

## Supporting Information

### Design, Synthesis and Biological Evaluation of Sulfur-Containing 1,1-Bisphosphonic Acids as Antiparasitic Agents

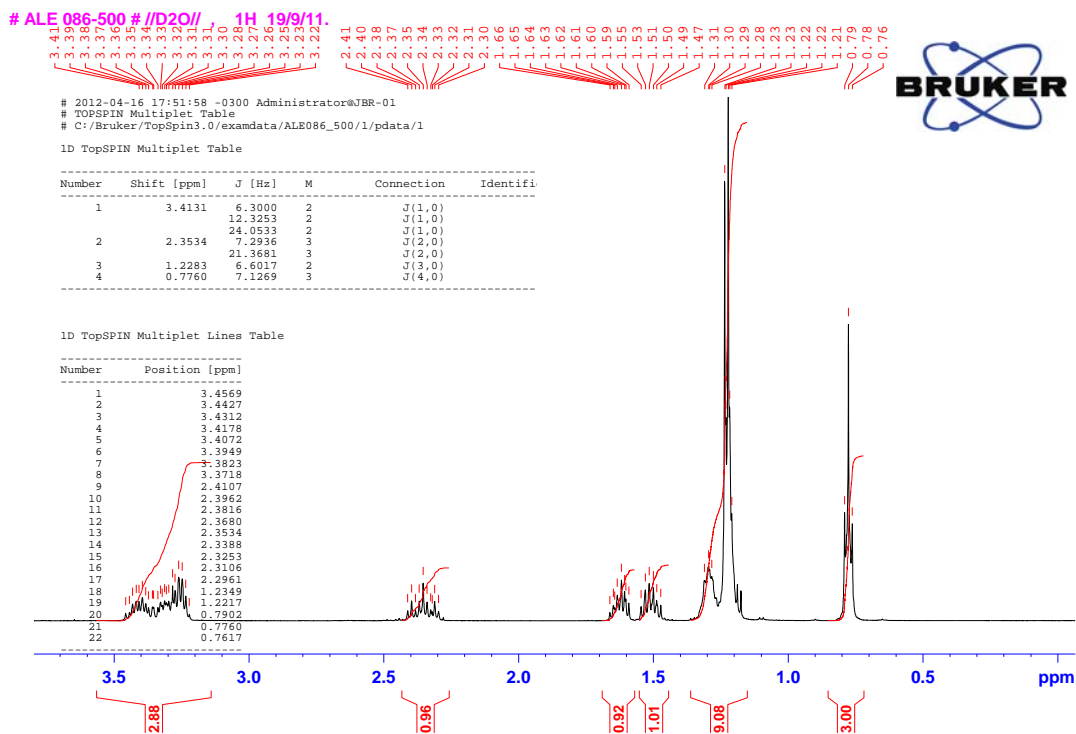
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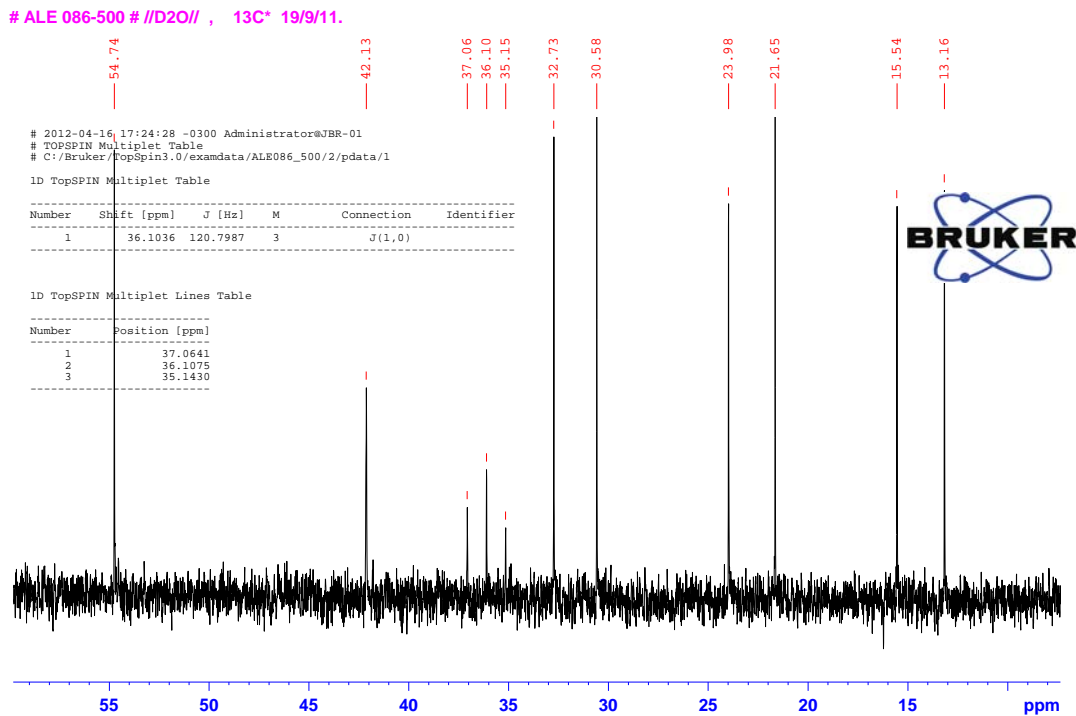
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<sup>1</sup>H NMR spectrum of compound 18.



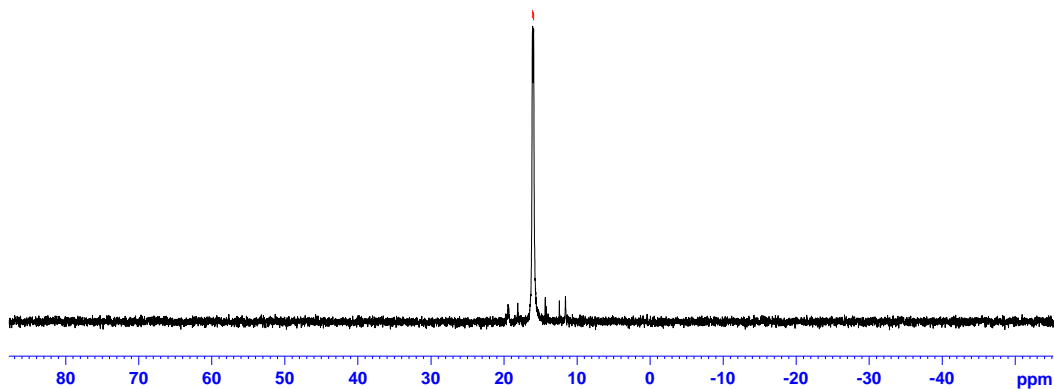
<sup>13</sup>C NMR spectrum of compound 18.

# ALE 086 500 # /D2O// , 31P\* 19/9/11.

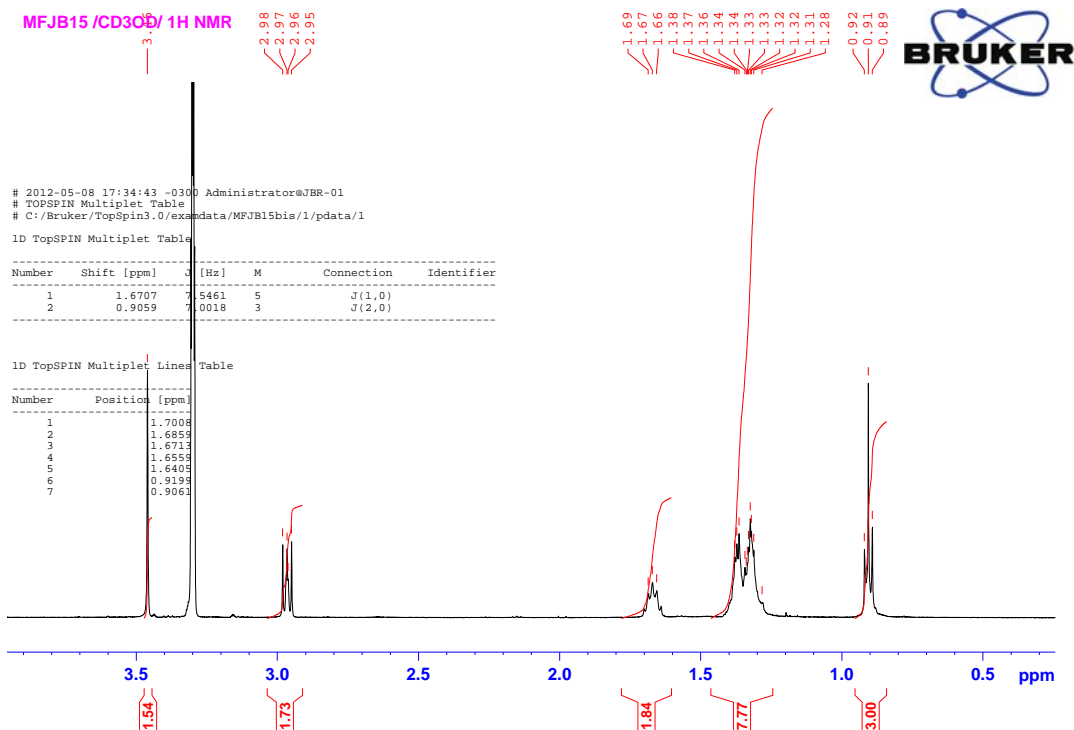
16.08  
15.94



+//...//...//info

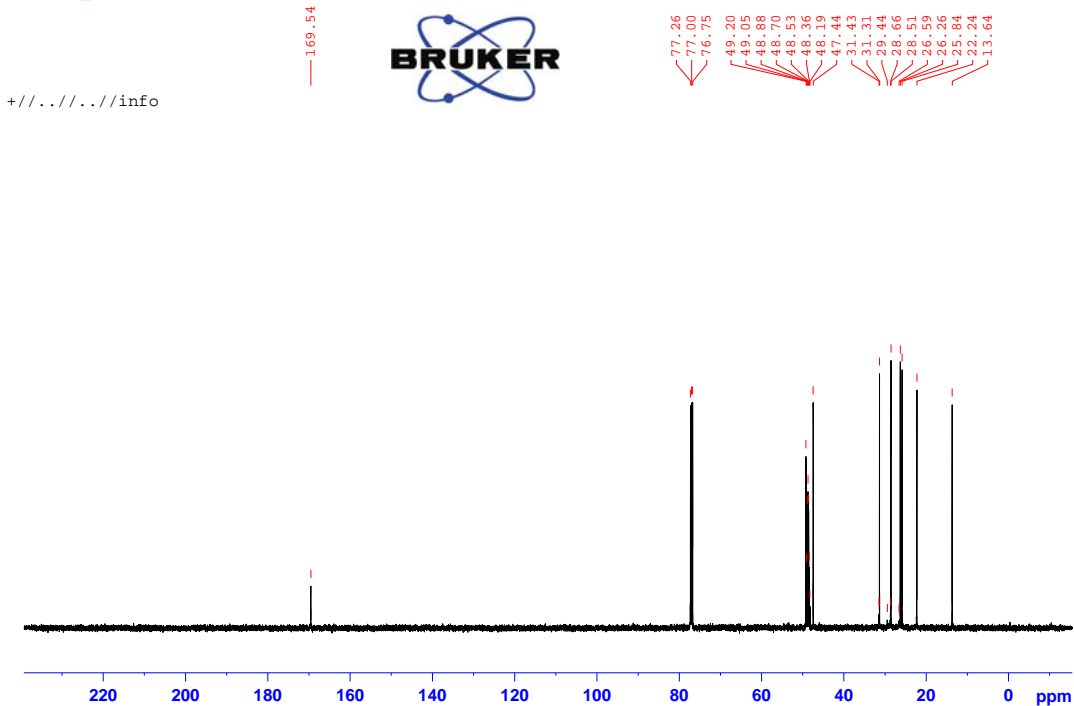


<sup>31</sup>P NMR spectrum of compound 18.



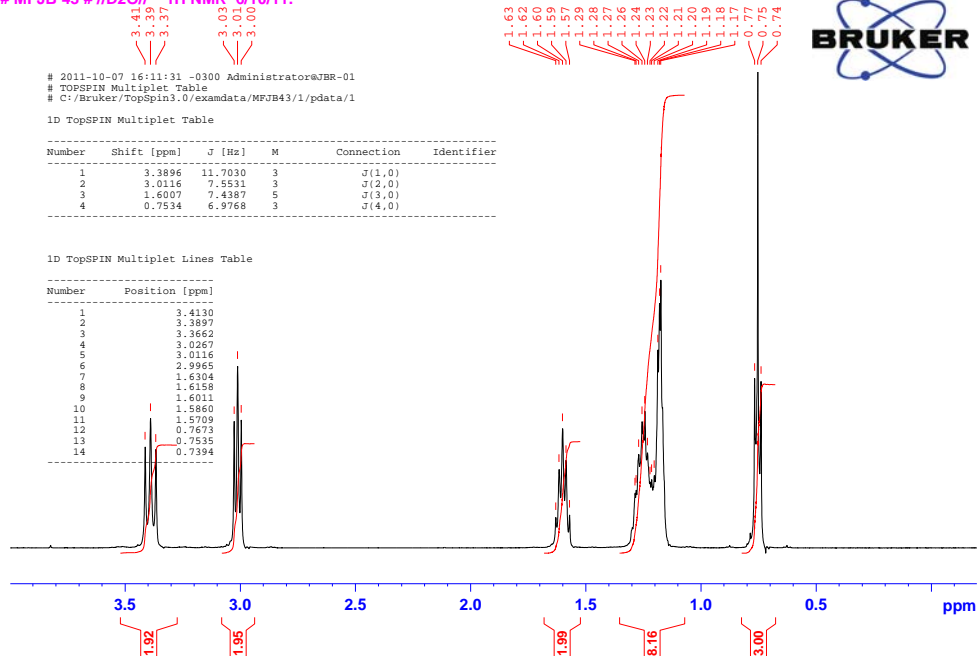
<sup>1</sup>H NMR spectrum of compound 20.

# MFJB\_15 #/CD3OD+(lock)CDCI3/ 13C NMR



<sup>13</sup>C NMR spectrum of compound 20.

# MFJB 43 # //D2O// 1H NMR 6/10/11.



<sup>1</sup>H NMR spectrum of compound 21.

MFJB\_17/D2O/ 13C NMR

71.39  
70.29  
69.20

49.85  
48.25



30.72  
27.79  
25.50  
25.34  
21.84

13.29

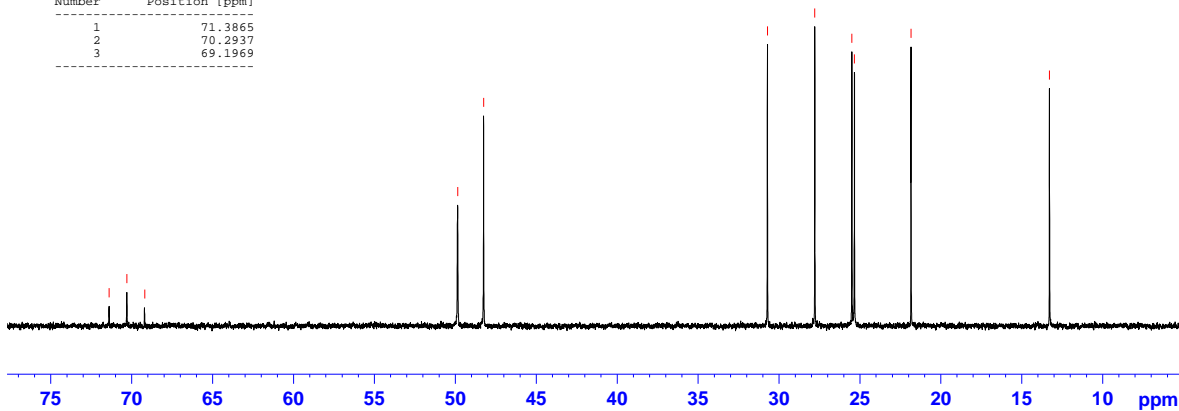
# 2012-04-19 16:45:06 -0300 Administrator@JBR-01  
# TOPSPIN Multiplet Table  
# C:/Bruker/TopSpin3.0/examdata/MFJB17-19-04-12/31/pdata/1

1D TopSPIN Multiplet Table

| Number | Shift [ppm] | J [Hz]   | M | Connection | Identifier |
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1D TopSPIN Multiplet Lines Table

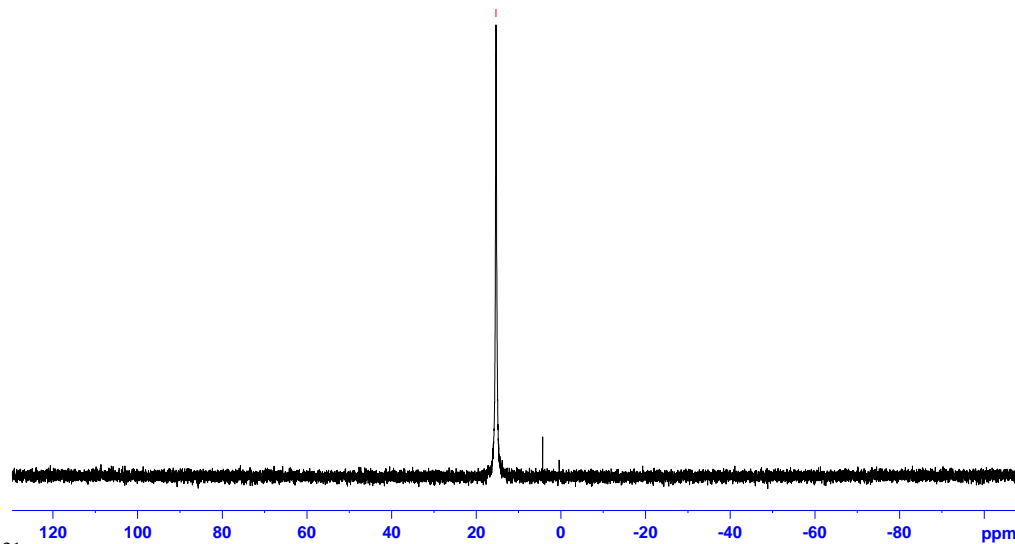
| Number | Position [ppm] |
|--------|----------------|
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| 2      | 70.2937        |
| 3      | 69.1969        |



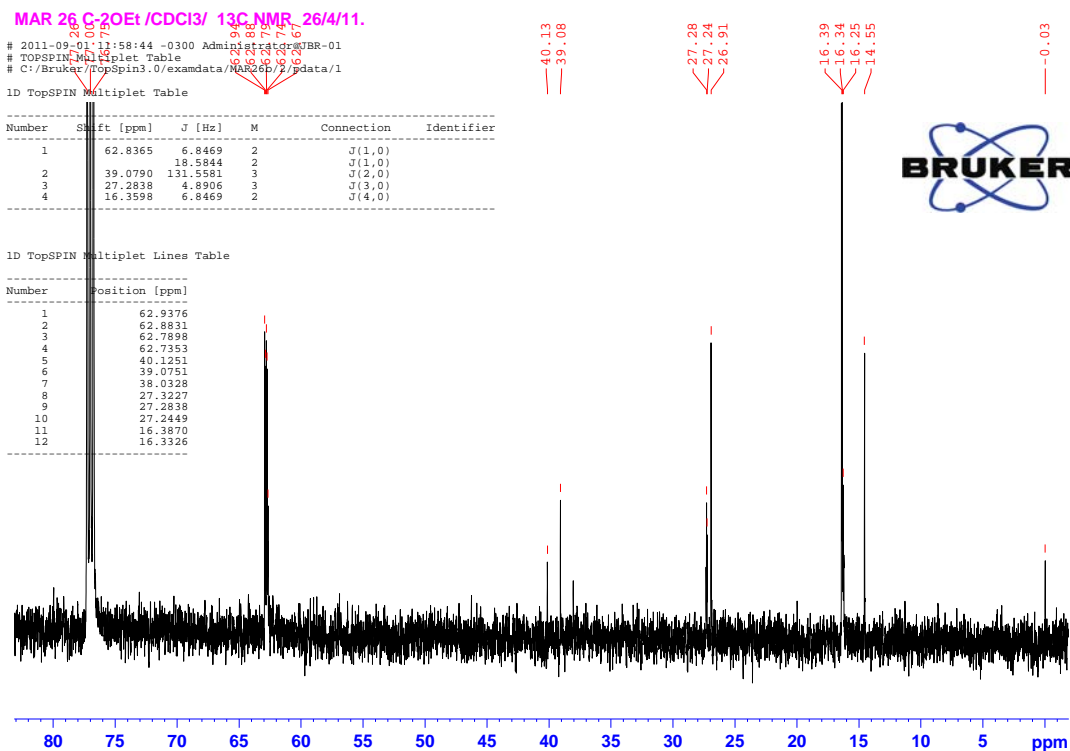
<sup>13</sup>C NMR spectrum of compound **21**.

# MFJB 43 # //D2O// , 31P\* 6/10/11.

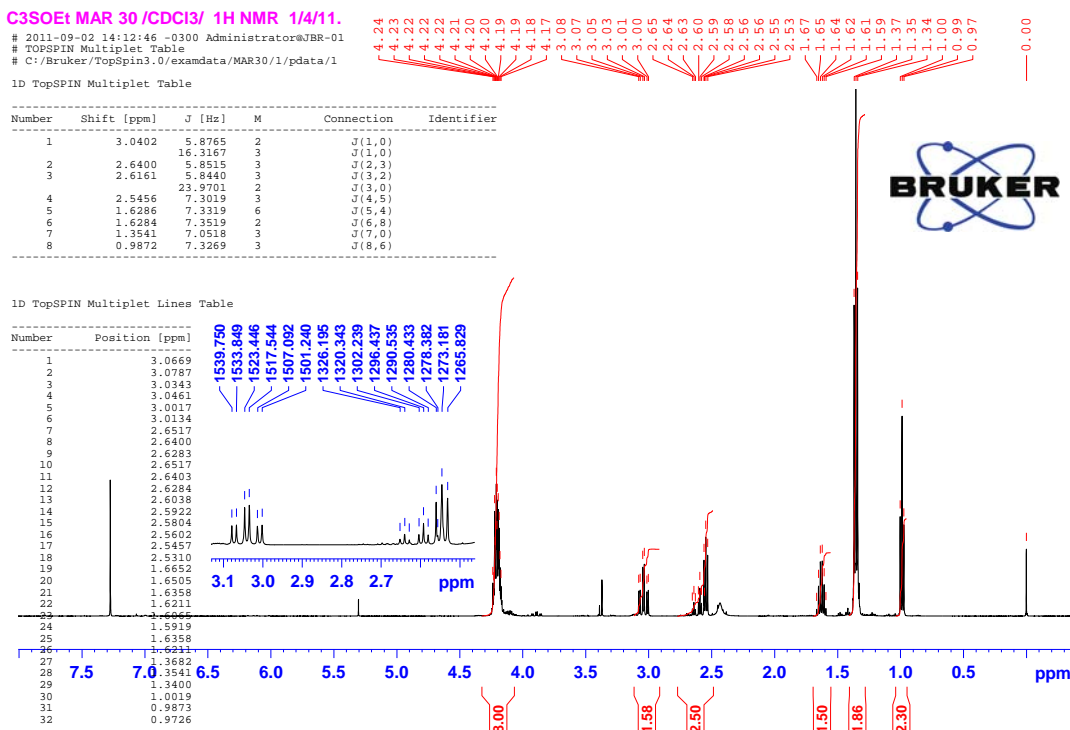
15.31



<sup>31</sup>P NMR spectrum of compound **21**.



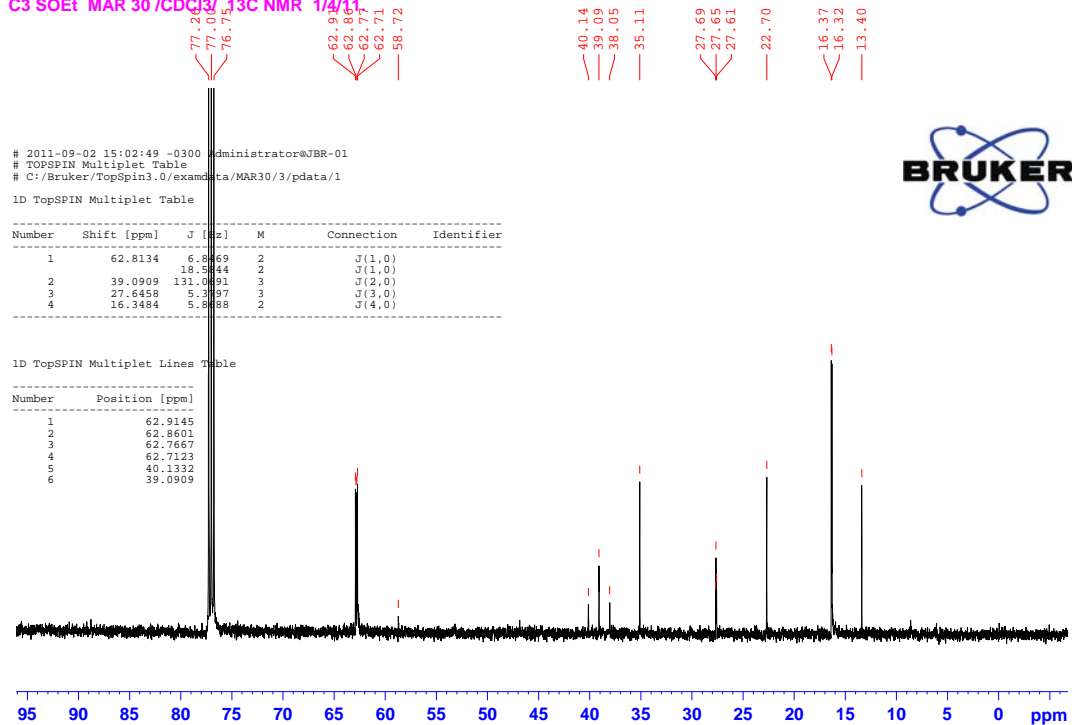
$^{13}\text{C}$  NMR spectrum of compound 22.



$^1\text{H}$  NMR spectrum of compound 23.

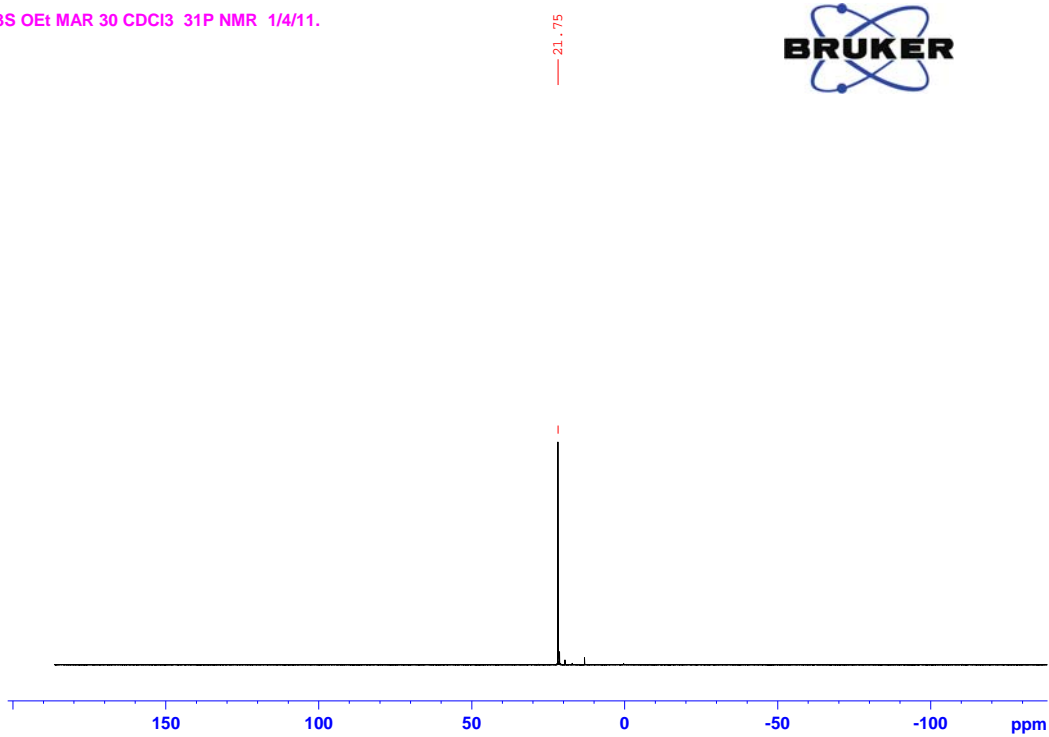


C3 SOEt MAR 30 /CDCl3/ 13C NMR 1/4/11



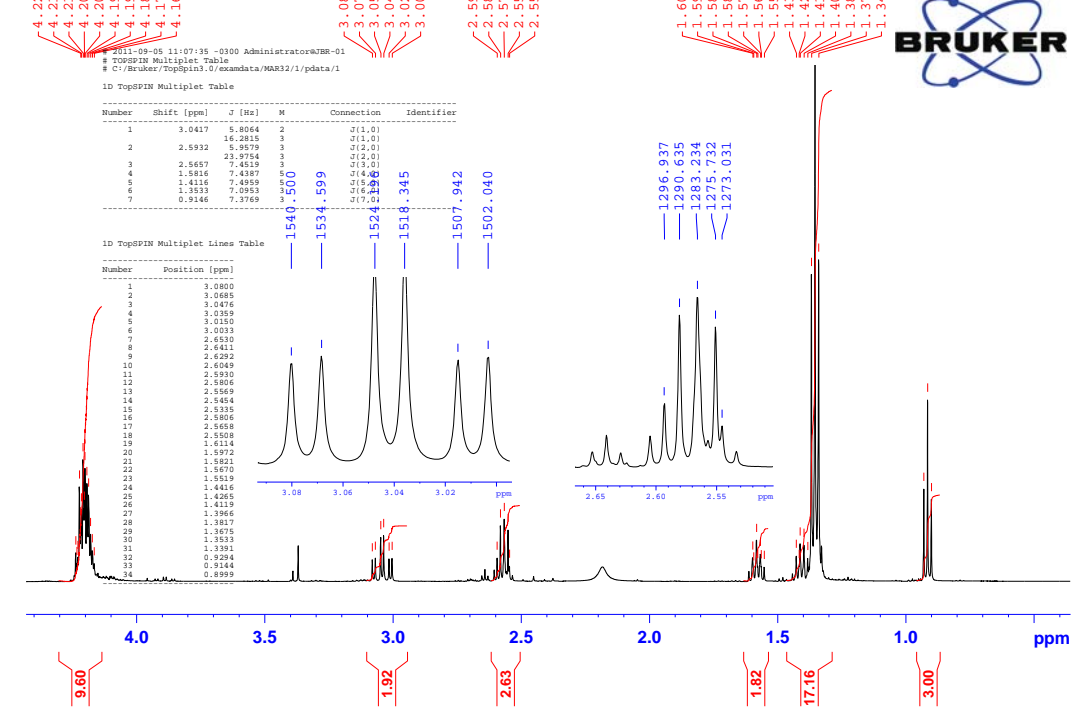
<sup>13</sup>C NMR spectrum of compound 23.

