Supporting Information

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

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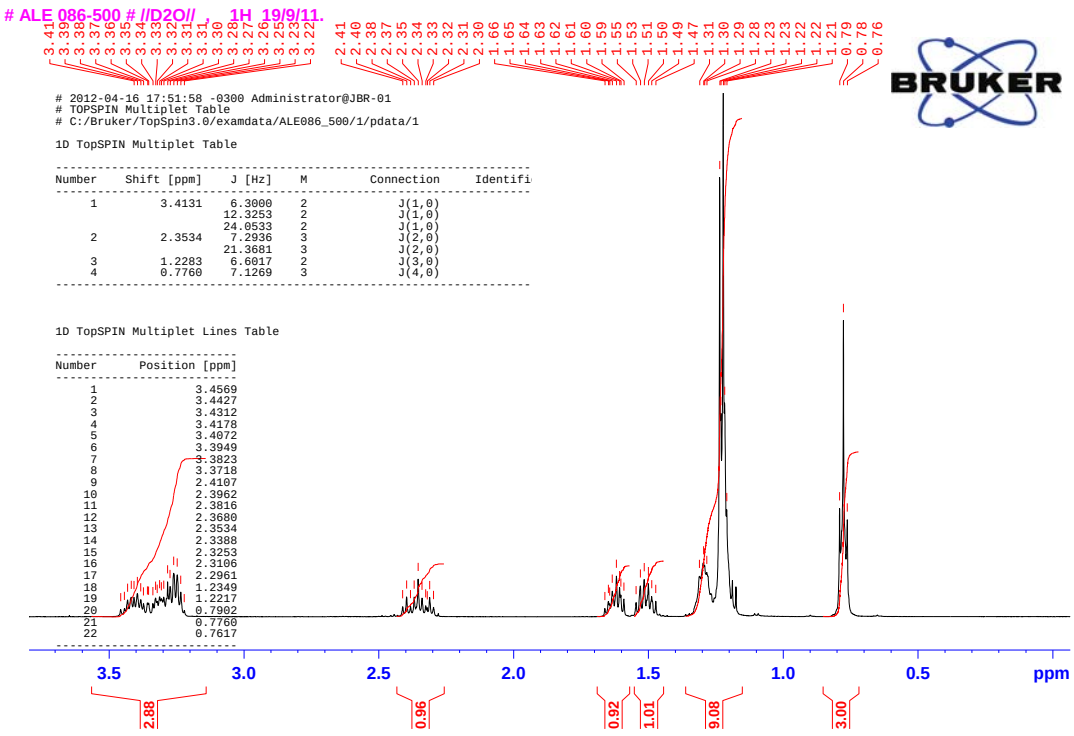
List of Contents



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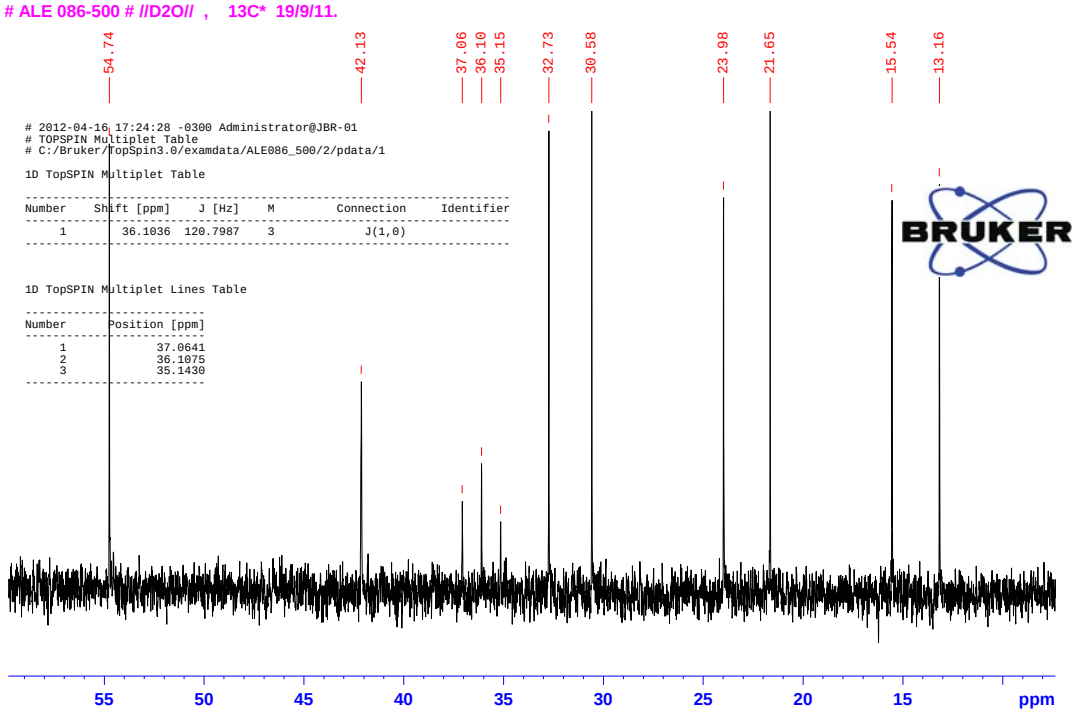

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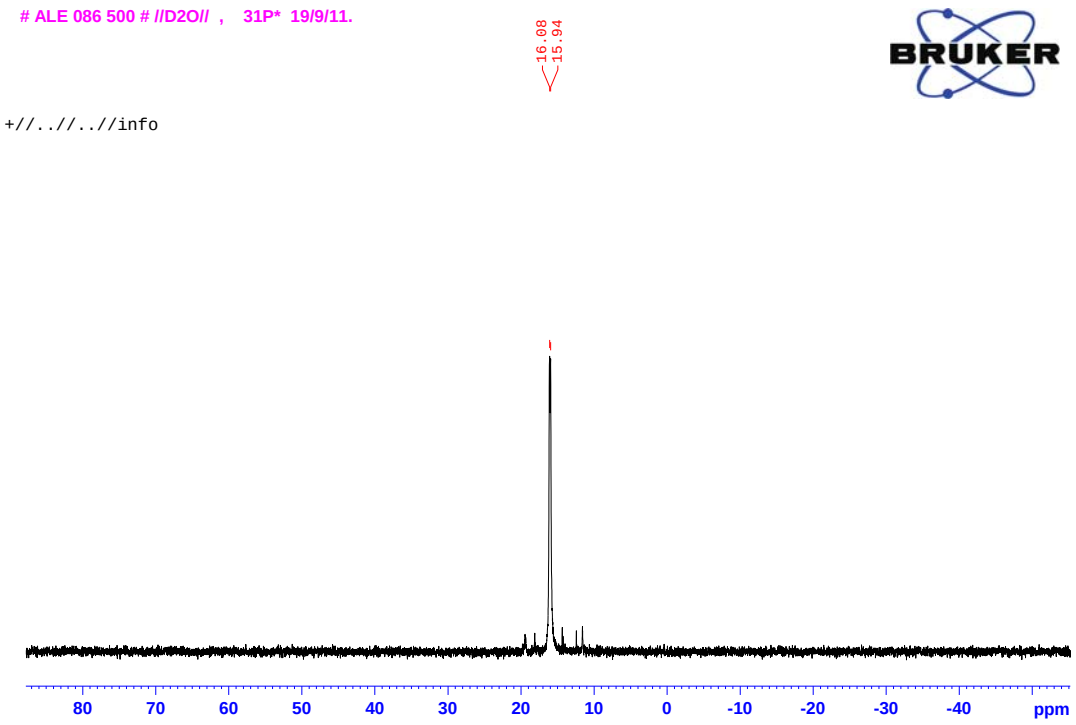

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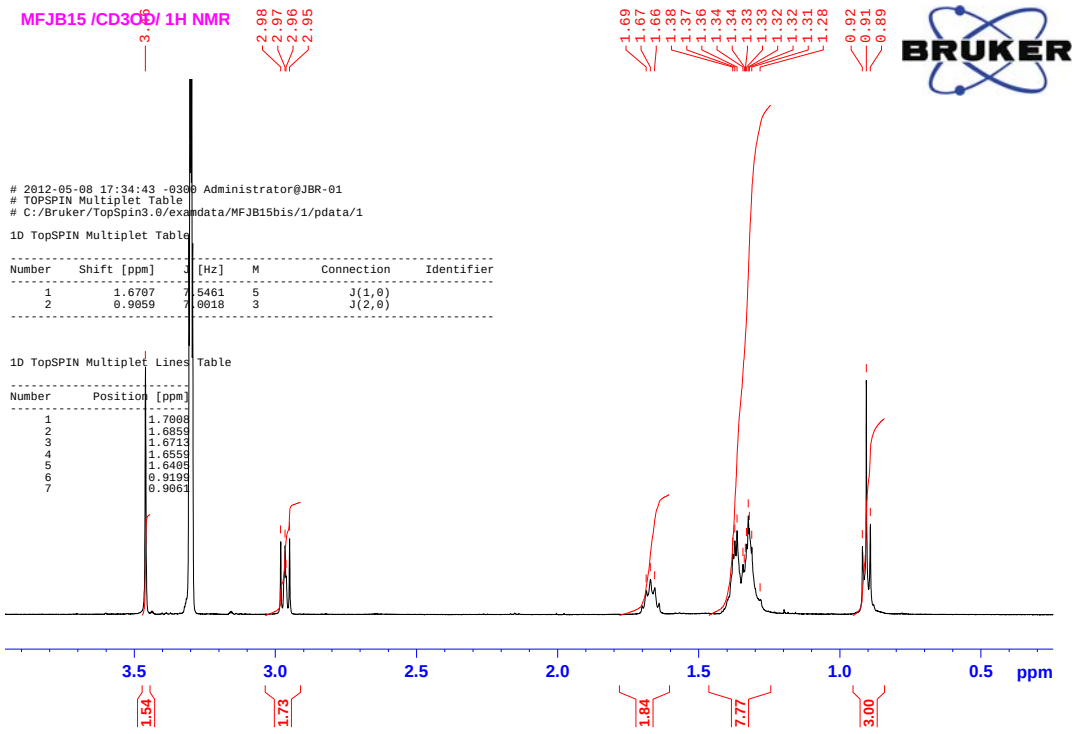

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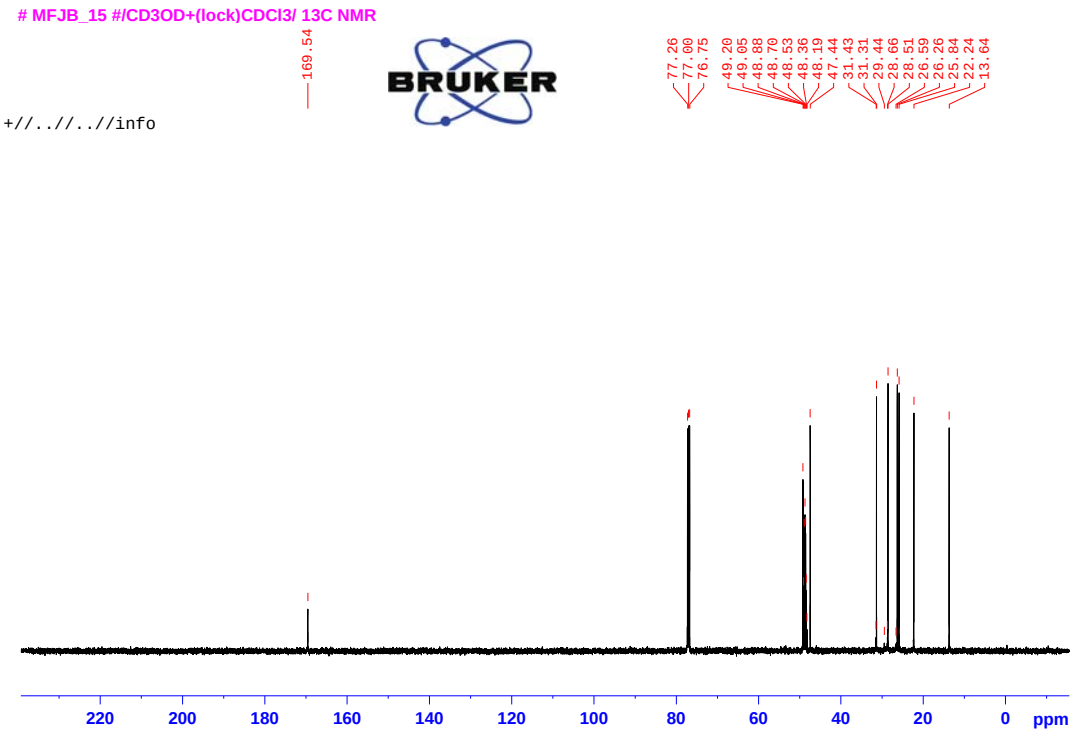

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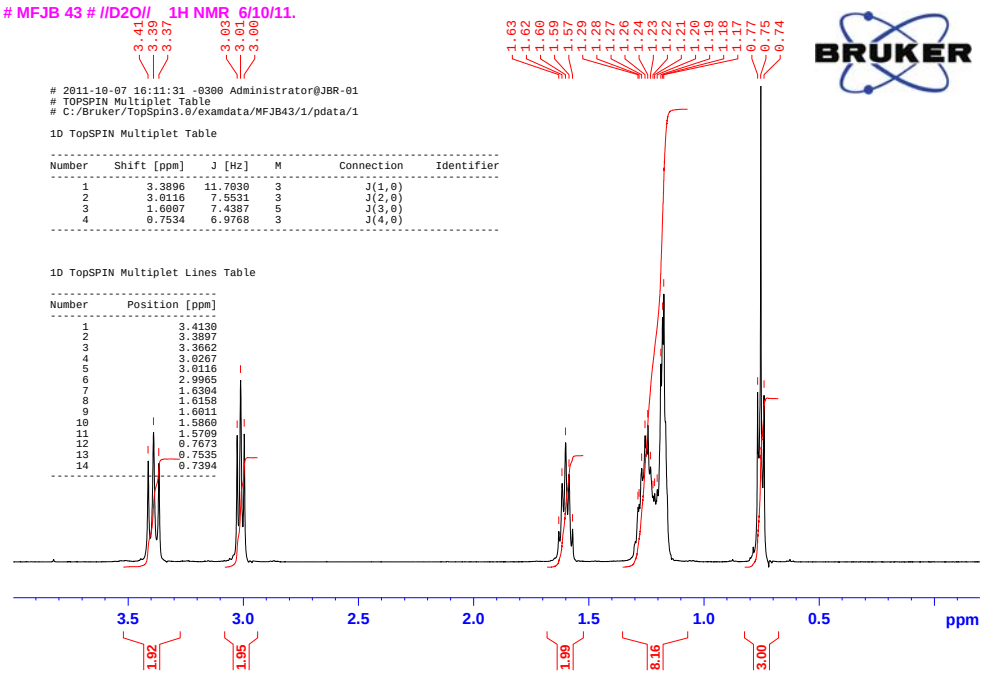

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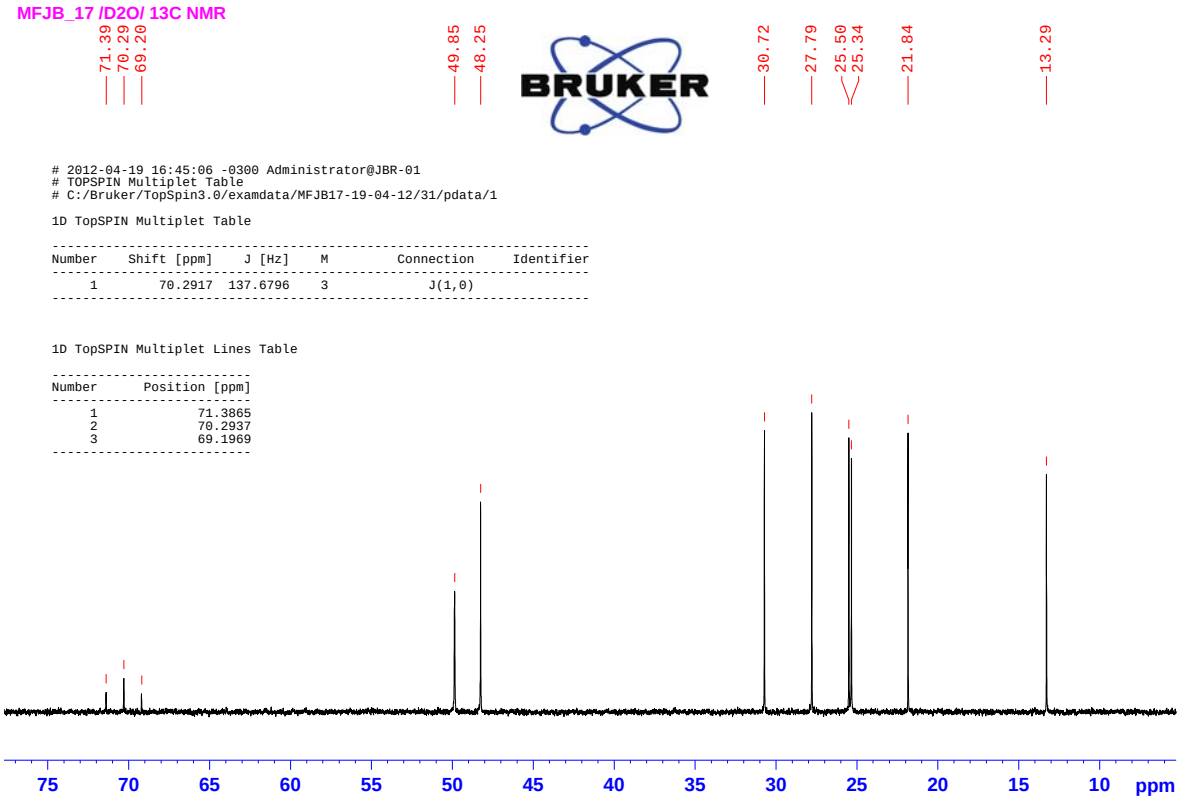

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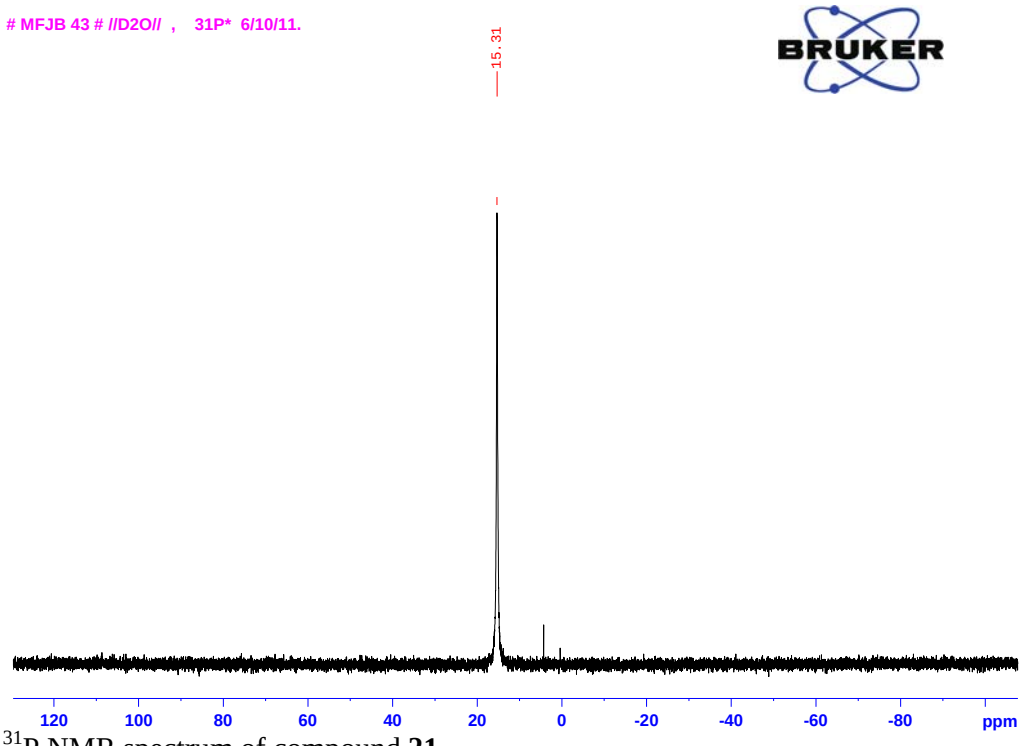

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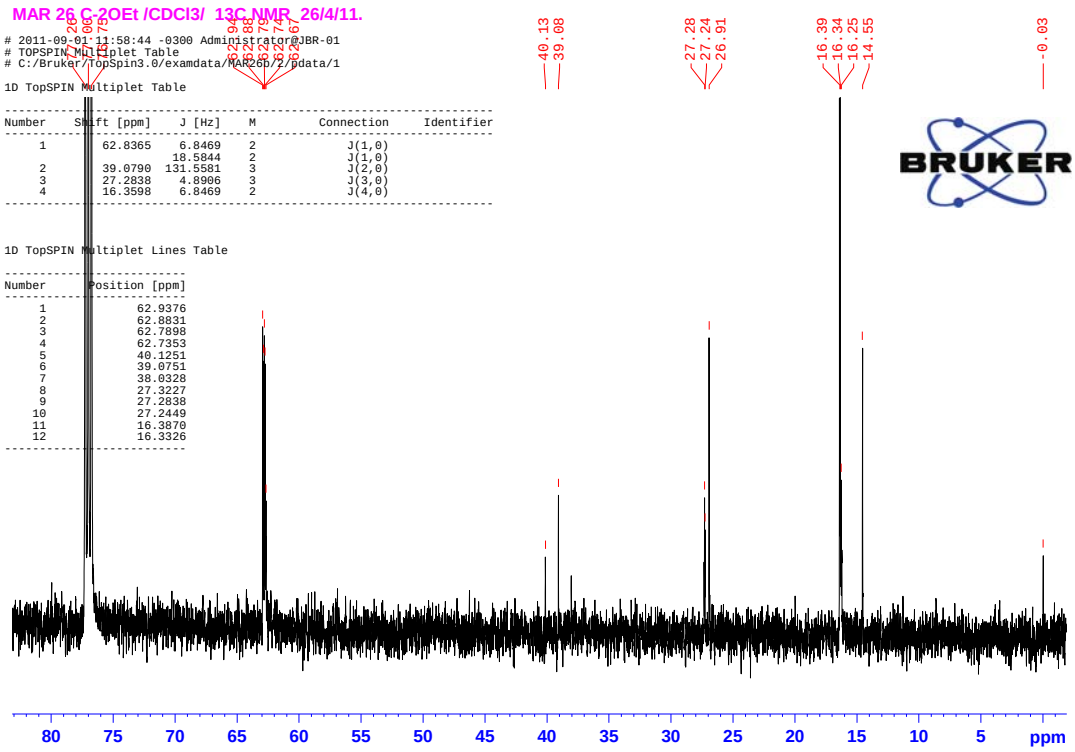

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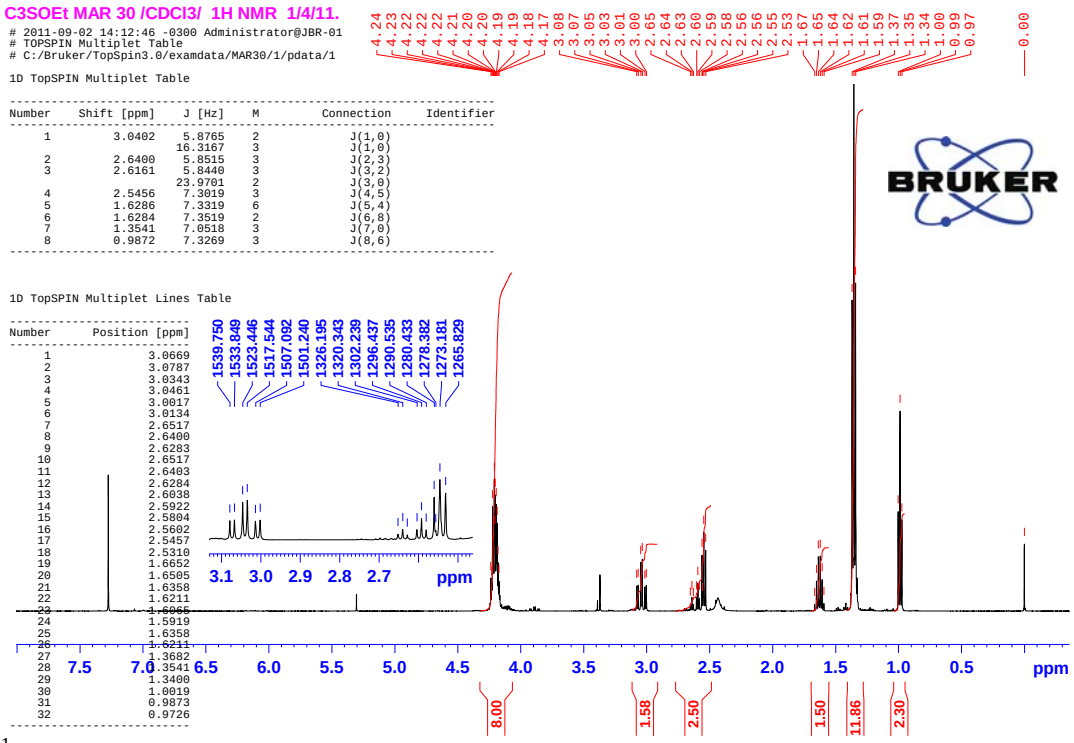

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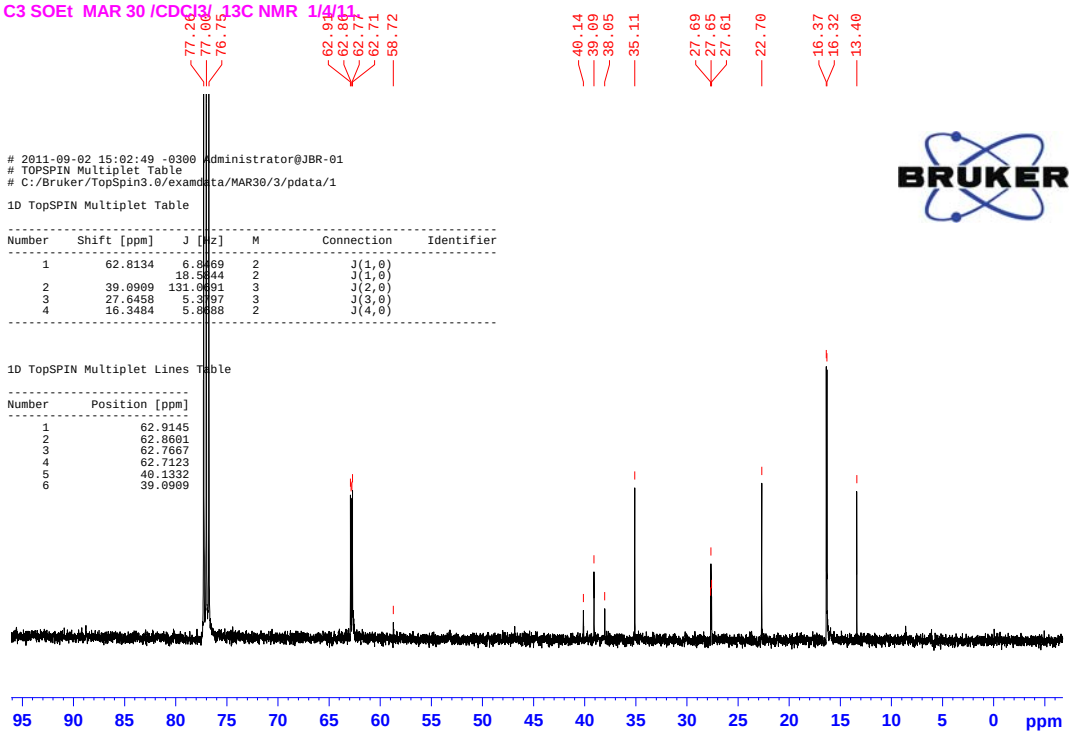

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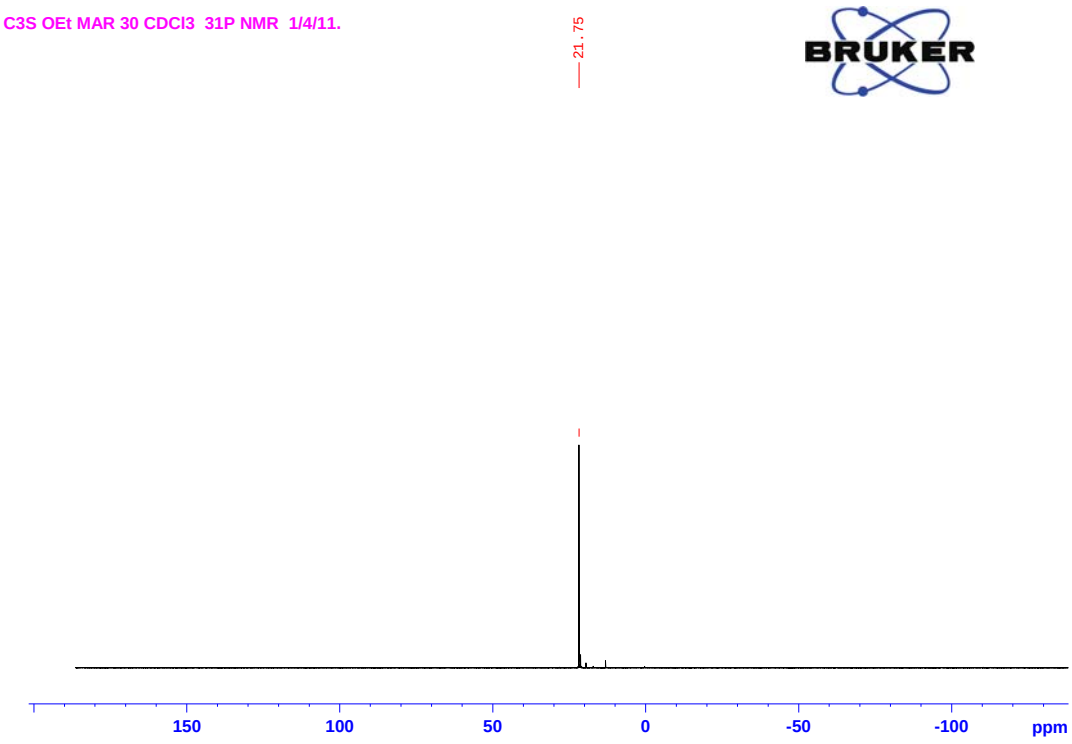

