 . Concentration in *vacuo* followed by preparative thin-layer chromatography provided the corresponding alkylidene bisphosphonate **6a-s** and **7a-d** 50-65% yield.

Tetraethyl-2-(3,5-di-t-butyl-4-hydroxyphenyl)ethene-1,1 diyldiphosphonate (6a). Yellow oil; yield 60%; HPLC: $t_{\text{R}} = 29.03$ min (95% purity); ^1H NMR (400 MHz, CDCl_3 , ppm): δ 8.23 (dd, $J_1 = 28$

Hz, $J_2 = 48$ Hz, 1H), 7.76 (s, 2H), 4.21-4.16 (m, 4H), 4.10-4.04 (m, 4H), 1.45 (s, 18H), 1.37 (t, $J = 8$ Hz, 6H), 1.18 (t, $J = 8$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3 , ppm): δ 162.91, 162.88, 157.03, 135.59, 129.87, 125.72, 125.64, 125.51, 125.43, 62.46, 62.41, 62.23, 62.17, 53.42, 34.53, 30.26, 16.39, 16.33, 16.12, 16.04; ^{31}P NMR (CDCl_3 , H_3PO_4 , 161.98 MHz): δ 19.58-19.26 (d, $J = 51.83$ Hz), 13.62-13.30 (d, $J = 51.83$ Hz); IR (CHCl_3): ν_{max} 3436, 2957, 2927, 2871, 1616, 1596, 1558, 1424, 1391, 1242, 1162, 1025 cm^{-1} ; ESI-MS: m/z 505 [M+1] $^+$; HRMS: m/z 505.2468 calcd for $\text{C}_{27}\text{H}_{43}\text{O}_7\text{P}_2+\text{H}^+$ (505.2478).

Tetraisopropyl-2-(3, 5-di-t-Butyl 4-hydroxy phenyl)ethene-1,1-diyldiphosphonate (6b). Yellow oil; yield 55%; HPLC: $t_R = 35.05$ min (93.5% purity); ^1H NMR (400 MHz, CDCl_3 , ppm): δ 8.21 (dd, $J_1 = 28$ Hz, $J_2 = 48$ Hz, 1H), 7.77 (s, 2H), 4.82-4.75 (m, 2H), 4.72-4.64 (m, 2H), 1.45 (s, 18H), 1.40-1.35 (m, 12H), 1.25-1.16 (m, 12H); ^{13}C NMR (100 MHz, CDCl_3 , ppm): δ 161.12, 161.09, 156.69, 135.50, 130.05, 125.91, 125.69, 117.32, 71.17, 71.11, 71.06, 71.00, 34.55, 30.30, 24.13, 24.08, 24.06, 24.01, 23.62, 23.57; ^{31}P NMR (CDCl_3 , H_3PO_4 , 161.98 MHz): δ 17.32-17.00 (d, $J = 51.83$ Hz), 10.80-10.48 (d, $J = 51.83$ Hz); IR (CHCl_3): ν_{max} 3436, 2976, 2874, 1557, 1425, 1385, 1242, 1141, 1106, 1013 cm^{-1} ; ESI-MS: m/z 561 [M+1] $^+$; HRMS: m/z 561.3100 calcd for $\text{C}_{28}\text{H}_{51}\text{O}_7\text{P}_2+\text{H}^+$ (561.3104).

Tetraethyl-2-phenylethene-1,1-diyldiphosphonate (6c). Yellow oil; yield 60%; HPLC: $t_R = 30.72$ min (96.6% purity); ^1H NMR (400 MHz, CDCl_3 , ppm): δ 8.32 (dd, $J_1 = 28$ Hz, $J_2 = 48$ Hz, 1H), 7.76-7.73 (m, 2H), 7.41-7.38 (m, 3H), 4.24-4.19 (m, 4H), 4.06-4.00 (m, 4H), 1.39 (t, $J = 4$ Hz, 6H), 1.16 (t, $J = 4$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3 , ppm): δ 161.49, 134.62, 130.49, 130.27, 128.01, 122.46, 120.77, 119.12, 62.74, 62.69, 62.49, 62.43, 16.31, 16.24, 15.99, 15.92; ^{31}P NMR (CDCl_3 , H_3PO_4 , 161.98 MHz) δ 16.21-15.88 (d, $J = 53.45$ Hz), 11.85-11.52 (d, $J = 53.45$ Hz); IR

(CHCl₃): ν_{max} 3449, 2982, 2929, 2861, 1727, 1586, 1567, 1445, 1392, 1368, 1248, 1097, 1026 cm⁻¹; ESI-MS: *m/z* 399.1 [M+Na]⁺; HRMS: *m/z* 377.1286 cald for C₁₆H₂₆O₆P₂+H⁺ (377.12046).

Tetraisopropyl-2-phenylethene-1,1-diyldiphosphonate (6d). Yellow oil; yield 54%; HPLC: *t_R* = 17.56 min (93% purity); ¹H NMR (400 MHz, CDCl₃, ppm): δ 8.21 (dd, *J*₁ = 28 Hz, *J*₂ = 48 Hz, 1H), 7.83-7.81 (m, 2H), 7.40-7.37 (m, 3H), 4.86-4.78 (m, 2H), 4.72-4.64 (m, 2H), 1.41-1.34 (m, 12H), 1.26-1.17 (m, 12H); ¹³C NMR (100 MHz, CDCl₃, ppm): δ 160.07, 134.93, 134.71, 130.85, 130.32, 129.98, 127.98, 71.61, 71.55, 71.47, 71.40, 24.14, 24.10, 24.03, 24.00, 23.95, 23.55, 23.50; ³¹P NMR (CDCl₃, H₃PO₄, 161.98 MHz): δ 15.28-14.96 (d, *J* = 51.83 Hz), 9.82-9.51 (d, *J* = 50.21 Hz); IR (CHCl₃): ν_{max} 3436, 2979, 2932, 2079, 1634, 1586, 1450, 1385, 1242, 1106 cm⁻¹; ESI-MS: *m/z* 433 [M+1]⁺; HRMS: *m/z* 433.1905 calcd for C₂₀H₃₅O₆P₂+H⁺ (433.1903).