C3S OEt MAR 30 CDCl3 31P NMR 1/4/11.



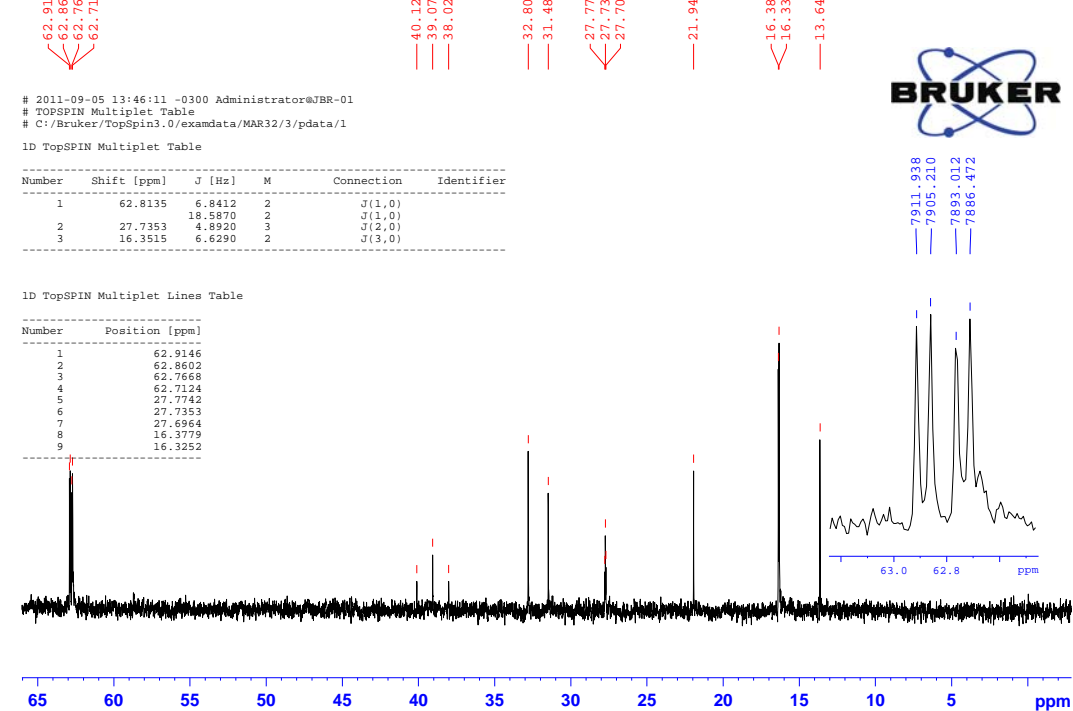
<sup>31</sup>P NMR spectrum of compound 23.

C4S OEI MAR 32 /CDCl3/ 1H NMR 1/4/11.

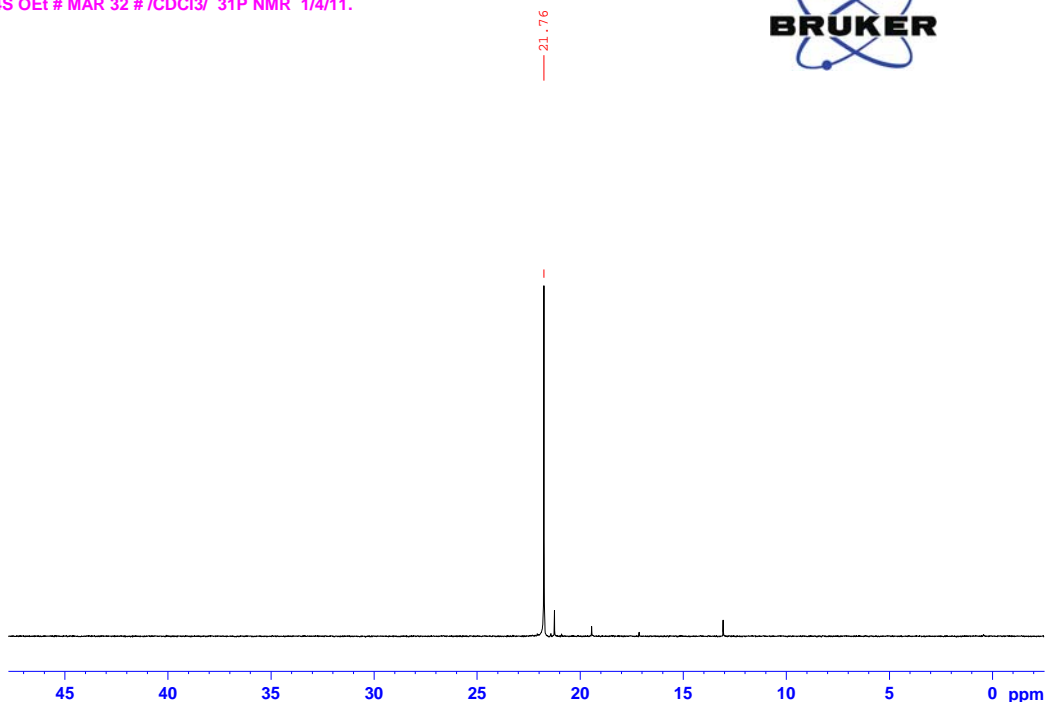


<sup>1</sup>H NMR spectrum of compound 24.

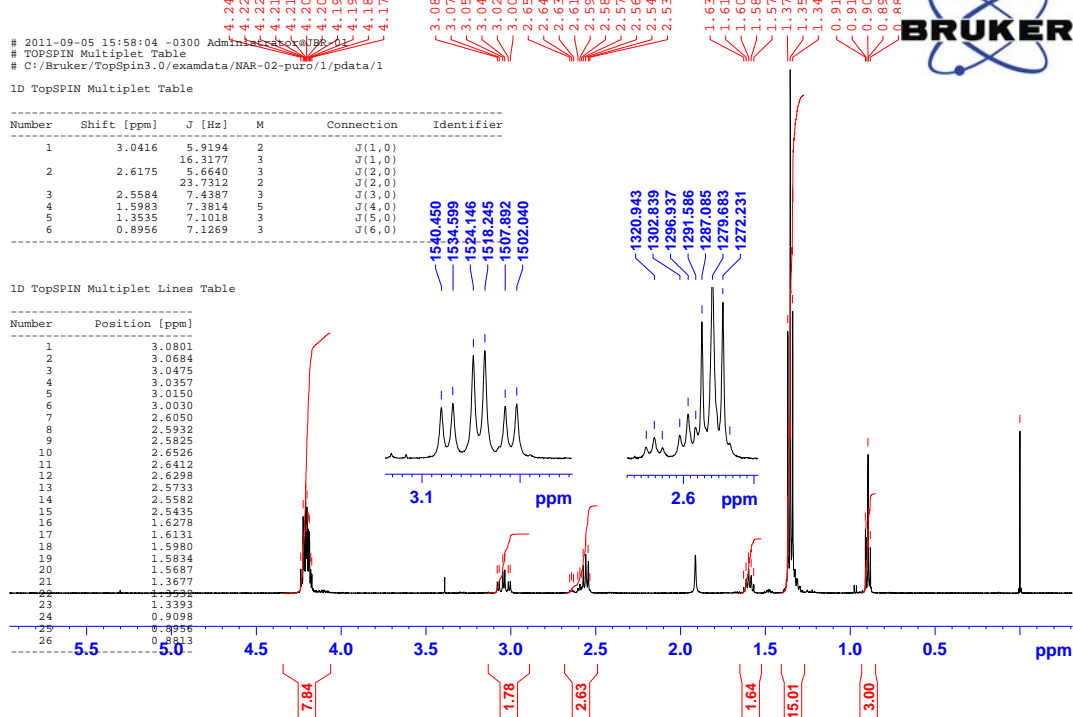
C4S OEI MAR 32 /CDCl3/ 13C NMR 1/4/11.



<sup>13</sup>C NMR spectrum of compound 24.

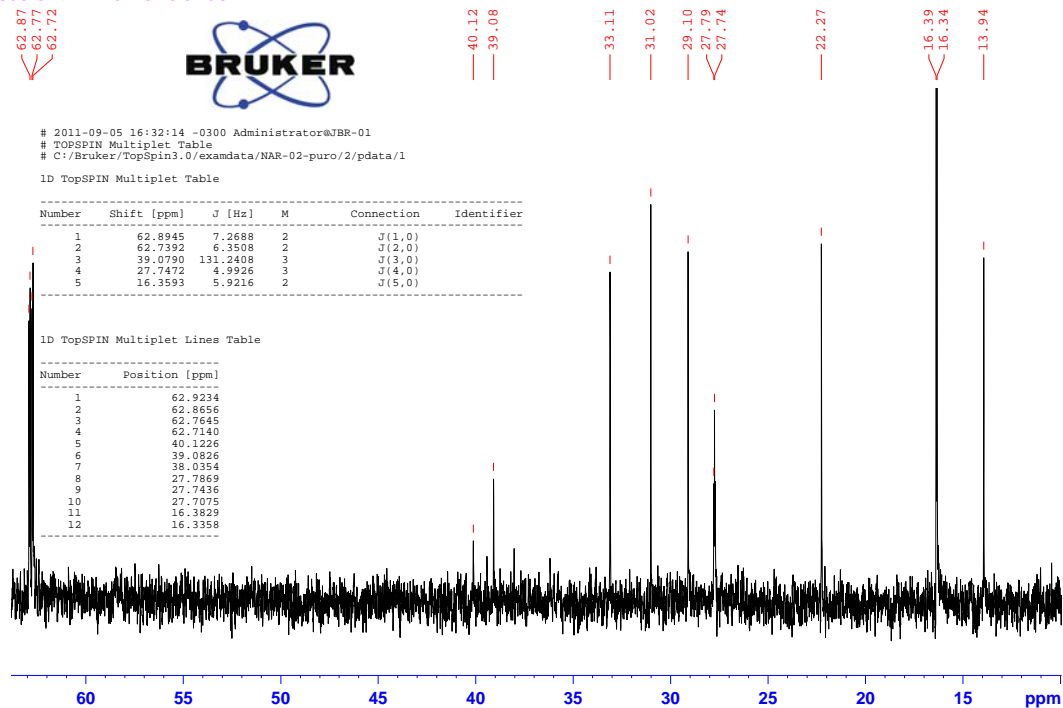


31P NMR spectrum of compound 24.



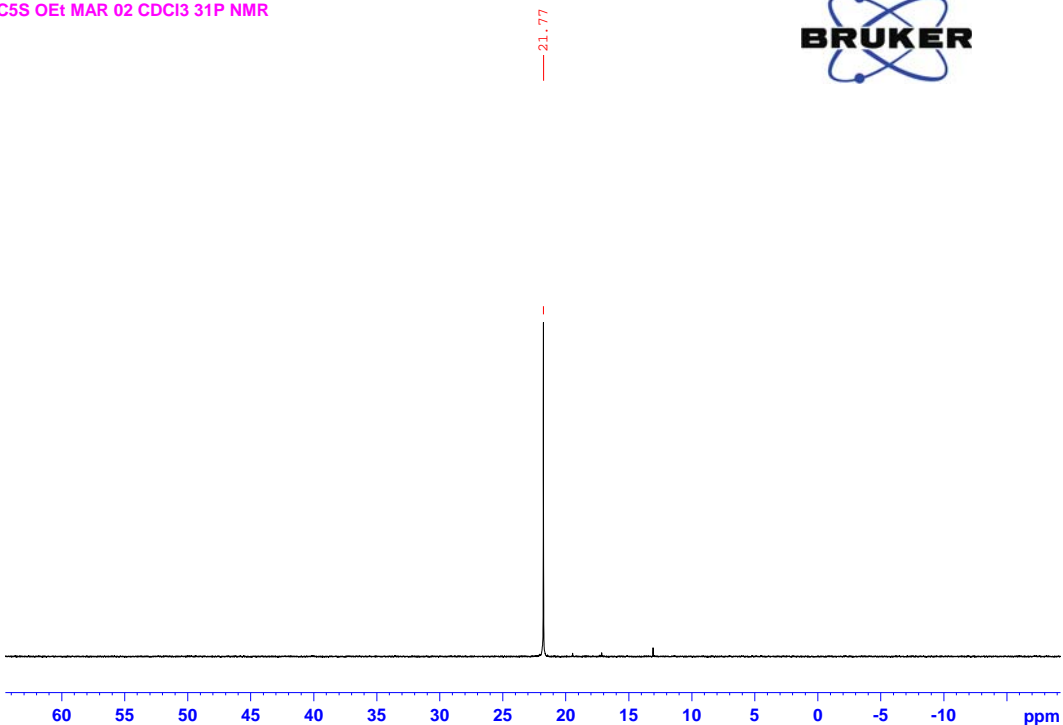
1H NMR spectrum of compound 25.

C5S OEt MAR 02 CDCl3 13C NMR



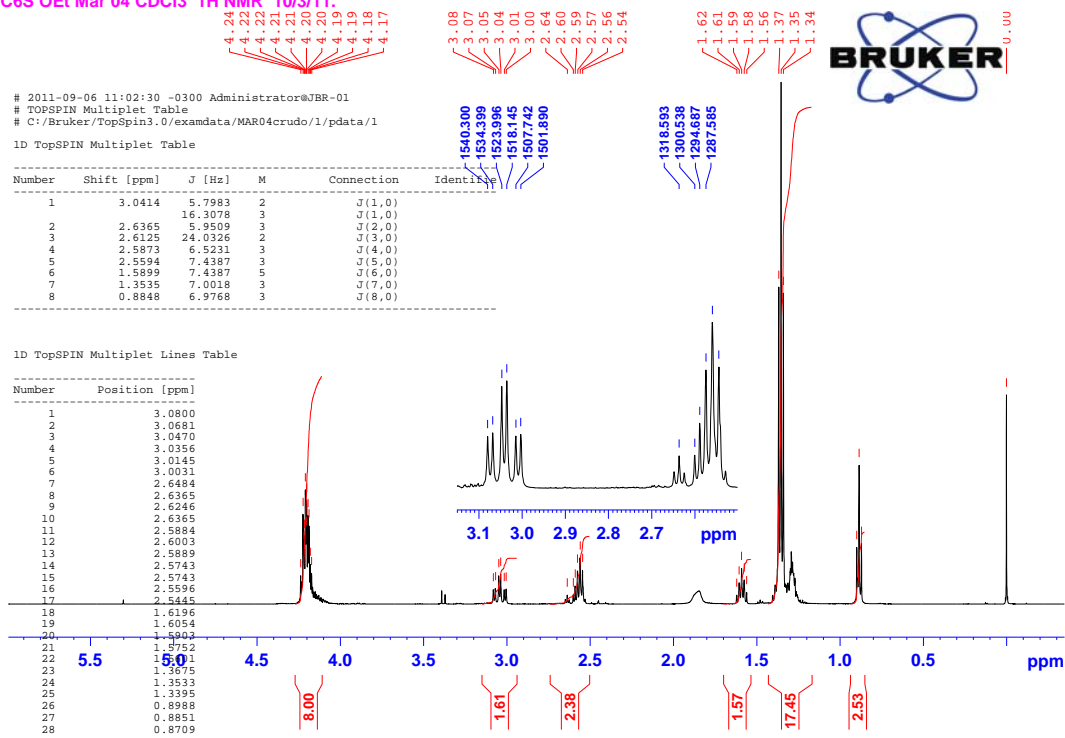
<sup>13</sup>C NMR spectrum of compound 25.

C5S OEt MAR 02 CDCl3 31P NMR



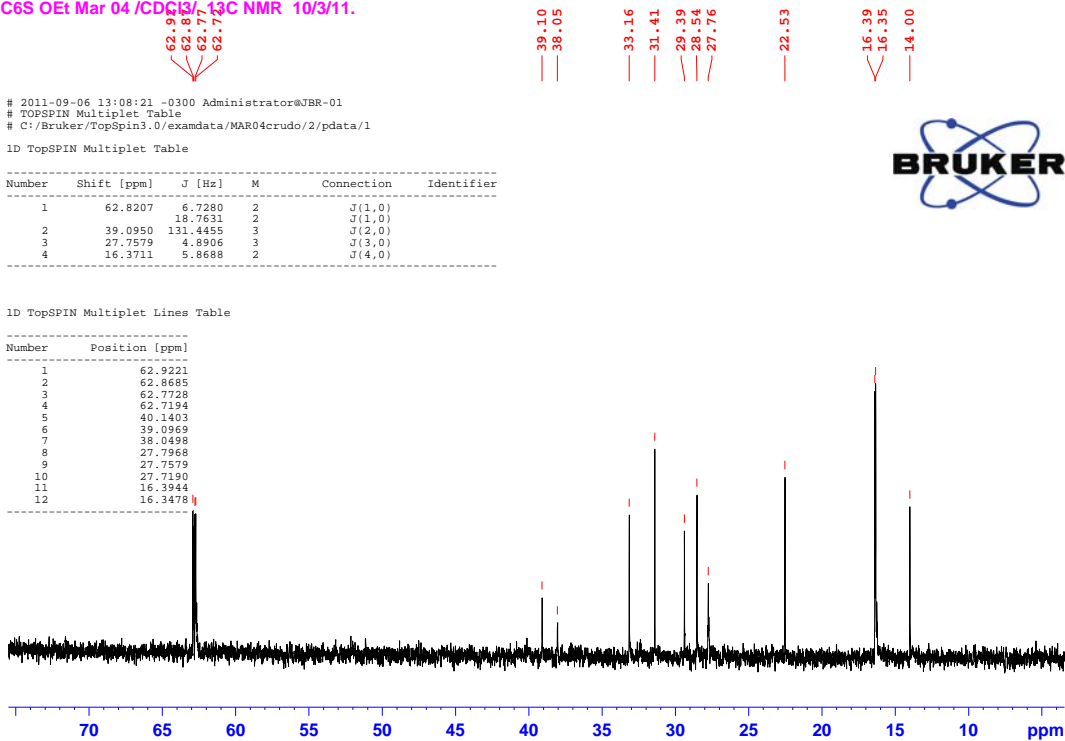
<sup>31</sup>P NMR spectrum of compound 25.

C6S OEt Mar 04 CDCI3 1H NMR 10/3/11.

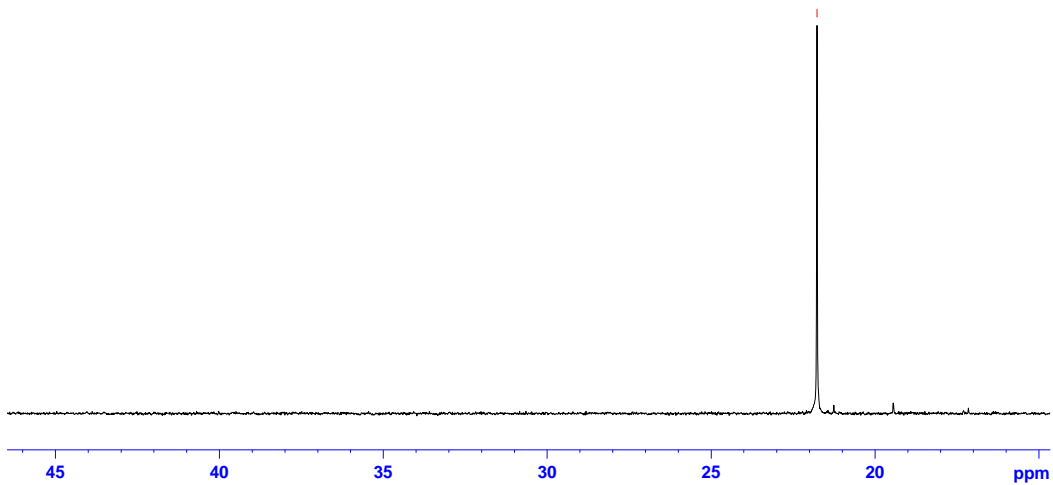


<sup>1</sup>H NMR spectrum of compound 26.

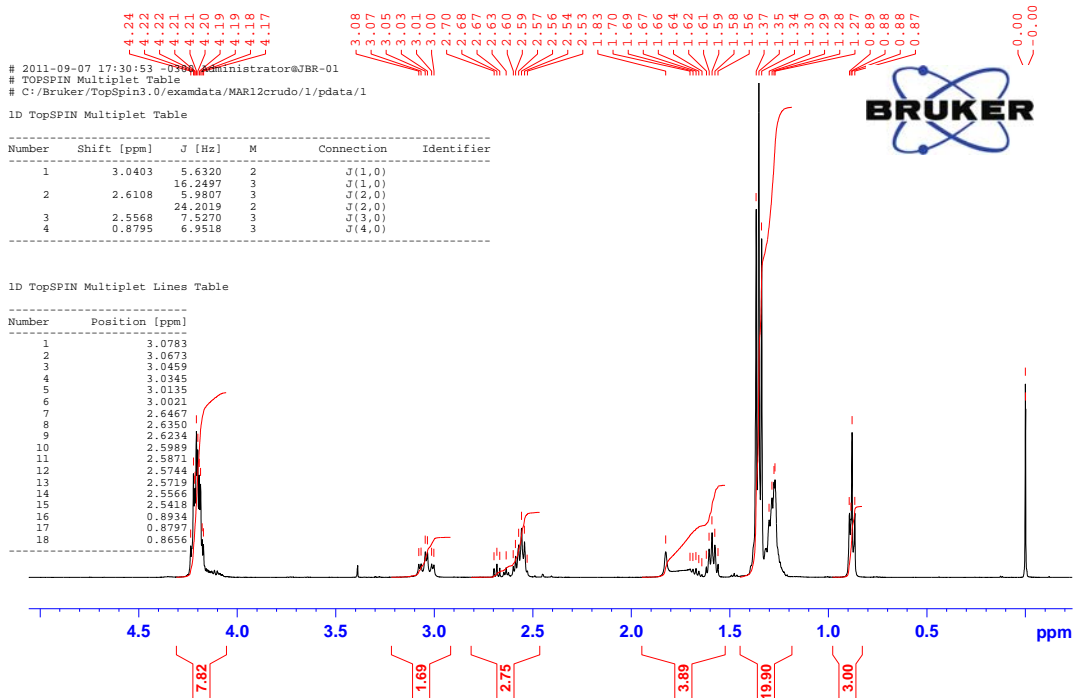
C6S OEt Mar 04 /CDCl3/ 13C NMR 10/3/11.



<sup>13</sup>C NMR spectrum of compound 26.

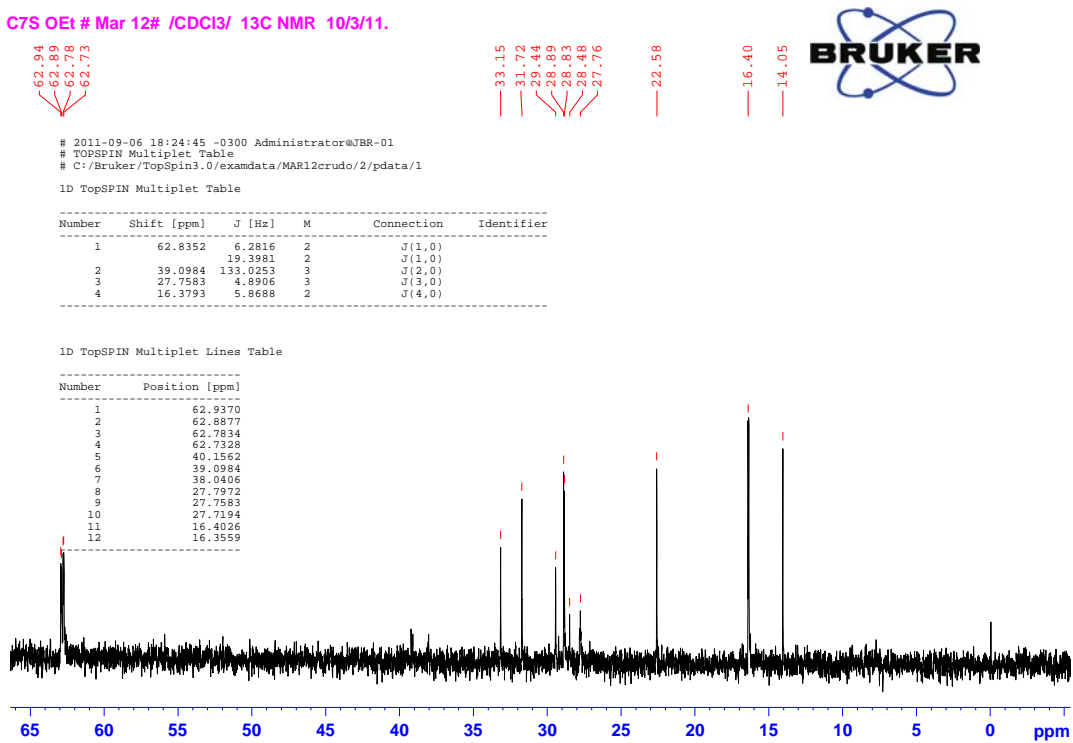


<sup>31</sup>P NMR spectrum of compound **26**.



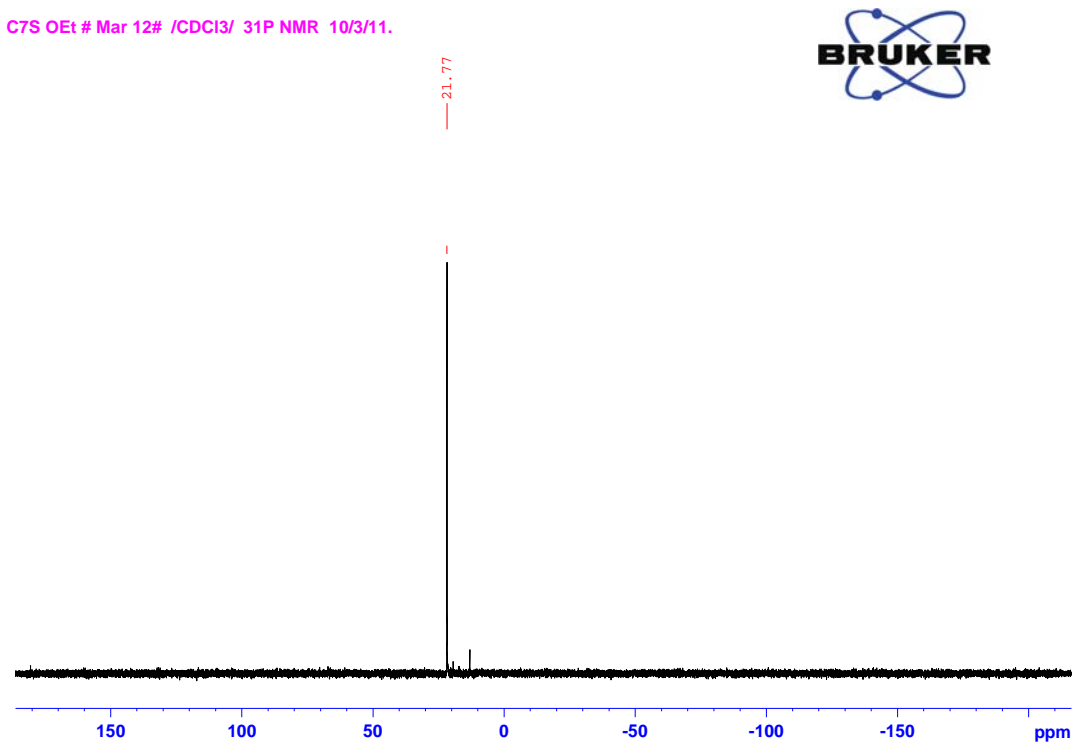
<sup>1</sup>H NMR spectrum of compound **27**.