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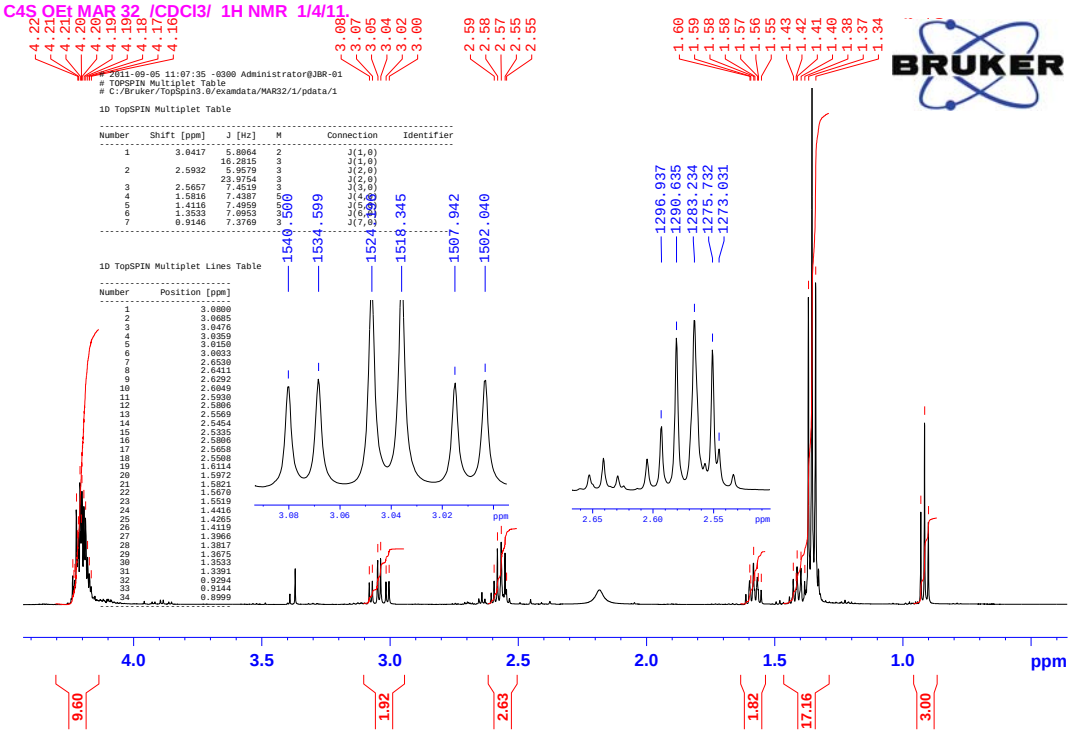

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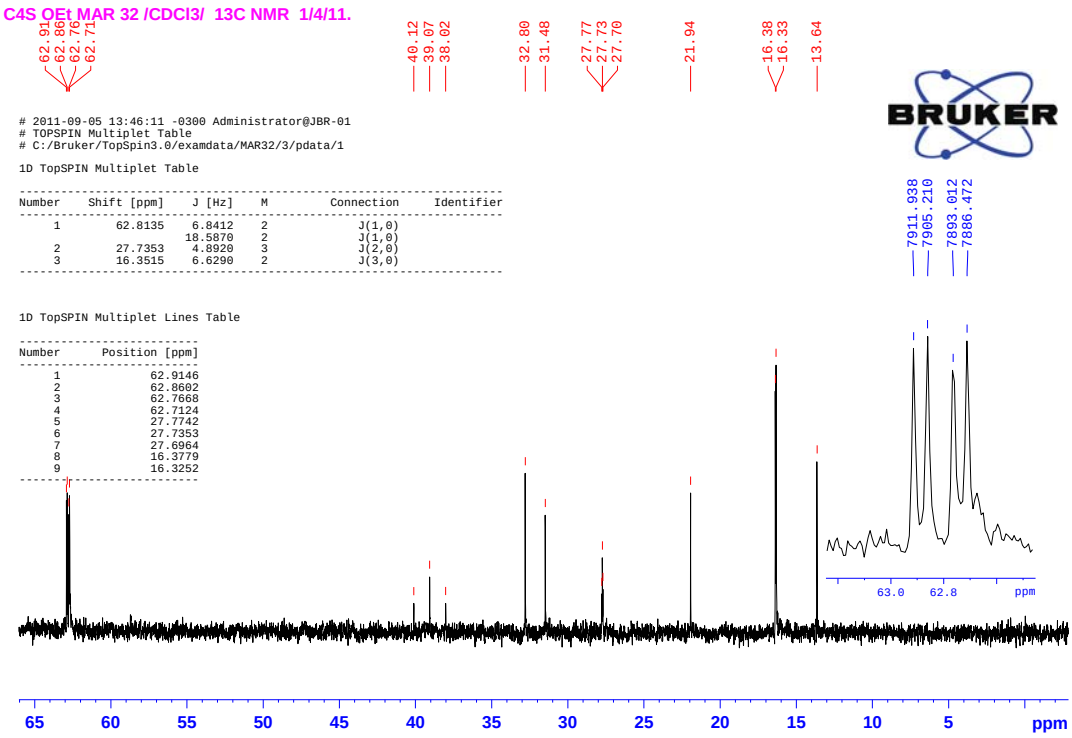

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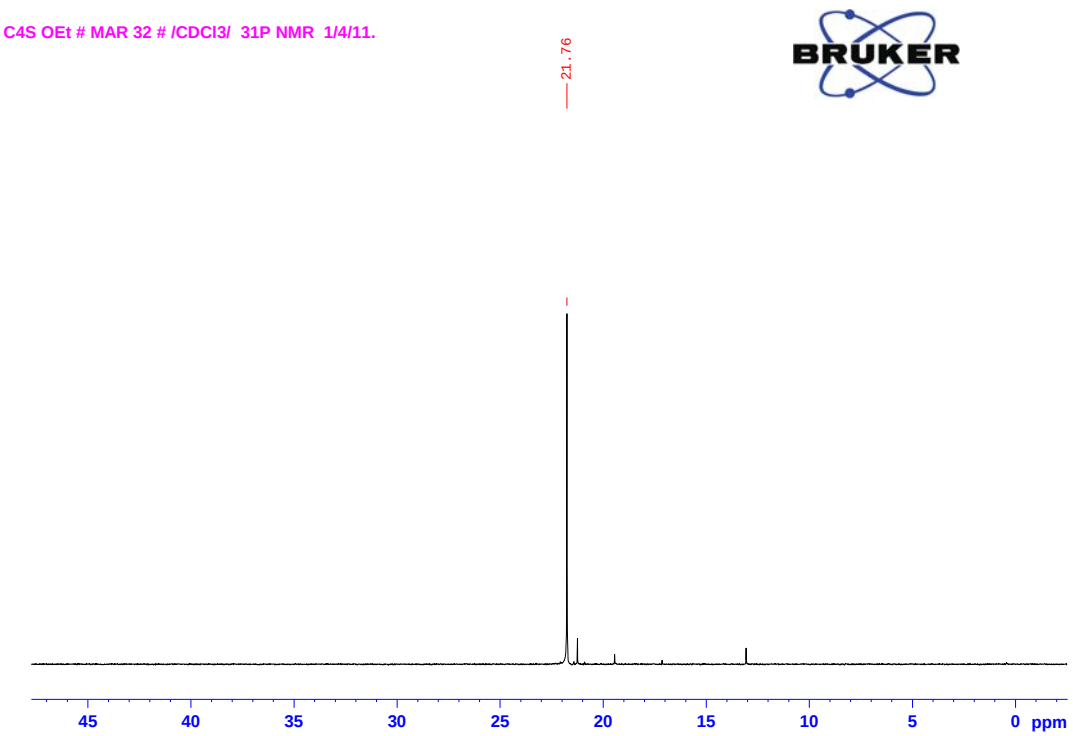

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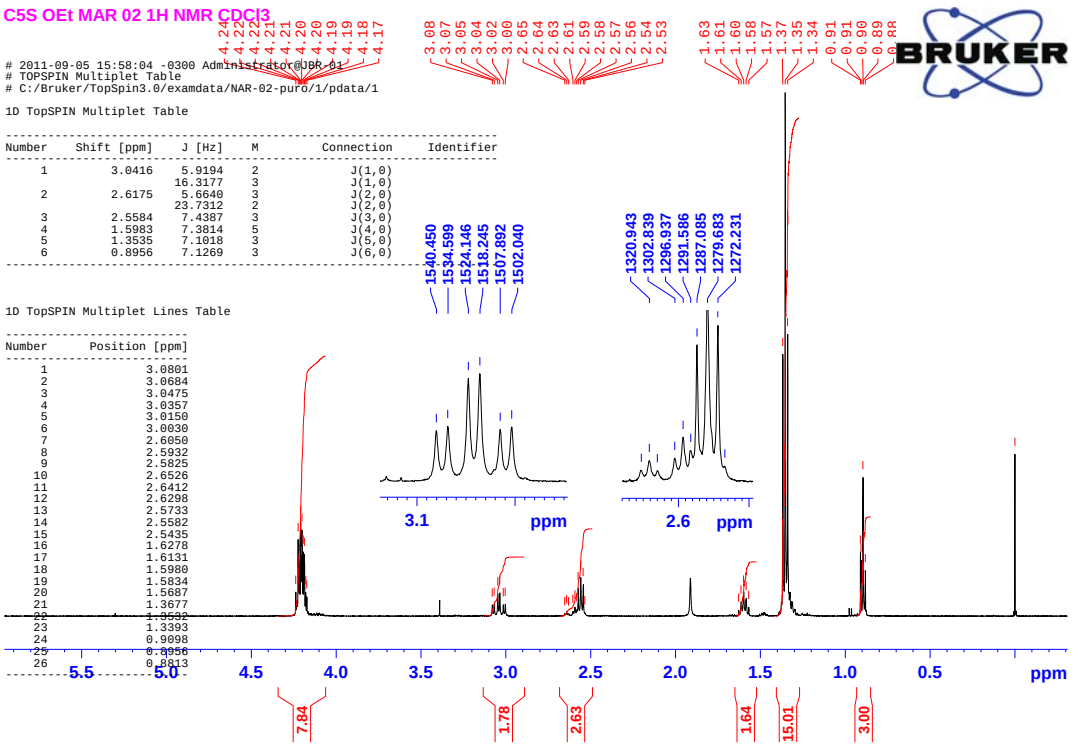

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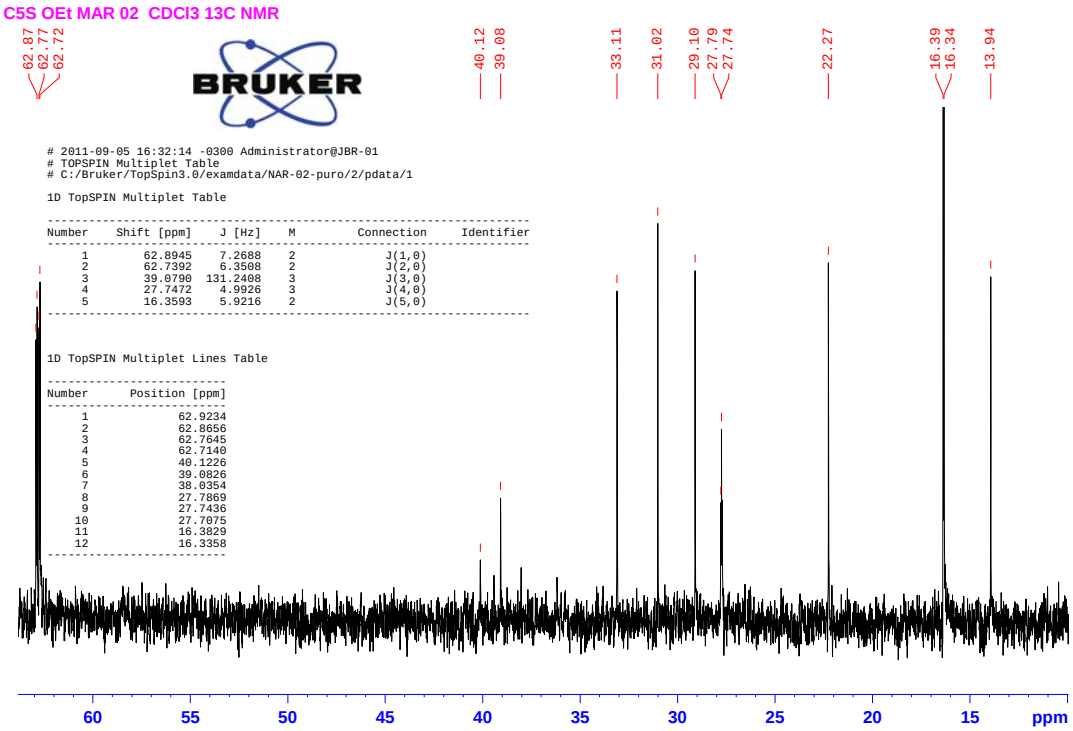

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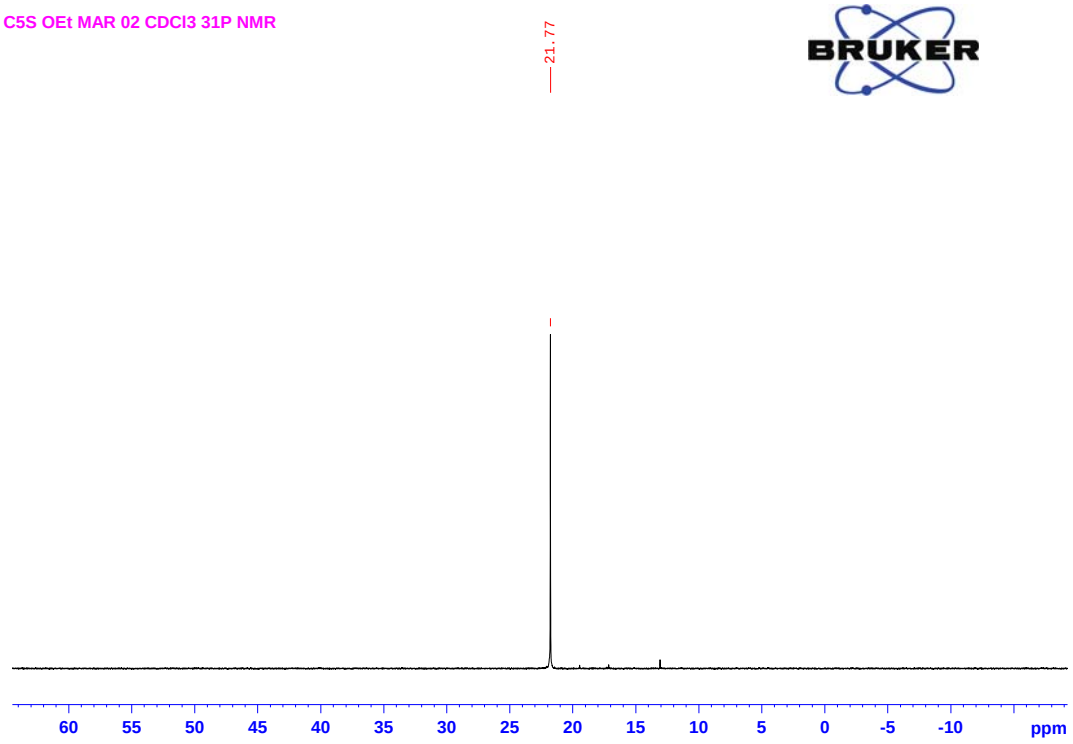

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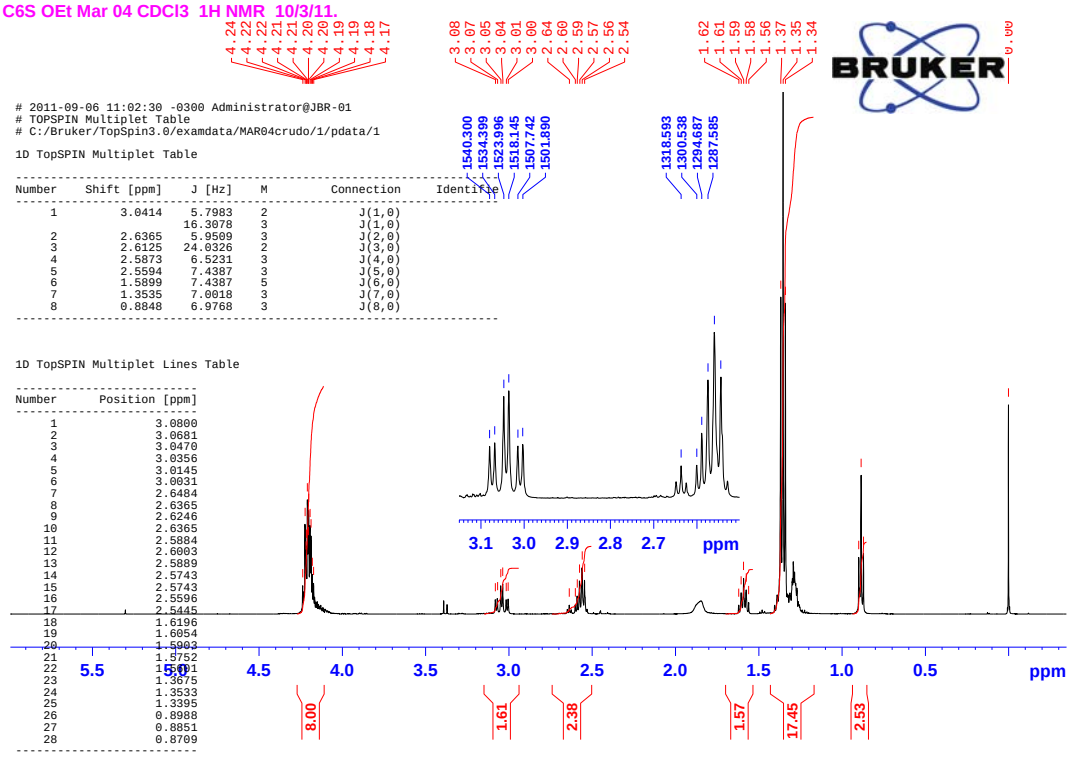

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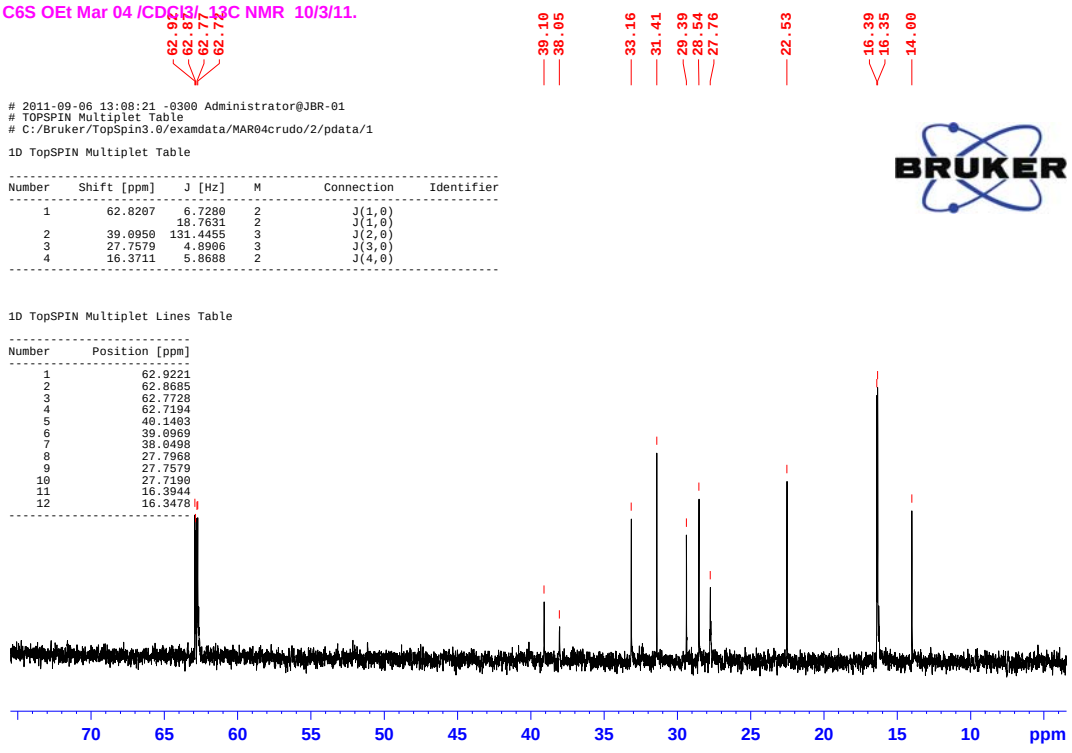

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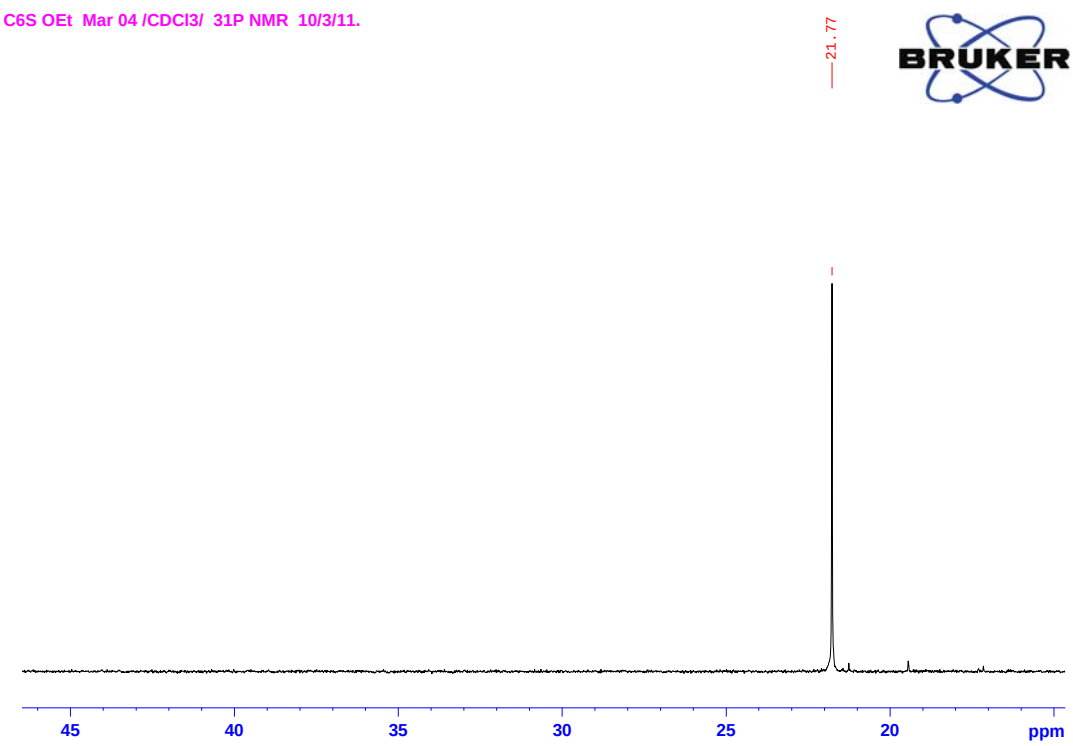

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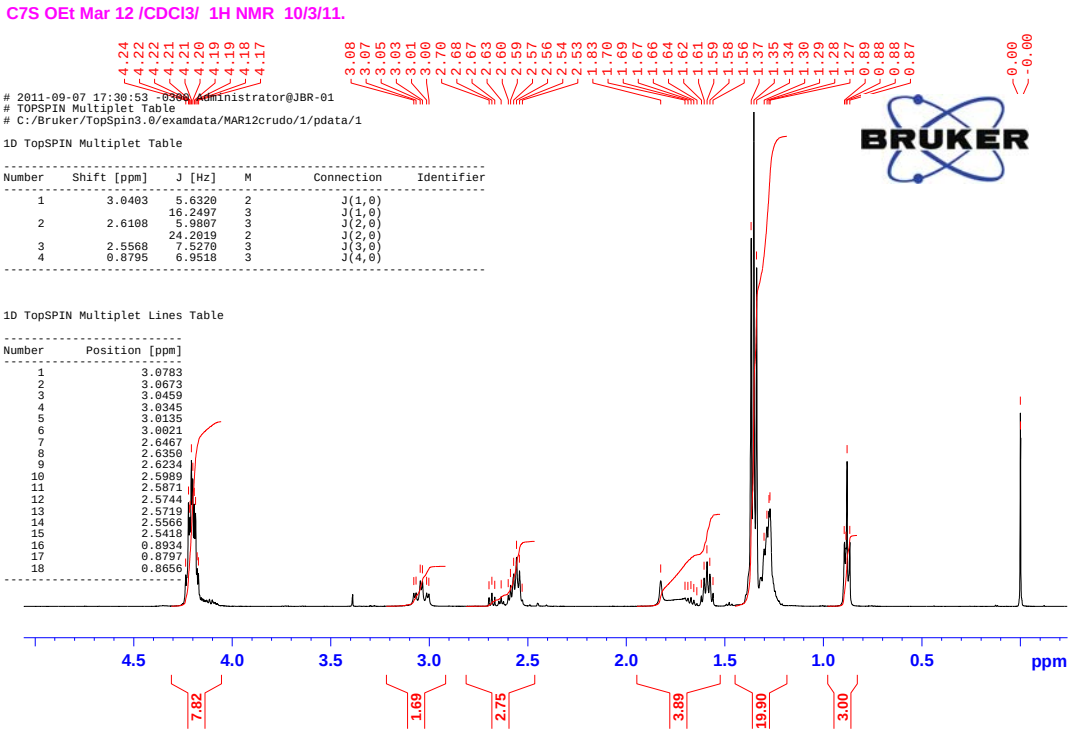

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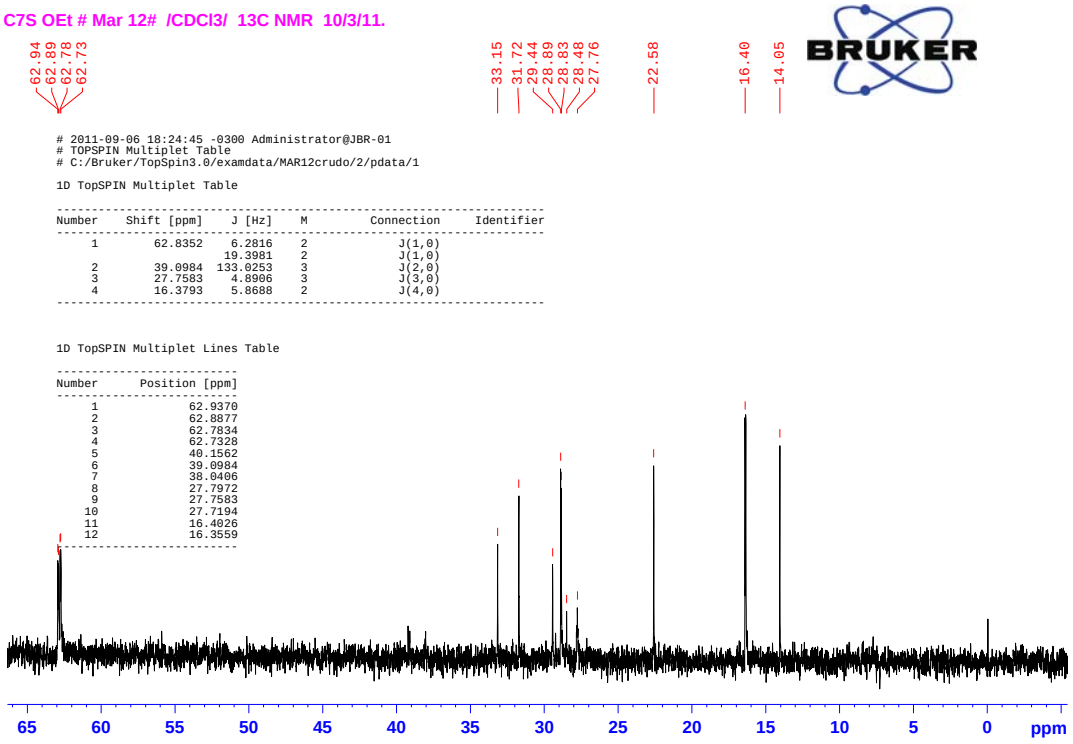