Tetraethyl-2-(2-nitrophenyl)ethene-1,1-diyldiphosphonate (6e). Yellow oil; yield 50%; HPLC: *t_R* = 6.27 min (92.1% purity); ¹H NMR (400 MHz, CDCl₃, ppm): δ 8. (dd, *J*₁ = 28 Hz, *J*₂ = 48 Hz, 1H), 8.24-8.22 (m, 1H), 7.70-7.68 (m, 1H), 7.58-7.55 (m, 2H), 4.28-4.24 (m, 4H), 3.96-3.90 (m, 4H), 1.43-1.40 (m, 6H), 1.14-1.11 (m, 6H); ¹³C NMR (100 MHz, CDCl₃, ppm): δ 159.04, 145.39, 133.59, 130.64, 129.74, 124.39, 62.99, 62.95, 62.48, 62.45, 15.39, 16.33, 16.12,, 16.07; ³¹P NMR (CDCl₃, H₃PO₄, 161.98 MHz): δ 14.92-14.62 (d, *J* = 48.59 Hz), 11.10-10.80 (d, *J* = 48.59 Hz); IR (CHCl₃): ν_{max} 3467, 2983, 2928, 2855, 1734, 1589, 1570, 1525, 1442, 1392, 1345, 1248, 1163, 1023 cm⁻¹; ESI-MS: *m/z* 443.94 [M+Na]⁺; HRMS: *m/z* 444.0954 calcd for C₁₆H₂₅NO₈P₂+Na⁺ (444.0947).

Tetraisopropyl-2-(3-bromophenyl)ethane-1,1-diyldiphosphonate (6f). Yellow oil; yield 58%; HPLC: *t_R* = 30.82 min (97.8% purity); ¹H NMR (400 MHz, CDCl₃, ppm): δ 8.19 (dd, *J*₁ = 28 Hz, *J*₂ = 48 Hz, 1H), 7.97 (s, 1H), 7.66 (d, *J* = 8 Hz, 1H), 7.50 (d, *J* = 8Hz, 1H), 7.27-7.23 (m, 1H), 4.74-4.66 (m, 2H), 4.74-4.66 (m, 2H), 1.41-1.36 (m, 12H), 1.26-1.18 (m, 12H); ¹³C NMR (100 MHz, CDCl₃, ppm): δ 157.62, 137.08, 136.94, 133.05, 132.81, 129.44, 129.00, 121.96, 71.75, 71.69,

71.54, 71.47, 29.68, 24.11, 24.06, 24.05, 24.01, 23.97, 23.92, 23.59, 23.53; ^{31}P NMR (CDCl_3 , H_3PO_4 , 161.98 MHz): δ 14.24-13.93 (d, $J = 50.21$ Hz), 9.12-8.81 (d, $J = 50.21$ Hz); IR (CHCl_3): ν_{max} 3436, 2978, 2930, 1581, 1385, 1242, 1105 cm⁻¹; ESI-MS: m/z 534 [M+Na]⁺; HRMS: m/z 511.1003 calcd for $\text{C}_{20}\text{H}_{34}\text{BrO}_6\text{P}_2+\text{H}^+$ (511.1008).

Tetraisopropyl-2-(4-N,N-dimethylaminophenyl)ethene-1,1-diyldiphosphonate (6g). Yellow oil; yield 52%; HPLC: $t_R = 21.17$ min (94.9% purity); ^1H NMR (400 MHz, CDCl_3 , ppm): δ 8.14 (dd, $J_1 = 28$ Hz, $J_2 = 48$ Hz, 1H), 7.92-7.89 (d, $J = 12$ Hz, 2H), 6.64 (d, $J = 8$ Hz, 2H), 4.81-4.69 (m, 4H), 3.01 (s, 6H), 1.39-1.34 (m, 12H), 1.34-1.24 (m, 12H); ^{13}C NMR (100 MHz, CDCl_3 , ppm): δ 160.68, 152.16, 135.0, 110.73, 71.28, 71.03, 70.99, 70.95, 39.94, 24.09, 24.05, 24.03, 23.98, 23.88, 23.65, 23.61; ^{31}P NMR (CDCl_3 , H_3PO_4 , 161.98 MHz): δ 18.46-18.14 (d, $J = 51.83$ Hz), 12.56-12.24 (d, $J = 51.83$ Hz); IR (CHCl_3): ν_{max} 3467, 2978, 2931, 2874, 1731, 1607, 1519, 1436, 1384, 1373, 1242, 1196, 1141, 1107 cm⁻¹; ESI-MS: m/z 476.1 [M+1]⁺; HRMS: m/z 476.2317 calcd for $\text{C}_{22}\text{H}_{40}\text{NO}_6\text{P}_2+\text{H}^+$ (476.2325).