C7S OEt # Mar 12# /CDCl3/ 13C NMR 10/3/11.



<sup>13</sup>C NMR spectrum of compound 27.

C7S OEt # Mar 12# /CDCl3/ 31P NMR 10/3/11.



<sup>31</sup>P NMR spectrum of compound 27.

C8S OEt # MAR 44 # /CDCl3/ 1H NMR 26/5/11.

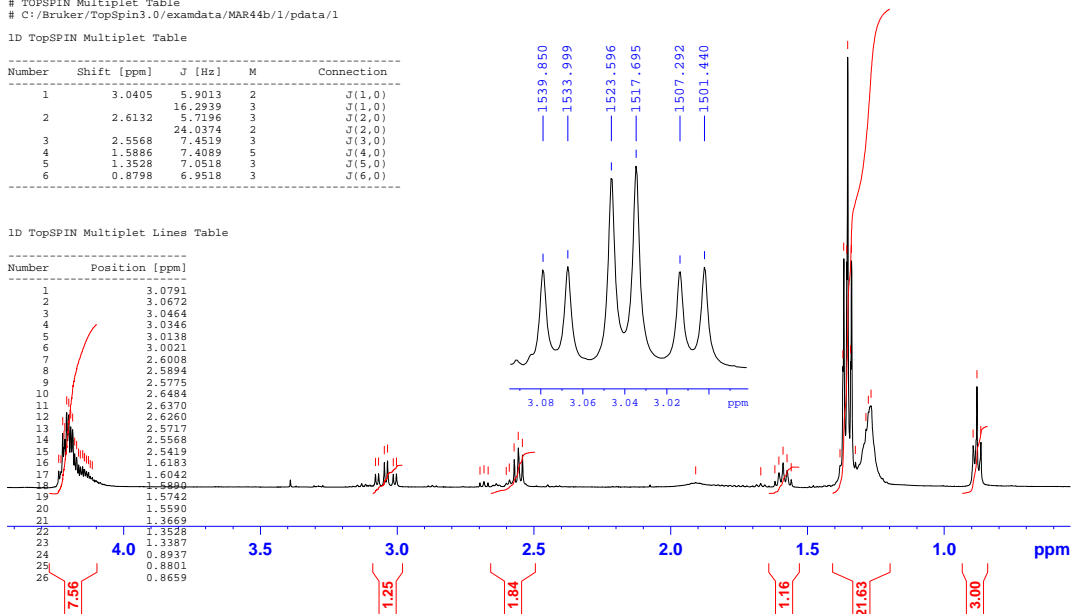
# 2011-09-08 11:53:10 -0300 Administrator@JBR-01  
 # TOPSPIN Multiplet Table  
 # C:/Bruker/TopSpin3.0/examdata/MAR44b/1/pdata/1

1D TopSPIN Multiplet Table

| Number | Shift [ppm] | J [Hz]  | M | Connection |
|--------|-------------|---------|---|------------|
| 1      | 3.0405      | 5.9013  | 2 | J(1,0)     |
| 2      | 2.6132      | 16.2939 | 3 | J(2,0)     |
| 3      | 2.5568      | 24.0374 | 2 | J(2,0)     |
| 4      | 1.5886      | 7.4519  | 3 | J(3,0)     |
| 5      | 1.3528      | 7.0518  | 3 | J(5,0)     |
| 6      | 0.8798      | 6.9518  | 3 | J(6,0)     |

1D TopSPIN Multiplet Lines Table

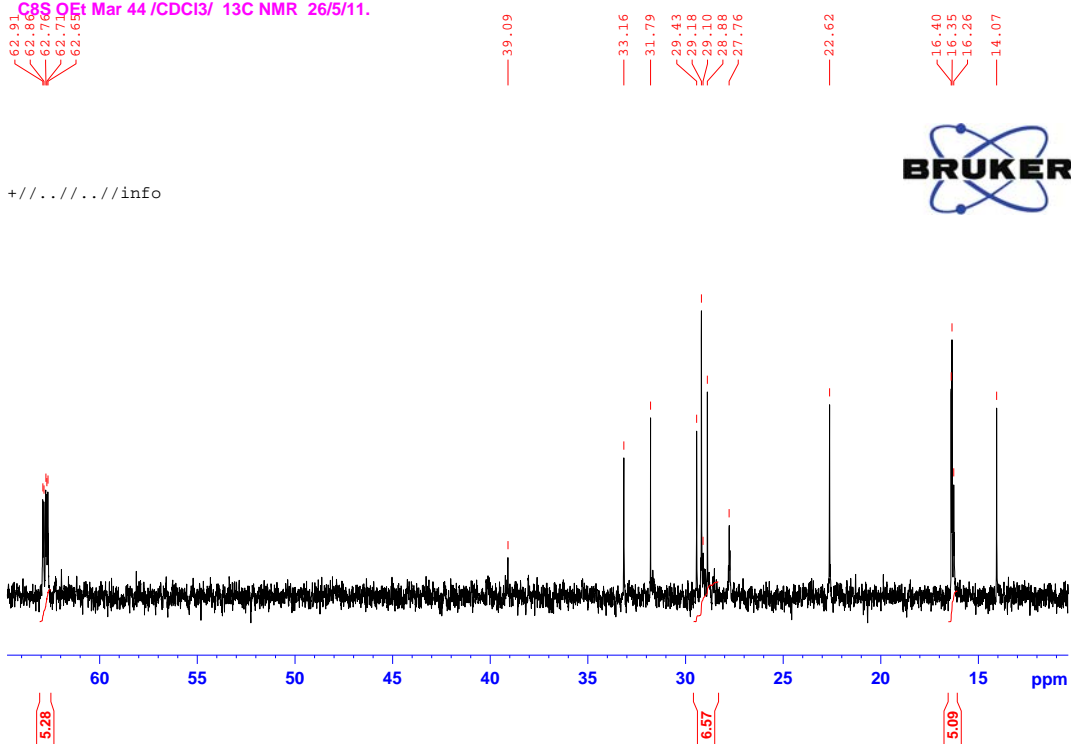
| Number | Position [ppm] |
|--------|----------------|
| 1      | 3.0791         |
| 2      | 3.0672         |
| 3      | 3.0464         |
| 4      | 3.0346         |
| 5      | 3.0138         |
| 6      | 3.0021         |
| 7      | 2.6008         |
| 8      | 2.5894         |
| 9      | 2.5775         |
| 10     | 2.6484         |
| 11     | 2.6370         |
| 12     | 2.6260         |
| 13     | 2.5717         |
| 14     | 2.5568         |
| 15     | 2.5419         |
| 16     | 1.6183         |
| 17     | 1.6042         |
| 18     | 1.5890         |
| 19     | 1.5742         |
| 20     | 1.5590         |
| 21     | 1.3669         |
| 22     | 1.3528         |
| 23     | 1.3387         |
| 24     | 0.8937         |
| 25     | 0.8801         |
| 26     | 0.8659         |



<sup>1</sup>H NMR spectrum of compound 28.

C8S OEt Mar 44 /CDCl3/ 13C NMR 26/5/11.

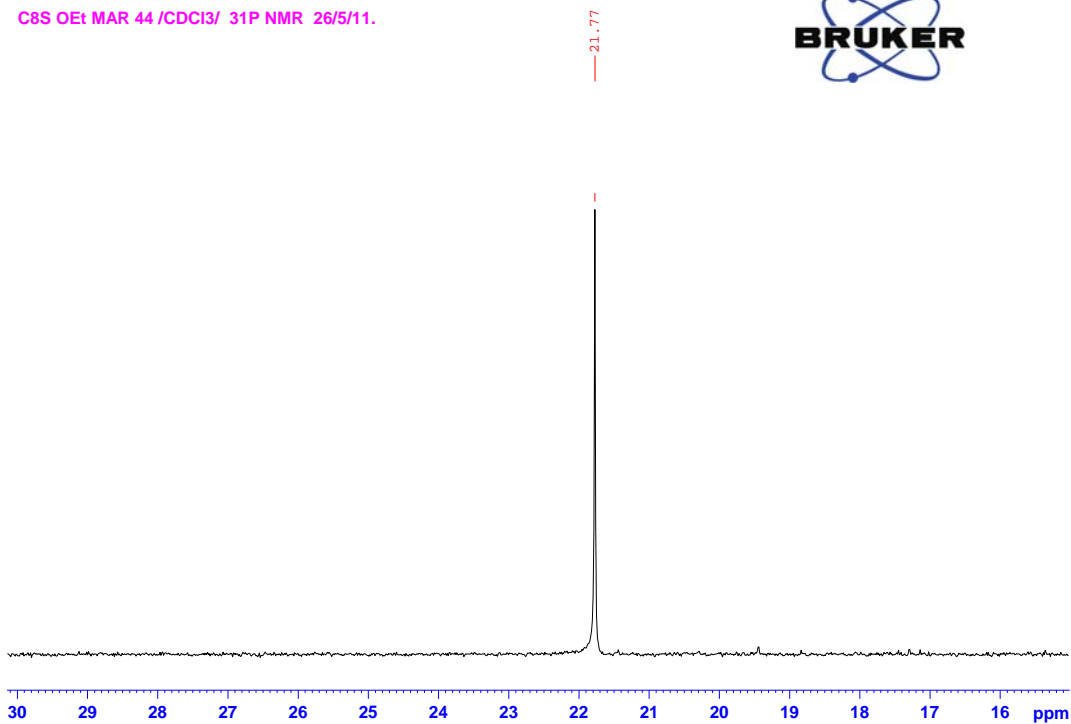
+//.....//info



<sup>13</sup>C NMR spectrum of compound 28.

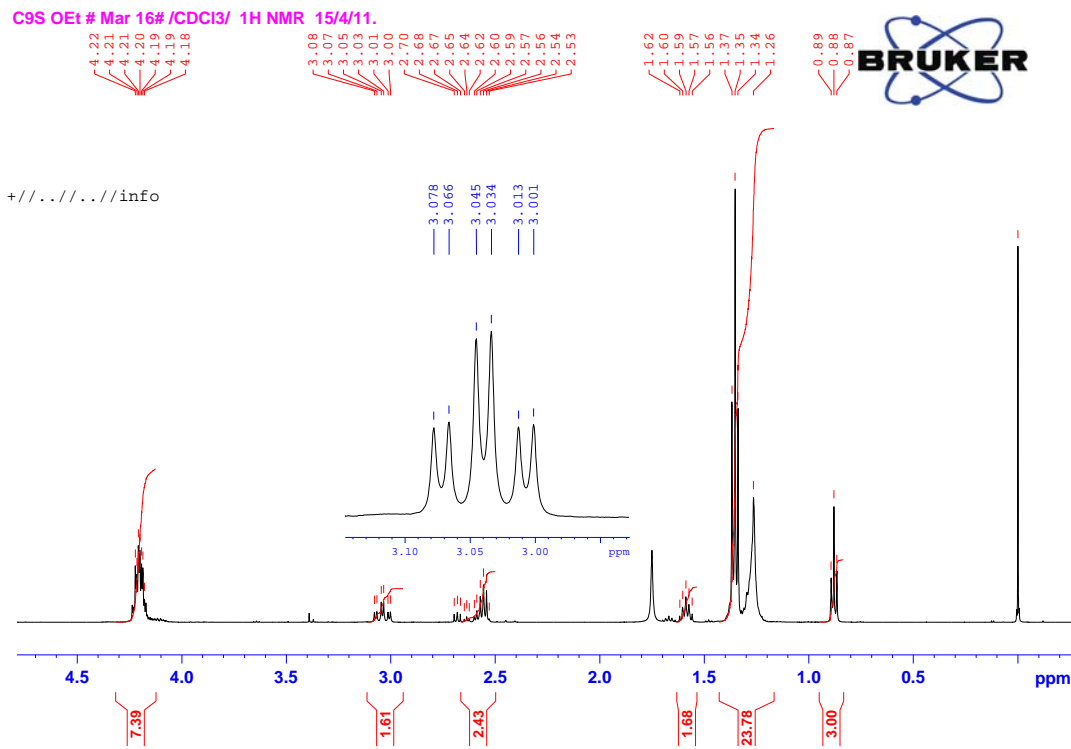


C8S OEt MAR 44 /CDCl3/ 31P NMR 26/5/11.



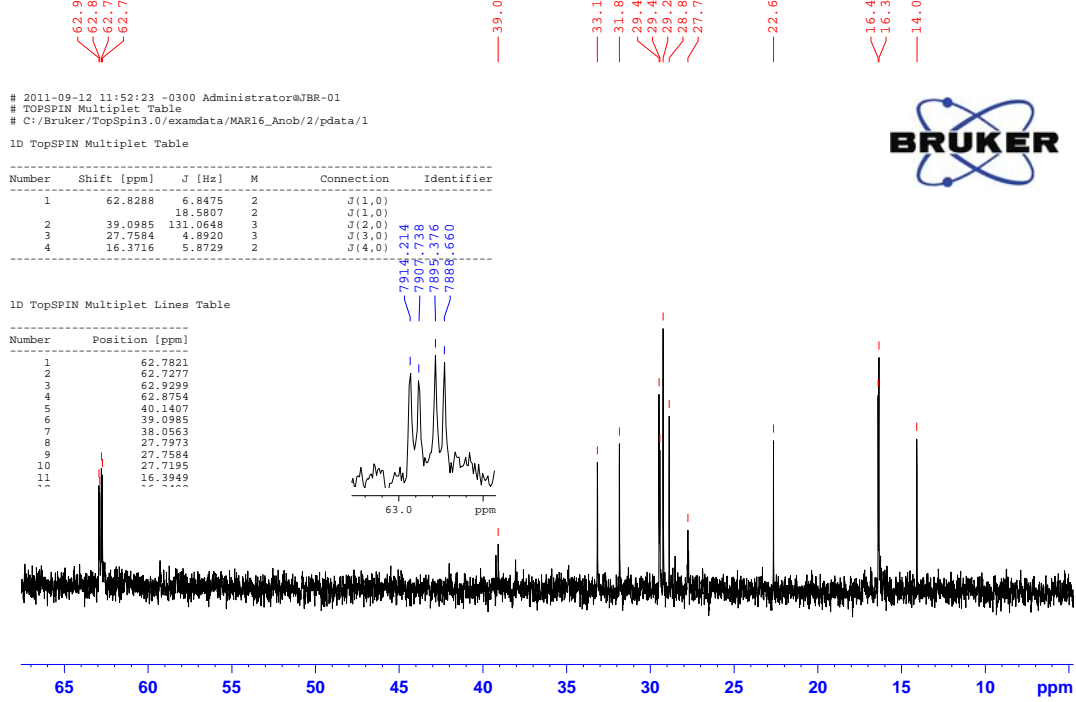
<sup>31</sup>P NMR spectrum of compound 28.

C9S OEt # Mar 16# /CDCl3/ 1H NMR 15/4/11.



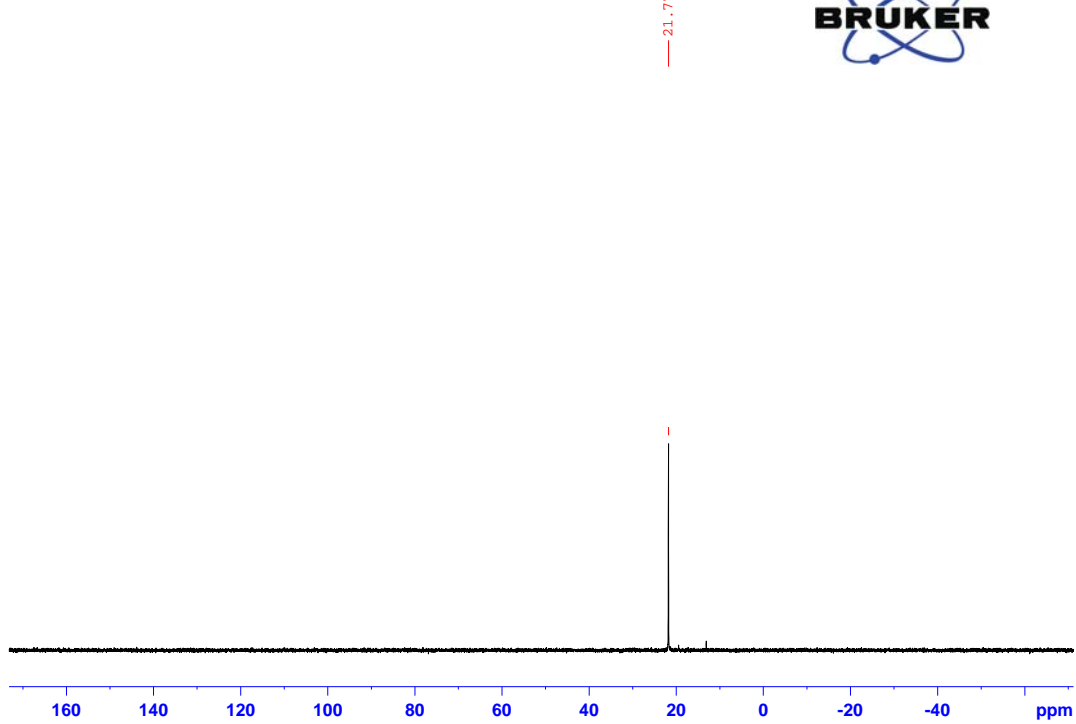
<sup>1</sup>H NMR spectrum of compound 29.

C9S OEt # Mar 16 # /CDCl3/ <sup>13</sup>C NMR 15/4/11.

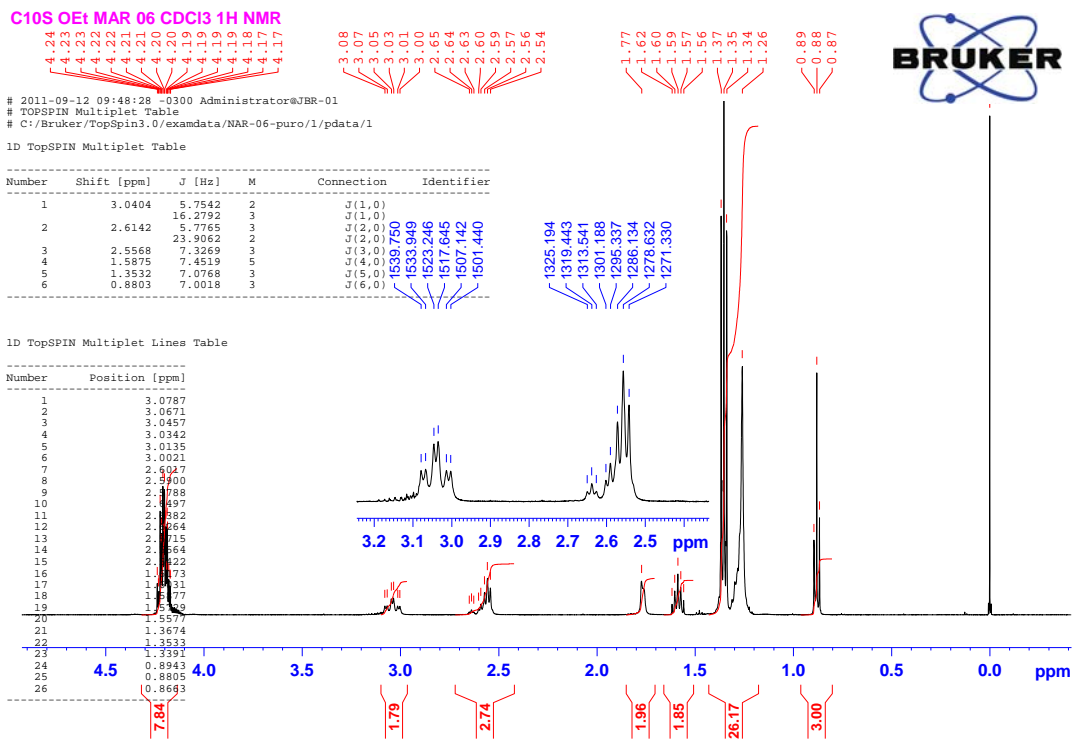


<sup>13</sup>C NMR spectrum of compound 29.

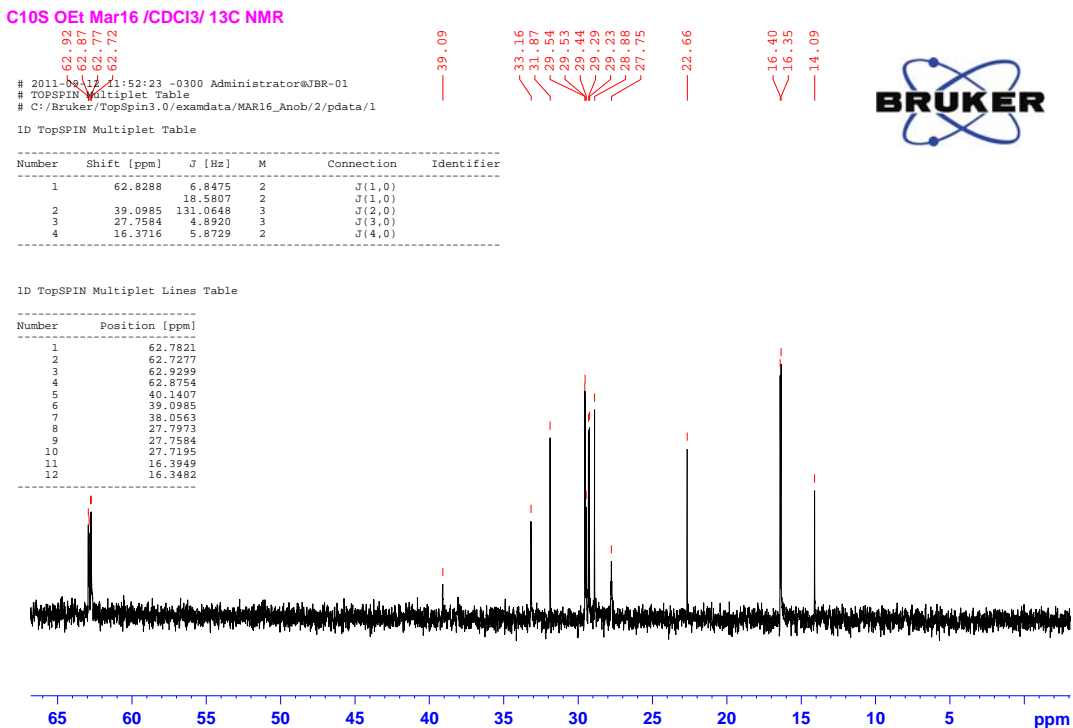
C9S OEt # Mar 16 # /CDCl3/ <sup>31</sup>P NMR 15/4/11.



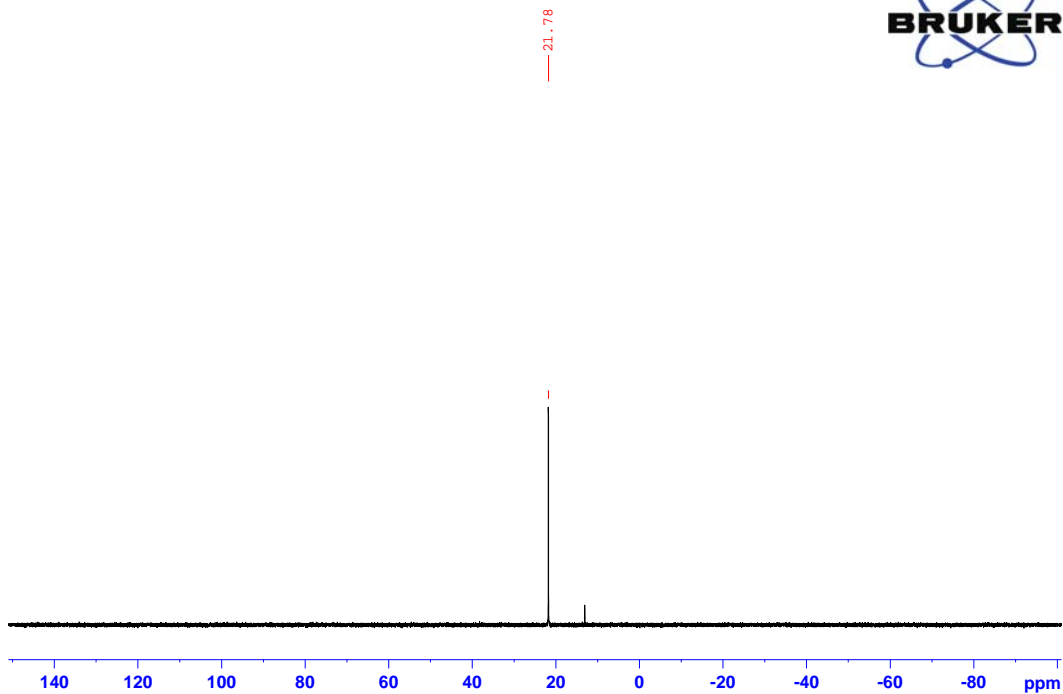
<sup>31</sup>P NMR spectrum of compound 29.



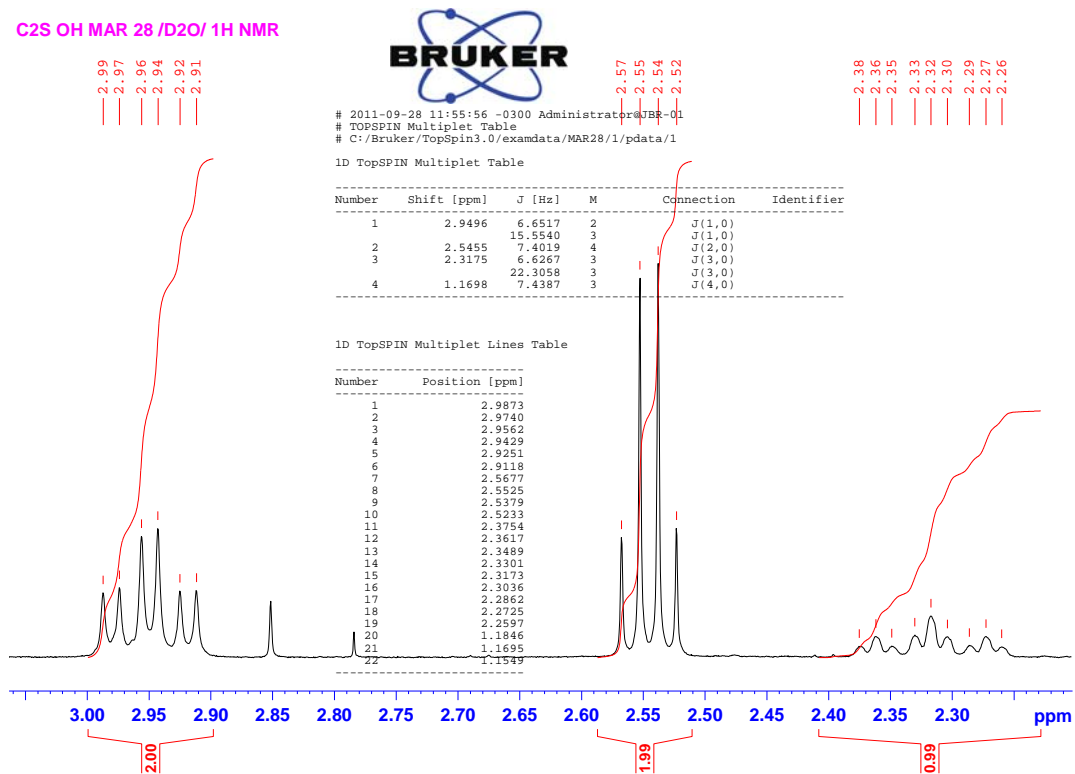
<sup>1</sup>H NMR spectrum of compound **30**.



<sup>13</sup>C NMR spectrum of compound **30**.


 $^{31}\text{P}$  NMR spectrum of compound **30**.

C2S OH MAR 28 /D2O/ 1H NMR


 $^1\text{H}$  NMR spectrum of compound **31**.

C2S OH # MAR 28 # //D2O/ 13C NMR 8/8/11.