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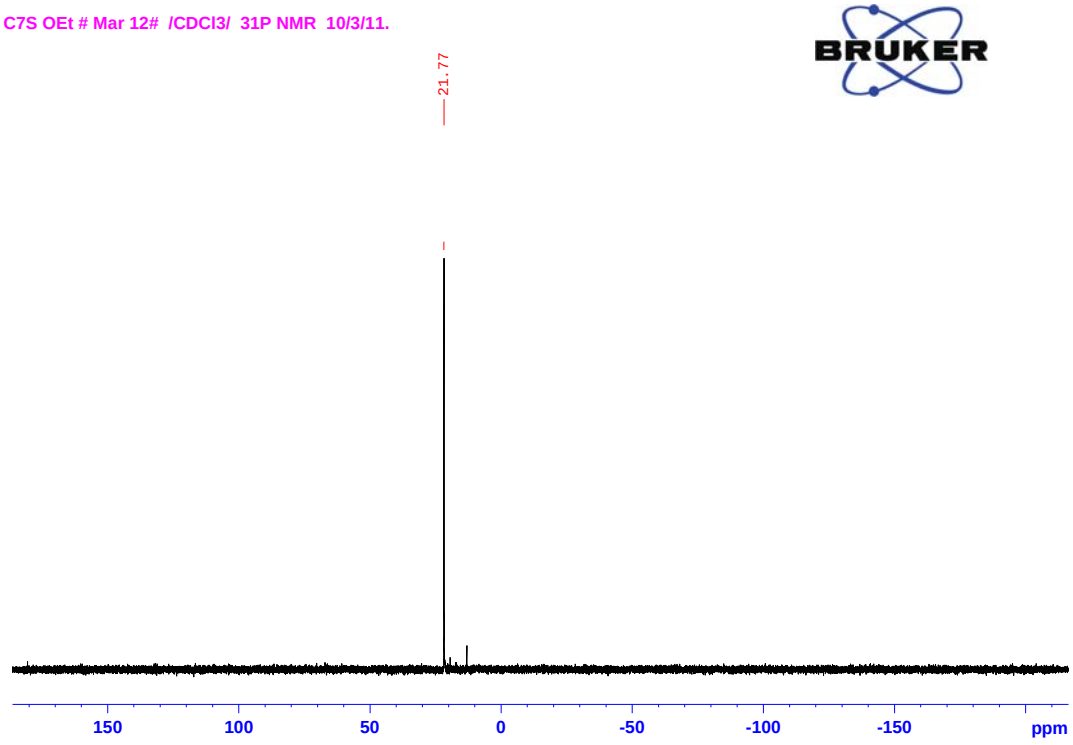

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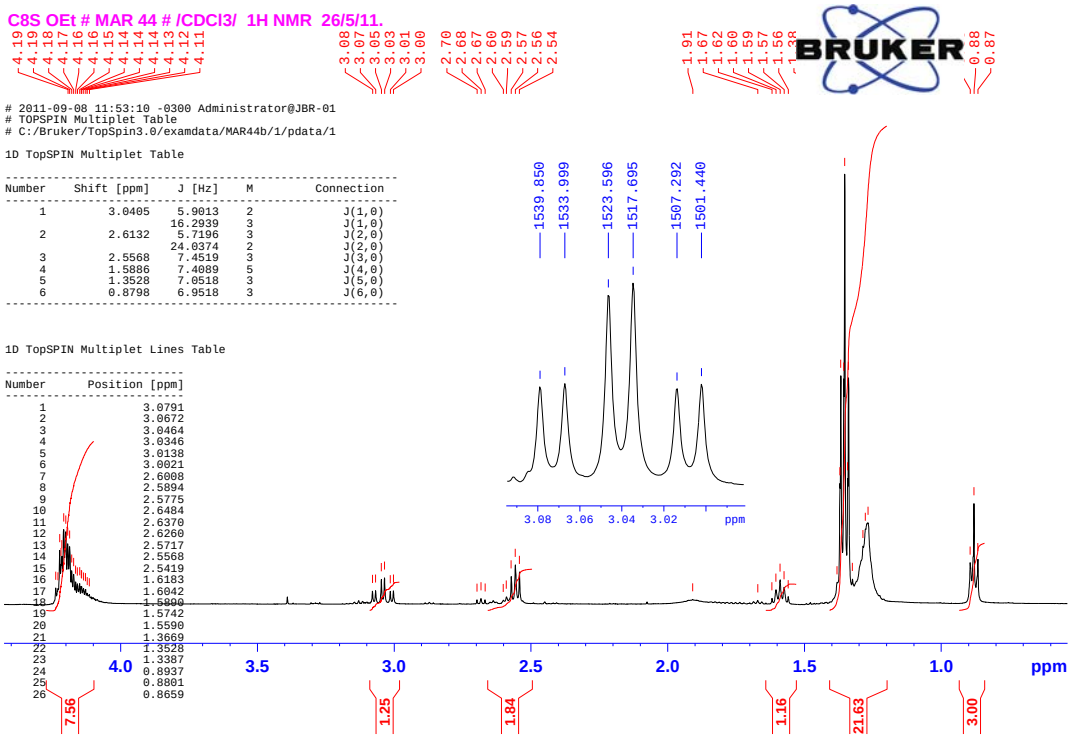

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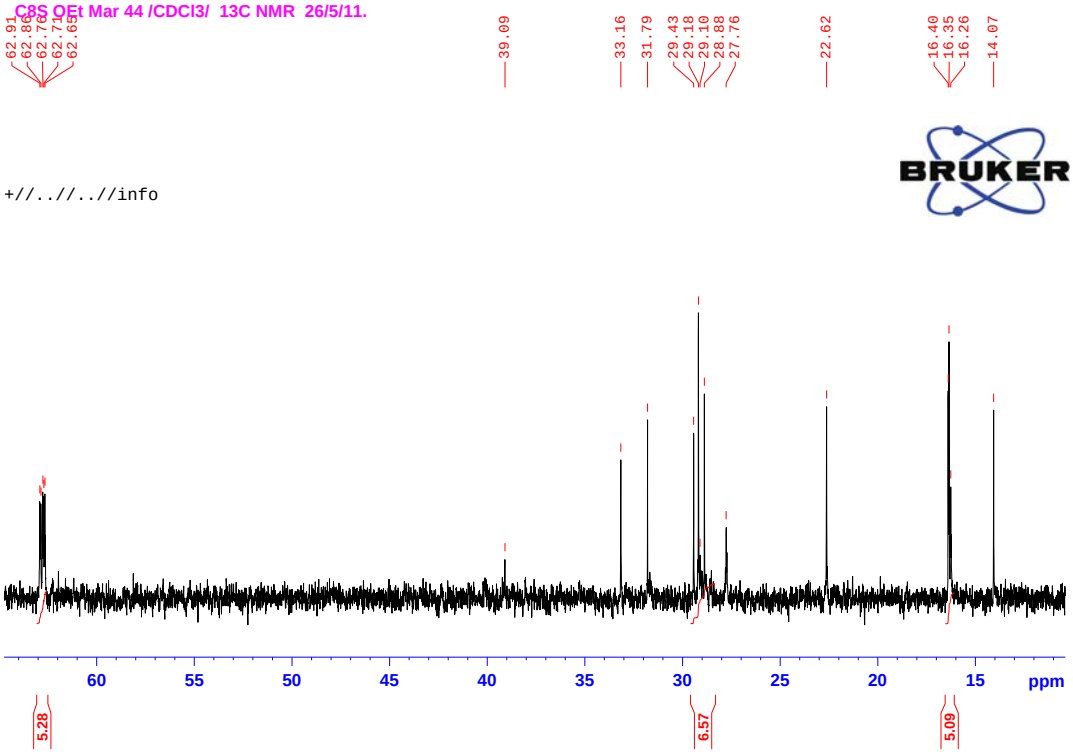

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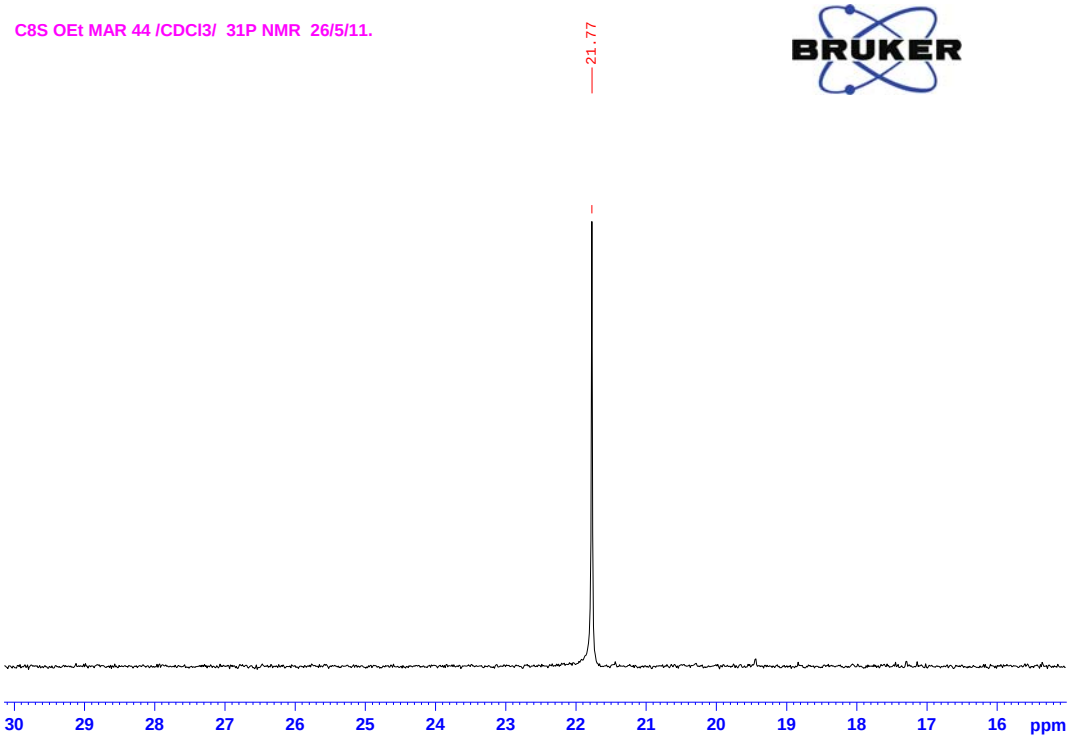

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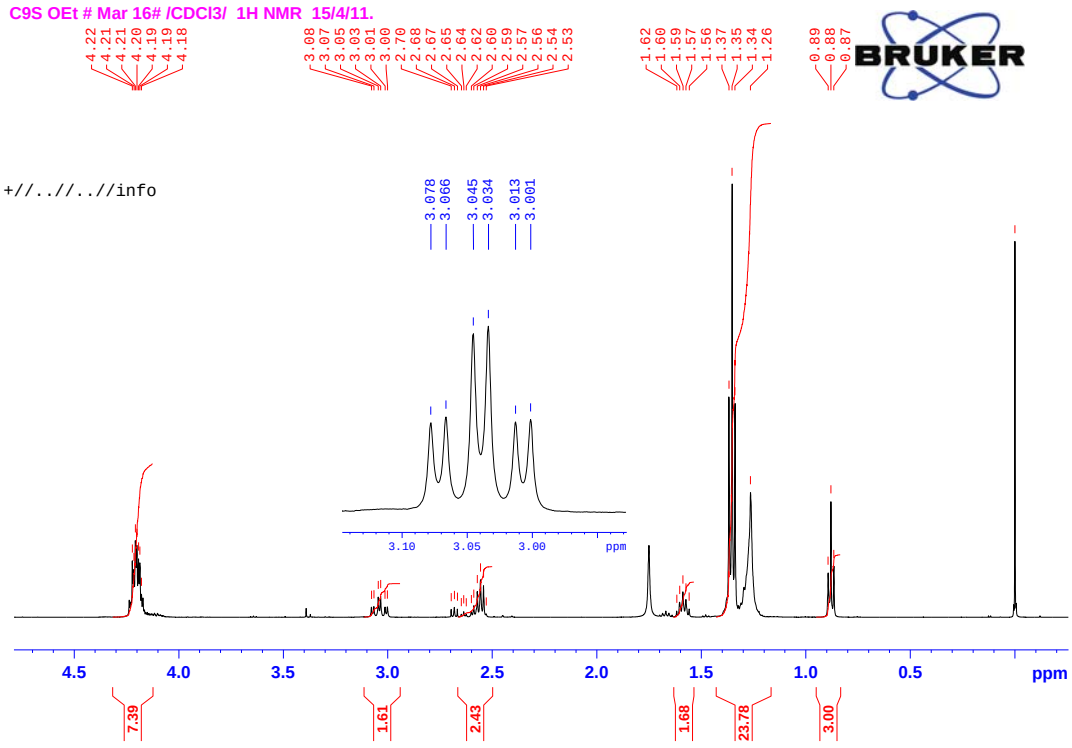

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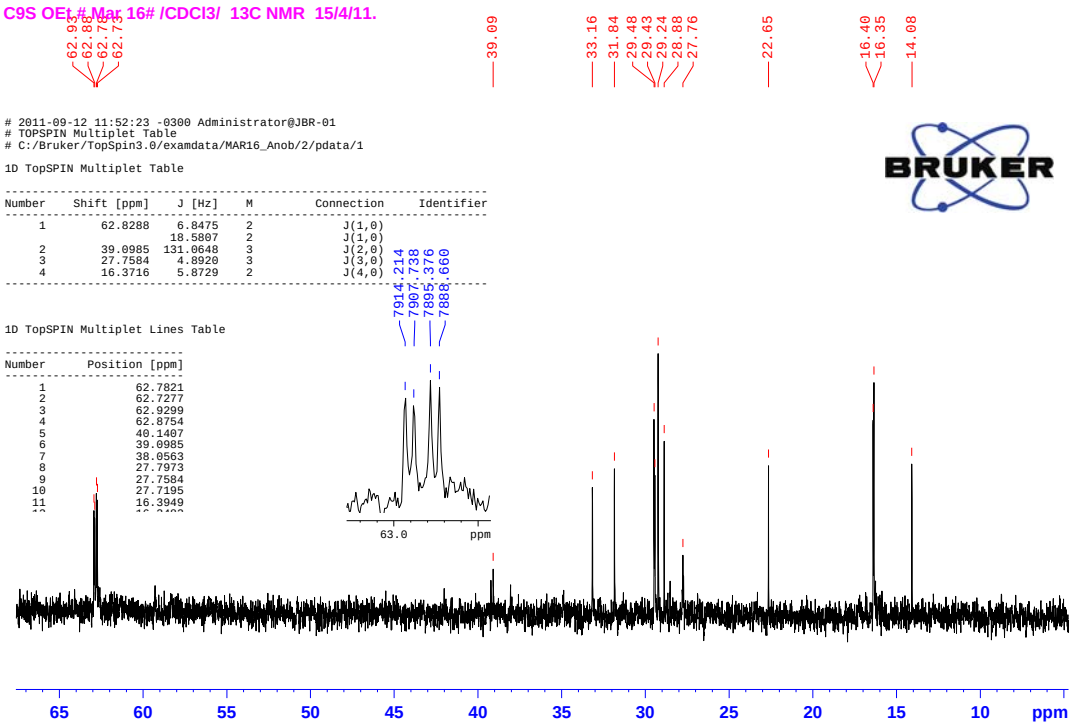

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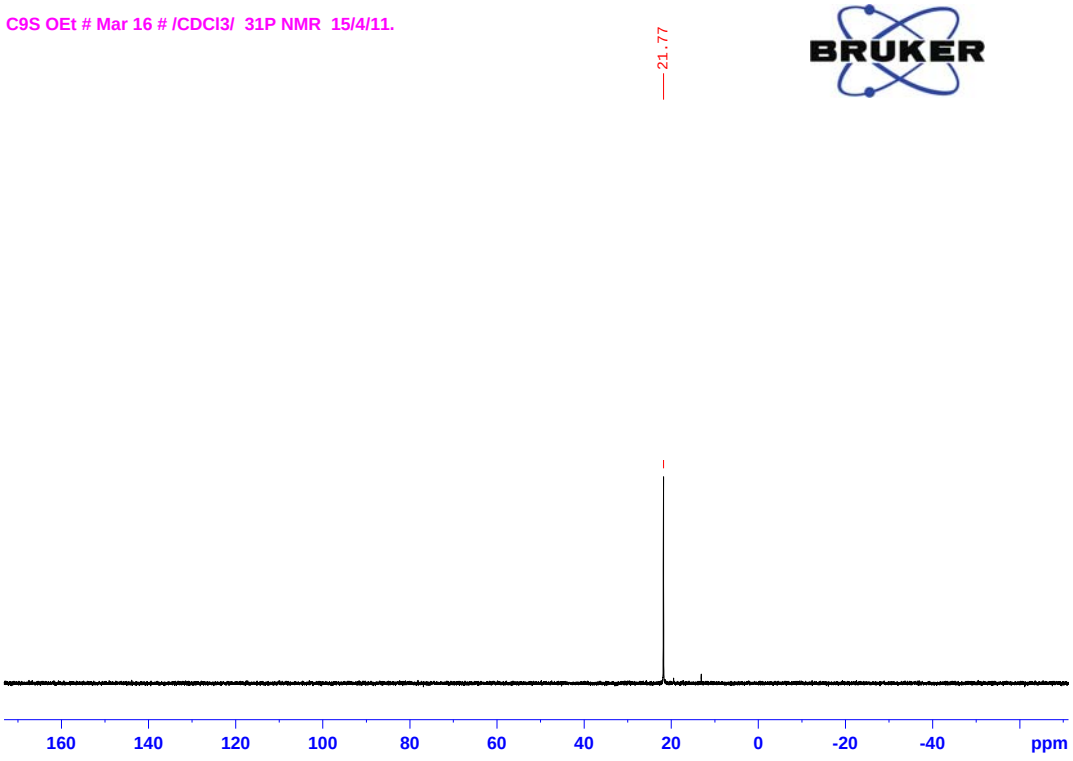

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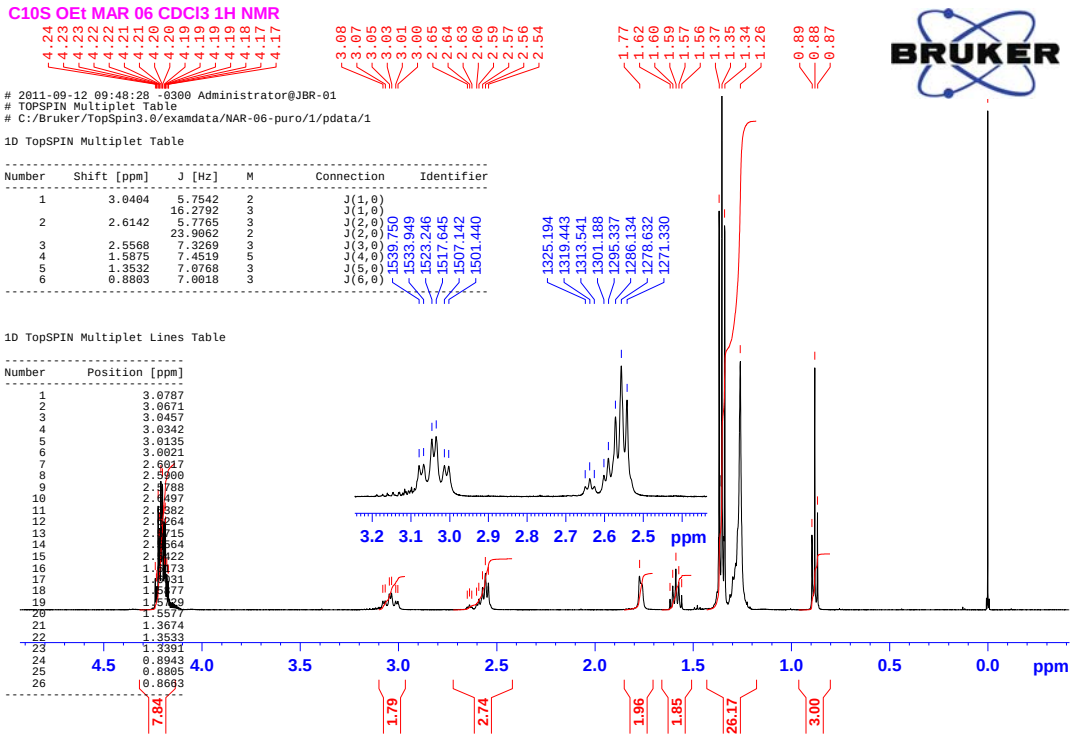

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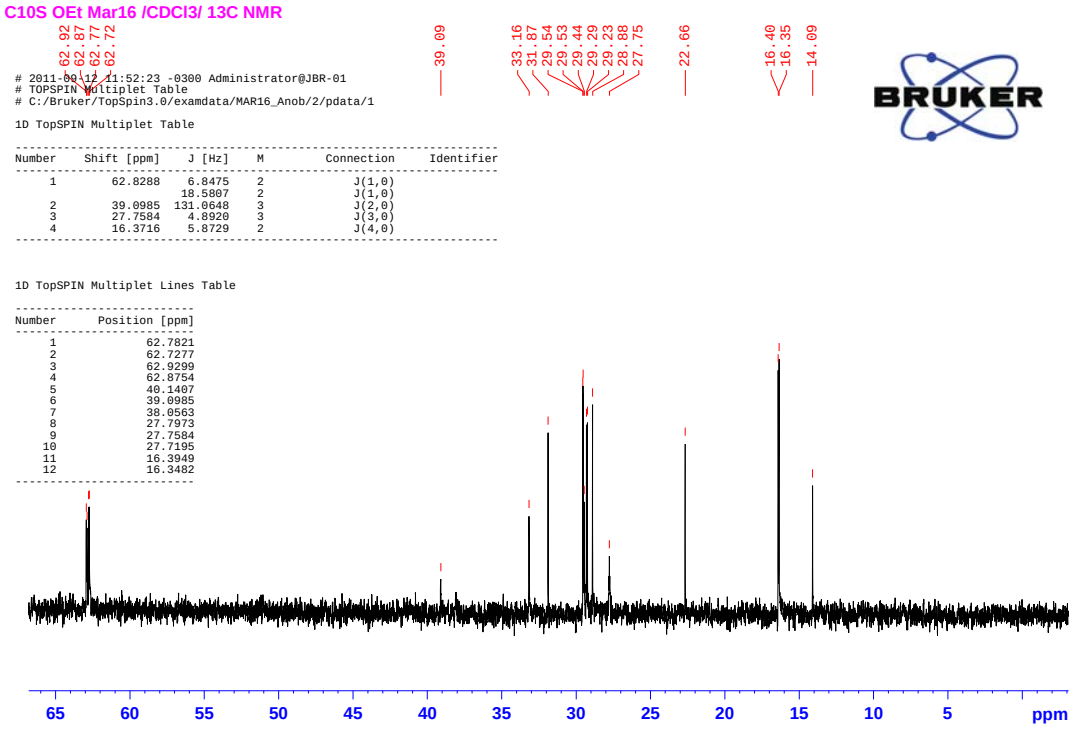

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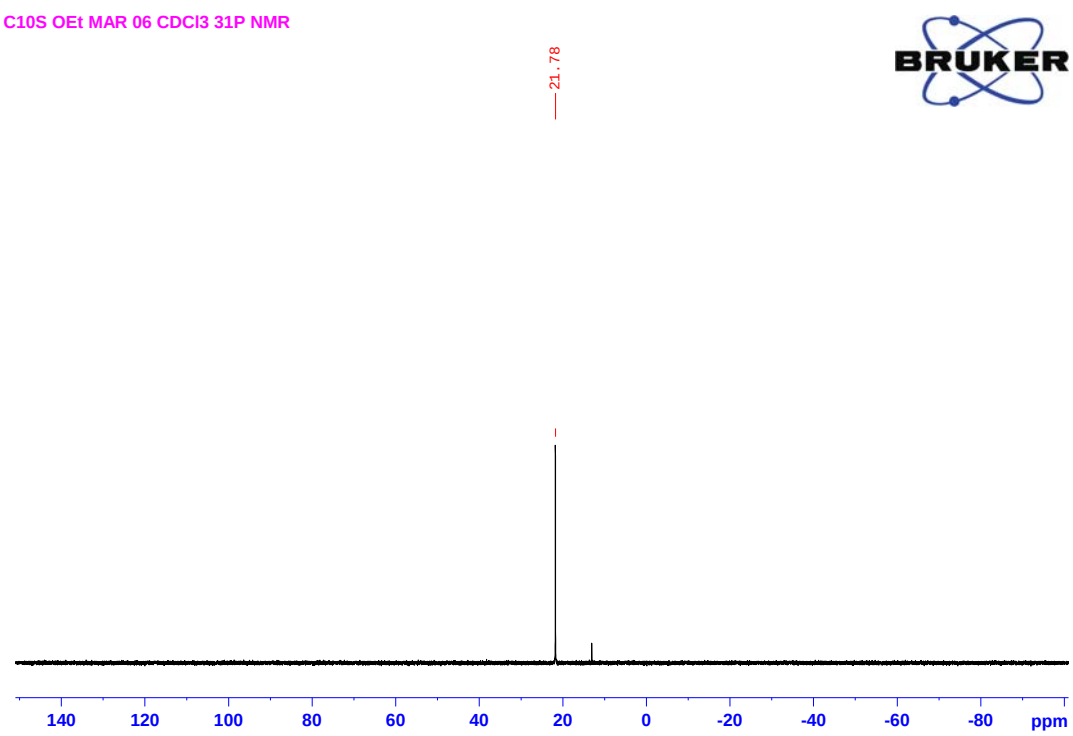

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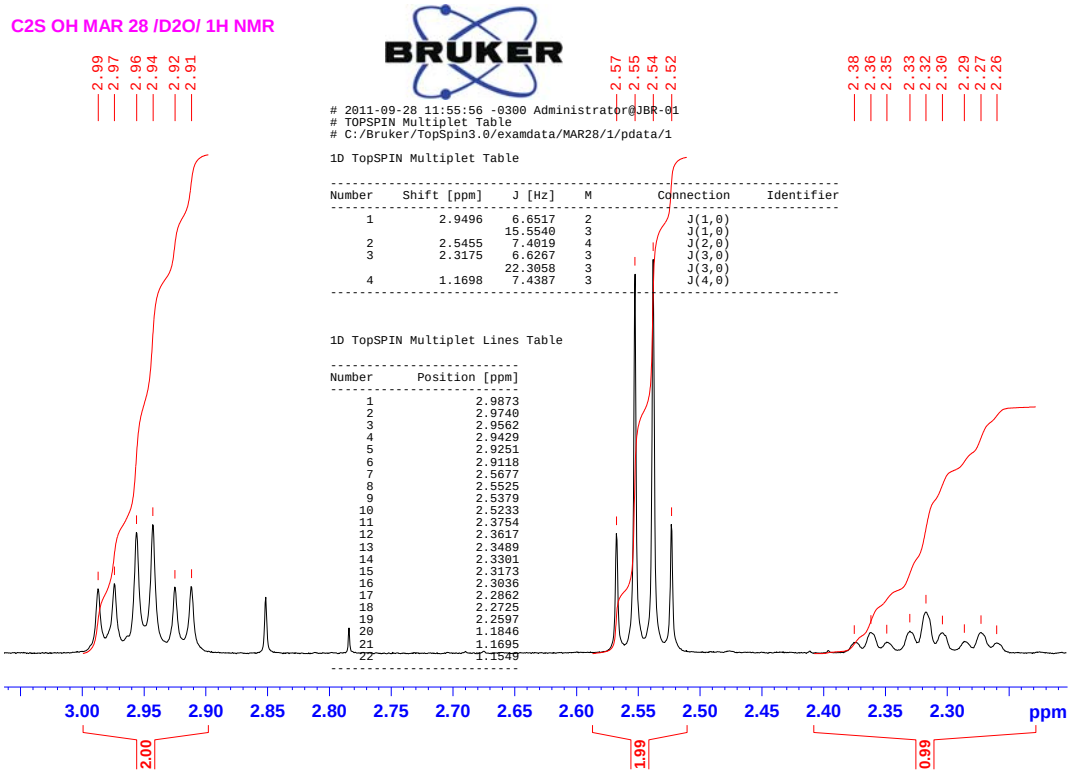

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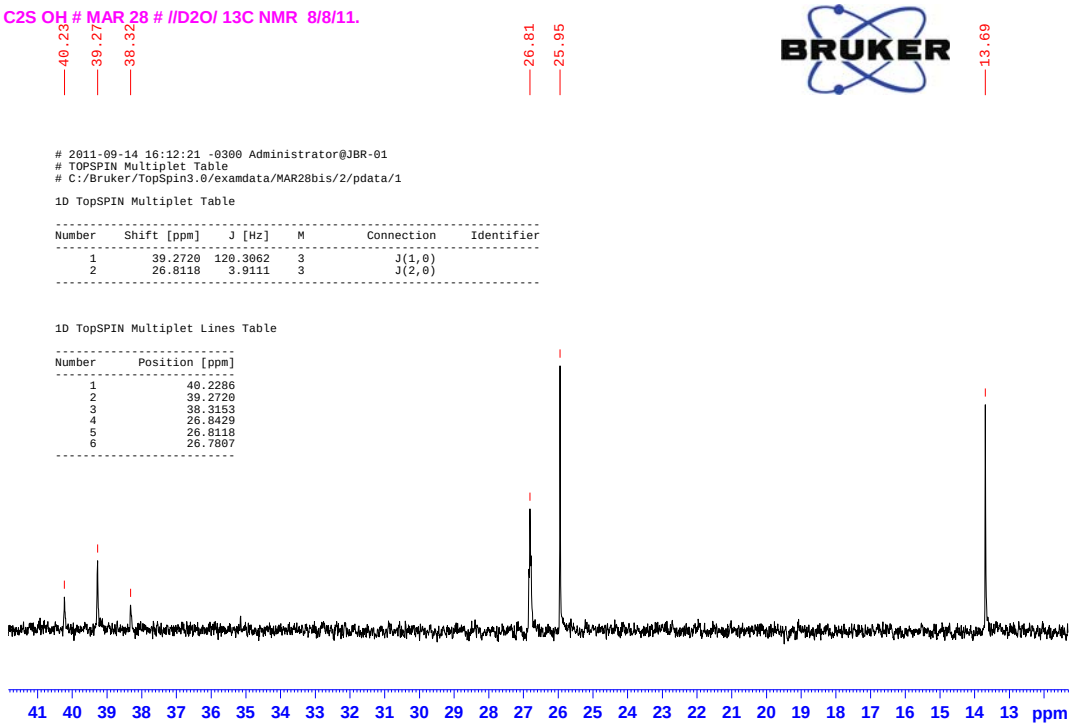