Tetraethyl-2-(3,5dimethoxyphenyl)ethene-1,1 diyldiphosphonate (6h). Yellow oil; yield 58%; ^1H NMR (400 MHz, CDCl_3 , ppm): δ 8.25 (dd, $J_1 = 32$ Hz, $J_2 = 48$ Hz, 1H), 6.99 (d, $J = 8$ Hz, 2H), 6.52 (s, 1H), 4.25-4.18 (m, 4H), 4.08-4.03 (m, 4H), 3.81 (s, 6H), 1.39 (t, $J = 8$ Hz, 6H), 1.19 (t, $J = 8$ Hz, 6H); ^{31}P NMR (CDCl_3 , H_3PO_4 , 161.98 MHz) δ 19.44 (s); ^{13}C NMR (100 MHz, CDCl_3 , ppm): δ 161.34, 160.24, 136.29, 122.89, 121.20, 119.56, 107.86, 103.45, 62.65, 62.59, 62.46, 62.40, 55.42, 16.28, 16.22, 16.03, 15.96;; IR (CHCl_3): ν_{max} 3436, 2981, 2928, 1586, 1568, 1445, 1391, 1248, 1163, 1025 cm⁻¹; ESI-MS: m/z 437.00 [M+1]⁺; HRMS: m/z 459.1308 calcd for $\text{C}_{18}\text{H}_{30}\text{O}_8\text{P}_2+\text{Na}^+$ (459.1308).

Tetraisopropyl-2-(3,5-dimethoxyphenyl)ethene-1,1 diyldiphosphonat (6i). Yellow oil; yield 55%; HPLC: $t_R = 19.39$ min (99.2% purity); ^1H NMR (400 MHz, CDCl_3 , ppm): δ 8.14 (dd, $J_1 = 32$ Hz, J_2

δ = 48 Hz, 1H), 6.98 (s, 2H), 6.43 (s, 1H), 4.77-4.69 (m, 2H), 4.63-4.58 (m, 2H), 3.74 (s, 6H), 1.33-1.26 (m, 12H), 1.18-1.11 (m, 12H); ^{13}C NMR (100 MHz, CDCl_3 , ppm): δ 160.26, 159.92, 108.50, 108.33, 103.36, 71.55, 71.50, 71.40, 71.35, 55.57, 24.15, 24.10, 24.07, 24.01, 23.97, 23.61, 23.57; ^{31}P NMR (CDCl_3 , H_3PO_4 , 161.98 MHz): δ 15.34-15.03 (d, J = 50.21 Hz), 9.81-9.50 (d, J = 50.21 Hz); IR (CHCl_3): ν_{max} 3436, 2978, 2926, 2852, 1738, 1595, 1573, 1458, 1385, 1307, 1241, 1206, 1156, 1106, 1065 cm^{-1} ; ESI-MS: m/z 493.1[M+1] $^+$; HRMS: m/z 493.2104 calcd for $\text{C}_{22}\text{H}_{39}\text{O}_8\text{P}_2+\text{H}^+$ (493.2114).

Tetraisopropyl-2-(4-fluoro3-methoxyphenyl)ethene-1,1diyldiphosphonat (6j). Yellow oil; yield 59%; HPLC: $t_{\text{R}} = 15.57$ min (96.8% purity); ^1H NMR (400 MHz, CDCl_3 , ppm): δ 8.08 (dd, J_1 = 32 Hz, J_2 = 48 Hz, 1H), 7.82-7.79 (m, 1H), 7.52 (d, J = 8.0 Hz, 1H), 6.90-6.86 (m, 1H), 4.74-4.62 (m, 4H), 1.36-1.28 (m, 12H), 1.20-1.18 (m, 12H); ^{13}C NMR (100 MHz, CDCl_3 , ppm): δ 158.28, 152.70, 150.30, 149.89, 129.36, 119.04, 118.85, 112.23, 71.54, 71.47, 71.46, 71.39, 56.20, 24.12, 24.08, 24.03, 23.99, 23.63, 23.58; ^{31}P NMR (CDCl_3 , H_3PO_4 , 161.98 MHz): δ 15.72-15.42 (d, J = 48.59 Hz), 10.14-9.83 (d, J = 50.21 Hz); IR (CHCl_3): ν_{max} 3436, 2978, 2928, 1668, 1615, 1511, 1443, 1385, 1285, 1138, 1105, 1017 cm^{-1} ; ESI-MS: m/z 481 [M+1] $^+$; HRMS: m/z 481.1908 calcd for $\text{C}_{21}\text{H}_{36}\text{FO}_7\text{P}_2+\text{H}^+$ (481.1914).

Tetraethyl-2(2,3,5-trimethoxyphenyl)ethane-1,1 diyldiphosphonate (6k). Yellow oil; yield 64%; HPLC: $t_{\text{R}} = 5.23$ min (95.6% purity); ^1H NMR (400 MHz, CDCl_3 , ppm): δ 8.54 (dd, J_1 = 28 Hz, J_2 = 48 Hz, 1H), 7.96 (s, 1H), 6.45 (s, 1H), 4.23-4.14 (m, 6H), 4.09-4.02 (m, 2H), 3.94-3.86 (s, 9H), 1.39-1.18 (m, 12H); ^{13}C NMR (100 MHz, CDCl_3 , ppm): δ 155.98, 154.36, 152.93, 151.42, 142.36, 114.45, 95.39, 62.51, 62.47, 62.40, 62.35, 56.43, 56.34, 56.02, 16.36, 16.31, 16.17; ^{31}P NMR (CDCl_3 , H_3PO_4 , 161.98 MHz): δ 19.22-18.89 (d, J = 53.45 Hz), 14.42-14.09 (d, J = 53.45 Hz); IR

(CHCl₃): ν_{max} 3436, 2927, 1612, 1579, 1508, 1466, 1440, 1335, 1282, 1221, 1128, 1025 cm⁻¹; MS: *m/z* 467.20 [M+1]⁺; HRMS: *m/z* 467.1596 calcd for C₁₉H₃₃O₉P₂+H⁺ (467.1594).