40.23  
39.27  
38.32

26.81  
25.95



13.69

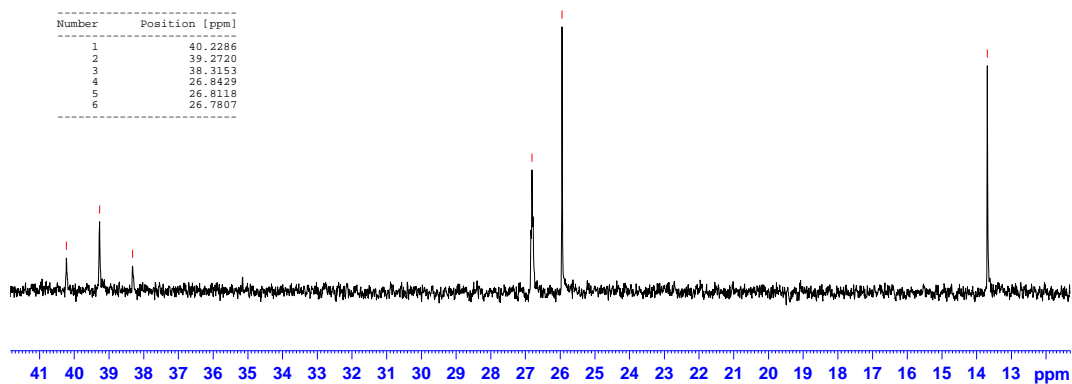
# 2011-09-14 16:12:21 -0300 Administrator@JBR-01  
# TOPSPIN Multiplet Table  
# C:/Bruker/TopSpin3.0/examdata/MAR28bis/2/pdata/1

1D TopSPIN Multiplet Table

| Number | Shift [ppm] | J [Hz]   | M | Connection | Identifier |
|--------|-------------|----------|---|------------|------------|
| 1      | 39.2720     | 120.3062 | 3 | J(1,0)     |            |
| 2      | 26.8118     | 3.9111   | 3 | J(2,0)     |            |

1D TopSPIN Multiplet Lines Table

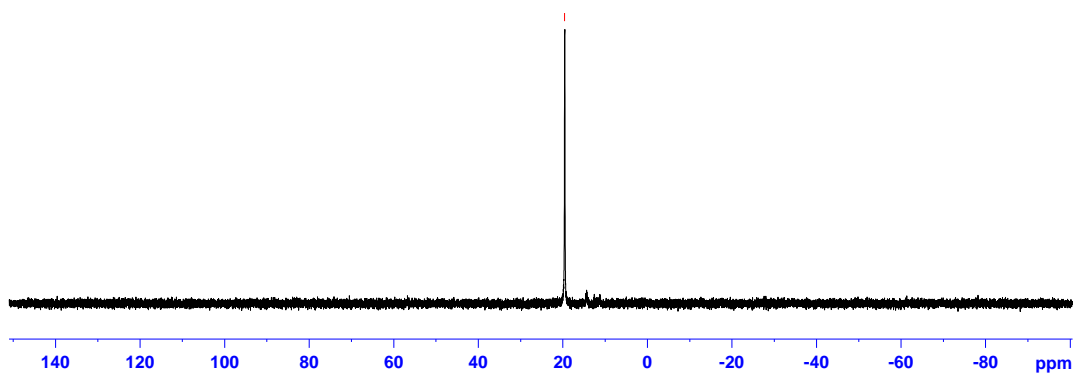
| Number | Position [ppm] |
|--------|----------------|
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| 2      | 39.2720        |
| 3      | 38.3153        |
| 4      | 26.8429        |
| 5      | 26.8118        |
| 6      | 26.7807        |



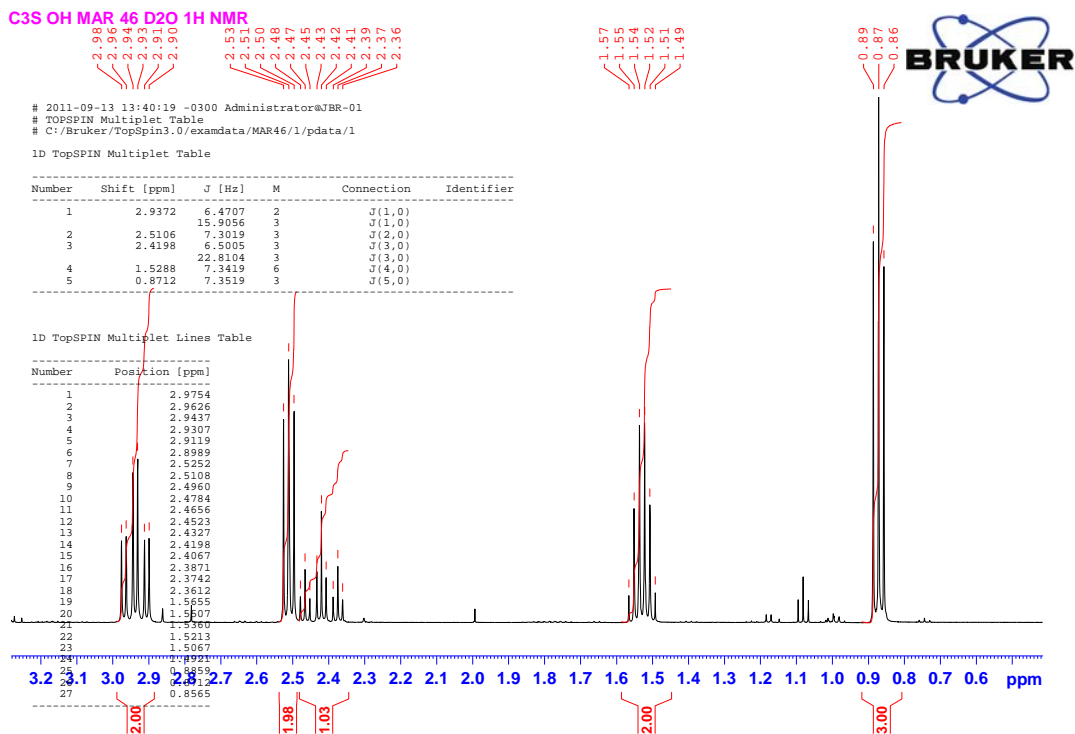
<sup>13</sup>C NMR spectrum of compound **31**.

C2S OH MAR 28 D2O 31P NMR

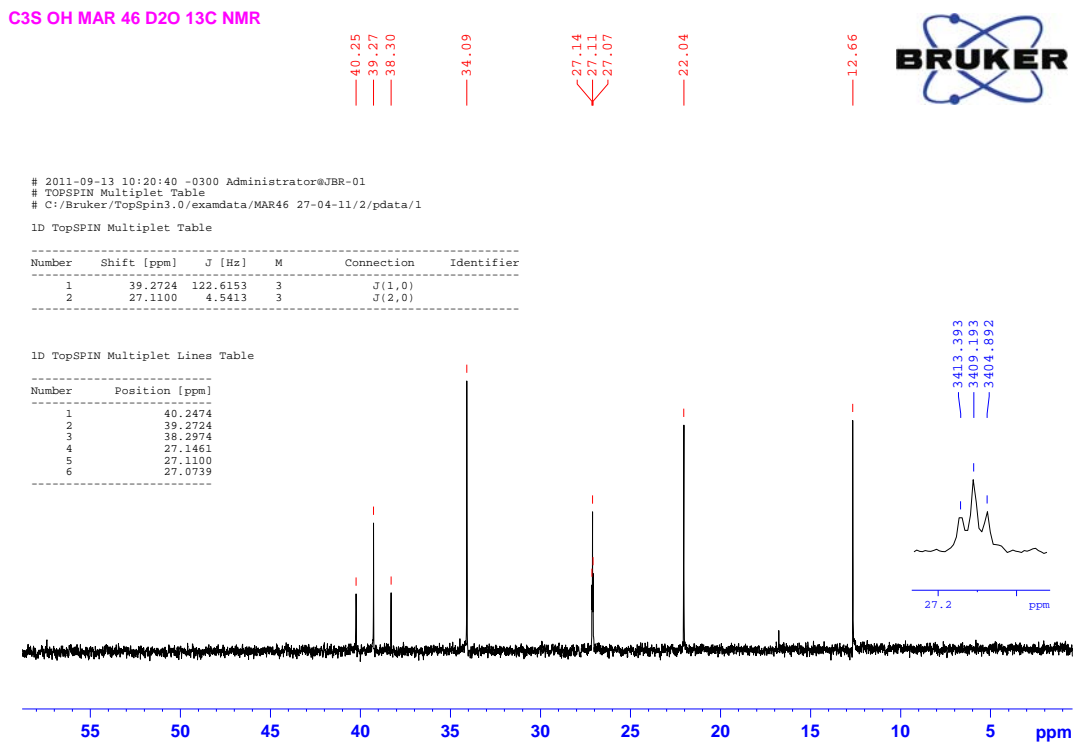
19.54



<sup>31</sup>P NMR spectrum of compound **31**.

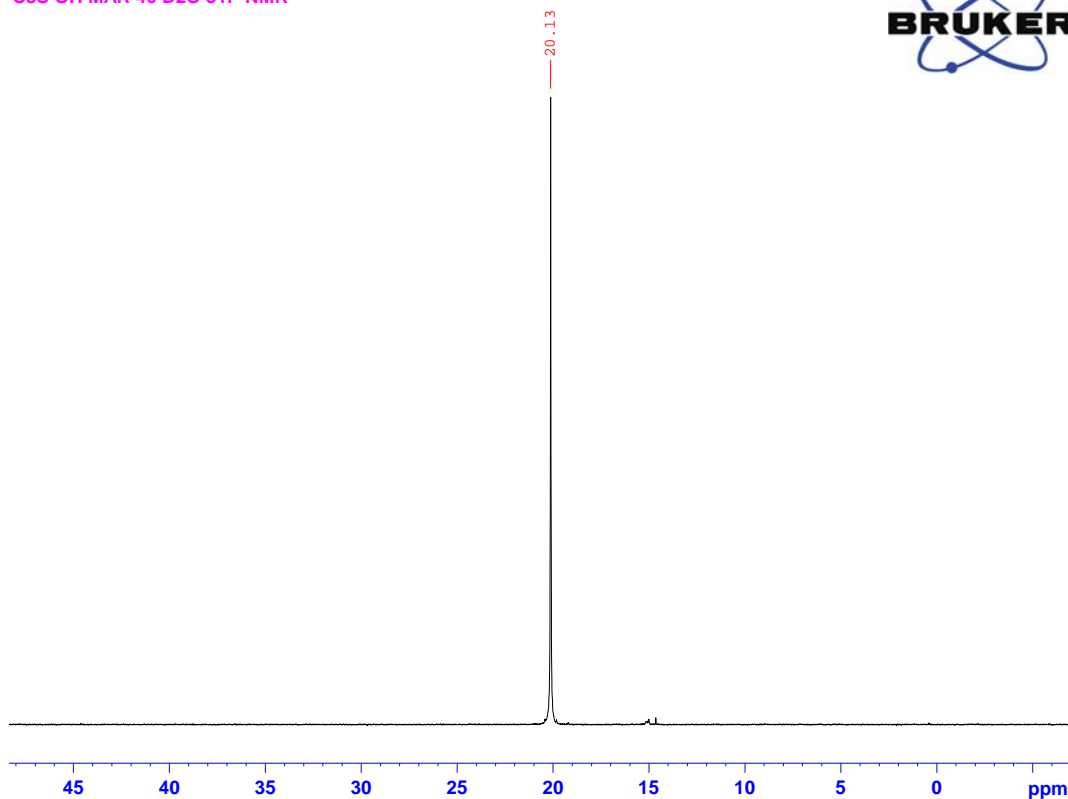


<sup>1</sup>H NMR spectrum of compound **32**.



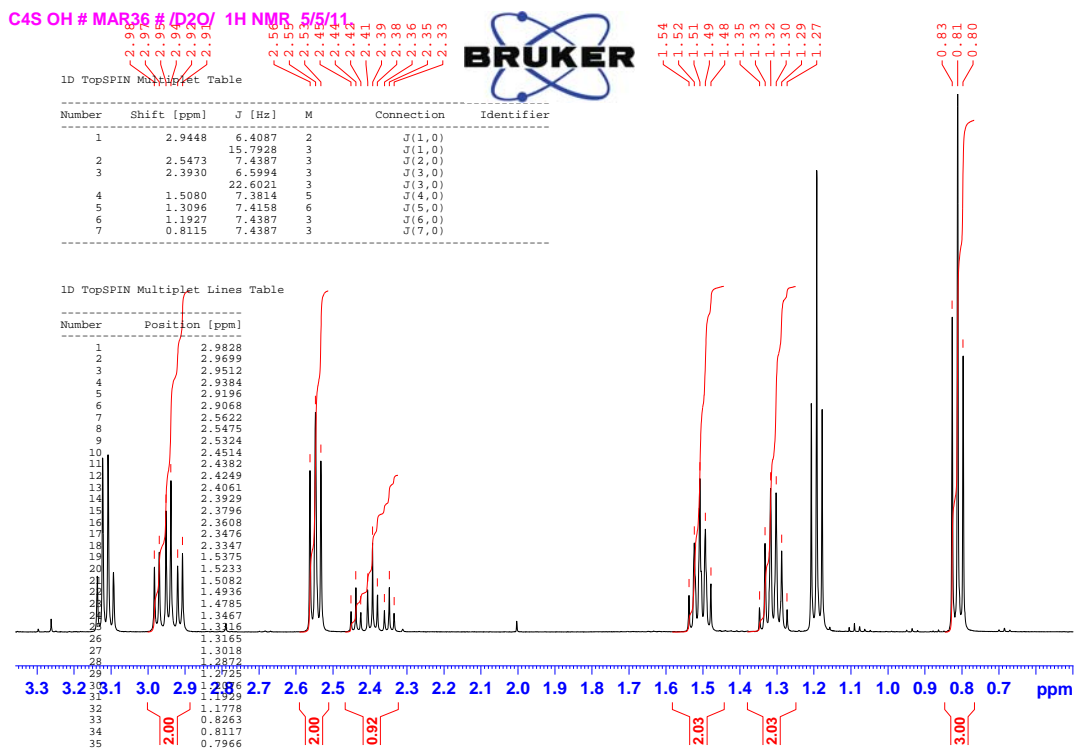
<sup>13</sup>C NMR spectrum of compound **32**.

C3S OH MAR 46 D2O 31P NMR



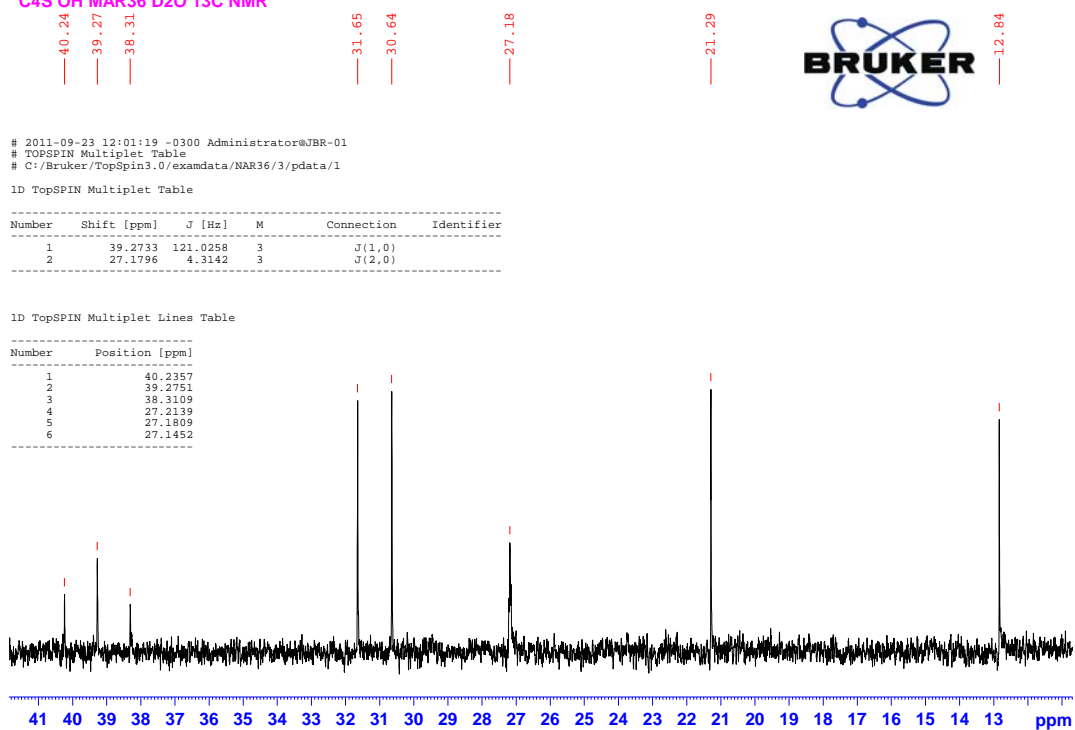
<sup>31</sup>P NMR spectrum of compound 32.

C4S OH # MAR36 # (D2O) 1H NMR 5/5/11



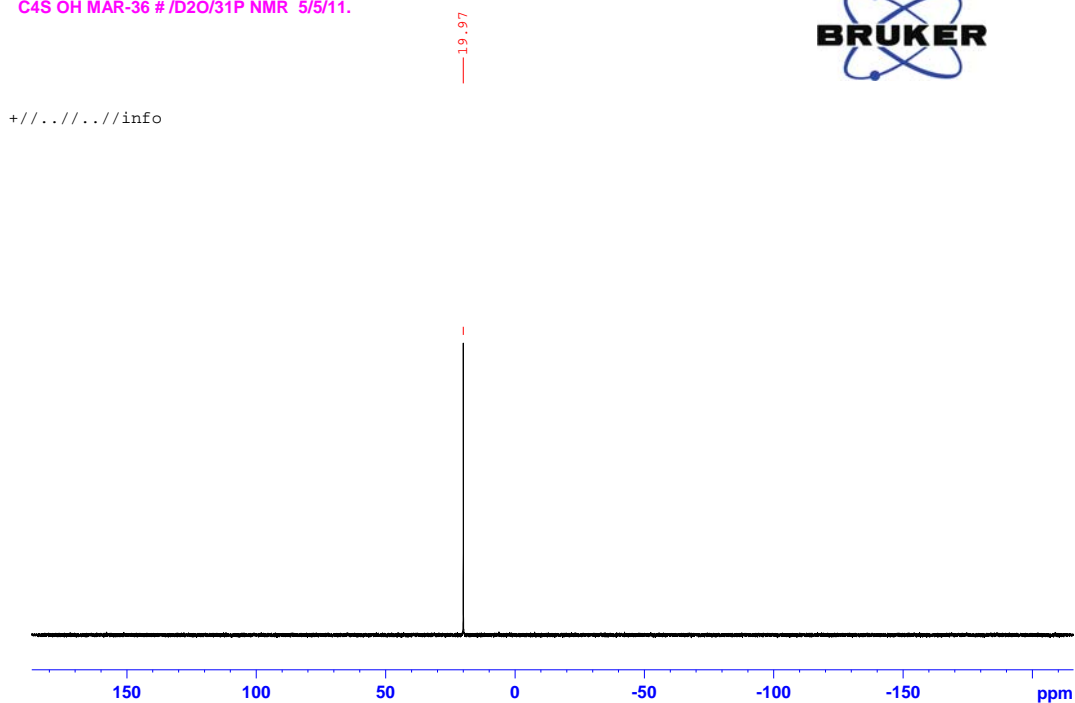
<sup>1</sup>H NMR spectrum of compound 33.

C4S OH MAR36 D2O 13C NMR



<sup>13</sup>C NMR spectrum of compound **33**.

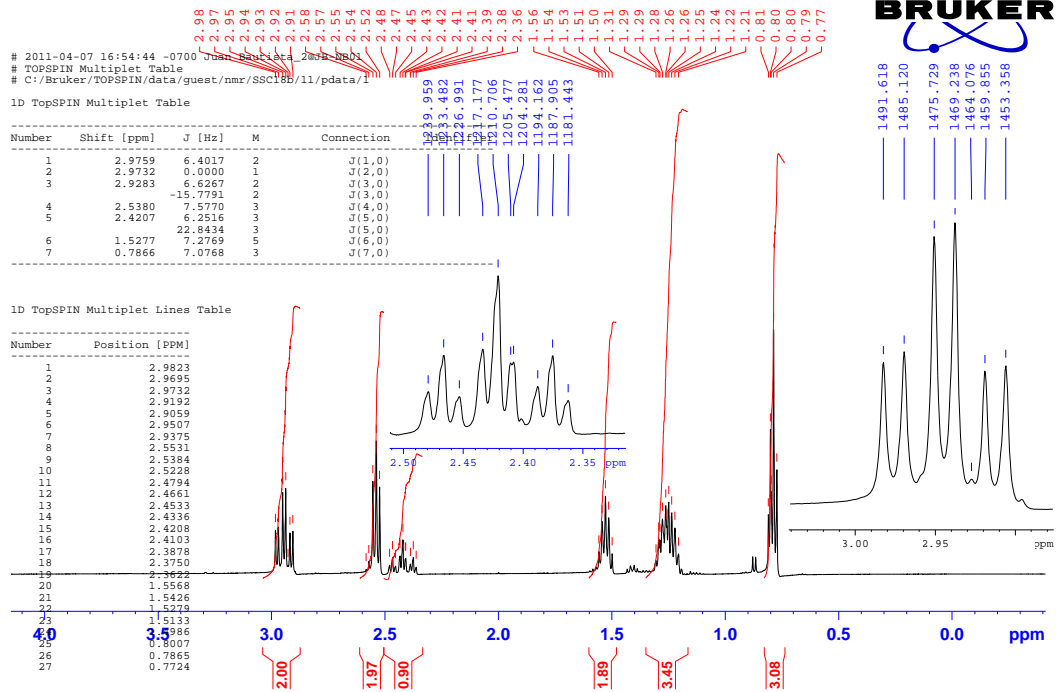
C4S OH MAR-36 # /D2O/31P NMR 5/5/11.



<sup>31</sup>P NMR spectrum of compound **33**.

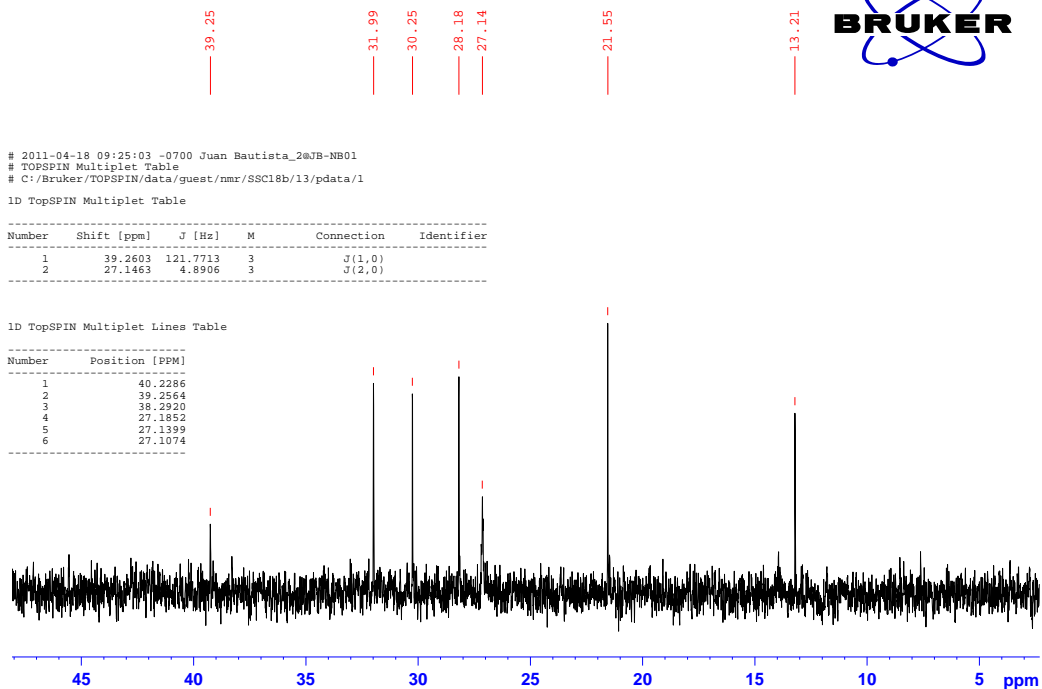


SSC18 S5 OH //D2O// 1H NMR 1/4/11.



<sup>1</sup>H NMR spectrum of compound 34.

S-5 OH # SSC 18 # //D2O//, 13C NMR 1/4/11.

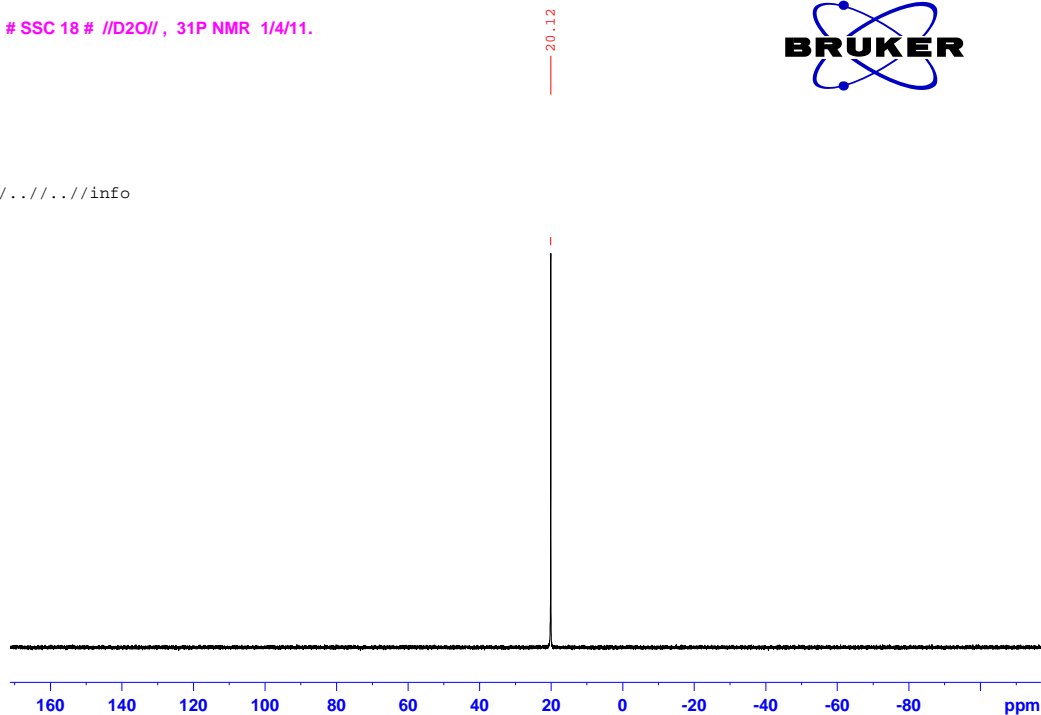


<sup>13</sup>C NMR spectrum of compound 34.

# SSC 18 # //D2O//, 31P NMR 1/4/11.

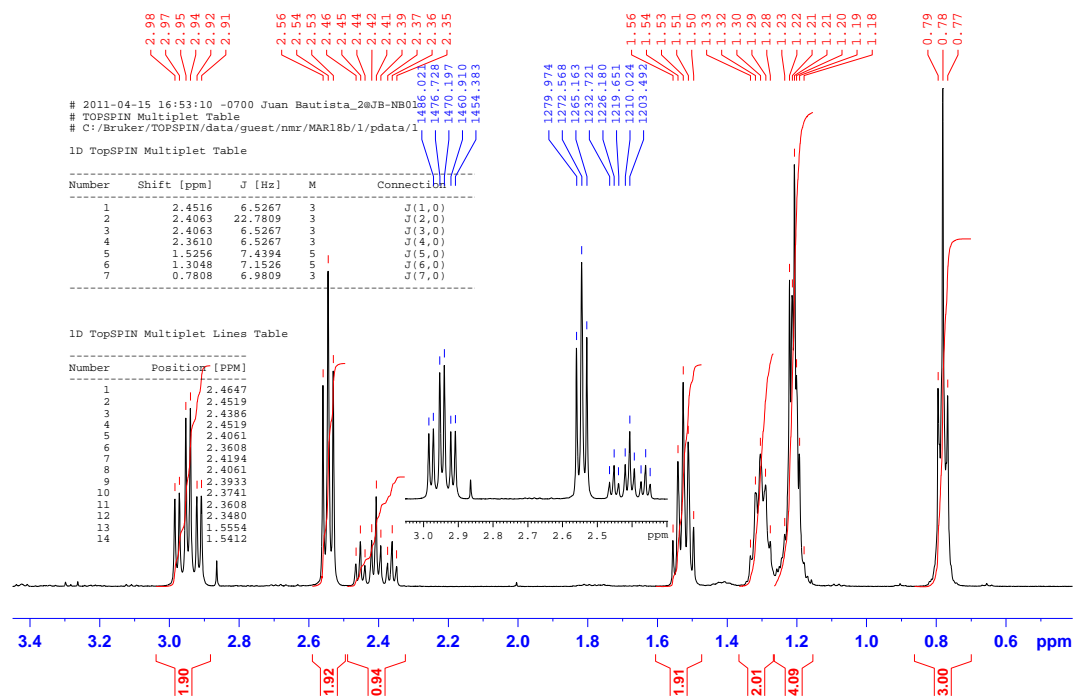


+//...//info



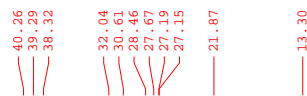
<sup>31</sup>P NMR spectrum of compound 34.