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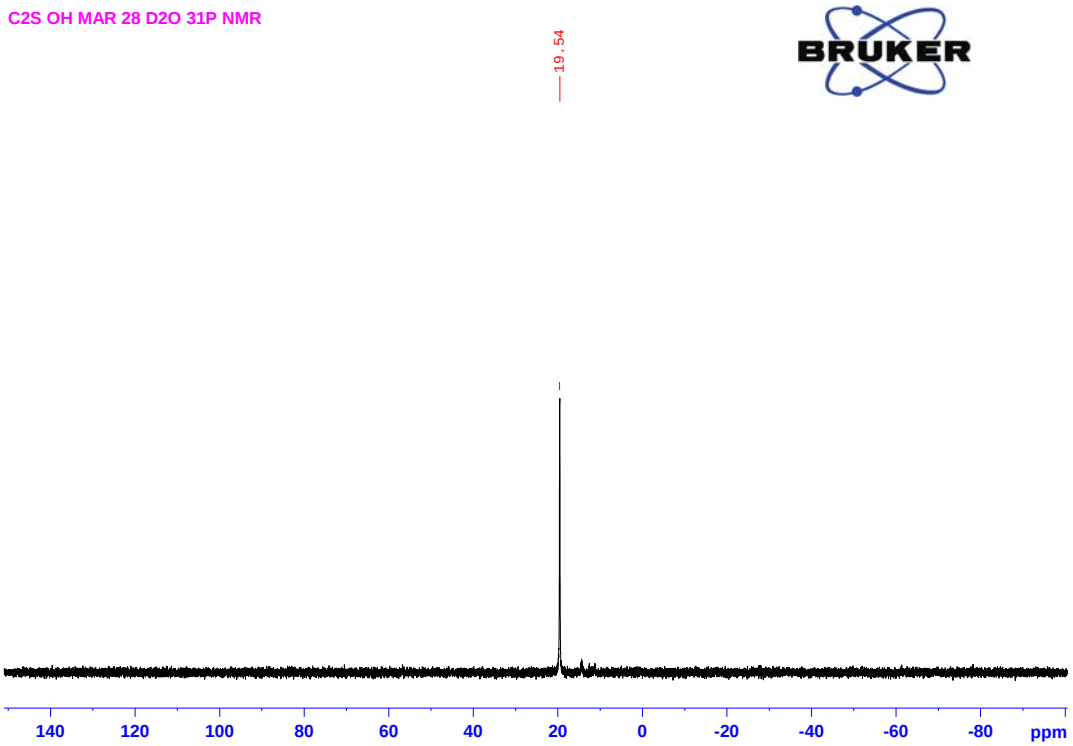

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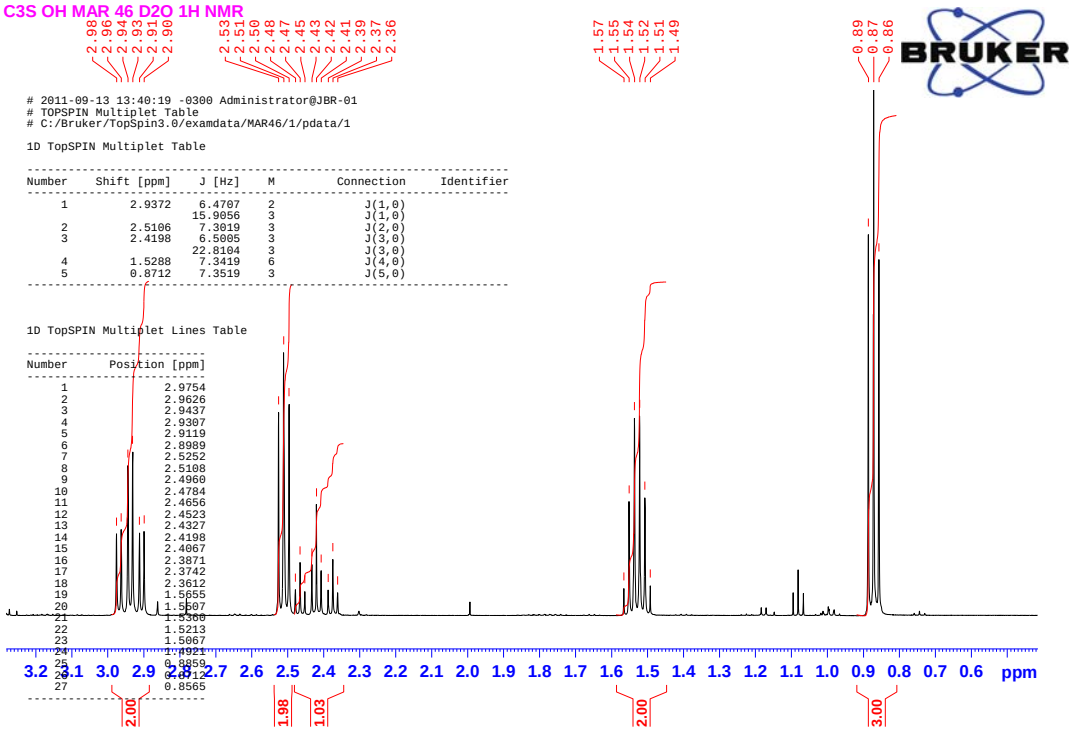

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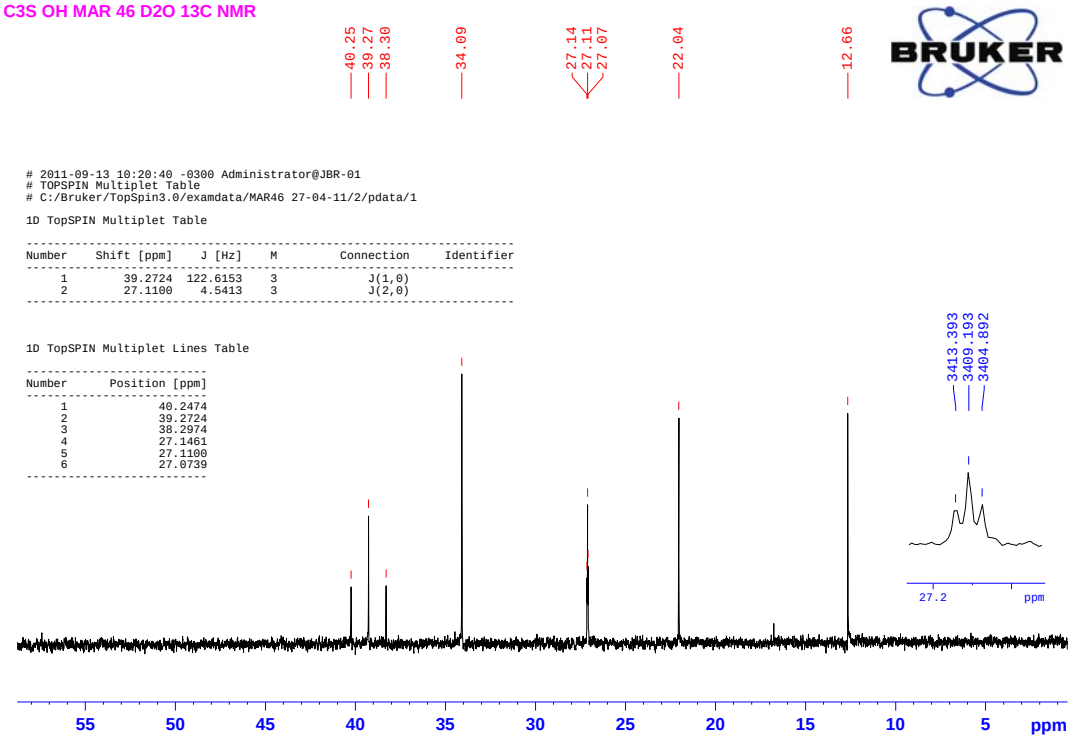

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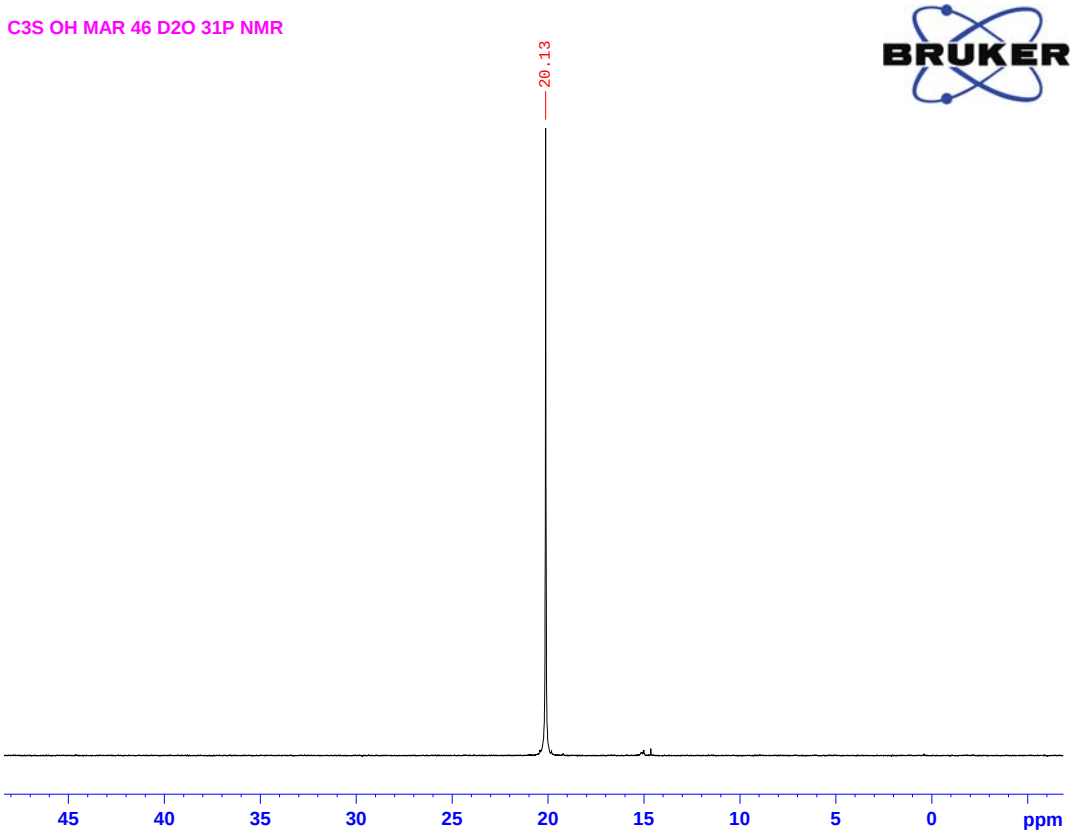

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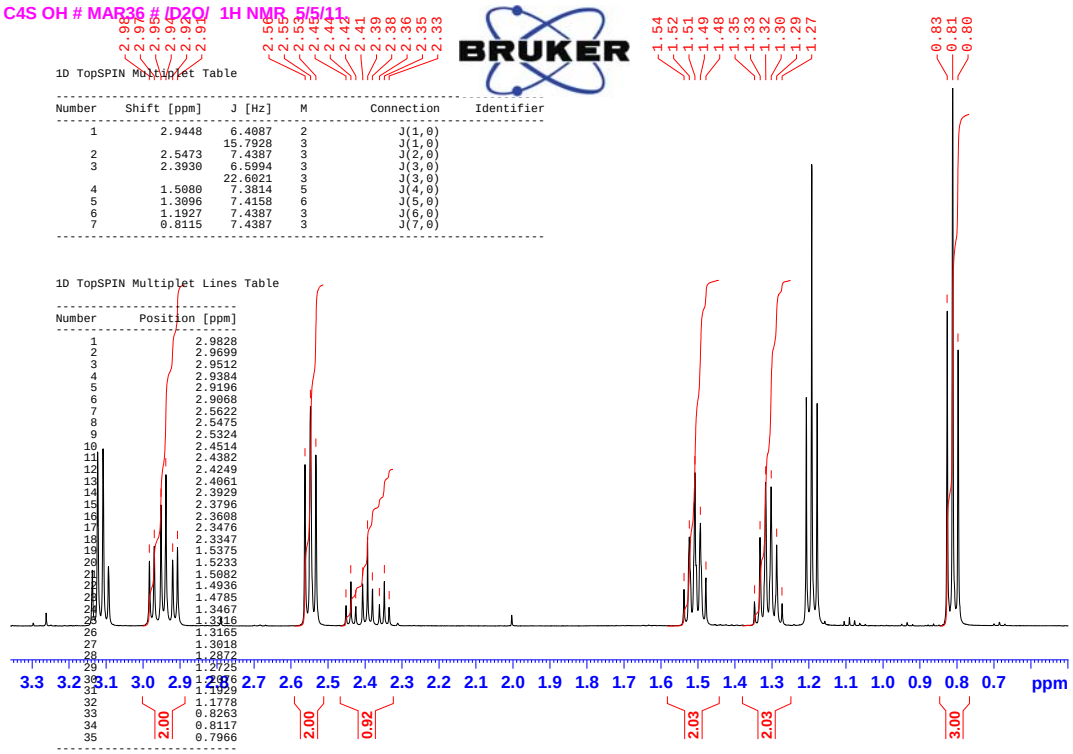

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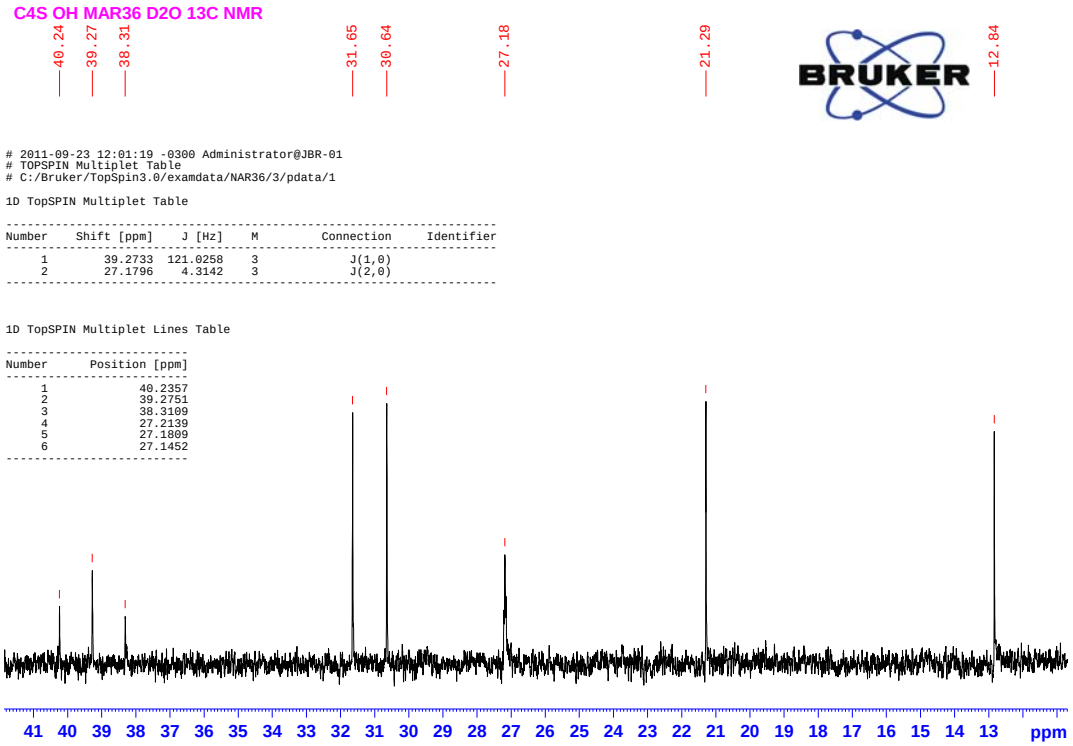

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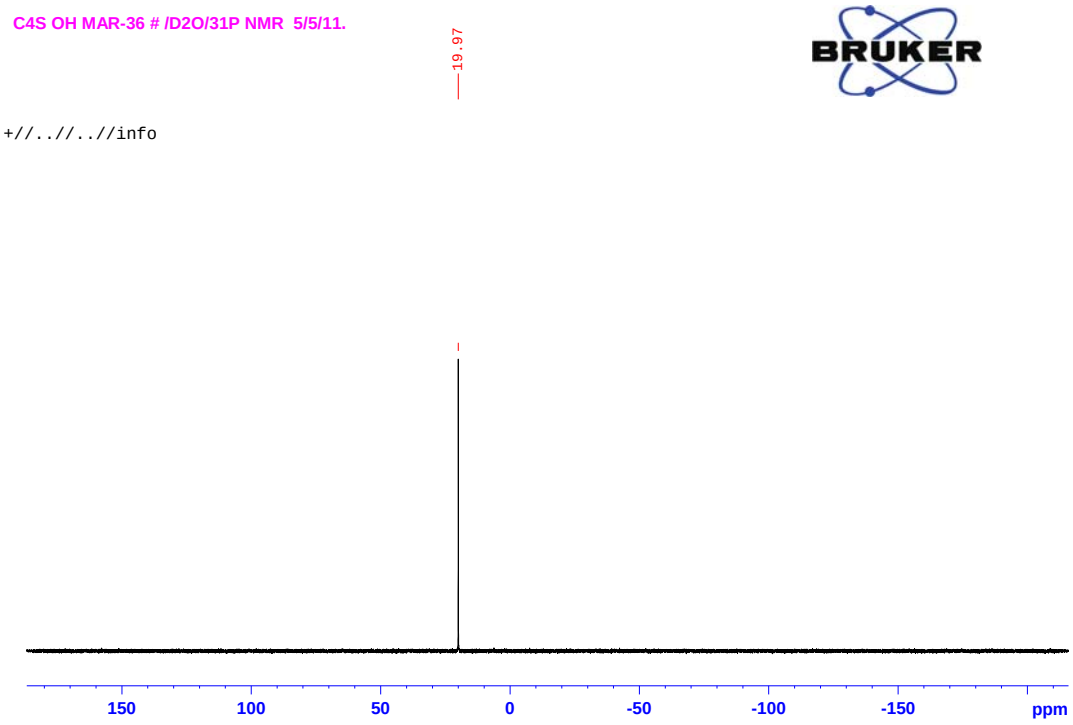

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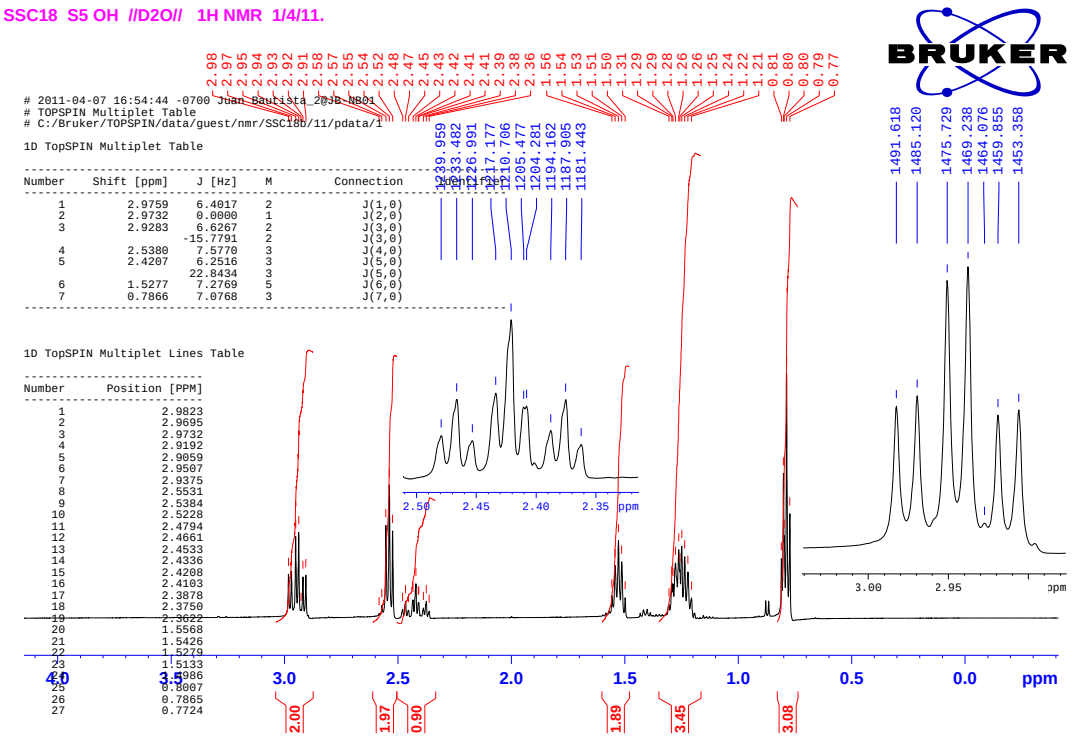

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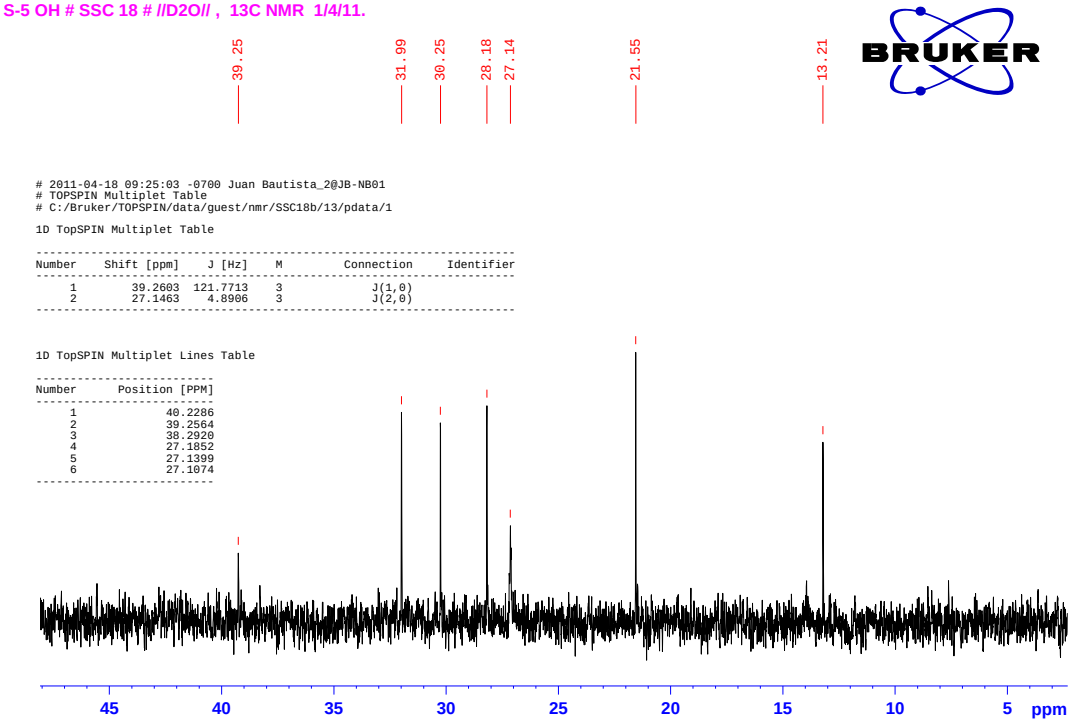

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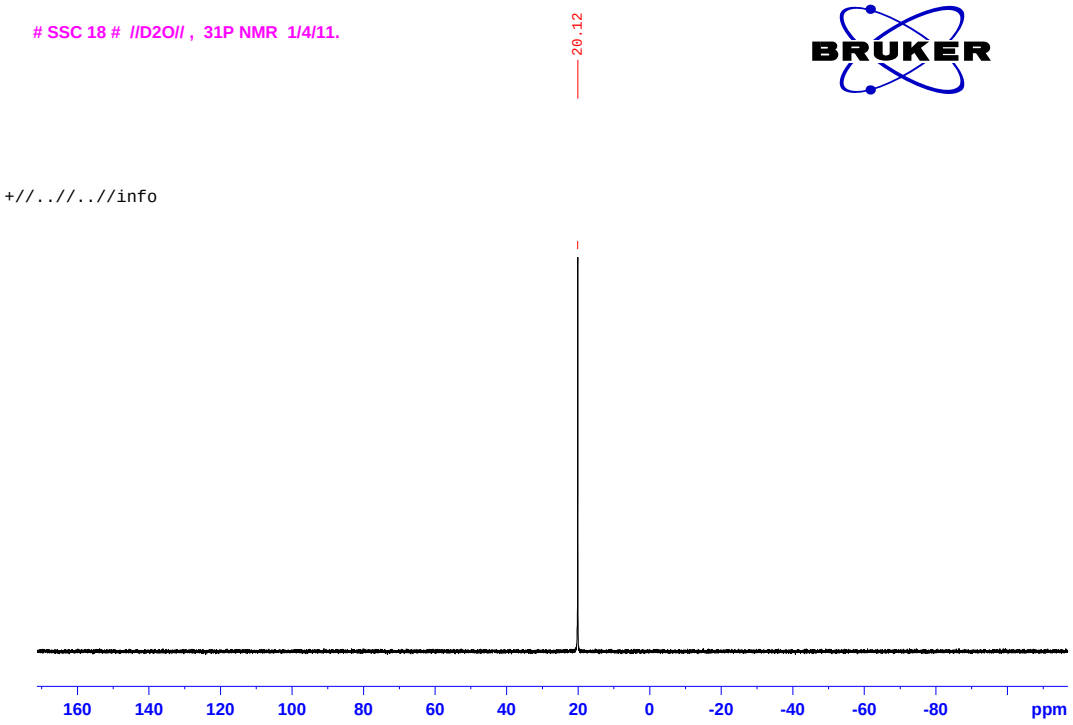

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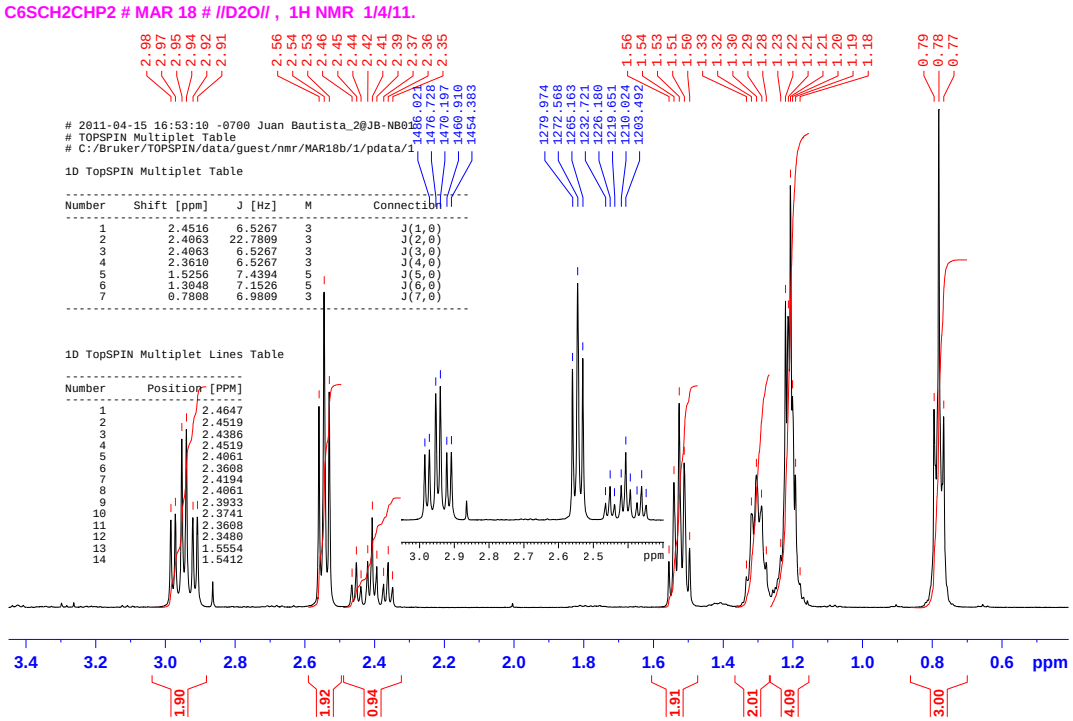