Tetraisopropyl-2-(2,4,5-trimethoxyphenyl)ethene-1,1-diyldiphosphonate (6l). Yellow oil; yield 58%; HPLC: *t_R* = 11.60 min (98.3% purity); ¹H NMR (400 MHz, CDCl₃, ppm): δ 8.48 (dd, *J*₁ = 28 Hz, *J*₂ = 48 Hz, 1H), 7.98 (s, 1H), 6.38 (s, 1H), 4.75-4.60 (m, 4H), 3.86 (s, 3H), 3.83 (s, 3H), 3.78 (s, 3H), 1.33-1.29 (m, 12H), 1.15-1.13 (m, 12H); ¹³C NMR (100 MHz, CDCl₃, ppm): δ 154.38, 154.07, 154.03, 152.60, 142.37, 128.70, 115.04, 95.62, 71.19, 71.13, 56.57, 56.43, 55.98, 29.67, 24.16, 24.12, 24.06, 23.94, 23.89, 23.65, 23.60; ³¹P NMR (CDCl₃, H₃PO₄, 161.98 MHz): δ 17.11-16.77 (d, *J* = 55.07 Hz), 11.81-11.48 (d, *J* = 53.45 Hz); IR (CHCl₃): ν_{max} 3435, 2979, 2931, 1612, 1579, 1508, 1466, 1374, 1243, 1221, 1141 cm⁻¹; ESI-MS: *m/z* 523.1 [M+1]⁺; HRMS: *m/z* 523.2222 calcd for C₂₃H₄₁O₉P₂+H⁺ (523.2220).

Tetraethyl-2-(4-nitrofuran-2-yl)ethene-1,1-diyldiphosphonate (6m). Yellow oil; yield: 59%; ¹H NMR (400 MHz, CDCl₃, ppm): δ 7.98 (dd, *J*₁ = 28 Hz, *J*₂ = 48 Hz, 1H), 7.81 (d, *J* = 4Hz, 1H), 7.38 (d, *J* = 4 Hz, 1H), 4.25-4.18 (m, 8H), 1.41-1.33 (m, 12H); ¹³C NMR (100 MHz, CDCl₃, ppm): δ 152.41, 150.75, 150.46, 142.54, 120.55, 112.73, 63.14, 63.08, 16.31, 16.24, 16.21, 16.15; ³¹P NMR (CDCl₃, H₃PO₄, 161.98 MHz): δ 14.96-14.67 (d, *J* = 46.97 Hz), 11.11-10.81 (d, *J* = 48.59 Hz); IR (CHCl₃): ν_{max} 3436, 2923, 1619, 1418, 1020, cm-1; ESI-MS: *m/z* 412 [M+1]⁺; HRMS: *m/z* 412.0921 calcd for C₁₄H₂₄NO₉P₂+H⁺ (412.0920).

Tetraisopropyl-2-(4-nitrofuran-2-yl)ethene-1,1-diyldiphosphonate (6n). Yellow oil; yield: 57%; HPLC: *t_R* = 12.24 min (98.3% purity); ¹H NMR (400 MHz, CDCl₃, ppm): δ 7.98 (dd, *J*₁ = 28 Hz, *J*₂ = 48 Hz, 1H), 7.85 (d, *J* = 4Hz, 1H), 7.35-7.34 (m, 1H), 4.83-4.76 (m, 4H), 1.40-1.24 (m, 24H); ¹³C NMR (100 MHz, CDCl₃, ppm): δ 149.85, 148.62, 139.02, 124.43, 117.87, 110.35, 69.74, 69.71, 69.69, 69.67, 21.65, 21.61, 21.58, 21.55, 21.51, 21.29, 21.25; ³¹P NMR (CDCl₃, H₃PO₄, 161.98

MHz): δ 12.70-12.45 (d, J = 40.49 Hz), 7.62-7.37 (d, J = 40.49 Hz); IR (CHCl₃): ν_{max} 3436, 2980, 2928, 1591, 1530, 1454, 1386, 1351, 1247, 1142, 1104 cm⁻¹; ESI-MS: m/z 468 [M+1]⁺; HRMS: m/z 468.1539 calcd for C₁₈H₃₂NO₉P₂+H⁺ (468.1546).

Tetraisopropyl-2-(benzo[d][1,3]dioxol-5-yl)ethene-1,1-diyldiphosphonate (6o). Yellow oil; yield: 55%; ¹H NMR (400 MHz CDCl₃, ppm): δ 8.16 (dd, J_1 = 32 Hz, J_2 = 48 Hz, 1H), 7.65 (s, 1H), 7.34-7.32 (d, J = 8 Hz, 1H), 6.83-6.80 (d, J = 12 Hz, 1H), 6.01 (s, 2H), 4.82-4.69 (m, 4H), 1.40-1.34 (m, 12H), 1.27-1.21 (m, 12H); ¹³C NMR (100 MHz, CDCl₃, ppm): δ 159.79, 149.88, 147.56, 128.34, 121.31, 120.0, 111.09, 107.86, 101.59, 71.49, 71.44, 71.41, 71.36, 24.08, 24.05, 23.98, 23.94, 23.59, 23.55; ³¹P NMR (CDCl₃, H₃PO₄, 161.98 MHz): δ 16.20-15.89 (d, J = 50.21 Hz), 10.51-10.20 (d, J = 50.21 Hz); IR (CHCl₃): ν_{max} 3447, 2979, 2932, 1725, 1620, 1564, 1505, 1490, 1449, 1244, 1106 cm⁻¹; ESI-MS: m/z 477 [M+1]⁺; HRMS: m/z 477.1796 calcd for C₂₁H₃₅O₈P₂+H⁺ (477.1801).