C6SCH2CHP2 # MAR 18 # //D2O//, 1H NMR 1/4/11.



<sup>1</sup>H NMR spectrum of compound 35.

MAR 18 13C NMR D2O



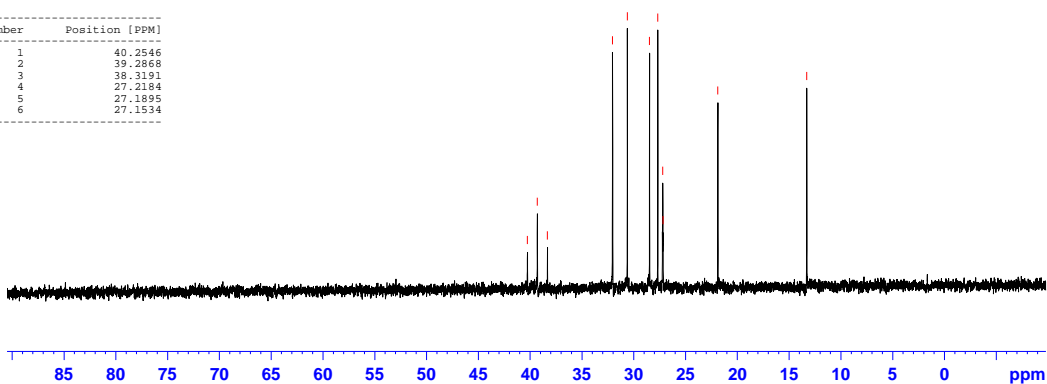
# 2011-05-05 16:18:37 -0700 Juan Bautista\_2@JB-NB01  
 # TOPSPIN Multiplet Table  
 # C:/Bruker/TOPSPIN/data/guest/nmr/MAR18c/2/pdata/1

ID TopSPIN Multiplet Table

| Number | Shift [ppm] | J [Hz]   | M | Connection | Identifier |
|--------|-------------|----------|---|------------|------------|
| 1      | 39.2868     | 121.7021 | 3 | J(1,0)     |            |
| 2      | 27.1859     | 4.0872   | 3 | J(2,0)     |            |

ID TopSPIN Multiplet Lines Table

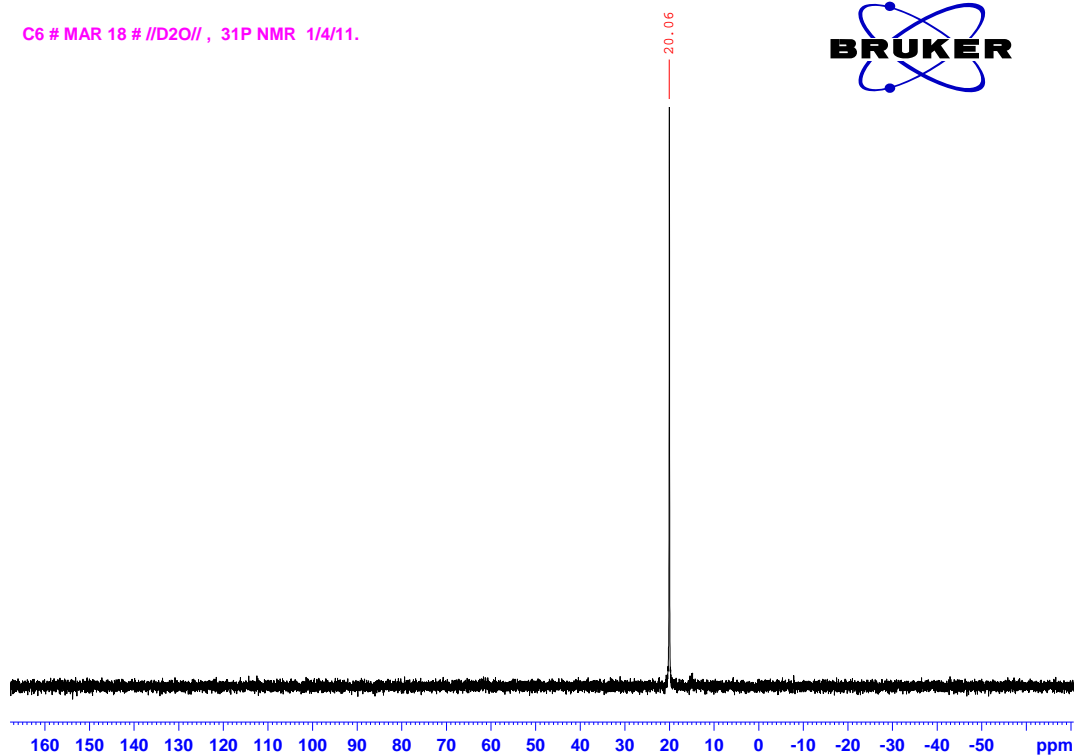
| Number | Position [PPM] |
|--------|----------------|
| 1      | 40.2546        |
| 2      | 39.2868        |
| 3      | 38.3191        |
| 4      | 27.2184        |
| 5      | 27.1895        |
| 6      | 27.1534        |



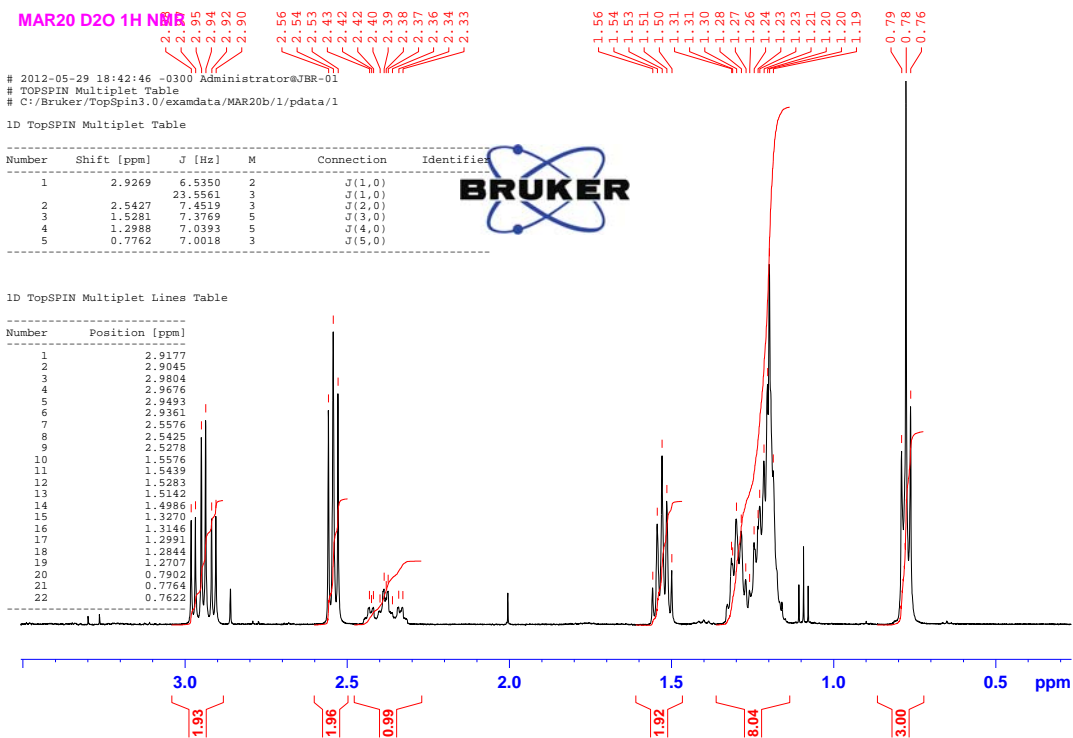
<sup>13</sup>C NMR spectrum of compound 35.

C6 # MAR 18 # //D2O// , 31P NMR 1/4/11.

20.06

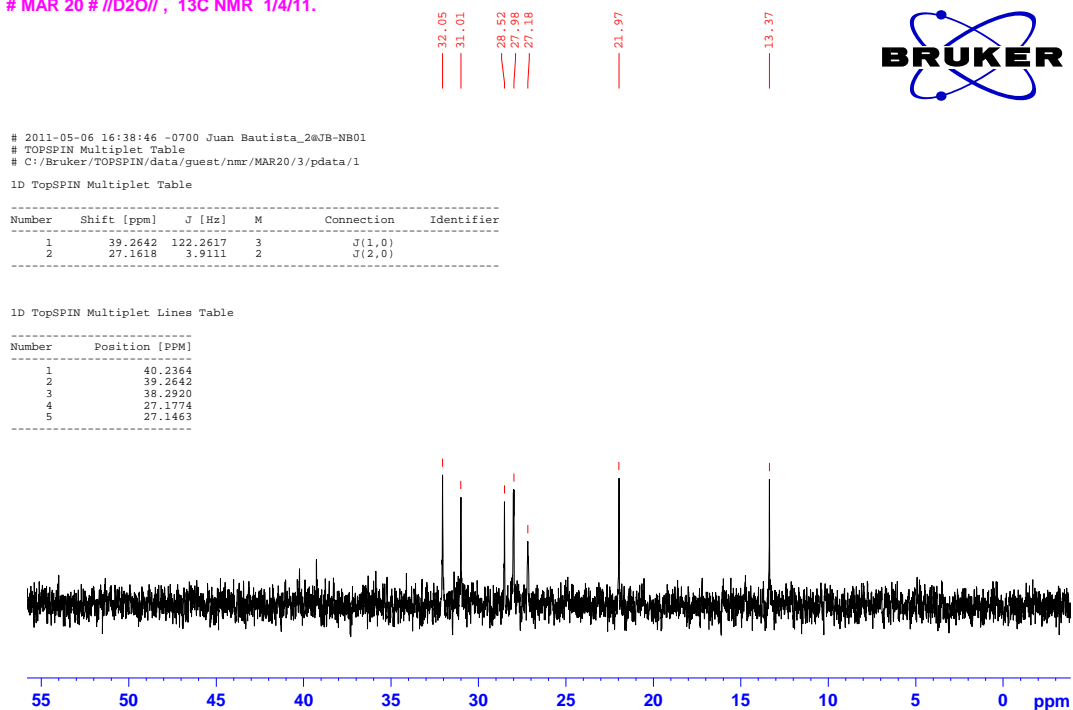


<sup>31</sup>P NMR spectrum of compound 35.

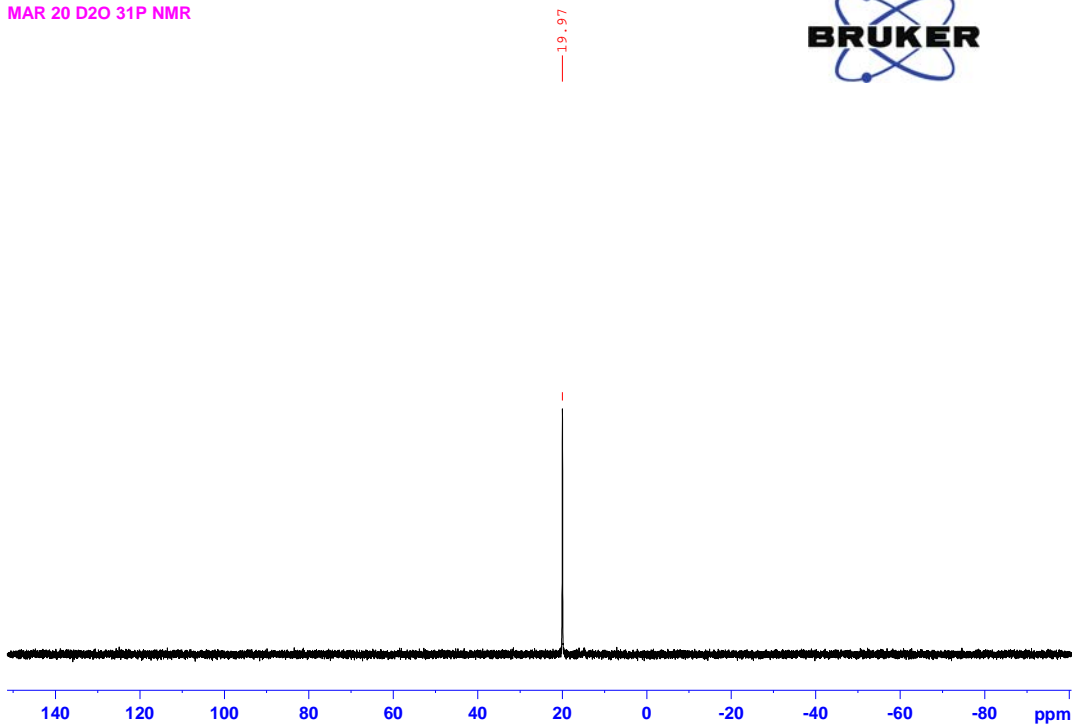


$^1\text{H}$  NMR spectrum of compound **36**.

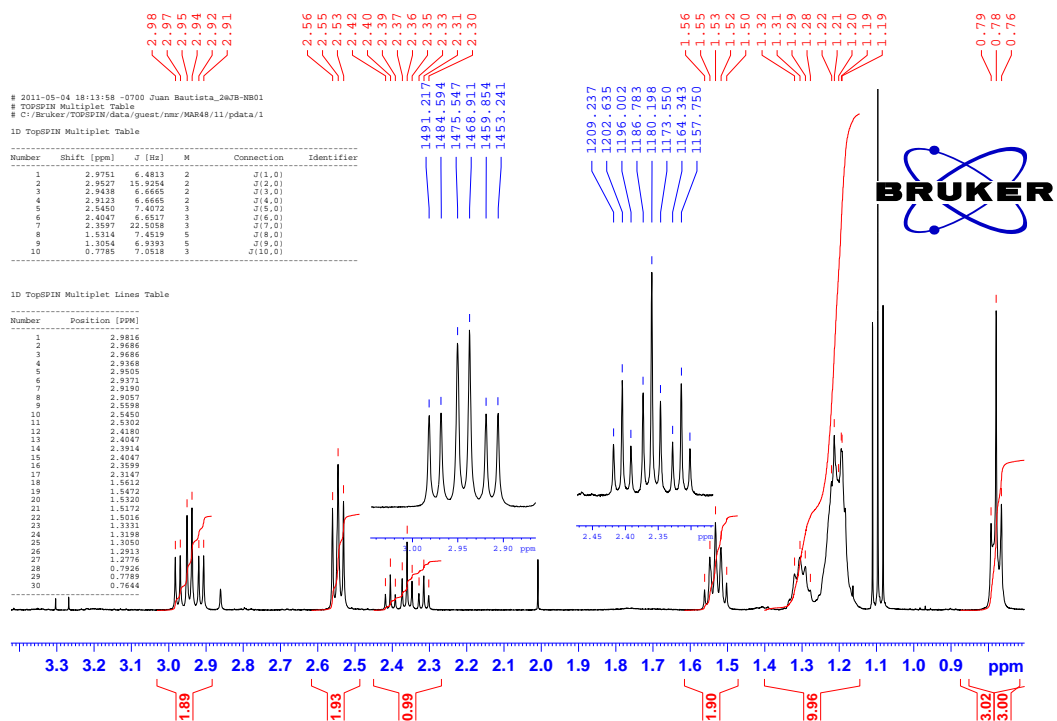
# MAR 20 # //D2O//,  $^{13}\text{C}$  NMR 1/4/11.



$^{13}\text{C}$  NMR spectrum of compound **36**.


 $^{31}\text{P}$  NMR spectrum of compound **36**.

MAR 48 # S-8 //D2O//, 1H NMR 3/5/11


 $^1\text{H}$  NMR spectrum of compound **37**.

C8S OH MAR 48 /D2O/ 13C NMR 3/5/11.

39.40

32.05

31.08

28.50

28.52

28.25

28.01

27.52

21.99

16.76



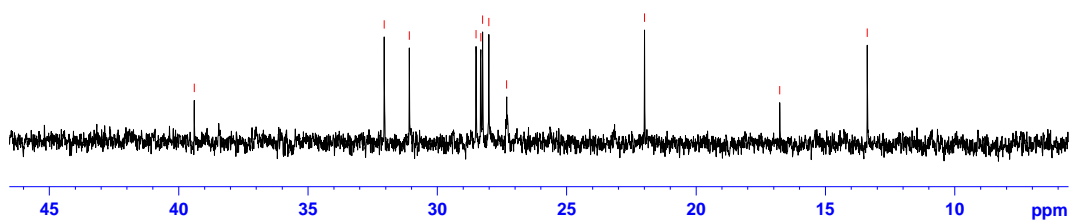
# 2011-09-28 17:50:06 -0300 Administrator@JBR-01  
# TOPSPIN Multiplet Table  
# C:/Bruker/TopSpin3.0/examdata/MAR48/3/pdata/1

ID TopSPIN Multiplet Table

| Number | Shift [ppm] | J [Hz]   | M | Connection | Identifier |
|--------|-------------|----------|---|------------|------------|
| 1      | 39.4042     | 119.3316 | 3 | J(1,0)     |            |
| 2      | 27.3174     | 3.9125   | 3 | J(2,0)     |            |

ID TopSPIN Multiplet Lines Table

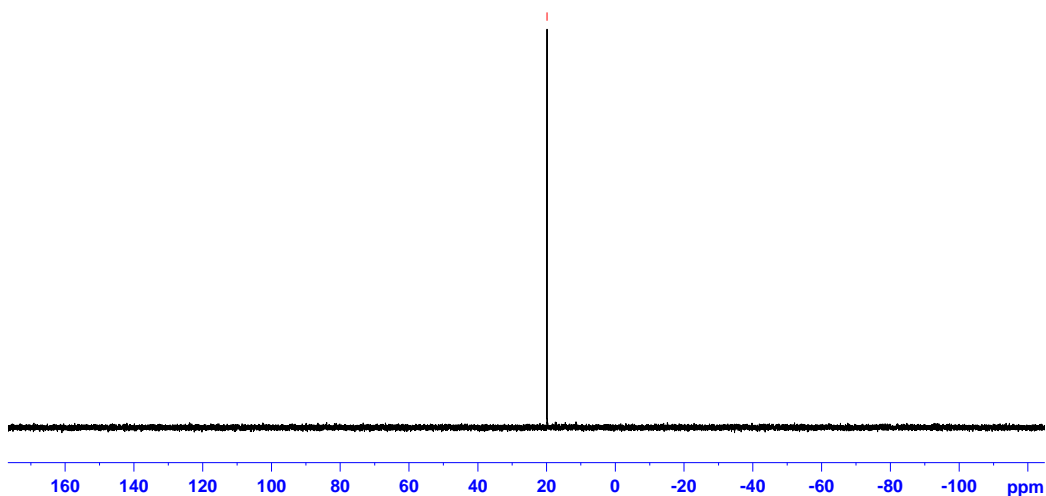
| Number | Position [ppm] |
|--------|----------------|
| 1      | 40.3531        |
| 2      | 39.3972        |
| 3      | 38.4553        |
| 4      | 27.3485        |
| 5      | 27.3174        |
| 6      | 27.2863        |



<sup>13</sup>C NMR spectrum of compound **37**.

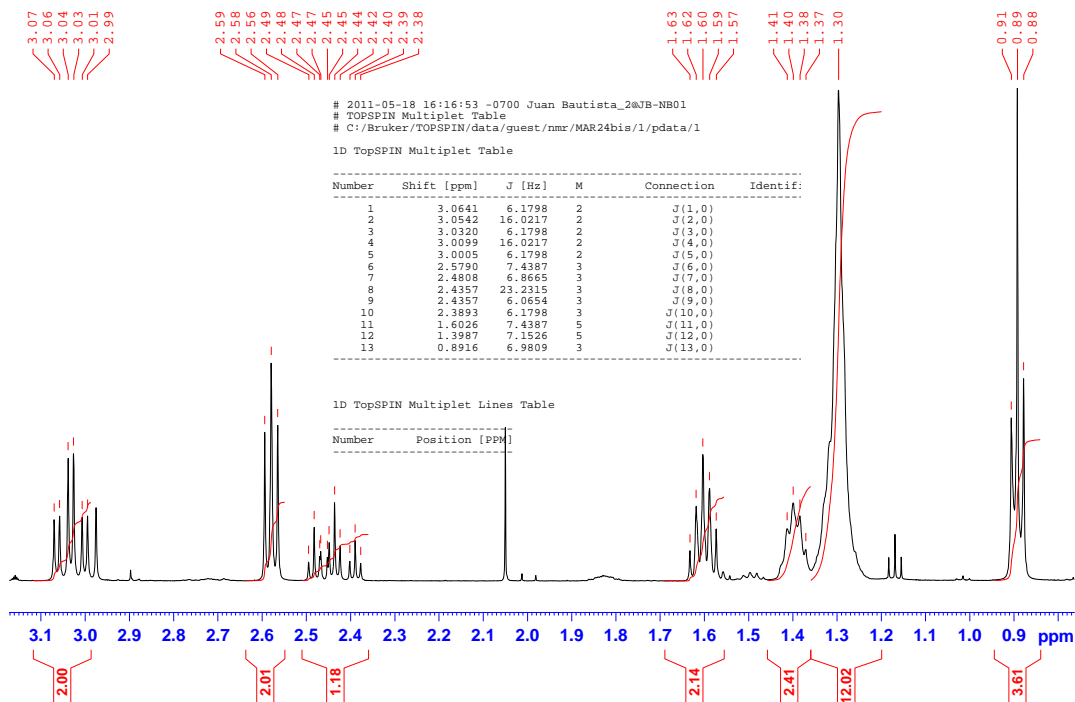
MAR 48 S8 OH //D2O//, 31P NMR 3/5/11.

19.80



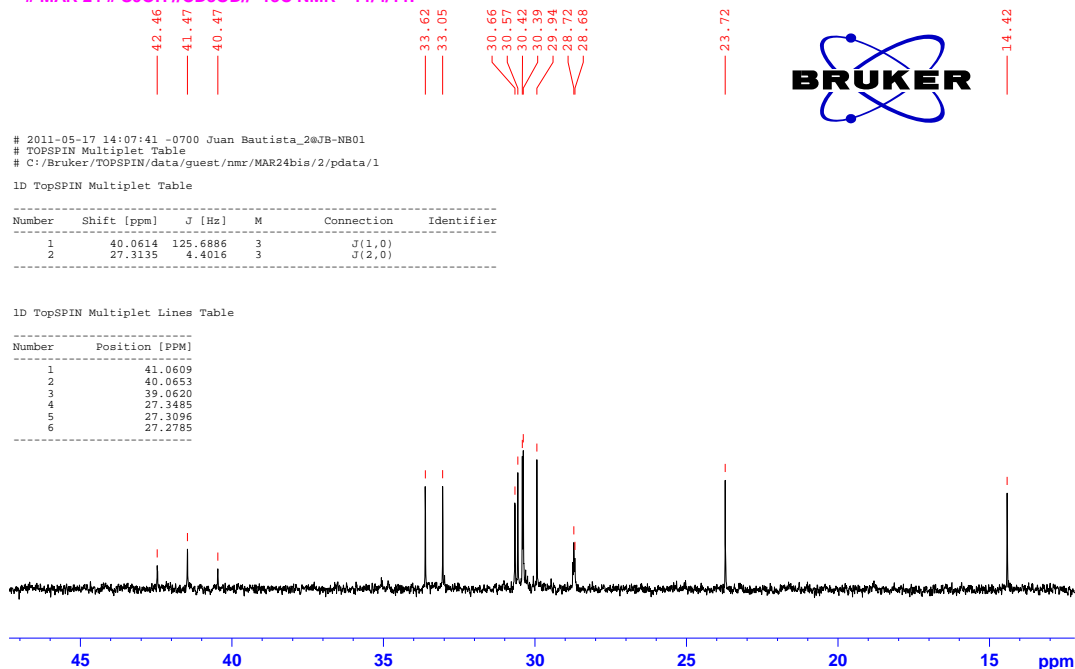
<sup>31</sup>P NMR spectrum of compound **37**.

MAR 24 S8OH/CD3OD/ 1H NMR 11/5/11.



<sup>1</sup>H NMR spectrum of compound 38.

# MAR 24 # S9OH //CD3OD// 13C NMR\* 11/4/11.



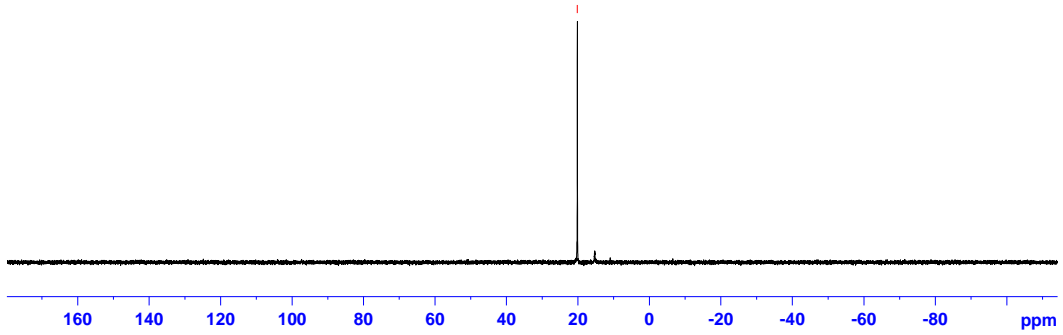
<sup>13</sup>C NMR spectrum of compound 38.

MAR 24 S)OH /CD3OD/ 31P NMR 3/5/11.



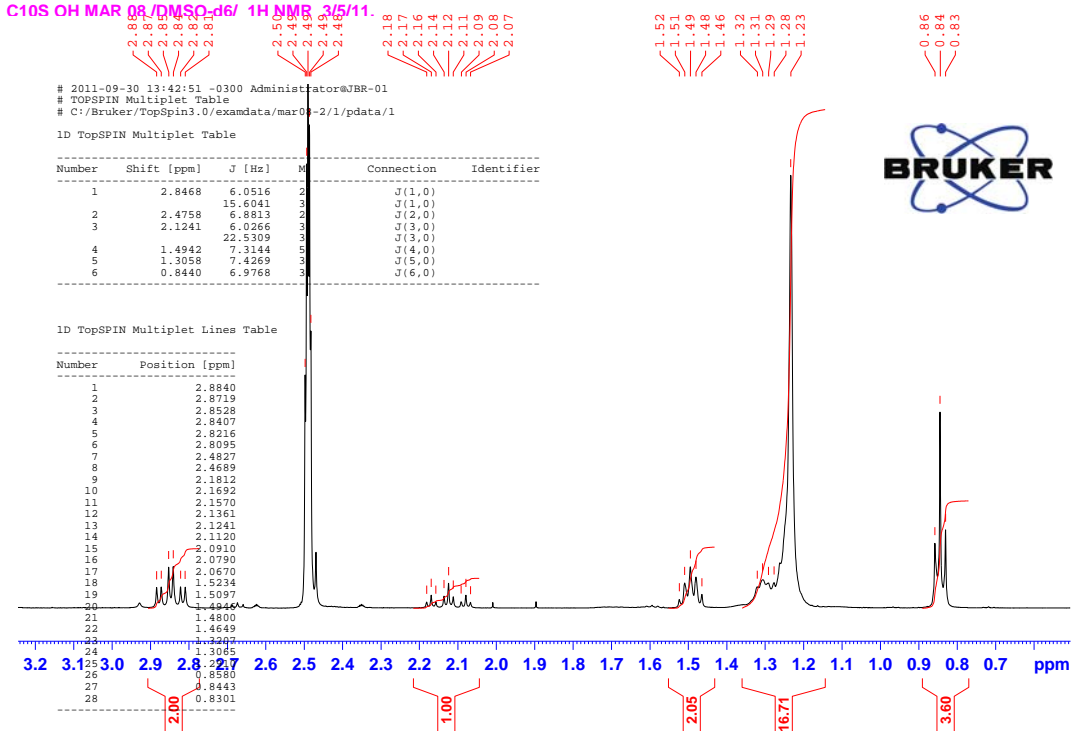
+//.////.//info

20.16



<sup>31</sup>P NMR spectrum of compound 38.