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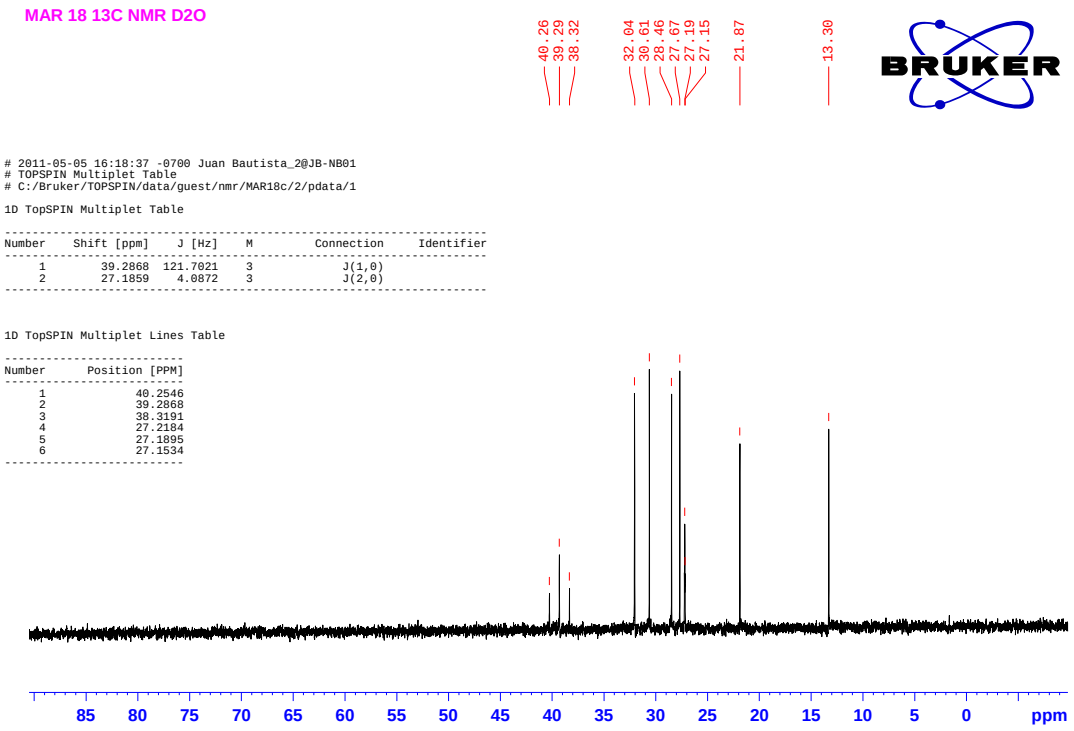

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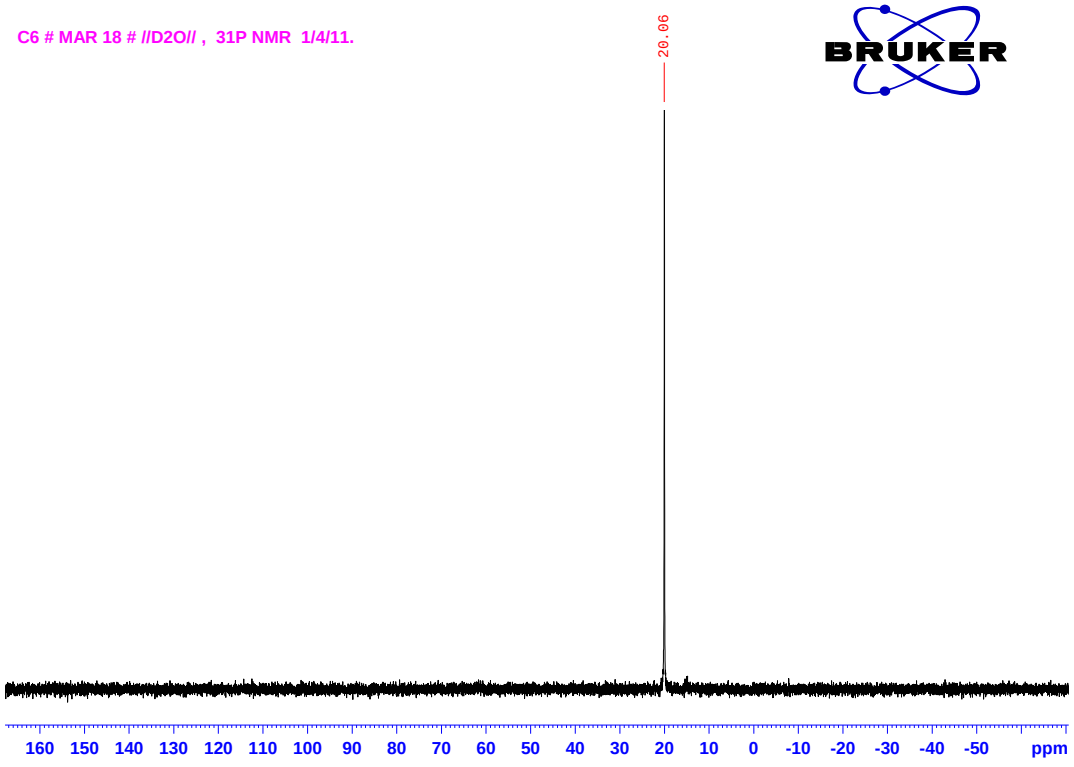

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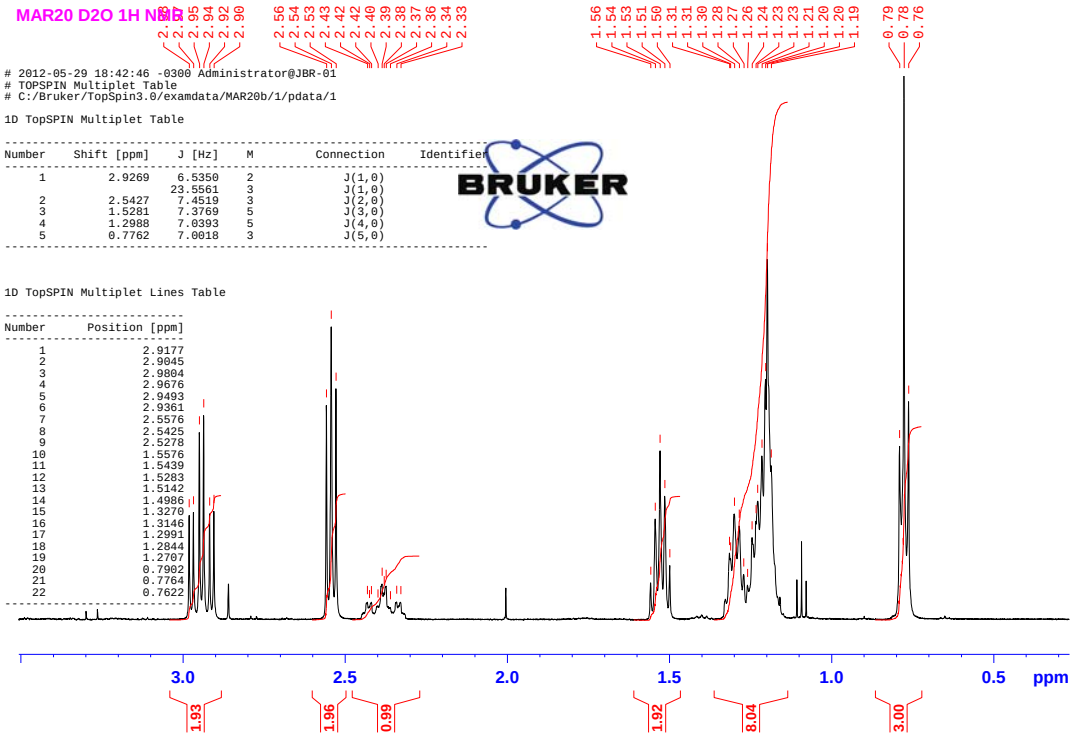

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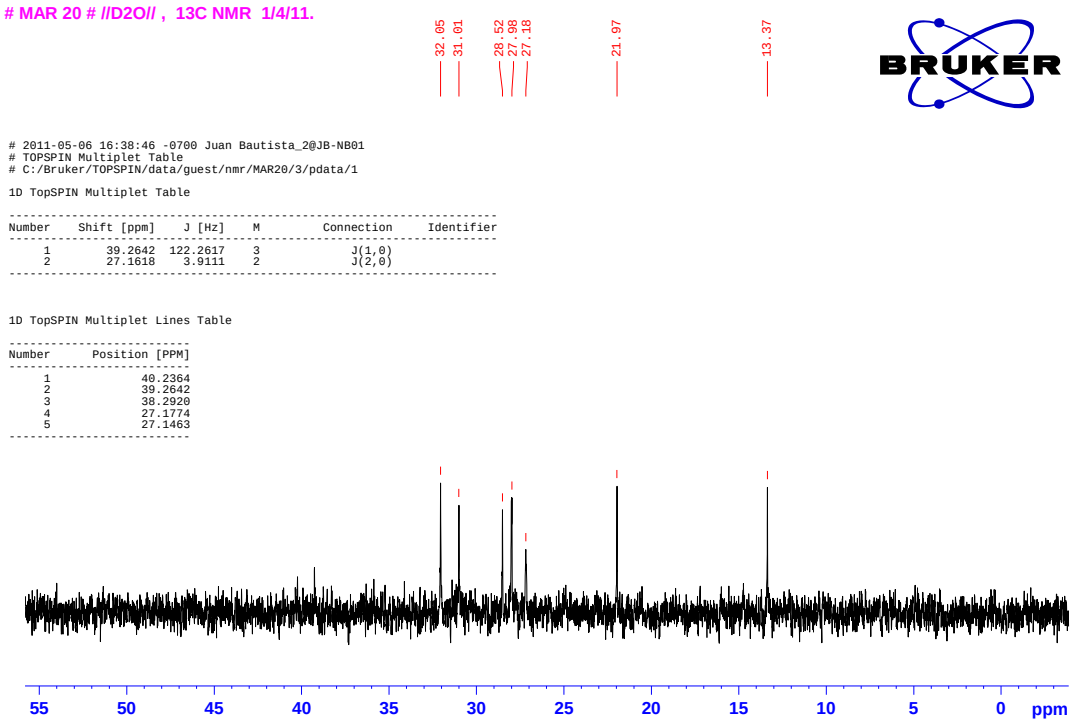

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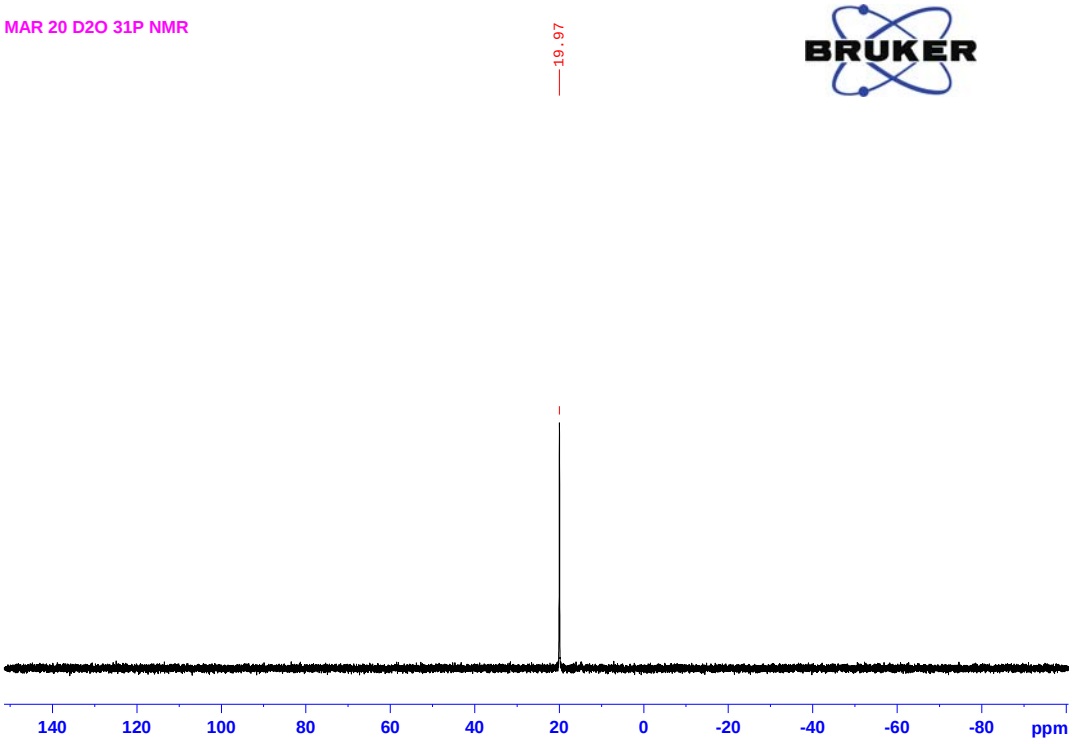

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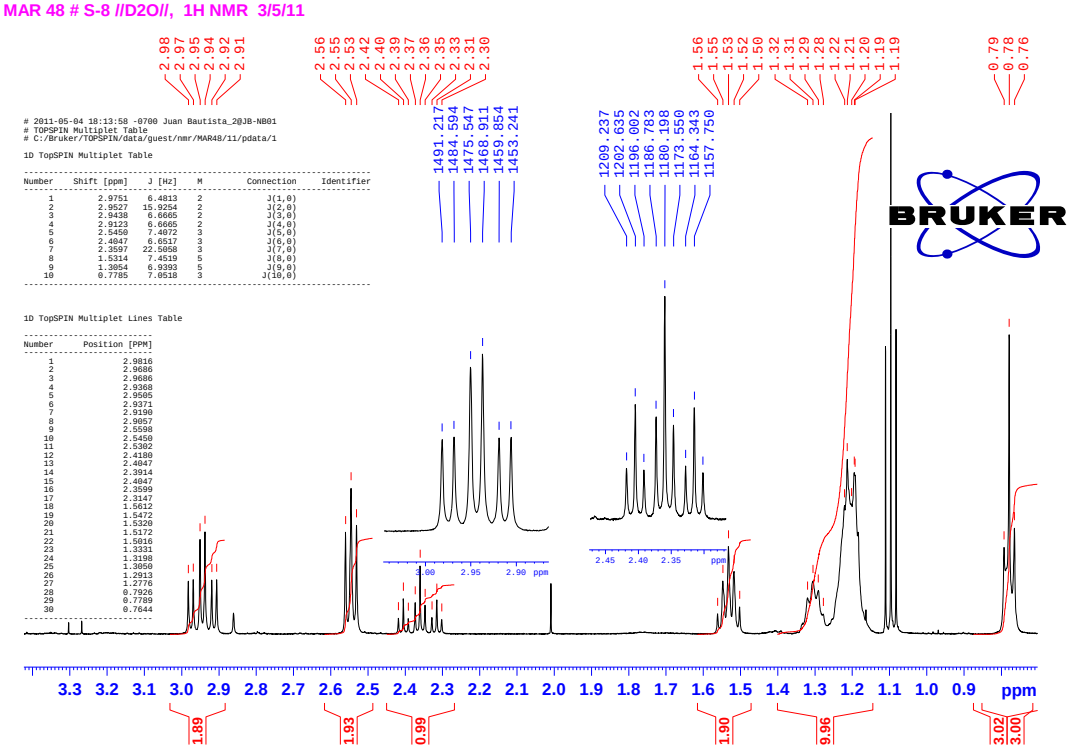

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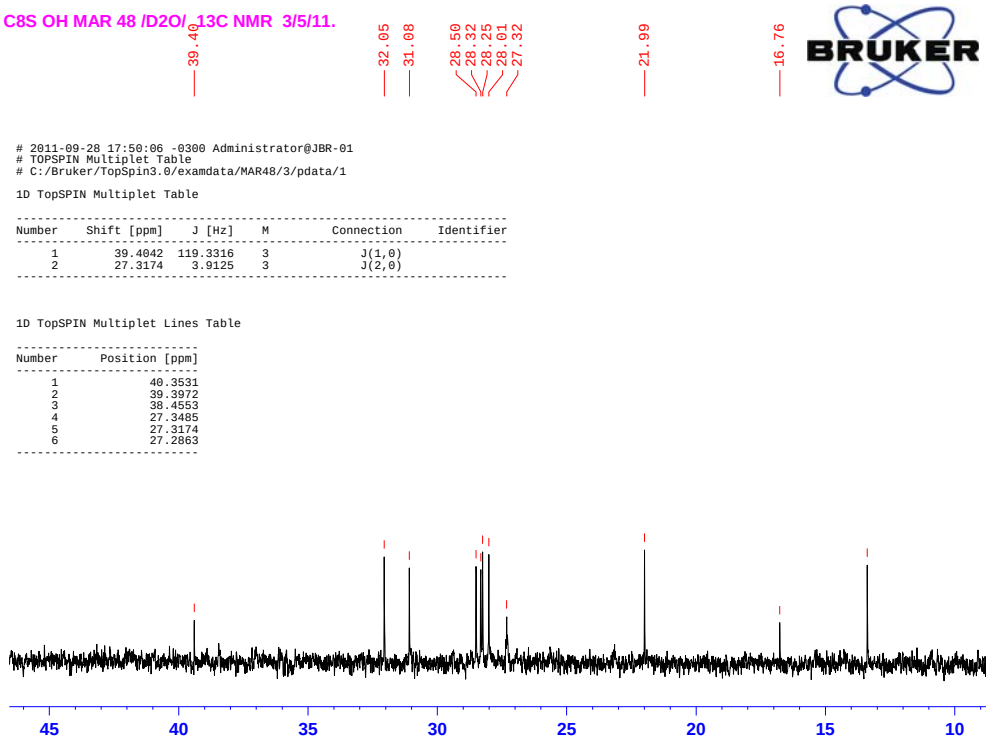

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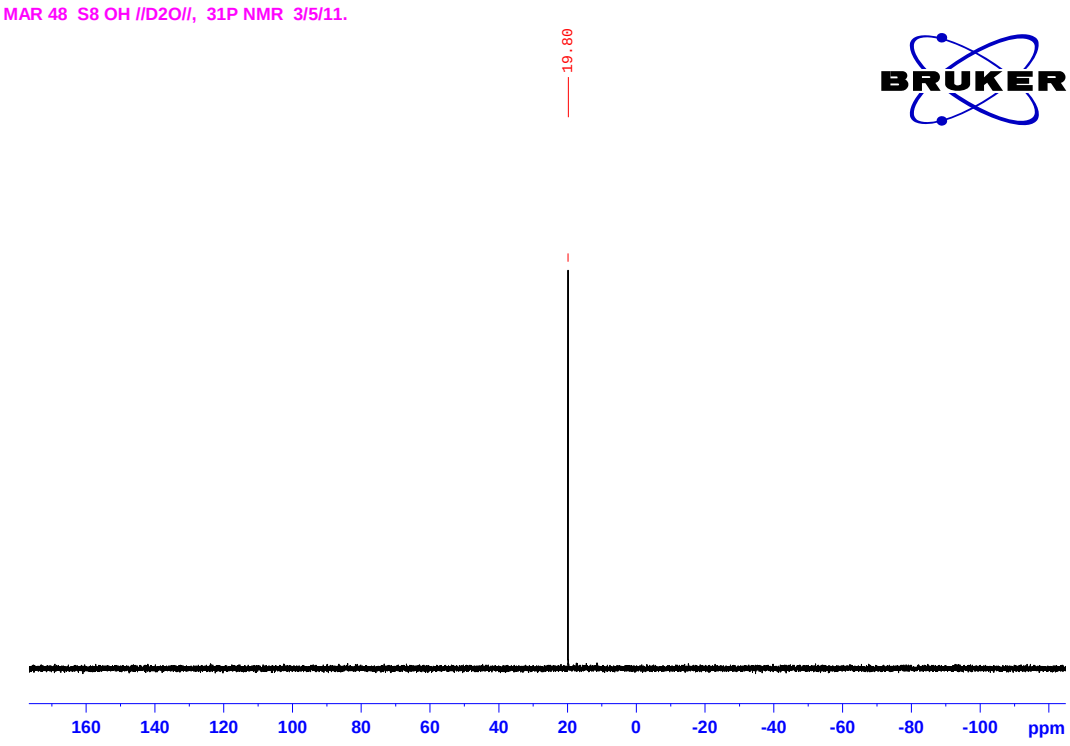

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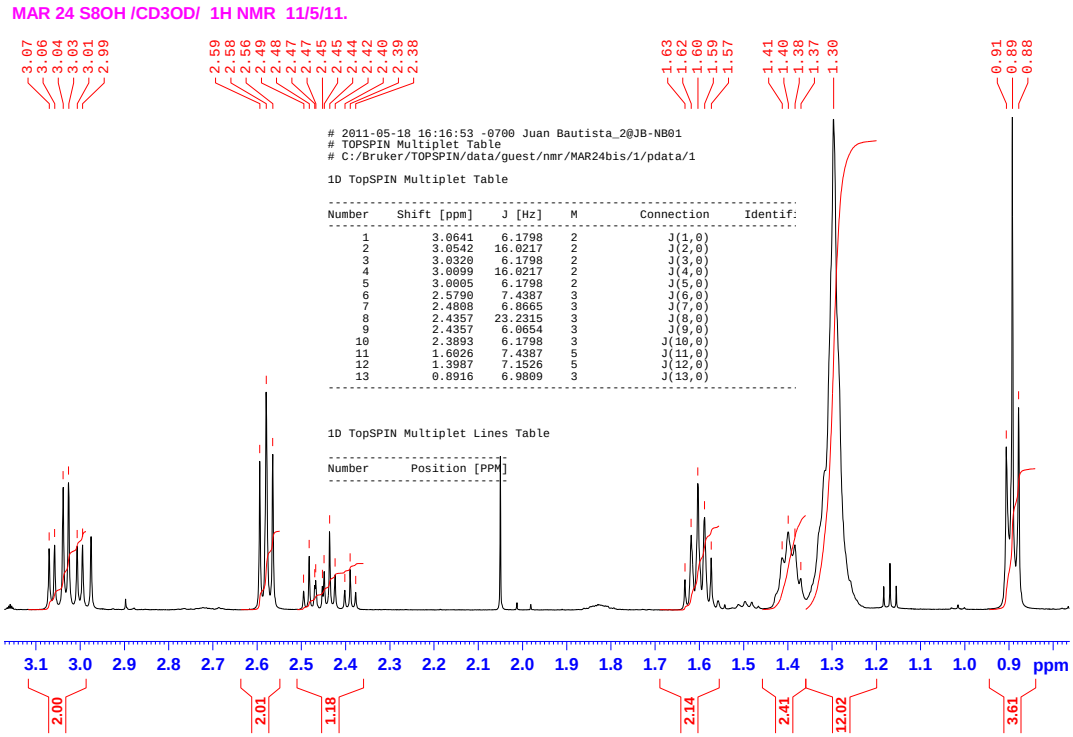
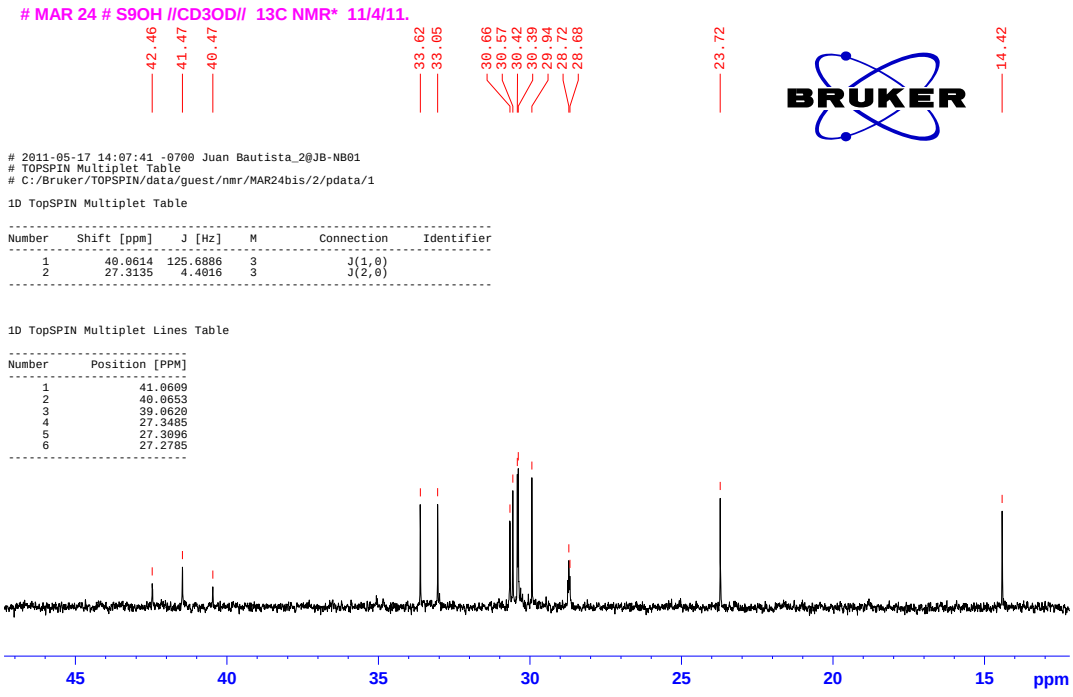
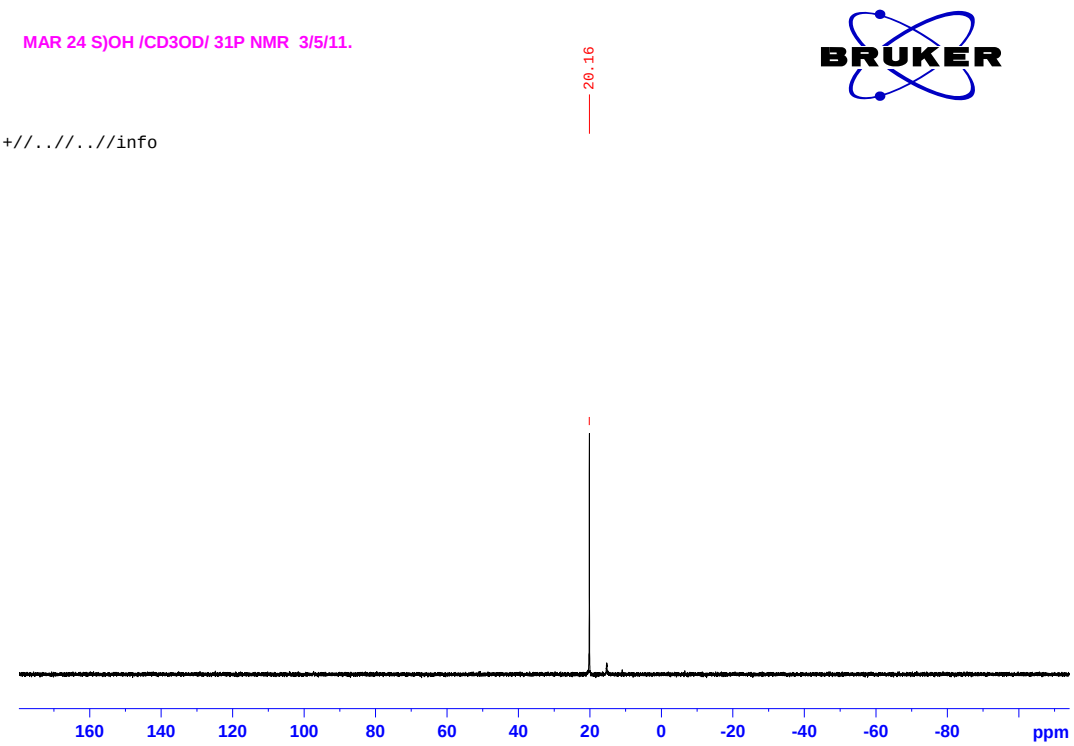


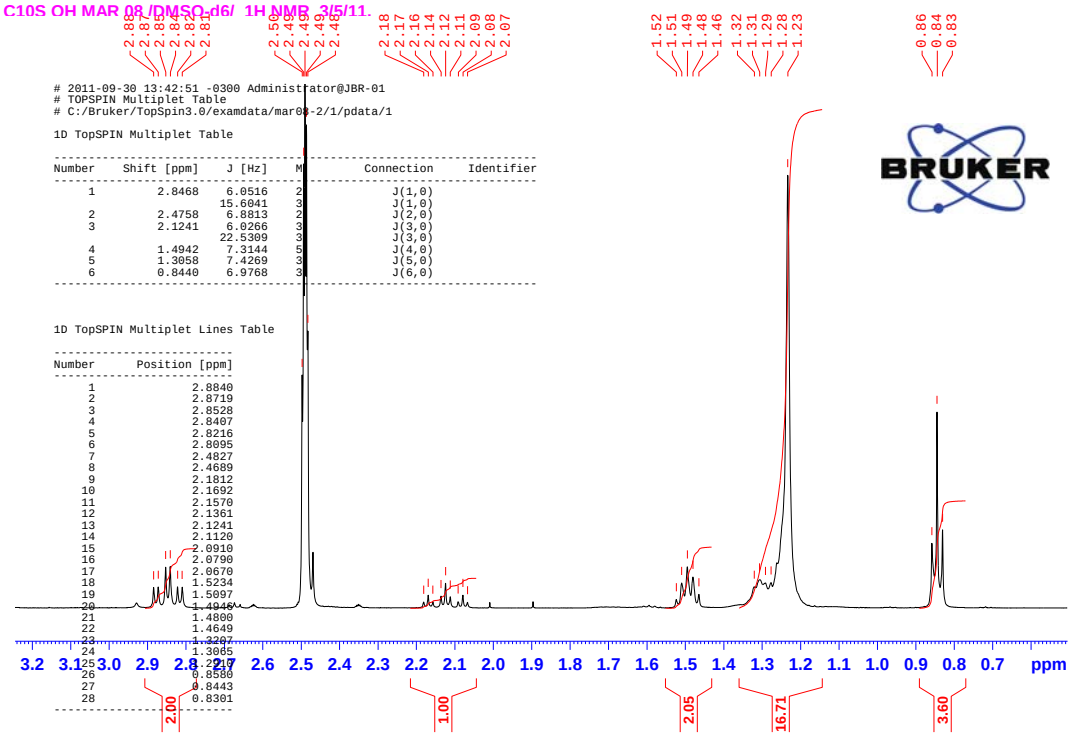
^{1}H NMR spectrum of compound **38**.