Tetraethyl-2-(naphthalen-1-yl)ethene-1,1-diyldiphosphonate (6p). Yellow oil; yield: 65%; HPLC: t_R = 10.37 min (95.8% purity); ¹H NMR (400 MHz, CDCl₃, ppm): δ 8.86 (dd, J_1 = 28 Hz, J_2 = 48 Hz, 1H), 7.89-7.81 (m, 4H), 7.56 -7.48 (m, 3H), 4.33-4.27 (m, 4H), 3.93-3.79 (m, 4H), 1.44 (t, J = 4 Hz, 6H), 0.95 (t, J = 4 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃, ppm): δ 160.14, 160.12, 132.95, 132.02, 130.54, 130.07, 128.61, 127.34, 126.77, 126.23, 125.05, 124.78, 124.72, 124.15, 62.88, 62.84, 62.42, 62.36, 16.42, 16.36, 15.86, 15.80; ³¹P NMR (CDCl₃, H₃PO₄, 161.98 MHz): δ 16.16-15.83 (d, J = 53.45 Hz), 11.81-11.48 (d, J = 53.45 Hz); IR (CHCl₃): ν_{max} 3437, 2929, 2983, 2095, 1634, 1392, 1238, 1162, 1022 cm⁻¹; ESI-MS: m/z 427.0 [M+Na]⁺; HRMS: m/z 427.1430 calcd for C₂₀H₂₉O₆P₂+H⁺ (427.1433).

Tetraisopropyl-2-(naphthalen-1-yl)ethene-1,1-diyldiphosphonate (6q). Yellow oil; yield: 60%; HPLC: t_R = 31.53 min (97.6% purity); ¹H NMR (400 MHz, CDCl₃, ppm): δ 8.76 (dd, J_1 = 28 Hz, J_2 = 48 Hz, 1H), 7.86-7.78 (m, 4H), 7.46-7.20 (m, 3H), 4.85-4.78 (m, 2H), 4.51-4.44 (m, 2H), 1.38-

1.36 (m, 12H), 0.98 (d, $J = 8$ Hz, 6H), 0.88 (d, $J = 4$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3 , ppm): δ 158.21, 132.53, 130.38, 129.72, 129.28, 128.12, 127.12, 126.14, 125.61, 124.59, 123.86, 71.25, 71.20, 70.76, 70.71, 23.77, 23.74, 23.58, 23.53, 23.50, 22.95, 22.91; ^{31}P NMR (CDCl_3 , H_3PO_4 , 161.98 MHz): δ 14.03-13.69 (d, $J = 55.07$ Hz), 9.66-9.33 (d, $J = 53.45$ Hz); IR (CHCl_3): ν_{max} 3436, 2979, 2930, 2079, 1633, 1452, 1385, 1240, 1177, 1106 cm^{-1} ; ESI-MS: m/z 483 [M+H] $^+$; HRMS: m/z 483.2057 calcd for $\text{C}_{24}\text{H}_{37}\text{O}_6\text{P}_2+\text{H}^+$ (483.2059).

Tetraisopropyl-2-(quinol-5-yl)ethene-1,1-diyldiphosphonate (6r). Yellow oil; yield: 62%; ^1H NMR (400 MHz, CDCl_3 , ppm): δ 8.77 (dd, $J_1 = 28$ Hz, $J_2 = 48$ Hz, 1H), 7.81-7.73 (m, 4H), 7.46-7.19 (m, 2H), 4.85-4.80 (m, 2H), 4.49-4.44 (m, 2H), 1.38-1.25 (m, 12H), 0.99-0.88 (m, 12H); ^{13}C NMR (100 MHz, CDCl_3 , ppm): δ 158.69, 133.15, 133.06, 132.98, 130.85, 130.83, 129.69, 128.54, 127.55, 126.55, 126.03, 124.98, 124.31, 71.67, 71.21, 71.15, 71.09, 24.68, 24.17, 23.98, 23.36; ^{31}P NMR (CDCl_3 , H_3PO_4 , 161.98 MHz): δ 14.02-13.68 (d, $J = 55.07$ Hz), 9.64-9.31 (d, $J = 53.45$ Hz); IR (CHCl_3): ν_{max} 3435, 2978, 2928, 1586, 1452, 1385, 1374, 1241, 1141, 1105 cm^{-1} ; ESI-MS: m/z 483.1 [M] $^+$.

Tetraethyl-2-(anthracene-10-yl)ethene-1,1-diyldiphosphonate (6s). Yellow oil; yield: 58%; HPLC: $t_R = 19.95$ min (98% purity); ^1H NMR (400 MHz, CDCl_3 , ppm): δ 8.89 (dd, $J_1 = 28$ Hz, $J_2 = 48$ Hz, 1H), 8.37 (s, 1H), 7.94-7.85 (m, 4H), 7.43-7.19 (m, 4H), 4.38-4.31 (m, 4H), 3.56-3.50 (m, 2H), 3.36-3.32 (m, 2H), 1.44 (t, $J = 4$ Hz, 6H), 0.62 (t, $J = 4$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3 , ppm): δ 159.67, 130.87, 130.14, 129.52, 128.49, 127.72, 127.32, 125.76, 125.73, 125.39, 63.10, 63.06, 62.11, 62.06, 16.52, 16.47, 16.32, 16.30, 15.56, 15.51; ^{31}P NMR (CDCl_3 , H_3PO_4 , 161.98 MHz): δ 14.95-14.61 (d, $J = 55.07$ Hz), 10.34-9.99 (d, $J = 56.69$ Hz); IR (CHCl_3): ν_{max} 3435, 2919, 1601, 1404, 1360, 1280, 1186, 1148, 1019 cm^{-1} ; ESI-MS: m/z 477 [M+1] $^+$; HRMS: m/z 477.1590 calcd for $\text{C}_{24}\text{H}_{31}\text{O}_6\text{P}_2+\text{H}^+$ (477.1590).