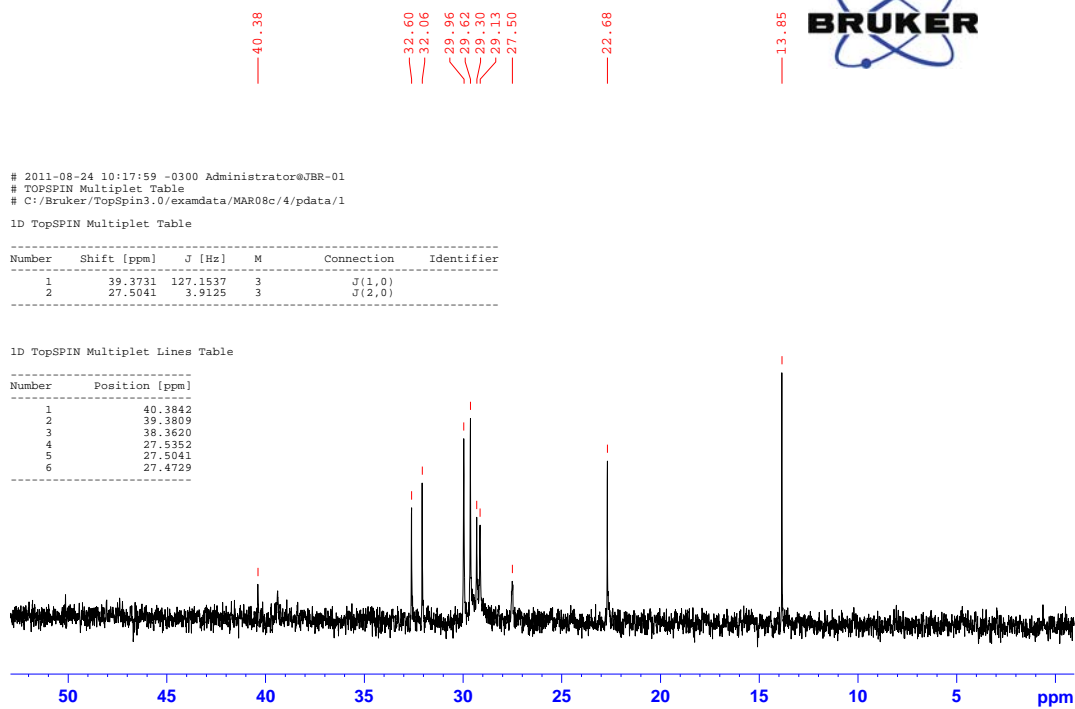
C10S OH MAR 08 /DMSO-d6/ 1H NMR 3/5/11.



<sup>1</sup>H NMR spectrum of compound 39.

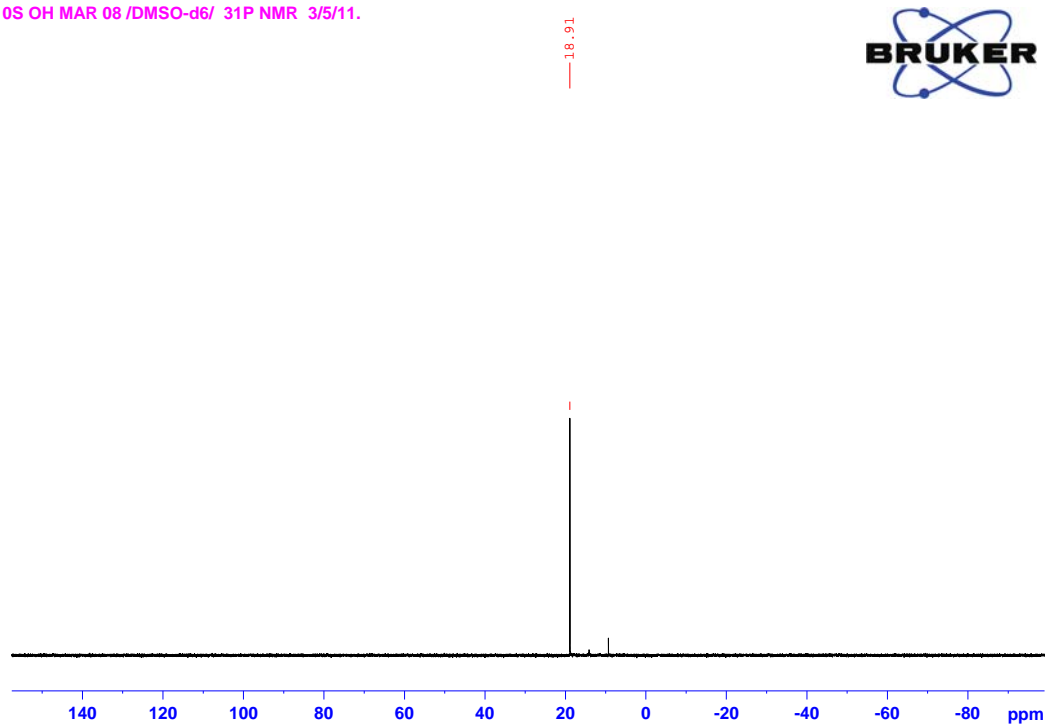


MAR 08 //D2O// <sup>13</sup>C NMR (C-10) 25/4/11.

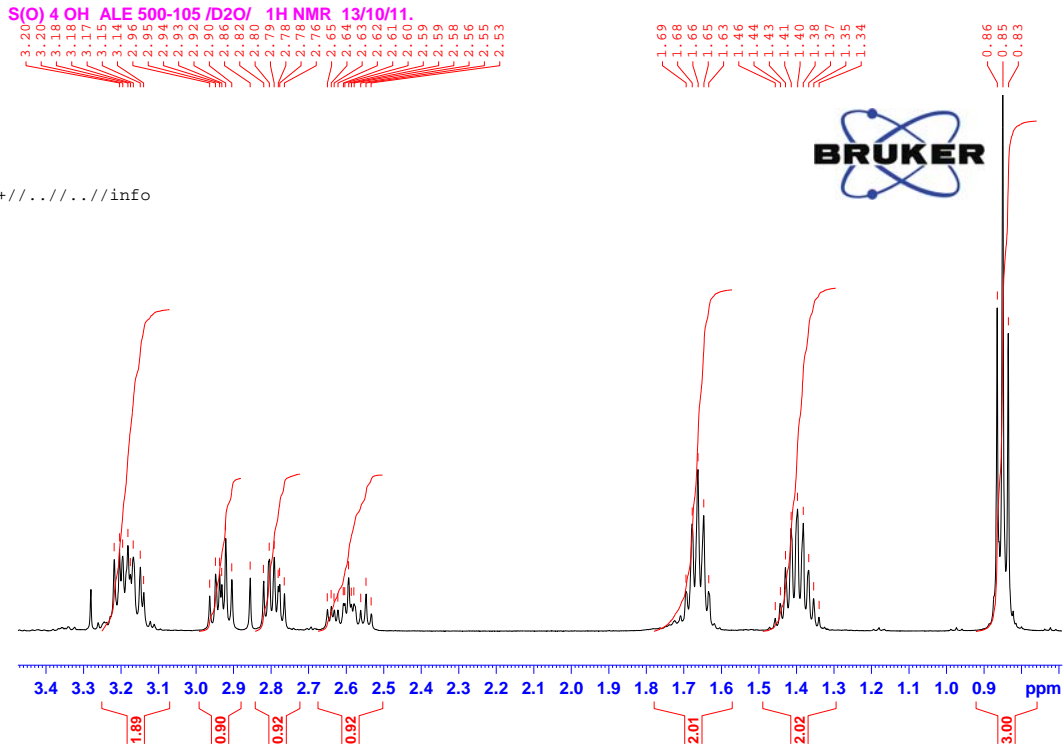


<sup>13</sup>C NMR spectrum of compound **39**.

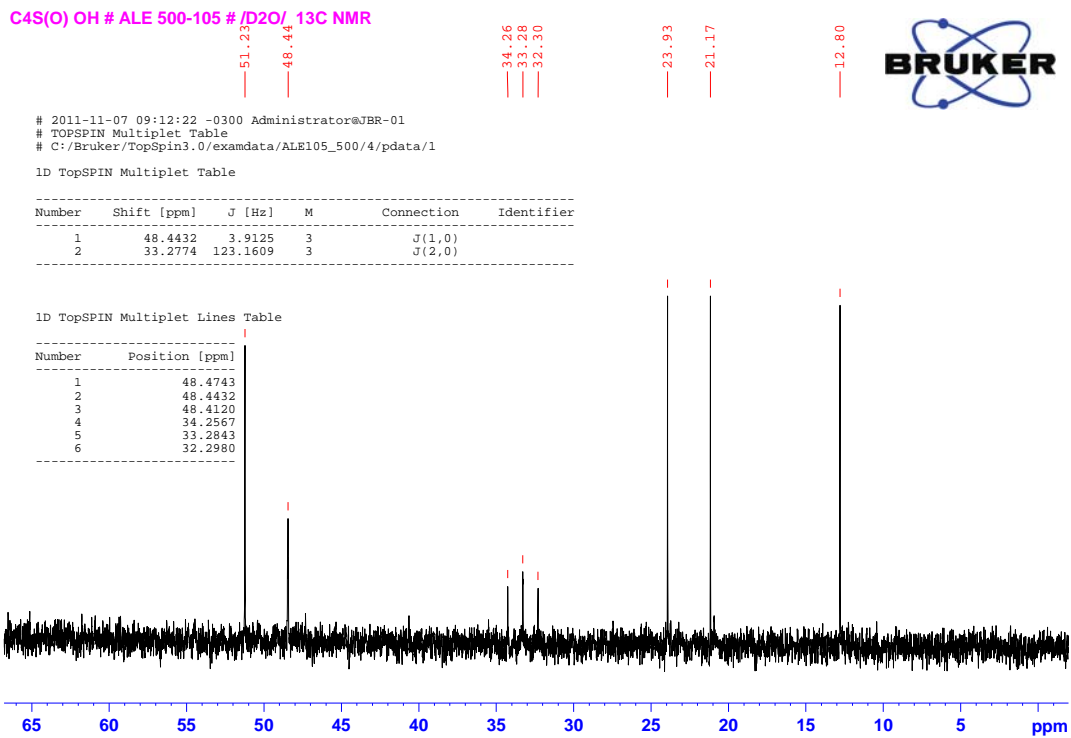
C10S OH MAR 08 /DMSO-d6/ <sup>31</sup>P NMR 3/5/11.



<sup>31</sup>P NMR spectrum of compound **39**.



$^1\text{H}$  NMR spectrum of compound **40**.

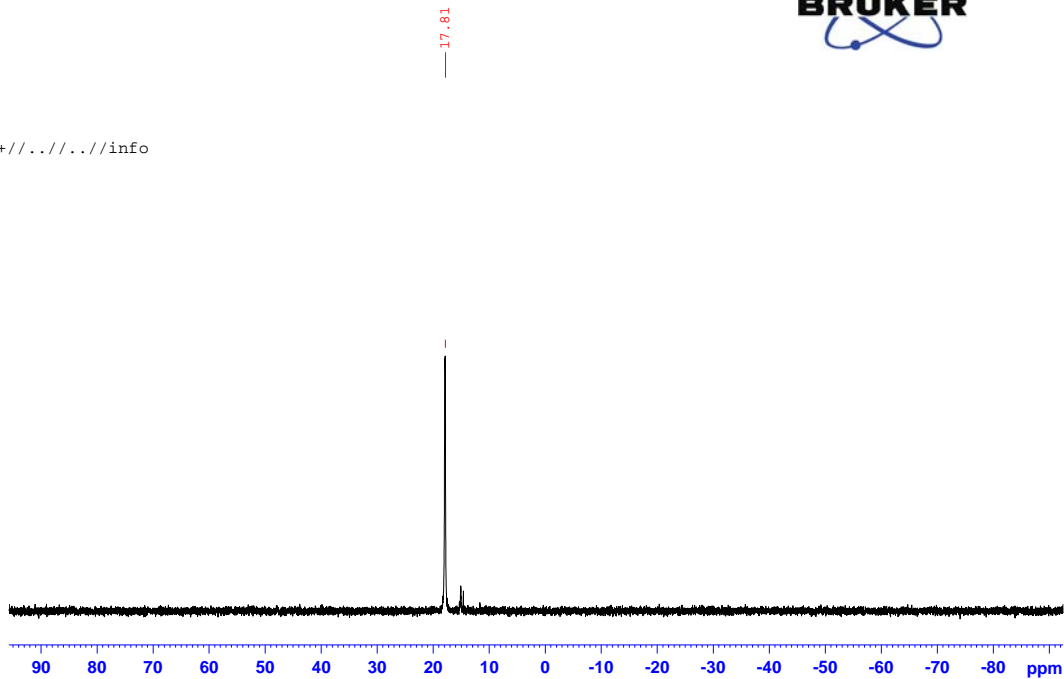


$^{13}\text{C}$  NMR spectrum of compound **40**.

S(O)4 OH ALE 500-105 /D2O/ 31P\* 13/10/11.



+//.....//info



<sup>31</sup>P NMR spectrum of compound 40.

S5(O) OH # ALE 107-500 # /D2O/ 1H NMR 27/10/11

3.10  
3.18  
3.17  
3.16  
3.15  
3.14  
3.13  
3.12  
3.11  
3.10  
3.09  
3.08  
3.07  
3.06  
3.05  
3.04  
3.03  
3.02  
3.01  
3.00  
2.99  
2.98  
2.97  
2.96  
2.95  
2.94  
2.93  
2.92  
2.91  
2.90  
2.89  
2.88  
2.87  
2.86  
2.85  
2.84  
2.83  
2.82  
2.81  
2.80  
2.79  
2.78  
2.77  
2.76

# 2012-02-28 20:23:52 -0300 Administrator@NBR-01  
# TOPSPIN Multiplet Table  
# C:/Bruker/TopSpin3.0/examdata/ALE107\_500C/2/pdata/1

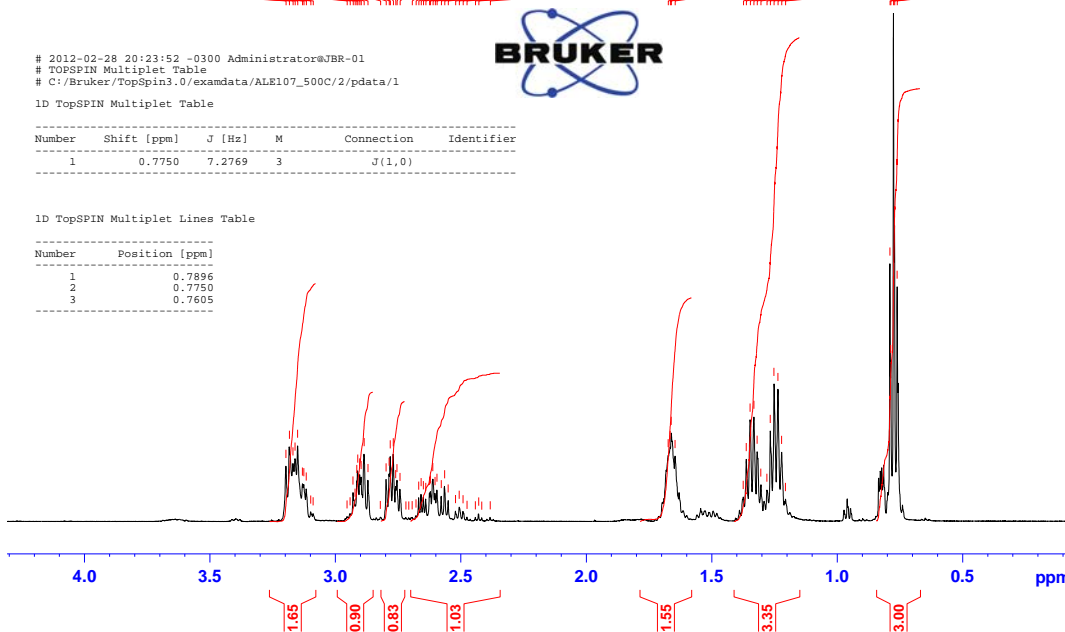


1D TopSPIN Multiplet Table

| Number | Shift [ppm] | J [Hz] | M | Connection | Identifier |
|--------|-------------|--------|---|------------|------------|
| 1      | 0.7750      | 7.2769 | 3 | J(1,0)     |            |

1D TopSPIN Multiplet Lines Table

| Number | Position [ppm] |
|--------|----------------|
| 1      | 0.7896         |
| 2      | 0.7750         |
| 3      | 0.7605         |



<sup>1</sup>H NMR spectrum of compound 41.

C5S(O) OH ALE 107 D2O 13C NMR

51.51  
48.26  
48.23  
48.20

34.10  
33.11  
32.12  
29.89

21.48  
21.45

12.98



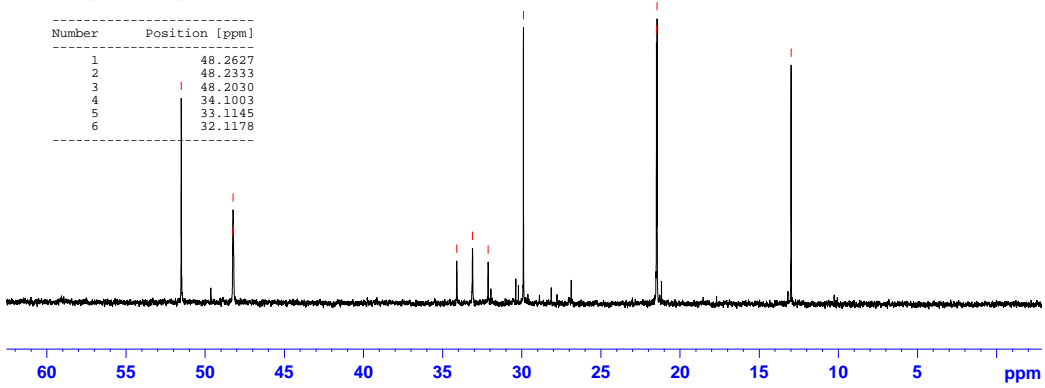
# 2011-11-07 11:46:41 \_0300 Administrator@JBR-01  
# TOPSPIN Multiplet Table  
# C:/Bruker/TopSpin3.0/examdata/ALE107\_500C/4/pdata/1

1D TopSPIN Multiplet Table

| Number | Shift [ppm] | J [Hz]   | M | Connection | Identifier |
|--------|-------------|----------|---|------------|------------|
| 1      | 48.2328     | 3.7539   | 3 | J(1,0)     |            |
| 2      | 33.1091     | 124.6589 | 3 | J(2,0)     |            |

1D TopSPIN Multiplet Lines Table

| Number | Position [ppm] |
|--------|----------------|
| 1      | 48.2627        |
| 2      | 48.2333        |
| 3      | 48.2030        |
| 4      | 34.1003        |
| 5      | 33.1145        |
| 6      | 32.1178        |



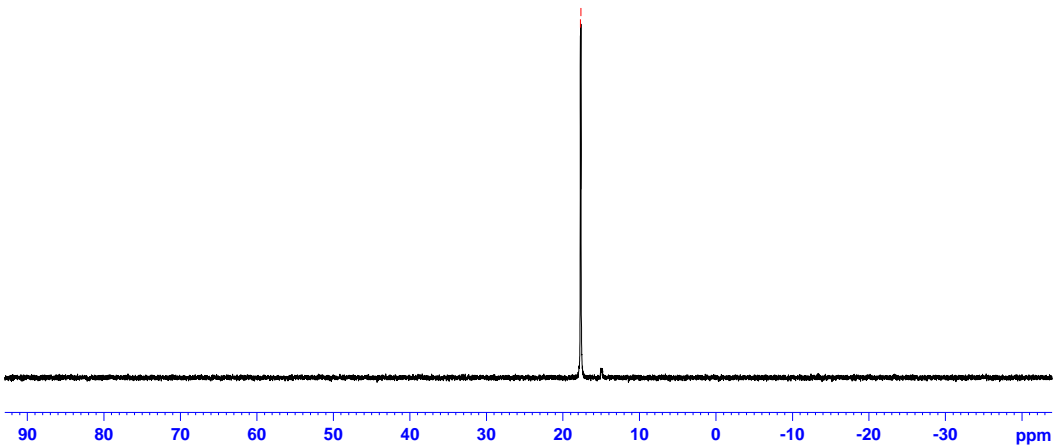
<sup>13</sup>C NMR spectrum of compound 41.

C5 S(O) OH D2O 31P NMR

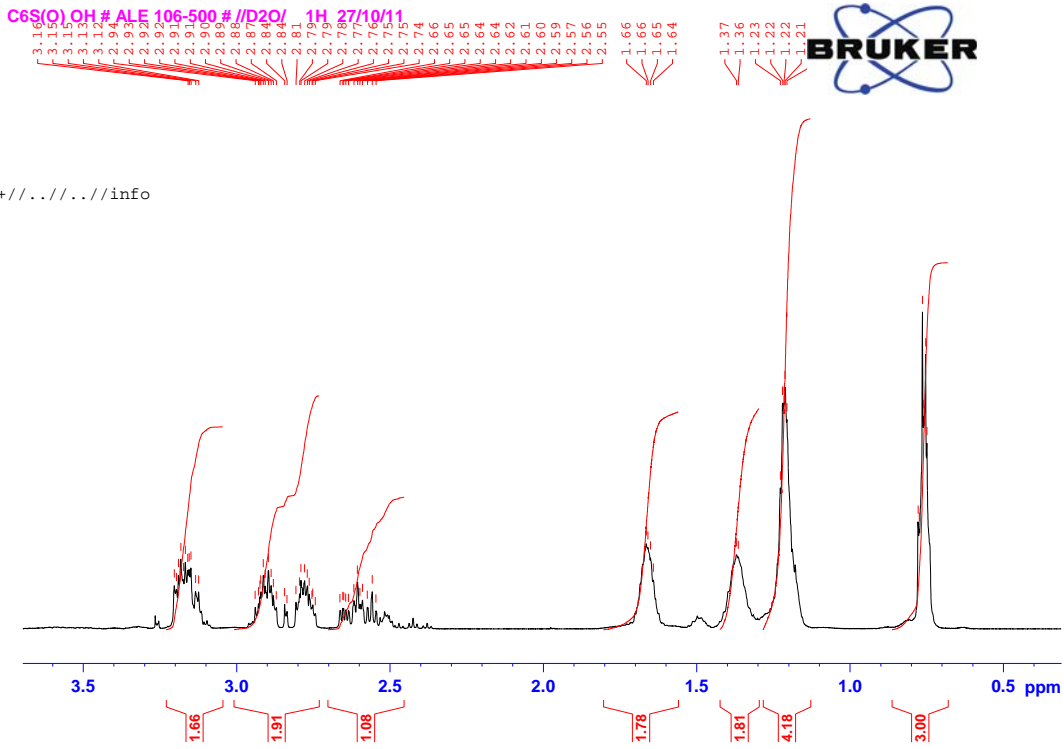
17.70  
17.64



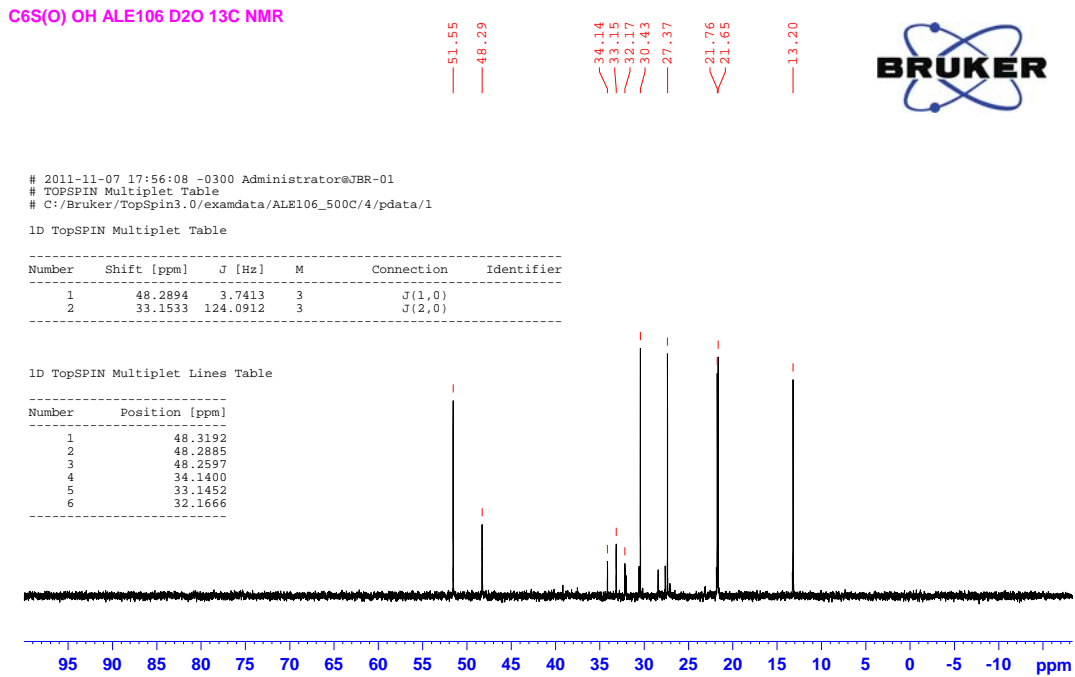
+//...//info



<sup>31</sup>P NMR spectrum of compound 41.

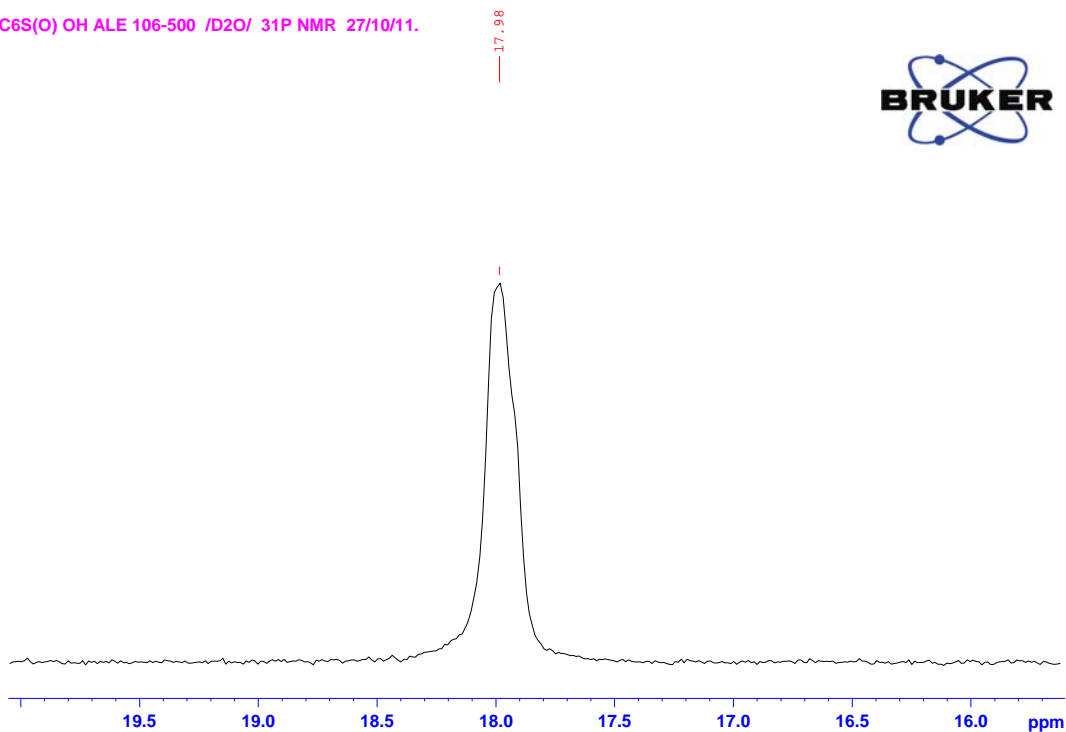


$^1\text{H}$  NMR spectrum of compound **42**.



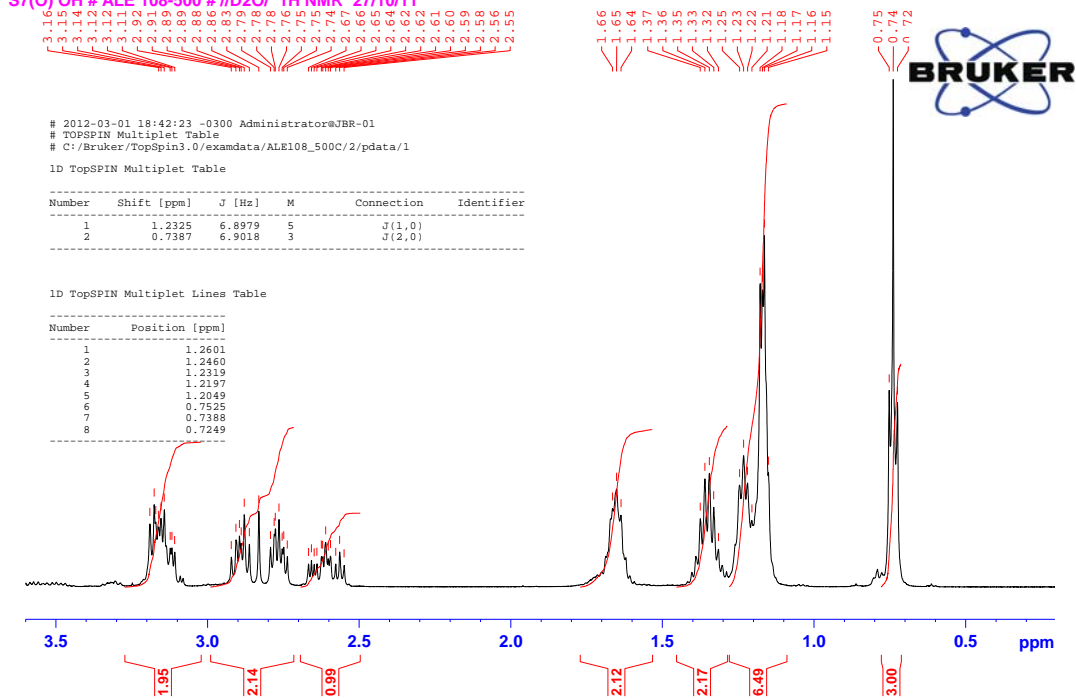
$^{13}\text{C}$  NMR spectrum of compound **42**.