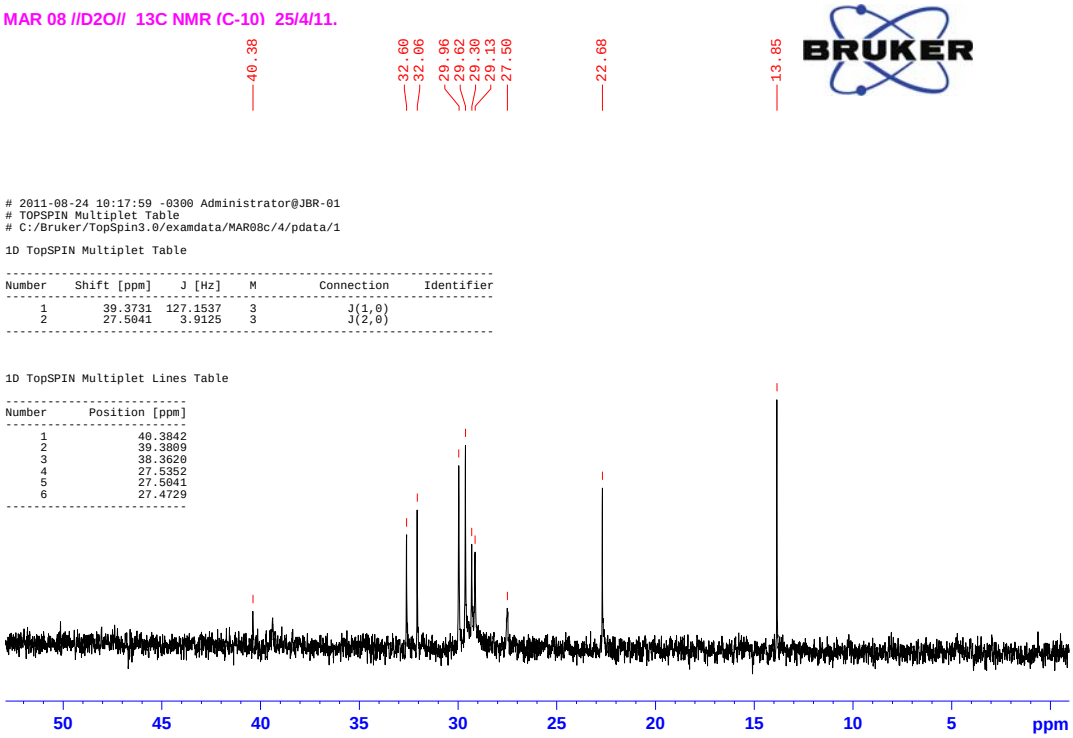
^{13}C NMR spectrum of compound **38**.



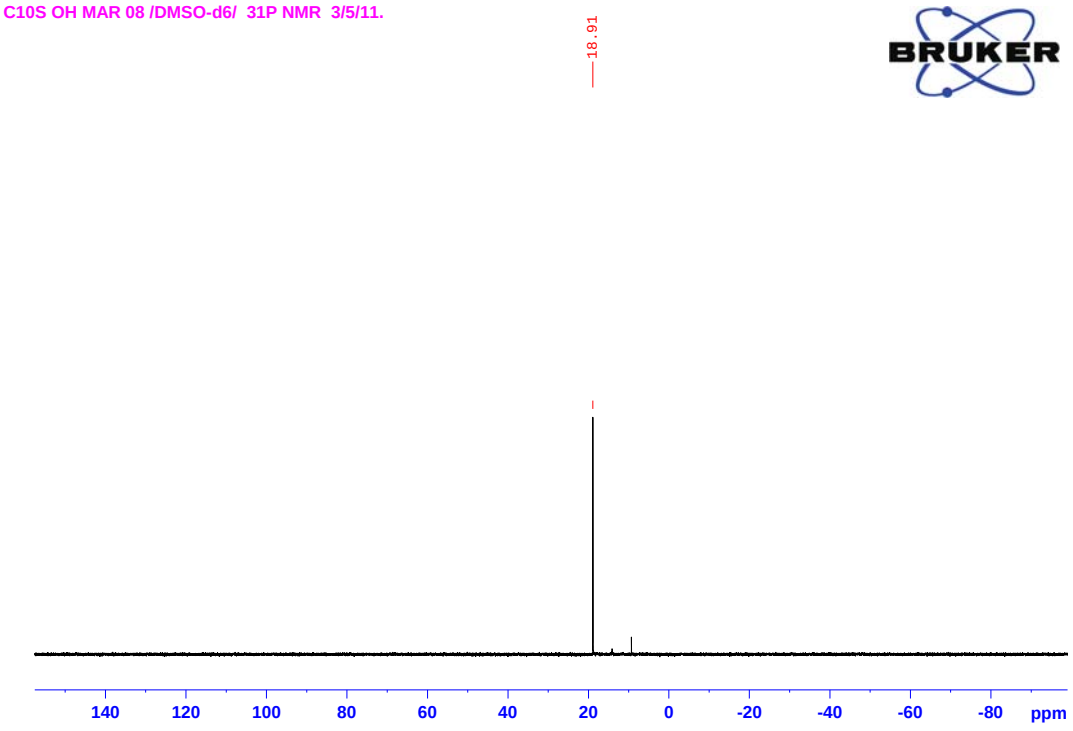
^{31}P NMR spectrum of compound **38**.



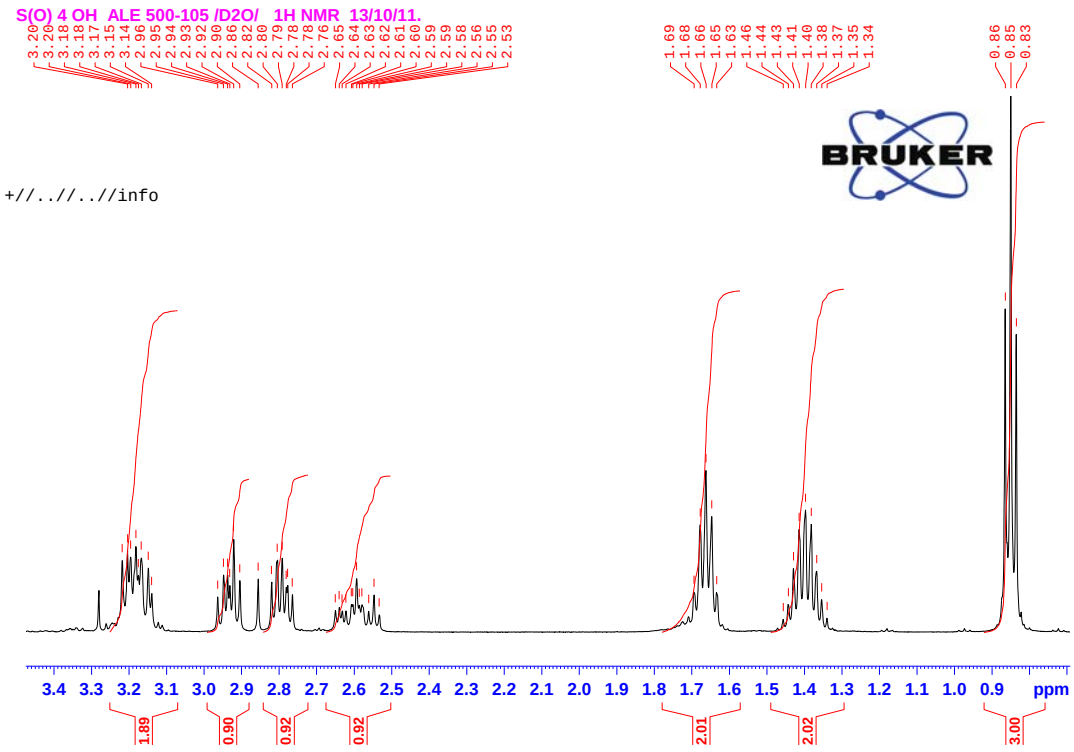
^{1}H NMR spectrum of compound **39**.



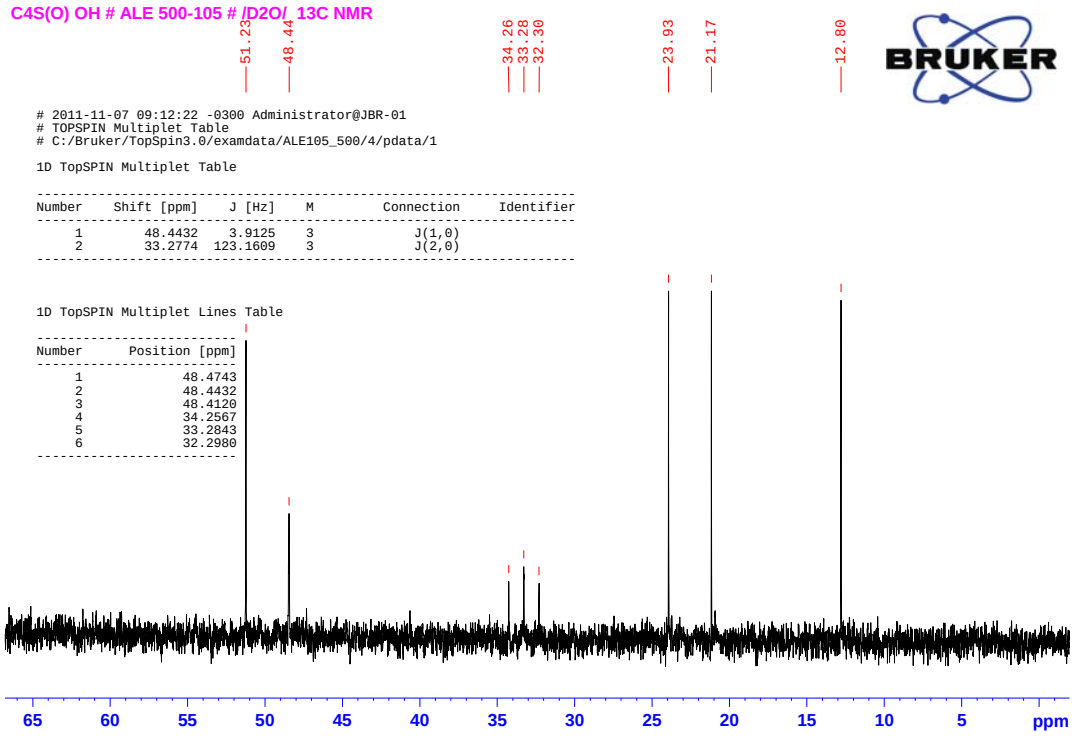
^{13}C NMR spectrum of compound **39**.



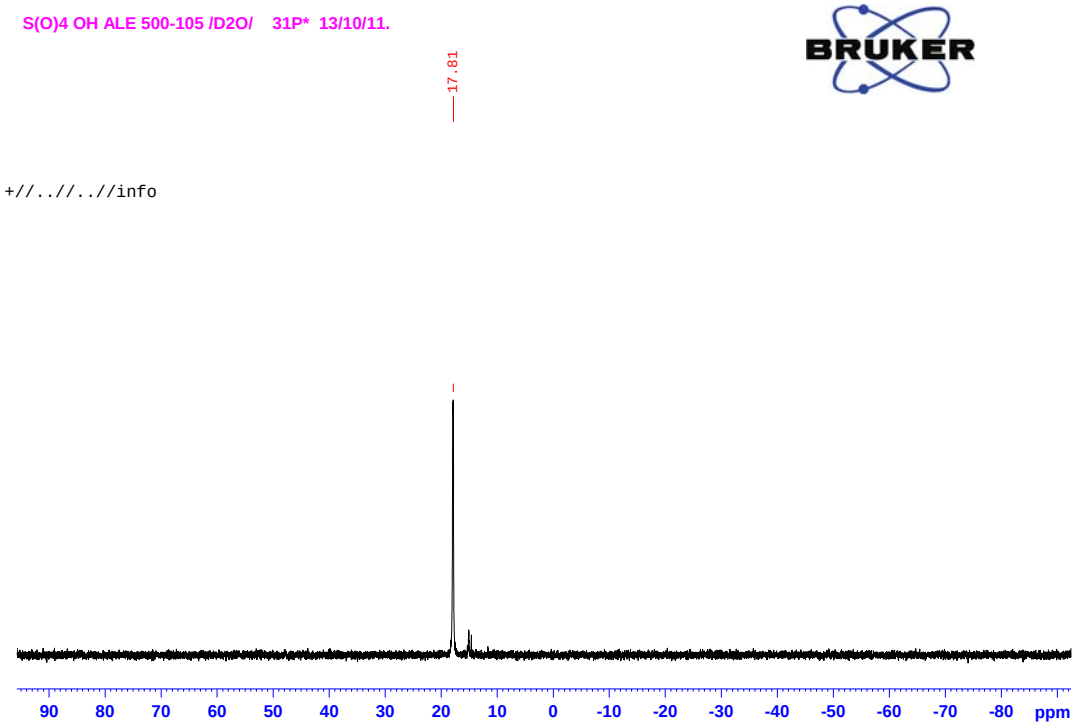
^{31}P NMR spectrum of compound **39**.



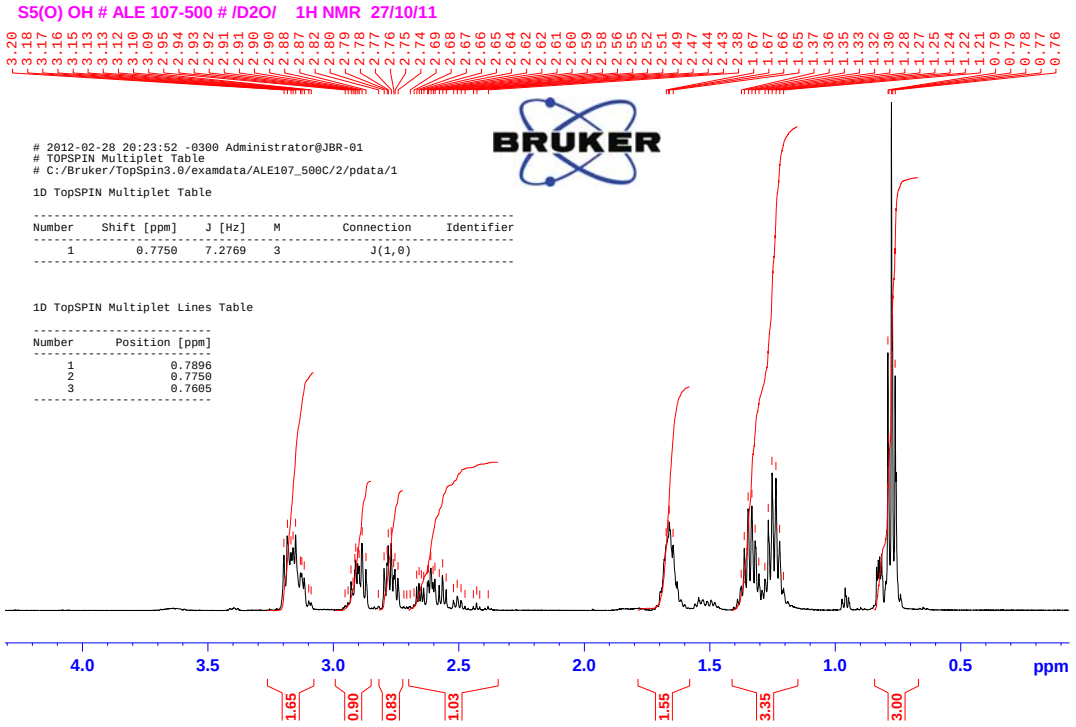
^{1}H NMR spectrum of compound **40**.



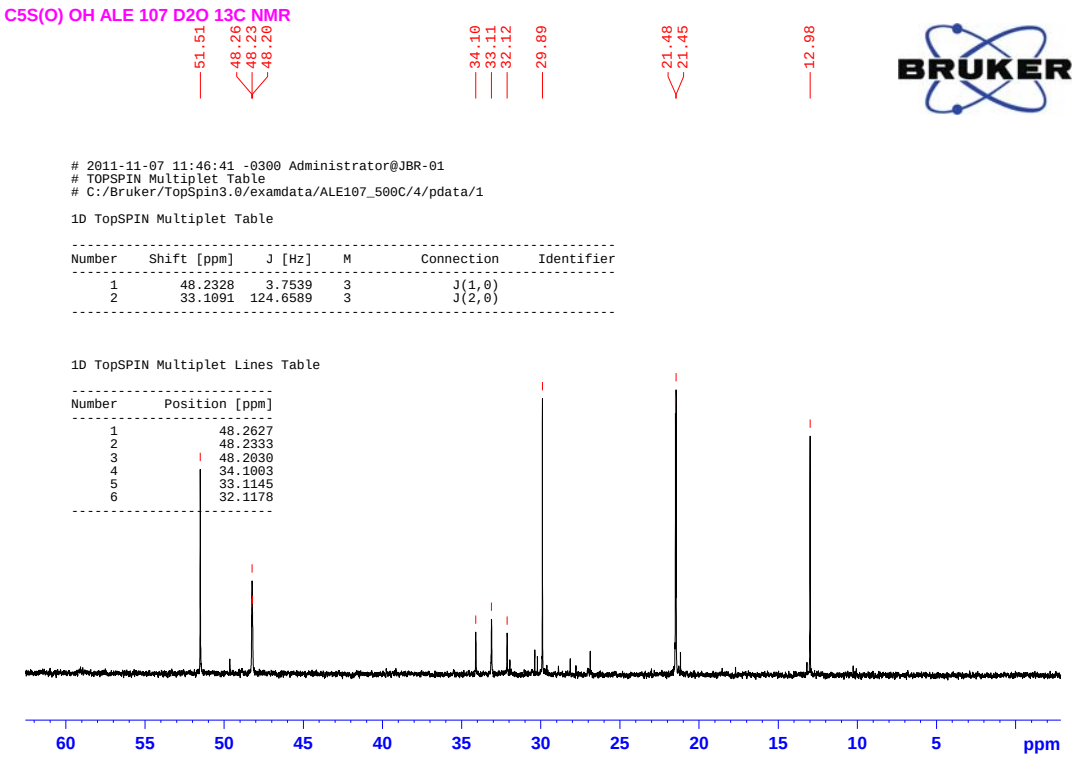
^{13}C NMR spectrum of compound **40**.



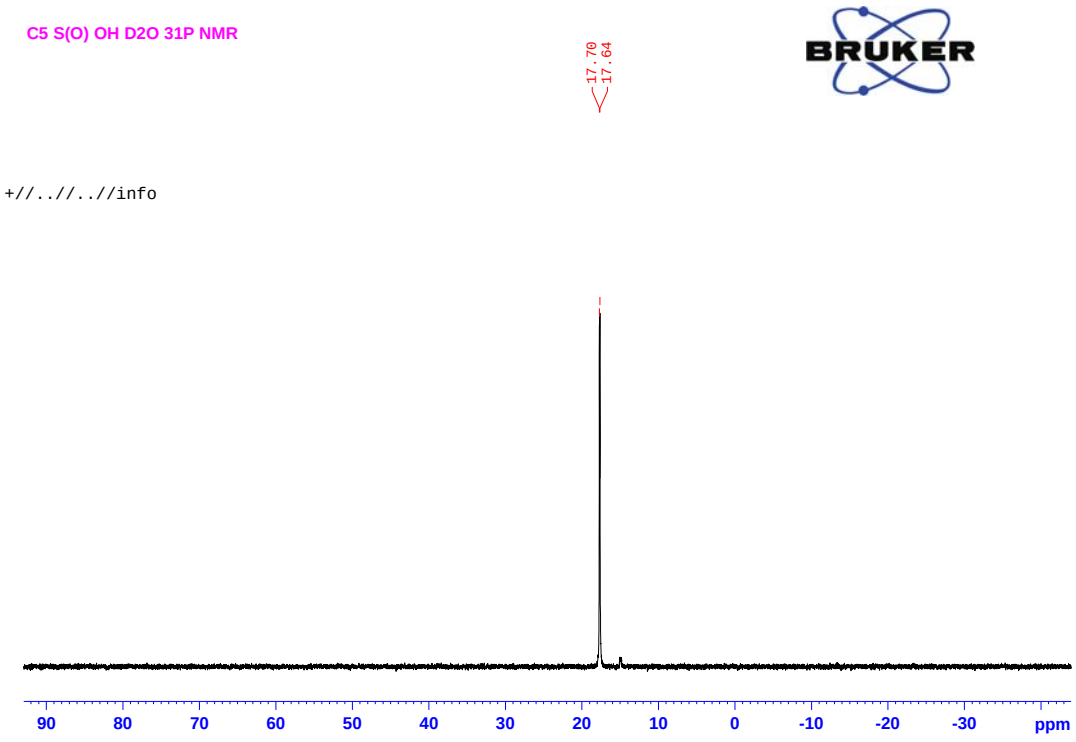
^{31}P NMR spectrum of compound **40**.



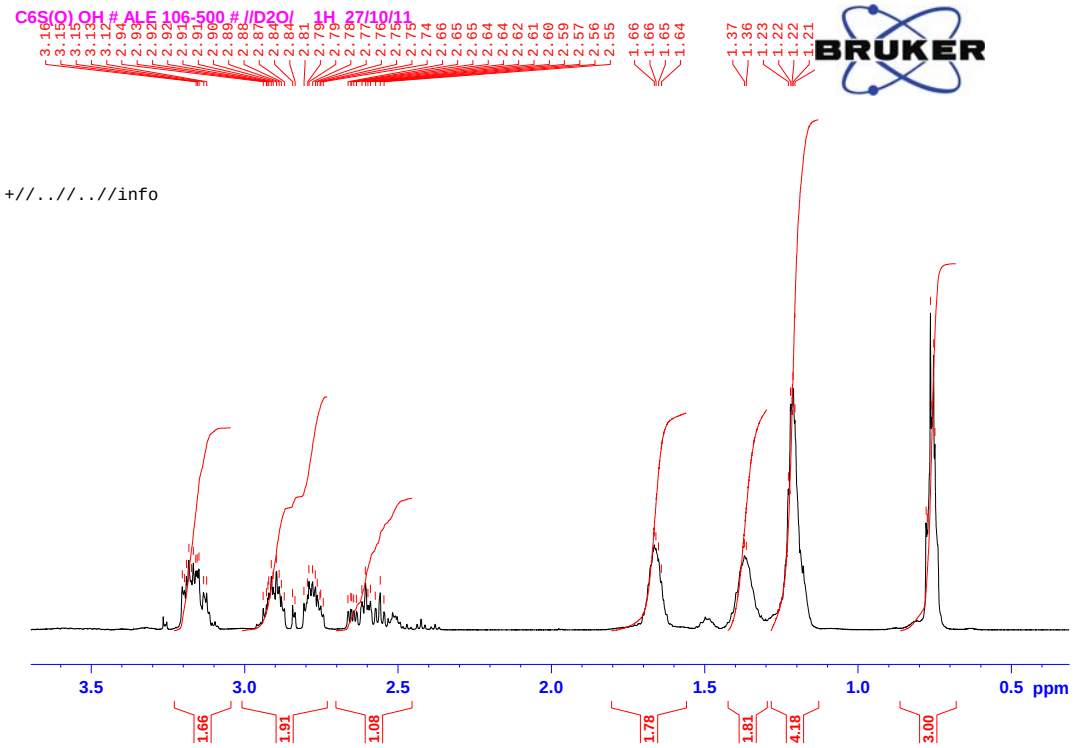
^{1}H NMR spectrum of compound **41**.



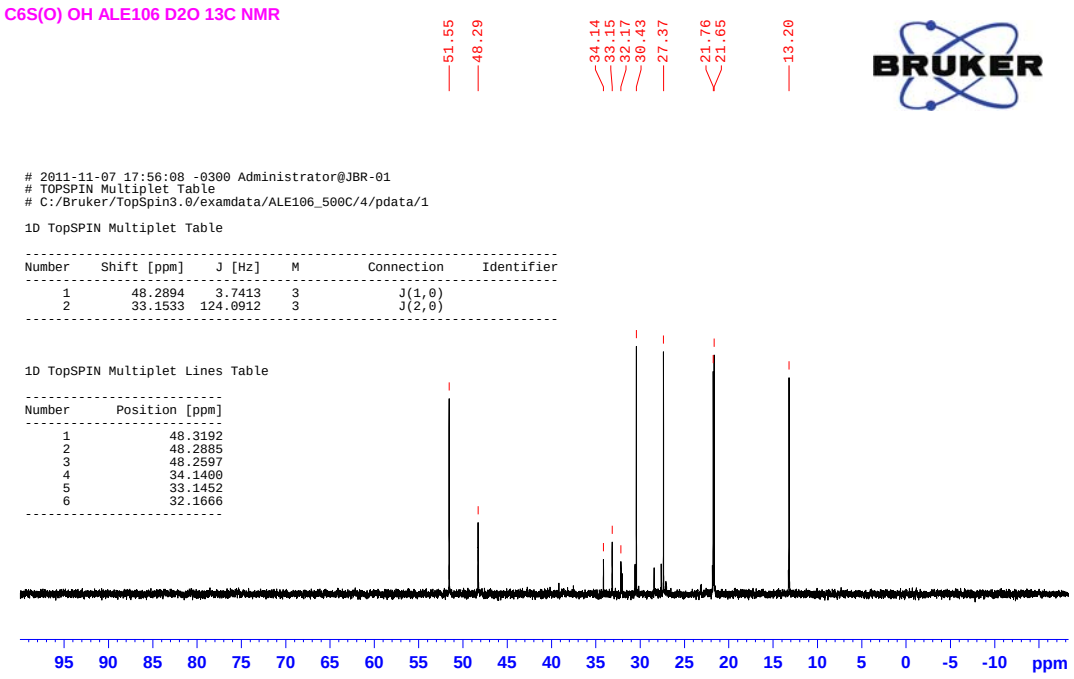
^{13}C NMR spectrum of compound **41**.



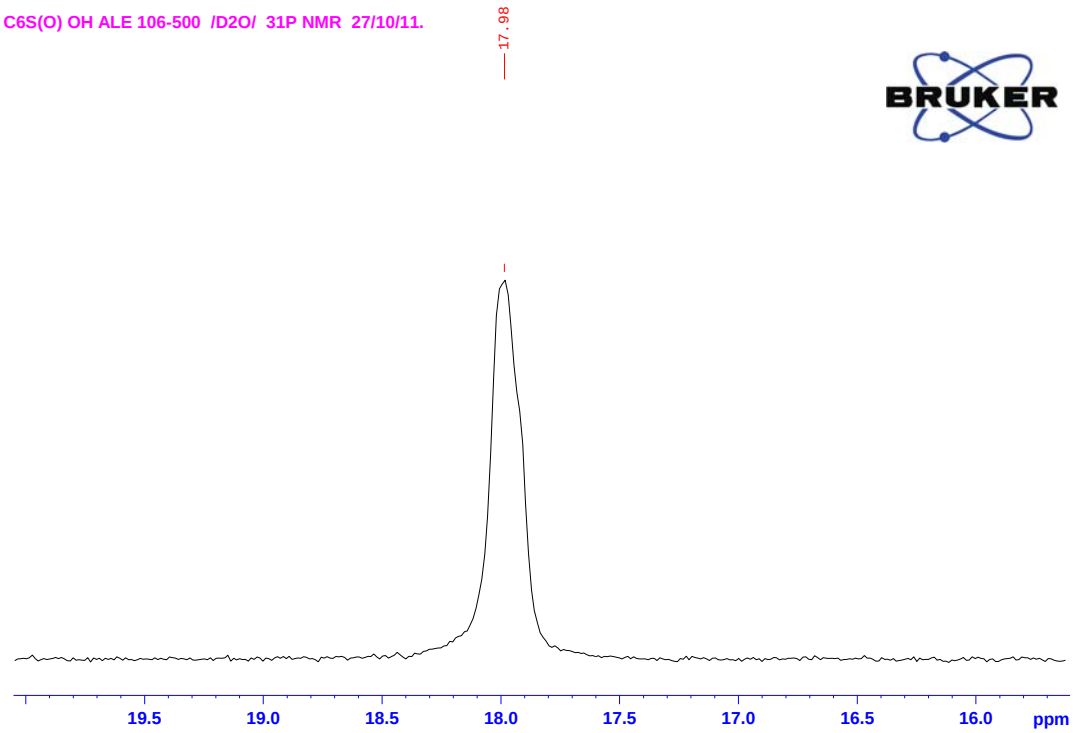
^{31}P NMR spectrum of compound **41**.