(E)-Diethyl 4-chlorostyrylphosphonate (7a). Yellow oil; yield: 55%; HPLC: t_R = 11.17 min (98.8% purity); ^1H NMR (400 MHz, CDCl_3 , ppm): δ 7.50-7.35 (m, 5H), 6.28 (t, J = 16 Hz, 1H), 4.18-4.10 (m, 4H), 1.36 (t, J = 4 Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3 , ppm): δ 147.31, 147.25, 136.15, 133.42, 129.13, 128.90, 115.46, 113.93, 61.98, 61.94, 16.43, 16.38; ^{31}P NMR (CDCl_3 , H_3PO_4 , 161.98 MHz) δ 18.98 (s); IR (CHCl_3): ν_{\max} 3449, 2981, 2928, 1593, 1618, 1443, 1246, 1163, 1052, 1025, 1094, cm^{-1} ; ESI-MS: m/z 296.94 [M+Na] $^+$; HRMS: m/z 275.0601 calcd for $\text{C}_{12}\text{H}_{17}\text{ClO}_3\text{P}+\text{H}^+$ (275.0598).

(E)-Diethyl 3, 5-difluoro styrylphosphonate (7b). Yellow oil; yield: 58%; HPLC: t_R = 8.69 min (91.3% purity); ^1H NMR (400 MHz, CDCl_3 , ppm): δ 7.44-7.34 (m, 1H), 7.01 (d, J = 8 Hz, 2H), 6.85-6.81 (m, 1H), 6.28 (t, J = 16 Hz, 1H), 4.17-4.12 (m, 4H), 1.36 (t, J = 4 Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3 , ppm): δ 163.33, (d, $^1J_{CF}$ = 249.5 Hz), 163.20 (d, $^1J_{CF}$ = 249.51 Hz), 145.95, 138.22 (d, $^2J_{CF}$ = 24.14 Hz), 118.54, 116.64, 110.47 (m), 105.35 (m), 70.10 (m), 62.10 (m), 45.00, 29.61 (m), 27.04 (m), 16.45, 16.38; ^{31}P NMR (CDCl_3 , H_3PO_4 , 161.98 MHz): δ 17.73 (s); IR (CHCl_3): ν_{\max} 3436, 2980, 2926, 2851, 2461, 1615, 1596, 1497, 1458, 1441, 1394, 1265, 1245, 1192, 1162, 1097, 1050, 1021 cm^{-1} ; MS: m/z 277.10 [M+1] $^+$; HRMS: m/z 299.0618 calcd for $\text{C}_{12}\text{H}_{15}\text{F}_2\text{O}_3\text{P}+\text{Na}^+$ (299.0618).

(E)-Diethyl 3-bromo 4-methoxystyrylphosphonate (7c). Yellow oil; yield 60%; HPLC: t_R = 11.1 min (95.4% purity); ^1H NMR (400 MHz, CDCl_3 , ppm): δ 7.73 (s, 1H), 7.43-7.38 (m, 2H), 6.90 (d, J = 8 Hz, 1H), 6.11 (t, J = 16 Hz, 1H), 4.18-4.09 (m, 4H), 3.93 (s, 3H), 1.35 (t, J = 4 Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3 , ppm): δ 159.31, 159.29, 157.82, 136.13, 132.28, 129.77, 111.24, 110.99, 62.69, 62.63, 62.56, 62.49, 56.36, 16.36, 16.29, 16.18, 16.12; ^{31}P NMR (CDCl_3 , H_3PO_4 , 161.98 MHz) δ 18.49 (s); IR (CHCl_3): ν_{\max} 3457, 2981, 2929, 2849, 1730, 1615, 1596, 1555, 1497, 1461,

1442, 1394, 1297, 1265, 1247, 1163, 1097, 1051, 1024 cm⁻¹; ESI-MS: *m/z* 351 [M+2]⁺; HRMS: *m/z* 349.0202 calcd for C₁₃H₁₉BrO₄P₂+H⁺ (349.0198).

(E)-Diethyl 3-bromo-4-fluorostyrylphosphonate (7d). Yellow oil; yield: 65%; HPLC: *t_R* = 12.86 min (97.8% purity); ¹H NMR (400 MHz, CDCl₃, ppm): δ 7.72-7.70 (m, 1H), 7.44-7.35 (m, 2H), 7.14 (t, *J* = 8 Hz, 1H), 6.20 (t, *J* = 16 Hz, 1H), 4.18-4.10 (m, 4H), 1.36 (t, *J* = 8 Hz, 6H); ³¹P NMR (CDCl₃, H₃PO₄, 161.98 MHz) δ 18.45 (s); IR (CHCl₃): *v_{max}* 3436, 2985, 2930, 2079, 1633, 1494, 1443, 1393, 1249, 1047, 1026 cm⁻¹; ESI-MS: *m/z* 336.88 [M+1]⁺; HRMS: *m/z* 336.9999 calcd for C₁₂H₁₆BrFO₃P₂+H⁺ (336.9999).

General procedure for preparation of alkynylphosphonates 8a-c. To a solution of ethynylbenzene **12a-c** (0.1 ml, 18.2 mmol) in dry THF (5ml) was added *n*-BuLi (0.2ml, 20 mmol) under nitrogen at -78 °C. The mixture was stirred at -78 °C for 2 hours, then diethylchlorophosphate **13** (0.3 ml, 20 mmol) in dry THF (5 ml) was added at -78 °C. The solution was stirred for 1 hour at -78 °C, warmed to room temperature and stirred for 3 hours. The mixture was evaporated, and the resulting residue was purified by column chromatography on silica gel to produced **8a-c** 80-85% yield.