C6S(O) OH ALE 106-500 /D2O/ 31P NMR 27/10/11.



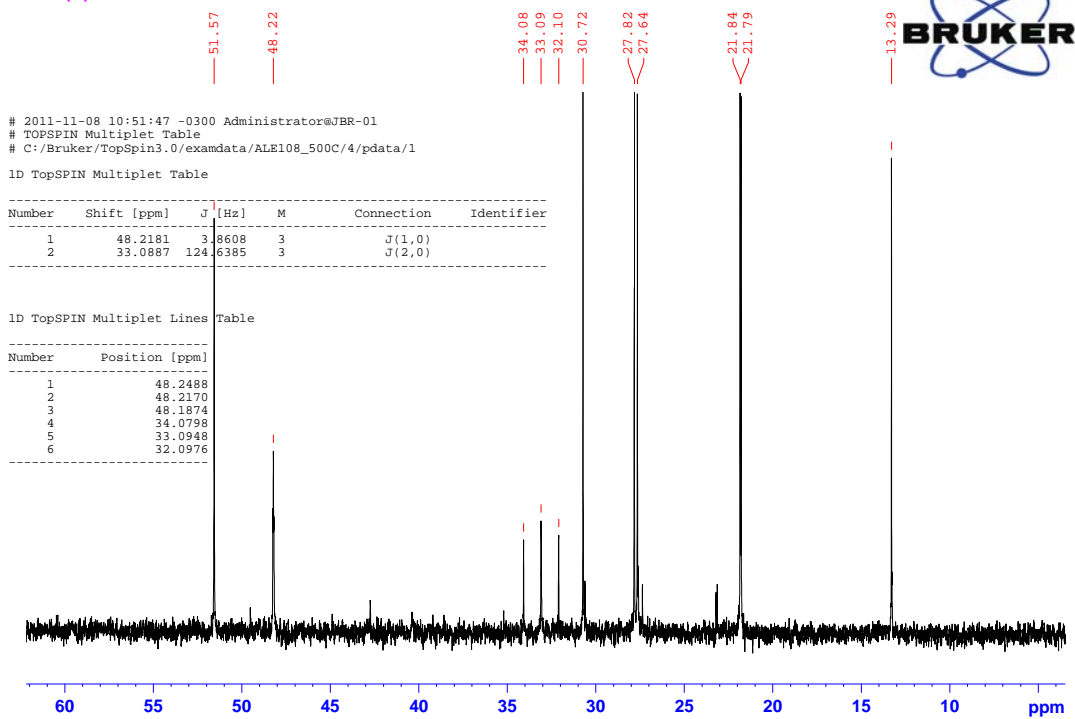
<sup>31</sup>P NMR spectrum of compound 42.

S7(O) OH # ALE 108-500 # /D2O/ 1H NMR 27/10/11



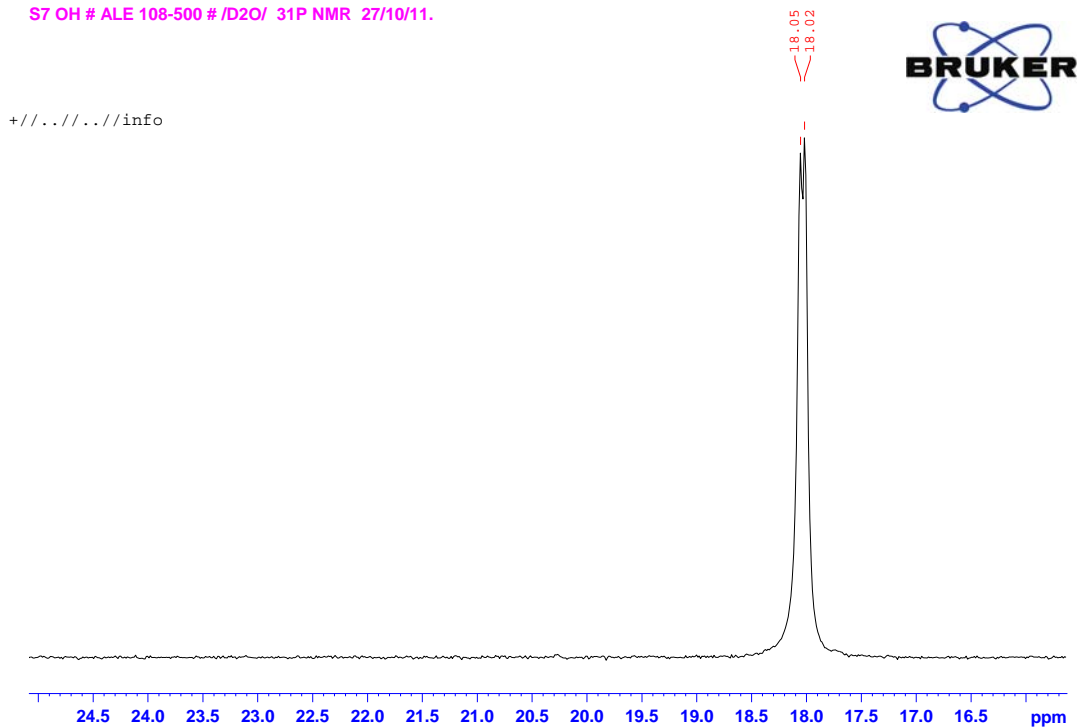
<sup>1</sup>H NMR spectrum of compound 43.

C7S(O) OH D2O 13C NMR



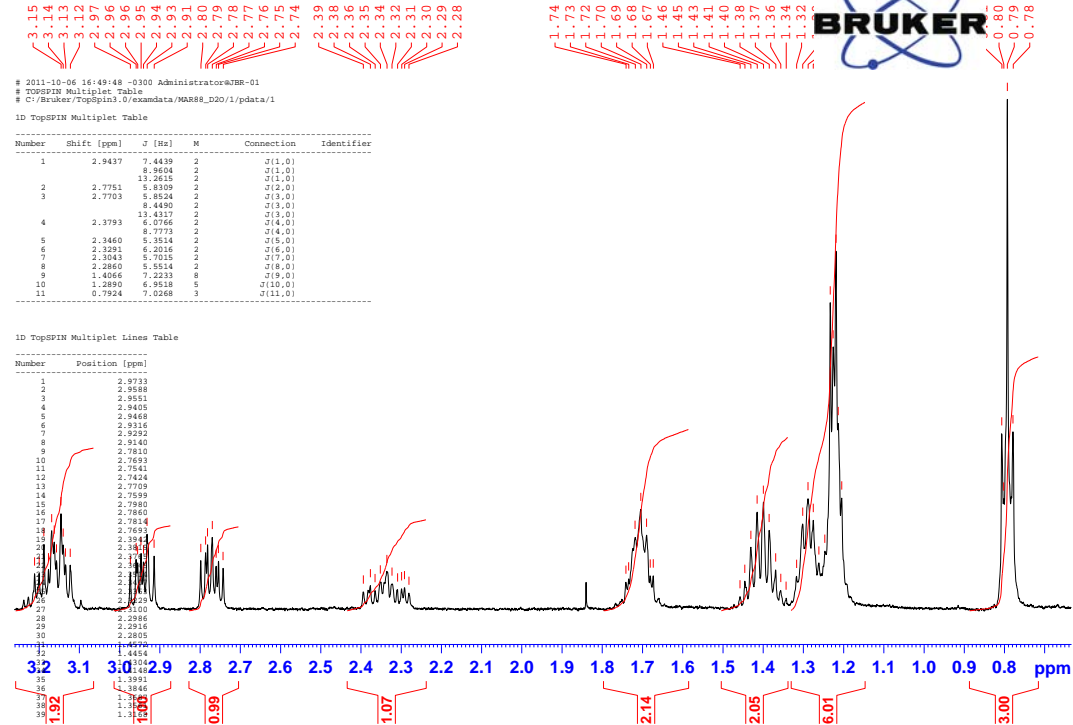
<sup>13</sup>C NMR spectrum of compound 43.

S7 OH # ALE 108-500 # /D2O/ 31P NMR 27/10/11.



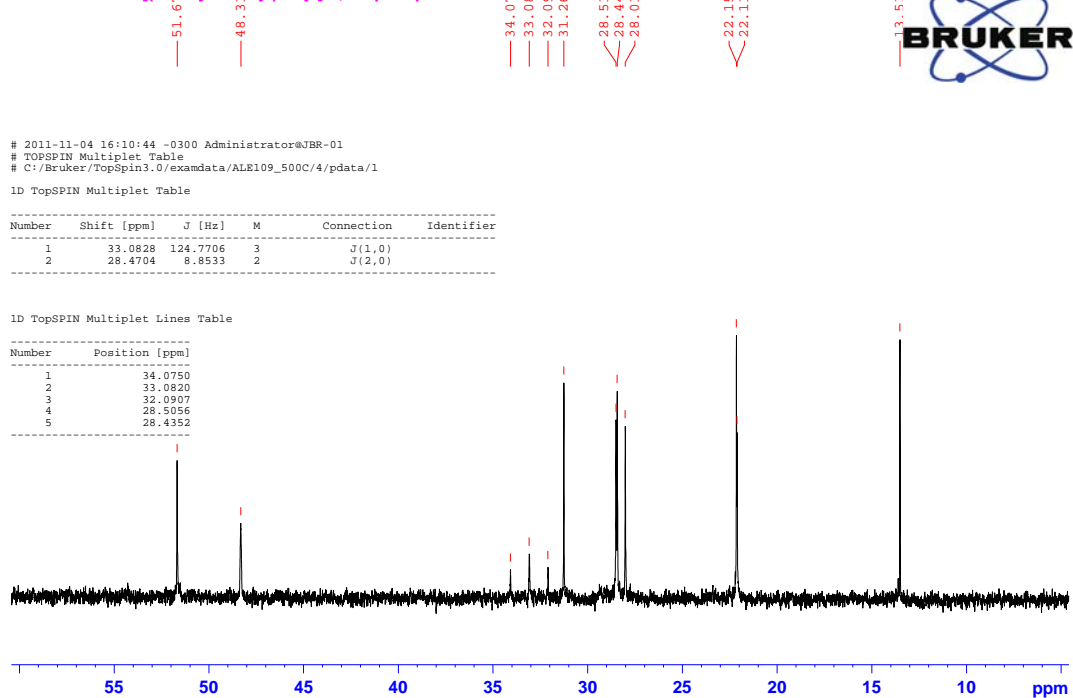
<sup>31</sup>P NMR spectrum of compound 43.

C8S(O) OH MAR 88 /D2O/ 1H NMR 11/8/11.



<sup>1</sup>H NMR spectrum of compound 44.

<sup>13</sup>C NMR D2O 1-[(n-Octylsulfinyl)ethyl]-1,1-biphosphonic



<sup>13</sup>C NMR spectrum of compound 44.



C8S(O) OH # MAR 88 # /D2O/ 31P NMR 11/8/11.



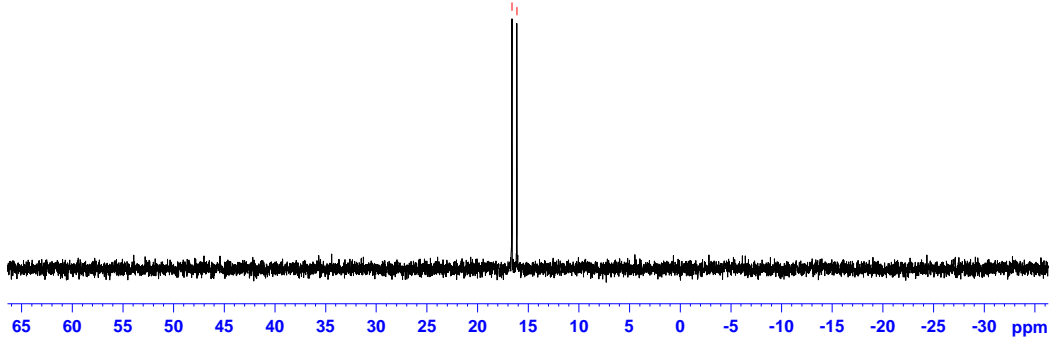
# 2011-10-06 14:17:35 -0300 Administrator@JBR-01  
# TOPSPIN Multiplet Table  
# C:/Bruker/TopSpin3.0/examdata/MAR88\_D2O/2/pdata/1

1D TopSPIN Multiplet Table

| Number | Shift [ppm] | J [Hz]  | M | Connection | Identifier |
|--------|-------------|---------|---|------------|------------|
| 1      | 16.3590     | 99.4060 | 2 | J(1,0)     |            |

1D TopSPIN Multiplet Lines Table

| Number | Position [ppm] |
|--------|----------------|
| 1      | 16.6045        |
| 2      | 16.1135        |

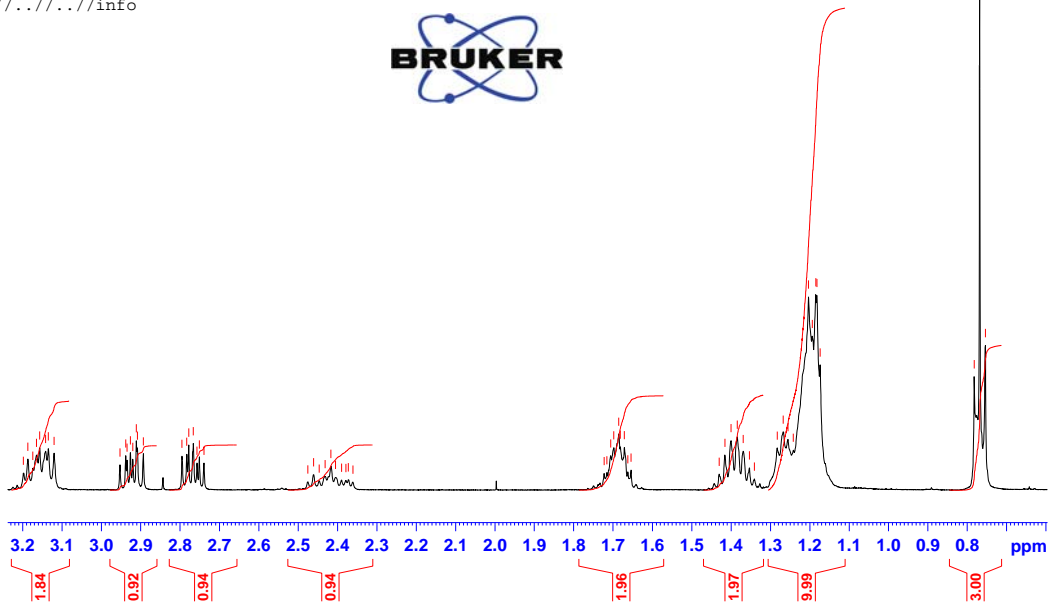


<sup>31</sup>P NMR spectrum of compound 44.

S(O)10 OH # MAR 122 # /D2O/ 1H NMR

3.13 3.12 2.95 2.94 2.93 2.92 2.91 2.81 2.79 2.78 2.77 2.76 2.75 2.74 2.48 2.46 2.45 2.43 2.42 2.41 2.39 2.38 2.37 2.36 1.72 1.71 1.70 1.69 1.68 1.67 1.66 1.65 1.43 1.42 1.40 1.38 1.37 1.35 1.34 1.28 1.27 1.26 1.24 1.20 1.19 1.18 1.17 0.78 0.77 0.75

+//.....//info



<sup>1</sup>H NMR spectrum of compound 45.

ALE216 C9S(O)CH2CHBP 13C NMR

51.83  
48.37  
34.02  
33.03  
32.00  
31.83  
31.73  
29.27  
28.51  
22.48  
13.71



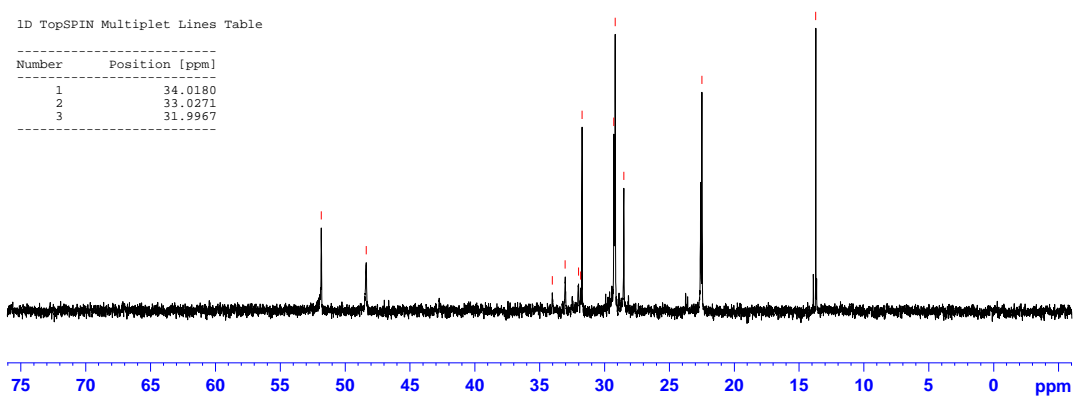
# 2012-08-17 17:29:22 -0300 Administrator@JBR-01  
# TOPSPIN Multiplet Table  
# C:/Bruker/TopSpin3.0/examdata/ALE216/39/pdata/1

1D TopSPIN Multiplet Table

| Number | Shift [ppm] | J [Hz]   | M | Connection | Identifier |
|--------|-------------|----------|---|------------|------------|
| 1      | 33.0074     | 127.0971 | 3 | J(1,0)     |            |

1D TopSPIN Multiplet Lines Table

| Number | Position [ppm] |
|--------|----------------|
| 1      | 34.0180        |
| 2      | 33.0271        |
| 3      | 31.9967        |



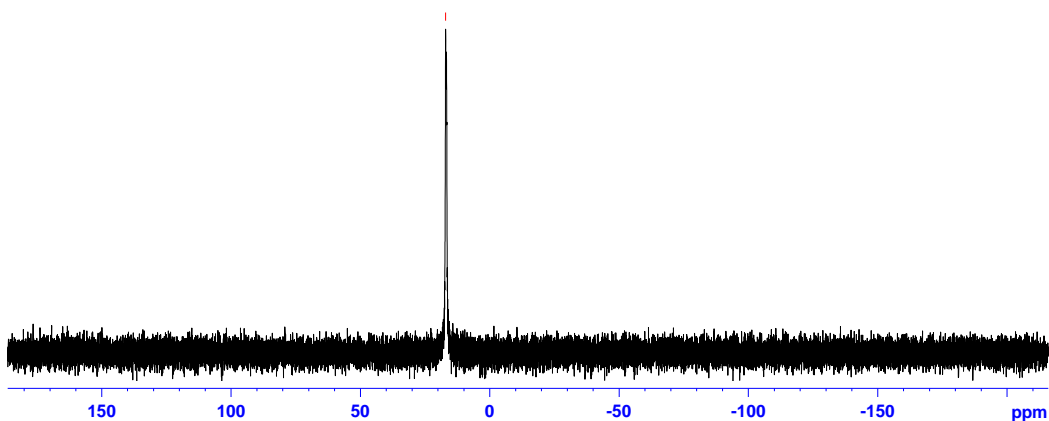
<sup>13</sup>C NMR spectrum of compound 45.

S(O)10 OH # MAR 122 # /D2O/ 31P NMR 8/8/11.

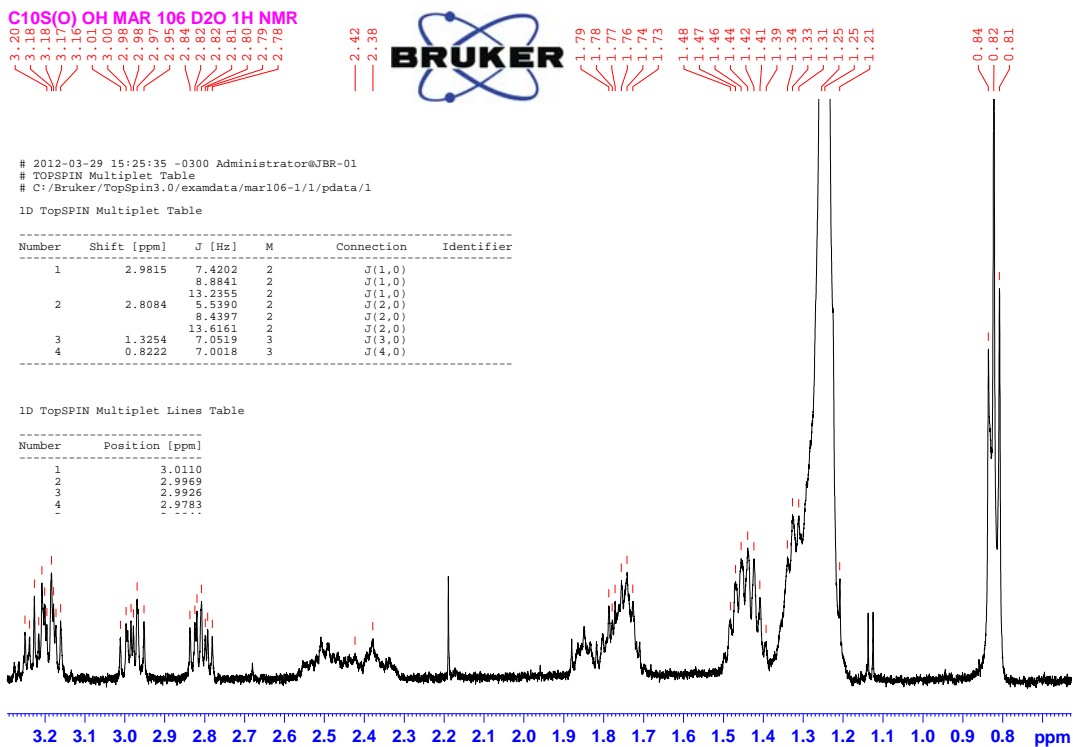
16.99



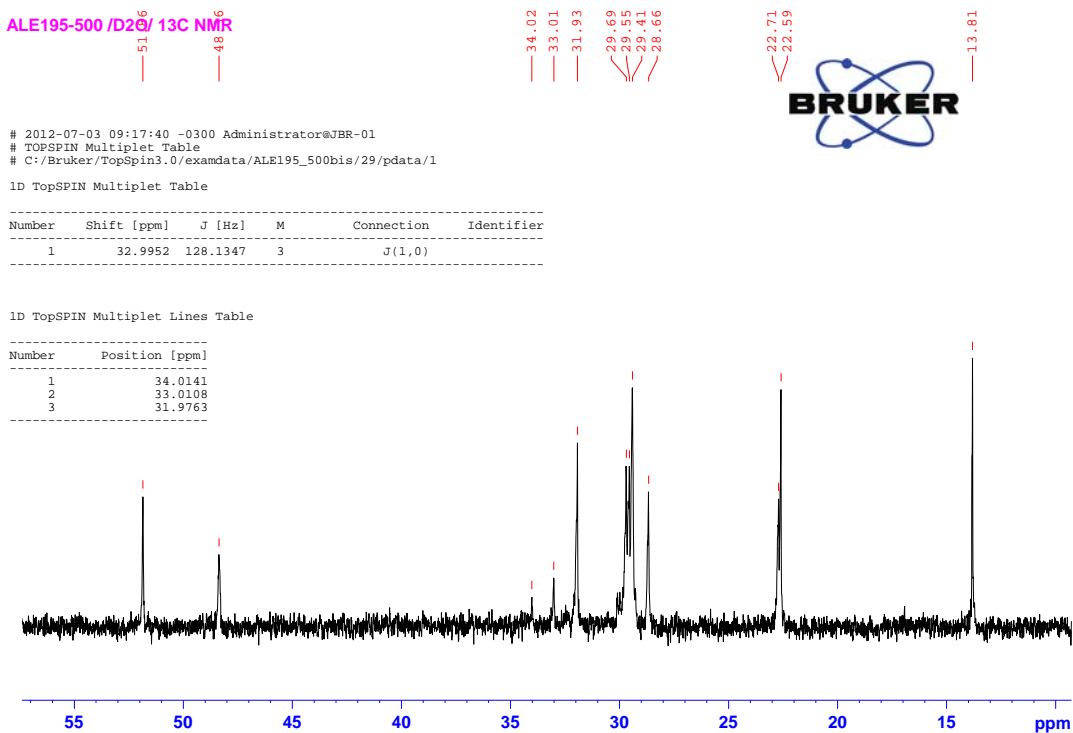
+//.////.//info



<sup>31</sup>P NMR spectrum of compound 45.

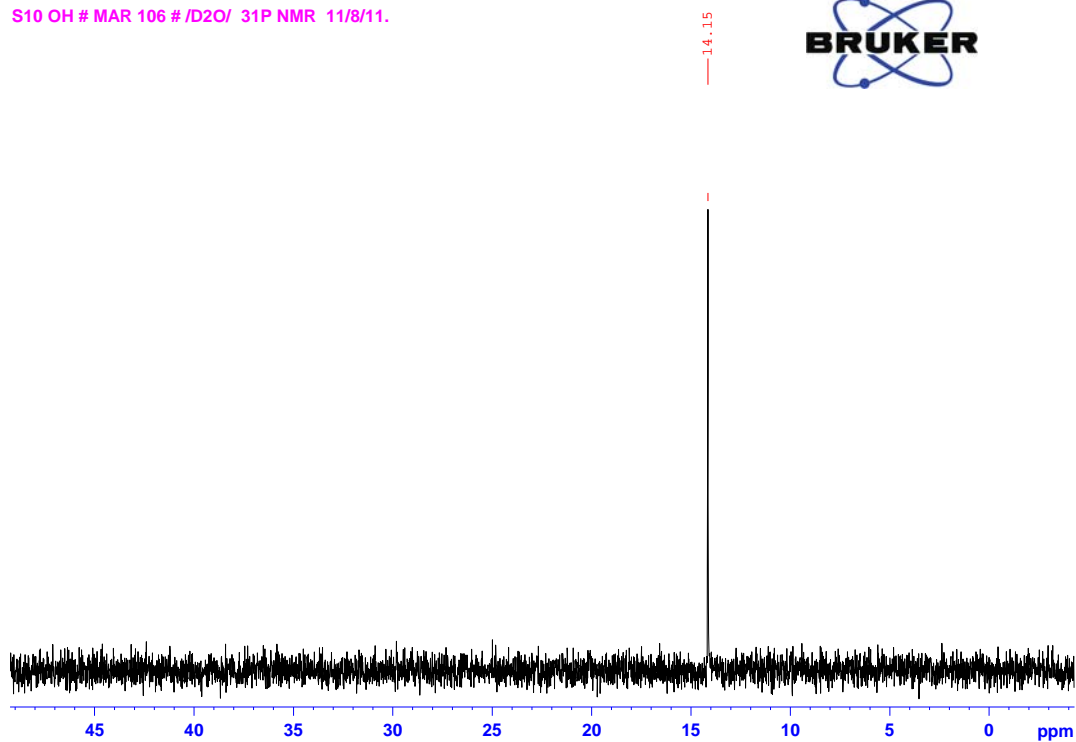


$^1\text{H}$  NMR spectrum of compound **46**.