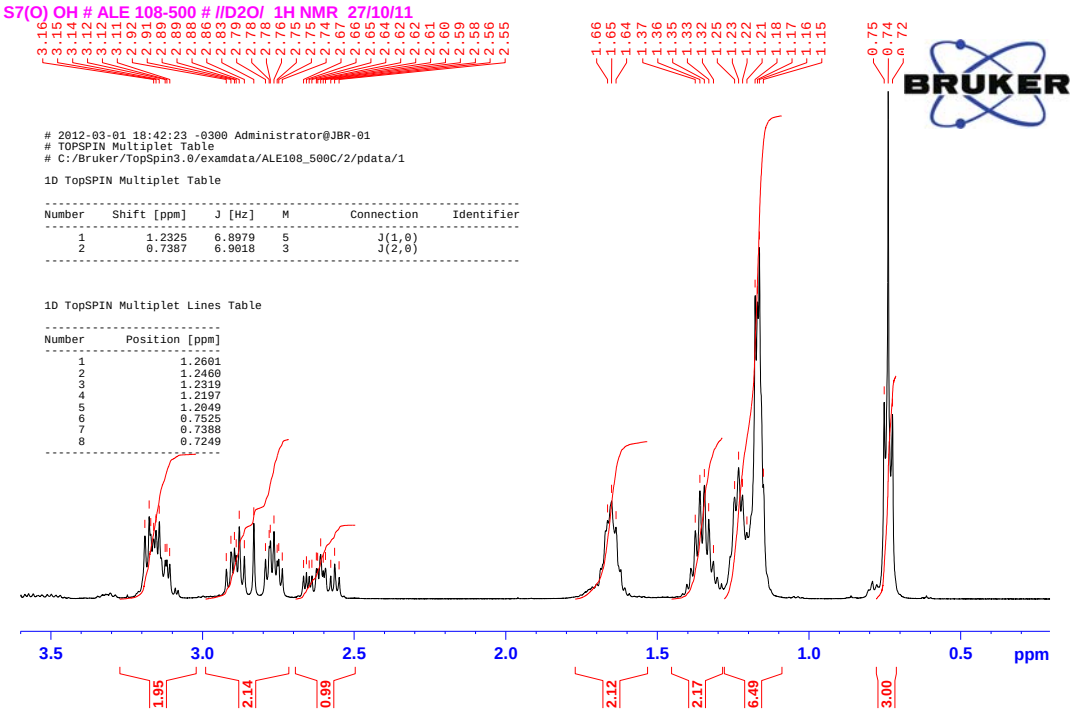
^{1}H NMR spectrum of compound **42**.



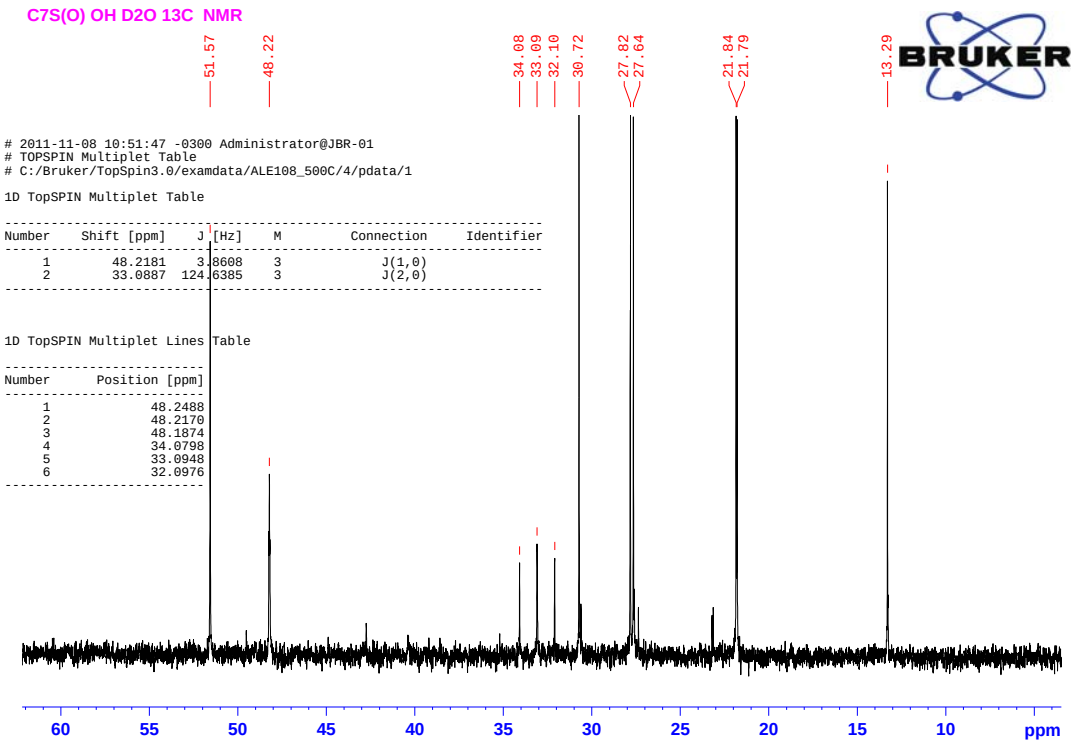
^{13}C NMR spectrum of compound **42**.



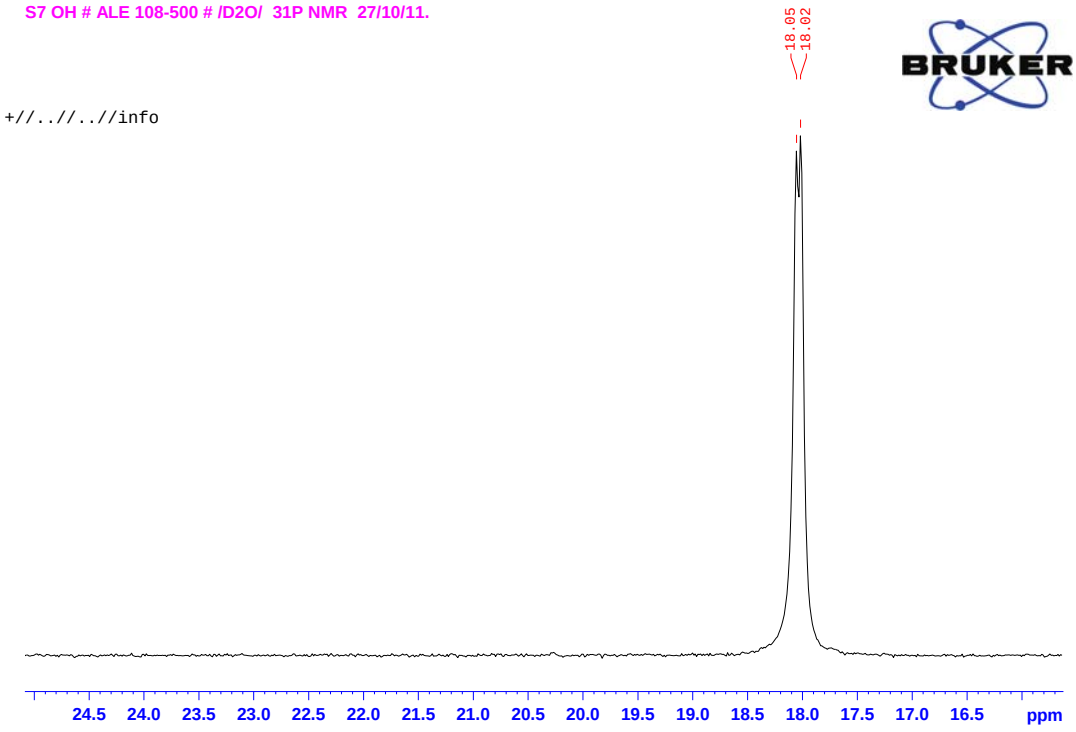
^{31}P NMR spectrum of compound **42**.



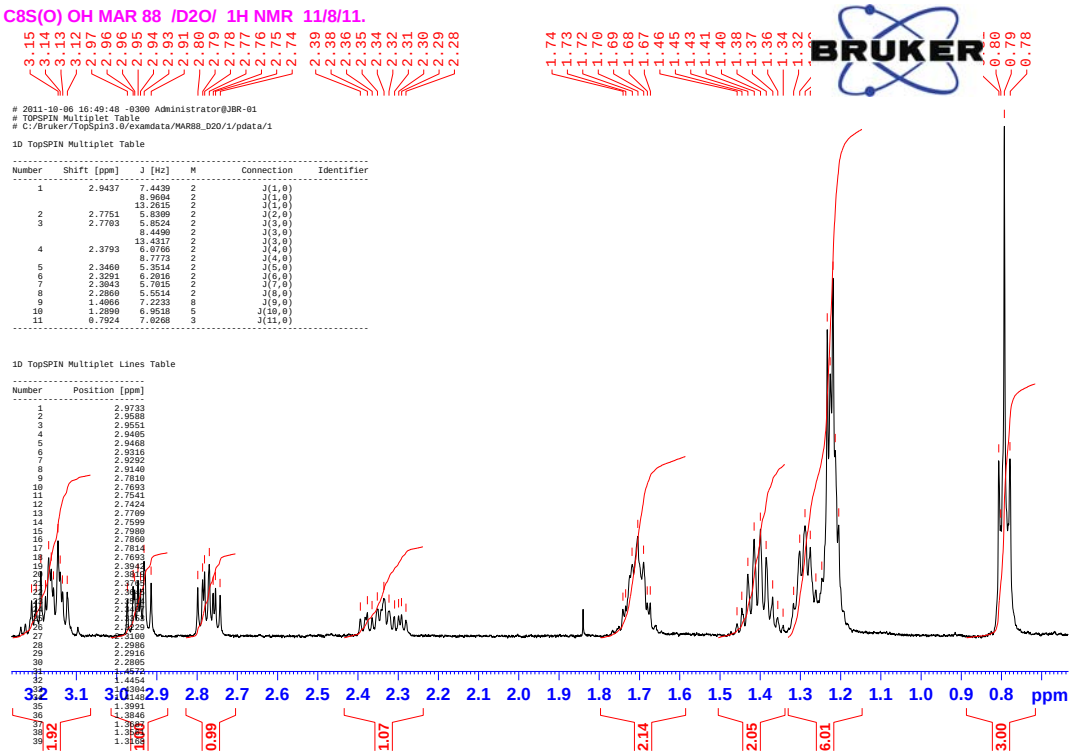
^{1}H NMR spectrum of compound **43**.



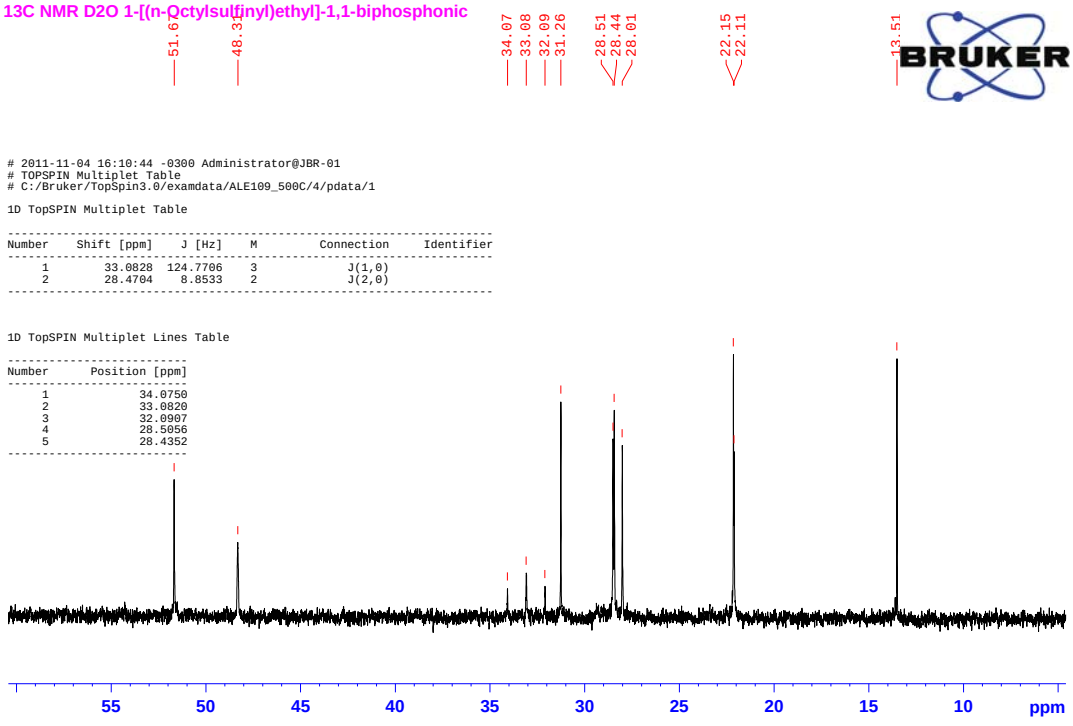
^{13}C NMR spectrum of compound **43**.



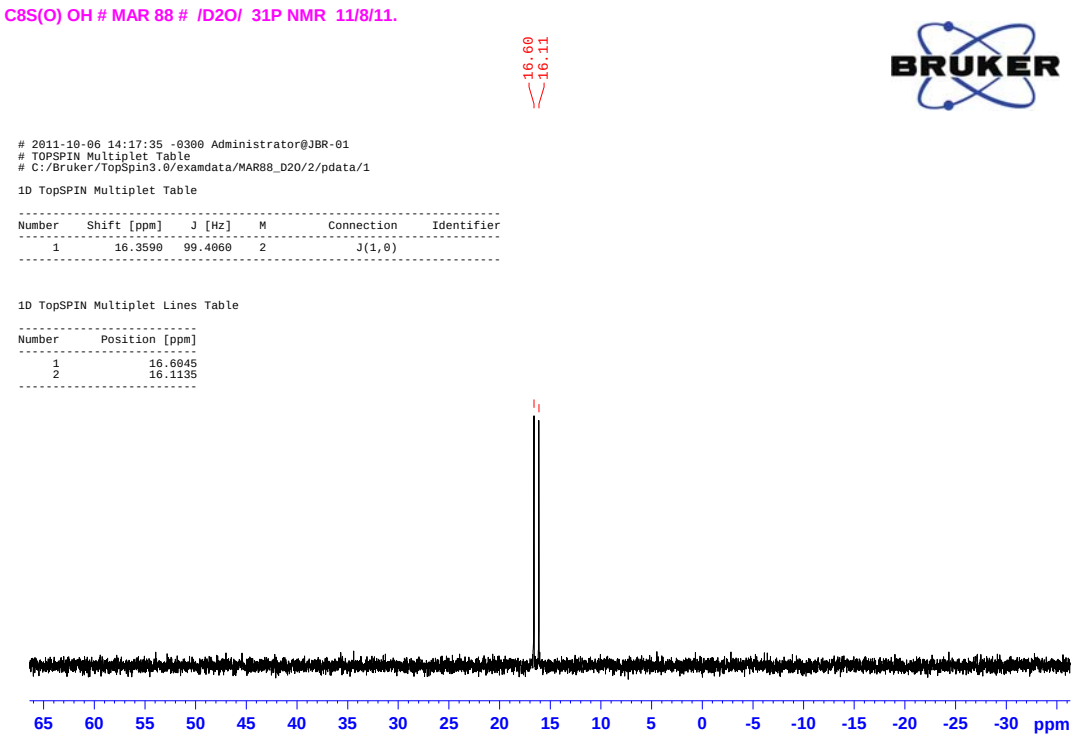
^{31}P NMR spectrum of compound **43**.



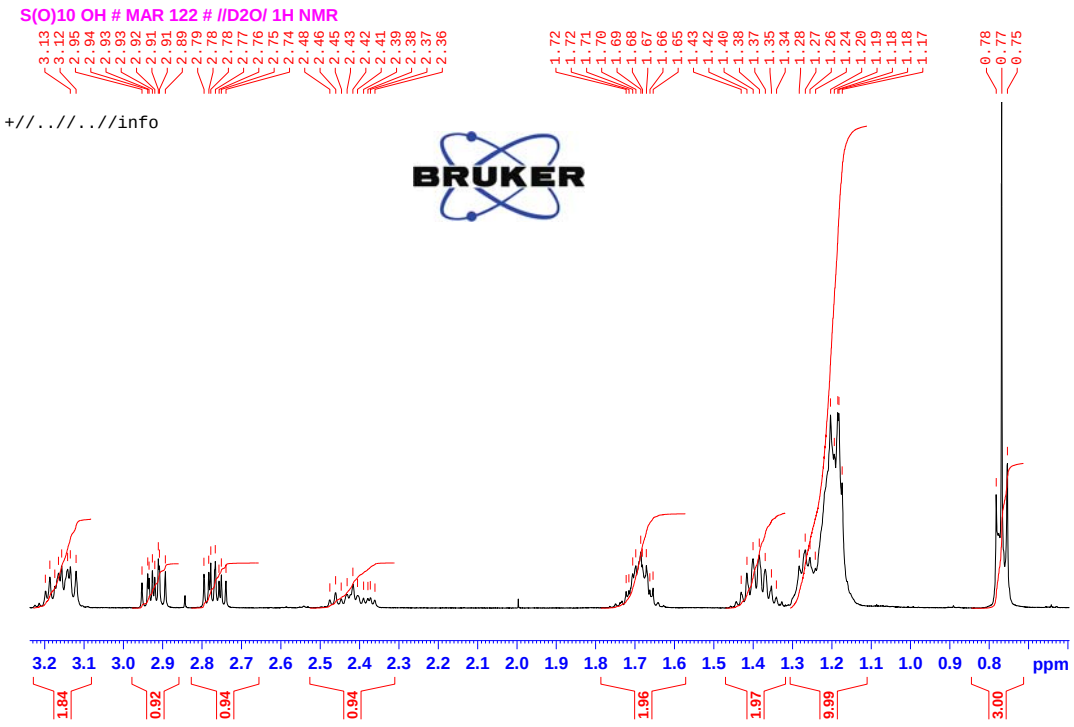
^{1}H NMR spectrum of compound **44**.



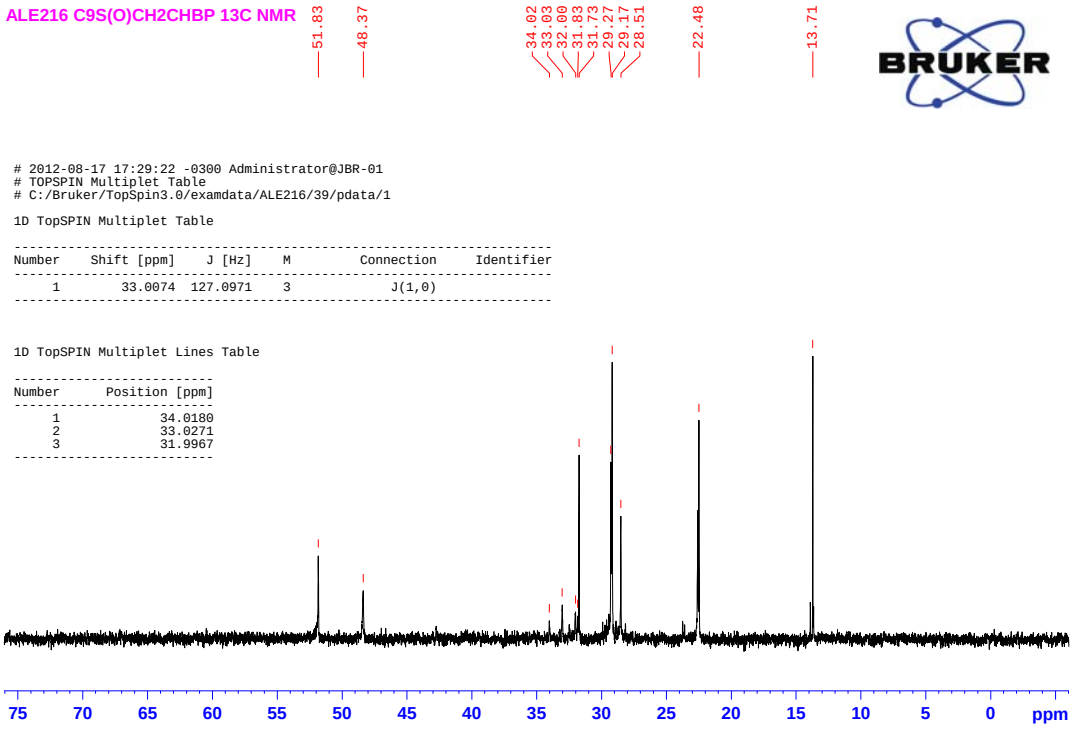
^{13}C NMR spectrum of compound **44**.



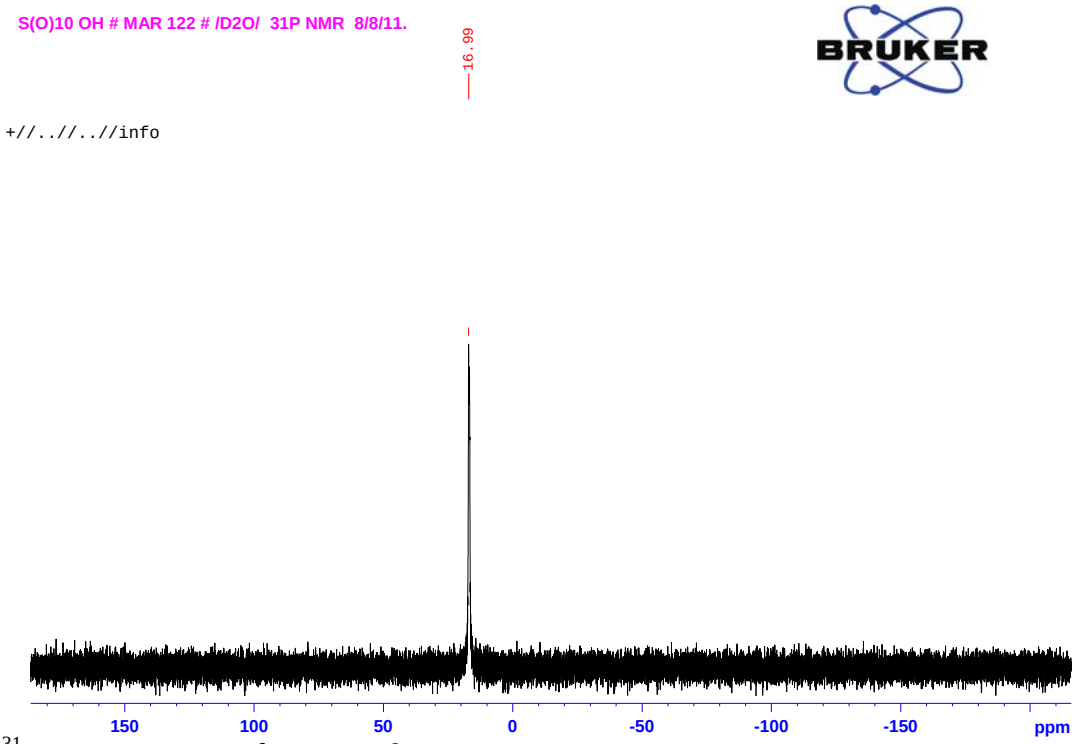
^{31}P NMR spectrum of compound **44**.



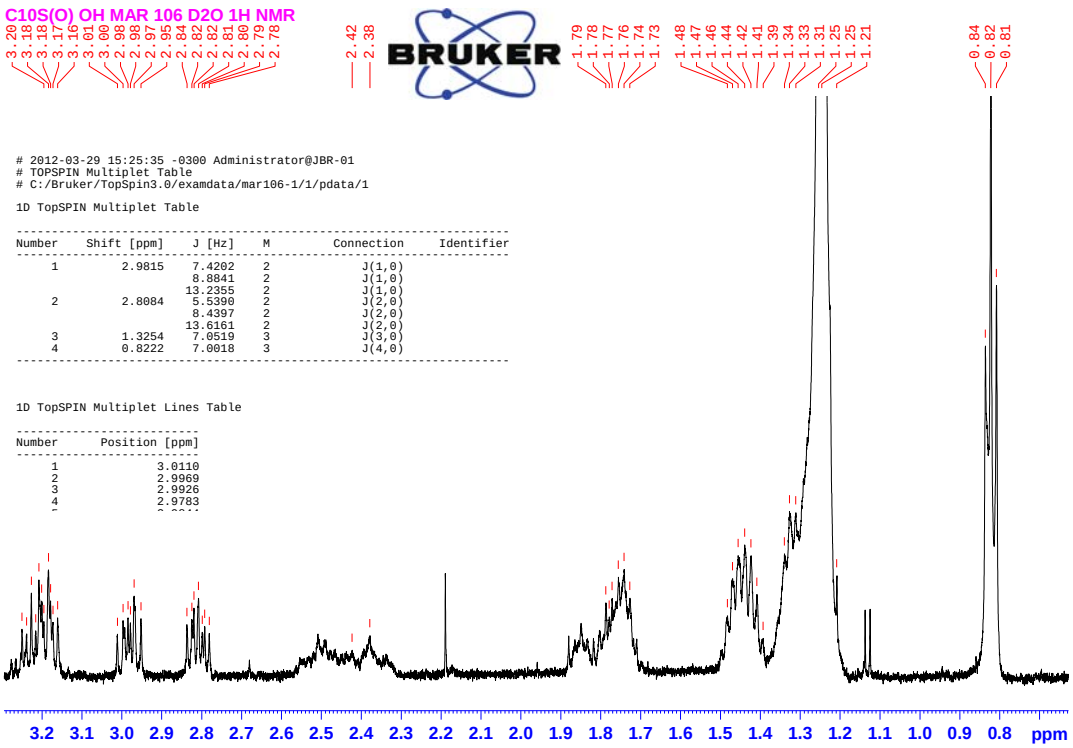
^{1}H NMR spectrum of compound **45**.



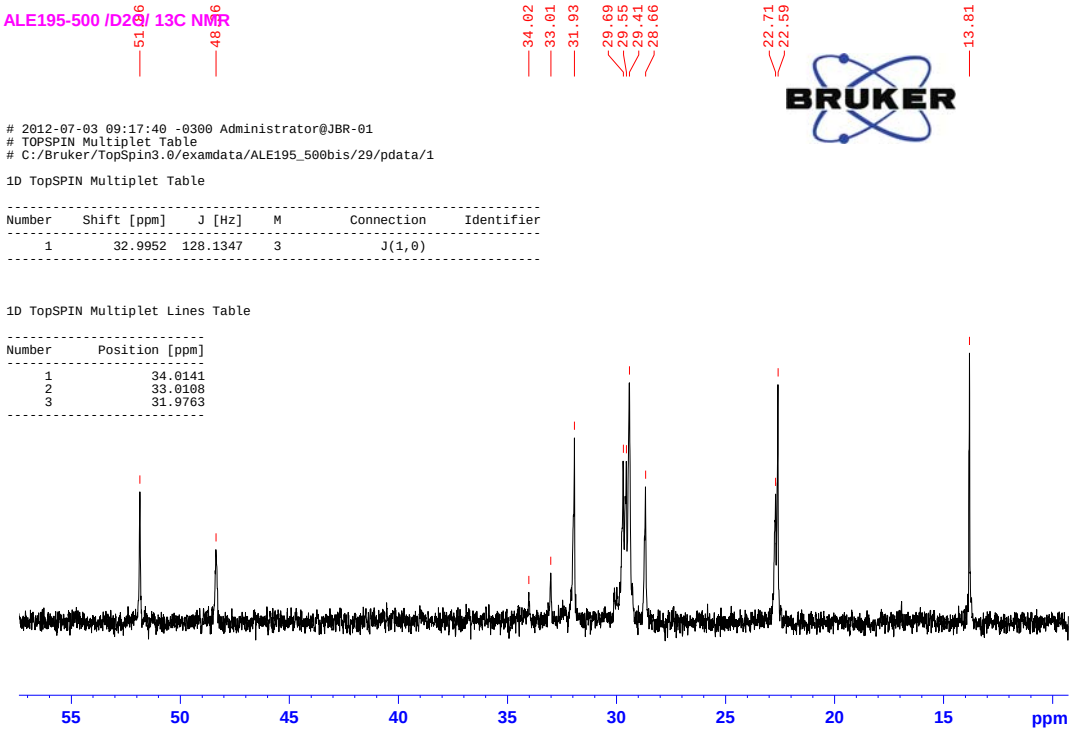
^{13}C NMR spectrum of compound **45**.



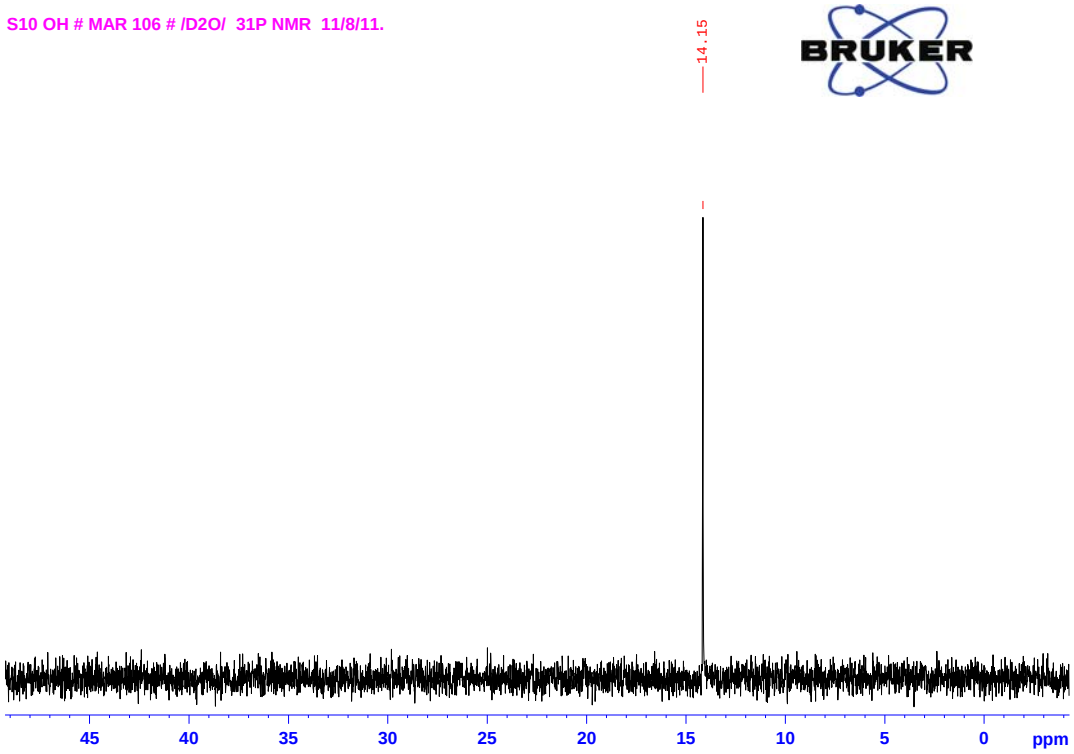
^{31}P NMR spectrum of compound **45**.