Diethyl 2-phenylethylnylphosphonate (8a). Yellow oil; yield 75%; HPLC: *t_R* = 11.64 min (98.8% purity); ¹H NMR (400 MHz, CH₃OD, ppm): δ 7.57 (d, *J* = 8Hz, 2H), 7.45 (d, *J* = 8Hz, 1H), 7.40-7.32 (m, 2H), 4.27-4.20 (m, 4H), 1.41 (t, *J* = 8Hz, 6H); ¹³C NMR (100 MHz, CDCl₃, ppm): δ 132.54, 130.70, 128.54, 119.45, 119.40, 99.34, 98.81, 79.76, 63.25, 63.19, 16.10, 16.03; ³¹P NMR (CDCl₃, H₃PO₄, 161.98 MHz): δ -6.16 (s); IR (CHCl₃): *v_{max}* 3480, 3061, 2909, 2985, 2187, 2081, 1638, 1490, 1227, 1263, 1024, cm⁻¹; ESI-MS: *m/z* 239 [M+1]⁺. HRMS: *m/z* 239.0826 calcd for C₁₂H₁₆O₃P+H⁺ (239.0831).

Diethyl-2-(4-(trifluoromethyl)phenyl)ethynylphosphonate (8b). Yellow oil; yield: 80%; HPLC: t_R = 11.46 min (99% purity); ^1H NMR (400 MHz, CH_3OD , ppm): δ 7.71- 7.64 (m, 4H), 4.29-4.22 (m, 4H), 1.42 (t, J = 4 Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3 , ppm): δ 131.55, 124.20, 124.18, 124.15, 124.12, 95.55, 95.14, 80.45, 78.09, 62.14, 62.09, 14.76, 14.70; ^{31}P NMR (CDCl_3 , H_3PO_4 , 161.98 MHz): δ -6.94 (s); IR (CHCl_3): ν_{max} 3486, 3101, 2936, 2986, 2641, 2192, 2085, 1614, 1479, 1445, 1405, 1325, 1266, 1170, 1132, 1066 cm^{-1} ; ESI-MS: m/z 307 [M+1] $^+$; HRMS: m/z 307.0701 calcd for $\text{C}_{13}\text{H}_{15}\text{F}_3\text{O}_3\text{P}+\text{H}^+$ (307.0705).

Diethyl-2-(3-(trifluoromethyl)phenyl)ethynylphosphonate (8c). Yellow oil; yield: 85%; HPLC: t_R = 11.41 min (98.4% purity); ^1H NMR (400 MHz, CH_3OD , ppm): δ 7.83 (s, 1H), 7.76-7.70 (m, 2H), 7.54 (t, J = 8Hz, 1H), 4.29-4.21 (m, 4H), 1.44-1.41 (m, 6H); ^{13}C NMR (100 MHz, CDCl_3 , ppm): δ 135.67, 131.42, 129.30, 127.24, 123.27 (d, $^1J_{\text{CF}} = 271.25$ Hz), 120.58, 96.66 (d, $^2J_{\text{CF}} = 52.50$ Hz), 81.15, 67.39, 63.61 (m), 32.26, 18.63, 16.12, 13.55; ^{31}P NMR (CDCl_3 , H_3PO_4 , 161.98 MHz): δ -6.93 (s); IR (CHCl_3): ν_{max} 3436, 2931, 2979, 1579, 1612, 1508, 1385, 1335, 1281, 1245, 1106 cm^{-1} ; MS: m/z 307 [M+1] $^+$; HRMS: m/z 307.0703 calcd for $\text{C}_{13}\text{H}_{15}\text{F}_3\text{O}_3\text{P}+\text{H}^+$ (307.0705).

General procedure for preparation of α -amino alkynylphosphonates 9a-b: To a solution of benzaldehyde **10a-b** (0.1ml, 2 mmol) in aceto nitrile (5 ml) was added amines **14a-b** (0.1 ml, 2 mmol) and diethyl phosphite **15** (0.1 ml, 2 mmol) then stirring the mixture for 2 h at room temperature. After complete reaction extracted with EtOAc and water. The organic layer was dried over Na_2SO_4 . Concentration in *vacuo* followed by column chromatography on silica gel provided the corresponding α -amino alkynylphosphonates **9a-b** with 80-85% yield.

Diethyl phenyl(phenylamino)methylphosphonate (9a). White powder; yield 80%; m.p. 86-88 °C; HPLC: t_R = 10.99 min (98% purity); ^1H NMR (400 MHz, CH_3OD , ppm): δ 7.40-7.39 (m, 2H), 7.24-7.15 (m, 3H), 6.96-6.93 (m, 2H), 6.60 (d, J = 6.4 Hz, 2H), 6.50-6.51 (t, J = 6.0 Hz, 1H), 4.85 (d, $^1J_{\text{PH}}$

= 19.6 Hz, 1H), 4.04-3.96 (m, 2H), 3.89-3.35 (m, 1H), 3.75-3.70 (m, 1H), 1.15 (t, J = 5.6 Hz, 3H), 1.04 (t, J = 5.6 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3 , ppm): δ 148.20, 148.06, 137.48, 129.99, 129.43, 128.93, 119.19, 115.07, 64.79, 64.72, 64.58, 64.51, 56.64 (d, $^1J_{\text{CP}} = 152.1$ Hz), 16.75, 16.69, 16.57, 16.51; ^{31}P NMR (CDCl_3 , H_3PO_4 , 161.98 MHz): δ 22.70 (s); IR (CHCl_3): ν_{max} 3435, 3294, 3029, 2981, 1605, 1497, 1454, 1386, 1234, 1057, 1024 cm^{-1} ; ESI-MS: m/z 342.18 [M+Na] $^+$; HRMS: m/z 320.1408 calcd for $\text{C}_{17}\text{H}_{23}\text{NO}_3\text{P}+\text{H}^+$ (320.1410).