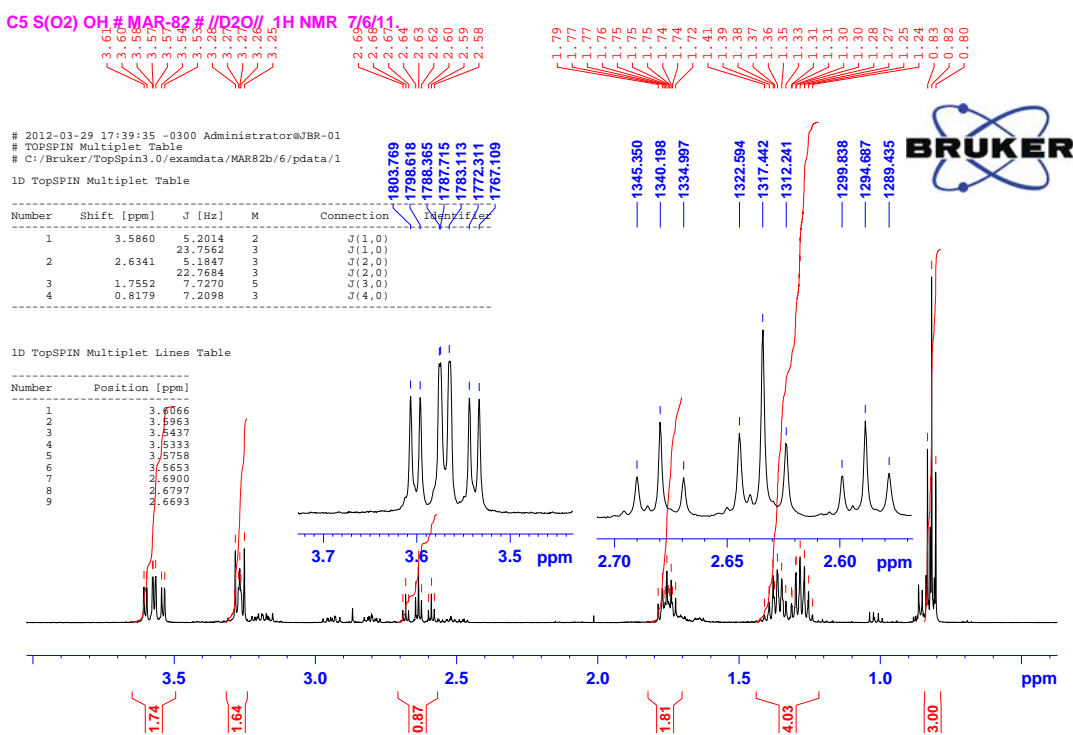
$^{13}\text{C}$  NMR spectrum of compound **46**.

S10 OH # MAR 106 # /D2O/ 31P NMR 11/8/11.



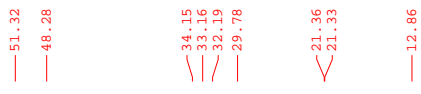
<sup>31</sup>P NMR spectrum of compound 46.

C5 S(O2) OH # MAR-82 # //D2O// 1H NMR 7/6/11



<sup>1</sup>H NMR spectrum of compound 47.

ALE-207 13C NMR D2O



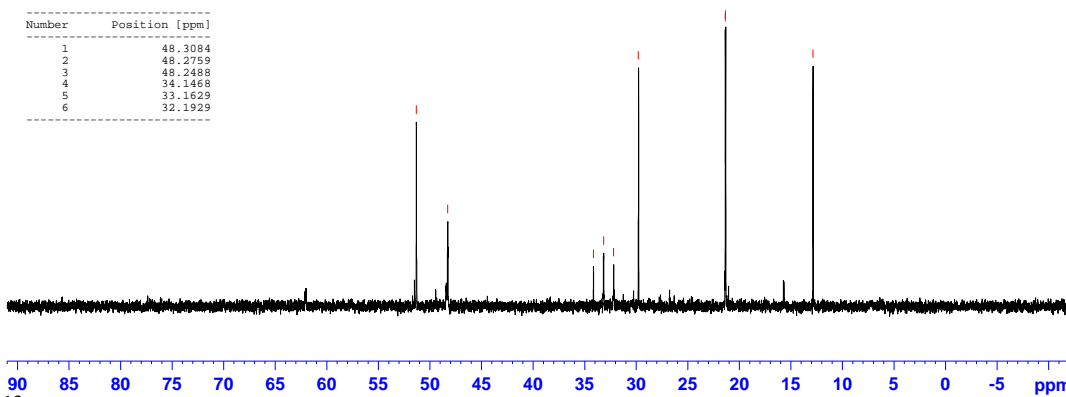
# 2012-08-03 17:54:20 -0300 Administrator@JBR-01  
 # TOPSPIN Multiplet Table  
 # C:/Bruker/TopSpin3.0/examdata/ALE207-bis/20/pdata/1

1D TopSPIN Multiplet Table

| Number | Shift [ppm] | J [Hz]   | M | Connection | Identifier |
|--------|-------------|----------|---|------------|------------|
| 1      | 48.2786     | 3.7466   | 3 | J(1,0)     |            |
| 2      | 33.1698     | 122.8591 | 3 | J(2,0)     |            |

1D TopSPIN Multiplet Lines Table

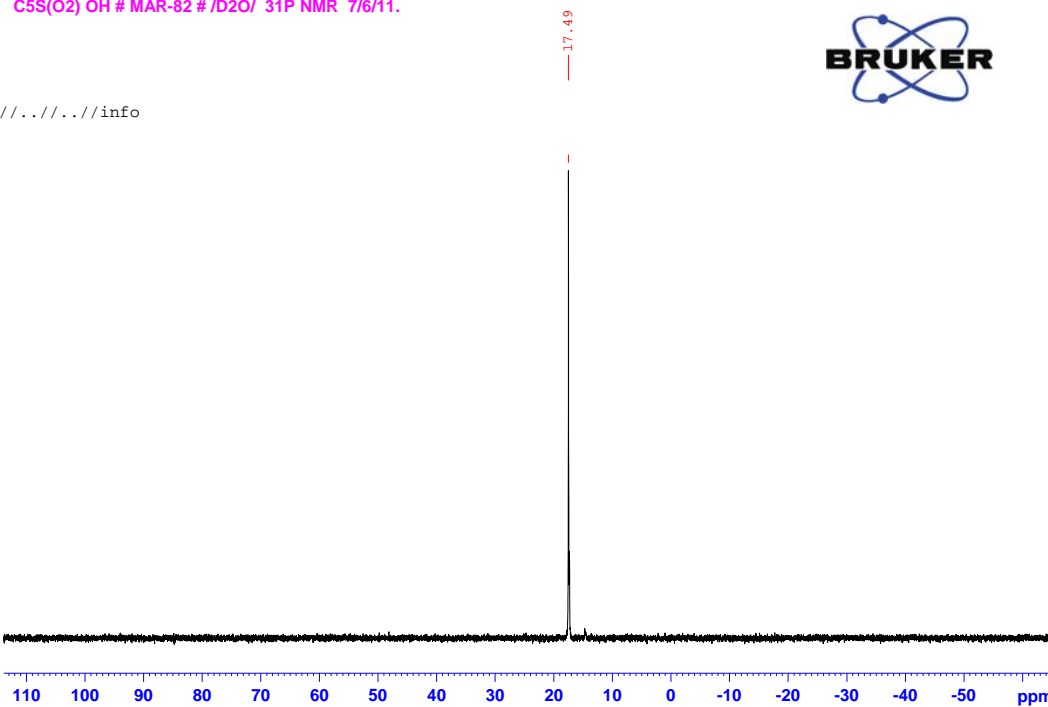
| Number | Position [ppm] |
|--------|----------------|
| 1      | 48.3084        |
| 2      | 48.2759        |
| 3      | 48.2488        |
| 4      | 34.1468        |
| 5      | 33.1629        |
| 6      | 32.1929        |



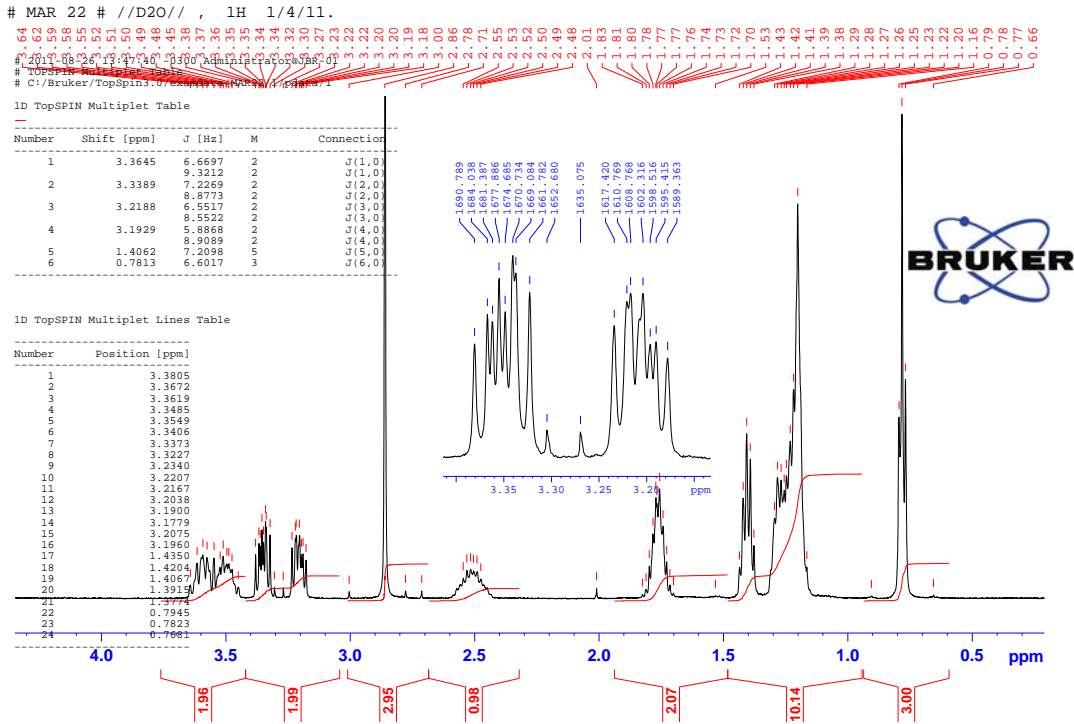
<sup>13</sup>C NMR spectrum of compound **47**.  
 C5S(O2) OH # MAR-82 # /D2O/ 31P NMR 7/6/11.



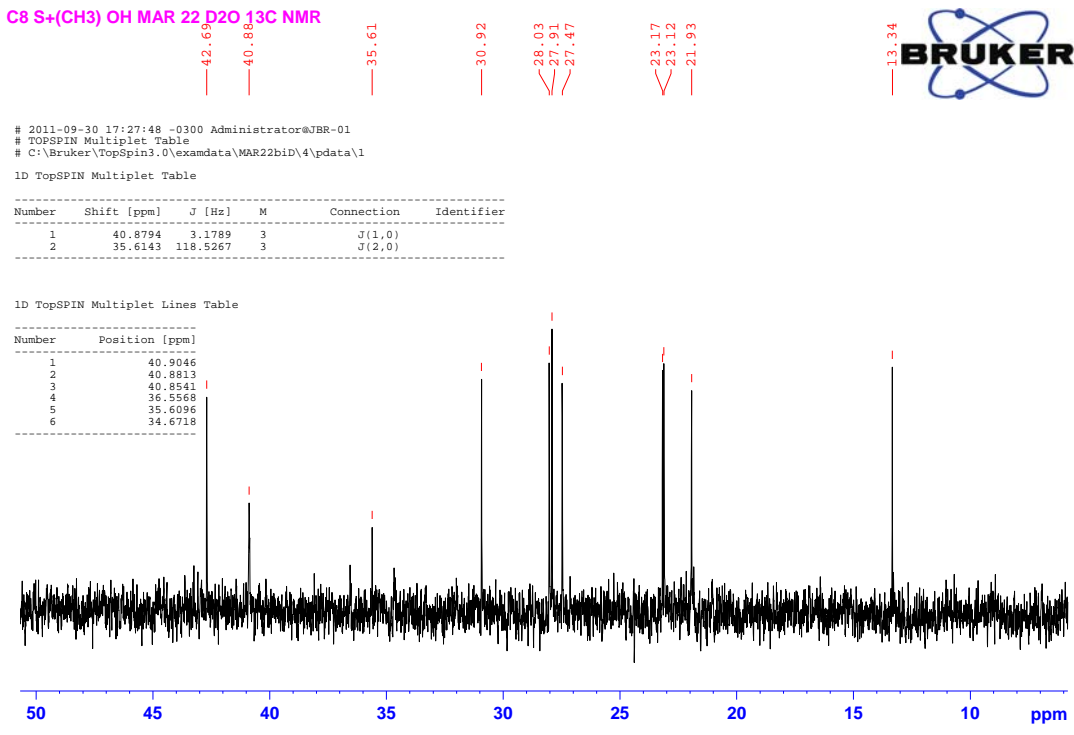
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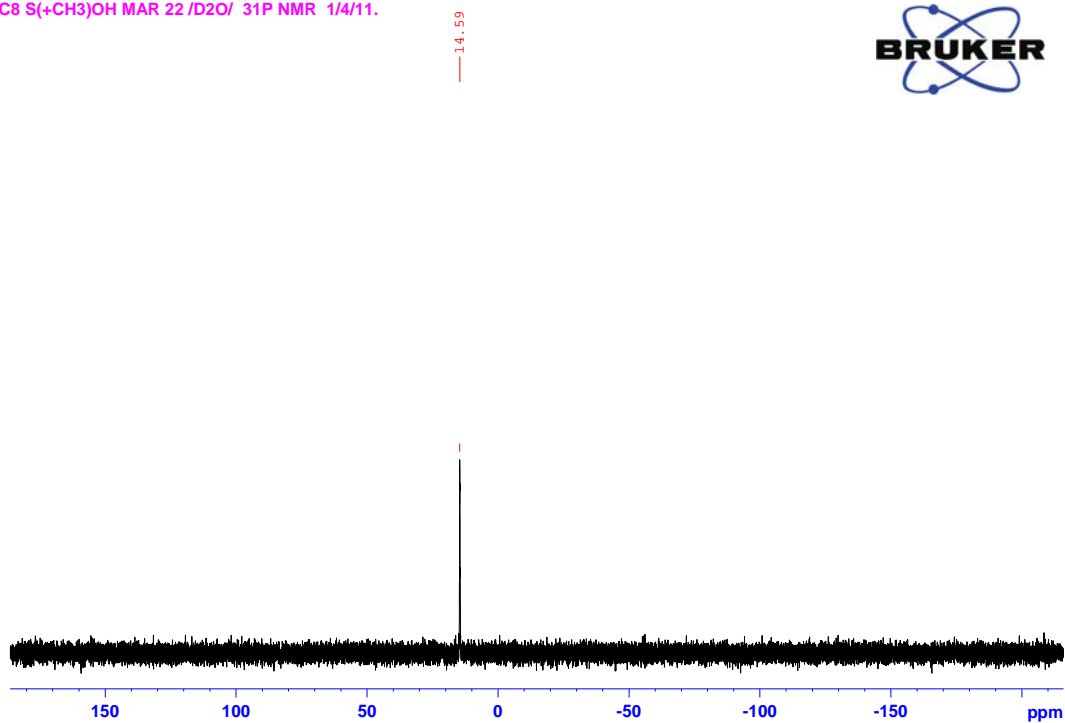
<sup>31</sup>P NMR spectrum of compound **47**.



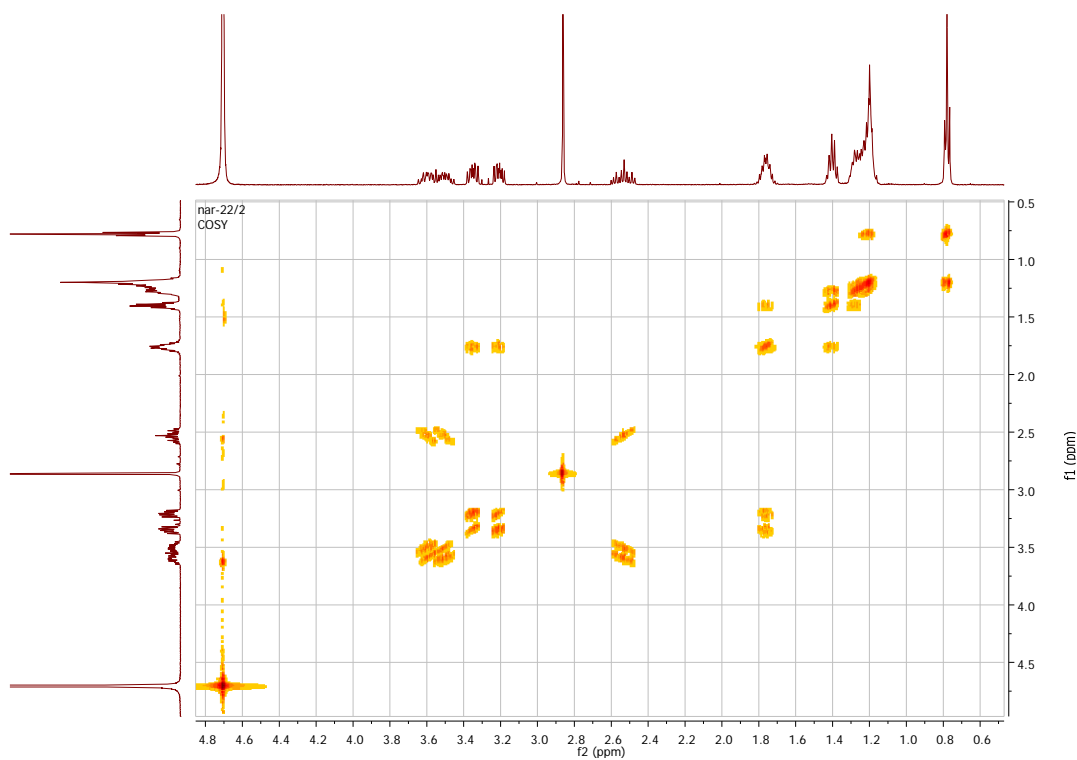
<sup>13</sup>C NMR spectrum of compound 48.



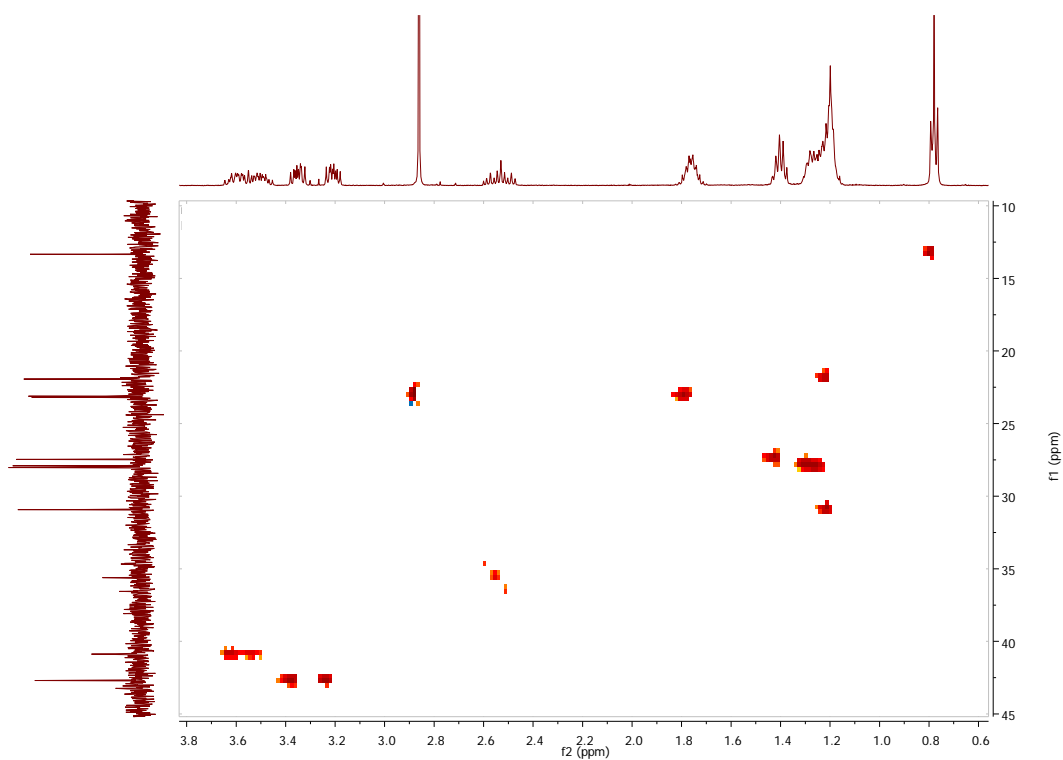
<sup>13</sup>C NMR spectrum of compound 48.



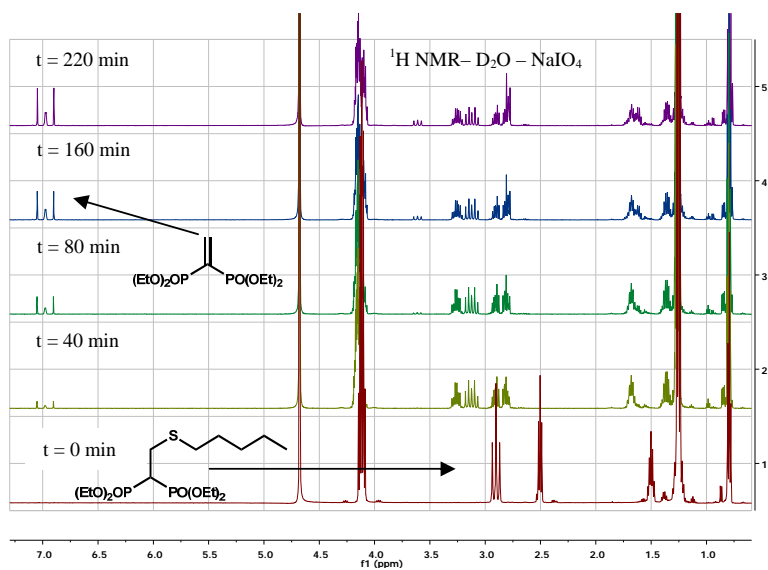
<sup>31</sup>P NMR spectrum of compound 48.



COSY spectrum of compound 48.

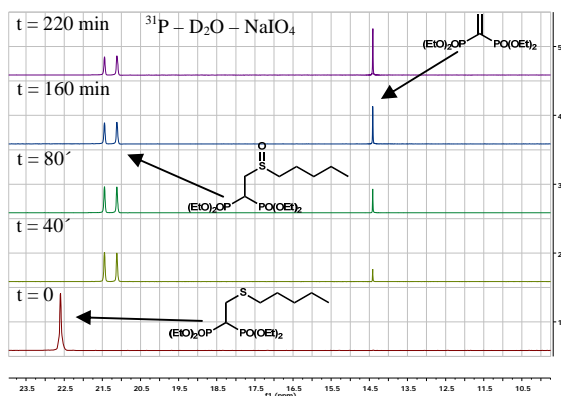


HSQC spectrum of compound **48**.

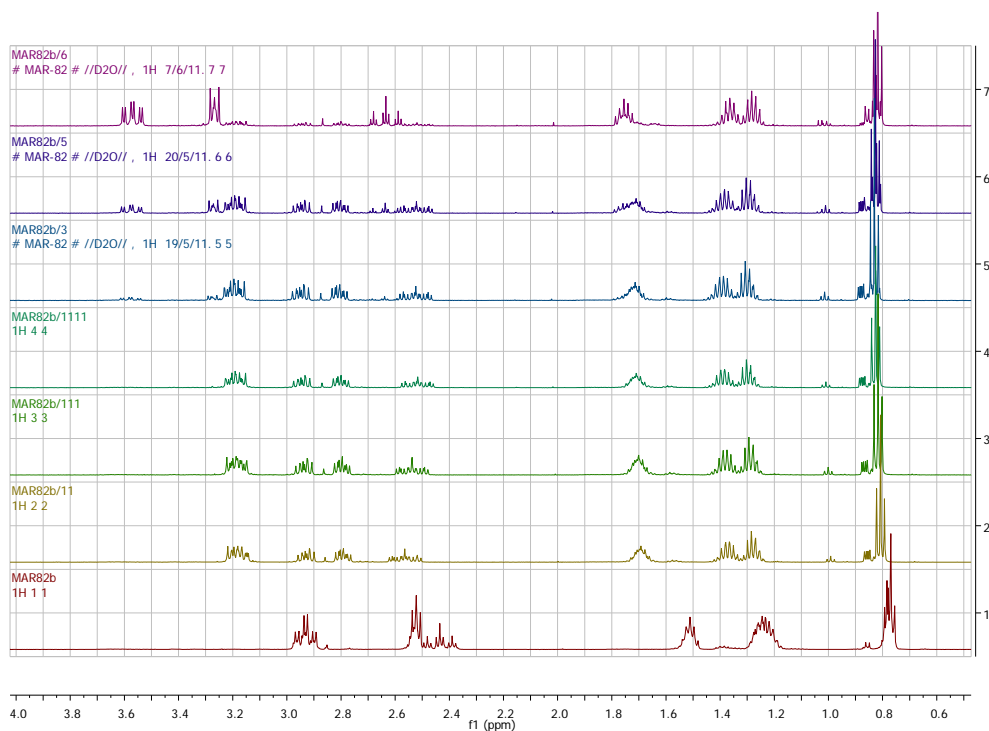


**Figure 1.**  $^1\text{H}$  NMR spectra for monitoring the oxidation reaction of **25** with  $\text{NaIO}_4$  in  $\text{D}_2\text{O}$ .  $^1\text{H}$  NMR analyses indicated that treatment of pentylsulfide derivative **25** with sodium metaperiodate afforded initially the expected oxidized species, the corresponding sulfoxide, but, on standing, this compound underwent a retro-Michael reaction as shown in the proton NMR sequence. Initially, it could be clearly observed the typical signal for the vinyl protons of **16** ( $\text{H}_2\text{C}=\text{}$ ) as a distorted doublet of doublets centered at 6.97 ppm ( $J = 39.0$  Hz, 35.3 Hz). The signal size increases as the coordinates of time goes.

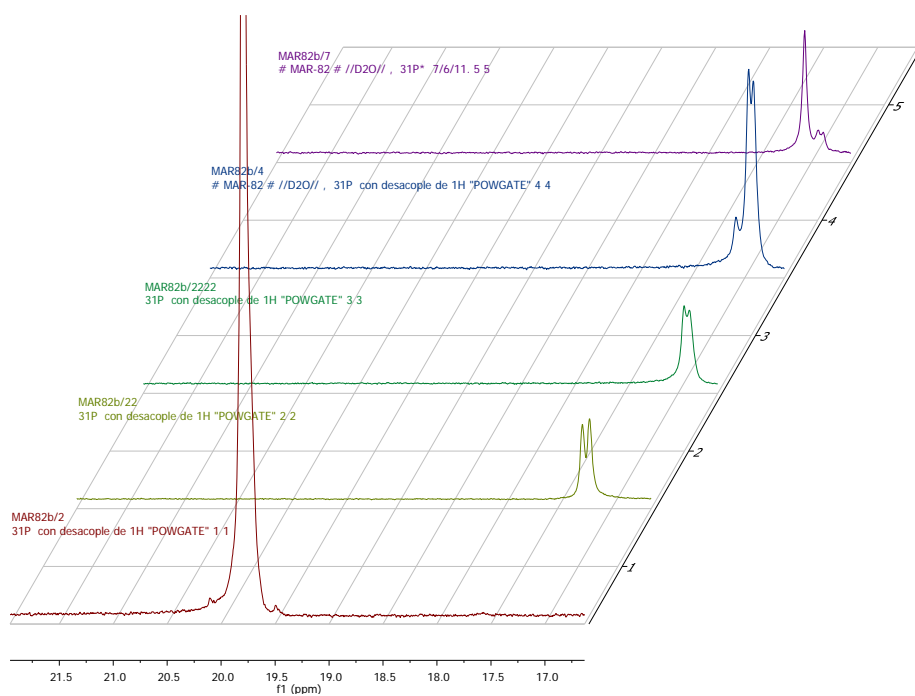




**Figure 2.**  $^{31}\text{P}$  NMR spectra for monitoring the oxidation reaction of **25** with  $\text{NaIO}_4$  in  $\text{D}_2\text{O}$ . The signal corresponding to the phosphorus atom present in **16** at 14.40 ppm also increases versus the peaks corresponding to the diastereotopic phosphorus atoms present in the sulfoxy-containing oxidized product (an AB multiplet centered at 21.27 ppm) as the time elapses. A similar behavior was observed if the reaction was conducted employing oxygen peroxide or *m*-chloroperbenzoic acid.



**Figure 3.**  $^1\text{H}$  NMR spectra of monitoring oxidation of sulfide **34** to sulfoxide **41**. In order to test the hypothesis that oxidation of the free bisphosphonic acids **31–39** would not undergo a retro-Michael addition, the reaction of compound **34** with hydrogen peroxide was monitored by  $^1\text{H}$  NMR. It is clearly illustrated that after addition of one equivalent of hydrogen peroxide, **34** was converted rapidly into sulfoxide **41**. After 10 minutes, a second equivalent of hydrogen peroxide was added. No overoxidation was observed. A third equivalent was added after 10 minutes and compound **41** remained intact. Four hours were required to barely notice the characteristic signal of the sulfone derivative **47**, that is, triplet of triplet centered at 2.63 ppm ( $J = 22.8$  Hz and 5.1 Hz), and a double of triplets centered at 3.59 ( $J = 23.8$  and 5.2 Hz). Certainly, the spectrum of **47** was much simpler than that corresponding to **41** due to lost of the asymmetric center. Twenty four hours later almost all the sulfoxide was transformed into **47**.



**Figure 4.**  $^{31}\text{P}$  NMR spectra of monitoring oxidation of sulfide **34** to sulfoxide **41**. The signal corresponding to the phosphorus atoms at  $t = 0$  appeared at 20.12 ppm. Then, the signal of the sulfoxide was observed as a strongly coupled system (18.02 ppm) that finally lead to a simplified signal of the phosphorus atoms bearing the sulfone group of **47** at 17.49 ppm.