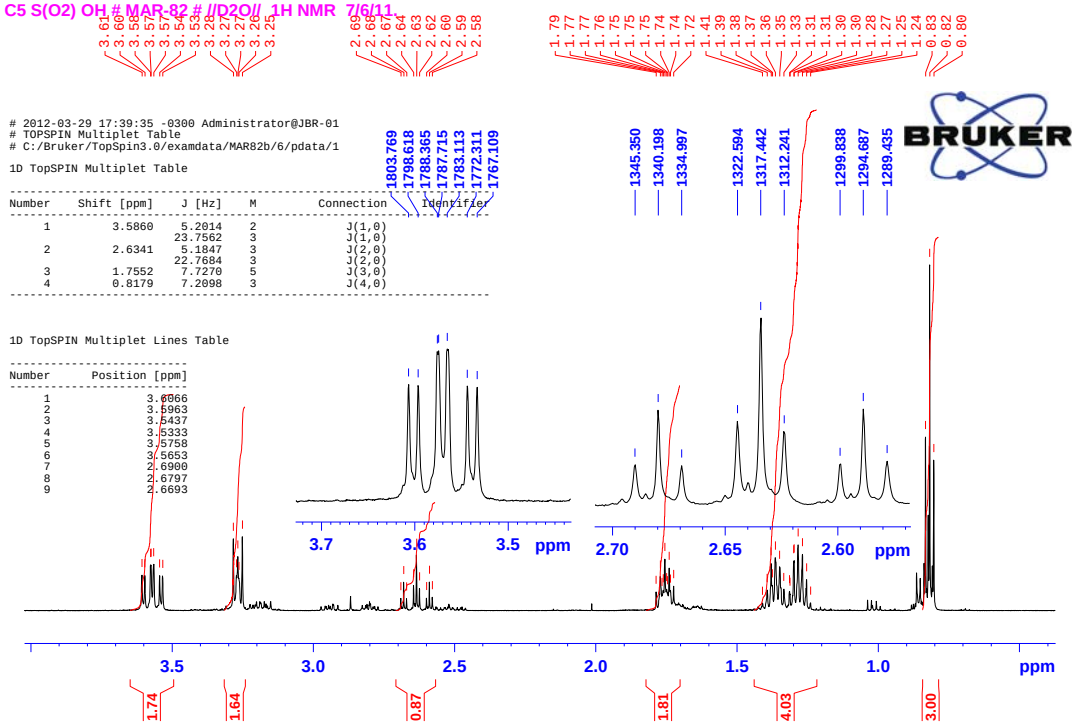
^{1}H NMR spectrum of compound **46**.



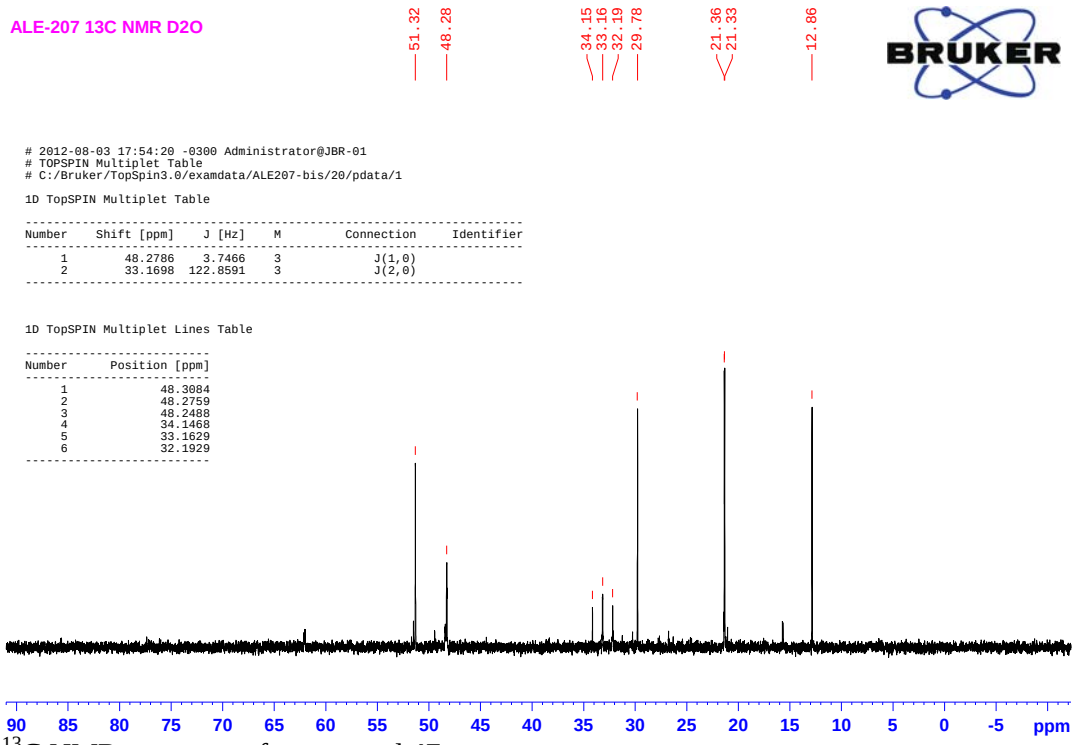
^{13}C NMR spectrum of compound **46**.



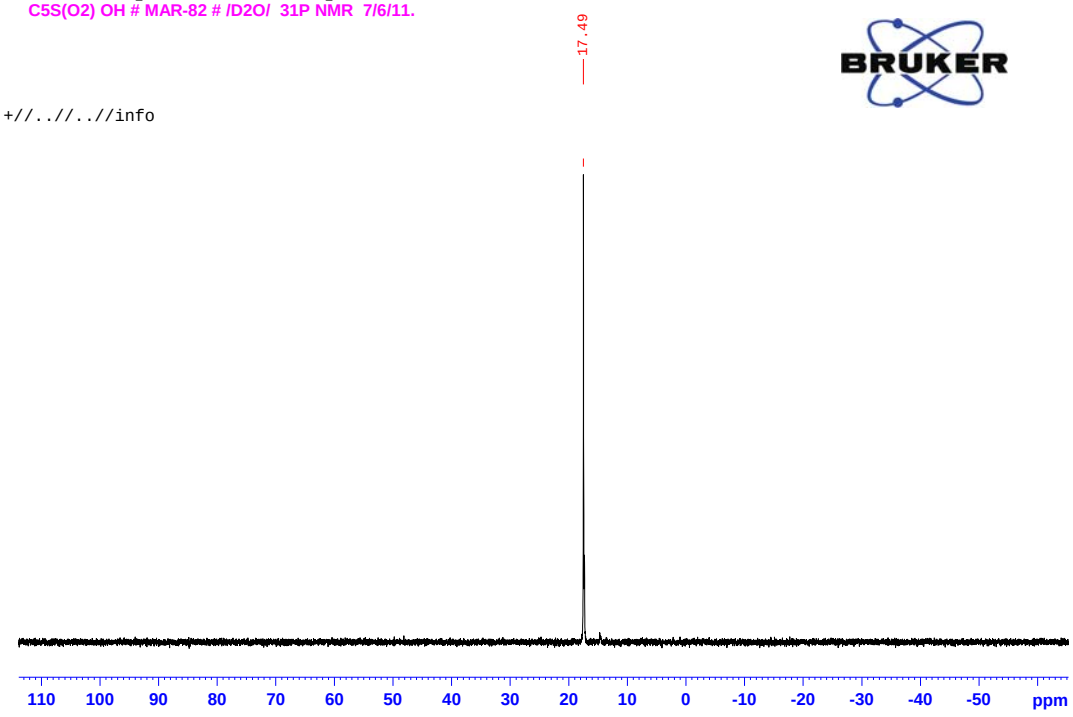
^{31}P NMR spectrum of compound **46**.



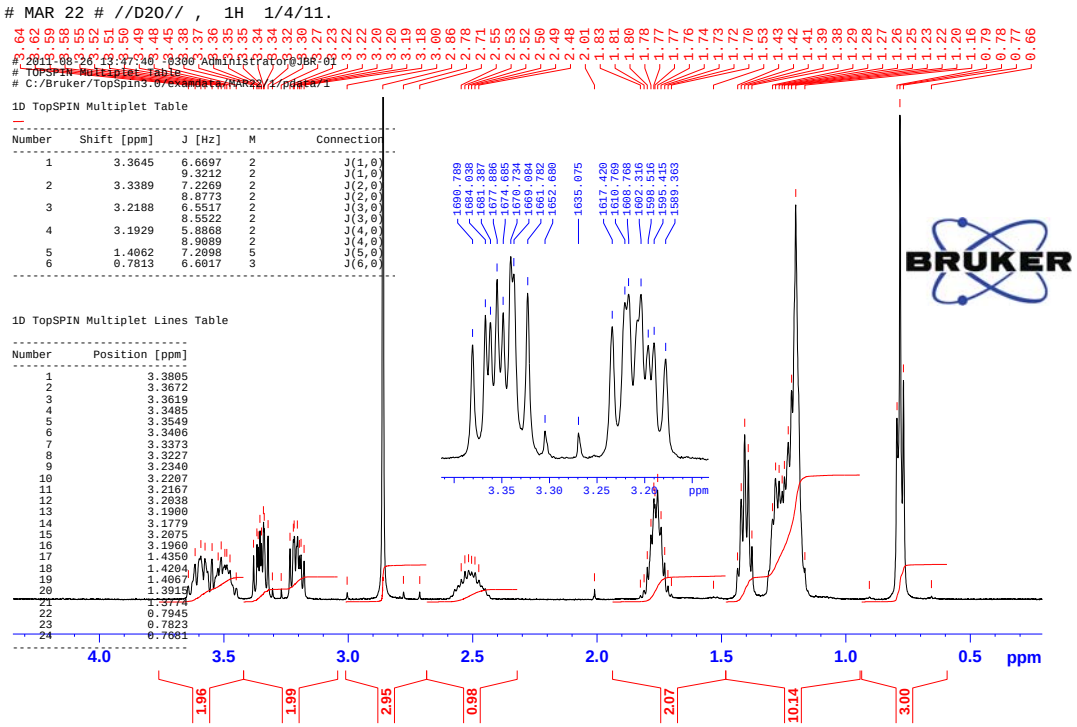
^{1}H NMR spectrum of compound **47**.



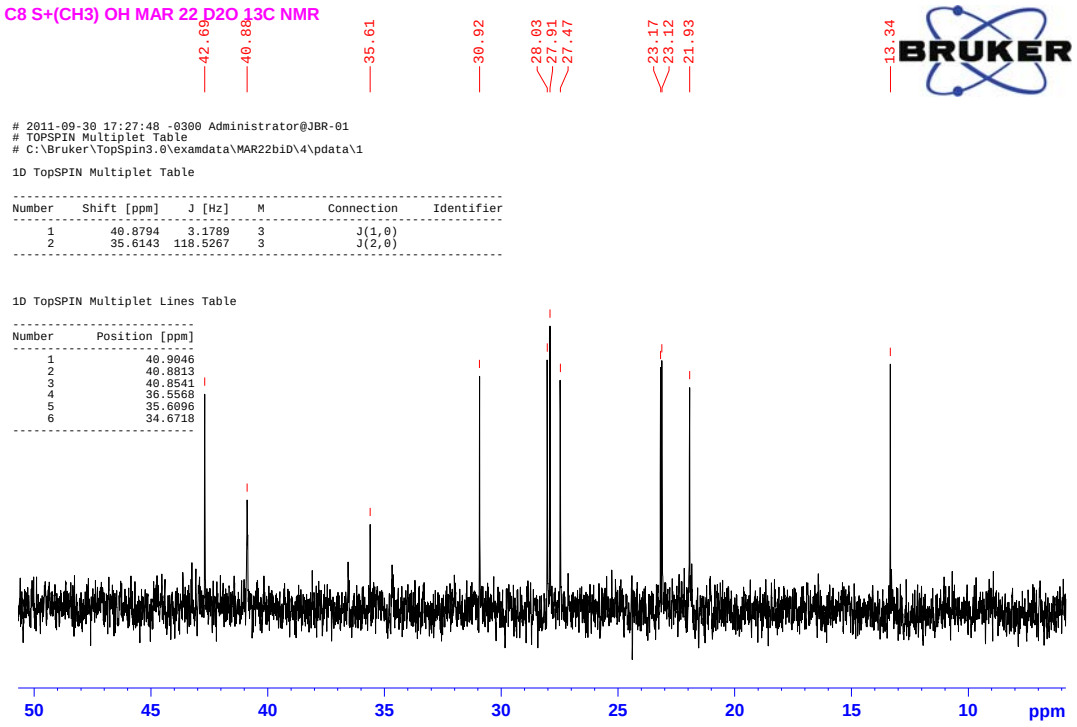
^{13}C NMR spectrum of compound **47**.



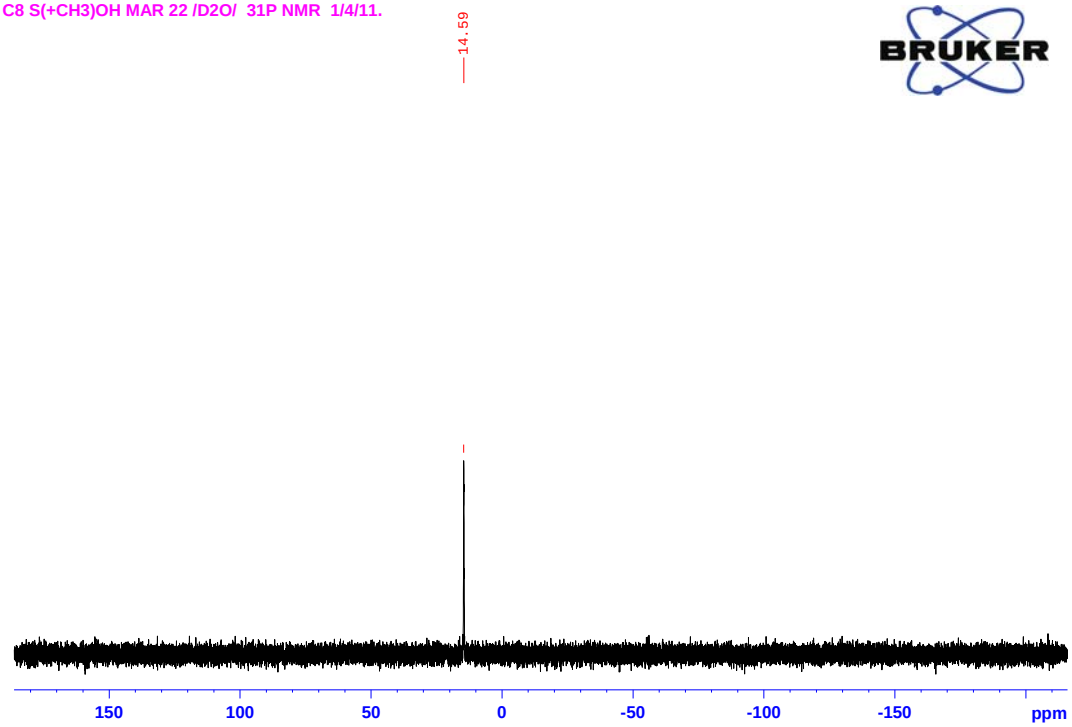
^{31}P NMR spectrum of compound **47**.



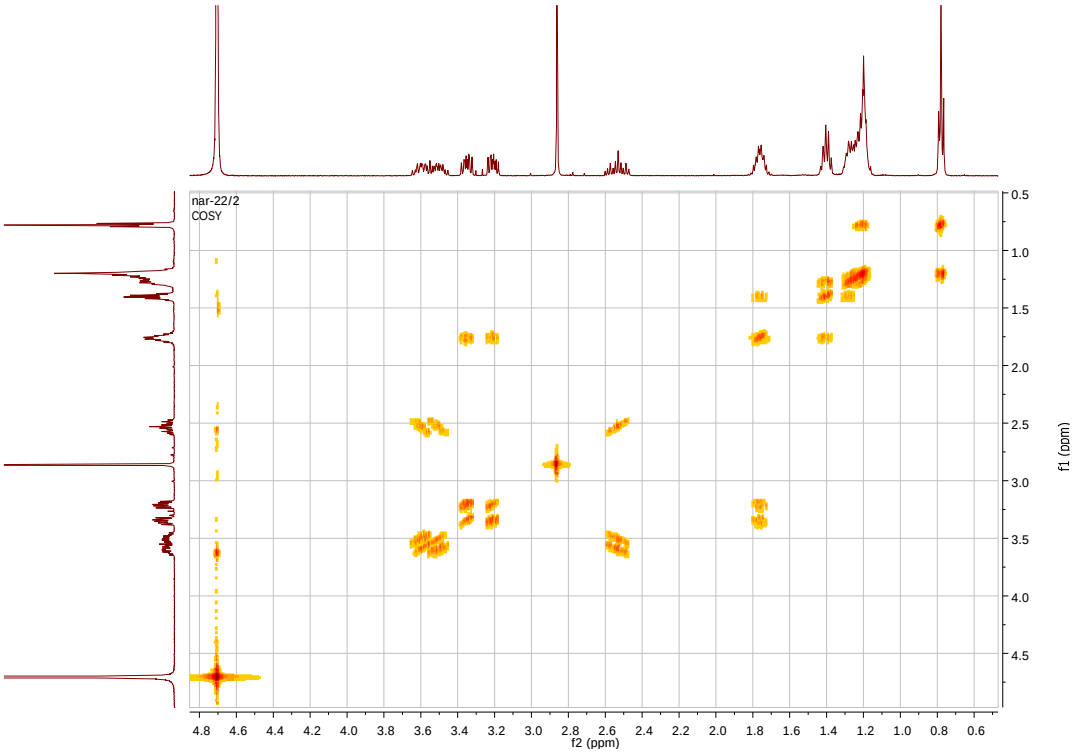
^{13}C NMR spectrum of compound **48**.



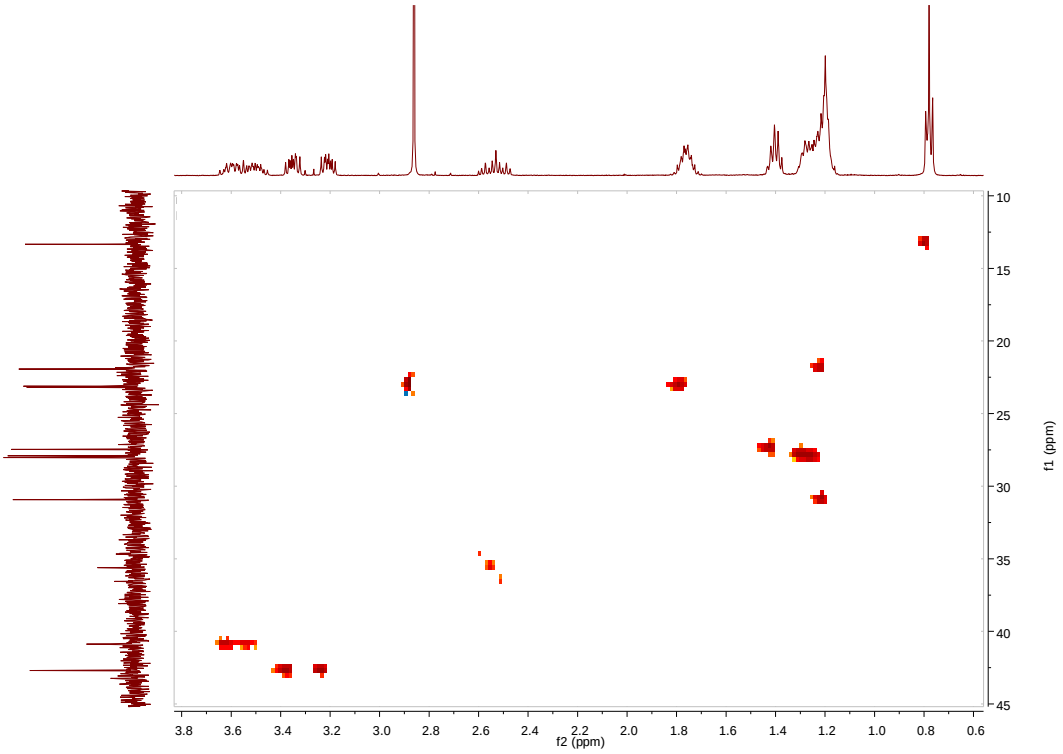
^{13}C NMR spectrum of compound **48**.



^{31}P NMR spectrum of compound **48**.



COSY spectrum of compound **48**.



HSQC spectrum of compound **48**.

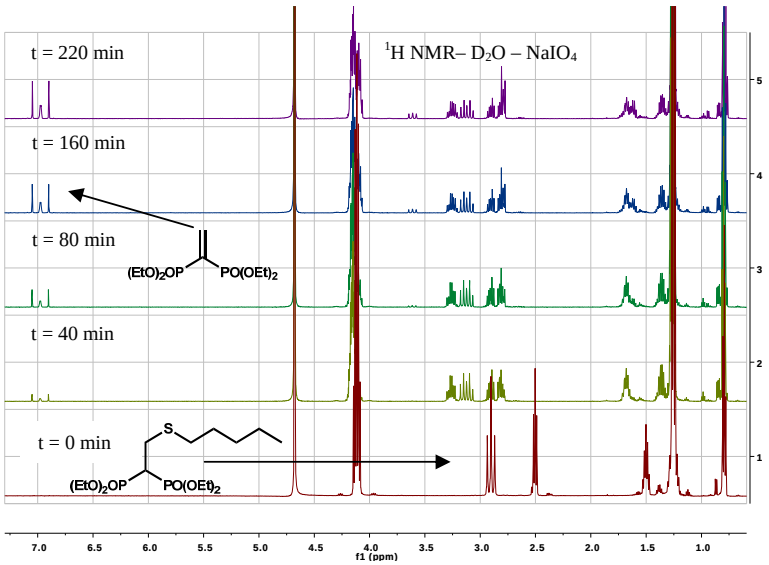


Figure 1. ^{1}H NMR spectra for monitoring the oxidation reaction of **25** with $NaIO_4$ in D_2O. ^{1}H NMR analyses indicated that treatment of pentylsulfide derivative **25** with sodium metaperiodate afforded initially the expected oxidized species, the corresponding sulfoxide, but, on standing, 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** (H_2C=) 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.

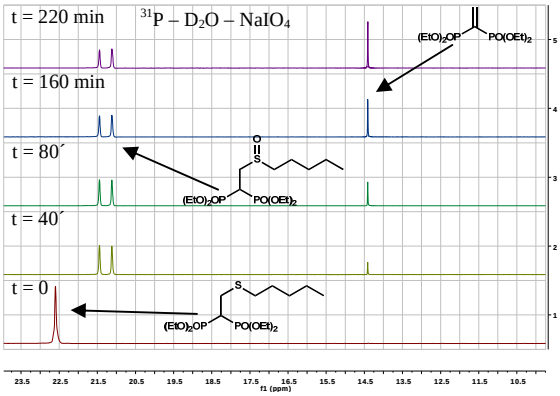


Figure 2. ^{31}P NMR spectra for monitoring the oxidation reaction of **25** with $NaIO_4$ in D_2O. The signal corresponding to the phosphorus atom present in **16** at 14.40 ppm also increases versus the peaks corresponding to the diastereotopic phosphorus atoms present in the sulfoxy-containing oxidized 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.

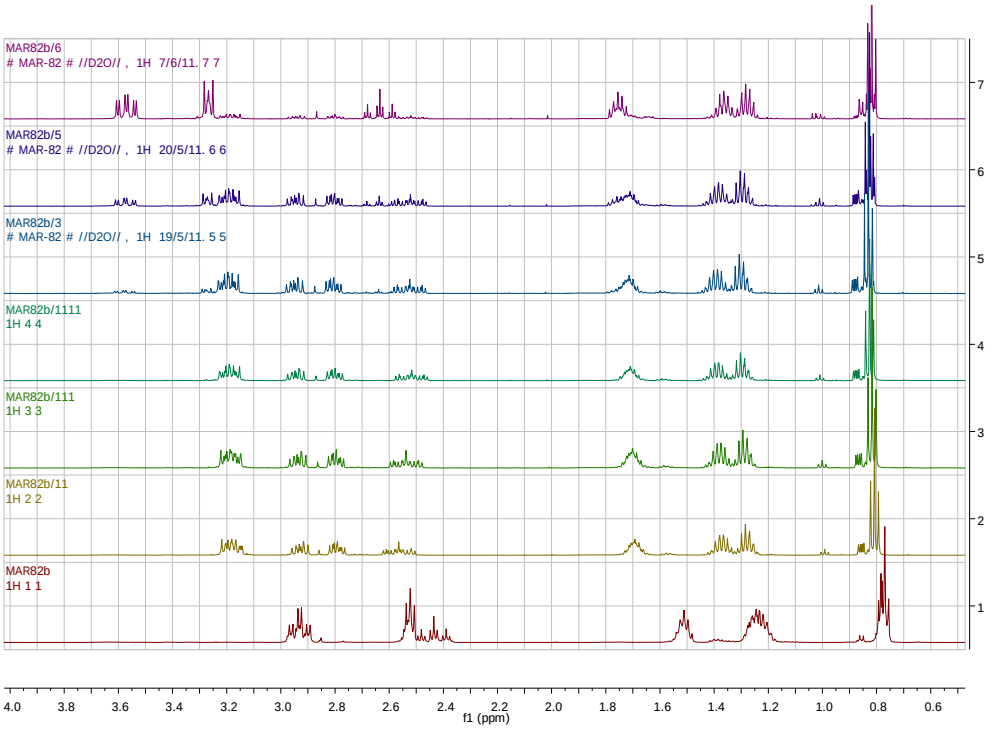


Figure 3. ^{1}H NMR spectra of monitoring oxidation of sulfide **34** to sulfoxide **41**. In order to test the hypothesis that oxidation of the free bisphosphonic acids **31**–**39** would not undergo a retro-Michael addition, the reaction of compound **34** with hydrogen peroxide was monitored by ^{1}H 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 corrresponding to **41** due to lost of the assymetric center. Twenty four hours later almost all the sulfoxide was transformed into **47**.

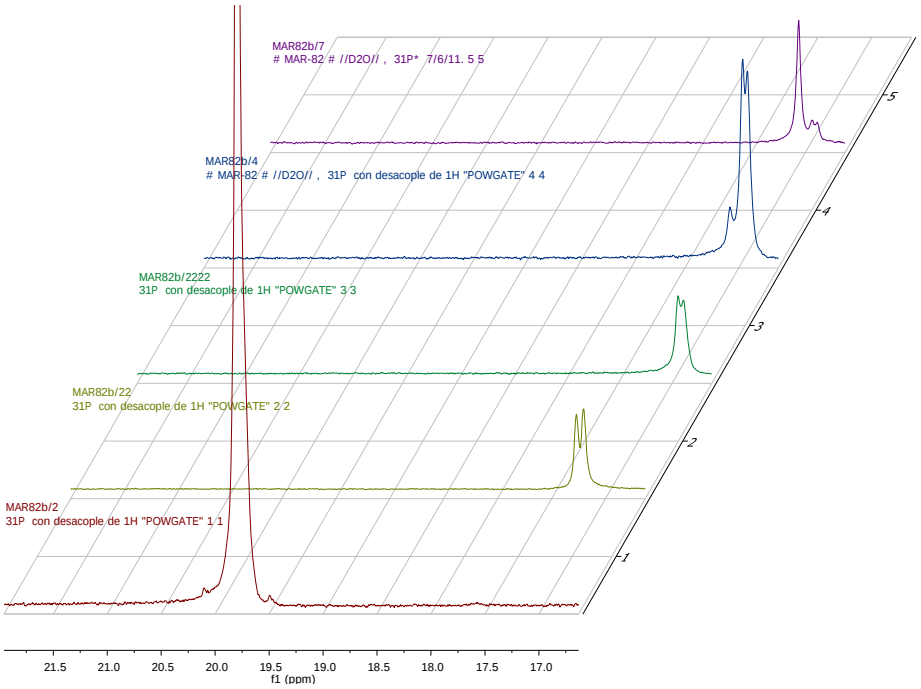


Figure 4. ^{31}P NMR spectra of monitoring oxidation of sulfide **34** to sulfoxide **41**. The signal corresponding to the phopshorus atoms at t = 0 appeared at 20.12 ppm. Then, the signal of the sulfoxide was observed as a strongly coupled system (18.02 ppm) that finally lead to a simplified signal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