Diethyl-(4-chlorophenyl)(phenylamino)methylphosphonate (9b). White solid power; yield: 90%; m.p. 60-62 °C; HPLC: $t_{\text{R}} = 16.71$ min (93.99% purity); ^1H NMR (400 MHz, CH_3OD , ppm): δ 7.40-7.37 (m, 2H), 7.22 (d, J = 8.0 Hz 2H), 6.98-6.94 (m, 2H), 6.59-6.51 (m, 3H), 4.88 (d, $^1J_{\text{PH}} = 24.8$ Hz, 1H), 4.05-3.97 (m, 2H), 3.95-3.89 (m, 1H), 3.83-3.77 (m, 1H), 1.16 (t, J = 8.0 Hz, 3H), 1.08 (t, J = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3 , ppm): δ 144.88, 133.39, 132.57, 132.54, 128.07, 127.99, 127.94, 127.65, 117.51, 112.67, 62.31, 62.26, 62.16, 54.36 (d, $^1J_{\text{CP}} = 150$ Hz), 15.28, 15.24, 15.10, 15.05; ^{31}P NMR (CDCl_3 , H_3PO_4 , 161.98 MHz): δ 22.02 (s); IR (CHCl_3): ν_{max} 3436, 2927, 2317, 1603, 1498, 1235, 1051, 1020 cm^{-1} ; ESI-MS: m/z 376.15[M+Na] $^+$; HRMS: m/z 376.0848 calcd for $\text{C}_{17}\text{H}_{21}\text{ClNNaO}_3\text{P}+\text{H}^+$ (376.0839).

Cell culture and treatments. Human colorectal adenocarcinoma LS180 cells were purchased from ECACC, England. These cells were grown in MEM growth medium. The media for cell line was supplemented with 1% MEM non-essential amino acids along with 10% FCS, 100 U penicillin G and 100 µg/ml of streptomycin. Cells were grown in 5% CO_2 at 37 °C with 95% humidity. All the test compounds were dissolved in DMSO for treatment of LS180 cells, while the untreated control cultures received only the vehicle (DMSO < 0.2%).

P-gp-induction assay. All synthesized compounds were screened for their ability to induce P-gp using rhodamine 123 cell exclusion method.¹ In this method, the P-gp function was evaluated in

terms of rhodamine 123 accumulation and efflux.² Briefly, the protocol used was as follows: Colorectal LS180 cells were seeded at a density of 2×10^4 per well of 96 well plate and were allowed to grow for next 24 h. Cells were further incubated with the test compounds, and were diluted to a final concentration of 5 μM and rifampicin (positive control) to a final concentration of 10 μM in complete media for 48 h. The final concentration of DMSO was kept at 0.1%. Drugs were removed and cells were incubated with HANKS buffer for 40 minutes before further incubation with HANKS buffer (containing 10 μM of Rh123 as a P-gp substrate) for 90 minutes. At the end of Rh123 treatment cells were washed four times with cold PBS followed by cell lysis for 1 h using 200 μl of lysis buffer (0.1% Triton X 100 and 0.2 N NaOH). A total of 100 μl of lysate was used for reading fluorescence of Rh123 at 485/529 nm. Samples were normalized by dividing fluorescence of each sample with total protein present in the lysate.

Cell viability assay. The cell proliferation assay was done in human colorectal adenocarcinoma LS180 cells. Cells (1×10^4) were seeded into each well of 96-well microplate for 24 h. Cells were treated with 30 μM of each compound for 24 h. The MTT dye was then added to each well 4 h prior to the termination of experiment. Formazan crystals were dissolved in DMSO before taking absorbance at 570 nm. Cell viability of the untreated control sample was considered to be 100%, while viability of test samples was calculated using the following formula:

$$\% \text{ cell viability} = \frac{\text{OD (test)}}{\text{OD (control)}} \times 100$$

Western-blot analysis of compounds 6c and 6s in LS180 cells. Protein was measured employing Bio-Rad protein assay kit using bovine serum albumin as standard. Proteins aliquots (70 μg) were resolved on SDS-PAGE and then electro transferred to PVDF membrane overnight at 4 °C at 30V. Nonspecific binding was blocked by incubation with 5 % non-fat milk in Tris-buffered saline

containing 0.1% Tween-20 (TBST) for 1 h at room temperature. The blots were probed with anti-Pgp antibody for 4 h and washed three times with TBST. Blot was then incubated with horseradish peroxidase conjugated antimouse secondary antibody for 1 h, washed again three times with TBST and signals detected using ECL plus chemiluminescence's kit on BioRad ChemiDoc XRS system.

Aqueous solubility, CYP liability and Caco-2 permeability and pharmacokinetic analysis was performed as reported in our earlier papers.³

The pharmacokinetic study was carried out at Jubilant Biosys Limited Bangalore (India) on a commercial basis. These experiments were approved by the Jubilant Biosys Institutional Animal Ethics Committee, Bangalore, India (IAEC/JDC/2012/27) and were in accordance with the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Social Justice and Environment, Government of India.

Statistical analysis. Data is expressed as mean \pm SD of three independent experiments unless otherwise indicated. The comparisons were made between control and treated groups or the entire intra group using Bonferroni test through Instat-2 software. p -values * <0.5 were considered significant.

S4. REFERENCES ASSOCIATED WITH ESI

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